NCT03367819

AMENDED CLINICAL TRIAL PROTOCOL NO. 05

COMPOUND: isatuximab/SAR650984

A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with REGN2810 or isatuximab alone in patients with advanced malignancies

STUDY NUMBER: SAR650984-ACT15319

VERSION DATE / STATUS: Approval date (11-Jun-2019) / Approved

Version Number:	1	EudraCT IND Number(s) WHO universal trial number:	2017-002846-61 IND 136026 U1111-1197-7792
Approval Date:	11-Jun-2019	Total number of pages:	187

NAMES AND ADDRESSES OF

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OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, Version
Amended Clinical Trial Protocol 05	All	11-Jun-2019, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 04	All	21-Nov-2018, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 03	All except UK	23-Jul-2018, Version 1 (electronic 3.0)
Amended Clinical Trial Protocol 04 (UK)	UK	23-Jul-2018, Version 1 (electronic 3.0)
Protocol Amendment 04	All	23-Jul-2018, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	All except UK	02-Apr-2018, Version 1 (electronic 2.0)
Amended Clinical Trial Protocol 03 (UK)	UK	02-Apr-2018, Version 1 (electronic 2.0)
Protocol Amendment 03	All except UK	02-Apr-2018, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02 (UK)	UK	03-Nov-2017, Version 1 (electronic 1.0)
Protocol Amendment 02 (UK)	UK	03-Nov-2017, Version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	05-Oct-2017, Version 1 (electronic 1.0)
Protocol Amendment 01	All	05-Oct-2017, Version 1 (electronic 1.0)
Clinical Trial Protocol	All	05-Sep-2017, Version 1 (electronic 1.0)

Amended Protocol 05 (11 June 2019)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Based on updated pharmacokinetic characterization of isatuximab, the plasma half-life has been re-estimated to 28 days. As duration of contraceptive measures is required to last for 5 half-lives (i.e. 5 months), a revised duration of contraceptive measures of 6 months after the last study treatment is included to align with the REGN2810 requirement for operational simplicity.

Section # and Name	Description of Change	Brief Rationale
1.3 & 1.4 Study Flowchart; and 12.5 Post treatment follow-up	Pregnancy test is extended to monthly until 6 months after last dose of study treatment.	Monthly pregnancy test is implemented until end of the extended contraception period.
4.3.2 Schedule and dose of administration	Re-estimation of isatuximab half-life of 28 days is included.	Based on updated pharmacokinetic characterization of isatuximab.
8.9.2 Contraceptive measures and pregnancy counseling	Contraceptive measures are required to extend to 6 months following the last dose of study treatment.	5 months of contraception period after last dose of isatuximab is required based on updated pharmacokinetic analysis. For operational simplicity and to be consistent with exclusion criterion E21, patients are required to maintain contraceptive measures up to 6 months after last dose of study treatment (aligned with requirement for REGN2810).

CLINICAL TRIAL SUMMARY

COMPOUND: isatuximab (SAR650984)	**STUDY No: ACT15319**
TITLE	A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with REGN2810, or isatuximab alone, in patients with advanced malignancies
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 1/2
STUDY OBJECTIVE(S)	**Primary objective** Phase 1 part: • To characterize the safety and tolerability of isatuximab in combination with REGN2810 (cemiplimab) in patients with metastatic, castration resistant prostate cancer (mCRPC) who are naïve to anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1)-containing therapy, or non-small cell lung cancer (NSCLC) who progressed on anti-PD-1/PD-L1-containing therapy, and to confirm the recommended Phase 2 dose (RP2D). Phase 2 part (applicable to Cohorts A-1, A-2, B, C, and D): • To assess the response rate (RR) of isatuximab in combination with REGN2810 in patients with either mCRPC who are anti-PD-1/PD-L1 therapy-naïve, or NSCLC who progressed on anti-PD-1/PD-L1 therapy, **or** of isatuximab as single agent in patients with mCRPC. **Secondary objectives** • To evaluate the safety of the combination of isatuximab with REGN2810 or isatuximab monotherapy. • To evaluate the immunogenicity of isatuximab and REGN2810. • To characterize the PK profile of isatuximab single agent or in combination with REGN2810, and to characterize the PK of REGN2810 in combination with isatuximab. • To assess overall efficacy of isatuximab in combination with REGN2810 or single agent (tumor burden change, duration of response [DOR], disease control rate [DCR], and progression-free survival [PFS]). **Exploratory objectives** • To explore the preliminary overall efficacy: Overall survival (OS), Time to response (TTR); for patients with mCRPC: prostate-specific antigen (PSA) RR, radiographic RR, duration of PSA response, duration of radiographic response, time to PSA response, time to radiographic response and time to PSA progression. • To explore the preliminary overall efficacy of isatuximab in combination with REGN2810 in patients with mCRPC who progress on isatuximab monotherapy. • To explore the relationship between clinical response and cluster of differentiation 38 (CD38) expression, PD-L1 expression and more broadly immune markers in tumor biopsy at baseline as potential predictive markers of response.

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To explore tumor genetic markers at baseline including tumor mutational load and microsatellite instability (MSI) status as potential markers of response to anti-PD-1 therapy.
To explore immune genetic markers in blood at baseline such as polymorphisms in FcγR receptors which are important for effector functions of isatuximab.
To evaluate pharmacodynamic biomarkers in response to investigational medicinal product (IMP): immunophenotype to analyze the modulation of different immune cell populations in peripheral blood, immune markers in tumor, transcriptomic analysis in tumor and plasma or serum cytokine levels.
A panel of tumor somatic mutations (ie, tumor mutational profile) will be analyzed at baseline and upon treatment in blood to explore potential mechanisms of escape in response to treatment.
To perform PK/pharmacodynamics analysis if possible with any relevant pharmacodynamics markers mentioned above, and correlation with safety/efficacy endpoints.

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<tr><td>STUDY DESIGN</td><td>
This is a Phase 1/2 open-label, non-comparative, multi-center, safety, preliminary efficacy and PK study of isatuximab in combination with REGN2810 or isatuximab alone in patients with advanced malignancies.
The study will be conducted in 3 parts:
<u>Phase 1 part (safety run-in):</u>
Patients with either mCRPC or NSCLC will be enrolled in the Phase 1 part.
Starting dose is 350 mg Q3W for REGN2810 with isatuximab given 10 mg/kg once weekly (QW) for 3 weeks followed by once every 3 weeks (Q3W). Overall safety monitoring will be performed throughout the conduct of the study.
Dose modification for Phase 1 part
<table>
<tr><th>Dose level (DL)</th><th>Isatuximab</th><th>REGN2810</th></tr>
<tr><td>Starting dose</td><td>10 mg/kg QW × 3 ->Q3W</td><td>350 mg Q3W</td></tr>
<tr><td>Minus -1 (DL-1)</td><td>5 mg/kg QW × 3 ->Q3W</td><td>350 mg Q3W</td></tr>
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The dose limiting toxicity (DLT) observation period is 1 cycle (21 days). All the adverse events (AEs) occurring during treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the maximum tolerated dose and RP2D for the isatuximab and REGN2810 combination.
At starting dose, DLTs will be assessed in the first 6 patients (1 cycle, 21 days):

If ≤1/6 patient has DLT, the starting dose will be the RP2D.
If 2/6 patients have DLT, 6 additional patients will be enrolled at starting dose level:

If a total of 2/12 patients treated at starting dose have DLT, starting dose will be the RP2D.
If a total of ≥3/12 patients have DLT, dose will be de-escalated to dose level minus 1 (DL-1).

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	• If ≥3/6 patients have DLT, dose will be de-escalated to DL-1. An additional 6 patients may be enrolled at DL-1: • If ≤1/6 patient has DLT, DL-1 will be the RP2D. • If 2/6 patients have DLT, 6 additional patients will be enrolled at DL-1: - If a total of 2/12 patients treated at DL-1 have DLT, DL-1 will be the RP2D. - If a total of ≥3/12 patients have DLT, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor after consulting with the Investigators who recruit patients for the Phase 1 part. IMP initiation in the Phase 1 part is to be staggered by at least 3 days. Following the identification of the RP2D, the Phase 2 part of the study will be initiated. The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator. The DLTs will be confirmed by the Sponsor and recruiting Investigators. **Dose limiting toxicity is defined as:** All AEs specified below occurring during the first cycle of treatment, unless due to disease progression or to a cause obviously unrelated to IMP. The duration of the DLT observation period will be longer for patients who delay initiation of Cycle 2 due to treatment-related AE for which the duration must be assessed in order to determine if the event is a DLT. **Hematological abnormalities** are defined as any of the following: • Grade 4 neutropenia for 7 or more consecutive days. • Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection. • Grade 3 to 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention. **Non-hematological abnormalities** • Grade 4 non-hematologic AE. • Grade ≥2 uveitis. • Grade 3 non-hematological AE lasting >3 days despite optimal supportive care, **except**: - Grade 3 fatigue. - Allergic reaction/hypersensitivity attributed to isatuximab or REGN2810. - A Grade 3 or 4 laboratory abnormality that is not clinically significant per recruiting Investigators and Sponsor. • Delay in initiation of Cycle 2 more than 14 days due to treatment-related laboratory abnormalities/AE. • In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

	Phase 2 part (efficacy signal search with Simon's 2-stage design): The Phase 2 part may include up to 5 cohorts: **Cohort A-1:** mCRPC, isatuximab and REGN2810 combination therapy. **Cohort A-2:** mCRPC, isatuximab monotherapy. **Cohort B:** NSCLC, isatuximab and REGN2810 combination therapy. **Possibly Cohort C:** mCRPC, isatuximab and REGN2810 combination therapy, or isatuximab monotherapy without initial isatuximab weekly dosing. **Possibly Cohort D:** NSCLC, isatuximab and REGN2810 combination therapy without initial isatuximab weekly dosing. A Simon's 2-stage design will be used in each cohort. Enrollment in Cohort A-2 will start only if the decision to proceed to Stage 2 in Cohort A-1 is made. The patients treated at the RP2D of isatuximab and REGN2810 in combination during Phase 1 will be included in the efficacy analysis together with patients of the same tumor type in Stage 1 of Phase 2. Based on the number of objective responses (observed at least 6 cycles after the last ongoing patient receives first dose of IMP) and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators. After enrollment completion of Phase 2 Stage 1, if efficacy results do not warrant initiation of Stage 2, enrollment will be paused until sufficient results or analyses warrant initiation of Phase 2 Stage 2. For patients with mCRPC, if it is decided to run Phase 2 Stage 2, an isatuximab monotherapy cohort will be initiated (Cohort A-2); patients with mCRPC will be randomly assigned in a 1:1 randomization ratio to Cohort A-1, isatuximab and REGN2810 combination therapy (Phase 2 Stage 2) or Cohort A-2, isatuximab monotherapy (Phase 2 Stage 1). The isatuximab single agent dose and schedule for cohort A-2 is 10 mg/kg QW for 3 weeks followed by Q3W. Based on the positive efficacy signal and the totality of data observed at the end of Phase 2 Stage 2, the Sponsor may decide to further study isatuximab 10 mg/kg Q3W in combination with REGN2810 or isatuximab 10 mg/kg Q3W as monotherapy in patients with mCRPC (Cohort C) or isatuximab 10 mg/kg Q3W in combination with REGN2810 in patients with NSCLC (Cohort D). The schedule without the initial weekly dosing may be more practical for patients and health care providers. Objectives and study design considerations for Cohort C and Cohort D are the same as those for other cohorts in the same tumor type, respectively. The Sponsor may decide to test an isatuximab dose of 20 mg/kg in case of inadequate efficacy and PK results. **Cross-over part (a subpart of Cohort A-2):** Patients from Cohort A-2 who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8).
STUDY POPULATION **Main selection criteria**	**Main selection criteria** Inclusion criteria: I 01. Signed written informed consent. I 02. ≥18 years of age. I 03. Disease location amenable to mandatory tumor biopsy at baseline (unless clinically unfeasible* as per the Investigator and after obtaining written agreement from Sponsor representative, only for NSCLC cohort), and possibly at Cycle 2 Day 1. Fine needle

	aspirates are not acceptable. Availability of a tissue specimen from core needle or excisional biopsies, or resected tissue are required. Provision of archival tumor tissue sample obtained at the time of or after progression of immediate previous line of anti-cancer treatment is allowed to replace mandatory baseline biopsy. *Clinically unfeasible: With a written opinion from the Investigator that performing a biopsy will put the wellbeing of the subject at an excessive risk due to the location of the lesion. I 04. Based on the Investigator's judgment, at this time, chemotherapy is not the best treatment option for this specific patient. The eligibility of patient to take part in the study will be validated at the multidisciplinary collegial meeting in countries listed in *Appendix I*. **For mCRPC patients (I05 to I11):** I 05. Histologically confirmed adenocarcinoma of the prostate (excluding neuroendocrine differentiation and/or small cell features). I 06. Metastatic disease documented by bone lesion on bone scan, or by measurable soft tissue disease by computed tomography (CT) or magnetic resonance imaging (MRI). Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible. I 07. Surgically or medically castrated, with testosterone levels of <50 ng/dL (<2.0 nM). Patients who have not had a bilateral orchiectomy must have started androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogue ≥4 weeks prior to initiation of IMP and continue such therapy throughout the study. I 08. At least 1 but no more than 2 previous androgen receptor-targeted agents (abiraterone and enzalutamide). I 09. Received up to 2 previous taxane-based chemotherapy regimens as per local standard of care (for example, docetaxel followed by cabazitaxel), unless per investigator's judgement a chemotherapy regimen is not appropriate for the specific patient. If the same taxane-based chemotherapy is used more than once, this will be considered as 1 regimen. I 10. No previous radium 223. I 11. Documentation of progressive disease (PD) as assessed by the Investigator with at least 1 of the following within 6 months prior to first dose of IMP per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria during or following the direct prior line of therapy: • PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at the Screening visit should be ≥1 µg/L (1 ng/mL) if confirmed rise is the only indication of progression. Patients on systemic glucocorticoids for control of symptoms must have documented PSA progression while on systemic glucocorticoids before initiation of IMP. • Radiographic progression of soft tissue disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per PCWG3 recommendation. Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 cm to <1.5 cm are

	pathologic, subject to clinical discretion, and are nonmeasurable. For existing pathologic adenopathy and other soft tissue disease, progression is defined per RECIST 1.1. • Progression of bone metastasis is defined as 2 or more documented new bone lesions on a bone scan. Confirmation of ambiguous results by other imaging modalities (eg, CT or MRI) is obligatory if metastatic disease to bone is only defined by bone scan. **For NSCLC patients (I12 to I16)** : I 12. Histologically or cytologically confirmed diagnosis of Stage IIIB/IV or inoperable recurrent NSCLC. I 13. At least 1 measurable lesion per RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site. I 14. One previous anti-PD-1/PD-L1 (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, or REGN2810) containing regimen as the most recent prior therapy to treat Stage IIIB/IV or inoperable recurrent NSCLC. An anti-PD-1/PD-L1 containing regimen is defined as either an anti-PD-1/PD-L1 monotherapy, or an anti-PD-1/PD-L1 agent administered in the same cycle as another systemic therapy. I 15. No more than 1 previous chemotherapy regimen to treat Stage IIIB/IV or inoperable recurrent NSCLC. I 16. Documentation of benefit (defined as complete response [CR], partial response [PR] or stable disease [SD] at ≥1 radiographic imaging scan) but subsequent progression per RECIST 1.1 during the anti-PD-1/PD-L1 containing regimen within 4 months prior to initiation of IMP. The site's study team must have reviewed previous tumor assessments(including screening tumor imaging) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the anti-PD-1/PD-L1 containing regimen. **Exclusion criteria**: E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2. E 02. Predicted life expectancy <3 months. E 03. Prior treatment with an agent (approved or investigational) that blocks CD38 (patients who joined a study with an anti-CD38 but have written confirmation they were on control arm are allowed). E 04. For patients with mCRPC, prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (patients who joined a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed). E 05. Active brain metastases or leptomeningeal metastases. Patients with asymptomatic central nervous system metastases which have been stable (defined as without evidence of progression by MRI or other imaging modality for at least 28 days prior to initiation of IMP and any neurologic symptoms have returned to baseline) following treatment with surgery or radiation therapy are allowed. E 06. Symptomatic or impending cord compression. E 07. Prior solid organ or hematologic transplant.

	E 08.	Last dose of prior investigational agent within 28 days from initiation of IMP.
	E 09.	Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents, anti-cytotoxic T-lymphocyte-associated protein 4 monoclonal antibodies, and PI3K δ inhibitors) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of IMP. For other agents, treatment-related immune-mediated (or immune-related) AEs that were Grade 2 or above.
	E 10.	Prior intravenous (IV) cytotoxic chemotherapy, antineoplastic biological therapy, major surgery, local prostatic intervention within 21 days prior to initiation of IMP; oral cytotoxic chemotherapy, hormonal therapy, tyrosine kinase inhibitor therapy, or completed palliative radiotherapy within 14 days prior to initiation of IMP.
	E 11.	Denosumab or bisphosphonate therapy initiation or dose/regimen adjustment within 28 days prior to initiation of IMP. Patients on a stable regimen are eligible and may continue their therapy without change.
	E 12.	Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of IMP initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.
	E 13.	Significant cardiac dysfunction, New York Heart Association classification for chronic heart failure III-IV, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG) abnormality, significant ventricular arrhythmias; myocardial infarction within 6 months; unstable or poorly controlled angina pectoris.
	E 14.	Ongoing AEs (excluding alopecia and fatigue) caused by any prior anti-cancer therapy ≥Grade 2 (NCI-CTCAE version 4.03).
	E 15.	Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc).
	E 16.	History of or current interstitial lung disease or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted); history of thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.
	E 17.	Receipt of a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
	E 18.	Known uncontrolled infection with human immunodeficiency virus, known uncontrolled hepatitis B infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment. To control HBV infection, patients with positive HBsAg should have started anti-HBV therapy before initiation of IMP, and the

	screening HBV viral load should be <2000 IU/mL (10^4 copies/mL). The anti-HBV therapy should continue throughout the treatment period. E 19. Known second malignancy either progressing or requiring active treatment within the last 3 years (except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy). E 20. Inadequate organ and bone marrow function at the Screening visit: • Absolute neutrophil count <1500 /uL (1.5 × 10^9/L). • Platelets <100 × 10^3 u/L (after at least 3 days without platelet transfusion). • Hemoglobin <9 g/dL or <5.6 mmol/L (without transfusions within 2 weeks of initiation of IMP). • Total bilirubin >2 upper limit of normal (ULN). • Aspartate aminotransferase and/or alanine aminotransferase >3 × ULN (or >5 × ULN for patients with liver metastases). • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (Modified Diet in Renal Disease Formula). E 21. Women of reproductive potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy 2 weeks before and during the study treatment period and for 6 months following discontinuation of study treatment by using effective contraceptive methods such as: • Diaphragm and spermicide PLUS male condom, or • Intrauterine device PLUS male condom, or • Medical method (such as hormonal contraceptive) PLUS male condom. • A woman of productive potential is a woman who: 1) has achieved menarche at some time point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). The choice of effective method is left to Investigator judgment, in accordance to local regulation. Sterilized or infertile subjects are exempted from the requirement to use of contraception. In order to be considered sterilized or infertile, subjects must have undergone surgical sterilization (vasectomy/bilateral tubectomy, hysterectomy, bilateral ovariectomy) or be a postmenopausal woman defined as 12 months or more with no menses prior to enrollment and 50 years of age. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. E 22. Pregnant or breastfeeding woman or woman who intends to become pregnant during the participation in the study. E 23. Known intolerance or hypersensitivity to any component of isatuximab and/or REGN2810. E 24. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is

	not in the best interest of the subject to participate, in the opinion of the treating Investigator. E 25. Patients who will receive REGN2810: prior treatment with idelalisib. E 26. Known epidermal growth factor receptor (EGFR) sensitizing mutation, anaplastic lymphoma kinase (ALK) rearrangement, ROS1 rearrangement, or BRAF mutation for patients with non-squamous NSCLC. Re-screening once is allowed.
Total expected number of patients	In the Phase 1 part, approximately 6 (assuming 6 patients for the starting dose) to 24 (assuming 12 patients for the starting dose plus 12 patients for DL-1) DLT evaluable patients are expected to be enrolled. The actual sample size will vary depending on DLTs observed and the number of dose levels explored. In the Phase 2 part, approximately 134 patients are expected to be enrolled (assuming Cohort A-1, A-2 and B complete 2 stages), including approximately 66 patients in Phase 2 Stage 1 and approximately 68 patients in Phase 2 Stage 2. The patients who are treated with RP2D in the Phase 1 part will be counted as Phase 2 part patients. If isatuximab 10 mg/kg Q3W in combination with REGN2810 or as monotherapy without the isatuximab 10mg/kg QW for 3 weeks is to be tested in a mCRPC or NSCLC cohort, 49 or 36 additional patients will be needed, respectively.
Expected number of sites:	Approximately 15 sites worldwide
STUDY TREATMENT(s) **Investigational medicinal product(s)**	Isatuximab (SAR650984) in combination with REGN2810 or alone
Formulation	**Isatuximab:** Drug product concentrated solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0. **REGN2810:** Drug product concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.
Route(s) of administration	**Isatuximab:** IV infusion **REGN2810:** IV infusion
Dose regimen	**Phase 1 part** **Starting dose:** • **Isatuximab:** 10 mg/kg weekly for 3 weeks (QW × 3), then every 3 weeks (Q3W) (ie, on Day 1 of each 21-day cycle). • **REGN2810 (administrated before isatuximab):** 350 mg Q3W, (ie, on Day 1 of each 21-day cycle). **Dose -1** (may be implemented if 2/6 patients with DLT and then ≥3/12 with DLT or if ≥3/6 patients with DLT at starting dose): • **Isatuximab:** 5 mg/kg QW × 3, then Q3W. • REGN2810 (administrated before isatuximab): 350 mg Q3W. **Phase 2 part** Combination dose for the Phase 2 part will be determined based on safety data from the Phase 1 part. Monotherapy dose for the Phase 2 part will be the isatuximab RP2D.

	Cross-over part The combination dose for the cross-over part is RP2D. **Cohort C** (may be implemented in the Phase 2 part if positive results are observed in mCRPC Cohort A-1 or Cohort A-2 Phase 2 Stage 2): • Combination RP2D without initial isatuximab weekly dosing, **OR** • Isatuximab 10 mg/kg Q3W. **Cohort D** (may be implemented in the Phase 2 part if positive results are observed in NSCLC Cohort B Phase 2 Stage 2): • Combination RP2D without initial isatuximab weekly dosing. • For the combination cohorts, REGN2810 will be administered first followed by isatuximab on Day 1 of each cycle.
Noninvestigational medicinal product(s) **Formulation** **Route(s) of administration** **Dose regimen**	All patients will receive following premedications to prevent or reduce infusion-associated reactions (IARs), 30 to 60 minutes prior to isatuximab infusion (no longer than 60 minutes). . Criteria for optional premedication for IARs • If a patient develops no IAR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions. • If a patient develops an IAR grade ≤2 during their first infusion only and then experiences no further IARs during their next 3 infusions: The Investigator should discuss with the Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IAR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the investigator's discretion. However, if during the next infusion without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions. • Acetaminophen (paracetamol) 650 to 1000 mg oral route. • Ranitidine 50 mg IV or equivalent (other approved H2 antagonists [eg, cimetidine], oral proton pump inhibitors [eg, omeprazole, esomeprazole]). • Diphenhydramine 25 to 50 mg IV or equivalent (eg, cetirizine, promethazine, dexchlorpheniramine according to local approval and availability. Intravenous route is preferred for at least the first 4 infusions). • Methylprednisolone 100 mg IV or equivalent. • Montelukast 10 mg orally or equivalent (Non-investigational products will be locally sourced and formulations may vary). See above Premedications will be administered 30 to 60 minutes prior to isatuximab infusion (no more than 60 minutes prior). When isatuximab and REGN2810 are to be administrated on the same day, the administration sequence is: premedications, followed by REGN2810, followed by isatuximab. When only isatuximab is to be administrated on a day, the administration sequence is: premedications, followed by isatuximab.

ENDPOINT(S)	**Primary endpoint**: **Phase 1 part:** Safety and tolerability will be assessed based on DLTs (in Cycle 1), AEs/serious adverse events (SAEs), DLTs, and laboratory abnormalities. **Phase 2 part:** RR (for the definition, please refer to "**Response evaluation definition for the primary efficacy endpoint**" below). **Secondary endpoints:** • Safety and tolerability will be assessed based on AEs/SAEs and laboratory abnormalities. • Immunogenicity: Anti-drug antibody (ADA) against isatuximab and against REGN2810. • PK evaluation using non-compartmental analysis for both compounds using serum concentrations for REGN2810 and plasma concentrations for isatuximab (except cross-over part). • Preliminary overall efficacy: Tumor burden change, DOR, DCR, and PFS. **Exploratory endpoints:** • For patients with mCRPC and patients with NSCLC, the following endpoints will be summarized: - OS and TTR. • For patients with NSCLC, the following endpoint will be summarized: - Objective response rate (ORR) by modified Response Evaluation Criteria in Solid Tumors for immune-based therapies (iRECIST). • For patients with mCRPC, the following endpoints will be summarized: - PSA response rate: PSA response is defined as a ≥50% decline from baseline and this decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later. - Radiographic response rate. - Duration of PSA response. - Duration of radiographic response. - Time to PSA response. - Time to radiographic response. - Time to PSA progression. • Preliminary overall efficacy of isatuximab in combination with REGN2810 in patients with mCRPC who progress on isatuximab monotherapy. • To explore the relationship between clinical response and CD38 expression (in infiltrating immune cells and tumor cells), PD-L1 expression (in tumor cells) and immune contexture in tumor at baseline as potential predictive markers of response. • To explore tumor and immune genetic markers at baseline: tumor mutational load and MSI status in tumor as well as tumor mutational profile and immune genetic determinants in blood. • To evaluate pharmacodynamic biomarkers in response to IMP: immunophenotype in peripheral blood, immune contexture in tumor and plasma or serum cytokine levels.

<table>
<tr><td></td><td>

A panel of tumor somatic mutations (ie, tumor mutational profile) will be analyzed at baseline and upon treatment in plasma cell free DNA from peripheral blood.
Determination of exposure-response relationships with efficacy, safety, and biomarkers, if possible.

Response evaluation definition for the primary efficacy endpoint:

In NSCLC: assessed and objective responses are confirmed by Investigators using RECIST 1.1.
In mCRPC: response will be defined per PCWG3 criteria on the basis of the following outcomes (if any of these occur, patients will be considered to have responded):

Radiographic objective response assessed and confirmed by the Investigators.
PSA decline of ≥50% (confirmed by a second PSA test).

</td></tr>
<tr><td>ASSESSMENT SCHEDULE</td><td>Please see Section 1.3 and Section 1.4 (study flowcharts) and Section 1.5 (PK/pharmacodynamics flowcharts) for additional details.</td></tr>
<tr><td>STATISTICAL CONSIDERATIONS</td><td>
Determination of the sample size
Phase 1 part
Approximately 6 (assuming 6 patients for the starting dose) to 24 (assuming 12 patients for the starting dose plus 12 patients for DL-1) DLT evaluable patients are expected to be enrolled. The actual sample size will vary depending on DLTs observed and the number of dose levels explored. Patients who are not evaluable for DLT assessment in the Phase 1 part may be replaced.
Phase 2 part
The Phase 2 part of the study is to evaluate initial anti-tumor activity based on tumor response using RECIST 1.1 criteria for NSCLC and PCWG3 criteria for mCRPC. The efficacy evaluation is based on Simon's 2-stage design with 90% power at 5% 1-sided alpha level for each of the patient cohorts of mCRPC and NSCLC patients respectively.
The assumption of RR, the required sample sizes, and the number of responders at each stage are provided below:
<table>
<tr><th rowspan="2">Indication</th><th rowspan="2">H_0</th><th rowspan="2">H_1</th><th colspan="2">Sample size</th><th colspan="2">Number (%) of responses to reject H_0</th></tr>
<tr><th>Stage 1</th><th>Final</th><th>Stage 1</th><th>Final</th></tr>
<tr><td>mCRPC (Combo)</td><td>10%</td><td>26%</td><td>23</td><td>49</td><td>≥3 (13.0%)</td><td>≥9 (18.4%)</td></tr>
<tr><td>mCRPC (Single)</td><td>10%</td><td>26%</td><td>23</td><td>49</td><td>≥3 (13.0%)</td><td>≥9 (18.4%)</td></tr>
<tr><td>NSCLC (Combo)</td><td>5%</td><td>22%</td><td>20</td><td>36</td><td>≥2 (10.0%)</td><td>≥5 (13.9%)</td></tr>
</table>
Abbreviations: H_0=null hypothesis; H_1=alternative hypothesis; mCRPC=metastatic, castration-resistant prostate cancer; NSCLC=non-small cell lung cancer.
Note: Based on the number of objective responses and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators.
Patients who received the RP2D in Phase 1 will be also included in Phase 2 Stage 1 (eg, if 6 NSCLC patients were enrolled in Phase 1, only 14 NSCLC patients will be needed to complete the Phase 2 Stage 1 NSCLC cohort).
</td></tr>
</table>

	Analysis populations All-treated/safety population: For both Phase 1 and Phase 2 parts of the study, the All-treated/safety population will include all patients who have given their informed consent and received at least 1 dose (even incomplete) of treatments either isatuximab or REGN2810. This population is the primary population for the analyses of efficacy and safety parameters, unless otherwise noted. All analyses using this population will be based on the dose level actually received in the first cycle. DLT evaluable population: The DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and REGN2810 during Cycle 1, and who completed the DLT observation period after the first IMP administration as per Section 9.1.1, unless they discontinue the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population. ADA evaluable population: The ADA evaluable population will include all patients from the all-treated population with at least 1 non-missing ADA result after the first dose of study treatment. PK population: The PK population will include all patients from the all-treated population with at least 1 drug concentration after the first dose of study treatment. Pharmacodynamic population: The pharmacodynamic population will include all patients from the all-treated population with at least 1 pharmacodynamic marker result after the first dose of study treatment. Cross-over population: The cross-over population is defined as patients in Cohort A-2 who progressed on isatuximab monotherapy and received isatuximab in combination with REGN2810. Response evaluable population: The response evaluable population will include all patients who fulfill all eligibility criteria in the all-treated population with an evaluable baseline assessment and at least one evaluable post-baseline response assessment during the treatment period. **General statistical approach** Data from mCRPC and NSCLC cohorts in the Phase 2 part will be analyzed and reported separately by cohort. Data from the Cohort A-2 cross-over part will be summarized separately unless otherwise noted. Analysis of efficacy endpoints: Primary efficacy endpoint (Phase 2): RR will be summarized with descriptive statistics. A 90% 2-sided confidence interval will be computed using Clopper-Pearson method. The statistical inference will be based on the hypothesis and alpha level defined in the sample size calculation section. Analysis of secondary efficacy endpoints: Tumor burden change: the best percent-change from baseline in tumor burden will be summarized and presented graphically for patients with measurable disease at baseline. In addition, a summary of the area under the curve (AUC) and the time adjusted AUC of percent-change from baseline in tumor burden will also be provided as an exploratory analysis. DOR and PFS will be summarized using Kaplan-Meier methods. DCR (complete response + partial response + stable disease) will be summarized with descriptive statistics.

