A PHASE 1A/1B STUDY OF FPT155 IN PATIENTS WITH ADVANCED SOLID TUMORS

Protocol Number:	FPT155-001
Investigational Product:	FPT155
Study Phase:	1a/1b
Indication Studied:	Advanced Solid Tumors
Protocol Version:	Amendment 4
Date of Protocol:	14 September 2020
Regulatory Agency Identifier Number(s):	NCT: NCT04074759
Sponsor: Name and Legal Registered Address:	Five Prime Therapeutics, Inc. 111 Oyster Point Boulevard South San Francisco, CA 94080
Responsible Medical Officer:	[redacted] MD PhD Senior Director, Clinical Sciences Five Prime Therapeutics, Inc.

PROTOCOL APPROVAL SIGNATURE PAGE

Declaration of Sponsor

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Essential study documents will be archived in accordance with applicable regulations.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1989, and the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on GCP.

DocuSigned by:
[redacted]
[redacted]

September 14, 2020

Date

Chief Medical Officer
Five Prime Therapeutics, Inc.

DECLARATION OF THE INVESTIGATOR

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except as necessary to eliminate an immediate hazard to the patients.

I confirm that I have read the above-mentioned protocol/protocol amendments and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, applicable laws, regulations and ICH E6 Guideline for GCP.

Principal Investigator's Signature	Date
Name (printed)	
Institution or Company Name	

Document History

Document	Date
Original Protocol	30 July 2018
Version 1	17 June 2019
Version 1.1 (South Korea)	23 July 2019
Version 2	08 October 2019
Version 2.1 (United States)	29 January 2020
Version 3	17 March 2020
Version 4	14 September 2020

SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 4 – 14 September 2020**

Supersedes: *Amendment 3 – 17 March 2020*

Protocol Section	Change	Rationale
Section 1.1 Synopsis, Section 4.0 Study Design, and Section 6.2 Pembrolizumab Identity	Added: Evaluation of FPT155 + pembrolizumab will be conducted in South Korea	Allows for South Korean enrollment in evaluation of FPT155 + pembrolizumab combination in South Korea as well as Australia
Section 1.1 Synopsis, Section 4.0 Study Design, and Section 6.2 Pembrolizumab Identity	Clarified that treatment with single-agent therapy for 12 months applies only to combination cohorts where one agent is discontinued due to toxicity. Patients enrolled into FPT155 monotherapy cohorts should continue treatment until protocol-specified end-of-treatment criteria are met.	Correction of erroneous language introduced in prior protocol amendment at time of addition of FPT155+pembrolizumab cohorts
Section 1.1 Synopsis, Section 2.3 Clinical Experience with FPT155, Section 4.0 Study Design, Section 4.6 Justification for Dose, Table 8: FPT155 Phase 1 Dose Escalation Cohorts	Updated dose escalation above 560mg: FPT155 700mg dose level replaced by FPT155 840mg; FPT155 1260mg dose level added. Addition of up to 20 patients in dose exploration for new dose levels. Addition of two Phase 1b cohorts (up to 60 patients total) to allow for potential expansion at higher doses. Potential total increase in number of patients: 86.	There have been no DLTs through the 560mg dose level and preliminary PK is consistent with dose proportional increases in exposure through 560mg. In the absence of identification of the MTD and immune related adverse events that have been manageable with standard of care supportive care, escalation will continue with 1.5-fold increments in dose.
Section 6.1 FPT155 Identity	FPT 155 drug product consisting of 140 mg/vial added	Facilitates preparation of higher doses
Appendix 11 Additional Cohorts for Phase 1b Expansion, Section 1.1 Synopsis, Section 5.2 Additional Inclusion Criteria – Monotherapy (Phase 1b Only)	Specification of dose and additional cohorts for Phase 1b	Specification of additional cohorts for phase 1b enrollment as outlined in protocol Section 4.1.3
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 3 – 17 March 2020**

Supersedes: *Amendment 2 – 08 October 2019*

Protocol Section	Change	Rationale
	Included language to incorporate for FPT155 in combination with pembrolizumab and to clarify existing objectives or endpoints for FPT155 monotherapy	Objectives and Endpoints for Safety, Pharmacokinetic, Immunogenicity, Efficacy, [redacted]
Table 1 Schedule of Assessments	Clarified that Schedule of Assessments is applicable to both monotherapy and combination therapy Added language to clarify the requirements for Study drug dosing	Clarified study procedures
Table 3 Dose Escalation (monotherapy and FPT155+pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory	Added language to include pembrolizumab to all impacted samples	Clarified study procedures
Table 4 Dose Exploration/Expansion (Monotherapy and FPT155 + pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory	Added language to include pembrolizumab to all impacted samples	Clarified study procedures
Section 2.2.2.2 In Vivo Pharmacology	Added background language to include pembrolizumab	Added to include pembrolizumab
Section 1.1 Synopsis, and Section 2.4 Benefit/Risk	Added supporting language regarding	

Protocol Section	Change	Rationale
Synopsis, Section 3.0 Objectives and Endpoints, Section 9.4.3 Pharmacokinetic Analyses, and Section 9.4.4 Immunogenicity Analyses	Included language to incorporate for FPT155 in combination with pembrolizumab and to clarify existing objectives or endpoints for FPT155 monotherapy	Objectives and Endpoints for Safety, Pharmacokinetic, Immunogenicity, Efficacy, [redacted]
Section 4.1 Overall Design, Section 1.1 Synopsis	Included language to clarify monotherapy treatment and to incorporate combination with pembrolizumab	Clarified monotherapy guidance and added pembrolizumab
Section 4.1.1.3 Dose Limiting Toxicity Definitions	Added language to define dose limiting toxicities for combination cohorts	Added to include pembrolizumab
Section 4.2 Study Treatment and Duration, Section 1.1 Synopsis	Added language to include pembrolizumab combination treatment	Added to include pembrolizumab
Section 4.5 Scientific Rationale for Study Design, Section 4.6 Justification for Dose, and Section 1.1 Synopsis	Added language for starting dose of combination treatment for FPT155	Added rationale to how the starting dose was defined
Section 5.1, and Section 1.1 Synopsis	Added language to Inclusion criteria 2.01 for combination treatment disease type	Added to include pembrolizumab
Section 6 Study Intervention	Added language to include pembrolizumab as a study intervention	Added to include pembrolizumab
Section 6.1 Study Intervention(s) Administered	Section was removed	All information is captured in other sections
Section 6.2 Pembrolizumab	Added language for pembrolizumab formulation and packaging	Added to include pembrolizumab
Section 6.3 Handling, Storage, and Accountability, 6.4 Administration	Added language to reference the local pembrolizumab package insert	Clarifying to ensure sites remember to refer to the pembrolizumab package insert.
Section 6.9.6 Dose Interruptions During Study Treatment Administration	Clarified sections for FPT155 and added language for pembrolizumab	Added to include pembrolizumab
Section 9.2 Sample Size Determination, and Section 1.1 Synopsis	Updated overall number of patients to include pembrolizumab	Added to include patients participating in combination treatment
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 2.1 – 29 January 2020**

Supersedes: *Amendment 2 – 08 January 2020*

Protocol Section	Change	Rationale
Section 1.1,Synopsis, Section 4.1 Overall Design	There will be approximately **45** study centers in Australia**, United States** and South Korea.	Added language and updated number of sites to include site participation in the United States.
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 2 – 08 October 2019**

Supersedes: *Amendment 1 – 17 June 2019*

Protocol Section	Change	Rationale
Section 1.2, Schedule of Assessments, Tables 1 & 2, Sample Collection	All samples are assessed locally. **Labs may be drawn up to 24 hours in advance of treatment.**	Added language to allow for labs to be drawn 24 hours in advance of treatment to provide flexibility for sites to collect labs in advance of treatment
Section 1.2, Schedule of Assessments, Tables 1 & 2, Sample Collection	During dose escalation, laboratory testing as outlined in the schedule of assessments will be performed weekly through Cycle 4 Day 1.	Additional monitoring to ensure patient safety.
Section 1.2, Schedule of Assessments, Tables 1 & 2, CT or MRI	Tumor evaluation by CT or MRI should be conducted according to RECIST v1.1 at screening, every 6 **(± 1)** weeks from the first dose for 24 weeks, and then ~~approximately~~ every 12 **(±2)** weeks thereafter. **Imaging performed as standard of care may be used if it has been performed within 28 days of treatment**	Addition of language to allow sites to submit previously-obtained CT or MRI evaluation as protocol required scans as long as the evaluation was performed within 28 days of starting treatment and satisfies protocol requirements otherwise.
Appendix 1, Table 13	blood urea level may be collected as an alternative to BUN: BUN **or Urea**	To allow for lab collection of blood urea level as an alternative to blood urea nitrogen in the evaluation of renal function per standard of care.
Appendix 1, Table 13	Added **TSH, Free T4 and ACTH** to routine lab testing	Systematic monitoring for potential endocrinopathies specified to be consistent with standard of care monitoring for anti-CTLA4 directed therapy. There have been no adverse events related to autoimmune disease in dose escalation with FPT155 to date.

<table>
<tr><th>Protocol Section</th><th>Change</th><th>Rationale</th></tr>
<tr><td>Section 1.1 Synopsis,
Section 4.6 (Table 8),
Section 6.1</td><td>
<table>
<tr><th>Cohort</th><th>Dose Level (mg)</th></tr>
<tr><td>1aM1</td><td>0.07</td></tr>
<tr><td>1aM2</td><td>0.21</td></tr>
<tr><td>1aM3</td><td>0.70</td></tr>
<tr><td>1aM4</td><td>2.1</td></tr>
<tr><td>1aM5</td><td>7</td></tr>
<tr><td>1aM6</td><td>21</td></tr>
<tr><td>1aM7</td><td>42</td></tr>
<tr><td>1aM8</td><td>70</td></tr>
<tr><td>1aM9</td><td>140</td></tr>
<tr><td>1aM10</td><td>280</td></tr>
<tr><td>1aM11</td><td>560</td></tr>
<tr><td>1aM12</td><td>700</td></tr>
</table>
</td><td>Addition of 4 additional dose escalation levels (1aM9 through 1aM12) given the ongoing absence of DLTs or significant clinical toxicity through 1aM7.</td></tr>
<tr><td>Section 1.1 Synopsis,
Section 5.3 Exclusion Criteria (Phase 1a and Phase 1b)</td><td>Added clarification that both male and woman of childbearing potential agree to follow contraceptive guidance as detailed in the protocol (Appendix 3) during the study treatment period and at least 2 months, or 5 half-lives, whichever is longer, after study treatment</td><td>Provided clarification on the contraception requirements following completion of study treatment.</td></tr>
<tr><td>Section 1.1 Synopsis,
Section 5.3 Exclusion Criteria (Phase 1a and Phase 1b)</td><td>Exclusion Criteria (Phase 1a and Phase 1b)

Active autoimmune disease, history of clinically significant autoimmune disease, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, are permitted to enroll</td><td>Clarified that patients with a history of clinically significant autoimmune disease are excluded from this study.</td></tr>
</table>

Protocol Section	Change	Rationale
Section 1.1 Synopsis, Section 4.1.1.5 Dose Escalation Within a Cohort, Section 6.6.1 Dose Escalation	Intra-patient dose escalation will be permitted in patients enrolled at dose levels below 7**0**~~.0~~ mg	Absence of DLTs or significant toxicity through 1aM7 (42mg)
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

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SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 1.1**

Date of Protocol Amendment **23 July 2019**

Supersedes: *Amendment 1 – 17 June 2019*

Protocol Section	Change	Rationale
Cover Page	Updated protocol version to amendment 1.1 and date of finalization	Updated version
Document History	Updated protocol version 1 and 1.1	Updated document version history
Section 1.2, Schedule of Assessments, Table 1	*In dose escalation subsequent Cycles 2 & 3 require a chemistry panel to be drawn on Day 2, 8 and 15 at the 21mg dose level and higher.	Additional chemistry testing added per MFDS recommendation

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SUMMARY OF CHANGES PROTOCOL FPT155-001

A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Protocol Version: **Amendment 1 – 17 June 2019**

Supersedes: *Original – 30 July 2018*

Protocol Section	Change	Rationale
Cover Page	Updated Protocol version to amendment 1 and date of finalization	Updated version
List of Key Study Personnel	[redacted] ~~MBBS,~~ ~~Executive Medical Director~~ [redacted] **MD PhD** **Senior Director, Clinical Development** Five Prime Therapeutics, Inc. 111 Oyster Point Boulevard South San Francisco, CA 94080 [redacted] (main) [redacted] (fax)	Updated medical director contact information

Protocol Section	Change	Rationale
Section 1.2, Schedule of Assessments, Tables 1 & 2; Appendix 1, Table 13	Specified additional pregnancy testing at the time of each cycle of treatment and prior to dosing. Section 1.2 (Tables 1 and 2): For WOCBP, a serum pregnancy test will be performed at screening (within 7 days of Cycle 1 Day 1) **and pregnancy testing will be performed at each subsequent cycle of treatment prior to dosing.** All samples are assessed locally. Appendix 1: **At Screening Only:** Serology for Hepatitis B (HBsAg), and Hepatitis C (HCV RNA) ~~Serum pregnancy test in women of childbearing potential only~~ **NOTES:** • For WOCBP, a serum pregnancy test will be performed at screening and pregnancy testing will be performed at each subsequent cycle of treatment prior to dosing. Additional serum pregnancy testing may be performed if there is a concern with pregnancy, the patient missed a menstrual period, or did not follow the contraceptive guidance in Appendix 3.	Regular pregnancy testing at each cycle of treatment will ensure prompt identification of pregnancies on study
Section 6.6.3	Added language to indicate the maximum length of treatment postponement which requires medical monitor attention: There is a ± 3-day window for subsequent cycles after Cycle 1. The first dose of each cycle is considered Day 1 of each cycle. Cycles will repeat every 21 days unless there is a treatment delay. **A treatment delay of longer than 4 weeks should be discussed with the medical monitor prior to continuation of that subject on study**. Treatment is administered Q3W until disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria.	Discussion in the event of an extended treatment interruption will help to ensure that the investigator's assessment of benefit relative to risk is favorable for the patient remaining on study.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
ANC	Absolute neutrophil count
APCs	Antigen presenting cells
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under serum concentration-time curve
β-hCG	B-human chorionic gonadotropin
BOR	Best overall response
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CD28	Cluster of differentiation 28
CD80	Cluster of differentiation 80
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CO_2	Carbon dioxide
C_{max}	Maximum observed serum concentration/ maximum concentration
C_{trough}	Trough observed serum concentration at the end of each dose interval
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response

Abbreviation	Definition
CrCl	Creatinine clearance
CRF	Case report form
CRC	Cohort review committee
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
ctDNA	Circulating tumor deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report forms
ELISA	Enzyme linked immunosorbent assay
EOT	End of Treatment
eSAE Form	Electronic serious adverse event form
GALT	Gut-associated lymphoid tissue
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte-colony stimulating factor
GCP	Good clinical practices
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good laboratory practices
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hb	Hemoglobin
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

Abbreviation	Definition
HPV	Human papilloma virus
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IHC	Immunohistochemistry
IGF-1	Insulin-like growth factor-1
IgG	Immunoglobulin G
IND	Investigational new drug (application)
IF	Immunofluorescence
IFNγ	Interferon gamma
IHS	Intrauterine hormone-releasing system
INR	International normalized ratio
IP	Investigational product
irAEs	Immune-related adverse events
IRB	Institutional review board
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulin G
IVRS/IWRS	Interactive voice/web response system
LCI	Liver cytosol 1 autoantibody
LDH	Lactate dehydrogenase
LFT	Liver function test
LH	Lactate dehydrogenase
LKM	Liver kidney microsome
LP	Lipoprotein
LTFU	Long-term follow-up
mAB	Monoclonal antibody
MABEL	Minimum anticipated biological effect level
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil

Abbreviation	Definition
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National cancer institute
NOAEL	No-observed-adverse-effect level
NYHA	New York heart association
ORR	Objective response rate
OS	Overall survival
PA	Pharmacological activity
PBMC	Peripheral blood mononuclear cell(s)
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PD-1	Programmed death 1
PDL-1	Programmed death ligand 1
PFS	Progression free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q3W	Once every 3 weeks
QTc	QT interval corrected for heart rate
RBC	Red blood cell
RCC	Renal cell carcinoma
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SGOT	Serum glutamic-oxaloacetic transaminase
SLA	Soluble liver antigen
SMA	Smooth muscle antibody
SPR	Surface plasmon resonance

Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TCR	T cell receptor
TK	Toxicokinetics
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
USPI	United States product insert
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
WOCBP	Women of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1a/1b Study of FPT155 in Patients with Advanced Solid Tumors

Study Phase: 1a/1b

Study Centers: There will be approximately 30 study centers in Australia and South Korea. FPT155 monotherapy and FPT155 + pembrolizumab will be conducted in Australia and South Korea.

Rationale: FPT155 is an immune modulating CD80-Fc (cluster of differentiation 80 fused with the fragment crystallizable [Fc] domain of human immunoglobulin G1 [IgG1]) fusion protein that is thought to act both as an agonist for cluster of differentiation 28 (CD28) and an inhibitor of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). This is a first in human clinical study of FPT155 to evaluate safety and tolerability in patients with advanced solid tumors, and to determine a recommended dose (RD) for further clinical evaluation.

The dual anti-CD28 and anti-CTLA-4 mechanisms of FPT155 lead to synergy with anti-PD1 antibodies in pre-clinical tumor models and may lead to similar clinical benefit in patients with advanced tumors. Evaluation of the combination of pembrolizumab and FPT155 for safety and tolerability in patients with advanced non-small cell lung cancer will determine a recommended dose of FPT155 in combination with pembrolizumab for further clinical evaluation.

Objectives and Endpoints – Phase 1a Dose Escalation/Exploration – FPT155 Monotherapy:

Objectives	Endpoints
Primary	
Safety • To assess the safety and tolerability of FPT155 as monotherapy in patients with advanced solid tumors • To determine the RD of FPT155 as monotherapy	**Safety** • The incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, and electrocardiogram (ECG) abnormalities • The incidence of AEs defined as dose limiting toxicities (DLTs), clinical laboratory abnormalities defined as DLTs, and overall assessment of pharmacokinetics (PK) and pharmacodynamics (PD)
Secondary	
Pharmacokinetics • To characterize the PK profile of FPT155 as monotherapy in patients with advanced solid tumors	**Pharmacokinetics** The following PK parameters will be derived from concentration-time data for FPT155 when appropriate and applicable. • Area under serum concentration-time curve (AUC) • Maximum observed serum concentration (C_{max})

	• Trough observed serum concentration at the end of each dose interval (C_{trough}) • Clearance (CL) • Terminal half-life ($t_{1/2}$) • Volume of distribution at steady state (V_{ss}) Other parameters, such as dose proportionality, accumulation ratio, and attainment of steady state, will also be calculated if the data are available.
Immunogenicity • To characterize the immunogenicity of FPT155 as monotherapy in patients with advanced solid tumors	**Immunogenicity** • Incidence of treatment emergent anti-FPT155 antibody response
Exploratory	
[redacted]	

Objectives and Endpoints – Phase 1b Dose Expansion – FPT155 Monotherapy:

Objectives	Endpoints
Primary	
Safety • To evaluate the safety and tolerability of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Safety** • The incidence of AEs, SAEs, clinical laboratory abnormalities, and ECG abnormalities • The incidence of treatment discontinuations, modifications, and interruptions due to AEs
Secondary	
Efficacy • To evaluate the clinical benefit of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD through the analysis of ORR, DOR., PFS, and DCR	**Efficacy** • ORR, DOR, and PFS • Disease Control Rate (DCR) defined as total number of patients with confirmed responses of either CR, PR, or stable disease as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response
Pharmacokinetics • To characterize the PK profile of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Pharmacokinetics** The following PK parameters will be derived from concentration-time data for FPT155 when appropriate and applicable. • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available. Assessment of time-dependence of PK, the effect of body weight as well as other covariates on PK, and the exposure-response relationship, when the data allow, will be conducted to determine the appropriate dosing approach (eg, body weight-based or fixed dosing) for future trials.
Immunogenicity • To characterize the immunogenicity of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Immunogenicity** • Incidence of treatment emergent anti-FPT155 antibody response
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

Objectives and Endpoints – Phase 1a Dose Escalation/Exploration – FPT155 + Pembrolizumab:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of FPT155 in combination with pembrolizumab in patients with advanced non-small cell lung cancer • To determine the RD of FPT155 in combination with pembrolizumab in patients with advanced non-small cell lung cancer	• The incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, and electrocardiogram (ECG) abnormalities • The incidence of dose limiting toxicities (DLTs)
Secondary	
• To evaluate the preliminary clinical response rate of FPT155 in combination with pembrolizumab in patients with non-small cell lung cancer	• Objective Response Rate (ORR), defined as the total number of patients with responses of either CR or PR, as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

Overall Design:

This study is a Phase 1a/1b open-label, multicenter, dose escalation, dose exploration, and dose expansion study to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of FPT155 in patients with advanced solid tumors. FPT155 (CD80-Fc) is a recombinant fusion protein composed of the extracellular domain (ECD) of human CD80 (cluster of differentiation 80, also known as B7, B7.1, B7-1) fused with the Fc domain of IgG1. It is designed to act as a potent stimulator of anti-tumor immunity. FPT155 as monotherapy and in combination with pembrolizumab will be evaluated.

FPT155 Monotherapy

FPT155 will be administered once every 3 weeks (Q3W) over approximately 60 minutes by intravenous (IV) infusion.

The monotherapy part of the study will initiate with Phase 1a dose escalation consisting of approximately 13 planned dose escalation cohorts, with the starting dose of 0.07 mg.

Phase 1a dose exploration consists of approximately 50 patients in total who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose levels clearing dose escalation criteria).

Phase 1b dose expansion consists of up to 8 tumor-specific expansion cohorts, enrolling approximately 30 patients each. Patients in Phase 1b will be treated with FPT155 at an RD selected after assessment of data obtained in Phase 1a. (See Appendix 11).

Treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or if any of the specified withdrawal criteria listed in Section 7.0 of the protocol are met.

Dose Escalation:

The Phase 1a dose escalation will include an initial accelerated titration design enrolling at least 1 patient at lower doses followed by a standard 3+3 design until the RD for Phase 1b is determined. Eligible patients with advanced solid tumors (except primary central nervous system [CNS] tumors) who are refractory to all standard therapy for their malignancy or for whom standard therapies would not be appropriate will be enrolled. All dose escalation decisions will be based on the assessment of DLTs, overall safety and tolerability, and will be made after the last patient enrolled in each cohort has completed the 21-day DLT evaluation interval. Dose escalation decisions will be agreed upon by the Cohort Review Committee (CRC) after all available laboratory and clinical information is reviewed.

Patients enrolled into the first monotherapy dose cohort will have 48 hours of inpatient monitoring from the start of infusion of FPT155 at Cycle 1 Day 1 to evaluate for any signs or symptoms of cytokine release syndrome (CRS). There will be an interval of at least 48 hours between administration of the first dose in each patient in the first dose cohort, if more than one patient is enrolled. For the second infusion of FPT155, patients in the first monotherapy dose cohort will undergo intensive monitoring in the outpatient setting, including a minimum 6-hour observation window.

For subsequent dose cohorts, intensive monitoring will occur in the outpatient setting and include a minimum 6-hour observation window following completion of the first and second infusions. There will be an interval of at least 24 hours between administration of the first dose in each patient in subsequent dose cohorts. Inpatient hospitalization will not be required for the first dose in subsequent dose cohorts unless there is evidence of CRS ≥ Grade 2 at the previous dose level.

If any patient reports a Grade 2 or higher drug-related toxicity in the first 24 hours after completion of their first dose, enrollment of subsequent patients will be delayed until the toxicity for that patient returns to baseline or ≤ Grade 1, or the CRC determines that it is safe to continue enrollment. In this setting, the CRC will review all available data to determine if enrollment should continue at the same or a lower dose level, or with a less frequent dosing schedule, or if enrollment should be discontinued.

The CRC is comprised of, but not limited to, Phase 1a study investigators, the Sponsor's medical monitor, and the Sponsor's safety representative.

FPT155 + Pembrolizumab

FPT155 will be administered once every 3 weeks (Q3W) over approximately 60 minutes by intravenous IV infusion followed by 200 mg of pembrolizumab administered over 30 minutes by

intravenous (IV) infusion a minimum of 30 minutes after the completion of FPT155. Eligible patients with advanced lung cancer will be enrolled for treatment with the combination of FPT155 and pembrolizumab.

Combination dose escalation will start with a FPT155 dose that is a minimum of two dose levels lower than the highest dose cleared in FPT155 monotherapy.

Combination dose exploration will include up to 30 patients who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose level clearing dose escalation criteria).

For patients enrolled for treatment with FPT155 and pembrolizumab, treatment will continue until disease progression, unacceptable toxicity or consent withdrawal. If one drug is discontinued, treatment may continue with the other alone for up to an additional 12 months.

Proposed FPT155 Dose Levels*:*

FPT155 will be initially administered Q3W, on Day 1 of each 21-day cycle. The anticipated dose levels are as follows:

Design	Dose	Regimen
Accelerated titration design	0.07 mg FPT155	Q3W
	0.21 mg FPT155	Q3W
	0.70 mg FPT155	Q3W
	2.1 mg FPT155	Q3W
3+3 design	7 mg FPT155	Q3W
	21 mg FPT155	Q3W
	42 mg FPT155	Q3W
	70 mg FPT155	Q3W
	140 mg FPT155	Q3W
	280 mg FPT155	Q3W
	560 mg FPT155	Q3W
	840 mg FPT155	Q3W
	1260 mg FPT155	Q3W

Planned dosing increments take into account conservative estimates of receptor occupancy (RO) and pharmacological activity (PA) through both CD28 and CTLA-4. Fixed 3-fold escalation increments are proposed while projected engagement of CD28 is low; more conservative increments (2-fold or less) are proposed at higher CD28 occupancy levels.

The Sponsor may add cohorts with alternative dose levels or dose regimens (eg, different dosing frequency, intermediate dose levels) upon review of safety, PK, and PD profiles to achieve optimal target exposure with acceptable tolerability.

Dose Limiting Toxicity Definitions:

The DLT evaluation interval begins on the first day of treatment upon start of infusion and continues for 21 days. Patients who receive at least 1 dose of study treatment and remain on study for the 21-day DLT evaluation interval or patients who discontinue study treatment for drug-related AEs before clearing the 21-day DLT evaluation interval will be considered evaluable for DLT determination.

DLTs during Phase 1a dose escalation are defined as any of the following deemed by the investigator as related to FPT155:

- Absolute neutrophil count (ANC) < 1.0 x 10^9/L for > 5 days duration or Grade 3 febrile neutropenia (eg, ANC < 1.0 x 10^9/L with a single temperature of > 38.3°C or fever > 38°C for more than 1 hour)
- Platelets < 25 x 10^9/L or platelets < 50 x 10^9/L with clinically significant hemorrhage
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) with concomitant total bilirubin > 2 x ULN not related to liver involvement with cancer
- Grade 3-4 non-hematological toxicity except:
  - Grade 3 fatigue < 7 days
  - Grade 3 nausea and Grade 3-4 vomiting and diarrhea lasting < 72 hours in patients who have not received optimal anti-emetic and/or anti-diarrheal therapy
  - Grade 3 endocrinopathy that is adequately treated by hormone replacement
  - Laboratory value that may be corrected through replacement within 48 hours
- Grade 2 neurological toxicity except headache and peripheral neuropathy in patients with Grade 1-2 peripheral neuropathy at entry

Dose Escalation Decisions in Phase 1a FPT155 Monotherapy:

An initial accelerated titration design enrolling at least 1 patient at each dose level is planned for dose levels 0.07, 0.21, 0.70, and 2.1 mg. Dose escalation to the next dose level may proceed after at least 1 patient completes the 21-day DLT evaluation interval.

If a single patient experiences a DLT during the 21-day DLT evaluation interval, standard 3+3 dose escalation criteria will apply for that cohort with enrollment of additional patients. All subsequent dosing cohorts will then follow standard 3+3 dose escalation criteria.

Alternatively, if 2 patients experience moderate AEs (at any planned accelerated titration dose level), standard 3+3 dose escalation criteria will apply for the highest dose level at which a moderate AE was experienced, with enrollment of additional patients. All subsequent dosing cohorts will then follow standard 3+3 dose escalation criteria. Moderate AEs are defined as

≥ Grade 2 AEs deemed by the investigator as related to FPT155. Grade 2 laboratory values will not be considered as moderate AEs for this purpose unless accompanied by clinical sequalae. The algorithm outlined in the table below will be used for all dose escalation decisions in Phase 1a. If not already applied at a lower dose level according to the criteria stated above, enrollment at all dose levels ≥ 7.0 mg will follow a standard 3+3 dose escalation design.

Algorithm for 3+3 Dose Escalation Decisions:

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3 or 1/6	Enroll 3 patients at next dose level (next/higher cohort)
1/3	Enroll 3 additional patients at current dose level (current cohort)
≥2	Stop enrollment. If at the starting dose level, the study will be stopped. If at any other dose level, enroll 3 more patients at the previous dose level (previous/lower cohort) if only 3 were previously enrolled, or at an intermediate dose level

Abbreviations**:** DLT = dose limiting toxicity.

The maximum tolerated dose (MTD) will be defined as the dose level below that in which ≥2 DLTs are identified. If dose escalation completes without the identification of 2 DLTs at a given dose level, no MTD will have been identified. The Sponsor may discontinue dose escalation prior to determining a MTD based on the available observed safety, tolerability, PK, and PD. Intra-patient dose escalation will be permitted in patients enrolled at dose levels below 70 mg provided the criteria in Section 4.1.1.5 are met. Intra-patient dose escalation will only be permitted after a discussion between the Sponsor and investigator, taking into account the overall safety experience, PK, and PD data available at the time of the request. Safety data from such patients will be reviewed as part of the overall safety and tolerability of FPT155.

The RD of FPT155 will be identified based on an evaluation of all available safety, tolerability, PK, and PD data. The determination of RD will consider toxicities observed both during and beyond the DLT evaluation period as well as dose reductions and discontinuations due to toxicity that do not meet the DLT criteria. The RD, therefore, may or may not be the same as the MTD but cannot be higher than the MTD.

FPT155 Monotherapy Dose Exploration:

Phase 1a dose exploration consists of up to approximately 50 patients in total who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose level clearing dose escalation criteria). Toxicities observed in these patients will contribute to the overall assessments of safety and tolerability, and may inform selection of the RD.

FPT155 Monotherapy Dose Expansion:

Enrollment in Phase 1b dose expansion will begin when the MTD and/or RD has been identified by the CRC. Up to 8 tumor-specific cohorts consisting of approximately 30 patients each will evaluate the safety, efficacy, PK, and PD of FPT155 at the RD (see Appendix 11). Patients with advanced renal cell carcinoma (RCC) and melanoma that have failed prior anti-programmed death-ligand 1 (PD[L]1) therapy will be enrolled in a minimum of 1 of the 8 cohorts. Additional tumor types are specified in Appendix 11 for the remaining Phase 1b cohorts and will be determined based on emerging safety, translational, and clinical data for FPT155, as well as any potential new safety signals from other immunotherapies, such as significant changes to prescribing information for approved immunotherapies.

FPT155+Pembrolizumab Dose Escalation:

FPT155 will start at a dose level a minimum of 2 levels below that cleared in dose escalation with FPT155 monotherapy.

Pembrolizumab will be administered Q3 weeks at 200mg over 30 minutes on Day 1 of each 21-day cycle.

Dose escalation decisions will follow the standard 3+3 algorithm described above and continue up to the dose level established as the MTD for FPT155 monotherapy. Additional intermediate dose levels or dose regimens may be considered upon review of emerging safety, PK and PD results.

Additional DLT Considerations for FPT155 in combination with pembrolizumab

Because pembrolizumab is a known immune checkpoint inhibitor and one of the proposed mechanisms of action of FPT155 is immune checkpoint blockade, immune-related adverse events (irAEs) are anticipated with this combination. An irAE is defined as a clinically significant AE that is associated with study drug exposure, without a clear alternate cause, and consistent with an immune-mediated mechanism. Based on that background, the first occurrence of the following irAEs will not be considered a DLT because they may occur with immune therapy and are likely to be fully reversable per Appendix 8:

- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 non-skin immune-related adverse event (irAE) that resolve to a Grade 1 or less within 14 days with management per Appendix 8
- Transient (resolving within 6 hours of onset) Grade 3 infusion-related AEs
- Grade 3 drug-related bronchospasm or anaphylactic or anaphylactoid reactions

Dose escalation may be discontinued prior to determining an MTD based on observed safety, tolerability, or emerging PK or PD results.

FPT155 + Pembrolizumab Dose Exploration:

Enrollment in combination dose exploration may occur at one more dose levels that have been cleared during combination dose escalation.

Requirements for Archival Tumor Tissue and Fresh Biopsies:

Dose Escalation (Monotherapy and FPT155 + pembrolizumab):

- Archival tumor tissue is required. If archival tumor tissue is not available, a fresh biopsy is required prior to treatment for retrospective biomarker analysis.
- Optional pre- and on-treatment biopsies will be requested during screening (prior to treatment) and during treatment (prior to the Cycle 3 Day 1 dose) to explore the relationship between baseline tumor immune phenotype and PD response.
- An additional optional biopsy will be requested at disease progression.

Dose Exploration/Expansion (Monotherapy and FPT155 + pembrolizumab):

- Archival tumor tissue is required for retrospective biomarker analysis. The fresh biopsy required at screening will be accepted in lieu of archival tumor tissue if archival tissue is not available.
- Pre- and on-treatment biopsies will be mandatory during screening (prior to treatment) and during treatment (prior to the Cycle 3 Day 1 dose) to explore the relationship between baseline tumor immune phenotype and PD response.

An additional optional biopsy will be requested at disease progression.

Number of Patients:

The total number of patients planned for this study is estimated to be up to approximately 408.

- FPT155 Monotherapy: Up to approximately 58 patients will participate in Phase 1a dose escalation, depending on the number of dose levels evaluated and the incidence of DLTs; up to approximately 50 patients in the Phase 1a dose exploration; up to approximately 240 patients in Phase 1b dose expansion in 8 cohorts of approximately 30 patients each.
- FPT155+pembrolizumab: Up to approximately 30 patients in Phase 1a dose escalation; up to approximately 30 patients in dose exploration.

Eligibility Criteria:

Inclusion Criteria

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

Age

1.01) Patient must be 18 years of age or older at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2.01) Histologically confirmed solid tumors (except primary CNS tumors). For patients enrolled for treatment with FPT155+pembrolizumab: histologically confirmed non-small cell lung cancer not eligible for curative therapy.

2.02) For patients in Phase 1a dose escalation (all) and Phase 1a dose exploration (FPT155 monotherapy) only: Disease that is unresectable, locally advanced, or metastatic and has progressed following all standard treatments or is not appropriate for standard treatments. Appendix 11

2.03) All patients must have at least one measurable lesion at baseline according to RECIST v1.1. Tumor sites situated in a previously irradiated area, or in an area subjected to other loco-reginal therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

2.04) Availability of archival tumor tissue and consent to provide archival tumor for retrospective biomarker analysis, or consent to undergo a fresh tumor biopsy during screening

2.05) For patients participating in Phase 1a dose exploration cohorts and Phase 1b dose expansion: consent to undergo a mandatory fresh tumor biopsy during screening and on treatment

2.06) ECOG performance status of 0 or 1

2.07) Life expectancy of at least 3 months in the opinion of the investigator

2.08) Willing and able to comply with all study procedures

2.09) Prior radiotherapy must be completed at least 2 weeks before first dose of study treatment administration. No radiopharmaceuticals (eg, strontium, samarium) within 8 weeks before first dose of study treatment administration

2.10) Prior surgery that requires general anesthesia must be completed at least 14 days before first dose of study treatment administration unless patients have recovered, and it is considered safe after discussion with medical monitor. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before first dose of study treatment administration and patients must have recovered.

2.11) Screening laboratory values must meet the following criteria:

Hematologic

a. Neutrophils ≥ 1.2 x 10^9/L

b. Platelets ≥ 75 x 10^9/L

c. Hemoglobin ≥ 9.0 g/dL

d. Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance of ≥ 40 mL/minute (using Cockcroft/Gault Formula)

$$\text{Female creatinine clearance (CrCl)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

e. Prothrombin time (PT)/International normalized ratio (INR) < 1.5x ULN and partial thromboplastin time (PTT) (activated partial thromboplastin time [aPTT]) < 1.5x ULN except for patients receiving anticoagulation, who must be on a stable dose of warfarin for 6 weeks prior to enrollment

Hepatic

f. AST or ALT < 3x ULN

g. Bilirubin < 1.5x ULN (except patients with Gilbert's syndrome, who must have total bilirubin < 3 mg/dL)

h. Albumin ≥ 3.0 g/dL (patients with pancreatic cancer only)

Sex

3.01) Male or female

General Inclusion Criteria

Reproductive Status

Male patients:

4.01) A male patient must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 2 months or 5 half-lives, whichever is longer, after the last dose of study treatment and refrain from donating sperm during this period.

Female patients:

5.01) A female patient is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 2 months or 5 half-lives, whichever is longer, after the last dose of study treatment.

Informed Consent

6.01) Capable of giving signed informed consent as described in Section 10.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Additional Inclusion Criteria – Monotherapy (Phase 1b Only)

Cohort 1b1: Renal Cell Carcinoma

7.01) Patients with histologically or cytologically confirmed advanced or metastatic renal cell carcinoma with a clear-cell component.

7.02) Must have received at least one prior anti-angiogenic therapy regimen (eg, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, or bevacizumab) in the advanced or metastatic setting

7.03) Must have received at least one anti-PD(L)1 therapy (eg, nivolumab, pembrolizumab, atezolizumab, durvalumab, or avelumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α) and anti-CTLA4 therapy (eg, ipilimumab) is allowed but not required.

Cohort 1b2: Melanoma

8.01) Patients with histologically- or cytologically-confirmed unresectable stage III or stage IV cutaneous melanoma not amenable to local therapy

8.02) Must have received at least one anti-PD(L)1 therapy (including but not limited to nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α) and anti-CTLA4 therapy (eg, ipilimumab) is also allowed.

8.03) Patients with BRAF mutations must have received prior BRAF inhibitor therapy (eg, vemurafenib and dabrafenib) in the advanced or metastatic setting.

9.01) Inclusion Criteria for Additional Phase 1b Cohorts are included in Appendix 11.

