Neoadjuvant immunotherapy for HR+/HER2- early-stage breast cancer

Laura Huppert, MD

Assistant Professor of Medicine

University of California, San Francisco

San Francisco, CA

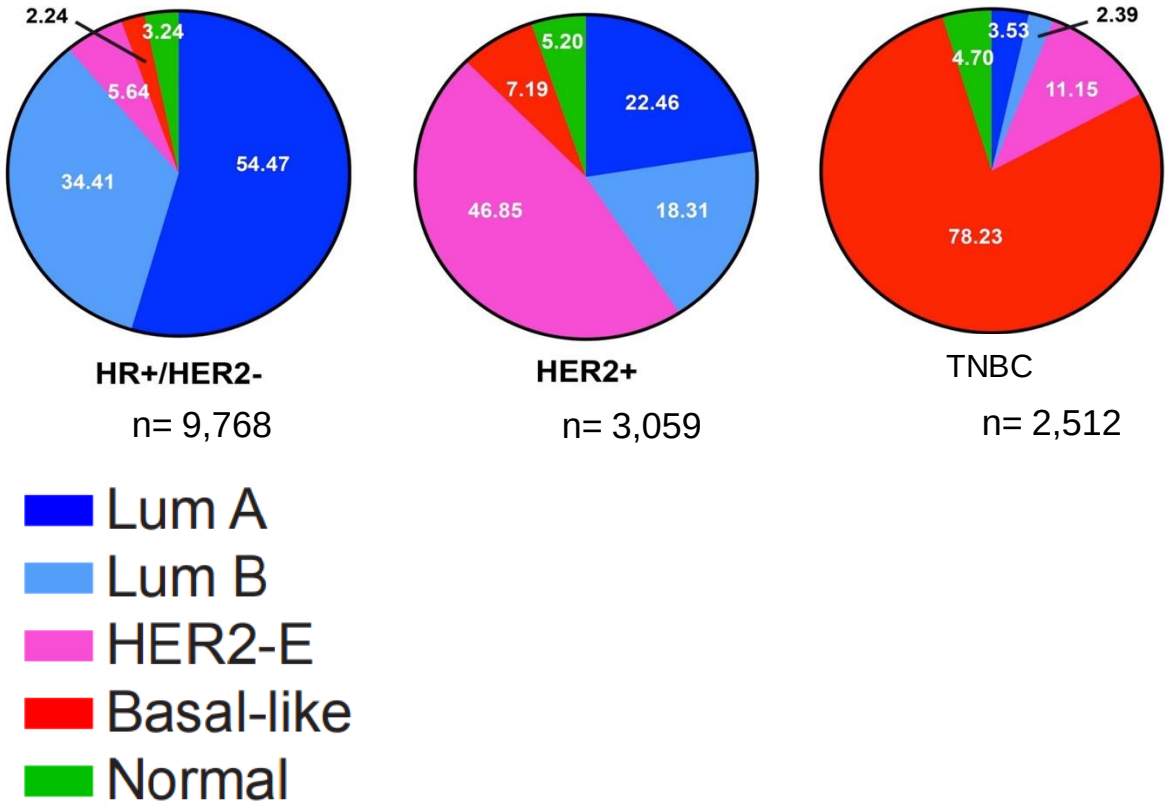
Background: Immunotherapy for HR+/HER2- early-stage breast cancer?

- **Hormone receptor positive breast cancer**
  - Most common subset of breast cancer worldwide
  - Heterogeneous
  - Most are luminal, but clear separation between luminal A and B
  - pCR rates overall following neoadjuvant chemotherapy are low (~5%)

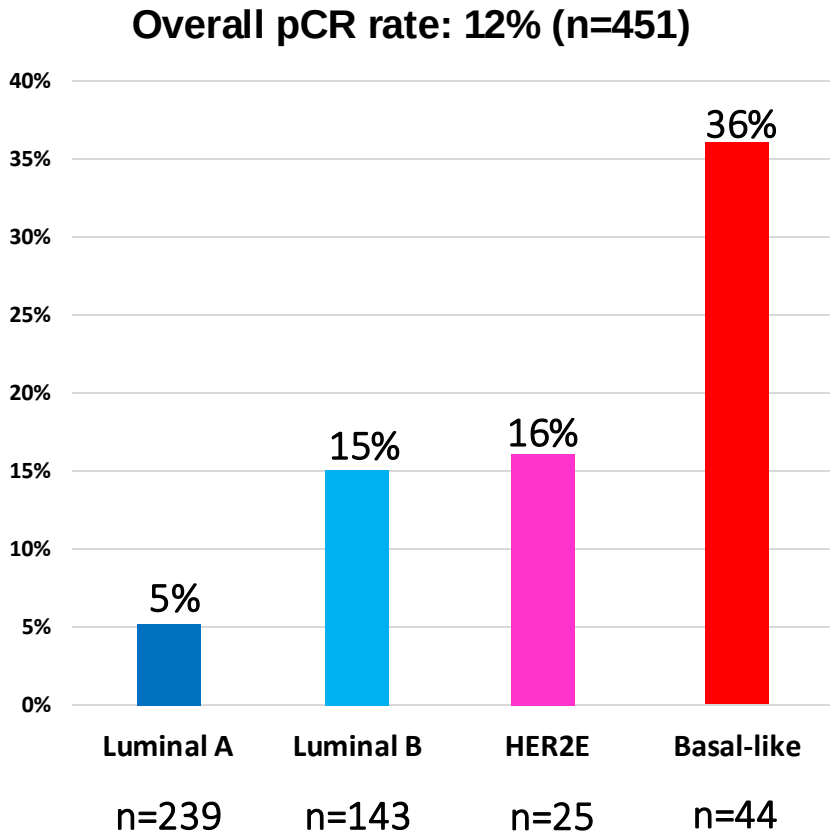
- **Gene expression tests**
  - Huge advance in understanding which tumors benefit from chemotherapy with DFS endpoint
  - More data for use in the adjuvant setting

- **Immunotherapy for HR+/HER2- EBC?**
  - Is there a subset of HR+ disease that may benefit from immunotherapy?
  - Biomarkers of IO response and resistance?

