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A Phase 1/2, Open Label, First-in-Human, Dose Escalation and Expansion Study of the Anti-PD-1/IL-15 Fusion Protein, SAR445877, Administered as Monotherapy in Adults with Advanced Solid Tumors

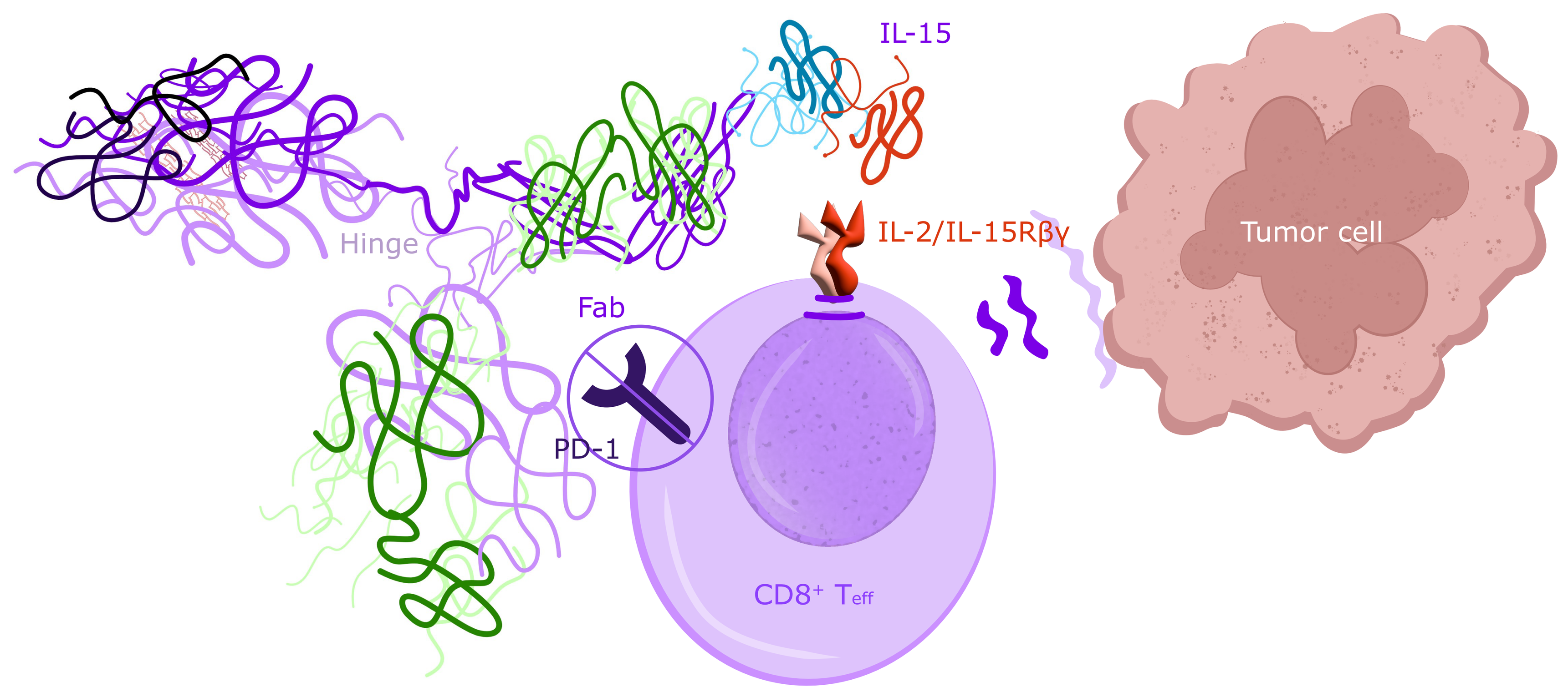
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BACKGROUND

- SAR445877 is a fusion protein of high affinity anti-programmed cell death protein-1 (PD-1) antibody combined with a detuned interleukin-15 (IL-15)
- PD-1/ programmed cell death ligand 1 (PD-L1) blockade serves as an effective target for anti-cancer therapy
 - Targeting PD-1/PD-L1 has demonstrated significant objective responses in multiple cancer types, though small fraction of patient population responds to PD-1/PD-L1 as monotherapy and many patients relapse after the initial response
 - Hence, there is a significant unmet medical need to improve anti-tumor immune response
- SAR445877, via its anti-PD-1 moiety, binds to PD-1-expressing T and natural killer (NK) cells and potentially leads to a targeted expansion and activation of CD8+ T and NK cells expressing both PD-1 and IL-2/15Rβγ **(Figure 1)**

Figure 1: Mechanism of Action of SAR445877


IL-15
Hinge
IL-2/IL-15Rβγ
Tumor cell
Fab
PD-1
CD8+ Teff

CD, cluster of differentiation; Fab, antibody fragment; IL-2, interleukin-2; IL-15, interleukin-15; IL-15Rβγ, interleukin-15 receptor beta gamma; PD-1, programmed cell death protein-1; Teff, effector T cell.

