bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

JOURNAL CLUB UPDATES

TNBC fase precoce

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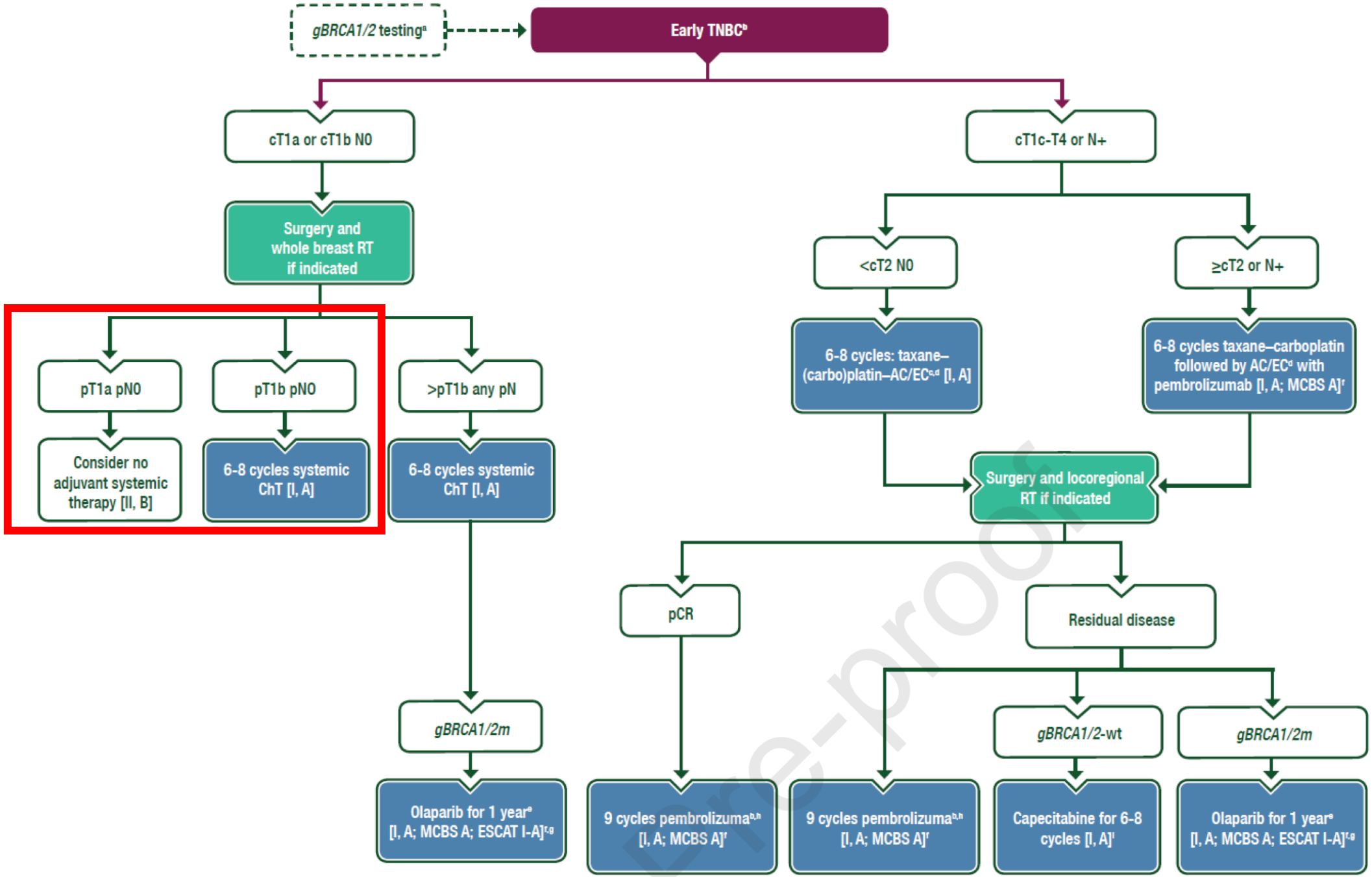
Università degli Studi di Milano
Istituto Europeo di Oncologia

Disclosure slide

Advisory/consultancy role/speaker bureau:

Eli Lilly, Pfizer, Novartis, Roche, AstraZeneca, MSD, Daiichi Sankyo, Gilead, Seagen


gBRCA1/2 testing[a]
Early TNBC[b]
cT1a or cT1b N0
cT1c-T4 or N+
Surgery and whole breast RT if indicated
<cT2 N0
≥cT2 or N+
pT1a pN0
pT1b pN0
>pT1b any pN
6-8 cycles: taxane–(carbo)platin–AC/EC[c,d] [I, A]
6-8 cycles taxane–carboplatin followed by AC/EC[d] with pembrolizumab [I, A; MCBS A][f]
Consider no adjuvant systemic therapy [II, B]
6-8 cycles systemic ChT [I, A]
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Surgery and locoregional RT if indicated
pCR
Residual disease
gBRCA1/2m
gBRCA1/2-wt
gBRCA1/2m
Olaparib for 1 year[e] [I, A; MCBS A; ESCAT I-A][f,g]
9 cycles pembrolizuma[b,h] [I, A; MCBS A][f]
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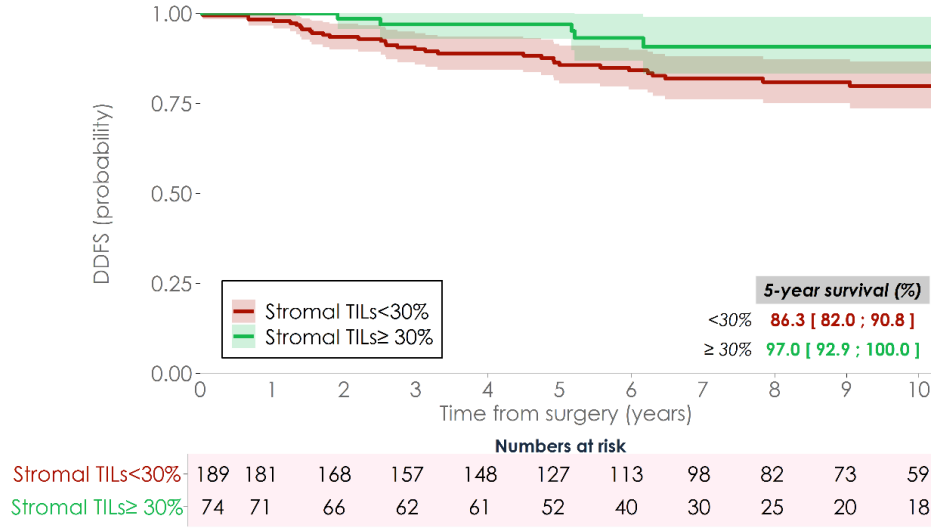
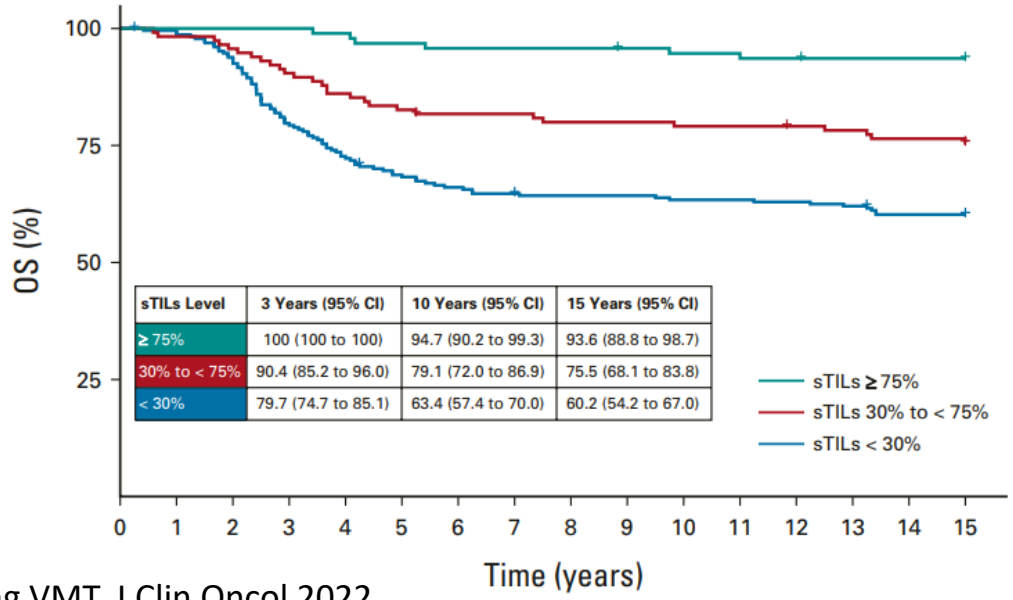
Capecitabine for 6-8 cycles [I, A][f]
Olaparib for 1 year[e] [I, A; MCBS A; ESCAT I-A][f,g]

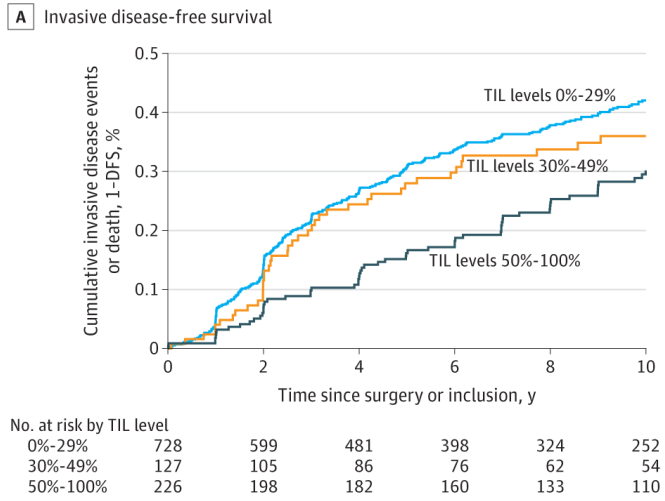
TILs in systemically untreated stage 1 TNBC

