

Can We Cure MBC with Systemic Therapy?

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Disclosures

I have the following relevant financial relationships to disclose:

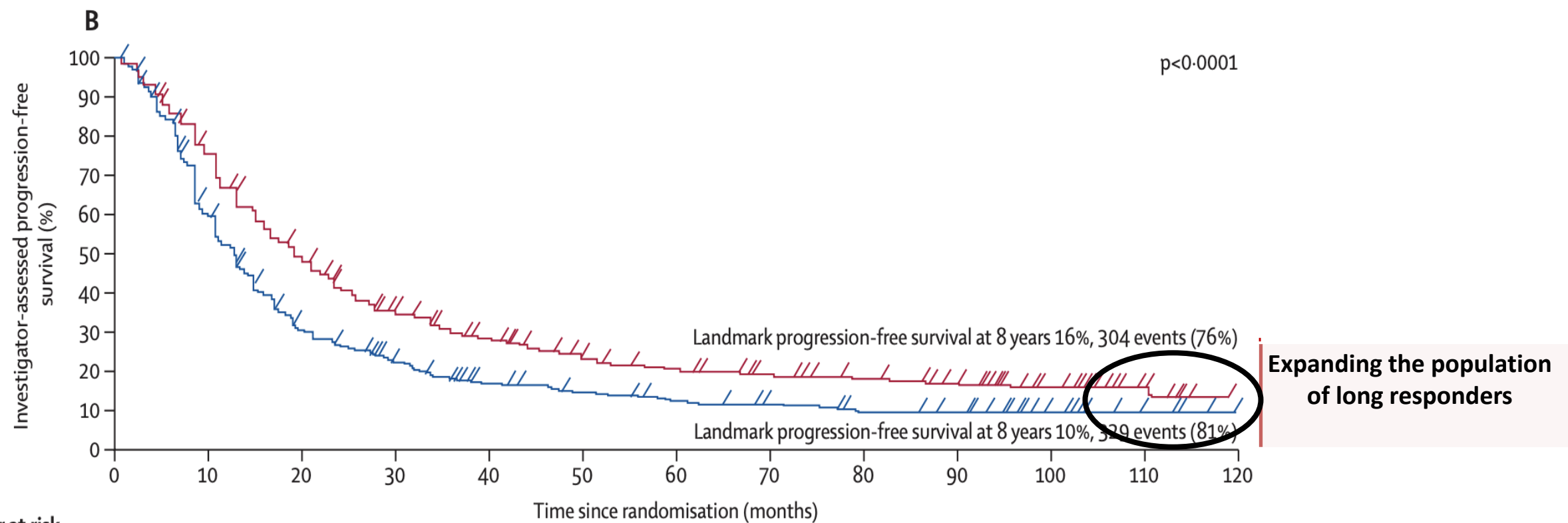
Consultant for: Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Genentech/Roche, Immunomedics, Merck, OBI Pharma, Pfizer, Puma, Spectrum Pharmaceuticals, Syndax Pharmaceuticals, Peregrine, Calithera, Daiichi-Sankyo, Seattle Genetics, AstraZeneca and TapImmune.

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HER2+

Long-term responders – HER2+ mBC - CLEOPATRA

CLEOPATRA 8y FUP

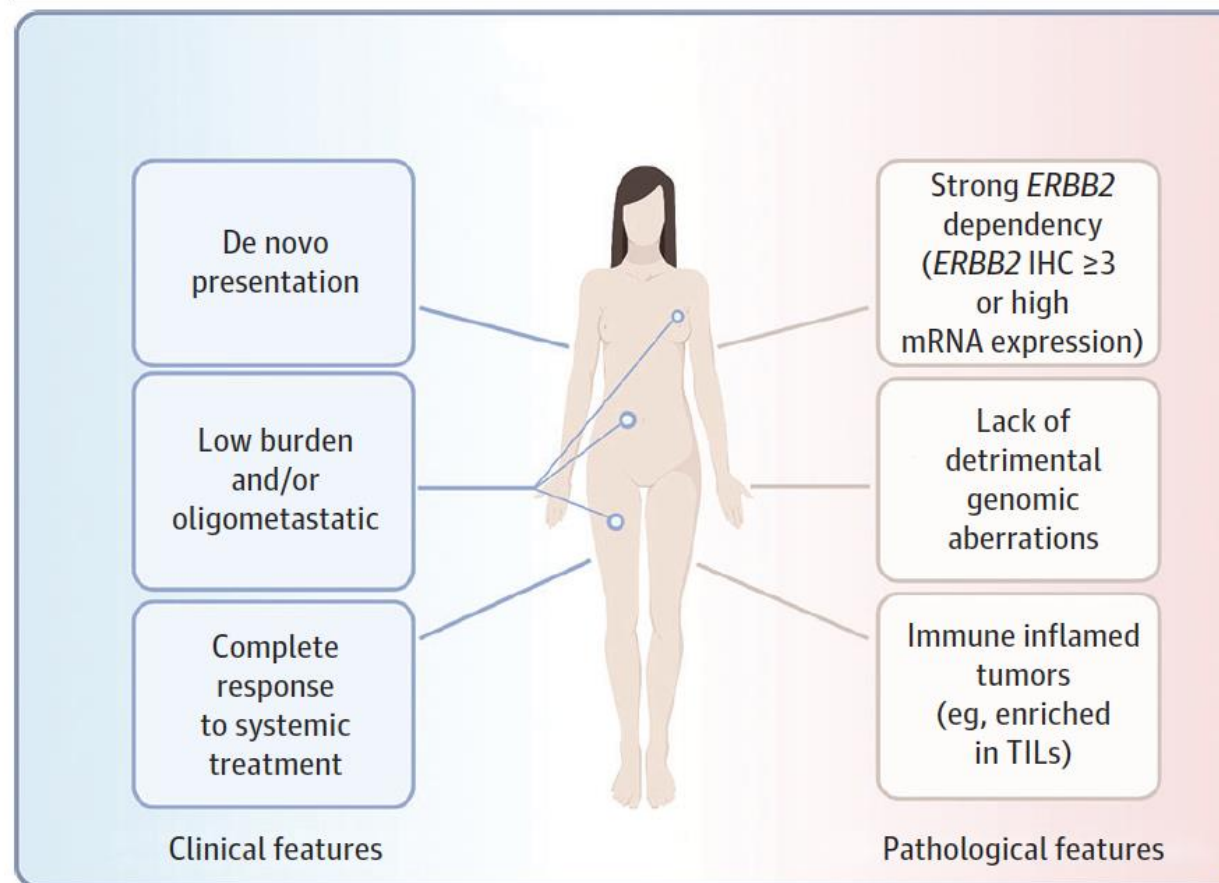


Number at risk
(number censored)

Pertuzumab	402 (0)	284 (18)	179 (24)	121 (34)	93 (40)	71 (47)	60 (49)	52 (54)	43 (60)	34 (66)	21 (78)	6 (92)	0 (98)
Placebo	406 (0)	223 (27)	110 (32)	76 (39)	53 (44)	43 (47)	35 (49)	30 (52)	23 (54)	21 (56)	10 (67)	4 (73)	0 (77)












Long term responders to 1L HER2+ mBC

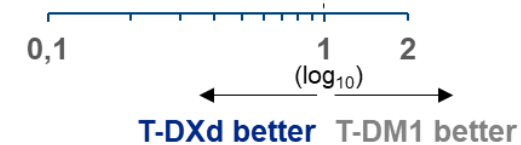
Figure 1. Features Associated With Favorable Long-term Outcomes in Patients With *ERBB2*-Positive MBC Treated With Anti-*ERBB2* Agents



