VIRTUAL 2020 ESMO congress

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

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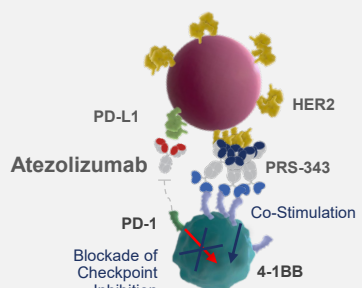
PRS-343, a HER2 4-1BB Bispecific, Drives 4-1BB Agonism in the Tumor Microenvironment in HER2 Positive Solid Tumors

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

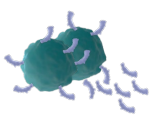
HER2
targeting
Antibody

4-1BB
targeting
Anticalin®
Proteins

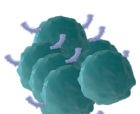


CLINICALLY-RELEVANT BIOMARKERS

4-1BB Pathway Activation
Soluble 4-1BB



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



Study Design: Monotherapy and Combination with Atezolizumab

Primary Objectives

- Characterize **safety profile** of **PRS-343** and in combination with fixed dose of **atezolizumab**
- Identify **MTD** and/or **RP2D** of **PRS-343** alone and in **combination** with **atezolizumab**

Secondary Objectives

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

Dose Levels

Monotherapy Dose Levels	Dose Levels in Combination with 1200mg Atezolizumab	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

Data cut-off: 27-Jul-20

Key Enrollment Criteria: Monotherapy and Combination with Atezolizumab

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 (monotherapy); HER2+ status documented by clinical pathology report (combination)**
- **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 (monotherapy); ECOG 0-2 (combination)
- 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 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

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

A Phase 1, Open-label, Dose Escalation Study of PRS-343 in Patients with HER2-Positive Advanced or Metastatic Solid Tumors

Treatment-Related Adverse Events for Monotherapy

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%)	
Abdominal pain		
Anemia	2 (1%)	1 (1%)
Anorexia		
Arthalgia	2 (1%)	
Asthenia	2 (1%)	
Cough	2 (1%)	
Decreased appetite	2 (1%)	
Diarrhea	6 (4%)	
Dizziness	2 (1%)	
Dry mouth		
Dyspnoea	3 (2%)	
Fever		
Flushing	5 (3%)	2 (1%)
Lightheadness		
Lymphocyte count decreased		
Neutrophil count decreased		
Non-cardiac chest pain	4 (3%)	
Paraesthesia	3 (2%)	1 (1%)
Peripheral sensory neuropathy		
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 at Active Dose Range of PRS-343 in Monotherapy

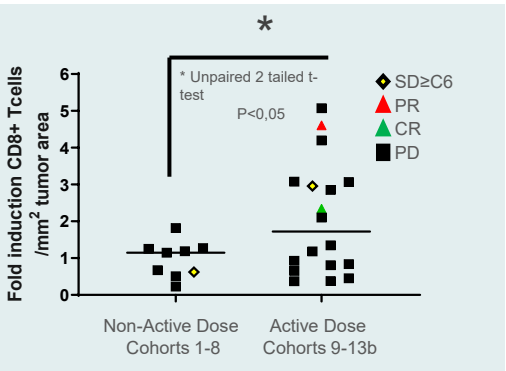
Based on clinical data, serum concentration of > 20 µg/ml defines active dose range (beginning at Cohort 9)

