Combination of cinrebafusp alfa with ramucirumab and paclitaxel is well tolerated and elicits encouraging clinical activity in patients with HER2-positive gastric/gastroesophageal junction (GEJ) adenocarcinoma

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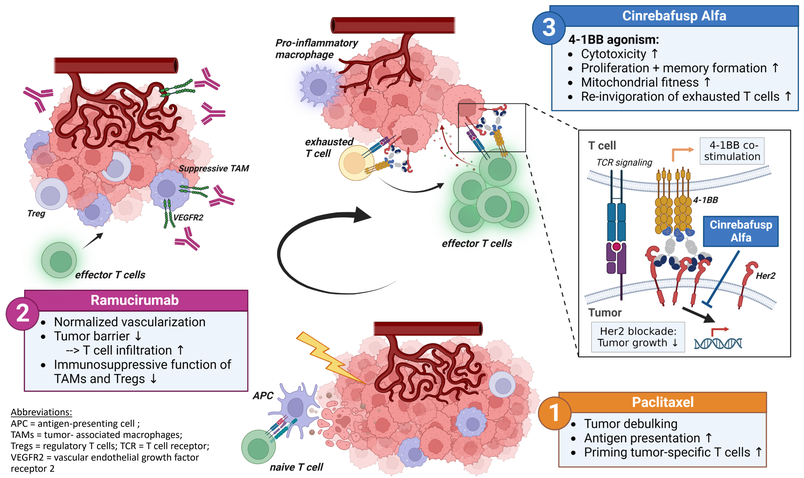
Geoffrey Ku[1], Jeeyun Lee[2], Kayti Aviano[3], Tim Demuth[4,5], Laura-Carolin Hasenkamp[4], Shane A Olwill[4]

[1]Memorial Sloan Kettering Cancer Center (MSKCC), New York City, NY; [2]Samsung Medical Center, Seoul, South Korea; [3]Pieris Pharmaceuticals Inc, Boston, MA; [4]Pieris Pharmaceuticals GmbH, Hallbergmoos, Germany; [5]MorphoSys AG, Planegg, Germany (current affiliation)

Background

- Anticalin® proteins are recombinant proteins based on human lipocalins.
- Cinrebafusp alfa (PRS-343), a first-in-class bispecific antibody-Anticalin fusion protein, targets both HER2 on tumor cells and the receptor 4-1BB (CD137) on T cells.
- Cinrebafusp alfa promotes tumor-localized 4-1BB clustering and activation by bridging T cells with HER2-positive tumor cells, providing a potent costimulatory signal to tumor-antigen-specific T cells.
- In a previous Phase I monotherapy study (NCT03330561), cinrebafusp alfa was found to be generally safe and showed durable responses in patients with HER2-positive gastrointestinal malignancies at doses of 8mg/kg Q2W (43% ORR) and 18mg/kg Q2W (25% ORR) (Piha-Paul, AACR Annual Meeting 2021).
- Here, we present the design and preliminary data of the ongoing Phase II PRS-343_PCS_09_20 clinical trial in patients with gastric/ gastroesophageal junction (GEJ) cancer (NCT05190445).

Rationale for Treatment Combination



Abbreviations:
APC = antigen-presenting cell ;
TAMs = tumor- associated macrophages;
Tregs = regulatory T cells; TCR = T cell receptor;
VEGFR2 = vascular endothelial growth factor receptor 2

Figure 1. Rationale for combining cinrebafusp alfa with ramucirumab & paclitaxel – Complementary mode of action.
1) Paclitaxel is a chemotherapeutic drug and promotes microtubule polymerization & stabilization, leading to death of tumor cells and release of tumor antigens, thereby enhancing immunogenic responses. **2) Ramucirumab** inhibits VEGF-mediated tumor angiogenesis, inducing vascular normalization and contributing to increased T cell penetration. **3) Cinrebafusp alfa** acts as HER2-dependent 4-1BB agonist, leading to clustering of 4-1BB on T-cell surfaces, thereby increasing T cell activation, proliferation, tumor cytolytic activity, and memory formation amongst others. Figure created with Biorender.com

Methods

Study design

- Phase II, multi-center, open-label study of cinrebafusp alfa in combination with standard doses of ramucirumab and paclitaxel.
- Patients enrolled receive cinrebafusp alfa in a dosing scheme of 18mg/kg Q2W in cycle 1 (loading dose) followed by 8mg/kg Q2W in subsequent cycles (maintenance dose).
- Dosing of cinrebafusp alfa and ramucirumab occurs at day 1 and day 15 of each cycle, while paclitaxel is administered on day 1, day 8, and day 15 of each cycle.

