Immunotherapy updates in breast cancer

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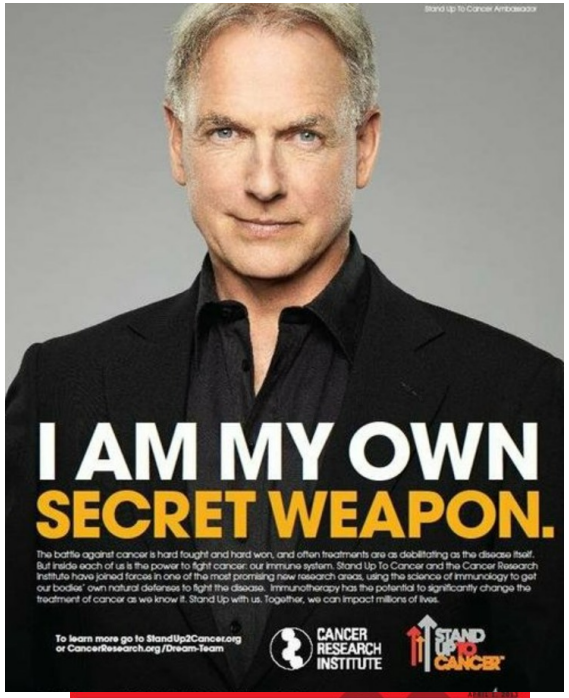
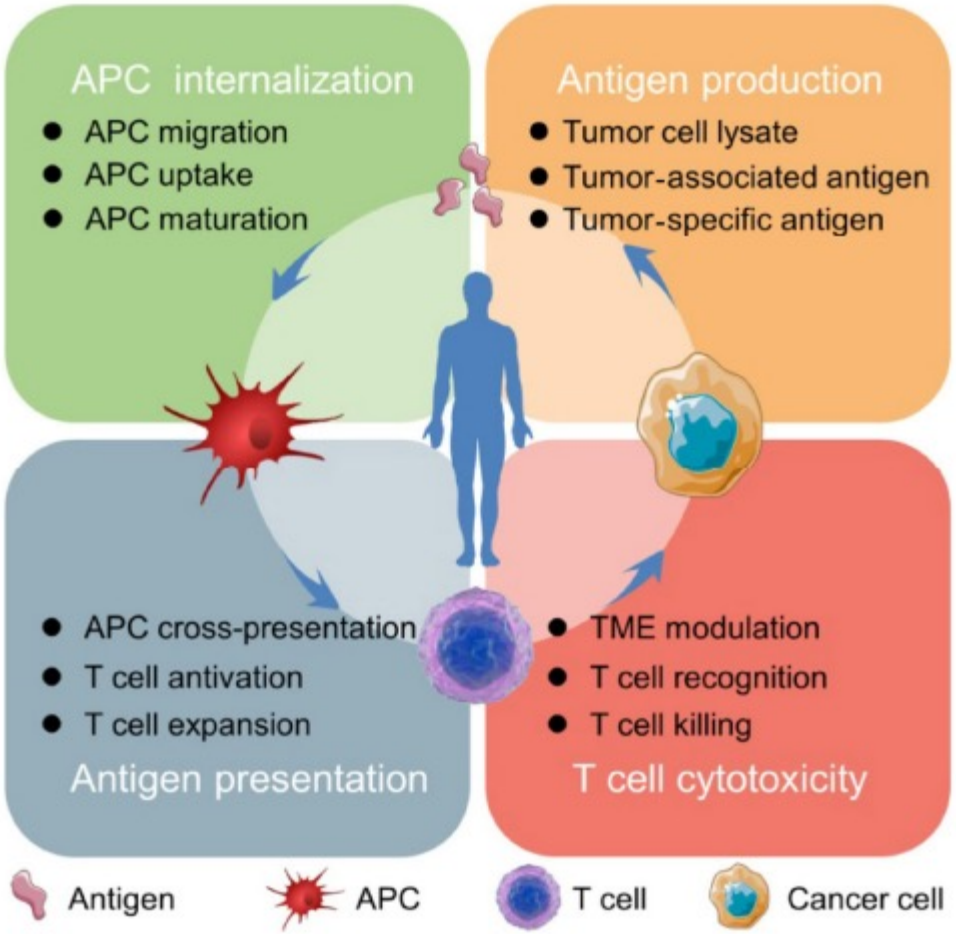


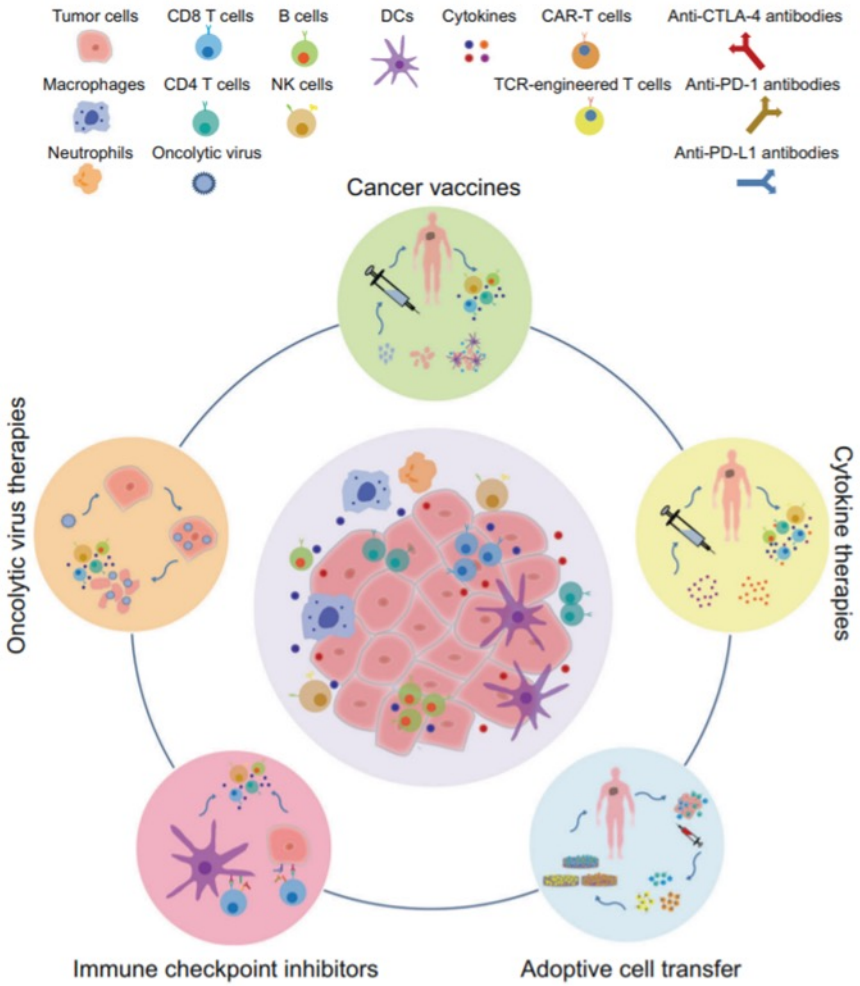
FIRST OPINION

Few people actually benefit from 'breakthrough' cancer immunotherapy

By Nathan Gay and Vinay Prasad March 8, 2017

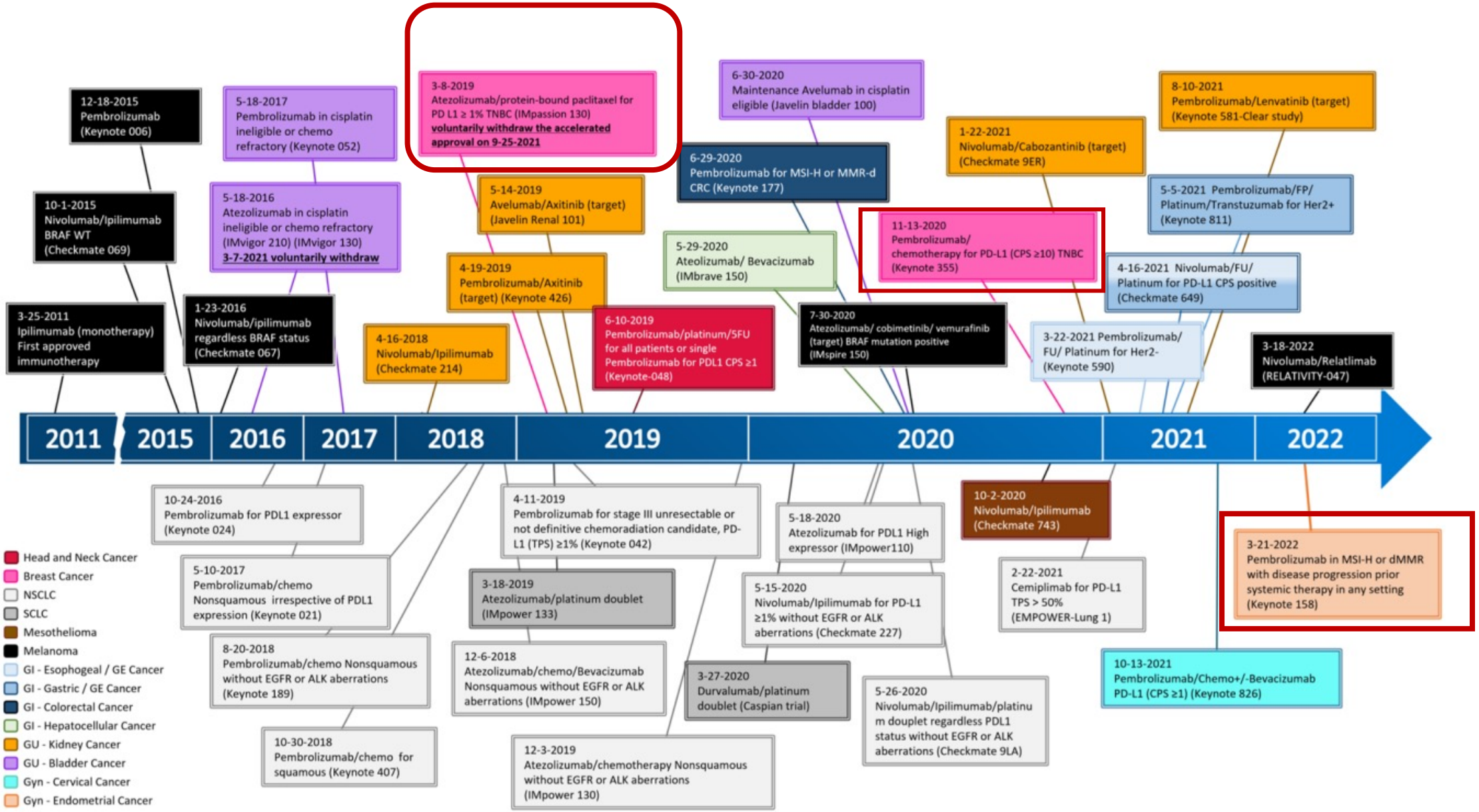


Li et al. Nano Research, 2018



Zhang and Zhang, Cellular and Molecular Immunology, 2020

Immunotherapy in metastatic breast cancer

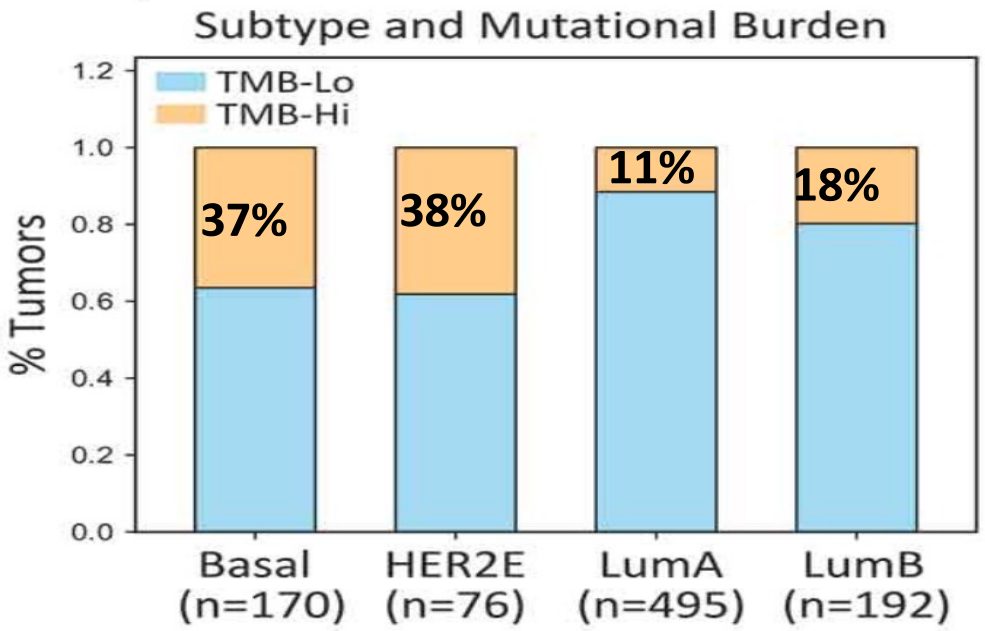


Ma et al Exp Hematology oncology 2023

Tumor Mutational Burden (TMB) in Breast Cancer

- Mean TMB* is breast cancer is 1.63 to 2.63 mut/Mb
  - Higher TMB in Metastatic vs Primary
  - Higher TMB in Basal > HER2 > Luminal

- Pembrolizumab granted FDA accelerated approval for TMB-High (≥10mut/Mb) tumors
  - Less than 5% of breast cancers are TMB-H
    - More common in metastatic (8.4%) vs primary (2.9%)
    - More common in metastatic lobular (17%) vs ductal (7.8%)

