The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

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TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Dr Abou-Alfa*

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Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

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Breast Cancer Faculty

Matthew P Goetz, MD
Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Enterprise Deputy Director, Translational Research
Director, Mayo Clinic Breast Cancer SPORE
Mayo Clinic
Rochester, Minnesota

Ian E Krop, MD, PhD
Associate Director, Clinical Research
Director, Clinical Trials Office
Chief Clinical Research Officer
Yale Cancer Center
New Haven, Connecticut

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Breast Cancer Agenda

MODULE 1: HER2-Positive and HER2-Low Disease

MODULE 2: ER-Positive, HER2-Negative Disease

MODULE 3: Triple-Negative Disease

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Breast Cancer Agenda

MODULE 1: HER2-Positive and HER2-Low Disease

MODULE 2: ER-Positive, HER2-Negative Disease

MODULE 3: Triple-Negative Disease

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Discussion Questions

- How are you interacting with your pathologists to assist in optimizing HER2 testing, particularly related to the identification of HER2-low tumors?

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New approaches to managing HER2-low breast cancer and HER2+ CNS disease

Ian Krop MD PhD

October 2022

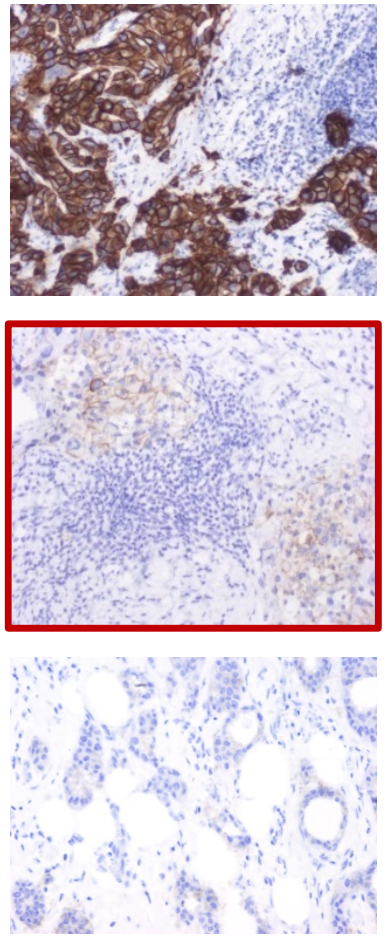
Prevalence of HER2-low Breast Cancer (IHC 1+/2+, FISH negative)

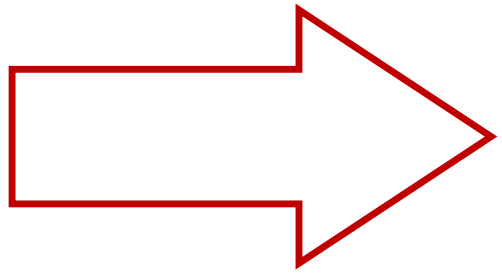
HER2 IHC examples

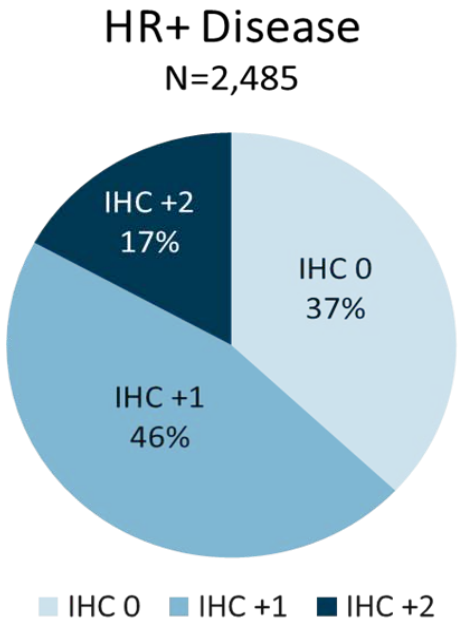
HER2+

HER2-low

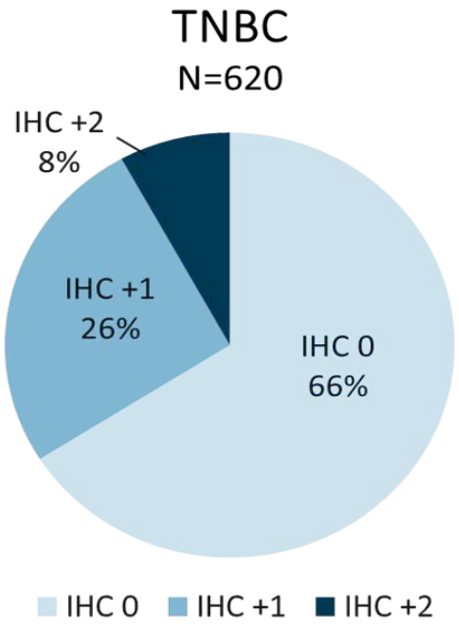
HER2-







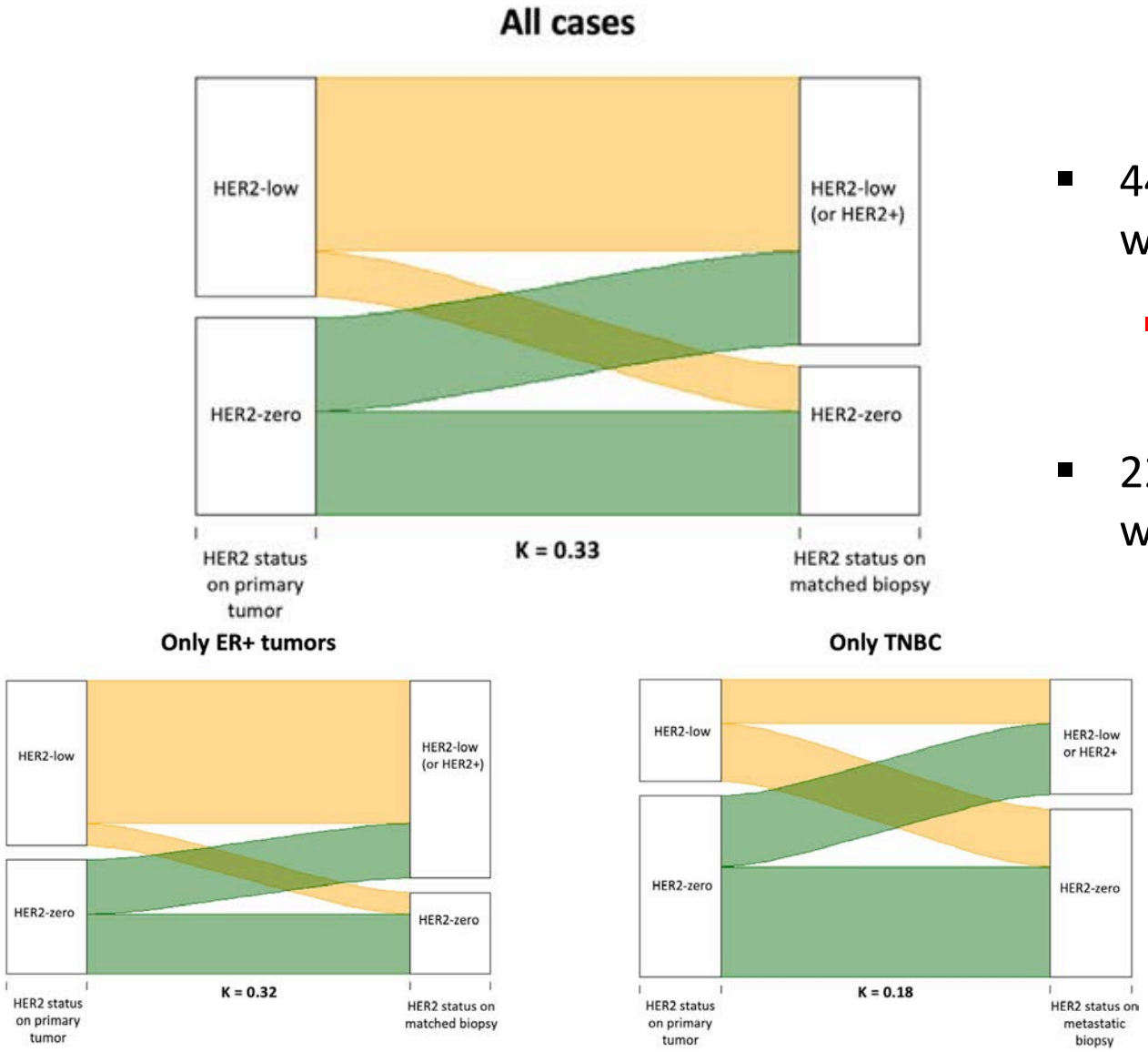
63% HER2 Low



34% HER2 Low

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

Evolution of HER2-low Between Primary and Metastatic Breast Cancer



- 44% of pts with HER2-zero primary cancer were HER2-low (or HER2+) in metastatic bx
  - 54% of ER+ pts and 31% of TN pts became HER2-low
- 22% of pts with HER2-low primary cancer were HER2-zero in metastatic bx

Tarantino et al. European Journal of Cancer (2022) 163:35.

Does HER2-low breast cancer have clinical significance?

- Does HER2 low expression predict sensitivity to HER2-therapy?

B-47: Adjuvant Trastuzumab in Patients with HER2 low Breast Cancer

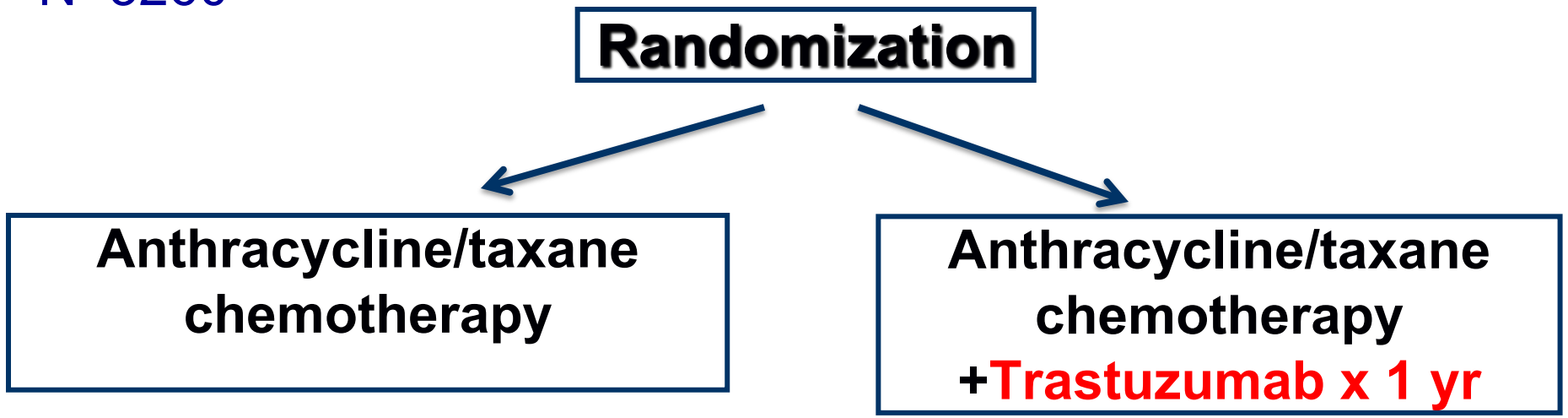
High Risk Primary Breast Cancer

IHC 1+ or 2+ for HER2

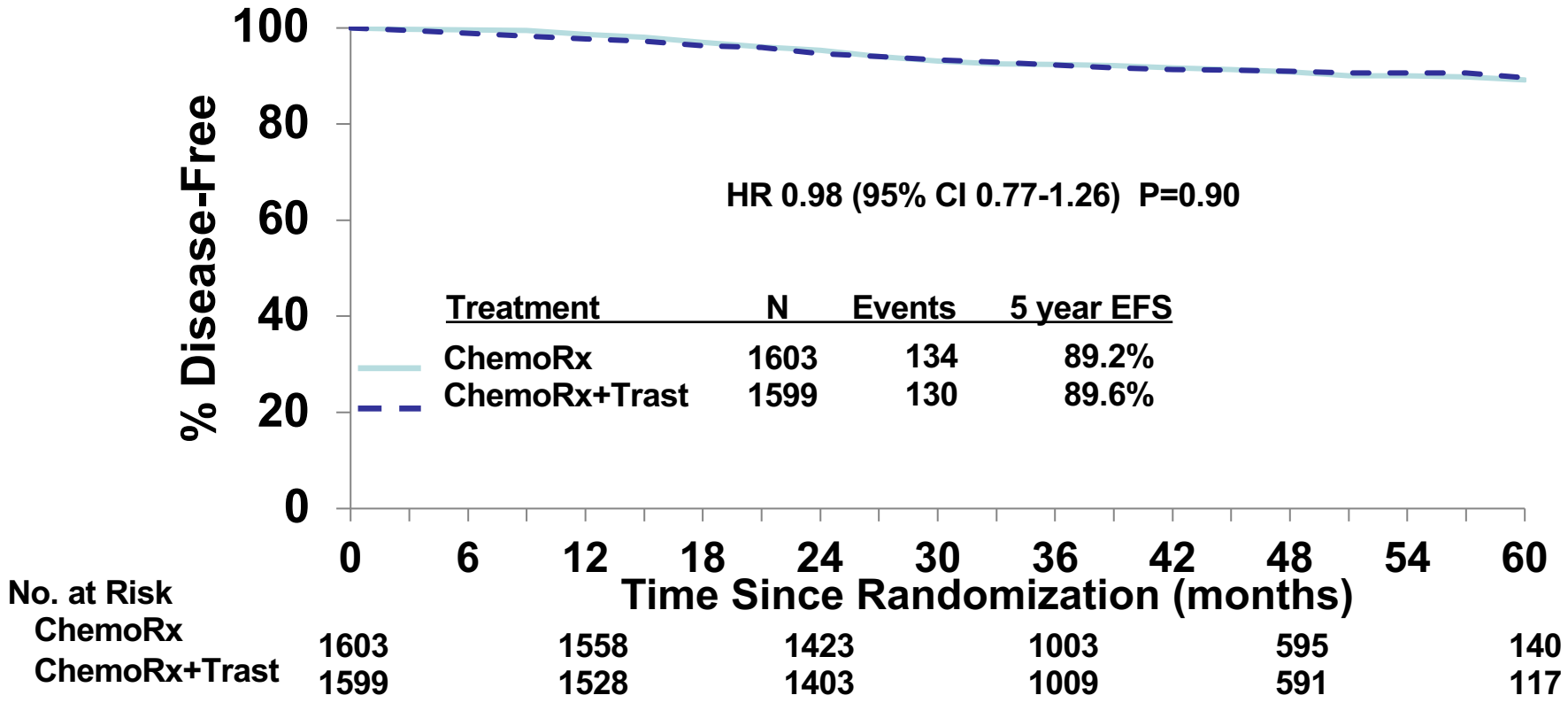
FISH Negative

(and HER2 copy number<4)

N=3260



B-47: Invasive Disease-Free Survival



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Does HER2-low breast cancer have clinical significance?

- Does HER2 low expression predict sensitivity to HER2-therapy?

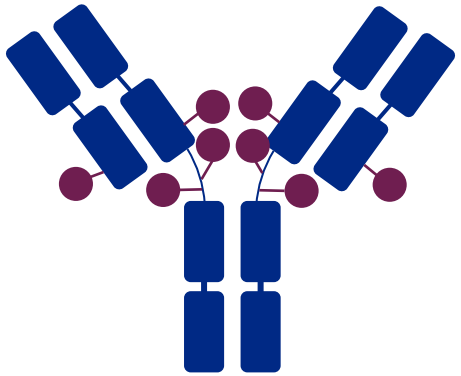
Does HER2-low breast cancer have clinical significance?

- Does HER2 low expression predict sensitivity to HER2-therapy?

NO

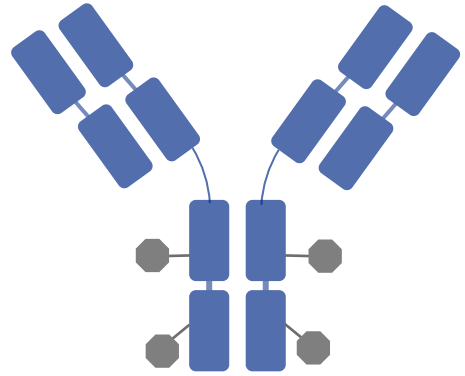
Trastuzumab deruxtecan: a 2nd generation HER2-targeted ADC

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

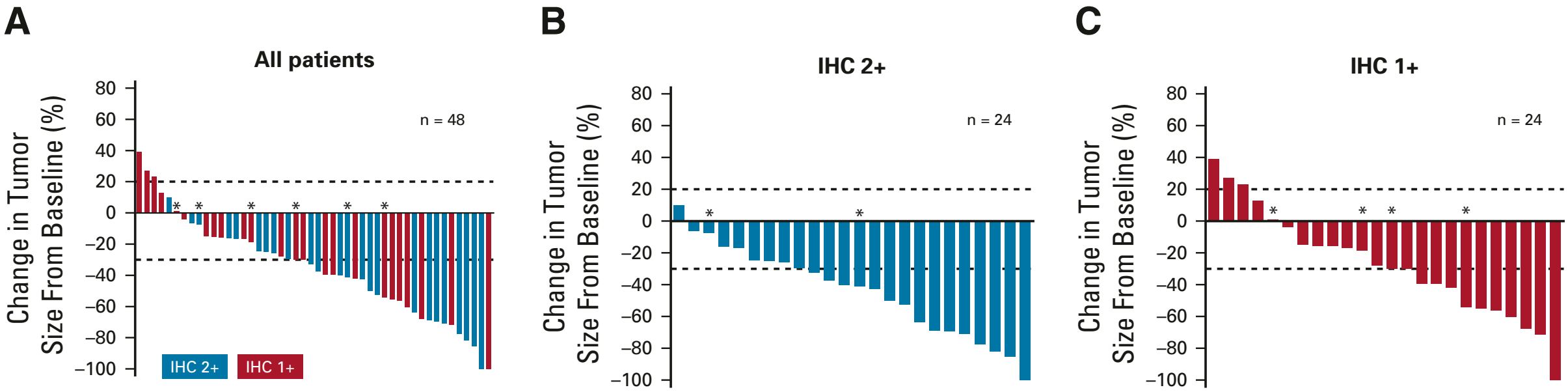
Trastuzumab emtansine (T-DM1)[5]



Adapted from J Cortes et al, ESMO 2021

Effect of trastuzumab deruxtecan in heavily pretreated* HER2-low metastatic breast cancer

Similar Benefit for HER2 2+ and 1+



ORR=37%

ORR=35.7%

ORR=38.5%

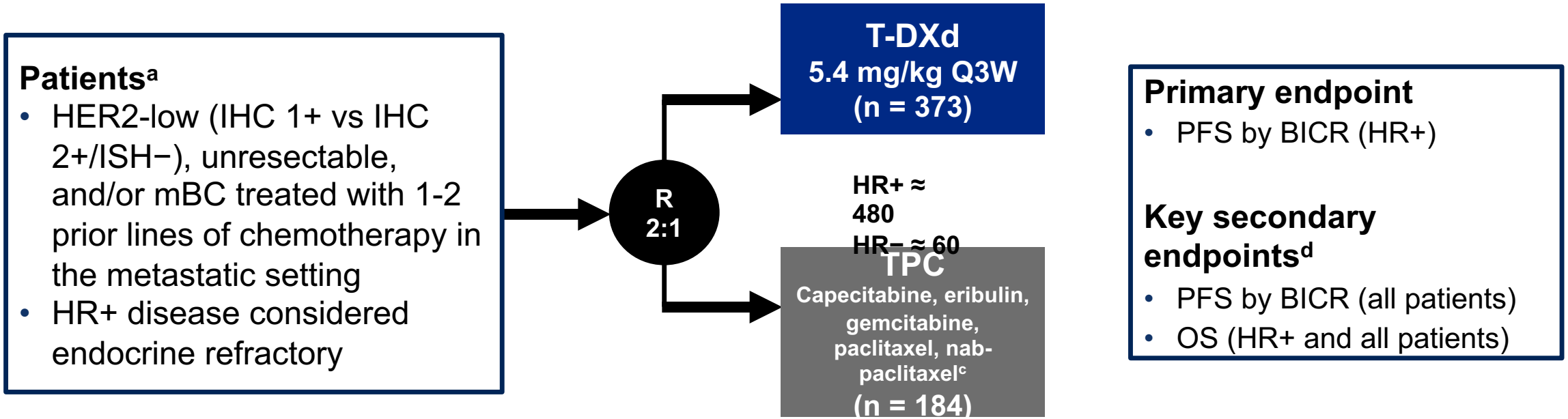
mPFS= 11.1 mo

***median of 7.5 prior regimens**

Modi S et al, JCO 2020

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR−

BICR, blinded independent central review; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. [c]TPC was administered accordingly to the label. [d]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint.

