Sponsor: Sanofi **Drug substance:** isatuximab	**Study Identifiers:** U1111-1202-0839, NCT03637764, EudraCT Number: 2018-000390-67 **Study code:** ACT15377

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 atezolizumab or isatuximab alone in patients with advanced malignancies.

Study centers: The study was conducted in 8 countries/regions worldwide: 2 sites in Belgium, 1 site in Canada, 2 sites in the Czech Republic, 4 sites in Italy, 1 site in the Netherlands, 6 sites in Spain, 6 sites in Taiwan, and 3 sites in the United States of America.

Study period:

Date first participant enrolled: 06 Aug 2018

Date last participant completed: 11 May 2022

Study Status: Terminated (Study ACT15377 was stopped after the performance of interim analysis for the 4 cohorts (HCC, SCCHN, EOC, GBM) indicated that the efficacy results observed in each cohort did not fulfill the preplanned interim analysis criteria allowing to move to Phase 2 stage 2 in these 4 cohorts.)

Phase of development: 1/2

Objectives:

Primary:

Phase 1:

- To characterize the safety and tolerability of isatuximab in combination with atezolizumab in patients with unresectable hepatocellular carcinoma (HCC), platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN), platinum-resistant/refractory epithelial ovarian cancer (EOC), or recurrent glioblastoma multiforme (GBM), and to determine the recommended Phase 2 dose (RP2D).

Phase 2:

- To assess response rate (RR) of isatuximab in combination with atezolizumab in patients with HCC or SCCHN or EOC.
- To assess the progression-free survival rate at 6 months (PFS-6) of isatuximab in combination with atezolizumab, or as a single agent in patients with GBM.

Secondary:

- To evaluate the safety (in Phase 2) profile of isatuximab monotherapy (GBM only) or in combination with atezolizumab.
- To evaluate the immunogenicity of isatuximab and atezolizumab.
- To characterize the PK profile of isatuximab single agent (GBM only) and atezolizumab in combination with isatuximab.
- To assess overall efficacy of isatuximab in combination with atezolizumab or single agent (GBM only).

Methodology:

The ACT15377 study was to have up to 2 phases. This is a Phase 1/2 open-label, nonrandomized, multicenter, safety, preliminary efficacy, and pharmacokinetic (PK) study of isatuximab in combination with atezolizumab, or isatuximab alone in patients with advanced malignancies. In Phase 1, approximately 6 to 24 dose limiting toxicity (DLT) evaluable patients were expected to be enrolled. In Phase 2, sufficient patients were planned to be screened to achieve 285 treated patients with study intervention in cohorts A, B, C, D-1, and D-2.

An interim analysis was planned to be performed for all the cohorts at 6 months after the last patient's first treatment in the cohort. A total of 17 EOC, 31 GBM, 26 HCC, and 26 SCCHN patients were expected to be enrolled.

As of 27 Sep 2019, a planned interim analysis was performed after the first 33 patients (4 patients in the Phase 1 part and 29 in the Phase 2 Stage 1 part) for the GBM Cohort and the first 18 patients (2 patients in Phase 1 part and 16 in the Phase 2 Stage 1 part) for the EOC Cohort were enrolled.

As of 22 Nov 2019, a planned interim analysis was performed after the first 27 patients (1 patient in the Phase 1 part and 26 in the Phase 2 Stage 1 part) for the HCC Cohort were enrolled.

As of 14 July 2020, a planned interim analysis was performed after the first 29 patients (2 patients in the Phase 1 part and 27 in the Phase 2 Stage 1 part) for the SSCHN Cohort were enrolled.

The Sanofi ACT15377 study team informed that it had been decided not to proceed to Phase 2 Stage 2 for the 4 cohorts as the overall efficacy results were not sufficient to satisfy the per protocol criteria to move forward with these cohorts.

Biomarker analyses were not performed at the first interim analyses; however, the analyses were performed at the second and third interim analyses. 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.

A description of the main safety aspects of this clinical study has been included in this abbreviated report.