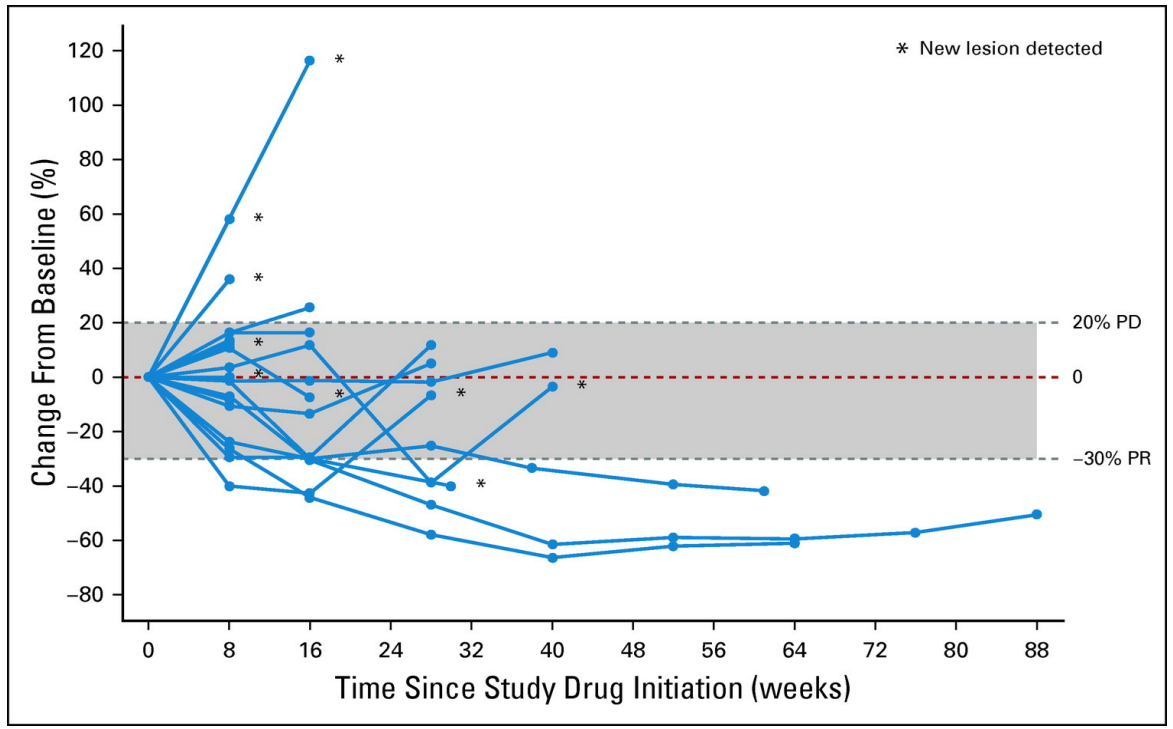


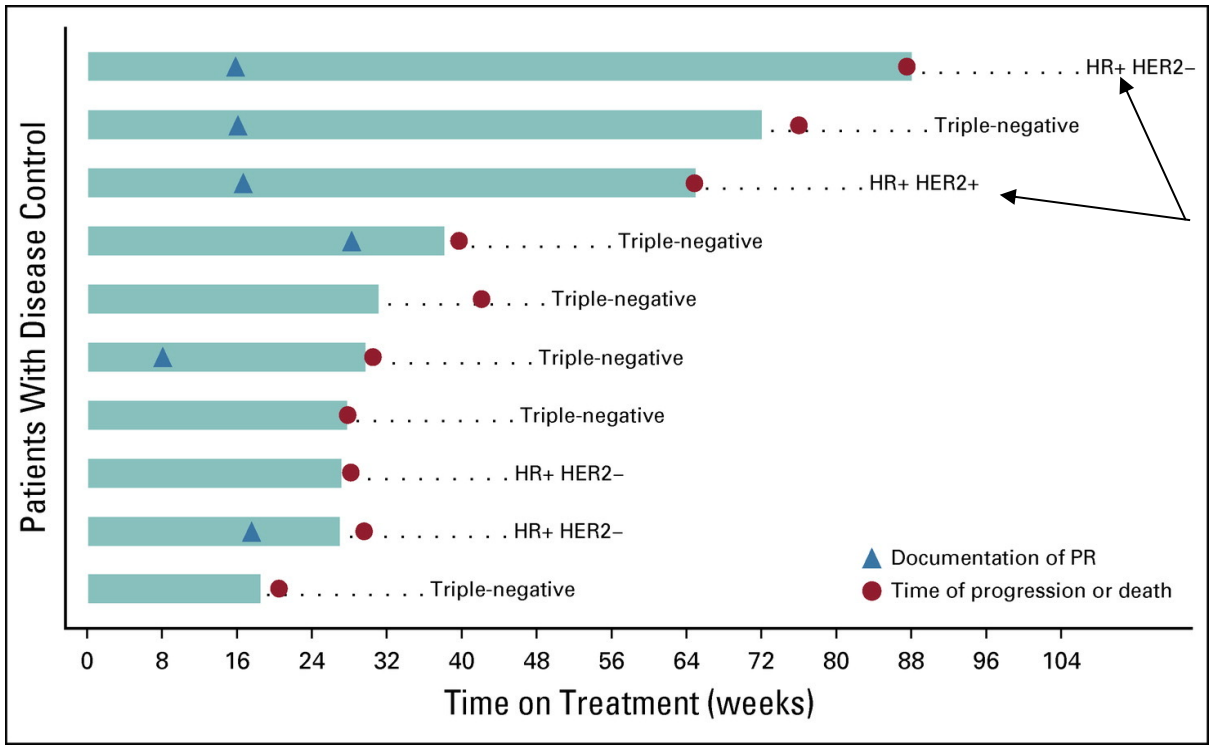
Above bar chart is based on the mean TMB with patients assigned to low (below-mean) or high (above-mean) TMB categories

Thomas et al. OncoImmunology. 2018.
Barroso-Sousa et al. Ann Onc. 2020.

Pembrolizumab in TMB-H Breast Cancer

- **TAPUR Study (Ph2 basket study)**
  - 28 patients with metastatic breast cancer [TNBC = 13 (46%), HR+/HER2- = 12 (43%)]
  - **TMB: median 13 mut/Mb** (range 9 to 37 mut/Mb); PD-L1 status unknown
  - **Disease Control Rate 37%, ORR 21%** with median PFS = 10.6 weeks

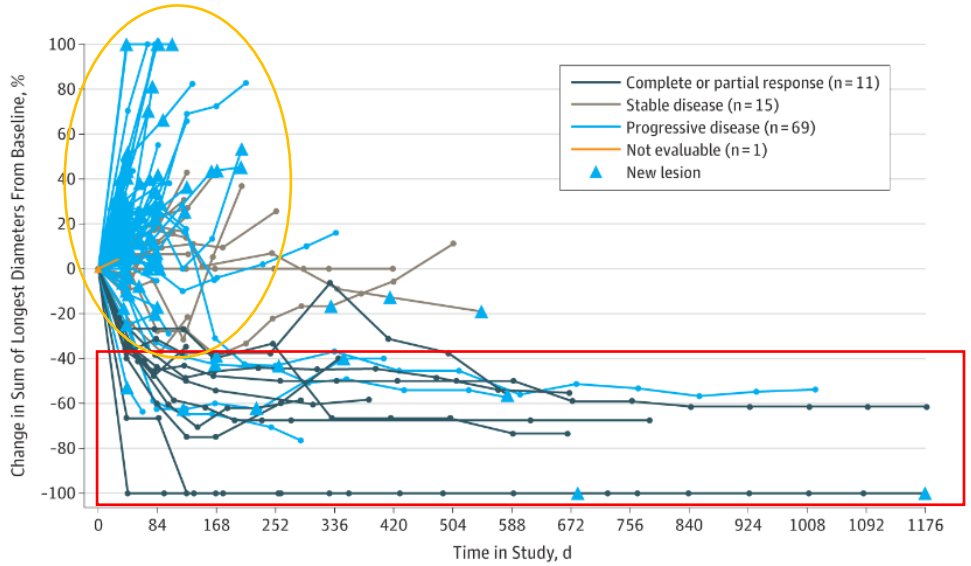




Alva et al. JCO. 2021

First Approval of ICI in Breast Cancer

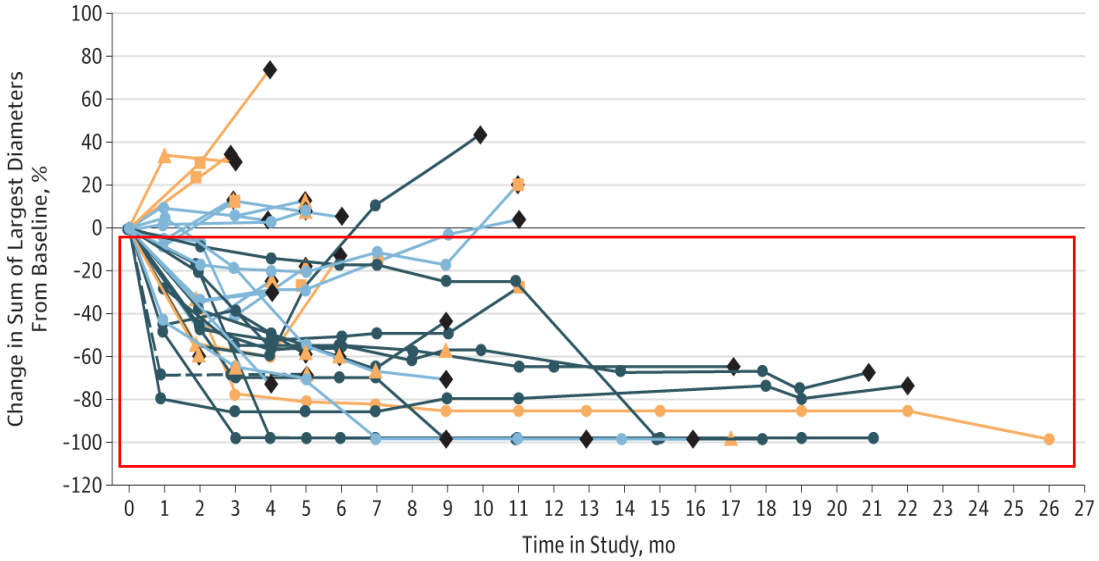
Atezolizumab



Some responses with atezolizumab but a lot of patients had rapid growth of their cancer

Much better control of the cancer when atezolizumab was combined with chemotherapy

Atezolizumab + Nab-Paclitaxel

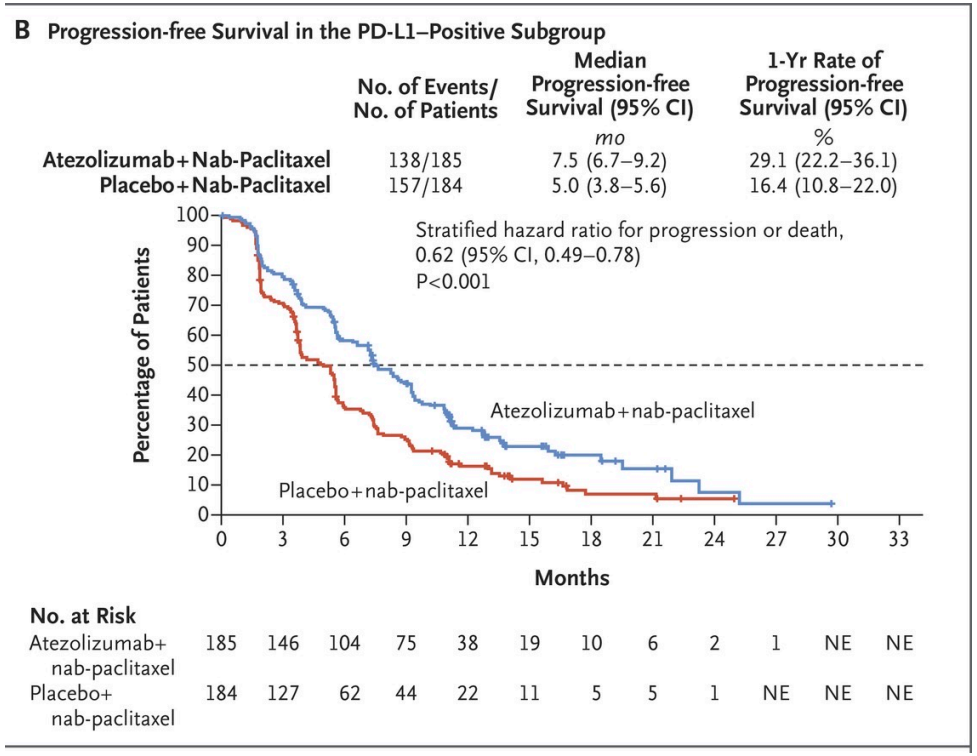


Emens et al. JAMA Onc 2019. Adams et al. JAMA Onc 2018.

