1495

A phase 1 multicenter study of the safety and efficacy of the NKG2A targeting antibody S095029 as single agent and in combination with anti-PD1 in patients with advanced malignancies

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AIM

- Primary objectives were to assess safety and tolerability and determine the maximum tolerated dose (MTD) of S095029 as single agent or in combination with Sym021.
- Secondary objectives were to evaluate the preliminary antitumor activity and to characterize the immunogenicity (antidrug antibodies [ADA]) and pharmacokinetic (PK) profile of S095029 as single agent or in combination with Sym021.
- Exploratory objectives were to explore potential pharmacodynamic (PD) biomarkers of activity in tumor biopsies (pre- and post-treatment) and/or peripheral blood, to explore any potential PK/PD relationships via population modeling, and to assess potential predictive biomarkers of response to S095029 from baseline tumor and/or peripheral blood samples.

CONCLUSIONS

- The combination was well tolerated with no unexpected safety events.
- S095029 concentrations increase with the dose and median half-life is 8 days and no apparent impact of an anti-PD1 administration on PK of S095029.
- Full NKG2A receptor occupancy in whole blood was achieved starting from low doses of 30 mg Q2W in monotherapy arm S095029 (part 1a) and combination arm (part 1b) S095029+Sym021 and retained throughout entire dosing interval.
- Increased levels of immune cell activating cytokines in peripheral blood were detected following treatment suggesting immune cell activation.
- S095029 in combination with anti-PD1 Sym021 exhibited antitumor activity in patients with advanced solid tumors.
- S095029 is currently investigated in combination with other anti-PD1 antibodies in phase 1/2 studies for non-small cell lung cancer (NCT06162572) and gastric cancer (NCT06116136).

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DISCLOSURES

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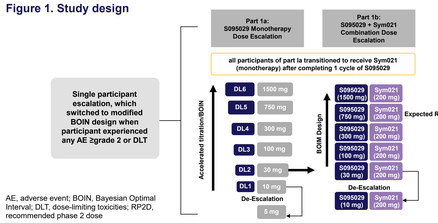
INTRODUCTION

- NKG2A (CD159a) is a C-type lectin that heterodimerizes with CD94 and creates an immune inhibitory receptor expressed on natural killer (NK) cells, natural killer T (NKT) cells, gamma delta (γδ) T cells, and a subset of cytotoxic T cells.
- S095029 (also called Sym025) is a fully human monoclonal IgG1 anti-NKG2A antibody with attenuated Fc effector functions (IgG1-LALA) that targets the human cell surface molecule NKG2A (CD159a). S095029 specifically binds the NKG2A part of the human NKG2A/CD94 heterodimer, blocking the interaction with its ligand HLA-E.
- Sym021 is a recombinant, humanized, effector function-silenced IgG1-LALA antibody that inhibits binding of PD-1 with its ligands, PD-L1 and PD-L2.
- Preclinical data demonstrated that S095029 combined with Sym021 results in enhanced immunostimulatory antitumor activity.

METHODS

Figure 1. Study design



AE, adverse event; BOIN, Bayesian Optimal Interval; DLT, dose-limiting toxicities; RP2D, recommended phase 2 dose

- In part 1a, starting dose of S095029 was 10 mg every 2 weeks (Q2W). All participants received a single 4-week cycle of treatment with S095029 on Day 1 and Day 15 and were evaluated for dose-limiting toxicities (DLTs). Thereafter they received Sym021 (200 mg) monotherapy with the same administration schedule (Q2W).
- In part 1b, starting dose of S095029 was 30 mg Q2W. All participants received the S095029+Sym021 in combination.
- All participants were treated until disease progression or unacceptable toxicity.
- As of August 13, 2024, S095029 as a single agent or in combination with Sym021, an anti-PD1 antibody, were investigated in 41 patients with advanced solid tumors. (NCT05162755)

PK and ADA:

- PK and ADA were measured in serum samples using validated immunoassay methods.

Receptor occupancy measurement:

- Receptor occupancy was measured by flow cytometry in fresh whole blood, in CD56+ NK cells, by measuring the binding of a competitive (Sym025-PE, Servier) and noncompetitive anti-NKG2A Ab (CD159a_REA110, Miltenyi). The calculation of the percentatge of receptor occupancy (RO) was done as follows: =[(CD159a+ – Sym25-PE+)/ CD159a+] x 100. It was assessed at different time points of the cycle 1: Predose, EOI, C1D1, C1D8, C1D15, C1D22, and C2D1.

Soluble factors measurement:

- Soluble factors were analyzed in human plasma by Meso Scale Discovery (MSD) technology with a V-PLEX for the detection of interferon (IFN) gamma, tumor necrosis factor (TNF) alpha, interleukin (IL)-1b, IL-6, IL-8, and IL-10, a V-Plex for the detection macrophage inflammatory protein (MIP)-1 alpha and MIP-1 beta, and a U-Plex for the detection of monokine induced by gamma IFN (MIG) (CXCL9). Analysis was performed on frozen plasma of n=38 patients at the following time points of the cycle 1: baseline, C1D1, C1D8, C1D15, and C1D22.

