Sponsor: Sanofi **Drug substance:** isatuximab	**Study Identifiers:** U1111-1211-9010; NCT03769181; EudraCT Number: 2018-002442-37 **Study code:** ACT15320
Title of the study: A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma	
Study centers: This study was conducted in 7 countries/regions worldwide including: 8 sites in France, 6 sites in Spain, 3 sites in Portugal, 3 sites in Taiwan, 3 sites in Korea, 2 sites in the Netherlands and 3 sites in Italy.	
Study period: Date first participant enrolled: 20/Dec/2018 Date last participant completed: 08/Nov/2022 Study Status: Terminated (Study was stopped after interim analysis for all 4 cohorts with results either not fulfilling the pre-planned interim analysis criteria or fulfilling the criteria but as per sponsor decision. It was not due to any safety concern)	
Phase of development: Phase1/Phase2	

Objectives:

Primary:

Phase 1:

- To characterize the safety and tolerability of isatuximab in combination with cemiplimab in participants with relapsed and refractory classic Hodgkin's lymphoma (cHL), diffuse large B-cell lymphoma (DLBCL), and peripheral T-cell lymphoma (PTCL), and to confirm the recommended Phase 2 dose (RP2D).

Phase 2:

- 1 - Cohort A1 (anti-PD-1/PD-L1 naïve cHL): To assess the complete remission (CR) rate of isatuximab in combination with cemiplimab.
- 2 - Cohort A2 (cHL progressing from PD-1/PD-L1), B (DLBCL), and C (PTCL): To assess the objective response rate (ORR) of isatuximab in combination with cemiplimab.

Secondary:

- 1 - To evaluate the safety of the RP2D of isatuximab in combination with cemiplimab.
- 2 - To evaluate the safety of the combination of isatuximab with cemiplimab and radiotherapy in participants with cHL.
- 3 - To evaluate the immunogenicity of isatuximab and cemiplimab when given in combination.
- 4 - To characterize the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.
- 5 - To assess overall efficacy of:

  Isatuximab in combination with cemiplimab,

  And

  Isatuximab in combination with cemiplimab and radiotherapy.

Methodology:

The study was early terminated after the performance of the interim analysis for the 4 cohorts (cHL anti-PD-1/PD-L1 naïve [A1], cHL anti PD 1/PD-L1 progressor [A2], DLBCL anti-PD-1/PD-L1 naïve [B], PTCL anti-PD-1/PD-L1 naïve [C]). The efficacy results observed in Cohorts B and C did not fulfill the pre-planned interim analysis criteria allowing the study to move to Phase 2 Stage 2 in these cohorts. The efficacy results observed in Cohort A1 and Cohort A2 did fulfill the pre-planned interim analysis criteria in Stage 1. However, due to the availability of competitive medications with better response rate reported so far in the same disease indication, the Phase 2 Stage 2 portion of these cohorts was not opened.

This was a Phase 1/2 open-label, non-comparative, multi-center, safety, preliminary efficacy, and PK study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma. The study was conducted in 2 phases:

In Phase 1 (safety run-in): participants with cHL, DLBCL, or PTCL were enrolled. The starting dose of isatuximab (Cycle 1) was 10 mg/kg every week. From Cycle 2 through Cycle 6, the isatuximab dose was 10 mg/kg every 2 weeks (Q2W) and cemiplimab 250 mg Q2W. For Cycle 7 and beyond, the isatuximab dose was 10 mg/kg every 3 weeks (Q3W) and cemiplimab dose was 350 mg Q3W. The RP2D was determined during Phase 1 according to the safety data observed in the DLT observation period ie, Cycle 1 (28 days). The safety profile was considered manageable and no DLT was observed during Cycle 1 among the 5 participants treated at this dose which was then declared as the RP2D. Then participants were treated in the Phase 2 Stage 1 at the RP2D.

In Phase 2 (efficacy signal/Simon 2-stage design): 4 cohorts were included:

Cohort A1: cHL anti-PD-1/PD-L1 naïve.

Cohort A2: cHL anti-PD-1/PD-L1 progressor.

Cohort B: DLBCL anti-PD-1/PD-L1 naïve.

Cohort C: PTCL anti-PD-1/PD-L1 naïve.

