



PRS-343 ESMO UPDATE

SEPTEMBER 2020



Forward Looking Statements

This presentation contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this presentation that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the timing for, and outcome of, the additional in-use and compatibility study for PRS-343 as requested by the FDA; whether data from patients enrolled to date will be sufficient to inform the recommended phase 2 dose for the Company's planned proof of concept study of PRS-343 in gastric cancer; the expected timing and potential outcomes of the reporting by the Company of key clinical data from its programs, references to novel technologies and methods and our business and product development plans, including the advancement of our proprietary and codevelopment programs into and through the clinic and the expected timing for reporting data, making IND filings or achieving other milestones related to our programs, including PRS-060/AZD1402, PRS-343, PRS-344, and PRS-352 and the expected timing of the initiation of the next stage of PRS-343's development in gastric cancer. Actual results could differ from those projected in any forward-looking statements due to numerous factors. Such factors include, among others, our ability to raise the additional funding we will need to continue to pursue our business and product development plans; the inherent uncertainties associated with developing new products or technologies and operating as a development stage company; our ability to develop, complete clinical trials for, obtain approvals for and commercialize any of our product candidates, including our ability to recruit and enroll patients in our studies; our ability to address the requests of the FDA, including with respect to the additional in-use and compatibility study for PRS-343, and the resolution of the partial clinical hold relating to that drug candidate; competition in the industry in which we operate; delays or disruptions due to COVID-19; and market conditions. These forward-looking statements are made as of the date of this presentation, and we assume no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all of the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents we file with the SEC available at www.sec.gov, including without limitation the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 and the Company's Quarterly Reports on Form 10-Q.

4-1BB Agonism Offers Promise of Material Clinical Benefit

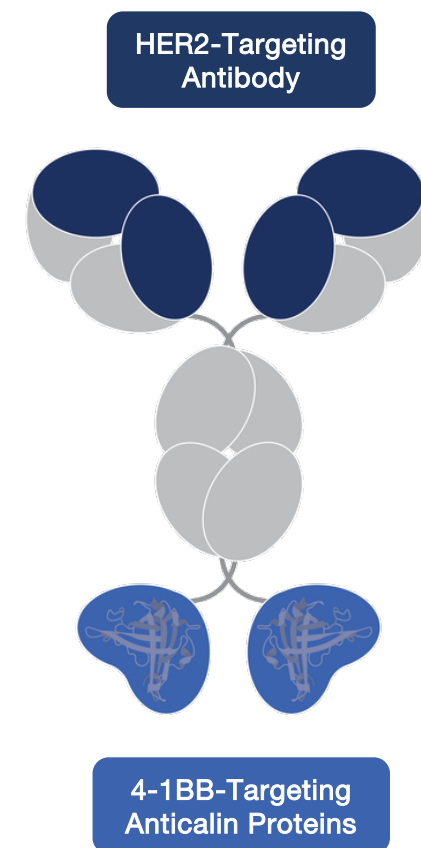
Unique Attributes of 4-1BB Agonism on Tumor-specific T Cells

- ✓ Increases T-cell proliferation to bolster immune repertoire
- ✓ Enhances cytotoxicity for tumor killing
- ✓ Improves metabolic fitness for increased survival of T cells
- ✓ Drives T-cell memory phenotype for increased durability

Pieris' 4-1BB bispecifics recognize that 4-1BB agonists have proven clinical potency, yet must be kept out of the liver to ensure suitable therapeutic index

PRS-343: Proprietary Lead IO Asset

Candidate	PRS-343
Function/MoA	Tumor-targeted 4-1BB agonism and HER2 antagonism
Indications	HER2+ solid tumors
Development	Initiating phase 2 in combination with ramucirumab and paclitaxel in second line gastric
Commercial Rights	Fully proprietary



PRS-343 Localizes 4-1BB Agonism Within HER2+ Tumors

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

PRS-343

HER2+
Tumor Cell

Tumor-specific
T Cell

Monotherapy and Combination Studies: Enabled Meaningful Clinical Characterization of PRS-343

Snapshot

- Patients with HER2+ solid tumors
- Monotherapy and combination with atezolizumab
- Data updates presented at ESMO 2020

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; 21-day cycle

Schedule 2 (b): Q2W dosing on days 1, 15; 28-day cycle

Schedule 3 (c): Q1W dosing on days 1, 8, 15; 21-day cycle

In combination with atezolizumab: Q3W dosing on day 1; 21-day cycle

Mono Dose Cohort*	Combo Dose Cohort**	Dose (mg/kg)
1		0.0005
2		0.0015
3		0.005
4		0.015
5	1	0.05
6	2	0.15
7	3	0.5
8	4	1
9	5	2.5
10	6	5
11	7	8
11 (b)		8
11 (c)		8
12 (b)		12
13 (b)		18
Obinutuzumab + 11(b)		8

9-13b: active dose cohorts in mono study

*Additional dose cohorts enrolling in monotherapy study

**1200mg flat dose of atezolizumab

Baseline Characteristics : Monotherapy and Combination with Atezolizumab

All Subjects (n = 74, 41)

Characteristic	Monotherapy; n (%)	In Combination with Atezolizumab; n (%)
Age, Median (range)	63 (24–92)	59 (26–87)
Gender		
F	44 (59%)	23 (56%)
M	30 (41%)	18 (44%)
ECOG PS*		
0	19 (26%)	12 (29%)
1	55 (74%)	18 (44%)
Prior Therapy Lines		
1	9 (12%)	5 (12%)
2	10 (14%)	7 (17%)
3	15 (21%)	6 (15%)
4	11 (15%)	6 (15%)
5+	28 (38%)	17 (41%)
Median no. of anti-HER2 Treatments		
Breast	7	3–4
Gastric	3	1

*Combination trial enrolled ECOG 2 patients as well (not shown on this chart)

Primary Cancer Type	Monotherapy; n (%)	In Combination with Atezolizumab; n (%)
Gastroesophageal	27 (36%)	7 (17%)
Breast	16 (22%)	12 (29%)
Colorectal	10 (14%)	5 (12%)
Gynecological	9 (12%)	4 (10%)
Biliary Tract	7 (9%)	6 (15%)
Non-Small Cell Lung	-	4 (10%)
Bladder	2 (3%)	1 (2%)
Pancreatic	1 (1%)	1 (2%)
Other – Cancer of Unknown Origin	1 (1%)	1 (2%)
Other – Salivary Duct	1 (1%)	-