RESULTS

Table 1. Baseline characteristics

Demographics and baseline characteristics	Part 1a (N=21)	Part 1b (N=20)
Median age (range), years	55.0 (29–82)	63.0 (35–77)
Gender, n (%)		
Female	13 (61.9)	7 (35.0)
Male	8 (38.1)	13 (65.0)
Ethnic origin, n (%)		
Asian	-	2 (10.0)
Black or African American	3 (14.3)	2 (10.0)
White	18 (85.7)	15 (75.0)
Unavailable	-	1 (5.0)
ECOG, n (%)		
0	7 (33.3)	5 (25.0)
1	13 (61.9)	15 (75.0)
Unavailable	1 (4.8)	-
Prior anti-PD1 therapy, n (%)	7 (33.3)	8 (40.0)
Prior treatment lines, n (%)		
0	1 (4.8)	-
1	1 (4.8)	2 (10.0)
2	3 (14.2)	10 (50.0)
≥3	16 (76.2)	8 (40.0)

ECOG = Eastern Cooperative Oncology Group; PD1 = programmed cell death protein 1

Table 2. Baseline characteristics – primary diagnosis

Primary diagnosis (PT), n (%)	Part 1a (N=21)	Part 1b (N=20)
Adenocarcinoma of colon	2 (9.5)	3 (15.0)
Adenocarcinoma pancreas	1 (4.8)	1 (5.0)
Adenoid cystic carcinoma of salivary gland	1 (4.8)	-
Cervix carcinoma	1 (4.8)	-
Clear cell renal cell carcinoma	-	1 (5.0)
Colon cancer	1 (4.8)	1 (5.0)
Epithelioid sarcoma	-	1 (5.0)
Gastrointestinal adenocarcinoma	1 (4.8)	-
Gastrointestinal stromal tumor	-	1 (5.0)
Invasive ductal breast carcinoma	-	1 (5.0)
Malignant melanoma	-	1 (5.0)
Malignant neoplasm of lacrimal duct	-	1 (5.0)
Metastatic squamous cell carcinoma	-	1 (5.0)
Nasopharyngeal cancer	-	1 (5.0)
Neuroendocrine carcinoma of the skin	-	1 (5.0)
Esophageal adenocarcinoma	1 (4.8)	-
Ovarian cancer metastatic	1 (4.8)	-
Ovarian endometrioid carcinoma	1 (4.8)	-
Ovarian granulosa cell tumor	1 (4.8)	-
Pancreatic carcinoma	-	1 (5.0)
Peritoneal mesothelioma malignant	-	1 (5.0)
Pleomorphic leiomyosarcoma	-	1 (5.0)
Porocarcinoma	1 (4.8)	-
Rectal adenocarcinoma	1 (4.8)	-
Rectosigmoid cancer	1 (4.8)	-
Salivary gland cancer	1 (4.8)	-
Sarcoma uterus	1 (4.8)	-
Sarcomatoid carcinoma of the lung	-	1 (5.0)
Small intestine carcinoma	1 (4.8)	-
Solid pseudopapillary tumor of the pancreas	1 (4.8)	-
Squamous cell carcinoma of head and neck	1 (4.8)	-
Thymic carcinoma	1 (4.8)	1 (5.0)
Triple negative breast cancer	-	1 (5.0)
Uterine leiomyosarcoma	1 (4.8)	-

PT = preferred term

- Related events to S095029 occured in 51.2% of patients. Most events were grade 1.
- No DLT events occured over 41 patients.
- No CRS events occured.
- 38 (92.7%) patients discontinued treatment, 32 (78.0%) due to disease progression.

Table 3. Safety overview

Safety Overview	Part 1a (N=21) NEAE n (%)	Part 1b (N=20) NEAE n (%)
EAE related to S095029	9 (42.9)	12 (60.0)
SEAE	7 (33.3)	7 (35.0)
SEAE related to S095029	-	1 (5.0)
Grade 3 or higher EAE	10 (47.6)	7 (35.0)
Grade 3 or higher EAE related to S095029	-	1 (5.0)
EAE leading to death	2 (9.5)	-
EAE related to S095029 leading to death	-	-
EAE leading to S095029 withdrawal (WEAE)	-	1 (5.0)
Related WEAE	-	1 (5.0)

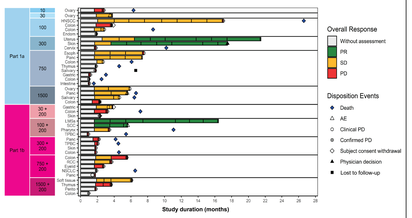
CRS = cytokine release syndrome; DLT = dose-limiting toxicity; EAE = emergent adverse events; NEAE = number of emergent adverse events; SEAE = serious emergent adverse events; WEAE = withdrawal emergent adverse events