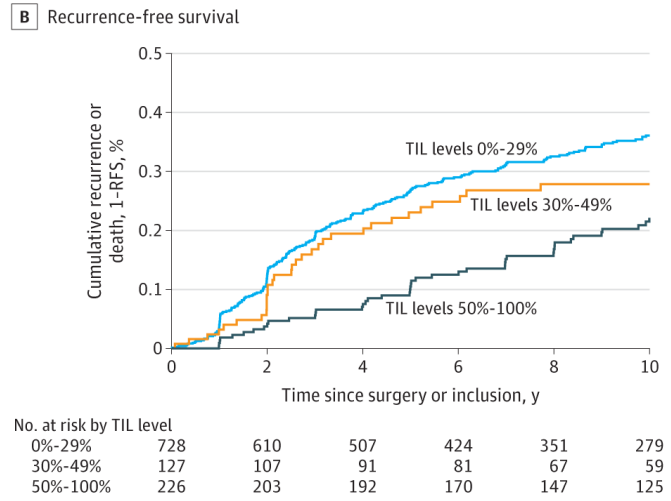


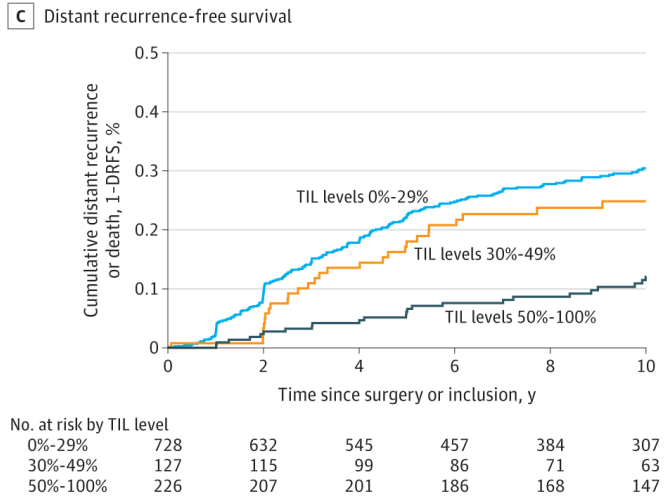
Park JH et al. Ann Oncol 2019

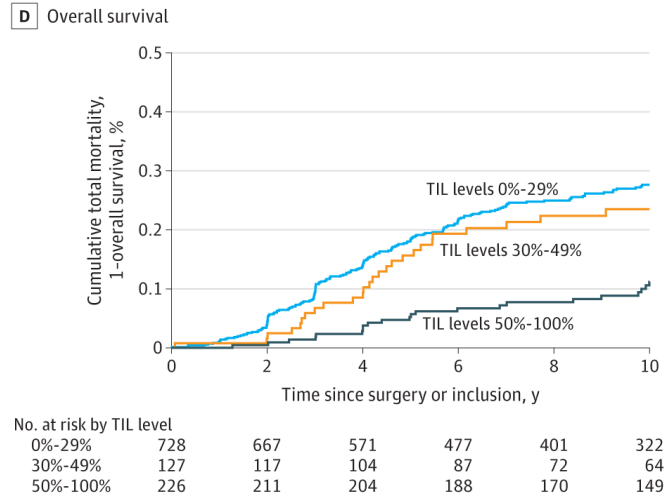


De Jong VMT, J Clin Oncol 2022

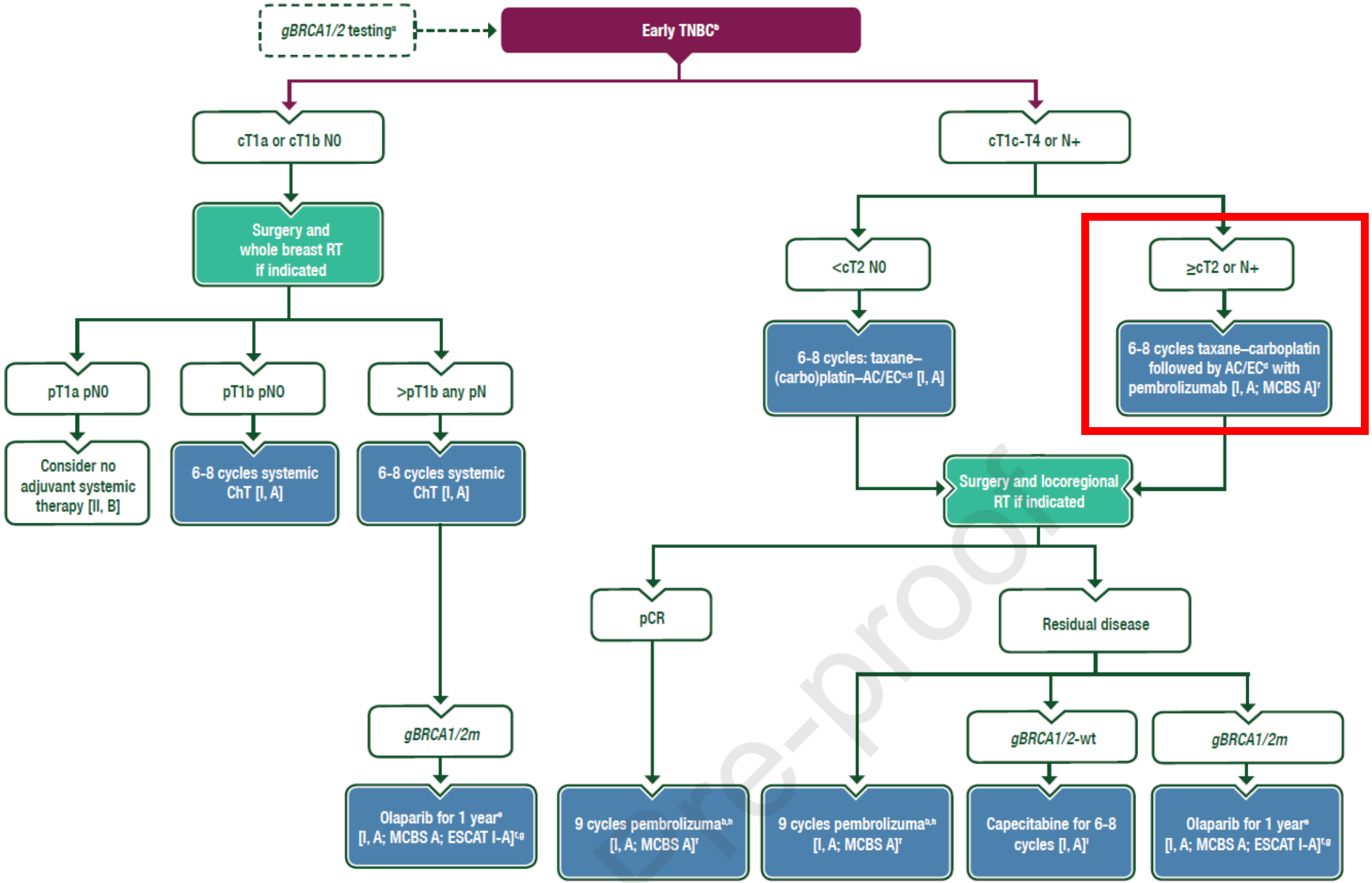








Leon-Ferre et al, JAMA 2024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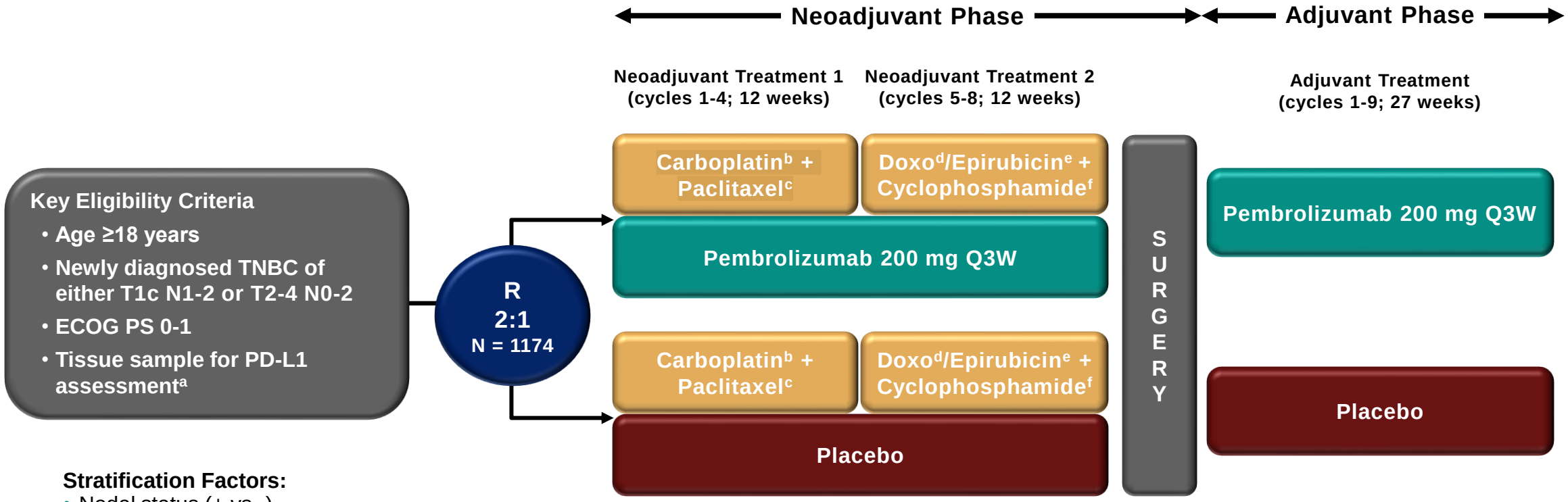
KEYNOTE-522 Study Design



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

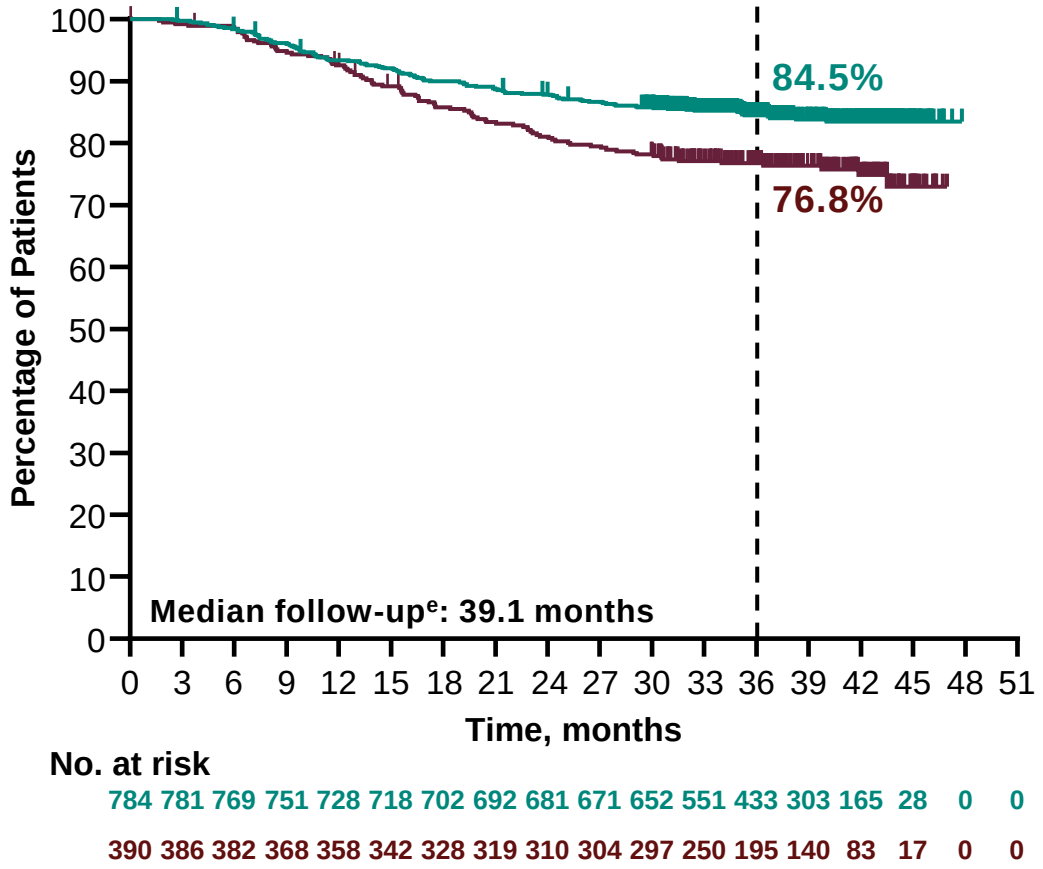
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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

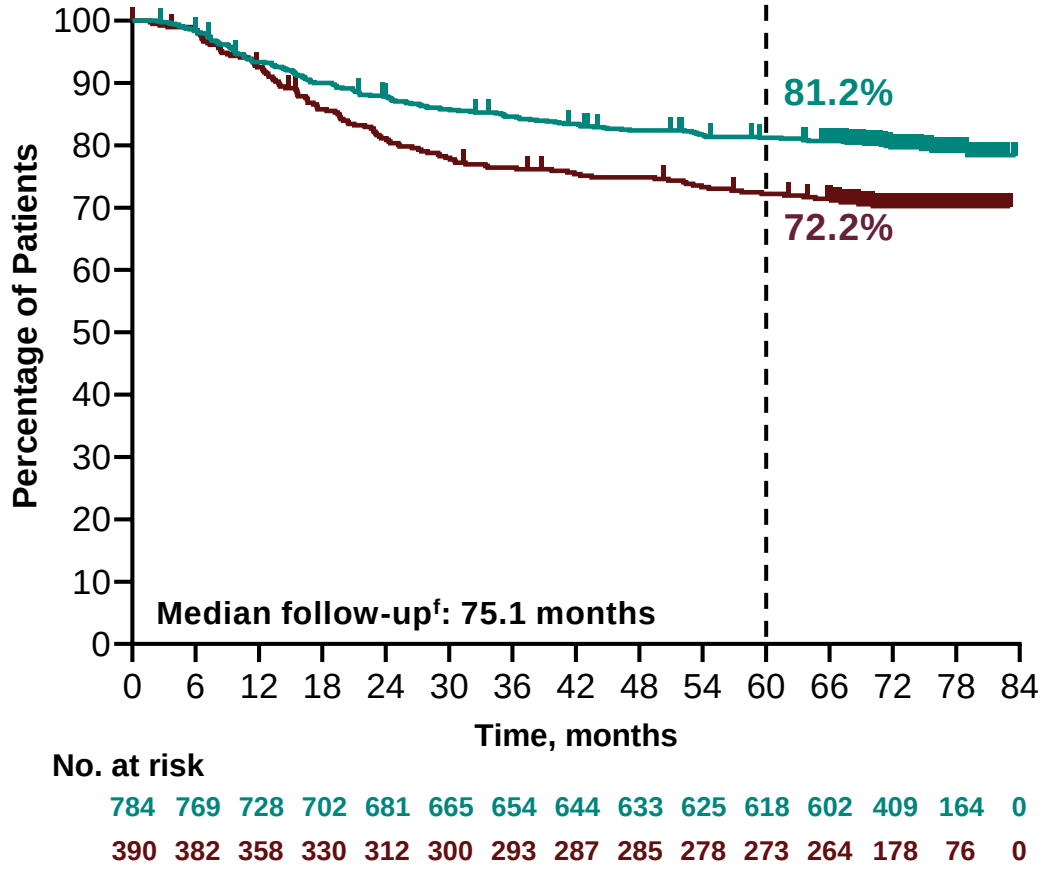
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Durable Event-Free Survival

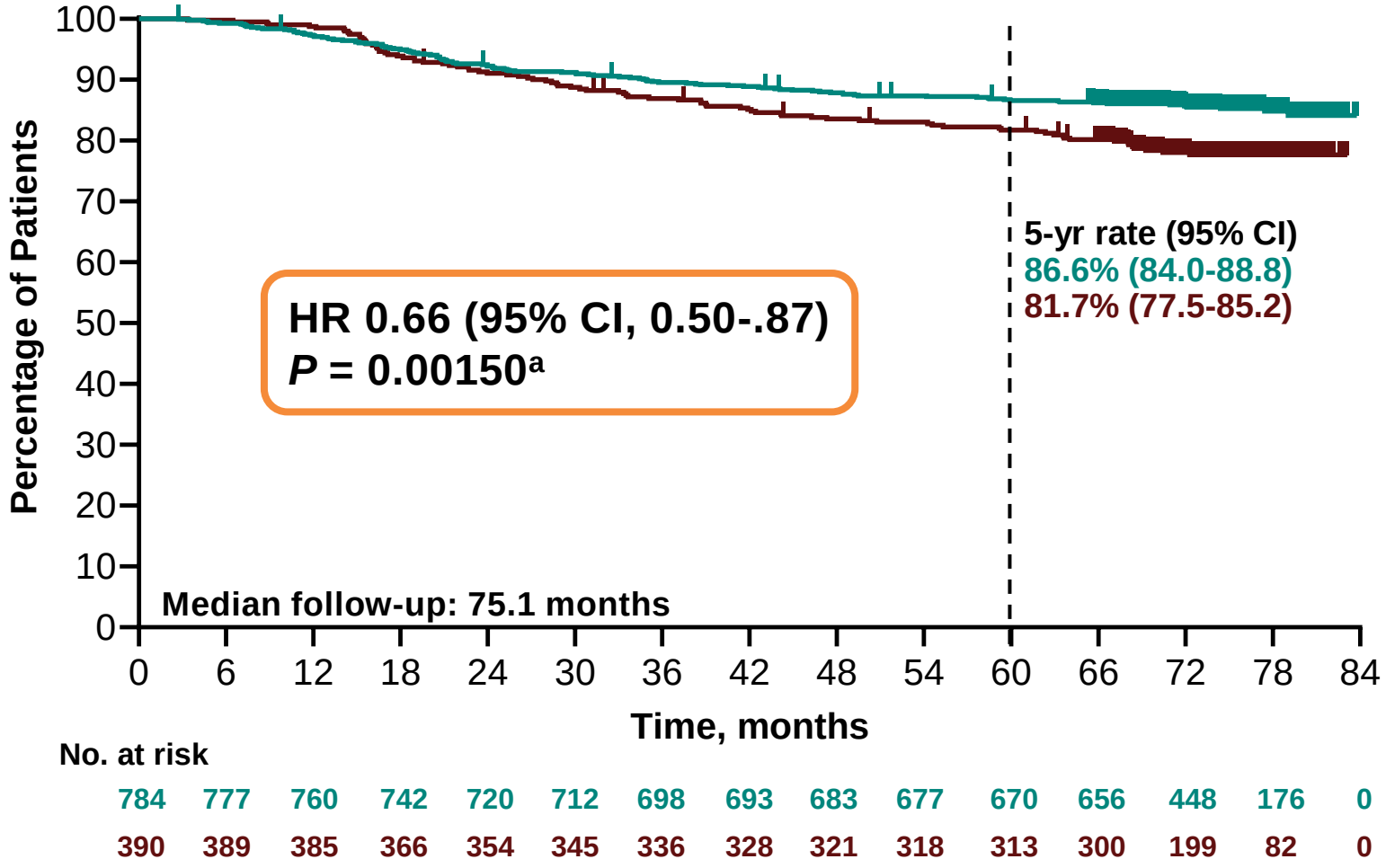
IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



