CLINICAL STUDY PROTOCOL

Title:	A Phase 1/2a, Multicenter, Open-Label, Dose-Escalation and Expansion Study of Intravenously Administered 23ME-00610 in Patients with Advanced Solid Malignancies
Protocol Number:	23ME-00610-CLIN-001
Version (Date):	Version 8.0, September 26, 2023
Study Drug:	23ME-00610
EudraCT Number:	TBD
IND Number:	154497
Study Sponsor:	23andMe, Inc. 349 Oyster Point Blvd, South San Francisco, CA 94080
Study Medical Monitor:	[redacted]
Backup Study Medical Monitor:	[redacted]
Responsible Medical Officer:	[redacted]

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Sponsor Signatory

[redacted]

[redacted]

[redacted]

Date

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LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase (SGOT)
AUC	area under the time-concentration curve
BUN	blood urea nitrogen
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
C_{tau}	minimum projected concentration of 23ME-00610 in Cycle 1
ccRCC	clear cell renal cell carcinoma
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CONSORT	consolidated standards of reporting trials
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CV	Cardiovascular
DCR	disease control rate
DICOM	Digital Imaging and Communications in Medicine
DLT	dose-limiting toxicity
DoR	duration of response
DRE	disease-related event
EC	ethics committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice

G-CSF	granulocyte-colony stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IND	Investigational New Drug
irAE	immune-related adverse event
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
LLOQ	lower limit of quantitation
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	Pharmacodynamic
PD1	programmed cell death protein 1
PDL1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors 1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SARS-CoV	severe acute respiratory syndrome - coronavirus
SD	standard deviation
SRC	Safety Review Committee
SSR	somatostatin receptor
$T_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TMB-H	tumor mutational burden-high
ULN	Upper Limit of Normal
VEGF	vascular endothelial growth factor

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/2a, Multicenter, Open-Label, Dose-Escalation and Expansion Study of Intravenously Administered 23ME-00610 in Patients with Advanced Solid Malignancies

Short Title: A Phase 1/2a Study of 23ME-00610 in Patients with Advanced Solid Malignancies

Background and Rationale:

23ME-00610 is being developed as a therapy for patients with cancer. Immune-checkpoint inhibitors have shown efficacy in patients across a broad range of cancers; however, the clinical benefit is confined to a minority of patients. This may be due to redundancy among immune checkpoints, leading to primary or emerging resistance to marketed immunotherapies. CD200R1 is an immune inhibitory receptor that is highly expressed by infiltrating immune cells that are found in certain human cancers. 23ME-00610 is a humanized monoclonal antibody that binds specifically to CD200R1 and blocks downstream immune-suppressive signaling. We hypothesize that blocking the CD200R1 immune checkpoint will reverse immune cell tolerance in the tumor microenvironment in patients with cancer, leading to immune-mediated disease control.

Objectives and Endpoints for Part A

Objectives	Endpoints
Primary	
• To determine the safety and tolerability, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of 23ME-00610, in patients with locally advanced (unresectable) or metastatic solid cancers	• Incidence and severity of dose-limiting toxicities (DLTs) • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Withdrawals due to AEs
Secondary	
• To evaluate the immunogenicity to 23ME-00610	• Prevalence and incidence of antidrug antibodies (ADA) to 23ME-00610
• To characterize the pharmacokinetic (PK) profile of multiple doses of 23ME-00610	• Serum PK parameters of 23ME-00610, as applicable, including: AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$
• To evaluate preliminary clinical (antitumor) activity of 23ME-00610 in evaluable patients by RECIST 1.1 criteria	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS) based on investigator assessment against RECIST 1.1 criteria • Overall survival (OS)

Objectives	Endpoints
Exploratory	
• To further evaluate preliminary clinical activity of 23ME-00610 in evaluable patients by iRECIST criteria	• ORR, DoR, DCR and PFS based on investigator assessment against iRECIST criteria (Lancet Oncol 2017;18: e143-52)
• To characterize the pharmacodynamic (PD) effects of 23ME-00610 by the assessment of changes in PD biomarkers in the blood and/or the tumor	• PD assessment of blood biomarkers may include, but not be limited to, target engagement, soluble factor analysis or immune cell enumeration.
• To evaluate the exposure-response relationships of 23ME-00610 and safety and PD biomarkers	• Relationships between PK parameters and safety, and/or PD biomarkers may be explored, and may include: • PK parameters of 23ME-00610, as applicable (i.e., AUC, C_{tau}) • Tumor and circulating blood PD parameters • Safety (e.g., laboratory parameters, AEs) • Polygenic risk scores (derived from saliva or blood genotyping) for immune-mediated adverse events
• To characterize the impact of 23ME-00610 on the QT-interval	• QTcF-interval changes from baseline on triplicate ECGs

Objectives and Endpoints for Part B

Objectives	Endpoints
Primary	
• To evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by RECIST 1.1 criteria	• ORR based on investigator assessment against RECIST 1.1 criteria

Objectives	Endpoints
• **Adolescents only:** To determine the safety and tolerability, MTD and/or RP2D of 23ME-00610, in adolescent patients with locally advanced (unresectable) or metastatic solid cancers	• Incidence and severity of DLTs • Incidence and severity of AEs and SAEs • Withdrawals due to AEs
Secondary	
• To further evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by RECIST 1.1 criteria	• DoR, DCR and PFS based on investigator assessment against RECIST 1.1 criteria • OS
• To determine the safety and tolerability of 23ME-00610	• Incidence and severity of AEs and SAEs • Withdrawals due to AEs
• **Cohort 3B only:** To characterize the pharmacodynamic (PD) effects of 23ME-00610 on target cells in evaluable tumor samples	• Assessment of changes to target cell enumeration and/or phenotype by IHC and/or RNA
Exploratory	
• To evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by iRECIST criteria	• ORR, DoR, DCR and PFS based on investigator assessment against iRECIST criteria (Lancet Oncol 2017;18: e143-52)
• To evaluate potential predictive markers associated with the clinical activity of 23ME-00610	• Correlation of PFS, OS, and ORR, DoR and DCR based on RECIST 1.1 criteria with predictive markers, including: immune-related AEs (irAEs) and tumor, saliva, blood biomarkers, and polygenic risk scores derived from genotyping
• To evaluate the immunogenicity to 23ME-00610	• Prevalence and incidence of ADA to 23ME-00610
• To characterize the PK profile of multiple doses of 23ME-00610	• Serum PK parameters of 23ME-00610, as applicable, including: AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$
• To characterize the PD effects of 23ME-00610 by the assessment of changes in PD biomarkers in the blood	• PD assessment of blood biomarkers may include, but not be limited to,

Objectives	Endpoints
	target engagement or soluble factor analysis.
• To evaluate the exposure-response relationships of 23ME-00610 and clinical activity, safety, and PD biomarkers	• Relationships between PK parameters and clinical activity, safety, and/or PD biomarkers may be explored, and may include: • PK parameters of 23ME-00610, as applicable (ie, AUC, C_{tau}) • Tumor and circulating blood PD parameters • ORR • Safety (eg, laboratory parameters, AEs, irAEs)

Overall Design:

This is an open-label Phase 1/2a study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary clinical activity of 23ME-00610 given by intravenous (IV) infusion in patients with advanced solid cancers who have progressed on all available standard therapies. This study includes a dose-escalation phase in Part A to determine the MTD and/or RP2D followed by 6 monotherapy expansion arms in Part B to further evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of 23ME-00610 in patients with solid cancers (Figure 1).

Overview of the 23ME-00610 Monotherapy Dose-Escalation Phase (Part A)

The dose-escalation phase will utilize a combination of accelerated titration and a standard "3 + 3" design to minimize exposing patients to subtherapeutic doses. During the dose-escalation phase, consented eligible patients will be enrolled into sequential cohorts of increasing doses of 23ME-00610 administered IV once every 3 weeks with a 21-day DLT observation period following administration of the first dose.

The safety at each dose level will be evaluated by the Safety Review Committee (SRC). The SRC will review a minimum of 21-day post-dose safety data, and available PK and PD data, from each cohort to determine if dose escalation will occur. Dose escalation decisions will be made based on all safety information available, including AEs that occur beyond the 21-day DLT period, from both ongoing and prior cohorts. Decisions to escalate the dose will be documented along with a summary of the information supporting the decision.

Accelerated titration dose-escalation phase: One patient will be enrolled into Cohort 1A at the 23ME-00610 2 mg dose level. If no Grade ≥ 2 AEs not clearly related to the underlying disease or pre-existing conditions are observed during the 21-day DLT evaluation period (i.e., Cycle 1), the study will proceed with dose escalation to the next cohort. The same procedure will be followed for Cohort 2A (23ME-00610 dose of 6 mg). If a patient experiences a Grade ≥ 2 AE

not clearly related to the underlying disease or pre-existing conditions during the first cycle, an additional 2 patients will be enrolled in that cohort and the study will subsequently follow the 3 + 3 design outlined below from this respective cohort onwards. The recommendation to escalate the dose or expand the cohort will be made by the SRC.

3+3 dose-escalation phase: Starting with Cohort 3A, a minimum of 3 patients will initially be enrolled in each subsequent dose cohort. If there are multiple patients in the screening process at the time the third patient within a cohort begins treatment, 1 additional patient may be enrolled, with approval of the medical monitor at 23andMe.

If after the third patient completes the 21-day DLT evaluation period, no DLTs are observed (Section 4.1.1.1), the study will proceed with dose escalation to the next cohort following a review by the SRC. If 1 of 3 patients experiences a DLT during the first cycle, 3 additional patients will be enrolled in that cohort. If none of the additional 3 patients experience a DLT (i.e., DLTs occurred in < 2 of 6 patients), dose escalation may continue to the next cohort following review by the SRC. If 2 or more patients in a cohort experience DLTs during the first cycle, dose escalation will be halted and the next lower dose level will be declared the MTD. Alternatively, a dose level intermediate between the non-tolerated dose level and the previously tolerated dose level may be explored based on review of safety and available PK and PD data and SRC approval and may be declared the MTD if < 2 out of 6 patients experience a DLT at that dose. If the MTD cohort included only 3 patients, an additional 3 patients will be enrolled at that dose level to confirm that < 2 of 6 patients experience a DLT at that dose.

Note that if a given cohort initially enrolled 4 patients (i.e., if there were multiple patients in the screening process at the time the third patient within a cohort began treatment), the dose escalation meeting can occur with SRC agreement once the third patient completes the 21-day DLT period. All safety data from ongoing and prior cohorts, including the first 3 patients enrolled in the cohort and from any additional patients enrolled in the same cohort up to the day of the SRC meeting will be considered for dose escalation decisions. The same rules for dose escalation rules will apply if more than 3 patients are initially enrolled in a cohort. If 1 of the 4 experiences a DLT, the cohort will be expanded to include a total of 6 patients; dose escalation will occur if only 1 of 6 patients experiences a DLT and will be halted if 2 or more patients experiences a DLT.

Beginning with cohort 3A, a sentinel strategy will be used for the first patient enrolled in every new ascending dose level. 24 hours must elapse after the first patient receives 23ME-00610 before the remaining patients in the cohort are administered the same dose. Dose-limiting toxicities will be evaluated during Cycle 1 of treatment.

23ME-00610 will be administered IV once every 3 weeks (Q3W) at the following planned dose levels:

- Cohort 1A: 2 mg
- Cohort 2A: 6 mg
- Cohort 3A: 20 mg

- Cohort 4A: 60 mg
- Cohort 5A: 200 mg
- Cohort 6A: 600 mg
- Cohort 7A: 1400 mg

Dose escalation may end prior to the maximum planned dose level based on SRC decision following review of the safety, PK, and PD data. Intermediate dose levels in additional dose-level cohorts may be evaluated if supported by emerging safety, PK, and PD data, and SRC approval.

Patients who do not meet any of the treatment withdrawal criteria may continue treatment beyond Cycle 1. To optimize the number of patients treated at a potentially clinically relevant dose, intra-patient dose escalation will be provided as an option for patients who have not experienced a Grade 3 or higher drug-related AE at the originally assigned dose, following SRC clearance of an incrementally higher dose as sufficiently safe and tolerable, with approval from the medical monitor at 23andMe (see Section 4.1.1.2).

PK/PD Backfill Cohort: To further evaluate PK and PD in Part A, additional patients may be enrolled in a PK/PD backfill cohort (up to a total of 12 patients, including the 3 to 6 patients initially enrolled during dose escalation) following SRC approval at the RP2D/MTD, or a previously evaluated dose level where there is pharmacologic or pharmacodynamic evidence of therapeutic effect.

Overview of the 23ME-00610 Monotherapy Expansion Phase (Part B)

Following the monotherapy dose-escalation phase (Part A), identification of the MTD and/or the RP2D, and approval by the SRC, 6 non-randomized expansion Cohorts (including 5 indication-specific cohorts and an adolescent solid cancer cohort) may be enrolled at a recommended dose(s) in Part B based on the safety, tolerability, and PK/PD data from Part A of the study. Following safety, tolerability, and available PK/PD data review, the SRC may recommend a dose level(s) for the expansion cohorts after ≥ 6 patients in Part A have been treated at or above the recommended dose level for ≥ 1 cycle. Multiple doses may be evaluated if there is pharmacologic or pharmacodynamic evidence of therapeutic effect below the MTD.

23ME-00610 1400 mg administered IV Q3W will be evaluated in all expansion Cohorts based on SRC review of safety, tolerability, and available PK/PD data from Part A.

Cohort 1B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic clear cell renal cell carcinoma (ccRCC).

Cohort 2B will enroll approximately 13 evaluable patients with locally advanced (unresectable) or metastatic epithelial ovarian, fallopian tube or primary peritoneal carcinoma of non clear-cell histology, and approximately 2 evaluable patients with clear cell histology (approximately 15 total).

Cohort 3B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic neuroendocrine cancers.

Cohort 4B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic microsatellite instability-high (MSI-H) and/or tumor mutational burden-high (TMB-H) solid cancers, including at least 5 evaluable patients that have TMB ≥ 10 mutations/megabase, and 10 evaluable patients that have either TMB ≥ 20 mutations/megabase and/or MSI-H cancers.

Cohort 5B will enroll approximately 8 evaluable adolescent patients with locally advanced (unresectable), or metastatic solid cancers (**see Inclusion of Adolescents in Part B**).

Cohort 6B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic extensive stage small cell lung cancer (ES-SCLC).

Approximately 15 additional evaluable patients may be added to any disease-specific cohort in Part B to evaluate another dose level with pharmacologic or PD evidence of therapeutic effect below the MTD/RP2D identified in Part A (for a maximum of 30 patients in total at the alternate dose) following SRC review and approval.

In jurisdictions where local regulations and IRB/EC allows, patients who reflect the characteristics with regards to age, sex, race and ethnicity for each disease-specific cohort will be prioritized for enrollment. Specifically, patients from historically underrepresented communities, including those from the Black, Latinx/Hispanic and Indigenous communities will be prioritized in Part A, and in each expansion cohort in Part B to ensure the trial population is representative of the intended patient population.

These indications were selected based on the expression of CD200R1 and its ligand, CD200, T-cell markers, and/or immune characteristics that suggest a higher likelihood of response to 23ME-00610. Additional Dose Expansion Cohorts may be enrolled in a specific tumor type or biomarker-defined population based on emerging nonclinical or clinical data.

Safety, PK/PD and preliminary clinical activity data will be reviewed by the SRC approximately every 8 weeks during the expansion phase.

Inclusion of Adolescents in Part B: In jurisdictions where local regulations and IRB/EC allows, adolescent patients will be included in the expansion phase after a minimum of 6 adult patients have been treated at the RP2D for ≥ 1 cycle and following SRC approval. Cohort 5B will enroll approximately 8 adolescent patients with locally advanced (unresectable), or metastatic solid cancers. The SRC will review the safety and PK data from the first 3 adolescent patients in Cohort 5B to determine if the remaining patients in the cohort will be enrolled.

Sample Size

Assuming that identification of the MTD/RP2D requires the evaluation of 7 dose levels of 23ME-00610 with 1 patient in each of the first 2 dose levels, and 3 patients in the following 5 dose levels, with the exception that the MTD requires 6 patients, then approximately 20 patients will be enrolled during the dose escalation phase (Part A) of the study. Additional

patients may be needed for cohort expansion and intermittent dose evaluation in Part A. A maximum of 12 patients may be enrolled in the PK/PD backfill cohort (including the 3 to 6 patients initially enrolled during dose escalation). For Part A, the total enrolled (expected to be 20-28 patients) is an estimate and will depend on the number needed to sufficiently characterize the MTD/RP2D.

Assuming 8-30 evaluable patients are enrolled in each of 6 expansion cohorts (Part B), approximately 83-113 evaluable patients will be enrolled in Part B and a total of 103-141 will be enrolled in the study.

Number and Location of Study Centers

Part A Escalation: up to approximately 5 sites globally

Part B Expansion: up to approximately 20 sites globally

Inclusion Criteria
Patients are eligible to be included in the study only if all of the following criteria apply:

101. **Part A (Dose Escalation):** Adults ≥ 18 years of age
Part B (Expansion):
    a. **Cohorts 1-4 and 6:** Adults and adolescents ≥ 12 years of age, weighing ≥ 40 kg (total body weight)
    b. **Cohort 5:** Adolescents ≥ 12 to < 18 years of age, weighing ≥ 40 kg (total body weight)

102. Able to understand and willing to sign an informed consent. A legally authorized representative (e.g., parent or legal guardian) may consent on behalf of a patient who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's Institutional Review Board (IRB) or Ethics Committee (EC).

103. **Part A (Dose Escalation):** Histologically-diagnosed locally advanced (unresectable), or metastatic carcinoma or sarcoma that has progressed after all available standard therapy for the specific tumor type, or for which standard therapy has proven to be ineffective, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe (Note: Patients whose cancers harbor molecular alterations for which targeted therapy or immunotherapy is standard of care should have received local health authority approved appropriate therapy for their tumor type prior to enrollment).

    Part B (Expansion):

    a. **Cohort 1B:** Histologically-diagnosed locally advanced (unresectable) or metastatic ccRCC that has progressed following all available standard therapy (e.g., anti-PD(L)-1, anti-vascular endothelial growth factor [VEGF] kinase inhibitors), or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

For patients eligible for anti-PD(L)-1 and/or anti-VEGF kinase inhibitors treatment according to the local country-specific prescribing information for metastatic ccRCC, prior treatment with these agents is required.

Adolescents that meet the criteria for both Cohort 1B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 1B following approval from the medical monitor at 23andMe.

b. **Cohort 2B:** Histologically-diagnosed locally advanced (unresectable) or metastatic, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal carcinoma (i.e., disease recurrence within 6 months of completion of platinum-based therapy) that has progressed following all available standard therapy, or if no further standard therapy exists. Patients who are platinum-refractory or for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

   Patients with molecular alterations for which targeted therapy is the standard of care (e.g., PARP inhibitors) should have progressed following the appropriate targeted therapy. Treatment with PARP inhibitors should be offered in line with institutional practice (i.e., BRCA 1/2).

   Cohort 2B will enroll ~13 patients with non-clear cell epithelial ovarian, fallopian tube or primary peritoneal carcinoma and ~2 patients with clear cell ovarian fallopian tube or primary peritoneal carcinoma (up to 15 total).

   Adolescents that meet the criteria for both Cohort 2B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 2B following approval from the medical monitor at 23andMe.

c. **Cohort 3B**: The following histologically-diagnosed locally advanced (unresectable) or metastatic neuroendocrine cancers that have progressed following all available standard therapy, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

   i. Merkel cell carcinoma

   ii. Well-differentiated Grade 3 neuroendocrine cancers with unfavorable biology (Ki67 ≥ 55%), rapid growth rate, fluorodeoxyglucose (FDG)-avid, negative somatostatin receptor (SSR) based on positron emission tomography (PET) (as per National Comprehensive Cancer Network [NCCN] guidelines) from any site

   iii. Poorly differentiated neuroendocrine carcinoma (or extrapulmonary large and small cell carcinoma)

   iv. Patients with other cancers that show evidence of focal neuroendocrine differentiation may be included with approval from the medical monitor at 23andMe.

Adolescents that meet the criteria for both Cohort 3B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 3B following approval from the medical monitor at 23andMe.

d. **Cohort 4B:** Histologically-diagnosed locally advanced (unresectable) or metastatic solid cancer that has progressed following all available standard therapy, or if no further standard therapy exists and meets the following criteria:

   TMB-H solid cancer that has been confirmed by the FoundationOne CDx assay using a cutoff of ≥ 10 mutations/megabase (other industry/institutional equivalent platforms for TMB assessment are permitted) and/or MSI-H solid cancer that has been confirmed by immunohistochemistry for MMR proteins or polymerase chain reaction (PCR) of microsatellites or MMR gene mutation by a next-generation sequencing (NGS) panel (e.g., FoundationOne CDx, or industry/institutional equivalent that has been validated for diagnostic use).

   Cohort 4B will aim to enroll ~15 patients; however, this cohort may be overenrolled to ensure at least 5 patients have TMB ≥ 10 mutations/megabase, and at least 10 patients have either TMB ≥ 20 mutations/megabase or are MSI-H (irrespective of TMB-H status) within the cohort.

   For patients eligible for anti-PD-1 treatment according to the local country-specific prescribing information for TMB-H and/or MSI-H cancer, prior treatment with anti-PD-1 is required.

   Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

   Patients with TMB-H and/or MSI-H primary central nervous system cancers are not eligible.

   Patients with TMB-H and/or MSI-H solid cancers that also meet the eligibility criteria for Cohorts 1B-3B should be enrolled in Cohort 4B. If there are no available slots in Cohort 4B at the time of enrollment, an exception may be made following approval from the medical monitor at 23andMe.

   Adolescents that meet the criteria for both Cohort 4B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 4B following approval from the medical monitor at 23andMe.

e. **Cohort 5B:** In jurisdictions where local regulations and IRB/EC allows, adolescents with histologically-diagnosed locally advanced (unresectable), or metastatic solid cancer that has progressed after all available standard therapies for the specific tumor type, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

f. **Cohort 6B**: Histologically-diagnosed locally advanced (unresectable) or metastatic ES-SCLC that has progressed following all available standard therapy, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

   Adolescents that meet the criteria for both Cohort 6B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 6B following approval from the medical monitor at 23andMe.

104. Have a performance status as defined below:

- Adults and adolescents ≥ 16 years of age: Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Adolescents ≥ 12 to < 16 years of age: Lansky Play Scale ≥ 50

105. Life expectancy ≥ 12 weeks

106. **Part A (Dose escalation):** Patients without RECIST measurable disease (e.g., evaluable disease only) will be eligible for enrollment in Part A, regardless of tumor type.

Part B (Dose expansion): Patients enrolled in Part B must have measurable disease by per RECIST 1.1 and have ≥ 1 site of measurable disease that has not been previously irradiated. Patients with ≥ 1 site of measurable disease per RECIST 1.1 who have previously irradiated lesions that have progressed after radiation therapy are eligible. Tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

107. **Part A (Dose escalation):** An archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening must be provided unless an exemption is granted by the medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

Patients enrolled in the PK/PD backfill cohort in Part A in whom collection of paired biopsies is judged to be safe and feasible by the investigator may consent to provide an optional fresh biopsy at screening and from the same lesion (if safe and feasible) approximately 4 to 6 weeks after the first dose of 23ME-00610.

Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

Part B (Expansion):

Cohorts 1B, 2B, 4B and 6B: Adult and adolescent patients ≥ 12 years of age must consent to provide an archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening unless an exemption is granted by the

medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe. On-treatment biopsies will not be collected in these cohorts.

Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

Cohort 3B: Adult patients ≥ 18 years of age must be able to have paired biopsies collected for the study and must agree to provide a fresh biopsy during screening, and from the same lesion (if safe and feasible) at approximately 4 to 6 weeks after the first dose of 23ME-00610. Eligible patients will have lesions which are judged to be safe and feasible by the investigator for biopsies. Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe. A recently collected biopsy with evaluable tumor tissue may be submitted in place of the Screening biopsy with approval from the medical monitor at 23andMe. Mandatory paired biopsies will not be collected from adolescent patients.

In addition, adult and adolescent patients ≥ 12 years of age must consent to provide an archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening unless an exemption is granted by the Medical Monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening for adolescent patients ≥ 12 years of age if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

Cohorts 5B: An archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening must be provided unless an exemption is granted by the medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening for adolescent patients ≥ 12 years of age if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Pregnancy/Breastfeeding/Contraception

201. Females who are pregnant (positive pregnancy test within 7 days prior to study drug administration) or breastfeeding. Females of childbearing potential who engage in heterosexual intercourse and males who are sexually active with female partners of childbearing potential must agree to use a highly effective form of contraception (e.g., females: male partner sterilization, estrogen/progestogen or progestogen-only hormonal contraceptives associated with inhibition of ovulation [oral, intravaginal, transdermal],

intrauterine devices [IUDs], intrauterine hormone-releasing systems; males: male condoms, vasectomy) throughout the study, starting with the time of consent and for at least 90 days after the last dose of study drug. Females of childbearing potential are those who have begun menstruating. In order to be considered NOT of childbearing potential, female patients must have had a hysterectomy or bilateral oophorectomy or be 1 year post-menopause or have had amenorrhea for a period of 12 months or longer in the absence of chemotherapy, anti-estrogens, or ovarian suppression. Male patients must not donate sperm throughout the study period.

Immune-Related Medical History

202. Active autoimmune disease that has required systemic disease-modifying or immunosuppressive treatment within the last 2 years. Stable, medically managed autoimmune endocrinopathies are acceptable if the patient otherwise meets entry criteria. Therefore, patients with thyroid and adrenal disorders that are stable on replacement therapy are permitted.

203. Receipt of systemic immunosuppressive therapy (e.g., steroids) within 4 weeks prior to the start of study drug administration. Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the patient is on a stable dose for at least 3 months. (Note: Corticosteroid premedication for contrast allergy is permitted.)

204. History of idiopathic pulmonary fibrosis, interstitial lung disease, organizing pneumonia, non-infectious pneumonia that required steroids, or evidence of active, non-infectious pneumonitis. (Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by medical monitor at 23andMe)

205. History of Grade ≥ 3 immune-mediated toxicity considered related to prior immunotherapy and that led to treatment discontinuation.

206. Prior allogeneic bone marrow transplant, or other solid organ transplant.

207. Receipt of any live vaccine within 30 days prior to the start of study drug administration.

208. Receipt of inactive or mRNA-based vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 5 days prior to the start of study drug administration or during the 21-day DLT period in Part A. For patients enrolled in Part B and following the 21-day DLT period for patients enrolled in Part A, receipt of inactive or mRNA-based vaccines for SARS-CoV-2 is permitted during the study if the vaccine is not administered within 5 days of study drug administration.

209. Patients with symptoms suggestive of active coronavirus disease 2019 (Covid-19) prior to study entry must have a negative molecular or antigen test for SARS-CoV-2 using an FDA-authorized test to be eligible for enrollment. Patients with a current positive molecular or antigen test for SARS-CoV-2 using an FDA-authorized test are not eligible for enrollment.

210. Any active uncontrolled systemic bacterial, viral or fungal infection requiring treatment, excluding exceptions noted below in exclusion criteria 211, 212 and 213.

211. History of a positive test for hepatitis C virus (HCV) infection, except for those who have completed curative therapy for HCV and have undetectable HCV RNA (< LLOQ [lower limit of quantitation]). HCV testing is required during screening for patients whose HCV status is unknown.

212. History of a positive test for hepatitis B virus (HBV) infection, except for those who are receiving treatment with HBV-active nucleos(t)ide antiviral therapy at the time of study entry and have undetectable HBV DNA (< 20 IU/mL). HBV testing is required during screening for patients whose HBV status is unknown.

213. History of a positive test for Human Immunodeficiency Virus (HIV) infection, except those who meet the following criteria: CD4+ T cells ≥ 350 cells/μL, no history of Acquired Immunodeficiency Syndrome (AIDS)-defining opportunistic infections, HIV RNA < 50 copies/mL, and on a stable antiretroviral regimen for at least 3 months. HIV testing is required during screening for patients whose HIV status is unknown.

214. Known hypersensitivity to 23ME-00610 or any of its excipients. See Table 2 for the list of excipients.

Prior Anticancer Therapy

215. Prior anticancer therapy, including chemotherapy, targeted therapy, biological therapy or immune-checkpoint inhibitors within 4 weeks or 5 drug half-lives (whichever is shorter) prior to the start of study drug administration.

216. Prior therapy directly targeting CD200 or CD200R1.

217. Adverse events from prior therapy that have not either returned to baseline or stabilized at Grade ≤ 1 (except alopecia, hearing loss, vitiligo, endocrinopathy managed with replacement therapy, and ≤ Grade 2 neuropathy) prior to study drug administration.

218. Patients who haven't recovered from Grade 2 or higher clinically significant radiation therapy-related toxicities before study drug administration. (Note for patients enrolled in Cohort 3B: At least 1 non-irradiated lesion must be available for collection of paired biopsy samples. In addition, patients must have ≥ 1 site of measurable disease for assessment via RECIST 1.1. Patients with ≥ 1 site of measurable disease per RECIST 1.1 who have previously irradiated lesions that have progressed after radiation therapy are eligible).

219. Patients who haven't recovered from Grade 2 or higher clinically significant major surgery-related adverse events and/or complications before study drug administration.

220. Use of investigational drugs within 4 weeks or 5 drug half-lives (whichever is shorter) before the start of study drug administration.

Other Medical History

221. History of another malignancy in the previous 2 years, unless cured by surgery alone and continuously disease free. Exceptions include appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage 1 uterine cancer, localized prostate cancer that has been treated surgically with curative intent and presumed cured, or other malignancies with an expected curative outcome. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with

the safety or efficacy assessment of the study drug may be included if approved by the medical monitor at 23andMe.

222. Uncontrolled or symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Patients with previously treated brain metastases may participate provided they are asymptomatic (any neurologic symptoms have returned to baseline), radiographically stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment), have no evidence of new or enlarging brain metastases, and are clinically stable off steroids with a stable dose of anticonvulsants (if required) for at least 4 weeks prior to study treatment. Patients with carcinomatous meningitis or leptomeningeal spread are excluded regardless of clinical stability. (Note: Imaging of the brain during screening is required in patients with a history of brain metastases, or signs/symptoms that are suggestive of brain metastases. A brain MRI is required at screening for patients with SCLC irrespective of whether the brain is a site of known disease).

223. History of any of the following cardiovascular diseases:

    a. Recent history (within the past 6 months) of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third-degree atrioventricular node block.

    b. Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.

    c. Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system.

    d. Recent history (within the past 6 months) of symptomatic pericarditis.

224. QTcF > 470 msec. QTcF is QT corrected for heart rate according to Fridericia's correction formula ($QTc = QT/RR^{0.3}$) and can be machine calculated or manually over-read.

225. Screening laboratory values that do not meet the criteria outlined in Table 1. Patients with lymphocyte counts below the threshold defined in Table 1 may be included with discussion and approval by the medical monitor at 23andMe.

Table 1 Laboratory Criteria that Represent Adequate Organ Function

Parameter[a]	Laboratory Values
Hematologic[b]	
Absolute neutrophil count	$\geq 1.5 \times 10^9$/L
Lymphocyte count	≥ 0.6/mm^3
Hemoglobin	≥ 8 g/dL
Platelets	$\geq 100 \times 10^9$/L
Renal	
eGFR	
Adults[c]	≥ 30 mL/min
Adolescents[d]	≥ 30 mL/min/1.73m^2
Hepatic	
Total bilirubin	
Adults	≤ 1.5 × ULN (except patients with Gilbert's syndrome who must have total bilirubin ≤ 3.0 mg/dL)
Adolescents	< 1.5 × ULN for age
AST and ALT	Both ≤ 2.5 × ULN (except patients with liver metastases / tumor infiltration where the limits are ≤ 5 × ULN)
Endocrine	
TSH[e]	Within institutional normal limits
Morning cortisol[f]	Within institutional normal limits
Cardiac	
Ejection fraction[g]	≥ 50% by echocardiogram or within institutional normal limits

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; G-CSF = granulocyte-colony stimulating factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] Screening laboratory values apply to both adults and adolescents unless otherwise stated.

[b] Hematologic criteria must be met without transfusion of blood products (including platelets or red blood cells) or administration of G-CSF for at least 14 days prior to sample collection.

[c] eGFR to be calculated using Cockgroft-Gault equation for adults (see Appendix 5)

[d] eGFR to be calculated per modified Schwartz equation for adolescents (see Appendix 5)

[e] If TSH is not within normal limits at baseline, the patient may still be eligible if: total T3 or free T3 and free T4 are within normal limits, or if the patient is asymptomatic with discussion and approval from the medical monitor at 23andMe or designee.

[f] Cortisol levels are not required for patients with primary adrenal tumors (e.g., adrenocortical carcinoma) or adrenal disorders that are stable on replacement therapy. If cortisol is not WNL at baseline. the patient may still be eligible if asymptomatic and no clinical suspicion of adrenal disorders with discussion and approval from the medical monitor at 23andMe or designee.

[g] MUGA scan is acceptable if echocardiography is not standard practice at the clinical site.

Consent and Protocol Compliance

226. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is a member of the study site or Sponsor staff directly involved with this study, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific patient.

227. Patients with any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.

228. Any condition that in the opinion of the investigator would interfere with evaluation of the investigational product or interpretation of the patient's safety or study results

Investigational Product and Dosage:

Table 2 23ME-00610 Dosage and Administration

Intervention Name	23ME-00610
Type	Biologic
Dose Formulation	Each 1 mL of solution contains 50 mg of drug and is formulated in 20 mM L-Histidine, 8% w/v sucrose, and 0.04% w/v polysorbate 80, pH 6.0.
Unit Dose Strength(s)	200 mg/4 mL vial (50 mg/mL)
Dosage Level(s)	Up to 1400 mg Q3W
Route of Administration	Intravenous infusion
Sourcing	Provided centrally by the study Sponsor (23andMe, Inc.)
Packaging and Labeling	The study intervention is supplied in a 10 mL single-use USP Type I glass Schott vial which is closed with a RayDyLyo®cap. Each vial is filled to deliver 200 mg/4 mL (with an overfill of 0.48 mL) and stored frozen at -20°C. Each vial will be labeled as required per country requirement.

General Study Conduct:

Following informed consent, all patients will undergo screening procedures within 28 days prior to the start of study drug treatment to determine eligibility. All patients are required to have locally advanced (unresectable) or metastatic solid cancer. Additional screening procedures include medical, surgical, and medication history; complete physical examination; vital signs; age-appropriate performance status; 12-lead ECG; evaluation of the left ventricular ejection fraction by transthoracic ECHO or MUGA; clinical laboratory assessments (thyroid function tests, morning cortisol, hematology, chemistry, coagulation, urinalysis, and pregnancy test [see Appendix 1]); staging CT scan; and blood and saliva samples (Part A only) for pharmacokinetic, exploratory pharmacodynamic and genotypic assessments.

Safety Assessments

All patients will undergo safety assessments during the treatment period to include non-directive questioning regarding adverse events, physical examination, vital signs, 12-lead ECGs, and clinical laboratory assessments (thyroid function tests, morning cortisol, hematology, chemistry, coagulation, urinalysis, and pregnancy testing; Table 3 and Table 4).

Clinical Activity Assessments

All patients will have the extent of their disease assessed by a staging CT scan, according to RECIST version 1.1 at screening, and every 8 weeks thereafter while on study drug treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Response to treatment in all patients will be determined by the investigators based on RECIST version 1.1. and iRECIST (Appendix 4) will be used by the investigator to assess tumor response in patients that can continue study drug treatment beyond initial progressive disease as defined by RECIST version 1.1. (Table 3 and Table 4).

Pharmacokinetics

Serial pharmacokinetic (PK) blood samples for evaluation of 23ME-00610 concentration will be collected at the Cycle 1, Day 1 and Cycle 4, Day 1 visits for each patient in Part A and Part B as described in Table 5.

Single PK blood samples will also be collected from all patients as described in Table 5**.**

The following PK parameters of 23ME-00610 will be estimated, as appropriate, for patients with serial PK samples: AUC_{inf} (first dose), AUC_{tau} (multiple-dose), AUC_{last}, accumulation index, C_{max}, C_{last}, C_{tau}, CL, Lambda z, T_{max}, $T_{1/2}$ and V_z.

PK data from patients with serial and sparse PK sampling may be combined with data from other studies for exposure-response or population PK analyses.

Immunogenicity

Blood samples for evaluation of ADAs to 23ME-00610 will be collected for each patient in Part A and Part B as described in Table 5.

Pharmacodynamics

Blood samples for evaluation of PD biomarkers will be collected for each patient in Part A and Part B as described in Table 5. Tumor samples will be collected to determine target pathway expression at baseline (Part A and Part B) and changes (Part B) in the immune environment elicited by 23ME-00610, using immunohistochemistry and/or RNA quantification approaches for each patient.

Genotypic assessment

Saliva will be collected to genotype nucleated cells found within the saliva using 23andMe's validated genotyping platform, where permitted by local regulations as shown in Table 3 and Table 4. Genotypic information will be correlated with adverse event information and clinical outcomes using polygenic risk scores to evaluate the potential predictive value of these scores.

End of Treatment and Follow-up:

Patients may continue treatment with 23ME-00610 until disease progression (as defined by iRECIST by the investigator to assess tumor response in patients that can continue study drug treatment beyond initial progressive disease as defined by RECIST version 1.1.), development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, lost to

follow-up, or Sponsor ending the study, whichever occurs first. Patients who experience disease progression per RECIST 1.1 criteria who are, in the opinion of the investigator, benefiting from treatment may be allowed to continue on study drug as described in Section 7.2.

All safety evaluable patients are to undergo an end of treatment assessment (within approximately 5 days of study drug discontinuation). In addition, follow-up safety assessments are to be scheduled 28 and 90 days after the last dose.

All safety evaluable patients will enter survival follow-up and will be contacted every 3 months during this period for assessment of survival status and new antineoplastic therapies since discontinuation of study drug until death, withdrawal of consent, lost to follow-up, or end of study. Patients will be asked to consent for contact of a third-party caregiver, relative, or medical professional in order to provide information on survival status if the patient is unable to be contacted.

Statistical Methods

Statistical analyses will be descriptive in nature. Tabulations will be produced for appropriate disposition, demographic, baseline disease characteristics, safety, PK, PD, and clinical activity parameters. Tabular summaries produced for Part A will be grouped by dose level and overall. Tabular summaries produced for Part B will be grouped by tumor type (i.e. cohort and dose level, as appropriate). Safety summaries will combine across Part A and Part B by dose level with the exception of adolescent patients which will be presented separately. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). All study results will be presented in by-patient data listings.

A separate statistical analysis plan will include details on the planned analyses.

Analysis Populations:

The Safety Population will consist of all patients who receive any amount of study drug. Patients treated during the dose-escalation phase will be grouped with those receiving the same dose and regimen during the dose expansion phase.

DLT evaluable population includes all patients who are enrolled in the Dose-Escalation Phase or adolescent cohort in Dose Expansion Phase and complete the study follow-up through the DLT evaluation period or experience a DLT. The DLT evaluable population will be used for the MTD/RP2D evaluation.

The Efficacy Evaluable Population consists of patients in the Safety Population with baseline (i.e., pre-dose) tumor measurements and at least one post-baseline tumor response assessment or clinical assessment if determined to be disease progression or death prior to the first post baseline tumor assessment.

The PK population consists of all patients who receive any amount of study drug and have at least one measurable postdose serum 23ME-00610 concentration. The PK population will be used for PK endpoint analyses.

The PD population consists of all patients who receive any amount of study drug and have sufficient data to derive at least one pharmacodynamic parameter for inclusion in the respective analyses. The Pharmacodynamic population will be used for Pharmacodynamic endpoint analyses.

The Immunogenicity population consists of all patients who receive any amount of study drug and have a non-missing baseline ADA result and at least one non-missing post-dose ADA result. The Immunogenicity population will be used for Immunogenicity endpoint analyses.

Additional analysis populations may be defined in a separate statistical analysis plan.

Safety:

Safety tabulations will include summaries of AEs overall, by relation to study drug, and by severity. Descriptive statistics of actual values and changes from baseline will be provided for clinical laboratory parameters, ECG interval results (including QTcF), and vital signs. Changes to last on-study value may also be reported. Shift tables from baseline to worst and to last observation on study will be presented for laboratory parameters.

Pharmacokinetics:

Concentrations of 23ME-00610 over time will be listed for each patient and summarized using descriptive statistics separately for Part A and Part B at each time point by cohort, dose level and cycle.

PK parameters (e.g., AUC_{tau}, C_{max} and C_{tau}) of 23ME-00610 will be listed for each patient and summarized using descriptive statistics separately for Part A and Part B by cohort, dose level and cycle.

Summary statistics will be tabulated by cohort, dose level and cycle for Part A and Part B separately. PK concentrations from sparse samples will be listed. Dose proportionality will be assessed by comparing PK parameters (e.g., AUC and C_{max}) across the dose cohorts in Part A using a power model to evaluate the population mean slope based on its 90% confidence interval (CI).

PK concentration data from this study may be used in combination with other studies for exposure-response or population PK analyses. The potential relationship between 23ME-00610 and clinical activity, safety endpoints, and/or PD biomarkers may be explored using descriptive and/or graphical methods.

Pharmacodynamics:

Pharmacodynamic measures (target engagement, target cell modulation, soluble biomarkers, and/or cytokines, as appropriate) will be listed for individual patients and summarized using descriptive statistics for 23ME-00610 by cohort and/or dose level over time.

PD biomarker data from this study may be used in combination with other studies to explore the relationship between biomarkers and clinical activity and safety endpoints.

Immunogenicity:

The frequency and percentage of patients with positive and negative immune response results may be summarized for each assessment time and overall for each patient separately for Part A and Part B by cohort and dose level. A summary of frequency and percentage of patients with positive results may be determined for all patients that received 23ME-00610. Additional analyses, including the relationship between immunogenicity and safety may be conducted, as appropriate.

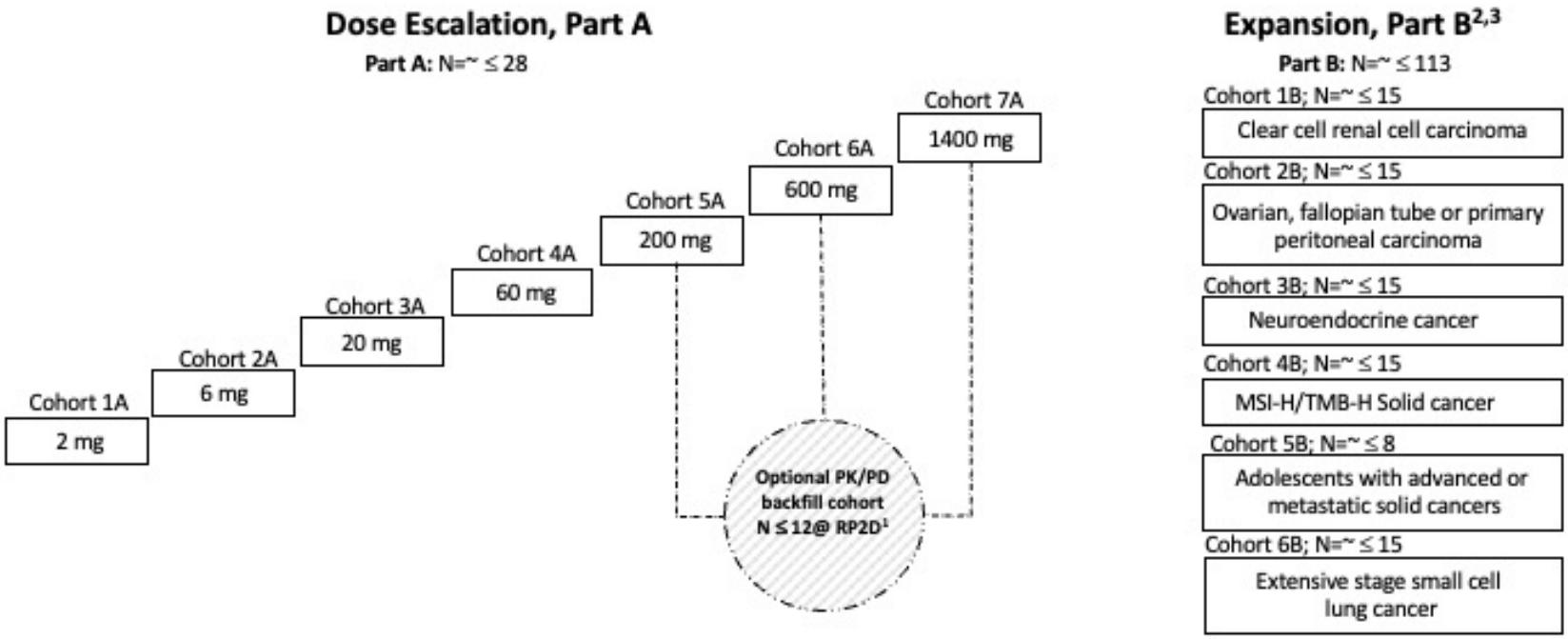
Clinical Activity:

Clinical Activity will be assessed by the site investigators using RECIST version 1.1. Antitumor response will be summarized by best overall response categories, ORR (best response confirmed CR + confirmed PR) and DCR (best response confirmed CR + confirmed PR + SD). Response rates will be accompanied by 90% confidence intervals. Durability of response (i.e., time-to-event endpoints) will also be reported.

The study data will be analyzed and reported based on all patients' data up to the time when all eligible patients have completed at least 6 months of treatment or discontinued study drug earlier. Any additional data for patients continuing to receive study treatment or in follow-up for survival past the data cutoff date for the primary clinical study report (CSR) will be reported at the end of the study.

