Slides for RTP NCOA/SCOS Joint Annual Congress

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Discussion Question

Do you believe it is likely that both tucatinib and trastuzumab deruxtecan will be incorporated into treatment for patients with HER2-positive tumors and residual disease after neoadjuvant therapy in the near future? Which patients with HER2-positive localized breast cancer should be offered 1 year of extended adjuvant therapy with neratinib?

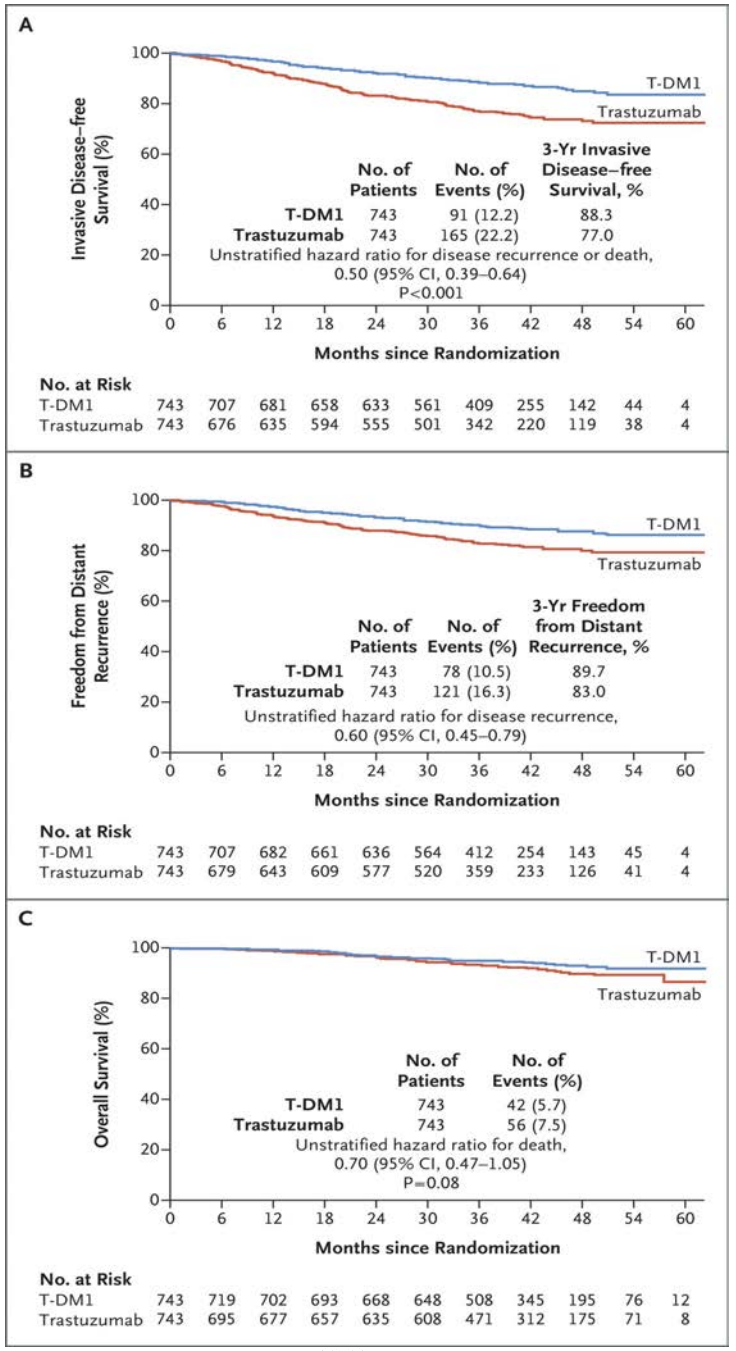
RTP
RESEARCH
TO PRACTICE

Chalk Talk – Harold J Burstein, MD, PhD

KATHERINE Study

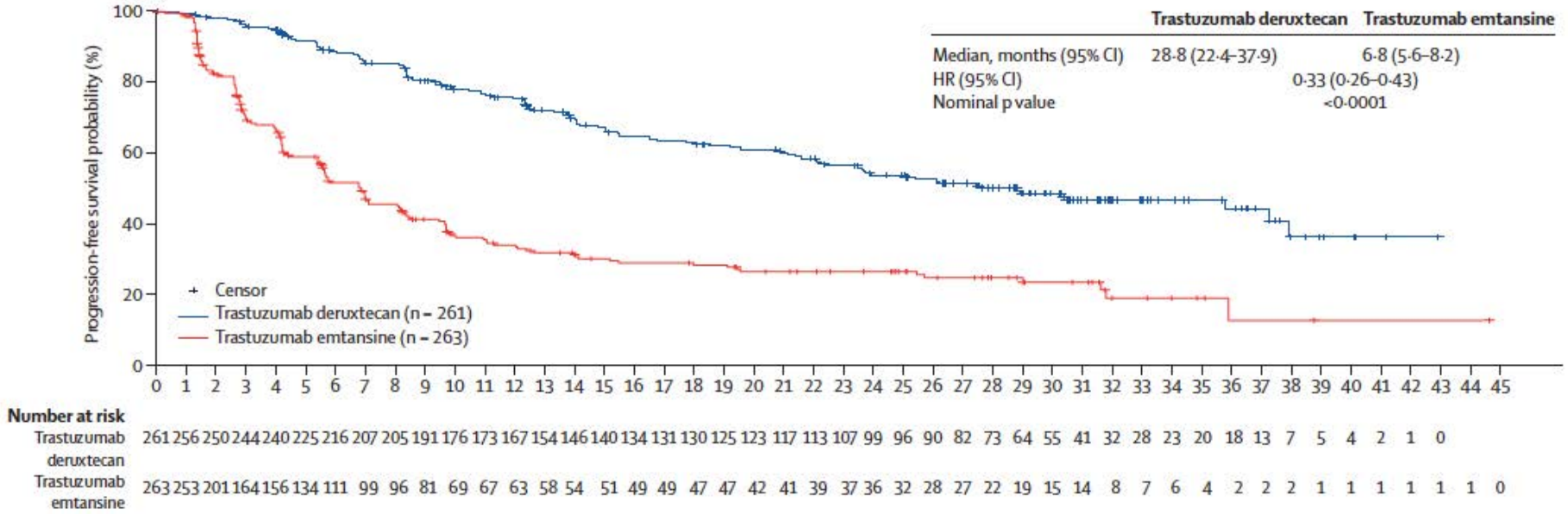
Trastuzumab vs TDM1 as adjuvant
Therapy after neoadjuvant chemotherapy/H[P]
In patients with residual invasive breast cancer

Will tucatinib and TDXd replace TDM1?

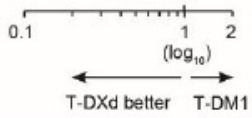


G von Minckwitz et al. N Engl J Med 2019;380:617-628.

