Sponsor: Sanofi **Drug substance(s):** SAR444245 - pegenzileukin	**Study Identifiers:** IND: 153864 EudraCT/EU trial number: 2020-005331-78 NCT: NCT04914897 WHO: U1111-1254-0107 **Study code:** ACT16849

Title of the study:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with lung cancer or pleural mesothelioma

Study center(s):

This study was conducted at 31 centers that enrolled participants in 11 countries (USA, Argentina, Chile, France, Italy, Poland, Spain, Japan, South Korea, Australia, and Taiwan).

Study period:

Study initiation date: 23 September 2021 (signed informed consent)

Study completion date: 17 October 2024 (last participant last visit)

Study Status: Terminated (Early discontinuation based on strategic sponsor decision not driven by any safety concerns.)

Phase of development: Phase 2

Objectives:

Primary

· To determine the antitumor activity of SAR444245 in combination with other anticancer therapies.

Secondary

·To confirm the dose and to assess the safety profile of SAR444245 when combined with other anticancer therapies.

·To assess other indicators of antitumor activity.

• To assess the plasma concentrations of SAR444245 when given in combination with pembrolizumab.

• To assess the immunogenicity of SAR444245.

Methodology:

This was a Phase 2, multi-cohort, uncontrolled, non-randomized, open-label, multicenter study assessing the antitumor activity and safety of SAR444245-based therapies in participants with NSCLC or mesothelioma. Six cohorts assessing SAR444245 in combination with pembrolizumab with or without chemotherapy were initially planned. An overview of the study intervention to be administered and disease indication being treated for each cohort is provided in Table 1.

Table 1 - Overview of study cohorts

Cohort	Study intervention	Disease
A1	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS ≥50%
A2	SAR444245 + pembrolizumab as 1L therapy	NSCLC, PD-L1 TPS 1%-49%
A3	SAR444245 + pembrolizumab + pemetrexed + carboplatin/cisplatin as 1L therapy	Non-squamous NSCLC
B1	SAR444245 + pembrolizumab as 2/3L therapy	NSCLC
B2	SAR444245 + pembrolizumab + nab-paclitaxel as 2/3L therapy	NSCLC
C1	SAR444245 + pembrolizumab as 2/3L therapy	Mesothelioma

Abbreviations: 1L = First-line ; 2/3L = Second- or third-line ; NSCLC = Non-small cell lung cancer; PD-L1 = Programmed cell death-ligand 1; TPS = Tumor proportion score.

The study was to consist of a safety run-in and core phase for all 6 cohorts, and an expansion phase for Cohorts B1 and/or B2.

The Sponsor decided to terminate the study early for non-safety reasons as of 21 October 2022. Following preliminary assessments performed across all SAR444245 studies in the Phase 1/2 program, observed antitumor activity at the current dose and schedule of Q3W in combination with pembrolizumab was lower than projected. The safety profile of SAR444245 in combination with pembrolizumab was manageable, with no actions needed for safety reasons.

Number of study participants:

Approximately 40 participants were to be enrolled and treated at the confirmed safe dose per cohort in the core phase. Of the 6 treatment cohorts planned in the study, 4 were initiated prior to the Sponsor's decision to terminate the study.

The actual number of participants analyzed per analysis population is shown for Cohorts A1 and A2 in Table 2 and for Cohorts B1 and C1 in Table 3.

Table 2 - Analysis populations - Cohorts A1 and A2

n (%)	Cohort A1 SAR444245 24 ug/kg + pembro (N=17)	Cohort A2 SAR444245 24 ug/kg + pembro (N=20)	All (N=37)
Enrolled population	17	20	37
Exposed population	17 (100)	20 (100)	37 (100)
Population without trial impact (disruption) due to COVID-19	17 (100)	20 (100)	37 (100)
Efficacy population	17 (100)	20 (100)	37 (100)
DLT-evaluable population	2 (11.8)	0	2 (5.4)
PDy population	17 (100)	20 (100)	37 (100)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 28SEP2023

PGM=PRODOPS/SAR444245/ACT16849/CSR/REPORT/PGM/dis_ana_pop_a_t.sas
OUT=REPORT/OUTPUT/dis_ana_pop_a1a2_a_t_i.rtf (23JAN2024 11:04)