1.2 Schema

Figure 1 Study Schematic



1. To further evaluate PK and PD in Part A, additional patients may be enrolled in a PK/PD backfill cohort following SRC approval at the RP2D/MTD, or a previously evaluated dose level where there is pharmacologic or pharmacodynamic evidence of therapeutic effect
2. Dose levels for expansion cohorts will be defined based on emerging safety, PK and PD data. Multiple dose levels may be evaluated if supported by emerging data
3. Adolescents may be enrolled in Cohorts 1B-6B following SRC approval

1.3 Schedule of Activities (SoA)

Table 3 Schedule of Activities for the Dose-Escalation Phase (Part A)

Visit/Cycle: (Study Day)	Screening (D -28 to -1)	Cycle 1 (D1)	Cycle 1 (D2)	Cycle 1 (D3)	Cycle 1 (D8)	Cycle 1 (D15)	Cycle 2 (D1)	Cycle 2 (D8)	Cycle 2 (D15)	Cycle ≥ 3 (D1)	End/Restart [17] of Treatment (within 5d)	Follow -up (D +28)[18]	Follow -up (D +90)[19]	Survival Follow-up (every 3 months)[20]
Informed Consent	X													
Eligibility Criteria	X													
Demographics[1]	X													
Medical and Surgical History[2]	X													
Medication History	X													
Physical Exam[3,21]	X	X					X			X	X			
Height	X													
Weight	X	X					X			X	X			
ECOG Performance Status[21]	X	X					X			X	X			
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X			
Single 12-Lead ECG	X													
Triplicate 12-Lead ECGs[5]		X					X							
Echocardiogram[6]	X													
Local Laboratory Evaluations[7]														
Thyroid function test[8]	X						Q6W				X			
Morning Cortisol[9]	X						1st 6 months: Q6W;> 6 months to ≤ 1 Year: Q12W;> 1 Year: Q24W							
Hematology and Serum Chemistry	X	X			X	X	X	X	X	X	X			
Coagulation	X	X					X			X	X			
Urinalysis	X	X					X			X	X			
Pregnancy Test[10]	X	X					X			X	X	X	X	
HIV/HBV/HCV Screening[11]	X													
PK/PD Blood Samples	See Table 5													
Optional tumor biopsy[12]	X									X				
Archival tumor specimen[13]	X													
Genotyping specimen[14]	X													
CT/MRI (lower neck, chest, abdomen, pelvis)[15]	X						Q8W				X			
Study Drug Administration[16]		X					X			X				
AEs	X	X					X			X	X	X	X	
Concomitant Medications and Procedures	X	X					X			X	X	X	X	
Survival Status												X	X	X
New Antineoplastic Therapy												X	X	X

Abbreviations: D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PD = pharmacodynamic; PK = pharmacokinetic.

Notes: All cycles are 21 days in duration, there are no rest periods between cycles.

Whenever possible, the study visit should occur on the scheduled visit day; a ± 2-day window is allowed to accommodate patients' and investigators' schedules, except for the following visits: C1D2, C1D3, C4D2 and C4D3.

Study assessments may be repeated at later or unscheduled patient visits if unanticipated issues or errors occur during collection or processing, eg. issues during sample processing resulting in sample failure. Sites should contact the 23andMe Medical Monitor prior to repeating assessments.

The timing and number of assessments, including safety, PK, and PD biomarker assessments may be altered over the course of the study based on emerging data to ensure appropriate patient monitoring.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK/PD data from this study must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and Ethics Committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and the EC before implementation.

Footnote	Notes
1	Demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during screening.
2	A complete medical and surgical history, and the date of confirmation of the pathologic diagnosis of the underlying malignancy, will be obtained during screening. The medical history is to include all relevant prior medical history as well as all current medical conditions. All medications administered and procedures conducted within 28 days prior to C1D1 should be reported in the eCRF. In addition, all prior treatment regimens for the underlying malignancy will be reported.
3	A full physical examination should be conducted at screening. A symptom-driven physical examination should be conducted at on-treatment visits prior to dosing. A full physical examination should be conducted if clinically indicated. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs as appropriate.
4	Vital signs include systolic and diastolic blood pressure, heart rate, and body temperature (skin). Assessments should be conducted while the patient is seated or supine with a completely automated device. Manual techniques will be used only if an automated device is not available. On dosing days, vital signs will be measured within 1 hour prior to dosing and 30 minutes, (+/- 2 minutes), 1 hour (+/- 10 minutes), 2 hours (+/- 10 minutes) and 4 hours (+/- 10 minutes) at the end of infusion (post-dose). After Cycle 4, on dosing days, vital signs will be measured within 1 hour prior to dosing and 30 minutes (+/- 2 minutes), 1 hour (+/- 10 minutes), 2 hours (+/- 10 minutes. Patient will be monitored post-infusion until considered clinically stable for discharge per investigator or designee assessment. Additional assessments should be performed if clinically indicated.
5	Triplicate ECG assessments should be conducted on C1D1 at pre-dose, and post-dose at the end of infusion and end-of-infusion + 4 hours, and on C2D1 at pre-dose and at the end of infusion. PK samples at matched timepoints should be collected immediately after ECG acquisition (see Table 3). Triplicate ECG assessments should be conducted using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Before each ECG assessment, the patient should be at rest for approximately 10 minutes. The patient should be in the semi-recumbent or supine position; the same position must be used for all subsequent ECG tests. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

6	Patients should receive a transthoracic ECHO to evaluate LVEF during screening. A multigated acquisition (MUGA) scan is acceptable if echocardiography is not standard practice at the investigational site. A consistent methodology should be used throughout the trial for each patient. The evaluation of the echocardiography should include an evaluation for left ventricular ejection fraction and both right- and left-sided valvular lesions.
7	Specimens for laboratory evaluations should be collected prior to dosing at on-treatment visits. If screening laboratory evaluations were performed ≤ 72 hours prior to the first dose of study drug (i.e., at Day -3, Day -2, or Day -1), these evaluations do not need to be repeated at Day 1. The results of C1D1 laboratory assessments are not required prior to the first dose of study drug provided the patient has met all the protocol-required eligibility criteria during screening. Local laboratory assessments collected at the D1 visit beginning with Cycle 1 may be collected ≤ 48 hours prior to the dose of study drug (i.e., at Day -2 or Day -1). If the screening laboratory evaluations were performed > 72 hours prior to the first dose of study drug, C1D1 labs can be collected ≤ 48 hours prior to the first dose of study drug.
8	TSH, T3 and free T4. For T3, free or total T3 is acceptable per local or institutional standard. After screening, samples should be collected beginning at Cycle 2 at a frequency of Q6W (+/- 2 weeks).
9	Samples for cortisol assessments should be collected in the morning. If morning sample collection for cortisol assessment is not feasible, afternoon sample collection may be permitted with 23andMe Medical Monitor or designee approval. For patients taking systemic or high-dose inhaled corticosteroids, the sample should be taken prior to the morning dose. After screening, samples should be collected beginning at Cycle 2 and according to the following frequency during the study: 1st 6 months: Q6W (+/- 2 weeks); > 6 months to ≤ 1 Year: Q12W (+/- 2 weeks); > 1 Year: Q24W(+/- 2 weeks)
10	For women of childbearing potential only. Must be performed within 7 days prior to the first dose of 23ME-00610.
11	Patients with known history of HIV, HCV, or HBV must have local laboratory results performed at screening to confirm eligibility. Please refer to Exclusion Criteria 211, 212, and 213 for details. Patients whose HIV/HCV/HBV status is unknown are required to have diagnostic testing performed at screening.
12	Patients enrolled in Part A may consent to provide an optional fresh biopsy at screening if an archival tumor sample is not available with approval from the Medical Monitor at 23andMe. Patients enrolled in the PK/PD backfill cohort in Part A may consent to provide an optional fresh biopsy at screening and approximately 4 to 6 weeks after the first dose of 23ME-00610 (from the same lesion, if safe and feasible). The post-treatment biopsy sample must be collected prior to the radiographic disease assessment (CT/MRI scan). Biopsies must be collected from a tumor lesion that has not previously been irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe. Refer to the Tissue Sample Collection manual for details.
13	An archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening must be provided unless an exemption is granted by the medical monitor at 23andMe. Refer to the lab manual for details.
14	In jurisdictions where local regulations and IRB/EC allows, a saliva sample for genotyping assessment is to be collected after a patient has met all eligibility requirements during screening, or on C1D1.

15	See Section 8.2 on the use of RECIST 1.1 and iRECIST guidelines to assess tumor response. All patients will have the extent of their disease assessed by a staging CT/MRI scan (contrast-enhanced is preferred but not required) of the lower neck (i.e., supraclavicular nodal region; chest MRI/CT scans which include the lower neck region meet this requirement and a separate scan of the neck is not required.), chest, abdomen, pelvis, at minimum, and any additional sites disease or symptoms are present, according to RECIST version 1.1 at screening. Subsequent scans are required (i.e., Q 8weeks and end/restart of treatment) for patients with measurable disease. A brain MRI (contrast-enhanced is preferred but not required) is required in patients with a history of brain metastases, or signs / symptoms that are suggestive of brain metastases and is required at screening for patient with SCLC irrespective of whether the brain is a site of known disease. A window of +/- 10 days is permitted for post-baseline assessments to allow for flexible scheduling. The same modality (e.g., where possible, the same scanner, scanning technique and the use of contrast) is to be used throughout the study for a given patient. All imaging assessments will be collected centrally. Target lesions being used to measure response should not be irradiated without discussion with the medical monitor at 23andMe. A radiographic assessment is required at the end/restart of treatment visit for all patients if the last radiographic assessment was more than 8 weeks prior to the end/restart of treatment visit and disease progression has not been documented. Patients whose disease responds (either complete response or partial response) should have a confirmatory disease assessment performed approximately 4 weeks after the date of assessment during which the response was demonstrated. Per iRECIST criteria, if imaging shows progressive disease, the imaging assessment should be performed a minimum of 4 weeks after the date of assessment during which disease progression was demonstrated in order to confirm progressive disease as described in Appendix 4.
16	IV infusion of 23ME-00610 to occur over approximately 30 minutes for all dose levels. See Section 6.1 for details.
17	The end of treatment visit should occur within 5 days of study drug discontinuation. Refer to Section 6.5.4. Patients who have a qualifying dose delay/interruption should have a “Restart of Treatment” visit conducted prior to reinitiating treatment.
18	If the end of treatment visit was performed ≤ 7 days of the Day 28 follow-up visit, the Day 28 follow-up visit does not need to be conducted. The Day 28 visit may be conducted by phone for patients who are not required to have pregnancy testing per protocol. Permissible time window for the Day 28 follow-up visit is +/- 2 weeks.
19	Day 90 visit may be conducted by phone for patients who are not required to have pregnancy testing per protocol. Permissible time window for the 90 day follow-up visit is +/- 2 weeks.
20	Survival status visits may be conducted in person, by phone, or via email. If patients are unable to be reached, patients’ third-party contacts (e.g., family member, caregiver, or general physician) may be contacted to confirm survival status. Permissible time window for the survival status visits is every three months (+/- 2 weeks).
21	These assessments may be completed up to 48 hours prior to study drug administration on dosing days

Table 4 Schedule of Activities for the Expansion Phase (Part B)

Visit/Cycle: (Study Day)	Screening (D -28 to -1)	Cycle 1 (D1)	Cycle 1 (D2)	Cycle 1 (D3)	Cycle 1 (D8)	Cycle 1 (D15)	Cycle 2 (D1)	Cycle 2 (D8)	Cycle 2 (D15)	Cycle ≥ 3 (D1)	End/Restart[21] of Treatment (within 5d)	Follow-up (D +28)[22]	Follow-up (D +90)[23]	Survival Follow-up (every 3 months)[24]
Informed Consent	X													
Eligibility Criteria	X													
Demographics[1]	X													
Medical and Surgical History[2]	X													
Medication History	X													
Physical Exam[3,25]	X	X					X			X	X			
Height[4]	X													
Weight[5]	X	X					X			X	X			
Age-appropriate Performance Status[6,25]	X	X					X			X	X			
Tanner Stage[7]	X						Q1 Year							
Disease Characteristics[8]	X													
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X			
Single 12-Lead ECG	X													
Echocardiogram	X													
Local Laboratory Evaluations[10]														
Thyroid function test[11]	X						Q6W				X			
Morning Cortisol[12]	X						1st 6 months: Q6W; > 6 months to ≤ 1 Year: Q12W; > 1 Year: Q24W							
Hematology and Serum Chemistry	X	X			X	X	X	X	X	X	X			
Coagulation	X	X					X			X	X			
Urinalysis	X	X					X			X	X			
Pregnancy Test[13]	X	X					X			X	X	X	X	
HIV/HBV/HCV Screening[14]	X													
PK/PD Blood Samples	See Table 5													
CT/MRI (lower neck, chest, abdomen, pelvis)[15]	X						Q8W				X			
Tumor biopsy[16]	X									Cohort 3B only				
Archival tumor specimen[17]	X													
Genotyping specimen[18]		X												
MSI-H and TMB-H status[19]	X													
Study Drug Administration[20]		X					X			X				
AEs	X	X					X			X	X	X	X	
Concomitant Medications and Procedures	X	X					X			X	X	X	X	
Survival Status												X	X	X
New Antineoplastic Therapy												X	X	X

Abbreviations: D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PD, pharmacodynamic; PK, pharmacokinetic.

Notes: All cycles are 21 days in duration, there are no rest periods between cycles.

Whenever possible, the study visit should occur on the scheduled visit day; a ± 2-day window is allowed to accommodate patients' and investigators' schedules, except for the following visits: C1D2, C1D3, C4D2 and C4D3.

Study assessments may be repeated at later or unscheduled patient visits if unanticipated issues or errors occur during collection or processing, eg. issues during sample processing resulting in sample failure. Sites should contact the 23andMe Medical Monitor prior to repeating assessments.

The timing and number of assessments, including safety, PK, and PD biomarker assessments may be altered over the course of the study based on emerging data to ensure appropriate patient monitoring.Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK/PD data from this study must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and Ethics Committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and the EC before implementation.

Footnote	Notes
1	Demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during screening.
2	A complete medical and surgical history, and the date of confirmation of the pathologic diagnosis of the underlying malignancy, will be obtained during screening. The medical history is to include all relevant prior medical history as well as all current medical conditions. All medications administered and procedures conducted within 28 days prior to C1D1 should be reported in the eCRF. In addition, all prior treatment regimens for the underlying malignancy will be reported.
3	A full physical examination should be conducted at screening and will include, at a minimum, assessments of the head, eye, ear, nose and throat, cardiovascular, dermatological, respiratory, gastrointestinal, and neurologic systems, along with any additional systems previously found to be involved by the disease. Investigators should pay special attention to clinical signs related to previous serious illnesses. A symptom-driven physical examination should be conducted at on-treatment visits prior to dosing and will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). A full physical examination should be conducted if clinically indicated. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs as appropriate.
4	For adult patients ≥ 18 years of age, a height measurement collected only during screening is required. For adolescent patients ≥ 12 to < 18 years of age: In addition to the height measurement collected during screening, a historical measurement (within 6 to 12 months prior to enrollment) should also be obtained. Height should also be collected at the same visit the annual Tanner stage is collected.
5	For adolescent patients ≥ 12 to < 18 years of age only: In addition to the weight measurement collected during screening and D1 of every cycle, weight should also be collected at the same visit the annual Tanner stage is collected.
6	Use of Performance scale is dependent upon age: Lansky Play scale for adolescent patients 12 to < 16 years of age and ECOG performance status for adult and adolescent patients ≥ 16 years of age. The same Performance scale used for a given patient at baseline will be used throughout the trial for each patient.

7	For adolescent patients ≥ 12 to < 18 years of age only: Tanner stage is required at screening and annually (+/- 1 month) until the patient reaches 18 years of age.
8	Genetic and molecular characterization of cancer. Any molecular characterization of the cancer should be recorded in the eCRF, if known. If FoundationOne testing has been previously performed, the results must be recorded. It is not necessary to perform this test if it was not previously performed. Tumor markers (e.g., CEA, CA-125, AFP) are to be recorded in the eCRF at screening if they are being measured as part of disease surveillance. If PD-L1 expression has previously been determined, results and type of assay utilized (e.g., Ventana SP263, Ventana SP142, Dako 28-8, or Dako 22C3) must be recorded. If PD-L1 expression was not previously determined, it is not necessary to perform this test. If TMB score has previously been determined, results and the type of assay utilized must be recorded in the eCRF. For patients in Cohort 4B, see additional criteria for TMB-testing in footnote 19 below. If MSI-H status has previously been determined, the result and type of assay utilized must be recorded. For patients in Cohort 4B, see additional criteria for MSI-testing in footnote 19 below. For patients in Cohort 2B (ovarian carcinoma), the mutational status of BRCA1/2 or HRD is to be recorded if known.
9	Vital signs include blood pressure, heart rate, and body temperature. Assessments should be conducted while the patient is seated or supine. For cycles 1-4, on dosing days vital signs will be measured within 1 hour prior to dosing and 30 minutes (+/- 2 minutes), 1 hour (+/- 10 minutes), 2 hours (+/- 10 minutes) and 4 hours (+/- 10 minutes) at the end of infusion (post-dose). After Cycle 4, on dosing days, vital signs will be measured within 1 hour prior to dosing and 30 minutes (+/- 2 minutes), 1 hour (+/- 10 minutes), 2 hours (+/- 10 minutes. Patient will be monitored post-infusion until considered clinically stable for discharge per investigator or designee assessment. Additional assessments should be performed if clinically indicated.
10	Specimens for laboratory evaluations should be collected prior to dosing at on-treatment visits. If screening laboratory evaluations were performed ≤ 72 hours prior to the first dose of study drug (i.e., at Day -3, Day -2, or Day -1), these evaluations do not need to be repeated at Day 1. The results of C1D1 laboratory assessments are not required prior to the first dose of study drug provided the patient has met all the protocol-required eligibility criteria during screening. Local laboratory assessments collected at the D1 visit beginning with Cycle 1 may be collected ≤ 48 hours prior to the dose of study drug (i.e., at Day -2 or Day -1). If the screening laboratory evaluations were performed > 72 hours prior to the first dose of study drug, C1D1 labs can be collected ≤ 48 hours prior to the first dose of study drug.
11	TSH, T3 and free T4. For T3, free or total T3 is acceptable per local or institutional standard. After screening, samples should be collected beginning on Cycle 2 at a frequency of Q6W (+/- 2 weeks).
12	Samples for cortisol assessments should be collected in the morning. If morning sample collection for cortisol assessment is not feasible, afternoon sample collection may be permitted with 23andMe Medical Monitor or designee approval. For patients taking systemic or high-dose inhaled corticosteroids, the sample should be taken prior to the morning dose. After screening, samples should be collected beginning on Cycle 2 and according to the following frequency during the study: 1st 6 months: Q6W (+/- 2 weeks); > 6 months to ≤ 1 Year: Q12W (+/- 2 weeks); > 1 Year: Q24W (+/- 2 weeks)
13	For women of childbearing potential only. Must be performed within 7 days prior to the first dose of 23ME-00610.

14	Patients with known history of HIV, HCV, or HBV must have local laboratory results performed at screening to confirm eligibility. Please refer to Exclusion Criteria 211, 212, and 213 for details. Patients whose HIV/HCV/HBV status is unknown are required to have diagnostic testing performed at screening.
15	See Section 8.2 on the use of RECIST 1.1 and iRECIST guidelines to assess tumor response. All patients will have the extent of their disease assessed by a staging CT/MRI scan (contrast-enhanced is preferred but not required) of the lower neck (i.e., supraclavicular nodal region; chest MRI/CT scans which include the lower neck region meet this requirement and a separate scan of the neck is not required.), chest, abdomen, pelvis, at minimum, and any additional sites disease or symptoms are present, according to RECIST version 1.1 at screening. Historical scans acquired within the 28-day screening window that meet the aforementioned criteria can be provided in lieu of a new baseline scan. Subsequent scans are required (i.e., Q 8weeks and end/restart of treatment) for patients with measurable disease. A brain MRI (contrast-enhanced is preferred but not required) is required in patients with a history of brain metastases, or signs / symptoms that are suggestive of brain metastases and is required at screening for patient with SCLC irrespective of whether the brain is a site of known disease. A window of +/- 10 days is permitted for post-baseline assessments to allow for flexible scheduling. The same modality (e.g., where possible, the same scanner, scanning technique and the use of contrast) is to be used throughout the study for a given patient. All imaging assessments will be collected centrally. Target lesions being used to measure response should not be irradiated without discussion with the medical monitor at 23andMe. A radiographic assessment is required at the end/restart of treatment visit for all patients if the last radiographic assessment was more than 8 weeks prior to the end/restart of treatment visit and disease progression has not been documented. Patients whose disease responds (either complete response or partial response) should have a confirmatory disease assessment performed approximately 4 weeks after the date of assessment during which the response was demonstrated. Per iRECIST criteria, if imaging shows progressive disease, the imaging assessment should be performed a minimum of 4 weeks after the date of assessment during which disease progression was demonstrated in order to confirm progressive disease as described in Appendix 4.
16	Adult patients ≥ 18 years of age enrolled in **Cohort 3B only** must consent to provide a fresh biopsy during screening, and at approximately 4 to 6 weeks after the first dose of 23ME-00610 (from the same lesion). Eligible patients will have lesions which are judged to be safe and feasible by the investigator for biopsies. The post-treatment biopsy sample must be collected prior to the radiographic disease assessment (CT/MRI scan). Adult patients ≥ 18 years of age enrolled in Cohorts 1B, 2B, 4B and 6B; and adolescent patients ≥ 12 of age enrolled in Part B may consent to provide an optional fresh biopsy at screening if an archival tumor sample (see footnote 17) is not available with approval from the Medical Monitor at 23andMe. Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe. Refer to the Tissue Sample Collection manual for details.
17	Adult and adolescent patients ≥ 12 of age must provide an archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening unless an exemption is granted by the medical monitor at 23andMe. Refer to the Tissue Sample Collection manual for details.
18	In jurisdictions where local regulations and IRB/EC allows, a saliva sample for genotyping assessment is to be collected after a patient has met all eligibility requirements on C1D1.
19	For Cohort 4B (TMB-H and/or MSI-H solid cancers), patients must have a TMB-H solid cancer that was previously determined by the FoundationOne CDx assay (other industry/institutional equivalent platforms for TMB assessment are permitted) using a cutoff of ≥ 10 mutations/megabase and/or MSI-H solid cancer that was previously confirmed by one of the following validated diagnostic tests:

	immunohistochemistry of four MMR proteins (MLH1, MSH2, MSH6, PMS2) or by detection of microsatellite loci using a PCR assay or MMR gene mutation by a NGS panel (e.g., FoundationOne CDx, or industry/institutional equivalent that has been validated for diagnostic use). Assay type information and results report must be provided to the Sponsor.
20	IV infusion of 23ME-00610 to occur over approximately 30 minutes for all dose levels. See Section 6.1 for details.
21	The end of treatment visit should occur within 5 days of study drug discontinuation. Refer to Section 6.5.4. Patients who have a qualifying dose delay/interruption should have a "Restart of Treatment" visit conducted prior to reinitiating treatment.
22	If the end of treatment visit was performed ≤ 7 days of the Day 28 follow-up visit, the Day 28 follow-up visit does not need to be conducted. The Day 28 visit may be conducted by phone for patients who are not required to have pregnancy testing per protocol. Permissible time window for the Day 28 follow-up visit is +/- 2 weeks.
23	Day 90 visit may be conducted by phone for patients who are not required to have pregnancy testing per protocol. Permissible time window for the 90 day follow-up visit is +/- 2 weeks.
24	Survival status visits may be conducted in person, by phone, or via email. If patients are unable to be reached, patients' third-party contacts (e.g., family member, caregiver, or general physician) may be contacted to confirm survival status. Permissible time window for the survival status visits is every three months (+/- 2 weeks).
25	These assessments may be completed up to 48 hours prior to study drug administration on dosing days

Table 5 Schedule of Peripheral Blood Sampling for Pharmacokinetic, Pharmacodynamic, and Antidrug Antibody Studies in the Dose-Escalation and Dose Expansion Phases (Part A and B)

Visit/Cycle	Screening			Cycle 1			Cycle 2			Cycle 3			Cycle ≥ 4			End of Treatment		
Assessment	PK[2]	PD[3]	ADA[4]	PK[2]	PD[3]	ADA[4]	PK[2]	PD[3]	ADA[4]	PK[2]	PD[3]	ADA[4]	PK[2]	PD[3]	ADA[4]	PK[2]	PD[3]	ADA[4]
Anytime		X														X	X	X
Pre-dose (up to 1 h prior) (D1)				X	X	X	X	X	X	X	X	X	X	Cycle 4 & 6	Cycle 4 & 6			
Post-dose (from the end of infusion)[1] (D1)																		
0 min (D1)				X									Cycle 4					
1 h (D1)				X									Cycle 4					
4 h (D1)				X	X		X	X					Cycle 4					
24 h (D2)				X	X								Cycle 4					
48 h (D3)				X	X								Cycle 4					
D8				X	X		X	X					Cycle 4					
D15				X	X		X	X					Cycle 4					

Abbreviations: ADA, antidrug antibodies; D, day; PD, pharmacodynamic; PK, pharmacokinetic.

Note: All cycles are 21 days in duration, there are no rest periods between cycles.

All sampling times are relative to Day 1 for each cycle

Note: Whenever possible, the study visit should occur on the scheduled visit day; a ± 2-day window is allowed to accommodate patients' schedules except for the following visits: C1D2, C1D3, C4D2 and C4D3.

Footnote	Notes
1	The exact time of blood draw should be documented for all PK and PD samples. Permissible time windows for PK and PD samples are provided in parentheses: 0 min (+5min), 1 h (+/- 10 min), 4 h (+/- 10 min), 24 h (+/- 4 h), 48 h (+/- 4 h), D8 (+/- 24 h), D15 (+/- 24 h), trough (≤ 1 h pre-dose).
2	Details on PK sampling, volume, type of tube, refer to lab manual for details.
3	Details on PD sampling, volume, type of tube, refer to lab manual for details
4	Details on ADA sampling, volume, type of tube, refer to lab manual for details

2 INTRODUCTION

2.1 CD200R1 Biology

CD200R1 is an immune inhibitory receptor whose expression is restricted to immune cells, with expression observed predominantly on myeloid cell subtypes (including neutrophils, eosinophils, basophils, mast cells, microglia, macrophages, and dendritic cells) and subsets of both $CD4^+$ and $CD8^+$ T cells (Wright, 2003). $CD4^+$ T cells express higher levels of CD200R1 than $CD8^+$ T cells, and memory cells express higher levels of CD200R1 than naïve or effector cells. A small subset of B cells also express low levels of CD200R1, with highest expression reported on memory B cells and plasmablasts (Wright, 2003).

Both CD200R1 and its only known ligand, CD200, are type 1 transmembrane proteins with 2 extracellular IgG superfamily domains (Wright, 2000). However, their expression patterns differ. CD200R1 is exclusively expressed on immune cells, whereas CD200 is expressed by a wide variety of normal and cancer cells (Wright, 2000; Wright, 2001; Wright, 2003). CD200 is highly expressed by endothelial cells in blood vessels and this endothelial expression is further upregulated in various tumors (Kyi and Postow, 2016). Published research reports CD200 expression in many tumor types (Moreaux, 2008), including multiple myeloma (Moreaux, 2006; Conticello, 2013), renal cell carcinoma (Lenburg, 2003; Love, 2017), head and neck cancer (Ginos, 2004), hepatocellular carcinoma (Sun, 2016), testicular cancer (Korkola, 2006), mesothelioma (Gordon, 2005), colorectal cancer (Zou, 2002), chronic lymphocytic leukemia (Klein, 2001; McWhirter, 2006) and bladder cancer (Rexin, 2018). Single-cell RNA sequencing studies have found that CD200 and CD200R1 expression is significantly elevated in $CD8^+$/PD-1^{high} TILs isolated from hepatocellular carcinoma (Zheng, 2017) and non-small cell lung carcinoma (Thommen, 2018) tumors. Within the immune system, CD200 expression is reported on naïve and memory B cells, dendritic cells, and both $CD4^+$ and $CD8^+$ T cells that have been activated with IFNγ or TNFα (Wright, 2000; Wright, 2001; Wright, 2003; Chen, 2009).

CD200 and CD200R1 expression levels were evaluated in-house and their expression was observed to be elevated in TILs from clear-cell renal, breast, melanoma, endometrial adenocarcinoma, and ovarian cancer patients, including $CD4^+$ T cells and $CD8^+$ T cells, relative to matched PBMC pairs. In-house analysis of gene expression for both CD200R1 and CD200 revealed enriched expression in many tumor types relative to normal adjacent tissue (NAT), and high CD200 protein expression by immunohistochemistry was confirmed in all tumor types evaluated that showed high overall gene expression, including ovarian, carcinoid, small cell lung and clear cell renal cancer.

Multiple in vivo and in vitro studies in mammalian systems have shown that signaling through the CD200/CD200R1 pathway fosters immunosuppression by downregulating the production of proinflammatory cytokines by activated myeloid and/or T cells (Foster-Cuevas, 2004; Zhang, 2004; McWhirter, 2006; Kretz-Rommel, 2007; Snelgrove, 2008; Gorczynski, 2010; Mukhopadhyay, 2010; Akkaya, 2013; Salek-Ardakani, 2019). CD200/CD200R1 signaling has been shown to promote the activity of myeloid-derived suppressive cells and upregulate secretion of immunosuppressive proteins including TGFβ, arginase 1 (Hayakawa, 2016) and indoleamine-pyrrole 2,3-dioxygenase (Zhang, 2004). Moreover, activation of the CD200/CD200R1 signaling pathway in vivo tempers the immune response to a wide variety of

infectious agents (Snelgrove, 2008; Mihrshahi, 2009; Mukhopadhyay, 2010; Misstear, 2012; Salek-Ardakani, 2019). Several viruses, including human herpesvirus 8 (HHV8, which induces Kaposi sarcoma) (Foster-Cuevas, 2004; Shiratori, 2005; Misstear, 2012; Hatherley, 2013) have co-opted CD200 analogues to facilitate an immunosuppressive environment. Activation of the CD200R1 pathway has also been shown to ameliorate allergic diseases such as food allergies (Czarnowicki, 2017) and asthma (Lauzon-Joset, 2015). Taken together, these data demonstrate that activation of the CD200R1 pathway contributes to suppression of immune cell responses and suggests that inhibition of CD200R1 activity has the potential to restore exhausted immune cell function.

Indeed, published clinical data from samalizumab (ALXN6000), a monoclonal antibody that targets the CD200R1 pathway via blockade of CD200 demonstrated that modulation of the CD200/CD200R1 pathway results in anticancer activity in patients with CD200-expressing B-cell malignancies (Mahadevan, 2019). Administration of samalizumab to 26 patients with chronic lymphocytic leukemia (CLL; N = 23) or multiple myeloma (MM; N = 3) demonstrated that samalizumab was safe and well tolerated across the doses evaluated (50 to 600 mg/m^2 administered intravenously (IV) every 4 weeks); the maximum tolerated dose (MTD) was not reached, and no dose-limiting toxicities (DLTs) were observed.

In addition to enhancing immune cell function by targeting CD200R1, mRNA expression data from patients with a poor response to anti-PD1 therapy suggests that blockade of CD200R1 signaling also has the potential to address primary or secondary resistance to marketed cancer immunotherapies. Increased mRNA expression of several immune checkpoints, including CD200R1 was reported on CD4$^+$ and CD8$^+$ T cells from patients who had a suboptimal response to anti-PD1 treatment (Markowitz, 2018).

Collectively these data demonstrate that CD200R1 is a key immune suppressor checkpoint in T cells and myeloid cells, with both clinical and nonclinical data to support a pivotal role in certain human cancers. These data support the hypothesis that blocking the CD200R1/CD200 immune checkpoint in the tumor microenvironment has the potential to prevent or reverse immune cell tolerance.

2.2 Immunotherapy Background

Cancer is a leading cause of morbidity and mortality worldwide, with an estimated 19 million incident cases and 10 million deaths in 2020 (World Health Organization – GLOBOCAN). The development of immune checkpoint inhibitors that enhance the immune system's ability to identify and kill cancer cells has altered the treatment paradigm for a broad range of cancers (National Comprehensive Cancer Network). Inhibitors of the cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein-1 (PD1) checkpoints have demonstrated durable responses and clinically meaningful improvements in survival across numerous solid and hematological malignancies, predominantly via a T-cell targeting mechanism (Kyi and Postow, 2016; Chen, 2017). However, a significant proportion of patients are refractory to anti-PD1 and anti-CTLA4 therapies. Translational research has shown that the exploitation of additional immune checkpoints by the tumor is responsible, in part, for resistance to anti-PD1 therapies (Jenkins, 2018; Schoenfeld and Hellmann, 2020), and effective therapy may require targeting additional cell populations in addition to T cells in the tumor microenvironment. Therefore,

development of inhibitors against novel immune checkpoints on T cells and myeloid cells have the potential to address tumors that are refractory to existing therapies and/or to extend the duration of benefit from anti-PD1 therapies in responding patients.

2.2.1 Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for approximately 2% of global cancer diagnoses and deaths worldwide, with the highest incidence in North America and Western Europe. Clear cell RCC is the most prevalent and aggressive histological subtype, making up ~75% of RCC diagnoses. Although the 5-year relative survival is > 90% for patients diagnosed with stage I localized disease, and ~70% for patients with stage II/III regional disease, survival outcomes decrease dramatically to ~12% in patients with stage IV metastatic disease (Padala, 2020). Renal cell carcinoma has been shown to be susceptible to immunotherapies and antiangiogenic treatments, and agents that target the PD-1 and VEGF pathways are standard of care, first-line treatments for advanced disease (NCCN Guidelines, 2021). Despite these advances, the majority of patients will eventually experience disease relapse, underscoring the need to develop treatments with novel mechanisms of action.

2.2.2 Ovarian Cancer

Ovarian cancer is the fifth most common cause of death from cancer in women and is the leading cause of death from gynecological cancer (Bray, 2018). The majority of patients with ovarian cancer are diagnosed with advanced disease and ~70% relapse after receiving first-line platinum/taxane-based chemotherapy (Ledermann, 2013). Survival outcomes differ dramatically between patients with platinum-sensitive or resistant disease, with poorer outcomes (~9−12 months median survival) associated with platinum-resistant ovarian cancer compared to those with platinum-sensitive tumors (~2-3 years) (Friedlander, 2011; Davis, 2014).

Although targeted therapies such as bevacizumab and poly (ADP ribose) polymerase (PARP) inhibitors have improved treatment outcomes in ovarian cancer, particularly in those with high-grade serous carcinoma, the most common histological subtype, subsequent disease recurrences are increasingly platinum and treatment resistant, highlighting the need for additional treatment options for patients with recurrent, platinum-resistant disease. Early studies of anti-PD-(L)1 therapies in this population were promising, however they have failed to demonstrate clinically meaningful outcomes (Hamanishi, 2015; Disis, 2016; Varga, 2017; Matulonis, 2019). These data suggest that blockade of the PD-1 immune checkpoint is insufficient to overcome disease progression in recurrent ovarian cancer and additional therapeutic strategies are needed.

Recent data indicate that clear cell ovarian carcinoma, a distinct histological subtype of ovarian cancer with a prevalence of ~5-11% in North America and ~25% in Japan, shares similar morphological and molecular characteristics with clear cell RCC, suggesting clear cell ovarian carcinoma may be similarly susceptible to immune checkpoint blockade. Although platinum/taxane-based chemotherapy remains the standard-of-care clear for clear cell ovarian carcinoma, these patients have suboptimal responses compared to patients with the high-grade serous subtype (Crotzer, 2007; Takano, 2012; Ji, 2018). Emerging data from studies of anti-PD1 alone or in combination with anti-CTLA4 in clear cell ovarian cancer patients suggests that immune checkpoint blockade has the potential to provide clinical benefit in this subtype and

these tumors may be responsive to treatment with other therapies that target distinct immune checkpoints (Disis, 2019; Zamarin, 2020; Matulonis, 2019).

2.2.3 Neuroendocrine Cancers including Small Cell Lung Cancer

Neuroendocrine cancers represent a heterogenous group of malignancies which can arise from neuroendocrine cells throughout the body, with the gastrointestinal (GI) tract and lungs being the most common primary sites. Prognosis, treatment and management of neuroendocrine neoplasms differs based on whether they are categorized as low-grade indolent tumors, which typically progress slowly and have a low risk of distant metastasis, or high-grade aggressive carcinomas, which are associated with rapid progression and poor long-term survival outcomes (Oronsky, 2017).

Many patients present with inoperable disease and treatment of unresectable, symptomatic low-grade tumors includes somatostatin analogs to control hormone hypersecretion and tumor growth (Kvols, 1986; Rinke, 2009; Caplin, 2014). High-grade metastatic disease is generally treated with platinum/etoposide-based chemotherapy. Tumor-targeted peptide receptor radionuclide therapy (PRRT) and targeted therapies including sunitinib and everolimus have improved PFS for neuroendocrine cancer patients (Raymond, 2011; Yao, 2011; Strosberg, 2017), and anti-PD-L1 in combination with chemotherapy demonstrated a compelling OS benefit in small cell lung carcinoma (Horn, 2018; Paz-Ares, 2019). However, treatment options for patients with advanced disease who progress on standard therapies remain limited.

2.2.4 Microsatellite Instability-high Solid Cancers

Microsatellite instability-high (MSI-H) cancers are characterized by a high burden of somatic mutations and lymphocyte infiltrates, and as such are hypothesized to have a greater abundance of neo-antigens, some of which may increase T-cell reactivity. Thus, MSI-H tumors are hypothesized to be more immunogenic and responsive to immunotherapy compared to those that are not. MSI-H tumors have genetic defects in mismatch-repair pathways, which makes them more susceptible to accumulating somatic mutations, particularly in regions of repetitive DNA known as microsatellites (Le, 2015). The incidence of MSI-H cancers varies across solid tumors, and is highest in endometrial, gastric, and colorectal cancer (Lorenzi, 2020). Treatment of advanced MSI-H cancer with anti-PD-1 therapies in first-line colorectal cancer or relapsed, refractory settings across various tumor types has demonstrated compelling durable response rates of > 30% (Overman, 2017; Overman, 2018; Marcus, 2019; Andre, 2020). These data suggest that MSI-H cancers may be similarly responsive to therapies that target other immune checkpoints.

2.2.5 Tumor Mutational Burden-High Cancers

Tumor mutational burden (TMB) is a measure of the total nonsynonymous somatic mutations within tumor DNA. Similar to MSI-H tumors, TMB-high (TMB-H) tumors are hypothesized to have a greater abundance of neo-antigens, and therefore are predicted to be more immunogenic and sensitive to immunotherapy compared to tumors with a low TMB. Several studies of immune checkpoint inhibitors, including anti-CTLA-4 and anti-PD(L)-1 therapies, have shown a correlation between high TMB and improved clinical outcomes (Van Allen, 2015;

Yarchoan, 2017; Herbst, 2019; Marabelle, 2020; Hainsworth, 2021) and durable response rates ≥ 30% have been observed in patients with recurrent or metastatic advanced disease across a broad range of tumor types (Marabelle, 2020; Hainsworth, 2021). These data indicate that TMB is a robust predictive biomarker of immune checkpoint inhibitor response and that TMB-H tumors may respond to treatment with other immunotherapies.

2.2.6 Adolescent Solid Cancer

Cancer is the most common fatal disease in the pediatric population (Ward, 2014). The spectrum of solid cancers in pediatric patients differs significantly from adults and differs considerably between children and adolescents. The most common primary pediatric malignancies in adolescents include CNS cancers, soft tissue sarcomas, germ cell cancers, thyroid cancers, melanoma and bone cancers. Solid cancers represent approximately 60% of adolescent cancers (Allen-Rhoades, 2018). While survival for older adults and younger pediatric patients has improved over the last few decades, fewer gains have been made for metastatic solid cancers in adolescent patients (Chen, 2018). Studies of immune checkpoint inhibitors including anti-CTLA4 and anti-PD-1 in pediatric patients with solid cancers have generally demonstrated low response rates (less than 10%) (Merchant, 2016; Davis, 2020; Geoerger, 2020). Thus, the need for effective anticancer therapies for adolescent solid cancers remains high.

2.3 Nonclinical Overview of 23ME-00610

23ME-00610 is a fully humanized, monoclonal, effectorless immunoglobulin G subclass 1 (IgG1) antibody that binds specifically to the human CD200R1 immune inhibitory receptor. It is aglycosylated due to the presence of an engineered asparagine to glycine mutation (N297G), which eliminates binding to Fcγ receptors, thereby impairing Fc-mediated effector function (Leabman, 2013). Refer to the Investigator's Brochure for detailed background information on 23ME-00610.

2.4 Summary of Nonclinical Data

2.4.1 Nonclinical Pharmacology and Pharmacokinetics

Nonclinical pharmacology studies confirmed that 23ME-00610 binds human CD200R1 and potently blocks the interaction with its ligand, CD200. Furthermore, 23ME-00610 inhibited intracellular signaling events downstream of CD200/CD200R1 binding. In multiple, primary immune-cell assays that mimic the immunosuppressive tumor microenvironment, 23ME-00610 stimulated proinflammatory cytokine production and enhanced effector T-cell proliferation and function. Critically, treatment with 23ME-00610 potently enhanced peripheral blood mononuclear cell (PBMC)-mediated tumor cell killing in a mixed immune and tumor cell assay.

23ME-00610 binds to human CD200R1, but it does not cross-react with CD200R1 from nonhuman primate species. Therefore, to understand the pharmacokinetics (PK) of 23ME-00610 in the absence of potential target-mediated elimination mechanisms and to support dose selection of 23ME-00610 in humans, the PK of 23ME-00610 was studied in cynomolgus monkeys. After a single-dose IV administration to cynomolgus monkeys, the PK profile of 23ME-00610 was biphasic with linear elimination, and exposure was approximately dose proportional in the dose

range studied and similar in both males and females. Thus, the PK of 23ME-00610 was as expected for a typical therapeutic IgG1 in a non-binding species.

Refer to the Investigator's Brochure for detailed information on the nonclinical pharmacology of 23ME-00610.

2.4.2 Nonclinical Toxicology Studies

The potential for the 23ME-00610 therapeutic antibody to cause cytokine release in unstimulated immune cells was evaluated in vitro in whole blood or PBMC from 10 healthy human donors. 23ME-00610 did not cause increases in cytokine levels, indicating a low potential for cytokine-related toxicities.

Tolerability was assessed in cynomolgus monkeys in the context of the single-dose non-Good Laboratory Practice (GLP) PK study described above. 23ME-00610 was well-tolerated and no overt toxicity was observed that would indicate off-target binding of 23ME-00610 in the cynomolgus monkeys following a single IV dose up to 20 mg/kg.

The potential human tissue binding of 23ME-00610 was examined in a panel of normal human tissues to support a clinical study of a test article for which there is no clinically relevant species. 23ME-00610-Biotin positive membranous and cytoplasmic immunoreactivity was observed consistently in the tissue resident mononuclear cells in numerous tissues as expected and inconsistently in the squamous/transitional epithelium in a few tissues suggesting low likelihood for off-target binding of 23ME-00610 to healthy, non-target cells and tissues.

Because 23ME-00610 does not bind CD200R1 from common toxicology species, including cynomolgus monkey, a surrogate antibody that binds to cynomolgus monkey CD200R1 (23ME-00611) was developed to evaluate potential hazards associated with CD200R1 inhibition in toxicology studies. The 23ME-00611 (surrogate antibody) binding affinity, cell-surface binding EC_{50}, and cell-surface blocking half-maximal inhibition constant (IC_{50}) values for monkey CD200R1 were comparable to the values observed with 23ME-00610 (therapeutic antibody) for human CD200R1, suggesting that the surrogate antibody 23ME-00611 is a suitable antibody for hazard identification of risks resulting from CD200R1 blockade in cynomolgus monkeys.

In a 4-week GLP toxicity study with the surrogate antibody 23ME-00611, no adverse toxicity was identified following the administration of 4 once weekly doses at 0, 10, and 100 mg/kg of 23ME-00611. Monkeys were exposed to 23ME-00611 throughout the dosing period of the study as evidenced by the dose- and time-dependent 23ME-00611 receptor occupancy observed on neutrophils and T cells of treated monkeys. These findings confirmed the cynomolgus monkey was a relevant species for CD200R1 hazard identification. No hazards due to the antagonism of CD200R1 interaction were identified including no evidence of treatment-related effects noted on central nervous system (CNS) function, electrocardiograms (ECGs), or respiratory rate.

2.5 Study Rationale

23ME-00610 is a high-affinity anti-CD200R1 monoclonal antibody that functionally inhibits CD200R1 signaling and relieves immune cell suppression. 23ME-00610 has been extensively evaluated in nonclinical studies and has been shown to disrupt interactions between CD200 and CD200R1, resulting in enhanced immune cell-mediated killing of CD200-expressing tumor cells in vitro.

The high unmet need of patient with advanced solid cancers who have exhausted all standard therapy options and the favorable benefit-risk of 23ME-00610 based on preclinical data (see Section 2.6) supports a first-in-human Phase 1/2a evaluation of 23ME-00610. The PK and PD profile of 23ME-00610 may be influenced by disease-related characteristics such as tumor burden, and by other factors including age and target expression. Other immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 agents have demonstrated the potential for delayed immune-related AEs (Ramos-Casals, 2020). Thus, a first-in-human multiple-dose Phase 1/2a study in patients with advanced solid cancers is considered most appropriate to characterize the key objectives of this study, including safety and tolerability following multiple doses of 23ME-00610, and to determine the MTD and/or recommended phase 2 dose (RP2D) of 23ME-00610.

Study 23ME-00610-CLIN-001 consists of a multiple dose escalation phase in Part A and an expansion phase in Part B. The primary objectives of the dose escalation phase are 1) to assess the safety and tolerability of treatment with 23ME-00610 monotherapy in patients with advanced solid cancers, and 2) to determine MTD and/or the RP2D of 23ME-00610 monotherapy in patients with advanced solid cancers for further clinical investigation. The primary objective of the expansion phase of the study is to assess preliminary evidence of anticancer activity of 23ME-00610 in disease-specific cohorts that were selected based on the expression of CD200R1 and its exclusive ligand, CD200, T-cell markers, and/or other immune characteristics that suggest a higher likelihood of response to 23ME-00610.

