Breast Cancer Review 2023
HER2+ and TNBC

January 27th , 2024

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Disclosures

- Honoraria with Medscape
- Advisory Board: Seagen Pfizer / Consulting fees : Seagen Pfizer

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Content

- HER2+ early breast cancer
  - Katherine trial update update (SABCS2023)
- HER2+ advanced breast cancer
  - HER2CLIMB02 trial (SABCS2023)
- TNBC early breast cancer
  - KEYNOTE522 update (ESMO2023)
  - NeoTrip trial (ESMO2023)
  - Impassion030/ALEXANDRA (SABCS2023)
- TNBC advanced breast cancer
  - Begonia trial (ESMO2023)

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HER2 +
Early breast cancer

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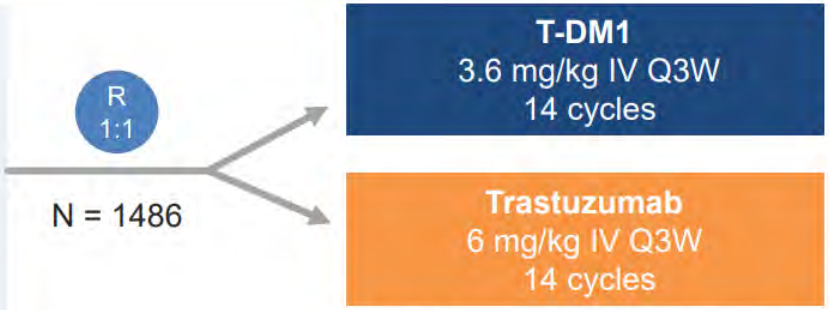
KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

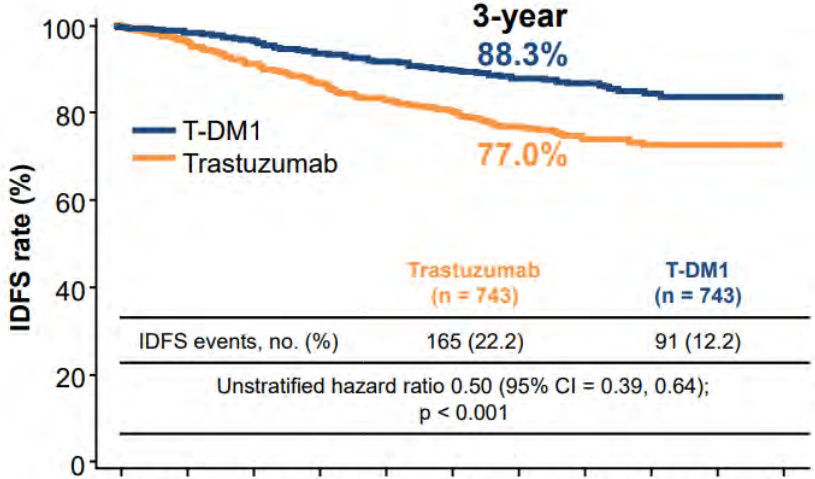
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free surviva
HR, hormone receptor; IDFS, invasive disease
Q3W, every 3 weeks; QoL, quality of life; R, ra

al., Trastuzumab emtansine for residual invasive positive breast cancer, Vol. 380, Pages 617–628.

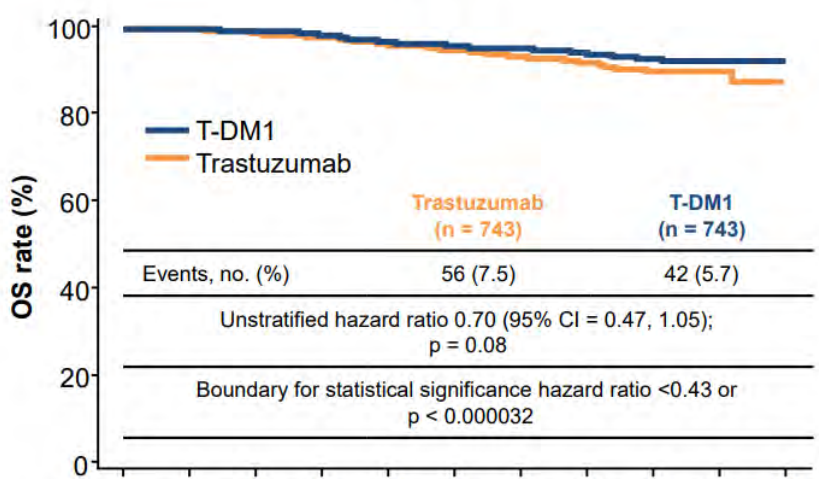
KATHERINE primary analysis (2018)

IDFS



No. at risk											
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4
T-DM1	743	707	681	658	633	561	409	255	142	44	4

OS



No. at risk											
Trastuzumab	743	695	677	657	635	608	471	312	175	71	8
T-DM1	743	719	702	693	668	648	508	345	195	76	12

CCOD: July 25, 2018; median follow-up: 41.4 months (T-DM1) and 40.9 months (trastuzumab).
CCOD, clinical cutoff date; CI, confidence interval; IDFS, invasive disease-free survival; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

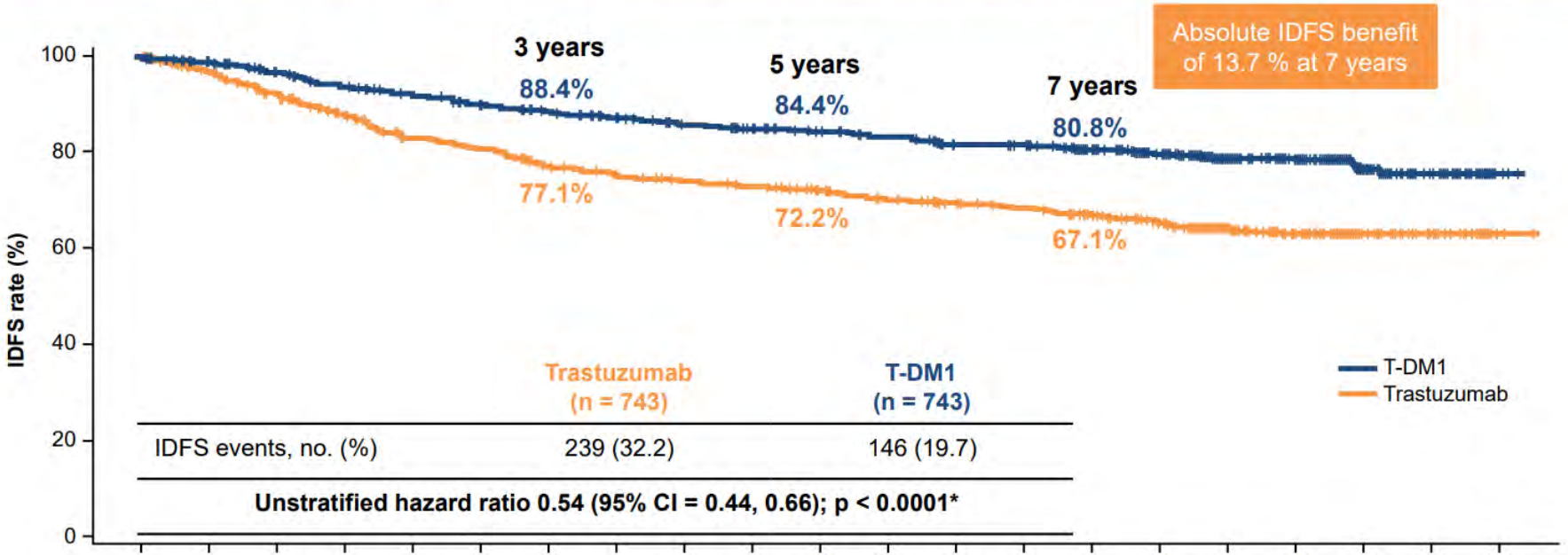
Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

Baseline characteristics of the ITT population

	Trastuzumab (n = 743)	T-DM1 (n = 743)
Clinical stage at presentation, n (%)		
Stages cT1–3N0–1M0 (operable)	553 (74.4)	558 (75.1)
Stage cT4NxM0 or cTxN2–3M0 (inoperable)	190 (25.6)	185 (24.9)
HR status, n (%)		
ER- and/or PgR-positive	540 (72.7)	534 (71.9)
ER-negative and PgR-negative/-unknown	203 (27.3)	209 (28.1)
Preoperative HER2-directed therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-directed agent(s)* – Trastuzumab plus pertuzumab	147 (19.8) 139 (18.7)	143 (19.2) 133 (17.9)
Pathologic nodal status after preoperative therapy, n (%)		
Node-positive	345 (46.4)	343 (46.2)
Node-negative/not done	398 (53.6)	400 (53.8)
Prior anthracycline, n (%)	564 (75.9)	579 (77.9)

Data have been updated since the primary analysis.
* Non-pertuzumab HER2-directed agents included neratinib, afatinib, and lapatinib.
ER, estrogen receptor; HR, hormone receptor; ITT, intention-to-treat; PgR, progesterone receptor; T-DM1, ado-trastuzumab emtansine.

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)

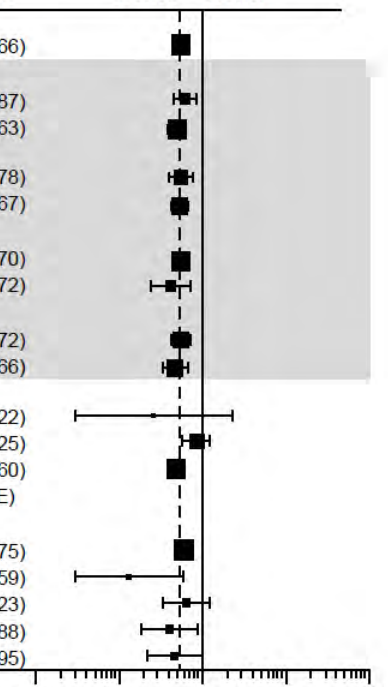


No. at risk																					
Trastuzumab	743	677	636	595	556	540	511	495	485	475	460	444	431	421	397	368	238	187	74	42	2
T-DM1	743	708	682	658	637	620	605	591	574	561	548	537	521	516	481	443	281	236	89	50	3

* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Final IDFS analysis: Subgroups (1/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year IDFS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year IDFS	Hazard ratio	95% CI
All	1486	743	239	67.1	743	146	80.8	0.54	(0.44, 0.66)
Clinical stage at presentation									
Inoperable	375	190	87	51.3	185	62	66.7	0.63	(0.45, 0.87)
Operable	1111	553	152	72.3	558	84	85.4	0.48	(0.37, 0.63)
Hormone receptor status									
Negative (ER-negative and PgR-negative/-unknown)	412	203	75	59.4	209	53	75.0	0.55	(0.39, 0.78)
Positive (ER- and/or PgR-positive)	1074	540	164	69.8	534	93	83.1	0.52	(0.40, 0.67)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	198	66.4	600	128	79.5	0.56	(0.45, 0.70)
Trastuzumab plus additional HER2-directed agent(s)	290	147	41	69.8	143	18	87.2	0.42	(0.24, 0.72)
Pathologic nodal status after preoperative therapy									
Node-positive	688	345	142	57.7	343	96	71.6	0.56	(0.43, 0.72)
Node-negative/not done	798	398	97	74.8	400	50	88.8	0.47	(0.34, 0.66)
Central HER2 status by IHC									
0/1+	25	13	4	67.1	12	1	100.0	0.25	(0.03, 2.22)
2+	326	168	52	68.8	158	44	72.4	0.84	(0.56, 1.25)
3+	1132	559	183	66.5	573	101	82.8	0.47	(0.37, 0.60)
Unknown	3	3	0	100.0				NE	(NE, NE)
Race									
White	1081	530	158	69.3	551	110	80.7	0.59	(0.46, 0.75)
Black or African American	40	19	11	51.3	21	2	88.9	0.13	(0.03, 0.59)
Asian	129	64	22	62.9	65	16	75.3	0.65	(0.34, 1.23)
American Indian or Alaska Native	86	50	25	50.2	36	8	75.8	0.40	(0.18, 0.88)
Other or multiple or unknown	150	80	23	71.0	70	10	86.8	0.45	(0.22, 0.95)



