Clinical Study Protocol IMCgp100-102

A Phase 1/2, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 using the Intra-patient Escalation Dosing Regimen in Patients with Advanced Uveal Melanoma

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Protocol Versions:
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NCT02570308

This study will be conducted in compliance with the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

Protocol Version History

Version	Title	Date
1.0	Original Protocol	
2.0	Amendment 1	08 Dec 2015
3.0	Amendment 2	11 Jan 2016
4.0	Amendment 3	23 May 2016
5.0	Amendment 4	07 Sep 3016
6.0	Amendment 5	11 Apr 2017
7.0	Amendment 6	15 Dec 2017
7.0 DE	Local DE Amendment 1	15 May 2018
8.0	Amendment 7	26 November 2018

Amendment 7

Amendment Rationale

This amendment is done to clarify the interim and final analysis that will be done to assess the efficacy of IMCgp100 in the Phase 2 expansion phase. In addition, the amendment clarifies several changes that were made in prior amendments including the allowed prior therapies in the expansion phase, requirements for hospitalization, and further clarification of imaging assessments, contraceptive requirements and the informed consent process. This amendment incorporates the changes made in the local German amendment which updates the contraception requirement for women of child-bearing potential to be consistent across IMCgp100 clinical trials and to be consistent with Clinical Trial Facilitation Group recommendations.

Testing of all patients for HIV and hepatitis B and C infections if required by local regulations is added.

An overall benefit-risk assessment has been added to the protocol rationale.

Changes to the protocol

1. Clarification of the Interim and Final analyses for the Phase 2 expansion cohort (Sections 9.1 & 9.6.1): This amendment specifies the population and timing of the planned interim and final analyses.
2. Clarify allowed prior treatments (Sections 3.2, 5.2, 9.1 & 9.6.1): As defined in the prior amendment, the Phase 2 expansion cohort enrolls patients who have received prior therapy for metastatic uveal melanoma. This amendment seeks to clarify the allowable and required prior therapies.
3. Clarify the requirements for hospitalization (Section 6.2): As defined in the protocol, patients are required to have an overnight, inpatient hospitalization for the first 3 doses of IMCgp100. The amendment clarifies that “inpatient hospitalization” refers to a facility with fully functional resuscitation facilities, 24 hour monitoring and physician availability.
4. Clarified definition of confirmed irPD per modified irRECIST for patients who continue IMCgp100 therapy beyond initial PD per RECISTv1.1
5. Clarify imaging assessments (Sections 4.6): Hepatic MRI in addition to abdominal CT has been required to compare MRI and CT scanning in the Phase 1 dose escalation cohorts. Given the expansion of the study and to reduce the burden on patients, the imaging will be refined to allow either CT or MRI to be done for tumor assessment and no longer require both modalities.
6. Added exploratory objective (Sections 4.3, 4.6, and Table 4-1) to determine best response based on investigator assessment for subsequent anti-cancer therapy.
7. Revised secondary endpoint (Protocol Synopsis, Sections 4 and 9.6.1): The secondary endpoint to determine the rate and duration of immune responses was added.
8. Addition of biochemical assessments (LDH and CRP) before and after the initial 3 doses to explore pharmacodynamic changes after IMCgp100 administration and association with response.

9. Optimization of ctDNA collection timepoints and objectives (Section 7.4): Additional time points were added for ctDNA collection to assess pharmacodynamic changes after treatment as well as to evaluate for predictors of resistance to treatment.
10. Removal of screening window for HLA testing. Because HLA testing is a genetic test and does not change with time, the window of 120 days has been removed.
11. Change to exclusion criterion #19 and addition of Section 6.6 on contraception requirements (Section 5.3 and Section 6): Contraception requirement for women of child-bearing potential was changed to be consistent across IMCgp100 clinical trials and to be consistent with Clinical Trial Facilitation Group recommendations.
12. Update of exclusion criteria #7 and #8 to add testing for HIV and Hepatitis B and C as per local regulations (Section 5.3): Screening for HIV and Hepatitis B and C will be done if required by local regulations.
13. Addition of Section 2.4 regarding the overall benefit-risk assessment
14. Inclusion of Table 7-3 to clarify frequency of vital signs.
15. Modification of Section 11.3 to harmonize the informed consent procedures with inclusion criterion #2 and clarify the informed consent process.
16. Increased duration of safety follow up period (Sections 3.3, 7.2.3, 7.2.5, 8.1, 8.5, 9.1, & 9.6.2.1 as well as Table 7.1) to provide further safety information and be consistent across IMCgp100 clinical trials
17. Clerical Changes are made throughout the protocol to improve clarity.

Institutional Review Board/Independent Ethics Committee

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7.0 DE Local Amendment 1

Amendment Rationale

This amendment updates the contraception requirement for women of child-bearing potential to be consistent across IMCgp100 clinical trials and to be consistent with Clinical Trial Facilitation Group recommendations.

Testing of all patients for HIV and hepatitis B and C infections is added if required by local regulations.

An overall benefit-risk assessment has been added to the protocol rationale.

Changes to the Protocol

1. Change to exclusion criterion #19 and addition of Section 6.6 on contraception regulations (Section 5.3 and Section 6)

2. Update of exclusion criteria #7 and #8 to add testing for HIV and hepatitis B and C as per local regulations (Section 5.3)

3. Addition of Section 2.4 regarding the overall benefit-risk assessment

4. Modification of Section 11.3 to harmonize the informed consent procedures with inclusion criterion #2 and clarify the informed consent process.

Amendment 6

Amendment Rationale

This amendment transitions the dose expansion cohort component of the study, designed to explore the recommended Phase 2 dose that was defined in the Phase 1 testing of the intra-patient escalation regimen (RP2D-IE, 68 mcg) to more formal Phase 2 testing in patients with metastatic uveal melanoma who are treated in the second or third line setting in this trial (Amendment 6, Protocol version 7.0, 15 December 2017).

Tumor responses have been observed in the preliminary dose escalation cohorts of this study and these responses have been associated with long duration of response as reported recently (Sato, 2017; Carvajal, 2017). Based on the observation of durable partial responses and minor responses (defined as a tumor response where the sum of the longest diameters [SLD] of target lesions is reduced by 10%–to 29%) in the dose escalation cohorts of this study, the dose expansion cohort in the trial is modified to provide a formal analysis of the anti-tumor efficacy in this patient population using the objective response rate (ORR) by independent review as the primary efficacy endpoint in this portion of the study. Two separate expansion cohorts in this study are defined based on prior therapy:

1. Cohort A: Patients will have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior liver-directed therapy (LDT) is acceptable in this cohort.
2. Cohort B: Patients will have experienced disease progression with 1 or 2 prior lines of therapy, including up to 1 prior line of LDT. LDT will be considered a line of therapy for enrolling this cohort. Prior checkpoint inhibitor therapy is acceptable but not required in this cohort.

Given the formal efficacy measures implemented in this dose expansion cohort, the study will be designated as a Phase 1/2 to reflect this new endpoint.

The pattern of clinical response to immunotherapeutic agents differs from that observed with cytotoxic therapies. There is accumulating evidence that a proportion of patients with advanced melanoma treated with immunotherapy agents, including IMCgp100, may develop initial radiographic progression of the tumor before demonstrating meaningful clinical benefit. This delayed response to therapy or immune-mediated tumor flare (pseudo-progression) is followed by prolonged periods of disease stabilization in some patients or more rarely, objective tumor responses. To allow patients to continue therapy beyond an initial assessment of progressive disease according to RECISTv1.1, this amendment provides additional detail delineating criteria for treatment beyond progression (per modified irRECIST). Patients must meet specific clinical criteria and provide additional informed consent to continue therapy beyond an initial assessment of disease progression. If disease progression is subsequently confirmed per modified irRECIST, treatment must be discontinued.

This amendment removes screening ophthalmologic and audiology assessments. Prior to initiation of the IMCgp100 Phase 1 investigation, the eye and ear were identified as potential target organs for toxicity, based on expression of the antigen in these target tissues. To date, and across the IMCgp100 development program, there have been no clinically significant adverse events involving vision and/or hearing (please refer to the most recent IMCgp100 Investigator's Brochure for details). This amendment removes screening ophthalmologic and audiology assessments and retains these assessments in the setting of treatment-emergent toxicity. [redacted]

Changes to the Protocol

1. Increased the sample size of the Phase 2 expansion cohorts (from approximately 40 patients to approximately 150 patients) and added the primary endpoint of the single-arm Phase 2 expansion cohort of ORR assessed by independent central review based on RECISTv1.1

2. Clarified the criteria for treatment beyond progression and treatment discontinuation in the circumstance of treatment beyond progression using modified irRECIST. The rationale for treatment beyond progression is provided

3. [redacted]

4. Removed screening ophthalmologic exam and audiologic assessment

5. A window for the infusion time is added by extending the acceptable infusion time from 15 minutes to 15–20 minutes

6. Added additional guidance for the management of treatment-related toxicity including hypotension and cytokine release events (that are generally observed 2–24 hours after the dose of IMCgp100), rash, and pruritus

7. Clarified that anti-tumor response as assessed by immune-related response criteria (irRECIST) is an exploratory endpoint

8. Clarified that an Independent Data Monitoring Committee will review the safety data from the Phase 2 expansion cohorts on an ongoing basis and will also review both efficacy and safety after approximately 75 patients have been recruited to Cohort B to monitor the benefit-risk profile

9. Clarified tumor biopsy requirements in the Phase 1and Phase 2 cohorts

10. Corrected typographical errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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Amendment 5

Amendment Rationale

This amendment will update the nomenclature of the dose levels and the recommended Phase 2 dose (RP2D) of IMCgp100 utilizing the intra-patient escalation (Amendment 5, protocol version 6.0, dated 11 April 2017). No changes are made in the dose preparation guidance; thus, there is no change in the actual doses administered in this study. Recent information described below indicates that the actual doses administered and defined in this Phase 1 study are more accurately defined and lower than the original protocol-specified dose levels.

Individual doses of IMCgp100 are prepared from a concentrated, frozen stock solution (0.5 mg/mL) by a 2-step dilution procedure in the drug preparation guidelines, requiring dilution of approximately 2500-fold to accurately achieve the microgram (mcg) doses. The dilution procedure is described in the Pharmacy Handling Instructions, provided for each dose level administered, e.g., 20 mcg and 30 mcg. The dilution procedure utilizes 2 saline infusion bags; the first is the dilution bag (a labelled 50 mL bag) and the second is the actual infusion bag (100 mL).

The protocol-specified doses in this study were intentionally determined before the study began to represent the maximum theoretical dose that could be prepared and administered based on the labelled fill volumes of the dilution bags (range of 54–64 mL). The Pharmacy Handling Instructions are authored using the lowest potential dilution bag volumes as the start volume and thus, the highest initial concentrations of IMCgp100 at dilution step 1 to calculate doses. Setting the protocol-specified dose based on the maximum theoretical dose ensured that no patients received actual doses with IMCgp100 quantities above the protocol-specified dose. However, newly available empirical data demonstrate that although there is a labelled range of bag volumes (54–64 mL per packaging), there exists a narrow distribution of the actual fill volumes at the first dilution step (generally 57–59 mL). Thus, the doses actually prepared and administered in this study were accurate and represented a lower point estimate than stated in the original protocol.

Based on the 2-step dilution procedure used to prepare IMCgp100 doses and considering the conservative approach to the variance in the fill range for the primary dilution bag, the protocol-specified doses for the higher dose cohorts in the IMCgp100-102 trial and the final RP2D were over-estimates of the actual administered dose. Based on the available empirical evidence of dilution bag fill volumes (dilution step 1), it is important to correct the over-estimate of the actual dose administered (e.g., update to the RP2D from 75 mcg to 68 mcg). The 68-mcg dose level is the most accurate within the range produced by the dilution procedure and is the RP2D in this study. Doses of 75 mcg and 80 mcg have a differential of approximately 7 mcg based on the actual bag volumes, and doses below 75 mcg have an approximate 6 mcg differential. Based on the limited impact at the lower doses (20 mcg and 30 mcg doses) no change in these protocol-specified doses is warranted.

As safety data are collected in this study, the management guidance is updated for adverse events, based on the collective experience of the principal investigators in this study including updates of the events of cytokine release syndrome and hypotension.

Changes to the Protocol

1. The protocol-specified doses of IMCgp100 are updated throughout the protocol as described above from Cycle 1 Day 15 and beyond for the various dose escalation cohorts. This includes updates to the 60 mcg, 70 mcg, 75 mcg, and 80 mcg dose levels
2. Table 6-2 Dose Level has been updated to reflect the conduct of the dose escalation cohorts and updated protocol-specified dose levels
3. Updated adverse event management guidance is provided, including updated management of the events of cytokine release syndrome and hypotension
4. Updated the instruction that the intravenous bag containing IMCgp100 must be used within 16 hours of dilution/mixing

Institutional Review Board/Independent Ethics Committee

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Amendment 4

Amendment Rationale

[redacted], this trial will only enroll patients with expression of the HLA-A*0201 allele determined centrally.

In addition, this amendment will implement several changes principally related to the recommended Phase 2 dose intra-patient escalation (RP2D-IE) expansion cohort. Given the encouraging emerging clinical safety and efficacy data with IMCgp100 in uveal melanoma (UM) where a strong signal of disease stabilization has been observed in early dosing cohorts in this study, the size of the RP2D-IE expansion cohort increased from 20 to 40 patients. This increase in sample size will provide a larger safety dataset and more robust point estimate of overall survival in the selected patient population. This cohort will enroll a second line population following disease progression a checkpoint inhibitor, including inhibitors of CTLA-4, PD-1, and PD-L1 to assess the safety and efficacy of IMCgp100 following prior immunotherapy to inform future development in this setting. An independent central review of imaging assessments will be performed in this Phase 2 dose expansion cohort. As a substantial majority of patients with metastatic UM harbor hepatic metastases, and these metastatic lesions can be difficult to assess even with current high resolution imaging techniques, the central review is designed to assess the utility of computed tomography versus magnetic resonance imaging in imaging of hepatic metastases and provide cross-validation of the investigator-reported tumor responses.

Finally, further translational work is incorporated into the Phase 2 RP2D-IE cohort in this study. The landscape of somatic genetic mutations in UM differs significantly from cutaneous melanoma. Analysis of circulating tumor DNA is an emerging platform technology that detects tumor-derived somatic mutations from the peripheral blood on an individual patient and allows for longitudinal evaluation of these mutations during the course of treatment. Early response markers of mutation load in the circulation will be studied in the RP2D-IE expansion cohort. These markers will be studied to determine if either specific somatic mutations present at Baseline or if early changes in mutation load in the peripheral circulation is predictive of patients with favorable response to IMCgp100.

Changes to the Protocol

1. Increased the sample size (Section 9.9) and changed the inclusion criteria (Section 5.2) for the RP2D-IE expansion cohort to include approximately 40 patients treated in the second-line setting following disease progression with a checkpoint inhibitor

2. Changed inclusion criteria (Section 5.2) to require central testing for the HLA-A*0201 allele expression and increased the pre-screening window for HLA assessments to 60 days

3. Reduced the number of electrocardiogram and pharmacokinetic assessments to be performed in patients enrolled in the RP2D-IE expansion cohort (Section 7.3, Tables 7-5 and 7-6, respectively)

4. Added description of central review of imaging data (Section 7.3.1.1)

5. [redacted]

6. Added additional guidance for the management of treatment related toxicity including updated guidance for infusion-related reactions (that are generally observed 2–24 hours after the dose of IMCgp100) and added guidance regarding hepatic function abnormalities (Section 6.8, Table 6-6)

7. Corrected a discrepancy in the Statistical Methods section to clarify that overall survival is a secondary study endpoint

8. Corrected typographical errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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Amendment 3

Amendment Rationale

This amendment will implement a change in the definition of dose limiting toxicity (DLT) with respect to the recent observations of transient elevations of hepatic transaminases, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), in patients with uveal melanoma (UM) in the 2 ongoing Phase 1 trials with IMCgp100, the first-in-human (FIH) study (IMCgp100-01) and this UM Phase 1 study (Amendment dated 23 May 2016). In these 2 studies, 3 patients with UM and hepatic metastases experienced transient grade 2 (n=2) and grade 3 (n=1) elevations of ALT and AST at the first dose of IMCgp100 that resolved within days of dosing and did not recur with rechallenge. In each of the 3 patients with grade 2–3 elevations, the next dose was not delayed due to the liver function test (LFT) changes. In addition, 1 patient with extensive hepatic metastases treated in the FIH study experienced a grade 4 elevation of hepatic transaminases with the first dose that resolved over a longer time course than the 3 transient grade 2 and 3 elevations discussed above. This patient with the grade 4 LFT elevations was rechallenged with a second dose of IMCgp100 with no recurrence of LFT elevations. Based on the observation of multiple patients with UM and hepatic metastases with transient and non-dose limiting elevations of ALT and/or AST, the DLT criterion for elevations in ALT and AST has been modified to exclude patients with transient grade 3 elevations in ALT and/or AST that are associated with normal bilirubin and where the elevated ALT and/or AST resolves to grade 1 or lower within 72 hours. Grade 4 elevations in ALT and/or AST, regardless of time course, will remain as DLTs.

In this Phase 1 study (IMCgp100-102), 1 patient with a history of adrenal insufficiency developed hypotension approximately 24 hours following the sixth dose of IMCgp100. Based on the observation of the immune-related infusion toxicity in patients with UM, combined with the increased risk for hypotension in patients with adrenal insufficiency due to an inability to mount a stress cortisol response in the setting of treatment with IMCgp100, this amendment will now exclude all patients with adrenal insufficiency. Similarly, patients receiving chronic corticosteroid therapy for any reason are also excluded due to the potential dysfunction of the hypothalamic-pituitary-adrenal axis in mediating response to stress.

Changes to the Protocol

- Implemented new DLT criterion for transient grade 3 ALT and/or AST elevations to be excluded from DLT provided these events are not associated with change in bilirubin and resolve to grade 1 or lower within 72 hours
- Changed exclusion criterion number 14 to exclude any patient with a history of adrenal insufficiency or any patient requiring long-term corticosteroid treatment
- The definition of lost to follow up is clarified in Section 7.2.6
- Corrected typographical errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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Amendment 2

Amendment Rationale

This amendment will implement monitoring changes for the event of hypotension in the intra-patient dose escalation regimen (Amendment dated 12 January 2016). These monitoring changes are in response to infusion related toxicity with associated hypotension that has been observed in the ongoing first-in-human Phase 1 study of IMCgp100 in metastatic melanoma (study number IMCgp100-01).

Patients with the diagnosis of uveal melanoma have been treated with IMCgp100 in the recommended Phase 2 dose expansion cohort in the Phase 1 study (IMCgp100-01) and have experienced infusion-related toxicity at Cycle 1 Day 1 (C1D1) or Cycle 1 Day 8 (C1D8), including pyrexia, facial edema, and hypotension. Based on review of the clinical cases of hypotension, additional monitoring procedures are implemented here to screen all patients for risk of hypotension during the intra-patient dose escalation.

Updates have been made to the monitoring for patients during the first weeks of dosing with IMCgp100. Patients will be monitored overnight as an in-patient for each of the first 3 doses of IMCgp100 during the intra-patient escalation at C1D1, C1D8, and C1D15. In-patient observation for C1D22 will be mandatory if the patient experienced infusion toxicity involving NCI CTCAE grade 2 or greater hypotension requiring medical intervention at the previous dose on C1D15.

Changes to the Protocol

1. Implemented new monitoring strategy for occurrence of hypotension in the study. Mandatory hospitalization for the C1D8 dose is implemented. This hospitalization is in addition to the previous mandatory inpatient observations for the C1D1 and C1D15 doses. (Section 6.2 and Section 7.3.4)
2. Guidance for inpatient monitoring for the C1D22 dose are provided and based upon the individual patient's tolerability of the first 3 doses (C1D1, C1D8, and C1D15; Section 6.2)
3. Revised safety data for IMCgp100-01 study to the current Investigator's Brochure (Ed 7, issued 17 December 2015) and to reflect recent infusion-related toxicity events of grade 2 or greater hypotension
4. Revised exclusion criteria to reflect the appropriate methods of highly effective contraception
5. Corrected typographical errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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Amendment 1

Amendment Rationale

This amendment will implement dosing changes in the intra-patient dose escalation regimen (Amendment 1, protocol version 2.0, dated 08 December 2015). These dosing changes are in response to infusion-related toxicity with associated hypotension that has been observed in the ongoing first-in-human Phase 1 study of IMCgp100 in metastatic melanoma (study number IMCgp100-01).

Patients with the diagnosis of uveal melanoma (UM) have been treated with IMCgp100 in the recommended Phase 2 dose expansion cohort in the Phase 1 study (IMCgp100-01) and have experienced infusion-related toxicity at Cycle 1 Day 1 (C1D1) or Cycle 1 Day 8 (C1D8), including pyrexia, facial edema, and hypotension. Based on these observations in the Phase 1 study, and considering that (1) UM is defined with a higher expression of the antigen (gp100), and (2) the preclinical observation (described in the protocol below) of potentially enhanced sensitivity of UM cells to IMCgp100, the doses in this Phase 1 study in the first 2 weeks will be reduced further in all patients in this study.

The first doses administered as part of this intra-patient escalation regimen at C1D1 and C1D8 in this dosing regimen will be reduced from the previous dose of 40 mcg to 20 mcg (at C1D1) and 30 mcg (at C1D8) in all patients treated as part of this study to mitigate the potential for infusion toxicity associated with hypotension. Dose escalation will then proceed at C1D15 as planned.

Changes to the Protocol

1. Implemented dosing changes in the intra-patient dose escalation regimen with reduction of the starting dose on C1D1 to 20 mcg and C1D8 to 30 mcg
2. Added large disease burden in the liver as an exclusion criterion in the dose escalation portion of the study (patients with replacement of > 60% of the liver with disease are excluded), due to the possibility of hepatic toxicity
3. Sponsor emergency contact information has been updated
4. Added an immunogenicity sample at C1D8
5. Corrected typographical errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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Protocol Signatures

Sponsor Signature

I have read the amended protocol and confirm that the protocol follows the current Good Clinical Practice guidelines.

Approved By:

[redacted]

Principal Investigator Signature

I, the undersigned, have reviewed the amended protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the tripartite International Conference on Harmonisation (ICH) guideline E6 (R2): Guideline for Clinical Practice (GCP) and all the ethical and regulatory considerations stated.

