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Protocol PI	Tina Cascone, MD
Department	Thoracic Head & Neck
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Clinical Study Protocol

Drug Substance: Bintrafusp alpha
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PHASE II STUDY OF NEOADJUVANT IMMUNE CHECKPOINT BLOCKADE-BASED THERAPY WITH M7824 (bintrafusp alpha) FOR UNTREATED RESECTABLE NON-SMALL CELL LUNG CANCERS

Sponsor & Study center:
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030

Principal Investigator
Tina Cascone, MD, PhD
The University of Texas MD Anderson Cancer Center
Department of Thoracic/Head and Neck Medical Oncology
1515 Holcombe Blvd. Unit 432
Houston, TX 77030

Co-Principal Investigator
Boris Sepesi, MD
Department of Cardiothoracic Surgery
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd. Unit 432
Houston, TX 77030

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1 Protocol Summary

1.1 SYNOPSIS

Clinical Trial Protocol Number	2019-0910
Title	Phase II study of neoadjuvant immune checkpoint blockade-based therapy with M7824 (bifunctional anti-PD-L1/ TGF-β Trap fusion protein) for untreated stage I-IIIA non-small cell lung cancers amenable for surgical resection
Trial Phase	II
IND Number	146722
Coordinating Investigator	Tina Cascone, MD, PhD The University of Texas – MD Anderson Cancer Center Houston, TX USA
Sponsor	The University of Texas – MD Anderson Cancer Center, Houston, TX
Trial center/country	Single institution trial / United States
Planned trial period (first subject in-last subject out)	TBD
Trial Registry	Pending NCT identifier

Endpoints:

Primary

Endpoints:

To evaluate the rate of major pathologic response, defined as ≤ 10% viable tumor cells in the resected specimen using the methods described by Pataer et al. in patients treated with induction M7824 monotherapy.

Secondary

Endpoints: To estimate:

Toxicity (assessed by the NCI CTCAE v.

5) Peri-operative morbidity and mortality

Response rates to induction treatment (by RECIST version 1.1) (1)

Recurrence-free survival and Overall survival

Survival rates at 12, 18 and 24 months

To correlate major pathologic response with recurrence-free and overall survival

Complete resection (R0) rate

Pathologic complete response (pCR) in resected tumor specimens

To correlate response assessed by imaging studies with outcomes (both major pathologic response to treatment and long-term recurrence-free survival)

CD8+ TILs in resected tumor tissues of patients treated with M7824

Exploratory Endpoints:
PD-L1 expression in tumor tissue
Multi-region next generation DNA and/or RNA sequencing in tumor tissue (including whole exome and/or whole genome sequencing) and in blood/normal tissue, so that tumor heterogeneity and mutational load can be correlated with efficacy of immunotherapy and/or other correlative markers

Immunophenotyping or characterization of the immune cell subsets in tumor tissue, including markers of T cell exhaustion, T cell activation, T regulatory cells, T cell function, antigen presenting cells, as well as CD20, Ki67, granzyme B, IFN-γ, TGF-beta, GATA-3, RORgt,BCL2, as well as CD68 and other markers relevant to immune profiling

Expression of immunoregulatory and co-stimulatory markers in TILs by flow cytometry, including, but not limited to, PD1, CTLA4, LAG3, 41BB, and TCR zeta chain

RNA and protein expression in tumor and adjacent normal tissue, including assessment of immune/inflammatory pathways

Immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immunecell types

Single cell genomics in tumor (including tumor positive nodes) and adjacent normal tissue

Serum soluble factors, including IFN-gamma and interferon inducible factors (such as CXCL9 and CXCL10), PD-L1, PD-1, anti-tumor antibodies, microRNAs (such as miR-513, and miR19b), IL-12, TNFα, IL-10, TGF-β, VEGF, IL-6, IL-8, IL-17, IL-18, C-reactive protein and, as well as other cytokines, chemokines, inflammatory factors and immune mediators

T cell receptor repertoire (TCR) sequencing in tumor tissue, adjacent normal lung and the periphery (pre- and post-neoadjuvant therapy)

Next generation sequencing of cell-free circulating DNA

Immunopeptidome analysis

Enteric microbiome analysis

CT imaging analysis.

Methodology and design:
This is an open label, phase 2 study with modular design assessing the experimental agent M7824 in the neoadjuvant setting.We will start investigating M7824 monotherapy (Arm A) induction treatment in patients with resectable NSCLC, with the primary objective to estimate the MPR in each arm. After confirmation of eligibility criteria, patients will be enrolled in Arm A. Sequential armsinvestigating induction M7824-based strategies may be added after completion of enrollment in Arm A (23 patients) based on emerging data with a protocol amendment

Planned number of subjects:
Arm A: 23

Investigational Medicinal Product: M7824
Dose/mode of administration/ dosing schedule:
M7824 will be administered intravenously at a dose of 1200 mg every 14 days (+/- 3 days).

Planned trial and treatment duration per subject:
Subjects will receive M7824 monotherapy for three doses prior to surgery. Administration will be stopped due to documented progressive disease, unacceptable toxicity, consent withdrawal, or any criterion for withdrawal as outlined in this protocol.

Statistical methods
The study is a phase II trial with a modular design. Currently, eligible patients will be accrued to the M7824 monotherapy (Arm A). The primary objective is to evaluate the rate of MPR, rather than hypothesis testing with pre-specified null and alternative MPR rates. There will be no interim futility nor efficacy monitoring. A sample size of 23 patients is proposed for the study. With an estimated accrual rate of approximately 2 patients a month, the accrual period is approximately 15-24 months.

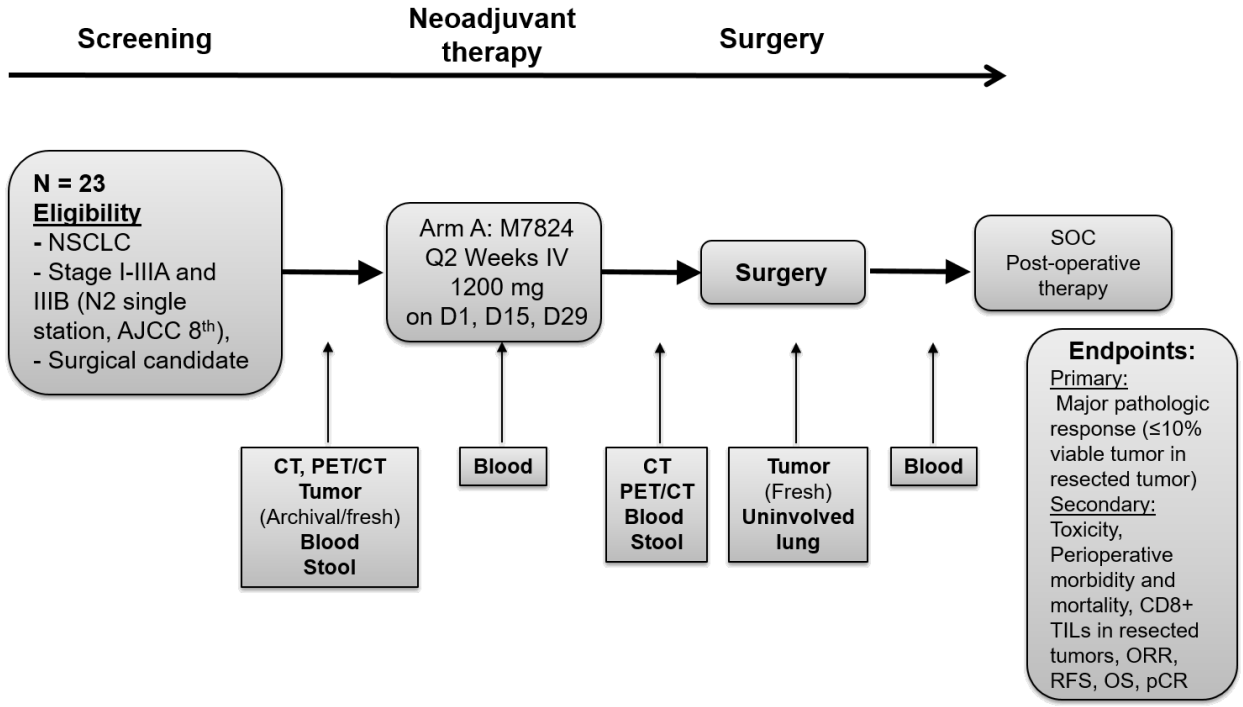
Analysis of primary endpoint of major pathologic response (MPR):
The primary endpoint is major pathologic response (MPR). We will estimate the MPR rate with a 95% credible interval (CI) assuming that the MPR rate follows a prior beta distribution (0.5, 0.5). For example, if the M7824 monotherapy indeed has a true MPR rate of 30% and 7 patients with MPR are observed in this study, the corresponding 95% CI of the observed MPR rate would be (14.8%, 50.7%). Furthermore, we calculated predictive probability of Prob(p > 0.15 | data and true MPR rate) for a variety of true MPR rates, where p is the MPR rate. As shown in Statistical consideration section in Table 3, there will be a fairly high chance (81 – 89%) for the study to observe a MPR rate > 15% with a sample size of 23 patients if the true MPR rates are 25% and higher. We chose to use 15% MPR rate as cutoff because a historic MPR rate to neoadjuvant chemotherapy alone of 19% is observed (as described by Pataer et al.) (2). However, some patients that receive neoadjuvantchemotherapy may not receive surgery for one reason or another, and these cases will be considered treatment failure. Assuming the 19% major pathologic response rate is calculated from 80% of patients who receive surgery, a conservative estimate of the major pathologic response is 15%.

Analysis of Secondary/Exploratory Endpoints:
Analysis for the secondary/exploratory endpoints will be descriptive and exploratory in nature. Descriptive statistics will be provided to summarize the data distribution. Association analysis by Pearson or Spearman correlation coefficient will be calculated for continuous data and chi-square or Fisher's exact test for categorical data. Time-to-event endpoints will be computed using the Kaplan-Meier method.

Toxicity monitoring: A Bayesian method to monitor the toxicity in the perioperative phase will be used. We consider that neoadjuvant therapy with either one of the regimens is not feasible if it results in unacceptable toxicities in at least 20% of the patients with 70% or higher probability. The toxicity monitoring will start after a minimum of 6 patients have

been enrolled. With a prior probability of toxicity as Beta (0.5,0.5), the toxicity stopping boundaries are defined as seeing unacceptable toxicity in >= 3 of 6-7, 4 of 8-10, 5 of 11-13, 6 of 14-16, 7 of 17-19, 8 of 20-22 or 9 of 23 patients. When the true toxicity rates are 0.1, 0.3, and 0.5, the probabilities of early stopping are 0.04, 0.56, and 0.97 with the corresponding average sample sizes of 22.4, 15.1 and 8.0, respectively.

1.3 Study Schema



2. Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

The University of Texas - MD Anderson Cancer Center. The trial will be conducted within the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas - MD Anderson Cancer Center in Houston, TX.

All clinical assessments will be performed in the outpatient clinic setting.
Study drug will be administered in the Cancer Therapy and Research Center (CTRC), an outpatient infusion center at MD Anderson.

Additional sites may be added in the future upon agreement with the study sponsors and the conducting investigator.

The Principal Investigator represents all Investigators for decisions and discussions regarding this trial, consistent with the International Conference on Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP).

The trial will appear in the following clinical trial registry: www.clinicaltrials.gov

3. BACKGROUND

Surgical resection remains the preferred treatment approach for patients with stage I, II, and selected stage III non-small cell lung cancers. Nonetheless, a substantial number of patients will recur after surgical resection alone. As such, the use of perioperative cytotoxic therapy has been developed to improve outcomes in this setting.

3.1 Adjuvant platinum-based chemotherapy

Cisplatin-based adjuvant chemotherapy has become the standard of care treatment following surgical resection of patients with lymph node positive non-small cell lung cancer, based on data from three randomized controlled studies (3-5). A meta- analysis including 4584 patients and 5 trials demonstrated a hazard ratio (HR) for death of 0.89 in favor of adjuvant chemotherapy compared to surgery alone (95% CI 0.82-0.96, p=0.005), which translates to an absolute improvement in 5-year overall survival of 5.4% (6).

3.2 Neoadjuvant (induction) platinum-based chemotherapy

Early randomized, single-institution, small-scale studies evaluating the role of induction chemotherapy in patients with stage III NSCLC provided evidence for potential benefits from systemic therapy prior to surgical resection. Despite the small sample size, Roth et al., and Rosell et al. found statistically significant improvements in overall survival for patients assigned to receive induction treatment, compared to the control arm of surgery alone (7, 8). Following this experience, several multi- institutional, randomized, phase III studies were launched to evaluate the effects of induction chemotherapy in patients with stage I-III NSCLC (9-13). Collectively, these studies demonstrated that (1) induction treatment had activity in NSCLC and elicited objective responses in at least 40% of the patients; (2) there was no significant increase in

perioperative mortality; (3) induction chemotherapy did not seem to negatively impact disease resectability. Furthermore, a meta-analysis including seven induction randomized trials (988 patients), demonstrated a HR for death of 0.82 (95% CI 0.69-0.97, p=0.002) in favor of induction treatment, translating into an absolute improvement of overall survival at 5 years of 6% (14). Since these figures are very similar to the benefits seen in the adjuvant chemotherapy meta-analysis, one could argue that chemotherapy, either before or after surgery, are reasonable treatment options in patients that are candidate for peri-operative systemic therapy.

Potential advantages of neoadjuvant compared to adjuvant treatment include: (1) the ability to deliver treatment with higher dose intensity, due to better tolerability (12); (2) the ability to demonstrate sensitivity to treatment in vivo (since one can follow response to therapy by imaging studies, and assess pathologic response in the resected specimen) – the in vivo assessment of treatment efficacy provides important prognostic information, since patients with a partial or complete radiographic response to treatment (15), and patients with lymph node pathologic downstaging after therapy have been shown to have improved survival (16-18); (3) the ability to study biomarker modulation in response to therapy, and correlate them with short- term (i.e., response rates), and long-term (i.e., disease-free or overall survival) efficacy outcomes, thus streamlining translational research.

Induction systemic therapy may be particularly important in the setting of immune checkpoint inhibitor use. One might postulate that, in contrast to the adjuvant setting (in which only micro-metastatic disease is present), the higher tumor burden present at the time of induction treatment may be necessary for abundant antigen release and presentation to the immune system, and consequently, development of a robust immune response. The possible superiority of induction immune therapy, as compared to adjuvant immune therapy, is currently being investigated in pre-clinical models at MD Anderson (Cascone et al, AACR 2018, manuscript in preparation).

3.3 Investigational agent M7824

M7824 (MSB0011359C, bintrafusp alfa) is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of TGFβ receptor II (TGFβRII or TGFβ Trap) covalently linked via a flexible linker to the C-terminus of each heavy chain of an immunoglobulin (IgG1) antibody blocking programmed death-ligand 1 (anti-PD-L1). Bintrafusp alfa is the proposed international nonproprietary name for M7824. Complete information on the chemistry, pharmacology, efficacy, and safety of M7824 is in the Investigator's Brochure". This anti-PD-L1 / TGFβ-Trap molecule is designed to target 2 major mechanisms of immunosuppression in the tumor microenvironment.

3.4 Preclinical studies with M7824 in cancer

A recent report found that blockade of TGFβ signaling in T cells or deletion of TGFβ1 from T cells in a mouse model led to diminished PD-1 expression in tumor-infiltrating CD8+ T cells. Concomitant PD-1 and TGFβ blockade can restore pro-inflammatory cytokines. In a murine model of hepatocellular carcinoma, TGFβ appeared to increase the expression of PD-L1 in dendritic cells, which in turn promoted T-cell apoptosis and increased percentage of CD25+, Foxp3+ T regulatory cells (19). Higher levels of circulating myeloid-derived suppressor cells (MDSCs), a significant source of TGFβ, are associated with failure to respond to anti-PD-1

therapy. Experiments demonstrate that M7824 strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 antibody, or TGFβRII control alone. Tumor rechallenge experiments in cured mice show durable protective immunity. In vivo studies showed that the antitumor effects were mediated by CD8+ T cells and NK cells. CD8+ T-cell tumor infiltrates were observed and, overall, the CD8+ response was associated with long-term protective immunity. Importantly, in the MC38 model, M7824 showed significantly improved efficacy than the combination of avelumab plus TGFβ Trap control, supporting the rationale of combining the 2 active moieties in 1 molecule.