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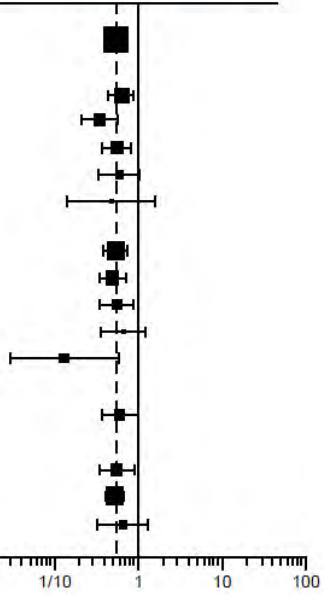
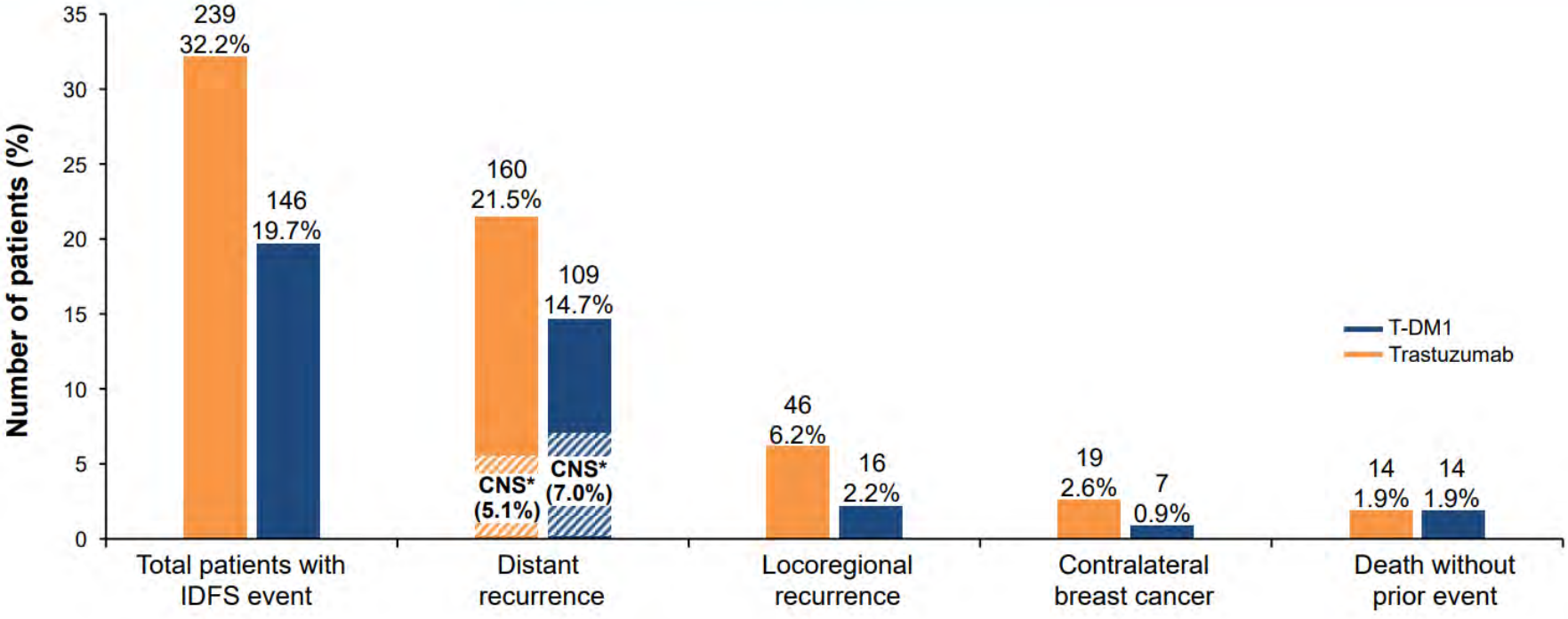
Final IDFS analysis: Subgroups (2/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year IDFS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year IDFS	Hazard ratio	95% CI
All	1486	743	239	67.1	743	146	80.8	0.54	(0.44, 0.66)
Primary tumor stage (at definitive surgery)									
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	306	78	74.6	331	59	82.0	0.65	(0.46, 0.90)
ypT1, ypT1c	359	184	60	66.8	175	22	87.4	0.35	(0.21, 0.56)
ypT2	359	185	67	62.9	174	41	78.4	0.55	(0.37, 0.80)
ypT3	108	57	28	46.4	51	19	62.0	0.59	(0.33, 1.06)
ypT4*	23	11	6	33.8	12	5	70.0	0.49	(0.15, 1.61)
Regional lymph node stage (at definitive surgery)									
ypN0	673	332	83	74.0	341	48	87.1	0.53	(0.37,0.75)
ypN1	432	212	76	63.6	220	47	78.0	0.50	(0.35, 0.72)
ypN2	189	103	47	52.4	86	28	69.5	0.56	(0.35, 0.89)
ypN3	67	30	19	32.1	37	21	38.6	0.67	(0.36, 1.24)
ypNX	125	66	14	79.1	59	2	98.2	0.13	(0.03, 0.59)
Residual disease ≤1 cm with negative axillary lymph nodes									
ypT1a, ypT1b or ypT1mic and ypN0	328	160	36	76.7	168	25	85.7	0.62	(0.37, 1.03)
Age group (years)									
<40	296	153	46	67.2	143	28	81.2	0.56	(0.35, 0.90)
40–64	1064	522	170	66.7	542	104	80.9	0.52	(0.41, 0.66)
≥65	126	68	23	69.4	58	14	78.6	0.67	(0.34, 1.30)

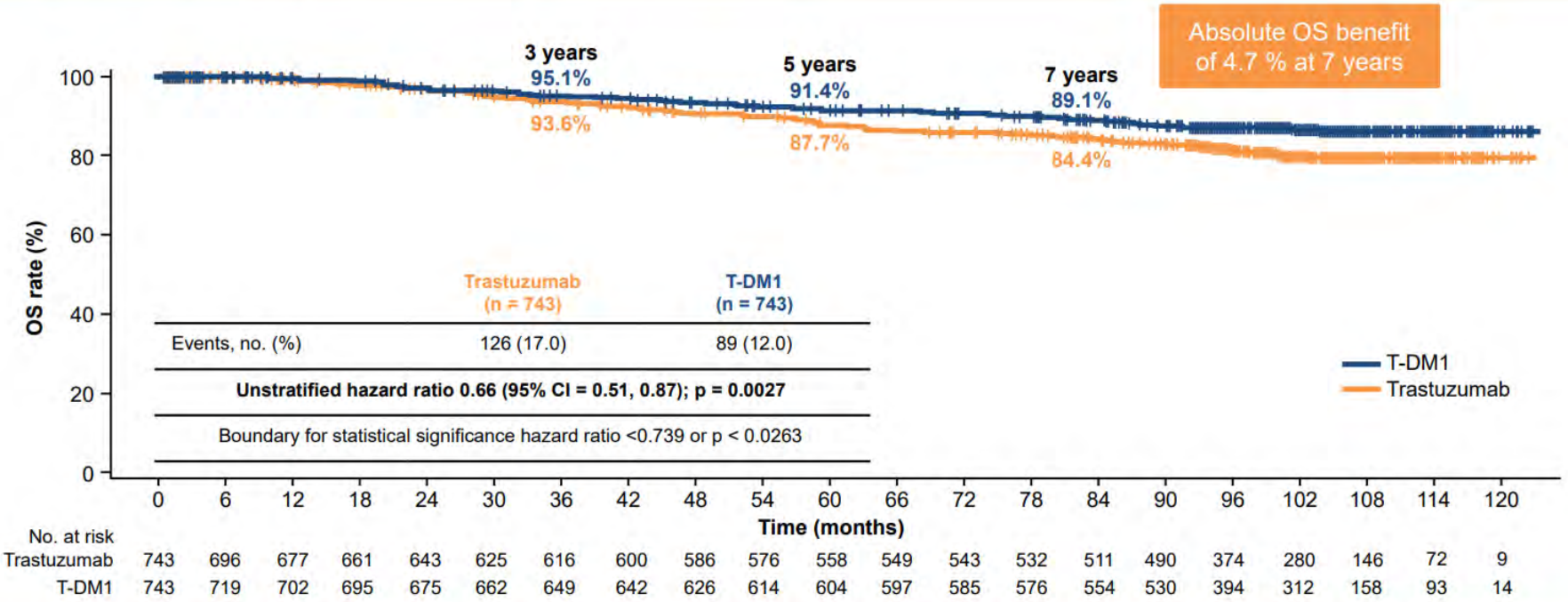


Site of first occurrence of an IDFS event



*** CNS metastases as component of distant recurrence (isolated or with other sites).**
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

2nd OS interim analysis: Subgroups (1/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
All	1486	743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
Clinical stage at presentation									
Inoperable	375	190	57	69.0	185	44	77.5	0.71	(0.48, 1.05)
Operable	1111	553	69	89.4	558	45	92.7	0.62	(0.42, 0.90)
Hormone receptor status									
Negative (ER-negative and PgR-negative/-unknown)	412	203	44	79.9	209	38	83.4	0.73	(0.48, 1.13)
Positive (ER- and/or PgR-positive)	1074	540	82	85.9	534	51	91.3	0.60	(0.42, 0.85)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	105	84.1	600	77	88.6	0.68	(0.51, 0.91)
Trastuzumab plus additional HER2-directed agent(s)	290	147	21	85.7	143	12	91.0	0.57	(0.28, 1.16)
Pathologic nodal status after preoperative therapy									
Node-positive	688	345	90	75.6	343	62	83.4	0.61	(0.44, 0.84)
Node-negative/not done	798	398	36	91.4	400	27	94.0	0.74	(0.45, 1.21)
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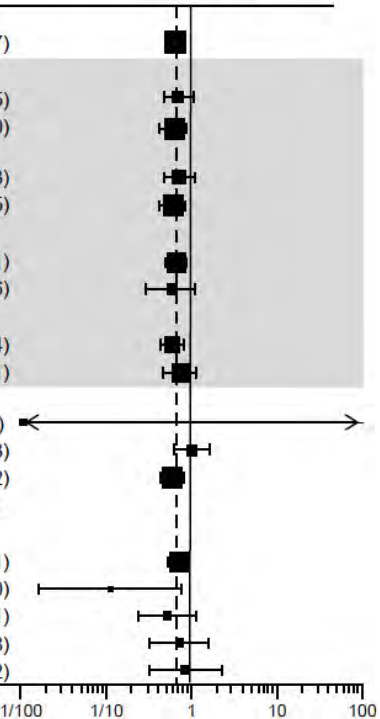
2+	326	168	28	83.4	158	28	83.3	1.03	(0.61, 1.73)
3+	1132	559	94	84.8	573	61	90.4	0.59	(0.43, 0.82)
Unknown	3	3	0	100.0				NE	(NE, NE)
Race									
White	1081	530	80	86.3	551	64	89.0	0.72	(0.52, 1.01)
Black or African American	40	19	8	73.3	21	1	94.1	0.10	(0.01, 0.80)
Asian	129	64	15	78.0	65	9	90.0	0.53	(0.23, 1.21)
American Indian or Alaska Native	86	50	14	68.9	36	8	78.8	0.75	(0.31, 1.78)
Other or multiple or unknown	150	80	9	89.3	70	7	92.3	0.87	(0.32, 2.32)



