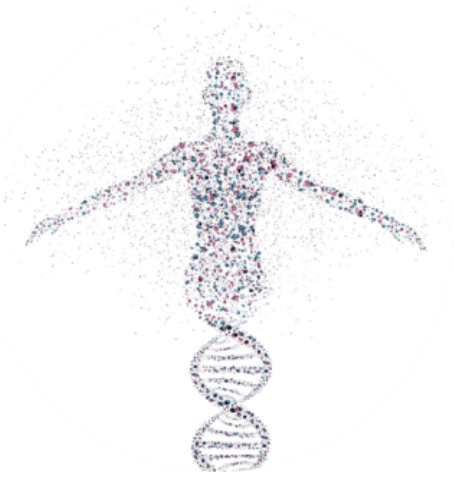


Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Claudine Isaacs, Rita Nanda, Christina Yau, Jo Chien, Megna Trivedi, Erica Stringer-Reasor, Christos Vaklavas, Judy Boughey, Amy Sanford, Anne Wallace, Amy Clark, Alexandra Thomas, Kathy Albain, Laura Kennedy, Tara Sanft, Kevin Kalinsky, Heather Han, Williams N, Mili Arora, Anthony Elias, Carla Falkson, Smita Asare, Ruixiao Lu, Maria Pitsiouni, Amy Wilson, Jane Perlmutter, Hope S Rugo, Richard Schwab, Frasier Symmans, Nola Hylton, Laura Van 't Veer, Douglas Yee, Angela DeMichele, Don Berry, Laura Esserman

on behalf of the I-SPY 2 TRIAL Consortium

Disclosures

Consultancies: Genentech, PUMA, Seattle Genetics, AstraZeneca, Novartis, Pfizer, ESAI, Sanofi; ION; Gilead

Royalties: Wolters Kluwer (UptoDate); McGraw Hill (Goodman and Gillman)

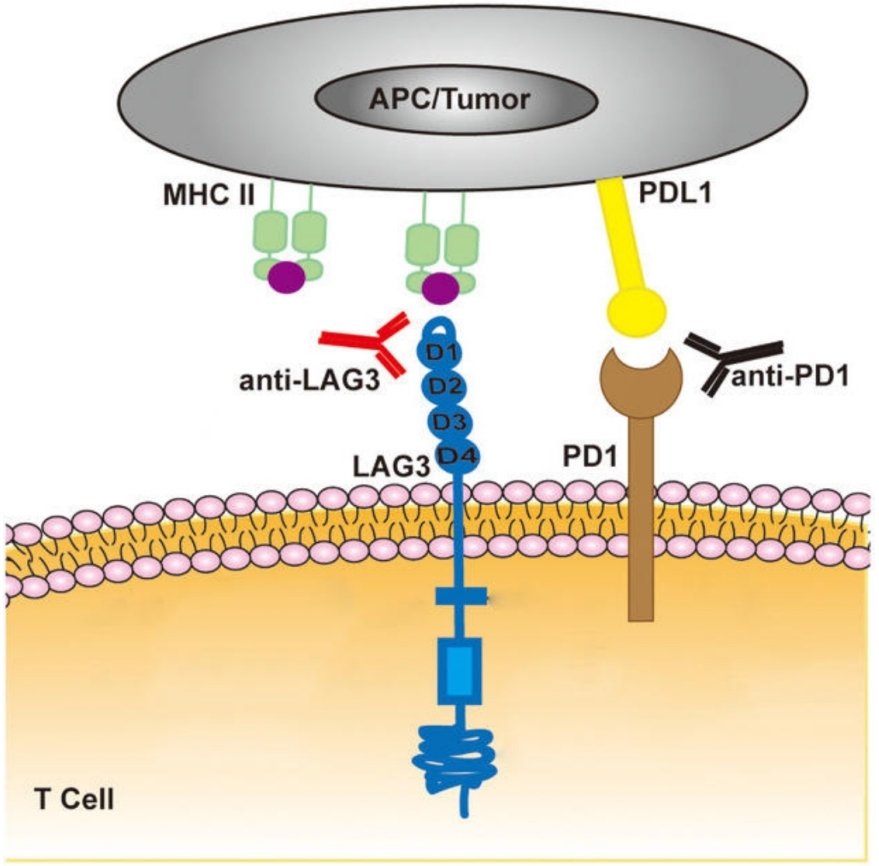
Medical Director: SideOut Foundation (non-profit)

Research Support (to institution): Tesaro/GSK; Seattle Genetics; Pfizer; AZ; BMS; Genentech; Novartis

[1]Nanda et al, JAMA Oncology 2020; [2]Schmid et al, NEJM 2020; [3]Hamid et al. ESMO 2022; Tawbi et al. NEJM 2022

REGN3767: LAG-3 Antagonist

- REGN3767 (Fianlimab) is a fully humanized, high-affinity mAb that binds to and antagonizes lymphocyte activation gene 3 (LAG-3)[1]
- LAG-3
  - Cell surface molecule expressed on immune cells including T cells
  - Binds to MHC class II leading to inhibition of T-cell proliferation and activation[1]
  - REGN3767 blocks LAG-3/MHC class II-driven T cell inhibition[1]
  - Often co-expressed with PD-1
- Cemipimab is anti-PD-1[2] approved for treatment of NSCLC and cutaneous and squamous cell CA