Given the emerging picture for PD-1 / PD-L1 class, in which responses are apparent but with room for increase in effect size, it is assumed that co-targeting a complementary immune modulation step will improve tumor response. A similar TGF-targeting agent, fresolimumab, which is a monoclonal antibody targeting TGFβ1, 2, and 3, showed initial evidence of tumor response in a Phase I trial in subjects with melanoma. The objective response was observed in 1 of 28 subjects with 6 subjects showing stable disease. Internal data shows that the TGFβRII portion of M7824 has dose dependent antitumor activity in a mouse pharyngeal carcinoma xenograft model, similar to antitumor findings with soluble receptor reported elsewhere. Given the preclinical and clinical evidence of both pathways, it is anticipated that M7824 may have enhanced antitumor activity compared with immunotherapy agents which target a single pathway and is an attractive anticancer strategy.

3.5 Pharmacokinetics / Immunogenicity Findings

Preclinical PK data and PK / PharmDyn analysis for M7824 is available from mice and cynomolgus monkeys. The single-dose data in monkey shows non-linearity between the low doses of 0.8 and 4 mg/kg versus the high dose of 20 mg/kg, which had reduced clearance, suggesting a saturable component. The TGFβ-1 binding was assessed and showed suppression for prolonged periods beyond drug exposure at all dose levels; however, baseline data contained data below lower limit of quantification and therefore these data were not considered relevant for PK/PharmDyn projections. The fusion protein appeared stable since there was no evidence of intralinker cleavage. Mouse PK / PharmDyn models for tumor and peripheral blood (CD3+ splenic) PD-L1 occupancy were also generated.

A brief summary of PK and PK / PharmDyn is as follows:

- The predicted human terminal half-life ($t_{1/2}$) for M7824 is approximately 6 days
- Simulations predict that a 1 mg/kg dose will provide an average exposure of approximately 7 µg/mL in humans
- Based on PK / PharmDyn modeling and human projections:
  - At a human dose of 0.1 mg/kg, 95% PD-L1 total occupancy at maximum serum concentration observed post-dose (C_{max}) is expected in PBMCs, providing approximately 60% total occupancy in tumor

- At a human dose of 1.0 mg/kg, more than 95% of PD-L1 total occupancy at C_{max} is expected in PBMCs and tumor
- At a human dose of 1.0 mg/kg, 20% effect is projected in tumor regression in the PK / PharmDyn model compared with 95% at 7.5 mg/kg

- Human projections indicate a dose of 7.5 mg/kg and higher (range 4 to 20 mg/kg), on a biweekly schedule is needed to achieve full efficacy based on a mouse tumor model in which complete tumor regressions were observed.

Anti-drug antibodies were observed in some animals; however, the impact on PK or PK / PharmDyn is not known. Preclinical antidrug antibody formation is not predictive of human antibodies.

3.6 Toxicology

The toxicological profile of M7824 was investigated in vivo in mice and cynomolgus monkeys. In addition, an optimized in vitro cytokine release assay in human PBMCs as well as tissue cross-reactivity studies in normal human and cynomolgus monkey tissues were performed.

Investigations of local tolerance were integrated in the repeat-dose toxicity studies. The investigation of safety pharmacology relevant parameters (CNS, respiratory, cardiovascular) was included in the pivotal 4-week intravenous (IV) repeat-dose toxicity study in cynomolgus monkeys. Please refer to the investigator brochure for M7824 for further details (M7824 IB v 4.0).

3.7 Safety of M7824

A reasonable safety profile is anticipated when targeting these pathways. The safety of the PD-1 / PD-L1 class continues to emerge but appears to be substantially less adverse compared with the CTLA-4 class of T cell checkpoint inhibitors. TGFβ inhibiting biologics administered in clinical trials also showed an acceptable human safety profile in humans. Fresolimumab was studied in Phase I trial in subjects with cancer (28 with melanoma, 1 with renal cell carcinoma). No DLTs were observed and 15 mg/kg, the highest dose tested, was determined to be safe. The major AE was emergent skin tumors and hyperkeratosis. In a small trial of idiopathic pulmonary fibrosis, the most common AE was fatigue (20). In a study of 16 subjects with focal segmental glomerulosclerosis, the only AE was pustular rash in 2 subjects (21). TβM1, an antibody inhibiting the TGFβII receptor, was well tolerated when studied at doses as high as 240 mg with diarrhea as the only DLT event. Notably, one event of low hemoglobin (Hgb) was observed in the high dose group. Importantly, the preclinical profile of M7824 is predominantly benign and highly comparable to that of other checkpoint inhibitors.
Overall, evidence suggests non-overlapping toxicity profiles for anti-PD-L1 and anti-TGFβ agent classes. There is a theoretical potential of immune-related adverse events (irAEs) that would be the consequence of a double blockade of negative regulatory loops of the immune system; however, taken together, the preclinical profile of M7824 and clinical evidence of each

pathway suggests a low risk of synergistic toxicity stemming from the dual-functionality of M7824. The safety profile is described in the IB for M7824 and is briefly summarized here (refer to M7824 IB v5). Safety tolerability, PK, and biological and clinical activity of M7824 have been evaluated in subjects with metastatic or locally advanced solid tumors and expansion to selected indications in the global Phase I Study EMR200647-001 in subjects with metastatic or locally advanced solid tumors, and the phase I study MS200647-0008 in subjects with metastatic or locally advanced solid tumors in Asia. To date, over 700 patients have been treated with M7824 and an acceptable safety profile has been observed. Randomized phase 2 trials have recently been initiated using M7824. The dose selection for the dose expansion cohorts and phase 2 studies was based on the review of the available clinical safety/tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) (PD-L1 TO and TGFβ concentrations in PBMCs and plasma, respectively) data from the ongoing Phase I Study EMR200647-001 informed by population PK (popPK), modeling and simulation approaches and a translational PK/efficacy model from mouse studies.

Analysis of the available preliminary PK data in dose escalation cohorts of Study EMR200647-001 at doses from 1 to 20 mg/kg supports flat dosing approach. The dose for the expansion cohorts of both studies has been selected as 1200 mg/infusion (flat dose) iv once every 2 weeks. The safety summary for this Investigator's Brochure includes data from 377 subjects treated in the pooled expansion cohort from the ongoing Phase I EMR200647-001 (as of interim analysis at 3 months after the 30th or 40th subject's 1st dose). The pooled safety data are from 10 expansion cohorts including hepatocellular carcinoma (HCC) second-line (2L), NSCLC 2L, NSCLC anti-PD-L1 failure, melanoma anti-PD-L1 failure, pancreatic adenocarcinoma 2L, colorectal cancer (CRC) 3L or greater, triple-negative breast cancer (TNBC) 2L, esophageal adenocarcinoma 2L or greater, glioblastoma 2L, squamous cell carcinoma head and neck (SCCHN) 2L or greater.

In EMR200647-001 pooled expansion cohort of the first 377 subjects, 364 (96.6%) subjects experienced TEAE, treatment-related Grade ≥ 3 TEAEs occurred in 58 (15.4%) subjects, treatment related SAEs were reported in 28 (7.4%) subjects, and 16 (4.2%) subjects had treatment discontinuations due to treatment related TEAEs (M7824 IB v 4.0). The preliminary safety assessment of M7824 from EMR200647-001 and MS200647-0008 studies suggested an acceptable safety profile in subjects with advanced or metastatic solid tumors. Overall, the patterns of TEAEs in both studies are consistent with the types of AEs commonly observed in subjects with advanced or metastatic malignancies that have progressed after ≥ 1 lines of prior anticancer therapy with the exception of the identified risks of M7824.

Based on medical assessment (regular and periodic safety review which also includes external experts) of safety data emerging from the ongoing clinical studies with M7824, supported by scientific evidence from biological mechanism, observations with other check point inhibitors as well as TGFβ inhibitor, fresolimumab, the following events in the 3 AESI categories were reclassified as important identified risks (adverse reactions) at the end of safety reporting period (23 July 2017), the frequency and intensity are summarized in this Investigator's Brochure (M7824 IB v4).

- Infusion-related reactions (IRRs) including hypersensitivity (immediate): Signs and symptoms may include but are not limited to pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticarial

- Immune-related adverse events (irAEs) including colitis, pneumonitis/interstitial lung disease, endocrinopathies (thyroid disorders including hyperthyroidism, hypothyroidism, autoimmune thyroiditis and adrenal insufficiency), Type I diabetes mellitus, renal disorders (acute renal injury), hepatitis (increased transaminase), retinal microvasculitis, myositis, skin reactions like rash (generalized, maculo-papula, erythematous, pemphigoid).

- Skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGFβ inhibition.

Treatment-related anemia treatment-emergent adverse events (TEAEs), alterations in wound healing or repair of tissue damage and embryofetal toxicity remain important potential risks. Respective risk mitigation measures have been implemented in the protocols. TEAEs of special interest (AESI) are IRRs, irAEs, skin TEAEs, and treatment-related anemia TEAEs. Most of the AESI incidents were well managed or resolved. IRRs occurred in 23 (6.1%) subjects. All of the events were Grade 1 or 2 in intensity. Treatment-related irAE of any grade occurred in 34 (9.0%) subjects. Most irAEs were of Grade 1 or 2 in intensity, 7 (1.9%) subjects experienced treatment related Grade 3 irAEs. No subject experienced Grade 4 or 5 irAEs. The treatment-related irAEs that occurred in 2 or more subjects were rash maculo-papular in 11 (2.9%) subjects, rash in 4 (1.1%) subjects, pruritus in 3 (0.8%) subjects, and rash macular in 3 (0.8%) subjects, and hypothyroidism in 3 (0.8%) subjects. Skin AESIs include skin AEs possibly due to TGFβ inhibition (rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin) and immune-related skin AEs possibly mediated by PD-L1 inhibition. Treatment-related skin AESIs that are possibly due to TGFβ inhibition included keratoacanthoma in 11 (2.9%) subjects, squamous cell carcinoma of skin in 2 (0.5%) subjects, hyperkeratosis in 3 (0.8%) subjects, and actinic keratosis in 2 (0.5%) subjects. Treatment-related anemia AESIs occurred in 24 (6.4%) subjects including anemia in 23 (6.1%) subjects (Grade ≥ 3 in 13 subjects), and Grade 5 hemolysis in 1 (0.3%) subject.

3.8 Efficacy of M7824 in solid tumors

The efficacy data is based on the available data from the dose escalation cohorts of EMR200647-001 and MS200647-0008 presented at the ASCO annual meeting 2018. The clinical efficacy data of the dose expansion cohorts will be reported at a later point in time. Based on the limited efficacy data, initial signals of tumor response are evident. The subjects enrolled in the dose escalation cohorts in the two studies represent a variety of primary tumor types and had locally advanced, inoperable or metastatic disease with at least 1 type prior anticancer treatment.

In dose escalation cohorts of EMR200647-001, confirmed responses were complete response (CR) in 1 subject with cervical cancer who received M7824 at 10 mg/kg and partial response (PR) in 2 subjects (3 and 10 mg/kg). Stable disease (SD) was achieved in 6 subjects, in

particular 2 subjects with progressive disease at study entry achieved prolonged SD following treatment with M7824.

In dose escalation cohorts of MS200647-0008, confirmed responses were PR in 2 subjects (1 subject with colorectal cancer, who received 3 mg/kg and the other with ovarian cancer, who received 20 mg/kg M7824). Both PRs were ongoing beyond the data cutoff. SD was achieved in 3 subjects including 2 subjects at 3 mg/kg dose level, and 1 subject at 10 mg/kg dose level.

Overall, considering the preliminary clinical activity of M7824 observed in both EMR200647- 001 and MS200647-0008 dose escalation cohorts, together with the safety profile that appears to be manageable given the advanced disease of the studied patient populations, the benefit/risk evaluation is considered favorable for continued clinical development of M7824.

3.9 Summary of Clinical Findings for M7824 in NSCLC

Results of the expansion cohort of the ongoing, phase 1 trial NCT02517398 evaluating M7824 in refractory solid tumors were recently presented at ASCO Annual Meeting 2018 (22). Patients with advanced NSCLC unselected for PD-L1 who progressed following first-line standard treatment (no prior immunotherapy) were randomized to receive M7824 500 mg (n = 40) or 1200 mg (n = 40) intravenously q2 week until disease progression, unacceptable toxicity, or trial withdrawal. The primary objective is to assess best objective responses (BOR) per RECIST v1.1; other objectives include dose exploration and safety/tolerability assessment. Tumor cell PD-L1 expression was evaluable in 75 patients (Ab clone 73-10 [> 80% = > 50% with 22C3]). As of October 25, 2017, 80 patients received M7824 for a median of 11.9 (range, 2-48) weeks, with a median follow-up of 35.2 weeks; 17 patients remain on treatment. Investigator-assessed unconfirmed ORR was 25.0% (500 mg ORR, 22.5%; 1200 mg ORR, 27.5%). Clinical activity was observed across PD-L1 expression levels (**Table 1**); ORR was 40.7% in PD-L1+ and 71.4% in PD-L1–high patients at 1200 mg dose. The most common treatment-related adverse events (TRAEs) were pruritus (18.8%), maculopapular rash (17.5%), and decreased appetite (12.5%). Grade ≥3 TRAEs occurred in 20 pts (25.0%). 6 pts (500 mg, n = 2; 1200 mg, n = 4) discontinued treatment due to TRAEs. No treatment-related deaths occurred. M7824 monotherapy has shown promising efficacy across PD-L1 subgroups, with an ORR at the RP2D of 1200 mg of 40.7% and 71.4% in PD-L1+ and –high patients, respectively and with overall good tolerance.

Table 1. Investigator-assessed efficacy of M7824 observed in NSCLC patients across PD-L1 expression levels

	500 mg Q2W N=40	1200 mg Q2W N=40	Overall N=40
Best overall response, n (%)			
Complete response	0 (0)	1 (2.5)	1 (1.3)
Partial response	8 (20.0)	10 (25.0)	18 (22.5)
Stable disease	3 (7.5)	7 (17.5)	10 (12.5)
Progressive disease	22 (55.5)	21 (52.5)	43 (53.8)

Not evaluable	7 (17.5)	1 (2.5)	8 (10.0)
Investigator-assessed ORR, n (%) All PD-L1+ (≥1%) PD-L1–high (≥80%)	8/40 (20.0) 6/31 (19.4) 2/6 (33.3)	11/40 (27.5) 11/27 (40.7) 5/7 (71.4)	19/80 (23.8) 17/58 (29.3) 7/13 (53.8)
Disease control rate, n (%) All PD-L1+ (≥1%) PD-L1–high (≥80%)	11 (27.5) 9 (29.0) 2 (33.3)	18 (45.0) 15 (55.6) 5 (71.4)	29 (36.3) 24 (41.4) 7 (53.8)
Median PFS, months (95% CI) All PD-L1+ PD-L1–high	1.4 (1.3-2.7) 1.6 (1.3-3.3) 1.5 (0.2-NR)	2.7 (1.3-8.1) 6.8 (2.6-NR) NR (2.7-NR)	2.1 (1.4-2.9) 2.7 (1.6-6.8) 8.1 (1.4-NR)
Median OS, months All PD-L1+ PD-L1–high	10.9 (4.6-NR) 10.3 (4.5-NR) NR (1.0-NR)	NR (11.8-NR) NR (12.2-NR) NR (12.2-NR)	12.2 (10.5-NR) NR (10.3-NR) NR (9.5-NR)

3.10 Combination of immune checkpoint blockade and platinum-based chemotherapy for NSCLC

The PD-1 inhibitor pembrolizumab has shown superior efficacy as monotherapy in previously untreated patients with advanced NSCLC and a PD-L1 tumor proportion score ≥50% compared with standard platinum-based chemotherapy, with fewer toxicities (23). Based on this results, the investigators of the Keynote-021 phase II study assessed the efficacy of pembrolizumab added to platinum-doublet chemotherapy as first line therapy for advanced non-squamous NSCLC patients (24). The objective response rate was 55% in the pembrolizumab plus chemotherapy group compared with 29% in the chemotherapy alone group (p=0.0016) with an overall tolerable toxicity profile. More recently, the IMpower150 phase 3 trial evaluated the addition of the PD-L1 inhibitor atezolizumab (atezo) to carboplatin (C) + paclitaxel (P) ± bevacizumab (bev) in chemo- naive patients with metastatic non-squamous NSCLC. Patients who had not previously received chemotherapy were randomly assigned to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The two primary end points were investigator-assessed PFS both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with EGFR or ALK genetic alterations were excluded) and among patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff- high WT population) and OS in the WT population. The median PFS was longer in the ABCP group than in the BCP group (8.3 months vs. 6.8 months; HR 0.62; 95% CI, 0.52 to 0.74;

p<0.001); the corresponding values in the Teff-high WT population were 11.3 months and 6.8 months (HR 0.51; 95% CI, 0.38 to 0.68; p<0.001). PFS was also longer in the ABCP group than in the BCP group in the entire intention-to-treat population and among patients with low or negative programmed death ligand 1 (PD-L1) expression, those with low Teff gene-signature expression, and those with liver metastases. Median OS among the patients in the WT population was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; HR, 0.78; 95% CI, 0.64 to 0.96; p=0.02). The safety profile of ABCP was consistent with previously reported safety risks of the individual agents (25).

