Sponsor: Sanofi **Drug substance(s):** SAR444245 - pegenzileukin	**Study Identifiers:** IND: 156112 EudraCT: 2021-002150-91 NCT: NCT05179603 WHO: U1111-1251-5834 **Study code:** ACT16941

Title of the study:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) with or without other anticancer therapies for the treatment of adults and adolescents with relapsed or refractory B cell lymphoma

Study center(s):

This study was conducted at 7 centers that enrolled participants in 3 countries (Argentina, Chile, and Spain).

Study period:

Study initiation date: 07 December 2021 (signed informed consent).

Study completion date: 06 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 with or without other ancancer therapies.

Secondary

•To assess other indicators of antitumor activity

•To confirm the dose and to assess the safety profile of SAR444245 when combined with or without other anticancer therapies.

•To assess other indicators of antitumor activity.

•To assess the plasma concentrations of SAR444245 when given with or without other anticancer therapies.

•To assess the immunogenicity of SAR444245.

Methodology:

This was a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 with or without other anticancer therapies in adults and adolescents with relapsed or refractory B cell lymphoma.

This study was developed as a master protocol in order to accelerate the investigation of SAR444245 with or without other anticancer therapies by identifying early signals. This design was with the flexibility to open new treatment cohorts as new treatment become available and close existing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity.

The Sponsor decided to terminate the study early for non-safety reasons on 21 October 2022. Following preliminary assessments, observed antitumor activity at the current dose and schedule of once every 3 weeks (Q3W) in combination with pembrolizumab was lower than projected at the Sponsor's program level. The safety profile of SAR444245 in combination with pembrolizumab was manageable, with no actions needed for safety reasons.

At the time of the Sponsor's decision to terminate further screening in this study, participants were only enrolled in Cohort A. Cohort A was planned to include approximately 25 participants with classic Hodgkin lymphoma (cHL) who were anti-PD-(L)1-naïve and had received at least 2 or 3 lines of systemic therapy and assess SAR444245 combined with pembrolizumab as at least 3rd or 4th line of therapy.

For Cohort A, a maximum of 10 participants were enrolled in a safety run-in to confirm the dose of SAR444245. During the safety run-in phase, a minimum of 6 DLT-evaluable participants were required for safety data review by Study Board to confirm safe dose. Participants who were enrolled in the safety run-in and treated at the confirmed safe dose were included in the total number of participants.

Number of study participants:

Cohort A:

Number of planned participants: 25 participants

Enrolled population: 14 participants

Exposed population: 14 participants

Efficacy population: 14 participants

DLT-evaluable population: 7 participants

PDy population: 13 participants

PK population: 13 participants.

ADA population: 12 participants

Diagnosis and criteria for inclusion:

For participants in Cohort A, histologically or cytologically confirmed diagnosis of cHL, according to the WHO 2016 classification. Regarding to the prior anti-cancer treatment, participants must have received at least two prior lines of systemic therapy for cHL, including at least one containing an anthracycline or brentuximab; participants must have failed or declined autologous stem cell transplantation (ASCT), or not be a candidate for ASCT; participant might have received a prior autologous stem cell transplant but must be at least ≥100 days post-auto-transplant, and all transplant- related adverse events must have resolved to Grade 1 or less and meet all other eligibility criteria.

Study products

Investigational medicinal product(s):

SAR444245

Formulation: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.

Route(s) of administration: intravenous (IV) infusion.

Dose regimen: 24 µg/kg (or reduced to 16 µg/kg or another lower dose level recommended by Study Board) Q3W

Pembrolizumab

•Formulation: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single dose vials.

•Route of administration: IV infusion.

•Dose regimen: Pembrolizumab was administered at a dose of 200 mg (for pediatric participants: 2 mg/kg, up to maximum 200 mg) Q3W.

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:

- Screening period: up to 28 days.
- Treatment Period: up to 35 cycles, each cycle duration was 21 days.
- End of Treatment and Follow-up: End of Treatment Visit occurred 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants then entered the Observation period and were followed differently depending on the reason leading to End of Treatment (EOT):

1. Participants who discontinued study treatment without PD or who complete the maximum cycles allowed in the individual substudy without PD (per Lugano response criteria 2014), were followed every 3 months ±7 days from last IMP administration, for safety and tumor imaging assessments, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.
2. Participants who discontinued study treatment with PD (per Lugano response criteria 2014) were followed for safety in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-up Period** were contacted by telephone every 3 months ±14 days to assess for survival status Updated survival status may be requested by the Sponsor at any time during the study. Survival Phone Call Follow up continued until death, participant request to discontinue from follow-up, or cut-off date for final analysis has been reached, or upon cancellation of Survival follow-up at the discretion of the Sponsor at any prior timepoint.

After the cohort cut-off date for the primary analysis, participants could continue to receive IMP, if clinical benefit was observed, until full permanent discontinuation criteria were met and continued to undergo all assessments as per the study schedule of activities in the individual substudy.

