

# Lo stadio precoce di malattia: sottotipo triplo-negativo

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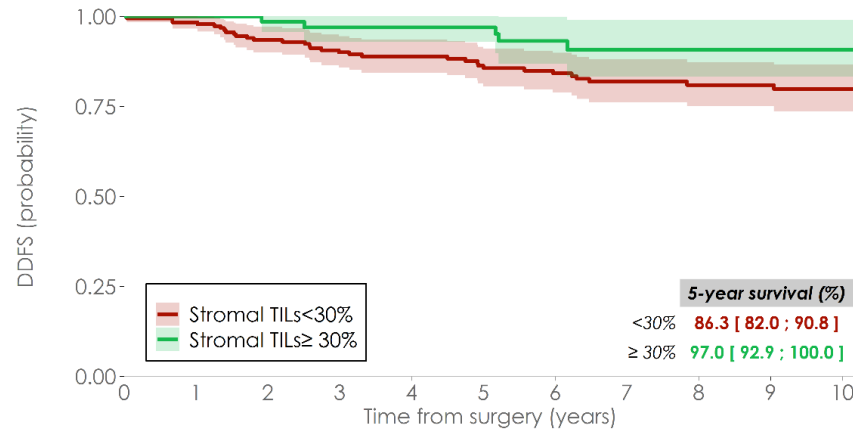
# Disclosure slide

Advisory/consultancy role/speaker bureau:

Eli Lilly, Pfizer, Novartis, Roche, AstraZeneca, MSD, Daiichi Sankyo,  
Gilead, Menarini Stemline

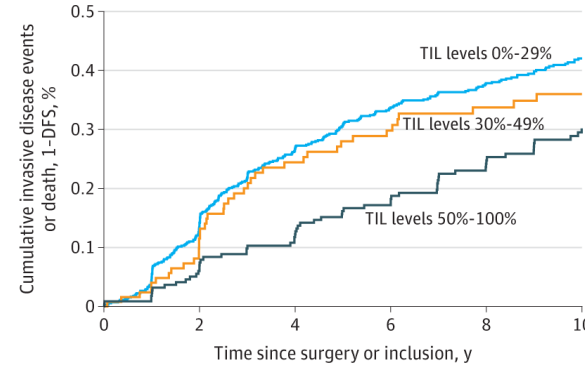


# TILs in systemically untreated stage 1 TNBC



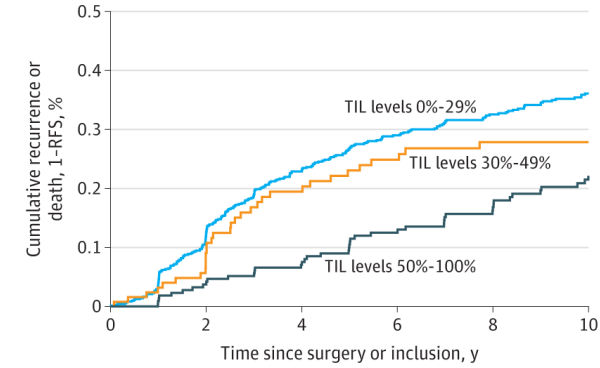
	189	181	168	157	148	127	113	98	82	73	59
Stromal TILs<30%	189	181	168	157	148	127	113	98	82	73	59
Stromal TILs≥30%	74	71	66	62	61	52	40	30	25	20	18

**A** Invasive disease-free survival



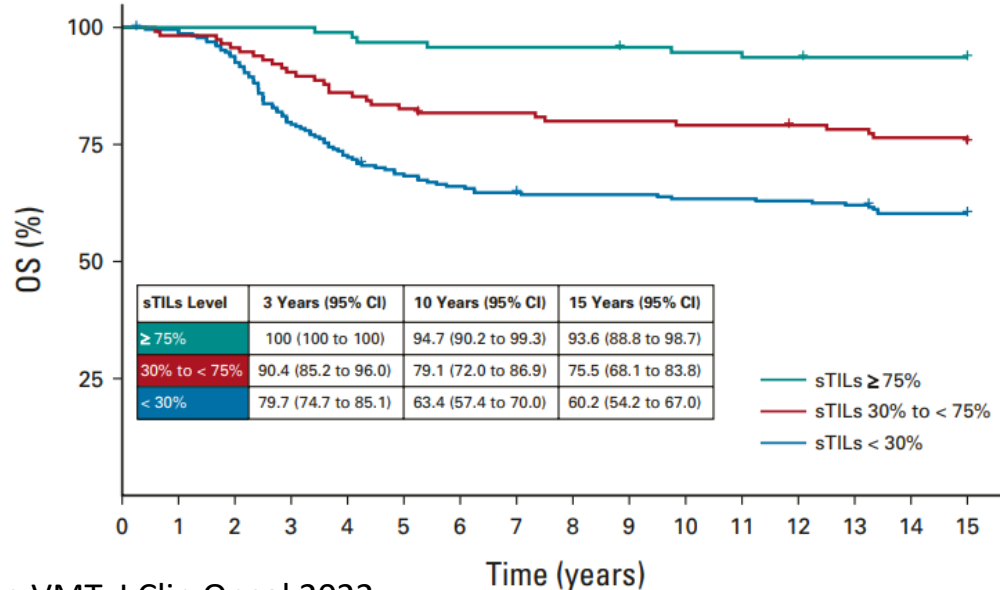
No. at risk by TIL level	728	599	481	398	324	252
0%-29%	728	599	481	398	324	252
30%-49%	127	105	86	76	62	54
50%-100%	226	198	182	160	133	110

**B** Recurrence-free survival

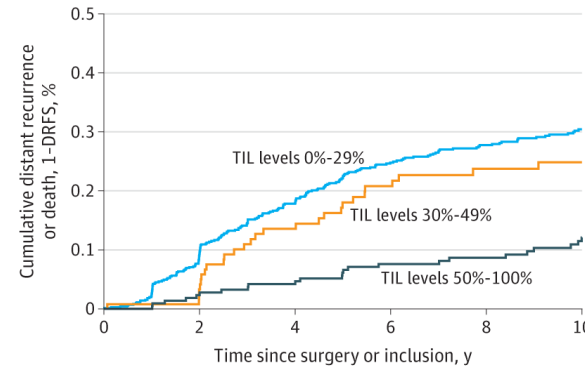


No. at risk by TIL level	728	610	507	424	351	279
0%-29%	728	610	507	424	351	279
30%-49%	127	107	91	81	67	59
50%-100%	226	203	192	170	147	125

Park JH et al. Ann Oncol 2019

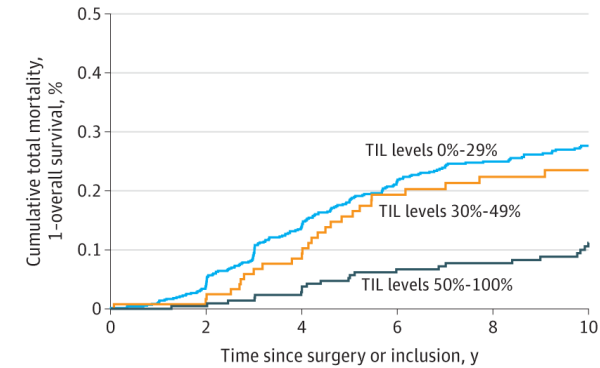


**C** Distant recurrence-free survival



No. at risk by TIL level	728	632	545	457	384	307
0%-29%	728	632	545	457	384	307
30%-49%	127	115	99	86	71	63
50%-100%	226	207	201	186	168	147

**D** Overall survival



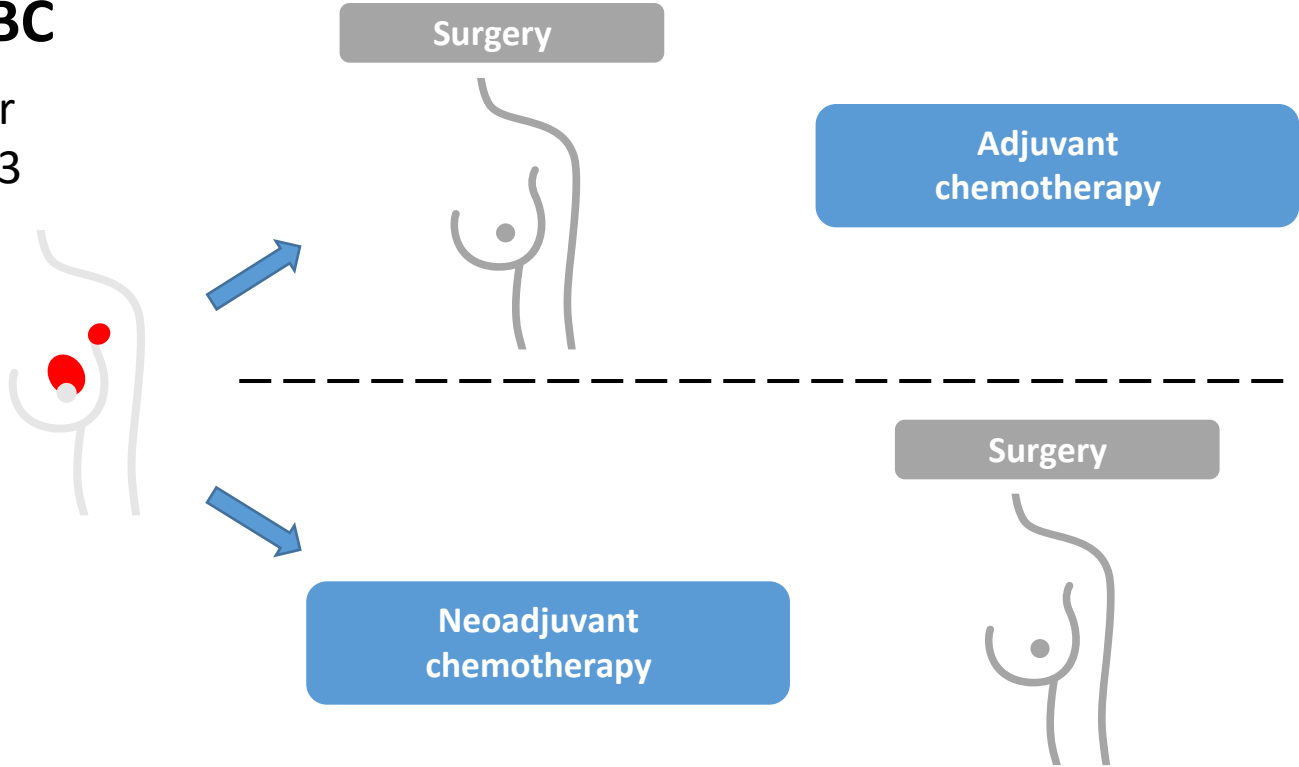
No. at risk by TIL level	728	667	571	477	401	322
0%-29%	728	667	571	477	401	322
30%-49%	127	117	104	87	72	64
50%-100%	226	211	204	188	170	149

# Neoadjuvant vs adjuvant therapy: different approaches, same results?

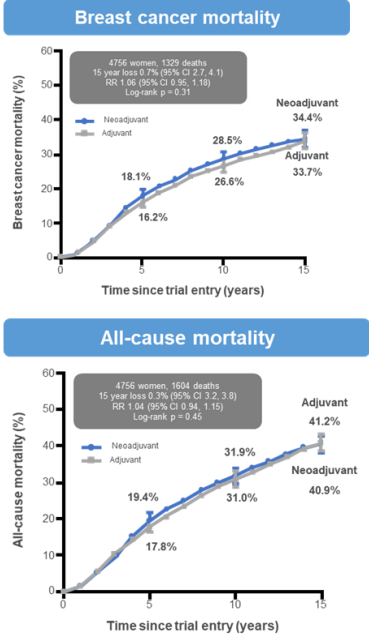
Same chemotherapy  
Same chance to be cured