The phase III trial, KEYNOTE-189, was a randomized, double blind, placebo controlled, study investigating pembrolizumab in combination with pemetrexed and cisplatin or carboplatin compared with pemetrexed and cisplatin or carboplatin alone in previously untreated patients with wild type (WT) advanced or metastatic nonsquamous NSCLC, regardless of PD-L1 expression (NCT02578680). The results of this phase 3 trial have been recently reported and demonstrated that in patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard pemetrexed plus platinum-based chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone. After a median follow-up of 10.5 months, the 12-month OS rate was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab-combination group vs. 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group (HR for death, 0.49; 95% CI, 0.38 to 0.64; p<0.001). Median PFS was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; p<0.001) (26).

Another phase III trial, CheckMate 227, compared nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum-based chemotherapy versus platinum-based chemotherapy in patients with chemotherapy-naïve stage IV recurrent NSCLC (NCT02477826). Results have been recently reported and demonstrated that PFS among patients with a high tumor mutational burden was significantly longer with nivolumab plus ipilimumab than with chemotherapy. The 1-year PFS rate was 42.6% with nivolumab plus ipilimumab vs. 13.2% with chemotherapy, and the median PFS was 7.2 months (95% CI, 5.5 to 13.2) vs. 5.5 months (95% CI, 4.4 to 5.8) (HR for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; p<0.001). The ORR was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy (27).

Collectively, these results and the ongoing studies support investigation of checkpoint inhibitors with or without platinum-based chemotherapy in the pre-operative setting. Given the platform design of this study, additional arms evaluating M7824-based combinations, including, but not limited to, platinum-based chemotherapy, will be launched with a protocol amendment based on ememrging results of combinatorial strategies in the metatstic setting.

3.11 Major pathologic response as a marker of induction chemotherapy efficacy

Several small studies have suggested that the degree of tumor regression after induction therapy, as determined by histopathologic findings in the resected tumor, may be an objective criterion of chemotherapy response and may correlate with long-term treatment outcomes (28-31). This issue was comprehensively evaluated recently by Pataer et al. in a retrospective study

with 192 patients treated with induction chemotherapy and 166 patients treated with surgery upfront at MD Anderson Cancer Center (2).Using a score system that quantifies the percentageof viable tumor cells in at least 1 section per cm of tumor greatest diameter (5-30 slides examined for each case), the authors demonstrated that in patients that received induction treatment, there is a statistically significant correlation between higher percentage of viable cellsand shorter disease-free and overall survival. This correlation was not evident in patients treated with surgery upfront. In this cohort, 89% of the neoadjuvantly treated patients received a platinum and a taxane-based regimen, and a pathologic response (defined as ≤ 10% viable tumor cells) occurred in 19% of the patients. The 5-year recurrence-free survival for patients withand without a pathologic response were 78% and 35%, respectively ($p<0.001$). The 5-year overall survival for patients with and without a pathologic response were 85% and 40%,respectively ($p<0.0001$). Taken together, these results support the use of major pathologicresponse as a surrogate endpoint for recurrence-free and overall survival in patients with NSCLC treated with neoadjuvant chemotherapy.

3.12 Neoadjuvant immune checkpoint blockade in resectable NSCLC

Recently published results of a small, pilot study evaluating the safety and feasibility of neoadjuvant nivolumab as monotherapy for a limited number of patients with resectable NSCLC has demonstrated that nivolumab is safe, does not delay surgery, and induces a major pathological response in 9 of 20 resected tumors (45%) (32). Translational analyses revealed a significant correlation between the pathological response and the pretreatment tumor mutational burden, and the number of T-cell clones that were found in both the tumor and peripheral blood expanded significantly after neoadjuvant nivolumab therapy in 8/9 patients evaluated. These remarkable results highlights the need to test additional immunotherapy- based combination in the neoadjuvant setting to discover efficacy signal of compounds to be tested in larger trials.

3.13 TCD8+ TILs as a prognostic marker.

Several studies have demonstrated that $TCD8^+$ TILs are associated with improved outcomes in resected NSCLCs (33-35). PD-1 and/or CTLA4 blockade are expected to recruit antigen specific $TCD8^+$ cells to the tumor microenvironment, and therefore contribute to an enhancedimmune response. As such, automated quantification of $TCD8^+$ cells in resected specimensfollowing induction immunotherapy may provide evidence for its role as a surrogate marker ofefficacy of these drugs, and is included as a secondary endpoint in this study. Additionally, phenotypic characterization of the immune infiltrate (such as evaluation of exhausted T cells)may also be important to evaluate potential differences in outcomes to single agent versus combined immune checkpoint blockade (36).

4. RATIONALE OF THE STUDY

Immunotherapy with anti-PD1 therapy has shown to improve response rates and survival outcomes in NSCLC patients. TGFβ, being a central determinant of an immune suppressive tumor microenvironment (TME) may be a key resistance mechanism in PD-L1 therapy

strategies. TGFβ signaling may promote an immune suppressive microenvironment by directly inducing T cells to differentiate into T_{regs} or indirectly via attraction of immunosuppressive immature myeloid and MDSCs into the TME. Upregulation of TGF-β signaling has been associated with primary (*de novo*) resistance to anti-PD-1 treatment in patients with metastatic melanoma and following development of acquired resistance to these agents following an initial response to therapy. Given the ability of M7824 to sequester TGF-β in the circulation away from the TME, we hypothesize that M7824 may promote T cell effector function via disruption of PD-1/PD-L1 axis to enhance anti-tumor response in patients with surgically resectable NSCLC.

5. HYPOTHESIS

The primary research question to be tested in this study is whether in patients with stage I-IIIA NSCLC amenable for surgical resection, induction immunotherapy with 3 doses of M7824 monotherapy will produce major pathologic responses in resected tumors as determined by Pataer et al. (JTO 2012).

The secondary research question to be tested in this study is that immunotherapy with M7824 will induce immune responses (as assessed by CD8+ TILs), tumor shrinkage (as assessed by CT), and improve recurrence-free survival (RFS) and overall survival (OS) in a subset of patients; analysis of correlative studies in these patients will assist in developing biomarkers predictive of response to immunotherapeutic agents in NSCLC and will assist in determining immune modulation by M7824.

5.1 Overall Benefit and Risk

The risk-benefit ratio has been carefully considered in the planning of the trial. Based on the preclinical data available to date, the conduct of the trial is considered justifiable using the dose and schedule of M7824 as specified in this protocol. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit ratio and would render continuation of the trial unjustifiable. The following are considered potential risks of exposure to M7824:

- Infusion-related reactions including hypersensitivity
- irAEs / autoimmune disorders
- Anemia
- Rash with hyperkeratosis, keratoacanthoma, and squamous cell carcinoma of the skin
- Alterations in wound healing or repair of tissue damage
- Embryofetal toxicities
- Mild to Moderate Mucosal Bleeding Events

Respective safety measures that comprise inclusion / exclusion criteria for participation in clinical trials with M7824, guidance for prevention, monitoring, and medical management of

potential risks, as well as guidance on study treatment interruption or discontinuation. See Section 3 above for a summary of clinical safety findings observed with M7824.

Infusion-related Reactions / Hypersensitivity

Infusion-related reactions hypersensitivity are a risk inherent to the administration of any recombinant protein to humans. Incidence of immunogenicity and character or severity of immunogenicity-induced side effects cannot be predicted by animal models because humanized or fully human proteins usually provoke a much stronger immune-response in rodents or non- human primates than in humans. The parent antibody caused lethal immune-mediated anaphylactic hypersensitivity reactions in mice after repeated application, while a control antibody lacking pharmacological activity only triggered a moderate immune reaction. However, in primates (cynomolgus monkeys), as a species closer to human, neither in the pilot 4-week IV repeat-dose toxicity trial nor in the pivotal 13-week IV infusion repeat-dose toxicity trial, clinical signs of hypersensitivity have been seen at dose levels of 20, 60, and 140 mg/kg, respectively.

Immune-related Adverse Events / Autoimmune Disorders

Since inhibition of PD-L1 and TGFβ signaling stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in the dedicated section of the protocol.

Anemia

As the 4-week toxicology studies in cynomolgus monkeys demonstrated reversible decreases in red blood cell counts, as well as corresponding Hgb and hematocrit, anemia is considered a potential risk. Inclusion criteria for the study will require adequate entry Hgb value. Risk management measures are provided in the dedicated section. The amount of blood drawn during the study for non-essential biomarkers will be carefully considered, especially given the preclinical finding of reduced Hgb levels.

Alterations in Wound Healing or Repair of Tissue Damage

Alternations of wound healing and tissue damage repair are considered a potential risk given the TGFβ mechanism. Management should be discussed with the principal investigator on a case-by-case basis.

Rash with HyperKeratosis / Keratoacanthoma /Squamous Cell Carcinoma of the Skin

Phase I information from a TGF antibody showed excess keratoacanthomas, some with atypical features, and one confirmed squamous cell carcinoma (Morris 2014). A genetic disorder in the TGF pathway is also known to be associated with skin tumors (Goudie 2011). In the NSCLC 2L cohort of EMR200647-001, 7% of patients treated with M7824 developed these events. No patients were required to be discontinued from trial due to these lesions: they were typically well managed with simple excision and/or observation (22). Based on this information, skin tumors are considered a potential risk. Monitoring will include skin assessments as defined in the schedule of assessments. Management should be discussed with the on a case-by-case basis. Dermatological consults should be requested as needed. Rash with hyperkeratosis / keratoacanthoma / squamous cell carcinoma of the skin are considered as AESIs requiring expedited reporting from the Investigator to the Sponsor. Any suspicious lesion should be biopsied. For non-serious AESIs, an AESI Report Form has to be completed; for serious events, an SAE Report Form has to be used.

Embryofetal Toxicity

Embryofetal toxicities are a known risk of the PD-1 / PD-L1 targeting class. Animal models link the PD-1 / PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Based on its mechanism of action (MoA), M7824 may cause fetal harm when administered to a pregnant female. An appropriate contraception warning is provided in this clinical protocol. Subjects with pregnancy or in lactation period are prohibited from being enrolled in clinical trials.

Mild to Moderate Mucosal Bleeding Events

Mucosal bleeding events of mild to moderate severity were observed in participants treated with M7824 in ongoing studies and are a potential risk for M7824. Events may include epistaxis, hemoptysis, gingival bleeding, or hematuria among others. In general, majority of these events were observed to be self-limiting, did not require intervention, and resolved without discontinuation of study treatment.

5.2 Potential Benefit

Although considerable progress has occurred in understanding the biological characteristics of cancer as well as the development of more effective treatment regimens, most patients with locally advanced NSCLC succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for this potentially curable patient population.

Immune checkpoint blockade with anti-PD-1 therapy offers the chance to improve outcomes of patients with NSCLC treated with surgical resection on an outpatient basis. Treatment with M7824 may have the potential to provide significant benefit by shrinking tumors and preventing loco-regional and/or distant metastasis by inhibiting TGFβ, a pivotal factor involved in establishing an immune suppressive tumor microenvironment and a potential mechanism of resistance in PD-L1 therapy strategies. M7824 therapy has the ability to sequester TGF-β in the circulation far from the tumor microenvironment and may promote T cell effector function via disruption of PD-1/PD-L1 axis to enhance anti-tumor responses in the induction setting.

Therefore, M7824, which targets a possible immunotherapy resistance mechanism in the form of TGFβ upregulation, may prove beneficial when administer as induction therapy in in early stage NSCLC patients.

6. STUDY ENDPOINTS

6.1 Primary Endpoints

- Major pathologic response (MPR) rate in patients treated with induction M7824 monotherapy.

MPR is defined as ≤ 10% viable tumor cells in the resected specimen using the methods described by Pataer et al (20). Briefly, at least 1 section per cm of tumor greatest diameter is evaluated, with a minimum of 5 slides. The percentage of residual tumor is determined by comparing the estimated cross sectional area of the viable tumor foci to estimated cross sectional areas of necrosis, fibrosis and inflammation on each slide. The results for all slides are averaged together to determine a mean value of viable tumor cells for each patient.

6.2 Secondary Endpoints

- Toxicity (assessed by the NCI CTCAE version 5)
- Peri-operative morbidity and mortality
- Response rates to induction treatment (by RECIST version 1.1) (1)
- Recurrence-free survival and Overall survival
- Survival rates at 12, 18 and 24 months
- To correlate major pathologic response with recurrence-free and overall survival
- Complete resection (R0) rate
- Pathologic complete response (pCR) in resected tumor specimens
- To correlate response assessed by imaging studies with outcomes (both major pathologic response to treatment and long-term recurrence-free survival)
- CD8+ TILs in resected tumor tissues of patients treated with M7824

Quantification of CD8+ TILs will be assessed by counting the cells positive for staining with an anti-CD8 antibody by immunohistochemistry and/or immunofluorescence in five random square areas (1 mm^2 each) in both intratumoral and peritumoral compartmentsusing anautomated system.

6.3 Exploratory Endpoints

An important aspect of this trial is to identify novel prognostic and predictive markers present at diagnosis, and to determine modulation of markers by induction M7824 monotherapy in order to

inform future translational studies. As such, blood, stools, tumor tissue and adjacent normal lung tissues will be collected throughout the study period. The markers to be assessed in these
specimens (likely with the use of high throughput technology) will be determined according to the best scientific knowledge and technology available at the time of batch analysis. Correlative studies will be interpreted as hypothesis- generating data, to be validated in subsequent trials. Candidate markers to be evaluated include (but are not restricted to):

- PD-L1 expression in tumor tissue
- Multi-region next generation DNA and/or RNA sequencing in tumor tissue (including whole exome and/or whole genome sequencing) and in blood/normal tissue, so that tumor heterogeneity and mutational load can be correlated with efficacy of immunotherapy and/or other correlative markers
- Immunophenotyping or characterization of the immune cell subsets in tumor tissue, including markers of T cell exhaustion (CD3, PD-1, CD4, CD8, CTLA-4, CD45), T cell activation (CD3, CD28, CD44, CD8, CD62L, CD45), T regulatory cells (CD3, FOXP3, CD8,CD4, CD25, CD45), T cell function (CD3, IFN-gamma, CD4, CD8, IL10, CD45), antigen presenting cells (CD11B, CD11C, GR-1, CD86, PD-L1, CD45), as well as CD20, Ki67, granzyme B, IFN-γ, TGF-beta, GATA-3, RORgt, BCL2 (thus allowing for estimation of T cell activation, and Th1/Th2/Th17 bias), as well as CD68 and other markers relevant to immune profiing.
- Expression of immunoregulatory and co-stimulatory markers in TILs by flow cytometry, including, but not limited to, PD1, CTLA4, LAG3, 41BB, and TCR zeta chain
- RNA and protein expression in tumor and adjacent normal tissue, including assessment of immune/inflammatory pathways
- Immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types
- Single cell genomics in tumor (including tumor positive nodes, where available) and adjacent normal tissue
- Serum soluble factors, including IFN-gamma and interferon inducible factors (such as CXCL9 and CXCL10), PD-L1, PD-1, anti-tumor antibodies, microRNAs (such as miR-513, and miR19b), IL-12, TNFα, IL-10, TGF-β, VEGF, IL-6, IL-8, IL-17, IL-18, C-reactive protein and, as well as other cytokines, chemokines, inflammatory factors and immune mediators T cell receptor repertoire sequencing in tumor tissue and the periphery
- Next generation sequencing of cell-free circulating DNA
- Immunopeptidome analysis
- Enteric microbiome analysis
- CT imaging analysis
- To correlate blood, tissue, and stool-based biomarkers with efficacy and toxicity

6.4 Additional assessments

In addition to the endpoints described above, post-treatment TILs will also be isolated, expanded and evaluated for anti-tumor activity *in vitro*. TILs may also be stored for future re-infusion into patients that develop disease recurrence as part of a separate clinical trial. We hypothesize that the efficiency of TIL isolation and efficacy of adoptive T-cell therapy will be

improved when cells are collected post exposure to checkpoint inhibitors, thus providing further rationale for developing induction immunotherapy strategies in resectable NSCLCs.

7. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives, and In compliance with the protocol.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

8. STUDY DESIGN AND PLAN

8.1 Modular design of neoadjuvant signal-finding study platform

Given the promising activity and safety demonstrated by neoadjuvant nivolumab, several immunotherapy-based regimens are now being tested in the neoadjuvant setting in phase 2 studies using the MPR as primary endpoint of efficacy. It follows that the best approach to expedite the evaluation of novel and active therapeutic strategies that merit further investigation in larger randomized trials, would be a modular platform clinical trial of single arm, signal-finding and efficacy-testing studies. M7824 has demonstrated promisingly clinical efficacy in NSCLC compared to prior immunotherapies, and therefore will be provide the backbone for this trial. Based on this modular design, upon completion of a proposed single arm study, a follow-on evaluation could result in either a randomized comparison, if a signal of activity is observed' or the launch of another single arm study evaluating a new immunotherapy combination, if the proposed study fails to demonstrate a signal of activity. A new arm will be launched based on emerging data in a protocol amendment.