HR+/HER2- is a heterogenous subtype with low rates of pCR to NACT



pCR rates with NACT by intrinsic subtype for **HR+/HER2-** EBC

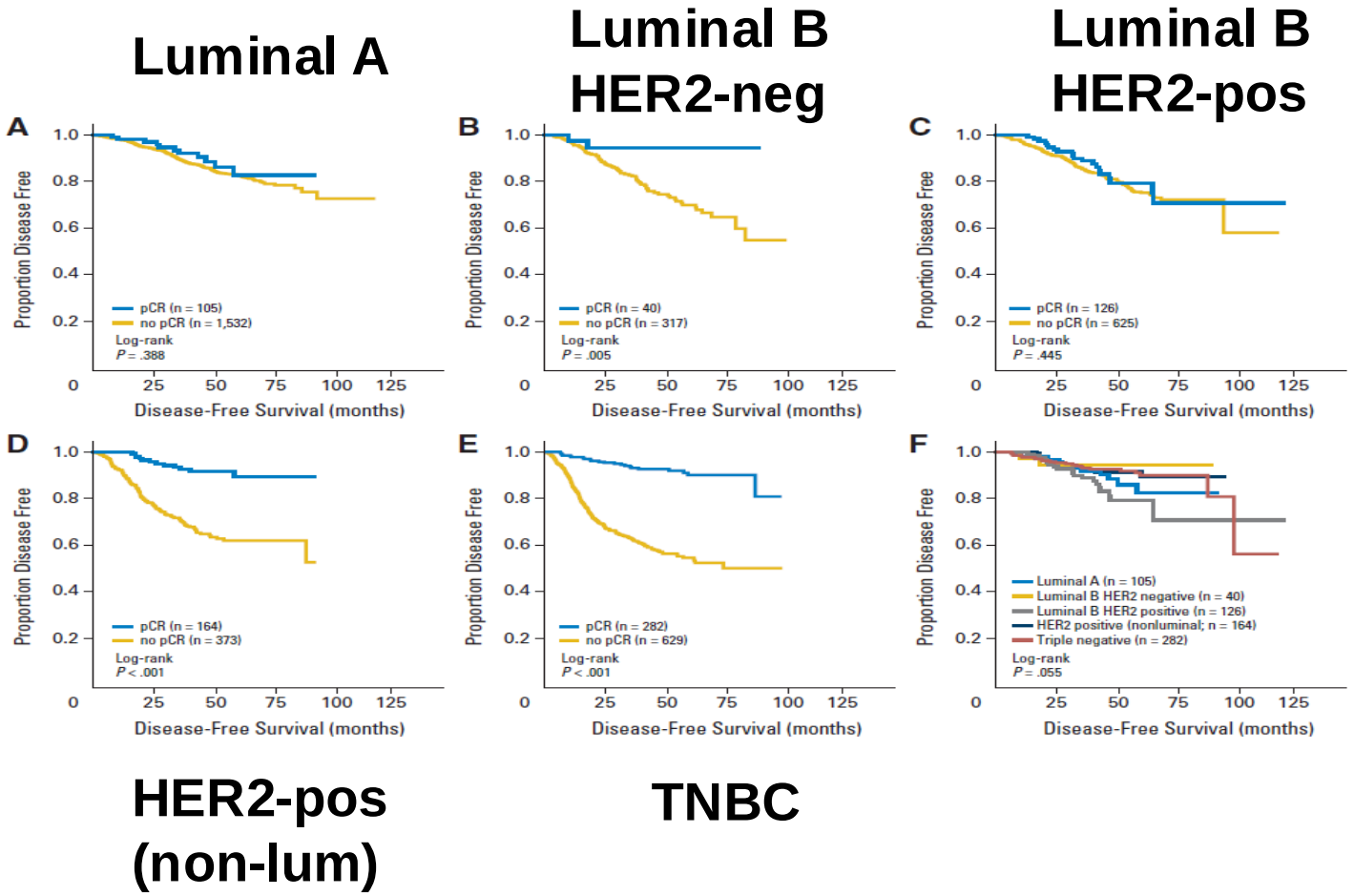


Cejalvo et al. *Cancer Treat Rev* 2019

Prat et. al. *BMC Med* 2015

Neoadjuvant Chemotherapy: pCR & Prognosis by Subtype

- Which pts will benefit from NACT and IO?
- Considerations:
  - pCR does not appear to be prognostic for very low proliferative disease
  - Adjuvant chemotherapy is now the SOC for many pre- and peri-menopausal women with 1-3 positive axillary nodes based on the data from RxPonder even with low proliferative disease
  - Response to NACT can help to modify treatment post-surgery to optimize outcome
    - This is only beneficial when response impacts prognosis



von Minckwitz et. al. *JCO* 2012

Select IO trials in metastatic HR+/HER2- breast cancer

IO only

- KEYNOTE-028: Phase 1b study of single agent pembrolizumab for PDL1+ HR+/HER2- MBC[1]
  - Only modest activity (objective response rate, ORR = 12%)
  - Limited activity of IO monotherapy in HR+/HER2- MBC

ET + CDK4/6i + IO

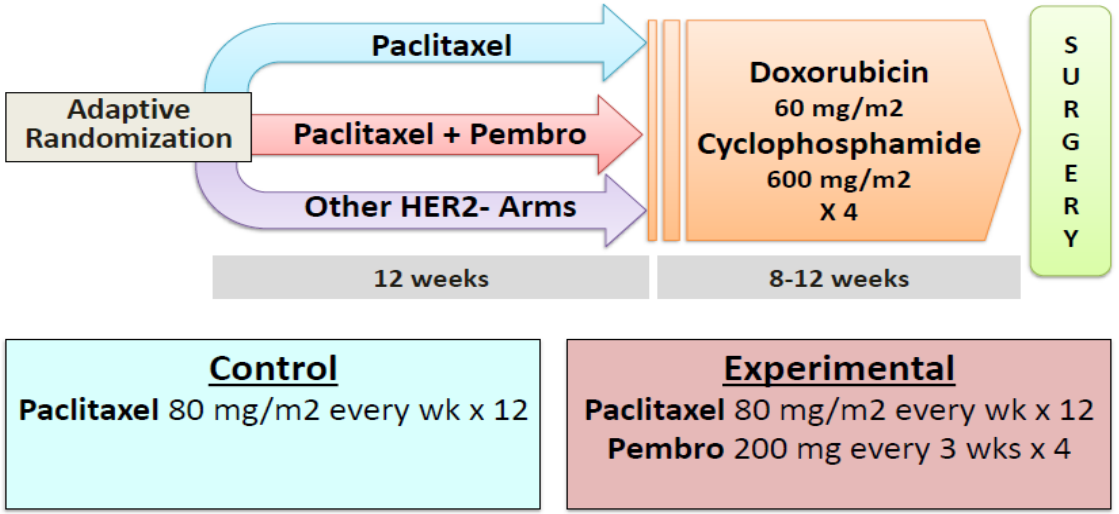
- Phase I study of abemaciclib + pembrolizumab +/- AI[2]
  - Median PFS 8.9 mo
  - Grade 3 AEs (tx naive / prior tx):
    - AST increase (34.6% / 17.9%); ALT increase (42.3% / 10.7%)
    - ILD/pneumonitis (7.7% / 3.6%)
- PACE: Phase II trial of fulvestrant +/- palbociclib +/- avalumab[3]
  - The combination of palbociclib and fulvestrant did not prolong PFS compared to fulvestrant alone
  - Triplet of fulvestrant/palbo/avalumab led to doubled PFS– small study but warrants further evaluation

Chemo/ADC + IO

- Phase II study of eribulin +/- pembrolizumab[4]
  - Median PFS, ORR, OS did not differ between groups
  - Two treatment related deaths due to colitis (IRAE + sepsis)
- Phase II study of sacituzumab govitecan +/- pembrolizumab[5]
  - PFS saci + pembro 8.4mo vs. saci 6.2mo (HR 0.76, p=0.26), No statistically significant difference (n=110)

1. Rugo et. al. *CCR* 2018
2. Rugo et. al. *NPJ Breast Cancer* 2022
3. Mayer et. al. *JCO* 2024
4. Tolaney et. al. *JAMA Oncology* 2020
5. Castro-Garrido ASCO 2024