Exclusion Criteria

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

Medical Conditions

1.01) Decreased cardiac function with New York Heart Association (NYHA) > Class 2

1.02) Uncontrolled or significant heart disorder such as unstable angina

1.03) Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the investigator, would preclude the patient from exposure to a biologic agent or pose a risk to patient safety

1.04) Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results

1.05) Active autoimmune disease, history of clinically significant autoimmune disease, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, are permitted to enroll

1.06) Symptomatic interstitial lung disease or inflammatory pneumonitis

1.07) Untreated or active CNS or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to the first dose of study treatment

1.08) Evidence of coagulopathy or bleeding diathesis

Prior/Concomitant Therapy

2.01) Treatment with any anti-cancer therapy or participation in another investigational drug or biologics trial within 28 days or ≤ 5 half-lives (whichever is shorter) prior to first dose of study treatment administration or while on this study

2.02) For patients participating in Phase 1a dose escalation and exploration cohorts: Prior treatment with a CTLA-4 antagonist, including ipilimumab and tremelimumab

2.03) Patients who have received prior immune-modulating therapies (including regimens containing an immune agonist or a programmed death-ligand 1 ([PD-L1]/programmed cell death protein 1 [PD-1] antagonist) are NOT permitted to enroll unless all the following apply:

a. Must not have experienced a drug-related toxicity that led to permanent discontinuation of prior immunotherapy

b. Last treatment was administered a minimum of 5 half-lives or 90 days (whichever is shorter) prior to first dose of study treatment

2.04) Ongoing adverse effects from prior treatment > National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.3) Grade 1 (with the exception of Grade 2 alopecia or peripheral neuropathy)

Other Exclusions

3.01) Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent daily) must be discontinued at least 2 weeks before study treatment administration

3.02) QTcF > 450 msec for males or > 470 msec for females at screening

3.03) Severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent

3.04) Known history of sensitivity to infusions containing Tween 20 (polysorbate 20), L-histidine, and sucrose

3.05) Vaccines (eg, human papillomavirus [HPV] vaccine) within 4 weeks of study treatment administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted, but must be discussed with the Sponsor's medical monitor and may require a study treatment washout period prior to and after administration of vaccine

3.06) Patients with abnormal serum chemistry values that in the opinion of the investigator are considered to be clinically significant. This will include patients who show clinical signs and symptoms related to their abnormal serum chemistry values as well as patients whose serum chemistry values are asymptomatic but clinically significant per investigator (eg, hypokalemia or hyponatremia).

3.07) Pregnant or breastfeeding

3.08) Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS)

3.09) Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection

3.10) Transfusion of blood or platelets or granulocyte-colony stimulating factor (G-CSF) administration completed within 72 hours prior to first dose of study treatment

No waivers of these inclusion or exclusion criteria will be granted

Treatment and Duration:

As monotherapy, FPT155 will be administered over approximately 60 minutes by IV infusion Q3W.

In combination, FPT155 will be administered over approximately 60 minutes by IV infusion Q3W. Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes, a minimum of 30 minutes after the completion of FPT155 infusion.

Dose reductions or delays for FPT155 or pembrolizumab may be permitted for patients on treatment beyond the DLT evaluation interval in Phase 1a dose escalation, or any patients enrolled in the exploration, or expansion parts of the study per the guidelines in Section 6.9.3. If dose reductions or interruptions that do not fall within these guidelines are being considered by the investigator, these will require discussion with and approval by the Sponsor or designee.

Treatment is administered Q3W until disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria. If one drug in the combination is discontinued, the other may be administered for up to an additional 12 months on study. If treatment is permanently discontinued for any reason other than consent withdrawal, the patient will undergo end of treatment (EOT) follow-up visits approximately 28 days and 100 days after the last dose of any study drug.

In the Phase 1b dose expansion portion of the study, patients will also undergo long-term follow-up (LTFU) for survival by clinic visit or by telephone approximately every 3 months after the Day 100 EOT visit, or until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor (whichever occurs first).

Tests and Observations:

In Phase 1a, safety monitoring at each study visit will include an evaluation of the signs and symptoms of autoimmune toxicities such as enterocolitis, dermatitis, neuropathy, and endocrinopathies. Management of immune-related adverse events (irAEs) and CRS are described in Section 6.9.4 and Appendix 10 respectively. Changes in key CRS-promoting cytokine levels from baseline (including IL-6, IFNγ, TNFα, and others) will be evaluated to assess the cytokine response to FPT155 in treated patients.

Safety assessments for all patients include vital signs, body weight, physical exam, ECOG score, laboratory tests (hematology, serum chemistries, coagulation, and urinalysis), ECG, and monitoring of AEs and concomitant medications. Specimens for PK, anti-drug antibodies

(ADA), and PD will be collected at the timepoints described in Table 1, Table 2, Table 3, and Table 4.

Tumor assessments will be performed at screening, then every 6 weeks from the first dose for 24 weeks, and then every 12 weeks thereafter. Once an initial CR or PR is reported by the investigator, confirmatory scans must be performed 4–6 weeks later. Responses will be assessed according to RECIST v1.1. In the Phase 1b portion of the study, patients in LTFU for survival must have tumor scans every 12 weeks if tumor progression was not previously determined and/or use of alternative anti-cancer therapy has not been initiated.

Data Monitoring Committee: No

Statistical Methods:

Hypothesis

This is an estimation trial. There is no clinical hypothesis.

General Approach

All analyses will be descriptive and will be presented by phase, dose group, cohort, and overall as appropriate. In addition, all patients dosed at the MTD and/or RD will also be summarized as appropriate. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of subjects, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

Sample Size Determination

This study is designed as a dose escalation, dose exploration, and dose expansion study with objectives that include determination of an MTD and/or RD and assessments of the safety and tolerability of FPT155 as monotherapy and in combination with pembrolizumab. The sample size of Phase 1a is defined by the requirements of the 3+3 dose escalation design. The total number of patients planned for this study is estimated to be approximately 408.

Approximately 108 patients will participate in Phase 1a monotherapy, depending on the number of dose levels evaluated and the incidence of DLTs; this includes up to 58 patients in the Phase 1a monotherapy dose escalation portion and allows for up to approximately 50 patients in the Phase 1a monotherapy dose exploration to further explore safety, PK, PD, and clinical activity at one or more dose levels (conditional upon the dose level clearing dose escalation criteria). Up to approximately 240 patients will participate in the Phase 1b monotherapy dose expansion in up to 8 cohorts of approximately 30 patients each.

Up to approximately 30 patients will participate in Phase 1a combination dose escalation, depending on the number of dose levels evaluated and the incidence of DLTs. Up to approximately 30 patients will participate in the combination dose exploration.

Safety Analysis

Safety analyses will be performed separately within phases of the study and by dose, cohort, and all patients combined. Data from all patients that receive any portion of at least 1 dose of FPT155 will be included in the safety analyses. AEs, SAEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized. In addition, the incidence of DLTs in Phase 1a dose escalation will be summarized.

Efficacy Analysis

Objective Response Rate (ORR) will be summarized with frequencies and percentages with 90% exact confidence interval (CI) using the binomial distribution. Progression-free survival (PFS) and overall survival (OS) will be summarized using Kaplan-Meier (KM) estimates and corresponding 90% CIs. Duration of response (DOR) will be summarized similarly as for PFS and OS for all treated subjects who achieved a confirmed CR of PR. ORR, DOR and PFS will be determined based on investigator's assessments as per RECIST v1.1.

Pharmacokinetic Analysis

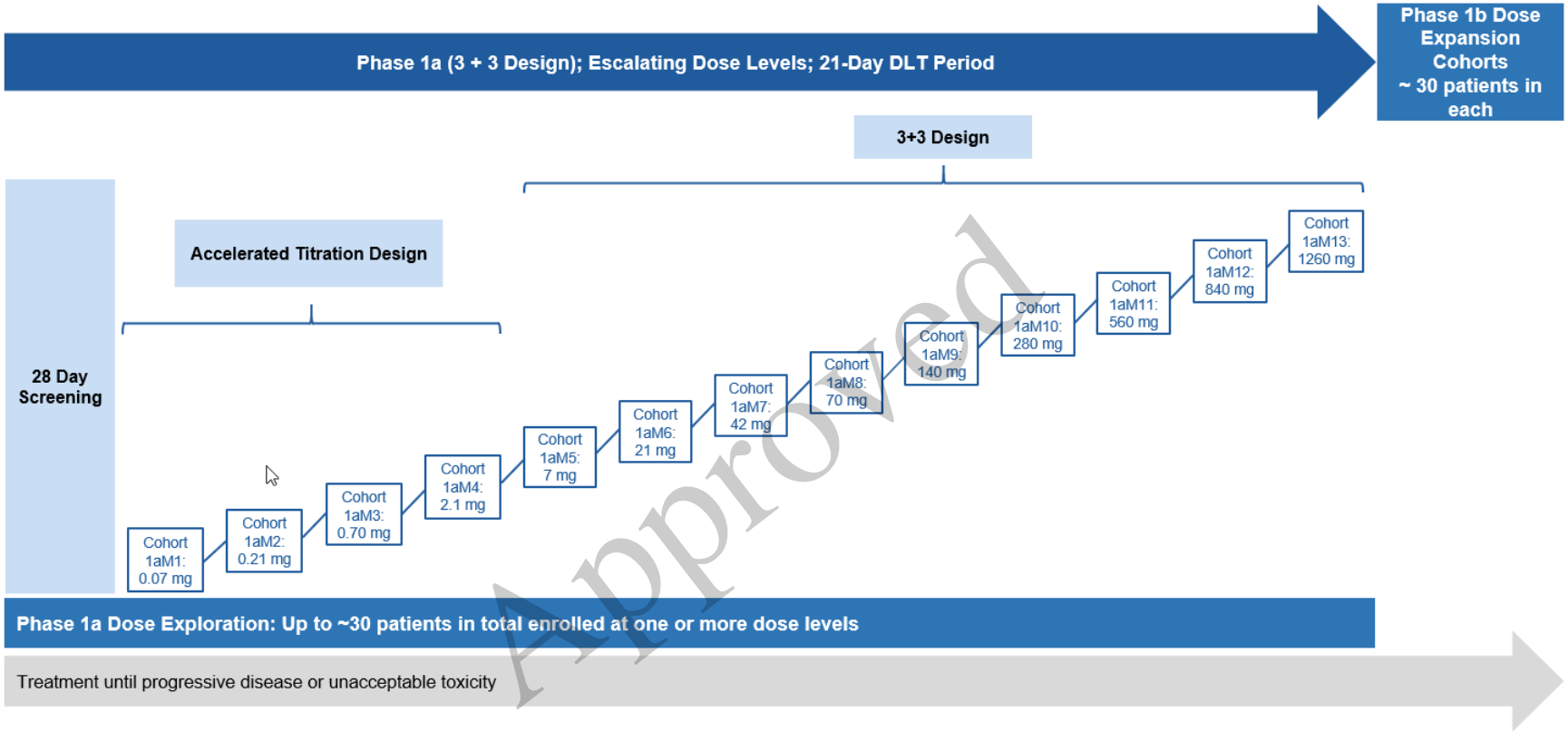
Individual and mean (± SD) serum FPT155 and pembrolizumab (if applicable) concentration-time data will be tabulated and plotted by dose level. PK parameters will be tabulated and summarized by dose level when appropriate and applicable. The impact of immunogenicity on FPT155 exposure will be assessed, tabulated, and summarized by dose level as data allow.

The effect of body size on PK and correlation of exposure with clinical outcomes and toxicity will be assessed when the data allow. These analyses will be used to determine the appropriate dosing approach (eg, body size-based or fixed dosing) to support the proposed dose and dose regimen(s) for further trials.

Immunogenicity Analysis

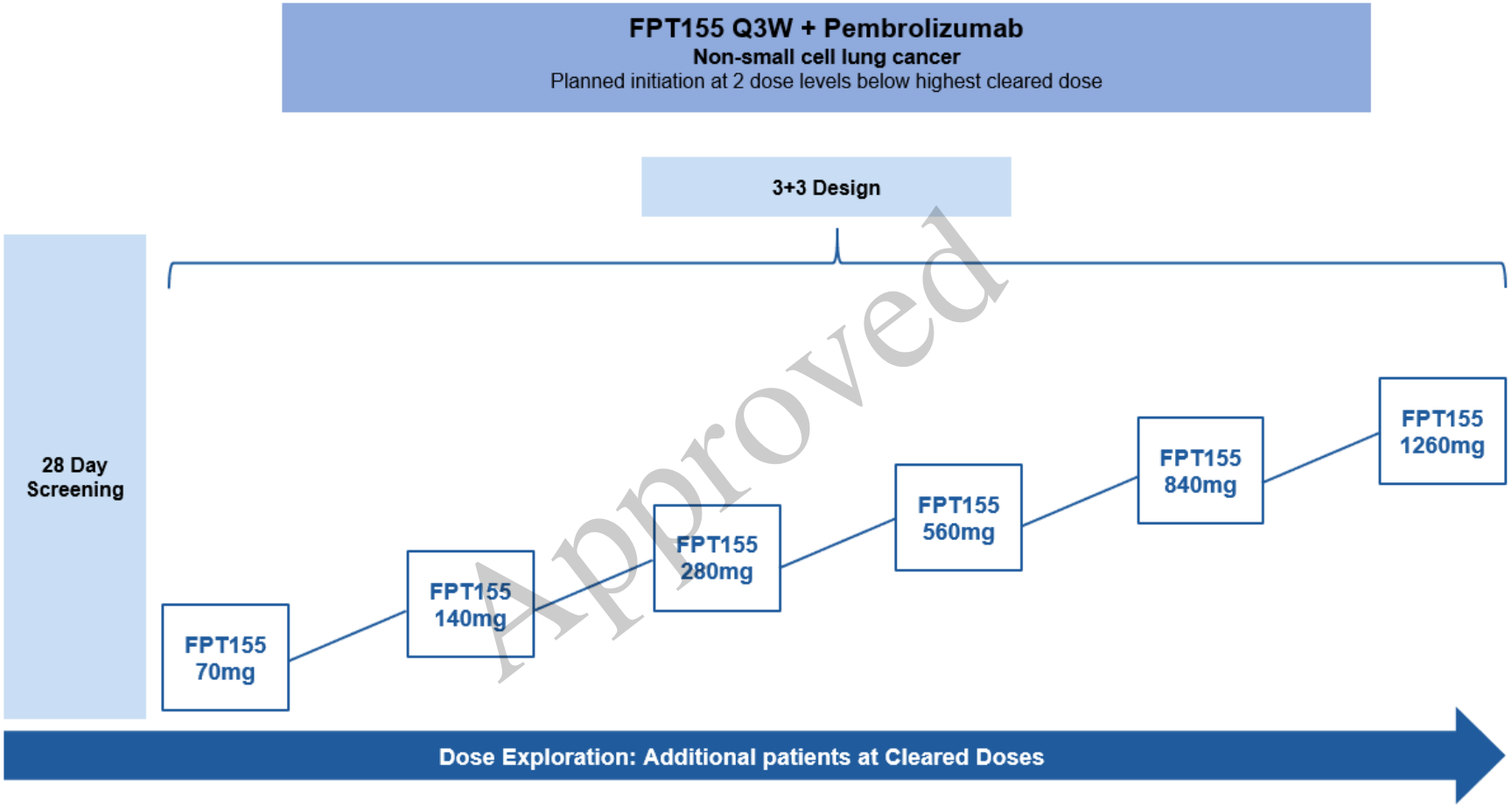
A baseline ADA-positive patient is defined as a patient who has an ADA positive sample at baseline. A treatment induced ADA-positive patient is a patient with at least 1 ADA-positive sample relative to baseline after initiation of the treatment. The frequency distribution of baseline ADA-positive patients and induced ADA-positive patients after initiation of study treatment will be summarized.

Figure 1: Schema Monotherapy Dose Escalation



Abbreviations: DLT = dose limiting toxicity; RCC = renal cell carcinoma; RD = recommended dose.

Figure 2: Schema Combination



1.2 Schedule of Assessments

Study assessments and procedures are presented in Table 1, Table 2, Table 3, and Table 4. Protocol waivers or exemptions are not allowed.

Table 1: Schedule of Assessments – Dose Escalation (monotherapy and FPT155 + pembrolizumab)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**	
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**Notes**
Study Assessments: Unless specified, procedure is to be performed prior to administration of study treatment. Any clinical assessment, laboratory test, or additional non-specified test may be obtained at any time if clinically indicated. If all study treatment is permanently discontinued for any reason other than withdrawal of consent, EOT follow-up visits should take place at the specified time points. The EOT follow-up visit at approximately 100 days after the last dose of study drug will be considered the end of study in Phase 1a.									
Review / Confirm Eligibility Criteria	X	X							
Informed Consent	X								
Medical History / Demographics	X	X							Medical history includes significant past medical events including surgeries or hospitalizations, a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
Physical Examination	X	X			X	X	X	X	A complete physical examination including height and weight will be performed at screening. A limited physical examination (e.g., symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening. Additional physical examinations may be performed as clinically indicated for patients in the first dose cohort that are hospitalized for the initial infusion or for any patients showing evidence of ≥ Grade 2 CRS.
Height and Weight	X	X			X	X	X	X	Height (without shoes) should be measured at screening only and recorded in centimeters. Weight (without shoes) should be measured at each physical examination and reported in kilograms.

Table 1: Schedule of Assessments – Dose Escalation (monotherapy and FPT155 + pembrolizumab) (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**	
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**Notes**
Vital Signs	X	X	X	X	X	X	X	X	Vital signs include blood pressure, respiratory rate, pulse and temperature. For the first and second infusions of FPT155, measure vital signs prior to dosing, every 15 minutes during the infusion, and after completion of each FPT155 IV infusion at the following timepoints: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours post-dose. Additional vital signs may be performed as clinically indicated for patients in the first dose cohort that are hospitalized for the initial infusion or for any patients showing evidence of ≥ Grade 2 CRS. For all subsequent infusions, measure vital signs prior to dosing, every 15 minutes during the infusion, and after completion of each FPT155 IV infusion.
12-Lead ECG	X	X					X	X	ECG is required at screening, pre-dose on Day 1 of every cycle, and at the EOT visits.
ECOG Performance Status	X	X					X	X	
Prior / Concomitant Medications		←═══════════════════════════════════→							
Adverse Events Review		←═══════════════════════════════════→							AEs will be assessed before and after study drug dosing on applicable visits. AEs ascribed to study drug and SAEs should be assessed through the Day 100 EOT visit.

Table 1: Schedule of Assessments – Dose Escalation (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**	
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**Notes**
CT or MRI	X						X	X	Tumor evaluation by CT or MRI should be conducted according to RECIST v1.1 at screening, every 6 (± 1) weeks from the first dose for 24 weeks, and then every 12 (± 2) weeks thereafter. Imaging performed as standard of care may be used if it has been performed within 28 days of treatment. Once an initial CR or PR is noted, confirmatory scans must be performed 4-6 weeks later. Patients who terminate treatment prior to the next scheduled CT or MRI assessment should have a scan performed at the EOT visits (if not conducted in the previous 8 weeks or if tumor progression was previously determined). After discontinuation of study treatment for reasons other than progressive disease, withdrawal of consent, or initiation of additional anti-cancer therapy, tumor assessments will continue approximately every 12 (± 1) weeks until disease progression, withdrawal of consent or start of new anti-cancer therapy.
Archival Tumor Tissue (or Fresh Biopsy if Archival Not Available)	X								In dose escalation cohorts, archival tumor tissue is required. If archival tumor tissue is not available, a fresh biopsy is required prior to treatment. Blocks are preferred, if not available, a minimum of 15 slides are acceptable.
Sample Collection									
Chemistry	X	X	X		X	X	X**	X	All samples are assessed locally. Labs may be drawn up to 24 hours in advance of treatment. Refer to Appendix 1 for additional details. Additional labs may be performed as clinically indicated for patients in the first dose cohort that are hospitalized for the initial infusion or for any patients showing evidence of ≥ Grade 2 CRS. ** During dose escalation, chemistry and hematology panel will be drawn on Day 2, 8 and 15 of Cycles 2 and 3.
Hematology	X	X	X		X	X	X**	X	
Coagulation	X	X					X	X	
Urinalysis	X	X					X	X	
HBsAg and HCV RNA	X								

Table 1: Schedule of Assessments – Dose Escalation (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	Screening	Cycle 1 (21 Days)					Subsequent Cycles* (21 Days)	EOT Follow-Up	
Cycle Day	Screening	D1	D1	D4	D8	D15	D1	28- and 100-Days Post Last Dose	
Window (Days)	-28			± 1	± 1	± 1	± 3	± 7	Notes
Pregnancy Test	X	X					X		For WOCBP, a serum pregnancy test will be performed at screening (within 7 days of Cycle 1 Day 1) and pregnancy testing will be performed at each subsequent cycle of treatment prior to dosing. All samples are assessed locally.
PK Sampling	Refer to Table 3								Blood samples will be collected for PK analyses at the timepoints specified in Table 3 and submitted to the central laboratory.
PD Sampling	Refer to Table 3								Blood samples will be collected for PD analyses at the timepoints specified in Table 3 and submitted to the central laboratory.
ADA Sampling	Refer to Table 3								Blood samples will be collected for ADA analyses at the timepoints specified in Table 3 and submitted to the central laboratory.
Tumor Tissue Biopsy	X						X	X	In dose escalation cohorts, optional pre- and on-treatment fresh biopsies will be requested from the primary tumor or metastatic tumor site at screening (prior to treatment) and Cycle 3 Day 1, from the same lesion where feasible. An additional optional biopsy will be requested at the Day 28 EOT visit from patients who have documented disease progression.
Study Drug Dosing									
Study Drug Dosing		X					X		FPT155 will be administered over approximately 60 minutes by IV infusion Q3W. Patients may continue receiving study treatment Q3W at the investigator's discretion until any of the protocol-specified treatment discontinuation criteria are met. For FPT155 + pembrolizumab cohorts, pembrolizumab will be administered 30 minutes after completion of the FPT155 IV infusion at a dose of 200 mg by 30 min IV infusion. If one study drug is discontinued, the other may be administered for up to 12 months or until protocol-specified discontinuation criteria are met. The DLT evaluation period consists of 21 days. Upon completion of the DLT evaluation period, patients may continue receiving study treatment per the parameters above.

Abbreviations**:** ADA = anti-drug antibody; AE = adverse event; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IV = intravenous; HBsAG = hepatitis B surface antigen; HCV RNA = hepatitis C virus ribonucleic acid; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PR = partial response; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; WOCBP = women of childbearing potential.

*There is a ± 3-day window for subsequent cycles after Cycle 1

Table 2: Schedule of Assessments – Dose Exploration/Expansion (monotherapy and FPT155 + pembrolizumab)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	**LTFU**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**		
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**± 14**	**Notes**
Study Assessments: Unless specified, procedure is to be performed prior to administration of study treatment. Any clinical assessment, laboratory test, or additional non-specified test may be obtained at any time if clinically indicated. If all study treatment is permanently discontinued for any reason other than withdrawal of consent, EOT follow-up visits should take place at the specified time points. In the Phase 1b portion of the study, patients will also undergo LTFU for survival by clinic visit or by telephone approximately every 3 months after the Day 28 EOT visit, or until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor (whichever occurs first), which will be considered the end of the study in Phase 1b.										
Review / Confirm Eligibility Criteria	X	X								
Informed Consent	X									
Medical History / Demographics	X	X								Medical history includes significant past medical events including surgeries or hospitalizations, a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
Physical Examination	X	X			X	X	X	X		A complete physical examination including height and weight will be performed at screening. A limited physical examination (e.g., symptom-directed examination of specific organ systems/body area) should be conducted at the specified time points after screening. Additional physical examinations may be performed as clinically indicated.
Height and Weight	X	X			X	X	X	X		Height (without shoes) should be measured at screening only and recorded in centimeters. Weight (without shoes) should be measured at each physical examination and reported in kilograms.

Table 2: Schedule of Assessments –Dose Exploration/Expansion (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	**LTFU**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**		
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**± 14**	**Notes**
Vital Signs	X	X	X	X	X	X	X	X		Vital signs include blood pressure, respiratory rate, pulse and temperature. For the first and second infusions of FPT155, measure vital signs prior to dosing, every 15 minutes during the infusion, and after completion of each FPT155 IV infusion at the following timepoints: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, and 6 hours post-dose. For all subsequent infusions, measure vital signs prior to dosing, every 15 minutes during the infusion, and after completion of each FPT155 IV infusion. Additional vital signs may be performed as clinically indicated.
12-Lead ECG	X	X						X		ECG is required at screening, pre-dose on Cycle 1 Day 1, and at the EOT visits. Additional ECGs may be obtained at any time if clinically indicated.
ECOG Performance Status	X	X					X	X		
Prior / Concomitant Medications		←==========→								
Adverse Events Review		←==========→								AEs will be assessed before and after study drug dosing on applicable visits. AEs ascribed to study drug and SAEs should be assessed through the Day 100 EOT visit.

Table 2: Schedule of Assessments –Dose Exploration/Expansion (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	**LTFU**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**		
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**± 14**	**Notes**
CT or MRI	X						X	X	X	Tumor evaluation by CT or MRI should be conducted according to RECIST v1.1 at screening, every 6 (± 1) weeks from the first dose for 24 weeks, and then every 12 (± 2) weeks thereafter. Imaging performed as standard of care may be used if it has been performed within 28 days of treatment. Once an initial CR or PR is noted, confirmatory scans must be performed 4-6 weeks later. Patients who terminate treatment prior to the next scheduled CT or MRI assessment should have a scan performed at the EOT visits (if not conducted in the previous 8 weeks or if tumor progression was previously determined). After discontinuation of study treatment for reasons other than progressive disease, withdrawal of consent, or initiation of additional anti-cancer therapy, tumor assessments will continue approximately every 12 (± 1) weeks until disease progression, withdrawal of consent or start of new anti-cancer therapy. Patients in LTFU for survival must have tumor scans every 12 (±2) weeks if tumor progression was not previously determined and/or use of alternative anti-cancer therapy has not been initiated. Any new anti-cancer therapy should be documented.
Archival Tumor Tissue (or Fresh Biopsy if Archival Not Available)	X									Archival tumor tissue is required. The fresh biopsy required at screening will be accepted in lieu of archival tumor tissue if archival tissue is not available. Blocks are preferred, if not available, a minimum of 15 slides are acceptable.

Table 2: Schedule of Assessments –Dose Exploration/Expansion (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	**LTFU**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**		
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**± 14**	**Notes**
Sample Collection										
Chemistry	X	X	X		X	X	X	X		All samples are assessed locally. Labs may be drawn up to 24 hours in advance of treatment. Refer to Appendix 1 for additional details. Additional labs may be performed as clinically indicated.
Hematology	X	X	X		X	X	X	X		
Coagulation	X	X					X	X		
Urinalysis	X	X					X	X		
HBsAg and HCV RNA	X									
Pregnancy Test	X	X					X			For WOCBP, a serum pregnancy test will be performed at screening (within 7 days of Cycle 1 Day 1) and pregnancy testing will be performed at each subsequent cycle of treatment prior to dosing. All samples are assessed locally.
PK Sampling		Refer to Table 4								Blood samples will be collected for PK analyses at the timepoints specified in Table 4 and submitted to the central laboratory.
PD Sampling		Refer to Table 4								Blood samples will be collected for PD analyses at the timepoints specified in Table 4 and submitted to the central laboratory.
ADA Sampling		Refer to Table 4								Blood samples will be collected for ADA analyses at the timepoints specified in Table 4 and submitted to the central laboratory.

Table 2: Schedule of Assessments –Dose Exploration/Expansion (monotherapy and FPT155 + pembrolizumab) (Contd)

Study Phase	**Screening**	**Cycle 1 (21 Days)**					**Subsequent Cycles* (21 Days)**	**EOT Follow-Up**	**LTFU**	
Cycle Day	**Screening**	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**28- and 100-Days Post Last Dose**		
Window (Days)	**-28**			**± 1**	**± 1**	**± 1**	**± 3**	**± 7**	**± 14**	**Notes**
Tumor Tissue Biopsy	X						X	X		In dose exploration and expansion, pre- and on-treatment fresh biopsies will be mandatory at screening (prior to treatment) and prior to the Cycle 3 Day 1 dose, from the same lesion where feasible. An additional optional biopsy will be requested at the Day 28 EOT visit from patients who have documented disease progression.
Study Drug Dosing										
Study Drug Dosing		X					X			FPT155 will be administered over approximately 60 minutes by IV infusion Q3W. Patients may continue receiving study treatment Q3W at the investigator's discretion until any of the protocol-specified treatment discontinuation criteria are met. For FPT155 + pembrolizumab cohorts, pembrolizumab will be administered 30 minutes after completion of the FPT155 IV infusion at a dose of 200 mg by IV infusion. If one study drug is discontinued, the other may be administered for up to 12 months or until protocol-specified discontinuation criteria are met.
Survival Assessment										
Survival Assessment									X	Patients will undergo LTFU for survival by clinic visit or by telephone approximately every 3 months ± 14 days after the Day 100 EOT visit, or until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor (whichever occurs first).

Abbreviations**:** ADA = anti-drug antibody; AE = adverse event; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; DLT = dose limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IV = intravenous; HBsAG = hepatitis B surface antigen; HCV RNA = hepatitis C virus ribonucleic acid; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PR = partial response; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; WOCBP = women of childbearing potential.

* There is a ± 3-day window for subsequent cycles after Cycle 1

Table 3: Dose Escalation (monotherapy and FPT155 + pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory

Study Cycle	Study Day	Time Point & Window	Type of Sample
Screening	Screening	Screening (Day-28)	Archival tumor, as specified in Table 1
			Tumor biopsy, as specified in Table 1
			Plasma for PD
			PBMC for PD
Cycle 1	Day 1	≤ 4 hours prior to infusion	FPT155 and/or pembrolizumab PK (serum)
			FPT155 and/or pembrolizumab ADA (serum)
			Plasma for PD
			PaxGene for PD
			ctDNA plasma for PD
			PBMC for PD
		15 (± 10) minutes after end of infusion	FPT155 and/or pembrolizumab PK (serum)
		1 hour (± 15 minutes) after end of infusion	FPT155 PK (serum)
			Plasma for PD
		2 hours (± 30 min) after the end of infusion	FPT155 PK (serum)
		6 hours (± 60 minutes) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 2	24 hours (± 2 hours) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 4	72 hours (± 1 day) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 8	168 hours (± 1 day) after infusion	FPT155 PK (serum)
			Plasma for PD
			PaxGene for PD
			PBMC for PD
	Day 15	336 hours (± 1 day) after infusion	FPT155 PK (serum)
			Plasma for PD
			PaxGene for PD
			PBMC for PD

Table 3: Dose Escalation (monotherapy and FPT155 + pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory (Contd)

Study Cycle	Study Day	Time Point & Window	Type of Sample
Cycles 2 -6	Day 1	≤ 4 hours prior to infusion	Tumor Biopsy (prior to Cycle 3 Day 1 ± 1 week), as specified in Table 1
			FPT155 PK (serum) Pembrolizumab PK (serum) (Cycle 2)
			FPT155 ADA (serum) (Cycles 2, 3, and 5) Pembrolizumab ADA (serum) (Cycle 2)
			Plasma for PD (Cycles 2, 3, and 5)
			PaxGene for PD (Cycles 2, 3, and 5)
			ctDNA plasma for PD (Cycle 3)
			PBMC for PD (Cycles 2, 3, and 5)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
		1 hour (± 15 minutes) after end of infusion	FPT155 PK (serum) (Cycle 3)
			Plasma for PD (Cycle 3)
Cycles 9, 13, and 17	Day 1	≤ 4 hours prior to infusion	FPT155 PK (serum) Pembrolizumab PK (Cycle 9)
			FPT155 ADA (serum) Pembrolizumab ADA (serum) (Cycle 9)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
Every 8 Cycles starting from Cycle 17	Day 1	≤ 4 hours prior to infusion	FPT155 PK (serum)
			FPT155 ADA (serum)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
EOT	Visit date (28 [±7] days and 100 [±7] days post-last dose)	During visit	Tumor Biopsy (Day 28 visit, as specified in Table 1
			FPT155 and/or pembrolizumab PK (serum)
			FPT155 and/or pembrolizumab ADA (serum)
			Plasma for PD (Day 28 visit)
			PaxGene for PD (Day 28 visit)
			ctDNA plasma for PD (Day 28 visit)
			PBMC for PD (Day 28 visit)

Abbreviations**:** ADA = anti-drug antibody; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic.

Table 4: Dose Exploration/Expansion (Monotherapy and FPT155 + pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory

Study Cycle	Study Day	Time Point & Window	Type of Sample
Screening	Screening	Screening (Day-28)	Archival tumor, as specified in Table 2
			Tumor biopsy, as specified in Table 2
			Plasma for PD
			PBMC for PD
Cycle 1	Day 1	≤ 4 hours prior to infusion	FPT155 and/or pembrolizumab PK (serum)
			FPT155 and/or pembrolizumab ADA (serum)
			Plasma for PD
			PaxGene for PD
			ctDNA plasma for PD
			PBMC for PD
		15 (± 10) minutes after end of infusion	FPT155 and/or pembrolizumab PK (serum)
		1 hour (± 15 minutes) after end of infusion	FPT155 PK (serum)
			Plasma for PD
		2 hours (± 30 min) after the end of infusion	FPT155 PK (serum)
		6 hours (± 60 minutes) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 2	24 hours (± 2 hours) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 4	72 hours (± 1 day) after end of infusion	FPT155 PK (serum)
			Plasma for PD
	Day 8	168 hours (± 1 day) after infusion	FPT155 PK (serum)
			Plasma for PD
			PaxGene for PD
			PBMC for PD
	Day 15	336 hours (± 1 day) after infusion	FPT155 PK (serum)
			Plasma for PD
			PaxGene for PD
			PBMC for PD

Table 4: Dose Exploration/Expansion (Monotherapy and FPT155 + pembrolizumab): Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Specimens to be Submitted to Central Laboratory (Contd)

Study Cycle	Study Day	Time Point & Window	Type of Sample
Cycles 2-6	Day 1	≤ 4 hours prior to infusion	Tumor Biopsy (prior to Cycle 3 Day 1 ± 1 week), as specified in Table 2
			FPT155 PK (serum) Pembrolizumab PK (serum) (Cycle 2)
			FPT155 ADA (serum) (Cycles 2, 3, and 5) Pembrolizumab ADA (serum) (Cycles 2)
			Plasma for PD (Cycles 2, 3, and 5)
			PaxGene for PD (Cycles 2, 3, and 5)
			ctDNA plasma for PD (Cycle 3)
			PBMC for PD (Cycles 2, 3, and 5)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
Cycles 9, 13, and 17	Day 1	≤ 4 hours prior to infusion	FPT155 PK (serum) Pembrolizumab PK (serum) (Cycles 9)
			FPT155 ADA (serum) Pembrolizumab ADA (serum) (Cycles 9)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
Every 8 Cycles starting from Cycle 17	Day 1	≤ 4 hours prior to infusion	FPT155 PK (serum)
			FPT155 ADA (serum)
		15 (± 10) minutes after end of infusion	FPT155 PK (serum)
EOT	Visit date (28 [±7] days and 100 [±7] days post-last dose)	During visit	Tumor Biopsy (Day 28 visit, as specified in Table 2
			FPT155 and/or pembrolizumab PK (serum)
			FPT155 and/or pembrolizumab ADA (serum)
			Plasma for PD (Day 28 visit)
			PaxGene for PD (Day 28 visit)
			ctDNA plasma for PD (Day 28 visit)
			PBMC for PD (Day 28 visit)

Abbreviations**:** ADA = anti-drug antibody; ctDNA = circulating tumor deoxyribonucleic acid; EOT = end of treatment; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic.

2.0 INTRODUCTION

T cell regulation involves the integration of multiple signaling pathways: signaling via the T cell receptor (TCR) complex and through co-signaling receptors, both co-stimulatory and co-inhibitory. CD80 (cluster of differentiation 80, also known as B7, B7.1, B7-1) is a well -characterized co-signaling ligand. It is expressed on professional antigen-presenting cells (APCs) such as dendritic cells and activated macrophages. Following TCR recognition of cognate peptide-major histocompatibility complex (MHC), CD80 acts as a co-stimulatory ligand via interactions with its receptor, cluster of differentiation 28 (CD28), expressed on T cells. In addition to signaling via CD28, CD80 also interacts with co-inhibitory molecules cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-ligand 1 (PD-L1). CD80 interactions with CTLA-4 are central for dampening the T cell response once activated T cell responses are no longer needed, while the biological significance of the CD80 interaction with PD-L1 is not as well understood. Together, the co-stimulatory and co-inhibitory ligands ensure both tolerance to self-antigens and the ability to mount an appropriate immune response to non-self antigens (Chen 2013).

Although the immune system is often initially able to mount an effective immune response against tumor cells via TCR-dependent and -independent mechanisms, some tumors can evade the immune response. Mechanisms by which this occurs include the upregulation of pathways that enforce peripheral tolerance to self-antigens (including CTLA-4 and PD-L1). Recent immuno-oncology approaches have focused on reprogramming the immune system to mount an effective immune response against tumors that have evaded the initial immune response. Specifically, blocking antibodies against both the programmed cell death protein (PD-1)/PD-L1 and CTLA-4 axes have been effective in anti-tumor immunity, including improved progression free survival (PFS) and overall survival (OS) in some patients (Postow 2015). However, responses have only been observed in select tumor types, within which only a fraction of patients respond to checkpoint inhibitors. Although some patients do achieve long term disease control with the use of blocking antibodies against the PD-1/PD-L1 and CTLA-4 axes, the majority of patients either do not respond or respond then subsequently relapse. Therefore, a need exists for additional immuno-oncology approaches, and the CD80 signaling axis may provide additional opportunities for intervention.

FPT155 (CD80-Fc) is a recombinant fusion protein composed of the extracellular domain (ECD) of human CD80 fused with the fragment crystallizable (Fc) domain of human immunoglobulin G1 (IgG1). It is designed to act as a potent stimulator of anti-tumor immunity through 2 mechanisms of action. FPT155 exerts direct agonism, but not superagonism, of CD28, thereby co-stimulating T cell activation in response to TCR signaling. FPT155 is also likely to prevent CTLA-4-mediated effector T cell inhibition. FPT155 is being developed for the treatment of solid tumors that are predicted to be responsive to an immune-mediated therapeutic approach.

