UT Southwestern
Medical Center

Immunotherapy for Breast Cancer: Efficacy and Toxicity Considerations

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New Orleans Summer Cancer Meeting
July 20, 2024

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**

Neoadjuvant chemo **+ placebo**

Surgery

Adjuvant **pembrolizumab** 9 cycles

Adjuvant **placebo** 9 cycles

Within 3-6 weeks

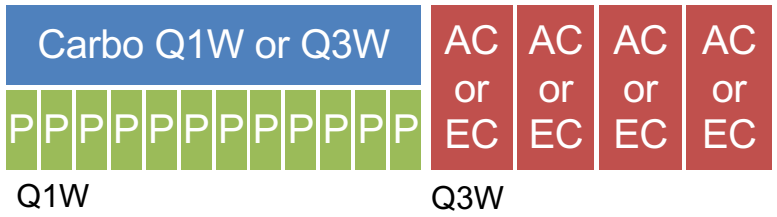
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

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

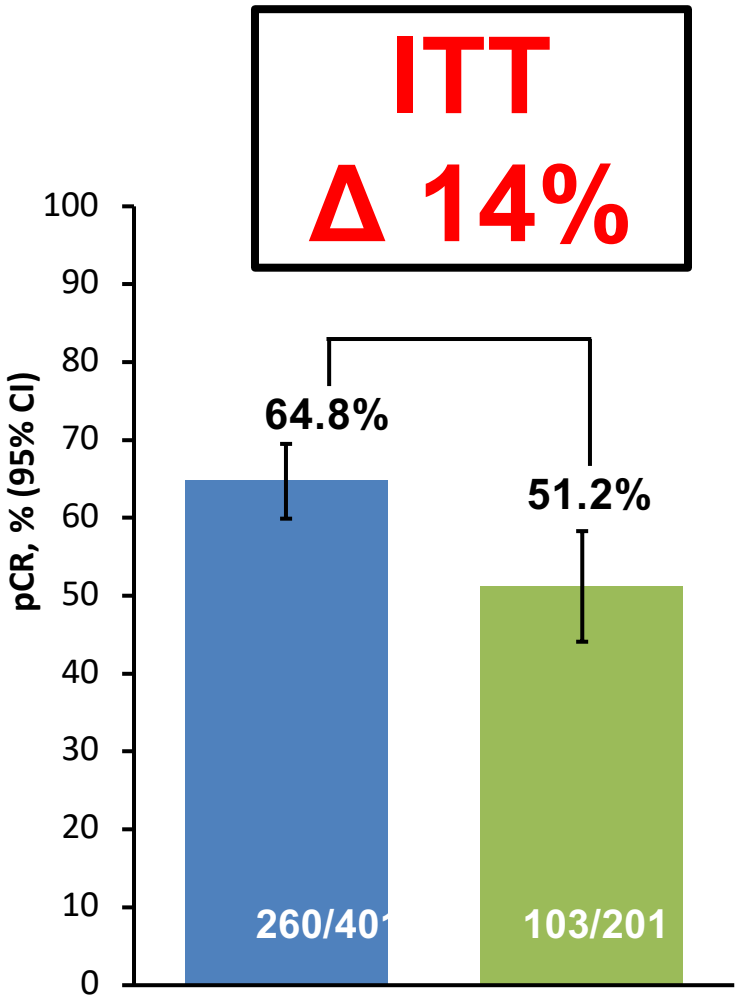
Study Treatment

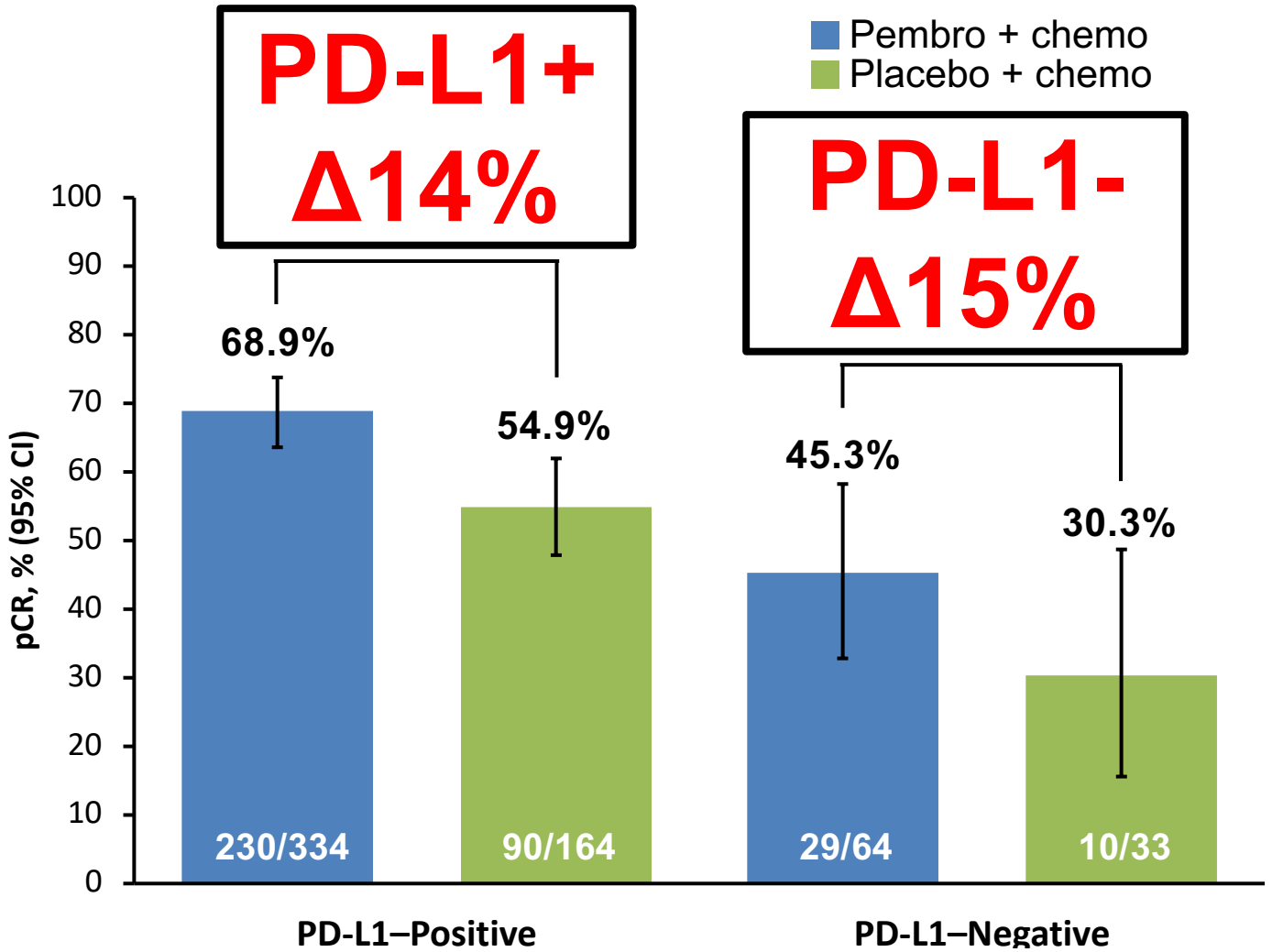


Paclitaxel 80 mg/m^2 IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m^2 IV Q3W
(Epirubicin 90 mg/m^2 IV Q3W)
Cyclophosphamide 600 mg/m^2 IV Q3W
Pembrolizumab 200 mg IV Q3W

Schmid P et al. *N Engl J Med*. 2020;382(9):810-821.

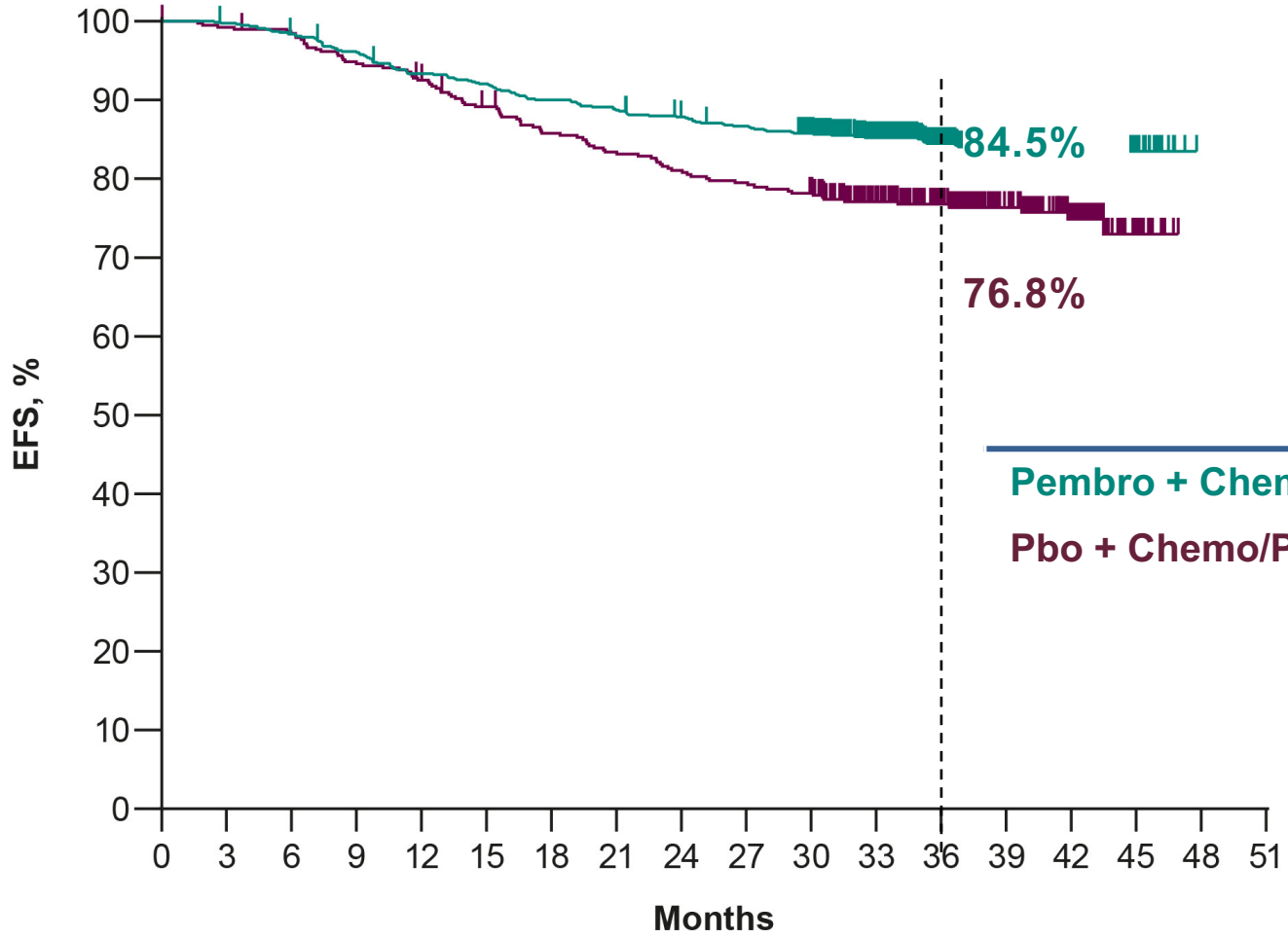
KEYNOTE-522: pCR at IA1





Schmid P et al. *N Engl J Med*. 2020;382(9):810-821.