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%

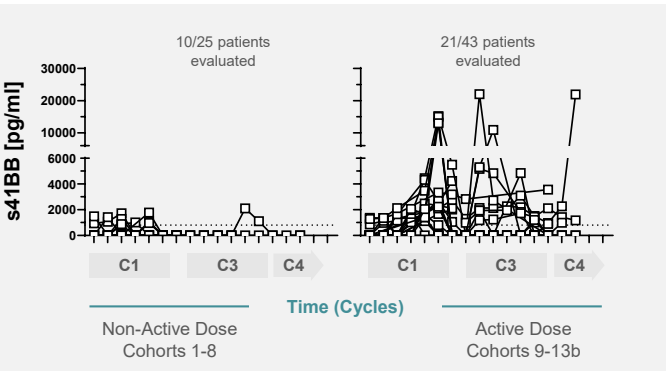
Data cut-off: 27-Jul-20

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

Tumor



Serum



Gastric Cancer Patient (107-012) with PR

Patient Profile, Treatment History and Treatment Outcome

Patient Profile

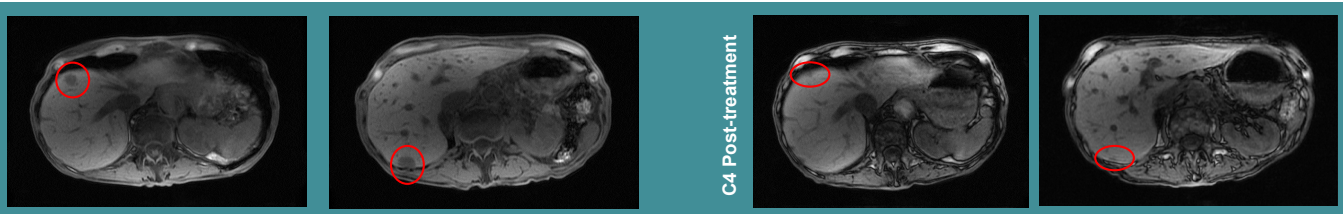
- Cohort 11b | 8 mg/kg every two weeks
- 80-year old woman; initial diagnosis in June 2017
- Stage IV gastric adenocarcinoma
- Metastases to liver, lymph node and adrenal glands
- HER2 IHC 3+; PD-L1 positive (CPS=3)
- NGS: ERBB2 amplification, TP53 mutation, alteration of CDK12 and SF3B1

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

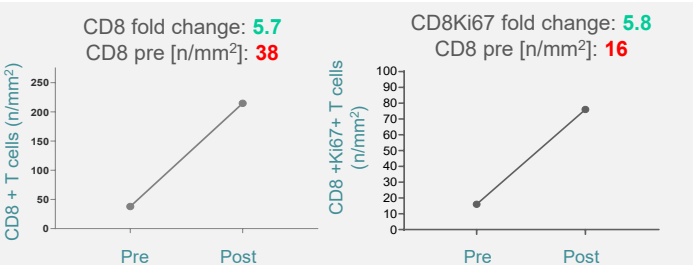
Lesions	Lesion Site	Lesion Size (mm)				
		Baseline	C2 Post-treatment	C3 Post-treatment	C4 Post-treatment	C6 Post-treatment
Target 1	Liver	14	12	10	9	8
Target 2	Liver	20	16	10	8	9
Target 3	Pancreas	19	16	14	14	14
% Change from Baseline			-17%	-36%	-42%	-42%
Non-target 1	Lung	Present	Present	Present	Present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

Data cut: 24-Jan-2020

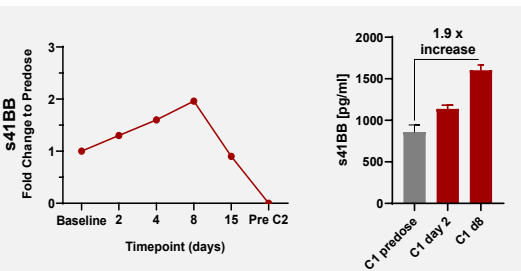
CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in responding Gastric Cancer Patient (107-012)



Tumor



Serum



Rectal Cancer Patient (103-021) with CR

Patient Profile, Treatment History and RECIST

Monotherapy: Rectal Cancer Patient with Confirmed CR

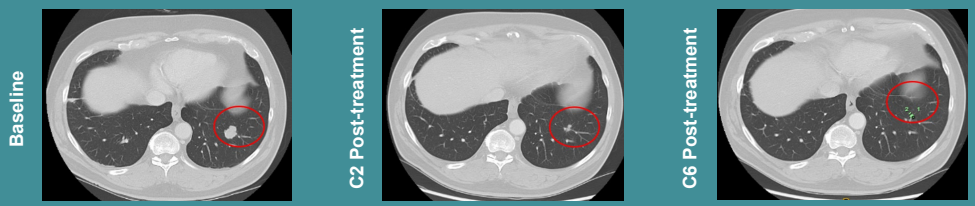
- Cohort 13b | 18 mg/kg Q2W
- 59-year-old male; initial diagnosis March 2017
- Stage 4 rectal adenocarcinoma cancer; metastasized to heart and lung
- FoundationOne Her2 amplification; in-house testing IHC 3+
- MSS, TMB low (2 mt/Mb)