2nd OS interim analysis: Subgroups (2/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
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ypT4*	23	11	3	63.5	12	3	80.0	0.72	(0.14, 3.58)
Regional lymph node stage (at definitive surgery)									
ypN0	673	332	32	90.7	341	27	92.8	0.82	(0.49,1.37)
ypN1	432	212	46	80.9	220	30	86.6	0.57	(0.36, 0.90)
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Residual disease ≤1 cm with negative axillary lymph nodes									
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Age group (years)									
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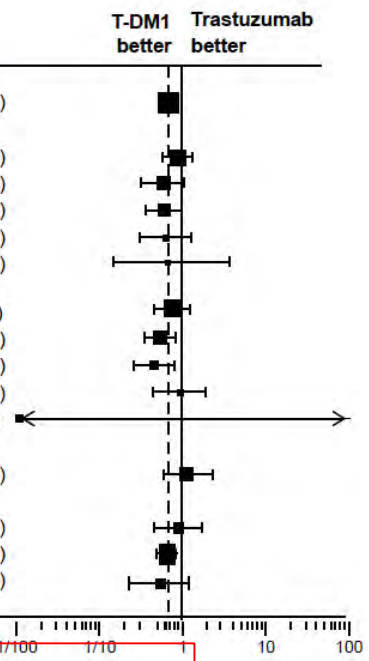

More residual disease had greater impact in OS

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Follow-up medications after IDFS events (ITT)

	Trastuzumab (n = 743)	T-DM1 (n = 743)
Total number of patients with an IDFS event, n	239	146
Total number of patients with documentation of ≥1 treatment following an IDFS event, n (%)	169 (70.7)	94 (64.4)
Class, n (%)*		
HER2-directed therapies	132 (78.1)	61 (64.9)
Pertuzumab	73 (43.2)	30 (31.9)
Trastuzumab	114 (67.5)	52 (55.3)
T-DM1	53 (31.4)	12 (12.8)
T-DXd	3 (1.8)	6 (6.4)
Tyrosine kinase inhibitors (lapatinib, neratinib, pyrotinib, pazopanib)	31 (18.3)	26 (27.7)
Platinum compounds	17 (10.1)	10 (10.6)
Taxanes	102 (60.4)	40 (42.6)
Capecitabine	51 (30.2)	44 (46.8)

* Percentages based on number of patients who received ≥1 follow-up medication.
IDFS, invasive disease-free survival; ITT, intention-to-treat; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Related AEs during the post-treatment period*

Patients, n (%) with ≥1:	Trastuzumab (n = 720)	T-DM1 (n = 740)
AE (any grade, >1 patient in either arm)	12 (1.7)	24 (3.2)
Investigations	5 (0.7)	9 (1.2)
Cardiac disorders	5 (0.7)	5 (0.7)
Nervous system disorders	0	4 (0.5)
Hepatobiliary disorders	0	2 (0.3)
Metabolism and nutrition disorders	0	2 (0.3)
Skin and subcutaneous tissue disorders	0	2 (0.3)
Serious AE	4 (0.6)	2 (0.3)
Cardiac disorders	3 (0.4)	0
Hepatobiliary disorders	0	2 (0.3)
Vascular disorders	1 (0.1)	0
Grade ≥3 AE	3 (0.4)	3 (0.4)
Cardiac disorders	3 (0.4)	1 (0.1)
Hepatobiliary disorders	0	2 (0.3)

* Related to study treatment or to study procedures.
Includes AEs with date of onset >30 days after last dose of study treatment. During the follow-up period, only deaths, serious AEs, or other AEs of concern that are believed to be related to prior treatment with study drug or study procedures were reported.
AE, adverse event; T-DM1, ado-trastuzumab emtansine.

Practice

- Reinforced current practice

Questions remaining

- Recurrences after adjuvant TDM1:
  - Ongoing trials with adjuvant TDxd vs TDM1 (Destiny Breast05) and TDM1+/-tucatinib (Compass HER2RD)
- CNS recurrence not tackled by adjuvant TDM1

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HER2 +
Advanced breast cancer

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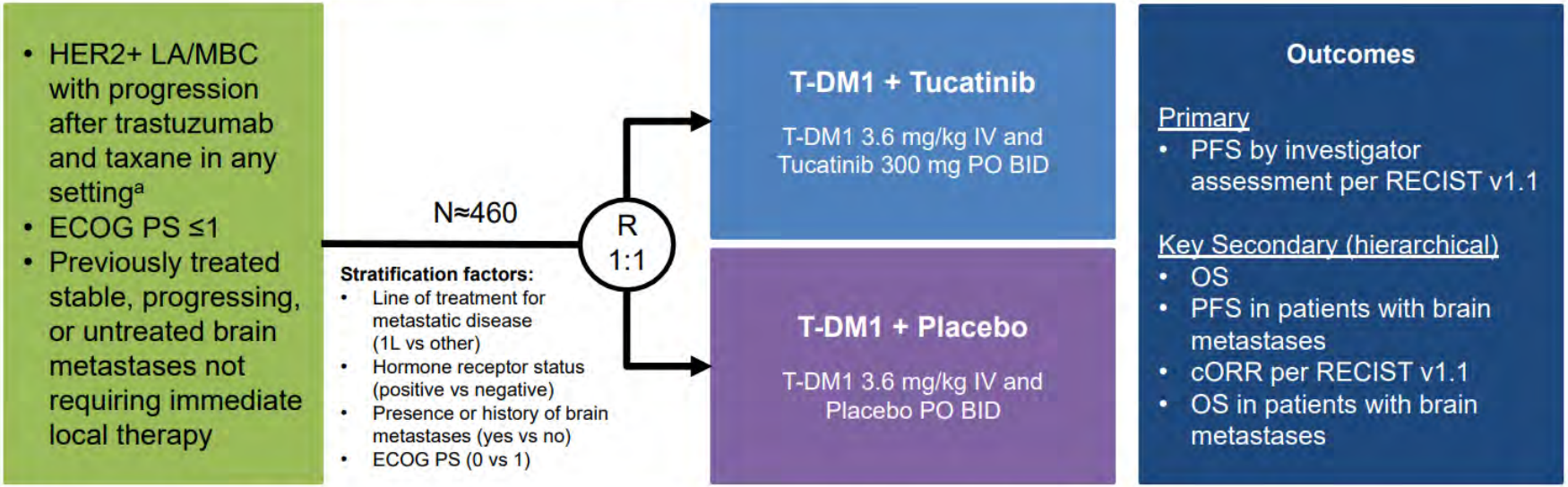
HER2CLIMB-02 Study Design



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b]

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
b Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.
1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

Demographics and Baseline Characteristics

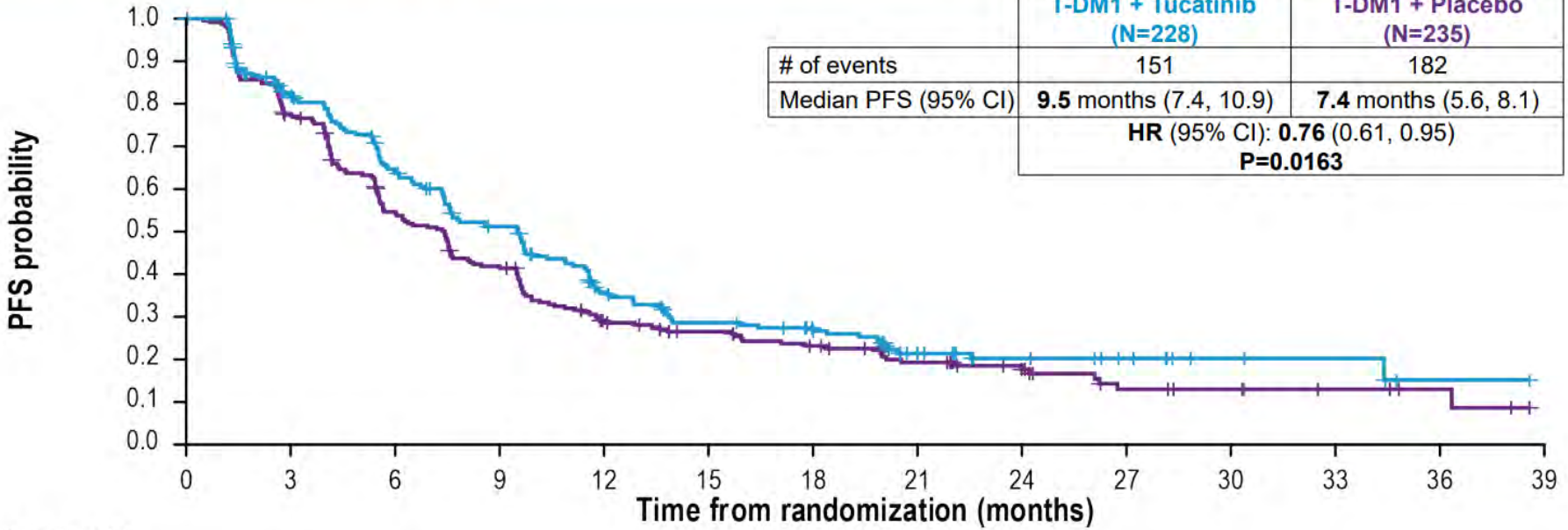
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Median age, years (range)	55.0 (26-83)	53.0 (27-82)
Female sex, n (%)	226 (99.1)	235 (100)
Geographic region, n (%)		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
Hormone-receptor status, n (%)		
Positive	137 (60.1)	140 (59.6)
Negative	91 (39.9)	95 (40.4)
ECOG performance status score, n (%)		
0	137 (60.1)	141 (60.0)
1	91 (39.9)	94 (40.0)

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)
Stage at initial diagnosis, n (%)[b]		
0-III	120 (52.6)	130 (55.3)
IV	103 (45.2)	98 (41.7)

a Includes 2 patients with missing brain metastases data.
b Five patients in T-DM1 + Tucatinib arm and 7 patients in T-DM1 + Placebo arm had unknown stage.
ECOG, Eastern Cooperative Oncology Group; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Progression-Free Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	



