Pharmacodynamic characterization of PRS-344/S095012, a PD-L1x4-1BB antibody-Anticalin fusion protein (Mabcalin), in a dose escalation study in patients with advanced solid tumors

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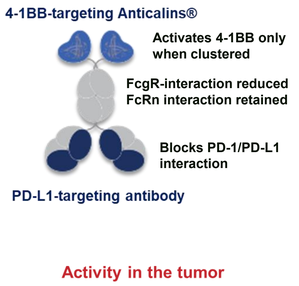
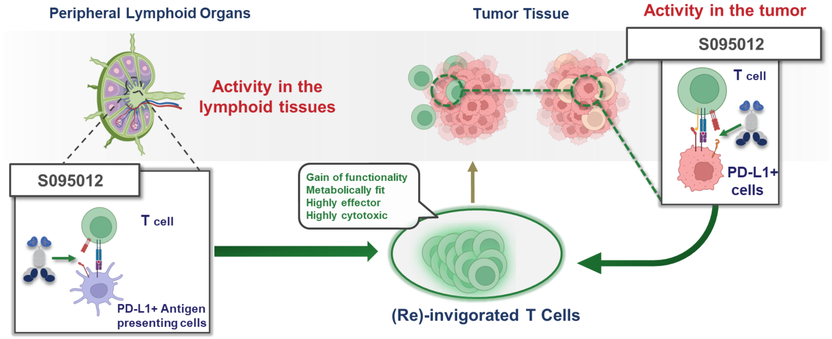
Introduction

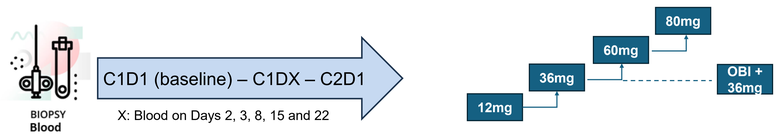
Conditional 4-1BB activation has emerged as an attractive strategy to overcome the hepatoxicity or suboptimal efficacy associated with 1St generation 4-1BB agonistic Mabs. S095012 is a PD-L1/4-1BB bispecific molecule designed to improve the efficacy of immune checkpoint inhibition while providing conditional 4-1BB co-stimulation i.e PD-L1 dependent 4-1BB trimerization and signaling as previously demonstrated in preclinical experiments (Peper-Gabriel JK et al., 2022). Here we report the Biomarker and pharmacodynamic results of S095012 in dose escalation study in patients with solid tumors.





S095012 is expected to stimulate antigen-experienced T cells both in the tumor and in peripheral lymphoid organs, where PD-L1 can be expressed.

Methods



45 patients received PRS-344/S095012 (12–80 mg IV) Q2W. A cohort of 12 patients at the 36mg dose level was pre-treated with Obinutuzumab (OBI) to mitigate anti-drug antibody (ADAs) formation. Plasma and PBMCs were collected pre-dose (Cycle 1 Day 1), and on-treatment (during cycle 1) to analyze pharmacodynamic biomarkers. DNA sequencing on PBMCs was used to evaluate changes in T cell receptor (TCR) diversity and clonality of T cell responses following treatment. Baseline tumor biopsies were analyzed by immunohistochemistry (IHC) to evaluate PD-L1 expression and immune infiltrates.

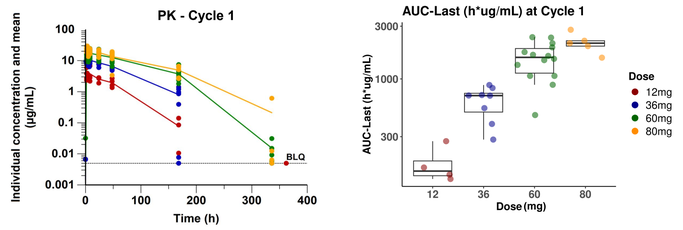
Conclusions

- **S095012 induced a potent, dose-dependent increase in systemic immune activation, which was further amplified by OBI pre-treatment, correlating with irAEs.**
- **Objective responses in patients with PD-L1+ tumors, consistent with MoA.**
- **A target with more specific tumor expression than PD-L1 might be better suited for selective 4-1BB agonism to minimize immune toxicities related to systemic immune cell activation.**

Results

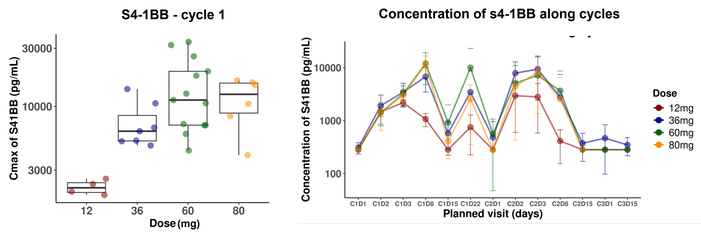
S095012 triggers robust immune activation