I-SPY2: Pembrolizumab graduated for efficacy in HER2-negative cohorts



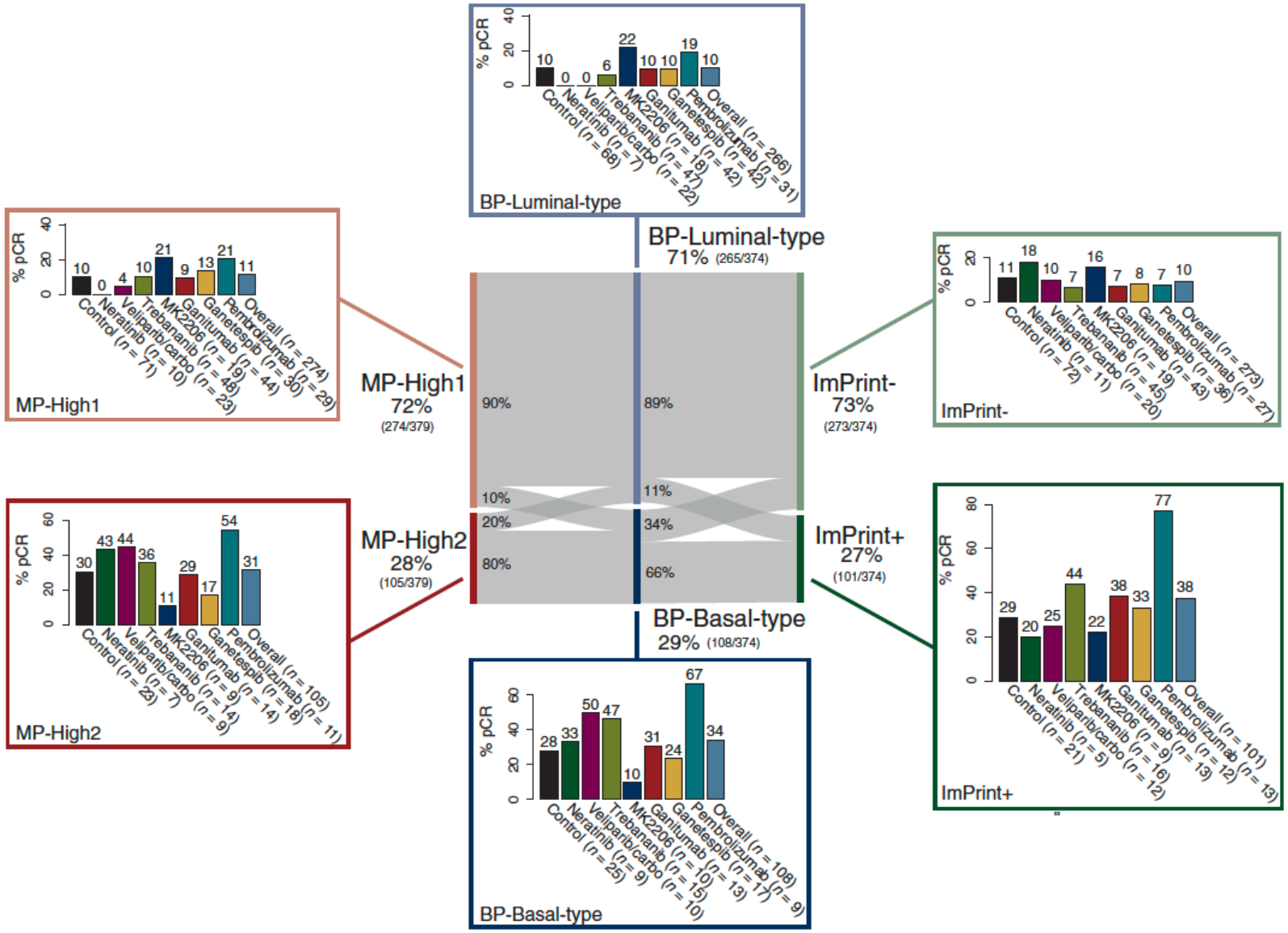
- 69 patients (40 HR+/HER2-; 29 TNBC) were randomized to 4 cycles of pembrolizumab in combination with weekly paclitaxel followed by AC

- Final estimated pCR rates for pembrolizumab vs. control:
  - 44% vs 17% in HER2-
  - **30% vs 13% HR+/HER2-**
  - 60% vs 22% TNBC

- Pembrolizumab shifted the RCB distribution to a lower disease burden for each cohort

Nanda et. al. *JAMA Oncology* 2020

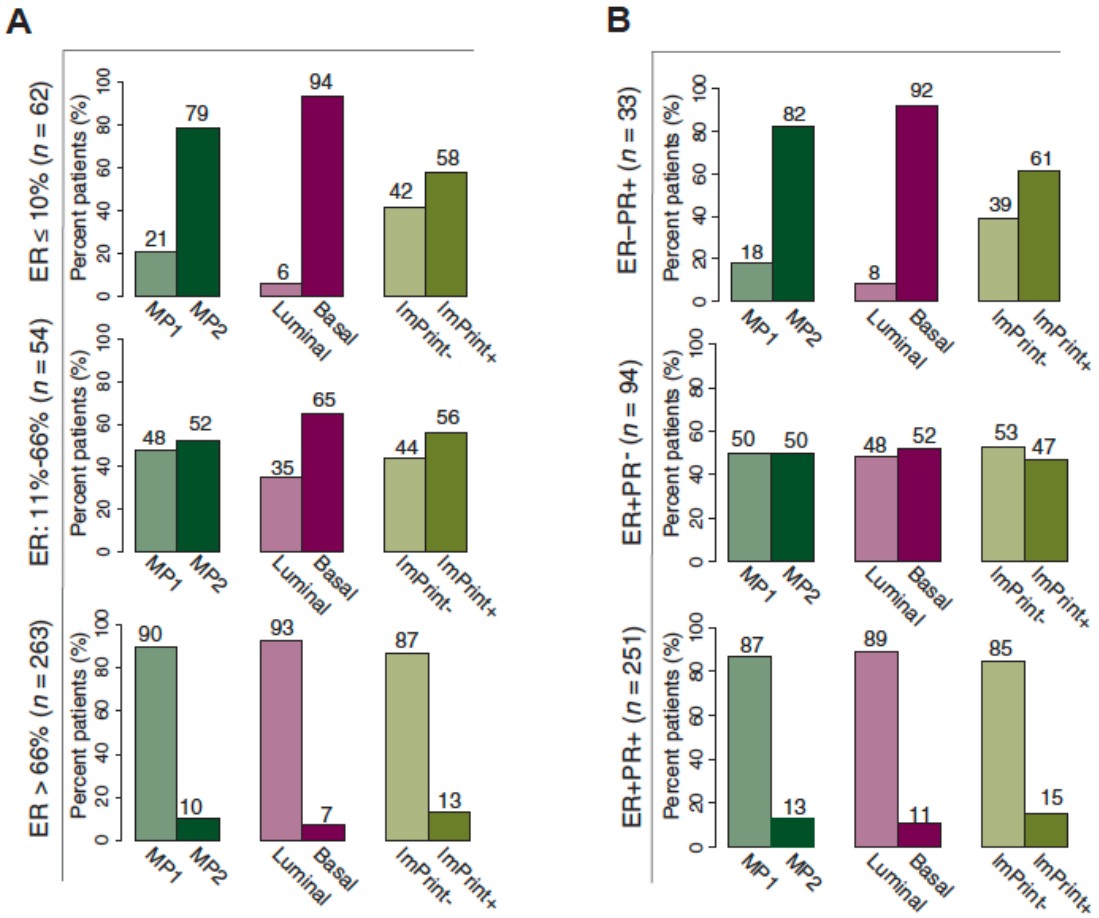
ISPY2: Observed pCR Rate by Mammaprint, BluePrint, and Imprint status among patients with HR+/HER2- early-stage breast cancer