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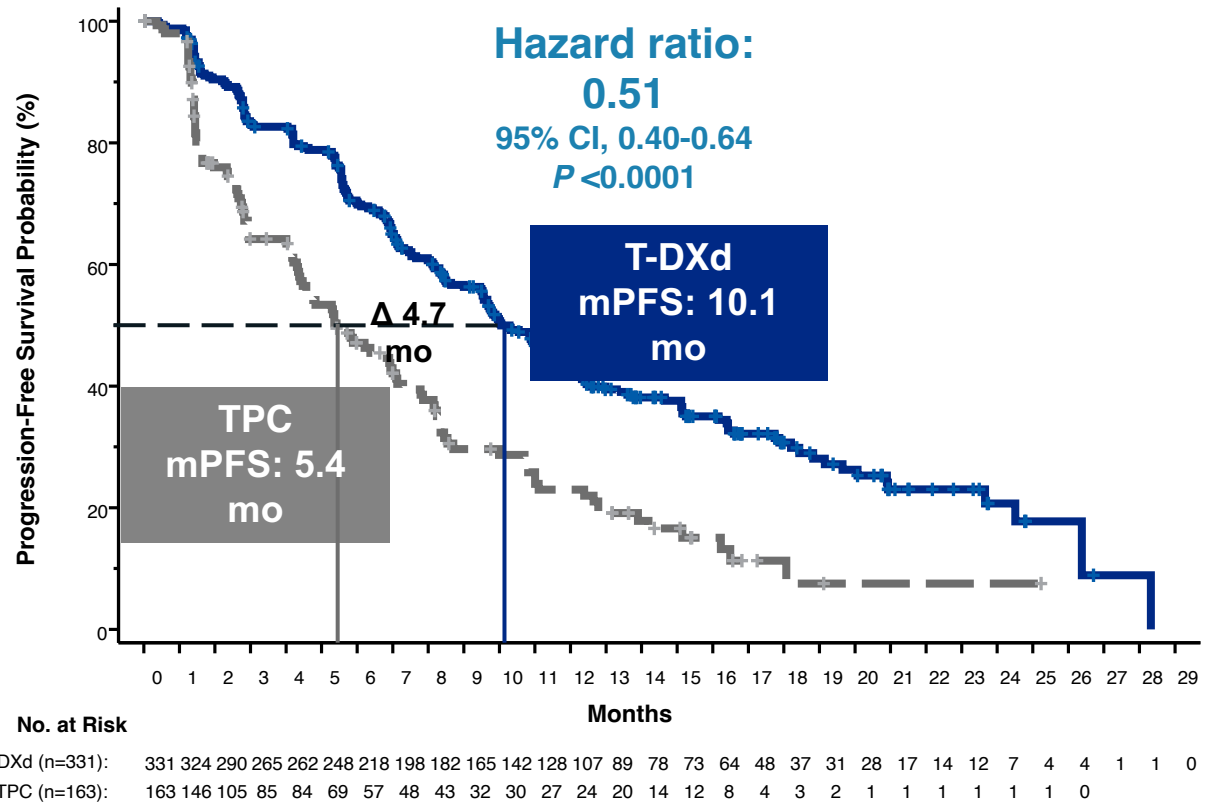
PFS in HR+ and All Patients

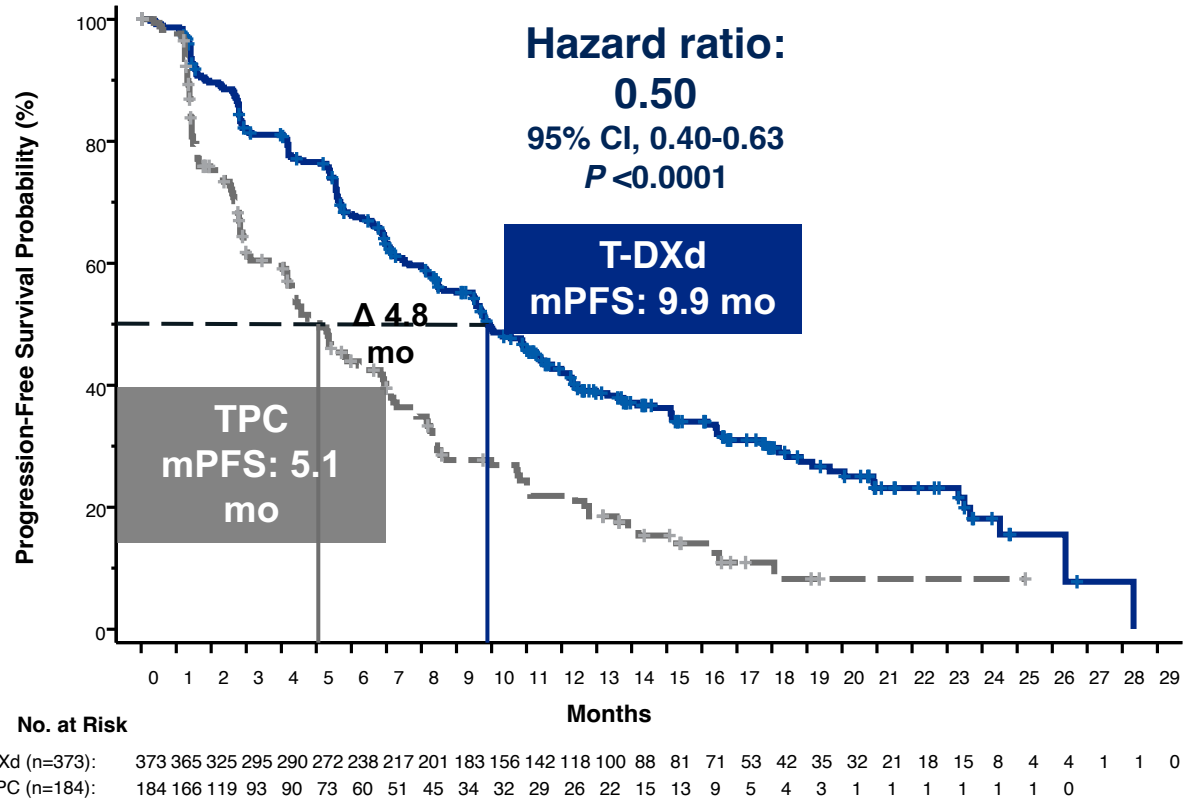
Hormone receptor-positive



No. at Risk

T-DXd (n=331):	331	324	290	265	262	248	218	198	182	165	142	128	107	89	78	73	64	48	37	31	28	17	14	12	7	4	4	1	1	0
TPC (n=163):	163	146	105	85	84	69	57	48	43	32	30	27	24	20	14	12	8	4	3	2	1	1	1	1	1	1	0			

All patients



No. at Risk

T-DXd (n=373):	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	0
TPC (n=184):	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	0			

PFS by blinded independent central review.

HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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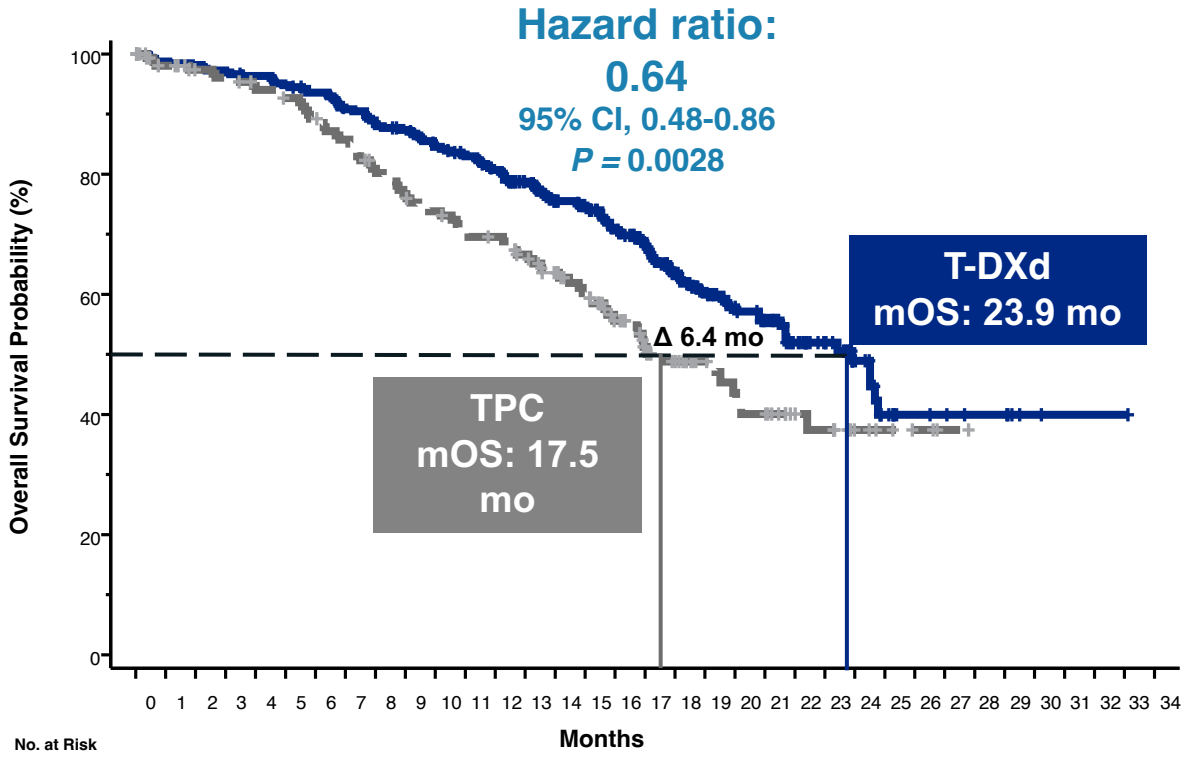
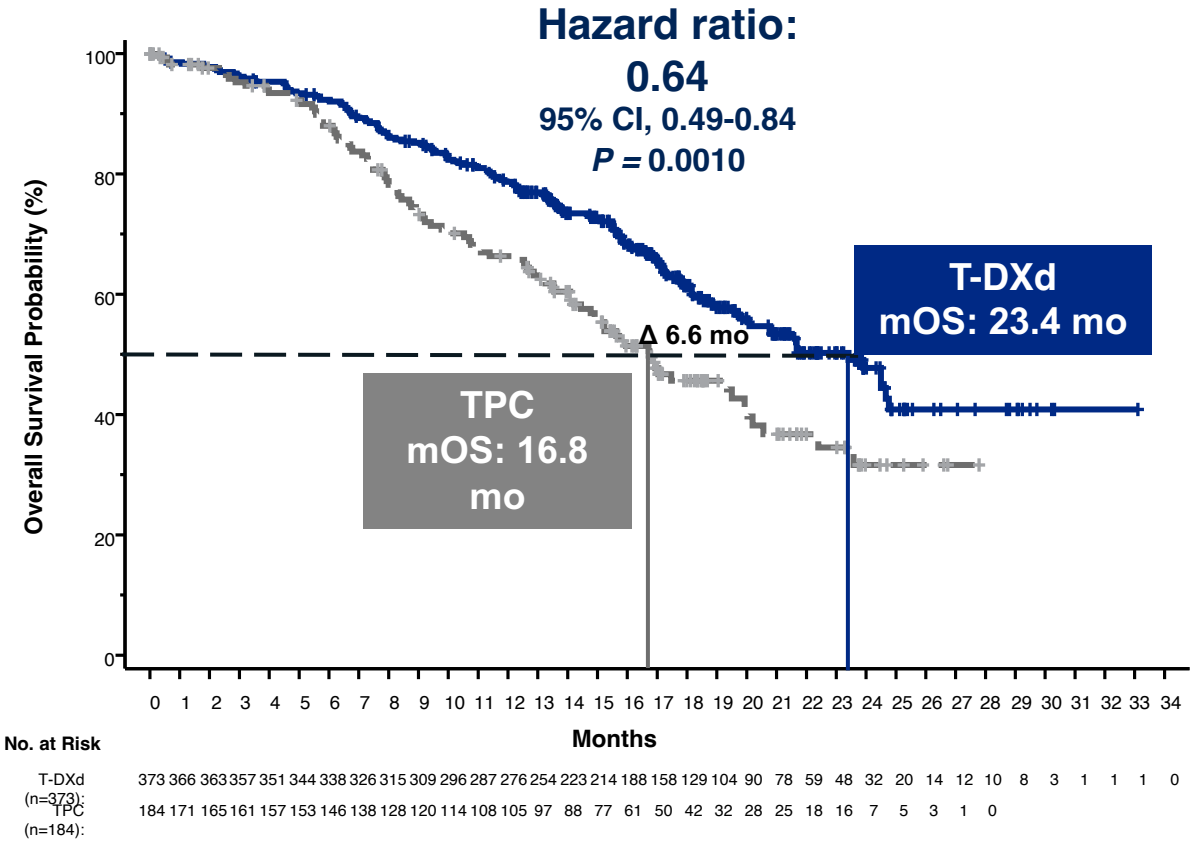
OS in HR+ and All Patients

Hormone receptor-positive



All patients



HR, hormone receptor; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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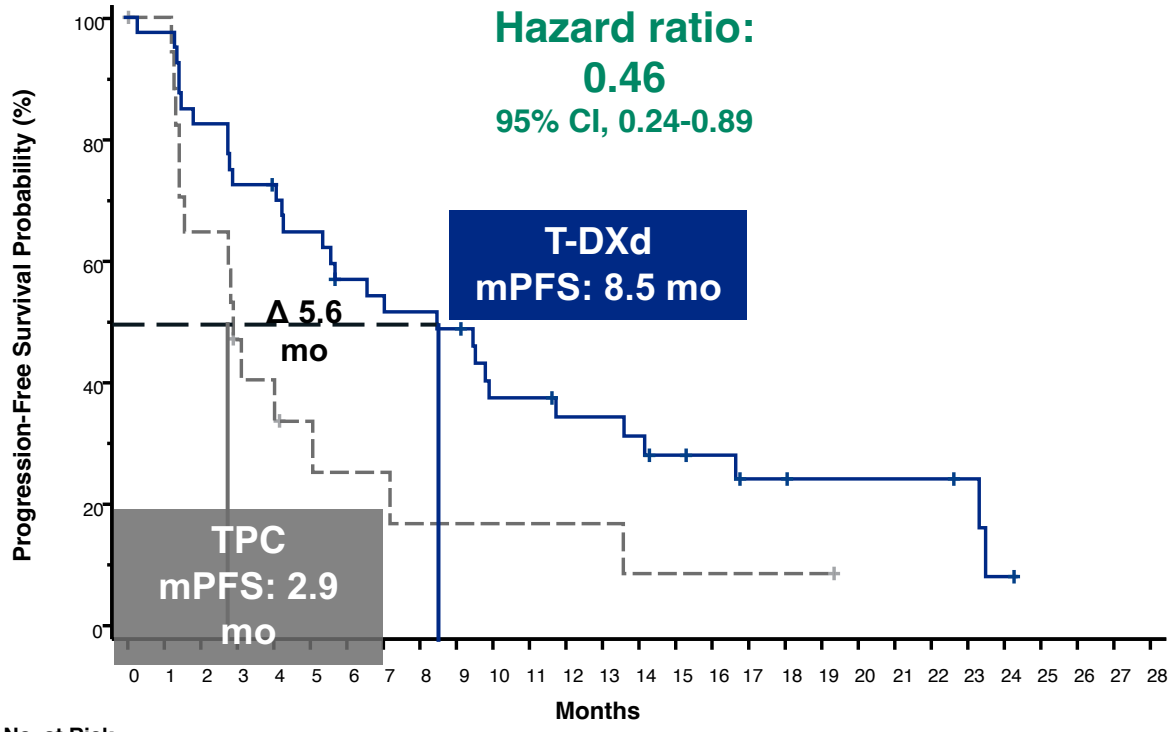
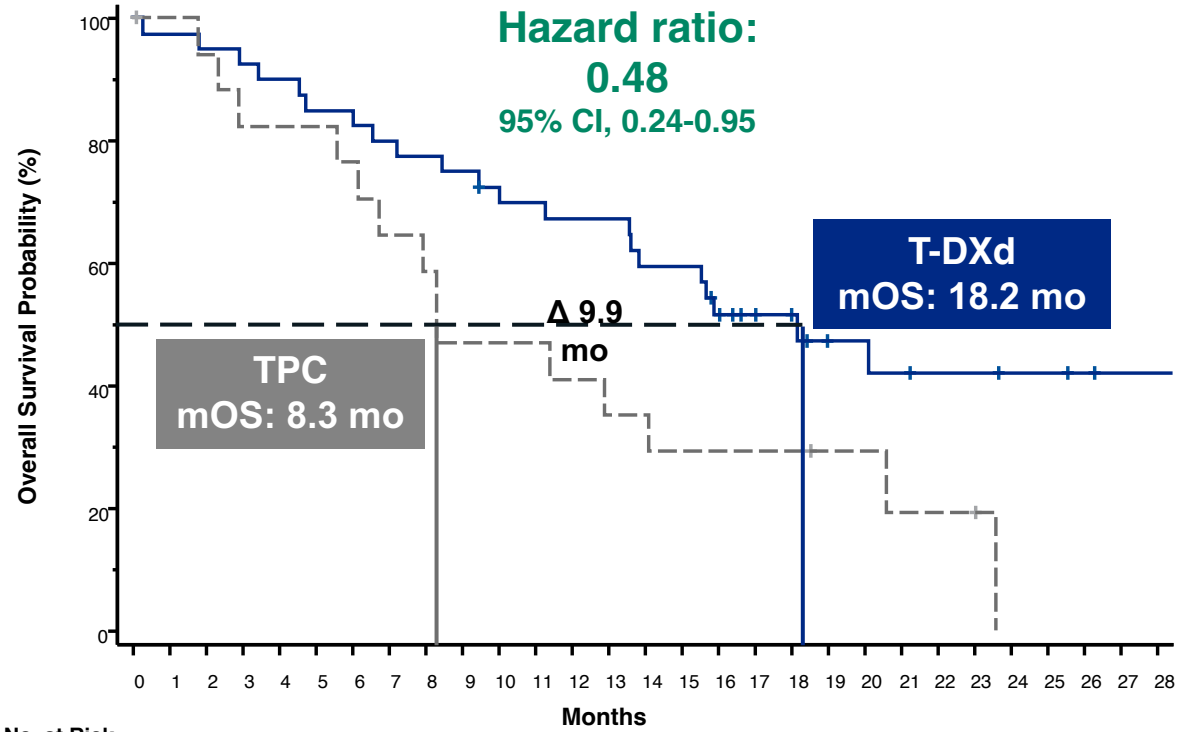
PFS and OS in HR− (Exploratory Endpoints)

Hormone receptor-negative





HR, hormone receptor; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor negative cohort, hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.

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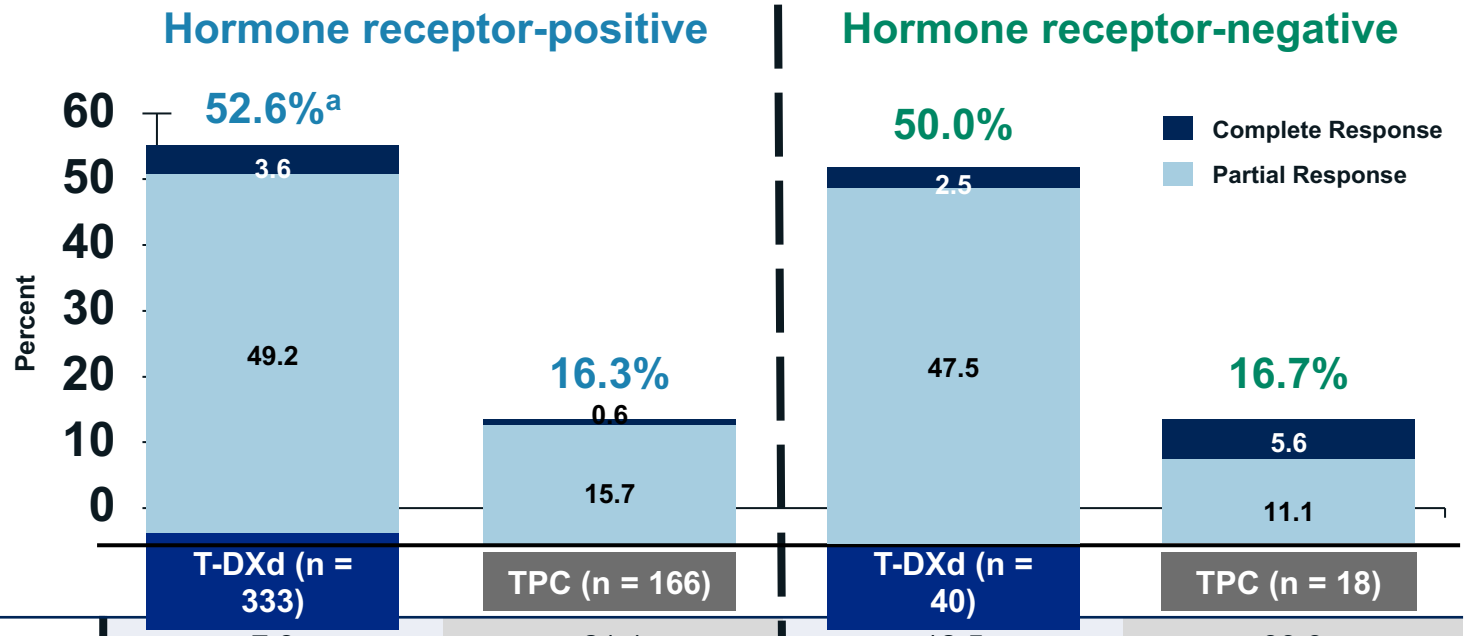
Confirmed ORR

Confirmed Objective Response Rate



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive Disease, %	7.8	21.1	12.5	33.3
Not Evaluable, %	4.2	12.7	7.5	5.6
Clinical Benefit Rate[b], %	71.2	34.3	62.5	27.8
Duration of Response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.
[a]The response of one patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded central independent review.

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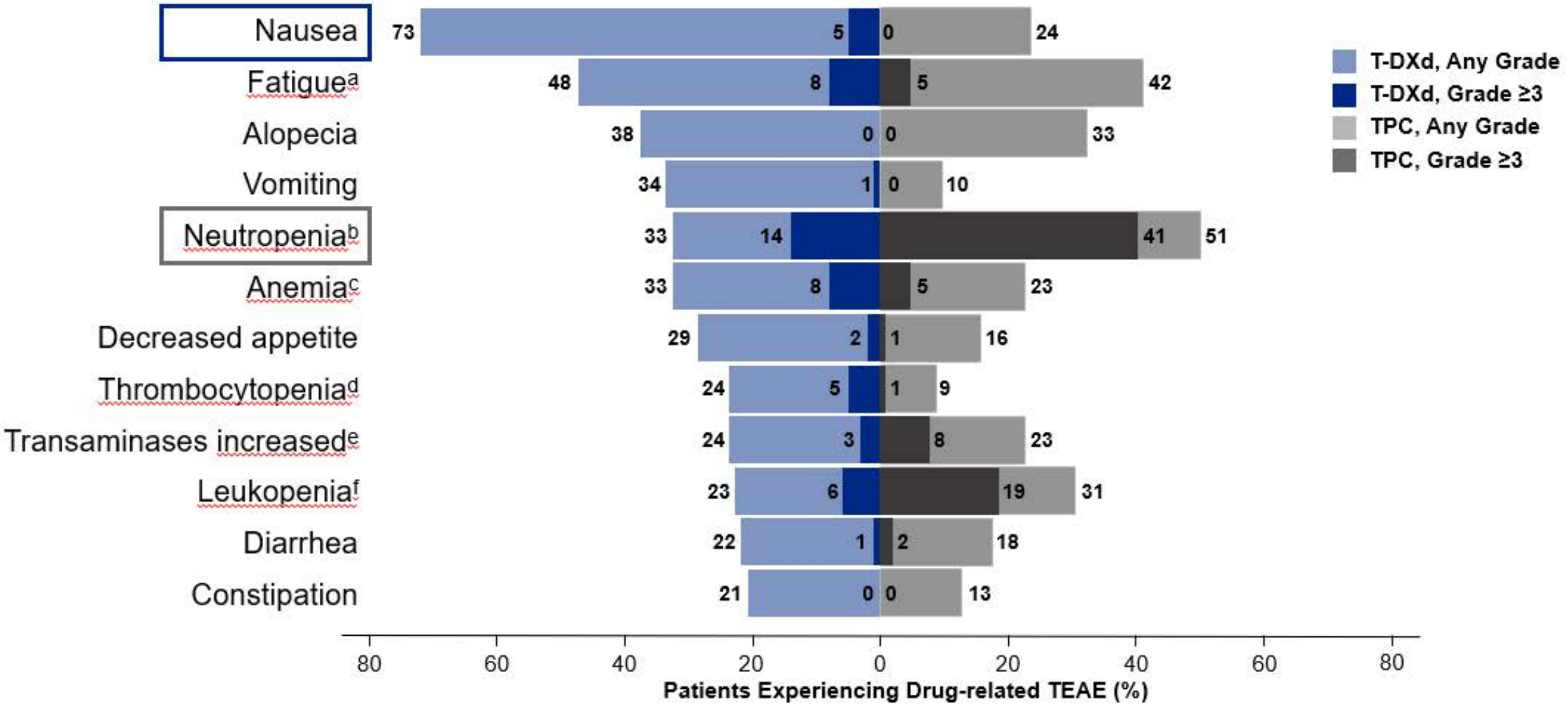
Drug-Related TEAEs in ≥20% of Patients (Safety Analysis Set)



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment with physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

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Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

