QU-FOR-0055625

Sponsor: Sanofi **Drug substance(s):** SAR444245 - pegenzileukin	**Study Identifiers:** IND: 156424 EudraCT/EU trial number: 2021-002181-41 NCT: NCT05104567 WHO: U1111-1251-4981 **Study code:** ACT16902

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 advanced and metastatic gastrointestinal cancer

Study center(s):

This study was conducted at 29 centers that enrolled participants in 11 countries (USA, Spain, Italy, South Korea, Belgium, France, Poland, Netherlands, China, Germany, and Chile).

Study period:

Study initiation date: 09 December 2021 (signed informed consent)

Study completion date: 09 September 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 assess the safety of SAR444245 in combination with other anticancer therapies

•To assess other indicators of antitumor activity

•To assess the pharmacokinetics of SAR444245 in combination with other anticancer therapies

•To assess active concentrations of cetuximab when given in combination with SAR444245

•To assess the immunogenicity of SAR444245

Methodology:

This was a Phase 2, multi-cohort, uncontrolled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with advanced or metastatic gastrointestinal cancer. Seven cohorts assessing SAR444245 in combination with pembrolizumab or cetuximab 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
A	SAR444245 + pembrolizumab as 2/3L therapy	ESCC, post PD-1/PD-L1,
B1	SAR444245 + pembrolizumab as 1-3L therapy	GC or Siewert Type 2 & 3 GEJ, CPS ≥1, PD-1/PD-L1 naïve
B2	SAR444245 + pembrolizumab as 1-3L therapy	GC or Siewert Type 2 & 3 GEJ, CPS <1, PD-1/PD-L1 naïve
B3	SAR444245 + pembrolizumab as 2-4L therapy	GC or Siewert Type 2 & 3 GEJ, post PD-1/PD-1
C	SAR444245 + pembrolizumab as 2/3L therapy	HCC, post PD-1/PD-L1
D1	SAR444245 + pembrolizumab as 3-6L therapy	CRC, any *RAS*, PD-1/PD-L1 naïve
D2	SAR444245 + Cetuximab as 3-6L therapy	CRC, *RAS* wide type

1-3L = first-line to third-line; 2-4L = second-line to fourth-line; 3-6L = third-line to sixth-line; 2/3L = second-line or third-line; CPS = combined positive score; CRC = colorectal carcinoma; ESCC = esophageal squamous cell carcinoma; GC = gastric cancer; GEJ = gastro-esophageal junction adenocarcinoma; HCC = hepatocellular carcinoma; PD-1 = programmed cell death 1; PD-L1 = Programmed cell death-ligand 1.

The Sponsor decided to terminate the study early for non-safety reasons on 21 October 2022. Following preliminary assessments, the observed antitumor activity at the current dose and schedule of Q3W in combination with pembrolizumab or cetuximab was lower than projected. The safety profile of SAR444245 in combination with pembrolizumab or cetuximab was generally manageable, with no actions needed for safety reasons.

Number of study participants:

In each cohort, approximately 40 participants were to be enrolled and treated. Of the 7 treatment cohorts planned in the study, all were initiated prior to the Sponsor's decision to terminate the study.

The actual number of participants analyzed per analysis population is provided in Table 2 for Cohorts B1, B2, and B3, Table 3 for Cohorts D1 and D2, and Table 4 for Cohorts A and C.

Table 2 - Analysis populations - Gastric cohorts

n (%)	Cohort B1 SAR444245 24 ug/kg + pembro (N=22)	Cohort B2 SAR444245 24 ug/kg + pembro (N=19)	Cohort B3 SAR444245 24 ug/kg + pembro (N=18)	All (N=59)
Enrolled population	22	19	18	59
Exposed population	22 (100)	19 (100)	18 (100)	59 (100)
Population without trial impact (disruption) due to COVID-19	21 (95.5)	19 (100)	18 (100)	58 (98.3)
Efficacy population	22 (100)	19 (100)	18 (100)	59 (100)
PDy population	22 (100)	19 (100)	16 (88.9)	57 (96.6)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 07OCT2023

