UT Southwestern
Medical Center

Innovation in Tackling Triple Negative Residual Disease Following Preoperative KN-522 Regimen

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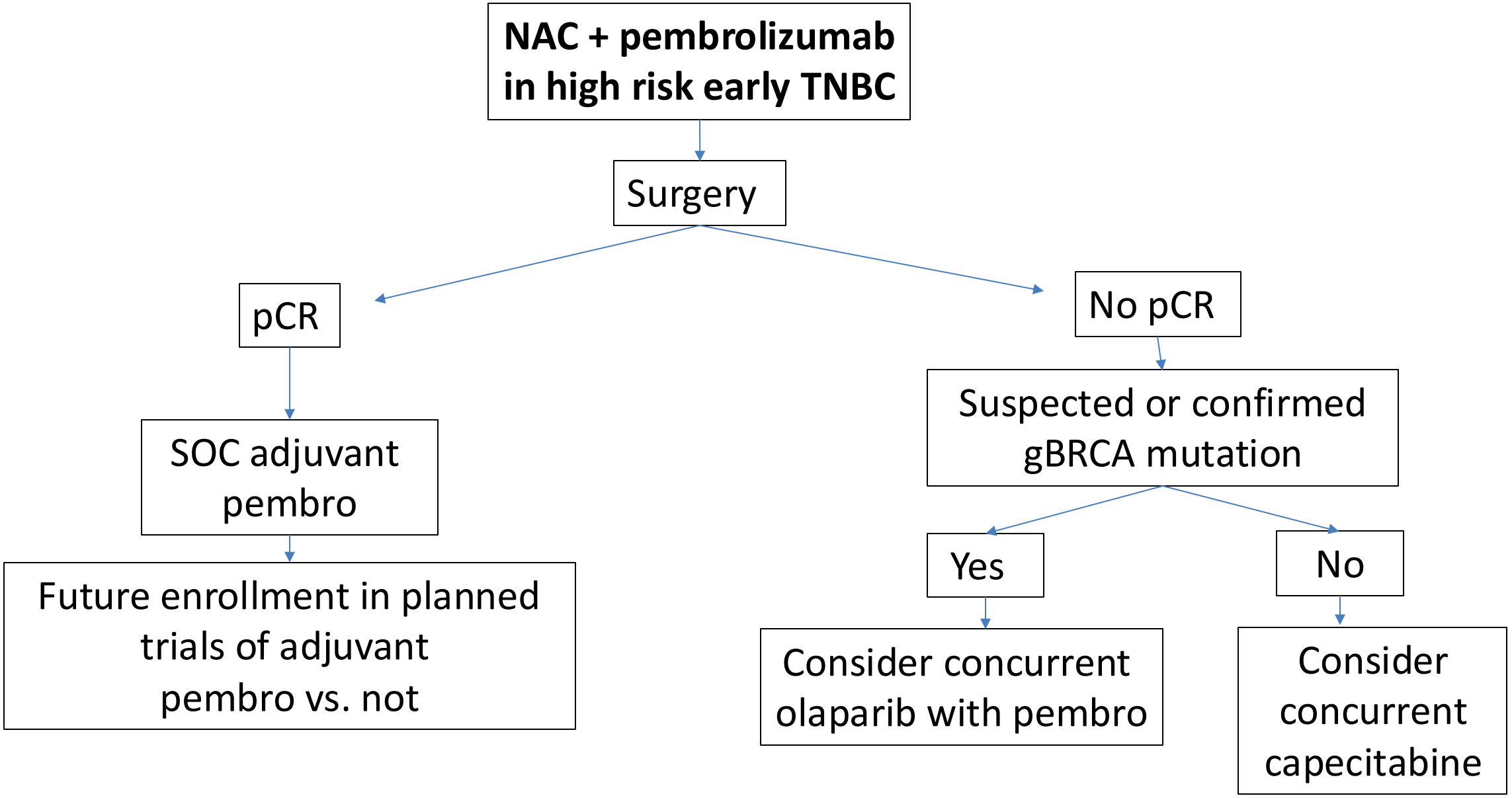


Consider concurrent pembro with radiation

KEYNOTE-522

Eligibility

- Newly diagnosed TNBC (central confirmation)
- T1c N+ or T≥2 N0-2
- PD-L1+ or PD-L1-

Stratification

- T1/T2 vs T3/T4
- N0 vs N+
- Carboplatin Q1W vs Q3W

N = 1,174

R

Neoadjuvant chemo **+ pembrolizumab** → Surgery → Adjuvant **pembrolizumab** 9 cycles

Neoadjuvant chemo **+ placebo** → Surgery → Adjuvant **placebo** 9 cycles

Within 3-6 weeks

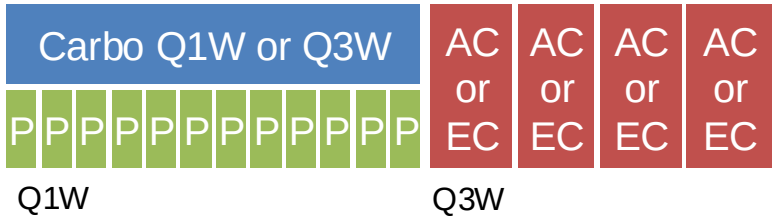
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

- Alternative pCR rate (ypT0 ypN0)
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS

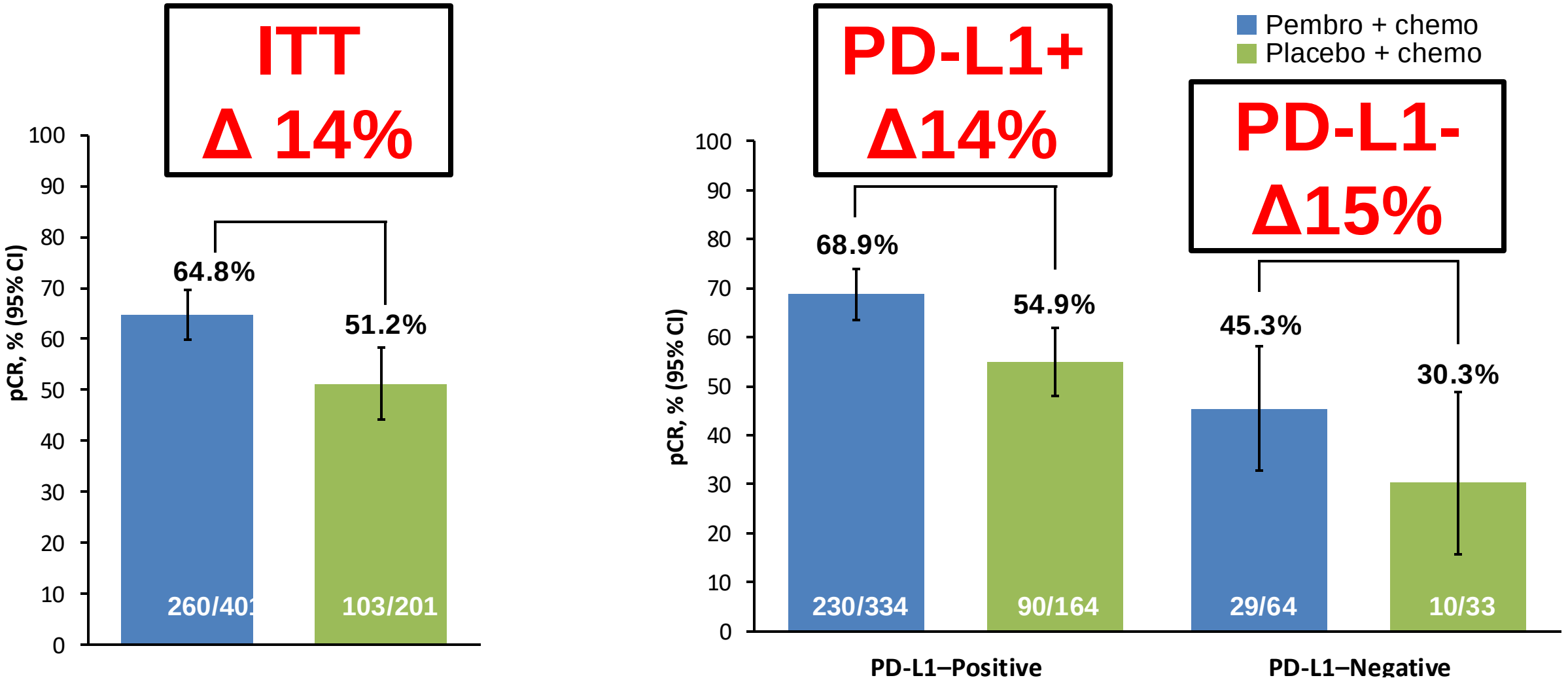
Study Treatment



Paclitaxel 80 mg/m^2 IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m^2 IV Q3W
(Epirubicin 90 mg/m^2 IV Q3W)
Cyclophosphamide 600 mg/m^2 IV Q3W
Pembrolizumab 200 mg IV Q3W

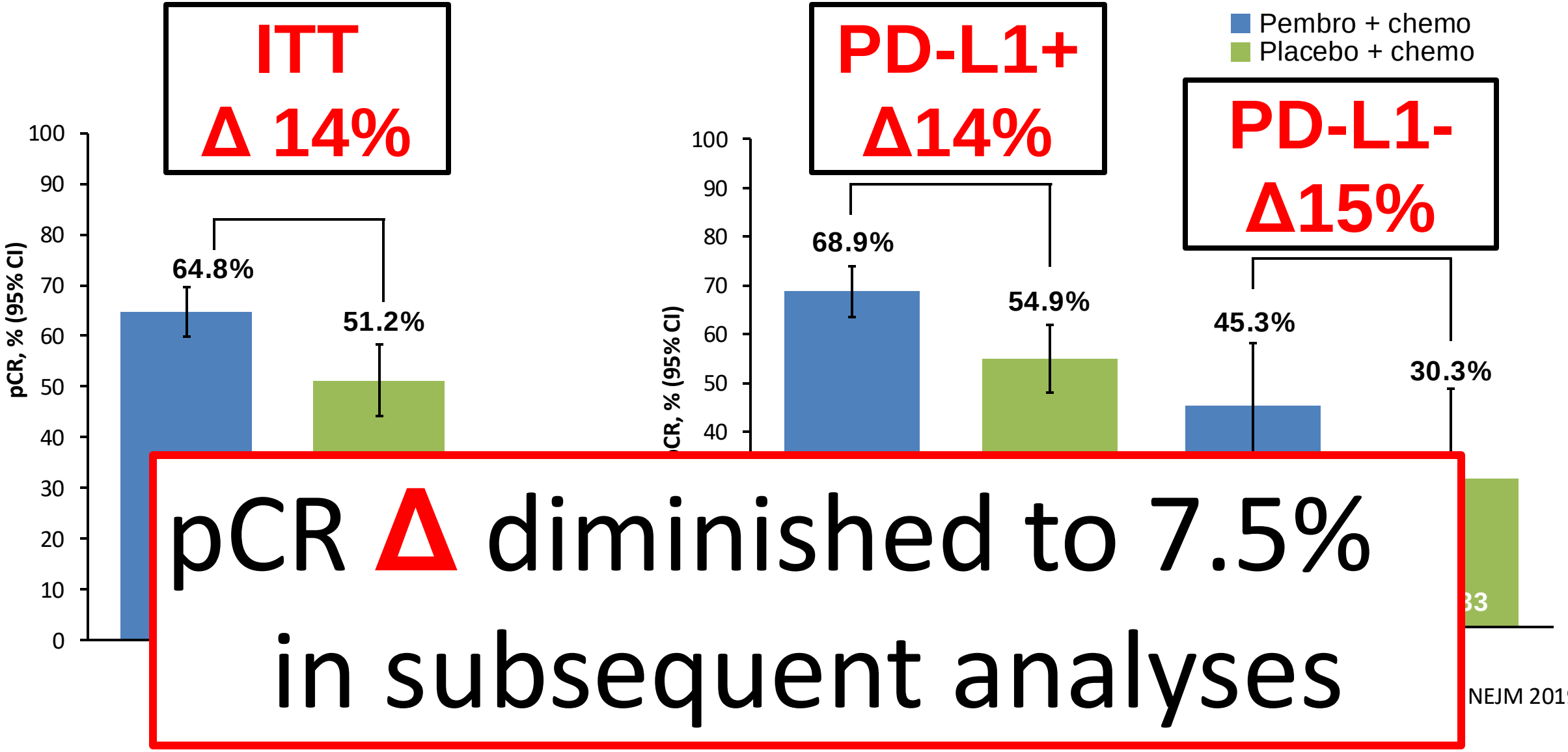
Schmid P et al. NEJM 2019.

KEYNOTE-522: pCR at IA1



Schmid P et al. NEJM 2019.

KEYNOTE-522: pCR at IA1

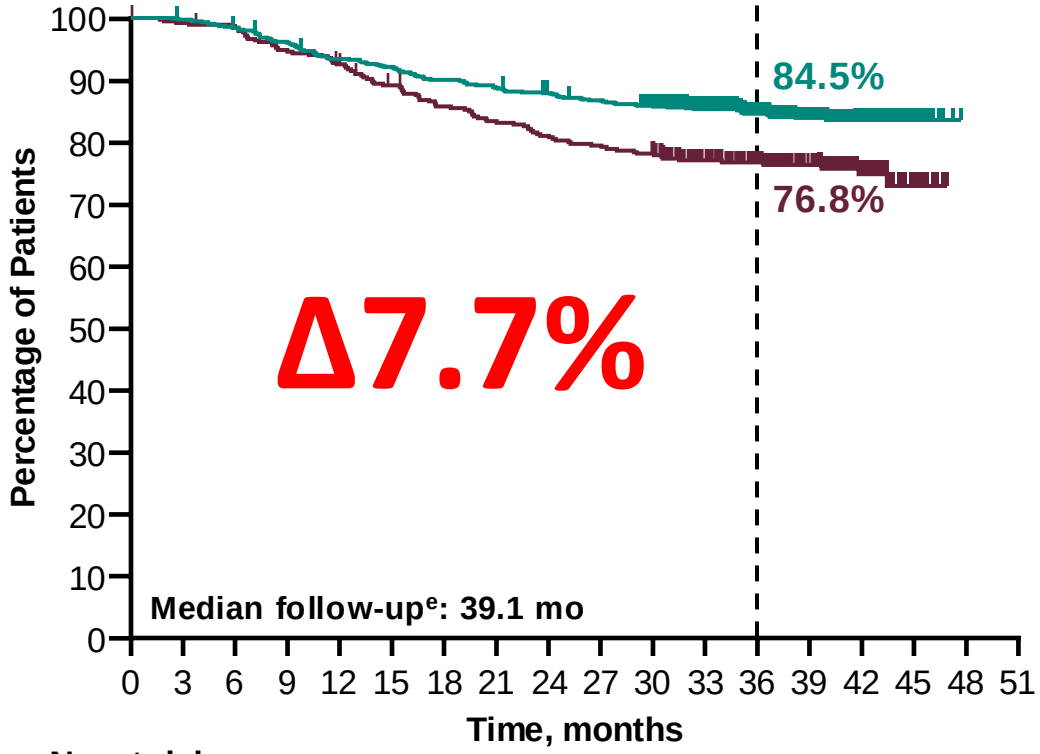


pCR Δ diminished to 7.5% in subsequent analyses

NEJM 2019.