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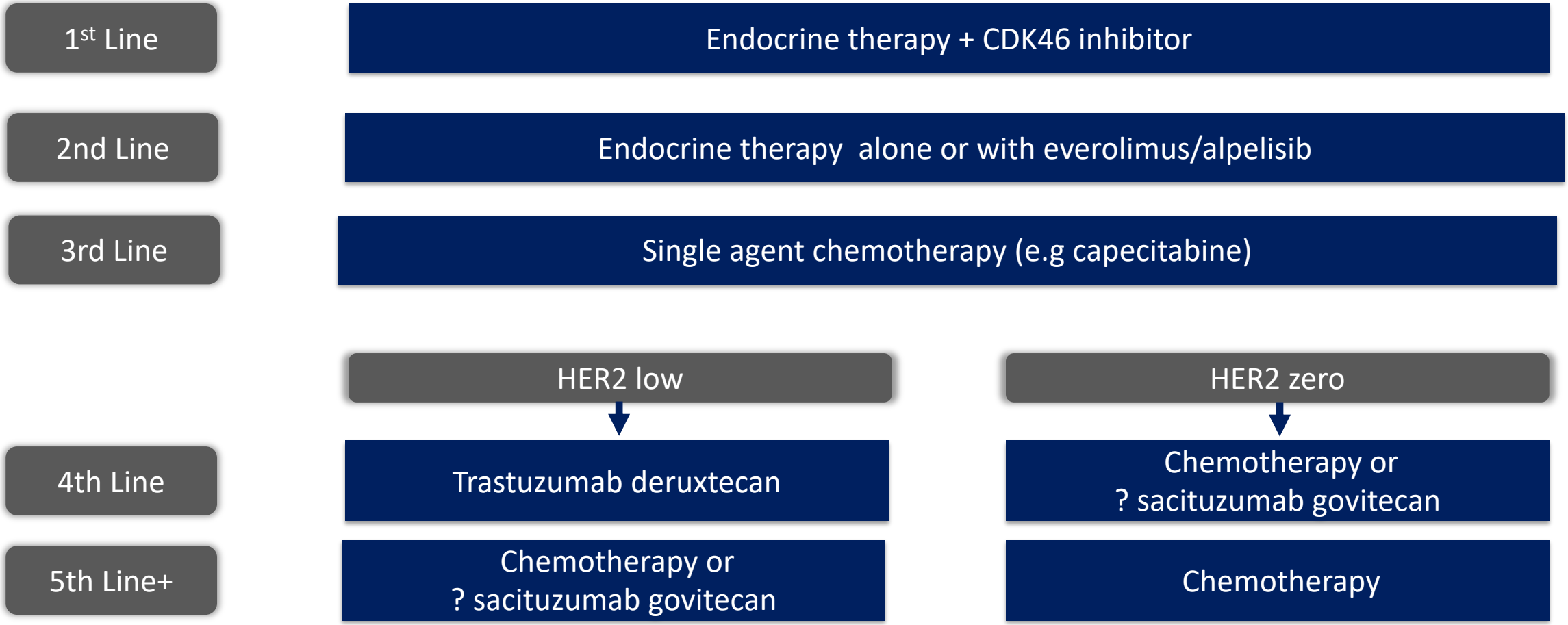
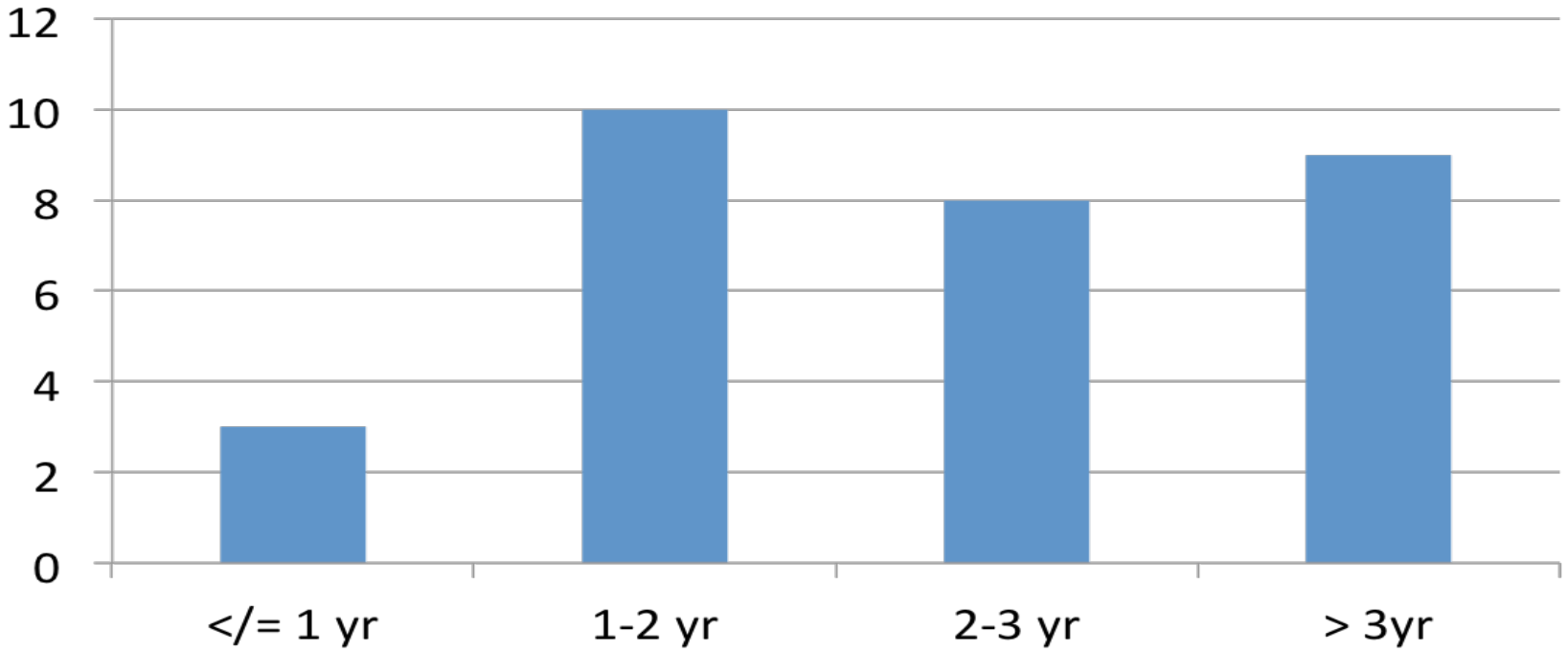
Approach to Therapy for Metastatic Hormone Receptor Positive Breast Cancer



CNS Disease is Frequent in HER2+ MBC

- 30-50% incidence—risk continues over time



Of N=64 patients alive ≥3 yrs from HER2+ MBC diagnosis, the number of patients who developed new brain metastases in each time interval

Olson et al, under review; Brufsky et al, CCR 2011; Lin et al, JCO 2008; Lin et al, CCR 2009; Boccardo et al, ASCO 2008; Sutherland et al, Br J Ca 2010; Metro et al, Ann Oncol 2011; Lin et al J Neurooncol 2011; Bachelot et al, ASCO 2011

Management options for HER2+ CNS disease

- Radiation is typically first line modality for HER2+ brain mets
  - SRS preferred
    - Only for limited number of lesions
  - Whole brain RT effective but goal to delay as long as possible to minimize cognitive toxicity
- Surgery occasionally used
  - Solitary lesions
  - Large, highly symptomatic lesions
  - When diagnosis unclear

Tucatinib – A Potent & Selective HER2 Inhibitor

- Selective small molecular tyrosine kinase inhibitor with nanomolar potency
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
  - Phase 1 single agent data had no treatment-related g3 diarrhea in heavily pretreated patients
- Penetrates CNS very well

Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
Lapatinib	49	31
Neratinib	7	8
Tucatinib	**8**	**>10,000**

Moulder et al. AACR-NCI-EORTC 2011; Koch et al. AACR 2011

Slide adapted from S Tolaney ASCO 2018

HER2CLIMB Trial Design

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

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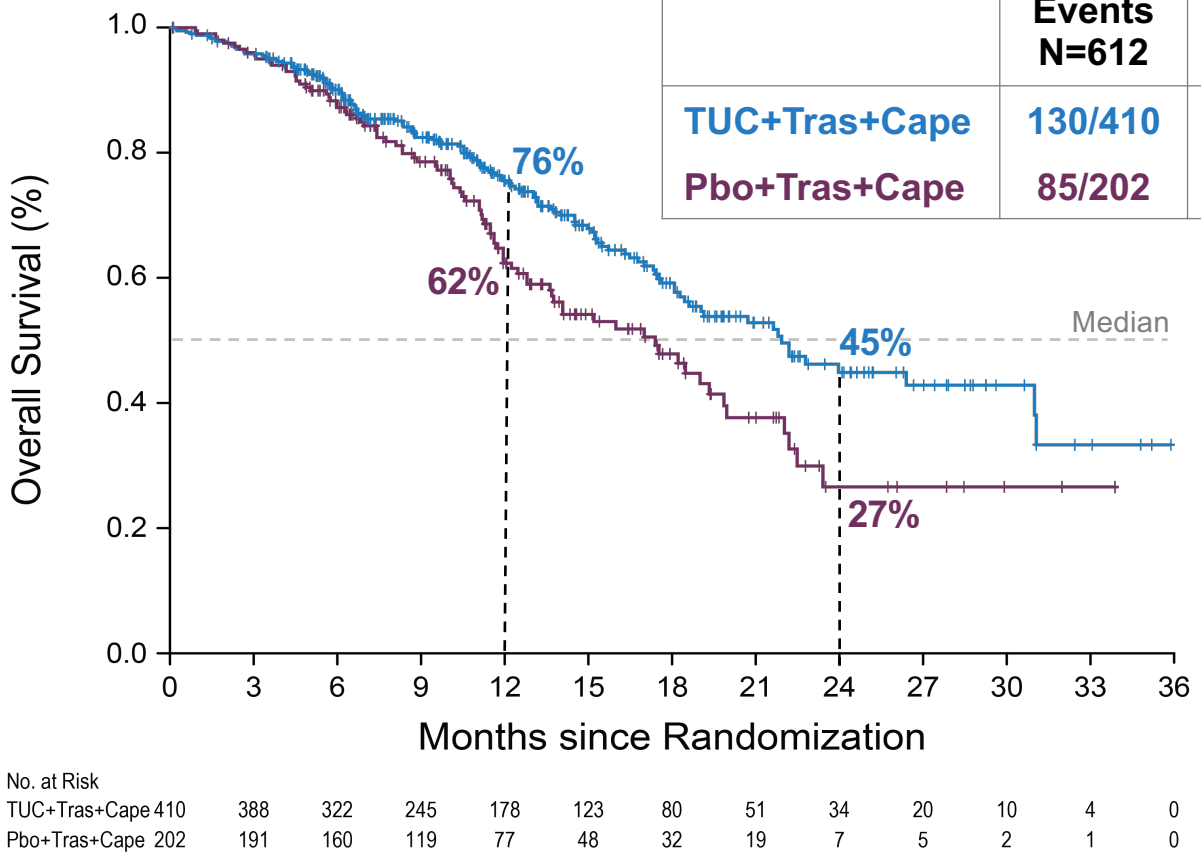
Overall Survival in the Total Study Population



	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		

Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC+Tras+Cape	**Pbo+Tras+Cape**
45%	**27%**
(37, 53)	**(16, 39)**
Median OS (95% CI):	
21.9 months	**17.4 months**
(18.3, 31.0)	**(13.6, 19.9)**

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

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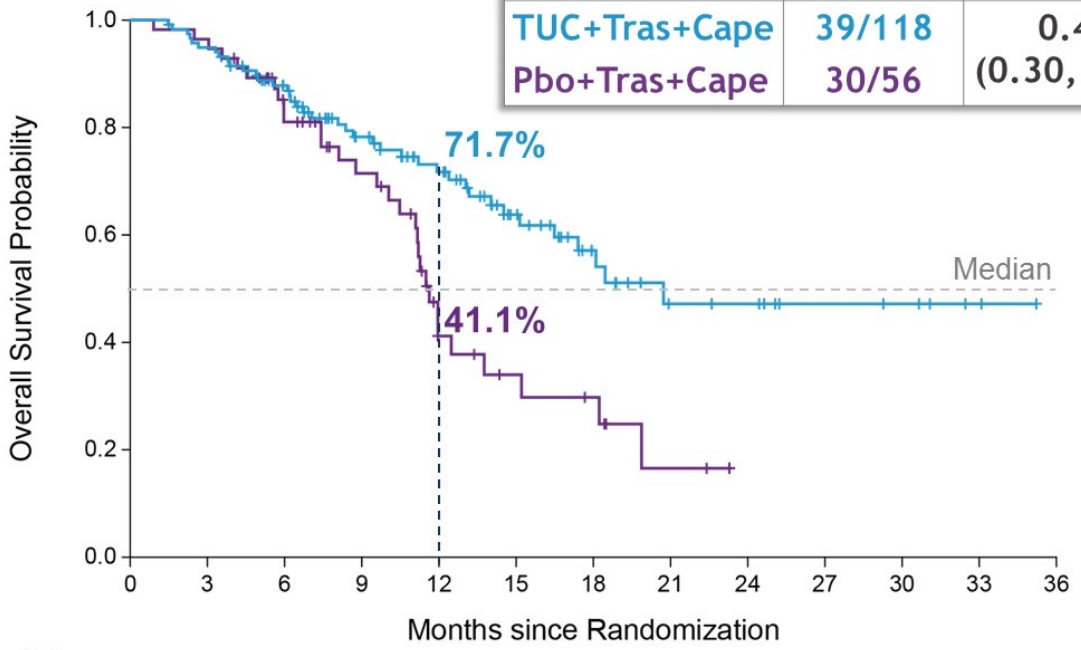
OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
71.7% (61.4, 79.7)	41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

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PRESENTED BY: Nancy Lin, nlin@partners.org

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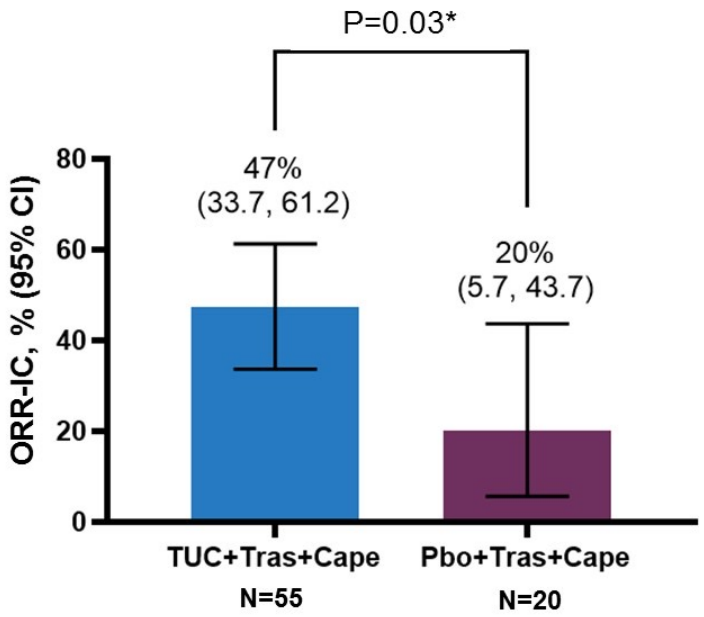
Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

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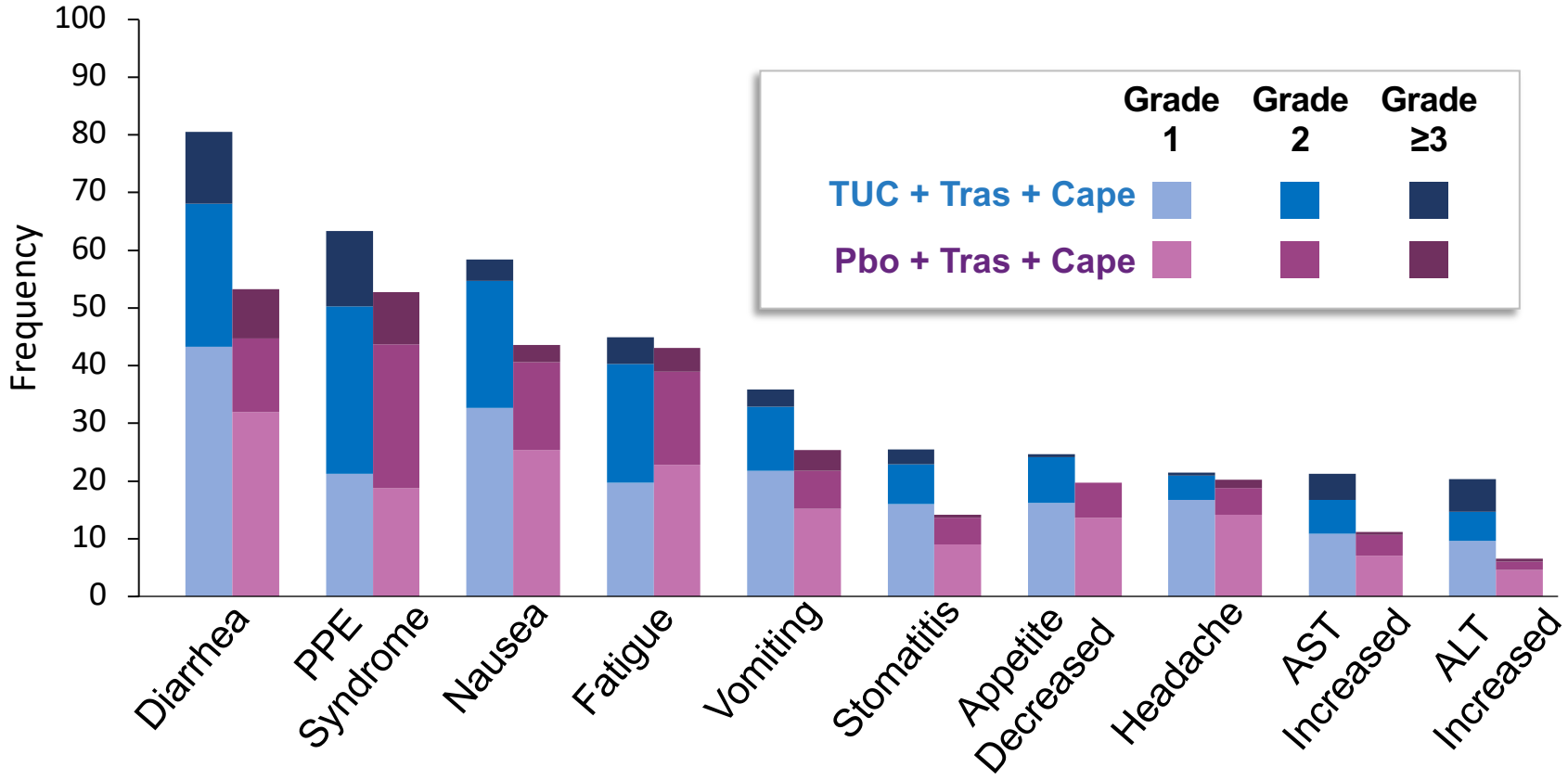
Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

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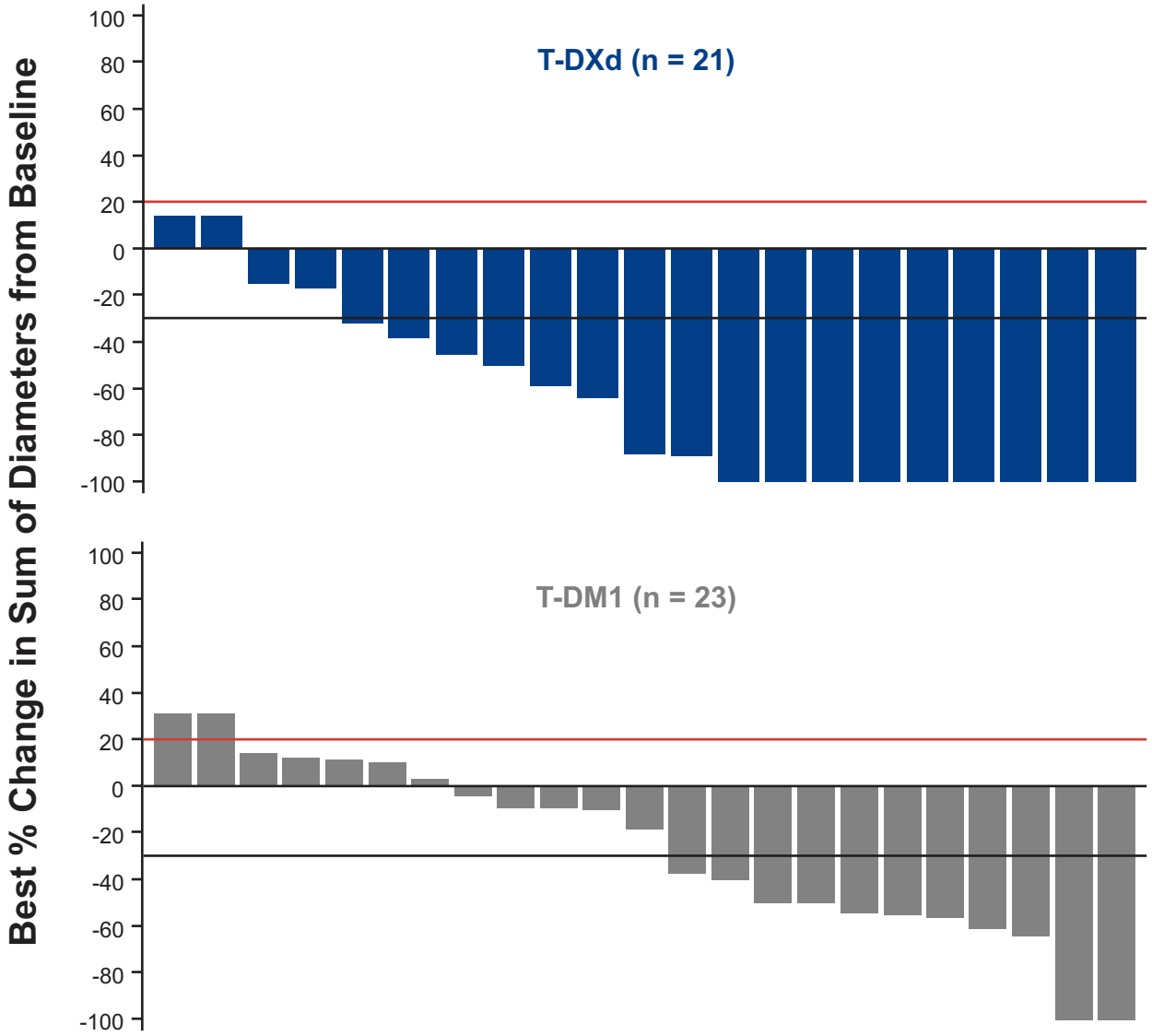
Unanswered questions in HER2+ MBC

- Does trastuzumab deruxtecan have activity in HER2+ brain metastases?

