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Phase 1 Dose Escalation Study of PRS-343, a HER2/4-1BB Bispecific Molecule, in Patients with HER2+ Malignancies

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Disclosures

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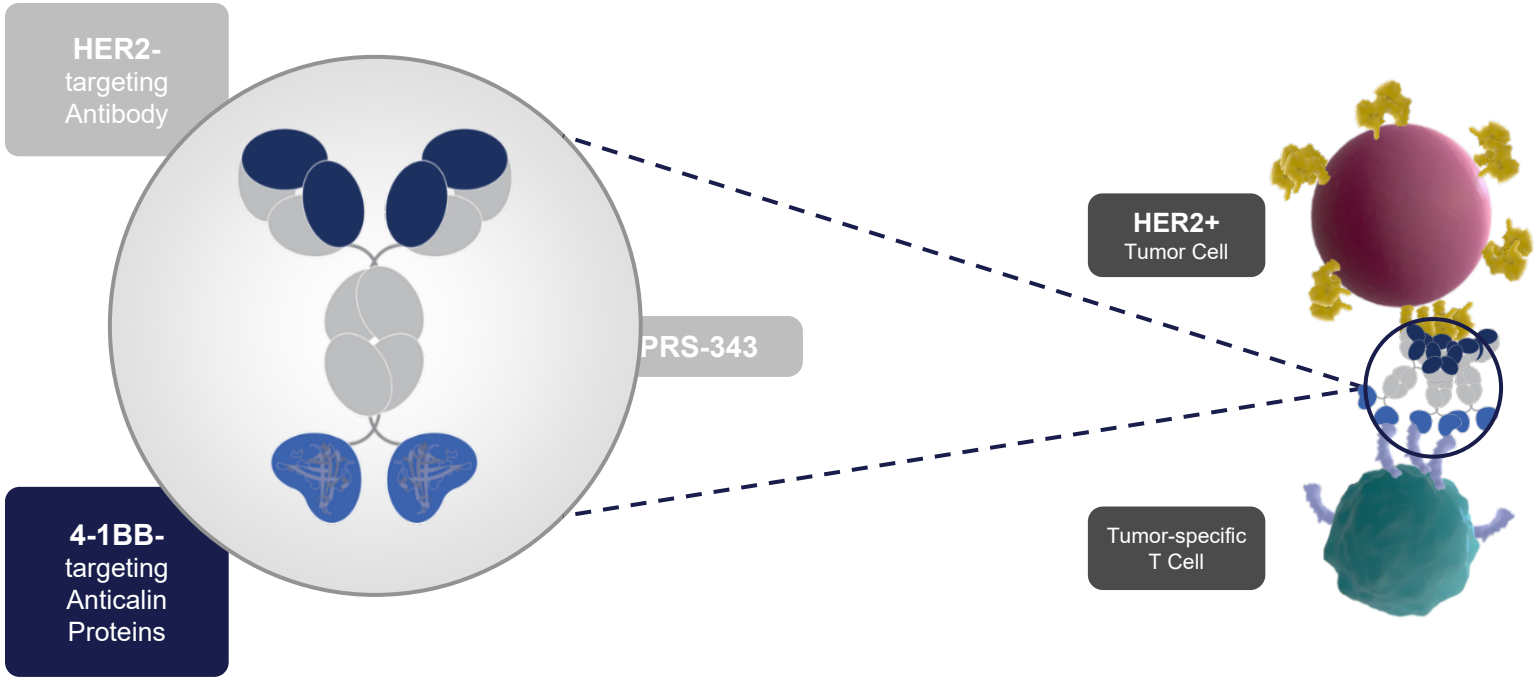
PRS-343: A HER2 4-1BB Bispecific

HER2-targeting moiety of the drug localizes to the tumor microenvironment and facilitates 4-1BB cross-linking

4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion



Study Design

Primary Objectives

- Characterize safety profile
- Identify MTD or RP2D

Secondary Objectives

- Characterize PK profile
- Investigate dosing schedule
- Assess potential immunogenicity and PD effects
- Investigate efficacy