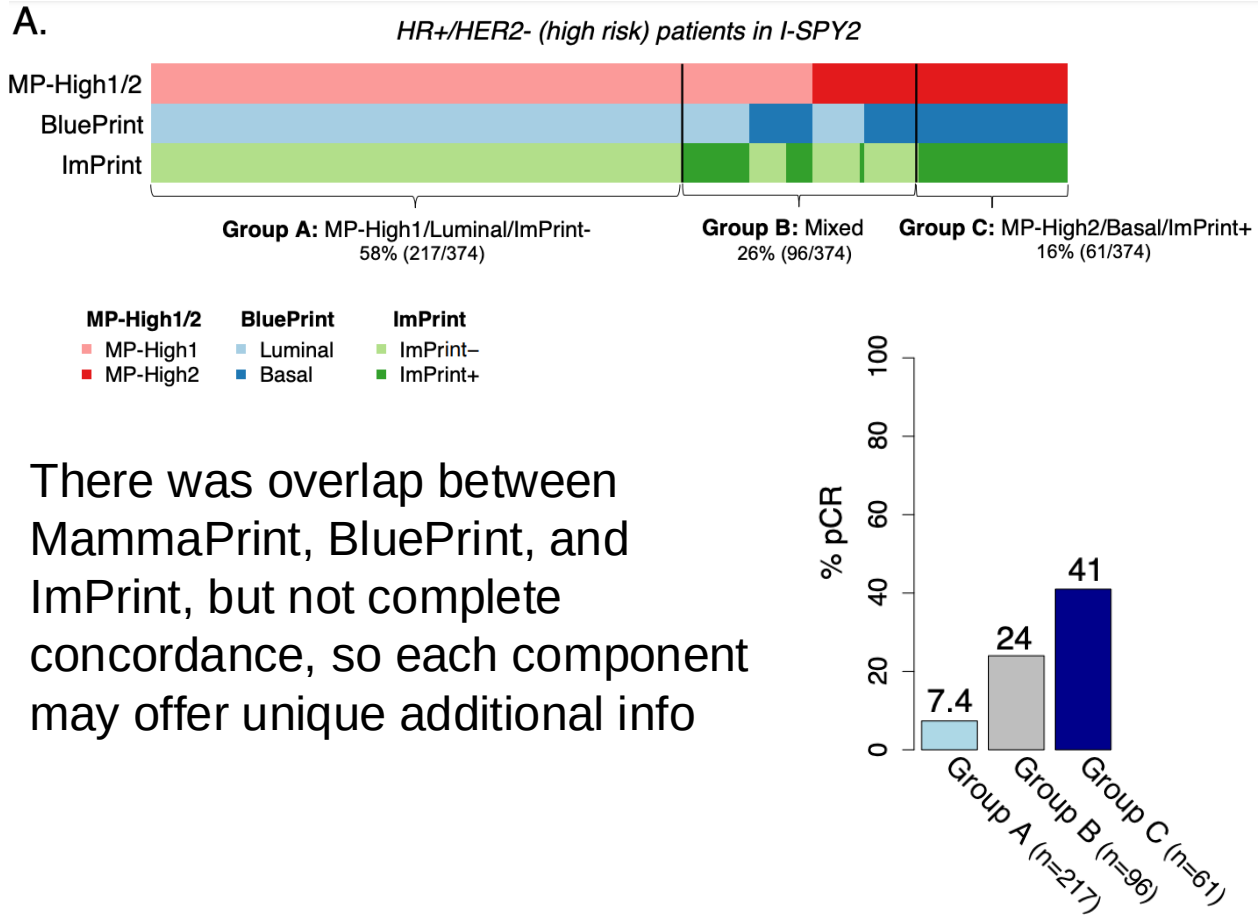


- Analysis of clinical and molecular characteristics associated with pCR in patients with HR+/HER2- disease in ISPY (n=379) across 8 treatment arms
- Most patients with MP-High1 disease were Luminal and Imprint-
- Most patients with MP-High2 disease were Basal and Imprint+
- Patients with MP-High 2, Basal, and/or Imprint+ disease were more likely to achieve pCR than patients with MP-High1, Luminal, and/or Imprint- disease

Huppert et. al. *Annals of Oncology* 2025

ISPY2: Observed pCR Rate by Mammaprint, BluePrint, and Imprint status among patients with HR+/HER2- early-stage breast cancer



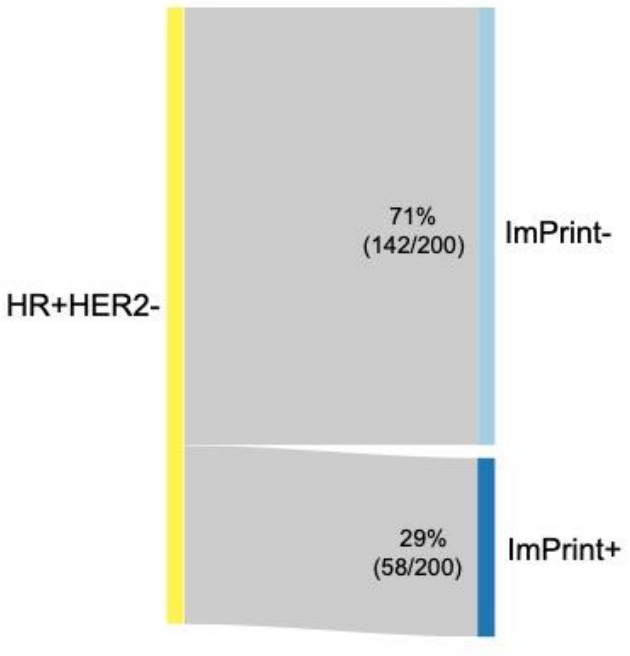


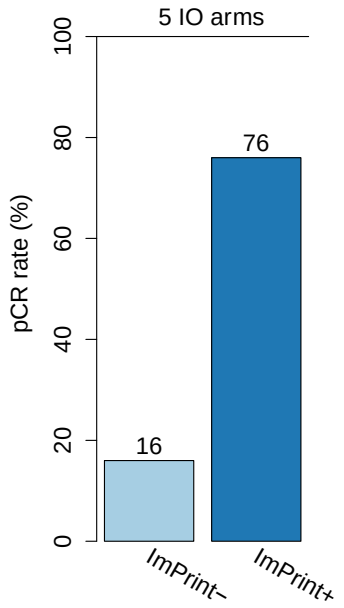
There was overlap between MammaPrint, BluePrint, and ImPrint, but not complete concordance, so each component may offer unique additional info

Patients with lower %ER and ER-/PR+ or ER+/PR- were more likely to be MP-High2, BP-Basal, and/or ImPrint+

Huppert et. al. *Annals of Oncology* 2025

ISPY2: Evaluation of ImPrint across 5 IO arms in HR+/HER2- EBC





29% ImPrint+ in HR+HER2-

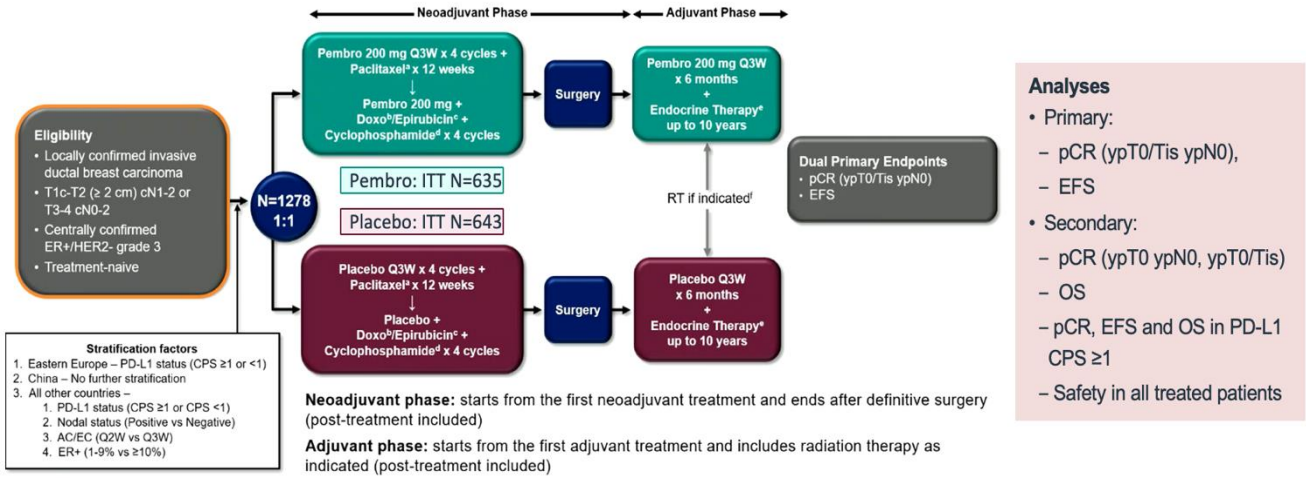
- 76% pCR in ImPrint+
- 16% pCR in ImPrint-

