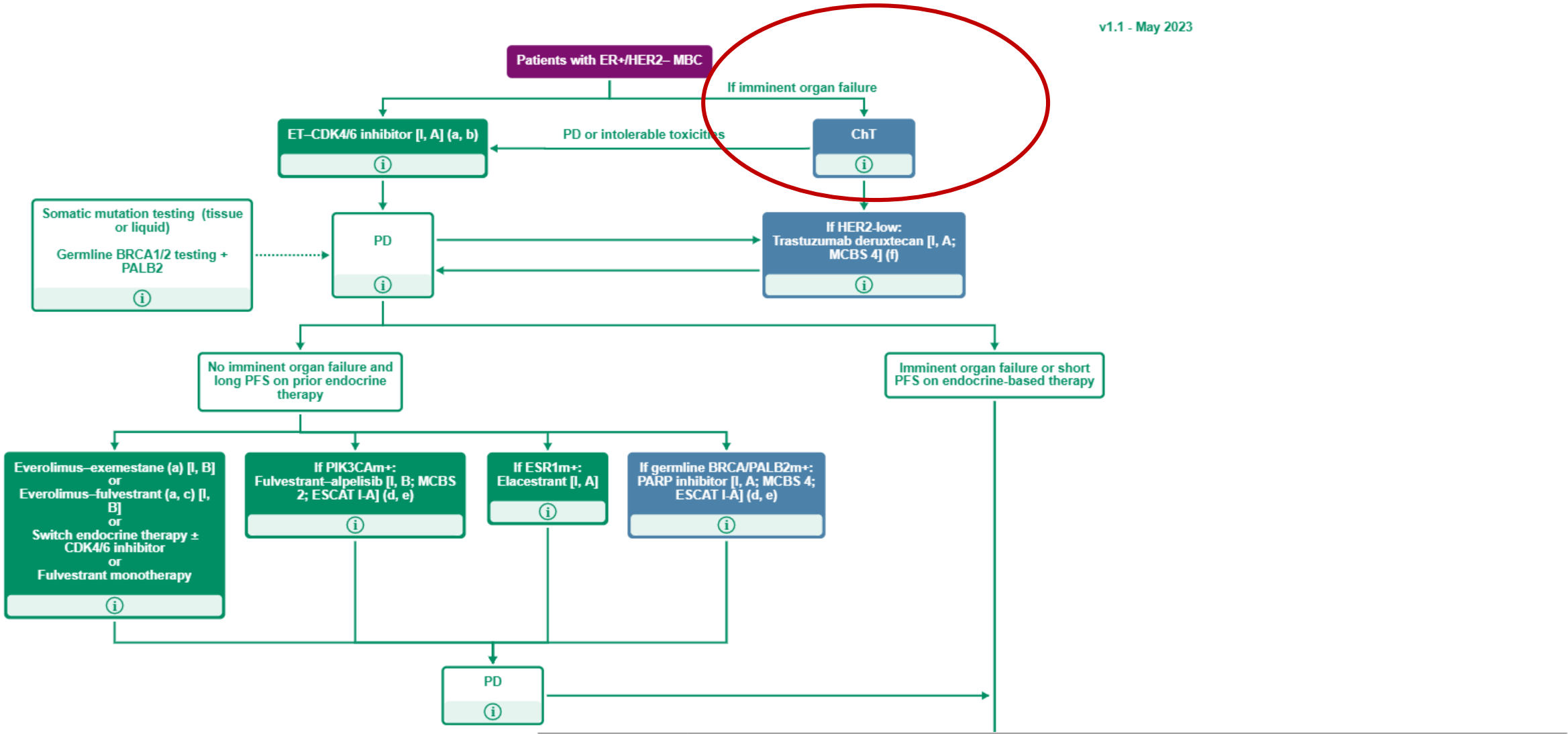
La chemioterapia nel carcinoma mammario metastatico: quale ruolo ha oggi?

Antonella Ferro

Trento

....THE CHEMO IN THE TARGET THERAPIES AND ADCs ERA

HR+/HER2 NEGATIVE MBC



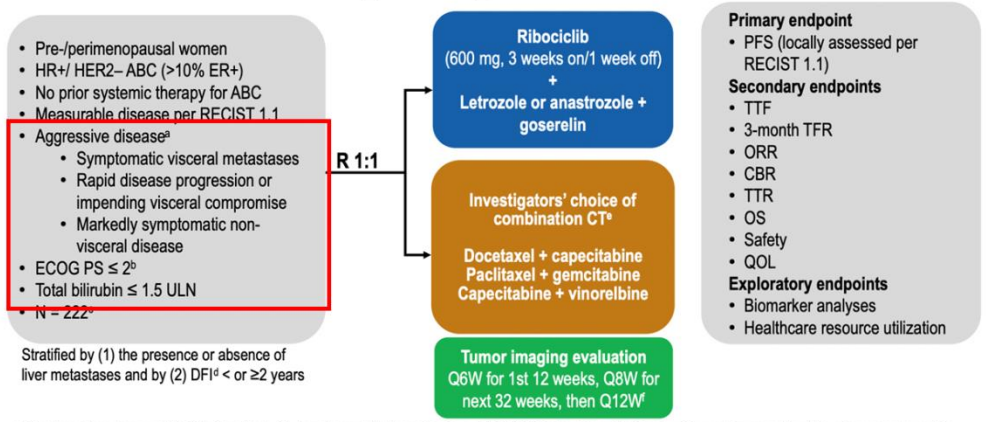
According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1623-1649) for advanced breast cancer visceral crisis is defined as: “severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.”

Esmo living guidelines 2023

Chemo or ET +CDK4/6i as first line in very aggressive disease?

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

RIGHT Choice study design



ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

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

Baseline characteristics were well balanced

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

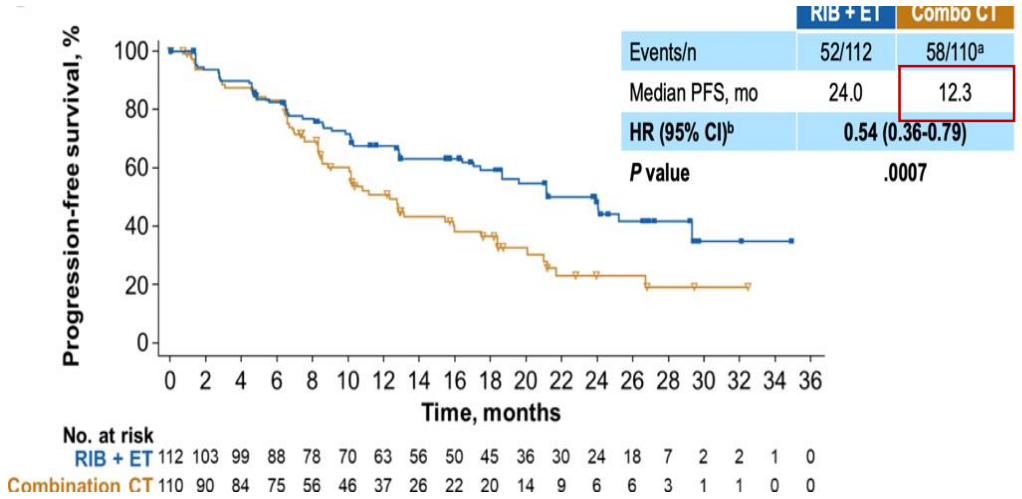
Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

Combo CT, combination chemotherapy; ER+, estrogen receptor positive; ET, endocrine therapy; RIB, ribociclib.
[a] One patient (0.9%) in the RIB arm was African American; [b] The same patient may have multiple visceral metastatic sites. [c] Based on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

RIGHT Choice trial: results

PFS



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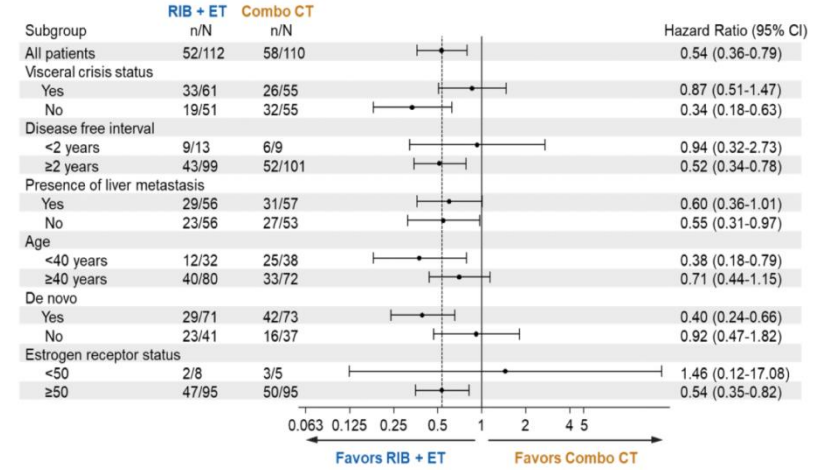
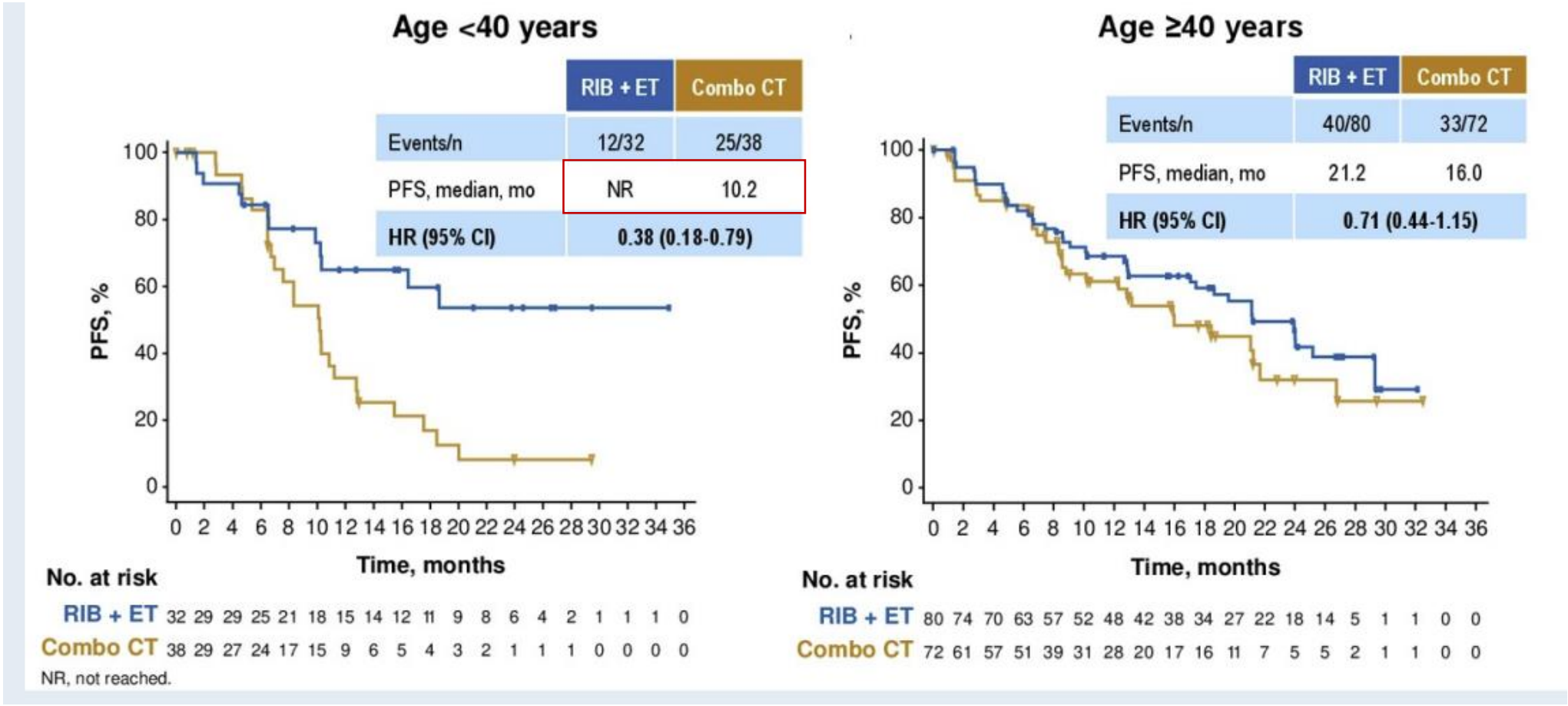
PFS benefit with RIB + ET over combination CT was consistent across most subgroups of patients with aggressive HR+/HER2− ABC



ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; RIB, ribociclib.

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

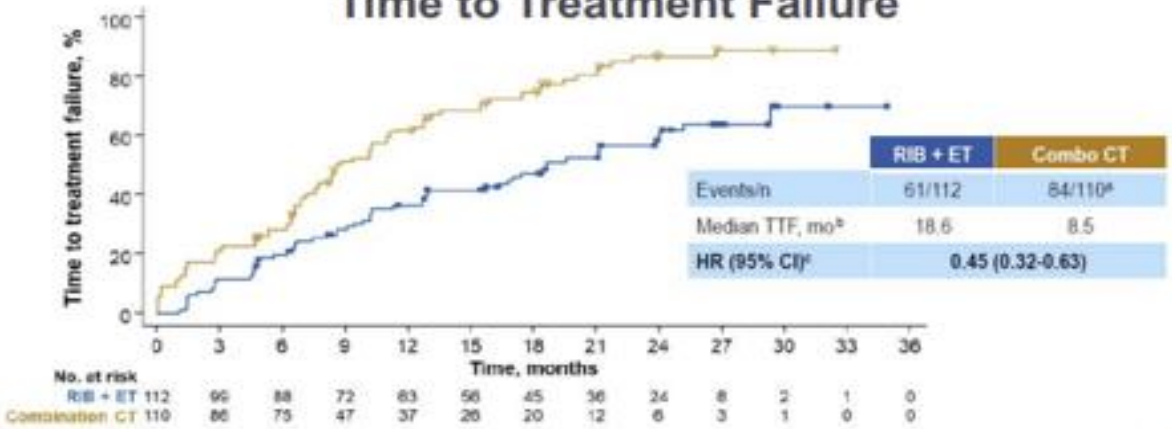
RIGHT Choice: Progression-Free Survival (PFS) by Age



El Saghir NS et al. ASCO 2023;Abstract 1063.

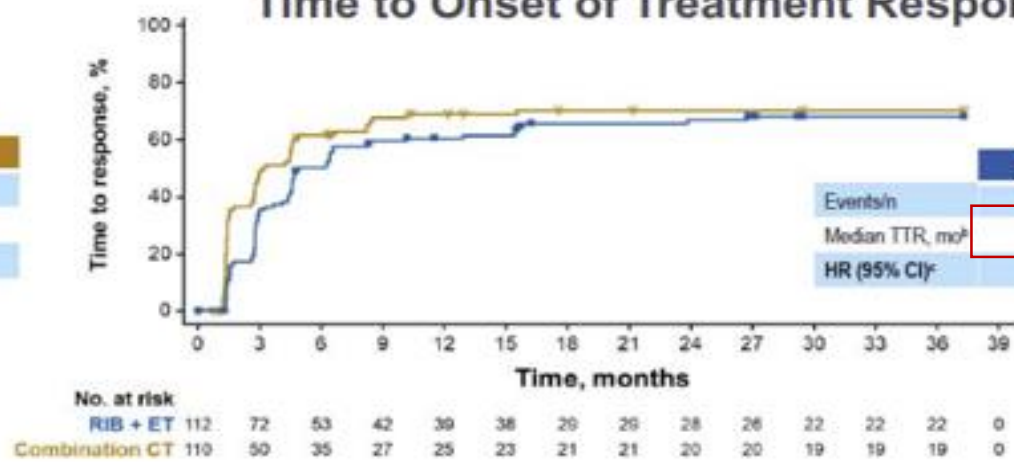
RIGHT Choice
TTF and Response

Time to Treatment Failure



	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	0.45 (0.32-0.63)	

Time to Onset of Treatment Response



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	0.78 (0.56-1.09)	

Dose Reductions

Parameter, n (%)	Ribociclib + ET (n = 112)	Combination CT (n = 100)
0	81 (72.3)	54 (54.0)
1	27 (24.1)	12 (12.0)
2	4 (3.6)	14 (14.0)
≥ 3	0	20 (20.0)

	Ribociclib + ET (n = 112)	Combination CT (n = 100)
ORR, %	65.2	60.0
CBR, %	80.4	72.7

Lu Y-S, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS1-10.

What is best therapy post-CDK4/6 progression?