2.1 Study Rationale

Recently approved immune therapies, particularly inhibitors of immune checkpoints such as CTLA-4 and PD-1 have resulted in durable responses across many solid tumors (KEYTRUDA 2018, OPDIVO 2018, Yervoy 2018). Anti-PD(L)1 inhibitors have received regulatory approval across a range of solid tumors including melanoma and renal cell carcinoma (RCC). The median objective response rate (ORR) in patients with advanced melanoma who received up to 1 prior therapy for metastatic disease ranged from 33-40% with a median PFS of approximately 5 months (Robert 2015). Ipilimumab, a CTLA-4 inhibitor, is approved as monotherapy in advanced melanoma with an ORR of 10% and median OS of 10 months (Hodi 2010). The combination of nivolumab, an anti-PD-1 antibody, and ipilimumab has demonstrated superior efficacy in advanced melanoma compared to either agent alone with an ORR of 58% and a median PFS of 11.5 months compared to 44% and 6.5 months with nivolumab alone (Wolchok 2017). In patients with advanced RCC who failed prior anti-angiogenic therapy, nivolumab resulted in an ORR of 25% and median PFS of 4.6 months (Motzer 2015). In RCC the combination of ipilimumab and nivolumab was superior to sunitinib with an ORR 42% and median PFS of 11.6 months (Motzer 2018). Thus, even the combination of 2 checkpoint inhibitor therapies results in objective responses in < 60% of patients with a median PFS of less than 1 year. Efficacy of anti-PD(L)1 monotherapy in other solid tumors (eg squamous cell head and neck cancer and urothelial carcinoma) is even more limited compared to melanoma and RCC (Ferris 2016, Bellmunt 2017). Ipilimumab has shown limited activity in other solid tumors beyond melanoma and RCC. While additional combination studies of anti-PD(L)1 and anti-CTLA4 therapies with or without standard of care chemotherapy and targeted agents are ongoing, a novel immune therapy with a differentiated mechanism of action that results in improved response rates and durability across a broad range of solid tumors is necessary.

This study is a Phase 1a/1b open-label, multicenter study to evaluate the dosing, safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD), and preliminary efficacy of FPT155 in patients with advanced solid tumors as monotherapy and in combination with pembrolizumab.

2.2 Background

2.2.1 FPT155, A CD80-Fc Fusion Protein

FPT155 is a recombinant fusion protein composed of the ECD of human CD80 fused with human IgG1 wild type Fc. FPT155 is designed to elicit immune responses in patients with advanced solid tumors via 2 key T cell regulators or modulators: CD28 and CTLA-4. Endogenous CD80 acts as an agonist but not superagonist of the CD28 receptor, and FPT155 is thought to engage CD28 similarly to endogenous CD80. This engagement of CD28 co-stimulates T cell responses only in the presence of TCR signaling. FPT155 also binds to CTLA-4, preventing its ability to inhibit effector T cells via sequestration of endogenous CD80. FPT155 thus enhances CD28 signaling to promote T cell activation both directly, in the context

of Fc-mediated co-presentation with TCR stimulus in a cellular synapse, and indirectly, in the context of endogenous CD80 expression.

2.2.2 Nonclinical Pharmacology Studies with FPT155

FPT155 promotes T cell activation through CD28 costimulation via 2 potential mechanisms: direct agonism of CD28 signaling, and prevention of CTLA-4-mediated inhibition of CD28 activity. Both of these mechanisms were explored in vitro and in vivo.

2.2.2.1 In Vitro Biology

In vitro pharmacology studies focused on the binding of FPT155 to CD80 ligands and on the ability of FPT155 to co-stimulate T cell activation, as summarized below.

CD80 has been reported to interact with 3 binding partners: CD28, CTLA-4, and PD-L1. Binding studies were performed to determine the relevant binding partners of FPT155 using surface plasmon resonance (SPR), enzyme-linked immunosorbent assay (ELISA), and flow cytometry. The SPR studies demonstrated that FPT155 has the highest affinity for CTLA-4 (1.8 nM), moderate affinity for PD-L1 (183 nM), and low affinity for CD28 (> 1 μM). The low affinity of FPT155 for CD28 is consistent with literature reports (Greene 1996, Collins 2002). Results from an ELISA study also supported the strong affinity of FPT155 for CTLA-4, and flow cytometry studies showed engagement of FPT155 with cell surface CTLA-4 and CD28 but not PD-L1. When FPT155 binding was tested on human peripheral blood mononuclear cells (PBMCs), FPT155 primarily bound to T cell subsets in a concentration-dependent manner. Potent binding was also demonstrated with in vitro-activated conventional CD4+ T cells and T_{reg}. FPT155 binding to T cells was mediated via CD28 and CTLA-4; no binding to cell-surface PD-L1 could be demonstrated.

The costimulatory activity of FPT155 was assessed in 3 different cell-based in vitro assays. Two of these studies utilized an "artificial APC" (aAPC) in co-culture with a reporter cell line or primary human T cells. The aAPC were generated by engineering HEK293T cells to stably co-express a scFv derived from the anti-human CD3 antibody OKT3 and a form of CD64 (high affinity Fc gamma receptor 1). These aAPC thus co-presented TCR stimulus and FPT155 (captured by CD64) in the context of a cellular synapse. The reporter cell line was generated by introducing a Luciferase reporter gene that requires the integration of TCR/CD3 and CD28 signals into Jurkat cells, which express endogenous TCR/CD3 and CD28. When aAPC and the Jurkat reporter cells were incubated together with increasing concentrations of FPT155, FPT155-mediated induction of IL-2 reporter activity was evident, indicating binding and signaling through CD28. The aAPC were also capable of activating primary human T cells in a CD28-sensitive fashion. FPT155 induced concentration-dependent enhancement of proliferation, cytokine, and activation marker responses when added to purified T cells co-cultured with aAPC. Activity in these assays was dependent upon the presence of a TCR stimulus, and FPT155 alone did not induce T cell activation. The potential for FPT155 to be CD28 superagonist was also examined by cytokine release experiments in vitro. As in the

co-culture assays, FPT155 alone did not induce spontaneous cytokine release by primary human immune cells, in contrast to a CD28 superagonist antibody that exerts TCR stimulus-independent activity. Based on these results, FPT155 likely does not pose the same risk to induce cytokine release syndrome (CRS) as a CD28 superagonist antibody.

2.2.2.2 In Vivo Pharmacology

For preclinical studies in murine models, a surrogate molecule, was generated. mFPT155 (mCD80-Fc) composed of the ECD of murine CD80 fused with the Fc domain of murine IgG2a. Tumor efficacy studies demonstrated that FPT155 and mFPT155 significantly inhibited tumor growth in multiple models, including models that are typically refractive to I/O therapy. Dose dependent antitumor activity was observed in the CT26, MC38, and EMT6 tumor models, and complete CT26 tumor rejections were observed following a single 0.3 mg/kg dose. Mice that rejected tumors in response to mFPT155 treatment were resistant to subsequent rechallenge, indicating the formation of protective antitumor immunity.

During primary CT26 tumor challenge, mFPT155 monotherapy treatment altered the tumor microenvironment to one that is favorable for a productive antitumor immune response. This included increased frequency of effector T cell subsets, a shift towards an immune "memory" phenotype, enhanced CD4+ and CD8+ T cell activation, and the upregulation of downstream effectors of T cell cytolytic activity. These findings were supported by the observation that tumor antigen AH1-specific T cells were increased in mice that rejected CT26 tumors in response to mFPT155 treatment. This increase correlated with protection from other tumors that share the AH1 antigen (ie, Renca tumors).

The combination of mFPT155 and anti-PD1 treatment was evaluated in the murine CT26 tumor model. At the anti-PD-1 dose evaluated, anti-PD--1 did not have activity but the combination of mFPT155 and anti-PD-1 resulted in synergistic activity and significant tumor growth reduction. The additional of anti-PD-1 to mFPT155 resulted in a higher number of complete tumor regressions than mFPT155 alone.

2.2.3 Nonclinical Pharmacokinetics

The PK/toxicokinetics (TK) characteristics of FPT155 were investigated in mice, rats, and cynomolgus monkeys. These studies included 1 single-dose PK study in mice that examined doses of FPT155 from 0.03 mg/kg to 3 mg/kg and 2 repeat-dose studies with 4-weekly dosing each in rats and cynomolgus monkeys that examined doses of FPT155 from 1 mg/kg to 100 mg/kg. Among 4 repeat-dose studies, there was 1 PK study in rats, 1 pilot toxicology study in cynomolgus monkeys, and 1 Good Laboratory Practice (GLP) toxicology study in each species. In all studies FPT155 was administered by intravenous (IV) administration.

Following single IV dose ranging from 0.03 to 3 mg/kg in mice, the maximum observed serum concentration (C_{max}) increased more than dose proportionally from 0.03 mg/kg to 0.9 mg/kg and dose proportionally from 0.9 mg/kg to 3 mg/kg. The area under serum concentration (AUC)-

time curve from day 0 to day 4 increased in a dose-proportional manner from 0.03 mg/kg to 3 mg/kg with estimated clearance of 18.0 to 26.3 mL/day/kg and terminal half-life of 1-2 days. Following 4-weekly doses in rats or cynomolgus monkeys, following the first and fourth doses both C_{max} and the AUC-time curve from day 0 to day 7 increased approximately in proportion with dose level in the dose range from 1 mg/kg to 100 mg/kg. The estimated terminal half-life was 4-6 days. Following 4-weekly dosing, there was little to no accumulation. Anti-drug antibodies (ADA) were present in the majority of rats (11/16 and 23/24 for the PK study and the GLP toxicology study, respectively). Seven out of 12 and 2 out of 30 cynomolgus monkeys treated with FPT155 from the pilot toxicology study and the GLP toxicology study, respectively, were ADA positive. The impact of ADA on FPT155 serum concentration was observed and highly variable in ADA positive animals.

In summary, FPT155 has linear clearance for the dose range tested from 0.03 mg/kg to 3 mg/kg in mice and from 1 mg/kg to 100 mg/kg in rats and cynomolgus monkeys. FPT155 has faster clearance and shorter half-life than a typical monoclonal antibody (mAb) in animals.

2.2.4 Toxicology

Toxicology studies performed with FPT155 include a pilot repeat-dose toxicity study in cynomolgus monkeys and Investigational New Drug (IND)-enabling GLP repeat-dose toxicity studies in rats and cynomolgus monkeys.

Repeat Dose GLP Toxicology Study in Rats

In the repeat-dose GLP toxicology studies in rats, FPT155 was administered at dose levels of 0 (vehicle), 1, 10, or 100 mg/kg/dose for 4 weekly doses. Reversibility of toxicity was evaluated during a 7-week recovery period following the final administration.

FPT155 was clinically well tolerated in rats up to 100 mg/kg. At the 100 mg/kg dose, changes in hematologic parameters were observed including increases in neutrophils, lymphocytes, and monocytes; slight decrease in red blood cells (RBCs) and an increase in reticulocytes. Changes in clinical chemistry parameters were mostly seen at 100 mg/kg, and including a decrease in triglycerides, increase in alanine aminotransferase (ALT) and alkaline phosphatase (ALP), a decrease in albumin and an increase in globulins, with an associated decrease in the albumin/globulin ratio. Microscopic changes were observed in male and female rats at doses of 10 and 100 mg/kg consisting of mononuclear cell inflammation in multiple tissues, changes in lymphoid tissue, hepatic changes, and mononuclear cell infiltrates in the thyroid gland and kidney. Mononuclear cell inflammation was seen in the stomach, intestine, pancreas, salivary gland, and Harderian gland and was primarily observed at 100 mg/kg with only rare and minimal findings at 10 mg/kg. Increased lymphoid cellularity was observed in lymph nodes, spleen, and gut-associated lymphoid tissue (GALT) and was also primarily observed at 100 mg/kg, with lower frequency and less extensive changes observed at 10 mg/kg. Hepatic changes observed at 100 mg/kg included increased cellularity, hepatocellular hypertrophy, extramedullary hematopoiesis, mononuclear cell infiltrates, lymphoid/histiocytic aggregates, and necrosis with

mixed cell infiltrates. In conclusion, the no-observed-adverse-effect level (NOAEL) in the pivotal rat study was determined to be 10 mg/kg for 4 weekly doses due to the treatment related effects of the more severe mononuclear cell inflammation in the pancreas, gastrointestinal tract, salivary, and Harderian glands observed at 100 mg/kg.

Repeat Dose Pilot Toxicology Study in Cynomolgus Monkeys

In the pilot repeat-dose toxicology study, cynomolgus monkeys received 4 weekly IV doses of 0 (vehicle), 1, 10 and 50 mg/kg FPT155. All dose levels were well tolerated by cynomolgus monkeys. Immunophenotyping analysis showed FPT155-related dose-dependent expansion and proliferation of central memory T cells in the 10 mg/kg and 50 mg/kg dose groups but not at 1 mg/kg. Histopathologically, at terminal necropsy, increased numbers of mononuclear cell infiltrates were seen in the liver, follicular hypertrophy was seen in the spleen and mesenteric lymph node, and increased cellularity of the bone marrow was seen at all dose levels. These findings resolved following the 6-week recovery period.

Repeat Dose GLP Toxicology Study in Cynomolgus Monkeys

In the repeat-dose GLP toxicology studies in cynomolgus monkeys, FPT155 was administered at dose levels of 0 (vehicle), 1, 10, or 100 mg/kg/dose for 4 weekly doses. Reversibility of toxicity was evaluated during a 6-week recovery period following administration of the last dose.

FPT155 was well tolerated and no clinical or pathological changes were identified at 1 mg/kg when given as 4 weekly doses, but FPT155 was not tolerated at doses of 10 and 100 mg/kg, necessitating unscheduled sacrifice and necropsy of 6/10 and 4/10 animals, respectively, between study days 14 and 30.

The affected animals displayed weight loss and lethargy, had signs consistent with dehydration, and were cold to the touch. Some monkey had sporadic diarrhea. Significant body weight loss was observed several days prior to euthanasia. Affected animals showed significant electrolyte imbalance, including hyponatremia, blood urea nitrogen (BUN) and creatinine elevation, and signs of acute phase reaction (increased fibrinogen, increased globulin, increased C-reactive protein [CRP], and decreased albumin). Aldosterone and cortisol level were increased and adrenocorticotropic hormone (ACTH) decreased. No urinalysis was performed. Hematologic analysis showed a severe reduction of reticulocytes in 5 animals. No coagulation changes were observed. Serum cytokine measurements (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, and granulocyte-macrophage colony-stimulating factor [GM-CSF]) on the day of unscheduled euthanasia showed signs of acute stress responses (TNF-α and IL8 increases) but the pattern of affected cytokines as well as the magnitude of changes did not indicate an acute cytokine release syndrome (no increase in IL2 or IL6).

Treatment related pathological findings in the unscheduled necropsy animals were predominantly seen in large intestine and lymphoid tissues, with possible treatment related microscopic changes in the kidneys and adrenals. In the digestive tract, mucosal erosion, crypt

dilatation, and/or infiltration of mononuclear cells in the lamina propria of the large intestine, specifically the rectum, were observed. The observed changes in the lymphoid system include changes in the lymphoid cellularity (increases and decreases) of the inguinal, mandibular, and mesenteric lymph nodes. Decreased lymphoid cellularity was observed in the spleen and thymus. Findings of uncertain relationship to FPT155 included an increased incidence of tubular dilatation with tubular casts and mineralization in the kidney, and an increased incidence of adrenal hypertrophy (zona fasciculata) in the adrenal.

In the surviving animals in the 10 and 100 mg/kg group, the clinical observations of reduced body weight and decreased activity that were common with unscheduled euthanasia animals were also seen in 2 animals that reached scheduled euthanasia. Sporadic minimal to mild diarrhea was seen with higher incidence in animals administered 10 mg/kg and 100 mg/kg. FPT155-related changes in clinical chemistry parameters in the 10 and 100 mg/kg group included a mild reduction in albumin and a mild increase in globulin at 10 and 100 mg/kg. These changes were accompanied by increased fibrinogen, suggestive of an acute phase response. These changes returned to baseline at the end of recovery period. No signs indicative of CRS, such as fever or cytokine increases consistent with CRS events, were observed.

Ophthalmic examination and cardiac evaluation did not show any FPT155 related changes at any dose level. Histopathological mucosal erosion and crypt dilatation was seen in the large intestine of animals given 100 mg/kg with sporadic findings in animals given 10 mg/kg. Increased lymphoid cellularity was observed in the lymph nodes, whereas decreased lymphoid cellularity was observed in the spleen and thymus.

Overall, the histopathological changes were not of a magnitude that would explain the observed moribundity at doses of ≥ 10 mg/kg. The changes observed in the intestine were minimal to mild, and the diarrhea was sporadic among the affected animals. The timing and magnitude of changes in cytokine levels were not consistent with acute cytokine release syndrome and were more consistent with a stress response. Hyponatremia combined with the elevated BUN and creatinine could be indicative of renal or adrenal/pituitary effects; however, the histopathological findings in the kidney and adrenal were minimal and no histopathological findings were detected in the pituitary gland. The observed dehydration could be indicative of primary renal toxicity, however only minimal histopathological kidney damage was identified, and the lack of urinalysis at the time of euthanasia limits interpretation. Changes in ACTH, aldosterone, and cortisol hormone levels could indicate underlying endocrinopathy, however, these changes could also be explained by fluid loss and a compensatory stress response.

In summary, FPT155 was clinically well tolerated in rat and the NOAEL in rats is considered 10 mg/kg for 4-weekly doses. In cynomolgus monkeys, based on the GLP-toxicology study, doses of 10 and 100 mg/kg were not tolerated and the NOAEL in cynomolgus monkeys is 1 mg/kg for 4 weekly doses. No explanation has been found for the difference in tolerability between the pilot toxicology study and the pivotal GLP toxicology study in cynomolgus monkeys, though the small number of animals used in the pilot toxicology study and the lack of full penetrance in the affected study groups in the pivotal study could be contributing factors.

2.3 Clinical Experience with FPT155

This is a first in human clinical study and there is no prior clinical experience with FPT155 in any setting. In dose escalation with FPT155, no dose limiting toxicities have been identified through the 560mg dose level. As of September 1, 2020, patients have enrolled in dose exploration cohorts at 280mg and 560mg. Cumulative safety results include evidence of immune-related adverse events that have been manageable with standard of care treatment. To date, with the exception of one patient with an unconfirmed partial response, the investigator-assessed best overall response has been stable disease. Enrollment of expansion cohorts are ongoing with additional dose escalation proposed if cumulative safety results continue to demonstrate favorable tolerability.

Please reference the FPT155 Investigator's Brochure for more detailed information.

2.4 Benefit/Risk Assessment

This first in human study is planned to evaluate the safety and tolerability of FPT155 and to determine a recommended dose (RD) for further clinical evaluation as monotherapy and in combination with pembrolizumab.

Despite recent advances in immunotherapy, an unmet need remains in patients with advanced solid tumors since a majority of patients are either refractory to currently available therapies or eventually relapse. A novel immune therapy with a differentiated mechanism of action that results in improved response rates and durability across a broad range of solid tumors is necessary. FPT155 is designed to act as a potent stimulator of anti-tumor immunity that acts through CD28 to co-stimulate T cell responses only in the presence of antigenic TCR signaling. FPT155 also blocks CTLA-4 from competing for endogenous CD80, allowing CD28 signaling to prevail in T cell activation. Potential benefit for humans is based on data that a murine surrogate of FPT155 (mFPT155) is a potent inhibitor of tumor growth in multiple tumor models (ie, CT26, MC38, and EMT6) and results in complete tumor regressions in a majority of animals in the highly responsive CT26 model. Moreover, in the CT26 tumor model, mice that reject tumors after treatment with mFPT155 remain tumor free and have durable T cell immunity to subsequent CT26 re-challenge. FPT155 therefore has the potential to demonstrate durable anti-tumor immune responses in patients with advanced solid tumors by acting through 2 key T cell regulators or modulators: CD28 and CTLA-4.

Risks of FPT155 are anticipated to be related to possible overstimulation of T cell function and subsequent auto-immune adverse events similar to those reported by approved immunotherapies such as CTLA-4 antagonists. Pre-clinical toxicology studies showed that FPT155 was clinically well tolerated in rats with no adverse clinical findings or treatment-related changes in most major organ systems. The NOAEL in rats was determined to be 10 mg/kg when administered to animals once per week for 4 weekly doses. FPT155 was not well tolerated in cynomolgus monkeys at doses ≥ 10 mg/kg. Some monkeys at the 10 mg/kg dose had sporadic diarrhea, dehydration, lethargy, and were cold to the touch, although due to the method of conduct of the

study it isn't clear that the same monkeys who had diarrhea also became moribund. Intravenous hydration only temporarily improved the symptoms. Diffuse lymphocytic and monocytic infiltrates were observed in a variety of organs, however, the mechanism of this toxicity is undetermined. No clinical observations or adverse findings were seen in the low dose group of 1 mg/kg which was, therefore, determined to be the NOAEL. The starting dose of 0.07 mg (0.001 mg/kg for a 70 kg human) has been calculated based on the minimum anticipated biologic effect level (MABEL) approach and is approximately 1000-fold below the NOAEL. Significant antitumor activity is evident even at doses as low as 0.1 mg/kg in the CT26 tumor model, which is approximately 10-fold below the NOAEL in both rats and monkeys. Therefore, a potential therapeutic window for FPT155 exists.

Based on the underlying mechanism of action, immune-related adverse events (irAEs; e.g., endocrinopathies, colitis, hepatitis, dermatitis) associated with the anti-CTLA-4 class of drugs (eg, ipilimumab) may potentially be observed with FPT155. Since anti-CTLA-4 therapies have been in clinical use for several years, the toxicities associated with these agents are well characterized. The protocol also includes specific guidelines for monitoring and managing these toxicities. As immune-oncology agents are associated with delayed immune-mediated toxicities, the RD will consider toxicities observed both during and beyond the 21-day dose limiting toxicity (DLT) evaluation period.

The CD28 pathway has been a target for investigational drugs in the clinic but no agents are approved. TeGenero 1412 (TGN1412) is a humanized IgG4 kappa anti-CD28 superagonist antibody that activates T cell activation independently of TCR ligation, in contrast with physiological CD80 signaling which activates T cells via CD28 only when there is also TCR recognition of cognate peptide-MHC. TGN1412 was initially dosed in 6 healthy male volunteers at doses of 0.1 mg/kg. Each of these patients developed a severe inflammatory reaction characterized by rapid production of circulating cytokines (CRS) within 60 minutes after the infusion of TGN1412, leading to multi-organ failure within 24 hours of dosing (Suntharalingam 2006). Follow up analysis of the trial revealed that the dose of TGN1412 given to patients was sufficient to occupy 90% of all CD28 receptors in the body (Duff 2006, Kenter 2015). TGN1412, now renamed TAB08, has subsequently been given in lower doses to healthy volunteers, patients with rheumatoid arthritis, and patients with solid tumors (Cabo 2017).

FPT155 activates T cells in a TCR-dependent manner and therefore is not expected to have TCR-independent superagonist activity. However, given the history of CRS associated with TGN1412, the Sponsor has performed in vitro cytokine release assays on human PBMCs and confirmed that FPT155 does not activate CD28 signaling in the absence of TCR signaling supporting the hypothesis that FPT155 should not induce CRS. Nonetheless a conservative approach is being used with a low starting dose of FPT155 where the pharmacological activity (PA) for CD28 is expected to be <1% (Section 4.6). As a further precaution, 48-hour inpatient admission following the first infusion of the first dose cohort to monitor for signs of CRS is mandated, and a 6-hour post infusion observation period is required for all patients in all cohorts.

As this is the first clinical study of FPT155, the safety profile in humans has not been established, unanticipated side effects may occur, and efficacy in humans remains unproven. Accordingly, Phase 1a enrollment is limited to patients with late stage tumor types without other efficacious treatment options.

In summary, a conservative starting dose based on the MABEL approach, close patient monitoring, staggered enrollment, and cautious dose escalation is designed to limit the risk to patients during FPT155 dose escalation.

For the combination of FPT155 with pembrolizumab, preclinical results suggest the potential for synergistic activity. However, the combination of both agents may lead to an increase in immune related adverse events. Preclinical results are consistent with the hypothesis that an approximately 4-fold reduction in FPT155 dose will decrease the combined effect with anti-PD-1 directed therapy and to mitigate the risk of potential autoimmune toxicity, dose escalation with FPT155 in combination with pembrolizumab will start a minimum of 2 dose levels below the MTD for FPT155 monotherapy. Careful surveillance for immune related adverse events is specified in the protocol including consensus guidelines for diagnosis and management of these adverse events (Appendix 8).

3.0 OBJECTIVES AND ENDPOINTS

Objectives and Endpoints – Phase 1a Dose Escalation/Exploration – FPT155 Monotherapy:

Objectives	Endpoints
Primary	
Safety • To assess the safety and tolerability of FPT155 as monotherapy in patients with advanced solid tumors • To determine the RD of FPT155 as monotherapy	**Safety** • The incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, and electrocardiogram (ECG) abnormalities • The incidence of AEs defined as dose limiting toxicities (DLTs), clinical laboratory abnormalities defined as DLTs, and overall assessment of pharmacokinetics (PK) and pharmacodynamics (PD)
Secondary	
Pharmacokinetics • To characterize the PK profile of FPT155 as monotherapy in patients with advanced solid tumors	**Pharmacokinetics** The following PK parameters will be derived from concentration-time data for FPT155 when appropriate and applicable. • Area under serum concentration-time curve (AUC) • Maximum observed serum concentration (C_{max}) • Trough observed serum concentration at the end of each dose interval (C_{trough}) • Clearance (CL) • Terminal half-life ($t_{1/2}$) • Volume of distribution at steady state (V_{ss}) Other parameters, such as dose proportionality, accumulation ratio, and attainment of steady state, will also be calculated if the data are available.
Immunogenicity • To characterize the immunogenicity of FPT155 as monotherapy in patients with advanced solid tumors	**Immunogenicity** • Incidence of treatment emergent anti-FPT155 antibody response
Exploratory	
[redacted]	

Efficacy • To evaluate the clinical benefit of FPT155 as monotherapy in patients with advanced solid tumors	**Efficacy** • Objective Response Rate (ORR), defined as the total number of patients with confirmed responses of either complete response (CR) or partial response (PR), as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response • Duration of Response (DOR) defined as the time from first response (CR or PR determined by the investigator per RECIST v1.1) that is subsequently confirmed until the onset of progressive disease or death from any cause, whichever comes first • Progression Free Survival (PFS) defined as the total number of patients with confirmed responses of either CR or PR, as determined by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Objectives and Endpoints – Phase 1b Dose Expansion – FPT155 Monotherapy:

Objectives	Endpoints
Primary	
Safety • To evaluate the safety and tolerability of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Safety** • The incidence of AEs, SAEs, clinical laboratory abnormalities, and ECG abnormalities • The incidence of treatment discontinuations, modifications, and interruptions due to AEs
Secondary	
Efficacy • To evaluate the clinical benefit of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD through the analysis of ORR, DOR, PFS, and DCR	**Efficacy** • ORR, DOR, and PFS • Disease Control Rate (DCR) defined as total number of patients with confirmed responses of either CR, PR, or stable disease as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response

Objectives	Endpoints
Pharmacokinetics • To characterize the PK profile of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Pharmacokinetics** The following PK parameters will be derived from concentration-time data for FPT155 when appropriate and applicable. • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • V_{ss} Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be calculated if the data are available. Assessment of time-dependence of PK, the effect of body weight as well as other covariates on PK, and the exposure-response relationship, when the data allow, will be conducted to determine the appropriate dosing approach (eg, body weight-based or fixed dosing) for future trials.
Immunogenicity • To characterize the immunogenicity of FPT155 as monotherapy in patients with selected advanced solid tumors treated at the RD	**Immunogenicity** • Incidence of treatment emergent anti-FPT155 antibody response
Exploratory	
[redacted]	

Objectives and Endpoints – Phase 1a Dose Escalation/Exploration – FPT155 + Pembrolizumab:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of FPT155 in combination with pembrolizumab in patients with advanced non-small cell lung cancer • To determine the RD of FPT155 in combination with pembrolizumab in patients with advanced non-small cell lung cancer.	• The incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, and electrocardiogram (ECG) abnormalities • The incidence of dose limiting toxicities (DLTs)
Secondary	
• To evaluate the preliminary clinical response rate of FPT155 in combination with pembrolizumab in patients with non-small cell lung cancer	• Objective Response Rate (ORR), defined as the total number of patients with responses of either CR or PR, as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response
Exploratory	
[redacted]	

4.0 STUDY DESIGN

4.1 Overall Design

This study is a Phase 1a/1b open-label, multicenter, dose escalation, dose exploration, and dose expansion study to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of FPT155 in patients with advanced solid tumors. FPT155 is a recombinant fusion protein composed of the ECD of human CD80 fused with the Fc domain of IgG1. It is designed to act as a potent stimulator of antitumor immunity. FPT155 as monotherapy and in combination with pembrolizumab will be evaluated. The combination portion of the study will be conducted in Australia and South Korea.

FPT155 Monotherapy

FPT155 will be administered once every 3 weeks (Q3W) over approximately 60 minutes by IV infusion.

- The monotherapy part of the study will initiate with Phase 1a dose escalation consisting of approximately 13 planned dose escalation cohorts, with the starting dose of 0.07 mg.
- Phase 1a dose exploration consists of up to approximately 50 patients in total who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose level clearing dose escalation criteria).
- Phase 1b dose expansion consists of up to 8 tumor-specific expansion cohorts, enrolling approximately 30 patients each. Patients in Phase 1b will be treated with FPT155 at an RD selected after assessment of data obtained in Phase 1a. (See Appendix 11).

Treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or if any of the specified withdrawal criteria listed in Section 7.0 of the protocol are met.

4.1.1 Phase 1a Dose Escalation

FPT155 Monotherapy

The Phase 1a dose escalation will include an initial accelerated titration design enrolling at least 1 patient at lower doses followed by a standard 3+3 design until the RD for Phase 1b is determined. Eligible patients with advanced solid tumors (except primary central nervous system [CNS] tumors) who are refractory to all standard therapy for their malignancy or for whom standard therapies would not be appropriate will be enrolled.

All dose escalation decisions will be based on the assessment of DLTs, overall safety and tolerability, and will be made after the last patient enrolled in each cohort has completed the 21-day DLT evaluation interval. Dose escalation decisions will be agreed upon by the Cohort Review Committee (CRC) after all available laboratory and clinical information is reviewed.

Patients enrolled into the first FPT155 monotherapy dose cohort will have 48 hours of inpatient monitoring from the start of infusion of FPT155 at Cycle 1 Day 1 to evaluate for any signs or symptoms of CRS. There will be an interval of at least 48 hours between administration of the first dose in each patient in the first dose cohort, if more than one patient is enrolled. For the second infusion of FPT155, patients in the first dose cohort will undergo intensive monitoring in the outpatient setting, including a minimum 6-hour observation window.

For subsequent dose cohorts, intensive monitoring will occur in the outpatient setting and include a minimum 6-hour observation window following completion of the first and second infusions. There will be an interval of at least 24 hours between administration of the first dose in each patient in subsequent dose cohorts. Inpatient hospitalization will not be required for the first dose in subsequent dose cohorts unless there is evidence of CRS ≥ Grade 2 at the previous dose level.

If any patient reports a Grade 2 or higher drug-related toxicity in the first 24 hours after completion of their first dose, enrollment of subsequent patients will be delayed until the toxicity for that patient returns to baseline or ≤ Grade 1, or the CRC determines that it is safe to continue enrollment. In this setting, the CRC will review all available data to determine if enrollment should continue at the same or a lower dose level, or with a less frequent dosing schedule, or if enrollment should be discontinued.

FPT155+pembrolizumab

FPT155 will be administered once every 3 weeks (Q3W) over approximately 60 minutes by intravenous IV infusion followed by 200 mg of pembrolizumab administered by intravenous (IV) infusion after the completion of FPT155. Eligible patients with advanced non-small cell lung cancer will be enrolled,

Combination dose escalation will start with a FPT155 dose that is a minimum of two dose levels lower than the highest dose cleared in FPT155 monotherapy.

Combination dose exploration will include up to 30 patients who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose level clearing dose escalation criteria).

For patients enrolled for treatment with FPT155 and pembrolizumab, treatment will be administered Q3W until disease progression, unacceptable toxicity or consent withdrawal; if one study drug is discontinued, the other may be continued for up to an additional 12 months.

4.1.1.1 Cohort Review Committee

Safety will be monitored throughout the study by the Sponsor's CRC, comprised of, but not limited to, Phase 1a study investigators, the Sponsor's medical monitor, and the Sponsor's safety representative. The CRC will meet routinely to review the emerging safety, PK, PD, and efficacy data, and to make dose escalation decisions. The CRC may recommend further

evaluation of the safety at a given dose. The CRC will also review cumulative safety data in order to identify safety concerns that may emerge due to cumulative exposure beyond the DLT window. The process for dose escalation decisions, dose interval recommendations, and the roles and responsibilities of the CRC will be detailed in the CRC Charter.

4.1.1.2 Proposed FPT155 Dose Levels

FPT155 will be initially administered Q3W, on Day 1 of each 21-day cycle.

The anticipated dose levels are outlined in Table 5.

Table 5: Anticipated Dose Levels

Design	Dose	Regimen
Accelerated titration design	0.07 mg FPT155	Q3W
	0.21 mg FPT155	Q3W
	0.70 mg FPT155	Q3W
	2.1 mg FPT155	Q3W
3+3 design	7 mg FPT155	Q3W
	21 mg FPT155	Q3W
	42 mg FPT155	Q3W
	70 mg FPT155	Q3W
	140 mg FPT155	Q3W
	280 mg FPT155	Q3W
	560 mg FPT155	Q3W
	840 mg FPT155	Q3W
	1260 mg FPT155	Q3W

Abbreviations: Q3W = once every 3 weeks.

Planned dosing increments take into account conservative estimates of RO and PA through both CD28 and CTLA-4. Fixed 3-fold escalation increments are proposed while projected engagement of CD28 is low; more conservative increments (2-fold or less) are proposed at higher CD28 occupancy levels.

The Sponsor may add cohorts with alternative dose levels or dose regimens (e.g., different dosing frequency, intermediate dose levels) upon review of safety, PK, and PD profiles to achieve optimal target exposure with acceptable tolerability. The dose level of 700mg was replaced by 840mg based on preliminary PK showing dose-proportional increases in exposure and approximately 30-50% interpatient variability in exposure at a given dose level – the range of exposures from FPT155 560mg and from FPT155 700mg (25% increase in dose) were predicted not to be significantly different. A 1.5-fold increment in dose levels has been selected

above 560mg based on early safety results showing an absence of DLTs or cytokine release syndrome through the 560mg dose level with the presence of immune-related toxicity manageable with standard of care treatment for irAEs. Following clearance of a dose at the Q3W schedule, more frequent (eg Q2W) dosing at the same dose level may be evaluated using the 3+3 framework.

4.1.1.3 Dose Limiting Toxicity Definitions

The DLT evaluation interval begins on the first day of treatment upon start of infusion and continues for 21 days. Patients who receive at least 1 dose of study treatment and remain on study for the 21-day DLT evaluation interval or patients who discontinue study treatment for drug-related AEs before clearing the 21-day DLT evaluation interval will be considered evaluable for DLT determination.

DLTs during Phase 1a dose escalation are defined as any of the following deemed by the investigator as related to FPT155:

- Absolute neutrophil count (ANC) < 1.0 x 10^9/L for > 5 days duration or Grade 3 febrile neutropenia (eg, ANC < 1.0 x 10^9/L with a single temperature of > 38.3°C or fever > 38°C for more than 1 hour)
- Platelets < 25 x 10^9/L or platelets < 50 x 10^9/L with clinically significant hemorrhage
- Aspartate aminotransferase (AST) or ALT > 3 x upper limit of normal (ULN) with concomitant total bilirubin > 2 x ULN not related to liver involvement with cancer
- Grade 3-4 non-hematological toxicity except:
  - Grade 3 fatigue < 7 days
  - Grade 3 nausea and Grade 3-4 vomiting and diarrhea lasting < 72 hours in patients who have not received optimal anti-emetic and/or anti-diarrheal therapy
  - Grade 3 endocrinopathy that is adequately treated by hormone replacement
  - Laboratory value that may be corrected through replacement within 48 hours
- Grade 2 neurological toxicity except headache and peripheral neuropathy in patients with Grade 1-2 peripheral neuropathy at entry

Additional DLT Considerations for FPT155 in combination with pembrolizumab

Because pembrolizumab is a known immune checkpoint inhibitor and one of the proposed mechanisms of action of FPT155 is immune checkpoint blockade, immune-related adverse events (irAEs) are anticipated with this combination. An irAE is defined as a clinically significant AE that is associated with study drug exposure, without a clear alternate cause, and consistent with an immune-mediated mechanism. Based on that background, the first occurrence of the following irAEs will not be considered a DLT because they may occur with immune therapy and are likely to be fully reversable per Appendix 8:

- Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 non-skin immune-related adverse event (irAE) that resolve to a Grade 1 or less within 14 days with management per Appendix 8
- Transient (resolving within 6 hours of onset) Grade 3 infusion-related AEs
- Grade 3 drug-related bronchospasm or anaphylactic or anaphylactoid reactions

Dose escalation may be paused prior to determining an MTD based on observed safety, tolerability, or emerging PK or PD results.

4.1.1.4 Dose Escalation Decisions in Phase 1a FPT155 Monotherapy

An initial accelerated titration design enrolling at least 1 patient at each dose level is planned for FPT155 dose levels 0.07, 0.21, 0.70, and 2.1 mg. Dose escalation to the next dose level may proceed after at least 1 patient completes the 21-day DLT evaluation interval.

If a single patient experiences a DLT during the 21-day DLT evaluation interval, standard 3+3 dose escalation criteria will apply for that cohort with enrollment of additional patients. All subsequent dosing cohorts will then follow standard 3+3 dose escalation criteria.

Alternatively, if 2 patients experience moderate AEs (at any planned accelerated titration dose level), standard 3+3 dose escalation criteria will apply for the highest dose level at which a moderate AE was experienced, with enrollment of additional patients. All subsequent dosing cohorts will then follow standard 3+3 dose escalation criteria. Moderate AEs are defined as ≥ Grade 2 AEs deemed by the investigator as related to FPT155. Grade 2 laboratory values will not be considered as moderate AEs for this purpose unless accompanied by clinical sequalae.

If not already applied at a lower dose level according to the criteria stated above, enrollment at all dose levels ≥ 7.0 mg will follow a standard 3+3 dose escalation design.

The algorithm outlined in Table 6 below will be used for all dose escalation decisions.

Table 6: Algorithm for 3+3 Dose Escalation Decisions

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3 or 1/6	Enroll 3 patients at next dose level (next/higher cohort)
1/3	Enroll 3 additional patients at current dose level (current cohort)
≥2	Stop enrollment. If at the starting dose level, the study will be stopped. If at any other dose level, enroll 3 more patients at the previous dose level (previous/lower cohort) if only 3 were previously enrolled, or at an intermediate dose level

Abbreviations: DLT = dose limiting toxicity.

4.1.1.5 Dose Escalation Within a Cohort

In Phase 1a dose escalation, intra-patient dose escalation will be permitted in patients enrolled at dose levels below 70 mg, provided:

- The patient did not experience a DLT
- All other AEs have recovered to Grade 1 or lower prior to dose escalation
- The patient may only dose escalate by a maximum of 1 dose level every 21 days and only after that dose level has cleared DLT review by the CRC (eg, a patient enrolled at 0.07 mg may escalate to 0.21 mg only after the 0.21 mg dose level has been cleared by the CRC).
- The patient cannot dose escalate beyond the 70 mg dose level

Intra-patient dose escalation will only be permitted after a discussion between the Sponsor and investigator, taking into account the overall safety experience, PK, and PD data available at the time of the request. Safety data from such patients will be reviewed as part of the overall safety and tolerability of FPT155.