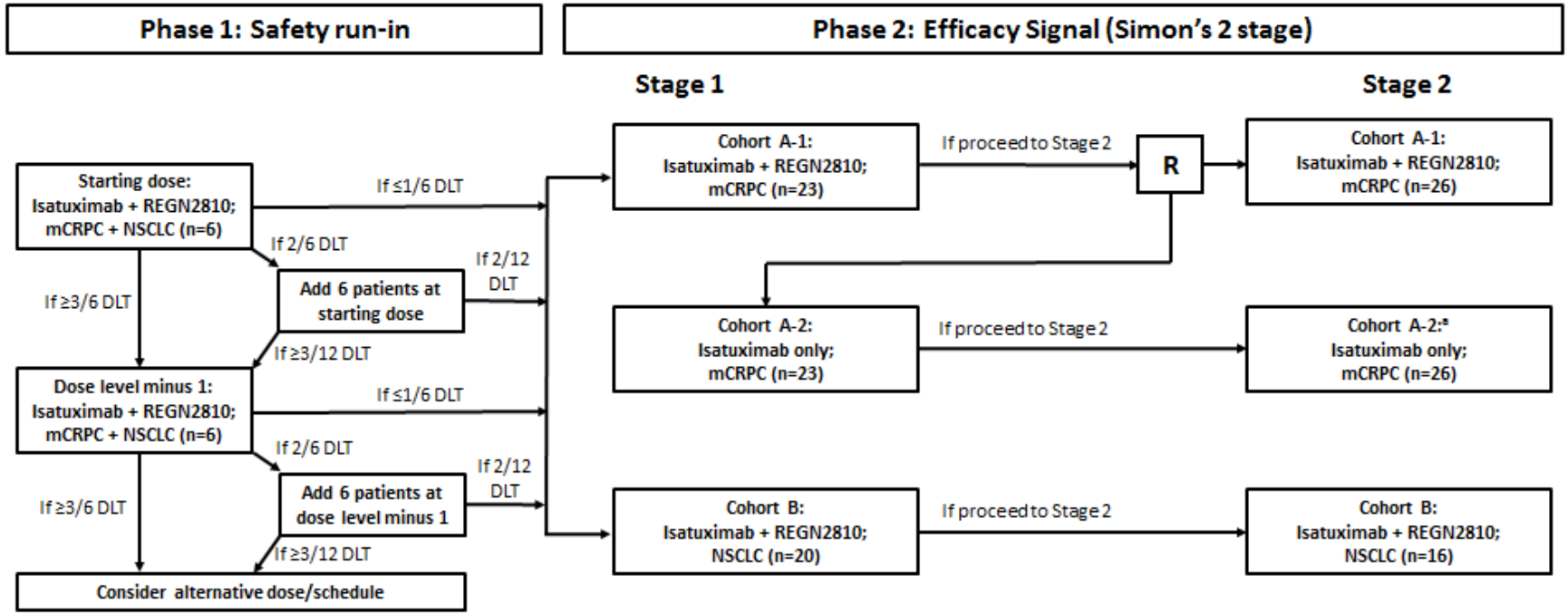
	Analysis of safety endpoints: In the Phase 1 part, the DLTs will be listed by patient using the DLT evaluable population. The treatment emergent adverse events (TEAEs) will be coded according to Medical Dictionary for Regulatory Activities. AEs and laboratory abnormalities will be graded according to the NCI-CTCAE version 4.03. Number (%) of patients experiencing TEAEs by primary system organ class and preferred term will be summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated/safety population. Same table will be prepared for drug related TEAEs, TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. Number (%) of patients with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the all-treated/safety population. The immunogenicity for isatuximab and REGN2810 will be summarized. The impact of positive immune response will be evaluated on efficacy, PK, and safety endpoints when relevant. Analysis of PK endpoints: Descriptive statistics (mean, geometric mean, median, and standard deviation, coefficient of variation, and minimum and maximum) on concentrations and PK parameters will be provided for both REGN2810 and isatuximab. Analysis of pharmacodynamics endpoints: Findings from pharmacodynamics markers will be descriptively summarized and tabulated. **Interim analysis** An interim analysis will be performed for each cohort after the first 23 patients for mCRPC cohorts or the first 20 patients for NSCLC cohort(s) in the Phase 2 part have completed 6 cycles. The interim analysis may be conducted earlier if the required number of responses for proceeding to Phase 2 Stage 2 is achieved. **Planned date for analysis cut-off**: For each cohort, the analysis cut-off date for the primary analysis of RR will be 6 months after the last patient's first treatment in the cohort. The analysis cut-off date for secondary efficacy endpoints including DoR and PFS will be 12 months after the last participant's first treatment in the cohort. The primary analysis of RR will be updated. **Planned date for study cut-off:** The study cut-off is planned at 12 months after the last ongoing patient initiates IMP, or when all participants have had the opportunity to complete the end-of-treatment (EOT) visit 30 days after the last study treatment administration, whichever is the earliest.
DURATION OF STUDY PERIOD (per patient)	The duration of the study for a patient will include a screening period (up to 28 days), a treatment period (up to 2 years), a safety follow-up period (90 days or until negative ADA testing if ADA test is positive or inconclusive at Day 90), and a survival phone call follow-up period (until death or study cut-off).

	Treatment period: The cycle duration is 21 days. Patients will continue treatment until disease progression confirmed by imaging 4 weeks after initial evidence of progression (radiographic progression of mCRPC defined by bone scan should be confirmed by a second bone scan 6 weeks later also using the 2+2 rule [at least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan]) providing they are clinically stable, unacceptable AEs, patient's decision, 2 years of IMP treatment without documented PD, or administrative reasons. Patients with PSA progression in the absence of radiographic progression should continue IMP. **Safety follow-up period:** After treatment discontinuation, patients will return to the study site 30 days (±7 days) after the last dose of IMP, or when the patient receives another anti-cancer therapy, whichever is earlier, for end of treatment (EOT) assessments. In addition, there will be an extended safety follow-up period for 90 days after the last dose of IMP for ADA assessment and for safety assessment. If REGN2810 or isatuximab ADA testing is positive or inconclusive during post treatment follow-up, ADA testing will be repeated every 3 months until negative. Patients who discontinue the study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first. **Survival phone call follow-up period:** The further follow-up schedule beyond 90 days after last dose of IMP is according to the disease progression status: Patients who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP administration until death or study cut-off date. Patients who discontinue the study treatment without PD, and without PD confirmed during the safety follow-up period: will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever occurs first. After PD patient will be followed by phone call until death or study cut-off date. Patients who are still on study treatment after study cut-off date: will continue to receive study treatment and will undergo planned study procedures (except PK and ADA) until confirmation PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first. **Cross-over**: The patients in Cohort A-2 treated with isatuximab monotherapy who experience PD will be permitted to cross over to isatuximab in combination with REGN2810 for up to 2 years after progression on isatuximab monotherapy. Safety and efficacy assessments for these patients during the cross-over period are the same as the assessments in the Phase 2 part. The Sponsor has the right to terminate the study at 1 or more sites for any reason.

1 FLOWCHARTS

1.1 DESIGN DIAGRAM

Figure 1 - Overall study schema



Cohort C and/or Cohort D may be initiated per Section 6.3. No randomization will be needed.

a Patients from Cohort A-2 who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8).

Abbreviations: DLT=dose limiting toxicity; mCRPC=metastatic, castration-resistant prostate cancer; N=number of patients; NSCLC=non-small cell lung cancer; R=randomization.

1.2 STUDY TREATMENT ADMINISTRATION

Cohort	IMP	Cycle 1			Cycle 2			Cycle 3 and subsequent cycles		
		D1	D8	D15	D1	D8	D15	D1	D8	D15
Phase 1 and Phase 2 Cohort A-1 and Cohort B	Isatuximab	X	X	X	X			X		
	REGN2810	X			X			X		
Phase 2 Cohort A-2	Isatuximab	X	X	X	X			X		
Phase 2 Cohort C[a]	Isatuximab	X			X			X		
	REGN2810 (may not be administered if isatuximab monotherapy is chosen for further study)	X			X			X		
Phase 2 Cohort D[b]	Isatuximab	X			X			X		
	REGN2810	X			X			X		

a Depending on the positive efficacy signal and the totality of data observed at the end of Phase 2 Stage 2, the Sponsor may decide to further study isatuximab 10 mg/kg Q3W in combination with REGN2810 or as monotherapy (without isatuximab initial weekly dosing) in patients with mCRPC.

b Depending on the positive efficacy signal and the totality of data observed at the end of Phase 2 Stage 2, the Sponsor may decide to further study isatuximab 10 mg/kg Q3W in combination with REGN2810 (without isatuximab initial weekly dosing) in patients with NSCLC.

Abbreviations: mCRPC=metastatic, castration resistant prostate cancer; NSCLC=non-small cell lung cancer; Q3W=once every 3 weeks.

1.3 STUDY FLOWCHART FOR PHASE 1, PHASE 2 COHORTS A-1, A-2, B AND CROSS-OVER PART

Evaluation[a]	Screening/ Baseline	Cycle 1[b]			Subsequent Cycles[b]	End of Treatment (EOT)	Post treatment safety follow-up period[c]		Survival follow-up[c]
	D-28 to D1	D1	D8	D15	D1	30 (±7) days after last IMP admin	At 60 (±7) days after last IMP admin	At 90 (±7) days after last IMP admin	Beyond 90 (±7) days after last IMP admin
Informed Consent / Inclusion/Exclusion Criteria	X								
Demography, Medical/Surgical and Disease History[d]	X								
Physical Examination[e]	X	X	X	X	X	X	X	X	
Weight/Height (at baseline only)[f]	X	X	X	X	X	X			
Vital Signs[g]	X	X	X	X	X	X	X	X	
Performance Status (ECOG)	X	X	X	X	X	X			
12-Lead ECG[h]	X	As clinically indicated							
Laboratory Assessments:									
Pregnancy Test[i]	X (within 7 days prior to first dose)	X			X	X	X	X[i]	
Blood Chemistry[j]	X	X[k]	X	X	X	X	X	X	
Hematology[l]	X	X[k]	X	X	X	X	X	X	
Coagulation[m]	X	As clinically indicated							
Testosterone level	X								
Blood typing interference test[n]	X				Cycle 2 only				
Urinalysis[o]	X	X[k]	As clinically indicated			X	X	X	
PK[p]	See PK/pharmacodynamics Flow-Chart								
ADA[q]	See PK/pharmacodynamics Flow-Chart								
Exploratory biomarkers:									
Tumor biopsy for IHC analyses: CD38, PD-L1, immune contexture[r]	X				X (Cycle 2 Day 1, unless clinically unfeasible and after discussion with Sanofi Medical Monitor)				

Evaluation[a]	Screening/ Baseline	Cycle 1[b]			Subsequent Cycles[b]	End of Treatment (EOT)	Post treatment safety follow-up period[c]		Survival follow-up[c]
	D-28 to D1	D1	D8	D15	D1	30 (±7) days after last IMP admin	At 60 (±7) days after last IMP admin	At 90 (±7) days after last IMP admin	Beyond 90 (±7) days after last IMP admin
Tumor biopsy for transcriptomic analysis[s]	X				X (Cycle 2 Day 1, unless clinically unfeasible and after discussion with Sanofi Medical Monitor)				
Tumor biopsy for genomic characterization (tumor mutational load and MSI status)[t]	X								
Blood sample for tumor mutational load control[u]	X								
Blood sample for immune genetic markers[v]		X							
Tumor genetic markers (blood)[w]		X			X (Cycle 2 and Cycle 3 only)	X			
Immunophenotyping (blood)[x]		X			X (Cycle 2, Cycle 3, then every other cycle)	X	X		
Plasma or serum cytokines (blood)[y]	X	X			X (Cycle 2, Cycle 3, then every other cycle)	X	X		
Disease Assessment									
- CT/MRI[z]	X				X (repeat every 9 weeks)	X	X		
- PSA assessment[aa]	X	X[k]			X (repeat every 9 weeks)	X	X		
- Bone scan[bb]	X				X (repeat every 9 weeks)	X	X		
Isatuximab Administration[cc]		X	X	X	X				
REGN2810 Administration[cc]		X			X				
AE/SAE Assessment[dd]	X	Continuously throughout study period					X (ongoing related AEs, ongoing SAEs, new related AE/SAEs)		
Prior/Concomitant Medication	X (within 28 days prior to first dose)	Continuously throughout study period					X (related to AE/SAEs)		
New anticancer therapy						X	X		X
Survival status								X	X

a **Evaluation:** Assessments to be performed prior to study treatment and prior to premedication administration unless otherwise indicated. Inform consent should be signed before any study specific procedures. It can be signed more than 28 days prior to enrollment/randomization. Screening time indicates the time frame in which study procedures used to support eligibility have to be done prior to enrollment/randomization.

b **Cycle:** A cycle is 21 days. The treatment window is ±1 day for each of the weekly administrations and ±2 day for each of the Q3W administrations. A dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, and ≥3 days beyond the theoretical day of treatment for Q3W dose. The window for blood chemistry, hematology, urinalysis, PSA assessment (Cycle 1 Day 1 only), and biomarker blood draw is within 1 day prior to IMP administration (where applicable) for Cycle 1 and beyond.

c **Follow-up:** Patients who discontinue the study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first. The further follow-up schedule beyond 90 days after last dose of IMP is according to the disease progression status:
Patients who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP administration until death or study cut-off date.
Patients who discontinue the study treatment without PD, and without PD confirmed during the safety follow-up period: will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever occurs first. After PD patients will be followed by phone call until death or study cut-off date.

d **Demography:** Includes age, gender, and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies and smoking status. **Disease History:** Includes stage at diagnosis and at study entry, and previous anti-tumor therapy (type, duration, reason for discontinuation and response to the therapy). In addition, results of additional procedures (such as EGFR mutation test, ALK, ROS1 fusion detection etc for patients with NSCLC) performed as part of standard of care to assess disease status are also to be collected. The transfusion service should be made aware that the patient is receiving an anti-CD38 treatment (isatuximab). During the study treatment period the transfusion service should follow the recommendations issued in the AABB bulletin in case a blood red cells transfusion is needed. The web link to the AABB bulletin will be indicated on the study patient card (see Appendix E). Patients should keep together their study patient card with their blood type card throughout the duration of the study treatment.

e **Physical Examination:** To be performed at screening (<7 days prior to first dose), prior to study treatment administration, at the EOT visit and during follow-up. Consists of examination of major body systems, including neurological, digestive, respiratory (signs and symptoms, respiratory rate), lymph node examination. Only main diagnoses will be reported in the e-CRF as AEs or medical history. Signs and symptoms related to either mCRPC or NSCLC ongoing at baseline will be recorded in medical history and will be reported in AE page in case they worsen or become serious during study treatment. Laboratory abnormalities at baseline will be recorded in laboratory pages.

f **Weight/Height:** Height is required at baseline only. Weight is required at Screening, prior to starting infusion and at the EOT visit.

g **Vital Signs:** Vital signs including blood pressure, heart rate, temperature, and respiration rate are required at Screening. The measurements will also be performed at the EOT visit, and post treatment follow up visits at 60 and 90 days after last treatment. For all patients, vital signs should be obtained prior to the start of each isatuximab infusion, 1 hour after the start of the infusion, at the end of infusion, and if clinically indicated during the infusion.

h **12-Lead ECG:** Single (not triplet). To be performed at Screening and then as clinically indicated.

i **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration. A pregnancy test (serum or urine) is to be done on Day 1 of each cycle prior to the study treatment, at the EOT visit, and every 30 (± 7) days until 6 months after the last dose of study treatment.

j **Blood Chemistry:** To be done at Screening, then prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Biochemistry should be performed every 7 days in case of Grade 3/4 abnormalities. Blood chemistry includes: AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin and total protein. TSH will be assessed at baseline, every second cycle, EOT, during follow-up visits (60 and 90 days after last treatment); free T4 will be assessed if TSH is outside of the normal range.

k **Blood chemistry, hematology, PSA and urinalysis** assessments are not required to be repeated prior to Cycle 1 Day 1 if the screening laboratory assessments were performed within 3 days prior to first IMP administration.

l **Hematology:** To be done at Screening, then prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L. Blood group card to be obtained before study entry.

m **Coagulation:** To be done at Screening and then as clinically indicated. Coagulation includes: prothrombin time or INR and activated PTT.

n **Blood typing interference test:** at screening: blood type (if not already done) and phenotype (according to the site protocol). Recommended phenotype includes Rh system (C/c and E/e), Kell system (K/k); Duffy system (Fya/Fyb); Kidd system (Jka/Jkb); MNS system (M/N, S/s), and indirect antiglobulin test (indirect Coombs test). On Cycle 2 Day 1 and before each transfusion: IAT (indirect Coombs test or antibody screen). Blood type card will be kept by the patient with the study card. Blood transfusions are to be recorded in the e-CRF. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible.

o **Urinalysis:** Quantitative or semi-quantitative (according to site practice and if such method can provide absolute numeric value of the parameters) urinalysis (includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity) to be done at baseline, Cycle 1 Day 1, EOT, during follow-up and during the treatment period if hematuria is observed or clinically indicated – Dipstick (qualitative) will be performed on Day 1 of each new cycle if clinically indicated.

p **Pharmacokinetics:** Isatuximab and REGN2810. See PK/pharmacodynamics flow chart.

q **ADA:** Isatuximab and REGN2810. See PK/pharmacodynamics flow chart.

r **Tumor biopsy for IHC analysis of CD38, PD-L1, and immune contexture:** 1 tumor biopsy procedure per time point is required (fine needle aspirate is not acceptable, core needle or excisional biopsies, or resected tissue are required): at baseline (mandatory, details please refer to Section 7.2 I 03) and Cycle 2 Day 1 (unless clinically unfeasible and after discussion with Sponsor Medical Monitor). Adequate archival pre-treatment tumor tissue sample may replace mandatory baseline biopsy if sample was obtained at the time of or after progression of immediate previous line of anti-cancer treatment, and can be performed more than 28 days from Day 1 as long as it is performed after progression to prior therapy. Refer to lab manual for description of adequate archival tumor tissue. On-treatment biopsy at Cycle 2 Day 1 maybe obtained within 7 days prior to IMP administration on Cycle 2 Day 1 (after IMP administration on C1D15 wherever applicable). From this tumor biopsy procedure, the priority is to prepare tumor core biopsies for IHC analysis, at least 1 tumor core biopsy is required but 2 tumor core biopsies are preferable. If additional tumor material is available, the additional tumor core biopsies are detailed below for transcriptomic analysis (at baseline and Cycle 2 Day 1) and genomic characterization (at baseline).

s **Tumor biopsy for transcriptomic analysis:** At baseline and Cycle 2 Day 1, if enough tumor material is available after sampling for IHC, 1 additional tumor core biopsy will be collected from the same biopsy procedure for transcriptomic analysis.

t **Tumor biopsy for genomic characterization**: At baseline, if enough tumor material is available after sampling for IHC and transcriptomic analysis, 2 additional tumor core biopsies will be collected as follows: 1 for tumor mutational load and 1 for MSI status.

u **Blood used as a control for tumor mutational load**: a sample of peripheral blood will be drawn at baseline as a control for the tumor mutational load assessment in tumor core biopsy.

v **Immune genetic markers:** a sample of peripheral blood for genetic markers will be drawn at Cycle 1 Day 1, prior to IMP administration.

w **Tumor genetic markers:** a sample of peripheral blood will be drawn at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 prior to IMP administration, and at the EOT visit.

x **Immunophenotyping:** a sample of peripheral blood will be drawn at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 and then on Day 1 prior to IMP administration of each odd cycle starting from Cycle 5 (eg Cycle 5, Cycle 7, Cycle 9, Cycle 11, etc), at the EOT visit, and at follow-up (60 days after last IMP administration).

y **Plasma or serum cytokine concentration:** A sample of peripheral blood will be drawn at baseline and Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then on Day 1 prior to IMP administration at each odd cycle starting from Cycle 5 (ie, Cycle 5, Cycle 7, Cycle 9, Cycle 11 etc), at the EOT visit and at follow-up (60 days after last IMP administration).

z **Tumor assessment**: CT or MRI of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is to be performed in all patients at screening (diagnostic quality scans performed as part of routine clinical management within 28 days prior to IMP initiation are acceptable). Repeat every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), whenever disease progression is suspected, at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days), using the same method for each assessment. If tumor assessment status is partial or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Initial evidence of progression should be confirmed no less than 4 weeks later, see Section 6.7.1. Tumor assessment is not needed for patients who start another anti-cancer treatment regimen. Study sites must retain disease assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

aa **PSA assessment**: For patients with mCRPC, to be performed at baseline (within 14 days before initiation of IMP). Repeat at Cycle 1 Day 1, every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days). PSA responses are to be confirmed no less than 4 weeks later. PSA assessment is not needed for patients who start another anti-cancer treatment regimen.

bb **Bone scan**: Mandatory for patients with mCRPC (diagnostic quality scans performed as part of routine clinical management within 6 weeks prior to IMP initiation are acceptable). Repeat every 9 weeks at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days). If progression is defined by bone scan only, the bone scan should be repeated no less than 6 weeks to confirm the progression, see Section 6.7.1. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not). Study sites must retain disease assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

cc **REGN2810/Isatuximab Administration:** At the start of each treatment cycle, the patient's weight will be determined. REGN2810 administration is only applicable in cohorts receiving isatuximab in combination with REGN2810.

dd **AE/SAE assessment**: All AEs, including adverse events of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 day all ongoing related non-serious AEs, ongoing SAE and new related AE/SAEs are to be followed to resolution or stabilization. Stabilization is defined as an AE ongoing without any change for at least 3 months. Severity will be graded according to NCI-CTCAE version 4.03.

Cross-over part: patients in Cohort A-2 who progressed on isatuximab monotherapy are allowed to enter the cross-over part if clinically stable at the discretion of the Investigators. The screening period for the cross-over part is up to 28 days from PD confirmation. All screening processes for the patients in the Phase 1 and Phase 2 parts are to be conducted before combination IMP initiation for the cross-over part, except informed consent, demography, medical/surgical and disease history, and height. Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor. On-treatment biopsy at Cycle 2, Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1) of the cross-over part is optional (fine needle aspirate is not acceptable). Patients who are included in the cross over part should be evaluated as Cohort A-1 and Cohort B (except PK). Patients who do not meet the cross-over part eligibility criteria should be followed up for safety and survival.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; ALK=anaplastic lymphoma kinase; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=Cycle; CD38=cluster of differentiation 38; CR=complete remission; CRF=case report form; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FFPE=formalin-fixed, paraffin embedded; FUP=follow-up visit; IAT=indirect antiglobulin test; IFN=interferon; IHC=immunohistochemistry; IL=interleukin; IMP=investigational medicinal product; INR=international normalized ratio; LDH=lactate dehydrogenase; mCRPC=metastatic, castration resistant prostate cancer; MDRD=Modification of Diet in Renal Disease Study; MSI=microsatellite instability; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-L1=programmed cell death ligand 1; PK=pharmacokinetic; PR=partial remission; PS=performance status; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; RBC=red blood cell count; SAE=serious adverse event; TNF=tumor necrosis factor; TSH=thyroid stimulating hormone; WBC=white blood cell.

1.4 STUDY FLOWCHART FOR COHORT C AND COHORT D

The alternative schedule may be implemented as an additional cohort in the Phase 2 part in 1 indication when positive results are observed in Phase 2 Stage 2 for such indication.

Evaluation[a]	Screening/ Baseline	Cycle 1[b]	Subsequent Cycles[b]	End of Treatment (EOT)	Post treatment safety follow-up period[c]		Survival follow-up[c]
	D-28 to D1	D1	D1	30 days after last IMP admin	At 60 days after last IMP admin	At 90 days after last IMP admin	Beyond 90 days after last IMP administration
Informed Consent / Inclusion/Exclusion Criteria	X						
Demography, Medical/Surgical and Disease History[d]	X						
Physical Examination[e]	X	X	X	X	X	X	
Weight/Height(at baseline only)[f]	X	X	X	X			
Vital Signs[g]	X	X	X	X	X	X	
Performance Status (ECOG)	X	X	X	X			
12-Lead ECG[h]	X	As clinically indicated					
Laboratory Assessments:							
Pregnancy Test[i]	X (within 7 days prior to first dose)	X	X	X	X	X[i]	
Blood Chemistry[j]	X	X[k]	X	X	X	X	
Hematology[l]	X	X[k]	X	X	X	X	
Coagulation[m]	X	As clinically indicated					
Testosterone level	X						
Blood typing interference test[n]	X		Cycle 2 only				
Urinalysis[o]	X	X[k]	As clinically indicated	X	X	X	
PK[p]	See PK/pharmacodynamics Flow-Chart						
ADA[q]	See PK/pharmacodynamics Flow-Chart						
Exploratory biomarkers:							
Tumor biopsy for IHC analyses: CD38, PD-L1, immune contexture[r]	X		X (Cycle 2 Day 1, unless clinically unfeasible and after discussion with Sanofi Medical Monitor)				

Evaluation[a]	Screening/ Baseline	Cycle 1[b]	Subsequent Cycles[b]	End of Treatment (EOT)	Post treatment safety follow-up period[c]		Survival follow-up[c]
	D-28 to D1	D1	D1	30 days after last IMP admin	At 60 days after last IMP admin	At 90 days after last IMP admin	Beyond 90 days after last IMP administration
Tumor biopsy for transcriptomic analysis[s]	X		X (Cycle 2 Day 1, unless clinically unfeasible and after discussion with Sanofi Medical Monitor)				
Tumor biopsy for genomic characterization (tumor mutational load and MSI status)[t]	X						
Blood sample for tumor mutational load control[u]	X						
Blood sample for immune genetic markers[v]		X					
Tumor genetic markers (blood) [w]		X	X (Cycle 2 and Cycle 3 only)	X			
Immunophenotyping (blood)[x]		X	X (Cycle 2, Cycle 3, then every other cycle)	X	X		
Plasma or serum cytokines (blood)[y]	X	X	X (Cycle 2, Cycle 3, then every other cycle)	X	X		
Disease Assessment							
- CT/MRI[z]	X	X	X (repeat every 9 weeks)	X	X		
- PSA assessment[aa]	X	X[k]	X (repeat every 9 weeks)	X	X		
- Bone scan[bb]	X	X	X (repeat every 9 weeks)	X	X		
Isatuximab Administration[cc]		X	X				
REGN2810 Administration[cc]		X	X				
AE/SAE Assessment[dd]	X	Continuously throughout study period	X (ongoing related AEs, ongoing SAEs, new related AE/SAEs)				
Prior/Concomitant Medication	X (within 28 days prior to first dose)	Continuously throughout study period			X (related to AE/SAEs)		
New anticancer therapy				X	X		X
Survival status							X

a **Evaluation:** Assessments to be performed prior to study treatment and prior to premedication administration unless otherwise indicated. Inform consent should be signed before any study specific procedures. It can be signed more than 28 days prior to enrollment/randomization. Screening time indicates the time frame in which study procedures used to support eligibility have to be done prior to enrollment/randomization.

b **Cycle:** A cycle is 21 days. The treatment window is ±2 day for each of the Q3W administrations. A dose is deemed to have been delayed if the treatment is ≥3 days beyond the theoretical day of treatment for Q3W dose. The reason for dose delay will be captured. The window for blood chemistry, hematology, urinalysis, PSA assessment (Cycle 1 Day 1 only), and biomarker blood draw is within 1 day prior to IMP administration (where applicable) for Cycle 1 and beyond.

c **Follow-up:** Patients who discontinue the study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first. The further follow-up schedule beyond 90 days after last dose of IMP is according to the disease progression status:
Patients who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP administration until death or study cut-off date.
Patients who discontinue the study treatment without PD, and without PD confirmed during the safety follow-up period: will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever occurs first. After PD patients will be followed by phone call until death or study cut-off date.

d **Demography:** Includes age, gender, and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies and smoking status. **Disease History:** Includes stage at diagnosis and at study entry, and previous anti-tumor therapy (type, duration, reason for discontinuation and response to the therapy). In addition, results of additional procedures (such as EGFR mutation test, ALK, ROS1 fusion detection etc for patients with NSCLC) performed as part of standard of care to assess disease status are also to be collected. The transfusion service should be made aware that the patient is receiving an anti-CD38 treatment (isatuximab). During the study treatment period the transfusion service should follow the recommendations issued in the AABB bulletin in case a blood red cells transfusion is needed. The web link to the AABB bulletin will be indicated on the study patient card (see Appendix E). Patients should keep together their study patient card with their blood type card throughout the duration of the study treatment.

e **Physical Examination:** To be performed at screening (<7 days prior to first dose), prior to study treatment administration, at the EOT visit and during follow-up. Consists of examination of major body systems, including neurological, digestive, respiratory (signs and symptoms, respiratory rate), lymph node examination. Only main diagnoses will be reported in the e-CRF as AEs or medical history. Signs and symptoms related to either mCRPC or NSCLC ongoing at baseline will be recorded in medical history and will be reported in AE page in case they worsen or become serious during study treatment. Laboratory abnormalities at baseline will be recorded in laboratory pages.

f **Weight/Height:** Height is required at baseline only. Weight is required at Screening, prior to starting infusion and at the EOT visit.

g **Vital Signs:** Vital signs including blood pressure, heart rate, temperature, and respiration rate are required at Screening. The measurements will also be performed at the EOT visit, and post treatment follow up visits at 60 and 90 days after last treatment. For all patients, vital signs should be obtained prior to the start of each isatuximab infusion, 1 hour after the start of the infusion, at the end of infusion, and if clinically indicated during the infusion.

h **12-Lead ECG:** Single (not triplet). To be performed at Screening and then as clinically indicated.

i **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration. A pregnancy test (serum or urine) is to be done on Day 1 of each cycle prior to the study treatment, at the EOT visit, and every 30 (± 7) days until 6 months after the last dose of study treatment.

j **Blood Chemistry:** To be done at Screening, then prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Biochemistry should be performed every 7 days in case of Grade 3/4 abnormalities. Blood chemistry includes: AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin and total protein. TSH will be assessed at baseline, every second cycle, EOT, during follow-up visits (60 and 90 days after last treatment); free T4 will be assessed if TSH is outside of the normal range.

k **Blood chemistry, hematology, urinalysis and PSA** assessments are not required to be repeated prior to Cycle 1 Day 1 if the screening laboratory assessments were performed within 3 days prior to first IMP administration.

l **Hematology:** To be done at Screening, then prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L. Blood group card to be obtained before study entry.

m **Coagulation:** To be done at Screening and then as clinically indicated. Coagulation includes: prothrombin time or INR and activated PTT.

n **Blood typing interference test:** at screening: blood type (if not already done) and phenotype (according to site protocol). Recommended phenotype includes Rh system (C/c and E/e), Kell system (K/k), Duffy system (Fya/Fyb), Kidd system (Jka/Jkb), MNS system (M/N, S/s), and indirect antiglobulin test (indirect Coombs test). On Cycle 2, Day 1 and before each transfusion: IAT (indirect Coombs test or antibody screen). Blood type card will be kept by the patient with the study card. Blood transfusions are to be recorded in the e-CRF. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible.

o **Urinalysis:** Quantitative or semi-quantitative (according to site practice and if such method can provide absolute numeric value of the parameters) urinalysis (includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity) to be done at baseline, Cycle 1 Day 1, EOT, during follow-up and during the treatment period if hematuria is observed or clinically indicated – Dipstick (qualitative) will be performed on Day 1 of each new cycle if clinically indicated.

p **Pharmacokinetics:** Isatuximab and REGN2810. See PK/pharmacodynamics flow chart.

q **ADA:** Isatuximab and REGN2810. See PK/pharmacodynamics flow chart.

r **Tumor biopsy for IHC analysis of CD38, PD-L1, and immune contexture:** 1 tumor biopsy procedure per time point is required (fine needle aspirate is not acceptable, core needle or excisional biopsies, or resected tissue are required): at baseline (mandatory, details please refer to Section 7.2, I 03) and Cycle 2 Day 1 (unless clinically unfeasible and after discussion with Sponsor Medical Monitor). Adequate archival pre-treatment tumor tissue sample may replace mandatory baseline biopsy if sample was obtained at the time of or after progression of immediate previous line of anti-cancer treatment, and can be performed more than 28 days from Day 1 as long as it is performed after progression to prior therapy. Refer to lab manual for description of adequate archival tumor tissue. On-treatment biopsy at Cycle 2 Day 1 maybe obtained within 7 days prior to IMP administration on Cycle 2 Day 1 (after IMP administration on C1D15 wherever applicable). From this tumor biopsy procedure, the priority is to prepare tumor core biopsies for IHC analysis, at least 1 tumor core biopsy is required but 2 tumor core biopsies are preferable. If additional tumor material is available, the additional tumor core biopsies are detailed below for transcriptomic analysis (at baseline and Cycle 2 Day 1) and genomic characterization (at baseline).

s **Tumor biopsy for transcriptomic analysis:** At baseline and Cycle 2 Day 1, if enough tumor material is available after sampling for IHC, 1 additional tumor core biopsy will be collected from the same biopsy procedure for transcriptomic analysis.

t **Tumor biopsy for genomic characterization**: At baseline, if enough tumor material is available after sampling for IHC and transcriptomic analysis, 2 additional tumor core biopsies will be collected as follows: 1 for tumor mutational load and 1 for MSI status.

u **Blood used as a control for tumor mutational load**: a sample of peripheral blood will be drawn at baseline as a control for the tumor mutational load assessment in tumor core biopsy.

v **Immune genetic markers:** a sample of peripheral blood for genetic markers will be drawn at Cycle 1 Day 1, prior to IMP administration.

w **Tumor genetic markers:** a sample of peripheral blood will be drawn at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 prior to IMP administration, and at the EOT visit.

x **Immunophenotyping:** a sample of peripheral blood will be drawn at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 and then on Day 1 prior to IMP administration of each odd cycle starting from Cycle 5 (eg, Cycle 5, Cycle 7, Cycle 9, Cycle 11, etc), at the EOT visit, and at follow-up (60 days after last IMP administration).

y **Plasma or serum cytokine concentration:** A sample of peripheral blood will be drawn at baseline and Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then on Day 1 prior to IMP administration at each odd cycle starting from Cycle 5 (ie, Cycle 5, Cycle 7, Cycle 9, Cycle 11 etc), at the EOT visit and at follow-up (60 days after last IMP administration).

z **Tumor assessment**: CT or MRI of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is to be performed in all patients at screening (diagnostic quality scans performed as part of routine clinical management are acceptable). Repeat every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), whenever disease progression is suspected, at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days), using the same method for each assessment. If tumor assessment status is partial or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Initial evidence of progression should be confirmed no less than 4 weeks later, see Section 6.7.1. Tumor assessment is not needed for patients who start another anti-cancer treatment regimen. Study sites must retain disease assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

aa **PSA assessment**: For patients with mCRPC, to be performed at baseline (within 14 days before initiation of IMP). Repeat at Cycle 1 Day 1, every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days). PSA responses are to be confirmed no less than 4 weeks later. PSA assessment is not needed for patients who start another anti-cancer treatment regimen.

bb **Bone scan**: For patients with mCRPC, bone scan performed within 6 weeks prior to first study dose is allowed at baseline. Repeat every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD, repeat every 90 days). If progression is defined by bone scan only, the bone scan should be repeated no less than 6 weeks to confirm the progression, see Section 6.7.1. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not). Study sites should retain disease assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

cc **REGN2810/Isatuximab Administration:** At the start of each treatment cycle, the patient's weight will be determined. REGN2810 administration is only applicable in cohort(s) receiving isatuximab in combination with REGN2810.

dd **AE/SAE assessment**: All AEs, including adverse events of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 day all ongoing related non-serious AEs, ongoing SAE and new related AE/SAEs are to be followed to resolution or stabilization. Stabilization is defined as an AE ongoing without any change for at least 3 months. Severity will be graded according to NCI-CTCAE version 4.03.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; ALK=anaplastic lymphoma kinase; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=Cycle; CD38=cluster of differentiation 38; CR=complete remission; CRF=case report form; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; e-CRF=electronic case report form; EOT=end-of-treatment; FFPE=formalin-fixed, paraffin embedded; FUP=follow-up visit; IAT=indirect antiglobulin test; IFN=interferon; IHC=immunohistochemistry; IL=interleukin; IMP=investigational medicinal product; INR=international normalized ratio; LDH=lactate dehydrogenase; mCRPC=metastatic, castration resistant prostate cancer; MDRD=Modification of Diet in Renal Disease Study; MSI=microsatellite instability; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-L1=programmed cell death ligand 1; PK=pharmacokinetic; PR=partial remission; PS=performance status; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; RBC=red blood cell count; SAE=serious adverse event; TNF=tumor necrosis factor; TSH=thyroid stimulating hormone; WBC=white blood cell.