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



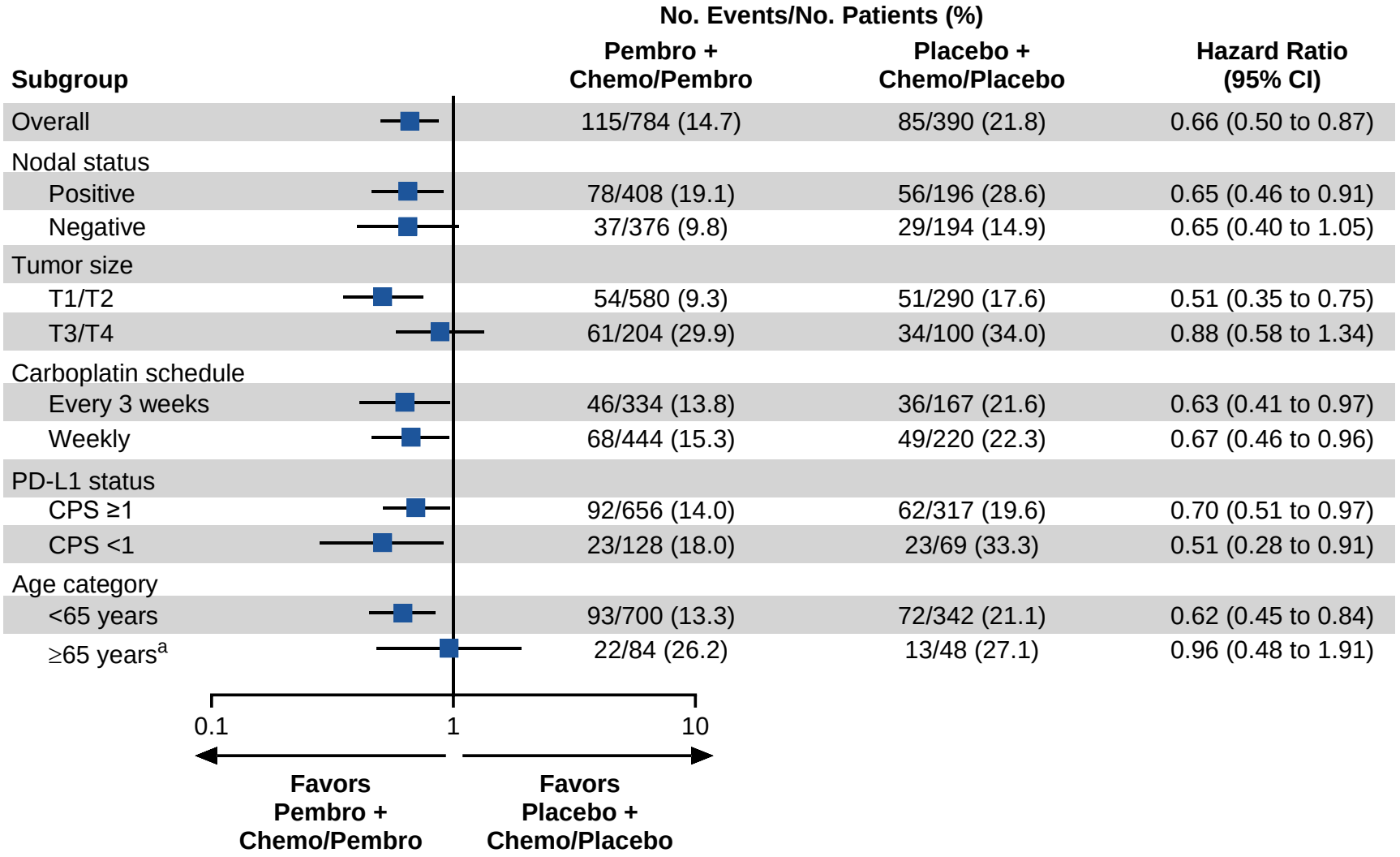
Key Secondary Endpoint: Overall Survival



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

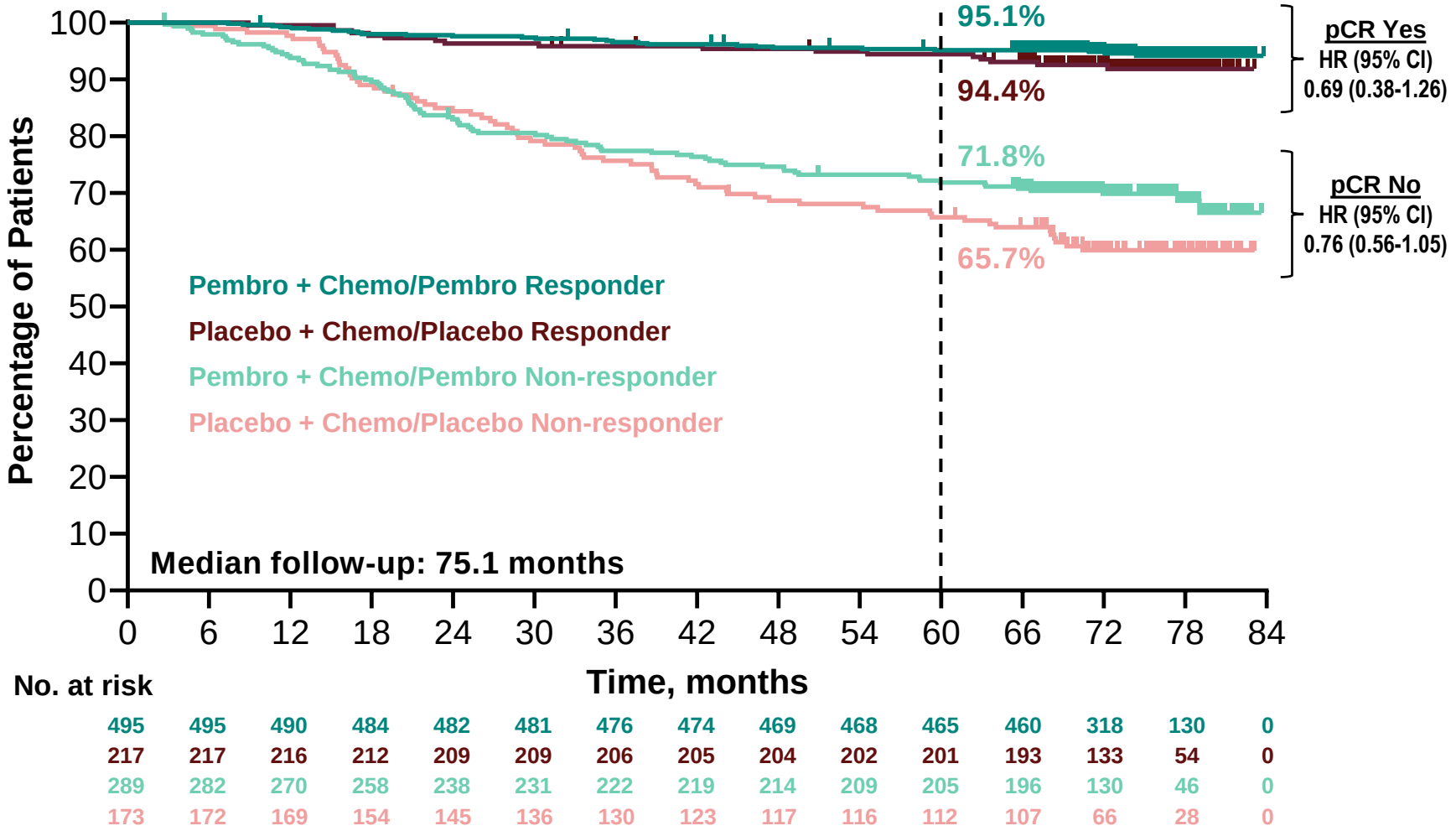
67.3% information fraction[a]

Overall Survival in Patient Subgroups

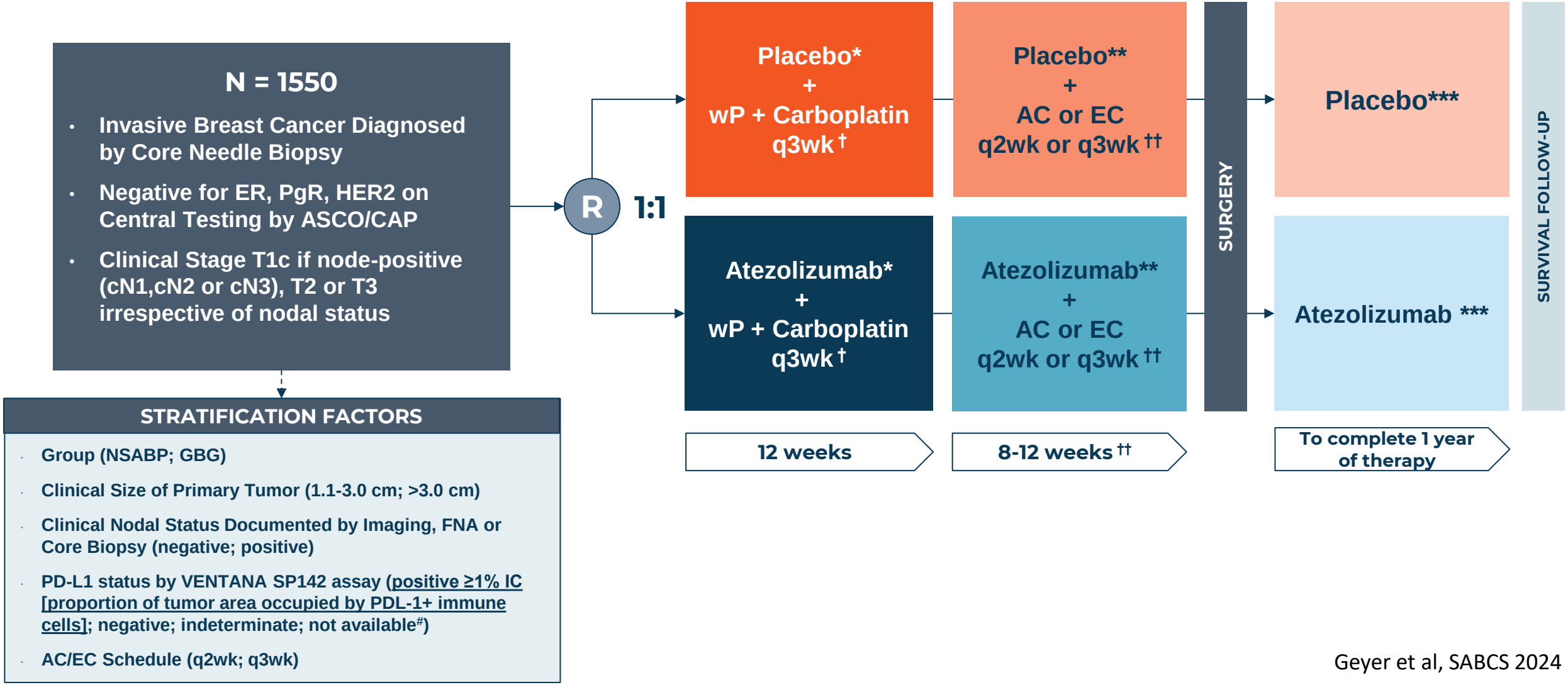


Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)