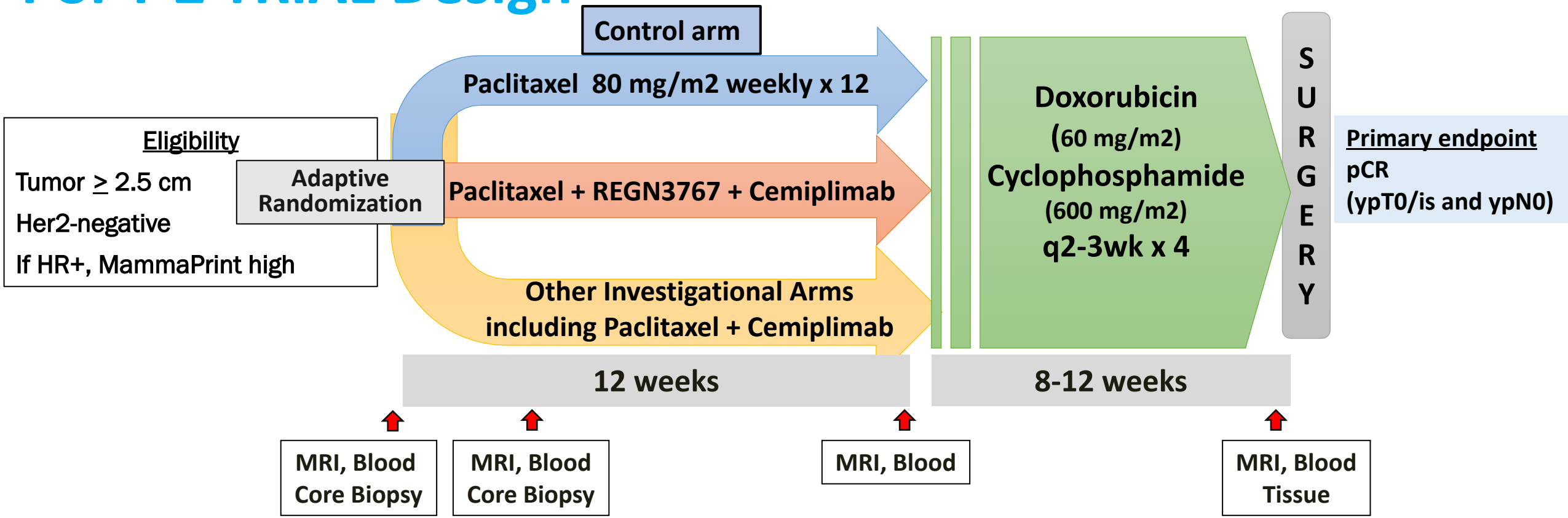
1. Burova E et al. Mol Cancer 2019;18:2051–2062; 2. Burova E et al. Mol Cancer 2017;16:861–870

Rationale for REGN3767 + Cemiplimab Combination

- The addition of pembrolizumab, an anti-PD-1, to standard neoadjuvant chemotherapy improves outcomes
  - Phase 2 I-SPY2 trial: near tripling of estimated pathologic complete response (pCR) rate in TN and high-risk HR+ signatures[1]
  - Phase 3 Keynote 522: improved pCR and EFS in TNBC[2]
- Preclinical data suggest a synergistic interaction between anti-LAG3 and anti-PD-1 therapy
- In previously untreated melanoma:
  - Phase 1 expansion cohort (n=80) of cemiplimab + REGN3767 in anti-PD-1/PDL-1- naïve advanced melanoma[3]: ORR 64%
  - RELATIVITY-047 phase 2/3 RCT[4]: median PFS 10.1 months with nivolumab + relatlimab (anti-LAG-3) vs 4.6 months with nivolumab + placebo (p = 0.006)

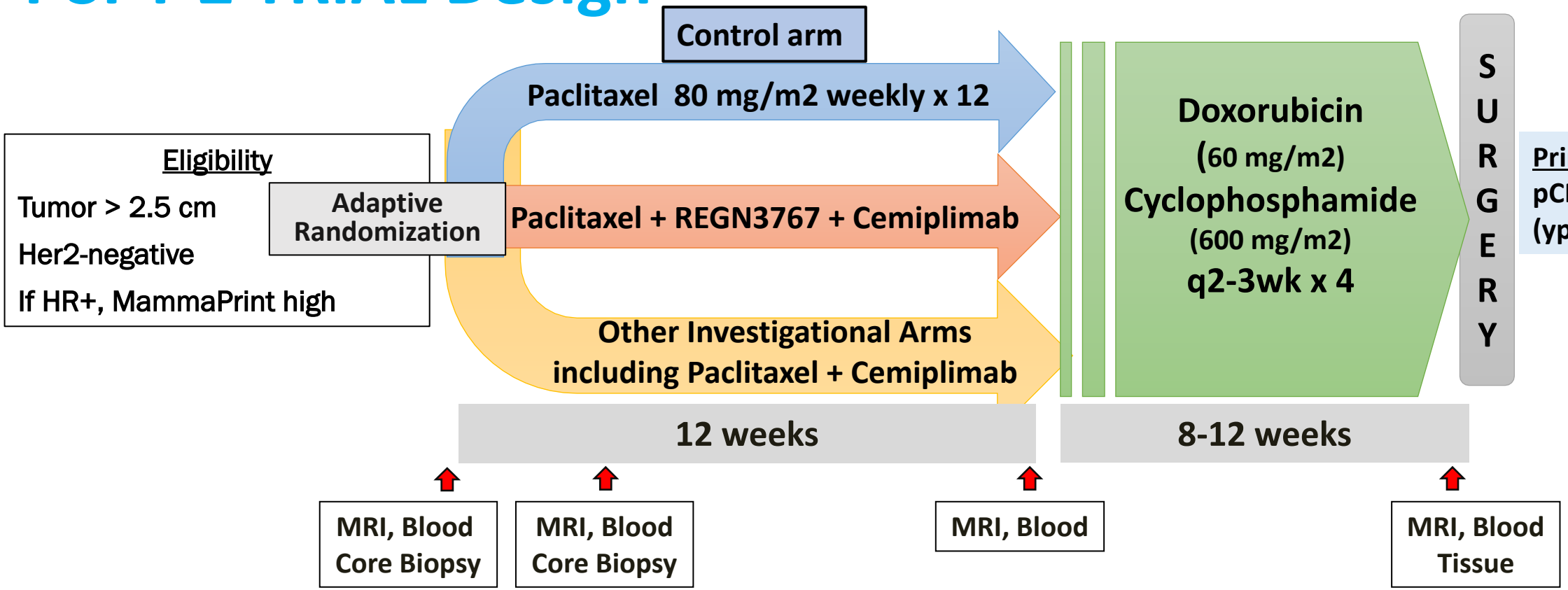
[1]Nanda et al, JAMA Oncology 2020; [2]Schmid et al, NEJM 2020; [3]Hamid et al. ESMO 2022; Tawbi et al. NEJM 2022

I-SPY 2 TRIAL Design



- REGN3767 + Cemiplimab was studied in **3 HER2-negative** biomarker signatures: **all HER2-; TNBC; HR+/HER2**
- Agent Graduation:
  - ≥85% predicted probability of success in a 300-patient phase 3 neoadjuvant trial
- Graduation is assessed for each pre-specified biomarker signature

