Phase II Prospective Study of Bintrafusp Alfa in Previously Treated Patients with Recurrent and Metastatic (R/M) Non-keratinizing Nasopharyngeal Carcinoma (NPC)

Sponsor: The University of Hong Kong, Hong Kong

Funder: Merck Healthcare KGaA, Darmstadt, Germany

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Local Institutional Review Boards: UW 19-675

Study Summary

Protocol Title:	Phase II prospective study of bintrafusp alfa in previously treated patients with recurrent and metastatic (R/M) non-keratinizing nasopharyngeal carcinoma (NPC)
Protocol Version and Date	Version 2.0 dated 01 Dec 2021
Principal Investigator:	**Dr. CHIANG Chi Leung** Department of Clinical Oncology The University of Hong Kong E-mail: chiangcl@hku.hk Telephone: +852-2255-4352
Co-Investigators:	**Dr. LAM Tai Chung** Department of Clinical Oncology The University of Hong Kong E-mail: lamtc@hku.hk Telephone: +852-2255-4352 **Dr. LI Chun Bong James** Department of Paediatrics and Adolescent Medicine The University of Hong Kong E-mail: jamesli@hku.hk Telephone: +852-2819-9863
Consulting Statistician:	**Dr. Horace CHOI Cheuk Wai** Department of Clinical Oncology The University of Hong Kong E-mail: hcchoi@hku.hk Telephone: +852-2255-4352
Sponsor:	The University of Hong Kong
Funder:	Merck Healthcare KGaA, Darmstadt, Germany (monetary and drug support)
Laboratory:	Hospital Pathology Service, Queen Mary Hospital, Pokfulam, Hong Kong

Protocol-specific Sponsor contact information can be found in the Investigator(s) Study File. Laboratory-related information can be found in the Investigator(s) Study File, Section named 'Laboratory Documents'.

Investigator Signatory

I agree to conduct this Clinical Study in accordance with the designed outlined in this protocol and to abide by all provisions of this protocol.

Name	Signature	Date

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1 BACKGROUND

Background of the Study Population

Nasopharyngeal cancer (NPC) represents a unique malignancy with skewed geographical distribution and greater tendency among head and neck cancer for metastases. (1) Worldwide, NPC is an uncommon cancer with approximately 87,000 incident cases and 50,000 deaths reported in 2012. Over 80% of new cases occurred in Asia and its incidence peaks at Southern China, which is 20-50 times higher than that in Western Countries. (2)

Even the best available treatment in modern practice, retrospective reports of patients treated with intensity-modulated radiotherapy (IMRT) over the past decade revealed that 5% to 15% of patients would develop local failure, and 15% to 30% will experience distant failure. Also, around 5% of patients present with de novo metastases. (3) Despite the varying success of aggressive local therapy for metastatic lesion(s) in highly selected population, a vast majority of R/M cases are only amendable to systemic therapy.

Platinum-containing doublet chemotherapy regimens are generally considered the standard first-line systemic therapy. Evidence suggests that the combination of Cisplatin plus Gemcitabine is the preferred regime. In the randomized study, this combination was associated with better median progression-free survival (7.0 months vs. 5.6 months, hazard ratio [HR] 0.55, 95% CI 0.44-0.68) and overall survival (29.1 versus 20.9 months, HR 0.62, 95% CI 0.45-0.84) compared to Cisplatin plus 5-fluorouracil (5-FU). (4)

Second-line systemic therapy may be considered for patients with a good performance status who become refractory to Cisplatin-based regimens. Multiple single-arm phase II trials have demonstrated several mono-therapies were associated with overall response rates ranging from 3% to 50%, and in approximately time to progression (TTP) of 4 months. (5-10) However, we lack randomized data to recommend single regime over the others. Among the most commonly used salvage chemotherapy regimens are Gemcitabine, Capecitabine, and Docetaxel as follows:

Regime	Line	Phase	N	ORR	PFS/TTP	OS
Gemcitabine	2/3	II	27	48.1%	5.1 months	10.5 months
Gemcitabine	1+	II	32	43.8%	5.1 months	16 months
Capecitabine	2-4	II	17	23.5%	4.9 months	7.6 months
Docetaxel	2-4	II	30	36.7%	5.3 months	12.8 months

Table 1. Mono Chemotherapy Regimens Overview

Attempts have been made to increase the overall response rate (ORR) by using combination regime. Despite the increased ORR, there were minimal improvement of durability of response with progression-free survival (PFS) and TTP of 5-6 months but more toxic. (11-12) Also, several exploratory phase II studies of targeted therapy have been conducted, for example using epidermal growth factor receptor inhibitors (e.g., Gefitinib and Cetuximab) or angiogenesis inhibitors (e.g. Pazopanib and Sunitinib). (13-16) However these studies were failed to meet their primary endpoints. For instance, in the studies of pazopanib and sunitinib, the median TTP was only around 4 months.

In brief, despite the advancement of treatment and the fact that NPC was historically described as chemo-sensitive and radio-sensitive disease, over half of those diagnosed with NPC will eventually succumbed of their disease. Patients who failed the first line Platinum based therapy, multiple options exist, but the responses are usually modest, and none have gained the regulatory approval.

Pre-clinical Evidence for the Role of PD-1/PD-L1 in NPC

NPC is distinguished from other head and neck cancers as being an Epstein-Barr virus (EBV)-driven malignancy. The chronic EBV infection leads to increased viral EBV load. This chronically increased virus load results in and correlates with increased expression of PD-1 on cytotoxic memory T-cells, leading to T-cell exhaustion with resultant decreased function and number of these cells. (17) This up-regulation is specific for PD-1 as CTLA-4 levels were unaffected. (18-19) Increased PD-1 expression also occurs in the virally affected host cells. The relative quantitative and qualitative CD 8+ T-cell decrease leads to altered T-cell immunity, which prevents clearance of the EBV infection and allows further increase of viremia. EBV-latent infection is associated with expression of LMP-1 protein, which induces PD-L1 expression. (20) Increased PD-1 and PD-L1 work together to suppress the immune system, leading to decreased EBV cellular immunity. In vitro, anti-PD-L1 blockade was demonstrated to restore exhausted CD8+ T-cell function and decrease viral load. (18) Therefore, anti-PD-L1 blockade holds the promising potential in restoring anti-EBV tumor CD-8 positive T-cells, decrease viral load and target NPC.

Clinical Evidence for anti-PD1 / anti-PD L1 Therapy in NPC

KEYNOTE-028 (NCT02054806) is a non-randomized, multi-cohort, phase Ib trial of Pembrolizumab in patients with PD-L1–positive advanced solid tumors. PD-L1 positivity, defined as PD-L1 expression by immunohistochemistry (IHC) (≥ 1% PD-L1 membrane staining of tumor cells or tumor-infiltrating lymphocytes), was required for the study entry. The key eligibility criteria of NPC cohort was unresectable or metastatic NPC patients who are not amendable to curative treatment whose disease progressed on at least one line of prior therapies. (21)

Enrolled subjects were predominantly of Asian ethnicity (67%), male (77.8%), with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (74%). Of note, approximately two-thirds had received 3 or more prior treatments for metastatic disease. All patients had received prior platinum-based therapy. 98% of screened and 100% of evaluable subjects were PD-L1 positive. In this heavily pre-treated cohort, evidence of clinical activity was demonstrated, as 22.2% had a confirmed ORR, 25.9% had unconfirmed response, and 51.9% had stable disease (SD). With a median follow-up of 7.8 months, the 6-month and 12-month progression free survival (PFS) rate was 49.7% and 30.1% respectively. Notably, a 6-month and 12-month overall survival (OS) rate was 85.2% and 66.7% demonstrated respectively. Grade 3 ≥ drug-related adverse events occurred in 29.6% of patients, and there was one drug-related death due to sepsis.

NCI-9742 is an international, multi-center study of Nivolumab in recurrent or metastatic NPC. (22) Similar population of advanced or metastatic NPC patients who are not amendable to curative treatment whose disease progressed on at least one line of platinum therapies was enrolled. However, PD-L1 positivity is not the mandatory eligibility requirement.

Enrolled subjects were predominantly of Asian ethnicity (82%), male (77.8%), with an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2 (62%). Again, the enrolled subjects are heavily pre-treated with approximately 60% had received 3 or more prior treatments for metastatic disease. A total of 44 patients were evaluated and the overall ORR was 20.5% (CR = 1; PR= 8). Nine patients received nivolumab for ≥12 months (20%). The 1-year OS rate was 59% and 1-year PFS rate was 19.3%. Treatment was well tolerated and 22.2% of subjects experienced ≥ grade 3 drug-related adverse events.

Collectively, anti-PD1 therapy has promising activity in R/M NPC and manageable toxicity profile. The overall survival rate was compared favorably with historical data in similar populations. PD-L1 is a potential predictive biomarker of efficacy.

Rationale of Blocking TGF-B Pathway

Despite the promising clinical activity, only 20% of NPC patients respond to anti–PD-1/PD-L1 therapies. Thus, there is an urgent need to improve objective response rates. One strategy is to combine anti–PD-L1/PD-1 with other immunotherapies, (23) as exemplified by the combination of anti–PD-1 and anti–CTLA-4, which has been approved for advanced melanoma. (24)

In normal physiology, the regulatory cytokine transforming growth factor-β (TGF-β) functions to maintain immunological self-tolerance. (25-27) However, TGF-β can promote tumor progression and facilitate tumor immune evasion through its effects on the innate and adaptive immune systems. The three TGF-β isoforms, TGF-β1, TGF-β2, and TGF-β3 (25, 27), are highly expressed in many tumor types, and their serum concentrations correlate with poor clinical outcome. (27-29) TGF-β functions as an autocrine or paracrine signal within the tumor microenvironment, where it promotes tumor progression via stromal modification, angiogenesis, and induction of epithelial-mesenchymal transition (EMT). (30-32) TGF-β signaling in myeloid cells is also critical in driving metastasis. (33) In addition, TGF-β1 can directly inhibit T cell division and acquisition of effector function and natural killer (NK) cell function. (34-38) Furthermore, because the up-regulation of TGF-β signaling–associated genes has been linked to anti–PD-1 resistance, blockade of TGF-β signaling may target mechanisms of resistance and sensitize tumors to anti–PD-1/PD-L1 therapies. (39)

In NPC patients, high levels of TGF-β1 are positively correlated with disease stage. (40) Up-regulation of TGF-β pathway is associated with aggressive phenotype of NPC by inducing EMT, that ZEB1/2 genes, Flot1/2, human high mobility group A2 (HMGA2) are the possible mediators. (41-44) Furthermore, a recent report found that miR-449b, a miRNA strongly associated with NPC distant metastasis, activates of the TGF-β pathway, which subsequently induces Cisplatin resistance in NPC through the PTEN/AKT pathway. (45)
All these provide rationale for dual blockage of PD-1/PD-L1 axis and TGF-b pathway. Merck Healthcare KgGA, Darmstadt, Germany developed M7824 (MSB0011359C) – International Nonproprietary Name (INN) known as bintrafusp alfa, a bi-functional fusion protein designed to simultaneously block the TGF-β and PD-L1 pathways. Bintrafusp alfa (M7824) is an investigational bifunctional immunotherapy designed to simultaneously block 2 pro-tumorigenic immunosuppressive pathways, TGF-β and PD-L1, to inhibit tumor growth by potentially restoring and enhancing antitumor responses.