Table 3 - Analysis populations - Cohorts B1 and C1

n (%)	Cohort B1 SAR444245 24 ug/kg + pembro (N=40)	Cohort C1 SAR444245 24 ug/kg + pembro (N=29)
Enrolled population	40	29
Exposed population	40 (100)	29 (100)
Population without trial impact (disruption) due to COVID-19	40 (100)	29 (100)
Efficacy population	40 (100)	29 (100)
DLT-evaluable population	1 (2.5)	4 (13.8)
PDy population	37 (92.5)	27 (93.1)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 28SEP2023

PGM=PRODOPS/SAR444245/ACT16849/CSR/REPORT/PGM/dis_ana_pop_a_t.sas
OUT=REPORT/OUTPUT/dis_ana_pop_b1c1_a_t_i.rtf (23JAN2024 11:04)

Diagnosis and criteria for inclusion:

For participants in Cohorts A1 and A2 - Histologically or cytologically confirmed diagnosis of Stage IV NSCLC, and at least 1 measurable lesion per RECIST 1.1 criteria. PD-L1 expression TPS ≥50% for participants in Cohort A1 and TPS 1%-49% for participants in Cohort A2 as determined at local laboratory. No prior systemic therapy for advanced/metastatic NSCLC.

For participants in Cohort B1 - Histologically or cytologically confirmed diagnosis of Stage IV NSCLC, and at least 1 measurable lesion per RECIST 1.1 criteria. Patients with metastatic NSCLC should have progressed after having received prior benefit from an anti-PD1/PD-L1 containing regime given concurrently or sequentially with a platinum-based chemotherapy.

For participants in Cohort C1 - Histologically confirmed unresectable malignant pleural mesothelioma and at least 1 measurable lesion per modified RECIST criteria for mesothelioma. At least 1 but no more than 2 prior systemic treatments for advanced mesothelioma that included a pemetrexed-based regimen in combination with platinum agent.

Study products

Investigational medicinal product(s):

SAR444245:

Dose regimen: 24 µg/kg once every 3 weeks (Q3W)

Route of administration: intravenous (IV) infusion

Pembrolizumab

Dose regimen: 200 mg Q3W

Route of administration: IV infusion

Non-investigational medicinal products

Premedication for SAR444245:

All participants received the following premedication to prevent or reduce the acute effect of infusion related reactions (IRR) or flu-like symptoms, preferably 30 to 60 minutes prior to SAR444245 infusion for the first 4 cycles:

・Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO), and then optionally thereafter as needed.

・Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

SAR444245 premedication may have been optional after 4 cycles.

Duration of study intervention:

Duration of treatment: the cycle duration was 21 days.

Duration of observation:

・ A Screening period: up to 28 days.

・ A Treatment Period: up to 35 cycles.

• An End of Treatment and Follow-up period: End of Treatment Visit to occur 30 days from last IMP administration or prior to initiation of further therapy followed by an Observation period depending on the status of the participant:

- Participants who discontinued study treatment without PD or who completed 35 cycles of treatment without PD were to be followed every 3 months from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever occurred first.

- Participants who discontinued study treatment with PD were to be followed in the Follow-Up Visit 1 occurring 3 months from last IMP administration.

• Survival Phone Call Follow-Up Period: until death, participant request to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival Follow-up at the discretion of the Sponsor.

Cohorts A1 and A2

Of a total of 37 participants in Cohort A1 and A2, 3 participants (8.1%) completed the study treatment period and 6 participants (16.2%) were still receiving the study intervention as of the partial database lock (28 September 2023). At study completion, 6/37 participants had completed the study treatment period, while the remining 31/37 participants had permanent full intervention discontinuation, most commonly due to disease progression (19 participants [51.4%]. Followed by AE, not related to coronavirus-19 (COVID-19) (7 participants [18.9%].

Out of 6 participants (5 in Cohort A1 and 1 in Cohort A2) who were still on study intervention as of the partial database lock (28 September 2023), 3 participants completed the study treatment period. Of the 3 remaining participants, 1 participant each in Cohort A1 and Cohort A2 had permanent full intervention discontinuation due to progressive disease, and one participant in Cohort A1 withdrew from the study. As of final database lock, no participants were on treatment.

Cohort B1

Of a total of 40 exposed participants in Cohort B1, 1 participant (2.5%) completed the study intervention period and 39 participants (97.5%) did not complete study intervention period. The most common reason for permanent full discontinuation of study intervention in Cohort B1 was disease progression (30 participants [75.0%]), followed by AE, not related to COVID-19 (7 participants [17.5%]). As of final database lock, no participants were on treatment.