EFS at IA4 and IA6

IA4[a]	Events	HR (95% CI)	*P* value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48–0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



EFS at IA4 and IA6

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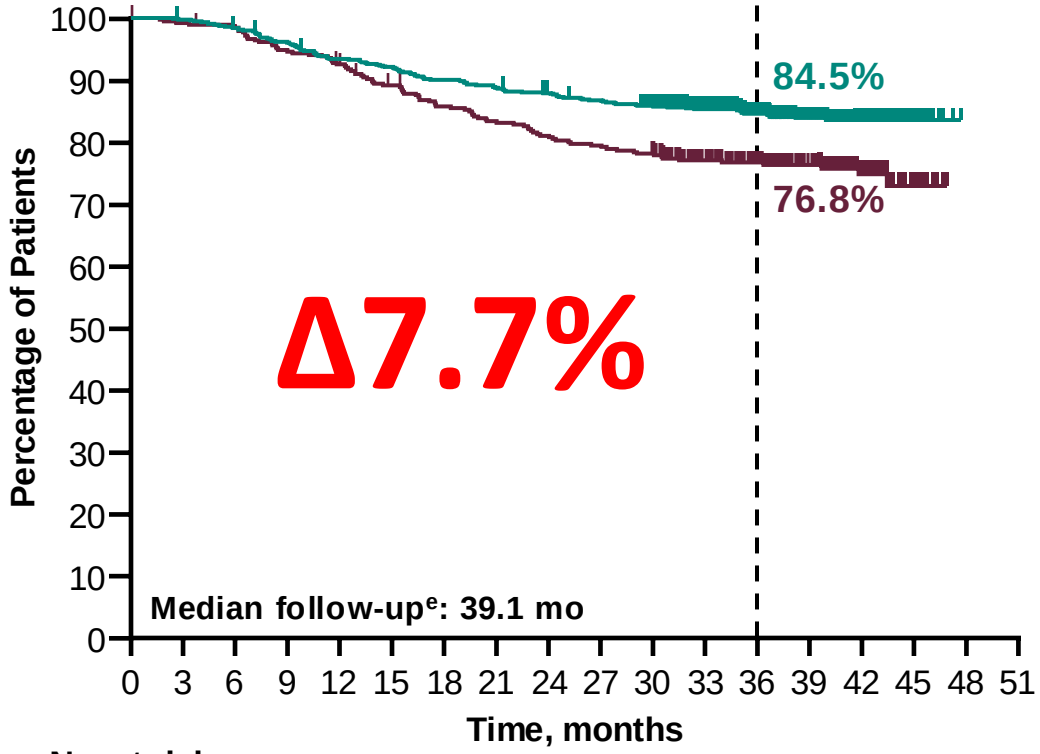
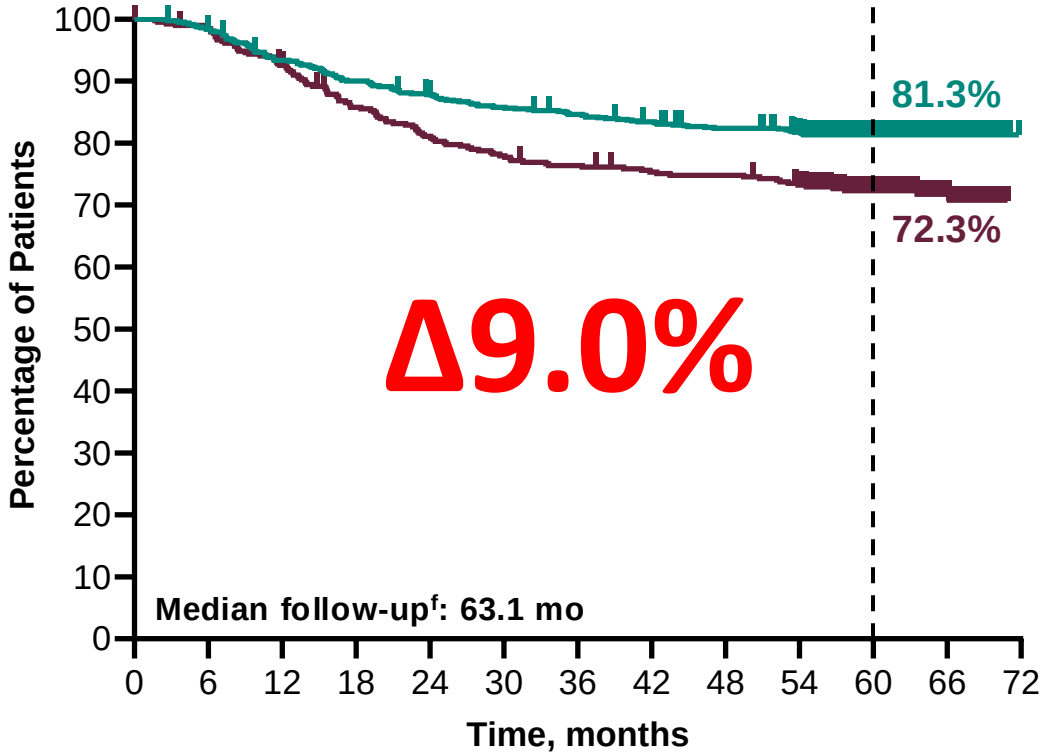


No. at risk

784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	

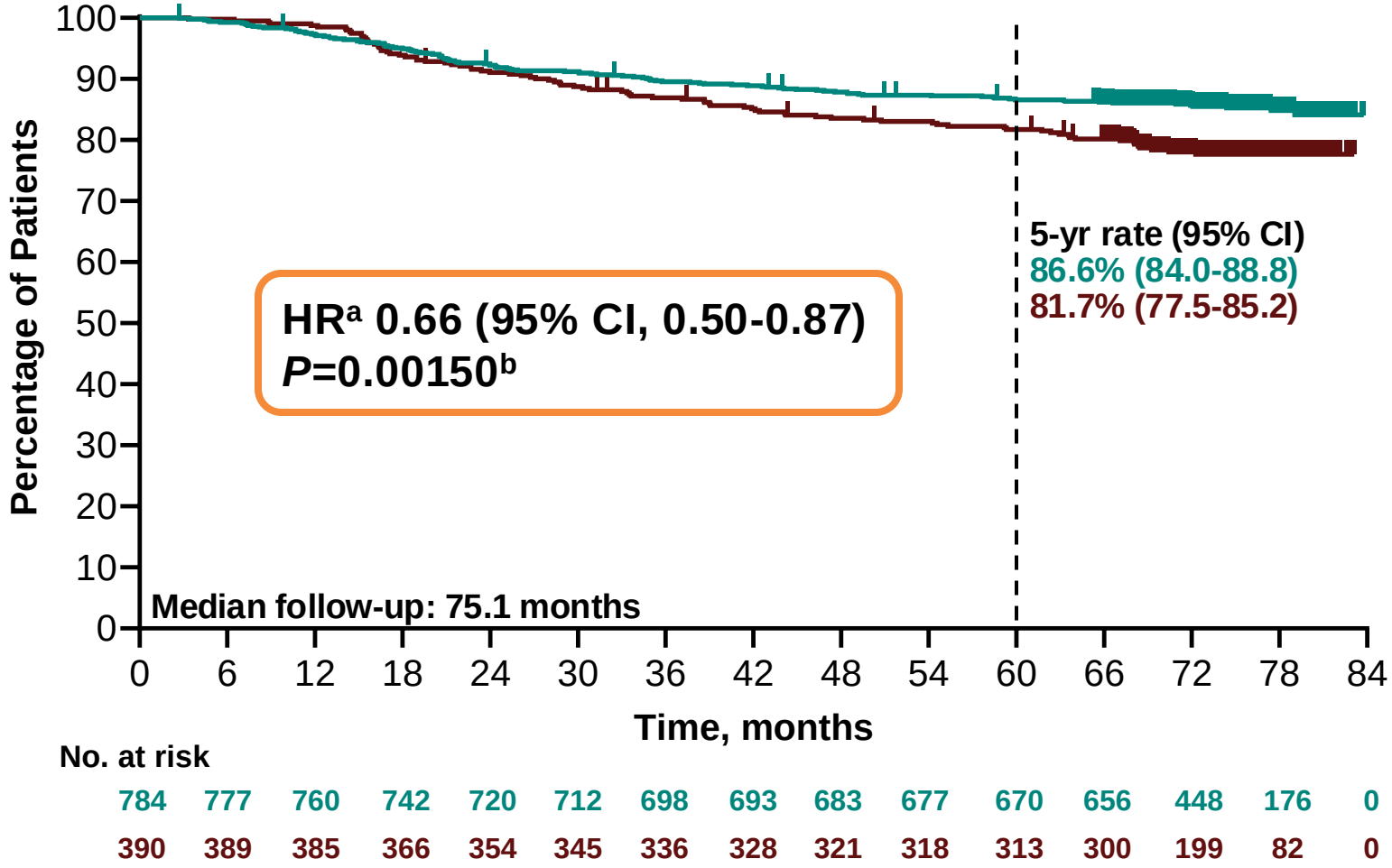


No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

Schmid et al. NEJM 2024

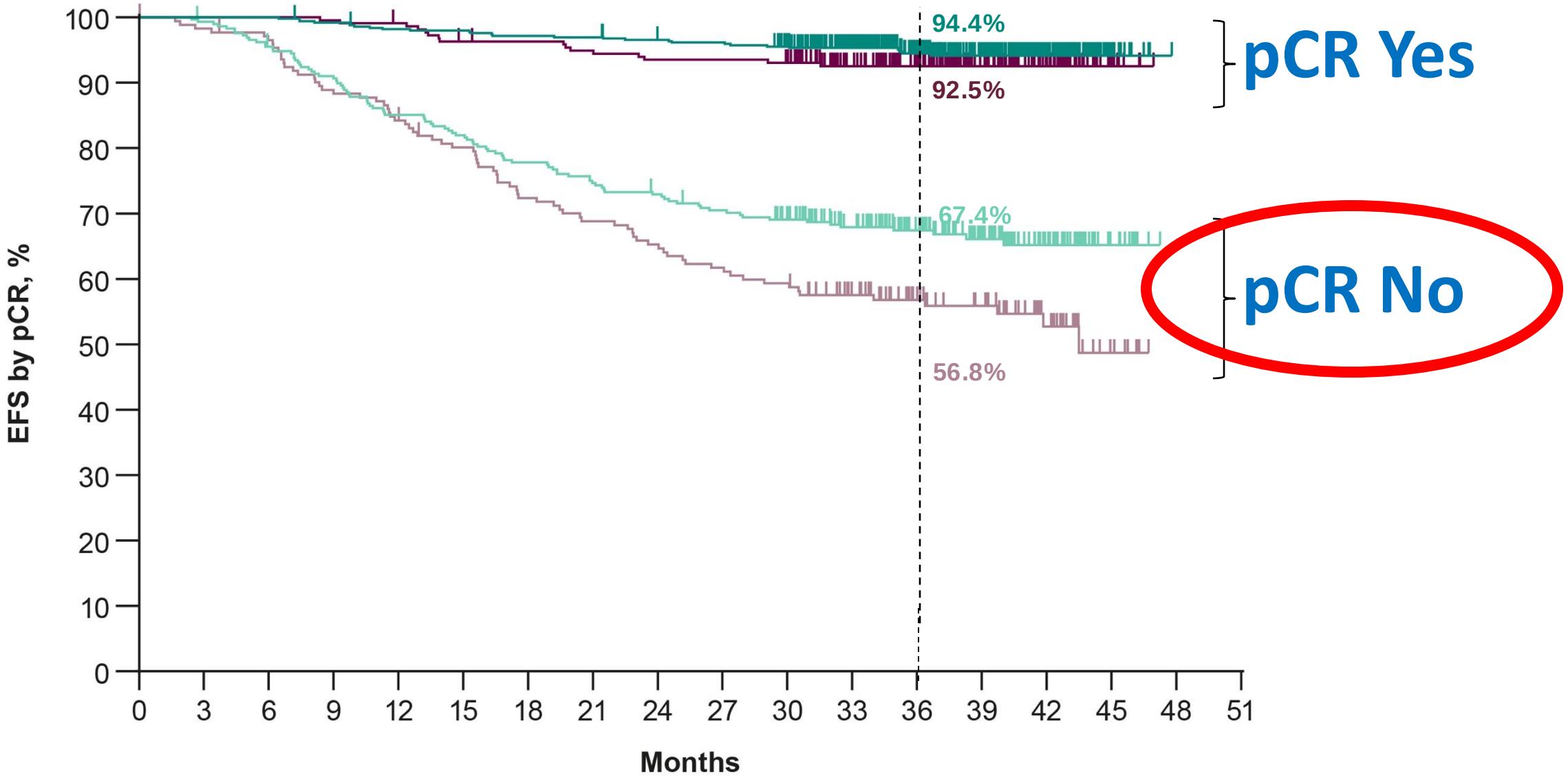
Key Secondary Endpoint: Overall Survival