Pre-Clinical Evidence for Bintrafusp Alfa

Bintrafusp alfa induces superior tumor regression compared with equimolar dose of anti-PD-L1 therapy in the EMT-6 orthotopic breast tumor model and MC38 colorectal cancer model. Bintrafusp alfa has been shown to reduce the incidence of lung metastases than anti-PD L1 therapy in vitro. In addition, bintrafusp alfa provides long-term antitumor immunity in tumor re-challenge mouse models. When bintrafusp alfa-cured mice were re-challenged subcutaneously with EMT-6 cells without additional bintrafusp alfa treatment, they did not develop tumors, whereas treatment-naive mice rapidly developed tumors. (46)

Clinical Evidence for Bintrafusp Alfa in Other Cancers

In the first-in-human phase I trial of bintrafusp alfa to determine its safety, pharmacokinetics, and efficacy in 19 patients with heavily pretreated advanced solid tumors using a 3+3 dose-escalation design (NCT02517398), eligible patients received bintrafusp alfa at 1, 3, 10, or 20 mg/kg once every 2 weeks until confirmed progression, unacceptable toxicity, or trial withdrawal. Grade ≥3 treatment-related adverse events (TRAE) occurred in four patients (skin infection secondary to localized bullous pemphigoid, asymptomatic lipase increase, colitis with associated anemia, and gastroparesis with hypokalemia). (47) The maximally tolerated dose (MTD) was not reached. Bintrafusp alfa saturated peripheral PD-L1 and sequestered any released plasma TGF-β1, -β2, and -β3 throughout the dosing period at >1 mg/kg. There were signs of efficacy across all dose levels, including one ongoing confirmed complete response (cervical cancer), two durable confirmed partial responses (PR; pancreatic cancer; anal cancer), one near-PR (cervical cancer), and two cases of prolonged stable disease in patients with growing disease at study entry (pancreatic cancer; carcinoid).

In the phase I trial by J Strauss et al. to evaluate the efficacy and safety of bintrafusp alfa in human papilloma virus (HPV) associated cancers (NCT03427411), (48) 16 patients (9 cervical, 4 anal, and 3 head and neck squamous cell cancer) were enrolled, objective response rate (ORR) of 35.3% and 41.7% in HPV-associated cancer and HPV-positive patients were observed respectively. Grade 3 or above treatment-related toxicities were seen in 18.8% (3/16) of patients (colitis, cystitis, and gastroparesis).

In the expansion cohort of ongoing phase I trial NCT02517398, patients with advanced non-small cell lung cancer (NSCLC) unselected for PD-L1 who progressed following first line standard treatment were randomized to receive bintrafusp alfa 500 mg (n = 40) or 1200 mg (n = 40) every 2 weeks. At the recommended phase II dose 1200mg, clinical activity was seen across PD-L1 sub-group. The ORR was 27.5%, 40.7%, and 71.4% in the entire group, PD-L1 + (≥1%), and PD-L1 high (≥80%) respectively. Treatment was well tolerated with Grade ≥3 TRAEs occurred in 25% of patients; the commonest TRAEs were pruritus (18.8%), maculo-papular rash (17.5%), and decreased appetite (12.5%). 7.5% patients discontinued treatment due to TRAEs. No treatment related death reported. (49)

In another phase I study in Asian patients pretreated recurrent or refractory gastric cancer (NCT 02699515), 31 heavily pretreated patients received bintrafusp alfa for a median duration of 6.1 (range: 2-30) weeks; 8 patients remained on treatment. Four patients (12.9%) experienced grade 3 TRAE (anemia and diarrhea 1 each and 2 rash). No treatment-related grade 4 AEs occurred. One

grade 5 event was suspected due to rupture of pre-existing thoracic aortic aneurysm. The ORR of 16.1% based on investigator assessment was reported. (50)

Taken together, bintrafusp alfa has encouraging anti-tumor activity and compared favorably to anti-PD-1 or anti-PD-L1 antibodies. The treatment is well tolerated and has manageable toxicity profile.

Three clinical studies in two types of cancers (a type of lung cancer called NSCLC and biliary tract cancer) have been recently discontinued as improved efficacy versus other available therapies could not be shown. In some patients in these studies, the patients' tumors continued to grow resulting in fatal outcome in some cases. It is therefore possible that the symptoms of patients' condition will not improve during the study or may even worsen and have a fatal outcome.

Rationale for Dose Selection of Bintrafusp Alfa

The selection of 1200 mg q2w RP2D for bintrafusp alfa is based on the available clinical data from Phase I Study EMR200647-001 and Study MS200647 0008, including safety/tolerability, PK, and PD (PD-L1 TO in PBMCs and TGFβ plasma concentrations), PK-PD correlation analysis, as well as efficacy of bintrafusp alfa following 500 and 1200 mg q2w in 2L NSCLC cohorts from Study EMR200647-001. The selection of RP2D for bintrafusp alfa is also supported by popPK and exposure-response modeling and simulation.

Specifically:

- Clinical PK-PD profiles from dose escalation cohorts of Phase I studies were used to establish a target serum concentration (50 µg/mL) that inhibits all 4 targets of bintrafusp alfa in blood. Based on popPK modeling, > 95% of participants dosed with 1200 mg q2w of bintrafusp alfa are expected to achieve trough concentration at steady-state ($C_{trough,ss}$) above the target concentration of 50 µg/mL. Following a single IV infusion, approximately dose-proportional increase in all exposure metrics and constant terminal $t_{1/2}$ was observed at doses higher than 3 mg/kg, suggesting that target-mediated clearance mechanism is saturated at 1200 mg q2w dose.

- Exposure-response and dose-response for efficacy were assessed in participants with the 2L NSCLC randomized into 2 dose levels: 500 mg q2w and 1200 mg q2w. There was a trend towards an association between exposure variables and efficacy variables, but the effect size was relatively small. Overall, dose-efficacy and exposure-efficacy evaluations supported selection of 1200 mg q2w as the RP2D for NSCLC participants. Based on the mechanism of action of bintrafusp alfa, clinical experience with other checkpoint inhibitors, and the fact that there were no clinically relevant differences in bintrafusp alfa exposures among tumor types, there is no evidence to suggest that the pharmacologically active/efficacious dose would differ substantially among tumor types.

- Overall safety/tolerability data from Phase I studies and exposure-safety analysis conducted on an integrated data-set with > 670 participants supported the selection of 1200 mg q2w as the RP2D. The highest dose for bintrafusp alfa tested was 30 mg/kg (2100 mg for a 70 kg participant) and the MTD was not reached. At 1200 mg q2w the overall emerging safety profile of bintrafusp alfa is considered manageable. Although apparent exposure-safety associations were observed for some AE, bintrafusp alfa exposure metrics were generally weakly correlated

with probability of AEs and effect size were relatively small.

- The selection of flat dose versus mg/kg dosing approach is supported by modeling and simulations, which showed that variability in exposure was indeed lower for flat dosing compared with weight-based dosing.

In summary, integration of all available Phase I data and modeling and simulations support the selection of 1200 mg as the RP2D for q2w dosing of bintrafusp alfa. In addition, none of the examined intrinsic factors were considered clinically meaningful and no dose adjustments related to these intrinsic factors are warranted.

Study Hypothesis

Based on the above findings, we hypothesize that bintrafusp alfa offers better response rate than historical results by anti-PD-1/ anti-PD L1 therapy in previously platinum treated recurrent or metastatic NPC patients.

Rationale for biomarkers and exploratory analysis

(a) PD-L1 status

NPC often exhibits a dense lymphocytic infiltrate and increased PD-L1 expression. (51) The prognostic role of PD-L1 expression in NPC remains inconclusive, but it probably because of different assays and scoring methods used across studies; (52-54) and the predictive utility of PD-L1 expression is affected by the differential expression in immune cells versus tumor cells. (55) Studies that had made such a distinction found that PD-L1 was expressed in 24% to 33% of tumor cells and 40% to 75% of immune cells. (53-54) In the NCI-9742 study, a non-significant higher ORR rate was observed in PD-L1 positive tumor among R/M NPC patients who receiving Nivolumab;(22) similar findings were reported in another study using Pembrolizumab. (21) The findings are consistent with other disease sites that checkpoint inhibitor is more efficacious in PD-L1+ tumors. (56-57)

(b) Plasma EBV-DNA Level

Circulating fragments of EBV-derived deoxyribonucleic acid (DNA) can be detected in 95% of patients with advanced NPC and have been shown to carry prognostic and predictive value. (58) High plasma EBV-DNA levels are a poor prognostic factor (59), and the dynamic change of plasma EBV-DNA level after chemotherapy or chemo-radiotherapy correlate with the efficacy. (60-61) Similar findings were seen in patients receiving Pembrolizumab, but the sample size is small. (62)

(c) HLA Protein Expression

Loss of human leukocyte antigen (HLA) class I expression in solid tumor associated with poor prognosis and more immunosuppressive environment. (63) Around 30% of primary NPC tumors harbor major histocompatibility complex (MHC) class I gene aberrations, with inactivating mutations and rearrangements in the human leukocyte antigen (HLA)–A and HLA-B genes being

the most common and account for 50% of cases, which invariably results in the loss of HLA-A and HLA-B protein expression. (64) Even a higher percentage of MHC down-regulation is expected in metastatic tumor in allowing the MHC-class I negative tumors to escape from T-cell killing. (65) Although the intact MHC-antigen presenting machinery is thought to be the perquisite of the actions of PD1 inhibitors; it is intriguing to find that in R/M NPC patients receiving Nivolumab, those with loss of HLA protein expression had better prognosis. (22) Similarly, over half of patients with Hodgkin's lymphoma who responded to PD-1 inhibitors have total loss of MHC class I expression. (66) However, in melanoma, an association between response to PD-L1 inhibitor and intact MHC-I gene expression has been reported. (67-68) The role of MHC class I down-regulation in NPC patients receiving immunotherapy thus remains to be evaluated, and this will shed light on the mechanism of action of bintrafusp alfa in R/M NPC patients.