8.2 Study Plan

This is an open label, phase 2 platform study with modular design testing the experimental agent M7824 in the neoadjuvant setting. We will start investigating M7824 monotherapy induction treatment in patients with resectable NSCLC, with the primary objective to determine the MPR in each arm, and compare it not between arms, but to the benchmark from historical controls of neoadjuvant chemotherapy.

After confirmation of eligibility criteria, patients will be enrolled in Arm A. Sequential arms investigating induction M7824-based strategies may be added after completion of enrollment in Arm A.

Arm A — M7824 monotherapy

9. TREATMENT

9.1 Induction Treatment

Patients will receive induction treatment, as follows:

Arm A: M7824 1200 mg intravenously (IV) on days 1, 15, and 29

9.2 Surgery

Surgery will be performed after completion of induction therapy. It is strongly recommended that 3 doses of M7824 (Arm A) are administered prior to surgery. However, less than 3 doses of M7824 will be allowed in case of excessive toxicities or other reasons identified by the treating physician that may lead to an unfavorable benefit/risk ratio of proceeding with therapy as planned per protocol, after discussing the case with the principal investigator.

There must be at least 4 to 6 weeks M7824-free interval before surgery (i.e., surgery will only be performed at least 4 to 6 weeks after the last dose of M7824, unless there is a strong clinical indication to perform surgery sooner, in the opinion of the treating physician). It is strongly recommended that surgery be performed within 4 to 6 weeks after the last dose of M7824 induction therapy.

The operative approach (thoracoscopy versus thoracotomy) and the extent of surgical resection will be based on the treating surgeon's judgment and may include wedge resection, segmentectomy, lobectomy, or pneumonectomy with mediastinal lymph node dissection of nodal stations 4, 7, 8, 9, 10, 11-14 for right sided resections, and nodal stations 5, 6, 7, 8, 9, 10, 11-14 for left sided resection.

9.3 Post-operative (Adjuvant) Systemic Therapy

Since the primary efficacy endpoint of this study is major pathologic response (which will be assessed at the time of surgery), mandatory use or mandatory prohibition of post-operative (adjuvant) systemic therapy will not be defined by this protocol. Patients may receive adjuvant systemic therapy at the discretion of the treating physician. For patients with stage IB (with tumor size 4 cm or greater), II, and III, at least 3 cycles of adjuvant cisplatin- based chemotherapy are recommended. In case adjuvant systemic therapy is used, this information will be captured by retrospective chart review and may be used for interpretation of analysis of long-term treatment outcomes.

9.4 Post-operative (Adjuvant) Radiation Therapy

Since the primary efficacy endpoints of this study is major pathologic response (which will be assessed at the time of surgery), mandatory use or mandatory prohibition of post-operative (adjuvant) radiation therapy will not be defined by this protocol. Post-operative radiation therapy

will be delivered according to institutional guidelines and the treating physician's best judgement, preferably within 6 weeks of surgical resection or completion of adjuvant systemic therapy (whichever is longer). While radiation therapy is not formally required per protocol, it is strongly suggested that the following principles of radiation therapy be followed:

- Consider post-operative radiation therapy in patients with pathologic confirmation of mediastinal lymph node involvement by cancer either before or after inductiontreatment.
- Consider post-operative radiation therapy in patients with positive margins at surgical resection.
- When recommended, deliver either photon- or proton-based external beam radiation therapy between 50-66 Gy depending on the completeness of tumor resection.Typically 50 Gy in 25 fractions is given for R0 resection, 60 Gy in 30 fractions for R1, and 66 Gy in 33 fractions for R2 resection. The final dose will be left up to the treating radiation oncologist.

In case adjuvant radiation therapy is used, this information will be captured by retrospective chart review and may be used for interpretation of analysis of long-term treatment outcomes.

10 ELIGIBILITY CRITERIA

All eligibility criteria must be met prior to initiating treatment.

10.1 Inclusion Criteria

1. Age ≥ 18 years
2. Histologically or cytologically confirmed previously untreated NSCLC. If a diagnostic biopsy is available, a pre-treatment biopsy is not required. Patients with a suspected lung cancer are eligible, but pathology must be confirmed prior to initiating treatment on study. Neuroendocrine carcinomas (e.g. SCLC, large cell neuroendocrine carcinoma, atypical carcinoid, carcinoid) are not eligible. Non-small cell carcinomas with neuroendocrine differentiation are eligible.
3. Patients with stage I-IIIA disease and IIIB (T3N2 only, and N2 single station), according to AJCC 8th edition, are eligible for arm A of the study. Patients with stage III, N2 single station, must not have more than one mediastinal lymph node station involved by tumor.
4. All patients must have lymph node evaluation of contralateral stations 2 and/or 4 to exclude N3 disease.
5. The patient must be a suitable candidate for surgery, in the opinion of the treating physician.
6. Predicted FEV1 ≥ 50%
7. Predicted DLCO ≥ 50%
8. Signed and dated written informed consent must be provided by the patient prior to admission to the study in accordance with ICH-GCP guidelines and to the local

legislation

9. ECOG performance status score 0-1
10. Patients must have organ and marrow function as defined below:
    a. Absolute neutrophil count (ANC): $\geq 1.5 \times 10^9$/L
    b. Hemoglobin: ≥9.0 g/dL
    c. Platelets $\geq 100 \times 10^9$/L
    d. Total bilirubin: ≤ 1.5 X ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
    e. AST and ALT: ≤3 X ULN
    f. Creatinine: ≤1.5 X ULN or Calculated creatinine clearance[1]: ≥50 mL/min or 24-hour urine creatinine clearance: ≥50 mL/min

[1] *Cockcroft-Gault formula for creatinine clearance calculation:*

Female CrCl = (140 - age in years) x weight in kg x 0.85
72 x serum creatinine in mg/dL

Male CrCl = (140 - age in years) x weight in kg x 1.00
72 x serum creatinine in mg/dL

10.2 Exclusion Criteria

1. Mixed SCLC and NSCLC histology.
2. Major surgery within 4 weeks prior to the first dose of study intervention
3. Thoracic RT of > 30 Gy within 6 months prior to the first dose of study intervention.
4. Prior systemic therapy, including treatment with anti-PD-1/PD-L1 therapies and M7824, for treatment of the current lung cancer.
5. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy) or investigational anti-cancer drug.
6. Previous malignant disease (other than the target malignancy to be investigated in this study) within the last 2 years. Participants with a history of cervical carcinoma in situ, superficial or noninvasive bladder cancer, or basal cell or squamous cell carcinoma in situ previously treated with curative intent are NOT excluded. Participants with other localized malignancies treated with curative intent need to be discussed with the PI of the study.
7. Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (eg, corneal transplant, hair transplant).
8. Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV steroids
9. Pregnant or lactating female:
    - Women of childbearing potential (WOCB) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of immunotherapy.
    - Women of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or

bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

10. Unwillingness or inability to follow the procedures required in the protocol.
11. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment are also excluded.
12. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
13. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
14. Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief 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 contact allergen) is permitted.
15. History of positive hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid indicating acute or chronic infection.
16. History of positive human immunodeficiency virus or known acquired immunodeficiency syndrome.
17. History of severe hypersensitivity reaction to any monoclonal antibody and/or to study drug components, any history of anaphylaxis, or recent (within 5 months) history of uncontrolled asthma.
18. Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study.
19. Vaccine administration within 4 weeks of M7824 administration. Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).
20. Patients who are sexually active, with preserved reproductive capacity, and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females, condoms for participating males) during and after the trial as detailed below:

a. WOCBP should use an adequate method to avoid pregnancy for 65 days after the last dose of investigational drug.
b. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year.
c. Men receiving immunotherapy and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 125 days after the last dose of investigational product.
d. Women who are not of childbearing potential as well as azoospermic men do not require contraception.

21. Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule.

11. STUDY ASSESSMENTS

11.1 Performance status

The performance status of all patients will be graded according to the ECOG PS scale.

11.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed to assess eligibility for enrolment and will be repeated according to the schedule of assessment. Laboratory tests can be repeated more frequently, if clinically indicated.

11.3 Symptoms and toxicity assessment

The symptoms and adverse events of all patients will be graded at scheduled intervals according to the NCI CTCAE, v5.0. Patients will be monitored continuously throughout the study for the occurrence of adverse events. Planned medical interventions (e.g., planned surgical resection) will not be considered an adverse event. For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned surgical procedure (e.g., usual pain, usual bleeding, intra- or post-operative electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported. Unexpected surgical complications will be retrospectively reviewed at the end of treatment assessments.

11.4 Radiology assessments

CT chest, PET-CT, and CT brain / MRI brain will be obtained according to the study calendar included in the clinical trial protocol. CT chest examinations maybe obtained with dual energy modality. Response and progression will be evaluated in the study using the international criteria proposed by the RECIST committee, and preferably by the same investigator or collaborator.

Patients enrolled to this study may also be offered optional participation in a separate IRB-approved protocol evaluating additional imaging modalities for NSCLC. An independent informed consent process will be followed for accrual to such protocol.

11.5 Mediastinal Staging

Mediastinal staging should be accomplished by obtaining at least a CT chest or PET-CT. It is strongly recommended that patients with suspicious mediastinal lymph node involvement by PET-CT and/or CT chest undergo a mediastinoscopy or endobronchial ultrasound with biopsies for more detailed mediastinal staging. It is also strongly recommended that patients with clinical N1 disease and/or central tumors undergo mediastinoscopy or endobronchial ultrasound with biopsies. Patients with clinical N0 disease and a peripheral lesion may not warrant mediastinoscopy or endobronchial ultrasound with biopsies, however this will be at the discretion of the treating physicians.

11.6 Surgical Pathology

To determine the pathologic response, specimens will be grossed and processed by the pathologists assistant under the supervision of the thoracic pathologist to include gross measurement of specimen and residual tumor size. At least 1 block/1 cm of tumor will be submitted (average of 5-10 blocks/patient). All slides prepared from blocks taken from each specimen will be reviewed by the thoracic pathologist, The surgical specimens will then be evaluated histopathologically as per routine surgical pathology standard to include tumor classification and evaluation of lymph node and margin status. In addition, specimens will be evaluated for pathologic complete response and quantification of percentage of viable tumor cells. Pathologic staging is performed as per AJCC staging for lung cancer (8th edition).

11.7 Correlative Research: Biomarkers profiling

All patients consented to collection and analysis of biospecimen for correlative research will have their respective sample(s) collected as outlined below. All biospecimen will utilize our institution's approved biospecimen secured tracking platform such as BIMS or Prometheus. With each patient's sample collection, unique sample identifier labels are generated with a 2-D barcode to link/associate with the specific biospecimen collection. For each biospecimen type, a collection/processing/storage SOP is generated. All tissue and microbiome samples will be stored at ITB until analysis. All blood samples will be processed and stored in Drs. Tran and Cascone's Lab until analysis. At time of analysis, distribution of specific sample matrices to specified collaborator as described below. Again, the biospecimen tracking system will be used to provide the provision of the status in real-time of each and every collected, processed, and distributed biospecimen.

11.7.1 Tumor tissue collection, processing and analysis

11.7.1.1 Pre-Surgery

Archival tissue samples will be collected for histopathological examination and biomarkers, when available (at least 15 to 20 unstained slides and/or a tissue block are preferred). For patients without archival specimen, a new baseline tumor tissue sample from the primary tumor may be collected for histopathological examination and biomarkers. Samples will be obtained by an outpatient image-guided biopsy procedure (preferably core biopsy) or bronchoscopy. These

specimens should be fixed in 10% formalin, preferably immediately and not more than 1 (one) hour after excision. Fixed biopsy samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. A portion of the specimen obtained (or a second biopsy) will also be embedded in optimal cutting temperature compound and/or RNA later and/or culture media immediately after received and not more than 1 (one) hour after excision, frozen, and processed and/or stored at -80°C until analysis. All samples will be processed by and stored in ITB at -80°C should be placed in appropriate containers, labeled with the protocol number and the patient's unique study identification number. Tissue obtained during mediastinal staging may also be collected for biomarker evaluation.

11.7.1.2 Surgery

Tumor tissue will also be obtained at surgical resection and will be directly delivered to the pathology department to be processed as per Pathology SOP. The recommended procedure for obtaining the tissue specimens is as follows: a portion of the resected tumor tissue will be fixed in 10% formalin immediately after received and not more than 1 (one) hour after excision. Fixed samples will be processed for paraffin-embedding according to the Institutional Standard Operating Procedures. The paraffin blocks and slides should be labeled with the protocol number and the patient's unique study identification number and stored at room temperature. Another portion of the tumor specimen (preferably at least one sample ≥ 2 mm^3 or 100 mg) will be embedded in optimal cutting temperature compound and/or RNA later and/or culture media immediately after received and not more than 1 (one) hour after excision, frozen and processed by and stored at -80°C in ITB until biomarkers analysis.

11.7.1.3 Tissue Research Correlatives Analysis

The following plan is for residual tissue collected for research of correlative analysis ONLY after all standard pathlological clinical care has been completed. All residual tissue samples will be processed and stored in ITB until biomarkers analysis. The residual tumor tissues with or without adjacent lung tissue samples placed in culture media immediately after received will be processed for single cell suspension for single cell genomics and other biomarkers as specified below (37). Each cell will be bar-coded using 10x genomics technology (or other equivalent technologies) and libraries (RNA, DNA, or epigenomics) for sequencing. The sequenced data will be analyzed and we plan to associated sequencing data with clinical parameters.

Based on pathologist's assessment, clinical practice and discussion with pathology collaborator, if there are any residual normal lymph node tissue uninvolved by tumor may also be collected and processed by and stored in ITB until biomarker analysis. Additional analysis with new technical advancement and technologies in collaborative efforts may occur; these will be completed according to institutional's guidelines and approvals such as alliance or agreements with outside vendor(s).

Analyzed at UTMDACC labs based on availability of tumor tissue at each timepoint from pre-surgery (archival, biopsy) and at surgical resection:

a) whole exome (WES) and RNA sequencings: Ignacio Wistuba, Tina Cascone
b) tumor infiltrating lymphocytes (TIL): Chantale Bernatchez
c) single-cell RNA sequencing: Tina Cascone
d) T-cell receptors repertoire (TCR): Tina Cascone

11.7.2 Blood-based biomarkers

Blood will be collected (60 mL) – 4 x 10 mL sodium heparin, 1 x 10 mL STRECK or PAXGENE ctDNA, 1 x 10 mL EDTA, at scheduled intervals according to the study calendar as follows:

a) prior to treatment initiation (+/- 7 days),
b) within 7 days prior to dose #2 of M7842
c) within 7 days prior to dose #3 of M7842
d) at least 14 days after last dose of M7842
e) within 8 weeks after surgery

Blood samples collected and sent to the core laboratory to be processed and stored at -80°C or LN until analysis.

All blood samples will be analyzed at UTMDACC labs based on availability of blood samples at each timepoint as listed above:

a) cytokines and angiogenic factors (CAF) profiling: Hai Tran, Tina Cascone
b) circulating tumor DNA (ct-DNA) profiling: Hai Tran, Tina Cascone
c) circulating lymphocytes profiling: Chantale Bernatchez
d) TCR sequencing/exome sequencing: Tina Cascone

Additional analysis with new technical advancement and technologies in collaborative efforts may occur; these will be completed according to institutional's guidelines and approvals such as alliance or agreements with outside vendor(s).

11.7.3 Stool-based biomarkers

Patients will provide their stool samples as detailed in the study calendar follows:

a) prior to treatment initiation (+/- 7 days)
b) at least 14 days after last dose of M7842

Stool collection will be performed with commercially available collection kits OMNIgene-Gut from DNA Genotek company. These kits will be provided to patients at no cost. The collected stool samples will be stored by ITB until analysis

a) microbiome profiling: Boris Sepesi, Tina Cascone.

11.7.4 CT imaging-based biomarkers

The imaging data will be saved to retrospectively reconstruct and post-process the images for further investigating advanced quantitative algorithms with the goal to improve detection and characterization of disease along with potential biomarkers to assess response to immune checkpoint blockade.

11.7.5 Pharmacokinetics and Anti-Drug Antibody

To evaluate population steady-state concentrations (PK) and potential development of anti-drug antibody (ADA), blood will be collected at the following timepoints as sponsor's lab manual.