DESTINY BREAST-03: TDM1 vs TDXd



Subgroup		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)



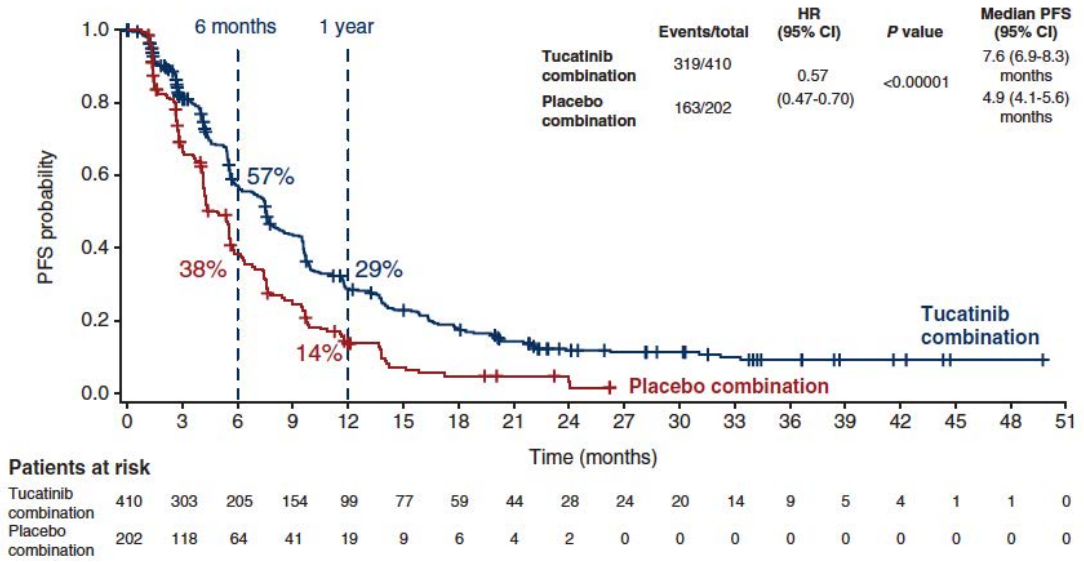
RR 79% vs 35%

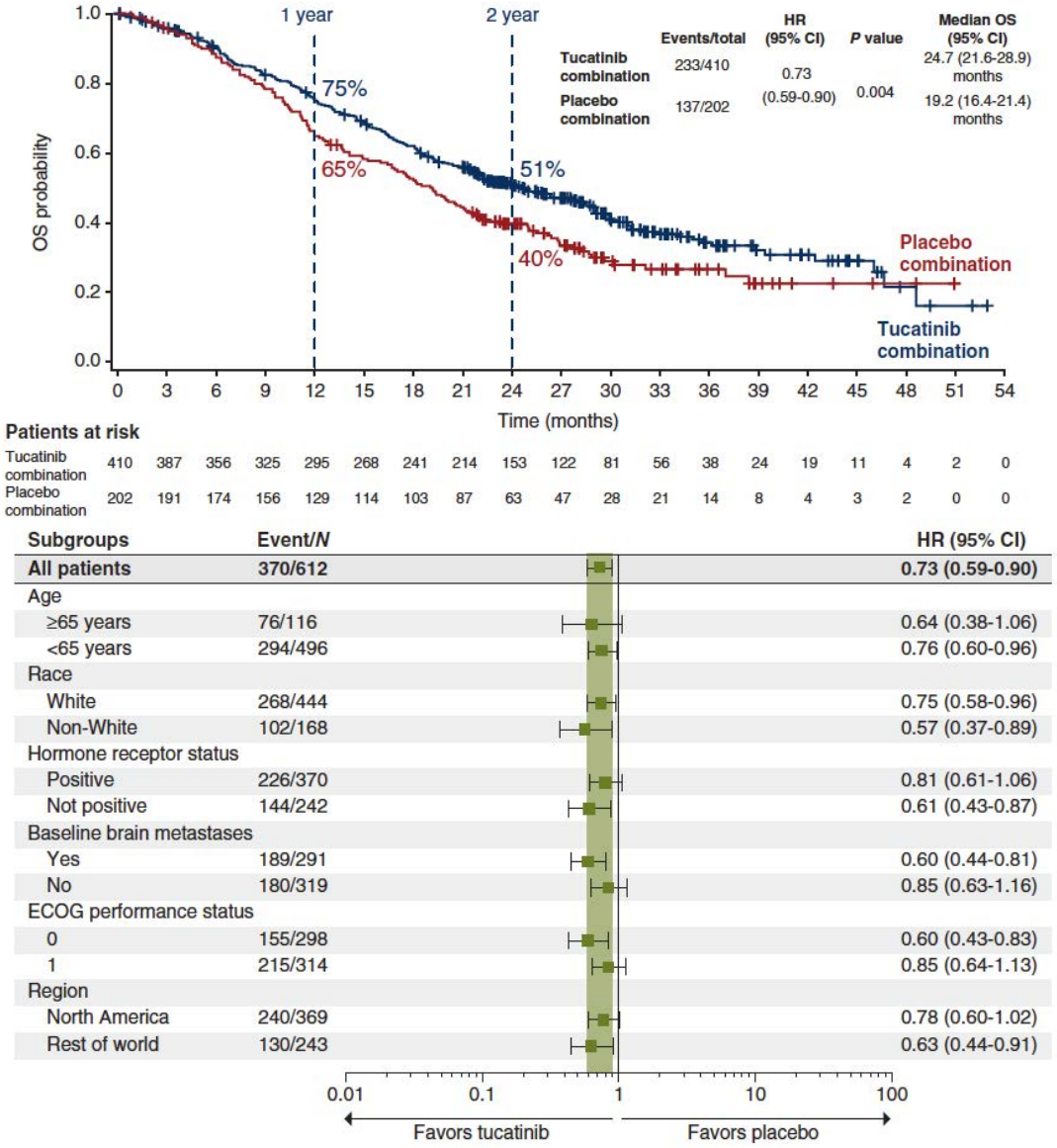
12-month PFS rate
75.2% vs 33.9%

24-month PFS rate
53.7% vs 26.4%

Hurvitz SA et al. Lancet 2023;401(10371):105-117.

HER2CLIMB: Trastuzumab/capecitabine +/- tucatinib





Curigliano G et al. Ann Oncol 2022 March;33(3):321-9.

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Prior Rx:

Trastuz	100%
TDM1	100%
Pertuz	78%
Taxane	96%

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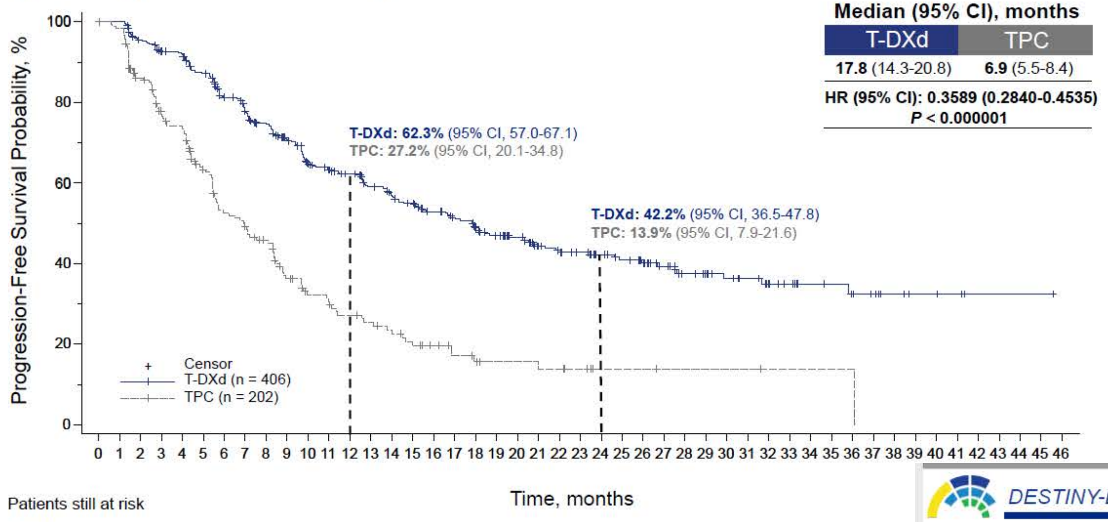
Primary Endpoint: PFS by BICR