(d) Immune Markers

Flow cytometry analyses revealed that, bintrafusp alfa increased the density of CD8+ tumor-infiltrating lymphocytes (TIL), tumor-infiltrating NK cells (TINKs), tumor-associated dendritic cells (TADCs), tumor-associated monocytes, but significantly decreased the density of tumor-associated neutrophils (TANs) and PD-1+ tumor-associated macrophage (TAM). Further analysis by immune cell depletion studies shown that the anti-tumor activity of bintrafusp alfa was mainly mediated by CD8+ T-cells and NK cells. Also, RNA sequencing has demonstrated that bintrafusp alfa promotes the expression of immune cell signature genes (69).

There are also recent findings suggest that exosomal PD-L1 plays an important role by causing immuno-suppression in melanoma and breast cancer. (70-71) High level of circulating exosomal PD-L1 pre-anti-PD-1 treatment may reflect the "exhaustion" of T-cells, while an increase in the level of circulating exosomal PD-L1 after anti-PD-1 treatment may reflect re-invigoration of T-cell activity against melanoma. So exosomal PD-L1 may be a sensitive marker to predict response check-point inhibitor immunotherapy.

(e) Immune-related RECIST (ir-RECIST)

Immunotherapeutic agents may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of bintrafusp alfa. Based on an analysis of patients with melanoma enrolled with KEYNOTE-001, 7% of evaluable patients experienced delayed or early tumor pseudo-progression. Of note, patients who had progressive disease by RECIST 1.1, but not immune-related response criteria, has longer OS than patients with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of anti-PD1 therapy in approximately 15% of patients. (72) These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression. Immune-related RECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapy as described in Nishino et al. (73)

2 STUDY OBJECTIVES

2.1 Primary Objective

1. To evaluate the tumor objective response rate (ORR) to bintrafusp alfa in previously treated R/M NPC patients per response evaluation criteria of solid tumor (RECIST) version 1.1

2.2 Secondary Objectives

1. To assess the progression-free survival (PFS) per RECIST version 1.1
2. To assess the time-to-progression (TTP) per RECIST version 1.1
3. To assess the median survival, overall survival (OS) and survival rate in 12 months and 24 months
4. To evaluate the disease control rate (DCR), duration of response (DOR), and time to response (TTR) in previously treated R/M NPC patients receiving bintrafusp alfa
5. To measure the toxicities and tolerability in previously treated R/M NPC patients receiving bintrafusp alfa
6. To investigate the relationship between the response to bintrafusp alfa and plasma Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) level
7. To evaluate ORR, PFS and TTP, OS, and DCR per immune-related RECIST (irRECIST)
8. To evaluate the patient-reported quality of life (QoL) during treatment

2.3 Exploratory Objectives

1. To investigate the association between treatment outcome and expression of programmed cell death-ligand (PD-L1) in archived NPC tissues
2. To explore the relationship between response to treatment (ORR, PFS, and overall survival OS) and TGF-β1
3. To explore the relationship between response to treatment (ORR, PFS, and overall survival OS) and the profile of exosomal PD-L1

2.4 Study Design

This is a prospective phase II, single arm clinical trial conducted in Queen Mary Hospital (Hong Kong) assessing the efficacy and safety of bintrafusp alfa in previously treated recurrent / metastatic nasopharyngeal cancer patients.

2.5 Study Participants

A total of 38 patients will be accrued to assess the potential benefit of bintrafusp alfa.

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

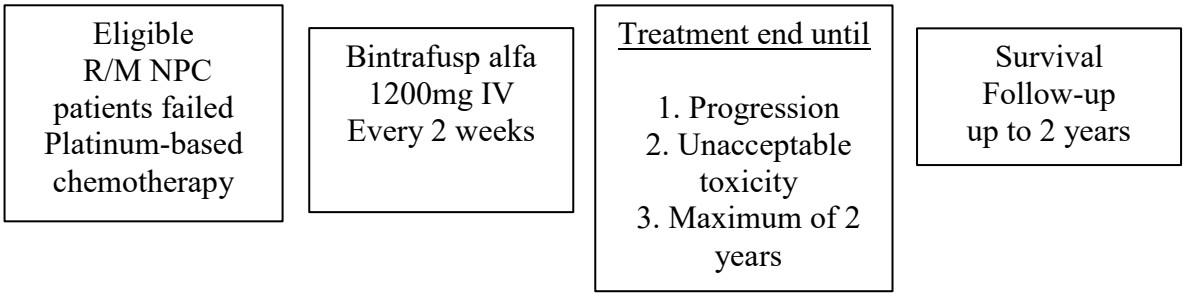
1. Histologically or cytologically confirmed non-keratinizing differentiated (World Health Organization WHO Type II) or undifferentiated (WHO Type III) nasopharyngeal carcinoma (NPC) that has recurred at regional or / and distant sites
2. Measurable disease according to the RECIST criteria (version 1.1) for the evaluation of measurable disease
3. Received one or more lines of chemotherapy, which must include prior treatment with a platinum agent either
    a. For the treatment of metastatic or recurrent disease
    b. Experienced progression of disease within 6 months following completion of a platinum-based combination therapy as part of (neo)-adjuvant therapy
4. Male or female subjects with age: 18-79 years old
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
6. No prior immunotherapy
7. Written informed consent obtained for clinical trial participation and providing archival tumor tissue, if available
8. Females of childbearing potential or non-sterilized male who are sexually active must use a highly effective method of contraception
9. Females of childbearing potential must have negative serum or urine pregnancy test
10. Have life expectancy ≥ 3 months
11. Adequate organ function as defined as:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin >= 8.0 g/dL
    d. Serum alanine aminotransferase ([ALT]; serum glutamate-pyruvate transferase [SGPT]), or serum aspartate aminotransferase [AST] where available at the center) < 2.5 x upper limit of normal (ULN), OR < 5 x ULN in the presence of liver metastases
    e. Serum total bilirubin < 2 x ULN
    f. Serum creatinine < 1.5 x ULN

3.2 Exclusion Criteria

1. Prior invasive malignancy within 2 years except for non-invasive malignancies such as cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, lobular or ductal carcinoma in situ of the breast that has been surgically cured
2. Isolated local recurrence or persistent disease
3. Has disease that is suitable for local therapy administrated with curative intent

4. Severe, active co-morbidity
5. Currently participating in and receiving clinical trial treatment or has participated in a trial of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment
6. Has prior chemotherapy, targeted therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (≤ grade 1 or at baseline) from adverse events due to previous administered agent
7. Untreated active central nervous system (CNS) metastatic disease, lepto-meningeal disease, or cord compression
8. Clinically significant (active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
9. Prior treatment with any other anti-programmed cell death protein-1 (anti-PD-1), or PD Ligand-1 (PD-L1) or PD Ligand-2 (PD-L2) agent or an antibody targeting other immuno-regulatory receptors or mechanisms
10. Irritable bowel syndrome or other serious gastrointestinal chronic conditions associated with diarrhea within the past 3 years prior to the start of treatment
11. Known history of testing positive for HIV or known acquired immunodeficiency syndrome.
12. On chronic systemic steroid or any other forms of immunosuppressive medication within 14 days prior to the treatment. Except:
    a. Intra-nasal, inhaled, topical steroids, or local steroid injection (e.g., intraarticular injection);
    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
    c. Steroids as premedication for hypersensitivity reactions due to bintrafusp alfa
13. Active or prior documented autoimmune or inflammatory disorders in the past 2 years, except diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment
14. Known active hepatitis B or known hepatitis C is detected; subjects who have been treated and now have an undetectable viral load are eligible
15. History of primary immunodeficiency or solid organ transplantation
16. Receipt of live, attenuated vaccine within 28 days prior to the study treatment
17. Active infection requiring systemic therapy
18. Severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb)
19. Females who are pregnant, lactating, or intend to become pregnant during their participation in the study
20. Psychiatric disorders and substance (drug/alcohol) abuse

4 STUDY SCHEMA



Study Treatment: Bintrafusp alfa 1200mg IV Every 2 weeks until progression or unacceptable toxicity or maximum of 2 years.

4.1 Informed Consent

The Investigator(s) (according to applicable regulatory requirements), or a person designated by the Investigator(s), and under the Investigator(s)'s responsibility, should fully inform the patient of all pertinent aspects of the clinical study including the written information giving approval/favorable opinion by the Ethics Committee (IRB/EC). All participants shall be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patients' participation in the clinical study, the written Informed Consent Form (Form B) and any other local applicable documents in accordance with local laws and regulations, should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent From used by the Investigator(s) for obtaining the patient's informed consent must be reviewed and approved by the appropriate Ethics Committee (IRB/EC) for approval/favorable opinion.

During a patient's participation in the trial, any updates to the consent form any updates to the written information will be provided to the patient.

Further information about the informed consent is available in Section 8.2 and Section 8.3.

4.2 Registration Guidelines

- All the patients must be registered with the Investigator(s) prior to initiation of treatment
- Forms A (registration) and B (consent) will be submitted
- The registration desk will confirm all eligibility criteria and obtain essential information (including patient number)

5 STUDY INTERVENTION

5.1 General Information of Study Intervention Bintrafusp alfa

Bintrafusp alfa is a first-in-class, bifunctional fusion protein comprised of the ECD of the human TGF-βRII or TGF-β Trap covalently linked to the C terminus of the heavy chain of the fully human IgG1, anti-PD L1 antibody via a flexible $(Gly_4Ser)_4G$ linker.

5.2 Pharmaceutical Properties and Description of the Formulation

Bintrafusp alfa drug product is primarily provided as a sterile liquid formulation.

The Powder for Concentrate for Solution for Infusion (freeze-dried formulation) is packaged in United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) type I glass vials. Each vial is filled with 45 mg of bintrafusp alfa (45 mg/vial) as a preservative-free powder containing histidine, trehalose dihydrate, sodium chloride, L-methionine, and polysorbate 20 (Tween 20). The vials are closed with a rubber stopper in lyophilization format complying with USP and Ph. Eur. and sealed with an aluminum plastic crimping cap. Only excipients that conform to the current USP and/or Ph. Eur. are used for bintrafusp alfa drug product.

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 liquid formulation, compared with the freeze-dried formulation, has the same composition in terms of excipients, qualitatively and quantitatively, except for the addition of water. Of note, there is no change to the drug substance process.

The excipients are viewed as standard, and therefore, not a safety risk. The estimated volumes of delivery are anticipated to be either 250 or 500 mL, which are clinically acceptable.

5.3 Handling of the Dosage Form

For applications in clinical studies, the freeze-dried drug product must be reconstituted with 4.5 mL of water for injection and further diluted with 0.9% saline solution (sodium chloride injection)

supplied in an infusion bag. The liquid formulation is diluted directly with 0.9% saline solution. The estimated volumes of delivery are anticipated to be either 250 mL or 500 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, and assigned dose levels and concrete volumes to be replaced to prepare the target doses are described in the Pharmacy Manual.

