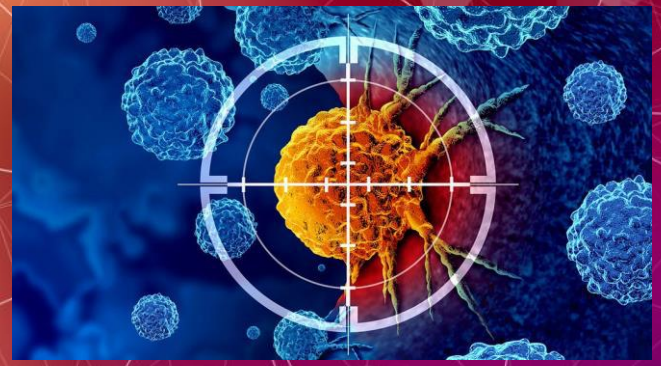
Precision breast cancer:

Tailoring treatments based on pathological response



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Edinburgh Cancer Centre
Western General Hospital

ACP Trainees Weekend, November 2024

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- Consulting/Educational: AstraZeneca, Eli Lilly, Gilead, Novartis, Pfizer, Roche, Exact Sciences, MSD, Seagen
- Travel grants: Roche, Novartis, MSD
- Advisory Board: Astra Zeneca, Gilead, Eisei, Menarini Stemline
- Institutional research support: Astra Zeneca

Edinburgh Cancer Centre
Western General Hospital

Agenda

- Background
- The role of neoadjuvant therapy and pCR
- Case-based discussions:
  - HER2 positive breast cancer: KATHERINE
  - Triple negative breast cancer: Established practice and new studies
  - BRCA1/2 mutated breast cancer: OLYMPIA
  - ER+ HER2 negative breast cancer – KEYNOTE756
- Experimental data – iSPY2
- Summary

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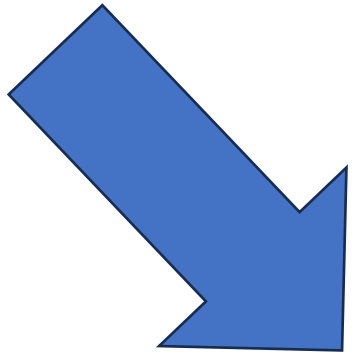


SLIDO for MCQs

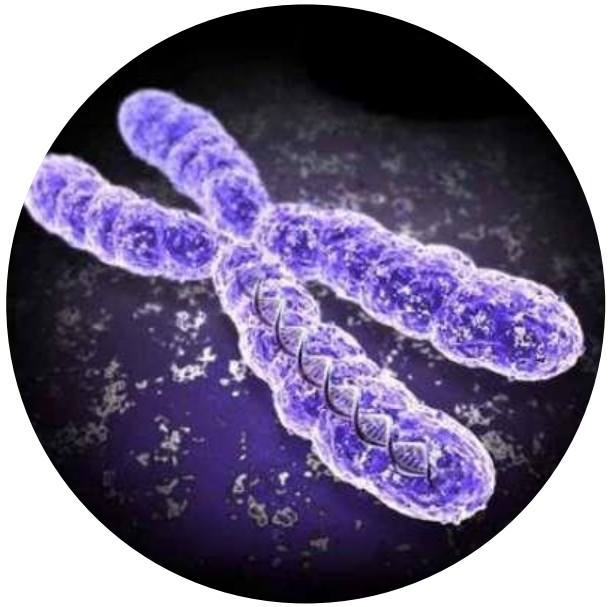
1. www.slido.com

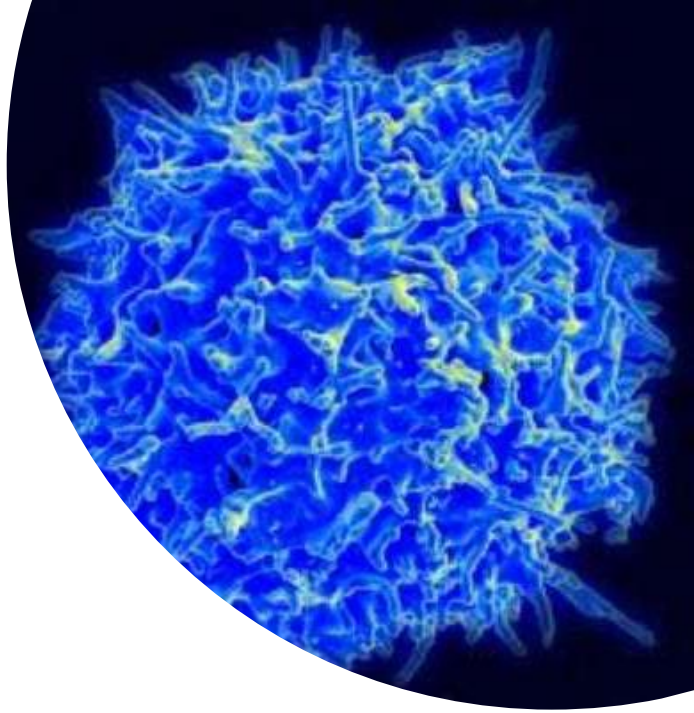
2. #7931176

- In 2000:

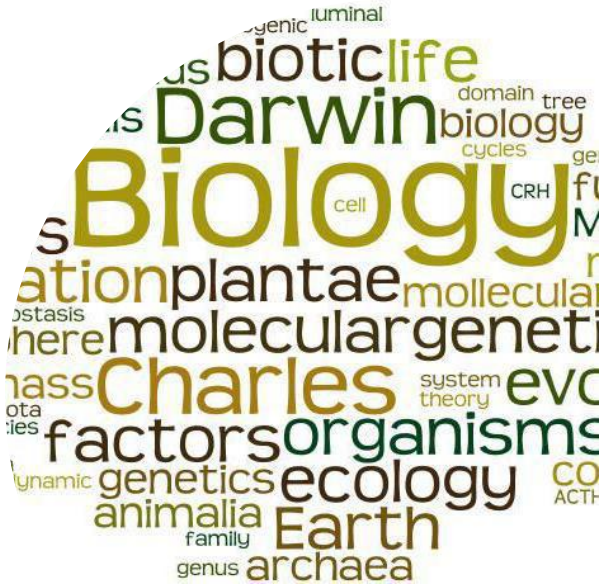
Tamoxifen personified ‘personalised therapy’

- We weren’t really sure who to treat when
- We weren’t really sure why some cancers recurred while others didn’t...
- We had a small number of only modestly effective agents





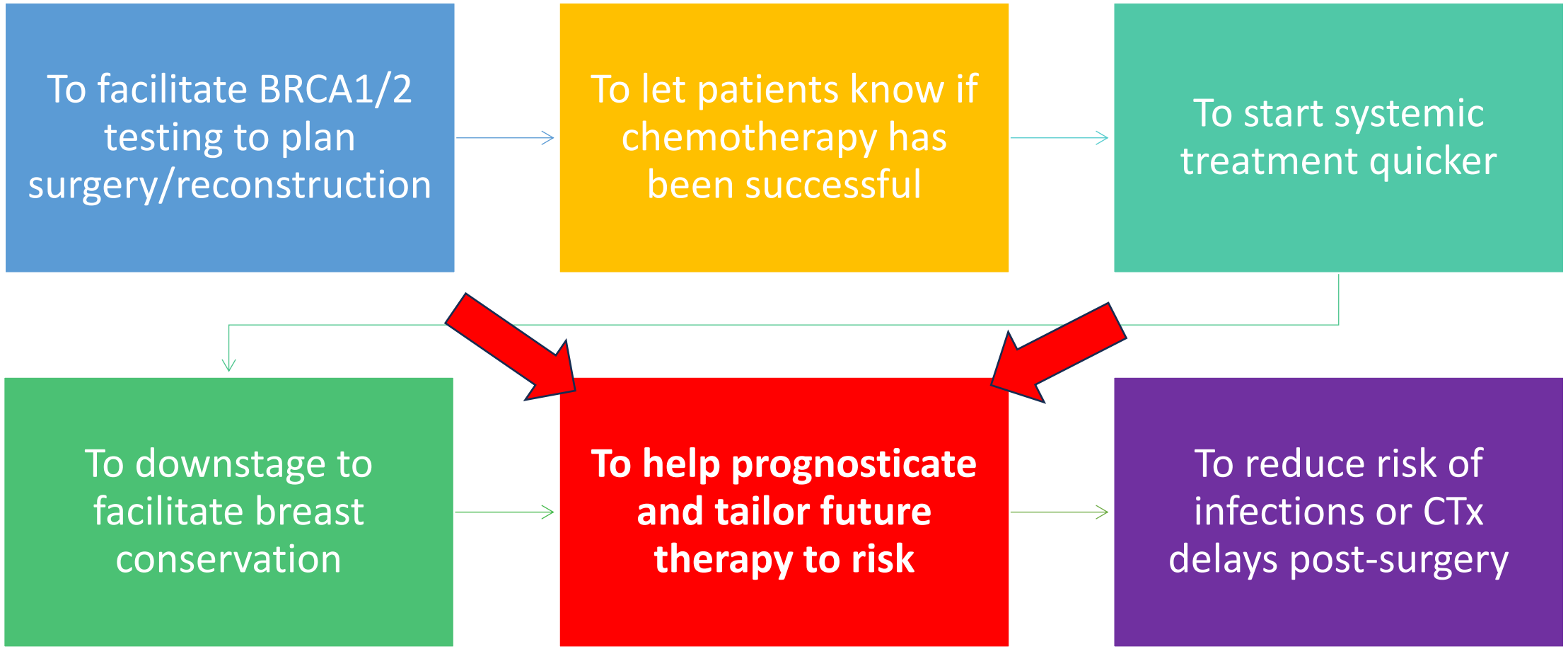
What changed?



Breast cancer - biology matters

With agreement from facingourrisk.org

Why do we give neoadjuvant therapy for breast cancer?



For whom is NACT recommended?

- Biology:
  - TNBC – fit patients with T2 or N+ disease [?T1c]
  - HER2+ - fit patients with T2 or N+ disease [?T1c]
  - ER+ HER2 negative: possibly – if grade 3 and/or lower ER eg ER5 PR0 with T2 or N+ disease
- Stage:
  - Locally advanced BC eg T4, inoperable

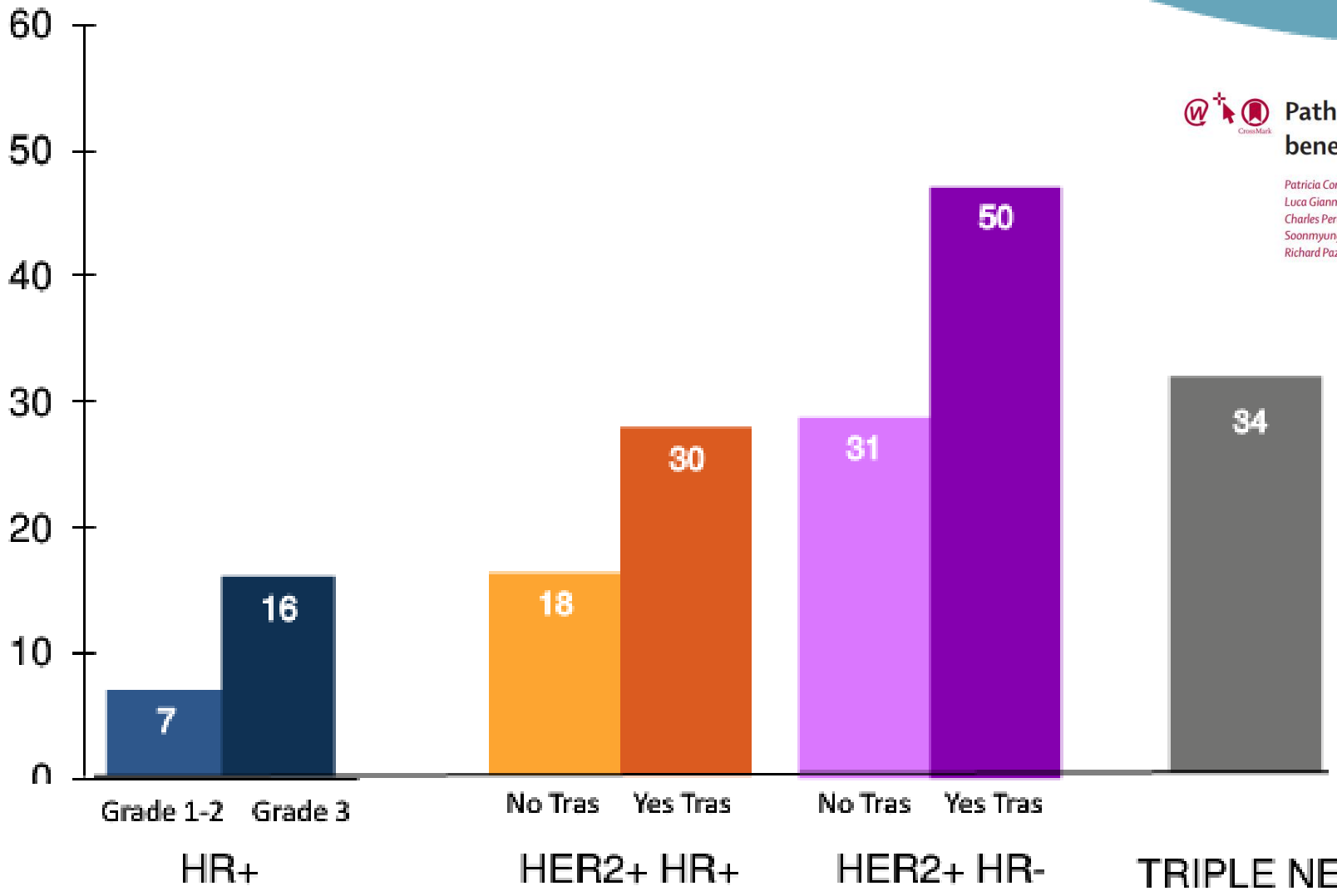
- Who is it NOT good for: (classical) lobular BC, grade 1/2, strongly ER/PR+

pCR Rates by Tumor Subtypes

CTNeoBC

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz



Outdated RRs now due to improvements in SACT since 2012

Cortazar et al, CTNEoBC, SABCS 2012

Residual Cancer Burden (RCB)

- The higher the RCB score, the more residual invasive breast cancer there is in the breast and lymph nodes:

  - RCB-0 = No residual invasive breast cancer (same as pCR)
  - RCB-I = Small amount of residual invasive breast cancer
  - RCB-II = Moderate amount of residual invasive breast cancer
  - RCB-III = Extensive residual invasive breast cancer

Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area:	(mm) X	(mm)
Overall Cancer Cellularity (as percentage of area):		(%)
Percentage of Cancer That Is *in situ* Disease:		(%)

(2) Lymph Nodes

Number of Positive Lymph Nodes:		
Diameter of Largest Metastasis:		(mm)

Reset Calculate

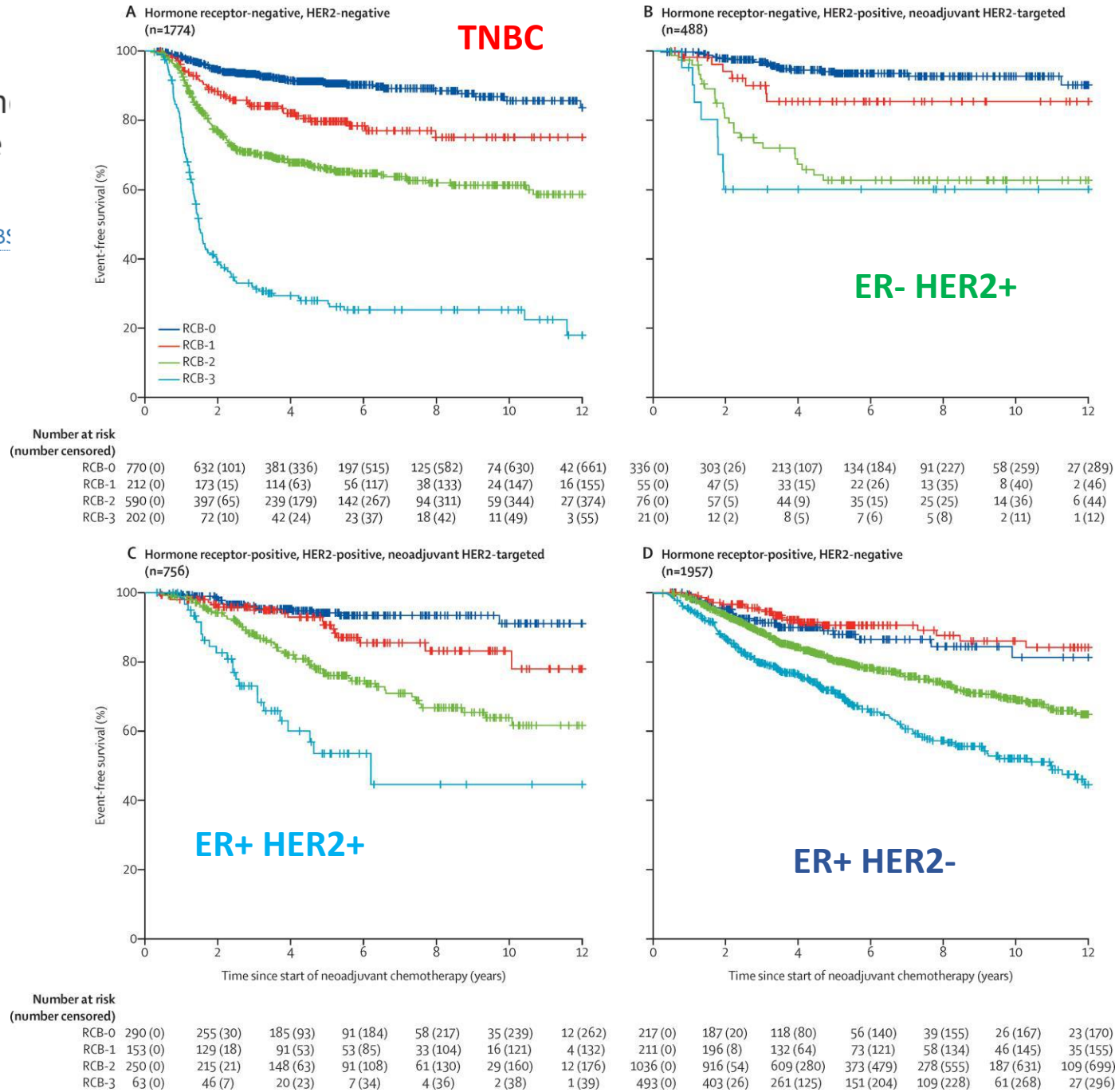
Residual Cancer Burden:	
Residual Cancer Burden Class:	

https://www3.mdanderson.org/app/medcalc/

Residual cancer burden after neoadjuvant chemotherapy an long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients

Christina Yau, PhD [a,†] · Marie Osdoit, MD [a,d,†] · Marieke van der Noordaa, MD [a] · Sonal Shad, BS
Jane Wei, BS [a] · Diane de Croze, MD [e] · et al. Show more

Lancet Oncology, Volume 23, Issue 1, 149 - 160



HER2 positive breast cancer

De-escalation

KATHERINE

Endocrine therapy

Case 1: HER2+

A 43yo pre-menopausal teacher presents with L sided 35mm grade 3 ER negative HER2 positive BC (stage T2 N0 M0). Staging CT scan clear

She commences neoadjuvant docetaxel/carboplatin with pertuzumab & trastuzumab for 6 cycles

Imaging after C3 and C6 show an excellent response to treatment with a radiological CR on MRI

She proceeds to L WLE and SNB

Pathology: complete pathological response with 36mm tumour bed but DCIS present ypTis ypN0. Margins clear

What would you advise next?