A grey zone between 1st line ET and 1st line chemotherapy with PFS ranged from 3 to 7months

1) Can we Continue CDK4/6i therapy after progression to CDK4/6?
2) Have a role mono-endocrine therapies?
    - Fulvestrant and Novel Oral SERDs
3) Have a role inhibitors of PI3K/AKT/mTOR signaling pathway?
4) Chemotherapy

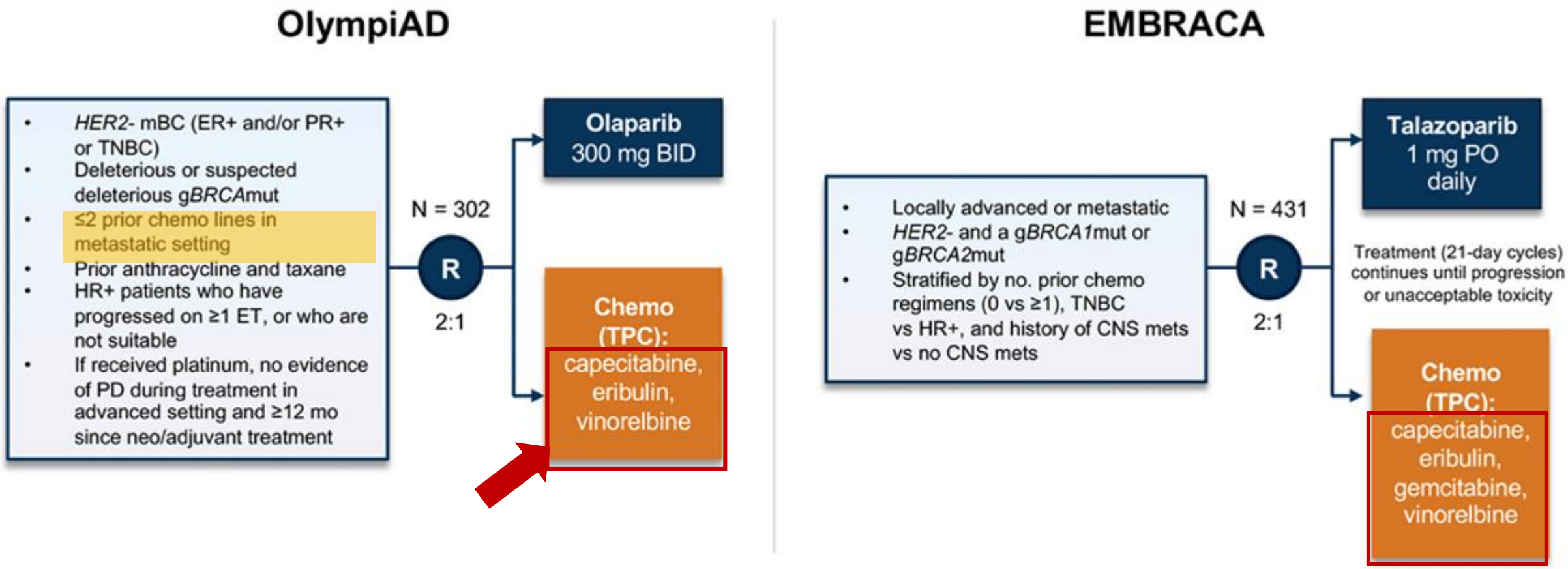
Endocrine refractory HR+HER2negative disease

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)

NCCN 2024

Phase 3 PARPi trials in MBC



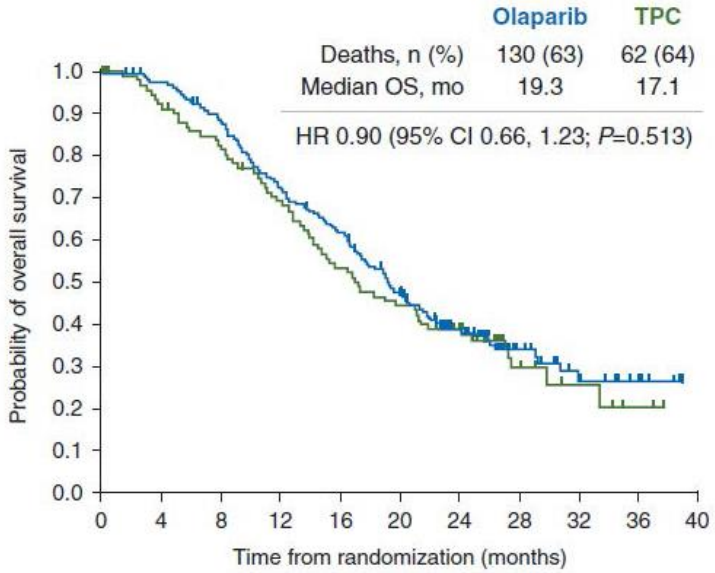
- OlympiAD and EMBRACA: phase 3 trials, PARPi vs standard nonplatinum chemo (first to third line)

1. Litton JK et al. *N Engl J Med.* 2018;379:753-763. 2. Robson M et al. *N Engl J Med.* 2017;377:523-533.

Phase III Trials: Final Overall Survival Data

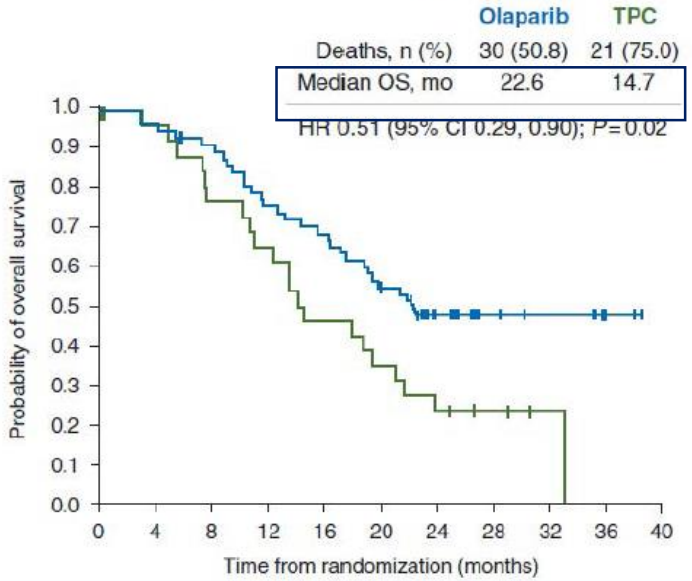
OlympiAD

A



B

No prior chemotherapy for mBC (1L)

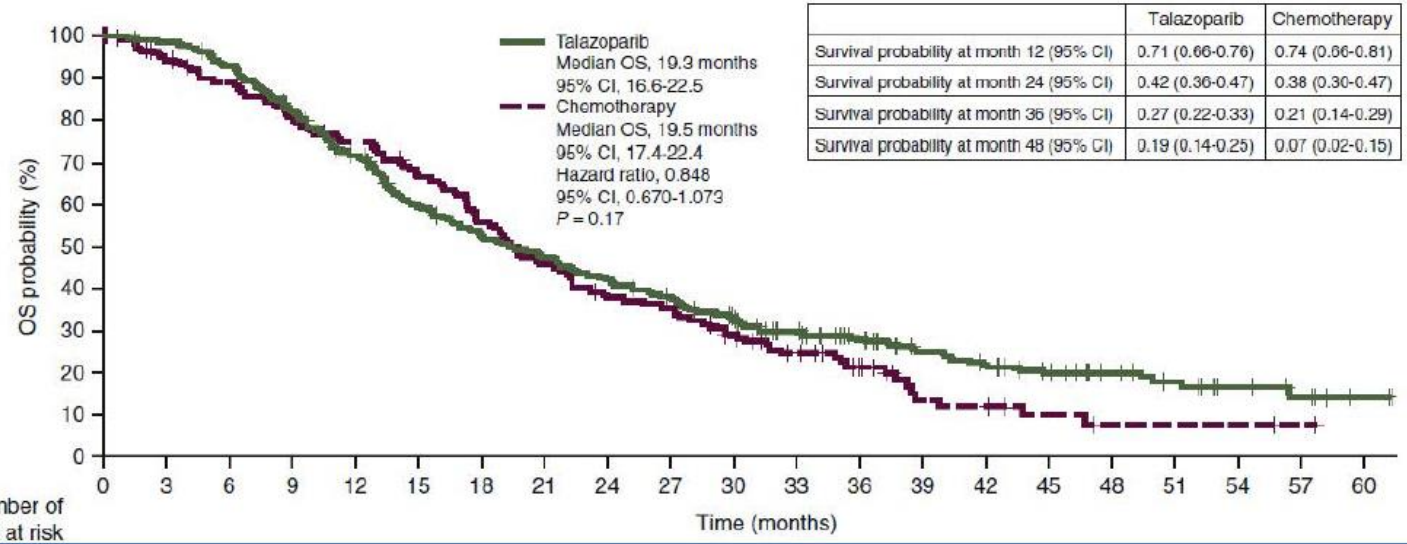


- No crossover
- No approved PARPi available at progression.

Robson, Annals of Oncology 30: 558–566, 2019

EMBRACA

A



	Talazoparib	Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

- 25% of chemo received olaparib in subsequent lines v. 2.8% of talazoparib.
- CDK4/6i: 13.6% talazoparib v. 10.4% chemotherapy

Litton, Annals of Oncology, 31: 1526-1535, 2020

Endocrine resistant setting

- Patients with tumours that are endocrine resistant should be considered for ChT [V, B]
- Sequential single-agent ChT is generally preferred over combination strategies.
- In patients where a rapid response is needed due to imminent organ failure, combination ChT is preferred [II, A]
- The optimal sequence of regimens preferably includes low toxic agents in early lines of treatment

Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a,s,t,u,v]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**

• Anthracyclines
  ▸ Doxorubicin
  ▸ Liposomal doxorubicin
• Taxanes
  ▸ Paclitaxel
• Anti-metabolites
  ▸ Capecitabine
  ▸ Gemcitabine
• Microtubule inhibitors
  ▸ Vinorelbine
  ▸ Eribulin
	• Cyclophosphamide
	• Docetaxel
	• Albumin-bound paclitaxel
	• Epirubicin
	• Ixabepilone
		• AC (doxorubicin/cyclophosphamide)
		• EC (epirubicin/cyclophosphamide)
		• CMF (cyclophosphamide/ methotrexate/fluorouracil)
		• Docetaxel/capecitabine
		• GT (gemcitabine/paclitaxel)
		• Gemcitabine/carboplatin
		• Carboplatin + paclitaxel or albumin-bound paclitaxel

What does the real world tell us?

Real-world treatment (Tx) patterns in patients (pts) with HR+/HER2 neg MBC treated with chemotherapy (CT) in the United States (US)

- Capecitabine and paclitaxel were most commonly used in earlier lines of CT included.

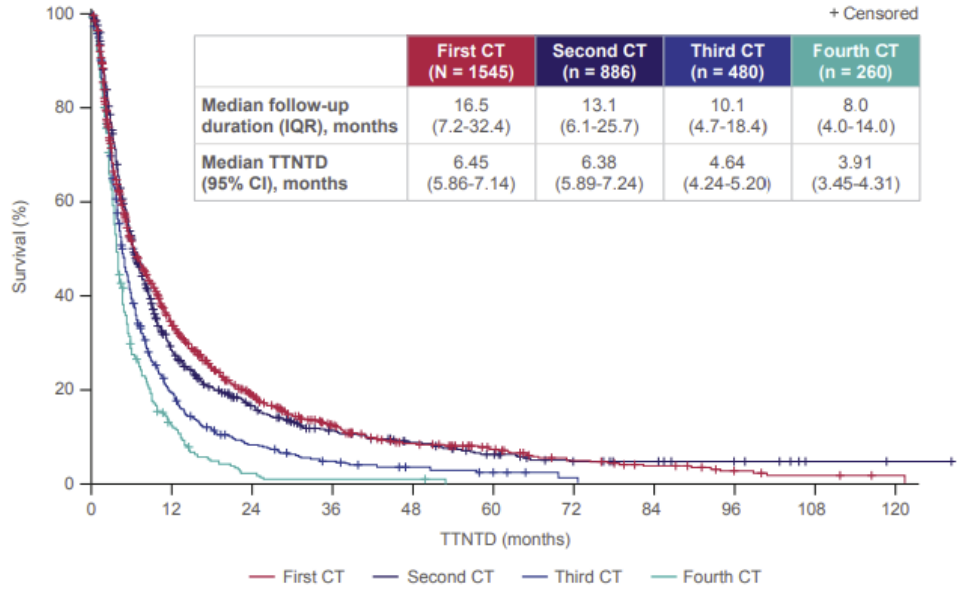
Table: 238P Use of CT agents in pts with HR+/HER2– mBC

Treatment type*	1st CT N=1545	2nd CT n=886	3rd CT n=480	4th CT n=260
Taxanes				
Paclitaxel	29%	35%	25%	17%
Docetaxel	7%	5%	3%	4%
Anthracyclines				
Doxorubicin	11%	7%	12%	11%
Epirubicin	<1%	<1%	1%	<1%
Platinum agents				
Cisplatin	1%	1%	<1%	<1%
Carboplatin	6%	7%	8%	8%
Pyrimidine analogues				
Capecitabine	45%	30%	22%	16%
Gemcitabine	8%	13%	18%	22%
Other				
Eribulin	3%	11%	19%	20%
Vinorelbine	1%	4%	4%	11%

*The proportion of pts may add up to greater than 100% as the subgroups are not mutually exclusive.
CT, chemotherapy; mBC, metastatic breast cancer; pts, patients.

K. Punie, K. Jhaveri, S.M. Tolaney et al ESMOBreast 2023

Figure 5. TTNTD by line of CT



CT, chemotherapy; IQR, interquartile range; TTNTD, time to next treatment or death.

- At 12-month follow up, the median (95% CI) percentage of patients surviving was 70% (67%-72%)
  - In patients who subsequently received a second, third, and fourth CT during the study period, median OS rates decreased with each line of CT

- Time to next Tx or death decreased with each subsequent CT received, indicating a high unmet need for more efficacious treatment options for ET resistant HR+/HER2- mBC

What does the MBC history tell us?

Use and Duration of Chemotherapy in MBC patients

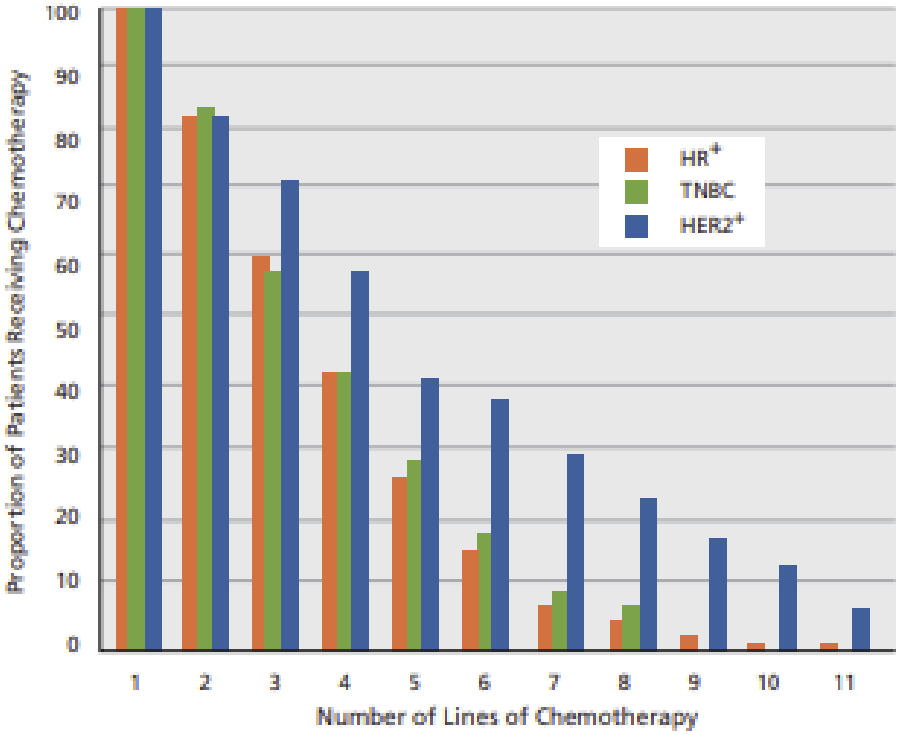
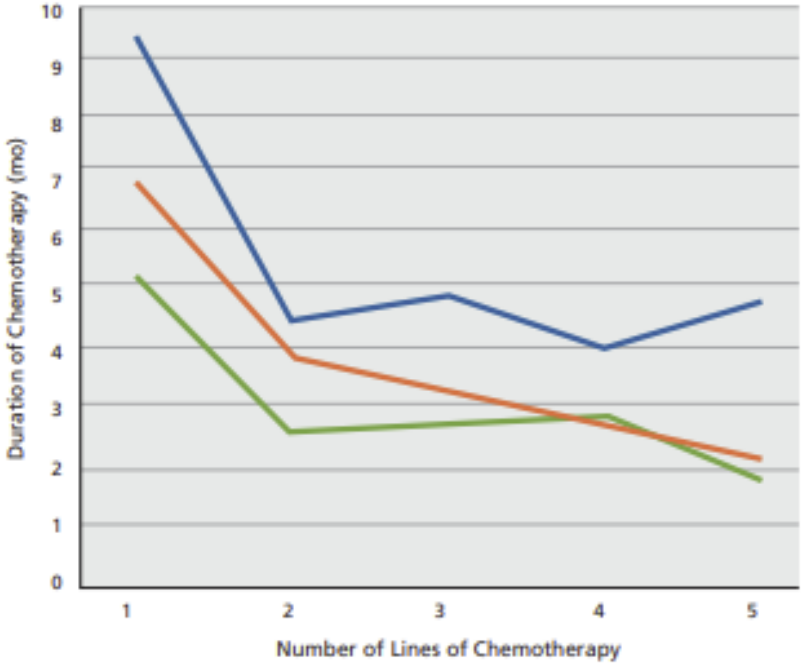


Figure 2 Number of lines of chemotherapy by line and subtype. Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



	Number of Patients				
	First line	Second line	Third line	Fourth line	Fifth line
HR+	96	80	59	41	26
TNBC	44	37	26	19	13
HER+	59	49	43	35	25

Seah et al JNCCN 2014

What does the MBC history tell us?