Signed By:

_____ _____

Principal Investigator Date

_____

Print Name

_____

Institution Name

Protocol Synopsis

Study Number	IMCgp100-102
Title	A Phase 1/2, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 using the Intra-patient Escalation Dosing Regimen in Patients with Advanced Uveal Melanoma
Brief Title	Phase 1/2 Study of the Intra-patient Escalation Dosing Regimen
Sponsor and **Clinical Phase**	Immunocore, Ltd. Phase 1/2
Investigational Agents	IMCgp100
Study Type	Interventional
Study Purpose and Rationale	IMCgp100-102 is a Phase 1/2 study of the weekly (QW) intra-patient escalation dose regimen with IMCgp100 as a single agent in patients with metastatic uveal melanoma (mUM). The Phase 1 testing of this regimen will aim to achieve a higher exposure and maximal plasma concentration of IMCgp100 after doses at Cycle 1 Day 15 (C1D15) and thereafter than the exposures achievable at the recommended Phase 2 dose (RP2D) of the fixed QW dose of 50 mcg (RP2D-QW) without additional toxicity. Phase 1 testing will follow the standard 3+3 design with dose-limiting toxicity (DLT) as the endpoint and identification of the maximum tolerated dose (MTD) and/or the RP2D for the intra-patient escalation regimen (RP2D-IE). In the Phase 1 first-in-human (FIH) study of IMCgp100 in advanced melanoma, a dose escalation was conducted with IMCgp100 administered on a QW basis. Results of this study have been presented (Middleton, 2015). In this study, the MTD when IMCgp100 is administered on a QW basis was determined to be 600 ng/kg. With a data cut off of 18 August 2015, it was observed that DLT of grade 3 (n=3) and 4 (n=1) hypotension in the QW dosing cohort was observed with the first or second dose in this trial. Based on observed safety and the pharmacokinetic (PK) profile a flat dosing regimen was implemented across the program and the RP2D of the weekly schedule (RP2D-QW) was identified as 50 mcg QW. This dose and regimen have been adjusted based on emerging safety in the trial and dosing adjustments were implemented in the FIH QW dosing expansion cohort (IMCgp100-01, NCT01211262).

	In this same FIH study, several patients with mUM were treated in the QW dosing regimen at the MTD dose level (600 ng/kg) and at the dose level above MTD, 900 ng/kg (n=5, data cut off 18 August 2015). Based on review of the observed objective responses in the Phase 1 trial in uveal melanoma (UM) as well as objective responses noted in cutaneous melanoma, it was noted that patients with larger diameters of disease burden (both cutaneous and UM) experienced objective tumor responses at the higher overall exposures to IMCgp100. The current study of the intra-patient dose escalation regimen is based on 2 observations in the clinic: (1) objective partial and minor tumor responses in patients with higher tumor burdens were generally observed at the higher absolute doses in the Phase 1 trial, and (2) the occurrences of more severe toxicity leading to dose limitation were limited to the first 2 weeks of dosing on C1D1 and C1D8. Based on these 2 observations, it is hypothesized that an increased exposure to drug in the weeks following the occurrence of the more severe toxicity (at the first 2 doses) may lead to an enhanced tumor response in a setting of an unfavorable tumor microenvironment such as UM.
Primary Objectives	Phase 1 Dose Escalation: The primary objective is to identify the MTD and/or the RP2D of IMCgp100 in the intra-patient dose escalation regimen (RP2D-IE). Phase 2 Dose Expansion: The primary objective is to estimate the objective response rate by independent central review (ICR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECISTv1.1) in patients with advanced UM who are treated with the RP2D-IE of IMCgp100.
Secondary Objectives	• To characterize the safety and tolerability of IMCgp100 in the intra-patient dose escalation regimen • To characterize the PK profile of single-agent IMCgp100 in the intra-patient dose escalation regimen • To assess the anti-tumor efficacy of IMCgp100 with the parameters of objective response rate (Phase 1), overall survival, progression-free survival (PFS), disease control rate (DCR), time to response, and the duration of response (DOR). • To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100 in the intra-patient dose escalation regimen • To determine the rate and duration of minor responses (defined as tumor response with a reduction in the sum of longest diameters of

	10%–29%) and immune responses (as assessed by area under the tumor response curves [AUC])
Study Design	This is a Phase I12 study of IMCgp100 administered on a QW basis with an intra-patient escalation dosing regimen. The intra-patient escalation occurs at the third QW dose on C1D15. According to this regimen, all patients in the trial will receive 2 QW doses of IMCgp100 at a dose level below the identified RP2D-QW, and then a dose escalation will commence at the third QW dose at C1D15 with the goal to achieve a long-term dosing regimen at a dose higher than that identified for the RP2D-QW. In this dosing regimen, each patient will undergo a fixed intra-patient dose escalation (fixed dosing of 20 mcg at C1D1 and 30 mcg at C1D8), followed by the dose escalation beginning at C1D15. Patients will continue to receive the same escalated dose from C1D15 and thereafter. The dose escalation will identify the RP2D-IE. The Phase 1 portion of the study will be a standard 3+3 dose escalation design. After the dose escalation portion is complete and the MTD or the RP2D-IE is identified, the Phase 2 expansion cohorts in mUM will be enrolled. These two cohorts will enroll patients with mUM and will enroll approximately 150 patients combined. • Cohort A will enroll patients with mUM in the second-line setting after disease progression following systemic treatment with a checkpoint inhibitor with any prior liver directed therapy (LDT) • Cohort B will enroll patients with mUM in the second or third-line setting with up to one prior LDT regimen • Additional details regarding expansion cohorts are outlined in Key Inclusion Criteria below, Section 3.2 and Section 5.2.
Population Under Study	The trial will enroll patients with a diagnosis of advanced mUM, defined as histologically confirmed diagnosis of UM and metastatic stage IV disease at study entry. In the Phase 1 dose escalation portion of the trial, patients are eligible with any prior therapy including systemic treatments or LDT with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and meeting all additional eligibility criteria. Once the dose is identified in the Phase 1 dose escalation, 2 Phase 2 expansion cohorts will be enrolled in 2 patient populations: 1. Cohort A: Patients will have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or

	tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior LDT is acceptable in this cohort. 2. Cohort B will enroll patients with mUM in the second or third-line setting with up to one prior LDT regimen. Additional details regarding expansion cohorts are outlined in Key Inclusion Criteria below, Section 3.2 and Section 5.2 These Phase 2 expansion cohorts are designed to further characterize the safety, tolerability, and preliminary PK and anti-tumor activity of IMCgp100.
Key Inclusion Criteria	1. Male or female patients age ≥ 18 years of age at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed diagnosis of mUM 4. Surgically sterile patients or patients of child-bearing potential who agree to use highly effective methods of contraception during study dosing and for 6 months after last dose of study drug 5. Life expectancy of > 3 months as estimated by the investigator 6. Human leukocyte antigen-A*0201 positive by central assay 7. ECOG Performance Status of 0 or 1 at Screening 8. Patients must have disease (measurable or non-measurable acceptable) according to RECIST v.1.1 criteria in the Phase 1 dose escalation cohorts. Patients must have measurable disease in the Phase 2 dose expansion cohorts 9. Phase 1 dose escalation cohorts only: any prior therapy is acceptable 10. Phase 2 dose expansion cohorts: • Cohort A: Patients will have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior LDT is acceptable in this cohort • Cohort B: Patients will have experienced disease progression with 1 or 2 prior lines of therapy in the metastatic or advanced setting including chemotherapy, immunotherapy or targeted therapy. Only a single line of local, LDT including chemotherapy, radiotherapy, radiofrequency ablation or embolization is allowed. A line of LDT is defined as one

	modality of treatment that is administered until completion of treatment or disease progression. For patients who have received prior LDT, this will count as a line of therapy. Prior surgical resection of oligometastatic liver disease is allowed and is not counted as a line of LDT.A patient may have discontinued systemic therapy prior to disease progression if the patient experienced a significant adverse reaction that required treatment discontinuation, as per Investigator's judgment and applicable labelling. Prior checkpoint inhibitor therapy is acceptable but not required in this cohort. A. This means patients with the following treatments are eligible under Cohort B: ○ 1 systemic therapy and 1 LDT ○ 1 – 2 systemic therapies and 0 LDT ○ 0 systemic therapy and 1 LDT b. Adjuvant therapies and local therapies for treatment of disease outside of the liver do not count towards the lines of prior therapy. 11. All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug
Key Exclusion Criteria	1. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Asymptomatic and adequately treated CNS metastases are not exclusionary 2. History of severe hypersensitivity reactions to other biologic drugs or monoclonal antibodies 3. Patient with any out-of-range laboratory values defined as: • Serum creatinine > 1.5 x upper limit of normal (ULN) and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/min • Total bilirubin > 1.5 x ULN, except for patients with Gilbert's Syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN • Alanine aminotransferase (ALT) > 3 x ULN

	• Aspartate aminotransferase (AST) > 3 x ULN • Absolute neutrophil count < 1.0 x 10^9/L • Absolute lymphocyte counts: (1) Phase 1 and Phase 2 Expansion Cohort A: Absolute lymphocyte count < 0.5 x 10^9/L; (2) Phase 2 Expansion Cohort B: Absolute lymphocyte count < 1.0 x 10^9/L • Platelet count < 75 x 10^9/L • Hemoglobin < 8 g/dL • Potassium, magnesium, corrected calcium or phosphate abnormality of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) > grade 1 4. Phase 1 dose escalation only: Presence of high tumor burden, defined as liver replacement of > 60% hepatic organ volume with tumor 5. Clinically significant cardiac disease or impaired cardiac function, including any of the following: • Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia currently requiring medical treatment • QTcF > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome • Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening 6. Patients may not have been included in any prior IMCgp100 trial, regardless of assigned treatment cohort
Efficacy Assessments	Radiologic assessments should be performed as scheduled every 8 or 12 weeks using a reference to C1D1 and should NOT follow delays incurred in the treatment period. Tumor response will be determined according to 2 sets of criteria: 1. RECIST v.1.1 2. Modified immune-related response criteria (irRECIST) for patients who continue treatment beyond RECISTv1.1 progression Phase 1: The local investigator's assessment will be used for the analysis of response according to RECIST v.1.1 for efficacy endpoints of the study

	and modified irRECIST, and for treatment decision making (study discontinuation due to progressive disease [PD] as per RECISTv.1.1/modified irRECIST). Phase 2: For the expansion cohorts only, an independent central review (ICR) will be used for the analysis of objective response rate and all other tumor-related endpoints based on RECIST v.1.1 and irRECIST. Investigator assessment data will be used for treatment decision making during the study. PFS will be assessed using RECIST v.1.1. Patients experiencing PD per RECIST v.1.1 criteria may consent to continue to be treated according to irRECIST guidelines until confirmed, unequivocal progression is documented via modified irRECIST. Progression based on modified irRECIST will be assessed as an exploratory endpoint. Imaging per CT or MRI will be performed at baseline and scheduled follow-up timepoints- additional details are outlined in Section 7.3.1.
Safety Assessments	Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing, as well as collecting of the adverse events at every visit.
Biomarker Assessments	[redacted]

	[redacted]
Keywords	IMCgp100, uveal melanoma, T cell redirection, gp100

List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
Akt	Protein kinase B
ALT	Alanine aminotransferase
anti-CD3	Anti-cluster of differentiation 3
AST	Aspartate aminotransferase
AUC	Area under the curve
C#D#	Cycle 1 Day 1; Cycle 8 Day 1; Cycle 15 Day 1; Cycle 2 Day 15
C1D8	Cycle 1 Day 8
CD3	Cluster of differentiation 3
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor deoxyribonucleic acid
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T lymphocyte associated protein-4
DCR	Disease control rate
DETC	Dose escalation teleconference
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
[redacted]	[redacted]
EOT	End of treatment
[redacted]	[redacted]
FAS	Full analysis set

FIH	First-in-human
GCP	Good clinical practice
GNAQ	Heterotrimeric G protein alpha subunit q
GNA11	Heterotrimeric G protein alpha subunit 11
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-A2	Human leukocyte antigen-A2
HLA-A*0201	Human leukocyte antigen-A*0201
HLA-DR	Human leukocyte antigen-DR
HRQoL	Health-related quality of life
IDMC	Independent data monitoring committee
ICH	International Conference on Harmonization
ICR	Independent central review
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IHC	Immunohistochemistry
IL-#	Interleukin-# (e.g., IL-6, IL-10)
IMCgp100	77 kDa bi-specific protein
IRB	Institutional Review Board
irPD	Immune-related progressive disease
irRC	Immune-related response criteria
irRECIST	Immune-related response criteria in solid tumors
IV	Intravenous
LDH	Lactate dehydrogenase
LDT	Liver-directed therapy
LFT	Liver function test
MEK	Mitogen-activated protein kinase/ Extracellular signal-regulated kinase
MinR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mUM	Metastatic uveal melanoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PI3-kinase	Phosphatidylinositol 3-kinase
PPS	Per protocol set
PR	Partial response
QD	Every day
QW	Every week
REB	Research ethics board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RP2D-IE	Recommended Phase 2 dose — intra-patient escalation
RP2D-QD	Recommended Phase 2 dose — daily
RP2D-QW	Recommended Phase 2 dose — weekly
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SLD	Sum of longest diameters
SUSAR	Suspected, unexpected, serious adverse reaction
$t_{1/2}$	half-life
TIL	Tumor infiltrating lymphocyte
TMTB	total measured tumor burden
ULN	Upper limit of normal
UM	Uveal melanoma

1 BACKGROUND

1.1 Overview of Disease Setting

Melanoma arises from pigment containing cells (melanocytes) present in the skin, eye, and mucus membranes. Melanoma most frequently occurs in the skin; however, ocular melanoma arises from pigmented cells in the eye. The primary cause of melanoma is thought to be radiation-induced DNA damage from ultraviolet light exposure. Melanoma is the most deadly of skin cancers. Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000 deaths (Cancer Research UK). Cutaneous and uveal melanoma (UM) is more common in men than women. UM is a rare type of melanoma where the incidence has ranged from 5.3 to 10.9 cases per million (Singh, 2011). Despite its rare incidence rate (representing approximately 3% of melanoma cases, approximately 4,000 cases globally per year), UM is the most frequent primary intraocular malignancy of the adult eye (85%) (Patel, 2011; Maio, 2013). UM is an extremely malignant neoplasm that affects the vascular layers of the eye (iris, ciliary body, and choroid) (Maio, 2013). The majority of UM cases in the United States occur in the Caucasian population (Andreoli, 2015). UM is biologically distinct from cutaneous melanoma with differences in the mutational landscape, where *BRAF* and *NRAS* mutations dominate the landscape in cutaneous melanoma and mutations in G protein coupled receptors, q polypeptide (*GNAQ*) and alpha 11 (*GNA11*), dominate in UM (Shoustari, 2014). In addition, the mode of spread of disease is distinct between the 2 disease settings, with hematogenous spread of uveal versus lymphatic spread in cutaneous, leading to the different patterns of metastatic disease with primary liver metastases in UM, contrasted with visceral, bone, and brain metastases predominant in cutaneous melanoma (Dunavoelgyi, 2011; Yu, 2014).

Local therapy approaches in UM generally rely on radiation and surgical enucleation; however, despite adequate local therapy, UM metastases are very common and develop in 50% of patients with the liver being the predominant metastatic site (90%) (Carvajal, 2014). UM has also been shown to spread to the lungs, bones, and skin (Carvajal, 2014; Maio, 2013). The American Joint Committee on Cancer Tumor-Node-Metastasis staging system is used for UM (Edge, 2010) and represents 1 aspect of the estimated prognosis. Molecular markers such as monosomy 3 are used to guide prognosis and risk of metastasis in addition to classic histology such as the presence of spindle versus epithelioid (Campbell, 1998). Once patients have developed metastatic disease, the prognosis and outcomes are very poor with a median survival of less than 12 months, and for those with liver metastases, the median survival is approximately 6 months (Singh, 2011). Despite much investigation of metastatic uveal melanoma (mUM) in the clinic, to date, no systemic therapy has improved survival and no effective therapy has been achieved (Maio, 2013; Carvajal, 2014; Luke, 2013; Zimmer, 2015).

UM has a poor response to cytotoxic chemotherapy, and radiotherapy and therapies for cutaneous melanoma have had little impact in the treatment of UM (e.g., BRAF inhibitors, due to the absence of the target mutation in UM; Buder, 2013). UM has been characterized by specific driver mutations in guanine nucleotide binding protein (G protein), *GNAQ* or *GNA11* leading to the downstream activation of multiple signaling nodes, including mitogen-activated protein kinase/ extracellular signal-regulated kinase (MEK), phosphatidylinositol 3-kinase (PI3-kinase)/protein kinase B (Akt), protein kinase C, and Yes-associated

protein (Shoustari, 2014; Yu, 2014). Treatments for mUM can be divided into (1) liver-directed treatments; such as surgical resection, ablation, radiation, hepatic arterial chemoinfusion; and (2) systemic treatments; such as chemotherapy (anti-neoplastic drugs used alone or in combinations), immunotherapy (interferon, interleukin-2, programmed death-1 (PD-1) inhibition and ipilimumab), anti-angiogenetic drugs, and recently the targeted agents such as MEK and Akt inhibitors. The targeted agents are applied based on the high percentage of patients' tumors harboring *GNAQ* or *GNA11* mutations; however, these therapies have not been as effective as other targeted agents in the BRAF mutation subset (Buder, 2013).

Recent evidence suggests that immunotherapy for UM is only marginally more effective than cytotoxic therapy, where the estimates of the response rate of dacarbazine are between 0–5%. Response rates with ipilimumab in this setting range from 0–8% across multiple studies (Maio, 2013; Luke, 2013; Zimmer, 2015; Carvajal, 2014). The response to new immunotherapy approaches in the uveal subset is significantly diminished compared to that for cutaneous melanoma, possibly due to the low mutational burden of UM compared to that of cutaneous melanoma (Furney, 2014). The tumor microenvironment of UM is characterized by a uniquely suppressive environment with the presence of M2 macrophages and immature myeloid cells along with strong FoxP3 expression and CD8+ T cells (Bronkhorst, 2012). Both phenotypes are associated with a distinctly immune suppressive environment and this immune infiltrate is associated with monosomy 3 in UM and poor prognosis (Maat, 2008; Bronkhorst, 2011). The suppressive environment and lack of activity of checkpoint inhibition suggests that mobilization of activated T cells with a tumor-specific focus may have anti-tumor activity in this disease setting. With the wide and strong expression of gp100 in UM, the application of a redirected T cell approach to gp100 in this setting may have enhanced anti-tumor activity (Van Dinten, 2005). Furthermore, with the immunologically privileged site of UM, immunotherapy represents a promising treatment approach for this devastating and life-threatening condition (Buder, 2013; Woodman, 2012).

1.2 Overview of IMCgp100

IMCgp100 is a 77 kDa bi-specific protein with targeting and effector moieties which is manufactured in *Escherichia coli (E coli)*. The targeting portion of IMCgp100 (the T cell receptor) functions to bind to the gp100 antigen as presented by major histocompatibility complex Class I on the surface of melanoma cells. The targeted gp100 peptide is presented by a subset of the population that express a specific variant of the major histocompatibility complex Class I complex known as human leukocyte antigen-A2 (HLA-A2). This variant is carried by approximately 50% of the population in the Western World (Middleton, 2003).

The effector function (anti-cluster of differentiation 3 [anti-CD3]) works by binding and activating T cells via cluster of differentiation 3 (CD3). These T cells can be tumor specific cells which are already resident in the tumor (tumor infiltrating lymphocytes [TIL]), but circulating polyclonal T cells may also be activated as they traffic through the tumor as part of the normal blood supply. CD4+ and CD8+ T cells are both activated by IMCgp100 triggering cytolytic activity associated with release of immune mediators potentially resulting in a cascade of anti-tumor immune effector mechanisms. T cell proliferation studies on CD8 T cell subtypes have shown that effector memory, central memory, and naïve cells all respond to IMCgp100 stimulation as well as CD4+ T cells. Memory T cell activation following exposure to IMCgp100

[redacted]

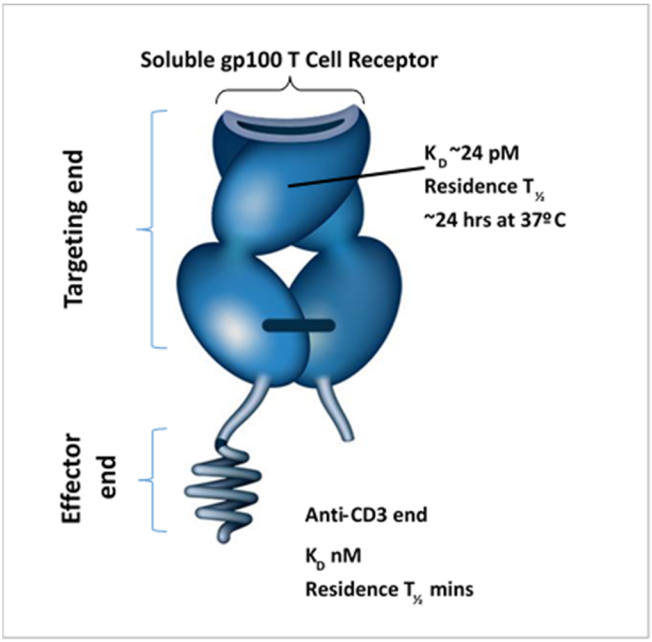


Figure 1-1 IMCgp100 Structure

IMCgp100 is a biologic with dual effector and targeting ends. The targeting end is an affinity enhanced soluble T cell receptor recognizing the gp100 antigen and the effector end is an anti-CD binding domain.

1.3 Non-clinical Experience with IMCgp100

1.3.1 Preclinical Pharmacology Summary

IMCgp100 has been shown to induce the full repertoire of cytotoxic T lymphocyte (CTL) activation events in a dose-dependent manner in vitro when combined with target melanoma cells. This activation is evident at concentrations as low as 1 picomolar (pM) and activity is maximal at a concentration of 1 nanomolar (nM) irrespective of whether isolated CD8 or peripheral blood mononuclear cells (PBMC) are used as the effector cells. Furthermore, maximal killing effects may require up to a few days exposure with cancer cells. The activation of CD4 T cells has also been demonstrated at similar concentrations and with similar kinetics. Such activation would be expected to augment the CTL mediated immune response through the recruitment of other inflammatory cells.

Using PBMCs from melanoma patients, IMCgp100 has been shown to augment an already present anti-tumoral response. Finally, the tumor infiltrating T cells that would be the first line of attack in a clinical situation would be expected to be outnumbered by melanoma targets. Thus, it has been shown that a single T cell is capable of serial killing in vitro. These data demonstrate that IMCgp100 is a potent tumor-killing agent.

[redacted]

[redacted]

1.3.2 Non-clinical Toxicology Summary

Both the gp100-specific soluble T cell receptor and the CD3 targeting ends of IMCgp100 have been demonstrated to have high specificity for the human HLA-A2-gp100 peptide complex and human CD3. Therefore, binding and activation of IMCgp100 cannot be demonstrated in non-human primates, which show a relatively high degree of sequence homology to human CD3. In addition, both the T cell receptor targeting end and CD3 activation arm do not interact at any level in any other species. Given the limitations in binding of IMCgp100 and activation of any T cell subsets in any standard toxicology species, there is no relevant toxicology species in which IMCgp100 can be tested.