4.1.1.6 Determination of Recommended Dose and Maximum Tolerated Dose

The maximum tolerated dose (MTD) will be defined as the dose level below that in which ≥2 DLTs are identified. If dose escalation completes without the identification of 2 DLTs at a given dose level, no MTD will have been identified. The Sponsor may discontinue dose escalation prior to determining a MTD based on the available observed safety, tolerability, PK and PD. The RD of FPT155 will be identified based on an evaluation of all available safety, tolerability, PK, and PD data. The determination of RD will consider toxicities observed both during and beyond the DLT evaluation period as well as dose reductions and discontinuations due to toxicity that do not meet the DLT criteria. The RD, therefore, may or may not be the same as the MTD but cannot be higher than the MTD.

4.1.2 Phase 1a FPT155 Monotherapy Dose Exploration

Phase 1a dose exploration consists of up to approximately 50 patients in total who may be enrolled at one or more dose levels to further evaluate safety, PK, PD, and clinical activity (conditional upon the dose level clearing dose escalation criteria). Toxicities observed in these patients will contribute to the overall assessments of safety and tolerability, and may inform selection of the RD. The Sponsor may choose to evaluate clinical activity in specific tumor types based on emerging safety, PK, PD, and efficacy data.

Intensive monitoring will occur in the outpatient setting and include a minimum 6-hour observation window following completion of the first and second infusions. There will be an interval of at least 24 hours between administration of the first dose in each patient.

4.1.3 Phase 1b FPT155 Monotherapy Dose Expansion

Enrollment in Phase 1b dose expansion will begin when the MTD and/or RD has been identified by the CRC. If additional cumulative safety or preliminary efficacy results from dose escalation or exploration suggest that an alternate dose or schedule may improve the benefit relative to risk in treatment with FPT155, more than one dose or schedule may be evaluated in the phase 1b cohorts.

Up to 8 tumor-specific cohorts consisting of approximately 30 patients each will evaluate the safety, efficacy, PK, and PD of FPT155 at a RD (see Appendix 11). Patients with advanced RCC and melanoma who have failed prior anti-PD(L)1 therapy will be enrolled in 2 of the 8 cohorts.

Additional tumor types for the remaining Phase 1b cohorts will be determined based on emerging safety, translational, and clinical data for FPT155, as well as any potential new safety signals from other immunotherapies, such as significant changes to prescribing information for approved immunotherapies.

Intensive monitoring will occur in the outpatient setting and include a minimum 6-hour observation window following completion of the first and second infusions. Additional monitoring requirements may be implemented based on emerging safety data from Phase 1a dose escalation.

Table 7: Phase 1b Monotherapy Dose Expansion Cohorts and Tumor Types

Cohort	Tumor Type
1	Renal cell carcinoma
2	Melanoma
3-8	Cohorts to be determined based on emerging safety, translational, and clinical data for FPT155, as well as any potential new safety signals from other immunotherapies, such as significant changes to prescribing information for approved immunotherapies (see Appendix 11)

4.1.4 Phase 1a FPT155+Pembrolizumab Dose Escalation

FPT155 will start at a dose level a minimum of 2 levels below that cleared in dose escalation with FPT155 monotherapy.

Dose escalation decisions will follow the standard 3+3 algorithm described above and continue up to the dose level established as the MTD for FPT155 monotherapy. Additional intermediate dose levels or dose regimens may be considered upon review of emerging safety, PK and PD results.

4.1.5 FPT155 + Pembrolizumab Dose Exploration

Enrollment in combination dose exploration may occur at one more dose levels that have been cleared during combination dose escalation.

4.1.6 Requirements for Archival Tumor Tissue and Fresh Biopsies

Dose Escalation (Monotherapy and FPT155 + pembrolizumab):

- Archival tumor tissue is required. If archival tumor tissue is not available, a fresh biopsy is required prior to treatment for retrospective biomarker analysis.
- Optional pre- and on-treatment biopsies will be requested during screening (prior to treatment) and during treatment (prior to the Cycle 3 Day 1 dose) to explore the relationship between baseline tumor immune phenotype and PD response.
- An additional optional biopsy will be requested at disease progression.

Dose Exploration/Expansion (Monotherapy and FPT155 + pembrolizumab):

- Archival tumor tissue is required for retrospective biomarker analysis. The fresh biopsy required at screening will be accepted in lieu of archival tumor tissue if archival tissue is not available.
- Pre- and on-treatment biopsies will be mandatory during screening (prior to treatment) and during treatment (prior to the Cycle 3 Day 1 dose) to explore the relationship between baseline tumor immune phenotype and PD response.
- An additional optional biopsy will be requested at disease progression.

4.2 Study Treatment and Duration

FPT155 will be administered Q3W over approximately 60 minutes by IV infusion.

In combination with FPT155 and pembrolizumab, pembrolizumab will be administered a minimum of 30 minutes following completion of the FPT155 infusion. Pembrolizumab should be administered per the pembrolizumab Product Information.

Treatment is administered Q3W until disease progression, unacceptable toxicity, or patient withdrawal. If one drug is discontinued, treatment may continue with the other alone for up to an additional 12 months. Treatment beyond disease progression may be allowed in patients with initial RECIST v1.1 defined progressive disease if the criteria in Section 4.3 are met.

Patients should have end of treatment (EOT) follow-up visits approximately 28 days and 100 days after the last dose of treatment on study. In addition, patients enrolled in dose expansion will be followed for survival.

4.3 Treatment Beyond Disease Progression

For patients in all cohorts, if progressive disease (based on RECIST v1.1) occurs, then the patient may continue to be treated with the scheduled regimen assigned after study enrollment until one of the following criteria is met:

- Confirmed disease progression: The assessment of disease progression by RECIST v1.1 (baseline disease progression assessment) will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later. If any subsequent tumor assessment time point demonstrates disease progression by RECIST v1.1 or demonstrates further increase in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the baseline disease progression assessment (the sum of diameters of target lesions or the presence of a new lesion), then the subject would be deemed as having confirmed disease progression.
- Meets any of the investigational product discontinuation criteria.
- Clinical symptoms or signs indicating clinically significant disease progression such that the benefit-risk ratio of continuing therapy is no longer justified.
- Rapid disease progression or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention.

4.4 End of Study Definition

The EOT follow-up visit approximately 100 days after the last dose of treatment on study will be considered the end of the study in Phase 1a.

In the Phase 1b portion of the study, patients will also be followed for survival by clinic visit or by telephone approximately every 3 months after the Day 100 EOT visit. Death, loss to follow-up, or withdrawal of consent of the last study subject, or study termination by the Sponsor (whichever occurs first), will be considered the end of the study in Phase 1b.

4.5 Scientific Rationale for Study Design

The study is designed as an initial accelerated titration followed by a standard 3+3 dose escalation. The initial accelerated titration component may reduce the number of patients receiving potentially subtherapeutic doses of the study drug. The 3+3 design is chosen to avoid selection of a Phase 2 clinical trial dose that causes a treatment-limiting toxicity in more than 17% of patients, which is a standard that has been considered acceptable as an outpatient therapeutic for patients with limited options and life-threatening disease. This design has the advantage of being rule-based, allocates the lowest dose level to the first cohort, and adaptively escalates/de-escalates based on observed DLTs. Its execution is straightforward and generally well understood by clinicians and investigators, decreasing the potential for deviations from protocol.

Phase 1a dose exploration with mandatory pre- and on-treatment biopsies at doses ≤ MTD will provide additional insight into the safety, PK, PD and mechanism of action of FPT155 and may help in determining the RD for Phase 1b.

Phase 1b for FPT155 monotherapy includes up to 8 tumor-specific cohorts. Patients with advanced RCC and melanoma that have failed prior anti-PD(L)1 therapy will be enrolled in 2 of the 8 cohorts. These patients have a poor prognosis and enrolling them will enable evaluation of the clinical activity of FPT155 in these typically immune-competent tumors that have progressed on a checkpoint inhibitor. Additional tumor types for the remaining 6 Phase 1b cohorts (Appendix 11) will be determined based on emerging safety, translational, and clinical data for FPT155, as well as any potential new safety signals from other immunotherapies, such as significant changes to prescribing information for approved immunotherapies.

Combination dose escalation with FPT155 and pembrolizumab will start with a FPT155 dose that is a minimum of two dose levels lower than the highest dose cleared during evaluation of FPT155 monotherapy as outlined below in Table 8. Additional patients may be added in combination dose exploration at one or more dose levels that are cleared during combination dose escalation to better characterize the safety profile and preliminary clinical activity. The combination will be limited to patients with non-small cell lung cancer to maximize on the ability to interpret results from the limited enrollment that is planned.

4.6 Justification for Dose

The MABEL approach was used to determine a safe first in human starting dose for FPT155. This approach was used because FPT155 functions through 2 key T cell regulators or modulators, including co-stimulation of CD28 on T cells after T cell receptor engagement, and blocking CTLA-4 from competing for endogenous CD80.

The FPT155 starting dose was based on the established guidelines for MABEL dosing and relevant literature (Saber 2016). Based on these guidelines, RO and PA between 20-80% are appropriate for selecting starting doses. For FPT155, assessments of RO and PA through both CTLA-4 and CD28 were considered. To project the human dose based on C_{max}, assumptions of a plasma volume of distribution of central compartment of 2800 mL and a 70 kg average patient weight were used in calculating the percent RO and PA.

Integrating the assessments of RO and PA through both CTLA-4 and CD28, a starting dose of 0.07 mg was selected. Among the PA assays examined, CTLA-4 ELISA was thought to be both biologically relevant and sensitive. Using this ELISA assay, 50% PA leads to a predicted starting dose, when rounded down, of 0.07 mg. Several PA assays for CD28 activity were considered, however these assays were either thought to be not biologically relevant or predicted a much higher starting dose.

The Sponsor has selected a Q3W dosing interval. Although the half-life of FPT155 in patients is predicted to be less than 10 days, preclinical evidence suggests that the total exposure, not C_{trough}, may be an important driver of efficacy. A Q3W interval between was thought to be appropriate because no target trough concentration has been identified to achieve between dose interval from nonclinical efficacy studies.

The Phase 1a dose escalation portion of the study will use an initial accelerated titration design followed by a standard 3+3 design, with patients enrolled across approximately 13 planned dose levels. The starting dose of 0.07 mg is predicted to attain a nominal (< 1%) PA for CD28 using the binding assay of Chinese hamster ovary (CHO) cells overexpressing CD28. The proposed dosing increments also take into consideration PA through both CD28 and CTLA-4. Fixed 3-fold escalation increments are proposed while PA of CD28 is low, with more conservative increments proposed at higher expected CD28 activity levels. Two fold or smaller increments in dose were used in dose escalation from 21mg to 560mg. During dose escalation, FPT155 is projected to achieve 99% PA for CTLA-4 at C_{max} for doses ≥ 7 mg. Based on the K_D and observed C_{max}, ipilimumab, an anti-CTLA4 antibody, was projected to achieve 99% RO for CTLA-4 at the clinically approved dose of 3 mg/kg (BMS 2011, He 2017, Yervoy 2018).

Preliminary pharmacokinetic results are consistent with dose-proportional increases in exposure with an absence of dose-limiting toxicities through the 560 mg dose level. As immune-related adverse events have been manageable in accordance with consensus guidelines and no MTD has been identified, dose escalation above 560mg uses 1.5-fold increments. The dose escalation cohorts are summarized below (Table 8).

Table 8: FPT155 Phase 1 Dose Escalation Cohorts

Cohort	Dose Level (mg)
1aM1	0.07
1aM2	0.21
1aM3	0.7
1aM4	2.1
1aM5	7
1aM6	21
1aM7	42
1aM8	70
1aM9	140
1aM10	280
1aM11	560
1aM12	840
1aM13	1260

Given many practical advantages, such as decreased operational difficulty, decreased compound waste, and reduced dosing errors, flat dosing will be used for this Phase 1 trial. PK variability introduced by either body weight-based or fixed dosing regimens is moderate relative to the variability generally observed in PD, efficacy, and safety (Bai 2012). Therefore, testing either body weight-based or fixed dosing regimens in phase 1 can achieve the goal of characterizing

PK. Assessment of the effect of body weight on PK will be conducted to determine the appropriate dosing approach and to support the proposed dose and dose regimen(s) for future trials using PK data collected from Phase 1.

Preclinical results show the potential for synergistic benefit from the combination of FPT155 and pembrolizumab. Pembrolizumab will be administered at the approved dose and schedule – 200mg IV Q3W. To mitigate the risk of increased immune-related toxicity, FPT155 dose escalation in combination with pembrolizumab will start at least two dose levels below the highest cleared FPT155 monotherapy dose level reflecting a four-fold reduction in FPT155 dose. Preclinical animal models demonstrated a reduction in the activity of the FPT155 and pembrolizumab combination with a three-fold reduction in FPT155 dose.

5.0 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:

Age

1.01) Patient must be 18 years of age or older at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2.01) Histologically confirmed solid tumors (except primary CNS tumors). For patients enrolled for treatment with FPT155+pembrolizumab: histologically confirmed non-small cell lung cancer not eligible for curative therapy.

2.02) For patients in Phase 1a dose escalation (all) and Phase 1a dose exploration (FPT155 monotherapy) only: Disease that is unresectable, locally advanced, or metastatic and has progressed following all standard treatments or is not appropriate for standard treatments.

2.03) All patients must have at least one measurable lesion at baseline according to RECIST v1.1. Tumor sites situated in a previously irradiated area, or in an area subjected to other loco-reginal therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

2.04) Availability of archival tumor tissue and consent to provide archival tumor for retrospective biomarker analysis, or consent to undergo a fresh tumor biopsy during screening

2.05) For patients participating in Phase 1a dose exploration cohorts and Phase 1b dose expansion: consent to undergo a mandatory fresh tumor biopsy during screening and on treatment

2.06) ECOG performance status of 0 or 1

2.07) Life expectancy of at least 3 months in the opinion of the investigator

2.08) Willing and able to comply with all study procedures

2.09) Prior radiotherapy must be completed at least 2 weeks before first dose of study treatment administration. No radiopharmaceuticals (eg, strontium, samarium) within 8 weeks before first dose of study treatment administration

2.10) Prior surgery that requires general anesthesia must be completed at least 14 days before first dose of study treatment administration unless patients have recovered, and it is considered safe after discussion with medical monitor. Surgery requiring local/epidural

anesthesia must be completed at least 72 hours before first dose of study treatment administration and patients must have recovered.

2.11) Screening laboratory values must meet the following criteria:

Hematologic

a. Neutrophils ≥ 1.2 x 10^9/L

b. Platelets ≥ 75 x 10^9/L

c. Hemoglobin ≥ 9.0 g/dL

d. Serum creatinine < 1.5 x ULN or creatinine clearance of ≥ 40 mL/minute (using Cockcroft/Gault Formula)

$$\text{Female creatinine clearance (CrCl)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

e. Prothrombin time (PT)/International normalized ratio (INR) < 1.5x ULN and partial thromboplastin time (PTT) (activated partial thromboplastin time [aPTT]) < 1.5x ULN except for patients receiving anticoagulation, who must be on a stable dose of warfarin for 6 weeks prior to enrollment

Hepatic

f. AST or ALT < 3x ULN

g. Bilirubin < 1.5x ULN (except patients with Gilbert's syndrome, who must have total bilirubin < 3 mg/dL)

h. Albumin ≥ 3.0 g/dL (patients with pancreatic cancer only)

Sex

3.01) Male or female

General Inclusion Criteria

Reproductive Status

Male patients:

4.01) A male patient must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and at least 2 months or 5 half-lives, whichever is longer, after the last dose of study treatment and refrain from donating sperm during this period.

Female patients:

5.01) A female patient is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 2 months or 5 half-lives, whichever is longer, after the last dose of study treatment.

Informed Consent

6.01) Capable of giving signed informed consent as described in Section 10.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2 Additional Inclusion Criteria - Monotherapy (Phase 1b Only)

Cohort 1b1: Renal Cell Carcinoma

7.01) Patients with histologically or cytologically confirmed advanced or metastatic renal cell carcinoma with a clear-cell component.

7.02) Must have received at least one prior anti-angiogenic therapy regimen (eg, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, or bevacizumab) in the advanced or metastatic setting

7.03) Must have received at least one anti-PD(L1) therapy (eg, nivolumab, pembrolizumab, atezolizumab, durvalumab, or avelumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α) and anti-CTLA-4 therapy (eg, ipilimumab) is allowed but not required.

Cohort 1b2: Melanoma

8.01) Patients with histologically- or cytologically-confirmed unresectable stage III or stage IV cutaneous melanoma not amenable to local therapy

8.02) Must have received at least one anti-PD(L1) therapy (including but not limited to nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α) and anti-CTLA-4 therapy (eg, ipilimumab) is also allowed.

8.03) Patients with BRAF mutations must have received prior BRAF inhibitor therapy (eg vemurafenib and dabrafenib) in the advanced or metastatic setting.

9.01) Inclusion Criteria for Additional Phase 1b Cohorts are included in Appendix 11.

5.3 Exclusion Criteria

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

Medical Conditions

1.01) Decreased cardiac function with New York Heart Association (NYHA) > Class 2

1.02) Uncontrolled or significant heart disorder such as unstable angina

1.03) Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the investigator, would preclude the patient from exposure to a biologic agent or pose a risk to patient safety

1.04) Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results

1.05) Active autoimmune disease, history of clinically significant autoimmune disease, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger, are permitted to enroll

1.06) Symptomatic interstitial lung disease or inflammatory pneumonitis

1.07) Untreated or active CNS or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to the first dose of study treatment

1.08) Evidence of coagulopathy or bleeding diathesis

Prior/Concomitant Therapy

2.01) Treatment with any anti-cancer therapy or participation in another investigational drug or biologics trial within 28 days or ≤ 5 half-lives (whichever is shorter) prior to first dose of study treatment administration or while on this study

2.02) For patients participating in Phase 1a dose escalation and exploration cohorts: Prior treatment with a CTLA-4 antagonist, including ipilimumab and tremelimumab

2.03) Patients who have received prior immune-modulating therapies (including regimens containing an immune agonist or a PD-L1/PD-1 antagonist) are NOT permitted to enroll unless all the following apply:

a. Must not have experienced a drug-related toxicity that led to permanent discontinuation of prior immunotherapy

b. Last treatment was administered 5 half-lives or 90 days (whichever is shorter) prior to first dose of study treatment

2.04) Ongoing adverse effects from prior treatment > National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 (with the exception of Grade 2 alopecia or peripheral neuropathy)

Other Exclusions

3.01) Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent daily) must be discontinued at least 2 weeks before study treatment administration

3.02) QTcF > 450 msec for males or > 470 msec for females at screening

3.03) Severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent

3.04) Known history of sensitivity to infusions containing Tween 20 (polysorbate 20), L histidine, and sucrose

3.05) Vaccines (eg, human papillomavirus [HPV] vaccine) within 4 weeks of study treatment administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted, but must be discussed with the Sponsor's medical monitor and may require a study treatment washout period prior to and after administration of vaccine

3.06) Patients with abnormal serum chemistry values that in the opinion of the investigator are considered to be clinically significant. This will include patients who show clinical signs and symptoms related to their abnormal serum chemistry values as well as patients whose serum chemistry values are asymptomatic but clinically significant per investigator (eg, hypokalemia or hyponatremia).

3.07) Pregnant or breastfeeding

3.08) Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS)

3.09) Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection

3.10) Transfusion of blood or platelets or granulocyte-colony stimulating factor (G-CSF) administration completed within 72 hours prior to first dose of study treatment

No waivers of these inclusion or exclusion criteria will be granted.

5.4 Lifestyle Considerations

There is not enough information currently available to make any specific recommendations.

5.5 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study and enter the screening period but are not subsequently enrolled. 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 after discussion with the Sponsor. Patients who screen fail may repeat screening procedures one time, within the 28-day screening window, inclusive of informed consent. A patient who is rescreened is not required to sign another ICF is the rescreening occurs within the 28-day screening window.

6.0 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol. For patients enrolled for evaluation of FPT155 monotherapy, the study intervention administered is FPT155. For patients enrolled for evaluation of combination treatment, the study interventions administered are FPT155 and pembrolizumab.

6.1 FPT155 Identity

FPT155 drug product is supplied for IV administration as a sterile, aqueous, colorless to slightly yellow, pyrogen-free solution supplied in single-use glass vials. The composition of the drug product contains 10 mg/mL active ingredient, 20 mM L-histidine, 270 mM sucrose, 0.05% (w/v) polysorbate 20 at pH 6.7. The drug product is providedin two configurations consisting of 20 mg/vial or 140 mg/vial. The container-closure systems consist of either an ISO 2R Type I glass vial, sealed with a 13 mm bromobutyl rubber stopper, and an orange flip-off cap containing a nominal volume of 2 mL or an ISO 20R Type I glass vial, sealed with a 20 mm bromobutyl rubber stopper, and a white flip-off cap containing a nominal volume of 14 mL. The final drug product will be provided as 2ºC to 8ºC refrigerated liquid which is diluted for administration per instructions provided in a separate Pharmacy Manual.

FPT155 will be supplied in a sterile vial for dilution into an IV container for administration by the study center.

6.2 Pembrolizumab Identity

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL solution. Each 1 mL solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and Water for Injection. For additional information, refer to the local Keytruda® (pembrolizumab) Prescribing Information. FPT155 + pembrolizumab combination cohorts will enroll in Australia and South Korea.

Pembrolizumab is available for injection as a 50 mg lyophilized powder in single-use vial for reconstitution and in 100 mg/4 mL (25 mg/mL) solution in single use vial.

The injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for Injection. Please refer to local pembrolizumab package insert.

6.3 Handling, Storage, and Accountability

6.3.1 FPT155

1. FPT155 should be stored under refrigerated temperature of 2-8ºC. Shaking and long-term exposure to light should be avoided.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
3. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. The Investigator is responsible for returning all unused study treatment to the Sponsor (or designee) and must verify that no remaining supplies are in the Investigator's possession. The study site is permitted to destroy used or partially used study treatment vials according to the site policy once Sponsor approval of their documented destruction procedure has been obtained. On completion of the study, the number of FPT155 vials shipped, destroyed, and returned must be reconciled.
6. Further guidance and information for the final disposition of unused study treatment are provided in the pharmacy manual.

6.3.2 Pembrolizumab

For the combination cohorts pembrolizumab packaging, labelling, and storage of pembrolizumab should be in accordance with the local Keytruda® package insert, the Pharmacy Manual, and relevant local guidelines.

6.4 Administration

6.4.1 FPT155

FPT155 will be administered as a 60 minute IV infusion Q3W in 21-day cycles. Proposed dose levels to be studied are outlined in Section 4.1.1.2.

There is no pre-specified maximum number of doses of FPT155.

A pharmacist (or other responsible person) will prepare FPT155 for administration. Doses in different cohorts should be prepared and administered according to the instructions provided in the Pharmacy Manual.

Infusion of FPT155 must be stopped, reduced, interrupted, or discontinued according to Section 6.9.3 (Dose Modification and Delay Criteria) and Section 6.9.6 (Dose Interruptions During Study Treatment Administration). If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

6.4.2 Pembrolizumab

Pembrolizumab should be prepared and administered according to the pembrolizumab Product Information.

6.5 Method of Treatment Assignment

An Interactive Voice/Web Response System (IVRS/IWRS) will be used to assign patients to study treatment.

Patients in Phase 1a dose escalation will be sequentially assigned to dose levels at the time of enrollment, as described in Section 4.1.1.2. Patients in Phase 1a dose exploration will be assigned to the dose level and schedule selected based on the results of the Phase 1a dose escalation, as described in Section 4.2. Patients in Phase 1b dose expansion will be assigned to the dose level and schedule selected based on the results of Phase 1a, as described in Section 4.3.

6.6 Measures to Minimize Bias: Randomization and Blinding

This is an open label study. There is no randomization or blinding.

6.7 Study Intervention Compliance

Only qualified study center personnel may administer FPT155 or pembrolizumab. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. Records of study medication administered (date, time, and dose administered

relative to time of preparation) will be recorded on the patient's electronic case report form (eCRF).

6.8 Concomitant Therapy

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

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Permitted Concomitant Medications

Supportive care (e.g., antiemetics, analgesics, bisphosphonates, and RANK-L inhibitors) may be used at the investigator's discretion and in accordance with institutional procedures. Patients should receive antiemetic and other prophylactic treatments according to the local standard of care and manufacturer's instruction. Patients should receive full supportive care, transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Hematopoietic stimulating agents may be used if indicated. Short course of focal radiation for palliation of symptoms is allowed. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (approximately less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) and for the treatment of tumor-related AEs is permitted.

6.8.2 Prohibited Concomitant Medications

Concomitant anticancer therapies of any kind including extensive non-palliative radiation are not permitted. Immunosuppressive doses of systemic corticosteroids are prohibited (unless utilized to treat a drug-related AE).

6.8.3 Imaging Restrictions and Precautions

Tumor evaluation by CT or MRI will be conducted according to RECIST v1.1 in accordance with the schedule of assessments. Patients with a heart pacemaker, brain aneurysm clips, and some implanted metallic or electrical devices should not have an MRI. Patients with known allergies or discomfort from contrast agents may have imaging without contrast.

6.9 Dose Modifications

6.9.1 Dose Escalation

The algorithm for dose escalations is described in Table 6. Intra-patient dose escalation will be permitted in patients enrolled at dose levels below 70 mg provided the criteria in Section 4.1.1.5 are met.

Safety will be monitored throughout the study by the Sponsor's CRC, comprised of Phase 1a study investigators, the Sponsor's medical monitor, and the Sponsor's safety representative. The CRC will meet routinely to review the emerging safety, PK, pharmacodynamics, and efficacy data, and to make dose escalation decisions.

In Phase 1a dose exploration, patients will be enrolled at one or more dose levels from Phase 1a, and dose escalation will not be permitted.

In Phase 1b, patients will be treated at the MTD and/or RD as determined from Phase 1a dose escalation, and dose escalation will not be permitted.

6.9.2 Toxicity at Lowest Dose Level

If the MTD is unexpectedly exceeded at the first dose level of FPT155 (0.07 mg), dosing will be suspended. Decisions on how to next proceed including decision on evaluating a lower dose will be based on safety, tolerability, and PK data, and will be determined by the CRC (refer to Section 4.1.1).

6.9.3 Dose Modification and Delay Criteria

Dose reductions or delays for FPT155 may be permitted for patients on treatment beyond the DLT evaluation interval in Phase 1a dose escalation, any patients in the Phase 1a dose exploration, or any patients in Phase 1b per the guidelines in Table 9. Dose reductions can be assessed using local laboratories. If a patient in Phase 1a dose escalation requires a dose reduction of FPT155 during the DLT period, they will be considered a DLT and be permanently discontinued from FPT155.

Dose reductions and delays for FPT155-related AEs or laboratory abnormalities should follow the guidelines outlined in Table 9. Refer to Section 6.9.4 and Appendix 10 for additional specific guidelines for irAEs and CRS. Any variations from these guidelines must be discussed with the Sponsor prior to dosing and must take into consideration the overall benefit and risks for the patient of continued participation in the study.

Table 9: Dose Modification and Delay Criteria for FPT155 (Non-Infusion Toxicity)

FPT155-related Toxicity Grade	Dose Schedule	New FPT155 Dose
Grade 1	No delay or missed dose required	100% of dose
Grade 2	Delay or miss dose until recovery to Grade 1 for suspected irAEsa and CRSb No delay or missed dose required for other AEs	100% of dose
Grade 3 (first occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 14 days, may resume at 100% of starting dose or 1 dose lower[c]
Grade 3 (second occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 14 days, may resume at 1 level lower[b] than previous dose or discontinue
Grade 3 (third occurrence) Grade 3 which does not recover to baseline or Grade 1 within 14 days Any Grade 4	Permanently Discontinue	N/A

[a] Refer to Section 6.9.4 and Appendix 8 for additional guidance regarding irAEs

[b] Refer to Section 6.9.5 and Appendix 10 for additional guidance regarding CRS

[c] E.g., 1 dose level lower for patients treated at 70.0 mg is 42.0 mg; 1 dose level lower for patients treated at 42.0 mg is 21.0 mg.

Abbreviations: AE = adverse event; irAEs = immune-related adverse events; CRS = cytokine release syndrome.

The first dose of each cycle is considered Day 1 of each cycle. Cycles will repeat every 21 days unless there is a treatment delay. A treatment delay of longer than 4 weeks should be discussed with the medical monitor prior to continuation of that subject on study. Treatment is administered Q3W until disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria.

6.9.4 Management of irAEs

Based on the underlying mechanism action, irAEs associated with the anti-CTLA-4 class of drugs (eg, ipilimumab) may potentially be observed with FPT155. Given the differentiated mechanism of action of FPT155 and the absence of any clinical data, the actual timing, incidence and severity of these AEs may differ significantly from anti-CTLA-4 therapies. General guidelines for management of suspected irAEs are provided here. These may be supplemented by discussions with the Sponsor as well as institutional guidelines on management of these toxicities.

In all instances, patients should be thoroughly evaluated to rule out a non-inflammatory etiology (eg, disease progression, concomitant medication, infections etc.). Symptomatic or topical therapy should be considered for most Grade 1 or 2 events unless otherwise specified in Appendix 8. Corticosteroids are the primary therapy for irAEs. Corticosteroids should be tapered over at least 2-4 weeks in patients experiencing Grade 2 AEs and at least 4-8 weeks in

patients experiencing Grade 3/4 AEs. Appropriate antiviral, antifungal (e.g. pneumocystis) and antibacterial prophylaxis must be considered in patients receiving corticosteroids for prolonged durations to reduce the risk of opportunistic infections. More potent immunosuppressive agents such as TNF inhibitors (eg, infliximab) should be considered for events not responding to systemic steroids. Refer to Appendix 8 for additional specific guidelines for individual irAEs.

6.9.5 Management of CRS

Refer to Appendix 10 for specific guidelines for grading and management of CRS.

6.9.6 Dose Interruptions During Study Treatment Administration

6.9.6.1 FPT155

Infusion of FPT155 must be stopped if any AE ≥ Grade 3 occurs during the infusion.
If bronchospasm or dyspnea occurs in a patient during the infusion, the infusion must be stopped.

In addition, at the investigator's discretion, the infusion rate for FPT155 may be reduced or stopped if a less severe AE (Grade 1 or 2) occurs during the infusion. If a Grade 3 or less severe AE resolves within 4 hours, the infusion may be restarted at half the previous rate and promptly managed according to the discretion of the Investigator. If the same AE appears again with the same severity at any time during the restarted infusion, the infusion should be discontinued, and no further dosing of FPT155 will occur without consultation with the Sponsor or Sponsor's designee.

If a patient experiences an infusion reaction prior to completion of the infusion, the infusion must be stopped, and the patient should be promptly managed and monitored according to signs and symptoms, and local clinical protocol until there is a complete resolution of the event. Symptoms of infusion reactions may include: fever, chills, rigors, urticaria, hypotension and hypertension with headache, wheeze, breathlessness, hypoxia, and pulmonary infiltrates. For patients whose infusion-associated events were either Grade 1 or 2, and completely resolved on the day of the infusion, the infusion may be resumed at the discretion of the Investigator at a slower rate with premedication. All subsequent infusions for that patient should then be administered at the reduced rate of infusion with pre-medications. Pre-medications may include medications such as corticosteroids, diphenhydramine, acetaminophen and/or bronchodilators as indicated. FPT155 will be permanently discontinued for patients who have experienced Grade 3 (lasting longer than 4 hours) or above infusion -associated AEs, and for patients who have recurrent infusion-associated reactions after restarting the infusion despite pre-medications and slower infusion.

If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion, as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

6.9.6.2 Pembrolizumab

Dose modifications for pembrolizumab will be allowed in accordance with the local Keytruda® package insert. Dose reductions for pembrolizumab are not permitted.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management for infusion reactions associated with pembrolizumab should be in accordance with the guidelines provided in the Keytruda® USPI.

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. irAEs may be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. Dose modification and toxicity management for irAEs associated with pembrolizumab should be done in accordance with the guidelines provided in the local Keytruda® package insert.

6.10 Treatment After the End of the Study

At the end of the study, the Sponsor will not continue to provide Sponsor-supplied study intervention to patients/investigators unless the Sponsor extends the study. The investigator should ensure that the patient receives appropriate standard of care to treat the condition under study.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

See the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) for data to be collected at the time of treatment discontinuation and for any further evaluations that need to be completed.

Study treatment may be discontinued for any of the following reasons:

- Consent withdrawal at the request of the patient or their legally authorized representative
- Progressive disease as assessed by the investigator. Treatment beyond disease progression may be allowed in select patients in accordance with Section 4.3.
- Any event that would pose an unacceptable safety risk to the patient
- A concurrent illness that would affect assessments of the clinical status to a significant degree
- A positive pregnancy test at any time during the study
- Specific request of the Sponsor or its authorized representative (e.g., if the study is terminated for reasons of patient safety)
- AE
- Investigator decision
- Patient decision, non-AE
- Other

7.2 Patient Discontinuation/Withdrawal from the Study

See the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

The Sponsor or its designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and eCRF.

Any patient may be discontinued from the study for any of the following reasons:

- Consent withdrawal at the request of the patient or their legally authorized representative
- AE
- Death
- Investigator decision

- Lost to follow-up
- Significant noncompliance to protocol
- Study termination by Sponsor
- Other

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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 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.
- 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 with a primary reason of lost to follow-up.

Discontinuation of specific sites or of the study as a whole are described in Section 10.0.

7.4 Replacement of Patients

Patients in Phase 1a dose escalation will be replaced if they are unevaluable for DLT (refer to Section 4.1.1.3).

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Protocol waivers or exemptions are not allowed.
- Specific clinical laboratory tests to be conducted: Appendix 1
- Guidance for ECOG assessment: Appendix 5
- RECIST v1.1: Appendix 6
- NYHA Classification: Appendix 7
- Immediate safety concerns should be discussed with the Sponsor 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 Schedule of Assessments, 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 (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments.

8.1 Efficacy Assessments

8.1.1 Tumor Assessment for the Study

Tumor assessments consist of clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v 1.1; MRI is acceptable). Assessments should be performed as outlined in the Schedule of Assessments. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Tumor response assessment will be performed by the investigator per RECIST v 1.1 guidelines (Eisenhauer 2009).

Tumor assessments will be performed at screening, then every 6 weeks from the first dose for 24 weeks, and then every 12 weeks thereafter. Once an initial CR or PR is reported by the investigator, confirmatory scans must be performed 4–6 weeks later.

If patient terminates study treatment prior to scheduled CT/MRI scans, patient should have scans done at the EOT visits (does not need to be repeated if performed within 8 weeks prior to the end of treatment visits, or if tumor progression was previously determined).

After discontinuation of study treatment for reasons other than progressive disease, withdrawal of consent, or initiation of additional anti-cancer therapy, tumor assessments will continue every 12 weeks until disease progression, withdrawal of consent or start of new anti-cancer therapy.

In the Phase 1b portion of the study, patients in LTFU for survival must have tumor scans every 12 weeks if tumor progression was not previously determined and/or use of alternative anti-cancer therapy has not been initiated.

8.1.2 Methods of Measurement

Every attempt should be made to image each patient using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator.

Bone scan or PET scan is not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain nontarget organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Bone scans may be collected per local standards, as clinically indicated.

Screening assessments are to be performed within 28 days prior to treatment assignment. In addition to the chest, abdomen, pelvis, and brain (if brain metastases are suspected at baseline), all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease using the same imaging method and technique as was used at baseline.

In addition, subjects receiving study treatment beyond progression must continue tumor assessments until such treatment has been discontinued. Treatment beyond disease progression is detailed in Section 4.3.

8.2 Informed Consent, Screening, and Enrollment

Patients must be able to provide written informed consent and meet all eligibility criteria prior to enrollment.

Only patients who meet all eligibility criteria outlined in Section 5.0 will be enrolled in this study. No waivers of inclusion or exclusion criteria will be granted by the Investigator and Sponsor or its designee for any patient enrolled in the study. Patients who qualify for Phase 1a of the study will be enrolled into the first available cohort. A patient may be enrolled into either Phase 1a or Phase 1b of the study, but not both.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments.

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor on eCRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the patient's medical record and should not be provided to the Sponsor, unless specifically requested.

8.3.1 Medical History and Demographics

Patient medical and surgical history includes a thorough review of significant past medical and surgical history, current conditions, concomitant therapies, alcohol and smoking history, and smoking status. Demographics including age, gender, race, and ethnicity will be recorded.

8.3.2 Physical Examinations

A complete physical examination including height and weight will be performed at screening. A limited physical examination (eg, symptom-directed examination of specific organ systems/ body area) should be conducted at the specified time points after screening in accordance with the Schedule of Assessments. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.3 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting.

8.3.4 Electrocardiograms

Twelve-lead ECG will be obtained as outlined in the Schedule of Assessments. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

The exact time of ECG should be recorded. The ECGs should be reviewed promptly by a qualified physician and any clinically important finding should be recorded on the appropriate eCRF. The Investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval.

Additional ECGs may be obtained at any time if clinically indicated. If abnormal (excluding sinus tachycardia), ECGs should be obtained as clinically indicated until the abnormality is

resolved or clinically stable. Any clinically significant changes in ECG that occur during the study should be reported as an AE in the eCRF.

8.3.5 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in accordance with the Schedule of Assessments. The ECOG performance scale is provided in Appendix 5. The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

8.3.6 Clinical Safety Laboratory Assessments

See Appendix 1 for the list of clinical laboratory tests to be performed and the Schedule of Assessments 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 eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

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 (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.4 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

Assessment of AEs will follow the guidelines provided in the NCI CTCAE version 4.03.

Abnormal laboratory results that lead to a change in patient treatment management (e.g., dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE page of the eCRF.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any 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 to resolution.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of study treatment (Cycle 1 Day 1). In addition, any SAE occurring between signing of ICF and start of treatment will be recorded if it is due to a study related procedure. The SAEs will be collected through the Day 100 EOT visit.

All AEs will be collected from the start of study treatment (Cycle 1 Day 1) through completion of study, at the time points specified in the Schedule of Assessments. AEs ascribed to study treatment and SAEs should be assessed through the Day 100 EOT visit.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History section of the eCRF, not the AE section, unless they directly correlate to a study-related procedure, in which case they will be reported on the AE eCRF page.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.

SAEs occurring after the Day 100 EOT visit should be reported to the Sponsor by the Investigator only if the Investigator considers the event reasonable related to FPT155. SAEs should always be recorded on the AE eCRF.

Investigators are not obligated to actively seek AE or SAE in former study patients. 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 treatment or study participation, the investigator must promptly notify the sponsor.

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 2.

8.4.2 Method of Detecting 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 2.

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.

8.4.3 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, 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 2.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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 a safety report describing a SAE or other specific safety information (eg, 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.