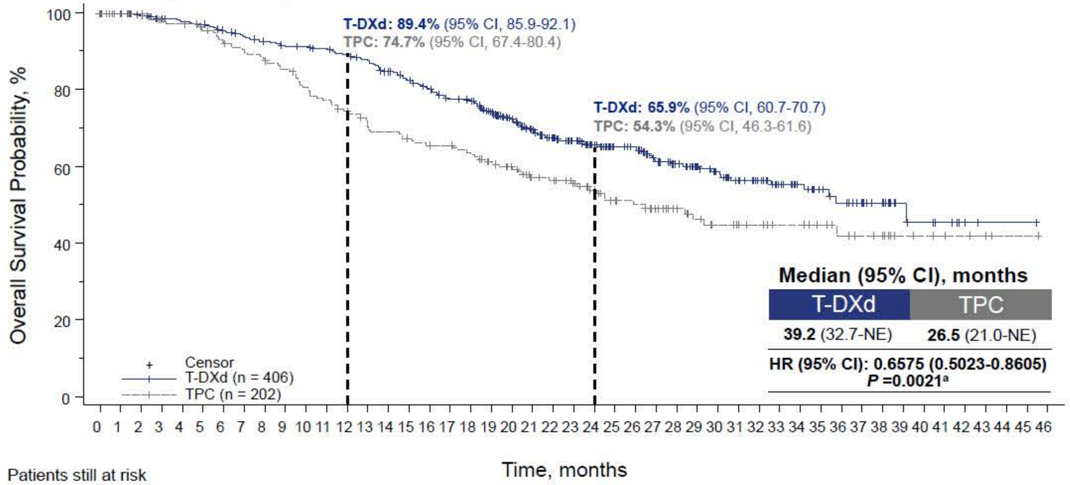
Median (95% CI), months	
T-DXd	TPC
17.8 (14.3-20.8)	**6.9** (5.5-8.4)
HR (95% CI): 0.3589 (0.2840-0.4535) *P* < 0.000001	

Patients still at risk

T-DXd (406)	406	400	374	359	355	330	296	278	260	239	213	203	194	179	170	161	149	141	132	119	109	88	83	76	65	60	55	47	38	35	31	27	23	19	15	14	12	10	6	4
TPC (202)	202	180	148	126	118	95	78	72	64	48	39	37	32	28	24	20	17	13	11	9	9	8	8	6	3	3	3	2	2	2	2	2	1	1	1	1	1	0		

DESTINY-Breast02
San Antonio Breast Cancer Symposium® – December 6-10, 2022

Key Secondary Endpoint: OS



Median (95% CI), months	
T-DXd	TPC
39.2 (32.7-NE)	**26.5** (21.0-NE)
HR (95% CI): 0.6575 (0.5023-0.8605) *P* =0.0021[a]	

Patients still at risk

T-DXd (406)	406	404	400	390	385	382	374	366	357	352	350	346	339	331	317	306	295	282	277	257	234	215	196	183	160	144	139	122	104	93	82	72	63	51	40	34	29	25	19	10	8	6	3	1	1	1	0
TPC (202)	202	192	187	182	178	173	167	161	157	151	142	136	130	124	118	114	111	110	106	95	89	79	76	72	61	53	50	46	38	33	29	28	25	22	22	18	15	13	12	7	6	5	4	3	1	1	0

In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Which is better?

		HER2CLIMB		DESTINY 03
Prior Rx	Trastuzumab	100		>99
	Pertuzumab	100		62
	TDM1	100		<1
Response Rates		41% vs 23%		79% vs 35%
PFS median		7.6 m vs 5.6m		28.8 m vs 6.8 m
OS median		24.7m v 19.2 m		NR vs NR

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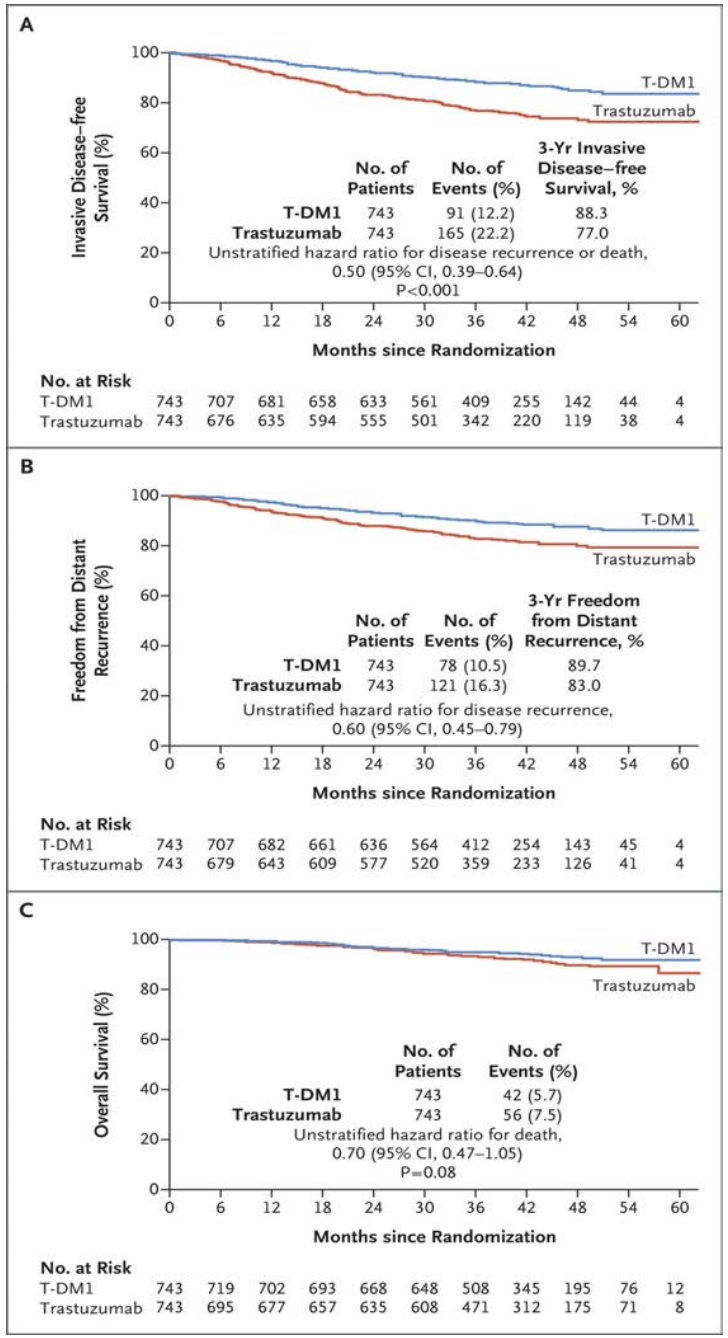
KATHERINE Study

Trastuzumab vs TDM1 as adjuvant
Therapy after neoadjuvant chemotherapy/H[P]
In patients with residual invasive breast cancer

Will tucatinib and TDXd replace TDM1?

YES, <u>but</u> both are more toxic/less well tolerated than TDM1 so there will be risk stratification



G von Minckwitz et al. N Engl J Med 2019;380:617-628.