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OUT=REPORT/OUTPUT/dis_ana_pop_gas_a_t_i.rtf (31JAN2024 8:48)

Table 3 - Analysis populations - CRC cohorts

n (%)	Cohort D1 SAR444245 24 ug/kg + pembro (N=30)	Cohort D2 SAR444245 24 ug/kg + cetux (N=24)	All (N=54)
Enrolled population	30	24	54
Exposed population	30 (100)	24 (100)	54 (100)
Population without trial impact (disruption) due to COVID-19	30 (100)	24 (100)	54 (100)
Efficacy population	30 (100)	24 (100)	54 (100)
PDy population	29 (96.7)	22 (91.7)	51 (94.4)

Percentages are calculated using the number of participants exposed as denominator

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Table 4 - Analysis populations - ESCC and HCC cohorts

n (%)	Cohort A SAR444245 24 ug/kg + pembro (N=5)	Cohort C SAR444245 24 ug/kg + pembro (N=20)
Enrolled population	5	20
Exposed population	5 (100)	20 (100)
Population without trial impact (disruption) due to COVID-19	5 (100)	20 (100)
Efficacy population	5 (100)	20 (100)
PDy population	5 (100)	19 (95.0)

Percentages are calculated using the number of participants exposed as denominator

Extraction date: 07OCT2023

PGM=PRODOPS/SAR444245/ACT16902/CSR/REPORT/PGM/dis_ana_pop_a_t.sas
OUT=REPORT/OUTPUT/dis_ana_pop_eh_a_t_i.rtf (31JAN2024 8:48)

Diagnosis and criteria for inclusion:

For participants in Cohort A - Histologically or cytologically confirmed diagnosis of esophageal cancer of the squamous cell carcinoma subtype, and at least 1 measurable lesion per RECIST 1.1 criteria. Participants must have either unknown microsatellite instability (MSI) status or if MSI status is known, participants must have non-MSI-H disease. Participants should have received at least one but no more than 2 prior lines of treatment.

For participants in Cohorts B1, B2, and B3 - Histologically or cytologically confirmed diagnosis of gastric cancer (GC) or Siewert Type 2 & 3 gastro-esophageal junction adenocarcinoma (GEJ), and at least 1 measurable lesion per RECIST 1.1 criteria. PD-L1 expression combined positive score (CPS) ≥1 for participants in Cohort B1, <1 for participants in Cohort B2, and any CPS scoring for participants in Cohort B3. Participants must have MSI status known, determined locally and must have non-MSI-H disease. Participants in Cohorts B1 and B2 should have failed or relapsed on no more than 2 prior lines of treatment, and which did not include an anti PD 1/PD-L1-based treatment. Participants in Cohort B3 should have received at least one but no more than 3 prior lines of treatment.

For participants in Cohort C - Histologically or cytologically confirmed diagnosis of hepatocellular carcinoma (HCC), or clinically by AASLD criteria in cirrhotic patients, and at least 1 measurable lesion per RECIST 1.1 criteria. Participants must have received 1 or 2 prior lines of treatment per local standard or care.

For participants in Cohorts D1 and D2 - Histologically or cytologically confirmed diagnosis of colorectal cancer, and at least 1 measurable lesion per RECIST 1.1 criteria. Participants must have MSI status known or determined locally and must have non MSI-H disease. Participants in Cohort D2 must have RAS wild-type disease. Participants should have failed or relapsed on at least 2 but no more than 5 prior regimens have contained fluoropyrimidine, oxaliplatin, irinotecan, with bevacizumab and/or cetuximab.

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

Cetuximab:

Dose regimen: An initial loading dose of 400 mg/m2 on Cycle 1 Day 1, followed by 250 mg/m2 once weekly

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, 30 to 60 minutes prior to SAR444245 infusion (no longer than 60 minutes) for the first 4 cycles:

・Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO) (or equivalent), 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:

The duration of the study for a participant included:

・ 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 ±7 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 ±7 days 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 ±7 days 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.