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

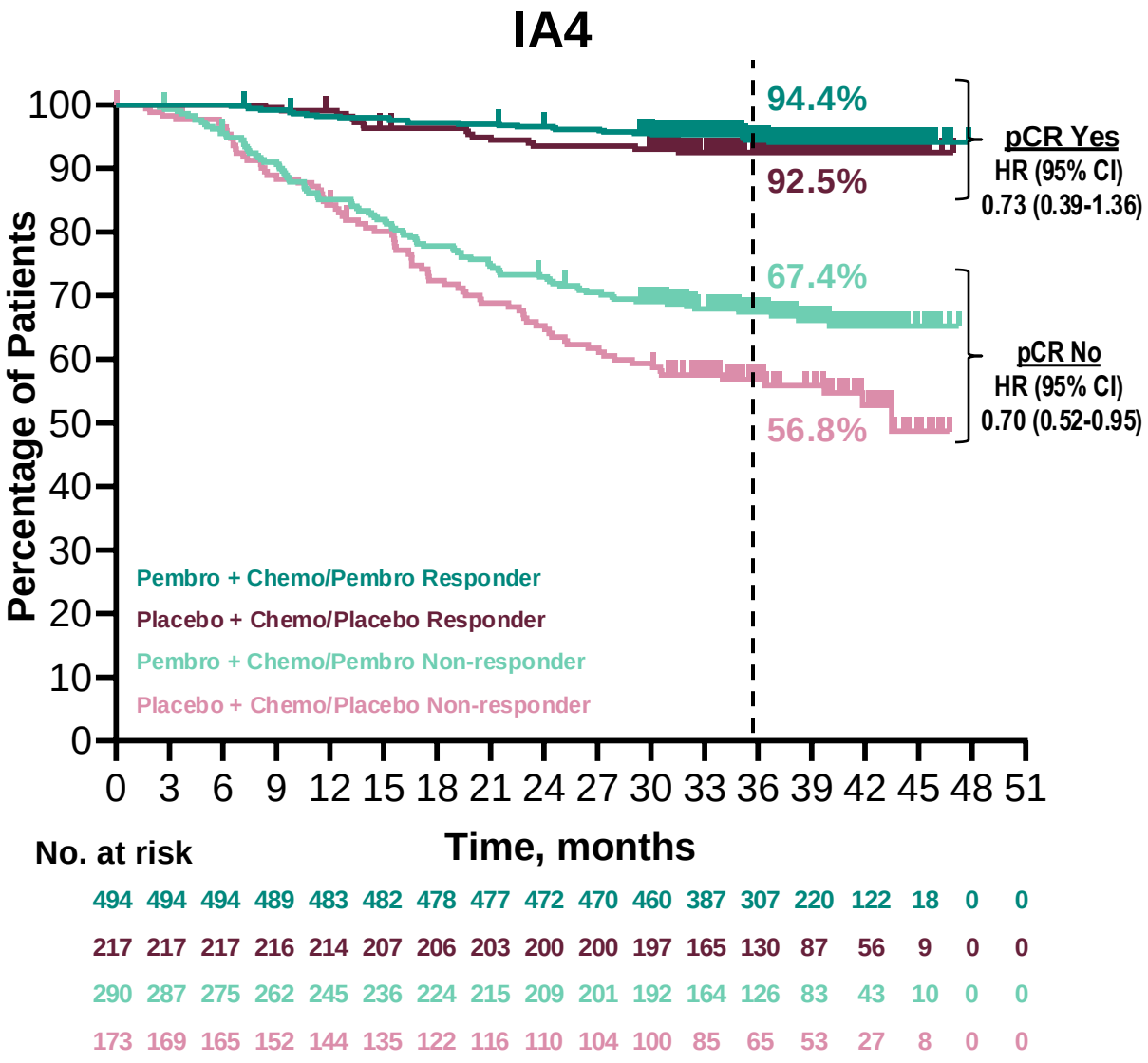
Schmid et al. ESMO 2024
Schmid et al. NEJM 2024

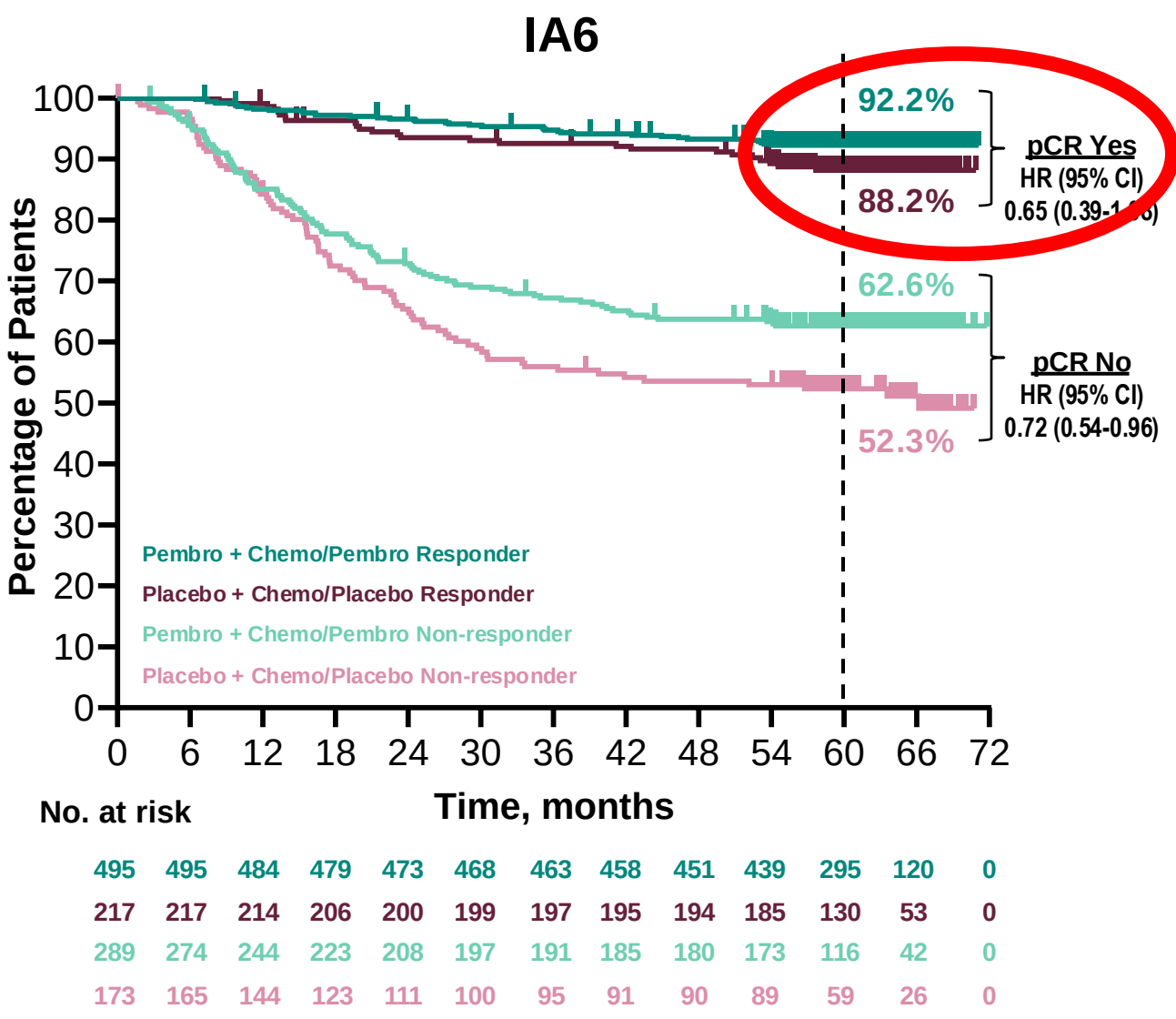
EFS by pCR



Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021.

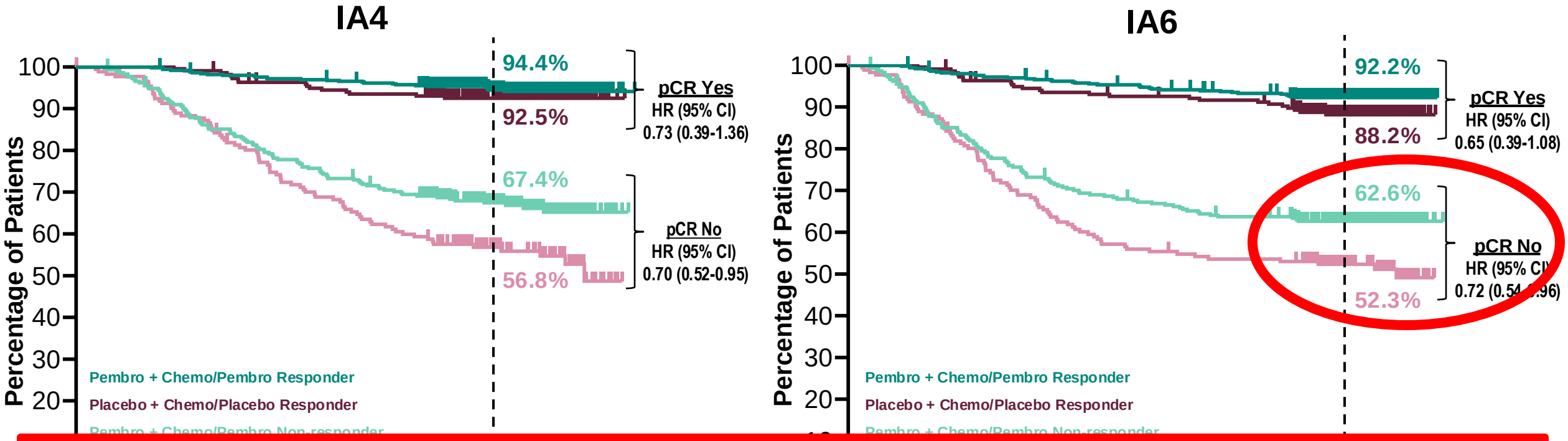
EFS by pCR (ypT0/Tis ypN0)





Schmid et al. ESMO 2023; Schmid et al. NEJM 2024

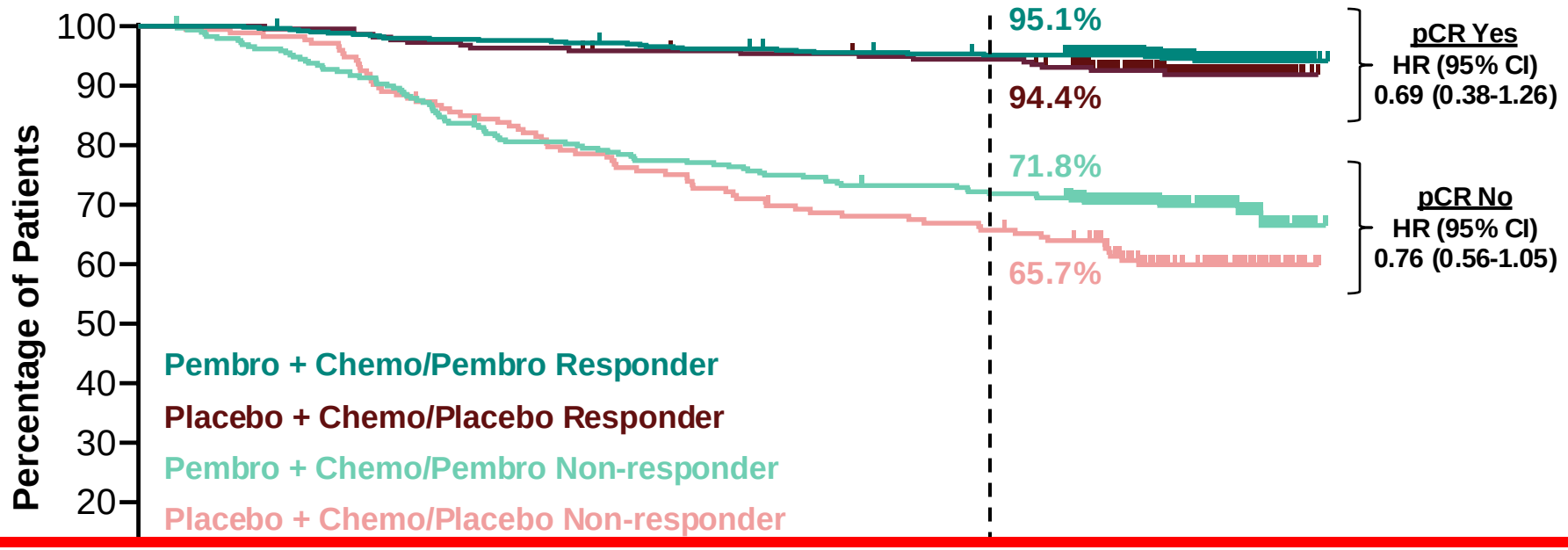
EFS by pCR (ypT0/Tis ypN0)



>1/3 of K522 treated RD patients experience an event within 5y

Schmid et al. ESMO 2023; Schmid et al. NEJM 2024

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)

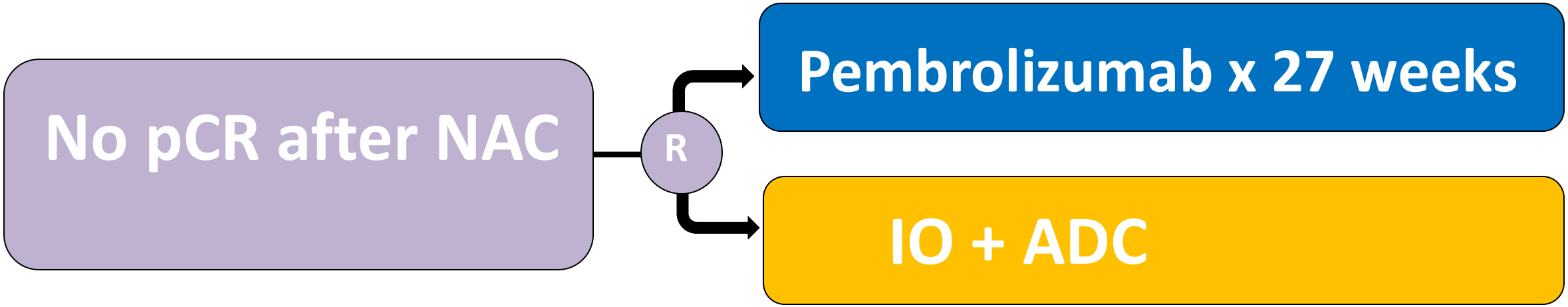


30% of K522 treated RD patients

DIE within 5y

Schmid et al. ESMO 2024; Schmid et al. NEJM 2024

Studies for patients with RD



A Randomized, Open-label, Phase 3 Study of Adjuvant Sacituzumab Govitecan + Pembrolizumab Versus Treatment of Physician's Choice in Patients With TNBC Who Have Residual Disease After Neoadjuvant Therapy and Surgery (ASCENT-05 / OptimICE-RD)

ascent-05

Study Design[1,2]

Trial registration number: NCT05633654

Residual invasive TNBC in breast or positive node(s) after neoadjuvant therapy and surgery

- History of cT1, cN1–2 or cT2–4, cN0–2 disease
- Received at least 6 cycles of neoadjuvant anthracycline- and/or taxane-based chemotherapy with or without an anti-PD-(L)1 agent
- TNBC diagnosis: ER and PR <10%, HER2-negative per ASCO/CAP
- Known gBRCA mutants excluded

N=1514

1:1 randomization

Sacituzumab Govitecan + Pembrolizumab x 8 cycles
SG: 10 mg/kg IV on d 1 and 8 of 21-d cycles
Pembro: 200 mg IV on d 1 of 21-d cycles

Treatment of Physician's Choice x 8 cycles

Pembro: 200 mg IV on d 1 of 21-d cycles
or
Pembro + capecitabine: pembro 200 mg IV on d 1 plus capecitabine 1000 mg/m^2 PO BID on d 1–14 of 21-d cycles