I-SPY 2 TRIAL Design



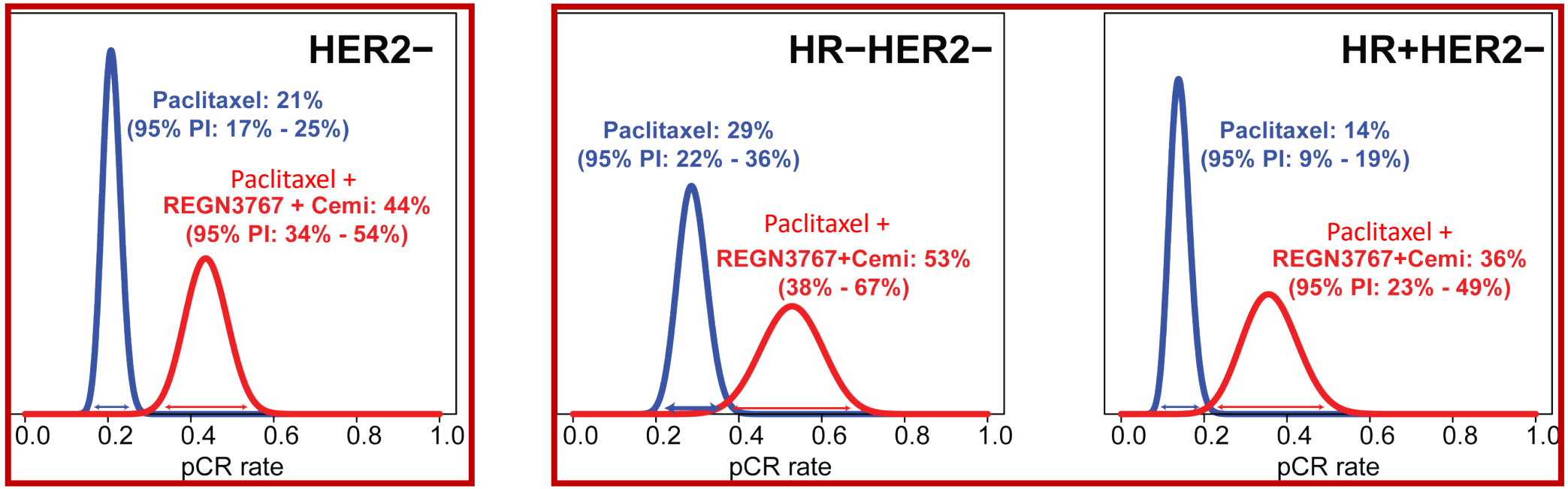
Agent	Dose	Route	Treatment Week
REGN3767	1600 mg q3wks	IV	wk 1,4,7,10
Cemiplimab	350 mg q3wks	IV	wk 1,4,7,10
Paclitaxel	80 mg/m^2 q1wk	IV	wk 1–12

Demographics (all HER2-negative)

	Randomization period
REGN3767 + Cemiplimab	Feb. 13, 2020 – Dec. 9, 2021
Paclitaxel (control)	Apr. 12, 2010 – Dec. 9, 2021

Patient characteristics	REGN 3767 + Cemiplimab (n=76)	Control (n=350)
Age, yrs		
Median (Range)	47 (26-78)	48 (19-80)
Race, n (%)		
White	57 (75%)	273 (78%)
African American	11 (14%)	46 (13%)
Asian	5 (7%)	30 (9%)
Other	3 (4%)	1 (0%)
HR status, n (%)		
Positive	40 (53%)	195 (56%)
Negative	36 (47%)	155 (44%)
Tumor size by MRI, cm		
Median (Range)	3.45 (1.6 - 10.9)	3.8 (1.2 - 15.0)
Clinical nodal status		
Node positive	31(41%)	151(43%)

