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TNBC: Neoadjuvant Updates

Tiffany A. Traina, MD FASCO
Associate Attending, Breast Medicine Service
Vice Chair, Department of Medicine
Section Head, TNBC Clinical Research Program
Memorial Sloan Kettering Cancer Center
Associate Professor, Weill Cornell Medicine

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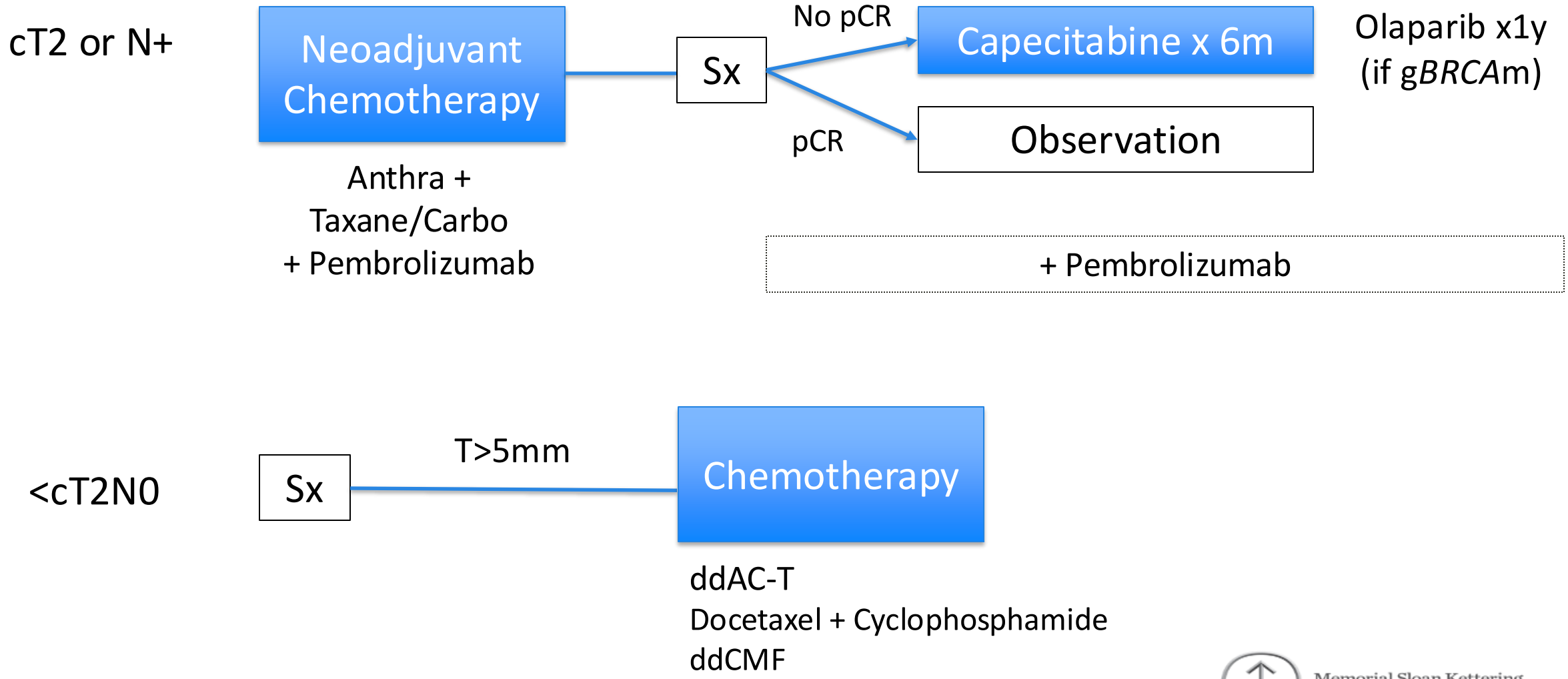
General Paradigm for Early-Stage TNBC



NCCN. Clinical Practice Guidelines in Oncology. Breast cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

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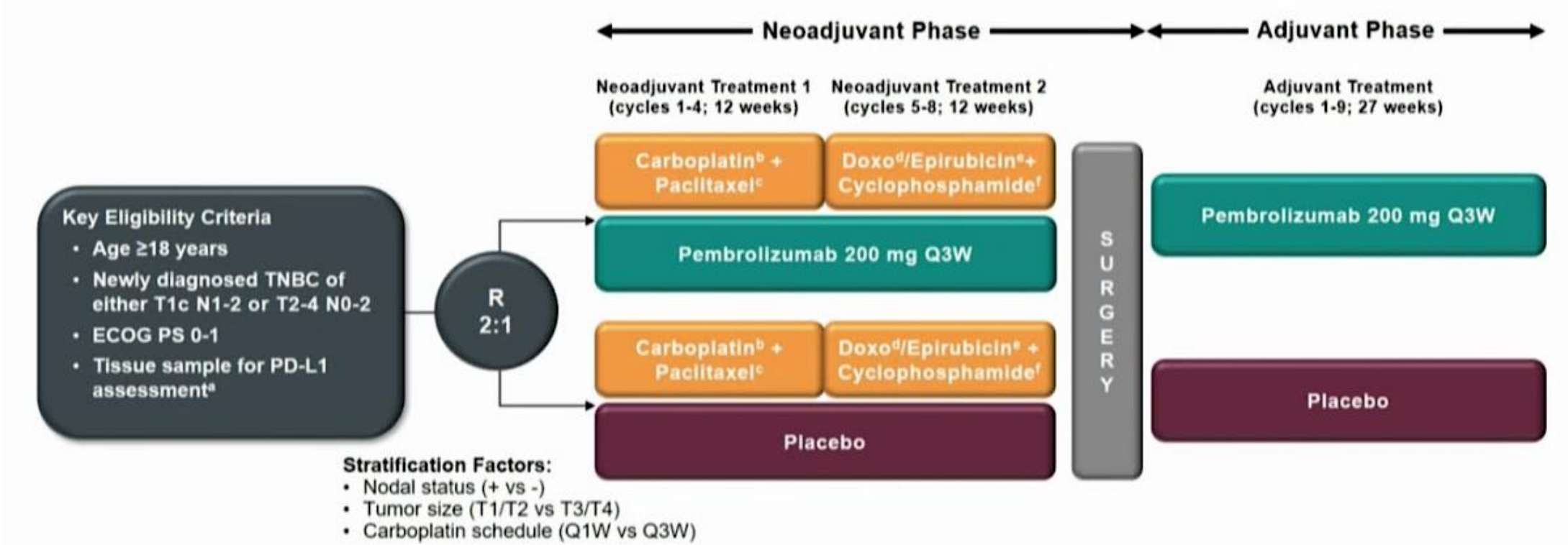
KEYNOTE-522: Neoadjuvant Pembrolizumab



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)

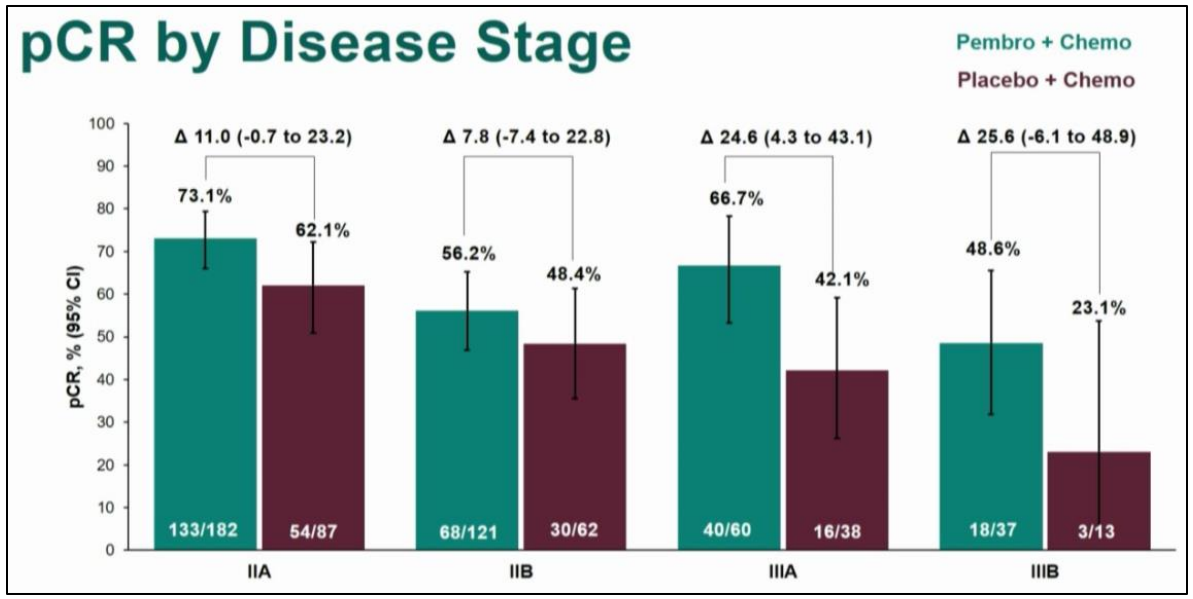
[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Primary Endpt = PCR and EFS
Secondary = PCR alternate def, OS, Endpoints by PD-L1 status, Safety

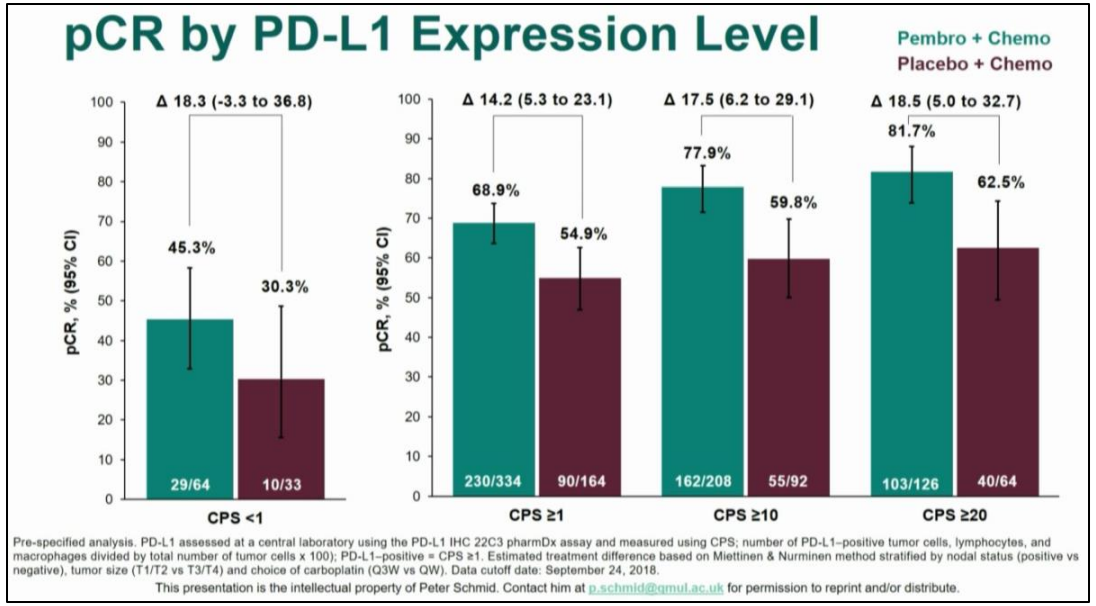
Schmid P et al. *N Engl J Med*. 2020;382:810-812.

KEYNOTE-522: Results

Bigger pCRΔ in LN+



Consistent pCRΔ across PD-L1



pCR: 64.8% vs. 51.2% (95% CI 5.4% -21.8%)
p <0.001
Δ 13.6%

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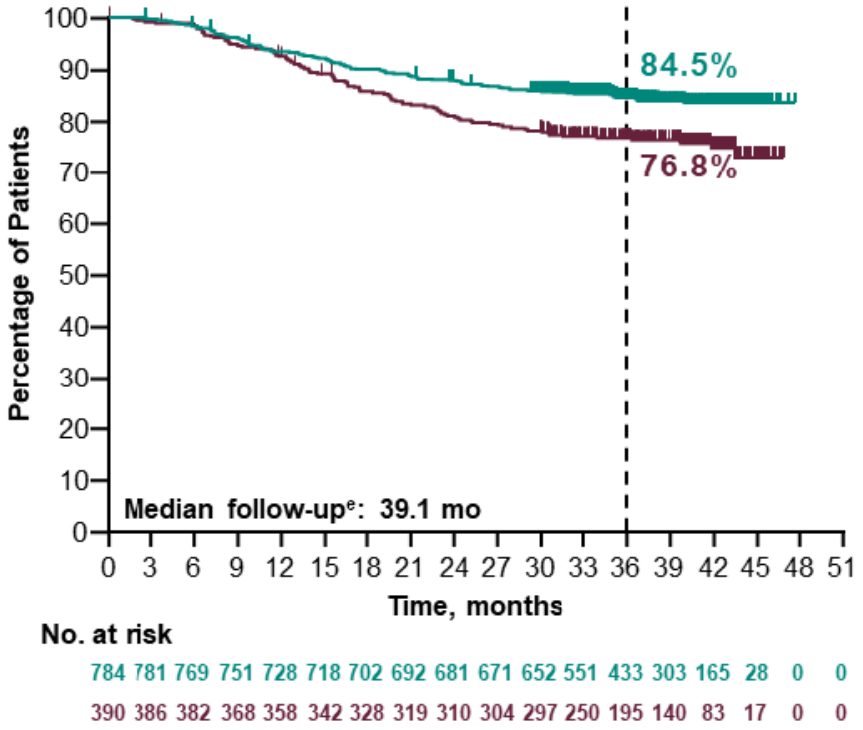
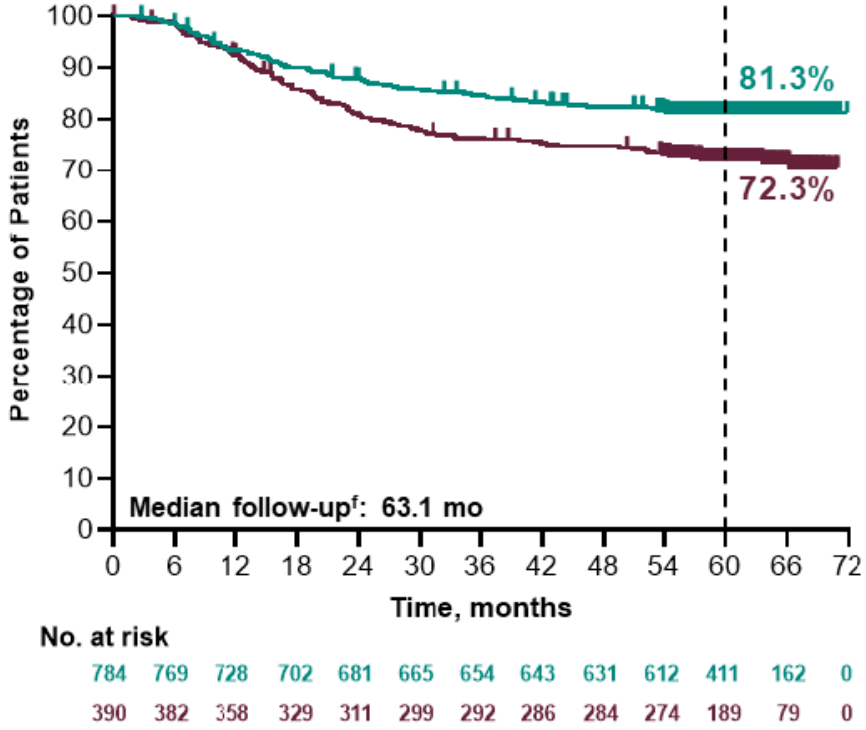
Schmid P et al. *N Engl J Med*. 2020;382:810-812.