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study treatment and until the Day 100 EOT visit.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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

Disease progression is an expected event in patients with advanced cancer. Therefore, disease progression itself diagnosed clinically or based on laboratory/testing should not be considered as an AE.

Since disease progression is an efficacy endpoint of this study it should be recorded separately in the appropriate eCRFs intended to capture tumor response assessment.

8.5 Treatment of Overdose

There are no clinical data with FPT155. In the event of a medical emergency due to suspected FPT155 overdose the Sponsor should be contacted as soon as possible. Monitoring and reporting a suspected treatment overdose should follow guidelines for AEs and SAEs.
No specific antidote is available for treating overdose with FPT155. Management of any AEs due to overdose should be managed per Institutional practice.

8.6 Tumor Tissue

Tumor tissue should be collected in accordance with the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and Section 4.1.4.

8.6.1 Archival Tumor Tissue

Archival tumor tissue from an excisional, incisional or core needle biopsy, as fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Patients must consent to undergo a fresh tumor biopsy during screening if archival tumor tissue is not available. Archival tissue will be collected as follows:

[redacted]

8.6.2 Tumor Tissue Biopsy

The following guidelines apply to patients who consent for tumor biopsy:

- All patients that consent to a pre-treatment biopsy must have at least one tumor site that can be biopsied and be willing to have pre-treatment and on-treatment biopsies, from the same lesion where feasible.
- Biopsies will be performed according to the treating institution's own guidelines. These biopsies must be excisional, incisional or core needle biopsies, as fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses.
- If a pre-treatment biopsy has been performed as part of the patient's standard of care within 28 days prior Cycle 1 Day 1, if the sample is available to study Sponsor and has sufficient evaluable tumor content, the pre-treatment biopsy does not need to be repeated.
- Sites for biopsy must be distinct from target lesions used for efficacy assessment
- Patient must have recovered from any acute adverse effects of the biopsy procedure prior to dosing

Patients may also have an (optional) biopsy upon documented disease progression. If available, tumor tissue obtained from post-treatment procedures such as surgery may also be collected.

8.7 Pharmacokinetics

PK parameters are evaluated in this study in accordance with the Schedule of Assessments (Table 3 and Table 4).

Serum samples will be collected for measurement of concentrations of FPT155 and pembrolizumab as specified in the Schedule of Assessments. Instructions for the collection and handling of biological samples are in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded. The measurement of serum FPT155 and pembrolizumab concentration will be performed using validated ELISAs.

8.8 Pharmacodynamics

Pharmacodynamic parameters will be evaluated in this study in accordance with the Schedule of Assessments (Table 3 and Table 4).

Venous blood samples will be collected for measurement of immune phenotype changes due to study intervention by (including but not limited to) flowcytometry or cytokine or ribonucleic acid (RNA) analysis. Specific time points are listed in the Schedule of Assessments.

Tumor biopsy samples at screening and prior to Cycle 3 Day 1 will be collected from select patients for measurement of immune phenotype changes due to study intervention by (including but not limited to) immune histochemistry or RNA analysis. Specific time points are listed in the Schedule of Assessments.

8.9 Biomarkers

Samples for predictive and pharmacodynamic biomarker assessment will be collected and processed according to instructions provided in a separate laboratory manual. Additional guidance for sampling and procedures is provided in the following sections:

- Specific timing requirements for study assessments and procedures are outlined in the Schedule of Assessments.
- Guidance for the specific timing and sample collection of PK, immunogenicity, and pharmacodynamic sample collection: Table 3 and Table 4 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collection.

A variety of endpoints that could monitor drug activity or potentially predict clinical response to study intervention may be investigated in peripheral blood and archival and/or fresh tumor specimens, collected from patients prior to and during treatment. Data from these analyses will be evaluated for association with response and/or safety data.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality.

8.9.1 Immunogenicity Assessments

Antibodies to FPT155 and pembrolizumab will be evaluated in serum samples collected from all patients according to the Schedule of Assessments.

Serum samples will be screened for antibodies binding to FPT155 and pembrolizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize ADAs to FPT155 and pembrolizumab.

The detection and characterization of antibodies to FPT155 will be performed using a validated ligand binding assay. Samples collected for detection of antibodies to FPT155 will also be evaluated with concurrent FPT155 serum concentration samples to enable interpretation of the effect of the antibody on serum concentration and other pharmacokinetic parameters. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of FPT155. Samples may be stored until the Clinical Study Report (CSR) is written and approved or up to the stability date established during assay validation (typically this will be the stability period established for serum drug concentration samples) to enable further analysis of immune responses to FPT155 if needed.

8.9.2 RNA Expression Research

Transcriptome studies may be conducted using RNA sequencing or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood and tumor sample. Alternatively, targeted RNA expression analysis may be performed using targeted RNA sequencing assays and/or alternative equivalent technologies. This will enable the evaluation of baseline correlates, or changes in transcriptome profiles that may correlate with biological response relating to study intervention.

The samples may also be used to confirm findings by application of alternative technologies.

8.9.3 Immunohistochemistry/Immunofluorescence

Immunohistochemistry (IHC) or immunofluorescence (IF) studies may be conducted using archival tumor and fresh biopsy samples. This will enable the evaluation of baseline correlates, or changes in tumor immune profiles that may correlate with biological response relating to study intervention.

The samples may also be used to confirm findings by application of alternative technologies.

8.9.4 PBMC Collection

PBMCs will be isolated from peripheral blood samples at various time points. Flow cytometry and/or alternative equivalent technologies may be performed to understand baseline correlates of immune phenotype, and/or changes in immune phenotype due to study intervention.

The samples may also be used to confirm findings by application of alternative technologies.

8.9.5 Cytokine Analysis

Cytokine analysis by ELISA based and/or alternative equivalent technologies may be performed to understand baseline correlates, and/or changes in cytokine profile due to study intervention.

The samples may also be used to confirm findings by application of alternative technologies.

8.9.6 Circulating Tumor DNA Blood Assay

Circulating tumor DNA-containing plasma will be isolated from peripheral blood samples at various time points. Targeted deoxyribonucleic acid (DNA) sequencing and/or alternative equivalent technologies may be performed to identify tumor driver mutations and/or estimate tumor mutation burden and understand their association with biological response relating to study intervention.

The samples may also be used to confirm findings by application of alternative technologies.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

All analyses will be descriptive and will be presented by phase, dose group, cohort and overall as appropriate. In addition, all patients dosed at the MTD and/or RD will also be summarized as appropriate. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of subjects, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The statistical analysis plan (SAP) will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

This study is designed as a dose escalation, dose exploration, and dose expansion study with objectives that include determination of an MTD and/or RD and assessments of the safety and tolerability of FPT155 as monotherapy and in combination with pembrolizumab. The sample size of this study was not determined by strict statistical considerations. The total number of patients planned for this study is estimated to be approximately 408.

The sample size of Phase 1a is defined by the requirements of the accelerated titration and 3+3 dose escalation design. Approximately up to 108 patients will participate in Phase 1a monotherapy, depending on the number of dose levels evaluated and the incidence of DLTs; this includes up to 58 patients in the Phase 1a monotherapy dose escalation portion and allows for up to approximately 50 patients in the Phase 1a monotherapy dose exploration to further explore safety, PK, PD, and clinical activity at one or more dose levels (conditional upon the dose level clearing dose escalation criteria). Approximately up to 60 patients will participate in Phase 1a combination, depending on the number of dose levels evaluated and the incidence of DLTs; this includes up to 30 patients in the Phase 1a combination dose escalation, and up to 30 patients in the Phase 1a combination dose exploration.

For the objective of estimating the ORR of FPT155 in Phase 1b monotherapy, it is estimated that up to 30 patients will be enrolled to ensure 25 evaluable patients in each cohort. Table 10 displays the corresponding 2-sided 90% confidence interval (CI) and the precision for the various observed response rates (Agresti 1998) based on 25 evaluable patients. The sample size of 25 is chosen to ensure that it will allow to exclude 10% when the observed ORR is 24% or higher in each cohort.

Approximately 240 patients will participate in Phase 1b monotherapy. Phase 1b monotherapy will consist of up to 8 cohorts of approximately 30 patients each.

Table 10: Two-Sided 90% Confidence Intervals of the Observed Response Rates

Sample Size	Observed Response Rate	90% CI	Precision (longest one-sided CI length*)
25	5/25 (20%)	(8%, 38%)	18%
	6/25 (24%)	(11%, 42%)	18%
	7/25 (28%)	(14%, 46%)	18%
	8/25 (32%)	(17%, 50%)	18%
	9/25 (36%)	(20%, 54%)	18%
	10/25 (40%)	(24%, 58%)	18%

Abbreviations: CI = confidence interval.

*Distance from the observed response rate to the lower or upper CI boundary.

9.3 Populations for Analyses

The following analysis populations are defined for the study as follows:

Population	Description
Enrolled	All patients who sign informed consent and are registered as enrolled in IVRS/IWRS.
Efficacy Population	All patients who have received any portion of at least one dose of study drug.
DLT-Evaluable Population	All patients enrolled into Phase 1a dose escalation portion of the study who received at least 1 dose of all assigned study drug(s) and remain on study for the 21-day DLT evaluation, or who experienced a DLT before clearing the 21-day DLT evaluation interval.
Safety Population	All patients who have received any portion of at least one dose of any study drug.
Response-Evaluable Population	All patients who met eligibility criteria, received at least one dose of any study drug, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment unless the death and clinical progressive disease occurred prior to the first post baseline disease assessment.
PK-Evaluable Population	All patients who have received at least one dose of study drug and have had sufficient PK sample for the calculation of at least one PK parameter on at least one Study Day.

9.4 Statistical Analyses

The 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.

9.4.1 Efficacy Analyses

The primary efficacy analyses (Table 11) will be performed on the efficacy population. Efficacy analyses based on the response-evaluable population may be performed as a sensitivity analysis. Details of the censoring scheme on time-to-event endpoints such as DOR and PFS will be described in the SAP.

Table 11: Efficacy – Statistical Analyses

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of patients whose BOR is either confirmed CR or PR per RECIST v1.1 in the population of interest. BOR for a patient will be assessed per RECIST v1.1 by the investigator, unless otherwise specified. DCR defined as total number of patients with confirmed responses of either CR, PR, or stable disease as determined by the investigator per RECIST v1.1, divided by the total number of patients who are evaluable for a response	Estimate of ORR and corresponding 2-sided exact 90% CI using the Clopper-Pearson method Estimate of DCR and corresponding 2-sided exact 90% CI using the Clopper-Pearson method
DOR DOR for a patient with a BOR of confirmed CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 90% CI using Brookmeyer and Crowley methodology (using log-log transformation)
PFS PFS for a patient is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 90% CI using Brookmeyer and Crowley methodology (using log-log transformation)
OS OS for a patient is defined as the time from the first dose of study treatment until death from any cause.	Estimate by the Kaplan-Meier method and corresponding 2-sided 90% CI using Brookmeyer and Crowley methodology (using log-log transformation)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; DCR= disease control rate; PFS = progression free survival; OS = overall survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety analyses will be performed separately within both phases of the study and for all patients combined. In addition, the incidence of DLTs in Phase 1a will be summarized for the DLT-Evaluable Population.

Table 12: Safety – Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, and AEs leading to discontinuation, modifications, and interruptions, and death AEs will be graded according to CTCAE v4.03.	Frequency distribution of treated patients with AE using the worst CTC grade. Patients will only be counted (1) once at the preferred term level, (2) once at the SOC level, and (3) once in the "Total subject" row at their worst CTC grade, regardless of SOC or preferred term.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on treatment per patient.
ECG abnormality	Frequency distribution of treated patients with post baseline ECG abnormality by visit.

Abbreviations**:** AE = adverse event; CTCAE = common terminology criteria for adverse events; DLT = dose limiting toxicity; ECG = electrocardiogram; SOC = system organ class.

9.4.3 Pharmacokinetic Analyses

The following PK parameters of FPT155 will be summarized.

Endpoint	Statistical Analysis Methods
The following PK parameters will be derived from concentration-time data for FPT155 when appropriate and applicable to characterize single-dose/multiple dose PK. • AUC • C_{max} • C_{trough} • CL • $t_{1/2}$ • Vss • C_{max} and C_{trough} as well as the accumulation ratio of C_{max} and C_{trough} for pembrolizumab may be calculated if the data are available Other parameters, such as dose proportionality, accumulation ratio, attainment of steady state, will also be estimated if the data are available.	Individual and mean (± SD) serum FPT155 and pembrolizumab concentration-time data will be tabulated and plotted by dose level, respectively. PK parameters of FPT155 and pembrolizumab will be tabulated and summarized by dose level when appropriate and applicable, respectively. The impact of immunogenicity on FPT155 and pembrolizumab exposure will be assessed, tabulated, and summarized by dose level as data allow.
Assessments of time-dependence of PK, the effect of body weight as well as other covariates on PK, and exposure-response relationship for FPT155 will be conducted, when the data allow, to determine the appropriate dosing approach (eg, body weight-based or fixed dosing) for future trials.	The effect of body size on PK and correlation of exposure with clinical outcomes and toxicity will be assessed for FPT155 when data allow. These analyses will be used to determine the appropriate dosing approach (eg, body size-based or fixed dosing) to support the proposed dose and dose regimen(s) for further trials.

9.4.4 Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to FPT155 and pembrolizumab	Frequency distribution of baseline ADA-positive subjects for FPT155 and pembrolizumab and FPT155 and pembrolizumab treatment induced ADA-positive subjects after initiation of the treatment; titer (titer range), respectively. May characterize ADA as either transient or persistent ADA.

9.4.5 Other Analyses

[redacted]

9.5 Interim Analyses

There is no planned interim analysis in this study.

10.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Regulatory and Ethical Considerations

10.1.1 Good Clinical Practice

The procedures set forth in this study protocol are designed to ensure that the Sponsor and investigator abide by all applicable laws, regulations and guidelines, including ICH Good Clinical Practice (GCP) guidelines and international guidelines for ethical practices, including the Declaration of Helsinki (1989) and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.

Before the first patient is screened, the study protocol, including any amendments thereto, the form ICF, the Investigator Brochure and any other relevant documents must be approved by the IRB/IEC, in accordance with applicable laws, regulations and guidelines. The Sponsor, Sponsor's agents, and investigator must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

If a significant safety issue is identified by the Sponsor, either from an individual case report or review of aggregate data, the Sponsor will promptly notify the applicable regulatory authorities and investigators. Investigators will then notify local IRB/IECs as deemed appropriate based on individual IRB/IEC policy. A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

All potential serious breaches must be reported to the Sponsor or designee immediately.
A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

The investigator will also be responsible for providing oversight of the conduct of the study at the site, including oversight of all personnel involved in the study, and adherence to all applicable laws and regulations, as set forth in the Clinical Trial Agreement.

Personnel involved in conducting this study will be qualified by education, training, and experience prior to performing their respective tasks.

The study will not use the services of study personnel against whom sanctions have been invoked or who have engaged in scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

10.1.2 Institutional Review Board/Independent Ethics Committee

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 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.

The investigator should notify the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

10.1.3 Compliance with the Protocol and Protocol Revisions

This protocol is to be followed exactly. The investigator may not implement any deviation or change to the protocol, except where necessary to eliminate an immediate hazard to study subjects.

Any amendments to the protocol must be written and receive approval from the appropriate personnel and the IRB/IEC (and, if applicable, also by the local health authority) prior to implementation. Following approval, the protocol amendment will be submitted to the IND application / Clinical Trial Application under which the study is being conducted. If an amendment substantially alters the study design or increases the potential risk to patients: (1) the informed consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form of informed consent must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form of informed consent must be used to obtain consent from new subjects prior to enrollment.

If a deviation or change to a protocol is implemented by an investigator to eliminate an immediate hazard to a study subject, the investigator must report such the deviation or change as soon as possible to:

- the IRB/IEC; and
- any applicable Regulatory Authority(ies), if required by local regulations.

Investigator must send to Sponsor documentation of approval/favorable opinion of such deviation or change, signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local health authority.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

10.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with complete and accurate information required by Part 54 of Title 21 of the Code of Federal Regulations about such investigators' and sub-investigators' financial interests, as requested by Sponsor, to allow the Sponsor to submit financial certifications or disclosure statements to the appropriate regulatory authorities, as required by Part 54 of Title 21 of the Code of Federal Regulations. Investigators are responsible for providing such information during the course of the study and for one year after completion of the study.

10.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study. Patients must be informed that their participation in the study is voluntary. If a patient cannot provide his or her consent, the investigator must ensure that the patient's legally authorized or other legally acceptable (as per country-specific guidelines) representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding the study.

Investigator, with the assistance of Sponsor, will prepare forms of written statements of informed consent (each, an ICF) for use in the study that meet the requirements of Part 50 of Title 21 of the Code of Federal Regulations, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act ("HIPAA"), where applicable, and the IRB/IEC or study center. Each form ICF must be approved by the IEC/IRB and the Sponsor before any patients are enrolled in the study.

Patients or their legally authorized representatives will be required to sign the appropriate forms of ICF to provide their consent prior to their enrollment in the study. The authorized person that obtained the patient's informed consent must also sign the ICF. The original ICFs will be filed in the investigator's study center file, unless otherwise agreed by the Sponsor and the study center. A copy of each patient's signed ICFs will be provided to such patient or such patient's legally authorized representative.

The investigator will not undertake any investigation with respect to a patient specifically required only for the study until valid consent has been obtained from such patient. The terms of the consent and when it was obtained must be documented in the source documents and in the eCRF.

Patients must always be consented to the most current approved version of the ICF during their participation in the study. If a protocol amendment is required, the ICFs may need to be revised to reflect the changes to the protocol. If any ICF form is revised, it must be reviewed and

approved by the appropriate IRB/IEC and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

Each patient's 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.

10.4 Data Protection

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other pertinent data for each study patient. All information recorded in the case histories or eCRFs for this study must be consistent with the patients' source documentation (ie, medical records).

Investigator and study center must maintain the anonymity of participating patients. Each patient will be assigned a unique patient identifier by the Sponsor that may consist of one or more of the following: the patient's patient number, initials, and/or birth date. Investigator and study center will include only such patient identifier on any eCRFs or other patient records, datasets or other documents that are transferred or submitted to the Sponsor or Sponsor's designee during the course of the study and will redact patient's name and all other personally-identifiable patient information from such documents. In addition, investigator must maintain in confidence any documents that include personally-identifiable patient information (e.g., the signed ICF) and take all reasonable precautions to prevent the disclosure of any personally identifiable patient information by any employee or agent of the study center to any third party or otherwise into the public domain.

The investigator or study center must inform study patients that their personal study-related data will be used by the Sponsor in accordance with local data protection law and must explain the level of disclosure to patients. In addition, each 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 IRB/IEC members of the study center, and by inspectors from regulatory authorities.

The Sponsor (or designee) may conduct a site visit prior to study initiation at a site to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of investigator's responsibilities for ensuring study compliance and procedures for preparing and maintaining adequate and correct eCRFs.

10.5 Clinical Study Data and Publication Policy

A signatory investigator must be selected to sign the clinical study report.

For this protocol, the signatory investigator will be selected as appropriate based on the following factors:

- Role of investigator in study, including role as
  - External principal investigator designated at protocol development
  - National coordinating investigator
- Investigator's success in patient recruitment (e.g., among the top quartile of enrollers)
- Investigator's involvement in the study design
- Investigator's regional representation (e.g., among the top quartile of enrollers from a specified region or country)
- Other factors (as determined by the study team)

All data obtained during this study are confidential information of the Sponsor. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor, in accordance with the Clinical Trial Agreement. Any publications or abstracts arising from this study require approval by the Sponsor prior to publication or presentation and must adhere to the Sponsor's publication requirements as set forth in the Clinical Trial Agreement.

10.6 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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

All data obtained during the study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. eCRF fields for which source documents will typically be needed include laboratory assessments, physical examination reports, nursing notes, ECG recordings, hospital records, CT scans, and/or MRI reports.

During the study, study monitors will perform routine site monitoring visits and ongoing source data verification to confirm that data entered into the eCRF 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. Instances of missing or uninterpretable data will be discussed with the investigator for resolution. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel and other support for study monitoring visits. Moreover, regulatory authorities, IRBs, IECs, and/or the Sponsor's Quality Assurance group may wish to carry out additional source data checks and/or on-site audit inspections. The investigator must provide direct access to source data documents upon request during study-related monitoring visits, audits, IRB/IEC review, and regulatory agency inspections, provided that such visits, audits, reviews and inspections must be carried out giving due consideration to data protection and medical confidentiality. In addition, investigator will ensure that the Sponsor and/or Sponsor's designee will receive the necessary support to complete these activities.

The Data Management Plan, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. All processes for data processing and query handling will be described in the Data Management Plan.

Each study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments thereto, the protocol for tissue sampling, drug accountability records, any material correspondence with the IEC/IRB and the Sponsor (or its designee), and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the Sponsor or its designees. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator shall retain records related to the study, including patient medical records, in accordance with the requirements set forth in the Clinical Trial Agreement.

No data should be destroyed without the agreement of the Sponsor. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.7 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, and any discrepancies must be explained. The investigator may need to request a patient's previous medical records or transfer records, depending on the study. Also, each patient's current medical records must be available.

All participating centers should take particular care in ensuring that original imaging source data (CT images, MRI images, echo images, etc.) are maintained and accessible for monitoring, and that these original source data are then archived on a long-term basis in compliance with ICH GCP Section 8. These images must be stored in a secure location until the Sponsor or Sponsor's designee authorizes their destruction and must be retrievable by study patient number in the event of an audit.

10.8 Study and Site Closure

The Sponsor may close the study site or terminate the study at any time for any reason at its sole discretion.

The study may also be terminated if an investigator, Sponsor, or Sponsor's designee becomes aware of conditions or events that suggest a possible hazard to patients if the study continues.

Conditions that may warrant termination of the study site or the study 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
- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of a study site to enroll patients at an acceptable rate
- Decision on the part of the Sponsor to suspend or discontinue development of the study intervention

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.

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12.0 APPENDICES

APPENDIX 1: PHASE 1A AND PHASE 1B CLINICAL LABORATORY TESTS

- The laboratory parameters outlined in Table 13 will be determined in accordance with the Schedule of Assessments and assessed locally.
- The results of each test must be entered into the eCRF.
- Investigators must document their review of each laboratory safety report.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.0 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 13: Protocol-Required Clinical Laboratory Assessments

Hematology: CBC with differential:	
ANC	lymphocytes (%)
ALC	monocytes (%)
basophils (%)	neutrophils (%)
eosinophils (%)	platelets
hemoglobin	RBC
hematocrit	WBC
Clinical Chemistry*:	
Albumin	Glucose
alkaline phosphatase	LDH
ALT (SGPT)	magnesium
AST (SGOT)	phosphate
BUN or Urea	potassium
calcium	sodium
chloride	total bilirubin
CO_2 (bicarbonate)	total cholesterol
creatinine	total protein
CRP	uric acid
direct bilirubin	TSH
	Free T4
	ACTH
Coagulation:	
INR, PT, PTT and APTT	
Urinalysis:	
Dipstick (appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood). If dipstick is positive (2+ or greater) for blood or protein, perform a microscopic examination.	
At Screening Only:	
Serology for Hepatitis B (HBsAg), and Hepatitis C (HCV RNA)	

Table 13: Protocol-Required Clinical Laboratory Assessments (Contd)

Hematology: CBC with differential:	
ANC	lymphocytes (%)
ALC	monocytes (%)
basophils (%)	neutrophils (%)
eosinophils (%)	platelets
hemoglobin	RBC
hematocrit	WBC

NOTES:

- If either AST or ALT is elevated, obtain total serum bilirubin and alkaline phosphatase; repeat daily or other interval, as clinically indicated, until resolved or stable
- Additional tests to rule out drug-induced liver injury (eg, abdominal ultrasound, serum GGT, hepatitis serology) may be obtained at any time, if clinically indicated
- For WOCBP, a serum pregnancy test will be performed at screening and pregnancy testing will be performed at each subsequent cycle of treatment prior to dosing. Additional serum pregnancy testing may be performed if there is a concern with pregnancy, the patient missed a menstrual period, or did not follow the contraceptive guidance in Appendix 3.
- Phase 1a: Additional labs may be performed locally as clinically indicated for patients in the first dose cohort that are hospitalized for the initial infusion or for any patients showing evidence of ≥ Grade 2 CRS
- Phase 1b: Additional labs may be performed locally as clinically indicated
- Samples for PK, PD, and ADA analyses should be submitted to the central laboratory as listed in Table 3 and Table 4. Cytokines will be assessed at a central and/or specialty laboratory, however, may also be performed locally for assessment of CRS.
- During dose escalation, a chemistry and hematology panel will be drawn on Day 2, 8 and 15 of Cycles 2 and 3.

Abbreviations: ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CO2 = carbon dioxide; CRP = c-reactive protein; GGT = gamma-glutamyltransferase; INR = international normalized ratio; HBsAG = hepatitis B surface antigen; HCV RNA = hepatitis C virus ribonucleic acid; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

APPENDIX 2: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

1. 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 treatment, whether or not considered related to the study treatment. 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 treatment.

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. 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 treatment or a concomitant medication. "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. Abnormal laboratory findings that are judged by the investigator to be not clinically significant. Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. 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.

2. Definition of SAE

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 as it occurred. 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 admitted for at least 24 hours 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. 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 (e.g., 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, 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.

3. Recording an AE and/or SAE

AE and SAE Recording

The investigator will record all available relevant AE/SAE information in the CRF and send it to the sponsor or designee within 24 hours of becoming aware of the event.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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.

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

Investigators need to assess the severity of AEs according to the guidelines provided in NCI-CTCAE, version 4.03. CTCAE v 4.03 Severity Grades are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; mild AE

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; moderate AE

Grade 3: Severe or medically significant but non-immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; severe AE

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Fatal AE

If the AE is not specified in the CTCAE or the study protocol, the grading of severity will be assessed as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death due to the AE (Grade 5) using the following definitions:

Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the patient is unable to carry out usual activities.

Very severe (life-threatening): The patient's life is at risk from the event.

Assessment of Causality

The investigator is should assess the relationship between study treatment and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment 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 treatment 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, all SAE data should be sent to the Sponsor or designee within 24 hours of becoming aware of the event and should include an assessment of causality for every event.

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 or as requested by the Sponsor 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. • If a patient dies during participation in the study or during a recognized follow-up period, the investigator will try to obtain the cause of death and autopsy report if they are available and provide it to the Sponsor. New or updated information will be recorded in the originally completed CRF. The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

4. Reporting of SAEs

SAE Reporting to Sponsor/Designee via Paper CRF
Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor/designee/medical monitor or the SAE coordinator. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting: Novotech (Australia) Safety Department Fax number: +61 2 85690970 Email: fiveprime.safety@novotech-cro.com

APPENDIX 3: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-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.

2. Contraception Guidance:

Male patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and for up to 100 days after last dose of FPT155.

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for up to 100 days after last dose of FPT155.

Male patients must refrain from donating sperm for the duration of the study and for up to 100 days after last dose of FPT155.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 14.

Table 14: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent Failure rate of <1% per year when used consistently and correctly. [a]
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] Oral Intravaginal Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation Oral Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] Intrauterine device (IUD)[c] Intrauterine hormone-releasing system (IHS) [c] Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient*.

NOTES:

[a] Typical-use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] IUDs and IHSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from IUDs do not alter contraception effectiveness.

3. Pregnancy Testing

WOCBP should only be included after a confirmed negative, highly sensitive serum pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and at the times specified in the protocol.

4. Collection of Pregnancy Information

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.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. This information will reside in the site's source documents and will be submitted to the sponsor as indicated but will not be captured within the clinical database. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. 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 appropriate form and submitted to the sponsor 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. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. 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 treatment by the investigator will be reported to the sponsor as described in Appendix 2. 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 treatment or be withdrawn from the study

APPENDIX 4: GENETICS

Use/Analysis of DNA

- Genetic variation (eg, mutations) in the tumor may impact a patient's tumor response to study intervention, and these mutations might determine severity and progression of disease. To determine tumor genetic variations, comparison to the normal genome to the patient is necessary to computationally be able to identify tumor specific genetic alterations. Therefore, tumor and blood samples that will be collected for pharmacodynamic analysis such as immune phenotyping might be used to isolate tumor and normal DNA.
- DNA samples might be used for research related to tumor mutation analysis and correlates of efficacy or safety.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

APPENDIX 5: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, 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.

APPENDIX 6: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], *P. Therasse*[b], *J. Bogaerts*[c], *L.H. Schwartz*[d], *D. Sargent*[e], *R. Ford*[f], *J. Dancey*[g], *S. Arbuck*[h], *S. Gwyther*[i], *M. Mooney*[g], *L. Rubinstein*[g], *L. Shankar*[g], *L. Dodd*[g], *R. Kaplan*[j], *D. Lacombe*[c], *J. Verweij*[k]

[a]*National Cancer Institute of Canada – Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, ON, Canada*
[b]*GlaxoSmithKline Biologicals, Rixensart, Belgium*
[c]*European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium*
[d]*Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[e]*Mayo Clinic, Rochester, MN, USA*
[f]*RadPharm, Princeton, NJ, USA*
[g]*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA*
[h]*Schering-Plough, Kenilworth, NJ, USA*
[i]*East Surrey Hospital, Redhill, Surrey, UK*
[j]*National Cancer Research Network, Leeds, UK*
[k]*Erasmus University Medical Center, Rotterdam, The Netherlands*

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed*: based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a *short* axis of $\geqslant$15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

* *Corresponding author*: Tel.: +1 613 533 6430; fax: +1 613 533 2411.
E-mail address: eeisenhauer@ctg.queensu.ca (E.A. Eisenhauer).
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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment *or* to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

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 (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, 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:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. *Specifications by methods of measurements*

3.2.1. *Measurement of lesions*

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.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise 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 assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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. See Appendix II for more details.

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. As is described in Appendix II, 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). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

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 (described in greater detail in Appendix II). 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 utilisation of these techniques for objective tumour 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 complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour 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.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

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 tumour types such as germ cell tumours, where known residual benign tumours 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 tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$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 tumour. Nodal size is normally reported as two 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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 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 (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$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 characterise any objective tumour regression in the measurable dimension of the disease.

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 nodes' or 'multiple liver metastases').

4.3. Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

4.3.1. 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.

4.3.2. Special notes on the assessment of target lesions

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 complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions 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 case report form. 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. As noted in Appendix II, 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'.

4.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group 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 normalisation of tumour 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 tumour 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).

4.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

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 tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality 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 III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply 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 tumour 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 localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient 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.

4.3.5. *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 tumour (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 study 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 patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient'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:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. 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.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. 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 patient'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 study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. *Best overall response: all time points*

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 patient 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 patient's best response depends on the subsequent assessments. For example, a patient 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 patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/– non-target) disease.

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 all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. *Special notes on response assessment*

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised 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 (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease 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 studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *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 progressive disease is objectively documented (taking as reference for progressive disease 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.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) 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).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above; no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval*.

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

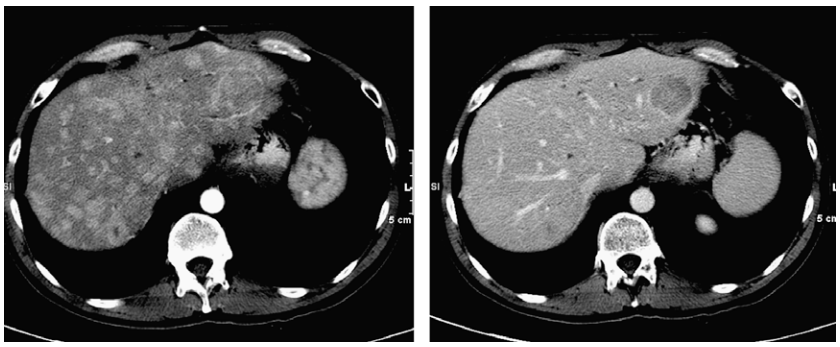

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

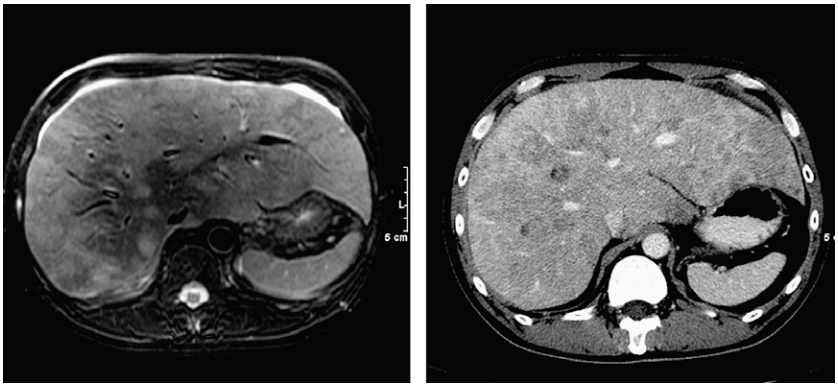

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

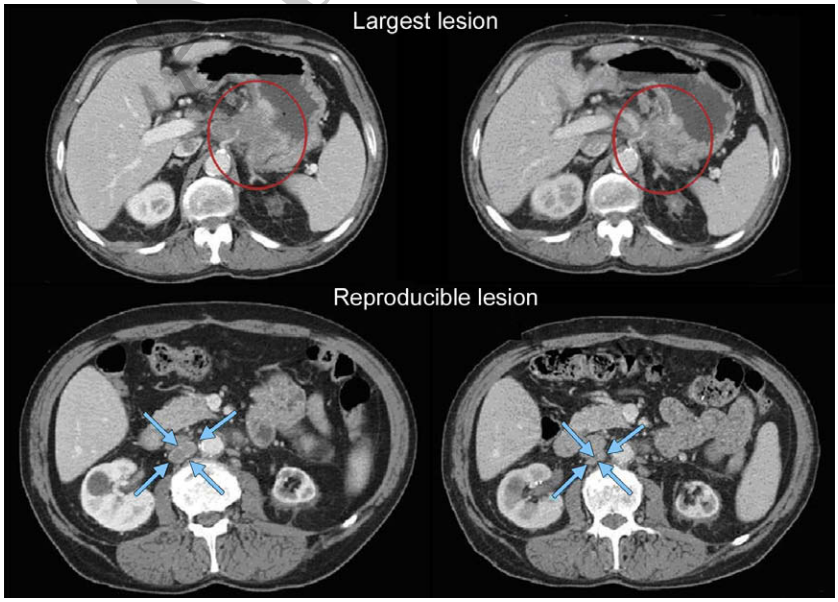

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

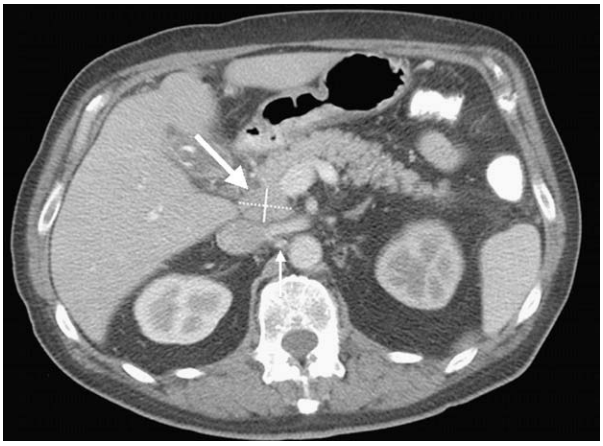

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters 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 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

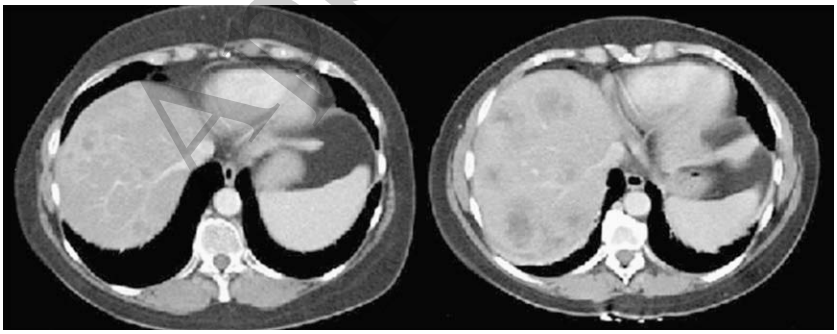

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

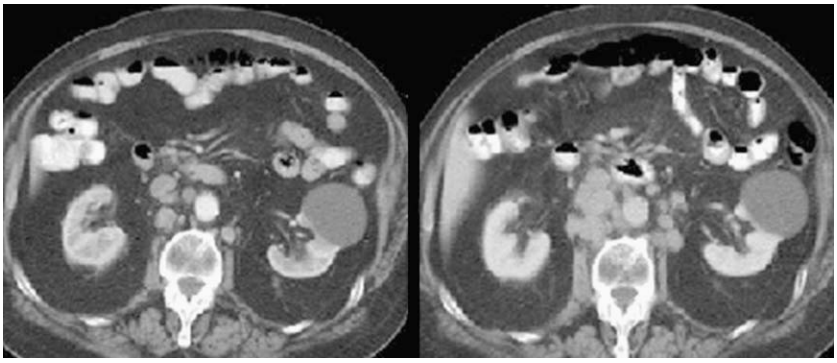

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients…in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(*continued on next page*)

Appendix III – *continued*

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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APPENDIX 7: NEW YORK HEART ASSOCIATION CLASSIFICATION

Table 15: New York Heart Association Classification

Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX 8: ALGORITHMS FOR EARLY DETECTION AND TREATMENT OF IMMUNE RELATED ADVERSE EVENTS (IRAES)

The guidelines provided below have been adapted from the European Society for Medical Oncology (ESMO) clinical practice guidelines for management of toxicities from immunotherapy (Haanen 2018). Please refer to the full publication for management of irAEs not specifically discussed below (Appendix 9). These may be supplemented by discussions with the sponsor's medical monitor as well as institutional guidelines on management of these toxicities.