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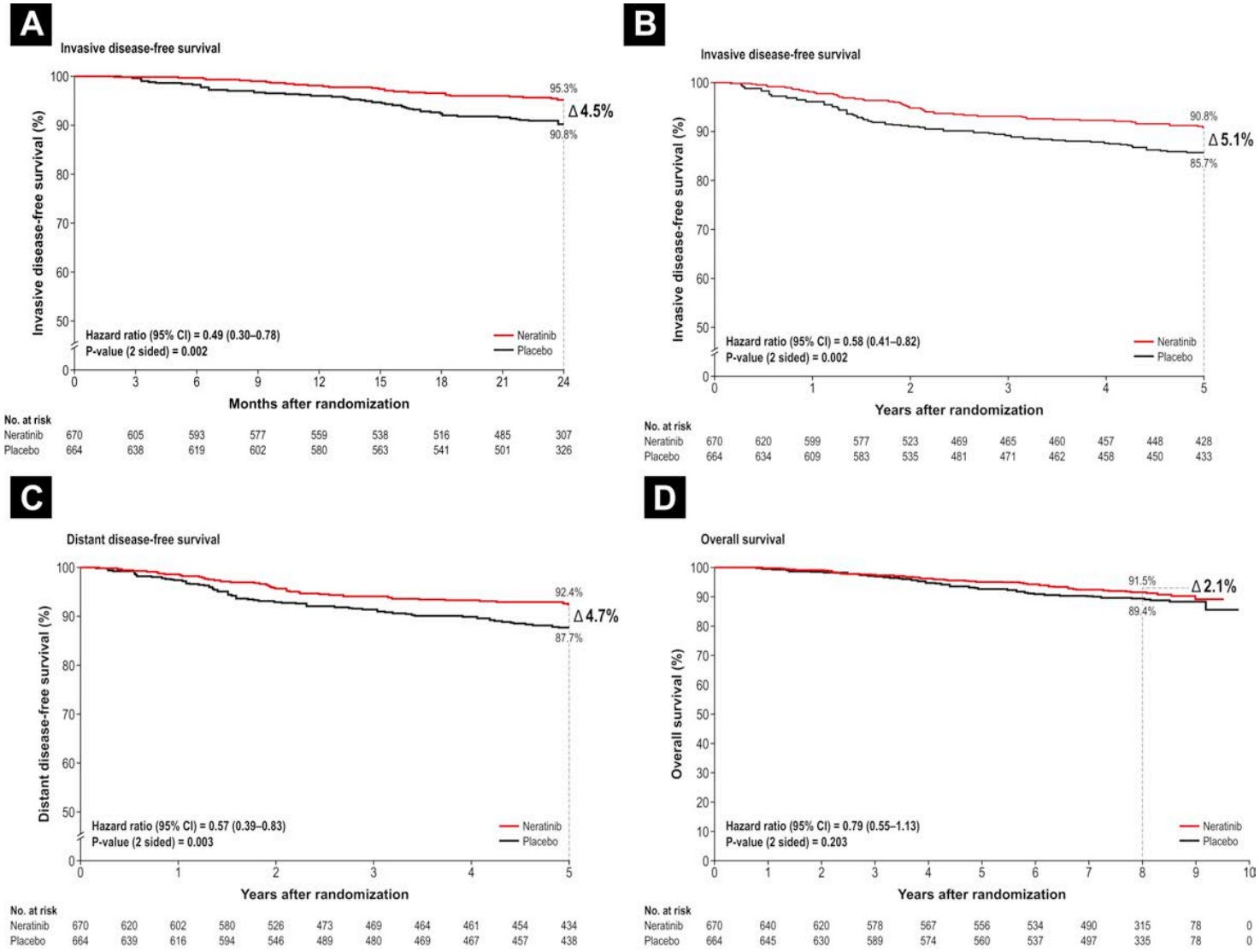
Which patients should be offered
One year of extended adjuvant neratinib?



Chan A, et al. Clinical Breast Cancer 2021;21:80-91.

What was treatment at that time?

- 2009 to 2011
- 2840 patients, 1631 with ER+ HER2+ tumors
- Neo/adjuvant trastuzumab: 100%
- Endocrine therapy: 100% (50% tamoxifen, 50% AI; 6% OFS)
- Neoadjuvant treatment ~ 25%
- Pertuzumab 0%
- TDM1 0%
- The challenge is that these treatments do not look like current management of ER+ HER2+ early stage breast cancer

Current standards for HER2+ early stage BC

- Stage 1. TH. Recurrence risk < 5%

- Stage 2/3. T[C]HP as neoadjuvant
  - Adaptive treatment based on residual risk
  - pCR → HP; residual → TDM1

- ET OFS, AI more common

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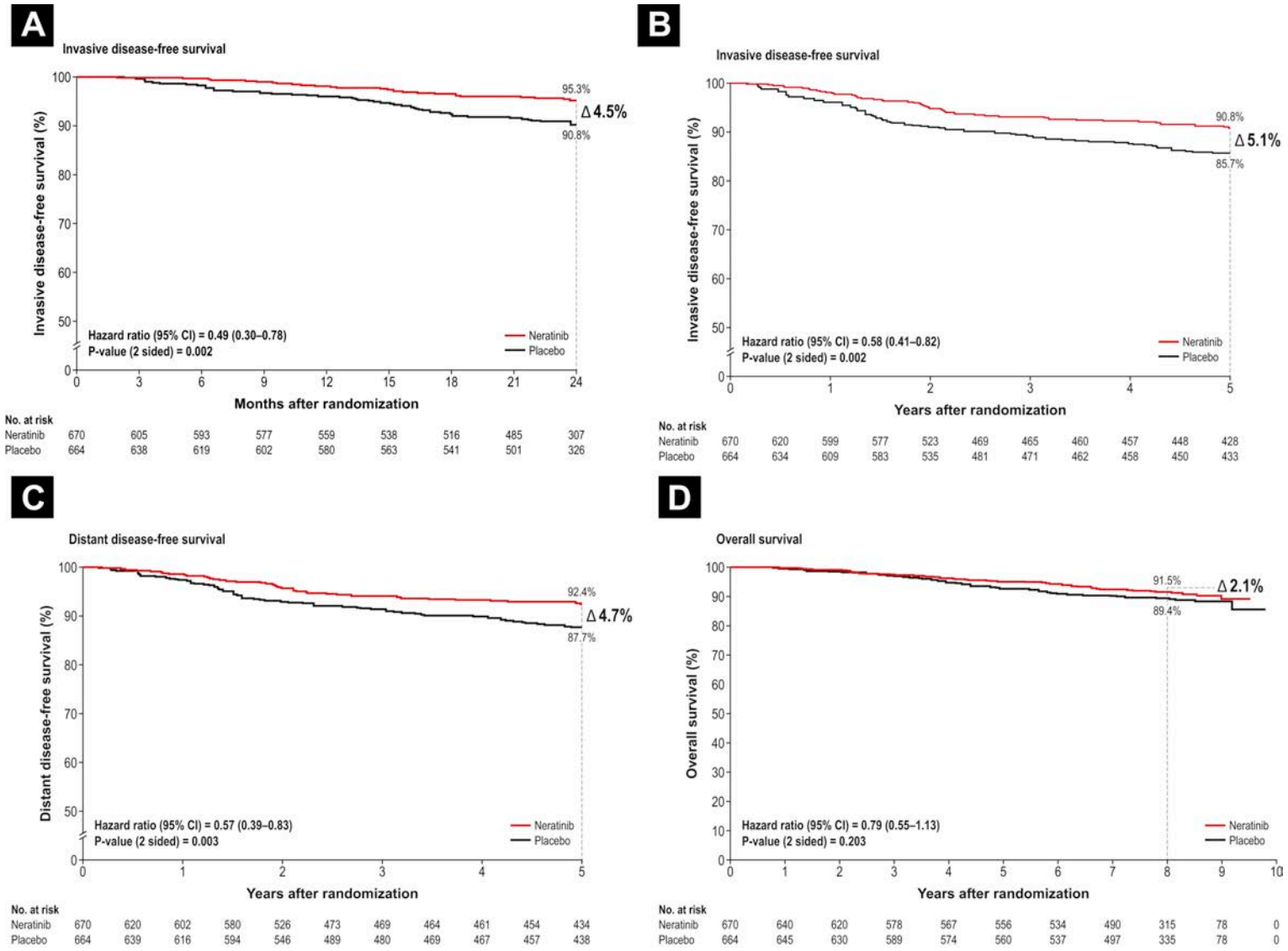
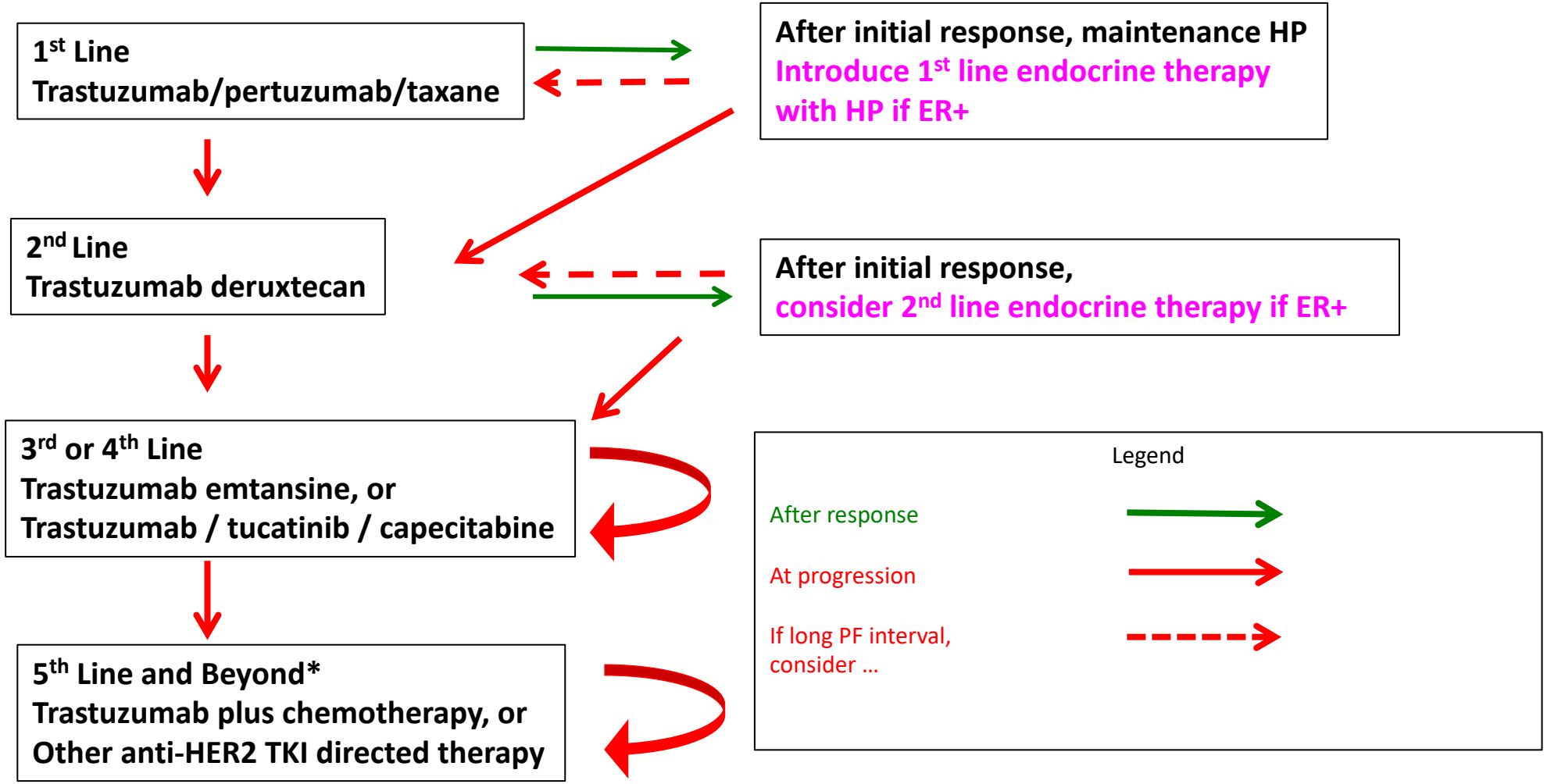
Which patients should be offered
One year of extended adjuvant neratinib?