Data cut-off: 27-Jul-20



Monotherapy

Treatment-Related Adverse Events (Monotherapy Trial)

All Subjects

Occurred in > 1 Patient	Monotherapy	
	n = 145 (%)	% Grade 3
Infusion Related Reaction	27 (19%)	3 (2%)
Fatigue	11 (8%)	1 (1%)
Nausea	11 (8%)	
Vomiting	8 (6%)	
Chills	8 (6%)	
Anemia	2 (1%)	1 (1%)
Arthralgia	2 (1%)	
Asthenia	2 (1%)	
Cough	2 (1%)	
Decreased appetite	2 (1%)	
Diarrhea	6 (4%)	
Dizziness	2 (1%)	
Dyspnoea	3 (2%)	
Flushing	5 (3%)	2 (1%)
Non-cardiac chest pain	4 (3%)	
Paraesthesia	3 (2%)	1 (1%)
Pruritis	3 (3%)	
Rash	2 (1%)	

One TRAE above Grade 3: Grade 4 Infusion Related Reaction in cohort 10 (5mg/kg PRS-343, Q3W).

Data cut-off: 27-Jul-20

Summary of Responses of PRS-343 in Monotherapy

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

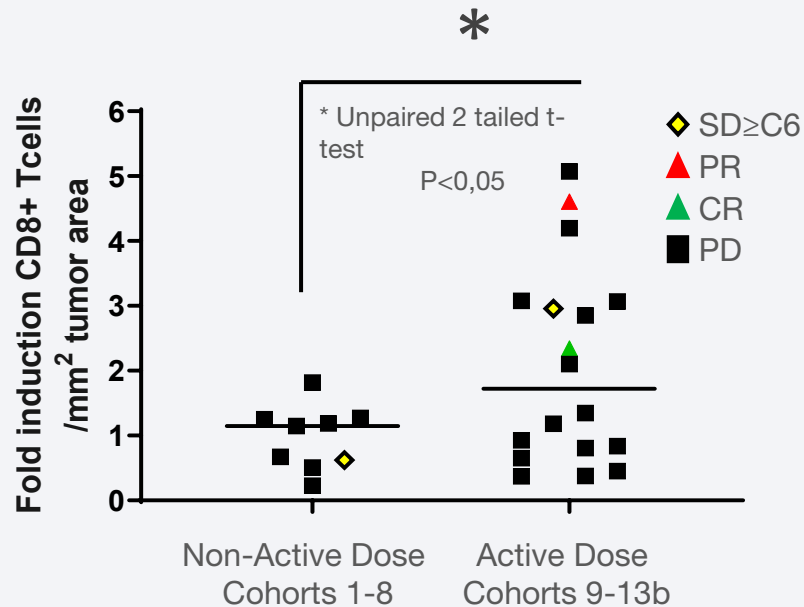
Cohort	13b	12b	11c	Obi	11b	11	10	9	Total
Best Response	18 mg/kg, Q2W	12 mg/kg, Q2W	8 mg/kg, QW	8 mg/Kg, Q2W	8 mg/kg, Q2W	8 mg/kg, Q3W	5 mg/kg, Q3W	2.5 mg/kg, Q3W	
Evaluable Patients	3	2	4	2	7	4	6	5	33
CR	1	-	-		-	-	-	-	1
PR	-	-	-		3	-	-	-	3
SD	-	-	1	1	3	3	3	2	13
ORR	33%	0%	0%	0%	43%	0%	0%	0%	12%
DCR	33%	0%	25%	50%	86%	75%	50%	40%	52%

Data cut-off: 27-Jul-20

Increase in CD8+ T Cells and Circulating Soluble 4-1BB Support 4-1BB Engagement by PRS-343