Tissue cross-reactivity studies with IMCgp100 and published gp100 immunohistochemistry (IHC) demonstrate gp100 expression in human melanocytes, and expression levels have been demonstrated directly in the retina, melanocytes, the substantia nigra, and the thymus (Takase, 2005; Wagner, 1997). Other tissues that are known to contain melanocytes, but to our knowledge have not been directly tested for gp100 expression, include the iris, the inner ear, and the choroid plexus of the brain.

In the absence of a relevant toxicology species, IMCgp100 was investigated for potential reactivity to normal tissues other than target melanoma tissue in vitro. IMCgp100 could redirect T cell activity to normal cells that are known to express gp100; however, higher concentrations of IMCgp100 were required to elicit an effect in these normal tissue cells indicating that there may be a therapeutic window between a dose of drug required to effect melanoma cells and that which may cause potential organ specific toxicity. These assays were also used to determine a minimal anticipated biological effect level, and the starting dose for the first IMCgp100 dose escalation study. Other assays designed to assess unexpected reactivity of both the T cell receptor and the anti-CD3 were entirely negative.

1.4 Clinical Program and Safety Summary

IMCgp100 is being studied in an ongoing first-in-human (FIH), open-label, dose escalation study (IMCgp100-01). Patients with advanced melanoma were enrolled into 2 separate dose escalation cohorts: (1) a weekly (QW) dosing regimen cohort (Arm 1), and (2) a daily (QD) dose x 4 days repeated every 3 weeks dosing regimen cohort (Arm 2). The study is designed to identify the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of IMCgp100 in the 2 repeat dosing regimens: (1) QW dosing (the RP2D-QW) and (2) daily dosing x 4 days (the RP2D-QD).

1.4.1 Weekly Dosing: Dose Escalation Results

The QW dosing regimen dose escalation included dose levels from 5 ng/kg up to 900 ng/kg and the MTD for this dosing regimen was identified at 600 ng/kg QW (Middleton, 2015). In the review of the safety and pharmacokinetic (PK) data for the QW dosing regimen, the RP2D-QW was initially identified as a flat dose of 50 mcg administered intravenously (IV) on a QW basis; [redacted]

[redacted]

Please refer to the most recent version of the IMCgp100 Investigator's Brochure for further details.

1.4.2 Weekly Dosing: RP2D-QW Cohort Results

[redacted]

[redacted]

1.4.3 Daily Dosing: Dose Escalation Results

[redacted]

For further details refer to the most recent version of the IMCgp100 Investigator's Brochure.

1.4.4 Preliminary Pharmacokinetic Data from First-in-Human IMCgp100-01 Study

[redacted]

[redacted]

For detailed information regarding PK data of IMCgp100, refer to the most recent version of the IMCgp100 Investigator's Brochure.

2 RATIONALE

2.1 Study Rationale and Purpose

This is a Phase 1/2 clinical study of IMCgp100 in patients with advanced UM. In the Phase 1 FIH study of IMCgp100 in advanced melanoma, a dose escalation was conducted with IMCgp100 administered on a QW basis (Middleton, 2015). [redacted]

2.1.1 Suppressive Tumor Microenvironment in Uveal Melanoma

In general, cutaneous melanoma is thought to be 1 of the more immunogenic tumors with significant activity observed with immunotherapy options and the first drug approvals in this space (e.g., ipilimumab and nivolumab [Bristol Meyers Squibb] and pembrolizumab [Merck]). In contrast, the biology of UM suggests potent immunosuppressive properties, unlike the cutaneous subset with a corresponding lack of activity with the checkpoint inhibitors (Maio, 2013; Luke, 2013; Zimmer, 2015). Ironically, T cell infiltration in UM is predictive of poor survival. In the preclinical setting, there are 2 main hypotheses to explain the immunosuppressive nature of UM and none appears mutually exclusive: (1) T cell extrinsic immunosuppression due to negative myeloid influences with high IL-10, NKT activity with M2 wound healing phenotype of macrophages possessing potent immunosuppressive capabilities (Sadegh, 2015; Vu, 2013); and (2) T lymphocyte intrinsic immunosuppression with enhanced regulatory T cell development and indoleamine 2-3 dioxygenase expression by existing T cell responses in the setting of metastases as opposed to the primary lesions (Verbik, 1997; Whelchel, 1993; Mougiakokos, 2010; Lagouros, 2009). Preclinical studies suggest that the development of melanoma liver metastases is associated with upregulation of IL-10 in the liver and an elevated expression of IL-10 receptor on liver natural killer cells.

This impairment of liver natural killer activity is natural killer T cell-dependent and only occurs in hosts with melanoma liver metastases.

2.2 Rationale for Study Design

IMCgp100-102 is a Phase 1/2 study of the QW intra-patient escalation dose regimen with IMCgp100 as a single agent in patients with mUM. The Phase 1 testing of this regimen will aim to achieve a higher exposure and C_{max} of IMCgp100 after doses at Cycle 1 Day 15 (C1D15) and thereafter than the exposures achievable at the RP2D of the fixed 50 mcg RP2D-QW without additional toxicity. Phase 1 testing will follow the standard 3+3 design with DLT as the endpoint and identification of the MTD and/or the RP2D for the Phase 2 intra-patient escalation regimen (RP2D-IE).

Once the appropriate dose for Phase 2 is identified (RP2D-IE), the Phase 2 expansion cohorts in UM will begin. Cohort A will recruit approximately 20 patients to further characterize the safety, tolerability, PK, and anti-tumor response of IMCgp100 in patients following therapy with a checkpoint inhibitor and any potential liver-directed therapy (LDT). Cohort B will recruit approximately 130 patients to further characterize the safety, tolerability, PK, and anti-tumor response of IMCgp100 in patients who have been previously treated with 1 or 2 prior lines of therapy in the metastatic or advanced setting, including chemotherapy, immunotherapy or targeted therapy and up to a single line of local, LDT.Prior checkpoint inhibitor is acceptable in Cohort B but is not required.

Additional details on Phase 2 Expansion cohorts are provided in Section 3.2 and Section 5.2.

These cohorts will provide homogenous populations in which to assess safety and anti-tumor efficacy with the goal to inform subsequent development of IMCgp100.

2.3 Rationale for Dose and Regimen Selection

[redacted]

[redacted]

2.3.1 Rationale for Dose Level Updates

[redacted]

2.3.2 Rationale for Definition of Recommended Phase 2 Dose in the Intra-patient Escalation Regimen

The dose escalation cohorts of this study have been analyzed and the RP2D-IE (dosed at C1D15 and beyond) identified at 68 mcg. The preliminary results of the Phase 1 have been presented (Sato, 2017) and are summarized here.

[redacted]

2.4 Overall Benefit-Risk Assessment

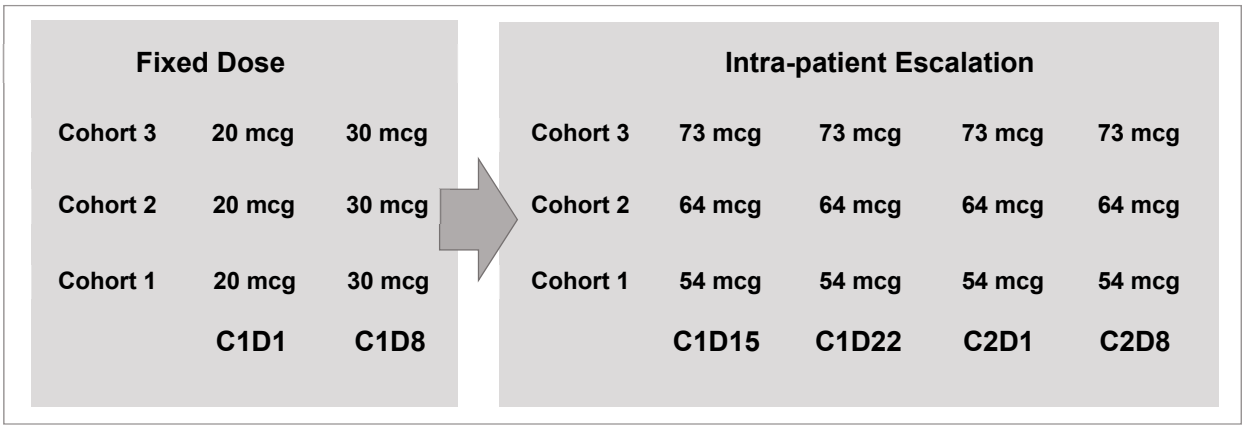
A significant degree of unmet need exists in the setting of advanced UM. Compared to standard treatments utilized in cutaneous melanoma, no treatments have consistently demonstrated a survival benefit in UM clinical studies, including dacarbazine and immunotherapy with checkpoint inhibition (e.g., ipilimumab or pembrolizumab). IMCgp100 has an acceptable tolerability profile, with generally mild-to-moderate toxicity beyond the first 2 doses where manageable immune-based toxicities have been observed (Middleton, 2016). The study is designed to minimize potential risks through intensive patient monitoring and frequent safety assessments based upon available early phase clinical safety data for IMCgp100. The preliminary, robust clinical activity of IMCgp100 in the setting of advanced UM, combined with the lack of any therapies demonstrating a survival benefit in this indication supports the further development of IMCgp100 in patients with advanced UM.

3 STUDY DESIGN

3.1 Description of Study Design and Populations

This is a Phase 1/2 study of IMCgp100 administered on a QW basis with an intra-patient escalation dosing regimen. The intra-patient escalation occurs at the third weekly dose on C1D15. According to this regimen, all patients in the trial will receive 2 QW doses of IMCgp100 at a dose level below the identified RP2D-QW, and then a dose escalation will commence at the third weekly dose at C1D15 with the goal to achieve a long-term dosing regimen at a dose higher than that identified for the straight QW dosing regimen (RP2D-QW). The dose escalation will identify the RP2D-IE. (Intra-patient dose escalation regimen schematic, see Figure 3-1).

Phase 1: Dose Escalation



Phase 2: Expansion

Enrollment into the Phase 1 dose escalation portion has been completed and RP2D-IE was determined to be 68 mcg.

Figure 3-1 Intra-patient Escalation Regimen

In this dosing regimen, at C1D1 and C1D8, patients will all receive single-agent IMCgp100 at a dose below the 2RP2D-QW of 50 mcg. Patients will receive 20 mcg IMCgp100 on C1D1 and 30 mcg IMCgp100 on C1D8. The intra-patient escalated dose will then commence at C1D15 and will continue at that same escalated dose level thereafter.

The Phase 1 portion of the study will be a standard 3+3 dose escalation design. Dose cohort levels are presented in Table 6-2. After the dose escalation portion is complete and the MTD or the RP2D-IE is identified, the Phase 2 expansion cohorts in mUM will be enrolled. The Phase 2 expansion Cohort A will enroll patients with mUM in the second-line setting after disease progression following systemic

treatment with a checkpoint inhibitor and will recruit approximately 20 patients. The Phase 2 expansion Cohort B will enroll patients with mUM in the second/third-line setting with up to one prior line of LDT and will recruit approximately 130 patients. A total of approximately 150 patients will be enrolled into the Phase 2 expansion phase of the study. See Figure 3-2.

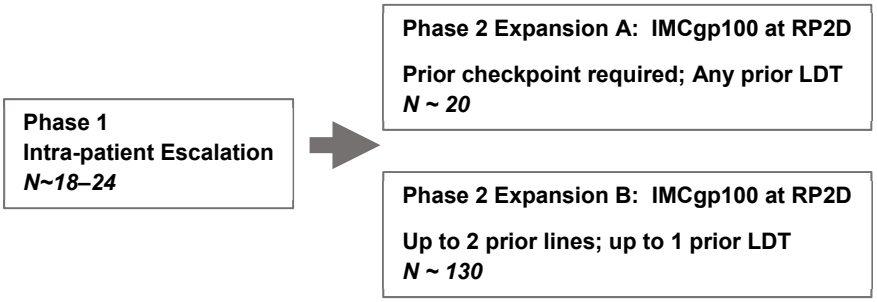


Figure 3-2 Study Design

LDT = liver-directed therapy; ORR = objective response rate; RP2D = recommended Phase 2 dose; RP2D-IE = recommended Phase 2 dose — intra-patient escalation.

Phase 1 testing of the intra-patient escalation regimen to identify the RP2D-IE will implement a standard 3+3 design. Once the dose is identified in the Phase 1 dose escalation, 2 Phase 2 expansion cohorts will be enrolled in 2 patient populations: (1) Cohort A will enroll patients with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a cytotoxic T lymphocyte associated protein-4 (CTLA-4) inhibitor (ipilimumab or tremelimumab) and/or a PD-1/programmed death-ligand 1 (PD-L1 inhibitor and any prior LDT, and (2) Cohort B will recruit approximately 130 patients to further characterize the safety, tolerability, PK, and anti-tumor response of IMCgp100 in patients who have been previously treated with 1 or 2 prior lines of therapy in the metastatic or advanced setting (including chemotherapy, immunotherapy or targeted therapy) and up to a single line of local, LDT. Prior checkpoint inhibitor is acceptable in Cohort B but is not required.

Additional details on Phase 2 Expansion cohorts are provided in Section 3.2 and Section 5.2.

These expansion cohorts are designed to further characterize the safety, tolerability, and preliminary PK and anti-tumor activity of IMCgp100.

3.2 Patient Population

The trial will enroll patients with a diagnosis of advanced UM, defined as histologically confirmed diagnosis of UM and metastatic stage IV disease at study entry. In the Phase 1 dose escalation portion of the trial, patients are eligible with any prior therapy including systemic treatments or LDT with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and meeting all additional eligibility criteria.

Enrollment into the Phase 1 dose escalation portion has been completed and RP2D-IE was determined to be 68 mcg. Two Phase 2 expansion cohorts will be enrolled in 2 patient populations based on prior therapy:

1. Cohort A: Patients will have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior LDT is acceptable in this cohort.
2. Cohort B: Patients will have experienced disease progression with 1 or 2 prior lines of therapy in the metastatic or advanced setting including chemotherapy, immunotherapy or targeted therapy. Only a single line of local, LDT including chemotherapy, radiotherapy, radiofrequency ablation or embolization is allowed. A line of LDT is defined as one modality of treatment that is administered until completion of treatment or disease progression. For patients who have received prior LDT, this will count as a line of therapy. Prior surgical resection of oligometastatic liver disease is allowed and is not counted as a line of LDT. A patient may have discontinued systemic therapy prior to disease progression if the patient experienced an adverse reaction that required treatment discontinuation, as per Investigator's judgment and applicable labelling. Prior checkpoint inhibitor therapy is acceptable but not required in this cohort.
    a. This means patients with the following treatments are eligible under Cohort B:
        - 1 systemic therapy and 1 LDT
        - 1 – 2 systemic therapies and 0 LDT
        - 0 systemic therapy and 1 LDT
    b. Adjuvant therapies and local therapies for treatment of disease outside of the liver do not count towards the lines of prior therapy.

These Phase 2 expansion cohorts are designed to further characterize the safety, tolerability, and preliminary PK and anti-tumor activity of IMCgp100.

Emerging preclinical data (Section 1.3.1) suggest that the residence time of IMCgp100 to the HLA-A*0201 allele is considerably longer resulting in enhanced effects compared to non-HLA-A*0201 alleles. This is borne out in the clinical data (Section 1.4.2), where patients expressing non-HLA-A*0201 alleles appear to have fewer T cell mediated toxicities and no clinical responses have been observed. Given these preclinical and clinical data, enrollment is limited to patients expressing the HLA-A*0201 allele.

3.3 Definition of Study Periods

The **Pre-screening Period** will begin once a patient has signed the Pre-screening Informed Consent Form (ICF) and concludes with the HLA-A*0201 testing results. A blood test will determine whether the patient is HLA-A*0201 positive (eligible) or HLA-A*0201 negative (not eligible). Patients will either be designated as pre-screening failure (negative test result or if positive and the patient chooses not to enter the study), or eligible for the study (HLA-A*0201 positive) and the patient can proceed and sign the Main Study ICF. Patients who re-screen for the trial need not return to the pre-screen period once HLA results are known. Patients known to be HLA-A*0201 positive by prior testing done outside the study may complete the pre-screening and screening periods in parallel.

The **Screening Period** will begin once a patient has signed the consent form and concludes with either a screen failure decision or initiation of study dosing on C1D1. Patients will not sign the main study ICF until the HLA-A2 status is known via central laboratory testing (see Pre-screening Period above). During the Screening Period, patients are evaluated against the study inclusion and exclusion criteria (see Section 5) and all screening procedures and observations are performed. The screening window for all procedures will be 21 days, other than imaging studies which will have a 28-day window. Patients who screen negative may re-screen for the trial without re-entering the pre-screen period.

The **Treatment Period** will begin with the first treatment in the first cycle with C1D1. For the purpose of treatment scheduling, a cycle consists of 4 weeks (28 days). The Treatment Period consists of the time from C1D1 until the end of study treatment.

The **90-day Safety Follow-up Period** consists of the time from the last dose of study medication for a period of 90 days. Safety observations during this 90-day Follow-up Period are outlined in Section 7.2.3 and include reporting of all AEs and all serious adverse events (SAEs) in the same manner as the **Treatment Period**. Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

The **Disease Progression Follow-up Period** is defined for all patients who discontinue for reasons other than death, progressive disease (PD) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) or modified irRECIST as outlined below, lost to follow up, withdrawal of consent, or study termination.

- All patients who discontinue for reasons other than PD per RECIST v1.1 will be followed with imaging until evidence of PD per RECIST v.1.1 (see Section 7.2.4 and Section 7.3.1)
- For patients who consent to and continue treatment beyond progression per RECISTv.1.1, imaging should continue until progression per modified irRECIST (irPD) or treatment discontinuation.
- If patients choose not to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient has had disease progression. .
- Patients who discontinue treatment for reasons of disease progression by either RECISTv1.1 or modified irRECIST criteria will not enter the Disease Progression Follow-up Period.
- Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

The **Survival Follow-up Period** will initiate after either the 90-day Follow-up Period (in patients who have discontinued for PD) or after the Disease Progression Follow-up Period (for patients discontinuing study treatment for reasons other than PD) and continue until death. As possible, all patients will be followed for survival until the end of the study is reached. Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

3.4 End of Treatment

In all patients in this study, IMCgp100 will be administered IV according to the defined regimen. Reasons for discontinuation of study treatment are described in Section 6.10.

Patients who discontinue treatment will remain in the study and be followed for the overall survival (OS) endpoint.

Each patient's disease will be assessed for efficacy using 2 sets of criteria: (1) RECIST v.1.1 and (2) modified irRECIST. The objective response rate (ORR) endpoint will be assessed as ORR per RECIST v.1.1; however, patients experiencing PD per RECIST v.1.1 criteria may consent to continue to be treated until meeting the criteria for unequivocal, confirmed PD by modified irRECIST as defined in Section 13.2.1.

Please refer to Section 6.9 for details regarding imaging assessment of PD for purposes of treatment discontinuation.

3.5 Definition of End of Study

The end of the study will be when a minimum of 80% of the patients have completed the follow-up for disease progression or discontinued the study for any reason, and all patients have completed treatment and the 90-day Follow-up Period, or if the study is terminated early.

An individual patient may end participation in the study for reasons described in Section 6.11. Please refer to Section 9, Statistical Methods and Data Analysis for details of timing of the primary analysis and final reporting of data.

3.6 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, any ongoing patient should be seen as soon as possible for End of Treatment (EOT) visit and the assessments should be performed as described in Table 7-1 for the EOT visit.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. Under guidance of the Sponsor, the investigator will be responsible for informing the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) of the termination of the trial.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

Phase 1 dose escalation: The primary objective is to identify the MTD and/or the RP2D of IMCgp100 in the intra-patient dose escalation regimen (RP2D-IE).

Phase 2 dose expansion: The primary objective is to estimate the ORR by independent central review (ICR) based on RECISTv.1.1 in patients with metastatic UM who are treated with the RP2D-IE of IMCgp100.

4.2 Secondary Objectives

- To characterize the safety and tolerability of IMCgp100 in the intra-patient dose escalation regimen
- To characterize the PK profile of single-agent IMCgp100 in the intra-patient dose escalation regimen
- To assess the anti-tumor efficacy of IMCgp100 with the parameters of ORR [Phase 1], OS, progression-free survival (PFS), disease control rate (DCR), time to response, and the duration of response (DOR)
- To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100 in the intra-patient dose escalation regimen
- To determine the rate and duration of minor responses (MinR) (defined as tumor response with a 10%–29% reduction in the sum of longest diameters [SLD])
- To determine immune responses (as assessed by area under the tumor response curve [AUC])

4.3 Exploratory Objectives

[redacted]

[redacted]

4.4 Primary Endpoints

Phase 1 dose escalation: The primary endpoint is incidence of DLT.

Phase 2 dose expansion: The primary endpoint is ORR by RECISTv.1.1 assessed by ICR.

4.5 Secondary Endpoints

- Tolerability: Dose interruptions, reductions, and dose intensity of all administered agents
- Serum PK parameters (e.g., AUC, C_{max}, T, $t_{1/2}$)
- Tumor response endpoints (ORR [Phase 1], PFS, DCR, DOR, time to response) as determined by RECIST v.1.1
    - Note: For the Phase 2 expansion cohorts, primary assessment of tumor-based endpoints will be provided by an ICR. Investigator assessment data will also be collected for both Phase 1 dose escalation cohort (primary assessment) and Phase 2 expansion cohorts (secondary assessment)
- OS
- Assessments of anti-IMCgp100 antibody formation
- Minor tumor responses (10% to 29% reduction in the SLD) and immune responses (as assessed by AUC)

4.6 Exploratory Endpoints

[redacted]

[redacted]

Table 4-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
Phase 1 dose escalation: To identify the MTD and/or the RP2D of IMCgp100 in the weekly RP2D-IE **Phase 2 dose expansion**: To estimate the ORR by ICR based on RECISTv.1.1 in patients with advanced UM who are treated with the RP2D of IMCgp100 in the RP2D-IE	**Phase 1 dose escalation**: Incidence of DLT **Phase 2 dose expansion**: ORR by RECISTv.1.1 assessed by ICR
Secondary	
To characterize the safety and tolerability of IMCgp100 in the intra-patient dose escalation regimen	Tolerability: Dose interruptions, reductions and dose intensity of all administered agents
To characterize the PK profile of single-agent IMCgp100 in the intra-patient dose escalation regimen	Serum PK parameters (e.g., AUC, C_{max}, T_{max}, $t_{1/2}$)
To assess the anti-tumor efficacy of IMCgp100 with the parameters of ORR [Phase 1], OS, PFS, DCR, time to response, and the DOR	• ORR (Phase 1), PFS, DCR, DOR, and time to response as per RECISTv.1.1 • For the Phase 2 expansion cohorts, primary assessment of tumor-based endpoints will be provided by an ICR. Investigator assessment data will also be collected for both Phase 1 dose escalation cohort (primary assessment) and Phase 2 expansion cohorts (secondary assessment) • Overall survival
To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100 in the intra-patient dose escalation regimen	Assessments of anti-IMCgp100 antibody formation
To determine the rate and duration of MinR (defined as tumor response with a 10%–	• Minor tumor responses (10% to 29% reduction in the SLD)

Objective	Endpoint
29% reduction in the SLD) and immune responses	• Immune responses (as assessed by area under the tumor response curve [AUC])
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; AUC = area under the curve; C_{max} = maximum observed serum concentration; ctDNA = circulating tumor deoxyribonucleic acid; DLT = dose limiting toxicity; DOR = duration of response; ECG = electrocardiogram; [redacted] ICR = independent central review; irRECIST = immune-related RECIST = Response Evaluation Criteria in Solid Tumors; MDSC = myeloid-derived suppressor cell; MinR = duration of minor responses; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; RP2D-IE = recommended Phase 2 dose — intra-patient escalation; SAE = serious adverse event; SLD = sum of the longest diameters; $t_{1/2}$ = half-life; T_{max} = time of maximum concentration; UM = uveal melanoma.