- Preclinical studies have demonstrated SAR445877 as an immune-modulatory agent with good tolerability and therapeutic benefits in various neoplastic disease models including PD-1/PD-L1 resistant models as a monotherapy[1]
- SAR445877 treatment in preclinical models showed increased cytotoxic immune cell recruitment to the tumor microenvironment, prolonged survival, and tumor clearance[2]
- Thus, this first-in-human study has been initiated to identify the safety, pharmacokinetics, pharmacodynamics, recommended dose(s), and to evaluate the preliminary clinical efficacy of SAR445877 as a monotherapy in patients with advanced solid tumors (EudraCT 2022-001239-95/ NCT05584670)

METHODS

- This is a first-in-human, open-label, multicenter, dose escalation and expansion Phase 1/2 study in adult patients with advanced unresectable or metastatic solid tumors; approximately 240 participants will enroll in this study
- The study comprises of 2 parts: Part 1 dose escalation and Part 2 dose expansion in advanced solid tumors (non-small cell lung cancer [NSCLC], hepatocellular carcinoma [HCC], gastric cancer/gastro esophageal junction adenocarcinoma [GC/GEJ]) **(Figure 2)**
- The duration of each cycle is 14 days and the DLT observation period consists of the first 2 cycles of treatment

Figure 2: Study Design

Adults with advanced or metastatic solid tumors (N=240)

Dose escalation (Part 1 Q2W or QW)

SAR445877 IV monotherapy over a 14-day cycle

DL1 (Q2W) → DL2 (Q2W) → DL4 (QW) → MTD/ MAD

- Dose escalation monotherapy using QW dosing will be staggered to begin after monotherapy Q2W DL3 has been cleared
- Q2W (N = ~ 33)
- QW (N = ~ 42)

Dose expansion (Part 2)

SAR445877 Monotherapy: (N = ~ 165)

- Cohort A: Patients with NSCLC
- Cohort B: Patients with HCC
- Cohort C: Patients with GC/GEJ
- Cohort D: Patients with infiltrated tumor type

DL, dose level; GC, gastric cancer; GEJ, gastro esophageal junction adenocarcinoma; HCC, hepatocellular carcinoma; IV, intravenously; MAD, maximum administered dose; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; QW, weekly.

KEY INCLUSION CRITERIA

- Age ≥18 years
- **Dose escalation (Part 1)**
 - Advanced unresectable or metastatic solid tumors for which no standard alternative therapy is available or is not in the best interest of the participant
- **Dose expansion (Part 2)**
 - Cohort A: Histologically or cytologically confirmed diagnosis of metastatic NSCLC
 - Cohort B: Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic HCC, or clinically by American Association for the Study of Liver Diseases criteria in cirrhotic patients (participants without cirrhosis must have had histological confirmation of diagnosis)
 - Cohort C: Histologically or cytologically confirmed advanced unresectable or metastatic GC or GEJ, combined positive scoring of <1, metastatic microsatellite instability (MSI) or mismatch repair (MMR) or microsatellite instability-high non-(MSI-H) or proficient MMR disease, HER2/neu status must be determined locally and HER2/neu negative are eligible
 - Cohort D: Biomarkers cohort in infiltrated tumor type(s)
 - At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria
 - Eastern Cooperative Oncology Group performance status of <2

KEY EXCLUSION CRITERIA

- Other malignancies either progressing or requiring active treatments within 2 years prior to enrollment
- Active brain metastases or leptomeningeal metastases
- History of treatment-related immune-mediated (or immune-related) adverse events from immunomodulatory agents that caused permanent discontinuation of the agent, or that were grade 4 in severity, or have not resolved to grade ≤1
- Any condition requiring ongoing/continuous corticosteroid therapy (>10 mg prednisone/day or an anti-inflammatory equivalent) within 1 week prior to the first dose of the study medicine
- Ongoing or recent (within 2 years) significant autoimmune disease
- Known history or evidence of interstitial lung disease or active, non-infectious pneumonitis within 3 years prior to the first dose of the study drug
- History of organ allotransplant requiring immunosuppressive treatment