Atezolizumab in Metastatic TNBC

Clinical Trial Name	IMpassion130
Patient Population	Untreated patients with metastatic triple negative breast cancer; subgroup analysis in PD-L1+ tumors (SP142 IC ≥ 1%)
# Patients on Trial	902 patients
FDA Approval Status	Accelerated Approval (2019) **Withdrawn 8/2021**

When Nab-Paclitaxel PLUS Atezolizumab to Nab-Paclitaxel alone…	was compared
Was cancer better controlled (**improved PFS**)?	**YES*** *(7.5 vs 5.0 months)*
Did patients live longer (improved OS)?**	No (*25 vs 18 months)*
Were side effects worse?	NO



statistically significant

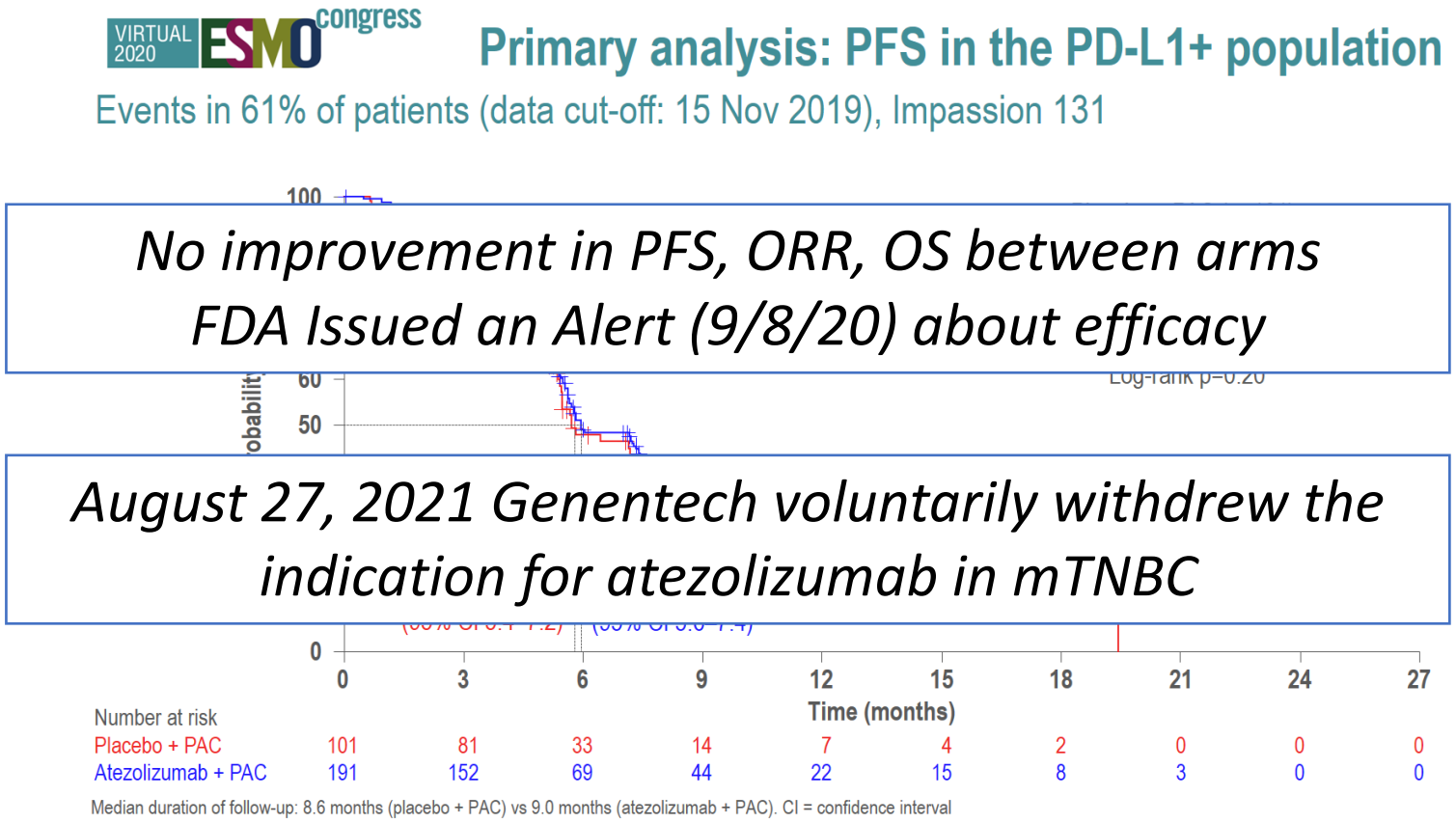
***** not statistically significant but an impressive clinical improvement***

Schmid P et al. N Engl J Med 2018
Schmid P et al. Lancet Onc 2020.

IMpassion131: Paclitaxel +/- Atezolizumab

- 1L, mTNBC, randomized 2:1 (n =651)

Miles et al, ESMO 2020



No improvement in PFS, ORR, OS between arms
FDA Issued an Alert (9/8/20) about efficacy

August 27, 2021 Genentech voluntarily withdrew the indication for atezolizumab in mTNBC

Miles D. ESMO. 2020

Pembrolizumab in Metastatic TNBC

Clinical Trial Name	KEYNOTE-355
Patient Population	Untreated patients with metastatic triple negative breast cancer; subgroup analysis in patients with PD-L1+ tumors (22C3 CPS ≥ 10)
# Patients on Trial	847 patients
FDA Approval Status	Accelerated Approval (2020); Regular Approval (7/23/2021)

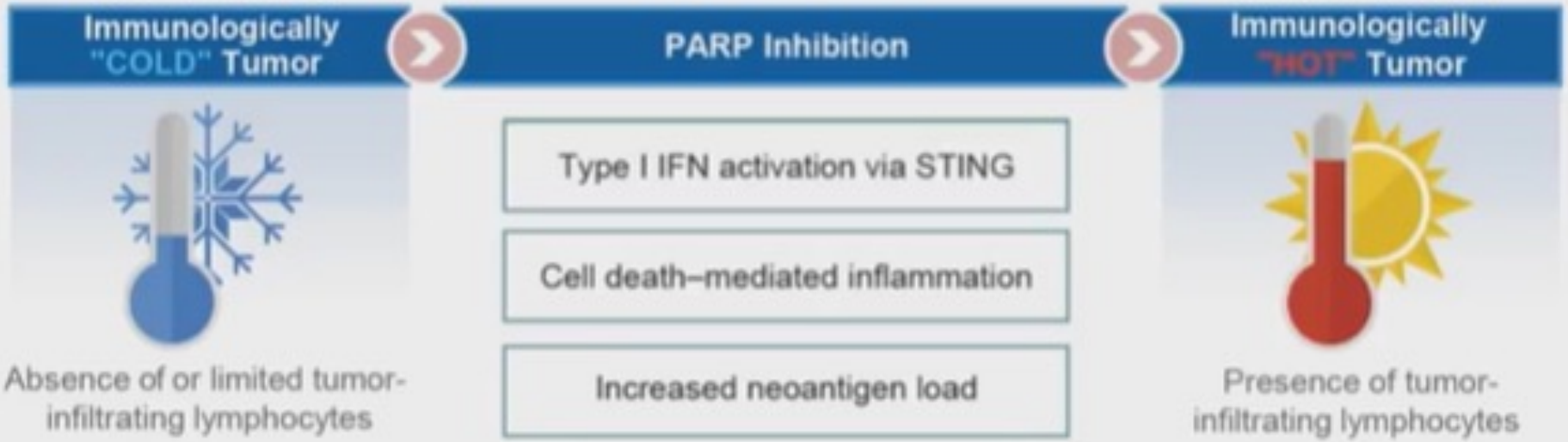
When Chemotherapy (gemcitabine/carboplatin, nab-paclitaxel or paclitaxel) PLUS Pembrolizumab (Keytruda) was compared to chemotherapy alone…

Was cancer better controlled (**improved PFS**)?	**YES*** *(9.7 vs 5.6 months)*
Did patients live longer (**improved OS**)?	**YES*** *(23 vs 16.1 months)*
Were side effects worse?	NO

statistically significant

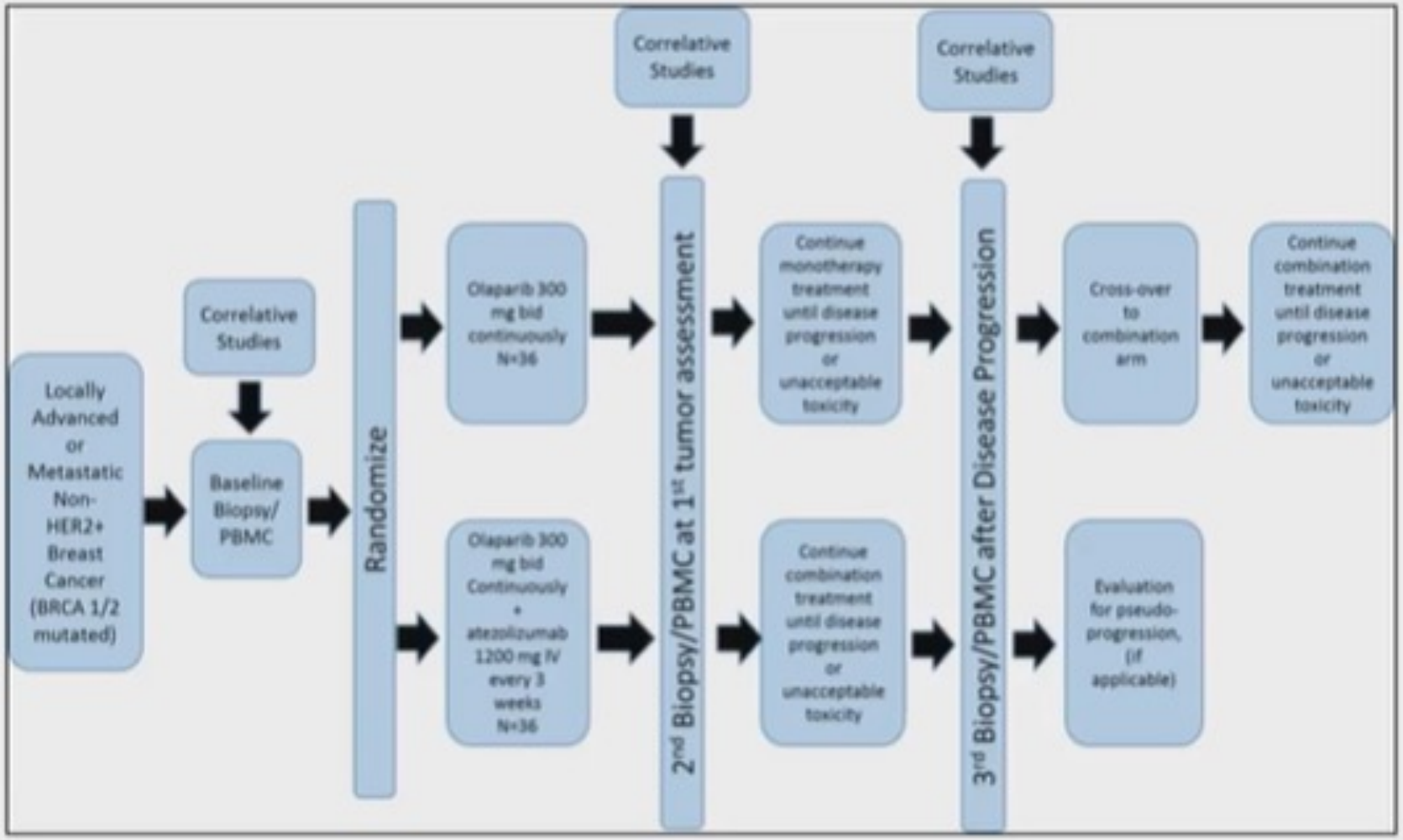
Cortes, J. Lancet. 2020; Rugo et al. ESMO Congress. 2021.

PARP Inhibition May Enhance Immune Surveillance Through Multiple Mechanisms



Vinayak et al, PD5-02, SABCS 2018

ETCTN Trial: NCI 10020



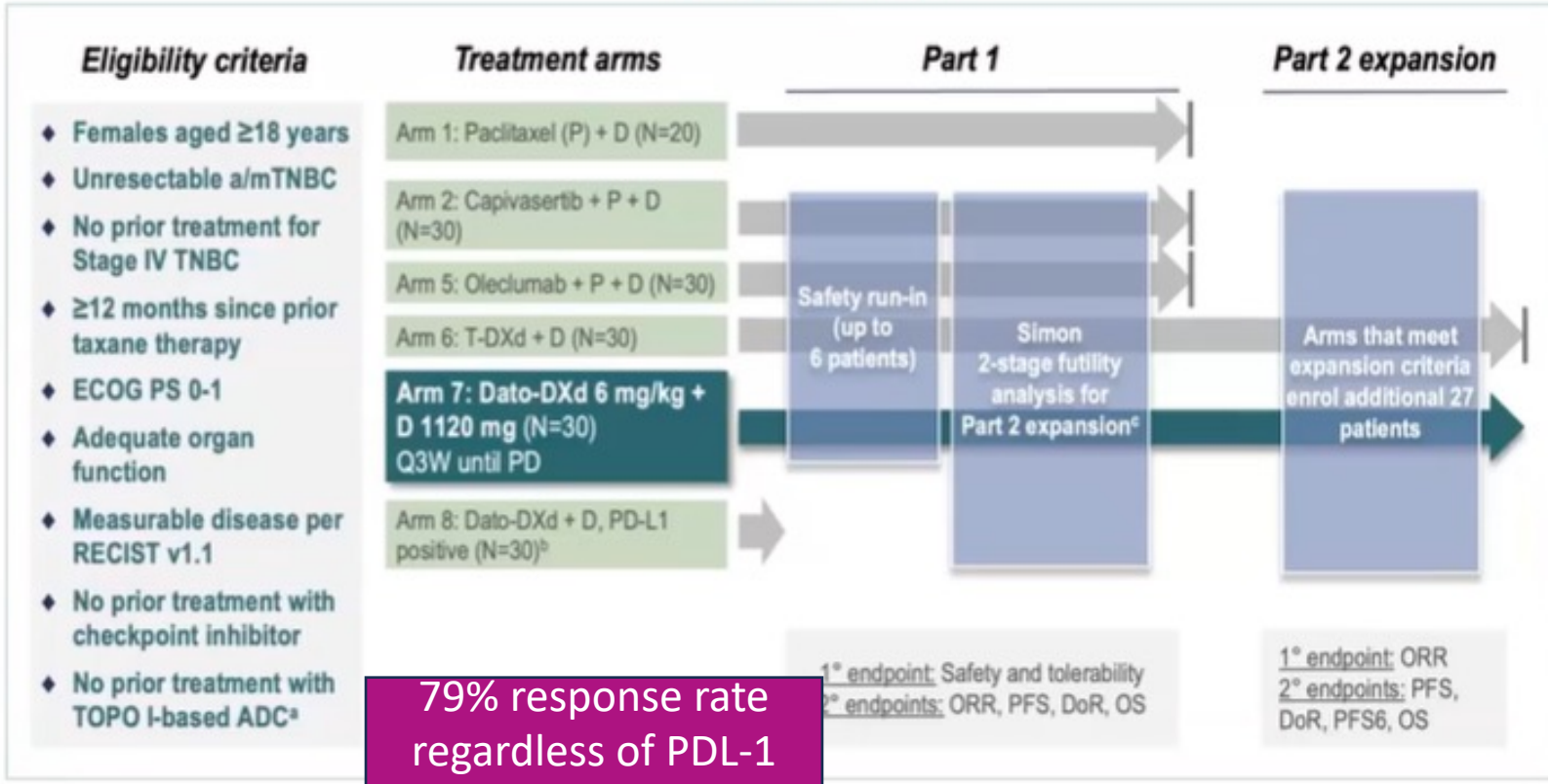
PI: Patricia LoRusso

The BEGONIA Study (NCT03742102)

Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design



79% response rate regardless of PDL-1 status

ESMO2-23

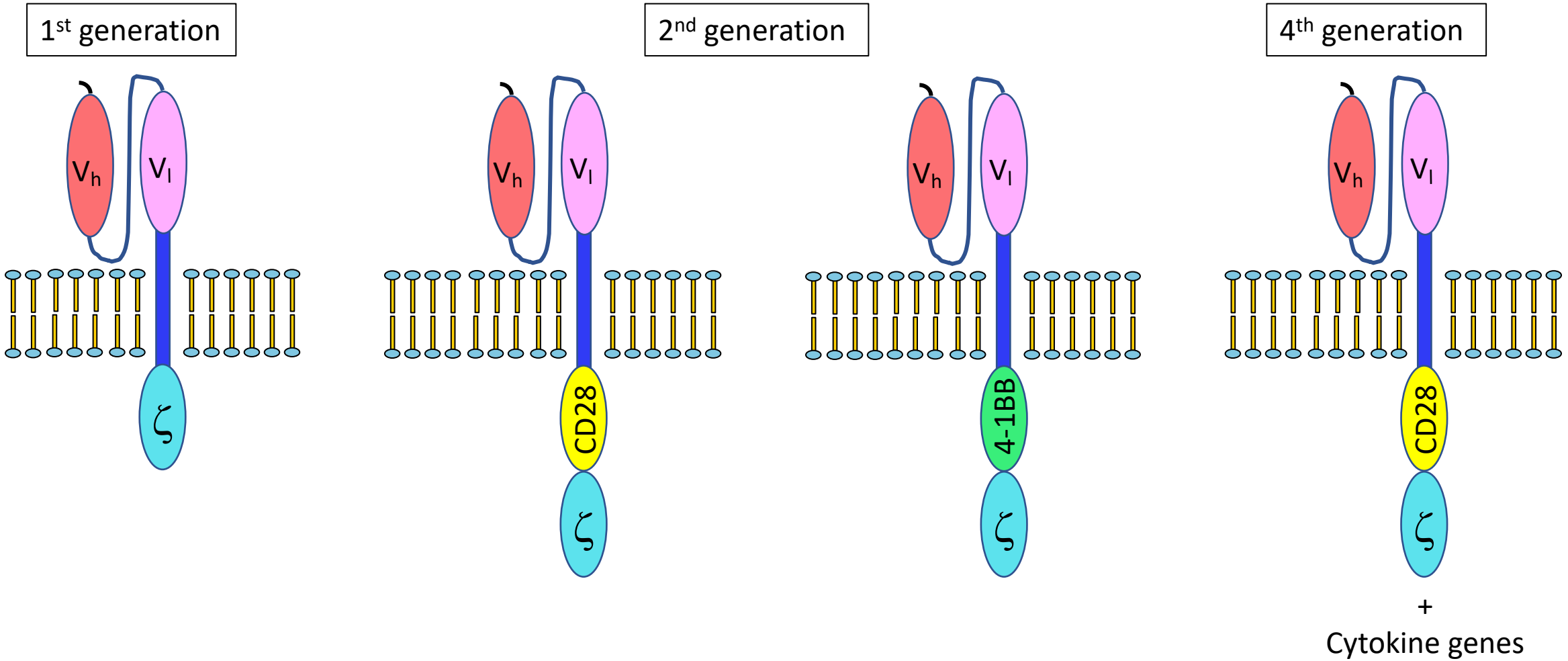
TROPION-05

- Advanced/metastatic TNBC
- PDL-1 positive
- N=550
- 1: 1 randomization
- Primary endpoint: PFS

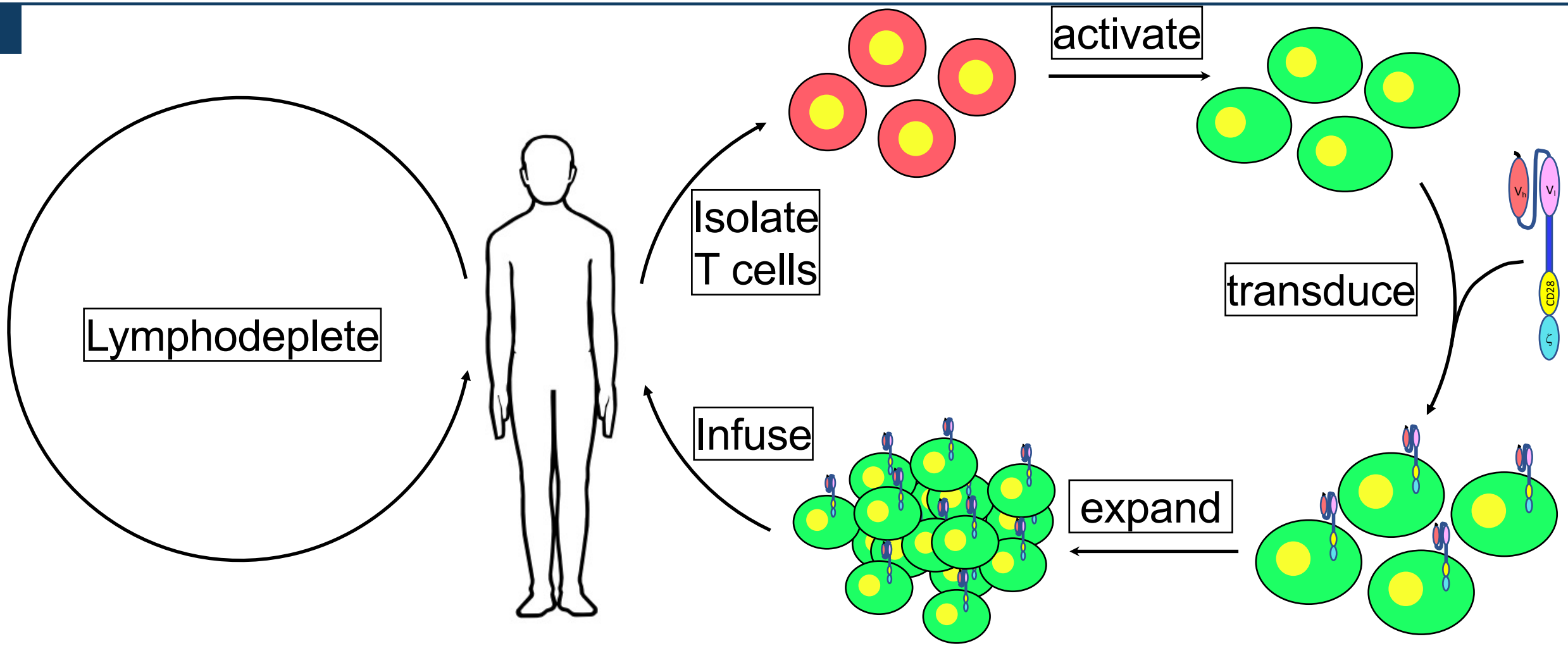
Investigator's Choice Chemotherapy[b]
+
Pembrolizumab
200 mg IV Q3W

Dato-DXd
6.0 mg/kg IV Q3W
+
Durvalumab
1120 mg IV Q3W

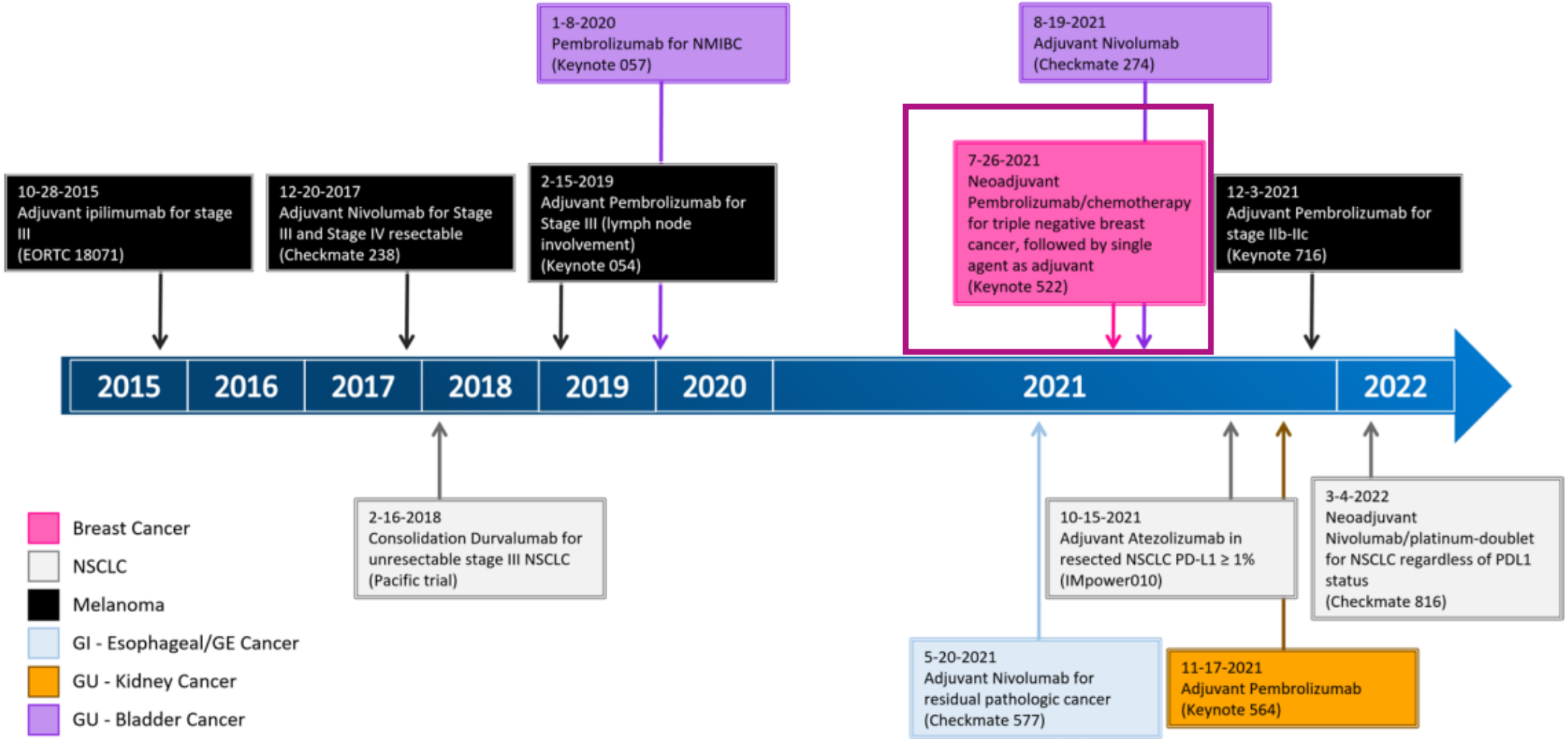
Chimeric Antigen Receptors (CARs)



CAR-T production and infusion



Immunotherapy in early stage breast cancer


1-8-2020
Pembrolizumab for NMIBC
(Keynote 057)
8-19-2021
Adjuvant Nivolumab
(Checkmate 274)
10-28-2015
Adjuvant ipilimumab for stage III
(EORTC 18071)
12-20-2017
Adjuvant Nivolumab for Stage III and Stage IV resectable
(Checkmate 238)
2-15-2019
Adjuvant Pembrolizumab for Stage III (lymph node involvement)
(Keynote 054)
7-26-2021
Neoadjuvant Pembrolizumab/chemotherapy for triple negative breast cancer, followed by single agent as adjuvant
(Keynote 522)
12-3-2021
Adjuvant Pembrolizumab for stage IIb-IIc
(Keynote 716)
2015
2016
2017
2018
2019
2020
2021
2022
2-16-2018
Consolidation Durvalumab for unresectable stage III NSCLC
(Pacific trial)
10-15-2021
Adjuvant Atezolizumab in resected NSCLC PD-L1 ≥ 1%
(IMpower010)
3-4-2022
Neoadjuvant Nivolumab/platinum-doublet for NSCLC regardless of PDL1 status
(Checkmate 816)
5-20-2021
Adjuvant Nivolumab for residual pathologic cancer
(Checkmate 577)
11-17-2021
Adjuvant Pembrolizumab
(Keynote 564)
Breast Cancer
NSCLC
Melanoma
GI - Esophageal/GE Cancer
GU - Kidney Cancer
GU - Bladder Cancer