Primary endpoint

- Objective response rate (ORR) per RECIST1.1.

Key Secondary endpoints

- Treatment emergent adverse events (TEAEs).
- Disease control rate (DCR = CR + PR + SD).
- Duration of response (DOR).

Key Inclusion criteria

- Histologically or cytologically confirmed gastric or GEJ adenocarcinoma.
- Confirmed HER2 status (IHC 3+ or IHC 2+ with positive [F]ISH).
- 1-2 prior treatment regimens including platinum, fluoropyrimidine, and HER2-directed therapy (prior therapy with T-DXd is allowed).
- ECOG performance status 0 or 1.

Results

Patient characteristics

At time of data cut-off (28th Feb 2023), 5 patients were enrolled and received at least 1 dose of study treatment; of those, 3 patients remain on treatment.

Characteristics		Total (n=5)
Age , median (range), years		61 (43-68)
Sex	Male	5
	Female	0
Country	United States	4
	South Korea	1
ECOG performance status	0	2
	1	3
Time from initial diagnosis in months, median (range)[1]		52 (11.4 - 61.2)
Prior anticancer regimes	1 prior line	2
	2 prior lines	3
	Chemotherapy	5
	Trastuzumab	5
	T-DXd	3
	PD-1/PD-L1 inhibitors	5
HER2 expression (IHC)[2]	3+	5
	2+	0

[1] Calculated as (date of study entry - date of initial diagnosis +1) x 12/365.25
[2] Local assessment

Safety

- At data cut-off, the most commonly reported drug related TEAEs were fatigue (60%), diarrhea (60%), and nausea (60%).
- The most commonly reported TEAEs ≥ grade 3 were febrile neutropenia (40%) and neutrophil count decreases (40%); no grade 5 events have occurred.
- 5 SAEs occurred in 3 patients (60%), 3 deemed related to study drug but none deemed related to cinrebafusp alfa.

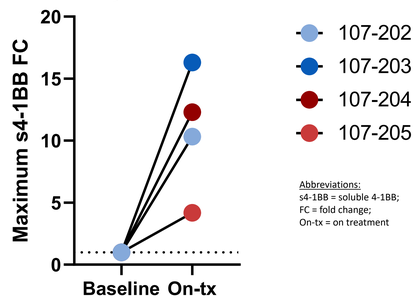
Tolerability

5 patients (100%) required dose reduction of paclitaxel: dosing at day 8 being skipped eventually due to AEs of neutrophil count decreased (Grade 2-4) and/or platelet count decreased (Grade 1-3).

In addition, the following dose modifications/interruptions occurred as of data cut-off:

- 1 patient (20%) experienced recurrent Grade 2-3 Infusion related reactions (IRRs) despite pre-medication, leading to dose interruption and eventually discontinuation of cinrebafusp alfa.
- Drug interruption of ramucirumab and paclitaxel occurred in 1 patient (20%) each, due to Grade 2 pruritus and Grade 2 urticaria (ramucirumab) and Grade 2 IRR (paclitaxel).

Pharmacodynamic markers



Abbreviations:
s4-1BB = soluble 4-1BB;
FC = fold change;
On-tx = on treatment

Figure 2. Maximum fold change of soluble 4-1BB (s41BB) throughout study. Samples from 4 patients taken at various timepoints during the study have been analyzed. All 4 patients show induction of s4-1BB upon treatment with cinrebafusp alfa compared to baseline indicating effective target engagement to 4-1BB and activation of the 4-1BB pathway.

Efficacy

- The unconfirmed ORR is 100% (5/5), the confirmed[3] ORR is 60% (3/5).
- DCR is 100% with BOR of partial response (PR) for all 5 patients (100%).
- Median DOR[4] as of cut-off date is 3.8 months (range: 1.9 – 6.8 months).