(a) Adjuvant radiotherapy and trastuzumab for total of 12 months

(b) Adjuvant Trastuzumab Emtansine after radiotherapy

(c) Adjuvant radiotherapy and phesgo for total of 12 months

(d) Adjuvant radiotherapy, trastuzumab for 12 months & Zoledronic Acid

(e) Adjuvant radiotherapy and trastuzumab for 6 months

What would you advise next?

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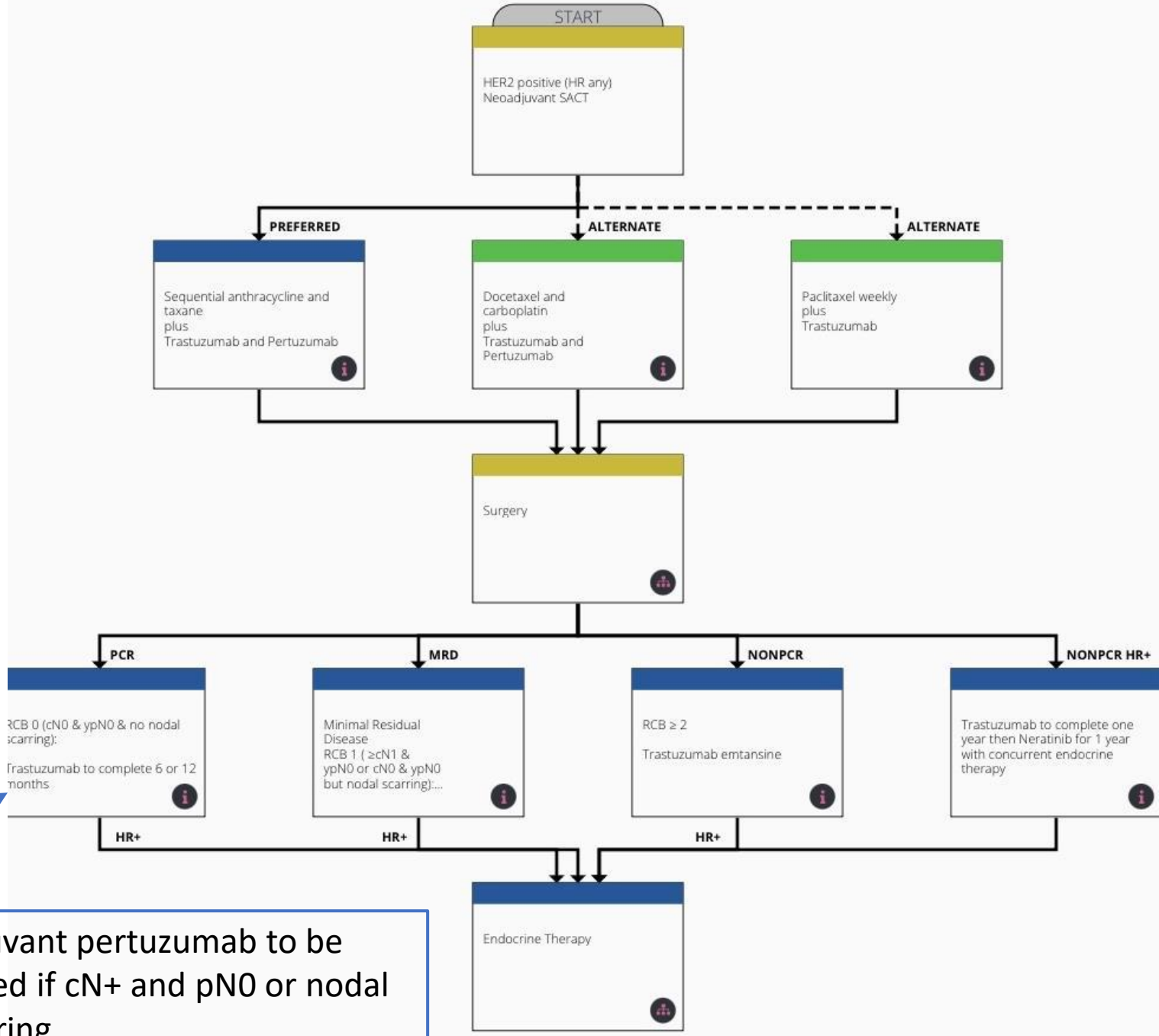
(d) Adjuvant radiotherapy, trastuzumab for 12 months & Zoledronic Ac 

(e) Adjuvant radiotherapy and trastuzumab for 6 months 

Right Decisions app (Scotland)

HER2 positive NACT pathway:



Adjuvant trastuzumab for 6 or 12 months (6 for lower risk)

Adjuvant pertuzumab to be added if cN+ and pN0 or nodal scarring

HER2 RADiCAL

HER2-RADiCAL: A study looking at personalised treatment for early HER2 positive breast cancer

6 versus 12 months of ongoing trastuzumab for moderate risk patients with pCR to NACT

[PERSEPHONE – 6 vs 12 months adjuvant T was non-inferior]
(Earl, Lancet 2019)

What if there had not been a pCR - and pathology showed a 13mm area of residual cancer with 50% cellularity?

(RCB II)

What if there had not been a pCR - and pathology showed a 13mm area of residual cancer with 50% cellularity? (RCB=II)

(a) Adjuvant radiotherapy and trastuzumab for total of 12 months

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(d) Adjuvant radiotherapy, trastuzumab for 12 months & Zoledronic Acid

(e) Adjuvant radiotherapy and trastuzumab for 6 months

What if there had not been a pCR - and pathology showed a 13mm area of residual cancer with 50% cellularity? (RCB=II)

(a) Adjuvant radiotherapy and trastuzumab for total of 12 months

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(c) Adjuvant radiotherapy and phesgo for total of 12 months

(d) Adjuvant radiotherapy, trastuzumab for 12 months & Zoledronic Acid

(e) Adjuvant radiotherapy and trastuzumab for 6 months

KATHERINE trial

KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

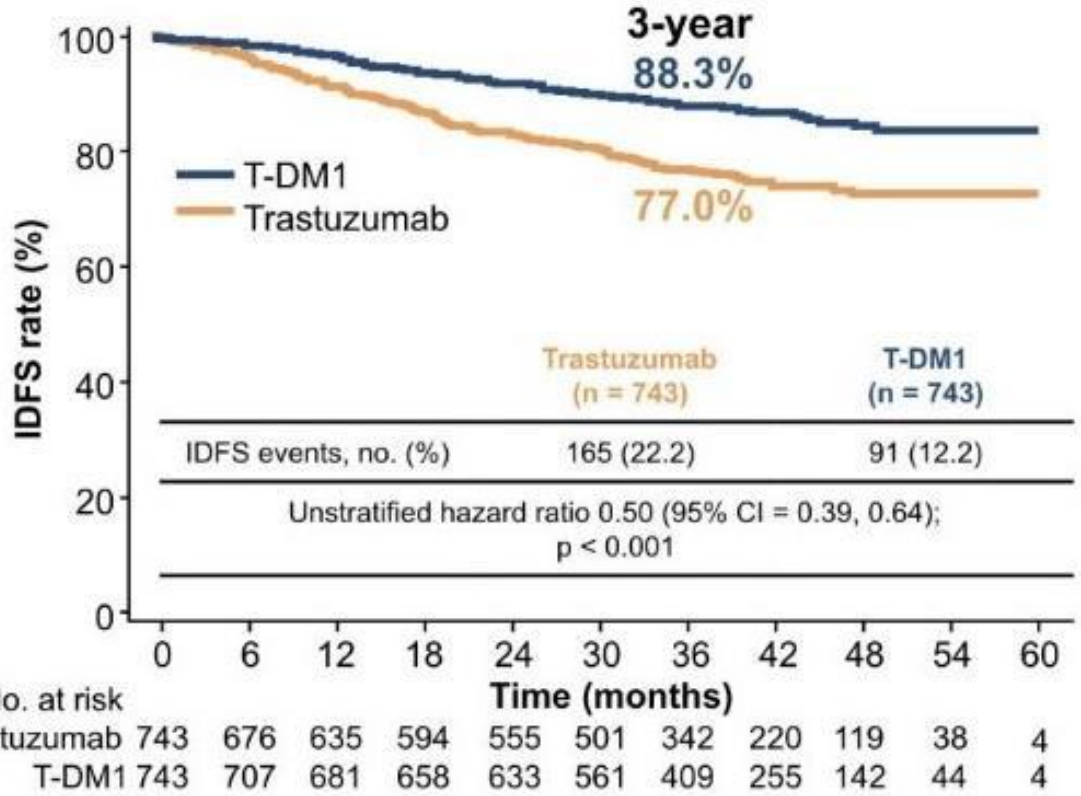
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

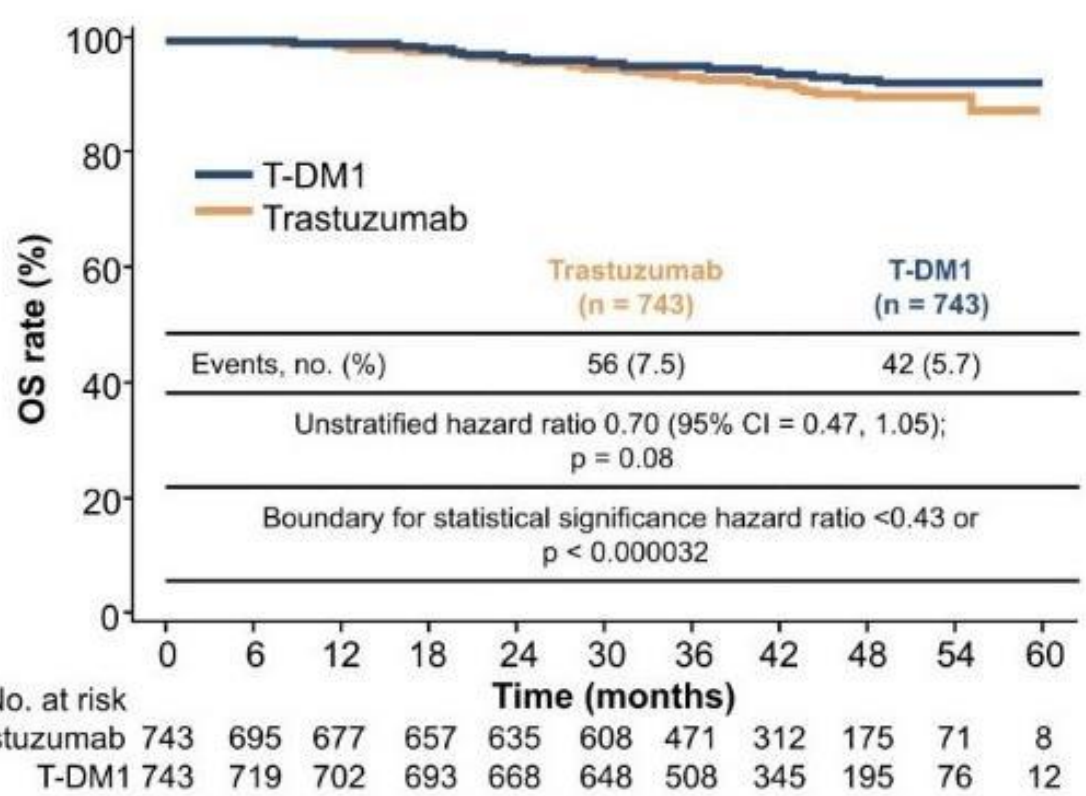
Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

KATHERINE primary analysis (2018)

IDFS



OS

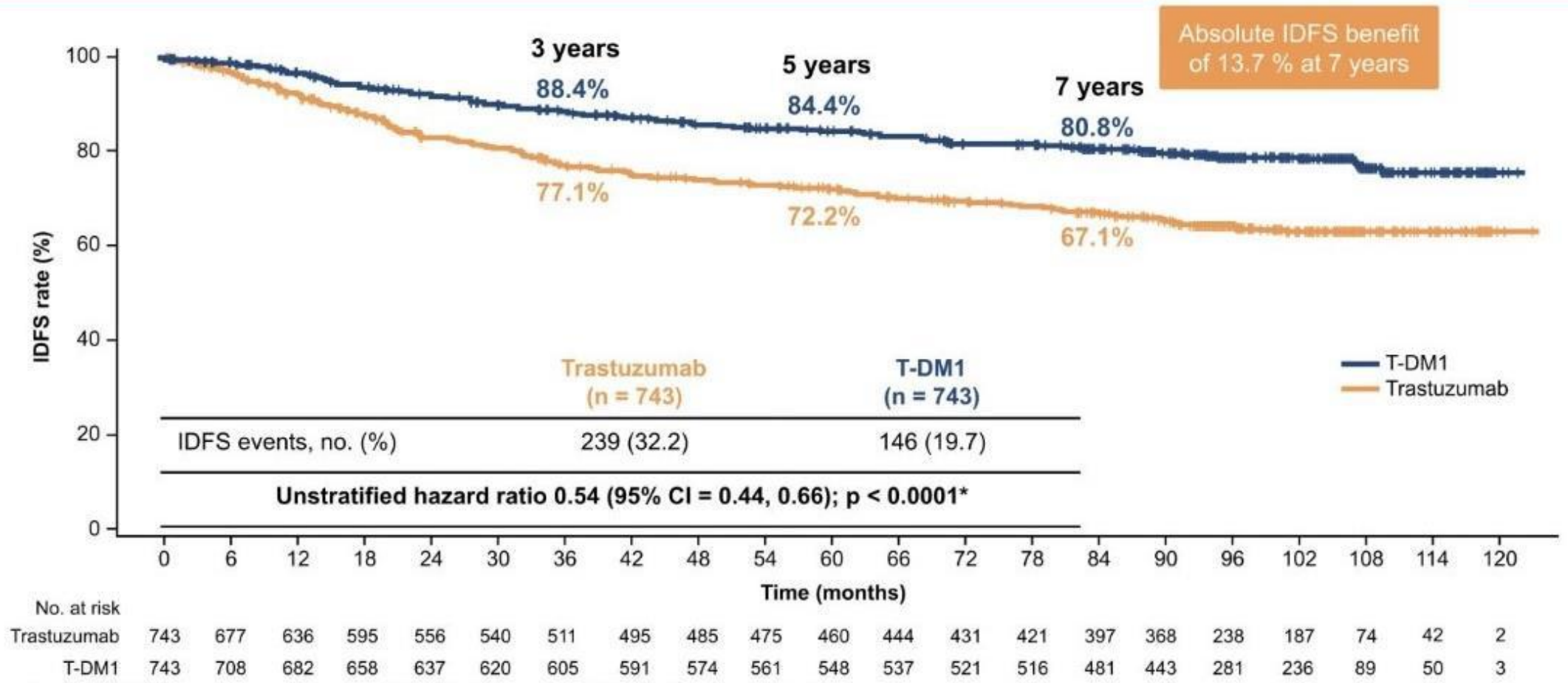


CCOD: July 25, 2018; median follow-up: 41.4 months (T-DM1) and 40.9 months (trastuzumab).
CCOD, clinical cutoff date; CI, confidence interval; IDFS, invasive disease-free survival; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