DESTINY-Breast03

Progression-Free Survival by Subgroups¹

		Number of Events		Median PFS time, months (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)	
		T-DXd	T-DM1	T-DXd	T-DM1		
All patients		117/261	171/263	28.8 (22.4-37.9)	6.8 (5.6-8.2)		0.33 (0.26-0.43)
Hormone receptor status	Positive (n = 272)	62/133	93/139	26.2 (21.1-35.8)	6.9 (4.2-9.7)		0.38 (0.27-0.52)
	Negative (n = 248)	54/126	77/122	37.3 (18.0-NE)	6.8 (5.4-8.3)		0.34 (0.24-0.48)
Prior pertuzumab	Yes (n = 320)	75/162	105/158	30.4 (21.4-37.9)	6.8 (5.4-8.3)		0.36 (0.27-0.49)
	No (n = 204)	42/99	66/105	27.4 (18.0-NE)	7.0 (4.2-9.7)		0.36 (0.24-0.53)
Baseline visceral disease	Yes (n = 384)	96/195	132/189	23.9 (18.5-30.4)	5.7 (4.2-7.0)		0.33 (0.25-0.43)
	No (n = 140)	21/66	39/74	NR (28.9-NE)	11.3 (6.8-31.8)		0.37 (0.21-0.63)
Prior lines of systemic therapy^a	<3 (n = 379)	81/188	116/191	37.3 (22.1-NE)	8.2 (6.8-9.9)		0.39 (0.29-0.52)
	≥3 (n = 145)	36/73	55/72	23.9 (16.5-30.4)	4.3 (2.9-5.7)		0.30 (0.19-0.46)
Baseline brain metastases	Yes (n = 82)	28/43	28/39	14.1 (12.4-18.5)	3.0 (2.8-5.8)		0.28 (0.16-0.50)
	No (n = 442)	89/218	143/224	37.3 (25.4-NE)	7.1 (5.6-9.7)		0.35 (0.26-0.45)



^aPrior lines of systemic therapy not including hormone therapy.
1. Hurvitz SA et al. *The Lancet*. 2022;400 [supplement] [in press].

DESTINY-Breast03

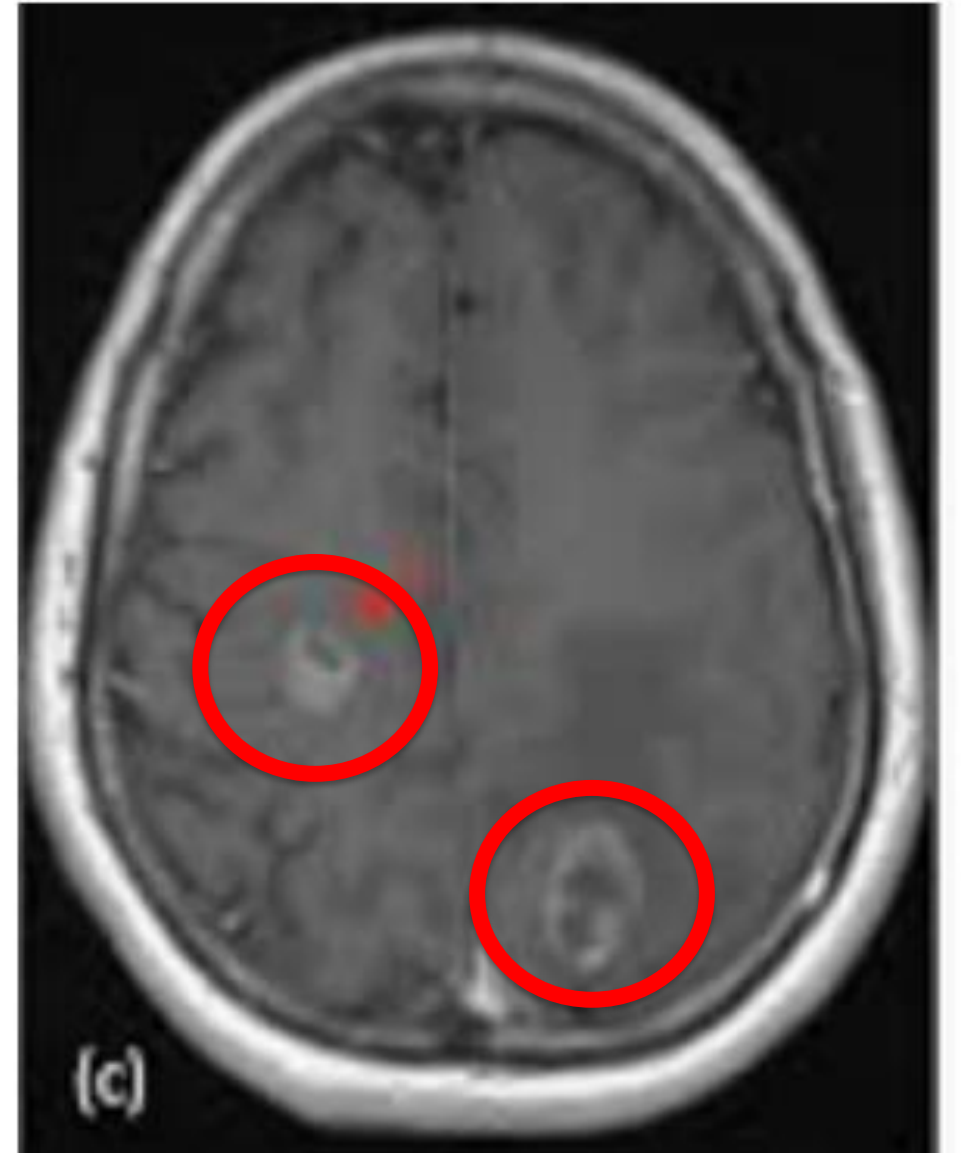
	T-DXd (n = 261) ^a	T-DM1 (n = 263) ^a
Confirmed ORR by BICR		
n (%)	205 (78.5)	92 (35.0)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal <i>P</i> value	< 0.0001	
CR, n (%)	55 (21.1)	25 (9.5)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)

Case Study #1

- 37 y.o. female, initially diagnosed in late 20's with *de novo* metastatic breast cancer to bone
 - ER+, PR+, HER2+ by bone biopsy
 - Initially treated with Taxotere/Trastuzumab and Pertuzumab (THP)
 - Transitioned to endocrine therapy/Trastuzumab/Pertuzumab

3 years later:

- Brain MRI performed due to subtle changes in handwriting and word-finding difficulty
- CNS mets in right parietal lobe and left cerebellum
 - SRS to cerebellar and parietal lobe lesions
 - Continued systemic therapy with endocrine therapy/
trastuzumab/pertuzumab



Case Study #1

1y later:

- MRI brain: Growth of R cerebellar lesion, concerning for either radiation therapy necrosis vs. progression
 - Brain biopsy: metastatic adenocarcinoma, consistent with breast primary, ER 5%, PR 0%, HER2 3+ positive
- Enrolled in Destiny Breast 01 with trastuzumab deruxtecan

Case Study #1

- NED for 6y on TDxd

Case Study #1

- NED for 6y on TDxd
- MRI brain: Development of ~multiple small lesions (all sub-cm) amenable to SRS
 - In addition, 2 lesions in the liver consistent with extracranial progression
- No non-CNS mets
- Transition to the HER2Climb regimen
- Now on neratinib plus IT chemotherapy with trastuzumab

DESTINY-Breast09 phase 3 trial

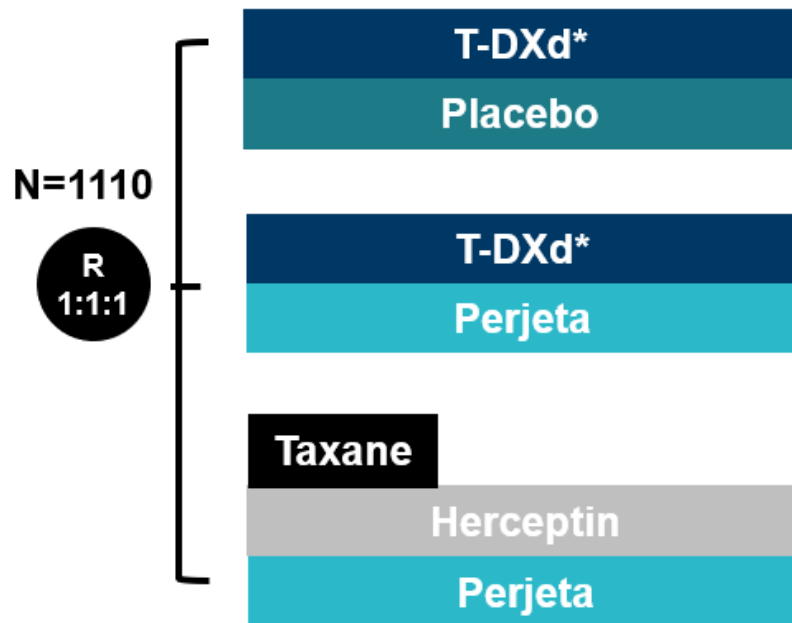
POPULATION

- HER2+ MBC
- DFI >6 months from last chemo or HER2-targeted therapy
- No prior systemic treatment for mBC except for endocrine therapy

Stratification factors :

- *De novo* vs. recurrent (cap at 50% *de novo*)
- HR pos vs. neg
- PIK3CAm (yes vs. no)

STUDY DESIGN



- * Patients can continue with Herceptin if T-DXd is discontinued due to toxicity.
- Use of ET is allowed for HR+ patients after discontinuation of taxane or after 6 cycles of T-DXd.
- Taxane can be paclitaxel or docetaxel.
- Perjeta-blinded in the T-DXd arms.