Criteria for evaluation:

Primary

•Objective response rate (ORR) defined as the proportion of participants who have a confirmed CR or PR determined by Investigator per RECIST 1.1

Secondary

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

•Time to response (TTR), 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

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

•Clinical benefit rate (CBR) including confirmed CR or PR at any time or SD of at least 6 months determined by Investigator per RECIST 1.1

•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 or death due to any cause, whichever occurs first

•Plasma concentrations and where applicable PK parameters of SAR444245

•Cohort D2: C_{trough} and C_{end} of infusion of cetuximab

•Incidence of ADAs against SAR444245

Statistical methods:

As the study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design and 90% CIs will be provided for primary and secondary efficacy endpoints for descriptive purposes only.

Primary endpoint:

For all cohorts, the ORR is defined as the proportion of participants who have a confirmed CR or PR as per Investigator's assessment.

The BOR is the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anti-cancer therapy, whichever occurs first.

ORR and BOR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed using the Clopper-Pearson method. All objective responses need to be confirmed by a subsequent assessment performed at least 4 weeks apart from the initial response observation.

Secondary endpoints:

The secondary endpoints include safety, efficacy (TTR, DOR, CBR, PFS per RECIST 1.1), immunogenicity, and PK.

All AEs were categorized according to NCI-CTCAE v5.0 (except for CRS and ICANS that were graded using ASTCT criteria) and classified by system organ class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

The primary focus of AE reporting 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 GC/GEJ Cohorts B1, B2, and B3, participants had a median age of 58.0 years, were predominantly male (72.9%), White (64.4%) and most had an ECOG PS score at baseline of 1 (64.4%).

In CRC Cohort D1 (SAR444245 + pembrolizumab), participants had a median age of 63.0 years, were predominantly male (63.3%). All participants were White. Most participants had an ECOG PS score at baseline of 1 (66.7%).

In CRC Cohort D2 (SAR444245 + cetuximab), participants had a median age of 62.0 years, were predominantly male (70.8%), White (75.0%), and most had an ECOG PS score at baseline of 1 (62.5%).

In ESCC Cohort A, participants had a median age of 62.0 years, 3 out of 5 (participants) were male (60.0%), White (60.0%). Two (40.0%) participants had an ECOG PS score of 1 and 3 (60.0%) had a score of 0 at baseline.

In HCC Cohort C, participants had a median age of 64.0 years, were predominantly male (70.0%), White (70.0%), and had an ECOG PS score at baseline of 0 (65.0%).

Exposure:

Across Cohorts B1, B2, and B3, 59 participants were exposed; the median duration of exposure to investigational medicinal product (IMP) (pegenzileukin and pembrolizumab) was 2.1 months and the median cumulative doses of pegenzileukin and pembrolizumab were 72.0 µg/kg and 600.0 mg, respectively.

In Cohort D1, 30 participants were exposed; the median duration of exposure to IMP (SAR444245 and pembrolizumab) was 2.1 months and the median cumulative doses of SAR444245 and pembrolizumab were 72.0 µg/kg and 600.0 mg, respectively.

In Cohort D2, 24 participants were exposed; the median duration of exposure to IMP (SAR444245 and cetuximab) was 3.8 months and the median cumulative doses of SAR444245 and cetuximab were 88.4 µg/kg and 3750.9 mg/m2, respectively.

In Cohort A, 5 participants were exposed; the median duration of exposure to IMP (SAR444245 and pembrolizumab) was 3.4 months and the median cumulative doses of SAR444245 and pembrolizumab were 96.1 µg/kg and 800.0 mg, respectively.

In Cohort C, 20 participants were exposed; the median duration of exposure to IMP (pegenzileukin and pembrolizumab) was 2.1 months and the median cumulative doses of pegenzileukin and pembrolizumab were 72.5 µg/kg and 600.0 mg, respectively.

Anti-tumor activity:

In 1-3L GC/GEJ Cohort B1, 3 out of 22 (13.6%) participants were responders and had a BOR of PR. Stable disease was the BOR in 5 of 22 (22.7%) participants. The ORR was 13.6% (3/22; 90% CI: 3.8% to 31.6%).