Intracranial Response per BICR using RECIST 1.1



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

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Trastuzumab Deruxtecan in patients with progressive brain metastases

- Tuxedo study
  - Newly diagnosed HER2+ BM or progression after prior local therapy
  - Interim results: Intracranial response (RANO BM) in 5 of 6 pts (83.3%)

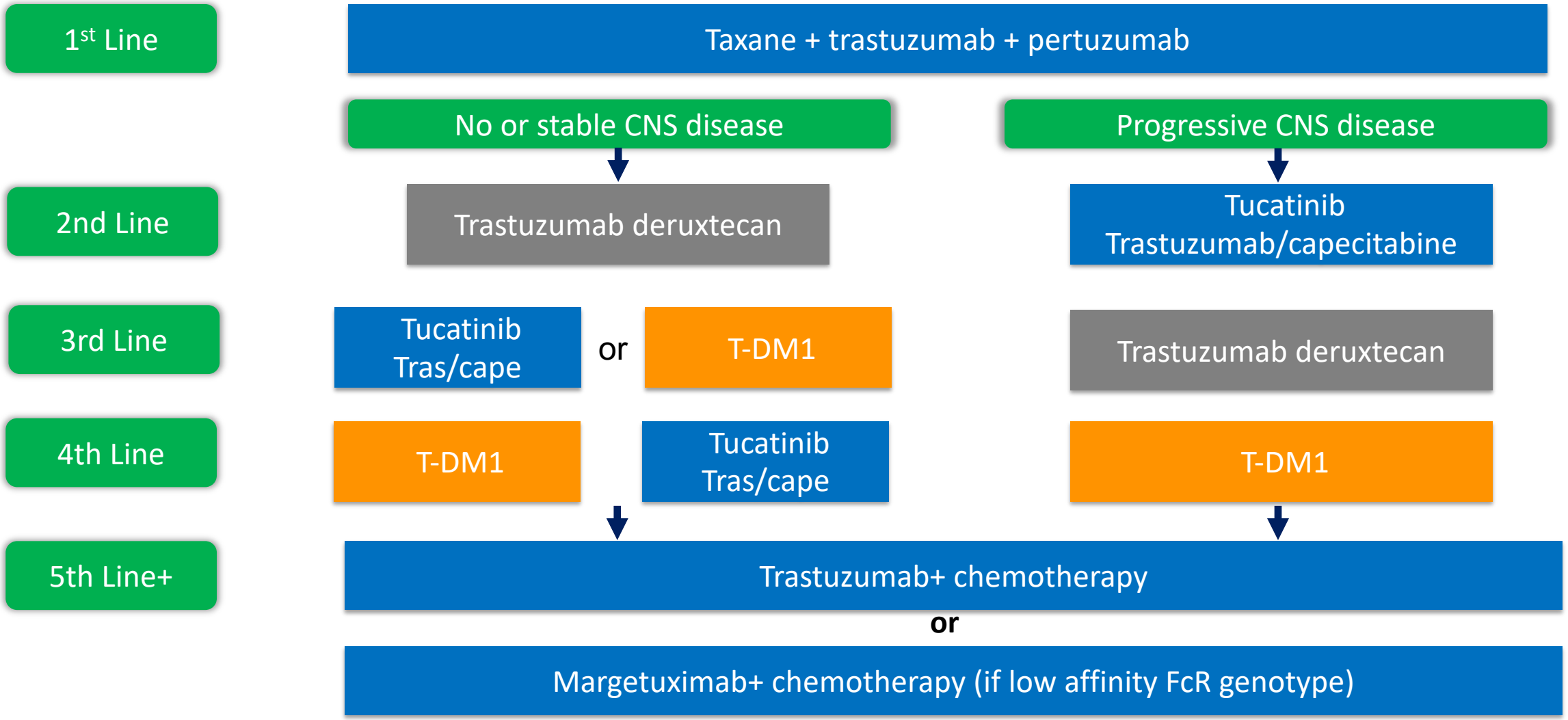
- DEBBRAH study
  - HER2+ or HER2 low with progression after local therapy
  - Interim results: Intracranial response (RANO BM) in 4 of 9 pts (44.4%)

- Case series
  - Newly diagnosed HER2+ BM or progression after prior local therapy
  - CNS objective response in 7 of 10 pts (70%)

Bartsch et al, ESMO 2021,
Vaz Batista et al, SABCS 2021
Kabraji et al, SABCS 2021

What if the patient did not have brain mets?

Approach to Therapy for Metastatic HER2+ disease



Adapted from Modi et al, ESMO 2021

Summary

- HER2low breast cancer is common and represents ~50-55% of all breast cancer
- DB-04 study shows T-DXd offers significantly improved efficacy compared to chemotherapy in patients with 2nd-3rd line HER2low MBC
  - FDA approved for HER2 low MBC after 1 prior chemotherapy
  - ILD is potential risk that requires monitoring
  - Benefit likely not related to HER2 inhibition, but rather due to the delivery of the cytotoxic payload
  - HER2-low status can be acquired in MBC, so critical to bx pts in metastatic setting to assess HER2 expression

Summary

- CNS disease is common in patients with HER2+ MBC
  - Systemic therapy with tucatinib/capecitabine/trastuzumab has clearly demonstrated efficacy in pts with progressive brain mets
  - Systemic therapy may be considered with goal to delay use of whole brain RT
  - In small studies, trastuzumab deruxtecan appears to have efficacy in progressive brain mets and more research is needed to confirm its role in this population

Later-Line Therapy for HER2-Positive Metastatic Breast Cancer; Management of Interstitial Lung Disease

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Discussion Questions

- In which situations, if any, would you prefer to use T-DXd before chemotherapy in HER2-low disease?
- Is there a role for T-DXd in HER2 IHC 0 mBC? What about HER2-mutant disease?
- What preemptive scanning or other evaluation, if any, is indicated in patients receiving T-DXd?
- What are the indications to hold T-DXd for ILD, and in which situations, if any, can it be restarted?
- What is the optimal second-line treatment for HER2-positive mBC, and how does CNS disease play a role?

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Discussion Questions

- How do you manage diarrhea in a patient receiving tucatinib/trastuzumab/capecitabine?
- In which situations are you comfortable using systemic treatment (eg, tucatinib) without radiation therapy for brain metastases?
- For a patient who has a systemic response to first-line taxane/pertuzumab/trastuzumab and then develops new brain metastases without systemic progression, would you continue the taxane/pertuzumab/trastuzumab or switch therapy?

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N Engl J Med 2022 March 24;386(12):1143-54.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

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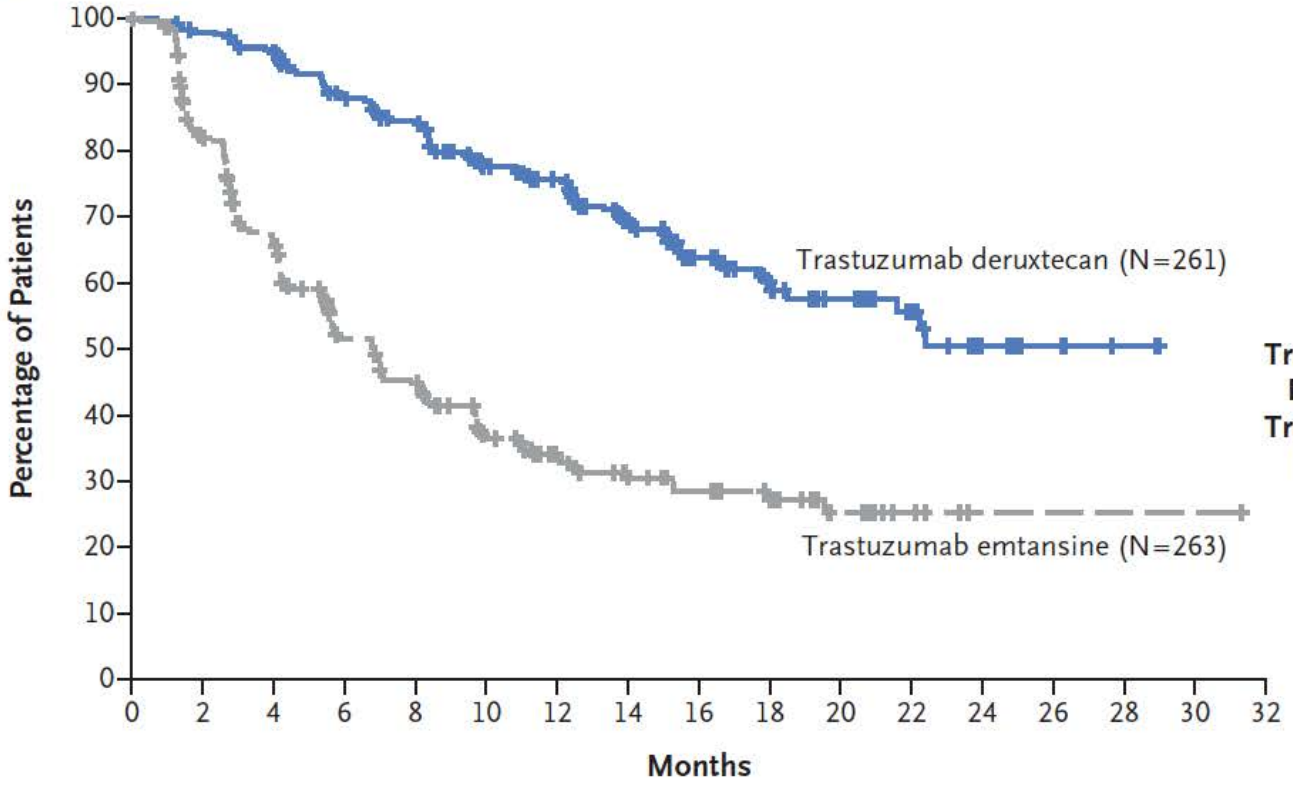
DESTINY-Breast03: Progression-Free Survival



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

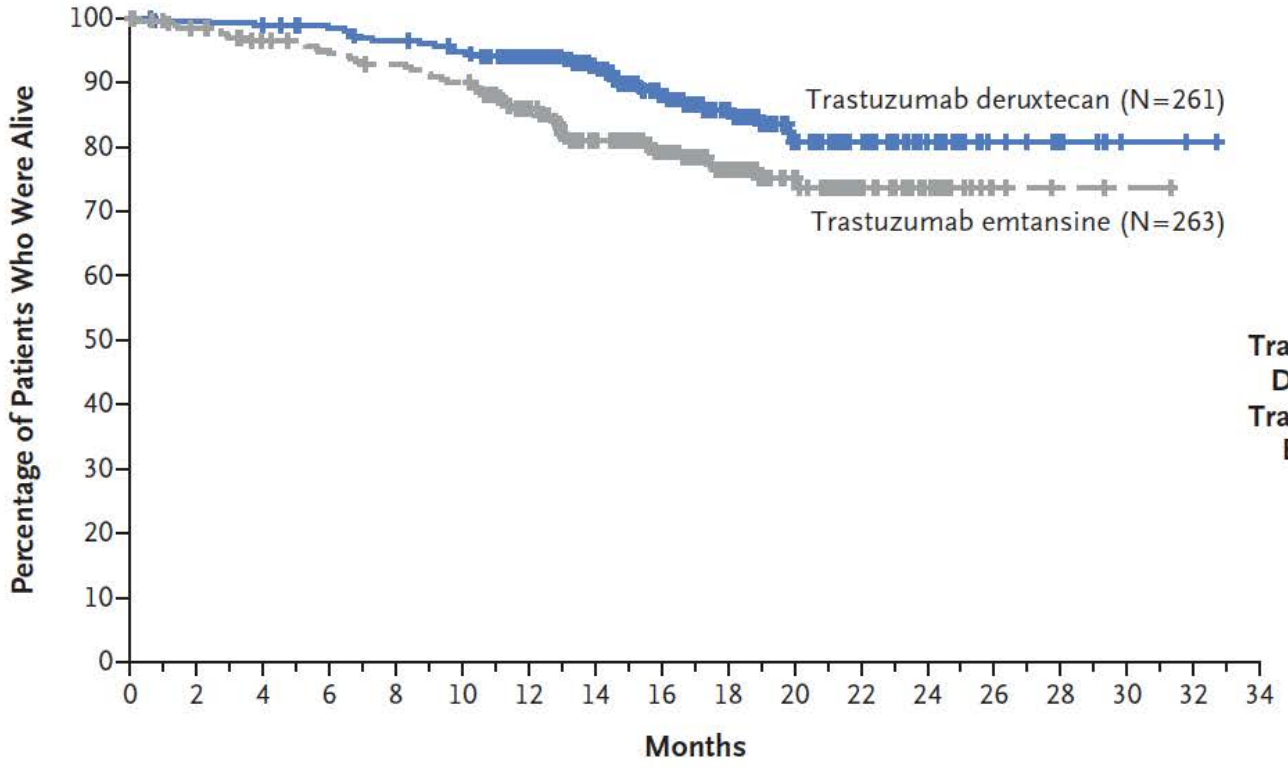
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

No. at Risk

Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	0

Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

DESTINY-Breast03: First Interim Analysis of Overall Survival



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

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DESTINY-Breast03: Safety Update Overview

n (%)	T-DXd n = 257	T-DM1 n = 261
Patients discontinued from study treatment	141 (54.9)	222 (85.1)
Any grade TEAE	256 (99.6)	249 (95.4)
Grade ≥3 TEAE	137 (53.3)	130 (49.8)
Any grade serious TEAE	54 (21.0)	50 (19.2)
Grade ≥3 serious TEAE	39 (15.2)	38 (14.6)
TEAE associated with drug discontinuation	38 (14.8)	19 (7.3)
TEAE associated with dose reduction	59 (23.0)	36 (13.8)

- Rates of TEAEs (any grade and grade ≥3) and serious TEAEs were similar between the T-DXd and T-DM1 arms
- TEAEs associated with drug discontinuation occurred in 38 patients (14.8%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm

TEAE = treatment-emergent adverse event

Hamilton E et al. ASCO 2022;Abstract 1000.

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DESTINY-Breast03: Adjudicated Drug-Related ILD/Pneumonitis

	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

For this safety update:

- Majority of adjudicated ILD/pneumonitis cases were low grade and no new grade 4 or 5 events occurred in either treatment arm
- One additional grade 2 adjudicated drug-related ILD/pneumonitis occurred
- The majority of events resolved with ongoing follow-up

Hamilton E et al. ASCO 2022;Abstract 1000.

RTP RESEARCH TO PRACTICE

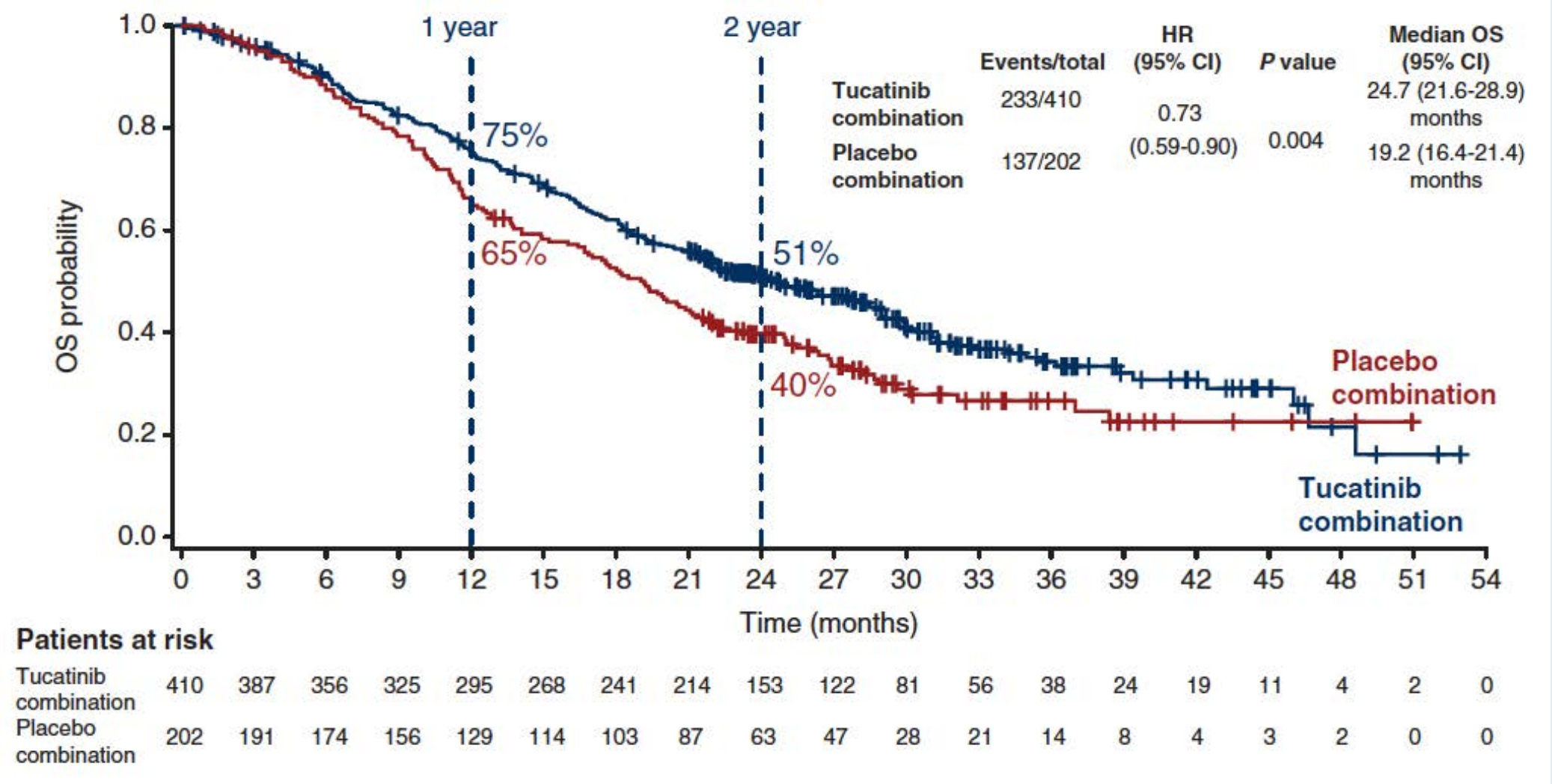
Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis

G. Curigliano[1*], V. Mueller[2], V. Borges[3], E. Hamilton[4], S. Hurvitz[5], S. Loi[6], R. Murthy[7], A. Okines[8], E. Paplomata[9†], D. Cameron[10], L. A. Carey[11], K. Gelmon[12], G. N. Hortobagyi[7], I. Krop[13], S. Loibl[14], M. Pegram[15], D. Slamon[5], J. Ramos[16], W. Feng[16] & E. Winer[13]

Ann Oncol 2022 March;33(3):321-9.

RTP RESEARCH TO PRACTICE

HER2CLIMB: Final Overall Survival (OS) Analysis



	Events/total	HR (95% CI)	*P* value	Median OS (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	0.004	24.7 (21.6-28.9) months
Placebo combination	137/202			19.2 (16.4-21.4) months

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

Breast Cancer Agenda

MODULE 1: HER2-Positive and HER2-Low Disease

MODULE 2: ER-Positive, HER2-Negative Disease

MODULE 3: Triple-Negative Disease

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(Neo) Adjuvant treatment of HR+ and BRCA mutant Breast Cancer

Matthew Goetz, M.D.
Erivan K. Haub Family Professor of Cancer Research
Honoring Richard F. Emslander, M.D.
Professor of Oncology and Pharmacology
Department of Oncology
Mayo Clinic, Rochester, MN

Outline

- Treating patients based on an “adaptive” biomarker (Ki-67)
- Key efficacy and safety outcomes observed in the Phase III monarchE
- FDA approval of adjuvant abemaciclib with endocrine therapy and identification of appropriate patients for this strategy
- (Neo)Adjuvant PARP inhibitors

CDK 4/6i: PFS and OS Results from First Line Metastatic Trials

Trial	N=	CDK4/6i	Endocrine Therapy	Design & Population	PFS - Median (Months)	OS – Median (Months)	Comment
PALOMA 1	165	**Palbociclib (P)**	Letrozole (L)	Phase II Postmen	**10.2 (L)** vs **20.2 (L+P)** HR=0.49, P=0.0004	**33.3 (L)** vs **37.5 (P+L)** HR=0.813, P = 0.42	**OS - NS**
PALOMA 2	666	**Palbociclib (P)**	Letrozole (L)	Phase III Postmen	**14.5 (L)** vs **24.8 (L+P)** HR=0.58, P<0.001	**51.2 (L)** vs **53.9 (P+L)** (HR, 0.956, P=0.3378)	**OS - NS**
MONARCH 3	493	**Abemaciclib (A)**	NSAI	Phase III Postmen	**14.8 (A)** vs **28.2 (ET+ A)** HR=0.54, P=0.000002	2nd Interim Analysis: **54.3 (ET)** vs **67.1 (A+ ET)** (HR, 0.784, **P=0.0301**)*	**Final OS data pending**
MONALEESA 2	668	**Ribociclib (R)**	Letrozole (L)	Phase III Postmen	**16.0 (L)** vs **25.3 (L+R)** HR: 0.568	**51.4 (L)** Vs **63.9 (R+L)** (HR=0.76)	**OS advantage**
MONALEESA 7	672	**Ribociclib (R)**	ET (Tam or AI) + OFS	Phase III Pre & Perimen	**13.0** (ET+plac) vs **23.8** (R+ET) (HR: 0.55; p<0.0001)	**OS** at 42 M: **46.0%** (RT+Plac) vs **70.2%** (ET+R) (HR: 0.71; P=0.00973)	**OS advantage**

* At 2nd interim OS analysis, stopping boundary not crossed.

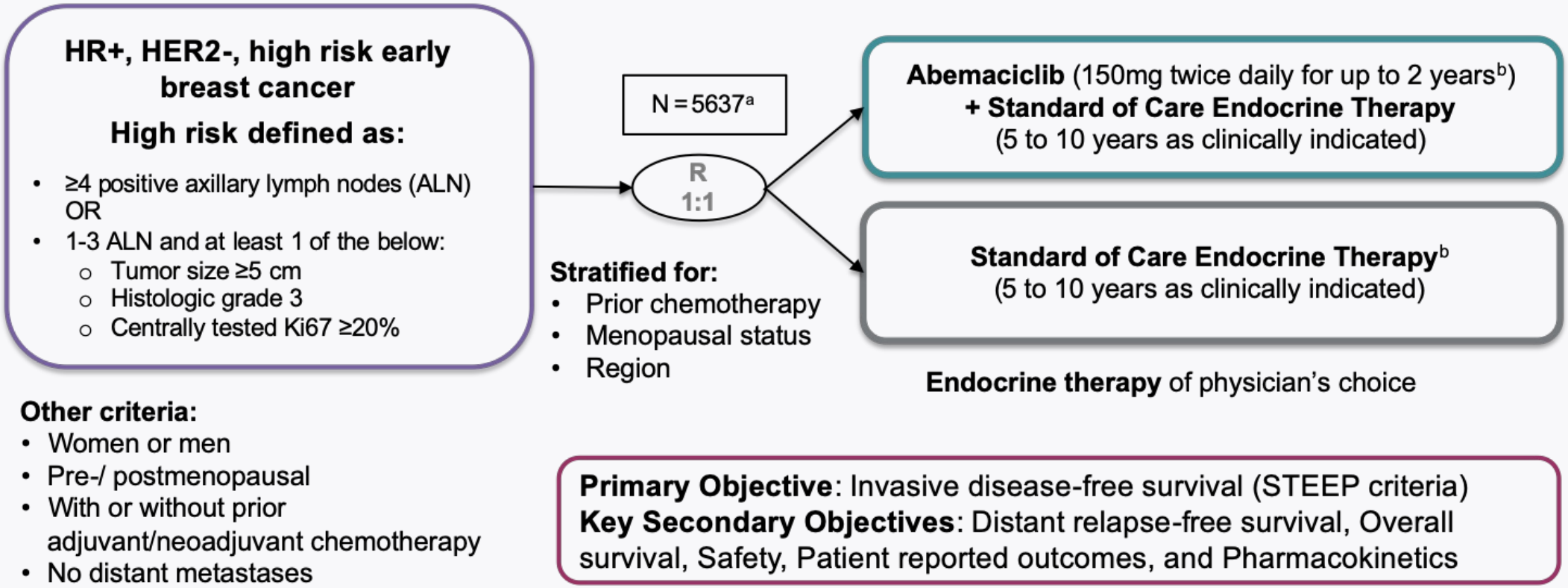
Finn. Lancet Oncol 2014
Finn et al. NEJM. 2016;375:1925. .
Goetz. JCO. 2017;35:3638.
Hortobagyi. NEJM. 2016;375:1738
Tripathy. Lancet Oncol. 2018;19:904.