5 POPULATION SELECTION CRITERIA

5.1 Patient Population

This study will be conducted in patients with metastatic UM with any prior systemic therapy in the metastatic and advanced setting in the dose escalation cohorts. Two Phase 2 expansion cohorts will be enrolled in 2 patient populations defined by prior therapy for metastatic UM. Given the mechanism of action of IMCgp100, the study is limited to patients with the HLA-A*0201 subtype.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Male or female patients age ≥ 18 years of age at the time of informed consent
2. Ability to provide and understand written informed consent prior to any study procedures
3. Histologically or cytologically confirmed diagnosis of metastatic UM
4. Surgically sterile patients or patients of child-bearing potential who agree to use highly effective methods of contraception during study dosing and for 6 months after last dose of study drug
5. Life expectancy of > 3 months as estimated by the investigator
6. HLA-A*0201 positive by central assay
7. ECOG Performance Status of 0 or 1 at Screening
8. Patients must have disease (measurable or non-measurable acceptable) according to RECIST v.1.1 criteria in Phase 1 dose escalation cohorts. Patients must have measurable disease in the Phase 2 dose expansion cohorts
9. Phase 1 dose escalation cohorts only: any prior therapy is acceptable

Prior therapy in Phase 2 expansion cohorts:

- Cohort A: Patients will have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior LDT is acceptable in this cohort
- Cohort B: Patients will have experienced disease progression with 1 or 2 prior lines of therapy in the metastatic or advanced setting including chemotherapy, immunotherapy or targeted therapy. Only a single line of local, LDT including chemotherapy, radiotherapy, radiofrequency ablation or embolization is allowed. A line of LDT is defined as one modality of treatment that is administered until completion of treatment or disease progression. For patients who have received prior LDT, this will count as a line of therapy. Prior surgical resection of oligometastatic liver disease is allowed and is not counted as a line of LDT. A patient may have

discontinued systemic therapy prior to disease progression if the patient experienced an adverse reaction that required treatment discontinuation, as per Investigator's judgment and applicable labelling. Prior checkpoint inhibitor therapy is acceptable but not required in this cohort.

a. This means patients with the following treatments are eligible under Cohort B:
    - 1 systemic therapy and 1 LDT
    - 1 – 2 systemic therapies and 0 LDT
    - 0 systemic therapy and 1 LDT

b. Adjuvant therapies and local therapies for treatment of disease outside of the liver do not count towards the lines of prior therapy.

10. All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug

5.3 Exclusion Criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to Study Day 1. Asymptomatic and adequately treated CNS metastases are not exclusionary
2. History of severe hypersensitivity reactions to other biologic drugs or monoclonal antibodies
3. Patient with any out-of-range laboratory values defined as:
    - Serum creatinine > 1.5 x upper limit of normal (ULN) and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/min
    - Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
    - ALT > 3 x ULN
    - AST > 3 x ULN
    - Absolute neutrophil count < 1.0 x 10^9/L
    - Absolute lymphocyte count: (1) Phase 1 and Phase 2 Expansion Cohort A: Absolute lymphocyte count < 0.5 x 10^9/L; (2) Phase 2 Expansion Cohort B: Absolute lymphocyte count < 1.0 x 10^9/L
    - Platelet count < 75 x 10^9/L
    - Hemoglobin < 8 g/dL
    - Potassium, magnesium, corrected calcium or phosphate abnormality of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) > grade 1

4. Dose escalation only: Presence of high tumor burden, defined as liver replacement of > 60% hepatic organ volume with tumor
5. Clinically significant cardiac disease or impaired cardiac function, including any of the following:
    - Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled hypertension, or clinically significant arrhythmia currently requiring medical treatment
    - QTc > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome
    - Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening
6. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy before Screening
7. Known history of human immunodeficiency virus (HIV) infection. Testing for HIV status is not necessary unless clinically indicated or if required by local regulations
8. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection or if required by local regulations
9. Patients receiving systemic treatment with systemic steroid therapy or any other immunosuppressive medication at any dose level that would interfere with the action of the study drugs in the opinion of the investigator
10. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type
11. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results
12. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic or immunotherapy agents that can present with major delayed toxicity (e.g., anti-CTLA-4), 4 weeks is indicated as washout period
13. Presence of NCI CTCAE ≥ grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ NCI CTCAE grade 3 and hypothyroidism adequately managed with replacement therapy) due to prior cancer therapy
14. Patients with adrenal insufficiency or patients currently requiring chronic, systemic corticosteroid therapy at any dose for longer than 2 weeks. Local steroid therapies (e.g., otic, ophthalmic, intra-articular, or inhaled medications) are acceptable

15. Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary)
16. Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass
17. Use of hematopoietic colony-stimulating growth factors (e.g., G-CSF, GMCSF, M-CSF) ≤ 2 weeks prior to start of study drug. Patients must have completed therapy with hematopoietic colony-stimulating factor at least 2 weeks before the first dose of study drug is given. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is not red blood cell transfusion dependent
18. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation)
19. Women of child-bearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment, must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods of contraception are described in Section 6.6.
20. Male patients must be surgically sterile or use double barrier contraception method from enrollment through treatment and for 6 months following administration of the last dose of study drug
21. Patients may not have been included in any prior IMCgp100 trial, regardless of assigned treatment cohort

6 STUDY TREATMENTS AND ADMINISTRATION

6.1 Study Treatment

For this study, the investigational drug refers to IMCgp100. Study drug will be supplied by the Sponsor, Immunocore.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form (eCRF).

Table 6-1 Dose and Treatment Schedule

Phase	Study Treatments	Pharmaceutical Form and Route of Administration	Dose	Frequency and/or Regimen
I	IMCgp100	Concentrate for solution for infusion (single use vials)	20 mcg Cycle 1 Day 1 and 30 mcg Cycle 1 Day 8 then, Dose as determined by cohort from Cycle 1 Day 15 and thereafter (refer to Table 6-2 for Dose Levels)	Every week
2	IMCgp100	Concentrate for solution for infusion (single use vials)	20 mcg Cycle 1 Day 1 and 30 mcg Cycle 1 Day 8 then 68 mcg from Cycle 1 Day 15 and thereafter	Every week

For all study medication administration, a physician must be present at the site or immediately available to respond to emergencies during all administrations of all study medications. Fully functional resuscitation facilities should be available.

6.1.1 IMCgp100

IMCgp100 will be supplied as a liquid formulation for dilution prior to administration. IMCgp100 will be administered via IV infusion over 15–20 minutes QW. Each vial is designed for single use only and is not to be used to treat more than one patient for more than one dose.

6.1.1.1 IMCgp100 0.5 mg/mL drug product

IMCgp100 0.5 mg/mL drug product will be provided as a sterile, frozen solution in glass vials. Detailed instructions for dose preparation and administration are provided in the study pharmacy manual and a summary is provided below.

6.1.2 Dispensing, Dose Preparation and Administration

IMCgp100 will be supplied as concentrate for solution for infusion and require dilution prior to administration. Detailed instructions for dose preparation and administration are provided in the study pharmacy manual and/ or on the relevant pharmacy handling instructions. Once prepared for administration, the final infusion bag containing IMCgp100 must be administered within 4 hours at room temperature from the time of initial puncture of the supplied drug vial.

The target duration of administration of IMCgp100 will be 15–20 minutes. The entire content of the IV bag will be infused using an infusion pump. The IV line should be flushed after the contents of the IV bag are fully administered according to institutional policy to ensure the full dose is administered. It must be documented if the line was not flushed.

6.2 Summary of Intra-patient Dose Escalation Treatment Regimen

Patients enrolled in this study will receive treatment with single-agent IMCgp100 on C1D1 and C1D8 at 20 mcg and 30 mcg per week, respectively. The majority of moderate-to-severe toxicity associated with IMCgp100 in the FIH study was observed at these 2 dose time points and included hypotension, rash, pruritus, fever, and chills (please refer to Section 1.4, Clinical Experience with IMCgp100 for a full discussion of the safety data with IMCgp100). After this initial dosing period, beginning at C1D15, patients will receive an escalated dose of IMCgp100 according to the cohort into which they are enrolled (please see Table 6-2 below, for dose levels to be tested). This escalated dose administered at C1D15 will be the dose used for the remainder of the treatment period unless dose reduction is implemented for toxicity. See schematic for intra-patient dose escalation regimen described in Section 3.1 and Figure 3-1.

In this intra-patient escalation regimen, all patients will require overnight inpatient hospitalization and a minimum of pre-dose and monitoring vital signs every 4-hours after the first administration of IMCgp100 (C1D1), after the second administration (C1D8), and after the escalated dose of IMCgp100 on C1D15 is administered. For the first 3 administrations of IMCgp100, patients should be monitored for at least 16 hours after dosing. “Inpatient hospitalization” refers to a facility with fully functional resuscitation facilities, 24 hour monitoring and physician availability.

Inpatient monitoring at Cycle 1 Day 22 (C1D22) will be determined by the toxicity observed in the C1D1–C1D15 doses as follows:

1. If the escalated dose at C1D15 administered as an inpatient does not raise safety concerns (and the patient does not experience an adverse reaction involving hypotension of grade 2 or greater), the subsequent dose at C1D22 and all subsequent doses can be administered on an outpatient basis
2. If the patient experiences hypotension requiring any medical intervention (Common Terminology Criteria for Adverse Event [CTCAE] grade 2 or greater) at C1D15, then the C1D22 dose must be administered with inpatient monitoring, similar to C1D1–C1D15. If the patient does not experience hypotension requiring medical intervention at the C1D22 dose administered as an inpatient, then all subsequent doses can be administered on an outpatient basis

3. Hospitalization at other days (e.g., Cycle 2 and beyond) are determined at the discretion of the principal investigator based on the patient's history and tolerance for the initial doses of the study medication with the exception of patients experiencing a treatment delay (please refer to bullet 5 below)
4. Until Cycle 2 Day 15 (C2D15), patients who have experienced a prior CTCAE grade 3 or 4 hypotension event with IMCgp100 dosing and are receiving a dose in the outpatient setting, must be observed in the clinic for a minimum of 8 hours after completion of the IMCgp100 dose.
5. Patients experiencing a break or delay in treatment for any reason of more than 2 weeks AND have a history of a grade 3 or 4 hypotension event with IMCgp100 dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to the break in dosing, regardless of the timing of the break in dosing.

Due to the risk of hypotension, all patients receiving anti-hypertensive medications must **discontinue all anti-hypertensive therapy** for 24 hours prior to dosing and for 24 hours after dosing for the first 6 QW doses of IMCgp100 unless discussed and agreed with the Sponsor's Medical Monitor. After the sixth weekly dose, anti-hypertensive therapy can be restarted on a continuous basis thereafter with the dosing of IMCgp100 (eliminating the 24 hour hold during IMCgp100 dosing) at the discretion of the principal investigator.

In addition, due to the risk of hypotension, IV fluids may be administered prior to IMCgp100 administration and, if given, IV fluids will be recorded as a concomitant medication in the eCRF. The administration of IV fluids should be guided by clinical evaluation and the volume status of the patient. Pruritus is a common adverse event with IMCgp100, so premedication with an antihistamine may be considered. See Table 6-3 for further recommendations regarding treatment of skin toxicity. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days after consultation with the Sponsor Medical Monitor. Pre-medications should include, but are not limited to, paracetamol/acetaminophen and an antihistamine. Corticosteroid premedication should be avoided; corticosteroids should only be considered if the paracetamol/acetaminophen and antihistamine combination is not effective and only after consultation with the Sponsor Medical Monitor.

If 2 or more patients experience moderate-to-severe acute infusion reactions on C1D1 or if > 25% of patients experience mild infusion reactions, then mandatory primary prophylaxis regimens (i.e., before dosing on C1D1 or C1D15) will be instituted for subsequent patients beginning treatment after discussion and agreement among principal investigators and the Sponsor. Primary and secondary prophylaxis regimens will include both paracetamol/acetaminophen and an antihistamine. The decision taken to mandate primary prophylaxis will be communicated in writing to all principal investigators participating in the study.

Acute allergic reactions should be treated as needed using institutional guidelines. In the event of anaphylactic/anaphylactoid reactions, any therapy necessary to restore normal cardiopulmonary status should be implemented immediately. Such acute allergic reactions will be reported to the Sponsor in an expedited manner. These should be designated as reportable as a SAE regardless of hospitalization as medically important events. Please refer to SAE reporting section for details. The individual symptoms of

the infusion-related reaction should be captured in order to best characterize the study drug infusion reactions, unless the investigator considers another category, such as “allergic reaction,” “anaphylaxis,” or “cytokine release syndrome” more appropriate in a specific situation.

6.3 Dose Escalation Guidelines

6.3.1 Dose-limiting Toxicities Observation Period

The DLT observation period for the Phase 1 cohorts will be the first cycle during IMCgp100 dosing (C1D1 until C1D28).

6.3.2 Starting Dose Rationale

[redacted]

6.3.3 Dose Levels

This study will begin with Phase 1 dose escalation of the intra-patient escalation dosing regimen to assess the safety and tolerability of the C1D15 intra-patient escalation. [redacted]

[redacted]

[redacted]

6.3.4 Dose Escalation Guidelines

Three to 6 patients will be enrolled in sequentially enrolling dose cohorts (see Table 6-2 dose levels). In each cohort, patients will be treated during Cycle 1 with IMCgp100 as a single agent (Days 1 and 8 of Cycle 1, all patients receive the 20 and 30 mcg, retrospectively). At C1D15, the intra-patient dose escalation will begin. The study will begin with Cohort 1 (See Table 6-2 dose levels) receiving dose level 1 (54 mcg) at CD15 and thereafter. Other cohorts enrolling after Cohort 1 will follow the dose escalation guidelines. Cohorts will enroll to escalation by increments of 10 mcg until an MTD and/or RP2D-IE for the intra-patient dose escalation regimen is identified.

An individual cohort will initially enroll 3 to 6 patients. If none of the 3 patients experiences a DLT, then dose escalation decision may proceed after agreement among study team members (participating investigators and Sponsor) within the DETC. The decision to escalate the dose will be determined based on available toxicity, PK, and pharmacodynamic data following a discussion among members of the study team (all participating investigators and Sponsor Medical Monitor) during DETC. The cohort will be expanded to 6 patients if DLT is observed during the DLT period according to the dose escalation rules noted below. If toxicity is managed adequately to resume IMCgp100 dosing, patients experiencing DLT may continue treatment with IMCgp100 only after agreement with the Sponsor Medical Monitor. Patients in the Phase 1 cohorts will be considered evaluable for dose escalation decisions (DLT Analysis Set) if they receive a minimum of 3 doses of IMCgp100 (with 2 of the 3 doses at the escalated level of C1D15 and thereafter) or have experienced DLT during the DLT observation period.

Dose-escalation in the study will occur after the study team (Sponsor and investigators) have jointly reviewed available safety data for the 3 to 6 patients at the current dose level at a safety team DETC. The decision to dose-escalate will be taken by the study team (participating investigators and the Sponsor Medical Monitor). Additional cohorts may be added if necessary to explore alternate/intermediate dose levels if deemed necessary by the members of the dose escalation teleconference.

6.3.4.1 Dose Escalation Decision Making

Dose-escalation decisions will be made based on treatment-emergent AE, clinical laboratory data, and available PK, and pharmacodynamic data after all patients in a cohort complete the 28-days of study treatment in Cycle 1. Safety data from patients on preceding cohorts will also be taken into consideration. The data will be reviewed and a decision taken whether or not to proceed to the next dose cohort (at the planned or an alternative dose level), whether more patients are required to be dosed at the dose level under review or whether the MTD and/or the optimal RP2D-IE has been reached.

The following dose-escalation rules will be used:

If none of the first 3 evaluable patients experiences a DLT by the end of the DLT observation period, the dose will be escalated and the next cohort of patients can start treatment at the next highest dose level.

- If 1 of the first 3 patients experiences a DLT in Cycle 1, the cohort will be expanded to 6 patients. If none of these additional patients experiences a DLT, then the dose will be escalated to the next higher dose level
- If 2 or more patients in the dose level experience a DLT in the DLT observation period, then the MTD has been exceeded and 3 more patients will be treated at the next lower dose level, if only 3 patients were previously treated at that dose level
- If 0 or 1 DLT is observed at this lower dose level, this dose will be determined to be the MTD
- If 2 DLTs occur at this level, the next lower dose will need to be evaluated similarly
- A minimum of 6 patients will be evaluated at the dose level identified as the RP2D-IE in this study

6.3.4.2 **Definition of MTD and RP2D-IE**

The **MTD** is defined as the highest dose level with an observed incidence of DLT in fewer than 33% of the patients enrolled in a cohort level. If all evaluated dose levels demonstrate an observed incidence of DLT in fewer than 33% of patients, the MTD has not been reached. If this proves to be the case, then a total of 6 patients will be treated at the highest dose tested to gain additional safety data before proceeding to the dose-expansion part of the study. If a DLT occurs at the MTD, a total of 6 patients must be treated at the MTD.

Determination of the **RP2D-IE** will be based on the sum of the safety, tolerability, pharmacodynamic and PK data, as well as preliminary efficacy data emerging over the course of the Phase 1 testing. The MTD and RP2D-IE may be not be the same dose level for implementation in the UM expansion cohort.

The **RP2D-IE** will be based on the sum of the safety, tolerability, pharmacodynamic, and PK data, as well as preliminary efficacy data emerging over the course of the Phase 1 testing. The RP2D-IE will be defined as the dose level selected for testing in the expansion cohort by the study team, based on all available safety, tolerability, PK, and pharmacodynamic data. The MTD and RP2D-IE may not be the same dose level; the RP2D-IE will be the same dose or a lower dose than an identified MTD. If the MTD and RP2D are different, the RP2D-IE will be implemented in the expansion cohorts. A minimum of 6 patients will be

treated at the identified RP2D-IE for the DLT period before the expansion cohorts with this dose can begin enrollment.

During the course of the UM expansion cohorts, if the rate of grade 3 and/or grade 4 toxicity is considered related to the study drugs and meeting the definition of DLT is higher than 30%, a safety teleconference will be convened with the study team (Sponsor and investigators) to determine if the cohort should continue enrollment.

6.3.4.3 **Replacement of Patients**

Patients will be replaced in the Phase 1 cohorts according to the guidelines for Phase 1 dose escalation. Patients deemed not eligible for the DLT Analysis Set in Phase 1 will be replaced.

6.4 Definition of Dose-limiting Toxicities

A DLT is defined as an AE or abnormal laboratory value assessed as having a suspected relationship to study drug, and unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first cycle of treatment, and meets any of the criteria included in Table 6-3. NCI CTCAE version 4.03 will be used for all grading unless otherwise specified. The investigator must notify the Sponsor immediately of any unexpected NCI CTCAE grade ≥ 3 AEs or laboratory abnormalities. Prior to enrolling patients into a higher dose level, all NCI CTCAE grade ≥ 2 AEs will be reviewed for all patients at the current dose level by the study team at the DETC.

Table 6-3 Criteria for Defining Dose Limiting Toxicities

DLTs include any related AE of NCI CTCAE grade 3 or higher occurring in the first cycle of weekly IMCgp100, during the dose escalation Phase 1 part of the study with the following exceptions:	
Hematology	Neutropenia is a DLT if it is NCI CTCAE grade 4 Thrombocytopenia is a DLT if it is NCI CTCAE grade 4 Anemia is a DLT if it is NCI CTCAE grade 4 Lymphopenia of grade ≥ 3 persistent for more than 14 days or the presence of an infection indicating clinically significant lymphopenia Febrile neutropenia of grade ≥ 3 is a DLT
Hepatic	NCI CTCAE grade ≥ 2 total bilirubin with NCI CTCAE grade ≥ 2 ALT is a DLT NCI CTCAE grade 3 elevation of ALT and/or AST is a DLT if a concurrent elevation of bilirubin is observed (≥ grade 1) or if the elevated ALT and/or AST is not resolved to grade ≤ 1 within 72 hours Grade 4 elevation of ALT and/or AST is a DLT
Gastrointestinal	Nausea and vomiting are DLTs if they are NCI CTCAE grade ≥ 3 for > 2 days despite optimal anti-emetic therapy Diarrhea is a DLT if it is NCI CTCAE grade ≥ 3 for > 2 days despite optimal anti-diarrhea treatment
Hypotension	NCI CTCAE grade 3 hypotension is a DLT if not resolved to ≤ grade 1 within 24 hours of the dose administration. Any event of hypotension requiring pharmacologic blood pressure support of any duration is a DLT. NCI CTCAE grade 4 hypotension of any duration is a DLT
Hypertension	NCI CTCAE grade 3 hypertension is a DLT if it persists > 7 days despite treatment. Grade 4 hypertension of any duration is a DLT
Infection	NCI CTCAE grade 3 infection or fever in the absence of neutropenia are DLTs if they persist > 5 days. Grade 4 infection of any duration is a DLT
Tumor flare	Grade 3 inflammatory reaction at a tumor site associated with a local anti-tumor immune response is a DLT if not resolved to grade ≤2 within 7 days
Electrolytes	NCI CTCAE grade 3 electrolyte abnormalities are DLTs if they persist > 7 days despite treatment or are clinically significant. Grade 4 electrolyte abnormality of any duration is a DLT
Rash and/or photosensitivity	NCI CTCAE grade 3 rash is a DLT if rash persists > 7 days despite optimal treatment. Grade 4 cutaneous toxicity of any duration is a DLT
Fatigue	Fatigue is a DLT if it is NCI CTCAE grade ≥ 3 and lasts > 7 days
Infusion-related reaction	Grade 3 infusion-related reaction will not be considered a DLT if resolved with appropriate medical management within 6 hours of occurrence. Grade 4 infusion reaction is a DLT
Other AEs	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in Cycle 1, may be considered to be DLTs by the investigators and Sponsor, even if not

	NCI CTCAE grade 3 or higher. Infusion reactions will not be considered as dose limiting because they are idiosyncratic and not related to dose

AE = adverse event; ALT = alanine aminotransferase; DLT = dose limiting toxicity; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

6.5 Concomitant Therapy

Concomitant therapy will be continuously monitored through the 90-day safety follow up.