KEYNOTE-522: 37% Improvement in EFS

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%		



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



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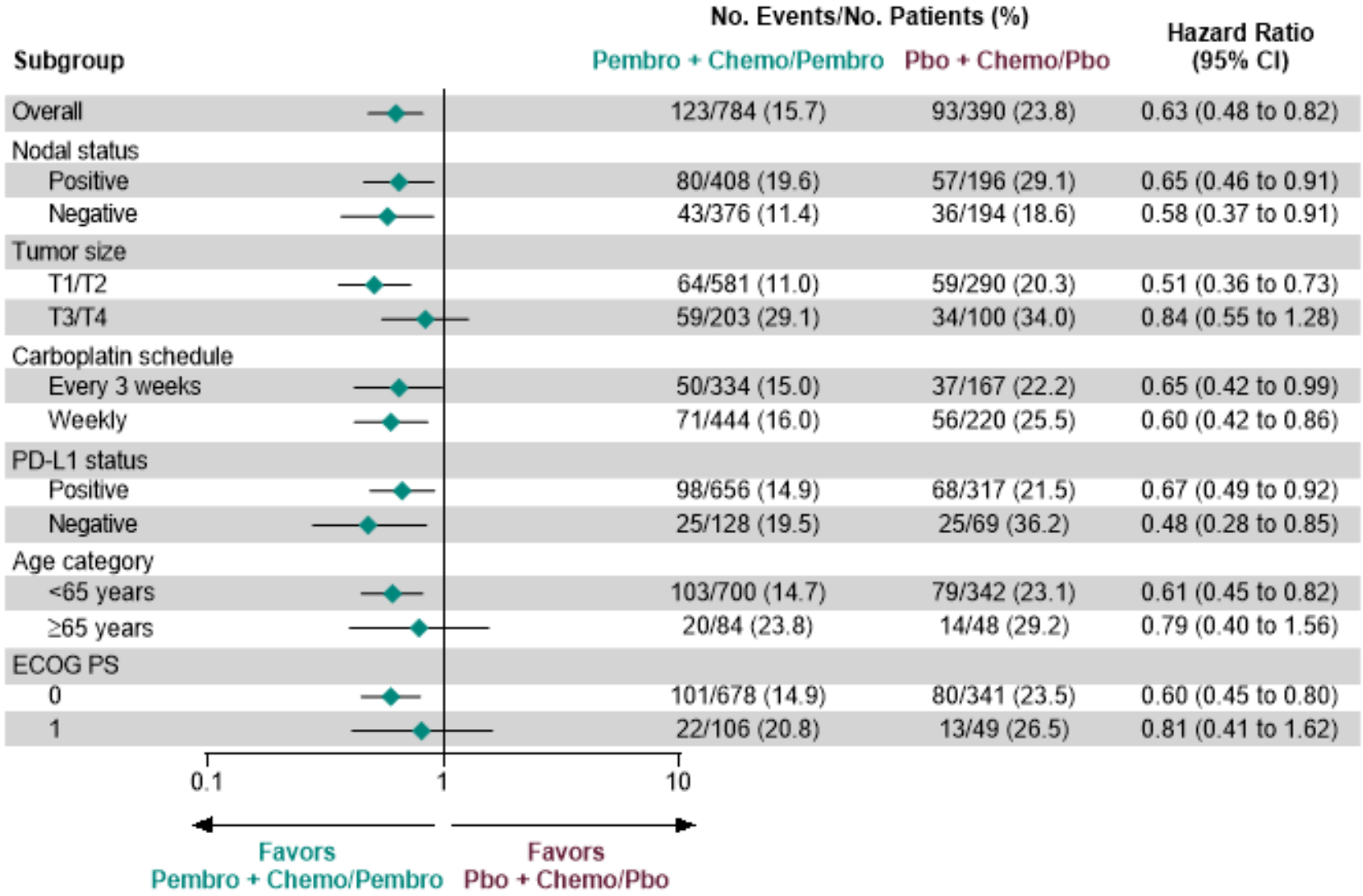
Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Schmid P et al, NEJM, 2022; ESMO 2023

KEYNOTE-522: EFS in Patient Subgroups



Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Pbo + Chemo/Pbo	Hazard Ratio (95% CI)
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Tumor size			
T1/T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36 to 0.73)
T3/T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55 to 1.28)
Carboplatin schedule			
Every 3 weeks	50/334 (15.0)	37/167 (22.2)	0.65 (0.42 to 0.99)
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42 to 0.86)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49 to 0.92)
Negative	25/128 (19.5)	25/69 (36.2)	0.48 (0.28 to 0.85)
Age category			
<65 years	103/700 (14.7)	79/342 (23.1)	0.61 (0.45 to 0.82)
≥65 years	20/84 (23.8)	14/48 (29.2)	0.79 (0.40 to 1.56)
ECOG PS			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45 to 0.80)
1	22/106 (20.8)	13/49 (26.5)	0.81 (0.41 to 1.62)

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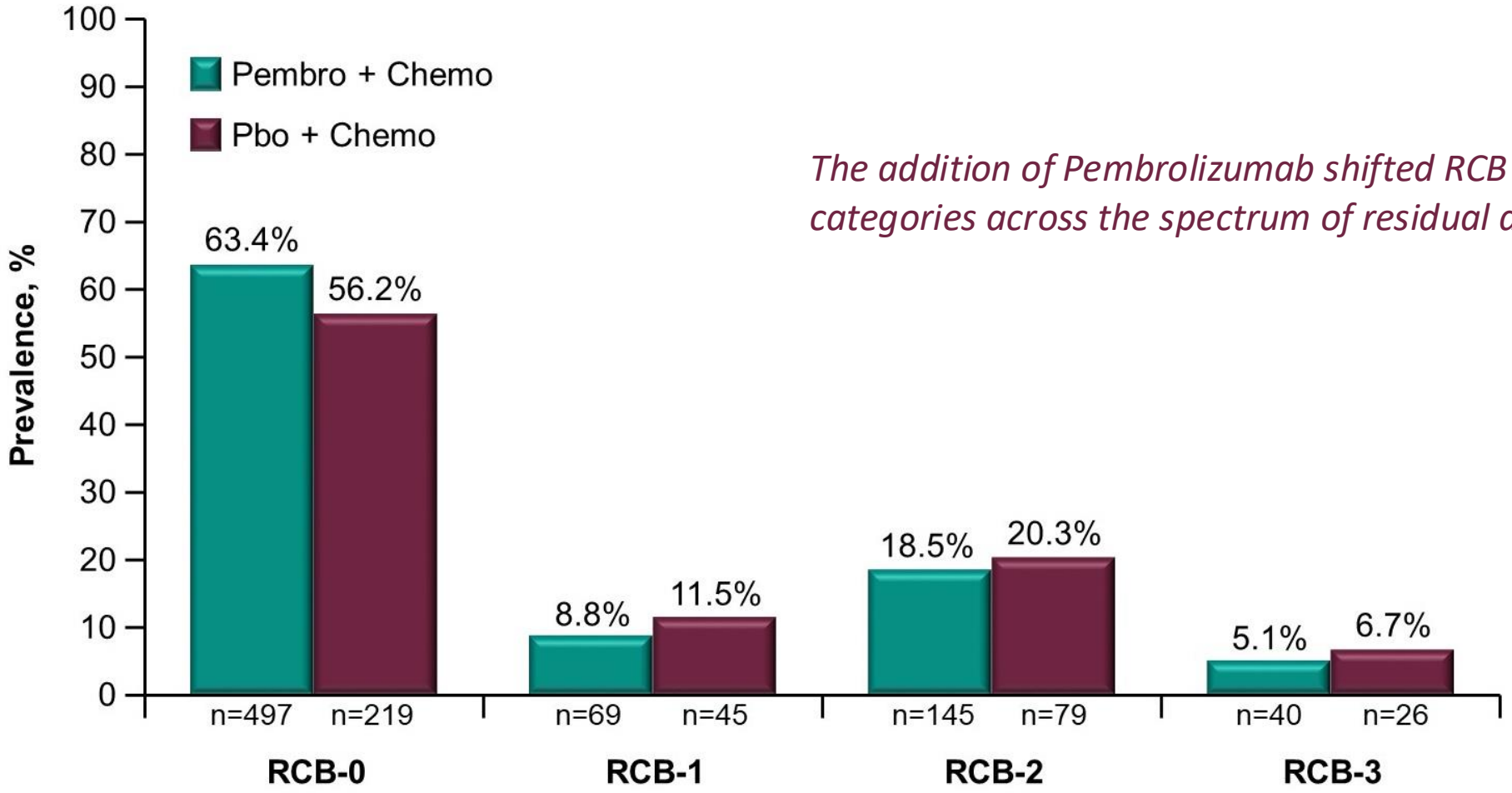
Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Schmid P et al, NEJM, 2022

KEYNOTE-522: RCB Outcomes



The addition of Pembrolizumab shifted RCB to lower categories across the spectrum of residual disease.

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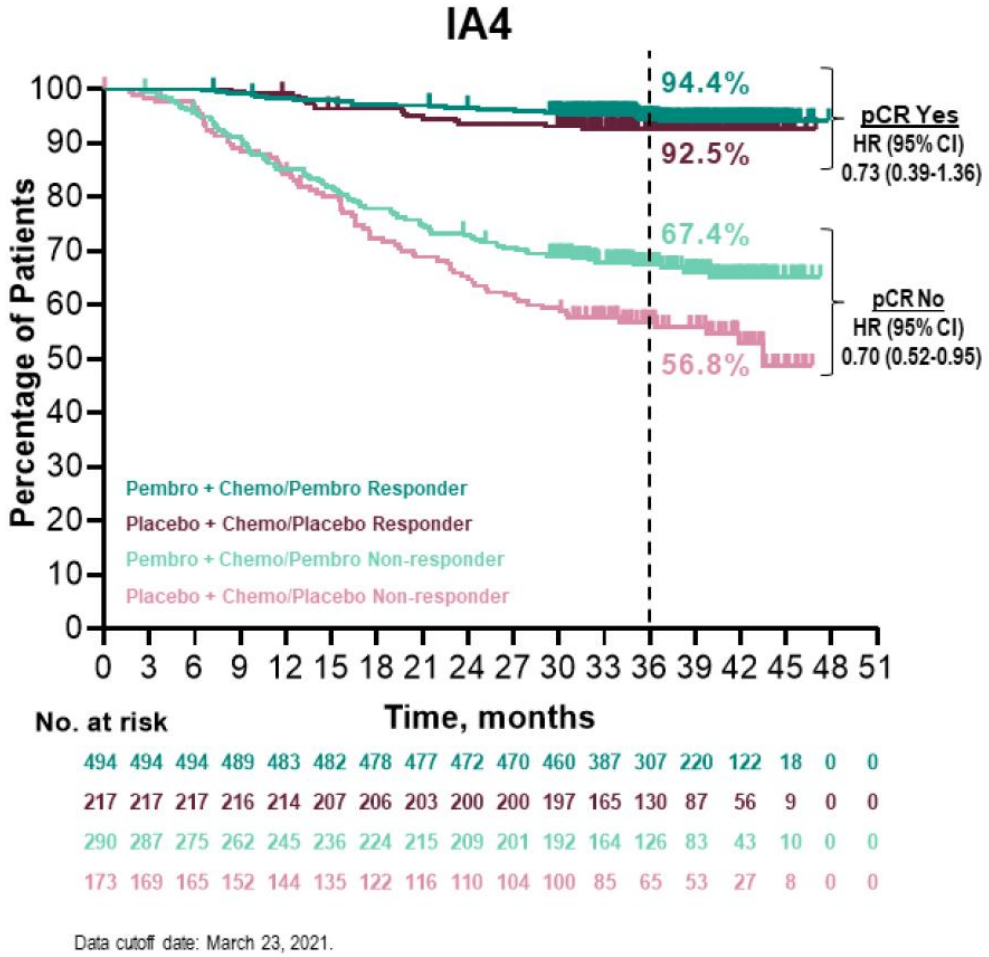
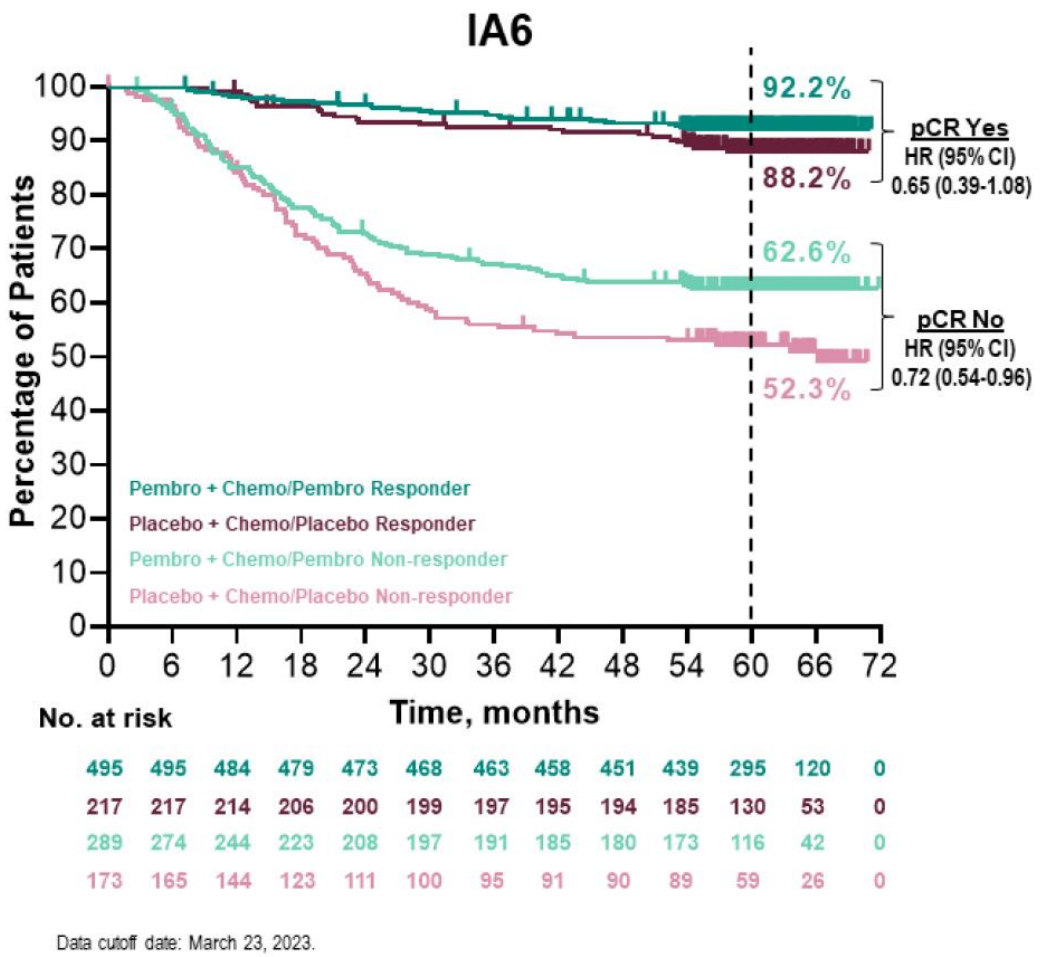
Puzstai L et al. 2022 ASCO Annual Meeting. Oral Abstract Session #503

Failure of pCR Is an Indicator of Poor Outcome ESMO 2023 Update



Data cutoff date: March 23, 2021.



Data cutoff date: March 23, 2023.

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

Pembrolizumab significantly improves OS!