This study will also evaluate the PK/PD profile of 23ME-00610. It is anticipated that this study will provide evidence of biologic activity at one or more dose levels by demonstration of an effect on immune cell function and/or clinical anticancer activity. The expansion phase (Part B) will allow further evaluation of the safety and tolerability profile, and PK of 23ME-00610, in addition to an assessment of anticancer activity in disease-specific cohorts of patients. Thus, evaluation of patients in the expansion phase will allow exploration of relationships between anticancer activity and pharmacodynamic biomarkers.

Adolescents will be included in the expansion phase of this study (Part B). Inclusion of pediatric patients, including adolescents, in clinical trials is often deferred until much later in development programs. This has resulted in a significant delay and lack of access for adolescent cancer patients to approved, effective anticancer therapies that are available to adults (Gaspar, 2018; Noel, 2021). To address this, strategies have been proposed to include adolescent cancer patients earlier in clinical development, including in Phase 1 first-in-human clinical trials. This is supported by analyses of anticancer agents, including immune checkpoint inhibitors, which have generally shown similar safety profiles and PK parameters in adult and adolescent cancer patients (Gaspar, 2018). Inclusion of adolescents with advanced solid cancers in Part B will

allow an assessment of the safety, PK, PD, and anticancer activity of 23ME-00610 and a determination of the RP2D for this population with a high unmet need.

Adolescent patients will not be included in the dose escalation phase (Part A) as initial PK and safety data in adults is needed to inform dose selection prior to enrollment of adolescents to minimize risk **(**see Section 2.6**)**. Adolescent patients with clear cell renal cell carcinoma, ovarian cancer, neuroendocrine, ES-SCLC, MSI-H and TMB-H cancers are often treated with adult standard therapies and while data on optimal treatment in this population are limited, cases reported in the literature suggest similar responses to therapy (Perlman, 2010, Keytruda IP, Say-Tin 2011, Tronnes, 2012). As such, adolescent patients with solid cancers will be enrolled into Cohort 5B first, and if Cohort 5B has completed enrolment and is no longer open, adolescent patients that meet the criteria for Cohorts 1B-4B and 6B may be enrolled into these cohorts with 23andMe medical monitor approval to assess the safety, tolerability, PK, PD and anticancer activity of 23ME-00610. As noted in Section 4.2.1.1. and 4.4.6., data from all adolescents enrolled in the study will be used to confirm the adolescent RP2D.

The safety, tolerability, PK, PD, and anticancer activity observed in this study will form the basis for further clinical development of 23ME-00610.

2.6 Benefit/Risk Assessment

23ME-00610 has been administered to humans for the first time in this study. While no molecule that directly inhibits CD200R1 has been evaluated in humans previously, samalizumab, an anti-CD200 monoclonal antibody, has been studied in patients with advanced B cell malignancies and solid cancers. Published data from the Phase 1 study in 26 patients with CLL and MM demonstrated that inhibiting the CD200R1 pathway by targeting CD200 with samalizumab is safe and tolerable; the MTD was not reached, and no DLTs were observed. Most AEs were mild to moderate in severity and the most common Grade 3 or 4 treatment-related AEs were blood lymphatic system disorders (i.e., anemia, neutropenia, and thrombocytopenia reported in 3 of 26 patients) (Mahadevan, 2019).

23ME-00610 has demonstrated the ability to restore immune cell function and enhance human immune cell-mediated killing in several in vitro studies. However, it is unknown whether these observations will translate into anticancer activity in human patients, or improve how patients with advanced solid cancers feel, function, or survive. Therefore, the probability of benefit from 23ME-00610 prior to starting this first-in-human study should be considered low.

The multiple-dose GLP hazard identification study with a surrogate antibody in cynomolgus monkeys did not identify any toxicity associated with CD200R1 inhibition up to the highest dose tested. Additionally, treatment of unstimulated immune cells in whole blood or PBMCs from 10 healthy human donors with 23ME-00610 in vitro did not cause increases in cytokines, indicating a low potential for cytokine-related toxicities. Nevertheless, species differences in safety and disease-specific safety considerations in human patients with advanced solid cancers pose a risk of unanticipated toxicity with 23ME-00610.

For these reasons, this study restricts eligibility to adult and adolescent patients with advanced solid cancers that are relapsed and/or refractory to standard therapies or are ineligible for

standard of care treatments and thus, need alternate therapy options with novel modes of action. Therefore, despite the unknown risk associated with 23ME-00610 treatment in this first-in-human study, the risk-benefit is considered positive for this study with the safety monitoring plan outlined below.

The risks associated with 23ME-00610 will be mitigated through a safety plan that includes exclusion of patients at unacceptable risk, sentinel patients for each new dose level, stringent DLT criteria, rigorous safety monitoring and clear dose modification and treatment guidelines for immune-related adverse events (irAEs) (Section 6.5.1) and cytokine release-related AEs (Section 6.5.2), the key potential risks of immune activation. The 2 mg starting dose of 23ME-00610 was selected based on a minimal anticipated biologic effect level (MABEL) approach using the totality of available data to minimize the risk of prolonged and meaningful immune cell activation in the initial dose cohort (Section 4.4.2). To reduce the risk of exposing large numbers of patients to subtherapeutic doses, an accelerated titration design will be utilized for the first 2 dose cohorts in Part A. The study will convert to a 3+3 design at doses ≥ 20 mg if no ≥ Grade 2 toxicity that is not clearly related to the underlying disease or pre-existing conditions is observed during the 21-day DLT period.

No meaningful difference in the mechanism of action, PK, or safety profile of 23ME-00610 is expected between adult and adolescent patients weighing ≥ 40 kg based on available preclinical data. To minimize risk to adolescent patients enrolled in Part B, adolescents will be treated at RP2D dose defined based on adult data, and the PK, safety, and available PD data from the first 3 adolescents receiving the RP2D will be reviewed to determine if additional adolescent patients should be enrolled and treated at this dose level.

A SRC committee provides oversight for the study.

More detailed information about the known and expected benefits and risks of 23ME-00610 may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objectives and Endpoints for Part A

Objectives	Endpoints
Primary	
• To determine the safety and tolerability, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of 23ME-00610, in patients with locally advanced (unresectable) or metastatic solid cancers	• Incidence and severity of dose-limiting toxicities (DLTs) • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) • Withdrawals due to AEs
Secondary	
• To evaluate the immunogenicity of 23ME-00610	• Prevalence and incidence of antidrug antibodies (ADA) to 23ME-00610
• To characterize the pharmacokinetic (PK) profile of multiple doses of 23ME-00610	• Serum PK parameters of 23ME-00610, as applicable, including: AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$
• To evaluate preliminary clinical (antitumor) activity of 23ME-00610 in evaluable patients by RECIST 1.1 criteria	• Objective response rate (ORR), duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS) based on investigator assessment against RECIST 1.1 criteria • Overall survival (OS)
Exploratory	
• To further evaluate preliminary clinical activity of 23ME-00610 in evaluable patients by iRECIST criteria	• ORR, DoR, DCR and PFS based on investigator assessment against iRECIST criteria (Lancet Oncol 2017;18: e143-52)
• To characterize the pharmacodynamic (PD) effects of 23ME-00610 by the assessment of changes in PD biomarkers in the blood and/or the tumor	• PD assessment of blood biomarkers may include, but not be limited to, target engagement, soluble factor analysis or immune cell enumeration.
• To evaluate the exposure-response relationships of 23ME-00610 and safety and PD biomarkers	• Relationships between PK parameters and safety, and/or PD biomarkers may be explored, and may include: • PK parameters of 23ME-00610, as applicable (i.e., AUC, C_{tau})

Objectives	Endpoints
	• Tumor and circulating blood PD parameters • Safety (e.g., laboratory parameters, AEs) • Polygenic risk scores (derived from saliva or blood genotyping) for immune-mediated adverse events
• To characterize the impact of 23ME-00610 on the QT-interval	• QTcF-interval changes from baseline on triplicate ECGs

Objectives and Endpoints for Part B

Objectives	Endpoints
Primary	
• To evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by RECIST 1.1 criteria	• ORR based on investigator assessment against RECIST 1.1 criteria
• **Adolescents only:** To determine the safety and tolerability, MTD and/or RP2D of 23ME-00610, in adolescent patients with locally advanced (unresectable) or metastatic solid cancers	• Incidence and severity of DLTs • Incidence and severity of AEs and SAEs • Withdrawals due to AEs
Secondary	
• To further evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by RECIST 1.1 criteria	• DoR, DCR and PFS based on investigator assessment against RECIST 1.1 criteria • OS
• To determine the safety and tolerability of 23ME-00610	• Incidence and severity of AEs and SAEs • Withdrawals due to AEs
• **Cohort 3B only:** To characterize the pharmacodynamic (PD) effects of 23ME-00610 on target cells in evaluable tumor samples	• Assessment of changes to target cell enumeration and/or phenotype by IHC and/or RNA

Objectives	Endpoints
Exploratory	
• To evaluate clinical (antitumor) activity of 23ME-00610 in evaluable patients with locally advanced (unresectable) or metastatic solid cancers for each tumor-specific disease cohort by iRECIST criteria	• ORR, DoR, DCR and PFS based on investigator assessment against iRECIST criteria (Lancet Oncol 2017;18: e143-52)
• To evaluate potential predictive markers associated with the clinical activity of 23ME-00610	• Correlation of PFS, OS, and ORR, DoR and DCR based on RECIST 1.1 criteria with predictive markers, including: immune-related AEs (irAEs) and tumor, saliva, blood biomarkers, and polygenic risk scores derived from genotyping
• To evaluate the immunogenicity to 23ME-00610	• Prevalence and ADA to 23ME-00610
• To characterize PK profile of multiple doses of 23ME-00610	• Serum PK parameters of 23ME-00610, as applicable, including: AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$
• To characterize the PD effects of 23ME-00610 by the assessment of changes in PD biomarkers in the blood	• PD assessment of blood biomarkers may include, but not be limited to, target engagement or soluble factor analysis.
• To evaluate the exposure-response relationships of 23ME-00610 and clinical activity, safety, and PD biomarkers	• Relationships between PK parameters and clinical activity, safety, and/or PD biomarkers may be explored, and may include: • PK parameters of 23ME-00610, as applicable (i.e., AUC, C_{tau}) • Tumor and circulating blood PD parameters • ORR • Safety (eg, laboratory parameters, AEs, irAEs)

4 STUDY DESIGN

4.1 Overall Design

This is an open-label Phase 1/2a study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary clinical activity of 23ME-00610 given by intravenous (IV) infusion in patients with advanced solid cancers who have progressed on all available standard therapies. This study includes a dose-escalation phase in Part A to determine the MTD and/or RP2D followed by 6 monotherapy expansion arms in Part B to further evaluate the safety, tolerability, PK, PD, and clinical activity of 23ME-00610 in patients with solid cancers.

4.1.1 Overview of the 23ME-00610 Monotherapy Dose-Escalation Phase (Part A)

The dose-escalation phase will utilize a combination of accelerated titration and a standard "3 + 3" design to minimize exposing patients to subtherapeutic doses. During the dose-escalation phase, consented eligible patients will be enrolled into sequential cohorts of increasing doses of 23ME-00610 administered IV once every 3 weeks with a 21-day DLT observation period following administration of the first dose.

The safety at each dose level will be evaluated by the SRC (see Section 4.2.1.2). The SRC will review a minimum of 21-day post-dose safety data, and available PK and PD data, from each cohort to determine if dose escalation will occur. Dose escalation decisions will be made based on all safety information available, including AEs that occur beyond the 21-day DLT period, from both ongoing and prior cohorts.

Accelerated titration dose-escalation phase: One patient will be enrolled into Cohort 1A (23ME-00610 dose of 2 mg). If no Grade ≥ 2 AEs not clearly related to the underlying disease or pre-existing conditions are observed during the 21-day DLT evaluation period (i.e., Cycle 1), the study will proceed with dose escalation to the next cohort. The same procedure will be followed for Cohort 2A (23ME-00610 dose of 6 mg). If a patient experiences a Grade ≥ 2 AE not clearly related to the underlying disease or pre-existing conditions during the first cycle, an additional 2 patients will be enrolled in that cohort and the study will subsequently follow the 3 + 3 design outlined below from this respective cohort onwards. The recommendation to escalate the dose or expand the cohort will be made by the SRC.

3+3 dose-escalation phase: Starting with Cohort 3A, a minimum of 3 patients will initially be enrolled in each subsequent dose cohort and will follow the 3+3 dose-escalation procedure shown in Table 6. If there are multiple patients in the screening process at the time the third patient within a cohort begins treatment, 1 additional patient may be enrolled, with approval of the medical monitor at 23andMe.

If after the third patient completes the 21-day DLT evaluation period, no DLTs are observed (Section 4.1.1.1), the study will proceed with dose escalation to the next cohort following a review by the SRC (Table 6). If 1 of 3 patients experiences a DLT during the first cycle, 3 additional patients will be enrolled in that cohort. If none of the additional 3 patients experience a DLT (i.e., DLTs occurred in < 2 of 6 patients), dose escalation may continue to the next cohort following review by the SRC. If 2 or more patients in a cohort experience DLTs during the first cycle, dose escalation will be halted and the next lower dose level will be

declared the MTD. Alternatively, a dose level intermediate between the non-tolerated dose level and the previously tolerated dose level may be explored based on review of safety and available PK and PD data and SRC approval and declared the MTD if < 2 out of 6 patients experience a DLT at that dose. If the MTD cohort included only 3 patients, an additional 3 patients will be enrolled at that dose level to confirm that < 2 of 6 patients experience a DLT at that dose.

Table 6 3+3 Dose-Escalation Guidelines

Number of Patients with a DLT(s) at a Dose Level	Action
0 of 3	Escalate to the next dose level
1 of 3	Accrue 3 additional patients at the current dose level for a total of 6 evaluable patients If 0 of the additional 3 patients experience a DLT, escalate to next dose level If ≥ 1 patient experiences a DLT, stop the dose escalation
1 of 6	Escalate to the next dose level
≥ 2 of up to 6	Stop dose escalation

Abbreviation: DLT = dose-limiting toxicity.

Beginning with Cohort 3A, a sentinel strategy will be used for the first patient enrolled in every new ascending dose level. 24 hours must elapse after the first patient receives 23ME-00610 before the remaining patients in the cohort are administered the same dose.

Note that if a given cohort initially enrolled 4 patients (i.e., if there were multiple patients in the screening process at the time the third patient within a cohort began treatment), the dose escalation meeting can occur with SRC agreement once the third patient completes the 21-day DLT period. All safety data from ongoing and prior cohorts, including the first 3 patients enrolled in the cohort and from any additional available data from the additional patient enrolled in the same cohort up to the day of the SRC meeting will be considered for dose escalation decisions. The same rules for dose escalation rules will apply if more than 3 patients are initially enrolled in a cohort. If 1 of the 4 patients experiences a DLT, the cohort will be expanded to include a total of 6 patients; dose escalation will occur if only 1 of 6 patients experiences a DLT and will be halted if 2 or more patients experiences a DLT.

Patients who do not meet any of the treatment withdrawal criteria may continue treatment beyond Cycle 1.

23ME-00610 will be administered once every 3 weeks (Q3W) at the following planned dose levels:

- Cohort 1A: 2 mg
- Cohort 2A: 6 mg
- Cohort 3A: 20 mg

- Cohort 4A: 60 mg
- Cohort 5A: 200 mg
- Cohort 6A: 600 mg
- Cohort 7A: 1400 mg

If no DLTs are identified during Part A, dose escalation may continue to a maximum of either 1400 mg or the dose level that provides the maximum exposure that is expected to provide anticancer activity (> 99% activity in the tumor killing assay at C_{tau} on C1D21), as determined by an ongoing assessment of PK/PD and any observed clinical activity; this may occur in parallel with the expansion phase. Dose escalation may end prior to the maximum planned dose level based on SRC decision following review of the safety, PK, and PD data. Intermediate dose levels may be evaluated if supported by emerging safety, PK, and PD data, and SRC approval.

PK/PD Backfill Cohort: To further evaluate PK and PD in Part A, additional patients may be enrolled in a PK/PD backfill cohort (up to a total of 12 patients, including the 3 to 6 patients initially enrolled during dose escalation) following SRC approval at the RP2D/MTD, or a previously evaluated dose level where there is pharmacologic or pharmacodynamic evidence of therapeutic effect. These additional patients will contribute to the assessment of safety and preliminary anticancer activity, as well as the characterization of the PK/PD profile of 23ME-00610.

4.1.1.1 Dose-Limiting Toxicity

Dose-limiting toxicities will be evaluated during Cycle 1 of treatment. Toxicities will be graded and documented according to the NCI-CTCAE, version 5.0. A DLT is defined as outlined below in Table 7.

A DLT is defined as an AE that meets at least 1 of the criteria listed in Table 7 and is considered by the investigator to be clinically relevant and not clearly related to the underlying disease during the 21-day DLT observation period. An AE considered to be clearly related to the underlying disease that is under investigation is not a DLT.

Table 7 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition[a]
	• Any death not clearly related to the underlying disease or extraneous causes
Hematologic	• Grade 4 neutropenia of > 7 days in duration • Febrile neutropenia • Grade 4 anemia of any duration • Grade 4 thrombocytopenia > 7 days in duration or Grade 3 thrombocytopenia with clinically significant bleeding of any duration
Nonhematologic	• Any AE requiring permanent discontinuation of study drug • ALT and/or AST ≥ 3x ULN plus bilirubin ≥ 2x ULN (> 35% direct) or plus INR > 1.5, if measured (possible Hy's law)[b] • ALT or AST increase > 5x to 10x ULN not resolving to > 3x to 5x ULN within 7 days or > 1x to 3x ULN within 14 days. • Bilirubin increase > 5x ULN, or 3x to 5x ULN and not resolving to > 3x to 5x ULN within 7 days or > 1x to 3x ULN within 14 days. Patients with a known history of Gilbert's require discussion with the medical monitor at 23andMe. • Grade 2 uveitis, eye pain, or blurred vision that does not resolve to baseline with topical therapy within 2 weeks • Grade 2 colitis or diarrhea that persists without resolution to Grade ≤ 1 or baseline for ≥ 7 days despite adequate steroid therapy • Grade ≥ 2 immune-related endocrine toxicity that requires hormone replacement (except Grade 2 thyroiditis or thyroid dysfunction) • Any Grade ≥ 3 nonhematologic clinical toxicity (including irAEs) are considered as a DLT except for the following: o Grade ≥ 3 nausea, vomiting or diarrhea that resolves to baseline within 72 hours with adequate antiemetic and other supportive care o Grade ≥ 3 electrolyte abnormalities without clinical symptoms that resolve to baseline within 72 hours (all Grade ≥ 3 electrolyte abnormalities with clinical symptoms of any duration are considered as a DLT) o Grade 3 fatigue that lasts for ≤ 7 days

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLT = dose-limiting toxicity; INR = international normalized ratio; irAE = immune-related adverse event; ULN = upper limit of normal.

[a] Grading according to NCI-CTCAE v5 [US Department of Health and Human Services, 2017].

[b] Not applicable to patients taking anticoagulants

If a patient experiences a DLT during the DLT observation period, the patient will be discontinued from study drug unless the investigator considers it in the best interest of the patient to continue in the study (e.g., in cases of tumor regression, symptomatic disease improvement, and/or if the type of DLT is considered as potentially preventable in subsequent dosing periods [e.g., with premedication]). Such cases will require approval by the investigator AND medical monitor at 23andMe before continuation with study drug at the same dose. If a DLT that can be prevented or managed with premedication and/or supportive care measures occurs within a cohort, the SRC can implement requirements regarding these procedures/treatments for subsequent patients in the cohort (e.g., IV fluids for prevention of hypotension).

Toxicity management and dose modification guidelines are provided in the protocol for irAEs that may be expected with the administration of immune-checkpoint inhibitors such as 23ME-00610 (Section 6.5.1). Guidance for the identification, evaluation, and management of irAEs, including dose modification algorithms, is provided in Section 6.5.1 and Appendix 2.

In the event there is a delay in administration of study intervention, refer to Section 6.5.4 for guidance on the planning of subsequent study visits.

4.1.1.2 Optional Intra-patient Dose Modification Criteria for 23ME-00610

To optimize the number of patients treated at a potentially clinically relevant dose, intra-patient dose escalation will be permitted in Part A only, with approval of the medical monitor at 23andMe.

Specifically, patients who are receiving a lower dose of 23ME-00610 than has been evaluated and determined to be safe (i.e., following safety review of that cohort there are < 2 of 6 [or 0 of 3] patients with DLTs who have completed at least one cycle of treatment) may be escalated to a higher dose that has been determined to be safe, given the patient has not experienced a Grade 3 or higher drug-related AE at the originally assigned dose. There is no limit to the number of times the dose for a given patient may be increased if it does not exceed the MTD and/or RP2D. Intra-patient dose reductions are not permitted unless the dose the patient is receiving is subsequently determined to exceed the MTD and/or RP2D, or if a higher dose level is deemed intolerable for a patient who had previously tolerated a lower dose level and was escalated to a higher dose level, by approval from the medical monitor at 23andMe. All intra-patient dose-modification decisions will be documented.

4.2 Overview of the 23ME-00610 Monotherapy Expansion Phase (Part B)

Following the monotherapy dose-escalation phase (Part A), 6 non-randomized expansion Cohorts (including 5 indication-specific cohorts and an adolescent solid cancer cohort) may be enrolled in Part B following approval by the SRC at a recommended dose based on the safety, tolerability, and PK/PD data from the dose escalation portion of the study. Following safety, tolerability, and available PK/PD data review, the SRC may recommend a dose level(s) for the expansion cohorts after ≥ 6 patients in Part A have been treated at or above the recommended dose level for ≥ 1 cycle to collect additional data on safety, PK, PD, and preliminary clinical activity. Multiple doses may be evaluated if there is pharmacologic or PD evidence of

therapeutic effect below the MTD. Patients who do not remain on study to be evaluated for efficacy may be replaced at the discretion of the medical monitor at 23andMe.

23ME-00610 1400 mg administered IV Q3W will be evaluated in all expansion Cohorts based on SRC review of safety, tolerability, and available PK/PD data from Part A.

Cohort 1B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic ccRCC. Cohort 2B will enroll approximately 13 evaluable patients with locally advanced (unresectable) or metastatic epithelial ovarian, fallopian tube or primary peritoneal carcinoma of non clear-cell histology, and approximately 2 evaluable patients with clear cell histology (approximately 15 total). Cohort 3B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic neuroendocrine cancers. Cohort 4B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or MSI-H and/or TMB-H solid cancers, including at least 10 evaluable MSI-H cancers. Cohort 5B will enroll approximately 8 evaluable adolescent patients with locally advanced (unresectable), or metastatic solid cancers (**see Inclusion of Adolescents in Part B**). Cohort 6B will enroll approximately 15 evaluable patients with locally advanced (unresectable) or metastatic ES-SCLC.

Approximately 15 additional evaluable patients may be added to any disease-specific cohort in Part B to evaluate another dose level with pharmacologic or PD evidence of therapeutic effect below the MTD/RP2D identified in Part A (for a maximum of 30 patients in total at the alternate dose) following SRC review and approval.

In jurisdictions where local regulations and IRB/EC allows, patients who reflect the characteristics with regards to age, sex, race and ethnicity for each disease-specific cohort will be prioritized for enrollment. Specifically, patients from historically underrepresented communities, including those from the Black, Latinx/Hispanic and Indigenous communities will be prioritized in Part A, and in each expansion cohort in Part B to ensure the trial population is representative of the intended patient population.

These indications were selected based on the expression of CD200R1 and its ligand, CD200, T-cell markers, and/or immune characteristics that suggest a higher likelihood of response to 23ME-00610. Additional Dose Expansion Cohorts may be enrolled in a specific tumor type or biomarker-defined population based on emerging nonclinical or clinical data.

Safety, PK/PD, and preliminary clinical activity data will be reviewed by the SRC approximately every 8 weeks during the expansion phase.

Inclusion of Adolescents in Part B: In jurisdiction where local regulations and IRB/EC allows, adolescent patients will be included in the expansion phase after a minimum of 6 adult patients have been treated at the RP2D for ≥ 1 cycle and following SRC approval. Cohort 5B will enroll approximately 8 adolescent patients with locally advanced (unresectable), or metastatic solid cancers. The SRC will review the safety, PK, and available PD data from the first 3 adolescent patients in Cohort 5 to determine if the remaining patients in the cohort will be enrolled.

4.2.1.1 Dose Confirmation in Adolescents

Following SRC approval, as outlined in Section 4.2, adolescents will be enrolled in Cohort 5 and treated at the RP2D determined in adults (1400 mg administered IV Q3W). Once the first 3 adolescent patients are enrolled, the cohort will be expanded to confirm the RP2D following SRC review of a minimum of 21-day safety data, PK data from the first cycle, and available PD data. Safety data from the first 3 adolescent patients will be used to inform dose de-escalation decisions. If 1 of 3 adolescent patients experiences a DLT, an additional 3 adolescents will be enrolled. If 2 of 6 adolescent patients experience a DLT, no further adolescents will be treated at that dose and 3 adolescent patients will be enrolled at a lower dose (half log decrease) and the same procedure will be followed to determine further enrollment at this dose level. The SRC will perform an ongoing review (approximately quarterly) of the safety and available PK/PD data from all adolescents enrolled in the study.

Confirmation of the RP2D in adolescents will be determined by evaluation of safety and PK data, targeting a DLT rate < 30% and 23ME-00610 exposures (measured by AUC) that are comparable to adults. The RP2D will be confirmed based on safety, PK, PD, and anticancer activity data after approximately 8 adolescents have been enrolled in the study at a given dose level.

4.2.1.2 Safety Review Committee

The safety at each dose level will be evaluated by the SRC, which is comprised of the Sponsor Representative(s), Study Medical Monitor(s), Drug Safety Representative(s) and investigator(s) and additional 23andMe personnel and/or their third-party partners, as appropriate. Safety, and available PK, PD and preliminary anticancer activity data will be reviewed by the SRC at least every 2 weeks after the first patient is enrolled during the dose-escalation phase (Part A). The SRC will review a minimum of 21-day post-dose safety data, and available PK and PD data, from each cohort in Part A to determine if dose escalation will occur. Dose escalation decisions will be made based on all safety information available, including AEs that occur beyond the 21-day DLT period, from both ongoing and prior cohorts. SRC meetings in Part A will be scheduled to occur at the end of each cohort's DLT observation period after the required data are available and have been reviewed. Decisions to escalate the dose will be documented along with a summary of the information supporting the decision.

Review of Part A data and agreement by the SRC must occur prior to the enrollment of an adolescent cohort in Part B (Section 4.2.1.1). SRC review meetings will continue through Part B in accordance with the SRC Charter. Safety, PK/PD, and preliminary clinical activity data will be reviewed by the SRC approximately every 8 weeks during the expansion phase.

The SRC may recommend alternate dosing schedules based on evolving clinical safety and PK data (e.g., weekly, or bi-weekly dosing). The study, or individual expansion cohorts, may be stopped if the SRC determines there is excessive toxicity or a demonstrated lack of clinical benefit that does not support an appropriate benefit-risk for continued investigation in this phase 1/2a oncology patient population based on review of the evolving clinical data (see Section 7.2).

Additional details will be provided in a separate SRC Charter that will govern the committee.

4.3 Scientific Rationale for Study Design

The primary objectives of this study are 1) to assess the safety and tolerability of treatment with 23ME-00610 monotherapy in patients with advanced solid cancers, and 2) to determine the MTD and/or the RP2D of 23ME-00610 monotherapy in patients with advanced solid cancers for further clinical investigation. The primary objective of the expansion phase of the study is to assess preliminary evidence of anticancer activity of 23ME-00610 in disease-specific cohorts that were selected based on the expression of CD200R1 and its exclusive ligand, CD200, T-cell markers, and/or other immune characteristics that suggest a higher likelihood of response to 23ME-00610.

The monotherapy escalation part of the study design follows a combination of an accelerated titration and standard "3+3" design to assess ascending, multiple doses of 23ME-00610 with evaluation of the safety of each dose cohort prior to dose escalation. The accelerated titration design for Cohort 1 and 2, followed by a 3+3 design for Cohorts 3-7 was selected to minimize the numbers of patients exposed to subtherapeutic doses of 23ME-00610 while allowing appropriate characterization of the safety, PK and PD profile of 23ME-00610 across multiple dose levels in a stepwise fashion.

A comprehensive series of safety evaluations, including laboratory parameters, physical examinations, vital signs, ECGs, and monitoring for AEs, will be conducted to evaluate the safety profile of 23ME-00610 and will inform on the recommended dose for continued development.

The study includes serial blood sampling in all cohorts to assess the PK and immunogenicity profile of 23ME-00610, which will enable the selection of an appropriate dose and schedule to be selected for further evaluation. The PK data will be collected across multiple dose levels and multiple cycles in Parts A and B to allow an assessment of dose proportionality and drug accumulation. These data will also be used to evaluate the relationships between dose/exposure and observed AEs, clinical activity, and PD effects to inform dose selection for further clinical development. Exploratory objectives of the study include the assessment of multiple PD biomarkers that will inform on target engagement and allow the interrogation of the potential mechanism of action and resistance to 23ME-00610 in patients with advanced solid cancers. The selection of these biomarkers was based on scientific hypotheses involving the CD200R1 pathway and solid tumor pathophysiology.

Preclinical data suggests that CD200R1 and CD200 are upregulated in certain human cancers, which may make them more sensitive to CD200R1 pathway blockade by 23ME-00610. Thus, mandatory archival tumor tissue will be required for entry into the study to retrospectively evaluate the association between anticancer activity and expression of CD200R1 and CD200. Baseline and on-treatment biopsies will be collected from adult patients in whom collection of paired biopsies is judged to be safe and feasible by the investigator in the PK/PD backfill cohort in Part A (optional) and in Part B (mandatory) to assess changes in immune cell and CD200R1 pathway-related biomarkers by immunohistochemistry following treatment with 23ME-00610. These analyses may identify potential biomarkers that correlate with anticancer responses to 23ME-00610. It is unknown how CD200R1 or CD200 expression will change upon inhibition of CD200R1. Thus, these samples will also be used to examine changes in the expression of

CD200R1 pathway markers prior to and following 23ME-00610 treatment. Other biomarkers related to the tumor immune microenvironment may also be evaluated.

The archival and tumor tissue specimens may be used to extract DNA and RNA to evaluate changes in genes related to immune cell function and activation, tumor mutation parameters and other potential biomarkers that may predict response to 23ME-00610. To assess the relationship between total mutation burden and response to treatment with 23ME-00610, a blood sample to isolate cell free DNA for tumor mutation analysis will be taken at screening and following 23ME-00610 administration to allow monitoring of anti-tumor activity using cell free DNA kinetics.

23ME-00610 functions by inhibiting the binding of CD200 to CD200R1. It is unknown if circulating level of CD200R1 or CD200 are modulated by anti-CD200R1 blockade by 23ME-00610, and if these markers can be used to assess target engagement. As such, blood samples will be collected to determine baseline levels and longitudinal changes in CD200R1 pathway components. In preclinical experiments, 23ME-00610 demonstrated the ability to relieve immune suppression and rescued the secretion of proinflammatory cytokines including IFNγ and IL-2. Thus, blood samples will be used to evaluate potential changes in peripheral cytokine levels elicited by 23ME-00610 and PBMC samples will be isolated from patient blood across multiple timepoints to allow analysis of immune cell protein surface expression and potential changes induced by 23ME-00610.

Saliva will be collected from patients at study entry to genotype nucleated cells found within the saliva using 23andMe's validated genotyping platform. These samples will be used to evaluate genotypic information, which will be correlated with adverse event information and clinical outcomes using polygenic risk scores (PRS) for autoimmune and other phenotypes, or genetic variants to evaluate the potential predictive value of these scores or associations.

Genome-wide association studies (GWAS) have identified genetic variants that are associated with risk of developing numerous complex diseases. Data from individual genetic variants can be combined to calculate a PRS, which is a cumulative estimation of risk for a given disease. PRSs are increasingly being used in the clinical setting to guide therapy decisions, aid in diagnosis and predict clinical outcomes of disease or therapy (Yanes, 2020; Lewis and Vassos, 2017). The utility of PRSs have been recognized in several disease states such as coronary artery disease, in which the addition of PRS to the existing risk evaluation framework has been shown to more accurately define disease risk and identify patients most likely to benefit from statin therapy (Lambert, 2019). Furthermore, results from a retrospective analysis of a Phase 3 study of the PD-L1 inhibitor atezolizumab in bladder cancer patients revealed an association between improved OS and PRSs for dermatological immune-related AEs (Khan, 2020). These data provide a strong rationale to examine genetic factors that may predict response to 23ME-00610.

Expansion arms in 5 specific tumor types will allow for a more robust evaluation of the safety, tolerability, PK/PD profile, and clinical activity in a more homogenous subsets of patients. Cancer patients from the Black, Latino and Indigenous communities have historically been underrepresented in clinical trials and are disproportionately impacted by certain types of cancer, including those being evaluated in this study (Batai, 2019; Stenzel, 2019; Swaby, 2021). As

such, these patients will be prioritized for enrollment within each Cohort to ensure the trial population appropriately represents the demographics of people with cancer.

4.4 Rationale for Dose Selection

This section describes the analyses conducted to estimate the 23ME-00610 PK parameters in humans by scaling PK data from cynomolgus monkeys and predict the 23ME-00610 pharmacologic activity in cancer patients from nonclinical data. The analyses inform the MABEL-based starting dose and the projected human efficacious dose and justify the range of doses proposed in this study based on predicted pharmacologic activity in cancer patients.

4.4.1 Human PK Prediction

For therapeutic monoclonal antibodies like 23ME-00610, cynomolgus monkeys are the most relevant species for conducting preclinical PK studies (International Council for Harmonisation [ICH]S6) and thus are used for predicting human PK (Ling, 2009; Wang and Prueksaritanont, 2010). The PK of single IV doses (2 and 20 mg/kg) of 23ME-00610 was assessed in cynomolgus monkeys.

23ME-00610 PK in monkeys was linear, exposure was approximately dose proportional, and no differences were observed between males and females (Section 2.4). Based on retrospective analyses demonstrating the use of allometry to accurately predict human PK using the PK in cynomolgus monkeys for mAbs with linear PK properties (Ling, 2009; Wang and Prueksaritanont, 2010), these results support that allometric methods are appropriate to predict human PK of 23ME-00610.

Scaling from monkey to human assumed that volume of distribution terms (V1 and V2) scale with the allometric exponent 1.0, and that clearance terms (CL and Q) scale with the allometric exponent 0.85 (Deng, 2011). Body weights of 2.14 kg (mean body weight of monkeys in the 23ME-00610 single-dose PK study) and 70 kg were adopted for monkey and human weights, respectively. Based on the scaled 23ME-00610 human PK parameters (Table 8), the 23ME-00610 elimination half-life is estimated to be 17 days, which supports dosing once every 3 weeks (Q3W) at the projected efficacious dose.

Table 8 Predicted Pharmacokinetic Parameters of 23ME-00610 in Humans

Parameter	(Unit)	Value
CL	(L/day)	0.242
	(mL/day/kg)*	3.457
V1	(L)	3.43
Q	(L/day)	1.46
	(mL/day/kg)*	20.9
V2	(L)	2.50

Abbreviations: CL = clearance; V1 = volume of distribution of the central compartment; Q = intercompartmental clearance; V2 = volume of distribution of the peripheral compartment; L = liter; mL = milliliter; kg = kilogram;
* calculated using a 70-kg human body weight

Because 23ME-00610 is specific to human CD200R1 and does not bind to CD200R1 from monkeys, only nonspecific clearance could be assessed preclinically. Therefore, the human PK parameters obtained and scaled from monkeys might not be sufficient for full characterization and prediction in humans, particularly at doses below saturation where target-mediated drug disposition (TMDD) may contribute to the clearance of 23ME-00610. Although TMDD would result in a shorter half-life and lower exposure than predicted, TMDD was not included in the human PK projection because it is expected to be a minor clearance pathway in humans at the projected efficacious dose (i.e., doses ≥ 600 mg) and it is anticipated to have a negligible impact at doses that achieve saturation, which is anticipated to be approximately 10-fold below the predicted efficacious dose.

4.4.2 Planned Doses and Predicted Pharmacologic Activity

The planned doses for this study are 2, 6, 20, 60, 200, 600, and 1400 mg. Intermediate dose levels may be explored based on emerging clinical data as additional dose-level cohorts. 2 mg is the MABEL-based starting dose, and each subsequent cohort escalates a maximum of one-half log higher than the previous dose, with final dose selection made by the SRC. The planned doses and maximum dose to be tested will be informed by emerging safety, PK, PD, and clinical activity data. The predicted efficacious dose range of 23ME-00610 is described below.

4.4.2.1 Emax Model-Based Predictions

Dose predictions are based on predicted receptor occupancy (RO) or the predicted effect, based on the E_{max} Equation with E_0 set to 0 and E_{max} set to 1. In this model, Cp is the drug concentration predicted via the human PK model (Section 4.4.1) and EC_{50} is the half-maximal concentration for saturation binding (0.32 nM), the half-maximal concentration for ligand binding disruption (1.04 nM), or the half-maximal effective concentration in the PBMC-mediated $CD200^+$ tumor killing assay (2.09 nM).

RO and E_{max} Equation:

$$RO\ or\ Effect = E_0 + \frac{E_{max} * C_p}{C_p + EC_{50}} = \frac{C_p}{C_p + EC_{50}}, when\ E_0 = 0; E_{max} = 1$$

A blood-to-tumor partition coefficient of 10% (Bensch, 2018) was used to estimate the concentration of 23ME-00610 in the tumor. Predicted RO and pharmacological activity in the peripheral blood or in the tumor at each dose level are shown in Table 10.

Table 9 Predicted Pharmacological Activity

	Blood		Tumor		
Dose (mg)	**C_{tau} (µg/mL)**	**%RO**	**%EC**	**%IC**	**%RO**
2	0.138	74.8	4.4	8.4	22.9
6	0.411	89.9	11.9	21.4	47.0
20	1.37	96.7	31.1	47.6	74.7
60	4.11	98.9	57.5	73.1	89.9
200	13.7	99.7	81.9	90.0	96.7

600	41.1	99.9	93.1	96.5	98.9
1400	96.0	> 99.9	96.9	98.5	99.5

Notes: C_{tau} = cycle 1 minimum concentration in interval; %RO = receptor occupancy, based in EC_{50} binding affinity to primary human T cells (EC_{50} = 0.32 nM); %EC = percent of maximal effective concentration in the PBMC-mediated $CD200^+$ tumor killing assay (EC_{50} = 2.09 nM); %IC = percent of maximal inhibitory concentration in the CD200R1 ligand binding disruption and displacement assay (IC_{50} = 1.04 nM); Blood refers to the predicted concentration in circulation; Tumor uses a concentration that is 10% of the peripheral Blood C_{tau}.

Consistent with its mechanism of action, wherein 23ME-00610 relieves local immune suppression in the tumor, 23ME-00610 pharmacologic activity is based on predicted tumor concentrations and activity in the PBMC-mediated $CD200^+$ tumor assay.

4.4.2.2 Projected Human Efficacious Dose

The projected human efficacious dose of 23ME-00610 is expected to maintain near-complete functional inhibition of the CD200/CD200R1 pathway in the tumor (≥ EC_{90}) based on the PBMC-mediated $CD200^+$ tumor killing assay. Based on this criterion, projected human doses of 23ME-00610 ≥ 600 mg Q3W are expected to maximize efficacy in cancer patients throughout the dosing interval (Table 10). 23ME-00610 doses ≥ 600 mg are predicted to maintain concentrations of ≥ 93.1% of the maximal effective concentration in the PBMC-mediated tumor killing assay, ≥ 96.5% of the maximal inhibitory concentration in the CD200/CD200R1 ligand binding disruption assay, and ≥ 98.9% RO in the tumor at the end of the dosing interval (C_{tau}) (Table 10).

4.4.2.3 Maximum Dose

The relationship between 23ME-00610 in vitro pharmacology and anticancer activity in human cancer patients is currently unknown. Therefore, a dose of 1400 mg Q3W is the currently planned maximum proposed dose and has been selected to maximize pharmacologic activity in the tumor as shown in Table 10, and account for uncertainties and potential differences between clinical activity and pharmacologic activity observed in vitro. Doses may exceed the currently proposed maximum dose of 1400 mg if supported by emerging PK, PD, and safety data.

4.4.2.4 Dose Prediction Summary

In summary, based on predicted PK and pharmacologic activity, 2 mg and 6 mg 23ME-00610 are expected to have low potential for efficacy and thus those cohorts (Cohorts 1A and 2A) have been designated as accelerated titration cohorts. Doses between 60 mg and 200 mg are expected to be on the dose-response curve and have the potential to provide anticancer activity. Doses ≥ 600 mg Q3W are predicted to provide efficacy based on predicted linear PK, full RO, and predicted pharmacologic activity in the tumor. A dose of 1400 mg is currently proposed as the maximum dose to maximize the CD200R1 pharmacology and anticipate potential differences between nonclinical and clinical data (Table 10). Therefore, the range of planned doses in the FIH study covers the range of 23ME-00610 predicted pharmacology and is consistent with the range of doses examined in FIH studies with molecules of the same class (IgG1 mAb checkpoint inhibitors).

4.4.2.5 Dose Rationale for Part B (Expansion Phase)

Based on the totality of data from Part A of this study, 23ME-00610 1400 mg administered IV Q3W will be evaluated in the expansion phase as the preliminary RP2D (See investigator's Brochure for the summary of safety, PK and PD data from Part A). This preliminary RP2D of 23ME-00610 was determined after review of all safety and available PK and PD data from Part A of this study, and after at least 6 adults patients completed at least 1 cycle of treatment with 1400 mg 23ME-00610 as required per protocol. All AEs, including those occurring outside of the 21-day DLT observation period, were included in the assessment.

Anticancer activity of 23ME-00610 was predicted based on a preclinical in vitro tumor cell killing assay and predicted tumor concentrations of 23ME-00610. Doses that provide 23ME-00610 concentrations that exceed EC_{90} in the tumor throughout the entire dosing interval (i.e., serum $C_{trough} > 28$ µg/mL) are expected to be efficacious and achieve near-complete functional inhibition of the CD200R1 inhibitory checkpoint in the tumor microenvironment. Based on the observed preliminary 23ME-00610 PK data, 1400 mg Q3W meets this criterion, as explained below.

For antagonist immune checkpoint inhibitors such as 23ME-00610, near-complete target engagement is needed to elicit anticancer activity (Patnaik, 2015; Li, 2021). Based on the available target engagement data, doses of at least 60 mg are required to saturate 23ME-00610 binding to CD200R1 on T cells and neutrophils in peripheral blood, indicating that 10 to 20-fold higher doses of 23ME-00610 are likely needed to saturate CD200R1 in the tumor microenvironment due to the following considerations. Based on the published literature of other immune checkpoint inhibitors, only ~10% of 23ME-00610 is expected to penetrate into the tumor (Bensch, et al., 2018; Li, 2021). Additionally, tumor penetration has been shown to vary based on tumor type, disease burden, and anatomical location of metastases, with ~2-fold variation in drug penetration observed between lesions in the same patient (Bensch, et al., 2018). Furthermore, expression of CD200R1 varies between tumor types, and clinical data from studies of anti-PD1 antibodies suggests that differences in target expression can further contribute to variability, with a ~2-fold difference in drug uptake observed based on target expression (Niemeijer, 2018). Thus, with the expected variability in the expanded patient population, a dose of 1400 mg Q3W increases the likelihood that the majority of patients will achieve sufficient drug levels in the tumor for complete target saturation in Cycle 1, including in the poorly vascularized lesions. Thus, the available pharmacodynamic data support 1400 mg Q3W as the RP2D.

Consistent with the PD data, 23ME-00610 doses ≥ 60 mg are in the linear PK range. The half-life of 23ME-00610 increased with dose, plateauing at ~11-13 days for doses ≥ 200 mg, and 1.13 to 2.20-fold accumulation in exposure (C_{max} and AUC) was observed with repeat dosing every three weeks (Q3W) for doses ≥ 60 mg. Based on the PK properties of 23ME-00610 (i.e., half-life) and the concentration of 23ME-00610 required at the end of the dosing interval (EC_{90}) for near-complete inhibition of CD200R1 in the tumor microenvironment based on preclinical data, the current dosing frequency of Q3W is considered appropriate for further evaluation in the expansion phase.

The preliminary safety data from Part A across the 2 to 1400 mg dose levels indicate that 23ME-00610 was well-tolerated, with no DLTs or treatment-related SAEs observed as of the May 15th, 2023 data cut-off date (see Investigator's Brochure for the summary of safety data from Part A). Thus, the preliminary safety data supports assessment of 1400 mg Q3W in the expansion phase.

In summary, the safety and available PK and PD data support a preliminary RP2D of 1400 mg Q3W for the expansion phase. Based on all available safety data from Part A, this dose is tolerable, and the PK and PD data suggest it will provide near-complete inhibition of the CD200R1 pathway in the tumor throughout the entire dosing interval for the majority of patients, including those with poorly vascularized lesions. As expected for doses in the linear PK range, exposures of 23ME-00610 were generally comparable between patients with different tumor types within each dose cohort. Considering the available PK data, uncertainties in translational modeling, an expanded population and associated variability, 1400 mg Q3W increases the likelihood that the majority of the patient population achieves the EC_{90} PK target in Cycle 1, and thus is an appropriate dose level to initiate preliminary efficacy assessments. The SRC will continue to meet on an ongoing basis to review the safety and available PK and PD data in the expansion phase. Additional dose levels of 23ME-00610 with pharmacologic or pharmacodynamic evidence of therapeutic effect below the RP2D may be evaluated if supported by the emerging clinical data and will proceed after SRC approval.

The adult RP2D of 1400 mg Q3W will be evaluated in adolescent patients ≥ 12 years of age who weigh at least 40 kg (total body weight) as exposures of 23ME-00610 in this population are expected to be similar to adults. This approach is supported by previous analyses that have demonstrated that there is no clinically meaningful difference in the exposure of most drugs in adults and adolescents (Momper, et al., 2013; Gaspar, et al., 2018). Safety and available PK and PD data from the first 3 adolescent patients enrolled in the expansion phase will be compared to adult data to determine the appropriateness of the adult RP2D for the remaining adolescent patients. The RP2D in adolescents will be defined based on the observed PK, PD, and safety data with 23ME-00610 in this population and will take the totality of available adult data from the dose escalation and expansions phase into account, including analyses of the effect of body-size on PK, safety, and available dose/exposure-response relationships.

4.4.3 23ME-00610 Starting Dose Rationale

The proposed starting dose of 23ME-00610 is 2.0 mg Q3W. This dose is based on a MABEL approach and justification is provided below.

4.4.3.1 Minimally Anticipated Biologic Effect Level (MABEL) Approach

CD200R1 is predominantly expressed on immune cells, and CD200, the sole ligand of CD200R1, is highly expressed on several types of tissues, including endothelial cells, some immune cells, and in several tumor types (Wright, 2001; Wright, 2003; Moreaux, 2006; Tonks, 2007; Alapat, 2012).Thus, the interaction between CD200 and CD200R1 can contribute to immune suppression, as seen with other immune checkpoints. Accordingly, 23ME-00610 is expected to bind to CD200R1 on the surface of TILs, disrupt the interaction between CD200R1 and CD200 in the tumor or stroma, and release the TILs from immune suppression. Consistent

with this mechanism of action (antagonism of CD200/CD200R1), the in vitro PBMC-mediated $CD200^+$ tumor killing assay was selected as the most relevant nonclinical data for a MABEL-based dose selection as it most closely mimics the tumor microenvironment.

Prior to immune activation and tumor cell killing, 23ME-00610 must bind to the TILs and inhibit the interaction between CD200R1 and CD200, or otherwise disrupt the interaction and displace CD200 from CD200R1. Therefore, other pharmacologically relevant experiments used to determine the proposed starting dose included cell-based in vitro binding to primary human immune cells and ligand binding disruption.

The MABEL for 23ME-00610 in patients with advanced cancer is 65.8% of the maximal effective concentration in the PBMC-mediated tumor killing assay (EC_{50} of 2.09 nM, or 0.303 µg/mL), which corresponds to 0.583 µg/mL. This concentration also corresponds to approximately 79.4% of ligand binding disruption and a predicted peripheral RO of 92.6%. The MABEL for 23ME-00610 was identified based on the totality of data, including nonclinical safety data in human cytokine release assay and published safety data with the anti-CD200 antibody samalizumab. Taken together, EC_{65} is expected to be a safe and minimally active starting dose in patients with cancer.

A 2.0 mg starting dose minimizes the risk of exposing large numbers of patients with no available therapeutic options to subtherapeutic doses, while maintaining an adequate safety margin. Notably, there was no meaningful increase in cytokine release in vitro in healthy donor human whole blood (soluble format) or donor PBMCs (plate-bound format) at a concentration of 23ME-00610 that is 34-fold higher than the predicted C_{max} (0.583 µg/mL) for the proposed starting dose of 2.0 mg.

Moreover, no significant hazards were identified in the repeat-dose GLP study in monkeys conducted with the 23ME-00611 surrogate antibody at doses up to 100 mg/kg weekly for 4-weeks. Based on these results, the no-observed-adverse-effect level (NOAEL) of 23ME-00611 in monkeys was 100 mg/kg, the highest dose tested. Furthermore, clinical data with an anti-CD200 antibody, samalizumab, suggests that antagonism of the CD200/CD200R1 pathway in humans is likely to be safe and tolerable (Mahadevan, 2019).

A 2 mg starting dose (EC_{65} in the PBMC-mediated tumor killing assay) is expected to be maximize the benefit to risk ratio in cancer patients. Although the 2 mg starting dose is expected to result in 92.6% RO at C_{max}, past clinical experience with immune-activating biologics showed that doses above saturation had acceptable toxicities for non-ADCC enhanced antibodies like 23ME-00610 (Saber, 2016).

In summary, a starting dose of 2 mg of 23ME-00610 is expected to provide a reasonable balance between risk and benefit for patients with advanced disease (Table 9).

Table 10 Estimated Pharmacologic Activity at the Projected C_{max} of the Proposed MABEL-Based Starting Dose

Dose (mg)	C_{max}[1] (µg/mL)	Receptor Occupancy[2] (%)	CD200/CD200R1 binding disruption[3] (%)	PBMC-mediated tumor cell killing[4] (%)	Fold Margin Relative to Concentration in CRA[5]
2	0.583	92.6	79.4	65.8	34.3

[1] Human PK prediction
[2] Predicted, based on EC50 binding to T cells of 0.32 nM (or ~ 0.05 µg/mL)
[3] Predicted, based on CD200/CD200R1 binding disruption IC_{50} of 1.04 nM (or ~ 0.15 µg/mL)
[4] Predicted, based on $CD200^+$ tumor cell killing assay EC50 of 2.09 nM (or ~ 0.303 µg/mL)
[5] Based on the highest concentration tested (20 µg/mL), which resulted in no clinically significant increase in cytokine release

Abbreviations: CRA: cytokine release assay; EC: effective concentration; IC: inhibitory concentration; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RO: receptor occupancy.

4.4.4 Flat Dose Justification

Flat doses of 23ME-00610 will be administered in this study.

Studies evaluating interpatient variability in exposure have shown no difference between body weight-based and flat (or fixed) dosing for biologics, with mAbs typically exhibiting relatively flat dose-response relationships (Hendrikx, 2017). For many mAbs, this results in wide therapeutic windows with a reduced impact on clinical efficacy/safety for flat dosing compared with body weight-based dosing.

Administration of flat doses in this study will allow for the evaluation of the effect of body weight on drug exposure and will facilitate comparison and combination of data collected from similar studies later in development.

4.4.5 Dosing Frequency

Based on the predicted half-life of 2 to 3 weeks (Section 4.4.1), and consistent with a standard human IgG1 linear PK profile in humans, a dosing frequency of Q3W was selected for 23ME-00610. Analyses performed as part of the efficacious dose projections support that this regimen is likely to provide pharmacologic activity over the duration of the dosing interval. The predicted C_{tau} for doses ≥ 600 mg Q3W, the projected efficacious dose, is estimated to provide ≥ 90% of the maximal activity of 23ME-00610 in the $CD200^+$ tumor killing assay in the tumor.

4.4.6 Adolescent Dose Selection

The adult RP2D is proposed for evaluation in adolescent patients ≥ 12 years of age who weigh at least 40 kg (total body weight) as exposures of 23ME-00610 in this population are expected to be similar to adults. This approach is supported by previous analyses that have demonstrated that there is no clinically meaningful difference in the exposure of most drugs in adults and adolescents (Momper, 2013; Gaspar, 2018; EMA, 2009; FDA, 2018).

Preclinical data suggests that 23ME-00610 is expected to have a PK profile similar to other IgG1 mAbs in humans, which have not shown meaningful differences in clearance between adolescents and adults. Furthermore, analyses of publicly available CD200R1 mRNA data suggests that expression levels are expected to generally be comparable between adult and adolescent cancer patients.

Safety, PK, and available PD data from the first 3 adolescent patients enrolled in the expansion phase will be compared to adult data (a minimum of 6 adult patients treated at the RP2D) to determine the appropriateness of the adult RP2D for the remaining adolescent patients.

The RP2D in adolescents will be defined based on the observed PK, PD, and safety data with 23ME-00610 in this population and will take the totality of available data from the dose escalation and expansion phases into account, including analyses of the effect of body-size on PK, safety, and available dose/exposure-response relationships.

4.4.7 Immunogenicity Risk Assessment

The immunogenicity risk of 23ME-00610 is currently unknown. However, humanized antagonist IgG1 mAbs administered by IV infusion typically present low immunogenicity risk in the clinic (Davda, 2019). As such, 23ME-00610 is expected to present a low immunogenicity risk in humans. Because nonclinical assessments often fail to adequately predict immunogenicity in humans, immunogenicity risk, and subsequent impact on 23ME-00610 exposure, toxicity, PD, and activity, will be evaluated in this study.

4.5 End of Study Definition

The end of the study is defined as the date at which the last patient has withdrawn consent, has died, or been lost to follow-up.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

101. **Part A (Dose Escalation):** Adults ≥ 18 years of age
Part B (Expansion):
    a. **Cohorts 1-4 and 6:** Adults and adolescents ≥ 12 years of age, weighing ≥ 40 kg (total body weight)
    b. **Cohort 5: Adolescents** ≥ 12 to < 18 years of age, weighing ≥ 40 kg (total body weight)

102. Able to understand and willing to sign an informed consent. A legally authorized representative (e.g., parent or legal guardian) may consent on behalf of a patient who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's Institutional Review Board (IRB) or Ethics Committee (EC).

103. **Part A (Dose Escalation):** Histologically-diagnosed locally advanced (unresectable), or metastatic carcinoma or sarcoma that has progressed after all available standard therapy for the specific tumor type, or for which all available standard therapy has proven to be ineffective or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe (Note: Patients whose cancers harbor molecular alterations for which targeted therapy or immunotherapy is standard of care should have received local health authority approved appropriate therapy for their tumor type prior to enrollment).

    Part B (Expansion):

    a. **Cohort 1B:** Histologically-diagnosed locally advanced (unresectable) or metastatic ccRCC that has progressed following all available standard therapy (e.g., anti-PD(L)-1, anti-VEGF kinase inhibitors) or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

        For patients eligible for anti-PD(L)-1 and/or anti-VEGF kinase inhibitors treatment according to the local country-specific prescribing information for metastatic ccRCC, prior treatment with these agents is required.

        Adolescents that meet the criteria for both Cohort 1B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 1B following approval from the medical monitor at 23andMe.

    b. **Cohort 2B:** Histologically-diagnosed locally advanced (unresectable) or metastatic, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal carcinoma (i.e., disease recurrence within 6 months of completion of platinum-based therapy)

that has progressed following all available standard therapy, or if no further standard therapy exists. Patients who are platinum-refractory or for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

Patients with molecular alterations for which targeted therapy is the standard of care (e.g., PARP inhibitors) should have progressed following the appropriate targeted therapy. Treatment with PARP inhibitors should be offered in line with institutional practice (i.e., BRCA 1/2).

Cohort 2B will enroll ~13 patients with non-clear cell epithelial ovarian, fallopian tube or primary peritoneal carcinoma and ~2 evaluable patients with clear cell ovarian fallopian tube or primary peritoneal carcinoma (up to 15 total).

Adolescents that meet the criteria for both Cohort 2B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 2B following approval from the medical monitor at 23andMe.

c. **Cohort 3B**: The following histologically-diagnosed locally advanced (unresectable) or metastatic neuroendocrine cancers that have progressed following all available standard therapy, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

    i. Merkel cell carcinoma

    ii. Well-differentiated Grade 3 neuroendocrine cancers with unfavorable biology (Ki67 ≥ 55%, rapid growth rate, FDG-avid, negative SSR based on PET [as per NCCN Guidelines]) from any site

    iii. Poorly differentiated neuroendocrine carcinoma (or extrapulmonary large and small cell carcinoma)

    iv. Patients with other cancers that show evidence of focal neuroendocrine differentiation may be included with approval from the medical monitor at 23andMe.

    Adolescents that meet the criteria for both Cohort 3B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 3B following approval from the medical monitor at 23andMe.

d. **Cohort 4B:** Histologically-diagnosed locally advanced (unresectable) or metastatic solid cancer that has progressed following all available standard therapy, or if no further standard therapy exists and meets the following criteria:

    TMB-H solid cancer that has been confirmed by the FoundationOne CDx assay using a cutoff of ≥ 10 mutations/megabase (other industry/institutional equivalent platforms for TMB assessment are permitted) and/or MSI-H solid cancer that has been confirmed by immunohistochemistry for MMR proteins or PCR of microsatellites or MMR gene mutations by a next-generation sequencing (NGS) panel (e.g.

FoundationOne CDx, or industry/institutional equivalent that has been validated for diagnostic use).

Cohort 4B will aim to enroll ~15 patients, however this cohort may be overenrolled to ensure at least 5 patients have TMB ≥ 10 mutations/megabase, and at least 10 patients have either TMB ≥ 20 mutations/megabase or are MSI-H (irrespective of TMB-H status) within the cohort.

For patients eligible for anti-PD-1 treatment according to the local country-specific prescribing information for TMB-H and/or MSI-H cancer, prior treatment with anti-PD-1 is required.

Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

Patients with TMB-H and/or MSI-H primary CNS cancers are not eligible. Patients with TMB-H and/or MSI-H solid cancers that also meet the eligibility criteria for Cohorts 1B-3B should be enrolled in Cohort 4B. If there are no available slots in Cohort 4B at the time of enrollment, an exception may be made following approval from the medical monitor at 23andMe.

Adolescents that meet the criteria for both Cohort 4B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 4B following approval from the medical monitor at 23andMe.

e. **Cohort 5B:** In jurisdictions where local regulations and IRB/EC allows, adolescents with histologically-diagnosed locally advanced (unresectable), or metastatic solid cancer that has progressed after all available standard therapies for the specific tumor type, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

f. **Cohort 6B**: Histologically-diagnosed locally advanced (unresectable) or metastatic ES-SCLC that has progressed following all available standard therapy, or if no further standard therapy exists. Patients for whom standard therapies are intolerable or considered inappropriate are eligible with approval from the medical monitor at 23andMe.

   Adolescents that meet the criteria for both Cohort 6B and 5B should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescents may be enrolled in Cohort 6B following approval from the medical monitor at 23andMe.

104. Have a performance status as defined below:

- Adults and adolescents ≥ 16 years of age: Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Adolescents ≥ 12 to < 16 years of age: Lansky Play Scale ≥ 50

105. Life expectancy ≥ 12 weeks

106. **Part A (Dose escalation):** Patients without RECIST measurable disease (e.g., evaluable disease only) will be eligible for enrollment in Part A, regardless of tumor type.

Part B (Dose expansion): Patients enrolled in Part B must have measurable disease by per RECIST 1.1 and have ≥ 1 site of measurable disease that has not been previously irradiated. Patients with ≥ 1 site of measurable disease per RECIST 1.1 who have previously irradiated lesions that have progressed after radiation therapy are eligible. Tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

107. **Part A (Dose escalation):** An archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening must be provided unless an exemption is granted by the medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

Patients enrolled in the PK/PD backfill cohort in Part A in whom collection of paired biopsies is judged to be safe and feasible by the investigator may consent to provide an optional fresh biopsy at screening and from the same lesion (if safe and feasible) approximately 4 to 6 weeks after the first dose of 23ME-00610.

Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

Part B (Expansion):

Cohorts 1B, 2B, 4B and 6B: Adult and adolescent patients ≥ 12 years of age must consent to provide an archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening unless an exemption is granted by the medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe. On-treatment biopsies will not be collected in these cohorts.

Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from the medical monitor at 23andMe.

Cohort 3B: Adult patients ≥ 18 years of age must be able to have paired biopsies collected for the study and must agree to provide a fresh biopsy during screening, and from the same lesion (if safe and feasible) at approximately 4 to 6 weeks after the first dose of 23ME-00610. Eligible patients will have lesions which are judged to be safe and feasible by the investigator for biopsies. Biopsies must be collected from a tumor lesion that has not been previously irradiated and tumor lesions planned for biopsy must not be followed as target lesions for disease assessments unless an exemption is granted from

the medical monitor at 23andMe. A recently collected biopsy with evaluable tumor tissue may be submitted in place of the Screening biopsy with approval from the medical monitor at 23andMe. Mandatory paired biopsies will not be collected from adolescent patients.

In addition, adult and adolescent patients ≥ 12 years of age must consent to provide an archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening unless an exemption is granted by the Medical Monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening for adolescent patients ≥ 12 years of age if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

Cohorts 5B: An archival paraffin-embedded, formalin-fixed tumor sample that is no more than 6 months old at the time of screening must be provided unless an exemption is granted by the medical monitor at 23andMe. An optional fresh biopsy may be collected at the time of screening for adolescent patients ≥ 12 years of age if an archival tumor sample is not available, if judged to be safe and feasible by the investigator with approval from the Medical Monitor at 23andMe.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Pregnancy/Breastfeeding/Contraception

201. Females who are pregnant (positive pregnancy test within 7 days prior to study drug administration) or breastfeeding. Females of childbearing potential who engage in heterosexual intercourse and males who are sexually active with female partners of childbearing potential must agree to use a highly effective form of contraception (e.g., females: male partner sterilization, estrogen/progestogen or progestogen-only hormonal contraceptives associated with inhibition of ovulation (oral, intravaginal, transdermal), IUDs, intrauterine hormone-releasing systems; males: male condoms, vasectomy) throughout the study, starting with the time of consent and for at least 90 days after the last dose of study drug. Females of childbearing potential are those who have begun menstruating. In order to be considered NOT of childbearing potential, female patients must have had a hysterectomy or bilateral oophorectomy or be 1 year post-menopause or have had amenorrhea for a period of 12 months or longer in the absence of chemotherapy, anti-estrogens, or ovarian suppression. Male patients must not donate sperm throughout the study period.

Immune-Related Medical History

202. Active autoimmune disease that has required systemic disease-modifying or immunosuppressive treatment within the last 2 years. Stable, medically managed autoimmune endocrinopathies are acceptable if the patient otherwise meets entry criteria. Therefore, patients with thyroid and adrenal disorders that are stable on replacement therapy are permitted.

203. Receipt of systemic immunosuppressive therapy (e.g. steroids) within 4 weeks prior to the start of study drug administration. Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the patient is on a stable dose for at least 3 months. (Note: Corticosteroid premedication for contrast allergy is permitted.)

204. History of idiopathic pulmonary fibrosis, interstitial lung disease, organizing pneumonia, non-infectious pneumonia that required steroids, or evidence of active, non-infectious pneumonitis. (Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by medical monitor at 23andMe)

205. History of Grade ≥ 3 immune-mediated toxicity considered related to prior immunotherapy and that led to treatment discontinuation.

206. Prior allogeneic bone marrow transplant, or other solid organ transplant.

207. Receipt of any live vaccine within 30 days prior to the start of study drug administration.

208. Receipt of inactive or mRNA-based vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 5 days prior to the start of study drug administration or during the 21-day DLT period in Part A. For patients enrolled in Part B and following the 21-day DLT period for patients enrolled in Part A, receipt of inactive or mRNA-based vaccines for SARS-CoV-2 is permitted during the study if the vaccine is not administered within 5 days of study drug administration.

209. Patients with symptoms suggestive of active coronavirus disease 2019 (Covid-19) prior to study entry must have a negative molecular or antigen test for SARS-CoV-2 using an FDA-authorized test to be eligible for enrollment. Patients with a current positive molecular or antigen test for SARS-CoV-2 using an FDA-authorized test are not eligible for enrollment.

210. Any active uncontrolled systemic bacterial, viral or fungal infection requiring treatment, excluding exceptions noted below in exclusion criteria 211, 212 and 213.

211. History of a positive test for hepatitis C virus (HCV) infection, except for those who have completed curative therapy for HCV and have undetectable HCV RNA (< LLOQ [lower limit of quantitation]). HCV testing is required during screening for patients whose HCV status is unknown.

212. History of a positive test for hepatitis B virus (HBV) infection, except for those who are receiving treatment with HBV-active nucleos(t)ide antiviral therapy at the time of study entry and have undetectable HBV DNA (< 20 IU/mL). HBV testing is required during screening for patients whose HBV status is unknown.

213. History of a positive test for Human Immunodeficiency Virus (HIV) infection, except those who meet the following criteria: CD4+ T cells ≥ 350 cells/μL, no history of Acquired Immunodeficiency Syndrome (AIDS)-defining opportunistic infections, HIV RNA < 50 copies/mL, and on a stable antiretroviral regimen for at least 3 months. HIV testing is required during screening for patients whose HIV status is unknown.

214. Known hypersensitivity to 23ME-00610 or any of its excipients. See Table 12 for the list of excipients.

Prior Anticancer Therapy

215. Prior anticancer therapy, including chemotherapy, targeted therapy, biological therapy or immune-checkpoint inhibitors within 4 weeks or 5 drug half-lives (whichever is shorter) prior to the start of study drug administration.

216. Prior therapy directly targeting CD200 or CD200R1

217. Adverse events from prior therapy that have not either returned to baseline or stabilized at Grade ≤ 1 (except alopecia, hearing loss, vitiligo, endocrinopathy managed with replacement therapy, and ≤ Grade 2 neuropathy) prior to study drug administration.

218. Patients who haven't recovered from Grade 2 or higher clinically significant radiation therapy-related toxicities before study drug administration. (Note for patients enrolled in Cohort 3B: At least 1 non-irradiated lesion must be available for collection of paired biopsy samples. In addition, patients must have ≥ 1 site of measurable disease for assessment via RECIST 1.1. Patients with ≥ 1 site of measurable disease per RECIST 1.1 who have previously irradiated lesions that have progressed after radiation therapy are eligible.)

219. Patients who haven't recovered from Grade 2 or higher clinically significant major surgery-related adverse events and/or complications before study drug administration.

220. Use of investigational drugs within 4 weeks or 5 drug half-lives (whichever is shorter) before the start of study drug administration

Other Medical History

221. History of another malignancy in the previous 2 years, unless cured by surgery alone and continuously disease free. Exceptions include appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage 1 uterine cancer, localized prostate cancer that has been treated surgically with curative intent and presumed cured, or other malignancies with an expected curative outcome. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the study drug may be included if approved by the medical monitor at 23andMe.

222. Uncontrolled or symptomatic CNS metastases and/or carcinomatous meningitis. Note: Patients with previously treated brain metastases may participate provided they are asymptomatic (any neurologic symptoms have returned to baseline), radiographically stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment), have no evidence of new or enlarging brain metastases, and are clinically stable off steroids with a stable dose of anticonvulsants (if required) for at least 4 weeks prior to study treatment. Patients with carcinomatous meningitis or leptomeningeal spread are excluded regardless of clinical stability. (Note: Imaging of the brain during screening is required in patients with a history of brain metastases, or signs / symptoms that are suggestive of brain metastases. A brain MRI is required at screening for patients with SCLC irrespective of whether the brain is a site of known disease.)

223. History of any of the following cardiovascular diseases:

    a. Recent history (within the past 6 months) of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third-degree atrioventricular node block

    b. Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment

    c. Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system

    d. Recent history (within the past 6 months) of symptomatic pericarditis

224. QTcF > 470 msec. QTcF is QT corrected for heart rate according to Fridericia's correction formula ($QTc = QT/RR^{0.3}$) and can be machine calculated or manually over-read.

225. Screening laboratory values that do not meet the criteria in Table 11. Patients with lymphocyte counts below the threshold defined in Table 11 may be included with discussion and approval by the medical monitor at 23andMe.

Table 11 Laboratory Criteria that Represent Adequate Organ Function

Parameter[a]	Laboratory Values
Hematologic[b]	
Absolute neutrophil count	$\geq 1.5 \times 10^9$/L
Lymphocyte count	≥ 0.6/mm^3
Hemoglobin	≥ 8 g/dL
Platelets	$\geq 100 \times 10^9$/L
Renal	
eGFR	
Adults[c]	≥ 30 mL/min
Adolescents[d]	≥ 30 mL/min/1.73m^2
Hepatic	
Total bilirubin	
Adults	$\leq 1.5 \times$ ULN (except patients with Gilbert's syndrome who must have total bilirubin ≤ 3.0 mg/dL)
Adolescents	$< 1.5 \times$ ULN for age
AST and ALT	Both $\leq 2.5 \times$ ULN (except patients with liver metastases / tumor infiltration where the limits are $\leq 5 \times$ ULN)
Endocrine	
TSH[e]	Within institutional normal limits
Morning cortisol[f]	Within institutional normal limits
Cardiac	
Ejection fraction[g]	$\geq 50\%$ by echocardiogram or within institutional normal limits

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; G-CSF = granulocyte-colony stimulating factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] Screening laboratory values apply to both adults and adolescents unless otherwise stated.

[b] Hematologic criteria must be met without transfusion of blood products (including platelets or red blood cells) or administration of G-CSF for at least 14 days prior to sample collection.

[c] eGFR to be calculated using Cockgroft-Gault equation for adults (see Appendix 5)

[d] eGFR to be calculated per modified Schwartz equation for adolescents (see Appendix 5)

[e] If TSH is not within normal limits at baseline, the patient may still be eligible if: total T3 or free T3 and free T4 are within normal limits , or if the patient is asymptomatic with discussion and approval from the medical monitor at 23andMe or designee.

[f] Cortisol levels are not required for patients with primary adrenal tumors (e.g., adrenocortical carcinoma) or adrenal disorders that are stable on replacement therapy. If cortisol is not WNL at baseline. the patient may still be eligible if asymptomatic and no clinical suspicion of adrenal disorders with discussion and approval from the medical monitor at 23andMe or designee.

[g] MUGA scan is acceptable if echocardiography is not standard practice at the clinical site.

Consent and Protocol Compliance

226. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is a member of the study site or Sponsor staff directly involved with this study, unless

prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific patient.

227. Patients with any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.

228. Any condition that in the opinion of the investigator would interfere with evaluation of the investigational product or interpretation of the patient's safety or study results

5.3 Lifestyle Considerations

There are no constraints on lifestyle considerations for this study.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to a dose-level cohort. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if approved by the Medical Monitor at 23andMe. Patients who are found to be eligible but are not able to enroll due to administrative reasons (eg. no dose-level cohort is open for enrollment) may be rescreened at a later date. Rescreened patients will be assigned a new patient number.

6 STUDY INTERVENTION

6.1 Study Intervention

1. 23ME-00610 will be administered IV to patients over approximately 30 minutes (see Pharmacy Manual for further details) under medical supervision of an investigator or designee. The infusion time may be adjusted as clinically indicated.

2. The Pharmacy Manual will provide details on product administration as well as specific instructions for the calculation of the 23ME-00610 dose, preparation of the 23ME-00610 infusion and for administration of the infusion, including the duration of the infusion.

Table 12 23ME-00610 Dosage and Administration

Intervention Name	23ME-00610
Type	Biologic
Dose Formulation	Each 1 mL of solution contains 50 mg of drug and is formulated in 20 mM L-Histidine, 8% w/v sucrose, and 0.04% w/v polysorbate 80, pH 6.0.
Unit Dose Strength(s)	200 mg/4 mL (50 mg/mL)
Dosage Level(s)	Up to 1400 mg Q3W
Route of Administration	Intravenous infusion
Sourcing	Provided centrally by the study Sponsor (23andMe)
Packaging and Labeling	Study Intervention will be provided in a frozen 10 mL glass Schott vial which is closed with a RayDylo® cap and contains a volume of 4 mL/vial (with an overfill of 0.48 mL). Each vial will be labeled as required per country requirement.

Q3W = every 3 weeks

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention (see Pharmacy Manual for further details).
2. Only patients enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Enrollment and Cohort Assignment

This is an open-label, competitive enrollment study. In Part A (Dose-Escalation phase) of the study, an IRT system will be used to assign eligible patients to the currently enrolling dose-level cohort on their Day 1 visit or within the 24-hours prior to their Day 1 visit. If more than one cohort is open at a time, patients will be assigned to one of the open cohorts. Adolescents that meet the criteria for more than one cohort should be enrolled into Cohort 5B. If Cohort 5B is not open for enrollment, adolescent patients that meet the criteria for Cohort 1B, 2B, 3B, 4B or 6B should be enrolled into the disease-specific cohort following approval from the medical monitor at 23andMe.

6.4 Prior and Concomitant Therapy

6.4.1 Prior Therapy and Procedures

All medications administered and procedures conducted within 28 days prior to the first day of study drug administration are to be recorded on the eCRF. In addition, all prior treatments for the underlying malignancy should be recorded.

6.4.2 Prohibited Concomitant Therapy

Use of the following therapies or vaccines is prohibited unless otherwise specified below:

- Any investigational agent.
- Any concomitant therapy intended for the treatment of the advanced malignancy under investigation, including chemotherapy, radiation therapy (unless administered palliatively with approval from the medical monitor at 23andMe), radiotherapy, immunotherapy, targeted therapy, biologic therapy, or hormone therapy other than for replacement.
- Receipt of live vaccines is prohibited within 30 days prior to the start of study drug administration and throughout the study.
- Receipt of inactive or mRNA-based vaccine for SARS-CoV-2 is prohibited within 5 days prior to the start of study drug administration or during the 21-day DLT period in Part A. For patients enrolled in Part B and following the 21-day DLT period for patients enrolled in Part A, receipt of inactive or mRNA-based vaccines for SARS-CoV-2 is permitted during the study if the vaccine is not administered within 5 days of study drug administration.
- Transfusion of blood products (including platelets or red blood cells) or administration of G-CSF within 14 days prior to collection of screening laboratory samples

The concomitant medications described above do not need to be avoided while patients are no longer receiving 23ME-00610 (i.e., the survival follow-up period).

6.4.3 Permitted Concomitant Therapy

Medications and treatments other than those specified above are permitted during this study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to the acceptable local standards of medical care. Patients should receive analgesics, antiemetics, anti-infectives, and antipyretics, etc as necessary.

Steroids: Use of steroids is permitted for the treatment of AEs (as specified in Section 6.5 and Appendix 2) while the patient is receiving study drug. Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the patient is on a stable dose for at least 3 months. Use of steroids as premedication for contrast-enhanced computed tomography (CT) in patients with contrast allergy is permitted.

Bisphosphonates and RANK-L inhibitors: The use of bisphosphonates and RANK-L inhibitors is permitted while participating in this study if the patient has been on a stable dose for at least 4 weeks prior to the first dose of study drug. Initiation of bisphosphonates and RANK-L inhibitors during the study for the management of toxicity is permitted if agreed upon by the investigator and medical monitor at 23andMe.

Somatostatin analogs: Use of somatostatin analogs is permitted while participating in this study provided the patient has been on a stable dose for at least 2 months prior to the first dose of study drug and has had documented disease progression while on this dose.

In general, patients should not be treated prophylactically for gastrointestinal (GI) AEs (i.e., diarrhea, nausea, vomiting, etc). Initiation of treatment is permitted during the study for GI toxicity management.

If a toxicity that can be prevented or managed with premedication and/or supportive care measures occurs within a cohort, the SRC can implement requirements regarding these procedures/treatments for subsequent patients in the cohort.

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that the patient is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor at 23andMe and/or designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.5 Dose Modification and Safety Management Guidelines

Safety management and dose modification guidelines are provided below in Sections 6.5.1 to 6.5.3. Management of irAEs from the joint American Society of Clinical Oncology (ASCO) are provided in Appendix 2 for patients treated with 23ME-00610. Sites are encouraged to use site-specific standard of care practice of medicine and/or institutional management guidelines to supplement the guidelines provided below at the investigator's discretion. Therefore, these guidelines are not mandatory except where the investigator is directed to discontinue study drug permanently.

When restarting or rechallenge is permitted as noted in the ASCO guidelines, 23ME-00610 will be administered at the same dose, based on consultation with the medical monitor at 23andMe. For patients who experience a ≥ Grade 3 irAE, retreatment with study drug at the same dose may be considered on a case-by-case basis if agreed upon by the investigator AND medical monitor at 23andMe.

For patients who experience a recurrence of the same AE(s) or SAE at the same grade or higher with rechallenge of study drug, a consultation between the medical monitor at 23andMe and the investigator should occur to determine whether the patient should continue in the study.

Investigators must contact the medical monitor at 23andMe and/or designee for all ≥ Grade 2 study drug related toxicities within 48 hours. Investigators are encouraged to contact the medical monitor at 23andMe and/or designee as needed to discuss any case that requires discussion that is outside of the scope of the clinical guidelines.

All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

6.5.1 Potential Immune-Related Adverse Events and Supportive Care Measures or General Guidelines

23ME-00610 is an immune checkpoint inhibitor and thus administration of 23ME-00610 may be associated with immune-mediated AEs.

An irAE is defined as a clinically significant AE of any organ that is associated with exposure to study drug, is of unknown etiology, and is consistent with an immune-related mechanism. Onset of irAEs can occur shortly after the first dose, later after several doses have been administered, or several months after the last dose of treatment (Ramos-Casals 2020).

The majority of irAEs are reversible with the use of steroids and other immune suppressants (Pardoll, 2012; Weber, 2012). Thus, early detection of irAEs and initiation of treatment are critical in mitigating their severity and reducing the risk of complications. If an irAE is suspected, the patient should return to the study site as soon as possible. Patients who experience a new or worsening irAE should be contacted and/or evaluated at the study site more frequently.

If an irAE is suspected, a thorough evaluation should be conducted in an effort to rule out neoplastic, infectious, metabolic, or other etiologies before diagnosing the irAE. Serological, immunological, and histological (e.g., biopsy) data should be considered to support the diagnosis

of an immune-related toxicity. Consultation with an appropriate medical specialist should be considered when investigating a potential irAE.

Immune-related AEs most frequently occur in the pituitary and thyroid glands, the colon, lungs, liver, and the skin. They may also affect other organs like the CNS, cardiovascular, musculoskeletal, and hematologic systems (Dolladille, 2020). Mild (Grade 1) irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate interrupting or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents when systemic steroids are not effective.

Details of considerations relating to specific subtypes of irAEs are described below, and the ASCO clinical practice guidelines for dose modification and management of irAEs are provided in Table 13 to Table 20 and Appendix 2.

Gastrointestinal Adverse Events (Diarrhea or Colitis)

Signs and symptoms of GI events may include, but are not limited to diarrhea, constipation, abdominal pain, cramping and/or bloating, nausea and/or vomiting, blood and/or mucus in stool with or without fever, rectal bleeding, peritoneal signs consistent with bowel perforation, and ileus. Refer to Table 13 and the ASCO clinical practice guidelines (Appendix 2) for the management of diarrhea and colitis.

Attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer.

Table 13 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related GI AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Diarrhea/ colitis	Grade 1	Continue	Monitor for dehydration and recommend dietary changes. Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged Grade 1 cases

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 2	Hold until improvement to ≤ Grade 1	Concurrent immunosuppressant maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for Grade 2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to Grade 1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment with study drug, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases Grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming study drug Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of Grade 2 or higher to differentiate functional vs inflammatory diarrhea, and use calprotectin to monitor treatment response if investigator prefers Repeat colonoscopy is optional for cases of Grade 2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume study drug
	Grade 3	Hold temporarily until improvement to ≤ Grade 1	Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or non-corticosteroid (e.g., infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (i.e., cytomegalovirus [CMV] colitis) and for those who are anti-TNF or corticosteroid refractory Discuss with medical monitor at 23andMe.

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 4	Permanently discontinue	Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/day methylprednisolone or equivalent until symptoms improve to Grade 1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections Discuss with medical monitor at 23andMe.

Liver Adverse Events

In the event of treatment-emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis, and other infectious causes, choledocholithiasis, hepatic metastases, and myositis should be investigated. Concomitant medications known to be hepatotoxic that may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function.

AST or ALT ≥3-fold the upper limit of normal (ULN) and concomitant bilirubin ≥2 fold the ULN (> 35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury. If liver injury is suspected, alcohol use should be recorded in the eCRF. Liver dysfunction must be fully evaluated even if the clinical signs and symptoms indicate progression of tumor lesions in the liver. Imaging studies must be obtained to document potential progression of malignancy.

See Table 14 and the ASCO clinical practice guidelines (Appendix 2) for additional information regarding management and follow-up.

Table 14 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Liver AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Hepatitis	Grade 1	Continue	• Consider alternate etiologies • Monitor laboratories one to two times weekly • Manage with supportive care for symptom control
	Grade 2	Hold until improvement to ≤ Grade 1 or prednisone dose is ≤ 10 mg/day	• For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/day prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days • Increase frequency of monitoring to every 3 days • Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) • In follow-up, may resume study drug followed by taper only when symptoms improve to Grade 1 or less and corticosteroid ≤ 10 mg/day; taper over at least 1 month • Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
	Grade 3	Permanently discontinue	• Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent • If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) • Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 x ULN and/or elevated total bilirubin 3 x ULN • Increase frequency of monitoring to every 1-2 days • Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants • Refer to hepatologist for further pathologic evaluation of hepatitis

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			• Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear • Discuss with Medical Monitor at 23andMe
	Grade 4	Permanently discontinue	• Administer 2 mg/kg/day methylprednisolone equivalents • If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil • Monitor laboratories daily; consider inpatient monitoring • Avoid the use of infliximab in the situation of immune-mediated hepatitis • Hepatology consult if no improvement was achieved with corticosteroids • Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to Grade 1 or less; re-escalate if needed; optimal duration unclear • Consider transfer to tertiary care facility if necessary • Discuss with Medical Monitor at 23andMe

Skin-Related Adverse Events

Attempts should be made to rule out other causes of skin toxicity such as metastatic disease, infection, allergic dermatitis, an effect of a concomitant medication, or a skin condition linked to another systemic disease or unrelated primary skin disorder.

For specific skin toxicities, refer to the ASCO clinical practice guidelines (Table 15 and Appendix 2). For all grades, a diagnostic work-up should include relevant medical history and physical examination, blood tests as needed (including blood cell count, liver and kidney tests), and directed serology if an autoimmune condition is suspected. Skin biopsy and clinical photography should be performed when clinically indicated.

Table 15 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Skin AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Rash/inflammatory dermatitis	Grade 1	Continue	Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
	Grade 2	Hold until improvement to ≤ Grade 1	Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high- potency topical corticosteroids
	Grade 3	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks Discuss with Medical Monitor at 23andMe
	Grade 4	Hold until improvement to ≤ Grade 1 and prednisone dose is ≤ 10 mg/day. Consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Discuss with Medical Monitor at 23andMe
Bullous dermatoses	Grade 1	Continue	Observation and/or local wound care
	Grade 2	Hold and consult with Medical Monitor at 23andMe to determine	Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
		appropriateness of resuming study drug	Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease Initiate class 1 high-potency topical corticosteroid (e.g., clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with Grade 2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Discuss with Medical Monitor at 23andMe
	Grade 3	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc. Discuss with Medical Monitor at 23andMe
	Grade 4	Permanently discontinue	Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc Discuss with Medical Monitor at 23andMe

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Severe cutaneous adverse reactions, including, but not limited to, Stevens-Johnson Syndrome (SJS), acute generalized exanthematous pustulosis and drug-induced hypersensitivity syndrome (DIHS) / drug reaction with eosinophilia and systemic symptoms (DRESS)	Grade 2	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	Monitor patients closely every 3 days with Gade 2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high- strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks Discuss with Medical Monitor at 23andMe
	Grade 3	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g., ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate) Discuss with Medical Monitor at 23andMe
	Grade 4	Permanently discontinue	Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			IV immunoglobulin or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations Discuss with Medical Monitor at 23andMe

Endocrine Adverse Events

Signs and symptoms of endocrine-related AEs may include, but are not limited to, fatigue, weakness, headache, mental status and/or behavior changes, fever, visual disturbances, cold intolerance, abdominal pain, unusual bowel habits, loss of appetite, nausea and/or vomiting, and hypotension. Endocrine events may include the following: adrenal insufficiency, hyperthyroidism, hypophysitis, hypopituitarism, hypothyroidism, thyroid disorder, and thyroiditis.

Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and/or electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes an adrenal crisis and is considered a medical emergency.

See Table 16 and the ASCO clinical practice guidelines (Appendix 2) for guidance regarding specific endocrine events.

Table 16 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Endocrine AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Primary hypothyroidism	Grade 1	Continue	• Close follow-up and monitoring of TSH and free T4
	Grade 2	Hold until symptoms resolve to baseline	• Consider endocrine consultation • Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) • Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH; free T4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the free T4 was initially low • Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on study drug or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
	Grade 3 and 4	Hold until symptoms resolve to baseline with appropriate supplementation	• Endocrine consultation • May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) • Thyroid supplementation and reassessment as in Grade 2 primary hypothyroidism
Hyperthyroidism	Grade 1	Continue	• Close follow-up and monitoring of TSH, free T4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see above)
	Grade 2	Hold until symptoms resolve to baseline	• Consider endocrine consultation • Beta-Blocker (e.g., atenolol, propranolol) for symptomatic relief • Hydration and supportive care • Corticosteroids are not usually required to shorten duration

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			• For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (thyroid stimulating immunoglobulin or thyroid-stimulating hormone receptor antibody) and consider thionamide (methimazole or propylthiouracil) • Refer to endocrinology for Graves disease • Discuss with Medical Monitor at 23andMe
	Grade 3 and 4	Hold until symptoms resolve to baseline with appropriate therapy	• Beta-Blocker (e.g., atenolol, propranolol) for symptomatic relief • For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/day or equivalent tapered over 1-2 weeks; consider also use of potassium iodide or thionamide (methimazole or propylthiouracil). • Discuss with Medical Monitor at 23andMe
Primary Adrenal Insufficiency	Grade 1	Hold until stabilized on replacement hormone	• Endocrine consultation • Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) • May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency • Titrate dose up or down as symptoms dictate
	Grade 2	Hold until stabilized on replacement hormone	• Endocrine consultation • Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20 to 30 mg in the morning, and 10 to 20 mg in the afternoon) to manage acute symptoms. • Taper stress-dose corticosteroids down to maintenance doses over 5-10 days • Maintenance therapy as in Grade 1 above.

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 3 and 4	Hold until stabilized on replacement hormone	• Endocrine consultation • See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) • Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge • Maintenance therapy as in Grade 1 above • Discuss with Medical Monitor at 23andMe
Hypophysitis	Grade 1	Hold until stabilized on replacement hormones	• Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (e.g., hydrocortisone 10 to 20 mg orally in the morning, 5 to 10 mg orally in early afternoon; levothyroxine by weight) • Testosterone or estrogen therapy as needed in those without contraindications • Endocrine consultation • Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities with or without new severe headaches or complaints of vision changes • Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis • Follow free T4 for thyroid hormone replacement titration (TSH is not accurate)
	Grade 2	Hold until stabilized on replacement hormones	• Endocrine consultation • Hormone supplementation as in Grade 1 hypophysitis above • Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities with or without new severe

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			headaches or complaints of vision changes
	Grade 3 and 4	Hold until stabilized on replacement hormones	• Endocrine consultation • Hormone supplementation as in Grade 1 hypophysitis above • Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities with or without new severe headaches or complaints of vision changes • Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks • Discuss with Medical Monitor at 23andMe
Diabetes	Grade 1	Continue	• Close clinical follow-up and laboratory evaluation • May initiate oral therapy for those with new-onset Type 2 Diabetes Mellitus (T2DM) • Screen for Type 1 Diabetes Mellitus (T1DM) if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
	Grade 2	Hold until glucose control is obtained	• Titrate oral therapy or add insulin for worsening control in T2DM • Should administer insulin for T1DM (or as default therapy if there is confusion about type) • Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice • Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 3 and 4	Hold until improvement to ≤ Grade 1 and glucose control is obtained with therapy	• Urgent endocrine consultation for all patients • Initiate insulin therapy for all patients • Admit for inpatient management: concerns for developing diabetic ketoacidosis, symptomatic patients regardless of diabetes type, new-onset T1DM unable to see endocrinology • Discuss with Medical Monitor at 23andMe

Pneumonitis

Signs and symptoms of pneumonitis may include, but are not limited to, dyspnea, dry cough, hemoptysis, fever, chest pain and/or tightness, abnormal breath sounds, and fatigue. If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered. Pneumonitis events may include the following: pneumonitis, interstitial lung disease, and acute interstitial pneumonitis.

Attempts should be made to rule out other causes such as metastatic disease and bacterial or viral infection. It is important that patients with a suspected diagnosis of pneumonitis be managed as specified in the ASCO clinical practice guidelines (Table 15, Appendix 2) until treatment-related pneumonitis is excluded. If an alternative diagnosis is established, the patient does not require management as detailed in the ASCO clinical practice guidelines (Table 17, Appendix 2). Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.

Table 17 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Pneumonitis

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Pneumonitis	Grade 1	Hold if radiographic evidence of pneumonitis progression	• May offer one repeat CT scan in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks • May resume study drug with radiographic evidence of improvement or resolution. If no improvement, should treat as Grade 2 below • Monitor patients weekly with history and physical examination and pulse oximetry; may also offer chest X-ray
	Grade 2	Hold until improvement to ≤ Grade 1	• Prednisone 1-2 mg/kg/day and taper by 5-10 mg/week over 4-6 weeks • Consider bronchoscopy with bronchoalveolar lavage • Consider empirical antibiotics • Monitor every 3 days with history and physical examination and pulse oximetry, consider chest X-ray • If no clinical improvement after 48-72 hours of prednisone, treat as Grade 3 below
	Grade 3 and 4	Permanently discontinue	• Empirical antibiotics; (methyl)prednisolone IV 1−2 mg/kg/day; if no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IV immunoglobulin for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks • Pulmonary and infectious disease consults if necessary • Bronchoscopy with bronchoalveolar lavage +/- transbronchial biopsy • Patients should be hospitalized for further management • Discuss with Medical Monitor at 23andMe

Hematologic Adverse Events

Dose modification and management guidelines for hematologic AEs are provided in Table 18. For further information about work-up and management of specific hematologic events, refer to ASCO clinical practice guidelines (Appendix 2).

Table 18 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Hematologic AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Autoimmune hemolytic anemia	Grade 1	Continue	• Close clinical follow-up and laboratory evaluation
	Grade 2	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	• Administer 0.5-1 mg/kg/day prednisone equivalents • Discuss with Medical Monitor at 23andMe
	Grade 3	Permanently discontinue	• Should use clinical judgment and consider admitting the patient • Hematology consult • Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms/speed of development) • If worsening or no improvement, 1-2 mg/kg/day prednisone equivalents • Consider red blood cell (RBC) transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hemoglobin range (7-8 g/dL in stable, noncardiac inpatients) • Should offer patients supplementation with folic acid 1 mg once daily • Discuss with Medical Monitor at 23andMe
	Grade 4	Permanently discontinue	• Admit patient • Hematology consult • IV prednisone corticosteroids 1-2 mg/kg/day • If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IV immunoglobulin, cyclosporin A, and mycophenolate mofetil

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			• RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible immune checkpoint inhibitor serious AE is in house.
Acquired thrombotic thrombocytopenic purpura (TTP)	Grade 1 and 2	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	• Hematology consult • Administer 0.5-1 mg/kg/d prednisone
	Grade 3 and 4	Permanently discontinue	• Hematology consult • In conjunction with hematology, initiate plasma exchange (PEX) according to existing guidelines with further PEX dependent on clinical progress • Administer methylprednisolone 1 gram IV daily for 3 days, with the first dose typically administered immediately after the first PEX • May offer rituximab
Hemolytic uremic syndrome	Grade 1 and 2	Continue	• Close clinical follow-up and laboratory evaluation • Supportive care
	Grade 3 and 4	Permanently discontinue	• Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks • Red blood transfusion according to existing guidelines
Aplastic anemia	Grade 1	Hold until improvement to ≤ Grade 1	• Provide growth factor support and close clinical follow-up, and laboratory evaluation • Supportive transfusions as per local guidelines

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 2	Hold until improvement to ≤ Grade 1	• Provide growth factor support and close clinical laboratory evaluations daily • Administer antithymocyte globulin (ATG) + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered • Supportive care with granulocyte colony-stimulating factor may be added in addition
	Grade 3 and 4	Hold until improvement to ≤ Grade 1	• Monitor weekly for improvement; if not resolved, discontinue study drug until AE has reverted to Grade 1 • Hematology consult, growth factor support • Horse ATG plus cyclosporine • If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide • For refractory patients, consider eltrombopag plus supportive care
Lymphopenia	Grade 3	Continue	• Checking CBC weekly for monitoring, initiation of CMV screening
	Grade 4	Hold until improvement to ≤ Grade 1 and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	• Initiate Mycobacterium avium complex prophylaxis and Pneumocystis jirovecii prophylaxis, CMV screening. HIV/hepatitis screening if not already done • May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease • Discuss with Medical Monitor at 23andMe
Immune thrombocytopenia	Grade 1	Continue	• Close clinical follow up and laboratory evaluation
	Grade 2	Hold until improvement to ≤ Grade 1	• Administer prednisone 1 mg/kg/day (dosage range, 0.5-2 mg/kg/d) orally for 2−4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose • IV immunoglobulin may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
	Grade 3 and 4	Hold until improvement to ≤ Grade 1	• Hematology consult Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms) • If worsening or no improvement, 1-2 mg/kg/day prednisone equivalents and permanently discontinue treatment • IV immunoglobulin used with corticosteroids when a more-rapid increase in platelet count is required • If IV immunoglobulin is used, the dose should initially be 1 gram/kg as a one-time dose. This dosage may be repeated if necessary • If previous treatment with corticosteroids and/or IV immunoglobulin unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia; consult for further details) • Discuss with Medical Monitor at 23andMe
Acquired hemophilia	Grade 1	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	• Administer 0.5-1 mg/kg/day prednisone • Transfusion support as required • Treatment of bleeding disorders with hematology consult • Discuss with Medical Monitor at 23andMe
	Grade 2	Hold and consult with Medical Monitor at 23andMe to determine appropriateness of resuming study drug	• Hematology consult • Administration of factor replacement (choice based on Bethesda unit of titer) • Administer 1 mg/kg/day prednisone with or without rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/day); choice of rituximab versus cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			• Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor • Discuss with Medical Monitor at 23andMe
	Grade 3 and 4	Permanently discontinue	• Admit patient • Hematology consult • Administration of factor replacement, choice based on Bethesda unit level of inhibitor • Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease • Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms) with or without rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/day). • Transfusion support as required for bleeding • If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption

Ocular Adverse Events

Attempts should be made to rule out other causes of uveitis or iritis such as metastatic disease, infection, or other ocular disease (e.g., glaucoma or cataracts). Table 19 and Appendix 2 presents guidance regarding the management of uveitis and iritis.

Table 19 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Ocular AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Uveitis/Iritis	Grade 1	Continue	• Refer to ophthalmology within 1 week • Artificial tears
	Grade 2	Hold until improvement to ≤ Grade 1 with no use of corticosteroids for ocular AEs or prednisone dose is ≤ 10 mg/day for other concurrent irAEs	• Urgent ophthalmology referral • Topical corticosteroids, cycloplegic agents, systemic corticosteroids • Continued topical/ocular corticosteroids are permitted when resuming study drug to manage and minimize local toxicity
	Grade 3	Permanently discontinue	• Urgent ophthalmology referral. • Systemic corticosteroids and intravitreal/periocular/topical corticosteroids • Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment
	Grade 4	Permanently discontinue	• Emergent ophthalmology referral • Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion • Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment

Cardiovascular Adverse Events

Signs and symptoms of cardiovascular irAEs may include chest pain, arrythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion and fatigue. Table 20 and Appendix 2 presents guidance regarding the management of cardiovascular irAEs.

Table 20 Dose Modification and Management Guidelines for Study Drug-Related Immune-Related Cardiovascular AEs

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
Myocarditis, pericarditis, arrythmias, impaired ventricular function with heart failure and vasculitis	Grade 1, 2, 3 and 4	Permanently discontinue	• All grades warrant work-up and intervention given potential for cardiac compromise • High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV • depending on symptoms) • Admit patient, cardiology consultation • Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology • Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities • In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 gram every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin • Discuss with Medical Monitor at 23andMe
Venous thromboembolism	Grade 1	Continue	• Warm compress • Clinical surveillance
	Grade 2 and 3	Continue	• Management according to CHEST, ACC, and/or AHA guidelines and • Consider consult from cardiology or other relevant specialties • LMWH is suggested over vitamin K agonist, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment • IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
		Permanently discontinue	• Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology • Respiratory and hemodynamic support • LMWH is suggested over vitamin K agonist, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment

irAE	NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management
			• IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term • Further clinical management as indicated based on symptoms

Refer to ASCO clinical practice guidelines (Appendix 2) for further information about work-up and management of other specific irAEs.

6.5.2 Guidelines for Infusion Reactions and Cytokine Release Syndrome

6.5.2.1 Infusion Reactions and Cytokine Release Syndrome

Infusion reactions may affect any organ system in the body and can occur following administration of mAbs. Most infusion reactions are mild in severity, however severe or life-threatening reactions can occur. Signs and symptoms usually develop during or within a few hours of mAb infusion and generally resolve within 24 hours of following the end of the infusion. Guidelines for dose modifications and management of infusion reactions associated with 23ME-00610 are shown in Table 21.

Cytokine release syndrome (CRS) is a non–antigen-specific toxicity that occurs because of strong immune activation and has been identified as sequelae of immune system activation associated with infusion reactions (Shimabukuro-Vornhagen, 2018). Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.

The NCI-CTCAE v5 grading scale will be utilized when determining the grade of CRS in this study (see Appendix 3 for NCI-CTCAE v5 toxicity grading scale). Since there is a commonality in the clinical presentation of infusion reactions and CRS, the guidelines for management and immediate treatment are the same (Table 21).

Table 21 Dose Modification and Management Guidelines for 23ME-00610-Related Infusion Reactions and Cytokine Release Syndrome

NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management	Follow-Up
Grade 1	Continue infusion	• Increase monitoring of vital signs as clinically indicated until the patient is medically stable. • The patient should be closely monitored until resolution of symptoms. • Additional appropriate medical therapy may include but is not limited to: o IV fluids o antihistamines (e.g., diphenhydramine) o acetaminophen o NSAIDs	• Prophylactic medications before subsequent infusions of study drug may be considered and must be discussed with the medical monitor at 23andMe.
Grade 2	**Stop infusion of study drug**	**Monitor Symptoms.** • Additional appropriate medical therapy may include but is not limited to: o IV fluids o antihistamines (e.g., diphenhydramine) o acetaminophen o NSAIDs o narcotics • Increase monitoring of vital signs as medically indicated. The patient should be closely monitored until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician. • Consider administration of etanercept or tocilizumab [Lee, 2014].	• When symptoms resolve, restart the infusion at 50% of the original infusion rate; if there are no further complications after 30 minutes, the rate may be increased to 100% of the original infusion rate. • Monitor patient closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Treat symptoms and continue to monitor the patient closely until resolution of symptoms. • Further administration of study drug should be discussed with medical monitor at 23andMe. • Prophylactic medications should be given before all subsequent infusions of study drug. • Patient may be premedicated with diphenhydramine 50 mg orally (or equivalent) and/or acetaminophen

NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management	Follow-Up
			325 to 1000 mg orally at least 30 minutes before additional study drug administrations. • Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.
Grade 3 or Grade 4	**Stop infusion of study drug**	• Additional appropriate medical therapy may include but is not limited to: ○ Epinephrine[a] ○ Bronchodilators ○ IV fluids ○ Corticosteroids (methylprednisolone 100 mg IV or equivalent) ○ Antihistamines (e.g., diphenhydramine) ○ Acetaminophen ○ NSAIDs ○ Narcotics ○ Oxygen ○ Pressors • Consider administration of etanercept or tocilizumab [Lee, 2014]. • Consider additional intervention in consultation with the investigator and the medical monitor at 23andMe. • Increase monitoring of vital signs as clinically indicated until patient is medically stable. The patient should be closely monitored until resolution of symptoms. • Hospitalization may be indicated.	• The amount of study drug infused must be recorded in the eCRF. • No further study drug will be administered, unless approved by the investigator AND medical monitor at 23andMe (criteria for rechallenge include but are not limited to patients who are receiving compelling benefit with study drug that exceeds risk, and no effective alternative treatment is available).

Abbreviations: eCRF = electronic case report form; IV = intravenous(ly); NSAID = nonsteroidal anti-inflammatory drug.

[a] In cases of anaphylaxis, epinephrine should be used immediately. Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

6.5.3 Other Potential Adverse Events and Supportive Care Measures or General Guidelines

Although specific guidance is provided for irAEs in Section 6.5.1 and Appendix 3, it is possible that other clinically significant study drug-related AEs that are not specifically described may occur and warrant dose modification as shown in Table 22.

Table 22 General Dose Modification and Management Guidelines for Study Drug-Related Nonhematologic Adverse Events Not Otherwise Specified

NCI-CTCAE v5 Toxicity Grade	Action To Be Taken with Study Drug	Management	Follow-Up
Grade 1	• Continue	• Administer symptomatic treatment as appropriate.	***Symptoms resolve to baseline within 7 days:*** • Provide close follow-up to evaluate for increased severity. ***Symptoms ongoing > 7 days:*** • Consider following instructions for Grade 2 events.
Grade 2	• Hold until improvement to ≤ Grade 1 and steroid dose is ≤ 10 mg/day prednisone	• Administer symptomatic treatment. • Investigate etiology. • Consider consulting subspecialist, biopsy, and/or diagnostic procedure. • Discuss with medical monitor at 23andMe.	***Symptoms ongoing > 7 days or worsening*** • Consider starting moderate dose systemic corticosteroids (e.g., 0.5 mg/kg/day of prednisone or equivalent). • Continue steroids until improvement to Grade 1 or resolution; taper steroids as medically appropriate. • If symptoms continue or worsen to Grade 3 or Grade 4, see below.
Grades 3 and 4	• Permanently discontinue	• Consult subspecialist. • Administer 1-2 mg/kg/day IV methylprednisolone. • Discuss with medical monitor at 23andMe.	***Symptoms improve to ≤ Grade 2:*** • Continue steroids until improvement to ≤ Grade 1 or baseline; taper steroids over at least 1 month • If symptoms resolve to ≤ Grade 1 or baseline, retreatment with study drug at the same dose may be considered on a case-by-case basis if agreed upon by the investigator AND medical monitor at 23andMe. ***Symptoms ongoing:*** • Discuss further management with medical monitor at 23andMe. • Consider alternative immunosuppressive therapy.

6.5.4 Dose Delay

Administration of 23ME-00610 may be delayed for treatment-related AEs or for other reasons such as medical/surgical events or logistical reasons not related to treatment with study drug.

If there is a dose delay of 7 days or less, the procedures at the originally scheduled visit (including dosing) should be performed as soon as possible in accordance, when applicable, with the dose modification and safety management guidelines specified in Section 6.5.

If the delay is greater than 7 days, the dose(s) will be considered 'on hold', and a "Restart of Treatment" visit should be performed as described in the SoA (Section 1.3). Once this visit is performed and the patient is considered to be in appropriate health to continue on study drug by the investigator, the next scheduled treatment visit should be performed.

Anticancer activity assessments, including tumor assessments, should be collected as scheduled in reference to Day 1 and should not be adjusted in response to treatment delays. Patients with dose delays greater than 6 weeks (equivalent to 2 cycles) due to toxicity should permanently discontinue study drug unless the treating investigator and medical monitor at 23andMe agree there is strong evidence to support continued treatment. For patients requiring elective surgery or palliative radiation therapy, surgery or radiation therapy should be initiated at least 1 week after the last dose of study drug, if possible. Study drug should not be administered again until at least 1 week after recovery from surgery or radiation. The investigator must inform the medical monitor at 23andMe of any elective surgery or palliative radiation therapy, surgery, or radiation therapy prior to restarting or continuing study drug.

6.6 Intervention after the End of the Study

The study intervention will not be available to study patients at the end of study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue study intervention in certain circumstances, including if the patient experiences a Dose-Limiting Toxicity. If study drug is permanently discontinued, the patient will continue to be followed.

See the Schedule of Activities (Table 3, Table 4, and Table 5) for data to be collected at the time of study drug discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Stopping Rules for the Study

The stopping rules for the dose escalation phase (Part A) of the study are defined in Section 4.1.1.

The SRC will review all safety data from the study as described in Section 4.2.1.2. The study, or individual expansion cohorts, may be stopped if the SRC or the Sponsor or regulatory authorities determine there is excessive toxicity or a demonstrated lack of clinical benefit that does not support an appropriate benefit-risk for continued investigation in this phase 1/2a oncology patient population.

The stopping rules for clinical deterioration for individual patients in the study are described in Section 7.2.1 below.

7.2.1 Stopping Rules for Clinical Deterioration

Accumulating clinical evidence indicates that the emergence of objective responses to immune checkpoint inhibitors may follow delayed kinetics of weeks or months. The potential delay in tumor regression can be preceded by an initial apparent progression with the appearance of new lesions or increase in some lesions while certain index lesions are regressing thereby producing an overall "mixed response." Therefore, to make an adequate assessment of the antitumor effect of immunotherapeutic agents, it is reasonable to allow patients experiencing apparent progression as defined by RECIST 1.1 guidelines (Appendix 4) to continue to receive treatment until progression is confirmed at the next imaging assessment at least 4 weeks later as indicated by iRECIST guidelines (Appendix 4). These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued study drug.

In cases where deterioration was assessed to have occurred after a clinical event that, in the investigator's opinion, is attributable to disease progression and is unlikely to reverse with continued study drug or managed by supportive care (e.g., bisphosphonates and/or bone-directed radiotherapy, thoracentesis, or paracentesis for accumulating effusions), study drug should be discontinued. The decision to stop treatment should be discussed with the medical monitor at 23andMe. Examples of events that may, in the investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- ECOG PS decrease of at least 2 points from baseline for patients ≥ 16 years age and Lansky Play scale decrease of at least 40 points from baseline for patients < 16 years of age (Appendix 5).
- Skeletal-related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement
  - cancer-related surgery to bone, and/or
  - spinal cord or nerve root compression
- Development of new CNS metastases
- Any setting where the initiation of new antineoplastic therapy has been deemed beneficial to the patient even in the absence of any such documented clinical event.

7.3 Temporary Discontinuation

Dose modification guidelines, including instructions for temporary discontinuation, are provided in Section 6.5.

7.4 Rechallenge

Dose modification guidelines, including instructions for rechallenge, are provided in Section 6.5.

7.5 Patient Discontinuation/Withdrawal from Study

- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator.
- At the time of discontinuing from the study, if possible, an end of treatment visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- Patients may be permanently discontinued from study drug or withdraw consent from treatment but continued to be monitored for follow-up assessments. Patients may also withdraw consent for treatment and any study assessments/procedures but be requested to be followed for outcomes/survival information.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study entirely (withdraws consent for further collection/use of their data), he/she may request destruction of any samples that have been collected but not yet analyzed, and the investigator must document this in the site study records.

7.6 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. Where permitted, if the patient has consented and provided information for a third-party contact for survival confirmation/follow-up, the investigator should contact the third-party to determine status.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.7 Patient Replacement

Patients who are lost to follow-up, withdraw from the study, or are discontinued from study treatment may be replaced within any given cohort in Parts A and B with Sponsor approval to ensure sufficient data is available for a given cohort. Patients who do not remain on study to be evaluated for efficacy in Part B may be replaced at the discretion of the medical monitor at 23andMe.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the medical monitor at 23andMe immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Screening Assessments

Following informed consent, all patients will undergo screening procedures within 28 days prior to the start of study drug treatment to determine eligibility as outlined in the SoA (Table 3, Table 4, and Table 5).

All patients are required to have locally advanced (unresectable) or metastatic solid cancer in Part A and meet the disease-specific criteria specified for each expansion cohort in Part B. Additional screening procedures include medical, surgical, and medication history; complete physical examination; vital signs; age-appropriate performance status; 12-lead ECG; evaluation of the left ventricular ejection fraction; clinical laboratory assessments (thyroid function tests, morning cortisol, hematology, chemistry, coagulation, urinalysis, and pregnancy test, HIV/HBV/HCV screening); staging CT scan; Tanner stage (adolescents only); and blood and saliva samples (Part A only) for pharmacokinetic, exploratory pharmacodynamic and genotypic assessments. Additionally, an optional fresh tumor biopsy sample may be collected from adult patients in the dose-escalation phase in Part A and adolescent patients in Part B if an archival tumor sample is not available. A mandatory fresh tumor tissue biopsy sample will be collected from adult patients enrolled in Cohort 3B in the expansion phase. In Parts A and B, availability of an archival tumor tissue biopsy sample should be confirmed and collected at screening.

8.2 Clinical Activity Assessments

All patients will have the extent of their disease assessed during screening by a staging MRI/CT scan (contrast-enhanced is preferred but not required) of the lower neck (i.e., supraclavicular nodal region), chest, abdomen, and pelvis at a minimum, according to RECIST version 1.1

(Eisenhauer, 2009) (Appendix 4). Chest MRI/CT scans which include the lower neck region meet this requirement and a separate scan of the neck is not required. Any additional regions such as head, neck or extremities should also be imaged if disease or symptoms are present. A brain MRI (contrast-enhanced is preferred but not required) is required in patients with a history of brain metastases, or signs / symptoms that are suggestive of brain metastases and is also required at screening for patient with SCLC irrespective of whether the brain is a site of known disease. Historical scans acquired within the 28-day screening window that meet the aforementioned criteria can be provided in lieu of a new baseline scan. After screening, tumor measurements and disease response measurements are to be performed for patients who have measurable disease every 8 weeks thereafter while on study drug treatment, and at the end of treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. iRECIST (Seymour, 2017) (Appendix 4) will be used by the investigator to assess tumor response in patients that can continue study drug treatment beyond initial progressive disease as defined by RECIST 1.1.

RECIST 1.1 will be used in the assessment of disease burden (target and nontarget lesions determination) at Screening and as the primary measure of tumor response endpoints. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions.

All tumor images will be obtained and transmitted to a central imaging vendor for potential central review. Digital copies of all scans (Digital Imaging and Communications in Medicine [DICOM] formatted and preferably noncompressed) are to be stored at the study site as source documents. The process for tumor imaging, anatomical coverage, modalities, and transmission to the central imaging vendor are detailed in the imaging manual. Disease assessment modalities may include imaging (e.g., CT scan, MRI) and physical examination (as applicable for palpable/superficial lesions).

The same imaging modality (e.g., where possible, the same scanner, scanning technique and the use of contrast) should be used for a patient throughout the study to optimize reproducibility and accuracy of assessment of existing and new tumor burden.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. All patients will undergo safety assessments during the treatment period to include non-directive questioning regarding adverse events, physical examination, vital signs, 12-lead ECGs, and clinical laboratory assessments.

8.3.1 Clinical Safety Laboratory Assessments

- See Appendix 1 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the electronic case report form (eCRF). The laboratory reports must be filed with the source documents.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor at 23andMe.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.4 Age-Appropriate Performance Status and Tanner Stage Assessment

Planned timepoints for age-appropriate performance status score and Tanner Stage assessment (for adolescents < 18 years of age only) are provided in the SoA.

8.5 Third-Party Contact Information

Where permitted, patients will be asked to provide information for a third-party contact such as a caregiver, relative, or general physician who may be contacted for survival status/follow-up if the patient is unable to be contacted during the study.

8.6 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative). The investigator and any qualified designees are responsible for asking the patient about experiencing any AEs at the time points specified in the SoA (Section 1.3).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue from the study intervention and/or study overall (see Section 7).

8.6.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start of first dose of study drug until the final follow-up visit (Day 90). AEs and SAEs related to study procedures during the screening period should also be recorded.

All SAEs will be recorded and reported electronically in the electronic data capture (EDC) system to Medpace Clinical Safety immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will record any updated SAE data in the EDC system to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.6.2 Method of Reporting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.6.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-serious AEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.6.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.6.5 Pregnancy

- Details of all pregnancies which occur in female patients and female partners of male patients will be collected after the start of study intervention and until 90 days post-dose.
- If a pregnancy is reported, the investigator must inform Medpace Clinical Safety within 24 hours of learning of the pregnancy and follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.6.6 Death Events

For all deaths, irrespective of whether they are considered SAEs, death sections of the eCRF will be required to be completed.

The death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.6.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in patients with solid malignancies and can be serious/life-threatening:

- Disease progression
- Hospitalization due to disease progression or events clearly related to disease progression

Because these events are typically associated with the disease under investigation, they will not be reported according to the standard process for expedited reporting of SAEs to Medpace Clinical Safety even though the event may meet the definition of a SAE. Death due to the disease under investigation is to be recorded in the eCRF. These DREs will be monitored by a Safety Review Committee on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.7 Treatment of Overdose

There is no specific information on overdose of 23ME-00610. For this study, an overdose of 23ME-00610 is defined as administration of more than the protocol-specified dose.

23andMe does not recommend specific treatment for an overdose of 23ME-00610.

In the event of an overdose, the investigator/treating physician should:

1. Immediately interrupt the infusion and administer supportive therapy (if indicated).
2. Contact the medical monitor at 23andMe immediately.
3. Closely monitor the patient for any AE/SAE and laboratory abnormalities for at least 3 weeks.
4. Obtain a blood sample for PK analysis within 3 days (where possible) from the date of the last dose of study intervention if requested by the medical monitor at 23andMe (determined on a case-by-case basis).
5. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor at 23andMe based on the clinical evaluation of the patient.

8.8 Pharmacokinetics

Serial PK blood samples for evaluation of 23ME-00610 concentration will be collected at the visits listed in Table 5 for each patient in Part A and Part B. See Section 4.3 for rationale for the collection of PK samples.

Single PK blood samples will also be collected from all patients as described in Table 5.

The following PK parameters of 23ME-00610 will be estimated, as appropriate, for patients with serial PK samples: AUC_{inf} (first dose), AUC_{tau} (multiple-dose), AUC_{last}, accumulation index, C_{max}, C_{last}, C_{tau}, CL, Lambda z (first dose), T_{max}, $T_{1/2}$ and Vz.

PK data from patients with serial and sparse PK sampling may be combined with data from other studies for exposure-response or population PK analyses.

Samples collected for analyses of 23ME-00610 serum concentration may also be used to evaluate safety, anticancer activity, and/or biomarkers.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the study laboratory manual(s). The actual date and time (24-hour clock time) of each sample will be recorded.

8.9 Immunogenicity

Blood samples for evaluation of ADA to 23ME-00610 will be collected for each patient in Part A and Part B as described in Table 5. See Section 4.3 for rationale for the collection of immunogenicity samples.

8.10 Biomarkers

Collection of samples for other biomarker research is also part of this study. See Section 4.3 for rationale for the collection of biomarker samples. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA:

8.10.1 Pharmacodynamics

Blood samples for evaluation of pharmacodynamic biomarkers (target engagement, soluble pathways components, cytokines) will be collected for each patient in Part A and Part B as described in the SoA (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor in the study laboratory manual(s).

8.10.2 Genetic Assessments

8.10.2.1 Host Genetic Assessments

Saliva will be collected to genotype nucleated cells found within the saliva using 23andMe's validated genotyping platform. These samples will be used to evaluate genotypic information, which will be correlated with adverse event information and clinical outcomes on the single genetic variant or polygenic level (which includes polygenic risk scores for autoimmune and other phenotypes) to evaluate the potential predictive value of these genetic variants.

In addition, or if genotyping on saliva samples fails, blood PBMCs may be used to perform host genotyping using 23andMe's genotyping platform or other DNA sequencing approaches. See Section 4.3 for rationale for the collection of the saliva genotyping sample.

8.10.2.2 Tumor Genetic Assessments

To enable determination of genetic changes, MMR status and TMB in the tumors of patients, and their kinetics following administration of 23ME-00610, blood samples to isolate cell free DNA will be collected. In addition, or in cases where no cell free DNA can be isolated, the archival and/or biopsy tumor samples may be used to isolate DNA for central confirmation of TMB-H/MSI-H status and baseline tumor genetic changes, where appropriate. DNA may be isolated from PBMC samples to enable determination of genetic variants in the tumor as

applicable. Instructions for the collection and handling of biological samples will be provided by the Sponsor in the study laboratory manual(s).

8.10.3 RNAseq

The effect of 23ME-00610 on immune-relevant gene expression will be evaluated in tumor tissue and/or blood samples to confirm mechanism of action.

8.10.4 Archival Tissue and Tumor Biopsies

Archival tumor samples from all patients in Part A and B (or fresh optional biopsy at baseline if an archival sample is not available, where appropriate), and fresh biopsy samples from adult patients ≥18 years of age in Part A and B at baseline and following 2 cycles of treatment (approximately 4-6 weeks after the first dose of 23ME-00610 from the same lesion where feasible) will be collected to determine target pathway expression and changes in the immune environment elicited by 23ME-00610, using immunohistochemistry and/or RNA quantification approaches. Baseline tumor samples may be used to isolate DNA to evaluate the relationship between tumor mutation parameters and anticancer activity.

8.10.5 Proteome Research

Blood samples will be collected to determine baseline levels and longitudinal changes in CD200R1 pathway components as well as peripheral cytokine levels elicited by 23ME-00610. In addition, PBMC will be isolated from patient blood at various time point to allow analysis of immune cell protein surface expression and changes therein induced by 23ME-00610.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The statistical analyses described in this protocol will be primarily descriptive in nature. This study is designed to establish the safety of 23ME-00610 in patients with advanced solid tumors. No inferential statistical hypotheses will be tested. Any reported statistics and statistical comparisons will be interpreted as exploratory.

9.2 General Methods

Data collected during the study will be presented in summary tables and graphical figures, as appropriate. Tabular summaries will be produced for appropriate disposition, demographic, baseline disease characteristics, safety, PK, PD, and clinical activity parameters. Tabular summaries produced for Part A will be grouped by dose level and overall. Tabular summaries produced for Part B will be grouped by tumor type (i.e., cohort) and dose level, as appropriate. Safety summaries will combine results across Part A and Part B by dose level, with the exception of adolescent patients who will be summarized separately. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). For time-to-event variables, percentages of patients experiencing that event will be presented and median time-to-event will be estimated using Kaplan-Meier methodology. As appropriate, a 90% CI will be presented. Graphical displays will be presented, as appropriate. All study results will be presented in by-patient data listings.

9.3 Sample Size Determination

This is a Phase 1/2a, 2-part dose escalation and expansion study. Part A will include a dose escalation design where patients with advanced solid cancers will be treated with 23ME-00610 at increasing dose levels, followed by 5 monotherapy expansion arms in Part B to further evaluate the safety, tolerability, PK, PD, and clinical activity of 23ME-00610. The study is not statistically powered. The sample size was determined to provide evidence of safety, PK, PD, and initial clinical activity while limiting unnecessary patient exposure.

In Part A, an expected 20 adult patients will be treated at up to 7 dose levels during dose escalation. Additional patients may be needed for cohort expansion and intermittent dose evaluation in Part A. To further evaluate PK and PD in Part A, additional patients may be enrolled in a PK/PD backfill cohort (up to a total of 12 patients, including the 3 to 6 patients initially enrolled during dose escalation) following SRC approval at the RP2D/MTD or a previously evaluated dose level. A total of 20-28 patients are expected in Part A, with the total enrolled depending on the number needed to sufficiently characterize the MTD/RP2D.

In Part B, approximately 83-113 patients will be enrolled and a total of 103-141 will be enrolled in the study. (Note: More than one dose may be selected for expansion into Part B.)

9.4 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Pharmacokinetic (PK) Population	The Pharmacokinetic population consists of all patients who receive any amount of study drug and have at least one measurable postdose serum 23ME-00610 concentration.
Pharmacodynamic (PD) Population	The Pharmacodynamic population consists of all patients who receive any amount of study drug and have sufficient data to derive at least one pharmacodynamic parameter for inclusion in the respective analyses.
Immunogenicity (I) Population	The Immunogenicity population consists of all patients who receive any amount of study drug and have a non-missing baseline ADA result and at least one non-missing post-dose ADA result.
Dose-Limiting Toxicity (DLT) Evaluable	The Dose-Limiting Toxicity (DLT) Evaluable population consists of all patients who are enrolled in the Dose-Escalation Phase and complete the study follow-up through the DLT evaluation period or experience a DLT. The DLT evaluable population will be used for the MTD/RP2D evaluation.
Safety	The Safety Population consists of all patients who received any amount of study drug. Patients will be grouped according to the dose level received.
Efficacy	The Efficacy Evaluable Population consists of patients in Safety Population with baseline (i.e., pre-dose) tumor measurements and at least one post-baseline tumor response assessment or clinical assessment if determined to be disease progression or death prior to the first post baseline tumor assessment.

The PK, PD and I population will be used for PK, PD, and Immunogenicity endpoint analyses, respectively. Safety will be summarized on the Safety Population. Clinical Activity will be analyzed using the Efficacy Population with the exception of OS which will be analyzed using the Safety Population, regardless of whether patients have tumor measurements collected. Additional populations may be described in the study Statistical Analysis Plan (SAP).

9.5 Statistical Analyses

A detailed SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1 Safety Analyses

Safety analyses will be performed on the Safety Population. A subset of safety parameters may be summarized on the DLT evaluable population for support of MTD and dose selection for expansion in Part B.

Treatment-Emergent Adverse Events (TEAEs) are defined as any adverse events AEs that begin or worsen on or after the start of study drug through 90 days after the last dose of study drug. Frequency and percentages of subjects with TEAEs, DLTs, treatment-related TEAEs (those considered by the investigator to be related to study drug), Serious TEAEs (SAEs), discontinuations due to AEs, and AEs of at least Grade 3 severity will be reported overall and by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

By-patient listings will be provided for all AEs, deaths, SAEs, DLTs, and AEs leading to discontinuation of treatment.

Descriptive statistics of actual values and changes from baseline will be provided for clinical laboratory parameters, ECG interval results (including QTcF) where measured, and vital signs. Changes to last on-study value may also be reported. Shift tables from baseline to worst and to last observation on study will be presented for laboratory parameters. Clinically significant laboratory abnormalities will be listed.

Use of concomitant medications will be listed.

All safety data will be listed in by-patient data listings.

9.5.2 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses

PK Endpoints	Statistical Analysis Methods
PK Parameters	PK parameters (e.g., AUC, C_{max}, C_{tau}, T_{max}, $T_{1/2}$) of 23ME-00610 will be summarized using descriptive statistics for Part A and Part B by cohort, dose level and cycle. Graphical representations may be presented.
Drug Concentration	Drug concentrations of 23ME-00610 over time will be listed for each patient and summarized using descriptive statistics separately for Part A and Part B at each time point by cohort, dose level and cycle.
Dose Proportionality	Summary statistics will be tabulated by cohort, dose level and cycle for Part A and Part B separately. PK concentrations from sparse samples will be listed. Dose proportionality will be assessed by comparing PK parameters (e.g., AUC and C_{max}) across the dose cohorts in Part A using a power model to evaluate the population mean slope based on its 90% confidence interval (CI).

PK concentration data from this study may be used in combination with other studies for exposure-response or population PK analyses. The potential relationship between 23ME-00610 and clinical activity, safety endpoint, and/or PD biomarkers may be explored using descriptive and/or graphical methods.

PD Endpoints	Statistical Analysis Methods
PD Parameters	Pharmacodynamic measures (target engagement, target cell modulation, soluble biomarkers, cytokines) will be listed for individual patients and summarized using descriptive statistics for 23ME-00610 by cohort and/or dose level over time.

Immunogenicity Endpoints	Statistical Analysis Methods
Antidrug Antibody	Prevalence and incidence of antidrug antibodies (ADA) to 23ME-00610 will be summarized
	The frequency and percentage of patients with positive and negative immune response results may be summarized for each assessment time and overall for each patient separately for Part A and Part B by cohort and dose level. A summary of frequency and percentage of patients with positive results may be determined for all patients that received 23ME-00610. Additional analyses, including the relationship between immunogenicity and safety may be conducted, as appropriate.

All PK, PD, and immunogenicity results will be presented in by-patient data listings.

9.5.3 Clinical Activity Analyses

Clinical Activity will be analyzed using the Efficacy Population among patients with baseline (i.e., pre-dose) tumor measurements and at least one post-baseline tumor response assessment or clinical assessment if determined to be disease progression. Summarized results will be presented by dose level and expansion cohort, as appropriate. OS will be analyzed using all patients in the Safety Population, regardless of whether they have tumor measurements collected.

Endpoint	Statistical Analysis Methods
Antitumor Response	Clinical Activity will be assessed by the site investigators using RECIST version 1.1. Antitumor response will be summarized by best overall response categories, ORR (best response confirmed CR + confirmed PR) and DCR (best response confirmed CR + confirmed PR + SD). Response rates will be accompanied by 90% confidence intervals.
Durability of Response	Clinical activity duration measurements, including time to overall response (time from first treatment to first response of CR or PR), duration of response (time from first occurrence of CR or PR to disease progression or death), PFS (time from first treatment to disease progression or death), and OS (time from first treatment to death) will be summarized using Kaplan-Meier methods. Summary statistics including 25th percentile, median (50th percentile), 75th percentile of durations with corresponding 90% confidence intervals will be presented.

Clinical activity summaries will also be presented for iRECIST endpoints. Additional detail will be provided in the SAP.

9.6 Interim Analyses

While no formal interim analyses are planned beyond the scope of the SRC, interim reporting may occur to summarize safety, PK, PD, immunogenicity, and/or clinical activity endpoints. As no statistical hypothesis testing methods are planned, no type I error adjustments are required. Further detail will be provided in the SAP.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines:

      The investigator must obtain IRB/EC approval for the conduct of this clinical trial and must submit written documentation of the approval to the Sponsor before he or she can enroll any patient into the study. The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC. The IRB/EC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions are to be provided to the IRB/EC according to local regulations and guidelines.
    - Applicable ICH Good Clinical Practice (GCP) Guidelines:

      The investigator will be fluent with the appropriate use of the study drug as described in the protocol and Investigator's Brochure (IB). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Patient Confidentiality

In order to maintain patient privacy, all source documents/eCRFs, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Protocol Compliance

The investigator will conduct the study in compliance with the protocol. Modifications to the protocol must not be made without agreement of both the investigator and the Sponsor. Changes to the protocol will require written IRB/EC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/EC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB/EC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the medical monitor at 23andMe, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

Financial Disclosure

Include text related to financial disclosure if not included in another document.

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative (LAR) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the

IRB/IEC or study center. Patients under 18 years of age will also sign an informed assent form.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- Patients who are rescreened are required to sign a new ICF.

Data Protection

- Patients will be assigned a unique identifier (study code) by the Sponsor. Any patient records or study-related datasets that are transferred from the clinical site to the Sponsor will contain the identifier only.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for approval of the CSR and relevant reports and will have the opportunity to review the complete study results at a Sponsor site or other mutually agreeable location.
- The Sponsor will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with patients who participated in the study, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary will be in accordance with local regulations.

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator

is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained and kept secure by the investigator for a period of two years following marketing of the investigational product or for two years after study centers have been notified that the IND has been discontinued, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Data Management

All data for the patients recruited for the trial will be entered onto the eCRFs via an EDC system provided by the Sponsor or designee. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Electronic case report forms will be checked for correctness against source document data by the Sponsor’s monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the eCRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Direct Access to Source Data

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. Remote review of source documents may occur as required e.g. due to COVID-19 related restrictions. The review of source documents and medical records, whether at the study center or through remote review, will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, email, and fax).

All unused study drug and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed, as directed by the Sponsor.

Regulatory authorities, the EC/IRB, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for an on-site or remote audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator

- Discontinuation of further study intervention development

Publication Policy

- All information regarding 23ME-00610 supplied by the Sponsor or designee to the investigator is confidential information of the Sponsor. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of 23ME-00610 and, if necessary, a companion diagnostic device and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX 1 CLINICAL LABORATORY TESTS

- The tests detailed in Table 23 will be performed by the site local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 23 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit Red blood cell indices: MCV, MHC, reticulocytes White blood cell count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical Chemistry	BUN Creatinine Glucose Potassium Sodium Calcium Amylase Lipase AST ALT Alkaline phosphatase Total and direct bilirubin Total protein Albumin
Thyroid Function	Thyroid stimulating hormone Free T4 Free or total T3 (per local or institutional standard)
Morning Cortisol	Cortisol
Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick
Coagulation Tests	INR/PT PTT
Other	Serology (e.g., HBsAg, HCV and HIV antibody/antigen testing) HCV RNA[a] HBV DNA[b] HIV RNA[c] CD4 lymphocyte count[c] hCG Pregnancy test[d]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CD4 = cluster of differentiation 4; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] As applicable for patients with a diagnosis of hepatitis C, or per institutional screening viral testing standard.

[b] As applicable for patients with a diagnosis of hepatitis B, or per institutional screening viral testing standard.

[c] Applies only to patients with a diagnosis of HIV.

[d] Urine or blood pregnancy test. Applies only to female patients of childbearing potential.

Investigators must document their review of each laboratory safety report.

APPENDIX 2 AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINES

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ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose
To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events in patients treated with immune checkpoint inhibitor (ICPi) therapy.

Methods
A multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, trialist, and advocacy was convened to develop the clinical practice guideline. Guideline development involved a systematic review of the literature and an informal consensus process. The systematic review focused on guidelines, systematic reviews and meta-analyses, randomized controlled trials, and case series published from 2000 through 2017.

Results
The systematic review identified 204 eligible publications. Much of the evidence consisted of systematic reviews of observational data, consensus guidelines, case series, and case reports. Due to the paucity of high-quality evidence on management of immune-related adverse events, recommendations are based on expert consensus.

Recommendations
Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert to grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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ASSOCIATED CONTENT

Appendix
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Data Supplement
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INTRODUCTION

Immune checkpoint inhibitors (ICPis) have revolutionized the treatment of many different types of cancers. These inhibitors work by blocking pathways called checkpoints. These checkpoint pathways are mechanisms for the human immune system to control the immune response. The immune checkpoint proteins cytotoxic T-lymphocyte–associated-4 (CTLA-4) and programmed cell death protein 1 (PD-1) are

THE BOTTOM LINE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Question

How should clinicians manage immune-related adverse events (irAEs) in adult patients with cancer treated with immune checkpoint blockade antibodies?

Target Population

Adult patients with cancer receiving treatment with immune checkpoint blockade inhibitors alone.

Target Audience

Health care practitioners, including oncologists, medical specialists, emergency medicine, family practitioners, nurses, and pharmacists, who provide care to patients with cancer as well as patients receiving immune checkpoint inhibitors (ICPis) and their caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

The following are general recommendations that should be followed irrespective of affected organs. For organ-specific management, see Tables 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10. (Note: Definition of grades are found in each table and, for the most part, follow the Common Terminology Criteria for Adverse Events [version 5.0]).[3]

It is recommended that clinicians manage toxicities as follows:

- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs prior to initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment related.
- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Hold ICPis for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone IV 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, with the exception of endocrinopathies that have been controlled by hormone replacement.

All recommendations in this guideline are based on expert consensus, benefits outweigh harms, moderate strength of recommendation.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

receptors expressed on the surface of cytotoxic T cells that interact with their ligands CD80/CD86 in the case of CTLA-4 and programmed death-ligand 1 (PD-L1) in the case of PD-1. These pathways can be co-opted to help cancer cells to evade cytotoxic T-cell–mediated death.[1] ICPis work by preventing the receptors and ligands from binding to each other, thereby disrupting signaling.[1]

Currently, there are several ICPis approved by the US Food and Drug Administration. Ipilimumab, an anti–CTLA-4 antibody, was the first agent approved for use in patients with advanced melanoma.[2] Pembrolizumab and nivolumab target PD-1 and have been approved for melanoma, metastatic non–small-cell lung cancer (NSCLC), head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, and mismatch-repair–deficient solid tumors as well as for classic Hodgkin lymphoma.[2] Nivolumab is approved for use for hepatocellular carcinoma and patients with renal cell carcinoma. The combination of ipilimumab and nivolumab for patients with advanced melanoma has also received US Food and Drug Administration approval.[2] Most recently, PD-L1 antibodies atezolizumab (approved for use in urothelial cancers and NSCLC), durvalumab (approved for use in urothelial cancers), and avelumab (approved for use in Merkel cell carcinoma and urothelial carcinoma) have also been developed to block the PD-1 pathway. The indications for use continue to expand at a rapid pace. Development of novel ICPi agents and combinations continue to be evaluated for multiple indications. Thus, this field is rapidly changing.

Despite the often durable clinical benefits of the immune checkpoint blockade therapy, ICPi use is associated with a spectrum of adverse effects related to the mechanism of action that is quite different from other systemic therapies such as cytotoxic chemotherapy. The adverse effects can affect multiple organs of the body and are most commonly seen in the skin; GI tract; lungs; and endocrine, thyroid, adrenal, pituitary, musculoskeletal, renal, nervous, hematologic, cardiovascular, and ocular systems, and there should be a high level of suspicion that any changes are treatment-related (Appendix Fig A1, online only). ICPi therapy can usually continue in the presence of mild immune-related adverse events (irAEs) with close monitoring. However, moderate to severe irAEs may be associated with severe declines in organ function and quality of life, and fatal outcomes have been reported; hence, these toxicities require early detection and proper management. Use of ICPis in patients with preexisting autoimmune disease or history of prior organ transplant requires an especially thoughtful discussion of potential risks and benefits.

In recognition of an increasing need for guidance, ASCO and the National Comprehensive Cancer Network partnered to develop guidelines on the management of irAEs. Organizational representation from the Society for Immunotherapy of Cancer, the American Society of Hematology, and the Oncology Nursing Society and informal collaboration with the Friends of Cancer Research and the Parker Institute helped to ensure coordination of efforts and a harmonization of recommended care options for this patient population. With the increasing use of immunotherapy in cancer treatment regimens, it is imperative that clinicians are knowledgeable about the symptoms associated with these agents, their recommended management, and how best to monitor for them.

GUIDELINE QUESTION

This clinical practice guideline addresses one overarching clinical question: How should clinicians manage irAEs in adult patients with cancer treated with immune checkpoint blockade antibodies?

METHODS

Guideline Development Process

A multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, trialist, and advocacy was convened to develop the clinical practice guideline (Appendix Table A1, online only). The Expert Panel met in person, via teleconference, and webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. All funding for the administration of this project was provided by ASCO.

ASCO guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee's Supportive Care Guideline Advisory Group.

Study eligibility was guided by the population, intervention, comparator, and outcome (PICO) framework as described in the Cochrane Handbook for Systematic Reviews of Interventions. In addition, the review took into account specific timing, setting, and study design as appropriate. The PICO criteria for the studies that were included in this review are as follows:

- Population: Adult patients with cancer receiving treatment with immune checkpoint blockade inhibitors alone (not in combination with chemotherapy)
- Intervention: Corticosteroids; immunosuppressive therapy; dose modification or discontinuation of therapy; organ-specific management, including hormone replacement, disease-modifying antirheumatic drugs (DMARDs), plasmapheresis, hospitalization, consultation to subspecialties, and best supportive care
- Comparator: No intervention or best supportive care
- Outcomes: Hospitalization, discontinuations of immunotherapy due to AE, AE-related morbidity or mortality, organ dysfunction based on organ system affected, required treatment due to irAEs, retreatment with immunotherapy, recovery from AEs, and health-related quality of life

The searches were designed and conducted by a team of expert medical librarians at Doctor Evidence in established clinical and medical bibliographic databases by using a range of Medical Subject Headings, EMTREE, and free-text terms based on the PICO criteria. All searches were peer reviewed by a senior Doctor Evidence (DOC) librarian. Bibliographic sources included MEDLINE In-Process via PubMed, Embase via OvidSP, and Cochrane Central Register of Control Trial via Wiley.

All study selection and screening were conducted using the DOC Library software platform (Doctor Evidence). DOC Library is a Web-based platform featuring duplicate removal, keyword emphasis (coloring or bolding of keywords), and search and ranking functionalities and can assign and manage reasons for exclusion. Before screening began, duplicate studies and those that did not meet language or date restrictions were excluded. Screening guidelines based on the protocol were then developed by consensus between methodology staff and the lead librarian and checked by a senior methodologist.

The screening procedure was conducted based on a two-step process: (1) title/abstract screening and (2) full-text screening. At both stages, the reasons for exclusion were documented. Full-text screening was conducted by two reviewers. Discrepancies between reviewers were resolved by an independent third reviewer. Articles were excluded from the systematic review if they were editorials, commentaries, letters, news articles, narrative reviews, or published in a non-English language.

The guideline recommendations are crafted, in part, by using the Guidelines Into Decision Support (GLIDES) methodology. In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice.