Rather few as treatment standards have shifted.



Chan A, et al. Clinical Breast Cancer 2021;21:80-91.

Treatment algorithm for HER2+ MBC circa Q1 2023



**no data for lapatinib, neratinib, margetuximab post-ADCs, other TKIs*

Discussion Question

How do you generally sequence trastuzumab deruxtecan and tucatinib/trastuzumab/capecitabine for patients with HER2-positive mBC with and without brain metastases?

The Lin Rule

The drugs that work best outside the CNS are

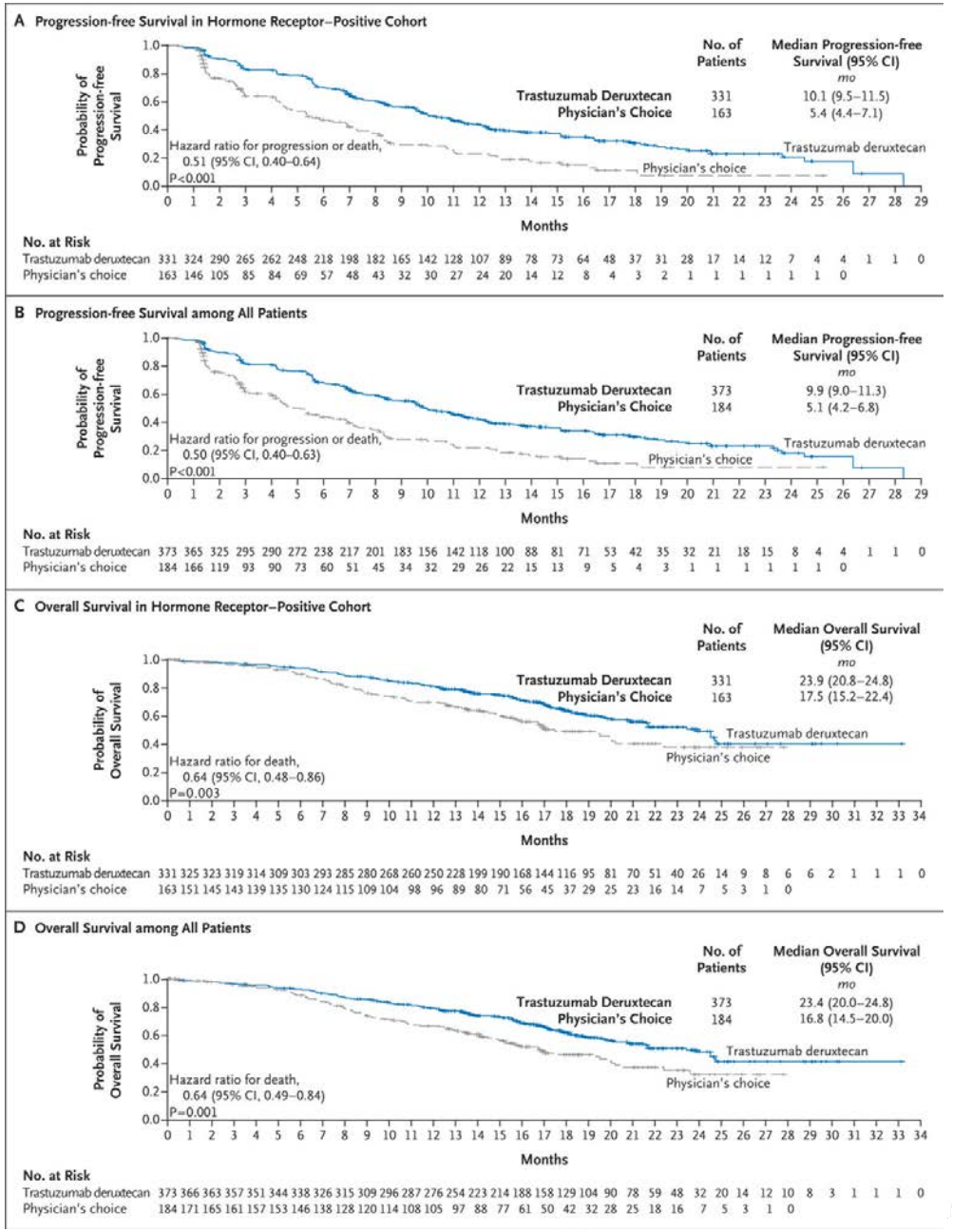
also the drugs that work best inside the CNS.

Discussion Question

How should trastuzumab deruxtecan be sequenced relative to other available therapies for patients with ER-positive or ER-negative, HER2-low mBC?

DESTINY Breast04: TDXd vs TPC in HER2-low breast cancer

How should TDXd be sequenced in
ER+ HER2 low
metastatic breast cancer?



TPC

Erib	51%
Cape	20%
Nab-pac	10%
Gem	10%
Pacl	8%

S Modi et al. N Engl J Med 2022;387:9-20.

Algorithm for ER+ HER2-low MBC

- Maximize use of endocrine + targeted approaches
- Maximize use of endocrine + targeted approaches
- Maximize use of endocrine+ targeted approaches
- Choose chemotherapy based on prior treatment, tolerability, side effects, and logistics
  - **Capecitabine**
  - **TDXd or paclitaxel**
  - **Eribulin, carboplatin, gemcitabine, anthracyclines, cyclophosphamide, vinorelbine, ixabepilone, and so forth**

Discussion Question

Which patients with localized triple-negative breast cancer (TNBC) should be offered treatment with neoadjuvant pembrolizumab in combination with chemotherapy? For which patients should pembrolizumab be continued in the adjuvant setting?