1.5 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART

1.5.1 For Phase 1 part, Stage 1 Phase 2 part of Cohort A-1 and Cohort B (not applicable for the patients with NSCLC who are enrolled for Phase 2 Stage 1 after implementation of Amendment #5 at individual sites)

Study Phase	**Treatment Phase**																			**Post treatment**
Cycle	**Cycle 1**											**Cycle 3**		**Cycle 4**				**Subsequent Cycles**		**Follow-up period**
Day within cycle	**D1**				**D4**	**D8**	**D15**		**D22 (Cycle 2 Day 1)**			**D1**		**D1**				**D1**		**90 ±7 days after last study treatment**
Sample RNT (h) Ref: **REGN2810 SOI**	**SOI**	**EOI**	**EOI +4h**	-	**72h**	**168h**	**336h**	-	**504h (SOI)**	**EOI**	-	**SOI**	**EOI**	**SOI**	**EOI**	-	-	**SOI**	-	-
Sample Time window[a]	[-24h, SOI]	[-5 min, EOI]	±30 min	-	±5h	±24h	±48h	-	[-24h, SOI]	[-5 min, EOI]	-	[-24h, SOI]	[-5 min, EOI]	[-24h, SOI]	[-5 min, EOI]	-	-	[-24h, SOI]	-	-
Sample RNT (h) Ref: **Isatuximab SOI**	**SOI**	**-**	**EOI**	**EOI + 4h**	**72h**	**168h (SOI)**	**SOI**	**EOI**	**SOI**	**-**	**EOI**	**SOI**	**-**	**SOI**		**EOI**	**EOI +1h**	SOI		-
Sample Time window[a]	-	-	±10 min	±30 min	±5h	[-24h, SOI]	[-24h, SOI]	±10 min	-	-	±10 min	-	-	-	-	±10 min	±10 min	-	-	-
IMP administration (IV infusion)																				
REGN2810	X-------X								X-------X			X-------X		X-------X				X		
Isatuximab		X-------X				X	X-------X			X-------X			X		X-------X				X	
Pharmacokinetics[b]																				
REGN2810 Sample ID	S00[f]	S01[d]	S02[e]	-	S03	S04	S05	-	S06[f,g]	S07[d]	-	S00[f]	S01[d]	S00[f]	S01[d]	-	-	S00[f]	-	SF00
Isatuximab[h] Sample ID	P00[c]	-	P01[i]	P02	P03	P04[j, k]	P05[j]	P06[i]	P07[c,j]	-	P08[i]	P00[c,j]	-	P00[c,j]	-	P01[i]	P02	P00[c,j, h]	-	-

Study Phase	Treatment Phase																		Post treatment
Cycle	Cycle 1										Cycle 3		Cycle 4			Subsequent Cycles			Follow-up period
Day within cycle	D1		D4	D8	D15	D22 (Cycle 2 Day 1)					D1		D1			D1			90 ±7 days after last study treatment
Immunogenicity (ADA)[l]																			
REGN2810[m]	AS00[f,m]	-				AS01[f, m]	-				-		-			AS00[f, m]	-		ASF00[n]
Isatuximab[h,o]	AP00[c,o]	-				AP01[c, o]	-	-			AP00[c, o]	-	AP00[c, o]	-	-	AP00[c, h ,o]	-		APF00[h, p]

a Time windows targeted for PK/pharmacodynamics and ADA sampling.

b Refer to the laboratory manual for sample collection, processing and shipping. REGN2810 PK samples to be collected: Cycle 1 predose (corresponding to SOI) and actual end of infusion (ie, EOI), EOI+ 4h, 72h, 168h, 336h, and 504h (predose second administration) after start of first dose; EOI of second administration (Day 22 [Day 1 of Cycle 2]); then Cycles 3 and 4: predose and EOI; subsequent cycles: predose and at 90 days after last study treatment administration; isatuximab PK samples to be collected: Cycle 1 predose and EOI, EOI+ 4h, 72h and 168h (predose second administration, Day 8 of Cycle 1) after start of first dose; Cycle 1 Day 15 and Cycle 1 Day 22 (corresponding to Cycle 2 Day 1): predose and EOI; then Cycle 3 Day 1 predose; Cycle 4 Day 1 predose, EOI, EOI+ 1h; subsequent cycles Day 1 predose. For the patients with NSCLC who are enrolled for Phase 2 Stage 1 after implementation of Amendment #5 at individual sites, no PK samples for REGN2810 and isatuximab will be collected.

c Predose sample: isatuximab PK or ADA assessment could be drawn at the same time just before REGN2810 administration.

d Sample collected just before (within 5 minutes) the actual end of infusion of REGN2810.

e Sample collected for REGN2810 could be drawn at the same time as the end of infusion sample of isatuximab.

f REGN2810 sample collected strictly before the start of REGN2810 infusion.

g S06 sample must be collected even if the second infusion of REGN2810 is not done or delayed

h Isatuximab PK and ADA samples to be collected each cycle until the last study treatment for PK and until follow-up for ADA or at the cut-off date, whichever comes first. However, collection can be stopped earlier or reduced upon notification from the Sponsor based on the updated knowledge of isatuximab immunogenicity and PK.

i Sample collected just before actual end of infusion of isatuximab.

j Predose sample for isatuximab collected strictly before the start of isatuximab infusion.

k P04 sample must be collected even if the patient withdraws the study without receiving the second administration of isatuximab.

l After start of study treatment, if 1 drug is prematurely discontinued, ADA samples for this drug will be collected on Day 1 of the 2 next cycles. If ADA test at the second cycle is positive or inconclusive, ADA testing will be repeated every 3 months until negative. The ADA sample collection for other drug should be done as planned.

m During the treatment phase, the ADA samples for REGN2810 must be collected before REGN2810 treatment administration at each time point: Cycle 1 Day1, Cycle 1 Day 22 (predose Cycle 2), and on Day 1 every 3 cycles afterwards (ie, Cycle 5, Cycle 8, Cycle 11, Cycle 14 etc). In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. For the patients with NSCLC who are enrolled for Phase 2 Stage 1 after implementation of Amendment #5 at individual sites, no REGN2810 ADA samples will be collected.

n During the posttreatment follow-up period REGN2810 ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until the sample is negative (ASF01, ASF02…).

o During the treatment phase, the ADA samples for isatuximab must be collected before isatuximab treatment administration on Day 1 of each Cycle (could be drawn at the same time just before REGN2810 administration). ADA samples are not collected at Cycle 1 Day 8 or Cycle 1 Day 15. For the patients with NSCLC who are enrolled for Phase 2 Stage 1 after implementation of Amendment #5 at individual sites, no isatuximab ADA samples will be collected.

p During the posttreatment follow-up period isatuximab ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until the sample is negative (APF01, APF02…).

Abbreviations: AB=antibody; ADA=anti-drug antibody; AP=antibody plasma (for isatuximab); AS=antibody serum (for REGN2810); EOI=end of IV infusion; IMP=investigational medicinal product; P=Plasma; PD=pharmacodynamics; PK=pharmacokinetics; RNT=relative nominal time; S=Serum; SOI=start of IV infusion.

1.5.2 For Phase 2 part of Cohort A-2, Stage 2 Phase 2 part of Cohort A-1 and Cohort B (tests for REGN2810 are not applicable for Cohort A-2, tests for PK are not applicable for cross-over part)

Study phase	**Treatment phase**																	**Post treatment**
Cycle	**Cycle 1**										**Cycle 3**		**Cycle 4**			**Subsequent cycles**		**Follow-up period**
Day within cycle	**D1**				**D8**	**D15**		**D22 (Cycle 2 Day 1)**			**D1**		**D1**			**D1**		**90 ±7 days after last study treatment**
Sample RNT (h) Ref: **REGN2810 SOI**	**SOI**	**EOI**	**EOI+4h**	**-**	**168h**	**336h**	**-**	**504h (SOI)**	**EOI**	**-**	**SOI**	**EOI**	**SOI**	**EOI**	**-**	**SOI**	**-**	-
Sample Time window[a]	[-24h, SOI]	[-5 min,EOI]	±30 min	-	±24h	±48h	-	[-24h, SOI]	[-5 min,EOI]	-	[-24h, SOI]	[-5 min,EOI]	[-24h, SOI]	[-5 min,EOI]	-	[-24h, SOI]	-	-
Sample RNT (h) Ref: **Isatuximab SOI**	**SOI**	**-**	**EOI**	**EOI+1h**	**168h (SOI)**	**SOI**	**EOI**	**SOI**	**-**	**EOI**	**SOI**	**-**	**SOI**	**-**	**EOI**	**SOI**	**-**	-
Sample Time window[a]	-	-	±10 min	±10 min	[-24h, SOI]	[-24h, SOI]	±10 min	-	-	±10 min	-	-	-	-	±10 min	-	-	-
IMP administration (IV infusion)																		
REGN2810	X-------X							X-------X			X-------X		X-------X			X		
Isatuximab		X-------X			X	X-------X			X-------X			X-------X		X-------X			X	
Pharmacokinetics[b]																		
REGN2810 Sample ID	S00[f]	S01[d]	S02[e]	-	S03	S04	-	S05[f,g]	S06[d]	-	S00[f]	S01[d]	S00[f]	S01[d]	-	S00[f]	-	SF00
Isatuximab[h] Sample ID	P00[c]	-	P01[i]	P02	P03[i,k]	P04[j]	P05[i]	P06[c,j]	-	P07[i]	P00[c,j]	-	P00[c,j]	-	P01[i]	P00[c, h,j]	-	-
Immunogenicity (ADA)[l]																		
REGN2810[m]	AS00[f,m]	-						AS01[f,m]	-		-		-			AS00[f,m]	-	ASF00[n]
Isatuximab[h,o]	AP00[c,o]	-						AP01[c,o]	-	-	AP00[c,o]	-	AP00[c,o]	-	-	AP00[c, h ,o]	-	APF00[h,p]

a Time windows targeted for PK/pharmacodynamics and ADA sampling.

b Refer to the laboratory manual for sample collection, processing and shipping. REGN2810 PK samples to be collected: Cycle 1 predose (corresponding to SOI) and actual end of infusion (ie, EOI), EOI+ 4h, 168h, 336h, and 504h (predose second administration [Day 1 of Cycle 2]) after start of first dose; EOI of second administration (Day 22 [Day 1 of Cycle 2]); then Cycles 3 and 4: predose and EOI; subsequent cycles: predose and at 90 days after the last study treatment administration; isatuximab PK samples to be collected: Cycle 1 predose and EOI, EOI+ 1hand 168h (predose second administration, Day 8 of Cycle 1) after start of first dose; Cycle 1 Day 15 and Cycle 1 Day 22 (corresponding to Cycle 2 Day 1): predose and EOI; then Cycle 3 Day 1 predose; Cycle 4 Day 1: predose and EOI; subsequent cycles: Day 1 predose.

c Predose sample: isatuximab PK or ADA assessment could be drawn at the same time just before REGN2810 administration.

d Sample collected just before (within 5 minutes) the actual end of infusion of REGN2810.

e Sample collected for REGN2810 could be drawn at the same time as the end of infusion sample of isatuximab.

f REGN2810 sample collected strictly before the start of REGN2810 infusion.

g S05 sample must be collected even if the second infusion of REGN2810 is not done or delayed.

h Isatuximab PK and ADA samples to be collected each cycle until the last study treatment for PK and until follow-up for ADA or at the cut-off date, whichever comes first. However, collection can be stopped earlier or reduced upon notification from the Sponsor based on the updated knowledge of isatuximab immunogenicity and PK.

i Sample collected just before actual end of infusion of isatuximab.

j Predose sample for isatuximab collected strictly before the start of isatuximab infusion.

k P03 sample must be collected even if the patient withdraws the study without receiving the second administration of isatuximab.

l After start of study treatment, if 1 drug is prematurely discontinued, ADA samples for this drug will be collected on Day 1 of the 2 next cycles. If ADA test at the second cycle is positive or inconclusive, ADA testing will be repeated every 3 months until negative. The ADA sample collection for other drug should be done as planned.

m During treatment phase, the ADA samples for REGN2810 must be collected before REGN2810 treatment administration at each time point: Cycle 1 Day1, Cycle 1 Day 22 (predose Cycle 2), and on Day 1 every 3 cycles afterwards (ie, Cycle 5, Cycle 8, Cycle 11, Cycle 14 etc). In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor.

n During posttreatment follow-up period REGN2810 ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until sample is negative (ASF01, ASF02…).

o During treatment phase, the ADA samples for isatuximab must be collected before isatuximab treatment administration on Day 1 of each Cycle (could be drawn at the same time just before REGN2810 administration). ADA samples are not collected at Cycle 1 Day 8 or Cycle 1 Day 15.

p During posttreatment follow-up period isatuximab ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until sample is negative (APF01, APF02…).

Abbreviations: AB=antibody; ADA=anti-drug antibody; AP=antibody plasma (for REGN2810); AS=antibody serum (for isatuximab); EOI=end of IV infusion; P=plasma; PD=pharmacodynamic; PK=pharmacokinetic; RNT=relative nominal time; S=serum; SOI=start of IV infusion.

1.5.3 For Cohort C and Cohort D (tests for REGN2810 are not applicable for Cohort C if isatuximab monotherapy is administered)

Study phase	**Treatment phase**																		**Post treatment**
Cycle	**Cycle 1**										**Cycle 3**		**Cycle 4**				**Subsequent cycles**		**Follow-up period**
Day within cycle	**D1**				**D4**	**D8**	**D15**	**D22 (Cycle 2 Day 1)**			**D1**		**D1**				**D1**		**90 ±7 days after last study treatment**
Sample RNT (h) Ref: **REGN2810 SOI**	**SOI**	**EOI**	**EOI+4h**	**-**	**72h**	**168h**	**336h**	**504h (SOI)**	**EOI**	**-**	**SOI**	**EOI**	**SOI**	**EOI**	**-**	**-**	**SOI**	**-**	-
Sample Time window[a]	[-24h, SOI]	[-5 min,EOI]	±30 min	-	±5h	±24h	±48h	[-24h, SOI]	[-5 min, EOI]	-	[-24h, SOI]	[-5 min,EOI]	[-24h, SOI]	[-5 min,EOI]	-	-	[-24h, SOI]	-	-
Sample RNT (h) Ref: **Isatuximab SOI**	**SOI**	**-**	**EOI**	**EOI+4h**	**72h**	**168h**	**336h**	**-**	**504h (SOI)**	**EOI**	**SOI**	**-**	**SOI**	**-**	**EOI**	**EOI+1h**	**SOI**	**-**	-
Sample Time window[a]	-	-	±10 min	±30 min	±5h	±24h	±48h	-	-	±10 min	-	-	-	-	±10 min	±10 min	-	-	-
IMP administration (IV infusion)																			
REGN2810	X-------X							X-------X			X-------X		X-------X				X		
Isatuximab		X-------X							X-------X			X		X-------X				X	
Pharmacokinetics[b]																			
REGN2810 Sample ID	S00[f]	S01[d]	S02[e]	-	S03	S04	S05	S06[f,g]	S07[d]	-	S00[f]	S01[d]	S00[f]	S01[d]	-	-	S00[f]	-	SF00
Isatuximab[h] Sample ID	P00[c]	-	P01[i]	P02	P03	P04	P05	P06[c, j,k]	-	P07[i]	P00[c,j]	-	P00[c,j]	-	P01[i]	P02	P00[c,j]	-	-
Immunogenicity (ADA)[l]																			
REGN2810[m]	AS00[f,m]	-						AS01[f,m]	-		-		-				AS00[f m]	-	ASF00[n]
Isatuximab[h,o]	AP00[c,o]	-						AP01[c,o]	-	-	AP00[c,o]	-	AP00[c,o]	-	-		AP00[c,h,o]	-	APF00[h,p]

a Time windows targeted for PK/pharmacodynamics and ADA sampling.

b Refer to laboratory manual for sample collection, processing and shipping. REGN2810 PK samples to be collected: Cycle 1 predose (corresponding to SOI) and actual end of infusion (ie, EOI), EOI+ 4h, 72h, 168h, 336h, and 504h (predose second administration [Day 1 of Cycle 2]) after start of first dose; EOI of second administration (Day 22 [Day 1 of Cycle 2]); then Cycles 3 and 4: predose and EOI; subsequent cycles: predose and at 90 days after the last study treatment administration); isatuximab PK samples to be collected: Cycle 1 predose and EOI, EOI+ 4h, 72h, 168h, 336h and 504h (predose second administration, Day 1 Cycle 2); Cycle 1 Day 22 (corresponding to Day 1 of Cycle 2): EOI; then Cycle 3 Day 1: predose; Cycle 4 Day 1: predose, EOI, EOI+ 1h; subsequent cycles Day 1 predose.

c Predose sample: isatuximab PK or ADA assessment could be drawn at the same time just before REGN2810 administration.

d Sample collected just before (within 5 minutes) the actual end of infusion of REGN2810.

e Sample collected for REGN2810 could be drawn at the same time as the end of infusion sample of isatuximab.

f REGN2810 sample collected strictly before the start of REGN2810 infusion.

g S06 sample must be collected even if the second infusion of REGN2810 is not done or delayed.

h Isatuximab PK and ADA samples to be collected each cycle until the last study treatment for PK and until follow-up for ADA or at the cut-off date, whichever comes first. However, collection can be stopped earlier or reduced upon notification from the Sponsor based on the updated knowledge of isatuximab immunogenicity and PK.

i Sample collected just before actual end of infusion of isatuximab.

j Predose sample for isatuximab collected strictly before the start of isatuximab infusion.

k P06 sample must be collected even if the patient withdraws from the study without receiving the second administration of isatuximab.

l After start of study treatment, if 1 drug is prematurely discontinued, ADA samples for this drug will be collected on Day 1 of the 2 next cycles. If ADA test at the second cycle is positive or inconclusive, ADA testing will be repeated every 3 months until negative. The ADA sample collection for other drug should be done as planned.

m During treatment phase, the ADA samples for REGN2810 must be collected before REGN2810 treatment administration at each time points: Cycle 1 Day1, Cycle 1 Day 22 (predose Cycle 2), and on Day 1 every 3 cycles afterwards (ie, Cycle 5, Cycle 8, Cycle 11, Cycle 14 etc). In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor.

n During posttreatment follow-up period REGN2810 ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until sample is negative (ASF01, ASF02…).

o During treatment phase, the ADA samples for isatuximab must be collected before isatuximab treatment administration at each time (could be drawn at the same time just before REGN2810 administration). ADA samples are not collected at Cycle 1 Day 8 or Cycle 1 Day 15.

p During posttreatment follow-up period isatuximab ADA samples are collected at 90 ±7 days after last study treatment and every 3 months thereafter until sample is negative (APF01, APF02…).

Abbreviations: AB=antibody; ADA=anti-drug antibody; AP=antibody plasma (for isatuximab); AS=antibody serum (for REGN2810); EOI=end of IV infusion; P=plasma, PK=pharmacokinetic; RNT=relative nominal time; S=serum; SOI=start of IV infusion.

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3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
ATC:	Anatomincal Therapeutic Chemical
AUC:	area under the curve
BUN:	blood urea nitrogen
CD38:	cluster of differentiation 38
CR:	complete response
CRF:	case report form
CSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
CTCAE:	common terminology criteria for adverse events
CTLA-4:	cytotoxic T-lymphocyte-associated protein 4
DL-1:	dose level minus 1
DLT:	dose limiting toxicity
DOR:	duration of response
DRF:	discrepancy resolution form
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
FDA:	Food and Drug Administration
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FFPE:	formalin-fixed, paraffin-embedded
GCP:	good clinical practice
GnRH:	gonadotropin-releasing hormone
IARs:	infusion associated reactions
IECs:	institutional ethics committees
IHC:	immunohistochemistry
IL:	interleukin
IMP:	investigational medicinal product
INR:	international normalized ratio
irAEs:	immune-related adverse events
IRBs:	institutional review boards
iRECIST:	modified Response Evaluation Criteria in Solid Tumors for immune‑based therapies

ITSM:	immunoreceptor tyrosine-based switch motif
IV:	intravenous
mCRPC:	metastatic, castration resistant prostate cancer
MDRD:	Modified Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
MRI:	magnetic resonance imaging
MSI:	microsatellite instability
MTD:	maximum tolerated dose
NCI:	National Cancer Institute
NE:	not evaluable
NGS:	next-generation sequencing
NIMPs:	non-investigational medicinal products
NK:	natural killer
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormality
PCWG3:	Prostate Cancer Clinical Trials Working Group 3
PD:	progressive disease
PD-1:	programmed cell death 1
PD-L1:	programmed cell death-ligand 1
PD-L2:	programmed cell death-ligand 2
PFS:	progression-free survival
PI 3-K:	phosphatidylinositol 3-kinase
PK:	pharmacokinetics
PR:	partial response
PSA:	prostate-specific antigen
PT:	preferred term
PTT:	partial thromboplastin time
Q2W:	once every 2 weeks
Q3W:	once every 3 weeks
QW:	once weekly
RBC:	red blood cell
RECIST:	modified Response Evaluation Criteria in Solid Tumors
RP2D:	recommended Phase 2 dose
RRs:	response rates
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SD:	stable disease
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TSH:	thyroid stimulating hormone
TTR:	time to response
ULN:	upper limit of normal
VGPR:	very good partial response

WBC:	white blood cell
WOCBP:	woman of childbearing potential

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

4.1.1 Cluster of differentiation 38

Cluster of differentiation 38 (CD38) is a type II glycosylated 45 kilodalton membrane protein that was identified as a lymphocyte marker (1). Cluster of differentiation 38 functions as a receptor binding to CD31 and is involved in cell adhesion and signal transduction. Cluster of differentiation 38 is also an ecto-enzyme catalyzing the synthesis and hydrolysis of cyclic adenosine-diphosphate-ribose from nicotinamide adenine dinucleotide to adenosine diphosphate-ribose (1). Adenosine diphosphate-ribose can be further converted into adenosine, a multifunctional immunosuppressive nucleoside that binds to different specific receptors expressed by immune effector cells (2).

The expression of CD38 in healthy humans can be detected on natural killer (NK) cells, monocytes, dendritic cells, macrophages, granulocytes, activated T and B cells, and plasma cells. Several hematological malignancies express CD38 including those of B-lymphocyte, T-lymphocyte and myeloid origin. Moreover, in some solid tumors, such as prostate, CD38 expression has been shown.

4.1.2 Programmed cell death 1 protein

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (3). The programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (4). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin superfamily member related to cluster of differentiation 28 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death-ligand 1 [PD-L1] and/or programmed cell death-ligand 2 [PD-L2]). The structures of murine PD-1 alone (5) and in complex with its ligands were first resolved (6, 7) and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of the interactions with its ligands were also reported (8).

Programmed cell death 1 protein and family members are type I transmembrane glycoproteins containing an immunoglobulin Variable-type domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and

ZAP70, which are involved in the CD3 T cell signaling cascade (9). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (10). Programmed cell death 1 protein was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, regulatory T cells and NK cells (11). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (12) as well as subsets of macrophages (13) and dendritic cells (14). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (15). Programmed cell death-ligand 1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (15). Both ligands are Type I transmembrane receptors containing both immunoglobulin variable- and immunoglobulin constant-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. Programmed cell death-ligand 2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (16, 17) which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (18). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (19).

Five anti-PD-1 and anti-PD-L1 antibodies, nivolumab, pembrolizumab, atezolizumab, avelumab and durvalumab, are now approved in multiple indications including lung cancer (20, 21, 22, 23, 24, 25, 26, 27).

4.1.3 Solid tumors

4.1.3.1 Non-small cell lung cancer

Despite remarkable advances in targeted therapy, advanced lung cancer patients have not experienced a significant improvement in survival rates. Lung cancer has been shown to be responsive to checkpoint blockade therapy (28, 29). Checkpoint signals such as PD-1/PD-L1 dampen T cell activation and allow tumors to escape the adaptive immune response. Response rates (RRs) in patients with pretreated, advanced non-small cell lung cancer (NSCLC) were much higher and more durable with PD-1 blockade therapy compared to standard-of-care, cytotoxic chemotherapy. Therefore, PD-1 inhibitors such as nivolumab, pembrolizumab and atezolizumab (20, 21, 22, 23) were rapidly approved for both squamous and non-squamous lung cancer in the pretreated population. Recently pembrolizumab was also approved, either as a monotherapy, or in combination with pemetrexed and carboplatin, as first-line treatment of patients with a subset of metastatic NSCLC (24, 25).

However, the majority of patients with NSCLC who respond to PD-1/PD-L1 inhibition will eventually progress. This leaves an unmet need for a large and growing population, especially those patients without actionable oncogenic driver mutations who are not eligible for subsequent chemotherapy. A recent preclinical study from researchers at MD Anderson suggested that CD38 may be involved in the resistance to anti-PD-1 in a NSCLC in vivo model (30, 31).

In this study (ACT15319), the efficacy endpoints for patients with NSCLC are selected based on modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix B ;32) and modified Response Evaluation Criteria in Solid Tumors for immune-based therapies (iRECIST) (Appendix D;33).

4.1.3.2 Metastatic, castration resistant prostate cancer

The prognosis for patients with castration resistant prostate cancer with disseminated metastatic spread remains poor. For the men who have metastatic prostate cancer at the time of diagnosis, their 5-year survival, although improved from 2 decades ago, is still only 28.2% (34). For men with metastatic, castration resistant prostate cancer (mCRPC), the median overall survival (OS) in recent Phase 3 studies has ranged from 12.2 to 34.7 months (35, 36, 37, 38, 39). The approved androgen deprivation therapy and chemotherapy have demonstrated significant improvements in OS but ultimately metastatic prostate cancer remains incurable. The current standard of care for this population is cabazitaxel. From limited retrospective studies, the best clinical response of partial response (PR) may be as high as 25% to 30% (40, 41, 42, 43).

Targeting the immune system represents an appealing option for the development of anti-cancer treatment. The cancer vaccine sipuleucel-T has been approved in the USA for use in mCRPC. A preliminary analysis of a Phase 2 trial which studied the efficacy of pembrolizumab in patients with mCRPC progressing on enzalutamide, demonstrated 4 of 20 patients had achieved a confirmed prostate-specific antigen (PSA) reduction ≥50%. Two of the 4 PSA responders had measurable disease achieved a durable PR (44, 45). In another Phase 2 study, in PD-L1 positive patients with mCRPC who failed or were unable to receive standard of care therapy, 13% of the patients had a confirmed PR with median duration of response of 59 weeks. Stable disease (SD) rate was 39% (46). These data indicate PD-1 inhibitors may have activity in a subset of patients with mCRPC.

Cluster of differentiation 38 is expressed on prostate adenocarcinoma. Based on preclinical studies indicating that isatuximab induced antibody-dependent cellular-mediated cytotoxicity can be enhanced through the inhibition of PD-1, the combination therapy of isatuximab and REGN2810 (an anti-PD-1 antibody currently in clinical development) may provide another option for the treatment of patients with mCRPC who have failed or are not eligible for standard of care (47).

In this study (ACT15319), the primary efficacy endpoint for patients with mCRPC are selected based on PCWG3 guidance (Appendix A;48) and similarly with TOPARP, which led to the breakthrough designation of olaparib in prostate cancer by the US Food and Drug Administration (FDA) in 2016 (49).

4.2 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

4.2.1 Isatuximab

Isatuximab (SAR650984) is a monoclonal antibody that binds selectively to a unique epitope on the human surface antigen CD38. Isatuximab kills tumor cells via multiple biological mechanisms; antibody-dependent cellular-mediated cytotoxicity, antibody-dependent cellular-mediated phagocytosis, complement-dependent cytotoxicity and direct induction of apoptosis (pro-apoptosis) without crosslinking. Isatuximab treatment of CD38-expressing cells also results in inhibition of CD38 enzymatic activity (50).

4.2.1.1 Clinical data

At the cut-off date of 05 January 2017, a total of 323 patients were treated with isatuximab in 7 ongoing studies: TED10893, TCD11863, TCD14079, TCD13983, TED14154, TED14095, and EFC14335. All patients had hematological malignancy. The Phase 1 portion of the TED10893 study (monotherapy; relapsed/refractory multiple myeloma [MM] and other hematological malignancies) and TCD11863 were completed.

For TED10893 (Phase 1, monotherapy; relapsed/refractory MM and other hematological malignancies), a total of 89 patients with CD38+ hematological malignancies were treated with isatuximab. Median time on treatment was 10.1 weeks (2 to 16 weeks) and 8 patients remained on therapy at the analysis cut-off date. In patients with MM (N = 84), the median age was 64 years (40 to 81 years). The median time from diagnosis to first isatuximab dosing was 5.8 years (1.2 to 22.8 years). Median number of prior lines of therapies was 5.0 (1 to 13); 94.0% previously received lenalidomide, 40.5% previously received pomalidomide, 98.8% previously received bortezomib, and 42.9% previously received carfilzomib. Objective response rate (ORR) according to Investigator assessment European Society for Blood and Marrow Transplantation criteria among the 84 MM treated-patients was 20.2% (1 complete response [CR], 16 PR). Clinical benefit response (≥minimal response) was 26.2% and best response was SD in 42.9% of the MM treated-patients. The minimal response or better occurred at all dose levels ≥1 mg/kg. In patients treated at doses ≥10 mg/kg in dose escalation and expansion cohorts (n = 63), ORR was 23.8% (n = 15/63), and the clinical benefit response was 30.2% (n = 19/63). In patients treated at 10 mg/kg once every 2 weeks (Q2W) in the high-risk cohort (n = 18), ORR was 16.7% (n = 3/18) and clinical benefit response was 27.8% (n = 5/18).

Study TCD11863 evaluated the combination of isatuximab with standard doses of lenalidomide and dexamethasone. Two schedules of isatuximab administration were evaluated, Q2W and once weekly (QW)/Q2W. Fifty-seven patients were enrolled in this study. The first part of the trial evaluated 3 doses of isatuximab 3, 5, and 10 mg/kg using the Q2W schedule of administration; among the patients treated at 10 mg/kg (n = 24), the ORR was 62.5% with a PR rate of 20.8%, very good partial response (VGPR) of 33.3% and stringent complete response of 8.3%. Among the patients treated in the second part of the trial (QW/Q2W schedule), the ORR was 50% for both 10 mg/kg (n = 12) and 20 mg/kg (n = 10) QW/Q2W. At 10 mg/kg QW/Q2W, best overall

response was PR for 2 patients and VGPR for 4 patients, whereas at the 20 mg/kg QW/Q2W dose, all responses were VGPR.