In 1-3L GC/GEJ Cohort B2, 1 out of 19 (5.3%) participants was responder and had a BOR of PR. Stable disease was the BOR in 4 of 19 (21.1%) participants. The ORR was 5.3% (1/19; 90% CI: 0.3% to 22.6%).

In 2-4L GC/GEJ Cohort B3, 2 out of 18 (11.1%) participants were responders and had a BOR of PR. Stable disease was the BOR in 3 of 18 (16.7%) participants. The ORR was 11.1% (2/18; 90% CI: 2.0% to 31.0%).

In 3-6L CRC Cohort D1, out of 30 participants, none of participants were responders. Stable disease was the BOR in 7 of 30 (23.3%) participants.

In 3-6L CRC Cohort D2, 2 out of 24 (8.3%) participants were responders and had a BOR of PR. Stable disease was the BOR in 8 of 24 (33.3%) participants. The ORR was 8.3% (2/24; 90% CI: 1.5% to 24.0%).

In 2/3L ESCC Cohort A, 1 out of 5 (20.0%) participants was responder and had a BOR of PR. The ORR was 20.0% (1/5; 90% CI: 1.0% to 65.7%).

In 2/3L HCC Cohort C, 1 out of 20 (5.0%) participants was responder and had a BOR of PR. The ORR was 5.0% (1/20; 90% CI: 0.3% to 21.6%).

Safety results:

Of the N=59 exposed participants in Cohorts B1, B2, and B3, all 59 (100%) participants had a treatment-emergent adverse event (TEAE) of any grade, 39 (66.1%) participants had a treatment-emergent (TE) serious adverse event (SAE), 41 (69.5%) participants had a Grade ≥3 TEAE, 8 (13.6%) participants had a TEAE leading to permanent full intervention discontinuation, and 14 (23.7%) participants had a fatal Grade 5 TEAE (a TEAE with a fatal outcome during the TE period). Treatment-related TEAEs were reported in 49 (83.1%) participants, treatment-related serious TEAEs were reported in 13 (22.0%) participants, and treatment-related Grade ⩾3 TEAEs were reported in 14 (23.7%) participants.

Of N=30 exposed participants in Cohort D1 (pegenzileukin + pembrolizumab), all 30 (100%) participants had a TEAE of any grade, 19 (63.3%) participants had a TE SAE, 14 (46.7%) participants had a Grade ⩾3 TEAE, 2 (6.7%) participants had a TEAE leading to permanent full intervention discontinuation, and 1 (3.3%) participant had a fatal Grade 5 TEAE. In Cohort D1, treatment-related TEAEs were reported in 29 (96.7%) participants, treatment related serious TEAEs were reported in 4 (13.3%) participants, and treatment related Grade ⩾3 TEAEs were reported in 7 (23.3%) participants.

Of N=24 exposed participants in Cohort D2 (pegenzileukin + cetuximab), all 24 (100%) participants had a TEAE of any grade, 11 (45.8%) participants had a TE SAE, 9 (37.5%) participants had a Grade ≥3 TEAE, no participants had a TEAE leading to permanent full intervention discontinuation, and 5 (20.8%) participants had a fatal Grade 5 TEAE. In Cohort D2, treatment-related TEAEs were reported in 24 (100%) participants, treatment related serious TEAEs were reported in 3 (12.5%) participants, and treatment related Grade ≥3 TEAE was reported in 1 (4.2%) participant.

Of the N=5 enrolled and exposed participants in Cohort A, all 5 (100%) participants had a TEAE of any grade, 2 (40.0%) participants had a TE SAE, 2 (40.0%) participants had a Grade ≥3 TEAE, none of the participants had a TEAE leading to permanent full intervention discontinuation, and none of the participants had a fatal Grade 5 TEAE. In Cohort A, treatment related TEAEs were reported in 5 (100%) participants, treatment related serious TEAEs were reported in 2 (40.0%) participants, and none of participants had a treatment related Grade ≥3 TEAE.