Cohort C1

Of a total of 29 exposed participants in Cohort C1, 28 participants (96.6%) did not complete the study intervention and 1 participant (3.4%) was still receiving the study intervention as of the partial database lock (28 September 2023). At study completion, 1 participant who was still receiving the study intervention at the date of partial database lock, had permanent full intervention discontinuation due to progressive disease. Disease progression was the most common reason of permanent full intervention discontinuation in Cohort C1 (21 participants [72.4%]). As of final database lock, no participants were on treatment.

Criteria for evaluation:

Primary

•Objective response rate (ORR), defined as the proportion of participants who have a confirmed CR or partial response (PR), determined by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for Cohort A1, Cohort A2, Cohort A3, Cohort B1 and Cohort B2; per modified RECIST (mRECIST) for Cohort C1.

Secondary

•Incidence of TEAEs, DLTs, SAEs, laboratory abnormalities according to NCI CTCAE V5.0 and ASTCT consensus gradings.

•Time to response defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma).

•Duration of response (DOR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until progressive disease (PD) determined by investigator per RECIST 1.1 (for NSCLC) or mRECIST (for mesothelioma) or death from any cause, whichever occurs first.

•Clinical benefit rate (CBR) including CR or PR at any time plus stable disease (SD) of at least

6 months (determined by investigator per RECIST 1.1 [for NSCLC] or mRECIST [for mesothelioma]).

•Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by investigator as per RECIST 1.1 for NSCLC) or mRECIST (for mesothelioma) or death due to any cause, whichever occurs first.

•Plasma concentrations of SAR444245.

- Incidence of anti-drug antibodies (ADAs) against SAR444245.

Statistical methods:

This study was not intended to explicitly test a hypothesis, and calculations of power and Type I error were not considered in the study design. No formal testing procedure was planned.

Analysis populations

Exposed: All participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or pembrolizumab).

Efficacy: All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.

DLT-evaluable: All exposed participants in the safety run-in who have been observed for at least 21 days. Any participants who experienced a DLT during DLT observation period were also DLT-evaluable.

All efficacy analyses were to be performed on the efficacy population and analyzed by cohort. The objective response rate (ORR) was derived using the local radiologist's/Investigator's assessment for all cohorts.

The primary endpoint was the best overall response (BOR) observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anticancer therapy, whichever occurred first. The BOR was summarized with descriptive statistics. The ORR was summarized with descriptive statistics and the corresponding two-sided 90% CIs calculated from Clopper Pearson exact method. All objective responses had to be confirmed by a subsequent assessment performed at least 4 weeks apart from the initial response observation.

All safety analyses were performed on the exposed population and were descriptive in nature.

All AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 26.0 and graded according to National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE version 5.0). Cytokine release syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) were graded using the American Society for Transplantation and Cellular Therapy Consensus grading.

The primary AE analyses was on treatment-emergent adverse events (TEAEs), ie AEs that occurred during the TEAE period, defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.

Summary Results:

Demographic and other baseline characteristics:

Across 1L NSCLC Cohorts A1 and A2, participants had a median age of 68.0 years, were predominantly male (62.2%), White (91.9%) and most had an ECOG PS score at baseline of 0 (23 [62.2%]).

In 2/3L NCSLC Cohort B1, participants had a median age of 65.0 years, were predominantly male (67.5%) and White (80.0%), and most had an ECOG PS score at baseline of 1 (52.5%) or 0 (47.5%).

In mesothelioma Cohort C1, participants had a median age of 71.0 years, were predominantly male (72.4%), and most were of unreported race (51.7%) or White (41.4%). ECOG PS score at baseline was 1 in 58.6% of participants and 0 in 41.4% of participants.

Exposure:

Cohorts A1 and A2: Across participants in Cohorts A1 and A2 (N=37 exposed participants), the median duration of exposure to investigational medicinal product (IMP) (pegenzileukin and pembrolizumab) was 5.1 months (range:1 to 27 months). Approximately half of participants were treated for at least 9 cycles (18 out of 37 participants [48.6%]). The median total cumulative dose of pegenzileukin was 120.1 µg/kg (range: 24 to 805 µg/kg). The median relative dose intensity of pegenzileukin was 97.5%. The median total cumulative dose of pembrolizumab was 1200.0 mg (range: 200 to 7000 mg) and relative dose intensity was 97.7% (80% to 102%).