The NEW ENGLAND JOURNAL of MEDICINE

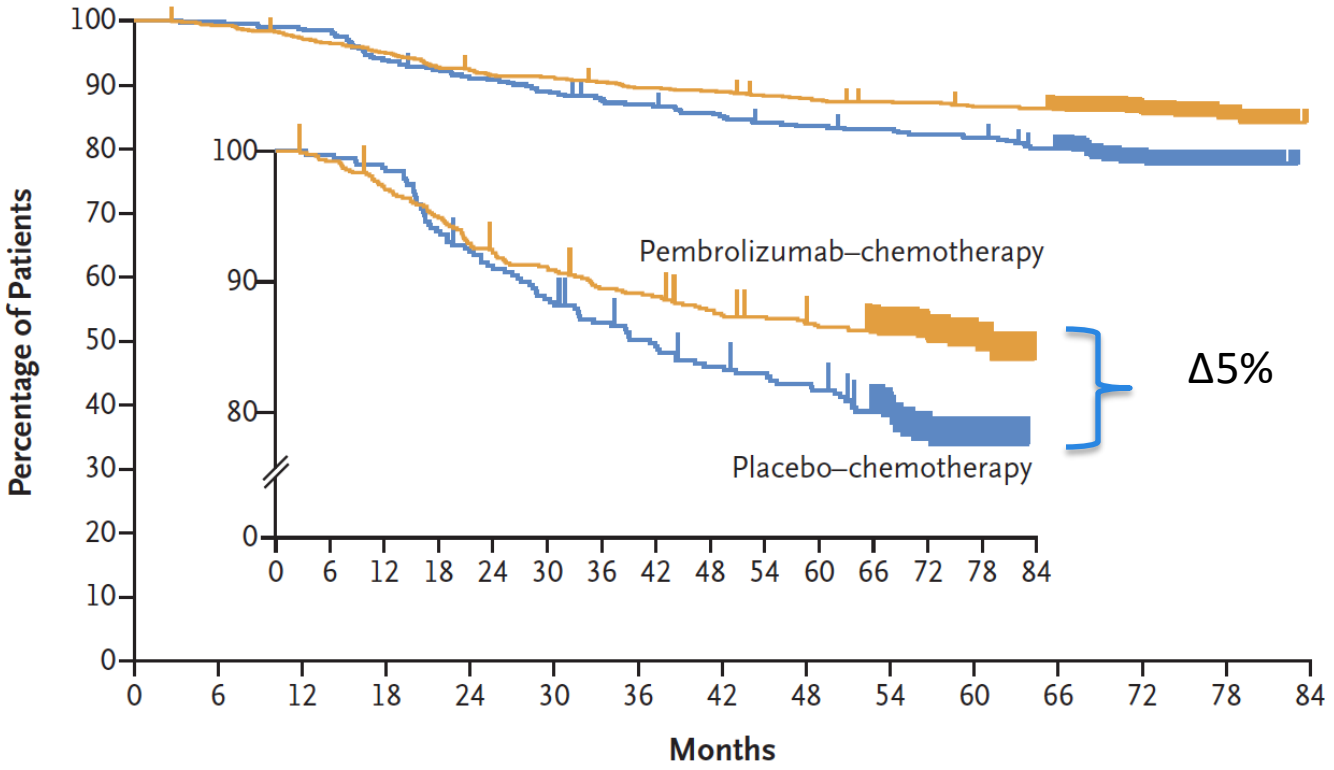
ORIGINAL ARTICLE

Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer

Peter Schmid, M.D., Javier Cortes, M.D., Rebecca Dent, M.D., Heather McArthur, M.D., Lajos Pusztai, M.D., Sherko Kümmel, M.D., Carsten Denkert, M.D., Yeon Hee Park, M.D., Rina Hui, Ph.D., Nadia Harbeck, M.D., Masato Takahashi, M.D., Seock-Ah Im, M.D., Michael Untch, M.D., Peter A. Fasching, M.D., Marie-Ange Mouret-Reynier, M.D., Theodoros Foukakis, M.D., Marta Ferreira, M.D., Fatima Cardoso, M.D., Xuan Zhou, Ph.D., Vassiliki Karantza, M.D., Konstantinos Tryfonidis, M.D., Gursel Aktan, M.D., and Joyce O'Shaughnessy, M.D., for the KEYNOTE-522 Investigators*

- Median follow up 75.1 mo
- Estimated OS at 60m:
  - 86.6% (95% CI 84% to 88.8%) Pembro/CT vs. 81.7% (95% CI 77.5% to 85.2%) CT
  - p=0.002

Overall Survival According to Treatment Group in the Intention-to-Treat Population

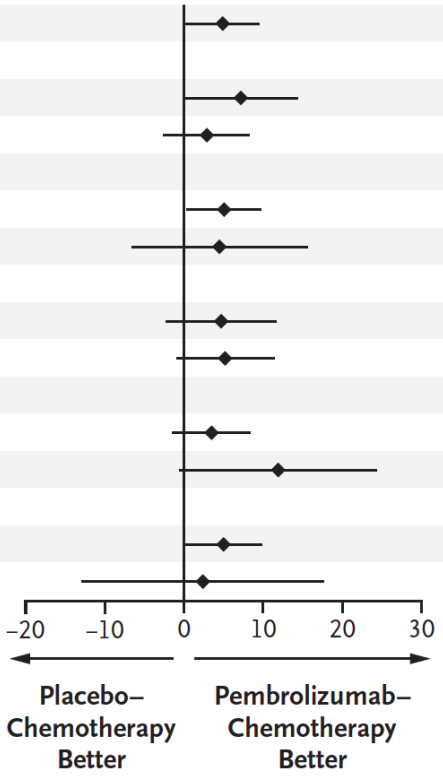


Schmid et al NEJM September 15, 2024.

Subgroup analysis for OS

B Subgroup Analyses of Overall Survival

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in 5-Year Overall Survival (95% CI)
	no. of patients who died/total no. (%)		*percentage points*
Overall	115/784 (14.7)	85/390 (21.8)	4.9 (0.3 to 9.4)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	7.2 (0.0 to 14.3)
Negative	37/376 (9.8)	29/194 (14.9)	2.9 (–2.5 to 8.2)
Tumor size			
T1 to T2	54/580 (9.3)	51/290 (17.6)	5.1 (0.5 to 9.6)
T3 to T4	61/204 (29.9)	34/100 (34.0)	4.5 (–6.5 to 15.5)
Carboplatin schedule			
Every 3 wk	46/334 (13.8)	36/167 (21.6)	4.7 (–2.1 to 11.6)
Weekly	68/444 (15.3)	49/220 (22.3)	5.2 (–0.8 to 11.3)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	3.5 (–1.4 to 8.3)
CPS <1	23/128 (18.0)	23/69 (33.3)	11.9 (–0.4 to 24.2)
Age			
<65 yr	93/700 (13.3)	72/342 (21.1)	5.0 (0.3 to 9.7)
≥65 yr	22/84 (26.2)	13/48 (27.1)	2.4 (–12.8 to 17.6)



Schmid et al NEJM September 15, 2024.

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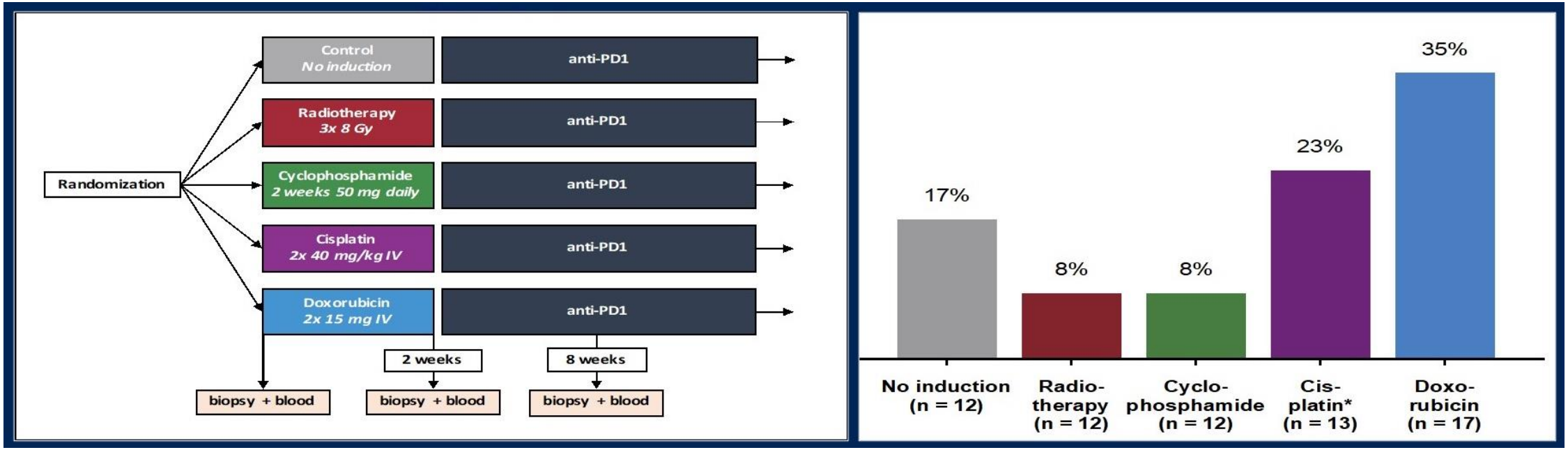
KN522 is Standard of Care … Yet Questions Remain

- Optimal chemotherapy backbone?
- Do we need adjuvant pembrolizumab?
- How to best address patients with residual disease?

KN522 is Standard of Care … Yet Questions Remain

- Optimal chemotherapy backbone?
- Do we need adjuvant pembrolizumab?
- How to best address patients with residual disease?

Does chemotherapy backbone matter in the combination treatment with ICI?



Induction with doxorubicin or cisplatin appeared to upregulate immune related genes

Voorkerk L et al, Nat Med 2019

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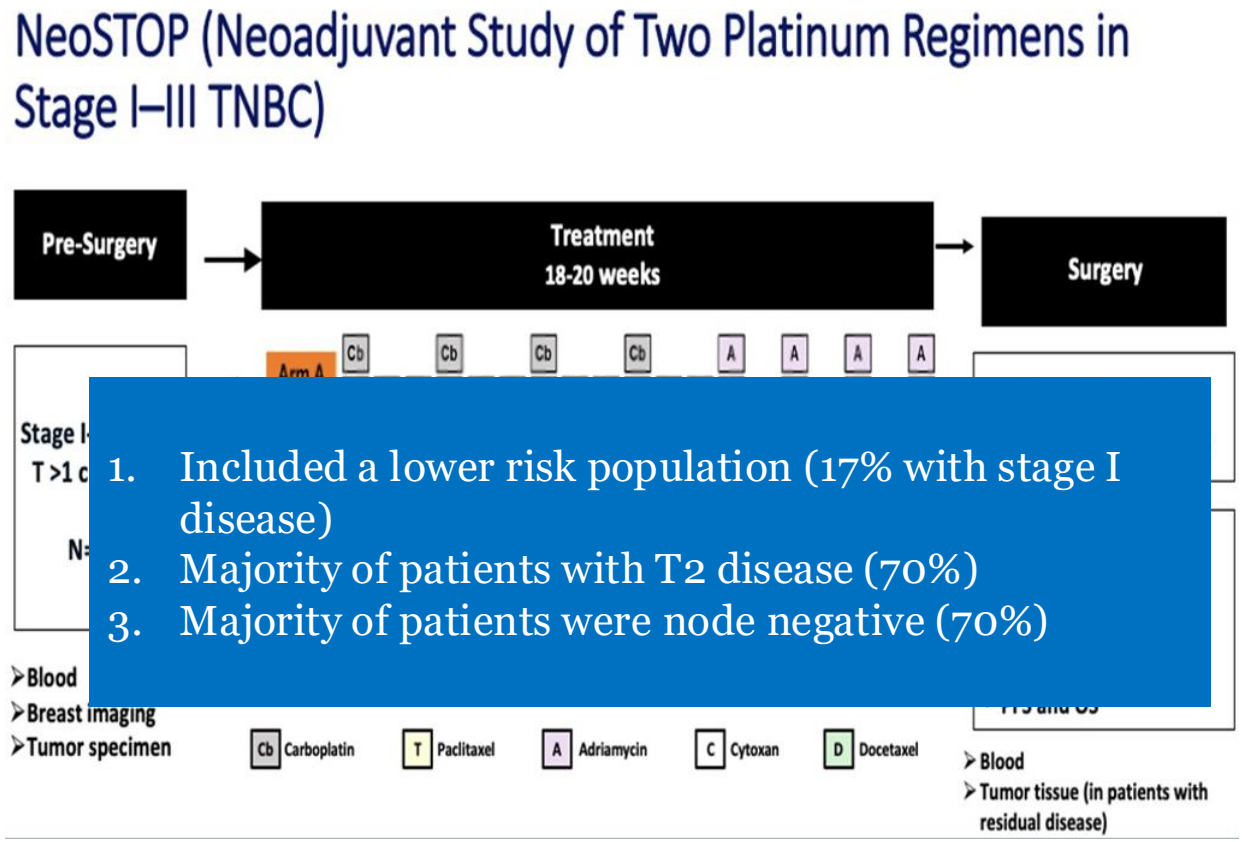
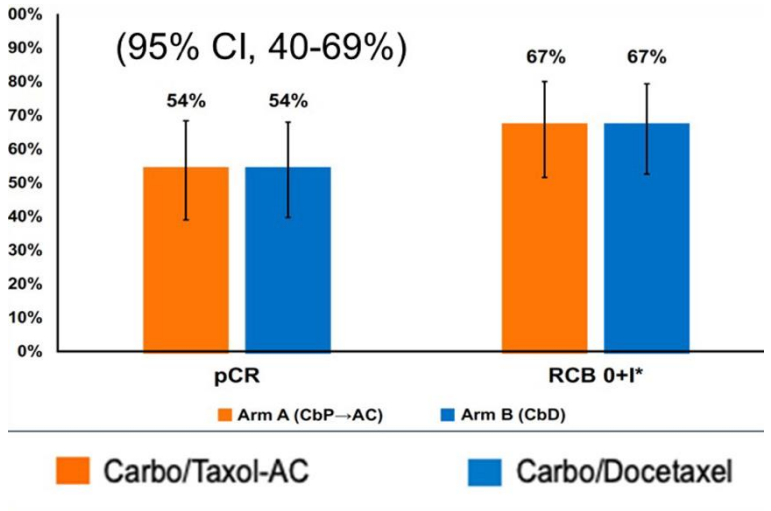
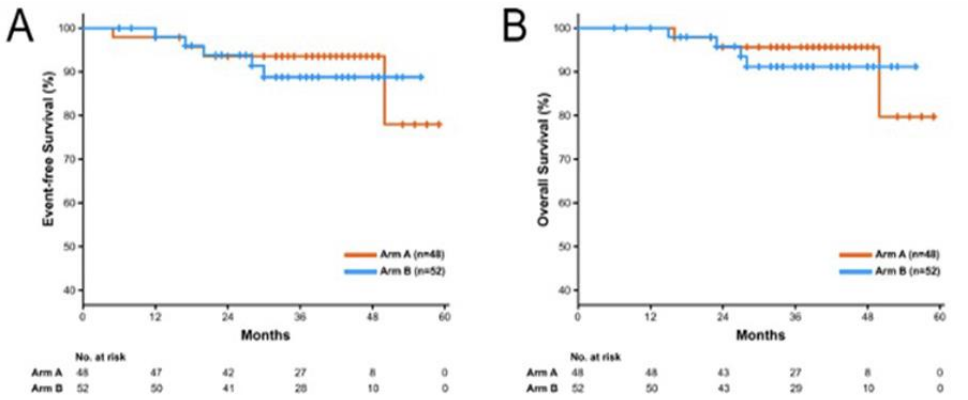
NeoSTOP: Can we omit anthracycline-based chemotherapy?