Active schedules

Schedule 1:
Q3W dosing on Day 1

Schedule 2 :
Q2W dosing on Days 1, 15

Current Enrollment

Dose Level	No. Patients	Dose (mg/kg)
1	1	0.0005 (Q3W)
2	1	0.0015
3	1	0.005
4	2	0.015
5	2	0.05
6	5	0.15
7	7	0.5
8	6	1
9	6	2.5
10	9	5
11	7	8
11b	6	8 (Q2W)
Total	53	

Data cut-off: 23-Oct-19 for subjects up to Cohort 11b; additional cohorts enrolling

Key Enrollment Criteria

Inclusion Criteria

- **Diagnosis of HER2+ advanced/metastatic solid tumor malignancy that has progressed on standard therapy or for which no standard therapy is available**
- **HER2+ solid tumors documented by ASCO, CAP or institutional guidelines**
- **Patients with breast, gastric and GEJ cancer must have received at least one prior HER2-targeted therapy for advanced / metastatic disease**
- Measurable disease per RECIST v1.1
- ECOG 0 or 1
- Adequate liver, renal, cardiac and bone marrow function

Exclusion Criteria

- **Ejection fraction below the lower limit of normal with trastuzumab and/ or pertuzumab**
- **Systemic steroid therapy or any other form of immunosuppressive therapy within seven days prior to registration**
- Known, symptomatic, unstable or progressing CNS primary malignancies
- Radiation therapy within 21 days prior to registration (limited field radiation to non-visceral structures is allowed, e.g., limb bone metastasis)

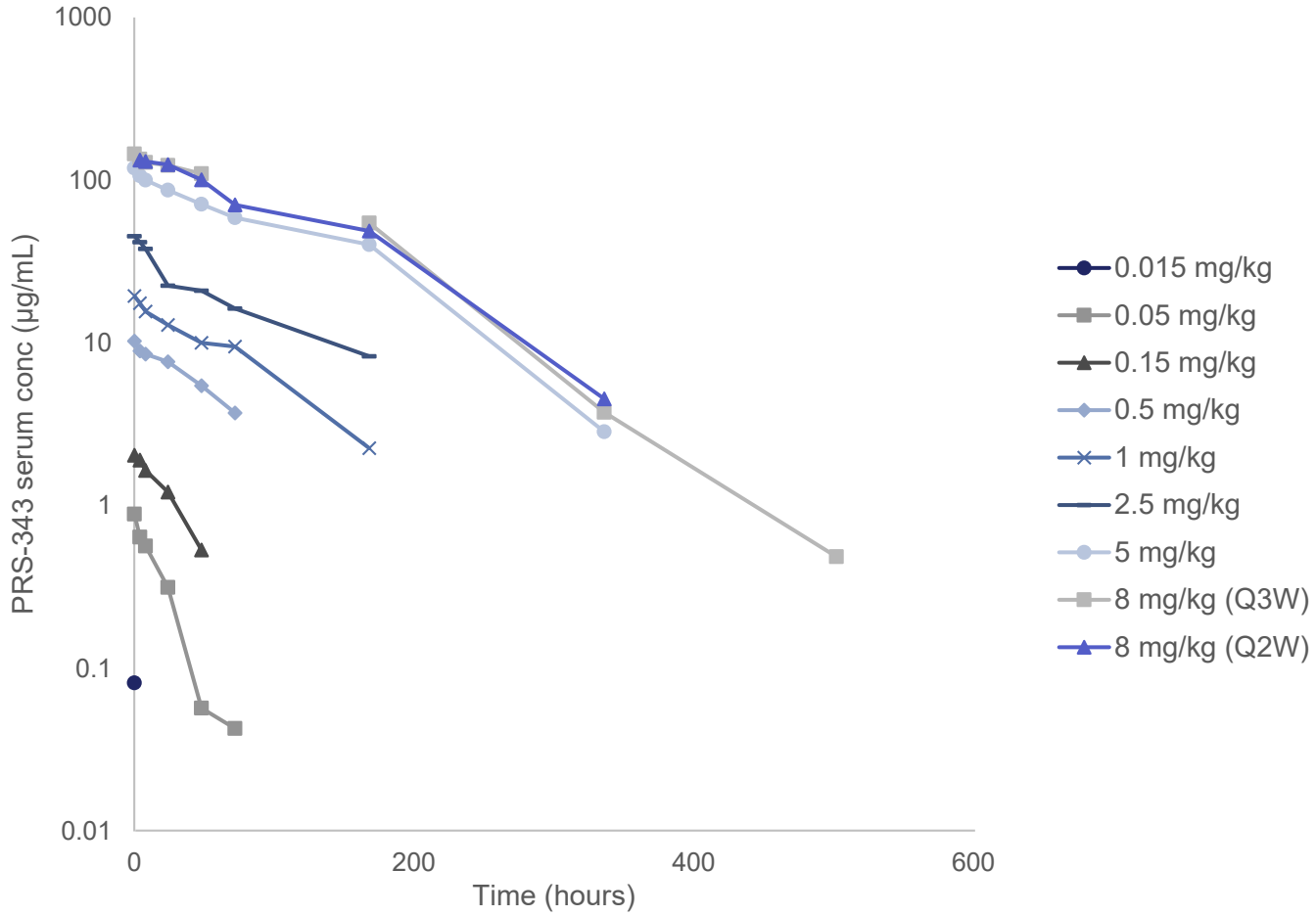
Baseline Characteristics
All Subjects (n = 53)

Characteristic	n (%)
Age, Median (range)	61 (29–92)
Gender	
F	33 (62%)
M	20 (38%)
ECOG PS	
0	12 (23%)
1	41 (77%)
Prior Therapy Lines	
1	6 (11%)
2	5 (9%)
3	11 (21%)
4	10 (19%)
5+	21 (40%)
Median no. of anti-HER2 Treatments	
Breast	4
Gastric	2

Primary Cancer Type	n (%)
Gastroesophageal	19 (36%)
Breast	14 (26%)
Gynecological	6 (11%)
Colorectal	5 (9%)
Gallbladder/ Biliary	4 (8%)
Bladder	2 (4%)
Pancreatic	1 (2%)
Other – Salivary Duct	1 (2%)
Other – Melanoma	1 (2%)

Data cut-off: 23-Oct-19

PRS-343 Clinical Pharmacology



Note: PRS-343 concentrations are below limit of quantification for dose levels < 0.015 mg/kg

Preliminary PRS-343 Pharmacology Profile

- Preliminary PK: Mean terminal half-life of PRS-343 is approximately five days
- 27.8% of patients are ADA+ with titers above 1:150 in cohorts covering active dose range (≥2.5 mg/kg)

Treatment-Related Adverse Events
All Subjects

Occurred in ≥ 1 Patient	n = 111 | n (%)	% Grade 3
Infusion Related Reaction	10 (9%)	2 (2%)
Fatigue	10 (9%)	1 (1%)
Chills	7 (6%)	0
Flushing	7 (6%)	3 (3%)
Nausea	7 (6%)	0
Diarrhea	7 (6%)	0
Vomiting	6 (5%)	0
Non-Cardiac Chest Pain	5 (4%)	1 (1%)

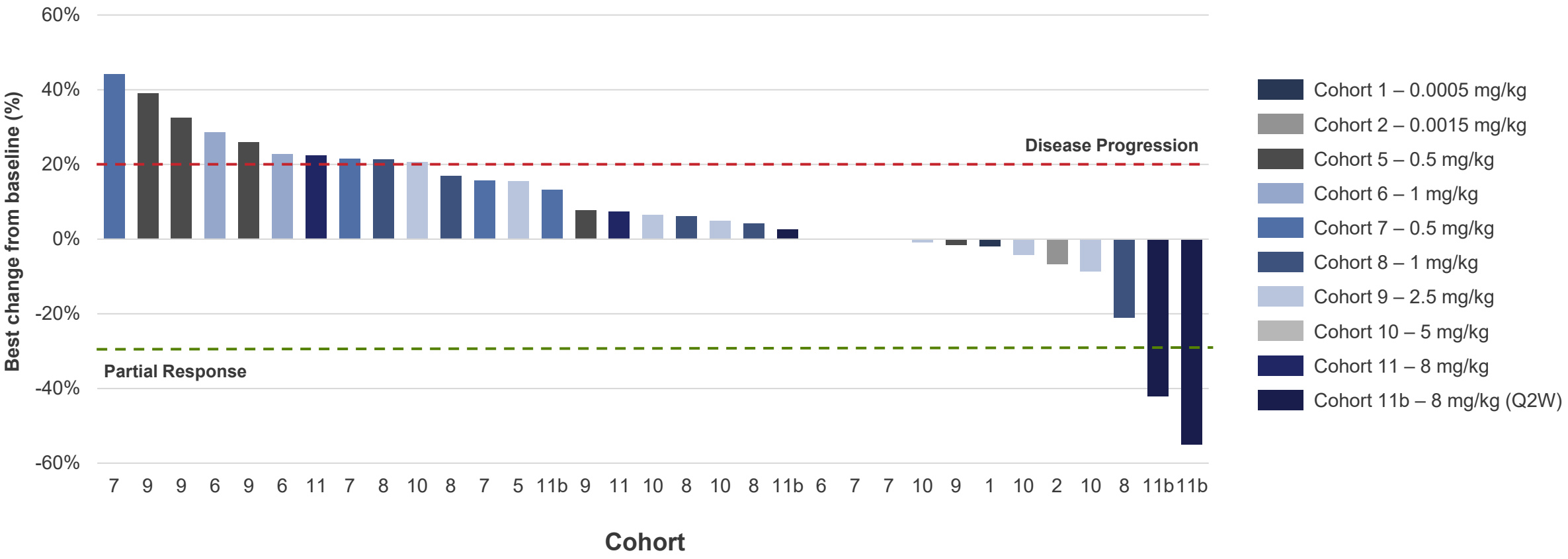
No Grade 4 or 5 Treatment-Related AEs

Summary of Responses at Active Dose Range of PRS-343

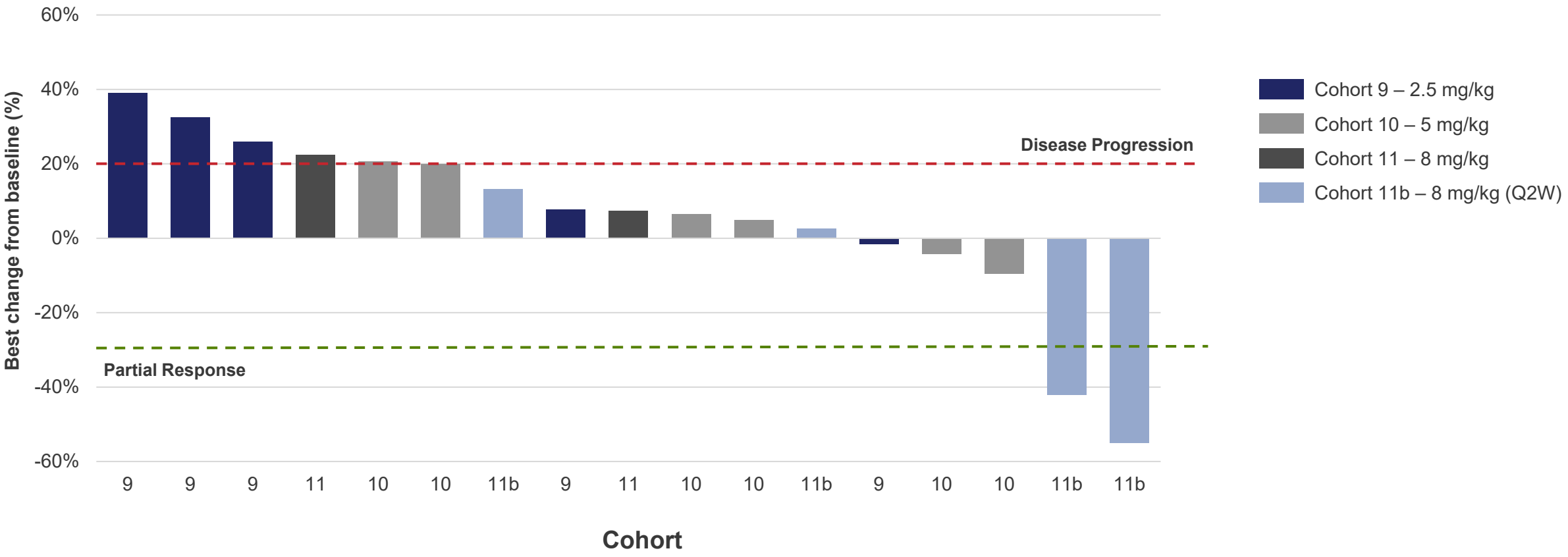
Based on clinical data, serum concentration of > 20 µg/ml defines active dose range (beginning at Cohort 9)

Cohort	11b	11	10	9	Total
Best Response	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Response Evaluable Patients	5	4	4	5	18
PR	2	-	-	-	2
SD	3	2	1	2	8
PD	-	2	3	3	8
ORR	40%	0%	0%	0%	11%
DCR	100%	50%	25%	40%	55%

Best Response in Target Lesions Monotherapy Study Cohorts 1-11b

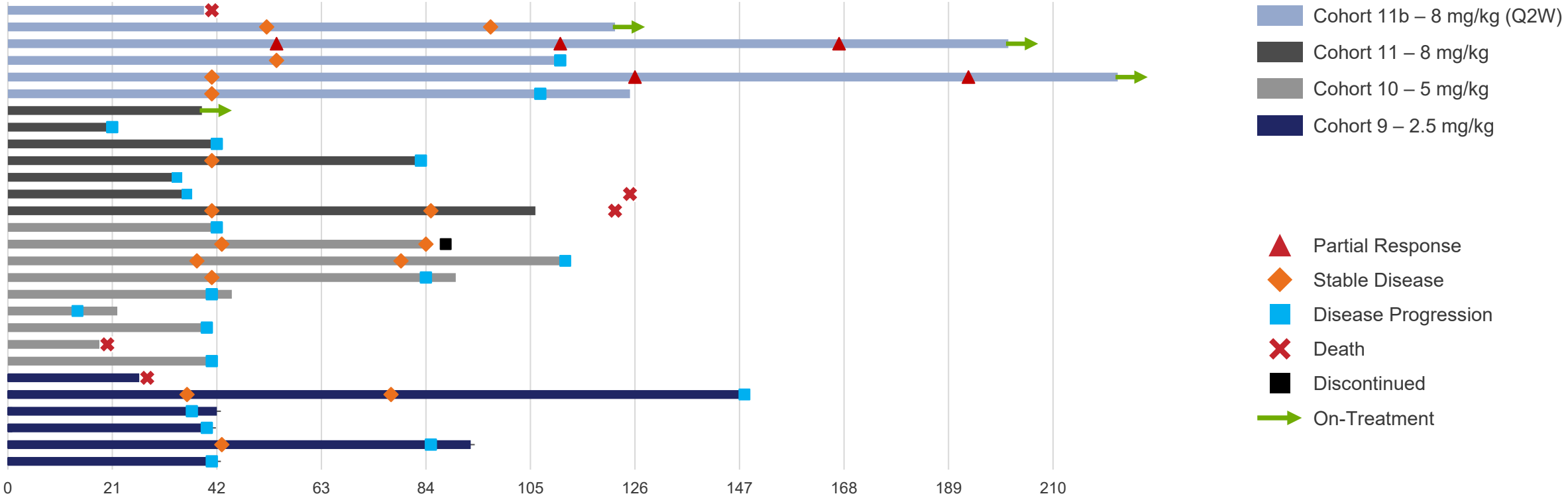


Best Response in Target Lesions Monotherapy Study Cohorts 9-11b



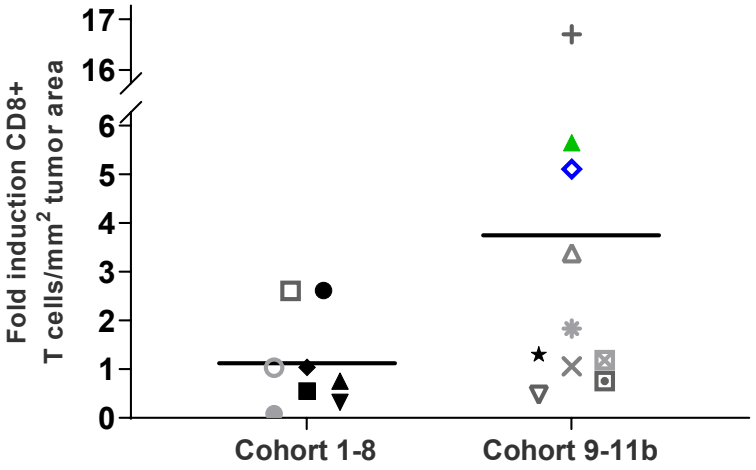
Average Time on Treatment with PRS-343 Significantly Increases in Cohort 11b (8 mg/kg Q2W)

Duration (Days)
Number of Subjects = 28

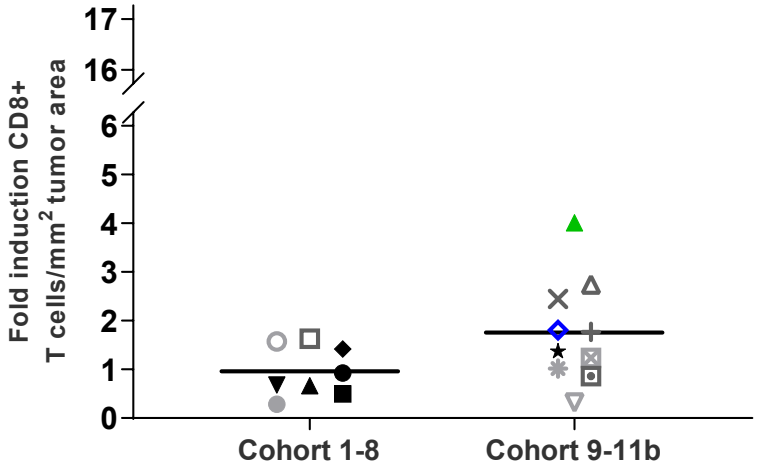


Increased CD8+ T Cell Numbers in Tumor Biopsies Post-Treatment

Tumor



Stroma



Pronounced increase in CD8+ T cell numbers is observed post-treatment in patients receiving doses ≥ 2.5 mg/kg

Patients benefiting from treatment (SD > 120 days (blue) and PR (green) had more pronounced increase in CD8+ T cell number in tumor vs. stroma

Gastric Cancer Patient with Confirmed PR

Patient Profile, Treatment History and RECIST

Patient Profile

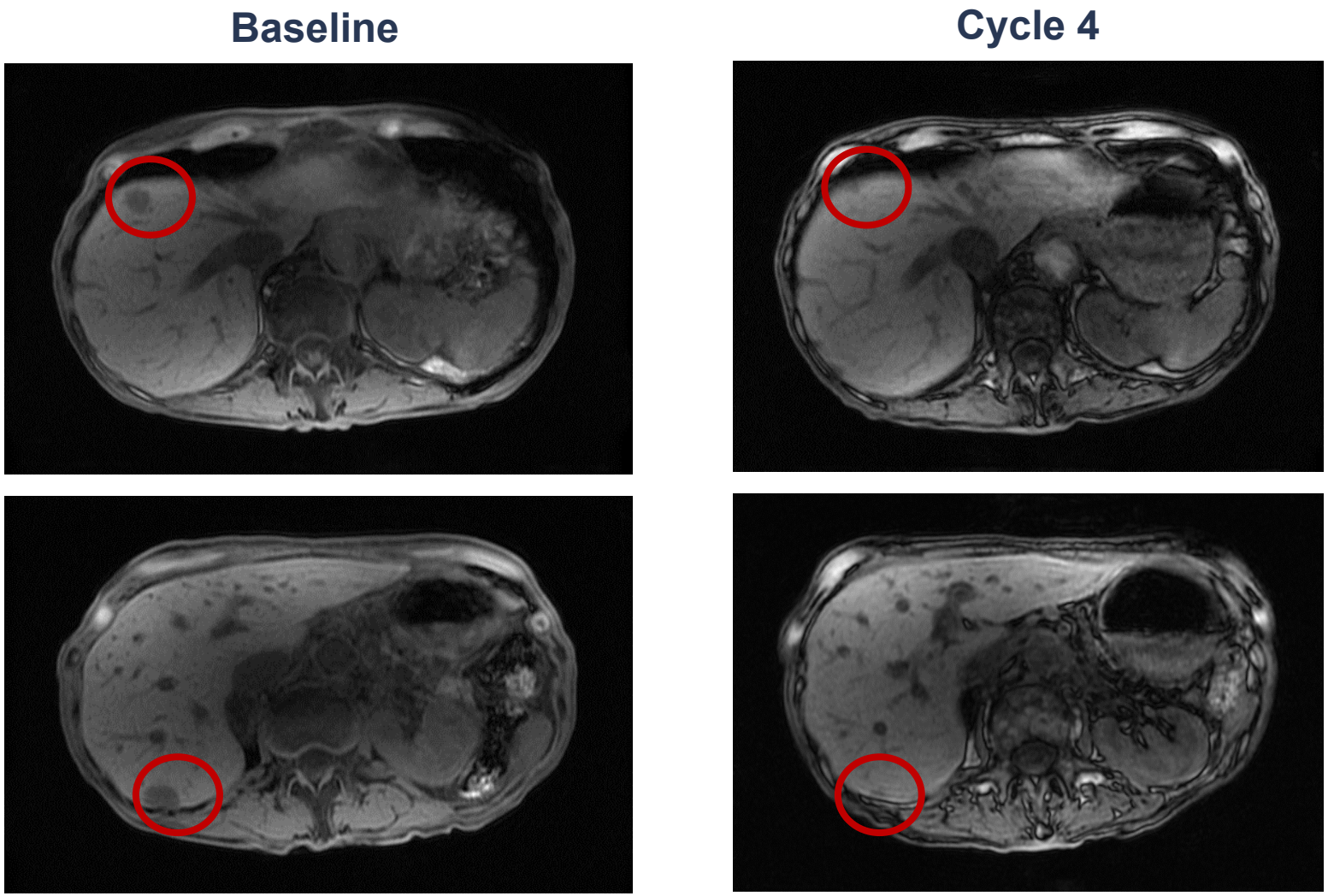
- Cohort 11b | 8 mg/kg every two weeks
- 80-year old woman; initial diagnosis on June 2017
- Stage IV gastric adenocarcinoma
- Metastases to liver, lymph node and adrenal glands
- HER2 IHC 3+; PD-L1 positive (CPS=3)
- NGS: ERBB2 amplification, TP53 mutation, alteration of CDK12 and SF3B1

Oncology Treatment History	Duration	Best Response
Trastuzumab, Pembrolizumab + Capecitabine/oxaliplatin	July 2017 – June 2018	Stable Disease
Nivolumab with IDO1 inhibitor (investigational drug)	Aug 2018 – Jan 2019	Stable Disease

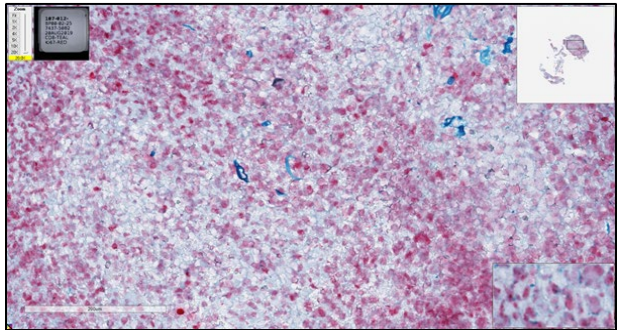
Lesions	Lesion Site	Lesion Size (mm)				
		Baseline	C2 Post-treatment	C3 Post-treatment	C4 Post-treatment	C6 Post-treatment
Target 1	Liver	14	12	10	9	9
Target 2	Liver	20	16	10	8	8
Target 3	Pancreas	19	16	14	14	14
% Change from Baseline			-17%	-36%	-42%	-42%

PR, partial response; HER2, human epidermal growth factor receptor 2; PD-L1, Programmed Death Ligand 1; CPS, combined positive score; NGS, next-generation sequencing

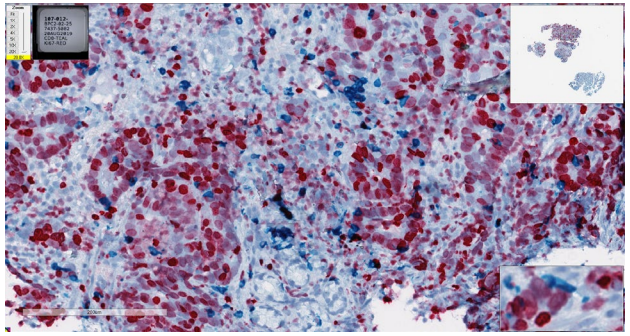
Gastric Cancer Patient with Confirmed Partial Response



CD8+ T Cell Numbers Increase Post-Treatment in Responding Gastric Cancer Patient



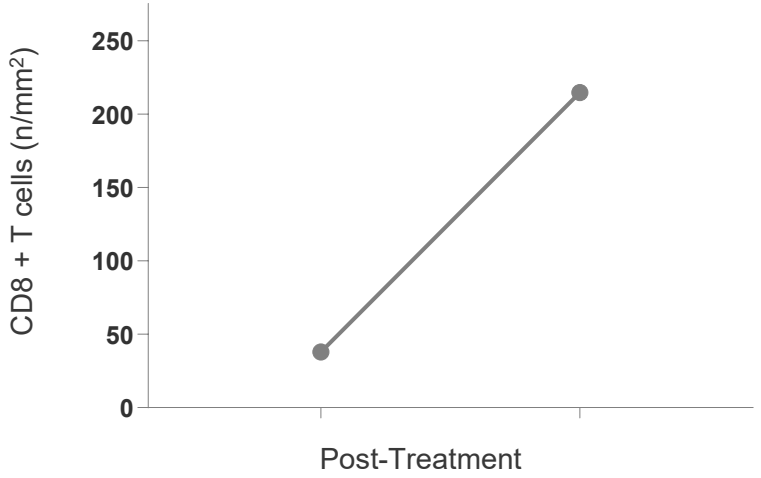
Pre-Treatment (CD8: Teal | Ki67: Red)



Post-Treatment (CD8: Teal | Ki67: Red)

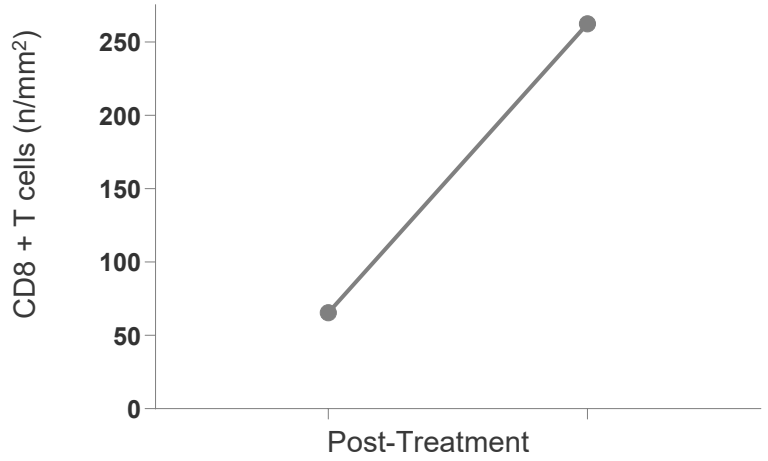
Tumor

CD8 fold change: **5.7** CD8 pre [n/mm^2]: **38**



Stroma

CD8 fold change: **4** CD8 pre [n/mm^2]: **66**



CD8+ T cell numbers increase post-treatment. This is more pronounced in tumor tissue, consistent with the predicted MoA of PRS-343.

Conclusions: PRS-343 as Monotherapy

Well-tolerated, with a good safety profile in all doses and schedules tested

Demonstrated anti-tumor activity in heavily pre-treated patient population across multiple tumor types; treatment history indicative of 4-1BB-driven mechanism-of-action

Showed a clear increase in $CD8^+$ T cell numbers and proliferative index in the tumor microenvironment of responders

Future studies are planned for continued development in defined HER2+ indications

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Appendix

Adverse Events Unrelated to Treatment
All Subjects

Adverse Events Unrelated to Treatment	n = 303 | n (%)
Fatigue	14 (5%)
Abdominal pain	11 (4%)
Anemia	10 (3%)
Constipation	9 (3%)
Decreased appetite	9 (3%)
Dyspnea	9 (3%)
Diarrhea	7 (2%)
Dysphagia	6 (2%)
Nausea	6 (2%)

Adverse Events Unrelated to Treatment	n = 303 | n (%)
Alanine aminotransferase increased	5 (2%)
Blood bilirubin increased	5 (2%)
Headache	5 (2%)
Hyperglycemia	5 (2%)
Pain	5 (2%)
Pruritus	5 (2%)
Vomiting	5 (2%)
Weight decreased	5 (2%)