Cohort B1: Across participants in Cohort B1 (N=40 exposed participants), the median duration of exposure to IMP (pegenzileukin and pembrolizumab) was 2.1 months (range: 1 month to 14 months), with 7 participants (17.5%) completing ≥9 cycles. The median total cumulative dose of pegenzileukin was 71.2 µg/mg (range: 23 to 432 µg/mg) with median relative dose intensity of 99.9% (range: 73% to 103%). The median total cumulative dose of pembrolizumab was 600 mg (range: 200 to 4200 mg) with median relative dose intensity of 100% (range: 81% to 103%).

Cohort C1: Across participants in Cohort C1 (N=29 exposed participants), the median duration of exposure to IMP (pegenzileukin and pembrolizumab) was 2.8 months (range: 1 month to 24 months), with 3 participants (10.3%) completing ≥16 cycles and 1 participant (3.4%) completed ≥31 cycles. The median total cumulative dose of pegenzileukin was 74.0 µg/mg (range: 24 to 737 µg/mg) with median relative dose intensity of 98.7% (range: 80% to 104%). The median total cumulative dose of pembrolizumab was 800 mg (range: 200 to 6400 mg) with median relative dose intensity of 100% (range: 88% to 102%).

Anti-tumor activity:

In 1L NSCLC Cohort A1, 7 out of 17 participants (41.2%) were responders: 1 (5.9%) had a BOR of CR and 6 (35.3%) had a BOR of PR. Stable disease was the BOR in 5 of 17 participants (29.4%). The ORR was 41.2% (90% CI: 21.2% to 63.6%).

In 1L NSCLC Cohort A2, 3 out of 20 participants (15.0%) were responders: all 3 participants (15.0%) had a BOR of PR. The ORR was 15.0% (90% CI: 4.2% to 34.4%).

In 2/3L NSCLC Cohort B1, 1 out of 40 participants (2.5%) had a BOR of PR. The ORR was 2.5% (90% CI: 0.1% to 11.3%).

In mesothelioma Cohort C1, 1 out of 29 participants (3.4%) had a BOR of PR. The ORR was 3.4% (90% CI: 0.2% to 15.3%).

Safety results:

The cumulative data indicates that treatment with pegenzileukin in combination with pembrolizumab generally remains manageable with standard therapies.

Cohorts A1 and A2:

Of 37 exposed participants in Cohorts A1 and A2, 36 participants (97.3%) had treatment emergent adverse events (TEAEs), 17 participants (45.9%) had treatment emergent serious adverse events (SAEs), 21 participants (56.8%) had Grade ≥3 TEAEs, 8 participants (21.6%) had TEAEs leading to permanent full intervention discontinuation, 2 participants (5.4%) had TEAEs leading to permanent partial discontinuation of pegenzileukin, and 3 participants (8.1%) had Grade 5 TEAEs. Serious treatment-related TEAEs were reported in 8 (21.6%) participants and Grade ≥3 treatment related TEAEs were reported in 10 (27%) participants.

Infusion related reaction (IRR) (17 participants [45.9%]) and cytokine release syndrome (CRS) (5 participants [13.5%]) were among the most frequently reported (≥10%) all grade TEAEs. No events of anaphylaxis have been reported.

The most frequently reported (>1 participant) Grade ≥3 TEAEs were CRS and hypertransaminasemia (2 participants [5.4%] each). One participant (2.7%) in Cohort A1 was reported with Grade ≥3 event of infusion-related reaction.

The most frequently reported (in ≥2 participants) SAEs were CRS (3 participants [8.1%]) and IRRs (2 participants [5.4%]). The most frequently reported (in ≥2 participants) Grade ≥3 treatment emergent SAE was CRS (2 participants [5.4%]).

Grade ≥3 TEAEs leading to permanent full intervention discontinuation were reported in 7 participants (18.9%). Most frequently reported TEAE was hypertransaminasaemia (2 participants [5.4%]). All TEAEs (except the event of pneumonia in Cohort A1) leading to permanent full intervention discontinuation were Grade ≥3 TEAEs. Two participants (5.4%) had TEAEs leading to permanent partial discontinuation of pegenzileukin (1 participant in Cohort A1 had immune-mediated enterocolitis and 1 participant in Cohort A2 had CRS). Of these, only the event of immune-mediated enterocolitis was Grade ≥3.