ENDPOINTS

Primary:

- PFS (BICR)

Secondary:

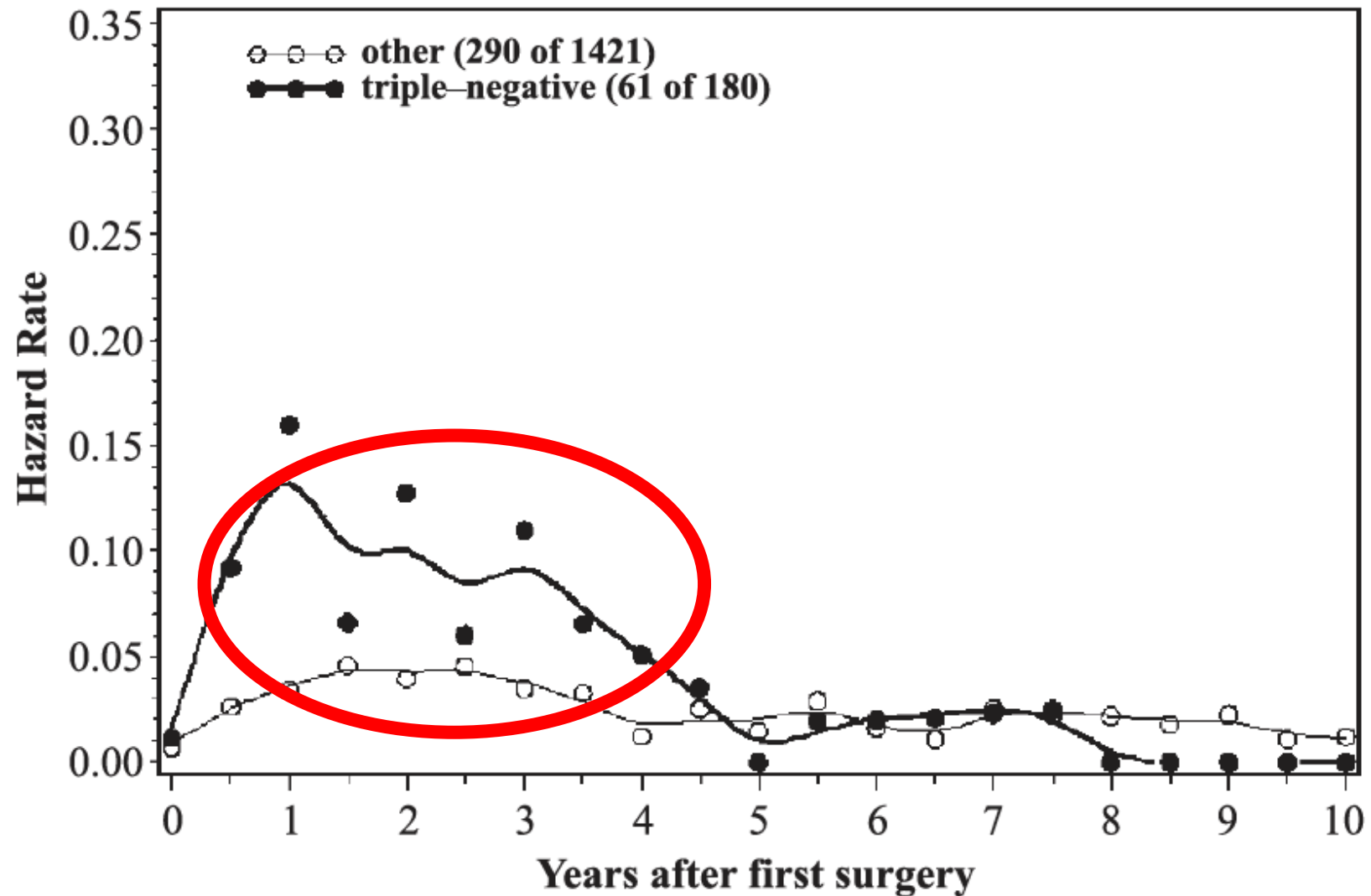
- OS
- PFS (Inv. assessed)
- ORR, DOR
- PFS2
- PRO/HRQoL
- Safety and tolerability

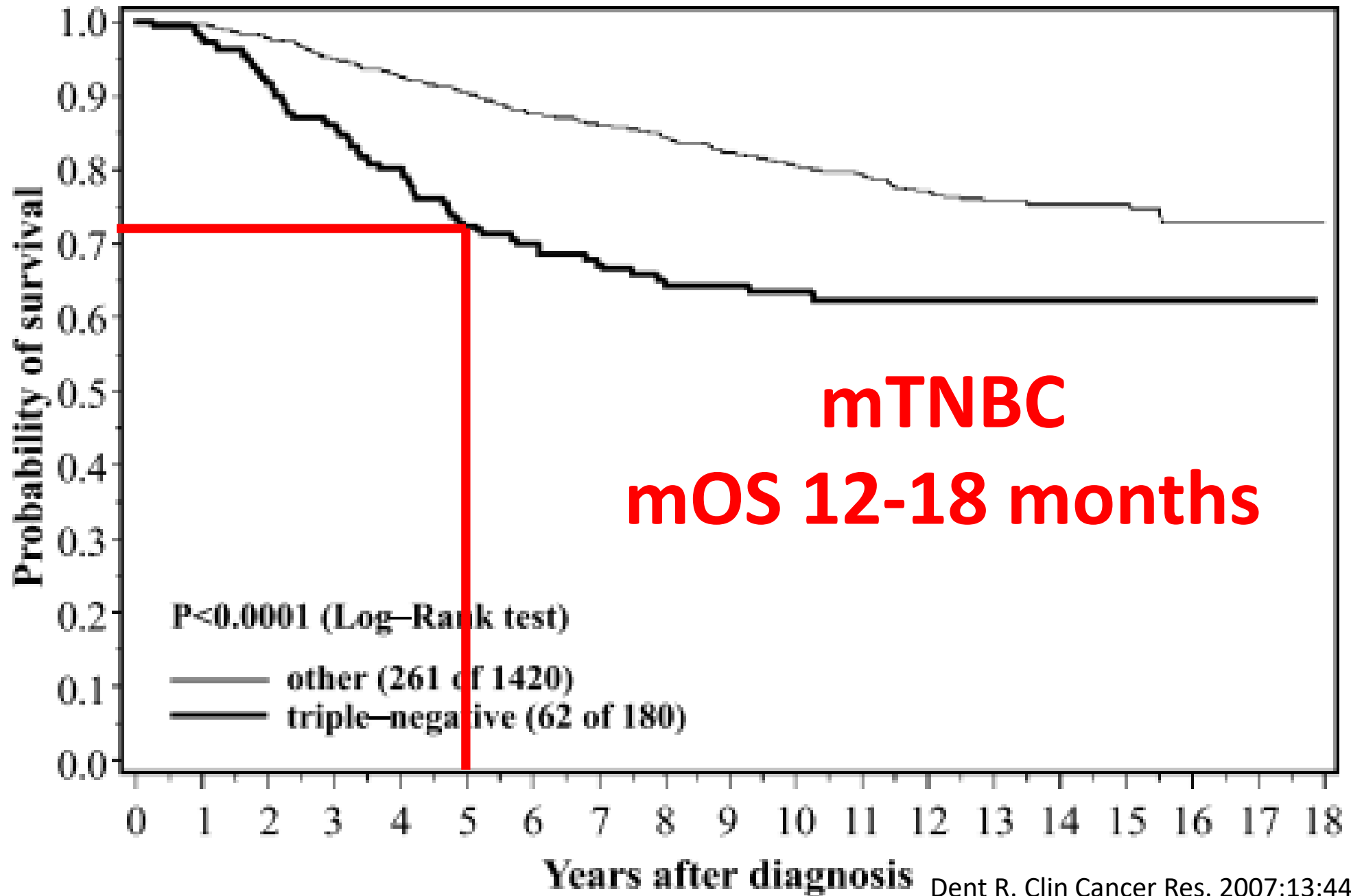
Exploratory:

- TTF, TFST, TSST
- BMFS, CNS-PFS
- Patient-reported tolerability
- Exploratory biomarkers

TNBC

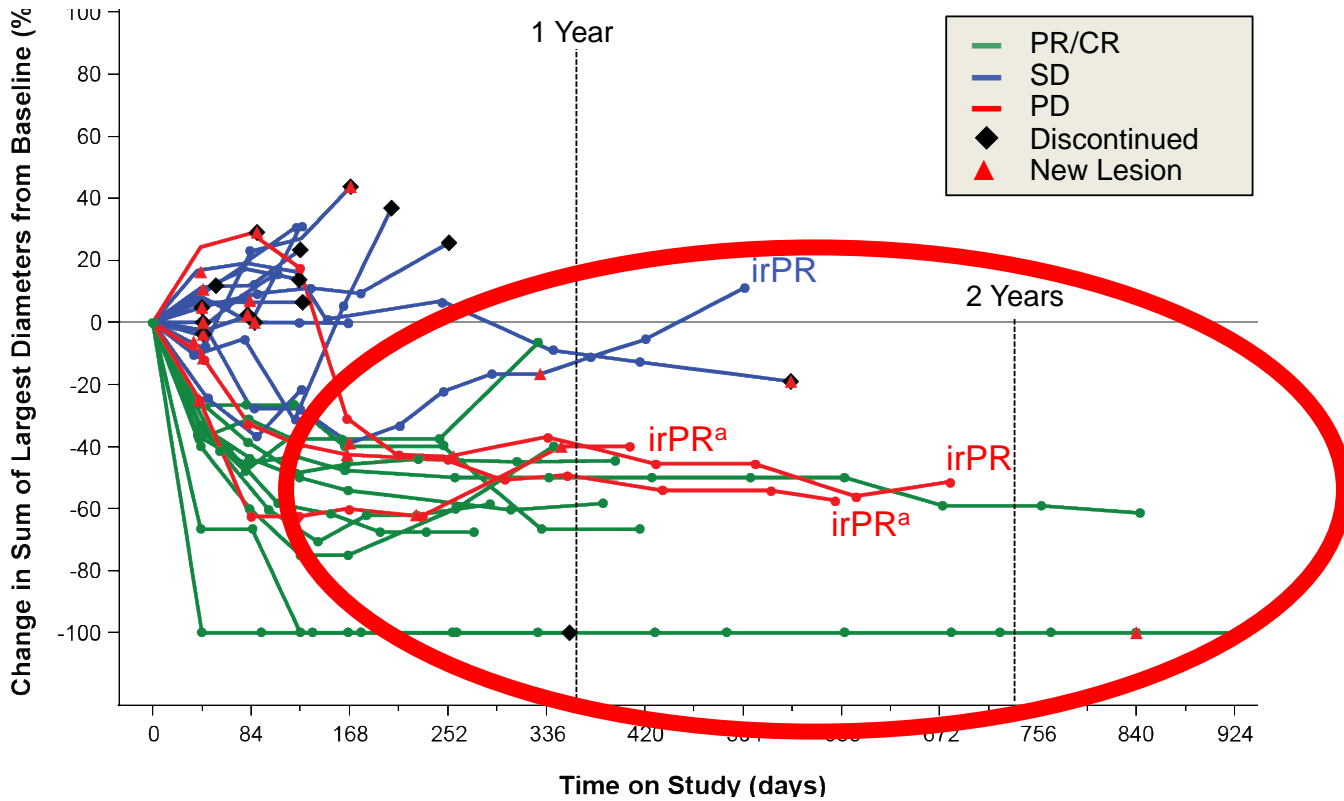
TNBC Risk of Recurrence Occurs Early





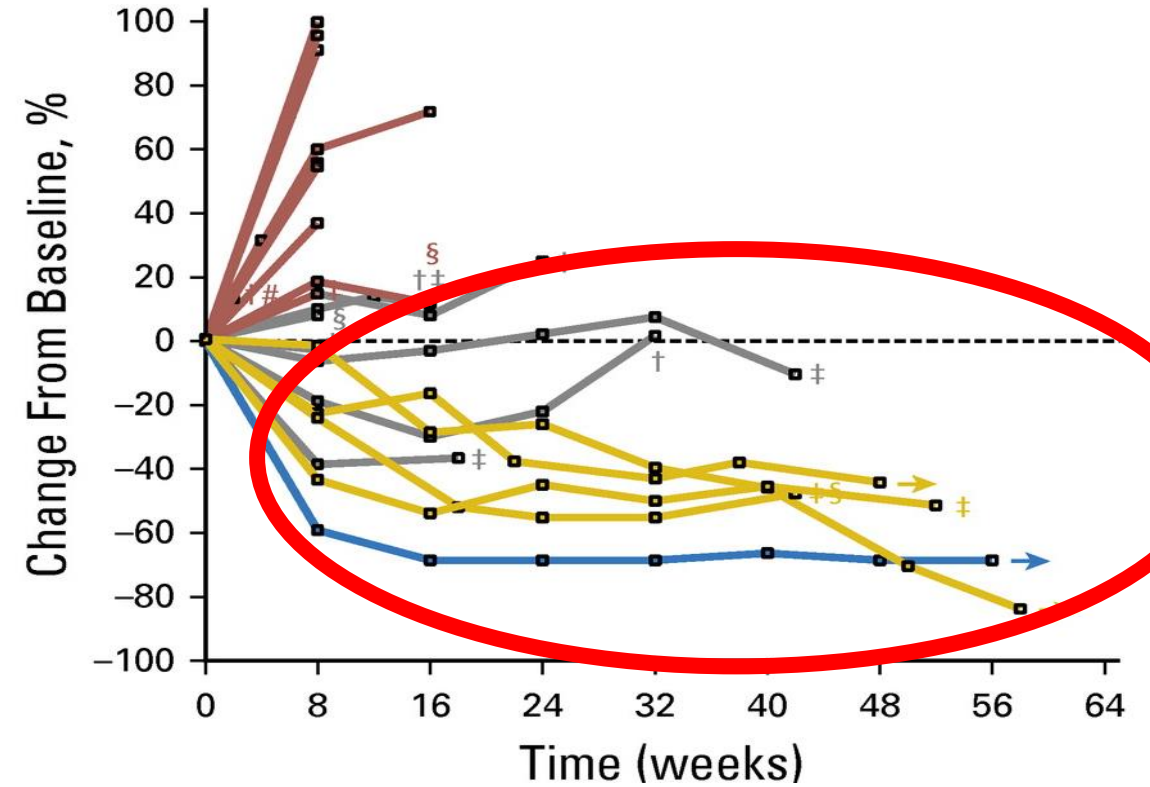
Checkpoint blockade confers durable responses ...