Adjuvant CDK 4/6 Inhibitor Trials

Trial	N	CDK Inhibitor	Duration of CDK Inhibitor	Eligibility	IDFS Hazard Ratio
Penelope	1250	palbociclib	1 yr.	residual disease after 16 wks of neoadjuvant CT; CPS-EG score ≥ 3 or 2 with ypN+	**HR 0·93;** 95% CI, 0.74 to 1.17; p = 0.53
Pallas	5650	palbociclib	2 yrs..	Stage II-III	**HR 0.96;** 95% CI, 0.81 to 1.14; P= 0.65
MonarchE	5637	abemaciclib	2 yrs.	>4 ALN or 1-3 ALN and at least 1 below: • T >5 cm • G3 • Ki-67>20%	**HR 0.696;** 95% CI 0.588-0.823 P<0.0001
Natalee	Est: 4000	ribociclib	3 yrs.	Stage II (either N0 with grade 2-3 and/or Ki67 ≥ 20% or N1) or III	NR

Loibl et al. J Clin Oncol 2021
Gnant et al. J Clin Oncol 2022
Hrbeck et al. Ann Oncol

MonarchE Study Design



[a] Recruitment from July 2017 to August 2019; [b] Treatment period = first 2 years on study treatment after randomization

Johnston et al. J Clin Oncol 2020

MonarchE Patient Characteristics

		Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Number of positive lymph nodes	0	7 (0.2)	7 (0.2)
	1-3	1119 (39.9)	1143 (40.4)
	≥4 or more	1680 (59.8)	1679 (59.3)
Histological grade	Grade 1	209 (7.4)	215 (7.6)
	Grade 2	1373 (48.9)	1395 (49.3)
	Grade 3	1090 (38.8)	1066 (37.7)
Primary tumor size by pathology following definitive surgery	<2 cm	780 (27.8)	765 (27.0)
	2-5 cm	1369 (48.8)	1419 (50.2)
	≥5 cm	610 (21.7)	612 (21.6)
Central Ki-67	<20%	953 (33.9)	973 (34.4)
	≥20%	1262 (44.9)	1233 (43.6)
	Unavailable	593 (21.1)	623 (22.0)
Progesterone receptor status	Positive	2421 (86.2)	2453 (86.7)
	Negative	298 (10.6)	294 (10.4)

Note: where values do not add up to 100%, remaining data are missing, unavailable or could not be assessed

Additional high risk eligibility criteria for patients with 1-3 nodes	Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Tumor size ≥5 cm (pathology) [a]	249 (8.9)	236 (8.3)
Tumor size ≥5 cm (imaging) [a, b]	152 (5.4)	158 (5.6)
Histologic grade 3 [a]	629 (22.4)	618 (21.8)
Central Ki-67 ≥20% only [c]	216 (7.7)	237 (8.4)

[a] Patients could be counted in more than one of the sub-categories under 1-3 positive lymph nodes; [b] Patients who received neoadjuvant chemotherapy may have been eligible based on imaging tumor size prior to receiving systemic therapy; [c] Patients not double counted; patients did not have tumor size ≥5 cm (either by pathology or imaging) or histologic grade 3

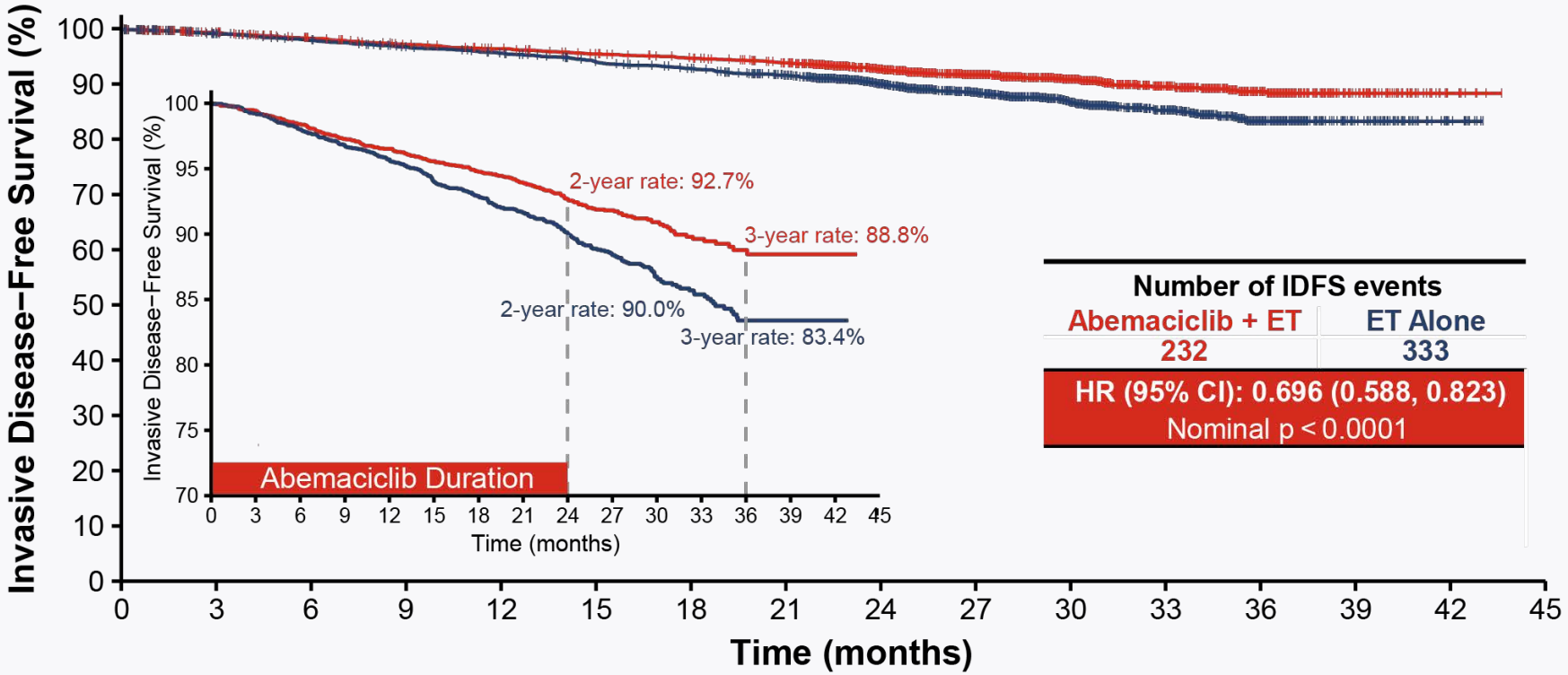
Johnston et al. J Clin Oncol 2020

Description of Analysis Timepoints

Analysis Timepoints	Interim Analysis[a],*	Primary Outcome[b]	Additional Follow-Up 1 (AFU1)[c]
Date	16 March 2020	08 July 2020	01 April 2021
Median follow-up (months)	15.5	19.1	27.1
IDFS Events	323	395	565
Off study treatment	26.4%	41.0%	89.6%
Completed 2-year treatment period	12.5%	25.5%	72.2%

- *Statistically significant improvement in IDFS in ITT population declared at this timepoint.
- a.Johnston SRD, et al. J Clin Oncol. 2020;38:3987-3998; b. . Rastogi P et al SABCS 2020; c. Harbeck et al. Ann Onco 2021 Dec;32(12):1571-1581

IDFS Benefit Maintained With Additional Follow-Up in the ITT Population



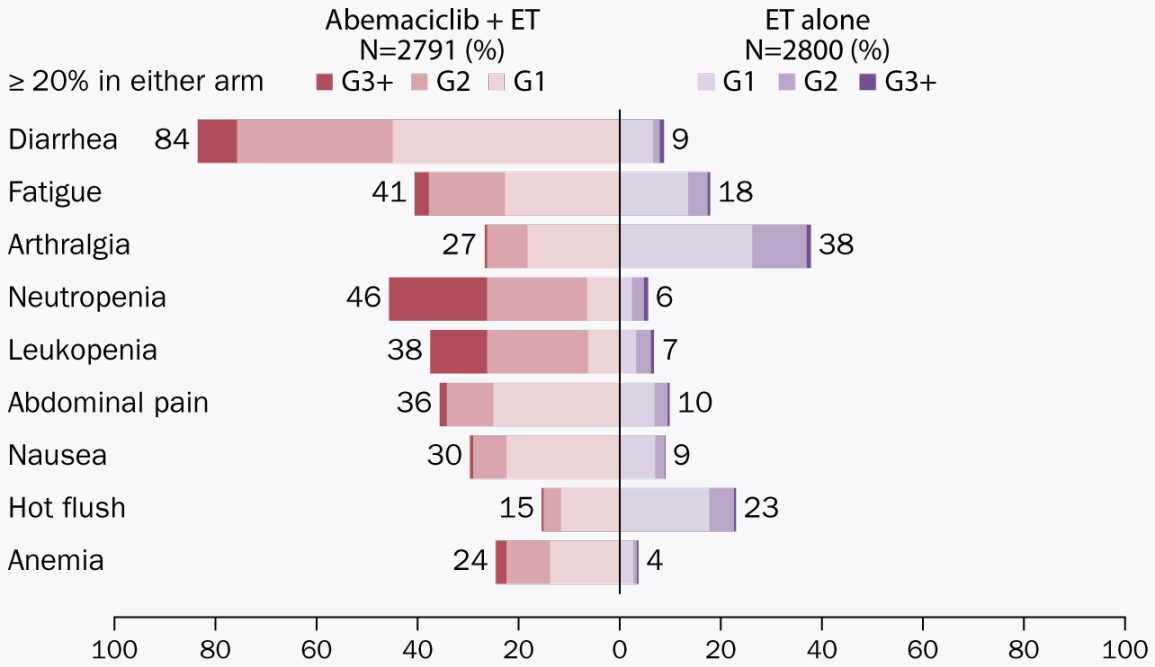
Number at risk																
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET Alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

30.4% reduction in the risk of developing an IDFS event.
The absolute difference in IDFS rates between arms was 5.4% at 3 years.

Harbeck et al. Ann Onco 2021 Dec;32(12):1571-1581.

MonarchE Safety Summary

AEs ≥20% in Both Treatment Arms[2]



Among the 2304 patients who experienced diarrhea[3]

- Median time to onset (any grade) was 8 days
- 20.5% had ≥1 dose reduction
- 22.9% had dose holds
- 5.0% of patients had their treatment discontinued

Other events of interest,[2] any grade	Abemaciclib + ET (n=2791)	ET alone (n=2800)
VTE, %	2.5	0.6
PE, %	1.0	0.1
ILD, %	3.2	1.3

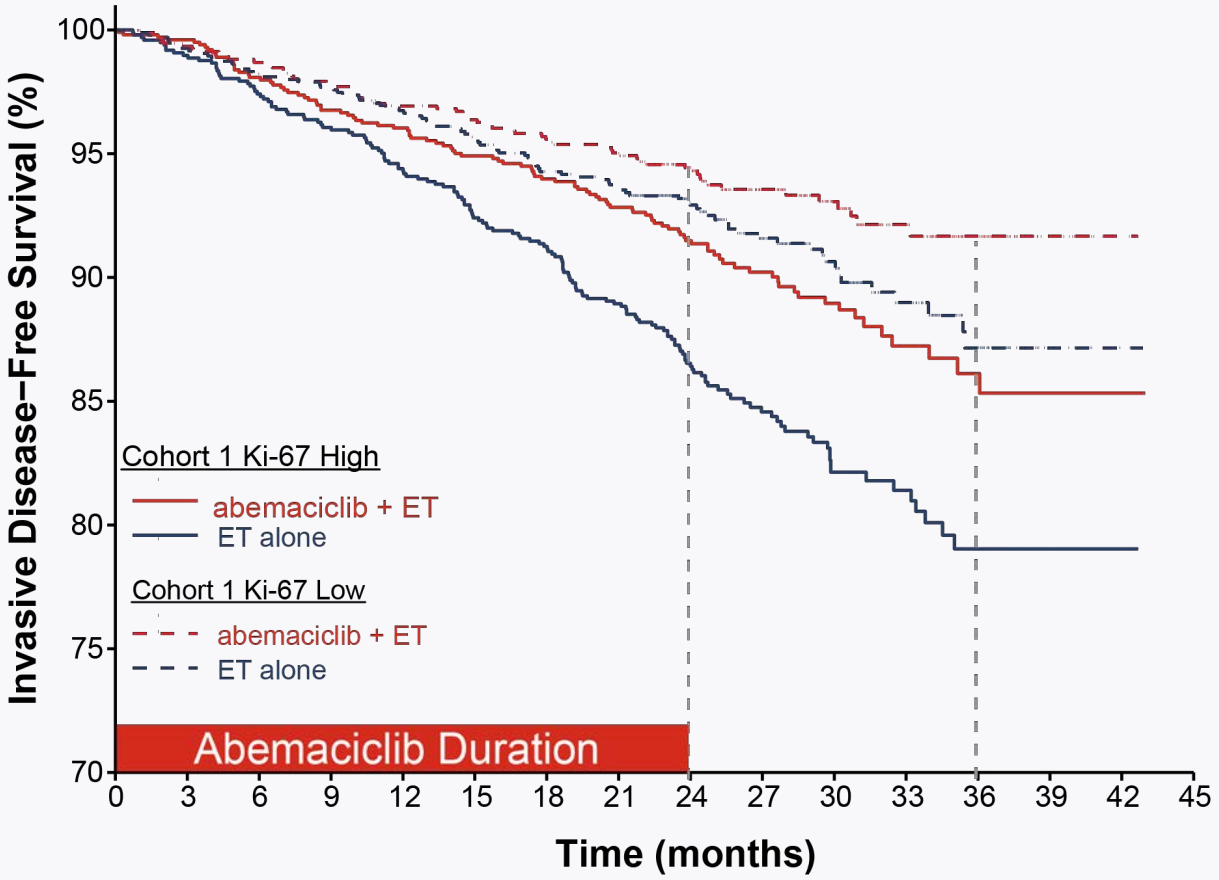
Safety data at additional follow-up are **consistent** with the known safety profile of abemaciclib[1]

Median duration of treatment: **24 months**

The safety population includes patients who received at least 1 dose of study treatment

1. Harbeck N, et al. *Ann Oncol.* 2021;S0923-7534(21):04494-X. 2. O'Shaughnessy J, et al. ESMO Virtual Plenary 2021. Abstract VP8-2021. 3. Tolaney S, et al. St. Gallen 2021. Abstract PO13.

Ki-67 as a Prognostic Marker in Cohort 1



	Abemaciclib + ET	ET Alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

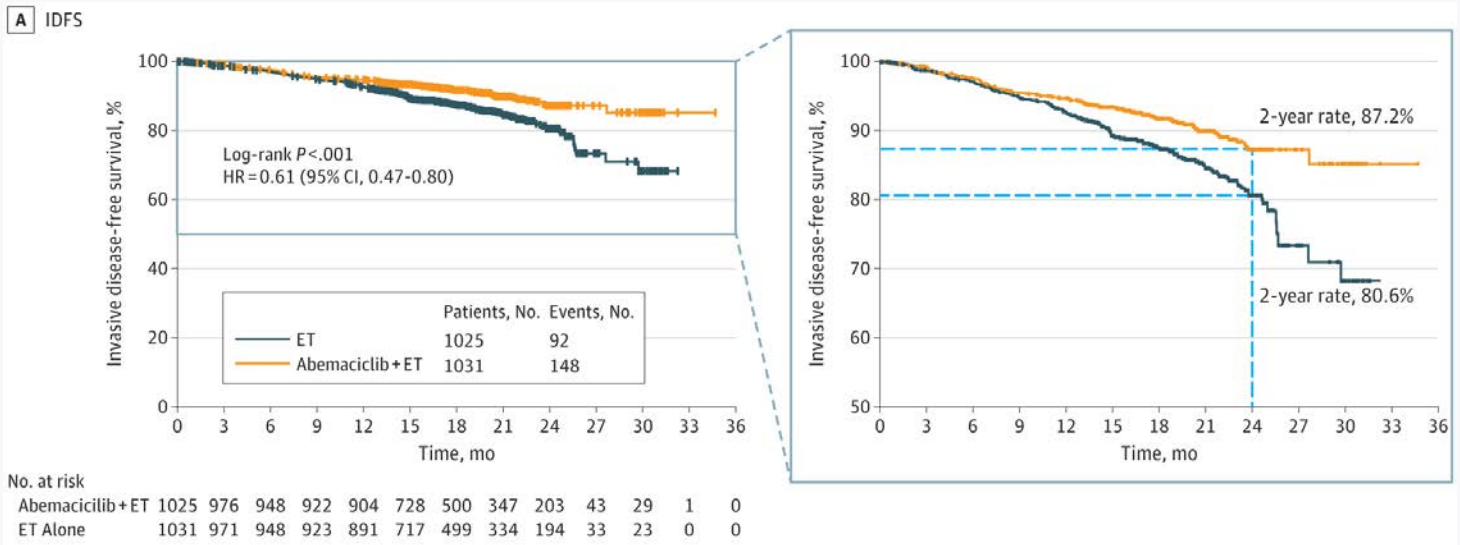
Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

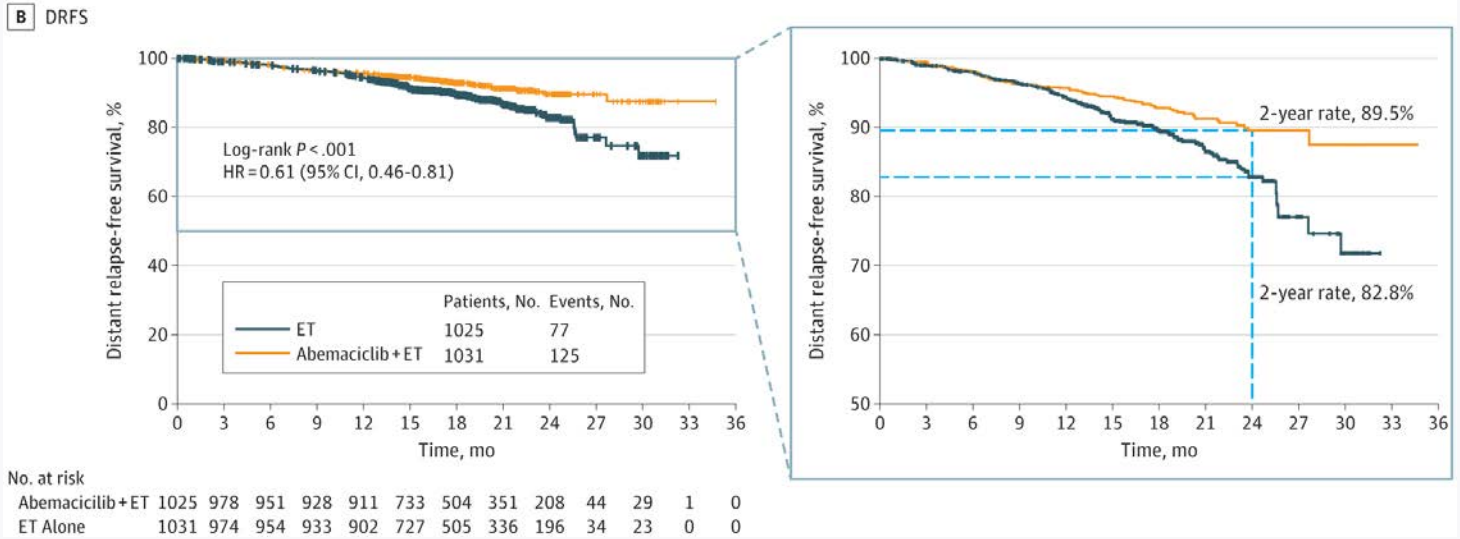
Ki-67 index was prognostic of worse outcome.
However, abemaciclib benefit was consistent regardless of Ki-67 index.