Efficacy Analysis

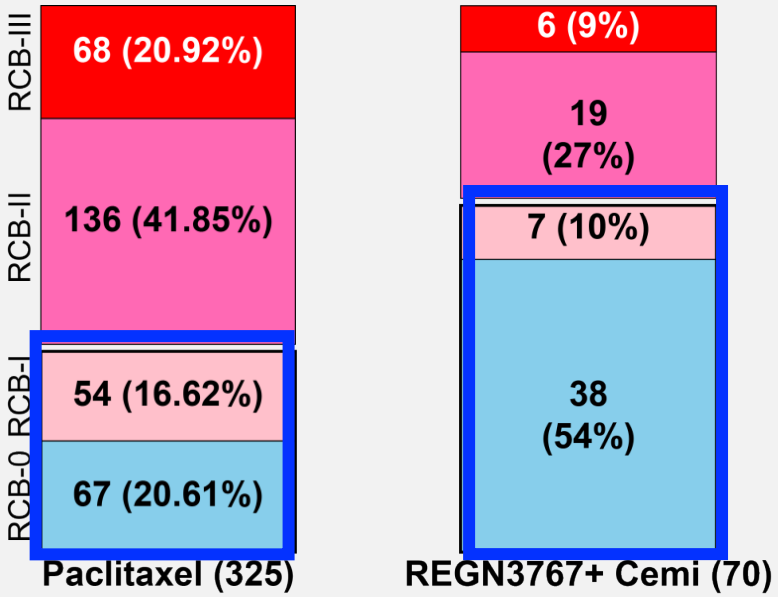


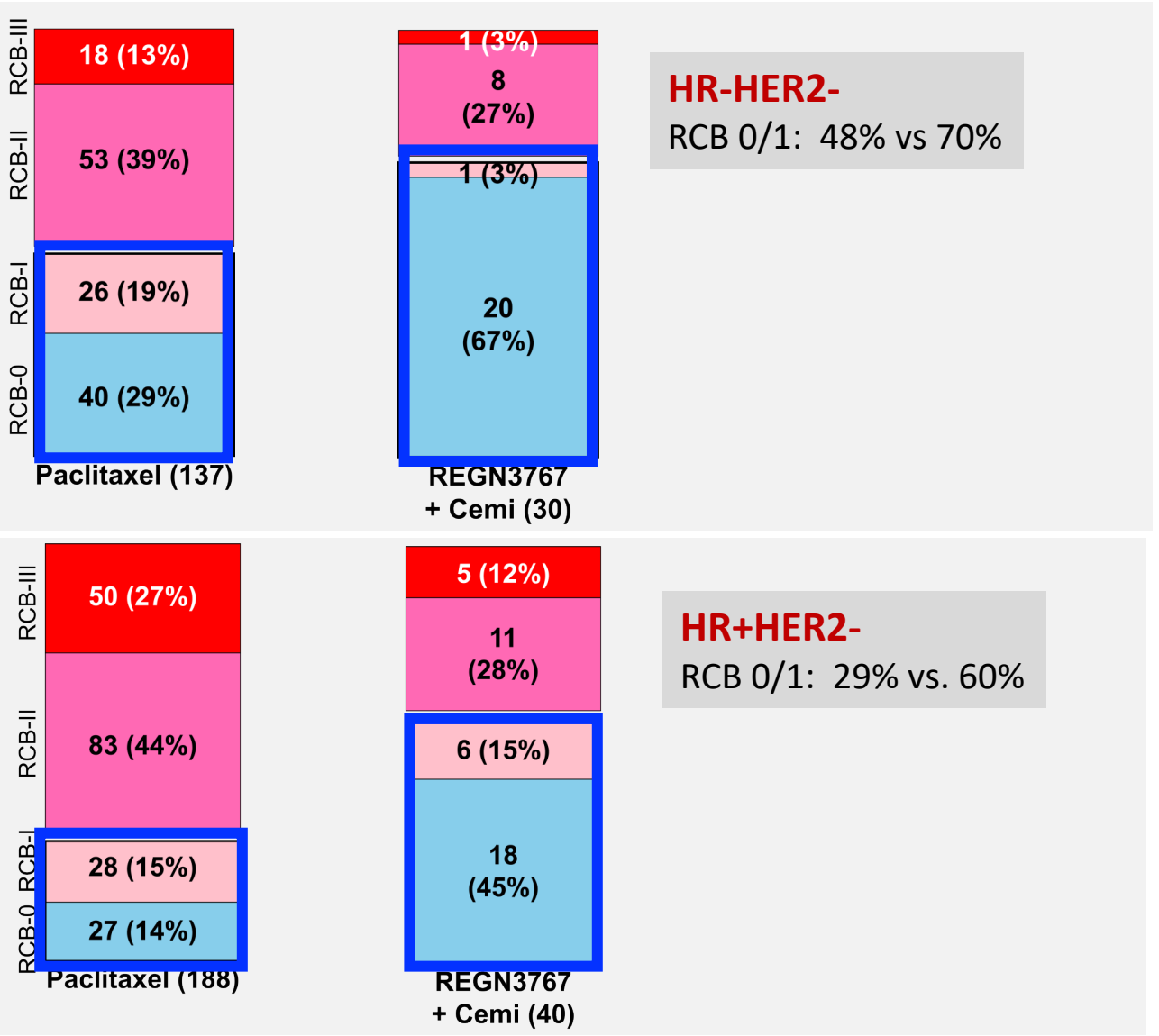
Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pac + REGN3767 + Cemi Superior to Control	Predictive Probability of Success in Phase 3 (relative to Control)
	Pac + REGN3767 + Cemi (n=76)	Control (n=350)		
HER2-	44% (34% - 54%)	21% (17% - 25%)	>0.999	0.955
HR-HER2-	53% (38% - 67%)	29% (22% - 36%)	0.999	0.915
HR+HER2-	36% (23% - 49%)	14% (9% - 19%)	>0.999	0.940

Pac + REGN3767 + Cemiplimab graduated in all 3 eligible biomarker signatures by demonstrating increased pCR

Cemiplimab + REGN 3767 downshifted residual cancer burden class (RCB)[1] across all subtypes