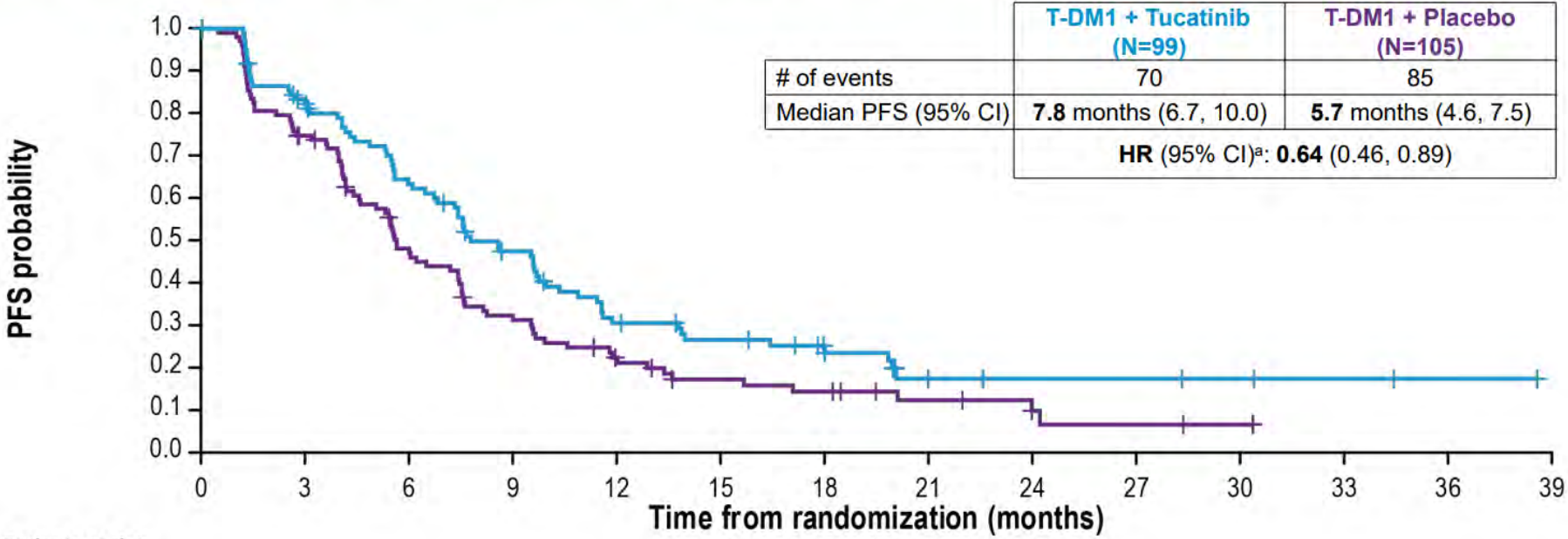
Patients at risk

T-DM1 + Tucatinib	228	165	126	96	62	47	40	22	14	10	5	4	1	0
T-DM1 + Placebo	235	177	120	91	58	48	40	29	19	10	8	5	3	0

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

PFS in Patients with Brain Metastases

	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	

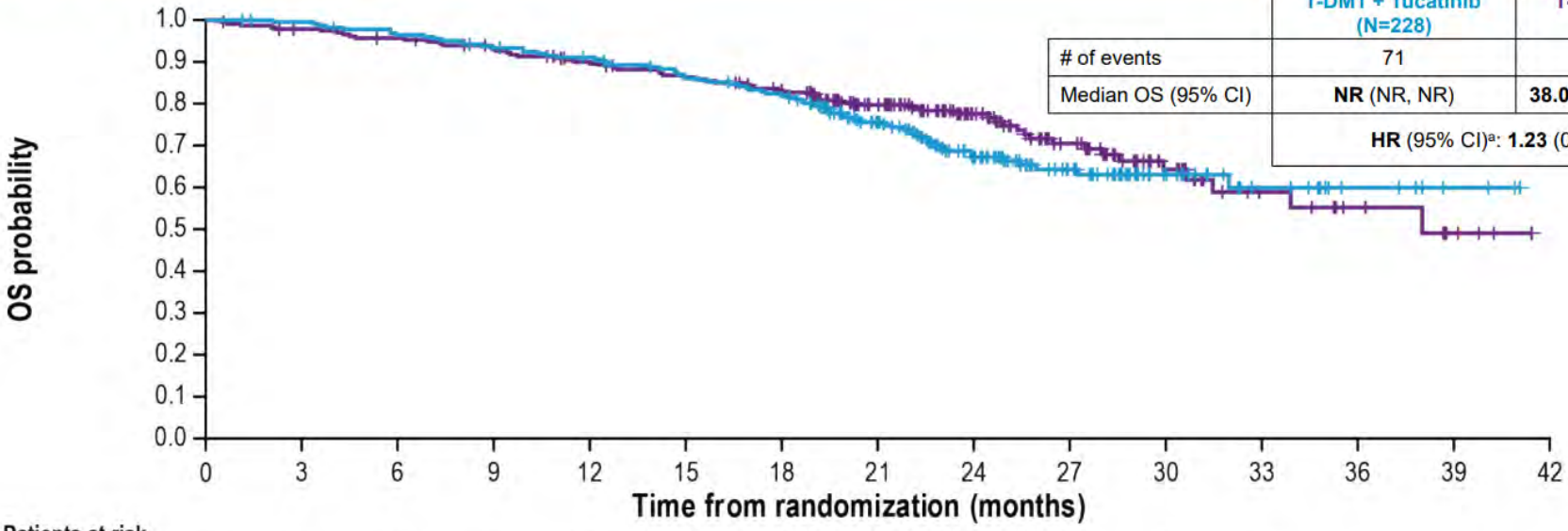


Patients at risk

T-DM1 + Tucatinib	99	76	57	40	25	20	15	6	4	4	3	2	1	0
T-DM1 + Placebo	105	75	46	30	18	12	10	6	3	2	1	0	0	0

a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Overall Survival



	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
	HR (95% CI)[a]: **1.23** (0.87, 1.74)	

Patients at risk

T-DM1 + Tucatinib	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
T-DM1 + Placebo	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of P≤0.0041.

he proportional hazard assumption was not maintained post-18 months, with extensive censoring on both arms.
, hazard ratio; NR, not reached; OS, overall survival; T-DM1, trastuzumab emtansine.
te of data cutoff: Jun 29, 2023.

Overall Safety Summary

	T-DM1 + Tucatinib (N=231) n (%)	T-DM1 + Placebo (N=233) n (%)
Any TEAE	230 (99.6)	233 (100)
Grade ≥3 TEAE	159 (68.8)	96 (41.2)
Any TESAE	70 (30.3)	52 (22.3)
TEAE leading to death	3 (1.3)	2 (0.9)
Discontinued tucatinib or placebo due to TEAE	40 (17.3)	16 (6.9)
Discontinued T-DM1 due to TEAE	47 (20.3)	26 (11.2)

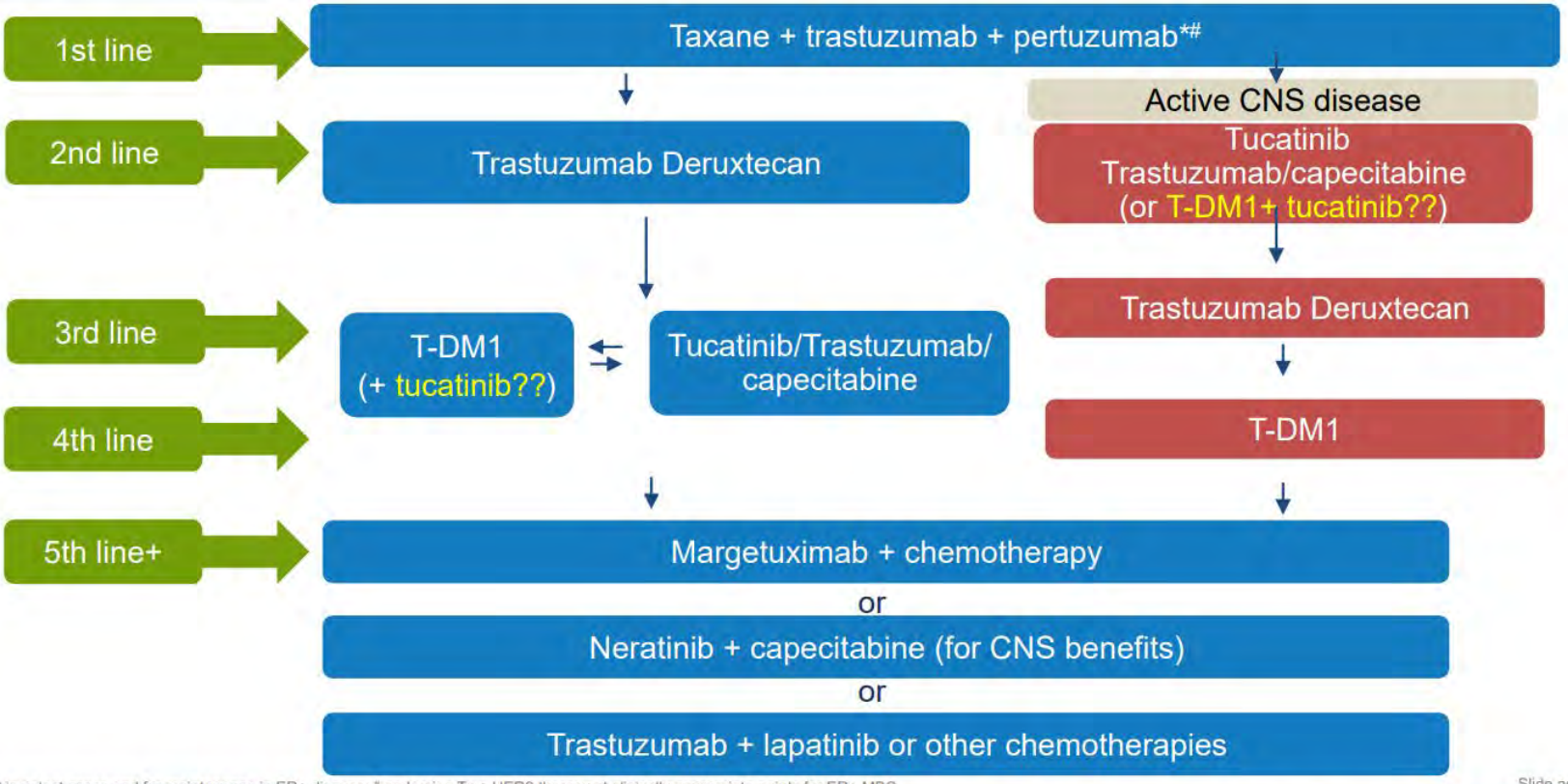
Median duration of tucatinib or placebo treatment: 7.4 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo
Median duration of T-DM1 treatment: 7.5 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

Most common TEAEs (≥2%) leading to tucatinib or placebo discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo) :
- ALT increased (2.6% vs 0%)

Most common TEAEs (≥2%) leading to T-DM1 discontinuation (T-DM1 + Tucatinib vs T-DM1 + Placebo) :
- ALT increased (2.2% vs 0%)
- Thrombocytopenia (2.2% vs 0%)
- Interstitial lung disease (0% vs 2.1%)

ALT, alanine aminotransferase; T-DM1, trastuzumab emtansine; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.
Date of data cutoff: Jun 29, 2023.