KEYNOTE-522: EFS update at IA4 (39.1mo)



Δ7.7%

	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a]	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

No. at Risk

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

Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

FDA Approval

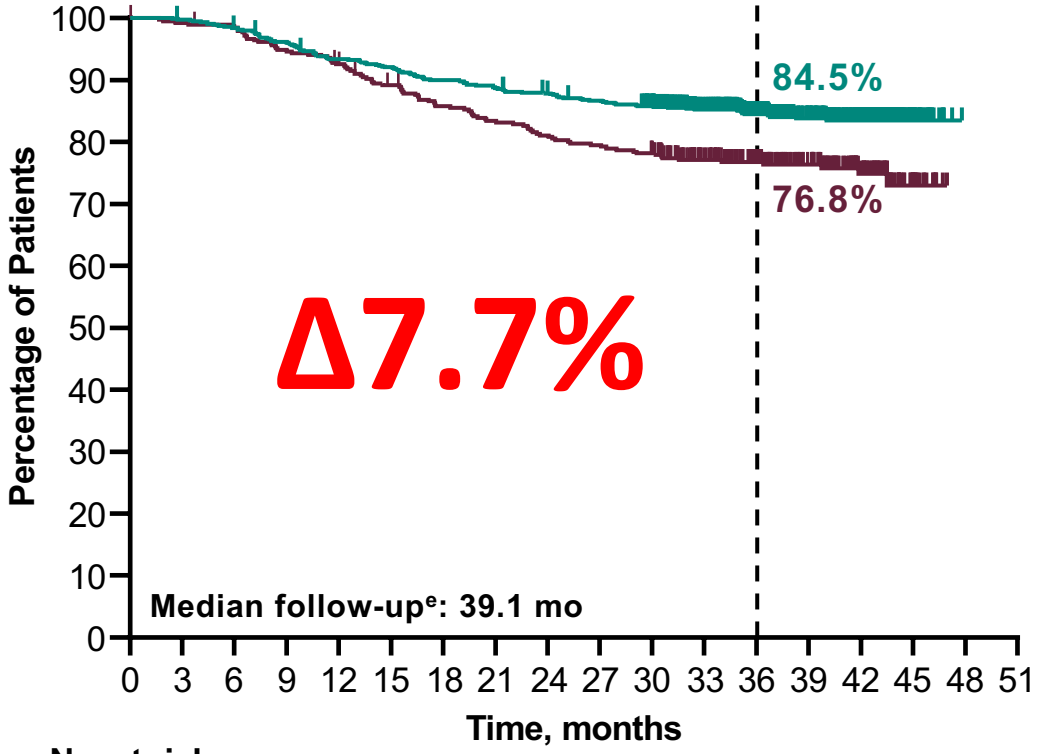
On **July 26, 2021**, the FDA approved pembrolizumab for high-risk early-stage TNBC with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery

Based on KEYNOTE-522, the indication for palliative pembrolizumab was converted from accelerated to full approval

FDA. News Release. July 26, 2021. www.fda.gov.

EFS at IA4 and IA6

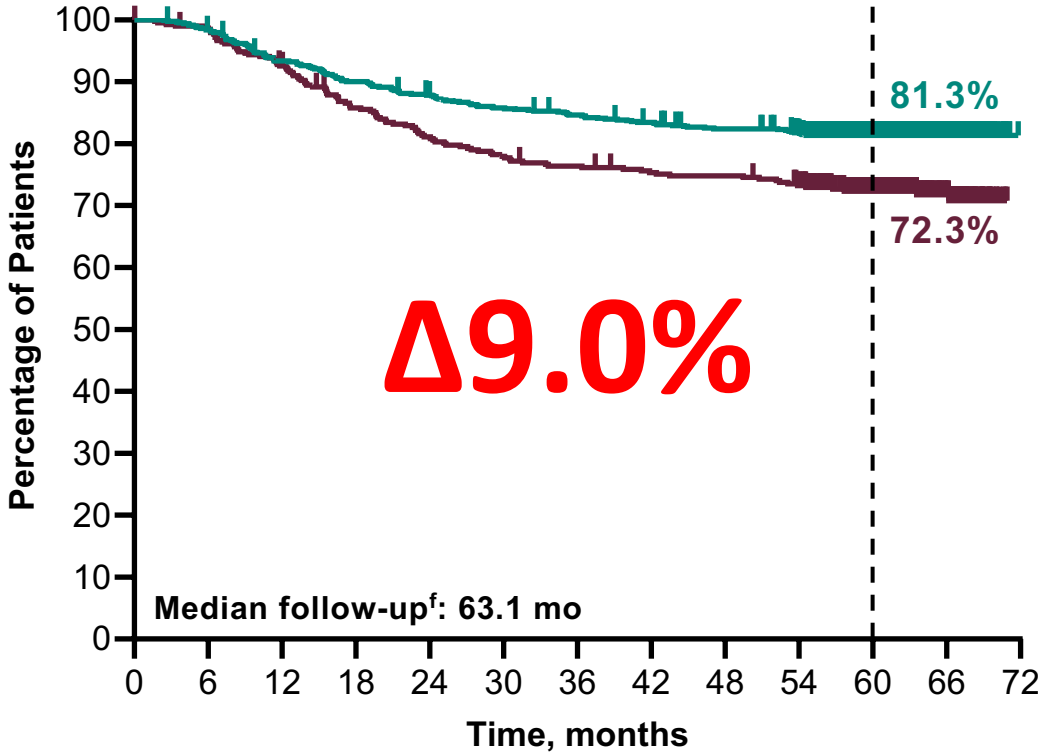
IA4[a]	Events	HR (95% CI)	*P* value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48–0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



No. at risk

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

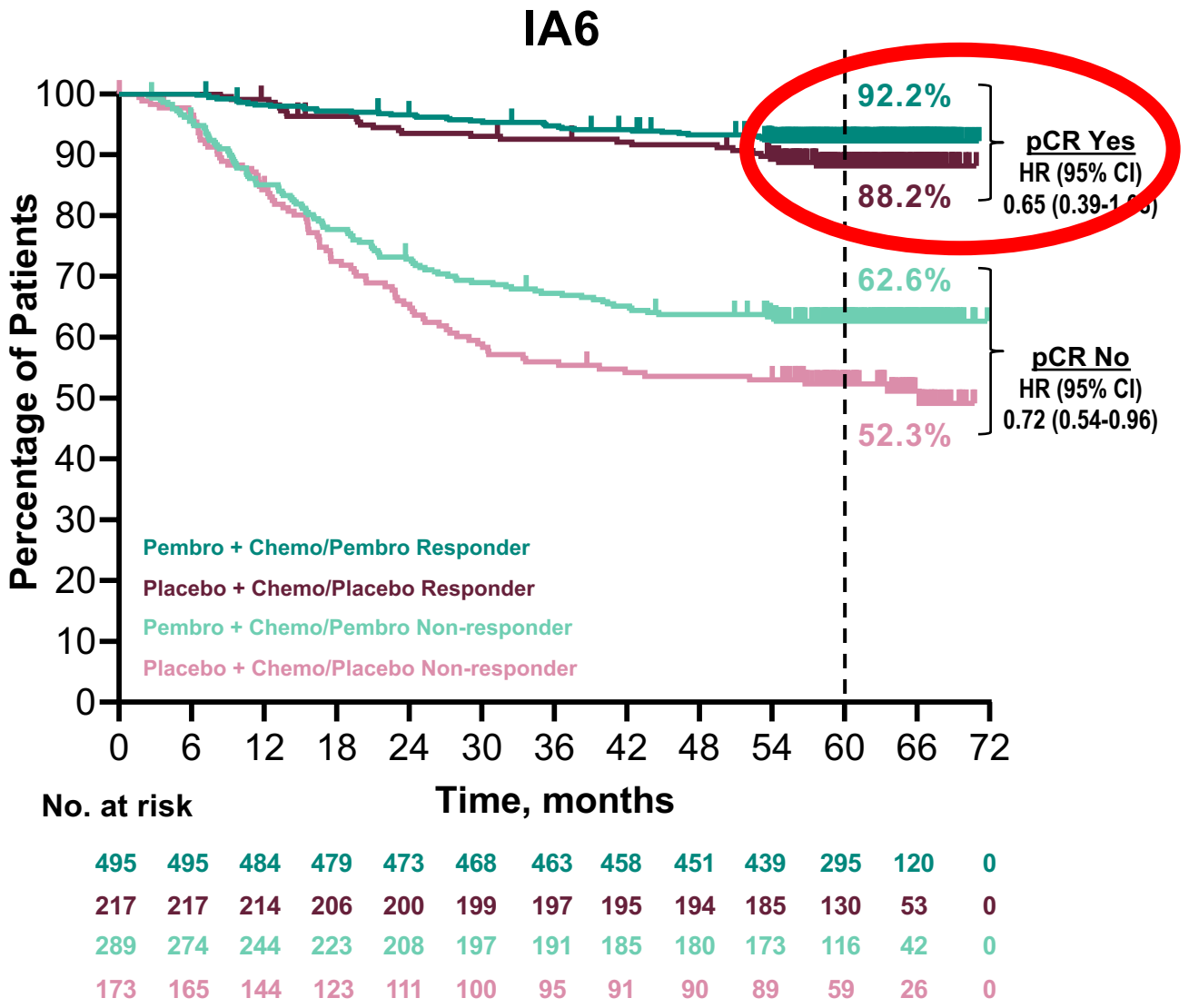
IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



No. at risk

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

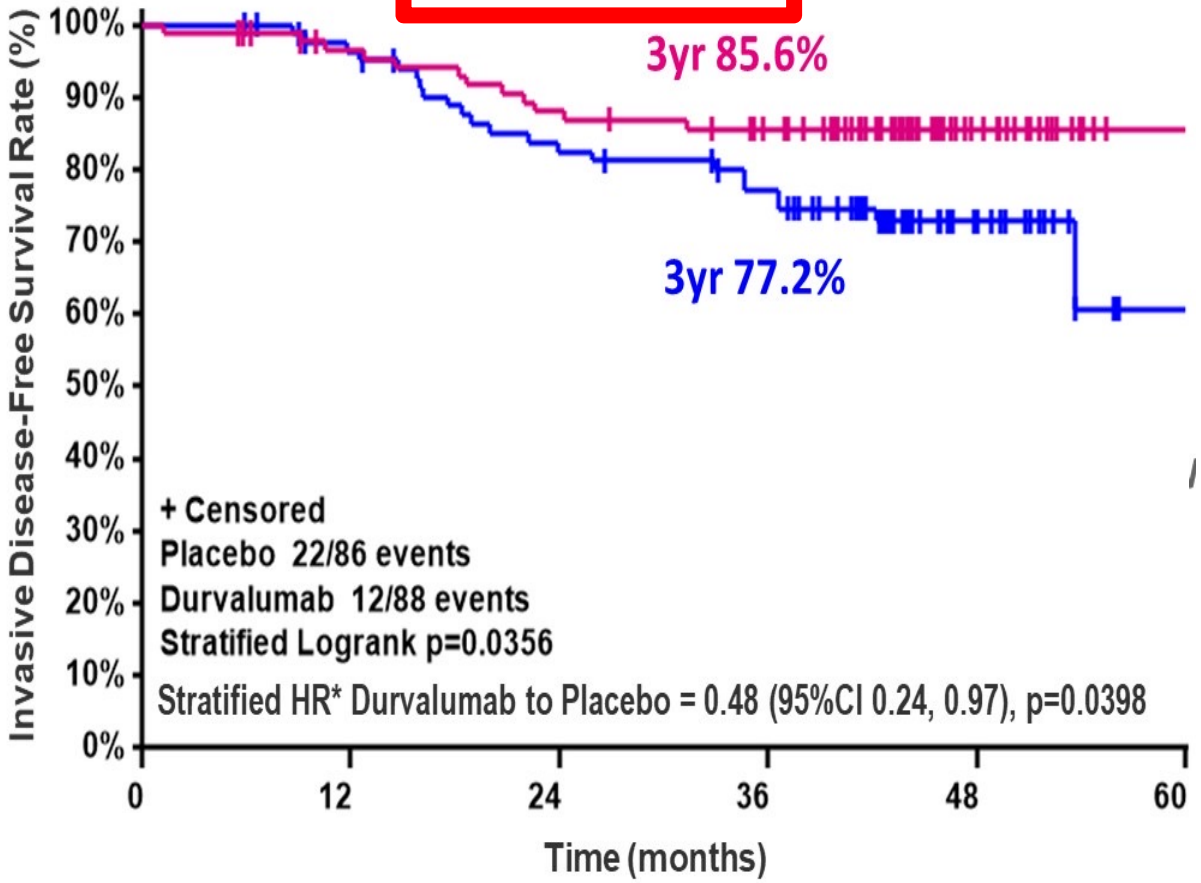
Which subset derives benefit?