The participants treated at the RP2D of isatuximab and cemiplimab in combination during Phase 1 were included in the efficacy and safety analyses together with participants of the same indication in Stage 1 of Phase 2.

An interim analysis was planned to be performed for all the cohorts at 6 months after the last participant's first treatment in the cohort. A total of 18 cHL PD-1 naïve, 12 cHL PD-1 progressor, 17 DLBCL, and 11 PTCL participants were enrolled.

Number of participants: Planned: approximately 3 to 12 (Phase 1); approximately 118 (Phase 2; 57 in Stage 1 and 61 in Stage 2) Phase 2 Stage 1: Screened: 24 (Cohort A1); 14 (Cohort A2); 24 (Cohort B); 16 (Cohort C) Enrolled: 18 (Cohort A1); 12 (Cohort A2); 17 (Cohort B); 11 (Cohort C) Treated and Evaluated: 18 (Cohort A1); 12 (Cohort A2); 17 (Cohort B); 11 (Cohort C)
Diagnosis and criteria for inclusion: For Phase 1 and Cohort A1 (cHL anti-PD-1/PD-L1 naïve): Histologically confirmed advanced cHL that had relapsed or progressed after at least 3 lines of systemic therapies that may have included auto-hematopoietic stem cell transplantation (HSCT) OR auto-HSCT and brentuximab vedotin. For Phase 1 and Cohort A2 (cHL anti-PD-1/PD-L1 progressor): Histologically confirmed advanced cHL which had relapsed or progressed after one previous anti-PD-1/PD-L1 containing regimen as the most recent prior therapy. In Cohort A2 Phase 1: Documentation of benefit (defined as CR, PR, or SD ≥6 months at ≥1 radiographic imaging scans) but subsequent progression during or after the prior anti-PD1/PD-L1 containing regimen. In Cohort A2 Phase 2: Participants who had achieved CR were excluded unless they relapsed on an anti-PD1/PD-L1 containing regimen. Documentation of benefit (defined as PR or SD ≥6 months at ≥1 radiographic imaging scans) but subsequent progression during or after the prior anti-PD1/PD-L1 containing regimen. For Phase 1 and Cohort B (DLBCL): Histologically confirmed advanced DLBCL that had relapsed or progressed after 2 lines of systemic therapy including auto-HSCT, **OR** lines of systemic therapy for participants who were not eligible for auto-HSCT. For Phase 1 and Cohort C (PTCL): Histologically confirmed advanced PTCL that had relapsed or progressed after chemotherapy and auto-HSCT as consolidation of first remission, **OR** first-line chemotherapy if participants were ineligible for auto-HSCT.

Study products

Investigational medicinal product(s): Isatuximab with cemiplimab and optional radiotherapy (cHL anti-PD-1/PD-L1 naïve Cohort A1 and cHL anti-PD-1/PD-L1 progressor A2) OR isatuximab in combination with cemiplimab (DLBCL Cohort B and PTCL Cohort C).

Route of administration: intravenous (IV) infusion for both Isatuximab and cemiplimab

Dose regimen: Phase 1:

Starting dose:
Isatuximab: 10 mg/kg every week × 4 on Cycle 1, then Q2W from Cycle 2 to Cycle 6, then Q3W from Cycle 7 to Cycle 30.
Cemiplimab (administrated before isatuximab): 250 mg Q2W from Cycle 1 to Cycle 6, then 350 mg Q3W from Cycle 7 to Cycle 30.

Dose Level -1: implemented if ≥2/3 participants with DLT or if ≥2/6 participants with DLT at starting dose.
Isatuximab: 5 mg/kg every week × 4 on Cycle 1, then Q2W from Cycle 2 to Cycle 6, then Q3W from Cycle 7 to Cycle 30.
Cemiplimab (administrated before isatuximab): 250 mg Q2W from Cycle 1 to Cycle 6, then 350 mg Q3W from Cycle 7 to Cycle 30.

Dose regimen: Phase 2:

For the combination Cohorts A1, A2, B, and C, cemiplimab was administered first followed by isatuximab on Day 1 of each cycle. Isatuximab was to be administered at the RP2D determined based on safety data from Phase 1.