**TNBC**

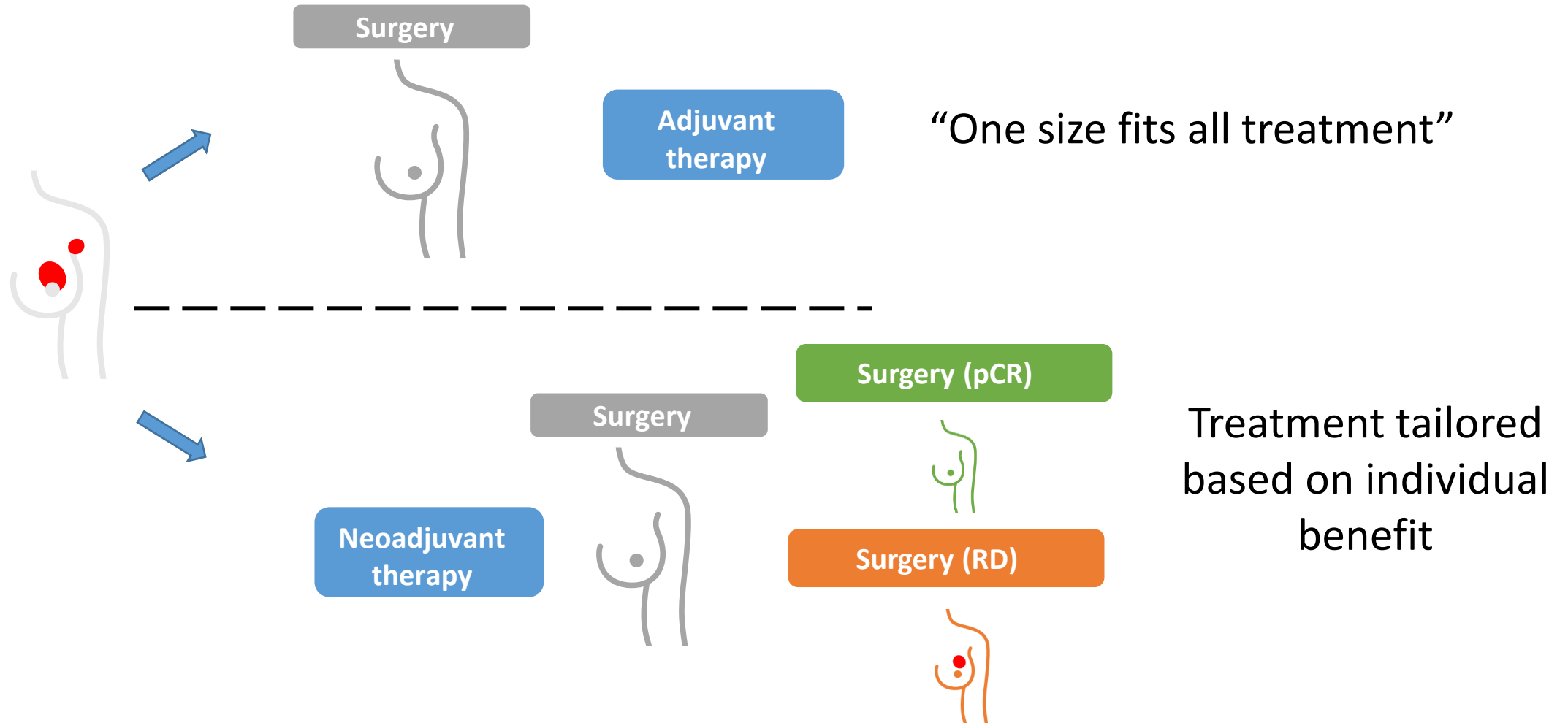
cN+ or  
cT2/T3

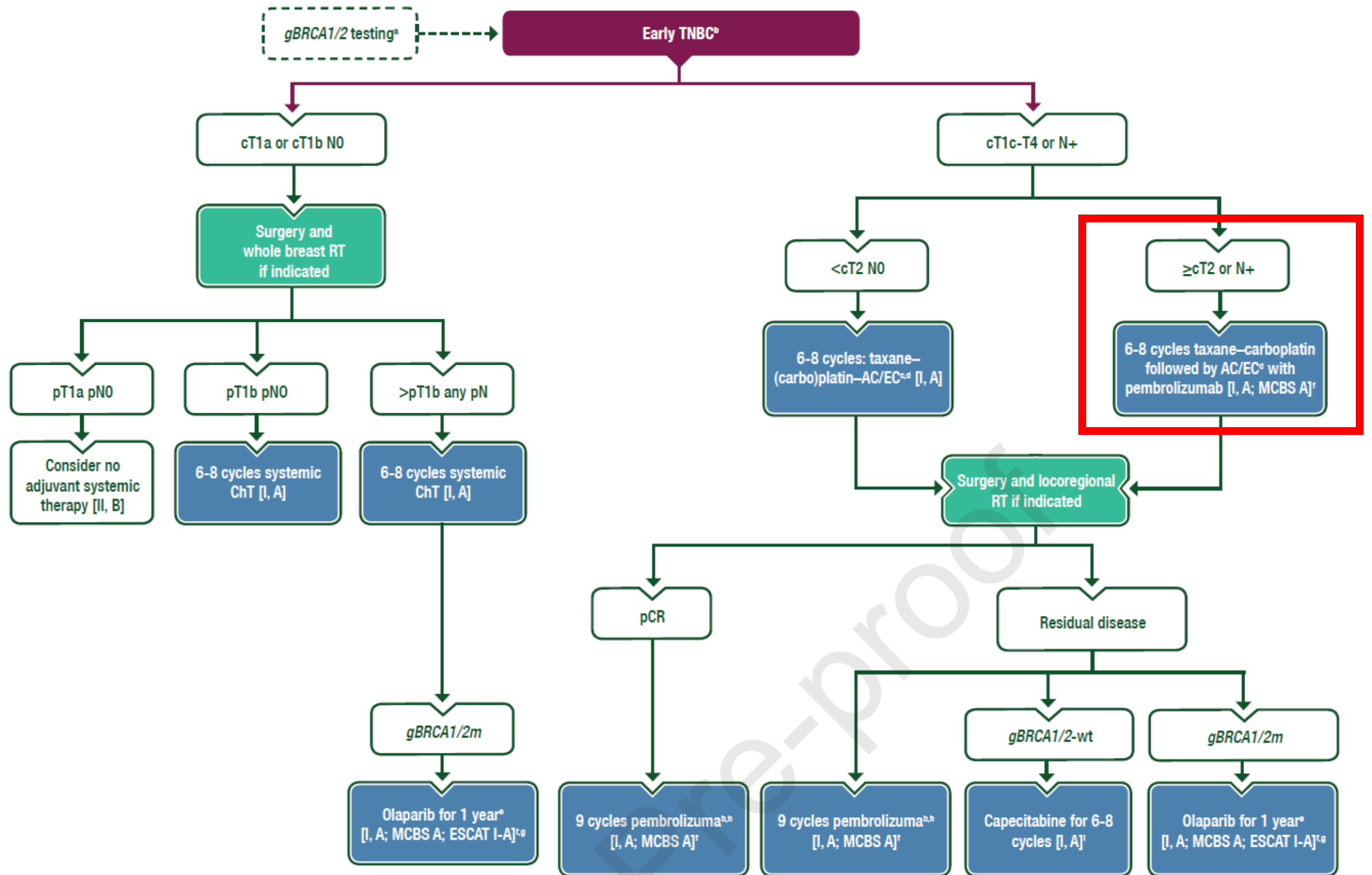


EBCTCG Meta-analysis

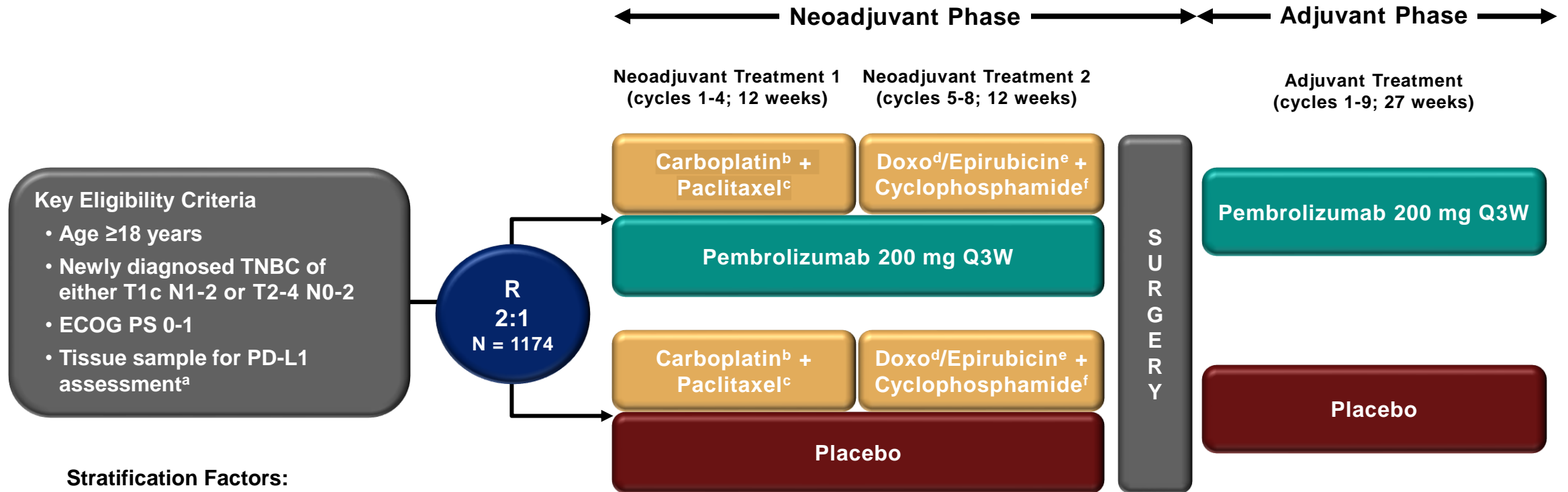


# Early-stage TNBC: treatment strategy may impact long term outcome





# KEYNOTE-522 Study Design



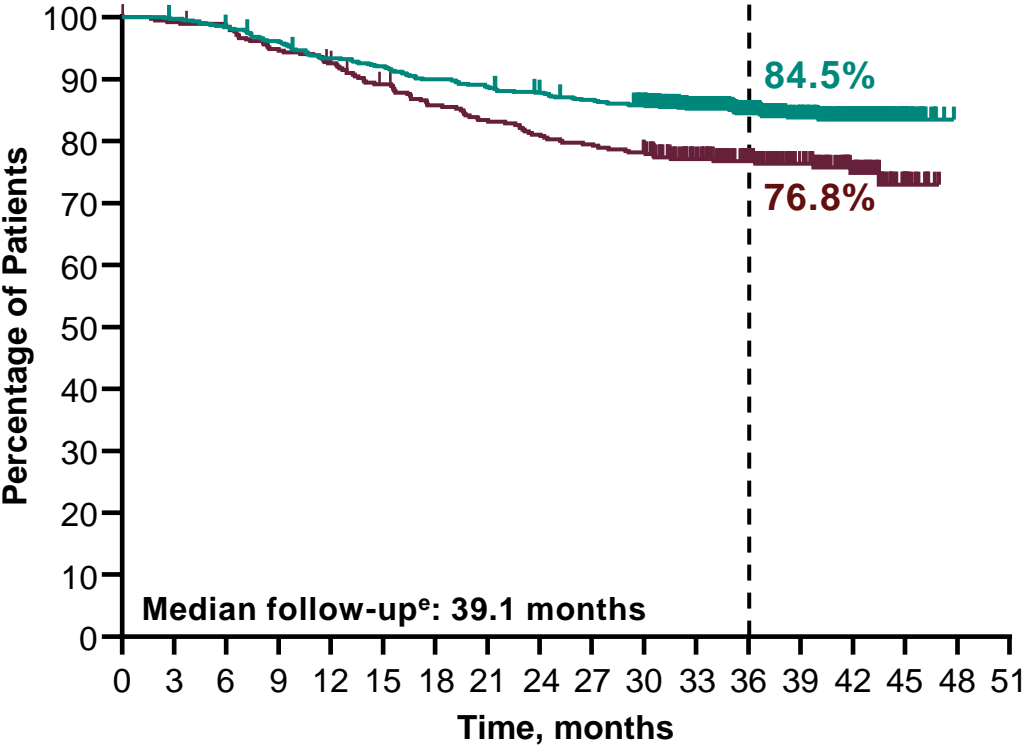
**Noadjuvant phase:** starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

<sup>a</sup>Must consist of at least 2 separate tumor cores from the primary tumor. <sup>b</sup>Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. <sup>c</sup>Paclitaxel dose was 80 mg/m<sup>2</sup> QW. <sup>d</sup>Doxorubicin dose was 60 mg/m<sup>2</sup> Q3W. <sup>e</sup>Epirubicin dose was 90 mg/m<sup>2</sup> Q3W. <sup>f</sup>Cyclophosphamide dose was 600 mg/m<sup>2</sup> Q3W.