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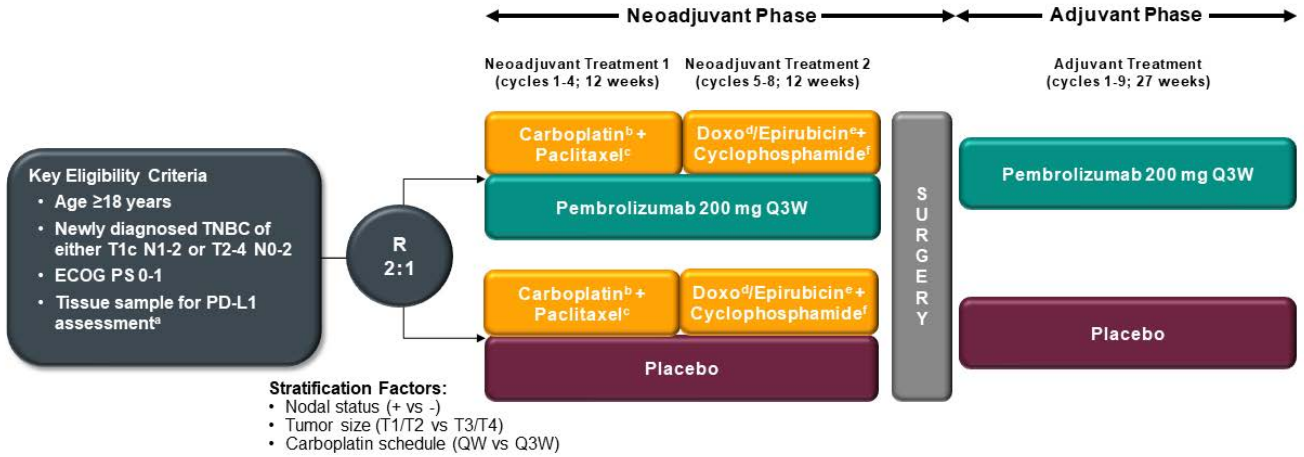
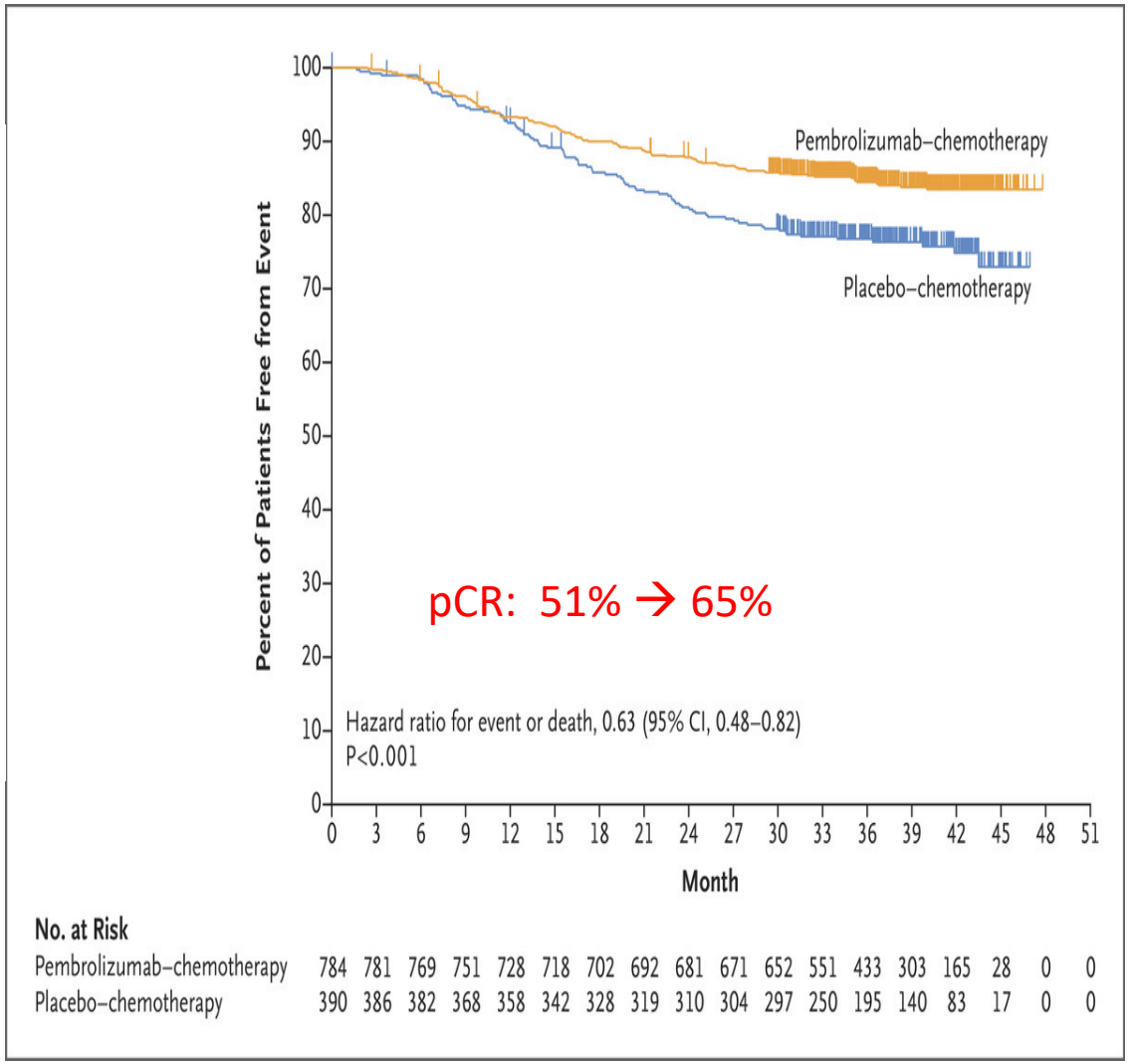
Which patients with localized TNBC should be offered Neoadjuvant pembrolizumab with chemotherapy?
Should pembro be continued in adjuvant setting?



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/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.



P Schmid et al. N Engl J Med 2022;386:556-567.

Chalk Talk – Harold J Burstein, MD, PhD

Which patients with localized TNBC should be offered
Neoadjuvant pembrolizumab with chemotherapy?
Should pembro be continued in adjuvant setting?

- This regimen is challenging for patients
- A lot more toxicity than with AC/T chemotherapy
- Recommended for fit patients with:
  - Stage 3
  - Stage 2, node-positive
  - Stage 2, larger primary tumors