Safety data are detailed in Section 4.4.2.1. Please refer to the isatuximab Investigator's Brochure for more information on the current safety and efficacy of isatuximab.

4.2.2 REGN2810

REGN2810 (cemiplimab) is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD-L1-mediated T cell inhibition. REGN2810 displayed a robust, dose-dependent suppression of MC38.Ova tumors in the syngeneic mouse tumor model. The nonclinical activity of REGN2810 is similar to 2 in-house generated anti-PD-1 comparator antibodies with identical amino acid sequence to nivolumab and pembrolizumab (based on publically available sequence data).

4.2.2.1 Clinical data

Cumulatively, as of 20 January 2017, 459 patients have been treated with REGN2810 either as monotherapy or in combination with radiotherapy and/or other cancer therapy in the 3 ongoing studies. A total of 287 patients (62.5%) experienced at least 1 treatment-related adverse event (AE) of which 62 patients (13.5%) experienced Grade 3 or higher treatment-related AEs.

Thirty-five patients (7.6%) experienced treatment-related serious adverse events (SAE).

Efficacy data are available from the ongoing first in human study with REGN2810 (Study R2810-ONC-1423) in patients with advanced solid malignancies, which includes tumor types known to respond poorly to PD-1/PD-L1 blockade. Preliminary efficacy has been observed in NSCLC cohorts in R2810-ONC-1423, with an overall RR of 27.2% and a disease control rate of 69.1%. All RRs are by Investigator assessments.

Safety data are detailed in Section 4.4.2.2. Please refer to the REGN2810 Investigator's Brochure for more information on the current safety and efficacy of REGN2810.

4.3 RATIONALE

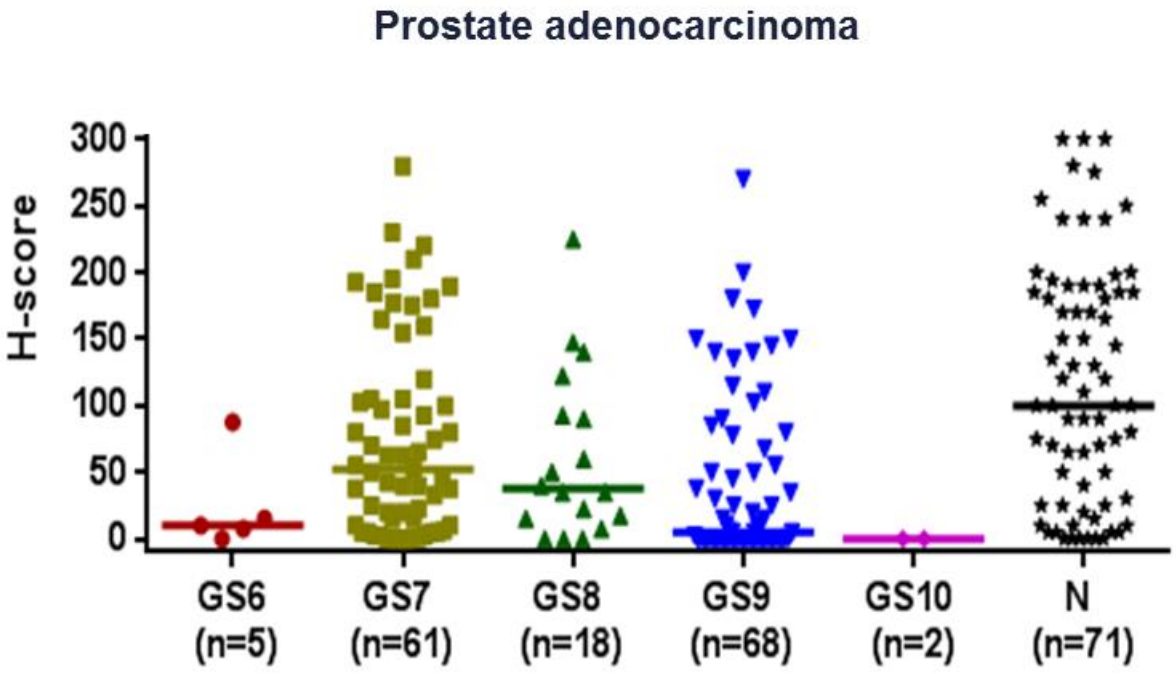
4.3.1 Study rationale

Anti-PD-1 monoclonal antibodies have changed the landscape of cancer therapy. Nivolumab and pembrolizumab were granted accelerated approval by the US FDA in 2014. Despite their success, optimal outcomes for many patients will require combination therapies. Numerous clinical studies are currently evaluating anti-PD-1 antibodies in combination with chemotherapy, targeted therapies and other immunotherapies in patients with solid tumors and hematological malignancies.

Cluster of differentiation 38 expression is well documented in hematological cancers, including MM, lymphomas and leukemias. In solid tumors, CD38 is found expressed on the tumor cells of

treatment naïve prostate adenocarcinoma and glioblastoma biopsies (Sanofi report NCB16V1). Therefore isatuximab monotherapy cohort will be initiated in patients with prostate adenocarcinoma upon positive signal of isatuximab and REGN2810 combination Phase 2 Stage 1. Figure 2 shows the H-scores for CD38 in tumor tissues from prostate adenocarcinoma patients at different stages of the disease (Gleason score 6 to 10). H-scores in normal prostate tissues (N) are also shown.

Figure 2 - Cluster of differentiation 38 H-scores (3 × (% cells 3+) + 2 × (% cells 2+) + 1 × (% cells 1+) in treatment naive prostate adenocarcinoma



Abbreviations: GS=Gleason score; N=normal prostate tissues.

In other solid tumor types, CD38 is not detected on the tumor cells, although it can be detected within the tumor microenvironment. The role of CD38 in the solid tumor environment is not completely understood, but there are several findings indicating that CD38 can contribute to the immune-suppressive tumor microenvironment:

A) CD38 catalyzes the conversion of nicotinamide adenine dinucleotide into immunosuppressive adenosine.

B) CD38 expression is highly correlated with the expression of PD-1 and its ligands in solid tumor biopsies.

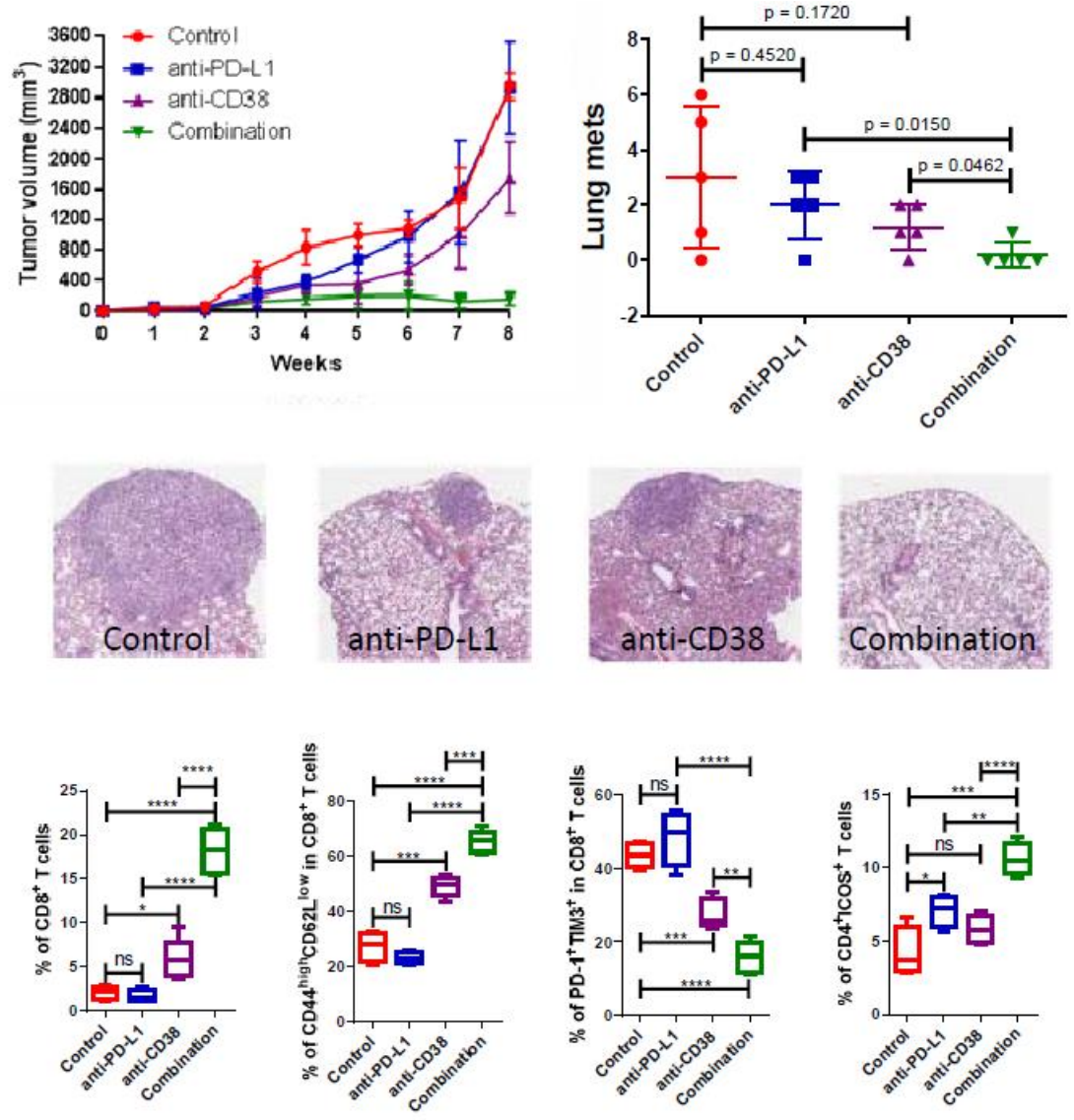
C) CD38 is found upregulated in tumor models that have acquired resistance to anti-PD-L1 (30, 31).

D) CD38 expressing myeloid derived suppressor cells promote growth of human tumors in mice (51).

E) CD38 expressing mouse tumor cells inhibit the proliferation of autologous T cells (47).

A recent report has shown that the combination of anti-PD-L1 and CD38 antibodies induces a greater anti-tumor immune response than anti-PD-L1 in a mouse lung cancer model (Figure 3) (30, 31).

Figure 3 - Combination of anti-CD38 and anti-PD-L1 in a mouse lung cancer model results in enhanced anti-tumor activity, decreases incidence of lung metastasis and increases the tumor infiltration of CD8+ T cells



Details provided in bibliographic reference (30, 31).
Abbreviations: PD-L1=Programmed cell death-ligand 1.

Isatuximab can induce different immuno-modulatory mechanisms that can contribute to reshape the tumor microenvironment and enhance the anti-tumor activity of anti-PD-1 antibodies:

A) Isatuximab decreases circulating regulatory T cell counts and increases total T cell counts in MM patients.

B) Isatuximab restores T cell function inhibited by regulatory T cells (47).

C) Isatuximab induces activation of NK cells and increases their cytolytic activity.

D) Isatuximab increases macrophage phagocytic activity and M1 polarization.

Isatuximab single agent has shown clinical response in relapsed/refractory MM patients and in combination with immuno-modulatory agents. Although isatuximab has not been tested in solid tumors, we hypothesize, based on the immunomodulatory activities described above, that isatuximab may contribute reshaping the tumor immune-environment and will enhance the activity of anti-PD-1 therapy (or antibody).

4.3.2 Schedule and dose of administration

REGN2810 is administered as an intravenous (IV) infusion every 3 weeks at 350 mg dose.

A flat IV REGN2810 dose of 350 mg once every 3 weeks (Q3W) was selected, based on population pharmacokinetics (PK) modeling and simulation, as it is expected to provide exposure that closely replicates that observed in patients (mean weight: 80 kg) for the 3 mg/kg Q2W IV regimen in the ongoing first-in-human study R2810-ONC-1423 (NCT02383212). Simulations of REGN2810 exposure in 1000 patients using population PK analyses indicated that:

- A 350 mg Q3W dose in patients resulted in similar (≤20% difference) C_{trough}, $AUC_{12\ weeks}$, and C_{max} as compared to the 3 mg/kg Q2W dose in the first-in-human patient population (80 kg), and exceeded those observed at the 1 mg/kg Q2W dose.
- The variability in REGN2810 exposure (coefficient of variation) was similar for body-weight adjusted doses as compared to flat doses.

Given the similar predicted exposure for 350 mg Q3W when compared to the 3 mg/kg Q2W regimen, a similar efficacy/safety profile is also expected. Therefore, the 350 mg Q3W IV dose of REGN2810 is being proposed across the REGN2810 program.

In patients with MM, isatuximab exhibits non-linear PK due to the presence of target mediated drug disposition. In addition, tumor burden impacts the PK of isatuximab.

Based on safety, efficacy, PK, and PK/pharmacodynamic analyses, the dose/schedule of isatuximab when used in combination with other therapies for the treatment of MM is 10 mg/kg QW × 4 followed by Q2W. The half-life of isatuximab associated to the linear elimination is 18 days and we hypothesized that the immuno-modulatory mechanisms of isatuximab will be mainly involved in the pharmacological activity of isatuximab; therefore, a less intensive schedule of administration for isatuximab is proposed compared to the schedule used in patients with MMs: 10 mg/kg QW × 3 followed by Q3W. Of note, based on updated pharmacokinetic characterization of isatuximab in 2019, the plasma half-life has been re-estimated to 28 days.

Based on internal safety, efficacy, PK, and PK/pharmacodynamic data analyses, the dose/schedule of isatuximab when used as monotherapy for the treatment of MM is 20 mg/kg QW × 4 followed by Q2W. However, based on the reasons mentioned above and the hypothesis that tumor burden will be lower in patients with prostate cancer compared to MM (ie, less target-mediated drug

disposition), and because isatuximab monotherapy demonstrated activity at doses ≥10 mg/kg with no clear dose response between 10 mg/kg and 20 mg/kg, 10 mg/kg QW × 3 followed by Q3W is proposed to be tested in the monotherapy arm of this study.

Once the plan of care is established with isatuximab 10 mg/kg QW × 3/Q3W, Q3W will be tested as the loading period may not be necessary to ensure activity.

4.4 BENEFIT/RISK ASSESSMENT

4.4.1 Benefits

4.4.1.1 Non-small cell lung cancer

Please refer to Section 4.1.3.1.

4.4.1.2 Metastatic, castration resistant prostate cancer

Please refer to Section 4.1.3.2.

4.4.2 Potential and identified risks

4.4.2.1 Isatuximab

As of 05 January 2017, 323 patients have received isatuximab across 5 ongoing or completed Phase 1/2 clinical studies conducted in patients with MM or other hematological malignancies (319 patients with MM). Isatuximab has been investigated either as monotherapy or in combination with conventional treatment regimens in MM. The safety profile of isatuximab monotherapy has been best characterized in 186 patients (including 181 patients with MM) from study TED10893 (Phase 1 and Phase 2), where the most common treatment emergent AEs, excluding the AEs corresponding to laboratory abnormalities, include infusion-associated reactions (IARs), fatigue, nausea, upper respiratory infection, cough, back pain and diarrhea. Infusion reactions occurred in 49.4% and 51.5% of the patients from TED10893 Phase 1 (concluded) and Phase 2 Stage 1 (ongoing), respectively.

The infusion-associated reactions (IARs) associated with isatuximab in patients who are administered appropriate primary prophylaxis (see also Section 4.4.4) are most common with the first administration of the drug, are not dose-dependent, are Grade 1 to 2 severity, are manageable with standardized precautions detailed in each study protocol, are resolved either spontaneously or with standard medication by the next day following the infusion, and the patients do not appear to sustain sequelae. The IARs generally do not cause treatment discontinuation, and do not tend to recur at subsequent administrations of isatuximab. Primary prophylaxis routinely administered to all the patients consists of diphenhydramine 25 to 50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV, acetaminophen 650 to 1000 mg orally, and montelukast 10 mg orally 30 to 60 minutes (and never longer than 60 minutes) prior to the isatuximab infusion.

In the event of a mild or moderate IAR, the isatuximab infusion should be interrupted and may subsequently resume after recovery at a slower infusion rate under close monitoring and with supportive care, as needed. Prior to restarting the infusion, patients may receive additional medication based on medical judgment; recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In case of a severe hypersensitivity reaction, however, treatment with isatuximab is to be immediately and permanently discontinued.

In addition to the occurrence of infusion reactions, cytokine release syndrome described above, influenza like illness, and fever have also been observed in patients treated with isatuximab; these reactions may involve immunogenicity mechanisms (human antihuman antigen) and hypersensitivity reactions, and are well-known to occur in association with other therapeutic mAb proteins. These adverse reactions, whether acute or delayed, may be serious and systemic (eg, anaphylactic reaction).

To investigate the potential for immunogenicity, anti-drug antibodies (ADAs) are systematically tested across the isatuximab program, using a validated PandA method (DOH1297). As of 30 September 2016, 285 patients (2747 samples) from studies TED10893 (Phase 1 and Phase 2 Stage 1), TED14154, TCD10479, TCD11863, and TCD13983 have been evaluated for ADAs. Isatuximab induced ADAs in 4.2% of the patients (12/285 patients), with 8 patients from study TED10893 Phase 1 and 4 patients from study TCD11863 being found positive for ADAs. Among the 12 patients with positive ADA status, 8 had transiently positive ADA (positive ADA at 1 time point), 1 patient had transiently non-treatment induced positive ADA (positive ADA at baseline), 2 patients had persistently positive ADA (positive ADA titers in samples from 2 separate time points), and 1 patient had pending status (transient versus persistent) depending on subsequent time points to be analyzed. Monitoring of ADAs will continue in current and future clinical trials.

4.4.2.2 REGN2810

The safety profiles of the known anti-PD-1 agents are similar and most notably include a range of AEs considered as immune-related adverse events (irAEs) listed in the REGN2810 Investigator's Brochure. The most commonly observed treatment-related irAEs associated with these monoclonal antibodies are: fatigue, pyrexia, chills, infusion reactions, skin rash, diarrhea/colitis, endocrine toxicities, hepatic toxicities (mainly asymptomatic elevations in aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels), pneumonitis, uveitis, interstitial nephritis, pancreatitis and neurologic syndromes (52, 53). Increasing use and an understanding of how to manage the adverse reactions associated with these agents appears to be have lessened the morbidity as well as the mortality associated with severe irAEs (53).

Cumulatively, as of 20 January 2017, 459 patients have been treated with REGN2810 either as monotherapy or in combination with radiotherapy and/or other cancer therapy in the 3 ongoing studies. Below are summary from the 2 studies in solid tumors (REGN2810 is being evaluated in two Phase 1 clinical studies: R2810-ONC-1423 and R1979 ONC-1504), and one Phase 2 clinical study: R2810-ONC-1540.

R2810-ONC-1423 is a first-in-human repeat dose study with REGN2810 as single therapy and in combination with other anti-cancer therapies in patients with advanced malignancies. As of 20 January 2017, a total of 353 patients have been enrolled and treated with different dose levels

(1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W, and 200 mg Q2W) of REGN2810 as monotherapy as well as in combination with hypofractionated radiation therapy and/or cyclophosphamide or in combination with hypofractionated radiation therapy, cyclophosphamide and granulocyte macrophage colony-stimulating factor or in combination with chemotherapy agents (low dose carboplatin plus docetaxel, low dose docetaxel, full dose carboplatin plus paclitaxel or carboplatin plus pemetrexed); in 2 NSCLC Expansion Cohorts (21 and 22) REGN2810 is given at 3 mg/kg Q3W in combination with chemotherapy. Among 353 patients, the most common treatment-emergent adverse events (TEAEs) occurring in 10% or more of all patients were fatigue (n = 105, 29.7%), nausea (n = 84, 23.8%), decreased appetite (n = 56, 15.9%), anemia (n = 53, 15.0%), constipation (n = 52, 14.7%), arthralgia (n = 45, 12.7%), diarrhoea (n = 45, 12.7%), dyspnea (n = 45, 12.7%), cough (n = 43, 12.2%), pyrexia (n = 40, 11.3%), vomiting (n = 40, 11.3%), asthenia (n = 37, 10.5%) and back pain (n = 37, 10.5%).

R2810-ONC-1540 is a Phase 2, non-randomized, 2-group, multicenter study of REGN2810 at a dose of 3 mg/kg Q2W for patients with advanced cutaneous squamous cell carcinoma (CSCC). The study has 2 groups. Group 1 is for patients with metastatic (nodal or distant) CSCC. Group 2 is for patients with unresectable locally advanced CSCC. As of 20 January 2017, a total of 53 patients have been enrolled and treated with 3 mg/kg REGN2810 in this study. Thirty-two patients were enrolled in the metastatic CSCC group and 21 patients in the unresectable locally advanced CSCC group. The most common TEAEs occurring in 10% or more of all patients included fatigue (n = 13, 24.5%), nausea (n = 7, 13.2%) and decreased appetite (n = 6, 11.3%).

4.4.3 Potential risk related to the combination

Based on the available pre-clinical and clinical data from each individual drug, the potentially overlapping adverse drug reactions anticipated with the isatuximab and REGN2810 combination consist of fatigue, diarrhea, and infusion related reactions, which are all manageable.

4.4.4 Preventative measures to minimize the risk of the combination

To minimize the risk of IARs, all the patients treated with isatuximab should routinely receive primary prophylactic treatment with diphenhydramine 25 to 50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV, acetaminophen 650 to 1000 mg orally and montelukast 10 mg orally, 30 to 60 minutes (and never longer than 60 minutes) prior to the isatuximab infusion to minimize the incidence and severity of IAR commonly observed with monoclonal antibodies. In an attempt to further mitigate the incidence and severity of IARs, it is recommended that the initial infusion rate should not exceed 175 mg of isatuximab per hour. In the absence of IARs after 1 hour of infusion, the infusion rate can be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. In the event of a mild or moderate hypersensitivity reaction, the isatuximab infusion should be interrupted and may subsequently resume after recovery, at a slower infusion rate, under close monitoring and with supportive care as needed. Prior to restarting the infusion, patients may receive additional medication per the judgment of the Investigator; recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In the event of a severe hypersensitivity reaction, treatment with isatuximab is to be immediately and permanently discontinued.

For all patients, vital signs should be obtained prior to the start of each isatuximab infusion, 1 hour after the start of the infusion, at the end of infusion, and if clinically indicated during the infusion.

Criteria for optional premedication for IARs

- For a patient who has no IAR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IAR grade ≤2 during their first infusion only and then experiences no further IARs during their next 3 infusions: The Investigator should discuss with the Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IAR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the investigator's discretion. However, if during the next infusion without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.

To minimize the risk of potential immune-related treatment emergent adverse events related to REGN2810, the exclusion criteria in the Study ACT15319 include:

- Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc).
- Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents, anti-CTLA-4 monoclonal antibodies, and PI3K δ inhibitors) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of investigational medicinal product (IMP).
- Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of IMP initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.
- History of or current interstitial lung disease or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted); history of thoracic radiation received thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

Additionally, careful monitoring of AEs and laboratory abnormalities, continuous direct communication between the Investigators and the monitoring team, and the adherence to the dose modification rules specified in the study protocol, are the measures that will continue to be implemented to minimize the risks in study patients.

General guidelines for the management of irAEs, including some specific irAEs such as colitis, endocrine AEs, pneumonitis, renal AEs, dermatologic AEs, hepatitis, ophthalmologic AEs (eg, uveitis) are also provided in the study protocol.

4.4.5 Conclusion

Overall, the anticipated benefit/risk ratio of isatuximab in combination with REGN2810 supports the conduct of study ACT15319 in patients with mCRPC and NSCLC.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

Phase 1:

- To characterize the safety and tolerability of isatuximab in combination with REGN2810 in patients with mCRPC who are naïve to anti-PD-1/PD-L1-containing therapy naive, or NSCLC who progressed on anti-PD-1/PD-L1-containing therapy, and to confirm the recommended Phase 2 dose (RP2D).

Phase 2 (applicable to Cohorts A-1, A-2, B, C, and D):

- To assess the RR of isatuximab in combination with REGN2810 in patients with either mCRPC who are anti-PD-1/PD-L1 therapy naive, or NSCLC who progressed on anti-PD-1/PD-L1 therapy, **or** of isatuximab as single agent in patients with mCRPC.

5.2 SECONDARY OBJECTIVES

- To evaluate the safety of the combination of isatuximab with REGN2810 or isatuximab monotherapy.
- To evaluate the immunogenicity of isatuximab and REGN2810.
- To characterize the PK profile of isatuximab single agent or in combination with REGN2810, and to characterize the PK of REGN2810 in combination with isatuximab.
- To assess overall efficacy of isatuximab in combination with REGN2810 or single agent (tumor burden change, duration of response [DOR], disease control rate [DCR], and progression-free survival [PFS]).

5.3 EXPLORATORY OBJECTIVES

- To explore the preliminary overall efficacy: OS, time to response (TTR); for patients with mCRPC: PSA RR, radiographic RR, duration of PSA response, duration of radiographic response, time to PSA response, time to radiographic response and time to PSA progression.
- To explore the preliminary overall efficacy of isatuximab in combination with REGN2810 in patients with mCRPC who progress on isatuximab monotherapy.
- To explore the relationship between clinical response and CD38 expression, PD-L1 expression and more broadly immune markers in tumor biopsy at baseline as potential predictive markers of response.
- To explore tumor genetic markers at baseline including tumor mutational load and microsatellite instability (MSI) status as potential markers of response to anti-PD-1 therapy.

- To explore immune genetic markers in blood at baseline such as polymorphisms in FcγR receptors which are important for effector functions of isatuximab.
- To evaluate pharmacodynamic biomarkers in response to investigational medicinal product: immunophenotype to analyze the modulation of different immune cell populations in peripheral blood, immune markers in tumor, transcriptome in tumor and plasma or serum cytokine levels.
- A panel of tumor somatic mutations (ie, tumor mutational profile) will be analyzed at baseline and upon treatment in blood to explore potential mechanisms of escape in response to treatment.
- To perform PK/pharmacodynamics analysis if possible with any relevant pharmacodynamics markers mentioned above, and correlation with safety/efficacy endpoints.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is an open-label, multi-center, non-comparative, Phase 1/2 study to evaluate the safety, preliminary efficacy and PK of isatuximab in combination with REGN2810 or isatuximab alone in patients with advanced malignancies.

The study will be conducted in up to 3 parts:

- The Phase 1 part (safety run-in) is to characterize the safety and tolerability of isatuximab in combination with REGN2810 and to confirm the RP2D.
- The Phase 2 part (efficacy signal search with Simon's 2-stage design) is to assess the preliminary efficacy of isatuximab in combination with REGN2810 or isatuximab alone.
- Cross-over part (a subpart of Cohort A-2) in which patients who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8).

Isatuximab and REGN2810 are defined in this protocol as "study treatments".

6.2 PHASE 1 PART (SAFETY RUN-IN)

Patients with either mCRPC or NSCLC will be enrolled in the Phase 1 part. There is no minimum patient number requirement for either tumor type.

6.2.1 Starting dose and de-escalation design

The starting dose is selected based on past and ongoing clinical trials. Starting dose is 350 mg Q3W for REGN2810 with isatuximab given 10 mg/kg QW for 3 weeks followed by Q3W. Dose de-escalation will be performed if necessary as defined in Table 1 below:

Table 1 - Dose modification for Phase 1

Dose level	Isatuximab	REGN2810
Starting dose	10 mg/kg QW × 3->Q3W	350 mg Q3W
Minus 1 (DL-1)	5 mg/kg QW × 3->Q3W	350 mg Q3W

Abbreviations: DL=dose level; QW=once weekly; Q3W=once every 3 weeks.

At the starting dose, dose limiting toxicity (DLT) will be assessed in the first 6 patients (1 cycle; 21 days):

- If ≤1/6 patient has DLT, the starting dose will be the RP2D.

- If 2/6 patients have DLT, 6 additional patients will be enrolled at starting dose level:
  - If a total of 2/12 patients treated at starting dose have DLT, starting dose will be the RP2D.
  - If a total of ≥3/12 patients have DLT, dose will be de-escalated to dose level minus 1 (DL-1).
- If ≥3/6 patients have DLT, dose will be de-escalated to DL-1.

An additional 6 patients may be enrolled at DL-1; if ≤1/6 patient has DLT, DL-1 will be the RP2D. At DL-1, if ≥2/6 patients have DLT, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor after consulting with the Investigators who recruit patients for the Phase 1 part. If 2/6 patients have DLT, 6 additional patients will be enrolled at DL-1; if a total of 2/12 patients treated at DL-1 have DLT, DL-1 will be the RP2D. If a total of ≥3/12 patients have DLT, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor after consulting with the Investigators who recruit patients for the Phase 1 part.

The DLT observation period is 1 cycle (21 days). The duration of the DLT observation period will be longer for patients who delay initiation of Cycle 2 due to treatment-related AE for which the duration must be assessed in order to determine if the event is a DLT. All AEs during treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be taken into consideration by the Sponsor and recruiting Investigators for the determination of the maximum tolerated dose (MTD) and RP2D.

IMP initiation of patients in the Phase 1 part is to be staggered by ≥3 days.

The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.03 (Appendix F) will be used to assess the severity of AEs. Causal relationship is to be determined by the Investigator. The DLTs will be confirmed by the Sponsor and recruiting Investigators.

6.2.2 Maximum tolerated dose

The MTD is defined as the highest dose level at which no more than 1 out of 6 patients (starting dose or DL-1) or 2 out of 12 patients (starting dose) experience an IMP related DLT. The RP2D is defined as the dose selected for the Phase 2 portion. The Sponsor and recruiting investigators will review the overall data observed to decide MTD and RP2D for the isatuximab and REGN2810 combination.

6.3 PHASE 2 PART (EFFICACY SIGNAL)

The Phase 2 part may include up to 5 cohorts (see design diagram in Section 1.1):

- **Cohort A-1:** mCRPC, isatuximab and REGN2810 combination therapy.
- **Cohort A-2:** mCRPC, isatuximab monotherapy.
- **Cohort B:** NSCLC, isatuximab and REGN2810 combination therapy.

- **Possibly Cohort C**: mCRPC, isatuximab and REGN2810 combination therapy, or isatuximab monotherapy without initial isatuximab weekly dosing.
- **Possibly Cohort D**: NSCLC, isatuximab and REGN2810 combination therapy without initial isatuximab weekly dosing.

A Simon's 2-stage design will be used in each cohort. Enrollment in Cohort A-2 will start only if the decision to proceed to Phase 2 Stage 2 in Cohort A-1 is made.

The patients treated at the RP2D of isatuximab and REGN2810 in combination during Phase 1 will be included in the efficacy analysis together with patients of the same tumor type in Stage 1 of Phase 2. Based on the number of objective responses (observed at least 6 cycles after the last ongoing patient receives first dose of IMP) and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators. After enrollment completion of Phase 2 Stage 1, if efficacy results do not warrant initiation of Stage 2, enrolment will be paused until sufficient results or analyses warrant initiation of Phase 2 Stage 2.

For patients with mCRPC, if it is decided to run Phase 2 Stage 2, an isatuximab monotherapy cohort will be initiated for this population (Cohort A-2); patients with mCRPC will be randomly assigned in a 1:1 randomization ratio to enter Cohort A-1, isatuximab and REGN2810 combination (Phase 2 Stage 2) or Cohort A-2, isatuximab monotherapy (Phase 2 Stage 1). The isatuximab single agent dose and schedule for cohort A-2 is 10 mg/kg QW for 3 weeks followed by Q3W.

Based on the efficacy signal and the totality of data observed within a tumor type at end of Phase 2 Stage 2, the Sponsor may decide to further study isatuximab 10 mg/kg Q3W in combination with REGN2810 or isatuximab as a monotherapy in patients with mCRPC (Cohort C) or isatuximab 10 mg/kg Q3W in combination with REGN2810 in patients with NSCLC (Cohort D), without the isatuximab doses of 10 mg/kg QW for 3 weeks. The schedule without the initial weekly dosing may be more practical for patients and health care providers. Objectives and study design considerations for Cohort C and Cohort D are the same as those for other cohorts in the same tumor type. The Sponsor may decide to test an isatuximab dose of 20 mg/kg in case of inadequate efficacy and PK results.

6.4 CROSS-OVER PART (A SUBPART OF COHORT A-2)

Patients from Cohort A-2 who progress on isatuximab monotherapy may receive isatuximab plus REGN2810 at the discretion of the Investigators and if they still fulfill the eligibility criteria (except exclusion criteria #3 and #8). The screening period for the cross-over part is 28 days from PD confirmation.