HER2-
RCB 0/1: 37% vs 64%

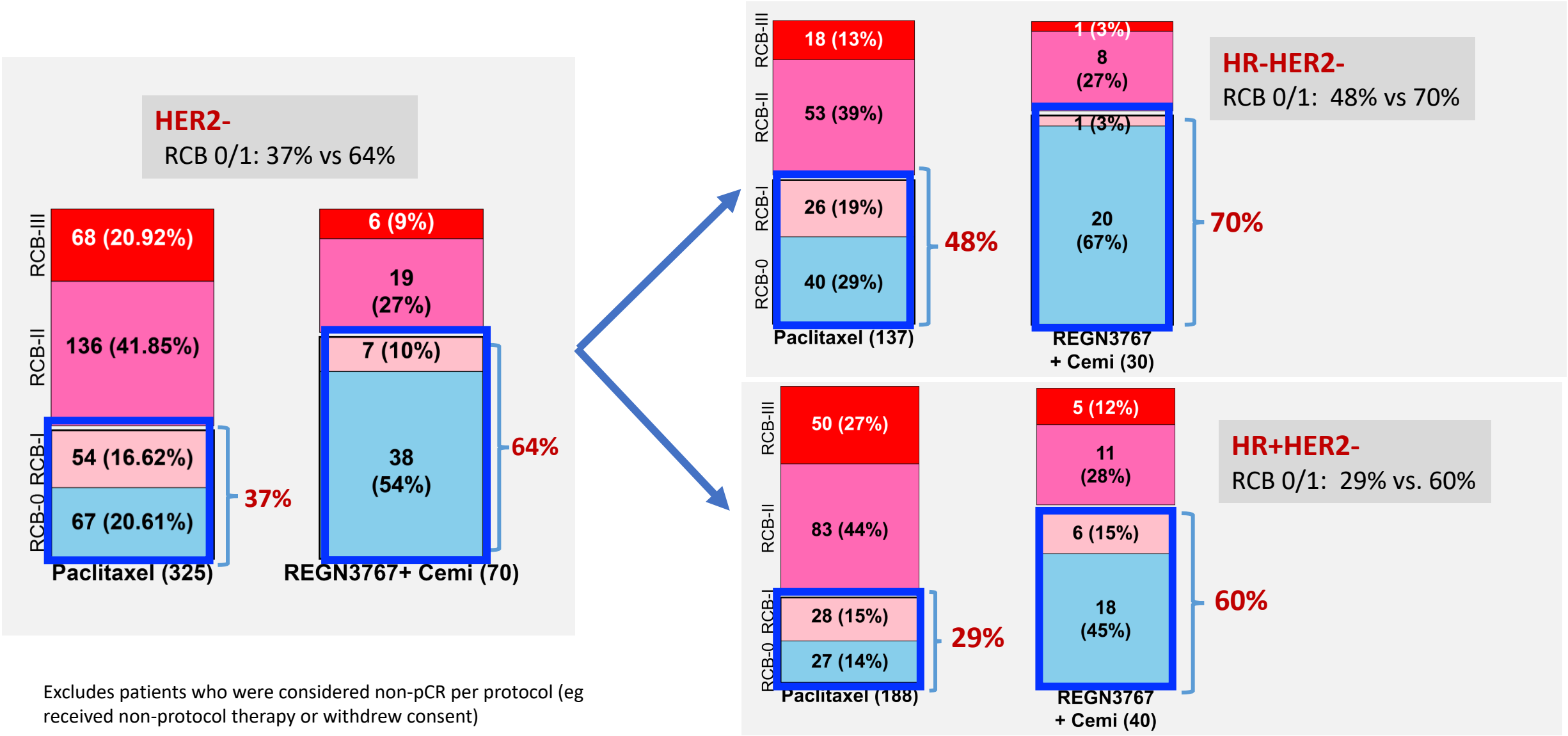




Excludes patients who were considered non-pCR per protocol (eg received non-protocol therapy or withdrew consent)

* Symmans WF et al.. J Clin Oncol. 2007;25(28):4414-22.

Cemiplimab + REGN 3767 downshifted residual cancer burden class (RCB)[1] across all subtypes



Excludes patients who were considered non-pCR per protocol (eg received non-protocol therapy or withdrew consent)

* Symmans WF et al.. J Clin Oncol. 2007;25(28):4414-22.

Treatment-Emergent Adverse Events (non-immune) (≥ 10% difference)

Adverse Event	REGN3767 + Cemi (n=76)		Control (n=350)	
	Grade>=3	All Grade	Grade>=3	All Grade
Blood and lymphatic system disorders				
Anemia	1 (1%)	24 (32%)	14 (4%)	67 (19%)
General Disorders				
Fatigue	3 (4%)	64 (84%)	4 (1%)	238 (68%)
Headache	2 (3%)	35 (46%)	3 (1%)	105 (30%)
Fever	0	20 (26%)	1 (<1%)	40 (11%)
Pain	0	22 (29%)	0	50 (14%)
Dizziness	0	21 (28%)	0	58 (17%)
Gastrointestinal disorders				
Diarrhea	1 (1%)	37 (49%)	6 (2%)	118 (34%)
Constipation	0	37 (49%)	0	137 (39%)
Dry mouth	0	13 (17%)	0	23 (7%)
Decreased appetite/dysgeusia	0	26 (34%)	0	77 (22%)
Laboratory/Investigations				
Alanine aminotransferase increased	1 (1%)	16 (21%)	4 (1%)	36 (10%)
Other				
Peripheral neuropathy	0	27 (36%)	6 (2%)	174 (50%)
Alopecia	na	52 (68%)	na	202 (58%)
Hot flashes	0	31 (41%)	1 (<1%)	94 (27%)

Pulmonary embolism 2 (3%) vs 1 (0.3%); Sepsis 5 (7%) vs 2 (1%)

Based on available data as of October 15th, 2022

Immune-Related Adverse Events (irAEs)

40 (53%) patients in REGN3767 + Cemi arm experienced irAE

irAE	Grade 1/2	Grade 3	All Grade
Hypothyroidism	24 (32%)	0 (0%)	24 (32%)
Adrenal insufficiency/ Hypophysitis	10 (12%)	6 (5%)	16 (21%)
Type 1 diabetes mellitus	0	3 (4%)	3 (4%)
Autoimmune hepatitis	0	2 (3%)	2 (3%)
Pneumonitis	2 (3%)	0 (0%)	2 (3%)
Renal failure acute	1 (1%)*	1 (1%)	2 (3%)

1 case of arthritis (G3)
1 case of immune-related Rash maculo-papular (G3)
1 case of thyroiditis (G2)
No Grade 4+ irAEs

Based on available data as of October 15th, 2022

Immune-Related Adverse Events (irAEs)

40 (53%) patients in REGN3767 + Cemi arm experienced irAE

- 63% of irAEs occurred after > 12 weeks of treatment start
- Timing of irAE onset similar to prior I-SPY2 experience with other immune-targeting agents

irAE	Grade 1/2	Grade 3	All Grade
Hypothyroidism	24 (32%)	0 (0%)	24 (32%)
Adrenal insufficiency/ Hypophysitis	10 (12%)	6 (5%)	16 (21%)
Type 1 diabetes mellitus	0	3 (4%)	3 (4%)
Autoimmune hepatitis	0	2 (3%)	2 (3%)
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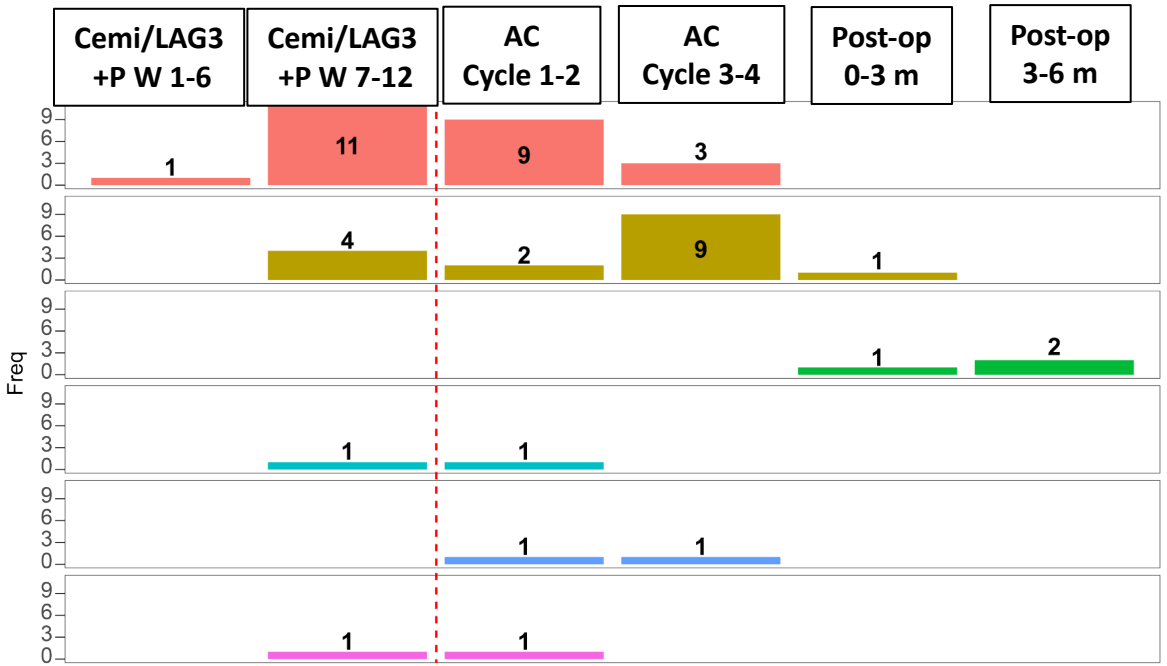
1 case of arthritis (G3)
1 case of immune-related rash maculo-papular (G3)
1 case of thyroiditis (G2)
No Grade 4+ irAEs