6.5.1 Permitted Concomitant Therapy

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed in general. Examples include anti-diarrheal medications, anti-emetics, or electrolyte supplementation.

Patients must be told to notify the investigational site staff about any new medications, herbal remedies, or dietary supplements that he or she takes after the start of the study treatment, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications, and blood transfusions) administered during the study must be listed on the Concomitant Medications eCRF.

IV hydration required to manage toxicity associated with any of the study medications (e.g., hypotension) and any IV hydration administered prior to study drug dosing should be recorded in the Concomitant Medications eCRF.

6.5.2 Permitted Concomitant Therapy Requiring Caution

Treatment with hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF, M-CSF or erythroid stimulating agents) may not be initiated during the first cycle in any arm of the study, unless the patient has already experienced a DLT. If a patient is using erythropoiesis-stimulating agent prior to enrollment (beginning at least 2 weeks before start of study treatment), they may continue at the same dose.

Anti-coagulant therapy is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin for > 2 weeks at time of first dose. Prophylactic use of low molecular weight heparin during the inpatient hospitalization is allowed. International normalized ratio should be monitored as clinically indicated per investigator's discretion. Ongoing anti-coagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of IMCgp100 and monoclonal antibodies, **treatment with anti-hypertensives should be held 24 hours before and 24 hours after IMCgp100** in the first 6 weeks of treatment and thereafter at the discretion of the principal investigator, unless discussed and agreed with the Sponsor's Medical Monitor.

6.5.3 Prohibited Concomitant Therapy

During the course of the study, patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Additionally, no other systemic therapeutic monoclonal antibodies, except for denosumab and tocilizumab if required for patient care, and no immunosuppressive medication may be administered while on this study, unless prescribed to manage toxicity. While systemic corticosteroid therapy will interfere with the mechanism of action of the study medications, its use is recommended in some settings.

The use of systemic corticosteroid therapy is permitted/recommended in the following settings: (1) infusion reactions, (2) immune-mediated toxicities and toxicity management as directed in Table 6-5 (e.g., hypotension not resolving with fluid support), and (3) replacement-dose steroids in the setting of adrenal insufficiency (patients with a pre-existing history of adrenal crisis are excluded from study participation, see Section 5.3 Exclusion Criteria). Any additional uses of systemic corticosteroid therapy during the course of the study should be discussed with the Sponsor Medical Monitor.

6.6 Contraception

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, can be included in the study provided they are using highly effective methods of contraception during dosing and for 6 months after the last dose of IMCgp100.

Highly effective contraception methods include the following:

- Total abstinence from sexual relations for the duration of the treatment when applicable to the lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this applies only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
- Male sterilization (at least 6 months prior to Screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient
- The combination of any 2 of the following methods when both are used simultaneously:
    - Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device or intrauterine system

- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) when used with spermicidal foam, gel, film, cream, or used of a spermicidal vaginal suppository

6.7 Patient Numbering and Treatment Assignment

6.7.1 Patient Numbering

Each patient is identified in the study by a number that is assigned when the patient is first enrolled for Screening. The patient number is retained as the primary identifier for the patient throughout participation in the trial. The patient number consists of the center number assigned by the Sponsor and a sequential patient number suffix so that each patient is numbered uniquely across the entire database. Patient numbers will be assigned by the Sponsor via the interactive response technology system at the time of Screening.

6.7.2 Treatment Assignment and Randomization

Patients enrolled in the Phase 1 portion of the study will be assigned to the appropriate open Phase 1 cohort by the Sponsor. Patients enrolled in the expansion cohort will be assigned by the Sponsor. Assignments will be coordinated via the interactive voice response system for the study.

6.8 Study Drug Packaging/Labelling, Preparation and Dispensation

Further instructions for the preparation and dispensation of IMCgp100 are described in the study Pharmacy Manual, relevant Pharmacy Handling Instructions and Section 6.1 Study Treatment.

Packaging and labelling details are outlined in the study Pharmacy Manual and relevant Pharmacy Handling Instructions.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.8.1 Study Drug Compliance and Accountability

Study treatment will be administered to the patient by the trained study site staff at the study sites and as outlined in the study Pharmacy Manual and Section 6.1. Compliance with the prescribed regimen will be assured by administration of the study treatment under the supervision of investigator or his/her designee.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. Full drug accountability for IMCgp100 is required in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the

completed drug accountability logs to the site study monitor. Additional details including receipt of study products, storage and management of temperature excursions are provided in the study Pharmacy Manual.

6.8.2 Drug Supply, Storage, and Disposal

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, IMCgp100 supply should be recorded and stored according to the instructions specified on the drug labels.

All IMCgp100 supply remaining at the end of the study, following appropriate drug accountability procedures at each site, can be destroyed per local institutional practice at the study site or at a third party vendor as appropriate and agreed to with Sponsor. All destruction of study medications must be documented appropriately.

6.9 Management and Follow-up of Toxicity

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary for any AEs observed in the course of the trial. In the case of a toxicity suspected to be related to a cytokine release syndrome, the immunologic assessments outlined in Section 7.3.7.7 should be performed. In case of a worsening rash or other related skin toxicity (e.g., pruritus), a skin punch biopsy, as outlined in Section 7.3.7.10, should be considered.

Guidelines for management of AE and dose modifications are presented below in Table 6-5 (below). Institutional protocols for management of immune-related AE should be implemented in cases of immune-related AE and will take precedence over guidance in Table 6-5. All patients must be followed up for the occurrence of AE and SAE for 90 days following the last dose of IMCgp100. If more than 3 consecutive doses of single-agent IMCgp100 are not administered due to drug-related toxicities or if a treatment gap occurs of greater than 21 days, the default position is that then the patient must be discontinued from the study. However, if a patient who misses more than 2 consecutive doses due to a drug-related toxicity is experiencing clinical benefit, and in the opinion of the investigator it is in the patient's best interest to remain on study, then the patient may restart treatment after discussion with the Sponsor.

6.9.1 Hypotension

Cases of severe hypotension have been observed across the IMCgp100 clinical trials. Initial therapy for low-grade hypotension is aggressive IV fluid (crystalloid or colloid) therapy. In cases of hypotension, where blood pressures are not immediately responding to fluid management, IV corticosteroid therapy should be considered. Cases of hypotension not complicated by additional symptoms associated with cytokine

release syndrome (CRS) (e.g., nausea, vomiting, malaise, and fever) have been observed with IMCgp100. Retrospective analyses of peripheral cytokines in the IMCgp100-102 study have suggested that mild-to-moderate elevations in IL-6 after the first dose of IMCgp100 may be associated with more severe presentations of hypotension. Intervention with early IV corticosteroid in cases of hypotension without initial response to fluid therapy is warranted as described in Table 6-5.

6.9.2 Cytokine Release Syndrome

Cases of CRS have been observed across the IMCgp100 clinical trials (as of 12 August 2018, CRS cases have been seen in 6% of patients in the current study overall, and 2 of these cases were ≥ Grade 3). The pattern of CRS generally begins 2–12 hours following the first 3 doses of IMCgp100 and the observed toxicities include hypotension (which has been severe in some patients), rash or general erythema, pruritus, facial and general edema, pyrexia and chills. Other commonly reported symptoms, typically mild to moderate, include headache, fatigue, nausea, and vomiting. Grading of CRS is based on the modified grading system (Table 6-5). Aggressive management in cases of suspected CRS is warranted per guidance in Table 6-5. Early intervention with immunosuppression therapy (e.g., high-dose corticosteroid therapy) is warranted in cases of suspected CRS.

Table 6-4 describes updated grading for events of CRS.

Table 6-4 Cytokine Release Syndrome Grading Scalea

Grade	Symptoms
1	Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, and malaise)
2	Symptoms require and respond to moderate intervention: • Oxygen requirement < 40% • Hypotension responsive to fluids or 1 low-dose vasopressor • Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention • Oxygen requirement > 40% • Hypotension requiring high-dose or multiple vasopressors • Grade 3 organ toxicity • Grade 4 transaminitis
4	Life-threatening symptoms • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)
5	Death

a. Lee 2014.

Table 6-5 Recommended Management and Dose Modifications of IMCgp100 by Toxicity Grade for Study Medications

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Management and Dose Modifications
Skin Toxicity	
Pruritus	
Grade 1	Continue dosing. If symptomatic, consider systemic antihistamine regimen (see grade 2 guidance below).
Grade 2	Treat according to institutional practice and/or implement guidance below. Use systemic management and/or local skin management as indicated by symptoms. **Anti-pruritic regimen:** 1. **Systemic antihistamine regimen** recommended as first-line management of pruritus. Non-sedating, long-acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (e.g., evening dosing) consider diphenhydramine 25 mg oral or intravenous. The use of sedating anti-histamines should be minimized in patients with co-morbid pulmonary pathology including pulmonary metastases or underlying inflammatory airways disease such as chronic obstructive pulmonary disease or asthma 2. **Topical corticosteroid regimens** Preparation of recommended regimens: • For face and/or intertriginous areas (including genitalia) recommend alclometasone 0.05% or hydrocortisone 2.5% creams • For other body areas (i.e., trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation Prophylaxis for subsequent doses is generally not required after grade 2 pruritus, but a non-sedating anti-histamine may be considered.
Grade 3	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. Manage pruritus according to institutional protocol and guidance below. **Management:** Treat according to institutional practice which generally includes an anti-pruritic regimen (see grade 2 management above). In addition, corticosteroid treatment (oral or intravenous) can be considered for pruritus that does not respond to antihistamine therapy (recommend oral prednisone 20–40 mg or a single dose of 25 mg hydrocortisone intravenous or the equivalent for refractory pruritus). For recommended systemic or topical regimens, refer to grade 2 management above). **Prophylaxis:** In patients experiencing grade 3 pruritus, administration of a non-sedating antihistamine prophylaxis dose is recommended for the subsequent dose of IMCgp100, approximately 1–2 hours prior to the IMCgp100 dose being administered (e.g., cetirizine 10 mg or equivalent). Prophylaxis with corticosteroid can be considered if pruritus recurs at a similar or worse severity despite antihistamine prophylaxis (recommend oral

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Management and Dose Modifications
	prednisone 20–40 mg or a single dose of 25 mg hydrocortisone intravenous or the equivalent). If steroid prophylaxis is used, the steroid dose should be titrated to the minimum effective dose and ultimately discontinued if possible.
Rash/Photosensitivity	
Grade 1	Continue dosing. If symptomatic, consider systemic antihistamine regimen according to management guidance for pruritus (above).
Grade 2	Hold all doses of study IMCgp100 until returned to NCI CTCAE grade ≤1. Use local skin management and systemic antihistamine regimen as indicated for symptoms. With observation of bullous formation or blistering rashes, consider dermatology consultation to rule out other causes (e.g., bullous pemphigoid). Oral or topical corticosteroids can be used for bullous formations or blistering. If bullous formation or blistering recur, consult Sponsor Medical Monitor for guidance. **Antihistamine (anti-pruritic) regimen:** 1. **Systemic antihistamine regimen** recommended as first line management of pruritus. • Non-sedating, long acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (e.g., evening dosing) consider diphenhydramine 25 mg oral or intravenous. The use of sedating anti-histamines should be minimized in patients with co-morbid pulmonary pathology including pulmonary metastases or underlying inflammatory airway disease such as chronic obstructive pulmonary disease or asthma • Use of oral corticosteroid dosing for shorter time frames (e.g., 3 days or fewer) may not require tapering dosing 2. **Topical corticosteroid regimens** Preparation of recommended regimens: • For face and/or intertriginous areas (including genitalia) recommend alclometasone 0.05% or hydrocortisone 2.5% creams • For other body areas (i.e., trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation
Grade 3	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. **Management:** Treat according to institutional practice which generally includes an anti-pruritic regimen (see grade 2 management above). In addition, corticosteroid treatment (oral or topical) can be considered for symptomatic rash that does not respond to anti-pruritic regimen. For topical regimens, refer to grade 2 management above. Oral or topical corticosteroids can be used for bullous formations or blistering. If bullous formation or blistering recur, consult Sponsor Medical Monitor for guidance.

	Dose adjustments: If grade 3 rash observed with IMCg100 resolves to NCI CTCAE grade ≤ 1 within 7 days, restart at the same dose level. If grade 3 rash resolves to NCI CTCAE grade ≤ 1 in 7–21 days, restart with 1 dose-level reduction in IMCgp100[1].
Grade 4	Any grade 4 rash regardless of presentation, permanently discontinue IMCgp100. Manage according to institutional practice, consultation with a dermatologist is recommended.
Hypotension	
Mild, asymptomatic decrease[2]: e.g., < 15 mmHg systolic blood pressure Grade 1	Increase frequency of vital sign assessments to every 2 hours. Consider maintenance intravenous fluids if mild decrease in blood pressure (e.g., systolic blood pressure < 110 mmHg or decrease in SBP of approximately less than 15 mmHg). • Admit for inpatient monitoring (unless already hospitalized per protocol). Consider associated symptoms present and consider diagnosis of cytokine release syndrome (see below) • Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If hypotension does not resolve with intravenous fluid therapy, consider intravenous corticosteroid therapy (e.g., methylprednisolone 2 mg/kg initial dose or equivalent) Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum phosphorus or magnesium electrolyte levels.
Moderate, asymptomatic decrease[2]: e.g., ≥ 15 mmHg, but < 35 mmHg systolic blood pressure Grade 2	Increase frequency of vitals to every 1 to 2 hours, or more frequently as medically necessary. Monitor fluid balance status with careful attention to clinical volume status, as assessed by degree of peripheral edema or rales on pulmonary examination. Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If the patient is asymptomatic and non-orthostatic after infusion of 2-3 L administered over 2–3 hours, consider transition to maintenance intravenous fluids until resolved. If hypotension is not rapidly resolved with intravenous crystalloid therapy, add intravenous corticosteroid therapy of methylprednisolone 2 mg/kg initial dose or equivalent Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels.
Moderate, symptomatic decrease[2]: e.g., ≥ 15 mmHg and orthostasis Grade 3	Increase frequency of vitals to every 1 hour, or more frequently as medically necessary. Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If the patient has symptomatic orthostatic hypotension after infusion of 2–3 L administered over 2–3 hours, consider administration of corticosteroids such as intravenous methylprednisolone 2 mg/kg or equivalent. Initiate vasopressor therapy as required to maintain blood pressure.

	Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. If appropriate, consider additional measures according to the institutional cytokine release protocol (also see management of Infusion-related Reactions below). If resolved within 48 hours of onset, no change in dosing is necessary. If repeat hypotension occurs, consult with the Sponsor Medical Monitor prior to subsequent dosing. Please refer to guidance for continued inpatient monitoring to determine need for continued inpatient monitoring (Section 6.2). Consider the diagnosis of cytokine release syndrome and management (below).
Severe, symptomatic decrease[2]: e.g., ≥ 35 mmHg systolic and symptomatic when supine or mean arterial pressure[3] ≤ 55 mmHg Grade 4	Immediately administer high-dose intravenous corticosteroid therapy of methylprednisolone 2 mg/kg initial dose or equivalent. Maximize vasopressor therapy and fluid management. Administer bolus intravenous fluids (1 L crystalloid as rapidly as feasible) and consider escalation to higher level of care i.e., intensive care unit). Consider maximal immunosuppression with high-dose intravenous corticosteroid therapy and consider additional measures (e.g., anti-IL6, tocilizumab) as required. If appropriate, aggressive fluid therapy as indicated and described above; consider additional measures according to prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. Monitor vital signs every hour until resolved. Consider additional measures according to the institutional cytokine release protocol (also see management of Infusion-related Reactions / Cytokine Release Syndrome below). IMCgp100 must be dose reduced or discontinued. The Sponsor Medical Monitor should be consulted for discussion of individual case management.
Infusion-related Reactions/Anaphylaxis (occurring during infusion)	
Grade 1	Administer medications for symptomatic relief as needed. Infusion interruption may be considered until resolution of the event (up to 4 hours). The infusion rate of the study medication may be decreased by 50%. If resolved with decreased rate of infusion, any subsequent infusions can be administered at the reduced rate.
Grade 2	Stop infusion and keep intravenous line open. Treat according to institutional practice. Provide all supportive measures as indicated. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (e.g., blood pressure, pulse, and temperature) until resolution. Administer medications for symptomatic relief as needed. Antihistamines, acetaminophen (paracetamol), or corticosteroids may be administered, as needed at the discretion of the investigator.

	Restart infusion only once infusion reaction resolves (within 4 hours of initial start of infusion), ensuring there is minimum observation period of one hour from stop of initial infusion to restart at reduced rate. Administer oral pre-medication (e.g., 1000 mg of acetaminophen or paracetamol, 50–100 mg diphenhydramine hydrochloride or alternative antihistamine), 60 minutes prior to restarting the infusion, accounting for prior doses/time given for management of initial reaction. Restart infusion at 50% of previous rate under continuous observation. If the adverse event recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue the patient from study treatment.
Grade 3 or 4	Discontinue infusion immediately, and permanently discontinue patient from study treatment. Grade 3 infusion-related reactions that improve by at least 1 grade within 6 hours of onset with medical management will not require permanent discontinuation. If treatment is continued all guidance provided for the management of grade 2 reactions must be followed. Manage severe infusion-related reactions per institutional standards. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) until resolution.
Infusion-related Reactions/Cytokine Release Syndrome — refer to modified grading system provided in Table 6-4	
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, and malaise) • Admit for inpatient monitoring (unless already hospitalized per protocols) and manage according to individual symptoms. Assess for potential infection and treat fever and neutropenia. Initiate bolus and/or maintenance intravenous fluids and carefully monitor fluid balance • Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels • Vigilantly monitor for escalation to grade 2 cytokine release syndrome with frequent vital signs (e.g., every-hour vital signs). Strongly consider early, high-dose corticosteroid therapy with changes in vital signs (see grade 2 below)
Grade 2	Symptoms are moderate and require medical management. Management as above (grade 1) and include the following measures: • Increase monitoring with continuous cardiac and pulse oximetry monitoring and continue or increase vital sign monitoring (e.g., every hour vital signs) • To manage hypotension, administer bolus intravenous fluids (recommended rate of approximately 1 L per hour). If not rapidly resolved with fluids, high-dose intravenous corticosteroid therapy should be considered, e.g., methylprednisolone 2 mg/kg initial dose (or equivalent) until symptoms (e.g., hypotension) resolve • Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels • Manage respiratory distress and oxygen requirement with supplemental oxygen and additional respiratory support as needed

Grade 3	Symptoms are severe and require enhanced management. Management as above (grade 2) and include the following measures: • Maximize immunosuppression with continued high-dose intravenous corticosteroid (e.g., methylprednisolone 2 mg/kg/day or equivalent). Consider adding further immunosuppression measures or additional interventions according to the institutional cytokine release protocol (e.g., anti-IL6, tocilizumab) • Continue to manage symptoms and vigilantly monitor for escalation Patient may restart IMCgp100 if symptoms resolve and only after discussion and written approval of Sponsor Medical Monitor.
Grade 4	Symptoms are severe and organ toxicity observed. Management as above (grade 3) and include the following measures. • Additional immunosuppression recommended (e.g., anti-IL6, tocilizumab) with continued high-dose intravenous corticosteroid therapy as described above (e.g., methylprednisolone 2 mg/kg/day or equivalent) • If appropriate, consider additional measures according to the institutional cytokine release protocol Permanently discontinue all study medications.
Hepatic Function Abnormalities	
Grade 2	Regular monitoring of liver function tests until improving or resolved. Evaluate concurrent medications for agents that may prolong or exacerbate laboratory abnormalities. Consider intravenous corticosteroid therapy (e.g., hydrocortisone 100 mg or the equivalent) if not improving within 72 hours.
Grade 3	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. Regular monitoring of liver function tests until improving or resolved. Consider intravenous corticosteroid therapy (e.g., hydrocortisone 100 mg or the equivalent). Dosing may resume after discussion with the Sponsor Medical Monitor once all laboratory abnormalities returned to NCI CTCAE grade ≤ 1.
Grade 4	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. Regular monitoring of liver function tests until improving or resolved. Promptly consider intravenous corticosteroid therapy (e.g., hydrocortisone 100 mg or the equivalent) if not resolving within 24 hours. Consider hepatology consult and additional abdominal imaging. Dosing may resume after discussion with the Sponsor Medical Monitor and once all laboratory abnormalities returned to NCI CTCAE grade ≤ 1.
Vomiting	
Grade 2	Anti-emetic therapy as per institutional standard. Intravenous fluid support and other supportive measures for additional adverse events as needed.
Grade 3 or 4	Consider holding all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. Anti-emetic therapy as per institutional standard. Intravenous fluid support and other supportive measures for additional adverse events.

Other Adverse Events
In patients experiencing adverse events (not meeting the specific criteria above) of grade ≥ 3, study drugs should be omitted until resolved to grade ≤ 1, unless discussed and agreed with Sponsor Medical Monitor. Treat according to institutional practice and for immune-related adverse event of grade ≥ 3, treatment with corticosteroids should be considered. Consult Sponsor Medical Monitor for further guidance as needed.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

1. Dose reductions of IMCgp100 for toxicity is as follows: from a starting dose IMCgp100 dose of 68 mcg, the dose will be reduced to 54 mcg for any toxicity requiring dose reduction. The dose may be reduced further to 50 mcg for recurrent toxicity. Patients who require more than 2 dose reductions of IMCgp100 should discontinue treatment. All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it may be increased to the initial dose level if there is no recurrence of toxicity with subsequent doses of IMCgp100.

2. The absolute systolic blood pressure change is provided as guidance for management, and must be interpreted in the clinical context of the patient. Patients with baseline hypertension may not require intervention for mild or moderate decreases in systolic blood pressure.

3. Mean arterial pressure = 1/3 (systolic blood pressure – diastolic blood pressure) + diastolic blood pressure.

6.10 Treatment Discontinuation

Reasons for discontinuation of study treatment will include:

- Unequivocal, confirmed disease progression referring to the modified irRECIST criteria (Wolchok, 2009; Nishino, 2013; Bohnsack, 2014; refer to Section 6.10.1 and Appendix 1)
- Initiation of alternative anti-cancer therapy including another investigational agent
- Unacceptable toxicity defined as an AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing
- Withdrawal of consent from further treatment with investigational product by the patient or the investigator or lost to follow-up
- Patient is determined to have met 1 or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation AND continuing to receive investigational product might constitute a safety risk. Patients who fall into this category and for whom continuation of treatment is not thought to pose a safety risk in the opinion of the investigator may continue to receive study treatment after discussion with the Sponsor Medical Monitor
- Pregnancy or intent to become pregnant

At the time patients discontinue study treatment, the EOT visit should be scheduled as soon as possible and in the appropriate window of 14 days after the last dose was administered. At this visit, all of the assessments listed for the EOT visit will be performed (see Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit (safety follow-up will still continue for the full 90-day observation period, see Section 7.2 for details of assessments required at EOT). An End of Treatment Phase Disposition eCRF page should be completed at the EOT visit, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of the study. Patients should still be followed for survival information and, if the patient does not have PD, imaging data should continue to be collected to capture progression based on RECISTv.1.1.