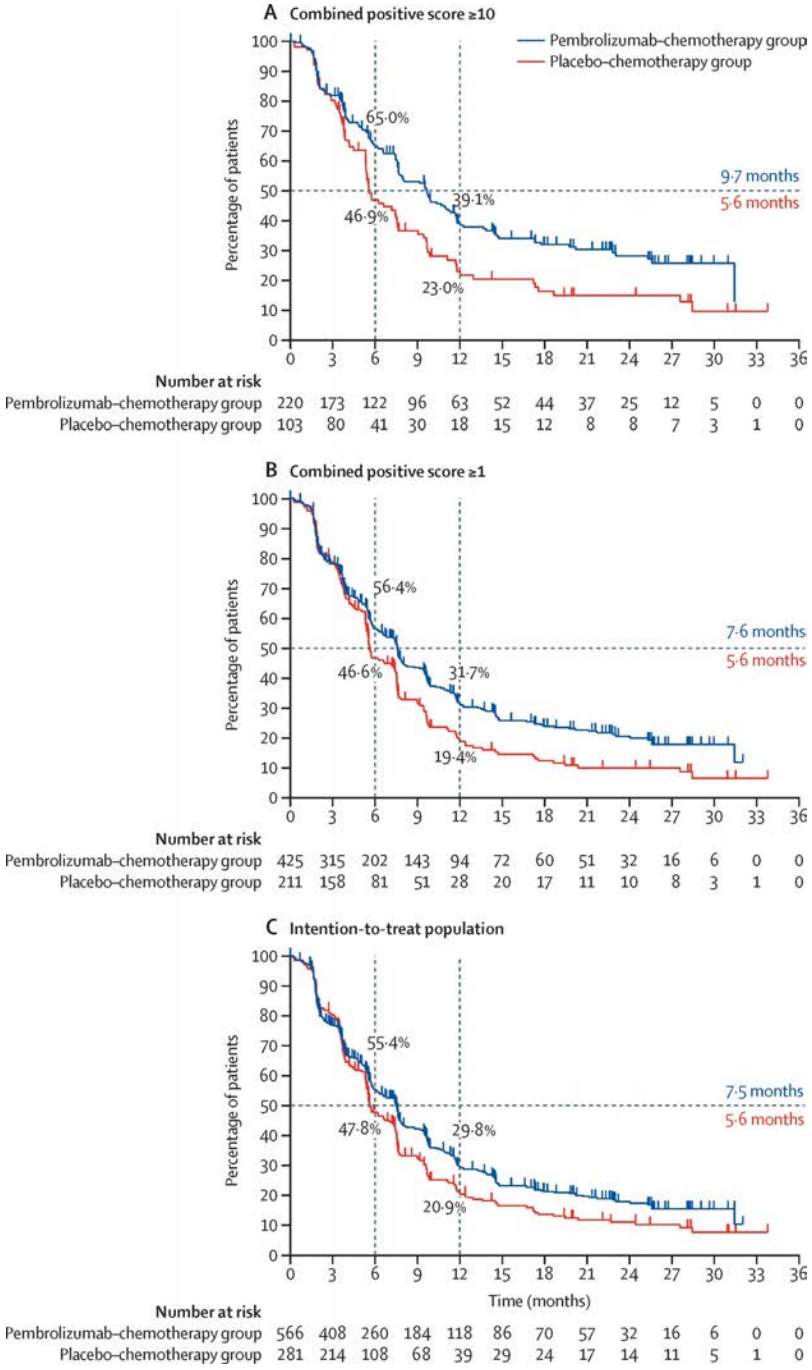
- No data on whether adjuvant phase is needed, or not

Discussion Question

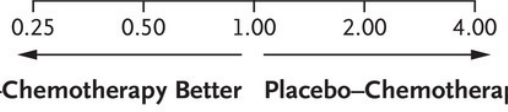
How do you generally approach therapeutic sequencing for patients with metastatic TNBC, and how do PD-L1 and BRCA status affect this decision?

RTP
RESEARCH
TO PRACTICE

KN355: Chemotherapy +/- pembrolizumab as 1st line treatment for triple-negative breast cancer.

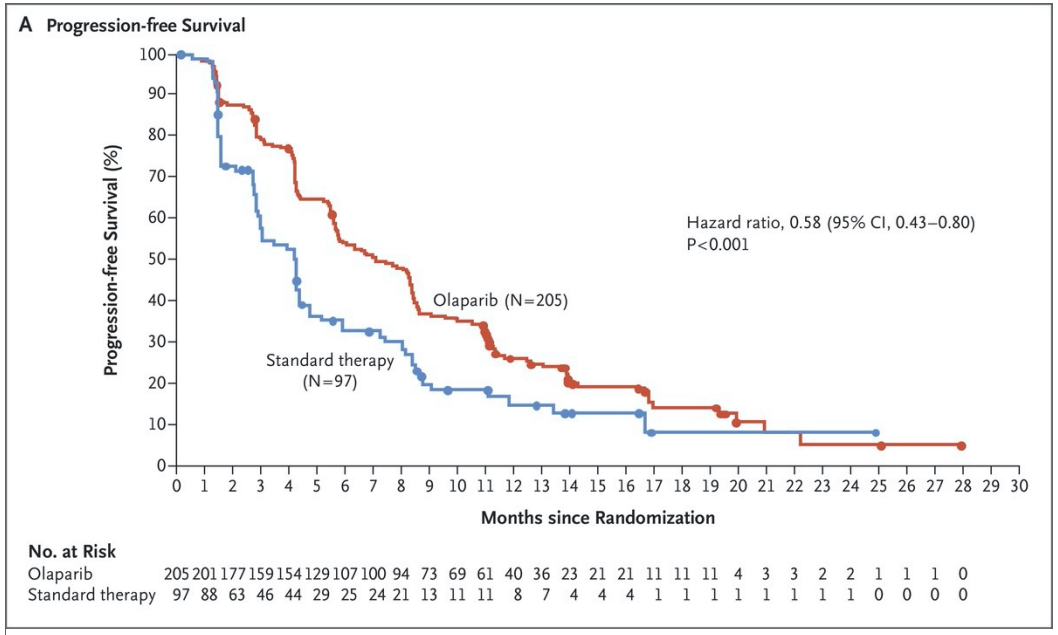


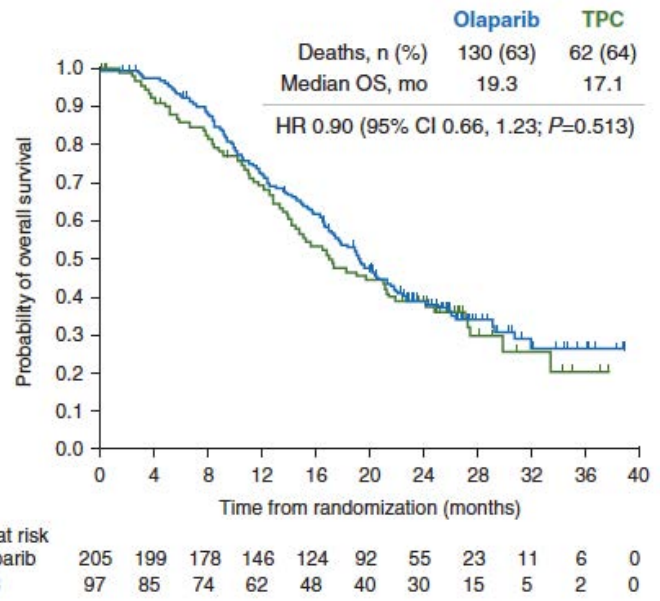
Subgroup	No. of Patients	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



J Cortes et al. N Engl J Med 2022;387:217-226.

OlympiAD Trial of Olaparib in BRCA-associated MBC

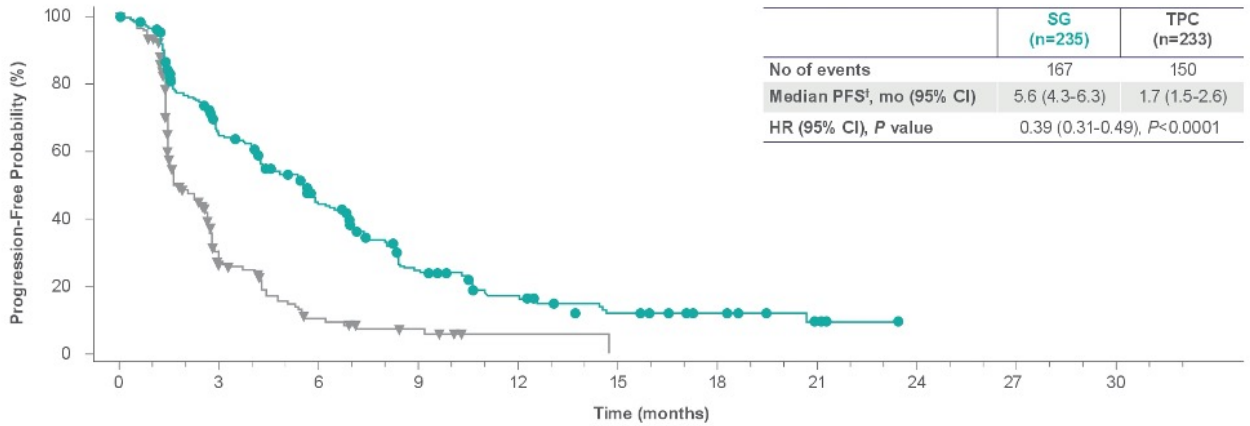




Robson M et al. N Engl J Med 2017;377:523-533.
Robson M et al. Ann Oncol 2019;30:558-566.