- Among patients with HR+/HER2- EBC across 5 IO arms in ISPY, 29% of patients were ImPrint+
- Patients who were ImPrint+ had much higher pCR rates vs. patients who were ImPrint-neg

Wolfe et. al. ASCO 2023
Wolfe et. al. submitted *JCO Precision Oncology* 2025

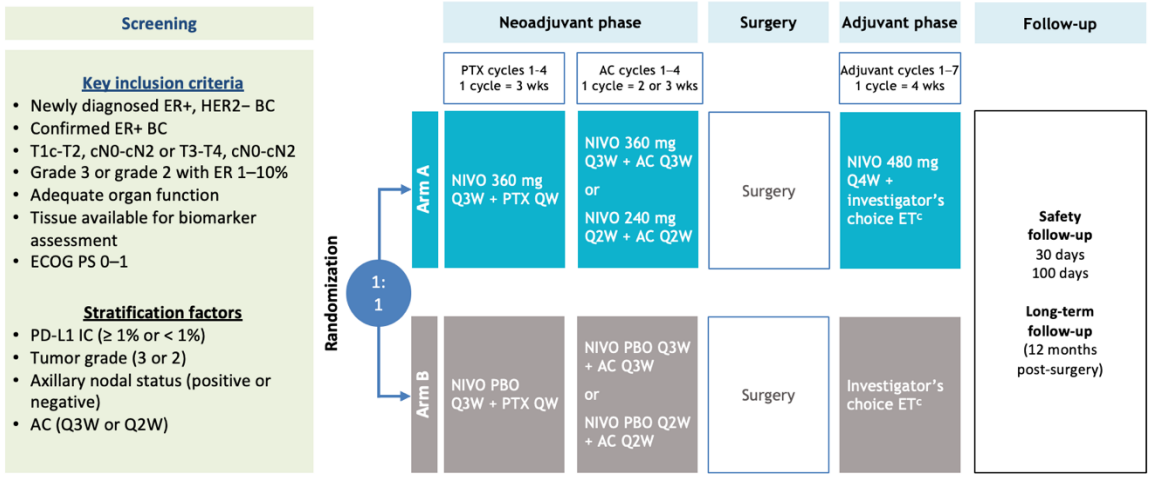
Phase III clinical trials of immunotherapy for high-risk HR+/HER2- EBC

KN756 n=1278 Cardoso et. al. ESMO 2023



Analyses
- Primary:
  - pCR (ypT0/Tis ypN0),
  - EFS
- Secondary:
  - pCR (ypT0 ypN0, ypT0/Tis)
  - OS
  - pCR, EFS and OS in PD-L1 CPS ≥1
  - Safety in all treated patients

Checkmate-7FL n=510 Loi et. al. ESMO 2023



Trial element	Similarities	Differences

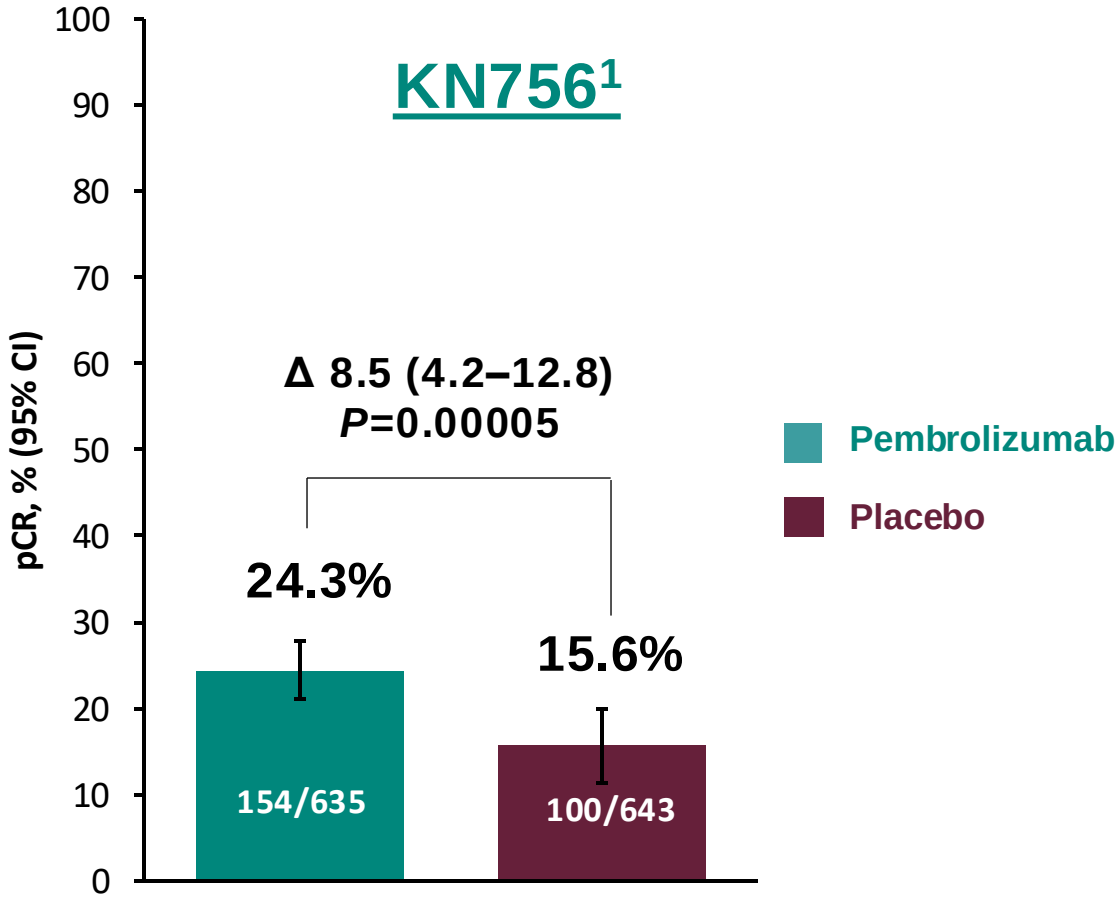
Trial design	• Both phase III, placebo-controlled RCTs that evaluated neoadj/adj PD1 inhibitors in combination with the same NACT regimen for high-risk HR+/HER2- EBC	• Use of different PD1 inhibitors:
		  • KN756: Pembrolizumab
		  • 7FL: Nivolumab
		• Keynote-756 enrolled over twice as many pts

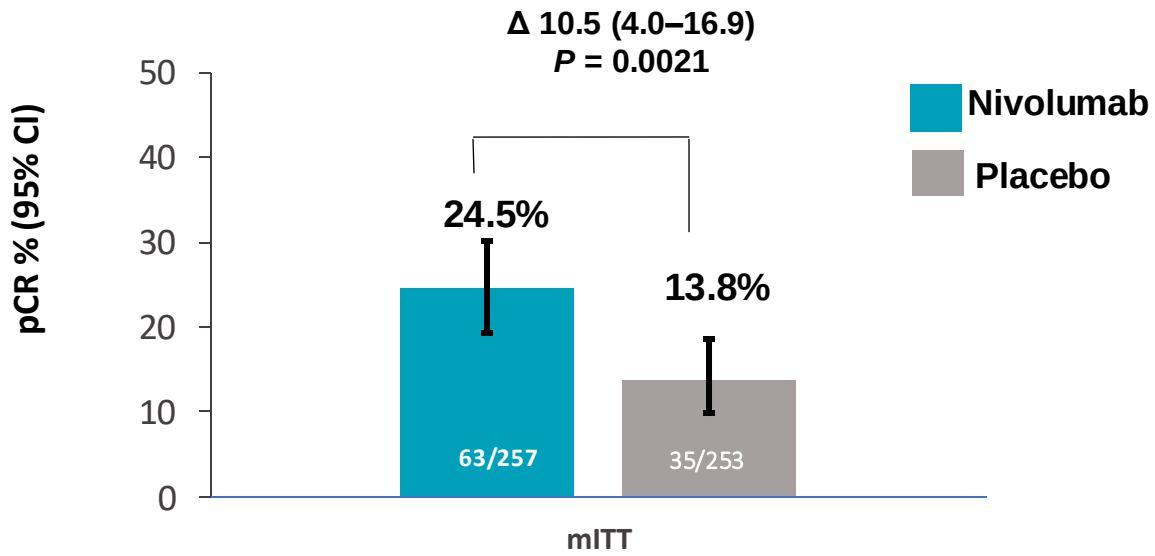
Eligibility criteria	• Overall similar: pts with high-risk HR+/HER2- EBC	• Slight differences in enrollment criteria:
		  • KN756: All grade 3, T1c-T2/ N1-2 or T3/T4
		  • 7FL: Gr **2**/3, T1c-T2/N**0**-2 or T3/T4 N0-2