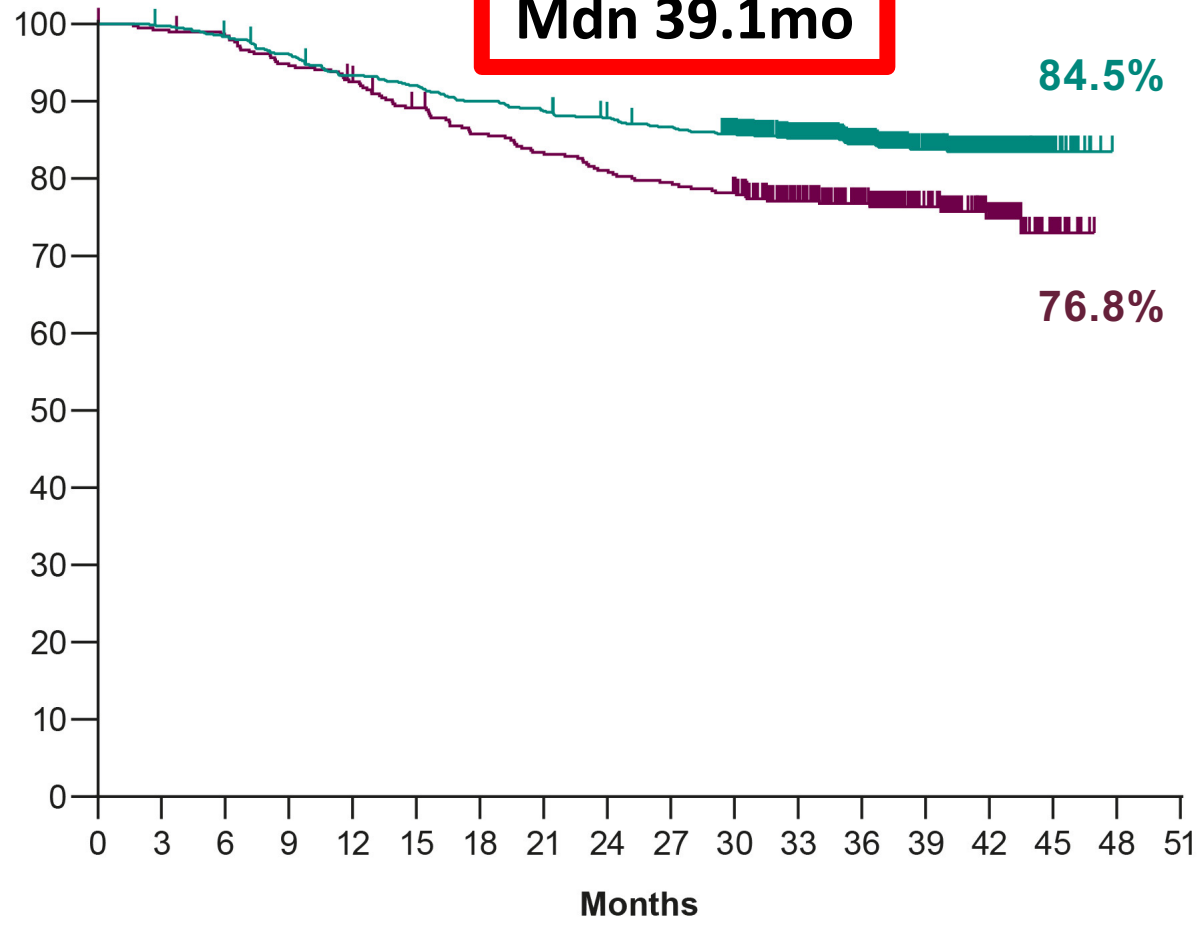
Schmid P et al. 2023 ESMO Annual Congress. Abstract LBA18.

Is the benefit of IO conferred with neoadjuvant administration?

GeparNuevo
Mdn 43.7mo

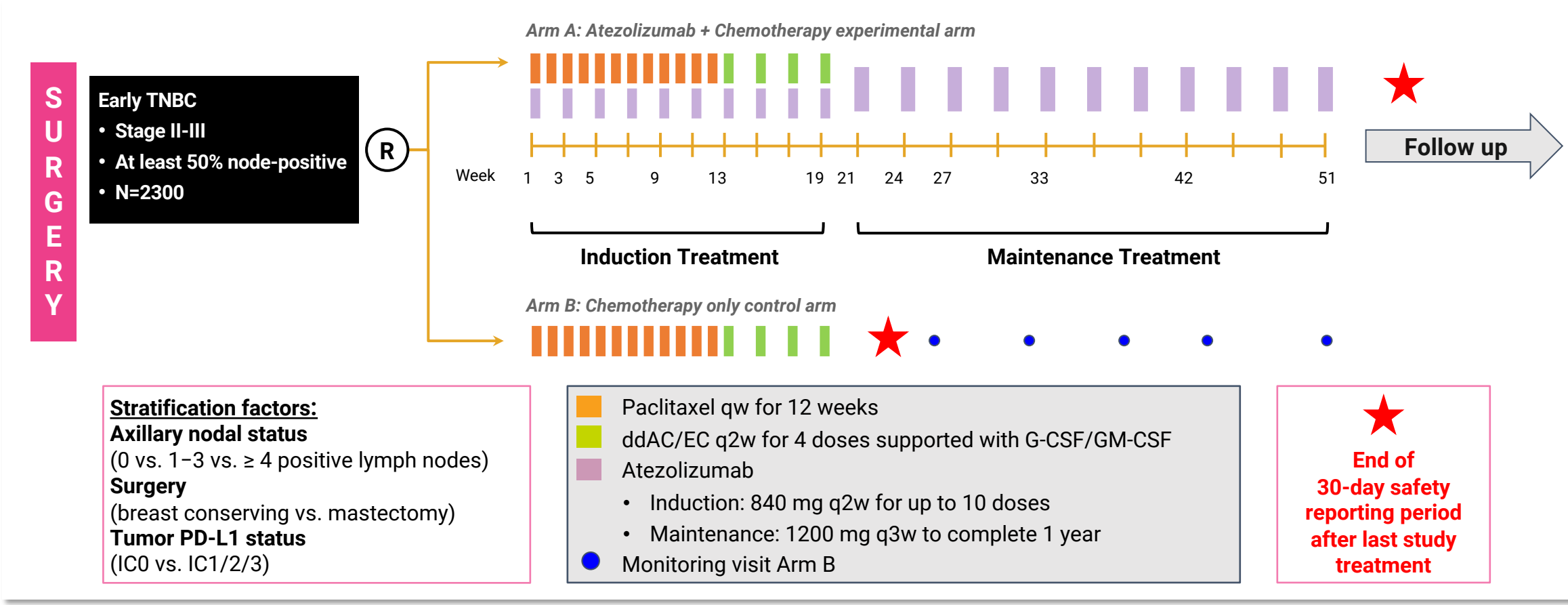


KEYNOTE-522
Mdn 39.1mo



Loibl S et al. 2021 ASCO Annual Meeting. Abstract 506. Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7_2021.

ALEXANDRA/IMpassion030 phase 3 Open-label Study Design



Ignatiadis M et al. 2023 SABCS. Abstract GS01-05.
McArthur H et al. 2024 EBCC. Abstract 1LBA.
NCT03498716

Statistical Considerations
Final Analysis

Updated Statistical Analysis Plan (SAP v3):

- Health Authority request for additional interim and futility analysis
- SAP amended to add additional interim analysis
- 2199 patients randomized at time of amendment
- Two planned interim analyses at 62% and 80% information (242 and 312 iDFS events)
- **Futility boundary at a Hazard Ratio (HR) > 1**
- Final analysis at 390 iDFS events
  - Two-sided, stratified log-rank test with alpha 0.05, power 80%, hazard ratio 0.75, ITT population

Final Analysis using SAP v3:

- Futility boundary crossed at Interim Analysis
- 2199 patients randomized
- **266 iDFS events** (lower than pre-planned)
- Overall alpha remains at 0.05 (type-1 error control)
- Significance boundary calculated taking into account;
  - **Interim Analysis at 239 iDFS events** *and*
  - **Final Analysis at 266 iDFS events**
- Final significance boundary for iDFS (2-sided) 0.04988

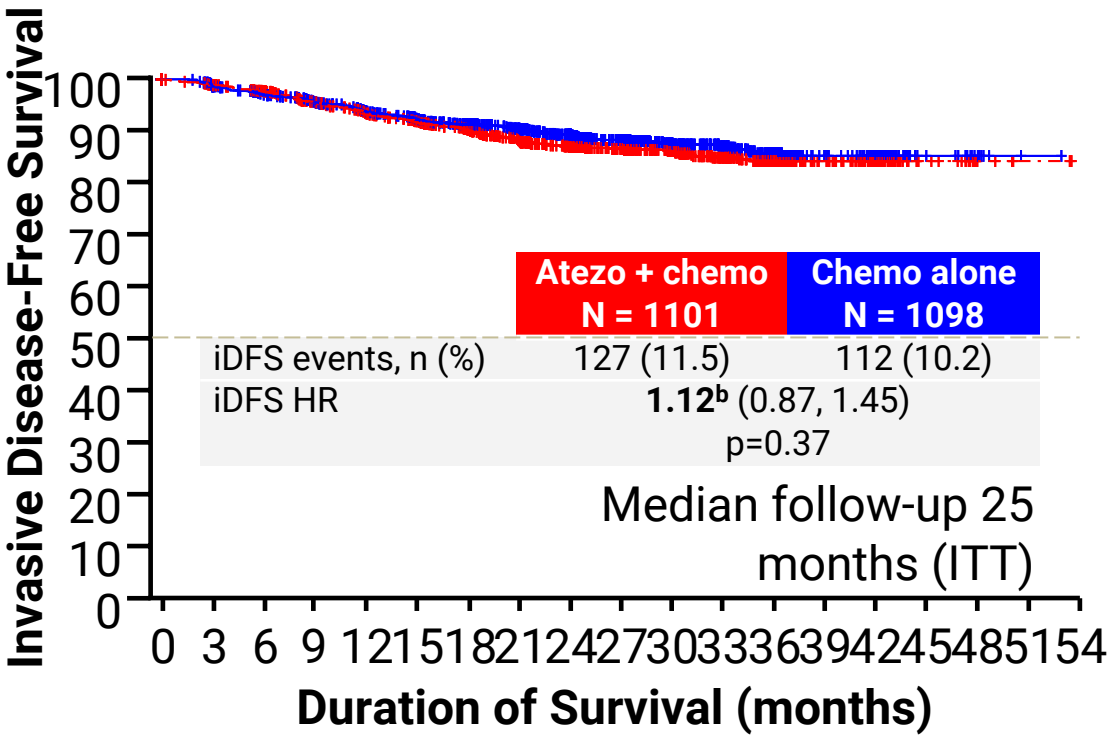
- 18 Aug 2023: Data cut off at Last Patient Last Visit (LPLV)
- 20 Nov 2023: Final database snapshot; database locked

McArthur H et al. 2024 EBCC. Abstract 1LBA.

iDFS IA and Final Analysis

Primary Efficacy Endpoint (ITT population)

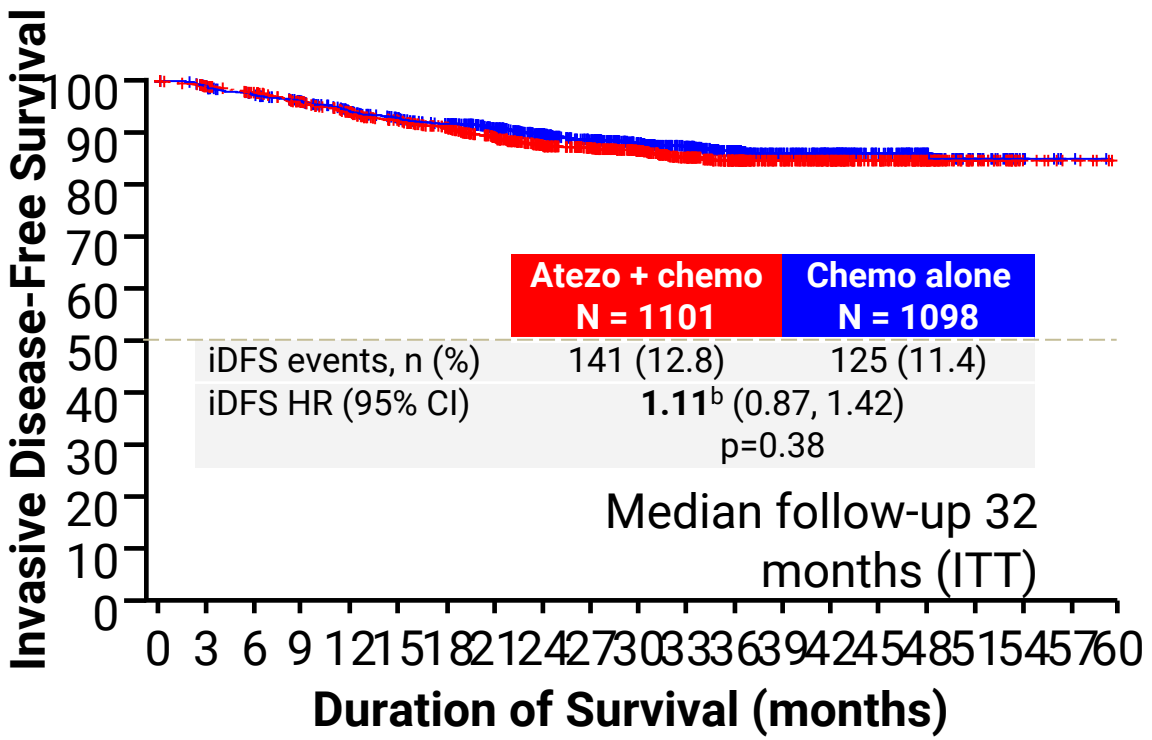
Interim Analysis[a]