Pharmacokinetics Samples:

a) PK 1 - Dose #1 M7824: Prior to infusion of Dose #1 (60 minutes prior to infusion)
b) PK 2 - Dose #1 M7824: immediately after infusion (within 60 minutes after infusion)
c) PK 3 - Dose #2: Prior to infusion Dose #2 (60 minutes prior to infusion)
d) PK 4 - Dose #3 M7824: Prior to infusion Dose #3 (60 minutes prior to infusion)
e) PK 5 - Dose #3 M7824: immediately after infusion Dose #3 (within 60 minutes after infusion)
f) PK 6 - at least 14 days after Dose #3

Anti-Drug Antibody samples:

g) ADA 1 - Dose #1 M7824: Prior to infusion of Dose #1 (60 minutes prior to infusion)
h) ADA 2 - Dose #3 M7824: Prior to infusion Dose #3 (60 minutes prior to infusion)
i) ADA 3 - at least 14 days after Dose #3

12. Study Intervention(s) Preparation, Handling, Storage, and Accountability

Further guidance and information for the preparation, handling, and storage of study intervention(s) are provided in the Pharmacy Manual.

The Investigator and MD Anderson Cancer Center are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply or administer it. All study intervention(s) must be stored in a secure, environmentally-controlled, an monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, container numbers, expiry dates, formulation (for study interventions prepared at the site), and the

participant numbers.

- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- Destruction of used and unused study intervention(s) should be performed at site if allowed by local law only after Sponsor authorization.

13 Study Intervention Compliance

In this study, participants will receive study intervention at the investigational site. Well-trained medical staff will monitor and perform the study intervention administration. The information of each administration including the date, time, and dose of study intervention will be recorded on the electronic Clinical Oncology research System (DMI). The Investigator will make sure that the information entered into the system regarding study intervention administration is accurate for each participant. Any reason for nonadherence should be documented. Nonadherence is defined as a participant missing > 1 cycle of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. Extenuating circumstances should be documented, and when possible, discussed with the Sponsor in advance. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons, the criterion for insufficient adherence is met as well.
Consequences of noncompliance may lead to discontinuation of study interventions as described in the dedicated section. In case of overdose, see section below.

13.1 Overdose

Experience with overdose of M7824 is not available. In case of overdose symptomatic treatment has to be applied, there are no known antidotes for the compound.

For this study, any dose of immunotherapy greater than 2 times more than the planned dose administered within a 24-hour time period will be considered an overdose.
In event of overdose, infusion should be discontinued and participants should be observed closely for any signs of toxicity. Supportive treatment should be provided if clinically indicated. If an AE occurs resulting from overdose, it should follow SAE reporting criteria.
If an incidence of overdose occurs meeting the protocol-defined definition without any association of symptoms or laboratory abnormalities, then it should be reported as a non-serious AESI, using the terminology “accidental or intentional overdose” without adverse effects

14. Concomitant Therapy

Record in the electronic system, the EMR, all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed

consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

14.1 Permitted Medicines

The only permitted medications are the following:

1. Any medications (other than those excluded by the exclusion criteria or the prohibited medicines) that are considered necessary for the participants' welfare and will not interfere with the study intervention may be given at the Investigator's discretion.
2. Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described as part of precautions

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

14.2 Prohibited Medicines

As stated for the exclusion criteria, participants must not have had prior systemic cytotoxic chemotherapy for their NSCLC OR any antibody or drug targeting T-cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody OR concurrent anticancer treatment including:

- Cytoreductive therapy
- Radiotherapy delivered for non-palliative indications
- Use of any investigational drug as specified in Schedule of Activities.
- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products. Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs is allowed).
- Vaccine administration within 30 days before M7824 administration.
- Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines). If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study intervention and should complete the End-of-Treatment Visit and be followed for survival.

14.3 Permitted/Prohibited Procedures

<u>Permitted Procedures</u>
Bone-directed organ-sparing radiotherapy may be administered for palliative and/or specific clinical indications during the study. The assessment of PD will be made according to RECIST 1.1 and not based on the necessity for palliative radiotherapy. The indication for palliative radiotherapy should be documented in the patient medical

record.

Prohibited Procedures
The following nondrug therapies must not be administered during the study (or within 28 days before enrollment):

- Major surgery (excluding prior diagnostic biopsy and surgical resection of lung cancer for which patient is being treated on trial) within 4 weeks before the start of the study.

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14.4 Other Interventions

The following nondrug therapies must not be administered during the study:

- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).

14.5 Dose Selection and Modification

Justification for M7824 dose
The RP2D for M7824 is 1200 mg administered as an iv infusion q2w. The selection of RP2D is based on the available clinical data from Phase I Study EMR200647-001 and Study MS200647-0008, including safety/tolerability, pharmacokinetics (PK), and pharmacodynamic (such as PDL1 target occupancy [TO] in PBMCs and TGFβ trapping in blood), as well as efficacy in 2L NSCLC cohorts from Study EMR200647-001. The selection of RP2D is also supported by population PK (pop PK) and exposure-response modeling and simulation.

Safety/tolerability in Phase I
The highest dose for M7824 tested in EMR200647-001 was 30 mg/kg, which corresponds to 2100 mg for a 70-kg participant (the median body weight in the current dataset) and to 2400 mg for an 80-kg participant (corresponding to a typical median body weight for solid tumor type participants) (Freshwater, 2017; Bajaj, 2017; Zhao, 2017). Based on clinical observations, M7824 is well tolerated up to 30 mg/kg and the maximum tolerated dose was not reached. In addition, for the 2 dose levels evaluated in 2L NSCLC cohorts of Study EMR200647-001 (500 and 1200 mg iv q2w), there was no apparent dose-dependency in observed toxicities.

Preclinical pharmacology and Phase I dose escalation PK and pharmacodynamics
The PK dose-proportionality, peripheral PD-L1 TO/TGFβ trapping from the dose escalation phase of Study EMR200647-001 (at doses of 1, 3, 10, 20, and 30 mg/kg q2w), and preclinical pharmacology studies with M7824 supporting the RP2D of 1200 mg q2w are described in the Investigator's Brochure. In brief, the dose of 1200 mg q2w (corresponding to approximately 17 mg/kg for a 70-kg participant and to 15 mg/kg for an 80-kg participant) is within the efficacious dose range predicted based on modeling of preclinical pharmacology data in tumor-bearing mice. In participants with solid tumors, full pharmacological activity on PD-L1 in PBMC on TGFβ1 and

TGFβ3 (in blood) were observed at doses ≥ 3 mg/kg. It is important to consider that full pharmacological activity, including PD-L1 TO and TGFβ trapping is required at the tumor site, for which no data are available for M7824 in humans. It is likely that doses higher than 3 mg/kg q2w are required for full pharmacological activity at the tumor site (refer to the M7824 IB v4).

Flat dose rationale

To achieve less variability in exposure, mitigate the risk of dosing errors, reduce the time necessary for dose preparation, and reduce drug wastage compared with th weight-based dosing, a flat dose approach was adopted for expansion phases of Phase I clinical studies. The flat dosing approach for Phase II is supported by pop PK modeling and simulation using data from 350 participants from the 2 Phase I clinical studies of M7824 in multiple solid tumor types, which showed that although body weight was found to be a covariate for clearance, the estimated magnitude of the body weight exponent on clearance is < 0.5, predicting less exposure variability from flat dosing than that from body weight-based dosing (Wang, 2009).
Accordingly, simulations of AUC and Ctrough showed that variability in exposure was indeed slightly lower for flat dosing compared with weight-based dosing.

Preliminary efficacy and exposure-response analysis

Exposure-response and exposure-PFS assessments are based on data from 2L NSCLC 80 participants that were administered either 500 or 1200 mg of M7824 iv q2w) (n = 40 per cohort). As of the data cutoff of 25 October 2017, numerically higher confirmed ORR was observed in the 1200-mg cohort (25%), compared with the 500-mg cohort (20%) and the only CR was in the 1200-mg cohort. Similarly, there was a trend of longer PFS and OS in the 1200-mg cohort compared with the 500-mg cohort.

14.6 Study Intervention after the End of the Study

After a participant has completed the study at the postsurgical visit (approximately within 8 weeks after surgery) or has withdrawn early, participants may receive the care they and their physicians agree upon. Participants will be followed for survival and AEs. The overall end of the study is defined as when all protocol-defined assessments have been completed.

14.7 Special Precautions

As a part of precautionary safety measures, a risk management guidance is defined for M7824 treatment for IRRs and irAEs, which may arise due to the mAb inhibition of PD-L1.

14.7.1 Infusion-related Reactions Including Immediate Hypersensitivity

Infusion-related reactions including immediate hypersensitivity are defined in the dedicated section below and are important identified risks for M7824.

Infusion reactions may vary in manifestation and timing, and signs and symptoms usually develop during or shortly after drug infusion which generally resolves completely within 24 hours of completion of infusion. Infusion reactions like cytokine release syndrome may manifest similar signs and symptoms of an immediate hypersensitivity/allergic reaction.

The study intervention will be administered on an outpatient basis. As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents. At all times during M7824 treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions like anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. If no IRRs are observed during the first 2 infusions, the mandated 2-hour post infusion observation time is no longer required.

Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] iv or oral equivalent) approximately 30 to 60 minutes prior to each dose of M7824 is mandatory for the first 2 infusions, after which premedication is optional and at the discretion of the Investigator. Steroids as premedication are not permitted. If Grade ≥ 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped.

An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion. These possible IRRs are identified based on a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and divided into reactions versus signs and symptoms.

- An IRR should be considered when onset is on the day of infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for any infusion-related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.
- Signs and symptoms of IRRs and hypersensitivity/allergic reactions should be considered when onset is on the day of infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset. Signs and symptoms may include, but are not limited to: rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, fever, dyspnea, back pain, abdominal pain, and urticaria.

Table 2. Treatment Modification for Symptoms of Infusion-related Reactions

CI-CTCAE v5.0 Grade Treatment Modification	**Treatment modifications**
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Increased monitoring of vital signs as medically indicated, presuming these participants are deemed medically stable.
Grade 2 – moderate • Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 hours.	Stop M7824 infusion. Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending Investigator. If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next schedule. If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the M7824 infusion immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization may be indicated. Participants will be permanently withdrawn immediately from M7824 treatment and must not receive any further M7824 treatment
iv = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs. For Grade 3 or 4 infusion-related reactions, M7824 discontinuation is mandated. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation and infusion must be recorded.	

In the event of a Grade 2 IRR that does not improve or worsens after implementation of the dose modifications indicated in Table 2 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (for example, famotidine or ranitidine), in addition to premedication, for select participants. However, prophylactic steroids are NOT permitted. At next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication

to premedication, the infusion should be stopped and the participant removed from treatment.

Hypersensitivity Reaction

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdf. Participants should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms may include, but are not limited to:

- Impaired airway
  - Decreased oxygen saturation (< 92%)
  - Confusion
  - Lethargy
  - Hypotension
  - Pale/clammy skin
  - Cyanosis

Management of hypersensitivity includes:

1. Epinephrine injection and iv dexamethasone
2. Participant should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
3. Alert intensive care unit for possible transfer if required.

Prophylaxis of flu-like symptoms

For prophylaxis of flu-like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each iv infusion.

14.7.2 Immune-related Adverse Events

Immune-related AEs are specific to immunotherapies and vary by organ system. Immune-related AEs are important identified risks for M7824. The recommendations for irAE management, in accordance with the joint American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (Brahmer, 2018) and National Comprehensive Cancer Network (NCCN) (NCCN Guidelines®), are listed in Appendix 1. These irAEs include: pneumonitis, colitis, hepatitis, endocrinopathies (including hypophysitis, thyroid disorders, type 1 diabetes mellitus), and nephritis.

General management by NCI-CTCAE v5.0 grading, as per ASCO, is listed below:

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/d of prednisone or equivalent).

- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
- Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

For organ/system specific management guidelines, review ASCO guideline tables in Appendix 1.

14.7.3 Potential TGFβ-mediated Skin Adverse Events

Skin AEs possibly due to TGFβ inhibition, including hyperkeratosis, KA and/or cutaneous squamous cell carcinomas (cSCC), are important identified risks for M7824 and are described in Section 6.9.1. Cases of KA and cSCC have also been reported for patients under treatment with other checkpoint inhibitors as well (Freites-Martinez, 2017; Bednarek, 2018).
Skin assessments are performed at Baseline and 6 weekly for all participants (see Section 1.3 [Schedule of Activities]). A detailed medical history of genetic or iatrogenic skin conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried. For participants experiencing a dermatologic-related AE (hyperkeratosis, KA, or cSCC), initial biopsy with pathology report of initial AE is expected.
Additional excisional biopsies of suspicious lesions should occur, and management discussed with the Medical Monitor provided by the IND office as indicated. Dermatology consultation is encouraged for diagnosis,
outcome and follow-up.

14.7.4 Anemia

Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

General Guidance for anemia management and evaluation:

- Participants must enter the study with hemoglobin values at least 9 g/dL.
- All relevant hematologic testing for treatment-related anemias should be done prior to blood transfusion, if clinically feasible.
- Transfusion should be performed at the discretion of the Investigator, based on clinical assessment and considered when participant experiences significant anemia.

15 Management of Adverse Events of Interest

15.1 Adverse Events of Special Interest (AESI)

Adverse events of special interest are serious or nonserious AE specific to the known mechanism of action of the treatment drug. These events are of clinical interest, which require close monitoring and rapid communication for optimal management. The method of AESI recording and reporting will follow the guideline for AE recording and reporting (refer to Appendix 2). Safety measures to mitigate risks of AESIs include decisions for

Inclusion/exclusion criteria prior to study enrollment and guidance for prevention, monitoring, diagnostic work-up and management of potential risks, as well as guidance on study intervention interruption or discontinuation for study participants.

Infusion-related reactions, including immediate hypersensitivity

Any signs or symptoms experienced by participants during the infusion or any event occurring during or within 1 day of drug administration should be evaluated as a potential IRR. IRRs are common adverse drug reactions (ADRs) with mAbs that occur temporally related to drug administration. Reported signs/symptoms have included anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among others. IRRs are an AESI for M7824, and important identified risks for M7824; precautions and management are discussed in the dedicated section.

Immune-related adverse events

Immune-related adverse events are defined as off-target immune-mediated side effect associated with exposure to an immunogenic drug. In the evaluation of irAEs, a full differential diagnosis should be considered in the diagnostic work-up, including possible etiologies such as neoplastic, infectious, metabolic, toxin, etc. Serologic, histologic (biopsy), and/or immunologic work-up should be performed as indicated to evaluate the differential diagnosis and/or support an immune-mediated cause. Immune-related AEs are AESIs for M7824 and important identified risks for M7824; the precautions and management are discussed in the dedicated section.

Skin adverse events

Skin AEs are AESIs for M7824 and include 2 potential mechanisms:

1. Skin AEs possibly due to TGFβ inhibition are grouped as rash with hyperkeratosis, KA, and SCC of skin. Skin lesions with hyperkeratosis, KA, cutaneous squamous cell treatment-related skin AEs were well managed and did not require treatment discontinuation in Studies EMR200647-001 and MS200647-0008. Similar lesions have also been described with other immune checkpoint inhibitors; therefore, monitoring and diagnostic work-up is required for both treatment arms.
2. Immune-related skin AEs possibly mediated by PD-L1 inhibition (events in this category are also reported under irAE).

Treatment-related Anemia Adverse Events

Anemia is considered a potential risk based on toxicologic findings with M7824 in cynomolgus monkey indicating a decrease in hemoglobin, red blood cell count (RBC), and hematocrit, which was fully reversible or showed a trend toward recovery after treatment discontinuation. Treatment-related anemia AEs are AESIs for M7824. A consistent clinical risk of treatment-related anemia on M7824 was not observed in Study EMR200647-001. As summarized in the Investigator's Brochure (Version 4), treatment-related anemia was reported in 6.1% of participants in pooled cohort data (n=23; 3.4% Grade 3+ (n=13). In the NSCLC 2L cohort of the study, treatment-related anemias were reported in 2 participants (2.5%), both of which were in the 500-mg cohort (data cutoff 12 March 2018). No consistent and/or specific etiology was identified for related anemia events. For more information, refer to dedicated section in this protocol and the Investigator's Brochure.

15.2 Potential Risks

Alterations in Wound Healing or Repair of Tissue Damage

Due to the involvement of TGFβ in tissue and skin repair, alterations in wound healing or repair of tissue damage is considered an important potential risk. No relevant event is reported in the ongoing M7824 clinical studies. Monitoring of any surgical wounds while on study is recommended. In general, a 2-week delay from treatment is recommend following minor surgery and 4 week delay for major surgery.

Embryo-fetal Toxicities

Embryo-fetal toxicities are a known risk of the PD-1/PD-L1 targeting class. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (Guleria, 2005; Leber, 2010; Wafula, 2009; Zenclussen, 2013). Embryo-fetal and reproductive toxicities have also been investigated in animal models for a humanized monoclonal antibody targeting TGFβ1. At doses as high as 30 mg/kg, no maternal reproductive toxicity or embryo-fetal lethality were observed in rabbits (Hilbish, 2016). To mitigate these potential risks, pregnant participants are excluded from the study, and all participants of childbearing/conceiving potential must use highly-effective contraception.