Atezolizumab

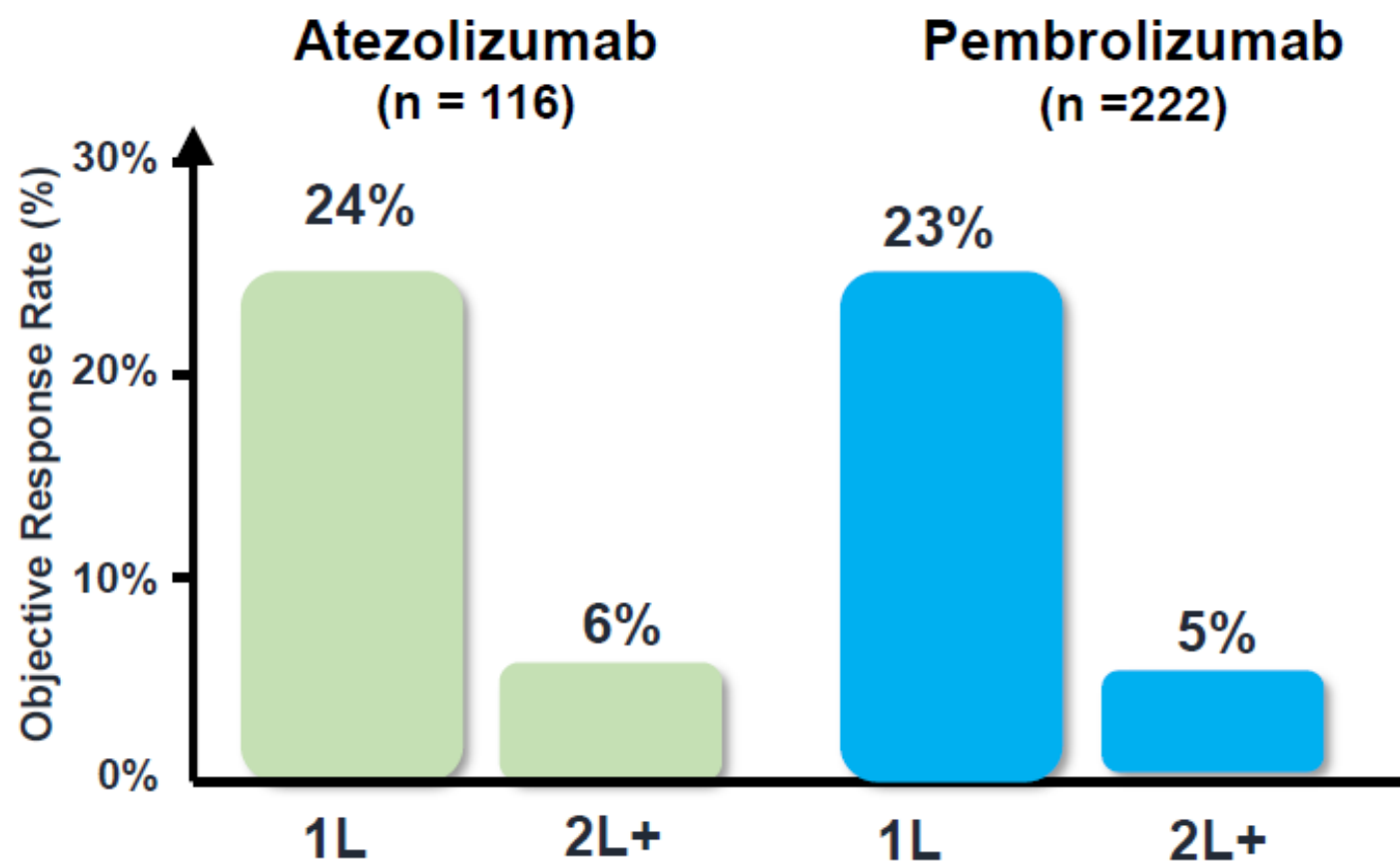


Schmid et al. AACR 2017;
Emens JAMA Oncol 2018

Pembrolizumab

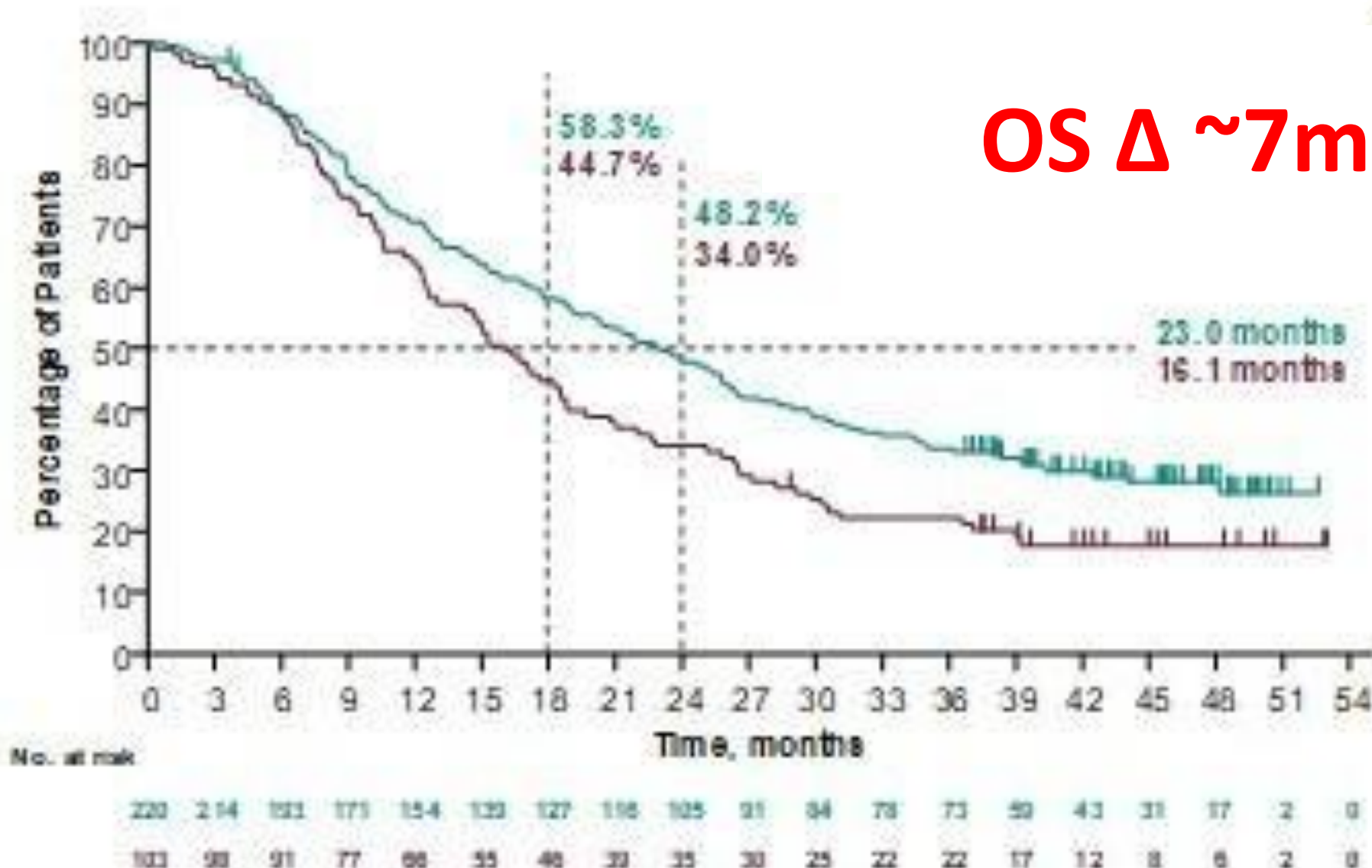


Nanda et al. JCO 2016;34:2460-7

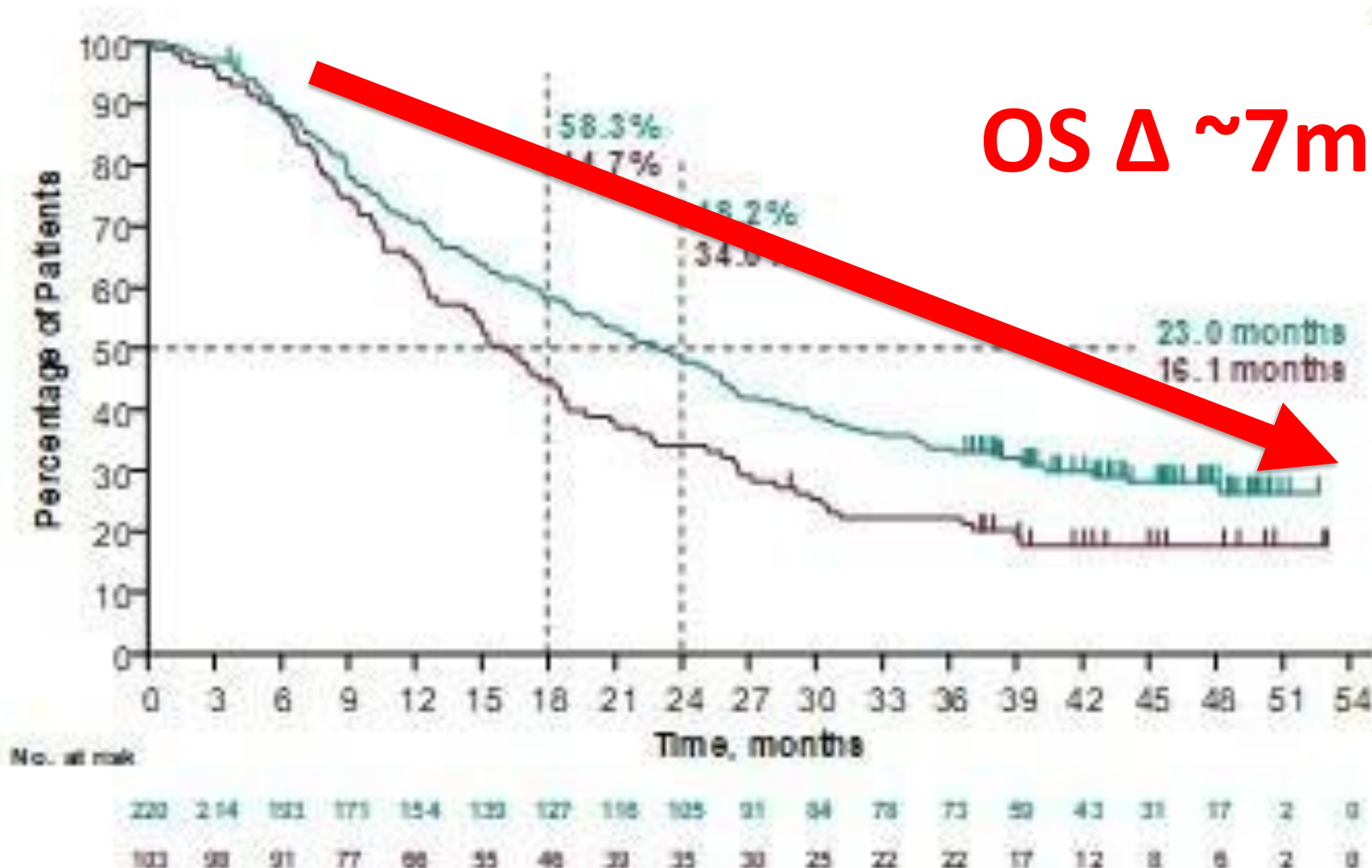


Metastatic Population	Agent	Evaluable (N)	ORR
TNBC	Avelumab	58	5%
HER2+	Avelumab	26	0%
HR+ HER2-	Pembrolizumab	25	12%
	Avelumab	72	3%

KEYNOTE 355 OS IN PD-L1 CPS ≥ 10



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Case Study #2

- 32yo physician diagnosed with stage IIA (pT2N0), 3 cm, grade 3, TNBC in 2013
- Received ddAC-T followed by lumpectomy/SLNB
- Good response to chemotherapy, but not a pCR
- Received adjuvant RT
- Placed on surveillance

Case Study #2

- 32yo physician diagnosed with stage IIA (pT2N0), 3 cm, grade 3, TNBC in 2013
- Received ddAC-T followed by lumpectomy/SLNB
- Good response to chemotherapy, but not a pCR
- Received adjuvant RT
- Placed on surveillance

- Within <1y she develops a local recurrence
- Underwent mastectomy and received “adjuvant” gem/carbo

Case Study #2

- Within a few months of completing gem/carbo she became SOB