Overall Survival by pCR

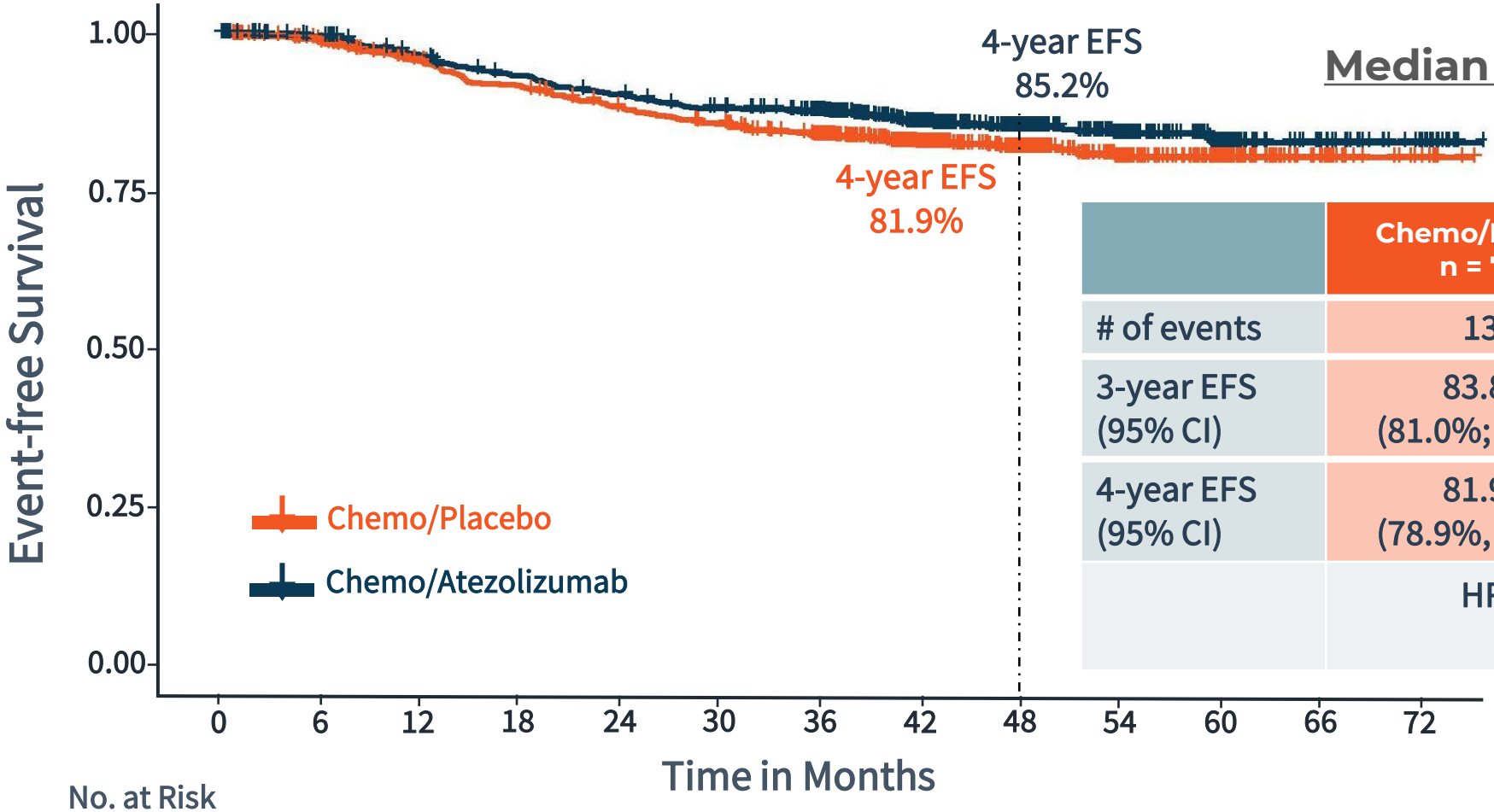


NSABP B-59/GBG-96-GeparDouze: Study Design



Geyer et al, SABCS 2024

NSABP B-59/GBG-96-GeparDouze: EFS



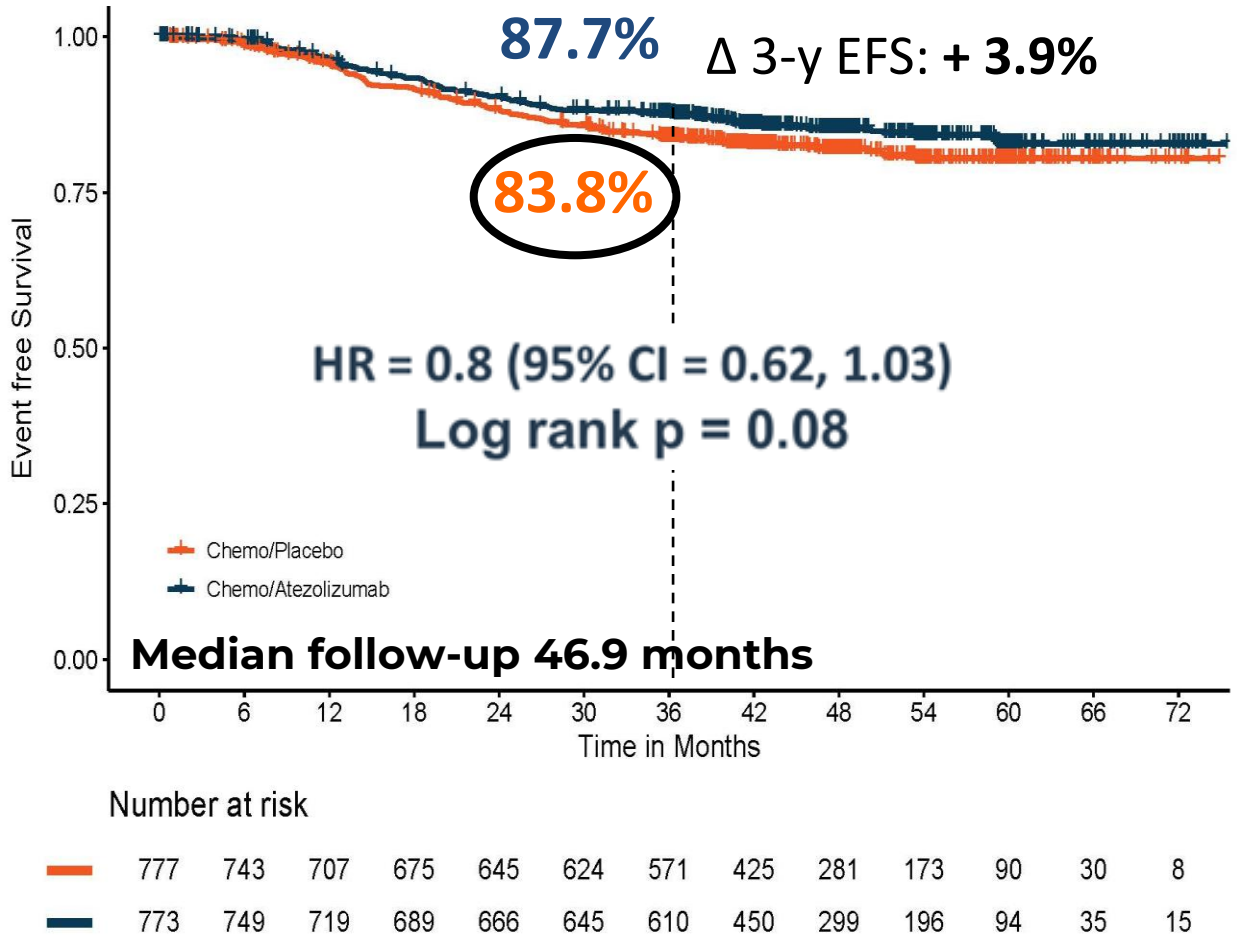
Median follow-up 46.9 months

	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	133	110
3-year EFS (95% CI)	83.8% (81.0%; 86.3%)	87.7% (85.1%; 89.9%)
4-year EFS (95% CI)	81.9% (78.9%, 84.6%)	85.2% (82.4%, 87.7%)
	HR = 0.8 (95% CI = 0.62, 1.03) Log rank p = 0.08	

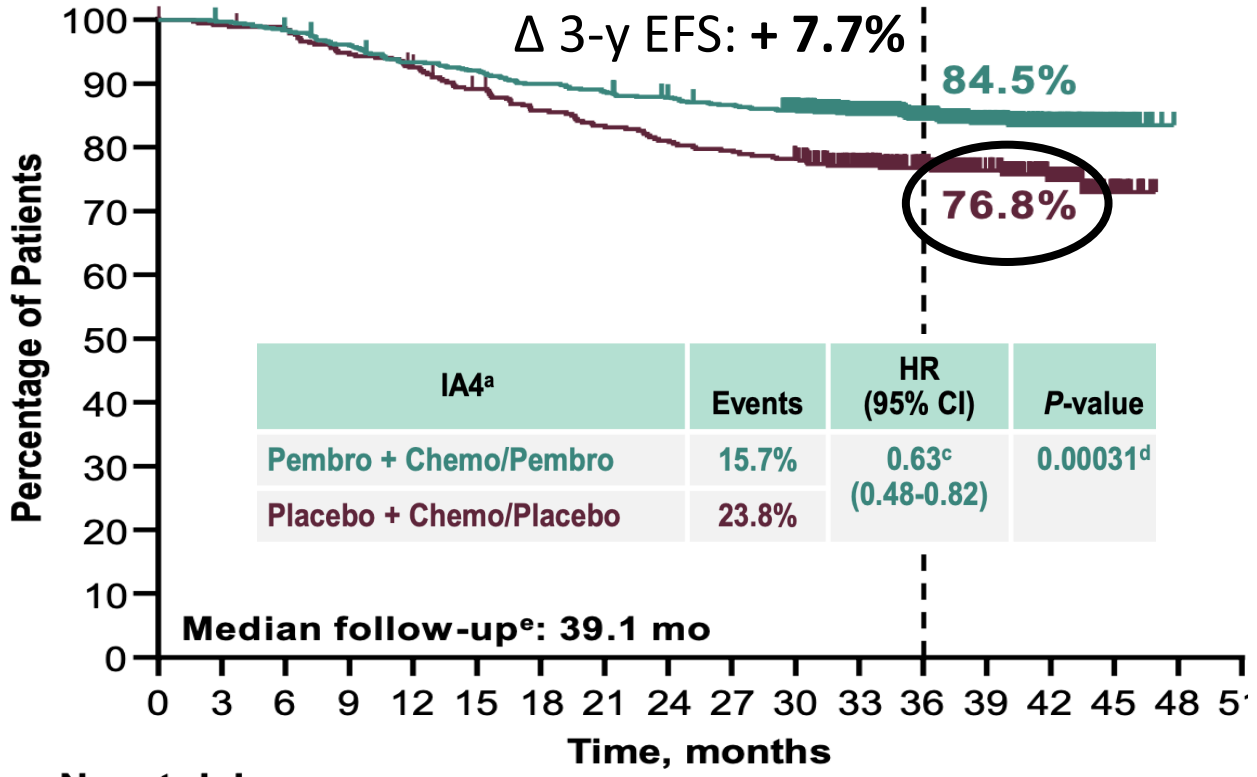
Geyer et al, SABCS 2024

3-year EFS

NSABP B-59/GBG-96-GeparDouze



KEYNOTE-522



Geyer SABCS 2024; Schmid et al. NEJM 2020

Courtesy of Giampaolo Bianchini

Some differences

Characteristic	GeparDouze (N=1550)		KEYNOTE-522 (N=1174)	
	Exp Arm	Std Arm	Exp Arm	Std Arm
Age Median (range)	49.0 (22-79)	49.0 (23-77)	49 (22–80)	48 (24–79)
Race White Asian Other	 89.5 2.3 8.2	 90.3 1.7 8.0	 64.3 19.0 16.7	 62.1 22.8 15.1
cT stage (%) † cT1-2 cT3-4	 - -	 - -	 74.0 26.0	 74.4 25.6
cN stage (%) ‡ cN0 cN+	 58.5 41.5	 59.1 40.9	 51.7 48.3	 51.3 48.7

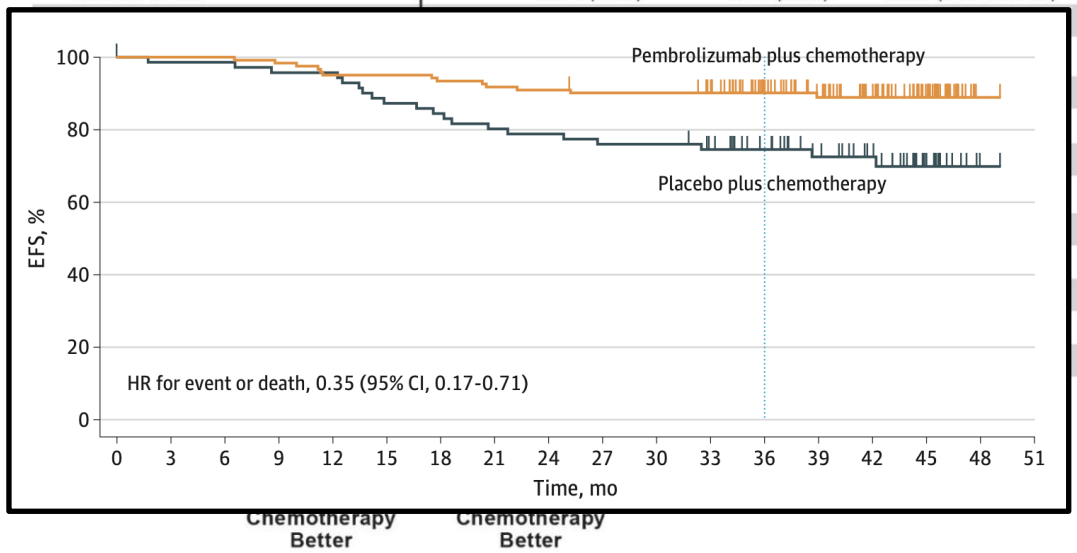
Adapted from G. Bianchini at SABCS 2024

Does the Asian population benefit the most from ICI?