Patients remaining at risk

Chemo alone	1098	1022	970	923	864	812	731	663	565	471	372	289	204	109	74	17	5	1	0
Atezo + chemo	1101	1042	995	932	869	820	735	648	564	481	391	294	202	120	66	22	5	2	0

Final Analysis



Patients remaining at risk

Chemo alone	1098	1041	1009	974	926	885	856	798	699	640	551	460	359	281	217	144	80	33	6	2	0
Atezo + chemo	1101	1053	1027	983	935	892	847	775	691	634	553	467	371	285	214	155	85	39	10	5	0

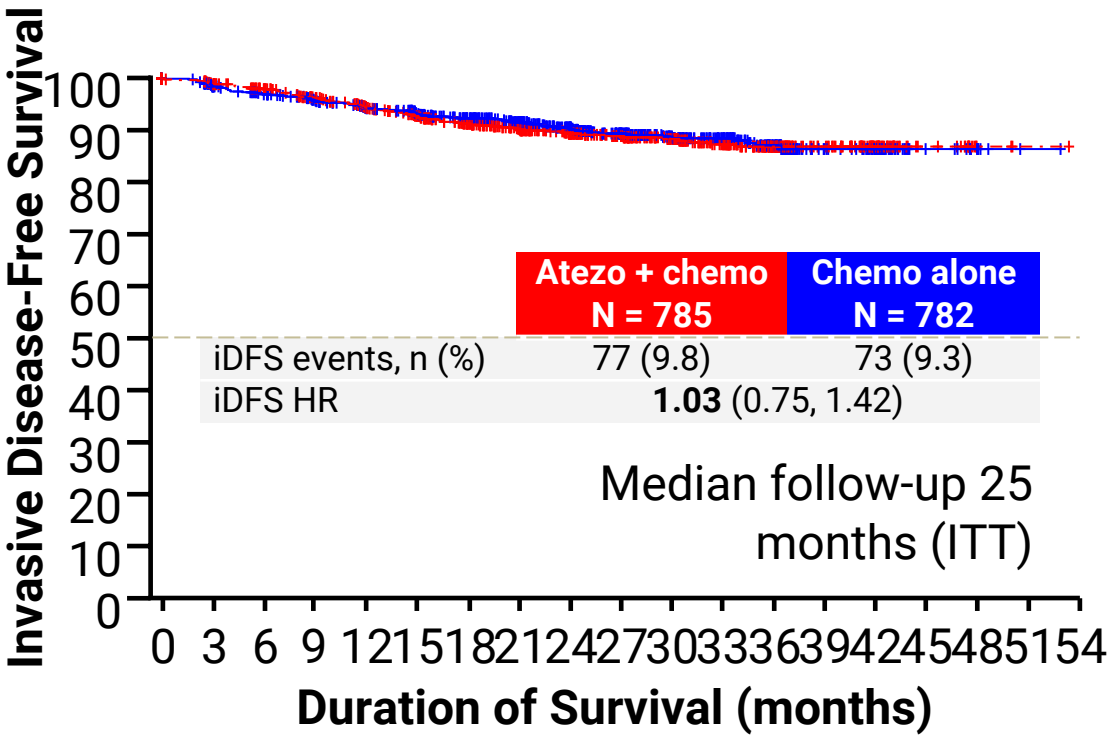
iDFS: defined as the interval from randomization until date of first occurrence of an iDFS event
[a]IA results previously presented at SABACs 2023 (database of 17 Feb 2023, not cleaned)
[b]Stratified by PD-L1 status, Surgery, and Axillary Nodal Status

McArthur H et al. 2024 EBCC. Abstract 1LBA.

iDFS PDL1+ IA and Final Analysis

Secondary Endpoint (ITT population)

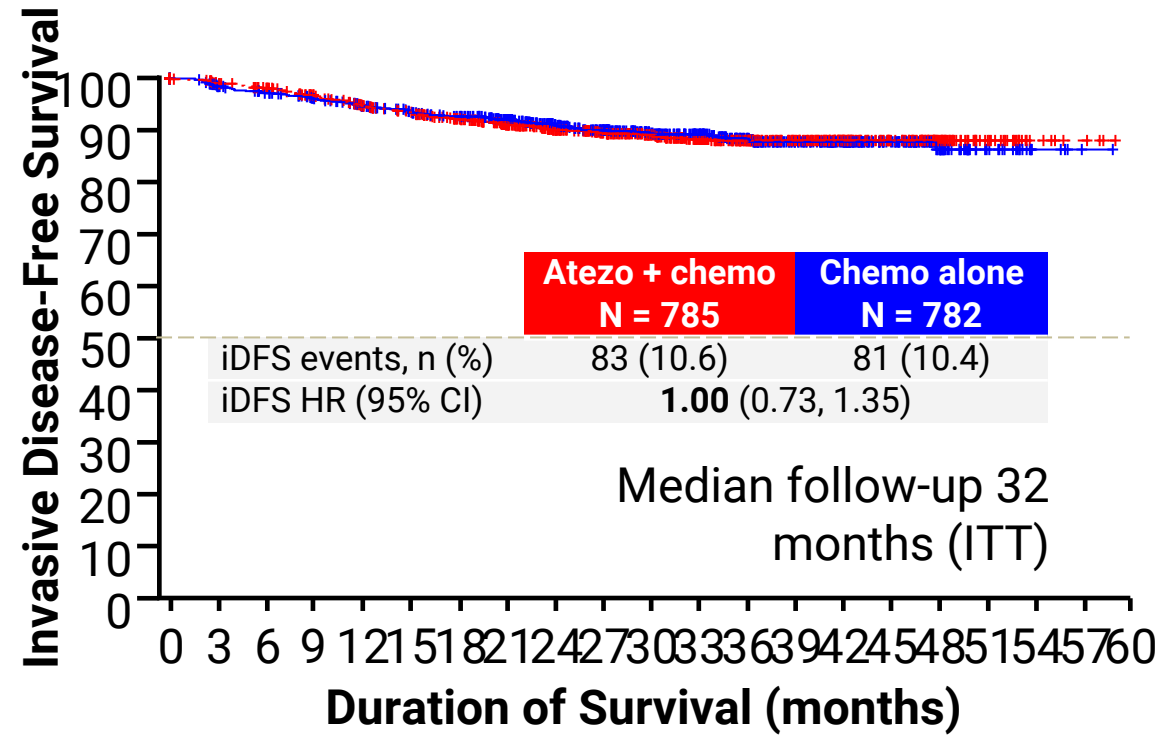
Interim Analysis[a]



Patients remaining at risk

Chemo alone	782	728	691	660	622	589	534	486	416	350	276	223	154	81	53	14	4	1	0
Atezo + chemo	785	749	718	680	640	601	536	480	425	366	300	230	156	90	48	17	3	1	0

Final Analysis



Patients remaining at risk

Chemo alone	782	738	713	691	664	639	618	578	515	470	405	344	271	214	168	109	55	23	5	2	0
Atezo + chemo	785	756	740	710	680	653	618	571	517	471	418	357	284	220	164	112	62	28	8	4	0

[a]IA results previously presented at SABCS 2023 (database of 17 Feb 2023, not cleaned)

McArthur H et al. 2024 EBCC. Abstract 1LBA.

A-BRAVE Trial - Study Design

Investigator-driven study, sponsored by University of Padova.
Drug supply and Grant support by Merck KGaA.

High Risk TNBC patients who completed locoregional and systemic treatment with curative intent

Key eligibility criteria:
- Age ≥18 years
- ECOG PS 0-1
- TNBC (ER & PgR <10%, HER2 0-1+ or 2+ FISH-)^
- Anthracycline and taxane (neo)-adjuvant ChemoRx
- Tissue samples for central PD-L1 assessment
- Randomization <10 weeks from last chemo or surgery

- **Stratum A (Adjuvant): pT2N1, pT3-4 N0-3, pN2-3 anyT#**
- **Stratum B (Post-neoadjuvant): residual invasive carcinoma in the breast and/or axillary lymph nodes§***

R 1:1
N=477

Avelumab
10mg/kg, iv, q 2 weeks for 52 weeks

Observation

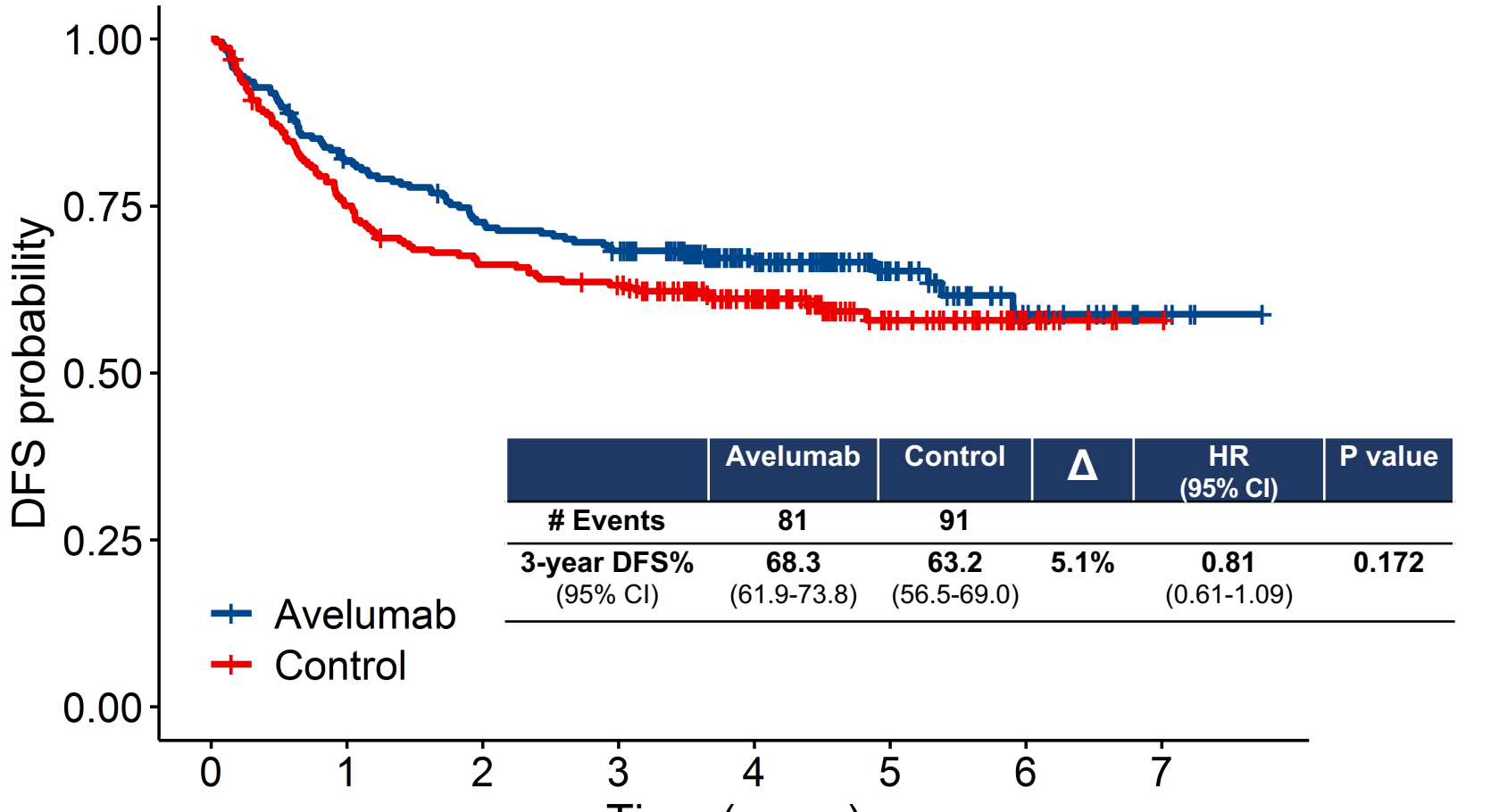
In case of ER 1-9%, adjuvant HT allowed at discretion of treating physicians.
Whenever indicated, radiotherapy allowed concomitantly with avelumab.