Median chemotherapy duration in observational studies in first- until third-line

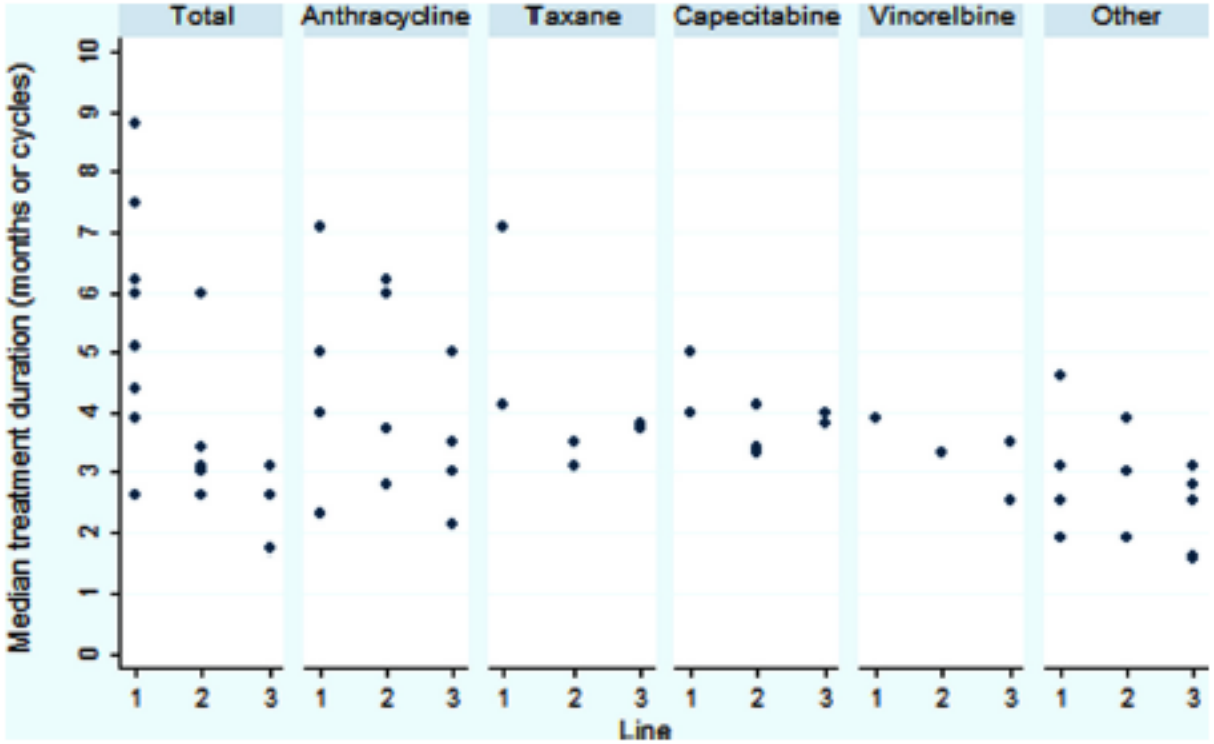


Fig. 1. Overview of median chemotherapy duration in observational studies in first- until third-line. Median chemotherapy duration per line without specification of agents used (overall) in 9 observational studies; and grouped per type of agent(s)* used (anthracyclines, taxanes, capecitabine, vinorelbine, others) in 3 observational studies. *Anthracylines included regimens containing either doxorubicin or epirubicin, taxanes included regimens containing either (liposomal) docetaxel or (nab-)paclitaxel. Other chemotherapy included regimens containing the following agents: bleomycin, carboplatin, cisplatin, cyclophosphamide, eribulin, (5-)fluorouracil, gemcitabine, ifosfamide, methotrexate, mitomycin C, mitozantrone, and vinblastine. NOTE: results shown here should be interpreted in relation with Fig. 2 which indicates that later-line chemotherapy is generally less effective; thereby limiting the treatment duration as a result of progression of disease. Additionally, comparison of treatment duration between different agents is biased by the imbalanced number of patients.

A.K.M. Claessens, et al. Critical Reviews in Oncology / Hematology 153 (2020)

What does the MBC history tell us?

Outcomes in observational studies on multiple lines of chemotherapy for MBC

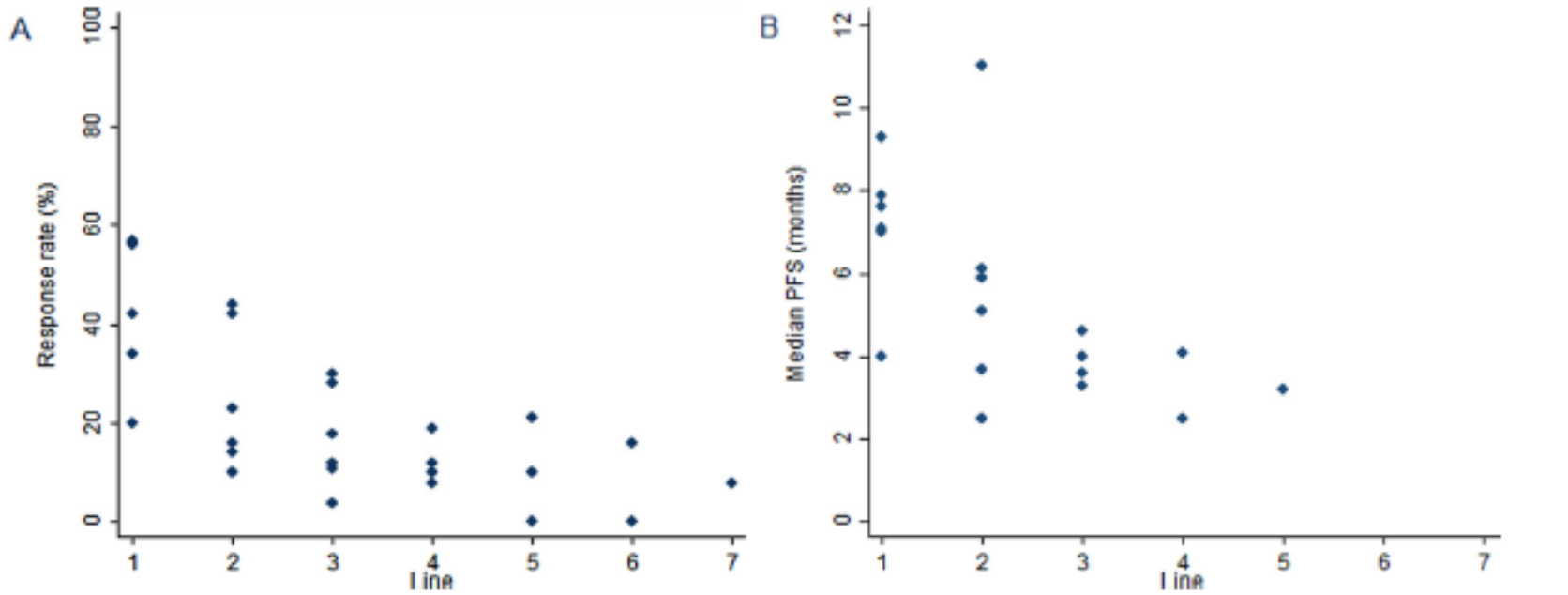


Fig. 2. Overview of outcomes in observational studies on multiple lines of chemotherapy for advanced breast cancer. A) Median line-specific overall response-rate of chemotherapy from 12 observational studies. B) Median line-specific progression-free survival of chemotherapy from 8 observational studies.

A.K.M. Claessens, et al. Critical Reviews in Oncology / Hematology 153 (2020)

What does the MBC history tells us?

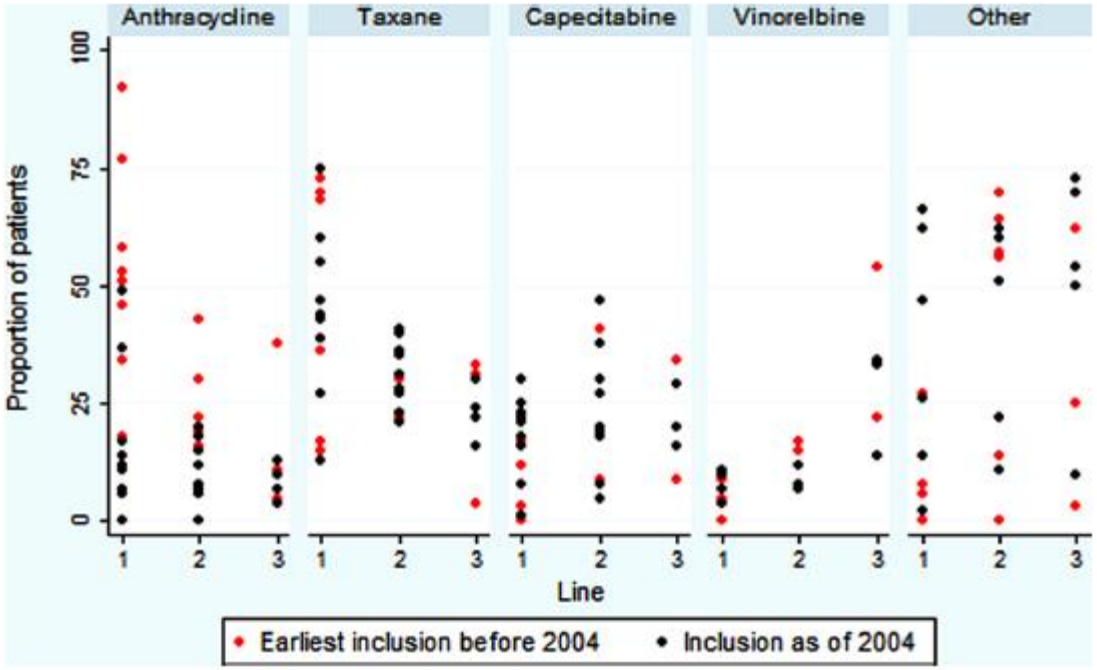


Fig. 3. Overview of the use of different groups of chemotherapy agents (proportion of patients) for first- until third-line in 16 observational studies.

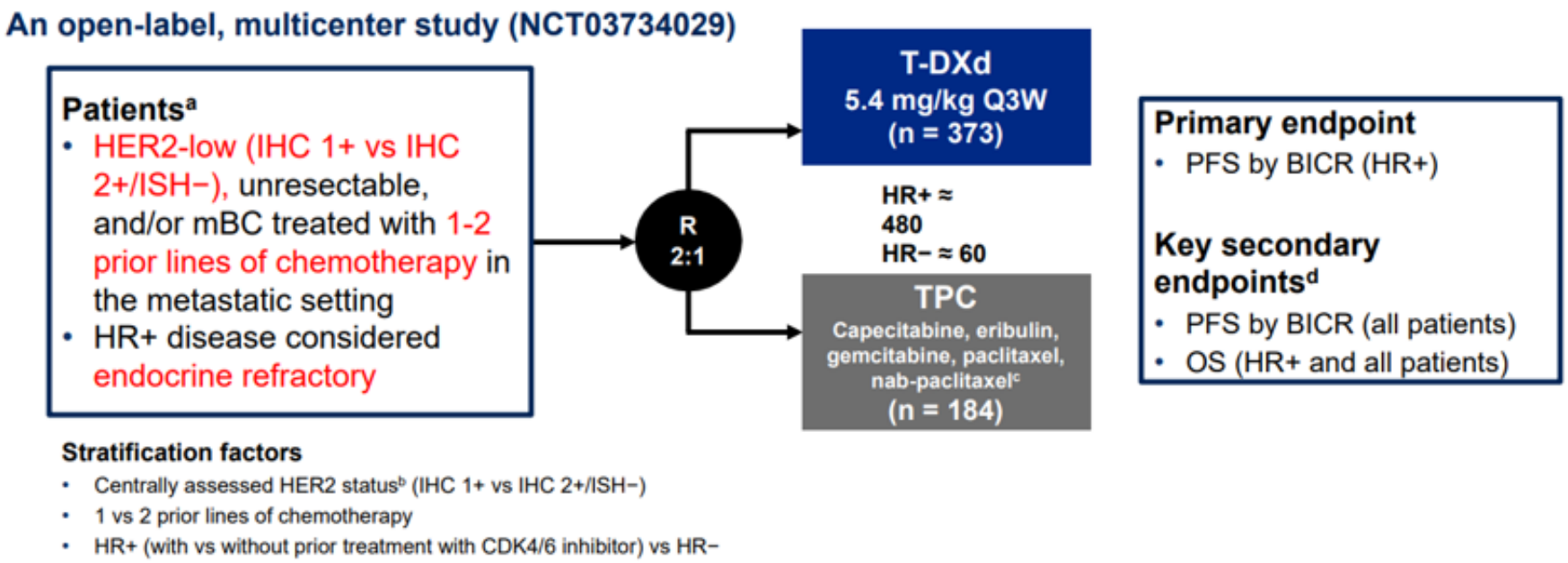
- The questions on the optimal agent for a specific treatment line and the optimal sequence of agents over multiple lines remains unanswered

- Capecitabine, despite the increasing use in first-line over the years, still more often prescribed from second-line onwards

A.K.M. Claessens, et al. Critical Reviews in Oncology / Hematology 153 (2020)

What do the recent history tell us?

Destiny 04: ADCs in HER2 low MBC



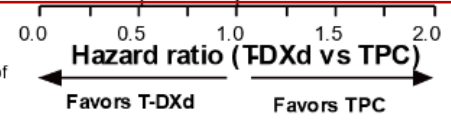
Modi. N Eng J Med. 2022;387:9.