All screening processes for the patients in the Phase 1 and Phase 2 parts are to be conducted before combination IMP initiation for the cross-over part, except informed consent, demography, medical/surgical and disease history, and weight/height. Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor. On treatment biopsy at Cycle 2, Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1) of the cross-over part is optional (fine

needle aspirate is not acceptable). Patients who are included in the cross-over part should be evaluated as Cohort A-1 and Cohort B (except PK).

Patients who do not meet the cross-over part eligibility criteria should be followed up for safety and survival.

6.5 RETREATMENT OF PATIENTS

The patient must have recovered to NCI CTC AE Grade ≤1 or to his/her baseline status before initiation of the next cycle at the same dose level. In those cases of clear clinical benefit, a patient will continue treatment until disease progression confirmed by imaging 4 weeks after initial evidence of progression (or 6 weeks for bone progression in mCRPC in Appendix A) as detailed in Section 6.7.1, unacceptable AE, patient's decision, 2 years of uninterrupted delivery of IMP without documented PD, or administrative reasons.

A cycle is 21 days, and deemed to have been delayed if the treatment is >3 days beyond the theoretical day of treatment. The reason for dose delay will be provided. In the event of toxicity including DLT, in order for patients to be retreated, see Section 6.6 and Appendix G for retreatment recommendations.

6.6 DOSE DELAYS/MODIFICATIONS

6.6.1 General rules

Dose modifications are permitted according to the guidelines described in this section.

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor unless required for immediate patient safety.

Dose adjustment, dose delay (ie, delay of either isatuximab or REGN2810 within a cycle for combination cohorts), cycle delay (ie, delay of both IMPs for combination cohorts, or delay of isatuximab for monotherapy cohorts), or dose omission (ie, omission of either isatuximab or REGN2810 within a cycle for combination cohorts) are permitted in case of toxicity. Dose adjustments will be made according to the worst grade of toxicity observed within a cycle. If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

If 1 of the 2 drugs (REGN2810 or isatuximab) is prematurely permanently discontinued, the other drug can be continued until disease progression confirmed by imaging 4 weeks after initial evidence of progression (or 6 weeks for bone progression in mCRPC in Appendix A) as detailed in Section 6.7.1, unacceptable AE, patient's decision, 2 years of uninterrupted delivery of IMP

without documented PD, or administrative reasons. The end of treatment (EOT) assessment in this case will be 30 days after the date of the last IMP administration.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.6.2 Dose delay and dose omission

Within a cycle, the treatment window is ±1 day for each of the weekly administrations and ±2 days for each of the Q3W administrations. Within a cycle, a dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, and ≥3 days beyond the theoretical day of treatment for Q3W dose. The patient will receive the next infusion after recovery of the toxicity as described in Section 6.6.3.

Patients may have dose delay, cycle delay, or dose omission if toxicity occurs and he/she does not recover according to following rules:

- In Cycle 1 (for weekly administration of isatuximab) if toxicity occurs and the patient does not recover on the day of planned infusion or within the following 3 days, infusion of isatuximab (in D8 or D15) may be omitted.
- In Cycle 2 and beyond, if toxicity occurs and the patient does not recover on the day of planned infusion or within the following 14 days, either infusion of isatuximab or REGN2810 may be omitted for combination cohort.
- In case of cycle delay or dose omissions for the recovery of toxicity, the following rules should be followed for restart or discontinue the treatment:
  - In case of a cycle delay up to 14 days or a dose omission, it is per Investigator's decision to restart the study treatment.
  - After a cycle delay of >14 days and ≤84 days, or 2 to 4 consecutive dose omissions, it is per Investigator's decision to restart the study treatment or the IMP that is omitted, if a clear benefit from therapy is observed and after consultation with the Sponsor.
  - The study treatment must be definitely permanently discontinued if the cycle delay is longer than 84 days, or if more than 4 consecutive dose omissions, the IMP will be prematurely discontinued.

6.6.3 Dose modifications

Guidelines for isatuximab and REGN2810 dose modifications and treatment discontinuation due to hematological and non-hematological adverse reactions in general are outlined in Table 2.

See Section 6.6.4 and Appendix G for guidance for irAEs correlated with REGN2810, and Section 6.6.5 for IARs correlated with isatuximab and REGN2810.

The final decision will be based on the Investigator's judgment, in the best interest of the patient.

Table 2 - Isatuximab and REGN2810 dose modification guidelines

Toxicity NCI CTCAE V4.03	Isatuximab dose management	REGN2810 Dose management	Action and Guidelines
Hematological toxicity			
Grade 1, 2, 3	No change		Patient should be given supportive care and monitored closely.
Grade 3 thrombocytopenia lasting >7 days or associated with bleeding	Delay the cycle until bleeding is controlled and platelet >50,000/mm^3. Restart treatment with same dose and schedule.		Patient should be given supportive care and monitored closely. Permanent discontinuation of study treatment should be considered if toxicity does not resolve within 84 days of last infusion.
Grade 4	Delay the cycle until ANC >1000/mm^3, and platelet >50 000/mm^3. Restart with same dose and schedule. Grade 4 lymphopenia: no change in dose		
Febrile neutropenia and/or neutropenic infection	Delay the cycle until fever and infection recover and ANC >1000/mm^3. Restart with same dose and schedule.		
Non-hematological toxicity (other than irAE and IAR)			
Grade 1	No change		N/A
Grade 2 (except alopecia)	Delay the cycle until improves to Grade ≤1 or baseline. Restart treatment at same dose and schedule		It is up to the Investigator's judgment whether to restart the treatment of isatuximab and REGN2810 if the cycle delay is within 14 days. If the cycle delay is longer than 14 days, before restarting the treatment, the Investigator must discuss with Sponsor; if it is determined that it is to the best interest of the patient, the treatment may be restarted. If the cycle delay is longer than 84 days, the treatment must be discontinued.
Grade 3			
Grade 4	Permanently discontinue treatment for treatment related AEs		
Immune-related AE: see Table 3 and Appendix G for dose modification and patient management guideline			
Infusion-Associated Reaction: see Table 4 for IAR management guideline			

Abbreviations: AE=adverse event; ANC=absolute neutrophil count; DL-1=dose level minus 1; IAR=infusion-associated reaction; irAE=immune-related adverse event.

6.6.4 General guidelines for the management of immune-related adverse events

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle.

- Detailed guidance for the management of specific irAEs (colitis, endocrine AE, pneumonitis, renal AE, dermatologic AE, hepatitis, ophthalmologic AE [uveitis]), plus nausea and vomiting is provided in Appendix G.

- General guidance is provided in Table 3.
- If a patient experiences several irAEs which involve different recommendations, the most conservative recommendation should be followed.

The recommendations provided in Table 3 and Appendix G should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 3 - General guidelines for immune-related adverse events

Severity	Withhold/restart /discontinue isatuximab treatment	Withhold/restart/discontinue REGN2810 treatment	Supportive care
Grade 1	No action		Provide symptomatic treatment.
Grade 2	No action	May delay or omit the dose until Grade ≤1	Consider systemic corticosteroids (Prednisone 0.5 to 1 mg/kg/day or equivalent) in addition to appropriate symptomatic treatment.
Grade 3 Grade 4	Delay the cycle until when toxicity improves to Grade ≤1 or baseline. Discontinue prematurely REGN2810 if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 84 days of toxicity.		For any Grade 3-4 immune-related adverse event, if symptoms worsen or do not improve on adequate corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) within 48 to 72 hours), consider additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine and mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

Any patient currently receiving REGN2810 who was previously treated with a phosphatidylinositol 3-kinase (PI3K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other irAE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI3K inhibitor should be reported as an adverse event of special interest (AESI).

6.6.5 General guidelines for the management of infusion-associated reactions

Patients should routinely receive premedications prior to isatuximab infusion as detailed in Section 8.2 to reduce the risk and severity of IARs commonly observed with monoclonal antibodies.

Infusion-associated reactions (which include NCI-CTCAE, version 4.03 terms “allergic/hypersensitivity reactions” and “cytokine release syndrome/acute infusion reaction”)

typically occur within 24 hours from the start of the infusion. If an IAR is observed, patients must also be informed of the potential risk of recurrent allergic reactions at subsequent infusions.

Summary of IAR management is provided in Table 4.

Patients who experience Grade 2 IARs may resume REGN2810/isatuximab infusion after temporary interruption, under close monitoring and with therapy as needed. Patients may receive additional medication per the judgment of the Investigator. Additional recommended medications are: diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent).

Once a Grade 2 IAR has improved or resolved to Grade ≤1, the infusion may be restarted:

- For REGN2810, the infusion should be restarted at half the original infusion rate.
- For isatuximab, the infusion should be restarted at half the original infusion rate, see Section 8.3.1.1 for infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Patients with Grade 3 or 4 IAR must have REGN2810 and/or isatuximab permanently discontinued and appropriate therapy should be administered:

- If a Grade 3 or higher IAR occurs during REGN2810 infusion, REGN2810 should be permanently discontinued. The patient can continue treatment with isatuximab.
- If a Grade 3 or higher IAR occurs after the start of isatuximab infusion, the patient should permanently discontinue treatment with both REGN2810 and isatuximab.

The infusion reaction and the therapy administered must be documented in the case report form (CRF).

Grade 2 or higher IARs must be reported as AESI (see Section 10.5.5). Study personnel should consult the Medical Monitor for further guidance regarding re-treatment of patients with infusion reactions and regarding issues of premedication management (eg, alternative medications for patients allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

Table 4 - Infusion-associated reaction management

Infusion related reaction grading (NCI-CTCAE v4.03 criteria)	Recommendation
Mild Grade 1 Infusion interruption or intervention not indicated	Continuation of REGN2810/isatuximab infusion is per the judgment of the Investigator following close direct monitoring of the patient's clinical status. REGN2810/isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2 as per NCI-CTCAE definition.
Moderate Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours)	Stop REGN2810/isatuximab infusion. Give additional medication(s) with IV diphenhydramine 25 mg (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. REGN2810[a]/Isatuximab[b] may be resumed only after patient recovery, with close monitoring.
Severe or Life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: Life-threatening consequences; urgent intervention indicated	Stop REGN2810/isatuximab infusion. Give additional medication(s) with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. If IAR occurred during REGN2810 infusion, permanently discontinue REGN2810. Continue treatment with isatuximab. If IAR occurred after the start of isatuximab infusion, permanently discontinue both REGN2810 and isatuximab.

a REGN2810: The prepared infusion bag should be kept no more than 8 hours at room temperature, or no more than 24 hours at 5°C (with an acceptable operating range of 2°C to 8°C refrigerator).

b Isatuximab: the infusion should be completed within 16 hours from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.

Abbreviations: AE=adverse event; CTCAE=common terminology criteria for adverse events; IAR=infusion-associated reaction; IFN=interferon; IL=interleukin; IV=intravenous; NCI=National Cancer Institute; TNF=tumor necrosis factor.

6.7 DURATION OF STUDY PARTICIPATION

6.7.1 Duration of study participation for each patient

The duration of the study for a patient will include a period of screening of up to 28 days, a treatment period (up to 2 years), a safety follow-up period (90 days or until ADA is negative, if ADA test is positive or inconclusive at Day 90), and a survival phone call follow-up period.

Treatment period: The cycle duration is 21 days. Patients will continue treatment until disease progression confirmed by imaging 4 weeks after initial evidence of progression (or 6 weeks for bone progression in mCRPC in Appendix A), unacceptable AEs, patient's decision, 2 years of uninterrupted delivery of IMP without documented progressive disease (PD), or administrative reasons.

Patients who have apparent radiographic progression by CT/MRI per RECIST v1.1 or bone scan per PCWG3 criteria are allowed to continue until PD is confirmed providing**:**

- Absence of clinical symptoms or signs indicating clinically significant disease progression;

- No decline in performance status;
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites [eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression] requiring urgent alternative medical intervention;
- No significant, unacceptable or irreversible toxicities related to study treatment.

Safety follow-up period: After treatment discontinuation, patients will return to the study site 30 days (±7 days) after the last dose of IMP, or when the patient receives another anti-cancer therapy, whichever is earlier, for end-of-treatment assessments. In addition, there will be an extended safety follow-up period for 90 days after the last dose of IMP for ADA assessment and for safety assessment. If ADA test is positive or inconclusive, ADA testing will be repeated every 3 months until negative. All ongoing related AEs, ongoing SAEs and new related AE/SAEs will also be followed up.

Patients who discontinue the study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first

Survival phone call follow-up period: The further follow-up schedule beyond 90 days after last dose of IMP is according to the disease progression status:

- **Patients who discontinue study treatment due to PD:** phone call follow-up will be done every 90 days from the date of last IMP administration until death or study cut-off date.
- **Patients who discontinue the study treatment without PD, and without PD confirmed during the safety follow-up period:** will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever occurs first. After PD patients will be followed by phone call until death or study cut-off date.
- **Patients who are still on study treatment after study cut-off date:** will continue to receive study treatment and will undergo planned study procedures (except PK and ADA) until confirmation PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

Cross-over: The patients in Cohort A-2 treated with isatuximab monotherapy who experience PD will be permitted to cross over to isatuximab in combination with REGN2810 for up to 2 years after progression on isatuximab monotherapy. Safety and efficacy assessments for these patients during the cross-over period are the same as the assessments in the Phase 2 part.

For post OS study cut-off date please refer to Section 12.5.3.

Sponsor has the right to terminate the study at 1 or more sites for any reason.

6.7.2 Determination of end of clinical trial (all patients)

The study cut-off is planned at 12 months after the last ongoing patient initiates IMP, or when all participants have had the opportunity to complete the end-of-treatment (EOT) visit 30 days after the last study treatment administration, whichever is the earliest.

6.8 INTERIM ANALYSIS

Refer to Section 13.5 for details of the interim analysis.

6.9 STUDY COMMITTEES

Sponsor representatives and Investigators who have enrolled at least 1 patient will review clinical data approximately every 2 weeks during the course of the Phase 1 part, at the end of Stage 1 and 2 of each tumor cohort, and ad hoc as required.

An independent Data Monitoring Committee (DMC) will periodically evaluate ongoing safety data at intervals planned to be no longer than 3 months (starting from the first data review meeting) and make appropriate recommendations regarding the conduct of Phase 2 of this study.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

Refer to Section 13.1.

7.2 INCLUSION CRITERIA

I 01. Signed written informed consent.

I 02. ≥18 years of age.

I 03. Disease location amenable to mandatory tumor biopsy at baseline (unless clinically unfeasible* as per the Investigator and after obtaining written agreement from sponsor representative, only for NSCLC cohort), and possibly at Cycle 2 Day 1. Fine needle aspirates are not acceptable. Availability of a tissue specimen from core needle or excisional biopsies, or resected tissue are required. Provision of archival tumor tissue sample obtained at the time of or after progression of immediate previous line of anti-cancer treatment is allowed to replace mandatory baseline biopsy. *Clinically unfeasible: With a written opinion from the investigator that performing a biopsy will put the wellbeing of the subject at an excessive risk due to the location of the lesion.

I 04. Based on the Investigator's judgment, at this time, chemotherapy is not the best treatment option for this specific patient. The eligibility of patient to take part in the study will be validated at the multidisciplinary collegial meeting in countries listed in Appendix I.

For mCRPC patients (I05 to I11):

I 05. Histologically confirmed adenocarcinoma of the prostate (excluding neuroendocrine differentiation and/or small cell features).

I 06. Metastatic disease documented by bone lesion on bone scan, or by measurable soft tissue disease by computed tomography (CT) or magnetic resonance imaging (MRI). Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible.

I 07. Surgically or medically castrated, with testosterone levels of <50 ng/dL (<2.0 nM). Patients who have not had a bilateral orchiectomy must have started androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) analogue ≥4 weeks prior to initiation of IMP and continue such therapy throughout the study.

I 08. At least 1 but no more than 2 previous androgen receptor-targeted agents (abiraterone and enzalutamide).

I 09. Received up to 2 previous taxane-based chemotherapy regimens as per local standard of care (for example, docetaxel followed by cabazitaxel), unless per investigator's judgement a chemotherapy regimen is not appropriate for the specific patient. If the same taxane-based chemotherapy is used more than once, this will be considered as 1 regimen.

I 10. No previous radium 223.

I 11. Documentation of PD as assessed by the Investigator with at least 1 of the following within 6 months prior to first dose of IMP per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Appendix A) during or following the direct prior line of therapy.

- Prostate-specific antigen progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. The PSA value at the Screening visit should be ≥1 µg/L (1 ng/mL) if confirmed rise is the only indication of progression. Patients on systemic glucocorticoids for control of symptoms must have documented PSA progression while on systemic glucocorticoids before initiation of IMP.
- Radiographic progression of soft tissue disease by RECIST 1.1 per PCWG recommendation (Appendix B). Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 cm to <1.5 cm are pathologic, subject to clinical discretion, and are nonmeasurable. For existing pathologic adenopathy and other soft tissue disease, progression is defined per RECIST 1.1.
- Progression of bone metastasis is defined as 2 or more documented new bone lesions on a bone scan. Confirmation of ambiguous results by other imaging modalities (eg, CT or MRI) is obligatory if metastatic disease to bone is only defined by bone scan.

For NSCLC patients (I12 to I16):

I 12. Histologically or cytologically confirmed diagnosis of Stage IIIB/IV or inoperable recurrent NSCLC.

I 13. At least 1 measurable disease per RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site.

I 14. One previous anti-PD-1/PD-L1 (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, or REGN2810) containing regimen as the most recent prior therapy to treat Stage IIIB/IV or inoperable recurrent NSCLC. An anti-PD-1/PD-L1 containing regimen is defined as either an anti-PD-1/PD-L1 monotherapy, or an anti-PD-1/PD-L1 agent administered in the same cycle as another systemic therapy.

I 15. No more than 1 previous chemotherapy regimen to treat Stage IIIB/IV or inoperable recurrent NSCLC.

I 16. Documented benefit (defined as CR, PR or SD at ≥1 radiographic imaging scan) but subsequent progression per RECIST 1.1 during the PD-1/PD-L1 containing regimen within 4 months prior to initiation of IMP. The site's study team must have reviewed previous tumor assessments (including screening tumor imaging) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the anti-PD-1/PD-L1 containing regimen.

7.3 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria:

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 (Appendix C).

E 02. Predicted life expectancy <3 months.

E 03. Prior treatment with an agent (approved or investigational) that blocks CD38 (patients who joined a study with an anti-CD38 but have written confirmation they were on control arm are allowed).

E 04. For patients with mCRPC, prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (patients who joined a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed).

E 05. Active brain metastases or leptomeningeal metastases. Patients with asymptomatic central nervous system metastases which have been stable (defined as without evidence of progression by MRI or other imaging modality for at least 28 days prior to initiation of IMP and any neurologic symptoms have returned to baseline) following treatment with surgery or radiation therapy are allowed.

E 06. Symptomatic or impending cord compression.

E 07. Prior solid organ or hematologic transplant.

E 08. Last dose of prior investigational agent within 28 days from initiation of IMP.

E 09. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents, anti-CTLA-4 monoclonal antibodies, and PI3K δ inhibitors) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of IMP. For other agents, treatment-related immune-mediated (or immune-related) AEs that were Grade 2 or above.

E 10. Prior IV cytotoxic chemotherapy, antineoplastic biological therapy, major surgery, local prostatic intervention within 21 days prior to initiation of IMP; oral cytotoxic chemotherapy, hormonal therapy, tyrosine kinase inhibitor therapy, or completed palliative radiotherapy within 14 days prior to initiation of IMP.

E 11. Denosumab or bisphosphonate therapy initiation or dose/regimen adjustment within 28 days prior to initiation of IMP. Patients on a stable regimen are eligible and may continue their therapy without change.

E 12. Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of IMP initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

E 13. Significant cardiac dysfunction, New York Heart Association classification for chronic heart failure III-IV, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG), significant ventricular arrhythmias; myocardial infarction within 6 months; unstable or poorly controlled angina pectoris.

E 14. Ongoing AEs (excluding alopecia and fatigue) caused by any prior anti-cancer therapy ≥Grade 2 (NCI-CTCAE version 4.03).

E 15. Active, known or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency).

E 16. History of or current interstitial lung disease or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted); history of thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

E 17. Receipt of a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 18. Known uncontrolled infection with human immunodeficiency virus, known uncontrolled hepatitis B infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment. To control HBV infection, patients with positive HBsAg should have started anti-HBV therapy before initiation of IMP, and the screening HBV viral load should be <2000 IU/mL (10^4 copies/mL). The anti-HBV therapy should continue throughout the treatment period.

E 19. Known second malignancy either progressing or requiring active treatment within the last 3 years (except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy).

E 20. Inadequate organ and bone marrow function at the Screening visit:

- Absolute neutrophil count (ANC) <1500 u/L (1×10^9/L).
- Platelets <100 × 10³ u/L (after at least 3 days without platelet transfusion).
- Hemoglobin <9 g/dL or <5.6 mmol/L (without transfusions within 2 weeks of initiation of IMP).
- Total bilirubin >2 upper limit of normal (ULN).
- AST and/or ALT >3 × ULN (or >5 × ULN for patients with liver metastases).
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (Modified Diet in Renal Disease [MDRD] Formula; Appendix H).

E 21. Women of reproductive potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy 2 weeks before and during the study treatment period and for 6 months following discontinuation of study treatment by using effective contraceptive methods such as:

- Diaphragm and spermicide PLUS male condom, or
- Intrauterine device PLUS male condom, or
- Medical method (such as hormonal contraceptive) PLUS male condom.
- A woman of productive potential is a woman who: 1) has achieved menarche at some time point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). The choice of effective method is left to Investigator judgment, in accordance to local regulation. Sterilized or infertile subjects are exempted from the requirement to use of contraception. In order to be considered sterilized or infertile, subjects must have undergone surgical sterilization (vasectomy/bilateral tubectomy, hysterectomy, bilateral ovariectomy) or be a postmenopausal woman defined as 12 months or more with no menses prior to enrollment and 50 years of age. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

E 22. Pregnant or breastfeeding woman or woman who intends to become pregnant during the participation in the study.

E 23. Known intolerance or hypersensitivity to any component of isatuximab and/or REGN2810.

E 24. History or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

E 25. Patients who will receive REGN2810: prior treatment with idelalisib.

E 26. Known epidermal growth factor (EGFR) sensitizing mutation, anaplastic lymphoma kinase (ALK) rearrangement, ROS1 rearrangement, or BRAF mutation for patients with non-squamous NSCLC.

Re-screening once is allowed.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

8.1.1 Isatuximab (SAR650984)

8.1.1.1 Pharmaceutical form

The drug product is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80 and pH 6.0 buffer.

Isatuximab is supplied as a sterile, non-pyrogenic, injectable, and colorless, 20 mg/mL concentrate for solution for infusion that may contain white to off-white particulates and is packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of isatuximab. The fill volume has been established to ensure removal of 25 mL.

For administration to patients, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution or 5% dextrose solution. The final infusion volume corresponding to the dose of isatuximab will be administered for a period of time that will depend on dose administered and on the amount of protein given per hour.

8.1.1.2 Dose of drug per administration

The starting dose of isatuximab is 10 mg/kg (see Section 6.2.1).

8.1.1.3 Preparation, reconstitution and administration

Isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution or 5% dextrose solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. In case of patients with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that depends on total dose administered.

Prior to dosing, each patient's dose will be individually prepared by the study pharmacist and labeled with the protocol number, patient number, and treatment description. The patient’s weight should be measured prior to each treatment to allow calculation of the isatuximab dose.

For infusion, an IV tubing administration set with a 0.20 µm in-line filter will be used; if an in-line filter is unavailable, a 0.20 µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

8.1.2 REGN2810 (SAR439684)

8.1.2.1 Pharmaceutical form

REGN2810 drug product is presented as a concentrate for solution for infusion of 50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, at pH 6.0.

8.1.2.2 Dose of drug per administration

The starting dose of REGN2810 is 350 mg per administration (see Section 6.2.1).

8.1.2.3 Preparation, reconstitution and administration

REGN2810 concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. In case of patients with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator. The final infusion volume corresponding to the dose of REGN2810 will be administered by IV infusion for the period of time that will depend on total dose administered.

Prior to dosing, each patient's dose will be individually prepared by the study pharmacist and labeled with protocol number, patient number, and treatment description.

For infusion, an IV tubing administration set with a 0.20 µm in-line filter will be used; if an in-line filter is unavailable, a 0.20 µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Patients should routinely receive premedication 30 to 60 minutes prior to the start of the isatuximab infusion (no longer than 60 minutes) to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. See Section 4.4.4 for additional information on premedication requirements.

- The recommended premedication agents are listed below:Acetaminophen (paracetamol) 650 to 1000 mg, taken orally.
- Ranitidine 50 mg IV or equivalent.
- Diphenhydramine 25 to 50 mg IV or equivalent.
- Methylprednisolone 100 mg IV or equivalent.
- Montelukast 10 mg orally or equivalent

Non-investigational products will be locally sourced and formulations may vary. Investigators must follow the Summary of Product Characteristics/Package Inserts in terms of contraindications for non-investigational medicinal products (NIMPs).

8.2.1 Acetaminophen (paracetamol)

Commercial supplies of acetaminophen or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes.

8.2.2 Ranitidine or equivalent

Ranitidine is presented as a solution for IV infusion. Commercial supplies of ranitidine or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes. Equivalents are other approved H2 antagonists (eg, cimetidine), oral proton pump inhibitors (eg, omeprazole, esomeprazole).

8.2.3 Diphenhydramine or equivalent

Diphenhydramine is presented as a solution for IV infusion. Commercial supplies of diphenhydramine or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes. Equivalents are, eg, cetirizine, promethazine, dexchlorpheniraminem according to local approval and availability. Intravenous route is preferred for at least the first 4 infusions.

8.2.4 Methylprednisolone or equivalent

Methylprednisolone is presented as a solution for IV infusion. Commercial supplies of methylprednisolone or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes.

8.2.5 Montelukast

Commercial supplies of montelukast will be used for the study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes.

8.3 DOSING SEQUENCE

8.3.1 Study treatment

All patients will receive isatuximab in combination with REGN2810 for Phase 1 (safety run-in) and isatuximab only or isatuximab in combination with REGN2810 for Phase 2 (efficacy signal).

Emergency equipment and medication for the treatment of IARs (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use.

A table showing planned study treatment administration is provided in Section 1.2.

Phase 1 and Phase 2 Cohort A-1 and B:

On Day 1 of each cycle (C1 to Cn) patients will receive:

- Premedications as described in Section 8.2

followed by

- REGN2810 infusion over 30 minutes

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

In Cycle 1 Day 8 and 15, patients will receive:

- Premedications as described in Section 8.2

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

Phase 2 Cohort A-2

On Day 1 of each cycle (C1 to Cn) patients will receive:

- Premedications as described in Section 8.2

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

In Cycle 1 Day 8 and 15, patients will receive:

- Premedications as described in Section 8.2

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

Phase 2 Cohort C

On Day 1 of each cycle (C1 to Cn) patients will receive:

- Premedications as described in Section 8.2

followed by

- REGN2810 infusion over 30 minutes (not applicable if isatuximab monotherapy is administered)

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

Phase 2 Cohort D

On Day 1 of each cycle (C1 to Cn) patients will receive:

- Premedications as described in Section 8.2

followed by

- REGN2810 infusion over 30 minutes

followed by

- Isatuximab IV infusion over approximately 2 to 4 hours.

8.3.1.1 Rate and duration of infusion

The duration of infusion for REGN2810 350 mg is 30 minutes per administration.

For isatuximab, the rate of infusion should be initiated at 175 mg/hour:

- First infusion: initiate infusion at 175 mg/hour. In the absence of IARs after 1 hour of infusion, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent infusions: initiate infusion at 175 mg/hour. In the absence of IAR after 1 hour of infusion, increase rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Guidelines for patients who develop IARs are provided in Section 6.6.5.

8.4 BLINDING PROCEDURES

This is an open-label study; therefore, blinding procedures are not applicable.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

All eligible patients will be enrolled into the Phase 1 (safety run-in) of the study. Any proportion of patients with each tumor type can be enrolled.

Patients who received the RP2D in Phase 1 and new patients will then enter the Phase 2 part of Cohort A-1 and Cohort B depending on the type of tumor. If the decision is made to initiate the mCRPC Cohort A-1 Phase 2 Stage 2, an isatuximab monotherapy cohort (Cohort A-2) will be initiated for patients with mCRPC. Patients with mCRPC will be randomly assigned in a 1:1 randomization ratio to Cohort A-1 (Phase 2 Stage 2; isatuximab plus REGN2810 combination therapy) or Cohort A-2 (Phase 2 Stage 1; isatuximab monotherapy).

Study treatment should be initiated within 3 working days after enrollment.

If the decision is to initiate Cohort C and/or Cohort D, patients will be assigned depending on the type of tumor.

8.6 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

8.6.1 Isatuximab

Isatuximab is packaged in 30 mL glass vials fitted with elastomeric closure. Packaging is in accordance with the administration schedule.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6.2 REGN2810

REGN2810 is packaged in USP Type 1 clear glass, 10 mL vial with 20 mm gray chlorobutyl rubber stopper with FluroTec® coating and 20 mm red flip-off seal. Packaging is in accordance with the administration schedule.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.7 STORAGE CONDITIONS AND SHELF LIFE

8.7.1 Isatuximab

Investigators or other authorized persons (eg, pharmacists) are responsible for storing isatuximab in a secure and safe place with restricted access in accordance with local regulations, labeling specifications, policies, and procedures.

Control of isatuximab storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.7.2 REGN2810

Investigators or other authorized persons (eg, pharmacists) are responsible for storing REGN2810 in a secure and safe place with restricted access in accordance with local regulations, labeling specifications, policies, and procedures.

Control of REGN2810 storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the compound should be managed according to the rules provided by the Sponsor.

REGN2810 is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen, and protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.8 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

The IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.8.1 Treatment accountability and compliance

Administration of the IMP will be supervised by the Investigator or Subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP is received from the Sponsor, dispensed to the patient and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the vial must be recorded on the drug accountability form.

The person responsible for drug administration to the patient will record precisely the date and the time of the drug administration to the patient.

8.8.2 Return and/or destruction of treatments

Partially-used and used study treatments will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study

treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization.

8.9 CONCOMITANT TREATMENT

A concomitant medication is any treatment received by the patient concomitantly to any study treatment(s). The administration of concomitant medication should be performed according to the relevant Summary of Product Characteristics/Package Inserts and potential contraindication should be avoided.

All treatments being taken by the patient 28 days prior to the first study treatment, at any time during the study in addition to the IMP are regarded as concomitant treatments and the type, dose and route of administration must be documented on the appropriate pages of the e-CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the e-CRF.

Supportive treatment as medically indicated for the patient’s well-being may be prescribed at the Investigator’s discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded in the e-CRF.

8.9.1 Prohibited concomitant treatments

- Concurrent treatment with any other anti-neoplasm therapy not specified in the protocol, including immunotherapy, hormonal therapy (except GnRH analogue which should continue throughout the study), targeted therapy or biological therapies, or other investigational drug or curative radiotherapy. However, palliative radiotherapy may be given to control pain. The irradiated area should be as small as possible. In all such cases, the possibility of tumor progression should be ruled out by physical, biochemical and radiological assessments of the tumor. The irradiated area cannot be used as a parameter for response assessment.
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Live vaccines should be avoided. However, given the increased risk of infection, routine vaccinations are recommended for the patients and their contacts. Prophylactic vaccination is recommended for influenza A and B virus, pneumococci and haemophilus influenza.
- Prophylactic use of hematopoietic growth factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, erythropoietin) during the DLT observation period. Curative treatment is allowed.

- Denosumab or bisphosphonate therapy initiation or dose/regimen adjustment is not permitted. Patients on a stable regimen may continue their therapy without change.
- Systemic use of interferon.

8.9.2 Contraceptive measures and pregnancy counseling

Females of child bearing potential or male patients with female partners of childbearing potential shall be required to use effective contraceptive methods (double barrier method, intrauterine device, oral contraception or abstinence) 2 weeks prior to first study treatment, while on therapy and for 6 months following the last dose of study treatment.

A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile.

The following highly effective methods of contraception are accepted:

- Sexual abstinence.
- Diaphragm and spermicide PLUS male condom, or,
- Intrauterine device PLUS male condom, or,
- Medical method (such as hormonal contraceptive) PLUS male condom.