Mild to Moderate Mucosal Bleeding Events

Mucosal bleeding events of mild to moderate severity were observed in participants treated with M7824 in ongoing studies and are a potential risk for M7824. Events may include epistaxis, hemoptysis, gingival bleeding, or hematuria among others. In general, majority of these events were observed to be self-limiting, did not require intervention, and resolved without discontinuation of study treatment.

15.3 Adverse Drug Reactions Requiring Treatment Discontinuation

Adverse drug reactions are defined in this study as any AEs related to study intervention assessed by the Investigator and/or Sponsor. Serious adverse reactions are ADRs which are assessed as serious.

Immune-related AEs, IRRs, anemia, and potentially TGFβ-mediated skin AEs are managed and followed-up in their respective sections as indicated below. Permanent treatment discontinuation may be recommended, so the relevant section must be reviewed:

- For management and guidance of suspected irAEs, see dedicated section in this protocol
- For infusion-related reactions and hypersensitivity reactions guidance, see dedicated section in this protocol
- For guidance and management for potentially TGFβ mediated skin AEs, see dedicated section in this protocol

General guidance:

- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is an indication for permanent treatment discontinuation (except for use of steroids as hormone substitution).
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0 to 1 within 12 weeks after last dose of study intervention is an indication for permanent treatment discontinuation.

Grade 4 ADRs:

Participants with any Grade 4 ADRs require permanent treatment discontinuation except:

a. isolated laboratory values out of normal range that do not have any clinical correlation.

b. endocrinopathies controlled with hormone replacement therapy.

See dedicated section for other suspected Grade 4 irAEs, as most require permanent treatment discontinuation.

Grade 3 ADRs:

1. Participants with any severe or Grade 3 treatment-related adverse reactions that recur should be permanently discontinued. Exceptions may be considered as follows:

a. Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.

b. Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or baseline.

c. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

d. Grade 3 hemoglobin decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor.

e. Increases in ECOG PS ≥ 3 that resolves to ≤ 2 by Day 1 of the next infusion (ie, infusions should not be given if the ECOG PS is ≥ 3 on the day of treatment and should be delayed until ECOG PS ≤ 2).

f. Keratoacanthomas and/or cSCC (see Section 6.8.3 for management).

2. See Appendix 1 for suspected Grade 3 irAEs as many require permanent treatment discontinuation, including pneumonitis and nephritis.

a. AST or ALT > 5 times ULN or total bilirubin greater than 3 times ULN must be permanently discontinued, except for participants with liver metastases (for example) who begin treatment with Grade 2 AST or ALT. These participants should be discontinued if AST or ALT increases by ≥ 50% relative to baseline and lasts for at least 1 week.

3. Persistent Grade 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0 to 1 within 12 weeks after dose of treatment.

Grade 2 ADRs should be managed as follows:

a. If a Grade 2 ADR resolves to Grade ≤ 1 by the day before the next infusion, treatment may continue.
b. If a Grade 2 ADR does not resolve to Grade ≤ 1 by the day before the next infusion, but it is manageable and/or not clinically relevant, the PI should be consulted to assess if clinically reasonable to administer the following infusion.

16 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

16.1 Discontinuation of Study Intervention

Participants will be withdrawn from treatment for any of the following reasons:

- A participant may withdraw from the study at any time, at his/her own request (ie, withdrawal of consent), and without giving a reason.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator.

The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

- Confirmed PD per RECIST 1.1 with the exception that participants receiving treatment may continue past PD if the participant's ECOG PS has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment.
  - Some ADRs require withdrawal from treatment.
  - Drug must not be given to a known pregnant participant.
- Use of a nonpermitted concomitant drug (without approval of MD Anderson and the Medical Monitor provided by the IND office), as defined in dedicated s of this protocol, where the predefined consequence is withdrawal from the study intervention.

16.2 Participant Discontinuation/Withdrawal from the Study

A participant must be withdrawn in the event of any of the following:

- A participant may withdraw from the study at any time, at his/her own request (ie, withdrawal of consent), and without giving a reason.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

In case of withdrawal from treatment, the day of End-of-Treatment will correspond to the day of withdrawal (or within 7 days).

17 Lost to Follow-up

A participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.

- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

18 Long-term follow-up

After the End of Treatment evaluation, information on additional oncologic treatment (including post-operative systemic therapy and radiation therapy), time to disease progression/recurrence, sites of recurrence, development of second primary tumors, additional therapy for recurrence, long-term survival, and other relevant clinical data will be obtained. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits after treatment discontinuation for collection of long-term follow-up data. Long-term follow-up clinical information may also be obtained through chart reviews. Long-term follow up will be conducted as long as needed to obtain relevant information for accurate interpretation of the study, but for no longer than five years.

19 Data Sharing

Researchers can do more powerful studies when they share with each other the information they get from studying human samples. NGS data may be placed in a local M.D. Anderson Institutional Data Repository, commonly referred to as BigData; where both deposition of and access to data require governance and approval. In some cases, grant requirements may require deposition of large-scale data into the public Genotypes and Phenotypes database (dbGaP) an access controlled database overseen by the National Center for Biotechnology Information (NCBI). In other cases peer reviewed Journals may require data to be shared through a resource such as dbGaP. Data submitted to those repositories will only be shared in a de-identified fashion and without associated clinical data or identifiers. This data will be used only for research purposes, and the data elements collected and analyzed will only be those that are necessary to conduct this research.

Database access additional protections: The precedent to publically broadcast sequence data has been set by large consortial projects, such as The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE), in order to maximize data utility. However, we know

there is the potential for privacy risks associated with the release of sequence data to databases and while the risk may be small, it could grow in the future as technology advances. To minimize this potential, we will implement good faith efforts to ensure patient confidentiality and reduce patient exposure. The database of Genotypes and Phenotypes and others like it are extremely access restricted. Only authorized researchers may deposit or access the data and either or both efforts require MD Anderson institutional approval. Sequence data will only be broadcast through secure transmission processes. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees. Only non- identifiable data will be deposited to dbGaP i.e., no linking table or access to a linking table will be available. Research records will be kept separate from medical records and patients will not have access to any of the research data.

Protected health information (PHI) may be collected from medical records that are related to health and/or disease history including test results, medical procedures, and images (such as X-rays) in addition demographic and environmental factors may be requested. Researchers will use this information to better understand how genes affect health and response to treatment.
All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees.

20 Study Medication - Pharmaceutical Formulation

Pharmaceutical Properties and Description of the Formulation M7824 drug product is provided as either a sterile liquid formulation.

The Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph. Eur. type I 50R or 20R vials which are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL) or 20 mL (200 mg/20 mL), respectively. The vials are closed with rubber stoppers with the same composition as used for freeze-dried formulation, but in serum format complying with USP and Ph. Eur. with an aluminum crimp seal closure.

The excipients are viewed as standard, and therefore, not a safety risk. The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable.

20.1 Study Medication - Handling of the Dosage Form

For applications in clinical studies the liquid formulation is diluted directly with 0.9% saline solution. The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

20.2 Study Medication - Instructions for Storage

M7824 drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with M7824.

M7824 drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. For application in clinical studies, the liquid formulation is diluted directly with 0.9% saline solution.
The chemical and physical in-use stability for the infusion solution of M7824 in 0.9% saline solution has been demonstrated for a total of 72 hours at 2°C to 8°C and 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. Do not freeze or shake the diluted solution.

No other drugs should be added to the infusion containers containing M782.

21 STUDY ASSESSMENTS AND PROCEDURES

Baseline evaluation:

Investigations			Timing
History and Physical Exam including:	Treatment history Medical history Smoking history Height and weight	Vital signs ECOG PS TNM stage	Within 14 days prior to treatment initiation
Current Smoking Status and Tobacco Use	Assessment of patient's current smoking status and tobacco use		Within 14 days prior to treatment initiation
Symptoms & Toxicities	Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v5.0		Within 14 days prior to treatment initiation
Concomitant Medications	Documentation of concomitant medications		Within 14 days prior to treatment initiation
Hematology and Coagulation	CBC with hemoglobin, platelets, and WBC with differential Prothrombin time (PT) / Partial thromboplastin time (PTT)		Within 14 days prior to treatment initiation
Biochemistry	Albumin Alkaline phosphatase Potassium Total bilirubin, direct, indirect BUN Creatinine Total protein Free T4, TSH	Glucose LDH SGOT (AST) SGPT (ALT) Sodium Magnesium Uric acid	Within 14 days prior to treatment initiation

Pregnancy Test	Urine or serum (for women of childbearing potential only)	Within 48 hours prior to treatment initiation
Radiology	CT chest	Within 30 days prior to treatment initiation
Radiology	PET-CT	Within 60 days prior to treatment initiation
Radiology	MRI brain or CT brain (only for patients with stage II or III on pre-operative staging)	Within 60 days prior to treatment initiation
Mediastinal staging	CT chest / PET-CT, mediastinoscopy, and/or endobronchial ultrasound	Within 60 days prior to treatment initiation
Pulmonary tests	Complete pulmonary function test	Within 60 days prior to treatment initiation
Tumor/Adjacent Lung Tissue Collection for Biomarkers	Archival tissue or new biopsy of primary tumor for biomarker analysis (optional) Tissue obtained for mediastinal staging (optional)	Prior to treatment initiation
Blood-based biomarkers	Blood sample	Prior to treatment initiation
Stool-based Microbiome	Stool sample	Prior to treatment initiation
Pharmakokinetic (PK) studies	Blood sample	Prior to infusion and immediately after infusion of dose #1 of M7824
Anti-Drug Antibodies (ADA) studies	Blood sample	Prior to infusion of dose #1 of M7824

Evaluation during neoadjuvant treatment (prior to each M7824 infusion):

Investigations			Timing
Physical Exam Including:	BSA Vital signs		Within 7 days prior to dose #2 and #3 of M7824
Hematology	CBC with hemoglobin, platelets, and WBC with differential		Within 7 days prior to dose #2 and #3 of M7824
Pregnancy Test	Urine or serum (for women of childbearing potential only)		Within 7 days prior to dose #2 and #3 of M7824
Biochemistry[1]	Albumin Alkaline phosphatase Total bilirubin, direct, indirect BUN Creatinine Total protein Free T4, TSH	Glucose LDH Potassium SGOT (AST) SGPT (ALT) Sodium Magnesium Uric acid	Within 7 days prior to dose #2 and #3 of M7824
Radiology[1]	CT chest PET-CT		At least 14 days after the last dose of M7824
Symptoms & Toxicities	Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v5.0		On an ongoing basis throughout the study until the final study visit
Concomitant Medications	Documentation of concomitant medications		On an ongoing basis throughout the study until the final study visit
Blood-based biomarkers[1]	Blood sample		Within 7 days prior to dose #2 and #3 of M7824 and at least 14 days after the last dose of M7824

Pharmakokinetic (PK) studies	Blood sample	Prior to infusion of dose # 2 Prior to infusion and immediately after infusion of dose # 3 At least 14 days after the last dose of M7824
Anti-Drug Antibodies (ADA) studies	Blood sample	Prior to infusion of dose #3 of M7824 At least 14 days after the last dose of M7824
Pulmonary tests	Complete pulmonary function test[2]	At least 14 days after the last dose of M7824
Stool-based Microbiome	Stool sample	At least 14 days after the last dose of M7824

[1] If information / studies have already been obtained but therapy is delayed for any reason, repeated studies are not necessary prior to next cycle of therapy. [2]Complete pulmonary function test may not be required if patient is no longer considered a surgical candidate post neoadjuvant therapy based on the treating physician's discretion.

Assessments at surgery:

Investigations		Timing
Surgical procedure	Title of operation Status of resection margins (R0, R1, R2)	Through chart review
Tumor Tissue Collection	ypTNM Major pathologic response Percentage of viable tumor cells Nodal stations dissected / sampled and nodal status (positive vs. negative) at each station Evaluation of extra-capsular nodal spread	As information becomes available

End of treatment assessments:

Investigations		Timing
Physical Exam Including:	Vital Signs	Approximately within 8 weeks after surgery
Blood-based biomarkers	Blood sample	Approximately within 8 weeks after surgery
Symptoms & Toxicities	Evaluation and documentation of symptoms and toxicities using the NCI CTCAE v5.0 Retrospective evaluation of any	Approximately within 8 weeks after surgery

22 STATISTICALCONSIDERATIONS

This is an open label phase II study with a modular design. Currently, eligible patients will be accrued to the M7824 monotherapy arm (Arm A). The primary objective is to evaluate the rate of MPR, ratherthan hypothesis testing with pre-specified null and alternative MPR rates. There will be no interim futility nor efficacy monitoring. The primary efficacy endpoint of the study is MPR evaluated in resected tumor tissues following neoadjuvant therapy and defined as ≤ 10% viable tumor cells in the resected specimen using the methods described by Pataer et al. (2).

Analysis of primary efficacy endpoint:

A sample size of 23 patients is proposed for each arm of the study. With an estimated accrual rate of 2-3 patients a month, the accrual period is approximately 15-24 months. We will estimate the MPR rate with a 95% credible interval (CI) assuming that the MPR rate follows a prior beta distribution (0.5, 0.5) with one patient worth of information. For example, if the M7824 monotherapy indeed has a true MPR rate of 30% and 7 patients with MPR are observed in this study, the corresponding 95% CI of the observed MPR rate would be (14.8%, 50.7%). Furthermore, we calculated predictive probability of Prob ($p > 0.15$ | data and true MPR rate)for a variety of true MPR rates, where p is the MPR rate. As shown in the table below (**Table 3**), there will be a fairly high chance (81 – 89%) for the study to observe a MPR rate > 15% with a sample size of 23 patients if the true MPR rates are 25% and higher.

Table 3. Predictive probabilities of true MPR rates.

True MPR rate	predictive probability of Prob($p > 0.15$ | data and true MPR rate) where a0=0.5, b0=0.5

0.05	12%
0.10	30%
0.15	50%
0.20	67%
0.25	81%
0.30	89%

We chose to use 15% MPR rate as cutoff because a historic major pathologic responserate to neoadjuvant chemotherapy alone of 19% is observed (as described by Pataer et al.) (2). However, some patients that receive neoadjuvant chemotherapy may not receive surgery for one reason or another, and these cases will be considered treatment failure.
Assuming the 19% major pathologic response rate is calculated from 80% of patients who receive surgery, a conservative estimate of the major pathologic response is 15%.

Analysis of Secondary/Exploratory Endpoints:

Analysis for the secondary/exploratory endpoints will be descriptive and exploratory in nature. Descriptive statistics will be provided to summarize the data distribution. Association analysis by Pearson or Spearman correlation coefficient will be calculated for continuous data and chi-square or Fisher's exact test for categorical data. Time-to-event endpoints will be computed using the Kaplan-Meier method. Multivariate analysis will be used to explore the role of biomarkers in predicting pathologic response to treatment, in an exploratory way. The goals forthese analyses are for hypothesis generating. The results will need to be confirmed by future studies.

23 STUDY MONITORING AND EARLYSTOPPING RULES

To ensure the safety of the proposed treatment in the neoadjuvant setting, precautions have been taken into consideration and implemented:

- A careful review of the literature has demonstrated that the use of neoadjuvant chemotherapy does not increase surgical morbidity or mortality (14). Because single agent M7824 has been found to have a more favorable adverse event profile than single agent chemotherapy (38, 39) it is expected that neoadjuvant immunotherapy will be feasible and safe.

- A Bayesian method to monitor the toxicity in the perioperative phase will be used (40)

Unacceptable toxicity is defined as: severe pneumonitis precluding performance ofplanned surgical resection, death during neoadjuvant treatment or within 30 days aftersurgery; severe post op acute respiratory distress syndrome (ARDS) not attributable to aspiration requiring prolonged ventilator support; development of broncho-pleural fistula not attributable to surgical technique; wound healing delays that require managementwith a major surgical procedure; wound infections that require intravenous antibiotic usefor more than 21 days; re-operation for bleeding or infection deemed secondary other factors than surgical technique; empyema; stroke or myocardial infarction within 30 days after surgery; any treatment-related adverse events leading to a delay in surgeryresulting in > 8 week interval between the last dose of neoadjuvant therapy and surgery, any surgical complication that is considered major by the treating physician and possibly, probably or definitely related the immunotherapy medications. The incidence of surgical complications for thoracoscopy/thoracotomy for non-small cell lung cancers is approximately 16-31% (41). We consider that neoadjuvant therapy with either one of the regimens is not feasible if it results in unacceptable toxicities in at least 20% of the patients with 70% or higher probability.