# Durable Event-Free Survival

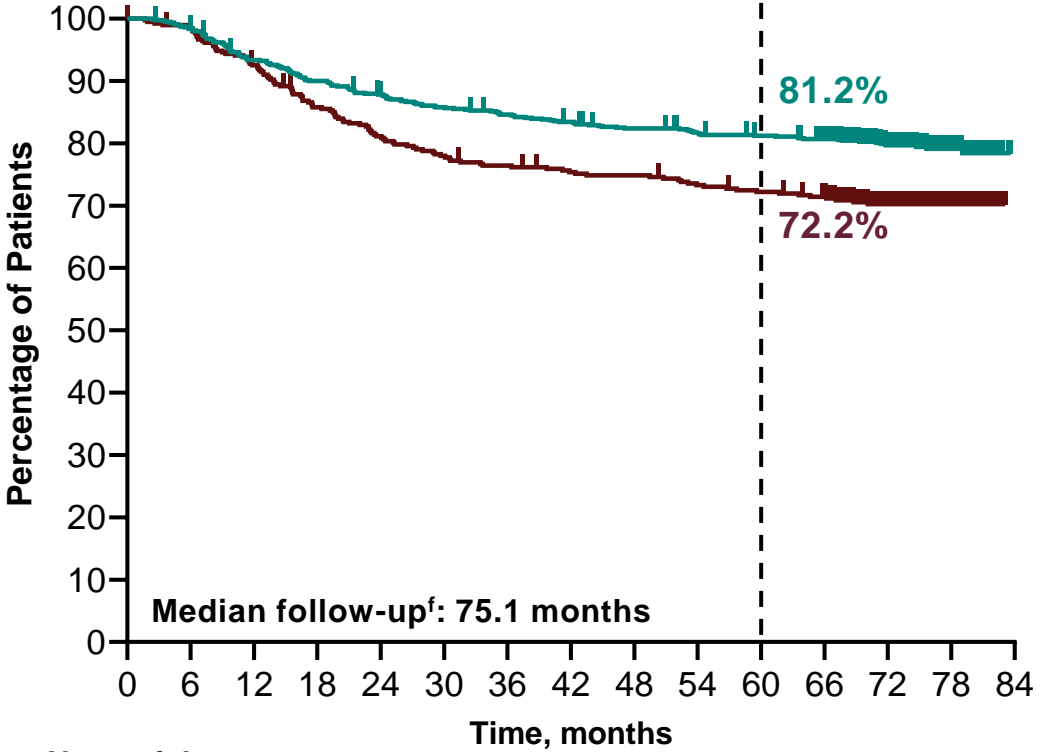
IA4 <sup>a</sup>	Events	HR (95% CI)	P-value
Pembro + Chemo/Pembro	15.7%	0.63 <sup>c</sup> (0.48-0.82)	0.00031 <sup>d</sup>
Placebo + Chemo/Placebo	23.8%		



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

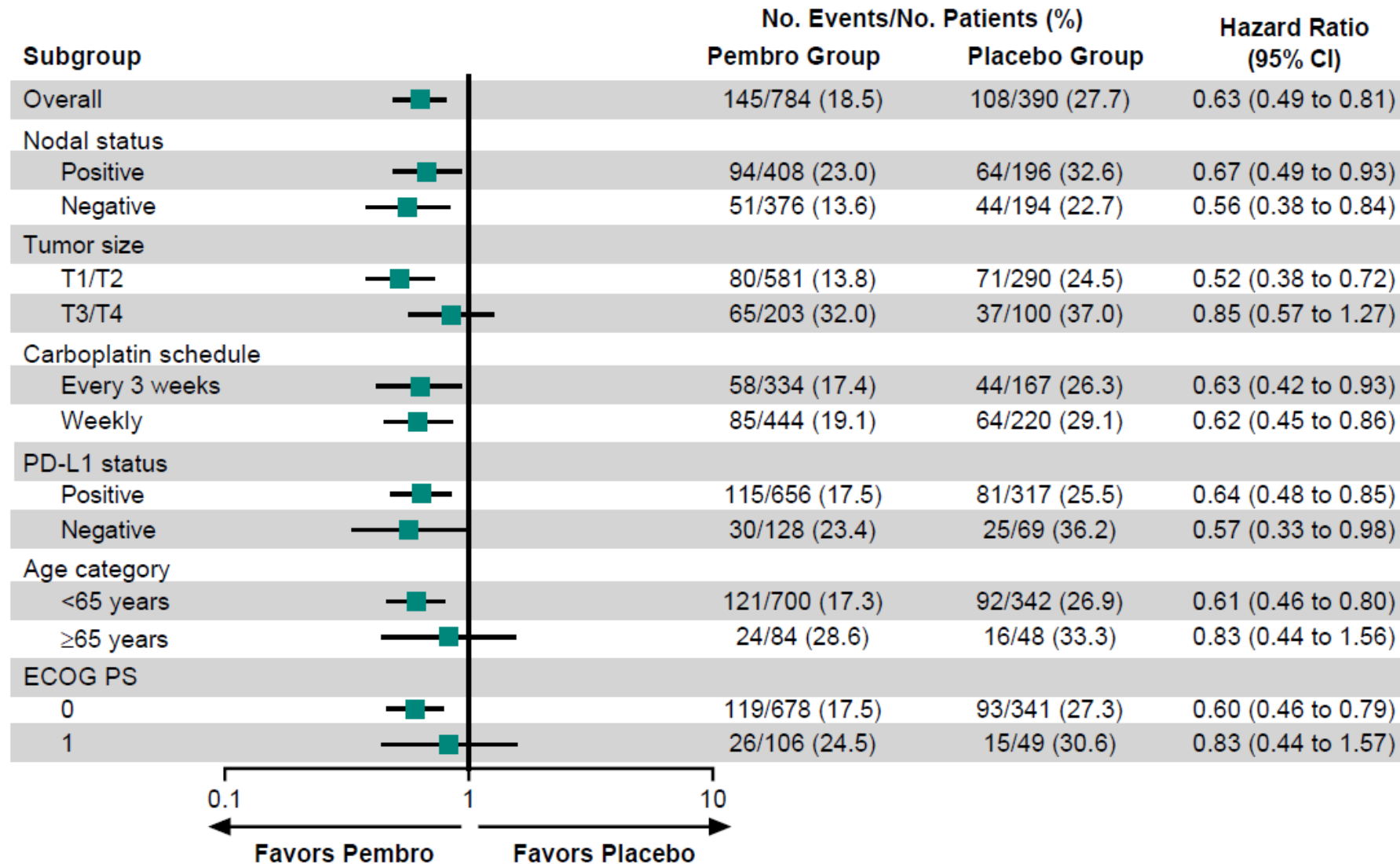
IA7 <sup>b</sup>	Events	HR (95% CI)
Pembro + Chemo/Pembro	20.3%	0.65 <sup>c</sup> (0.51-0.83)
Placebo + Chemo/Placebo	29.2%	



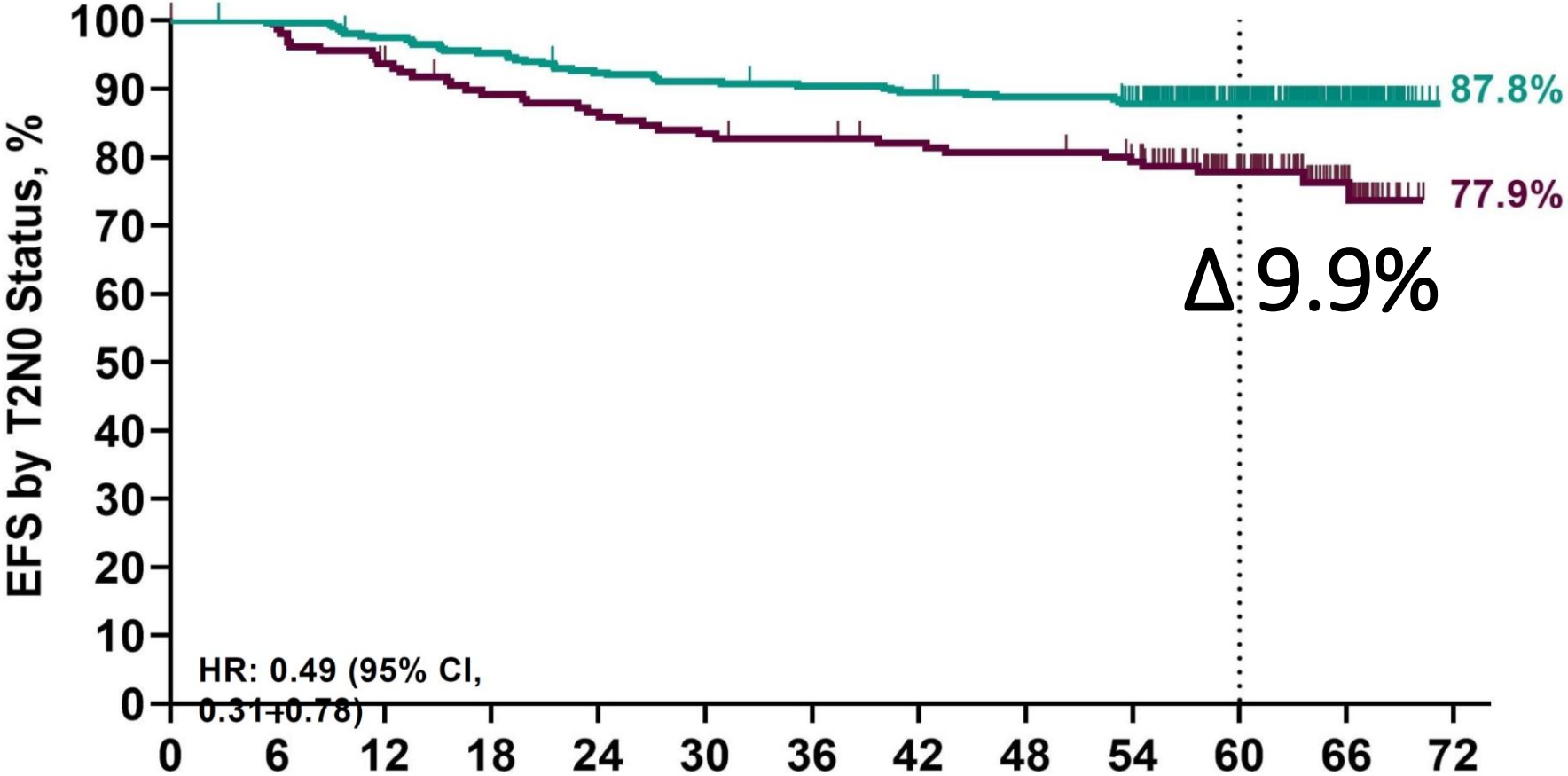
No. at risk

784	769	728	702	681	665	654	644	633	625	618	602	409	164	0
390	382	358	330	312	300	293	287	285	278	273	264	178	76	0

# EFS in patient subgroups

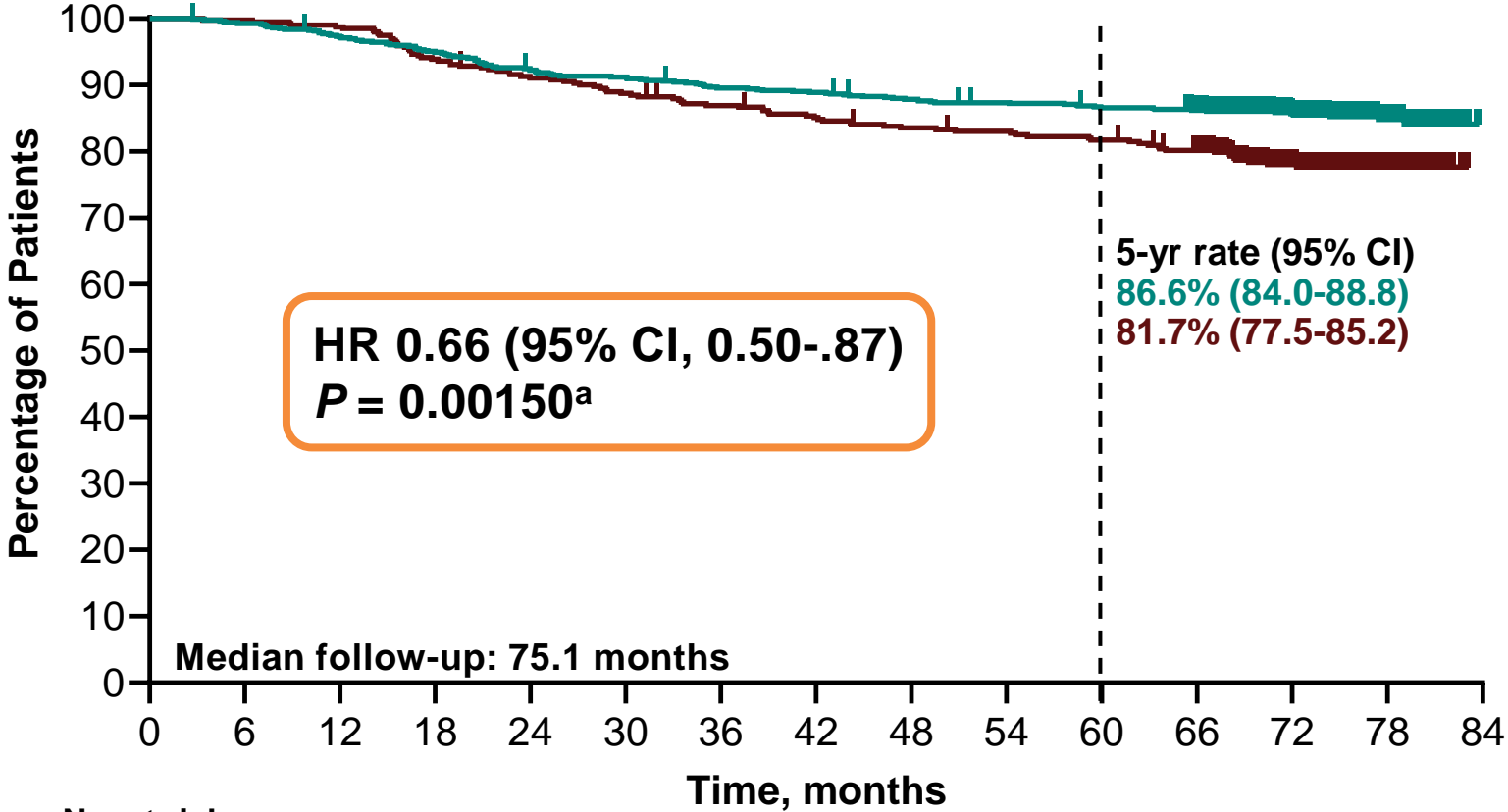


# EFS at IA6 by cT2 cN0 Status



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Pembro + Chemo/Pembro	316	314	306	299	288	284	281	278	274	265	179	71	0
Pbo + Chemo/Pbo	159	156	147	138	134	129	127	124	122	117	78	32	0