San Antonio Breast Cancer Symposium®, December 5–9, 2023

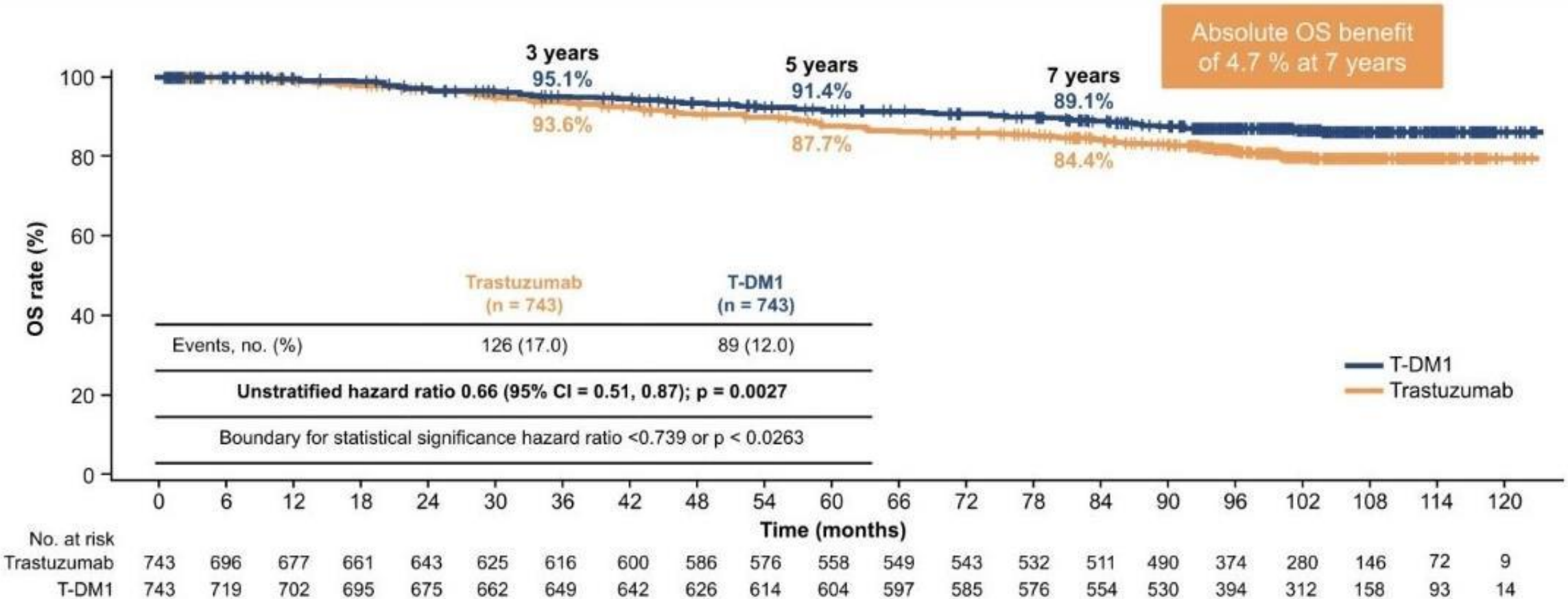
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, Proc SABCS 2023

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)

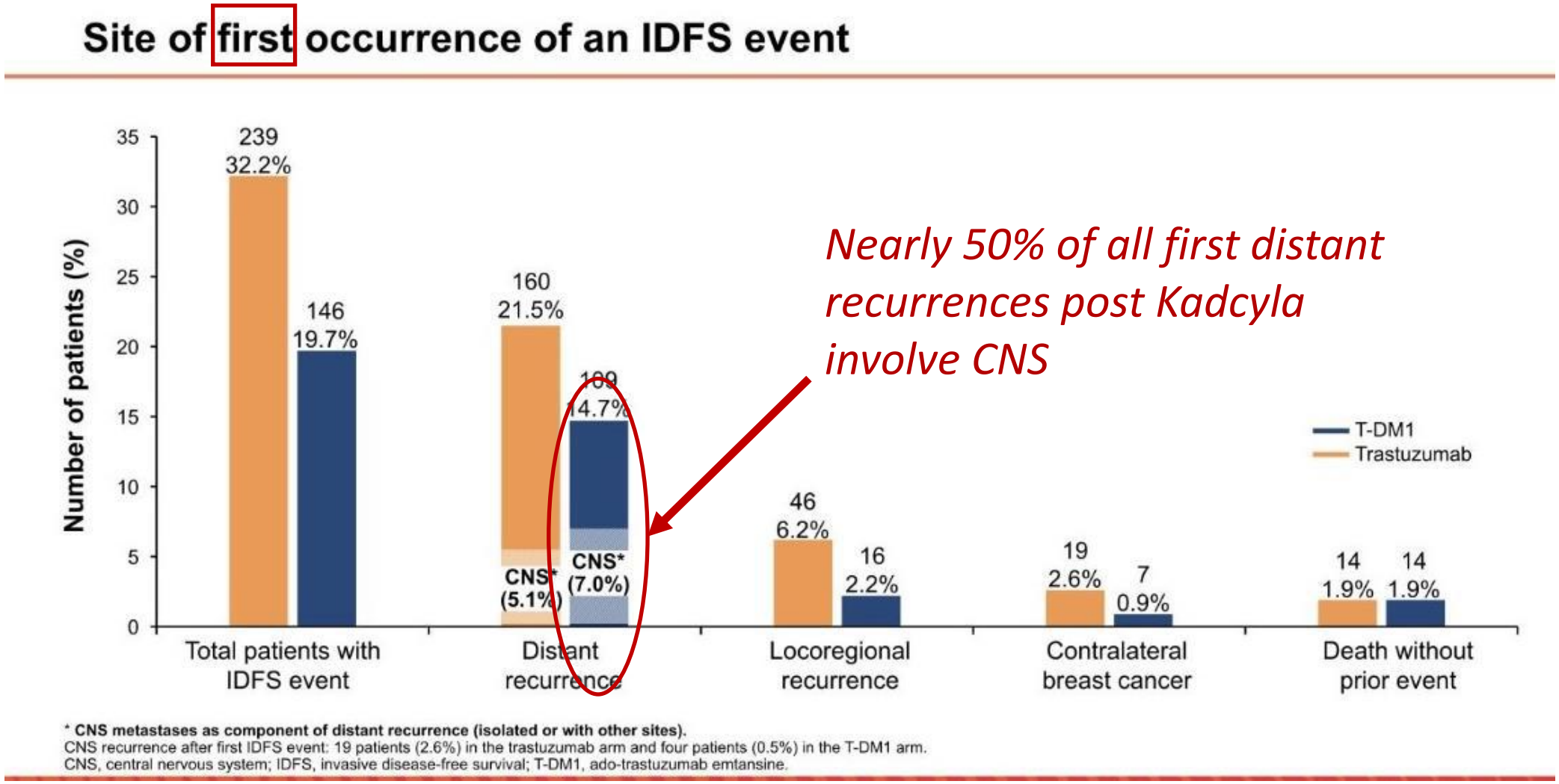


Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, Proc SABCS 2023

Site of first disease recurrence



Nearly 50% of all first distant recurrences post Kadcyla involve CNS

S Loibl, Proc SABCS 2023

De-escalation?

- Next question is whether 14 cycles of Kadcyla is really required for lower residual disease cases…

- Will be limited appetite for a commercial study for this

Endocrine therapy for ER+ HER2+ve disease

- Consider tailoring to risk/biology

- Exploratory analysis of HERA adjuvant Trastuzumab trial presented at ESMO 2024:
- 965 patients: 501 (51.9%) received tamoxifen alone vs 464 (48.1%) received antihormonal therapy with OFS (tamoxifen [n = 269] or exemestane [n = 195])
- OFS group had significantly better 10-year DFS (OFS 70.9% vs. non-OFS 59.6%, p < 0.001) and OS (OFS 84.7% vs. non-OFS 74.0%, p < 0.001)
- Addition of OFS was independently associated with improved prognosis
- Among those receiving OFS, those treated with an AI demonstrated better DFS (HR, 0.44; 95% CI, 0.29-0.68; p < 0.001) and OS (HR, 0.43; 95% CI, 0.18-0.60; p < 0.001)

Mini oral session: Breast cancer, early stage

233MO - Ovarian function suppression in HR-positive, HER2-positive breast cancer: An exploratory analysis from the HERA trial

Moon, S. et al. Annals of Oncology, V35, S310

TNBC

Case 2: TNBC

A 59yo F presents with 30mm G3 TNBC with axillary lymph node enlargement (stage T2 N1 M0). Staging CT scan clear.

She commences neoadjuvant accelerated EC (relative contraindication to immunotherapy)

Unfortunately, after 4 cycles of EC: minimal response in breast on imaging (4w interval between baseline US & C1D1)

MDT decision made to continue with carboplatin and paclitaxel with early repeat imaging. No BRCA1/2 mutations identified.

After 6 weeks of carbo/paclitaxel, imaging shows progression, with tumour enlarging to 55mm in size

Progress

- NACT is discontinued and she proceeds to surgery (L mastectomy and ANC)

- Post-operative pathology: 65mm grade 3 invasive ductal carcinoma with metaplastic features. 1/10 axillary lymph nodes involved but extensive vascular invasion. Residual Cancer Burden (RCB) score III

- Proceeds to adjuvant RT to L chest wall

What would you advise next?

(a) Add adjuvant pembrolizumab (KN522)

(b) Restaging CT scan

(c) Adjuvant capecitabine (CREATE-X)

(d) Clinical trial

(e) Adjuvant Olaparib (OLYMPIA)

(f) Complete carboplatin/paclitaxel

What would you advise next?

(a) Add adjuvant pembrolizumab (KN52

(b) Restaging CT scan

(c) Adjuvant capecitabine (CREATE-X)

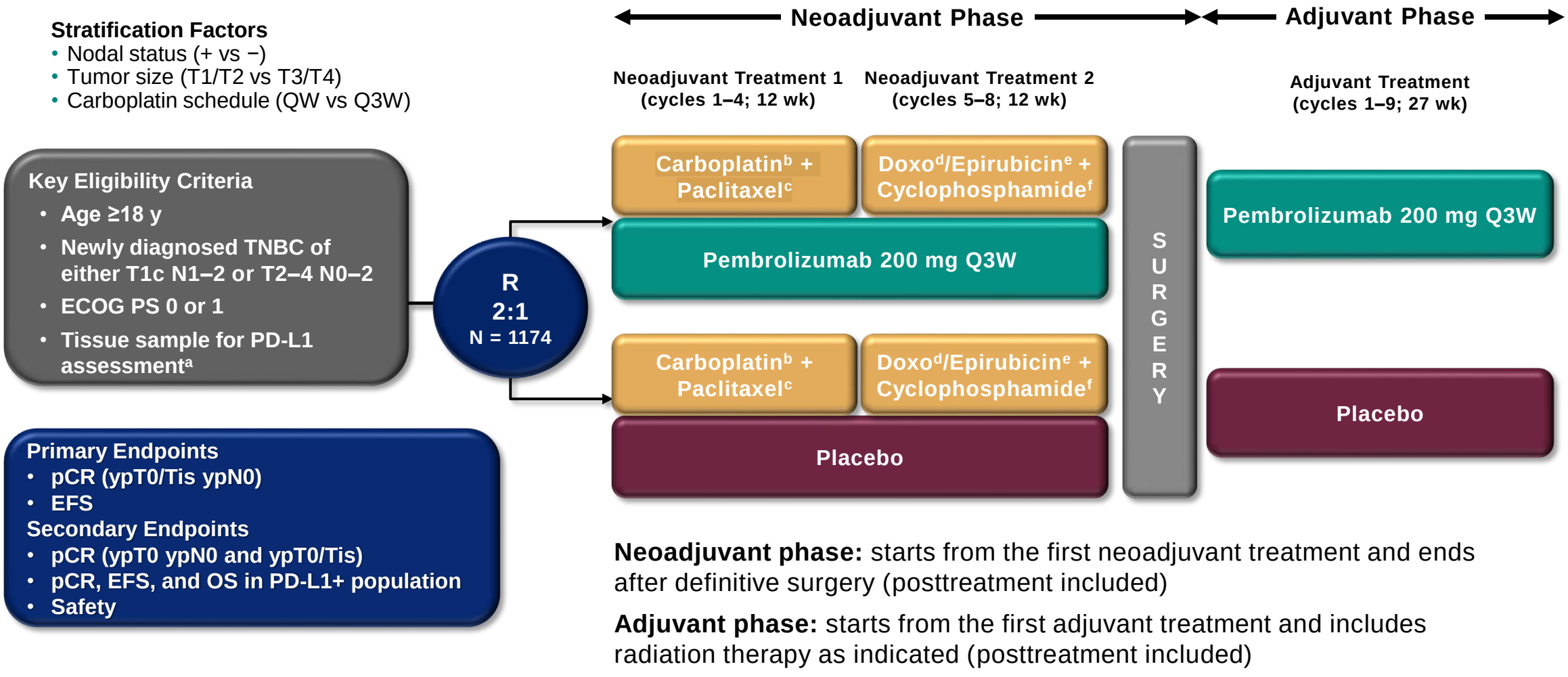
(d) Clinical trial if available

(e) Adjuvant Olaparib (OLYMPIA)

(f) Complete carboplatin/paclitaxel

Can select >1

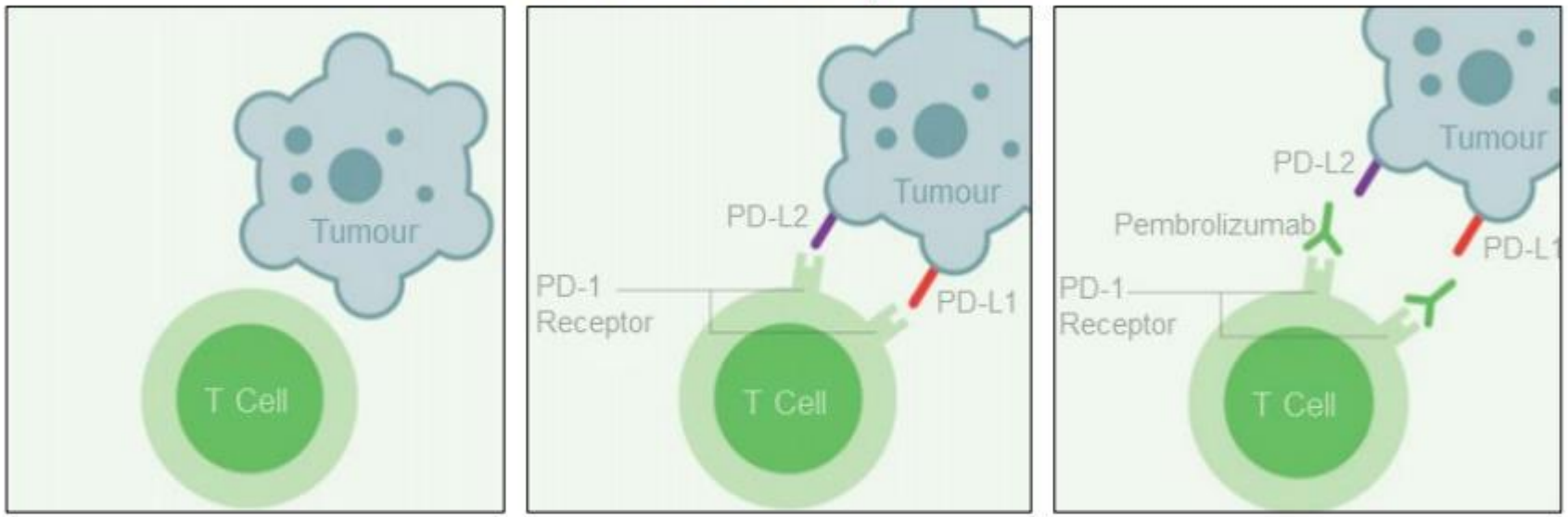
(iii) Neoadjuvant/Adjuvant Pembrolizumab for high risk early TNBC; KEYNOTE522



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

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

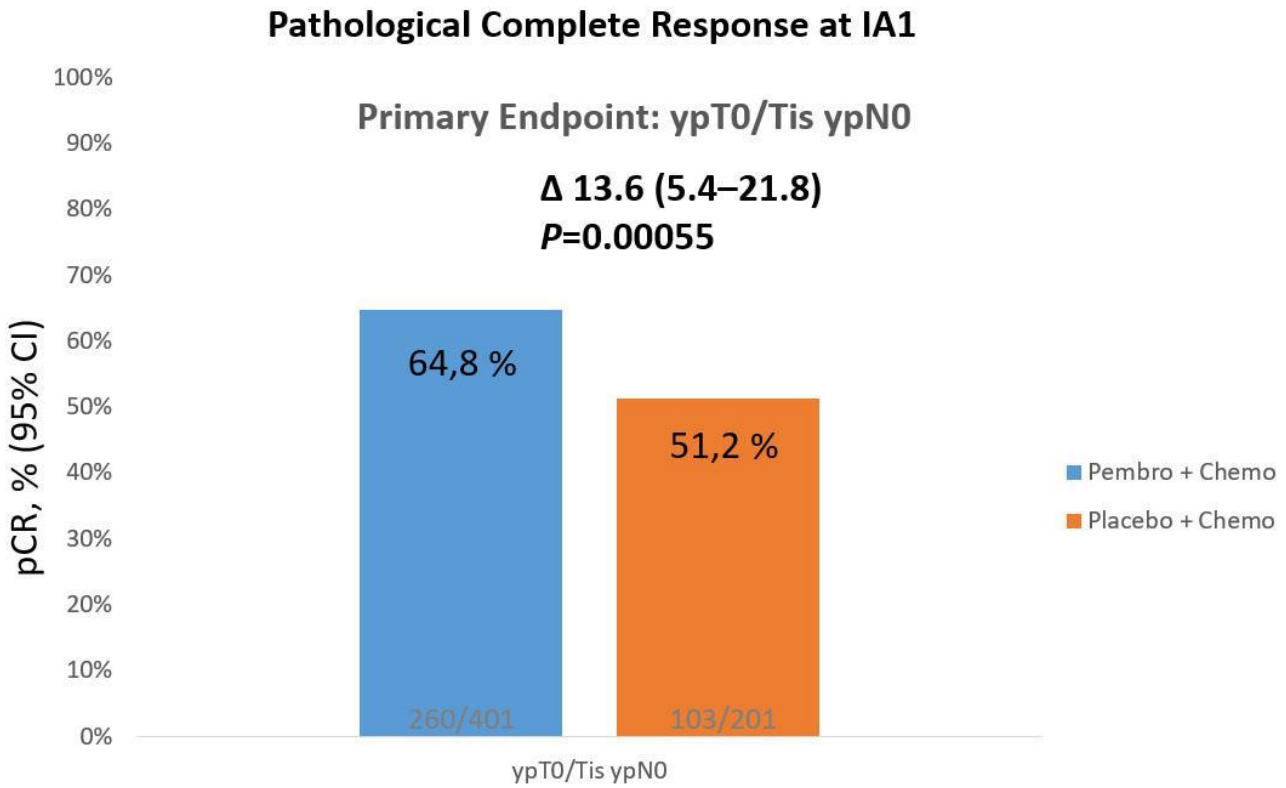
KEYTRUDA activates the anti-tumour immune response