Bintrafusp alfa 1200mg will be administered intravenously on Day 1 of each 2-week study cycle. Bintrafusp alfa may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

5.4 Instructions for Storage

Bintrafusp alfa 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 bintrafusp alfa.

Bintrafusp alfa drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation.

The liquid formulation is diluted directly with 0.9% saline solution. The chemical and physical in-use stability for the infusion solution of bintrafusp alfa 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 bintrafusp alfa.

5.5 Bintrafusp Alfa Administration

Pre-medication: Flat dose of 1200 mg administered over 60 minutes (± 10-20 minutes) intravenous infusion once every 2 weeks. In order to mitigate infusion-related reactions, a premedication regimen of diphenhydramine 25 to 50 mg IV or oral equivalent and paracetamol 500 mg IV or oral equivalent is mandatory approximately 30 to 60 minutes prior to each dose of bintrafusp alfa.

Setting: bintrafusp alfa should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Observation period: Following infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

Drug accountability and return, or local discard and destruction, if appropriate, must be completed with appropriate documentation for all study sites. Lot number, and expiry date for bintrafusp alfa is recorded in the study site as per local guidelines unless otherwise instructed by the Sponsor.

The Investigator is responsible for taking steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

5.6 Bintrafusp Alfa Adverse Event Management

5.6.1 Bintrafusp Alfa Adverse Events

Based on the available preclinical data, pharmacological class effect, and periodic safety reviews, the following were considered as adverse events upon Bintrafusp Alfa infusion and classified as:

- Important identified risks
    - Infusion-related reaction (IRR) 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 micro-vasculitis, myositis, skin reactions like rash (generalized, maculopapular, erythematous, pemphigoid)
    - Skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGF-β inhibition.

- Important potential risks
    - Treatment related anemia
    - Alterations in wound healing, repair of tissue damage, or mucosal bleeding events
    - Embryofetal toxicities

- Non-important potential risk:
    - Mucosal bleeding

Mucosal bleeding events are a potential risk for M7824. Respective risk mitigation measures have been implemented in the protocol.

The following side effects have been observed in ≥10% of patients among 630 patients treated with bintrafusp alfa according to the results from two oncology clinical studies in patients with advanced solid tumors. Common side effects (reported in more than to 1 in 10 people) include:

- Anemia (low number of red blood cells)
- Decreased appetite
- Fatigue
- Pruritis (itching)

- Dyspnea (shortness of breath)
- Constipation (difficulty passing stools)
- Nausea (feeling sick to the stomach)
- Pyrexia (raised body temperature)
- Asthenia (decreased muscle strength)
- Diarrhea (frequent loose, watery stools)
- Abdominal pain
- Vomiting
- Cough
- Headache
- Epistaxis (bleeding from the nose)
- Rash (maculo-papular rash)
- Aspartate aminotransferase increased (elevation of liver enzyme)
- Oedema peripheral (buildup of fluid in the body causing swelling)

5.6.2 Dose Modifications for Bintrafusp Alfa as Single Agent

No dose reductions are permitted in this study, but doses may be omitted based on persisting toxicity. Any adverse event suspected to be immune-related should be managed according to the guidance for management of irAEs

5.6.3 Adverse Drug Reaction Requiring Bintrafusp Alfa Discontinuation or Delays

The following adverse reactions (ADRs) require permanent treatment discontinuation of bintrafusp alfa:

Any Grade 4 ADRs require bintrafusp alfa treatment discontinuation except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator(s), do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require bintrafusp alfa treatment discontinuation except for any of the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤1
- Single laboratory values out of normal range (excluding Grade ≥3 liver function test increase) that are unlikely related to trial treatment according to the Investigator(s), do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to 3 that

resolve to ≤2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is 3 on the day of trial drug administration)

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤1 within 2 weeks treatment may continue
- If a Grade 2 ADR does not resolve to Grade ≤1 within 2 weeks, bintrafusp alfa should be held. If after another 2 weeks the event has not resolved to Grade 1, the patient should permanently discontinue treatment with bintrafusp alfa (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted)
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same patient, treatment with bintrafusp alfa has to be permanently discontinued

5.6.4 Management of Infusion Related Reaction (IRR)

IRRs including hypersensitivity (immediate) were listed as an important identified risk of bintrafusp alfa. IRR are divided into reactions versus signs and symptoms.

- Reactions are 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 infusion related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and Type 1 hypersensitivity
- Signs and symptoms are considered when onset is on the day of infusion (during or after the infusion) and resolved with the end date within 2 days after onset for pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain and urticaria

Pre-medication with an anti-histamine and with paracetamol (acetaminophen) was mandatory in order to mitigate potential infusion related reactions during the first 2 infusions in Study EMR200647-001 and Study MS200647-0008.

Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification
Grade 1 - mild Mild transient reaction; in general, infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • Hold infusion if deemed necessary by the investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• Stop the infusion of the study intervention. • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening signs and symptoms, otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. • If not improving, consider administration of glucocorticoids and stop the infusion for that day. • If the participant has a second IRR Grade ≥ 2 on the slower infusion rate despite premedication, the infusion should be stopped, and the investigator may consider withdrawal of this participant from the study.
Grade 3 or Grade 4 – severe or life-threatening o 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. o Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • For Grade 3 or 4 IRRs, permanent discontinuation of study intervention is mandated.
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	
IRR=infusion-related reactions, IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.	

Immediate Hypersensitivity Reaction Hypersensitivity reactions may require immediate intensive care. Bintrafusp alfa should be administered in a setting that allows immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Potent steroids (e.g. dexamethasone), catecholamines (e.g. epinephrine), allergy medications (IV antihistamines), bronchodilators, or equivalents and oxygen should be available for immediate access. 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. Flu-Like Symptoms Treatment is based on clinical assessment and at the discretion of the Investigator. For prophylaxis of flu like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions
If in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the Investigators may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigators may consider the addition of H2 blocker antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

Severe Hypersensitivity Reactions
If hypersensitivity reaction occurs, the patient 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) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigators immediately.

Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the intensive care unit (ICU) should be alerted for possible transfer if required.

5.6.5 Management of Immune-Related Adverse Events (IrAEs)

Because inhibition of PD-L1 by anti-PD-L1 component stimulates the immune system, bintrafusp alfa may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs).

Immune-related AEs are specific to immunotherapies and vary by organ system.
Following immune-related AEs are important identified risks for bintrafusp alfa:

- Immune-related pneumonitis
- Immune-related hepatitis

- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies
- (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders)
- Immune related rash
- Other immune-related events (myositis, myocarditis, encephalitis)

Following immune-related AEs are important potential risks for bintrafusp alfa:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

Recommended guidance and management for specific irAEs are provided in the current NCCN guideline available at http://www.nccn.org.

Requirements in addition to NCCN guidelines:

- Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura inflammatory arthritis, myositis and polymyalgia-like syndrome.

- For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade ≤ 1, restarting treatment may be considered.

- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry. If symptoms appear and/or changes in the physical exam are noted, treat as Grade 2.

- For myositis: in case of management with rituximab, treatment should be discontinued.

The side effects listed below may be temporary, long term, permanent, life-threatening or result in death. However, most of these side effects are reversible.

General Principle of Treatment of irAEs (NCI CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.

- Grades 1 to 2 (persistent): manage similar to high grade AE (Grades 3 to 4).

  Grades 3 to 4: treat with high dose corticosteroids or equivalent and/or other immunosuppressant as needed

MANAGEMENT OF SKIN irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">1.0 Skin Toxicities</th></tr>
<tr><td colspan="2">1.1 Rash/inflammatory dermatitis</td></tr>
<tr><td colspan="2">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)</td></tr>
<tr><td colspan="2">Diagnostic work-up</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.</td><td></td></tr>
<tr><td>G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic</td><td>Continue ICPi
Treat with topical emollients and/or mild-moderate potency topical corticosteroids
Counsel patients to avoid skin irritants and sun exposure</td></tr>
</table>

G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to Grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	**Permanently discontinue ICPi** Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves

1.0 Skin Toxicities	
	Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology
1.2 Bullous dermatoses	
Definition: Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction Diagnostic work-up Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease If needed, a biologic checkup, including a blood cell count, liver, and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister) Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)	
Grading	**Management**
G1: Asymptomatic, blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, asymptomatic, and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary, and only observation and/or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are observed on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least G2 See G2 management recommendations

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 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	

<table>
<tr><th colspan="2">1.0 Skin Toxicities</th></tr>
<tr><td colspan="2">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 pustulosis
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</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>All Grades</td><td>In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade</td></tr>
<tr><td>G1: NA</td><td>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</td></tr>
<tr><td>G2: Morbilliform (“maculopapular”) exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling</td><td>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</td></tr>
</table>

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

1.0 Skin Toxicities	
	For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% 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.

MANAGEMENT OF BLEEDING irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">2.0 Bleeding Adverse Events</th></tr>
<tr><td colspan="2">Bleeding adverse events are considered important identified risk for bintrafusp alfa.
In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment.
These events may include, but are not limited to the following:
Epistaxis
Hemoptysis
Gingival bleeding
Hematuria</td></tr>
<tr><th colspan="2">Mucosal/Non-tumor Bleeding</th></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>Grade 2</td><td>If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued
If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.</td></tr>
<tr><td>Grade ≥3</td><td>Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.)
In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1
If Grade ≥3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention bintrafusp alfa dose should be reduced by 50% (600 mg Q2W for participants dosed with 1200 mg, 1200 mg for participants dosed with 2400 mg). Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor on potential dose re-escalation after careful benefit-risk assessment.</td></tr>
<tr><td>Grade 4</td><td>Treatment must be permanently discontinued if no alternative explanation is identified.</td></tr>
<tr><td colspan="2">In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 2.0 g/dL across a 2 weeks period, withhold the subsequent cycles of study intervention until Hgb is</td></tr>
</table>

stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced by 50%. Once Hgb decrease is recovered to ≤ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of bintrafusp alfa may be re-escalated to full dose once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re escalation may need a case-by-case decision. See Section Table 5 regarding stabilization of anemia.	
Tumor Bleeding	
Grade ≥ 2	Study treatment must be held till the event recovers to Grade ≤ 1 Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.
Grade ≥ 3	If Grade ≥ 3 bleeding event had been observed, regardless of causality with the study intervention, upon resumption of the study intervention bintrafusp alfa dose should be reduced by 50%. Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor potential dose re-escalation after careful benefit-risk assessment. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding. In case of rapid decrease of hemoglobin (Hgb), see Section Mucosal/Non-Tumor bleeding.