Diarrhea and Colitis			
Grade	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Grade 1 Diarrhea: <4 stools/ day over baseline Colitis: asymptomatic	No delay or missed dose	Symptomatic management: Oral fluids, loperamide, avoid high fiber/lactose diet Persists >14 days or worsens, treat as Grade 2	Close monitoring for worsening symptoms Patient education to immediately report worsening symptoms
Grade 2 Diarrhea: 4-6 stools per day over baseline; Outpatient management if appropriate Colitis: abdominal pain, blood in stool	Delay or miss dose Reinitiate upon recovery to ≤Grade 1	Symptomatic management: Oral fluids, loperamide, avoid high fiber/lactose diet Persists > 3 days or worsens 0.5-1.0 mg/kg (methyl)prednisolone or oral equivalent Persists >3 days or worsens, treat as Grade 3/4	Clinical safety labs (eg, CBC, chemistry, CRP) Stool microscopy for leukocytes/ova/parasites, culture, viral polymerase chain reaction (PCR), clostridium difficile toxin, cryptosporidia
Grade 3/4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; requires hospitalization Colitis (G3): severe abdominal pain, fever, ileus, peritoneal signs; medical intervention indicated G4: Life-threatening, perforation	Permanently discontinue FPT155	1.0-2.0 mg/kg (methyl) prednisolone IV or IV equivalent Persists > 3 days, infliximab 5 mg/kg (if no contraindication)	Assess as above Urgent gastrointestinal (GI) consult and abdominal CT and/or sigmoido/colonoscopy

Hepatitis			
Grade	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Grade 1 AST or ALT > ULN-3.0 x ULN and/or T. bili > ULN-1.5 x ULN	No delay or missed dose	N/A	Close monitoring for worsening symptoms or laboratory parameters
Grade 2 AST or ALT > 3.0 -≤ 5 x ULN and/or T. bili > 1.5- ≤ 3 x ULN	Delay or miss dose Reinitiate upon recovery to ≤Grade 1	Monitor liver function tests (LFTs) every 3 days	Review concomitant medications (e.g. statins, antibiotics) alcohol use Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti- smooth muscle antibody (SMA)/anti-nuclear antibody (ANA)/liver kidney microsome (LKM)/soluble liver antigen (SLA) /lipoprotein (LP)/ Anti-liver cytosol 1 autoantibody (LCI), iron studies Consider Liver imaging
Grade 3/4 AST or ALT >5 x ULN or T.bili >3 x ULN	Permanently discontinue FPT155	Monitor LFTs every 1-2 days 1.0-2.0 mg/kg (methyl) prednisolone IV or IV equivalent (2 mg/kg/day IV methylprednisolone for Grade 4 AEs)	Assess as above Refer to Hepatologist Liver imaging Consider liver biopsy for Grade 4 AEs

Renal Adverse Events			
Grade	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Grade 1 Creatinine >1-1.5 x baseline or > ULN-1.5 x ULN	No delay or missed dose	Monitor serum creatinine weekly	Review hydration status, medications, urinalysis/culture if urinary tract infection symptoms Dipstick urine and send for protein assessment. If obstruction suspected: renal ultrasound +/- doppler to exclude obstruction/clot If worsens treat as below
Grade 2-3 G2: creatinine > 1.5-3 x baseline or > 1.5-3 x ULN G3: creatinine > 3 x baseline or > 3-6 x ULN	Delay or miss dose Reinitiate upon recovery to ≤Grade 1	Monitor serum creatinine every 2-3 days 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent Persists >7 days or worsens, treat as Grade 4	Assess as above If proteinuria: perform 24 h urine collection or urine protein to creatinine ratio (UPCR) Refer to nephrologist
Grade 4 Creatinine > 6x ULN	Permanently discontinue FPT155	Monitor serum creatinine daily 1.0-2.0 mg/kg methyl prednisolone IV or IV equivalent	Assess as above Refer to nephrologist Consider renal biopsy

Pneumonitis			
Grade	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Grade 1 Radiographic changes only Ground glass change, non-specific interstitial pneumonia	Consider delay or miss dose	Monitor symptoms every 2-3 days Re-image ≤ every 3 weeks	Consider pulmonary and Infectious disease referral Clinical safety labs (eg, CBC, chemistry, CRP) Consider sputum sample and screening for viral opportunistic or specific bacterial infections
Grade 2 Mild/moderate new symptoms Dyspnea, cough, chest pain	Delay or miss dose Reinitiate upon recovery to ≤Grade 1	Monitor symptoms daily Re-image ≤weekly 1.0 mg/kg/day methylprednisolone IV or oral equivalent Consider pneumocystis prophylaxis	Assess as above Pulmonary and Infectious disease referral Consider bronchoscopy, lung biopsy
Grade 3/4 Severe new symptoms New/worsening hypoxia Life threatening Difficulty in breathing, Acute Respiratory Distress Syndrome (ARDS)	Permanently discontinue FPT155	2.0-4.0 mg/kg/day methylprednisolone IV or IV equivalent Persists >2 days, add infliximab 5 mg/kg (if no contraindication) or additional immunosuppression (e.g., mycophenolate mofetil [MMF], cyclophosphamide, intravenous immunoglobulin G [IVIG])	Hospitalize and assess as above Pulmonary and Infectious disease referral Consider bronchoscopy, lung biopsy

Skin Adverse Events			
CTCAE Grade	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Grade 1/2 G1: Skin rash with or without symptoms; <10% body surface area (BSA) G2: rash covers 10-30% BSA	No delay or missed dose	Avoid skin irritants and sun exposure Symptomatic therapy (e.g. antihistamines, topical steroids and emollients) Persists >1-2 weeks, consider 0.5-1.0 mg/kg/ day methylprednisolone IV or oral equivalent	Physical exam, exclude other causes (eg viral infections, concomitant medication)
Grade 3/4 G3: rash covers >30% BSA or G2 with substantial symptoms G4: skin sloughing >30% BSA with associated symptoms or life-threatening consequences	Delay or miss dose or discontinue FPT155 permanently Reinitiate upon recovery to ≤Grade 1	Symptomatic therapy (e.g. antihistamines, topical steroids and emollients) 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent	Refer to dermatologist Consider skin biopsy

Endocrinopathy

Patients with unexplained symptoms such as fatigue, myalgias, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free thyroxine (free T4) levels should be obtained to determine if thyroid abnormalities are present. If a subject has thyroid dysfunction and concomitant symptoms (ie, fatigue), the subject should be monitored more frequently and be treated as per standard medical practice. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented.

Specific guidance for management of suspected hypophysitis is provided below.

Symptoms	**FPT155 Dosing**	**Management Escalation Pathway**	**Assessment and Investigations**
Vague symptoms (eg, mild fatigue, anorexia), no headache or Asymptomatic	No delay or missed dose	Perform pituitary axis assessment* to confirm diagnosis	Initiate hormone replacement therapy as necessary after consultation with endocrinologist
Moderate symptoms, ie, headache but no visual disturbance or Fatigue/mood alteration but haemodynamically stable, no electrolyte disturbance	Delay or miss dose Reinitiate upon recovery to baseline	Perform pituitary axis assessment* to confirm diagnosis Oral prednisolone 0.5-1 mg/kg/day (Taper over at least 1 month) If no improvement in 48h, treat as severe (see below)	MRI (pituitary protocol), exclude brain metastases Consider formal visual field assessment Refer to endocrinologist
Severe mass effects (ie, severe headache, any visual disturbance) or severe hypoadrenalism (ie, hypotension, severe electrolyte imbalance)	Delay or miss dose or permanently discontinue FPT155	Perform pituitary axis assessment* to confirm diagnosis Initiate IV methylprednisolone 1 mg/kg (Taper over at least 1 month) Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and nonsteroidal anti-inflammatory drugs [NSAIDs])	MRI (pituitary protocol), exclude brain metastases Consider formal visual field assessment Refer to endocrinologist

*Pituitary Axis assessment: 9 am serum cortisol (or random if unwell and treatment cannot be delayed), adrenocorticotropic hormone (ACTH), TSH/free T4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol if premenopausal, testosterone in men, insulin-like growth factor-1 (IGF-1), prolactin

APPENDIX 9: MANAGEMENT OF TOXICITIES FROM IMMUNOTHERAPY: ESMO CLINICAL PRACTICE GUIDELINES FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP

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CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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General aspects of immune checkpoints blockade

Incidence and epidemiology

Immunotherapy with monoclonal antibodies (MoAbs) targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its ligand PD-L1 has become standard of care for an increasing number of indications (Table 1). Therefore, an increasing number of patients will be exposed to these drugs with a chance of developing toxicities from these treatments. Depending on the immune checkpoint that is targeted, the incidence of toxicity varies. Toxicities from immune checkpoint inhibitors (ICPis) can be divided into infusion reactions and immune-related adverse events (irAEs) or adverse events of special interest (AEoSI). The latter will be the subject of these Clinical Practice Guidelines. Any organ or tissue can be involved, although some irAEs occur much more commonly than others. The most frequently occurring irAEs affect skin, colon, endocrine organs, liver and lungs. Others are very infrequent, but may be very serious, even lethal, such as neurological disorders and myocarditis.

Ipilimumab-associated immune-related toxicities

irAEs from ipilimumab, anti-CTLA4, at a dose of 3 mg/kg, have been documented to occur in 60%–85% of patients [1, 2], mostly grades 1 and 2, but between 10% and 27% of patients develop grade 3 to 4 toxicities, and 2.1% ipilimumab-related deaths have been reported in the first phase III trial [1]. The onset of these toxicities varies but usually starts within the first 8 to 12 weeks of initiation of treatment [an example of onset of adverse events (AEs) upon ipilimumab treatment is depicted in Figure 1], with skin toxicities often being the first to develop. These toxicities are dose-dependent as no grade 3 to 4 AEs were observed at a dose of 0.3 mg/kg ipilimumab, whereas these toxicities increased to 30% with a dose of 10 mg/kg [3]. In the adjuvant setting with ipilimumab 10 mg/kg followed by a maintenance dose, the recorded grade 3 to 4 irAE rate was 41.6%, and the grade 5 irAE rate 1.1% [4].

PD-1/PD-L1 blockade immune-related toxicities

The most frequently reported AE with anti-PD-1/PD-L1 is fatigue. Incidence of fatigue, of which the pathogenesis is poorly understood, across single drug studies, is 16%-37% for anti-PD-1 and 12%-24% for anti-PD-L1 [5]. Only in a minority of patients fatigue can be attributed to hypothyroidism. High-grade toxicities from anti-PD-1 (either nivolumab or pembrolizumab) are less common than for the CTLA4 blocking agent ipilimumab. For nivolumab, any treatment-related AE was documented in 74%–85% of patients, with 12%–20% being grade 3 and 4 [2, 6, 7] for metastatic melanoma patients, 58% and 7%, respectively, for advanced cisplatin refractory squamous non-small-cell lung cancer (NSCLC) [8], 69% and 10%, respectively, for metastatic cisplatin refractory non-squamous NSCLC [9] and 79% and

Table 1. Approved indications for ICPis

Drug	Indications	EMA/FDA approval
Ipilimumab	Metastatic melanoma	EMA + FDA
	Adjuvant therapy stage III melanoma	FDA
Nivolumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC	EMA + FDA
	2nd line metastatic RCC	EMA + FDA
	Classical Hodgkin's disease[a]	EMA + FDA
	Recurrent or metastatic SCCHN[b]	EMA + FDA
	Locally advanced or metastatic UCC[c]	EMA + FDA
Pembrolizumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC (PD-L1 $\geq$ 1%)	EMA + FDA
	1st line metastatic NSCLC (PD-L1 $\geq$ 50%)	EMA + FDA
	1st line metastatic NSCLC in combination with pemetrexed + carboplatin	FDA
	Classical Hodgkin's disease	EMA[a] + FDA[d]
	Locally advanced or metastatic UCC[c]	FDA
	MSI-H or MMR deficient metastatic malignancies[e]	FDA
Atezolizumab	Locally advanced or metastatic UCC[c]	FDA
	2nd line metastatic NSCLC	FDA
Avelumab	Locally advanced or metastatic UCC[c]	FDA
	Metastatic Merkel cell carcinoma	FDA
Durvalumab	Locally advanced or metastatic UCC[c]	FDA
Ipilimumab + nivolumab	Metastatic melanoma	EMA + FDA

[a]For the treatment of patients with cHL who have relapsed or progressed after auto-HSCT and post-transplantation brentuximab vedotin. [b]For the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy. [c]For patients with locally advanced or metastatic UCC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. [d]For the treatment of adult and pediatric patients with cHL who are refractory or have relapsed after 3 or more lines of therapy. [e]For adult and paediatric patients with unresectable or metastatic, MSI-H or dMMR that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Auto-HSCT, autologous hematopoietic stem cell transplantation; cHL, classic Hodgkin's lymphoma; CRC, colorectal cancer; dMMR, deficient MMR; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICPi, immune checkpoint inhibitor; MMR, DNA mismatch repair; MSI-H; microsatellite instability-high; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UCC, urothelial carcinoma.

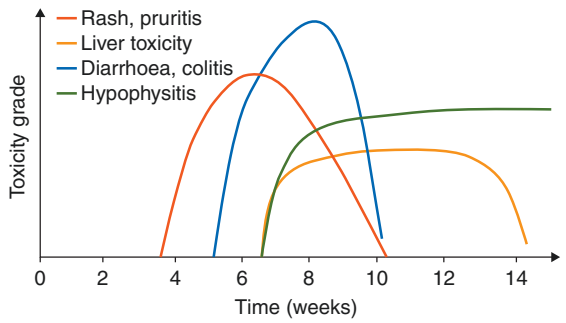

Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.
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19%, respectively, for tyrosine kinase inhibitor refractory metastatic renal cell carcinoma [10].

For pembrolizumab, the Keynote-002 study, comparing pembrolizumab at doses of 2 and 10 mg/kg to chemotherapy in ipilimumab pre-treated metastatic melanoma, showed grade 1 to 2 irAEs in 57%–60% and grade 3 to 4 toxicity in 14% of patients [11]. In the Keynote-006 study comparing pembrolizumab, given at 10 mg/kg either every 3 or 2 weeks, to ipilimumab, treatment-related toxicity was observed in 73%–80% of patients, with 10%–13.5% having grade 3 or higher AEs [12]. In a similar design to the Keynote-002, the Keynote-010 study in cisplatin refractory NSCLC patients compared pembrolizumab (2 mg/kg) and pembrolizumab (10 mg/kg) with docetaxel. The reported treatment-related AEs for the pembrolizumab-treated groups were 63% and 66% for any AE, and 13% and 16% for grade 3 to 4 toxicities, respectively [13]. In the Keynote-024 study pembrolizumab given at 200 mg flat dose every 3 weeks was compared with cisplatin-

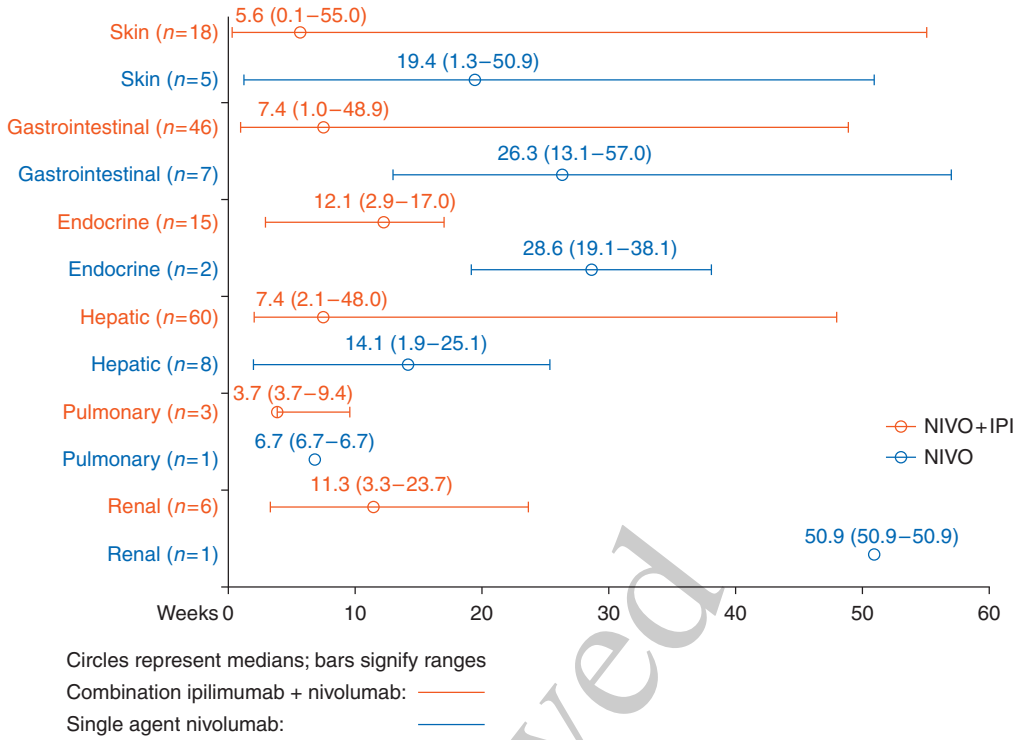

Figure 2. Time to onset of grade 3–4 treatment-related select AEs.
AE, adverse event; IPI, ipilimumab; NIVO, nivolumab.
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based chemotherapy as first-line treatment in metastatic NSCLC patients (tumour PD-L1 expression $\geq 50\%$). Treatment-related toxicity was reported in 73.4% (any AE) and 26.6% of patients with a grade 3 or higher AE [14].

Combination of CTLA4 and PD-1/PD-L1 blockade immune-related toxicities

Combination immunotherapy has only been approved for patients with metastatic melanoma. Treatment-related AEs were observed in 95% of patients. In 55% of patients these AEs were of grade 3 or higher [2]. The onset of grade 3 to 4 toxicities for either monotherapy with nivolumab or combination immunotherapy differs, as irAEs not only may develop earlier in combination therapy but also may start over a prolonged period of time (Figure 2).

General aspects of irAEs

In general, irAEs occur quite early, mostly within weeks to 3 months after initiation of immune checkpoint blockers. However, the first onset of irAEs has been documented as long as 1 year after discontinuation of treatment.

The role of tissue biopsy in the diagnosis of immune-therapy related toxicity is not established. Some recommendations suggest tissue biopsy in higher grade (3 and 4) toxicity [skin, gastrointestinal (GI), liver, kidney, lung] where there is diagnostic doubt about the aetiology of the complication and management would be altered by the outcome of the biopsy procedure [15]. In general, when biopsy is carried out in such circumstances, the reporting pathologist must be apprised of the specific reasons for the biopsy procedure.

Patient selection and baseline assessments

Before starting treatment, patients should be assessed in terms of susceptibility to develop irAEs. This includes a work-up consisting of patient history (and family history), general physical condition, autoimmune diseases, baseline laboratory tests and radiological exams (Supplementary Table S1, available at *Annals of Oncology* online) [mostly computed tomography (CT) scans of the chest, abdomen/pelvis and often brain magnetic resonance imaging (MRI)]. Patients with a history of autoimmune disease, or who are being actively treated for an autoimmune disease, are at risk for worsening of their autoimmune disease while on immune checkpoint blockade [16]. Similarly, patients that have had irAEs on ipilimumab are at risk of developing irAEs following anti-PD-1 treatment and vice versa [16, 17]. Results from these retrospective series showed a higher rate of grade 3 to 4 toxicity in patients treated with ipilimumab following anti-PD-1 (up to 35%) and patients with grade 3 to 4 toxicity on ipilimumab followed by anti-PD-1 developed grade 3 to 4 irAEs in $> 20\%$ of cases. The time between last dose of first drug and initiation of the second drug, however, may be important, considering the long half-lives of these MoAbs.

Patients should be informed of the potential AEs of immunotherapy before treatment initiation. In all cases, patients should report directly to the treating physician or team (nurse, nurse

practitioner, physician). Once irAEs have developed, prompt work-up is required and action should be taken to prevent further aggravation of AEs, In many cases, especially the most severe, immunotherapy should be discontinued and immunosuppressive or immune modulating drugs including high-dose corticosteroids, and sometimes tumour necrosis factor alpha (TNFα) antagonists, mycophenolate or tacrolimus, are needed to overcome these toxicities, followed by careful tapering of immunosuppression. Long-term (> 6 weeks) treatment with immunosuppressive drugs or use of infliximab increases the chance of opportunistic infections; therefore, pneumocystis prophylaxis should be considered according to local guidelines. Importantly, so far there is no evidence that the clinical outcome of patients on ICPis is affected by the use of immunosuppressive agents for the management of immune-related toxicities [7, 18].

Immune-related skin toxicity

Incidence

Skin AEs are among the most frequent AEs observed by patients treated with MoAbs inhibiting either immune checkpoints CTLA4 (ipilimumab in 43%–45% of the patients) or PD-1 (nivolumab and pembrolizumab in ∼34%) [1, 3, 19, 20] and usually develop early in the course of treatment (within the first few weeks after initiation).

However, serious skin AEs are rare and do not usually require dose reductions or treatment discontinuation.

One immune-related skin AE, vitiligo, seems to be associated with good clinical responses to anti-PD-1 MoAbs in patients treated for melanoma [21].

The most frequent skin AEs are rash, pruritus and vitiligo, but the latter is seen mostly in patients treated for melanoma [20]. Rash is reported in ∼24% of the patients treated with ipilimumab, in ∼15% of those receiving anti-PD-1 MoAbs and in 40% with the combination of ipilimumab and nivolumab. However, grade 3 or 4 rashes are rare, with an incidence of < 3% with monotherapy ipilimumab or anti-PD-1 and < 5% with the combination [2, 22]. Pruritus is reported in around 25%–35% of the cases with ipilimumab, 13%–20% with anti-PD-1 and 33% with the combination, but reaches a grade 3 and 4 in < 2.5% [22]. Vitiligo is reported in about 8% of patients with melanoma treated with anti-PD-1 MoAbs [20] or with the combination of checkpoint inhibitors, but is more rarely reported with ipilimumab alone. In a small prospective study, vitiligo was found in up to 25% of patients treated with pembrolizumab [21]. It is likely that the incidence is underreported in clinical trials, due to the fact that patients are not routinely seen and systematically subjected to a full-body skin exam by a dermatologist. In this study, the occurrence of vitiligo was significantly associated with the clinical response to the drug. Development of vitiligo is predominantly observed in melanoma patients treated with ICPis but not in NSCLC or renal cancer. More rarely, other skin AEs have been reported with checkpoint inhibitors: alopecia areata, stomatitis, xerosis cutis and photosensitivity. Exacerbation of psoriasis has also been anecdotally reported with these drugs, as well as psoriasiform or lichenoid skin reactions in patients without any history of such skin disease [19, 23].

Histopathologically, skin reactions may be categorised into four broad groups [24]:

- Inflammatory skin disorders, which comprise a range of changes reflecting acute, subacute or chronic inflammation of various patterns, associated with variable epidermal changes, including psoriasiform or lichenoid reactions. A lichenoid interface chronic dermatitis is a common finding [25, 26];
- Immunobullous skin lesions akin to dermatitis herpetiformis or bullous pemphigoid;
- Keratinocyte alteration—Grover's disease [27]/acantholytic dyskeratosis;
- Immune-reaction mediated by alteration of melanocytes (regression of nevi, prurigo nodularis, tumoural melanosis and vitiligo).

Diagnosis and pathology/molecular biology

When a patient treated with a checkpoint inhibitor presents with a skin AE, the first requirement is ruling out any other aetiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease. Next, the severity of the skin AE needs to be evaluated by a careful and thorough physical examination of the skin including the mucosal areas, an appreciation of the general patient status (fever, enlarged lymph nodes etc.), and if needed, a biological checkup including a blood cell count, liver and kidney tests. This will help to eliminate the possibility of a dermatological emergency such as drug rash with eosinophilia and systemic symptoms (DRESS), acute febrile neutrophilic dermatosis (Sweet syndrome), Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN). In such life-threatening cases (fatal cases have already been described), the treatment with checkpoint inhibitor(s) should be permanently discontinued, the patient should be hospitalised, and symptomatic treatment should be initiated immediately by a dermatologist or at a specialised dermatology unit.

To gauge the severity of the skin AE, the Common Terminology Criteria for Adverse Events (CTCAE) classification is usually used.

Concerning a maculopapular rash, the most frequent event with checkpoint inhibitors, the fourth version of the CTCAE classification proposes:

- Grade 1: macules/papules covering < 10% the body surface area (BSA) with or without symptoms (e.g. pruritus, burning, tightness);
- Grade 2: macules/papules covering 10%–30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental activities of daily living (ADL);
- Grade 3: macules/papules covering > 30% BSA with or without associated symptoms; limiting selfcare ADL;
- Grade 4: papulopustular rash associated with life-threatening superinfection; Stevens-Johnson syndrome, TEN and bullous dermatitis covering > 30% of BSA and requiring intensive care unit (ICU) admission.

The relation with impairment in instrumental or selfcare ADL seems appropriate to evaluate the severity of the AE as well as its impact on the patient's life. However, the fact that when > 30% BSA is involved, the rash is automatically graded 3, is subject to

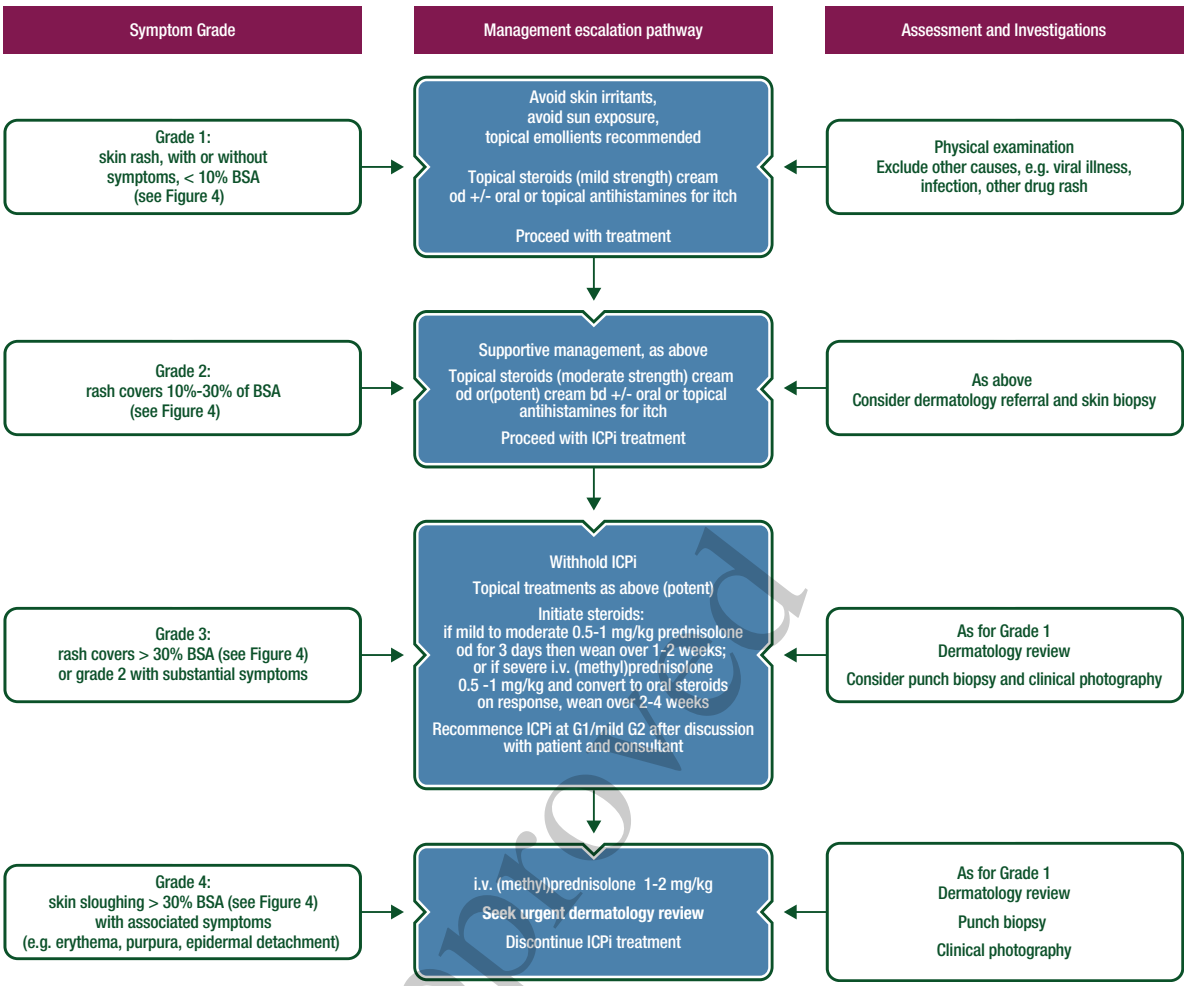

Figure 3. ICPi-related toxicity: management of skin rash/toxicity.
Recognised skin AEs include: (i) most common: erythema, maculopapular and pustulopapular rash; (ii) rare: toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS; (iii) vasculitis may also be present with purpuric rash.
AE, adverse event; bd, twice daily; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; ICPi, immune checkpoint inhibitor; i.v., intravenous; od, once daily.

discussion. Indeed, when the rash is diffuse but light and not associated with any additional symptoms, a grade 2 would seem more appropriate than grade 3.

The fifth version of the CTCAE classification will give a more appropriate classification for skin AEs.

Management of rash

For grade 1 skin AEs such as rash and/or pruritus, treatment with checkpoint inhibitors can be continued (see Figures 3 and 4). Symptoms can be treated with topical emollients, oral antihistamines and/or mild strength topical corticosteroids. In the case of grade 2 skin AEs, treatment with checkpoint inhibitors can be continued but should be checked weekly for improvement. If not resolved, treatment should be interrupted until the skin AE has reverted to grade 1. Symptomatic treatment consists of topical emollients, oral antihistamines and median-to-high strength topical steroids. Grade 3 skin AEs also require immediate interruption of checkpoint inhibition, until these are back to grade 1. Treatment includes topical emollients, oral antihistamines and high strength topical steroids [II, B]. Systemic corticosteroids 0.5–1 mg/kg can be considered, depending on the severity of the symptoms. In the rare event of grade 4 skin toxicity, treatment with checkpoint inhibitors should be interrupted, and patients should be admitted immediately and be placed under supervision of a dermatologist. Treatment consists of intravenous (i.v.) (methyl)prednisolone 1–2 mg/kg with tapering when the toxicity resolves to normal [II, B].

Immune-related endocrinopathies

Thyroid gland disorders

Although thyroid gland disorders have been observed quite frequently in patients treated with immunotherapies such as cytokines interleukin-2 and type I interferons, their incidence has increased

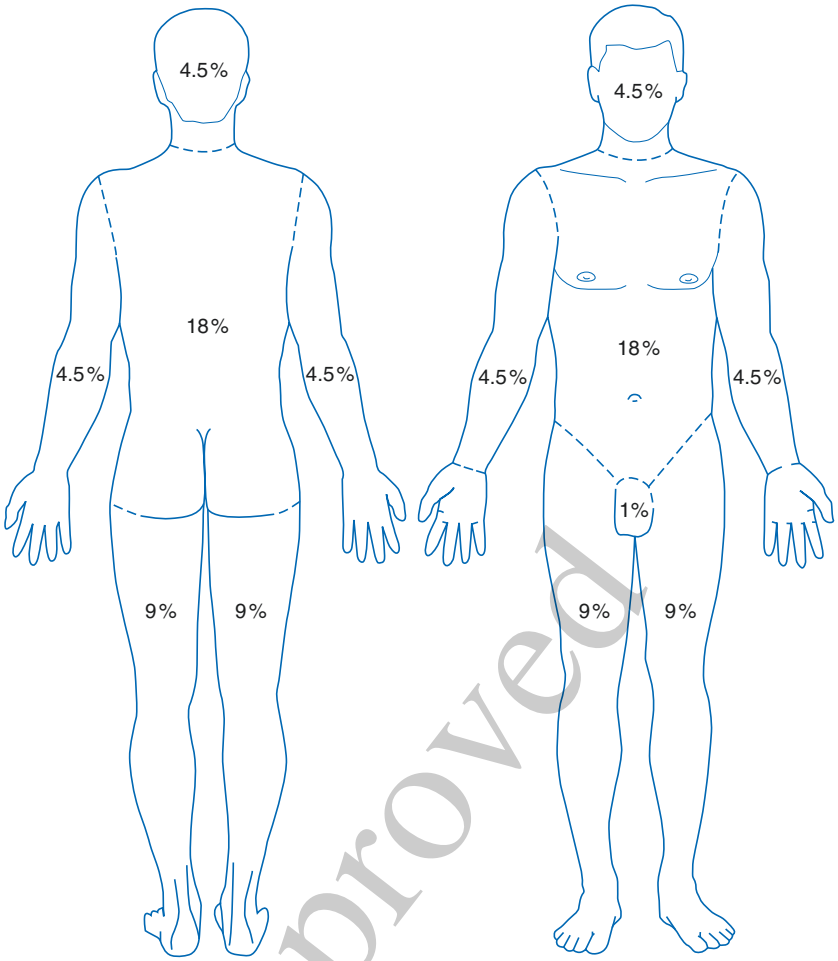

Figure 4. Schematic of body surface area (BSA).

considerably since the introduction of ICPis. Both hyper- and hypothyroidism have been reported, although hypothyroid disorders are more common than hyperthyroidism. The latter is often transient and may precede hypothyroidism. Still, little is known about the pathogenesis of thyroid disorders following ICPis. It is thought to be mediated by T cells and not by B cell autoimmunity. Recently, a cohort of 51 NSCLC patients treated with pembrolizumab in the Keynote-001 study was prospectively followed by thyroid-stimulating hormone (TSH), triiodothyronine and thyroxine (FT3, FT4) and anti-thyroid antibodies (Abs) measurement [28]. The incidence of thyroid dysfunction requiring thyroid hormone replacement was 21% (in 80% of these patients, anti-thyroid Abs were detected), compared with 8% in patients that did not develop thyroid dysfunction. These results suggest that the pathogenesis of autoimmune thyroid disease and thyroid gland dysfunction as irAEs might have a similar pathogenesis.

Thyroid dysfunction is most common upon treatment with anti-PD-1/PD-L1 or combination of anti-CTLA4 and agents blocking the PD-1/PD-L1 axis. With ipilimumab (3 mg/kg), the incidence was reported to be between 1% and 5% [1, 2], but higher incidence (up to 10%) has been observed with the higher doses of ipilimumab (10 mg/kg) [4].

With anti-PD-1 (either pembrolizumab or nivolumab) or anti-PD-L1 (atezolizumab) therapy, the reported thyroid dysfunction rate varies from 5% to 10% (irrespective of tumour type) [6, 10, 12]. With combination immunotherapy (ipilimumab 3 mg/kg plus nivolumab 1 mg/kg), the frequency of thyroid disorders increases to 20% [2]. These events are rarely higher than grade 2. In most cases, thyroid dysfunction is found by routine blood tests (TSH and FT4); they should be carried out before every infusion or at least once a month (in the case of 2-weekly infusions).

Management

Even with subclinical hypothyroidism, substitution with thyroid hormone should be considered in the case of fatigue or other complaints that could be attributed to hypothyroidism [IV–V, B]. In symptomatic patients, especially in the case of hyperthyroidism, treatment with beta-blockers should be started (propranolol or atenolol) [IV–V, B]. Rarely, carbimazole or steroids are required. In those cases, treatment with ICPis should be interrupted until recovery from symptoms. Hormone replacement therapy (HRT) is usually long lasting (see Figure 5).

Hypophysitis

Before introduction of anti-CTLA4 therapy, hypophysitis, an inflammation of the anterior lobe of the pituitary gland, was extremely rare. Now, incidence rates of hypophysitis have been

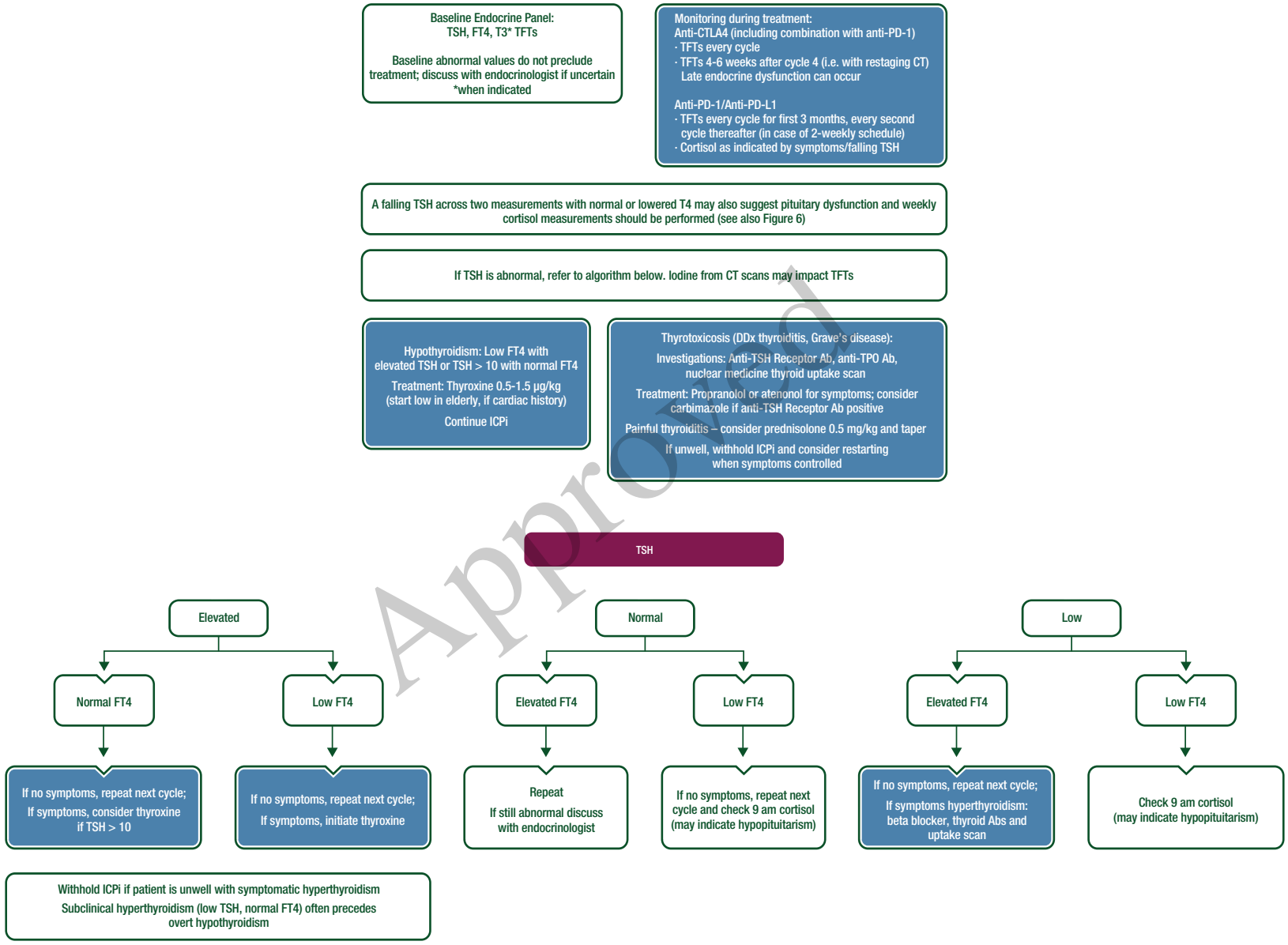

Figure 5. ICPi monitoring and management: thyroid function.
Ab, antibody; CT, computed tomography; CTLA4, cytotoxic T-lymphocyte associated antigen 4; DDx, differential diagnosis; FT4, free thyroxine; ICPi, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; T3, triiodothyronine; T4, thyroxine; TFTs, thyroid function tests; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

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reported for ipilimumab 3 mg/kg, ipilimumab 10 mg/kg and the combination of ipilimumab and nivolumab in 1%, 16% and 8%, respectively [1, 2, 4].