- PD-L1 (and PD-L2) on tumour cells bind to PD-1 on T cells to prevent their activation, leading to immune evasion[1,3]
- KEYTRUDA is a humanised monoclonal antibody that binds to PD-1, blocking its interaction with PD-L1/-L2 and leading to activation of the anti-tumour response[4,5]

Slide courtesy of MSD

KN522 pCR results

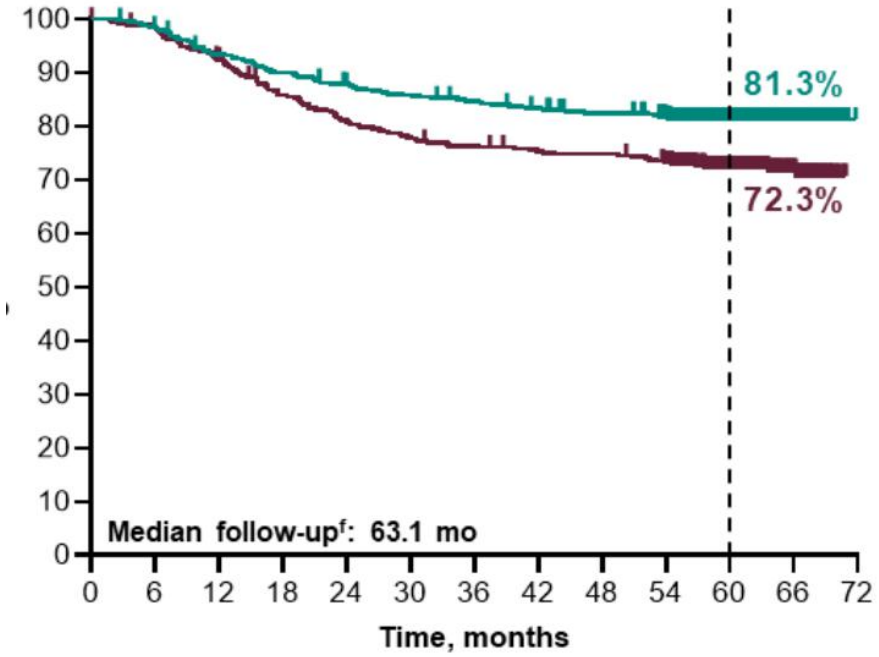


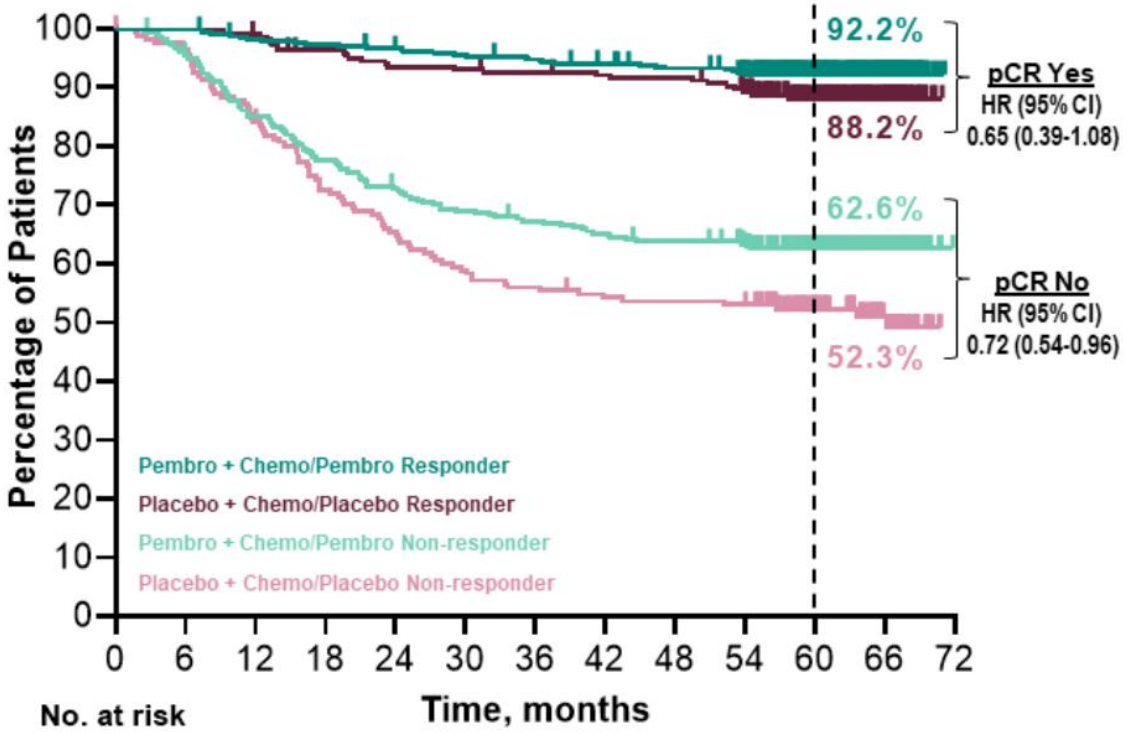
Adaptiert nach: Schmid, P. et al., "KEYNOTE-522: Phase III study of pembrolizumab (pembro)+ chemotherapy (chemo) vs placebo+ chemo as neoadjuvant therapy followed by pembro vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC)." (2018): TPS602-TPS602.

pCR % less in RWE studies (54.5% in US RWE study (Hofherr et al, SABCS 2023)

KN522 results; pCR and EFS at IA6

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



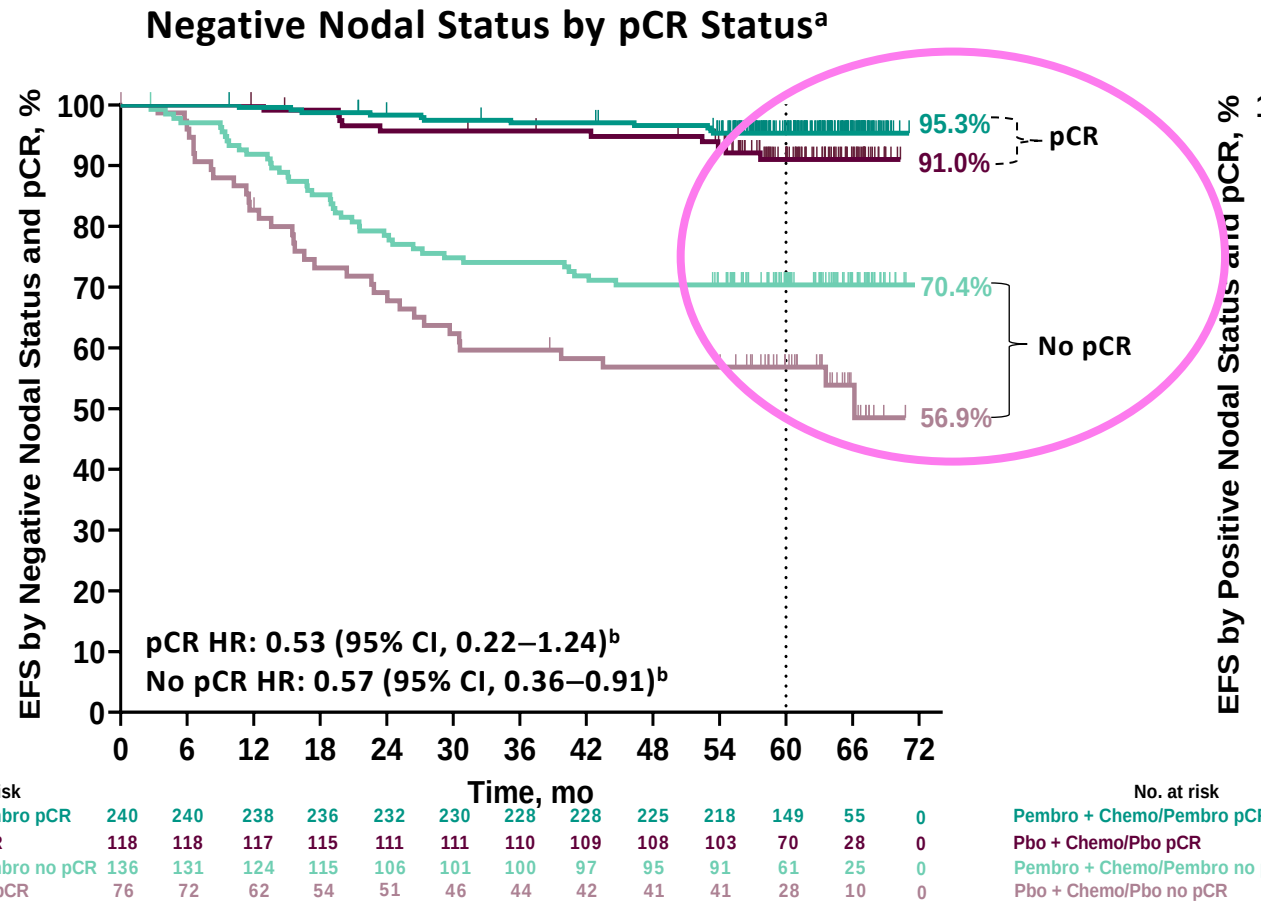


High risk defined as T1c N1-2 or T2-4 N0-2 disease

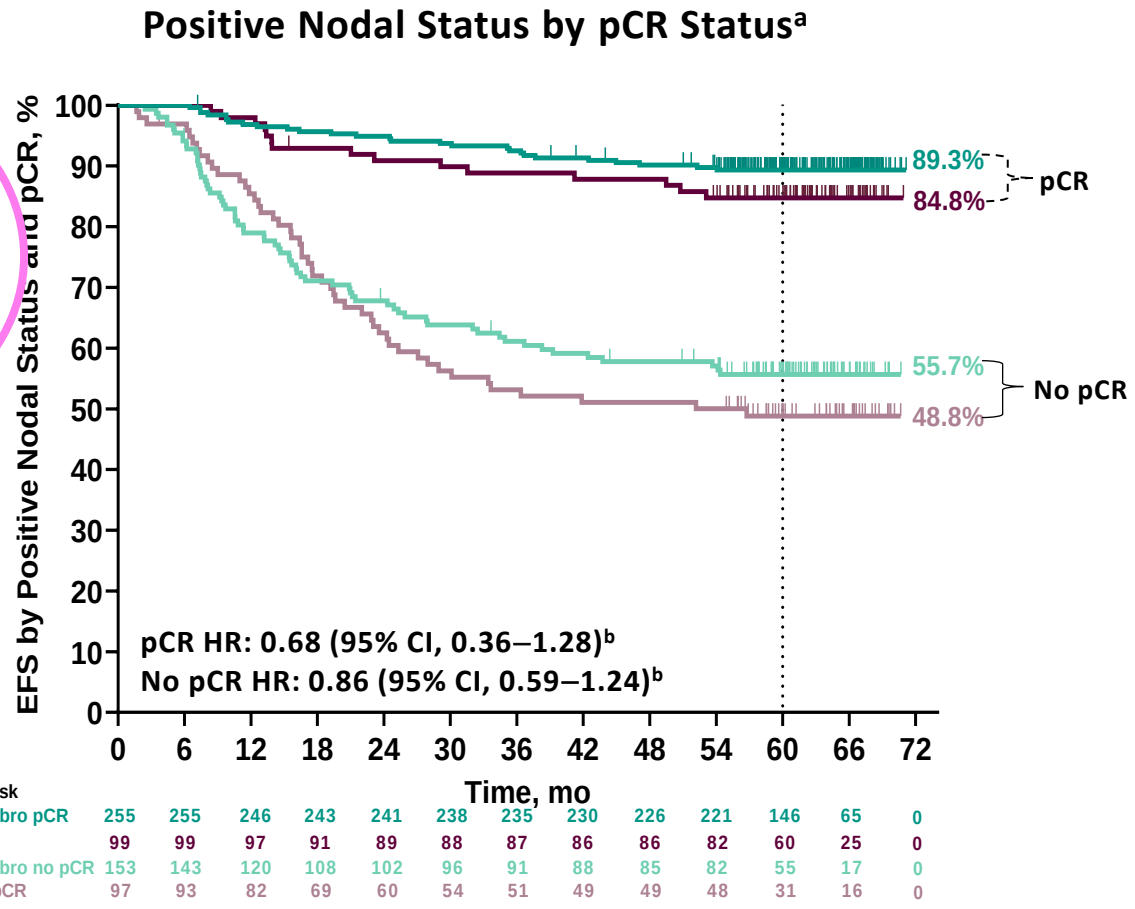
P Schmid et al, Proc ESMO 2023; slides courtesy of MSD

EFS at IA6 by Baseline Clinical Nodal Status

▲ 4% - a "better" pCR



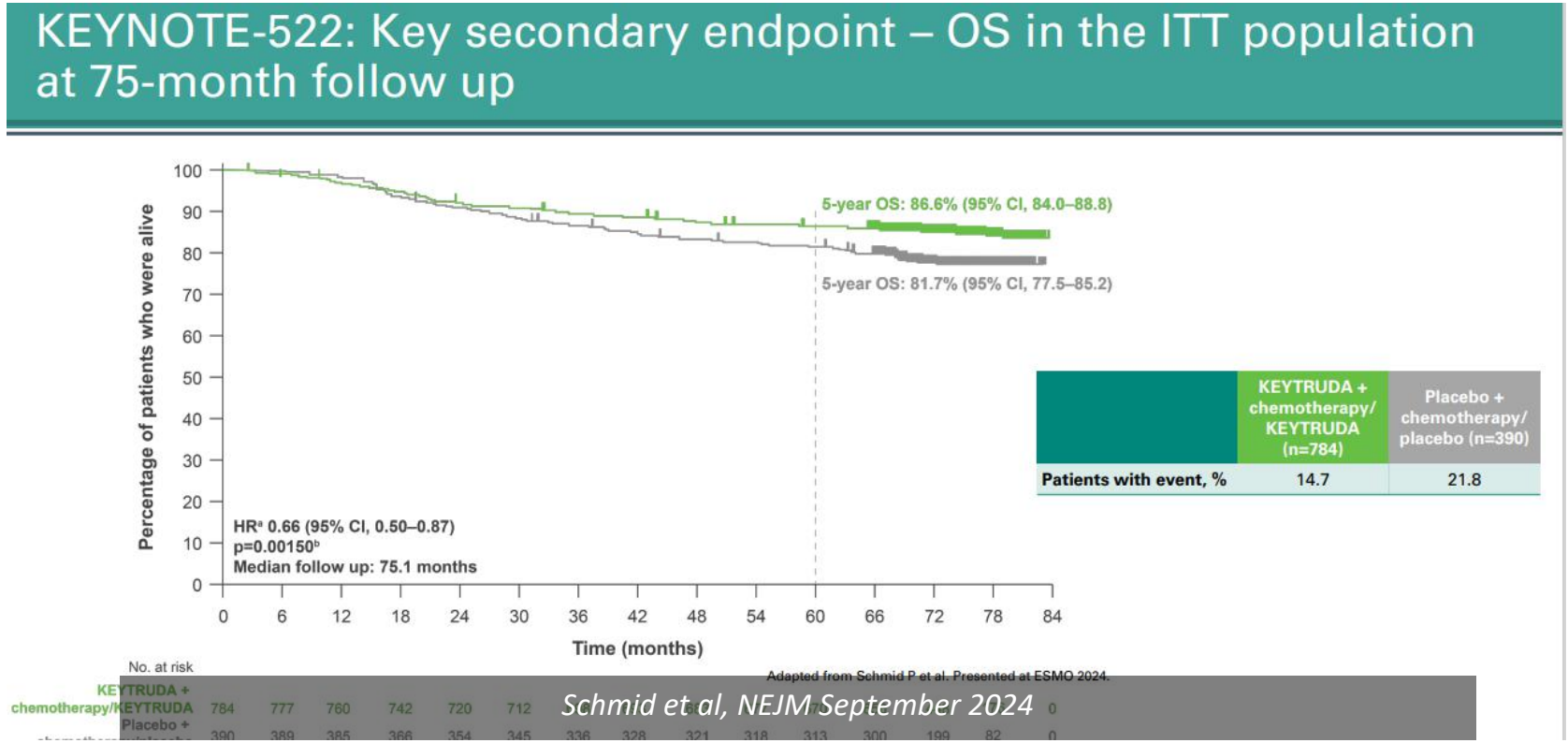
No. at risk													
Pembro + Chemo/Pembro pCR	240	240	238	236	232	230	228	228	225	218	149	55	0
Pbo + Chemo/Pbo pCR	118	118	117	115	111	111	110	109	108	103	70	28	0
Pembro + Chemo/Pembro no pCR	136	131	124	115	106	101	100	97	95	91	61	25	0
Pbo + Chemo/Pbo no pCR	76	72	62	54	51	46	44	42	41	41	28	10	0