MANAGEMENT OF GI irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">3.0 GI Toxicities</th></tr>
<tr><td colspan="2">3.1 Colitis</td></tr>
<tr><td colspan="2">Definition: A disorder characterized by inflammation of the colon Diagnostic work-up</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td>Grading (based on CTCAE for diarrhea, as most often used clinically)</td><td>Management</td></tr>
<tr><td>All patients</td><td>Counsel all patients to be aware of and inform their health care provider immediately if they experience:
Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation, constipation
For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases</td></tr>
</table>

G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher

3.0 GI Toxicities	
	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
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 (not approved in Japan) 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	

3.0 GI Toxicities	
3.2 Hepatitis	
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma Diagnostic work-up Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if G1 liver function test elevations. No treatment is recommended for G1 liver function test abnormality For G2 or higher: Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs, antismooth muscle antibodies, antineutrophil cytoplasmic antibodies. If patients with elevated alkaline phosphatase alone, 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 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

3.0 GI Toxicities	
	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 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.	

*not approved in Japan.

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.

MANAGEMENT OF LUNG irAES IN PATIENTS TREATED WITH ICPis

4.0 Lung Toxicities	
4.1 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	**Continue** ICPi **If clinically indicated. Monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry;** may also offer CXR. May offer one repeat CT scan in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks **If symptoms appear and/or changes in the physical exam are noted, treat as G2**
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Additional considerations
GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines
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.

MANAGEMENT OF ENDOCRINE irAES IN PATIENTS TREATED WITH ICPis

5.0 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	
5.1 Thyroid	
5.1.1 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) 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

5.0 Endocrine Toxicity	
	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	
5.1.2 Hyperthyroidism	
Definition: Suppressed TSH and high normal or elevated FT4 and/or triiodothyronine Diagnostic work-up Monitor TSH, FT4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease (eg, ophthalmopathy) Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1) 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	

5.0 Endocrine Toxicity	
Definition: Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone	
Diagnostic work-up for patients in whom adrenal insufficiency is suspected: Evaluate ACTH (AM), cortisol level (AM) Basic metabolic panel (Na, K, CO_2, glucose) Consider ACTH stimulation test for indeterminate results If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/d) for mineralocorticoid replacement in primary adrenal insufficiency Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone Endocrine consultation Initiate outpatient treatment at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.

G3-4: Severe symptoms, medically significant or life- threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in G1
Additional considerations Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per 4.3. Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see next section on hypophysitis).	

<table>
<tr><th colspan="2">5.0 Endocrine Toxicity</th></tr>
<tr><td colspan="2">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">5.3 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 ± new severe headaches or complaints of vision changes</td></tr>
<tr><th>Grading</th><th>Management</th></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 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.</td></tr>
<tr><td colspan="2">5.4 Diabetes</td></tr>
</table>

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**
5.0 Endocrine Toxicity	
G1: Asymptomatic or mild symptoms; fasting glucose value > ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	Can continue ICPi with close clinical follow-up and laboratory evaluation May initiate oral therapy for those with new-onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value> 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	May hold ICPi until glucose control is obtained Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any patient with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
G3-4: Severe symptoms, medically significant or life- threatening consequences, unable to perform ADL G3: > 250-500 mg/dL (> 13.9-27.8 mmol/L) G4: > 500 mg/dL (> 27.8 mmol/L)	Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to G1 or less Urgent endocrine consultation for all patients Initiate insulin therapy for all patients Admit for inpatient management: Concerns for developing DKA, Symptomatic patients regardless of diabetes type, New-onset T1DM unable to see endocrinology

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

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; CT, computed tomography; DKA, diabetic ketoacidosis; DM, diabetes mellitus; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; G, Grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; LH, luteinizing hormone; MRI, magnetic resonance imaging; PTU, propylthiouracil; 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.

MANAGEMENT OF MUSCULOSKELETAL irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">6.0 Musculoskeletal Toxicities</th></tr>
<tr><td colspan="2">6.1 Inflammatory arthritis</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td colspan="2">Diagnostic work-
up G1
Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion; examination of the spine Consider plain x-ray/imaging to exclude metastases and evaluate joint damage (erosions), if appropriate
Consider autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP) if symptoms persist; if symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing
G2
Complete history and examination as above; laboratory tests as above
Consider US ± MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)
Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms of arthralgia persist
> 4
weeks
G3-4
As for G2
Seek rheumatologist advice and review
Monitoring: Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>All Grades</td><td>Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi</td></tr>
<tr><td>G1: Mild pain with inflammation, erythema, or joint swelling</td><td>Continue ICPi
Initiate analgesia with acetaminophen and/or NSAIDs</td></tr>
</table>

G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	**For G3:** Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less **For G4: permanently discontinue ICPi** Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD

<table>
<tr><th colspan="2">6.0 Musculoskeletal Toxicities</th></tr>
<tr><td></td><td>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.</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td colspan="2">6.2 Myositis</td></tr>
<tr><td colspan="2">Definition: A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or myocardium are involved
Diagnostic work-up
Complete rheumatologic and neurologic history regarding differential diagnosis; rheumatologic and neurologic examination, including muscle strength; and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider preexisting conditions that can cause similar symptoms.
Blood testing to evaluate muscle inflammation
CK, transaminases (AST, ALT), LDH, and aldolase can also be elevated
Troponin to evaluate myocardial involvement and other cardiac testing, such as echocardiogram, as needed Inflammatory markers (ESR and CRP)
Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes, such as myasthenia gravis, is suspected
Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as myasthenia gravis Monitoring: CK, ESR, CRP</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><th>Grading</th><th>Management</th></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</td></tr>
</table>

	Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5-1 mg/kg

6.0 Musculoskeletal Toxicities	
	May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3-4: Severe weakness with or without pain, limiting self-care ADL	**For G3:** Hold ICPi until G1 or less and permanently discontinue if any evidence of myocardial involvement **For G4: permanently discontinue ICPi** Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise **(weakness severely limiting mobility, cardiac, respiratory, dysphagia)** Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration **In case of management with rituximab, ICPi treatment should be discontinued**
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

6.0 Musculoskeletal Toxicities	
G3-4: Severe stiffness and pain, limiting self-care ADL	**For G3:** Hold ICPi and may resume, in consultation with rheumatology, if recover to G1 or less; however, note that cases of toxicity returning upon rechallenge have been reported. **ICPi should be permanently discontinued in such cases** **For G4: permanently discontinue ICPi** Referral to rheumatology Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent such as methotrexate or IL-6 inhibition with tocilizumab (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases). Consider admission for pain control
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; 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.

MANAGEMENT OF RENAL irAES IN PATIENTS TREATED WITH ICPis

7.0 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	
7.1 Nephritis	
Definition: Inflammation of the kidney affecting the structure	
Grading	**Management**
G1: Creatinine level increase **> ULN - 1.5 x ULN**	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 **> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN**	Hold ICPi 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 **> 3.0 x baseline; > 3.0 - 6.0 x ULN**	Permanently discontinue ICPi
G4: Life-threatening consequences; dialysis indicated; **> 6.0 x ULN**	**Permanently discontinue ICPi** 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	
7.2 Symptomatic nephritis: follow-up	
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
7.0 Renal Toxicities	
	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.

MANAGEMENT OF NERVOUS SYSTEM irAES IN PATIENTS TREATED WITH ICPis

8.0 Nervous System Toxicities	
8.1 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 Daily neurologic review
Additional considerations Avoid medications that can worsen myasthenia: β-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolides Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement Pyridostigmine, wean based on improvement ICPi-associated myasthenia gravis may be monophasic, and additional corticosteroid-sparing agents may not be required	
8.2 Guillain-Barré syndrome	

<table>
<tr><th colspan="2">8.0 Nervous System Toxicities</th></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>All grades</td><td>Warrant work-up and intervention given potential for progressive Guillain-Barré syndrome to lead to respiratory compromise
Note: There is no G1 toxicity</td></tr>
<tr><td>G1: Mild, none</td><td>NA</td></tr>
<tr><td>G2: Moderate, some interference with ADL, symptoms concerning to patient</td><td>Discontinue ICPi</td></tr>
<tr><td>G3-4: Severe, limiting self-care and aids warranted, weakness, limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms</td><td><u>Permanently discontinue ICPi.</u>
Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic Guillain-Barré syndrome; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow corticosteroid taper
Pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis
Frequent neurochecks and pulmonary function monitoring
Monitor for concurrent autonomic dysfunction Nonopioid management of neuropathic pain Treatment of constipation/ileus</td></tr>
</table>

Additional considerations Slow prednisone taper after corticosteroid pulse plus IVIG or plasmapheresis May require repeat IVIG courses Caution with rechallenging for severe cases
8.3 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

8.0 Nervous System Toxicities	
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
8.4 Autonomic neuropathy	
Definition: Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function, and sexual function. A case of severe enteric neuropathy with ICPi has been reported. Can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.	
Diagnostic work-up An evaluation by neurologist or relevant specialist, depending on organ system, with testing that may include 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	
Grading	**Management**
G1: Mild, no interference with function and symptoms not concerning to patient	Low threshold to hold ICPi and monitor symptoms for a week; if to continue, monitor very closely for any symptom progression
G2: Moderate, some interference with ADL, symptoms concerning to patient	Hold ICPi and resume once return to G1 Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild) Neurologic consultation

G3-4: Severe, limiting self-care and aids warranted	Permanently discontinue ICPi Admit patient Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper Neurologic consultation
8.5 Aseptic meningitis	
Definition: may present with headache, photophobia, and neck stiffness; often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis). Diagnostic work-up MRI of brain with or without contrast + pituitary protocol AM cortisol, ACTH to rule out adrenal insufficiency Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology	

<table>
<tr><th colspan="2">8.0 Nervous System Toxicities</th></tr>
<tr><td colspan="2">May see elevated WBC count with normal glucose, normal culture, and Gram stain; may see reactive lymphocytes or histiocytes on cytology</td></tr>
<tr><th>Grading</th><th>Management</th></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">8.6 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</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><th>Grading</th><th>Management</th></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
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.</td></tr>
</table>

<table>
<tr><th colspan="2">8.7 Transverse myelitis</th></tr>
<tr><td colspan="2">Definition: Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><th>Grading</th><th>Management</th></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.</td><td>Permanently discontinue
ICPi Methylprednisolone
2 mg/kg</td></tr>
</table>

8.0 Nervous System Toxicities	
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	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.