Prior chemotherapies

- DESTINY-Breast04: January 11, 2022, DCO

Subgroup analysis: PFS in all patients [a]

		No. of Events/No. of Patients		Median PFS (mo, 95% CI[b])		Hazard Ratio (95% CI[b])
		T-DXd	TPC	T-DXd	TPC	
Disease burden[c]	Low (n = 235)	88/150	60/85	11.4 (9.8-16.2)	5.1 (3.1-7.3)	0.41 (0.30-0.58)
	High (n = 322)	155/223	67/99	9.5 (7.5-10.1)	4.8 (2.9-6.9)	0.58 (0.43-0.78)
Rapid progression[d]	Yes (n = 22)	9/14	6/8	8.2 (1.4-NE)	2.2 (0.6-NE)	0.38 (0.12-1.21)
	No (n = 535)	234/359	121/176	9.9 (9.0-11.3)	5.3 (4.2-6.9)	0.51 (0.41-0.64)
HER2 IHC status	IHC 1+ (n = 321)	134/214	75/107	10.0 (8.6-12.3)	4.8 (3.0-7.0)	0.48 (0.36-0.63)
	IHC 2+/ISH− (n = 236)	109/159	52/77	9.9 (8.0-11.5)	5.1 (2.9-7.1)	0.55 (0.39-0.76)
Prior lines of chemotherapy	1 (n = 321)	141/221	68/100	10.1 (8.4-12.2)	6.4 (4.3-7.8)	0.52 (0.39-0.70)
	2 (n = 234)	101/151	59/83	9.7 (8.1-11.4)	4.2 (3.0-5.4)	0.49 (0.35-0.68)
Age	<65 years (n = 426)	191/290	93/136	9.8 (8.4-11.1)	4.6 (2.9-5.9)	0.47 (0.37-0.61)
	≥65 years (n = 131)	52/83	34/48	11.4 (8.3-13.3)	6.2 (4.3-10.8)	0.57 (0.36-0.89)
Baseline CNS metastases	Yes (n = 32)	18/24	6/8	8.1 (4.0-11.3)	4.8 (0.6-11.0)	0.71 (0.28-1.80)
	No (n = 525)	225/349	121/176	10.1 (9.5-11.5)	5.1 (4.2-6.8)	0.49 (0.39-0.62)
Prior anthracycline treatment[e]	Yes (n = 342)	155/239	81/113	9.8 (8.5-11.7)	5.3 (3.0-7.9)	0.53 (0.40-0.70)
	No (n = 205)	88/134	46/71	10.0 (7.2-12.5)	4.6 (3.0-6.8)	0.46 (0.32-0.66)



Dashed line at 0.50 represents mPFS for all patients.
[a]mPFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. [b]Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. [c]Disease burden was defined by the number of metastatic disease sites at baseline (low = 2; high = 3+). At baseline, 69.8% of patients had liver metastases. [d]Rapid progressor status was defined as disease progression within 6 months of concluding a prior course of chemotherapy in early breast cancer. [e]Defined as prior anticancer therapy of "anthracyclines," "doxorubicin," "epirubicin," "daunorubicin," or "idarubicin" in CMDECOD and CMTRT in ADCM.

Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 6-9, 2022; San Antonio, TX. Poster P1-11-0.

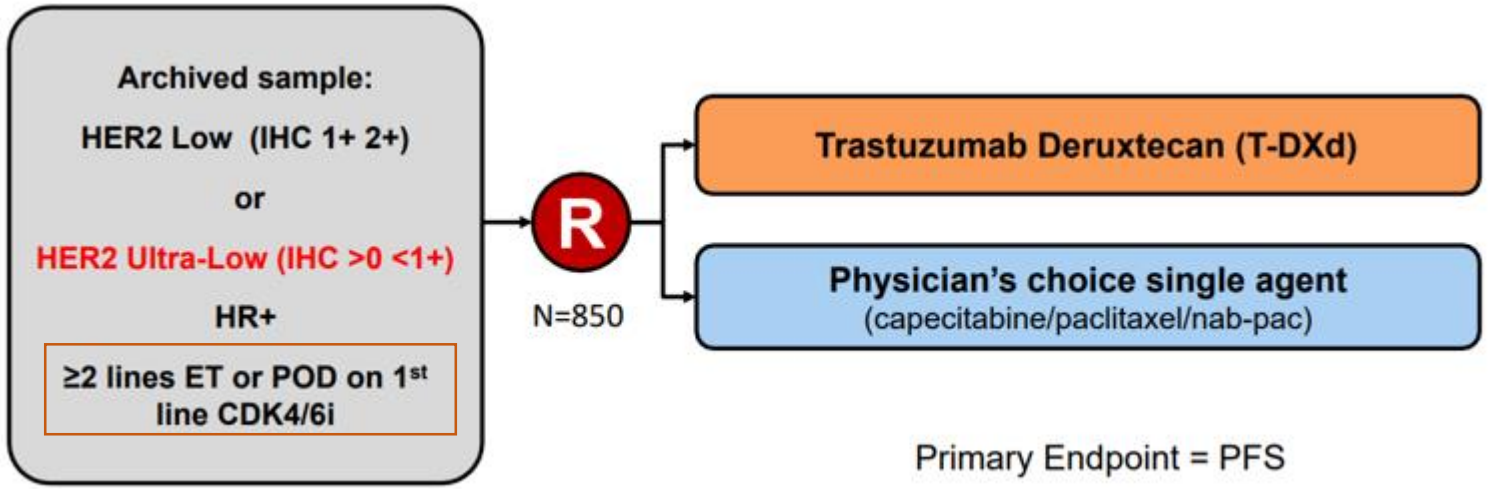
Which chemo?

In which setting?

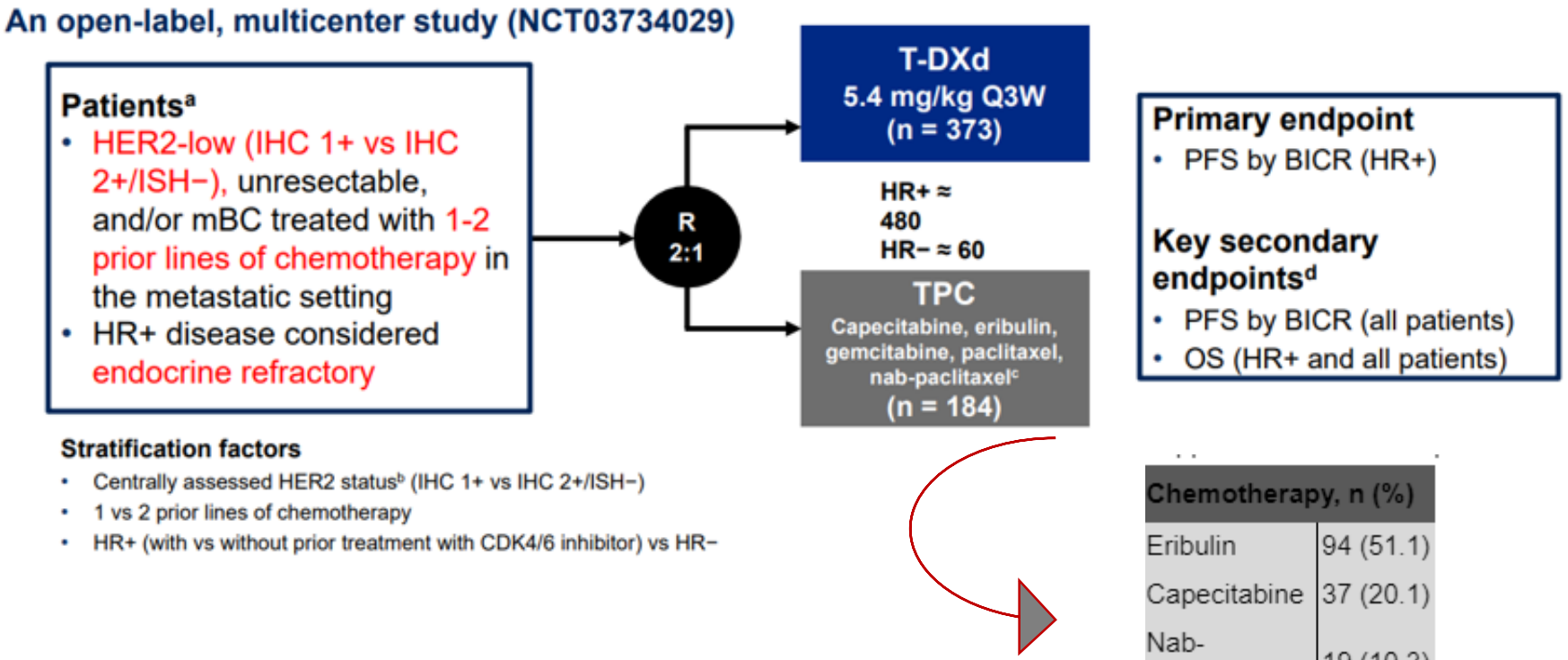
DESTINY Breast-06: Chemotherapy-naïve, HR+, HER2 LOW or HER2 Ultra-Low MBC

Key differences with DB-04:

- Includes IHC0 (ultra-low)
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients



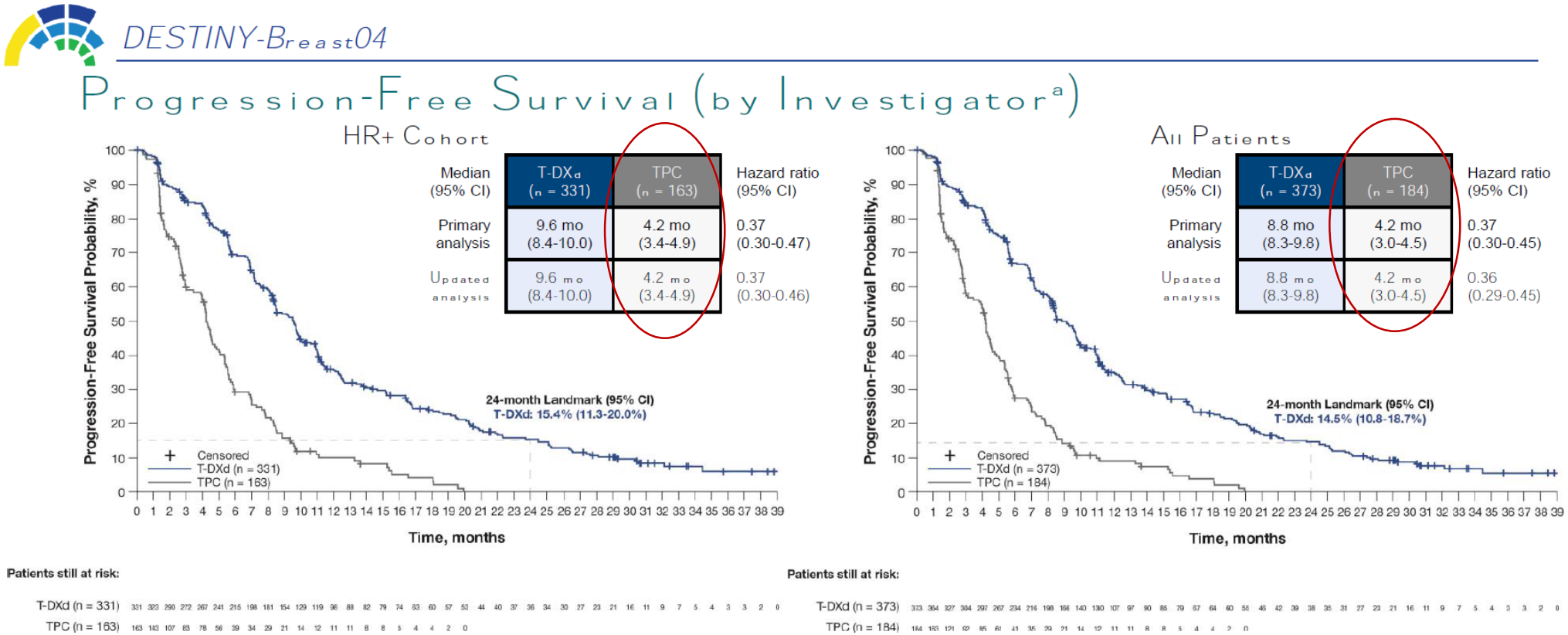
Destiny 04: ADCs in HER2 low MBC



Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

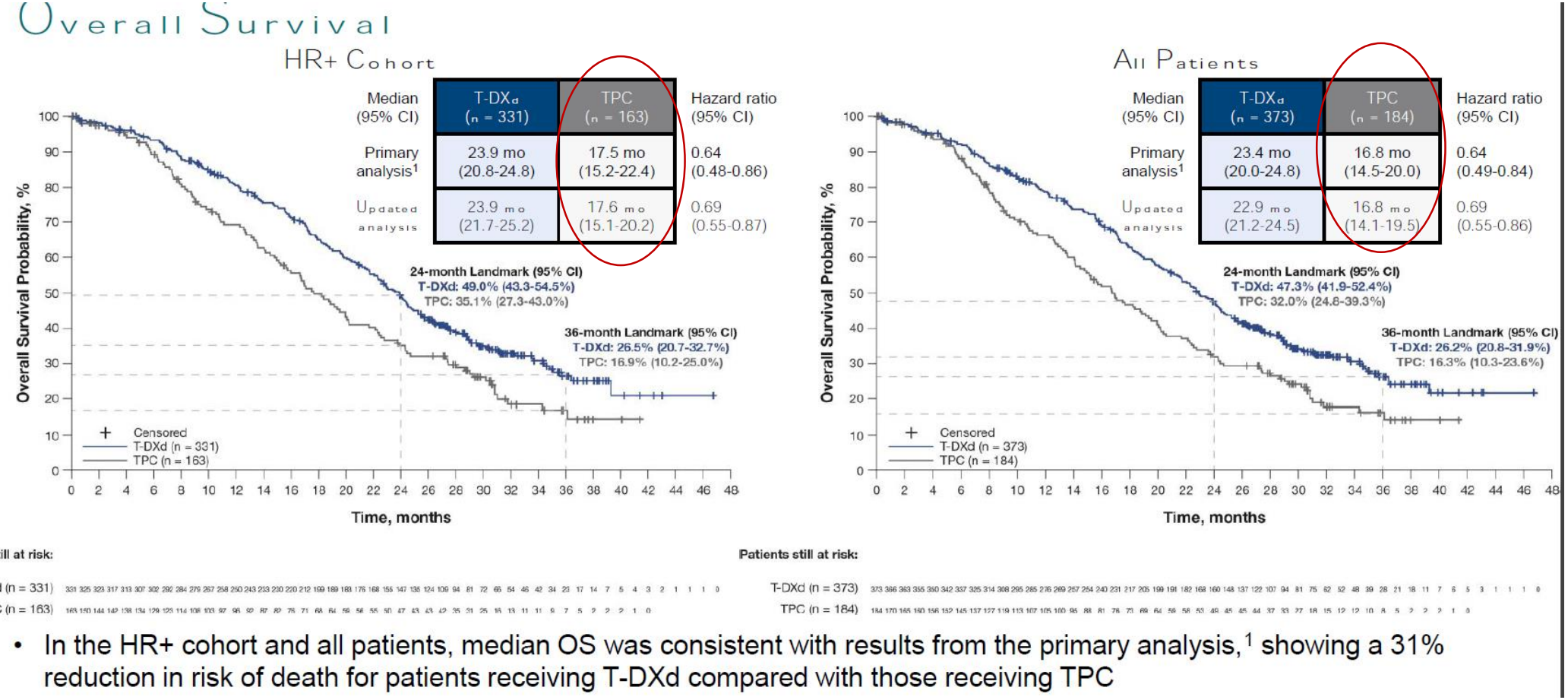
Modi. N Eng J Med. 2022;387:9.

Destiny 04: PFS 32 months Follow up



- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

Destiny 04: OS at 32 months Follow up



- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

Modi S ESMO 2023

PFS2

DESTINY-Breast04

PFS2[a] and Post-Study Anticancer Therapies[b]

	HR+ Cohort		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS2 by investigator, mo (95% CI)	15.5 (13.8-17.2)	10.5 (8.3-11.4)	15.4 (13.6-16.5)	9.7 (8.3-10.8)
Hazard ratio (95% CI)	0.51 (0.40-0.64)		0.51 (0.41-0.64)	
Post-study anticancer therapies				
Systemic treatment, n (%)	247 (74.6)	126 (77.3)	282 (75.6)	144 (78.3)
Targeted therapy[c]	119 (36.0)	70 (42.9)	134 (35.9)	75 (40.8)
CDK4/6 inhibitors	47 (14.2)	27 (16.6)	48 (12.9)	27 (14.7)
ADC	16 (4.8)	15 (9.2)	18 (4.8)	15 (8.2)
T-DXd	2 (0.6)	4 (2.5)	2 (0.5)	4 (2.2)
Sacituzumab govitecan	9 (2.7)	5 (3.1)	11 (2.9)	5 (2.7)
Endocrine therapy	102 (30.8)	56 (34.4)	103 (27.6)	57 (31.0)
Chemotherapy	222 (67.1)	109 (66.9)	257 (68.9)	126 (68.5)
Radiation, n (%)	32 (9.7)	25 (15.3)	37 (9.9)	29 (15.8)
Surgery, n (%)	3 (0.9)	1 (0.6)	5 (1.3)	1 (0.5)

Which chemo?