No. at risk													
Pembro + Chemo/Pembro pCR	255	255	246	243	241	238	235	230	226	221	146	65	0
Pbo + Chemo/Pbo pCR	99	99	97	91	89	88	87	86	86	82	60	25	0
Pembro + Chemo/Pembro no pCR	153	143	120	108	102	96	91	88	85	82	55	17	0
Pbo + Chemo/Pbo no pCR	97	93	82	69	60	54	51	49	49	48	31	16	0

Overall survival - ESMO 2024

- OS at 60 months was 86.6% (95% CI, 84.0 to 88.8) vs 81.7% (95% CI, 77.5 to 85.2) in the placebo group (P=0.002)



Schmid et al, NEJM September 2024

Safety in KN-522

14.7% G3 irAEs/infusion reactions vs 2%

7.8% Pembro discontinuation rate (vs 1% placebo)

Chemotherapy interruption higher in Pembro arm (11% vs 6%)

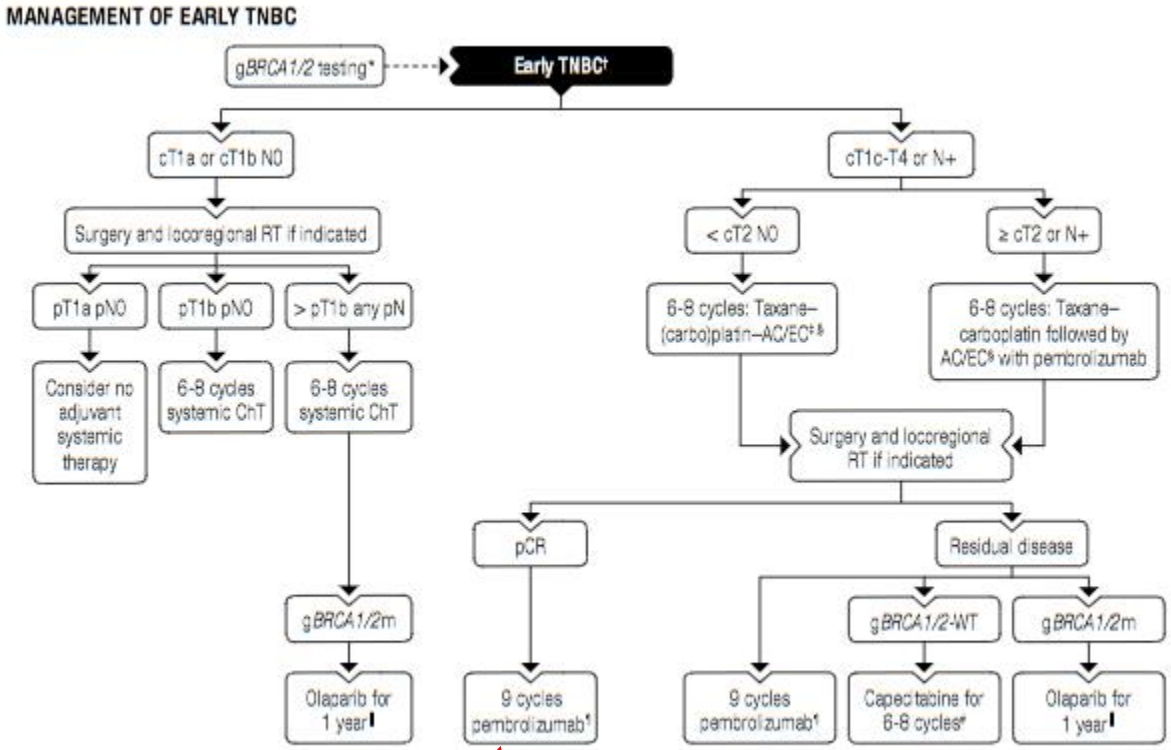
2 immune-related deaths (ILD in neoadjuvant phase and encephalitis in adjuvant phase)

Majority of irAEs occurred in neoadjuvant phase

Cortes, Proc SABCS 2023

Is the adjuvant phase really necessary after a pCR?

- **UK de-escalation study in set-up (Tim Robinson)…watch this space**
- **Significant additional burden on chemotherapy day units**
- ***Toxicity profile means:***
  - More clinic visits
  - More immune-related toxicity = more AO interaction and follow-up



Neoadjuvant Immune Checkpoint Inhibitors Plus Chemotherapy in Early Breast Cancer

A Systematic Review and Meta-Analysis

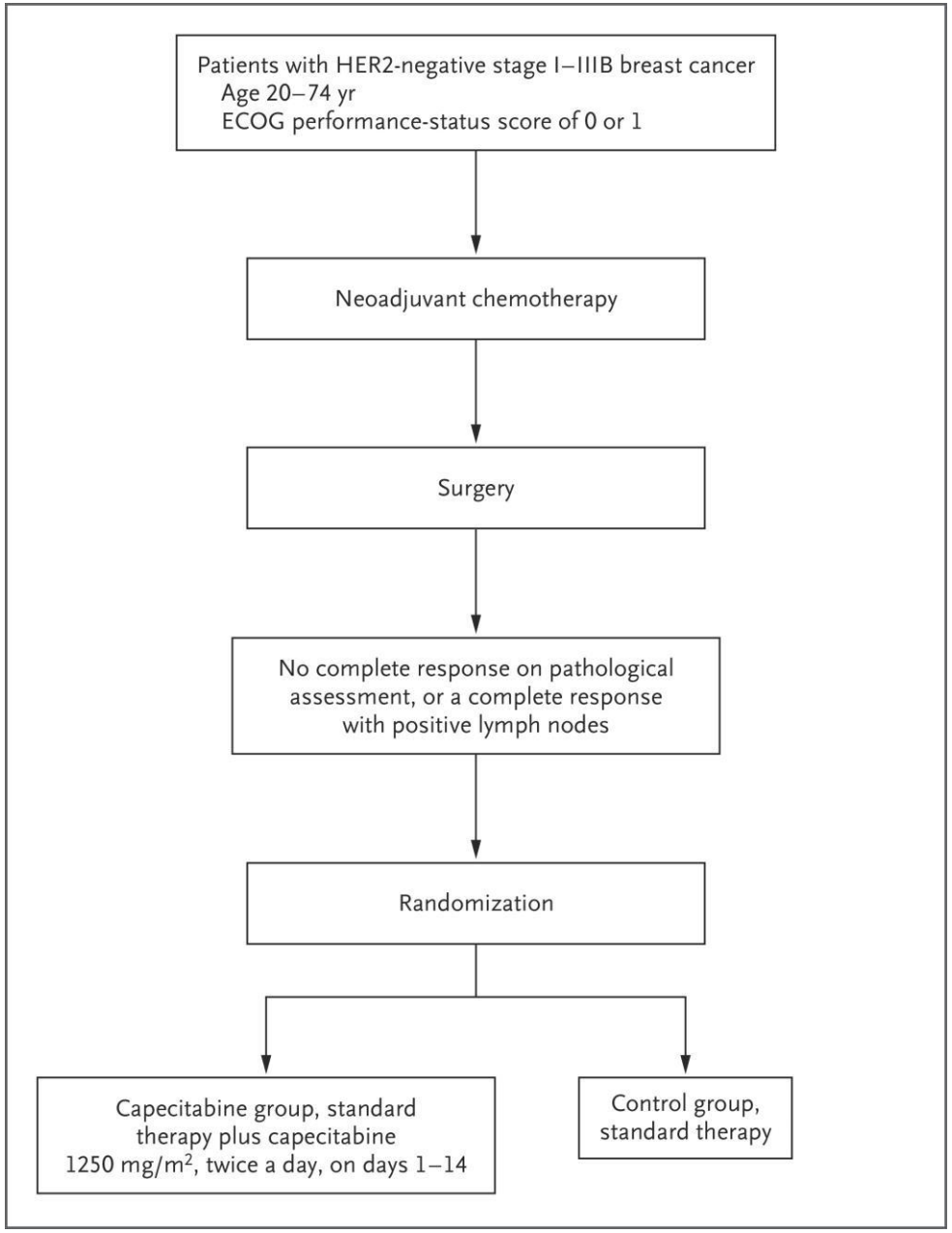
Guillermo Villacampa, MSc[1,2]; Victor Navarro, MSc[2]; Alexios Matikas, MD, PhD[3,4]; et al

ESMO guidelines say yes

CREATE-X

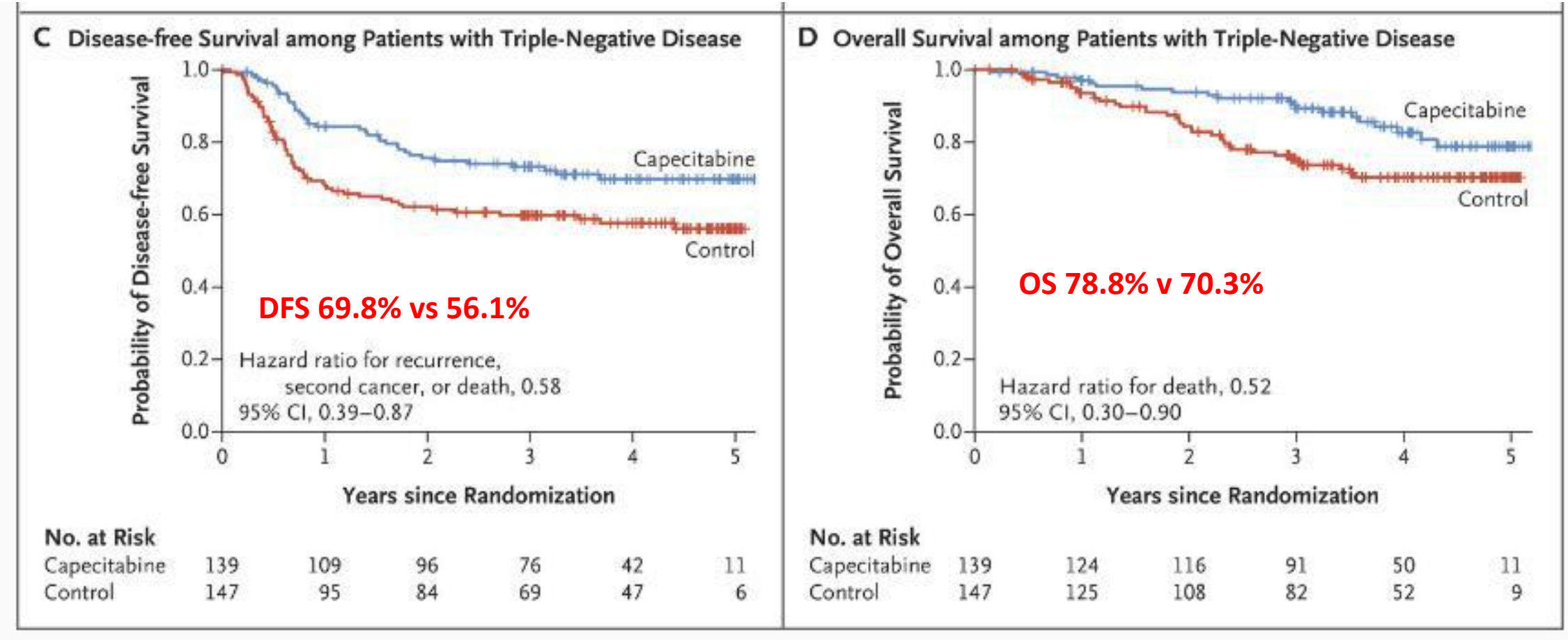
- 910 patients with HER2 negative eBC (31/33% TNBC) in Japan & S Korea
- All received neoadjuvant anthracycline, taxane or both (~94%) with non-pCR

- Randomised to 6 months adjuvant capecitabine or observation



Masuda, N Engl J Med 2017;376:2147-2159

DFS & OS in TNBC cohort

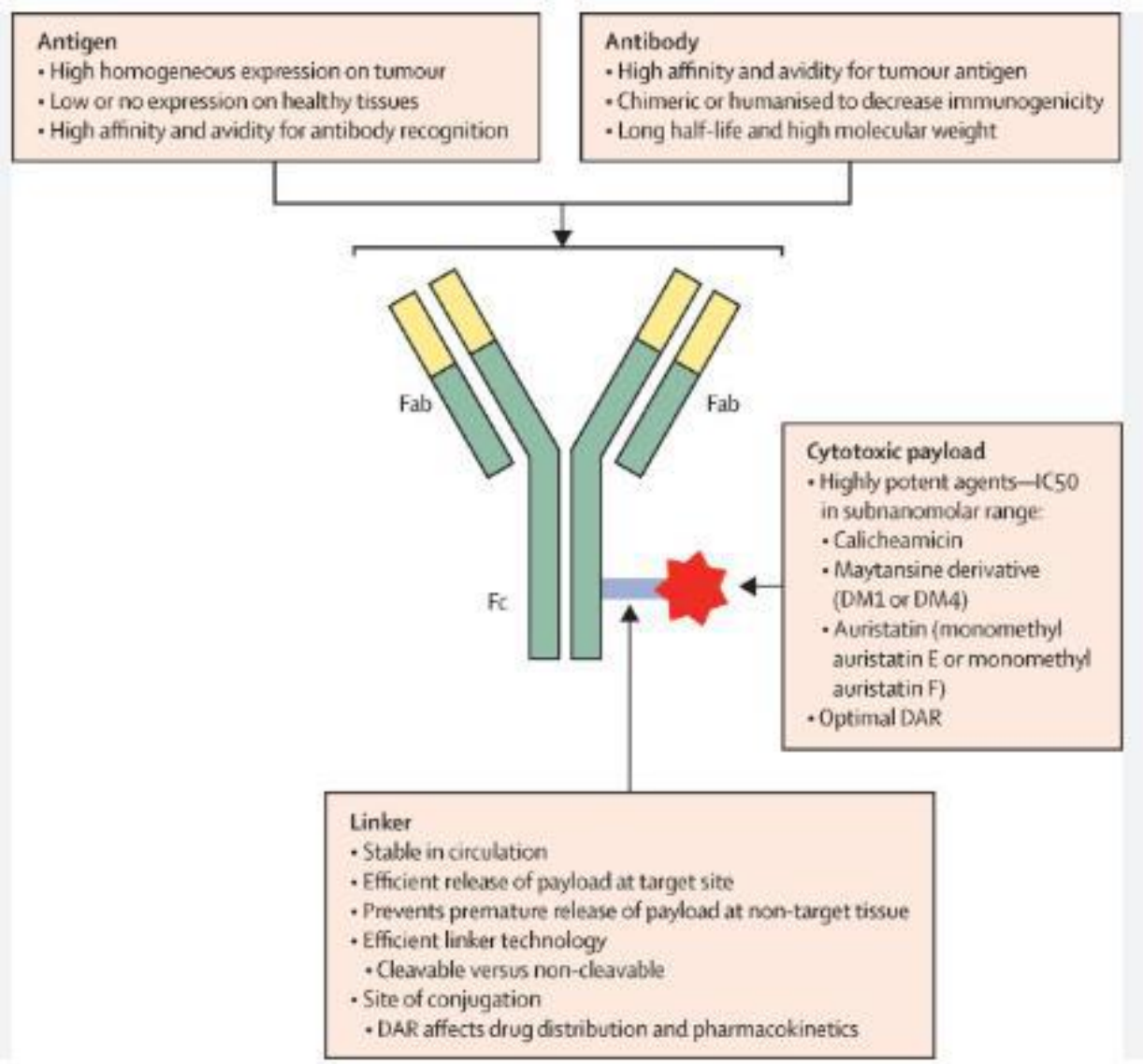


Masuda, N Engl J Med 2017;376:2147-2159

Reflection on CREATE-X

- Not replicated in Western population
- What is the efficacy post carboplatin?
- After carboplatin and Pembrolizumab?