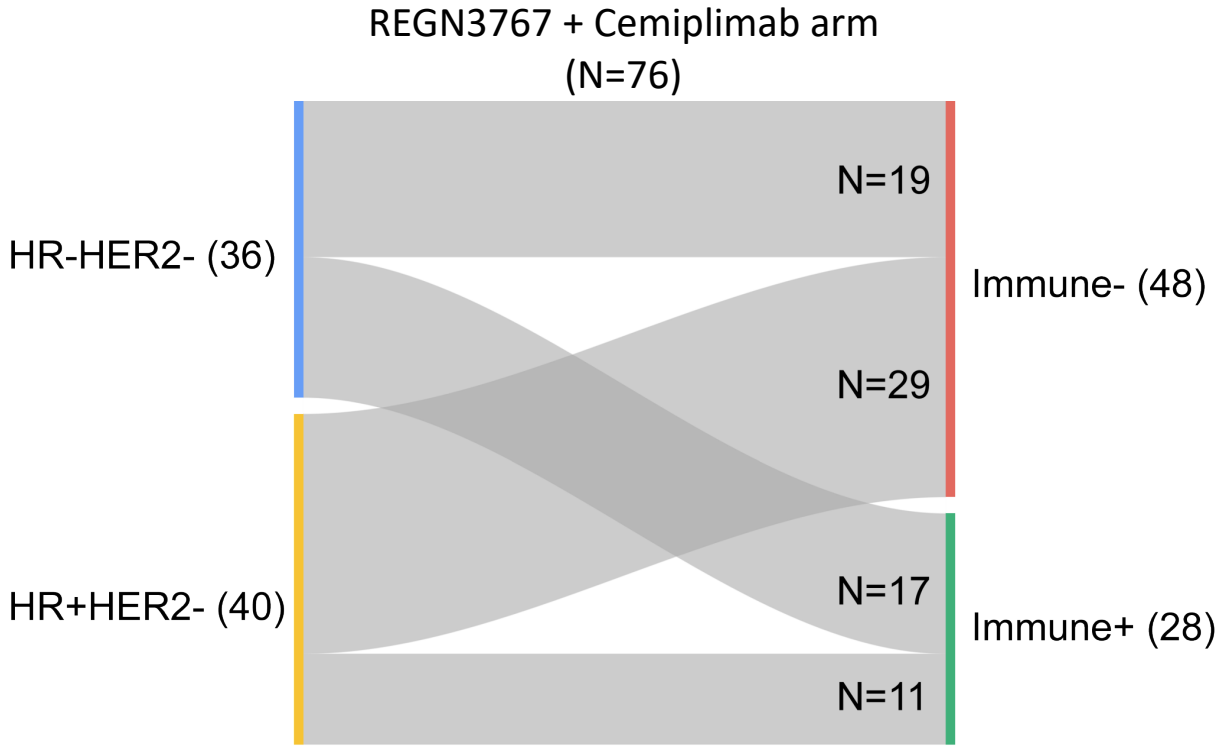
Timing of irAE onset by Time from Treatment Start



Based on available data as of October 15th, 2022

ImPrint: 53-gene Signature of Neoadjuvant Immunotherapy Response

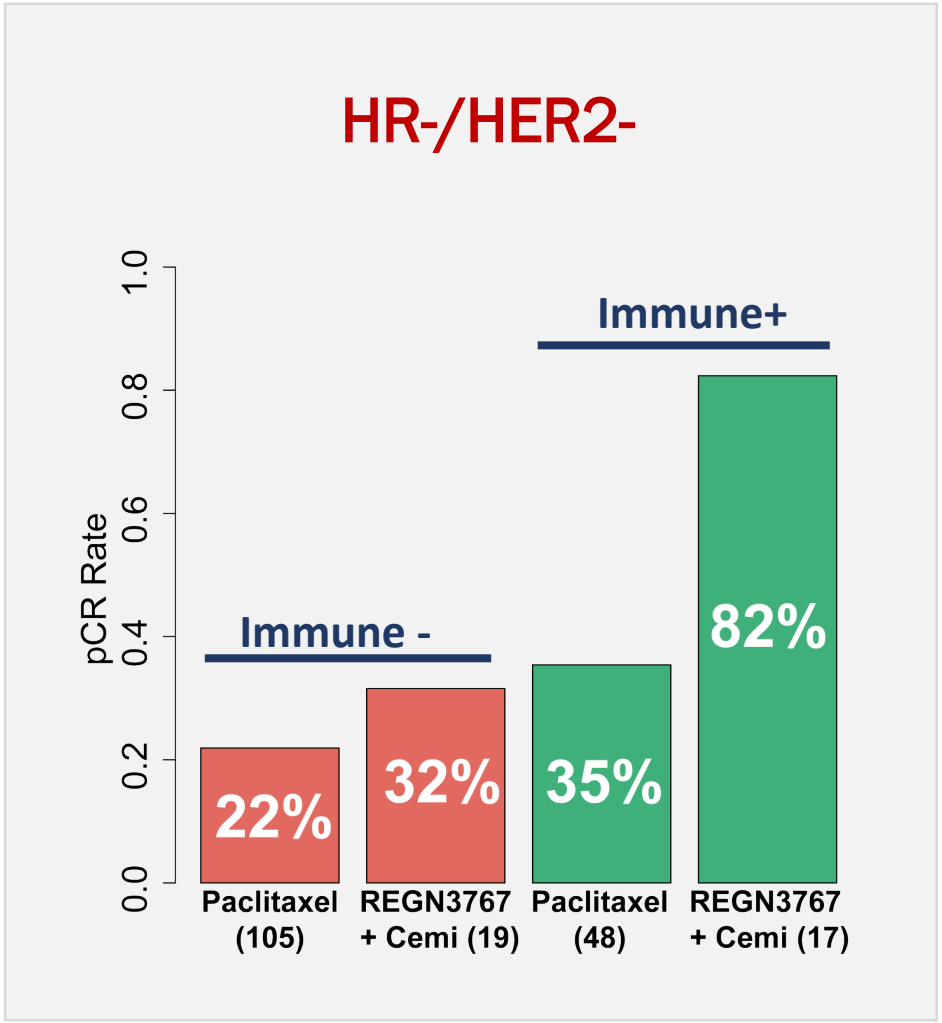
- Developed to predict response to neoadjuvant immunotherapy in pts with HR-HER2- and HR+HER2- BC[1]
- Derived from patients treated on the I-SPY 2 pembrolizumab arm and independently validated in durvalumab/olaparib arm
- In partnership with Agendia developed a diagnostic, ImPrint[2]
- IDE filed and approved on March 2022
- Further refined by introducing subtype-specific templates to improve performance in triple negative patients