# Key Secondary Endpoint: Overall Survival



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

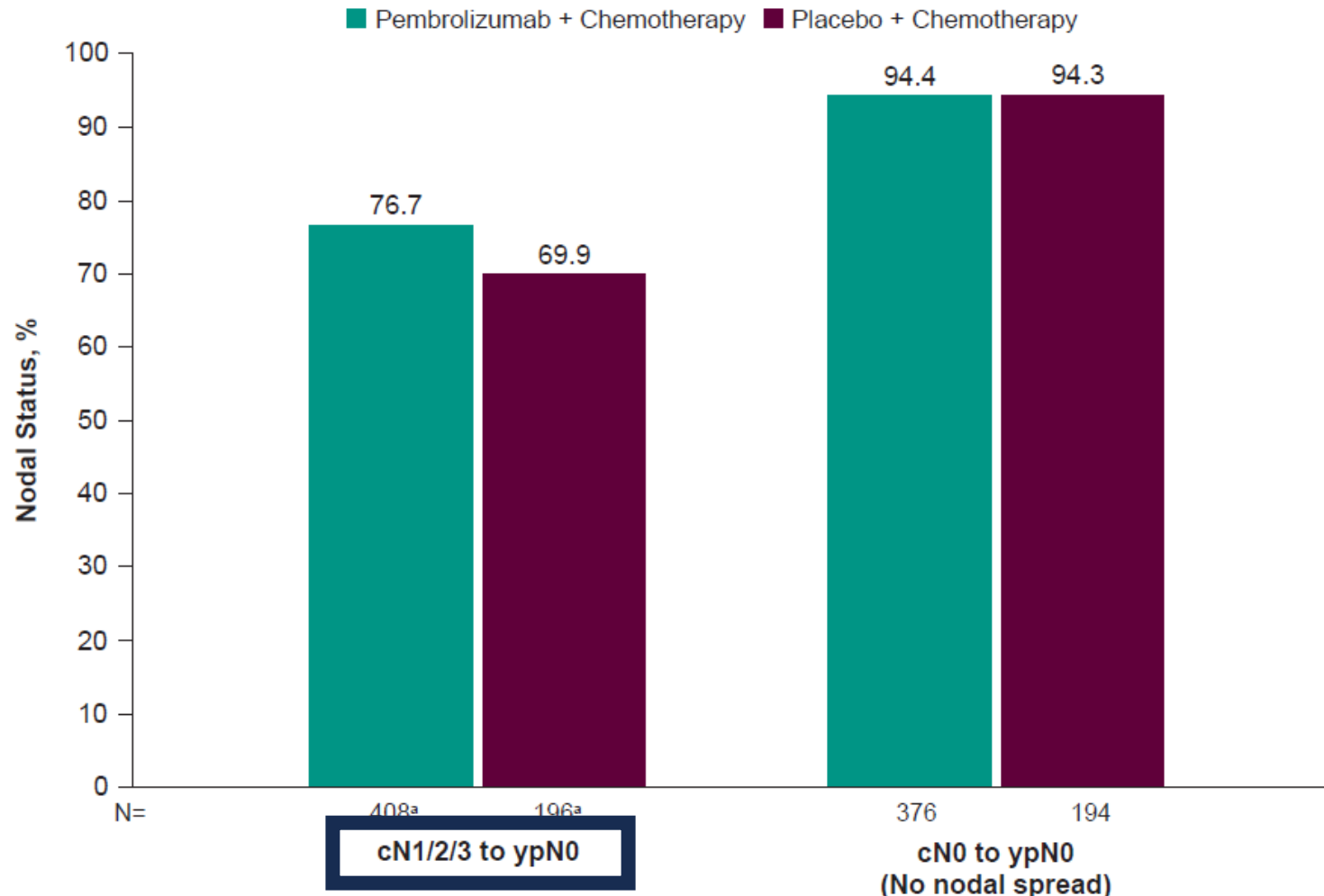
67.3% information fraction<sup>a</sup>

No. at risk

784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
390	389	385	366	354	345	336	328	321	318	313	300	199	82	0



# KEYNOTE-522: Benefit on Surgical Outcomes Nodal Status Following Definitive Surgery

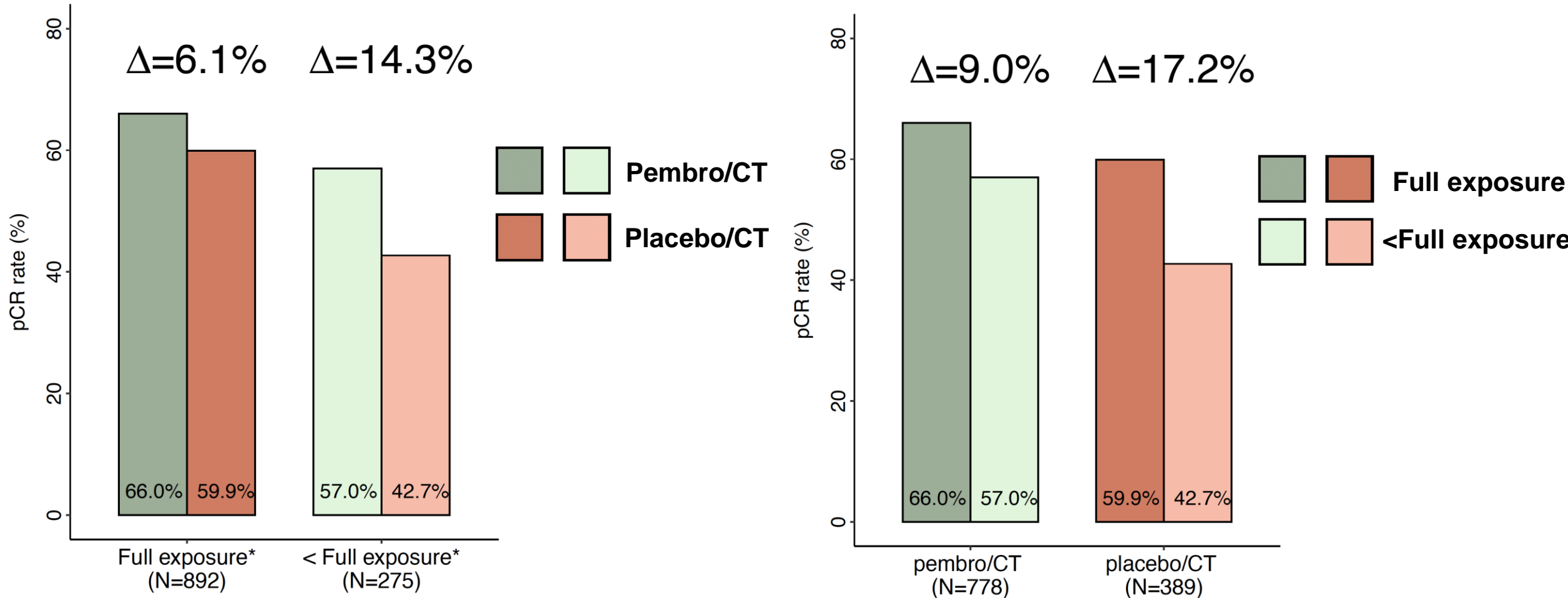


Data cutoff: 23 March 2021.

\*Includes patients with positive nodal status (cN1, cN2, and cN3) at baseline. Per protocol, patients with N3 disease were not eligible for the study, but 2 patients (1 in each group with N3) at baseline were enrolled.

Kummel S et al. Presented at SG-BCC 2023.

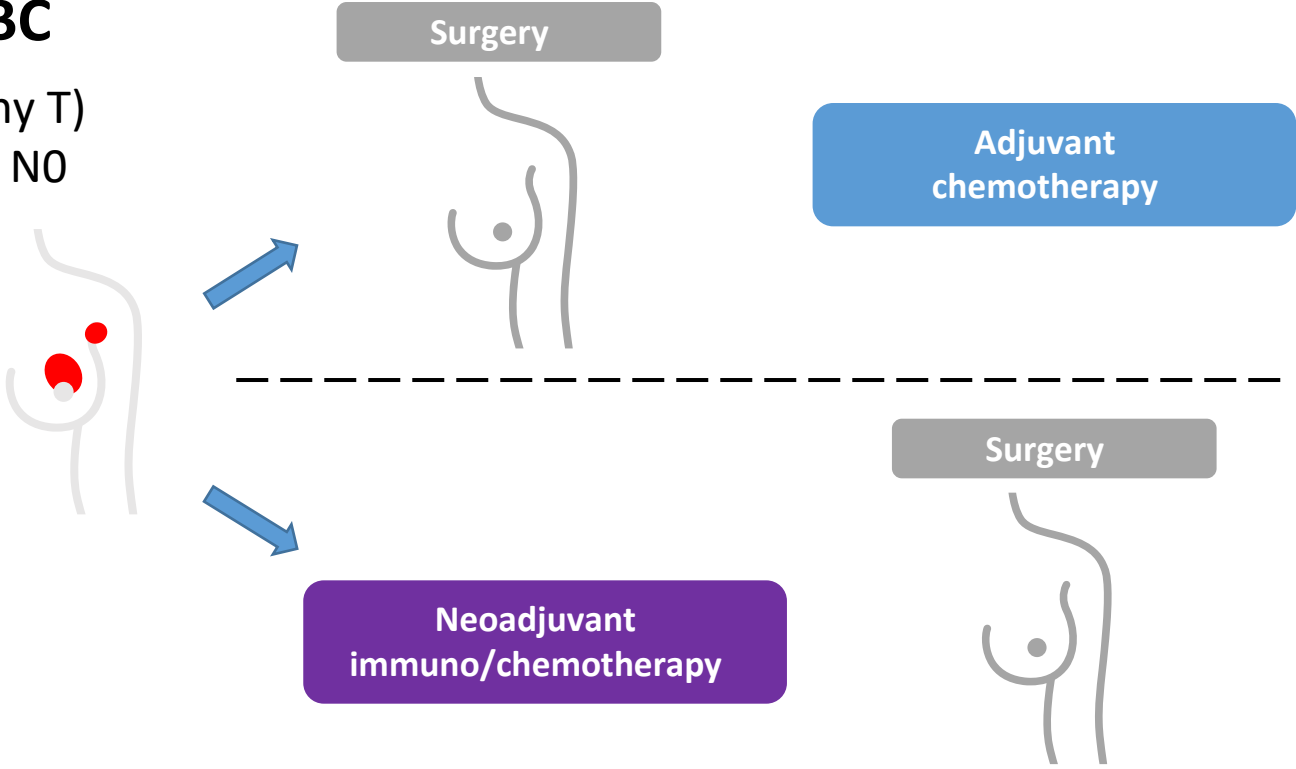
# Effect of exposure to chemotherapy (full versus less than full) in KEYNOTE 522