Number of participants:

Planned: 6 to 24 (Phase 1); 285 (Phase 2)

Treated: Phase 2 Stage 1: 27 (HCC Cohort A); 29 (SCCHN Cohort B); 18 (EOC Cohort C); 33 (GBM Cohort D-1)

Evaluated: 27 (HCC Cohort A); 29 (SCCHN Cohort B); 18 (EOC Cohort C); 33 (GBM Cohort D-1)

Efficacy: 27 (HCC Cohort A); 29 (SCCHN Cohort B); 18 (EOC Cohort C); 33 (GBM Cohort D-1)

Safety: 27 (HCC Cohort A); 29 (SCCHN Cohort B); 18 (EOC Cohort C); 33 (GBM Cohort D-1)

Diagnosis and criteria for inclusion:

For patients with HCC:

Histologically confirmed unresectable HCC (excluding fibrolamellar and mixed hepatocellular/cholangiocarcinoma). Radiology diagnosed HCC as per American Association for the Study of Liver Diseases criteria needs to be confirmed by histology before initiation of IMP.

For patients with SCCHN:

Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

For patients with EOC:

Histologically confirmed advanced epithelial ovarian, fallopian tube, or peritoneal cancer, excluding mucinous histology but including malignant mixed Müllerian tumors with high grade serous component.

For patients with GBM:

Have histologically confirmed glioblastoma. Patients with the original histology as low grade glioma were NOT eligible.

Exclusion criteria primarily included Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 (for patients with HCC, SCCHN, and EOC), or Karnofsky performance score of ≤70 (for patients with GBM).

Study product:

Investigational medicinal product(s): Isatuximab (SAR650984) in combination with Atezolizumab or alone

Formulation:

Isatuximab: The drug product was 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, and 0.02% (w/v) polysorbate 80 at pH 6.0 buffer.

Atezolizumab: The drug product was presented as a concentrate for solution for infusion in vials containing 60 mg/mL. Each 20 mL vial of concentrate contains 1200 mg atezolizumab. After dilution, 1 mL of solution contained approximately 4.4 mg of atezolizumab.

Route(s) of administration:

Isatuximab: intravenous (IV) infusion

Atezolizumab: IV infusion

Study products

Dose regimen:

Phase 1

Starting dose:

Isatuximab: 10 mg/kg weekly for 3 weeks (once weekly [QW] × 3; ie. on Day 1, Day 8, and Day 15 of Cycle 1), then once every 3 weeks (Q3W) (ie, on Day 1 of each 21-day cycle)

Atezolizumab (administrated before isatuximab): 1200 mg Q3W, (ie, on Day 1 of each 21-day cycle)

Dose Level -1 (may be implemented if ≥3/12 with DLT or if ≥3/6 patients with DLT at starting dose):

Isatuximab: 5 mgkg QW×3, then Q3W

Atezolizumab (administrated before isatuximab): 1200 mg Q3W

Phase 2:

For the combination Cohorts A, B, C, and D-1, atezolizumab was administered first followed by isatuximab on Day 1 of each cycle. Isatuximab was administered at the RP2D determined based on safety data from Phase 1.

Monotherapy dose for GBM in Cohort D-2 was determined based on results from Cohort D-1 and schedule of administration was weekly for first cycle, followed by 1 dose Q3W.

For the possible Cohort E, implemented if positive results were observed in the Phase 2 Stage 2 one tumor type (same as A, B, C, or D-1/D-2), atezolizumab was administered first followed by isatuximab on Day 1 of each cycle (for combination regimen), and isatuximab was administered at the RP2D determined based on safety data from Phase 1 RP2D without initial isatuximab weekly dosing.

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 650 to 1000 mg oral route (or equivalent).
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 to 50 mg IV (or equivalent).
- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg oral route (or equivalent).

Formulation: Noninvestigational 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 atezolizumab were administrated on the same day, the administration sequence was: atezolizumab, followed by premedications, 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 antidrug antibody testing if 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 report, because the study was stopped after the interim analysis for the 4 cohorts indicated that the efficacy results observed in each cohort do not fulfill the preplanned interim analysis criteria allowing to move to Phase 2 stage 2 in these 4 cohorts. Only the safety results are being presented in full. The following safety criteria were evaluated and analyzed using descriptive statistics; treatment exposure, treatment-emergent adverse events (TEAEs), serious adverse events, TEAEs leading to discontinuation, deaths, IARs, adverse events of special interest (AESIs), and clinical laboratory parameters.

Statistical methods:

Interim Analysis

An interim analysis for each cohort was performed for the HCC, SCCHN, EOC, and GBM cohorts after the last patients remaining in the treatment period among the first 26, 26, 17, and 31 patients, respectively, in Phase 2 completed approximately 6 months of study treatment or permanently discontinued both atezolizumab and isatuximab, whichever came first. The interim analysis was planned to be conducted earlier if the required number of responses for proceeding to Phase 2 Stage 2 was achieved for the HCC, SCCHN, and EOC cohorts.