1. Included a lower risk population (17% with stage I disease)
2. Majority of patients with T2 disease (70%)
3. Majority of patients were node negative (70%)





Similar EFS in Arm A and B

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Sharma P et al. Clin Cancer Res. 2021; 27(4):975-98

NeoPACT: Can we omit anthracycline-based chemotherapy?

Neoadjuvant *Single Arm Phase II*: P Sharma et al.

17

Primary endpoint: pCR

Non-anthracycline Regimen

Stage I-III TNBC
T >1 cm or N+
ER/PR ≤10%
Small Sample size:
N = 120

Taxotere 75mg/2
Carboplatin AUC 6
Pembrolizumab 200mg
Q3wk x 6 cycles

Surgery

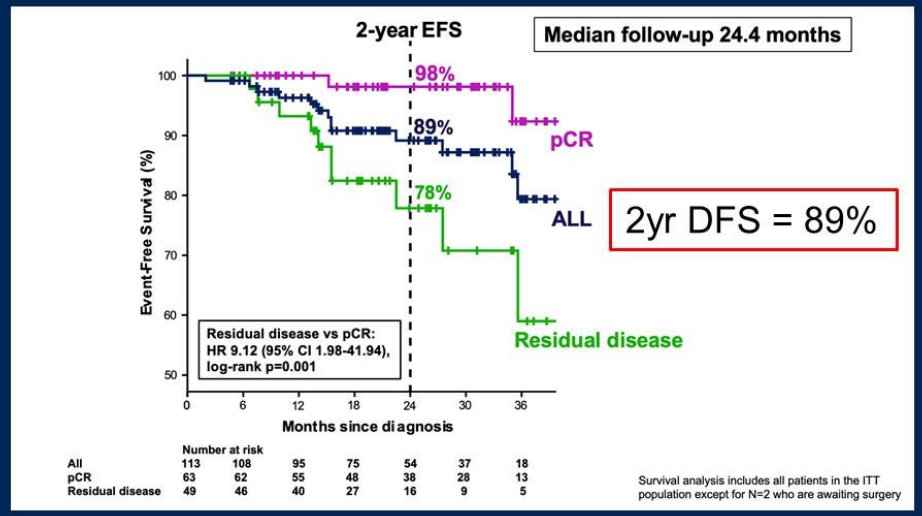
Adjuvant therapy at provider discretion

Overall pCR = 58%

LN neg vs.pos: 65% vs. 46%

PD-L1 pos vs. neg: 76% vs. 39%

ER/PR < 1% vs. 1-10%: 59% vs. 53%



Slides courtesy of Rebecca Dent (ASCO 2022); Sharma P et al, ASCO 2022

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Where does NeoPACT fit with other ICI Neoadjuvant Trials?

	GeparNuevo	KN-522	Impass-031	NeoTRIP	iSPY	NeoPACT
N	174	1174	333	280	69/181	150 (single arm)
Target	PD-L1	PD-1	PD-L1	PD-L1	PD-1	PD-1
Stage	35% stage 1	2/3	2/3	Incl N3	2/3	61% N neg
Anthracycline	Yes	Yes	Yes	No	Yes	No
Platinum	No	Yes	No	Yes	No	Yes
pCR (ITT)	**58%**	**65%**	**58%**	**44%**	**60%**	**58%**
△pCR	9%	14%	17%	3%	22-66%	N/A
EFS (HR)	0.48 (0.24-0.97)	0.63 (0.43-0.93) (p=.00031)	0.76 (0.4-1.44) (ns)	TBD	N/A	N/A
EFS	**3-yr DFS 85.6%**	**3-yr DFS 84.5%**	**TBD**	**TBD**	**N/A**	**2-yr DFS 89%**

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Slide courtesy of Rebecca Dent, ASCO 2022

Can we eliminate neoadjuvant chemotherapy altogether?

TNBC
Stage I-II
Node negative
TILS >/= 50%

→

6 weeks Nivo + Ipi
OR
8 weeks Nivo +
Relatlimab (anti-LAG3)

	Nivo/Ipi	Nivo/Rela
PCR	5/15 (33%)	7/15 (47%)
MRI Response	8/15 (53%	11/15 (73%)

Nederlof et al Annals of Onc (2024) 35 suppl_2

NeoTALA: Phase 2 Trial

g*BRCA1/2* mutation
St I – III, TNBC
Open-label, single arm
N = 61

Talazoparib 1mg daily x24 weeks

Primary Endpoint = pCR
EFS and OS immature and not powered

	Evaluable population (N=48)	ITT population (N=61)
pCR by ICR, n (%) [95% CI]	22 (45.8) [32.0, 60.6]	30 (49.2) [36.7, 61.6]
pCR by INV, n (%) [95% CI]	22 (45.8) [32.0, 60.6]	29 (47.5) [35.0, 60.1]
RCB by ICR, n (%) [95% CI]		
RCB 0	22 (45.8) [30.0, 62.6]	30 (49.2) [34.0, 64.5]
RCB I	0	1 (1.6) [0.2, 12.1]
RCB II	15 (31.3) [18.0, 48.5]	17 (27.9) [16.1, 43.7]
RCB III	0	0
Missing	11 (22.9) [11.8, 39.8]	13 (21.3) [11.2, 36.7]

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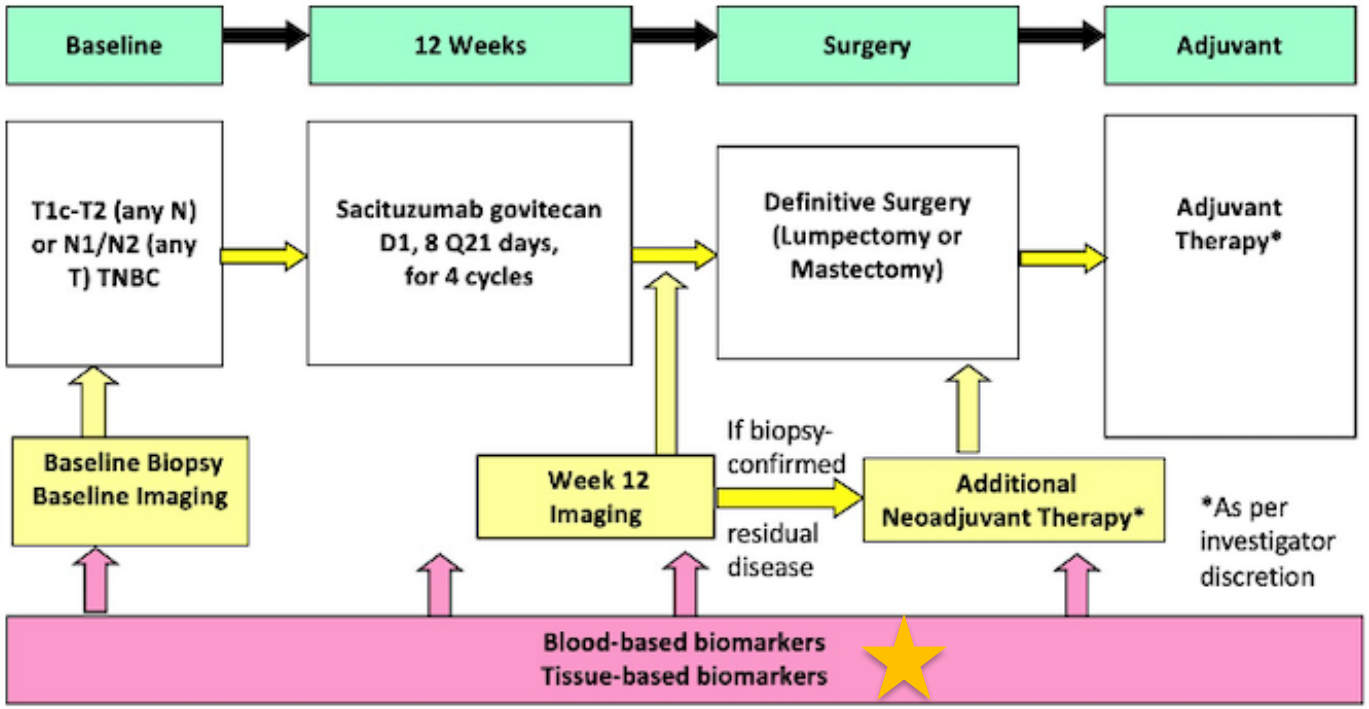
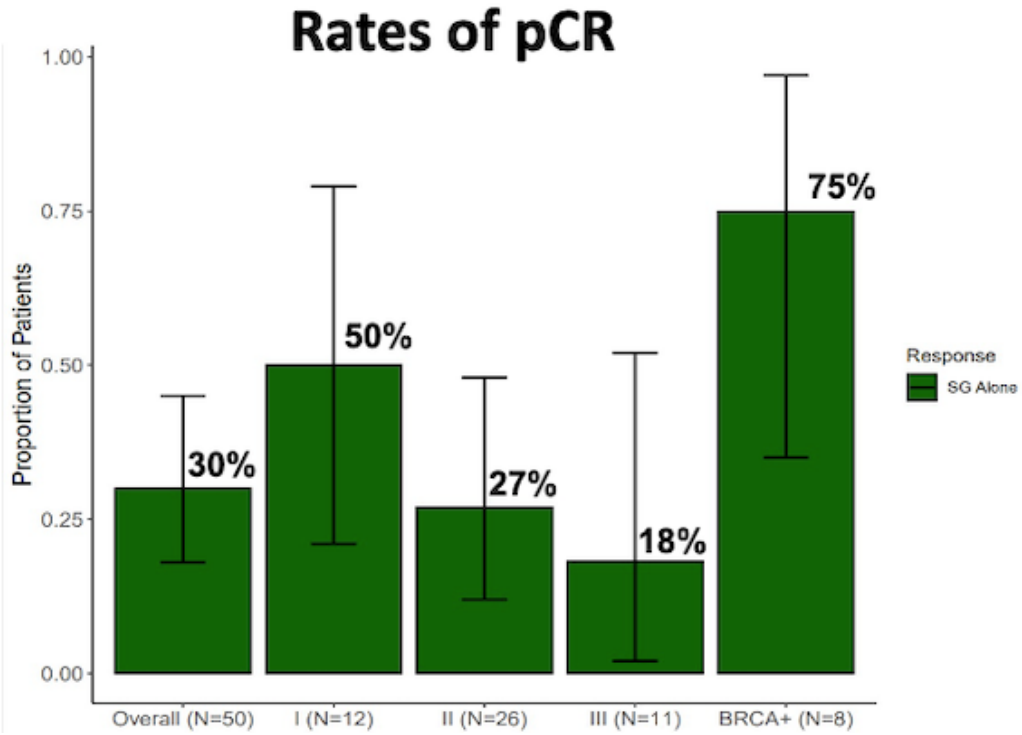
Litton JK et al. 2021 ASCO. Abstract 505.

NeoSTAR: Neoadjuvant Sacituzumab

CLINICAL TRIAL DESIGN



pCR = 30%



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Spring L et al. 2022 ASCO. Abstract 512.

NeoSTAR: Future Directions

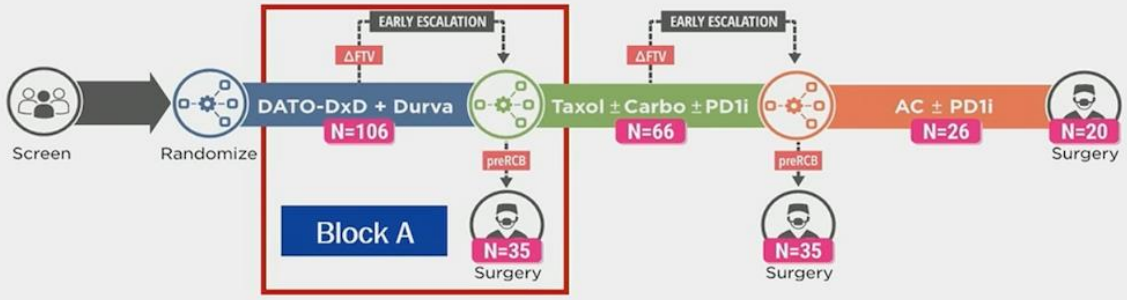
- pCR 30% for 4 cycles of single agent worthy of further exploration – promising in context of single agent
- pCR 75% in gBRCA intriguing but small sample size. Needs prospective validation.
- Would methylated BRCA or somatic BRCA behave similarly? Other DDR genes?
- Biomarkers of response? Better synergistic partners?
- Ongoing studies: looking at PARPi + Sacituzumab; IO + ADCs; Sacituzumab in RD

DatoDxd + Durvalumab graduated in I-SPY2.2

Key Takeaways

ASCO 2024

- ISPY 2.2 is a novel neoadjuvant trial for Mammaprint high-risk, Stage 2/3 BC that offers the opportunity to personalize treatment to maximize pCR rate for each individual patient.
- Dato + Durva for 4 cycles (Block A) was effective and allowed 33% of patients to go straight to surgery and skip traditional chemotherapy (i.e. skip taxane –>AC)
- Dato + Durva was particularly effective in the Immune+ response predictive subtype
  - 43% of patients in the immune subtype achieved a pCR after Block A (most conservative estimate)
  - The modeled pCR rate, based on all data after Block A, is 65%
- Reported toxicity profile of this combination was consistent with prior studies



Shatsky et al ASCO 2024

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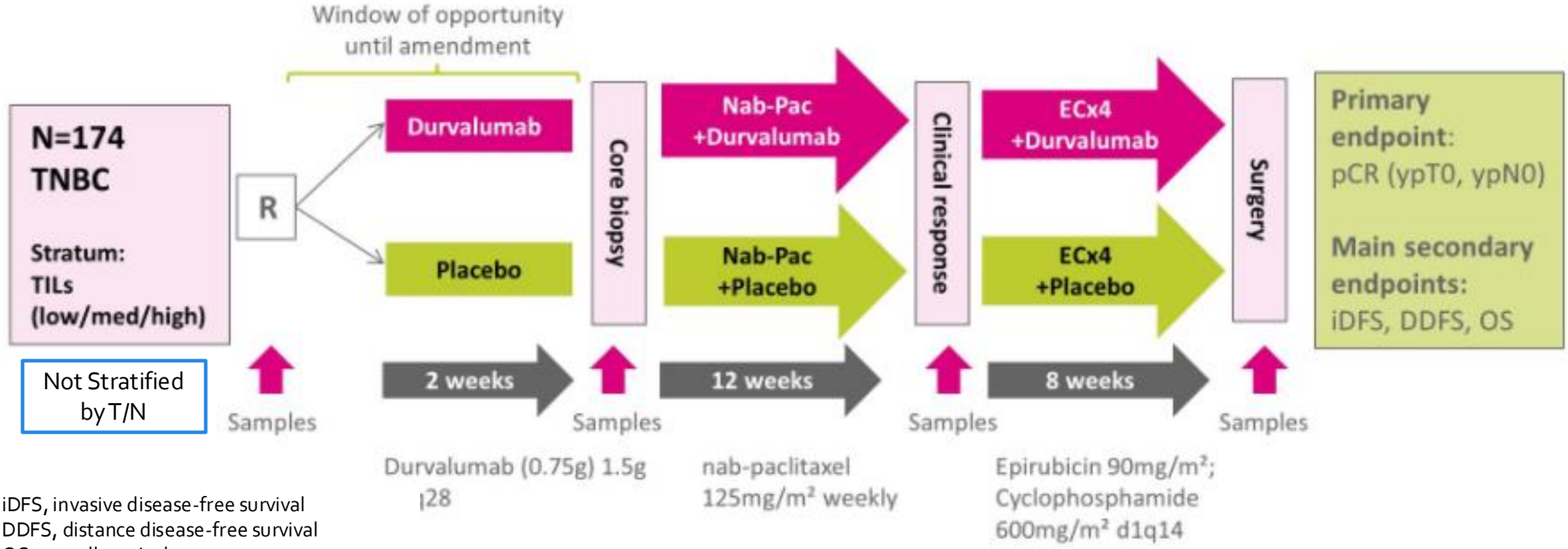
Other Neoadjuvant Trials of Interest

	Study drugs	Primary Endpoint
NCT04443348 (N = 120)	TBCRC 053: Pembrolizumab + RT prior to KN522 regimen in LN+ TNBC	Change in TILS pCR in LN
NCT05203445 (N = 23)	Olaparib + Pembro in g*BRCA*+ (TNBC or HR+HER2- BC)	Bx confirmed radiographic CR on MRI Secondary pCR/RCB0
NCT04584255 (N=62)	TBCRC 056 Niraparib + Dostarlimab in *gBRCA+* (TNBC or HR+HER2- BC)	Change in TILs pCR
NCT06112379	TropionBreast04: Ph III DatoDxd + Durva vs. Chemo + Pembro in ST II-III TNBC	pCR and EFS

KN522 is Standard of Care … Yet Questions Remain

- Optimal chemotherapy backbone?
- Do we need adjuvant pembrolizumab?
- How to best address patients with residual disease?