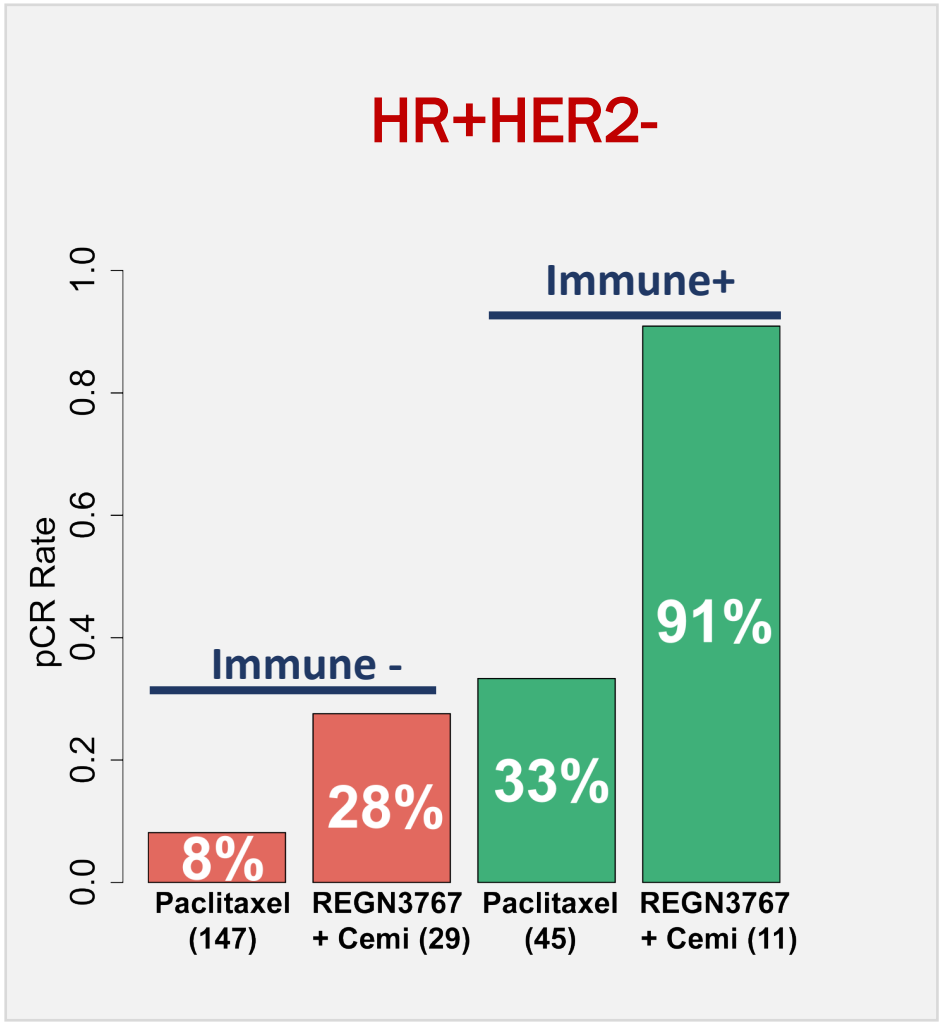


37% Immune+ overall
- **47% of TNBC Immune+**
- **28% of HR+/HER2- Immune+**

[1]*Wolff et al. Cancer Cell 2022;* [2] *Journal of Clinical Oncology* 40, no. 16_suppl (June 01, 2022) 514-514