Harbeck et al. Ann Onco 2021 Dec;32(12):1571-1581

MonarchE: Patients who received neoadjuvant chemotherapy (NAC)



Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference



Two-year DRFS rates were 89.5% in the abemaciclib + ET arm and 82.8% in ET arm – 6.7% difference

Martin et al. JAMA Oncol 2022

Guidelines for Abemaciclib Use in Patients With EBC

FDA-Approved Indication[1]

Abemaciclib plus ET (tamoxifen or an AI) for the adjuvant treatment of adult patients with HR+ HER2-, node-positive EBC at a high risk of recurrence and a Ki-67 score of ≥20%

In monarchE, patients had to have tumor involvement in at least 1 ALN and either:

- ≥4 ALN, or
- 1-3 ALN and at least one of the following:
  - tumor grade 3
  - tumor size ≥ 50 mm
- Patients with available untreated breast tumor samples were tested retrospectively at central sites using the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay to establish if the Ki-67 score was ≥20%, specified in the protocol as “Ki-67 high”

ASCO Guidelines[2]

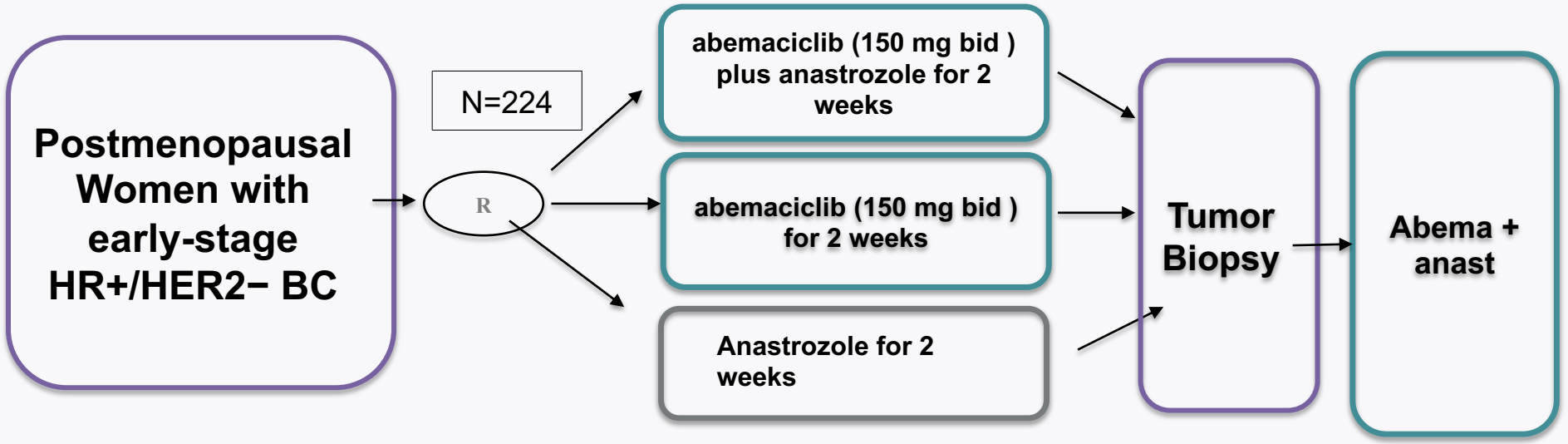
Abemaciclib for two years plus ET for ≥5 years may be offered to the broader ITT population of patients with resected, HR+ HER2-, node-positive, EBC at high risk of recurrence

High risk of recurrence is defined as having:

- >4 positive ALNs, or
- 1-3 ALNs, and one or more of the following
  - histologic grade 3 disease
  - tumor size >5 cm, or
  - Ki-67 index >20%

1. Verzenio. Package insert. Eli Lilly and Company; 2021. 2. American Society of Clinical Oncology. Accessed November 22, 2021. https://www.asco.org/practice-patients/guidelines/breast-cancer#/11081

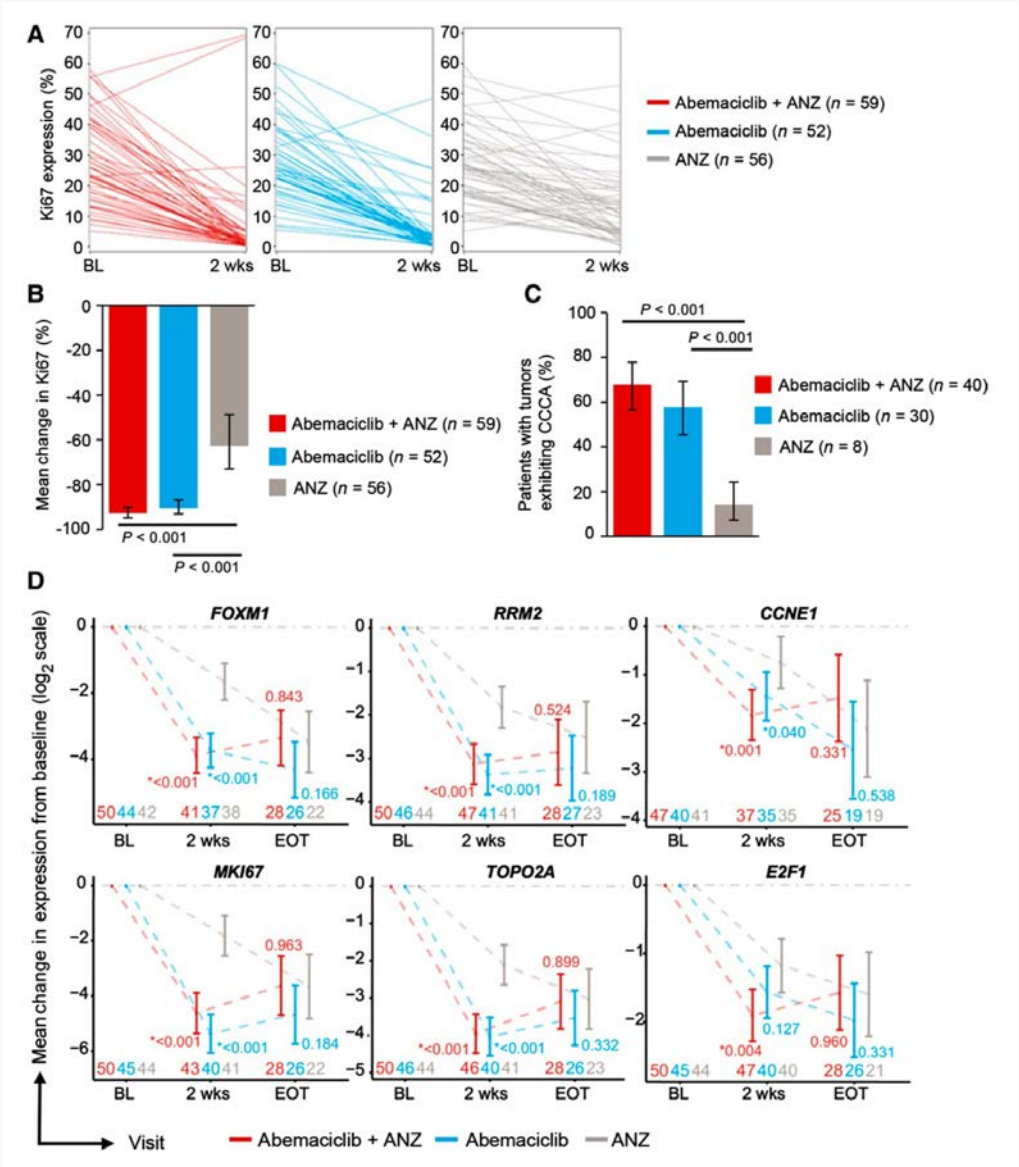
NeoMonarch

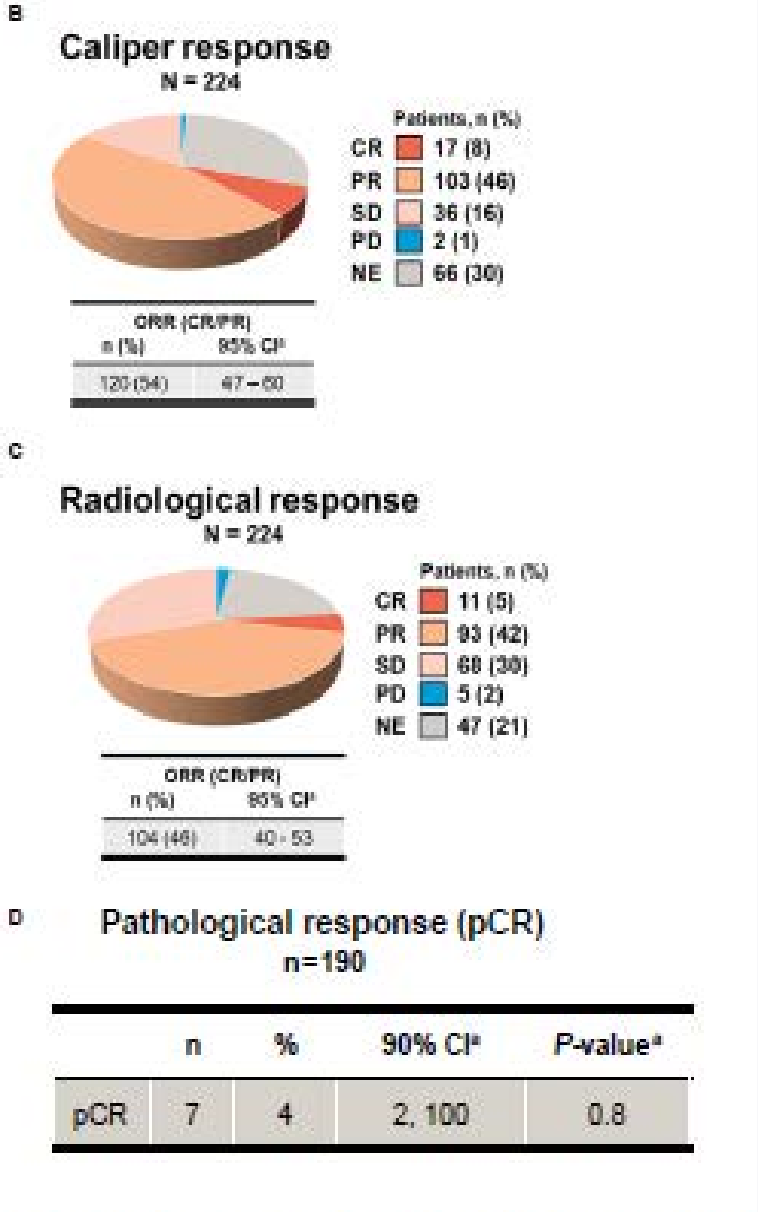


Primary Objective: Change in Ki67 expression from baseline to 2 weeks of therapy. **Key Secondary Objectives**: radiologic, pathologic, and clinical response, as well as safety and tolerability from baseline to 16 weeks of therapy

Hurvitz et al. Clin Can Res 2021.

NeoMonarch





Hurvitz SA et al. Clin Cancer Res 2020;26:566-580.

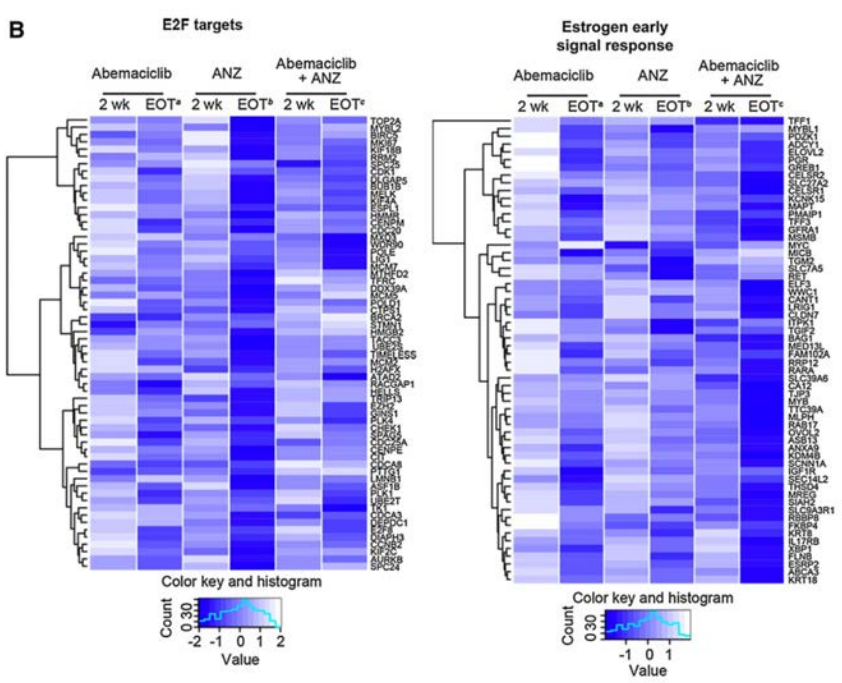
NeoMonarch: Effects of Abemaciclib and Anastrozole on ER and Immune targets

A Normalized enrichment score (NES) vs baseline, FDR q-val ≤.05

Class	Pathway	Abemaciclib		ANZ		Abemaciclib + ANZ	
		2 wk	EOT[a]	2 wk	EOT[b]	2 wk	EOT[c]
ADAPTIVE IMMUNE RESPONSE	CLASS I MHC MEDIATED ANTIGEN PROCESSING PRESENTATION	-2.0	-1.3*	-1.0*	-0.9*	0.6*	1.0*
	ACTIVATION OF NF KAPPAB IN B CELLS	-2.2	-1.7	-0.9*	-1.2*	0.8*	1.0*
	SIGNALING BY THE B CELL RECEPTOR BCR	-2.1	-0.7*	-0.7*	-1.1*	0.8*	1.3*
	ER PHAGOSOME PATHWAY	-2.3	-2.0	-1.3*	-1.6*	0.8*	1.3*
	CROSS PRESENTATION OF SOLUBLE EXOGENOUS ANTIGENS ENDOSOMES	-2.3	-1.6	-1.6	-1.2*	1.1*	1.3*
	MHC CLASS II ANTIGEN PRESENTATION	-2.2	-2.0	-2.1	-1.9	-1.5*	-1.4*
	ANTIGEN PROCESSING CROSS PRESENTATION	-2.3	-1.4*	-1.0*	-1.1*	1.4*	1.7
	GENERATION OF SECOND MESSENGER MOLECULES	-2.0	-1.0*	1.6*	-2.0	1.9	1.8
	PHOSPHORYLATION OF CD3 AND TCR ZETA CHAINS	-1.9	-1.1*	1.6*	-1.9	2.0	1.8
	PD1 SIGNALING	-1.9	-0.9*	1.5*	-1.8	2.1	1.9
	COSTIMULATION BY THE CD28 FAMILY	-1.7	-1.0*	1.1*	-1.7	1.9	1.9
	ANTIGEN ACTIVATES B CELL RECEPTOR LEADING TO GENERATION OF SECOND MESSENGERS	-1.5*	1.6*	1.0*	-0.8*	1.2*	1.9
	IMMUNOREGULATORY INTERACTIONS BETWEEN A LYMPHOID AND A NON LYMPHOID CELL	-2.0	0.8*	1.6*	-1.8	1.9	2.4
	ALLOGRAFT REJECTION	-2.1	0.9*	1.2*	-2.0	2.5	2.6
APOPTOSIS	REGULATION OF APOPTOSIS	-2.1	-1.7	-1.6	-1.1*	0.8*	1.0*
CELL CYCLE	MYC TARGETS V1	-2.8	-2.3	-2.7	-2.0	-1.4*	-0.9*
	DNA REPAIR	-2.3	-2.3	-2.1	-2.0	-1.9	-1.7
	MYC TARGETS V2	-1.7	-1.8	-2.3	-2.4	-1.8	-1.7
	CELL CYCLE	-3.4	-3.1	-3.2	-3.1	-2.9	-2.5
	G2M CHECKPOINT	-3.5	-3.3	-3.3	-3.2	-3.0	-2.9
	E2F TARGETS	-3.5	-3.2	-3.2	-3.3	-3.0	-2.8
	MITOTIC SPINDLE	-2.8	-2.4	-2.7	-2.5	-2.3	-2.1
CYTOKINE SIGNALING	INTERFERON ALPHA BETA SIGNALING	-1.8	-1.9	0.7*	-2.2	0.7*	0.8*
	INTERFERON SIGNALING	-2.0	-1.7	-0.7*	-2.0	1.2*	1.2*
	INTERFERON ALPHA RESPONSE	-2.1	-2.4	0.9*	-2.2	1.2*	1.2*
	IL2 STAT5 SIGNALING	-1.7	1.2*	-1.2*	-1.0*	1.7	2.0
	IL6 JAK STAT3 SIGNALING	-1.6	1.4*	-0.8*	-1.5	1.8	1.9
	INTERFERON GAMMA RESPONSE	-2.3	-1.4	0.8*	-2.0	1.9	2.2
	INFLAMMATORY RESPONSE	-1.7	1.2*	-1.3*	-1.4	1.9	2.1
ESTROGEN SIGNALING	**ESTROGEN RESPONSE EARLY**	-1.9	-2.4	-2.5	-2.2	-2.5	-2.6
	ESTROGEN RESPONSE LATE	-2.1	-2.2	-2.7	-2.1	-2.5	-2.4
EXTRACELLULAR MATRIX ORGANIZATION	COLLAGEN FORMATION	-1.2*	1.7*	-1.6	2.2	2.1	2.2
	EXTRACELLULAR MATRIX ORGANIZATION	-1.3*	1.4*	-1.7	2.1	2.1	2.2
HEMOSTASIS	CGMP EFFECTS	-0.7*	1.4*	0.9*	2.0	1.3*	1.8
	KINESINS	-2.6	-2.4	-2.4	-2.5	-2.3	-2.3
	FACTORS INVOLVED IN MEGAKARYOCYTE DEVELOPMENT AND PLATELET PRODUCTION	-2.9	-2.5	-2.6	-2.6	-2.3	-2.3
INNATE IMMUNE SYSTEM	COMPLEMENT CASCADE	0.9*	1.6	1.5*	2.1	1.8	2.2
	COAGULATION	-1.3	1.1*	-1.4*	1.5	1.8	1.9
METABOLISM	GLYCOLYSIS	-1.6	-1.3*	-2.0	-1.4	-1.0*	-1.1*
	LIPOPROTEIN METABOLISM	1.3*	1.5*	1.0*	1.0*	1.6*	2.0
SIGNAL TRANSDUCTION	SIGNALING BY WNT	-2.2	-1.7	-1.3*	-1.0*	0.5*	-0.4*
	CHEMOKINE RECEPTORS BIND CHEMOKINES	-1.8	1.7*	-1.0*	-1.7	1.6*	2.1
	TNFA SIGNALING VIA NFKB	-1.7	2.2	-2.1	-1.2*	1.3*	2.0
	EPITHELIAL MESENCHYMAL TRANSITION	-1.8	1.7	-2.5	2.4	2.7	2.8
SIGNALING	PI3K AKT MTOR SIGNALING	-2.0	-1.0*	-1.2*	-1.1*	-0.8*	0.8*
	MTORC1 SIGNALING	-2.7	-1.6	-2.4	-1.9	-1.2*	-0.9*
	KRAS SIGNALING UP	-1.5	1.6	-1.4*	1.6	1.8	2.4
STRESS SIGNALING	HYPOXIA	-1.5	1.8	-2.0	1.0*	1.4*	1.8

Significantly downregulated | Significantly upregulated | * Not significant

B



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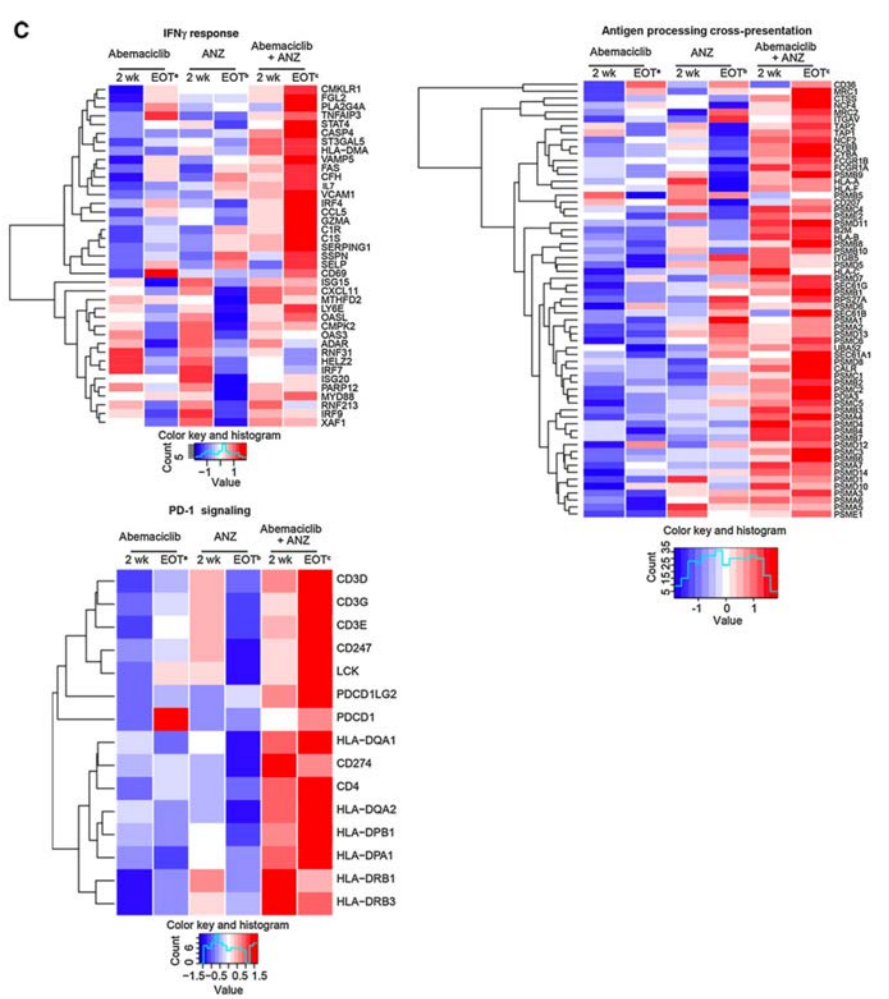

Hurvitz SA et al. Clin Cancer Res 2020;26:566-580.