# Neoadjuvant vs adjuvant therapy: different therapies, different results

## TNBC

N+ (any T)  
T2/T3 N0

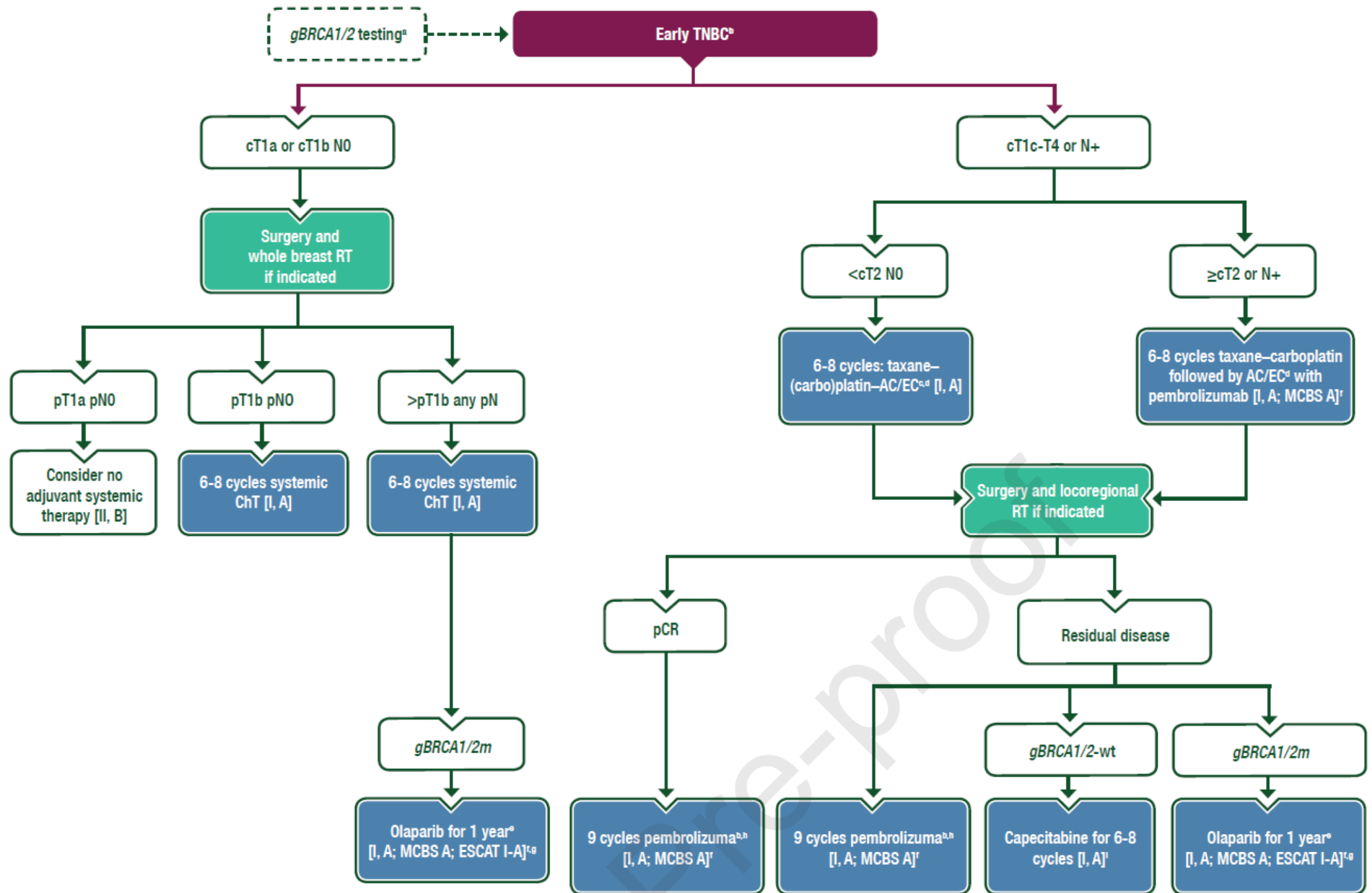


## DETRIMENTAL

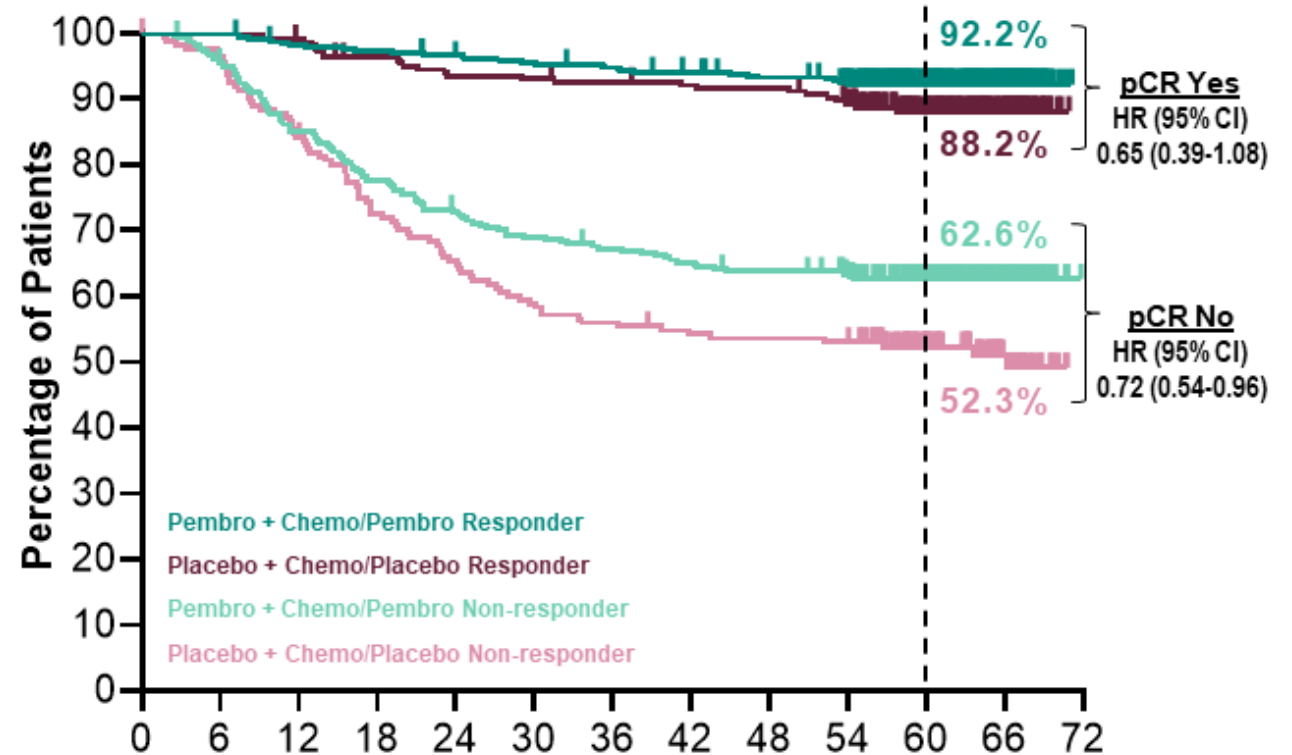
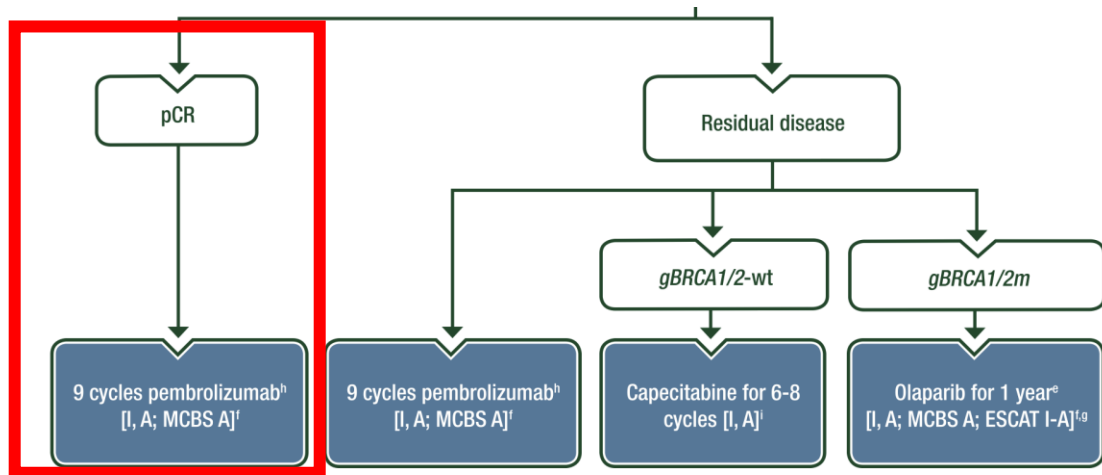
Different therapies  
Different chances to be cured

Neoadjuvant approach becomes **mandatory**  
(unless immunotherapy is not indicated)

# Tailoring post-neoadjuvant treatment



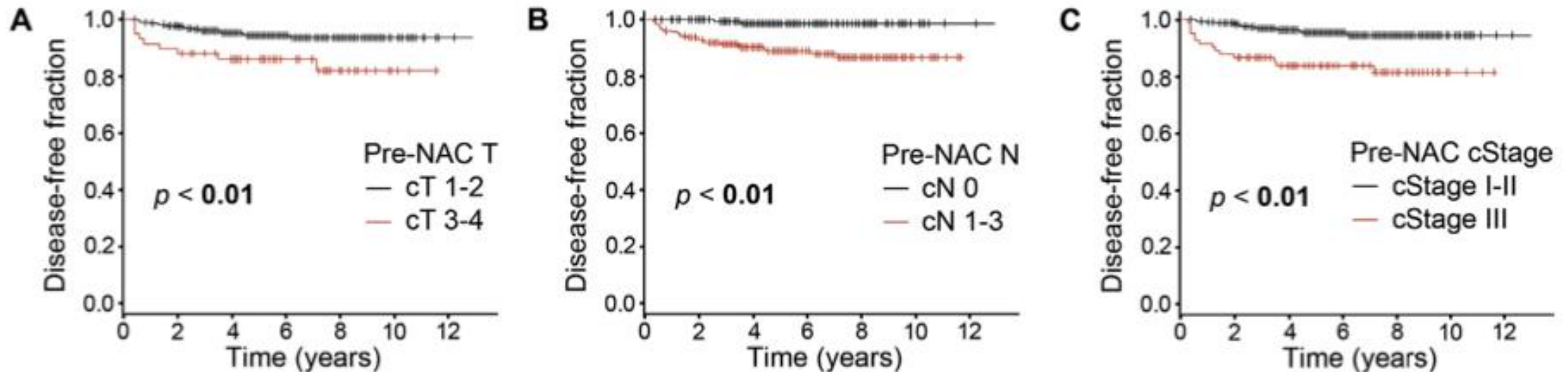
# Tailoring post-NAT treatment in pts with pCR



# Clinical prognostic factors in pts with pCR

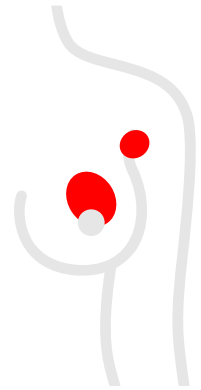
The strongest prognostic factor in patients with pCR is the baseline stage

Clinical T and N stage (cT3-4 and cN1-3)



# Tailoring post-NAT treatment in pts with pCR

Early-stage TNBC



Neoadjuvant  
CT/Pembro

Surgery: (pCR)