Patients who discontinue study treatment should NOT be considered withdrawn from the study as they will be followed for the OS endpoint. They should return for the assessments indicated in Section 7 and Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, email, and registered letter) should be made to contact them. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Disposition eCRF page.

6.10.1 Criteria for Treatment Beyond Initial RECIST v.1.1 Disease Progression

For patients in the study, if PD based on RECIST v.1.1 occurs, and the patient does NOT have clinical symptomatic progression that would require a change in therapy to adequately manage symptoms, the patient will be considered to continue in disease control (immune-related stable disease) and may consent to continue to be treated according to the protocol-specified regimens until 1 of the following criteria is met:

1. Unequivocal, confirmed irPD based on modified irRECIST (guidelines based on Wolchok, 2009; Nishino, 2013, Bohnsack, 2014): An initial assessment of PD by RECIST v.1.1 (initial PD assessment) will be confirmed with a repeat radiologic evaluation performed at least 4 weeks later as scheduled per protocol. For patients who continue IMCgp100 therapy beyond initial PD per RECISTv1.1, unequivocal, confirmed irPD is defined as an additional 20% increase or greater in tumor burden (sum of diameters of both target and measurable new lesions) or unequivocal progression of NTLs and/or new non-measurable disease from the initial PD assessment per RECISTv1.1

2. Meets any of the investigational product discontinuation criteria (Section 6.10)

3. Clinical symptoms or signs indicating clinically significant PD (not meeting radiologic PD) such as the benefit-risk ratio of continuing therapy is no longer justified

4. Rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention

Patients continuing treatment beyond the protocol-specified RECIST v.1.1 progression will continue to follow the treatment regimen of QW IMCgp100. Imaging data will continue to be collected until confirmed immune-related progression (irPD) based on modified irRECIST.

6.11 Study Discontinuation

Reasons for individual patients discontinuing from study include:

- Patient dies
- Patient is lost to follow-up
- Patient withdraws consent for any further participation including further survival follow-up

- The end of study is reached (please refer to Section 3.5 and Section 3.6)

7 STUDY SCHEDULE AND ASSESSMENTS

7.1 Screening Procedures and Assessments

All of the assessments required as part of the study are indicated in Table 7-1 organized by visit date, with assessments required indicated with an "X" at the specific visits when they should be performed. All assessments listed as "Screening" must be performed within 21 days before C1D1. The only exception to the Screening Period of 21 days are the baseline radiological evaluations which must be performed within 28 days of the screening visit. Assessments required on C1D1 that are performed as part of the screening evaluations and within 72 hours prior to the first dose of study treatment, do not need to be repeated on C1D1. Laboratory assessments required on subsequent dosing days may be performed 1 day prior to IMCgp100 administration. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening time window (21 days for laboratory assessments and 28 days for radiological assessments).

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of ± 7 days is allowed unless otherwise indicated in the protocol. If the study drug infusions are delayed, the assessments will be moved with the delayed study drug infusions. The only exception to moving study assessments with treatment are the radiological assessments, which must be performed ± 7 days of the scheduled date of the assessment (unless otherwise indicated in the protocol). The protocol specified radiologic assessments should be performed as scheduled every 8 or 12 weeks as indicated in the protocol, using as reference to C1D1 and should not follow delays incurred in the treatment period. Radiologic assessments should not move if delays in treatment are incurred.

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase																Follow-up Phase		
Procedure	Protocol Section	Screening	Cycle 1							Cycle 2				Cycle 3[a]				Later Cycles[a]	EOT	90-day Safety Follow Up	Disease Progression Follow Up	Survival Follow Up[b]
Day of Cycle		-21 to -1	1	2	8	9	15	16	22	1	8	15	22	1	8	15	22	1-28				
Informed consent	7.1.1	X																				
Demography	7.1.1.2	X																				
Inclusion/exclusion criteria	5.2 / 5.3	X																				
Medical history	7.1.1.2	X																				
Diagnosis and extent of cancer	7.1.1.2	X																				
Prior anti-cancer therapy	6.5	X																				
Prior/concomitant medications	6.5	X	Continuously assessed																			
Physical examination[c]	7.3.3	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X			
Height	7.3.5	X																				
Weight	7.3.5	X	X							X				X				X	X			
Vital signs[d]	7.3.4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG performance status[e]	7.3.6	X	X											X				X	X			
Hematology panel[f]	7.3.7.1	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Chemistry panel[g]	7.3.7.2	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Inflammatory Analytes[h]	7.3.7.3		X	X	X	X	X	X														
Coagulation	7.3.7.4	X																	X			
Urinalysis	7.3.7.5	X																	X			

		Screening Phase	Treatment Phase																Follow-up Phase		
Procedure	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**				**Cycle 3[a]**				**Later Cycles[a]**	**EOT**	**90-day Safety Follow Up**	**Disease Progression Follow Up**	**Survival Follow Up[b]**
Day of Cycle		**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1-28**				
Thyroid function	7.3.7.6	X	X							X				X					X			
[redacted]	[redacted]		[redacted]																			
Skin punch biopsy (optional)[j]	7.3.7.10		In case of increased skin toxicity in any patient at C1D15 or thereafter (optional)																			
Pregnancy test[k]	7.3.7.8	X								X				X				X	X			
Anti-neoplastic therapies since discontinuation of study treatment	7.2.4																			X	X	X
[redacted]	[redacted]	[redacted]	[redacted]																			
Tumor evaluation as per RECIST v.1.1 and as per irRECIST[m]	7.3.1 Table 7-2	X	Every 8 weeks from C1D1 to C11D1 (40 weeks), then every 12 weeks until confirmed PD per RECISTv1.1. Note, for patients who continue treatment beyond progression per RECISTv.1.1, imaging should continue while on treatment until disease progression per modified irRECIST. At EOT, if a scan was not conducted within 30 days prior to EOT. Note, if a patient discontinues treatment, but remains in Disease Progression Follow Up, then imaging visits should continue as per the original study plan and will not be needed at the EOT visit.																		
12-lead ECG	7.3.7.9 Table 7-6	X	Refer to ECG schedule Table 7-6																			
Adverse events	8		Continuously assessed																			
[redacted]																						

		Screening Phase	Treatment Phase															Follow-up Phase		
Procedure	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**				**Cycle 3[a]**				**Later Cycles[a]**	**EOT**	**90-day Safety Follow Up**	**Disease Progression Follow Up**	**Survival Follow Up[b]**
Day of Cycle		**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1-28**				
IMCgp100 administration[q]	6.1.1		IMCgp100 given intravenously **every week with C1D15 intra-patient escalation**																			
PK sampling[r]	7.3.8 Table 7-7		PK sampling to be scheduled according to Table 7-7																			
Immunogenicity sampling[r]	7.3.8 Table 7-7		See Table 7-7 for immunogenicity sampling timing																			
HLA-A2 determination[s]	7.1.1.3	X																				
[redacted]	[redacted]		[redacted]																		[redacted]	[redacted]
Survival contact for follow-up	7.2.5																					X

C#D# = Cycle # Day #; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HLA-A2 = human leukocyte antigen-A2; IFN-γ = interferon gamma; IL-6 = interleukin-6; irRECIST = immune-related response criteria; PD = progressive disease; PK = pharmacokinetic; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors.

FOOTNOTES:

a Cycles 4 and greater will follow the same schedule of assessments as outlined for Cycle 3 with exception of tumor imaging which will follow the noted schedule and PK and pharmacodynamic assessments which will follow the schedules in Table 7-7 and Table 7-8, respectively.

b Patients might be contacted earlier than the 3 month time point for survival follow-up during the interim and final analysis

c Physical Examination should be done prior to administration of IMCgp100 and from C1D8 onwards, a short physical examination will be performed

d Overnight inpatient hospitalization and frequent vital signs (minimum of pre-dose and Q4 hours vital signs) are required at C1D1, C1D8, and C1D15. Inpatient monitoring at C1D22 will be determined based on the toxicity profile in the individual patient at C1D15. Patients experiencing a grade 2 or greater hypotension event at C1D15 must be observed as an inpatient for the subsequent C1D22 dose. Patients experiencing a grade 3 or 4 hypotension event during the inpatient monitoring at C1D1, C1D8, or C1D15 will require additional monitoring for any doses administered as an outpatient through C2D15. If patients have experienced grade 3 or 4 hypotension at any of these doses, then outpatient monitoring through C2D15 must be for a minimum of 8 hours after the IMCgp100 dose with vital signs monitored every hour. Please refer to Section 6.2 weekly and Section 7.3.4 for details of overnight hospitalizations and vital signs monitoring.

e ECOG Performance Status will be determined on Day 1 of every odd-numbered cycle and at EOT.

f Hematology panel should be obtained at Screening and before every dose of IMCgp100. In addition, the hematology panel is obtained the day following the first and third doses, on C1D2 and C1D16. Hematology panel is performed at EOT visit as well.

g Chemistry panel should be obtained at Screening and before every dose of IMCgp100 and at EOT.

[redacted]

j Skin punch biopsy should be obtained in patients with worsened rash on C1D15 or beyond as compared to the rash experienced on IMCgp100 dosing days on C1D1 or C1D8. This skin biopsy is optional.

k Pregnancy testing is required only in all females with childbearing potential. At Screening, a serum pregnancy test must be performed within 72 hours before the first dose. During the study (Day 1 of each cycle starting with Cycle 2) a serum or urine pregnancy test must be performed. At EOT, a serum or urine pregnancy test must also be performed.

[redacted]

m Radiologic assessments should be performed as scheduled every 8 weeks from C1D1 to Week 40 (C11D1), then every 12 weeks until confirmed PD per RECISTv.1.1 (See Table 7-2), using as reference to C1D1 and should NOT follow delays incurred in the treatment period. Radiologic assessments at each timepoint are listed in Table 7-2. Partial response, minor response, and complete response, per both RECIST v.1.1 and modified irRECIST, should be confirmed by a new assessment after at least 4 weeks.

n Dose escalation cohorts: Submission of an archival tumor sample from each patient is required. In the absence of an archival tumor biopsy, a newly obtained tumor biopsy can be obtained. If the new tumor biopsy cannot be obtained or is not medically feasible this should be discussed with the Sponsor Medical Monitor prior to enrollment. Dose expansion cohorts: Submission of an archival tumor sample is requested, if available.

o **Dose escalation cohorts:** Collection of a tumor sample at Screening is mandatory, unless the tissue sample can be obtained from an archival tumor sample (see Table 7-8). On-treatment C1D2 and/or C1D16 biopsy is **optional** in all dose escalation cohorts. **Dose expansion cohorts:** Fresh tumor biopsy at Screening is MANDATORY. If the new tumor biopsy is not medically feasible, this must be discussed with the Sponsor Medical Monitor prior to enrollment. One on-treatment biopsy is mandatory in the expansion cohorts unless medically not feasible. See Section 7.4.3. Only non-significant risk procedures should be performed for accessing tumor tissue in patients enrolled in the trial.

p A biopsy obtained at the time of disease progression in the setting of treatment resistance is **optional** in the EOT or follow-up period for both the dose escalation and dose expansion cohorts.

q Please refer to Section 6.1 Study Treatment for details of **weekly** IMCgp100 administration and **intra-patient dose escalation regimen (at C1D15; Section 6.2)** used in this study.

t PK sampling should follow the PK and immunogenicity sampling table (Table 7-7).

s For all patients, HLA-A2 status will be determined via central assay during Pre-screening. Patients should not sign the Main Study ICF and enter Screening until the result of the central assay in Pre-Screening is known as HLA-A*0201 positive. Patients who re-screen for the trial need not return to the pre-screen period once HLA results are known.

[redacted]

7.1.1 Screening Assessments

The study IRB/IEC-approved ICF must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations performed as part of standard of care within the screening window (28 days for radiological assessments, 21 days for all other assessments).

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments required at Baseline will be performed. For details of all screening assessments, refer to Table 7-1. Screening assessments must be repeated if performed outside of the specified screening window. Patients may re-screen after abnormal labs or symptoms are corrected or treated after consultation with the Sponsor.

Radiologic assessments required at screening include CT or MRI of the chest, abdomen, and pelvis. Brain MRI is required at Screening only if there is clinical suspicion of brain metastasis at Screening.

7.1.1.1 Information to be Collected on Screening Failures

A patient who signed the Main Study ICF, but failed to be started on treatment for any reason will be considered a screen failure. If patients are found not eligible after signing the main study consent, the patients will be considered as screening failures, and data will be handled in the same manner.

The demographic information, informed consent, and screening pages (with reason for screen fail) must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during Screening, which would be reported in the usual manner via eCRF AE page (See Section 8.4).

7.1.1.2 Patient Demographics and Other Baseline Characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of cancer, details of prior anti-cancer treatments, prior/concomitant medications, prior procedures, significant non-drug therapies and any other assessments that are done for determining eligibility for inclusion in the study. Prior anti-neoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Anti-neoplastic Therapy eCRF during Screening.

7.1.1.3 HLA-A2 Status Determination

For all patients, HLA-A2 status will be determined during Pre-screening by central assay. Patients should not sign the Main Study ICF and enter Screening until the results of the central assay in Pre-screening is known as HLA-A*0201 positive. Patients who are known to be HLA-A*0201 positive from a prior assessment may complete the pre-screening and screening in parallel. A Pre-screening HLA sample should still be submitted for central analysis of HLA. Patients who re-screen for the trial need not return to the pre-screen period once HLA results are known.

7.2 Treatment, Treatment Discontinuation and Follow-up Phases

7.2.1 Treatment Period

For the purposes of scheduling procedures and evaluations, a treatment cycle is defined as 4 weeks (28 days). Please refer to Table 7-1 for details of the timing of required assessments and visit windows. Patients will be treated until they experience unacceptable toxicity, PD per modified irRECIST and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 6.10.1.

Patients who have disease progression per RECIST v.1.1, but have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment after discussion with the Sponsor. Patients who consent to continue treatment after RECIST v.1.1 disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the investigator and as per guidance in Section 6.10.1.

Patient reported outcomes (PRO) will be assessed before dosing on C1D1 and then throughout the treatment period using (1) the general health status EQ-5D, 5L questionnaires, and (2) the HRQoL instrument EORTC QLQ-C30. Details of PRO assessments are provided in Section 7.3.9.

7.2.2 Discontinuation of Study Treatment and End of Treatment Visit

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make every effort to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. Other reasons for discontinuation of study treatment are outlined in Section 6.10.

Patients will be considered withdrawn from therapy if they state an intention to withdraw, and fail to return for visits or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, and within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of the study.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7 and Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, email, postal letter) should be made to contact them. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study

assessments. At that time, the reason for study completion should be recorded on the Study Disposition eCRF page.

7.2.3 90-day Safety Follow-up Period

All patients must have safety evaluations 90 days after the last dose of study treatment. Information related to all AEs (including concomitant medication taken for on-going AEs) will be collected for 90 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly or as clinically indicated until resolution or stabilization.

Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

7.2.4 Disease Progression Follow-up Period

Patients who discontinue study treatment for any reason other than death, disease progression per RECIST v.1.1 , lost to follow-up, withdrawal of consent, or study termination, should return for tumor evaluation assessments every 8 weeks until 40 weeks, and then every 12 weeks until progression of disease per RECIST v.1.1.

- All patients who discontinue treatment for reasons other than PD per RECISTv1.1 will be followed with imaging until evidence of PD per RECISTv1.1 .
- For patients who consent to and continue treatment beyond progression per RECISTv1.1, imaging should continue until progression per modified irRECIST (irPD) or treatment discontinuation.
- If patients choose not to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient has had disease progression.
- Patients who discontinue treatment for reasons of disease progression by either RECISTv1.1 or modified irRECIST criteria will not enter the Disease Progression Follow-up Period.
- Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

See Table 7-2 for additional details on Disease Assessment Collection Plan.

7.2.5 Survival Follow-up Period

Upon completion of the 90-day safety follow up or disease progression follow up, patients will be followed for survival every 12 weeks (can be done by telephone call) until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up.

Anti-neoplastic therapies since discontinuation of study drug will be collected during the Survival Follow-up period.

For the Phase 2 expansion cohorts, survival calls will be made in the 2 weeks following the date of the data cut-off for any OS reporting. Thus, patients may be contacted more frequently than every 12 weeks at this time. If patients are confirmed to be alive, or if the death date is post the data cut-off date, these patients will be censored at the date of the data cut off in the OS reporting. Death dates may be found by checking publicly available death registries in line with local laws and regulations.

7.2.6 Lost to Follow Up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family, or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc, a patient should not be considered lost to follow up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Patient Disposition eCRF.

7.3 Details of All Assessment Types

7.3.1 Efficacy Assessments

Radiologic assessments should be performed as scheduled every 8 or 12 weeks as indicated in this section (See Table 7-2 below), using a reference to C1D1 and should NOT follow delays incurred in the treatment period.

Tumor response will be determined according to 2 sets of criteria:

1. RECIST v.1.1 (Appendix 1)
2. Modified irRECIST for patients who continue treatment beyond RECISTv.1.1 disease progression (Appendix 2)

For the Phase 1 cohort, the local investigator's assessment will be used for the analysis of response according to RECIST v.1.1 and modified irRECIST for efficacy endpoints of the study, and for treatment decision making (study discontinuation due to PD as per RECISTv.1.1/modified irRECIST).

Independent Central Review: An ICR will be used for the analysis of ORR and all other tumor related endpoints based on RECIST v.1.1 and modified irRECIST for the Phase 2 cohorts. ICR of the Phase 1 cohort may be done on an exploratory basis for patients who have consented to central reading.

PFS will be assessed using RECIST v.1.1. Patients experiencing PD per RECIST v.1.1 criteria may consent to continue to be treated according to irRECIST guidelines until confirmed, unequivocal progression (irPD) is documented via modified irRECIST. Progression based on modified irRECIST will be assessed as an exploratory endpoint.

Investigator assessment data will be used for treatment decision making during the study.

Assessments schedule: At Screening, all patients will undergo CT or MRI with IV contrast of the chest, abdomen, and pelvis. CT imaging is preferred and MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CT may be performed without contrast. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to

measure sites of disease. For a given target lesion, the same imaging modality should be used throughout the study (CT or MRI). See Table 7-2 for further details.

Tumor assessments will be performed at the following time points:

- Screening
- Every 8 weeks ± 1 week from C1D1 to 40 weeks (C11D1), then every 12 weeks (3 cycles) until PD per RECIST v.1.1 or discontinuation of study treatment. Note: For patients who continue treatment beyond progression per RECISTv.1.1, imaging should continue until disease progression per modified irRECIST.
- Partial response, minor response (MinR), or complete response (CR), per both RECIST v.1.1 and modified irRECIST, should be confirmed by a new assessment after at least 4 weeks. For patients who continue treatment beyond progression by RECISTv1.1, PD per modified irRECIST (irPD) should be confirmed after at least 4 weeks from PD by RECISTv.1.1. Further confirmation of irPD after its initial occurrence is not required but may be done at Investigator discretion.
- At EOT, if a scan was not conducted within 30 days prior to EOT. Note, if a patient discontinues treatment, but remains in Disease Progression Follow Up, then imaging visits should continue as per the original study plan and schedule and will not be needed at the EOT visit.

Disease progression follow-up should be performed as described in Section 7.2.4.

Table 7-2 Disease Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow Up
CT or MRI with contrast enhancement (chest, abdomen, pelvis)	Mandatory	Mandatory, every 8 weeks from C1D1 until C11D1 (40 weeks), then every 12 weeks until progressive disease per RECISTv1.1, irPD per modified irRECIST for patients who continue treatment beyond PD per RECISTv1.1 or discontinuation of study treatment The same imaging modality should be used throughout the study (CT or MRI) At EOT, if a scan was not conducted within 30 days prior to EOT. Note, if a patient discontinues treatment, but remains in Disease Progression Follow Up, then imaging visits should continue as per the original study plan/schedule and will not be needed at the EOT visit
Brain MRI with contrast	Required only if clinical suspicion of brain metastasis at Screening	If disease was detected at Baseline, or if clinically indicated

C#D# = Cycle # Day #; CT = computed tomography scan; EOT = end of treatment; MRI = magnetic resonance imaging; RECISTv1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

7.3.1.1 Independent Central Review

All on-study images acquired for tumor and treatment effect assessments will be submitted to an imaging contract research organization (CRO) for further blinded, independent, central review for analysis. A central imaging manual will be provided to all investigative sites detailing the procedures for de-identification and submission of imaging studies for central review. For endpoints assessed by ICR, review of all radiological imaging data will be carried out. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows), will be provided to the ICR. Further details of the ICR procedures and processes will be included in the study imaging manuals.

All patient management decisions will be based upon local assessment of imaging studies at the site and not on the ICR.

7.3.2 Safety and Tolerability Assessments

Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing. AE are collected at every visit. For details on AE collection and reporting, refer to Section 8.

7.3.3 Physical Examination

Physical examination will be performed according to Table 7-1.

At Screening and C1D1, prior to IMCgp100 infusion, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From C1D8 onwards, a short physical examination will be performed prior to IMCgp100 infusion. A short physical exam will include the examination of general appearance, vital signs (temperature, blood pressure, respiratory rate and pulse) and body sites as directed by symptoms.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the AE eCRF page.

7.3.4 Vital Signs

Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) must be performed before dosing and after the IMCgp100 administration as indicated in Table 7-1 and Table 7-3, and as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator if medically indicated, and will be recorded as unscheduled assessments.

See Section 6.2 for additional details on intra-patient dose escalation regimen.

Table 7-3 Post Dose Vital Signs Monitoring

C1D1, C1D8, C1D15 *Inpatient monitoring required for all patients*	Vital signs monitored per institutional standards at a minimum of every 4 hours. Patients should be monitored for at least 16 hours after dosing. • *Patients experiencing Grade 2 or greater hypotension at C1D15 require inpatient monitoring for the subsequent/next C1D22 dose.* • *Those experiencing Grade 3 or 4 hypotension at C1D1, C1D8 or C1D15 require **hourly** VS monitoring for minimum of 8 hours after dosing for any doses administered as outpatient through C2D15.*
C1D22 *Inpatient monitoring required for exception noted*	Patients experiencing a grade 2 or greater hypotension at C1D15 must be observed as an inpatient for C1D22 dose, with VS performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.
C1D22 through C2D15 *Monitoring requirements for exceptions noted*	Patients experiencing Grade 3 or 4 hypotension at C1D1, C1D8 or C1D15 require **hourly** VS monitoring for minimum of 8 hours after dosing for any doses administered as outpatient through C2D15. • *If patient experienced ≥ Grade 2 hypotension at C1D15, they must be monitored as inpatient for C1D22, as noted above.*
C2 and later cycles- Days 1, 8, 15 and 22 *Outpatient monitoring*	For patients without Grade 2 or greater hypotension at C1D15 or Grade 3 or 4 hypotension at C1D1, C1D8 or C1D15, outpatient VS must be monitored in clinic for minimum of one hour after infusion with at least 2 post-dose VS measurements performed. For patients who have received outpatient treatment with IMCgp100 for at least 3 months, outpatient monitoring in clinic may be decreased to minimum of 30 minutes post dosing after discussion with Sponsor Medical Monitor.
Treatment breaks/delays	Patients with break or delay in treatment for >2 weeks AND with history of a grade 3 or 4 hypotension with IMCgp100 dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to/following the break in dosing, with VS performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.