^for patients in the neoadjuvant stratum, TN status required in the preoperative and in the post-surgical specimen
 # trial initially limited to pN≥2; protocol amendment in 10/2017 to include patents with pT2N1 and pT3-4 N0-3 disease stage
§ excluding ypT1micN0, ypT1micN0i+, ypT0N0i+
*** After amendment on 06/2018, patients in stratum B were allowed to receive additional post-operative chemotherapy and were randomized at completion of treatment.**
Randomization balanced for Stratum A and Stratum B.

EUDRACT 2016-000189-45; NCT 02926196

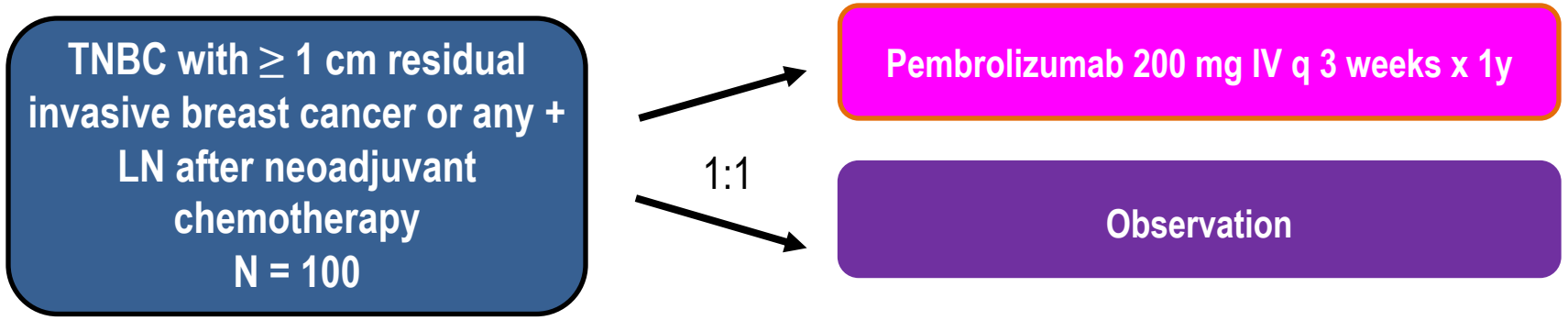
A-BRAVE Trial - Disease-Free Survival, ITT (co-primary end point)

median FUp: 52.1 months (95% CI: 49.8- 53.8)



	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	81	91			
3-year DFS% (95% CI)	68.3 (61.9-73.8)	63.2 (56.5-69.0)	5.1%	0.81 (0.61-1.09)	0.172

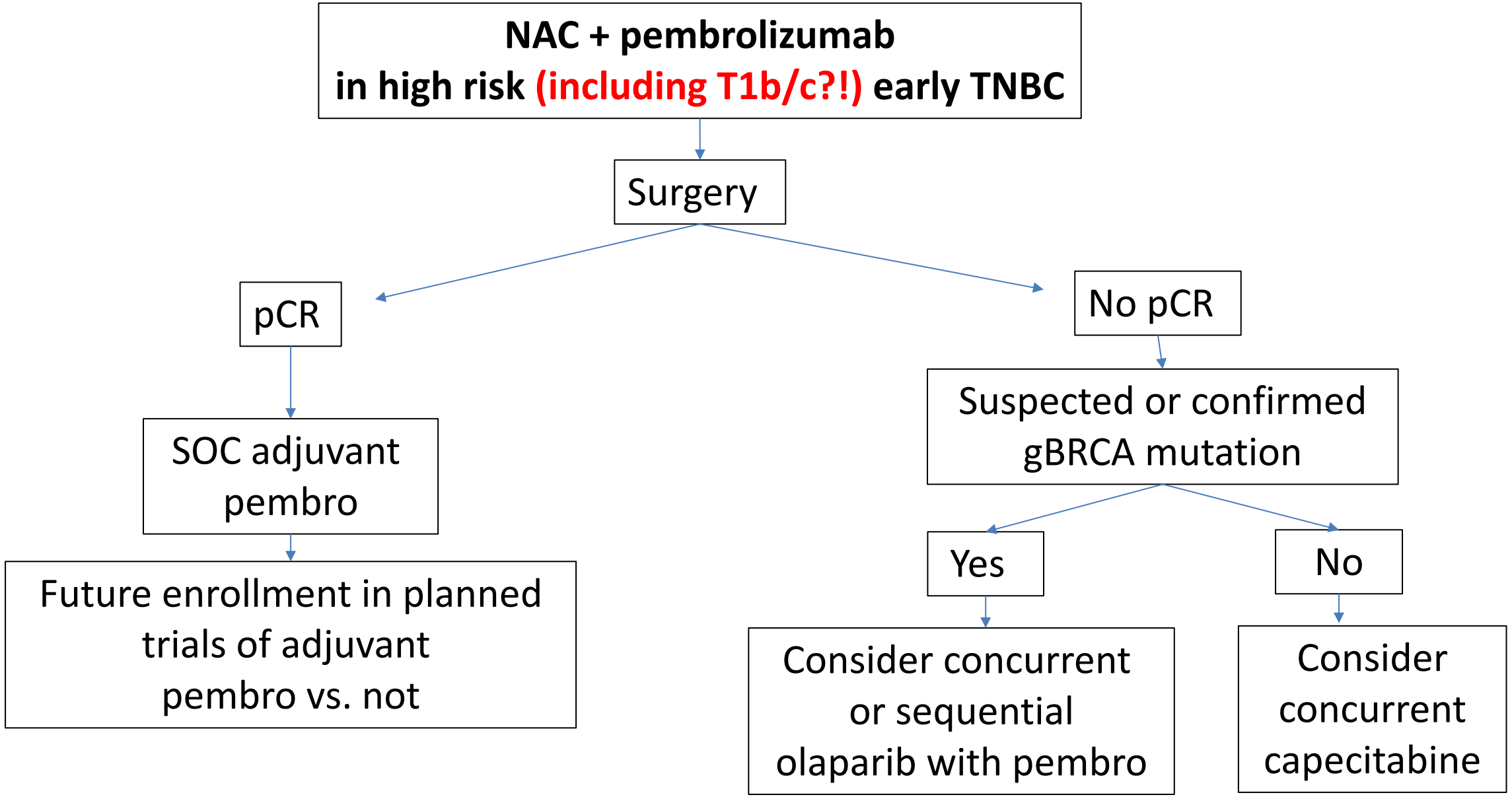
SWOG 1418/NRG BR006



- **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

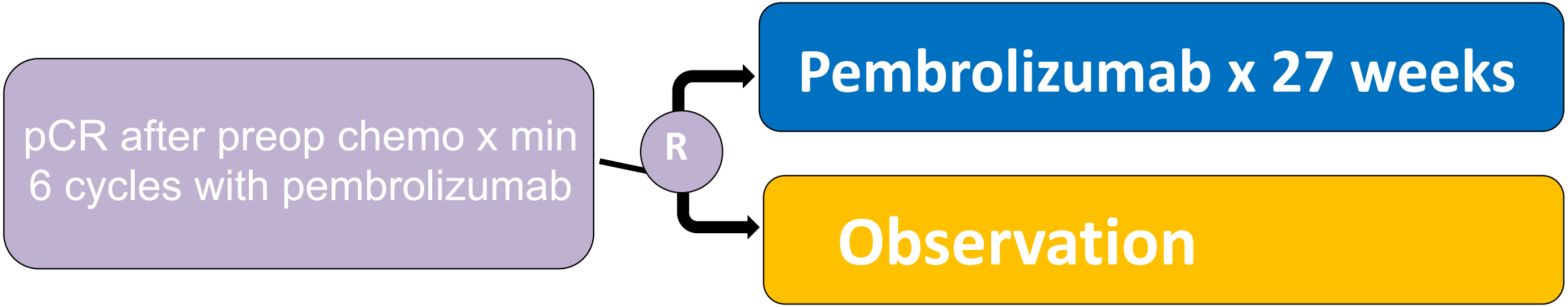
- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

PI: Lajos Pusztai
NCT02954874



Consider concurrent pembro with radiation

OptimeICE-PCR study: For patients with pCR



N = 1956 (56month accrual estimated)

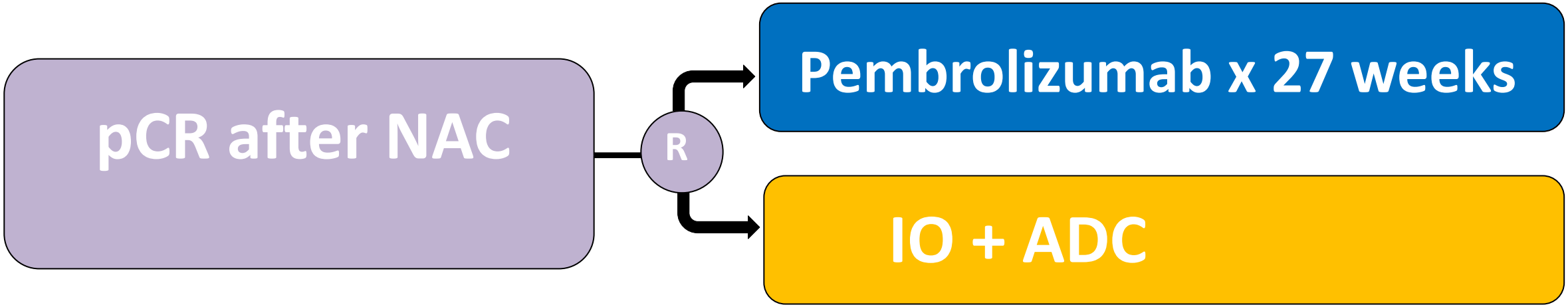
Stratification Factors:

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

1ºEndpoints: RFS and QOL at 27weeks

Alliance
NCT05812807

Planned study for patients w/o pCR



Adjuvant ADC combinations:

- Sacituzumab govitecan (Alliance) + pembro vs TPC
- DatoDXd (SWOG) +/- durvalumab vs TPC
- Sac-TMT (MK-2870/SKB264) +/- pembro (planned)

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

TROPION-Breast04

Neoadjuvant | Surgery | Adjuvant

Key Eligibility Criteria

- Histologically confirmed Stage II or III unilateral or bilateral primary invasive breast cancer.
- TNBC (ER and PR < 1%) or hormone receptor-low breast cancer (ER and/or PR 1% to < 10%, neither hormone receptor may be ≥ 10%), and HER2-negative.
- No evidence of distant disease.
- No prior surgery, radiation, or systemic anticancer therapy.
- ECOG PS 0 or 1.
- Adequate hematologic and organ function.

1:1

Experimental Arm

Dato-DXd + durvalumab
Q3W x 8 (24 weeks)

→ Durvalumab x 9 cycles +/- chemotherapy [a, b, c]

Control Arm

Pembrolizumab + carboplatin + paclitaxel
Q3W x 4 (12 weeks)

→ Pembrolizumab + doxorubicin or epirubicin + cyclophosphamide
Q3W x 4 (12 weeks)

→ Pembrolizumab x 9 cycles +/- chemotherapy [a, c, d]

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).