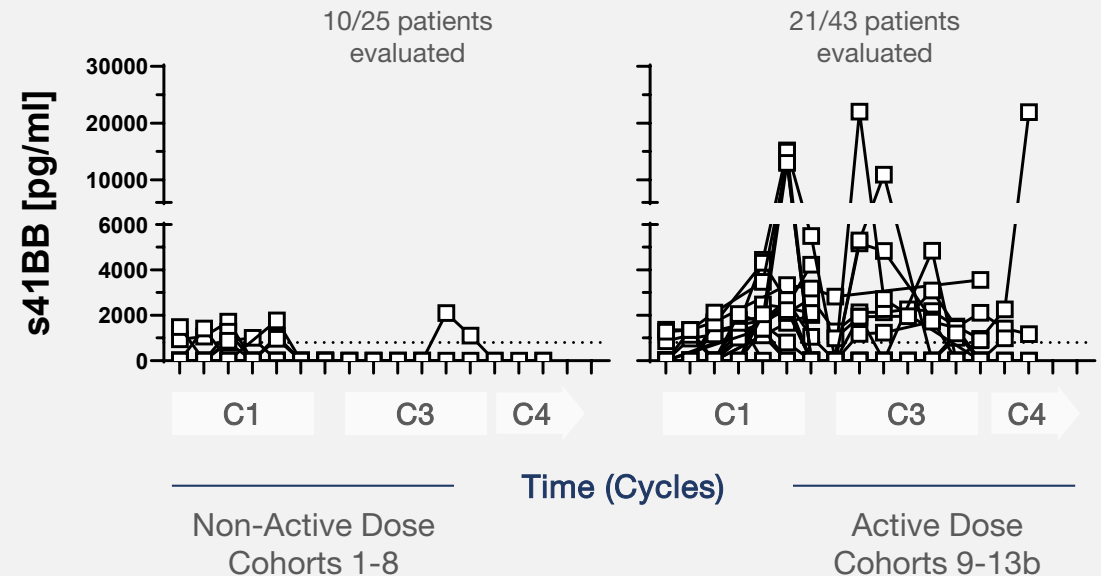


Tumor



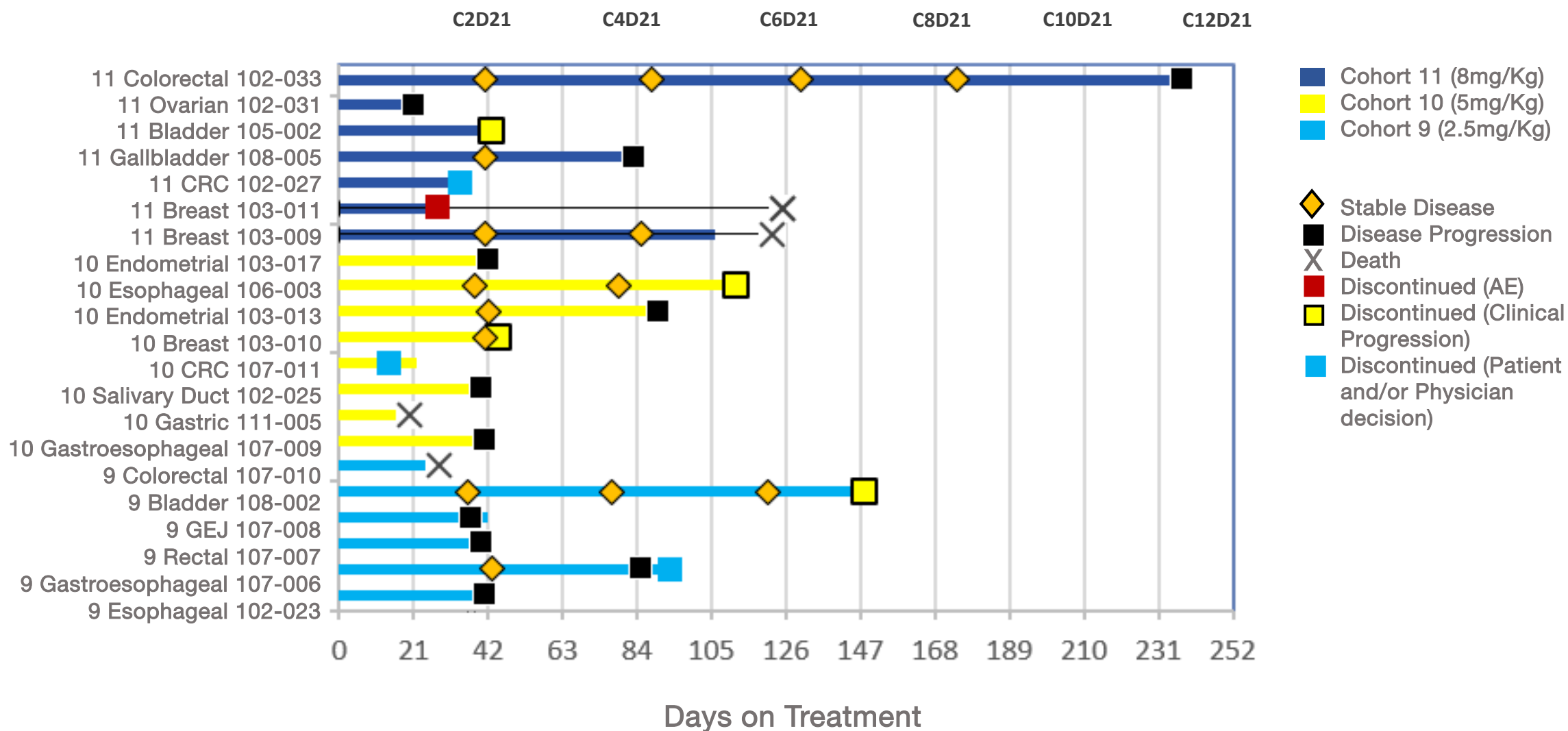
Data cut-off: 27-Jul-20

Serum



Average Time on Treatment with PRS-343

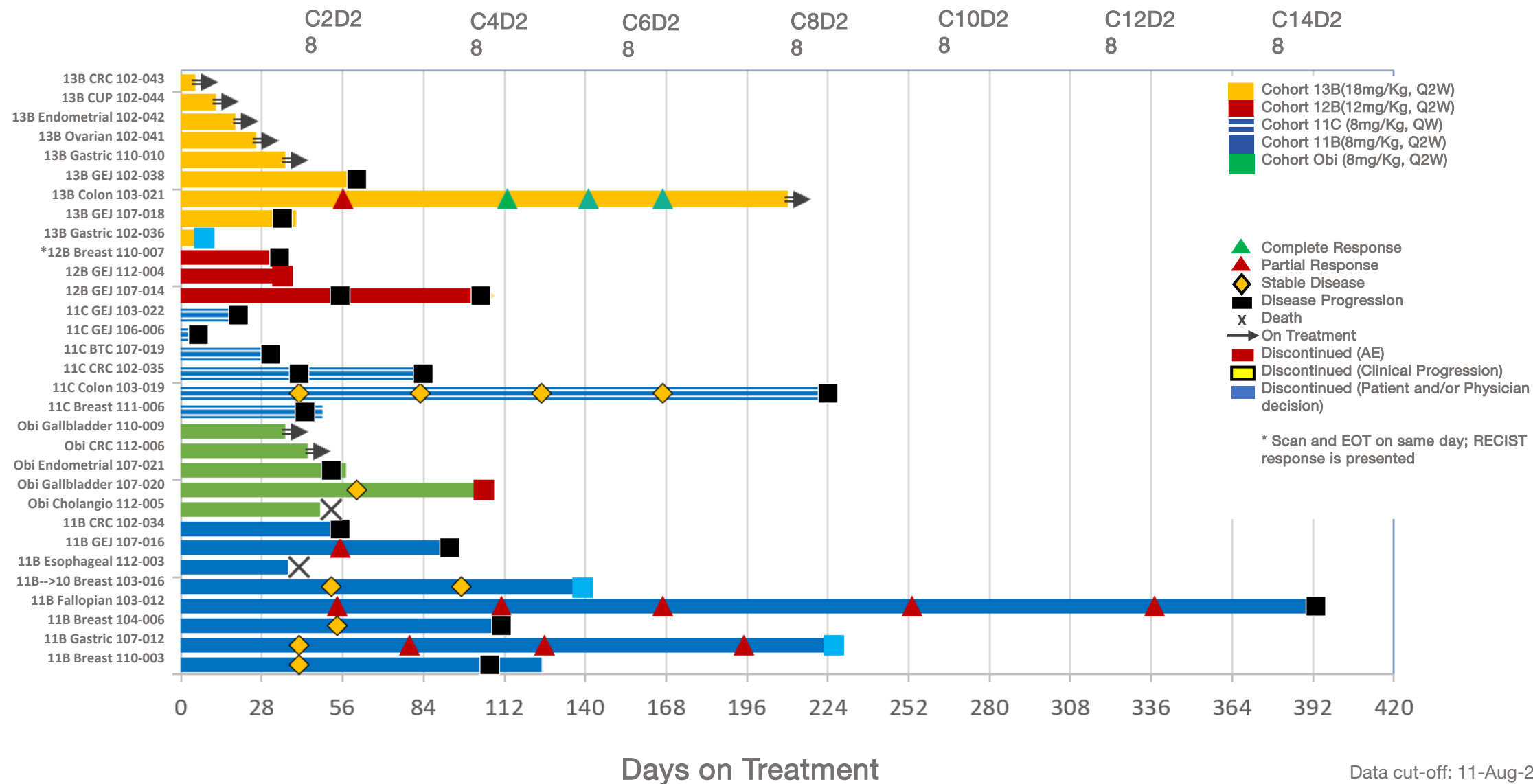
Cohorts 9-11a



Data cut-off: 27-July-20

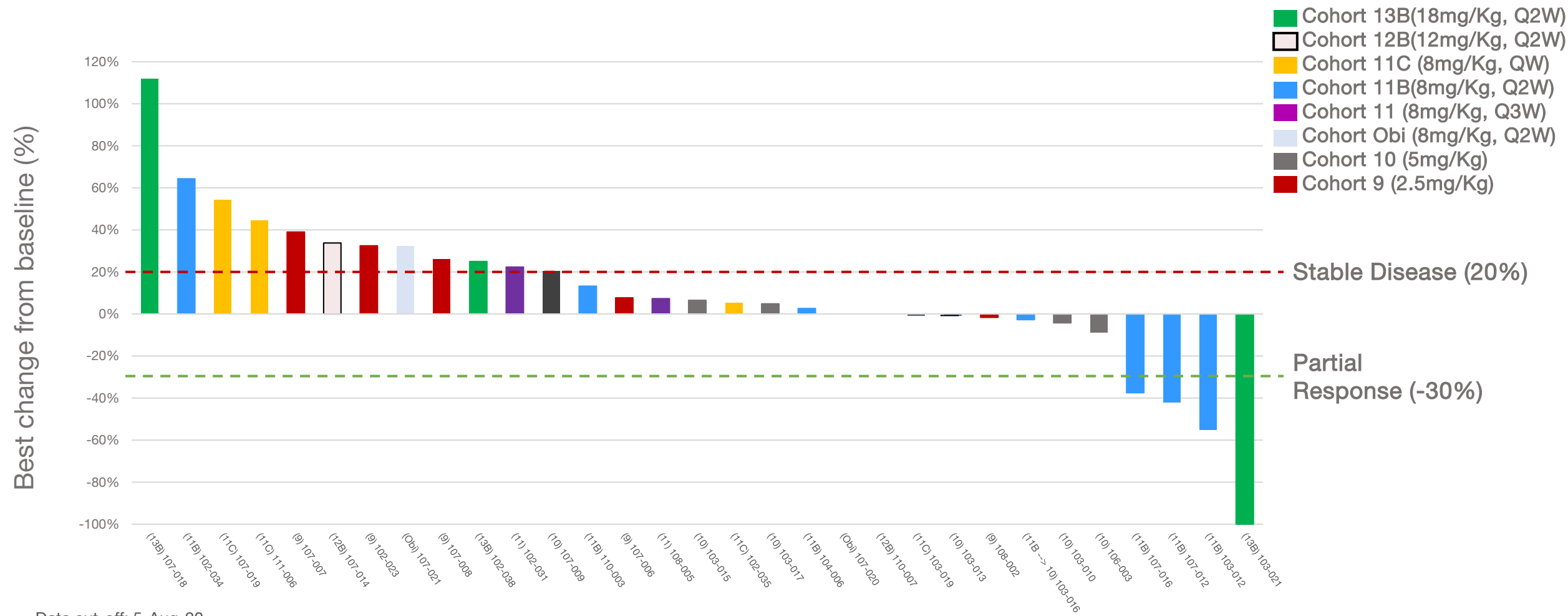
Average Time on Treatment with PRS-343

Cohorts 11b-13b



Best Response in Target Lesions (Monotherapy Trial)

Cohorts 9-13b



Data cut-off: 5-Aug-20

Case Study: Gastric Cancer Patient with Confirmed Partial Response

Patient Profile, Treatment History and Treatment Outcome

Patient Profile

- Cohort 11b | 8 mg/kg every two weeks
- 80-year old woman; initial diagnosis in 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