MANAGEMENT OF HEMATOLOGIC irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">9.0 Hematologic Toxicities</th></tr>
<tr><td colspan="2">9.1 Autoimmune hemolytic anemia</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L</td><td>Continue ICPi with close clinical follow-up and laboratory evaluation</td></tr>
<tr><td>G2: Hgb < 10.0 to 8.0 g/dL; < 6.2to4.9mmol/L; < 100 to 80 g/L</td><td>Hold ICPi and strongly consider permanent discontinuation
Administer 0.5-1 mg/kg/d prednisone equivalents</td></tr>
</table>

G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi Should use clinical judgment and consider admitting the patient Hematology consult Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms/speed of development) If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue ICPi treatment Consider RBC transfusion per existing guidelines; do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7-8 g/dL in stable, noncardiac inpatients) Should offer patients supplementation with folic acid 1 mg once daily
G4: Life-threatening consequences, urgent intervention indicated	Permanently discontinue ICPi Admit patient Hematology consult IV prednisone corticosteroids 1-2 mg/kg/d

9.0 Hematologic Toxicities	
	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	
9.2 Acquired TTP	
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Diagnostic work-up History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine) Physical examination, peripheral smear ADAMTS13 activity level and inhibitor titer LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes PT, activated PTT, fibrinogen Blood group and antibody screen, direct antiglobulin test, CMV serology Consider CT/MRI brain, echocardiogram, ECG Viral studies Note: This disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously	
Grading	**Management**
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition; hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity. Initially, the patient should be stabilized and any critical organ dysfunction stabilized
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically 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)	For G3: 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 **For G4: permanently discontinue ICPi** 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 **In case of management with rituximab, ICPi treatment will be discontinued**

<table>
<tr><th colspan="2">9.0 Hematologic Toxicities</th></tr>
<tr><td colspan="2">9.3 Hemolytic uremic syndrome</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">Diagnostic work-up
History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices
Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis. Serum creatinine
ADAMTS13 (to rule out TTP)
Homocysteine/methylmalonic acid
Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and mean corpuscular volume
Evaluation of infectious cause, including screening for EBV, CMV, HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes
Evaluation for diarrheal causes, shiga toxin, Escherichia coli 0157, etc
Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc) Evaluation for concurrent confusion</td></tr>
<tr><th>Grading</th><th>Management</th></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>For G1 and G2: Continue ICPi with close clinical follow- up and laboratory evaluation
Supportive care
<u>For G3 and G4: Permanently discontinue ICPi</u>
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>
</table>

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

9.0 Hematologic Toxicities	
Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	
Grading	**Management**
G1: Nonsevere, < 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count < 20,000	Hold ICPi and provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions as per local guidelines
G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily Administer ATG + cyclosporine; HLA typing and evaluation for bone marrow transplantation if patient is candidate; all blood products should be irradiated and filtered Supportive care with granulocyte colony-stimulating factor may be added in addition
G3-4: Very severe, ANC > 200, platelet count > 20,000, reticulocyte count > 20,000, plus hypocellular marrow > 25%	**For G3:** Hold ICPi and monitor weekly for improvement; if not resolved, discontinue treatment until AE has reverted to G1 **For G4: permanently discontinue ICPi** 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
9.5 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 for G1 to G2 For G3 single laboratory values out of normal range without any clinical correlates, hold treatment until resolution to G1 For G4, for single laboratory values out of normal range without any clinical correlates, permanent treatment discontinuation is not required. Treatment should be held until the etiology is determined. Permanent treatment discontinuation will only be required, if lymphopenia is considered of immune related in nature, no clear alternative explanation exists for the event, and grade 4 lymphopenia does not resolve within 14 days. If the event is not considered immune related and resolves to G ≤1 restarting treatment may be considered.

<table>
<tr><th colspan="2">9.0 Hematologic Toxicities</th></tr>
<tr><td></td><td>Check 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.</td></tr>
<tr><td colspan="2">9.6 Immune thrombocytopenia</td></tr>
<tr><td colspan="2">Definition: An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Platelet count < 100/µL G2: Platelet count < 75/µL</td><td>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.</td></tr>
<tr><td>G3: Platelet count < 50/µL</td><td>Hold ICPi but monitor for improvement; if not resolved, interrupt treatment until AE has reverted to G1</td></tr>
</table>

G4: Platelet count < 25/μL	**Permanently discontinue ICPi** 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

9.0 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)
9.7 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 ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor

G3-4: Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Permanently discontinue ICPi Admit patient Hematology consult Administration of factor replacement, choice based on Bethesda unit level of inhibitor Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity); caution should be taken in the elderly and those with coronary artery disease Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d). Transfusion support as required for bleeding If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
Additional considerations: 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.	

9.0 Hematologic Toxicities
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.

MANAGEMENT OF CARDIOVASCULAR irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">10.0 Cardiovascular Toxicities</th></tr>
<tr><td colspan="2">10.1 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><th>Grading</th><th>Management</th></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:
For G1: Hold ICPi
For G2, G3, and G4: Permanently discontinue ICPi For G1-G4: High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)
Admit patient, cardiology consultation
Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin</td></tr>
<tr><td colspan="2">Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular 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>
<tr><td colspan="2">10.2 Venous thromboembolism</td></tr>
</table>

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

10.0 Cardiovascular Toxicities	
Grading	**Management**
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi Warm compress Clinical surveillance
G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	Hold ICPi until AE reverts back to G1 or less. If reverts to G2, use benefit-risk assessment for ICPi continuation 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 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: 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.

MANAGEMENT OF OCULAR irAES IN PATIENTS TREATED WITH ICPis

<table>
<tr><th colspan="2">11.0 Ocular Toxicities</th></tr>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">11.1 Uveitis/iritis</td></tr>
<tr><td colspan="2">Definition: Inflammation of the middle layer of the eye Diagnostic work-up: as per above</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>G1: Asymptomatic</td><td>Continue ICPi
Refer to ophthalmology within 1 week Artificial tears</td></tr>
<tr><td>G2: Medical intervention required, anterior uveitis</td><td>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</td></tr>
</table>

	reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity Re-treat after return to G1 or less
G3: Posterior or panuveitis	Permanently discontinue ICPi Urgent ophthalmology referral. Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	Permanently discontinue ICPi Emergent ophthalmology referral

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

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

5.6.6 Management of Adverse Skin Reaction

TGF-β inhibition mediated skin reactions are considered important identified risk for bintrafusp alfa. Skin assessment must be performed at baseline and at least every 6 weeks during treatment and at the end of treatment or 28 (±5 days) days post-treatment safety follow-up (if not performed in the previous 6 weeks).

- Hyperkeratosis
- Keratoacanthoma
- Cutaneous squamous cell carcinoma (cSCC)
- Basal cell carcinoma
- Actinic keratosis

Management

- Baseline skin assessment with detailed medical history
- Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
- Emollients may be used
- Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
- Treatment follow-up will depend on number and localization of lesions.
    - Single lesion: full excision may be recommended
    - Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Retinoids may be used after discussion with Investigator.
- Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
- In general, treatment of TGF-β mediated skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing bintrafusp alfa.
Consult with Medical Monitor as needed for management of TGF-β mediated skin lesions.

5.6.7 Management of Treatment-Related Anemia

- Anemia is considered an important identified risk for bintrafusp alfa.
- Hematology assessment must be performed at baseline, prior to each bintrafusp alfa dose, at the end of treatment visit and at 28 (±5 days) days post-treatment safety follow-up.
- Participants must enter the study with Hgb values at least 9g/dl
- All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible

Basic Anemia Evaluation

- CBC with emphasis on red cell indices
- If indicated and at clinical discretion, the following should be considered:
    - Iron studies
    - Serum Folate and Vit B12 values
    - Coagulation factors
    - Fecal occult blood
    - Urinalysis
    - Hormone panel: TSH, Erythropoietin

○ Peripheral blood smear
Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)
• Suspected Hemolysis ○ bilirubin, LDH, Coombs test, haptoglobin • Suspected bleeding: ○ Consider imaging/interventional radiology consultation as indicated ○ Consider imaging and/or endoscopy as clinically indicated • Suspected aplastic anemia: ○ Hematology consultation ○ Consider bone marrow aspiration/morphologic evaluation
Additional consideration: In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Abbreviation: CBC: complete blood count, TSH: thyroid stimulating hormone, LDH: lactate dehydrogenase

5.6.8 Management of Bleeding Adverse Events

Bleeding Adverse Events	
• Bleeding adverse events are considered important identified risk for bintrafusp alfa. • In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment. • These events may include, but are not limited to the following: ○ Epistaxis ○ Hemoptysis ○ Gingival bleeding ○ Hematuria	
Mucosal/Non-tumor Bleeding	
Grading	**Management**
Grade 2	• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued • If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.
Grade ≥3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1

	• If Grade ≥3 bleeding event is observed, regardless of causality with the study intervention, upon resumption of study intervention bintrafusp alfa dose should be reduced by 50% (600 mg Q2W for participants dosed with 1200 mg, 1200 mg for participants dosed with 2400 mg). Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor on potential dose re-escalation after careful benefit-risk assessment.
Grade 4	• Treatment must be permanently discontinued if no alternative explanation is identified.
In case of rapid decrease of hemoglobin (Hgb), such as a decrease greater than 2.0 g/dL across a 2 weeks period, withhold the subsequent cycles of study intervention until Hgb is stabilized and do a thorough assessment of bleeding (for example, upper and lower GI endoscopy, enhancement CT etc.); if Grade 1 or greater bleeding is observed or suspected, withhold the bintrafusp alfa until the bleeding is resolved/controlled and resume the dose of bintrafusp alfa reduced by 50%. Once Hgb decrease is recovered to ≤ Grade 1 or baseline and stably controlled, the Investigator is encouraged to communicate with Medical Monitor to re-escalate the dose. The dose of bintrafusp alfa may be re-escalated to full dose once Hgb is stabilized without further need for blood transfusion in the subsequent cycles. The timing of re escalation may need a case-by-case decision. See Section Table 5 regarding stabilization of anemia.	
Tumor Bleeding	
Grade ≥ 2	• Study treatment must be held till the event recovers to Grade ≤ 1 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.
Grade ≥ 3	• If Grade ≥ 3 bleeding event had been observed, regardless of causality with the study intervention, upon resumption of the study intervention bintrafusp alfa dose should be reduced by 50%. Once there is stable resolution and no recurrence of bleeding on reduced dose, Investigator is encouraged to communicate with Medical Monitor potential dose re-escalation after careful benefit-risk assessment. Treatment should be permanently discontinued if the Investigator considers the participant to be at risk for additional severe bleeding. • In case of rapid decrease of hemoglobin (Hgb), see Section Mucosal/Non-Tumor bleeding.