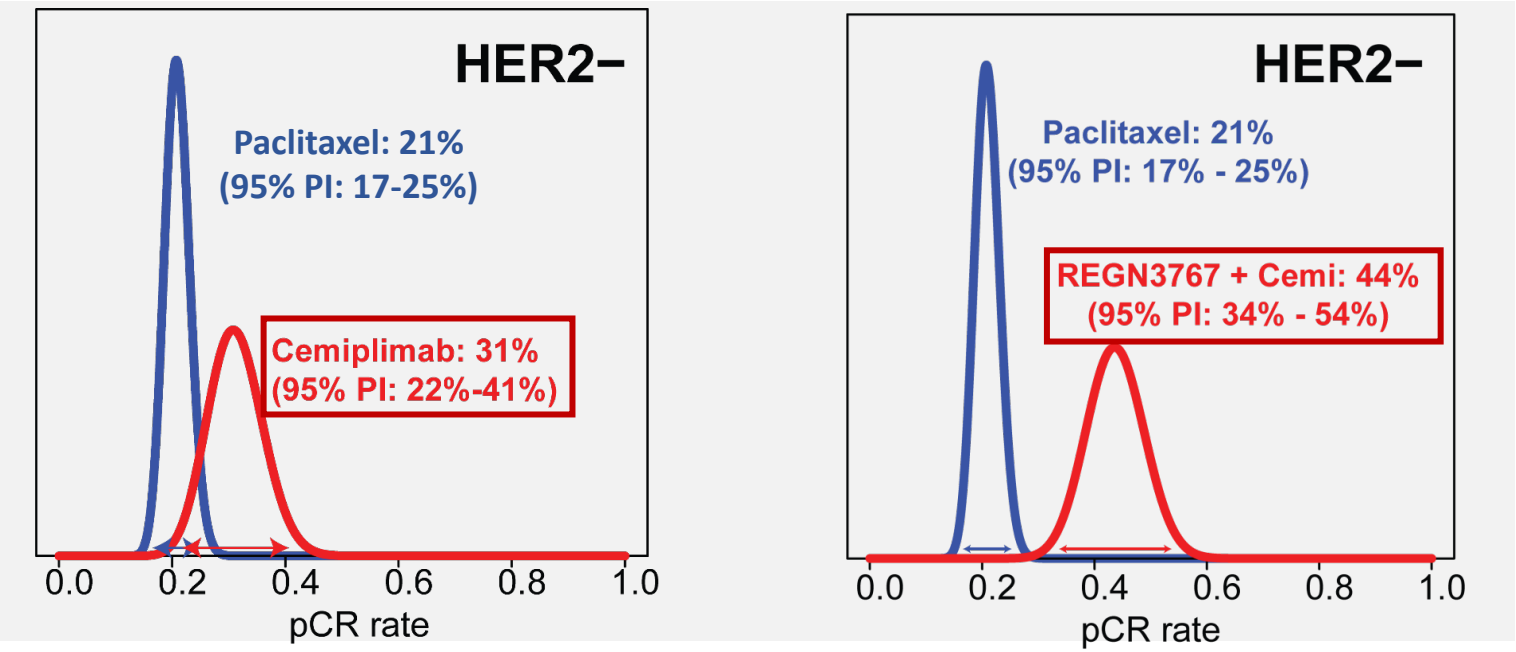
pCR by HR status and Immune Subtype

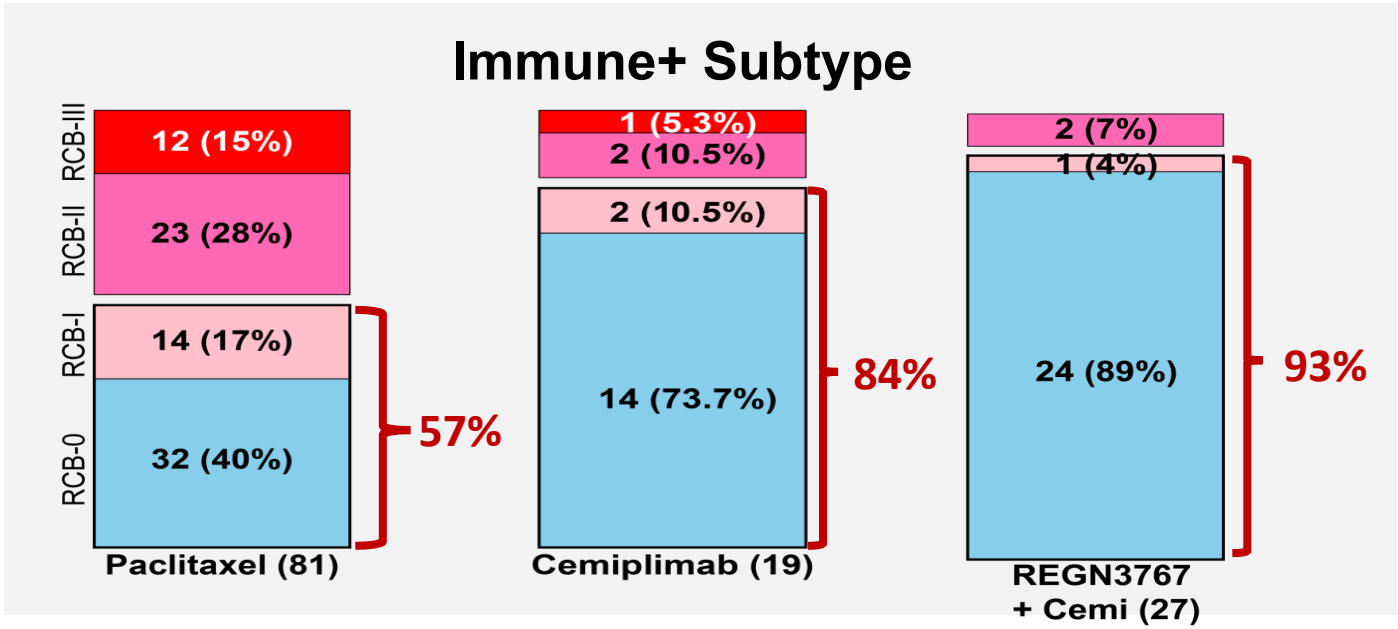




Observed (not modeled) pCR rates are shown
345 control and 76 cemi+REGN3767 of primary efficacy analysis population have ImPrint data

How do these results compare with cemiplimab + paclitaxel arm?





Conclusions

- Cemiplimab + REGN 3767 highly effective combination in both TNBC and HR+/HER2 negative breast cancer

- ImPrint signature identified greatest benefit from checkpoint inhibitor based therapy
  - In Immune+ signature, Cemiplimab + Paclitaxel (84%) performed very similarly to Cemiplimab + REGN3767 + paclitaxel (91%)

- Addition of REGN3767 associated with increased incidence of AI as well as 3 cases (5%) of Type 1 diabetes
  - This rate has not been observed in other patient populations
  - Small studies have suggested lower irAEs with lower doses of immunotherapy

- Given activity, evaluating safety profile of lower dose REGN3767 given in combination with cemiplimab + paclitaxel

The I-SPY Trials

Acknowledgements

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Thank you to the remarkable patients and families, our amazing advocates, all of the investigators, staff, and our DSMB for supporting the trial

Participating Organizations

FUNDING PARTNERS

William K Bowes, Jr. Foundation
Foundation for the National Institutes of Health (FNIH)
Give Breast Cancer the Boot
University of California San Francisco (UCSF)
The Biomarkers Consortium
The Breast Cancer Research Foundation (BCRF)
Safeway, an Albertsons Company
California Breast Cancer Research Program
Breast Cancer Research – Atwater Trust
Stand Up to Cancer
National Institutes of Health (NIH/NCI)

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