- PET/CT was suspicious for lung and lymph node metastases
- Distant lymph node biopsy confirmed metastatic TNBC
- What next?!



Case Study #2

- On nab-paclitaxel with atezolizumab she had 2 episodes of pneumonitis that improved with supportive management but ultimately necessitated discontinuation

Case Study #2

- On nab-paclitaxel with atezolizumab she had 2 episodes of pneumonitis that improved with supportive management but ultimately necessitated discontinuation
- Now **>6y** after her MBC diagnosis she remains NED on observation!!

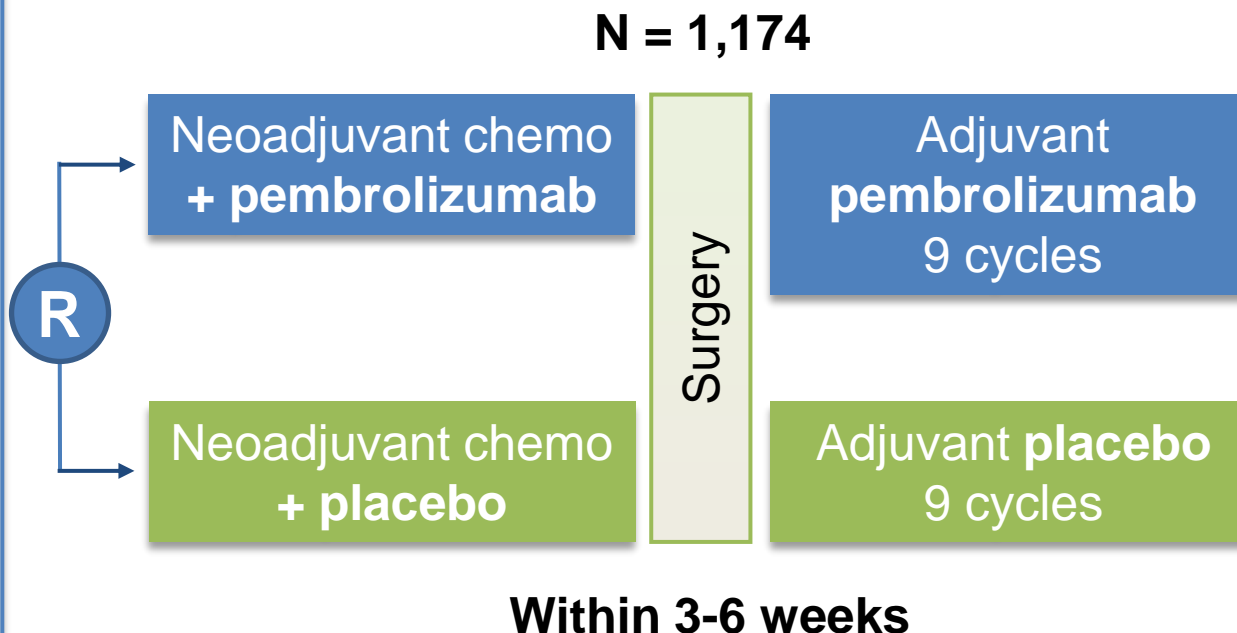
KEYNOTE-522

Eligibility

- Newly diagnosed TNBC (central confirmation)
- T1c N+ or T \geq 2 N0-2
- PD-L1+ or PD-L1-

Stratification

- T1/T2 vs T3/T4
- N0 vs N+
- Carboplatin Q1W vs Q3W



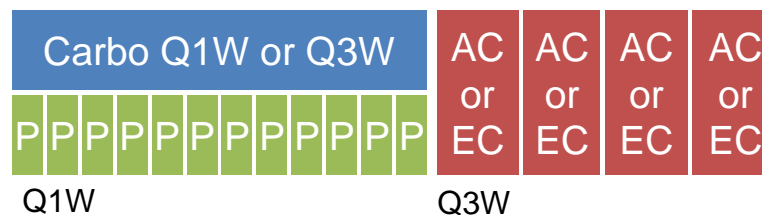
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

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

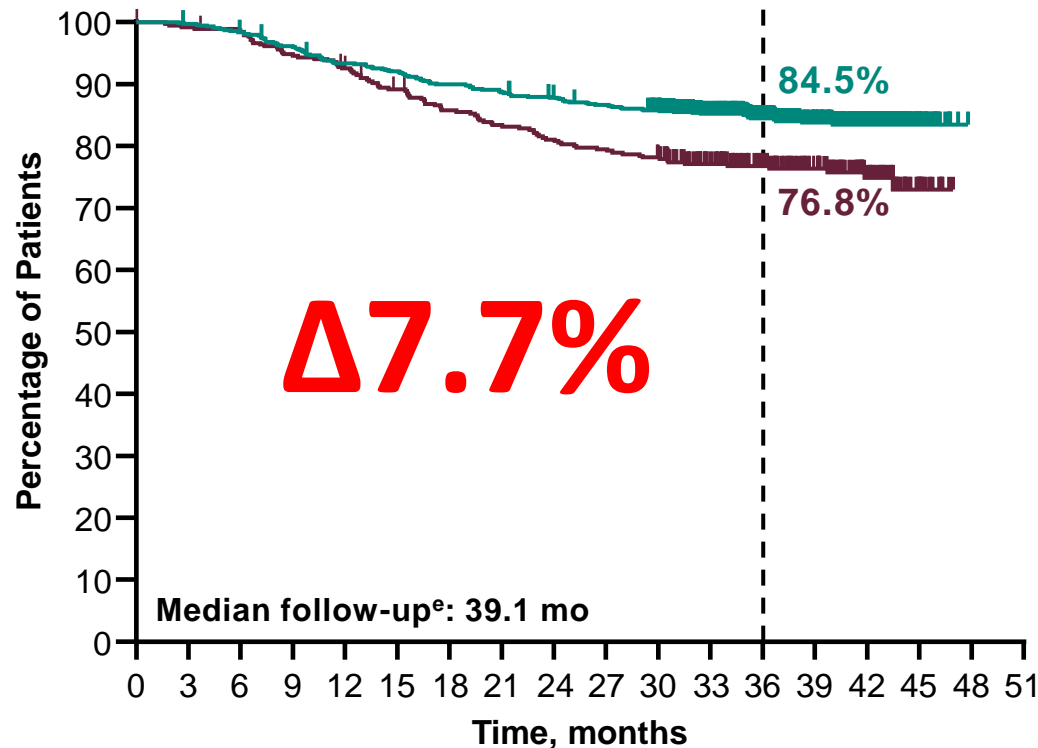
Study Treatment



Paclitaxel 80 mg/m² IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m² IV Q3W
(Epirubicin 90 mg/m² IV Q3W)
Cyclophosphamide 600 mg/m² IV Q3W
Pembrolizumab 200 mg IV Q3W