Immunotherapy based regimens in high risk TNBC

Variable	I-SPY	KEYNOTE-522	IMPASSION 031	NeoTRIP	GeparNUEVO
Total patients	69/180	1174 (602)	333	280	174
Type of CPi	PD1 Pembro x 4	PD1 Pembro x 1 year	PD-L1 Atezo x 1 year	PD-L1 Atezo x 8	PD-L1 Durva x 8
Stage	Stage II/III	Stage II/III	Stage II/III	+ N3 disease	35% stage I
Anthracycline pre-op	yes	yes	yes	No*	yes
Included carboplatin	no	yes	No (nab-pac)	Yes (nab-pac) 2 wks on, 1 wk off x 8	no
Improved pCR	Yes	Yes 51.2 v 64.8% P=0.00055	Yes 41.1 v 57.6% P=0.0044	No (43.5 v 40.5%)	Numeric improvement (53 v 44%, p=0.18)
Improved EFS	NR: pCR>nonpCR	Yes	NR	NR	Yes EFS, DDFS and OS

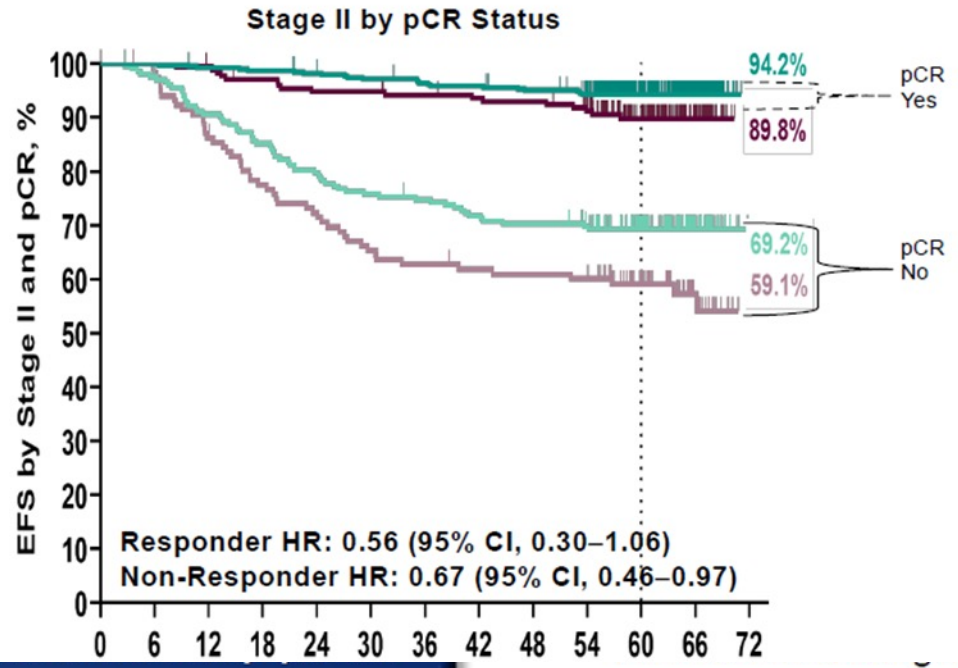
Nanda et al, JAMA Onc 2020; Schmid et al, NEJM 2020 & NEJM 2022; Mittendorf et al, Lancet 2020; Gianni et al, SABCS 2019; Loibl et al, Ann Oncol 2019 & Ann Oncol 2022

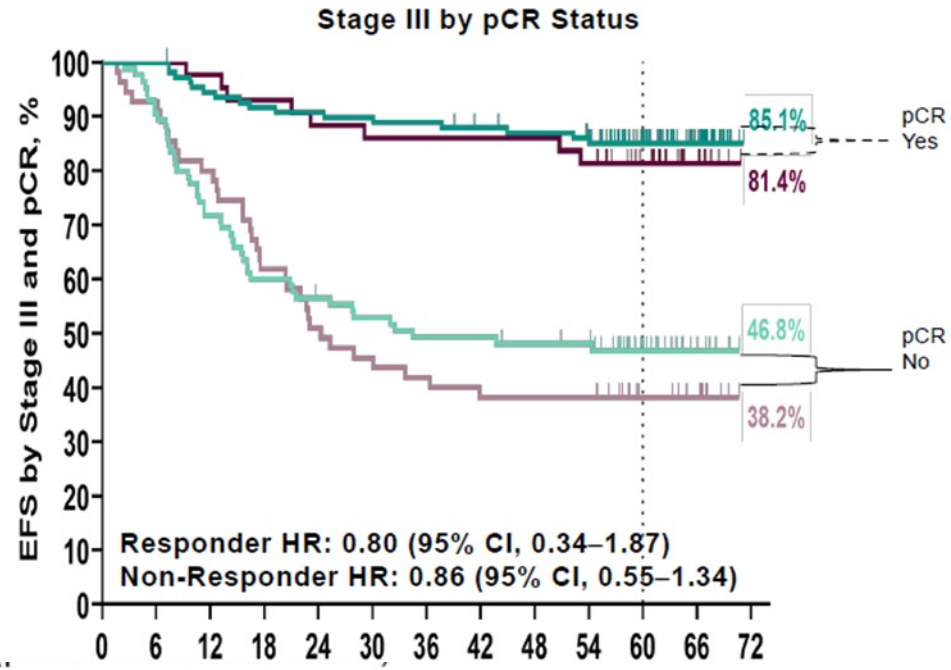
*Callari et al, PD10-09:, SABCS 2021: role of anthracyclines in the modulation of the immune microenvironment

Slide adapted from G. Curigliano ESMO Summit 2023

KEYNOTE-522 Study Design (NCT03036488)

EFS at IA6 by Disease Stage in Patients With and Without pCR

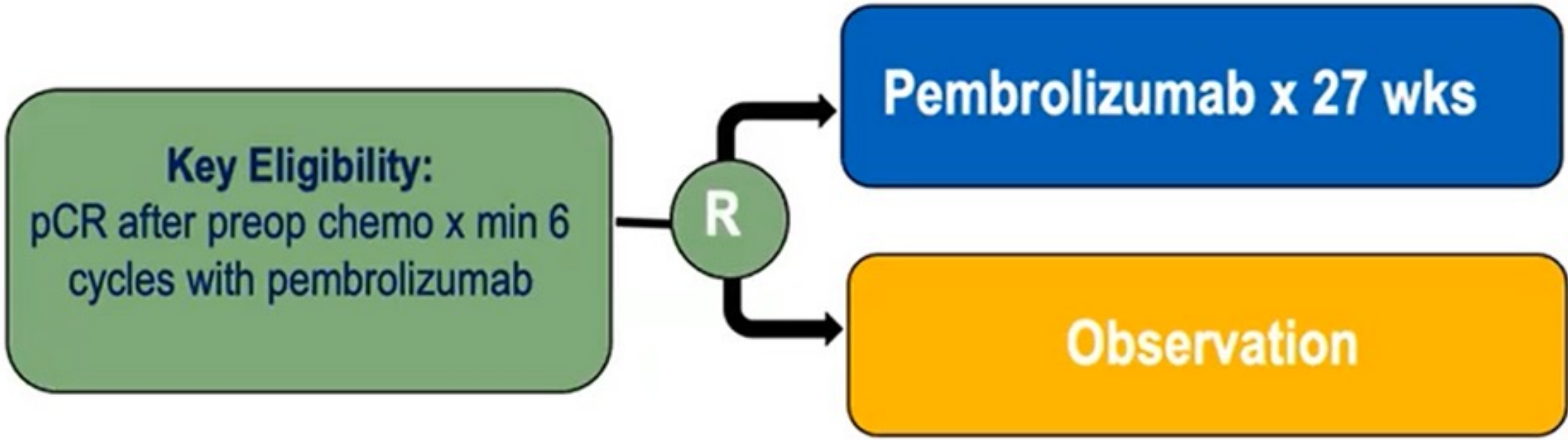




- Safety

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (posttreatment included)

OptimICE-pCR

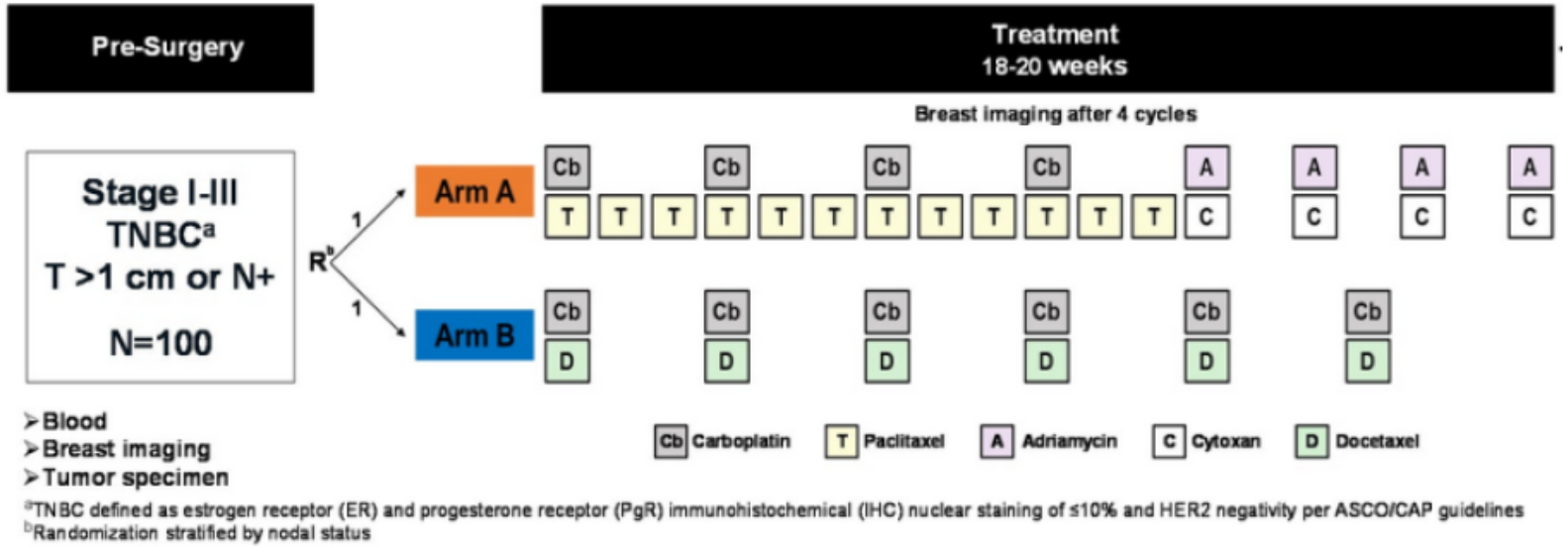


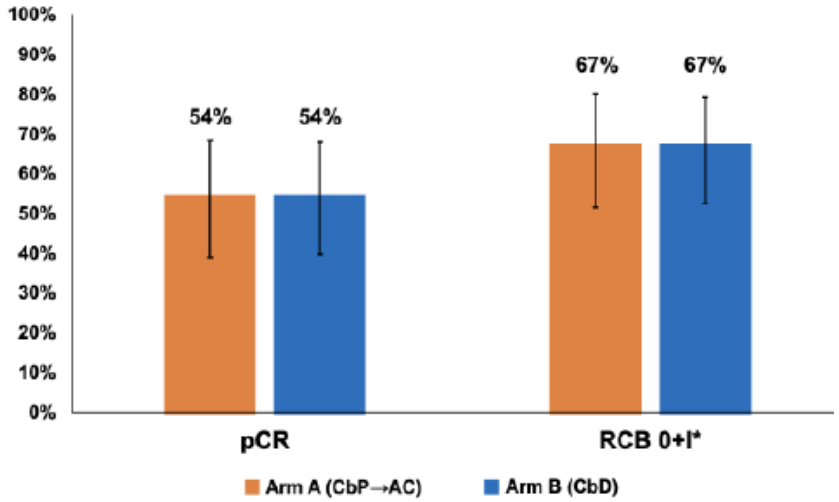
Stratification Factors:

- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Sara Tolaney/ALLIANCE

NeoSTOP: Docetaxel + carboplatin shows similar rate of pCR to Paclitaxel + Carboplatin -> AC