Dual primary endpoints:
pCR and EFS

Secondary endpoints:
OS, DDFS, safety and tolerability, PROs, PK, immunogenicity

Exploratory endpoints include but are not limited to:
TROP2, PD-L1

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

UT Southwestern
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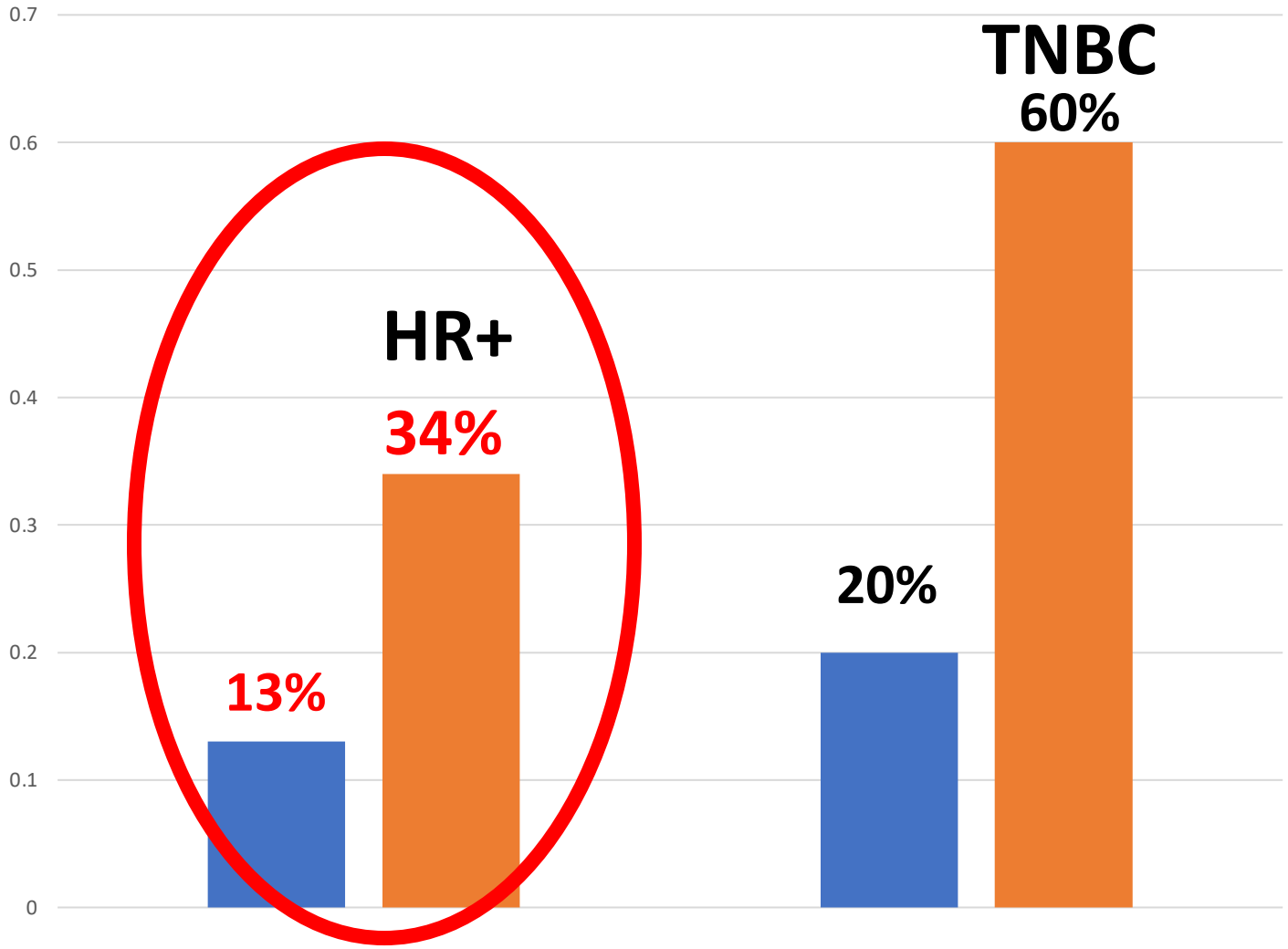
Is there a Role for Immune Therapy in EARLY STAGE HIGH RISK ER+ Breast Cancer?

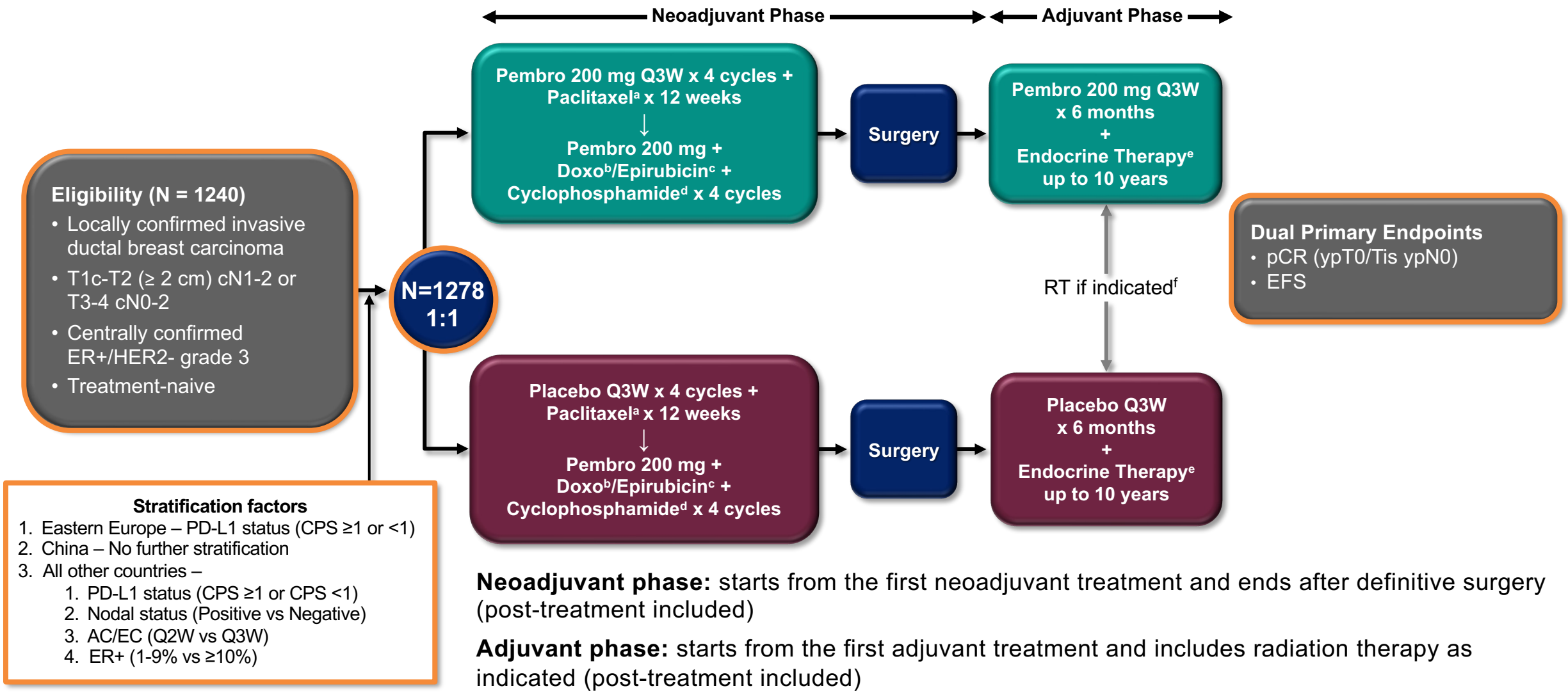
Estimated pCR Rates from ISPY2



Pembro graduates in all signatures
Including ER+

Nanda R et al. 2017 ASCO Annual Meeting. Abstract 506.

KEYNOTE-756 Study Design (NCT03725059)

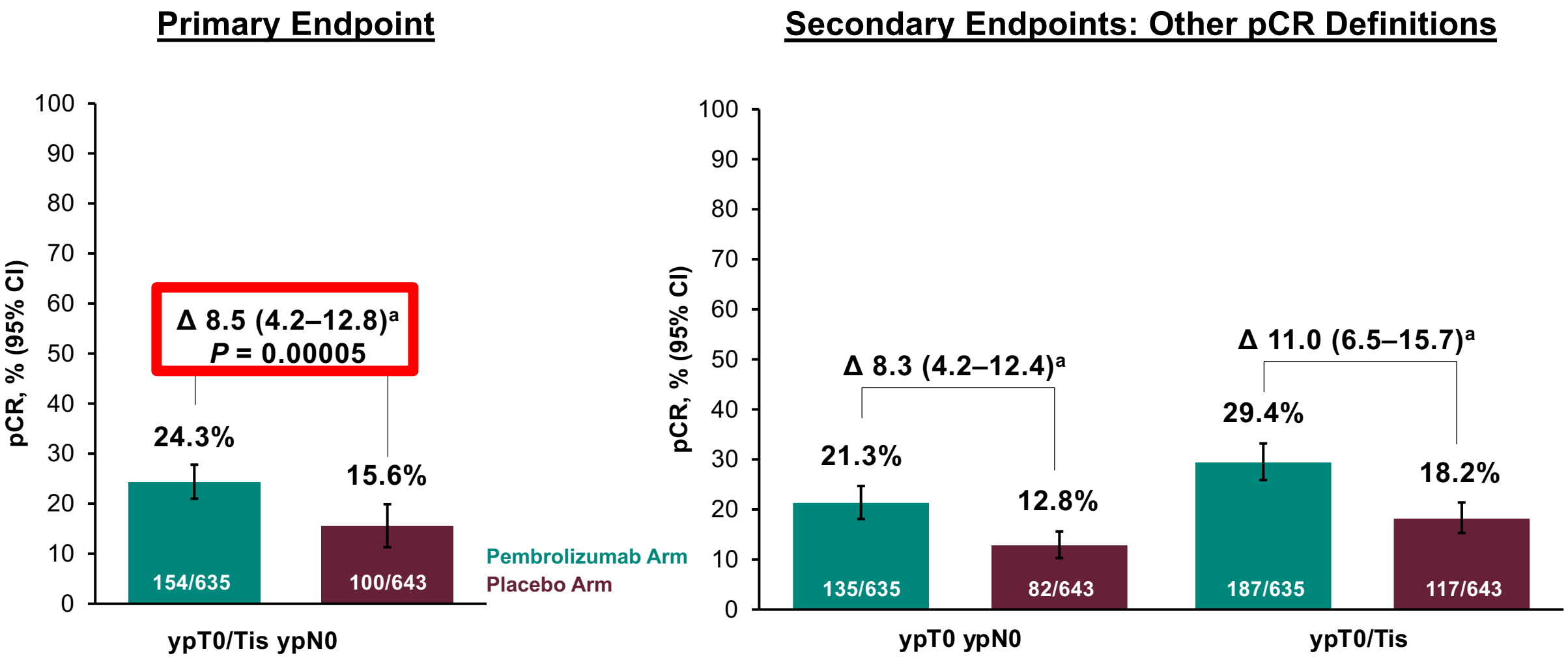


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

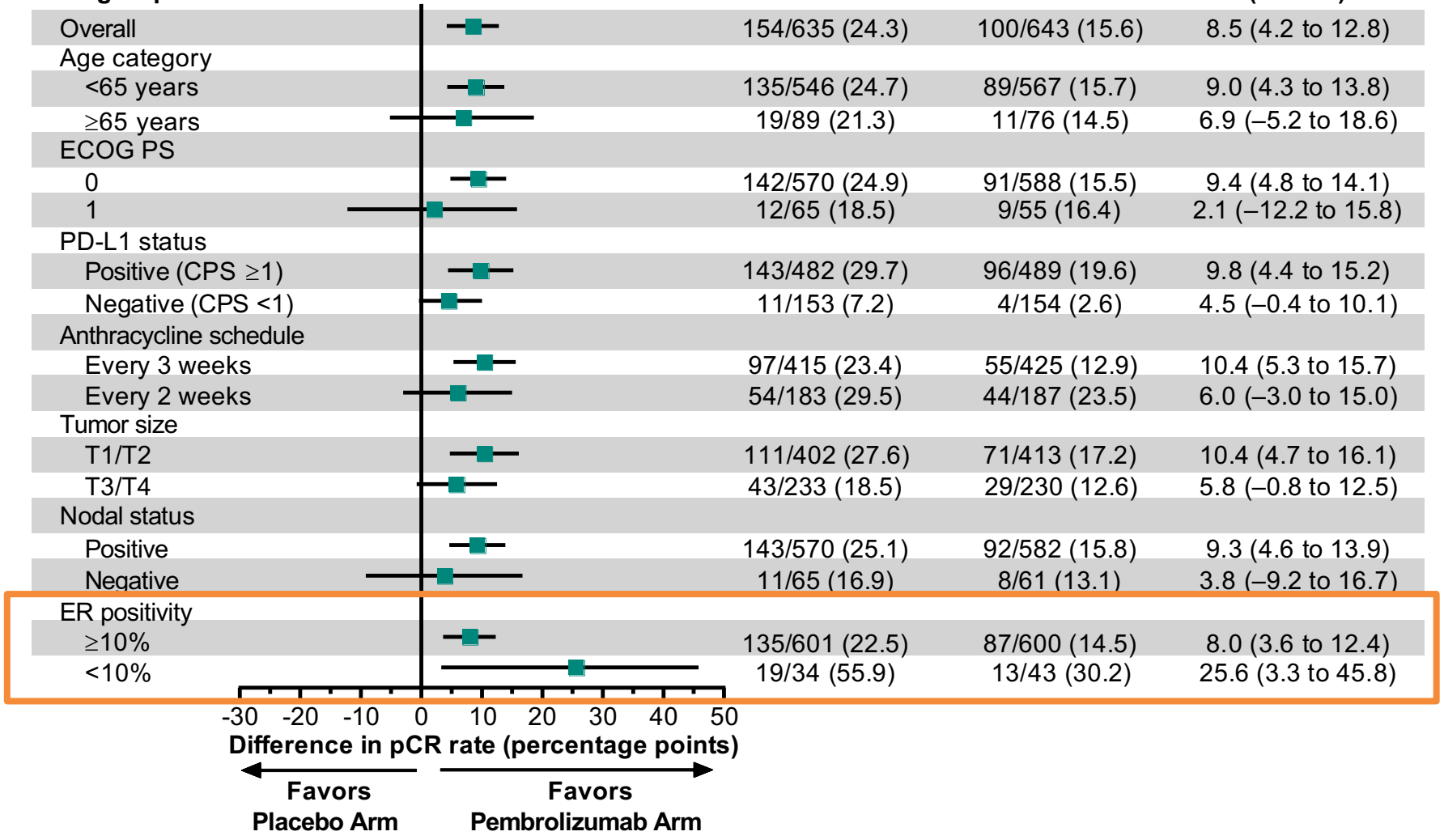
Cardoso F et al. 2023 ESMO Annual Congress. LBA21.