Algorithm for Metastatic HER2+ Disease

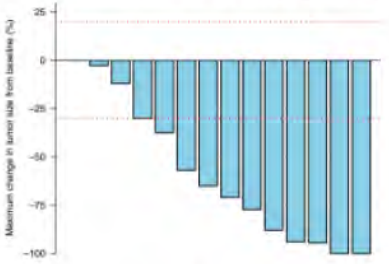


*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Slide adapted from Shanu Modi

Trastuzumab Deruxtecan in pts with active brain mets

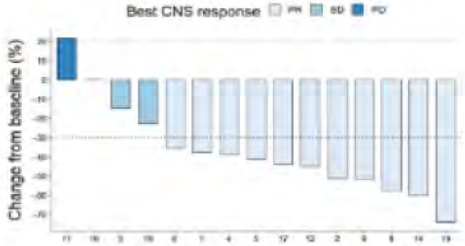
TUXEDO-1 study (n=15)



Intracranial RR = 73.3%

DFCI/MDACC/Duke (n=15*)

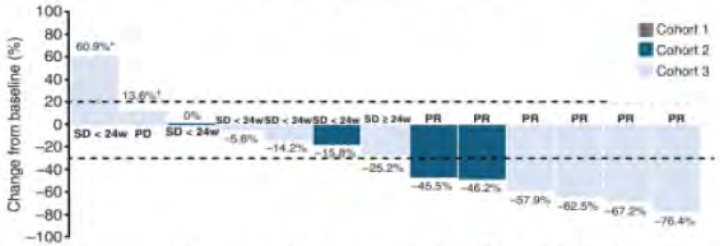
*15/17 with evaluable intracranial RR



Intracranial RR = 73%

DEBBRAH (n=13*)

*active BM cohorts (2 and 3)



Overall intracranial RR = 46.2%
(asymptomatic untreated + progressing BMs)

MADRID 2023 ESMO congress

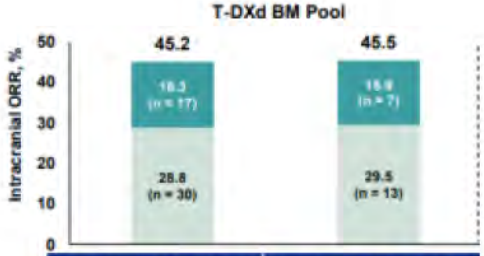
A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

Sara A. Hurvitz[1], Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaque, Anton Egorov, Fabrice André

On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

In T-DXd pool, 29.7% of pts had untreated/active BMs



	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)
Best overall IC response, n (%)		
Stable disease	48 (46.2)	15 (34.1)
Progressive disease	3 (2.9)	1 (2.3)
Not evaluable/Missing	6 (5.8)	8 (18.2)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)

Bartsch R et al, Nature Medicine 2022; Kabraji S et al, CCR 2023; Pérez-García JM et al, Neuro-Oncology 2023; Hurvitz S et al, ESMO 2023

Practice

- May become a potential alternative to trastuzumab + tucatinib + capecitabine regimen in brain metastases patients

OHSU

Questions remaining:

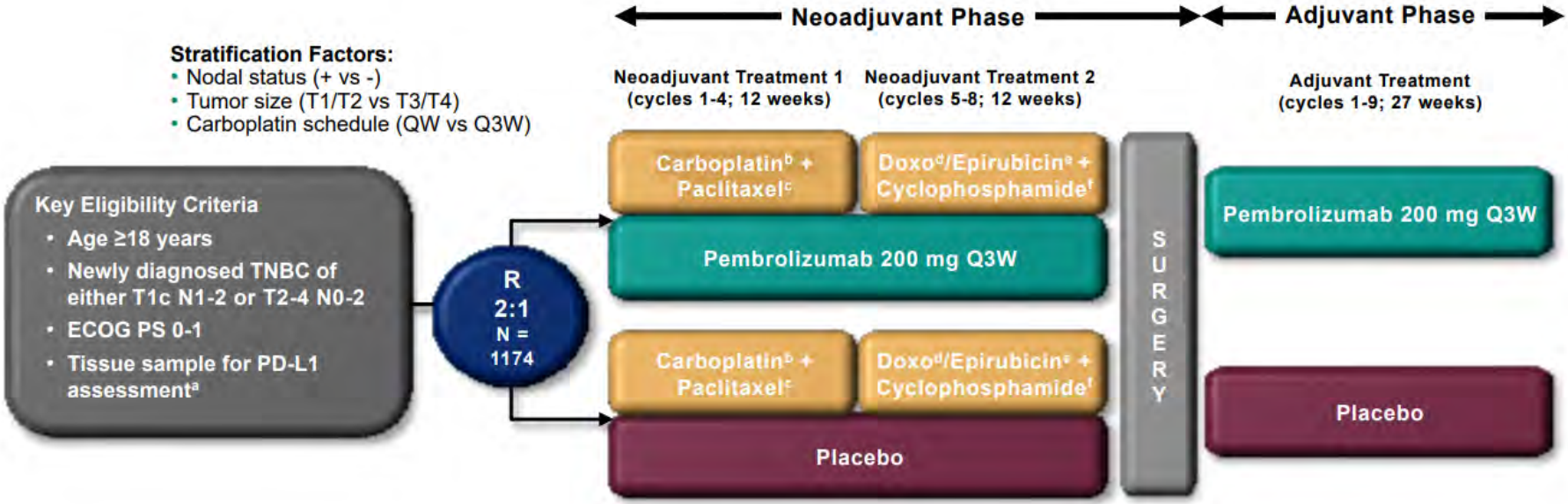
- Use of tucatinib and change backbone of chemo (considering HER2CLIMB data)
- Use of neratinib or lapatinib post tucatinib
- Comparison to TDxd or use after TDxd
- Implications of Katherine trial (adjuvant TDM1) and future results of CompassHER2 RD trial (adjuvant TDM1 +/- tucatinib)

OHSU

TNBC
Early breast cancer

OHSU

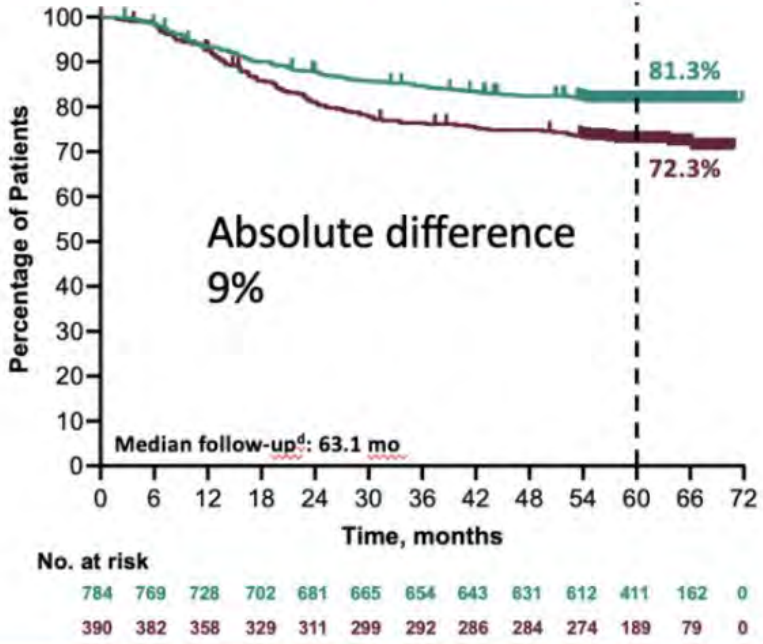
KEYNOTE-522 Study: 5-year Update

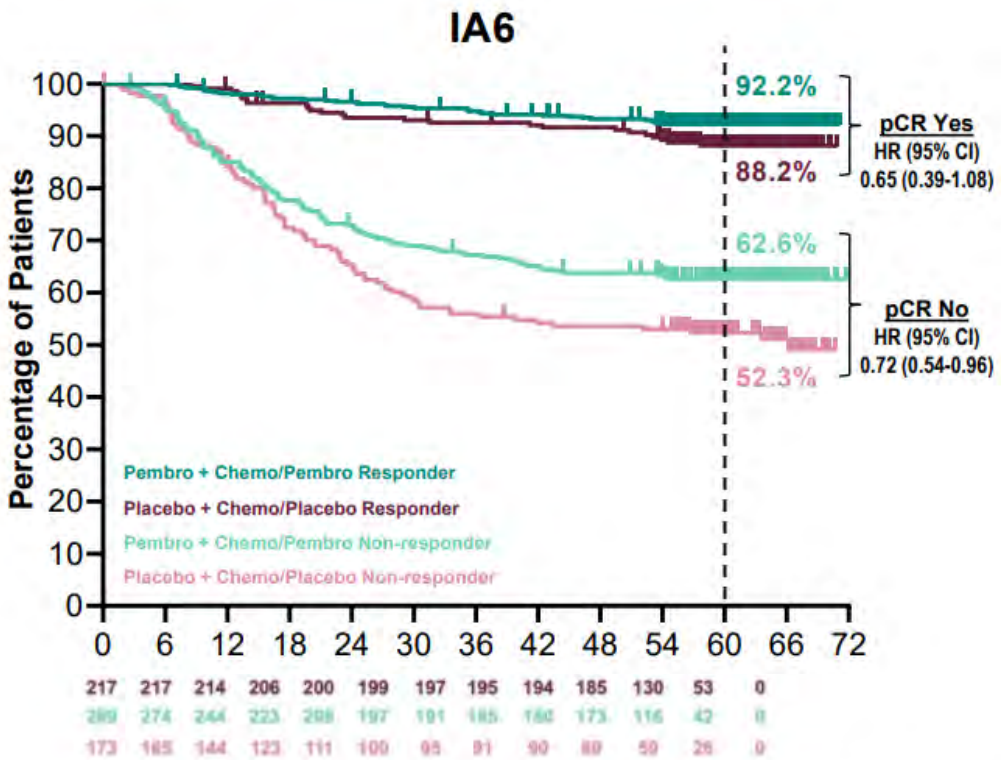


Schmid et al. ESMO 2023

KEYNOTE-522 Study: 5-year EFS and EFS by pCR

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

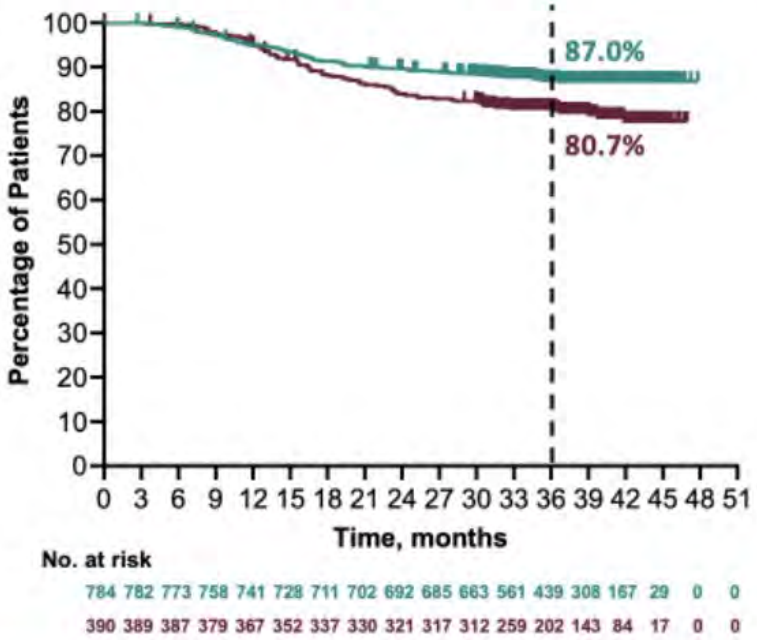




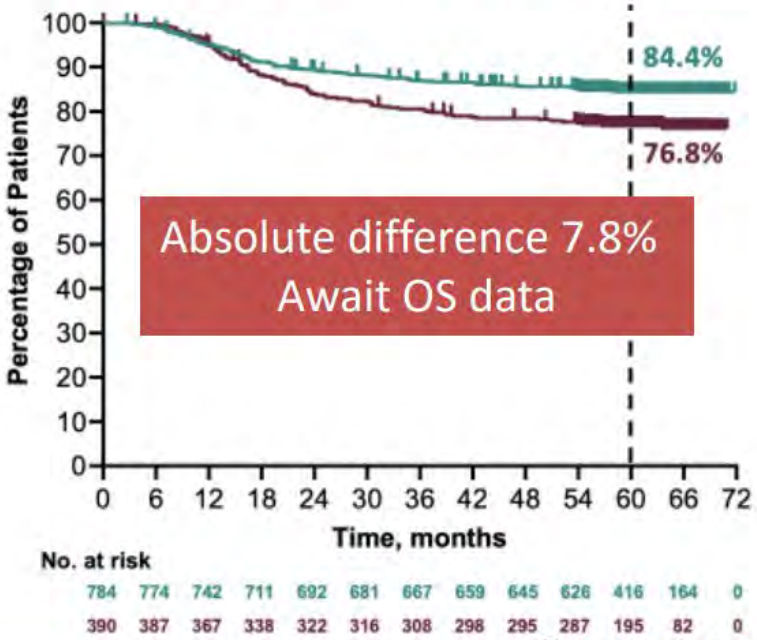
Schmid et al, ESMO 2023

KEYNOTE-522 Distant RFS

IA4	Events	HR (95% CI)
Pembro + Chemo/Pembro	12.8%	0.61[a] (0.46-0.82)
Placebo + Chemo/Placebo	20.3%	