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

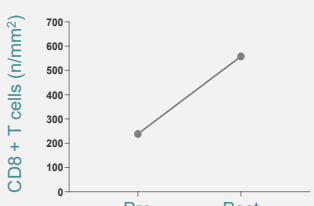
Data cut-off: 27-Jul-20

CD8+ T Cell Numbers in the Tumor and Circulating s4-1BB Increase Post-Treatment in CR Rectal Cancer Patient (103-021)

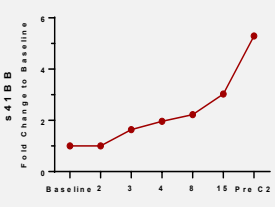


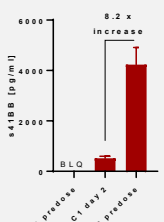
Tumor

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



Serum

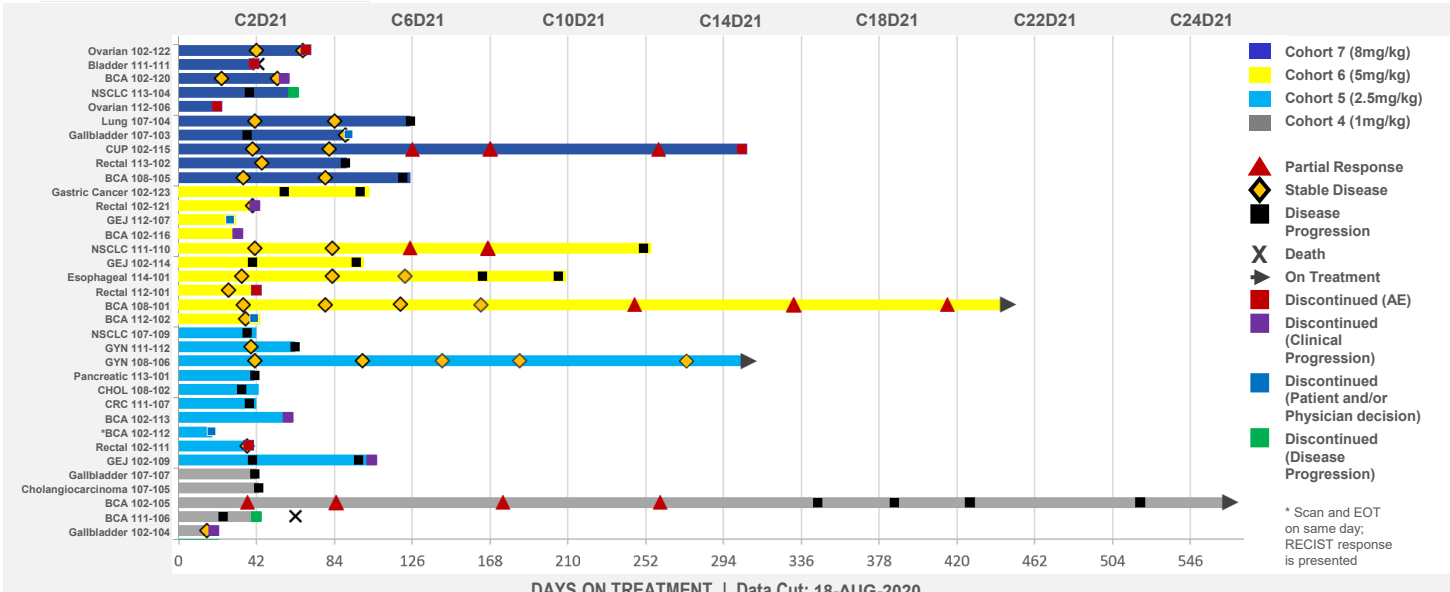




Combination Therapy with Atezolizumab

A Phase 1B, Open-label, Dose Escalation Study of PRS-343 in Combination With Atezolizumab in Patients with Specific HER2-Positive Advanced or Metastatic Solid Tumors

PRS-343 + Atezolizumab Duration of Exposure



Treatment-Related Adverse Events for Combination with Atezolizumab

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%)	
Chills		
Abdominal pain	2 (1%)	
Anemia	4 (3%)	2 (1%)
Anorexia	2 (1%)	
Arthalgia	2 (1%)	
Asthenia		
Cough		
Decreased appetite		
Diarrhea	5 (3%)	1 (1%)
Dizziness		
Dry mouth	3 (2%)	
Dyspnoea		
Fever	3 (2%)	
Flushing		
Lightheadness	2 (1%)	
Lymphocyte count decreased	3 (2%)	1 (1%)
Neutrophil count decreased	3 (2%)	1 (1%)
Non-cardiac chest pain		
Paraesthesia		
Peripheral sensory neuropathy	2 (1%)	
Pruritis	4 (3%)	
Rash		