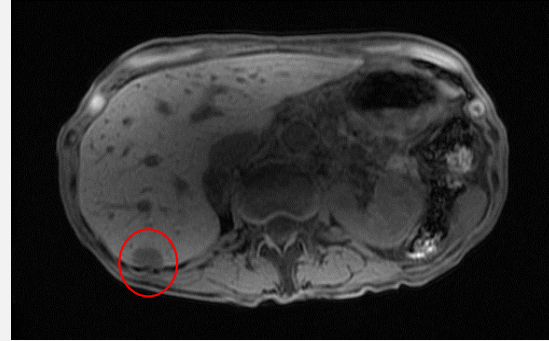
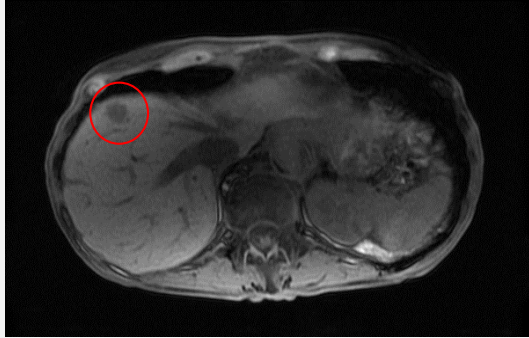
Oncology Treatment History	Duration	Best Response
Trastuzumab, Pembrolizumab + Capecitabine/oxaliplatin	July 2017 – June 2018	Stable Disease
Nivolumab with IDO1 inhibitor (investigational drug)	Aug 2018 – Jan 2019	Stable Disease

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	8
Target 2	Liver	20	16	10	8	9
Target 3	Pancreas	19	16	14	14	14
% Change from Baseline			-17%	-36%	-42%	-42%
Non-target 1	Lung	Present	Present	Present	Present	Present
Non-target 2	Stomach	Present	Present	Present	Present	Absent
Non-target 3	Stomach	Present	Present	Present	Present	Absent