Hypophysitis is very rare in patients treated with anti-PD-1 and anti-PD-L1 [29].

The aetiology of anti-CTLA4-induced hypophysitis remains unresolved. Recently, in a murine model, low-level ectopic RNA and protein expression of CTLA4 on thyrotropin and prolactin secreting cells of the pituitary gland [30] was demonstrated. So far, no explanation for this expression was found. Anti-CTLA4 treatment, however, led to mononuclear cell infiltration in the pituitary gland, anti-pituitary antibodies and activation of the complement cascade in these animals, causing inflammation of the gland, similar to what has been observed in full-blown hypophysitis in patients. Whether this ectopic CTLA4 expression occurs in human is unknown.

Patients may present with different complaints. Headache and visual disturbances require immediate evaluation and differentiation between cerebral metastasis, leptomeningeal disease, cerebrovascular disease and hypophysitis. On brain MRI, a swollen or enlarged pituitary gland may be visible. Frequently, simultaneous low blood levels of TSH, adrenocorticotropic hormone and/or follicle-stimulating hormone/luteinizing hormone (FSH/LH) point towards hypophysitis as the most likely diagnosis. Patients can present with hypothyroidism and/or hypocortisolism and with complaints relating to low testosterone levels.

Management

Once the diagnosis is confirmed, treatment with ICPis should be interrupted in any grade 2 or higher hypophysitis and treatment consisting of HRT should be instigated immediately [V, B]. In the case of headaches and other neurological problems, high-dose steroids should be given; however, high-dose steroids appear not to counteract the hormonal deficiency resulting from anti-CTLA4 treatment. In most cases, the immune checkpoint inhibition can be continued. Long-term HRT is required in most patients (see Figure 6).

Type 1 diabetes mellitus

De novo diabetes induced by treatment with ICPis occurs at low frequency (<1%). Diabetes mellitus (DM) appears to be more common with PD-1 and PD-L1 blockade (or combination immunotherapy) than with ipilimumab [31]. The PD-1 pathway plays a role in autoimmune DM as blockade of the PD-1/PD-L1 axis triggers the development of type 1 DM mediated by specific CD8 T cells in murine models. However, incidence of type 1 DM may rise as a consequence of treatment of larger patient populations with anti-PD-1 or anti-PD-L1 drugs.

It is recommended that blood glucose levels are regularly monitored in patients treated with ICPis in order to detect the emergence of DM. This could be either type 1 or type 2 DM. Even patients with type 2 DM may develop ketoacidosis, an infrequent but life-threatening event that should be treated according to standard local guidelines [I, A]. Whether treatment with high-dose steroids can prevent total loss of beta cells of the islands of Langerhans is unclear. Steroids will most likely negatively influence diabetes control in these patients.

C-peptide and Abs against glutamic acid decarboxylase (GAD) and islet cell (ICA) should be measured to distinguish between type 1 and type 2 DM.

Once the patient has been regulated with insulin substitution, restarting treatment with ICPis may be considered.

Immune-related hepatotoxicity

Incidence

Hepatitis occurs in 5%–10% (of which 1%–2% is grade 3) of patients during therapy with ipilimumab, nivolumab and pembrolizumab at the approved doses as single agents and in ~25%–30% (of which ~15% is grade 3) of those treated with the combination of ipilimumab 3 mg/kg and nivolumab 1 mg/kg [2, 12].

Diagnosis

All patients undergoing ICPi therapy should be assessed for signs and symptoms of hepatitis with serum transaminases and bilirubin measured before every cycle of treatment. Hepatitis is usually asymptomatic and detected on such routine blood monitoring. If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol) and infectious causes, particularly viral hepatitis, should be ruled out. However, initiation of therapy, if needed, should not be delayed while awaiting serological results if there is no other apparent cause.

Liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatitic reactions [15]. Lobular hepatitis indistinguishable from autoimmune hepatitis is most commonly reported [32, 33]; most cases are panlobular but inflammation may be confined to zone 3. Additional sinusoidal histiocytosis and central vein endothelitis may help identify ipilimumab-associated inflammation. Rare cases show portal tract inflammation and cholangitis or changes indistinguishable from non-alcoholic steatohepatitis (NASH).

Management

In the event of moderate (grade 2) transaminase or total bilirubin elevation, checkpoint inhibitor therapy should be withheld and transaminases and bilirubin measured twice weekly. Persistent grade 2 elevation lasting longer than 1–2 weeks, after having ruled out other causes, should be treated with corticosteroids at a dose of 1 mg/kg/day (methyl)prednisolone or equivalent. Upon improvement, checkpoint inhibitor therapy may be resumed after corticosteroid tapering. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 mg/kg/day (methyl)prednisolone or equivalent and checkpoint inhibitor therapy permanently discontinued [IV–V, B]. For grade 3 or 4 transaminase or total bilirubin elevation, checkpoint inhibitor therapy should be permanently discontinued, and corticosteroids started at 1–2 mg/kg/day (methyl)prednisolone or equivalent. If there is no response to corticosteroids within 2–3 days, mycophenolate mofetil should be added at 1000 mg twice daily [IV–V, B] [34]. Consultation with a hepatologist and consideration of liver biopsy (see above) is recommended in steroid and mycophenolate-refractory cases

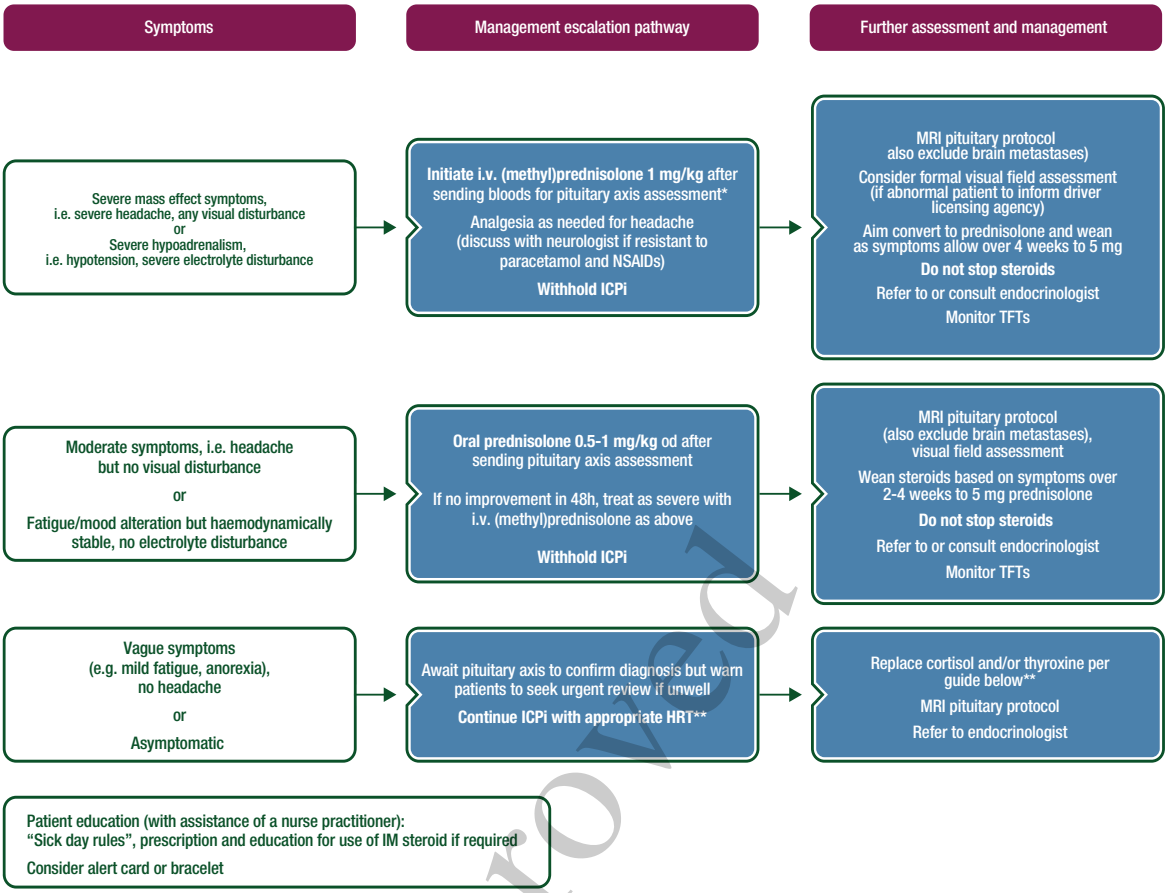

Figure 6. ICPi-related toxicity: management of hypophysitis.
*Pituitary Axis bloods: 9 am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/FT4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF-1, prolactin. Mineralocorticoids replacement is rarely necessary in hypopituitarism.
**Initial replacement advice for cortisol and thyroid hormones:
- If 9 am cortisol < 250 or random cortisol < 150 and vague symptoms:
  - Replace with hydrocortisone 20/10/10 mg
  - If TFTs normal, 1–2 weekly monitoring initially (always replace cortisol for 1 week prior to thyroxine initiation)
- If falling TSH +/- low FT4
  - Consider need for thyroxine replacement (guide is 0.5-1.5 μg/kg) based on symptoms +/− check 9 am weekly cortisol
  - See Thyroid Guidelines for further information regarding interpretation of an abnormal TSH/T4

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; HRT, hormone replacement therapy; ICPi, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; IM, intramuscular; i.v. intravenous; LH, luteinizing hormone; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; od, once daily; TSH, thyroid-stimulating hormone; TFTs, thyroid function tests.

[IV–V, B]. Third-line immunosuppressive therapy is not well defined but the successful use of anti-thymocyte globulin (ATG) has been reported in a case of ipilimumab-induced hepatitis refractory to steroids and mycophenolate. Another third-line immunosuppressive therapy option is tacrolimus. Infliximab is not recommended for the treatment of immune-related hepatitis (see Figure 7).

Hepatitis usually resolves within 4–6 weeks with appropriate treatment but in the event that it does not resolve, other contributory causes should be reconsidered and the initial diagnostic work repeated as necessary, particularly bearing in mind the concomitant administration of other hepatotoxic drugs (including herbal medications and those purchased over the counter) and cytomegalovirus (CMV) reactivation.

Gastrointestinal toxicity

GI toxicity from cancer immunotherapy is well described for anti-CTLA4 Abs. It is less well described for anti-PD-1 and anti-PDL-1 Abs as well as for combined anti-CTLA4 and anti-PD-1 Abs.

Gastrointestinal toxicity of anti-CTLA4 antibodies

Incidence. Diarrhoea occurs in 27%–54% of cancer patients treated with anti-CTLA4 Abs [35]. In most series, approximately one-third of patients have diarrhoea, while the frequency of colitis ranges from 8% to 22% [35]. GI toxicity is one of the most frequent and is the most severe (grade 3 or higher) of irAEs associated with anti-CTLA4 [18]. It is usually the first irAE

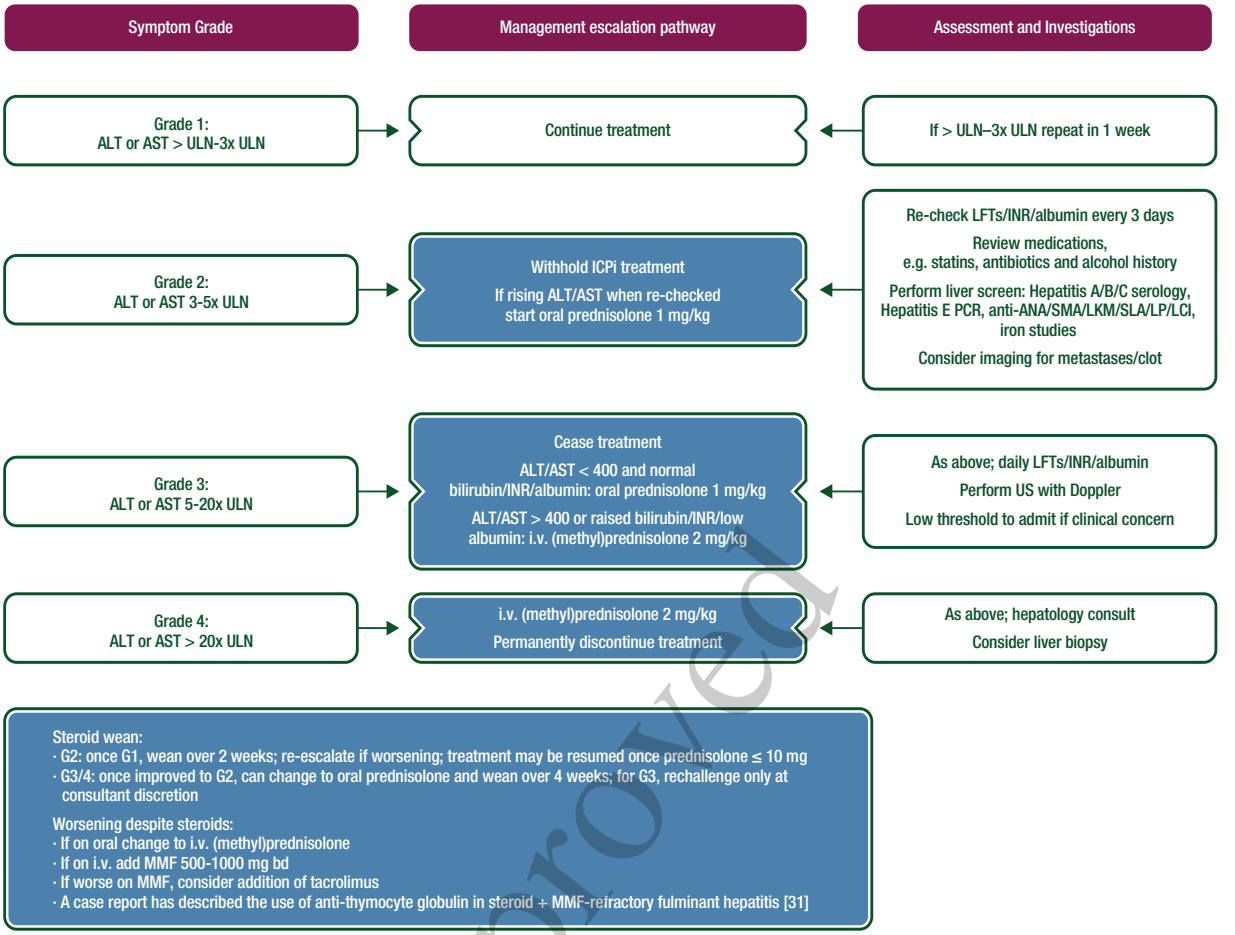

Figure 7. ICPi-related toxicity: management of hepatitis.
ALT, alanine transaminase; ANA, antinuclear antibodies; AST, aspartate transaminase; bd, twice daily; ICPi, immune checkpoint inhibitor; INR, international normalised ratio of prothrombin time; i.v. intravenous; LCI, lung clearance index; LFTs, liver function tests; LKM, liver kidney microsomal; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; SLA/LP, soluble liver antigen/liver-pancreas antibody; SMA, smooth muscle autoantibody; ULN, upper limit of normal; US, ultrasound.

leading to anti-CTLA4 discontinuation [18]. Colon perforation occurred in 1%–1.5% of melanoma patients receiving ipilimumab [35–37]; it may reach 6.6% of patients with renal cell carcinoma [36], and 1.1% of patients die of complications related to ipilimumab-induced enterocolitis [4].

In a recent series, non-steroidal anti-inflammatory drug (NSAID) use was associated with an increased risk of anti-CTLA4-induced enterocolitis [38]. Very few data are available on the risk of immune-related colitis in patients with Crohn's disease (CD) and ulcerative colitis (UC). Two out of six patients with CD or UC had ipilimumab-induced colitis or a relapse of UC or CD [39].

Diagnosis. Onset of GI symptoms may occur at any time during 1-10 infusions of anti-CTLA4 [36]. Enterocolitis may even occur several months after the last dose of ipilimumab [40]. The half-life of ipilimumab is 2 weeks; however, the biological effect may persist long after drug clearance.

The most common symptom of anti-CTLA4-induced enterocolitis is diarrhoea [1–4]. In a recent series, 92% of patients with anti-CTLA4-induced enterocolitis had diarrhoea [38]. Other presenting symptoms are abdominal pain, hematochezia, weight loss, fever and vomiting [38]. Mouth ulcers, anal lesions (fistulas, abscesses, fissures) and extra-intestinal manifestations (such as arthralgia, endocrine disorders, skin disorders, hepatitis, nephritis, pericarditis and pancreatitis) may be associated with anti-CTLA4-induced enterocolitis [38].

The main biological abnormalities observed in patients with anti-CTLA4-induced enterocolitis are anaemia, increased serum C-reactive protein and low serum albumin levels [38]. Faecal level of calprotectin has been found to be elevated in patients with ipilimumab-induced enterocolitis in one study [38] but failed to correlate with GI toxicity in another series [41]. Abs against the enteric flora and antineutrophil cytoplasmic Abs are found in the serum of a minority of patients with ipilimumab-induced enterocolitis [41].

The main differential diagnoses of anti-CTLA4 enterocolitis are GI infections and tumour-related symptoms. Stool analyses for bacterial enteropathogens and *Clostridium difficile* toxin should be carried out in every patient with significant diarrhoea treated with anti-CTLA4. In addition, GI metastases are not uncommon in patients with disseminated melanoma and are not

unknown in lung cancer; these should, therefore, be eliminated. Anti-CTLA4-induced enterocolitis should be confirmed by flexible sigmoidoscopy or colonoscopy with biopsies. Endoscopic lesions of anti-CTLA4 colitis are erythema/loss of vascular pattern, erosions and ulcerations. The sigmoid colon and the rectum are involved in most cases; therefore, a flexible sigmoidoscopy is generally sufficient to make the diagnosis of anti-CTLA4-induced enterocolitis [38]. However, endoscopic lesions of the colon are often extensive and may extend proximal to the sigmoid colon in two thirds of cases. Patchy discontinuous endoscopic lesions are observed in half of the patients [38]. The histological picture generally differs from that observed in inflammatory bowel disease (IBD). In most cases, it is that of an acute colitis (infiltration with neutrophils, eosinophils), either diffuse or focal with patchy crypt abscesses. In some cases, features of chronic IBD such as granulomas, basal plasmocytosis and crypt abnormalities (atrophy, distortion, branching, budding) have been reported [38].

Upper GI symptoms (dysphagia and epigastric pain) and endoscopic lesions (oesophageal ulcerations, gastritis, duodenitis) have been reported [35, 38]. About half of the patients with anti-CTLA4-induced enterocolitis have chronic, mild, patchy inflammation of the stomach and the duodenum (crypt distortion, focal and heterogeneous villus shortening, increased eosinophils and mononuclear inflammatory cells in the lamina propria) [38].

Staging and risk assessment. Assessment of severity relies upon the National Cancer Institute's CTCAE, version 4. Severe diarrhoea refers to grade 3 or 4 diarrhoea but also to patients with grade 1 or 2 diarrhoea with dehydration, fever, tachycardia or haematochezia. Flexible sigmoidoscopy or colonoscopy is recommended in patients with severe diarrhoea or persistent grade 2 diarrhoea.

Management. Two randomised trials have failed to show any benefit from oral administration of budesonide, in an attempt to prevent occurrence of ipilimumab-induced enterocolitis [41, 42]. Patients with diarrhoea on anti-CTLA4 therapy should undergo a workup including complete blood count, serum electrolyte

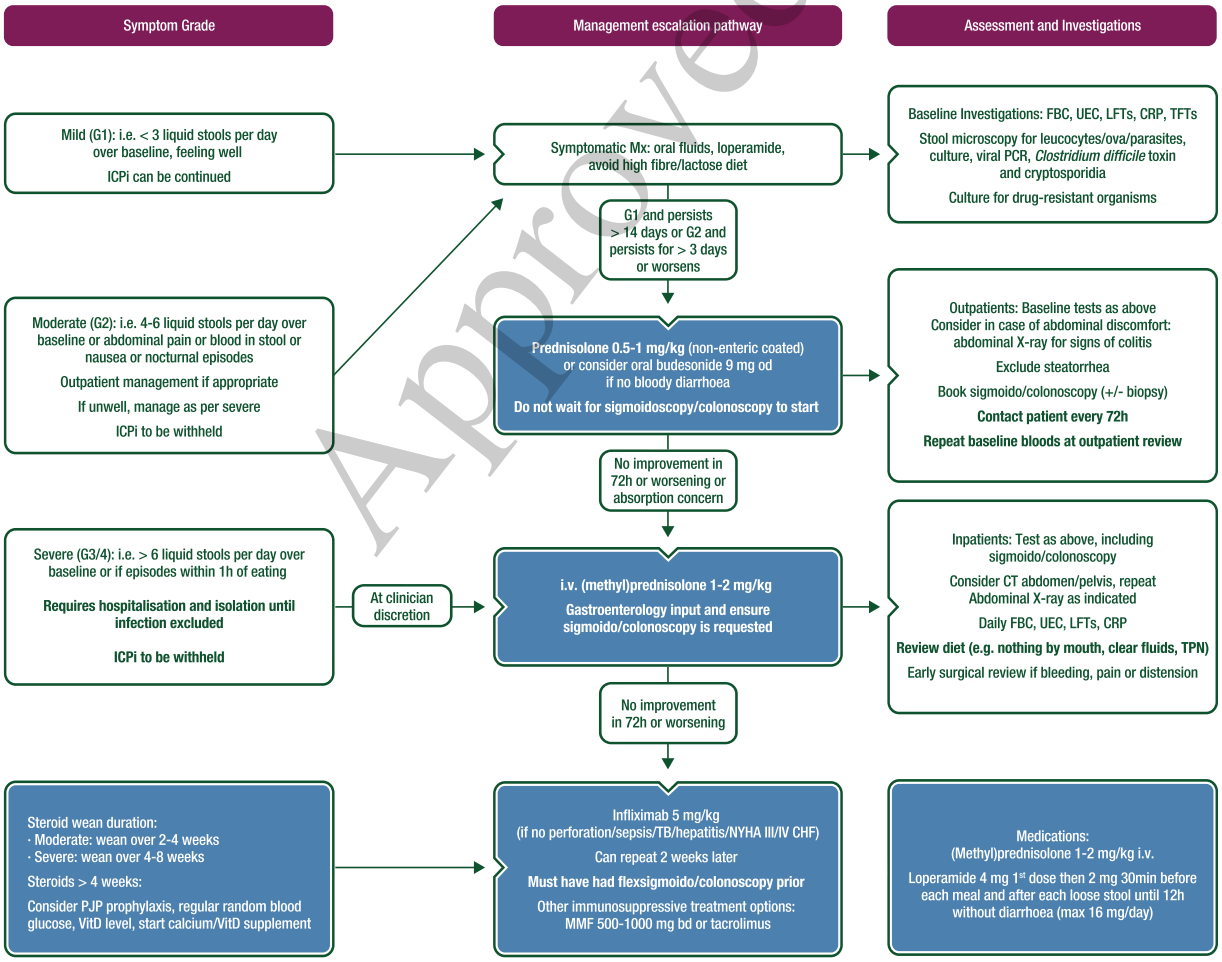

Figure 8. ICPi-related toxicity: management of diarrhoea and colitis.
bd, twice daily; CHF, congestive heart failure; CRP, C-reactive protein; CT, computed tomography; FBC, full blood count; ICPi, immune checkpoint inhibitor; i.v. intravenous; LFTs, liver function tests; MMF, mycophenolate mofetil; Mx, management; NYHA, New York Heart Association; od, once daily; PCR, polymerase chain reaction; PJP, Pneumocystis jiroveci pneumonia; TB, tuberculosis; TFTs, thyroid function tests; TPN, total parenteral nutrition; UEC, urea, electrolytes, creatinine; VitD, vitamin D.

profile, stool analyses for enteropathogens and *Clostridium difficile* toxin (see Figure 8).

Patients with non-severe diarrhoea should be treated with antidiarrhoeals, fluid and electrolyte supplementation, if needed [IV–V, B] [35]. Anti-CTLA4 therapy can be continued. Patients with persistent grade 2 diarrhoea or severe diarrhoea (grade 3/4 diarrhoea, or grade 1/2 diarrhoea with alarm symptoms, as detailed above) should discontinue anti-CTLA4 therapy and receive systemic corticosteroids (1–2 mg/kg per day, i.v.) [IV–V, B]. Patients who have a response to i.v. corticosteroids within 3–5 days should be switched to the oral form and tapered over 8–12 weeks [35]. Patients who do not respond to corticosteroids within 3–5 days should be switched to infliximab, unless it is contraindicated [IV–V, B] (see Figure 8). Overall, one-third to two-thirds of patients either do not respond to high-dose i.v. steroids, or have a relapse requiring an increase in the corticosteroid dosage during the course of steroid tapering. These patients require infliximab and usually have an excellent response. A single dose of infliximab (5mg/kg) is generally sufficient [18, 35, 36, 38]. Some patients may need a second dose of infliximab 2 weeks after the first administration.

Vedolizumab is a MoAb directed towards the integrin $\alpha_4\beta_7$. It inhibits the intestinal homing of T lymphocytes. Vedolizumab is a gut-specific immunosuppressive agent that is approved for UC and CD. A recent case series of seven patients with mild to moderate, steroid-dependent or steroid-refractory ipilimumab-induced enterocolitis has shown that six out of seven patients treated with vedolizumab went into remission; no AEs were reported with vedolizumab. This preliminary study suggests that vedolizumab is an alternative to infliximab [43]. Further studies are needed to confirm the efficacy and safety of vedolizumab in patients with ipilimumab-induced enterocolitis.

Recently, a colitis, possibly due to CMV reactivation, has been reported in a patient with medically refractory anti-CTLA4 colitis [44]. Further studies are needed to determine whether CMV plays a significant role in this setting.

Some patients develop a colonic perforation, with or without intra-abdominal abscess, either initially or during the course of medical treatment. They should have emergency colectomy. We recommend subtotal colectomy with ileostomy and sigmoidostomy because colonic lesions are generally extensive and segmental colonic resection is generally followed by a severe inflammation of the remaining colon in the postoperative phase [38].

Prediction of ipilimumab-related colitis. No routine biomarker has been found to predict ipilimumab-related colitis. Baseline microbiota composition may predict ipilimumab-induced colitis. More specifically, at baseline, an increased presence of bacteria belonging to the *Bacteroidetes* phylum species was found in patients who remained free of colitis after ipilimumab treatment [45]. A recent study has shown that distinct baseline gut microbiota composition is associated with colitis. Most of the baseline colitis-associated phylotypes were related to *Firmicutes* (e.g. relatives of *Faecalibacterium prausnitzii* and *Gemmiger formicilis*), whereas no-colitis related phylotypes were assigned to *Bacteroidetes* [46].

Follow-up and long-term implications. Several studies have found associations between ipilimumab-induced enterocolitis and tumour regression or overall survival (OS) [36, 47]. However, in a dose escalation study, higher serum levels and prolonged administration of anti-CTLA4 Abs resulted in a trend toward a greater incidence of grade 3/4 autoimmune toxicity, but did not seem to increase anticancer response rates [48].

Neither corticosteroids nor infliximab appear to affect response and OS of patients treated with ipilimumab [18, 47].

A study has shown that some patients have endoscopic or histological inflammation of the colon (including chronic inflammation) several months after the onset of enterocolitis [38]. In this study, three out of nine patients had chronic colitis on biopsies [38]. More studies are needed to determine whether the changes in these patients may evolve into chronic IBD.

In a recent study, four out of six patients who had an additional infusion of ipilimumab after going into enterocolitis remission relapsed [38]. Among them, three patients required a new steroid course, including one patient who had a severe steroid-refractory relapse requiring infliximab infusion. Reintroduction of anti-CTLA4 in patients, who had previously experienced enterocolitis, poses a high risk of relapse and should be discussed on an individual basis.

In a recent randomised trial that compared nivolumab followed by ipilimumab, or the reverse sequence, in patients with advanced melanoma, a severe AE with the first agent did not predict toxicity with the second one [49]. This was confirmed by a recent study, which showed that, among 47 patients who had an anti-CTLA4-induced colitis, only one relapsed under anti-PD-1 [49].

Gastrointestinal toxicity of anti-PD-1 antibodies

Very few data are available about GI irAEs associated with anti-PD-1 MoAbs. Diarrhoea and colitis are more frequent with anti-CTLA4 agents than with either nivolumab or pembrolizumab, with grade 3 to 4 AEs occurring in 1%–2% of cases [2, 50]. A case series of 19 patients with GI toxicity after anti-PD-1 Ab administration has been published [51]. The median time from drug initiation to symptom onset was 3 months. The most common symptom was diarrhoea, followed by nausea/vomiting and abdominal pain. Endoscopic findings consisted in normal mucosa or inflammation ranging from mild erythema to severe inflammation (mucosal friability or ulceration). Histological findings included lamina propria expansion, villus blunting, intra-epithelial neutrophils and increased crypt/gland apoptosis. Intra-epithelial lymphocytes were rarely prominent. A recent pathology study based upon eight cases has described two patterns: active colitis with neutrophilic crypt microabscesses and atrophy as well as crypt epithelial cell apoptosis ($n = 5$) or lymphocytic colitis characterised by increased intraepithelial lymphocytes ($n = 3$) [51]. A preliminary report confirmed and extended this description. It depicted four different patterns of GI irAEs induced by anti-PD-1 Abs: acute colitis similar to that induced by anti-CTLA4 Abs, microscopic colitis, upper GI involvement and pseudo-obstruction [52]. In this study, 87.5% of patients responded to corticosteroids.

Gastrointestinal toxicity of combined anti-CTLA4 and anti-PD-1 antibodies

Diarrhoea and colitis, including severe forms, occur earlier (Figure 2) and are more frequent with combined anti-CTLA4 and anti-PD-1 agents than with either ipilimumab [2, 53, 54] or anti-PD-1 [2]. Other GI toxicities may also occur, including

pancreatitis and small bowel enteritis, which may be visible on CT scan. These rare toxicities require discontinuation of ICPi treatment and initiation of immunosuppression treatment. There is a need for a more detailed description of GI irAEs associated with combined anti-CTLA4 anti-PD-1 Abs.

Immune-related pneumonitis

Pneumonitis associated with checkpoint blockade is a toxicity of variable onset and clinical, radiological and pathological appearances, which has been observed with anti-PD-1/PD-L1 MoAbs and, more rarely, with anti-CTLA4 MoAbs. It is more common when anti-PD-1/PD-L1 MoAbs are combined with anti-CTLA4 MoAbs. Several cases of distinct life-threatening respiratory events have been reported under anti-CTLA4 monotherapy. Acute interstitial pneumonitis/diffuse alveolar damage syndrome (DADS) is the most acute, life threatening event [55], but organising inflammatory pneumonia, as well as a sarcoidosis-like pulmonary granulomatosis have been described and may result in difficulties in differential diagnosis with progression of disease [56–58]. Rarely, pneumonitis worsens despite immunosuppression, and may be fatal due to infection or progressive disease.

Using treatment with anti-PD-1/PD-L1 MoAbs, respiratory events like cough and dyspnoea have been documented in up to 20%–40% of patients, with grade 3 to 4 cough in 2%–9% and grade 3 to 4 dyspnoea in 1%–2% of patients, respectively [59–61]. Documentation of pneumonitis occurs in 2%–4% of patients, with 1%–2% grade ≥ 3 events, frequency of fatal pneumonitis in 0.2% and discontinuation due to pneumonitis in 0.2%–4% [6, 7, 62–65]. In the absence of any direct comparison, to date there is no compelling evidence that this incidence might significantly differ between anti-PD-1 and anti-PD-L1 compounds [63].

Data documenting pulmonary immune-related toxicities have been progressively reported from retrospective series, from large published prospective trials and subsequent expanded access programs, especially in the treatment of melanoma, NSCLC and renal carcinoma. To date, however, immune-induced pneumonitis remains relatively poorly described.

Whereas pulmonary AEs are most often related to disease progression, particularly in the context of lung cancer or lung metastases, any new respiratory symptom should prompt a dedicated evaluation to formally exclude lung toxicity. All patients presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by CT. Any respiratory symptom or sign must be carefully monitored, since fatal and life-threatening cases of pneumonitis have been reported.

Incidence

The incidence of pneumonitis is higher—possibly 1.5–2 times more frequent, in patients receiving anti-PD-1 therapy compared with ipilimumab monotherapy, as reported across several melanoma trials [12].

The combination of anti-PD-1/PD-L1 MoAbs with CTLA4 inhibition significantly increases the risk of pneumonitis, with up to 3 times more all-grade and grade ≥ 3 events compared with monotherapy reported in a 3-arm randomised melanoma trial [2].

Incidence of pneumonitis was recently reported in a multicentre large retrospective analysis of patients receiving anti-PD-1/PD-L1 monotherapy or in combination with anti-CTLA4, as diagnosed by the treating investigator after exclusion of a tumoural or infectious aetiology [66]. Of 915 patients who received anti-PD-1/PD-L1 MoAbs, pneumonitis developed in 4.6%. Time to onset of pneumonitis ranged from 9 days to 19.2 months, with a median time to onset of 2.8 months, and tended to occur earlier in patients receiving combination therapy (2.7 versus 4.6 months). The incidence of pneumonitis was higher with combination immunotherapy versus monotherapy (10% versus 3%). Incidence was similar in patients with melanoma and NSCLC (5% versus 4%) overall, in monotherapy (3.6 versus 3.3%) and combination therapy (9.6% versus 7%). Of these, 72% were grade 1 to 2, and 86% improved or resolved with drug withholding and immunosuppression. Pneumonitis occurred irrespective of the line of therapy in which immunotherapy was received.

Although it may be observed at any time, pneumonitis tends to occur later than other irAEs, commonly some months after treatment was initiated. The rate of grade 3 to 4 pneumonitis is similar across tumour types and irrespective of dosage; however, there have been more treatment-related deaths due to pneumonitis in patients with NSCLC [13, 67]. Of note, detection, diagnosis and management of such symptoms have largely improved over time, and related mortality has been significantly reduced, making pooled analysis difficult to be interpreted in this context.

Importantly, radiological features of pneumonitis are not pathognomonic, and can include ground glass opacities, a cryptogenic organising pneumonia-like appearance and interstitial pneumonia pattern [55, 66, 68], as well as characteristics of hypersensitivity pneumonitis.

In general, lung biopsy is not required for subsequent patient management. However, if there is radiological or clinical doubt as to the aetiology of pulmonary infiltrates, then biopsy may provide an answer. It may assist in discriminating acute infection, or lepidic or lymphangitic spread of NSCLC, from a variety of inflammatory changes described above. If not apparent clinically, identification of DADS may be useful in terms of treatment and prognostication. Other patterns of lung reaction attributed to immunotherapy are not specific and reflect a range of chronic inflammatory, presumably immune-related processes, giving rise to changes such as non-specific interstitial pneumonitis, sarcoid-like [69] or hypersensitivity pneumonitis-like changes and organising pneumonia pattern of changes. All of these may be seen in other drug toxicities or in non-drug-related scenarios. While transbronchial lung biopsy may secure a diagnosis of infection or malignancy, and perhaps granulomatous disease or organising pneumonia, a surgical lung biopsy using video-assisted thoracoscopic surgery is more likely to secure a specific diagnosis. The decision to proceed with biopsy, and choice of technique, will depend on the location and distribution of disease on imaging, the availability of a thoracic surgical intervention team and any specific risks to the patient. If a biopsy is taken, it is vital that the reporting pathologist is informed about the background to, and reason for, the diagnostic procedure.

Alternatively, depending on the radiological pattern on CT scan, a bronchoscopy with bronchoalveolar lavage will support

the identification of infections, including potential opportunistic or atypical agents, and is recommended in any symptomatic pneumonia.

Management

In the case of documented or high suspicion of immune-related pneumonitis, immunosuppressive treatment should be started immediately. Ideally, an infection should be ruled out by bronchoscopy, especially in the case of grade ≥ 2 pneumonitis, in order to be able to safely introduce the immunosuppressive treatment. If the infectious status cannot be reliably assessed, most algorithms advocate the administration of oral or i.v. broad spectrum antibiotics in parallel to the immunosuppressive treatment in grade ≥ 3 pneumonitis (see Figure 9).

In grade 1 to 2 pneumonitis, treatment consists of oral steroids with prednisone 1 mg/kg daily or equivalent [IV–V, B]. Patients should be clinically assessed every 2–3 days initially and, ideally, also radiologically in grade 2 pneumonitis. Steroids should be tapered over 4–6 weeks after recovery and reintroduction of the checkpoint inhibitor should be delayed until the daily dose of steroids equals 10 mg of oral prednisone per day or less.

In grade 3 to 4 moderate to severe cases, the patient should be hospitalised and treatment should consist of high-dose i.v.