Stratification factors	• Similar: nodal status, AC/EC q2w/3w, PD-L1 status	• Use of different PD-L1 assays:
		  • KN756: 22C3 CPS
		  • 7FL: SP142 (and 28-8 CPS in biomarker analysis)

1º endpoint(s)	• Both powered to detect difference in pCR rates	• KN756 also powered to detect difference in EFS

Results: Pathological Complete Response (ypT0/Tis ypN0)



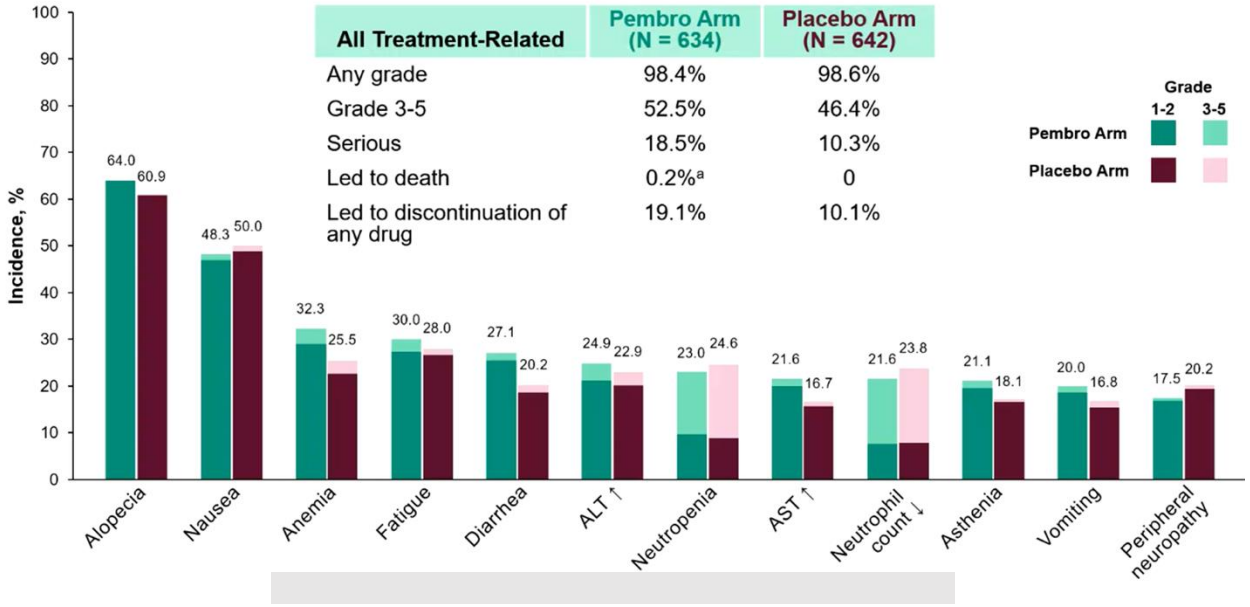


- Addition of neoadjuvant IO to NACT improved pCR rates in both studies
- EFS data still immature
- not yet FDA-approved

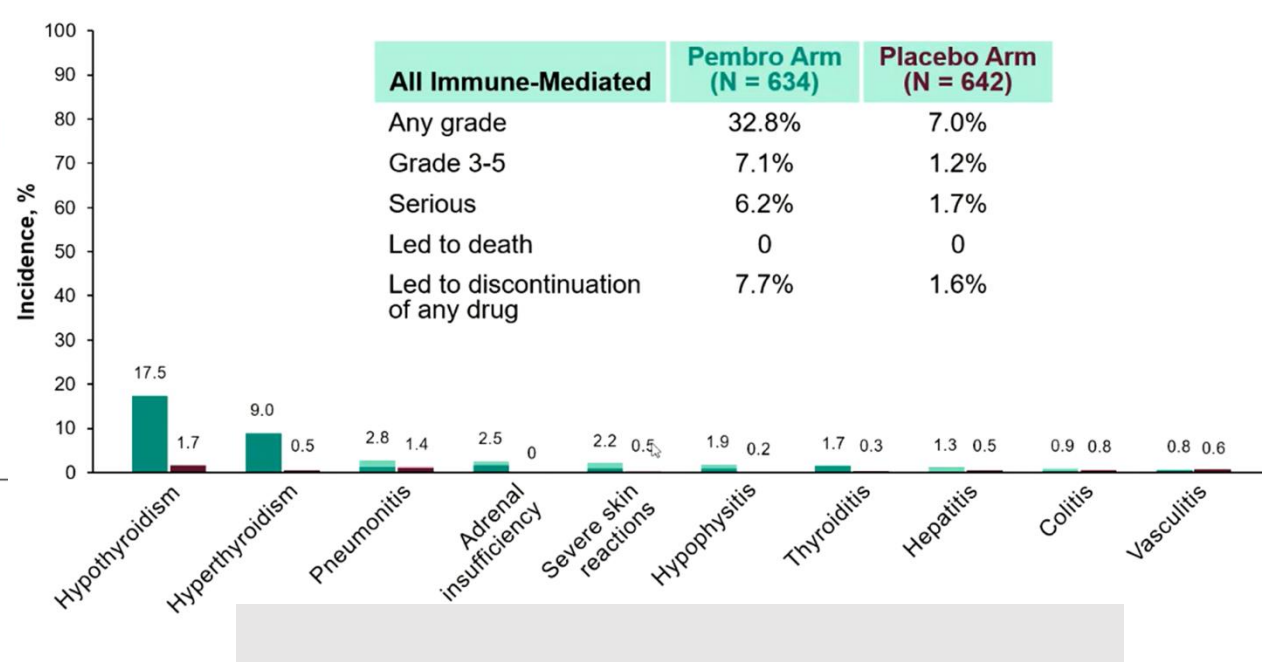
1. Cardoso et. al. ESMO 2023
2. Loi et. al. ESMO 2023

Keynote-756: Safety

Treatment-related AEs in Neoadjuvant Phase with incidence ≥ 20% in either treatment arm



Immune-related AEs in Neoadjuvant Phase with incidence ≥ 20% in either treatment arm



Safety profile consistent with known profiles of each regimen; no new safety signals