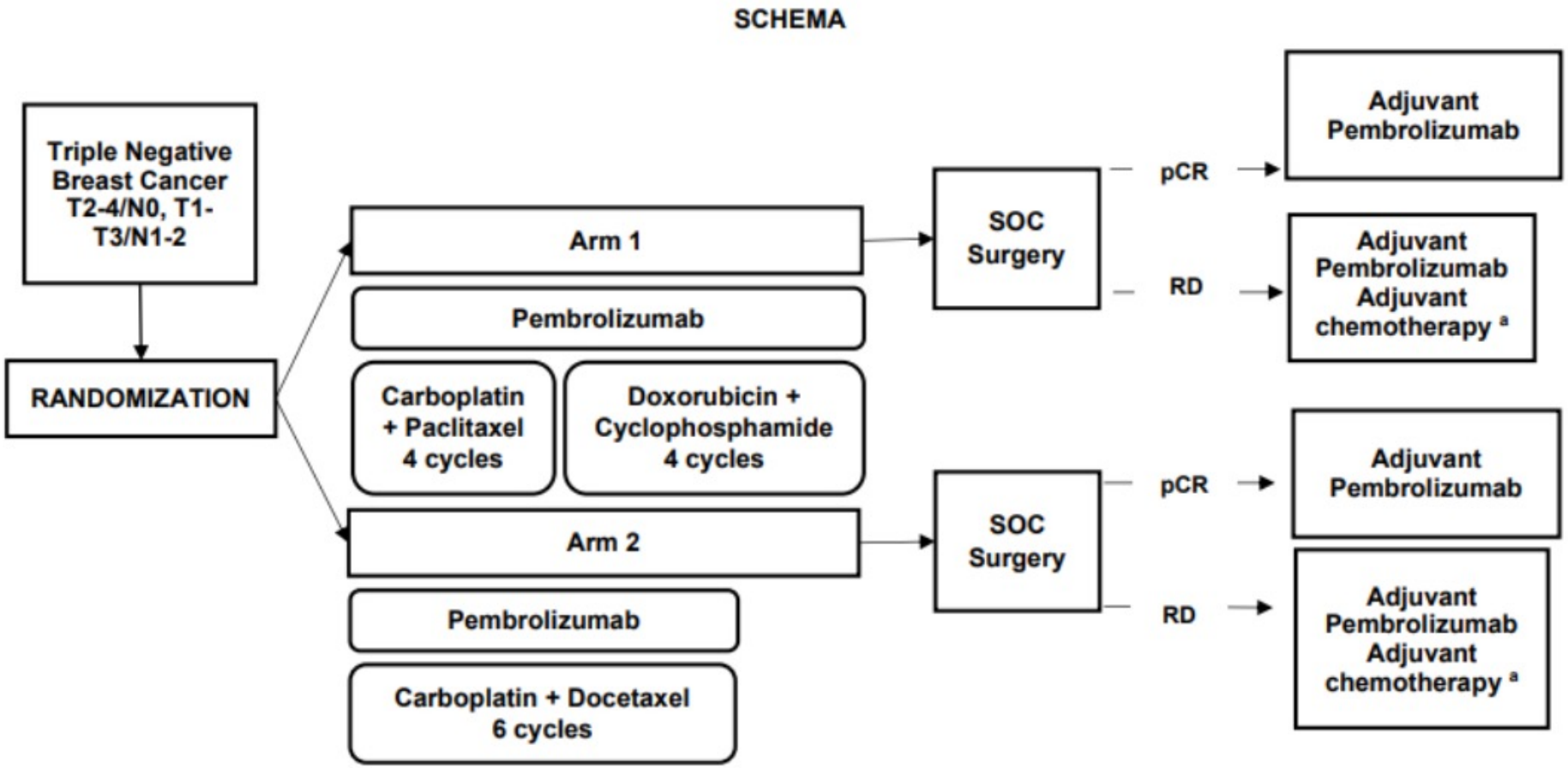




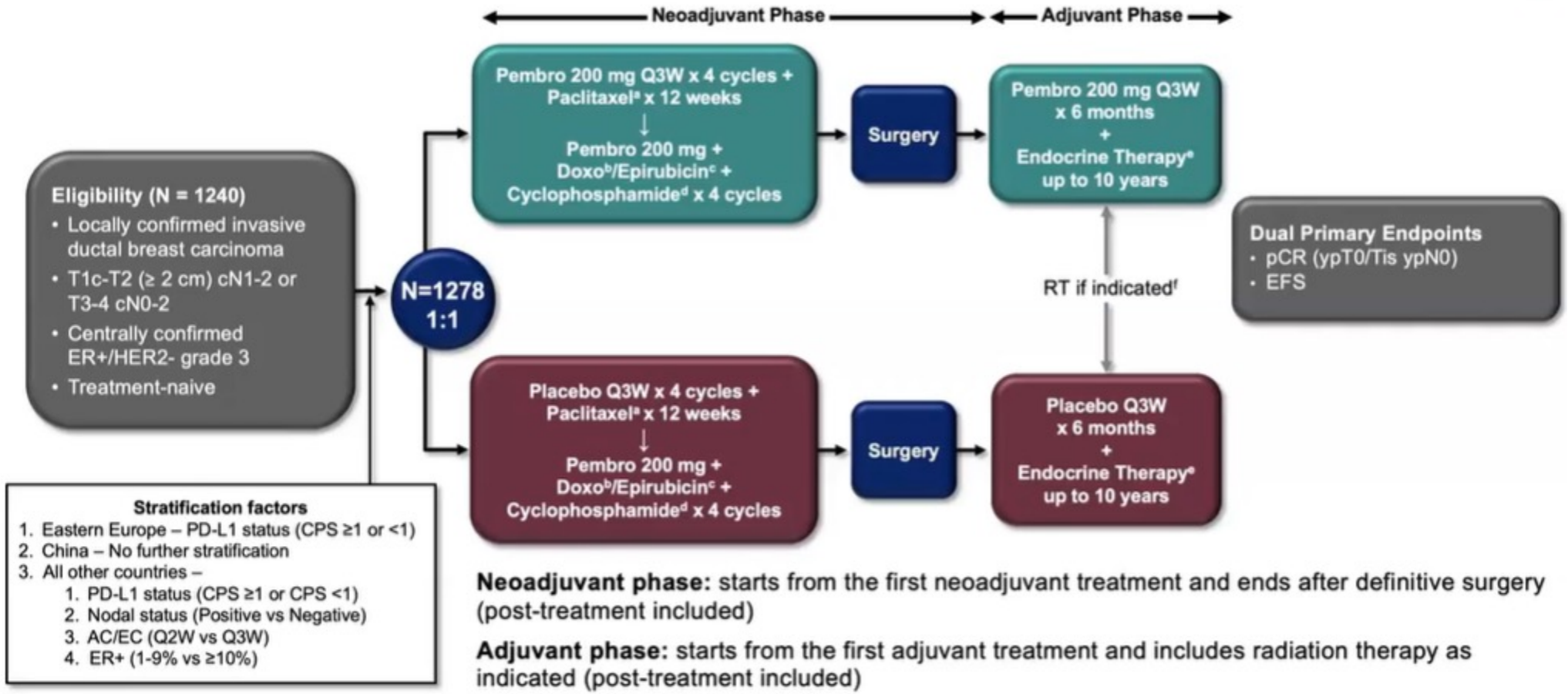
- Docetaxel + Carboplatin associated with significantly lower rates of neutropenia, febrile neutropenia, anemia and thrombocytopenia
- Docetaxel + Carboplatin associated with higher therapy completion rates compared to the 4-drug regimen of Paclitaxel + Carboplatin -> AC

Sharma P, et al. Clin Cancer Res 2021;27(4):975-982

S2212: SCARLET-SWOG NCI (Chair: Sharma)



KEYNOTE-756 Study Design (NCT03725059)



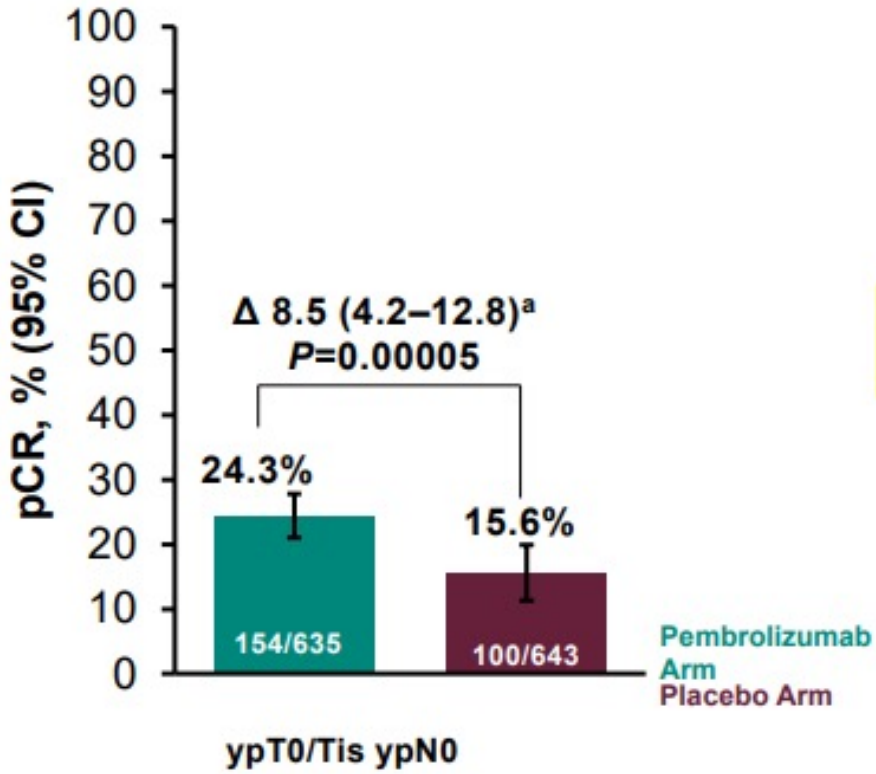
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m² QW. [b]Doxorubicin dose was 60 mg/m² Q3W. [c]Epirubicin dose was 100 mg/m² Q3W. [d]Cyclophosphamide dose was 600 mg/m² Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

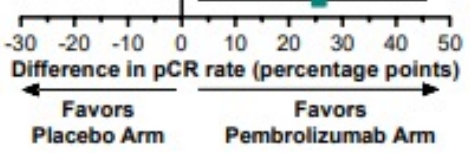
KEYNOTE-756- Pathological Complete Response (pCR) Rate

Primary Endpoint



ITT N=1278

Subgroup	No. with pCR/No. of Participants (%) Pembrolizumab Arm	Placebo Arm	pCR Rate Difference (95% CI)
Overall	154/635 (24.3)	100/643 (15.6)	8.5 (4.2 to 12.8)
Age category			
<65 years	135/546 (24.7)	89/567 (15.7)	9.0 (4.3 to 13.8)
≥65 years	19/89 (21.3)	11/76 (14.5)	6.9 (–5.2 to 18.6)
ECOG PS			
0	142/570 (24.9)	91/588 (15.5)	9.4 (4.8 to 14.1)
PD-L1 status			
Positive (CPS ≥1)	143/482 (29.7)	96/489 (19.6)	9.8 (4.4 to 15.2)
Negative (CPS <1)	11/153 (7.2)	4/154 (2.6)	4.5 (–0.4 to 10.1)
Every 3 weeks	97/415 (23.4)	55/425 (12.9)	10.4 (5.3 to 15.7)
Every 2 weeks	54/183 (29.5)	44/187 (23.5)	6.0 (–3.0 to 15.0)
Tumor size			
T1/T2	111/402 (27.6)	71/413 (17.2)	10.4 (4.7 to 16.1)
T3/T4	43/233 (18.5)	29/230 (12.6)	5.8 (–0.8 to 12.5)
Nodal status			
Positive	143/570 (25.1)	92/582 (15.8)	9.3 (4.6 to 13.9)
Negative	11/65 (16.9)	8/61 (13.1)	3.8 (–9.2 to 16.7)
ER positivity			
≥10%	135/601 (22.5)	87/600 (14.5)	8.0 (3.6 to 12.4)
<10%	19/34 (55.9)	13/43 (30.2)	25.6 (3.3 to 45.8)



Cardoso et al, LBA 21, ESMO 2023

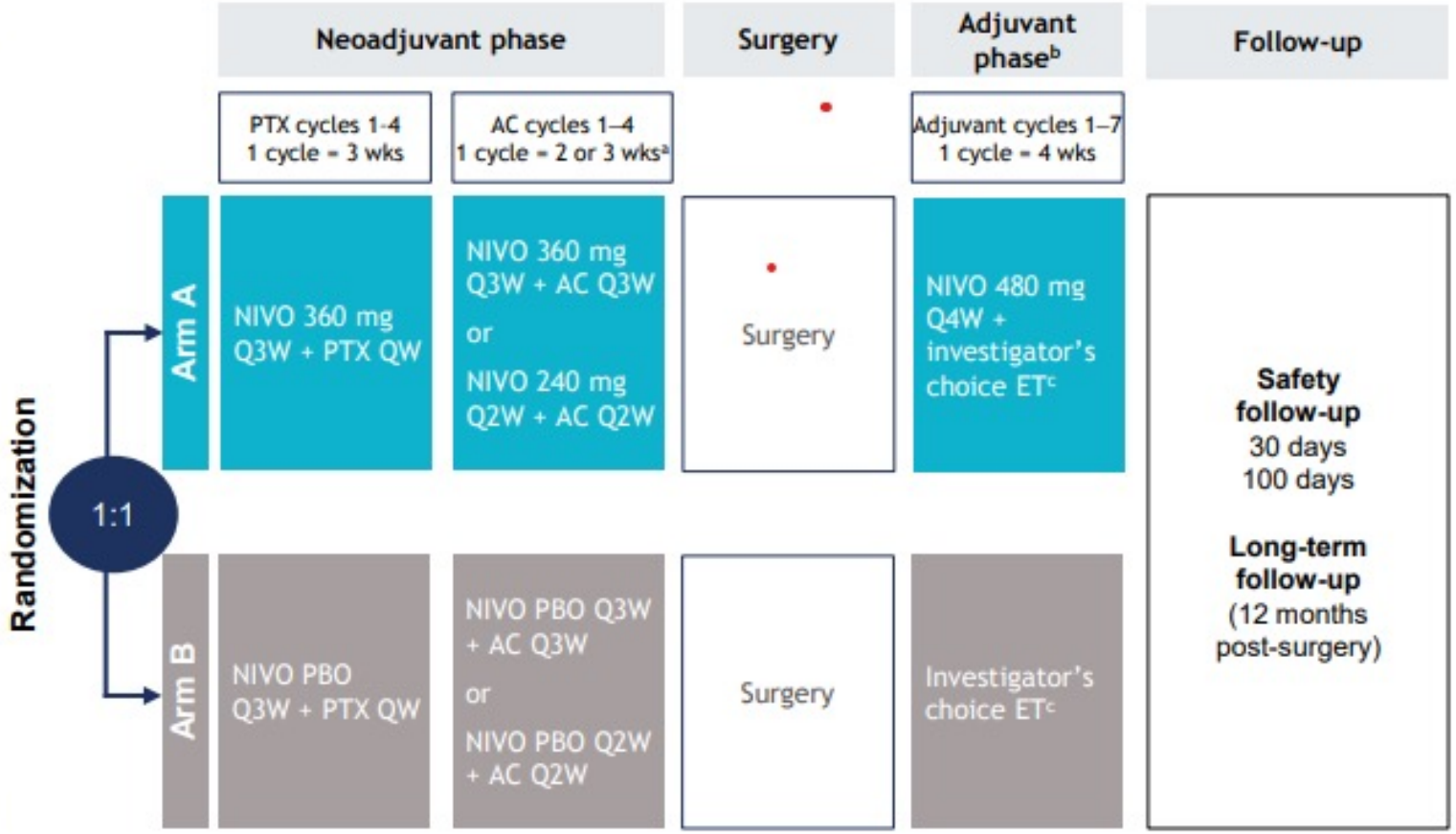
CheckMate-7FL study design (NCT04109066)