EMBRACE Compared Eribulin with 'Real-life' Treatment Choices

Global, open-label, randomised, phase III study

Patients (N=762)
- Locally recurrent or MBC
- 2–5 prior chemotherapies
  - ≥ 2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤ 6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG PS ≤ 2

Eribulin mesylate (n=508)
1.4 mg/m²* IV over
2–5 minutes on Day 1,8 q21 days

RANDOMISATION 2:1***

TPC (n=254):
- Any monotherapy (cytotoxic, hormonal, biological)**; or
- Palliative treatment; or
- Radiotherapy

Primary Endpoint:
- OS

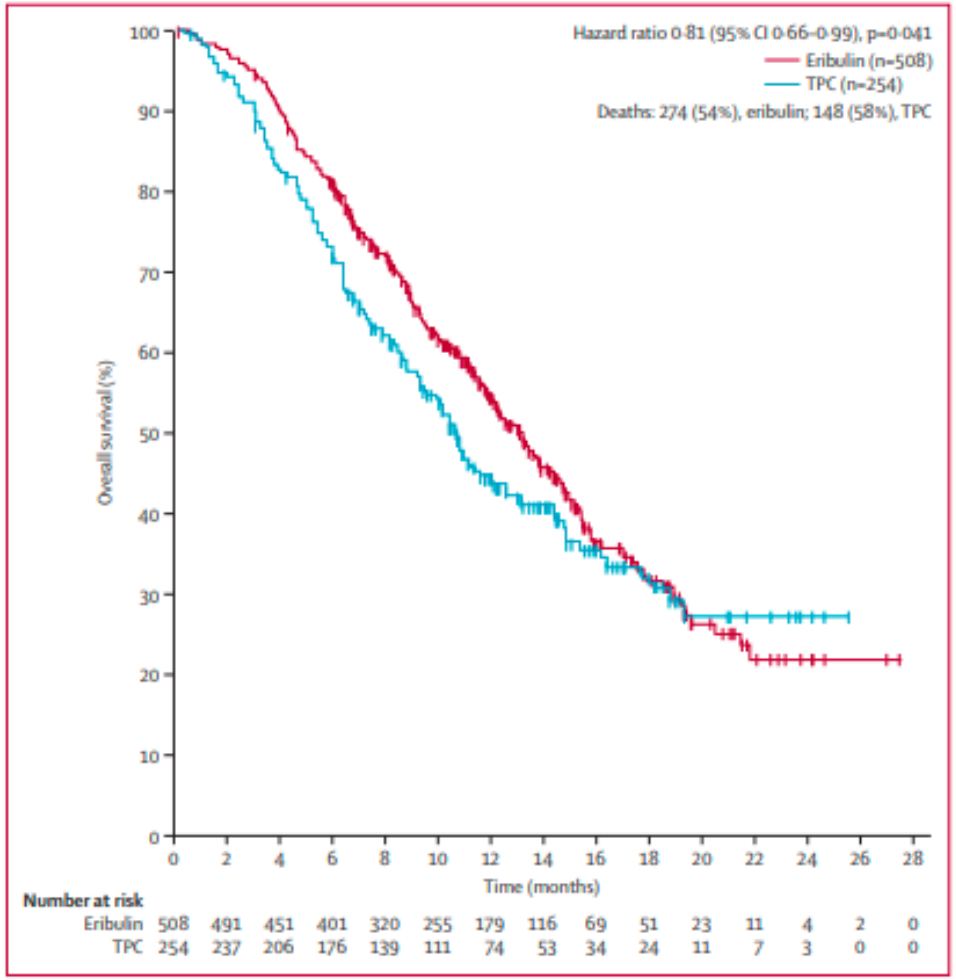
Secondary Endpoints:
- PFS
- ORR
- Safety

ECOG PS, Eastern Cooperative Oncology Group performance status

- *Equivalent to 1.23 mg/m² eribulin
- **Approved for treatment of cancer and administered according to local practice
- ***Patients were stratified by geographic region, prior capecitabine treatment, and human epidermal growth factor receptor 2 (HER2/neu) status before randomisation
- Patients were treated with eribulin mesylate or TPC until disease progression, unacceptable toxicity, patient/physician request to discontinue or serious protocol non-compliance
- Exploratory subgroups: Hormone receptor expression status (ER, PgR, HER2, triple-negative); number of organs involved; sites of disease

EMBRACE RESULTS: OS

Eribulin showed a significant and clinically meaningful improvement in overall survival compared with TPC in women with heavily pretreated metastatic breast cancer



The median duration of eribulin treatment (n=503) was 3·9 months (range 0·7–16·3)

Cortes J TheLancet 2011

Capecitabine in MBC

- Advantage: its oral administration
- Capecitabine as monotherapy is indicated for the second- and subsequent-line treatment of patients with MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or in patients resistant to paclitaxel and for who further anthracycline therapy is not indicated.
- In patients with MBC previously treated with anthracyclines and/or taxanes
  - Response rates 15%–28%
  - TtP was 3–5 months
  - OS was 10–15 months
- Approved dosing: 1250 mg/mq twice daily on days 1-14 every 21 days

Reichardt P, Ann Oncol 2003; 14(8): 1227–1233. 31.
Blum JL et al. J Clin Oncol 1999; 17(2): 485–493. 32.
Blum JL et al. Cancer 2001; 92(7): 1759–1768.
Fumoleau P, Eur J Cancer 2004; 40(4): 536–542

X-7/7 Study Design

ELIGIBILITY

- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION

- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

FD-7/7 Arm (N=80)

Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)

Capecitabine 1250* mg/m^2 PO BID x14 days followed by 7-day rest

**Physician had discretion to use alternative dosing of 1000 mg/m^2 PO BID (N=11)*

ENDPOINTS

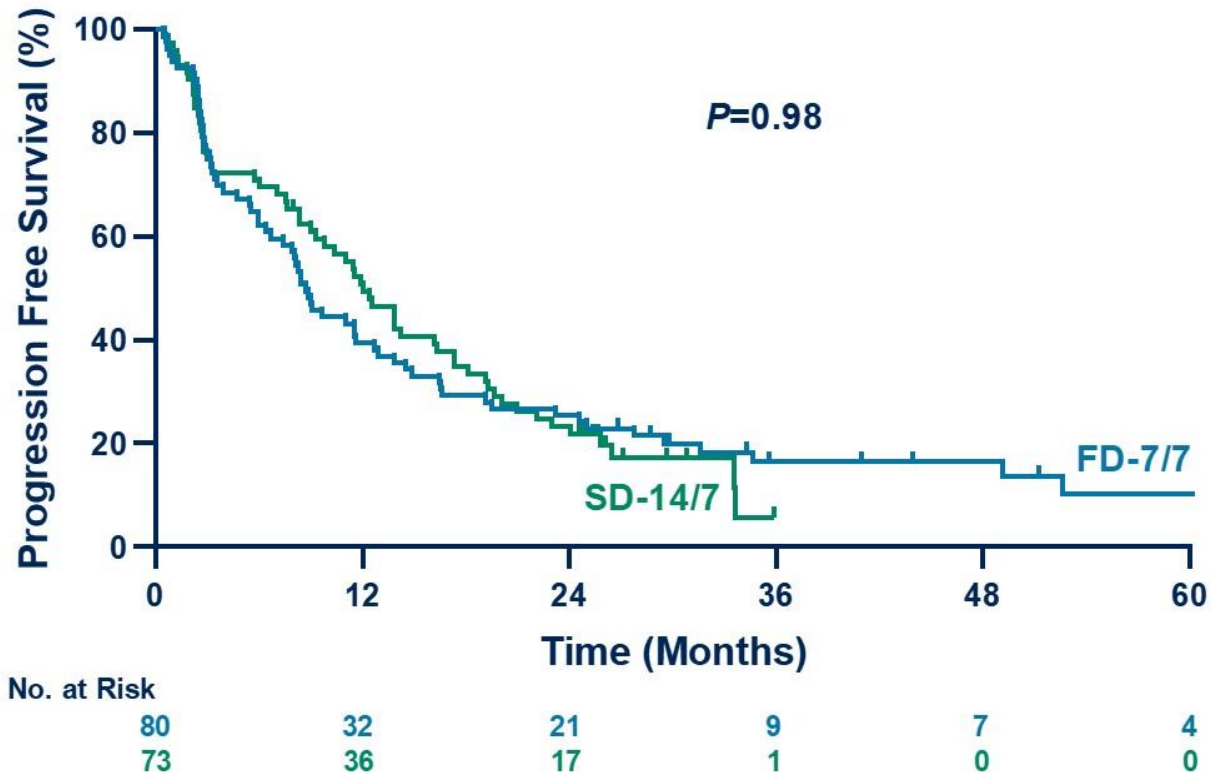
- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit

Baseline Characteristics

Characteristic	Overall (N=153)	FD-7/7 (N=80)	SD-14/7 (N=73)	P-value
Median Age, range- yr	60	59.1 (35-84)	60.9 (32-87)	0.33
Sex, Female- %	100	100	100	-
Race/ethnicity- n (%)				0.69
White	131 (85.6)	70 (87.5)	61 (83.6)	
African American	13 (8.5)	5 (6.3)	8 (11)	
Hispanic	5 (3.3)	3 (3.8)	2 (2.7)	
American Indian, Alaska Native	1 (0.7)	1 (1.3)	0	
Other	3 (2.0)	1 (1.3)	2 (2.7)	
Visceral metastasis- n (%)				0.89
Yes	68 (44)	36 (45)	32 (44)	
No	85 (56)	44 (55)	41 (56)	
Breast Cancer Subtypes- n (%)				0.993
HR positive, HER2 negative	119 (78)	63 (79)	56 (77)	
HER2 positive	17 (11)	8 (10)	9 (12)	
Triple negative	17 (11)	9 (11)	8 (11)	
Prior lines of chemotherapy- n (%)				0.151
0	99 (65)	56 (70)	43 (59)	
≥1	54 (35)	24 (30)	30 (41)	
Measurable Disease- n (%)				0.36
Yes	102 (67)	56 (70)	46 (63)	
No	51 (33)	24 (30)	27 (37)	

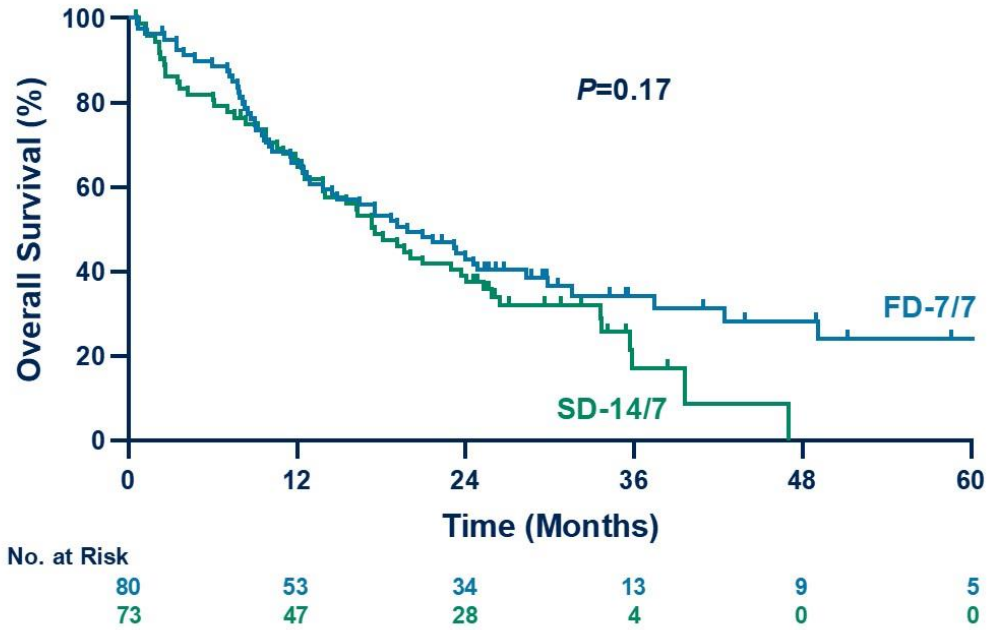
Progression Free Survival



	FD-7/7 (N=80)	SD-14/7 (N=73)
PFS events (%)	67 (83.7)	59 (80.8)
Median PFS, months (95% CI)	8.7 (6.4-11.6)	12.07 (8.9-16.3)
Log-rank test p-value	0.98	
HR (95% CI)	1.00 (0.70-1.43)	
Non-proportionality p-value*	0.045	
RMST at 36 months, months (95% CI)	13.9 (11.1-16.7)	14.6 (11.9-17.3)
RMST difference, months (95% CI)	0.7 (-3.14, 4.57)	

*Model assumptions were not valid; visually observed by KM curves crossing

Overall Survival



	FD-7/7 (N=80)	SD-14/7 (N=73)
Deaths (%)	53 (66.2)	53 (72.6)
Median OS, months (95% CI)	19.8 (12.9-28.3)	17.5 (12.5-34)
Log-rank test p-value	0.17	
HR (95% CI)	0.76 (0.52-1.12)	
Non-proportionality p-value	0.020	
RMST at 47 months, months (95% CI)	24.5 (20.7-28.3)	20.9 (17.3-24.5)
RMST difference, months (95% CI)	-3.6 (-8.89, 1.54)	

PRESENTED BY: Qamar Khan, MD

- Similar efficacy with no difference in PFS and OS
- Lower incidence of HFS, diarrhea, and stomatitis
- Fewer treatment discontinuations and dose modifications

FD-7/7 may be an alternative dosing option to minimize toxicity while maintaining outcomes in MBC

Metronomic chemotherapy and drug repurposing

- Metronomic chemotherapy involves the administration of chemotherapeutic regimens at lower doses, without long drug-free intervals that have previously been a hallmark of such treatments.

- This method offers a significant reduction in side effects and improved disease management

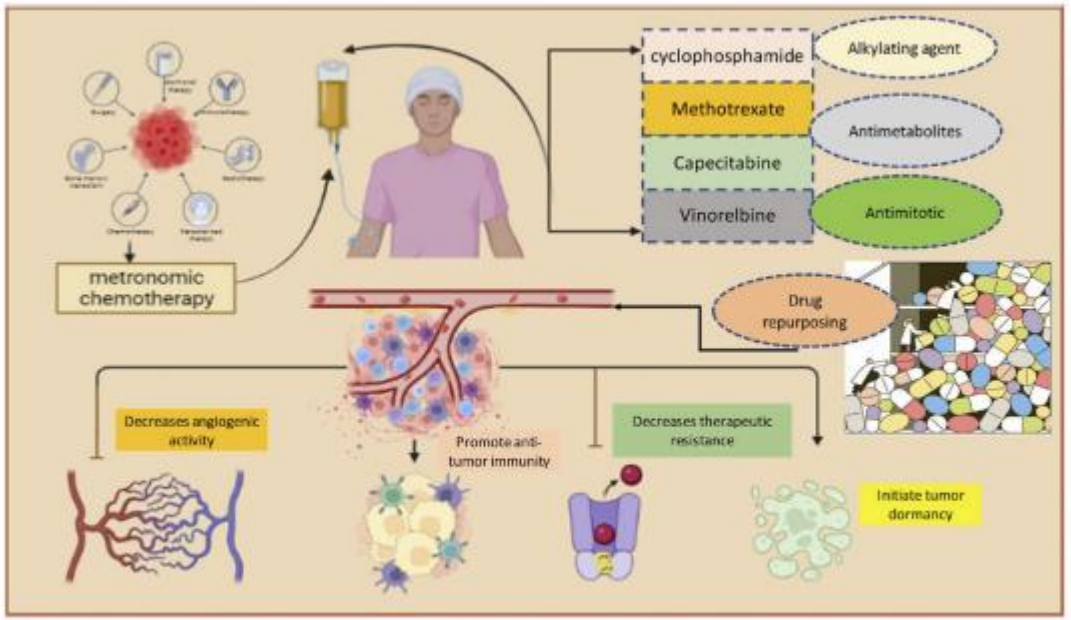


Fig. 1. Combinatorial role of metronomic chemotherapy and drug repurposing in initiating the anti-tumor activity via several mechanisms.