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 the HCC, SCCHN, EOC, and GBM cohorts.

Analysis population

For both Phase 1 and Phase 2 of the study, the all-treated population included all patients who had given their informed consent and received at least 1 dose (even incomplete) of either isatuximab or atezolizumab. This population was the primary population for the analyses of efficacy and safety parameters, unless otherwise noted. All analyses using this population were based on the dose level actually received in the first cycle.

The response evaluable population included all patients who fulfilled eligibility criteria in the all-treated population with an evaluable baseline assessment and at least 1 evaluable post baseline response assessment during the treatment period.

General statistical approach

Analysis of primary endpoint

For HCC, SCCHN, and EOC, RR was summarized with descriptive statistics. A 90% two-sided confidence interval was computed using the Clopper-Pearson method.

For GBM, PFS-6 was summarized using the Kaplan-Meier method.

Analysis of secondary endpoint

The best percent change from baseline in tumor burden (tumor burden change) was presented graphically.

- PFS was summarized using the Kaplan-Meier method.
- RR and disease control rate (complete response + partial response + stable disease) ≥6 months were summarized for GBM with descriptive statistics.

Analysis of safety endpoints

Number (%) of patients experiencing TEAEs by primary system organ class and preferred term (PT) 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, serious TEAEs, IARs, fatal (TE)AEs, TEAEs leading to isatuximab/atezolizumab discontinuation, and TEAEs leading to dose modification. Adverse events of special interest were listed.

Summary results:

Study ACT15377 was stopped after the performance of interim analysis for the 4 cohorts (HCC, SCCHN, EOC, GBM) indicated that the efficacy results observed in each cohort did not fulfill the preplanned interim analysis criteria allowing to move to Phase 2 stage 2 in these 4 cohorts.

In HCC Cohort A, 2 patients had confirmed PR. In SCCHN Cohort B, 3 patients had confirmed PR and 1 patient had confirmed CR. In EOC Cohort C, 1 patient had confirmed PR. In GBM Cohort D-1, there were no responders. The overall results were not sufficient to satisfy the per protocol criteria to move forward with these cohorts.

The safety profile was assessed from the findings of physical examination, laboratory tests and were based on incidence, severity (as graded in the NCI-CTCAE Version 4.03), and cumulative nature of TEAEs, and of AEs.

Isatuximab and atezolizumab combination have a manageable safety profile and no new safety signals were observed compared with what was described in the respective Investigator's Brochure.