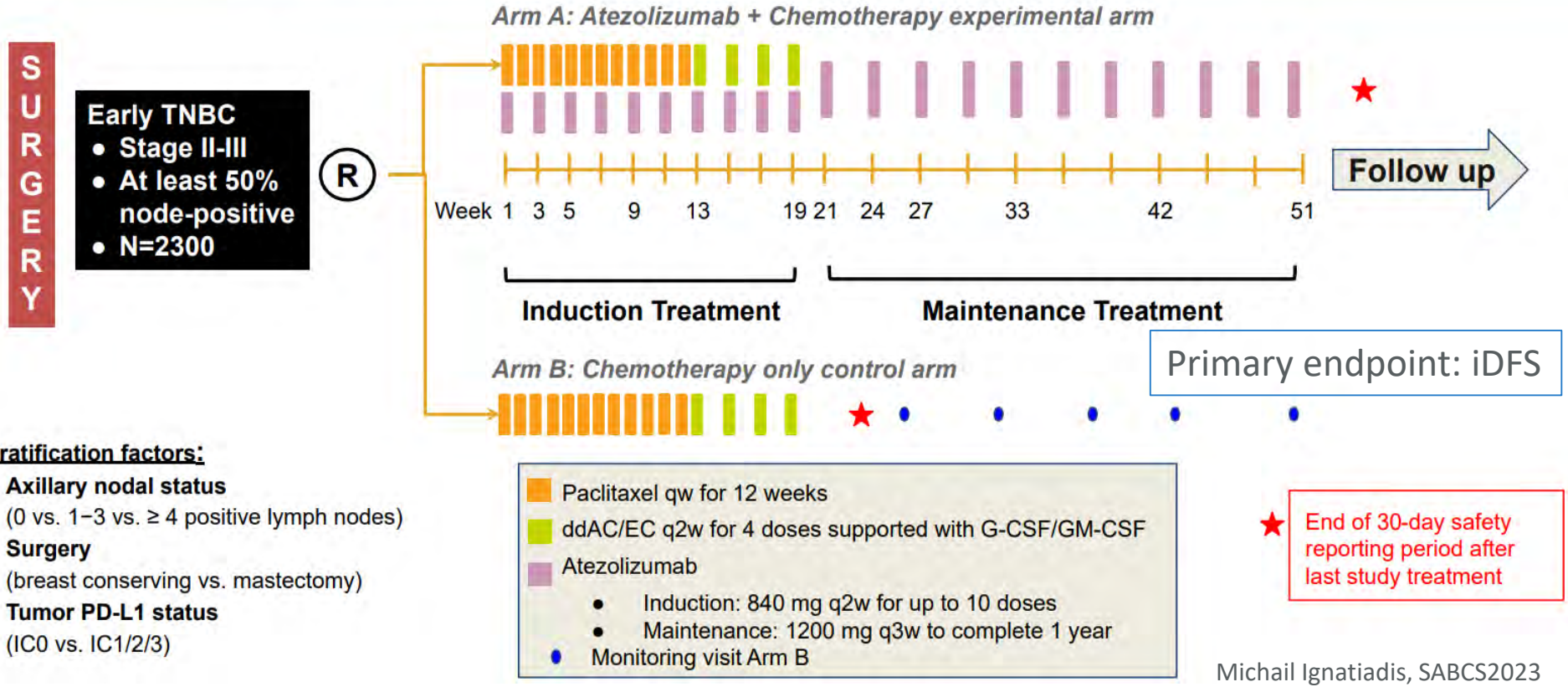
IA6	Events	HR (95% CI)
Pembro + Chemo/Pembro	15.3%	0.64[a] (0.49-0.84)
Placebo + Chemo/Placebo	23.1%	



Absolute difference 7.8%
Await OS data

Schmid et al, ESMO 2023

Alexandra/IMpassion030 Phase 3 Open-label Study Design



Baseline characteristics, ITT population (1)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Age (years), median (range)	53 (24–86)	53 (23–79)	53 (23–86)
Age Group (years)			
<65	916 (83.2)	904 (82.3)	1820 (82.8)
≥65	185 (16.8)	194 (17.7)	379 (17.2)
Race			
White	554 (50.3)	564 (51.4)	1118 (50.8)
Asian	423 (38.4)	401 (36.5)	824 (37.5)
American Indian or Alaska Native	28 (2.5)	27 (2.5)	55 (2.5)
Black or African American	8 (0.7%)	2 (0.2)	10 (0.5)
Other[1]	2 (0.2)	6 (0.5)	8 (0.4)
Unknown	86 (7.8)	98 (8.9)	184 (8.4)
ECOG Score at baseline			
0	887 (80.6)	895 (81.5)	1782 (81.0)
1	214 (19.4)	203 (18.5)	417 (19.0)

[1] Race category 'Other' includes 'Native Hawaiian or other pacific islander' and 'Multiple'

Baseline characteristics, ITT population (3)

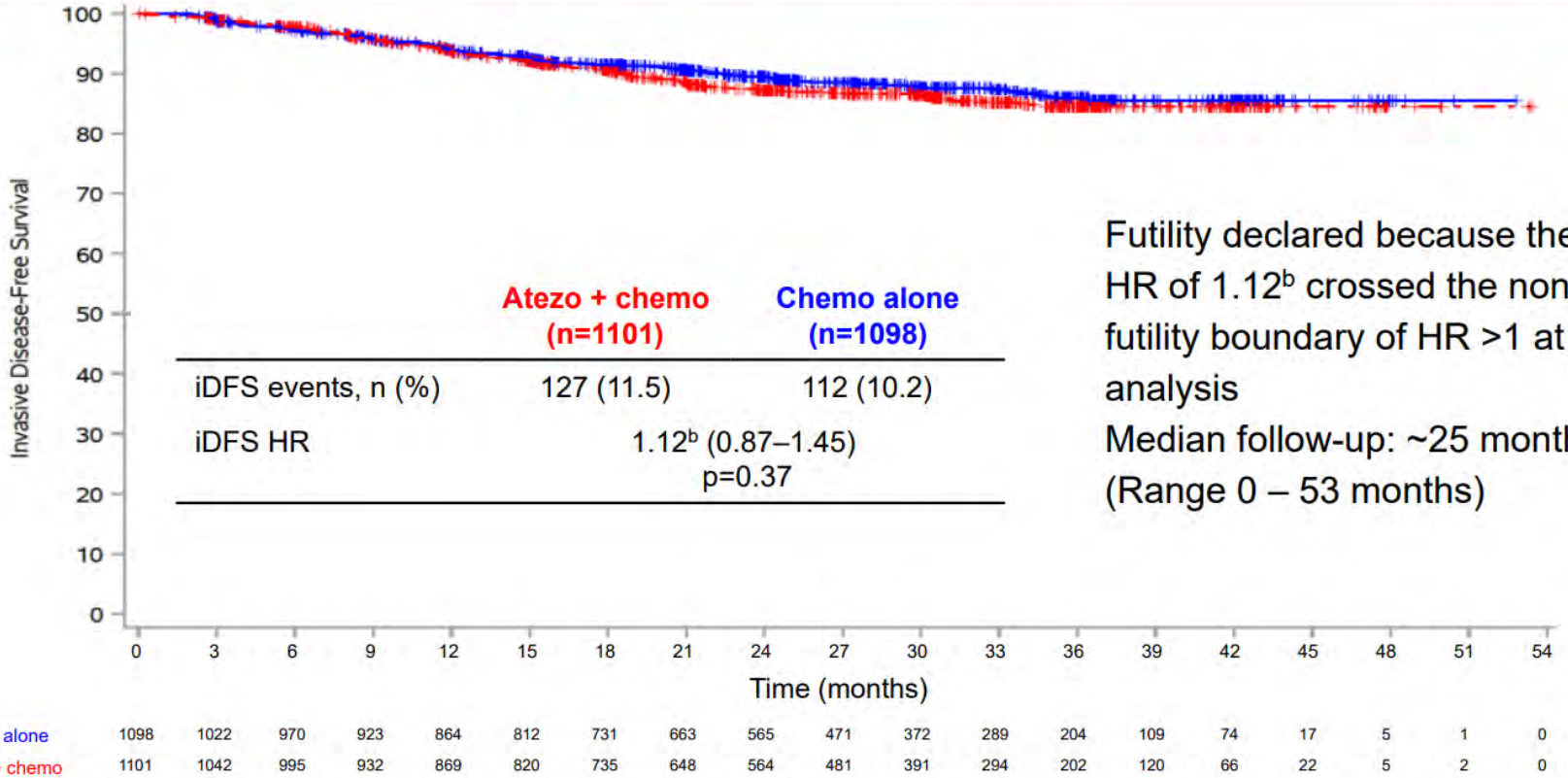
Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Primary Tumor Stage			
pT1-pT2	1024 (93.0)	1045 (95.2)	2069 (94.1)
pT3	71 (6.4)	51 (4.6)	122 (5.5)
Other[1]	6 (0.5)	2 (0.2)	8 (0.4)
Axillary Nodal Status (IxRS)			
0	577 (52.4)	573 (52.2)	1150 (52.3)
1-3	390 (35.4)	390 (35.5)	780 (35.5)
≥4	134 (12.2)	135 (12.3)	269 (12.2)
AJCC Stage at Surgery			
Stage II	935 (84.9)	940 (85.6)	1875 (85.3)
Stage III	161 (14.6)	157 (14.3)	318 (14.5)
Other[2]	5 (0.5)	1 (<0.1)	6 (0.3)

[1]Primary Tumor Stage category 'Other' includes 'pT0', 'pTis', 'pT4', 'pT4b' and missing
[2]AJCC Stage category 'Other' includes 'Stage I' and missing

Baseline characteristics, ITT population (4)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
PD-L1 Status (IxRS)			
IC 0	316 (28.7)	316 (28.8)	632 (28.7)
IC 1/2/3	785 (71.3)	782 (71.2)	1567 (71.3)
Surgery (IxRS)			
Breast conserving	524 (47.6)	523 (47.6)	1047 (47.6)
Mastectomy	577 (52.4)	575 (52.4)	1152 (52.4)