Of the N=20 exposed participants in Cohort C, 19 (95.0%) participants had a TEAE of any grade, 7 (35.0%) participants had a TE SAE, 6 (30.0%) participants had a Grade ≥3 TEAE, 3 (15.0%) participants had a TEAE leading to permanent full intervention discontinuation, and none of the participants had a fatal Grade 5 TEAE. In Cohort C, treatment-related TEAEs were reported in 19 (95.0%) participants, treatment-related serious TEAEs were reported in 6 (30.0%) participants, and treatment-related Grade ≥3 TEAEs were reported in 4 (20.0%) participants.

The most frequently reported TEAE in cohorts in combination with pembrolizumab was asthenia, reported in 37.3% of participants in Cohorts B1, B2, and B3 overall, in 60.0% (3 out of 5) of participants in Cohort A, in 45.0% of participants in Cohort C, and in 53.3% of participants in Cohort D1. Other most frequently reported TEAEs by PT (⩾10% of participants in Cohorts B1, B2, B3, D1, and C and ⩾2 out of 5 participants in Cohort A) included infusion related reaction, diarrhoea, and cytokine release syndrome.

The most frequently reported TEAE in Cohort D2 (SAR444245 + cetuximab) was infusion related reactions, reported in 45.8% of participants. Other most frequent reported TEAE by PT (⩾10% of participants) included folliculitis, cytokine release syndrome, decreased appetite, dyspnoea, nausea, vomiting, diarrhoea, abdominal pain, constipation, rash, pruritus, dry skin, dermatitis acneiform, back pain, asthenia, influenza like illness, fatigue, pyrexia, and disease progression.

The most frequently reported Grade ⩾3 event in cohorts in combination with pembrolizumab being disease progression (reported in 9 [15.3%] participants in Cohorts B1, B2, and B3 overall and 1 [3.3%] participant in Cohort D1). Four participants had Grade ⩾ 3 event of infusion-related reaction.

The most frequently reported Grade ⩾3 event in Cohort D2 (SAR444245 + cetuximab) being disease progression (reported in 5 [20.8%] participants).

The most frequently reported TEAEs related to any IMP in cohorts in combination with pembrolizumab (>10% of participants in Cohorts B1, B2, B3, D1, and C and ⩾2 out of 5 participants in Cohort A) were infusion-related reaction, asthenia, cytokine release syndrome, and diarrhoea.

The most frequently reported TEAEs related to any IMP in Cohort D2 (SAR444245 + cetuximab) (>10% of participants) were folliculitis, cytokine release syndrome, decreased appetite, nausea, vomiting, diarrhoea, rash, pruritus, dry skin, dermatitis acneiform, asthenia, influenza like illness, fatigue, and infusion related reaction.

Across cohorts in combination with pembrolizumab, 8 participants had a fatal AE in context other than disease progression: 2 participants had disease progression, 1 participant had COVID-19, 1 participant had pneumonia, 1 participant had respiratory tract infection, 1 participant had hypovolaemic shock, 1 participant had small intestinal perforation, 1 participant had jaundice cholestatic. Most deaths during the TE period or post-treatment period were due to progressive disease.

In Cohort D2 (SAR444245 + cetuximab), no participants had a fatal AE in context other than disease progression. All deaths during the TE period or post-treatment period were due to progressive disease.

Treatment-emergent SAEs were reported in approximately 35% to 77% of participants across the cohorts. The most frequently reported treatment-emergent SAE in cohorts in combination with pembrolizumab was disease progression (9 [15.3%] participants overall in Cohorts B1, B2, and B3 and 1 [3.3%] participant in Cohort D1).

The most frequently reported treatment-emergent SAE in Cohort D2 (SAR444245 + cetuximab) was disease progression (5 [20.8%] participants).

TEAEs leading to permanent full intervention discontinuation were reported in approximately 7% to 23% of participants across the cohorts. Almost all TEAEs leading to permanent full treatment discontinuation were Grade $\geqslant$3 TEAEs. One participant in Cohort B2 had a TEAE of disease progression leading to permanent full treatment discontinuation.

The most frequently reported AESI in cohorts in combination with pembrolizumab was Grade $\geqslant$2 infusion related reaction and Grade $\geqslant$2 cytokine release syndrome.

The most frequently reported AESI in Cohort D2 (SAR444245 + cetuximab) was infusion related reaction. One case of the AESI ICANS was reported by the Investigator in Cohort D2.