Non-investigational medicinal products (premedication): All participants received the 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 orally (or equivalent)
- Ranitidine 50 mg IV (or equivalent at the investigator's discretion)
- Diphenhydramine 25 to 50 mg IV (or equivalent)
- Methylprednisolone 100 mg IV (or equivalent)
- Montelukast 10 mg orally (or equivalent)

Duration of study intervention:

The **treatment cycle duration** was 28 days during the 6 first cycles then 21 days from Cycle 7. Participants continued treatment until disease progression, unacceptable AE, participant's decision to stop the treatment, 96 weeks (at least 48 weeks from initial signal of CR, whichever was longer) of delivery of investigational medicinal product(s) without documented progressive disease (PD), or any other reason.

The **duration of the study** for a participant included:

- A DLT observation period (28 days).
- A screening period (up to 28 days).
- A treatment period (up to 96 weeks, at least 48 weeks from initial signal of CR, whichever was longer).
- A post safety follow-up period (up to 90 days).
- A survival follow-up period (except for the cohorts where the results of interim analysis were not positive) until death or study cut-off date.

The data cut-off for the primary end-of-cohort analysis was to be up to 24 weeks from the date the last participant was treated in an individual cohort. The data cut-off for the intermediate and final end of cohort analysis was to be up to 48 and 96 weeks, respectively, from the date the last participant was treated in an individual cohort.

Criteria for evaluation:

Primary:

Phase 1:

- Safety and tolerability will be assessed based on dose limiting toxicities (DLTs, in Cycle 1), adverse events (AEs)/serious adverse events (SAEs), and laboratory abnormalities.

Phase 2:

- 1 - Cohort A1: CR rate as defined by as the proportion of participants who have a CR as a best overall response (BOR) during the isatuximab + cemiplimab therapy period using the Lugano response criteria 2014.
- 2 - Cohorts A2, B, and C:

  ORR defined as the proportion of participants who have a CR or partial response (PR) as a BOR during isatuximab + cemiplimab therapy period using the Lugano response criteria 2014.

Secondary:

- 1 - AEs/SAEs and laboratory abnormalities for isatuximab + cemiplimab.
- 2 - AEs/SAEs and laboratory abnormalities in isatuximab + cemiplimab + radiotherapy treated participants (Cohorts A1 and A2).
- 3 - Immunogenicity: Anti-drug antibody (ADA) against isatuximab and against cemiplimab.
- 4 - PK evaluation using non-compartmental analysis for both compounds using serum concentrations for cemiplimab and plasma concentrations for isatuximab.
- 5 – Efficacy:

- Tumor burden change, duration of response (DoR), disease control rate (DCR), defined as the percentage of participants who achieve CR, partial response (PR) or stable disease and progression-free survival (PFS).
- For Cohort A1, ORR during isatuximab + cemiplimab ± radiotherapy periods. CR rate during isatuximab + cemiplimab + radiotherapy period.
- For Cohort A2, ORR during isatuximab + cemiplimab + radiotherapy period. CR rate during isatuximab + cemiplimab ± radiotherapy periods.

Statistical methods:

As Phase 2 Stage 2 further recruitment was not initiated following interim analyses, it was, therefore, decided not to perform extra sampling and analyses of Phase 2 Stage 1 samples since these results/analyses would not be informative. Summaries of vital signs, physical findings, and electrocardiogram results were not prepared because they did not present a safety concern.

For both Phase 1 and Phase 2 parts of the study, the all-treated population included all participants who signed the study informed consent and received at least 1 dose (even incomplete) of the study treatment, either isatuximab or cemiplimab. This population was the primary population for the analyses of efficacy and safety parameters except for DLT evaluation. All analyses using this population were based on the dose level actually received in the first cycle.

The participants treated at the RP2D of isatuximab and cemiplimab in combination during Phase 1 were included in the efficacy analysis together with participants of the same indication in Phase 2 Stage 1. Data from cHL (Cohorts A1 and A2), DLBCL (Cohort B), and PTCL (Cohort C) cohorts in Phase 2 were analyzed and reported separately by cohort.