Current standard of care  
Pembrolizumab  
(up to 9 cycles)

cN+  
cT3/T4

Pembrolizumab

cT2cN0

+/- Pembrolizumab

OptimICE-pCR

Key Eligibility:  
pCR after preop chemo x min 6  
cycles with pembrolizumab

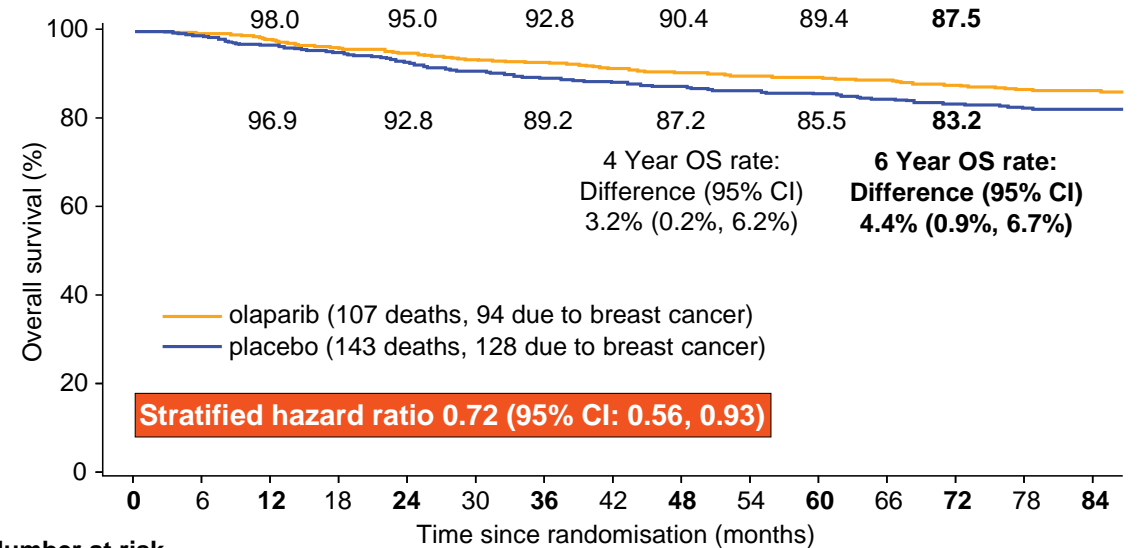
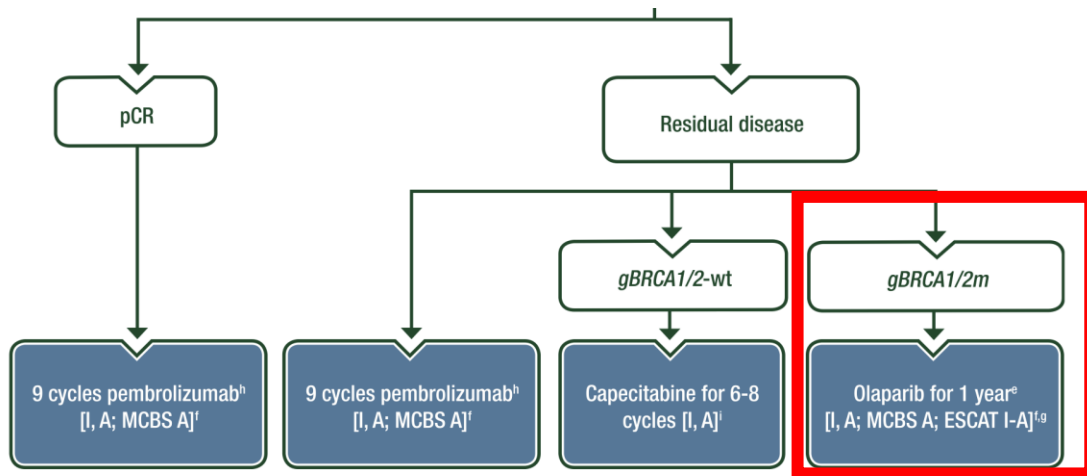


Pembrolizumab x 27 wks

Observation

De-escalation  
clinical trial  
+/- Pembrolizumab

# Tailoring post-NAT treatment in pts with RD and BRCA 1/2 mut



Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
<b>All patients</b>	107/921	143/915	0.725 (0.563 – 0.930)	NA
<b>Prior Chemo</b>				
Adjuvant	31/461	48/455	0.638 (0.402 – 0.997)	0.49
Neoadjuvant	76/460	95/460	0.774 (0.571 – 1.045)	
<b>Prior Platinum</b>				
Yes	35/247	34/238	0.979 (0.610 – 1.574)	0.15
No	72/674	109/677	0.653 (0.483 – 0.876)	
<b>HR status</b>				
HR+/HER2–	24/168	28/157	0.814 (0.469 – 1.404)	0.67
TNBC	83/751	115/758	0.713 (0.536 – 0.944)	
<b>BRCA</b>				
BRCA1	64/579	94/588	0.667 (0.484 – 0.914)	1.00
BRCA2	28/235	38/216	0.676 (0.412 – 1.098)	
BRCA1/2 both	0/2	0/3	NC	

Number at risk

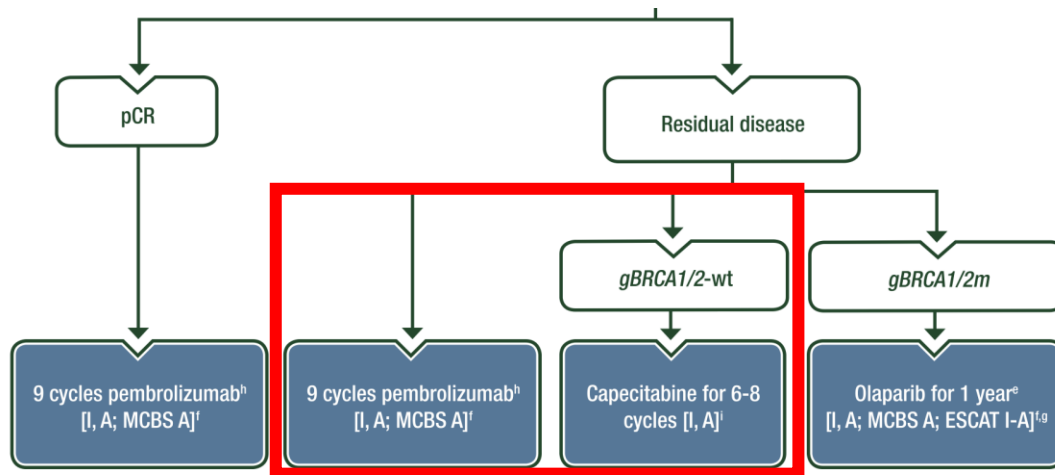
	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
olaparib	921	846	795	765	728	660	420	224							
placebo	915	843	788	739	698	616	390	221							

Number of patients with a death/total number

0.5 1

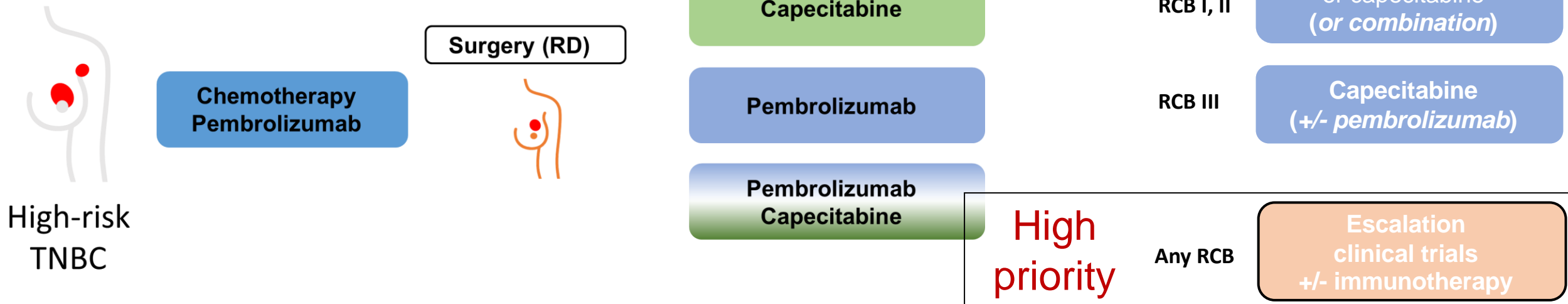
Favors olaparib Favors placebo

# Tailoring post-NAT treatment in pts with RD and BRCA wt



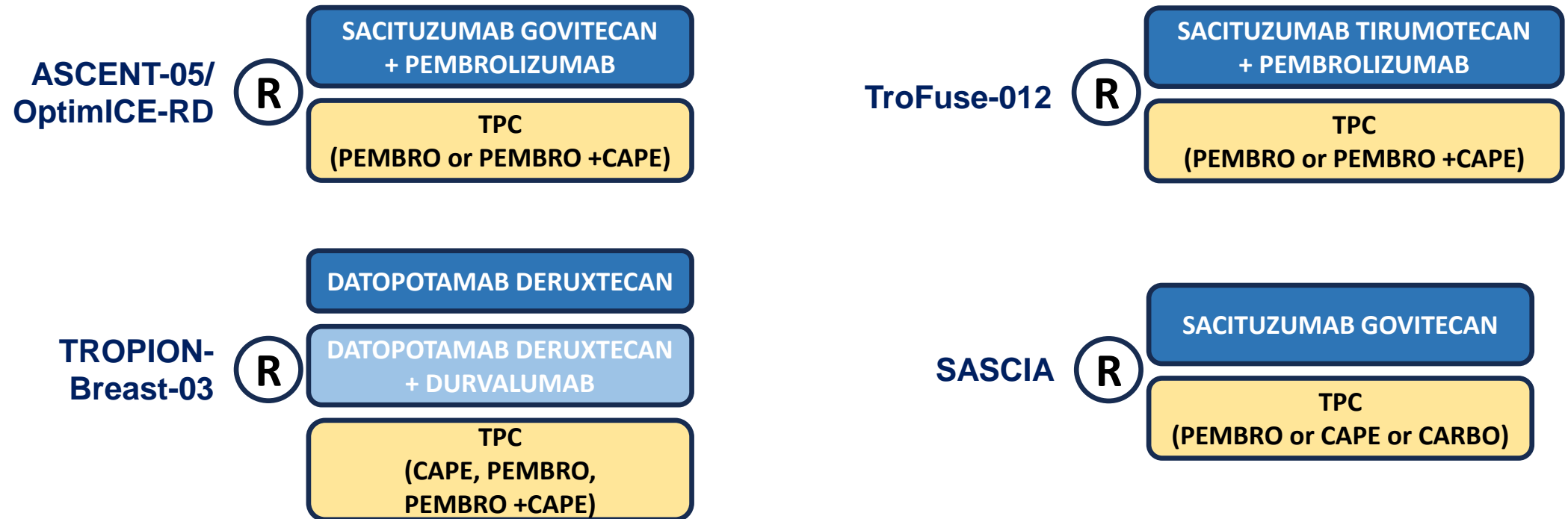
**Uncertainty arising from multiple available options in patients with RD and gBRCA1/2wt**