KEYNOTE-522

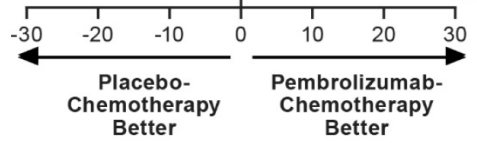
EFS

Subgroup	Pembrolizumab-Chemotherapy	Placebo-Chemotherapy	Hazard Ratio (95% CI)
	no. of patients with event/total no. (%)		
Overall	159/784 (20.3)	114/390 (29.2)	0.65 (0.51 to 0.83)
Menopausal status			
Pre-menopausal	75/438 (17.1)	56/221 (25.3)	0.64 (0.46 to 0.91)
Post-menopausal	84/345 (24.3)	58/169 (34.3)	0.66 (0.48 to 0.93)
Geographic region			
EU/Israel/NA/Australia	126/607 (20.8)	83/285 (29.1)	0.68 (0.52 to 0.90)
Asia	18/136 (13.2)	22/80 (27.5)	0.43 (0.23 to 0.81)
Rest of World	15/41 (36.6)	9/25 (36.0)	0.95 (0.42 to 2.18)



OS

Subgroup	Pembrolizumab-Chemotherapy	Placebo-Chemotherapy	Difference in 5-Year Overall Survival
	no. of patients with event/total no. (%)		*percentage points (95% CI)*
Overall	115/784 (14.7)	85/390 (21.8)	4.9 (0.3 to 9.4)
Menopausal status			
Pre-menopausal	55/438 (12.6)	39/221 (17.6)	4.0 (-1.7 to 9.7)
Post-menopausal	60/345 (17.4)	46/169 (27.2)	6.0 (-1.3 to 13.3)
Geographic region			
EU/Israel/NA/Australia	90/607 (14.8)	60/285 (21.1)	3.2 (-1.9 to 8.3)
Asia	12/136 (8.8)	16/80 (20.0)	10.8 (1.0 to 20.6)
Rest of World	13/41 (31.7)	9/25 (36.0)	4.3 (-19.3 to 27.9)
Ethnic origin			
Hispanic	23/85 (27.1)	14/39 (35.9)	2.5 (-14.5 to 19.5)
non-Hispanic	79/616 (12.8)	59/307 (19.2)	4.0 (-0.8 to 8.8)
HER2 status			
2+ by IHC (but FISH-)	28/188 (14.9)	22/104 (21.2)	3.4 (-5.4 to 12.2)
0-1+ by IHC	87/595 (14.6)	63/286 (22.0)	5.3 (0.0 to 10.6)
LDH			
>ULN	26/149 (17.4)	24/80 (30.0)	7.6 (-3.5 to 18.7)
≤ULN	88/631 (13.9)	60/309 (19.4)	3.9 (-1.0 to 8.8)
ECOG PS			
0	92/678 (13.6)	74/341 (21.7)	6.6 (1.7 to 11.4)
1	23/106 (21.7)	11/49 (22.4)	-6.5 (-18.9 to 6.0)



Schmid et al NEJM 2024; Takahashi et al. JAMA Netw Open 2023

Courtesy of Giampaolo Bianchini

Some differences

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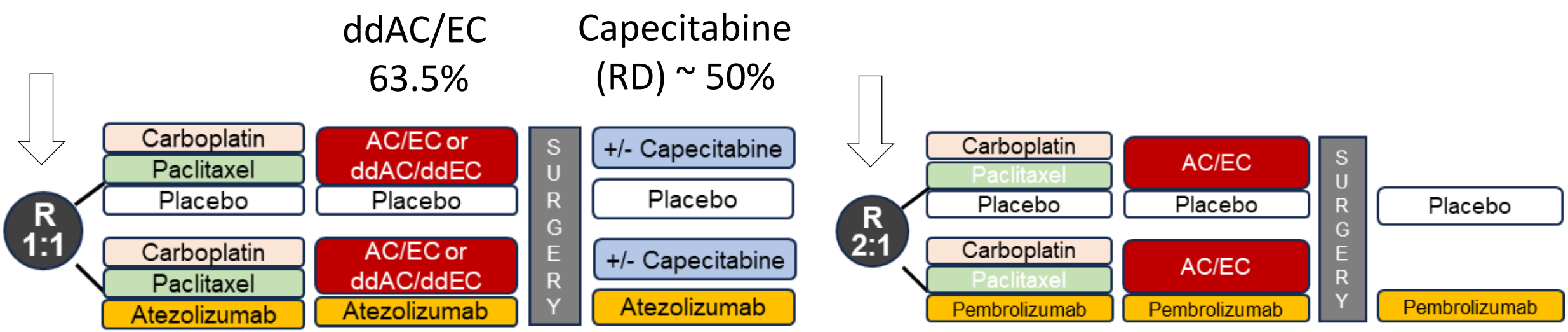
Adapted from G. Bianchini at SABCS 2024

More important differences



Atezolizumab
Anti-PD-L1

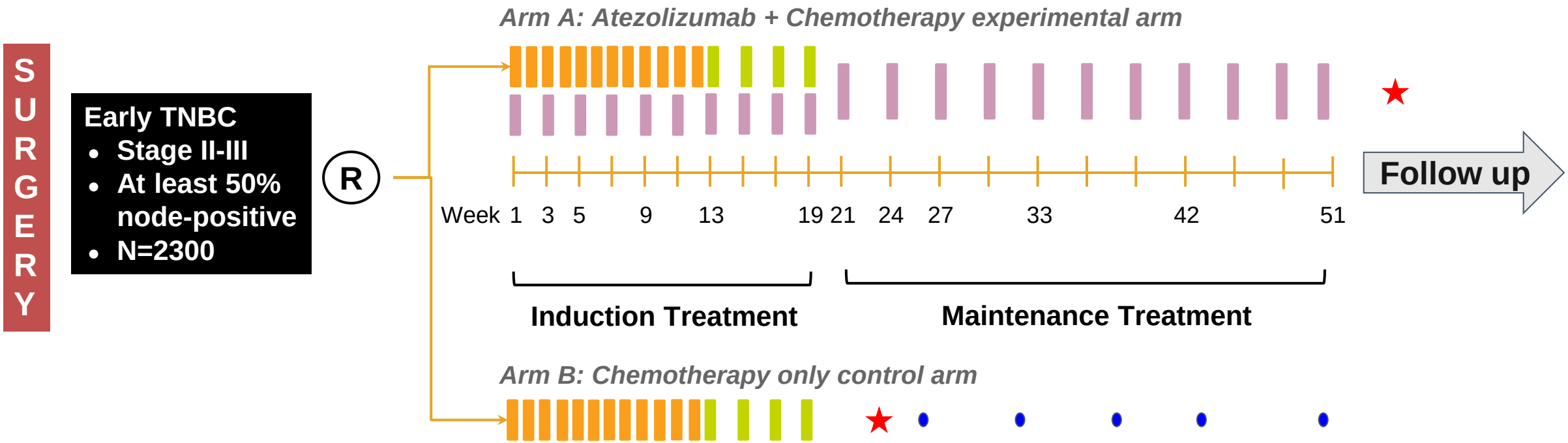
Pembrolizumab
Anti-PD1

Geyer SABCS 2024; Schmid et al. NEJM 2020

Courtesy of Giampaolo Bianchini

Adjuvant immunotherapy

Alexandra/IMpassion030: Study design



Stratification factors:

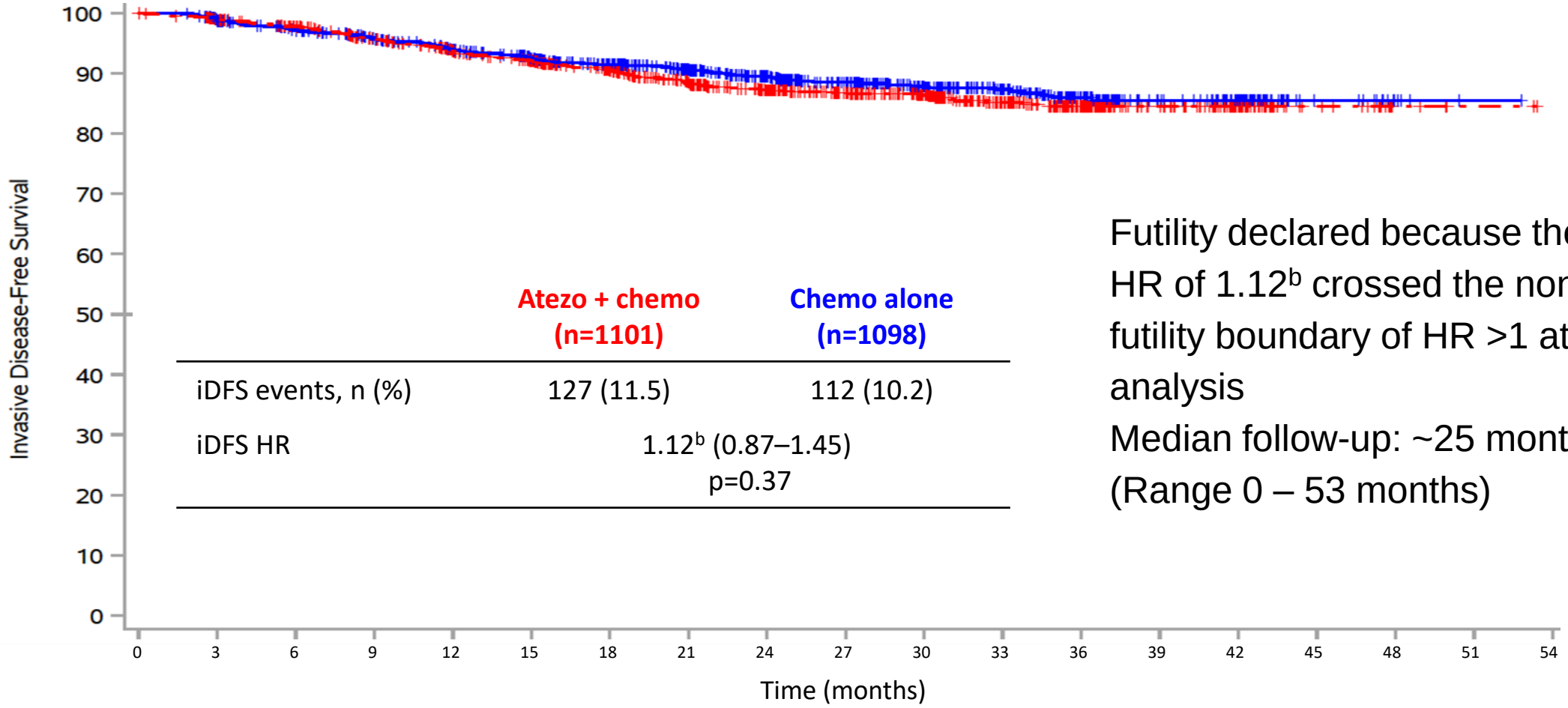
Axillary nodal status
(0 vs. 1−3 vs. ≥ 4 positive lymph nodes)
Surgery
(breast conserving vs. mastectomy)
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

- 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

M. Ignatiadis et al, JAMA 2025

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[b] (0.87–1.45) p=0.37	

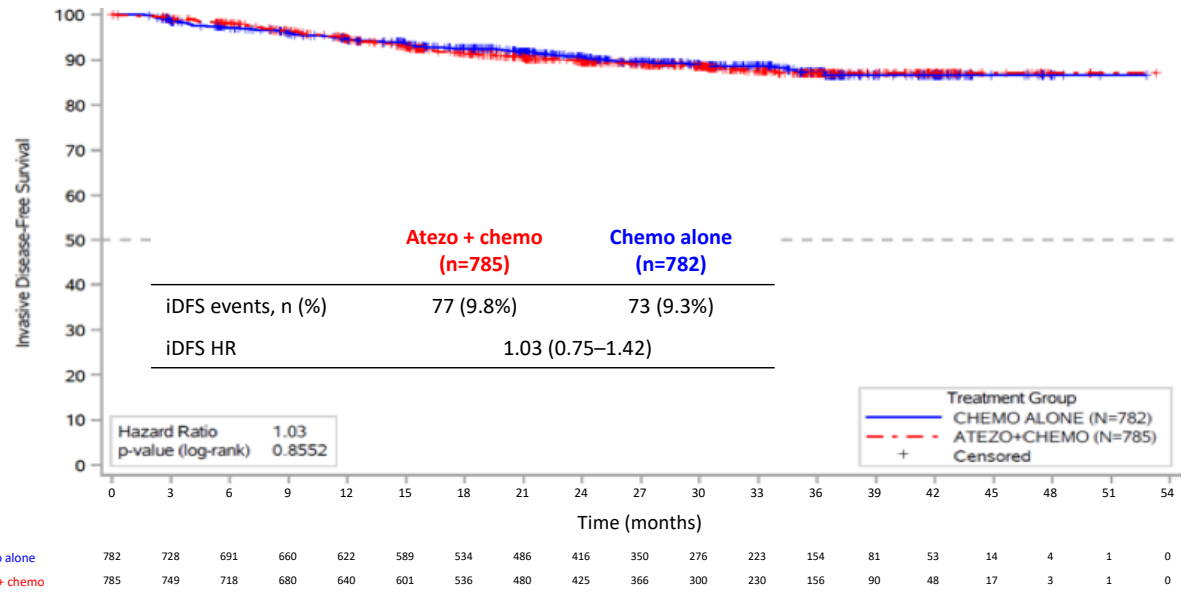
Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

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

M. Ignatiadis et al, JAMA 2025

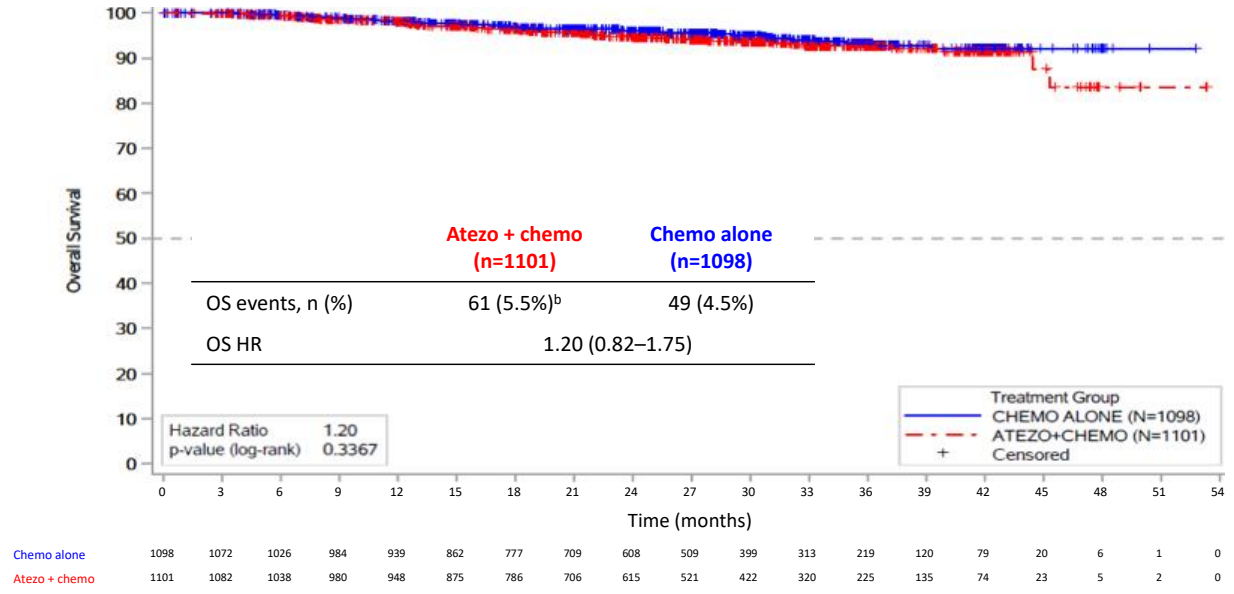
Key secondary efficacy endpoints

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



	Atezo + chemo (n=785)	Chemo alone (n=782)
iDFS events, n (%)	77 (9.8%)	73 (9.3%)
iDFS HR	1.03 (0.75–1.42)	

OS in ITT



	Atezo + chemo (n=1101)	Chemo alone (n=1098)
OS events, n (%)	61 (5.5%)[b]	49 (4.5%)
OS HR	1.20 (0.82–1.75)	

M. Ignatiadis et al, JAMA 2025

A-BRAVE Trial - Study Design

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

A-BRAVE-TRIAL

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.