Pathological Complete Response at IA1



Cardoso F et al. 2023 ESMO Annual Congress. LBA21.

Pathological Complete Response (ypT0/Tis ypN0) in Subgroups



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)
1	12/65 (18.5)	9/55 (16.4)	2.1 (–12.2 to 15.8)
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)
Anthracycline schedule			
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 F et al. 2023 ESMO Annual Congress. LBA21.

CA209-7FL Study Design

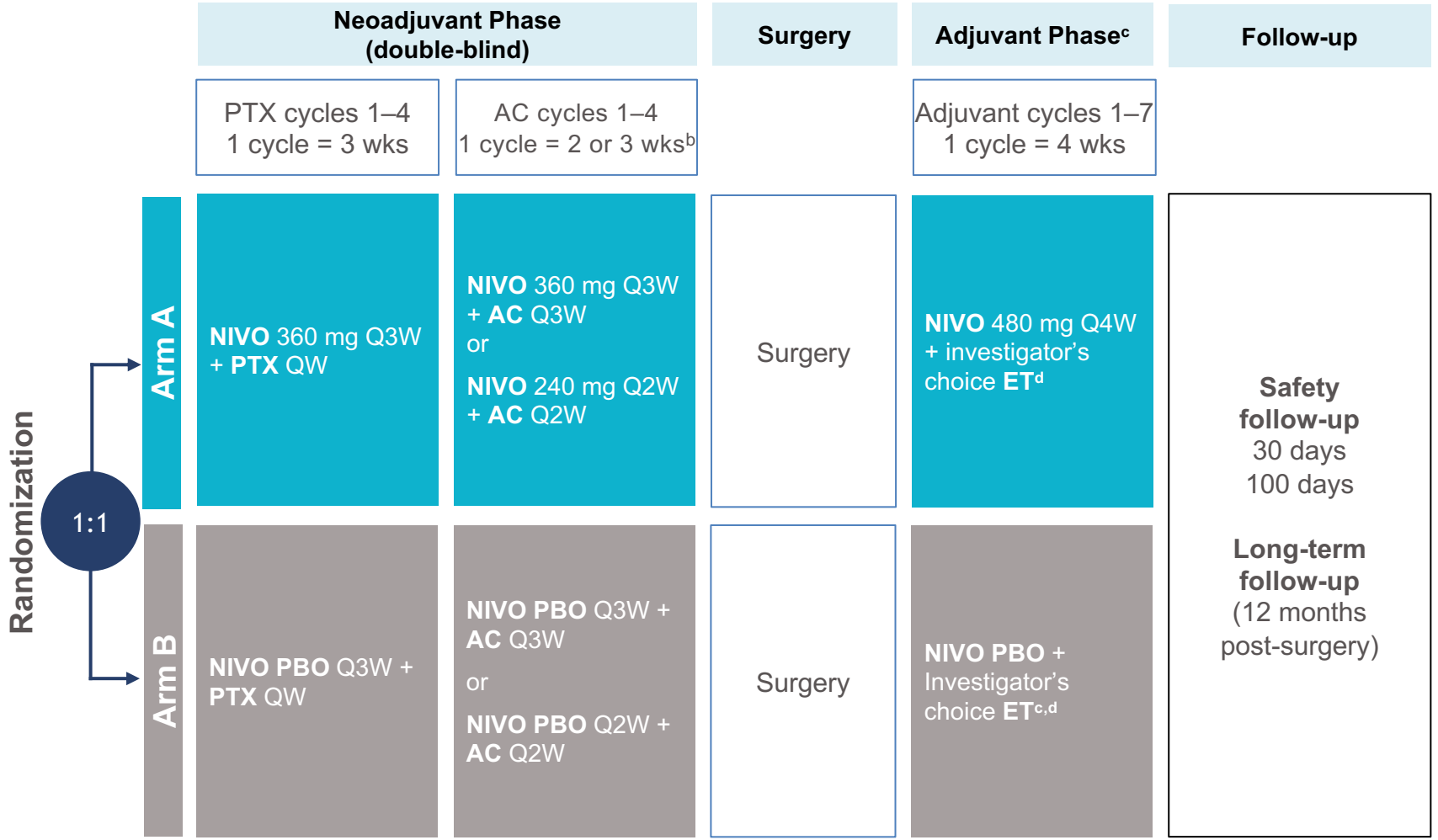
Screening

Key Inclusion Criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1–cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1–10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

Stratification Factors

- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)

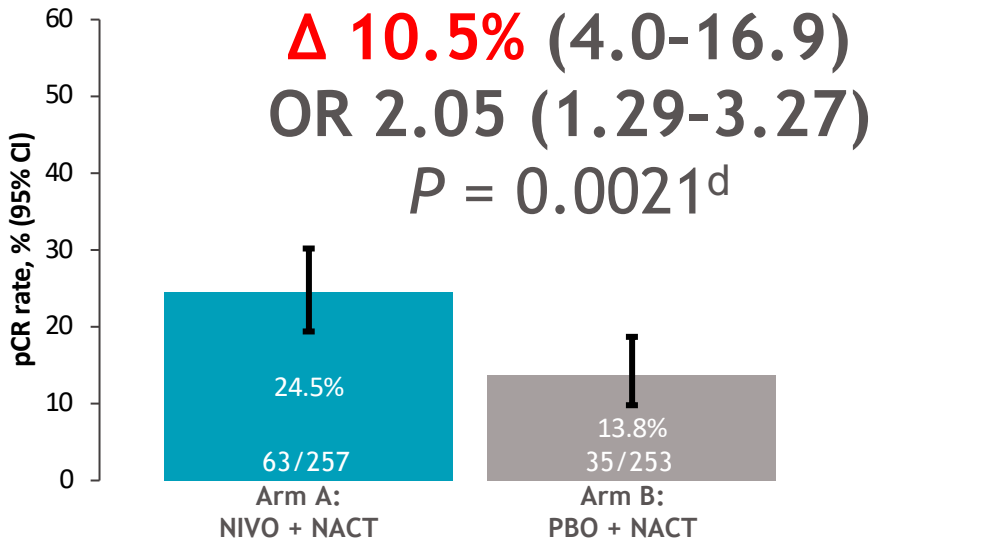


Loi S et al. 2023 ESMO Annual Congress. Abstract LBA20.

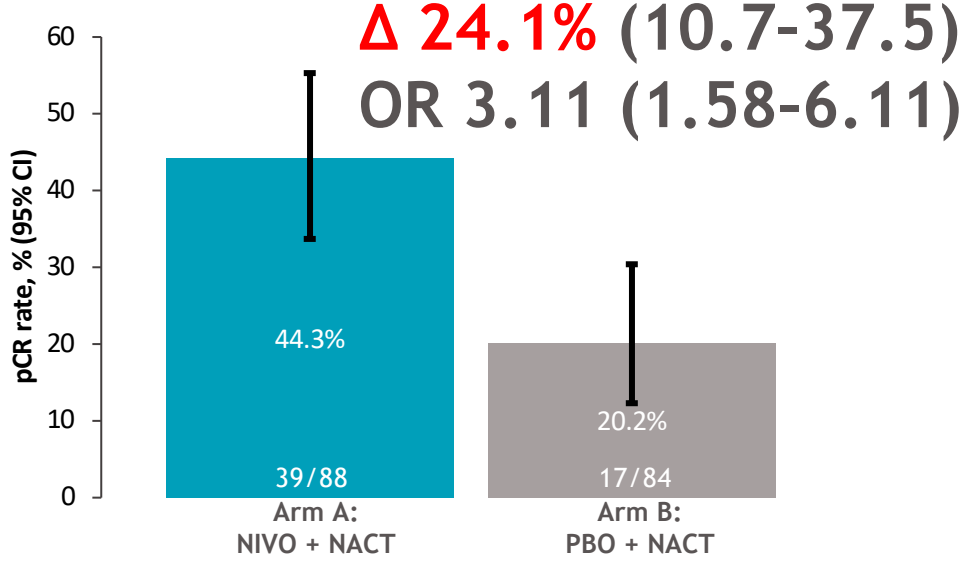
CM-7FL: Efficacy

- CheckMate 7FL (NCT04109066) is a prospective, randomized, multicenter, double-blind, placebo-controlled trial investigating NIVO in combination with NACT and adjuvant ET in patients with high-risk, ER+ HER2− primary BC
- The primary endpoint (pCR) was met, resulting in a statistically significant improvement with added NIVO to NACT; RCB 0–1 rate was also meaningfully improved[1]
- Benefit of NIVO was enriched in the PD-L1+ population (SP142 >1%)

mITT population (primary endpoint)



PD-L1 IC ≥ 1%e (secondary endpoint)

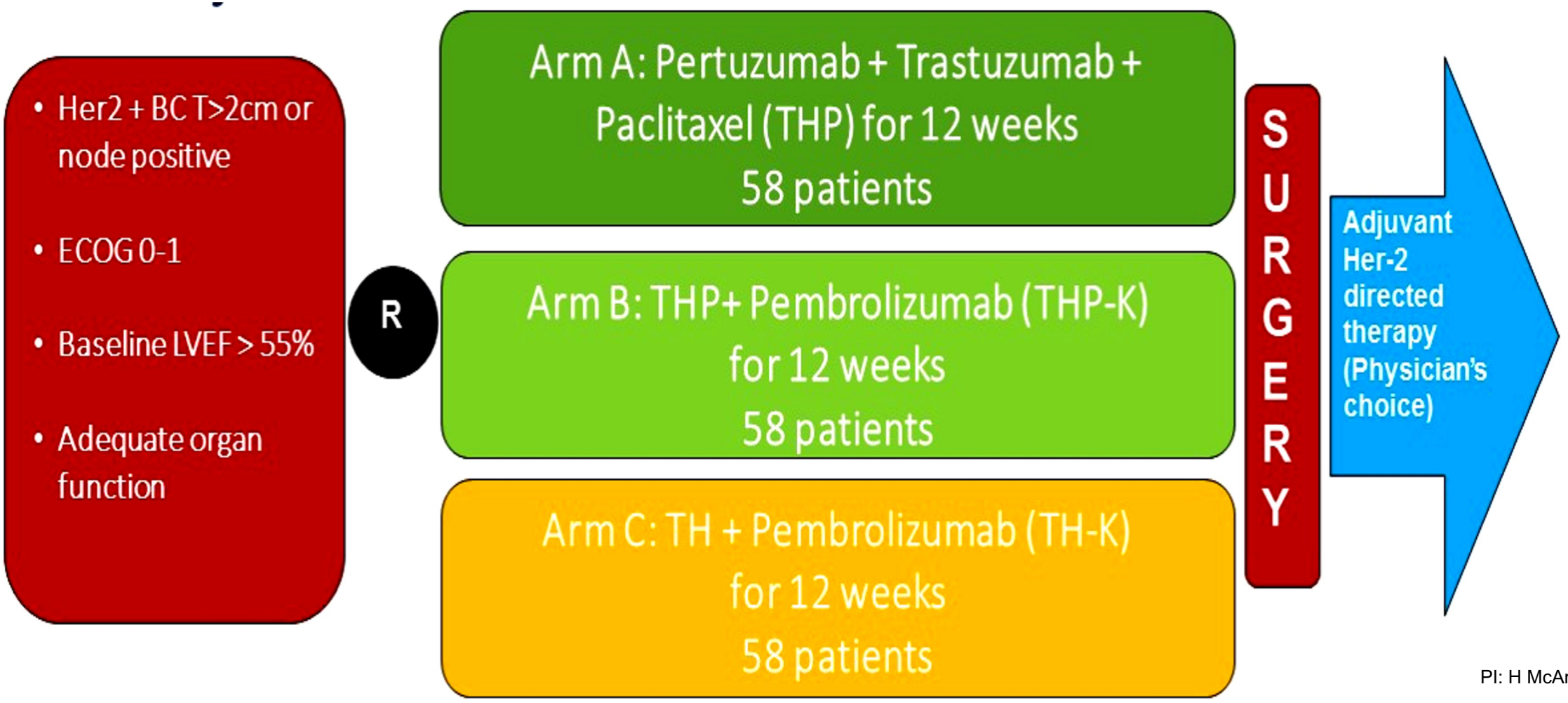


Loi S et al. 2023 ESMO Annual Congress. Abstract LBA20.