GeparNUEVO



iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival

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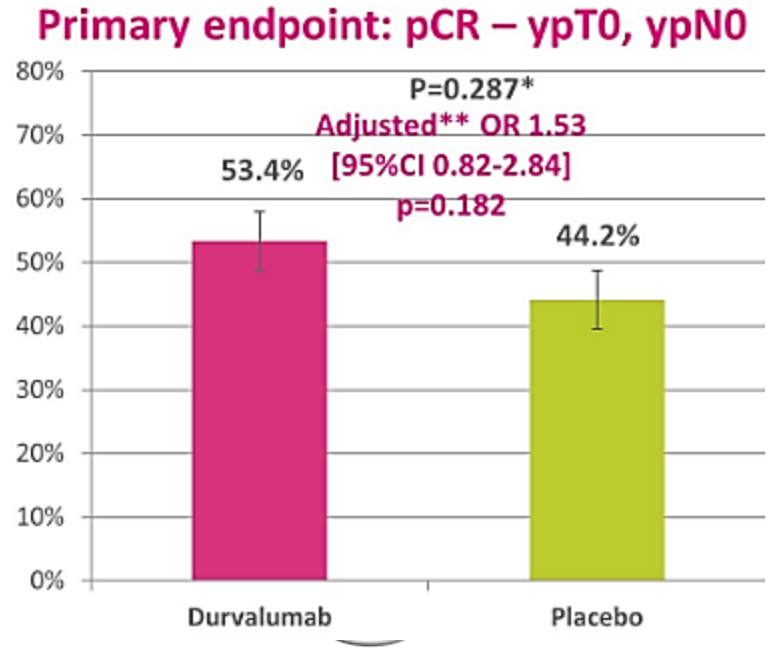
Loibl S et al. 2021 ASCO. Abstract 506.

GeparNUEVO: Primary Endpoint pCR

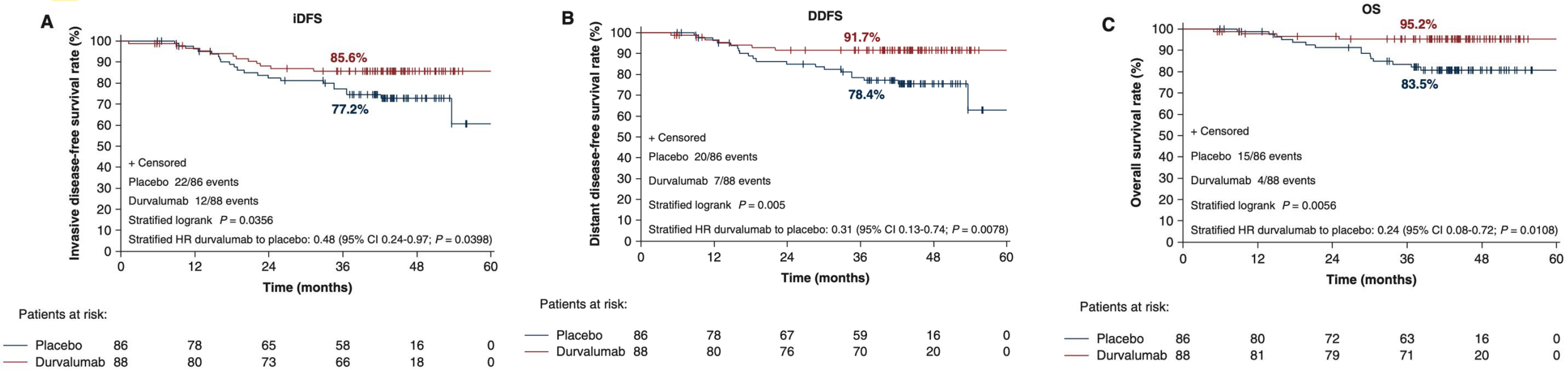
	Durvalumab N=88 N(%)	Placebo N=86 N(%)
Age (yrs), median (range)	49.5 (25.0, 74.0)	49.5 (23.0, 76.0)
cT3/4	7 (8.0)	3 (3.5)
cN+	27 (30.7)	27 (31.4)
Stage IIA and higher	56 (63.6)	57 (66.3)
G3	74 (84.1)	71 (82.6)
TILs		
low (0-10%)	34 (38.6)	32 (37.2)
intermediate (11-59%)	42 (47.7)	41 (47.7)
high (≥60%)	12 (13.6)	13 (15.1)
Durvalumab/placebo alone (window)	59 (67.0)	58 (67.4)

- **Primary endpoint was pCR at surgery**
- **iDFS, DDFS and OS were secondary endpoints**
- **Statistical considerations**
  - The time-to-event-analysis was changed from an initially planned event-driven analysis at 43 events (to detect HR=0.773 with 13.5% power) to a time-driven analysis after 3.5 years median follow-up.
  - No adjustment for multiple testing



Loibl S et al. 2021 ASCO. Abstract 506.

GeparNUEVO – Other Efficacy Endpoints



Median Follow-up 44 months

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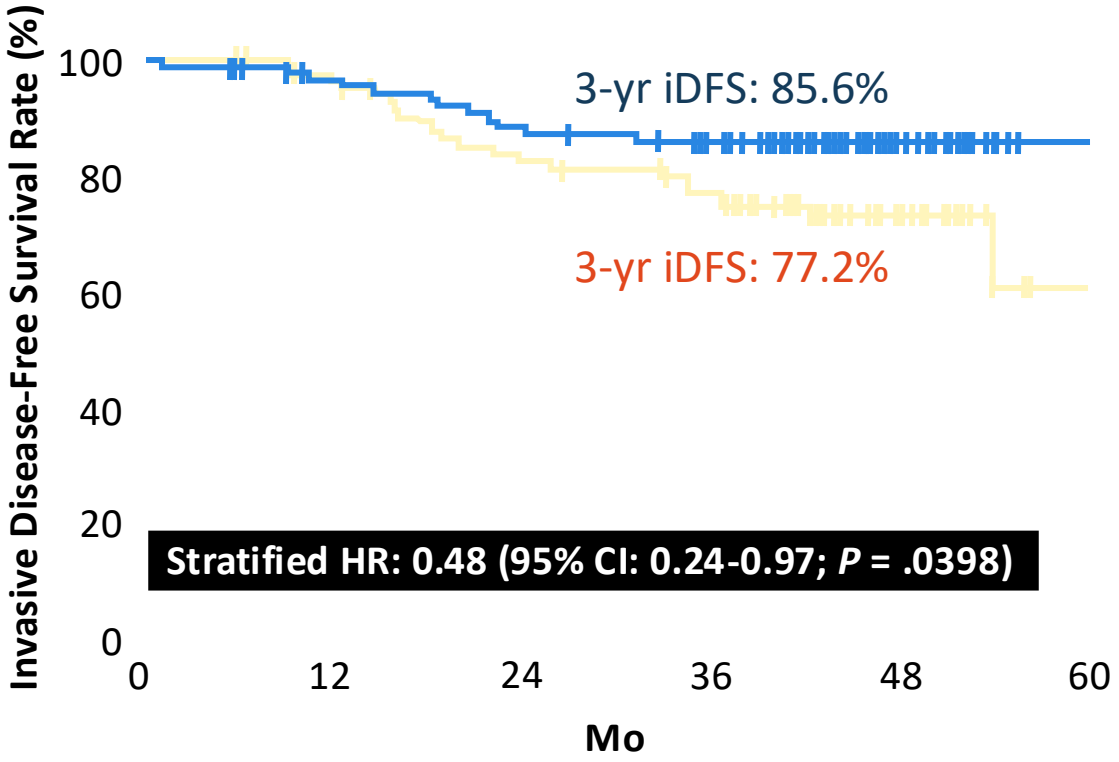
Loibl S et al. 2021 ASCO. Abstract 506. Annals of Oncology, 2022

Is All the IO Benefit Conferred With Neoadjuvant Administration?

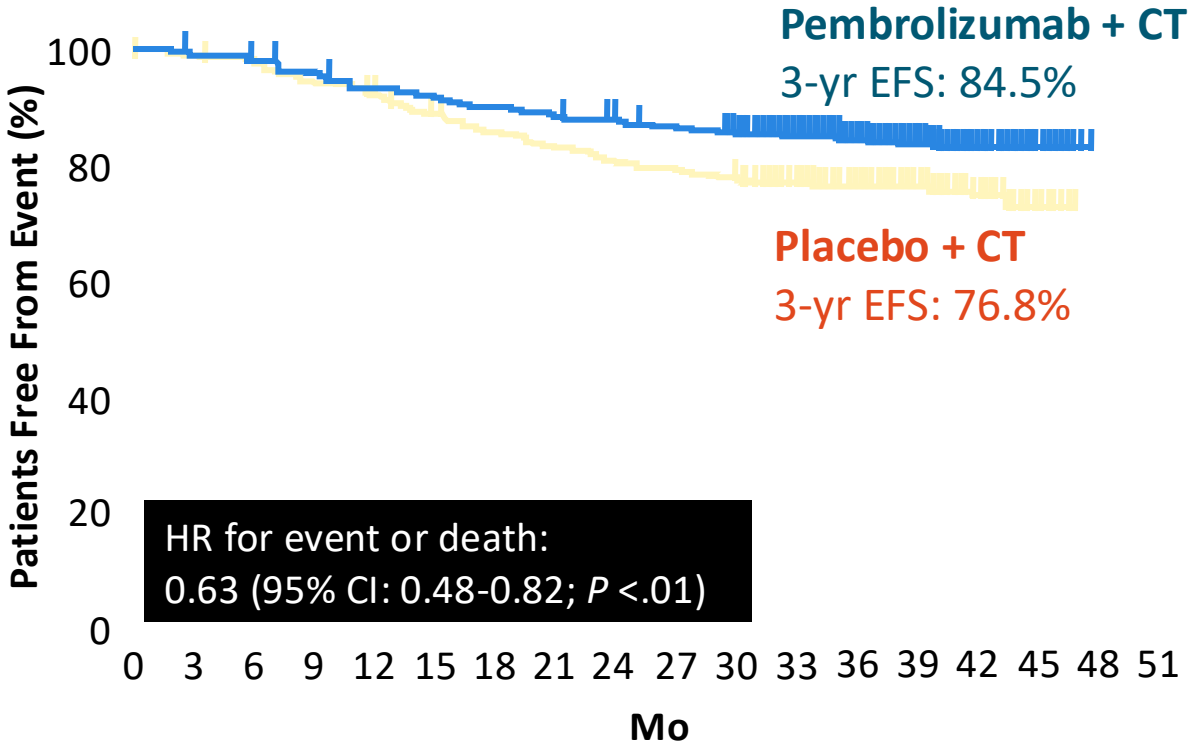
GeparNuevo: iDFS[1]

Median follow-up: 43.7 mo



KEYNOTE-522: EFS[2]

Median follow-up: 39.1 mo



Is all the benefit from IO conferred with neoadjuvant administration?

1. Loibl. ASCO 2021. Abstr 506. 2. Schmid. NEJM. 2022;386:556.

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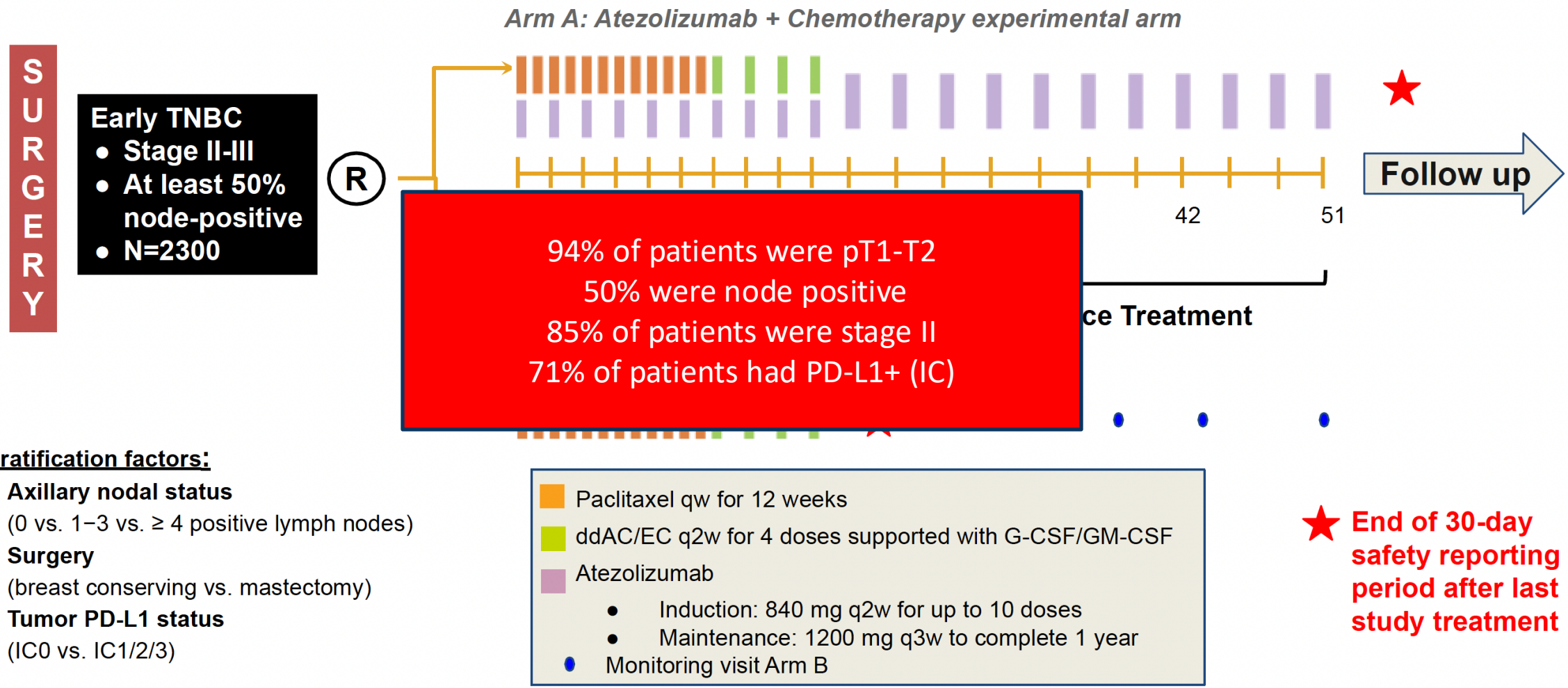
IMpassion 030: Phase 3 Study Design