METEORA-II trial (IBCSG 54-16)

- Histologically or cytologically confirmed ER+/HER2-negative locally advanced or metastatic (stage IV) breast cancer
- Measurable or non-measurable, but radiologically evaluable disease according to RECIST 1.1 criteria
- Female >18, ECOG PS 0 or 1
- No more than 1 line of CT for advanced or metastatic breast cancer
- No more than 2 lines of previous ET for locally advanced or metastatic breast cancer

R 1:1

Paclitaxel 90 mg/m2 iv days 1, 8, 15 q4w
until progression or lack of tolerability

Metronomic VEX *until progression or lack of tolerability*

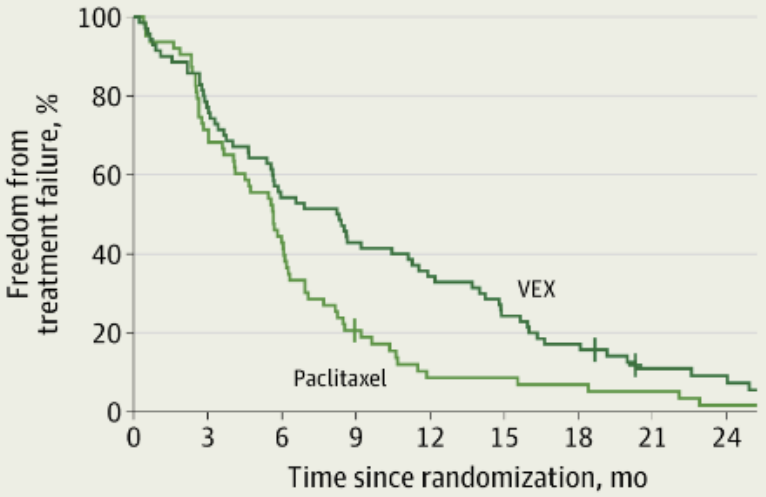
Vinorelbine	40 mg p.o. day 1,3,5 every week
Cyclophosphamide	50 mg daily p.o. continuous
Capecitabine	500 mg p.o. x3/day continuous

Primary Endpoint
- TTF

Secondary Endpoints
- PFS based on local Investigator assessment by RECIST 1.1
- Safety and tolerability, according to NCI CTCAE v4.0
- Disease control, based on RECIST 1.1 criteria
- Overall survival (OS)

FINDINGS

TTF was significantly longer for the VEX group than the paclitaxel group



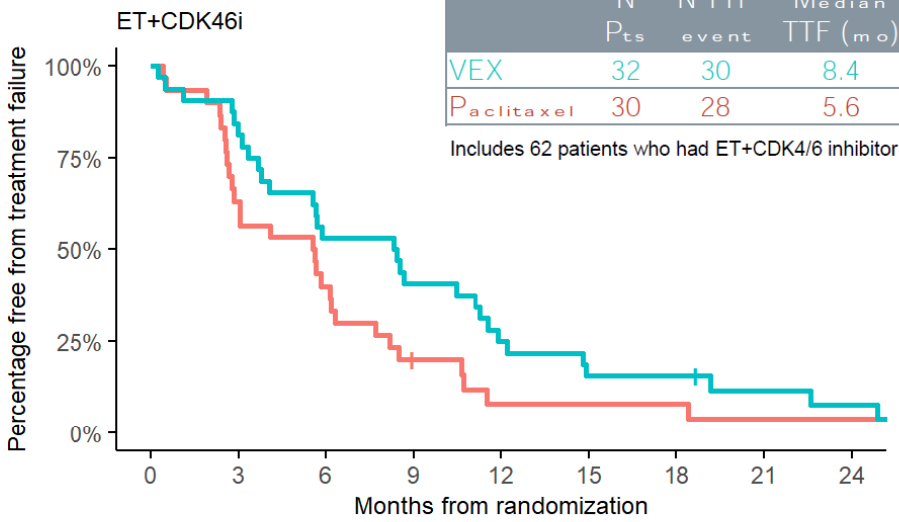
Median TTF for VEX, 8.3 (95% CI, 5.6-11.1)
Median TTF for paclitaxel, 5.7 (95% CI, 4.1-6.1)
Hazard ratio, 0.61 (95% CI, 0.42-0.88); *P*=.008

Munzone E et al JamaOncol 2023

Time to treatment failure (TTF) in the efficacy analysis population: prior ET with CDK4/6 inhibitor subgroup

	N Pts	N TTF event	Median TTF (mo)	12 mo TTF %	HR (95% CI)
VEX	32	30	8.4	25.0%	0.63 (0.37-1.06)
Paclitaxel	30	28	5.6	8.0%	

Includes 62 patients who had ET+CDK4/6 inhibitor for MBC any time prior to enrollment



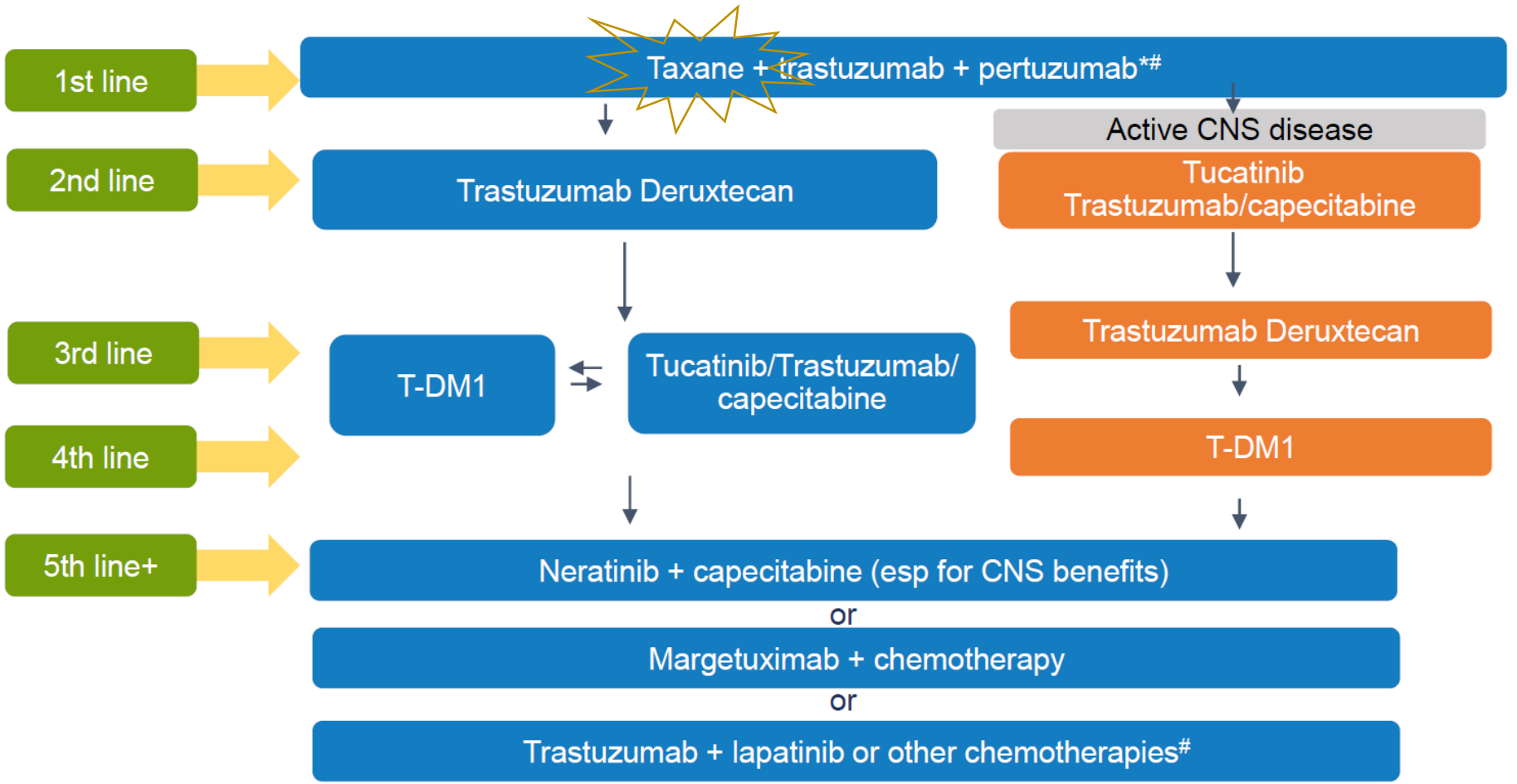
Number at risk

Paclitaxel	30	19	12	5	2	2	2	1	1
VEX	32	26	17	13	8	5	5	3	2

Munzone E et al JamaOncol 2023

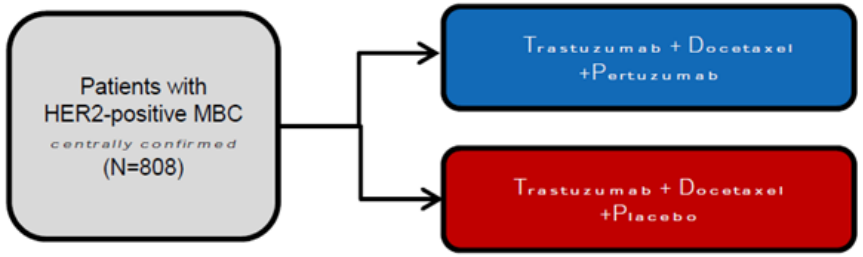
HER2 POSITIVE MBC

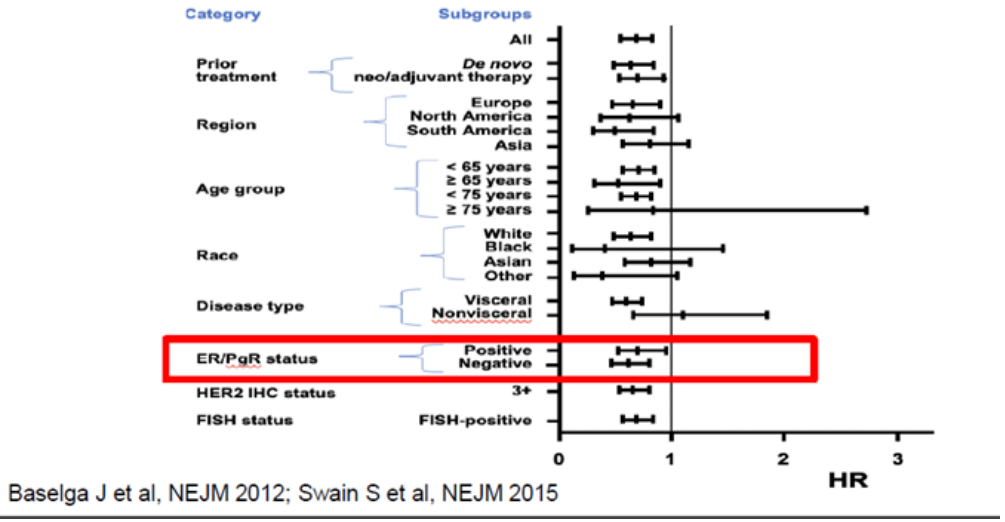
A 2023 Approach to Therapy for Metastatic HER2+ BC:



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

CLEOPATRA TRIAL





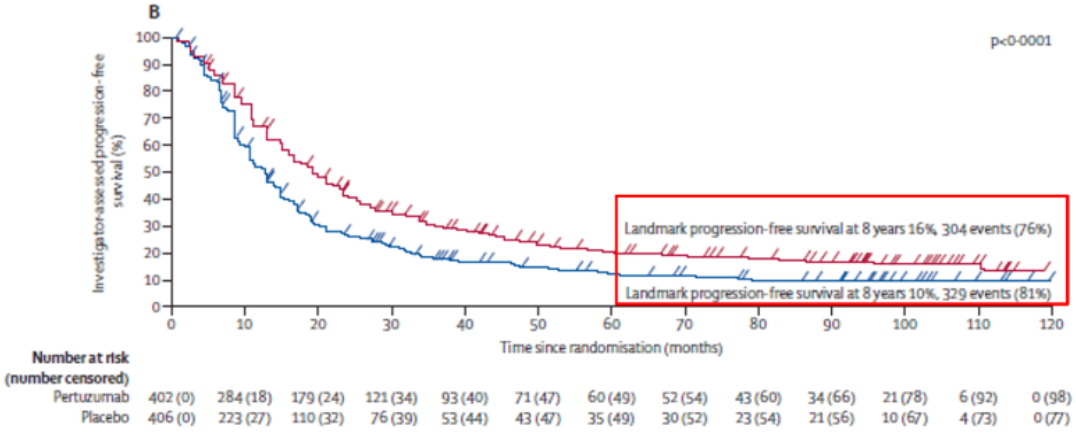
Baselga J et al, NEJM 2012; Swain S et al, NEJM 2015

1st line therapy

- Pertuzumab + trastuzumab + taxane is first line SOC

Addition of Pertuzumab Improves PFS

(median follow-up 99.9 months)

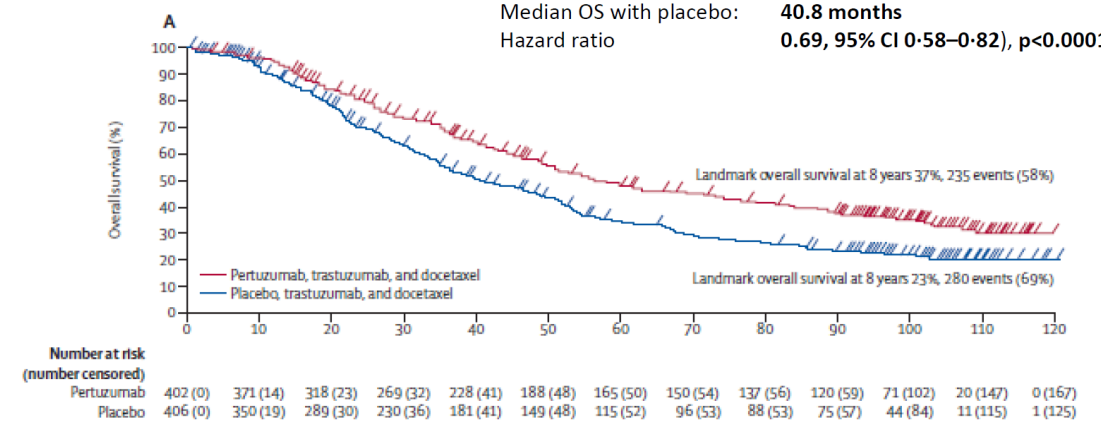


Swain S, et al. *Lancet Oncol.* 2020;21:519-530

Addition of Pertuzumab Improves Overall Survival

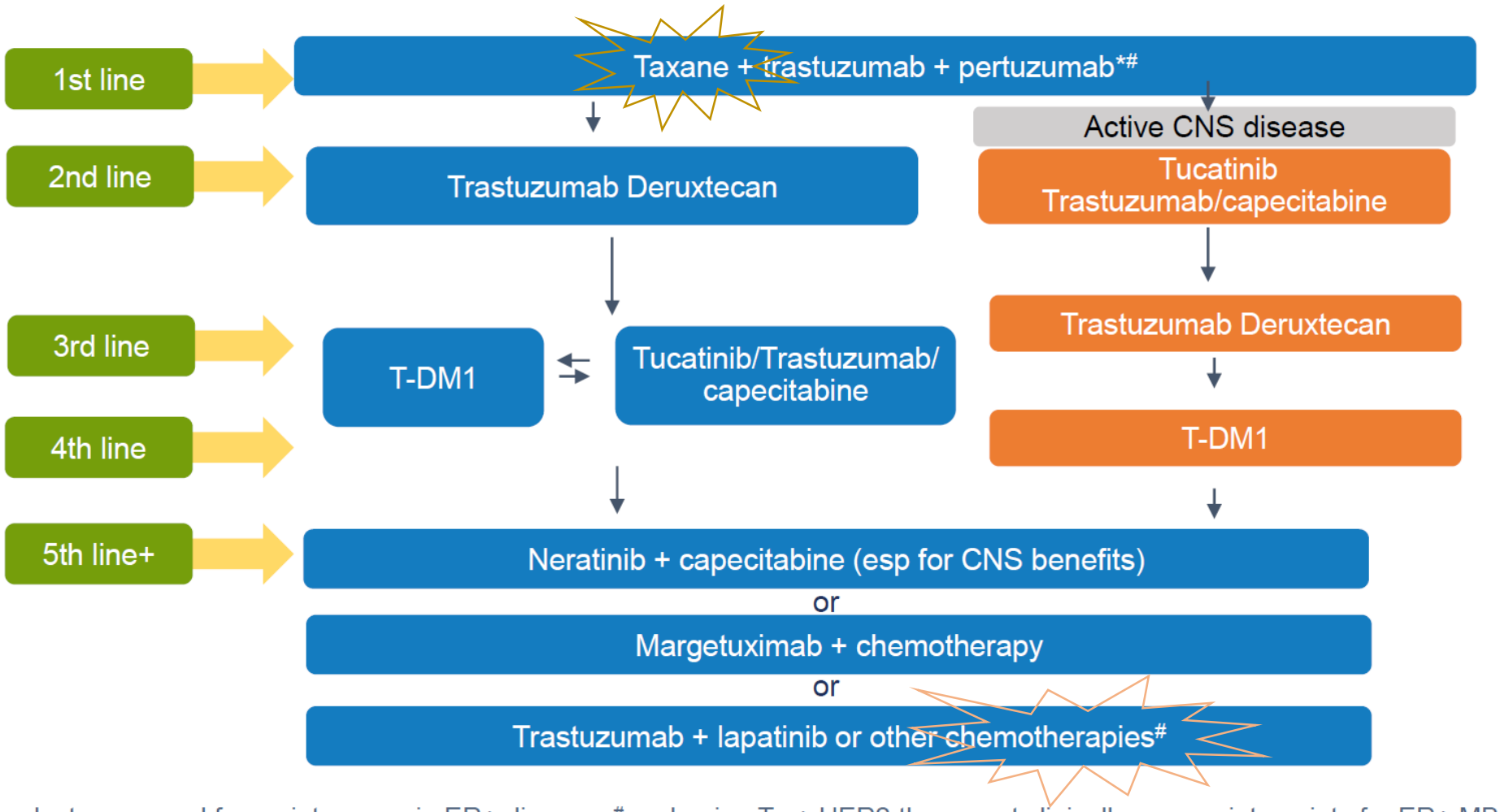
(median follow-up 99.9 months)