EFS at IA4 and IA6

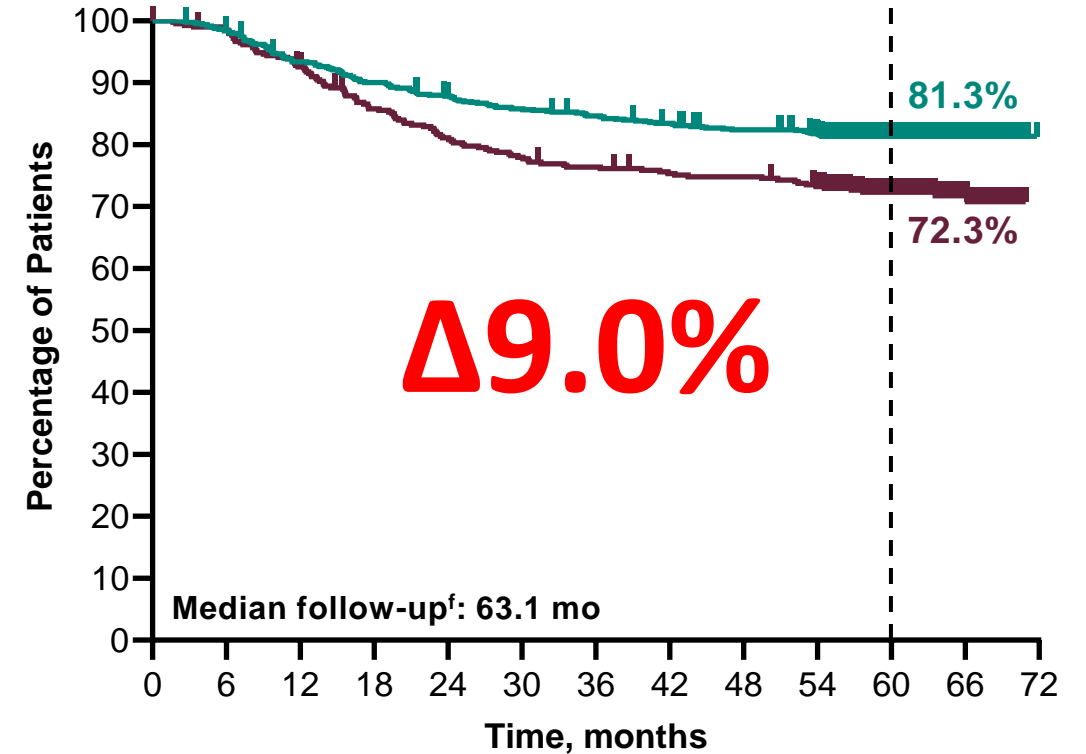
IA4 ^a	Events	HR (95% CI)	P value
Pembro + Chemo/Pembro	15.7%	0.63 ^c (0.48–0.82)	0.00031 ^d
Placebo + Chemo/Placebo	23.8%		



No. at risk

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

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

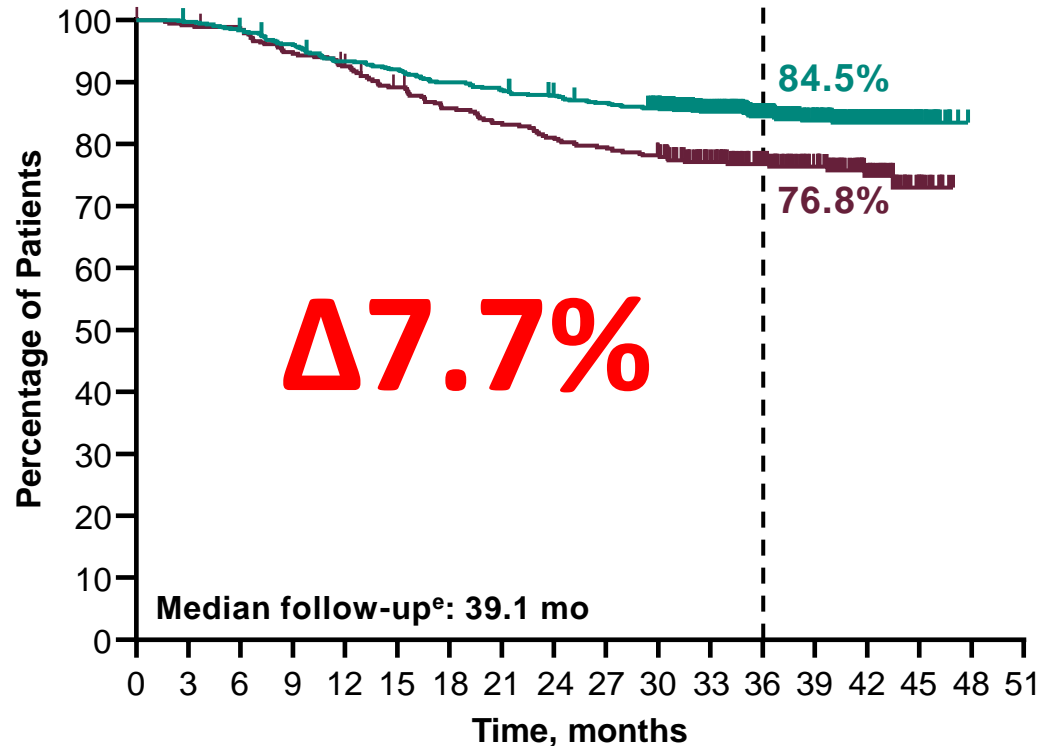


No. at risk

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

EFS at IA4 and IA6

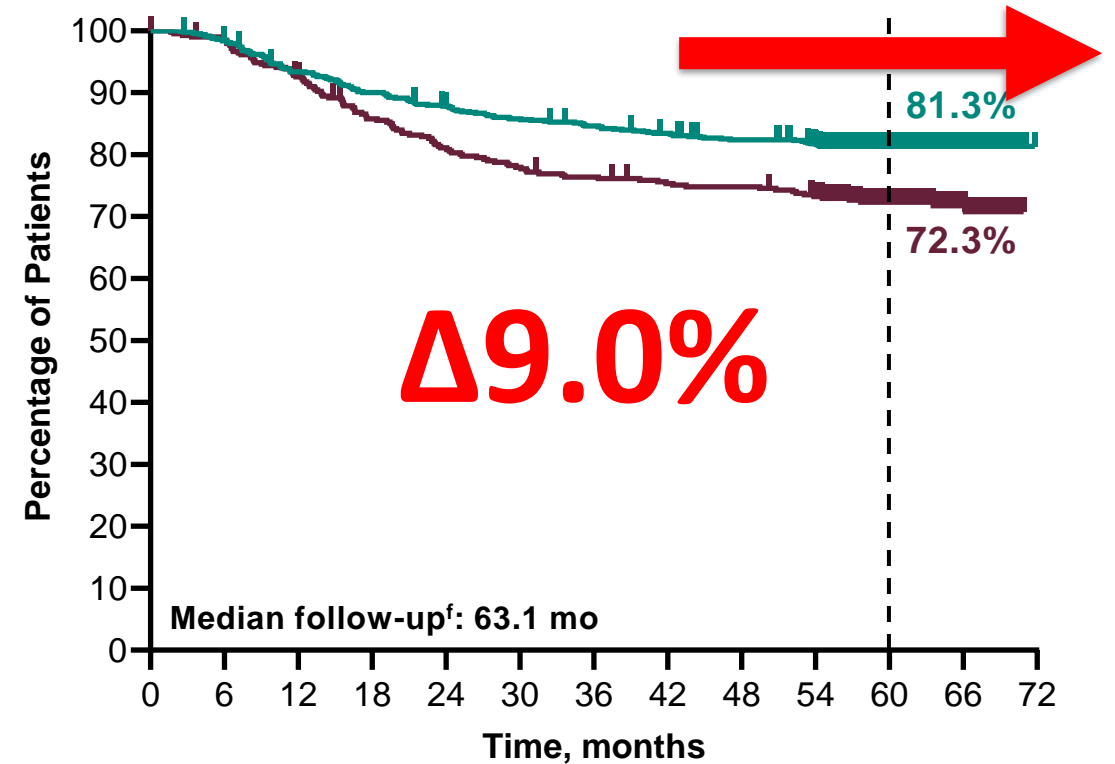
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ALEXANDRA/IMpassion030