Stratification factors:

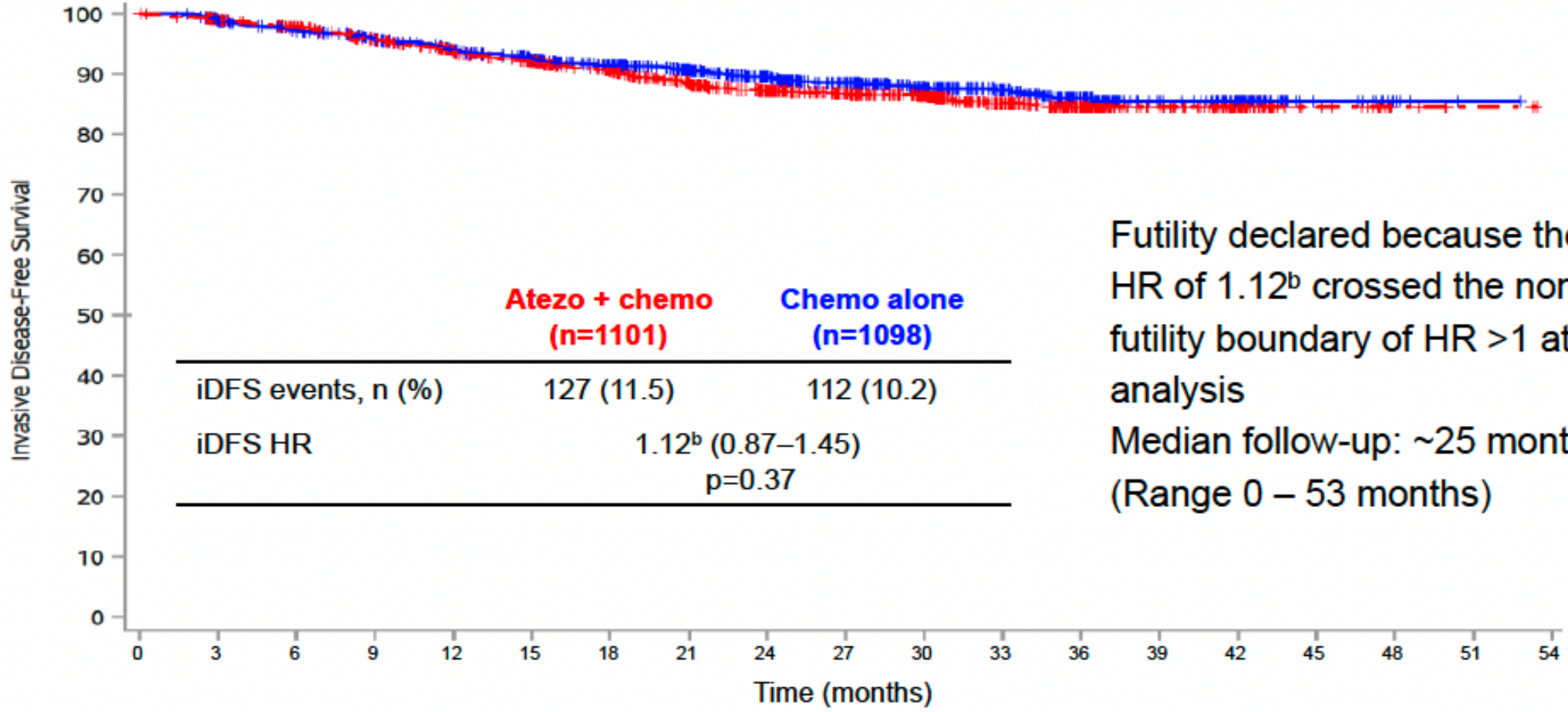
Axillary nodal status
(0 vs. 1–3 vs. ≥ 4 positive lymph nodes)
Surgery
(breast conserving vs. mastectomy)
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

Global PI: Heather McArthur

Memorial Sloan Kettering Cancer Center

GS01-03, Ignatiadis et al, SABCS 2023

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)

[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

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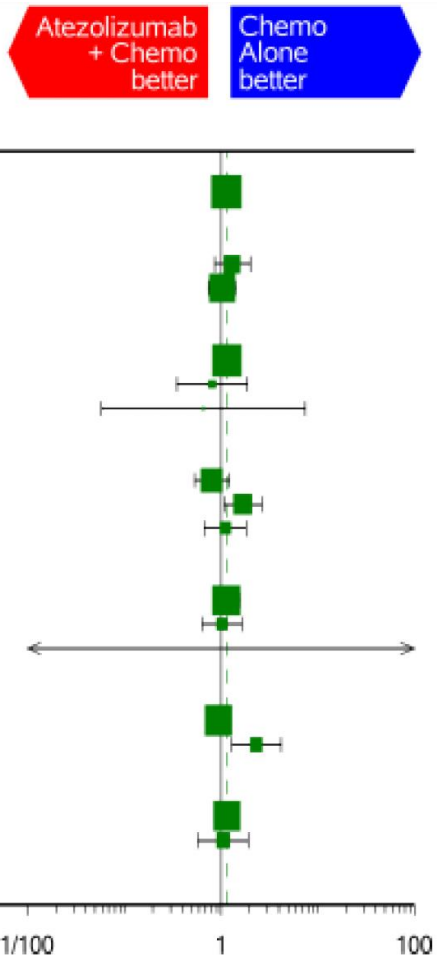
iDFS subgroup analysis (ITT population)

Baseline Risk Factors	Total n	Atezolizumab + Chemo (N=1101) n	Atezolizumab + Chemo (N=1101) Median (Months)	Chemo Alone (N=1098) n	Chemo Alone (N=1098) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	2199	1101	NE	1098	NE	1.13	(0.87, 1.45)
PD-L1 Status (IxRS)							
IC 0	632	316	NE	316	NE	1.32	(0.87, 2.01)
IC 1/2/3	1567	785	NE	782	NE	1.03	(0.75, 1.43)
Primary Tumor Stage at First Diagnosis (Grouped)							
pT1-pT2	2069	1024	NE	1045	NE	1.15	(0.88, 1.51)
pT3	122	71	NE	51	NE	0.81	(0.35, 1.86)
Other	8	6	23.7	2	NE	0.66	(0.06, 7.54)
Axillary Nodal Status (IxRS)							
0	1150	577	NE	573	NE	0.81	(0.54, 1.22)
1-3	780	390	NE	390	NE	1.69	(1.08, 2.64)
>=4	269	134	NE	135	NE	1.12	(0.68, 1.85)
AJCC Stage at Surgery (Grouped)							
Stage II	1875	935	NE	940	NE	1.15	(0.85, 1.56)
Stage III	318	161	NE	157	NE	1.03	(0.64, 1.65)
Other	6	5	NE	1	NE	>999.99	(0.00, NE)
Pooled Age Group 1							
<65	1820	916	NE	904	NE	0.95	(0.71, 1.26)
>=65	379	185	NE	194	NE	2.33	(1.28, 4.24)
Baseline ECOG Assessment Score							
0	1782	887	NE	895	NE	1.15	(0.87, 1.51)
1	417	214	NE	203	NE	1.06	(0.58, 1.95)



Hazard ratios and the associated Wald confidence intervals were estimated using *unstratified* Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.

For now…. NO ROLE for adjuvant immunotherapy in early stage TNBC.

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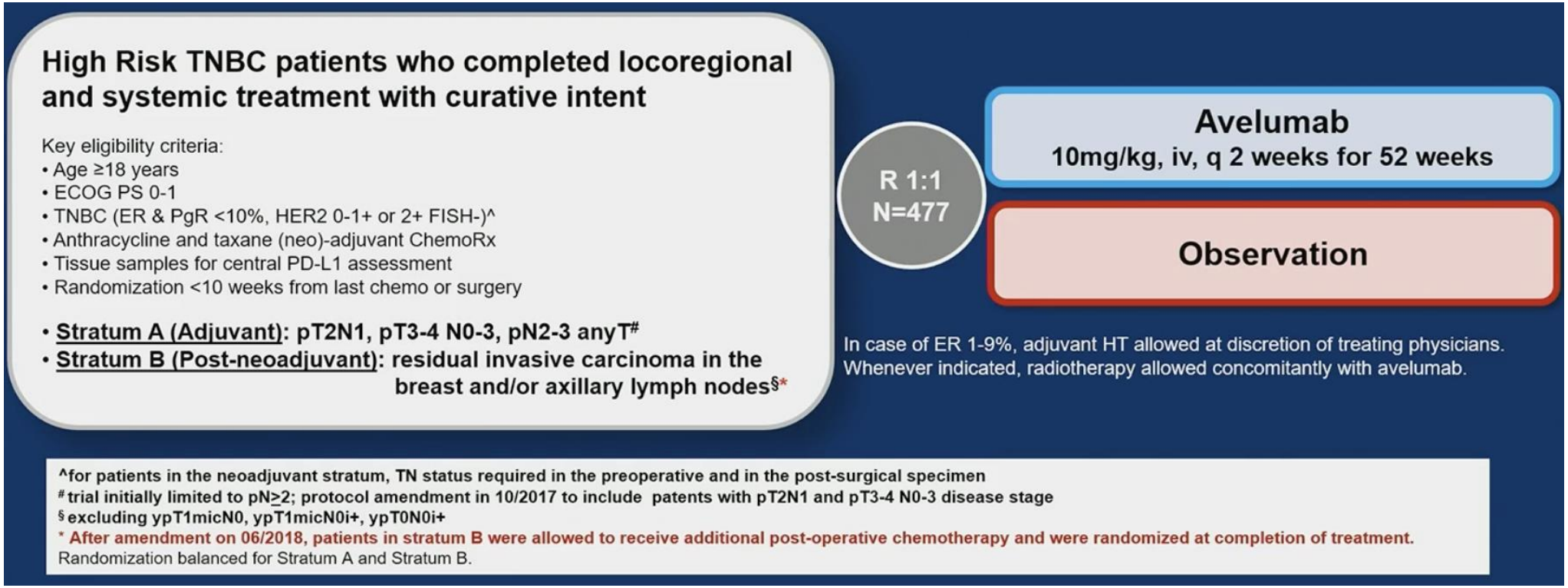
GS01-03, Ignatiadis et al, SABCS 2023

A-BRAVE (n=514)



Primary Efficacy Endpoints

- DFS
- DFS in Stratum B (post-neoadjuvant)

- Secondary Efficacy Objectives
- -OS
- -DFS in PD-L1 positive patients

Designed and conducted pre-KEYNOTE 522.

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A-BRAVE: Patient Characteristics

Patient characteristics		Avelumab (n= 235)	Control (n= 231)
Age, median (range)		50.9 (28.3-78.6)	51.9 (28.8-79.9)
ER & PgR <10%, n (%)		231 (98.3)	226 (97.8)
HER2 status, n (%)	0	150 (64.1)	147 (63.9)
	1+/2+ (ISH neg)	84 (35.7)	83 (35.9)
gBRCA status, n (%)	gBRCA mutated	24 (10.2)	27 (11.7)
Adjuvant (Stratum A)		**40 (17.8)**	**43 (18.6)**
AJCC stage at surgery, n (%)	II	20 (50.0)	22 (51.2)
	III	20 (50.0)	21 (48.8)
Post-neoadjuvant (Stratum B)		**195 (83.0)**	**188 (81.4)**
AJCC stage at surgery, n (%)	ypT1 & ypN0	93 (47.7)	85 (45.2)
	≥ypT2 & ypN0	31 (15.9)	38 (20.2)
	any ypT & ypN1	49 (25.1)	42 (22.3)
	any ypT & ≥ ypN2	22 (11.3)	23 (12.2)
RCB, n (%)	RCB 1	8 (4.1)	17 (9.0)
	RCB 2	98 (50.3)	77 (41.0)
	RCB 3	26 (13.1)	18 (9.6)
	Under evaluation	63 (32.3)	76 (40.4)
Adjuvant capecitabine, n(%)*		57 (24.2)	42 (18.2)

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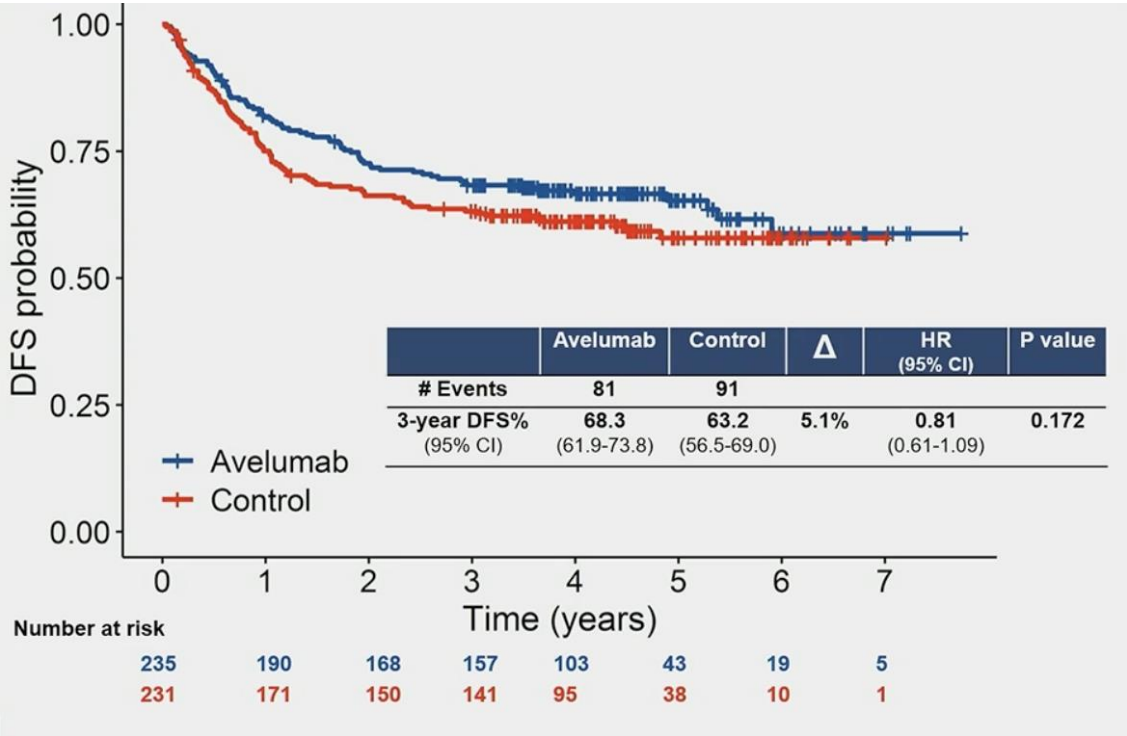
Conte, ASCO 2024

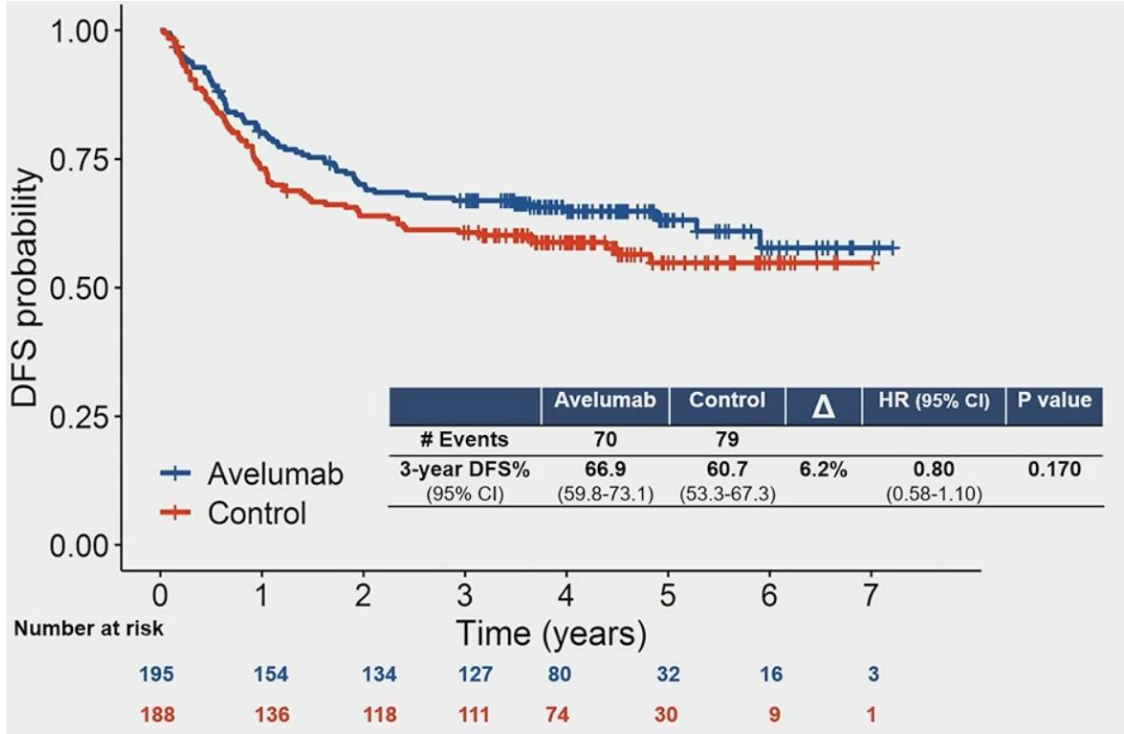
A-BRAVE DFS (ITT and Post-Neo)

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

Post-Neoadjuvant



	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

Median FU 52 months, 72% patients completed treatment.

