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Sponsor: Sanofi **Drug substance(s):**	**Study Identifiers:** EudraCT number: 2017-002846-61 IND Number: IND 136026 WHO universal trial number: U1111-1197-7792 ClinicalTrials.gov: NCT03367819 **Study code: ACT15319**
Title of the study: 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 center(s): 2 sites in France, 5 sites in Italy, 2 sites in Taiwan, Province of China, 2 sites in UK, and 5 sites in the United States	
Study period: Date first participant enrolled: 04 January 2018 Date last participant completed: 10 March 2021 Study Status: The study was stopped after the interim analysis due to overall results being insufficient to satisfy the per-protocol criteria to initiate Phase 2 Stage 2 in both mCRPC and NSCLC cohorts.	
Phase of development: Phase 1/2	

Objectives:

Primary Objectives

- Phase 1: To characterize the safety and tolerability of isatuximab in combination with REGN2810 in patients with metastatic, castration resistant prostate cancer (mCRPC) who were naïve to anti-programmed cell death (PD-1)/programmed cell death-ligand 1 (PD-L1) containing therapy naïve, 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: 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 naive, 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, disease control rate, and progression-free survival).

Methodology:

ACT15319 was a Phase 1/2 open-label, multi-center study evaluating safety, preliminary efficacy and pharmacokinetic (PK) of isatuximab (SAR650984) in combination with REGN2810 or isatuximab alone in patients with advanced malignancies (ACT15319).

The study was to be conducted in up to 3 parts:

- The Phase 1 part (safety run-in) was 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) was to assess the preliminary efficacy of isatuximab in combination with REGN2810 or isatuximab alone based on tumor response using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria for NSCLC and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for mCRPC.
- Cross-over part (a subpart of Cohort A-2) in which patients who progressed on isatuximab monotherapy may have received isatuximab plus REGN2810 if they still fulfilled the eligibility criteria.

A per-protocol interim analysis performed after the first 24 patients for mCRPC Cohort A-1 and the first 20 patients for NSCLC Cohort B in the Phase 2 part were enrolled did not achieve the pre-defined efficacy criteria and the study was stopped per-protocol. Isatuximab and REGN2810 combination demonstrated a manageable safety profile and no new safety signals were observed compared with previous isatuximab or REGN2810 trials in patients with other tumor types.

Biomarker analyses were not performed as there was insufficient efficacy response in the trial. It was decided not to perform extra sampling and analyses of Phase 2 Stage 1 samples since these results would not be informative.

Number of participants:

Planned: 6 to 24 (Phase 1); 134 (Phase 2)

Enrolled: Phase 2 Stage 1: 24 (mCRPC Cohort A-1); 20 (NSCLC Cohort B)

Treated: Phase 2 Stage 1: 24 (mCRPC Cohort A-1); 20 (NSCLC Cohort B)

Evaluated:

Efficacy: 24 (mCRPC Cohort A-1); 20 (NSCLC Cohort B)

Safety: 24 (mCRPC Cohort A-1); 20 (NSCLC Cohort B)

Pharmacokinetics isatuximab: 40

Pharmacokinetic cemiplimab (REGN2810): 43

Diagnosis and criteria for inclusion:

For mCRPC patients: Metastatic adenocarcinoma of the prostate documented by bone lesion on bone scan, or by measurable soft tissue disease by computed tomography or magnetic resonance imaging with documented progressive disease (PD) per PCWG3 criteria.

For NSCLC patients: Histologically or cytologically confirmed diagnosis of Stage IIIB/IV or inoperable recurrent NSCLC with at least 1 measurable lesion per RECIST 1.1 criteria.

Exclusion criteria primarily included Eastern Cooperative Oncology Group (ECOG) performance status of ≥2.

Study products

Investigational medicinal product(s):

Formulation:

- Isatuximab: Concentrated solution for infusion.
- REGN2810: Concentrated solution for infusion.