No events of capillary leak syndrome have been reported. No events of anaphylaxis have been reported. There were no cases of Hy's law across all cohorts.

Particular attention was given to analyzing data on infusion reactions, which were identified using coding lists for cytokine release syndrome, infusion-related reaction, 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 infusion-related reaction, flu-like symptoms and cytokine release syndrome. TEAEs in the infusion reaction category were predominantly Grade 2 and Grade 1. Most occurred on the day of infusion and resolved within 3 days. The most frequently reported infusion reaction symptom in each cohort was pyrexia, mostly low grade in intensity.

Across all cohorts, the most frequently reported hematological abnormalities (>60% of participants) during the TE period was anemia. Anemia was predominantly Grade 1.

While some PSCAs in laboratory parameters were observed during the TE period, all included plausible alternative etiologies and none required further actions for safety reason. This included one or more participants who met biochemical criteria for Hy's law, however, those observed PCSAs were attributable to alternative etiologies. As such, there were no PCSAs meeting all Hy's law criteria observed during the study.

Pharmacokinetic results:

Pharmacokinetics of pegenzileukin

On Cycle 4 Day 1, no accumulation of pegenzileukin in plasma was observed, with mean $R_{ac"Cmax"}$ and $R_{ac"AUC0-72h"}$ of 0.887 and 0.772, respectively.

Total variability in C_{max} and AUCs was low to moderate, with CV% ranging from 21% to 26% on Cycle 1 Day 1 and from 32% to 33% on Cycle 4 Day 1.

Table 1 - Mean ±SD (geometric mean) [CV%] pharmacokinetic parameters for SAR444245 on Cycle 1 Day 1 and Cycle 4 Day 1 following intravenous administration of SAR444245 Q3W in combination with pembrolizumab or cetuximab in adult participants with various types of cancer (all cohorts combined)

PK Parameters	Cycle 1 Day 1	Cycle 4 Day 1
N	35	12 Error! Reference source not found.
C_{max} (ng/mL)	417 ± 109 (404) [26]	369 ± 118 (350) [32]
AUC_{last} (ng·h/mL)	8940 ± 1930 (8720) [22]	7100 ± 2330 (6730) [33] Error! Reference source not found.
AUC (ng·h/mL)	9270 ± 1990 (9040) [22] Error! Reference source not found.	7330 ± 2340 (6970) [32] Error! Reference source not found.
t_{last} (h) Error! Reference source not found.	69.45 (43.00, 76.77)	68.82 (46.28, 72.58) Error! Reference source not found.
$R_{ac"Cmax"}$	NA	0.887 ± 0.173 (0.869) [20]
$R_{ac"AUC0-72h"}$	NA	0.772 ± 0.150 (0.759) [19] Error! Reference source not found.

NA = Not Applicable

a Median (Min, Max)

b n=34; parameter not calculable for 1 participant since linear regression analysis could not be performed as there were fewer than 3 quantifiable data points available after C_{max}.

c 1 participant was excluded from statistics due to having notably lower systemic exposure to SAR444245 on Cycle 4 Day 1.

d n=9; three participant profiles were included in the analysis for C_{max} and t_{max} only, due to missing at least the 48- and 72 hour post-end of infusion PK samples.

Other results:

Immunogenicity results:

Overall, 7 out of 56 (12.5%) participants had TE ADAs across B1, B2, and B3 Cohorts and none of the 7 participants with treatment induced ADA showed persistent ADA response.

In Cohort D1, 11 out of 30 (36.7%) participants had TE ADAs. In Cohort D2, 3 out of 23 (13.0%) participants had TE ADAs. Two of the 11 participants with treatment induced ADA in Cohort D1 showed persistent ADA response; and none of the 3 participants with treatment induced ADA in Cohort D2 showed persistent ADA response.

In Cohort A, 1 out of 5 (20.0%) participants had TE ADAs. In Cohort C, 3 out of 20 (15.0%) participants had TE ADAs. None of the participants with treatment induced ADA, showed persistent ADA response in any of the Cohorts A and C.

Issue date: 15-May-2025