Key inclusion criteria

- Newly diagnosed ER+, HER2− BC
- Confirmed ER+ BC
- T1c-T2, cN0-cN2 or T3-T4, cN0-cN2
- Grade 3 or grade 2 with ER 1–10%
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

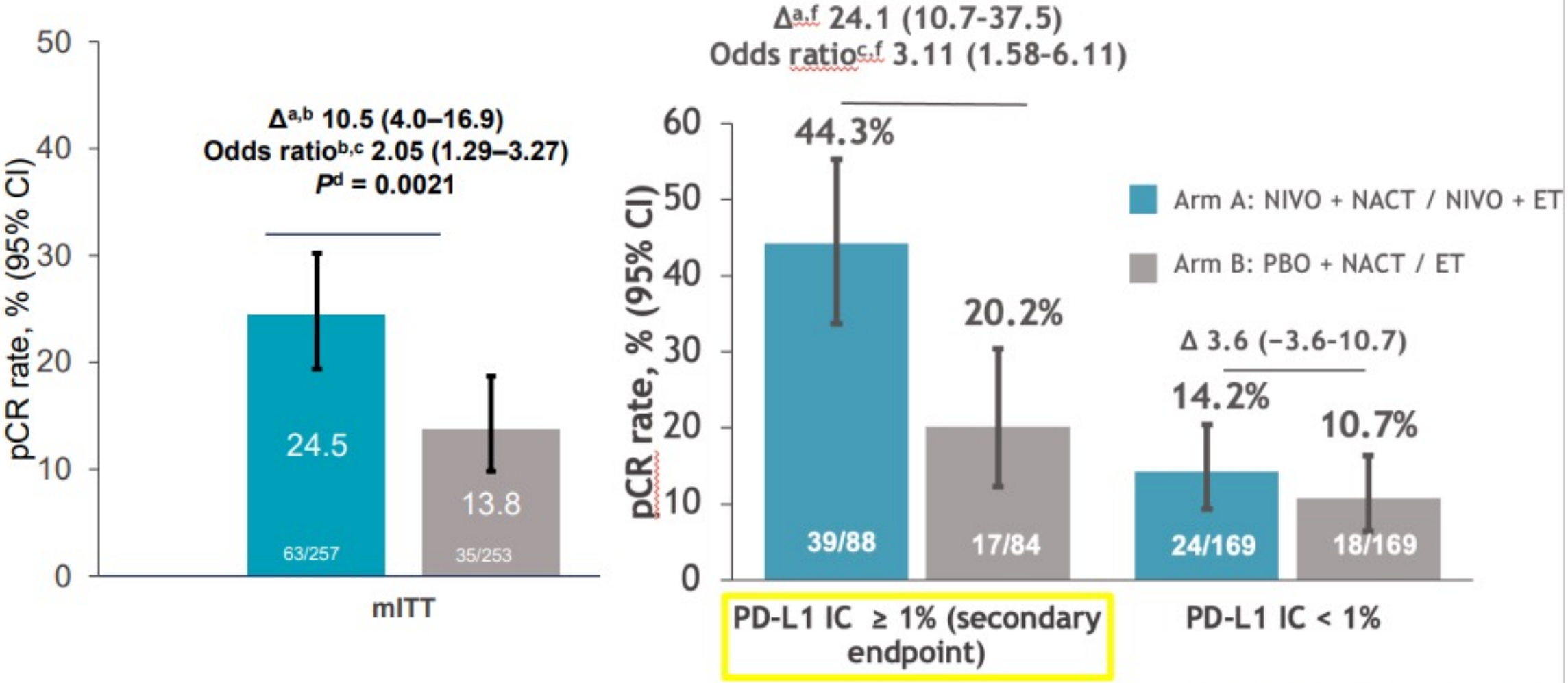
Stratification factors

- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC (Q3W or Q2W)



Loi et al LBA ESMO 2023

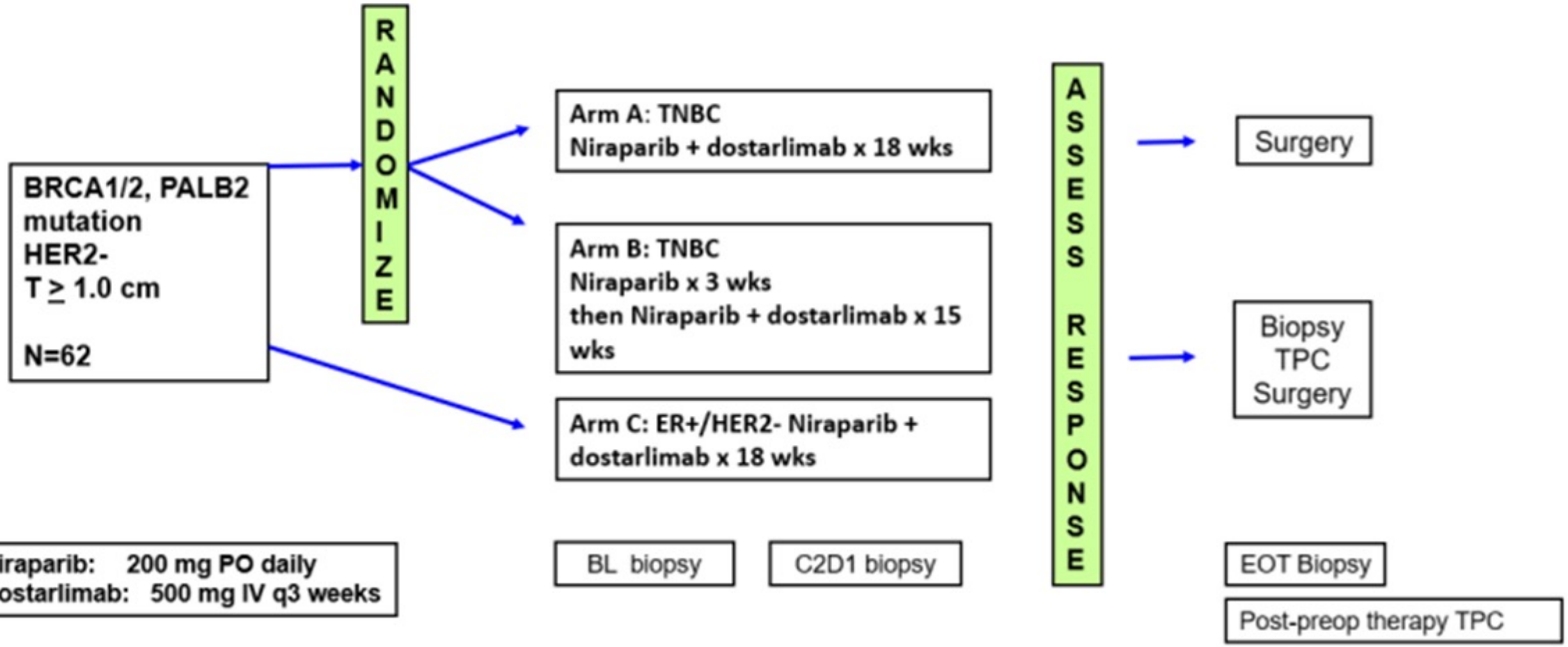
CheckMate-7FL Pathological Complete Response (pCR) Rate



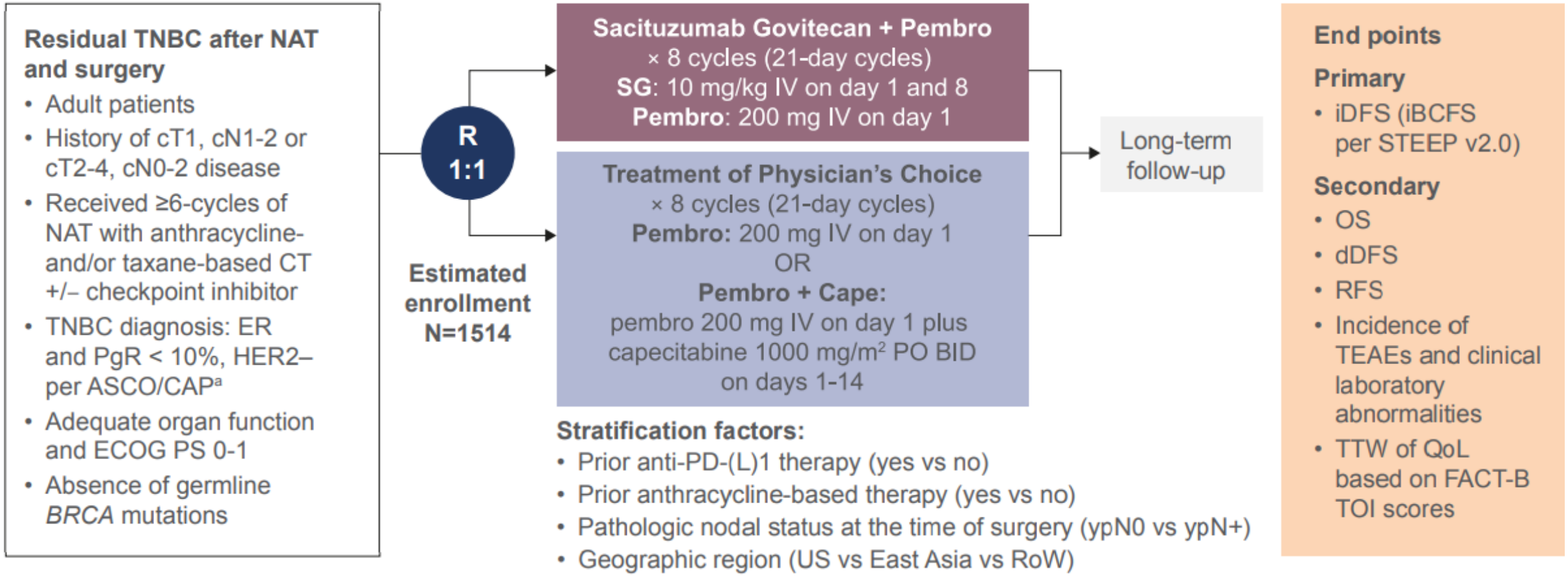
Loi et al, LBA 20, ESMO 2023

TBCRC 056: Trial Design

Preoperative Niraparib (PARPi) and dostarlimab (anti-PD1) for BRCA1/2 Deficient Breast Cancer



ASCENT-05/OptimICE-RD



TROPION-03

- High risk TNBC with residual disease after neoadjuvant chemo
- Randomized to standard of care investigator's choice vs
  - Dato-DXd vs Dato-DXd plus durva
  - Primary endpoint: IDFS Dato-DXd durva vs investigator's choice

TROPION-Breast03 Study Design FSI November 2023

Phase 3 Dato-DXd +/- Durvalumab in Adjuvant Residual Disease TNBC

Key Eligibility Criteria

- Histologically confirmed invasive TNBC (ER<1%, PR<1%, HER2-negative)
- Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without carboplatin, with or without pembrolizumab.
- Residual invasive disease after neoadjuvant therapy
- No evidence of locoregional or distant relapse
- Radiotherapy delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0 or 1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 or BRCA2 mutation

Stratification factors:

- Prior neoadjuvant pembrolizumab (Yes vs No); cap No at 40%
- Residual disease (< 1 cm vs ≥ 1 cm); cap < 1 cm (in the absence of lymph node involvement) at 20%
- Prior neoadjuvant platinum chemotherapy (Yes vs No)

2:1:2
n=1075

- **Dato-DXd** 6 mg/kg IV Q3W x 8 cycles + Durva 1120 mg IV Q3W x 9 cycles
- **Dato-DXd** 6 mg/kg IV Q3W x 8 cycles
- **Investigator's Choice of Therapy***

*capecitabine, pembrolizumab†,or capecitabine + pembrolizumab†

Primary endpoint
Dato+Durva vs ICT: iDFS

Secondary endpoints
Dato+Durva vs ICT: DDFS, OS
Dato vs ICT: iDFS, DDFS, OS
Dato+Durva vs Dato: iDFS, DDFS
PROs, PK, immunogenicity, safety

Exploratory endpoints
TROP2, PD-L1, ctDNA

Follow-up:
Safety
Disease
Survival

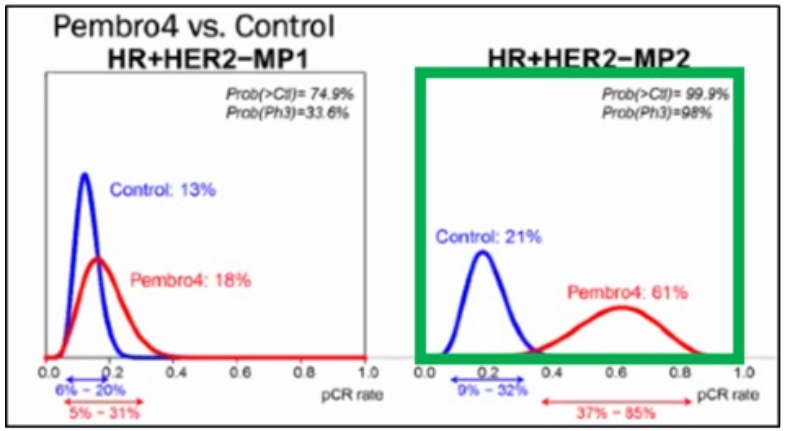
† Only participants who have received prior pembrolizumab in the neoadjuvant setting should receive pembrolizumab as part of their adjuvant therapy on Arm 3.