STUDY OBJECTIVES AND ENDPOINTS

	Objectives	Endpoints
Primary	**Dose escalation:** To determine the MTD or MAD, recommended dose(s), and the overall safety and tolerability	• DLTs in Cycle 1 and 2* • TEAEs*
	Dose expansion: To determine the ORR at recommended dose(s)	• ORR**
Secondary	**Dose escalation:** To assess preliminary clinical activity	• ORR**
	Dose escalation and expansion: To assess the preliminary clinical activity, PK and potential immunogenicity	• DoR** • PK • Incidence of ADAs
	Dose expansion: To assess other indicators and safety profile	• Time to response** • Clinical Benefit (confirmed CR or PR or SD) • PFS** • AEs*

*NCI CTCAE Tumors v5.0 or ASTCT criteria. **Investigator per RECIST v1.1.
ADA, anti-drug antibodies; AE, adverse events; ASTCT, American Society for Transplantation and Cellular Therapy; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; DoR, duration of response; MAD, maximum administered dose; MTD, maximum tolerated dose; NCI, National Cancer Institute; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumor; SD, stable disease; TEAE, treatment emergent AE; v, version.

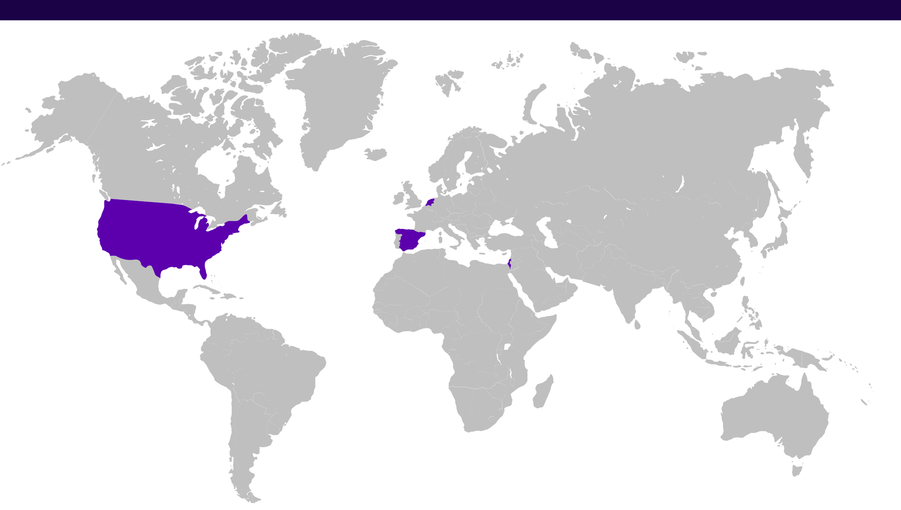
STATISTICAL ANALYSES

All tumor assessments in the primary or secondary analyses are based on RECIST 1.1

- **Primary endpoint analyses**
 - Analysis of presence of DLTs is based on an adaptive Bayesian logistic regression model guided by the escalation with overdose control principle
 - Treatment-emergent adverse events and serious adverse events will be categorized according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0 and classified by system organ class and Preferred Term according to the latest available version of the Medical Dictionary for Regulatory Activities
 - Overall response rate (ORR) (dose expansion): ORR and the corresponding 90% Clopper Pearson two-sided confidence interval (CI) will be derived
- **Secondary endpoint analyses**
 - Time to response will be descriptively summarized on the subgroup of participants who have achieved confirmed objective response
 - Duration of response (DoR) and progression free survival will be summarized with descriptive statistics using Kaplan-Meier methods. The median DoR and associated 90% CI will be provided
 - Participants will be considered as clinical benefit responders if they achieve a complete response or partial response as the best overall response, or have an overall response recorded as stable disease at 6 months

STUDY STATUS

- The study is enrolling participants
- Dose escalation Part 1 is planned to be conducted in United States of America, Spain, Netherlands and Israel



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1. Lu D et al, *J Immunother Cancer* (2020) 8(Suppl 3):A1–A559
2. Polonskaya Z et al. *Cancer Res* (2022) 82 (12_Supplement): 5215

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If you have questions about this poster, please email Martin Gutierrez (martin.gutierrez@hmhn.org) and Fatima Menas (Fatima.Menas@sanofi.com).
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