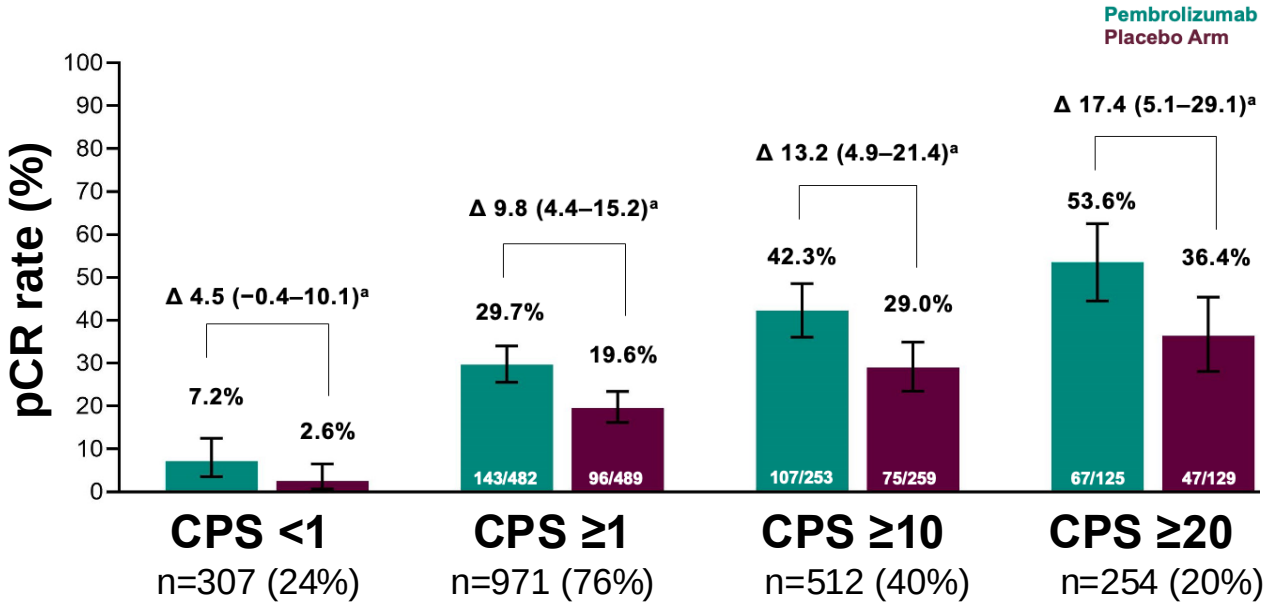
Cardoso et. al. ESMO 2023

KN756: Key subgroup and biomarker analyses

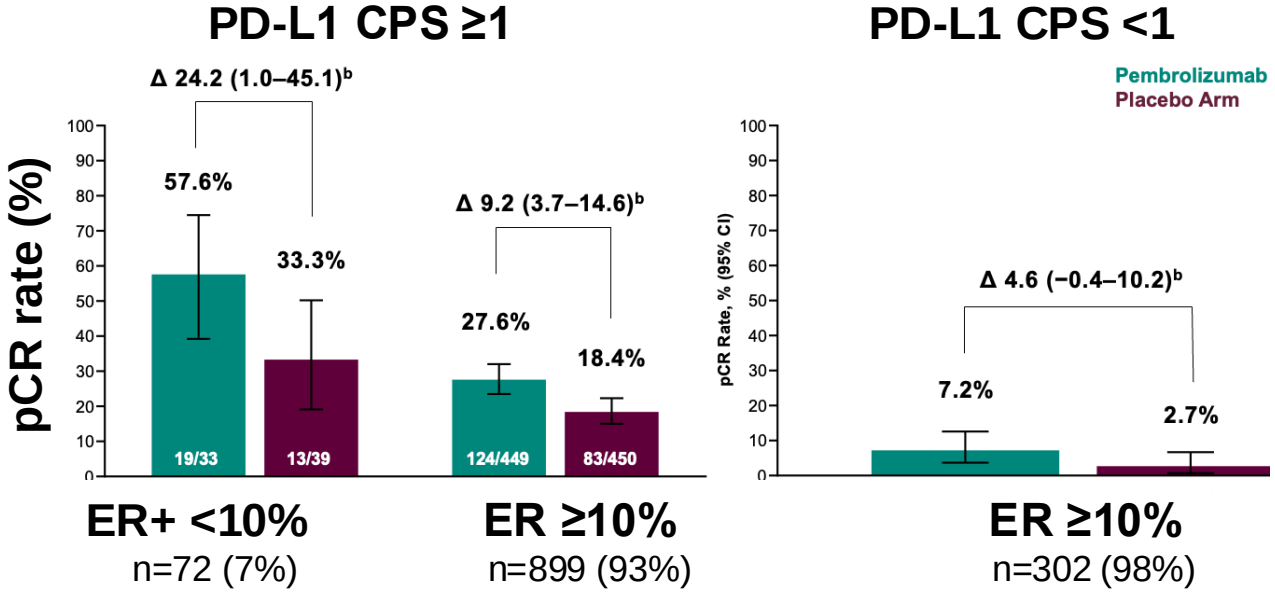
Clinical charact.	Impact of pembro on pCR rate
Stage II (n-807) III (n=471)	• Benefit regardless of stage - stage II (+Δ 9.1) and III (+Δ 8.0)
LN involvement pos (n=1152) neg (n=126)	• Benefit in LN pos (+Δ 9.3) • Benefit less clear LN neg (+Δ3.8)
Chemo exposure full (n=634) partial (n=641)	• Benefit regardless of whether chemotherapy completed

Biomarker	Impact of pembro on pCR rate
PD-L1 22C3 CPS	• Benefit if CPS ≥1. Higher pCR rates & larger Δ with higher CPS • Benefit less clear CPS <1
ER status Stratified by CPS score	• CPS ≥1: Benefit for all ER%, with larger benefit if ER <10% • CPS <1: Benefit less clear ER ≥10%

PD-L1 status (22C3 CPS)



ER status

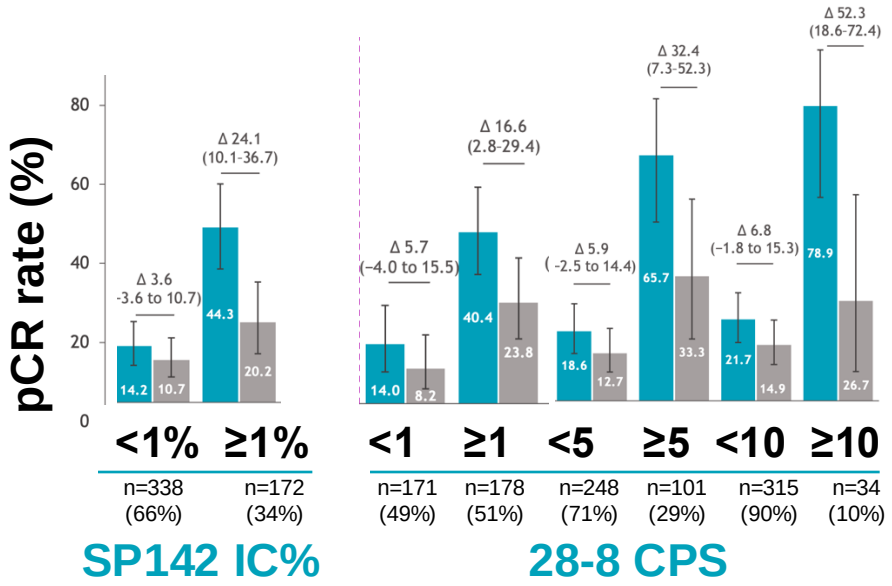


Cardoso et. al. SABCS 2023

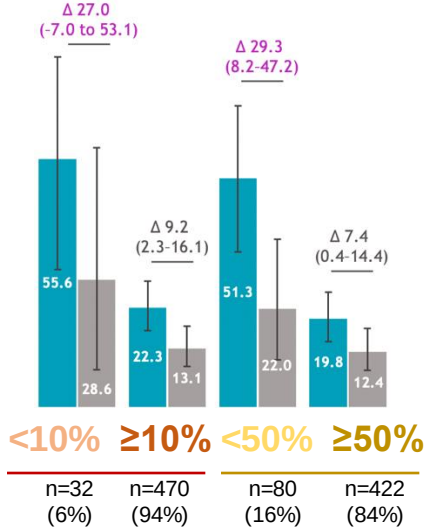
Checkmate-7FL: Biomarkers predictive of pCR or RCB 0/1