We consider that neoadjuvant therapy with either one of the regimens is not feasible if it results in unacceptable toxicities in at least 20% of the patients with 70% or higher probability. The toxicity monitoring will start after a minimum of 6 patients have been enrolled with known toxicity outcome. With a prior probability of toxicity as Beta(0.2,0.8), the toxicity stopping boundaries are defined as seeing unacceptable toxicity in >= 3 of 6-8, 4 of 9-12, 5 of 13-16, 6 of 17-20 or 7 of 21-23 patients. When the true toxicity rates are 0.1, 0.2, and 0.35, the probabilities of early stopping are 0.06, 0.34, and 0.84 with the corresponding average sample sizes of 22.2, 18.6, and 11.2, respectively. In case one arm needs to be closed due to excessive toxicity, accrual to the remaining arm will continue in a non-randomized way. The calculation was performed using the Shiny Application: Bayesian Toxicity Monitoring version 2.1 (http://ibl.mdanderson.org/BTM/).

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be

submitted after the first 6 evaluable patients per study arm, complete 30 days after surgery, and every 3 evaluable patients per arm, thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

24 Data Confidentiality Plan

Confidentiality of Data

All clinical and research information/data will be collected and placed in our institution's Data Management Initiative (DMI) supported by Biostatistical Department under Dr. Jack Lee's oversight. This is a secured, password-protected intranet-based (UTMDACC only) database. Access to this database is restricted to the PI, protocol research nurse, protocol research data coordinator and DMI database analyst.

The investigator affirms that information as pertains to the study will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication.

Confidentiality of Participant Records

The investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. The investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

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Appendix 1 The Recommendations for irAE Management, in Accordance with the Joint American Society of Clinical Oncology Clinical Practice Guidelines and National Comprehensive Cancer Network

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

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Tables of Management of irAEs in Patients Treated with ICPis:

Table A1 Management of Skin irAEs in Patients Treated With ICPis

1.0 Skin Toxicities	
1.1 Rash/inflammatory dermatitis	
Definition: Erythema multiforme minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiforme major, it and can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand- foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others)	
Diagnostic workshop	
Pertinent history and physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease or unrelated primary skin disorder If needed, a biologic checkup, including a blood cell count and liver and kidney tests Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, antihistone, double-stranded DNA, and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms Skin biopsy Consider clinical monitoring with use of serial clinical photography Review full list of patient medications to rule out other drug-induced cause for photosensitivity	
Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and equires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to Grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks

1.0 Skin Toxicities	
	In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister)	

1.0 Skin Toxicities	
Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	Management
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations
G2: Blistering that affects quality of life and requires intervention based on diagnosis not meeting criteria for Grade > 2 Blisters covering 10%-30% BSA	Hold ICPi therapy and consult with dermatology for work-up and to determine appropriateness of resuming Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens Work-up for autoimmune bullous disease as above Initiate Class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks Monitor patients with G2 irAEs closely for progression to involvement of greater BSA and/or mucous membrane involvement. Consider following patients closely using serial photography Primer on monitoring for complicated cutaneous adverse drug reactions:

1.0 Skin Toxicities	
	Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements
	Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of "dusky erythema," which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities	Permanently discontinue ICPi Admit patient immediately and place under supervision of a dermatologist

1.0 Skin Toxicities	
	Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc
1.3 SCARs, including SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS	
Definition: Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug Diagnostic work-up	
Total body skin examination with attention to examining all mucous membranes as well as complete review of systems Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease A biologic checkup, including a CBC with differential test, and liver and kidney function tests, including urinalysis, in addition to the blood work; if the patient is febrile, blood cultures should be considered as well Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pusulosis Consider following patients closely using serial clinical photography If mucous membrane involvement or blistering is observed on the skin, consider early admission to a burn center for further monitoring and management Primer on monitoring for complicated cutaneous adverse drug reactions: Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements Physical examination: Include vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of “dusky erythema,” which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN	
Grading	Management

1.0 Skin Toxicities	
All Grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform (“maculopapular”) exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)

1.0 Skin Toxicities	
G4: Skin erythema and blistering/sloughing covering ≥ 10% to > 30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate	

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

Table A2 Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities	
2.1 Colitis	
Definition: A disorder characterized by inflammation of the colon Diagnostic work-up	
G2 Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, Clostridium difficile, parasite, CMV or other viral etiology, ova and parasite) should be performed Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity) Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy	
G3-4 All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi	
Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically
G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1

2.0 GI Toxicities	
	Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (, 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases Grade $ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional versus inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi

2.0 GI Toxicities	
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist $ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections
Additional considerations The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results Patients with hepatitis and irAE colitis are rare, and management should include permanently discontinuing ICPi and offering other immunosuppressant agents that work systemically for both conditions Currently, enteritis alone as the cause of diarrhea is uncommon and requires small bowel biopsy as the evaluation tool. It may be managed similar as colitis, including corticosteroid and/or infliximab, etc	
2.2 Hepatitis	
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma Diagnostic work-	

2.0 GI Toxicities	
Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality For G2 or higher: Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, g-glutamyl transferase should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies	
Grading	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Yellowing of skin or whites of the eyes Severe nausea or vomiting Pain on the right side of the abdomen Drowsiness Dark urine (tea colored) Bleeding or bruising more easily than normal Feeling less hungry than usual
G1: Asymptomatic (AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN)	Continue ICPi with close monitoring; consider alternate etiologies Monitor laboratories one to two times weekly Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN)	Hold ICPi temporarily and resume if recover to G1 or less on prednisone ≤ 10 mg/d For Grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days Increase frequency of monitoring to every 3 days Infliximab might not be the most appropriate treatment option in the situation of immune- mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab from other studies) In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month

2.0 GI Toxicities	
	Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10x3 ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 x ULN and/or elevated TB 3 x ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-a agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid

2.0 GI Toxicities	
	Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations is moderate.	

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

Table A3 Management of Lung irAEs in Patients Treated With ICPis

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

3.0 Lung Toxicities
GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

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

Table A4 Management of Endocrine irAEs in Patients Treated With ICPis

4.0 Endocrine Toxicity	
Counsel patients to inform their health care provider immediately if they experience any changes in their health since their last visit, especially any of the following:	
Headaches that will not go away or unusual headache patterns Vision changes Rapid heartbeat Increased sweating Extreme tiredness or weakness Muscle aches Weight gain or weight loss Dizziness or fainting Feeling more hungry or thirsty than usual Hair loss Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness Feeling cold Constipation Voice gets deeper Urinating more often than usual Nausea or vomiting Abdominal pain	
4.1 Thyroid	
4.1.1 Primary hypothyroidism	
Definition: Elevated TSH, normal or low FT4 Diagnostic work-up TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients	
Grading	Management
G1: TSH < 10 mIU/L and asymptomatic G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	Should continue ICPi with close follow-up and monitoring of TSH, FT4 May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart)

4.0 Endocrine Toxicity	
	Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Thyroid supplementation and reassessment as in G2
Additional considerations For patients without risk factors, full replacement can be estimated with an ideal body weight–based dose of approximately 1.6 µg/kg/d For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mg Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase) Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated	
4.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	**Management**

4.0 Endocrine Toxicity	
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1) Consider holding ICPi until symptoms return to baseline Consider endocrine consultation b-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy Endocrine consultation b-Blocker (eg, atenolol, propranolol) for symptomatic relief For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks; consider also use of SSKI or thionamide (methimazole or PTU).
Additional considerations Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above. Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with antithyroid medical therapy. Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral.	
4.2 Adrenal – primary adrenal insufficiency	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results	

4.0 Endocrine Toxicity	
If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	Management
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3.	

<table>
<tr><th colspan="2">4.0 Endocrine Toxicity</th></tr>
<tr><td colspan="2">Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis).
Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg.
All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS.
Endocrine consultation prior to surgery or any procedure for stress-dose planning.</td></tr>
<tr><td colspan="2">4.3 Pituitary - hypophysitis</td></tr>
<tr><td colspan="2">Definition: Inflammation of the pituitary with varying effects on hormone function.
Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism. Diagnostic work-up
Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH.
Testing:
Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes
Consider evaluating LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities 6 new severe headaches or complaints of vision changes</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Asymptomatic or mild symptoms</td><td>Consider holding ICPi until patient is stabilized on replacement hormones
Endocrine consultation
Hormonal supplementation as in G1</td></tr>
<tr><td>G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</td><td>Hold ICPi until patient is stabilized on replacement hormones
Endocrine consultation
Hormonal supplementation as in G1
Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks</td></tr>
<tr><td colspan="2">Additional considerations
Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies
All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS
Corticosteroid use can cause isolated central adrenal insufficiency
Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions</td></tr>
</table>

4.0 Endocrine Toxicity	
Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued. For long-term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone.	
4.4 Diabetes	
Definition: T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for nonimmunologic reasons, such as corticosteroid exposure. Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement Diagnostic work-up Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new-onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM. Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti–glutamic acid decarboxylase, anti–islet cell, or anti–insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis.	
Grading	Management
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow- up and laboratory evaluation May initiate oral therapy for those with new- onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value> 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients

4.0 Endocrine Toxicity	
	Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to
Additional considerations Insulin therapy can be used as the default in any case with hyperglycemia Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/d). In T2DM, sliding-scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; CT, computed tomography; DKA, diabetic ketoacidosis; DM, diabetes mellitus; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging; PTU, propylthiouracil; 2L, second-line; SSKI, potassium iodide; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; ULN, upper limit of normal.

Table A5 Management of Musculoskeletal irAEs in Patients Treated With ICPis

5.0 Musculoskeletal Toxicities	
5.1 Inflammatory arthritis	
Definition: A disorder characterized by inflammation of the joints Clinical symptoms: Joint pain accompanied by joint swelling; inflammatory symptoms, such as stiffness after inactivity or in the morning, lasting > 30 minutes to 1 hour; improvement of symptoms with NSAIDs or corticosteroids but not with opioids or other pain medications may also be suggestive of inflammatory arthritis.	
Diagnostic work- up G1 Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing G2 Complete history and examination as above; laboratory tests as above Consider US 6 MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis) Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist > 4 weeks G3-4 As for G2 Seek rheumatologist advice and review Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.	
Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks

5.0 Musculoskeletal Toxicities	
	If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-a or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.
Additional considerations Early recognition is critical to avoid erosive joint damage. Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other irAEs Oligoarthritis can be treated early on with intra-articular corticosteroids; consider early referral. Consider PCP prophylaxis for patients treated with high dose of corticosteroids for 12 weeks, as per local guidelines.	
5.2 Myositis	
Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved Diagnostic work-up Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms. Blood testing to evaluate muscle inflammation CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated	

<table>
<tr><th colspan="2">5.0 Musculoskeletal Toxicities</th></tr>
<tr><td colspan="2">Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed
Inflammatory markers (ESR and CRP)
Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected
Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis Monitoring: CK, ESR, CRP</td></tr>
<tr><td colspan="2">G1: Complete examination and laboratory work-up as above
G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI of affected joints
Early referral to a rheumatologist or neurologist
G3-4: As for G2
Urgent referral to a rheumatologist or neurologist</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild weakness with or without pain</td><td>Continue ICPi
If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2
Offer analgesia with acetaminophen or NSAIDs if there are no contraindications</td></tr>
<tr><td>G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL</td><td>Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose 10 mg; if worsens, treat as per G3
NSAIDs as needed
Referral to rheumatologist or neurologist
If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg
May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)</td></tr>
<tr><td>G3-4: Severe weakness with or without pain, limiting self-care ADL</td><td>Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement
Consider hospitalization for severe weakness
Referral to rheumatologist or neurologist
Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis
Consider IVIG therapy</td></tr>
</table>

5.0 Musculoskeletal Toxicities	
	Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration
Additional considerations: Caution is advised with rechallenging	
5.3 Polymyalgia-like syndrome	
Definition: Characterized by marked pain and stiffness in proximal upper and/or lower extremities and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain Diagnostic work-up	
G1 Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy ANA, RF, anti-CCP CK to evaluate differential diagnosis of myositis Inflammatory markers (ESR, CRP) Monitoring: ESR, CRP	
G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist G3-4: As for G2; see rheumatologist advice and review	
Grading	Management
G1: Mild stiffness and pain	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain, limiting age- appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens, treat as per G3 Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose after 3-4 weeks If no improvement or need for higher dosages after 4 weeks, escalate to G3 Consider referral to rheumatology
G3-4: Severe stiffness and pain, limiting self- care ADL	Hold ICPi and may resume, in consultation with rheumatology, if recover toG1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. Referral to rheumatology

5.0 Musculoskeletal Toxicities	
	Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; CCP, citrullinated protein antibody; CK, creatine kinase; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EMG, electromyography; ESR, erythrocyte sedimentation rate; G, Grade; HLA, human leukocyte antigen; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging, NSAID, nonsteroidal anti-inflammatory drug; PCP, Pneumocystis pneumonia; RF, rheumatoid factor; TB, tuberculosis; TNF, tumor necrosis factor.

Table A6 Management of Renal irAEs in Patients Treated With ICPis

6.0 Renal Toxicities	
Nephritis and renal dysfunction: diagnosis and monitoring For any suspected immune-mediated adverse reactions, exclude other causes Monitor patients for elevated serum creatinine prior to every dose Routine urinalysis is not necessary, other than to rule out UTIs, etc; nephrology may consider further If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy Swift treatment of autoimmune component important	
6.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0 3 over baseline	Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still < 1.5 ULN could be meaningful
G2: Creatinine 2-3 x above baseline	Hold ICPi temporarily Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc); if other etiologies ruled out, administer 0.5-1 mg/kg/d prednisone equivalents If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment If improved to G1 or less, taper corticosteroids over 4-6 weeks If no recurrence of chronic renal insufficiency, discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine > 3 x baseline or > 4.0 mg/dL; hospitalization indicated	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated	Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent)
Additional considerations Monitor creatinine weekly Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted	
6.2 Symptomatic nephritis: follow-up	

6.0 Renal Toxicities	
Grading	Management
G1	Improved to baseline, resume routine creatinine monitoring
G2	If improved to G1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as G3
G3	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)
G4	If improved to G1, taper corticosteroids over at least 4 weeks If elevations persist 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AKI, acute kidney injury; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; ULN, upper limit of normal; UTI, urinary tract infection.

Table A7 Management of Nervous System irAEs in Patients Treated With ICPis

7.0 Nervous System Toxicities	
7.1 Myasthenia gravis	
Definition: Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. (Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain-Barré syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICPi may have overlapping symptoms.	
Diagnostic work-up AChR and antistriated muscle antibodies in blood; if AChR antibodies are negative, consider muscle specific kinase and lipoprotein-related 4 antibodies in blood Pulmonary function assessment with NIF and VC CPK, aldolase, ESR, CRP for possible concurrent myositis Consider MRI of brain and/or spine, depending on symptoms to rule out CNS involvement by disease or alternate diagnosis If respiratory insufficiency or elevated CPK, troponin T, perform cardiac examination with ECG and TTE for possible concomitant myocarditis Neurologic consultation Electrodiagnositic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis	
Grading	Management
All grades	All grades warrant work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADL MGFA severity class 1 (ocular symptoms and findings only) and MGFA severity class 2 (mild generalized weakness)	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve Should consult neurology Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis	Permanently discontinue ICPi Admit patient, may need ICU-level monitoring Neurology consult Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days Frequent pulmonary function assessment

7.0 Nervous System Toxicities	
	Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: b-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement Pyridostigmine, wean based on improvement ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required	
7.2 Guillain-Barré syndrome	
Definition: Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves.	
Diagnostic work-up Neurologic consultation MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening) Lumbar puncture: CSF typically has elevated protein and often elevated WBCs; even though this is not typically seen in classic Guillain-Barré syndrome, cytology should be sent with any CSF sample from a patient with cancer. Serum antibody tests for Guillain-Barré syndrome variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia) Electrodiagnostic studies to evaluate polyneuropathy Pulmonary function testing (NIF/VC) Frequent neurochecks	
Grading	Management
All grades	Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise Note: There is no G1 toxicity
G1: Mild, none	NA
G2: Moderate, some interference with ADL, symptoms concerning to patient	Discontinue ICPi
G3-4: Severe, limiting self-care and aids warranted, weakness, limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms	Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper

7.0 Nervous System Toxicities	
	Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis Frequent neurochecks and pulmonary function monitoring Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus
Additional considerations Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses Caution with rechallenging for severe cases	
7.3 Peripheral neuropathy	
Definition: Can present as asymmetric or symmetric sensory, motor, or sensory motor deficit. Focal mononeuropathies, including cranial neuropathies (eg, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present.	
Diagnostic work-up G1 Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic and autoimmune screen Neurologic consultation Consider MRI of spine with or without contrast G2: in addition to above MRI spine advised/MRI of brain if cranial nerve Consider EMG/NCS Consider neurology consultation G3-4: go to Guillain-Barré syndrome algorithm	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week If to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe, limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes) Severe may be Guillain-Barré syndrome and should be managed as such	Permanently discontinue ICPi Admit patient Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barré syndrome management