OlympiA: Overall Survival

ESMO VIRTUAL PLENARY

PRE-SPECIFIED EVENT DRIVEN ANALYSIS OF OVERALL SURVIVAL (OS) IN THE OLYMPIA PHASE III TRIAL OF ADJUVANT OLAPARIB (OL) IN GERMLINE *BRCA1/2* MUTATION (*gBRCAm*) ASSOCIATED BREAST CANCER

Andrew Nicholas James Tutt[1], Judy Garber[2], Richard D. Gelber[2], Kelly-Anne Phillips[3], Andrea Eisen[4], Oskar Thor Jóhannsson[5], Priya Rastogi[6], Karen Yongzhi Cui[7], Seock-Ah Im[8], Rinat Yerushalmi[9], Adam Matthew Brufsky[10], Maria Taboada[11], Giovanna Rossi[12], Greg Yothers[13], Christian Singer[14], Luis E. Fein[15], Niklas Loman[16], David Cameron[17], Christine Campbell[18], Charles Edward Geyer Jr[19]

[1]Breast Cancer Now Research Unit, Institute of Cancer Research, London, United Kingdom; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada; [5]Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; [6]Department of Oncology, NSABP Foundation, Pittsburgh, PA, USA; [7]Global Medicine Development, AstraZeneca US, Gaithersburg, MD, USA; [8]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [9]Department of Oncology, Clalit Health Services, Petah Tikva, Israel; [10]Department of Hematology-Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [11]AstraZeneca, Royston, United Kingdom; [12]Department of R&D, Breast International Group (BIG) – AISBL, Brussels, Belgium; [13]Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, USA; [14]Center for Breast Health, Medical University of Vienna, Vienna, Austria; [15]Department of Oncology, Instituto de Oncología de Rosario, Rosario, Santa Fe, Argentina; [16]Skane University Hospital, Lund, Sweden; [17]Department of Oncology, Edinburgh Cancer Centre, Edinburgh, United Kingdom; [18]Frontier Science Scotland, Kincraig, United Kingdom; [19]Department of Clinical Research, Houston Methodist Cancer Center, Houston, TX, USA

ESMO

OlympiA: Trial schema

- 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

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

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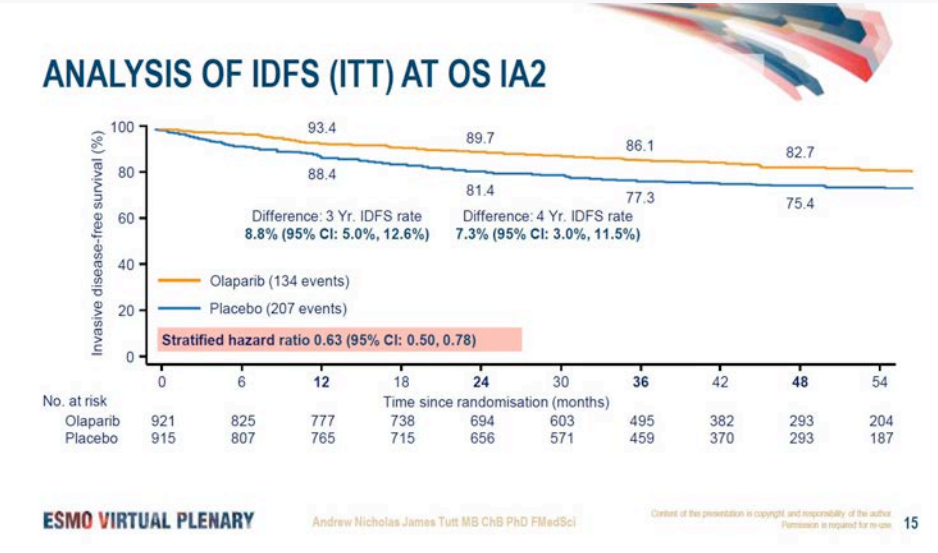
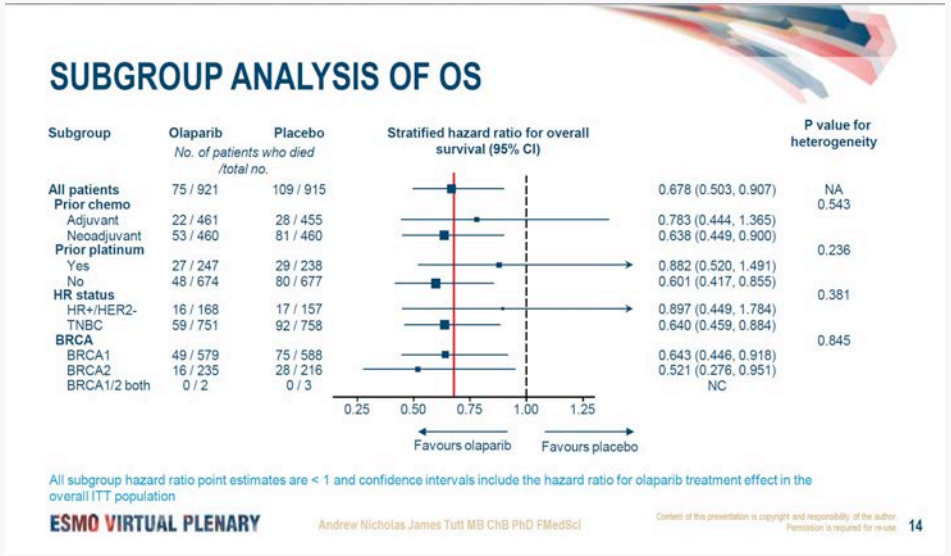
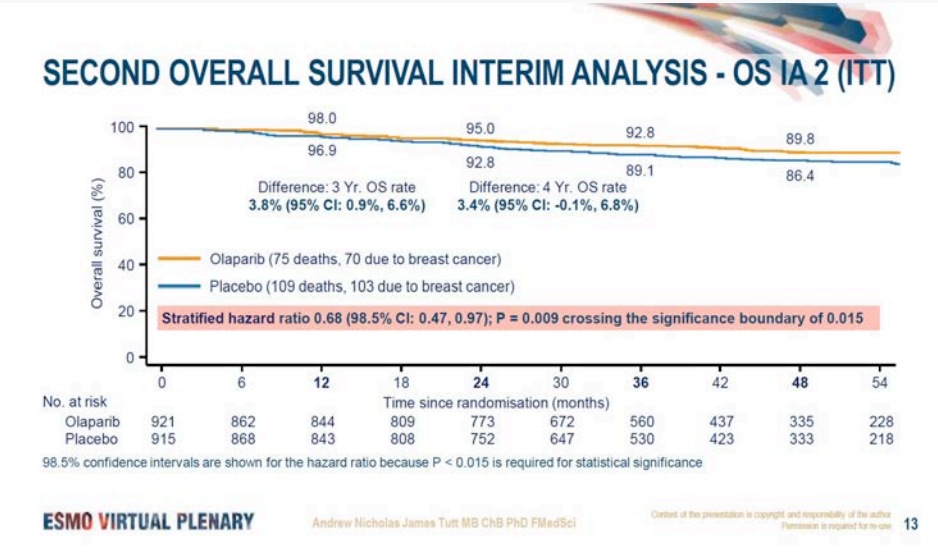
OlympiA: Overall Survival







Tutt et al.

Neoadjuvant PARPi for g*BRCA* mutations

Phase II study (n=20):

- 16 had gBRCA1 and 4 gBRCA2 positive.
- 15 with TNBC and 5 had HR+
- RCB-0 (pathologic complete response) rate was 53%
- RCB-0/I was 63%

Litton et al. J Clin Oncol 2020 Feb 10;38(5):388-394.

Neoadjuvant PARPi for g*BRCA* mutations

2021 ASCO ANNUAL MEETING

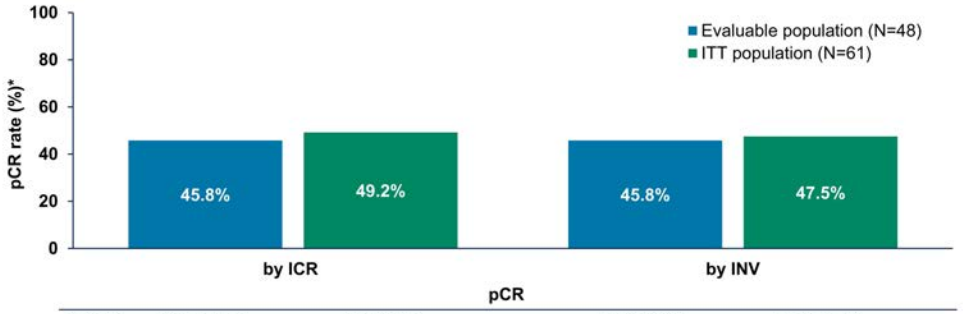
NEOADJUVANT TALAZOPARIB IN PATIENTS WITH GERMLINE *BRCA1/2* MUTATION-POSITIVE, EARLY HER2-NEGATIVE BREAST CANCER: RESULTS OF A PHASE 2 STUDY

Jennifer K. Litton,[1] J. Thaddeus Beck,[2] Jason M. Jones,[3] Jay Andersen,[4] Joanne L. Blum,[5] Lida A. Mina,[6] Raymond Brig,[7] Michael Danso,[8] Yuan Yuan,[9] Antonello Abbattista,[10] Kay Noonan,[11] Jayeta Chakrabarti,[12] Akos Czibere,[13] William F. Symmans,[1] Melinda L. Telli[14]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Highlands Oncology Group, Fayetteville, AR, USA; [3]Avera Cancer Institute, Sioux Falls, SD, USA; [4]Compass Oncology, West Cancer Center, Tigard, OR, USA; [5]Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology Network, Dallas, TX, USA; [6]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [7]Brig Center for Cancer Care and Survivorship, Knoxville, TN, USA; [8]Virginia Oncology Associates, Norfolk, VA, USA; [9]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [10]Pfizer Oncology, Milan, Italy; [11]Pfizer Inc., Groton, CT, USA; [12]Pfizer, Walton Oaks, Surrey, UK; [13]Pfizer Inc., Cambridge, MA, USA; [14]Stanford University School of Medicine, Stanford, CA, USA

June 6, 2021

Pathologic Complete Response



	by ICR		by INV	
95% CI†	(32.0–60.6)	(36.7–61.6)	(32.0–60.6)	(35.0–60.1)
80% CI†	(36.4–55.2)	(41.0–57.4)		
Posterior probability that true pCR rate exceeds 45%	0.55	0.75		

*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

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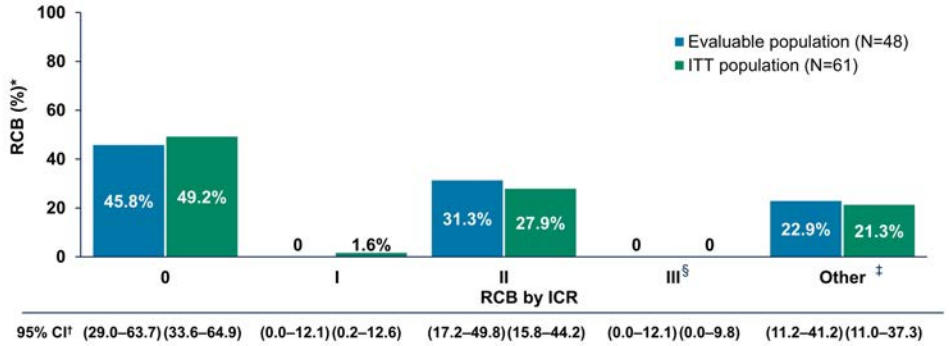
Residual Cancer Burden



	0		I		II		III§		Other ‡	
95% CI†	(29.0–63.7)	(33.6–64.9)	(0.0–12.1)	(0.2–12.6)	(17.2–49.8)	(15.8–44.2)	(0.0–12.1)	(0.0–9.8)	(11.2–41.2)	(11.0–37.3)

*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR.
†The simultaneous exact CI was calculated using Goodman's method.
‡None of the patients who had pathology submitted are classified as RCB III. Ten patients with clinical progression are being captured under "other"
§10 patients had PD and are counted in the 'other' category. Two patients did not have surgery for other reasons (early discontinuation and consent withdrawal) and one patient was unable to be assessed due to missing a required axillary specimen.

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PARP Inhibitors

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RESEARCH
TO PRACTICE

Discussion Questions

- Regulatory and reimbursement issues aside, in which clinical scenarios do you think the use of a PARP inhibitor (eg, olaparib) confers a positive risk-benefit ratio in the adjuvant setting, and how does that compare to the FDA indication?
- How do you approach the prevention and management of side effects/toxicity with PARP inhibitors (eg, olaparib)?
- Regulatory and reimbursement issues aside, in which clinical scenarios do you think the use of a CDK4/6 inhibitor (eg, abemaciclib) confers a positive risk-benefit ratio in the adjuvant setting, and how does that compare to the FDA indication and ASCO guidelines?
- How do you approach the prevention and management of side effects/toxicity with abemaciclib?
- Do you believe PARP inhibitors deliver similar benefit in HER2-positive BC?

RTP RESEARCH TO PRACTICE

ASCO 2021 Adjuvant PARP Inhibitor Updated Recommendations

- **For patients with localized, HER2-negative breast cancer** with high risk of recurrence and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, 1 year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation therapy.
- **For those who underwent surgery first**, 1 year of adjuvant olaparib should be offered for patients with triple-negative breast cancer and tumor size >2 cm or any involved axillary nodes.
- **For those with hormone receptor (HR)-positive disease**, 1 year of adjuvant olaparib should be offered to those with at least 4 involved axillary lymph nodes.
- **For patients who received neoadjuvant chemotherapy**, 1 year of adjuvant olaparib should be offered to patients with triple-negative breast cancer and any residual cancer; **for patients with HR-positive disease**, 1 year of adjuvant olaparib should be offered to patients with residual disease and a clinical stage, pathologic stage, estrogen receptor and tumor grade score ≥3.

Tung NM et al. *J Clin Oncol* 2021;39(26):2959-61.

RTP RESEARCH TO PRACTICE

Genomic Assays

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes, hormone receptor-positive (HR+) and HER2-negative breast cancer with recurrence score of 25 or less: SWOG S1007

Kevin Kalinsky, William E Barlow, Julie R Gralow, Funda Meric-Bernstam, Kathy S Albain, Daniel F Hayes, Nancy U Lin, Edith A Perez, Lori J Goldstein, Stephen K Chia, Sukhbinder Dhesy-Thind, Priya Rastogi, Emilio Alba, Suzette Delaloge, Miguel Martin, Catherine M Kelly, Manuel Ruiz-Borrego, Miguel Gil Gil, Claudia Arce-Salinas, Etienne G.C. Brain, Eun Sook Lee, Jean-Yves Pierga, Begoña Bermejo, Manuel Ramos-Vazquez, Kyung Hae Jung, Jean-Marc Ferrero, Anne F. Schott, Steven Shak, Priyanka Sharma, Danika L. Lew, Jieling Miao, Debasish Tripathy, Lajos Pusztai, Gabriel N. Hortobagyi

On Behalf of the RxPonder Investigators

SWOG CANCER RESEARCH NETWORK

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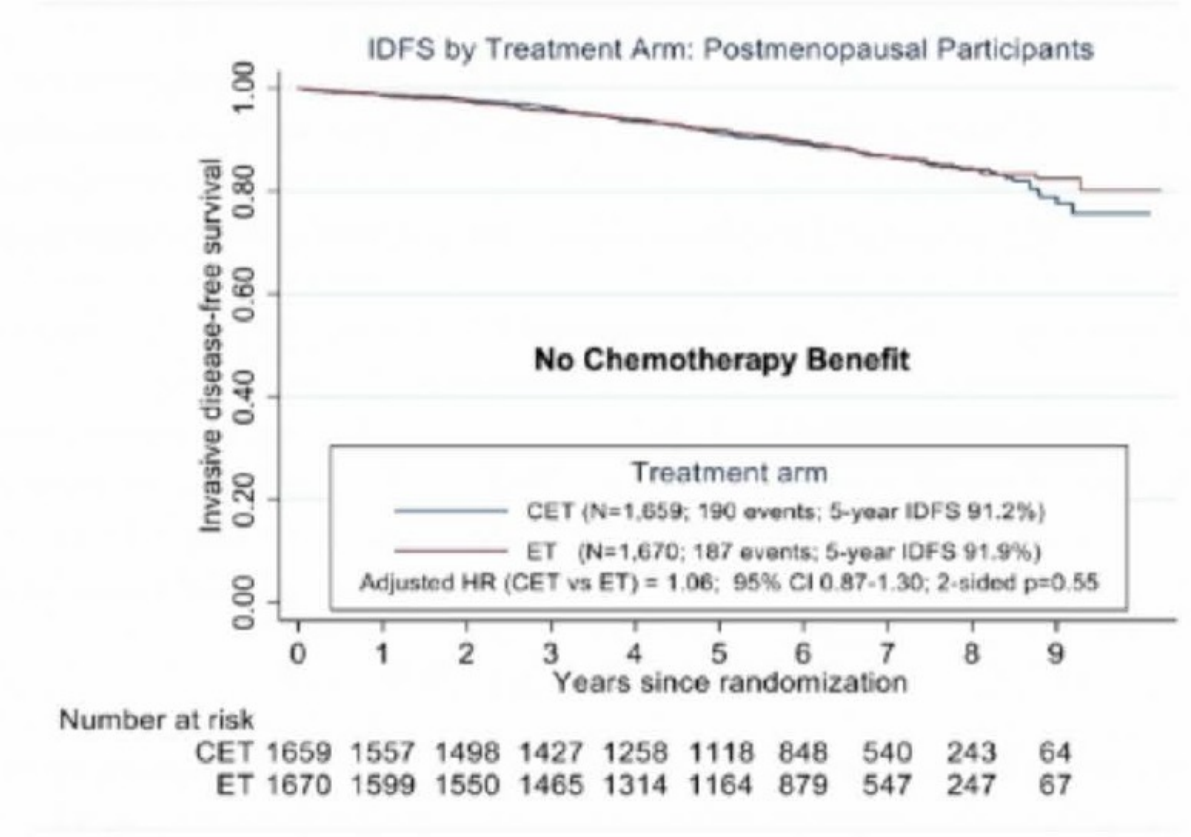
NCI National Clinical Trials Network NCI Community Oncology Research Program

SABCS 2021;Abstract GS2-07.

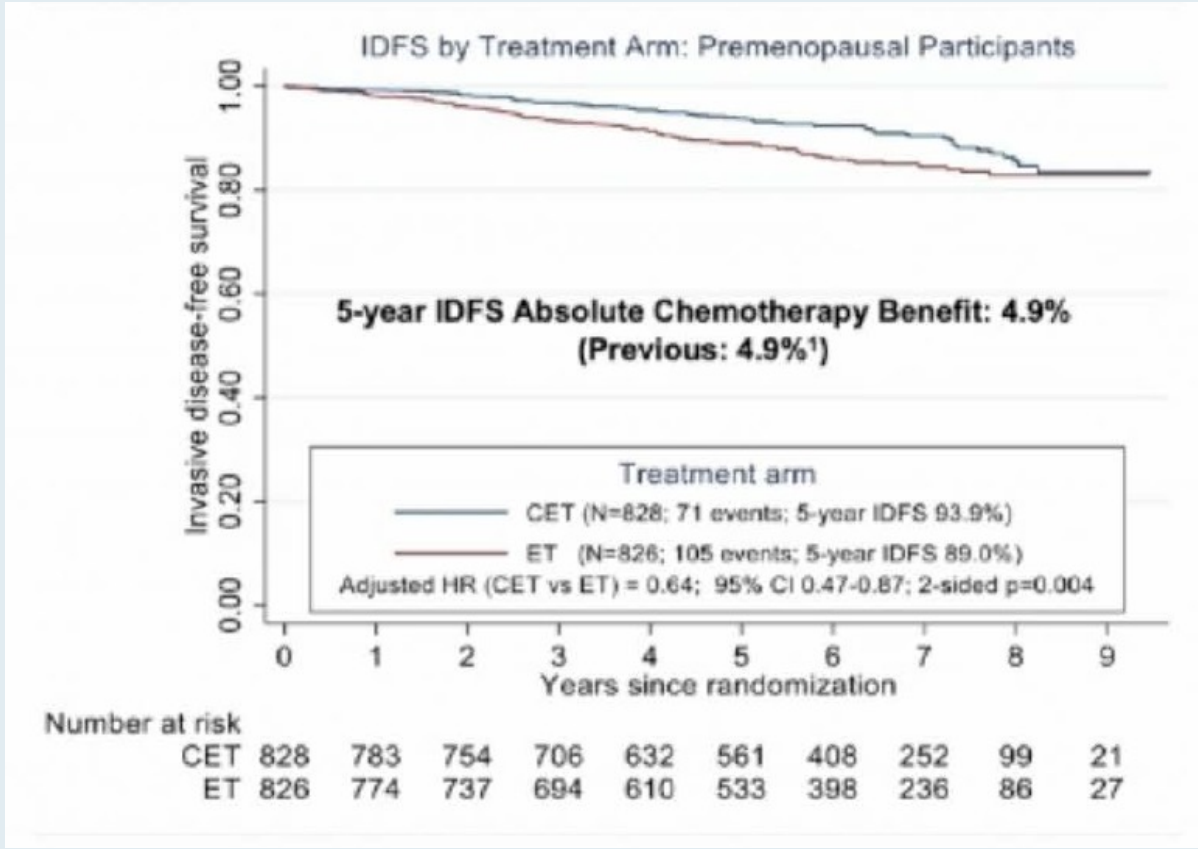
RTP RESEARCH TO PRACTICE

RxPONDER Updated Analysis: IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



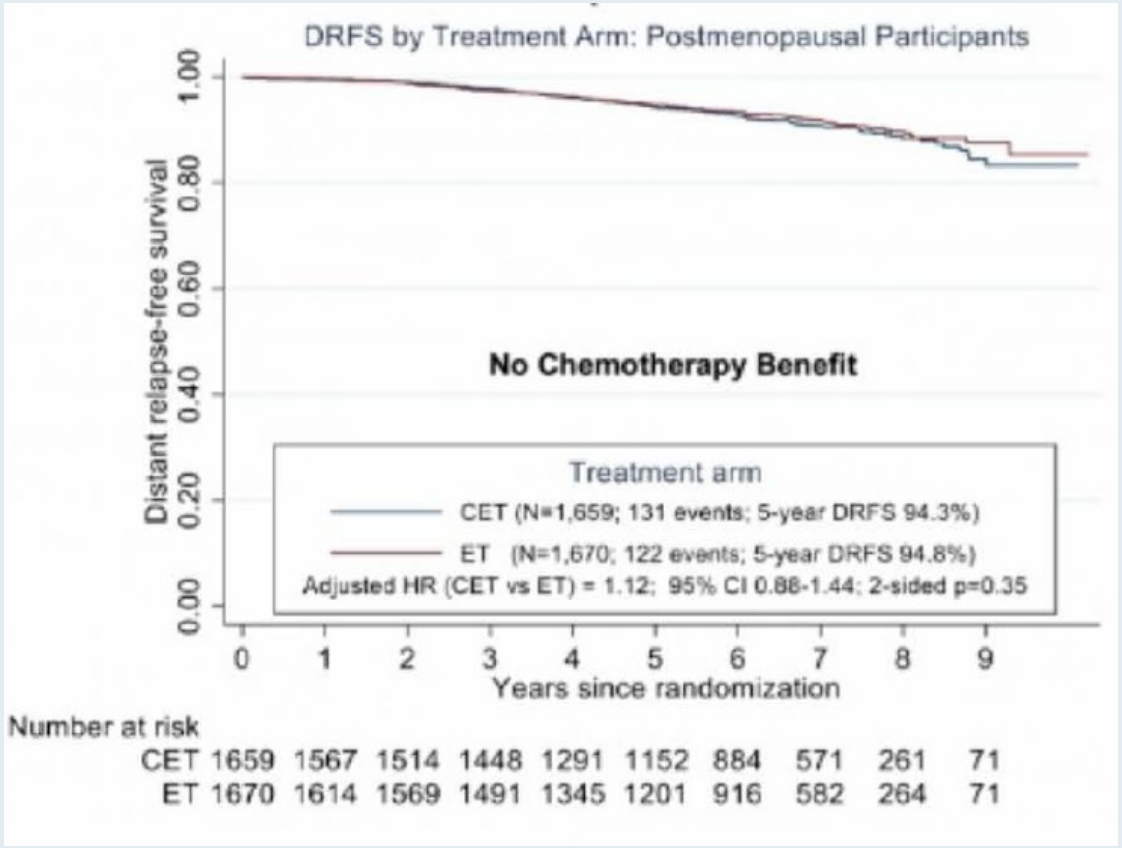
IDFS = invasive disease-free survival

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

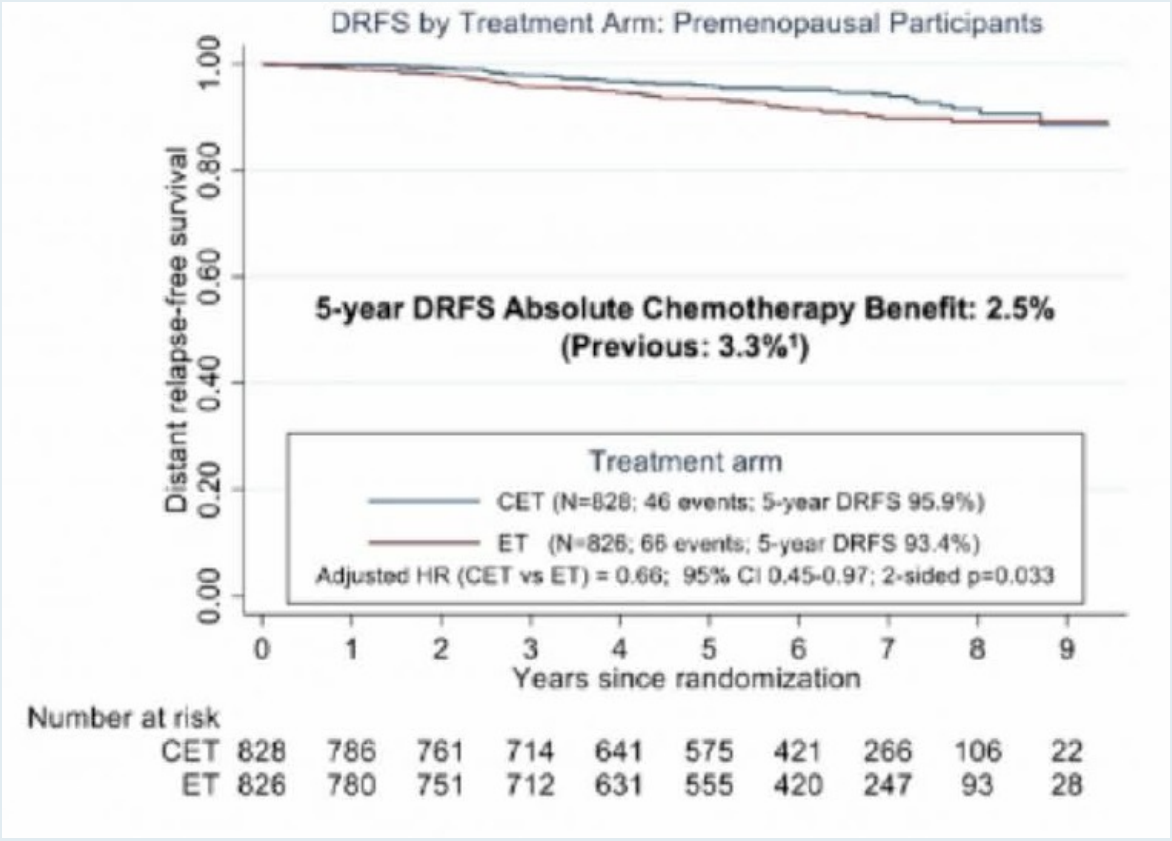
RTP RESEARCH TO PRACTICE

RxPONDER Updated Analysis: DRFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



DRFS = distant recurrence-free survival

Kalinsky K et al. SABCS 2021;Abstract GS2-07.