Median OS with pertuzumab: **57.1 months**
Median OS with placebo: **40.8 months**
Hazard ratio **0.69, 95% CI 0·58–0·82), p<0.0001**



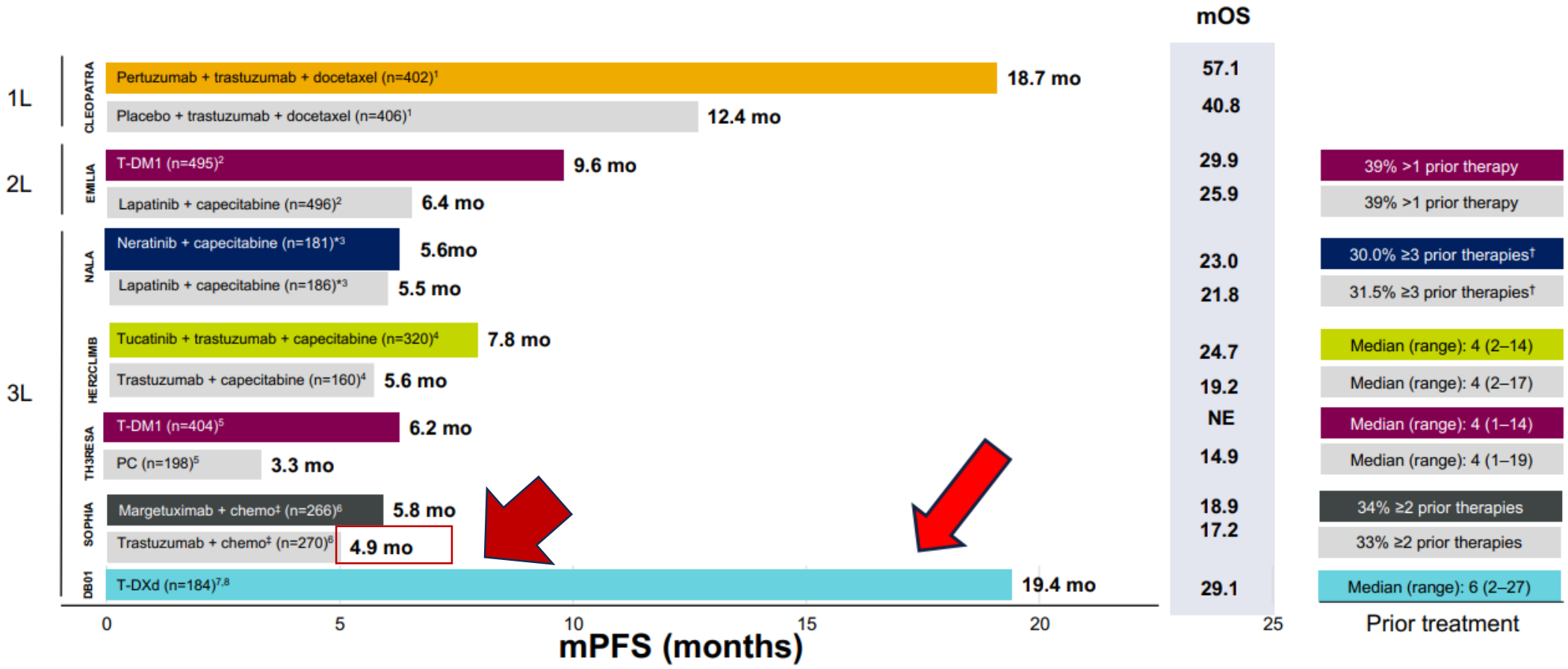
Swain S, et al. *Lancet Oncol.* 2020;21:519-530

A 2023 Approach to Therapy for Metastatic HER2+ BC:



*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

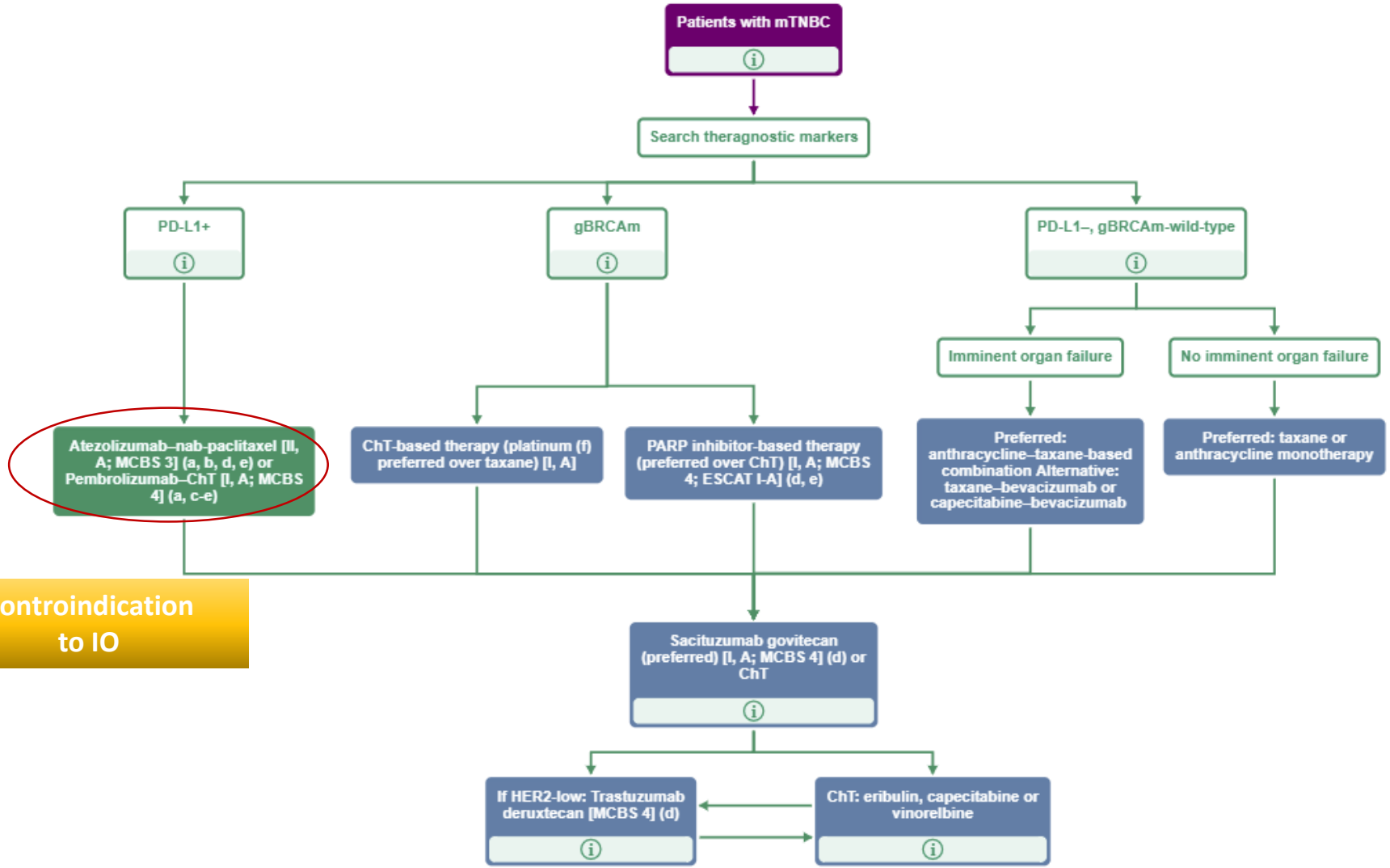
New 3L Therapies for HER2+ MBC: Cross-Trial Comparisons



Swain S, et al. Presented at ASCO, 31–4 June 2019, Chicago US. Abstract #1020; Diéras V, et al. *Lancet Oncol*. 2017;18(6):732–742; Saura C, et al. *J Clin Oncol*. 2020;38:3138–3149; Murthy RK, et al. *N Engl J Med*. 2020;382(7):597–609; Krop IE, et al. *Lancet Oncol*. 2014;15(7)689–699; Rugo HS, et al. Presented at ASCO 2019. Abstract 1000; Saura C et al. Presented at ESMO Congress 2021.

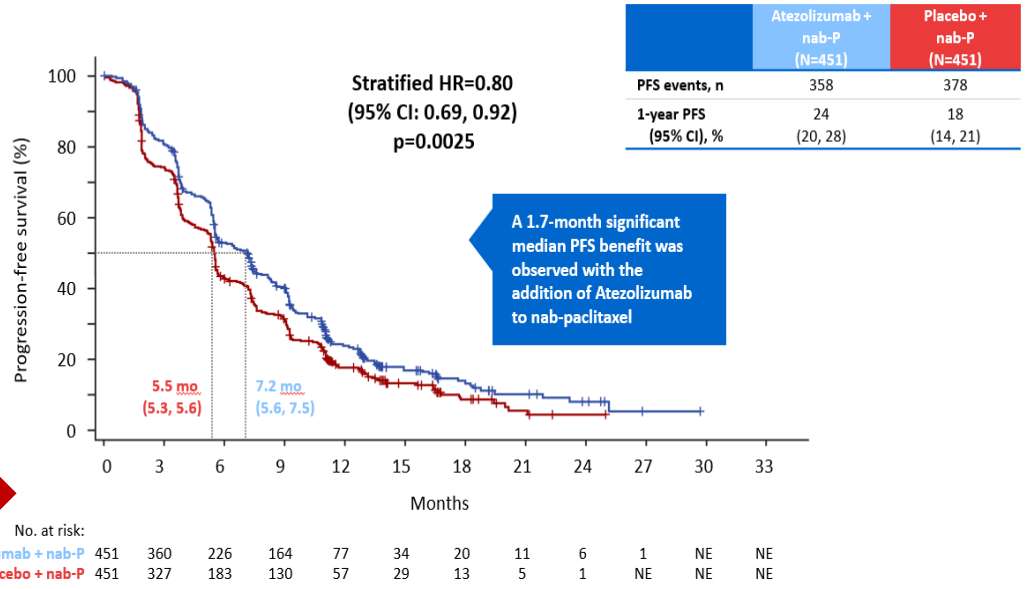
TN MBC

v1.1 - May 2023


Patients with mTNBC
Search theragnostic markers
PD-L1+
gBRCAm
PD-L1–, gBRCAm-wild-type
Imminent organ failure
No imminent organ failure
Atezolizumab–nab-paclitaxel [II, A; MCBS 3] (a, b, d, e) or Pembrolizumab–ChT [I, A; MCBS 4] (a, c-e)
ChT-based therapy (platinum (f) preferred over taxane) [I, A]
PARP inhibitor-based therapy (preferred over ChT) [I, A; MCBS 4; ESCAT I-A] (d, e)
Preferred: anthracycline–taxane-based combination Alternative: taxane–bevacizumab or capecitabine–bevacizumab
Preferred: taxane or anthracycline monotherapy
Controindication to IO
Sacituzumab govitecan (preferred) [I, A; MCBS 4] (d) or ChT
If HER2-low: Trastuzumab deruxtecan [MCBS 4] (d)
ChT: eribulin, capecitabine or vinorelbine

First line

IMPASSION 130

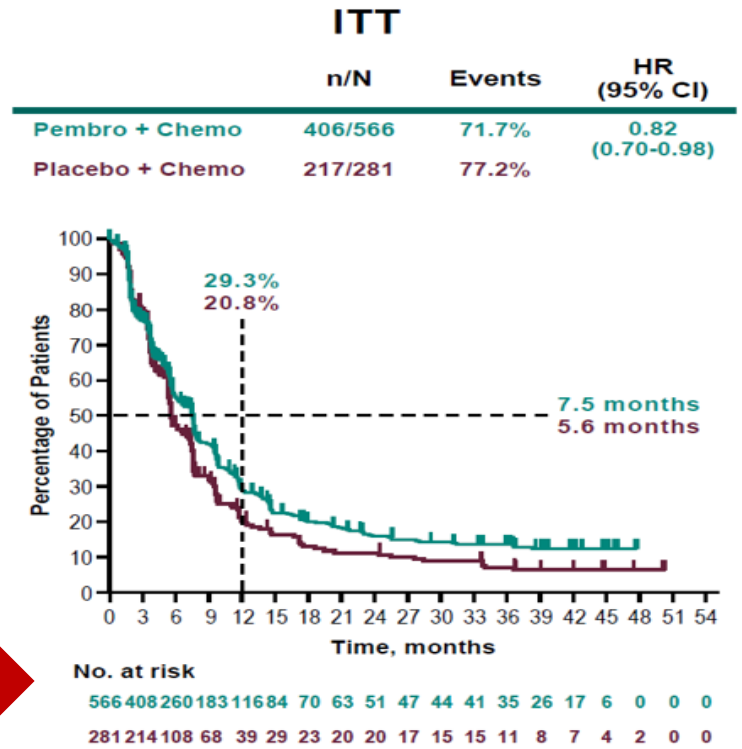


	Atezolizumab + nab-P (N=451)	Placebo + nab-P (N=451)
PFS events, n	358	378
1-year PFS (95% CI), %	24 (20, 28)	18 (14, 21)

A 1.7-month significant median PFS benefit was observed with the addition of Atezolizumab to nab-paclitaxel

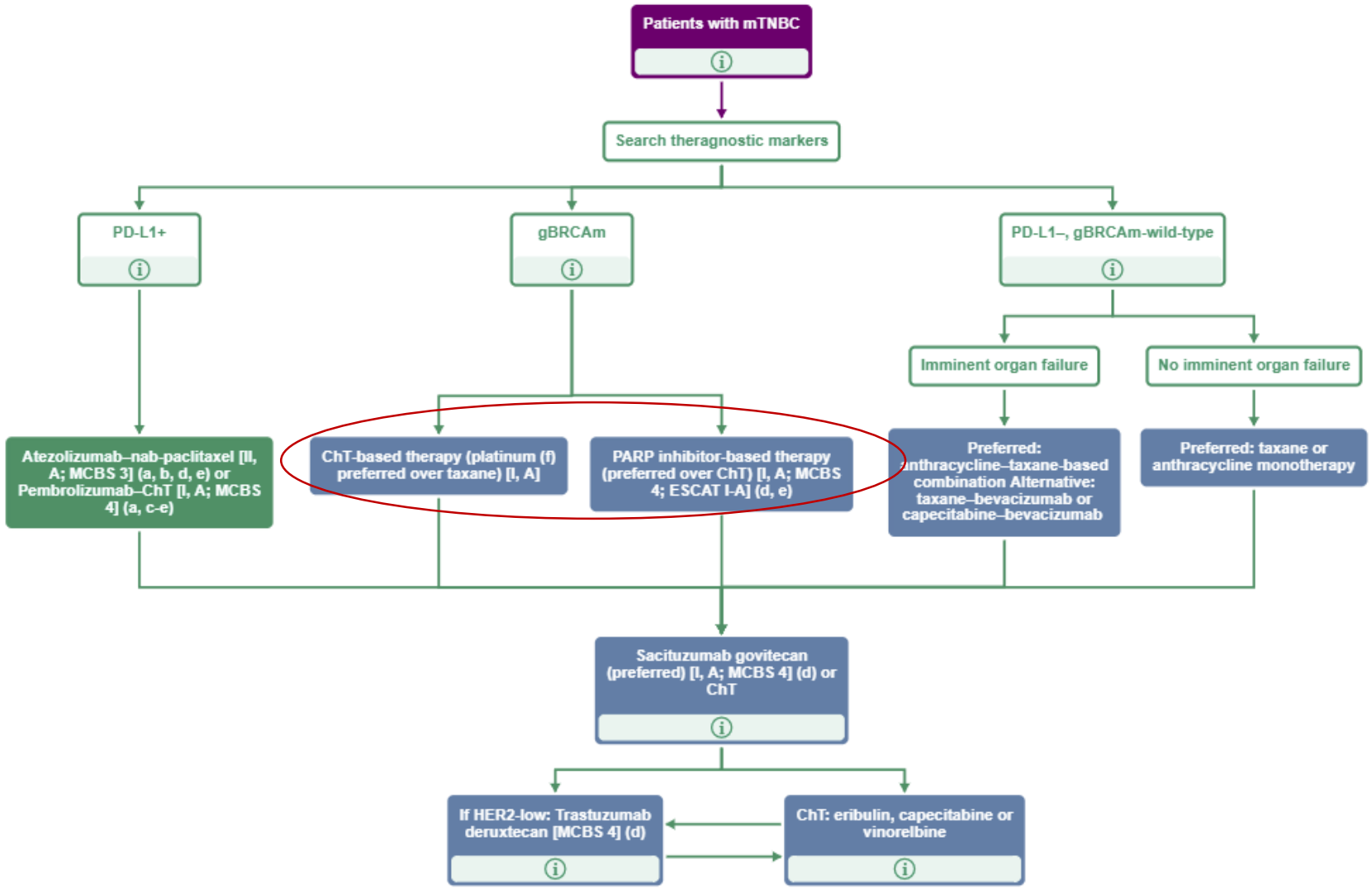
Nab 5.5 mo

Keynote 355



Chemo 5.6 mo

v1.1 - May 2023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TNT: Carboplatin vs Docetaxel First-Line Metastatic TNBC