Long-term follow up

Primary
- iDFS

Secondary
- OS
- dDFS
- Safety
- QoL

Exploratory Biomarkers

Stratification Factors:
- Prior anti-PD-(L)1 therapy (yes vs no)
- Prior anthracycline-based therapy (yes vs no)
- Pathologic nodal status at the time of surgery (ypN0 vs ypN+)
- Geographic region (US vs East Asia vs RoW)

PI: Sara Tolaney

Study Diagram

A Phase 3, Randomized, Open-label, Study to Compare the Efficacy and Safety of Adjuvant MK-2870 in Combination with Pembrolizumab (MK-3475) Versus Treatment of Physician's Choice in Participants With Triple Negative Breast Cancer (TNBC) Who Received Neoadjuvant Therapy and Did Not Achieve a Pathological Complete Response (pCR) At Surgery

- **Centrally confirmed TNBC (ER<1%, PR<1%, HER2-)**
- **Non-pCR after at least 5 cycles of pembrolizumab and chemotherapy, including 1 cycle of anthracycline-based neoadjuvant therapy**
- **Randomization within 12 weeks of definitive surgery**
- **Adjuvant RT if indicated, completed before randomization**

N=1530

RANDOMIZATION 1:1

Arm 1

Pembrolizumab 400 mg q6w x 5 doses
+
sac-TMT 4 mg/kg q2w x 12 doses

Arm 2

Treatment of Physician's Choice (TPC)
Pembrolizumab 400 mg q6w x 5 doses
or
Pembrolizumab 400 mg q6w x 5 doses and capecitabine 1000 mg/m2 to 1250 mg/m2 BID on Days 1-14 and Days 22-35 every 42 days x 4 (2 weeks on, 1 week off)

Stratification factors

1. Residual tumor and lymph node status:
   a. [Tumor < 1 cm (ypT1mi – T1b), ypN0] (capped at ~15%)
   vs
   b. [Tumor ≥ 1 cm (ypT1c+), ypN0] or [No tumor or tumor < 1 cm (ypT0 – T1b), ypN1]
   vs
   c. [Tumor ≥1 cm (ypT1c+), ypN1] or [No tumor or any tumor size (ypT0+), ypN2+]
2. TROP2 expression per IHC (low vs medium vs high).
3. Intention to use capecitabine (yes [capped at ~60%] vs no)

PI: Heather McArthur
NCT06393374

TROPION-Breast03
Study of Dato-DXd With or Without Durvalumab Versus ICT Without Pathological CR Following Neoadjuvant Therapy[1,2]

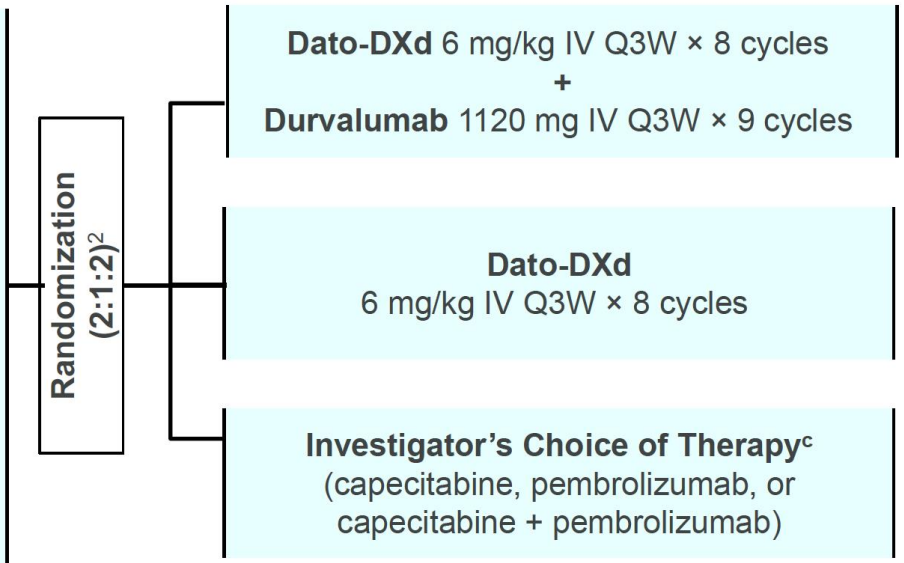
A Phase 3, Open-Label, Randomized Study of Dato-DXd With or Without Durvalumab Versus ICT in Patients With Stage I-III TNBC Who Have Residual Invasive Disease in the Breast and/or Axillary Lymph Nodes at Surgical Resection Following Neoadjuvant Systemic Therapy

Study Design

Patients with Stage I-III TNBC without pathological CR (N≈1075)

- Histologically confirmed invasive TNBC (ER <1%, PR <1%, HER2 negative)3,4,a
- 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
- Radiotherapyb delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0–1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 or BRCA2 mutation

Locations: North America, South America, Asia, Europe
ClinicalTrials.gov Identifier: NCT05629585



Stratification Factors[2]:

- Prior neoadjuvant pembrolizumab (yes vs no); cap no at 40%
- Residual disease (<1 cm vs ≥1 cm)[d]; cap <1 cm at 20%
- Prior neoadjuvant platinum CT (yes vs no)

Primary Endpoint

- **Dato-DXd + durvalumab vs ICT:** iDFS

Secondary Endpoints

- **Dato-DXd + durvalumab vs ICT:** DDFS, OS
- **Dato-DXd vs ICT:** iDFS, DDFS, OS
- **Dato-DXd + durvalumab vs Dato-DXd:** iDFS, DDFS
- PROs, PK, immunogenicity, safety

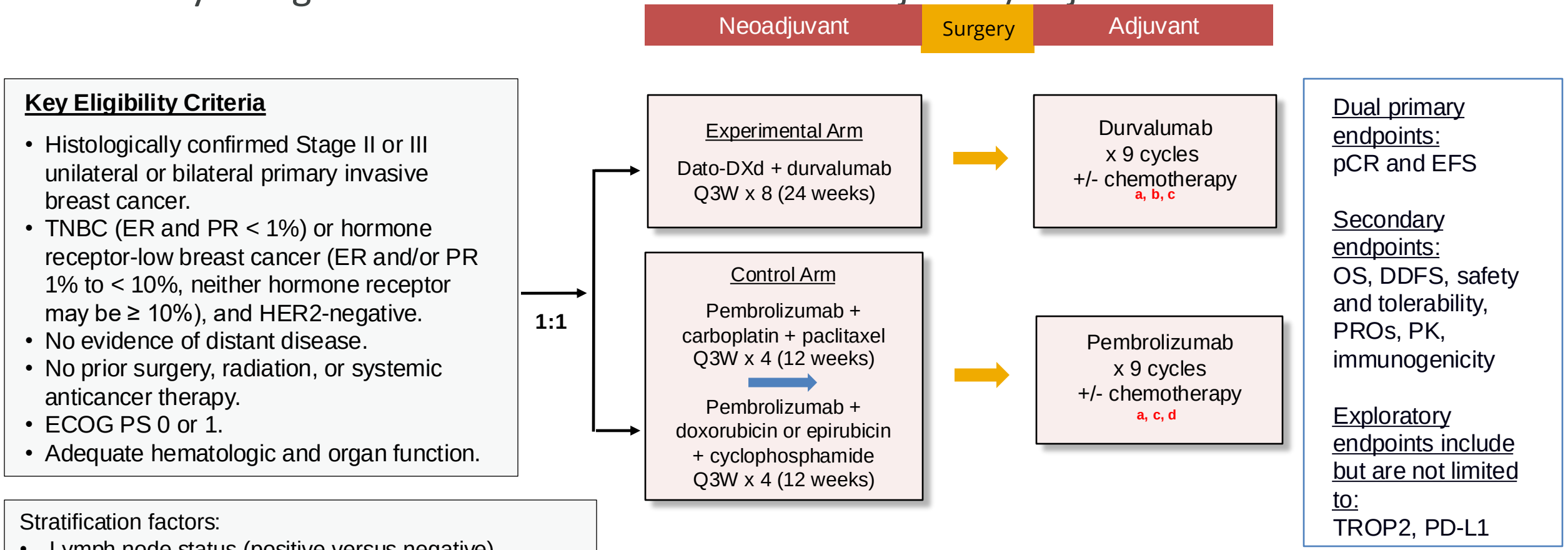
PI: Aditya Bardia

More Questions than Answers

If ADCs are more effective in the NEOADJUVANT setting will the post K522 question be relevant?

TROPION-Breast04

TB04 Study Design: Ph3 Dato-DXd + Durva in Neoadjuvant/Adjuvant TNBC



Stratification factors:

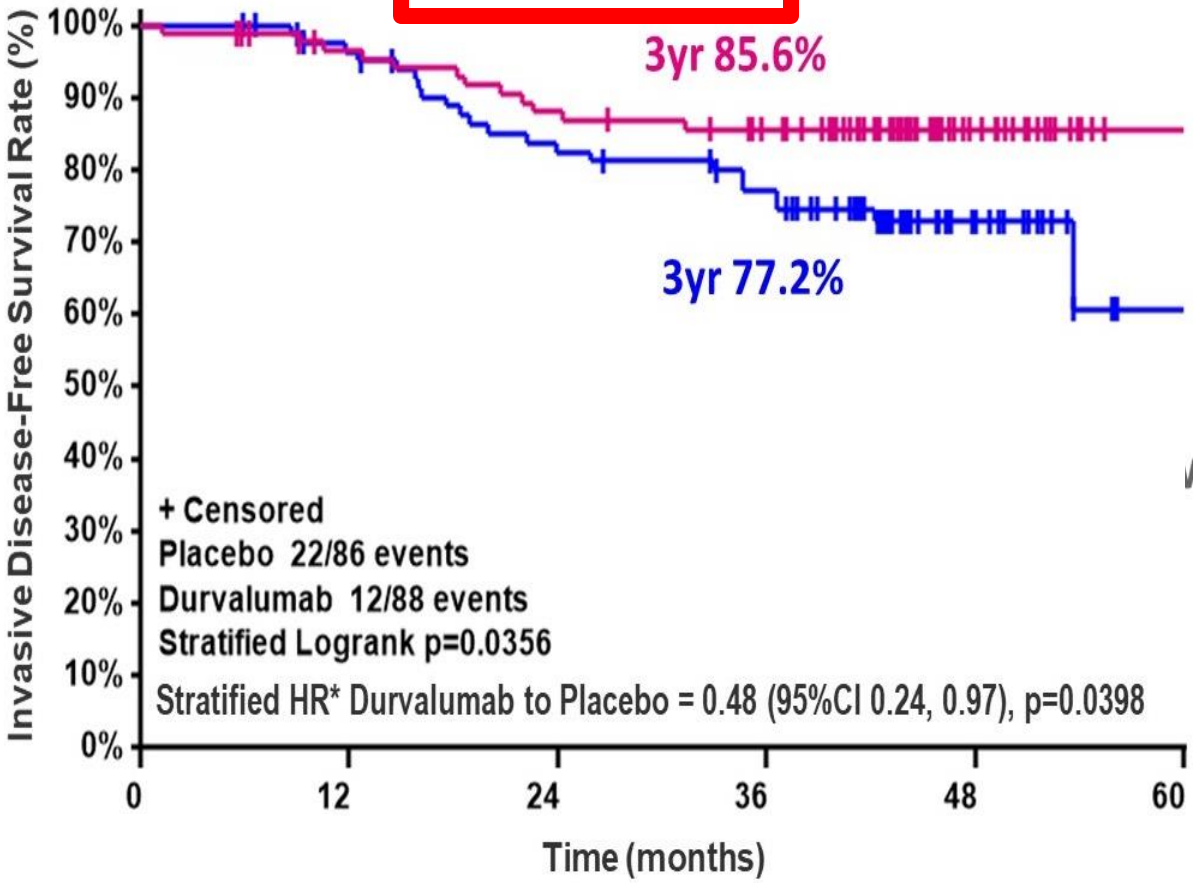
- Lymph node status (positive versus negative)
- Tumour stage (cT1 to cT2 versus cT3 to cT4
- Hormone receptor status (hormone receptor-negative [ER and PR < 1%] versus hormone receptor-low (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%])
- Geographic region (US/Canada/Europe/Australia versus Rest of World).

a. Endocrine therapy is permitted for participants with hormone receptor-low tumours. No adjuvant CDK4/6 inhibitor (eg, abemaciclib, ribociclib).
b. Adjuvant chemotherapy may be given in combination with durvalumab for participants with residual disease. Chemotherapy options at discretion of investigator, either: doxorubicin/epirubicin + cyclophosphamide, followed by paclitaxel + carboplatin; doxorubicin/epirubicin + cyclophosphamide followed by paclitaxel; carboplatin + paclitaxel; capecitabine.
c. Olaparib may be administered to participants who are g*BRCA*-positive with residual disease.
d. Adjuvant capecitabine may be given in combination with pembrolizumab for participants with residual disease, at the discretion of investigator.

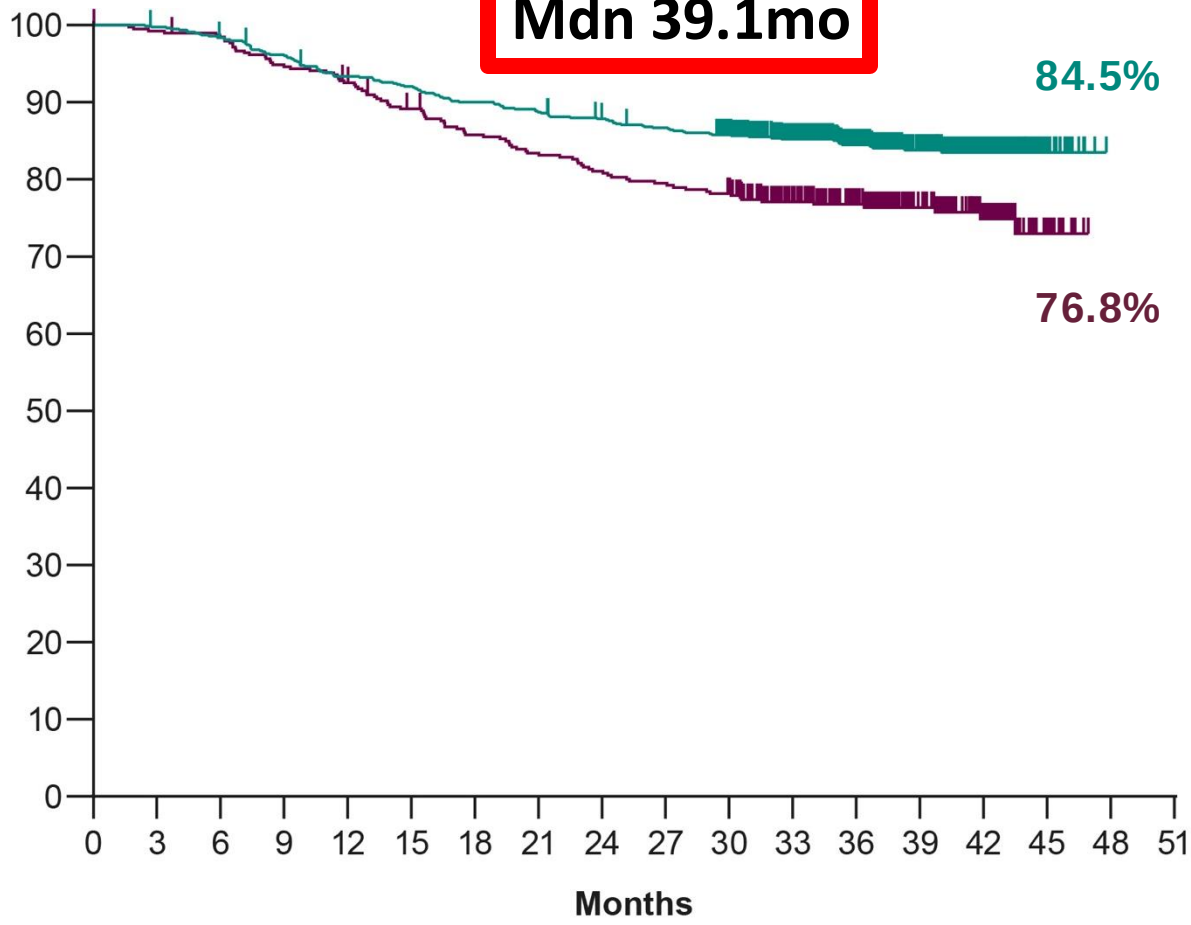
PI: Heather McArthur
NCT06112379

Is the benefit of IO conferred with neoadjuvant administration?