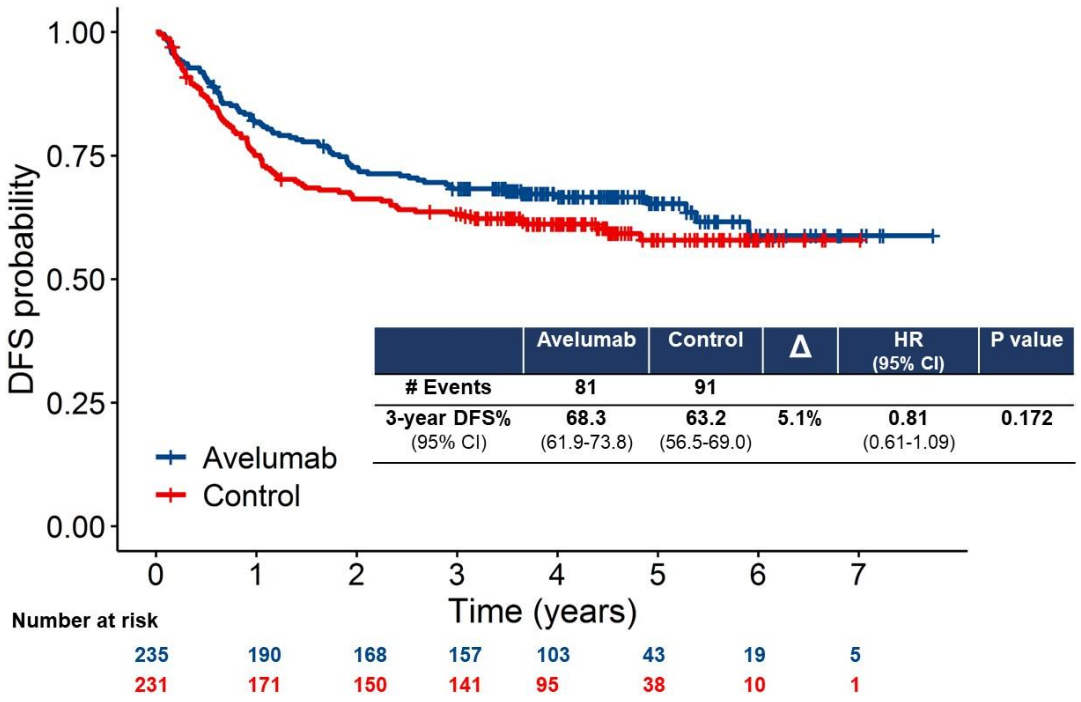
EUDRACT 2016-000189-45; NCT 02926196

PRESENTED BY: Pierfranco Conte, MD

A-BRAVE: Co-primary endpoints

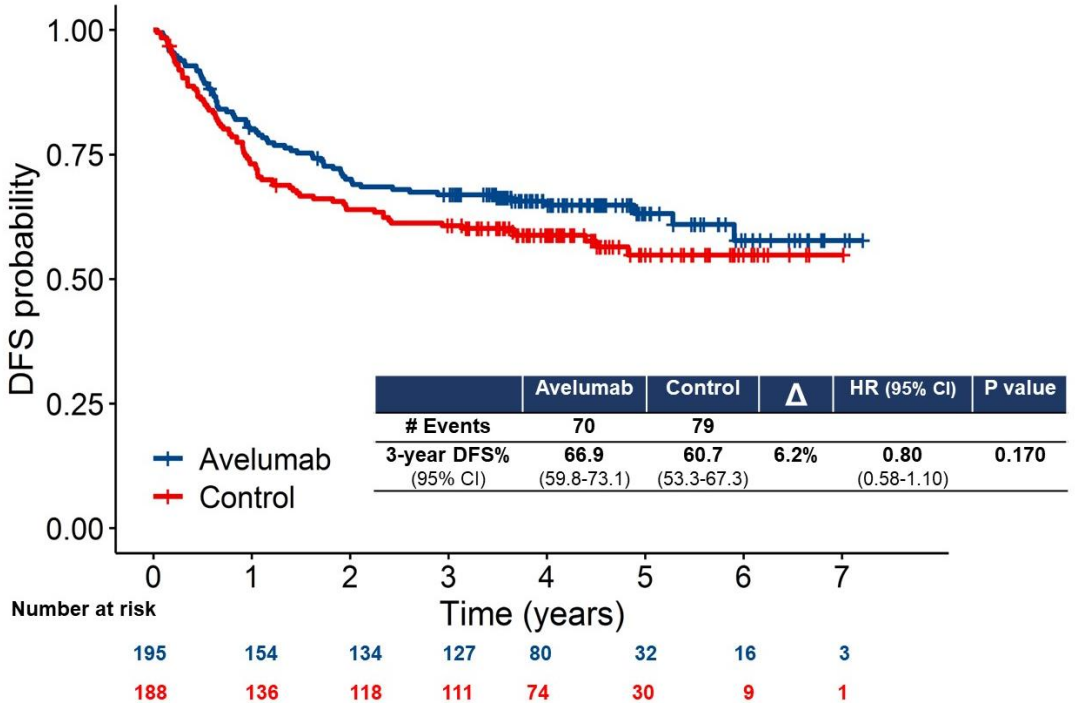
median FUp: 52.1 months (95% CI: 49.8- 53.8)

DFS, ITT



	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

DFS, post-NAT

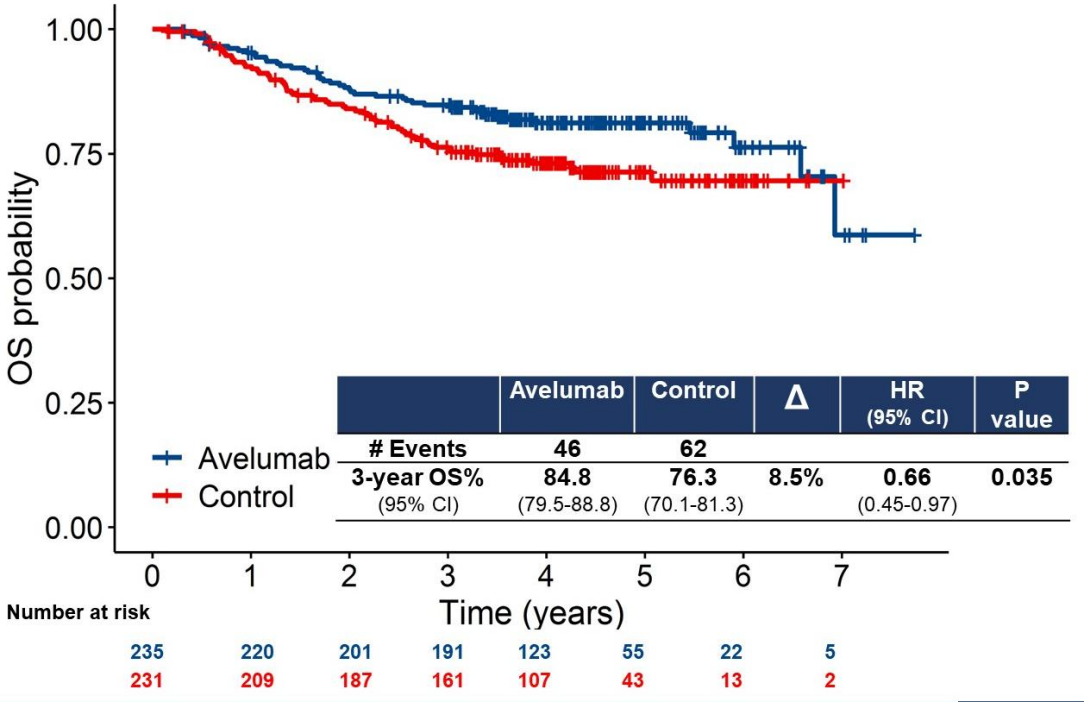


	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	70	79			
3-year DFS% (95% CI)	66.9 (59.8-73.1)	60.7 (53.3-67.3)	6.2%	0.80 (0.58-1.10)	0.170

Conte P, ASCO 2024

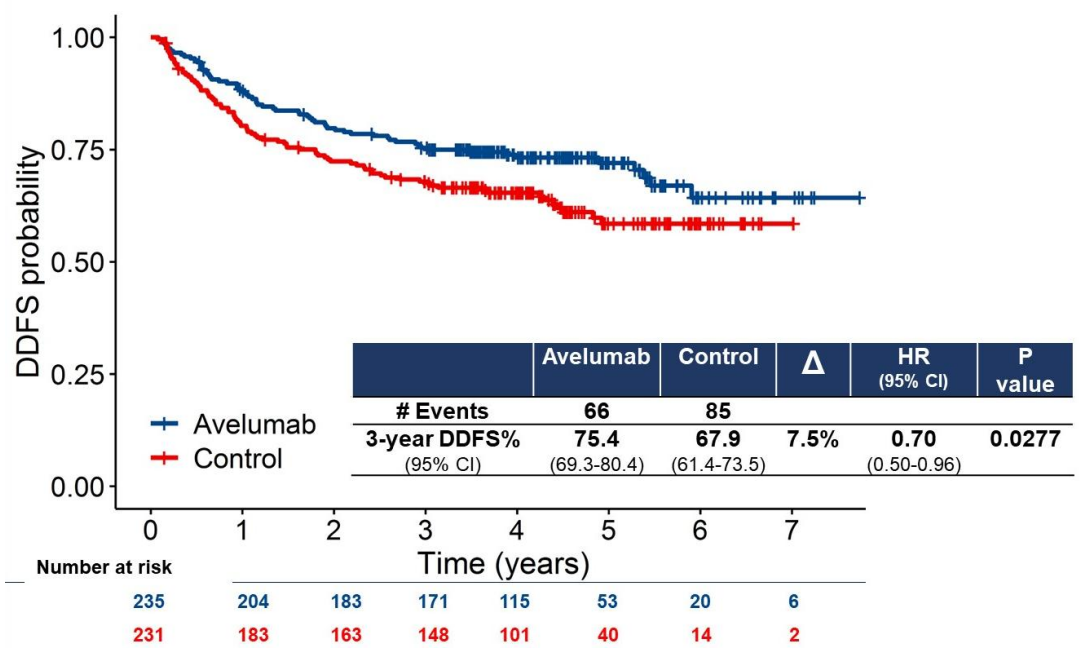
A-BRAVE: Secondary endpoints

OS, ITT



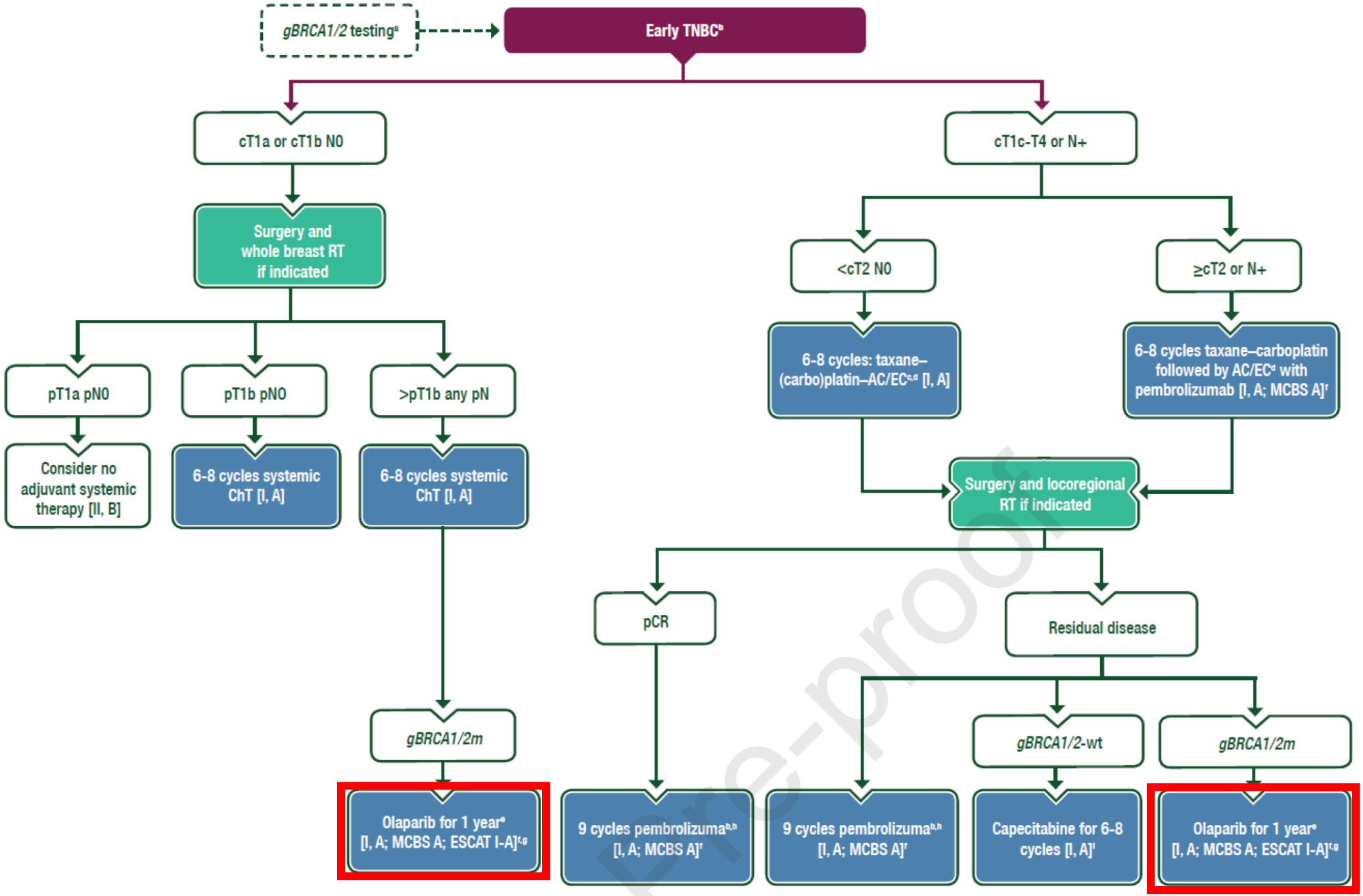
	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	46	62			
3-year OS% (95% CI)	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035