Antibody-Drug Conjugates (ADCs)



- Trastuzumab Emtansine (T-DM1/Kadcyla)
- Trastuzumab Deruxtecan (Enhertu)
- Sacituzumab Govitecan (Trodelvy - TNBC)
- Dato-Deruxtecan (in clinical trials)

Chau, Lancet 2019; Vol 394, Issue 10200, p793-804

Currently recruiting post-NACT ADC studies

- TROPION-breast 03: *A randomized phase III global trial of datopotamab deruxtecan ± durvalumab in patients with TNBC and residual invasive disease at surgical resection after neoadjuvant therapy (AZ)*

- TROFUSE-12– *Sacituzumab Tirumotecan (MK-2870) Plus Pembrolizumab Versus TPC in TNBC Who Did Not Achieve pCR (MSD)*

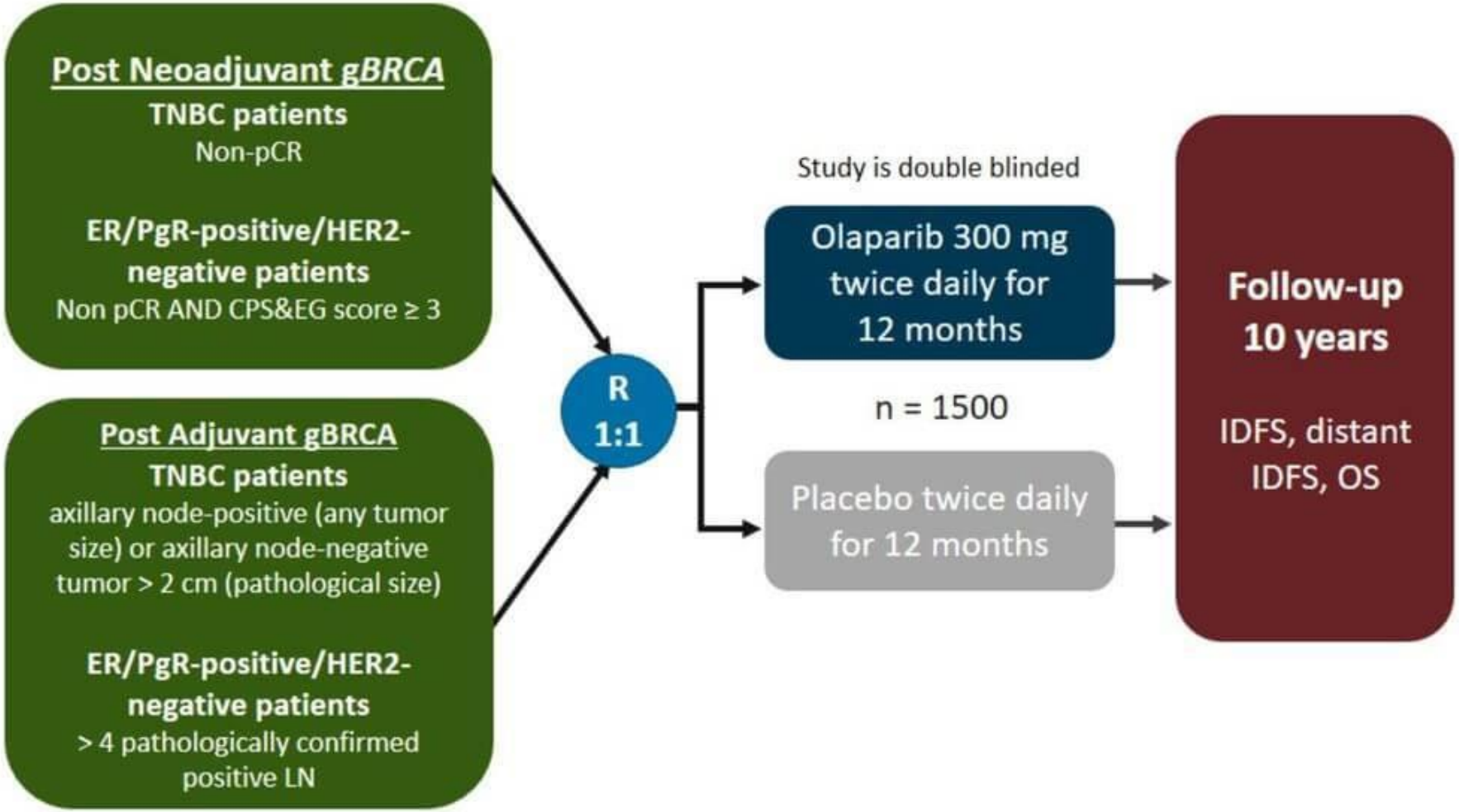
- ASCENT 5: *A phase 3, randomized, open-label study of adjuvant sacituzumab govitecan (SG) + pembrolizumab (pembro) vs pembro ± capecitabine (cape) in patients (pts) with TNBC and residual disease after neoadjuvant therapy (NAT) and surgery (Gilead)*

Watch this space….

=Edinburgh

OLYMPIA

OlympiA: Phase 3 Study of Olaparib vs Placebo as Adjuvant Treatment in g*BRCA* and High-Risk HER2-Negative Primary Breast Cancer



ClinicalTrials.gov. NCT02032823.

What is the definition of ‘high risk’?

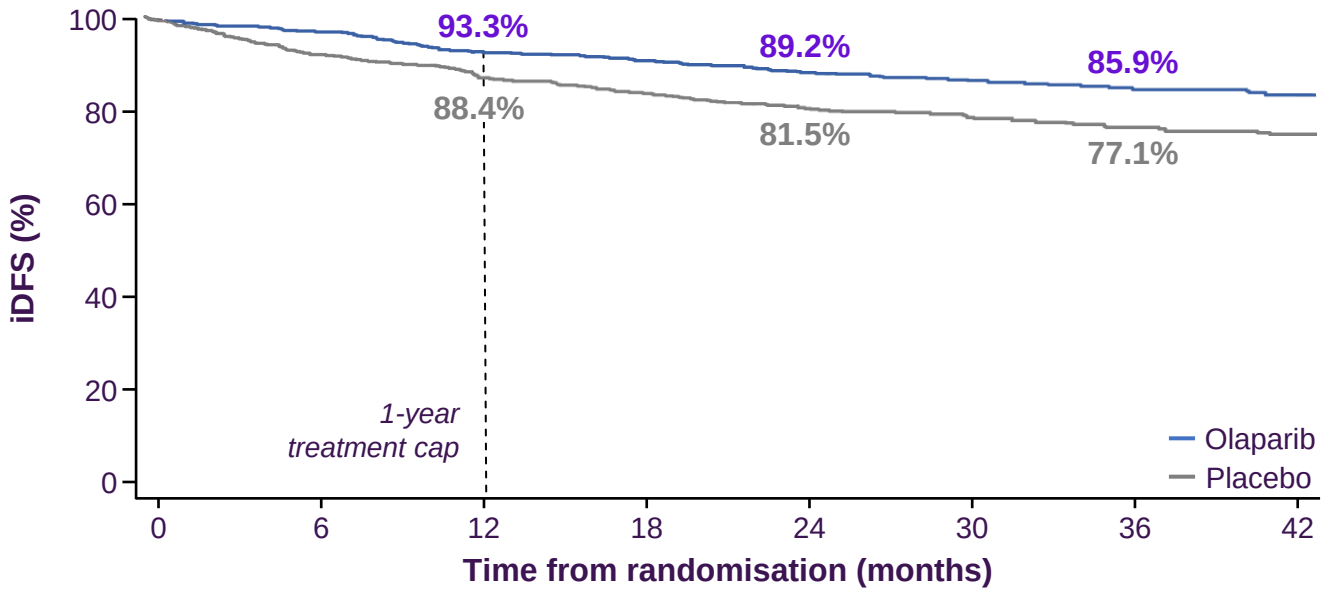
- All patients must have received at least 6 cycles of anthracycline and/or taxane based CT
- No concomitant adjuvant pembrolizumab, capecitabine or abemaciclib allowed

HER2 negative	Prior therapy	High risk criteria
TNBC	Neoadjuvant	Non-PCR
	Adjuvant	≥pT2 or ≥pN1
ER+	Neoadjuvant	Non-PCR & CPS + EG score* ≥3
	Adjuvant	≥pN2

**CPS&EG scoring system; score 0 for clinical stage 0-IIA, 1 for stages IIB and IIIA, 2 for stages IIIB and IIIC (AJCC staging); Pathological stage: 0 for stages 0 and I, 1 for stages IIA-IIIB, 2 for stage IIIC (AJCC staging); Receptor status: 0 for ER positive, 1 for ER negative; Nuclear grade: 0 for nuclear grade 1-2, 1 for nuclear grade 3*

OlympiA iDFS results

Olaparib significantly reduced the relative risk of invasive disease or death by 42% vs. placebo



No. at risk								
Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

iDFS[a]

Hazard ratio:
0.58[b]
99.5% CI: 0.41, 0.82
P<0.001

3-year iDFS rate

Olaparib (n=921)	**85.9%**
Placebo (n=915)	**77.1%**

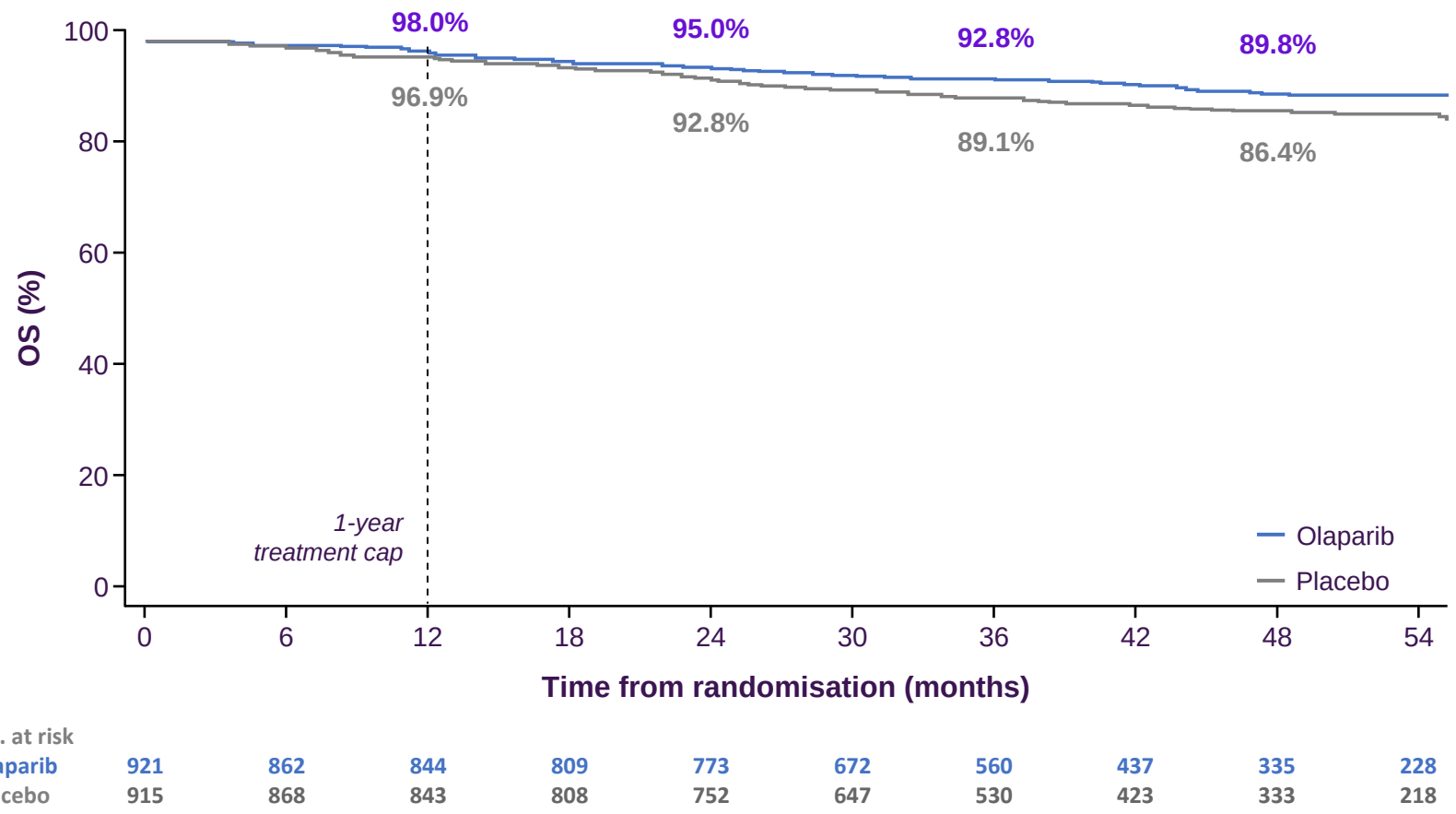
Difference: 8.8%
95% CI: 4.5, 13.0

For the HR-positive/HER2-negative subtype, the 3-year iDFS was 83.5% with olaparib vs. 77.2% with placebo (hazard ratio 0.70; 95% CI, 0.38–1.27) with no statistical evidence of divergence from the overall ITT population vs. placebo[1,2]

Adapted from Tutt ANJ et al. 2021

OlympiA OS results

Significant OS benefit compared with placebo at planned event driven OS analysis



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

4-year OS[a]

Hazard ratio:
0.68[b]
98.5% CI: 0.47, 0.97
P=0.009

4-year OS rate

Olaparib (n=921)	**89.8%**
Placebo (n=915)	**86.4%**

Difference: 3.4%
95% CI: −0.1, 6.8

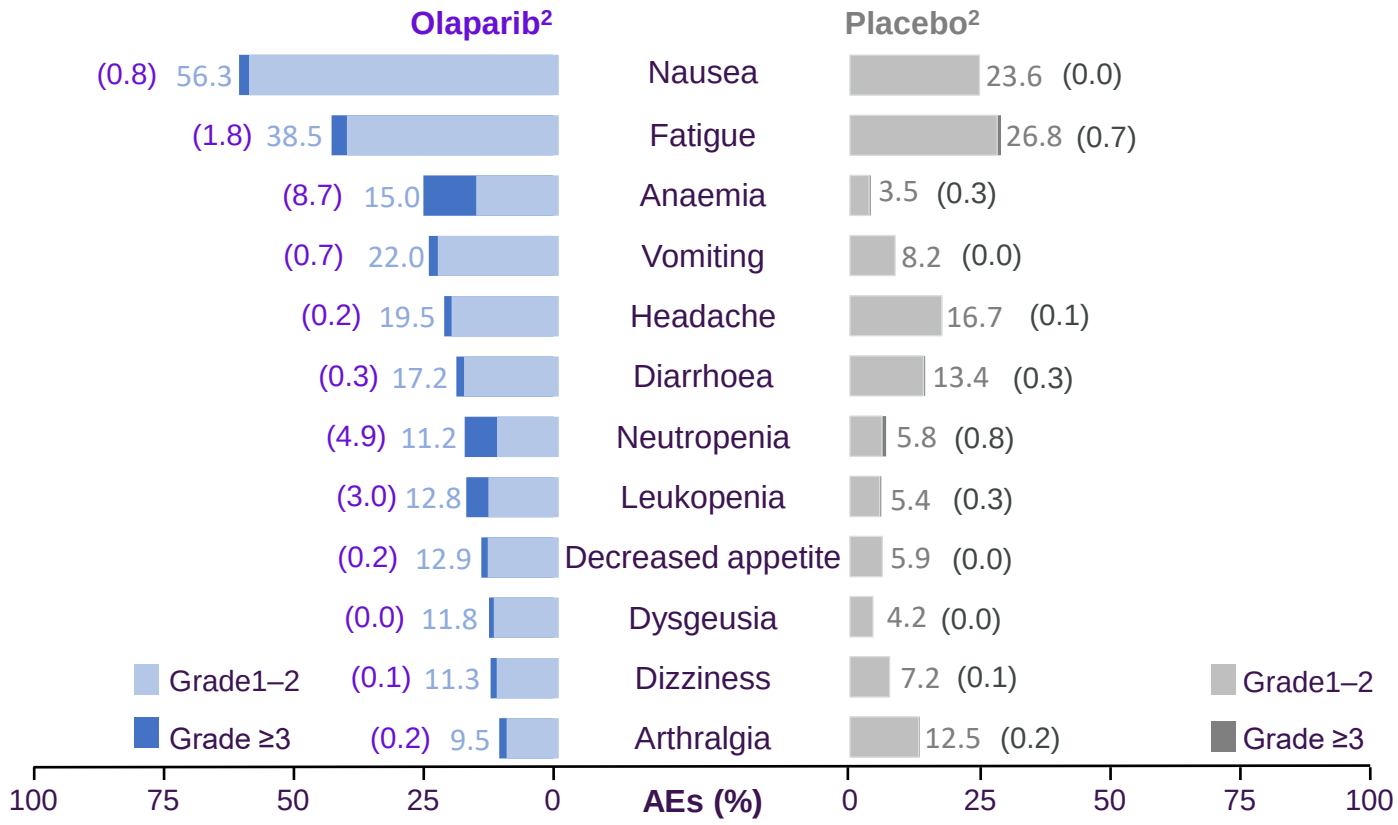
Adapted from Geyer JR et al. 2022

[a]Data cut-off:12 July 2021; median follow-up in ITT population was 3.5 years; [b]Non-proportional hazards; 98.5% CI is shown for the hazard ratio for OS because *P*<0.015 is required to indicate statistical significance for this endpoint.
CI, confidence interval; iDFS, invasive disease-free survival; ITT, intent-to-treat; OS, overall survival.
Geyer Jr CE, et al. *Ann Oncol* 2022;33:1250–1268.