Pharmacokinetics Profile of S095012 Dosed Q2W



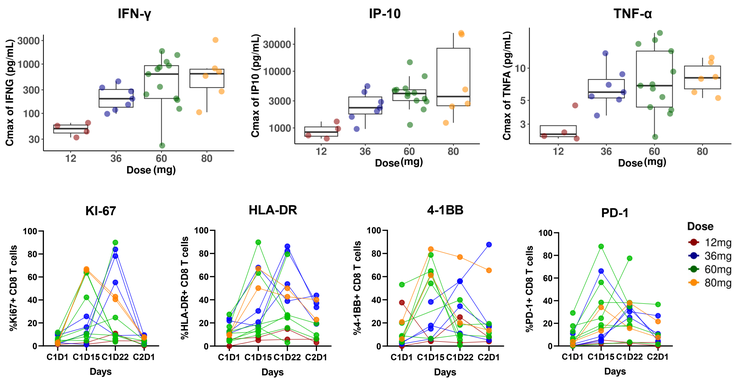
- Non-linear PK profile with exposure increasing non-proportionally to the dose
- Potential target-mediated drug disposition (TMDD) observed across dose levels.

Soluble 4-1BB (Target Engagement)



- A dose dependent increase in total soluble 4-1BB (s4-1BB) was observed, demonstrating engagement of 4-1BB target.
- No plateau or bell shape observed up to the 80mg Q2W dose.

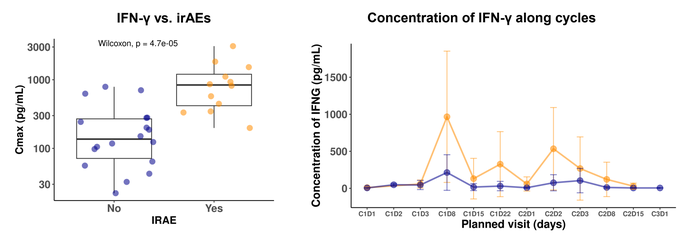
Plasma cytokines and CD8 T cell immunophenotyping



- A dose dependent increase in proinflammatory cytokines (IFN-γ, IP-10, and TNF-α) was observed in cycle 1 with no plateau or bell shape effect at tested doses.
- Remarkable levels of IFN-γ were induced by S095012 especially at the 60mg-80mg dose levels.
- Immunophenotyping by flow cytometry showed substantial increase in CD8 T cell proliferation and activation markers at 36mg dose and above.

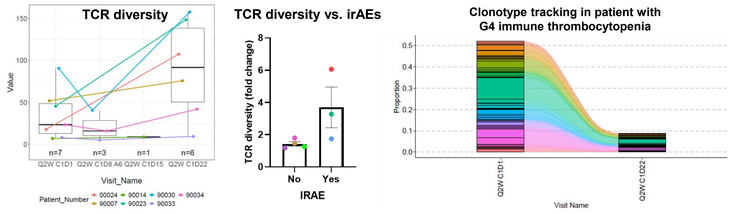
S095012-induced systemic immune activation correlated with irAEs

IFN-γ levels induced in cycle 1 vs. irAEs



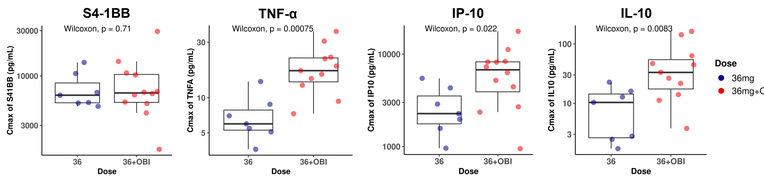
- High levels of IFN-γ (>300pg/ml) induced by S095012 in the first treatment cycle correlated with increased incidence of all grade immune-related adverse events (irAEs).

T cell repertoire diversity in the blood



- S095012 induced an increase in T cell repertoire diversity in the blood which was more pronounced in patients with irAEs suggesting polyclonal T cell activation.
- Example of patient with G4 immune thrombocytopenia shows a strong decrease in T cell clonality (increased diversity) after treatment consistent with polyclonal T cell activation.

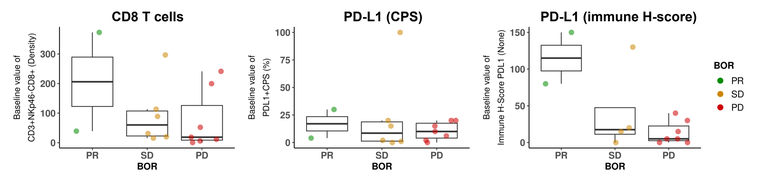
Impact of OBI pre-treatment on immune activation



- OBI pre-treatment did not impact levels of 4-1BB target engagement but led to higher levels of cytokines in cycle 1 compared to the same dose level (36mg) without OBI.

Correlation between baseline PD-L1 expression and response to S095012

CD8 and PD-L1 expression in baseline biopsies



- Overall, Low CD8 T cell density in most tumors at baseline except in one patient with PR.
- Most tumors were PD-L1+ with higher PD-L1 immune H-score in responding patients.

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