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/supportive-care-guidelines, including an overview (eg, panel composition, development process, revision dates), literature search and data extraction, recommendation development process, and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The Methodology Supplement (available at www.asco.org/supportive-care-guidelines) provides additional information about the signals approach to guideline updating.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

All abbreviations used in this Guideline can be found in Appendix Table A3, online only.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 38 systematic reviews and 166 primary studies met the eligibility criteria of the systematic review. Much of the evidence consisted of systematic reviews of observational data, consensus guidelines, case series, and case reports. Due to the limitations of the available evidence, the guideline relied on informal consensus for the recommendations. Use of formal consensus methodology was deemed unnecessary, favoring open discussion that allowed for articulation of views and opinions instead. Dissenting opinions, when raised, are noted.

RECOMMENDATIONS

Clinical Question

How should clinicians manage irAEs in adult patients with cancer treated with immune checkpoint blockade antibodies? All recommendations in this guideline are expert consensus based, with benefits outweighing harms, and a moderate strength of recommendation.

1.0 Skin Toxicities

Please refer to Table 1 for a complete set of recommendations, definition of grades, and additional considerations.

1.1 RASH/INFLAMMATORY DERMATITIS

Recommendation 1.1a – Diagnostic Work-up. It is recommended that for all grades, the diagnostic work-up should include the following:

- Pertinent history and physical examination.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder.
- A biologic checkup, including a blood cell count, liver, and kidney tests, may be performed if needed.
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody (ANA) test, SS-A/Anti-Ro, and SS-B/Anti-La if the rash is predominantly photodistributed or demonstrating photosensitivity. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered.
- Skin biopsy, clinical photography may be performed when indicated.

Table 1. Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)	
Diagnostic work-up Pertinent history and physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder If needed, a biologic checkup, including a blood cell count and liver and kidney tests Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms Skin biopsy Consider clinical monitoring with use of serial clinical photography Review full list of patient medications to rule out other drug-induced cause for photosensitivity	
Grading	**Management**
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction	
Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	**Management**
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations

(continued on following page)

Table 1. Management of Skin irAEs in Patients Treated With ICPis (continued)

1.0 Skin Toxicities	
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions: • Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements • Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug	
Diagnostic work-up Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis Consider following patients closely using serial clinical photography If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN	

(continued on following page)

Table 1. Management of Skin irAEs in Patients Treated With ICPis (continued)

1.0 Skin Toxicities	
Grading	Management
All grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

Abbreviations: ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; G, grade; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; NA, not applicable; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TENS, toxic epidermal necrolysis.

- Review full list of patient medications to rule out other drug-induced cause for photosensitivity.

Recommendation 1.1b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should treat skin with topical emollients (if predominately dry skin is observed) and/or mild to moderate potency (hydrocortisone 2.5% or equivalent to triamcinolone 0.1% or equivalent) topical corticosteroids (signs of inflammation/redness with or without itching).
- Should counsel patients to avoid skin irritants and sun exposure.

It is recommended that clinicians manage grade 2 toxicities, including intermittent pruritus, as follows:

- May hold ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 or less and consider dermatology referral.
- Should treat skin with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids.
- In addition, consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at least 4 weeks, depending on primary skin lesions observed on examination.

It is recommended that clinicians manage grade 3 toxicities, including constant pruritus, as follows:

- Should hold ICPi therapy and consult with dermatology, if available, to determine appropriateness of resuming.
- Should treat skin with topical emollients, oral antihistamines, and high-potency topical corticosteroids.
- Initiate intravenously (IV) (methyl)prednisolone (or equivalent) dosed at 1 to 2 mg/kg and taper over at least 4 weeks.
- If not resolved, refer to dermatology.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10 mg or less.

- Should administer IV (methyl)prednisolone (or equivalent) dosed at 1 to 2 mg/kg, with slow tapering when the toxicity resolves.
- Should monitor closely for progression to severe cutaneous adverse reaction (SCAR).
- Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology.
- Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to grade 1 or less. If ICPis are the patient's only option, consider restarting once these adverse effects have resolved to a grade 1 level.

1.2 Bullous Dermatoses

Recommendation 1.2a – Diagnostic Work-up. It is recommended that for all grades of irAEs the diagnostic work-up should include the following:

- Comprehensive physical examination, including evaluation of all mucous membranes.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder.
- If needed, a biologic checkup may be performed, including a blood cell count, liver and kidney tests, hepatitis antibody tests, and tuberculosis (TB) testing.
- Referral to dermatology for blisters that are not explained by infectious/transient other causes (eg, herpes simplex, herpes zoster infections, pressure/friction bullae).
- Skin biopsy (lesional biopsy of inflamed skin or the edge of a bulla or vesicle) for hematoxylin and eosin histology and biopsy of a perilesional or "near-inflamed" area for direct immunofluorescence testing.
- If the biopsy demonstrates a subepidermal blister and/or the direct immunofluorescence testing is suspicious or positive for a diagnosis of bullous pemphigoid (BP), or in cases where skin biopsies are not possible, consider serum testing to further evaluate tense bullae (BP 230 and BP 130 enzyme-linked immunosorbent assay serum testing). If negative, under the guidance of dermatology, sending the patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases could be considered.

Recommendation 1.2b – Management. If blisters are $< 10\%$ body surface area (BSA), asymptomatic, and noninflammatory (eg, the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. Once a blister or erosion, which is essentially a deroofed blister, is observed on examination, with associated erythema or symptoms, the reaction should be considered due to ICPi therapy and graded at 2 or above. It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi therapy and consult with dermatology (or skin care team, which may include general surgeon) to determine appropriateness of resuming ICPi and initiate general local skin/wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions that are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off.
- Should counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, and use sunscreens.
- Should order work-up for autoimmune bullous disease as above.
- Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement.
- Lower threshold to initiate treatment with prednisone (or equivalent) at 0.5 to 1 mg/kg dosing and taper over at least 4 weeks.
- Monitor patients with grade 2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography.
- Primer on monitoring for complicated cutaneous adverse drug reactions:
  - Review of systems: skin pain ("like a sunburn"), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements.
  - Physical examination: include vital signs and a full skin examination, specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of drug-induced hypersensitivity syndrome [DIHS]/drug reaction with eosinophilia and systemic symptoms [DRESS]). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis, demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should hold ICPi therapy and consult with dermatology to determine appropriateness of resuming.
- Should administer IV (methyl)prednisolone (or equivalent) at 1 to 2 mg/kg dosing tapered over at least 4 weeks.
- If BP is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE.
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient immediately and place under supervision of a dermatologist.
- Should administer IV (methyl)prednisolone (or equivalent) 1 to 2 mg/kg/d. When toxicity improves to grade 2 or less, start corticosteroid taper. Taper should be at least 4 weeks.

- If BP is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE.
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

1.3 Severe Cutaneous Adverse Reactions

Recommendation 1.3a – Diagnostic work-up. Severe cutaneous adverse reactions, or SCARs, include, but are not limited to, SJS/TEN and DRESS (also called DIHS).

It is recommended that for all grades of irAEs, the diagnostic work-up should include the following:

- Total body skin examination with attention to ALL mucous membranes as well as a complete review of systems.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease.
- A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work. If the patient is febrile, blood cultures should be considered as well.
- Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses, or other drug reactions, such as acute generalized exanthematous pusulosis.
- Consider following patients closely using serial clinical photography.
- If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management.
- Primer on monitoring for complicated cutaneous adverse drug reactions:
  - Review of systems: skin pain ("like a sunburn"), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements.
  - Physical examination: include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of dusky erythema, which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis, demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN.

Recommendation 1.3b – Management. In cases of suspected SJS or any mucous membrane involvement, it is recommended that clinicians should discontinue ICPi treatment and refer to dermatology. It would not be advisable to restart ICPi unless "cleared" by a dermatologist if SJS/TEN is suspected.

For SCARs, there is no grade 1 category. If lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to grade 3 or 4.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Hold ICPi and monitor patients closely every 3 days with grade 2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement.
- Consider following patients closely by using serial photography.
- Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids.
- Consider initiation of prednisone or equivalent at 0.5 to 1 mg/kg tapered over at least 4 weeks.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should hold ICPi therapy and consult with dermatology.
- Should treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids. Dimethicone may also be offered as an alternative to petrolatum.
- Administer IV (methyl)prednisolone (or equivalent) at doses of 1 to 2 mg/kg and taper over at least 4 weeks.
- Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection.
- Given the immune mechanism of action of these medicines, use of immune suppression, such as with systemic corticosteroids, is warranted and should be offered, though the use of systemic corticosteroids has been more controversial for the treatment of SJS/TEN, in general. For DRESS/DIHS, high-dose and usually prolonged courses of systemic corticosteroids is first-line therapy following cessation of the offending drug.
- For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate).
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient immediately with consideration to a burn unit or ICU in the case of SJS/TEN and consult dermatology.
- Administer IV (methyl)prednisolone or equivalent 1 to 2 mg/kg with tapering when the toxicity resolves to normal.
- May consider IV immunoglobulin (IVIG) or cyclosporine as an alternative or in corticosteroid-refractory cases.
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

Qualifying statement. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS. Additionally, patients with DRESS/DIHS may experience other autoimmune diseases as long-term sequelae, such as thyroid disease and recurrences as systemic corticosteroids are tapered or discontinued are not uncommon. Thus, continued monitoring should be considered for these patients. It is generally advisable to avoid rechallenge with an offending drug when a patient experiences SCARs, such as SJS/TEN or DRESS/DIHS. It is advisable to consider alternate antineoplastic therapies because rechallenge in these cases may result in an even more severe SCAR.

Discussion. The dramatic and durable responses seen with ICPis are often at the cost of increased toxicities due to unrestrained activity of T cells.[4] Among the diverse irAEs, cutaneous toxicities such as rash, pruritus, and vitiligo are by far the most common and the earliest to occur.[5] Although most cutaneous toxicities are transient, they can cause significant morbidity and impairment of patients' health-related quality of life.

Cutaneous toxicities are reported in 30% to 50% of patients treated with ICPis.[6] Our understanding of cutaneous toxicities stems mostly from the ipilimumab experience wherein the overall incidence ranges from 37% to 70% for all-grade and 1% to 3% for grade 3 or higher cutaneous toxicities.[7,8] Cutaneous toxicities are less frequently reported with anti–PD-1 agents (17% to 37%); however, the incidence of grade 3 or higher toxicities is the same as with ipilimumab.

Cutaneous toxicities pose a myriad of challenges. Rash is the most common cutaneous toxicity reported with ICPis. They span a variety of inflammatory conditions, including spongiotic, psoriasiform, and lichenoid dermatitides, mimicking eczema, psoriasis, and lichen planus, respectively. The clinical presentations vary with focal to diffuse distributions, including flexural, inverse, and erythrodermic variants. Pruritus can be severe and is the most common associated symptom. Vitiligo presents as well-demarcated depigmented macules and patches, reported exclusively in patients with melanoma. Besides varying clinical presentation, the time to onset varies greatly among these rashes, as vitiligo can appear months after treatment initiation; however, the inflammatory dermatoses usually present within the first one to two cycles of treatment. This mandates constant vigilance for signs and symptoms of cutaneous toxicities. In addition, these irAEs are increasingly recognized as a contributing factor to treatment noncompliance, discontinuation, or dose modification. As targeted systemic therapies are available for eczema and psoriasis, correlating the inflammatory patterns of the cutaneous toxicities with the inflammatory patterns that they mimic may lead to more efficacious treatments, fewer drug interruptions and dose modifications, and increased compliance and efficacy of the immune ICPis. However, classification of rashes has not been undertaken prospectively, and histologic characterization of the cutaneous toxicities is lacking.

Interestingly, emerging data suggest that development of cutaneous toxicity, especially rash and vitiligo, may correlate with response to ICPi therapy in patients with metastatic melanoma. In a retrospective analysis of 148 patients with melanoma treated with nivolumab plus peptide vaccine or nivolumab, survival benefit was reported in patients who developed rash (n = 64) or vitiligo (n = 19).[9] Overall survival (OS) was significantly longer in patients who developed rash (hazard ratio [HR], 0.423; 95% CI, 0.243 to 0.735; $P = .001$) and vitiligo (HR, 0.184; 95% CI, 0.036 to 0.94; $P = .012$). Objective response rate (ORR) was also significantly higher in patients with rash ($P = .03$) or vitiligo ($P = .009$). In a prospective study evaluating pembrolizumab in treatment of patients with melanoma, ORR was higher in patients who developed vitiligo than in those who did not (71% *v* 28%; $P = .002$).[10] Similarly, in a phase I study of ipilimumab for patients with melanoma, rash was the most common irAE reported among responders.[11] Furthermore, in a meta-analysis of 27 studies[12] in patients with melanoma treated with various immunotherapeutic agents, vitiligo was significantly associated with both progression-free survival (HR, 0.51; 95% CI, 0.32 to 0.82; $P = .005$) and OS (HR, 0.25; 95% CI, 0.10 to 0.61; $P = .003$). These findings from large clinical development programs suggest that cutaneous irAEs may be a surrogate for clinical benefit, and it would be important to correctly identify these skin changes so that the ICPi therapy is not discontinued in these cases with good prognoses. In addition, many cutaneous toxicities may be managed without the discontinuation of therapy. With early diagnosis and prompt management of cutaneous toxicities, patients may be able to stay on ICPi therapy, which could be crucial for improved treatment outcomes. However, little is known about the underlying mechanisms and the relationship between cutaneous toxicity and clinical outcome in patients with advanced cancer other than melanoma. This lack of knowledge presents challenges for prompt diagnosis and hampers the development of strategies to mitigate or minimize the occurrence of cutaneous toxicities in patients treated with ICPis. With increasing use of ICPis in the clinic, characterization and development of sensitive and robust markers of cutaneous toxicity is a priority.

2.0 GI Toxicities

Please refer to Table 2, for a complete set of recommendations, definition of grades, and additional considerations.

2.1 Colitis

Recommendation 2.1a – Diagnostic work-up. No specific diagnostic work-up is recommended for grade 1 adverse events.

It is recommended that the diagnostic work-up should include the following for grade 2 toxicity:

- Work-up of blood (CBC, comprehensive metabolic panel, thyroid-stimulating hormone [TSH], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), stool (culture, *Clostridium difficile*, parasite, cytomegalovirus [CMV] or other viral etiology, ova and parasite) should be performed.
- May test for lactoferrin for patient stratification to determine who needs urgent endoscopy, and calprotectin may be offered to follow up on disease activity.
- Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and in appropriately selected patients based on infectious disease expert's evaluation.

Table 2. Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities	
2.1 Colitis	
Definition: A disorder characterized by inflammation of the colon	
Diagnostic work-up G2 Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, *Clostridium difficile*, parasite, CMV or other viral etiology, ova and parasite) should be performed Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity) Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy G3-4 All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi	
Grading (based on CTCAE for diarrhea, as most often used clinically)	**Management**
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits Fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional *v* inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections

(continued on following page)

Table 2. Management of GI irAEs in Patients Treated With ICPis (continued)

2.0 GI Toxicities	
Additional considerations	
The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-α blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results[13-15]	
Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions	
Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc	
2.2 Hepatitis	
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma	
Diagnostic work-up	
Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality	
For G2 or higher:	
Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, γ-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies	
Grading	**Management**
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 × ULN and/or total bilirubin > ULN to 1.5 × ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated TB 3 × ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 × ULN and/or total bilirubin > 10 × ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

Abbreviations: ADL, activities of daily living; ANA, antinuclear antibody; CK, creatine kinase; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-cell lymphocyte-4; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; PD-1; programmed death 1; PD-L1, programmed death ligand 1; TB, tuberculosis; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

- Imaging with computed tomography (CT) scan of abdomen and pelvis and GI endoscopy with biopsy may be performed as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab. Infliximab or other tumor necrosis factor (TNF)–blocking agent should not be delayed while awaiting the results of these screening tests.
- Repeat endoscopy may be offered to patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring should only be offered when clinically indicated and when planning to resume therapy.

It is recommended that the diagnostic work-up should include the following for grade 3 to 4 toxicity:

- All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately.
- Repeat endoscopy may be offered for patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring should only be offered when clinically indicated and when planning to resume ICPi.

Recommendation 2.1b – Management. It is recommended that clinicians counsel all patients to be aware of and inform their health care provider immediately if they experience:

- Abdominal pain, nausea, cramping, blood or mucus in stool, or changes in bowel habits
- Fever, abdominal distention, obstipation, constipation

It is recommended that clinicians manage grade 1 toxicities as follows:

- May continue ICPi. Alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed grade 1.
- Should monitor for dehydration and recommend dietary changes.
- Should facilitate expedited phone contact with patient/caregiver.
- May obtain gastroenterology consult for prolonged grade 1 cases.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold the ICPi until patient's symptoms recover to grade 1 or less. Can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to grade 1 or less.
- Concurrent immunosuppressant maintenance therapy ($<$ 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases.
- May also include supportive care with medications such as Imodium if infection has been ruled out.
- Should consult with gastroenterology for grade 2 or higher.
- Should administer corticosteroids, unless diarrhea is transient, starting with an initial dose of 1 mg/kg/d prednisone or equivalent.
- When symptoms improve to grade 1 or less, should taper corticosteroids over at least 4 to 6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits.
- Should offer esophagogastroduodenoscopy/colonoscopy, endoscopy evaluation for cases of grade 2 or higher to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy.
- Testing for stool inflammatory markers, lactoferrin, or calprotectin may be offered in cases of grade 2 or higher to differentiate functional versus inflammatory diarrhea. Calprotectin testing may also be offered to monitor treatment response.
- Repeat colonoscopy is optional and may be offered for cases of grade 2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi.

Qualifying statement. Starting infliximab before colonoscopy is reasonable if negative infectious stool work-up is confirmed. However, prompt access to colonoscopy is advised to justify the dose and duration of infliximab. Once infliximab is indicated, patients most often have grade 2 and higher diarrhea/colitis, and most are hospitalized.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to grade 1 or less.
- Should administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent).
- Should refer to hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance.
- If symptoms persist $\geq$ 3 to 5 days or recur after improvement, may administer IV corticosteroid or noncorticosteroid (eg, infliximab).
- May offer colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue all ICPi treatment.
- Should admit patient when clinically indicated. Patients managed as outpatients should be very closely monitored.
- Should administer IV corticosteroid until symptoms improve to grade 1 and then start taper over 4 to 6 weeks.
- May offer early infliximab 5 to 10 mg/kg if symptoms are refractory to corticosteroid within 2 to 3 days.
- May offer lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections.

Qualifying statement. The use of vedolizumab may be offered to patients refractory to infliximab and/or contraindicated to TNF-α blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results.[13 15]

2.2 Hepatitis

Recommendation 2.2a – Diagnostic work-up. It is recommended that work-up should include the following:

- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if there are grade 1 liver function test elevations. No treatment is recommended for grade 1 liver function test abnormality.

For grade 2 or higher toxicity:

- Work-up for other causes of elevated liver enzymes, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis. If suspicion for primary autoimmune hepatitis is high, can consider ANA, anti–smooth muscle antibodies, and antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, γ-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking creatine kinase (CK) for other etiologies.

Recommendation 2.2b – Management. It is recommended that clinicians counsel all patients to be aware of and inform their health care provider immediately if they experience:

- Yellowing of skin or whites of the eyes
- Severe nausea or vomiting
- Pain on the right side of the abdomen
- Drowsiness
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal
- Feeling less hungry than usual

It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi, but with close monitoring.
- Should rule out alternate etiologies.
- Should monitor laboratories one to two times weekly.
- Should offer supportive care for symptom control.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi treatment temporarily and resume if recover to grade 1 or less on prednisone ≤ 10 mg/d.
- For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5 to 1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3 to 5 days.
- Should increase frequency of monitoring to every 3 days.
- Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows liver toxicity from infliximab from other studies).
- In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to grade 1 or less on corticosteroid ≤ 10 mg/d. Taper over at least 1 month.
- Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should permanently discontinue treatment with ICPi.
- Should immediately administer corticosteroid 1 to 2 mg/kg methylprednisolone or equivalent.
- If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil or azathioprine (if using azathioprine, should test for thiopurine methyltransferase deficiency).
- Should order laboratories daily or every other day; may offer inpatient monitoring for patients with AST/ALT more than eight times the upper limit of normal (ULN) and/or elevated TB three times ULN.
- Should increase frequency of monitoring to every 1 to 2 days.
- Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows liver toxicity from infliximab from other studies). Alternatives include non–TNF-α agents as systemic immunosuppressants.
- If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis.
- Corticosteroid taper should be attempted over a period of 4 to 6 weeks, re-escalate if needed, optimal duration unclear.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue treatment with ICPi.
- Should administer 2 mg/kg/d methylprednisolone equivalents.
- If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil.
- Should monitor laboratories daily; inpatient monitoring may be offered.
- Should not offer infliximab in the situation of immune-mediated hepatitis.
- Should refer to hepatology if no improvement is achieved with corticosteroid.
- Corticosteroid taper should be attempted over a period of 4 to 6 weeks when symptoms improve to grade 1 or less, re-escalate if needed, optimal duration unclear.
- Consider transfer to tertiary care facility if necessary.

Discussion. GI toxicities are some of the most common complications reported with ICPi use. While the frequency of colitis reported in the literature ranges from 8% to 27%, the incidence of diarrhea is as high as 54% in patients treated with anti–CTLA-4 antibodies,[16,17] especially in patients who receive anti–CTLA-4 and anti–PD-1 combination therapy.[18] GI toxicity is less common with anti–PD-1 monotherapy, with the incidence of diarrhea reported to be ≤ 19%.[16] In a recent meta-analysis of patients with cancer treated with ICPis, the relative risk (RR) of all-grade diarrhea and colitis was 1.64 (95% CI, 1.19 to 2.26; $P = .002$) and 10.35 (95% CI, 5.78 to 18.53; $P < .001$), the RR of high-grade diarrhea and colitis is reported to be 4.46 (95% CI, 1.46 to 13.57; $P = .008$) and 15.81 (95% CI, 6.34 to 39.42; $P < .001$), respectively.[19] On the contrary, RR of upper-GI symptoms (eg, vomiting) was not significant. Frequency of intestinal perforation has been described at approximately 1%.[16,20]

The most common clinical presentations of immune-related GI toxicities vary from very frequent and/or loose stools to colitis symptoms (eg, mucous in the stools, abdominal pain, fever, rectal bleeding).[18] The onset of these GI symptoms is most often in the range of 5 to 10 weeks after initiation of ICPi but can occur or recur months after discontinuation of immunotherapy.[5,18] While clinical factors associated with ICPi-induced colitis have not been well

established, nonsteroidal anti-inflammatory drug (NSAID) use is reported to be associated with an increase in ICPi-induced enterocolitis,[21] and care should be taken with NSAID use in this setting. There is a lot of similarity between ICPi-induced colitis and inflammatory bowel disease (eg, clinical presentations,[22,23] radiologic findings).[19] CT findings of ICPi-induced colitis include mesenteric vessel engorgement; bowel wall thickening; and fluid-filled colonic distention; and on positron emission tomography/CT scan, diffuse colonic wall thickening is observed.[19] The distribution of colitis has been reported to involve descending colon more often than other parts of the colon.[16,19] On the other hand, pathology from patients with colitis demonstrated changes that were more than what classic inflammatory bowel disease shows.[19,24] The histologic picture is often characterized by marked mixed inflammatory cell infiltrates in the lamina propria, consisting of neutrophils, lymphocytes, plasma cells, and eosinophils.[16,21,24] Inflammatory changes also tend to be more diffuse (75%).[16]

For patients with mild diarrhea symptoms (grade 1), usually conservative observation and maintenance of hydration are recommended rather than more-aggressive evaluation. Once diarrhea symptoms are grade 2 or higher or with apparent colitis symptoms, corticosteroid at 1 to 2 mg/kg is still the first-line treatment option if the stool infectious work-up is negative. Endoscopic evaluation can be considered if clinically deemed critical. If the symptoms are not improving after 3 to 5 days of corticosteroid treatment, stronger immunosuppressive agents (eg, TNF-α blocker infliximab, anti-integrin α4β7 antibody vedolizumab) have been shown in multiple case reports and case series to be very effective at achieving clinical remission and successful corticosteroid taper for patients who are corticosteroid refractory.[14] No significant adverse effects or negative effect on the overall survival on the patient's outcomes were identified.

Compared with lower-GI toxicities, upper-GI toxicity, characterized by dysphagia, nausea/vomiting, and epigastric pain, is much less common. Pathology can present as patchy chronic duodenitis or chronic gastritis with rare granulomas.[21,25] It can coexist with lower-GI toxicity or as an isolated condition. The treatment strategy is similar to colitis: corticosteroid followed by TNF-α blockers for refractory cases based on case studies.[21,25,26]

Hepatotoxicity has been reported to occur in 2% to 10% of patients treated with ipilimumab, nivolumab, and pembrolizumab monotherapy.[27,160 162] Combination treatment with ipilimumab and nivolumab has resulted in a reported 25% to 30% all-grade hepatitis and approximately 15% incidence of grade 3 toxicity. Onset develops predominately within the first 6 to 12 weeks after treatment initiation.[28] The mainstay of treatment is prednisone or equivalent at 1 to 2 mg/kg with frequent monitoring of liver tests. However, other etiologies that could contribute to liver dysfunction have to be thoroughly evaluated and ruled out. For corticosteroid refractory cases, mycophenolate mofetil has been reported in a case study with some success.[29] The TNF-α blocker infliximab is not recommended given the concern of liver toxicity, despite lack of evidence. Other alternative immunosuppressive agents still need further data proof for efficacy and safety. The patient with preexisting hepatitis who experiences ICPi-induced colitis is rare but represents a management challenge. Available options are more limited and should include permanent cessation of anti–CTLA-4 and possibly other ICPi treatment.

Acute pancreatitis has also been reported in the literature, but it is rare.[22] Routine monitoring of amylase/lipase in asymptomatic patients is not recommended unless pancreatitis is clinically suspected. In the absence of symptoms, corticosteroid treatment is not indicated for modest elevations in serum amylase and lipase.[2]

In terms of resumption of ICPi after toxicities have occurred, the recommendation is different based on the grade level of toxicities. For grade 4 toxicities, ICPi treatment should be permanently discontinued. In patients with grade 3 or less toxicities who improve from their irAE after adequate treatment, the risk of recurrent toxicities with rechallenge appears to vary with organ toxicity and type of ICPi therapy. Only a small proportion of patients with ICPi-related colitis are reported to experience recurrences with anti–PD-1 resumption alone.[30 32] Toxicities such as hepatitis and pancreatitis also have some risk of recurrence.[30] These most often occur early and are generally low grade and manageable with standard treatments. Nonetheless, care should be taken to ensure that proper monitoring and management strategies are implemented.[30]

3.0 Lung Toxicity

Please refer to Table 3 a complete set of recommendations, definition of grades, and additional considerations.

3.1 Pneumonitis

Recommendation 3.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Chest x-ray (CXR), CT, pulse oximetry
- For grade 2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, and urine culture and sensitivity

Recommendation 3.1b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should hold ICPi with radiographic evidence of pneumonitis progression.
- May offer one repeat CT in 3 to 4 weeks. In patients who have had baseline testing (Appendix Table A2, online only), may offer a repeat spirometry/diffusing capacity of lung for carbon monoxide in 3 to 4 weeks.
- May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as grade 2.
- Should monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold immunotherapy until resolution to grade 1 or less.
- Should administer prednisone 1 to 2 mg/kg/d and taper by 5 to 10 mg/wk over 4 to 6 weeks per institutional guidelines.
- May offer bronchoscopy with bronchoalveolar lavage.
- May prescribe empirical antibiotics.
- Should monitor every 3 days with history and physical examination and pulse oximetry; may also offer CXR. No clinical improvement after 48 to 72 hours of prednisone, should treat as grade 3.

Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis	
Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	**Management**
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and *Pneumocystis* prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines[34-37] Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines[33] Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should prescribe empirical antibiotics and administer (methyl)prednisolone IV 1 to 2 mg/kg/d. No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide. Taper corticosteroids over 4 to 6 weeks.
- Should consult pulmonary and infectious disease if necessary.
- Should offer bronchoscopy with bronchoalveolar lavage with or without transbronchial biopsy.
- Patients should be hospitalized for further management.

Qualifying statement. The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines.[33]

Discussion. ICPi-related pneumonitis is an uncommon but potentially serious toxicity. The reported incidence of pneumonitis in studies investigating anti–PD-1/PD-L1 is variable and ranges from 0% to 10%,[38,163] with an overall incidence of 2.7% reported in a recent meta-analysis of 20 studies with PD-1 inhibition.[39] The toxicity seems to be less common with anti–CTLA-4 treatment, with pneumonitis reported in < 1% of trial participants receiving ipilimumab.[40 44] A higher incidence was seen in patients who received combination therapy than those who received monotherapy (10% *v* 3%, respectively; $P < .001$),[38] and patients treated with combination immunotherapy may be less likely to experience resolution of the irAE compared with patients treated with monotherapy.[40,45] In patients who improve from their irAE, rechallenging with anti–PD-(L)1 therapy was associated with recurrent or new irAEs in half of patients and was more common in early-onset irAEs.[46] The majority of such patients were managed successfully, but two deaths have been reported.[46]

The evidence on whether the risk of ICPi-related pneumonitis and pneumonitis-related deaths varies by tumor type remains equivocal. The odds of all-grade pneumonitis was higher in patients with NSCLC than in those with melanoma (odds ratio [OR], 1.43; 95% CI, 1.08 to 1.89; $P = .005$) according to the Nishino et al[39] meta-analysis. Similarly, patients with renal cell carcinoma

were also significantly more likely to experience all-grade pneumonitis than patients with melanoma (OR, 1.59; 95% CI, 1.32 to 1.92; $P < .001$).[39] In contrast, other studies have reported similar rates of grades 3 to 4 pneumonitis across tumor types but with more treatment-related deaths due to pneumonitis seen in patients with NSCLC.[40,47 49] In a multicenter, large retrospective analysis, pneumonitis was reported to develop in both former/current smokers (56%) and never smokers (44%).[38] Recent evidence also demonstrated no significant difference in the rates of irAEs, including pneumonitis, between patients who received thoracic radiotherapy in addition to checkpoint inhibitors.[50]

The median onset of ICPi-related pneumonitis can vary, with a range of 2 to 24 months and a median time to onset of approximately 3 months reported in the literature.[38] However, onset does occur earlier with combination therapy versus monotherapy.[40] Clinical symptoms can include dyspnea (53%), cough (35%), fever (12%), and chest pain (7%).[51] Hypoxia may occur and progress rapidly, leading to respiratory failure.[40,52]

Ground-glass opacities or patchy nodular infiltrates, predominantly in the lower lobes, are common manifestations on chest imaging.[53] Radiologic abnormalities vary but are often reported to be focal and very different from the diffuse pneumonitis associated with targeted agents.[53] Naidoo et al[38] recently reported on five distinct radiologic subtypes: chronic obstructive pneumonia like, ground-glass opacities, hypersensitivity type, interstitial type, and pneumonitis not otherwise specified.

When the clinical picture is consistent with pneumonitis, biopsy is generally unnecessary. However, transbronchial biopsy may have a role in assisting to rule out other etiologies like lymphangitic spread of tumor or infection. The decision to perform lung biopsy in the evaluation of immune-related pulmonary reactions is based on the probability that this examination will yield a specific diagnosis, leading to a change in management. Yet, there is no specific pathology to confirm immune-related pneumonitis. Ultimately, the decision to proceed with biopsy should be taken after a careful risk-benefit analysis, with the optimal technique, number, size, and location of biopsies depending upon the suspected diagnosis, the anatomic distribution of the disease process, and the availability of pulmonologists.

In addition to typical findings of pneumonitis, sarcoid-like granulomatous reactions, including subpleural micronodular opacities and hilar lymphadenopathy, as well as pleural effusions have been associated with both CTLA-4– and PD-1/PD-L1–targeted therapies.[40,42,54 57] Clinical manifestations are diverse and often patient-specific and can include cough, wheezing, fatigue, chest pain, or no symptoms at all. With varying clinical presentation, it is prudent for clinicians to be aware of the possibility of such immune-related pulmonary reactions, as they may mimic disease progression on imaging and examination. Biopsy may assist in confirming the diagnosis.

4.0 Endocrine Toxicities

Please refer to Table 4 for a complete set of recommendations, definition of grades, and additional considerations.

Recommendation 4.0 – Endocrine general. It is recommended that clinicians counsel patients to inform their health care provider and team immediately if they experience any changes in their health since their last visit, especially any of the following:

- Headaches that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain

4.1 Thyroid

4.1.1 Primary Hypothyroidism

Recommendation 4.1.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Testing for TSH and free thryoxine (FT4) every 4 to 6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients.

Recommendation 4.1.1b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi with close follow-up and monitoring of TSH, FT4.

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi until symptoms resolve to baseline.
- May consult endocrinology.
- Should prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart).
- Should monitor TSH every 6 to 8 weeks while titrating hormone replacement to normal TSH.
- FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low.
- Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active therapy or as needed for symptoms to ensure appropriate replacement. Repeat testing annually or as indicated by symptoms once stable.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until symptoms resolve to baseline with appropriate supplementation.
- Should consult endocrinology.
- May admit for IV therapy if signs of myxedema (bradycardia, hypothermia).

Table 4. Management of Endocrine irAEs in Patients Treated With ICPis

4.0 Endocrine Toxicity	
Counsel patients to inform their health care provider immediately if they experience any changes in their health since their last visit, especially any of the following: Headaches that will not go away or unusual headache patterns Vision changes Rapid heartbeat Increased sweating Extreme tiredness or weakness Muscle aches Weight gain or weight loss Dizziness or fainting Feeling more hungry or thirsty than usual Hair loss Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness Feeling cold Constipation Voice gets deeper Urinating more often than usual Nausea or vomiting Abdominal pain	
4.1 Thyroid	
4.1.1 Primary hypothyroidism	
Definition: Elevated TSH, normal or low FT4	
Diagnostic work-up	
TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients	
Grading	Management
G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 μg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 μg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine	
Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	Management
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline Consider endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease

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Table 4. Management of Endocrine irAEs in Patients Treated With ICPis (continued)

4.0 Endocrine Toxicity	
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).
Additional considerations Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation(hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3. Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis). Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg. All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS. Endocrine consultation prior to surgery or any procedure for stress-dose planning.	
4.3 Pituitary - hypophysitis	
Definition: Inflammation of the pituitary with varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism.	
Diagnostic work-up Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Testing: Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes	

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Table 4. Management of Endocrine irAEs in Patients Treated With ICPis (continued)

4.0 Endocrine Toxicity	
Grading	Management
G1: Asymptomatic or mild symptoms	Considering holding ICPi until patient is stabilized on replacement hormones Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight) Testosterone or estrogen therapy as needed in those without contraindications Endocrine consultation Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones Endocrine consultation Hormonal supplementation as in G1 Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Additional considerations Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS Corticosteroid use can cause isolated central adrenal insufficiency Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.	
4.4 Diabetes	
Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure. Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement	
Diagnostic work-up Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM. Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.	
Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia. Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs.	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; CT, computed tomography; DKA, diabetic ketoacidosis; DM, diabetes mellitus; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging; PTU, propylthiouracil; SSKI, potassium iodide; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; ULN, upper limit of normal.

- Should prescribe thyroid supplementation and offer reassessment as in grade 2.

4.1.2 Hyperthyroidism

Recommendation 4.1.2a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Monitor TSH and FT4 every 4 to 6 weeks from the start of therapy or as needed for case detection in symptomatic patients.
- Test for TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy).
- Should closely monitor thyroid function every 2 to 3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism.

Recommendation 4.1.2b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi with close follow-up and monitoring of TSH and FT4 every 2 to 3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1).

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi until symptoms return to baseline.
- May consult endocrinology.
- Should offer a β-blocker (eg, atenolol, propranolol) for symptomatic relief.
- Should offer hydration and supportive care.
- Should note that corticosteroids are not usually required to shorten duration.
- For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, clinicians should work up for Graves disease (thyroid-stimulating immunoglobulin or TSH receptor antibody) and consider thionamide (methimazole or propylthiouracil).
- Should refer to endocrinology for Graves disease.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until symptoms resolve to baseline with appropriate therapy.
- Should consult endocrinology.
- Should offer a β-blocker (eg, atenolol, propranolol) for symptomatic relief.
- For severe symptoms or concern for thyroid storm, should hospitalize patient and initiate prednisone 1 to 2 mg/kg/d or equivalent tapered over 1 to 2 weeks. May also use saturated solution of potassium iodide or thionamide (methimazole or propylthiouracil).

4.2 Adrenal – Primary Adrenal Insufficiency

Recommendation 4.2a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following for patients in whom adrenal insufficiency is suspected:

- Evaluate adrenocorticotropic hormone (ACTH; AM), cortisol level (AM).
- Basic metabolic panel (Na, K, CO_2, glucose).
- Consider ACTH stimulation test for indeterminate results.
- For evidence of primary adrenal insufficiency (high ACTH, low cortisol), evaluate for a precipitating cause of crisis, such as infection, and perform an adrenal CT scan for metastasis/hemorrhage.

Recommendation 4.2b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- May hold ICPi until patient is stabilized on replacement hormone.
- Should consult endocrinology.
- Should offer replacement therapy with prednisone (5 to 10 mg daily) or hydrocortisone (10 to 20 mg orally in the morning, 5 to 10 mg orally in early afternoon)
- May prescribe fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency.
- Should titrate dose up or down as symptoms dictate.

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi until patient is stabilized on replacement hormone.
- Should consult endocrinology.
- Should initiate outpatient treatment at two to three times maintenance (eg, if prednisone, 20 mg daily; if hydrocortisone, 20 to 30 mg in the morning and 10 to 20 mg in the afternoon) to manage acute symptoms.
- Should taper stress-dose corticosteroids down to maintenance doses over 5 to 10 days.
- Should offer maintenance therapy as in grade 1.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until patient is stabilized on replacement hormone.
- Should consult endocrinology.
- Should see in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg if the diagnosis is not clear and stimulation testing will be needed).
- Should taper stress-dose corticosteroids down to maintenance doses over 7 to 14 days after discharge.
- Should offer maintenance therapy as in grade 1.

Qualifying statement. Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3. Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone, as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg.

4.3 Pituitary – Hypophysitis

Recommendation 4.3a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Evaluate ACTH, cortisol (AM), TSH, FT4, and electrolytes.
- Consider evaluating luteinzing hormone, follicle-stimulating hormone, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes.

- Consider magnetic resonance imaging (MRI) of brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities with or without new severe headaches or complaint of vision changes.

Recommendation 4.3b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- May hold ICPi until patient is stabilized on replacement hormones.
- Should offer hormonal supplementation as needed, using dosing as specified for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10 to 20 mg orally in the morning, 5 to 10 mg orally in early afternoon; levothyroxine by weight).
- Testosterone or estrogen therapy as needed in those without contraindications.
- Should consult endocrinology.
- Should always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis.
- Should follow FT4 for thyroid hormone replacement titration (TSH is not accurate).

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi until patient is stabilized on replacement hormones.
- Should consult endocrinology.
- Should offer hormonal supplementation as in grade 1.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until patient is stabilized on replacement hormones.
- Should consult endocrinology.
- Should offer hormonal supplementation as in grade 1.
- May administer initial pulse dose therapy with prednisone 1 to 2 mg/kg oral daily (or equivalent) tapered over at least 1 to 2 weeks.

Qualifying statement. Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies. All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by emergency medical services.

4.4 Diabetes

Recommendation 4.4a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Monitor patients for hyperglycemia or other signs and symptoms of new or worsening diabetes mellitus (DM), including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3 to 6 weeks thereafter.
- To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM.
- Laboratory evaluation in suspected type 1 DM (T1DM) should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.

Recommendation 4.4b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- May continue to offer ICPi with close clinical follow-up and laboratory evaluation.
- May initiate oral therapy for those with new-onset type 2 DM (T2DM).
- Should screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis.

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi until glucose control is obtained.
- Should titrate oral therapy or add insulin for worsening control in T2DM.
- Should administer insulin for T1DM (or as default therapy if there is confusion about type).
- Should seek urgent endocrine consultation for any patient with T1DM. In the absence of endocrinology, internal medicine may suffice.
- May admit for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until glucose control is obtained on therapy with reduction of toxicity to grade 1 or less.
- Should seek urgent endocrine consultation for all patients.
- Should initiate insulin therapy for all patients.
- Should admit for inpatient management for any of the following: concern for developing diabetic ketoacidosis (DKA), symptomatic patients regardless of diabetes type, new onset T1DM unable to see endocrinology.

Discussion. Endocrine adverse events with immune checkpoint therapy present a unique clinical challenge for the non-endocrinologist who faces the possibility of central as well as primary endocrine dysfunction in a patient with symptoms or abnormal laboratories. Diverse therapies and combinations have varied rates of targeting individual organs, for example, hypophysitis is most commonly seen when ipilimumab is used,[58 61] and primary ovarian failure has not yet been reported.[62] However, with sporadic autoimmune disease known for all endocrine organs, we anticipate the possibility of any condition as the use becomes more widespread. In a recent systematic review and meta-analysis that included 7,551 patients in 38 randomized trials, the overall incidence of clinically significant endocrinopathies was approximately 10% of patients treated with checkpoint inhibitors.[62]

Clinical measure of both the primary hormone and the pituitary hormone are needed to localize disease. For example, a low morning cortisol suggests adrenal insufficiency but not whether the problem is pituitary or adrenal. We would look for hypophysitis if a simultaneously measured ACTH is low, whereas in primary adrenal insufficiency (eg, Addison), the ACTH will be elevated. The same applies for systems where we typically screen with the pituitary hormone—low TSH suggests hyperthyroidism if the thyroid hormone level (FT4 is typically sufficient) is elevated and central hypothyroidism if FT4 is low. Drawing both hormones is

especially important when hypophysitis is suspected because TSH can be at low-normal levels but lack function with pituitary disease.

Distinguishing primary from secondary hormonal problems is necessary because there are treatment implications. Perhaps most importantly for preventing harm is recognizing that hypophysitis often causes both central hypothyroidism and secondary adrenal insufficiency.[62] If thyroid hormone is replaced first when cortisol is low, the increase in cortisol metabolism can trigger an adrenal crisis. Fludrocortisone is needed in addition to hydrocortisone in most cases of primary adrenal insufficiency, which involves the loss of mineralocorticoid as well as glucocorticoid, leading to more-profound blood pressure and electrolyte abnormalities.[63] Monitoring is also affected by localization, as pituitary hormones are not reliable indicators of status with central disease. TSH, therefore, is not helpful in monitoring therapy with levothyroxine in central hypothyroidism, and FT4 should be used instead.[64]

Diagnosis of endocrine dysfunction is complicated by any acute illness and the administration of medications that have an effect on pituitary function, including many therapies that patients with cancer are on, such as narcotics and megestrol acetate. Most relevant for the patients administered ICPis is the effect of corticosteroids, given for many irAEs, which will directly suppress ACTH and may cause persistent central adrenal insufficiency when stopped. Cortisol levels should not be routinely measured while patients are on corticosteroid therapy because of variable assay effects from synthetic corticosteroids, low endogenous levels from the exposure, and the fact that the patient is on supraphysiologic doses and therefore treated for any underlying adrenal insufficiency that might have developed. If a diagnosis is needed, for example, after acute treatment of presumed adrenal crisis is initiated, ACTH stimulation testing may be performed on dexamethasone, which is not measured by most assays. Endogenous levels can be directly measured 24 hours after the last dose of physiologic hydrocortisone replacement to assess for functional recovery. High-dose corticosteroids can also cause a low TSH and a pattern similar to nonthyroidal illness, neither of which are thought to benefit from therapy.[65,66] Especially in difficult cases, endocrinology consult is recommended.

The response of the oncologist to the development of endocrine dysfunction may be different from other irAEs because organ failure can be managed with hormone replacement. It is not a given that the patient benefits from stopping cancer therapy to get immunosuppressive therapy to reverse the autoimmune disease. For example, there is no good evidence at this time that high-dose corticosteroids improve the rate of pituitary hormone recovery.[59,61] Therefore, a clinical judgment is needed to balance benefits, such as the possibility of improved headache, with risks, such as corticosteroid adverse effects, on glycemic control and delay of therapy.

Rare cases of T1DM present an analogous challenge to the clinician in the need to distinguish these from the much more common cases of worsening glycemic control attributable to insulin resistance and T2DM. The acute risks of DKA in T1DM require vigilance on the part of treating oncologists, despite the very low occurrence rate. New-onset hyperglycemia in a patient without risk factors for T2DM (eg, preexisting disease, corticosteroid exposure) should raise the level of concern for T1DM. Acute onset of polyuria, polydipsia, weight loss, and lethargy are characteristic presenting features of T1DM. Urine ketones and acid base status can be evaluated as screening for DKA and the need for inpatient evaluation. Antibodies, insulin, and C-peptide levels can be sent to support diagnosis, although the initiation of therapy should not be delayed pending results. Insulin should be used to treat hyperglycemia in anyone where the diagnosis is in question. Endocrinology consultation is appropriate where the diagnosis of T1DM is suspected even without evidence of DKA.

5.0 Musculoskeletal Toxicities

Please refer to Table 5 for a complete set of recommendations, definition of grades, and additional considerations.

5.1 Inflammatory Arthritis

Recommendation 5.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following for grade 1:

- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion. Examination of the spine.
- Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate.
- Consider autoimmune blood panel, including ANA, rheumatoid factor (RF), and anti–citrullinated protein antibody (anti-CCP), and inflammatory markers (ESR and CRP) if symptoms persist. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing.

It is recommended that the diagnostic work-up should include the following for grade 2:

- Complete history and examination as above; laboratory tests as above.
- Consider ultrasound with or without MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis).
- Consider early referral to a rheumatologist if there is joint swelling (synovitis) or if symptoms of arthralgia persist $>$ 4 weeks.

It is recommended that the diagnostic work-up should include the following for grades 3 to 4:

- As for grade 2.
- Seek rheumatologist advice and review.

It is recommended that all patients with inflammatory arthritis be monitored with serial rheumatologic examinations, including inflammatory markers, every 4 to 6 weeks after treatment is instituted.