Safety profile

Consistent with other trials, with the majority of AEs being Grade 1 or 2

AE, n (%)1[a]	Olaparib n=911	Placebo n=904
Any AE	836 (91.8)	758 (83.8)
Serious AE	79 (8.7)	78 (8.6)
AE of special interest[b]	31 (3.4)	51 (5.6)
MDS/AML	2 (0.2)	3 (0.3)
Pneumonitis	9 (1.0)	12 (1.3)
New primary malignancy	21 (2.3)	36 (4.0)
Grade ≥3 AE	223 (24.5)	102 (11.3)
Grade 4 AE[c]	17 (1.9)	4 (0.4)
AE leading to permanent discontinuation of treatment	98 (10.8)	42 (4.6)
AE leading to death[d]	1 (0.1)	2 (0.2)



1. Geyer CE Jr, et al. *Ann Oncol* 2022;33:1250–1268; 2. Tutt ANJ, et al. *N Engl J Med*. 2021;384:2394–2405.

Case discussion

- Very early progression/recurrence and treatment refractory – **bad biology**

- Metaplastic breast cancers (~1% of BC) often respond poorly to chemotherapy *?appropriate for NACT approach*
  - *vs gBRCA1/2 or basal subtypes which tend to respond well*

- This disease is already refractory to anthracycline, taxane and platinum therapy

Long term safety; Ovarian data

SOLO1 (2 years maintenance Olaparib or placebo for EOC;
In the 7-year FU period, 4 (1.5%) cases of myelodysplastic syndrome/AML reported in olaparib group vs 1 (0.8%) in the placebo group[1]

New primary malignancies reported in 14 (5.4%) Olaparib arm vs 8 (6.2%) placebo group[1]

Study 19 (n=265), at 78mo FU, 2 patients had MDS/AML in olaparib group vs 0 in placebo (NB 11% of pts stayed on treatment for >6years)

1, DiSilvestro et al, Proc ESMO 2022; 2: Friedlander et al, Br J Cancer. 2018 Oct 30; 119(9): 1075–1085

Phase III trials for TNBC to watch

- *?What role will ADCs play in neoadj/adj/post-NACT setting?*

RESPONSE ⟺ TOXICITY

- *TROPION-breast 04:* A chemo-free NACT option of Dato-DxD plus durvalumab vs KEYNOTE 522 regimen
  - for TNBC and ER low HER2 negative eBC
  - MK2870 (anti-TROP2 ADC) similar study?
- Neoadjuvant PARP inhibitor studies in gBRCA1/2 associated BC
  - Small phase IIs reported/ongoing eg NOBLE EORTC study of Olaparib +/- durvalumab
  - Neoadj Talazoparib 24 week single arm phase II – pCR rate 45.8% *(Litton, Oncologist 2023; 28(10): 845-855)*
  - *PARTNER* trial of neoadjuvant carbo/pac +/- Olaparib - negative study in 559 gBRCAwt patients with TNBC *(Abraham et al, Nature 2024: 629: 1142-1148)*

Case 3: ER positive HER2 negative BC

A 48yo F presents with a 3.5cm left breast mass to the breast clinic. No family history of note and fit and well.

Imaging shows a 32mm mass with multiple enlarged axillary lymph nodes. Staging CT scan is clear.

Pathology confirms grade 3 ER5 PR3 HER2 1+ (neg) NST ductal breast cancer with axilla + on biopsy

On examination, the tumour is - just - still conservable

What would you advise the MDT?

(a) Neoadjuvant EC-paclitaxel

(b) Surgery with left WLE and ANC

(c) Neoadjuvant letrozole first

(d) Neoadjuvant EC/Paclitaxel with pembrolizumab

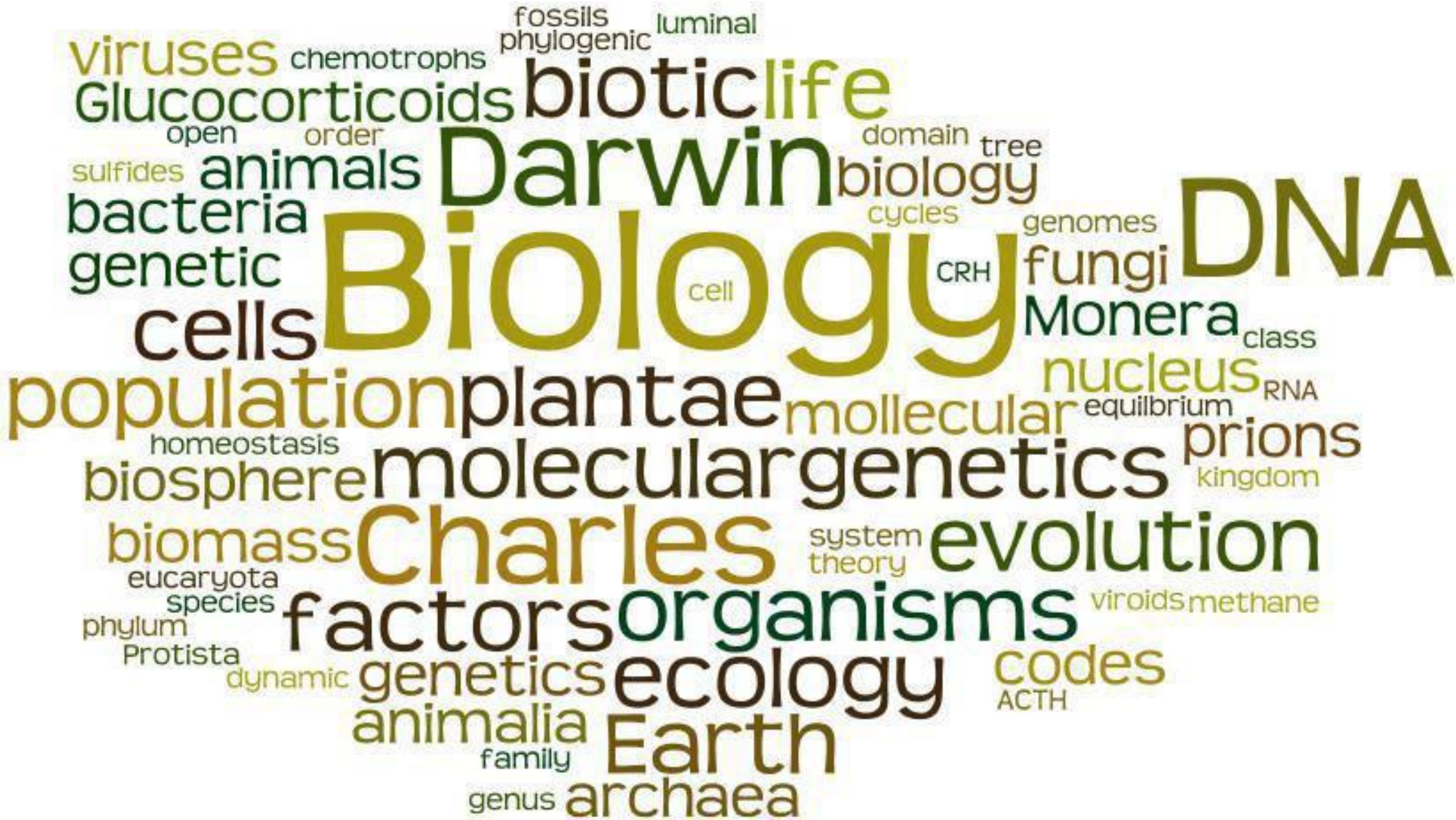
What if it was grade 2 ER8 PR8?

(a) Neoadjuvant EC-paclitaxel

(b) Surgery with left WLE and ANC

(c) Neoadjuvant letrozole first

(d) Neoadjuvant EC/Paclitaxel with pembrolizumab


fossils
luminal
phylogenic
viruses
chemotrophs
biotic
life
Glucocorticoids
open
order
domain
tree
Darwin
sulfides
animals
biology
bacteria
cycles
genomes
DNA
Biology
genetic
CRH
fungi
cell
cells
Monera
class
nucleus
population
plantae
RNA
mollecular
equilbrium
homeostasis
prions
biosphere
molecular
genetics
kingdom
biomass
Charles
system
theory
evolution
eucaryota
species
viroids
methane
factors
organisms
phylum
Protista
dynamic
genetics
ecology
codes
ACTH
animalia
Earth
family
genus
archaea

High-risk HER2-negative eBC[1–3]

ER-positive / HER2-negative

Neoadjuvant phase

Neoadjuvant chemotherapy
(anthracycline/taxane ± platinum)

TNBC

~~Neoadjuvant chemotherapy (anthracycline/taxane ± platinum) + pembrolizumab~~

Surgery
(lumpectomy or mastectomy, with or without radiotherapy)

Adjuvant phase

- *ET*
- *Bisphosphonates in certain patients**

Adjuvant chemotherapy
(anthracycline/taxane ± platinum)

Abemaciclib + ET

Olaparib for high-risk BRCAm patients[6]
(for up to 12 months)

Capecitabine[4,5†]

Pembrolizumab

Follow-up
(annual mammogram until patient enters national screening programme)

Diagram: Astra Zeneca

Neoadjuvant IO in ER+ breast cancer: Keynote 756 & Checkmate 7FL

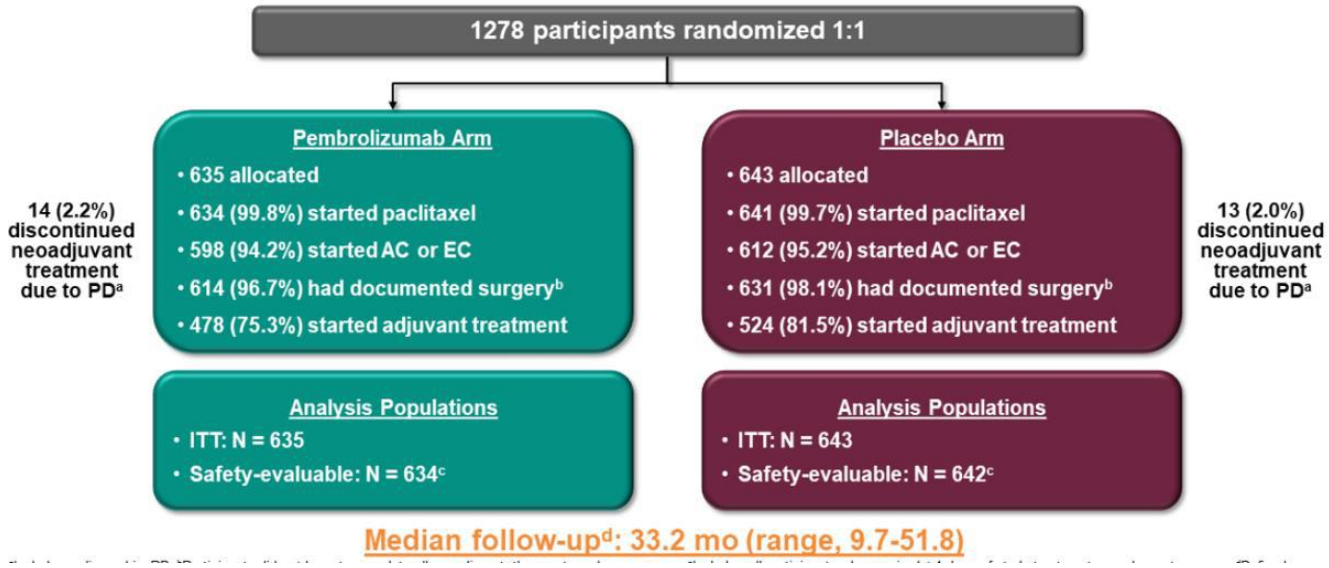


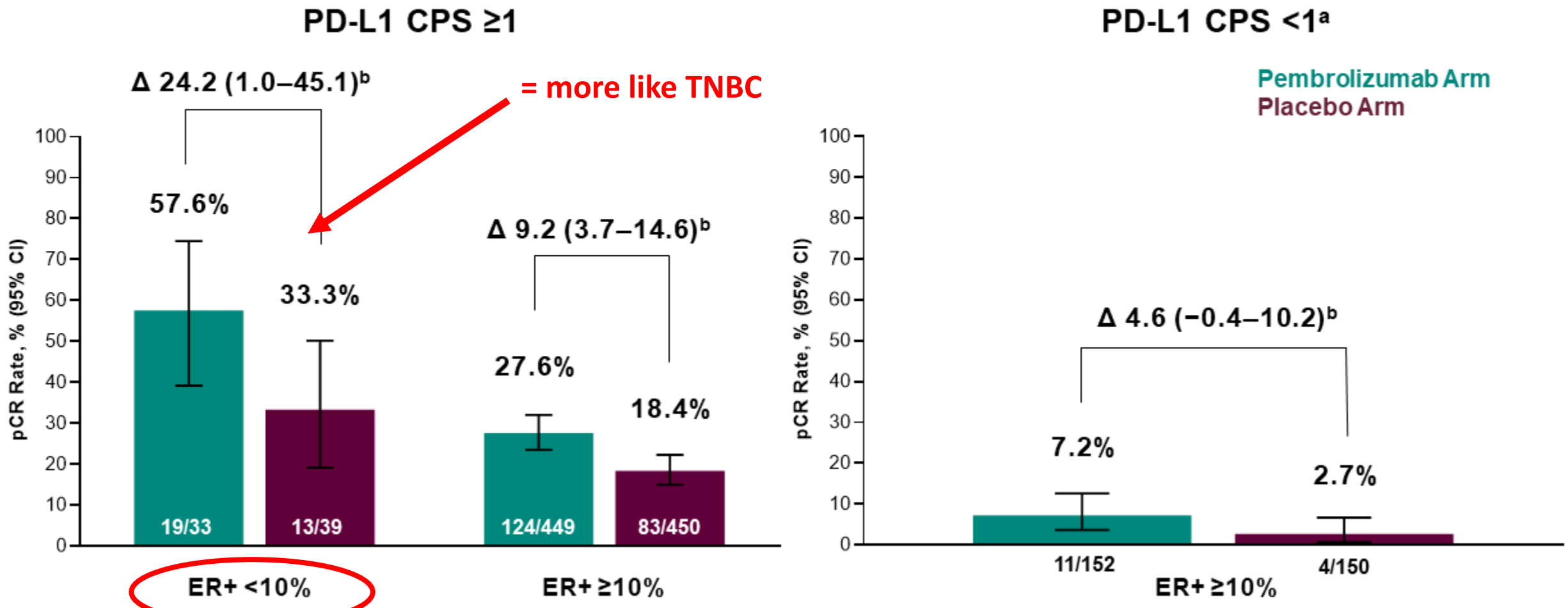
Table 1: Summary of similarities and differences between the trial designs

Element	Similarities	Differences
Trial design	Phase 3, PBO-controlled RCTs evaluating neoadjuvant/ adjuvant PD-L1 inhibitors in combination with the same NACT regimen for high-risk HR+/HER2- eBC	• PD-L1 inhibitors: pembrolizumab vs nivolumab • KEYNOTE-756 enrolled twice as many patients
Eligibility criteria	Overall similar: Patients with high-risk HR+/HER2- eBC	Enrolment criteria: • CheckMate-7FL: Grade 2/3, T1c–T2/N1–2 or T3/T4 N0–2 • KEYNOTE-756: All Grade 3, T1c–T2/ N1–2 or T3/T4
Stratification factors	Nodal status, anthracycline schedule, PD-L1 status	PD-L1 assays: • CheckMate-7FL: SP142 (and 28-8 CPS in biomarker analysis) • KEYNOTE-756: 22C3 CPS
Primary endpoint	Powered to detect difference in pCR rates	KEYNOTE-756 was also powered to detect difference in EFS

KEYNOTE 756 results

- 1278 patients randomised
- pCR rates (ypT0/Tis ypN0) were significantly greater with pembro + CT vs placebo + CT (24.3% [95% CI, 21.0–27.8] vs 15.6% [95% CI, 12.8–18.6]; P=0.00005)
  - More patients in the pembro vs placebo group had RCB-0 (24.7% vs 15.6%) or RCB-1 (10.2% vs 8.1%)
  - Fewer patients in the pembro vs placebo group had RCB-2 (40.8% vs 45.3%) or RCB-3 (20.5% vs 28.9%)
- EFS results are immature and continue to be evaluated

Pathologic Complete Response at IA1 by ER Status and PD-L1 Expression



[a]No pCR in patients with a PD-L1 CPS <1 with ER+ <10% (pembrolizumab arm, n = 1; placebo arm, n = 4). [b]Estimated treatment difference based on Miettinen & Nurminen method (unstratified).
Data cutoff date: May 25, 2023.