Primary efficacy endpoint: iDFS[a] (ITT population)



	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

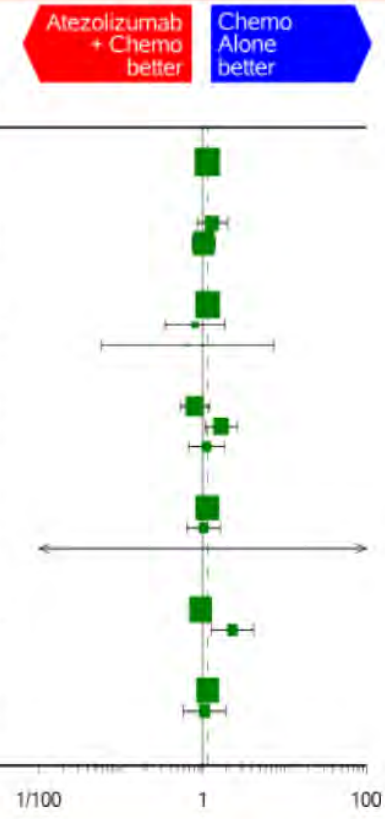
Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months (Range 0 – 53 months)

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

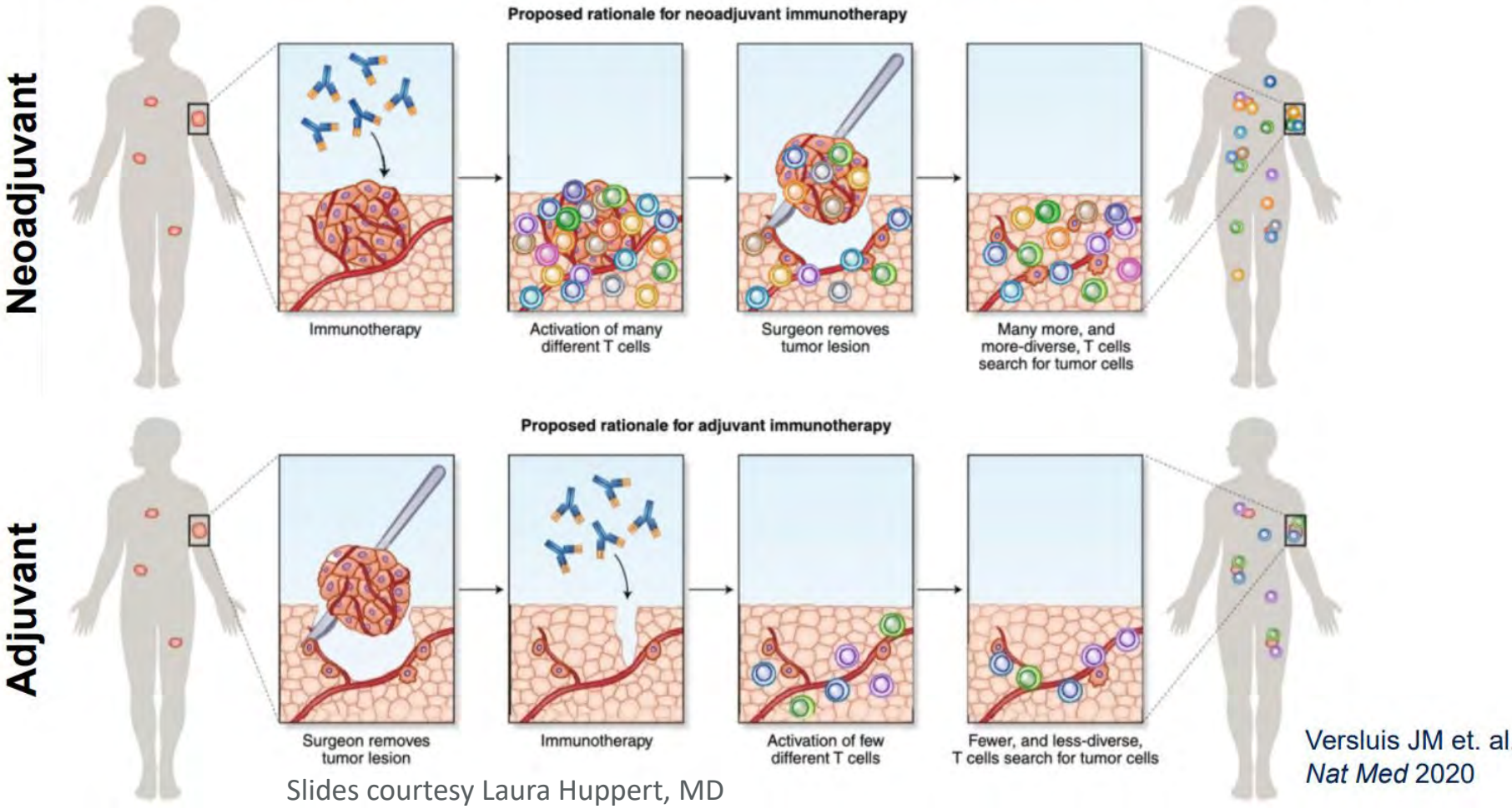
iDFS subgroup analysis (ITT Population)

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



Hazard ratios and the associated Wald confidence intervals were estimated using *unstratified* Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Proposed rationale for neoadjuvant vs. adjuvant immunotherapy

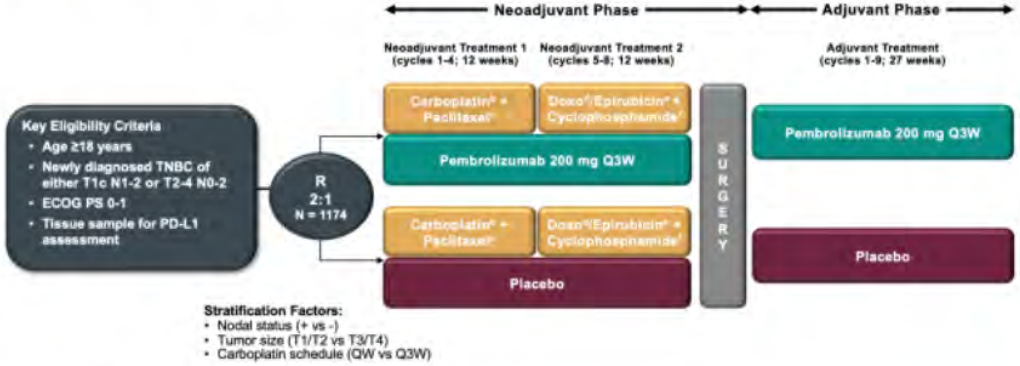


Versluis JM et. al.
Nat Med 2020

Slides courtesy Laura Huppert, MD

Phase III trials of NACT +/- neoadj and adj immunotherapy for early-stage TNBC

KEYNOTE-522



pCR rates

- Pembro arm: 64.8%
- Placebo arm: 51.2%

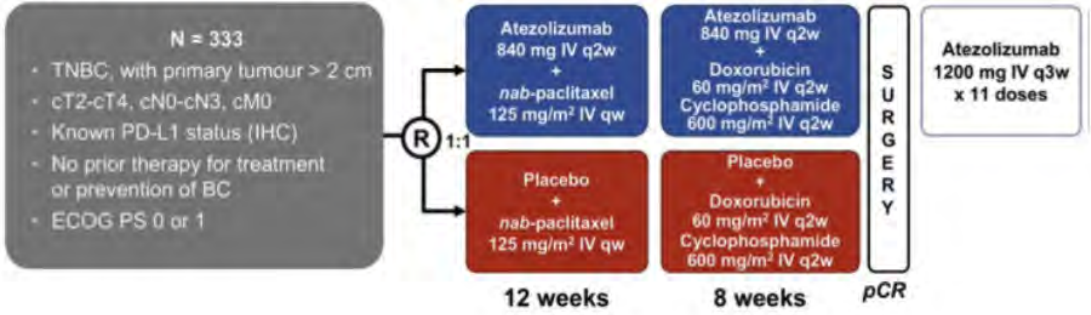
Δ13.6
p<0.001

EFS rates

- Pembro arm: 81.3%
- Placebo arm: 72.3%

Δ9.0%
HR 0.63

Impassion031



pCR rates

- Atezo arm: 57.6%
- Placebo arm: 41.1%

Δ16.5%
p=0.0044

EFS rates

Not reported

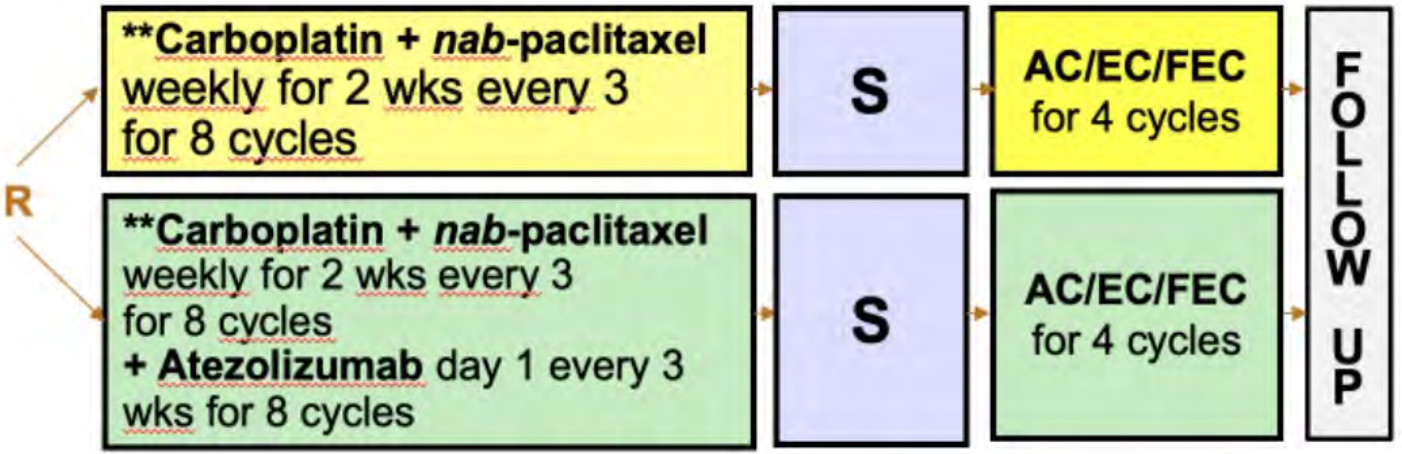
Slides courtesy Laura Huppert, MD

Schmid et. al. *NEJM* 2020, ESMO 2023
Mittendorf et. al. *Lancet* 2020

NeoTRIP Trial

At median follow-up of 54 months, the five-year EFS was 70.6% (95% CI 61.6 – 77.9) with atezolizumab and 74.9% (95% CI 66.6 – 81.5) w/o atezolizumab.