GeparNuevo
Mdn 43.7mo



Keynote-522
Mdn 39.1mo

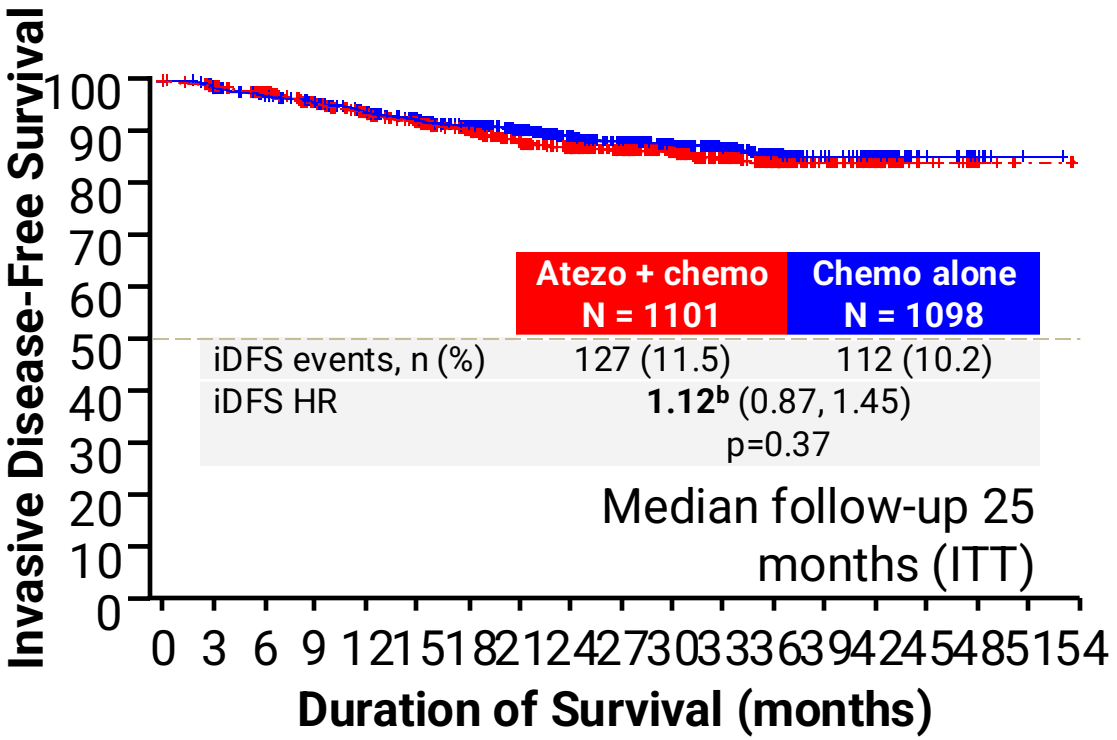


Loibl et al. ASCO 2021; Schmid ett al ESMO 2021.

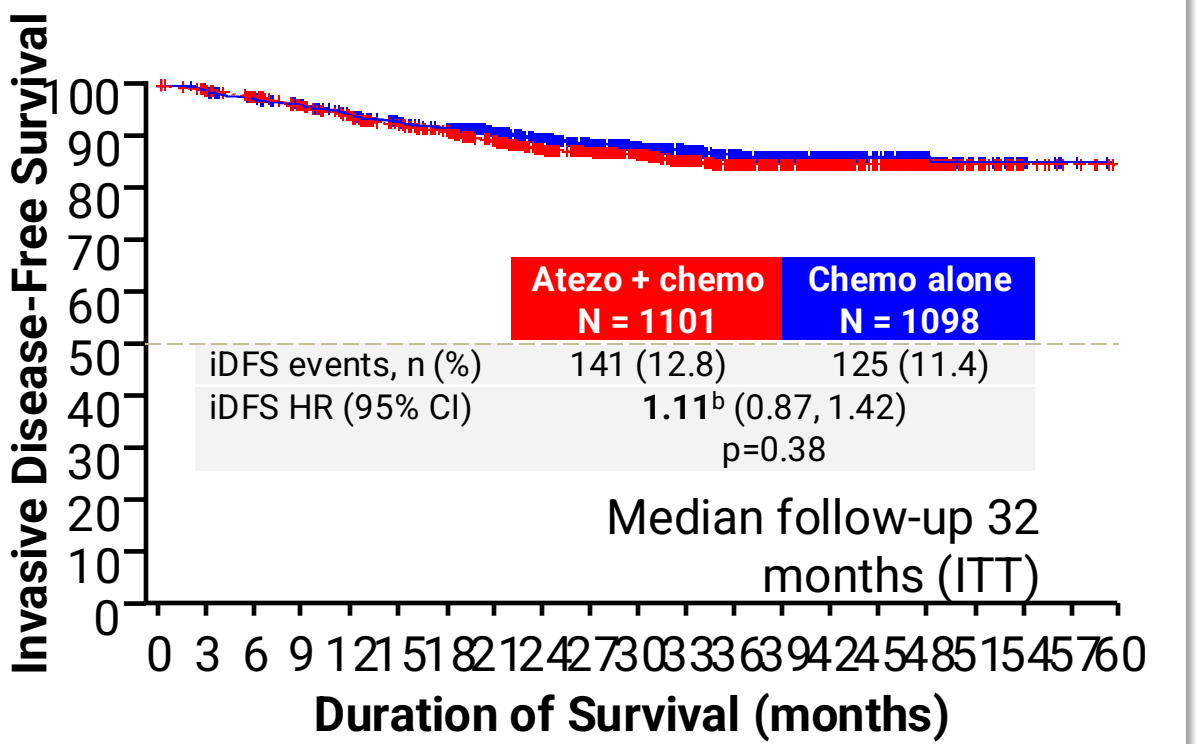
ALEXANDRA/IMpassion030: iDFS IA and Final Analysis

Primary Efficacy Endpoint (ITT population)

Interim Analysis[a]



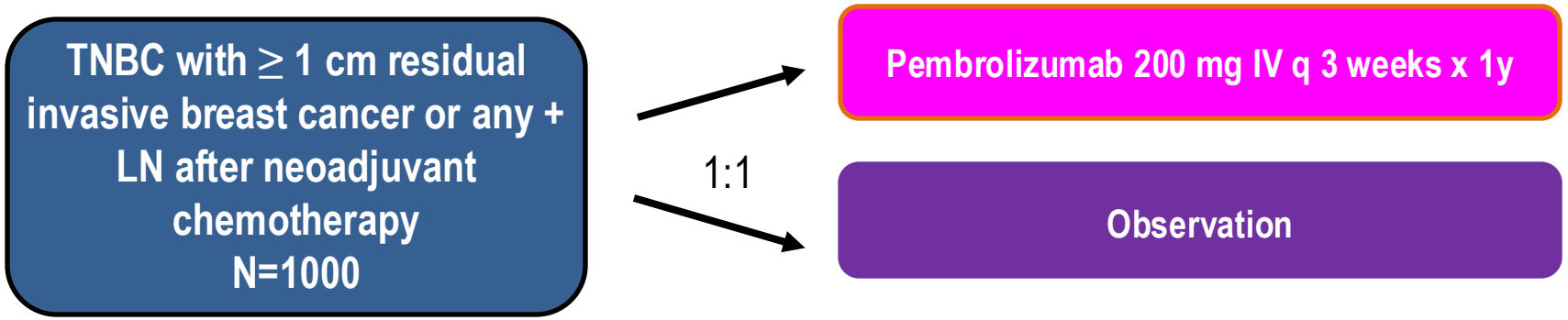
Final Analysis



iDFS: defined as the interval from randomization until date of first occurrence of an iDFS event
[a]IA results previously presented at SABACs 2023 (database of 17 Feb 2023, not cleaned)
[b]Stratified by PD-L1 status, Surgery, and Axillary Nodal Status

McArthur et al. EBCC 2024
Ignatiadis et al. JAMA 2025

SWOG 1418/NRG BR006



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

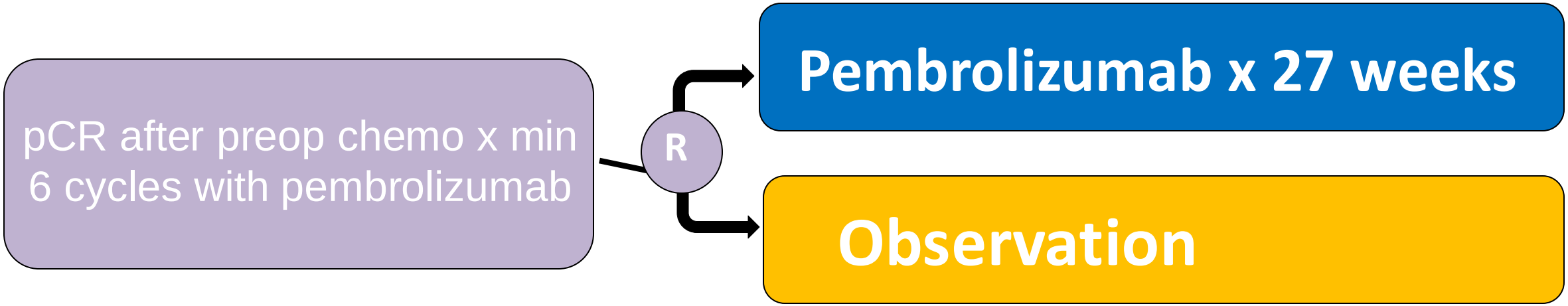
- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

Activated in 2016 and closed in 2021

PI Lajos Pusztai
NCT02954874

Will we ever de-escalate IO in RD?

OptimeICE-PCR study



N = 1956 (56month accrual estimated)

Stratification Factors:

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

1ºEndpoints: RFS and QOL at 27weeks

Alliance
NCT05812807

How will we reconcile RD study data with ongoing phase 3 studies?

Ongoing Phase 3 Trials of ADCs

Neoadjuvant	Adjuvant	1L cytotoxic, pre-ChT
DESTINY-Breast11 T-DXd vs T-DXd/THP vs AC-THP	**DESTINY-Breast05** T-DXd vs T-DM1	**DESTINY-Breast09** T-DXd +/- pertuzumab vs THP
TROPION-Breast04 Dato-DXd/Durva vs KN522 regimen	**SURVIVE-HERoes** T-DXd vs TPC	**TROPION-Breast02** Dato-DXd vs. TPC
	TROPION-Breast03 Dato-DXd +-/ Durva vs. TPC	**TROPION-Breast05** Dato-DXd/Durva vs. chemo/pembro
	ASCENT-05/OptimICE-RD SG/pembro vs pembro +/- cape	**ASCENT-03** SG vs. TPC
	NCT06393374 Sac-TMT/ pembro vs TPC	**ASCENT-04** SG/pembro vs. TPC/pembro
	SASCIA SG vs TPC	**ASCENT-07** SG vs. TPC
		DYNASTY-Breast02 DB-1303 vs. TPC
		TroFuse-010 Sac-TMT ± pembro vs.TPC

In the **probable future**, we will likely have **more Topo1 ADCs** approved in **earlier indications** **(curative setting, 1L setting)**

HER2+

TNBC

HR+/HER2-

Topo1 ADC

Tarantino SABCS 2024

Are ongoing sequencing studies going to be enough to inform the post-progression space?