IO in ER+ BC – Checkmate-7FL

Remarkably similar results for some groups

Figure 2: pCR results in CheckMate-7FL by PD-L1 expression and ER status

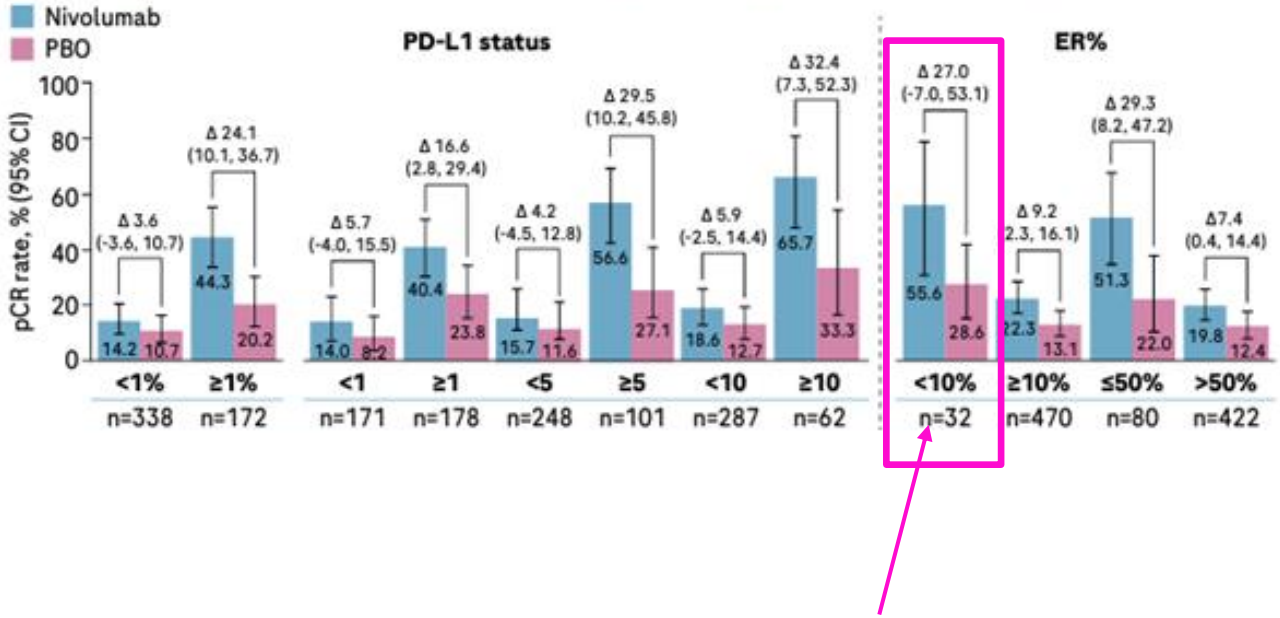
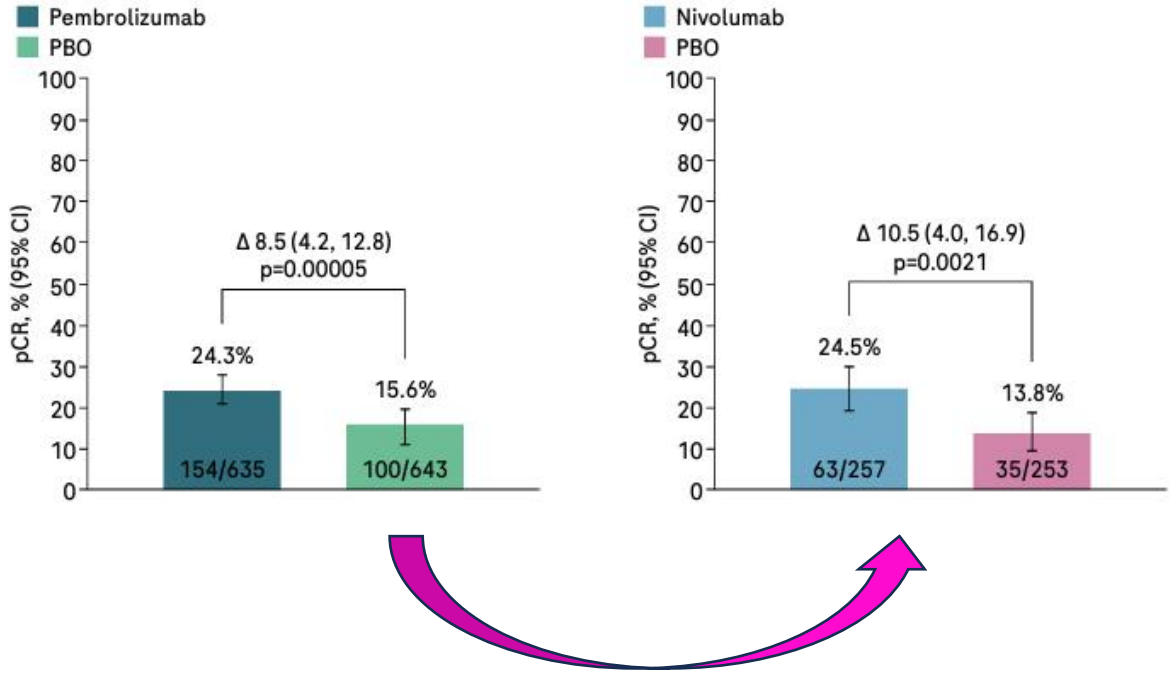


Figure 1: pCR results from KEYNOTE-756 and CheckMate-7FL (ESMO 2023)



1. *Cardoso F et al. SABCS 2023;GS01-02; 2. Cardoso F et al. ESMO 2023;LBA2.*

Discussion; IO in ER+ disease

- We don’t know pCR is as valid a surrogate for OS in ER+ HER2- disease
- In general we use less NACT in ER+ HER2 neg disease
- 2% PD seen in both arms during NACT
- Toxicity still a major concern for a very curable group of patients
- Not convinced this is right approach for majority of ER+ disease...maybe for lower ER disease

MONARCH-E & NATALEE
Adjuvant CDK4/6i

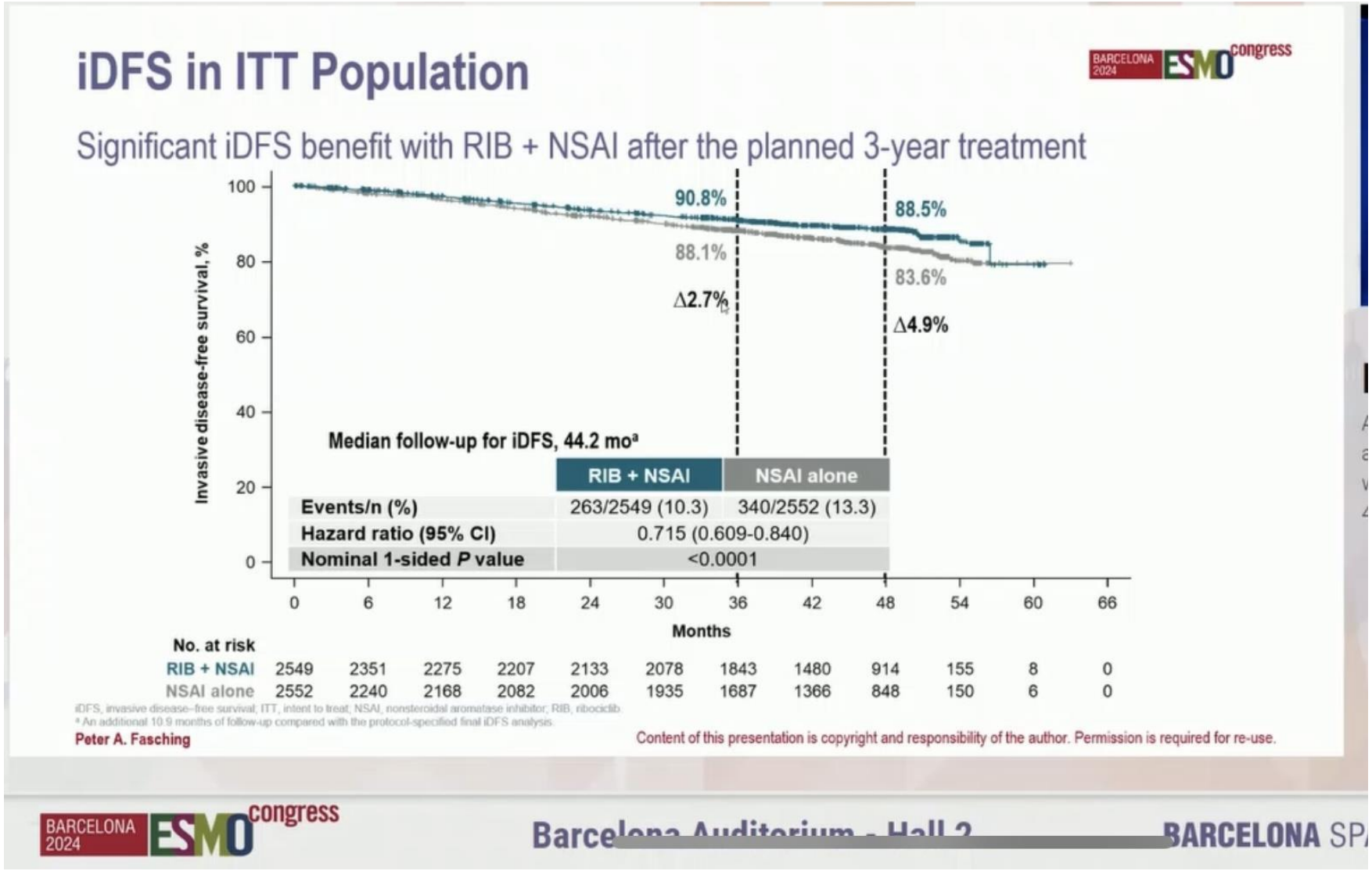
- MONARCH-E = Abemaciclib & NATALEE = Ribociclib
- *[No adjuvant data for adjuvant Palbociclib]*

- Criteria not based on pCR/response data

- Don’t forget Olaparib for ER+ HER2neg gBRCA1/2 carriers

NATALEE iDFS update ESMO 2024

(Not approved in NHS yet)



NATALEE a **broader** patient population than MONARCH-E:

- NICE decision anticipated ~ ?May 2025, SMC later

N0 not allowed in monarchE

AJCC Anatomical Staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IIA	T0N1	✓	Only if grade 3 or Ki-67 ≥20%
	T1N1	✓	Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if G3 or G2 with Ki-67 ≥20% or high genomic risk[a]	✗
Stage IIB	T2N1	✓	Only if grade 3 or Ki-67 ≥20%
	T3N0	✓	✗
Stage IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	✓	✗
	T4N1	✓	Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2	✓	✓
Stage IIIC	Any TN3	✓	✓

In monarchE, relatively few patients with stage II were allowed:
- N1 allowed only if grade 3 or Ki-67 ≥20%

In monarchE, within stage III,
- N0 not allowed (in IIIB)
- N1 (whether in IIIA or IIIB) allowed only if tumor size ≥5 cm, grade 3, or Ki-67 ≥20%

Slamon DJ, Fasching PA, Hurvitz S, et al. Therapeutic Advances in Medical Oncology. 2023;15.

Question: *Adjuvant Olaparib or Abemaciclib for high risk ER+ HER2 negative cancers?*

Cross-trial comparisons ideally avoided:

3 year iDFS HR **0.58**; 99.5% CI, 0.41 to 0.82; P<0.001) for Olaparib[1] vs 42 month iDFS HR **0.664** (95% CI 0·578–0·762, nominal p<0·0001[2] for abemaciclib

Overall survival HR **0.68** (99% CI, 0.44 to 1.05; P=0.02)[1] for olaparib versus HR **0·929** (95% CI 0·748–1·153; p=0·50)[2] for abemaciclib

BUT – note only 18% of patients in OLYMPIA (325/ 1836) were ER positive

1: Tutt, A et al: N Engl J Med 2021; 384:2394-2405; 2: Johnston, S et al; Lancet Oncol 2023: Vol 24: 1: 77-90

Outcomes with CDK4/6i therapy in HR-positive and *gBRCAmut* MBC patients

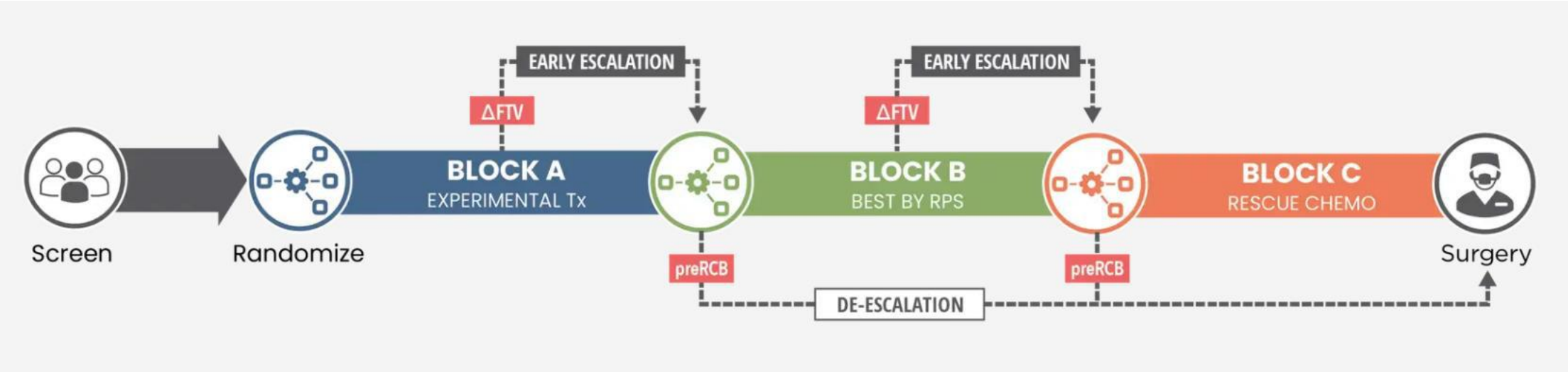
Author	Results/Conclusions
Frenel et al.	BRCA/PALB2 mutated patients with shorter PFS (14.3 vs. 26.7m)
Collins et al.	BRCA mutated patients with shorter OS (26 vs. 51m)
Bruno et al.	BRCA/CHECK/ATM mutated patients with worse outcomes
Safonov et al.	BRCA2 mutations with worse PFS
Fuentes Antras, et al.	BRCA1/2 and PALB2 mutations with shorter PFS (9.9 vs. 26.8m)

- **Recognize HR-positive/BRCA-mutated as a specific subgroup of patients**
- **Mostly retrospective and subgroup analyses data**
- **Unmet need for specific treatment approaches for HR+/BRCA-mutated patients**
- **Prospective data and combinations need to be explored**

Frenel J, et al. Ann Oncol 2020.
Bruno L, et al. JCO Precision Oncol, 2022.
Safonov A, et al. Cancer Res 2022.
Collins J, et al. Oncol Therapy, 2021.
Fuentes Antras J, et al. ASCO 2023.

Barrios, C; Proc SABCS 2023 with permission

The *iSPY 2.2* trial: Innovative adaptive design based on response

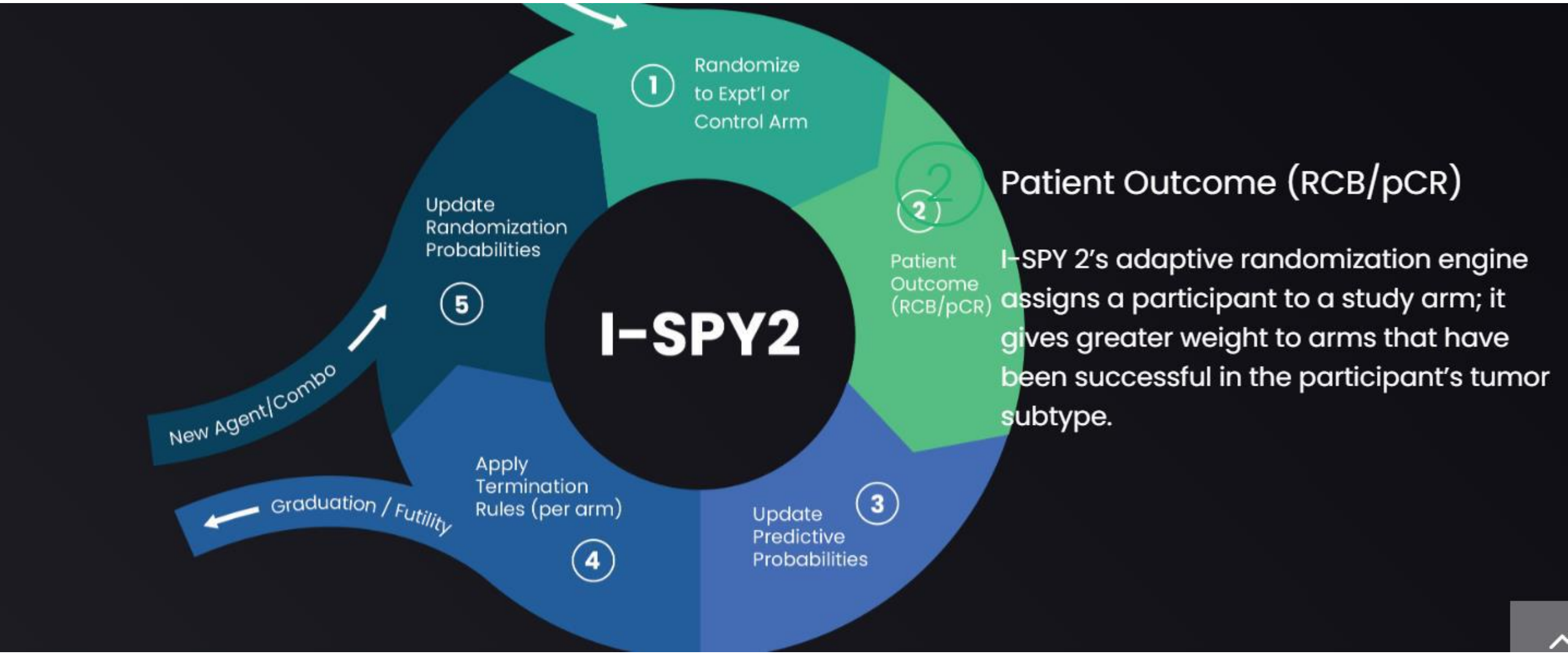


- Block A is a randomised platform design that evaluates up to 4 experimental therapies across multiple subtypes, without the use of paclitaxel
- Block B consists of multiple subtype-specific 'best in class' treatments assigned based on I-SPY's response-predictive subtypes (RPS)
- Block C is rescue therapy, consisting of anthracycline chemo at a minimum

i-SPY 2.2

- Serial MRI scans throughout
- All those receiving Block C therapy go to surgery when completed
- Aim is for participants to receive only the amount of treatment needed to achieve pCR, to limit potential side effects
- Also aims to limit exposure to ineffective treatments; halfway through blocks A and B, if MRI shows very little change, participants may forego the remainder of that block and proceed to the next
- 1 in 5 participants will be randomised to control arm in which treatment begins in Block B
- >2500 patients enrolled, 25 agents already evaluated and 3 already have accelerated approval…

I-SPY Trials - Quantum Leap



[I-SPY Trials - Quantum Leap]

Summary

- Biology biology biology
- The neoadjuvant setting is the perfect window to gain valuable early prognostic information to allow tailoring of post-op therapy
- TNBC and HER2 positive cases with significant residual disease/high RCB sadly often have worse outcomes
  - *Can we **cure** more patients with better therapy, now that we know their cancer doesn't respond well?*
- The NACT and post-NACT settings are very useful windows for drug development and biomarker discovery, improving efficiency
  - 93 published manuscripts already and counting for i-SPY trials…

Thank you