Recommendation 5.1b – Management. It is recommended that clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present. Clinicians should question whether symptoms are new since receiving ICPi.

It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should initiate analgesia with acetaminophen and/or NSAIDs.

Table 5. Management of Musculoskeletal irAEs in Patients Treated With ICPis

5.0 Musculoskeletal Toxicities	
5.1 Inflammatory arthritis	
Definition: A disorder characterized by inflammation of the joints	
Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.	
Diagnostic work-up	
G1	
Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine	
Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate	
Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing	
G2	
Complete history and examination as above; laboratory tests as above	
Consider US ± MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)	
Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks	
G3-4	
As for G2	
Seek rheumatologist advice and review	
Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.	
Grading	**Management**
All grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.
Additional considerations	
Early recognition is critical to avoid erosive joint damage.	
Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs	
Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral.	
Consider PCP prophylaxis for patients treated with high dose of corticosteroids for > 12 weeks, as per local guidelines.	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved	
Diagnostic work-up	
Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms.	
Blood testing to evaluate muscle inflammation	
CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated	
Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed	
Inflammatory markers (ESR and CRP)	
Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected	
Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis	
Monitoring: CK, ESR, CRP	

(continued on following page)

Table 5. Management of Musculoskeletal irAEs in Patients Treated With ICPis (continued)

5.0 Musculoskeletal Toxicities	
G1: Complete examination and laboratory work-up as above	
G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints Early referral to a rheumatologist or neurologist	
G3-4: As for G2 Urgent referral to a rheumatologist or neurologist	
Grading	**Management**
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose < 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration
Additional considerations: Caution is advised with rechallenging	
5.3 Polymyalgia-like syndrome	
Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain	
Diagnostic work-up G1 Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP) Monitoring: ESR, CRP	
G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist	
G3-4: As for G2; see rheumatologist advice and review	
Grading	**Management**
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology
G3-4: Severe stiffness and pain, limiting self-care ADL	Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; ANA, antinuclear antibodies; CCP, citrullinated protein antibody; CK, creatine kinase; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EMG, electromyography; ESR, erythrocyte sedimentation rate; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PCP, *Pneumocystis* pneumonia; RF, rheumatoid factor; TNF, tumor necrosis factor.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and resume upon symptom control and on prednisone $\leq$ 10 mg/d.
- Should escalate analgesia and consider higher doses of NSAIDs as needed.
- If inadequately controlled, should initiate oral prednisone 10 to 20 mg/d or equivalent for 4 to 6 weeks.
- If improvement, slow taper according to response during the next 4 to 6 weeks. If no improvement after initial 4 to 6 weeks, treat as grade 3.
- If unable to lower prednisone dose to $<$ 10 mg/d after 3 months, may offer DMARD.
- May offer intra-articular corticosteroid injections for large joints.
- Should refer to rheumatology.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi and may resume in consultation with rheumatology, if recover to grade 1 or less.
- Should initiate oral prednisone 0.5 to 1 mg/kg.
- If failure of improvement after 4 weeks or worsening in meantime, may offer synthetic or biologic DMARD:
  - Synthetic: methotrexate, leflunomide.
  - Biologic: consider anticytokine therapy, such as TNF-α or interleukin-6 (IL-6) receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis).
- Should test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment.
- Should refer to rheumatology.

5.2 Myositis

Recommendation 5.2a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms.
- Blood testing to evaluate muscle inflammation.
- CK, transaminases (AST, ALT), lactate dehydrogenase (LDH), and aldolase can also be elevated.
- Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed.
- Inflammatory markers (ESR and CRP).
- Consider electromyography (EMG), imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected.
- Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis.

It is recommended that the following should be included for monitoring:

- CK, ESR, CRP

It is recommended that the diagnostic work-up should include the following for grade 1:

- Complete examination and laboratory work-up as specified in Section 5.2a

It is recommended that the diagnostic work-up should include the following for grade 2:

- Complete history and examination as above; autoimmune myositis and neurologic panel; EMG, MRI of affected proximal limbs as needed. Consider muscle biopsy if diagnosis is uncertain.
- Early referral to a rheumatologist or neurologist.

It is recommended that the diagnostic work-up should include the following for grade 3:

- As for grade 2
- Urgent referral to a rheumatologist or neurologist

Recommendation 5.2b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- If CK is elevated and patient has muscle weakness, may offer oral corticosteroids and treat as grade 2.
- Should offer analgesia as needed for pain with acetaminophen or NSAIDs if there are no contraindications.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and may resume upon symptom control, if CK is normal, and prednisone dose $<$ 10 mg; if worsens, treat as per grade 3. Permanently discontinue if there is evidence of myocardial involvement.
- Should offer NSAIDs as needed.
- Referral to rheumatologist or neurologist.
- If CK is elevated (three times or more), should initiate prednisone or equivalent at 0.5 to 1 mg/kg.
- May require permanent discontinuation of ICPi therapy in most patients with grade 2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy).

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi until grade 1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement.
- Consider hospitalization for severe weakness.
- Referral to rheumatologist or neurologist.
- Should initiate prednisone 1 mg/kg or equivalent. Consider 1 to 2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia).
- May offer plasmapheresis.
- May offer IVIG therapy.
- May offer other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and laboratory findings do not improve or worsen after 4 to 6 weeks. Rituximab is used in primary myositis, but caution is advised given its long biologic duration.

5.3 Polymyalgia-Like Syndrome

Recommendation 5.3a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following for grade 1:

- Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin.
- Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist. If temporal arteritis is suspected, consider temporal artery biopsy.
- ANA, RF, anti-CCP.
- CK to evaluate differential diagnosis of myositis.
- Inflammatory markers (ESR, CRP).

It is recommended that the following should be included for monitoring:

- ESR, CRP

It is recommended that the diagnostic work-up should include the following for grade 2:

- Complete history and examination as above
- Autoimmune tests as above and others as required for differential diagnosis
- Early referral to a rheumatologist

It is recommended that the diagnostic work-up should include the following for grades 3 to 4:

- As for grade 2
- Seek rheumatologist advice and review

Recommendation 5.3b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications.

It is recommended that clinicians manage grade 2 toxicities as follows:

- May hold ICPi and resume upon symptom control, prednisone $<$ 10 mg; if worsens, treat as per grade 3.
- Should initiate prednisone 20 mg/d or equivalent. If symptoms improve, start to taper dose after 3 to 4 weeks.
- If no improvement or need for higher dosages after 4 weeks, escalate to grade 3.
- Consider referral to rheumatology.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi and may resume, in consultation with rheumatology, if recover to grade 1 or less. However, note that cases of toxicity returning upon rechallenge have been reported.
- Referral to rheumatology.
- Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, consider a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab. (Note: As caution, IL-6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis or GI metastases).
- Consider admission for pain control.

Discussion. Musculoskeletal symptoms such as arthralgia and myalgia are common in patients receiving ICPi therapy, as reported in up to 40% of those treated in clinical trials.[67,68] More-severe inflammatory AEs are not as frequent but can have an important effect on patients' quality of life because of their effect on function and daily activities.[69] The most common musculoskeletal and rheumatic irAEs are arthritis, polymyalgia-like syndromes, and myositis. These events can occur with either CTLA-4 or anti–PD-1/PD-L1 antagonists, but seem to be more frequent with the latter class of drugs and when these agents are used in combination.[67]

The clinical presentation of patients with immune-related arthritis secondary to ICPi can vary and affect large and/or small joints.[68] Some patients present with oligoarthritis of large joints, such as knees, ankles, or wrists. These patients can also have other features commonly seen with reactive arthritis, such as conjunctivitis or urethritis, and occasionally complain of back pain or cervical pain suggestive of sacroiliitis. Other patients present with symmetrical polyarthritis resembling rheumatoid arthritis and can have autoantibodies such as RF present in their seras. Many patients also develop sicca symptoms, with dry eyes and dry mouth; autoantibodies, such anti-SSA and anti-SSB, have occasionally been found, but most patients tend to be seronegative. Of interest, arthritis can occur at any time during treatment. Some patients have developed arthritis for the first time many months after initiation of ICPi therapy.[70] Most common differential diagnoses include other causes of joint pain, including degenerative joint disease or osteoarthritis and soft tissue rheumatic disorders, such as rotator cuff tendinitis, crystal arthropathies (gout and pseudogout), and septic arthritis. Diagnostic evaluation should include serum inflammatory markers (ESR, CRP), evaluation of autoantibodies (ANA, RF, and anti-CCP), and imaging as needed (x-rays, ultrasound, and/or MRI). Inflammatory markers are usually very elevated in patients with ICPi-induced arthritis and are useful to differentiate these events from other rheumatic syndromes. NSAIDs alone are usually not sufficient to control symptoms, and corticosteroids and synthetic or biologic DMARDs might be required.[71,72] Intra-articular corticosteroid injections are an option if only one or two joints are affected.

Patients receiving ICPis can develop severe myalgia in their proximal upper and lower extremities, with severe fatigue resembling polymyalgia rheumatica.[73] These patients can also have arthralgia but typically do not have definite synovitis, although ultrasound or MRI might show a mild effusion in the shoulder joints. Patients experiencing a polymyalgia-like syndrome have pain but not true weakness. Differential diagnoses include inflammatory myositis, fibromyalgia, statin-induced myopathy, and other types of arthritis or soft tissue rheumatic syndromes. RF and anti-CCP are negative, and inflammatory markers are highly elevated. CK levels should generally be within normal limits, differentiating this condition from myositis. Imaging with MRI and EMG should not show any evidence of myopathy or muscle inflammation.

Myositis is a rare complication of ICPis but can be severe and fatal. It is more common with PD-1/PD-L1 inhibitors than with ipilimumab.[68,74] It can present as reactivation of preexisting paraneoplastic polymyositis or dermatomyositis or as a de novo myositis. The main symptom of inflammatory myositis is

weakness, primarily in the proximal extremities, with difficulties in standing up, lifting arms, and moving around. In severe cases, patients can complain of myalgia as well. Patients with de novo myositis do not develop the typical rash seen with paraneoplastic dermatomyositis. Myositis can have a fulminant necrotizing course with rhabdomyolysis and can involve vital skeletal muscle, such as the myocardium, in which case it requires urgent treatment to avoid fatal complications.[75,76] Laboratory tests include measurement of muscle enzymes, especially CK, which often is markedly elevated, and inflammatory markers; autoantibody panels for myositis can be considered, although there is no evidence that any specific autoantibodies have a role in ICPi-associated myositis. Other diagnostic tests that may be useful include EMG, which can show muscle fibrillations indicative of myopathy, and/or MRI, which shows increased intensity and edema in affected muscles. Finally, biopsy can be performed to confirm the diagnosis. Differential diagnoses include generalized fatigue, polymyalgia rheumatica, fibromyalgia, adverse events from concomitant therapies (eg, statins, corticosteroids), and muscle dystrophies. These other disorders (other than some muscle dystrophies or drug-induced myopathy) have normal CK. The cornerstone of initial treatment is high-dose corticosteroids that should be administered as a bolus in severe cases. Plasmapheresis should be considered in cases with poor response to corticosteroids or in life-threatening situations. The use of other immunosuppressants and IVIG may also be indicated, as they are used for treatment of polymyositis/dermatomyositis. However, their efficacy in ICPi-induced myositis is not clearly documented.

A number of other rheumatic disorders have been occasionally documented as case reports of patients receiving ICPis.[77] These include vasculitis and lupus-like syndromes, among others. Management and treatment principles are similar to those reported for other ICPi-induced rheumatic syndromes.

Patients with preexisting autoimmune rheumatic conditions may be at higher risk of toxicity as either irAEs or flares of their preexisting disease.[78] Many of these patients, nevertheless, can continue ICPi therapy or be rechallenged after their AEs are properly managed, so having preexisting autoimmune disease does not represent an absolute contraindication for treatment. Close monitoring and multidisciplinary management is required for these patients, as they frequently need concomitant treatment of their preexisting autoimmune disease once they develop an AE. Management principles are similar to those described for irAE.

6.0 Renal Toxicities

Please refer to Table 6 for a complete set of recommendations, definition of grades, and additional considerations.

6.1 Nephritis

Recommendation 6.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- For any suspected immune-mediated adverse reactions, should exclude other causes.
- Monitor patients for elevated serum creatinine prior to every dose.

Qualifying Statement. Routine urinalysis is not necessary other than to rule out urinary tract infections, etc. Nephrology may be considered. If no potential alternative cause of acute kidney injury (AKI) is identified, then one should forego biopsy and proceed directly with immunosuppressive therapy. The swift treatment of the autoimmune component is important.

Recommendation 6.1b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- May hold treatment temporarily, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. (Note: A change that is still < 1.5 ULN could be meaningful).

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold treatment temporarily.
- Should consult nephrology.
- Should evaluate for other causes (recent IV contrast, medications, fluid status, etc). If other etiologies are ruled out, should administer 0.5 to 1 mg/kg/d prednisone equivalents.
- If worsening or no improvement, should administer 1 to 2 mg/kg/d prednisone or equivalent and permanently discontinue ICPi.
- If improved to grade 1 or less, taper corticosteroids over 4 to 6 weeks.
- If no recurrence of chronic renal insufficiency, discuss resumption of ICPi with patient after taking into account the risks and benefits.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should consult nephrology.
- Should evaluate for other causes (recent IV contrast, medications, fluid status, etc).
- Should administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent).

6.2 Symptomatic Nephritis

Recommendation 6.2a – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- If improved to baseline, should resume routine creatinine monitoring.

It is recommended that clinicians manage grade 2 toxicities as follows:

- If improved to grade 1, should taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring.
- If elevations persist > 7 days or worsen and no other cause found, should treat as grade 3.

It is recommended that clinicians manage grade 3 toxicities as follows:

- If improved to grade 1, should taper corticosteroids over at least 4 weeks.
- If elevations persist > 3 to 5 days or worsen, may offer additional immunosuppression (eg, mycophenolate).

Table 6. Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0 × over baseline	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine 2-3 × above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	
Grading	Management
G1	If improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist > 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AKI, acute kidney injury; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; ULN, upper limit of normal; UTI, urinary tract infection.

It is recommended that clinicians manage grade 4 toxicities as follows:

- If improved to grade 1, should taper corticosteroids over at least 4 weeks.
- If elevations persist > 2 to 3 days or worsen, may offer additional immunosuppression (eg, mycophenolate).

Discussion. AKI is an uncommon complication of checkpoint inhibitor immunotherapy. The estimated incidence of any-grade AKI was 1% to 2% in patients treated with a single agent (ipilimumab, nivolumab, pembrolizumab) and 4.5% in those treated with the combination of nivolumab plus ipilimumab. The incidence of grade 3 or 4 AKI was < 1% with single agents and 1.6% with the combination of nivolumab plus ipilimumab.[79,80] While initial studies had quoted a small incidence of AKI with ICPi use, emerging data suggest a higher incidence rate of AKI (range, 9.9% to 29%) with ICPi. The vast majority of this extra toxicity is stage I based on AKI network criteria[80] and typically involves electrolyte disturbances rather than declines in renal function.

In a retrospective series of 13 patients who underwent kidney biopsy at seven centers, renal toxicity was diagnosed a median of 91 days after initiation of checkpoint inhibitor immunotherapy (range, 21 to 245 days). The median peak serum creatinine was 4.5 mg/dL. Pathology from the kidney biopsies revealed acute

tubulointerstitial nephritis in 12 patients and thrombotic microangiography in one patient. Two of 13 patients required transient hemodialysis, and two remained on hemodialysis at the time of publication.[81] Checkpoint inhibitor immunotherapy was discontinued in all 13 patients. Eleven patients were treated with corticosteroids, and among these 11, nine improved. One patient with thrombotic microangiopathy did not improve, despite glucocorticoids, and another patient transiently improved but then worsened. Two additional patients did not receive immunosuppression and did not recover renal function.

Checkpoint inhibitor therapy appears to be safe in patients with baseline renal impairment from a nonimmune basis (eg, prior nephrectomy, old age, hypertension); however, patients with a renal allograft are at high risk of rejecting the transplanted kidney and requiring dialysis. Limited data suggest that the risk of renal allograft rejection with anti-CTLA-4 antibodies[82] may be less than the near-universal rejection seen with PD-1 pathway blockers.[82 85] Although some patients may be able to be treated with PD-1 pathway blockers with preservation of their allografts by having adjustments in their immunosuppressive agents,[86] this approach should only be considered with multidisciplinary input from the renal transplant nephrology team.

Patients should have their renal function (serum creatinine) checked prior to every dose of checkpoint inhibitor therapy. For those with new elevations in creatinine, one should consider holding therapy while other potential causes are evaluated (eg, recent IV radiographic contrast administration, dehydration, other medicines, urinary tract infection) and if identified, treat appropriately. Patients without other obvious causes or who do not respond to alternative treatment measures should be presumed to have immune-related renal toxicity and treated empirically according to the algorithm.

7.0 Nervous System Toxicities

Please refer to Table 7 for a complete set of recommendations, definition of grades, and additional considerations.

7.1 Myasthenia Gravis

Recommendation 7.1a – Diagnostic work-up. It is recommended that the diagnostic work-up for all grades should include the following:

- Acetylcholine receptor (AChR) and antistriated muscle antibodies in blood. If AChR antibodies are negative, consider muscle-specific kinase and lipoprotein-related 4 antibodies in blood.
- Pulmonary function assessment with negative inspiratory force and vital capacity.
- Creatine phosphokinase (CPK), aldolase, ESR, and CRP for possible concurrent myositis.
- Consider MRI of brain and/or spine, depending on symptoms, to rule out CNS involvement by disease or alternate diagnosis.
- If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and transthoracic echocardiogram (TTE) for possible concomitant myocarditis.
- Neurology consultation.
- Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, nerve conduction study (NCS), to exclude neuropathy, and needle EMG to evaluate for myositis.

Recommendation 7.1b – Management. All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise. (Note: There is no grade 1 toxicity).

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and may resume in grade 2 patients (Myasthenia Gravis Foundation of America 1 and 2) only if symptoms resolve.[87]
- Should consult neurology.
- Should offer pyridostigmine starting at 30 mg PO three times a day and gradually increase to a maximum of 120 mg orally four times day as tolerated and based on symptoms.
- May go directly to corticosteroids (prednisone 1 to 1.5 mg/kg PO daily) if symptoms grade 2. Wean based on symptom improvement.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient, may need intensive care unit monitoring.
- Consult neurology.
- Continue corticosteroids and initiate IVIG 2 g/kg over 5 days or plasmapheresis for 5 days.
- Should offer frequent pulmonary function assessment.
- Should offer daily neurologic evaluation.

Qualifying statement. Avoid medications that can worsen myasthenia, such as β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides. ICPi-associated myasthenia gravis may be monophasic; therefore, additional corticosteroid-sparing agents may not be required.

7.2 Guillain-Barré Syndrome

Recommendation 7.2a – Diagnostic work-up. It is recommended that the diagnostic workup should include the following:

- Neurology consultation.
- MRI of spine with and without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening).
- Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome (GBS), cytology should be sent with any CSF sample from a patient with cancer.
- Serum antiganglioside antibody tests for GBS and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia).
- Electrodiagnostic studies to evaluate polyneuropathy.
- Pulmonary function testing (negative inspiratory force/vital capacity).
- Frequent neurochecks.

Recommendation 7.2b – Management. All grades warrant work-up and intervention given the potential for progressive GBS to lead to respiratory compromise. (Note: There is no grade 1 toxicity).

Table 7. Management of Nervous System irAEs in Patients Treated With ICPis

7.0 Nervous System Toxicities	
7.1 Myasthenia gravis	
Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.	
Diagnostic work-up AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood Pulmonary function assessment with NIF and VC CPK, aldolase, ESR, CRP for possible concurrent myositis Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis Neurologic consultation Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis	
Grading	**Management**
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve[87] Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement Pyridostigmine, wean based on improvement ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required	
7.2 Guillain-Barré syndrome	
Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.	
Diagnostic work-up Neurologic consultation MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening) Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer. Serum antiganglioside antibody tests for Guillain-Barré syndrome and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia) Electrodiagnostic studies to evaluate polyneuropathy Pulmonary function testing (NIF/VC) Frequent neurochecks	
Grading	**Management**
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Discontinue ICPi Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus

(continued on following page)

Table 7. Management of Nervous System irAEs in Patients Treated With ICPis (continued)

7.0 Nervous System Toxicities	
Additional considerations Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses Caution with rechallenging for severe cases	
7.3 Peripheral neuropathy	
Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (eg, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.	
Diagnostic work-up	
G1 Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation Consider MRI of spine with or without contrast	
G2: in addition to above MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS Consider neurology consultation	
G3-4: go to Guillain-Barré syndrome algorithm	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management
7.4 Autonomic neuropathy	
Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.	
Diagnostic work-up An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, parproteinemia, amyloidosis, botulism, consider chronic diseases such as Parkinson's and other autoimmune screen • Orthostatic vital signs • Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy • Consider paraneoplastic autoimmune dysautonomia antibody testing (eg, anti-ganglionic acetylcholine receptor, antineuronal nuclear antibody type 1 [ANNA-1], and N-type voltage gated calcium channel antibodies)	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation
G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation
7.5 Aseptic meningitis	
Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).	
Diagnostic work-up MRI of brain with or without contrast + pituitary protocol AM cortisol, ACTH to rule out adrenal insufficiency Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology	

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Table 7. Management of Nervous System irAEs in Patients Treated With ICPis (continued)

7.0 Nervous System Toxicities	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms
7.6 Encephalitis	
Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV). Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic work-up Neurologic consultation MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels. May see elevated WBC count with lymphocytic predominance and/or elevated protein EEG to evaluate for subclinical seizures Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG Evaluation for urinary retention, constipation	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ANCA, antineutrophil cytoplasmic antibodies; CPK, creatine phosphokinase; CRP, C-reactive protein; EMG, electromyography; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IgG, immunoglobulin G; IV, intravenous; IVIG, intravenous immunoglobulin; irAE, immune-related adverse event; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; NA, not applicable; NCS, nerve conduction study; NIF, negative inspiratory force; PCR, polymerase chain reaction; RPR, rapid plasma reagin, TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; VC, vital capacity.

It is recommended that clinicians manage all-grade toxicities as follows:

- Should discontinue ICPi.
- Admission to inpatient unit with capability for rapid transfer to intensive care unit–level monitoring.
- Corticosteroids are not usually recommended for idiopathic GBS; however, in ICPi-related forms, a trial is reasonable. Should start IVIG 0.4 g/kg/d for 5 days for a total dose of 2 g/kg or plasmapheresis plus concurrent corticosteroids (methylprednisolone 2 to 4 mg/kg/d).
- Should offer frequent neurochecks and pulmonary function monitoring.
- Should monitor for concurrent autonomic dysfunction.
- Nonopioid management of neuropathic pain.
- Treatment of constipation/ileus.

7.3 Peripheral Neuropathy

Recommendation 7.3a – Diagnostic work-up. It is recommended that the diagnostic work-up for grade 1 should include the following:

- Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV. Consider serum protein electrophoresis and other vasculitic and autoimmune screen.
- Consider MRI of spine with or without contrast.
- Consider neurology consultation.

It is recommended that the diagnostic work-up for grade 2 should include the following, in addition to what is recommended for grade 1:

- MRI of spine advised; MRI of brain if cranial nerve.
- Consider EMG/NCS.
- Consider neurology consultation

It is recommended that the diagnostic work-up for grades 3 to 4 should follow that of GBS.

Recommendation 7.3b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should have a low threshold to hold ICPi and monitor symptoms for a week. If to continue, should monitor very closely for any symptom progression.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and resume once return to grade 1.
- Should offer initial observation OR may initiate prednisone 0.5 to 1 mg/kg (if progressing from mild).
- Should offer neurontin, pregabalin, or duloxetine for pain.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient.
- Should consult neurology.
- Should initiate IV methylprednisolone 2 to 4 mg/kg and proceed as per GBS management.

7.4 Autonomic Neuropathy

Recommendation 7.4a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include:

- Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism. Consider chronic diseases such as Parkinson and other autoimmune screening.
- Orthostatic vital signs.
- Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy.
- Consider paraneoplastic autoimmune dysautonomia antibody testing (eg, anti-ganglionic acetylcholine receptor, antineuronal nuclear antibody type 1 [ANNA-1], and N-type voltage gated calcium channel antibodies).

Recommendation 7.4b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should have a low threshold to hold ICPi and monitor symptoms for a week. If to continue, should monitor very closely for any symptom progression.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and resume once return to grade 1.
- Should offer initial observation OR may initiate prednisone 0.5 to 1 mg/kg (if progressing from mild).
- Should consult neurology.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient.
- Should initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper.
- Should consult neurology.

7.5 Aseptic Meningitis

Recommendation 7.5a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- MRI of brain with or without contrast and pituitary protocol.
- Cortisol (AM), adrenocorticotropic hormone (ACTH) to rule out adrenal insufficiency.
- Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, and polymerase chain reaction (PCR) for herpes simplex virus and other viral PCRs depending on suspicion, cytology.
- May see elevated WBC count with normal glucose, normal culture, and Gram stain. May see reactive lymphocytes or histiocytes on cytology.

Recommendation 7.5b – Management. It is recommended that clinicians manage all-grade toxicities as follows:

- Should hold ICPi.
- May offer empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results.
- Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5 to 1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms.

7.6 Encephalitis

Recommendation 7.6a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Neurologic consultation.
- MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
- Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for herpes simplex virus, and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.
- May see elevated WBC count with lymphocytic predominance and/or elevated protein.
- EEG to evaluate for subclinical seizures.

- Blood: metabolic; CBC; ESR; CRP; antineutrophil cytoplasmic antibodies (if suspect vasculitic process); and thyroid panel, including thyroid peroxidase and thyroglobulin.
- Rule out concurrent anemia/thrombotic thrombocytopenic purpura (TTP) as cause of encephalopathy; check peripheral smear.

Recommendation 7.6b – Management. It is recommended that clinicians manage all-grade toxicities as follows:

- Should hold ICPi.
- As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative.
- Should offer a trial of methylprednisolone 1 to 2 mg/kg.
- If severe or progressing symptoms or oligoclonal bands present, may offer pulse corticosteroid methylprednisolone 1 g IV daily for 3 to 5 days plus IVIG 2 g/kg over 5 days.
- If positive for autoimmune encephalopathy or paraneoplastic antibody and limited or no improvement, may offer rituximab or plasmapheresis in consultation with neurology.

7.7 Transverse Myelitis

Recommendation 7.7a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Neurologic consultation
- MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain done with and without contrast
- Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies
- Blood: B12, HIV, rapid plasma reagin, ANA, Ro/La, TSH, aquaporin-4 immunoglobulin G
- Evaluation for urinary retention and constipation

Recommendation 7.7b – Management. It is recommended that clinicians manage all-grade toxicities as follows:

- Should permanently discontinue ICPi.
- Should administer methylprednisolone 2 mg/kg.
- Should strongly consider higher doses of 1 g/d for 3 to 5 days.
- Should strongly consider IVIG.

Discussion. ICPi-related neurologic toxicities were originally reported with 1% incidence; however, more-recent analyses suggest that they are more common.[88 90] An analysis of 59 trials totaling 9,208 patients reported the overall incidence of neurologic irAEs to be 3.8% in patients receiving anti–CTLA-4 antibodies, 6.1% in patients receiving anti–PD-1 antibodies, and 12.0% in patients receiving a combination of both.[88] However, the incidence of grade 3 and 4 irAEs was $<$ 1% across all ICPis. A review of patients who received ICPi therapy for melanoma at the Royal Marsden Hospital found the rate of neurologic irAEs to be 2.4%.[90] The EORTC 18071 trial reported neurologic irAEs at a rate of 4% in the adjuvant ipilimumab arm.[91] Most neurologic events are mild; headache and peripheral sensory neuropathy are the most commonly encountered symptoms.[88] Severe neurologic irAEs grade 3 or higher occur in $<$ 1% of patients and may involve the peripheral nervous system or CNS. They encompass a broad spectrum of neurologic syndromes, including myasthenia gravis/myasthenic syndrome, aseptic meningitis, encephalitis, sensory motor neuropathy or Guillain-Barré-like syndromes, painful sensory neuropathy, enteric neuropathy, transverse myelitis, and posterior reversible encephalopathy syndrome.

The first step in management is to rule out CNS progression of cancer, seizure activity, infection, and metabolic derangement as causes of neurologic symptoms. Consultation with a neurologist is advised for all neurologic irAEs grade 2 or higher to help to determine the type and severity of neurologic impairment and guide selection and interpretation of further neurologic tests and management. In patients presenting with headache (which, in isolation, could suggest aseptic meningitis), it is important to evaluate for new confusion, altered behavior, aphasia, seizure-like activity, or short-term memory loss, any of which might suggest encephalitis. The distinction is important because suspected encephalitis triggers a distinct work-up and management from aseptic meningitis, including autoimmune encephalitis and paraneoplastic antibody evaluation and consideration of pulse-dose corticosteroids.[92,93]

For most neurologic irAEs, diagnostic work-up should include MRI of the brain and/or spine with and without contrast and CSF analysis, including cytology, to rule out leptomeningeal metastasis. CSF analysis is helpful in cases of clinical suspicion of encephalitis, aseptic meningitis, and sensory motor neuropathy or GBS, revealing lymphocytic pleocytosis and elevated protein in many cases. Abnormal leptomeningeal enhancement on neuroimaging may occur in aseptic meningitis, encephalitis, and sensory motor neuropathy, underscoring the importance of checking CSF cytology, which should be negative. NCSs and EMG may assist in diagnosis of sensory symptoms or weakness. Autonomic neuropathy may occur along with other neuropathy symptoms and should be screened for. EEG is helpful for ruling out seizure activity in cases of encephalopathy. Paraneoplastic neurologic syndromes and autoimmune encephalopathies should also be considered.[92]

For mild (grade 1) neurologic symptoms, checkpoint inhibitor therapy may be continued under close observation. For grade 2 or higher neurologic symptoms, checkpoint inhibitor therapy should be held until the nature of the irAE and symptom progression is defined. In the event of significant neurologic toxicity of grade 2 or higher, a corticosteroid equivalent of methylprednisolone 1 to 4 mg/kg, depending on the symptoms, should be started. For more-severe grade 3 or higher toxicity, immunotherapy should be discontinued. Symptom control may require escalation of corticosteroid therapy to pulse-dose methylprednisolone (1 g daily for 5 days) in addition to IVIG, or plasma exchange (PEX). Pyridostigmine may be helpful for myasthenia gravis in addition to corticosteroids.

8.0 Hematologic Toxicities

Please refer to Table 8 for a complete set of recommendations, definition of grades, and additional considerations.

8.1 Autoimmune Hemolytic Anemia

Recommendation 8.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites).

Table 8. Management of Hematologic irAEs in Patients Treated With ICPis

8.0 Hematologic Toxicities	
8.1 Autoimmune hemolytic anemia	
Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.	
Diagnostic work-up History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites) Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb DIC panel, which could include PTINR infectious causes Autoimmune serology Paroxysmal nocturnal hemoglobinuria screening Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies Protein electrophoresis, cryoglobulin analysis Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc) Assessment of methemoglobinemia	
Grading	**Management**
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 mg/kg/d prednisone equivalents
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.
Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed[164]	
8.2 Acquired TTP	
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Diagnostic work-up History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes PT, activated PTT, fibrinogen Blood group and antibody screen, direct antiglobulin test, CMV serology Consider CT/MRI brain, echocardiogram, ECG Viral studies Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously	
Grading	**Management**
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy
G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hematology consult Administer 0.5-1 mg/kg/d prednisone

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Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2)	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy
G4: Life-threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)	Hematology consult In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress[94-96] Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, *Escherichia coli* 0157, etc Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion	
Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade 2	Continue ICPi with close clinical follow-up and laboratory evaluation Supportive care
G3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae) G4: Life-threatening consequences (eg, CNS thrombosis/embolism or renal failure)	Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, then 1,200 mg every 2 weeks Red blood transfusion according to existing guidelines
8.4 Aplastic anemia	
Definition: Condition in which the body stops producing enough new blood cells	
Diagnostic work-up History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count Viral studies, including CMV, HHV6, EBV, parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D Serum LDH, renal function Work-up for infectious causes Identify marrow hypo/aplasia Bone marrow biopsy and aspirate analysis Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	Management
G1: Nonsevere, > 0.5 polymorphonuclear cells $\times 10^9$/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count > 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition

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Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
G3-4: Very severe, ANC < 200, platelet count < 20,000, reticulocyte count < 20,000, plus hypocellular marrow < 25%	Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count	Continue ICPi
G3: 250-499 PB lymphocyte count	Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening
G4: < 250 PB lymphocyte count	Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and *Helicobacter pylori* Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management
G1: Platelet count < 100/μL	Continue ICPi with close clinical follow up and laboratory evaluation
G2: Platelet count < 75/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia[97]; consult for further details)
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	

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Table 8. Management of Hematologic irAEs in Patients Treated With ICPis (continued)

8.0 Hematologic Toxicities	
Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01-0.05 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab *v* cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: Acquired hemophilia A requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.[98]	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AE, adverse event; ANC, antineutrophil cytoplasmic antibodies; ATG, antithymocyte globulin; CMV, cytomegalovirus; CT, computed tomography; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; G, grade; GPI, glycosylphosphatidylinositol; Hgb, hemoglobin; HHV6, human herpesvirus 6; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PB, peripheral blood; PEX, plasma exchange; PNH, paroxusmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.

- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear. LDH, haptoglobin, bilirubin, reticulocyte count, free hemoglobin.
- Disseminated intravascular coagulation panel, which could include Prothrombin Time and International Normalized Ratio (PT/INR), infectious causes.
- Autoimmune serology.
- Paroxysmal nocturnal hemoglobinuria screening.
- Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes.
- Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies.
- Protein electrophoresis, cryoglobulin analysis.
- Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, iron, thyroid, infection.
- Glucose-6-phosphate dehydrogenase.
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc).
- Assessment of methemoglobinemia.

Recommendation 8.1b – Management. It is recommended that clinicians manage all grade 1 toxicities as follows:

- Should continue to offer ICPi with close clinical follow-up and laboratory evaluation.

It is recommended that clinicians manage all grade 2 toxicities as follows:

- Should hold ICPi and strongly consider permanent discontinuation.
- Should administer 0.5 to 1 mg/kg/d prednisone equivalents.

It is recommended that clinicians manage all grade 3 toxicities as follows:

- Should permanently discontinue ICPi.
- Should use clinical judgment and consider admitting the patient.
- Should consult hematology.
- Should administer prednisone 1 to 2 mg/kg/d (oral or IV depending on symptoms/speed of development).
- If worsening or no improvement, should administer 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment.
- May offer RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, noncardiac inpatients).
- Should offer patients supplementation with folic acid 1 mg once daily.

It is recommended that clinicians manage all grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient.
- Should consult hematology.
- Should administer IV prednisone 1 to 2 mg/kg/d.
- If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, should initiate other

immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil.
- Should offer RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with a possible ICPi severe AE is in house.

8.2 Acquired Thrombotic Thrombocytopenic Purpura

Recommendation 8.2a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine).
- Physical examination, peripheral smear.
- ADAMTS13 activity level and inhibitor titer.
- LDH, haptoglobin, reticulocyte count, bilirubin.
- Prothrombin time (PT), activated partial thromboplastin time (PTT), fibrinogen.
- Blood group and antibody screen, direct antiglobulin test, CMV serology.
- Consider CT scan/MRI of brain, echocardiogram, ECG.
- Viral studies.
- Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously.

Recommendation 8.2b – Management. It is recommended that clinicians manage all-grade toxicities as follows:

- The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition. Hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity.
- Initially, the patient should be stabilized and any critical organ dysfunction stabilized.

It is recommended that clinicians manage grade 1 to 2 toxicities as follows:

- Should hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that currently, there are no data to recommend restarting ICPi therapy.
- Should consult hematology.
- Should administer 0.5 to 1 mg/kg/d prednisone.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that currently there are no data to recommend restarting ICPi therapy.
- Should consult hematology.
- In conjunction with hematology, should initiate PEX according to existing guidelines, with further PEX dependent on clinical progress.[94 96]
- Should administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX.
- May offer rituximab.

8.3 Hemolytic Uremic Syndrome

Recommendation 8.3a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes).
- CBC with indices.
- Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis.
- Serum creatinine.
- ADAMTS13 (to rule out TTP).
- Homocysteine/methylmalonic acid.
- Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial).
- Evaluate reticulocyte count and mean corpuscular volume.
- Evaluation of infectious cause, including screening for Epstein-Barr virus (EBV), CMV, human herpesvirus 6.
- Evaluation for nutritional causes of macrocytosis (B12 and folate).
- Pancreatic enzymes.
- Evaluation for diarrheal causes, shiga toxin, *Escherichia coli* 0157, etc
- Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia.
- Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc).
- Evaluation for concurrent confusion.

Recommendation 8.3b – Management. It is recommended that clinicians manage grade 1 to 2 toxicities as follows:

- Should continue to offer ICPi with close clinical follow-up and laboratory evaluation.
- Should offer supportive care.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Permanently discontinue ICPi.
- Begin eculizumab therapy 900 mg weekly for four doses, 1,200 mg on week 5, then 1,200 mg every 2 weeks.
- Red blood transfusion according to existing guidelines.

8.4 Aplastic Anemia

Recommendation 8.4a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections).
- CBC, smear, reticulocyte count.
- Viral studies, including CMV, human herpesvirus 6, EBV, parvovirus.
- Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D.
- Serum LDH, renal function.
- Work-up for infectious causes.
- Identify marrow hypo/aplasia.
- Bone marrow biopsy and aspirate analysis.
- Peripheral blood analysis, including neutrophil count, proportion of glycosylphosphatidylinositol-negative cells.
- Flow cytometry to evaluate loss of glycosylphosphatidylinositol-anchored proteins.
- Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered.

Recommendation 8.4b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should hold ICPi and provide growth factor support, close clinical follow-up, and laboratory evaluation.
- Supportive transfusions as per local guidelines.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and provide growth factor support and close clinical laboratory evaluations daily.
- Should administer ATG + cyclosporine. HLA typing and evaluation for bone marrow transplantation if patient is candidate. All blood products should be irradiated and filtered.
- May also offer supportive care with granulocyte colony-stimulating factor.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi and monitor weekly for improvement. If not resolved, should discontinue treatment until AE has reverted to grade 1.
- Should consult hematology.
- Should offer horse ATG plus cyclosporine.
- If no response, should repeat immunosuppression with rabbit ATG plus cyclosporine, alemtuzumab.
- For refractory patients, may offer eltrombopag plus supportive care.

8.5 Lymphopenia

Recommendation 8.5a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease).
- Evaluation of nutritional state as cause.
- Spleen size.
- CBC with differential and reticulocyte counts
- CXR for evaluation of presence of thymoma.
- Bacterial cultures and evaluation for infection (fungal, viral, bacterial, specifically CMV/HIV).

Recommendation 8.5b – Management. It is recommended that clinicians manage grade 1 to 2 toxicities as follows:

- Should continue to offer ICPi.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should hold ICPi and discuss resumption with patient only after taking into account the risks and benefits.
- Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* pneumonia prophylaxis, CMV screening. HIV/hepatitis screening if not already done.
- May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease.

8.6 Immune Thrombocytopenia

Recommendation 8.6a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy).
- Family history of autoimmunity or personal history of autoimmune disease.
- History of viral illness.
- CBC.
- Peripheral blood smear, reticulocyte count.
- Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis.
- Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and *Helicobacter pylori*.
- Direct antigen test should be checked to rule out concurrent Evan syndrome.
- Nutritional evaluation.
- Bone marrow evaluation if other cell lines affected and concern for aplastic anemia.

Recommendation 8.6b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue ICPi with close clinical follow-up and laboratory evaluation.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi but monitor for improvement. If not resolved, should interrupt treatment until AE has reverted to grade 1.
- Should administer prednisone 1 mg/kg/d (dosage range, 0.5 to 2 mg/kg/d) orally for 2 to 4 weeks after which time this medication should be tapered over 4 to 6 weeks to the lowest effective dose.
- IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should hold ICPi but monitor for improvement. If not resolved, should interrupt treatment until AE has reverted to grade 1.
- Should consult hematology.
- Should administer prednisone 1 to 2 mg/kg/d (oral or IV depending on symptoms).
- If worsening or no improvement, should administer 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment.
- IVIG may be used with corticosteroids when a more-rapid increase in platelet count is required.
- If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary.

- If previous treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include splenectomy, rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression.

Adapted from the American Society of Hematology guideline on immune thrombocytopenia[97]; consult for further details.

8.7 Acquired Hemophilia

Recommendation 8.7a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- Full blood count to assess platelet number, fibrinogen, PT, PTT, international normalized ratio. The typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT.
- MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding.
- Medication review to assess for alternative causes.
- Determination of Bethesda unit level of inhibitor.

Recommendation 8.7b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should hold ICPi and discuss resumption with patient only after taking into account the risks and benefits.
- Should administer 0.5 to 1 mg/kg/d prednisone.
- Transfusion support as required.
- May treat bleeding episodes in consultation with a hematologist and/or hemophilia center experienced in the treatment of inhibitors.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi and discuss resumption with patient only after taking into account the risks and benefits.
- Should consult hematology.
- Should administer 1 mg/kg/d prednisone ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1 to 2 mg/kg/d). Choice of rituximab versus cyclophosphamide is patient specific and should be done with assistance of hematology consult. Prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks.

It is recommended that clinicians manage grade 3 to 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient.
- Should consult hematology.
- Administration of factor replacement, choice based on Bethesda unit level of inhibitor.
- Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity). Caution should be taken in the elderly and those with coronary artery disease.
- Prednisone 1 to 2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1 to 2 mg/kg/d).
- Transfusion support as required for bleeding.
- If worsening or no improvement, should add cyclosporine or immunosuppression/immunoadsorption.

Qualifying statement. Acquired hemophilia A requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.[98]

Discussion. Review of literature for hematologic toxicities of checkpoint inhibitors revealed evidence of toxicity but relatively little in the form of comprehensive evaluation. A recent review has incorporated a systematic review of all phase I to III prospective clinical trials for Food and Drug Administration–approved ICPis and collated the incidence of common toxicities (unpublished data, J. Holter Chakrabarty, 2017).

Anemia (grades 1 to 4) occurs in approximately 11% of patients, with grades 3/4 at approximately 5.4% (1.1% to 17%).[99,100] If anemia progresses to pancytopenia or multiple cell lines are affected,[101] evaluation for pure red cell aplasia,[102] autoantibodies,[103] aplastic anemia, and myelodysplasia must be considered. Toxicities between checkpoint inhibitors appear relatively similar. The majority of patients respond to withdrawal and are managed successfully with corticosteroids, IVIG, and growth factor support. Hemolytic anemia has been described as having development of autoantibodies[103] and can commonly be treated by withholding ICPi, corticosteroids, and IVIG.

Thromobocytopenia is also relatively uncommon, occurring in approximately 8% (1% to 28%) of patients for all grades and 4.3% (3% to 6%) for grades 3/4.[99,104] Evaluation for causes of thrombocytopenia must be undertaken, including evaluation of TTP, disseminated intravascular coagulation, myelodysplastic syndrome, as well as immune-mediated thrombocytopenia related to ICPi. Corticosteroids have been shown to be effective with transfusion support as required.

Factor-related acquired bleeding disorders have been described with factor VIII.[105,106] Involvement of hematologic expertise should be considered, including evaluation for antibody titer formation and choice of factor replacement. At low titer levels, simple factor replacement and corticosteroids may be effective; however, at high Bethesda unit levels > 5, bypassing agents such as factor VIII inhibitor bypass activity or factor VII may be required. Care in elderly patients when using these agents should be considered

In most cases of mild hematologic toxicities, ICPi can be safely continued. However, cases of more-severe hemolytic anemia, pure red cell anemia, aplastic anemia, severe thrombocytopenia, or coagulation factor deficiencies have been described. In these cases, corticosteroids should be started and supportive care measures instituted. Of note, lymphopenia is not an uncommon event, and the degree of lymphopenia should be assessed with CD4 count and appropriate prophylaxis/assessment started for *Pneumocystis* and CMV undertaken.

Checkpoint inhibitors have been used in both organ and hematopoetic stem-cell transplantation. In both, caution is advised, and immediate involvement with subspecialty care is advised secondary to increased toxicities that have been seen in these populations.[107]

9.0 Cardiovascular Toxicities

Please refer to Table 9 for a complete set of recommendations, definition of grades, and additional considerations.

9.1 Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function With Heart Failure and Vasculitis

Recommendation 9.1a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

At baseline:

- ECG
- Consider troponin, especially in patient treated with combination immune therapies

Upon signs/symptoms (consider cardiology consult):

- ECG
- Troponin
- Brain natriuretic peptide (BNP)
- Echocardiogram
- CXR

Additional testing to be guided by cardiology and may include:

- Stress test
- Cardiac catherization
- Cardiac MRI

Recommendation 9.1b – Management. It is recommended that clinicians manage all-grade toxicities as follows, as all grades warrant work-up and intervention given potential for cardiac compromise:

- Should hold ICPi and permanently discontinue after grade 1.
- Should administer high-dose corticosteroids (1 to 2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms).
- Should admit patient and consult cardiology.
- Should manage cardiac symptoms according to American College of Cardiology (ACC)/AHA guidelines and with guidance from cardiology.
- May offer immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities.
- In patients without an immediate response to high-dose corticosteroids, may offer early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or ATG.

Qualifying statement. Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.[108]

9.2 Venous Thromboembolism

Recommendation 9.2a – Diagnostic work-up. It is recommended that the diagnostic work-up should include the following:

- An evaluation of signs and symptoms of pulmonary embolism (PE) or deep vein thrombosis (DVT), which may include a clinical prediction rule to stratify patients with suspected venous thromboembolism, venous ultrasound for suspected DVT, and CT pulmonary angiography for suspected PE.
- May also offer D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate.
- Ventilation/perfusion scan is also an option when CT pulmonary angiography is not appropriate.
- May make use of other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas.

Recommendation 9.2b – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should offer warm compress.
- Should offer clinical surveillance.