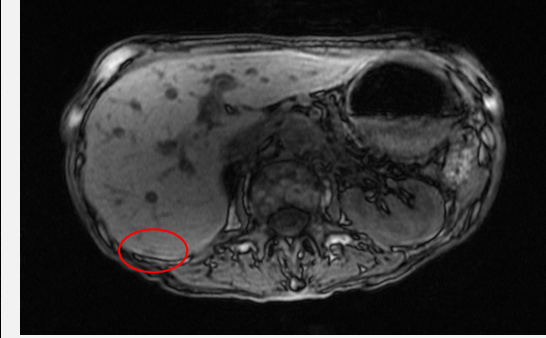
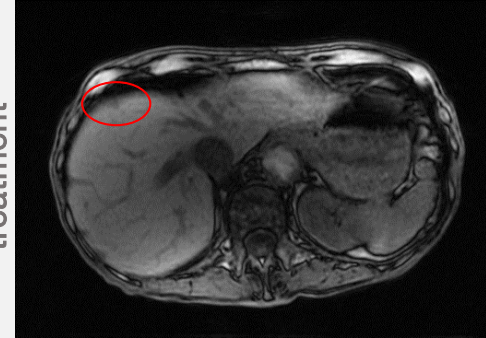
Data cut-off: 24-Jan-20

CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in Responding Gastric Cancer Patient

Baseline

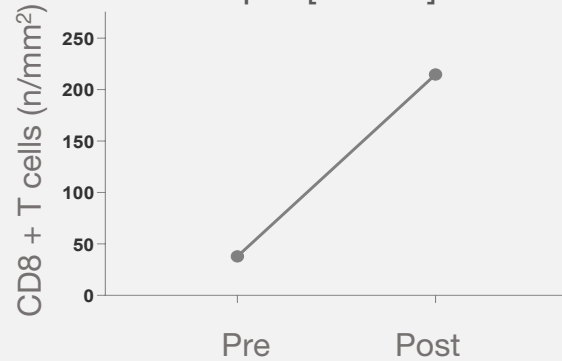


C4 Post-treatment



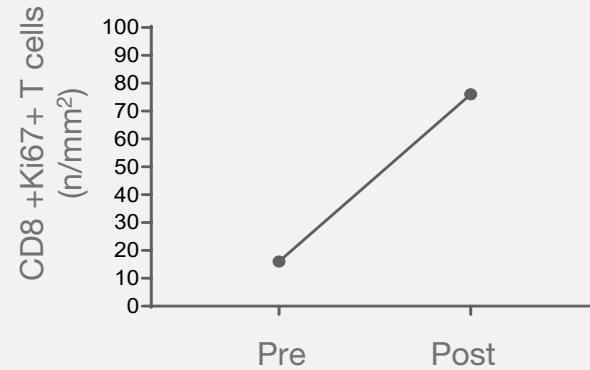
Tumor

CD8 fold change: **5.7**
CD8 pre [n/mm²]: **38**



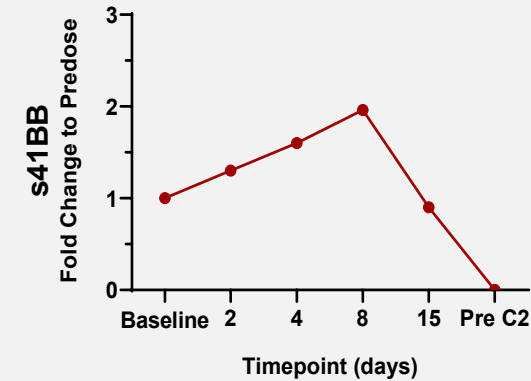
CD8+ T cell Numbers

CD8Ki67 fold change: **5.8**
CD8 pre [n/mm²]: **16**

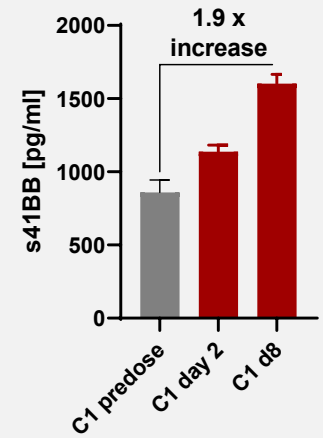


CD8+ T cell Proliferation

Serum



Soluble 4-1BB



Case Study #2: Rectal Cancer Patient with Confirmed Complete Response

Patient Profile, Treatment History and RECIST

Patient Profile

- Cohort 13b | 18 mg/kg Q2W
- 59-year-old male; initial diagnosis March 2017
- Stage 4 rectal adenocarcinoma cancer; metastasized to heart and lung
- FoundationOne Her2 amplification; in-house testing IHC 3+
- MSS, TMB low (2 mt/Mb)

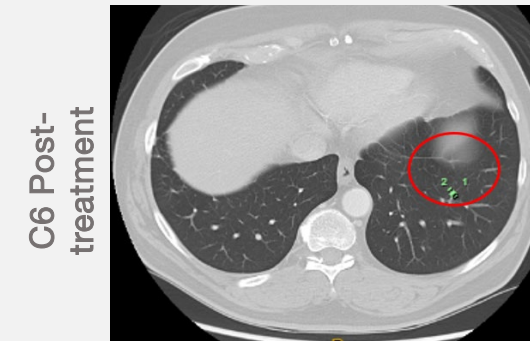
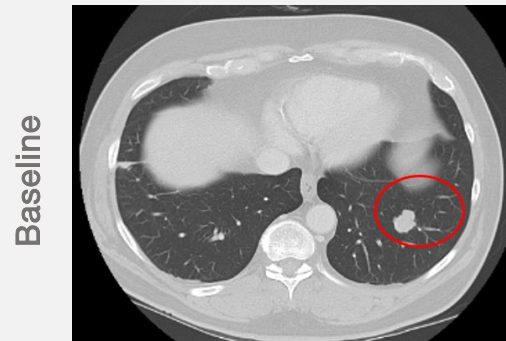
Oncology Treatment History	Duration
Capecitabine + XRT	Apr-May 2017
Neoadjuvant Folfox	May-Sep 2017
Resection	Dec 2017
Folfiri/Avastin	Mar-Jul 2018
5FU/Avastin maintenance	Aug 2018-May 2019
Irinotecan/Avastin	May-Nov 2019
SBRT	Nov 2019

Lesions	Lesion Site	Lesion Size (mm)			
		Baseline	C2 Post-treatment	C4 Post-treatment	C6 Post-treatment
Target 1	Lung	22	13	0	0
% Change from Baseline			-41%	-100%	-100%
Non-target 1	-	Present	Present	Absent	Absent