The choice of effective method is left to Investigator judgment, in accordance to local regulation. Sterilized or infertile patients are exempt from the requirement to use of contraception. In order to be considered sterilized or infertile, patients must have undergone surgical sterilization (vasectomy/bilateral tubectomy, hysterectomy, bilateral ovariectomy) or be a postmenopausal woman defined as 12 months or more with no menses prior to enrollment and 50 years of age.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The primary objective of the Phase 1 part of this study and a secondary endpoint in the Phase 2 part of the study is to characterize the safety and tolerability of isatuximab in combination with REGN2810 in patients with mCRPC who are anti-PD-1/PD-L1 therapy naïve, or with NSCLC and who progressed on anti-PD-1 therapy, and determine the RP2D. Overall safety monitoring will be performed throughout the whole conduct of the study.

The safety profile will be assessed from the findings of physical examination (preferably by the same physician in each center), laboratory tests and reports of AEs, etc, and will be based on incidence, severity (as graded in the NCI-CTCAE version 4.03), and cumulative nature of TEAEs (defined as AEs that develop or worsen in grade or become serious during the on-treatment period) and of AEs.

9.1.1 Dose-limiting toxicities (Phase 1 only)

Potential DLTs are defined all AEs specified below occurring during the first cycle of treatment, unless due to disease progression or to a cause obviously unrelated to IMP. The duration of the DLT observation period will be longer for patients who delay initiation of Cycle 2 due to treatment-related AE for which the duration must be assessed in order to determine if the event is a DLT.

Hematological abnormalities are defined as any of the following:

- Grade 4 neutropenia for ≥7 consecutive days.
- Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or by microbiologically or radiographically documented infection.
- Grade 3 to 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention.

Non-hematological abnormalities

- Grade 4 non-hematologic AE.
- Grade ≥2 uveitis.
- Grade 3 non-hematological AE lasting >3 days despite optimal supportive care, **except**:
  - Grade 3 fatigue.
  - Allergic reaction/hypersensitivity attributed to isatuximab or REGN2810.
  - Grade 3 or 4 laboratory abnormality that is not clinically significant per recruiting Investigator and Sponsor.
- Delay in initiation of Cycle 2 >14 days due to treatment related laboratory abnormalities/AE.

In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

At the end of Cycle 1, each patient must be assessed by the Investigator to determine if he or she experienced a DLT. This information must be recorded on the appropriate e-CRFs, and an electronic DLT notification (either DLT or not) will be sent to the Sponsor, before a subsequent cycle may begin.

Potential and IMP-related DLTs will be considered as AESIs. As such, Investigators are required to report them to the Sponsor within 24 hours of the Investigator becoming aware of each AE. The Investigator will attach the DLT-specific CRF page to the transmitted DLT/AESI form or will complete the specific DLT form in the e-CRF.

The reported potential DLTs will be reviewed by the Sponsor and recruiting Investigators in order to determine their relationship to the IMP and confirm them as DLTs.

9.1.2 Adverse events

Adverse events will be collected from the signing of the study informed consent form to 30 days after the last IMP administration. Beyond 30 days after last IMP administration all ongoing non-serious AEs, ongoing SAEs and new treatment-related AEs/SAEs are to be followed to resolution or stabilization. Adverse events encountered before the start of isatuximab and REGN2810 treatment or later than 30 days after the last IMP administration will be summarized separately.

All AEs will be graded according to the NCI-CTCAE version 4.03, and will be coded to a "Preferred Term" (PT) and associated primary "System Organ Class" (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized and analysed with respect to the type, frequency, severity, seriousness, relatedness, and outcome.

The general and study-specific safety criteria are presented in Section 10.

9.1.3 Laboratory safety variables

Please refer to "Study Procedures" Section 12.

9.1.4 Clinical examinations

Please refer to "Study Procedures" Section 12.

9.1.5 Immunogenicity

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

Samples missed or lost, for any reason, should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be precisely recorded.

The REGN2810 and isatuximab ADA sampling times for blood collection can be found in the PK Flow Chart. (Section 1.5). Bioanalytical methods used for immunogenicity assessments are summarized in Table 5.

Table 5 - Bioanalytical methods for immune response assessment

Analyte	Anti-isatuximab antibody	Anti-REGN2810 antibody
Matrix	Plasma	Serum
Analytical technique	PandA method	Non-quantitative bridging immunoassay
Site of bioanalysis	Covance Harrogate (UK)	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

9.1.6 Other safety endpoints

Please refer to "Study Procedures" Section 12.

9.2 PHARMACOKINETIC EVALUATION

9.2.1 Sampling time

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

Samples missed or lost, for any reason, should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be precisely recorded.

The REGN2810 and isatuximab PK sampling times for blood collection can be found in the PK Flow Chart (Section 1.5).

9.2.2 Pharmacokinetic sample handling procedure

Detailed instructions for sample preparation and shipping for REGN2810 and isatuximab ADA will be provided to the study sites in a separate Laboratory Manual.

9.2.3 Bioanalytical Methods

Bioanalytical methods are summarized in Table 6.

Table 6 - Bioanalytical methods for isatuximab and REGN2810 pharmacokinetic analysis

Analyte	Isatuximab	REGN2810
Matrix:	Plasma	Serum
Analytical technique:	Immunoassay	Immunoassay
Site of bioanalysis:	Covance (Harrogate, UK)	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

9.2.4 Pharmacokinetic parameters

9.2.4.1 Non-compartmental analysis

Pharmacokinetic parameters will be calculated with PKDMS software (Pharsight), using non-compartmental methods, from isatuximab plasma and REGN2810 serum concentrations. The parameters will include, but may not be limited to, the following:

Table 7 - List of pharmacokinetic parameters and definitions

Parameters	Analyte		Definition
	REGN2810	Isatuximab	
C_{eoi}	X	X	Concentration observed at the end of intravenous infusion
C_{max}	X	X	Maximum concentration observed after the first infusion
t_{max}	X	X	Time to reach C_{max}
C_{last}	X	X	Last concentration observed above the lower limit of quantification
t_{last}	X	X	Time of C_{last}
C_{trough}	X	X	Concentration observed just before treatment administration during repeated dosing
$AUC_{0\text{-}21d}$	X		Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (21 days) after the first administration
$AUC_{0\text{-}7d}$ or $AUC_{0\text{-}21d}$		X	Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (7 days and for cohorts C and D: 21 days) after the first administration

9.2.4.2 Population approach

Population PK approaches may be used for both compounds and more precisely to analyze the isatuximab plasma concentration-time profiles from Phase 2 Stage 2. If done, the data generated will be reported in a standalone report(s).

9.3 BIOMARKERS

- Tumor biopsies will be collected at baseline* and during screening period for the cross-over part* for the following biomarker analyses:
  - CD38, PD-L1 and immune-contexture (such as T cells, B cells, activating or inhibitory receptors) by immunohistochemistry (IHC) or Fluorescent Multiplex IHC in formalin-fixed, paraffin-embedded (FFPE) tumors.
  - Transcriptomic immune profiling by techniques such as next-generation sequencing (NGS) (RNAseq) on RNAlater preserved tumor if enough tumor material is available or by Nanostring on available FFPE tumor sample.
  - Tumor mutational load on RNAlater preserved tumor core biopsy and MSI status on snap frozen preserved tumor core biopsy if enough tumor material is available (for both analyses) or on FFPE tumor core biopsy. The techniques used could be, for example, NGS (DNA exome sequencing or Pentaplex). For the DNA exome sequencing, a sample of peripheral blood will be taken as a control and will not be used to determine the likelihood of the patient or his/her family members developing a disease.
  - Blood DNA for tumor mutational load control will not be used to determine sequences of other genes, nor will these analyses be used to determine the likelihood of the patient or his/her family members developing a disease.

    *Tumor biopsy at baseline or provision of adequate archival pre-treatment tumor tissue sample is mandatory (details please refer to Section 7.2 I 03). Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor.
- Peripheral blood samples will be collected at baseline for the following biomarker analyses:
  - Immune genetic determinants (including FcγR III polymorphism) will be analyzed. Blood DNA for Immune genetic determinants will not be used to determine the likelihood of the patient or his/her family members developing a disease.
- Tumor biopsies will be collected at baseline** and during treatment (including cross-over period treatment)**, for the following pharmacodynamics biomarker analyses:
  - CD38 positive cells and immune-contexture (such as T cells, B cells, activating or inhibitory receptors) by IHC or Fluorescent Multiplex IHC in FFPE tumors.
  - Transcriptomic immune profiling by techniques such as NGS (RNAseq) on RNAlater preserved tumor if enough tumor material is available or by Nanostring on available FFPE tumor sample.

    ** Tumor biopsy at baseline or provision of adequate archival pre-treatment tumor tissue sample is mandatory (details please refer to Section 7.2 I 03). Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor. During treatment (including cross-over period treatment), tumor biopsies will be taken at Cycle 2 Day 1 (≤7 days; after IMP administration on

C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1), unless clinically unfeasible and after discussion with Sanofi Medical Monitor. On-treatment biopsy at Cycle 2, Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1) of the cross-over part is optional.

- Peripheral blood samples will be collected at baseline and during treatment (including cross-over period), for the following pharmacodynamics biomarker analyses:
  - Immunophenotyping to assess the immunomodulatory effects of isatuximab and REGN2810. More particularly, immune cell subsets (such as B cells, T cells, NK cells, macrophages, neutrophils and regulatory cells), as well as immune regulatory markers (such as activating and inhibitory receptors) will be characterized by flow cytometry. For prostate cancer, the neutrophil lymphocyte ratio will be determined from this immunophenotyping analysis and correlated with clinical response, as a potential marker of response.
  - Tumor mutational profile (ie, somatic mutations in genes such as KRAS, for NSCLC) will be analyzed in plasma cell free DNA and followed as a potential marker of resistance to treatment. Subtractive mutation analysis will be performed with germline DNA data to identify tumoral specific variations.
  - Peripheral blood cytokine concentration (such as interferon-γ, tumor necrosis factor-α, interleukin (IL)-2, IL-6, IL-12, IL-4, IL-10, transforming growth factor-ß) will be evaluated by enzyme-linked immunosorbent assay-based techniques.

  During treatment, peripheral blood samples will be taken:

  - For immunophenotyping and peripheral blood cytokine dosage at Day 1 of each cycle during the first 3 cycles and then every other cycle and at EOT and 60 days (±7 days) after last-IMP administration.
  - For tumor mutational profile at Day 1 of each cycle during the first 3 cycles and then every other cycle and at EOT.

Additional analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab/REGN2810, may be conducted on remaining samples pending evolving literature.

9.4 SAMPLES BLOOD VOLUME

The volume of blood to be collected during Cycle 1 and further cycles will be provided to the study sites in a separate Laboratory Manual.

9.5 FUTURE USE OF SAMPLES

For patients who have consented to it, remaining samples will be kept for other possible exploratory analyses. Results of these analyses will not be included in the clinical study report but in a stand-alone report, if applicable.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 16.3 and Section 16.5). These samples may be stored for a period of up to 5 years after completion of the final study report. After that period, any samples remaining will be destroyed.

9.6 EFFICACY

9.6.1 Primary endpoint

The primary endpoint for the Phase 2 part of the study is RR. The RECIST 1.1 criteria (Appendix B) will be followed for assessment of tumor response in patients with NSCLC (54).

The PCWG3 criteria (Appendix A) will be followed for the assessment of tumor response in patients with mCRPC (48). For patients with mCRPC, response will be defined by radiographic objective response assessed and confirmed by the Investigators and/or a PSA decline of ≥50% from baseline that is subsequently confirmed per PCWG3 criteria (Appendix A). The PSA decline must be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.

The following disease assessment procedures will be performed at screening (for eligibility) and again at Cycle 1 Day 1 (if needed) prior to study treatment administration (baseline for response assessment) and then as detailed below:

- **Tumor imaging:** performed at screening (diagnostic quality scans performed as part of routine clinical management are acceptable) and then repeated every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), whenever disease progression is suspected, at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD), using the same method (CT or MRI) for each assessment. If tumor assessment status is partial or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.
- **Prostate-specific antigen assessment for patients with mCRPC:** performed at baseline (within 14 days before initiation of IMP). Repeat at Cycle 1 Day 1 and every 9 weeks starting at the end of Cycle 3 (63 ±7 days; disease assessment timing should follow calendar days and should not be adjusted for delays in cycle start), at the EOT visit (if not performed in the past 30 days) and during follow-up (if discontinue IMP without PD). PSA responses are to be confirmed no less than 4 weeks later.

9.6.2 Secondary endpoints

Secondary efficacy endpoints are:

- Tumor burden change: defined as the best percent-change from baseline in a sum of the diameters (longest for non-nodal lesion, short axis for nodal lesions) for all target lesions. In addition, the area under the curve (AUC) and the time-adjusted AUC of percent-change from baseline in a sum of the diameter for all target lesions will also be summarized in an exploratory fashion.
- Duration of response: defined as the time from the date of first response (PR or CR in radiographic objective response, or PSA decline ≥50% for patients with mCRPC) that is subsequently confirmed to the date of first disease progression or death, whichever occurs first. The RECIST 1.1 criteria (Appendix B) will be followed for assessment of tumor response in patients with NSCLC and the PCWG3 criteria (Appendix A) will be followed for the assessment of tumor response in patients with mCRPC. Disease progression includes radiographic disease progression or unequivocal clinical progression. For patients with mCRPC, radiographic progression includes progression by PCWG3 modified RECIST 1.1 for soft tissue and/or PCWG3 defined progression by bone scan. In the absence of disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DOR will be censored at the date of the last valid response assessment not showing disease progression performed prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients who do not achieve a response.
- Progression-free survival: defined as the time from first study treatment administration to the date of first documentation of PD (RECIST 1.1 for patients with NSCLC and PCWG3 criteria for patients with mCRPC) or the date of death from any cause. The same censoring rules as DOR will be used.
- Disease control rate (DCR): defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) or stable disease (SD), as assessed by Investigator relative to the total number of patients in the analysis population.

9.6.3 Exploratory endpoints

Exploratory efficacy endpoints are:

- Overall survival: defined as the time from first study treatment administration to death from any cause. Patients without death prior to the analysis cut-off date will be censored at the last date the patient was known to be alive or the cut-off date, whichever comes first.
- Time to response: defined as the time from first study treatment administration to the first response (PR or CR in radiographic objective response, or PSA decline ≥50% for patients with mCRPC) that is subsequently confirmed (RECIST 1.1 for patients with NSCLC and PCWG3 criteria for patients with mCRPC).

For patients with NSCLC, exploratory efficacy endpoint also includes:

- ORR by iRECIST (Appendix B) for patients with NSCLC.

For patients with mCRPC (to be assessed per PCWG3 criteria), exploratory efficacy endpoints also include:

- PSA RR: PSA response is defined as a PSA decline of ≥50% from baseline that is subsequently confirmed.
- Radiographic RR: radiographic response is defined as radiographic objective response assessed and confirmed by investigator.
- Duration of PSA response: defined as the time from the date of the PSA first decline of ≥50% from baseline that is subsequently confirmed to the date of first confirmed PSA progression or death, whichever occurs first. PSA progression for patients who have achieved a ≥50% decrease from baseline is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the nadir (the lowest PSA value on study). The same censoring rules as for DOR will be used.
- Duration of radiographic response: defined as the time from the date of the first radiographic response (PR or CR) that is subsequently confirmed to the date of first radiographic progression or death, whichever occurs first. The same censoring rules as for DOR will be used.
- Time to PSA response: defined as the time from first study treatment administration to the first PSA response that is subsequently confirmed.
- Time to radiographic response: defined as the time from first study treatment administration to the first radiograph response that is subsequently confirmed.
- Time to PSA progression: defined as the time from first study treatment administration to the date of first confirmed PSA progression. For patients who have achieved a ≥50% decrease from baseline, PSA progression is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the nadir (the lowest PSA value on study). For patients without a PSA decrease of this magnitude or no decrease at all, PSA progression is defined as at least a 25% increase and an absolute increase of ≥2 ng/mL above the baseline. Death from prostate cancer or any other cause without prior evidence of PSA progression will not count as an event. If no event exists, then time to PSA progression will be censored at the last scheduled PSA assessment on study or date of death, whichever occurs first.
- To explore the relationship between clinical response and CD38 expression (in infiltrating immune cells and tumor cells), PD-L1 expression (in tumor cells) and immune contexture in tumor at baseline as potential predictive markers of response.
- To explore tumor and immune genetic markers at baseline: tumor mutational load and MSI status in tumor as well as tumor mutational profile and immune genetic determinants in blood.
- To evaluate pharmacodynamic biomarkers in response to IMP: immunophenotype in peripheral blood, immune contexture in tumor and plasma or serum cytokine levels.
- A panel of tumor somatic mutations (ie, tumor mutational profile) will be analyzed at baseline and upon treatment in plasma cell free DNA from peripheral blood.
- Determination of exposure-response relationships with efficacy, safety, and biomarkers, if possible.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Refer to Section 9.1 for definition of safety criteria, parameters to be analyzed and method of sample collection.

10.2 SAFETY INSTRUCTIONS

The safety of the patients in this clinical trial is primarily dependent on the clinical Investigator's monitoring and assessment of their patients. Please refer to Section 9.1.2.

10.3 ADVERSE EVENTS MONITORING

All AEs will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which conditions are to be considered medically important events. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm.
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study, if judged unusual/significant by the Investigator.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse events

All AEs regardless of seriousness or relationship to the IMP, spanning from the signature of the informed consent form (ie, occurring during the baseline period even in the absence of any administration of IMP), up to 30 days following the last administration of study treatment, are to be recorded on the corresponding page(s) included in the e-CRF.

Whenever possible, a diagnosis or single syndrome should be reported instead if symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.

Vital signs or ECG abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or lead to treatment discontinuation and/or modification of dosing and/or fulfill a seriousness criterion and/or are defined as AESIs (see Section 10.5.5).

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a seriousness criterion and/or are defined as AESIs (see Section 10.5.5).

10.5.2 Timely handling of certain adverse events

In the case of an SAE, AESI, pregnancy report, or an overdose, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send e-notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, patient status) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the e-CRF system does not work.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow-up the outcome of any AEs (clinical signs, laboratory values or other, etc) until the return to normal or stabilization of the patient's condition. Ongoing related AEs at the end of study treatment will be followed until resolution or stabilization.
- In case of any SAE/AESI, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has discontinued study treatment or has left the clinical trial and that additional investigations may be requested by the monitoring team;
- In case of any AE or AESI brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.5.4 Treatment discontinuation due to non-serious adverse event

In the case of a treatment discontinuation due to a non-serious AE:

- ENTER (within 24 hours) the information related to treatment discontinuation due to a non-SAE in the appropriate screens of the e-CRF (AE with the box "action taken with IMP" ticked "permanently discontinued", together with the EOT form with reason that should be ticked "AE"); the system will automatically send the notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

10.5.5 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the isatuximab program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during the study by protocol amendment.

Dose limiting toxicities (as defined in Section 9.1.1) are considered as AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.

The following conditions are also considered AESIs and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the AE:

- **Grade ≥2 IARs**. An IAR occurs typically within 24 hours from the start of the infusion.
- **Grade ≥3 immune-related TEAEs.**
- **Immune-related AEs of any grade in a patient previously treated with a PI3K inhibitor (only applicable for patients who receive REGN2810).**
- **Pregnancy** of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP.

Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4),

  - In the event of pregnancy in a female participant, treatment with the IMP should be discontinued,
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

- **Symptomatic overdose** (serious or non-serious) with IMP/NIMP (see Section 10.5.2).
  - An overdose (accidental or intentional) with isatuximab is defined as an increase of at least 30% of the intended administered dose at each infusion (expressed in unit per body weight) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration,
  - REGN2810 symptomatic overdose: accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE,
  - An overdose (accidental or intentional) with the NIMP is defined as increase of at least 30% of the intended administered dose at each administration expressed in unit per body weight,

- In case of accidental or intentional overdose with the IMP/NIMP, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the e-CRF.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.5.6 Laboratory abnormalities

Laboratory abnormalities should be monitored, documented, and managed according to the related flowchart (see Section 1.3). Laboratory values will be reported in the appropriate pages of e-CRF.

Laboratory abnormalities should be reported as AEs, only in case they lead to an action on study treatment, if they are serious, or they meet the definition of AESIs (see Section 10.5.1).

10.5.7 Guidelines for reporting product complaints (IMP/NIMP)

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines. Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are unexpected and are at least reasonably related to the IMP (ie, suspected unexpected serious adverse reactions), to the regulatory authorities, institutional ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- The AESIs (eg, DLT) to those regulatory authorities who require such reporting.

Adverse events that are considered expected are specified in the reference safety information as specified in the current IB of each of the 2 IMPs.

The Sponsor will report all the safety observations made during the conduct of the trial in the clinical study report.

11 HANDLING OF PATIENT TEMPORARY AND PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.1 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

11.1.1 List of criteria for permanent treatment discontinuation

Patients may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation and this should be documented in the e-CRF.

Treatment with the IMP should be discontinued in any of the following cases:

- At the patient's request, at any time and irrespective of the reason (patient's decision), or at the request of their legally authorized representative without any effect on their care. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. Patient's decision for treatment should be distinguished from patient's decision for follow-up visits and from patient's decision for non-patient contact follow-up, eg, medical records check. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document any case of patient's decision.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the patient's well-being, such as:
  - Confirmation of disease progression (per Section 6.7.1).
  - Unacceptable AE.
  - Poor compliance to the study protocol.
  - Any other reason such as intercurrent illness that prevents further administration of study treatment (will be specified).
- Patient is lost to follow-up.
- Completion of the 2 year treatment period.

If patients are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, the patient will be maintained on treatment for the maximum period of time defined in Section 6.7.

11.1.2 Handling of patients after permanent treatment discontinuation

All permanent treatment discontinuation must be recorded by the Investigator in the appropriate screen of e-CRF when considered as confirmed. After study treatment is discontinued, patients should complete a visit 30 days after the last administration of the IMP as described in Section 12.4.

Patients who have been withdrawn from the study treatment cannot be re-entered into the study.

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

11.2 REPLACEMENT OF PATIENTS

During the Phase 1 part of the study, a patient may be considered not evaluable for DLT and may be replaced at the same dose level as described in Section 6.2.2.

Patients treated in the Phase 2 part of the study who are withdrawn from study treatment will not be replaced.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flow charts in Section 1 and described below. The results of the evaluation will be recorded in the e-CRF pages until the patient is not followed anymore. After the baseline visit, all eligible patients included in the study will return to the site for a study visit on Day 1, Day 4, Day 8 and Day 15 of Cycle 1 (note: patients in Phase 2 Cohort A-2, Stage 2 Phase 2 of Cohort A-1 and Cohort B will not return for study visit at Cycle 1 Day 4) and on Day 1 of all subsequent cycles. An EOT visit will be performed 30 days after the last administration of the IMP (see flow chart for investigations to be performed).

There will be an extended safety follow-up period for 90 days after the last dose of IMP for ADA assessment and safety assessment. If REGN2810 or isatuximab ADA testing is positive or inconclusive, ADA testing will be repeated every 3 months until negative.

Patients who discontinue study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first.

The further follow-up schedule beyond 90 days after last dose of IMP treatment is according to the disease progression status:

- **Patients who discontinue study treatment due to PD:** phone call follow-up will be done every 90 days from the date of last IMP administration until death or study cut-off date.
- **Patients who discontinue the study treatment without PD, and without PD confirmed during the safety follow-up period:** will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever occurs first. After PD, patients will be followed by phone call until death or study cut-off date.
- **Patients who are still on study treatment after study cut-off date:** will continue to receive study treatment and will undergo planned study procedures (except PK and ADA) until confirmation PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

12.2 BASELINE EVALUATION

The pretreatment examinations are to be performed within 28 days prior to the first administration of the IMP. All of the inclusion criteria (and none of the exclusion criteria) must be met (see Section 7). Patients from Cohort A-2 who progress on isatuximab monotherapy may enter cross-over part if they still fulfill the eligibility criteria (except exclusion criteria *E 03* and *E 08*). The informed consent form must be signed by the patient before any study-specific procedure can be performed. Re-screening once is allowed.

The following procedures are to be performed/assessed at this visit.

- Signed informed consent (not applicable for cross-over part baseline evaluation).
- Demography: includes age, gender and race (not applicable for cross-over part baseline evaluation).
- Medical/surgical history: includes history of previous/associated pathologies and smoking status (not applicable for cross-over part baseline evaluation).
- Disease history: includes stage at diagnosis and at study entry, previous anti-tumor therapy (type, duration, reason for discontinuation and response to) and the results of any additional procedures performed as part of standard of care to assess disease status, such as EGFR mutation test, anaplastic lymphoma kinase, ROS1 fusion detection etc for patients with NSCLC (not applicable for cross-over part baseline evaluation).
- Physical examination: to be performed <7 days prior to first dose of IMP. Includes examination of major body systems (neurological, digestive, respiratory [signs and symptoms, respiratory rate] and lymph node examination).
- Height and weight (not applicable for cross-over part baseline evaluation).
- Vital signs: includes blood pressure, heart rate, temperature, and respiration rate.
- Performance status (ECOG).
- 12-lead ECG (single).
- Adverse event/SAEs, including AEs of new onset as well as worsening baseline signs and symptoms, occurring after signed informed consent for all patients.
- Prior/concomitant medication within 28 days prior to first dose of IMP.

Laboratory assessments

- Serum pregnancy test: WOCBP must have a negative **serum** pregnancy test result within 7 days prior to the first dose IMP administration (local laboratory).
- Blood chemistry: includes AST, ALT, bilirubin (total and direct), alkaline phosphatase (ALP), LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or blood urea nitrogen (BUN), serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin, total protein, thyroid stimulating hormone (TSH), and free T4 if TSH is outside of the normal range (local laboratory).
- Hematology: includes hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L (local laboratory).
- Coagulation: includes prothrombin time or international normalized ratio (INR) and activated partial thromboplastin time (PTT) (local laboratory).
- Testosterone level (local laboratory).
- Blood typing interference test (local laboratory).
- Quantitative or semi-quantitative urinalysis: includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity (local laboratory).

Exploratory biomarkers (central laboratory, please refer to study flowchart in Section 1)

- Tumor biopsy for IHC, CD38, PD-L1, immune contexture.
- Tumor biopsy for transcriptomic analysis.
- Tumor biopsy for genomic characterization (tumor mutational load and MSI status).
- Blood sample for tumor mutational load.
- Blood sample for plasma or serum cytokines.

Disease assessment

- Tumor imaging: CT or MRI scan of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement (the same method of assessment should be used throughout the study). The initial tumor imaging will be performed within 28 days screening period (as close as possible to initiation of IMP). Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before IMP initiation.
  - mCRPC: Measureable lesion per RECIST 1.1 per local reading is not mandatory.
  - NSCLC: Patients with NSCLC must have at least 1 radiographically measurable lesion per RECIST 1.1 per local reading.
- Prostate-specific antigen assessment for patients with mCRPC (local laboratory).
- Bone scan for patients with mCRPC: The initial scan will be performed within 28 days screening period (as close as possible to initiation of IMP). Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 6 weeks before IMP initiation. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not).

All patients who signed the study informed consent form will be assigned a patient number. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study. Those patients, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible for registration in the study. A written confirmation of each eligible patient identification and treatment dose level will be forwarded to the Investigator.

12.3 TREATMENT PERIOD

12.3.1 Cycle 1 (Day 1, Day 8 and Day 15)

The treatment window is ±1 day for each of the QW administrations and ±2 days for each of the Q3W administrations. The following procedures are to be performed/assessed **on Day 1, Day 8 and Day 15 prior to study treatment administration unless specified otherwise**:

- Physical examination: includes examination of major body systems (neurological, digestive, respiratory [signs and symptoms, respiratory rate] and lymph node examination).
- Body weight prior to starting infusion.

- Vital signs including blood pressure, heart rate, temperature, and respiration rate, prior to starting infusion of IMP, every hour during infusion, and at the end of infusion, and if clinically indicated during the infusion.
- Performance status (ECOG).
- All AEs/SAEs throughout the cycle, including AEs of new onset as well as worsening of baseline signs and symptoms.
- Concomitant medications from registration and used throughout the cycle.
- Study treatment administration: REGN2810 on Cycle 1 Day 1 (only in cohorts receiving isatuximab and REGN2810 combination); isatuximab on Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 1 Day 15 (isatuximab is not administered on Cycle 1 Day 8 and Cycle 1 Day 15 in Cohort C and Cohort D).

Laboratory assessments

- Serum or urine pregnancy test: WOCBP must have a negative serum pregnancy test result within 7 days prior to first IMP administration. A pregnancy test (serum or urine, local laboratory) is to be done on Day 1 of each cycle prior to the study treatment. Pregnancy test is not required at Cycle 1 Day 8 or Cycle 1 Day 15.
- Blood chemistry: includes AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin, total protein, TSH, and free T4 if TSH is outside of the normal range. To be performed every 7 days in cases of Grade 3 or Grade 4 abnormalities. **Blood chemistry assessments are not required to be repeated prior to Cycle 1 Day 1 if performed ≤3 days prior to first study treatment administration at Screening** (local laboratory).
- Hematology: includes hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L. **Hematology assessments are not required to be repeated prior to Cycle 1 Day 1 if performed ≤3 days prior to first study treatment administration at Screening** (local laboratory).
- Quantitative or semi-quantitative urinalysis on Day 1: includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity. To be repeated if hematuria is observed or clinically indicated. **Urinalysis assessments are not required to be repeated prior to Cycle 1 Day 1 if performed ≤3 days prior to first study treatment administration at Screening** Dipstick (qualitative) will be performed on Day 1 of each new cycle if clinically indicated (local laboratory).
- Blood sample collection for PK and ADA evaluation (see Section 1.5).

Exploratory biomarkers (central laboratory, please refer to study flowchart in Section 1)

- Blood sample for immune genetic markers (Day 1 only).
- Blood sample for tumor genetic markers (Day 1 only).

- Blood sample for immunophenotyping (Day 1 only).
- Blood sample for plasma or serum cytokines (Day 1 only).

Disease assessment

- Prostate-specific antigen assessment on Day 1 for patients with mCRPC. **PSA assessments are not required to be repeated prior to Cycle 1 Day 1 if performed ≤3 days prior to first study treatment administration at Screening** (local laboratory).

If clinically indicated only

- 12-lead ECG (single).
- Coagulation: includes prothrombin time or INR and activated PTT (local laboratory).
- Qualitative urinalysis (dipstick) on Day 1 (local laboratory).
- Any other examinations that are clinically indicated.

12.3.2 Subsequent cycles (Day 1)

The treatment window is ±2 days for each of the Q3W administrations. The following procedures are to be performed/assessed on **Day 1 prior to study treatment administration unless specified otherwise:**

- Physical examination: includes examination of major body systems (neurological, digestive, respiratory [signs and symptoms, respiratory rate] and lymph node examination).
- Body weight.
- Vital signs including blood pressure, heart rate, temperature, and respiration rate, prior to starting infusion of IMP, every hour during infusion, and at the end of infusion, and if clinically indicated during the infusion.
- Performance status (ECOG).
- All AEs/SAEs throughout the cycle, including AEs of new onset as well as worsening of baseline signs and symptoms.
- Concomitant medications used throughout the cycle.
- Study treatment administration: REGN2810 on Day 1 (only in cohorts receiving isatuximab and REGN2810 combination); isatuximab on Day 1.

Laboratory assessments

- Serum or urine pregnancy test for WOCBP: a pregnancy test is to be done on Day 1 of each cycle prior to the study treatment (local laboratory).
- Blood chemistry: includes AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin, total protein, TSH (every second cycle), and free T4 if TSH is outside of the normal range. To be performed every 7 days in cases of Grade 3 or Grade 4 abnormalities (local laboratory).

- Hematology: includes hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L (local laboratory).
- Blood typing interference test on Cycle 2, Day 1 only (local laboratory).
- Blood sample collection for PK and ADA evaluation (see Section 1.5, central laboratory).

Exploratory biomarkers (central laboratory, please refer to study flowchart in Section 1)

- Tumor biopsy for IHC, CD38, PD-L1, immune contexture at Cycle 2 Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1), only if clinically feasible.
- Tumor biopsy for transcriptomic analysis at Cycle 2 Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1), only if clinically feasible.
- Blood sample for tumor genetic markers (Cycle 2 Day 1 and Cycle 3 Day 1 only).
- Blood sample for immunophenotyping (Cycle 2 Day 1, Cycle 3 Day 1, then on Day 1 prior to IMP administration at each odd numbered cycle starting from Cycle 5).
- Blood sample for plasma or serum cytokines (Cycle 2 Day 1, Cycle 3 Day 1, then on Day 1 prior to IMP administration at each odd numbered cycle starting from Cycle 5).

Disease assessment

- Tumor imaging: CT or MRI scan every 9 weeks starting at the end of Cycle 3 (63 ±7 days) and whenever disease progression is suspected (the same method of assessment should be used throughout the study). Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

  If initial evidence of RECIST 1.1 defined progression is documented, patients could continue treatment while waiting for PD confirmation scan 4 weeks after providing the patients are clinically stable as detailed in Section 6.7.1. When treatment is continued beyond RECIST 1.1 defined tumor progression, subsequent imaging assessments should be based upon iRECIST criteria (Appendix D).