It is recommended that clinicians manage grade 2 to 3 toxicities as follows:

- Should continue to offer ICPi.
- Should manage according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties.
- Low-molecular-weight heparin is suggested over vitamin K agonist, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment.
- IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should admit patient and manage according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology.
- Should seek respiratory and hemodynamic support.
- Low-molecular-weight heparin is suggested over vitamin K agonist, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment.
- IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term.
- Should offer further clinical management as indicated based on symptoms.

Qualifying statement. While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of grade 4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment. Anticoagulant therapy duration should continue for a minimum of 9 to 12 months to indefinitely in the setting of active cancer unless the patient is asymptomatic, doing well, or in remission.[109,110]

Discussion. Cardiovascular complications of ICPi therapy are rare but potentially life-threatening and/or of devastating clinical consequences. They have been reported with all currently approved agents.[111] However, due to their rarity and involvement of major organs leading to rapidly fatal consequences, data are sparse and generally have included case reports or small case series.[112] Cardiovascular irAEs occur in $< 0.1\%$ of patients receiving these therapies based on a review of pharmaceutical safety databases.[75] The risk may be increased when combination therapy is

Table 9. Management of Cardiovascular irAEs in Patients Treated With ICPis

9.0 Cardiovascular Toxicities	
9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis	
Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue	
Diagnostic work-up At baseline ECG Consider troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (consider cardiology consult) ECG Troponin BNP Echocardiogram CXR Additional testing to be guided by cardiology and may include Stress test Cardiac catherization Cardiac MRI	
Grading	**Management**
G1: Abnormal cardiac biomarker testing, including abnormal ECG G2: Abnormal screening tests with mild symptoms G3: Moderately abnormal testing or symptoms with mild activity G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	All grades warrant work-up and intervention given potential for cardiac compromise Consider the following: Hold ICPi and permanently discontinue after G1 High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin
Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.[108]	
9.2 Venous thromboembolism	
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE	
Diagnostic work-up Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT CTPA for suspected PE Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate Ventilation/perfusion scan is also an option when CTPA is not appropriate Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas	
Grading	**Management**
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Continue ICPi Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G4: Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Permanently discontinue ICPi Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms

(continued on following page)

Table 9. Management of Cardiovascular irAEs in Patients Treated With ICPis (continued)

9.0 Cardiovascular Toxicities
Additional considerations
While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of G4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment.
Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission.[109,110]
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CXR, chest x-ray; DVT, deep vein thrombosis; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; VKA, vitamin K agonist.

used. In these safety data, combination therapy of ipilimumab and nivolumab had greater rates of cardiovascular complications than nivolumab alone (0.28% *v* 0.06%).[75] Mortality is high, with death frequently secondary to refractory arrhythmia or cardiogenic shock.[75,113,114]

One review of compiled case reports and case series by Jain et al[111] found that the onset of cardiovascular irAEs can be as soon as 2 weeks and as long as 32 weeks after initiation of therapy, with a median onset of 10 weeks after initiation. Based on results of myocardial biopsies, these complications are thought to be caused by lymphocytic infiltration of the myocardium and myocardial conduction system.[75] Pathology has shown lymphocytic infiltration in the tumor specimens.

A wide range of cardiovascular complications have been reported. Pathologic review shows occurrences of myocarditis; myocardial fibrosis; cardiomyopathy; heart failure; conduction abnormalities, including heart block; and cardiac arrest.[111] Pericarditis and pericardial effusions have been described as well.[35,115] There has also been a case report of irAE-associated acute coronary syndrome.[116]

Immune-mediated myocarditis may result in heart failure or arrhythmia. The myocarditis may be fulminant, progressive, and life-threatening.[75,117] Acute heart failure may occur secondary to decreased cardiac function and diminished ejection fraction.[75,114]

Conduction abnormalities can include complete heart block[75,114] and arrhythmias. A variety of dysrhythmias may occur from the more benign (supraventricular tachycardias) to more fatal and can lead to sudden death (ventricular tachycardias).[75,76,112 114,118 120]

Presentation of cardiovascular complications of checkpoint inhibitors could include arrhythmia, palpitations, chest pain, or signs and symptoms of heart failure (shortness of breath, peripheral edema, pleural effusion, fatigue). Severe cases can present with cardiogenic shock or sudden death. Patients can also present with fatigue, malaise, myalgia, and/or weakness alone or in combination with more-specific cardiovascular symptoms. Symptoms can often be masked by other irAEs (eg, pneumonitis, hypothyroidism) or symptoms related to disease (eg, pulmonary symptoms).

Initial evaluation of patients with potential cardiovascular toxicity should include ECG, troponin, BNP, and CXR. Reported cases have invariably had elevations of troponin, CK, and CK-MB.[112] BNP will also be elevated in cases with decrease ejection fraction. Diagnostic evaluation should consider the possibility of other etiologies of the patient's symptoms and could include, for example, cardiac stress testing, heart catheterization, or cardiac MRI. Due to the possibility of arrhythmia and progression to life-threatening arrhythmias or heart block, continuous telemetry monitoring should be instituted. Typically, many of these patients will often be admitted to an inpatient unit and worked up there given the severity of the symptoms. Patients with mild shortness of breath of unclear etiology should get typical outpatient testing (ECG, BNP, troponin).

Echocardiogram to evaluate for cardiac function should be performed in symptomatic patients. Echocardiogram may reveal decreased left or right ventricular ejection fraction (with global or regional abnormalities). Cardiac MRI can demonstrate evidence of myocarditis but is less sensitive than endomyocardial biopsy.[112,117] Endomyocardial biopsy should be considered for patients who are unstable or failed to respond to initial therapy or in whom the diagnosis is in doubt. Typically, initial diagnostic testing reveals issues, and treatment is often administered empirically before confirmatory pathologic testing is obtained.

There is no clear evidence regarding the efficacy or value of routine baseline or serial ECGs or troponin measurements in patients receiving checkpoint inhibitor therapy. Some centers obtain baseline testing, and others continue this through the initial period of therapy. Some centers stratify management based on magnitude of troponin changes.[112] Baseline information can potentially be useful when patients present acutely with nonspecific symptoms and have equivocal diagnostic testing.

Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications of irAEs due to either malignant arrhythmia or the possibility of fulminant myocarditis with heart failure. Holding checkpoint inhibitor therapy is recommended for all grades of complications, including grade 1 (asymptomatic biomarker elevations), with reinstitution of treatment almost never happening.[111,112]

For patients with mild to moderate symptoms (grades 2 to 3), systemic prednisone or methylprednisolone is indicated at 1 to 2 mg/kg/day.[6,75,113] Those with more severe disease (grades 3 to 4), including clinical decompensation, highly abnormal testing, fulminant disease, cardiogenic shock, and acute heart failure, or with life-threatening arrhythmia should be considered for more-aggressive therapy, as should those who fail to respond to initial corticosteroid dosing within 3 to 5 days. This could include therapy with higher doses of corticosteroids (methylprednisolone at 1 g daily) and the possible addition of mycophenolate, infliximab, or ATG.[75,111 113,117] Management of symptoms of arrhythmia and

heart failure should be as per national cardiology guidelines and clinical judgment.[112]

Although some diseases are fulminant and progress to death, with appropriate therapy and holding of checkpoint inhibitors, cardiac contractility and conduction abnormalities can improve.[119] There have not been sufficient cases in the literature to determine the proportion expected to progress or improve. Given the potential severity of the symptoms, the patient's disease status must be taken into account before excessive support measures are performed (eg, defibrillator, resuscitation, balloon pump).

The evidence on how to distinguish among risk factors in patients with cancer treated with ICPi therapy is limited. Furthermore, determining the true cause of thromboembolic disease in such patients is difficult, if not impossible, given the thrombogenicity of both the disease and the treatment. Treating physicians are urged to use clinical judgment in the management of these patients.

10.0 Ocular Toxicities

Please refer to Table 10 for a complete set of recommendations, definition of grades, and additional considerations.

Recommendation 10.0 – Diagnostic work-up for all ocular toxicities. It is recommended that clinicians counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms:

- Blurred vision
- Change in color vision
- Photophobia
- Distortion
- Scotomas
- Visual field changes
- Double vision
- Tenderness
- Pain with eye movement
- Eyelid swelling
- Proptosis

It is recommended that the diagnostic work-up should include the following, under the guidance of ophthalmology:

- Check vision in each eye separately
- Color vision
- Red reflex
- Pupil size, shape, and reactivity
- Fundoscopic examination
- Inspection of anterior part of eye with penlight

Qualifying statement. Clinicians should be aware that ocular irAEs are many times seen in the context of other organ irAEs, and there should be a high level of clinical suspicion as symptoms may not always be associated with severity. It is best to treat ocular irAEs after ophthalmologist eye examination.

10.1 Uveitis/Iritris

Recommendation 10.1 – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should refer to ophthalmology within 1 week.
- Should offer artificial tears.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi temporarily until after ophthalmology consult.
- Should make an urgent ophthalmology referral.
- Should administer topical corticosteroids, cycloplegic agents, systemic corticosteroids.
- May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to $\leq$ 10 mg. Continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity. Should re-treat after return to grade 1 or less.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should permanently discontinue ICPi.
- Should make an urgent ophthalmology referral.
- Should administer systemic corticosteroids and intravitreal/periocular/topical corticosteroids.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should make an emergent ophthalmology referral.
- Should administer systemic corticosteroids (IV prednisone 1 to 2 mg/kg or methylprednisolone 0.8 to 1.6 mg/kg and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion)
- May use infliximab in cases that are severe and refractory to standard treatment.

10.2 Episcleritis

Recommendation 10.2 – Management. It is recommended that clinicians manage grade 1 toxicities as follows:

- Should continue to offer ICPi.
- Should refer to ophthalmology within 1 week.
- Should offer artificial tears.

It is recommended that clinicians manage grade 2 toxicities as follows:

- Should hold ICPi until after ophthalmology consult.
- Should make an urgent ophthalmology referral.
- Should administer topical corticosteroids, cycloplegic agents, systemic corticosteroids.

It is recommended that clinicians manage grade 3 toxicities as follows:

- Should permanently discontinue ICPi.
- Should make an urgent ophthalmology referral.
- Should administer systemic corticosteroids and topical corticosteroids with cycloplegic agents.

It is recommended that clinicians manage grade 4 toxicities as follows:

- Should permanently discontinue ICPi.
- Should make an emergent ophthalmology referral.
- Should administer systemic corticosteroids and topical corticosteroids with cycloplegic agents.

Table 10. Management of Ocular irAEs in Patients Treated With ICPis

10.0 Ocular Toxicities	
Counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms	
Blurred vision	
Change in color vision	
Photophobia	
Distortion	
Scotomas	
Visual field changes	
Double vision	
Tenderness	
Pain with eye movement	
Eyelid swelling	
Proptosis	
Evaluation, under the guidance of ophthalmology	
Check vision in each eye separately	
Color vision	
Red reflex	
Pupil size, shape, and reactivity	
Fundoscopic examination	
Inspection of anterior part of eye with penlight	
Prior conditions	
Exclude patients with history of active uveitis	
History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy	
Additional considerations	
Ocular irAEs are many times seen in the context of other organ irAEs	
High level of clinical suspicion as symptoms may not always be associated with severity	
Best to treat after ophthalmologist eye examination	
10.1 Uveitis/iritis	
Definition: Inflammation of the middle layer of the eye	
Diagnostic work-up: as per above	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]	
10.2 Episcleritis	
Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection	
Diagnostic work-up: As per 10.0	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment[121,122]	

(continued on following page)

Table 10. Management of Ocular irAEs in Patients Treated With ICPis (continued)

10.0 Ocular Toxicities	
10.3 Blepharitis	
Definition: Inflammation of the eyelid that affects the eyelashes or tear production	
Diagnostic work-up: As per 10.0	
Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous, TNF, tumor necrosis factor.

10.3 Blepharitis

Recommendation 10.3 – Management. It is recommended that clinicians manage all-grade toxicities as follows:

- Should offer warm compresses and lubrication drops.
- Should continue to offer ICPi unless irAE is persistent and serious.

Discussion. In the context of irAEs as a result of ICPi therapy in cancer, ocular toxicities are considered uncommon and less complex in their management compared with other immune-related toxicities.

A variety of ocular events have been reported with CTLA-4–, anti–PD-1–, and anti–PD-L1–inhibiting agents, including uveitis, iritis, episcleritis, and blepharitis. Like in other irAEs, the principal mechanism of the encountered toxicity is inflammatory and the principal management is immunosuppression with corticosteroids.

The overall incidence of uveitis with ICPis, including ipilimumab,[123,124] anti–PD-1 antibodies,[125 127] and anti–PD-L1 agents,[165,166] is up to 1%, although the incidence may be higher in patients receiving combination ICPis.[128] Presenting symptoms include blurred vision and photophobia, change in color vision, and distortion as well as physical signs like tenderness, swelling, and pain with eye movement, among others. The practitioner should be aware that symptoms of uveitis may not indicate severity of the syndrome and thus should seek consultation with ophthalmology and slit lamp examination. Rarely, a panuveitis is induced that can lead to exudative retinal detachment and can be vision threatening. Milder forms of uveitis respond to temporary holding of ICPis and topical corticosteroids, and any symptomatic presentation should prompt urgent ophthalmology evaluation. Typical management includes topical corticosteroids and often the addition of cycloplegic agents, and in rare cases, systemic corticosteroid administration is necessary.

Episcleritis is a rare, but clinically important event, occurring in < 1% of treated patients.[124] The management is similar to the one recommended for uveitis, and any visual compromise (vision < 20/40) should prompt urgent ophthalmology referral to assess the need for more-specific interventions. We recommend ophthalmology referral for all cases of episcleritis even if asymptomatic, and holding immune checkpoint therapy until such evaluation is completed. Artificial tears, topical corticosteroids, and cycloplegic agents are typically used and highly effective in managing this toxicity, but in rare cases, systemic corticosteroids may be required. In case of recurrent events or a grade 4 presentation (vision 20/200 or worse), permanent discontinuation of ICPi is advised. Infliximab may be considered for severe and treatment-refractory cases, although the data on this intervention rely on case reports only.

Blepharitis is equally rare as other ocular toxicities and is encountered < 1% of patients treated with ICPis. This toxicity is managed with warm compresses and artificial tears for lubrication. Disruption of therapy is not typically necessary but may be advised by the consulting ophthalmologist if symptoms are severe and treatment refractory.

In most cases of ocular toxicities, ICPi can be safely continued as most presenting grades are mild and manageable with topical corticosteroids. However, ocular toxicity is commonly associated with other systemic immune-related events, and systemic corticosteroids are often used in these patients to manage the more-prominent toxicities outside the eye. Modification and possible cessation of ICPi may need to be considered in these cases as well as in cases of higher grade, treatment-refractory, or recurrent ocular toxicity.

DISCUSSION

While identifying patients at an increased risk for irAEs would help to determine the need for surveillance and prompt, aggressive treatment, the evidence of who is at an elevated risk remains unclear. Patients with preexisting autoimmune diseases, such as ulcerative colitis, Crohn disease, lupus, and active rheumatoid arthritis, are usually not offered therapy with checkpoint inhibitors and typically have been excluded from clinical trials involving these agents. However, data suggest that they may be safely treated.[31,129] Indeed, a systematic review of case reports of patients with preexisting autoimmune diseases treated with ICPis found that 40% of patients did not experience an irAE or exacerbation of their autoimmune disease, despite many having active disease.[130] Ultimately, cautious use of ICPi therapy may be acceptable with close monitoring for recurrence of the underlying autoimmune condition.

The pattern of toxicity based on tumor type and location has not been well established. Some reports have claimed higher incidences of pneumonitis in patients with NSCLC compared with melanoma,[39] but other analyses found no statistically significantly differential effects according to cancer type.[131 133] Treatment-naive

patients are reported to have a higher incidence of pneumonitis compared with those previously treated.[134] Other evidence is also emerging on patient-related modifiers of risk. Personal ecologic factors, such as the patient's microbiome, may also play a role in the susceptibility to specific irAEs, such as enterocolitis.[77,135,136] Further studies are needed to investigate whether a patient's biologic profile predisposes to the occurrence of irAEs.[137]

Possible treatment-specific risks for increased irAEs include dose of therapy, individual checkpoint inhibitor (CTLA-4 *v* PD-1), and combination checkpoint blockade. Model-based pooled estimates from 498 trial patients who received ipilimumab monotherapy at 0.3, 3, or 10 mg/kg doses indicated that higher doses produce higher rates of irAEs.[138] Grade 3 or higher irAEs are reported to occur more frequently in patients receiving anti–CTLA-4 monotherapy (ipilimumab, 15% to 42%) than in those receiving anti–PD-1 (nivolumab, 8%; pembrolizumab, 5% to 10%) or anti–PD-L1 (atezolizumab, 5% to 7%; durvalumab, 2%; avelumab, 1% to 2%) monotherapy.[139] Evidence also exists for the elevated risk with combination therapy. A recent meta-analysis revealed the OR of all-grade pneumonitis was 3.7 (95% CI, 1.6 to 8.5; $P = .002$), with an anti–CTLA-4 and anti–PD-1 therapy combination (ipilimumab and nivolumab) versus anti–CTLA-4 monotherapy.[131] Combination anti–CTLA-4 and anti–PD-1 therapy also significantly increased the risk of grade 3 and 4 rash and fatigue.[140 142] As the use of ICPi therapy increases and incidences of irAEs are further collected, the understanding of which patient is at an elevated risk is sure to become clearer. In the meantime, clinicians should maintain a high level of suspicion for immune-related toxicities with checkpoint inhibitors, with early recognition and treatment of upmost importance in mitigating the severity of irAEs.[143]

While treatment with ICPis is sometimes well tolerated, the potential for life-disabling irAEs that are severe and/or irreversible exists.[137] A recent meta-analysis of approximately 6,000 patients with solid tumors reported a statistically significant increased risk of fatal AEs for patients treated with ipilimumab (pooled Peto OR, 2.3; 95% CI, 1.4 to 3.6; $P < .001$).[144] Among the specific causes of fatal AEs, ipilimumab was associated with an increased risk of fatal GI toxicity (OR, 4.5; 95% CI, 1.5 to 13.6).[144]

The decision to resume ICPi therapy after resolution of toxicity is complicated because the optimal duration of ICPi therapy is not defined. Early trials of ICPi used 1 year of therapy; later trials used 2 years of therapy or continued ICPi treatment until disease progression or patient intolerance. Recent evidence suggests that patients who discontinued induction immunotherapy due to AEs did just as well as those who continued treatment uninterrupted.[145] In a pooled analysis of randomized trials of patients with advanced melanoma who received nivolumab plus ipilimumab combination therapy, Schadendorf et al[145] found an ORR of approximately 60% in patients who discontinued compared with approximately 50% in those who completed induction therapy. Progression-free survival was also similar between the two groups. While these data are intriguing, prospective evidence is still required to gain a better understanding of the merits, liability, and optimal duration of ongoing anti–PD-1 therapy after discontinuing induction therapy due to irAEs.[146] A patient's tumor response status is an important factor in deciding whether to resume ICPi. If a patient has achieved objective response to initial ICPi, there is a reasonable likelihood that the response will be durable and that resumption of therapy (with attendant risk of recurrence of toxicity) may not be advisable. Conversely, for patients who have not yet responded or whose response is deemed inadequate, consideration of resumption of ICPi therapy after resolution of toxicity is reasonable.

Whether the appearance of irAEs is associated with efficacy parameters still remains unclear.[147] After adjusting for differences in number of nivolumab doses received, baseline LDH, and tumor PD-L1 expression, one analysis found that the ORR was significantly better in patients who experienced irAEs of any grade compared with those who did not, with the greatest benefit seen in patients who reported three or more irAEs.[148] No significant difference in ORR on the basis of the occurrence of grade 3 to 4 irAEs was observed.[148]

There are important studies under way that are evaluating the efficacy of various strategies in mitigating toxicities while maintaining efficacy, such as alternative dosing strategies or increasing the interval between treatment infusions.[146] Until such evidence becomes available, dose reductions of ICPi therapy should be avoided. Rather, therapeutic adjustments by way of temporary interruption or permanent discontinuation of treatment are recommended.

Guidance on the management of toxicities related to ICPi therapy is in demand. This guideline and its recommendations is intended to arm the clinician with strategies and best practices to rapidly recognize, diagnose, coordinate with other medical subspecialties, and manage these sets of unique toxicities.

PATIENT AND CLINICIAN COMMUNICATION

As immunotherapeutic treatment of cancer continues to evolve with single agents and in new combinations, it is imperative that patients and family caregivers receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs. Patient and caregiver education should occur prior to initiating therapy and continue throughout treatment and survivorship. It should be emphasized that immunotherapy works differently than traditional chemotherapy and that these treatments elicit unique therapeutic responses and corresponding irAEs.[149] This response can be unique to each patient, and irAEs may occur across the treatment trajectory from the start of treatment and into survivorship. Most notably, the ability to influence immune response even after discontinuation of the immunotherapeutic agent is a unique feature, and important education point for patients and their caregivers. As such, patients should be encouraged to alert all health care providers that they are receiving or have received an immunotherapeutic agent and to report any changes in health status to each provider. This is important as patients are often seen by multiple providers, and each provider should be aware of the potential for irAEs.

In most cases, irAEs can be managed with treatment interruption and/or supportive care and for some patients, will involve a multidisciplinary team (eg, endocrinologist, pulmonologist, gastroenterologist) to address specific symptoms.[150] Patients and caregivers need to know that AEs can often be managed effectively, especially when they are identified early. In addition, education addressing the safe handling

of medications, infection control, and safe sexual practices is important to supporting optimal management of irAEs.[149]

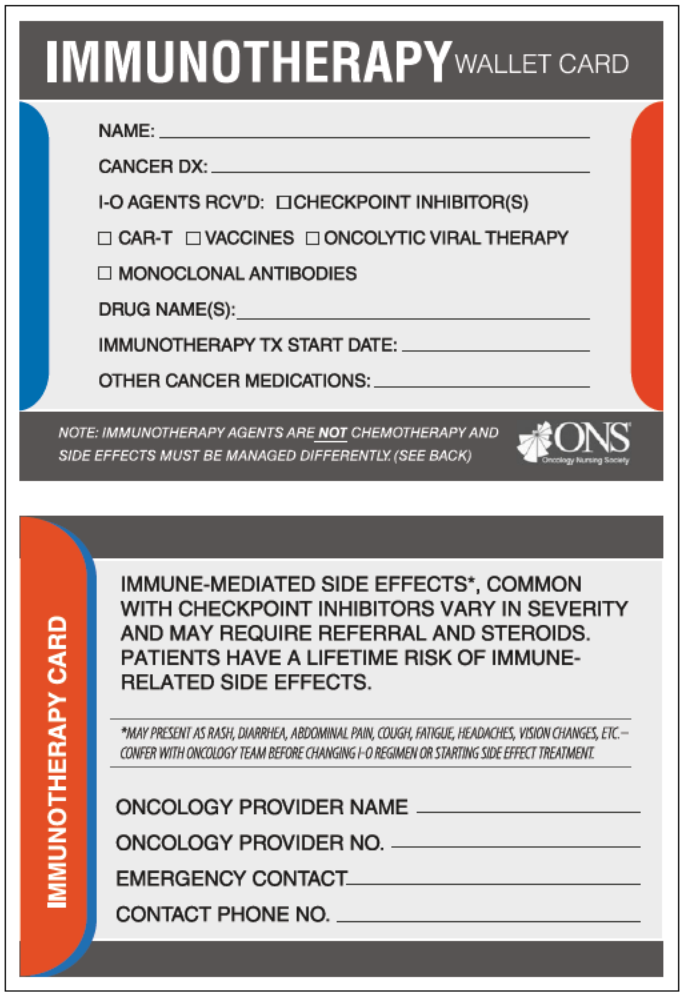
Using a questionnaire or standard assessment may assist the provider and patient to recognize possible irAEs. In addition, health care professionals should ask patients about any new symptoms or changes in their health, no matter how small they may seem. Minor changes in how a patient is feeling may indicate early signs of an AE, and patients may not attribute the change to their cancer treatment.[151] Consistent assessment and documentation at each encounter will also enable the clinical team to note changes that may occur over time. Close monitoring throughout treatment is important as minimal changes in a patient's baseline status may indicate an early irAE. Wallet cards detailing symptoms to watch for and how to notify their health care provider may be an effective tool in empowering patients and their caregivers to recognize and manage irAEs and may be useful to other health care providers (eg, emergency department staff) caring for patients with a history of immunotherapy.[150] The Oncology Nursing Society has an immunotherapy wallet card available for patients and providers (Fig 1). Copies of the card or additional information can be obtained by e-mail at clinical@ons.org.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[152]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[153 156] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Moreover, with evidence to suggest that patients with a higher mutation burden are at an increased likelihood of responding to ICPis[157,158] African American patients with lung cancer may be affected as the burden of somatic mutations appears to be different in such patients.[157] Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

While concerns about racial disparities in access to trials of new cancer drugs have been raised, including trials of anti–PD-1s, whether these disparities extend to patients in real-world practice has only recently been investigated.[159] In a retrospective analysis of electronic health records of 4,643 patients treated with anti–PD-1s, investigators found that racial distributions differed for anti–PD-1–treated patients compared with non–anti–PD-1–treated patients in a cohort of patients with advanced NSCLC ($P < .01$) but not in a cohort of patients with metastatic renal cell carcinoma ($P = .84$) or advanced melanoma ($P = .96$). In bivariate analyses of patients with advanced NSCLC, the use of anti–PD-1 treatment was associated with race, male sex, stage II at diagnosis, squamous histology, smoking history, and line of therapy (all $P < .05$).[159] Adjusted models showed that there were no significant differences in likelihood of receiving anti–PD-1s when comparing black and white patients undergoing systemic therapy for NSCLC.[159]


IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

I-O AGENTS RCV'D: ☐CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

NOTE: IMMUNOTHERAPY AGENTS ARE NOT CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)

ONS Oncology Nursing Society

IMMUNOTHERAPY CARD

IMMUNE-MEDIATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

*MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.—CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.

ONCOLOGY PROVIDER NAME _____

ONCOLOGY PROVIDER NO. _____

EMERGENCY CONTACT _____

CONTACT PHONE NO. _____

Fig 1. Example of an immunotherapy wallet card. Reprinted courtesy of the Oncology Nursing Society. All rights reserved.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude patients with MCC, such as preexisting autoimmune diseases, to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these

studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, including preexisting autoimmune diseases, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the management and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCCs.

EXTERNAL REVIEW

The draft set of recommendations was submitted to an external reviewer with content expertise to obtain direct feedback. A public open comment period was also held from October 30 through November 14, 2017. A total of 17 respondents, who had not previously reviewed the recommendations, either agreed or agreed with slight modifications to the vast majority of the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guideline Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line Box facilitates implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*. Dissemination is also expected through ASCO Communications (which will likely include www.asco.org, media outreach, ASCO e-mails/news releases, www.cancer.net, ASCO Connection [member magazine], social media, and other member communications; may also include ASCO University, depending on the program's needs).

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelinswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

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Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

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All Appendices and Acknowledgment material (including the table of Expert Panel members) are online only. It will appear on the JCO Web site but not in the print version.

Appendix

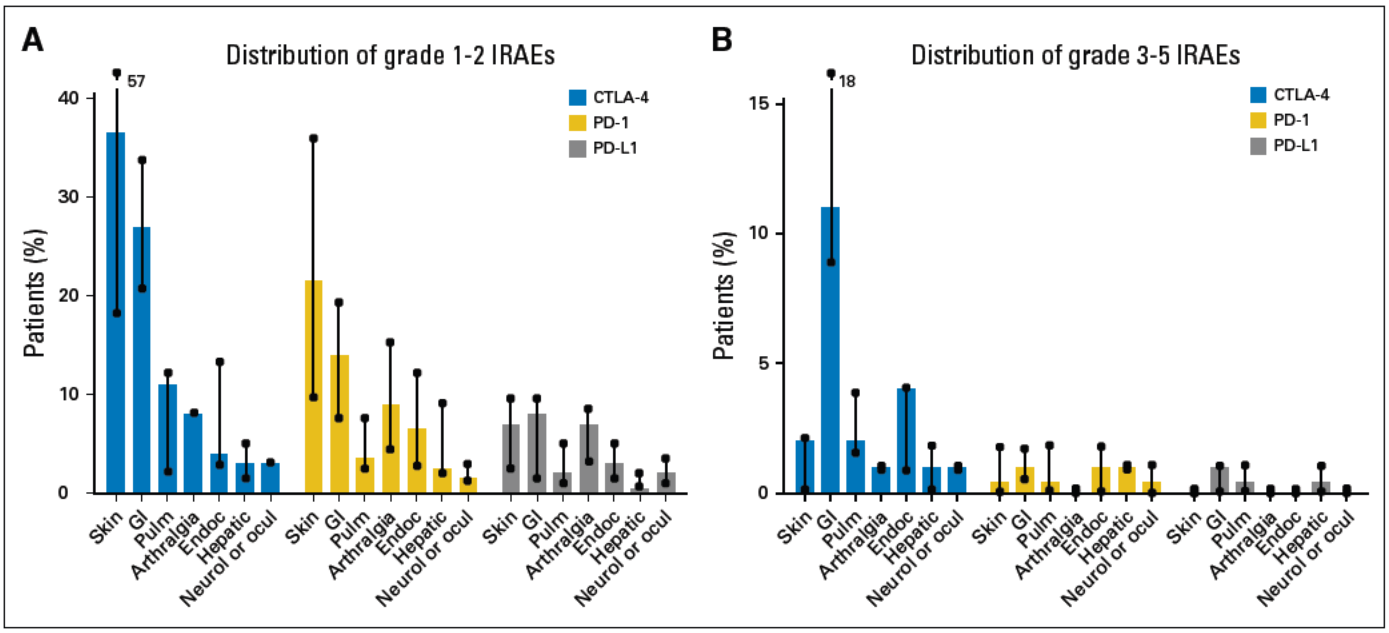

Fig A1. Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti– cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole. Adapted from European Journal of Cancer, Vol 54, J.M. Michot et al, Immune-Related Adverse Events With Immune Checkpoint Blockade: A Comprehensive Review, 139-149, Copyright 2016, with permission from Elsevier. Endoc, endocrinology; Neurol, neurology; ocul, ocular; Pulm, pulmonary.

Table A1. Management of Immune-Related Adverse Events Guideline Expert Panel Membership

Name and Designation	Affiliation/Institution	Role/Area of Expertise
Julie Brahmer, MD, MSc, Cochair	Johns Hopkins Kimmel Cancer Center	Thoracic oncology
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Cristina Reichner, MD	Georgetown University	Pulmonology
Aung Naing, MD	MD Anderson Cancer Center	Medical Oncology, Trialist
Jenna Mammen, MD, PhD	Johns Hopkins University	Endocrinology
Alexander Spira, MD, PhD	Virginia Cancer Specialists and US Oncology Research	Medical oncology
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Bianca Santomasso, MD, PhD	Memorial Sloan Kettering Cancer Center	Neuro-oncology
Sigrun Hallmeyer, MD	Oncology Specialists SC	Medical oncology, Practice Guidelines Implementation Network (PGIN) representative
Tanyanika Phillips, MD	CHRISTUS St Frances Cabrini Cancer Center	Medical Oncology, PGIN representative
Pamela Ginex, EdD, RN	Oncology Nursing Society	Oncology nursing, Oncology Nursing Society (ONS) representative
Kelly Brassil, PhD, RN	MD Anderson Cancer Center	Oncology nursing, ONS representative
Laura Porter, MD		Patient advocate
Carole Seigel		Patient advocate
Christina Lacchetti	American Society of Clinical Oncology	Staff, health research methodologist

Table A2. Commonly Conducted Testing at Baseline Prior to ICPi Therapy*

Testing
Clinical
Physical examination, including physical stature, weight, body mass index, heart rate, and blood pressure
Comprehensive history, including autoimmune, organ-specific disease, endocrinopathy, neuropathy, and infectious disease
Questioning of general health, including appetite, bowel habits, and asthenia. Preexisting symptoms involving bowel movements, dyspnea, cough, rash, headaches, and arthralgia should be noted.
Laboratory
CBC + differential test
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, CO_2), liver function (AST, ALT, alkaline phosphatase, γ-glutamyl transferase), creatinine, creatine kinase, total bilirubin
Glucose
Lactate dehydrogenase and aldolase
Thyroid-stimulating hormone, free thyroxine
Luteinizing hormone, follicle-stimulating hormone, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes
Urinalysis
Surveillance for latent tuberculosis
Virology including HIV, hepatitis C virus and hepatitis B virus, Epstein-Barr virus, cytomegalovirus
Troponin
Spirometry/diffusing capacity of lung for carbon monoxide
Imaging
Chest x-ray
Computed tomography
ECG

*Other testing may also be necessary based on patient's history and preexisting comorbidities and/or risk factors.

Table A3. Abbreviations

Acronym	Definition
ABG	arterial blood gas
ACC	American College of Cardiology
ACTH	adrenocorticotropic hormone
ADL	activities of daily living
AE	adverse event
AHA	acquired hemophilia A
AHA	American Heart Association
AI	adrenal insufficiency
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
ANNA-1	anti-neuronal nuclear antibody 1
APTT	activated partial thromboplastic time
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ASMA	anti–smooth muscle antibodies
AST	aspartate aminotransferase
ATG	antithymocyte globulin
BAL	bronchoalveolar lavage
BNP	brain natriuretic peptide
BSA	body surface area
CAR-T	chimeric antigen receptor T-cell
CBC	complete blood count
CMP	comprehensive metabolic panel
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinsase
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-cell lymphocyte-4
CTPA	computed tomographic pulmonary angiography
CXR	chest x-ray
DAT	direct antiglobulin test
DIC	disseminated intravascular coagulation
DEB	diepoxybutane
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EEG	electroencephalogram
EGD	esophagogastroduodenoscopy
EMG	electromyography
EMS	emergency medical services
ENT	ears, nose, and throat
ESR	erythrocyte sedimentation rate
FLAIR	fluid-attenuated inversion recovery
FSH	follicle-stimulating hormone
FT4	free thyroxine
G1	grade 1
G2	grade 2
G3	grade 3
G4	grade 4
GBS	Guillain-Barré syndrome
GCSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GPI	glycosylphosphatidylinositol
HCV	hepatitis C virus
Hgb	hemoglobin
HHV6	human herpesvirus 6
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
IA	inflammatory arthritis

(continued in next column)

Table A3. Abbreviations (continued)

Acronym	Definition
ICPi	immune checkpoint inhibitor
ICU	intensive care unit
IgG	immunogloblulin G
irAE	immune-related adverse event
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
IVIG	intravenous immunoglobulin
LEMS	Lambert-Eaton Myasthenic Syndrome
LFTs	liver function tests
LH	lutenizing hormone
LLN	lower limit of normal
LMWH	low molecular weight heparin
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MGFA	myasthenia gravis foundation of America
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
NCS	nerve conduction study
NIF	negative inspiratory force
O&P	ova and parasite
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PE	pulmonary embolism
PEX	plasma exchange
PMNs	polymorphonuclear cells
PNH	paroxysmal nocturnal hemoglobinuria
PPI	proton pump inhibitor
PT	prothrombin time
PTU	propylthiouracil
RBC	red blood cell
RPR	rapid plasma reagin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TID	three times a day
TPO	thyroid peroxidase
TSH	thyroid stimulating hormone
TSI	thyroid stimulation immunoglobulin
TTE	transthoracic echocardiogram
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
US	ultrasound
UTIs	urinary tract infections
V/Q	ventilation-perfusion lung scan
VC	vital capacity
VKA	vitamin K antagonists
VTE	venous thromboembolism
WBC	white blood cell

APPENDIX 3 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Medical or surgical procedures may be reported as an AE while waiting to determine the underlying condition which lead to the procedure.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant information on the AE/SAE eCRF in the EDC system.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records (i.e. discharge summary) for certain cases are requested by the Sponsor or Medpace Clinical Safety. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study according to the NCI-CTCAE, version 5.0. If the AE is not listed in the NCI-CTCAE version 5.0, it should be graded using the scale below:

- Grade 1 (Mild): An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Grade 2 (Moderate): An event that causes sufficient discomfort and interferes with normal everyday activities.
- Grade 3 (Severe): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for

rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
Grade 4 (Life-threatening): An event that puts the patient at immediate risk of death; urgent intervention required.

- Grade 5 (Fatal): An event that results in death.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE using the categories of Related or Not Related.
    - Not related: A causal relationship can be definitively excluded and another documented cause of the AE/SAE is most plausible.
    - Related: A causal relationship is clinically/biologically plausible and there exists a plausible time sequence between onset of the AE/SAE and the administration of the study drug.
- The investigator will use clinical judgment based on all available information to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory

tests or investigations, histopathological examinations, or consultation with other health care professionals.

- The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.
- New or updated information will be recorded in the AE/SAE eCRF in the EDC system.
- The investigator will report any updated SAE data Medpace Clinical Safety within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting

- The primary mechanism for reporting an SAE to Medpace Clinical Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the back-up paper SAE form in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on the back-up paper SAE form.
- **Contact for SAE reporting: medpace-safetynotification@medpace.com**

APPENDIX 4 GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA

RECIST 1.1 GUIDELINES

The text below was obtained from the following reference: Eisenhauer EA, Therese P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009; 45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

• Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or

MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are

included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the investigational product treatment until the end of treatment taking into account any requirement for confirmation (Table 24). On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Table 24 Overall Response Criteria: Time Point Response

Patients with Target and Nontarget Lesions			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
Patients with Nontarget Lesions Only			
Non-Target Lesions	**New Lesions**		**Overall Response**
CR	No		CR
Non-CR/Non-PD	No		Non-CR/Non-PD
Not all evaluated	No		NE
Unequivocal PD	Yes or No		PD
Any	Yes		PD

Source: (Eisenhauer, Therasse et al. 2009).

Available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Key: CR = complete response; NE = inevaluable; PD = progressive disease

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (Phase 2 or 3) or trials where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Evaluation of Response by iRECIST

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used to assess tumor response and progression, and make treatment decisions. When clinically stable, patients should not be discontinued until progression is confirmed according to the rules described below. This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG PS
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** may be discontinued from study intervention at site-assessed first radiologic evidence of progressive disease. It is strongly preferred to obtain the repeat tumor imaging, when feasible, for confirmation of progressive disease by iRECIST.

In a clinically unstable patient, if the investigator decides to continue treatment, following consultation with the medical monitor at 23andMe, the patient may continue to receive study drug. The tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm progressive disease by iRECIST. Images should continue to be sent in to the central imaging vendor for potential central review.

If repeat imaging does not confirm progressive disease per iRECIST and the patient continues to be clinically stable, study drug may continue and follow the regular imaging schedule. If progressive disease is confirmed, patients will be discontinued from study drug.

If a patient has confirmed radiographic progression as defined below, study drug should be discontinued; however, if the patient is achieving a clinically meaningful benefit, continuation of study drug may be considered following consultation with the medical monitor at 23andMe.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological progressive disease by RECIST 1.1, the investigator will decide whether to continue a patient on study intervention until repeat imaging is obtained (using iRECIST for patient management). This decision should be based on the patient's overall clinical condition (see discussion of Clinical stability above).

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines response categories, including iUPD (immune unconfirmed progressive disease) and iCPD (immune confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions (Target). The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions (Nontarget).

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (immune stable disease [iSD]/immune partial response [iPR]/ immune complete response [iCR]). Timing of confirmatory imaging is described in the SoA.

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening:
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD time point;
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared with a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1; or
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point;
        - Visible growth of new nontarget lesions; or
        - The appearance of additional new lesions.
- Any new factor appears that would have triggered progressive disease by RECIST 1.1.

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of diameters (initial target lesions) remains above the initial progressive disease threshold (by RECIST 1.1).

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs; AND

- The target lesion sum of diameters (initial target lesions) is not above the initial progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study drug may continue and follow the regular imaging schedule. If progressive disease is confirmed, patients will be discontinued from study drug.

NOTE: If a patient has iCPD as defined above, but the patient is achieving a clinically meaningful benefit, continuation of study drug may be considered following consultation with the medical monitor at 23andMe. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in the SoA and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudoprogression Resolves

After resolution of pseudoprogression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the progressive disease threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions.
- New lesions
  - New lesions appear for the first time.
  - Additional new lesions appear.
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum.

- Previously identified nontarget lesions show any significant growth.

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see *Assessment at the Confirmatory* Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial progressive disease, with 1 exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until a decrease in the new lesion burden allows resolution to iSD or iPR or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour, 2017).

APPENDIX 5

ECOG Performance Status Scoring

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Lansky Play Scale Scoring

Score	Activity
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

Source: Lansky SB et al. The Measurement of Performance in Childhood Cancer Patients. Cancer 1987; 60: 1651-1656.

Tanner Stage Progression

Boys Tanner Stage progression scale*

Genitalia:

1= The testes, scrotum and penis are about the same size and shape as they were during childhood

2= The testes and scrotum are bigger. The skin of the scrotum has changed. The scrotum, the sack holding the testes, has gotten lower. The penis has gotten only a little bigger.

3= The penis has grown in length. The testes and scrotum have grown and dropped lower.

4= The penis has gotten even bigger. It is wider. The glans (the head of the penis) is bigger. The scrotum is darker than before. It is bigger because the testes are bigger.

5= The penis, scrotum, and testes are the size and shape of an adult man.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long, lightly-colored hair. Most of the hair is at the base of the penis. This hair may be straight or a little curly.

3= The hair is darker in this stage. It is more curled. It has spread out and thinly covers a bigger area.

4= The hair is now as dark, curly, and course as that of an adult man. The area that the hair covers is not as big as that of an adult man. The hair has NOT spread out to the legs.

5= The hair has spread out to the legs. The hair is now like that of an adult man. It covers the same area as that of an adult man.

Girls Tanner Stage progression scale

Breast:

1= The nipple is raised a little. The rest of the breast is still flat.

2= This is the breast bud stage. In this stage, the nipple is raised more than in stage 1. The breast is a small mound. The areola is larger than stage 1

3= The breast and areola are both larger than in stage 2. The areola does not stick out away from the breast.

4= The areola and the nipple make up a mound that sticks up above the shape of the breast. NOTE: This stage may not happen at all for some girls. Some girls develop from stage 3 to stage 5 with no stage 4.

5= This is the mature adult stage. The breasts are fully developed. Only the nipple sticks out in this stage. The areola has moved back in the general shape of the breast.

Pubic Hair:

1= There is no pubic hair at all.

2= There is a little soft, long lightly-colored hair. This hair may be straight or a little curly.

3= The hair is darker in this stage. It is coarser more curled. It has spread out and thinly covers a bigger area.

4= The hair is now as dark, curly, and course as that of an adult female. The area that the hair covers is not as big as that of an adult female. The hair has NOT spread out to the legs.

5= The hair is now like that of an adult female. It covers the same area as that of an adult female. The hair usually forms a triangular (V) pattern as it spreads out to the legs.

*Adapted from: Morris, N.M., and Udry, J.R., (1980). Validation of a Self-Administered Instrument to Assess Stage of Adolescent Development. Journal of Youth and Adolescence, Vol. 9, No. 3: 271-280.

New York Heart Association Classification

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

NCI-CTCAE

The NCI-CTCAE, version 5.0, can be accessed using the following link:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Cockgroft-Gault Formula for calculation of eGFR in adults ≥ 18 years

$$\left(\frac{(140 - age)\ x\ body\ weight\ (kg)}{serum\ creatinine\ \left(\frac{mg}{dL}\right) x\ 72}\right) x\ 0.85\ (if\ female)$$

Modified Schwartz Formula for calculation of eGFR in adolescent ≥ 12 to < 18 years

$$0.413\ x\ \frac{height\ (cm)}{serum\ creatinine\ \left(\frac{mg}{dL}\right)}$$

From: Schwartz, G. J., Muñoz, A., Schneider, M. F., Mak, R. H., Kaskel, F., Warady, B. A., & Furth, S. L. (2009). New equations to estimate GFR in children with CKD. *Journal of the American Society of Nephrology : JASN*, *20*(3), 629–637. https://doi.org/10.1681/ASN.2008030287

Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human patients to adopt these principles.

B. General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human patients.
6. The primary purpose of medical research involving human patients is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is patient to ethical standards that promote and ensure respect for all human patients and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human patients must be conducted only by individuals with the appropriate ethics and scientific education, training, and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

C. Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.

17. All medical research involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

18. Physicians may not be involved in a research study involving human patients unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

D. Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E. Scientific Requirements and Research Protocols

21. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human patients must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F. Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any

other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any SAEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

G. Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

H. Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human patients capable of giving informed consent, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential patient, the research

cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research patient who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential patient's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the patient or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I. Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be patient to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

J. Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified

as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

K. Research Registration and Publication and Dissemination of Results

35. Every research study involving human patients must be registered in a publicly accessible database before recruitment of the first patient.

36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

L. Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 6 CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Female of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Female patients in the following categories are not considered of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Females of childbearing potential who engage in heterosexual intercourse and males who are sexually active with female partners of childbearing potential must agree to use a highly effective form of contraception (e.g., females: male partner sterilization, estrogen/progestogen or progestogen-only hormonal contraceptives associated with inhibition of ovulation (oral,

intravaginal, transdermal), IUDs, intrauterine hormone-releasing systems; males: male condoms, vasectomy) throughout the study, starting with the time of consent and for at least 90 days after the last dose of study drug. Male patients must not donate sperm throughout the study period.

Collection of Pregnancy Information

Any pregnancy must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the investigator/site the Exposure In Utero (EIU) form for completion. The investigator/site must complete the EIU form and email/fax it back to Medpace Clinical Safety who will notify the Sponsor of the event.

Male patients with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive 23ME-00610.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the EIU form and submit it to Medpace Clinical Safety within 24 hours of learning of the partner's pregnancy. The female partner will also be asked for consent to be followed to determine the outcome of the pregnancy for up to 1 year after birth. Information on the status of the mother and child will be forwarded to the Sponsor. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who become pregnant

- The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the EIU form and submitted to Medpace Clinical Safety within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention but will continue to be followed for up to 1 year after birth.