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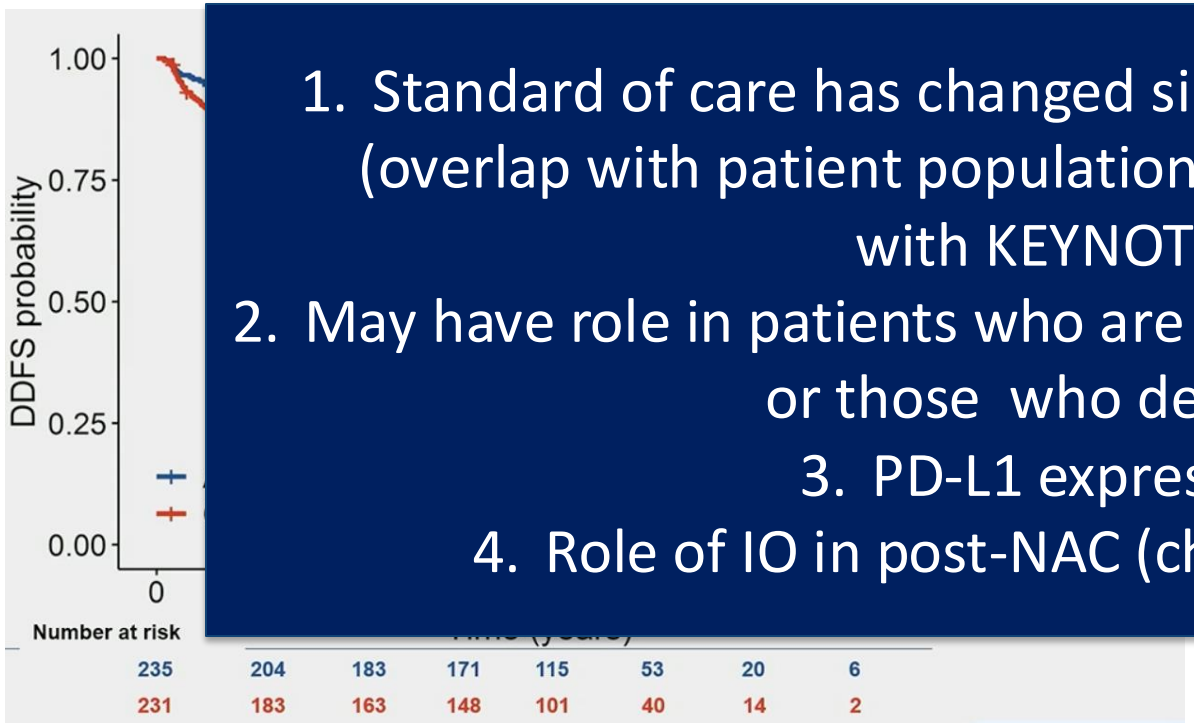
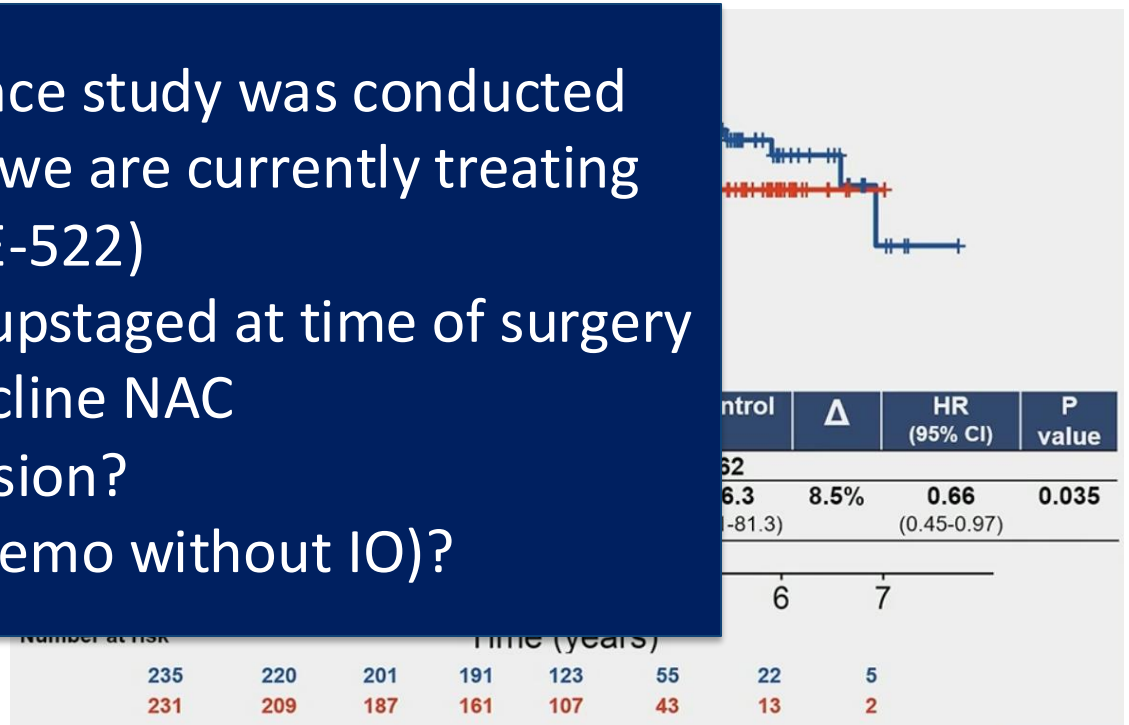
A-BRAVE Distant DFS and OS

30% reduction in risk of distant metastases and 34% reduction in risk of death

Distant DFS (ITT)

OS





1. Standard of care has changed since study was conducted (overlap with patient population we are currently treating with KEYNOTE-522)
2. May have role in patients who are upstaged at time of surgery or those who decline NAC
3. PD-L1 expression?
4. Role of IO in post-NAC (chemo without IO)?

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Conte, ASCO 2024

For Now… Adjuvant Pembrolizumab following Neoadjuvant Pembrolizumab is Standard of Care

01

Pembrolizumab as part of the KN522 regimen is the only FDA-approved checkpoint inhibitor in early-stage TNBC

02

The KN522 regimen includes both neoadjuvant AND adjuvant pembrolizumab

03

Adjuvant pembrolizumab appears to benefit both those with residual disease and those with pCR

04

Neoadjuvant and adjuvant pembrolizumab together are associated with improved overall survival

05

Supported by NCCN and ASCO guidelines

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KN522 is Standard of Care … Yet Questions Remain

- Optimal chemotherapy backbone?
- Do we need adjuvant pembrolizumab?
- How to best address patients with residual disease?

CREATE-X Trial:
Adjuvant capecitabine in those who fail pCR

Pathological-effect grade — no./total no. (%)§		
0	19/434 (4.4)	13/435 (3.0)
1a or 1b	232/434 (53.5)	220/435 (50.6)
2 or 3	183/434 (42.2)	202/435 (46.4)
No. of lymph nodes involved on histologic assessment — no. (%)		
0	176 (39.7)	171 (38.5)
1–3	165 (37.2)	174 (39.2)
≥4	102 (23.0)	99 (22.3)
Adjuvant endocrine therapy — no. (%)		
Yes	298 (67.3)	304 (68.5)
No	145 (32.7)	140 (31.5)
Radiotherapy — no. (%)¶		
Yes	321 (72.5)	326 (73.4)
No	122 (27.5)	118 (26.6)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Capecitabine Group (N=443)	Control Group (N=444)
Age at enrollment — yr		
Median	48	48
Range	25–74	25–74
Menopausal status — no. (%)		
Premenopausal	262 (59.1)	248 (55.9)
Postmenopausal	181 (40.9)	196 (44.1)
Body-mass index†		
Median	22.6	23.0
Range	15.6–39.9	15.6–41.2
Tumor size at diagnosis — no./total no. (%)		
≤2 cm	68/442 (15.4)	61/444 (13.7)
>2 to ≤5 cm	244/442 (55.2)	275/444 (61.9)
>5 cm	65/442 (14.7)	69/444 (15.5)
Skin or chest-wall infiltration of any size — no./total no. (%)	65/442 (14.7)	39/444 (8.8)
Hormone-receptor status — no. (%)		
Estrogen-receptor positive or progesterone-receptor positive	304 (68.6)	297 (66.9)
Estrogen-receptor negative and progesterone-receptor negative	139 (31.4)	147 (33.1)
Neoadjuvant chemotherapy — no. (%)		
Sequential anthracycline and taxane	357 (80.6)	372 (83.8)
Concurrent anthracycline and taxane	63 (14.2)	53 (11.9)
Anthracycline-containing chemotherapy only or docetaxel and cyclophosphamide only	23 (5.2)	19 (4.3)
Fluorouracil plus anthracycline‡	262 (59.1)	271 (61.0)

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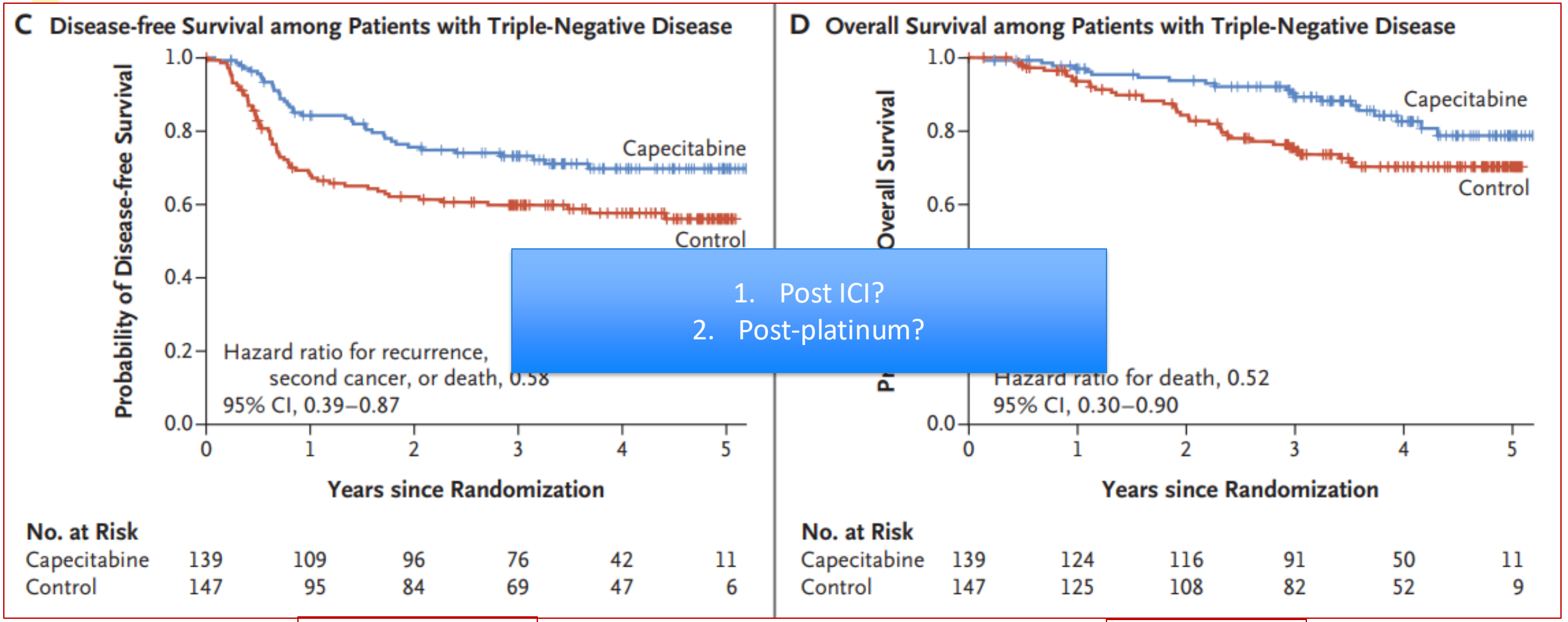
Masuda N, et al - N Engl J Med. 2017 Jun 1;376(22):2147-2159.

DFS & OS in TNBC

Prolonged with capecitabine



1. Post ICI?
2. Post-platinum?

Control Arm
5-year DFS: 56.1%

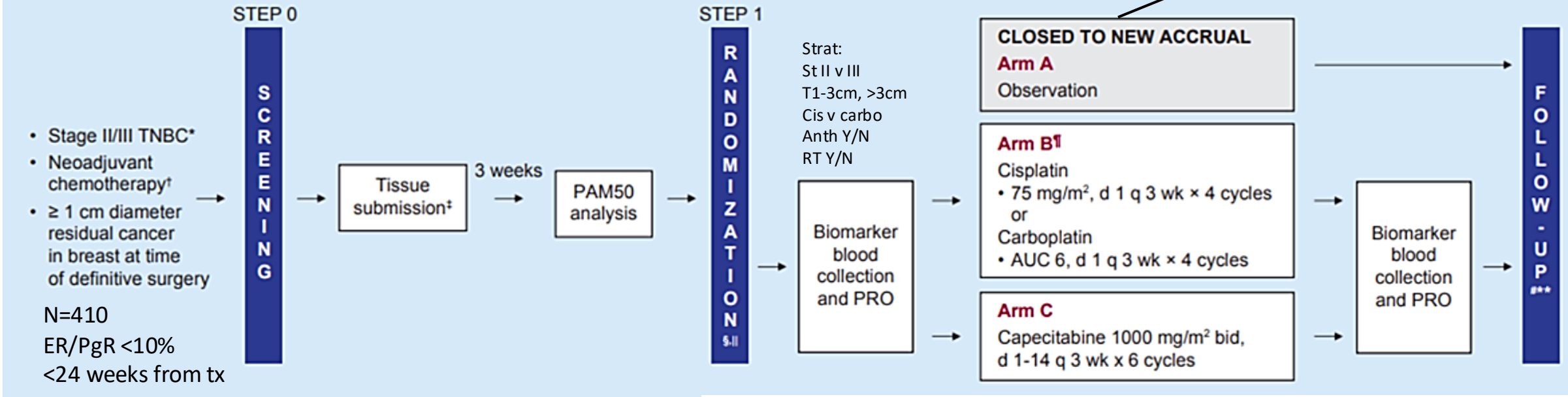
Control Arm
5-year OS: 70.3%

Masuda N et al. *N Engl J Med*. 2017;376:2147-2159.