Data cut-off: 27-Jul-20

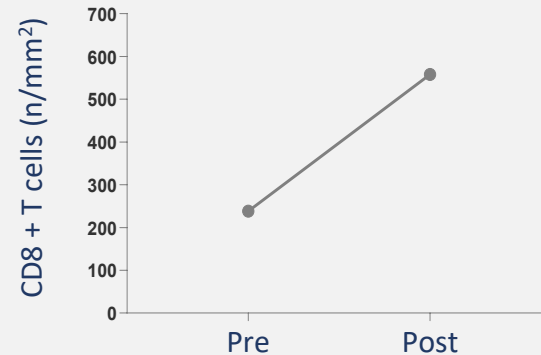


CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in CR Rectal Cancer Patient

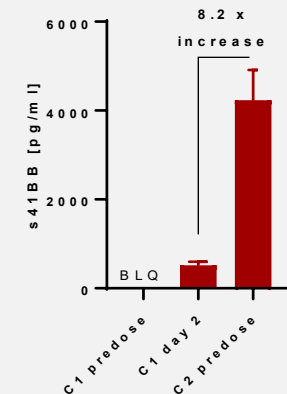
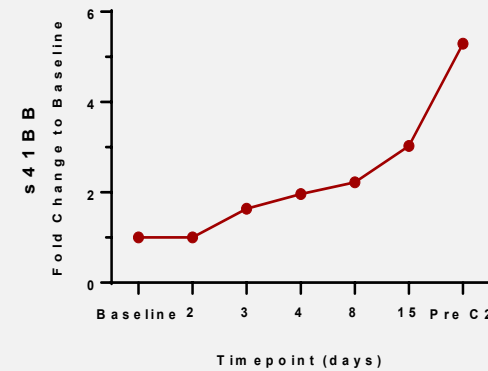


Tumor

CD8 fold change: **2.3** CD8 pre [n/mm²]: **238**



Serum





Combination Therapy with Atezolizumab

Treatment-Related Adverse Events (Combination Trial)

All Subjects

Occurred in > 1 Patient	Combination with Atezolizumab	
	n = 148 (%)	% Grade 3
Infusion Related Reaction	38 (26%)	3 (2%)
Fatigue	12 (8%)	
Nausea	8 (5%)	
Vomiting	38 (26%)	
Abdominal pain	2 (1%)	
Anemia	4 (3%)	2 (1%)
Anorexia	2 (1%)	
Arthralgia	2 (1%)	
Diarrhea	5 (3%)	1 (1%)
Dry mouth	3 (2%)	
Fever	3 (2%)	
Lightheadness	2 (1%)	
Lymphocyte count decreased	3 (2%)	1 (1%)
Neutrophil count decreased	3 (2%)	1 (1%)
Peripheral sensory neuropathy	2 (1%)	
Pruritis	4 (3%)	

Two TRAEs above Grade 3: Grade 4 AST increase, Grade 3 transaminitis, and eventually Grade 5 hepatic failure in cohort 7 (8mg/kg + 1200mg atezolizumab); Grade 4 hemolytic anemia (unrelated to PRS-343, related to atezolizumab) in cohort 7.

Data cut-off: 27-Jul-20

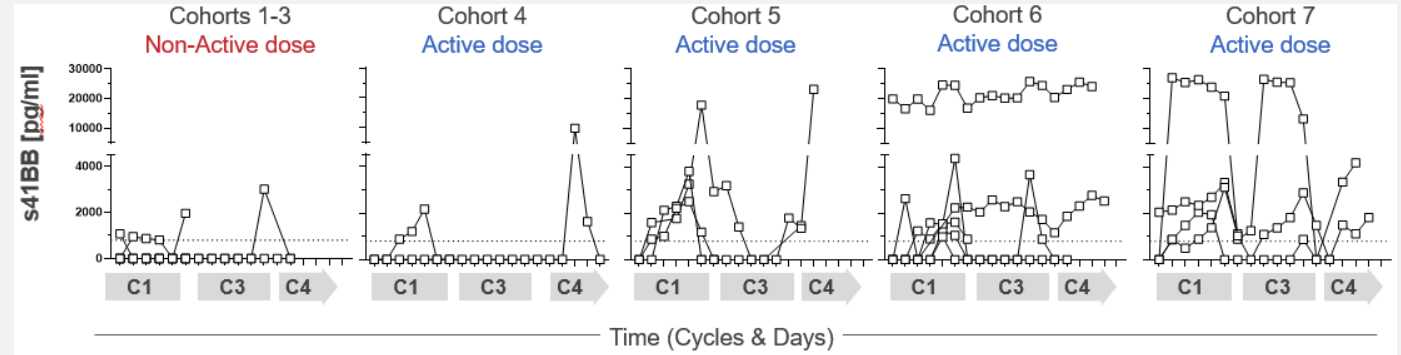
Summary of Responses of PRS-343 in Combination with Atezolizumab

Cohort	7	6	5	4	Total
Best Response	8mg/kg, Q3W	5mg/kg, Q3W	2.5mg/kg, Q3W	1mg/kg, Q3W	
Evaluable Patients	8	8	8	3	27
PR	1	2	-	1	4
SD	4	1	1	0	6
ORR	13%	25%	0%	33%	15%
DCR	63%	38%	13%	33%	37%

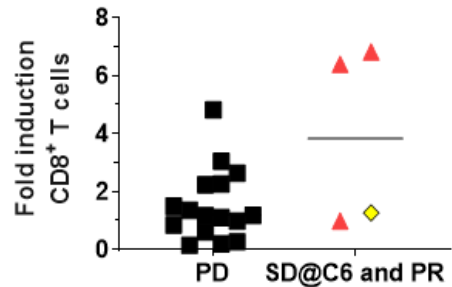
Data cut-off: 27-Jul-20

Soluble 4-1BB Increases in Active Dose Cohorts & Clinical Benefit is Associated with Tumoral Immune Cell Activation

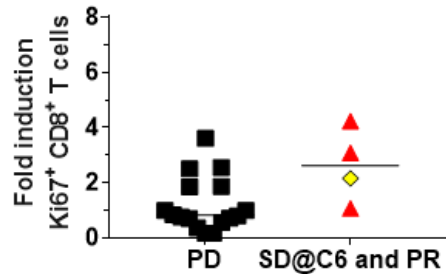
4-1BB target engagement →
Soluble 4-1BB in serum