Nineteen participants (51.4%) had treatment-emergent adverse event of special interests (AESIs), with Grade ≥3 AESIs in 7 participants (18.9%). The most frequently reported (in ≥2 participants) treatment emergent AESIs were IRR (12 participants [32.4%]), COVID 19 (5 participants [13.5%]), and CRS (4 participants [10.8%]). All Grade ≥3 treatment emergent AESIs (except CRS in 2 participants [5.4%]) were reported in 1 participant (2.7%).

Twenty three of 37 participants (62.2%) had at least one TEAE in the infusion reaction (IR) category. Infusion related reaction was reported in 17 participants (45.9%), CRS was reported in 5 participants (13.5%), and flu-like symptoms were reported in 3 participants (8.1%). No event of anaphylaxis was reported. The only change since the cut-off date of the primary CSR was that one participant's worst grade changed from Grade 1 to Grade 2. Most participants had ≥2 episodes of TEAEs within the IR category (18 participants [48.6%]), with up to 10 participants (27%) experiencing ≥5 episodes. A total of 130 episodes of adverse events (AEs) in the IR category occurred in the study and most occurred on the day of infusion (108 episodes [83.1%]). A majority of the episodes of AEs in the IR category lasted from 2 to 3 days (73 participants [56.2%]).

Since the cut-off date of the primary CSR, there were no other changes observed for the safety data for pegenzileukin in combination with pembrolizumab across Cohort A1 and Cohort A2, except 2 additional participants (1 participant each in Cohort A1 and Cohort A2) had Grade ≥3 TEAEs (pleurisy and diarrhea, respectively). The reported event of Grade ≥3 TEAEs diarrhea was also a treatment-related. Two additional participants (1 participant each in Cohort A1 and Cohort A2) had treatment emergent SAEs (1 participant in Cohort A1 had infection and pleurisy and 1 participant in Cohort A2 had dysarthria and hemiparathesia) since the primary CSR cut off. One additional participant in Cohort A1 had a TEAE (pneumonia) leading to permanent full intervention discontinuation, and one additional Grade ≥3 treatment-emergent AESI (hypertransaminasaemia) was reported in Cohort A2 since the primary CSR cut-off date.

Cohort B1:

All 40 exposed participants in Cohort B1 had TEAEs. Twenty-one participants (52.5%) were reported with treatment emergent SAEs. Thirteen participants (32.5%) were reported with ≥Grade 3 treatment-related TEAEs and 15 participants (37.5%) were reported with serious treatment-related TEAEs. Three participants (7.5%) were reported with Grade 5 TEAE. Eight participants (20.0%) had TEAEs leading to full intervention discontinuation and 2 participants (5.0%) had TEAEs leading to permanent partial discontinuation of pegenzileukin.

Infusion related reaction (20 participants [50.0%]) and CRS (9 participants [22.5%]) were among the most frequently reported (≥ 10%) all-grade-TEAEs.

Grade ≥3 TEAEs were reported in 20 of 40 exposed participants (50.0%), with the most frequently (>1 participant) reported events being CRS (4 participants [10.0%]), and dyspnea and pleural effusion (2 participants [5.0%] each). There were no Grade ≥3 events of IRR.

Twenty one of 40 exposed participants (52.5%) had treatment-emergent SAEs with 17 participants (42.5%) with Grade ≥3 SAEs. The most frequently reported (in ≥2 participants) treatment-emergent SAEs were CRS (7 participants [17.5%]), and dyspnea and

IRR (2 participants [5.0%] each). The most frequently reported (in ≥2 participants) Grade ≥3 treatment-emergent SAE was CRS (4 participants [10.0%]).

Eight of 40 exposed participants (20.0%) had TEAEs leading to permanent full intervention discontinuation with Grade ≥3 TEAEs leading to permanent full intervention discontinuation were reported in 7 participants (17.5%). All TEAEs (except the event of infusion related reaction) leading to permanent full intervention discontinuation were Grade ≥3 TEAEs. Two participants (5.0%) had TEAEs leading to permanent partial discontinuation of pegenzileukin (1 participant each had CRS and hepatomegaly). Only the event of CRS was Grade ≥3. No participant had a TEAE leading to permanent partial discontinuation of pembrolizumab.