5.6.9 Alterations in Wound Healing or Repair of Tissue Damages

- Impaired wound healing is considered important potential risk for bintrafusp alfa
- Management should be discussed with Medical Monitor for participants requiring surgery on study.
  It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. Post-operative wound healing should be closely monitored

5.6.10 Embryo-Fetal Toxicities

Embryofetal toxicities are known risk of the PD 1/PD L1 targeting class and are considered important potential risks for bintrafusp alfa. Animal models link the PD 1/PD L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Embryofetal toxicity is an important potential risk of bintrafusp alfa. An appropriate contraception warning is provided as part of the inclusion criteria. Pregnant and breastfeeding women are not allowed in the bintrafusp alfa study, and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus

5.6.11 Mild to Moderate Bleeding of the Mucous Membranes (Mucosal Bleeding Events)

Mucosal bleeding of mild to moderate severity has been observed in patients treated with bintrafusp alfa in ongoing studies and is a potential risk of bintrafusp alfa. This type of bleeding may include nosebleeds, cough with blood in the phlegm (sputum), bleeding of the gums (gingival bleeding), or blood in the urine, among others. In general, this bleeding resolves without stopping treatment.

6 FOLLOW UP AND OUTCOME EVALUATION

6.1 Follow-Up Schedule

All participants will be followed every 2 weeks during the intervention. At each visit, patient's performance status and toxicity of treatment will be monitored, and blood test will be checked for complete blood count, liver function, and renal function. Thyroid function test and early morning cortisol (9am) will be performed at least every 4 weeks while on bintrafusp alfa therapy. For female patients in reproductive age, urine or serum pregnancy test needs to be performed at least every month while the subject is on bintrafusp alfa therapy. All adverse events and laboratory abnormalities will be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

For blood-borne immune markers and exploratory biomarkers, plasma EBV DNA will be determined before treatment and every 2 weeks until disease progression; plasma TGFβ1 measurement will be performed every 8 weeks until disease progression; exo-PD-L1 concentration will be measured every 2 weeks until disease progression.

Tumor imaging by CT head, neck, chest, abdomen, and pelvis will be done at baseline, every 8 weeks for the first 12 months, then every 12 weeks thereafter. Response will be assessed per RECIST version 1.1. Treatment decisions will be based on Investigator(s) review.

6.2 Outcome Measures

Primary outcome:

- Objective response rate (ORR): The percentage of patients with radiologically complete or partial response as determined by the Investigator according to RECIST version 1.1.

Secondary outcomes:

- Progression-free Survival (PFS): PFS is measured from the date of informed consent to radiographically documented progression according to RECIST 1.1 or death from any cause (whichever occurs first). Participants alive and without disease progression or lost to follow-up will be censored at the date of their last radiographic assessment

- Time to progression (TTP): TTP is measured from the date of informed consent to radiographically documented progression according to RECIST 1.1. Participants death and without disease progression, alive without disease progression, or lost to follow-up will be censored at the date of their last radiographic assessment

- Overall survival (OS): OS is measured from date of informed consent to the date of death from any cause. Participants alive or lost to follow-up will be censored at the date of their last radiographic assessment

  Survival rate at 12 months and 24 months: The percentage of study population who are still alive for 12 months and 24 months from the date of study enrollment. Participants alive or lost to follow-up will be censored at the date of their last radiographic assessment

  Duration of response (DOR): DOR is the time from documentation of tumor response to radiographically documented disease progression

- ORR, TTP, and PFS of the same definitions as above are measured against immune-related RECIST (irRECIST) criteria as one of the secondary endpoints.

- Safety outcome measures: Incidence, nature, and severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4)

- Pre-treatment, serial post-treatment plasma EBV-DNA levels, and dynamics of

EBV DNA levels will be measured

- Disease control rate (DCR): The percentage of patients with a CR, PR, or SD ≥ 6 months per RECIST 1.1

- Time to response (TTR): TTR is measured from the date of informed consent to first radiographically documented tumor response per RECIST 1.1

- Quality of life (QoL): as assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) and the head and neck cancer-specific H&N-35 questionnaires

6.3 Follow-Up and Record of Events

- The patients should be followed-up for up to 2 years.

- The incidence of late toxicities > grade 3 by Common Toxicity Criteria for Adverse Events version 4.0 (NCI-CTCAE v.4) should be recorded.

- All causes of death (if occur) will be recorded. Deaths due to unknown cause are counted as deaths due to NPC if disease is still present at last assessment.

6.4 Criteria for Removal from Protocol Treatment

- Disease progression
- Inter-current disease that would affect assessments of clinical status to a significant degree, require discontinuation of drug, or both.
- Unacceptable toxicity.
- The patient may withdraw from treatment at any time for any reason. The reason should be recorded. Follow-up will be continued for all consenting patients for up to 2 years.

6.5 Exploratory Biomarkers

- Archived NPC tissues will be retrieved from various pathology laboratory in Hong Kong in FFPE slides

- For blood-based biomarkers, the logistics will be as follows,
  - Peripheral blood will be collected in lithium heparin tubes every 2 weeks for 8 weeks.
  - Extracellular Vesicle (EV) Isolation
    - Plasma will be extracted using low-speed centrifugation and cryopreserved for further analysis using standard protocols. Extracellular vesicles will be isolated and purified from cryopreserved plasma using ExoQuick® ULTRA EV Isolation Kit for Serum and Plasma or other commercially available kits. Purified EV will be obtained according to the kit manufacturer's instructions.

- Nanoparticle Tracking Analysis (NTA) and Total Protein Isolation of EV
    - EV characterisation will be performed by NTA provided by NanoSight NS300 or other commercially available tools. Total protein will be isolated from purified EV using Total Exosome RNA & Protein Isolation Kit (Invitrogen™) or other commercially available kits and obtained according to the kit manufacturer's instructions. Protein qualitative detection will be performed by western blot.
- Flow Cytometry of Total Protein from EV
    - Total protein will be labelled with antibodies directed against CD4, CD8, CD3, CD16, CD25, CD45RA, CD56, CD62L, CD-83, CD127, ICOS, PD-1, PD-L1, CTLA-4, FoxP3, TIM-3, Ki67 and other proteins of interest. Antibodies will be purchased from BD Bioscience, BioLegend, eBioscience, or Beckman Coulter. Permeabilization will be performed using FOXP3 Fixation/Permeabilization Concentrate and Diluent kit (eBioscience™) or other commercially available kits. Proteins will be interrogated by LSR II flow cytometer (BD) and results will be analysed using FlowJo software (Tree Star).

- Prognostic and predictive power of exploratory bio-markers will be explored
    - Expression level of PD-L1 levels in archived NPC tissues
    - Pre-treatment and post-treatment levels of TGFβ1
    - Pre-treatment and post-treatment plasma exosomal PD-L1 levels

6.6 Safety Reporting

6.6.1 Adverse Events

- According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

6.6.2 Serious Adverse Events (SAE)

- A serious adverse event is any adverse event that meets any of the following criteria:
    - Is fatal (i.e., the adverse event actually causes or leads to death)
    - Is life threatening (i.e., the adverse event, in the view of the Investigator(s), places the patient at immediate risk of death)
    - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
    - Requires or prolongs inpatient hospitalization
    - Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
    - Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
    - Is a significant medical event in the Investigator(s)'s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

- Severity and seriousness need to be independently assessed for each adverse event recorded in the clinical database.

6.6.3 Adverse Events of Special Interest (AESI)

- AESIs are a subset of Events to Monitor of scientific and medical interest specific to the Merck Drugs in this protocol. Such an event might require further investigation in order to characterize and understand it.

- AESIs include following:
    - Infusion-related reactions including immediate hypersensitivity.
    - Immune-related adverse events.
    - TGF-β inhibition mediated skin reactions.
    - Anemia.
    - Bleeding AEs.

- Any AE that is suspicious to be an AESI do not require expedited reporting unless they are serious. Should the AESI be serious, a SAE form should be filled instead and the reporting process for SAEs should be followed.

6.6.4 Pregnancy Reports

- Female patients of childbearing potential will be instructed to immediately inform the Investigator(s) if they become pregnant during the study.

6.6.5 Assessment of Causality of Adverse Events

Investigator(s) should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "Yes" or "No" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction,
- discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

6.6.6 Methods of Recording Adverse Events

- All AEs must be documented in the appropriate section of the CRF. An SAE report form (initial or follow up) must be completed in case of any of the seriousness criteria is met.

- The following aspects must be recorded for each event in the CRF:
    - A description of the AE in medical terms, not as reported by the subject;
    - The date of onset (start date)
    - The time of onset (start time)
    - The date of recovery (stop date)
    - The time of recovery (stop time)
    - The severity of the sign and/or symptom or clinically significant abnormal laboratory
    - Value according to NCI-CTCAE v.4. If no toxicity grade is described for a given sign, symptom or abnormal laboratory value, the Investigator(s) will grade the severity as mid (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or disabling (grade 4).
    - Death (grade 5) as defined by NCI-CTCAE v.4 is mainly regarded as an outcome and will be documented accordingly (see below).

- The causal relationship to bintrafusp alfa as assessed by the Investigator(s); the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:
    - Not Related = not suspected to be reasonably related to the

investigational product. AE could not medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
    - Related = suspected to be reasonably related to the investigational product. AE could medically (pharmacologically/ clinically) be attributed to the investigational product under study in this protocol
    - Action taken on bintrafusp alfa (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).
    - Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery).
- The outcome according to the following definitions:
    - Recovered without sequelae (AE disappeared)
    - Recovered with sequelae (AE has resulted in permanent disability/incapacity)
    - Not yet recovered
    - Not recovered at death
    - Change in toxicity grade/severity or seriousness (e.g., an AE with no change of toxicity grade but newly classified as an SAE due to hospitalization.
    - Fatal (AE resulted in death)

- Concomitant medication given: Yes or No (Note: If this question is answered "Yes" the corresponding serious criteria must be ticked) § Subject died
    - Life-threatening
    - New or prolonged hospitalization
    - Persistent/significant disability § Congenital abnormality
    - Important medical event
    - Seriousness: Yes or No

- If in any one patient the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

6.6.7 Procedure of Reporting Serious Adverse Events

- The Sponsor-Investigator primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to:

    - Evaluate and forward the information to the local regulatory authorities as required by local regulations

    - Forward to Merck/EMD Serono as required within the applicable contract executed between Merck/EMD Serono & the Sponsor-Investigator

- The following reportable events must be submitted to Merck within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Principal Investigator(s) will assume responsibility for submitting the reportable event(s) to Merck as well as ensuring that any local

reporting requirements are completed in parallel.