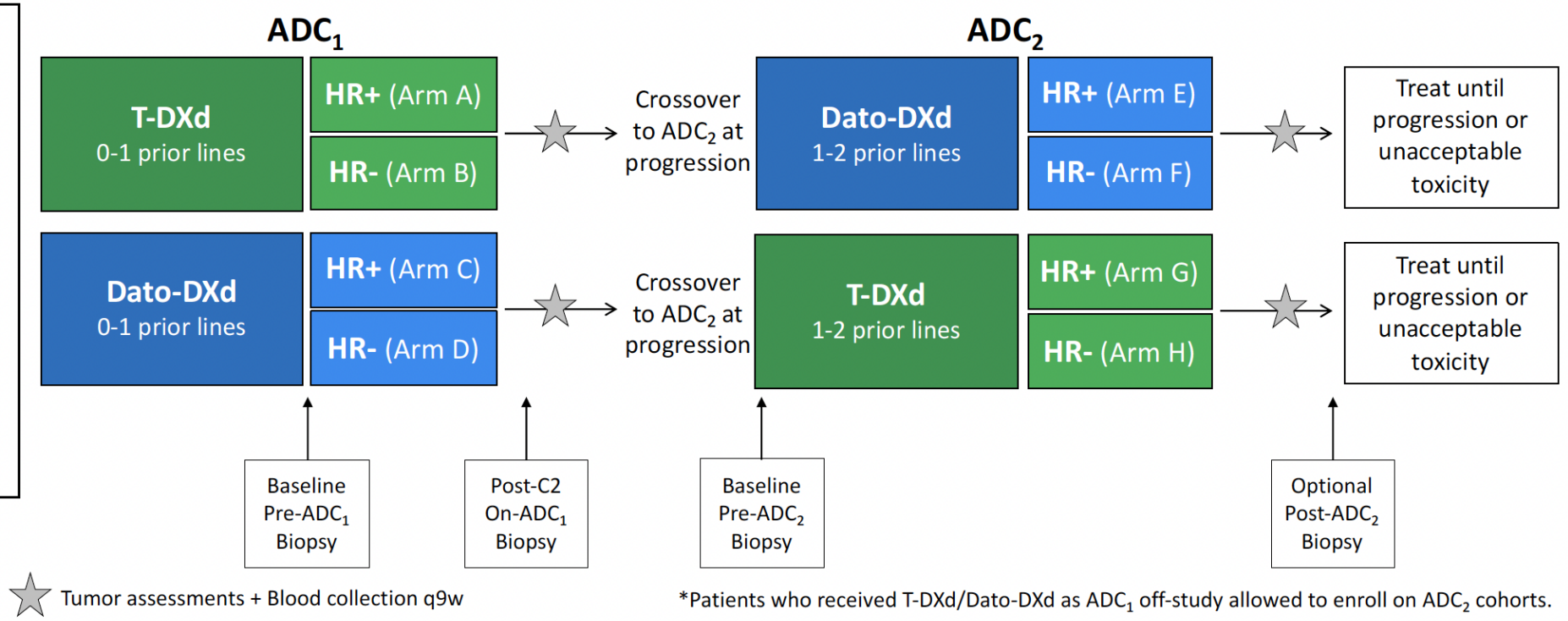
The **TRADE-DXd** phase 2 trial is ongoing to evaluate the activity of **T-DXd after Dato-DXd or viceversa** among patients with **HER2-negative MBC**

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

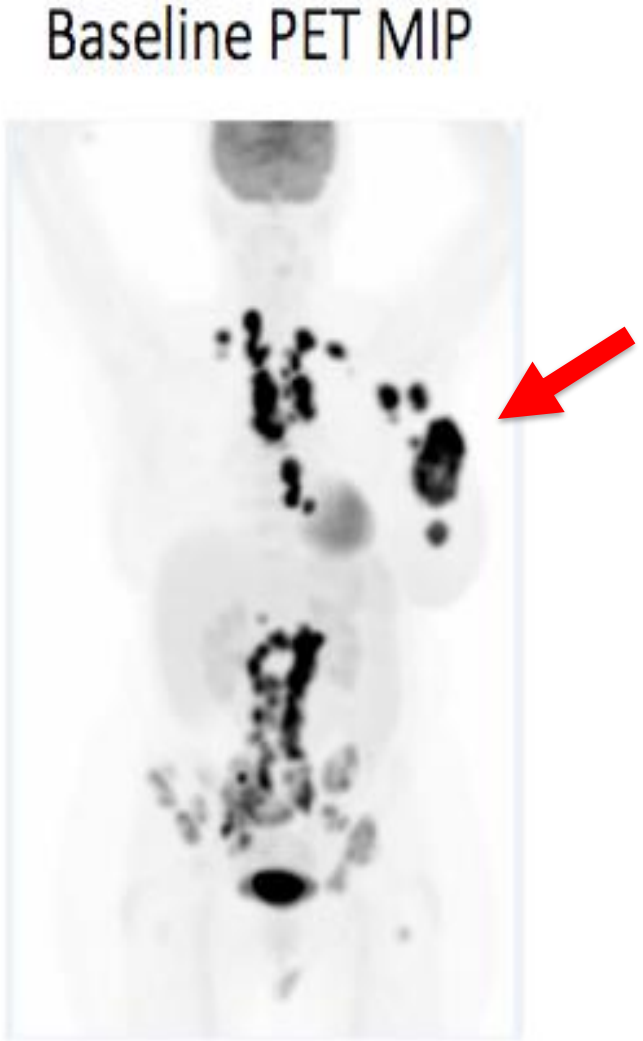
Allocation 1:1 to T-DXd or Dato-DXd as ADC_1



PI: A.C. Garrido-Castro

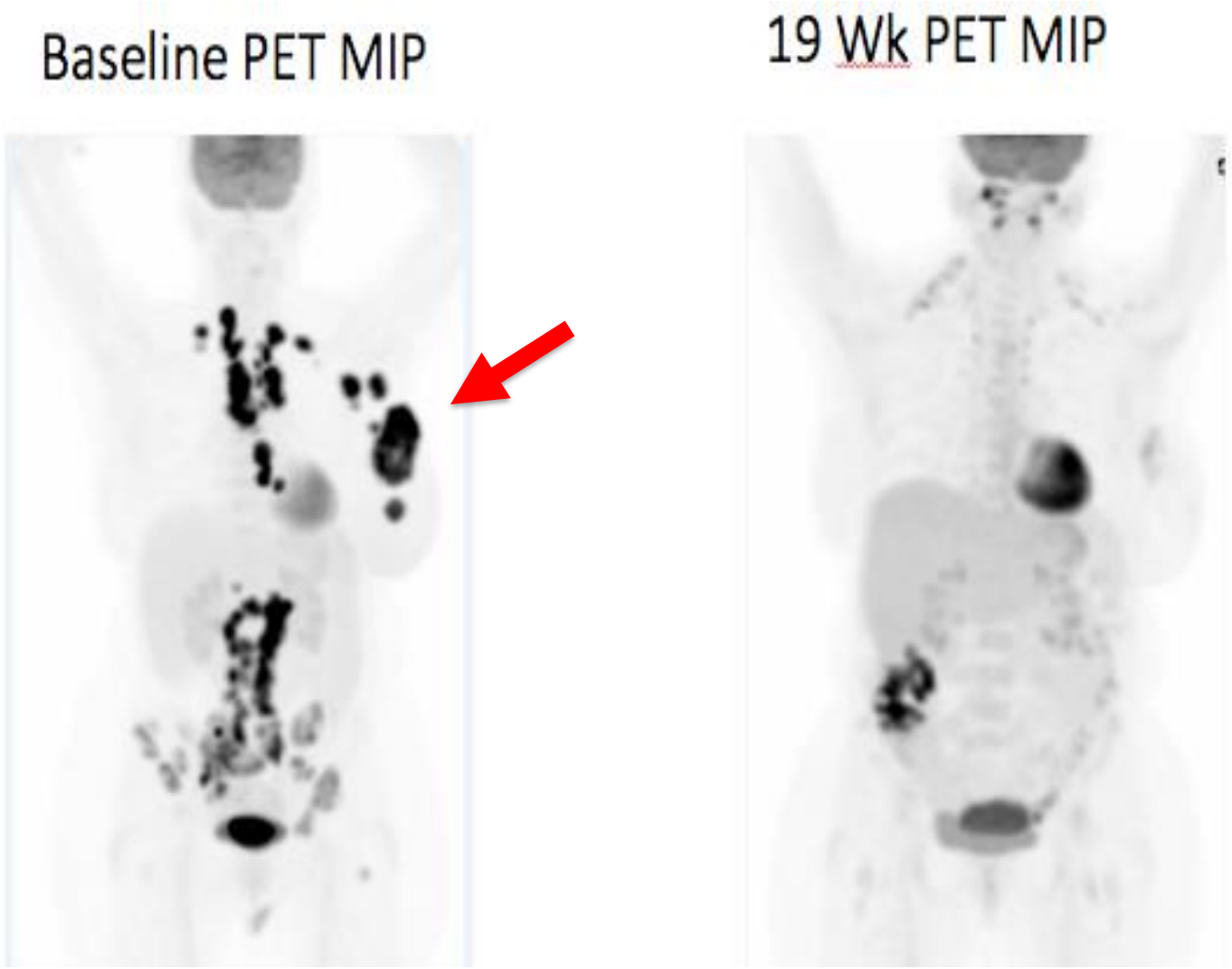
Other strategies we should be concurrently exploring?

Immune Therapy with RT in mTNBC



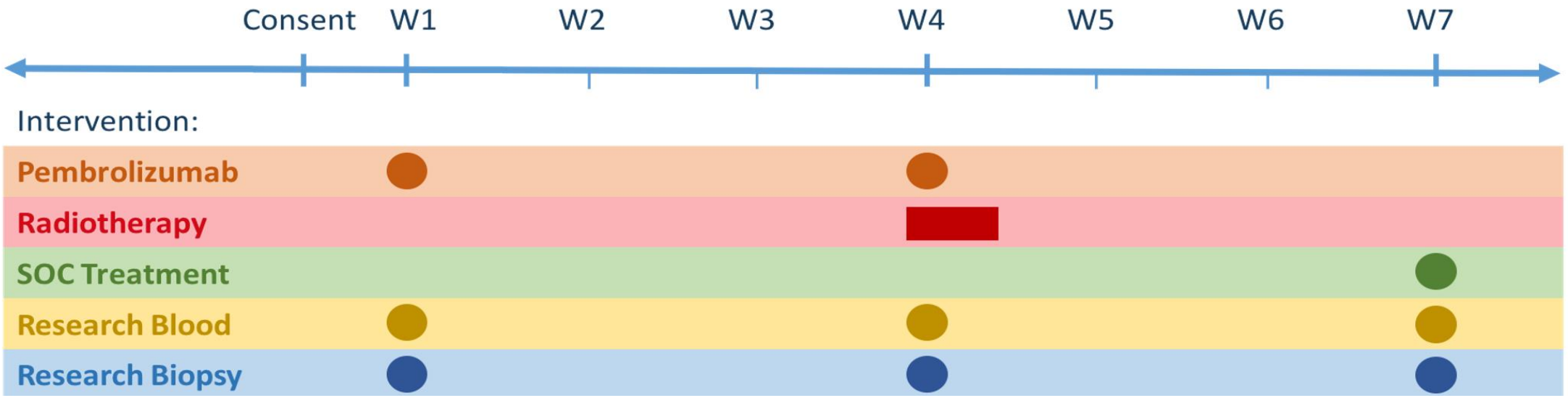
McArthur et al, ASCO 2018;
Ho et al, Cancer 2019

Immune Therapy with RT in mTNBC



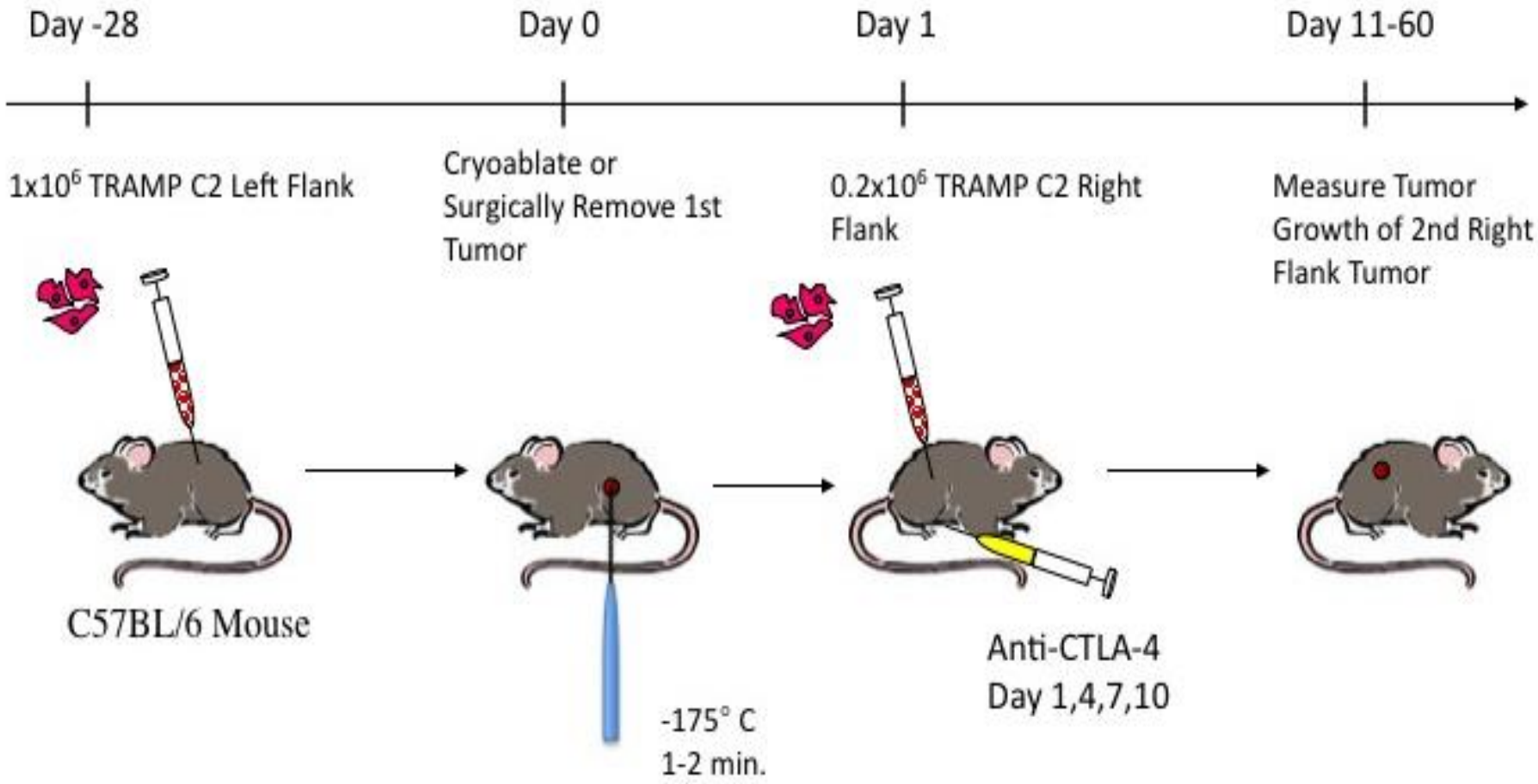
McArthur et al, ASCO 2018;
Ho et al, Cancer 2019

The **PEARL** trial: **P**re-operative p**e**mbrolizuma**a**b with **r**adiation therapy in ear**l**y stage TNBC[1]