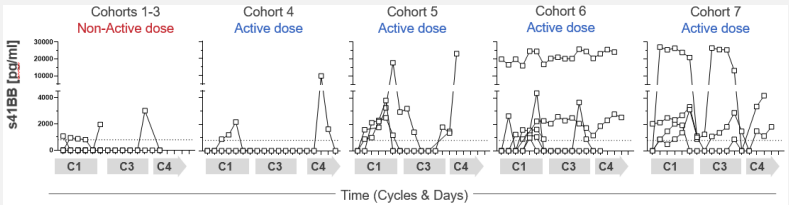
Two TRAEs above Grade 3: Grade 4 AST increase, Grade 3 transaminitis, and eventually Grade 5 hepatic failure in cohort 7 (8mg/kg + 1200mg atezolizumab); Grade 4 hemolytic anemia (unrelated to PRS-343, related to atezolizumab) in cohort 7.

Data cut-off: 27-Jul-20

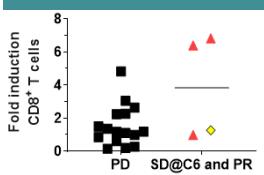
Soluble 4-1BB Increases in Active Dose Cohorts & Clinical Benefit is Associated with Tumoral Immune Cell Activation

4-1BB target engagement

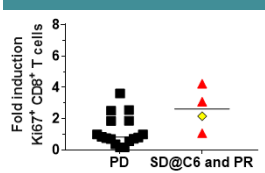
Soluble 4-1BB in serum



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

Breast Cancer Patient (108-101) with PR

Patient Profile, Treatment History and RECIST

PRS-343+Atezolizumab: Breast Cancer Patient with PR

- 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

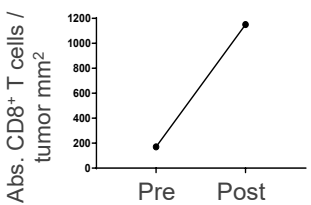
Oncology Treatment History	Duration
Trastuzumab/Docetaxel/ Tamoxifen/Carboplatin	Sep 2011-Jul 2013
Trastuzumab/Pertuzumab/Vinorelbine	Aug 2013-Jan 2016
T-DM1/Fulvestrant	Nov 2017-Mar 2018
Capecitabine/Lapatinib	Mar 2018
Palbociclib/Arimidex	Apr-May 2019

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

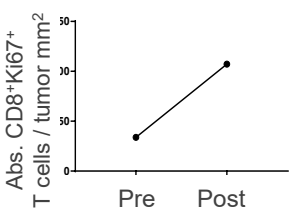
Data cut-off: 27-Jul-20

Tumoral and Circulating s4-1BB Increase Post-Treatment in PR Breast Cancer Patient (108-101)

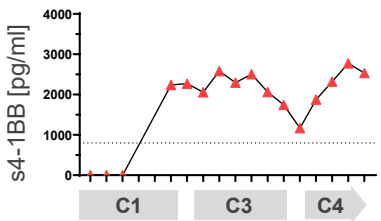
CD8+ T cell Numbers



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

Conclusions

- **Acceptable safety profile** in 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
- 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/gastroesophageal cancer trial in combination with Paclitaxel and Ramucirumab in preparation

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Monotherapy

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- The University of Texas MD Anderson Cancer Center – S. Piha-Paul, B. Bruggman
- Sarah Cannon Research Institute, LLC – J. Bendell, J. Costin
- NEXT Oncology – A. Tolcher, K. Dotson
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Combination with Atezolizumab

Study 0818 (NCT03650348, A Phase 1B, Open-label, Dose Escalation Study of PRS-343 in Combination With Atezolizumab in Patients with Specific HER2-Positive Advanced or Metastatic Solid Tumors) sponsored by Pieris, atezolizumab kindly supplied by F. Hoffmann-La Roche Ltd

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- The Ohio State University, Department of Internal Medicine – A. Noonan
- Ochsner Cancer Institute – M. Matrana, S. Jerdonek
- Memorial Sloan Kettering Cancer Center – G. Ku, T. Shrivastav

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