Twenty-four participants (60.0%) in Cohort B1 had treatment-emergent AESIs. The most frequently reported (in ≥2 participants) treatment emergent AESIs were IRR (14 participants [35.0%]), CRS (7 participants [17.5%]), and COVID-19 (7 participants [17.5%]). Seven participants (17.5%) were reported with Grade ≥3 treatment emergent AESIs. All Grade ≥3 treatment-emergent AESIs (except CRS in 4 participants [10%]) were reported in 1 participant.

Twenty eight participants (70.0%) had at least one TEAE in the IR category. Infusion related reaction was reported in 20 participants (70.0%), CRS was reported in 9 participants (22.5%), and flu-like symptoms were reported in 2 participants (5.0%). No events of anaphylaxis were reported. TEAEs in the IR category by worst grade were predominantly Grade 2 (16 participants [40.0%]) and Grade 1 (8 participants [20.0%]). Most of the participants (12 participants [30.0%]) had ≥2 episodes of TEAEs within IR category with up to 3 participants (7.5%) experiencing ≥5 episodes. A total of 64 episodes of AEs in the IR category occurred in the study and most TEAEs in the IR category occurred on the day of infusion (49 episodes [76.6]) and were resolved within 2 to 3 days (37 participants [57.8%]).

Cohort C1:

All 29 participants (100%) in Cohort C1 had TEAEs of any grade which were also treatment related. Thirteen participants (44.8%) were reported with treatment emergent SAE. Eleven participants (37.9%) were reported with Grade ≥3 treatment-related TEAEs and 6 participants (20.7%) were reported with serious treatment-related TEAEs. Seven participants (24.1%) had TEAEs leading to permanent full intervention discontinuation and 2 participants (6.9%) had TEAEs leading to permanent partial discontinuation of pegenzileukin.

There were no additional participants in Cohort C1 who experienced treatment-emergent SAEs, serious treatment-related TEAEs, Grade ≥3 TEAEs, Grade ≥3 treatment-related TEAEs, TEAEs leading to permanent full and partial intervention discontinuation, and Grade 5 TEAEs since the primary CSR cut-off date.

Infusion related reaction (22 participants [75.9%]) and CRS (6 participants [20.7%]) were reported among the most frequently reported (≥10%) all-grade-TEAEs. No events of anaphylaxis or flu-like symptoms were reported.

The most frequently (>1 participant) reported Grade ≥3 TEAEs were asthenia (5 participants [17.2%]), hypertension (4 participants [13.8%]), infusion related reaction and pleural effusion (3 participants [10.3%] each), and malignant ascites (2 participants [6.9%]). One participant (3.4%) was reported with Grade ≥3 CRS.

Thirteen of twenty-nine exposed participants (44.8%) had treatment-emergent SAEs with 12 participants (41.4%) with Grade ≥3 SAEs. The most frequently reported (in ≥2 participants) treatment-emergent SAEs were CRS and pleural effusion (3 participants [10.3%] each), and ischemic stroke and malignant ascites (2 participants [6.9%] each). The most frequently reported (in ≥2 participants) Grade ≥3 treatment emergent SAEs were pleural effusion (3 participants [10.3%]) and malignant ascites (2 participants [6.9%]). None of the participants had treatment-emergent SAEs since the primary CSR cut-off.

Seven of twenty nine exposed participants (24.1%) had TEAEs leading to permanent full intervention discontinuation with Grade ≥ 3 TEAEs leading to permanent full intervention discontinuation were reported in 6 participants (20.7%). All TEAEs (except herpes virus infection) leading to permanent full intervention discontinuation were Grade ≥3 TEAEs. Two participants (6.9%) in Cohort C1 had TEAEs leading to permanent partial discontinuation of pegenzileukin (1 participant each had CRS and infusion related reaction). Only the event of CRS was Grade ≥3.

Twenty-one participants (72.4%) had treatment-emergent AESIs. The most frequently reported (in ≥2 participants) treatment emergent AESIs were infusion related reaction (15 participants [51.7%]), and CRS (6 participants [20.7%]). Seven participants (24.1%) were reported with Grade ≥3 treatment-emergent AESIs. All Grade ≥3 treatment-emergent AESIs (except infusion related reaction in 3 participants [10.3%]) were reported in 1 participant.