As of the cutoff date of the primary CSR (12 October 2023), none of participants had completed the study treatment period, while 6/14 participants were still on intervention and were followed for safety assessment only and until Follow-up Visit 1. At study completion, 2/14 participants had completed the study treatment period, while the remaining 12/14 participants had permanent full intervention discontinuation, most commonly due to adverse event (4/14 participants).

Criteria for evaluation:

Primary

•Complete response rate (CRR) defined as the proportion of participants who have a complete response (CR) determined by Investigator per Lugano response criteria 2014.

Secondary

•Objective response rate (ORR) defined as the proportion of participants who have complete response (CR) or partial response (PR) determined by Investigator per Lugano response criteria 2014

•Incidence of treatment emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus gradings.

•Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by Investigator per Lugano response criteria 2014.

•Duration of response (DoR) defined as the time from first documented evidence of PR or CR until progressive disease (PD) determined by Investigator per Lugano response criteria 2014, or death from any cause, whichever occurs first.

•Clinical benefit rate (CBR) including CR or PR at any time or stable disease (SD) of at least 6 months (determined by Investigator per Lugano response criteria 2014).

•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 per Lugano response criteria 2014 or death due to any cause, whichever occurs first.

•Plasma concentrations of SAR444245.

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

Statistical methods:

- **Analysis of primary endpoint:**
  - The complete response rate (CRR) was summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for CRR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The objective response rate (ORR) was summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for ORR will be computed using the Clopper-Pearson method.
  - Time to response (TTR) was assessed on the subgroup of participants who have achieved objective response in the efficacy population.
  - Duration of response (DoR) was only summarized on the subgroup of participants who have achieved objective response in the efficacy population. The median DOR and associated 90% confidence interval (CI) were provided.
  - Clinical benefit rate (CBR) was estimated by dividing the number of participants with clinical benefit by the number of participants in the efficacy population. In addition, two-sided 90% CIs were computed using the Clopper-Pearson method.
  - Progression free survival (PFS) was summarized on the efficacy population using Kaplan-Meier methods. The median PFS and associated 90% confidence interval (CI) will be provided.
- **Analysis of secondary safety endpoints:**
  - Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class (SOC) and Preferred Term (PT) were summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5.0) grade (all grades and Grade ≥3) for the exposed population. Similar summaries were prepared for treatment-related TEAEs, TEAEs leading to full intervention discontinuation, TEAEs leading to partial intervention discontinuation (if applicable), TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (treatment-emergent adverse event [TEAE] and post-treatment) and participants who died by study period (treatment-emergent period, post-treatment period) and reasons for death were summarized. Immune Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS) events were graded using American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading and were summarized separately.
  - Hematology and clinical chemistry results were graded according to the NCI CTCAE V5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period were provided for the exposed population.

Summary Results:

Demographic and other baseline characteristics:

In Cohort A, the median age was 28.0 years (range: 21 to 40). Most of participants were female (10 participants, 71.4%) and had an ECOG PS score of 0 (13 participants, 92.9%). All participants were White and 13 (92.9%) were Hispanic.

The disease was initially diagnosed at Stage IV for most participants (7 [50%]). All histology type at initial diagnosis was cHL in all 14 participants. The median time from initial diagnosis to first IMP administration was 5.6 years (range: 1 to 14).

At study entry, all participants (14 [100%]) had FDG-avid histology. All participants (14 [100%]) did not have FDG bone marrow uptake. The disease was diagnosed at Stage IV (5 participants, 35.7%), Stage III (3 participants, 21.4%), Stage II (5 participants, 35.7%), or Stage I (1 participant, 7.1%). Six participants (42.9%) had presence of B symptoms, 1 participant (7.1%) had spleen involvement, and 3 participants (21.4%) had extranodal involvement at study entry.

All participants had received prior anti-cancer therapy. Six participants (42.9%) reported prior anti-cancer therapy in an advanced setting and 12 (85.7%) reported prior anti-cancer therapy in other setting (specified as curative, first or second line therapy). Four participants (28.6%) received autologous haematopoietic stem cell transplant. All participants had received chemotherapy (14 participants, 100%) and most participants had received radiation therapy (8 participants, 57.1%).

Exposure:

Across participants in Cohort A (N=14 participants exposed to pegenzileukin + pembrolizumab), the median duration of investigational medicinal product (IMP) exposure was 12.6 months (range: 1 to 28 months), with 3 (21.4%) participants completing ≥31 cycles.

The median duration of exposure to pegenzileukin was 12.6 months (range: 1 to 25 months). The median cumulative dose of pegenzileukin was 432.4 µg/kg (range: 48 to 841 µg/kg), with a median relative dose intensity of 98.0% (range: 80% to 100%). The median cumulative dose of pembrolizumab was 3600.0 mg (range: 400 to 7000 mg), with a median relative dose intensity of 97.9% (range: 85% to 100%).