RTP RESEARCH TO PRACTICE

Cancer Treatment Reviews 110 (2022) 102454

Contents lists available at ScienceDirect

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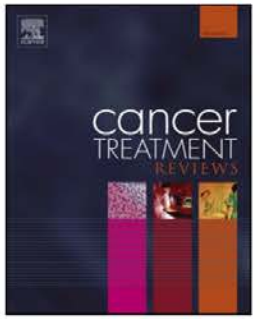
journal homepage: www.elsevier.com/locate/ctrv

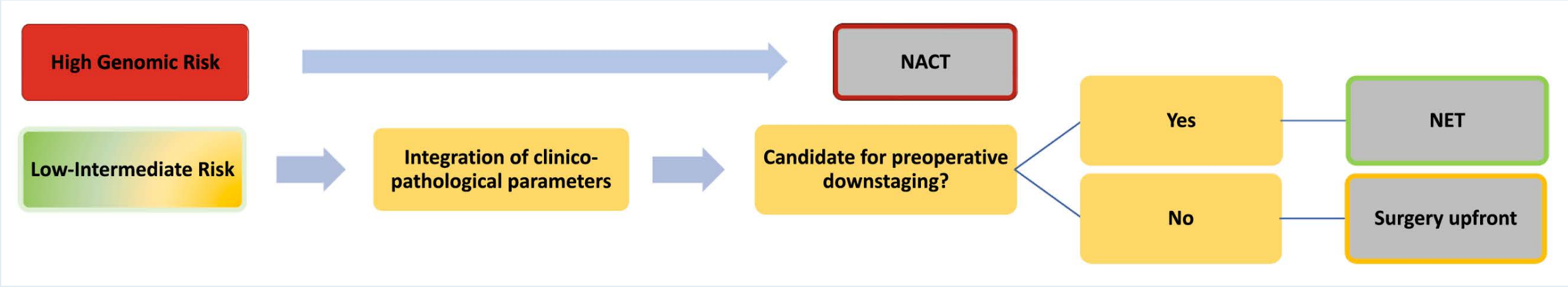


Tumour Review

Tailoring neoadjuvant treatment of HR-positive/HER2-negative breast cancers: Which role for gene expression assays?

Giovanna Garufi [a,*], Luisa Carbognin [b], Concetta Arcanà [c], Sara Parola [d], Anna Ventriglia [e], Antonio Doronzo [f], Mattia Garutti [g], Armando Orlandi [h], Antonella Palazzo [h], Alessandra Fabi [i], Emilio Bria [a,h], Giampaolo Tortora [a,h], Grazia Arpino [j], Mario Giuliano [j], Lucia Del Mastro [k,l], Michelino De Laurentiis [m], Fabio Puglisi [n,o]

Clinical Implications of Gene Expression Risk Score for Core Needle Biopsy for Patients Considered for Neoadjuvant Therapy



Garufi G et al. *Cancer Treat Rev* 2022;110:102454.

RTP RESEARCH TO PRACTICE

Cancer Treatment Reviews 102 (2022) 102323

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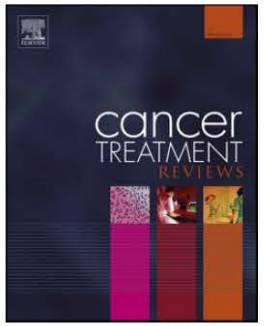
Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv



Hot Topic

Gene-expression signatures to inform neoadjuvant treatment decision in HR+/HER2− breast cancer: Available evidence and clinical implications

Gaia Griguolo [a,b], Michele Bottosso [a], Grazia Vernaci [a,b], Federica Miglietta [a], Maria Vittoria Dieci [a,b,*], Valentina Guarneri [a,b]

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J Clin Oncol 2022;40(29):3361-5.

Impact of RxPONDER and monarchE on the Surgical Management of the Axilla in Patients With Breast Cancer

Elizabeth A. Mittendorf, MD, PhD[1,2]; Tari A. King, MD[1,2]; and Sara M. Tolaney, MD, MPH[2,3]

“Although ALND may be considered in individual patients being managed by a multidisciplinary team, we suggest that routine ALND is not indicated to safely apply the results of RxPONDER or monarchE to determine systemic therapy recommendations for patients with HR1/HER2– breast cancer.”

Mittendorf EA et al. *J Clin Oncol* 2022;40(29):3361-5.

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CDK4/6 Inhibitors for ER-Positive Metastatic Breast Cancer

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Discussion Questions

- How do you go about selecting a CDK4/6 inhibitor as part of first-line treatment?
- In which situations, if any, will you use a CDK4/6 inhibitor in a patient who has previously received one?
- How do you approach the prevention and management of side effects/toxicity with alpelisib?

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2022 ASCO® ANNUAL MEETING

Abstract LBA1004

A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

PRESENTED BY:
Kevin Kalinsky, MD, MS

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KNOWLEDGE CONQUERS CANCER

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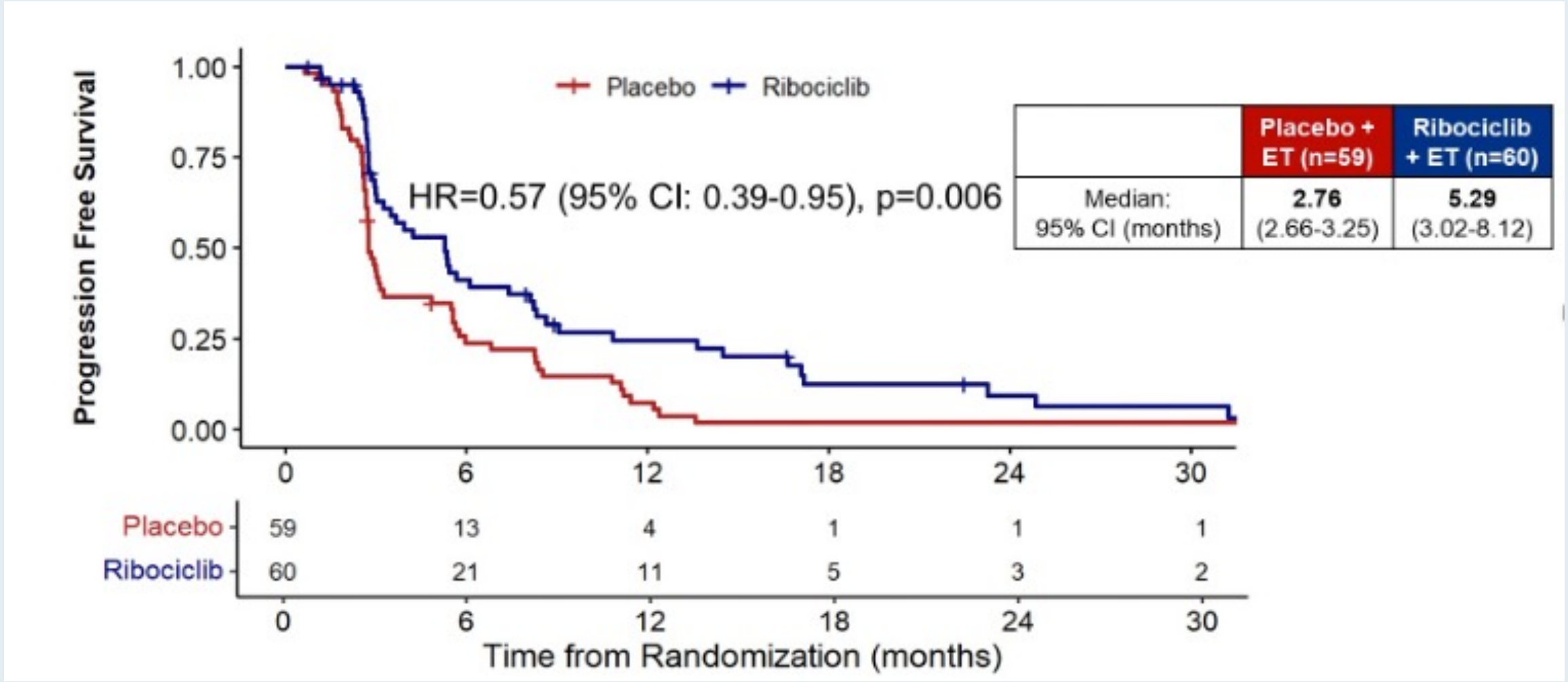
MAINTAIN: Progression-Free Survival (Primary Endpoint)



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

ET = endocrine therapy

Kalinsky K et al. ASCO 2022;Abstract LBA1004.

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MAINTAIN: Treatment-Related Adverse Events

	Placebo + ET (n=59)			Ribociclib + ET (n=60)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic						
Neutropenia*	9 (15%)	0 (0%)	1 (2%)	43 (72%)	23 (38%)	1 (2%)
Anemia	13 (22%)	1 (2%)	0 (0%)	14 (23%)	1 (2%)	0 (0%)
Thrombocytopenia	3 (5%)	0 (0%)	0 (0%)	15 (25%)	0 (0%)	0 (0%)
Non-Hematologic						
ALT increased	12 (20%)	1 (2%)	0 (0%)	10 (17%)	0 (0%)	0 (0%)
AST increased	17 (29%)	4 (7%)	0 (0%)	15 (25%)	1 (2%)	0 (0%)
Vomiting	3 (5%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Fatigue	19 (32%)	0 (0%)	0 (0%)	20 (33%)	1 (2%)	0 (0%)
Headache	6 (10%)	0 (0%)	0 (0%)	5 (8%)	0 (0%)	0 (0%)
Diarrhea	6 (10%)	0 (0%)	0 (0%)	9 (15%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)
Infection	3 (5%)	0 (0%)	0 (0%)	6 (10%)	3 (5%)	0 (0%)

ET = endocrine therapy

Kalinsky K et al. ASCO 2022;Abstract LBA1004.

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Breast Cancer Agenda

MODULE 1: HER2-Positive and HER2-Low Disease

MODULE 2: ER-Positive, HER2-Negative Disease

MODULE 3: Triple-Negative Disease

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Discussion Questions

- In which situations, in any, will you not use postoperative pembrolizumab (eg, pCR to neoadjuvant treatment)? How do you approach patients who go directly to surgery?

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N Engl J Med 2022;386(6):556-67.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

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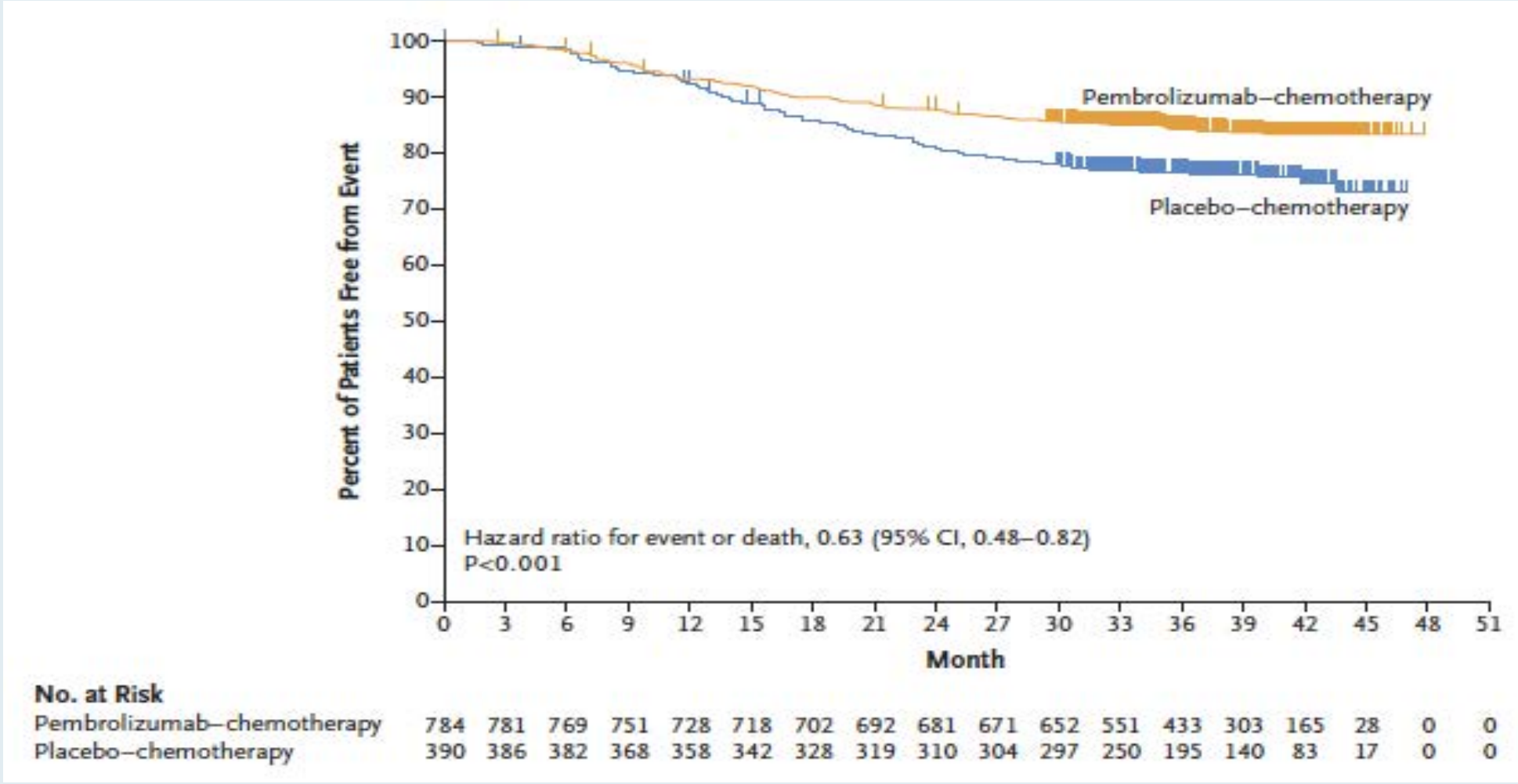
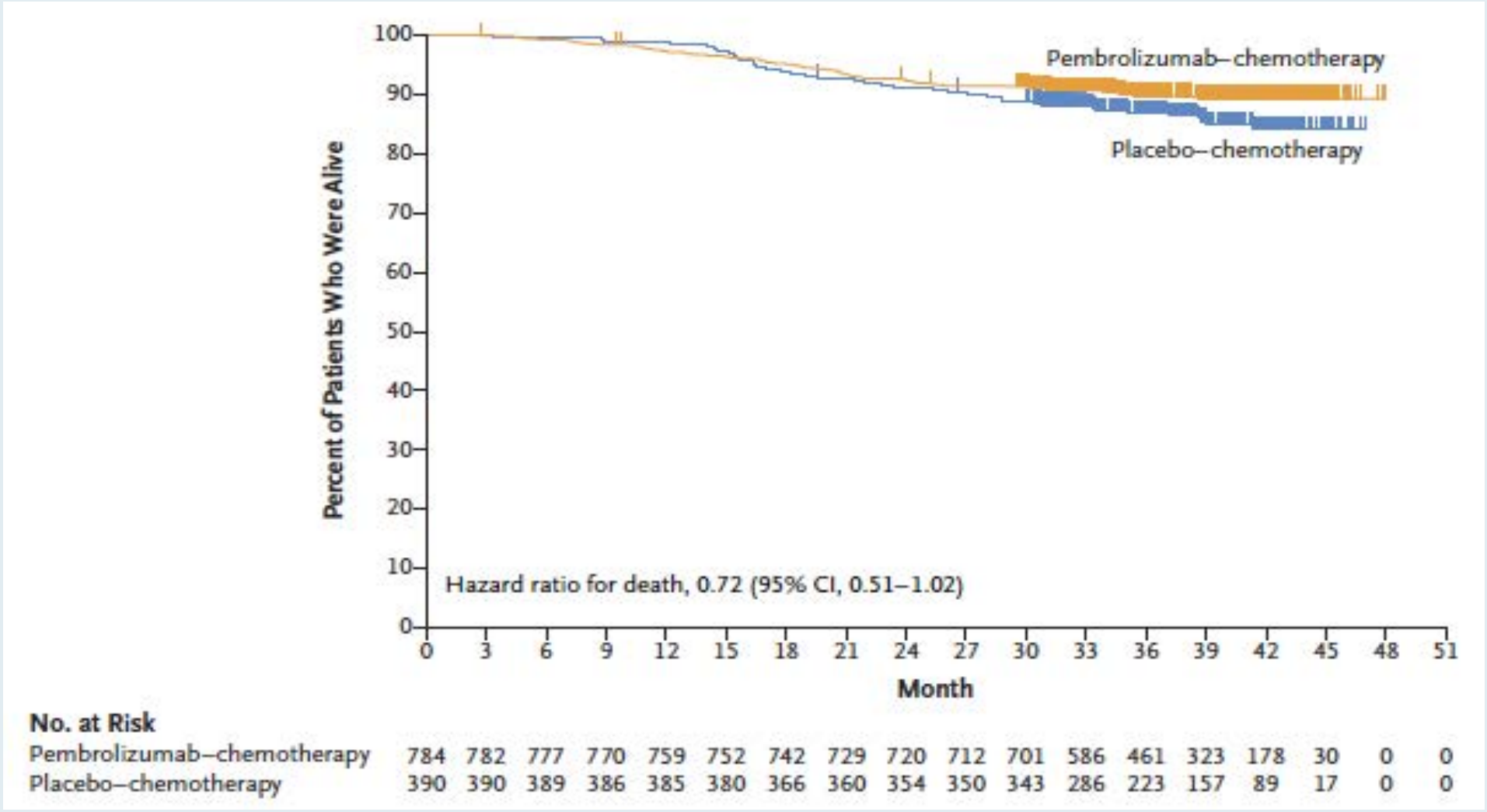
KEYNOTE-522: Event-Free Survival According to Treatment Group (ITT Population)



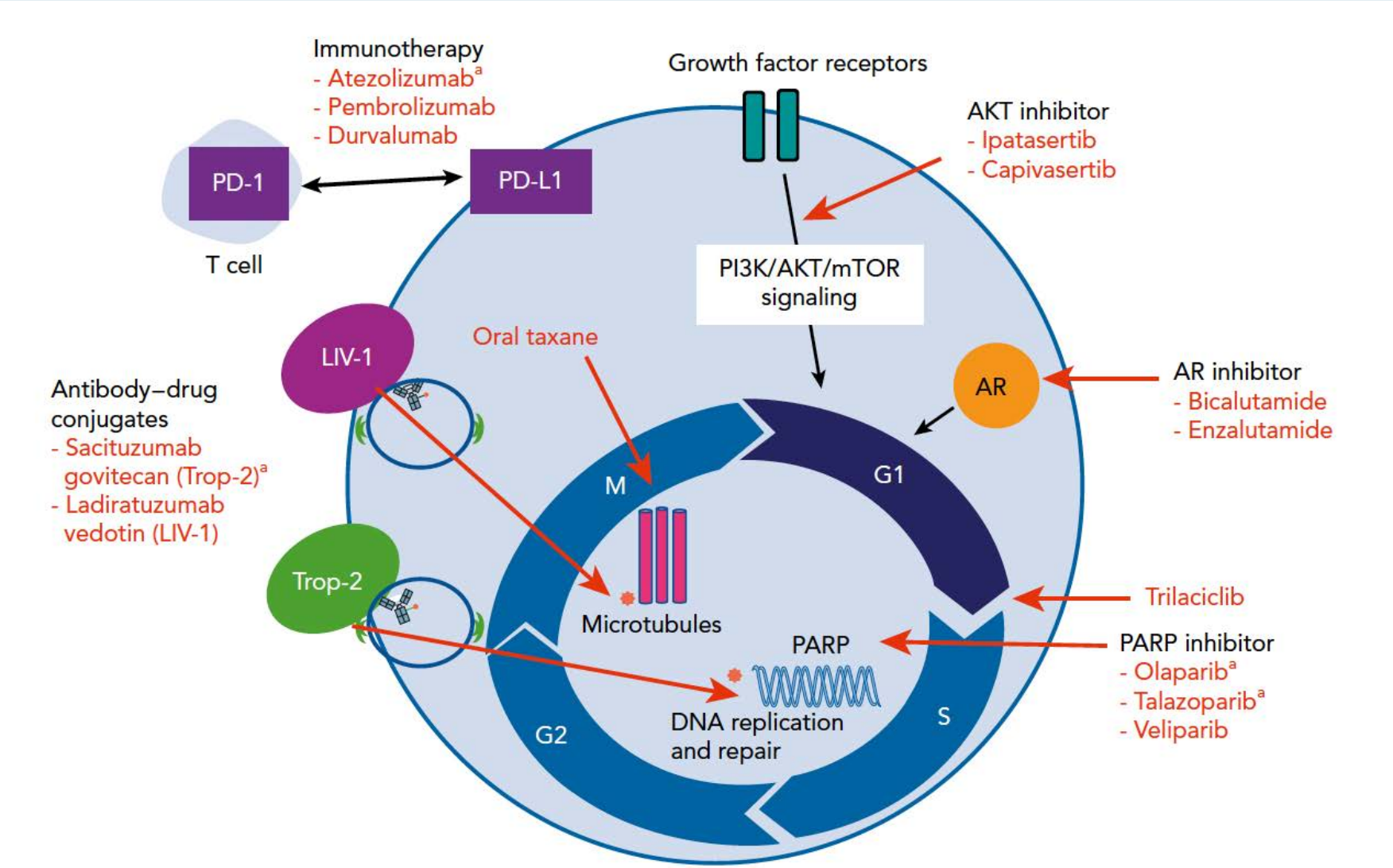
Schmid P et al. *N Engl J Med* 2022;386(6):556-67.

KEYNOTE-522: Overall Survival According to Treatment Group (ITT Population)



Schmid P et al. *N Engl J Med* 2022;386(6):556-67.

Novel Targets for Therapeutic Intervention in Triple-Negative Breast Cancer



Vidula N et al. *J Natl Compr Canc Netw* 2020;[Online ahead of print].

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Thank you for joining us!

CME/MOC and NCPD credit information will be emailed to each participant within 5 business days.

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