- Analysis of primary efficacy endpoints:
  - For cHL anti-PD-1/PD-L1 naïve Cohort A1: CR rate during the isatuximab + cemiplimab period was summarized with descriptive statistics. A 90% two-sided confidence interval (CI) were computed using the Clopper-Pearson method. The CR was defined as the proportion of participants who had a CR as a BOR during the isatuximab + cemiplimab therapy period using the Lugano response criteria 2014.
  - For cHL anti-PD-1/PD-L1 progressor Cohort A2, DLBCL Cohort B, and PTCL Cohort C: ORR during the isatuximab + cemiplimab period was summarized with descriptive statistics. A 90% two-sided CI was computed using the Clopper-Pearson method. The response rate was defined as the proportion of participants with CR or PR as the BOR during the isatuximab + cemiplimab therapy period using the Lugano response criteria 2014.
- Analysis of secondary endpoints: For each cohort, separate analyses of the following endpoints were to be performed for all participants during the isatuximab + cemiplimab period for all 4 cohorts, for participants in anti-PD-1/PD-L1 naïve Cohort A1 and anti-PD-1/PD-L1 progressor Cohort A2 including the data from both isatuximab + cemiplimab and isatuximab + cemiplimab + radiotherapy periods, and for participants in Cohorts A1 and A2 who received isatuximab + cemiplimab + radiotherapy.
  - Tumor burden change: the best percent-change from baseline in tumor burden for all target lesions was summarized and presented graphically.
  - Duration of response and PFS were summarized using the Kaplan-Meier method.
  - Disease control rate was summarized with descriptive statistics.

Analysis of safety endpoints

Number (%) of participants experiencing treatment-emergent adverse events (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 (all grades and Grade ≥3), serious TEAEs, serious treatment-related TEAEs, TEAEs leading to definitive/isatuximab/cemiplimab discontinuation, and adverse events of special interest (AESIs; all grades and Grade ≥3).

All the laboratory abnormalities were graded according to NCI CTCAE version 5.0, when applicable. The number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period were summarized for the all-treated population.

Summary Results:

Study ACT15320 was early terminated after the performance of the interim analysis for the 4 cohorts (cHL anti-PD-1/PD-L1 naïve [A1], cHL anti PD 1/PD-L1 progressor [A2], DLBCL anti-PD-1/PD-L1 naïve [B], and PTCL anti-PD-1/PD-L1 naïve [C]).

Demographic and other baseline characteristics:

The median age of participants was 36.0 years for the cHL anti-PD-1/PD-L1 naïve Cohort A1, 33.0 years for the cHL anti-PD-1/PD-L1 progressor Cohort A2, 64.0 years for the DLBCL Cohort B, and 69.0 years for the PTCL Cohort C. Most participants in Cohorts A1, A2, B, and C had an ECOG PS of 0 or 1.

Exposure:

In cHL anti-PD-1/PD-L1 naïve Cohort A1 (18 participants), the median number of cycles started by participants was 10, and the median duration of exposure was 37.3 weeks. For exposure to isatuximab, the median number of cycles started was 10, with a median duration of exposure of 37.1 weeks. The median cumulative dose was 180.09 mg/kg, with a median relative dose intensity of 96.59%. Thirteen participants (72.2%) had at least 1 cycle delayed.

In cHL anti-PD-1/PD-L1 progressor Cohort A2 (12 participants), the median number of cycles started by participants was 14.5, and the median duration of exposure was 51.1 weeks. For exposure to isatuximab, the median number of cycles started was 14.5, with a median duration of exposure of 51.0 weeks. The median cumulative dose was 220.20 mg/kg, with a median relative dose intensity of 98.29%. Eight participants (66.7%) had at least 1 cycle delayed.

In DLBCL Cohort B (17 participants), the median number of cycles started by participants was 1.0, and the median duration of exposure was 4.0 weeks. For exposure to isatuximab, the median number of cycles started was 1.0, with a median duration of exposure of 3.9 weeks. The median cumulative dose was 40.00 mg/kg, with a median relative dose intensity of 105.00%. One participant (5.9%) had at least 1 cycle delayed.

In PTCL Cohort C (11 participants), the median number of cycles started by participants was 1.0, and the median duration of exposure was 4.1 weeks. For exposure to isatuximab, the median number of cycles started was 2.0, with a median duration of exposure of 6.9 weeks. The median cumulative dose was 55.40 mg/kg, with a median relative dose intensity of 101.13%. Two participants (18.2%) had at least 1 cycle delayed.