S. Loibl, *ESMO Clinical Practice Guidelines – Ann Oncol 2024*



# Major ongoing trials in eTNBC with RD post-NAT

## Post-neoadjuvant ADCs ± IO



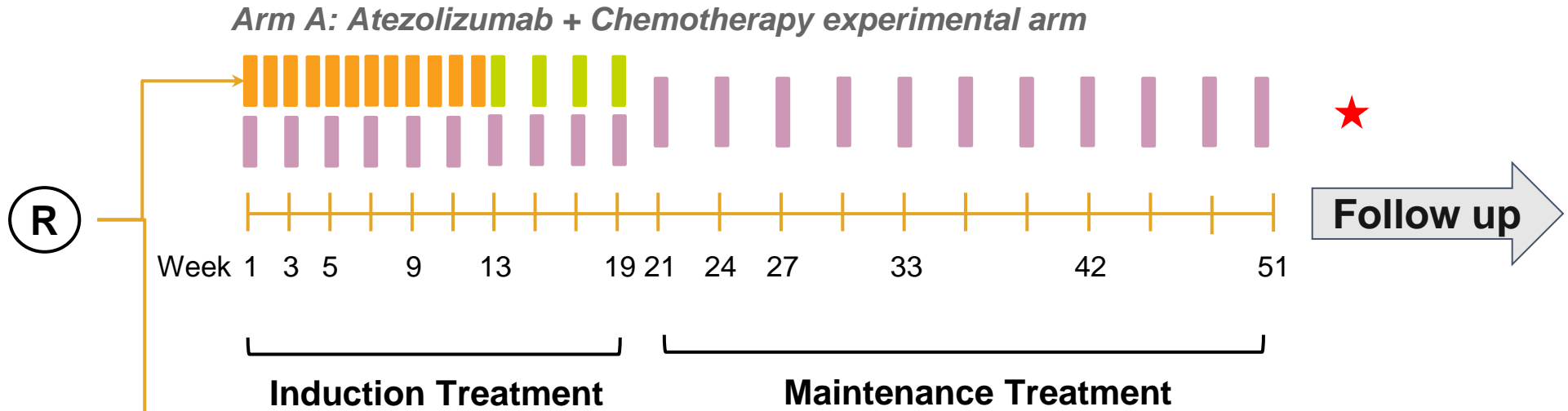
Adjuvant immunotherapy

# Alexandra/IMpassion030: Study design

SURGERY

**Early TNBC**

- Stage II-III
- At least 50% node-positive
- N=2300



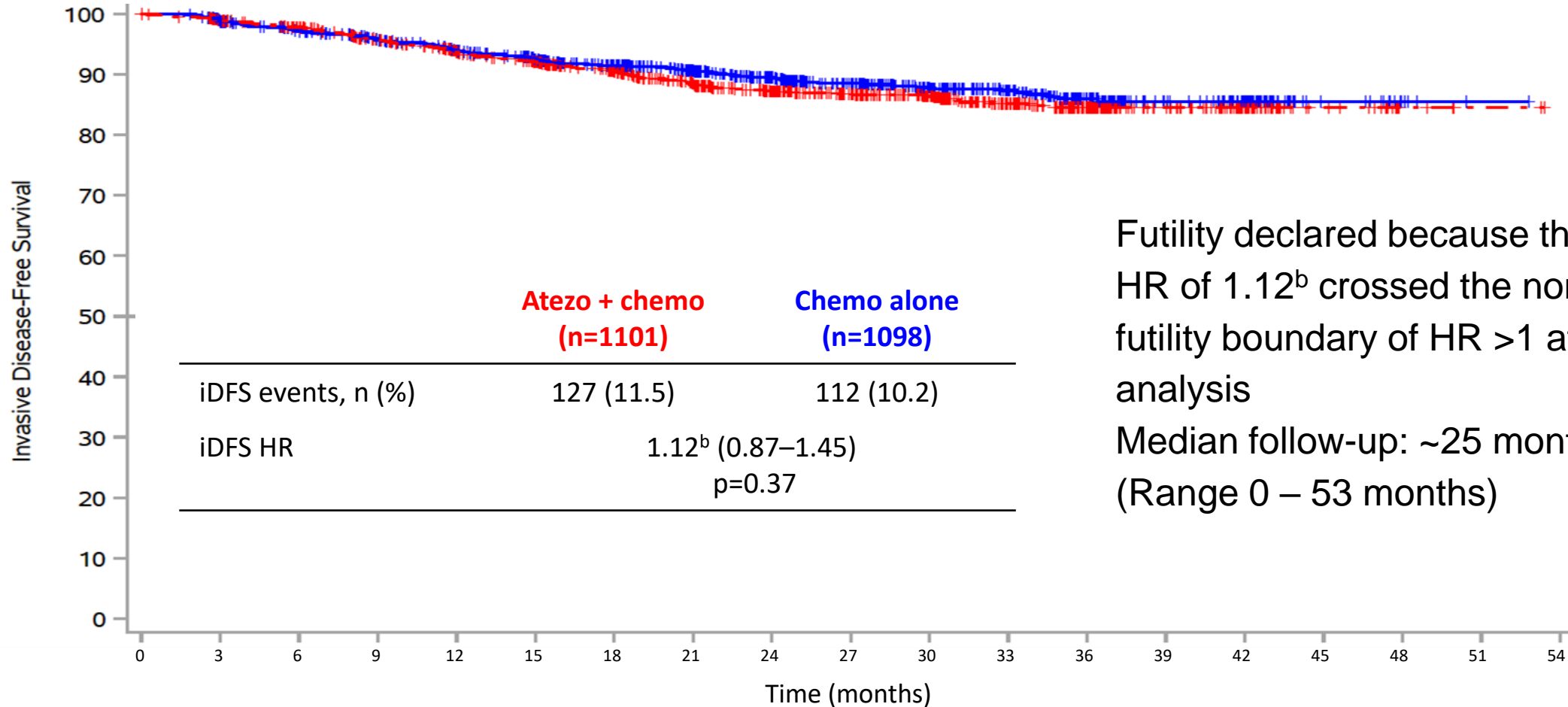
**Stratification factors:**

- Axillary nodal status**  
(0 vs. 1-3 vs. ≥ 4 positive lymph nodes)
- Surgery**  
(breast conserving vs. mastectomy)
- Tumor PD-L1 status**  
(IC0 vs. IC1/2/3)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
  - Induction: 840 mg q2w for up to 10 doses
  - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

★ End of 30-day safety reporting period after last study treatment

# Primary efficacy endpoint: iDFS (ITT population)



	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12 <sup>b</sup> (0.87–1.45) p=0.37	

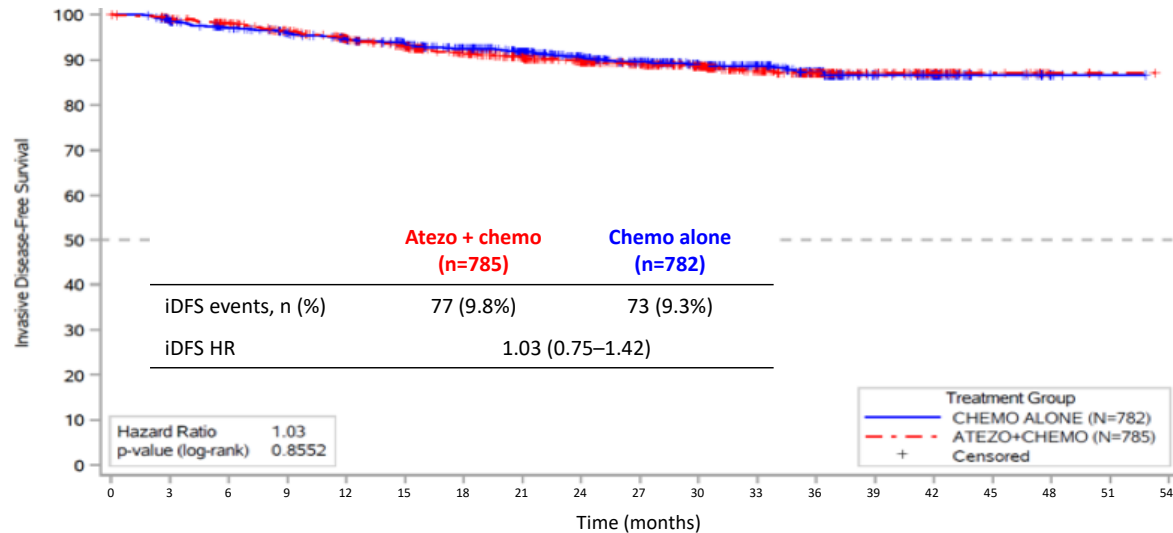
Futility declared because the observed HR of 1.12<sup>b</sup> crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months  
(Range 0 – 53 months)

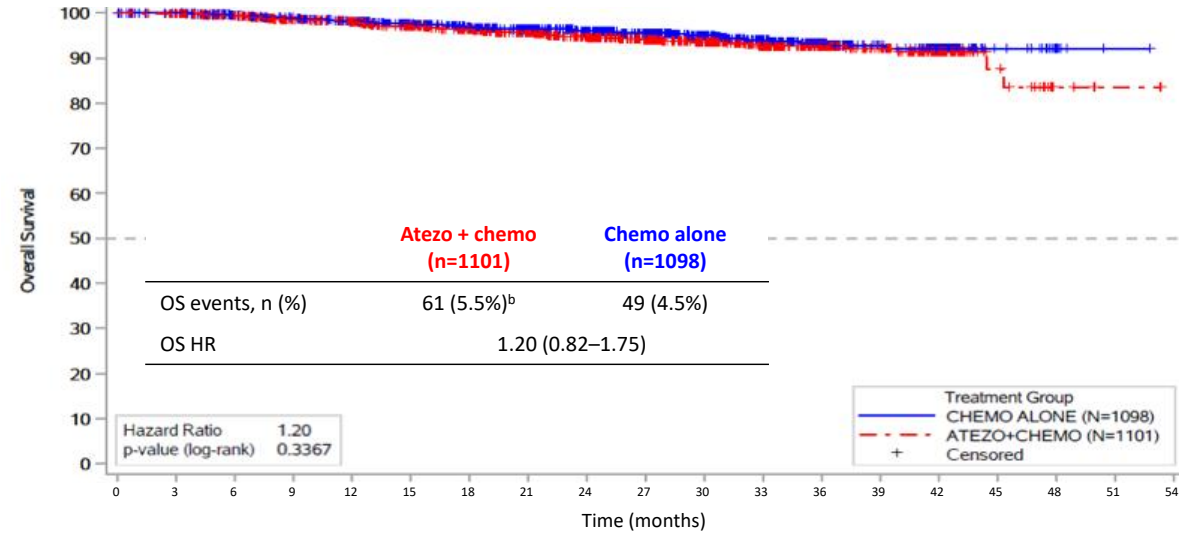
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Chemo alone	1098	1022	970	923	864	812	731	663	565	471	372	289	204	109	74	17	5	1	0
Atezo + chemo	1101	1042	995	932	869	820	735	648	564	481	391	294	202	120	66	22	5	2	0

# Key secondary efficacy endpoints

## iDFS in the PD-L1+ subgroup (71%)



## OS in ITT



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Cheмо 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

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Cheмо alone	1098	1072	1026	984	939	862	777	709	608	509	399	313	219	120	79	20	6	1	0
Atezo + chemo	1101	1082	1038	980	948	875	786	706	615	521	422	320	225	135	74	23	5	2	0

# 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  $\geq 18$  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<sup>§\*</sup>

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.

<sup>^</sup>for patients in the neoadjuvant stratum, TN status required in the preoperative and in the post-surgical specimen

<sup>#</sup> trial initially limited to pN $\geq 2$ ; protocol amendment in 10/2017 to include patents with pT2N1 and pT3-4 N0-3 disease stage

<sup>§</sup> excluding ypT1micN0, ypT1micN0i+, ypT0N0i+

<sup>\*</sup> **After amendment on 06/2018, patients in stratum B were allowed to receive additional post-operative chemotherapy and were randomized at completion of treatment.**

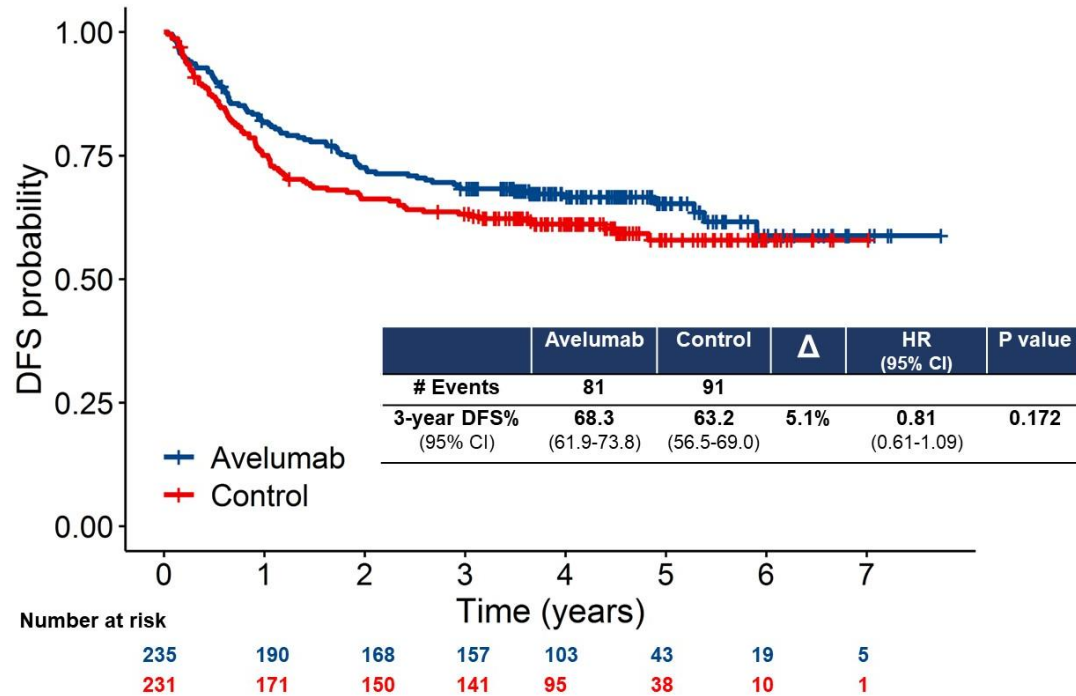
Randomization balanced for Stratum A and Stratum B.