DDFS, ITT

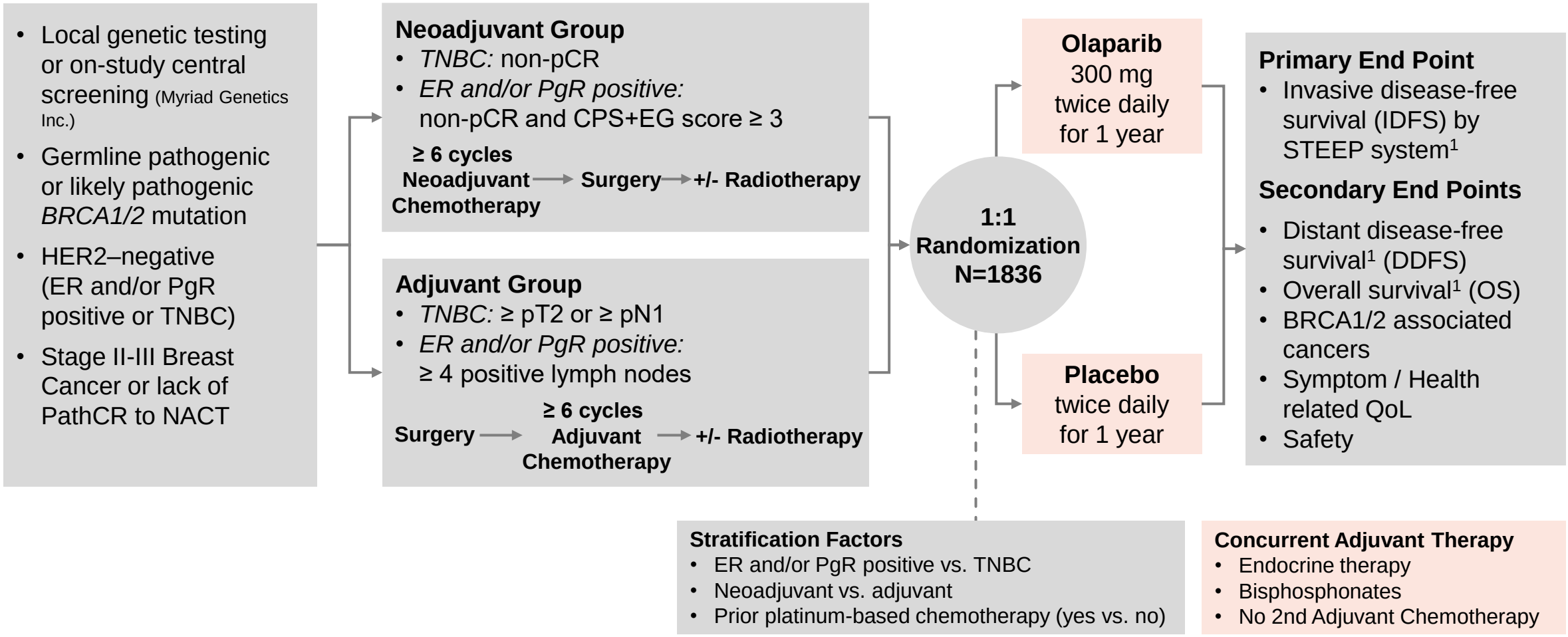


	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	66	85			
3-year DDFS% (95% CI)	75.4 (69.3-80.4)	67.9 (61.4-73.5)	7.5%	0.70 (0.50-0.96)	0.0277

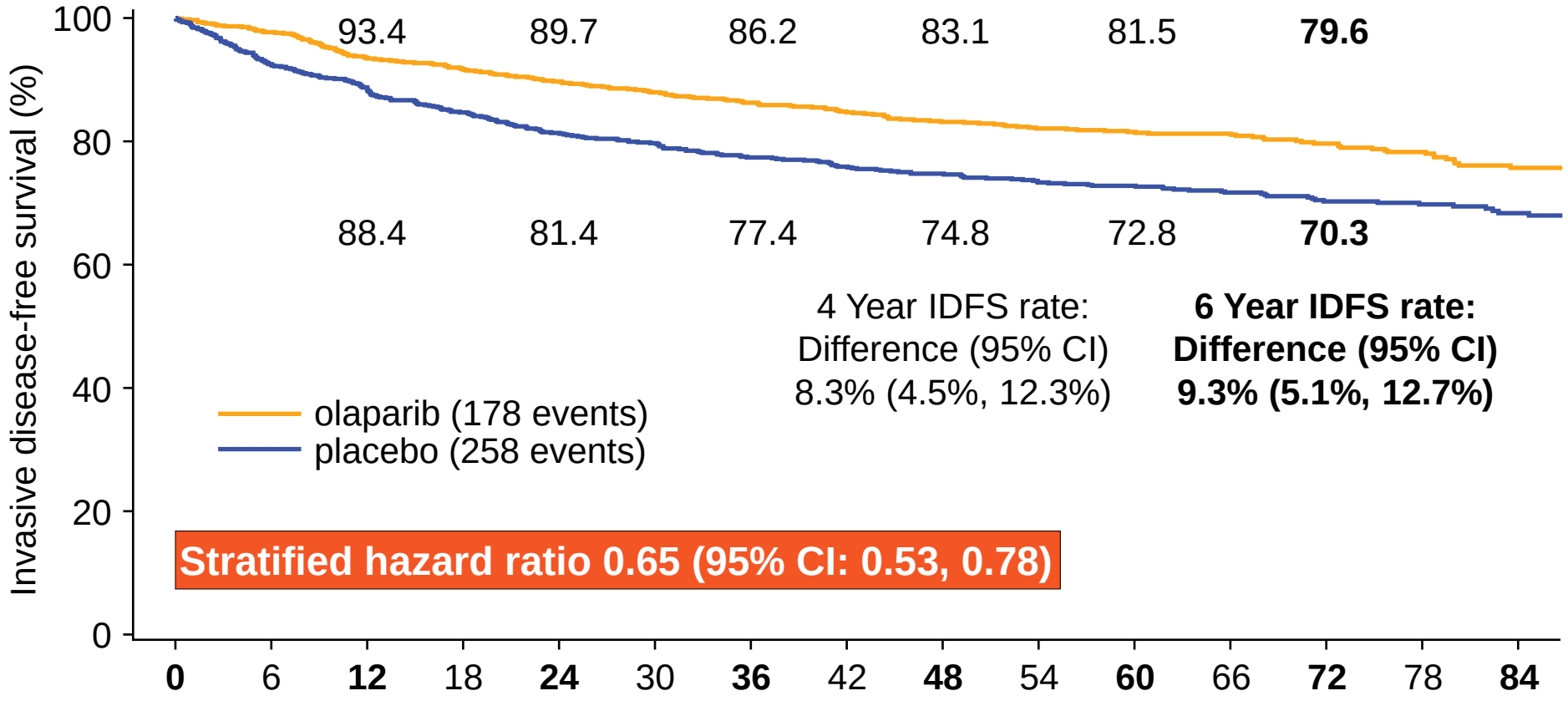
Conte P, ASCO 2024


gBRCA1/2 testing[a]
Early TNBC[b]
cT1a or cT1b N0
cT1c-T4 or N+
Surgery and whole breast RT if indicated
<cT2 N0
≥cT2 or N+
pT1a pN0
pT1b pN0
>pT1b any pN
6-8 cycles: taxane–(carbo)platin–AC/EC[c,d] [I, A]
6-8 cycles taxane–carboplatin followed by AC/EC[d] with pembrolizumab [I, A; MCBS A][f]
Consider no adjuvant systemic therapy [II, B]
6-8 cycles systemic ChT [I, A]
6-8 cycles systemic ChT [I, A]
Surgery and locoregional RT if indicated
pCR
Residual disease
gBRCA1/2m
gBRCA1/2-wt
gBRCA1/2m
Olaparib for 1 year[e] [I, A; MCBS A; ESCAT I-A][f,g]
9 cycles pembrolizuma[b,h] [I, A; MCBS A][f]
9 cycles pembrolizuma[b,h] [I, A; MCBS A][f]
Capecitabine for 6-8 cycles [I, A][i]
Olaparib for 1 year[e] [I, A; MCBS A; ESCAT I-A][f,g]

OlympiA: Trial schema



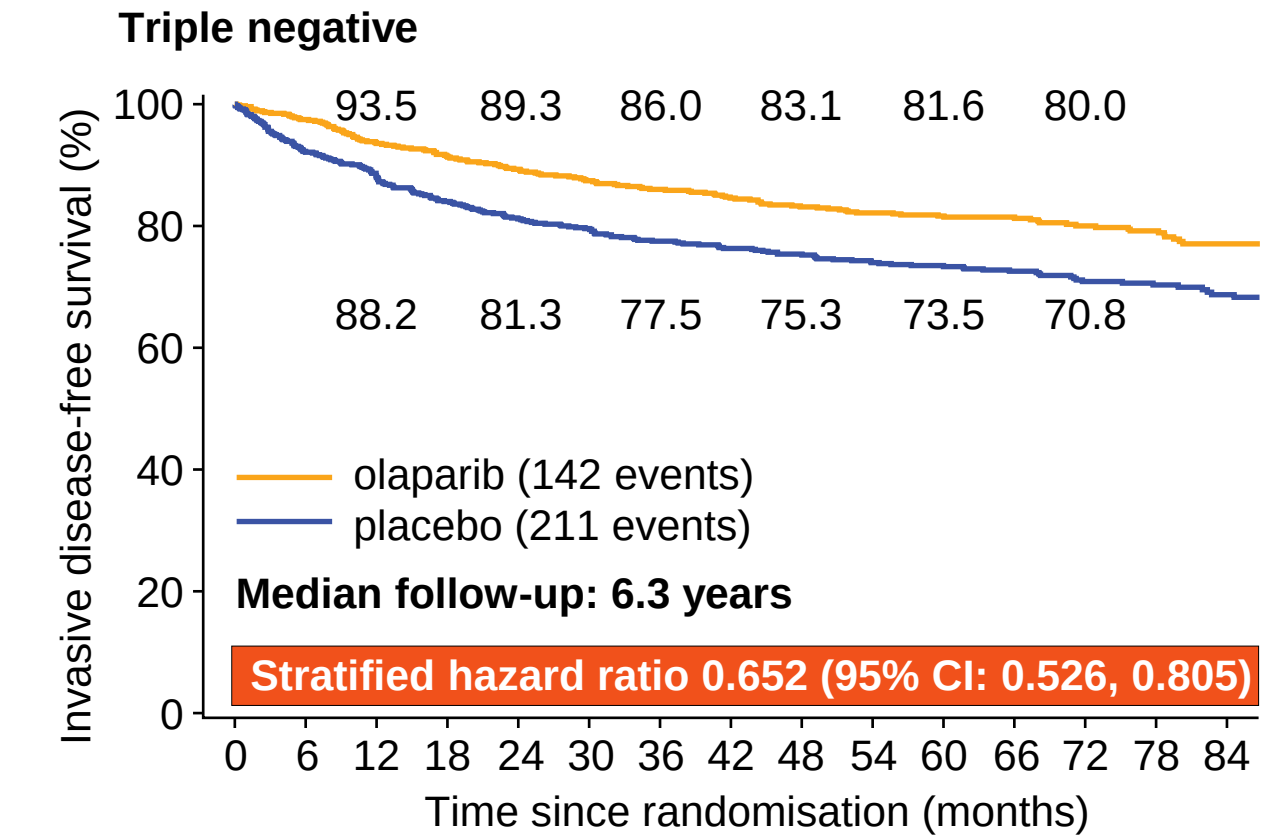
Analysis of IDFS (ITT)