- In HCC Cohort A, the overall duration of exposure to isatuximab + atezolizumab ranged from 3 to 106 weeks. The mean (SD) number of cycles started by patients were 7.6 (7.5) cycles and the mean (SD) duration of exposure to study treatment was 22.9 (22.6) weeks.
- In SCCHN Cohort B, the overall duration of exposure to isatuximab + atezolizumab ranged from 3 to 105 weeks. The mean (SD) number of cycles started by patients were 6.7 (8.3) cycles and the mean (SD) duration of exposure to study treatment was 21.0 (26.1) weeks.
- In EOC Cohort C, the overall duration of exposure to isatuximab + atezolizumab ranged from 3 to 61 weeks. The mean (SD) number of cycles started by patients were 5.0 (4.2) cycles and the mean (SD) duration of exposure to study treatment was 15.2 (12.9) weeks.
- In GBM Cohort D-1, the overall duration of exposure to isatuximab + atezolizumab ranged from 3 to 54 weeks. The mean (SD) number of cycles started by patients were 4.1 (3.6) cycles and the mean (SD) duration of exposure to study treatment was 12.4 (10.8) weeks.
- The median cumulative dose of isatuximab was 70.00 mg/kg and mean (SD) duration of exposure was 22.9 (22.6) weeks for HCC Cohort A.
- For SCCHN Cohort B, the median cumulative dose of isatuximab was 50.80 mg/kg and the mean (SD) duration of exposure was 20.9 (26.3) weeks.
- For EOC Cohort C, the median cumulative dose of isatuximab was 59.99 mg/kg and the mean (SD) duration of exposure was 15.2 (12.9) weeks.
- For GBM Cohort D-1, the median cumulative dose of isatuximab was 50.00 mg/kg and the mean (SD) duration of exposure was 12.3 (10.9) weeks.
- The median age of patients was 63.0 years in HCC Cohort A, 62.0 years in SCCHN Cohort B, and 55.0 years in EOC Cohort C and GBM Cohort D-1. Most patients in the HCC, SCCHN, and EOC cohorts had an ECOG PS of 0 or 1 and 1/3 of the patients in GBM Cohort D-1 had Karnofsky performance status of 80.
- No patients had TEAEs leading to premature discontinuation of isatuximab or atezolizumab in all cohorts.
- In HCC Cohort A, the most commonly reported PTs were infusion related reactions (17 patients [63.0%]), abdominal pain (6 patients [22.2%]), decreased appetite (6 patients [22.2%]), and nausea (6 patients [22.2%]). The PTs with intensity Grade ≥3 reported in more than 1 patient in the study were disease progression (3 patients [11.1%]) and renal failure (2 patients [7.4%]).
- In SCCHN Cohort B, the most commonly reported PTs were infusion related reactions (9 patients [31.0%]), pyrexia (7 patients [24.1%]), asthenia (6 patients [20.7%]), constipation (6 patients [20.7%]), and fatigue (6 patients [20.7%]). The PTs with intensity Grade ≥3 reported in more than 1 patient in the study were disease progression (4 patients [13.8%]) and tumour haemorrhage (2 patients [6.9%]).
- In EOC Cohort C, the most commonly reported PTs were infusion related reactions (15 patients [83.3%]), fatigue (7 patients [38.9%]), asthenia (6 patients [33.3%]), nausea (6 patients [33.3%]), diarrhoea (5 patients [27.8%]) dyspnoea (5 patients [27.8%]), abdominal pain (4 patients [22.2%]), decreased appetite (4 patients [22.2%]), oedema peripheral (4 patients [22.2%]), vomiting (4 patients [22.2%]). The PTs with intensity Grade ≥3 reported in more than 1 patient in the study were disease progression (3 patients [16.7%]) and ascites (2 patients [11.1%]).
- In GBM Cohort D-1, the most commonly reported PTs were infusion related reactions (18 patients [54.5%]), headache (13 patients [39.4%]), asthenia (9 patients [27.3%]), and fatigue (7 patients [21.2%]). The PTs with intensity Grade ≥3 reported in more than 1 patient in the study were hemiparesis (3 patients [9.1%]), headache (2 patients [6.1%]), and hypertension (2 patients [6.1%]).
- In HCC Cohort A, 3 patients (11.1%) died due to disease progression and 1 patient (3.7%) died due to AE. Eighteen (66.7%) post treatment deaths were reported, of which 17 (63.0%) occurred due to disease progression and 1 was due to other reasons.

- In SCCHN Cohort B, all of 8 (27.6%) on-treatment patient deaths and 14 (48.3%) post treatment deaths were due to disease progression.
- In EOC Cohort C, all of 3 (16.7%) on-treatment patient deaths were due to disease progression and 7 (38.9%) post treatment deaths were reported, of which 6 (33.3%) occurred due to disease progression and 1 was due to other reasons.
- In GBM Cohort D-1, only 1 patient (3.0%) had an on-treatment death due to AE. Twenty-five (75.8%) post treatment deaths were reported, of which 16 (48.5%) occurred due to disease progression and 9 (27.3%) were due to other reasons.
- There were 12 patients (44.4%) who reported serious TEAEs; all 12 patients (44.4%) reported events with intensity Grade ≥ 3 in HCC Cohort A.
- There were 16 patients (55.2%) who reported serious TEAEs; 11 patients (37.9%) reported events with intensity Grade ≥3 in SCCHN Cohort B.
- There were 8 patients (44.4%) who reported serious TEAEs; 5 patients (27.8%) reported events with intensity Grade ≥3 in EOC Cohort C.
- There were 9 patients (27.3%) who reported serious TEAEs; all 9 patients (27.3%) reported events with intensity Grade ≥3 in GBM Cohort D-1.
- Two (7.4%) patients had TEAEs leading to definitive treatment discontinuation in HCC Cohort A. No patients experienced TEAEs leading to definitive study drug discontinuation in SCCHN Cohort B and EOC Cohort C. One patient (3.0%) had a TEAE leading to definitive treatment discontinuation in GBM Cohort D-1.
- Overall, 17 patients (63.0%) in HCC Cohort A, 9 patients (31.0%) in SCCHN Cohort B, 15 patients (83.3%) in EOC Cohort C, and 18 patients (54.5%) in GBM Cohort D-1 reported IARs of all intensity grades.
- Overall, for hematology evaluations, valid post baseline values were available for 26 of 27 patients treated in HCC Cohort A and 32 of 33 patients treated in GBM Cohort D-1. Post baseline values were available for all patients in SCCHN Cohort B and EOC Cohort C.

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