  For patients with mCRPC, bone lesions are not considered “non-measurable” lesion pre RECIST 1.1. Bone lesions will be assessed by bone scan only.
- Prostate-specific antigen assessment every 9 weeks starting at the end of Cycle 3 (63 ±7 days) for patients with mCRPC. Patients with PSA progression (Appendix A) in the absence of radiographic progression should continue IMP (local laboratory).
- Bone scan for patients with mCRPC, every 9 weeks starting at the end of Cycle 3 (63 ±7 days). In cases of PD based on bone scan only, the bone scan should be repeated after 6 weeks to confirm the progression using the 2+2 rule (2 new lesions on first scan, with at least 2 additional lesions on the confirmatory scan; refer to Appendix A) as detailed in Section 6.7.1. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not).

If clinically indicated only

- 12-lead ECG (single).
- Coagulation: includes prothrombin time or INR and activated PTT (local laboratory).
- Quantitative urinalysis: includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity. To be repeated if hematuria is observed or clinically indicated (local laboratory).
- Qualitative urinalysis (dipstick) (local laboratory).
- Any other examinations that are clinically indicated.

12.4 END OF TREATMENT

The EOT visit will occur 30 (±7) days after the last IMP administration, or when the patient receives another anti-cancer therapy, whichever is earlier.

The following procedures are to be performed at the EOT visit:

- Physical examination: includes examination of major body systems (neurological, digestive, respiratory [signs and symptoms, respiratory rate] and lymph node examination).
- Body weight.
- Vital signs including blood pressure, heart rate, temperature, and respiration rate.
- Performance status (ECOG).
- All AEs/SAEs, including AEs of new onset as well as worsening of baseline signs and symptoms.
- Concomitant medications.
- New anticancer therapy.
- Blood sample collection for PK and ADA evaluation (central laboratory, see Section 1.5).

Laboratory assessments

- Serum or urine pregnancy test for WOCBP: a pregnancy test is to be done at the EOT visit (local laboratory).
- Blood chemistry: includes AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin, total protein, TSH, and free T4 if TSH is outside of the normal range. To be performed every 7 days in cases of Grade 3 or Grade 4 abnormalities (local laboratory).
- Hematology: includes hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L (local laboratory).
- Quantitative or semi-quantitative urinalysis: includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity (local laboratory).

Exploratory biomarkers (central laboratory, please refer to study flowchart in Section 1)

- Blood sample for tumor genetic markers.
- Blood sample for immunophenotyping.
- Blood sample for plasma or serum cytokines.

Disease assessment (if not performed in the past 30 days)

- Tumor imaging: CT or MRI scan (the same method of assessment should be used throughout the study).
- Prostate-specific antigen assessment for patients with mCRPC (local laboratory).
- Bone scan for patients with mCRPC. In cases of PD based on bone scan only, the bone scan should be repeated after 6 weeks to confirm the progression. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not).

If clinically indicated only

- 12-lead ECG (single).
- Coagulation: includes prothrombin time or INR and activated PTT (local laboratory).
- Qualitative urinalysis (dipstick) (local laboratory).
- Any other examinations that are clinically indicated.

12.5 POST TREATMENT FOLLOW-UP

The post treatment follow-up period includes an extended safety follow-up period of 90 days after the last dose of study treatment and further follow-up beyond 90 days after the last dose of study treatments until death or study cut-off date, whichever occurs first.

12.5.1 Safety follow-up period

There will be an extended safety follow-up period for 90 days after the last dose of IMP for ADA assessment and for safety assessment. If REGN2810 or isatuximab ADA testing is positive or inconclusive during post treatment follow-up, ADA testing will be repeated every 3 months until negative.

Patients who discontinue the study treatment without PD will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy, or until study cut-off date, whichever comes first.

The following procedures are to be performed/assessed at 60 and 90 days after the last IMP administration:

- Physical examination: includes examination of major body systems (neurological, digestive, respiratory [signs and symptoms, respiratory rate] and lymph node examination).

- Vital signs: includes blood pressure, heart rate, temperature, and respiration rate.
- Blood chemistry: includes AST, ALT, bilirubin (total and direct), ALP, LDH, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, urea or BUN, serum creatinine, eGFR (MDRD formula; Appendix H), glucose (fasting), albumin, total protein, TSH, and free T4 if TSH is outside of the normal range. To be performed every 7 days in cases of Grade 3 or Grade 4 abnormalities (local laboratory).
- Hematology: includes hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L (local laboratory).
- Quantitative or semi-quantitative urinalysis: includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity (local laboratory).
- Adverse events/SAEs: all ongoing related non-serious AEs, ongoing SAEs at the end of treatment visit (ie, 30 days after last IMP administration), and new related AEs/SAEs are to be followed to resolution or stabilization. Stabilization is defined as an event ongoing without any change for ≥3 months.
- Concomitant medications and relationship to AEs/SAEs.
- New anticancer therapy.
- Serum or urine pregnancy test for WOCBP: a pregnancy test is to be done at every 30 (± 7) days until 6 months after the last dose of study treatment.

Disease assessment (if discontinue IMP before PD, repeat every 90 days)

- Tumor imaging: CT or MRI scan (the same method of assessment should be used throughout the study).
- Prostate-specific antigen assessment for patients with mCRPC (local laboratory).
- Bone scan for patients with mCRPC. In cases of PD based on bone scan only, the bone scan should be repeated after 6 weeks to confirm the progression. In case of doubtful lesions on bone scan, bone-centered X-ray or MRI scan should be performed to confirm the nature of those lesions (metastatic or not).

Exploratory biomarkers (central laboratory, please refer to study flowchart in Section 1)

- Blood sample for immunophenotyping (60 days after the last IMP administration only).
- Blood sample for plasma or serum cytokines (60 days after the last IMP administration only).

12.5.2 Survival follow-up period

The further follow-up schedule beyond 90 days after last treatment is according to the disease progression status:

- **Patients who discontinue study treatment due to progression of disease:** phone call follow-up will be done every 90 days from the date of last study treatment administration

until death or study cut-off date. Every effort will be made to follow all patients. If survival follow-up is missed and is not obtained at the time of the scheduled interval, it should be retrieved immediately. For subsequent survival follow-up, the patient follow-up visit should be scheduled at the original scheduled survival follow-up interval. If the patient is unable to visit the clinical center, the follow-up may be done via phone from the Investigator or designee to the patient or the patient's caregiver or a family member, but this should be an exception and any effort should be done to schedule follow-up visit at clinical center.

- **Patients who discontinue the study treatment without progression of disease:** Will be followed every 90 days for disease assessment until confirmation of progression of disease or start treatment with another anti-cancer therapy. After progression of disease patients will be followed by phone call until death or study cut-off date.
- **Patients who are still on study treatment after study cut-off date:** will continue to receive study treatment and will undergo planned study procedures (except PK and ADA) until confirmation PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

12.5.3 Post overall survival study cut-off date

Patients still on study treatment after the study cut-off date (12 months after last patient initiates IMP) can continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 6.7 is met. The following information will be collected during the study treatment administration:

- IMP administration.
- Disease assessment (for patients who are still on study treatment, until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first)
- All SAEs regardless of relationship to study treatment and AEs considered related to study treatment.
- End of treatment reason.

One ADA sample should be drawn 90 days after last study treatment administration. If ADA is positive or inconclusive at 90 days, the repeat samples will be taken every 3 months days until the results become negative (see Section 1.5).

No follow-up information will be collected after these patients discontinue study treatment except all SAEs still ongoing at the end of study treatment and all AEs considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.

12.6 CROSS-OVER PERIOD

The patients in Cohort A-2 treated with isatuximab monotherapy who experience PD will be permitted to cross over to isatuximab in combination with REGN2810 for up to 2 years after progression on isatuximab monotherapy.

All screening processes for the patients in the Phase 1 and Phase 2 parts are to be conducted before combination IMP initiation for the cross-over part, except informed consent, demography, medical/surgical and disease history, and weight/height. Tumor biopsy at cross-over screening is required unless clinically unfeasible and after discussion with the Sanofi Medical Monitor. On treatment biopsy at Cycle 2, Day 1 (≤7 days; after IMP administration on C1D15 wherever applicable, prior to IMP administration on Cycle 2 Day 1) of the cross-over part is optional (fine needle aspirate is not acceptable). Patients who are included in the cross over part should be evaluated as Cohort A-1 and Cohort B (except PK) in Section 12.3, Section 12.4, and Section 12.5.

Patients who do not meet the cross-over part eligibility criteria should be followed up for safety and survival as detailed in Section 12.5.

13 STATISTICAL CONSIDERATIONS

The statistical considerations presented in this section forms the basis for the Statistical Analysis Plan (SAP), which will provide accurate definitions and more detailed specifications for the analyses to be performed on the data collected from this study.

13.1 DETERMINATION OF SAMPLE SIZE

Phase 1

In Phase 1, approximately 6 (assuming 6 patients for the starting dose) to 24 (assuming 12 patients for the starting dose plus 12 patients for DL-1) DLT evaluable patients are expected to be enrolled. The actual sample size will vary depending on DLTs observed and the number of dose levels explored. Patients who are not evaluable for DLT assessment in the Phase 1 part may be replaced.

Phase 2

The Phase 2 part of the study is to evaluate initial anti-tumor activity based on tumor response using RECIST 1.1 criteria for NSCLC and PCWG3 for mCRPC. The efficacy evaluation is based on Simon's 2 stage design with 90% power at 5% 1-sided alpha level for each of the patient cohorts of mCRPC and NSCLC patients, respectively. The assumption of RR, the required sample sizes and the number of responders at each stage are provided in Table 8.

Table 8 - Sample size calculation

Indication	H_0	H_1	Sample size		Number (%) of responses to reject H_0	
			Stage 1	Final	Stage 1	Final
mCRPC (Combo)	10%	26%	23	49	≥3 (13.0%)	≥9 (18.4%)
mCRPC (Single)	10%	26%	23	49	≥3 (13.0%)	≥9 (18.4%)
NSCLC (Combo)	5%	22%	20	36	≥2 (10.0%)	≥5 (13.9%)

Abbreviations: H_0=null hypothesis; H_1=alternative hypothesis; mCRPC=metastatic, castration-resistant prostate cancer; NSCLC=non-small cell lung cancer.
Note: Based on the number of objective responses and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators.

Patients who received the recommended dose regimen in Phase 1 will be also included in the Phase 2 Stage 1 (eg, if 6 NSCLC patients were enrolled in Phase 1, only 14 NSCLC patients will be needed to complete the Phase 2 Stage 1 NSCLC cohort).

In Phase 2, approximately 134 patients are expected to be enrolled (assuming Cohort A-1, A-2 and B complete 2 stages), including approximately 66 patients in Phase 2 Stage 1 and approximately 68 patients in Phase 2 Stage 2. The patients who are treated with RP2D in the Phase 1 part will be counted as Phase 2 part patients. If isatuximab 10 mg/kg Q3W in combination

with REGN2810 or monotherapy without the isatuximab 10 mg/kg QW for 3 weeks is to be tested in a mCRPC or NSCLC cohort, 49 or 36 additional patients will be needed, respectively.

The isatuximab monotherapy cohort (Cohort A-2) will be initiated when the initial anti-tumor activity of isatuximab combination therapy is observed in the Phase 2 Stage 1 according to the study design. When an isatuximab monotherapy cohort (Cohort A-2) is initiated, patients with mCRPC will be randomly assigned in a 1:1 randomization to either the isatuximab in combination with REGN2810 (Cohort A-1) or the isatuximab monotherapy (Cohort A-2). The purpose of the randomization is to avoid the potential bias of patient assignment, and is not to compare between 2 cohorts. Randomization will end when 1 of the 2 cohorts completes the enrollment.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of patients

Screened patients are defined as any patients who signed the study informed consent. The number of screened patients as well as the number and percentage of patients included in the analysis populations defined in Section 13.3 will be provided.

Reasons for treatment discontinuation will be summarized using the all-treated population.

13.2.2 Protocol deviations

Major protocol deviations which compromise the evaluation of the safety and efficacy will be derived adequately and determination of deviations will be finalized based on data review conducted prior to database lock. Decisions made on a patient's status will be documented.

13.3 ANALYSIS POPULATIONS

13.3.1 All-treated/safety population

For both Phase 1 and Phase 2 parts of the study, the all-treated/safety population will include all patients who signed the study informed consent and received at least 1 dose (even incomplete) of the study treatments, either isatuximab or REGN2810.

This population is the primary population for the analyses of efficacy and safety parameters except for DLT evaluation. All analyses using this population will be based on the dose level actually received in the first cycle.

13.3.2 Patients evaluable for dose-limiting toxicity assessment

The DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and REGN2810 during Cycle 1, and who completed the DLT observation period after the first IMP administration as per Section 9.1.1, unless they discontinue the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population.

13.3.3 Pharmacokinetic population

The PK population will include patients from the all-treated population with at least 1 drug concentration after the first dose of study treatment.

13.3.4 Pharmacodynamic population

The pharmacodynamic population will include patients from the all-treated population with at least 1 pharmacodynamic marker result after the first dose of study treatment.

13.3.5 Anti-drug antibody evaluable population

ADA evaluable population will include all patients from the all-treated population with at least 1 ADA non-missing result after the first dose of study treatment.

13.3.6 Cross-over population

The cross-over population is defined as patients in Cohort A-2 who progressed on isatuximab monotherapy and received isatuximab in combination with REGN2810.

13.3.7 Response evaluable population

The response evaluable population will include all patients in the all-treated population who fulfill all eligibility criteria with an evaluable baseline assessment and at least one evaluable post-baseline response assessment during the treatment period.

13.4 STATISTICAL METHODS

A list of study endpoints and their definitions are provided in Section 9.6.

Unless otherwise specified, analyses will be descriptive and performed based on the all-treated population. The baseline for a given parameter is defined as the last assessment for this parameter before first administration of study treatments unless otherwise noted.

Data from mCRPC and NSCLC cohorts in the Phase 2 part will be analyzed and reported separately by cohort. Data from the cohort A-2 cross-over part will be summarized separately unless otherwise noted.

Continuous data will be summarized using number of available data, mean, standard deviation, median, minimum and maximum for each dose level (if applicable). Categorical and ordinal data will be summarized using number and percentage of patients in each dose level (if applicable). Summary tables will be presented by dose level and overall (if applicable), unless otherwise noted.

13.4.1 Demographics and baseline characteristics

Demographic and baseline characteristics (including age, gender, race, ECOG performance status), medical or surgical history, and disease characteristics at diagnosis and at study entry will be summarized using descriptive statistics.

13.4.2 Extent of investigational medicinal product exposure

The following variables will be described to summarize the overall study treatment exposure (all study treatments together):

- Overall number of cycles started.
- Duration of overall exposure in weeks.

In addition, the following variables will be summarized with descriptive statistics for each IMP (ie, isatuximab and REGN2810):

- Number of cycles started with each drug.
- Duration of exposure of each drug in weeks.
- Number of infusions.
- Cumulative dose.
- Actual dose intensity.
- Relative dose intensity.
- Dose reduction and reason for dose reduction.
- Cycle delays.
- Infusion delays within a cycle.
- Infusion interruption.
- Dose omission.

13.4.3 Prior/concomitant medication/therapy

Prior and concomitant medications will be summarized according to the World Health Organization Drug Dictionary, considering the first digit of the Anatomical Therapeutic Chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

13.4.4 Analyses of efficacy variables

All efficacy analyses will be performed using the all-treated/safety population unless otherwise specified. More details on efficacy analyses including the analyses for exploratory endpoints will be provided in the SAP.

13.4.4.1 Analysis of primary efficacy endpoint

The RR will be summarized using descriptive statistics. A 90% 2-sided confidence interval will be computed using Clopper-Pearson method. The statistical inference will be based on the hypothesis defined in Section 13.1 using a 1-sided exact binomial test with a significance level of 0.05 for each cohort. For each cohort, the analysis cut-off date for the primary analysis of RR will be 6 months after the last patient's first treatment in the cohort. The analysis cut-off date for secondary efficacy endpoints including DoR and PFS will be 12 months after the last participant's first treatment in the cohort. The primary analysis of RR will be updated.

Same analysis will be performed for RR using the response evaluable population as a secondary analysis. Subgroup analyses for primary endpoint may be performed if relevant.

13.4.4.2 Analysis of secondary efficacy endpoints

The following secondary endpoints will be analyzed:

- Tumor burden change: the best percent-change from baseline in tumor burden will be summarized and presented graphically for patients with measurable disease at baseline. In addition, a summary of the AUC and the time-adjusted AUC of percent-change from baseline in tumor burden will also be provided as an exploratory analysis.
- Duration of response: Kaplan-Meier estimates such as median and Kaplan-Meier curves will be provided for patients who achieved a response.
- Progression-free survival: the PFS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted.
- Disease control rate: the DCR will be summarized using descriptive statistics.

Subgroup analyses for secondary endpoints may be performed if relevant.

13.4.5 Analyses of safety data

13.4.5.1 Dose-limiting toxicities

In the Phase 1 part, the DLTs will be listed by patient using the DLT evaluable population.

13.4.5.2 Analyses of adverse events

The observation period will be divided into 3 segments: pretreatment, TEAE and posttreatment:

- The pretreatment period is defined as the time informed consent is signed until the first dose of study treatments administration.
- The TEAE period is defined as the time from the first dose of study treatments up to 30 days after last dose of study treatments.

- The posttreatment period is defined as the time starting 31 days after the last dose of study treatments to study closure or death, whichever comes first.

Pretreatment AEs are defined as any AE during the pretreatment period.

Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator opinion) or become serious during the TEAE period.

Posttreatment AEs are defined as AEs that are reported during the posttreatment period.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately.

Treatment-emergent adverse events

The TEAEs will be coded according to MedDRA. The AEs will be graded according to the NCI-CTCAE version 4.03.

An overall summary of TEAEs will be provided. The number and percentage of patients who experience any of the following will be provided:

- TEAEs.
- TEAEs of ≥Grade 3.
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period).
- Serious TEAEs.
- Serious treatment-related TEAEs.
- TEAE leading to permanent (full study treatment) discontinuation/premature (partial study treatment) discontinuation.
- AESIs.
- Treatment-related TEAEs.
- Treatment-related TEAEs of ≥Grade 3.

The number and percentage of patients experiencing TEAEs by primary SOC and PT will be summarized by NCI CTCAE grade (all grades and ≥Grade 3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to permanent/premature discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome and AEs/SAEs occurring during the posttreatment dosing period.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (pretreatment, on-treatment and posttreatment). For that purpose, the table of all TEAEs will be presented by SOC and PT sorted by internationally agreed order unless otherwise specified.

13.4.5.3 Deaths

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE and posttreatment) and reasons for death summarized for the all-treated/safety population.
- TEAEs with fatal outcome (on the AE e-CRF page as reported by the Investigator), and related TEAEs with fatal outcome summarized by primary SOC and PT.

A listing of deaths will be provided.

13.4.5.4 Clinical laboratory evaluations

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Complete blood count and serum chemistry results will be graded according to NCI-CTCAE version 4.03, when applicable. For patients with multiple occurrences of the same laboratory variable during the TEAE period, the maximum grade (worst) per patient will be used. The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

The number and proportion of patients with abnormal laboratory tests at baseline (ie, last assessment before the first dose of study treatments administration) will be presented for all grades together and each grade separately. Similar tables showing abnormalities during the TEAE period will be provided.

When the NCI-CTCAE version 4.03 scale is not applicable, the number of patients with a laboratory abnormality out-of-normal laboratory range value will be displayed.

13.4.5.5 Vital signs

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. The incidence of PCSA during the TEAE period will be summarized.

13.4.5.6 Immunogenicity

The observation period for ADAs will be divided into 2 periods:

- The ADA pretreatment period will be defined as the time that informed consent is signed until the first study treatment administration.
- The ADA on-study observation period will be defined as the time from the first study treatment administration until the end of the study.

Definitions:

- Pre-existing ADA, defined as ADA that are present in samples drawn during the pretreatment period.

- Treatment-induced ADA, defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pretreatment samples).
- Treatment boosted ADA, defined as pre-existing ADA with a significant increase in the ADA titer during the study compared to the baseline titer.
- ADA positive patients, defined as patients with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time following the first study treatment administration.
- ADA prevalence, defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.
- ADA incidence, defined as the number of ADA positive patients divided by the number of evaluable patients.

The immunogenicity for isatuximab and REGN2810 will be assessed by summarizing the number and percentage of patients with pre-existing ADA and ADA negative at baseline, and by summarizing the number and percentage of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period.

ADA prevalence and ADA incidence will be also described.

The impact of positive immune response will be evaluated on efficacy, PK and safety endpoints when relevant.

13.4.6 Analyses of pharmacokinetic variables

Individual concentrations and PK parameters of isatuximab and REGN2810 will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum). Individual and mean profiles will be presented graphically.

13.4.7 Analyses of pharmacodynamic variables

Findings from pharmacodynamics markers will be descriptively summarized and tabulated.

13.5 INTERIM ANALYSIS

An interim analysis will be performed for each cohort after the first 23 patients for mCRPC cohorts or the first 20 patients for NSCLC cohorts in the Phase 2 part have completed 6 cycles. The interim analysis may be conducted earlier if the required number of responders proceeding to Phase 2 Stage 2 is achieved.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator(s), in accordance, with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation guidelines for good clinical practice (GCP), all applicable laws, rules, and regulations.

Information regarding the clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

14.2 INFORMED CONSENT

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 study, including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, with the name of the patient filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form 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.

14.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate ethics committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator’s Brochure with any

addenda, Investigator's CV, etc) and the date of the review should be clearly stated on the written ethics committee (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the ethics committee (IRB/IEC) should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the ethics committee (IRB/IEC) and to health authorities (competent regulatory authority), as required by local regulation.

A progress report will be sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, discrepancy resolution form [DRF], or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by the Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

15.2 RESPONSIBILITIES OF SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded in the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the Monitoring team must check the e-CRF entries against the source documents, except for the preidentified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the patient allowing the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data in the e-CRF (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUESTS

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to the Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES(S)

The Investigator must maintain confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

16.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information regarding the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

16.5 DATA PROTECTION

- The patient's personal data, which may be included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding the Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Japanese, Not Reported, or Unknown) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the PMDA in Japan or on Chinese population for the CFDA in China).

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy as required by applicable law. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

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

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

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

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

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

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

16.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the IMP leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance by the Investigator or Subinvestigator, or delegated staff with any provision of the clinical trial protocol, or breach of any applicable laws, regulations, or ICH GCP guidelines.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

16.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

16.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to Investigator.

16.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold his approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or of its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

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19 APPENDICES

Appendix A Prostate Cancer Clinical Trials Working Group 3 criteria for progression

Details provided in bibliographic reference (48).

Response evaluation definition for the primary efficacy endpoint (Table 9):

- In mCRPC: response will be defined per PCWG3 criteria on the basis of the following outcomes (if any of these occur, patients will be considered to have responded):
  - Radiographic objective response assessed and confirmed by the Investigators;
  - PSA decline of ≥50% (confirmed by a second PSA test).

For analysis of DoR (secondary efficacy endpoint), disease progression includes radiographic disease progression or unequivocal clinical progression (Table 9). For patients with mCRPC, radiographic progression includes progression by PCWG3 modified RECIST 1.1 for soft tissue and/or PCWG3 defined progression by bone scan.

Table 9 - Response evaluation definitions for ACT15319

	Primary endpoint (RR) in patients with mCRPC	Primary endpoint (RR) in patients with mCRPC	Disease progression in patients with mCRPC
Assessment criteria	PSA	Radiographic objective response – soft tissue (bone lesions are not considered "non-measurable" lesions for RECIST; bone lesions will be assessed by bone scan only)	Radiographic objective response – bone scan
Timing of baseline assessment	Cycle 1 Day 1	Screening CT/MRI	Screening bone scan
Frequency of assessment	Once every 9 weeks	Once every 9 weeks	Once every 9 weeks
Response criteria	Decline ≥50%	RECIST 1.1	NA
Timing for confirmation of response	4 weeks	4 weeks	NA
Timing for confirmation of PD and stop treatment		4 weeks	6 weeks (2+2 rule)

Abbreviations: CT=computed tomography; mCRPC=metastatic, castration resistant prostate cancer; MRI=magnetic resonance imaging; NA=not applicable; PD=progressive disease; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; RR=response rate.

Table 10 - Prostate Cancer Clinical Trials Working Group 3 criteria for progression at trial entry by disease manifestation

Variable	Progression criterion
Blood based	
PSA	Obtain sequence of rising values at a minimum of 1-week intervals.
	1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma.
	Estimate pretherapy PSADT if at least 3 values available ≥4 weeks apart.
Imaging	
Nodes	Nodal progression sufficient for trial entry independent of PSA.
	Measurable lesions not required for entry.
	Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to 5 nodal lesions total recorded.
	Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed.
	If the node progresses to ≥1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to <1.5 cm are pathologic, subject to clinical discretion, and non-measurable.
	For existing pathologic adenopathy, progression is defined per RECIST 1.1.
	Record presence of nodal and/or visceral disease separately. Nodal sites: Locoregional: pelvic only; Extrapelvic: retroperitoneal, mediastinal, thoracic, or other.
Viscera	Visceral progression sufficient for trial entry independent of PSA and recorded separately by site of spread (lung, liver, adrenal, CNS); up to 5 lesions per site of spread.
	Measurable lesions not required for entry.
	Use RECIST to record visceral lesions as target or non-target.
	Record presence of nodal and/or visceral disease separately. Visceral sites: lung, liver, adrenal, CNS.
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor.
	Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease.
Bone	2 new lesions.
	Confirm ambiguous results by other imaging modalities (eg, CT or MRI). Only positivity on the bone scan defines metastatic disease to bone.
	Patients with treated epidural lesions and no other epidural progression are eligible.

Variable	Progression criterion
Type of progression at trial entry	
	Report separately: PSA only; Bone only ±nodal disease; Nodal disease only (no bone disease present); Visceral (lung, liver, adrenal, CNS) disease (±other sites); Record new lesions and site of new lesions v growth of preexisting lesions, or both.
Other markers	
Patient-reported outcomes	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain.

Abbreviations: CNS=central nervous system; CT=computed tomography; MRI=magnetic resonance imaging; PCWG3=Prostate Cancer Clinical Trials Working Group 3; PET=Positron emission tomography; PSA=Prostate-specific antigen; PSADT=PSA doubling time; RECIST=Response Evaluation Criteria in Solid Tumors.

Table 11 - Prostate Cancer Clinical Trials Working Group 3 criteria for progression during study

Variable	Progression criterion
Blood based	
PSA	Recognize that a favorable effect on PSA may be delayed for ≥12 weeks, even for a cytotoxic drug.
	Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression.
	Ignore early rises (before 12 weeks) in determining PSA response.
	Standards for reporting PSA progression date may not indicate a need to stop treatment. After decline from baseline: record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%. No decline from baseline: PSA progression ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks. Recording the duration of PSA decline of little value.
Imaging	
Nodal and visceral	General: Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately. Use RECIST 1.1 but clearly record type of progression (growth of existing lesions versus development of new lesions) separately by site. The recommendations apply to both nmCRPC and mCRPC Record up to 5 lesions per site of spread. Report the proportion who have not progressed at fixed time points (6 or 12 months).
Nodal	Note that for some treatments, a lesion may increase in size before it decreases

Variable	Progression criterion
	Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST 1.1.
	Exclude pseudoprogression in the absence of symptoms or other signs of progression.
Bone Scan	At least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule). If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented. For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan. Date of progression is the date of the scan that first documents the second lesion. Changes in intensity of uptake alone do not constitute either progression or regression. Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months).

Abbreviations: CNS=central nervous system; mCRPC=metastatic, castration resistant prostate cancer; nmCRPC=nonmetastatic, castration resistant prostate cancer; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors.

Appendix B Response Evaluation Criteria in Solid Tumors version 1.1

Details provided in bibliographic reference (32).

Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Special considerations regarding lesion measurability:

- **Bone lesions:**
  - Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
  - Blastic bone lesions are non-measurable.

- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Lesions with prior local treatment:**
  - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Method of assessment

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- **Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.
- **Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- **Endoscopy, laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised.

- **Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response.
- **Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

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

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should not be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

Response criteria are described in Table 12.

Table 12 - Response criteria

Response criteria	Evaluation of target lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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

Special notes on the assessment of target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

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

When the patient also has measurable disease; in this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

When the patient has only non-measurable disease; to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

A) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

B) No FDG-PET at baseline and a positive FDG-PET at follow-up:
   - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

Time point response: At each protocol specified time point, a response assessment should occur. Table 13 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 13 - Response in patients with target disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

When patients have non-measurable (therefore non-target) disease only, Table 14 is to be used.

Table 14 - Response in patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Missing assessments and inevaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. When no imaging/measurement is done at all at a particular time point, the patient is NE at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Special notes on response assessment

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

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

The objective response status of such patients is to be determined by evaluation of target and non-target disease. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Appendix C Eastern Cooperative Oncology Group Performance Status Scale

Performance Status	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Dead.

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair (55).

Appendix D Modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics

Details provided in bibliographic reference (33).

Table 15 - Comparison of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified Response Evaluation Criteria in Solid Tumors for immune-based therapies (iRECIST)

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances - eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicated immune responses assigned using iRECIST.
Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; RECIST=Response Evaluation Criteria in Solid Tumors

Table 16 - Assessment of timepoint response using modified Response Evaluation Criteria in Solid Tumors for immune-based therapies (iRECIST)

Target lesions	Non-target lesions	New lesions	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category[a]
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/non-iUPD	No	iPR	iPR
iPR	Non-iCR/non-iUPD	No	iPR	iPR
iSD	Non-iCR/non-iUPD	No	iSD	iSD
iUPD with no change, or with a decrease from last timepoint	iUPD with no change, or decrease from last timepoint	Yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
iUPD	Non-iCR/non-iUPD, or iCR	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Non-iUPD or progression	Non-iUPD or progression	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

a Previously identified in assessment immediately before this timepoint.

"i" indicates immune responses assigned using iRECIST Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; non-iCR/non-iUPD=criteria for neither CR nor PD have been met; RECIST=Response Evaluation Criteria in Solid Tumors.

Appendix E Cluster of differentiation 38 blood test interference guideline AABB2016

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: [redacted]

Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

A new class of therapeutic agents for multiple myeloma, CD38 monoclonal antibodies, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. The bulletin includes recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background

CD38 monoclonal antibodies are a new treatment for multiple myeloma

CD38, an integral membrane protein that is highly expressed on myeloma cells, has been identified as an effective target antigen for monoclonal antibody therapies. In November 2015, the first therapeutic CD38 monoclonal antibody [daratumumab (Darzalex, Janssen Biotech, Horsham, PA)] was approved by the Food and Drug Administration.[1] Other CD38 monoclonal antibodies are under development.

CD38 monoclonal antibodies interfere with blood bank serologic tests

CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2,3] Plasma samples from anti-CD38-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol),

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and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti-CD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 variably interferes with direct antiglobulin tests (DATs) and antibody identification panel autocontrols.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody.[4,5]
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued.[1,3]
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients.[3,6]

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

1. ABO/RhD typing: no issues.
2. Antibody detection (screening) test: all cells positive.
3. Antibody identification panel: all cells positive (autocontrol may be negative).
4. DAT: positive or negative.
5. AHG crossmatches: positive with all RBC units tested.
6. Adsorptions: panreactivity cannot be eliminated.

This leads to delays in issuing RBCs to the patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations

To avoid problems with transfusion, hospitals should set up procedures to inform the transfusion service whenever any patient is scheduled to begin taking anti-CD38.

BEFORE a patient begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype is recommended.

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference.[2,7]
    - Because DTT treatment destroys Kell antigens, K-negative units should be provided unless the patient is known to be K-positive.
    - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-

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treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For patients with known alloantibodies, phenotypically or genotypically matched RBC units may be provided.[6,8]
    - As some typing antisera require the use of AHG, phenotyping should be performed before the patient receives anti-CD38.
    - Genotyping can be performed either before or after the patient receives anti-CD38.
    - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
    - Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.

Future/alternative approaches to mitigating the anti-CD38 interference

It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody.[2,3] Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Finally, antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells.[9]

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Appendix F National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI CTC AE version 4.03 (56) in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html.

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the 1 resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Appendix G Recommended dose modification or discontinuation and supportive care guidelines for specific REGN2810 drug-related adverse events

Table 17 - Colitis adverse event management

Colitis events CTCAE version 4.03	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Bowel obstruction Colitis Colitis microscopic	No change in dose	No change in dose	For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. Grade 1 diarrhea that persists for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate 4 times daily and budesonide 9 mg daily.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.