Biomarker	Impact of nivo on pCR and RCB 0/1 rates
PD-L1 score SP142 IC% (n=510) 28-8 CPS (n=349)	• Benefit if PD-L1+ by both assays, with increasing benefit in higher 28-8 CPS scores • Benefit less clear PD-L1 neg
ER%	• Benefit with low ER% (<50%) • Benefit less clear high ER% (≥50%)
PR% Stratified by ER	• Benefit with low PR% (<10%) • Benefit less clear high PR% (≥10%)
sTIL (<5%, ≥5%)	• Higher with sTIL ≥1% • Benefit less clear sTIL <1%
Ki67 (<20%, ≥20%)	• No association

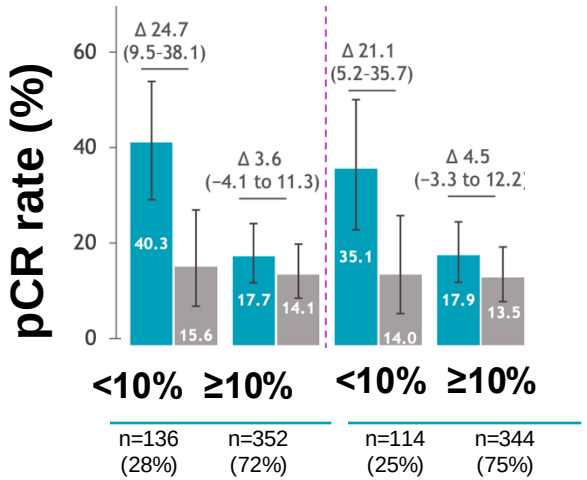
PD-L1 status



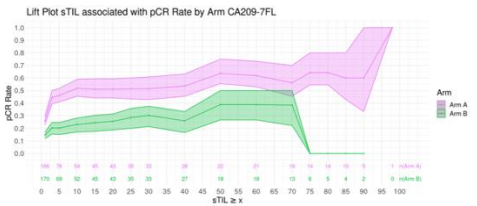
ER%



PR%

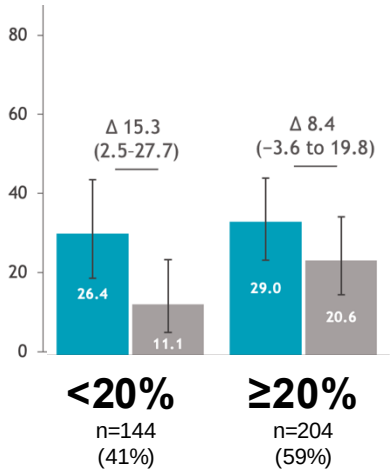


TILs



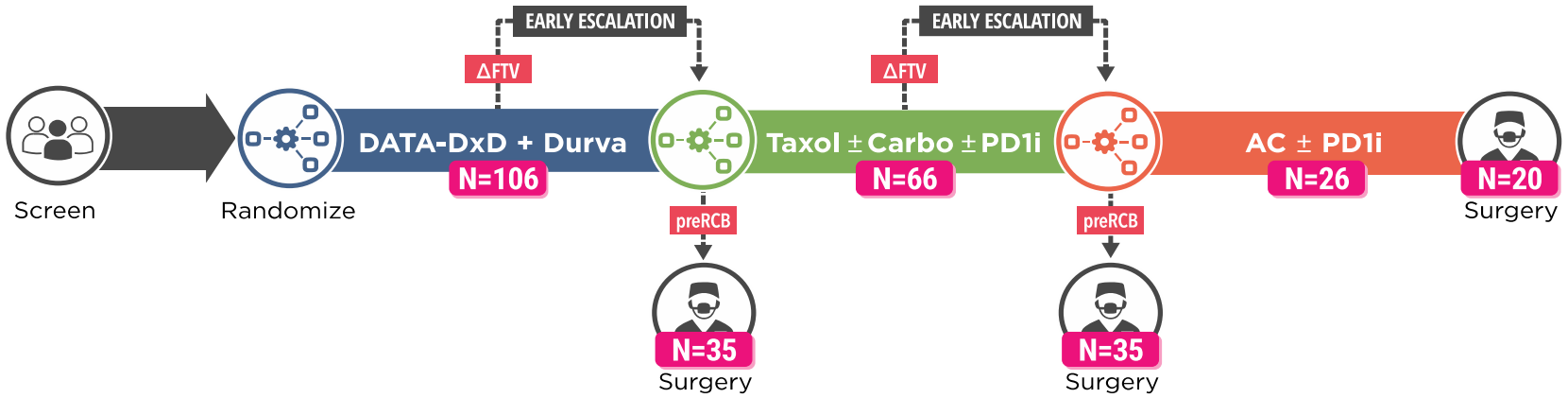
Greater nivolumab benefit observed with sTiL **≥1%**

Ki67



Loi et. al. SABCS 2023

ISPY: Datopotamab-DXd +/- durvaluamb for HER neg EBC



Patient Characteristics		Dato-DXd + Durva (N=106)
Median age (range), years		50.0 (25.0-77.0)
Response predictive subtype, n (%)	HR+/Immune–/DRD–	25 (23.6)
	HR–/Immune–/DRD–	23 (21.7)
	Immune+	47 (44.3)
	HR+	16 (15.1)
	HR–	31 (29.2)
	Immune–/DRD+	11 (10.4)
	HR+	1 (0.9)
	HR–	10 (9.4)
Receptor subtype, n (%)	HR+	42 (39.6)
	HR–	64 (60.4)

- 38% of HR+/HER2– patients are Immune+
- 49% of HR–/HER2– patients are Immune+

Response Predictive Subtype	N	pCR	non-pCR*	Modeled Rate (95% CI)	Threshold	P(>Thr)
HR+Immune-DRD-	25	0	23	3% (0%-7%)	15%	0.00
HR-Immune-DRD-	23	2	14	13% (3%-23%)	15%	0.33
Immune+	**47**	**20**	**11**	**65% (47%-83%)**	**40%**	**0.99**
Immune-DRD+	11	3	6	24% (4%-44%)	40%	0.06

Receptor Subtypes	N	pCR	non-pCR*	Modeled Rate (95% CI)	Threshold	P(>Thr)
HR+	42	4	29	18% (6%-30%)	15%	0.68
HR-	64	21	25	44% (32%-56%)	40%	0.74

- Dato-DXD + durvalumab graduated in Immune+ subtype
- TROPION-Breast04 ongoing phase III study evaluating Dato-DXd + durvalumab vs. KN522 regimen in TNBC

Shatsky et. al. *Nature Med* 2024

Conclusions: Current state of IO for HR+/HER2- EBC

- The phase III studies KN756 and Checkmate-7FL demonstrated that neoadjuvant IO + NACT improved pCR rates in high-risk HR+/HER2- early-stage breast cancer
  - Particular benefit in patients who were PD-L1+, low ER%, low PR%
  - EFS data immature -- Await EFS data!
    - Not yet FDA approved and would not yet use for most patients with HR+/HER2- EBC now
    - Are there individual cases with HR+/HER2- EBC for whom IO could be considered now?
      - Low ER% (1-10%) -- would consider treating with KN522 regimen
      - Low ER% (<50%) and Basal subtype – not yet approved but could consider for large tumors, acknowledging lack of EFS data at this time

- Can we identify an optimal composite biomarker of IO response to guide treatment selection?

- Important to consider balancing efficacy and toxicity (e.g., IRAEs, cost)

- Sequencing CDK4/6 inhibitors will be a critical issue given potential toxicity with combination therapy

- Novel combinations are of interest (e.g., ADC + IO, targeted therapies + IO)