CD8⁺ T cell Numbers



CD8⁺ T cell Proliferation



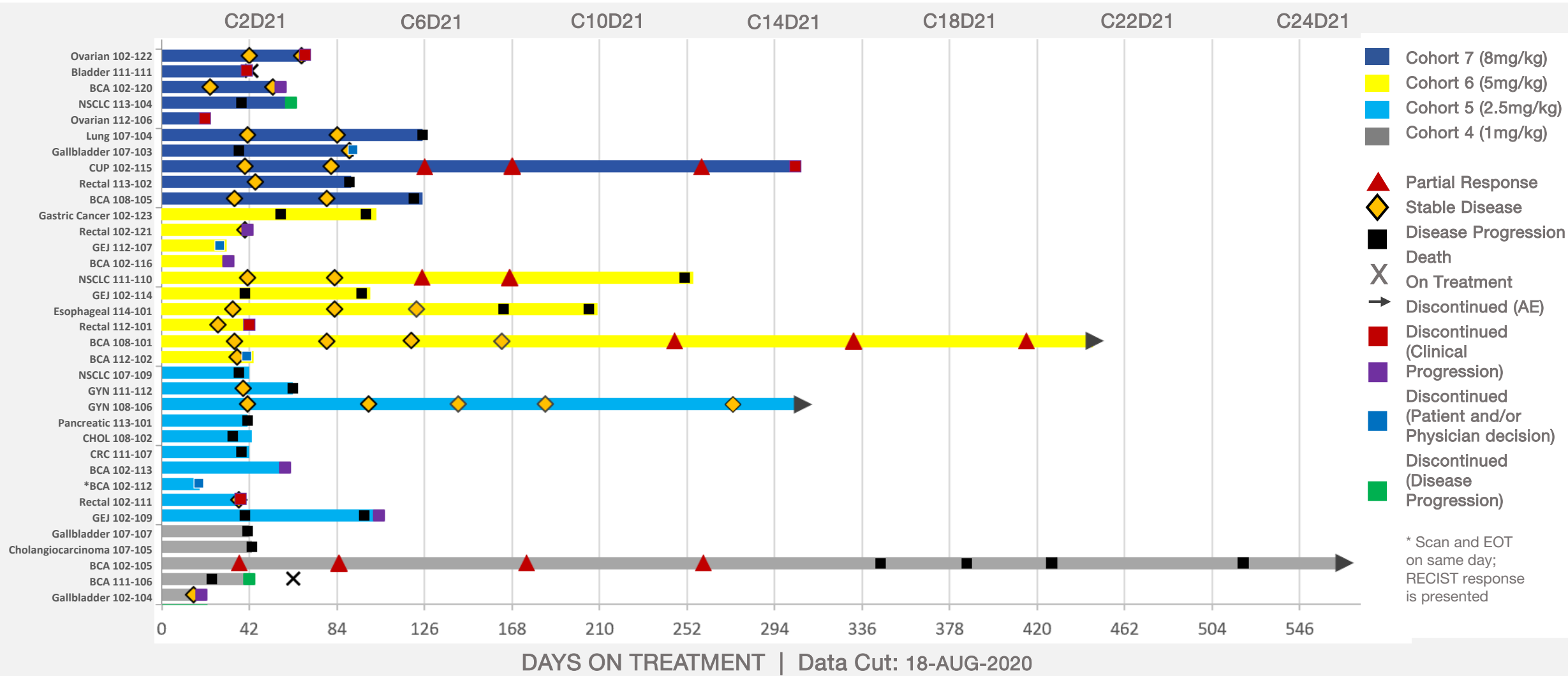
Tumor-localized activity

IHC on tumor tissue

Patients with prolonged clinical benefit show a trend of increased CD8⁺ T cell numbers, proliferation and elevated cytolytic function in tumor biopsies

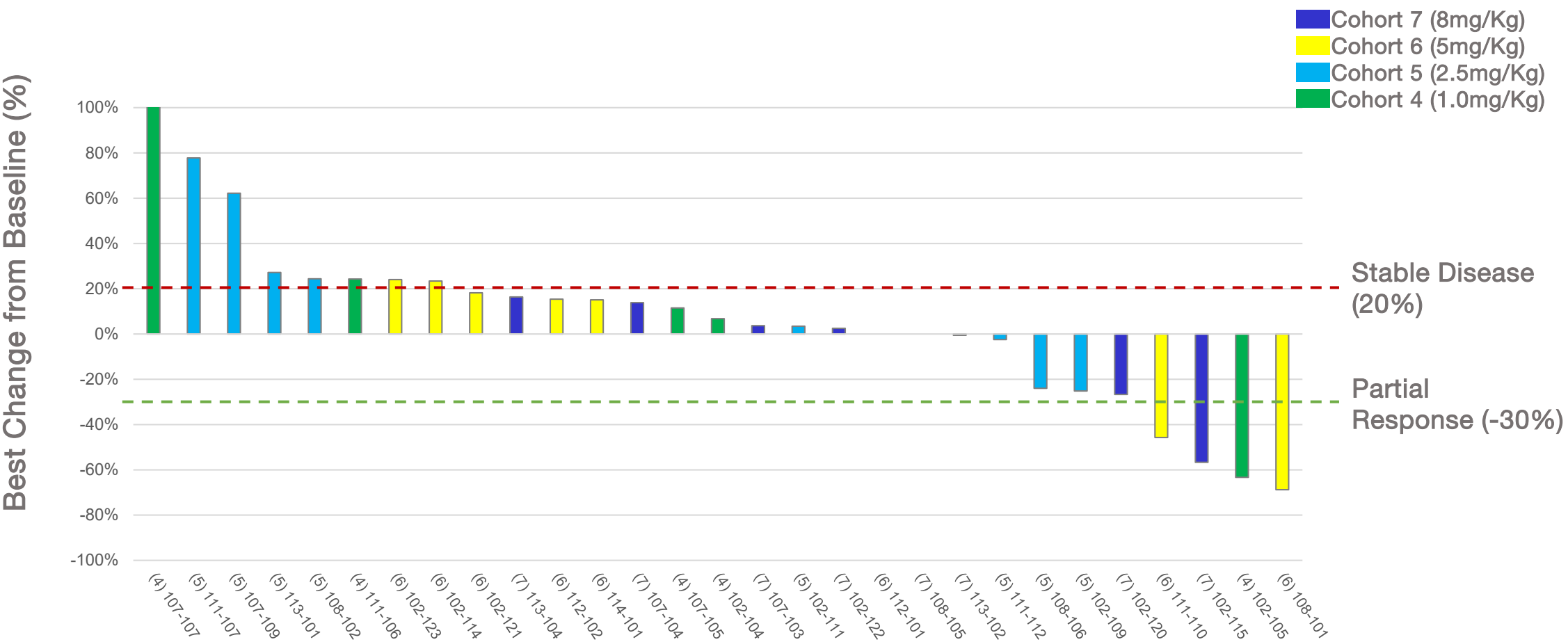
Substantial increase of s4-1BB is observed in active dose cohorts (4-7), suggesting PRS-343-mediated target engagement