Colitis events CTCAE version 4.03	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 2 Enterocolitis hemorrhagic GI perforation Necrotizing colitis Diarrhea: all patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	Delay or omit dose until ≤Grade 1 (See Section 6.6.2)	Delay or omit dose until ≤Grade 1 (See Section 6.6.2)	GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). Grade 2 diarrhea should be treated with addition of oral diphenoxylate hydrochloride and atropine sulfate 4 times daily and budesonide 9 mg daily. Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. In patients with Grade 2 enterocolitis, REGN2810 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.	

Colitis events CTCAE version 4.03	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3 Grade 4	Grade 3: delay or omit dose until ≤Grade 1 (See Section 6.6.2) Grade 4: discontinue treatment	Delay or Omit dose until ≤Grade 1 (See Section 6.6.2) Discontinue if unable to reduce corticosteroid dose to <10 mg/day prednisone equivalent within 12 weeks of toxicity	Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment): Rule out bowel perforation. Imaging with plain films or CT can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with IV steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: Infliximab is contraindicated in patients with bowel perforation or sepsis. If symptoms persist despite the above treatment a surgical consult should be obtained.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer. If symptoms are persistent and/or severe, endoscopic evaluation should be considered.

Abbreviations: CT=computed tomography' CTCAE=common terminology criteria for adverse events; GI=gastrointestinal; IV=intravenous.

Table 18 - Endocrine adverse event management

Endocrine events CTCAE version 4.03	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1-2 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	No change in dose	No change in REGN2810 dose	Monitor thyroid function or other hormonal level tests and serum chemistries more frequently (every 3 to 6 weeks) until returned to baseline values. Replacement of thyroid hormone or thyroid suppression therapy as indicated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Grade 3-4 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	Delay or omit dose until resolves to Grade ≤2 (see Section 6.6.2)	Delay or omit dose until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels (see Section 6.6.2)	Consider endocrine consultation. Rule out infection and sepsis with appropriate cultures and imaging. Replacement of thyroid hormone or thyroid suppression therapy as indicated.	
Grade 1-4 Adrenal insufficiency Hypophysitis Hypopituitarism Pan-hypopituitarism	Grade 1, 2: no change in dose, Grade 3, 4: delay or omit dose until resolves to Grade ≤2 (see Section 6.6.2)	Delay or omit dose until on stable replacement dose (see Section 6.6.2)	Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. If Grade 1-2 hypophysitis is considered, pituitary gland imaging should be considered (MRI with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended

Abbreviations: CTCAE=common terminology criteria for adverse events; IV=intravenous; MRI=magnetic resonance imaging.

Table 19 - Pneumonitis adverse event management

Pneumonitis events CTCAE version 4.03 Grade	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	No change in dose	Consider delay or omit dose (see Section 6.6.2). REGN2810 may be continued with close monitoring.	Radiological findings should be followed on serial imaging studies at least every 3 weeks. Monitor for symptoms every 2 to 3 days. Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Delay or omit dose until resolves to Grade ≤1 (see Section 6.6.2)	Delay or omit dose until resolves to Grade ≤1 (see Section 6.6.2)	To rule out other causes such as infection: Consider pulmonary consultation with bronchoscopy and biopsy/BAL. Consider pulmonary function tests Follow radiological findings on serial imaging studies every 1 to 3 days If the patient is determined to have study treatment-associated pneumonitis Monitor symptoms daily, consider hospitalization Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Treatment with REGN2810 may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply: First episode of pneumonitis: may decrease the dose to 1 mg/kg in subsequent cycles. Second episode of pneumonitis: Discontinue REGN2810 if upon re-challenge the patient develops a second episode of ≥Grade 2 pneumonitis.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection

Pneumonitis events CTCAE version 4.03 Grade	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3-4 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Grade 3: delay or omit dose until resolves to Grade ≤1 (see Section 6.6.2) Grade 4: discontinue treatment	Discontinue REGN2810	Consider pulmonary function tests with pulmonary consult. Bronchoscopy with biopsy and/or BAL is recommended. Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. Add prophylactic antibiotics for opportunistic infections. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection

Abbreviations: BAL= bronchoalveolar lavage; CTCAE=common terminology criteria for adverse events; IV=intravenous.

Table 20 - Renal adverse event management

Renal events CTCAE version 4.03 Grade	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Nephritis Nephritis autoimmune	No change in Dose	Consider delay or omit dose if event does not improve with symptomatic treatment (see Section 6.6.2)	Provide symptomatic treatment. Monitor creatinine weekly: when it returns to baseline, resume routine creatinine monitoring per protocol.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
Grade 2 Renal failure	Delay or omit dose until resolves to Grade ≤1 (see Section 6.6.2)	Consider delay or omit dose (see Section 6.6.2)	Systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued for at least 1 month. Consider prophylactic antibiotics for opportunistic infections. Consider renal biopsy. If elevations persist >7 days or worse, treat as Grade 4.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.

Renal events CTCAE version 4.03 Grade	Isatuximab Dose Management	REGN2810 Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3-4 Renal failure acute	Grade 3: delay or omit dose until resolves to Grade ≤1 (see Section 6.6.2) Grade 4: discontinue treatment	Discontinue REGN2810	Renal consultation with consideration of ultrasound and/or biopsy as appropriate. Monitor creatinine daily. Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. REGN2810 treatment may be restated and the dose modified as specified in the protocol.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.

Abbreviations: CTCAE=common terminology criteria for adverse events; irAEs=immune-related adverse events.

Table 21 - Dermatologic adverse event management

Skin events CTCAE version 4.03	Isatuximab Dosing managment	REGN2810 Dosing managemnt	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	No change in dose	Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruitics (eg, diphenhrdeamine HCl or hydroxyzine HCl) Treatment with oral steroids is at Investigator discretion for Grade 2 events.	All attempts should be made to rule out other causes such as metastatic disease, infectious, or allergic dermatitis.
Grade 3	No change in dose	Delay or omit dose until Grade ≤2 (see Section 6.6.2)	Consider dermatology consultation and biopsy for confirmation of diagnosis. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once daily or dexamethasone 4 mg 4 times per day. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no less than 4 weeks.	
Grade 4	Delay or omit dose until Grade ≤3 (see Section 6.6.2)	Discontinue treatment	Dermatology consultation and consideration of biopsy and clinical dermatology photograph. Initiate with oral steroids with 1 mg/kg prednisone or equivalent. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no less than 4 weeks.	

Abbreviations: CTCAE=common terminology criteria for adverse events.

Table 22 - Hepatitis adverse event management

Hepatitis CTCAE version 4.03	Isatuximab Dosing management	REGN2810 Dosing management	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	Delay or omit dose if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters (see Section 6.6.2)	Monitor liver function tests more frequently until returned to baseline values	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis
Grade 3, 4	Delay or omit dose until Grade ≤2 (see Section 6.6.2)	Discontinue treatment if: AST or ALT ≥5 x ULN Bilirubin ≥3 x ULN	Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24 to 48 hours. When symptoms improves to Grade ≤1, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. If AST/ALT levels bot not decease 48 hours after initiation of systemic steroids, oral mycophenolate mofdtil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. Several courses of steroids taper may be necessary as symptoms may worsen when the steroids dose is decreased.	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=common terminology criteria for adverse events; ULN=upper limit of normal.

Table 23 - Ophthalmology (uveitis) adverse event management

Uveitis CTCAE version 4.03	Isatuximab Dosing management	REGN2810 Dosing management	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy	Evaluation by an ophthalmologist is strongly recommended Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitis	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (eg, glaucoma or cataracts)
Grade 2	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy, and do not improve to Grade 1 within the retreatment period or requires systemic treatment		
Grade ≥3	Delay or omit dose until Grade ≤2 (see Section 6.6.2)	Discontinue treatment	Treatment with systemic corticosteroids such as prednisolone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks	

Abbreviations: CTCAE=common terminology criteria for adverse events.

Table 24 - Nausea and vomiting adverse event management

Nauea and Vomiting CTCAE version 4.03	Isatuximab Dosing management	REGN2810 Dosing management	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in dose	No change in dose	Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institution practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.	
Grade 2	Delay or omit dose until ≤Grade 1 (see Section 6.6.2) Restart treatment at same dose level	Delay or omit dose until ≤Grade 1 (see Section 6.6.2) May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities for resolve.		
Grade 3	Delay or omit dose until ≤Grade 1 (see Section 6.6.2) Restart at same dose level.	Delay or omit until ≤Grade 1 (see Section 6.6.2) May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities for resolve. Discontinue if toxicity do not resolve within 12 weeks.		
Grade 4	Discontinue treatment			

Abbreviations: CTCAE=common terminology criteria for adverse events.

Appendix H Modification of Diet in Renal Disease (MDRD) equation

Glomerular filtration rate (mL/min/1.73 m^2) = 175 × (Serum Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if Female) × (1.212 if African-American)

Appendix I Multidisciplinary Collegial Meeting Requirement

This appendix provides with country list where the eligibility of patient to take part in the study is to be validated at the multidisciplinary collegial meeting:

France

Appendix J PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (05 October 2017)

This amendment is not considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment was to include a subsection with specific criteria for patients allocated to immunotherapy-based treatment arms to continue treatment through RECIST-defined radiological progression of disease. Other changes were implemented to clarify footnotes in flowcharts for height, weight, and dosing; correct links; add de-escalation text where missing; and delete tables of blood draw volumes because they are provided in the Laboratory Manual.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, 1.1 Design diagram 1.5.2 For Phase 2 part of Cohort A-2, Stage 2 Phase 2 part of Cohort A-1 and Cohort B (tests for REGN2810 are not applicable for Cohort A-2, tests for PK are not applicable for cross-over part) 1.5.3 For Cohort C and Cohort D (tests for REGN2810 are not applicable for Cohort C if isatuximab monotherapy is administered) 8.3.1 Study treatment Appendix A Prostate cancer clinical trials working group 3 criteria for progression	Administrative and typographical changes	Correct typographical errors and note administrative changes
1.3 Study Flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and Cross-over part 1.4 Study Flowchart for Cohort C and Cohort D 6.5 Retreatment of patientss 6.6.1 General rules 6.7.1 Duration of study participation for each patient 11.1 Permanent treatment discontinuation with IMP product(s) 12.3 Treatment period	Add specific criteria required for patients to continue study treatment after apparent radiographic progression	Per FDA request, to include a subsection with specific criteria required for patients allocated to immunotherapy-based treatment arms to continue treatment through RECIST-defined radiological progression of disease. References to the subsection were also added in relevant sections.

Section # and Name	Description of Change	Brief Rationale
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and crossover part	Clarify weight/height data collection time point in study flowchart footnote	Ambiguity in flowchart table and footnote may lead to confusion of when to collect height and weight data.
1.4 Study flowchart for Cohort C and Cohort D 1.5.3 For Cohort C and Cohort D (tests for REGN2810 are not applicable for Cohort C if isatuximab monotherapy is administered)	Remove irrelevant/non-applicable text from study flowcharts	Flowcharts in section 1.4 and 1.5.3 are for cohorts without QW dosing, while the footnote included text regarding dose information for QW dosing.
6.2.1 Starting dose and de-escalation design	Add details on dose de-escalation design	Certain description of the dose de-escalation design in Clinical Trial Summary and Design Diagram was not transcribed to Section 6.2.1.
6.5 Retreatment of patients 6.6.3 Dose modifications 6.6.4 General guidelines for the management of immune-related adverse events	Correct reference to Appendix F to Appendix G	Incorrect hyperlinks in the document led to incorrect appendices referencing.
9.1.5 Immunogenicity 9.2.2 Pharmacokinetic sample handling procedure 9.4 Samples blood volume	Remove Tables 5, 7, 10, 11	Details on blood draw volumes should be provided to study sites in Laboratory Manual instead of inclusion in the protocol.
9.1.5 Immuogenicity 9.2.3 Bioanalytical methods 9.2.4.1 Noncompartmental analysis 13.1 Determination of sample size Appendix A Prostate cancer clinical trials Working Group 3 criteria for progression Appendix B Response Evaluation Criteria in Solid Tumors version 1.1 Appendix D Modified response evaluation criteria in solid tumors for immune-based therapeutics Appendix G Recommended dose modification or discontinuation and supportive care guidelines for specific REGN2810 drug-related adverse events.	Renumbering of Tables 6-28	Removal of Tables 5, 7, 10, and 11 require renumbering Tables 6-28.

FDA=Food and Drug Administration; RECIST=Response evaluation criteria in solid tumors; QW=once weekly

Amendment 2 (09 November 2017)

This amendment applied to the UK only and is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment was to clarify that pregnancy testing would be performed on Day 1 of each cycle as required by MRHA regulations.

Section # and Name	Description of Change	Brief Rationale
1.3 Study flowchart for Phase 1, Phase 2 Cohorts Q-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D 12.3.1 Cycle 1 (Day 1, Day 8 and Day 15) 12.3.2 Subsequent cycles (Day 1) 12.4 End of treatment	Clarify that pregnancy testing must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit	Per MHRA request, the current protocol is unclear to investigators whether the more frequency tests are a legal requirement or not in the UK according to the phrase "in countries where required by local regulations". In order to meet the legal requirement, MHRA is requesting to indicate that pregnancy testing must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit.

EOT=end of treatment; MHRA= Medicines and Healthcare Products Regulatory Agency

Amendment 3 (02 April 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to implement changes to the protocol in response to feedback provided by ANSM dated 07 December 2017. This amendment also includes extension of the analysis and study cut-off dates to 12 months instead of 6 months after last ongoing patient initiates study treatment, with rationale provided below. Administrative changes such as clarifications, corrections of inconsistencies and of typographic errors are also included in this amendment.

Local amendment for United Kingdom (amendment #2), relating to feedback provided by MHRA dated October 30th, 2017, is also included in this global amendment (amendment #3), to revert back to a unique protocol version for all participating countries.

Section # and Name	Description of Change	Brief Rationale
Clinical Summary 7.2 Inclusion criteria	Modify inclusion criterion I09 to allow mCRPC patients to receive up to 2 previous taxane-based chemotherapy regimens	In France, mCRPC patients typically receive docetaxel and cabazitaxel as standard treatment. ANSM requested the protocol to be amended to accommodate patients enrolling into this study should have received docetaxel and cabazitaxel as per local standard of care, unless an investigator believes that a chemotherapy regimen is not appropriate for a specific patient.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary 7.2 Inclusion criteria 7.3 Exclusion criteria	Exclude NSCLC patients with ROS translocation and BRAF mutation	In France, standard treatments are available for NSCLC patients with ROS translocation and BRAF mutation; therefore, ANSM requested the protocol to be amended to exclude patients with these genetic alterations. As molecular screening is not performed routinely in countries where ROS/BRAF targeted therapies are not available as standard treatment options, this eligibility criterion is now reflected in a new exclusion criterion E26, along with the other genetic alterations already specified in inclusion criterion I17, to exclude patients with known EGFR/ALK/ROS1/BRAF alterations.
Clinical Trial Summary 7.3 Exclusion criteria	Clarify exclusion criterion E18 regarding criteria that may interfere with the immune-modulation mechanism of study treatment	ANSM suggested adding “active tuberculosis” and “severe infection requiring parenteral antibiotic treatment” to E18. In addition, hepatitis definitions in E18 were modified to improve clarity following multiple inquiries from study sites.
Clinical Trial Summary 7.2 Inclusion criteria Appendix I Multidisciplinary collegial meeting requirement	Specify that patient eligibility is to be discussed at a multidisciplinary collegial meeting per local practice	ANSM requested to specify in inclusion criterion I04 that eligibility of patients to take part in the study will be validated at the multidisciplinary collegial meeting, as per local practice in France. The rationale is that NSCLC patients who are eligible for this study would have second line chemotherapies as standard treatment option, ANSM wanted assurance from a multidisciplinary collegial committee to decide that chemotherapy is not the best treatment option for this specific patient (I04).
6.9 Study Committees	Implement an independent data safety monitoring board for the Phase 2 part	ANSM requested to implement an independent review committee because this study includes a Phase 2 part which enrolls more than 100 patients.
Clinical Trial Summary 7.3 Exclusion criteria 8.9.2 Contraceptive measures and pregnancy counseling	Extend effective contraceptive requirement to 2 weeks before IMP initiation	ANSM requested effective contraceptive measures to be implemented starting 2 weeks prior to IMP initiation, in accordance with isatuximab IB.
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D 12.3.1 Cycle 1 (Day 1, Day 8 and Day 15) 12.3.2 Subsequent cycles (Day 1) 12.4 End of treatment	Clarify that pregnancy testing must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit (implemented in local amendment for United Kingdom – amendment #2)	Per MHRA request, the current protocol is unclear to investigators whether the more frequent tests are a legal requirement in the UK according to the phrase “in countries where required by local regulations”. In order to meet the legal requirement, MHRA is requesting to indicate that pregnancy testing (urine or serum) must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary 1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D 7.2 Inclusion criteria 9.3 Biomarkers	Clarify that archival pre-treatment tissue sample can be provided in place of mandatory baseline biopsy	Footnote in the original protocol specified that tumor tissue sample performed after progression to prior therapy may be considered as baseline biopsy. To avoid confusion, this is now incorporated into inclusion criterion I03.
Clinical Trial Summary 7.3 Exclusion criteria	Unify prior anti-cancer therapies washout period to within 14 days from IMP initiation	There is no rationale to support the use of two different washout periods for intravenous (21 days) and oral (14 days) anti-cancer therapies.
Clinical Trial summary 5.2 Secondary objectives 9.6.2 Secondary endpoints 13.4.4.1 Analysis of secondary efficacy endpoints	Add DCR as secondary endpoint	DCR, a typical endpoint for advanced malignancies, was intended to be included as a secondary endpoint in the original protocol.
Clinical Trial summary 6.7.1 Duration of study participation for each patient 6.7.2 Determination of end of clinical trial (all patients) 12.1 Visit schedule 12.5.2 Survival follow-up period 12.5.3 Post overall survival study cutoff date 13.4.4.1 Analysis of primary efficacy endpoint	Extend analysis and study cut-off dates from 6 months to 12 months after last ongoing patient initiates IMP	The rationale for this change is that time-to-event endpoints such as DoR and PFS for checkpoint inhibitors are often >12 months and cutting off tumor assessment data early will comprise the maturity of these secondary endpoints. In addition, patients who are still on study treatment after study-cutoff date will continue disease assessment until confirmation of PD or end of treatment period, whichever comes first, to ensure patients are not progressing while continuing to be treated with study drugs.
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D 6.4 Cross-over part (A subpart of cohor A-2) 12.3.2 Subsequent cycles (Day 1) 12.6 Cross-over period	Change in time window for biomarker sample collection (tumor biopsy and blood samples for cytokines analysis)	C2D1 tumor biopsy window is changed from ±7 days to -7 days (after C1D15 IMP administration). The rationale is that it would be a more robust analysis to collect samples from patients who have consistently received 1 cycle of study treatment. Blood draw for cytokine analysis between baseline and C1D1 is also specified to be at least 15 days apart.
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D Appendix A 9.6.1 Primary assessment	Clarify disease assessment should follow calendar days and not be adjusted for delays in cycle start	Disease assessment should be performed at regular frequency despite cycle delays. Currently protocol uses “at the end of every 3 cycles” in most sections, and in one section it specified “tumor imaging timing should follow calendars and should not be adjusted for delays in cycle starts”. For consistency, calendar days will be used to describe disease assessment schedule.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary 7.3 Exclusion criteria 8.9.1 Prohibited concomitant treatments	Add denosumab and interferon as prohibited concomitant medications, and clarify use of corticosteroids throughout study	Interferon is immunosuppressive and may affect the mechanism of study treatment. Denosumab, for treatment of osteoporosis and prevention of bone metastases, will be added as a prohibited concomitant medication (as for bisphosphonate therapy). Use of corticosteroids is also further elaborated to improve clarity.
10.5.5 Adverse event of special interest	Correct definition for REGN2810 symptomatic overdose	REGN2810 symptomatic overdose definition is incorrectly indicated on a body weight basis (note: REGN2810 is administered as a flat dose). The definition is corrected in accordance with REGN2810 IB edition No. 5, dated May 12, 2017.
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D 12.2 Baseline evaluation 12.3.1 Cycle 1 (Day 1, Day 8 and Day 15) 12.3.2 Subsequent cycles (Day 1) 12.4 End of treatment 12.5.1 Safety follow-up period	Add time window for clinical blood tests, urinalysis, and biomarker blood draw	Allow blood chemistry, hematology, urinalysis, PSA assessment (time window for C1D1 only), and biomarker blood draw to be performed within 24h prior to IMP administration, wherever applicable.
1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part 1.4 Study flowchart for Cohort C and Cohort D	To allow semi-quantitative urinalysis	Allow semi-quantitative urinalysis if semi-quantitative method used at site level can provide an absolute numeric value of the parameters.

Section # and Name	Description of Change	Brief Rationale
Throughout	Miscellaneous clarifications, correction of inconsistencies and typographic errors	Includes but not limited to: Correct typo in E14 and E20 Correct indicative clocks and clarify sampling timing in PK flow chart Biomarker exploratory endpoints stated in the Clinical Trial Summary is now also inserted under Section 9.6.3 Exploratory endpoints Remove biomarker sample preservation methods (keep details in laboratory manual) Correct units and typos of absolute neutrophil count under E20 Clarify isatuximab monotherapy dose is to be determined depending on the recommended Phase 2 dose Clarify inform consent form can be signed more than 28 days prior to enrollment/randomization and define screening period time frame, and redefine "pretreatment AEs" as AEs during "pretreatment period" instead of "screening period" Introduce INN (cemiplimab) when REGN2810 was first mentioned and in Introduction Remind study sites must retain disease assessment images as Sponsor may decide to collect images in the future for possible Independent Central Review Inconsistencies in visit schedule AESI specified in Section 6.6.4 was not mentioned in Section 10.5.5

ANSM= Agence Nationale de Sécurité du Médicament et des Produits de Santé; DCR=disease control rate; DoR=duration of response; EOT=end of treatment; IMP=investigational medicinal product; mCRPC=metastatic castration-resistant prostate cancer; MHRA= Medicines and Healthcare Products Regulatory Authority; PD=disease progression; PFS=progression-free survival

Amendment 4 (23 July 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment was to reduce the number of radiographic scans showing SD required for patients with NSCLC from 2 to 1, specify the frequency of DMC meetings. In addition, there were changes to the time window for PK and ADA sample collection and administrative changes such as clarifications and corrections.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary 7.2 Inclusion criteria	Modify inclusion criterion I16 for NSCLC patients to reduce requirement of at least 2 radiographic imaging scans to confirm SD to at least 1 radiographic imaging scan	In certain countries the standard of care for disease assessment using radiographic scan is every 3 months, this would in turn lead to documented benefits requirement of SD ≥ 6 months, which is inconsistent with that listed in I16 where documented benefit is defined as SD ≥ 4 months.
6.9 Study committees	Added frequency of DMC meeting	To specify DMC data review meeting will occur at intervals planned to be no longer than 3 months (starting from the first data review meeting).
1.5.1 For Phase 1 part, Stage 1 Phase 2 part of Cohort A-1 and Cohort B 1.5.2 For Phase 2 part of Cohort A-2, Stage 2 Phase 2 part of Cohort A-1 and Cohort B (tests for REGN2810 are not applicable for Cohort A-2, tests for PK are not applicable for cross-over part) 1.5.3 For Cohort C and Cohort D (tests for REGN2810 are not applicable for Cohort C if isatuximab monotherapy is administered) 9.1.5 Immunogenicity 9.2.1 Sampling time 9.2.3 Bioanalytical methods 9.2.4.1 Noncompartmental analysis	Clarifications, minor corrections, and change in time windows for PK and ADA samples collection	Clarified sample collection details and updated sample collection time windows within flow chart in consistent with footnote descriptions Extended follow-up period time window from 90 ± 5 days to 90 ± 7 days to improve sample collection feasibility Removed indicative clock time from flowchart to avoid confusion and inconsistencies Updated “Site of bioanalysis” to “Covance Harrogate (UK)” from “Refer to laboratory manual” Updated “Analytical technique” to “Immunoassay” from “ELISA” Clarified PK parameters definitions and added $AUC_{0\text{-}21d}$ as an additional PK parameter Updated lower limit of quantification for isatuximab PK analysis due to assay transfer to Covance Harrogate (UK)

ADA=anti-drug antibody; DMC=Data Monitoring Committee; ELISA=enzyme-linked immunosorbent assay; NSCLC=nonsmall cell lung cancer; PK=pharmacokinetic; SD=stable disease

Amended Protocol 04 [Amendment 05] (21 November 2018)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment was to modify the inclusion criteria for patients with nonsmall cell lung cancer (NSCLC) by allowing patients with NSCLC with best response as complete response (CR), partial response (PR) or stable disease (SD) at ≥1 radiographic imaging scan who had progressed radiographically to participate. Additional changes for patients with NSCLC include not requiring a tumor biopsy to qualify for enrollment if the procedure could put the patient at excessive risk and minimizing the number of pharmacokinetic (PK) and anti-drug antibody (ADA) samples to be collected. For all patients, premedication requirements were modified to allow patients with no or Grade ≤2 infusion associated reactions to omit premedications at Investigators' discretion. The window for collection of follow-up samples was also extended and text clarified that the follow-up period could extend beyond 6 cycles.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary Section 6.3 Phase 2 part (efficacy Signal)	In Part 2, the observation period after last dose of IMP was changed from up to 6 cycles to at least 6 cycles.	Clarified that due to the time needed to analyze biomarker and PK samples, the totality of data could be generated after the last ongoing patients in individual cohort received 6 cycles.
Clinical Trial Summary Section 1.3 Study flowchart for Phase 1, Phase 2 cohorts A-1, A-2, B and cross-over part Section 1.4 Study Flowchart for cohort C and cohort D Section 7.2 Inclusion criteria Section 9.3 Biomarkers	I 03: For NSCLC patients, the mandatory tumor biopsy requirement was modified to allow a patient to enter the study without a tumor biopsy at baseline if, in the written opinion of the investigator, performing a biopsy would put the wellbeing of the patient at an excessive risk due to the location of the lesion. Written agreement from the Sponsor was required.	To decrease risk for patients with NSCLC whose lesion is located in a site where performing a biopsy would but the wellbeing of the patient at an excessive risk.
Clinical Trial Summary Section 7.2 Inclusion criteria	I 12 Added that patients with NSCLC could enter the study with inoperable recurrent NSCLC rather than only Stage IIIB/IV NSCLC.	To clarify that patients with inoperable recurrent NSCLC could be enrolled.
Clinical Trial Summary Section 7.2 Inclusion criteria	I 14 Clarified that prior regimen containing anti-PD-1/PD-L1 therapy applied to all patients who entered with NSCLC (Stage IIIB/IV or inoperable recurrent).	Clarification
Clinical Trial Summary Section 7.2 Inclusion criteria	I 15 Clarified that having received no more than 1 previous chemotherapy applied to all patients who entered with NSCLC (Stage IIIB/IV or inoperable recurrent).	Clarification
Clinical Trial Summary,	I 16 For patients with NSCLC, removed time and scan	To allow sites with different scan

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Inclusion criteria	number requirements for prior documentation of clinical benefit by radiographic scan.	frequencies to recruit patients
Clinical Trial Summary Section 7.3 Exclusion criteria	E 10 Changed time limit from 14 to 21 days before initiation of IMP for patients who had received prior intravenous cytotoxic chemotherapy, antineoplastic biological therapy, major surgery, or local prostatic intervention.	To give patients an extra week to recover from intravenous cytotoxic chemotherapy, antineoplastic biological therapy, major surgery, or local prostatic intervention.
Clinical Trial Summary 4.4.2.1 Isatuximab Section 4.4.4 Preventive measures to minimize the risk of the combination Section 8.2 Noninvesti-gational medicinal product(s)	Premedication requirements were modified. Timing of premedication dosing modified to match Clinical Trial Summary.	Change based on data from completed and ongoing studies. This is also to allow patients with no or Grade ≤2 infusion associated reactions to omit premedications at Investigators' discretion.
Section 1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part Section 1.4 Study Flowchart for Cohort C and Cohort D Section 12.2 Baseline evaluation	Delete unused abbreviation for IAR.	Correction
Section 1.3 Study flowchart for Phase 1, Phase 2 cohorts A-1, A-2, B and cross-over part Section 1.4 Study Flowchart for cohort C and cohort D 4.4.4 Preventative measures to minimize the risk of the combination 12.3.1 Cycle 1 (Day 1, Day 8 and Day 15) 12.3.2 Subsequent cycles (Day 1)	Vital signs monitoring during isatuximab infusion was modified.	To add monitoring of vital signs during the isatuximab infusion, when clinically indicated.
Clinical Trial Summary Section 8.2 Noninvesti-gational medicinal product(s) 8.2.5 Montelukast	Montelukast 10 mg orally or equivalent was added as a premedication.	Change made based on data from recent references that adding montelukast could decrease incidence of infusion associated reaction.
Clinical Trial Summary, Section 13.3.7 Response evaluable population	Response evaluable population: Added that patients must fulfill all eligibility criteria.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Study flowchart for Phase 1, Phase 2 Cohorts A-1, A-2, B and cross-over part Section 1.4 Study Flowchart for Cohort C and Cohort D Section 12.2 Baseline evaluation Section 12.3.1 Cycle 1 (Day 1, Day 8 and Day 15) Section 12.3.2 Subsequent cycles (Day 1) Section 12.4 End of treatment Section 12.5.1 Safety follow-up period	Urinalysis: sodium, potassium, calcium, and chloride will no longer be analyzed.	Change based on data from completed and ongoing studies and to align with other isatuximab protocols.
Section 1.5.1 For Phase 1 part, Stage 1 Phase 2 part of Cohort A-1 and Cohort B	For the patients with NSCLC who are enrolled for Phase 2 Stage 1 after implementation of Amendment #5 at individual sites, PK/ADA will not be collected for REGN2810 and isatuximab. Section title modified to reflect changes.	To decrease burden for patients with NSCLC without increasing risk
Section 1.5.1 For Phase 1 part, Stage 1 Phase 2 part of Cohort A-1 and Cohort B Section 1.5.2 For Phase 2 part of Cohort A-2, Stage 2 Phase 2 part of Cohort A-1 and Cohort B (tests for REGN2810 are not applicable for Cohort A-2, tests for PK are not applicable for cross-over part) Section 1.5.3 For Cohort C and Cohort D (tests for REGN2810 are not applicable for Cohort C if isatuximab monotherapy is administered)	REGN2810 PK sample to be collected at EOI+ 4h rather than EOI+ 4.5h and EOI+ 1h rather than 1h post EOI. Clarified that S06 and S06 samples must be collected even if second REGN 2810 infusion is not done or is delayed. Added that PK and ADA collection could be reduced upon notification from the Sponsor based on the updated knowledge of isatuximab immunogenicity and PK. After start of study treatment, if 1 drug is prematurely discontinued, ADA samples for this drug will be collected on Day 1 of the 2 next cycles. If ADA test at the second cycle is positive or inconclusive, ADA testing will be repeated every 3 months until negative. The window for posttreatment follow-up samples was extended from 90±5 days to 90±7 days.	Typographical correction and to align with other protocols
Section 9.1.5 Immunogenicity	Shortened instructions for collection of immunogenicity samples and referred to the laboratory manual and flowchart for additional information. Deleted LLQ row in Table 5	The laboratory manual and flowchart information was more concise. Row not applicable
Section 9.2.1 Sampling time	Deleted information that could be found in PK flowchart	The information in the PK flowchart was more concise.
Section 9.2.3 Bioanalytical methods	Deleted LLQ row in Table 6	

Section # and Name	Description of Change	Brief Rationale
Appendix G Recommended dose modification or discontinuation and supportive care guidelines for specific REGN2810 drug related adverse events Table 23 Ophthalmology (uveitis) adverse event management	Corrected to include steroid dose for Grade ≥3 ophthalmology AEs (ie, mg/kg)	Dosing information was incomplete
Clinical Trial Summary 13.5 Interim analysis	Minor wording changes	Clarification
Appendix G Recommended dose modification or discontinuation and supportive care guidelines for specific REGN2810 drug related adverse events Table 20 Renal adverse event management	For patients with Grade 3-4 renal events, under Isatuximab Dose Management, “Grade 3: discontinue treatment” is corrected to “Grade 4: discontinue treatment” (as Grade 3 is already noted as “delay or omit dose until resolves to Grade ≤1”)	Correction of typographical error

ADA=anti-drug antibody; AE=adverse event; EOI=end of infusion; LLQ=lower limit of quantitation; NSCLC=nonsmall cell lung cancer; PK=pharmacokinetic(s)

Signature Page for VV-CLIN-0507776 v2.0
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