7.3.5 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

7.3.6 Eastern Cooperative Oncology Group Performance Status

Performance status is determined as indicated in Table 7-4 and should be determined on Day 1 of all odd-numbered cycles (e.g., C1D1, C3D1, C5D1, etc) and at EOT.

Table 7-4 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

ECOG = Eastern Cooperative Oncology Group.

7.3.7 Laboratory Evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-5 for a summary of the parameters to be evaluated according to Table 7-1. On dosing days of IMCgp100, samples for these parameters will be collected prior to the infusion of IMCgp100, and may be collected 1 day prior to dosing.

More frequent evaluations may be performed at the investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

Immunocore or the designated CRO will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Immunocore or the CRO must be provided with a copy of the certification and a tabulation of the normal ranges for that laborator

Table 7-5 Local Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, calcium, chloride, creatinine, glucose magnesium, phosphate, potassium, sodium, total bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), blood urea nitrogen or urea, amylase, lipase, lactate dehydrogenase.
Inflammatory Analytes	C-reactive protein (CRP) and lactate dehydrogenase (LDH).
Coagulation	Prothrombin time or international normalized ratio, activated partial thromboplastin time
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood glucose, ketones, pH, protein, specific gravity, white blood cells)
Thyroid	Free T4, thyroid stimulating hormone
[redacted]	[redacted]

7.3.7.1 Hematology

Hematology panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1.

7.3.7.2 Clinical Chemistry

Clinical chemistry panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1. Note: Serum calcium is measured and recorded in the eCRF. For purposes of eligibility assessment and AE grading, calcium should be corrected for abnormal albumin measurements.

7.3.7.3 [redacted]

[redacted].

7.3.7.4 Coagulation

Coagulation panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1.

7.3.7.5 Urinalysis

Urinalysis panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1.

7.3.7.6 Thyroid Function

Thyroid function panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1.

7.3.7.7 [redacted]

[redacted]

- Within 5 hours after the occurrence of the AE
- 1 week after the occurrence of the AE

7.3.7.8 Pregnancy and Assessment of Fertility

Pregnancy tests will be performed for women of child bearing potential.

At Screening, a serum pregnancy test must be performed within 72 hours before the first dose. During the study (Day 1 of each cycle starting with Cycle 2 and prior to study drug dosing) a serum or urine pregnancy test must be performed. At EOT, a serum or urine pregnancy test must also be performed.

7.3.7.9 Cardiac Assessments

A standard 12-lead ECG will be performed as per the assessment schedule in Table 7-1 and Table 7-6. Blood samples scheduled at the same time point should be taken after the ECGs are completed.

Clinically significant abnormalities present at Screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF page.

Table 7-6 12-lead Electrocardiogram Collection Plan‡

Cycle	Day	Time
Screening	-21 to -1	Anytime
1	1	Pre-dose
1	1	1 hour post dose**
2	1	Pre-dose
2	1	1 hour post dose
3	1	Pre-dose
3	1	1 hour post dose
5	1	Pre-dose
5	1	1 hour post dose
EOT	-	Anytime
Unscheduled*	-	As clinically indicated based on symptoms and/or exam

EOT = end of treatment; RP2D-IE = recommended Phase 2 dose — intra-patient escalation.
‡ During the RP2D-IE expansion cohorts, electrocardiogram assessments will be performed during Screening, Cycle 1 pre- and post-dose, Cycle 2 pre- and post-dose, Cycle 3 pre- and post-dose, Cycle 5 pre- and post-dose, and at EOT.
* An unscheduled pharmacokinetic sample should be collected just after an electrocardiogram is performed due to any unexpected cardiac signal.
**ECG should be collected between the end of infusion and 1 hour post dose.
NOTE: When ECGs are scheduled at the same time as blood draws, the ECG should be done prior to the blood draw.

7.3.7.10 Skin Punch Biopsy

An OPTIONAL skin punch biopsy is to be taken in patients experiencing a ≥ grade 3 rash, bullous rash of any grade, or worsened rash on C1D15 or beyond. Rash that worsens is defined as increase in grade or increased symptoms associated with the rash (e.g., pruritus) compared to skin toxicity observed on IMCgp100 dosing days, C1D1 or C1D8. Skin biopsies will be assessed for immune infiltrate characteristics, gp100 expression, and other markers of immune activation (e.g., HLA-DR, PD-L1) to determine the immune activation status in the skin and potentially the mechanisms of skin toxicity.

7.3.8 Pharmacokinetics and Immunogenicity Assessments

The PK and Immunogenicity blood samples should be taken according to Table 7-7. Details are also described in the laboratory manual for the handling, labelling and shipment of the PK and Immunogenicity blood samples. It is essential that the actual time and date of collection of each blood sample be recorded on the patient's eCRF.

All PK samples have a collection window of ± 1 hour, with the exception of the post-infusion time point which should be collected after the infusion completes and within 15 minutes of the completion time of the IMCgp100. PK samples on C1D2 and Cycle 1 Day 16 (C1D16) at the last post-infusion time point should be collected anytime in the 12- to 24-hour window after the completion of the IMCgp100 infusion. The time that the sample was collected must be reported with the sample.

Blood samples for the determination of IMCgp100 concentration time profiles in serum will be obtained throughout the study. The volume of blood to be collected per sample should be 2 mL to provide approximately 1 mL of serum split into 2 aliquots of 0.5 mL each.

Blood samples to look for the formation of any IMCgp100 anti-drug antibodies will be obtained throughout the study.

Table 7-7 Pharmacokinetic Assessments

Day of Treatment	Pharmacokinetic Sample Timing Dose Escalation	Pharmacokinetic Sample Timing RP2D-IE	Immunoglobulin Sample Timing
C1D1	Pre-dose	Pre-dose	Pre-dose^
C1D1	End of infusion	End of infusion	
C1D1	4-hour post-dose	4-hour post-dose	
C1D1	8-hour post-dose^^		
C1D2	12- to 24-hour post-dose^^	12- to 24-hour post-dose^^	
C1D8	Pre-dose	Pre-dose	Pre-dose^
C1D8	End of infusion	End of infusion	
C1D15	Pre-dose	Pre-dose	
C1D15	End of infusion	End of infusion	
C1D15	4-hour post-dose	4-hour post-dose	
C1D15	8-hour post-dose^^		
C1D16	12- to 24-hour post-dose^^	12- to 24-hour post-dose^^	
C1D22	Pre-dose		
C1D22	End of infusion		
C2D1	Pre-dose	Pre-dose	Pre-dose^
C2D1	End of infusion	End of infusion	
C2D15	Pre-dose		
C2D15	End of infusion		
C3D1	Pre-dose	Pre-dose	Pre-dose^
C3D1	End of infusion	End of infusion	
C3D15	Pre-dose		
C3D15	End of infusion		
CXD1*	Pre-dose	Pre-dose	Pre-dose^
CXD1*	End of infusion	End of infusion	
EOT		At visit^	At visit^

C#D# = Cycle#Day#; EOT = end of treatment; RP2D-IE = recommended Phase 2 dose — intra-patient escalation.

All PK samples have a window of ± 1 hour, with exception of the end of infusion time point which should be collected 15 minutes after the completion of the IMCgp100 infusion.

* "CX" will refer to Cycle 6 and then every 3rd cycle (e.g., C9, C12, etc.).

^ Immunoglobulin samples will be taken pre-dose at C1D1, C1D8, C2D1, C3D1 and then every 3rd cycle starting at C6 ("CX"), at the End of Treatment Visit.

^^ Pharmacokinetic sample should be obtained in the timeframe just prior to discharge. The time of sample must be recorded in the eCRF.

7.3.9 [redacted]

[redacted]

[redacted]

7.4 [redacted]

7.4.1 [redacted]

[redacted]

[redacted]

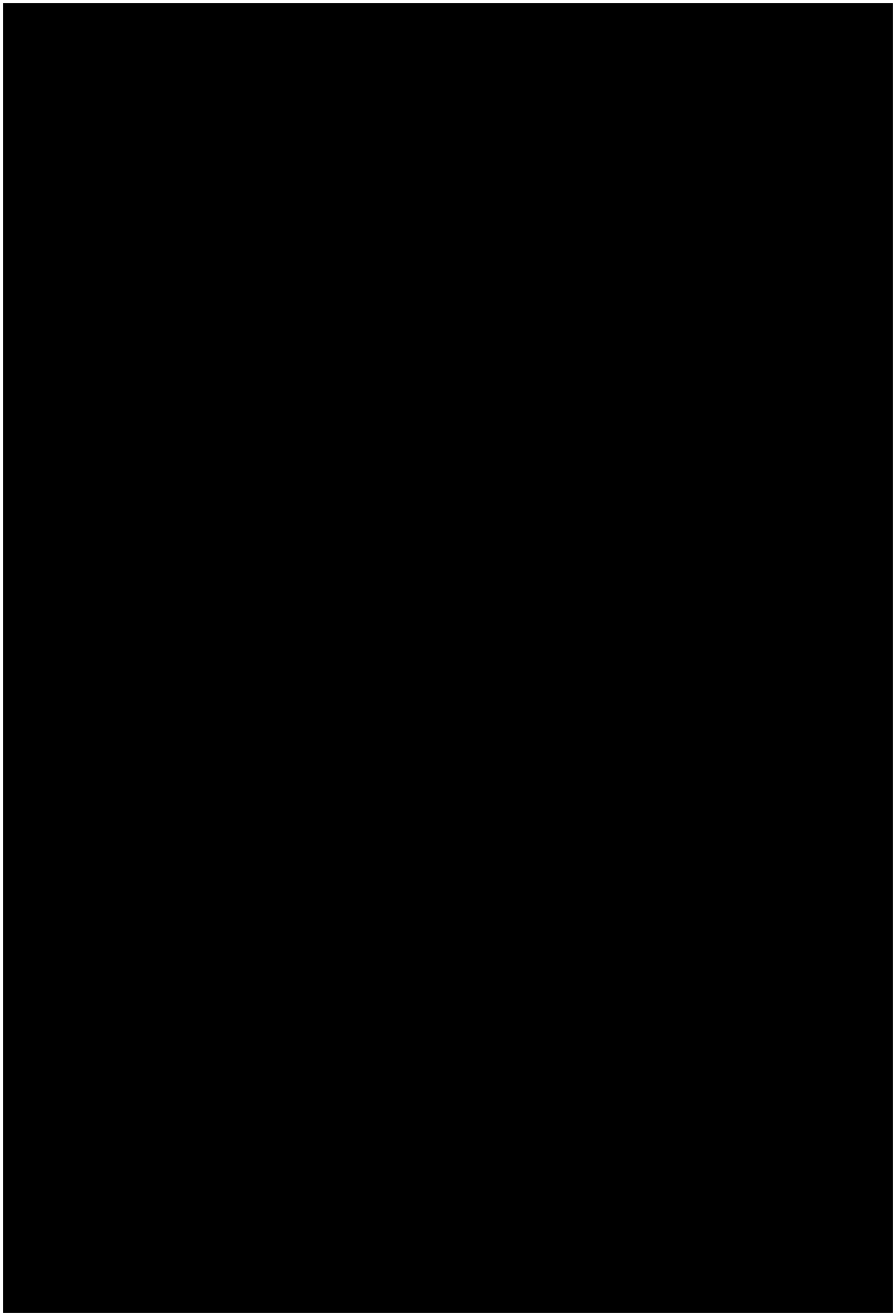
[redacted]

[redacted]

7.4.2 [redacted]

[redacted]

[redacted]



[redacted]

7.4.3 [redacted]

[redacted]

[redacted]

7.4.3.4 [redacted]

[redacted]

8 ADVERSE EVENTS AND SAFETY REPORTING

8.1 Assessment of Safety

All patients who receive any treatment with IMCgp100 will be considered evaluable for safety. All AE regardless of study drug relationship will be collected up to the 90-day follow-up.

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and is mandated by regulatory agencies worldwide. The Sponsor and CRO have established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Individual AEs should be evaluated by the investigator and should be reported to the CRO/Sponsor for evaluation. This includes the evaluation of the event's seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the AE. The CRO/Sponsor is required to maintain detailed records of all AEs reported by the investigator(s) and to perform an evaluation with respect to seriousness, causality, and expectedness. On request of a competent authority in whose territory the clinical trial is being conducted, the sponsor should submit detailed records of all AEs which are reported to him by the relevant investigators. Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

8.1.1 Definitions

Definitions of AEs, adverse drug reactions, SAEs and unexpected adverse drug reactions and AEs of special interest are presented below.

AE: An AE is defined as the appearance of (or worsening of pre-existing) an undesirable sign, symptom, or medical condition that occurs after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication.

Adverse drug reaction: is an unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug. Adverse drug reactions have traditionally been categorized as pharmacologic (predicted based on the pharmacology of the drug) or idiosyncratic (not predicted based on pharmacology).

SAE: A SAE is any AE that is defined as 1 of the following:

1. Is fatal or life-threatening
2. Results in persistent or significant disability or incapacity
3. Constitutes a congenital anomaly/birth defect
4. Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed above

5. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
6. Death due to the progression of malignancy should not be reported as a SAE, if documented by use of appropriate method (e.g., as per RECIST v.1.1). Any AE that occurred as a result of the PD should be reported in the appropriate manner

Unexpected adverse drug reaction: An adverse drug reaction that is not consistent with applicable product information or characteristics of the study drug.

Suspected, unexpected, serious adverse reaction (SUSAR): A SUSAR is an adverse reaction meeting serious criteria (above), the nature or severity of which is not consistent with the reference safety information for the investigational drug(s).

Adverse events of special interest (AESI): An AESI (serious or non-serious) is an AE with scientific and/or medical concern specific to the Sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Refer to the IMCgp100 Investigator's Brochures for details of the AESI.

8.2 Criteria for Expectedness

The concept of expectedness refers to events that may or may not have previously been observed and documented and not necessarily the known pharmacological properties of the medicine. An AE will be unexpected for purposes of regulatory reporting unless it is mentioned in the appropriate reference safety information within the current Investigator's Brochure for the investigational drug, even if it is a medical occurrence expected for the disease being treated.

8.3 Assessment of Causality

8.3.1 Causality Assessment Required for all Adverse Events

The investigator decides whether he or she interprets the observed AE as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terms are defined:

1. **Related**: a direct cause and effect relationship between the study treatment and the AE is likely
2. **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible

3. **Unrelated**: without question, the AE is definitely not associated with the study treatment

All “related” and “possibly related” AEs and SAEs will be defined as related to study drug.

8.4 Adverse Event Reporting

8.4.1 Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as serious are subject to expedited reporting. Expedited reporting of cases will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and Investigators. Additionally, any safety information from other observations that could change the risk benefit evaluation of the product will be communicated in an expedited manner to the regulatory authorities and all investigators by the Sponsor.

The CRO will be responsible for the processing and reporting of SAEs. AEs will be coded by using ICH Medical Dictionary for Regulatory Activities.

Minimum criteria for a valid adverse drug reaction case have been established by ICH and individual regulatory agencies and are listed as the following:

- An identifiable reporter
- An identifiable patient
- A reaction/event
- A suspected medicinal product

Other safety issues that also qualify for expedited reporting by the Sponsor are those that would materially alter the current benefit risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial). Although these events will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and all IEC of safety issues which might materially alter the benefit-risk assessment of the investigational agents.

8.4.2 Standards for Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as SUSARs are subject to expedited reporting. Additionally, any safety information from other observations that could change the risk benefit evaluation of the product should be promptly communicated to the regulatory authorities. Any other SUSARs associated with the investigational product should be reported as soon as the Sponsor becomes aware of them and this includes SUSARs which occur in another trial conducted by the same Sponsor, or which are identified by spontaneous reports or a publication, or which are transmitted to the Sponsor by another regulatory authority.

8.4.3 Reporting of Out-of-range Laboratory Test Results as Adverse Events

Out-of-range laboratory test results should be reported as AEs (not as abnormal laboratory values, i.e., report as anemia not low hemoglobin) if, in the opinion of the principal investigator, they are clinically significant. Abnormal laboratory results that are not considered to be clinically significant will not be reported as AEs. Significance of abnormal laboratory results should be documented in the study records.

8.4.4 Reporting Guidelines for Other Observations

Other safety issues that also qualify for expedited reporting where they might materially alter the current benefit risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial), for instance include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- A post study SUSAR that occurs after the patient has completed a clinical trial and is reported by the investigator to the Sponsor

Events which occur during the trial and are relevant in terms of patient safety, but which do not fall within the definition of SUSAR (and thus are not subject to the reporting requirements for SUSARs) are:

- An SAE which could be associated with the trial procedures and which could modify the conduct of the trial
- A significant hazard to the patient population such as lack of efficacy of an investigational medicinal product
- A major safety finding from a newly completed animal study (such as carcinogenicity)
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal product in another country by the same Sponsor
- Safety recommendations of the Independent Data Monitoring Committee (IDMC)

Although these events/observations will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and the IECs of safety issues which might materially alter the benefit-risk assessment of the investigational medicinal product.

Expedited reporting is not usually required for reactions that are serious but expected, or for non-serious adverse reactions whether expected or not.

It is usually also inappropriate to report events that are considered unrelated to the investigational medicinal product.

8.4.5 Pregnancy Reporting

Pregnancy will be reported through the Pregnancy Reporting Form (paper) as well as in the eCRF as an AE. The Pregnancy form (paper) should be completed and reported as indicated to the CRO Pharmacovigilance Team within 24 hours of being made aware of the event. Pregnancy will be considered as an AE and also reported in the eCRF. Women who become pregnant during the study will be withdrawn from treatment at the earliest opportunity. The investigator shall report all pregnancies immediately to the CRO. The CRO will then notify the Sponsor within 1 business day of being informed of the event. Following withdrawal from the study, every attempt will be made to follow the patient and any resulting offspring for up to 6-weeks postpartum, unless otherwise medically indicated. Abortion, stillbirth, or any malformation/disease in the offspring must be reported as an SAE.

For men participating in the study who report the pregnancy of a partner, the investigator will ask to collect information about the results of the pregnancy/birth using the Pregnant Partner forms. The partner may be asked to sign a consent form giving permission for information to be collected. This health information will become part of the research study records. It will be shared with the Sponsor.

8.5 Investigator's Responsibilities

The investigator is responsible for the collection of AE data. All AEs should be recorded in the eCRF. The investigator shall report all SAEs immediately within 24 hours of being made aware of the event to Pharmacovigilance via the clinical database by completing as much information as possible and checking Yes when prompted whether the event is classified as an SAE in the AEs eCRF. The initial reporting can be supplemented by written reports using the SAE report form provided.

The follow up reports (if required) shall identify the trial patients by unique code numbers assigned to the patient. The investigator shall supply the Sponsor with any additional requested information, notably for reported deaths of a patient.

All SAEs that occur between obtaining the patient's Informed Consent and 90 days after the last dose of study drug must be reported promptly to the CRO not later than 24 hours after the investigators or co-investigators become aware of their occurrence using the SAE eCRF in the study database.

The SAE eCRF is accessed via the study database. The following minimum information is required for the report:

- Patient identification (patient number and date of birth)
- Trial number
- Study therapy (dose, route, form, regime, start date, end date)
- Concomitant medication (including dose, route, form, regime, start date where available)
- Nature of SAE (overall diagnosis where available or alternatively signs and symptoms)
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study therapy

- Outcome
- Identify the reporter
- Action in relation to study (withdrawn from treatment, suspended, none)

The investigators or co-investigators are required to sign the SAE submission electronically in the clinical database within 24 hours of awareness of the event, even if the required information is incomplete or if the investigators are awaiting laboratory or diagnostic reports. Investigators may be asked for additional information for any reported SAE. An SAE follow up report with attached documents (if necessary) should be forwarded to CRO Pharmacovigilance as soon as the additional information is available by email. The study number IMCgp100-102 must be in the title of any email for study identification purposes.

8.6 Sponsor and Clinical Research Organization's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the investigational drugs being studied. The Sponsor and CRO are responsible for ensuring that expedited reports are made to all concerned investigators, to the IEC where required, and to all regulatory authorities of all adverse drug reactions that are both serious and unexpected, or findings that could adversely affect the health of patients, impact on the conduct of the trial, or alter the competent authority's authorization to continue the trial in accordance with local applicable regulations.

9 STATISTICAL METHODS AND DATA ANALYSES

9.1 General Principles

Data from Phase 1 will be summarized after approximately 80% of patients in Phase 1 have completed study treatment. Data will be presented by dose cohort and overall. At the end of Phase 2, any additional data collected for patients remaining on treatment after the Phase 1 data cut-off will be included in the final clinical study report.

For the Phase 1 escalation cohort, data will be reported based on all patient data up to the time when all patients have completed a minimum of 6 cycles of treatment or have discontinued the study. An updated analysis of DOR, PFS, and OS may be performed. Data will be presented by dose cohort and overall.

For the Phase 2 expansion cohort, the primary analysis of the study will be conducted after approximately 120 evaluable patients have been enrolled and treated/followed for at least 9 months. The primary analysis of Phase 2 will summarize data from the overall expansion cohort (approximately n=120 patients).

In order to explore whether results are consistent across prior therapy groups, key endpoints may be further summarized by prior therapy groups (for example: 1 systemic therapy and 1 LDT; 1-2 systemic therapies only; 1 LDT only, 1 checkpoint inhibitor and any LDT). Further details around the analysis plan, including any additional reporting of DOR, PFS, and OS with longer-term follow up that may be required will be defined in the Statistical Analysis Plan (SAP).

Data will be summarized using descriptive statistics. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The following rules will be followed for reporting results unless stated otherwise:

- Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses, but will be reported in the clinical study report as separate listings
- Baseline is defined as the last assessment prior to the first dose of treatment received (i.e., C1D1 pre-dose)
- Additional analyses not described here will be detailed in the SAP for the study

9.2 Analysis Sets

9.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients assigned to treatment, who received at least 1 full or partial dose of IMCgp100. The FAS will be used for all demography, baseline characteristics, and efficacy data summaries and analyses.

9.2.2 Safety Analysis Set

The Safety Set includes all patients who have received at least 1 full or partial dose of IMCgp100. Patients will be classified in this set according to initial treatment received. The safety set will be used for the safety summary of the study.