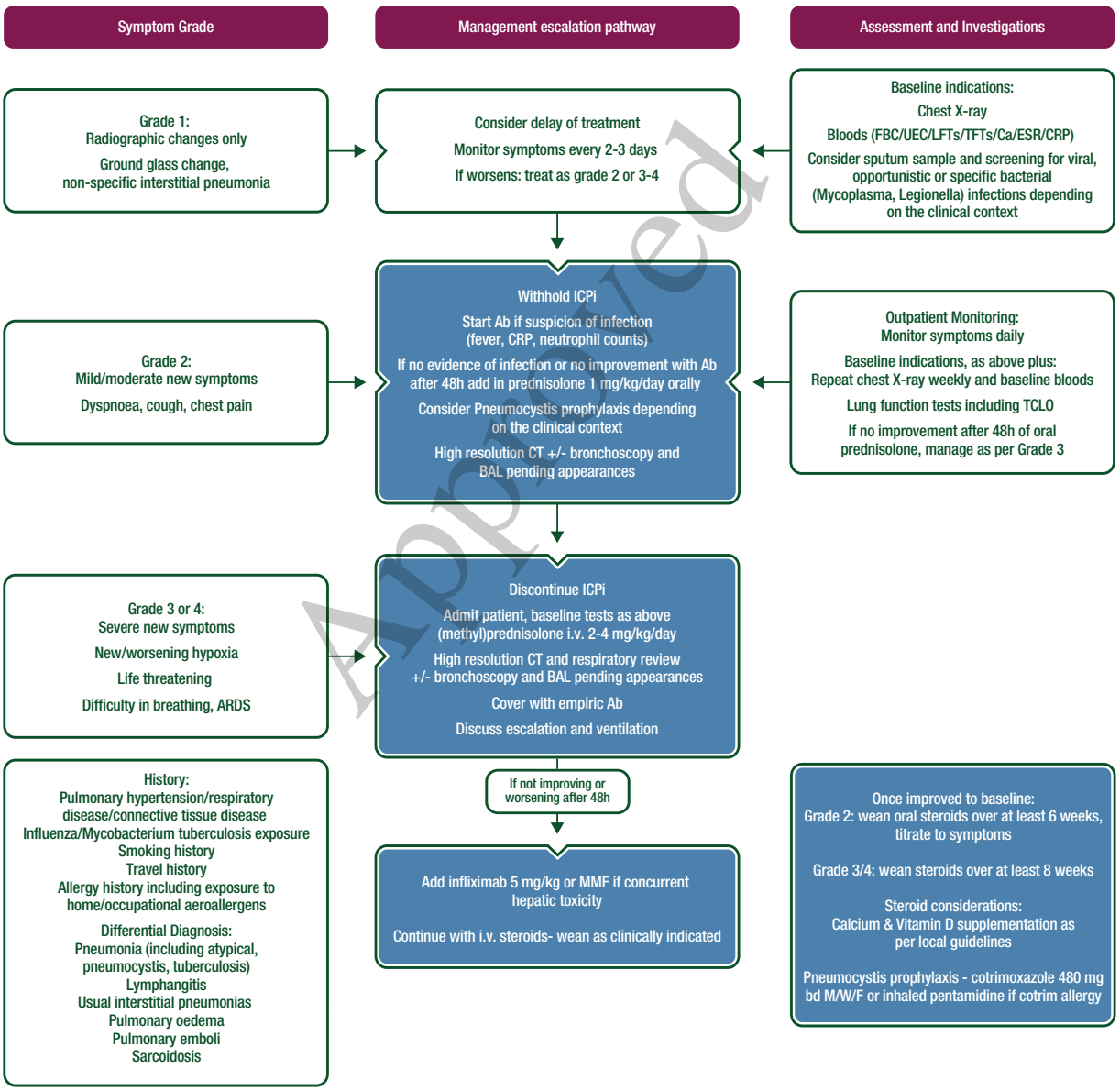

Figure 9. ICPi-related toxicity: management of pneumonitis.
Ab, antibody; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; bd M/W/F, twice daily Monday/Wednesday/Friday; Ca, calcium; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; ICPi, immune checkpoint inhibitor; i.v., intravenous; LFT, liver function tests; MMF, mycophenolate mofetil; TCLO, transfer factor for carbon monoxide; TFT, thyroid function tests; UEC, urea, electrolytes, creatinine.

corticosteroids [(methyl)prednisolone 2–4 mg/kg/day or equivalent], and immunotherapy treatment permanently discontinued [IV–V, B]. Where the patient's condition does not improve or there is no imaging improvement after 2 days, additional immunosuppressive strategies should be implemented [55, 70, 71]. The addition of infliximab, mycophenolate mofetil (MMF) or cyclophosphamide are possible options. Tapering of steroids should be very slow and careful, over 6 weeks or more; relapses of pneumonitis during steroid tapering have been reported, adding considerations about recurrence in patients who rechallenge immunotherapy [66].

Rare-immune related toxicities

Neurological toxicity

The incidence of neuro-related AEs is reported as 1%. However, a recent analysis of 59 trials, involving 9208 patients reported a higher incidence: 3.8% in patients receiving anti-CTLA4, 6.1% in patients receiving anti-PD-1 agents and 12% in patients receiving anti-CTLA4 in combination with anti-PD-1 drugs. The time to onset varied from 6 to 13 weeks. A range of neurological events have been described, including polyneuropathy, facial nerve palsy, demyelination, myasthenia gravis, Guillain Barré syndrome, posterior reversible leukoencephalopathy, transverse myelitis, enteric neuropathy, encephalitis and aseptic meningitis. It is important to rule out progression of the underlying cancer, seizure activity, infection and metabolic derangement as causes of neurological impairment. Depending on the clinical presentation and imaging of the central nervous system, nerve conduction studies and lumbar puncture may assist in diagnosis. Early consultation with a neurologist is advised.

For all but mild (grade 1) neurological symptoms, checkpoint inhibitor therapy should be withheld until the nature of the AE is defined [V, B]. In the case of moderate symptoms prednisolone 0.5–1 mg/kg should be considered. High-dose steroid therapy with oral prednisolone (1–2 mg/kg) or i.v. equivalent should be used in the event of significant neurological toxicity [V, B]. Additionally, plasmapheresis or i.v. immunoglobulin (Ig) may be required in the treatment of myasthenia and Guillain Barré syndrome [V, B] (see Figures 10–12).

Cardiac toxicity

The incidence of cardiac AEs is <1%, but a wide range of toxicities including myocarditis, pericarditis, arrhythmias, cardiomyopathy and impaired ventricular function have been reported after treatment with ipilimumab, pembrolizumab and nivolumab [72–75]. However, the incidence of cardiac toxicity is higher with the combination of ipilimumab and nivolumab (0.27%) compared with nivolumab alone (0.06%). Early consultation with a cardiologist is recommended [V, B]. High-dose corticosteroids have been used successfully to treat cardiac side-effects and should be instituted rapidly if checkpoint inhibitor induced cardiac AEs are suspected. Escalation to other immunosuppressive drugs, such as infliximab, MMF and ATG, may be necessary if symptoms do not promptly respond to steroids [V, B].

Rheumatological toxicity

Mild or moderate myalgias and arthralgias occur in 2%–12% of patients and are more common with anti-PD-1 agents [76]. Vasculitis, polymyositis, myositis and temporal arteritis have also been described [73]. For mild or moderate symptoms, analgesia with paracetamol and/or NSAIDs is recommended [V, B]. In addition, moderate symptoms may respond to prednisolone at a dose of 10–20 mg/day or equivalent. Severe symptoms should prompt consultation with a rheumatologist and consideration of the use of high-dose corticosteroids and TNFα-blocking agents [V, B] (see Figure 13).

Renal toxicity

Renal dysfunction is rare with ipilimumab and with anti-PD-1 therapies, occurring in <1% of treated patients [77]. The incidence is much higher with combination of ipilimumab plus nivolumab, reaching 4.9%, with 1.7% of grade 3 to 4 toxicity. Similarly, sequential therapy with ipilimumab followed by nivolumab is associated with a high incidence of 5.1%, of which 2.2% of cases developed grade 3 to 4 nephritis [78]. Serum sodium, potassium, creatinine and urea should be measured before every infusion of checkpoint inhibitor and derangement of renal function managed initially by stopping nephrotoxic drugs (including over the counter medications), ruling out infection, urinary tract obstruction and correcting hypovolaemia. Checkpoint inhibitor therapy should be withheld in the event of significant renal dysfunction and consideration given to the use of systemic corticosteroid therapy [0.5–2 mg (methyl)prednisolone or equivalent] [V, B]. In the event of severe renal dysfunction, a nephrologist should be consulted. Renal biopsy may be used to clarify a difficult differential diagnosis [V, B]. In one series of patients who were biopsied after developing acute kidney injury while on ICPis an acute tubulo-interstitial nephritis with lymphocytic infiltration was the most frequent finding [79]. Recently, a severe case of antineutrophil cytoplasmic antibody-associated rapid progressive glomerulonephritis was described in a patient with thymic epithelial carcinoma on pembrolizumab treatment [80]. In keeping with pathology described in other organs, granulomatous changes were seen in about a quarter of patients and one had thrombotic microangiopathy (see Figure 14).

Ocular toxicities

irAEs of the eye are rare and occur in <1% of patients treated with ICPis [81]. These AEs can be divided into ocular inflammation, such as peripheral ulcerative keratitis, uveitis and Vogt–Koyanagi–Harada syndrome, orbital inflammation, including thyroid-associated orbitopathy and idiopathic orbital inflammation (sceritis, myositis, neuritis, dacryadenitis) and retinal and choroidal disease (choroidal neovascularisation and melanoma-associated retinopathy). Treatment of these rare toxicities depends on their severity, with topical corticosteroids in the case of episcleritis and anterior uveitis, and systemic corticosteroids in the case of severe ocular inflammation and orbital inflammation. Intravitreal anti-vascular endothelial growth factor (VEGF) is indicated for choroidal neovascularisation.

Haematological toxicities

Immune-related haematological AEs have rarely been described in patients treated with ICPi and do seem to occur. So far, lethal aplastic anaemia, autoimmune haemolytic anaemia and immune thrombocytopenic purpura have been described [82–84]. The optimal treatment of these often severe AEs is unknown. Initiation of high-dose corticosteroids and other immunosuppressive drugs should be carried out in close collaboration with a haematologist.

Allograft rejection

The limited literature suggests that ipilimumab as a single agent may be administered without necessarily causing rejection of cardiac, renal and liver allografts. However, several recent case reports have documented the risk of acute allograft rejection after anti-PD-1 therapy [85]. As such, this very significant risk must be considered in discussing systemic therapy options in patients that might potentially benefit from anti-PD-1 therapy but who have allografted organs.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 2. Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

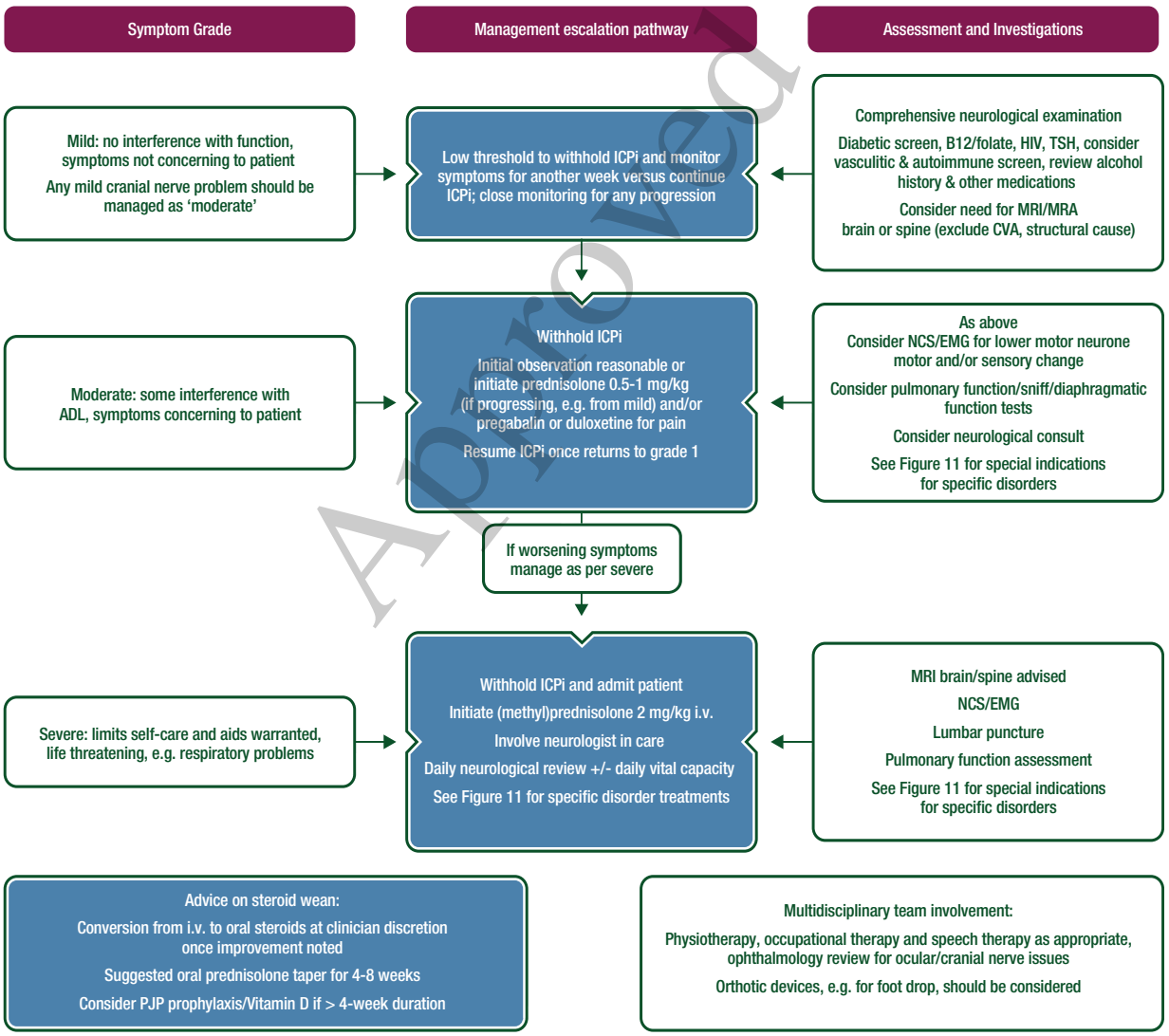

Figure 10. ICPi-related toxicity: management of suspected peripheral neurological toxicity.
ADL, activities of daily living; CVA, cerebrovascular accident; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; i.v. intravenous; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; NCS/EMG, nerve conduction studies/electromyography; PJP, Pneumocystis jiroveci pneumonia; TSH, thyroid-stimulating hormone.

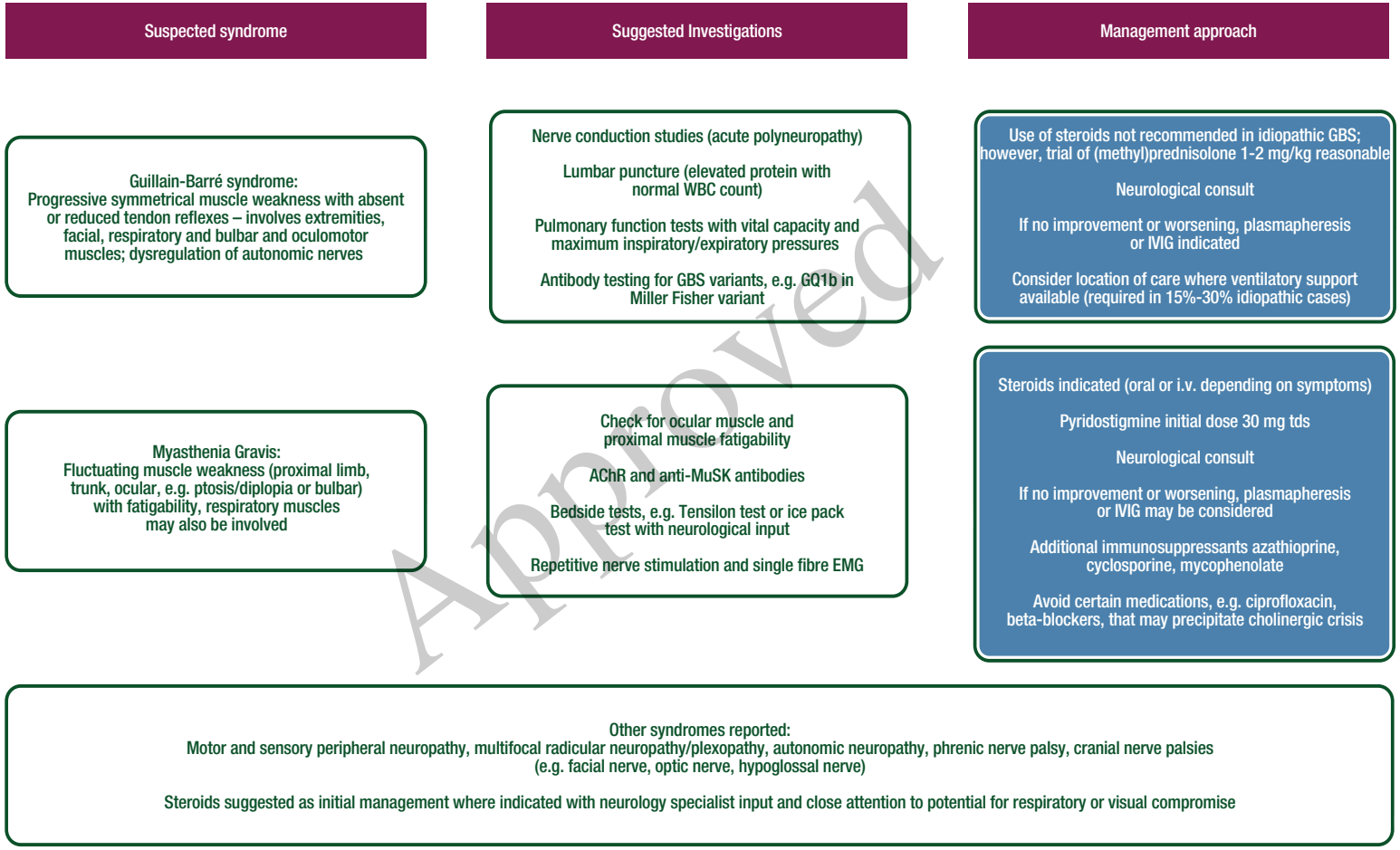

Figure 11. ICPi-related toxicity: management of suspected peripheral neurological toxicity.
AChR, acetylcholine receptor; EMG, electromyography; GBS, Guillain-Barré syndrome; ICPi, immune checkpoint inhibitor; i.v., intravenous; IVIG, intravenous immunoglobulin; MuSK, muscle specific kinase; tds, three times a day; WBC, white blood cell.

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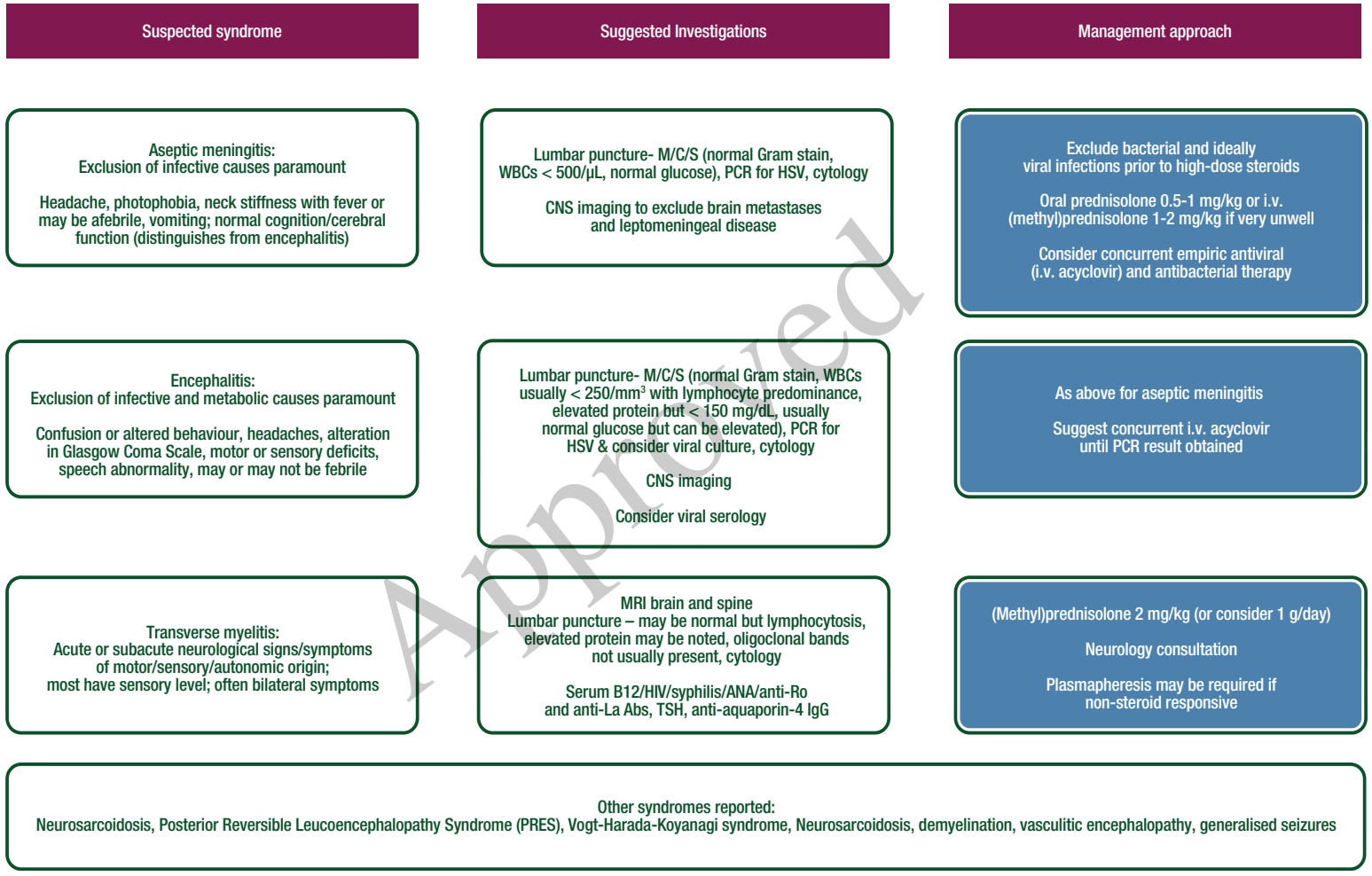

Figure 12. ICPi-related toxicity: management of suspected central neurological toxicity.
Abs, antibodies; ANA, antinuclear antibody; CNS, central nervous system; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; ICPi, immune checkpoint inhibitor; IgG, immunoglobulin G; i.v., intravenous; M/C/S, microscopy, culture and susceptibility; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TSH, thyroid-stimulating hormone; WBCs, white blood cells.

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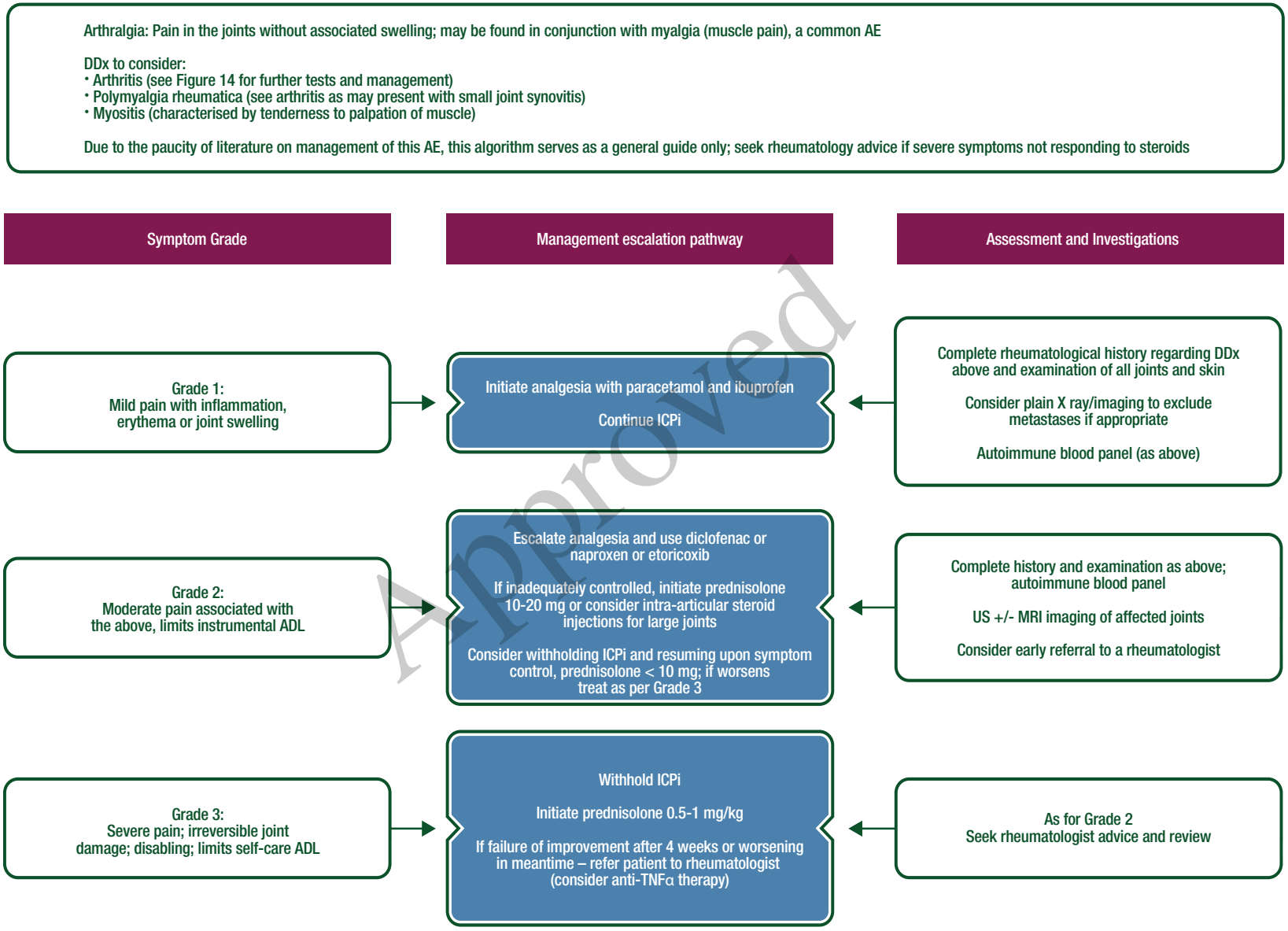

Figure 13. ICPi-related toxicity: management of arthralgia.
ADL, activities of daily living; AE, adverse event; DDx, differential diagnosis; ICPi, immune checkpoint inhibitor; MRI, magnetic resonance imaging; TNFα, tumour necrosis factor alpha; US, ultrasound.

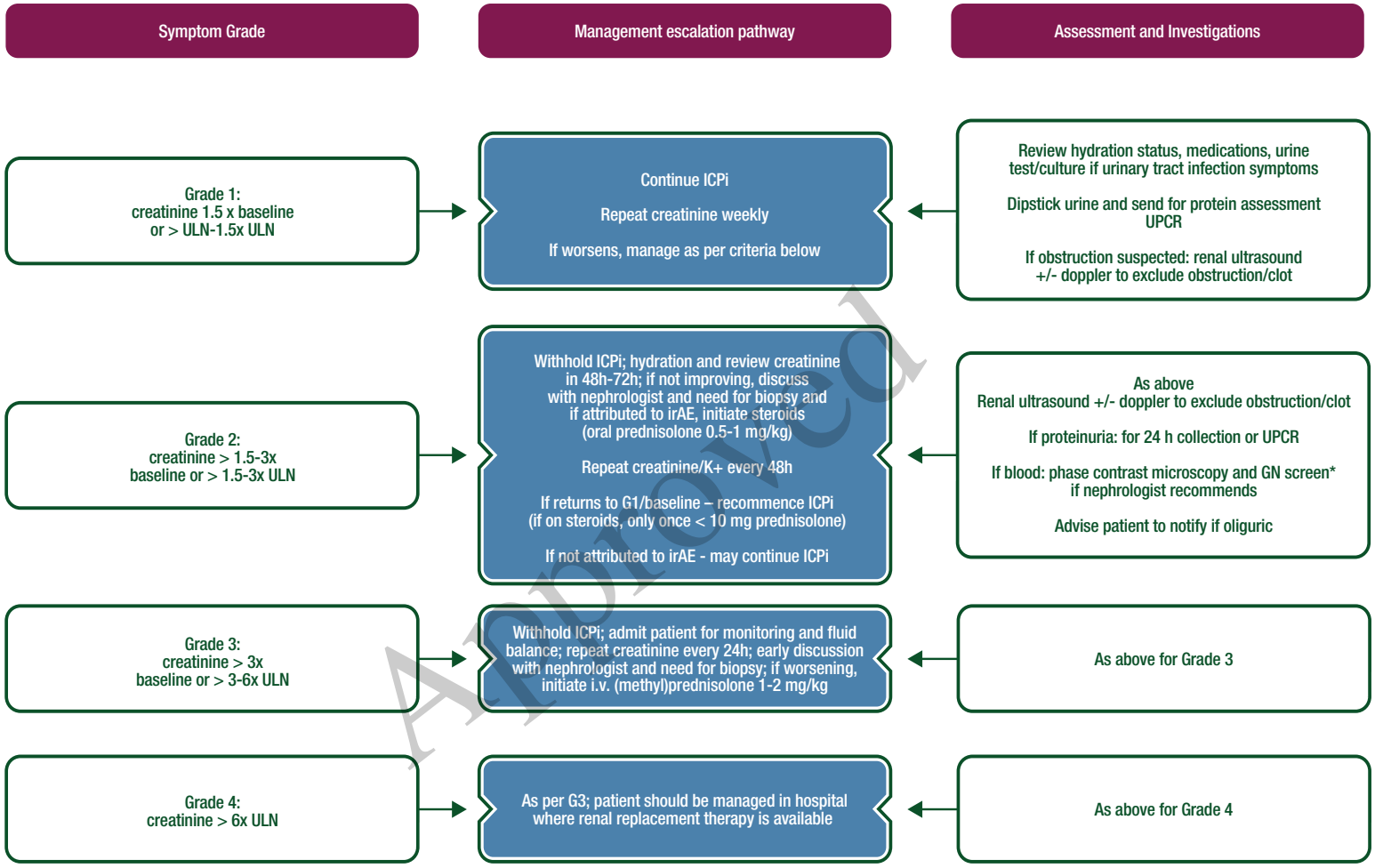

Figure 14. ICPi-related toxicity: management of nephretis.

Renal injury occurs in around 1%–4% of patients treated with ICPi, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate [79]. Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN. Confounding diagnoses include dehydration, recent i.v. contrast, urinary tract infection, medications, hypotension, or hypertension. Early consideration for renal biopsy is helpful which may negate the need for steroids and determine whether renal deterioration is related to ICPis or other pathology. Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy. Steroid wean: begin to wean once creatinine G1; G2 severity episode—wean steroids over 2–4 weeks; G3/4 episode—wean over $\geq$ 4 weeks. If on steroids for > 4 weeks—PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia. *GN screen: ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis.

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; GBM; glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; i.v., intravenous; K, potassium; PJP, Pneumocystis jiroveci pneumonia; ULN, upper limit of normal; UPCR, urine protein to creatinine ratio.

Table 2. Summary of recommendations for immune-related toxicities

Immune-related skin toxicity

- For grade 1–2 skin AEs, continue (at least 1 week) with ICPis. Start topical emollients, antihistamines in the case of pruritus and/or topical (mild strength) corticosteroid creams. Reinitiate ICPi when ≤ grade 1.
- For grade 3 skin AEs, interrupt ICPi and start immediate treatment with topical emollients, antihistamines and high strength corticosteroid creams [II, B].
- For grade 4 skin AEs, discontinue ICPi (permanently), consider admitting patient and always consult dermatologist immediately. Start i.v. corticosteroids [1–2 mg/kg (methyl)prednisone] and taper based on response of AE [II, B].

Immune-related endocrinopathies

- In symptomatic hyperthyroism patients, usually grade 1 or 2, interrupt ICPi, start beta-blocker therapy (propranolol or atenolol/metoprolol). Restart ICPi when asymptomatic [IV–V, B].
- In the case of hypothyroidism, rarely > grade 2, start HRT depending on the severity (50–100 μg/day). Increase the dose until TSH is normal. In the case of inflammation of the thyroid gland, start prednisone orally 1 mg/kg. Taper based on recovery of clinical symptoms. Consider interruption of ICPi treatment when symptomatic [IV–V, B].
- In the case of hypophysitis (rarely > grade 2), when headache, diplopia or other neurological symptoms are present, start (methyl)prednisone 1 mg/kg orally and taper over 2–4 weeks. Start HRT depending on the affected hormonal axis (levothyroxine, hydrocortisol, testosterone) [V, B].
- In patients with type I DM grade 3 to 4 [ketoacidotic (sub)coma], admit to hospital immediately and start treatment of newly onset type I DM [I, A]. Role of corticosteroids in preventing complete loss of insulin producing cells is unknown and not recommended.

Immune-related hepatotoxicity

- For grade 2 hepatitis, withhold ICPi and monitor AST/ALT levels closely (1–2 times/week). When no improvement over 1 week, start (methyl)prednisone (0.5–1 mg/kg). Taper over several weeks under close monitoring of AST/ALT and bilirubin [IV–V, B].
- For grade 3 hepatitis, discontinue ICPi and immediately start with (methyl)prednisone 1–2 mg/kg. When no improvement in 2–3 days, add MMF (1000 mg 3× daily). Taper immunosuppression over 4–6 weeks under close monitoring of AST/ALT and bilirubin [IV–V, B].
- For grade 4 hepatitis, permanently discontinue ICPi, admit patient to the hospital and initiate (methyl)prednisone 2 mg/kg i.v. Add MMF if no improvement is observed within 2–3 days. Consult hepatologist if no improvement under double immunosuppression. Other immunosuppressive drugs to consider are ATG and tacrolimus. Consult or refer patient to an experienced centre. Taper over 6 weeks under close monitoring of liver tests [IV–V, B].

Gastrointestinal hepatotoxicity

- In patients with non-severe diarrhoea (grade 1), ICPi can be continued. Treatment with antidiarrhoeal medication (e.g. loperamide) should be prescribed [IV–V, B].
- In grade 2 diarrhoea, ICPi should be interrupted and the patient should start with corticosteroids depending on the severity and other symptoms (either budesonide or oral corticosteroids 1 mg/kg). In the case of no improvement within 3–5 days, colonoscopy should be carried out and, in the case of colitis, infliximab 5 mg/kg should be administered [IV–V, B].
- In patients with severe diarrhoea (grade 3 to 4), permanently discontinue ICPi. Admit patient to the hospital and initiate (methyl)prednisone 2 mg/kg i.v. Add MMF if improvement is observed within 2–3 days. Consult a hepatologist if no improvement under double immunosuppression. Other immunosuppressive drugs to consider are ATG and tacrolimus. Consult or refer patient to an experienced centre. Taper over 6 weeks under close monitoring of liver tests [IV–V, B].

Immune-related pneumonitis

- In grade 1 and 2 pneumonitis, interrupt ICPi therapy, try to rule out infection and start with prednisone 1–2 mg/kg orally. Taper over 4–6 weeks [IV–V, B].
- In grade 3 and 4 pneumonitis, discontinue ICPi permanently, admit the patient to the hospital, even ICU if necessary and immediately start high-dose (methyl)prednisone 2–4 mg/kg i.v. Add infliximab, MMF or cyclophosphamide in the case of deterioration under steroids. Taper over a period of 4–6 weeks [IV–V, B].

Neurological toxicity

- In the case of mild neurological AEs, withhold ICPi and perform work-up (MRI scan, lumbar puncture) to define nature of neurotoxicity. In the case of deterioration or severe neurological symptoms, admit the patient and start (methyl)prednisone 1–2 mg/kg orally or i.v. In the case of Guillain-Barré or myasthenia-like symptoms, consider adding plasmapheresis or i.v. Ig [V, B].

Cardiac toxicity

- When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].

Rheumatological toxicity

- For mild arthralgia, start NSAIDs, and in the case of no improvement, consider low dose steroids (10–20 mg prednisone). In the case of severe polyarthritis, refer patient to or consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab or another anti-TNFα drug is required for improvement of arthritis [V, B].

Renal toxicity

- In case of nephritis, rule out other causes of renal failure first. Interrupt or permanently discontinue ICPi depending on the severity of the renal insufficiency. Stop other nephrotoxic drugs. Start (methyl)prednisone 1–2 mg/kg. Consider renal biopsy to confirm diagnosis [V, B].

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; ATG, anti-thymocyte globulin; DM, diabetes mellitus; HRT, hormone replacement therapy; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; Ig, immunoglobulin; i.v. intravenous; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFα, tumour necrosis factor alpha; TSH, thyroid-stimulating hormone.

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...). optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [88].

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FC has reported being a board member of Merck Sharpe & Dohme and Bristol-Myers Squibb and honoraria from Bristol-Myers Squibb; CR has reported consultancy for Roche, Bristol-Myers Squibb, Amgen, Merck Sharpe & Dohme, Novartis and Merck; KK has reported lecture honoraria and/or consultancy from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck KGaA, Merck Sharpe & Dohme, Novartis, Pfizer, Roche and Roche Diagnostics; JL has reported honoraria and research grants from Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, Pfizer, Eisai, GlaxoSmithKline, Kymab, Roche/Genentech, Secarna, Fabre and EUSA Pharma; JH, SP and KJ has reported honoraria from Amgen, Merck, MSD, Helsinn, Tesaro and Hexaland and being a member of the advisory board of Merck, MSD, Helsinn and Tesaro.

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APPENDIX 10: CYTOKINE RELEASE SYNDROME GRADING AND TREATMENT GUIDELINES

The following guidelines have been adapted from (Lee 2014). Please refer to the full publication for further details. These may be supplemented by discussions with the Sponsor's medical monitor as well as institutional guidelines on management of CRS.

Table 16: Cytokine Release Syndrome Grading and Treatment Guidelines

Grade/Toxicity	Treatment
Grade 1 Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	Vigilant supportive care Assess for infection Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity[3]	**Extensive comorbidities or older age:** Vigilant supportive care Tocilizumab[1] +/- corticosteroids[2] **No Extensive comorbidities or older age:** Vigilant supportive care (Monitor cardiac and other organ function closely)
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose[4] or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis	Vigilant supportive care Tocilizumab +/- corticosteroids
Grade 4 Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)	Vigilant supportive care Tocilizumab +/- corticosteroids
Grade 5 Death	NA

[1] Tocilizumab 4 mg/kg over 1 hour. Repeat dose if no improvement in 24-48 hours

[2] Methylprednisolone 2 mg/kg/day IV; dexamethasone 0.5 mg/kg (10 mg/dose) IV every 6 hours

[3] As determined by CTCAE Ver 4.03

[4] Refer to Table 17

Table 17: High Dose Vasopressors (all doses are required for ≥ 3 hours)

Pressor	**Dose**
Norepinephrine monotherapy	≥20 µg/min
Dopamine monotherapy	≥10 µg/kg/min
Phenylephrine monotherapy	≥200 µg/min
Epinephrine monotherapy	≥10 µg/min
If on Vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min*

*VASSST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)]+[dopamine (µg/kg/min)÷2+[epinephrine (µg/min) + [phenylephrine (µg/min) ÷10]

APPENDIX 11: ADDITIONAL COHORTS FOR PHASE 1B EXPANSION

Clinical safety results from Study 155-001 were reviewed at a meeting with participating investigators and the Sponsor on July 22, 2020 (GMT -7). No DLTs have been observed in dose escalation through the FPT155 560mg dose level. Following review of cumulative safety results, including those from 10 patients enrolled at the FPT155 280mg dose level and 7 patients at the FPT155 560mg dose level, there was unanimous endorsement of expansion of enrollment at a recommended dose of FPT155 560mg Q3W. Based on review of the available safety, pharmacokinetic and pharmacodynamic results and in accordance with Section 4.1.3 of the protocol, the following Phase 1b cohorts will open for enrollment:

Phase 1b Cohort	Inclusion Criteria
1	Patients with advanced renal cell carcinoma as specified per Section 5.2 of the protocol.
2	Patients with advanced melanoma as specified per Section 5.2 of the protocol.
3	Patients with previously-treated unresectable or metastatic solid tumors with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) and an absence of suitable standard treatment options.
4	Patients with previously-treated unresectable or metastatic non-small cell lung cancer and an absence of suitable standard treatment options.
5	Patients with previously-treated solid tumors with a response to prior PD-1 or PDL-1 directed treatment as defined by an objective response (partial or complete response) or a minimum of three months on prior PD-1 or PDL-1 directed therapy.

For these cohorts, patient enrollment continues to be subject to the inclusion and exclusion criteria as specified per protocol Sections 5.1 and 5.3.