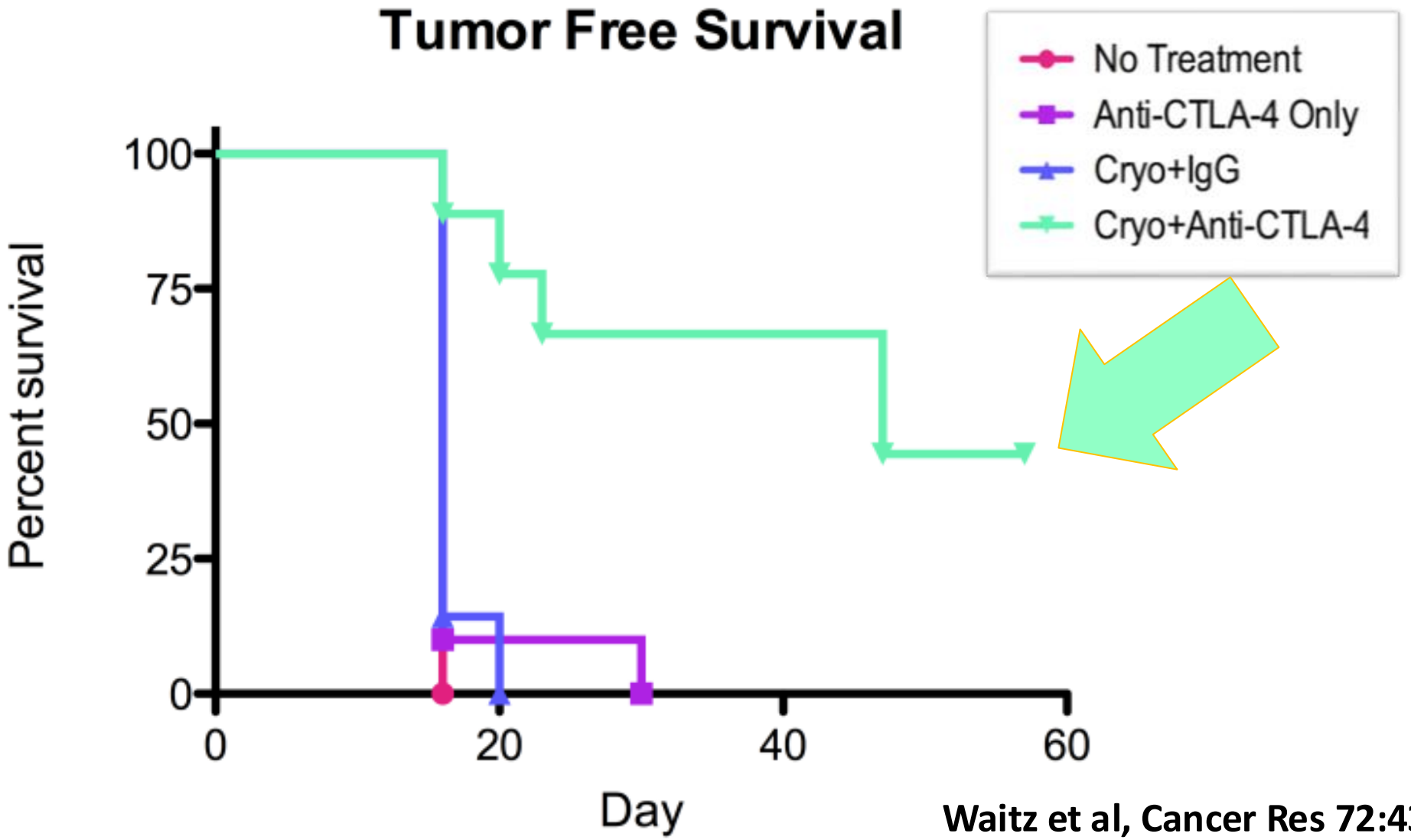
- 50 patients enrolled between 12/2017 to 04/2021
- 28/50 (56%) achieved a pCR
- 37/50 (74%) achieved RCB 0 or 1
- 13/17 (76%) LN+ became ypN0
- The P-RAD Study is exploring the optimal dose of curative intent RT with IO

Ho et al. J Clin Oncol 2024; McArthur et al. SABCS 2021



Waitz et al, Cancer Res 72:430-439; 2012

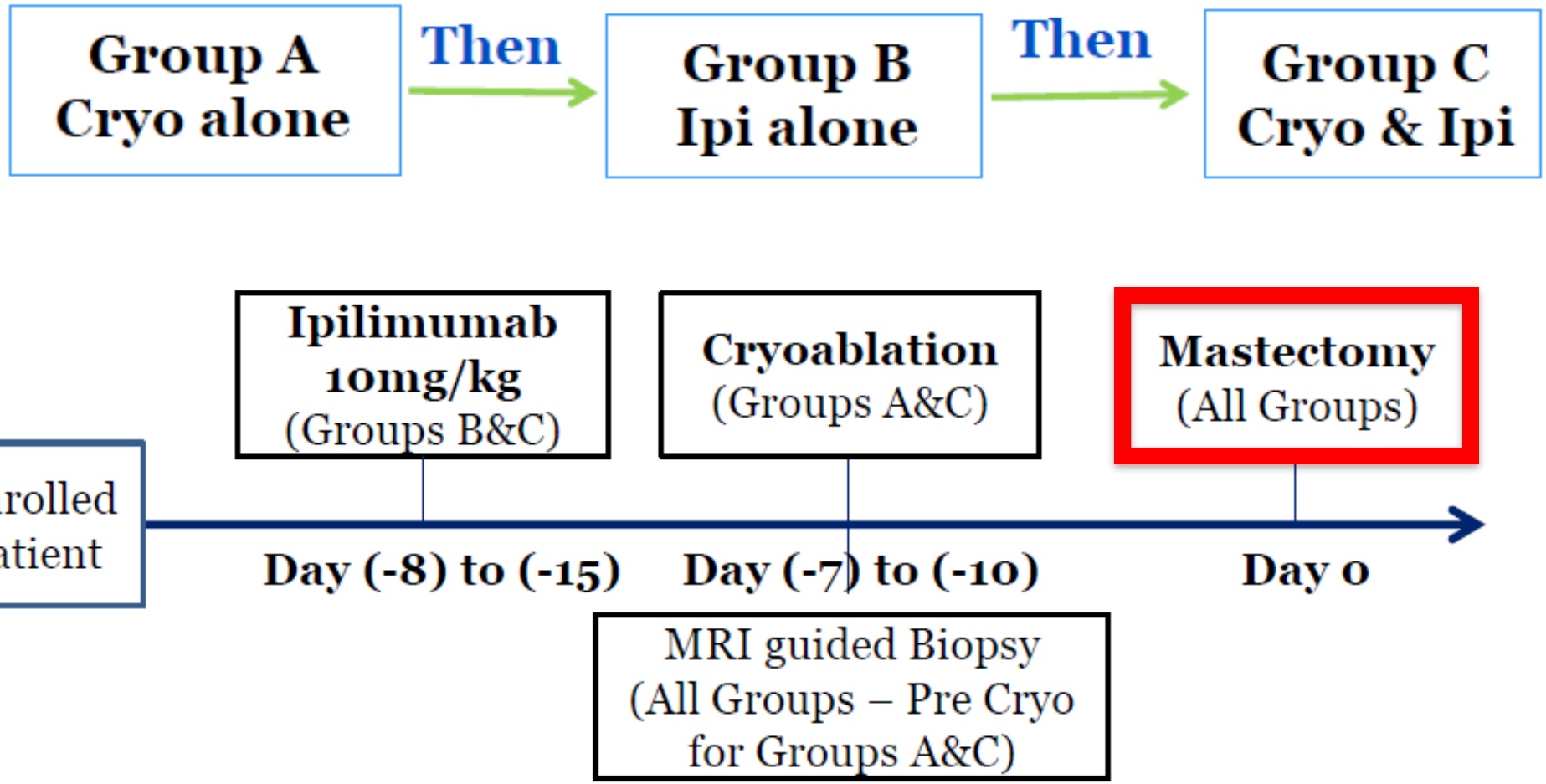
Immune stimulation with tumor freezing protects from tumor re-challenge



Waitz et al, Cancer Res 72:430-439; 2012.

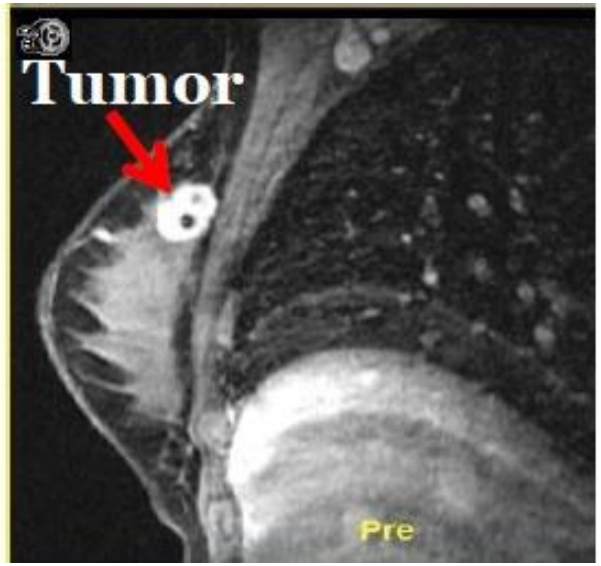
3 sequential groups of 6 patients

The timing of all study interventions was defined by the pre-determined, standard-of-care, non-study surgery date



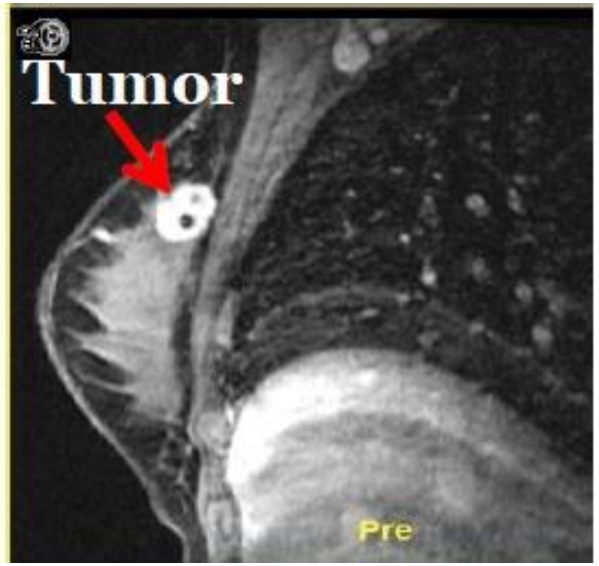
McArthur et al, CCR 2016

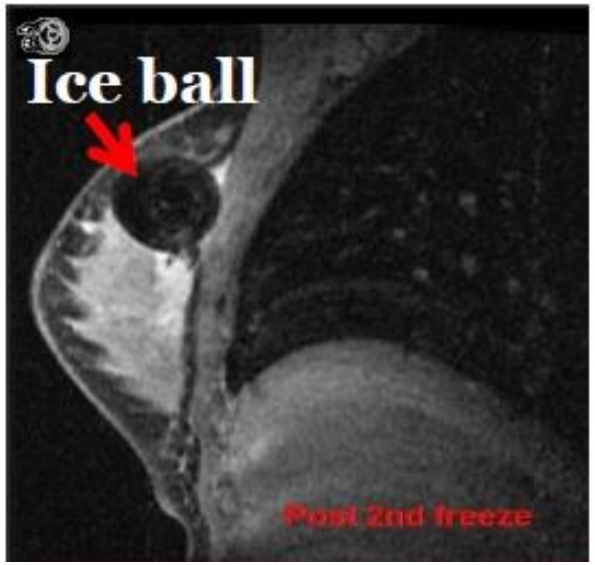
Cryoablation (tumor freezing)



McArthur et al, CCR 2016

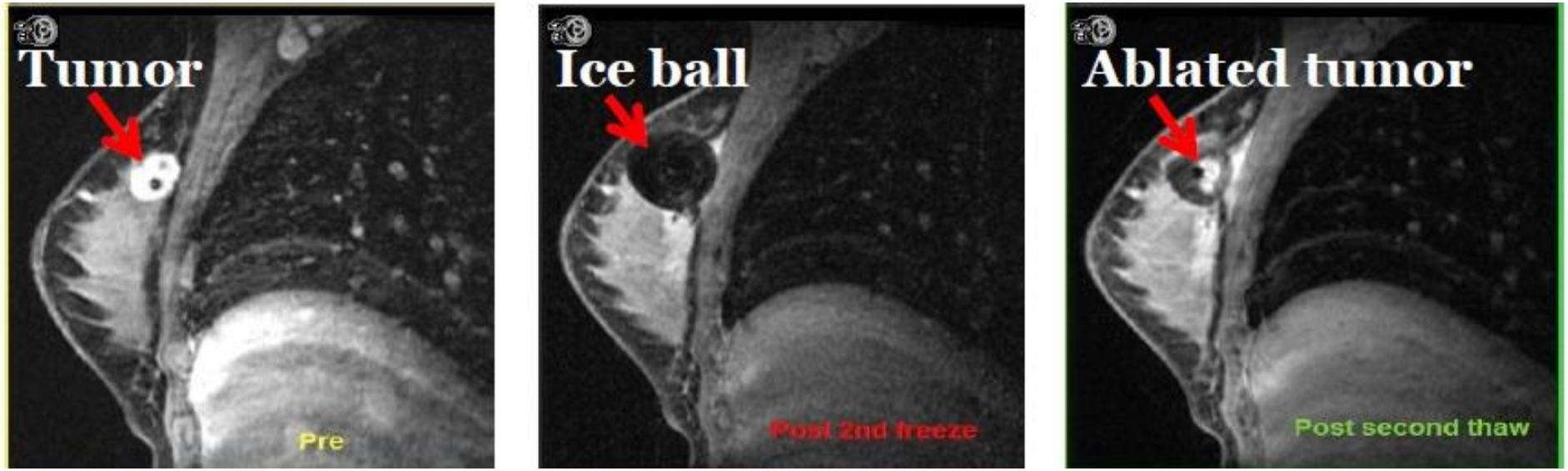
Cryoablation (tumor freezing)





McArthur et al, CCR 2016

Cryoablation (tumor freezing)



McArthur et al, CCR 2016

Next steps

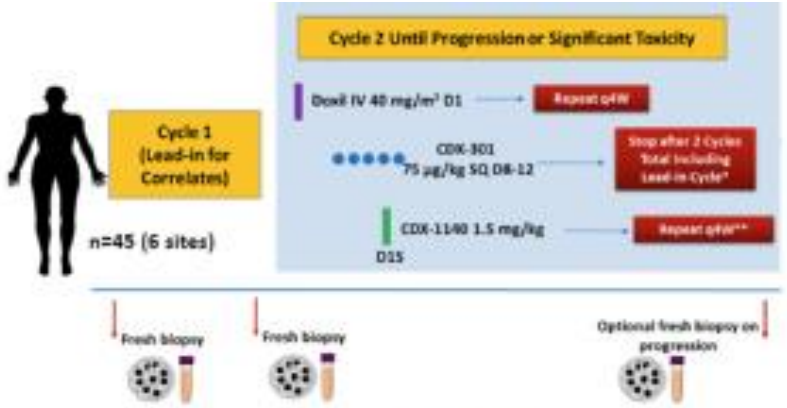
1. Reported 66month follow-up data with NO RECURRENCES![1-3]