Eligibility

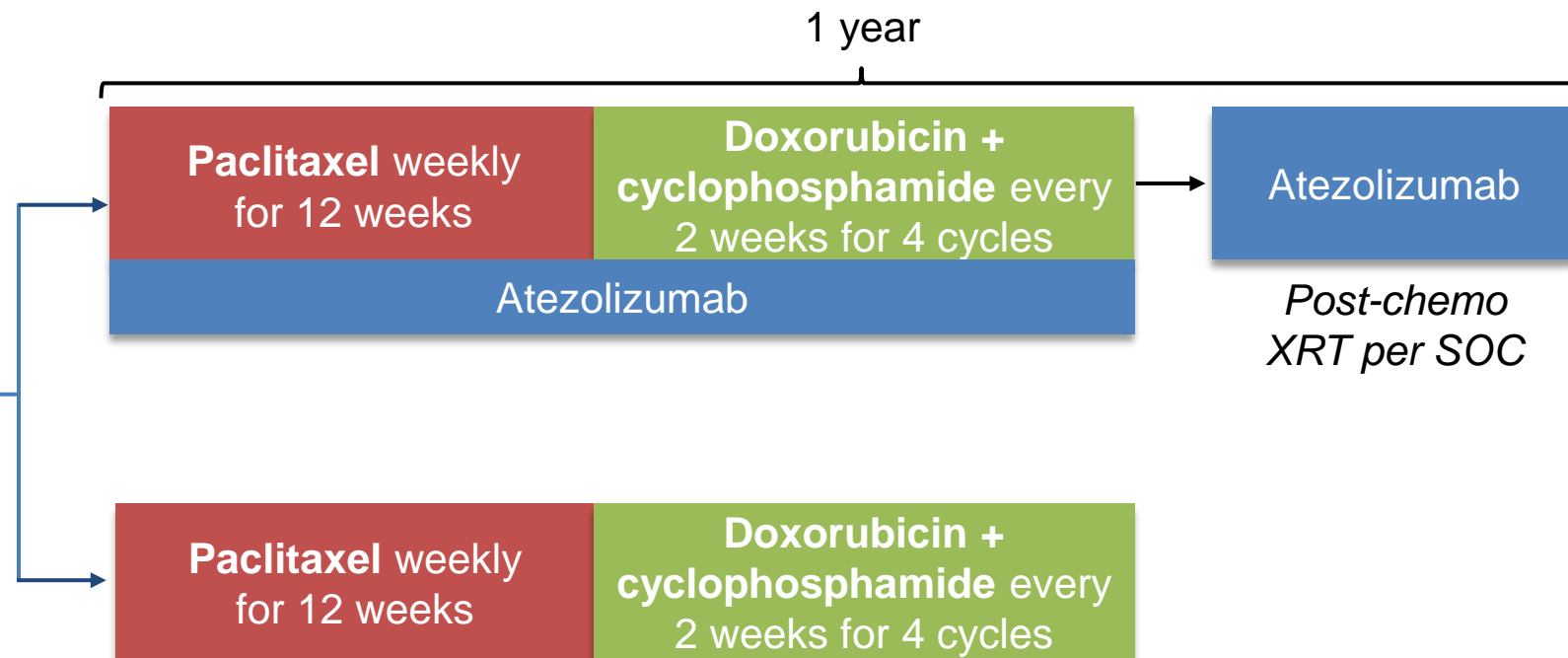
- Adequately excised primary invasive TNBC (stage II/III)
50:50 node negative/positive-enriched population

Stratification

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

N = 2,300

R
1:1

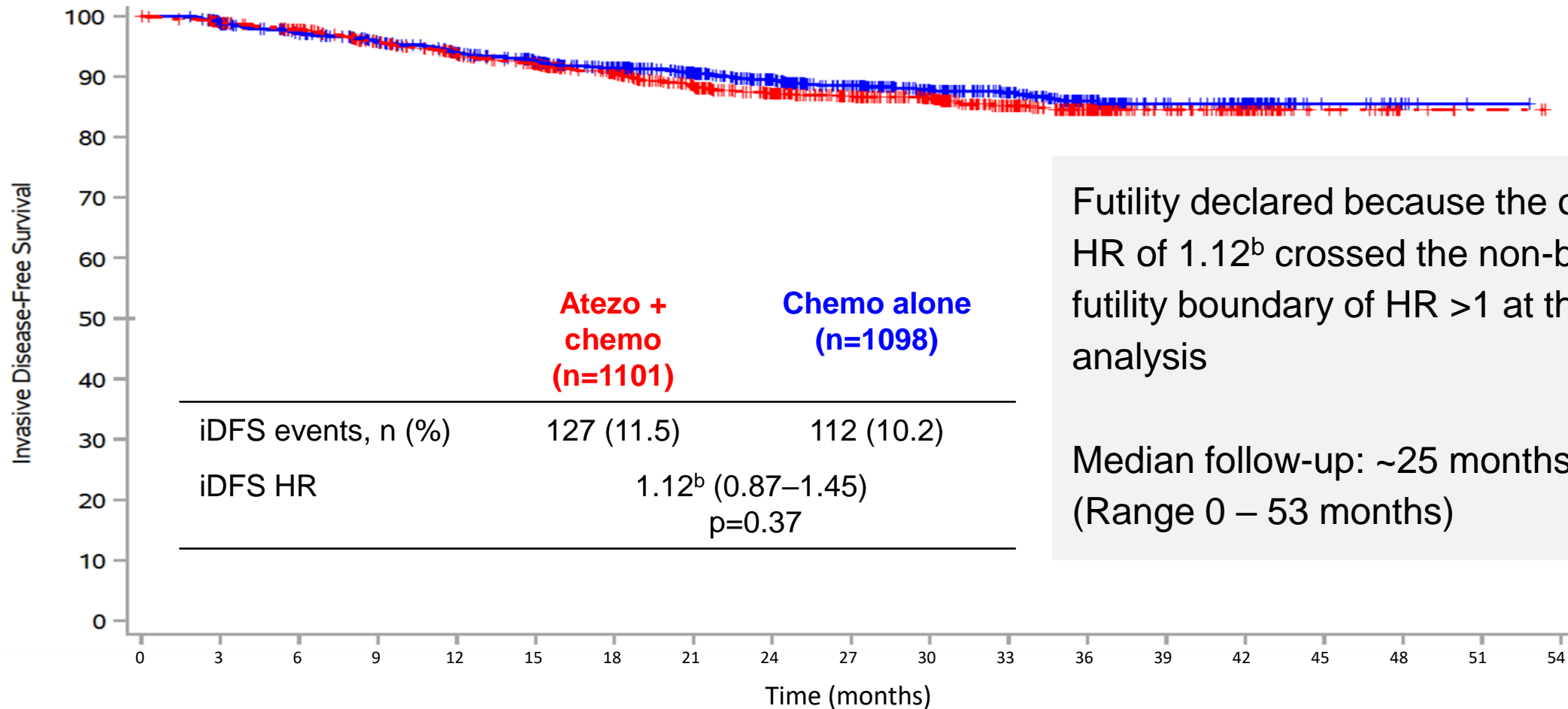


- **Primary endpoint:** iDFS in ITT
- **Secondary endpoints:** iDFS PD-L1 IC1/2/3, OS, RFI, distant RFI, safety, and health-related QoL

Co-PIs: Ignatiadis, McArthur, Saji

NCT03498716

IMpassion030: Primary Efficacy Endpoint: iDFS^a



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)

	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