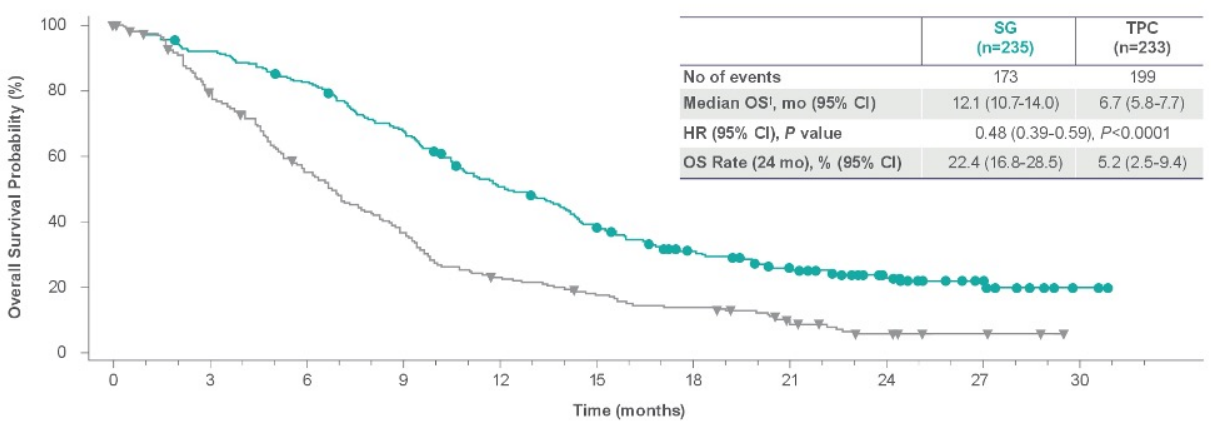
ASCENT trial: Sacituzumab govitecan vs TPC in mTNBC

Brain Metastases-Negative (BMNeg) Population



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[‡], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	

Median PFS in ITT: 4.8 mo vs 1.7 mo (HR 0.41, p<0.0001)



	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS[‡], mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

Median OS in ITT: 11.8 mo vs 6.9 mo (HR 0.51, p<0.0001)

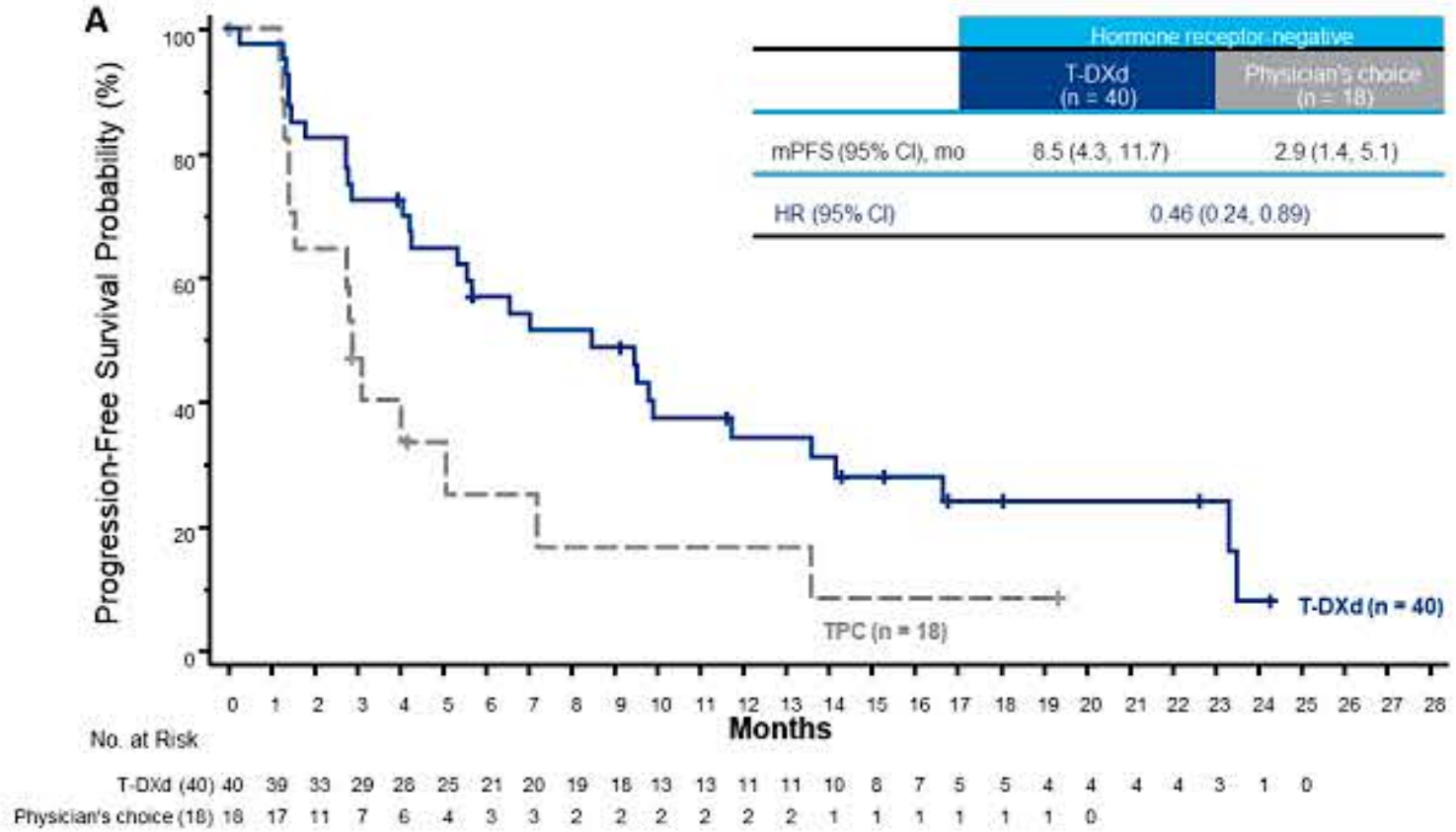
Responses in BMNeg

	SG (n=235)	TPC (n=233)
ORR, n (%)	82 (35)	11 (5)
OR (95% CI), *P* Value[†]	10.9 (5.6-21.1), *P*<0.0001	
Best overall response[‡], n (%)		
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR, n (%)	105 (45)	20 (9)
OR (95% CI), *P* Value[‡]	8.5 (5.1-14.4), *P*<0.0001	
Median DOR[§], mo (95% CI)	6.3 (5.5-7.9)	3.6 (2.8-NE)
Median TTR, mo (range)	1.5 (0.7-10.6)	1.45 (1.3-4.2)

Bardia A et al. ASCO 2022;Abstract 1071.

DB04
Supplement to
NEJM paper

Figure S3. Kaplan-Meier Analysis of Progression-Free Survival…in the Hormone Receptor-Negative Cohort. Panel A shows the Kaplan-Meier analysis of progression-free survival, as assessed by blinded independent central review, in the hormone receptor-negative cohort as derived by electronic data capture.



Key Point: exciting new options for mTNBC

- Precise sequencing not well established
- Most patients in the US will have already had prior chemotherapy, often extensive prior chemotherapy, in neo/adjuvant setting
- All patients should have tumor tested for PD-L1
- All patients should have genetic testing for BRCA1/2 mutations
- Common algorithm
  - 1st line. PD-L1 pos→ pembro + chemo; PD-L1 neg → chemo
  - 2nd line. ADC-based approaches
  - 3rd line. ? ongoing ADC approaches vs other chemotherapy options
  - 4th line. Additional chemotherapy