EUDRACT 2016-000189-45; NCT 02926196

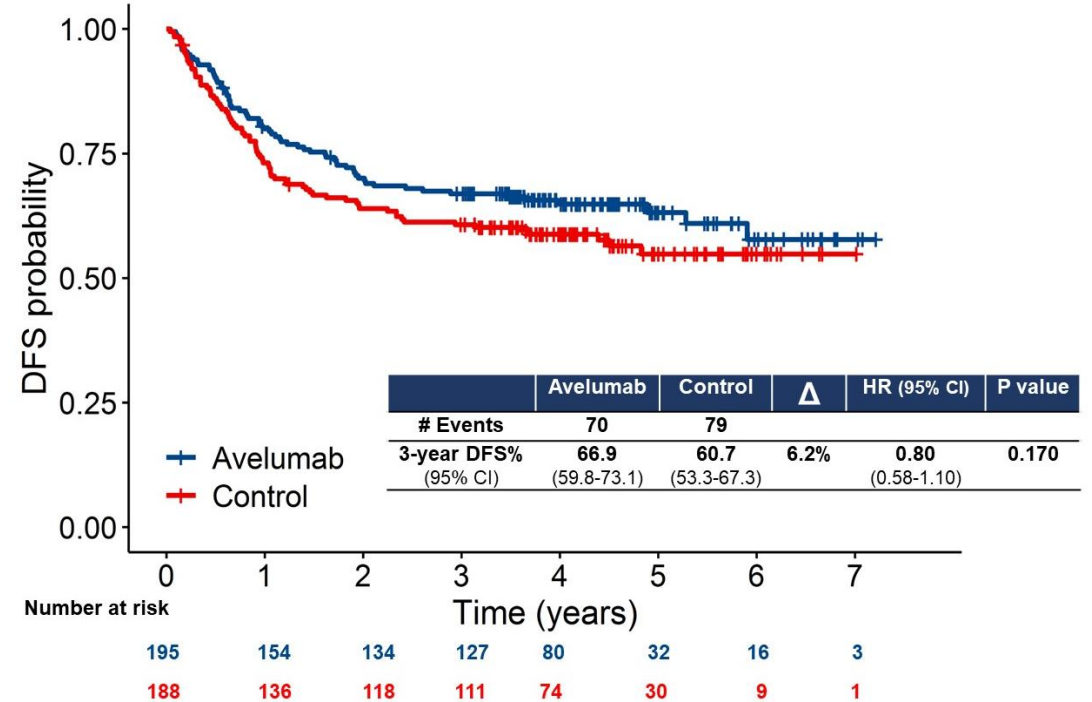
# A-BRAVE: Co-primary endpoints

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

## DFS, ITT

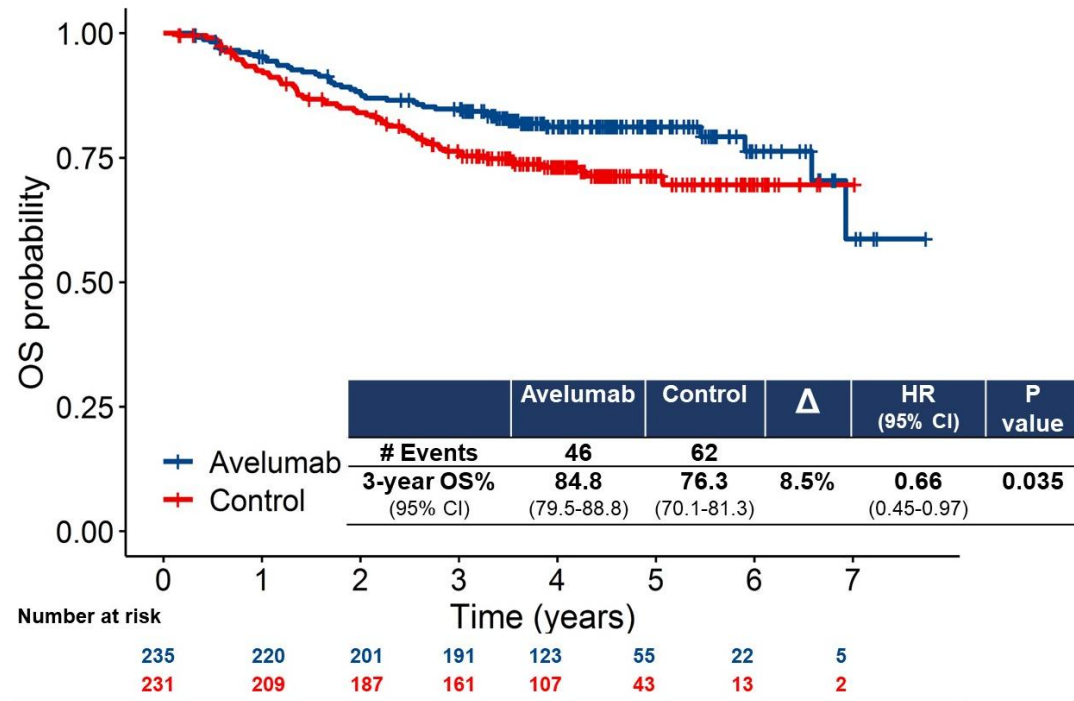


## DFS, post-NAT

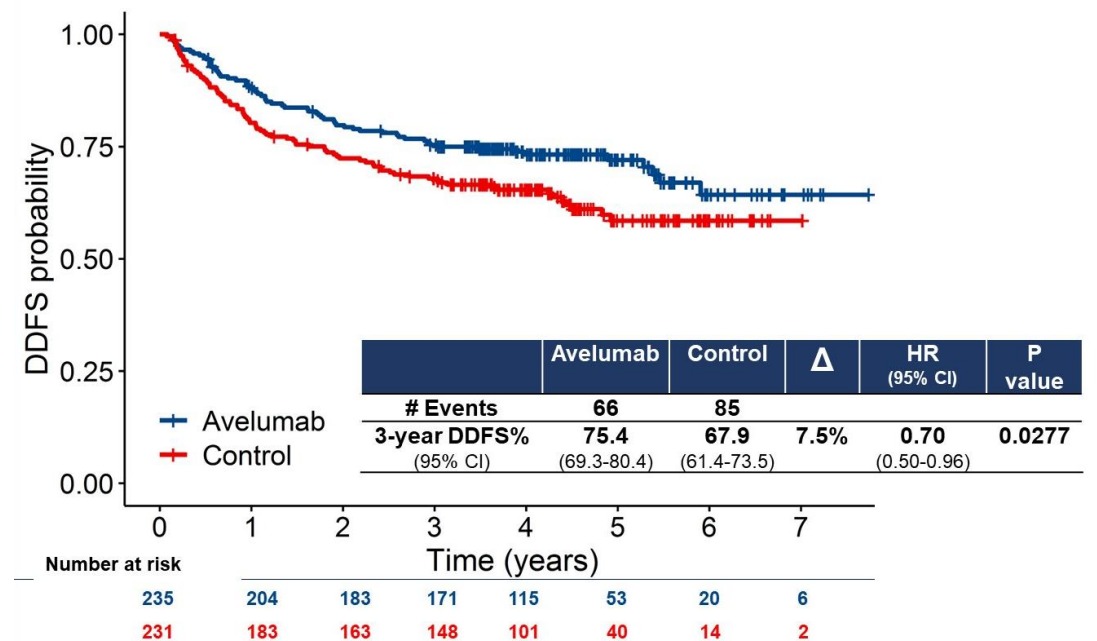


# A-BRAVE: Secondary endpoints

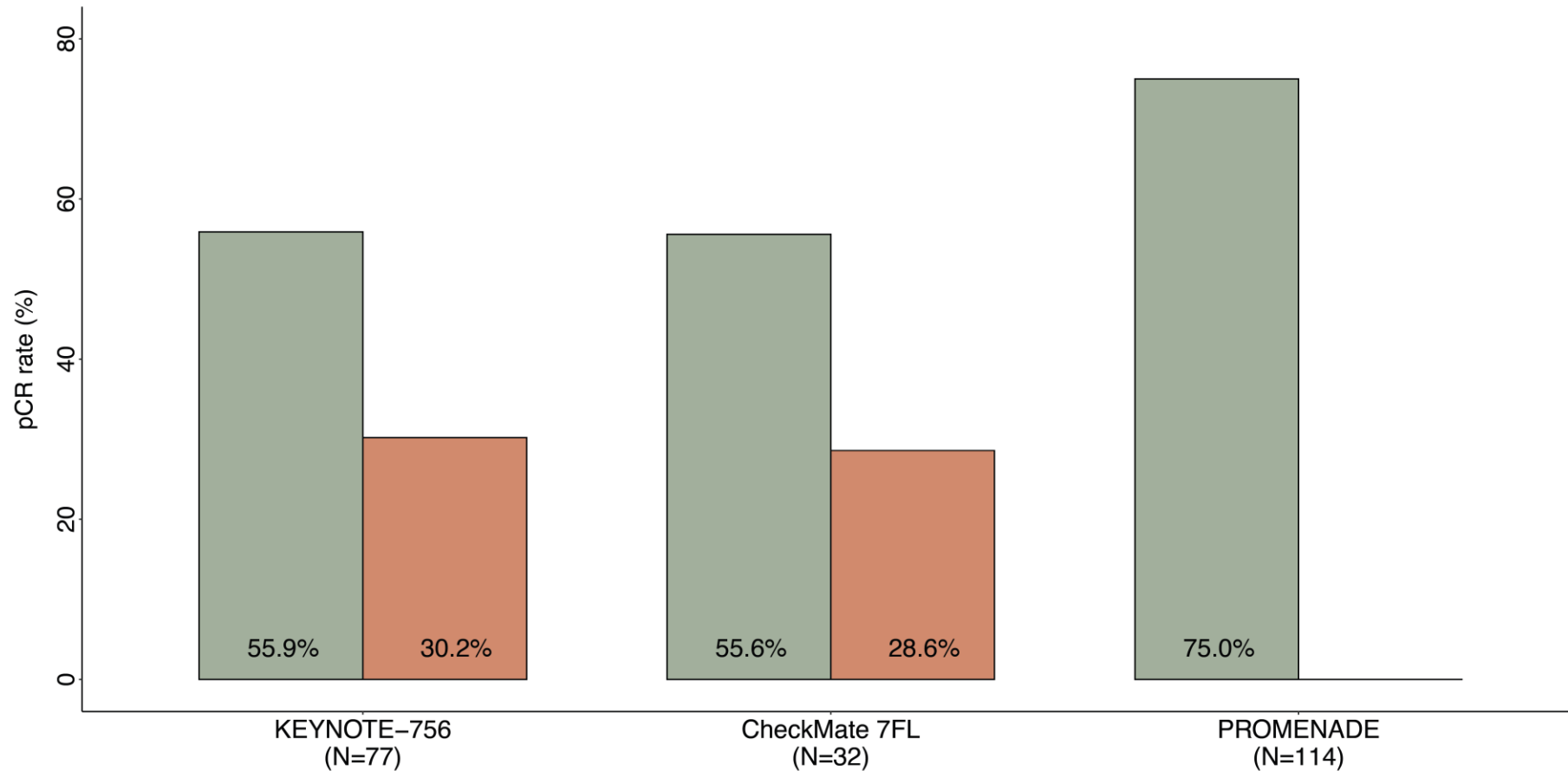
## OS, ITT



## DDFS, ITT











# ER-low (1-10% IHC) should be considered and treated similarly to TNBC



<sup>1</sup> Cardoso et al. ESMO 2023; <sup>2</sup> Loi et al. SABCS 2023; <sup>3</sup> Cherifi et al. ESMO 2024

# ER-low

## Comprehensive Diagnostic and Therapeutic Approaches for Estrogen Receptor–Low Breast Cancer: A Multidisciplinary Perspective From Oncologists and Pathologists

Paola Zagami, MD<sup>1,2</sup> ; Andrea Botticelli, MD<sup>3</sup>; Isabella Castellano, MD<sup>4</sup>; Giuseppe Curigliano, MD<sup>1,2</sup> ; Giulia d'Amati, MD<sup>3</sup> ; Carmine De Angelis, MD<sup>5,6</sup>; Maria Vittoria Dieci, MD<sup>7,8</sup> ; Veronica Errigo, MD<sup>9</sup>; Alessandra Fabi, MD<sup>10</sup>; Matteo Lambertini, MD<sup>11,12</sup> ; Antonio Rizzo, MD<sup>13</sup>; Alfredo Santinelli, MD<sup>14</sup>; Anna Sapino, MD<sup>15,16</sup> ; Cristian Scatena, MD<sup>17,18</sup>; Carmen Criscitiello, MD<sup>1,2</sup> ; and Nicola Fusco, MD<sup>2,19</sup> 

DOI <https://doi.org/10.1200/OP-25-00378>

### ABSTRACT

Estrogen receptor (ER)–low breast cancer (BC) is a rare subtype of BC defined by ER expression between 1% and 10% and is biologically more similar to triple–negative than hormone receptor–positive BC. Conflicting data have been published regarding the benefit of endocrine therapy (ET) in this subtype, whereas the response to neoadjuvant chemotherapy and prognosis seems to be comparable with that of TNBC. ER–low BC was not included in most of the randomized clinical trials conducted among patients with TNBC, missing the opportunity to access new drugs and collect data. Recent evidence has suggested that ER–low BC might benefit from an immune–chemotherapy regimen, aligning to TNBC. International guidelines should recognize ER–low BC as a unique and heterogeneous

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Conclusions

# Immunotherapy Outperforms Many New Options in Absolute Benefit

PEMBROLIZUMB (TNBC)

5-year EFS **9.0%**

5-year DDFS **7.6%**

5-year OS **4.9%**



PERTUZUMAB (HER2+)

ABEMACICLIB (ER+/HER2-)

RIBOCICLIB (ER+/HER2-)

OLAPARIB (TNBC e ER+/HER2-)

# Urgent need for “precision immunology”

Predicting benefit from adding immunotherapy to chemotherapy in early-stage TNBC remains challenging, with no biomarkers ready for prime time