- Serious Adverse Events (see section 6.6.2)
    - Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
    - Occupational exposure (even if not associated with an adverse event)

- Contact information for submission of reportable events to Merck:
    - Fax: +49 6151 72 6914 or
    - E-mail: ICSR_CT_GPS @merckgroup.com
    - Specifying:
        - PROTOCOL Number and/or Title
        - Funder's Study Identifier
        - SUBJECT Number
        - Principal Investigator Name
        - Sponsor Name
        - SAE/ONSET DATE

6.6.8 Monitoring of Subjects with Adverse Events

- Any AE that occurs in the course of a clinical study must be monitored and followed up until the last study visit. It is the responsibility of the Investigator(s) that any necessary additional therapeutic measures and follow-up procedures are performed.

7 STATISTICS

7.1 Statistical Analysis

Objective response rate (ORR) will be expressed based on exact binomial distribution. Survival outcomes, including TTP, PFS, OS, and survival rate their corresponding 95% confidence interval, will be estimated using Kaplan-Meier method. The Fisher exact test will be used to correlate the binary clinical and biomarker data. The cut-off values of baseline and changes in the exo-PD-L1 and TGF-β1 levels will be calculated by the Receiver Operating Characteristic (ROC) curve analyses.

All of the reported P values will be 2-tailed, and $P<0.05$ will be considered statistically significant. No multiplicity will be considered. The analyses will be performed using statistical software packages SPSS and R.

Procedures for Handling Missing, Unused, and Spurious Data: All available data will be included in the data listings and tabulations. Where appropriate, imputations of values for missing data for primary and secondary efficacy analyses will be performed as specified in the Statistical Analysis Plan. All data recorded on the CRF will be included in the data listings that will accompany the clinical study report.

If, after the study has begun, but prior to the conduct of any analysis, changes made to primary and / or key secondary endpoints, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory analyses made after the protocol finalized will be documented and referenced in the final report. Post hoc exploratory analyses will also be identified in the final report.

7.2 Sample Size Calculation

H0: The null hypothesis is that the overall response rate (ORR) is similar to historical result of immunotherapy, i.e. 20%

H1: The alternative hypothesis of treatment efficacy: experimental treatment with bintrafusp alfa would result in 40% ORR.

To detect 20% of differences from 20% to 40% in the number of patients proceeding to surgery, with Type I error of 0.05 and 80% power, the target sample size is 33 patients.

Modified Simon's two-stage optimal design will be used. In the first stage, 18 patients will be enrolled. If there are 4 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 33 valid cases. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients and the treatment will be considered worthy of further investigation. Patients may drop out before their objective response can be assessed. Such patients will be excluded for the ORR assessment and will be replaced by other patients that the objective response can be assessed. The study will be continued until the first or the second stage evaluation is achieved. Assuming 10% drop out rate, 38 patients will be accrued initially. We assume 50% of screened population will be eligible for the study, thus we plan to screen for 76 patients.

7.3 Early Stopping Rule

Excessive toxicity will also be monitored. Assuming no more than a 10% SAE rate on historical treatment, the increase of treatment-related SAE to a rate of 30% or greater in the studied treatment will be considered unacceptable, and the study will be then stopped prematurely and will early stop the trial if treatment related SAE >30%. Upon the recruitment of these 38 patients, if 10 or more patients had treatment-related SAE, the study will be stopped. The corresponding lower bound of exact one-sided 90% confidence interval is 30.5%.

8 ETHICAL, REGULATORY & STUDY OVERSIGHT CONSIDERATIONS

8.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the clinical study in accordance with this clinical study protocol, ICH guideline for Good Clinical Practice (GCP) (ICH E6 R2 Step 4) approved on November 9, 2016) and applicable regulatory requirements in Hong Kong. These documents state that the informed consent of the subjects is an essential precondition for participation in the clinical study.

8.2 Subject Information

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the Investigator(s) before informed consent is obtained. A person designated by the Investigator(s) may give the information, if permitted by local regulations. A subject information sheet in the local language and prepared in accordance with Good Clinical Practice will be provided by the Investigator(s) for the purpose of obtaining informed consent. In addition to this written information, the Investigator(s) or his/her/their designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

8.3 Informed Consent

The consent of the patient to participate in the clinical study has to be given in writing before any study-related activities are carried out. It must be signed and personally dated by the patient and by the Investigator(s)/person designated by the Investigator(s) to conduct the informed consent discussion.

Provision of consent will be confirmed in the case report form (CRF) by the Investigator(s). The signed and dated declaration of informed consent will remain at the Investigator(s)'s site and must be safely archived by the Investigator(s) so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.

If the patient or legally acceptable representative is unable to read, a reliable, impartial, and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative verbally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

Also, patient will be informed in a timely manner whenever new information becomes available that may be relevant to the patient's willingness to continue participation in the study; the revised informed consent form containing such information is to be provided to the patient, and communication of this information will be documented.

8.4 Compensation to Subjects

The patients will not receive payment for taking part in the study. Patients who are entitled to discounted or free health care, e.g. civil servants, will receive their entitled free treatment as normal. The study is covered by an insurance policy managed by the Clinical Trial Centre of The University of Hong Kong, in which to cover claim by, or compensation for, patients treated in study.

8.5 Ethics Committee or Institutional Review Board

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, IB) to the IRB/EC for their favourable opinion. The favourable opinion/approval of the IRB/EC will be filed in the study file. The study will only commence following provision of a written favourable opinion.

Any amendments to the protocol will be submitted to the IRB/EC and they will be informed about SAEs in accordance with national and/or local requirements.

8.6 Role of Funding Source

The study drug and partial funding will be provided by Merck Healthcare KGaA, Darmstadt, Germany. The Funder otherwise has no role in study design, data collection, data analysis, data interpretation, or in the writing of the study report. The Funder will review the manuscript before submission for publication.

8.7 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice.

The Sponsor agrees to submit all manuscripts or abstracts to the Funder for review before submission for publication. This allows the Funder to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9 STUDY MANAGEMENT

9.1 Data Quality Assurance

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible and timely fashion. The data in the CRF should be consistent with the relevant source documents.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the Investigator(s), stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g., Tipp-Ex®). The Investigator(s) must state his/her reasons for the correction of important data. In the case of missing data/remarks, the entry spaces provided in the case report form should be cancelled out so as to avoid unnecessary follow-up inquiries.

CRF entries will be done by the study team and checked against source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/EC), and the regulatory authorities to have direct access to source data which support the data on the CRF. Such personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

9.2 Direct Access to Source Data/Documents

For the purpose of ensuring compliance with the clinical study protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator(s) shall permit auditing by the Sponsor, the Funder, and inspection by applicable regulatory authority.

The Investigator(s) agree(s) to allow the auditors/inspectors to have direct access to the study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose personal identity or personal medical information.

The Investigator(s) will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator(s) is/are notified of a future inspection by the authority, he will inform the Sponsor and the Funder.

The confidentiality of the data verified, and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authority will be immediately communicated by the Investigator(s) to the Sponsor and the Funder as per timeframe stipulated in the ISS agreement.

The Investigator(s) shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

9.3 Study File and Archiving

The Investigator(s) shall maintain a Study File for the study purpose. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study in accordance with the local relevant regulations.

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11 APPENDIX Schedule of Assessments

Procedures	Screening	Treatment Period (bintrafusp alfa until PD; unacceptable toxicity; death or withdrawal; maximum of 2 years)									Disease Progression
		Cycle 1 [m] Cycle = 14 Days ± 7 Days	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9 and thereafter	
	Day -28 – 0	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	
Tests and Observations											
Informed Consent [d]	×										
Medical History	×										
Physical Examination (including skin examination) [e]	×	×	×	×	×	×	×	×	×	×[a]	×
Vital Signs	×	×	×	×	×	×	×	×	×	×[a]	×
ECOG Performance Status	×	×	×	×	×	×	×	×	×	×[a]	×
ECG	×	×				×				×[b]	×
Adverse Event Evaluation	×	×	×	×	×	×	×	×	×	×[a]	×
Concomitant Medication Review	×	×	×	×	×	×	×	×	×	×[a]	×
Laboratory Tests											
CBC [f]	×	×	×	×	×	×	×	×	×	×[a]	×
Coagulation Test [h]	×	×				×				×[b]	×
Comprehensive Serum Chemistry Panel [g]	×	×	×	×	×	×	×	×	×	×[a]	×
Exploratory blood-based biomarkers [i]	×	×[i]	×	×[i]	×	×[i]	×	×[i]	×	×[i]	×
Urinalysis	×	×	×	×	×	×	×	×	×	×[a]	×
Pregnancy Test [j]	×	Repeat only if necessary									
Thyroid Function Test		×		×		×		×		×[c]	×
Cortisol 9AM		×		×		×		×		×[c]	×
Disease Assessment											
CT Scan (Head, Neck, Chest, Abdomen, Pelvis) [k]	×	×				×				×[k]	×
MRI Scan (Brain)		Check if suspected brain metastasis									
Survival follow-up		◄								►	×
Quality of life assessment [l]	×	×						×			×

a. Assessments/procedures are to be performed on Day 1 every cycle and prior to treatment unless otherwise specified.
b. Assessments and procedures are to be performed on Day 1 every 4 cycles and prior to treatment unless otherwise specified.
c. Assessments and procedures are to be performed on Day 1 every 2 cycles and prior to treatment unless otherwise specified.
d. Informed Consent must be obtained ≤ 28 days prior to the initiation of trial treatment.
e. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, temperature).
f. Hematology parameters include the following laboratory tests: complete blood count with 3-part differential (i.e. total neutrophil count including bands, lymphocytes, and monocytes), hemoglobin, hematocrit and platelets.
g. Blood chemistry must include glucose, BUN, creatinine (eGFR), sodium, potassium, magnesium, chloride, calcium, CO2, alkaline phosphate, AST (SGOT), total bilirubin, total protein, albumin, phosphorus, uric acid.
h. Coagulation test include PT, PTT and INR.
i. Plasma EBV DNA will be determined before treatment and every 2 weeks until disease progression; plasma TGFβ1 measurement will be performed every 8 weeks until disease progression; PD-L1 concentration in the exosome will be measured every 2 weeks until disease progression.
j. Pregnancy test will be performed within 1 week prior to treatment, if a cycle is missed during treatment or pregnancy and at the end of treatment visit only for women of childbearing potential.
k. Patients will have CT scan at Screening/Baseline (≤ 28 days prior to initiation of trial treatment), every 8 weeks for the first 12 months, and every 12 weeks thereafter. Patients will also have CT scan whenever disease progression is suspected. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g. in patients who discontinue treatment for clinical progression or adverse reactions), disease assessment should continue as stated in schedule until radiographic disease progression or alternate therapy is given.
l. Quality of life (QoL) will be assessed by patient-reported EORTC QLQ-C30 and H&N-35 questionnaires every 12 weeks in the first year.
m. If screening assessments were completed within 28 days, they do not need to be repeated on Day 1 of Cycle 1 if patient's condition has not changed.