<table>
<tr><th colspan="2">7.0 Nervous System Toxicities</th></tr>
<tr><td colspan="2">7.4 Autonomic neuropathy</td></tr>
<tr><td colspan="2">Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.</td></tr>
<tr><td colspan="2">Diagnostic work-up
An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include
Screening for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson and other autoimmune screening
AM orthostatic vitals
Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy
Consider paraneoplastic Lambert-Eaton myasthenic syndrome, antineutrophil cytoplasmic antibodies, and ganglionic AChR antibody testing</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient</td><td>Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression</td></tr>
<tr><td>G2: Moderate, some interference with ADL, symptoms concerning to patient</td><td>Hold ICPi and resume once return to G1
Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild)
Neurologic consultation</td></tr>
<tr><td>G3-4: Severe, limiting self-care and aids warranted</td><td>Permanently discontinue ICPi
Admit patient
Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper
Neurologic consultation</td></tr>
<tr><td colspan="2">7.5 Aseptic meningitis</td></tr>
<tr><td colspan="2">Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
Diagnostic work-up
MRI of brain with or without contrast + pituitary protocol
AM cortisol, ACTH to rule out adrenal insufficiency
Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology
May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology</td></tr>
</table>

<table>
<tr><th colspan="2">7.0 Nervous System Toxicities</th></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate.
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)
G3-4: Severe, limiting self-care and aids warranted</td><td>Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits
Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms</td></tr>
<tr><td colspan="2">7.6 Encephalitis</td></tr>
<tr><td colspan="2">Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV).
Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality Diagnostic work-up</td></tr>
<tr><td colspan="2">Diagnostic work-up
Neurologic
consultation
MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal
Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.
May see elevated WBC count with lymphocytic predominance and/or elevated protein
EEG to evaluate for subclinical seizures
Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate.
G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)
G3-4: Severe, limiting self-care and aids warranted</td><td>Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits
As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative
Trial of methylprednisolone 1-2 mg/kg</td></tr>
</table>

7.0 Nervous System Toxicities	
	If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
7.7 Transverse myelitis	
Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	
Diagnostic work-up Neurologic consultation MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies Blood: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG Evaluation for urinary retention, constipation	
Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3- 5 days Strongly consider IVIG
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CBC, complete blood count; CNS, central nervous system; CPK, creatine phosphokinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyography; ESR, erythrocyte sedimentation rate; G, Grade; GI, gastrointestinal; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IgG, immunoglobulin G; IV, intravenous; IVIG, intravenous immunoglobulin; irAE, immune-related adverse event; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; NA, not applicable; NCS, nerve conduction study; NIF, negative inspiratory force; PCR, polymerase chain reaction; RPR, rapid plasma reagin, TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; VC, vital capacity; WBC, white blood cell count.

Table A8 Management of Hematologic irAEs in Patients Treated With ICPis

8.0 Hematologic Toxicities	
8.1 Autoimmune hemolytic anemia	
Definition: A condition in which RBCs are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur.	
Diagnostic work-up History and physical examination (with special consideration of history of new drugs and insect, spider, or snake bites) Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free Hgb DIC panel, which could include PTNIR infectious causes Autoimmune serology Paroxysmal nocturnal hemoglobinuria screening Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate for myelodysplastic syndromes Evaluation for viral/bacterial (mycoplasma, etc) causes of hemolysis studies Protein electrophoresis, cryoglobulin analysis Work-up for bone marrow failure syndrome if refractory, including B12, folate, copper, parvovirus, FE, thyroid, infection Glucose-6-phosphate dehydrogenase Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc) Assessment of methemoglobinemia	
Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation Administer 0.5-1 mg/kg/d prednisone equivalents
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment

8.0 Hematologic Toxicities	
	Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil RBC transfusion per existing guidelines; discuss with blood bank team prior to transfusions that a patient with possible ICPi serious AE is in house.
Additional considerations: Monitor Hgb levels on a weekly basis until the corticosteroid tapering process is complete; thereafter, less-frequent testing is needed	
8.2 Acquired TTP	
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Diagnostic work-up History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes PT, activated PTT, fibrinogen Blood group and antibody screen, direct antiglobulin test, CMV serology Consider CT/MRI brain, echocardiogram, ECG Viral studies Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously	

8.0 Hematologic Toxicities	
Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult Administer 0.5-1 mg/kg/d prednisone
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency > 2) G4: Life-threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy Hematology consult In conjunction with hematology, initiate PEX according to existing guidelines with further PEX dependent on clinical progress Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX May offer rituximab
8.3 Hemolytic uremic syndrome	
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Signs and symptoms of hemolytic uremic syndrome can include: Bloody diarrhea Decreased urination or blood in the urine Abdominal pain, vomiting, and occasionally fever Pallor Small, unexplained bruises or bleeding from the nose and mouth Fatigue and irritability Confusion or seizures High blood pressure Swelling of the face, hands, feet, or entire body	
Diagnostic work-up History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine	

<table>
<tr><th colspan="2">8.0 Hematologic Toxicities</th></tr>
<tr><td colspan="2">ADAMTS13 (to rule out TTP) Homocysteine/methylmalonic acid
Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial)
Evaluate reticulocyte count and mean corpuscular volume
Evaluation of infectious cause, including screening for EBV, CMV,
HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate)
Pancreatic enzymes
Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc
Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia
Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc)
Evaluation for concurrent confusion</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia Grade 2
G3: Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae)
G4: Life-threatening consequences (eg, CNS thrombosis/ embolism or renal failure)</td><td>Continue ICPi with close clinical follow-up and laboratory evaluation
Supportive care Permanently discontinue ICPi Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5,
then 1,200 mg every 2 weeks
Red blood transfusion according to existing guidelines</td></tr>
<tr><td colspan="2">8.4 Aplastic anemia</td></tr>
<tr><td colspan="2">Definition: Condition in which the body stops producing enough new blood cells</td></tr>
<tr><td colspan="2">Diagnostic work-up
History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections) CBC, smear, reticulocyte count
Viral studies, including CMV, HHV6, EBV, parvovirus
Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D
Serum LDH, renal function
Work-up for infectious
causes Identify marrow
hypo/aplasia
Bone marrow biopsy and aspirate analysis
Peripheral blood analysis, including neutrophil count, proportion of GPI-negative cells by flow for PNH
Flow cytometry to evaluate loss of GPI-anchored proteins
Type and screen patient for transfusions and notify blood bank that all transfusions need to</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Nonsevere, < 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count. 20,000, reticulocyte count < 20,000</td><td>Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation
Supportive transfusions as per local guidelines</td></tr>
</table>

8.0 Hematologic Toxicities	
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 Hematology consult, growth factor support Horse ATG plus cyclosporine If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide For refractory patients, consider eltrombopag plus supportive care
8.5 Lymphopenia	
Definition: An abnormally low level of lymphocytes in PB; for adults, counts of < 1,500/mm^3	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure, etc, as well as history of autoimmune disease, family history of autoimmune disease) Evaluation of nutritional state as cause Spleen size CBC with differential, peripheral smear and reticulocyte counts CXR for evaluation of presence of thymoma Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)	
Grading	Management
G1-2: 500-1,000 PB lymphocyte count G3: 250-499 PB lymphocyte count G4: < 250 PB lymphocyte count	Continue ICPi Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening Consider holding ICPi Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/hepatitis screening if not already done May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease

8.0 Hematologic Toxicities	
8.6 Immune thrombocytopenia	
Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic work-up History and physical examination (special attention for lymphocyte-depleting therapy, such as fludarabine, ATG, corticosteroids, cytotoxic therapy) Family history of autoimmunity or personal history of autoimmune disease History of viral illness CBC Peripheral blood smear, reticulocyte count Bone marrow evaluation only if abnormalities in the above test results and further investigation is necessary for a diagnosis Patients with newly diagnosed immune thrombocytopenia should undergo testing for HIV, hepatitis C virus, hepatitis B virus, and Helicobacter pylori Direct antigen test should be checked to rule out concurrent Evan syndrome Nutritional evaluation Bone marrow evaluation if other cell lines affected and concern for aplastic anemia	
Grading	Management
G1: Platelet count < 100/μL G2: Platelet count < 75/μL	Continue ICPi with close clinical follow-up and laboratory evaluation Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1 Administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.
G3: Platelet count < 50/μL	Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1
G4: Platelet count < 25/μL	Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more- rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary

8.0 Hematologic Toxicities	
	If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression (From American Society of Hematology guideline on immune thrombocytopenia97; consult for further details)
8.7 Acquired hemophilia	
Definition: Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors	
Diagnostic work-up Full blood count to assess platelet number, fibrinogen, PT, PTT, INR; the typical finding in patients with acquired hemophilia A is a prolonged activated PTT with a normal PT MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding Medication review to assess for alternative causes Determination of Bethesda unit level of inhibitor	
Grading	Management
G1: Mild, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits Administer 0.5-1 mg/kg/d prednisone Transfusion support as required Treatment of bleeding disorders with hematology consult
G2: Moderate, 1%-5% of normal factor activity in blood, 0.01- 0.05 IU/mL of whole blood	Hematology consult Administration of factor replacement (choice based on Bethesda unit of titer) Administer 1 mg/kg/d prednisone 6 rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult

8.0 Hematologic Toxicities	
	Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) 6 rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: The American Heart Association requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; ATG, antithymocyte globulin; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; CXR, chest x-ray; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; ECG, electrocardiogram; ER, extended release; FE, ferritin; G, Grade; GPI, glycosylphosphatidylinositol; Hgb, hemoglobin; HHV6, human herpesvirus 6; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PB, peripheral blood; PEX, plasma ex-change; PNH, paroxusmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell count; TTP, thrombotic thrombocytopenic purpura.

Table A9 Management of Cardiovascular irAEs in Patients Treated With ICPis

<table>
<tr><th colspan="2">9.0 Cardiovascular Toxicities</th></tr>
<tr><td colspan="2">9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis</td></tr>
<tr><td colspan="2">Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue</td></tr>
<tr><td colspan="2">Diagnostic work-up At baseline
ECG
Consider troponin, especially in patient treated with combination immune therapies Upon signs/symptoms (consider cardiology consult)
ECG
Troponin
BNP Echocardiogram CXR
Additional testing to be guided by cardiology and may
include Stress test
Cardiac catherization Cardiac MRI</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Abnormal cardiac biomarker testing, including abnormal ECG
G2: Abnormal screening tests with mild symptoms
G3: Moderately abnormal testing or symptoms with mild activity
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions</td><td>All grades warrant work-up and intervention given potential for cardiac compromise Consider the following:
Hold ICPi and permanently discontinue after G1
High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)
Admit patient, cardiology consultation
Management of cardiac symptoms according to ACC/AHA guidelines and with guidance
from cardiology
Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte</td></tr>
<tr><td colspan="2">Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.</td></tr>
</table>

9.0 Cardiovascular Toxicities	
9.2 Venous thromboembolism	
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing, or hemoptysis for PE	
Diagnostic work-up Evaluation of signs and symptoms of PE or DVT may include Clinical prediction rule to stratify patients with suspected venous thromboembolism Venous ultrasound for suspected DVT CTPA for suspected PE Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler are not available or appropriate Ventilation/perfusion scan is also an option when CTPA is not appropriate Consider other testing, including ECG, CXR, BNP and troponin levels, and arterial blood gas	
Grading	Management
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Continue ICPi Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term
G4: Life-threatening (eg, PE,cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated	Permanently discontinue ICPi Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology Respiratory and hemodynamic support LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term Further clinical management as indicated based on symptoms
Additional considerations	

9.0 Cardiovascular Toxicities
While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of G4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment. Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission. All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CXR, chest x-ray; DVT, deep vein thrombosis; ECG, electrocardiogram; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; VKA, vitamin K agonist.

Table A10 Management of Ocular irAEs in Patients Treated With ICPis

10.0 Ocular Toxicities	
Counsel all patients to inform their health care provider immediately if they experience any of the following ocular symptoms Blurred vision Change in color vision Photophobia Distortion Scotomas Visual field changes Double vision Tenderness Pain with eye movement Eyelid swelling Proptosis	
Evaluation, under the guidance of ophthalmology Check vision in each eye separately Color vision Red reflex Pupil size, shape, and reactivity Fundoscopic examination Inspection of anterior part of eye with penlight	
Prior conditions Exclude patients with history of active uveitis History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy Additional considerations Ocular irAEs are many times seen in the context of other organ irAEs High level of clinical suspicion as symptoms may not always be associated with severity Best to treat after ophthalmologist eye examination	
10.1 Uveitis/iritis	
Definition: Inflammation of the middle layer of the eye Diagnostic work-up: as per above	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Medical intervention required, anterior uveitis	Hold ICPi temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to # 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less

10.0 Ocular Toxicities	
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional considerations: Consider use of infliximab or other TNF-a blockers in cases that are severe and refractory to standard treatment	
10.2 Episcleritis	
Definition: Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection Diagnostic work-up: As per 10.0	
Grading	Management
G1: Asymptomatic	Continue ICPi Refer to ophthalmology within 1 week Artificial tears
G2: Vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional considerations: Consider use of infliximab or other TNF-α blockers in cases that are severe and refractory to standard treatment	
10.3 Blepharitis	
Definition: Inflammation of the eyelid that affects the eyelashes or tear production Diagnostic work-up: As per 10.0	
Grading	Management
No formal grading system	Warm compresses and lubrication drops Continue therapy unless persistent and serious

10.0 Ocular Toxicities
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.

Abbreviations: ICPi, immune checkpoint inhibitor; G, Grade; irAE, immune-related adverse event; IV, intravenous, TNF, tumor necrosis factor.

Appendix 2 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions Adverse Event

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first protocol intervention, even if the event is not considered to be related to study treatment. Medical conditions/diseases present before starting study therapy are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Compared to baseline (Screening or the Week 1, Day 1 visit), medical conditions that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are NOT to be considered as AEs.

All newly diagnosed or worsening pre-existing conditions (clinically significant changes in frequency, and/or intensity), signs, and symptoms observed from baseline (Screening or the Week 1, Day 1 visit), whether related to study intervention or not, are to be reported as AEs.

Progression of the cancer under study is not considered an AE.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE toxicity grade reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate Grade 3

or Severe

Grade 4 or Life-threatening Grade 5

or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death

will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other nonstudy interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (eg, anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AESIs and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. The following hospitalizations are also not considered SAEs:

- a visit to the emergency room or other hospital department < 72 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the patient's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period.

Adverse Events of Special Interest

Adverse events of special interest can be serious or nonserious events; however, must always be reported on the SAE/AESI Report Form, and will follow the procedure described below for reporting SAEs and AESIs.

Categories of AESIs related to M7824 include:

- Infusion-related reactions including immediate hypersensitivity
- Immune-related adverse events
- Potential TGFβ-mediated skin adverse events
- Treatment-related anemia adverse events

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Reporting Serious Adverse Events and Adverse Events of Special Interest Serious Adverse Events

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

SAEs, whether related or not related to study drug as detailed below, must be reported to EMD Serono within 5 working days from the time of knowledge of the event to: Pavithra Prasad, Fax: +49 6151 72 6914; E-mail: ICSR_CT_GPS@merckgroup.com
.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 5 working days to the EMD Serono (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The principal investigator will ensure that all SAEs in the clinical database are reported to EMD Serono and any applicable health authority during the conduct of the study.

SAEs will be reported on the EMD Serono approved form for prompt reporting (full form): "Internal

SAE Report Form for Prompt Reporting" Institutional Review Board.

SAEs will be submitted to both the Office of Protocol Research, Unit 1437 at The University of Texas MD Anderson Cancer Center and also sent to:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to EMD Serono to:
Pavithra Prasad, Fax: +49 6151 72 6914; E-mail: ICSR_CT_GPS@merckgroup.com

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 5 working days to EMD Serono using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent**. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- **Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Pregnancy and Reporting

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify EMD Serono of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures within 24 hours.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from EMD Serono].

Any pregnancy that occurs in a female partner of a male study participant should be reported to EMd Serono. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will notify EMD Serono by completing the AESI Report Form within 24 hours. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

Reporting of nonserious AESIs via paper report form is required as a back-up method only in the case of EDC failure. Names, addresses, and telephone and fax numbers will be included on the paper report form.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I	Phase I	Phase I
			Phase II	Phase II	Phase II
				Phase III	Phase III
Unlikely	Phase I	Phase I	Phase I	Phase I	Phase I
			Phase II	Phase II	Phase II
				Phase III	Phase III
Possible	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III
Probable	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III
Definitive	Phase I	Phase I	Phase I	Phase I	Phase I
	Phase II	Phase II	Phase II	Phase II	Phase II
		Phase III	Phase III	Phase III	Phase III

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.