PRS-343 + Atezolizumab Duration of Exposure



Best Response in Target Lesions (Combination Study)

Cohorts 4-7



Data cut-off: 27-Jul-20



Case Study: Breast Cancer Patient with Stable Disease (Update)

Patient Profile, Treatment History and RECIST

Patient Profile:

- Cohort 6 | 5 mg/kg Q3W + 1200mg atezolizumab
- 52-year-old male; Initial diagnosis July 2011
- Stage 2 Invasive Ductal Breast Cancer
- FISH HER2/CEP17 ratio 2.4, HER2 copy number 4.8
- In-house testing IHC2+, FISH+
- PD-L1 low in pre-treatment and high in post treatment biopsy

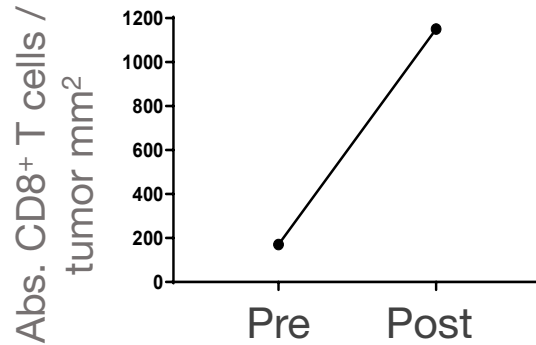
Oncology Treatment History	Duration
Trastuzumab/Docetaxel/ Tamoxifen/Carboplatin	Sep 2011-Jul 2013
Trastuzumab/Pertuzumab/Vinorelbine	Aug 2013-Jan 2016
T-DM1/Fulvestrant	Nov 2017-Mar 2018
Capecitabine/Lapatinib	Mar 2018
Palbociclib/Arimidex	Apr-May 2019

Lesions	Lesion Site	Lesion Size (mm)						
		Baseline	C2 Post-treatment	C4 Post-treatment	C6 Post-treatment	C8 Post-treatment	C12 Post-treatment	C16 Post-treatment
Target 1	right pulmonary ligament lymph node	16	18	15	13	13	6	5
% Change from Baseline			+12.5%	-6%	-19%	-19%	-63%	-69%
Non-target 1-4	-	Present	Present	Present	Present	Present	Present	Present

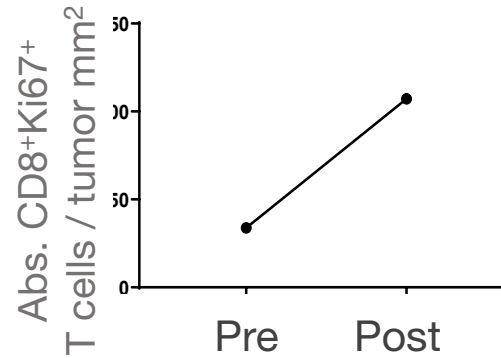
Data cut-off: 27-Jul-20

Tumoral and Circulating s4-1BB Increase Post-Treatment in PR Breast Cancer Patient

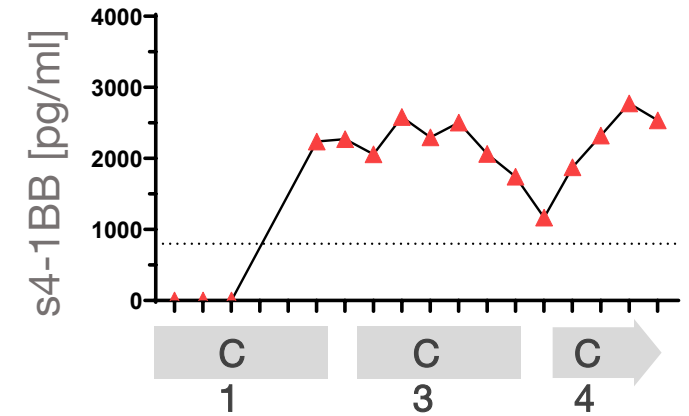
CD8⁺ T cell Numbers



CD8⁺ T cell Proliferation



Soluble 4-1BB



CD8⁺ T cell numbers, proliferation, cytolytic molecules and s4-1BB increase post-treatment, demonstrating 4-1BB arm activity of PRS-343

Summary



Acceptable safety profile at all doses and schedules tested in **monotherapy** as well as in combination with atezolizumab



Demonstrated **durable anti-tumor activity** in heavily pre-treated patient population across multiple tumor types, including those usually not responsive to immune therapy; novel and non-redundant MoA among HER2-targeting therapies and checkpoint inhibition



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



Soluble 4-1BB increase demonstrates activity of the 4-1BB arm of the molecule



2L HER2+ gastric cancer trial in combination with paclitaxel and ramucirumab in preparation

Phase 2 PoC Study in 2nd Line Gastric Cancer

Phase 2 Initiation

PRS-343 in combination with
ramucirumab and paclitaxel for
2nd-line HER2+ gastric cancer

Clinical trial collaboration with Eli Lilly and
Company; Lilly to supply ramucirumab

Single-arm, up to 60 patients

Primary endpoints: ORR and DCR

HER2+ subgroup from RAINBOW trial
as comparator enriched w/ RWD

GC 2L PIVOTAL TRIAL



PRS-343 PoC Trial Considers Several Value-driving Elements

Factor

Impact

Biology:
Synergistic MoA in IO-amenable Patients

- Vasculature normalization from ramucirumab for improved environment for T-cell infiltration
- Tumor debulking and antigen release from paclitaxel for improved disease control and enhanced immune priming

Regulatory:
Additive to Standard of Care

- Straightforward path from PoC to pivotal
- Reduced patient enrollment hurdles compared to monotherapy study

Commercial:
Meaningful Beachhead Indication

- Second line gastric cancer market size in US, EU5, and JP is up to \$1.7B
- Upside in several other tumors

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