Efficacy:

In Cohort A, in participants with cHL who had received at least 2 or 3 lines of systemic therapy, 10 out of 14 participants (71.4%) had a CR, 3 (21.4%) had PR, and 1 (7.1%) had PD as BOR. The CRR was 71.4% (90% CI: 46.0% to 89.6%) and ORR was 92.9% (90% CI: 70.3% to 99.6%). The median TTR was 2.0 months (range 2 to 2). As of the partial database lock, the median DoR could not be calculated (NC [90% CI: 6.3 to NC]) because only 4 out of 13 participants (30.8%) had progression (no death). The CBR was 92.9% (90% CI: 70.3% to 99.6%). The median time for PFS could not be calculated (NC [90% CI: 8.3 to NC]) because only 5 out of 14 participants (35.7%) had progression (no death).

Safety results:

The cumulative data indicates that treatment with pegenzileukin in combination with pembrolizumab generally remains manageable with standard therapies. All 14 exposed participants in Cohort A had treatment emergent adverse events (TEAEs), 8 participants (57.1%) had a Grade ⩾3 TEAE, 5 participants (35.7%) had a treatment-emergent serious adverse event (SAE), and none of the participants had a fatal Grade 5 TEAE. Treatment related SAEs were reported in 4 participants (28.6%) and treatment-related Grade ⩾3 TEAEs were reported in 5 participants (35.7%).

The most frequently reported (⩾20%) all-grade TEAE as well as treatment related TEAE by preferred term (PT) was infusion related reaction (11 participants, 78.6%). Since the cutoff date of the primary CSR, cytokine release syndrome (3 participants, 21.4%) was included among the most frequently reported all-grade TEAEs.

The most frequently reported (⩾10%) Grade ⩾3 events were lymphopenia, neutropenia, and immune-mediated myocarditis (each PT reported in 2 participants, 14.3%). While no Grade ⩾3 events of infusion-related reaction were reported, Grade ⩾3 cytokine release syndrome was reported in 1 participant (7.1%) since the cutoff date of the primary CSR.

Whereas none of the Grade ⩾3 SAEs had previously been events of cytokine release syndrome, since the cutoff date of the primary CSR, one Grade ⩾3 cytokine release syndrome was reported. Therefore, all SAEs have now been Grade ⩾3 except for 2 of the 3 participants who reported cytokine release syndrome that were Grade <3. There were no treatment emergent SAEs of infusion-related reaction. Four participants (28.6%) had at least one treatment-related SAEs.

All TEAEs leading to permanent full treatment discontinuation were Grade ⩾3 TEAEs. Most frequently reported was TEAE of immune-mediated myocarditis (2 participants, 14.3%). While none of the participants had TEAEs leading to permanent partial treatment discontinuation of pembrolizumab, 1 participant (7.1%) had TEAE leading to permanent partial treatment discontinuation of pegenzileukin (SAE of cytokine release syndrome) since the cutoff date of the primary CSR.

Most commonly reported, treatment-emergent adverse events of special interest (any grade) were infusion related reaction reported in 11 (78.6%), cytokine release syndrome reported in 3 (21.4%), and immune mediated myocarditis reported in 2 (14.3%) participants. As stated in the primary CSR, review of the cases of immune-mediated myocarditis showed both events followed infusion related reactions. Standard medical treatment including steroids was provided with response in both participants and one event recovered 10 days after being reported. In the other case, the participant responded to treatment and was discharged from the hospital, but there was no outcome noted. Although one investigator considered the event to have been attributed to both IMPs, the sponsor did not find, based on the totality of available data, any reason to suspect a new causal association between the event and pegenzileukin. No immune effector cell associated neurotoxicity syndrome was reported.

In Cohort A, 12/14 participants (85.7%) had at least one TEAE in the infusion reaction (IR) category, unchanged since the cutoff date of the primary CSR. Of these, infusion-related reaction was reported in 11 participants (78.6%) and cytokine release syndrome was reported in 3 participants (21.4%, 1 additional participant since the cutoff date of the primary CSR). No events of anaphylaxis or flu-like symptom were observed. The majority of TEAEs in the IR category by worst grade were Grade 2 (10 participants [71.4%]), while 1 participant (7.1%) reported Grade 3 TEAEs in the IR category. The only change since the cutoff date of the primary CSR was that one participant's worst grade changed from Grade 2 to Grade 3.

While some potentially clinically significant abnormalities (PCSAs) were observed, all included plausible alternative etiologies, and none required further actions for safety reasons. As such, there were no PCSAs meeting all Hy's law criteria observed during the study.

Pharmacokinetic results:

Pegenzileukin median concentrations at the end of infusion ranged from 325 to 591 ng/mL. Overall, pegenzileukin concentrations in plasma were in the expected range for the dose administered in study ACT16941. No signs for interferences of co-administered drugs on pegenzileukin concentrations were observed.

Other results:

Immunogenicity: Three participants were reported as positive for treatment emergent ADAs.

Issue date: 28-Apr-2025