9.2.3 Per-protocol Analysis Set

The Per Protocol Set (PPS) consists of a subset of FAS patients who meet these 4 criteria: (1) presence of measurable disease, (2) 1 post-baseline tumor assessment or discontinue prior to the first tumor assessment, (3) received at least 1 dose of treatment and, (4) no violation of key inclusion or exclusion criteria.

Patients in the PPS will be classified according to planned treatment. The PPS will define the patients used in the sensitivity analysis of the secondary endpoints. If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

9.3 Patient Demographics and Other Baseline Characteristics

Demographic data, baseline disease characteristics and other baseline data will be listed in detail. Qualitative data (e.g., performance status) and quantitative data (e.g., weight) will be summarized by descriptive statistics.

9.4 Treatment Data

Actual dose and duration in days of treatment for IMCgp100, as well as, the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be summarized by descriptive statistics by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by Anatomical Therapeutic Chemical term and treatment group.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last doses, duration of exposure to each study drug, and date of discontinuation for each patient.

9.5 Primary Analysis

9.5.1 Variables

The primary variable in the Phase 1 dose escalation phase of the study is the incidence of DLT.

The primary variable in the Phase 2 dose expansion phase of the study is ORR by RECISTv.1.1 assessed by ICR.

9.6 Secondary Analyses

9.6.1 Efficacy

Analysis of efficacy endpoints will be performed using the FAS unless otherwise noted.

For the Phase 1 escalation cohorts, tumor-based endpoints will be assessed using local investigator assessment and ICR where available for both RECISTv.1.1 and modified irRECIST. For the Phase 2 expansion cohorts, tumor-based endpoints will be assessed using ICR data for both RECIST v1.1 and modified irRECIST. ORR and other RECIST-based endpoints as assessed by the local radiologist will be summarized as a sensitivity analysis.

ORR is defined as the proportion of patients with measurable disease with at least 1 visit response of CR or PR that is confirmed at least 4 weeks later, as defined in RECIST v.1.1.

The denominator in the calculation of the ORR will be the number of patients in the FAS with measurable disease at baseline. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any CR or PR, which occurred after further anti-cancer therapy was received, will not be included in the numerator of the ORR calculation. Disease control rate is defined as the proportion of patients with a best overall response of CR or PR or SD recorded at least 24 weeks (± 1 week) after commencement of study drug and prior to any PD event.

For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group (dose cohort) for the Phase 1 dose escalation and overall for the Phase 2 expansion cohorts.

In order to explore whether the Phase 2 efficacy results are consistent across prior therapy groups, key endpoints (including ORR and DoR) may be further summarized by prior therapy groups (for example: 1 systemic therapy and 1 LDT; 1-2 systemic therapies only; 1 LDT only, 1 checkpoint inhibitor and any LDT).

Further subset analyses of efficacy by LDH (above or below institutional ULN) and hepatic metastases (present or absent) may be performed if an adequate number of patients with and without the prognostic factor are available for analysis (Valpione, 2015).

ORR and DCR will be summarized with accompanying 95% confidence intervals.

PFS, along with DOR and time to response for patients who experience a CR or PR at any time on study will be listed by patient.

PFS will be presented graphically using Kaplan Meier plots for all patients in the Phase 2 expansion cohorts. Median PFS time and the proportion of patients who are progression-free at 3, 6, 9, and 12 months will also be estimated. If there are a large number of patients achieving response (e.g., estimated ORR of 30%), the Kaplan-Meier plots for DOR will also be produced and the median DOR will be estimated. OS will be presented graphically using Kaplan Meier plots including all patients from the Phase 2 expansion. Median OS time and the proportion of patients who are alive at 3, 6, 9, and 12 months will be estimated.

The secondary endpoint to determine the rate and duration of MinR, defined as a reduction in the SLD of 10%–29% will be explored by: (1) summaries of the number (%) of MinR and associated durations; (2) summaries of the overall ORR + MinR and associated durations; and (3) waterfall plots of SLDs.

The secondary endpoint to determine the rate and duration of immune responses will be detailed in the SAP and be largely based on methods described by Gao et al. In summary, for each patient, the percentage change in the target lesion sum of longest diameters will be plotted over time and an AUC will be calculated over a fixed time-period (e.g., 9 months) post initial dose of IMCgp100. The AUC reflects both the depth and duration of tumor size reduction and may capture a delayed benefit of immunotherapy (Gao et al). Hepatic volume data will also be plotted and may be incorporated into the criteria for immune response.

Exploratory tumor assessments based on modified irRECIST will also be presented summarizing the best response by irRECIST and this will be compared with the best response from RECISTv.1.1.

The SAP will provide more detailed information on the data summaries for the Phase 1 dose escalation and the Phase 2 dose expansion.

[redacted]

9.6.2 Safety Objectives

9.6.2.1 Analysis Set and Grouping for the Analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into 3 mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 90 days after last dose of study medication
3. Post-treatment period: starting at Day 31 after last dose of study medication

9.6.2.2 Adverse Events

Summary tables for AEs include only AEs that are new or worsened during the on-treatment period (treatment-emergent AEs). However, all safety data (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs will be summarized by system organ class and/or preferred term, severity (based on NCI CTCAE v.4.03 grades), type of AE, and relation to study treatment by treatment group. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

Definitions of notably abnormal vital signs results (e.g., hypotension) will be specified in the SAP and a shift table baseline to worst on-treatment result will be produced by the Phase 1 dose escalation and Phase 2 dose expansion groups.

9.6.2.3 Laboratory Abnormalities

For laboratory tests covered by the NCI CTCAE version 4.03 the study team will grade laboratory data accordingly. For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and other laboratories:

- Frequency table for newly occurring on-treatment grades 3 or 4 and all grades
- Shift tables of laboratory and ECG data using CTCAE grades to compare Baseline to the worst on-treatment value
- Listing of all clinically relevant laboratory data and relevant ECG data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

9.6.2.4 Other Safety Variables

- Vital signs absolute values and changes from Baseline will be summarized. Normal ranges will be specified in the SAP and shift tables of Baseline to worst on-treatment results will be produced
- ECG data: QTc interval absolute values and changes from Baseline will be summarized. Abnormalities will be classified according to NCI CTCAE grades and shift tables of Baseline to worst on-treatment results will be presented
- Physical examination data will be listed and abnormalities will be flagged

9.6.2.5 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

9.6.2.6 Pharmacokinetics

The PK parameters that will be assessed are presented in Table 9-1.

Table 9-1 Pharmacokinetic Parameters to be Analyzed

AUC_{last}	The area under the curve (AUC) from time 0 to the last measurable concentration sampling time (t_{last}) (mass x time x volume-1)
AUC_{inf}	The AUC from time 0 to infinity (mass x time x volume-1)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time-1)
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation Ratio=C_{max} (multiple dose)/C_{max} (single dose)

The safety set will be used in all PK data analysis and PK summary statistics.

Pharmacokinetic Analyses

Descriptive statistics of all PK parameters for IMCgp100 will include arithmetic and geometric mean, median, stable disease, and coefficient of variation, geometric coefficient of variation, and minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since T_{max} is generally evaluated by a non-parametric method, median values and ranges will be given for this parameter. Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as 0 in summary statistics, and reported as is in data listings. Any missing PK parameter data will not be imputed.

Further analyses may be conducted using population PK approaches. In addition, a model based approach may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and IMCgp100 concentration and/or exposure metrics. All analyses will be reported either in the clinical study report or a stand-alone report.

The concentration-/AE-immunogenicity relationship will be explored graphically and tabulated to characterize a relationship between the changes from screening immunogenicity presence and serum concentration of IMCgp100. Further details will be described in the SAP.

9.7 Exploratory Analyses

9.7.1 [redacted]

[redacted]

9.7.1.2 [redacted]

[redacted]

9.8 Interim Analysis

For the Phase 1 cohorts, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose will be chosen depending on the observed data (based on safety, tolerability, PK, pharmacodynamic, and efficacy data, and recommendations from participating investigators). Details of this procedure and the process for communication with investigators are provided in Section 6.3.3.

For the Phase 2 expansion (approximately n=150), an IDMC will review the safety data on an ongoing basis. In addition, a benefit-risk assessment involving review of efficacy and safety data will take place once approximately 75 evaluable patients have been treated/followed for at least six months. The primary endpoint of ORR, as assessed by the ICR, will be summarised with 95% confidence intervals (Clopper Pearson method). ORR based on the local radiological assessment will be summarised as a sensitivity analysis. Duration of response and other secondary efficacy endpoints will be described. Further details will be provided in the SAP.

9.9 Independent Data Monitoring Committee

An IDMC will be established to provide oversight of safety and efficacy considerations in the Phase 2 expansion portion of this study. The IDMC will act in an advisory capacity and make recommendations regarding steps to ensure both subject safety and the ethical integrity of the trial. The voting members of the committee are external to Immunocore, and will not otherwise be involved with the trial. The IDMC will include 3 clinicians experienced in oncology/melanoma and 1 statistician. Specific details regarding IDMC responsibilities, governance, and documentation will be described in a separate charter that is reviewed and approved by the IDMC members. Immunocore has primary responsibility for design and conduct of the study.

The IDMC will monitor trial safety approximately every 4 months, or at a frequency described in the IDMC charter. In addition, they will perform a benefit-risk assessment by reviewing both efficacy and safety data after approximately 75 evaluable patients in the expansion phase have been treated/followed for at least 6 months.

Following each IDMC meeting, the IDMC will provide recommendations to the Sponsor on any changes that may be needed to the future conduct of the study or if the study should continue as planned.

9.10 Sample Size Calculation

9.10.1 Phase 1 Dose Escalation Cohorts

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least 6 patients at the MTD or RP2D in the RP2D-IE level, as described in Section 6.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D-IE for further elaboration of safety and PK parameters as required.

9.10.2 Phase 2 Dose Expansion Cohorts

The Phase 2 expansion cohorts of approximately 150 patients,including a minimum of 120 patients for RECIST evaluation, will provide a substantive dataset of safety, tolerability, and efficacy in uniform patient populations. Patients will be enrolled into 2 cohorts as described in Section 3.2:

The primary analysis of the Phase 2 expansion will focus on the overall Phase 2 population. With 120 patients and an observed ORR of 10% or more, the precision around the estimation of ORR as assessed by 95% confidence intervals will be 5.3% to 16.8%. The study will also provide an adequate number of patients in which to assess the safety and tolerability of the RP2D-IE. For example, for AEs of interest, if 0 AEs are observed in a cohort of 120 patients, there will be 95% confidence that the true event rate is less than 3%. For 150 patents there will be 95% confidence that the true event rate is less than 2.4%.

In addition, the Phase 2 expansion data will provide an assessment of whether OS may exceed that achieved with currently available therapies, [redacted]

An IDMC will review safety data on an ongoing basis (approximately every 4 months) in conjunction with a review of safety data from the ongoing randomized study (IMCgp100-202). An interim review of both efficacy and safety data from the Phase 2 expansion will be performed by the IDMC after approximately 75 evaluable patients have been treated/followed for at least 6 months to enable an overall assessment of risk versus benefit.

10 DATA HANDLING AND MANAGEMENT

10.1 Data Confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the protected health information that will be collected and the use or disclosure of that information. If the patient revokes authorization to collect or use this information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. To protect the health information of study patients, access to the data collection system will be controlled by a sequence of individual user identification codes and passwords that are made available only to authorized trained personnel.

10.2 Site Monitoring

Before study initiation at trial sites, Sponsor and/or CRO study team members will review the protocol and eCRFs with the investigators and the site study staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to good clinical practice, the progress of enrollment, and to ensure that study treatments are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. The investigator must assure that the site monitor is allowed access to all study files, including all site medical records, case and visit notes and laboratory reports.

10.3 Data Collection

The investigator is required to maintain source documents for each patient in the study, consisting of case and visit notes (site medical records), containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded in the eCRF must be traceable to source documents in the patient's file. The investigator must also keep the original signed ICF, with 1 signed copy given to the patient.

This study will use an electronic data capture (EDC) system and the principal investigator and site study staff will enter the data required by the protocol into the eCRF. The eCRF have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. The principal investigator and all identified site staff will not be given access to the EDC system until they have been trained. The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. Field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions.

Tissue samples obtained during the study (e.g., tumor, blood for PK or other analyses) will be collected from the investigator sites and analyzed by Immunocore laboratories, contracted central laboratories, or local laboratories. Radiological assessments will be reviewed retrospectively in a central repository as described. Field monitors will review the eCRF and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample by the site staff and 1 copy will be retained at the investigational site.

10.4 Database Management

Sponsor clinical study personnel and trial field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system.

Concomitant treatment and prior medication data in the database will be coded using the WHO Drug Reference List, based on the Anatomical Therapeutic Chemical classification. Medical history, current medical conditions and AEs in the database will be coded using the Medical Dictionary for Regulatory Activities terminology. After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice E6 (R2), with applicable local regulations (including European Directive 2001/20/EC and Unites States Code of Federal Regulations, CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the Investigator and Institutional Review Board/Independent Ethics Committee/Research Ethics Board

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB or IEC or Research Ethics Board (REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to field monitors, auditors, IQVIA Clinical Quality Assurance representatives, designated agents of Sponsor, the IRB or IEC or REB and regulatory authorities as required.

11.3 Informed Consent Procedures

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the Clinical Trial. All participants should be informed to the fullest extent possible about the study, both verbally and in written language and terms they are able to understand. Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC/REB-approved informed consent which documents their authorization, or if the patient is incapable of doing so, after such consent has been provided by a legally acceptable/authorized representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her level of understanding. If the patient is capable of doing so, he or she should indicate assent by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures; the 1 exception to this note are radiologic assessments performed before Screening within the specified window. A copy of the signed and dated written ICF will be provided to the patient and/or legal representative, where appropriate. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be captured in the eCRF.

The ICF used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

11.4 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 3.6.

11.5 Publication of Study Protocol and Results

The Sponsor will publish the key design elements of this protocol in a publicly accessible database (clinicaltrials.gov). At the time of study and clinical study report completion, the results of this study will be either submitted for publication and/or posted in a publicly accessible database.

11.6 Study Documentation, Record Keeping, and Retention of Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 (R2) Good Clinical Practice, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine any clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded.

The investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and guidelines. The investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for a period of not less than 15 years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and guidelines.

11.7 Confidentiality of Study Documents and Patient Records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Immunocore or the CRO. Signed ICFs and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and Inspections

Source data and all trial documents must be available to inspections by the Sponsor, the CRO, or designee or Health Authorities.

11.9 Financial Disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

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13 APPENDICES

13.1 Appendix 1: Guidelines for Modified RECISTv.1.1 Criteria

These guidelines are based on the original RECIST for tumor responses (Therasse, 2000), and the revised RECIST v.1.1 guidelines (Eisenhauer, 2009). The efficacy assessments and definitions of best response and PD for the purposes of the primary endpoint of ORR described in this study are based on the RECIST v.1.1 criteria.

13.1.1 Efficacy Assessments

Tumor evaluations for the purposes of the primary endpoint are made based on RECIST criteria (Therasse, 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, *Journal of National Cancer Institute*, Volume 92; pages 205–216 and revised RECIST guidelines (version 1.1) (Eisenhauer, 2009).

13.1.2 Definitions of Measurable and Non-measurable Disease

Measurable disease represents the presence of at least 1 measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions (both nodal and non-nodal): Measurable non-nodal — the minimum size of a measurable non-nodal target lesion at Baseline should be no less than double the slice thickness or 10mm whichever is greater — e.g., the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm.

Lytic bone lesions or mixed lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions, if the soft tissue component meets the definition of measurability. Measurable nodal lesions (i.e., lymph nodes) — Lymph nodes $\geq$ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring $\geq$ 10 mm and < 15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at Baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. Simple cysts with non-enhancing walls and low CT density are not considered malignant lesions unless proven by biopsy.

Non-measurable lesions: All other lesions are considered non-measurable, including small lesions (e.g., longest diameter < 10 mm with CT/MRI or pathological lymph nodes with $\geq$ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, ascites, pleural/pericardial effusion, and inflammatory breast disease.

13.1.3 Methods of Tumor Measurement

All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. For optimal evaluation of patients, the same methods of assessment and technique should be used to assess each reported lesion at Baseline and during Follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness. If a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

Other Tumor Response Considerations

MRI for liver disease: In some instances, liver disease in patients with UM can be imaged more effectively with MRI.

Fluorodeoxyglucose-positron emission tomography, Endoscopy and Laparoscopy: The utilization of PET imaging, endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. The utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers; however, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Clinical examination: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Clinical disease progression is acceptable and wherever possible should be confirmed by imaging studies.

13.1.4 Definitions of Target and Non-target Lesions

For the evaluation of lesions at Baseline and throughout the study, the lesions are classified at Baseline as either target or non-target lesions:

Target Lesions: All measurable lesions (nodal and non-nodal) up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at Baseline. Target lesions should be selected based on size (lesions with the longest diameter) and suitability for accurate repeated measurements (either by imaging techniques or clinically).

Each target lesion must be uniquely and sequentially numbered on the eCRF (even if it resides in the same organ). A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at Baseline must be followed at each subsequent evaluation and documented on eCRF.

Non-target Lesions: All other lesions are considered non-target lesions, i.e., lesions not fulfilling the criteria for target lesions at Baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e., multiple liver metastases). Each non-target lesion identified at Baseline must be followed at each subsequent evaluation and documented on eCRF.

13.1.5 Determination of Target Lesion Response

Table 13-1 Response Criteria for Target Lesions

Response Criteria	Evaluation of Target Lesions
Complete Response	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm[1]
Partial Response	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters
Progressive Disease	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after Baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2]
Stable Disease	Neither sufficient shrinkage to qualify for partial response or complete response nor an increase in lesions which would qualify for progressive disease

1. Sum of diameters for complete response may not be 0 when nodal lesions are part of target lesions.
2. Following an initial complete response, progressive disease cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are < 10 mm in size. In this case, the target lesion response is complete response.

Notes on Target Lesion Response

- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at Baseline and appears to be 1 mass can split to become 2 or more smaller sub-lesions. When this occurs, the diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the 2 split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target

lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation

- **Lesions coalesced**: Conversely, it is also possible that 2 or more lesions which were distinctly separate at Baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of 1 of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced

13.1.6 Determination of Non-target Lesion Response

Table 13-2 Response Criteria for Non-target Lesions

Response Criteria	Evaluation of Non-target Lesions
Complete Response	Disappearance of all non-target lesions. In addition, all lymph nodes assigned non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease	Unequivocal progression of existing non-target lesions[1]
Non-complete response/ Non-progressive disease	Neither complete response nor progressive disease

1. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the central review.

Non-target Lesion Response

- The response for non-target lesions is CR only if all non-target non-nodal lesions which were evaluated at Baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e., < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e., ≥ 10 mm) the response can only be 'Non-CR/Non-PD'

- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR, or stable disease (SD) in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at Baseline

New Lesions

The appearance of a new lesion is always associated with PD and has to be recorded as a new lesion in the eCRF.

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was not scanned at Baseline or where the particular baseline scan is not available for some reason, then this should be considered PD
- A lymph node is considered as a "new lesion" and, therefore, indicative of PD if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase

13.1.7 Evaluation of Overall Lesion Response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 13-3.

Table 13-3 Overall Lesion Response at Each Assessment

Target Lesions	Non-target Lesions	New Lesions	Overall Lesion Response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR[1]
SD	Non-PD	No	SD[1, 2]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

1. This overall lesion response also applies when there are no non-target lesions identified at Baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.

References:

Eisenhauer EA, Therasse P, Bogaerts J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247

Therasse P, Arbuck SG, Eisenhauer EA. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Natl Cancer Inst.* 2000;92(3):205–216.

13.2 Appendix 2: Modified Immune-related RECIST Comparison to RECIST v.1.1

The response criteria set known as irRECIST) (Bohnsack, 2014) is an adaptation of the immune-related response criteria (irRC) (Wolchok, 2009; Nishino, 2013) that is based upon World Health Organization criteria for tumor response evaluation utilizing bi-dimensional criteria. Nishino, et al, demonstrated that the irRC could be implemented using unidimensional criteria (Nishino, 2013). Some further modifications were proposed to further align the immune-related criteria with RECISTv.1.1 and this approach has been named irRECIST criteria (Bohnsack, 2014).

A further modification to the guidance is implemented in this study, such that for patients who continue IMCgp100 therapy beyond initial PD, unequivocal, confirmed PD is defined as an additional 20% increase in tumor burden (sum of diameters of both target and measurable new lesions) or unequivocal progression of NTLs and/or new non-measurable disease from the initial PD assessment per RECISTv1.1 rather than from the nadir. This modification is based on early observations of prolonged disease stabilization with IMCgp100 beyond progression in the dose escalation cohorts of this study (Sato, 2017). This definition is referred to in the protocol as irPD per modified irRECIST.

The key modifications between the RECISTv.1.1 assessments and modified irRECIST assessments are described below.

13.2.1 Key Changes from RECIST v.1.1 to Modified irRECIST Criteria

13.2.1.1 Total Measured Tumor Burden

Baseline-selected target lesions and new measurable lesions should NOT be assessed separately but combined for the total tumor burden. Measurements of those lesions should be combined into the total measured tumor burden (TMTB), and 1 combined assessment provided.

13.2.1.2 New Measurable Lesions

According to irRC (Wolchok, 2009), a measurable new lesion has to be at least 5 mm × 5 mm to be selected as an index lesion; for bi-dimensional measurements this threshold was acceptable. In irRECIST, criteria for unidimensional lesion measurement apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes (Bohnsack, 2014). Smaller lesions contribute to the non-target or new non-measurable tumor burden, but are not measured.

13.2.1.3 Non-target Lesions

In alignment with RECIST v.1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions measurable at first appearance can contribute to the TMTB for irRECIST. For example: A patient has multiple lung metastases, all smaller than 10 mm and selected as non-target lesions at Baseline. If, at

a subsequent timepoint some of these non-target lesions increase and become > 10 mm, and 1 new lesion >10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the non-target lesions that increased in size from baseline.

13.2.1.4 Immune-related Progressive Disease Based on Non-target Lesions

Unlike irRC that neglect non-target lesions for the assessment of irPD, in irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression.

13.2.1.5 Immune-related Progressive Disease Based on New Non-measurable Lesions

According to irRECIST, the reviewer may assign irPD for the patient with multiple new non-measurable lesions if they are considered to be a sign of unequivocal, massive worsening.

13.2.1.6 Immune-related Progressive Disease Confirmation per modified irRECIST

In this study, confirmed irPD is defined as an additional 20% increase in the total tumor burden (target lesions and any new measurable lesions) and/or increased/further unequivocal progression of NTLs and/or new non measurable lesions from the initial assessment of PD per RECISTv.1.1. Confirmation of irPD progression should occur at least 4 weeks after the initial assessment of RECISTv.1.1 PD.Further confirmation of irPD after its occurrence is not required, but may be done at Investigator discretion.