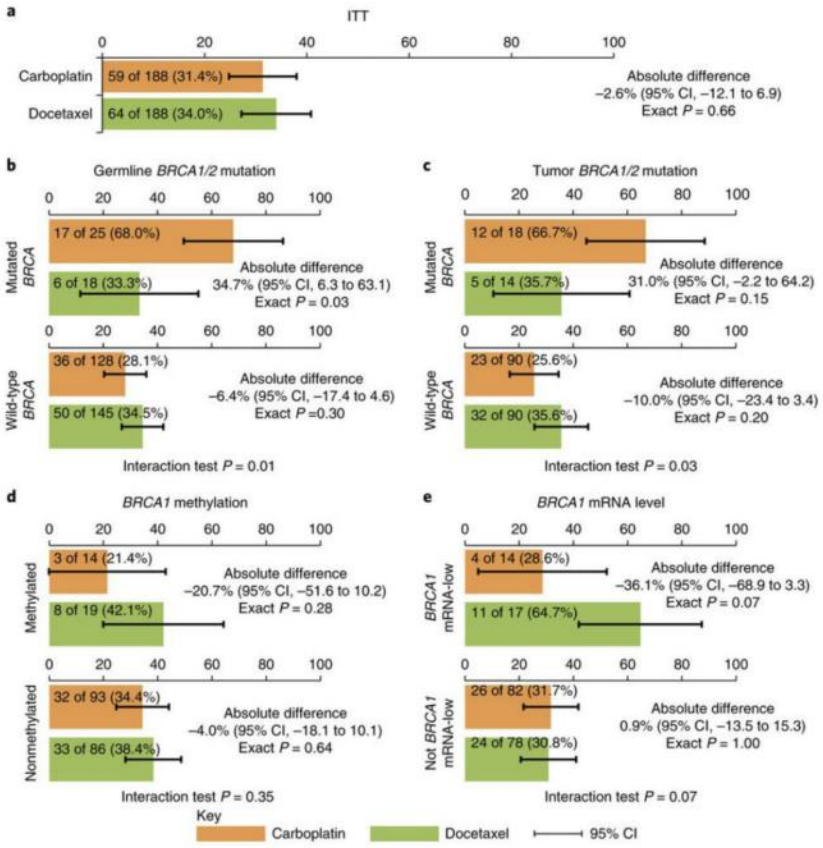
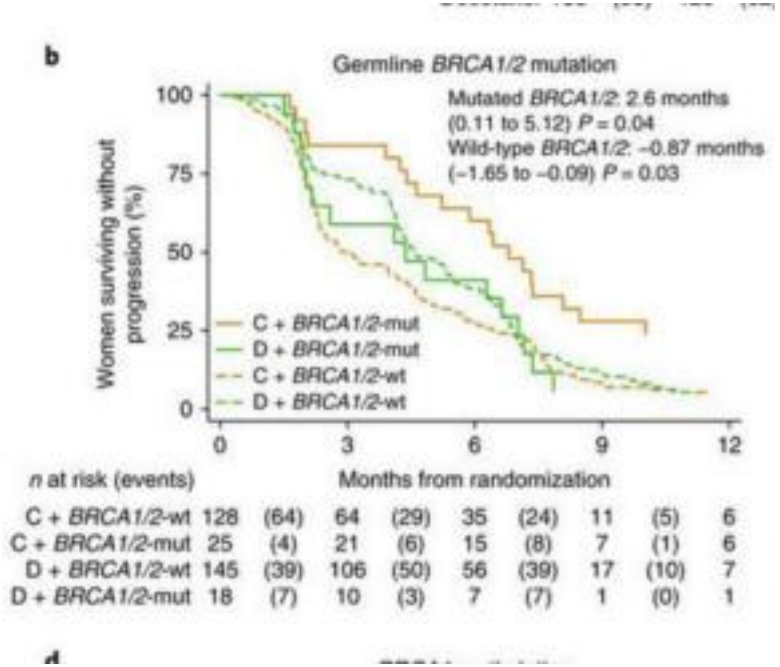


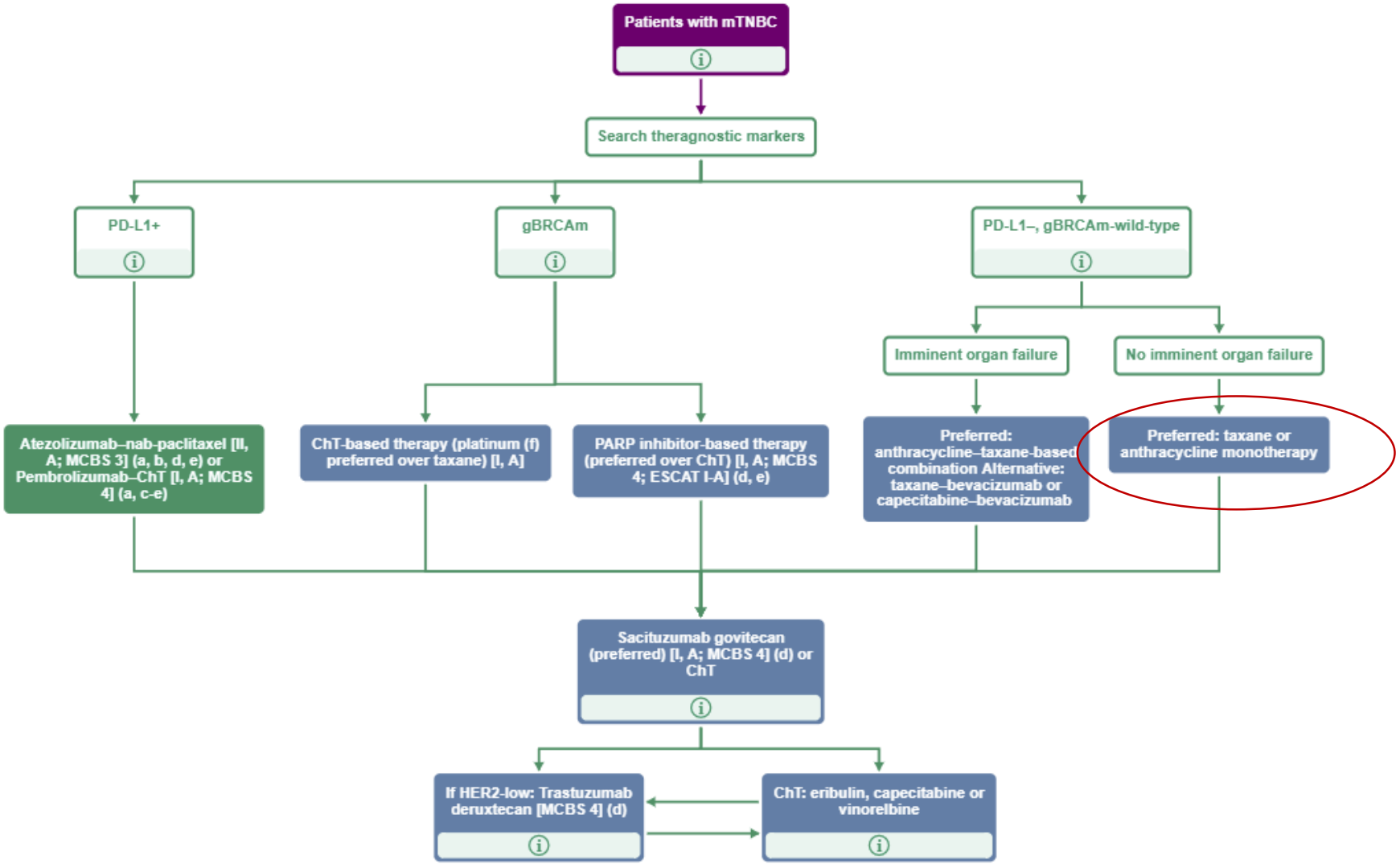
Figure 2. Response rates (overall and BRCA subgroups)
Absolute differences between treatment groups within biomarker subgroups are presented; p-values for the differences are calculated using a 2-sided Fisher's exact test. P-values for interactions are based on a logistic regression model of response with terms for biomarker status, treatment group and interaction.



Carboplatin may be considered as a superior treatment option to docetaxel, since median PFS was improved but only by 2.6 months without an OS benefit

Tutt, A. Nature Med 2018

v1.1 - May 2023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If HER2-low: Trastuzumab deruxtecan [MCBS 4] (d)
ChT: eribulin, capecitabine or vinorelbine

First line

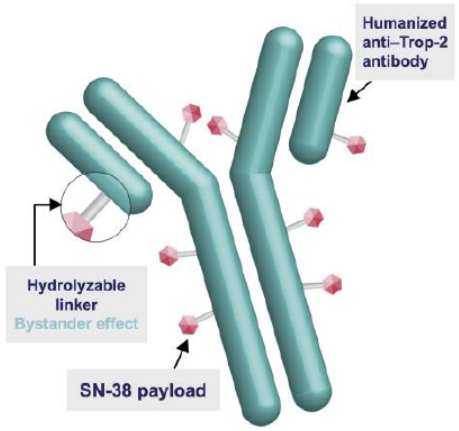
- Several options are possible according to previous treatment exposure in the EBC setting, DFI and disease presentation
- Taxane monotherapy is the most frequent option.
- Anthracyclines: Is a good option?
  - In case of no prior exposure or if rechallenge is possible.
  - Pegylated doxorubicin (PLD) and nonpegylated doxorubicin (NPLD)?
- Single-agent versus combination ChT?
  - Cochrane review combination ChT was associated with a longer OS(HR 0.88; 95% CI 0.83-0.94; P < 0.001), the clinical benefit was modest and at the cost of increased toxicity

Carrick S et al Cochrane Library 2009

Second and beyond line

Sacituzumab Govitecan: an anti-Trop2 antibody-drug conjugate

ASCENT Phase 3 trial in pretreated advanced TNBC



Metastatic TNBC

≥2 chemotherapies for advanced disease

OR

>1 therapy for advanced disease progressing within 12 months of (neo)adjuvant therapy

N=529

NCT02574455

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21 days
(n=267)

Treatment of Physician's Choice (TPC)
(n=262)

Capecitabine
eribulin
vinorelbine
gemcitabine

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS*

Secondary
- PFS for the full population†
- OS, ORR, DOR, TTR, safety

Data cutoff: March 11, 2020

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (Yes/No)

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation

*PFS measured by an independent centralized and blinded radiologists in patients without brain metastases
†The full population includes all randomized patients (with and without brain metastases).

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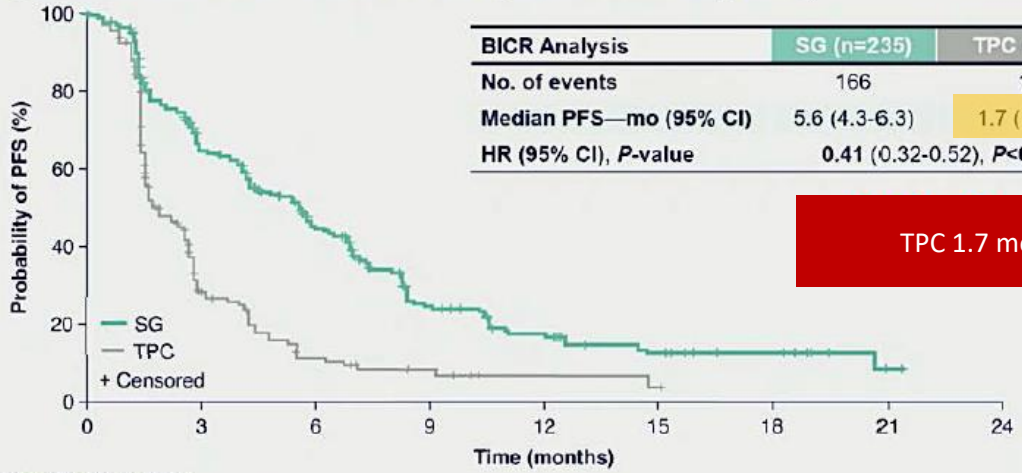
Demographics and Patient Characteristics

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA 1/2 mutational status—no. (%)		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease‖—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

ASCENT (Phase III): Sacituzumab Govitecan (SG) vs Treatment of Physician´s Choice (TPC) in pretreated mTNBC (N=529) – PFS and OS in BM-Neg Patients

Progression-Free Survival (BICR Analysis)



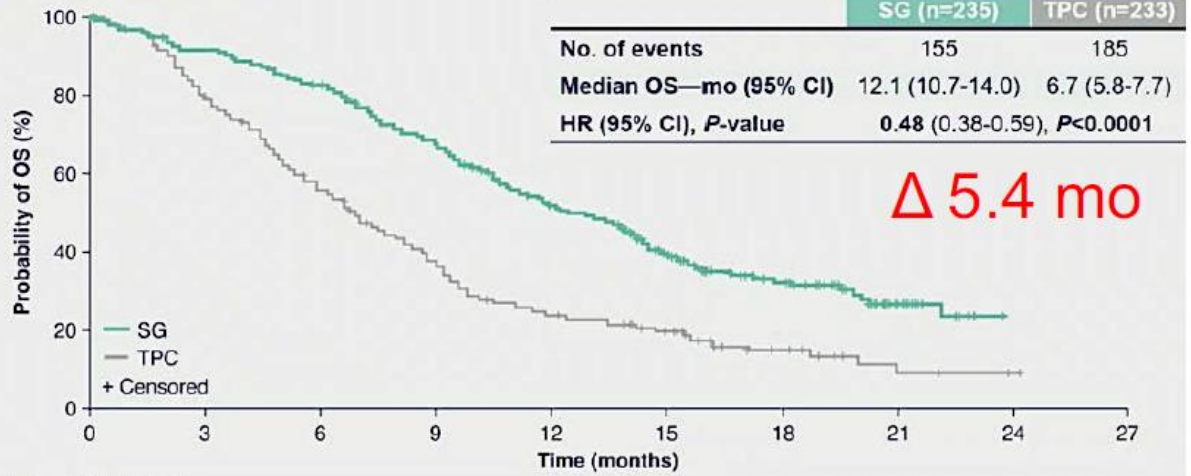
BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

TPC 1.7 mo

Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Δ 5.4 mo

Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

SG was well tolerated with manageable safety profile

- AE leading to treatment discontinuation 4.7%
- No severe cardiotoxicity
- No grade >2 neuropathy
- No grade >3 interstitial lung disease

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Conclusions

- Chemo: has it a role in MBC strategy? Yes….
- But
  - No evidence regarding its efficacy after ADCs (>ADCs sequences)
  - Will new ADCs and target therapies replace chemo?
  - ADCs are clearly winning in efficacy. But how much more tolerable are they?
  - First line: replacement by ADCs?
    - in HR+/HER2 low (Destiny 06)
    - in HR+/HER2 neg (Ascent 07)
    - in HER2 positive (Destiny 09)
    - In TN (ASCENT 03)