Twenty seven participants (93.1%) had at least one TEAE in the IR category. Infusion related reaction was reported in 22 participants [75.9%]) and CRS was reported in 6 participants [20.7%]. No events of anaphylaxis reactions or flu-like symptoms were reported. The TEAEs in the IR category by worst grade were predominantly Grade 2 (16 participants [55.2%]) and Grade 1 (7 participants [24.1%]). A total of 87 episodes of AEs in the IR category occurred in the study and most TEAEs in the IR category occurred on the day of infusion (77 episodes [88.5%]) and were resolved within 2 to 3 days (46 participants [52.9%]).

The nature, frequency, and severity of TEAEs showed no apparent disproportionality across cohorts. Across all 4 cohorts, the most frequently reported TEAE was infusion related reaction (IRR), reported in 45.9% of participants in Cohorts A1 and A2 overall, in 50.0% of participants in Cohort B1, and in 75.9% of participants in Cohort C1. The other most frequently reported TEAEs by PT (⩾10% of participants in all cohorts) included asthenia, nausea, CRS, decreased appetite, and vomiting.

The most frequently reported Grade ⩾3 event was CRS (reported in 2 participants in Cohort A2, 4 participants in Cohort B1, 1 participant in Cohort C1). Across all cohorts, 4 participants had Grade ⩾3 events of infusion related reaction (1 participant in Cohort A1 and 3 participants in Cohort C1).

Across all cohorts, the most frequently reported TEAEs related to any IMP (⩾10% of participants in all cohorts) were IRR, asthenia, CRS, fatigue, and nausea.

The most frequently reported AESIs were Grade ⩾2 IRR and Grade ⩾2 CRS. One event of capillary leak syndrome was reported in the study. It occurred in a participant in Cohort C1 and was of Grade ⩾3.

No ICANS was reported in the study. No events of anaphylaxis have been reported. There were no cases of Hy's law across all cohorts.

Across all cohorts 5 participants had a fatal TEAE in context other than disease progression: 2 participants had acute respiratory failure (1 each in Cohort A2 and B1), 1 participant had spinal cord edema (Cohort A1), 1 participant had malignant ascites (Cohort C1), and 1 participant had seizure (Cohort B1). Most deaths during the TE period or post-treatment period were due to progressive disease.

Treatment-emergent SAEs were reported in 40.5% to 52.5% of participants across the cohorts. The most frequently reported treatment-emergent SAE was CRS (3 participants [8.1%] overall in Cohorts A1 and A2, 7 participants [17.5%] in Cohort B1, and 3 participants [10.3%] in Cohort C1).

TEAEs leading to permanent full intervention discontinuation were reported in 18.9% to 24.1% of participants across the cohorts. Almost all TEAEs leading to permanent full intervention discontinuation were Grade ⩾3 TEAEs. Across the cohorts, 2 participants had a TEAE of CRS leading to permanent full intervention discontinuation.

Particular attention was given to analyzing data on infusion reactions which were identified using coding lists for CRS, IRR, flu-like symptoms, and other TEAEs considered by the Investigator as related to any IMP and that happened soon after the start of an infusion. The most frequently reported TEAEs in the infusion reaction category were IRR and CRS. TEAEs in the infusion reaction category by worst grade were predominantly Grade 2 and Grade 1. The most frequently reported infusion reaction symptom in each cohort was pyrexia, mostly low grade in intensity. Most TEAEs in the infusion reaction category occurred on the day of infusion and resolved within 3 days.

One DLT of Grade ⩾3 hypersensitivity was reported in a participant in Cohort B1.

Across all cohorts, the most frequently reported hematological abnormalities (>70% of participants) during the TE period were anemia and lymphocyte count decreased. Anemia was primarily low grade. Lymphocyte count decreased was predominantly Grade 4 in intensity and in most participants was not present at baseline.

While some PCSAs in laboratory parameters were observed during the TE period, all included plausible alternative etiologies, and none required further actions for safety reasons.

Pharmacokinetic results:

Pegenzileukin median concentrations at the end of infusion (Ceoi) ranged from 152 to 590 ng/mL. Overall, pegenzileukin concentrations in plasma were in the expected range for the dose administered. No signs for interferences of co-administered drugs on pegenzileukin concentrations were observed.

Immunogenicity:

Two participants in Cohort B1 were reported as positive for treatment-emergent ADAs.

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