Platinum vs. Cape in RD: ECOG-ACRIN EA1131

* 5 patients randomized prior to CREATE-X driven amendment excluded from analysis

Study Schema



Primary Endpoint: iDFS in basal subtype TNBC by PAM50

Statistics: Noninferiority design with superiority alternative, assuming 4y iDFS 67% with capecitabine

Noninferiority margin HR 1.154

Planned enroll N=775 → 562 basal → 196 events for 83% power, 1-sided alpha 0.025 to reject H0 of inferiority of platinum if 4y iDFS was at least 74% (ie, HR 0.754)

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Mayer IA et al. *J Clin Oncol*. 2021;39(23):2539-2551.

Platinum vs. Cape in RD: ECOG-ACRIN EA1131

- Tumor characteristics
  - cT2+ 90%; cN0 42% cN1+55%
  - Median ypT 2.4cm
  - ypN+ 54%
- Patient characteristics:
  - Prior taxane 100%; anthracycline 85%
  - Other neoadj tx 39%

- 82% completed platinum; 79% completed capecitabine
- Gr 3 or 4 tox: Platinum 26% vs. Cape 15%

Platinum: Common Gr 1-2 Anemia, Nausea, Dec WBC, Neuropathy; ≥Gr 3 Dec WBC (10%), Thrombocytopenia (7%), Neutropenia (4%), Anemia (7%), Fatigue (2%)

Capecitabine: Common diarrhea, nausea, HFS, Anemia; ≥Gr 3 HFS (5%), diarrhea (6%), colitis (2%), fatigue (2%)

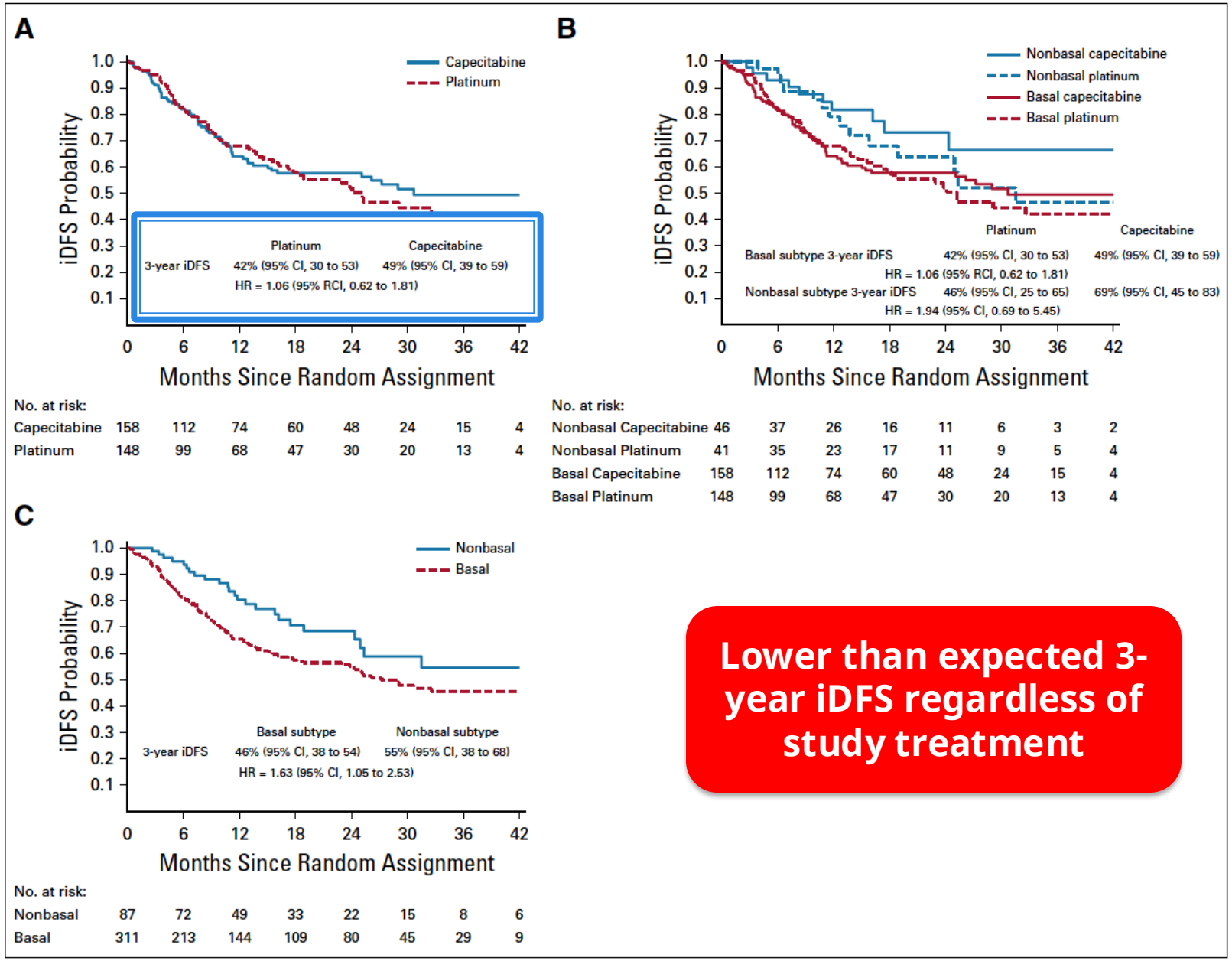
Mayer IA et al. *J Clin Oncol*. 2021;39(23):2539-2551.

ECOG/ACRIN 1131: Results

DSMC recommended stopping trial

3y iDFS platinum vs cape
HR 1.09 (95% CI 0.62-1.90)

Grade 3 and 4 toxicities were more common with platinum agents.



Lower than expected 3-year iDFS regardless of study treatment

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Mayer IA et al. *J Clin Oncol*. 2021;39(23):2539-2551.

ECOG-ACRIN EA1131

- Platinum agents are not likely to be non-inferior or superior to capecitabine as adjuvant therapy for high-risk, basal TNBC with residual ds after NAC
- 3-year iDFS was quite poor in both arms (~42-49%)
- Different population than CREATE-X which was all Asian, allowed any volume of residual ds and did not specify by molecular subtype
  - TNBC: 5y DFS 69% vs. 56%; 5y OS 79% vs. 70%
- Why was this an unexpected "negative" trial?
  - Does residual disease after NAC reflect genomics/epigenomics of MBC setting in terms of reduced BRCA1/2 methylation?
  - Duration of therapy capecitabine 18 weeks vs. platinum 12 weeks? Delays in initiation of treatment
- Await biomarker analyses but NO role for adjuvant platinum in those with residual disease. Capecitabine remains SOC

OlympiA:
Olaparib for gBRCA-associated breast cancer

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2−negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → Surgery → +/- Radiotherapy

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → ≥ 6 cycles Adjuvant Chemotherapy → +/- Radiotherapy

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- *BRCA1/2* associated cancers
- Symptom / Health related QoL
- Safety

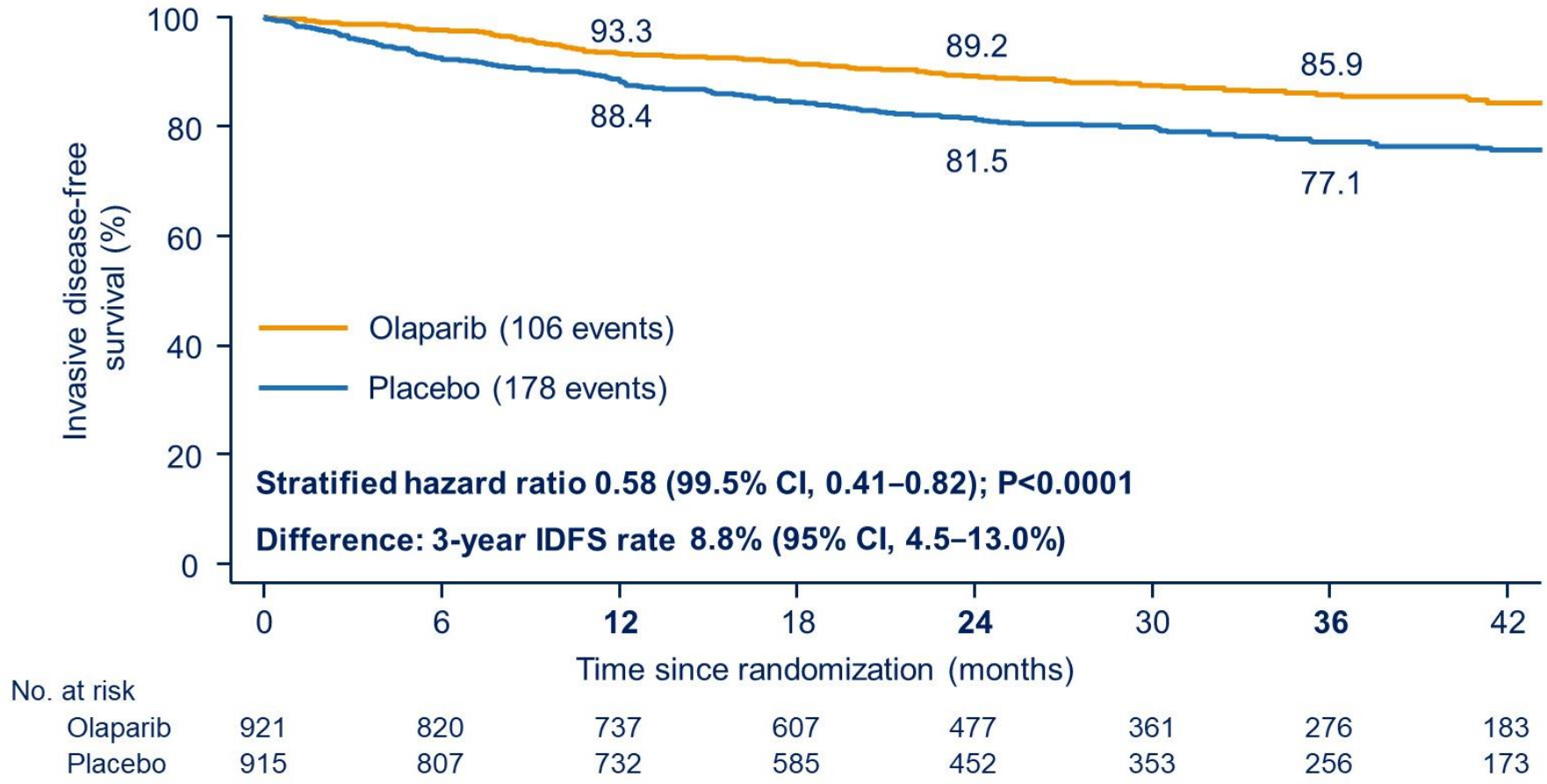
Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

TNBC 82%

Tutt ANJ et al. *N Engl J Med*. 2021;384:2394-2405.

OlympiA: Invasive disease-free survival (ITT)



Type of 1st iDFS Event:

Distant CNS event 2.4% vs. 3.9%

Locoregional 1.7% vs. 2.5%

Contralateral 0.9% vs. 1.3%

Second Primary Gyn Ca 1.2% vs. 2.3%

7.3% absolute improvement in 4-year DFS favoring olaparib

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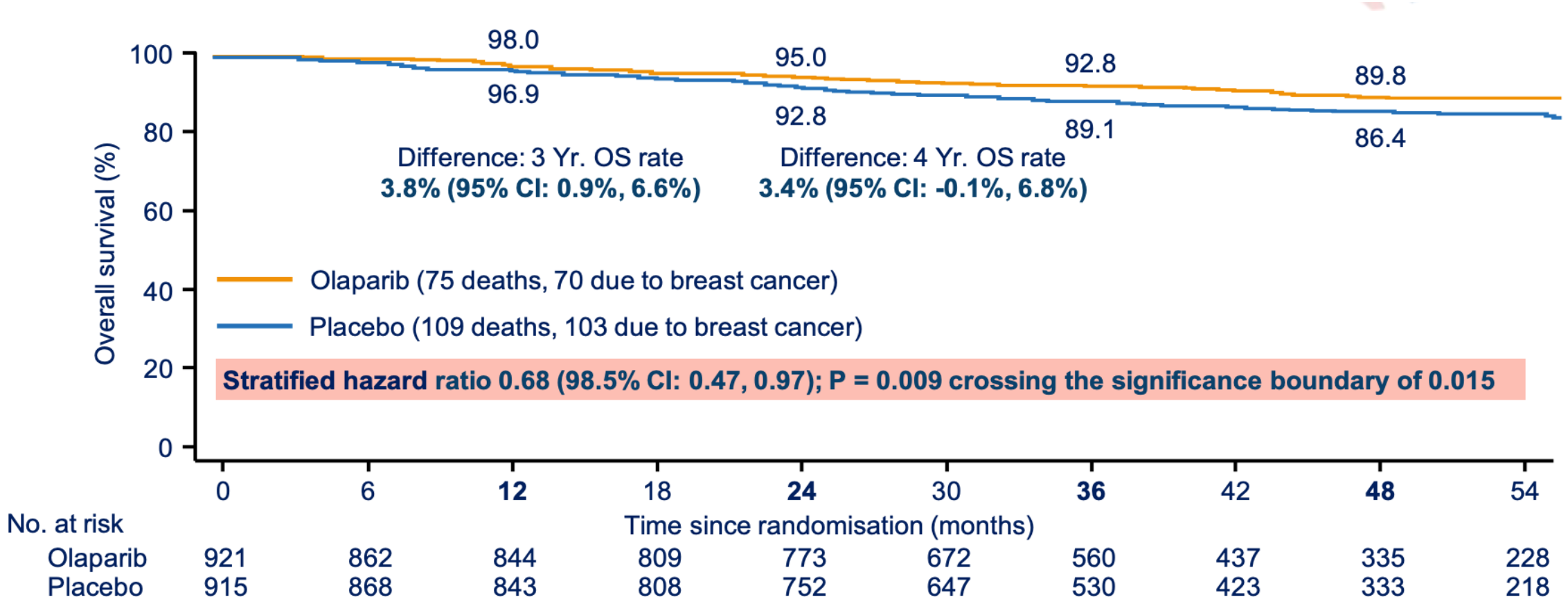
Tutt A et al. 2021 ASCO. Abstract LBA1.

OlympiA: Overall Survival Update



Reduced the risk of death over placebo by 32%
Absolute improvement of 3.8% at 3 years

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Tutt ANJ et al. 2022 ESMO Virtual Plenary. Abstract VP1-2022.

Ongoing Studies for Patients with Residual Disease Post-NAC

Study (N)	Treatment	Primary Endpoint
S1418 NCT02954874 (N 1155)	Pembrolizumab for one year vs observation (Minimum 1 cm RD post NAC and/or N+ post NAC)	iDFS
SASCIA NCT04595565 (N 1200) Accruing	Sacituzumab Govitecan-hziy x8 cycles vs TPC	iDFS
TROPION-Breast03 NCT05629585 (N=1075) Accruing	Dato-DXd With or Without Durvalumab vs TPC (Arm 1: Dato/Durva Arm 2: Dato Arm 3: TPC)	iDFS
ASCENT-05 NCT05633654 (N=1514) Accruing	Sacituzumab Govitecan-hziy and Pembrolizumab vs TPC	iDFS

Thank You!

trainat@mskcc.org

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