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 (might have been implemented if 2/6 patients with dose-limiting toxicity (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 was to be determined based on safety data from the Phase 1 part. Monotherapy dose for the Phase 2 part was to be the isatuximab RP2D.

Non-investigational medicinal product(s):

All patients received following premedications to prevent or reduce infusion-associated reactions (IARs), 30 to 60 minutes prior to isatuximab infusion (no longer than 60 minutes):

- 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

Formulation/Form & composition: Non-investigational products were locally sourced and formulations varied.

Route(s) of administration: Oral or IV

Dose regimen: Premedications were administered 30 to 60 minutes prior to isatuximab infusion (no more than 60 minutes prior).

When isatuximab and REGN2810 were administrated on the same day, the administration sequence was: premedications, followed by REGN2810, followed by isatuximab.

When only isatuximab was administrated on a day, the administration sequence was: premedications, followed by isatuximab

Duration of treatment: The cycle duration was 21 days.

Duration of observation:

The duration of the study for a patient included:

- A DLT observation period (21 days),
- A screening period (up to 28 days),
- A treatment period (up to 2 years),
- A safety follow-up period (90 days or until negative anti-drug antibody [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).

Criteria for evaluation:

The current report is an abbreviated document because the study was stopped after the interim analysis indicated that the overall result was not sufficient to satisfy the per-protocol criteria to move forward in both mCRPC Cohort A-1 and NSCLC Cohort B. Only the safety results are being presented in full. The following safety criteria were evaluated and analyzed using descriptive statistics; treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, deaths, IARs, adverse events of special interest (AESIs) and clinical laboratory parameters.

Pharmacokinetic sampling times and bioanalytical methods:

Isatuximab PK samples were to be collected at: Cycle 1 predose and end of infusion (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.

REGN2810 PK samples were to be collected at: Cycle 1 predose (corresponding to start of IV infusion) 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 plasma concentration and REGN2810 serum concentrations were determined using validated immunoassays. Non compartmental analyses were conducted for both the compounds.

Statistical methods:

Analysis of primary endpoint:

- Phase 1: Safety and tolerability were assessed based on dose limiting toxicities (DLTs) (in Cycle 1), AEs/serious adverse events (SAEs) and laboratory abnormalities
- Phase 2: The primary efficacy endpoint for the Phase 2 part of the study was RR. The best overall response was summarized with descriptive statistics.

Analysis of safety endpoints

Number (%) of patients experiencing TEAEs by primary system organ class and preferred term were summarized by National Cancer Institute-common terminology criteria for adverse events (NCI-CTCAE) grade (all grades and Grade ≥3) for the all-treated population. Similar tables were prepared for treatment related TEAEs, IARs, TEAEs leading to isatuximab/REGN2810 discontinuation, and TEAEs leading to dose modification.

Summary Results:

Study ACT15319 was stopped after the per-protocol interim analysis due to overall results being insufficient to satisfy the per-protocol criteria to initiate Phase 2 Stage 2 in both mCRPC and NSCLC cohorts. Therefore, the majority of efficacy evaluations originally planned were no longer considered relevant and were not performed.

Population characteristics:

- In the mCRPC Cohort A-1, the median age of patients was 69.5 years and in the NSCLC Cohort B the median age was 65.5 years. Most patients in both cohorts had an ECOG PS of 1.

Efficacy results:

- No patient achieved complete response either in the mCRPC Cohort A-1 or in the NSCLC Cohort B. Only 1 patient in the mCRPC Cohort A-1 achieved unconfirmed partial response. The overall results were not sufficient to satisfy the per-protocol criteria to move forward with these cohorts.