UT Southwestern
Medical Center

Is there a Role for Immune Therapy in EARLY STAGE HER2+ Breast Cancer?

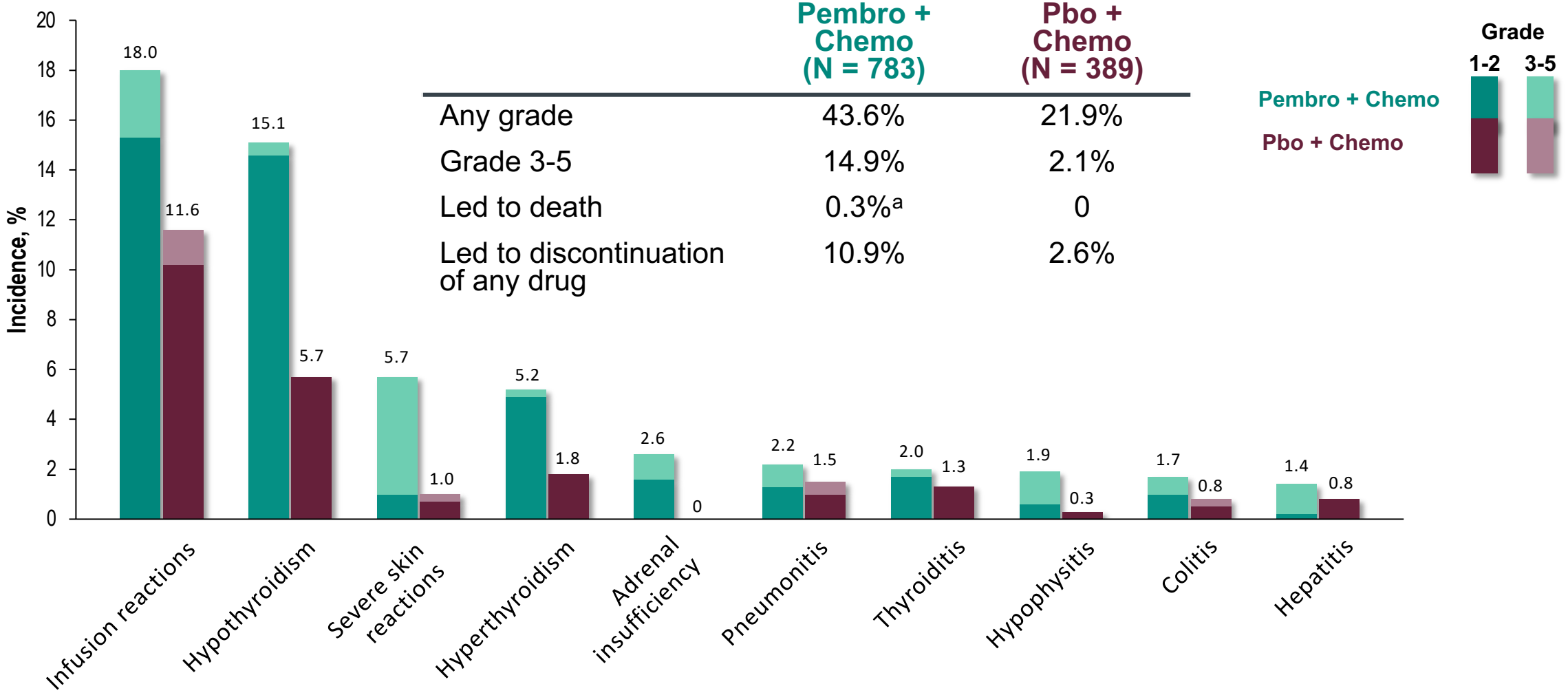
Can We Enhance Response to Checkpoint Blockade in HER2+ Breast Cancer?



PI: H McArthur

Keynote522: irAEs and Infusion Reactions in Combined Phases

	Pembro + Chemo (N = 783)	Pbo + Chemo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%



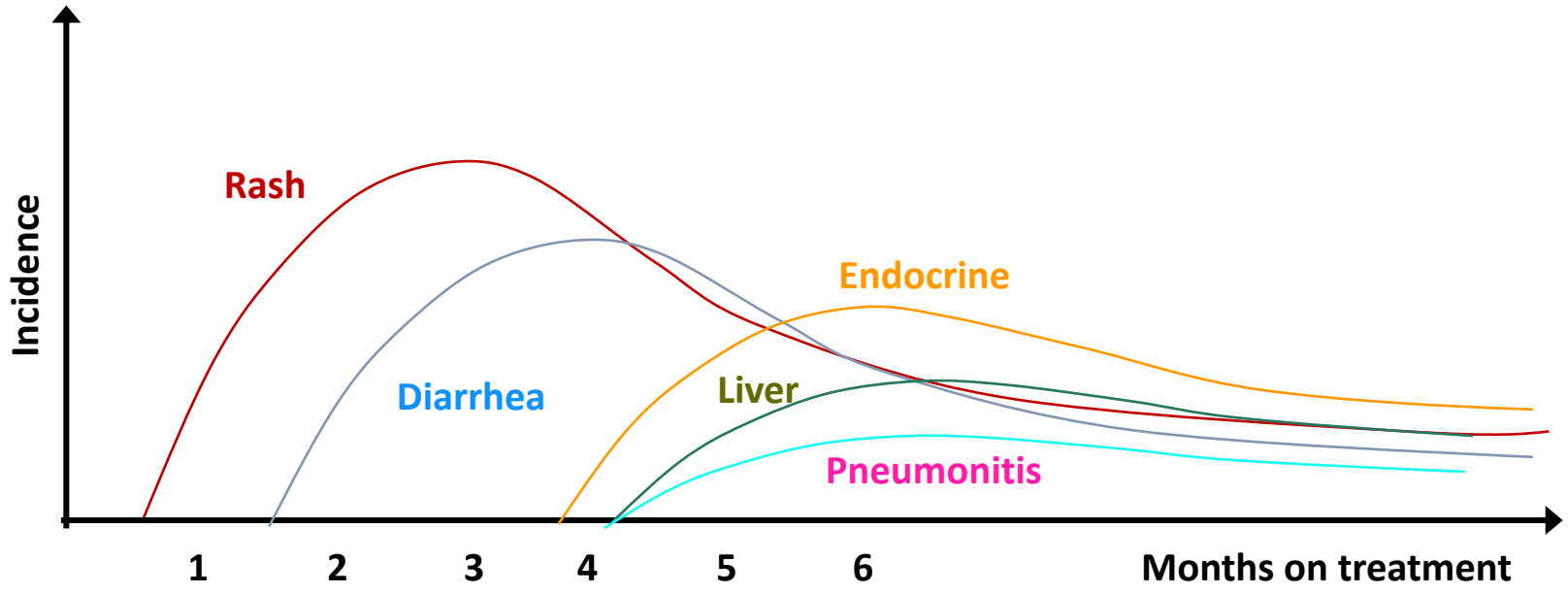
Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed.

Schmid et al. ESMO Virtual Plenary 2023

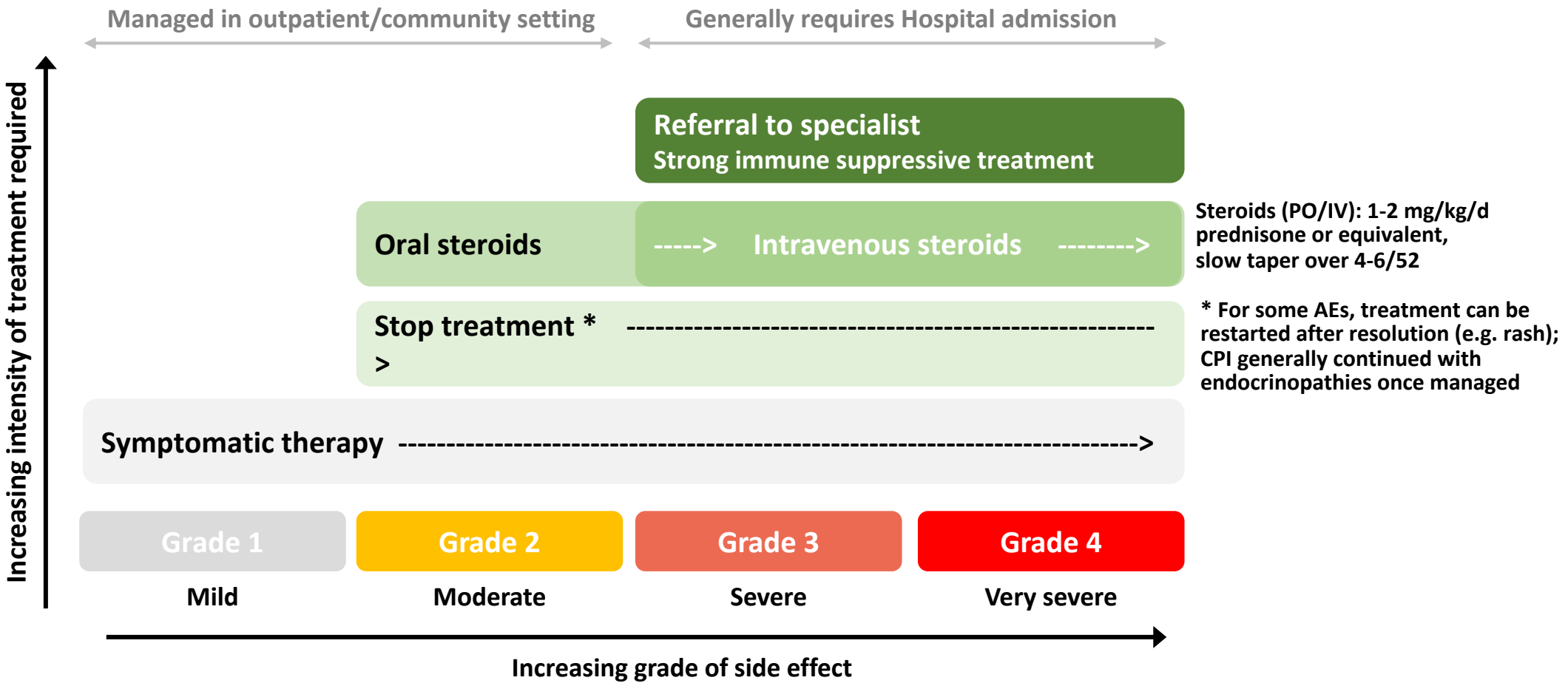
Toxicities With Immune Checkpoint Inhibitors

- **Timing can be highly variable**
- **irAE can occur months or even a year after the end of treatment**
- **Time course might be even more variable with novel combinations**



Slide courtesy of Peter Schmid

Managing AEs From Immune Checkpoint Inhibitors



Adapted from Champiat. ESMO Patient Guide Series.

Resources for irAE Management

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

IO Toxicity Considerations

- Consistency across curative intent IO trials
- Toxicity can occur on treatment and up to 1y later
- Cannot co-administer with CDK4/6 inhibitors
- Novel considerations with ADC coadministration
  - ILD/pneumonitis, neutropenia, stomatitis, ocular surface toxicity

An Exciting Era!