Efficacy: Primary endpoint of response rate

In cHL anti-PD-1/PD-L1 naïve Cohort A1, of 18 participants the ORR was 55.6% (10 participants; 90% CI, 34.1-75.6). Five participants (27.8%) achieved complete metabolic response (CMR)/CR, 5 participants (27.8%) achieved partial metabolic response (PMR)/PR, 1 participant (5.6%) had no metabolic response (NMR)/SD, and 7 participants (38.9%) had progressive metabolic disease (PMD)/PD.

In cHL anti-PD-1/PD-L1 progressor Cohort A2, of 12 participants the ORR was 33.3% (4 participants; 90% CI, 12.3-60.9). Two participants (16.7%) achieved CMR/CR, 2 participants (16.7%) achieved PMR/PR, 3 participants (25.0%) had NMR/SD, and 5 participants (41.7%) had PMD/PD.

In DLBCL Cohort B, of 17 participants the ORR was 5.9% (1 participant; 90% CI, 0.3-25). This 1 participant (5.9%) achieved CMR/CR and no participants achieved PMR/PR, 6 participants (35.3%) had PMD/PD, and 10 participants (58.8%) were not evaluable.

In PTCL Cohort C, of 11 participants the ORR was 9.1% (1 participant; 90% CI 0.5-36.4). This 1 participant achieved CMR/CR and no participants achieved PMR/PR, 1 participant (9.1%) had NMR/SD, 4 participants (36.4%) had PMD/PD, and 5 participants (45.5%) were not evaluable.

Safety results:

Overall, of the 18 participants in cHL anti-PD-1/PD-L1 naïve Cohort A1, 16 (88.9%) participants experienced any TEAE, with only 1 (5.6%) participant experiencing a Grade ⩾3 TEAE. There were no Grade 5 TEAEs. Three participants (16.7%) experienced at least 1 serious TEAE, of which 1 participant experienced 1 serious TEAE that was considered treatment-related. There were 9 participants (50.0%) who experienced related TEAEs. No participants experienced a TEAE leading to premature discontinuation of the study drug. One participant (5.6%) experienced a TEAE leading to definitive discontinuation of the study drug. Seven participants (38.9%) experienced an AESI; all of these were events of infusion reaction.

Overall, of the 12 participants in cHL anti-PD-1/PD-L1 progressor Cohort A2, all participants experienced any TEAE, with only 2 (16.7%) participants experiencing a Grade ⩾3 TEAE. There were no Grade 5 TEAEs. Two participants (16.7%) experienced at least 1 serious TEAE, of which 1 participant experienced 1 serious TEAE that was considered treatment related. There were 11 participants (91.7%) who experienced related TEAEs. No participants experienced a TEAE leading to premature or definitive discontinuation of the study drug. Eight participants (66.7%) experienced an AESI; all of these were events of infusion reaction. There were, however, no Grade ⩾3 infusion reactions or AESIs.

Overall, of the 17 participants in DLBCL Cohort B, all participants experienced any TEAE, with 11 (64.7%) participants experiencing a Grade ⩾3 TEAE. There were 4 participants (23.5%) with Grade 5 TEAEs. Ten participants (58.8%) experienced at least 1 serious TEAE, of which 2 participants experienced 1 serious TEAE each that was considered treatment related. There were 9 participants (52.9%) who experienced related TEAEs. No participants experienced a TEAE leading to premature discontinuation of the study drug. Two participants (11.8%) experienced a TEAE leading to definitive discontinuation of the study drug. Seven participants (41.2%) experienced an AESI; all of these were events of infusion reaction. There were, however, no Grade ⩾3 infusion reactions or AESIs.

Overall, of the 11 participants in PTCL Cohort C, all participants experienced any TEAE, with 9 (81.8%) participants experiencing a Grade ⩾3 TEAE. There were 2 participants (18.2%) with Grade 5 TEAEs. Seven participants (63.6%) experienced at least 1 serious TEAE, of which 3 participants experienced at least 1 serious TEAE each that was considered treatment related. There were 9 participants (81.8%) who experienced related TEAEs. No participants experienced a TEAE leading to premature discontinuation of the study drug. Four participants (36.4%) experienced a TEAE leading to definitive discontinuation of the study drug. Seven participants (63.6%) experienced an AESI; all of these were events of infusion reaction, 1 participant (9.1%) experienced an AESI which was Grade ⩾3.

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