Number at risk

olaparib	921	778	712	670	632	570	361	194
placebo	915	766	683	628	588	512	327	181

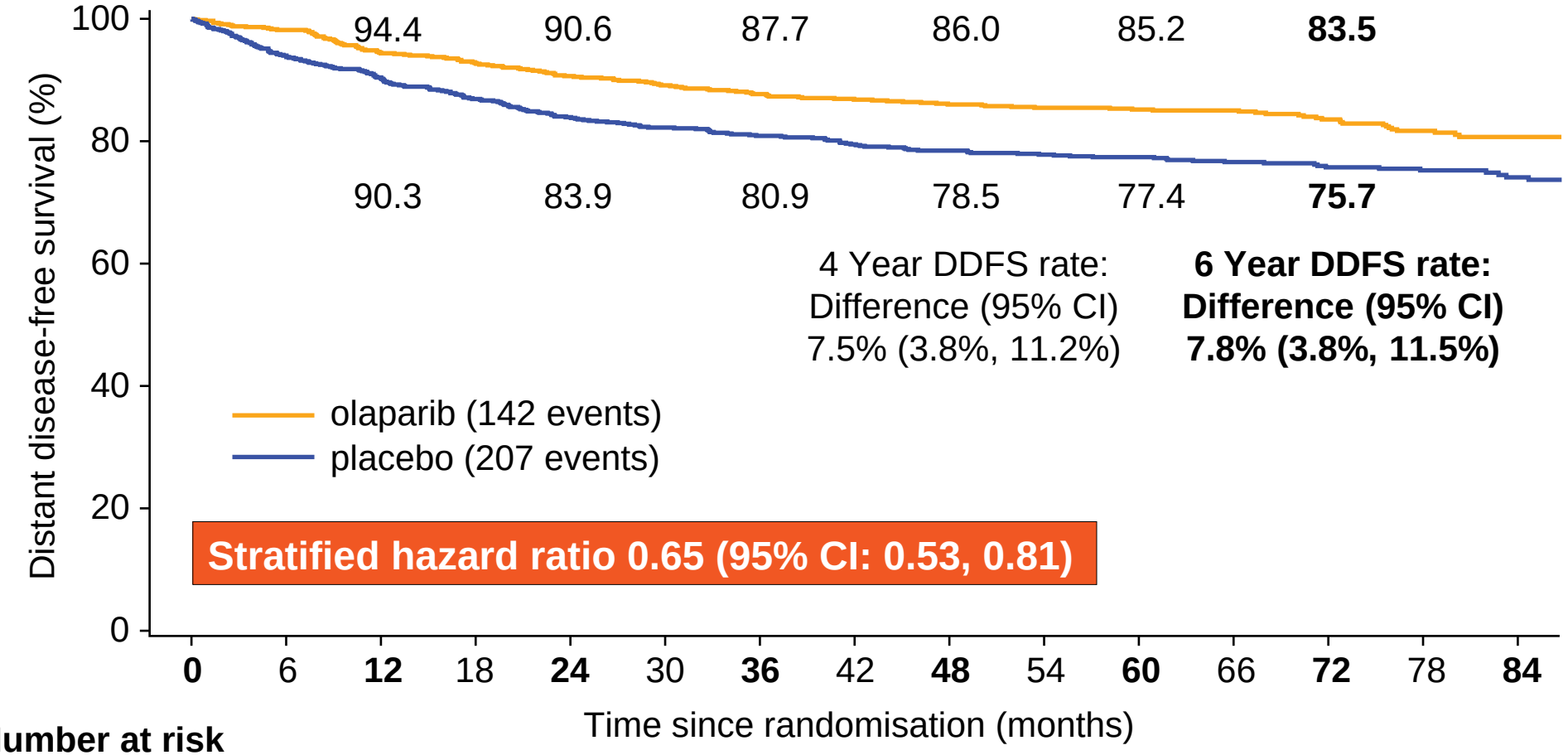
Analysis of IDFS by HR status



Number at risk

Olaparib	751	636	579	544	514	463	306	178
Placebo	758	632	565	519	489	430	282	162

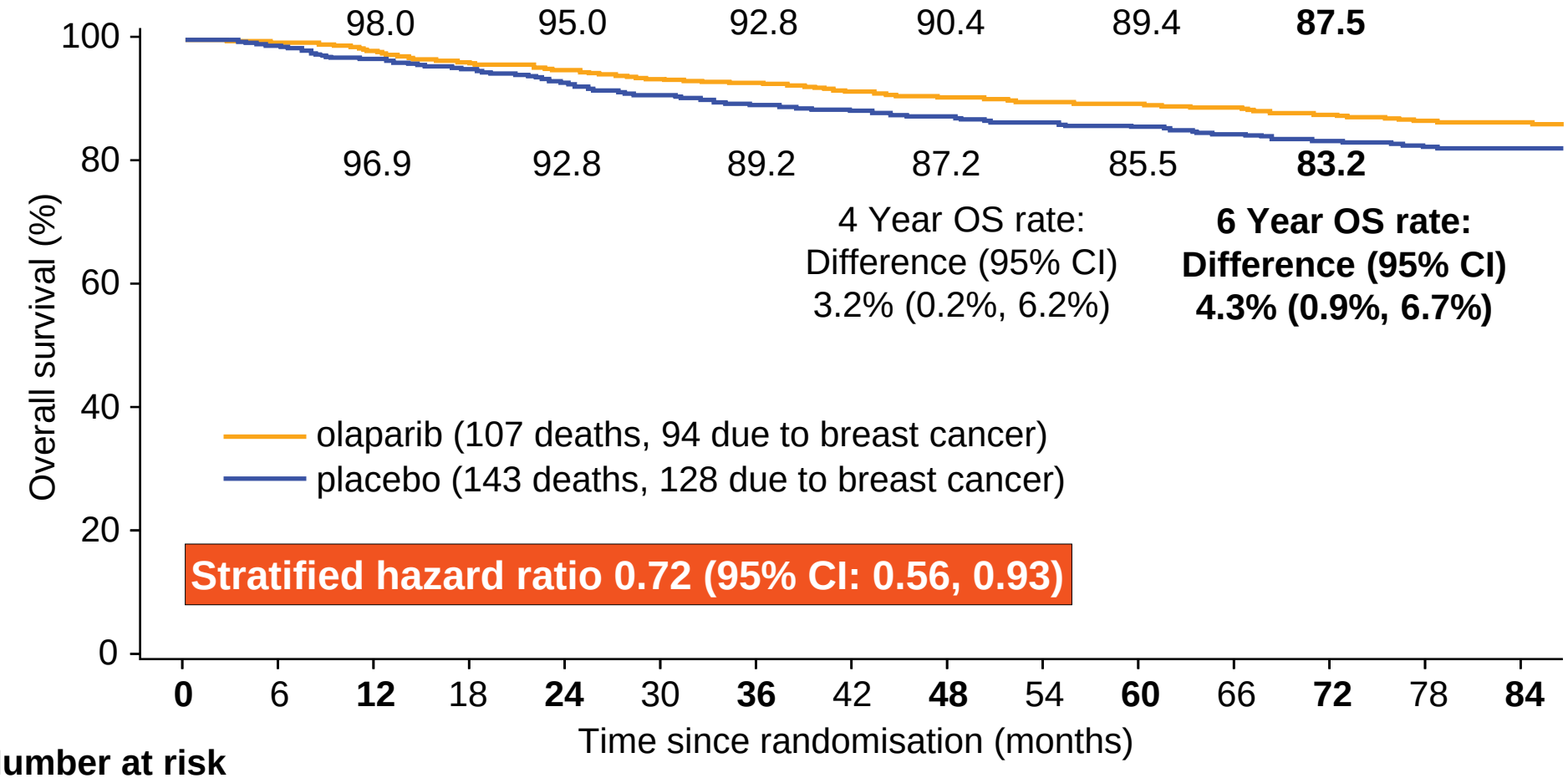
Analysis of DDFS (ITT)



Number at risk

olaparib	921	785	718	679	649	588	373	200
placebo	915	778	698	649	604	534	340	189

Analysis of OS (ITT)

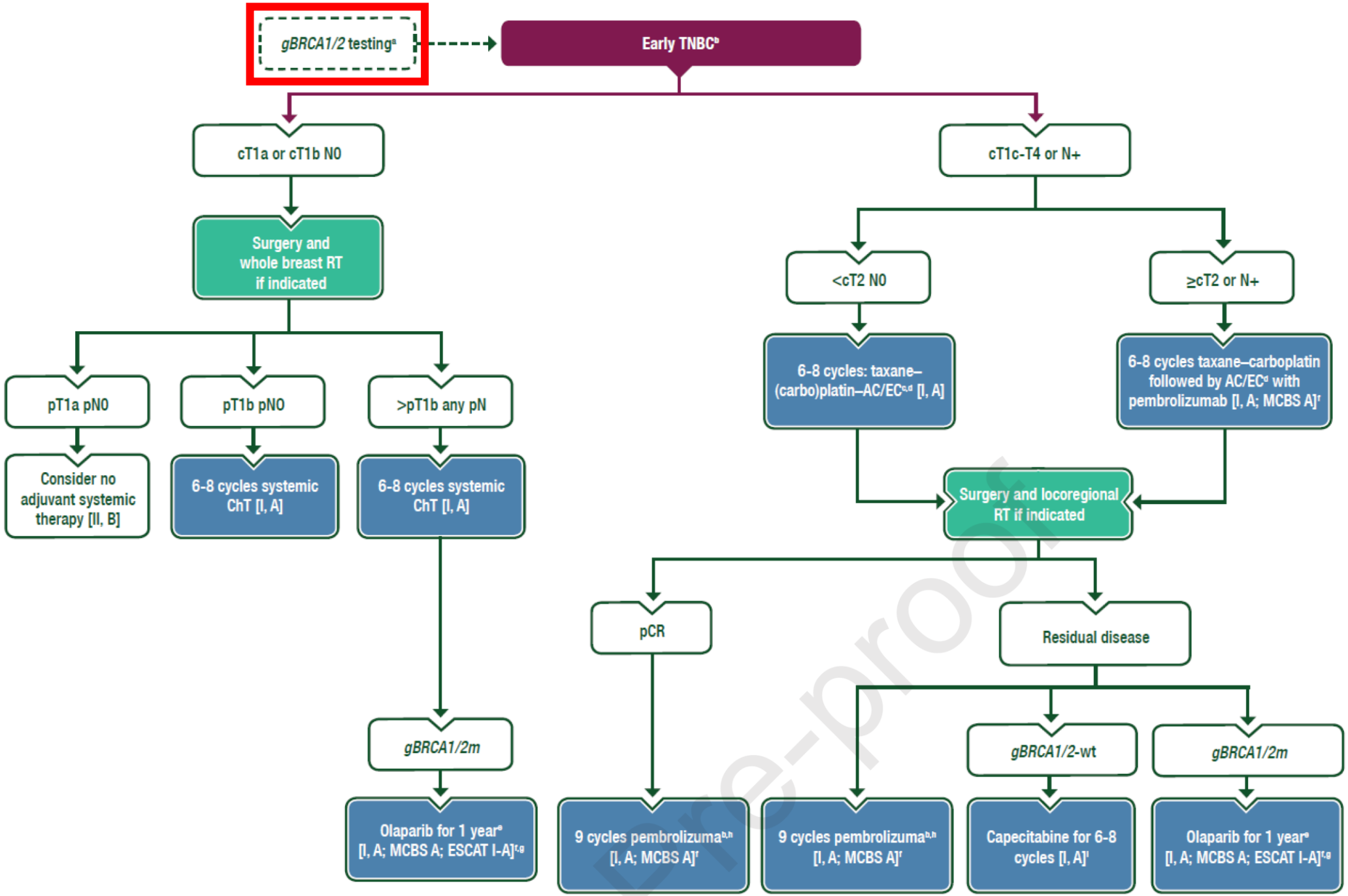


Number at risk

olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

Summary of new breast and ovarian cancers during follow-up

	Olaparib (N = 921)	Placebo (N = 915)
Bilateral mastectomy prior to randomization	339 (36.8%)	321 (35.1%)
Bilateral mastectomy post randomization	143 (15.5%)	163 (17.8%)
Patients with contralateral invasive breast cancer [1]	**34**	**42**
Patients with contralateral non-invasive breast cancer	**3**	**4**
Bilateral salpingectomy or BSO prior to randomization [2]	186 (20.2%)	168 (18.4%)
Bilateral salpingectomy or BSO post randomization [3]	239 (26.0%)	249 (27.2%)
Patients with new primary ovarian or fallopian tube cancer [4]	**5**	**14**
	39	56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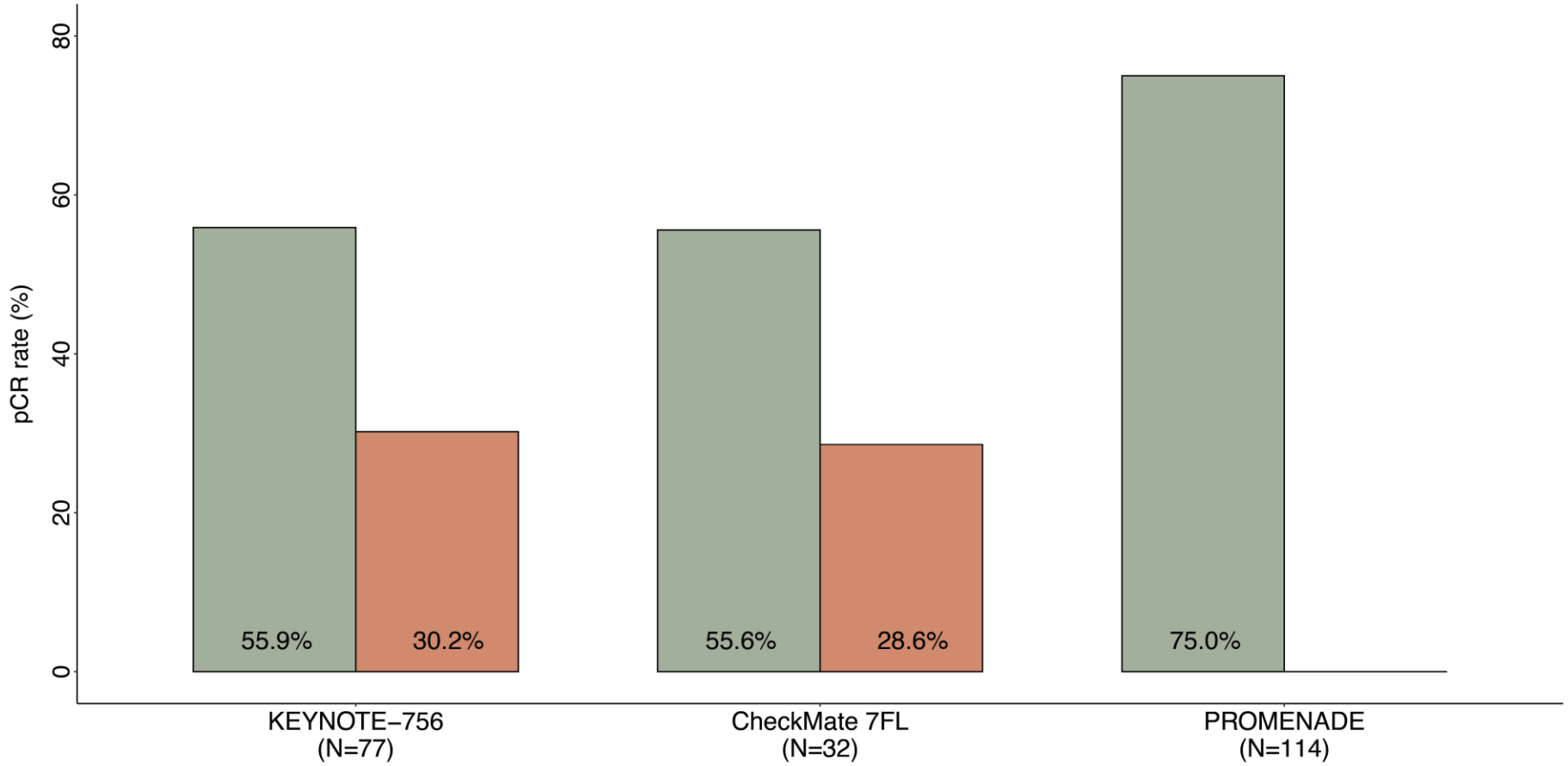
Capecitabine for 6-8 cycles [I, A][i]
Olaparib for 1 year[e] [I, A; MCBS A; ESCAT I-A][f,g]

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



[1] Cardoso et al. ESMO 2023; [2] Loi et al. SABCS 2023; [3] Cherifi et al. ESMO 2024

Grazie!