SWOG CLINICAL TRIALS PARTNERSHIPS

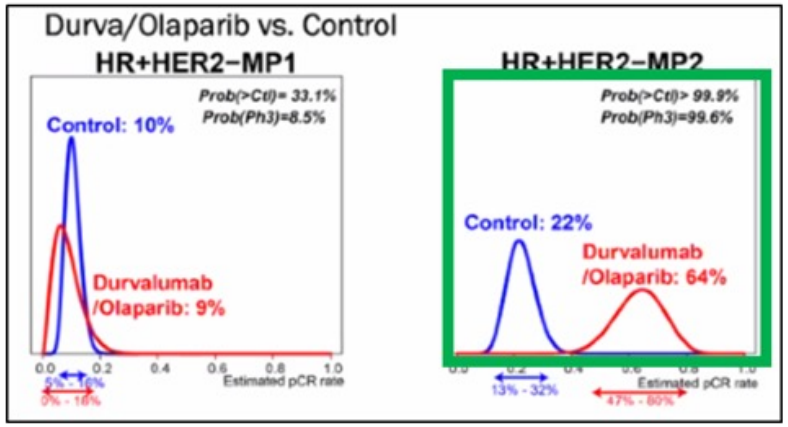
Immunotherapy in HR+: Background and Rationale

- I-SPY 2 results define a subset of HR+ BC (MammaPrint ultra-high risk, MP2) that are highly chemotherapy sensitive and may also benefit from IO therapy

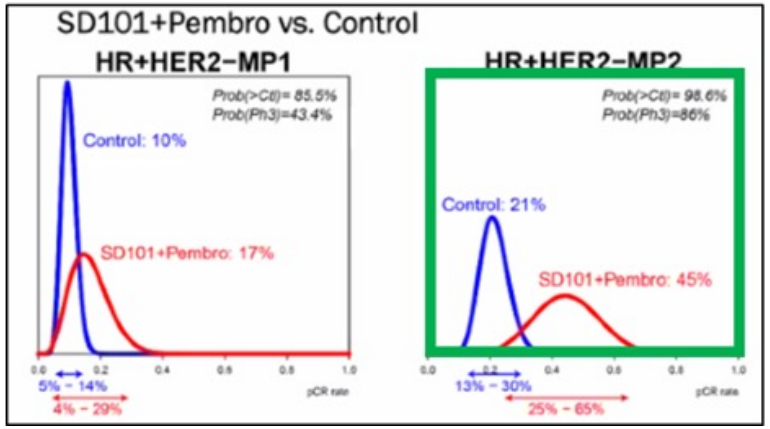
Pembrolizumab + paclitaxel



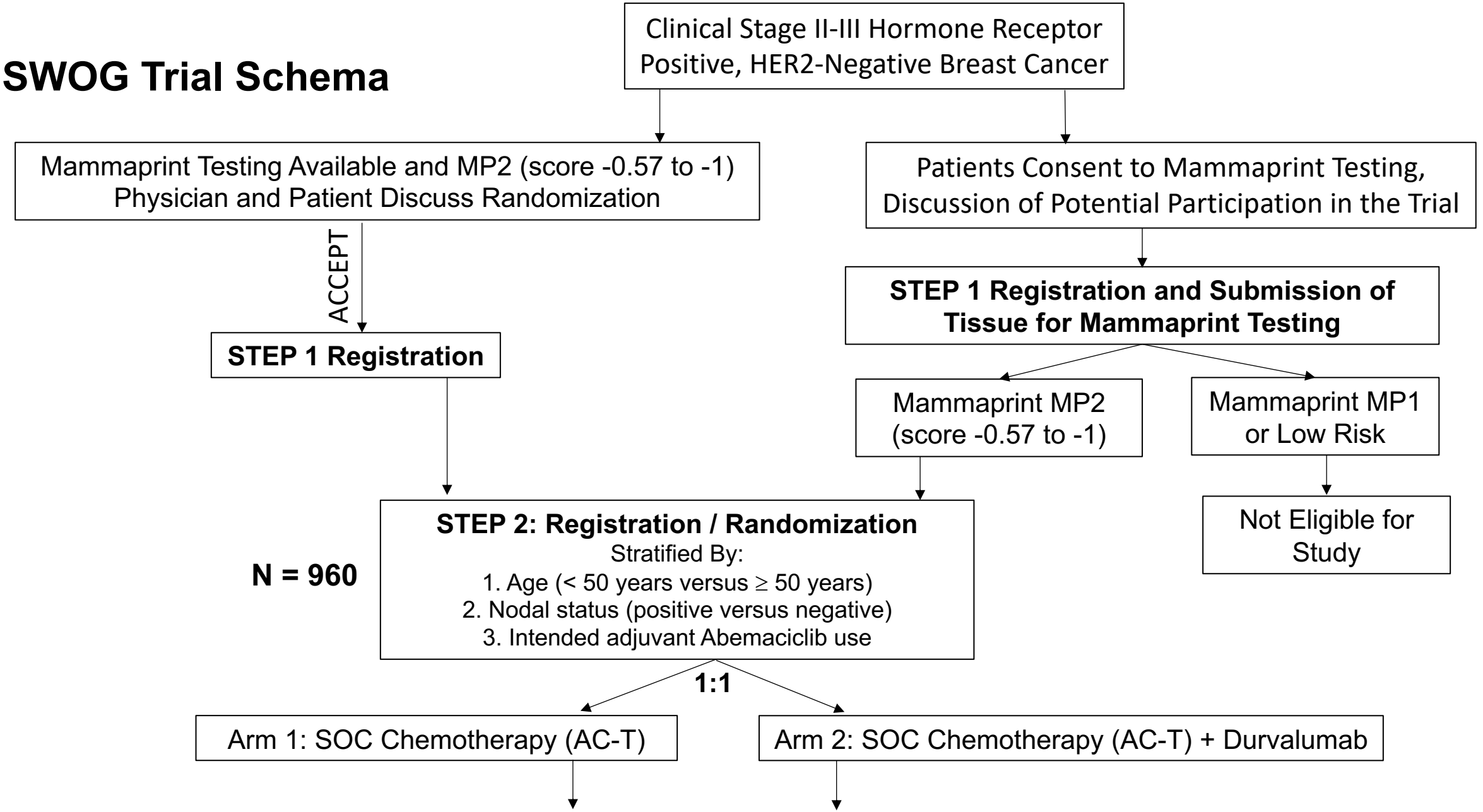
Durvalumab + olaparib + paclitaxel



Pembrolizumab + SD101 + paclitaxel



SWOG Trial Schema

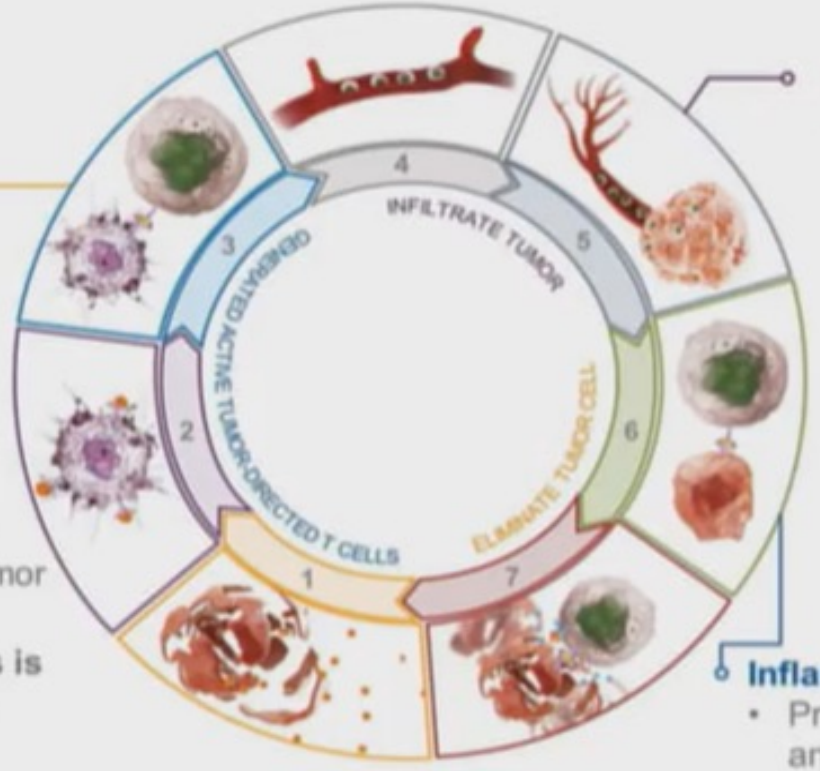


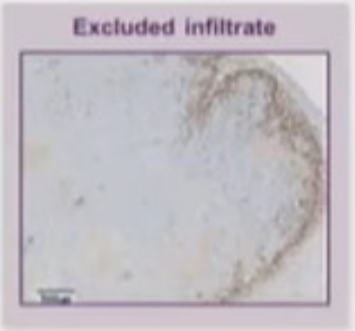
Future directions in immunotherapy options in breast cancer

Need for personalized approaches to stimulate T-cell mediated antitumor immunity

Immune desert

- Characterized by the paucity of T cells in either the parenchyma or the stroma of the tumor
- **The generation of tumor-specific T cells is the rate-limiting step**



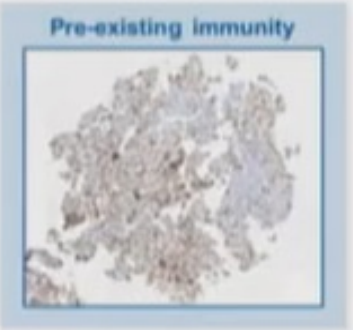


Immune excluded

- Characterized by abundance of immune cells, but these do not penetrate the tumor
- **T-cell migration through tumor stroma is the rate-limiting step**

Inflamed

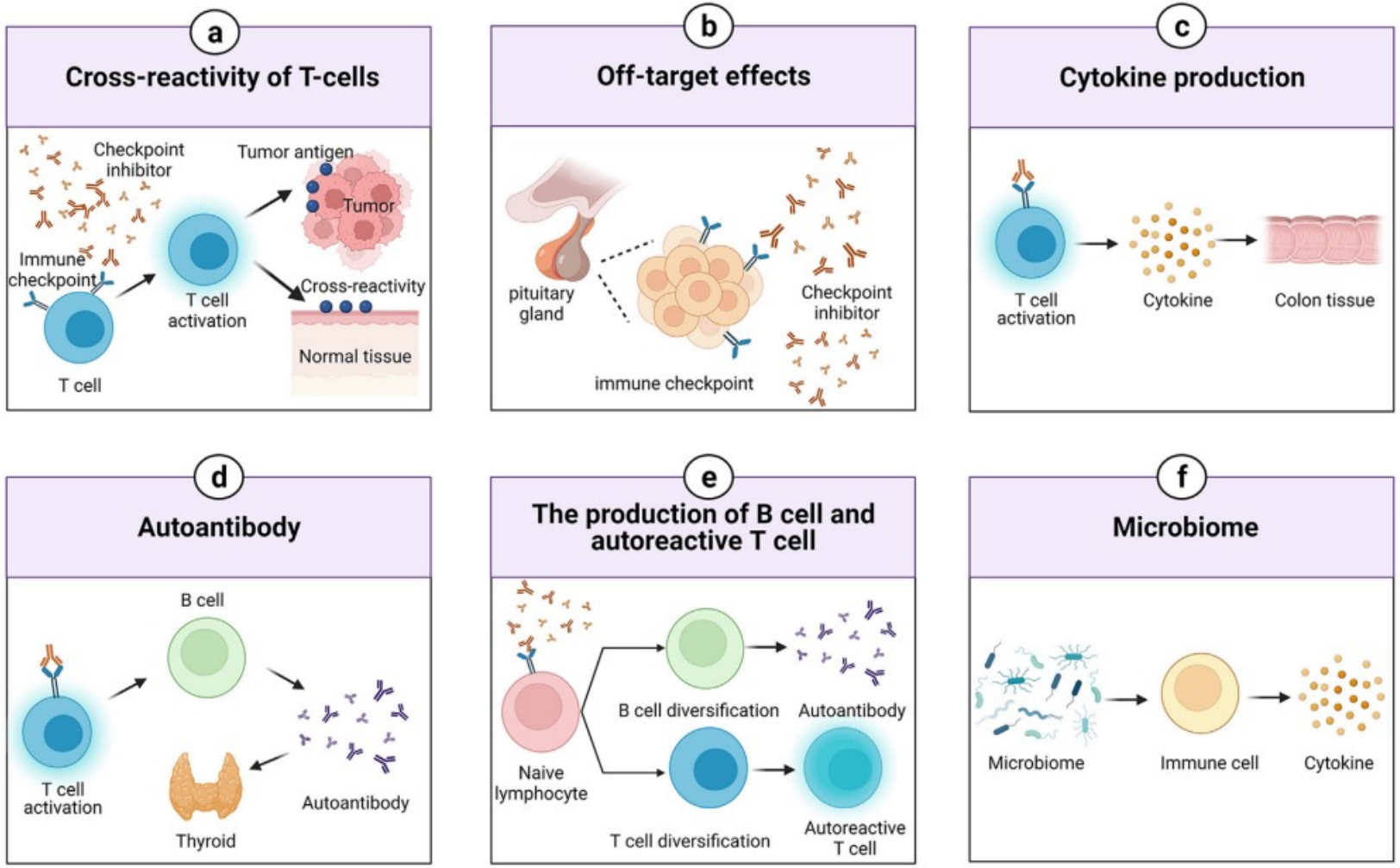
- Presence of pre-existing antitumor response, but was arrested
- **Immune-cell infiltration is necessary but insufficient for inducing a response**



Because of the distinct immune phenotypes, a personalized cancer approach should be considered

Hedge et al, CCR 2016; Chen and Melman, Nature 2017

Balancing therapeutic efficacy with immune related adverse events



Zheng et al Elsevier 2022

Thank You

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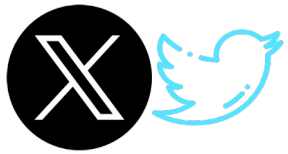

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