*HER-2 negative, ER and PgR negative early high-risk (T1cN1; T2N1; T3N0) or locally advanced unilateral breast cancer



*ER, PgR, HER2 and PD-L1 (SP142; pos ≥ 1% IC) were centrally assessed before randomization

Tumour & Blood Banked for Correlative Studies

Gianni et al, ESMO 2023

Practice

- Reinforced current practice of immunotherapy in neoadjuvant setting for early TNBC – KEYNOTE522

OHSU

Questions remaining

- Is the PDL-1 inhibitor inferior
  - GeparDouze/NSABP B-59: A randomized double-blind phase III clinical trial of NACT with atezolizumab or placebo in patients with TNBC followed by adjuvant atezolizumab or placebo
- Timing of immunotherapy
  - S1418 (SWOG): A randomized phase III trial of pembrolizumab as adjuvant therapy for TNBC with >/=1 cm residual invasive cancer or positive lymph nodes (ypN1mi, ypN1-3) after NACT
- Need of IO in both neoadjuvant and adjuvant
  - OptimICE-pCR (NCT05812807): Pembrolizumab vs. observation in TNBC with pCR after NACT plus pembrolizumab

Questions remaining

- Patients with no pCR after NACT + IO
  - SASCIA: phase III postneoadjuvant Sacituzumab Govitecan in HER2-negative breast cancer after standard neoadjuvant treatment
  - ASCENT-05: Sacituzumab Govitecan and pembrolizumab vs. physician's choice in TNBC with residual disease after NACT
  - TROPION-Breast03: Dapotomab deruxtecan +/- durvalumab vs. Capecitabine/pembrolizumab in TNBC without pCR after NACT

OHSU

TNBC
Advanced breast cancer

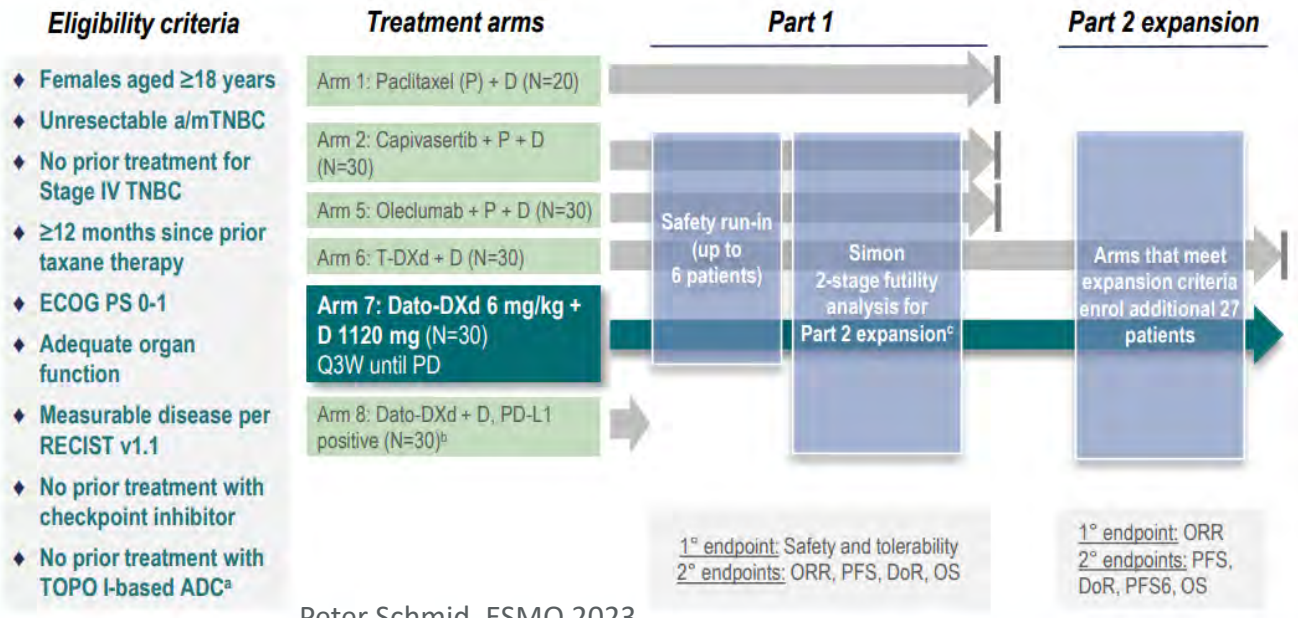
OHSU

The BEGONIA Study (NCT03742102)

Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design



Peter Schmid, ESMO 2023

We report updated results with longer follow-up for patients from Parts 1 and 2 treated with Dato-DXd + D in BEGONIA Arm 7

[a]ADC-cohort-specific criteria. [b]Currently enrolling; a safety run-in will not occur for this arm as Dato-DXd + D was already evaluated and found to be tolerable with no dose-limiting toxicities reported. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

1. Cortes J, et al. *Lancet*. 2020;396(10265):1817-1828. 2. Emens LA, et al. *J Natl Cancer Inst*. 2021;113(8):1005-1016. 3. Bardia A, et al. Presented at SABCS 2022. P6-10-03. 4. Schmid P, et al. Presented at SABCS 2022. PD11-09.

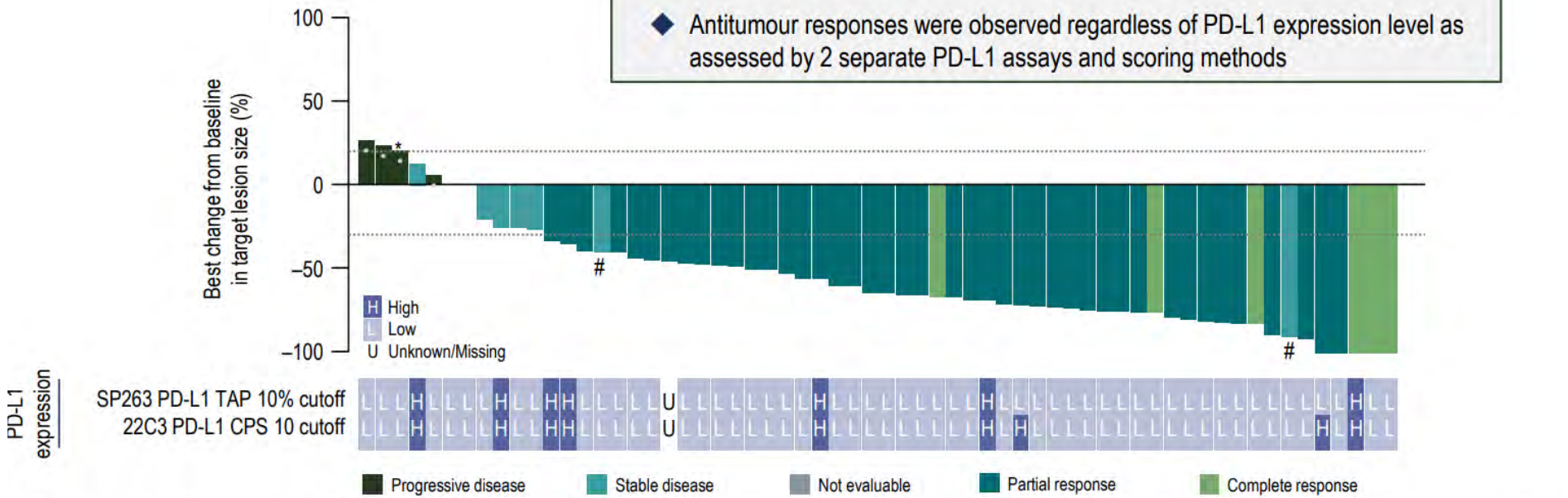
ADC, antibody-drug conjugate; a/mTNBC, advanced/metastatic triple-negative breast cancer; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PFS6, progression-free survival at 6 months; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastuzumab deruxtecan; TOPO I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with PD as best overall response. #Unconfirmed response.

1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

Data cutoff: 02 Feb 2023

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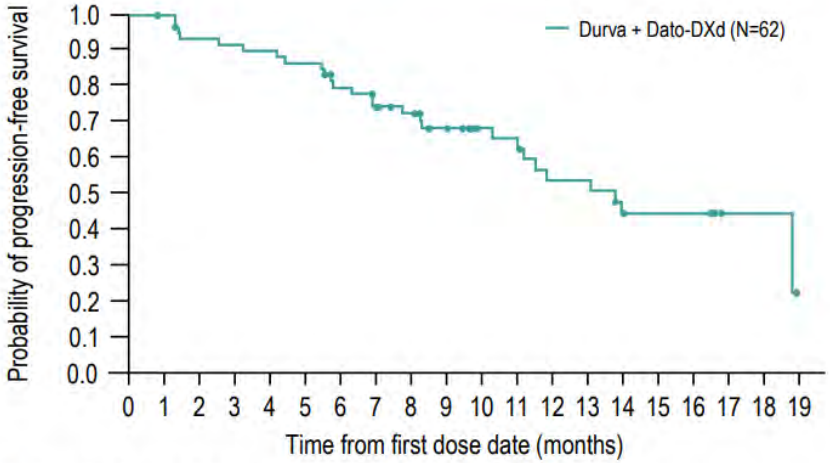
Progression-Free Survival and Duration of Response

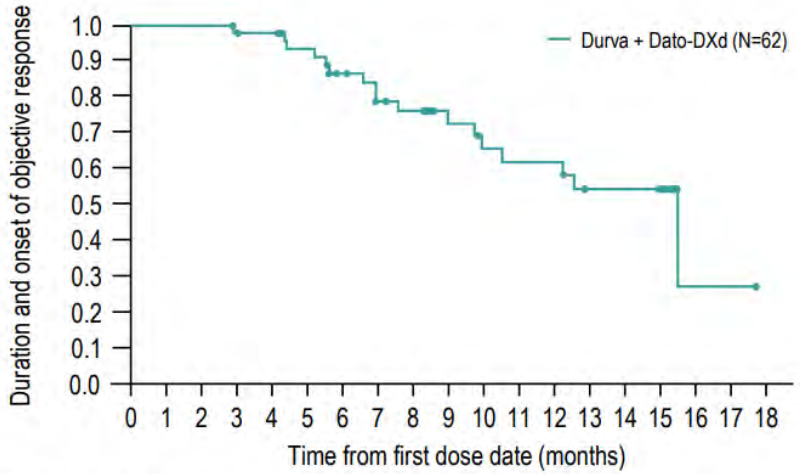
Median PFS was 13.8 months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was 15.5 months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

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Adverse Events

Most frequently reported adverse events (≥15%) (N=62)

AE preferred term	Any grade, n (%)	Grade 3/4, n (%)
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

- The most common AEs were gastrointestinal and generally of low grade (**Table**)
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)
- Limited rates of diarrhea (13% any grade, 1 grade 3 event) and neutropenia (5% any grade, 1 grade 3 event) were reported
- The most frequent AESIs for Arm 7 were stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis* (14.5%)

*1 grade 1 event, 3 grade 2 events, 5 grade 3 events.

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease.

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Safety Summary

Patients, n (%)	Dato-DXd + D N=62
Any AEs	62 (100)
Grade 3/4	35 (57)
Any treatment-related AEs[a]	62 (100)
Grade 3/4	27 (44)
Any serious AEs	14 (23)
Treatment-related	6 (10)
AEs leading to discontinuation of any treatments	10 (16)
AEs leading to death[b]	1 (2)
Dose adjustments	
Dato-DXd dose reduction	18 (29)
Dato-DXd dose delay	28 (45)
Durvalumab dose delay	31 (50)

[a]Per investigator assessment. [b]Patient died due to dehydration, unrelated to treatment.
AE, adverse event; Dato-DXd, datopotamab deruxtecan; D, durvalumab.

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Practice

- Not yet practice changing

Questions remaining

- Efficacy in comparison to current lines of therapy
- Possible drug combinations
- Biomarkers for activity

OHSU

Thank You