Table 4. Related EAEs

EAE related to S095029	Part 1a (N = 21)		Part 1b (N=20)	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
All	9 (42.9)	-	12 (60.0)	1 (5.0)
Nausea	2 (9.5)	-	1 (5.0)	-
Diarrhea	2 (9.5)	-	-	-
Gastroesophageal reflux disease	1 (4.8)	-	-	-
Immune-mediated enterocolitis	-	-	1 (5.0)	1 (5.0)
Chills	2 (9.5)	-	1 (5.0)	-
Fatigue	2 (9.5)	-	1 (5.0)	-
Pyrexia	-	-	1 (5.0)	-
Pruritus	-	-	3 (15.0)	-
Rash maculopapular	-	-	3 (15.0)	-
Alopecia	1 (4.8)	-	-	-
Rash	-	-	1 (5.0)	-
Infusion-related reaction	1 (4.8)	-	3 (15.0)	-
Headache	1 (4.8)	-	1 (5.0)	-
Dizziness	1 (4.8)	-	-	-
Immune-mediated hypothyroidism	1 (4.8)	-	-	-
Immune-mediated hepatitis	1 (4.8)	-	-	-
Tumor pain	-	-	1 (5.0)	-
Hot flush	-	-	1 (5.0)	-

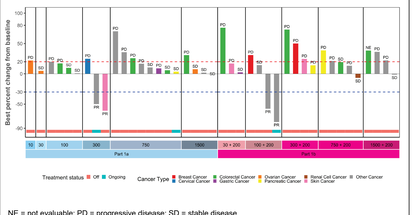
EAE = emergent adverse events

Figure 2. Patient status by investigator assessment per RECIST v1.1



AE = adverse event; endom = endometrial; esoph = esophageal; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small cell lung cancer; panc = pancreatic; PD = progressive disease; peritn = peritoneal; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TPBC = triple-negative breast cancer

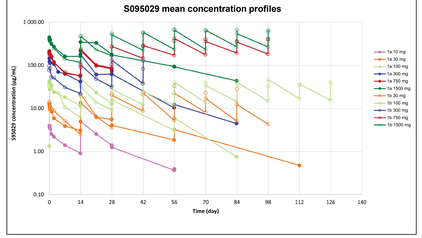
Figure 3. Percent change from baseline in tumor size by dose level



NE = not evaluable; PD = progressive disease; SD = stable disease

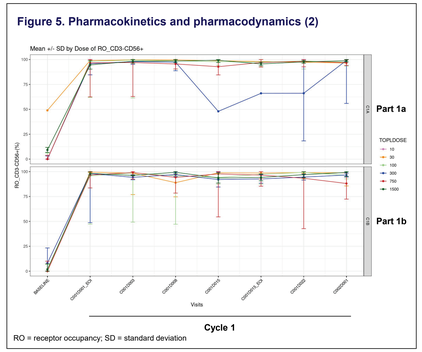
- Based on preliminary data on a limited number of patients, the exposure of S095029 increased with the dose between 10 and 1500 mg.
- The PK exposure of S095029 was apparently not affected by the co-administration of an anti-PD1.
- The median S095029 half-life was 8 days.
- Overall, accumulation based upon C_{trough} (before S095029administration) appeared to be moderate at least up to cycle 5, after a Q2W administration.
- No treatment-induced S095029 ADA detected.

Figure 4. Pharmacokinetics and pharmacodynamics (1)



- **Full NKG2A receptor occupancy** in whole blood was achieved starting from low doses of **30 mg Q2W** in monotherapy arm S095029 (part 1a) and combination arm (part 1b) S095029+Sym021.
- **Retained** and full NKG2A receptor occupancy by S095029 throughout **entire dosing interval.**
- The data represent the **mean of percentage of** receptor occupancy at the 5 doses of the study in the complete cohort, n=41 patients, during the first cycle of treatment.

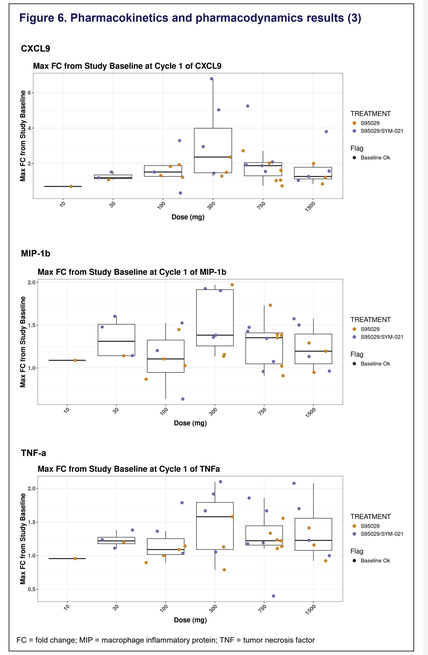
Figure 5. Pharmacokinetics and pharmacodynamics (2)



RO = receptor occupancy; SD = standard deviation

- **Longitudinal analysis of soluble factors,** including CXCL9, TNF-alpha, and MIP-1b, was performed in frozen plasma at the following time points: baseline, C1D1, C1D8, C1D15, and C1D22. Results are presented as maximum fold change from baseline.
- **CXCL9** levels tended to increase in plasma of patients following treatment with S095029 and S095029+Sym021, suggesting immune cell activation upon treatment.

Figure 6. Pharmacokinetics and pharmacodynamics results (3)



FC = fold change; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor