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ANNUAL MEETING 2021
VIRTUAL #AACR21
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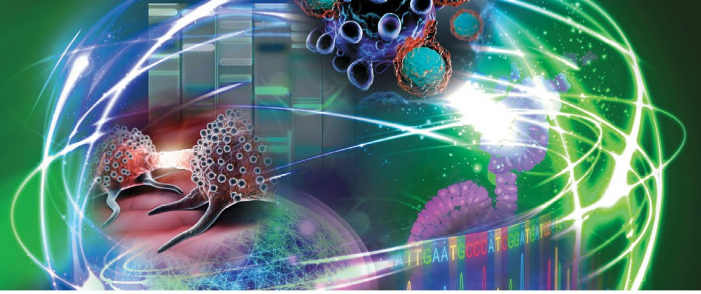

Phase 1 Dose Escalation Study of PRS-343, a HER2/4-1BB Bispecific Molecule, in Patients with HER2+ Malignancies

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Disclosure Information

My Disclosures:

I receive the following Clinical Trial Research Support/Grant Funding through the institution:

AbbVie, Inc.; ABM Therapeutics, Inc.; Acepodia, Inc; Alkermes; Aminex Therapeutics; Amphivena Therapeutics, Inc.; BioMarin Pharmaceutical, Inc; Boehringer Ingelheim; Bristol Myers Squib; Cerulean Pharma, Inc.; Chugai Pharmaceutical Co., Ltd; Curis, Inc.; Daiichi Sankyo; Eli Lilly; ENB Therapeutics; Five Prime Therapeutics; Gene Quantum; Genmab A/S; GlaxoSmithKline; Helix BioPharma Corp.; Incyte Corp.; Jacobio Pharmaceuticals Co., Ltd.; Medimmune, LLC.; Medivation, Inc.; Merck Sharp and Dohme Corp.; Novartis Pharmaceuticals; Pieris Pharmaceuticals, Inc.; Pfizer; Principia Biopharma, Inc.; Puma Biotechnology, Inc.; Rapt Therapeutics, Inc.; Seattle Genetics; Silverback Therapeutics; Taiho Oncology; Tesaro, Inc.; TransThera Bio; and

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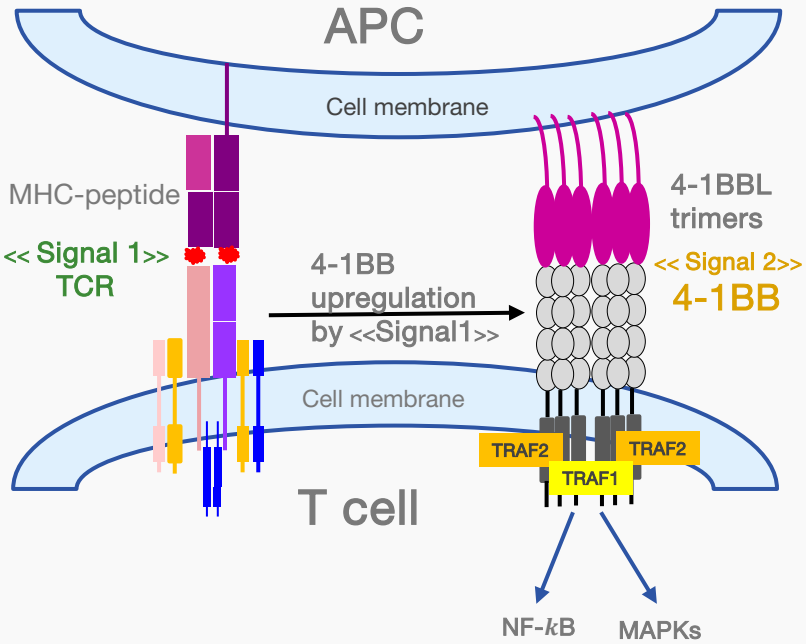
and

I will discuss off label use and/or investigational use in my presentation.

Unique Attributes of 4-1BB Agonism



- Proliferation
- Cytotoxicity
- Cytokine Secretion
- Th1 Polarization
- Memory Formation
- T cell Survival
- Resistance to Exhaustion
- Metabolic Fitness

Pieris' 4-1BB bispecific strategy recognize that 4-1BB agonists have proven clinical potency, yet activity must be localized in order to minimize toxicity and ensure suitable therapeutic index

PRS-343 (Cinrebafusp alfa): HER2 x 4-1BB Bispecific

Drives 4-1BB Agonism in the Tumor Microenvironment of HER2+ Solid Tumors

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

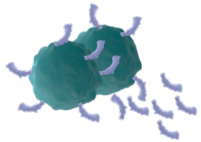
4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion

HER2
targeting
Antibody

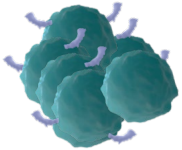
4-1BB
targeting
Anticalin®
Proteins

CLINICALLY-RELEVANT BIOMARKERS

4-1BB Pathway Activation
Soluble 4-1BB



T-cell Proliferation
$CD8^+$ and $CD8^+/Ki67^+$



Ph 1 Monotherapy PRS-343 Study

Study Objectives

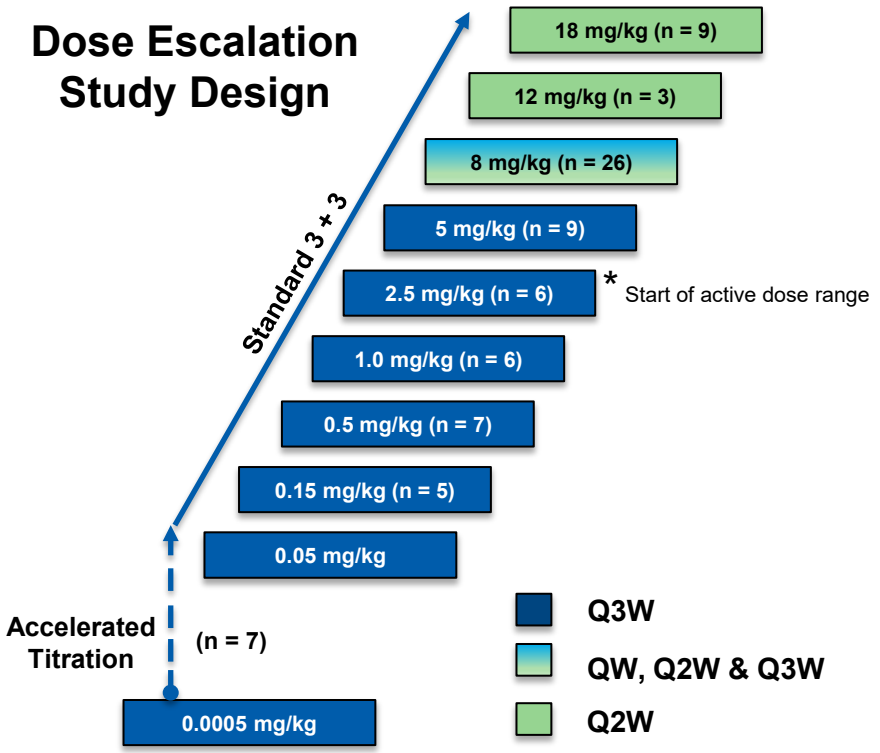
Primary: Characterize Safety Profile
Identify MTD or RP2D

Secondary: Characterize PK/PD & Immunogenicity
Preliminary anti-tumor activity

Key Eligibility Criteria

Inclusion: Metastatic HER2+ solid tumors
Breast & Gastric/GEJ ≥ 1 prior anti-HER2 Tx
Measurable disease (RECIST v1.1)
ECOG 0 or 1

Exclusion: Symptomatic or unstable brain metastasis
Abnormal cardiac EF (< 45%)



Baseline Characteristics (N = 78)

Characteristic	n (%)
Age, Median (range)	**63 (24–92)**
Gender	
F	**46 (59%)**
M	**32 (41%)**
ECOG PS	
0	**19 (24%)**
1	**59 (76%)**
Prior Therapy Lines	
1	**11 (14%)**
2	**10 (13%)**
3	**16 (21%)**
4	**12 (15%)**
5+	**29 (37%)**
Median # of anti-HER2 Tx	
Breast	**6**
Gastric	**2**

Primary Cancer Type	n (%)
Gastroesophageal	**34 (44%)**
Breast	**16 (21%)**
Colorectal	**12 (15%)**
Gynecological	**9 (12%)**
Bladder	**2 (3%)**
Pancreatic	**1 (1%)**
Other – Cancer of Unknown Origin	**2 (3%)**
Other – Salivary Duct	**1 (1%)**
Melanoma	**1 (1%)**

PRS-343 Treatment Related Adverse Events at Active Doses (≥ 2.5 mg/kg)

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Treatment Related Adverse Events (TRAEs occurring in > 1 patient; n = 53)	All Grades n (%)	Grade 1-2 n (%)	Grade 3-4 n (%)
Infusion related reaction	13 (25%)	9 (17%)	4 (8%)
Nausea	7 (13%)	7 (13%)	
Chills	6 (11%)	6 (11%)	
Vomiting	6 (11%)	6 (11%)	
Dyspnoea	4 (8%)	4 (8%)	
Fatigue	4 (8%)	4 (8%)	
Arthralgia	3 (6%)	2 (4%)	1 (2%)
Decreased appetite	3 (6%)	3 (6%)	
Non-cardiac chest pain	3 (6%)	3 (6%)	
Asthenia	2 (4%)	2 (4%)	
Diarrhoea	2 (4%)	2 (4%)	
Dizziness	2 (4%)	2 (4%)	
Headache	2 (4%)	2 (4%)	
Paraesthesia	2 (4%)	1 (2%)	1 (2%)
Pruritus	2 (4%)	2 (4%)	
Pyrexia	2 (4%)	2 (4%)	
Rash	2 (4%)	2 (4%)	

1 Gr 3 Ejection Fraction dec and 1 Gr 3 Heart Failure; both events occurred in one patient and resolved w/o sequelae.

PRS-343 Efficacy Data Overview

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Cohort	13b	12b	11c	Obi	11b	11	10	9	Total
Best Response	18 mg/kg, Q2W	12 mg/kg, Q2W	8 mg/kg, QW	8 mg/Kg, Q2W	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Evaluable Patients	8	2	5	4	7	4	7	5	42
CR	1								1
PR	1				3				4
SD	3		1	2	3	3	3	2	17
ORR	25%	0%	0%	0%	43%	0%	0%	0%	12%
DCR	63%	0%	20%	50%	86%	75%	43%	40%	52%

PRS-343 Efficacy Data: Analysis of Patients Treated at Active Doses

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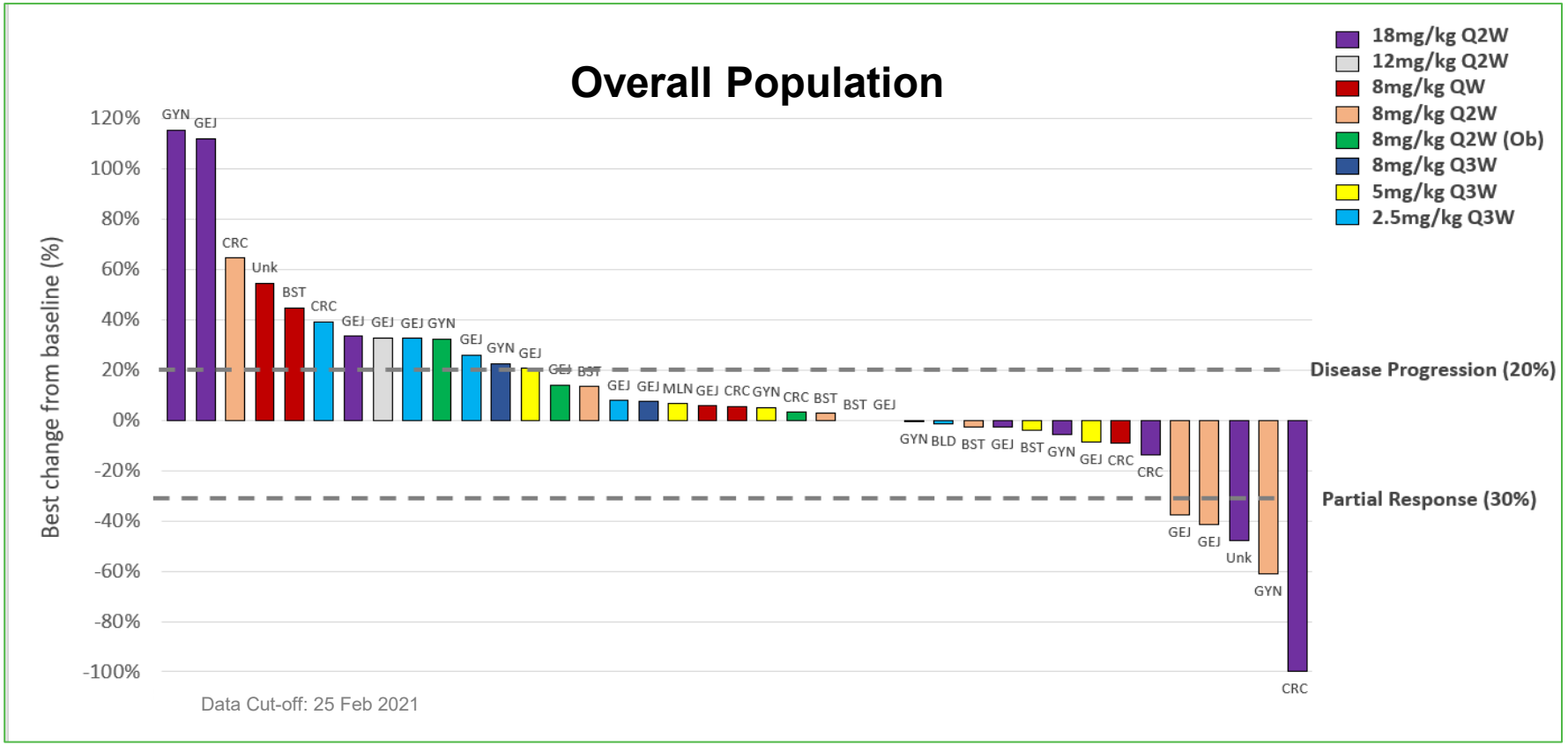

PRS-343 Efficacy Data: Analysis of Patients Treated at Active Doses

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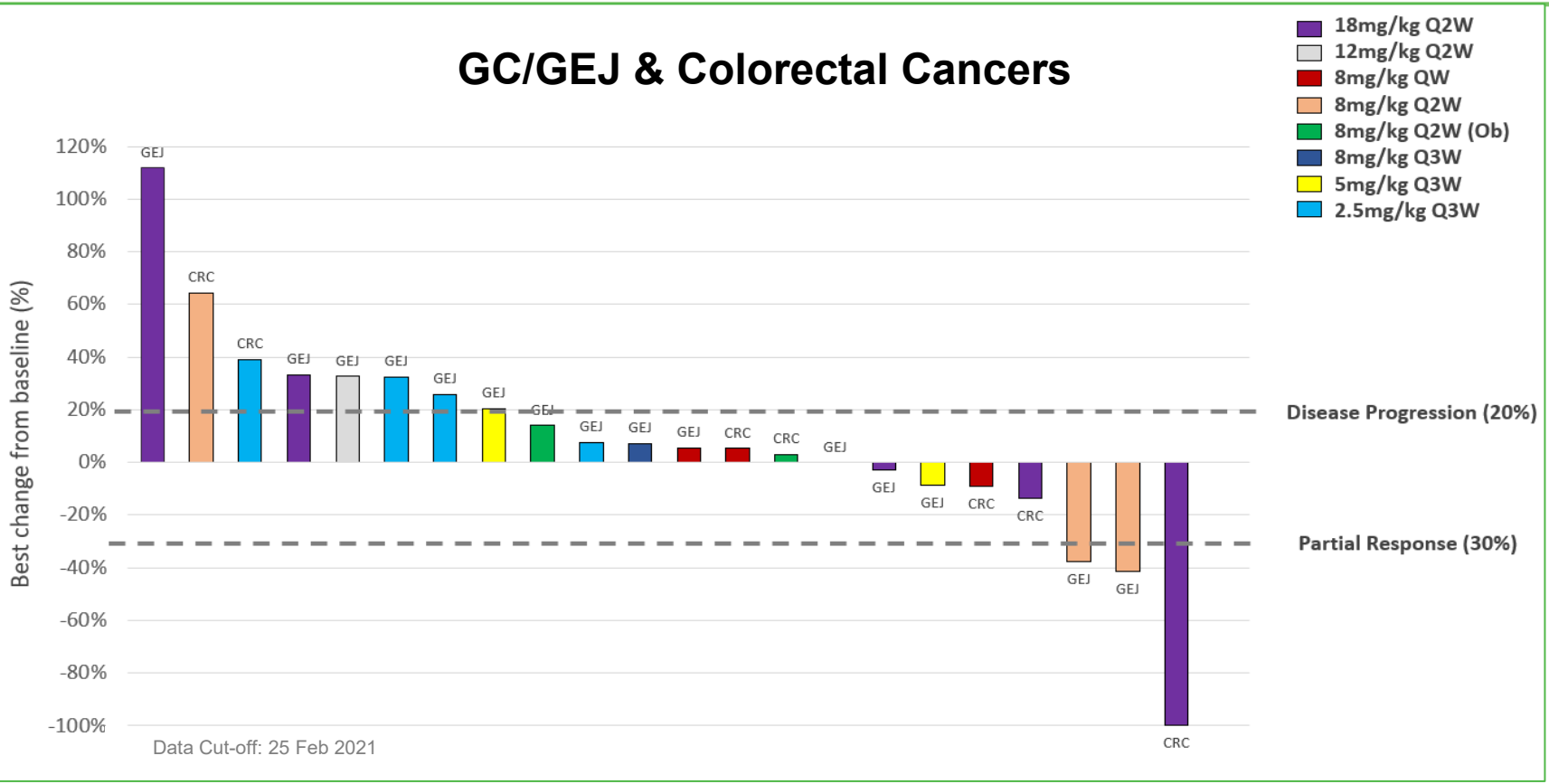

Durable Responses with PRS-343 among Heavily Pre-treated Population

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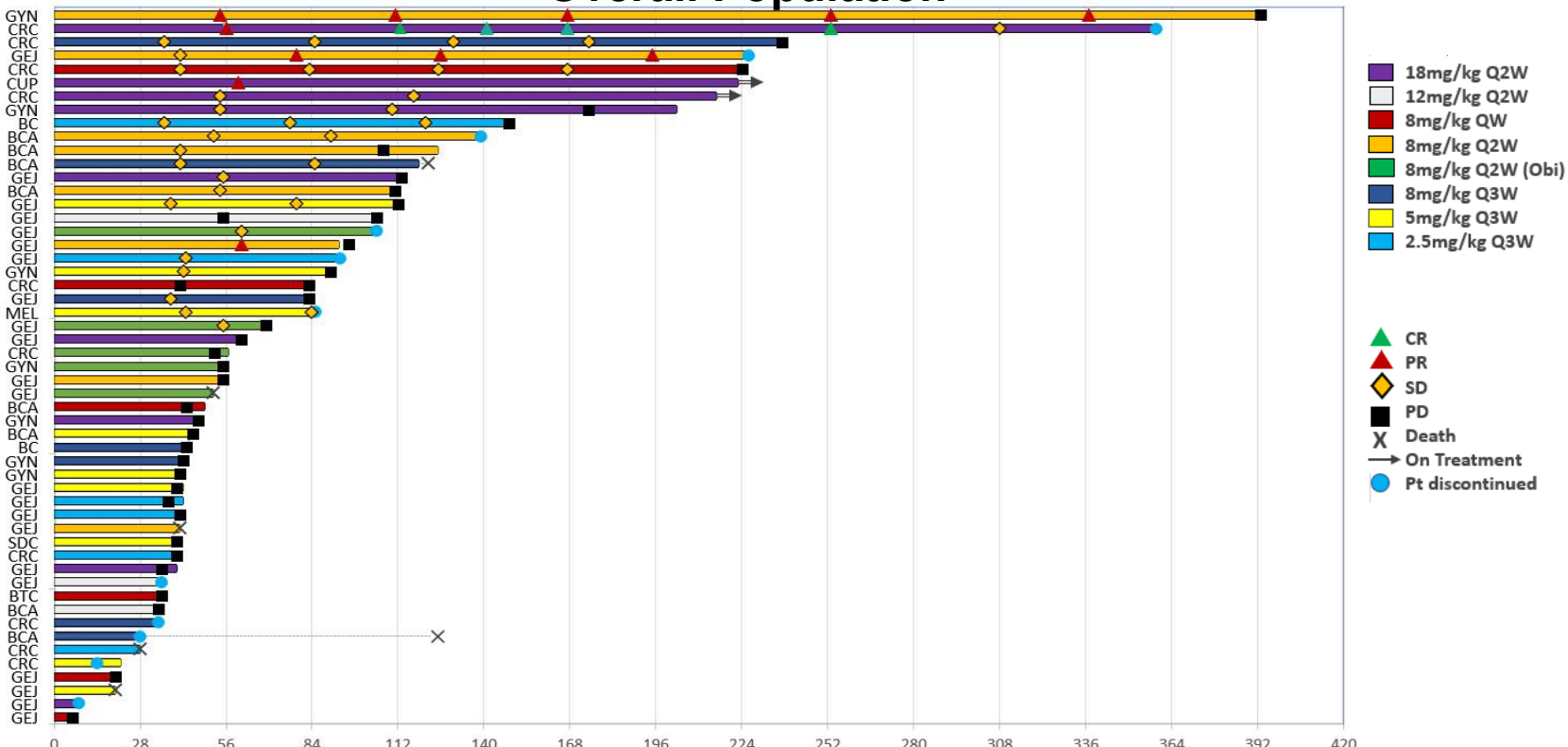
Overall Population



Data Cut-off: 25 Feb 2021

PRS-343 Generates Immunogenic Responses

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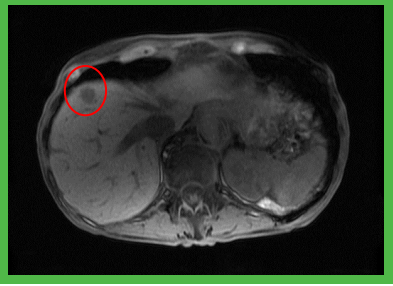
Gastric Cancer Patient with Partial Response

- 80-year-old woman; initial diagnosis in June 2017
- Gastric adenoca with mets to liver, LN and adrenals
- Treated with 8 mg/kg Q2W of PRS-343
- HER2 IHC 3+; PD-L1 positive (CPS=3) ; NGS: ERBB2 amplification

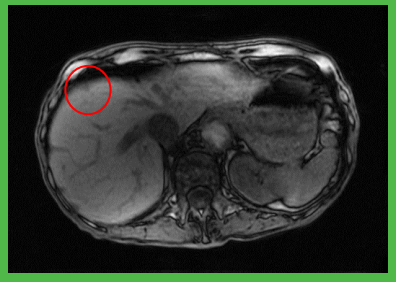
Prior Treatment includes:

- Trastuzumab, Pembrolizumab + Capecitabine/oxaliplatin
- Nivolumab with IDO1 inhibitor (investigational drug)

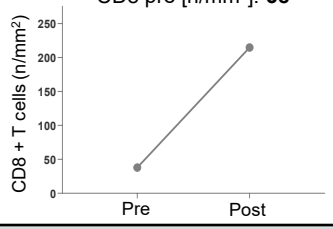
Baseline

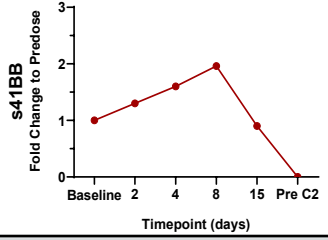


C4 Post-treatment



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





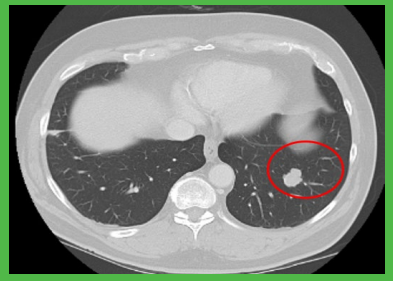
Rectal Cancer Patient with Complete Response

- 59-year-old male; initial diagnosis in March 2017
- Rectal cancer with cardiac and lung mets
- Treated with 18 mg/kg Q2W of PRS-343
- Foundation One Her2 amplification; verified in-house to be IHC 3+; MSS, TMB low

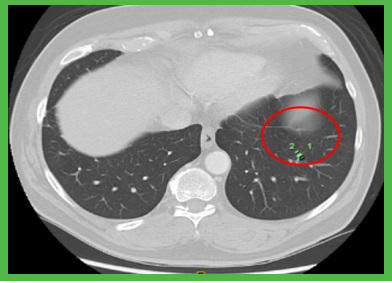
Prior Treatment includes:

- 5FU/Avastin maintenance
- Irinotecan/Avastin & SBRT

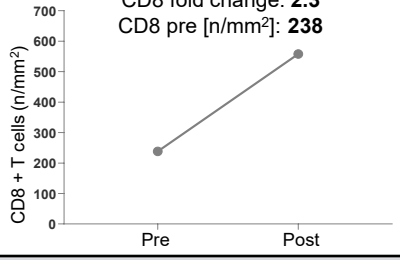
Baseline

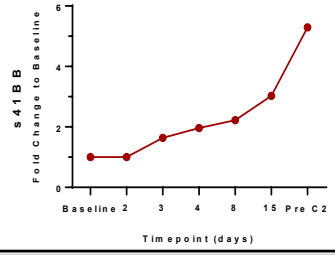


C6 Post-treatment



CD8 fold change: **2.3**
CD8 pre [n/mm^2]: **238**





PRS-343 Shows Dose Dependent Activity across Key Pharmacodynamic Parameters

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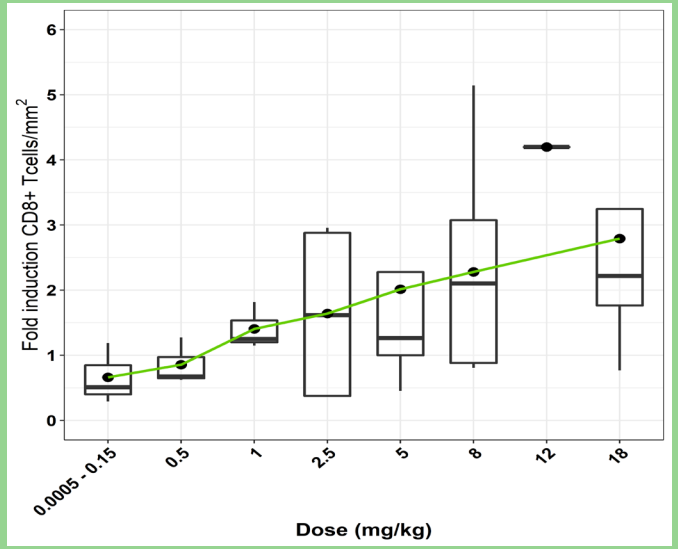
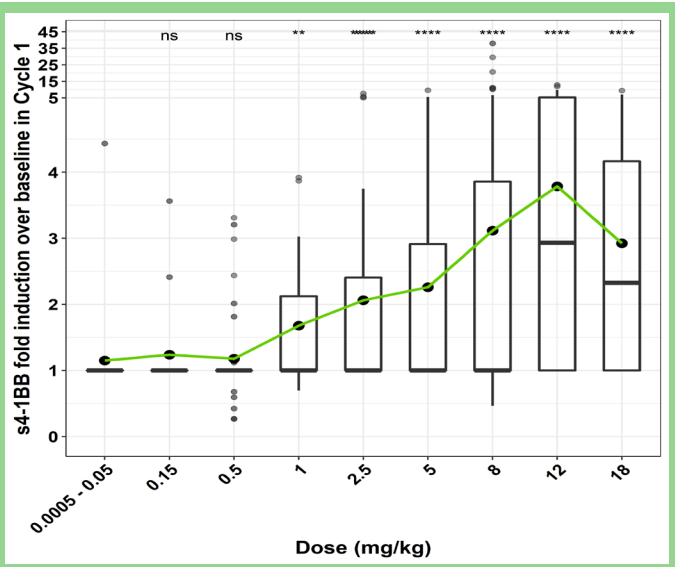
Tumor (CD8+)



Serum (s4-1BB)



Connects group averages | Median | Mann-Whitney U test

Dose at 8 mg/kg incorporates patients treated at Q1W, Q2W or Q3W

PRS-343 Activates Adaptive and Innate Immunity in the Tumor

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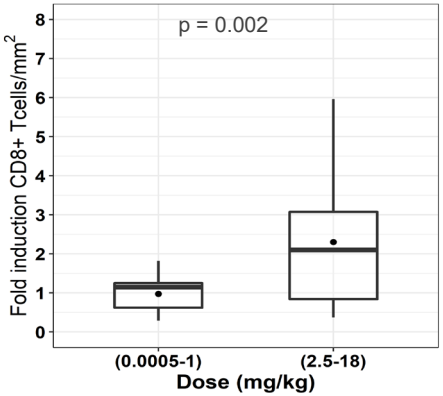
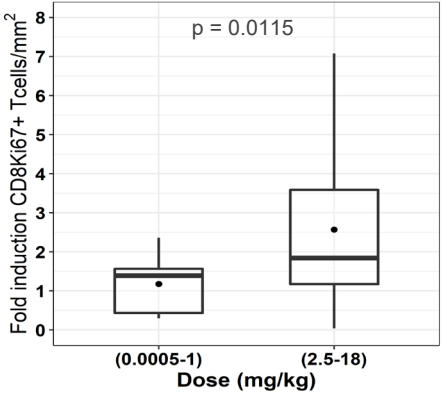
Based on preclinical and clinical data, serum concentration of > 20 µg/ml defines active dose range beginning at 2.5 mg/kg (Cohort 9)

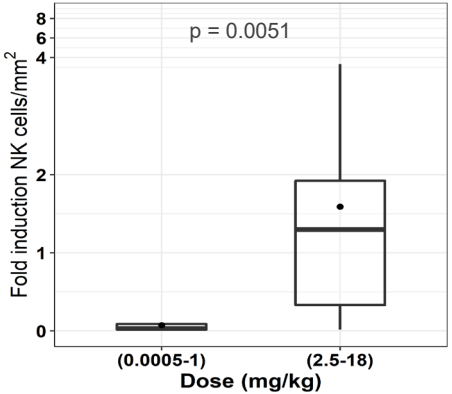
CD8+ cells



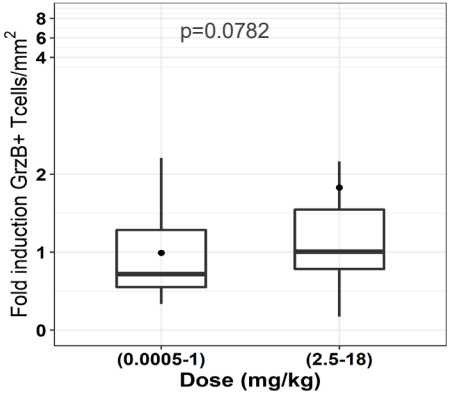
CD8+Ki67+ cells



NK cells



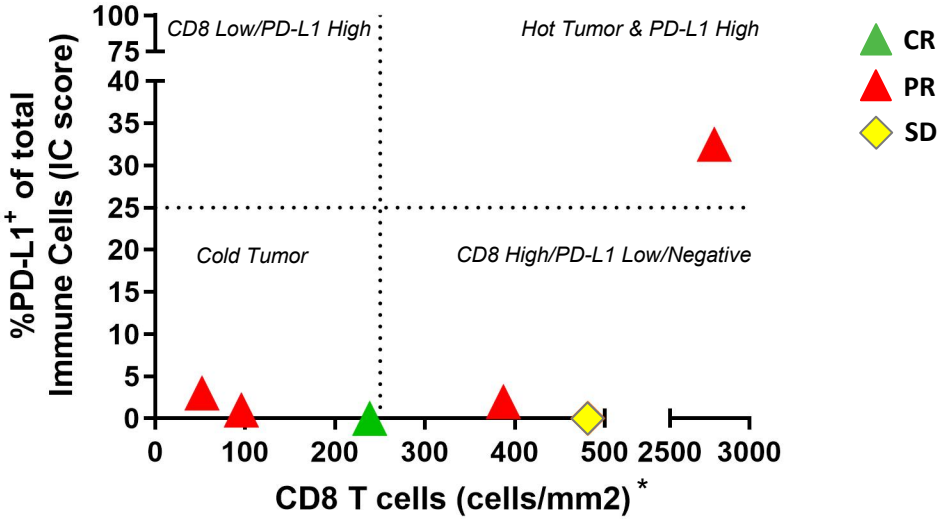
GrzB+ cells



denotes group averages | Median | Unpaired one-tailed Welch`s

PRS-343 Shows Clinical Activity in Both "Hot" and "Cold" Tumors

PD-L1 status and CD8+ T cells levels in tumor biopsies



* Threshold informed by (Tumeh et al., 2014 and Blando et al., 2019)

Several patients with clinical benefit have low/negative PD-L1 status and low CD8 T cell numbers

PRS-343 Shows Signs of Preclinical and Clinical Activity in the HER-2 Low Setting

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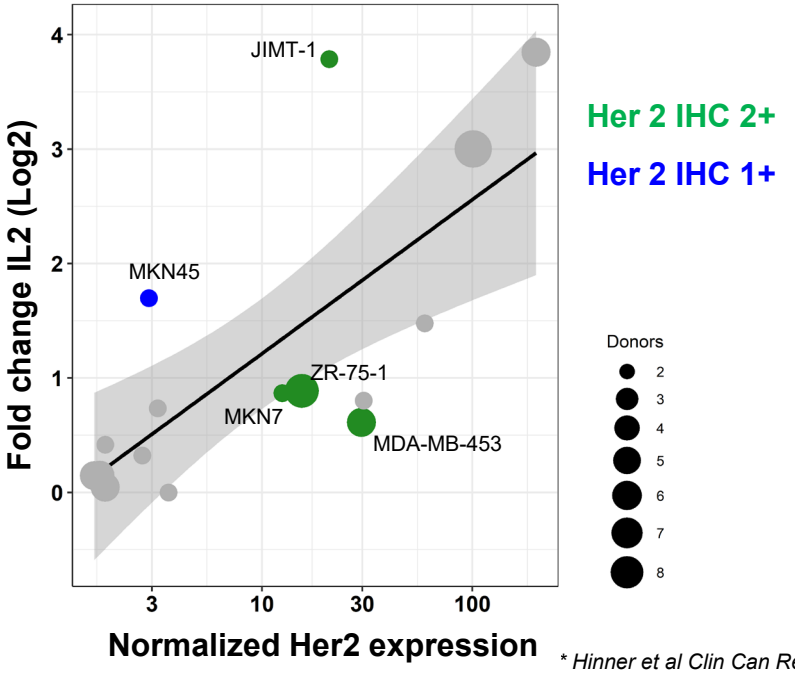
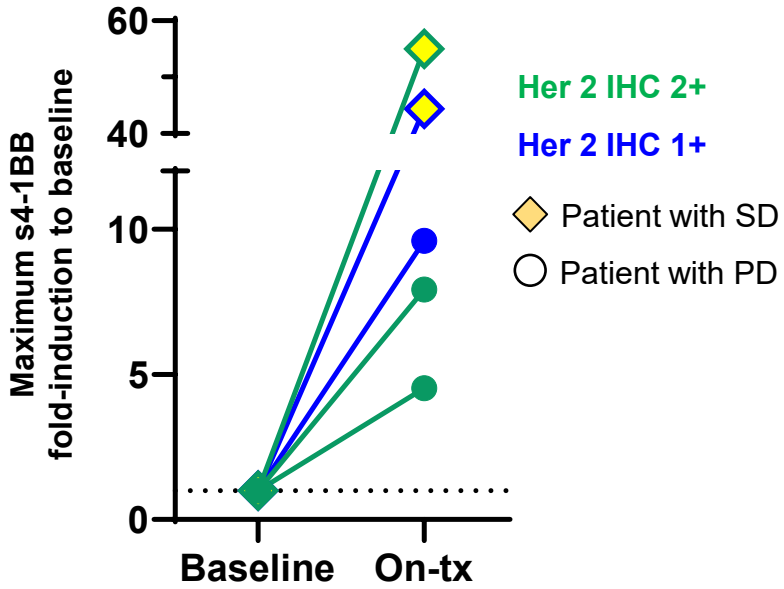
PRS-343 enhances T cell activation in *in vitro* co-cultures with HER-2 low tumor cell lines*



* *Hinner et al Clin Can Res 2019*

PRS-343 increases soluble 4-1BB in HER-2 low-expressing patients



Summary Conclusions

- Monotherapy PRS-343 is well tolerated and safe up to 18 mg/kg
  - No significant specific anti-HER2 or anti-4-1BB safety signal
  - No dose limiting toxicity identified
- Dose-dependent Immune activation demonstrated
  - Increase in CD8+ T cell, NK cells and cytotoxic activity in tumor microenvironment
  - Soluble 4-1BB increases in the blood indicating target engagement of 4-1BB and activation of immune cells
- Demonstrated durable anti-tumor activity in heavily pre-treated population
  - Preliminary evidence of activity among “cold” tumor types and HER2 low patients
- Emerging data supports continued Ph 2 development of PRS-343

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