Safety results:

- No DLT was observed in this study.
- For the mCRPC Cohort A-1, the most commonly reported preferred terms (PTs) were infusion related reactions (12 patients [50.0%]), decreased appetite (9 patients [35.7%]), back pain and fatigue (8 patients [33.3%] each), and asthenia and pyrexia (6 patients [25.0%] each). Only infusion related reactions with intensity Grade ≥3 were reported in more than 1 patient in the study.
- In the NSCLC Cohort B, most patients experienced infusion related reactions (9 patients [45.0%]), cough (6 patients [30.0%]) followed by asthenia, dyspnea, and pyrexia (4 patients [20.0%] each). The PTs with intensity Grade ≥3 reported in more than 1 patient in the study were infusion related reaction and pneumonia (2 patients [10.0%] each).
- No patients in either cohort had TEAEs leading to premature discontinuation of isatuximab or REGN2810.
- In the mCRPC Cohort A-1, the most frequently reported treatment-related PTs that occurred in 12 patients (50.0%) was infusion related reaction followed by 6 patients (25.0%) who experienced fatigue. Intensity Grade ≥3 drug-related TEAEs were reported by 4 patients.

  Fourteen patients (70.0%) experienced treatment-related TEAEs in the NSCLC Cohort B. Intensity Grade ≥3 drug-related TEAEs were reported by 4 patients (20.0%).
- In the mCRPC Cohort A-1, 9 patients (37.5%) reported serious TEAEs with intensity Grade ≥3.

  Overall, 14 patients (70.0%) reported serious TEAEs in the NSCLC Cohort B, of which 11 patients (55.0%) experienced TEAEs with intensity Grade ≥3.
- No treatment-related deaths occurred during the study.

  Of the 2 on-treatment patient deaths in the mCRPC Cohort A-1, 1 patient died because of an AE of urosepsis and 1 patient death was due to respiratory failure. During post-treatment period, 5 deaths (20.8%) were due to PD.

  The 2 on-treatment patient deaths reported in the NSCLC Cohort B were due to disease progression (1 patient [5.0%]) and AE of pneumonia (1 patient [5.0%]). During the post-treatment period, 4 patient deaths (20.0%) occurred due to PD, and 1 patient died due to an AE of dyspnea.

- Four (16.7%) patients had TEAEs leading to definitive treatment discontinuation in the mCRPC Cohort A-1: infusion related reaction (2 patients [8.3%]) which was related to isatuximab, and respiratory failure (1 patient [4.2%]) and urosepsis (1 patient [4.2%]) which were not related to study treatment.

  In the NSCLC Cohort B, 4 patients (20.0%) experienced TEAEs leading to definitive treatment discontinuation: 2 patients (10.0%) had an infusion related reaction related to isatuximab, 1 patient (5.0%) discontinued due to pneumonia that was unrelated to the study treatment, and 1 patient (5.0%) discontinued due to metastases to spinal cord that was unrelated to the study treatment.
- Of the 12 patients (50.0%) who reported IARs in the mCRPC Cohort A-1, 9 patients (37.6%) had IARs meeting AESI criteria with intensity ranging from Grade 2 to Grade 4. Symptoms of IAR reported in more than 1 patient (4.2%) included nausea (5 patients [20.8%]), vomiting and cough, 4 patients (16.7%) each, and rhinitis, abdominal pain, dysphonia, and nasal congestion, 2 patients (8.3%) each.

  In the NSCLC Cohort B, 9 patients (45.0%) reported IARs and all IARs met AESI criteria with intensity ranging from Grade 2 to Grade 3. All the reported IARs were infusion related reactions and related to isatuximab treatment. Symptoms of IAR reported in more than 1 patient (4.2%) included cough (5 patients [25.0%]), dyspnea and hypertension, 4 patients (20.0%) each, rhinorrhea (3 patients [15.0%]), and conjunctivitis, tachycardia, bronchospasm, and dry mouth, 2 patients (10.0%) each.
- In the mCRPC Cohort A-1, hematology parameters worsened by 1 or more Grades during the treatment period:
  - Anemia: 23 patients (100.0%; intensity Grade 1 to Grade 3) during on-treatment period; 22 patients (91.7%; intensity Grade 1 to Grade 2) at Baseline
  - Platelet count decreased: 8 patients (34.8%; intensity Grade 1 to Grade 3) during on-treatment period; only 1 patient (4.2%; intensity Grade 1) at Baseline
  - Lymphocyte count decreased: 18 patients (78.3%; intensity Grade 1 to Grade 4) during on-treatment period; 6 patients (25.0%; intensity Grade 1 to Grade 3) at Baseline
  - Neutrophil count decreased: 5 patients (21.7%; intensity Grade 1 to Grade 2) during on-treatment period; only 1 patient (4.2%) with intensity Grade 1 at Baseline.
  - WBC decreased: 13 patients (56.5%) with intensity Grade 1 during on-treatment period compared to 3 patients (12.5%) with same grade intensity at Baseline