[3] Response was confirmed by confirmatory scan at least 4 weeks after initial response
[4] Calculated as date of first response until date of documented disease progression or most recent scan

Figure 3. Swimmer plot shows durable responses with most patients on treatment for over 150 days.
For patient 107-204, treatment was on hold between study day 161 and 267 due to an AE not related to study drug. During the treatment break the tumor increased in size to 20.2 mm compared to 15.7 mm at baseline. Following the physician's decision in accordance with the Sponsor, the patient remains on treatment given they responded prior to treatment break.

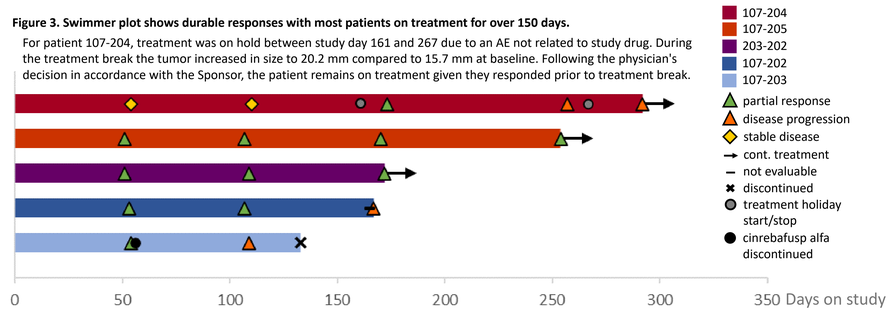


Figure 4. Waterfall plot with best change from baseline, all 5 patients achieved PR as BOR.

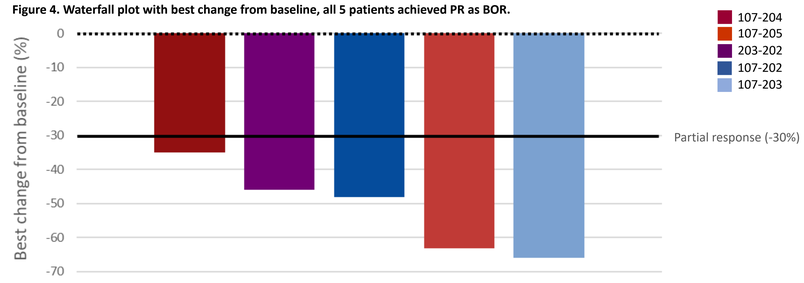
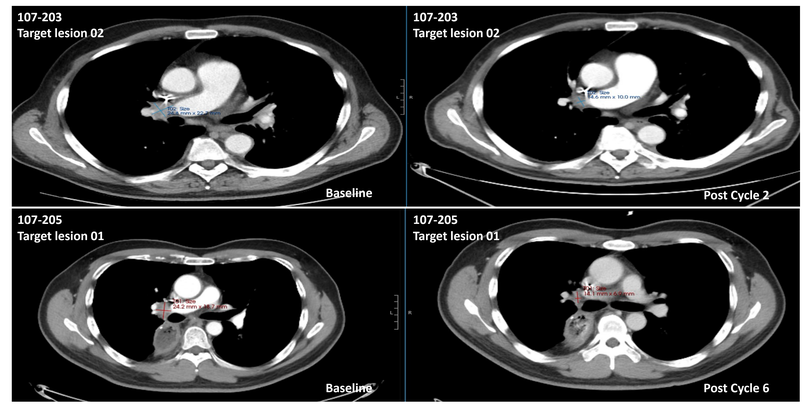


Figure 5: CT scans from baseline (left) and on-treatment (right) for 2 patients.



Conclusions

- The combination of cinrebafusp alfa with ramucirumab and paclitaxel has demonstrated encouraging signs of clinical activity (5/5 PRs).
- Noteworthy, cinrebafusp alfa with ramucirumab and paclitaxel can elicit clinical responses in patients who have progressed on T-DXd or checkpoint inhibitor regimens.
- The combination of cinrebafusp alfa with ramucirumab and paclitaxel demonstrates an emerging safe and tolerable profile.
- Preliminary data on s4-1BB confirms effective activation of the 4-1BB pathway in T cells.

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