2. Pilot study of peri-op ipi, nivo + cryo[3]

3. Phase 2 study of peri-op IO in women with residual TNBC after chemo (NCT03546686)

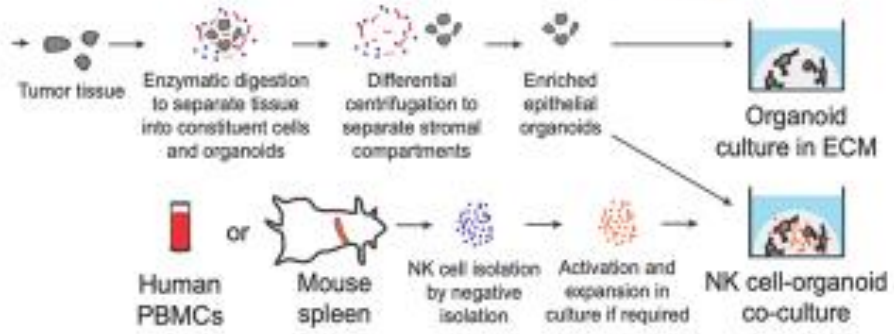
[1]McArthur et al. CCR 2016
[2]Page et al. CIR 2016
[2]Comen et al. iScience 2023

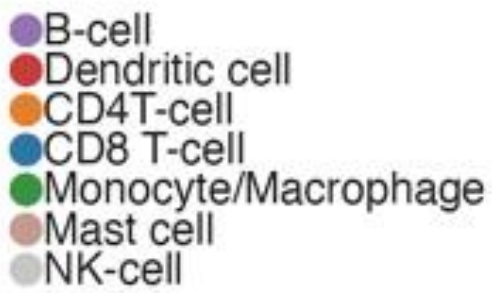
UTSW Breast Cancer Program: Focus on the Tumor Immune Microenvironment

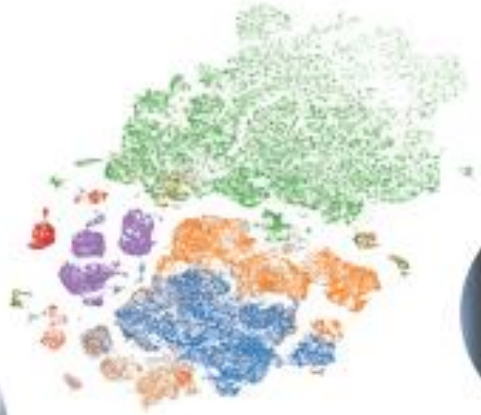


Reddy
(ET)

Chan
(CNC)



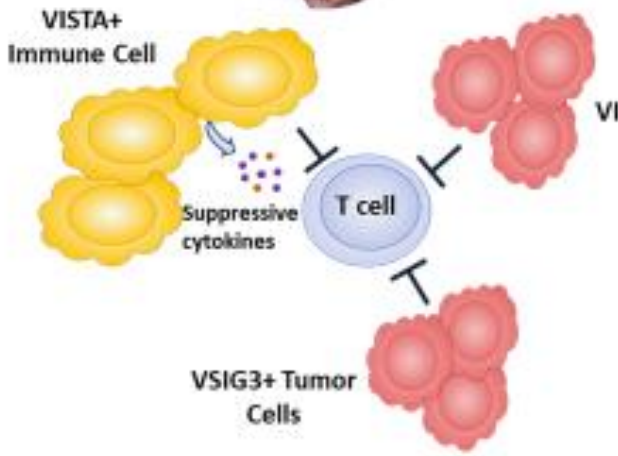


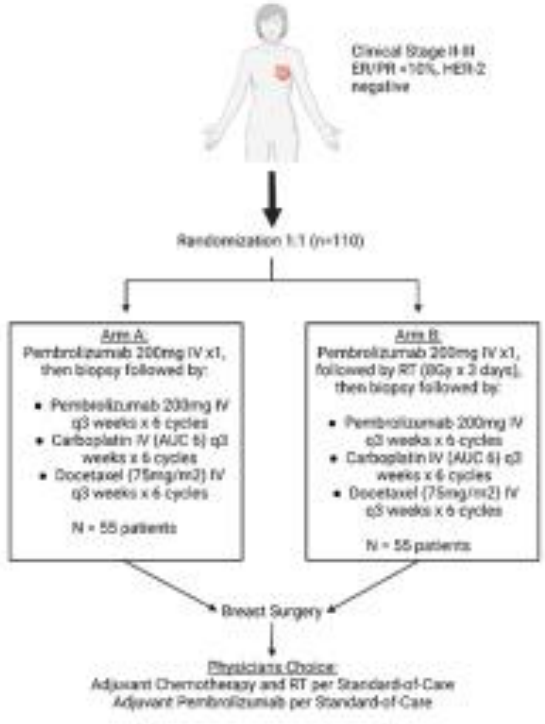


Alluri
(ET)

McArthur
(ET)

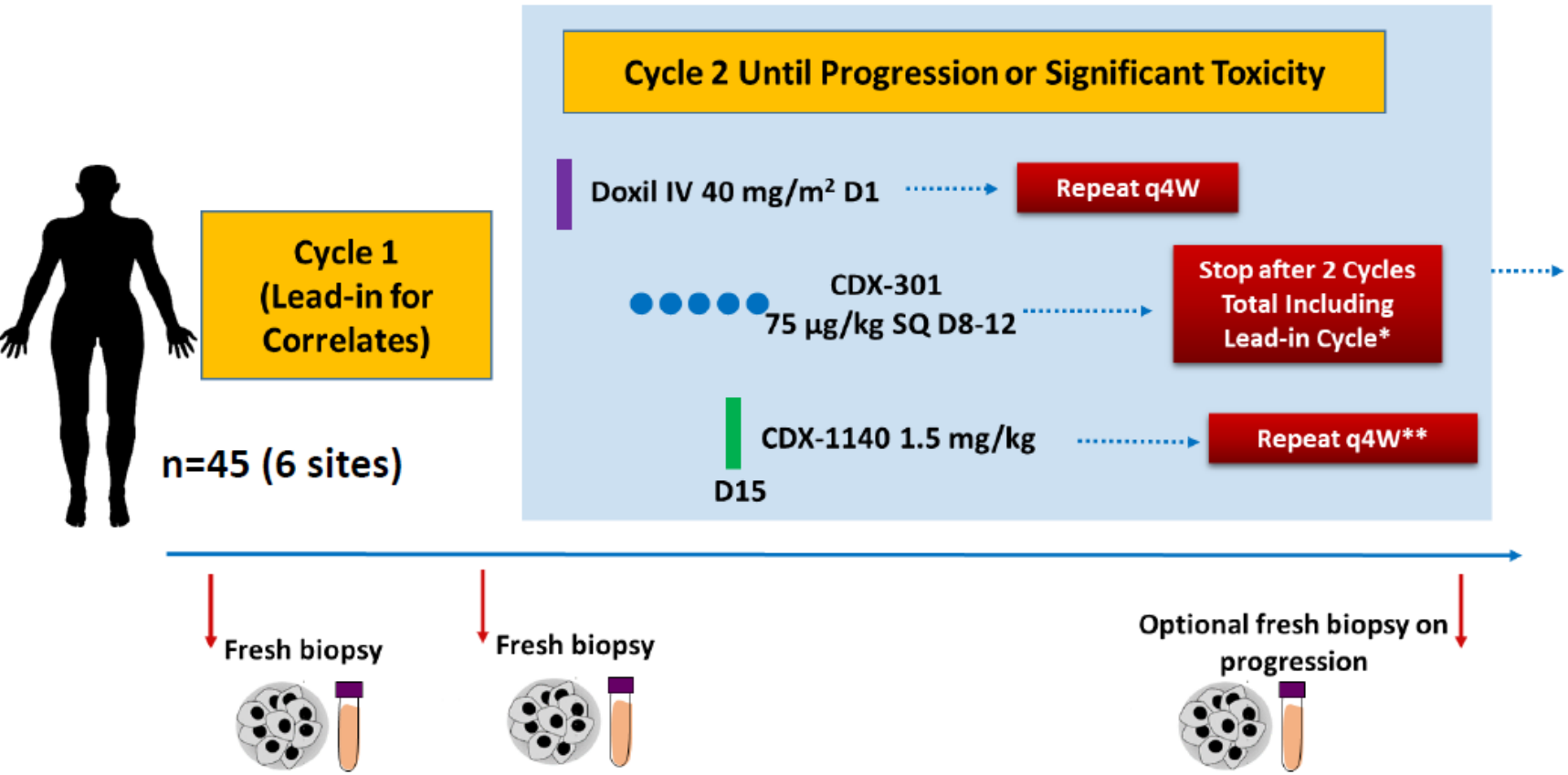
Gruber
(CC)





K08CA245024
K08CA267189
CPRIT RR200090
CPRIT RR190020
ASCO ACRA
Damon Runyon 112-21
V Foundation
DOD W81XWH-21-1-0112

Multi-site phase 1 with dose expansion pilot IIT of CD40 agonism (CDX-1140) + Flt3 ligand (CDX-301) + anthracycline (Doxil) chemotherapy.



*This will stop after cycle 2 for Cohort A and B, after cycle 3 for Cohort C.
**Move CDX-1140 to day 8 after CDX-301 stopped.

Endpoints:

Primary

Safety and tolerability; determination of RP2D

Secondary:

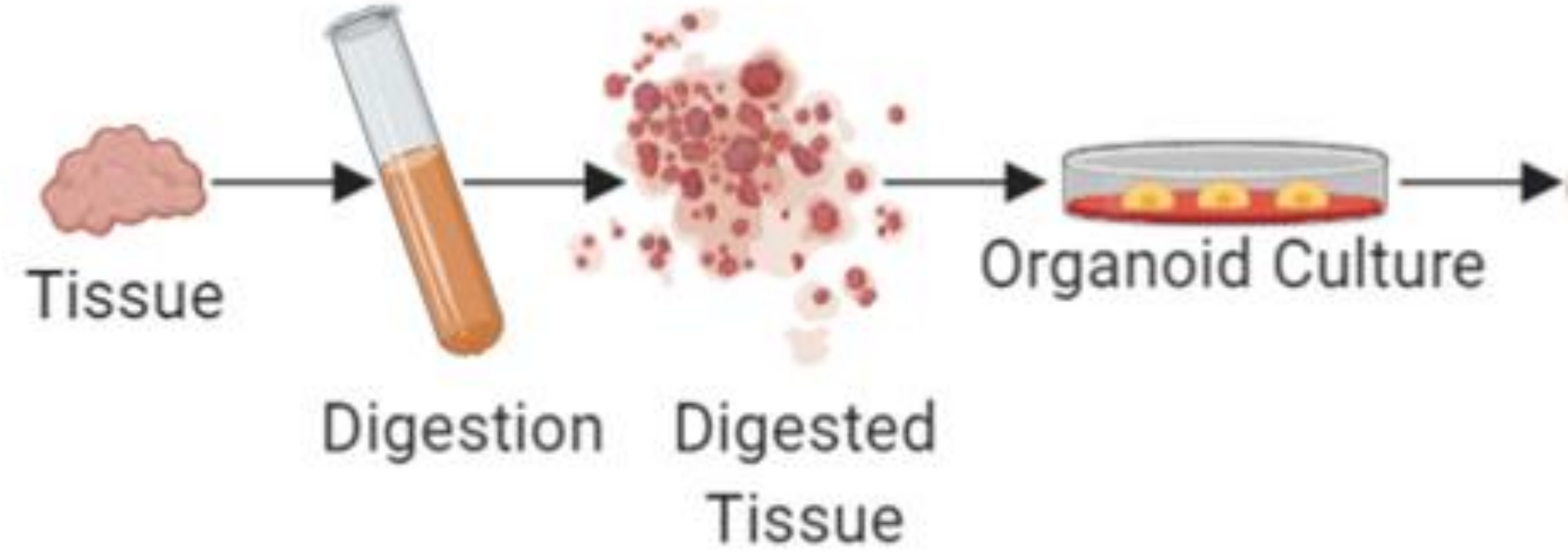
- Immune response with triplet combination
- Immune response with immunotherapy only
- Immune response with triplet combination compared to immunotherapy or chemo
- PFS, ORR, DOR, CBR

Exploratory:

- Association between baseline, on-treatment, or Δ in immune environment and response
- Mechanisms of resistance
- Δ in outcomes by cycle 1 treatment
- Overall survival

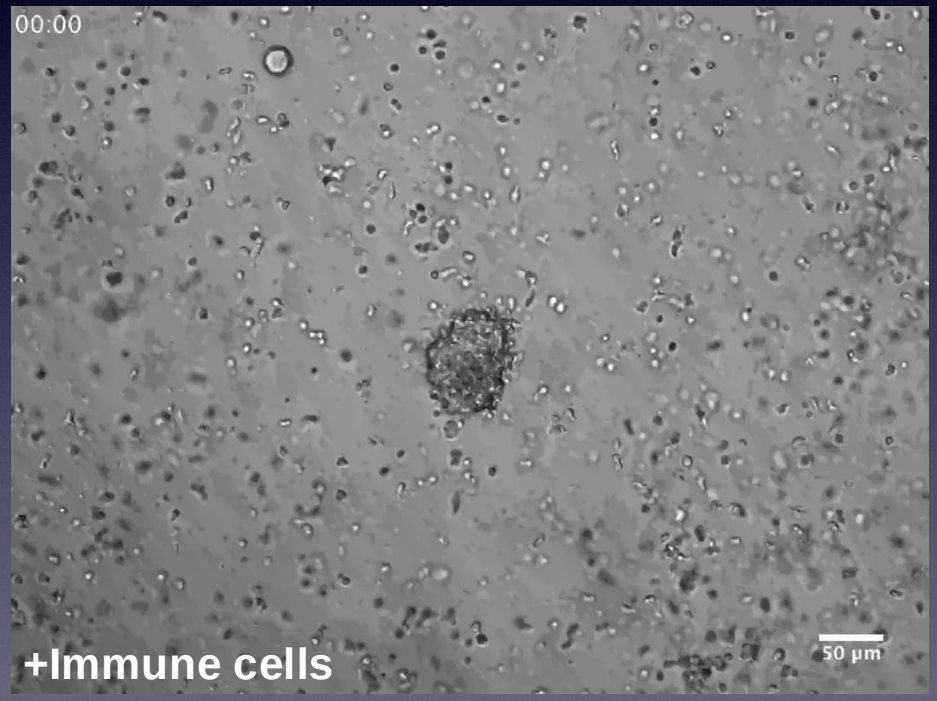
Courtesy of Dr. Sangeetha Reddy

Laboratory to Clinic to Laboratory



Courtesy of Dr. Isaac Chan

A novel platform to discover new immune strategies



Chan et. al., Journal of Cell Biology, 2020

Clinical challenges and opportunities

- Is SOC adjuvant pembro effective/needed?
- No trials dedicated to POD after K522
- If ADC's are effective in the curative intent adjuvant setting, will 1 prevail?
- Many 1L trials allow prior pembro but have to be ≥6mos from exposure (ie. ASCENT 03/04/TB02, etc.)
- Relevance of IO after IO?
- Relevance of ADC after ADC?
- Novel approaches: Application of local strategies? Combinations with drugs that target other elements of the TME?
- Bench to bedside to bench learning