  In the NSCLC Cohort B, hematological abnormalities occurred during the on-treatment period as follows:
  - Anemia: 14 patients (70.0%; intensity Grade 1 to Grade 3) during on-treatment period; 9 patients (45.0%; intensity Grade 1 to Grade 2) at Baseline
  - Lymphocyte count decreased: 13 patients (65.0%; intensity Grade 1 to Grade 3) during on-treatment period; 5 patients (25.0%; intensity Grade 1 to Grade 2) at Baseline
  - There were no patients with platelet count decreased and neutrophil count decreased at Baseline. During the on-treatment period, 1 patient (5.0%) had Grade 1 platelet count decreased and 2 patients (10.0%) had Grade 1 neutrophil count decreased.
- One patient (4.2%) had Grade 4 hyponatremia at Baseline. An increase in the number of patients experiencing Grade 1 and Grade 2 electrolyte abnormalities was noted during the on-treatment period. No other notable electrolyte abnormality was observed above Grade 2 either at Baseline or during the TEAE period.

  No electrolyte abnormality was noted above Grade 2 both at Baseline and during the on-treatment period for the NSCLC Cohort B.

- The number of patients experiencing Grade 1 and Grade 2 hyperglycemia and hypoalbuminemia increased during the on-treatment period for the mCRPC Cohort A-1.

  For the NSCLC Cohort B, hypoalbuminemia Grade 3 occurred in 1 patient (5.0%) during the on-treatment period. No other abnormalities above Grade 2 were observed either at Baseline or on-treatment period.
- No serum creatinine increase was observed above Grade 1 both at Baseline and during the on-treatment period, for the mCRPC Cohort A-1 although, the number of patients experiencing Grade 1 creatinine increased were higher in the latter case. A similar trend was observed for patients in the NSCLC Cohort B.
- For the mCRPC Cohort A-1, hyperuricemia Grade 3 was noted in 1 patient (4.2%) at Baseline and 2 patients (8.7%) during the on-treatment period; 1 patient (4.3%) had Grade 4 hyperuricemia. In the NSCLC Cohort B, 4 patients (20.0%) had Grade 3 hyperuricemia at Baseline and 3 patients (15.0%) had Grade 3 hyperuricemia during the TEAE period.
- In the mCRPC Cohort A-1, 1 patient (4.2%) each had Grade 2 and Grade 3 ALP increased at Baseline. During the on-treatment period, 4 patients (17.4%) had Grade 2 and 6 patients (26.1%) had Grade 3 ALP increased. One patient (4.2%) had Grade 1 AST increased at Baseline in comparison to 6 patients (26.1%) during the on-treatment period; one patient (4.3%) also had Grade 2 AST increased during the on-treatment period.
- For the NSCLC Cohort B, no abnormality above Grade 1 was noted both at Baseline and during the on-treatment period.

Pharmacokinetic results:

- Briefly, after the first administration of isatuximab at 10 mg/kg in combination with REGN2810 at 350 mg in NSCLC and mCRPC patients, mean isatuximab Cmax and AUC0-168h were 285 µg/mL and 26600 µg.h/mL, respectively with low variability (CV% for Cmax and AUC0-168h: 21% and 24%, respectively) and mean REGN2810 Cmax and AUC0-504h were 106 mg/L and 934 mg.day/L, respectively, with low variability (CV% for Cmax and AUC0-504h: 24% and 27%, respectively).

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