CPO
Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

REGIONE PIEMONTE

Evento Formativo Residenziale

PROGRAMMA REGIONALE DI SCREENING PER IL TUMORE DELLA MAMMELLA

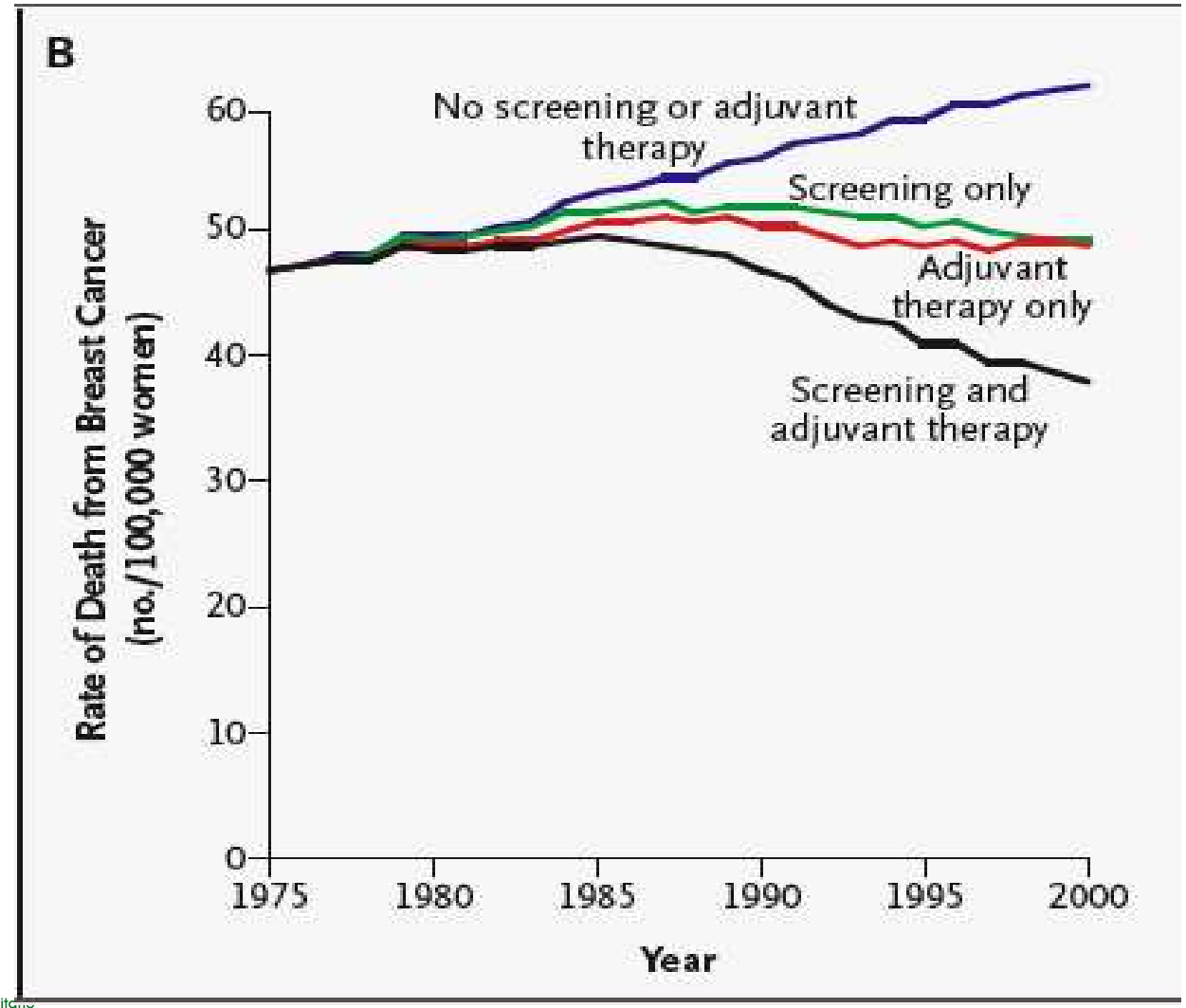
PREVENZIONE SERENA – WORKSHOP 2021

NOVITA' IN CAMPO ONCOLOGICO

Ornella Garrone
Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico, Milano

EPIDEMIOLOGIA

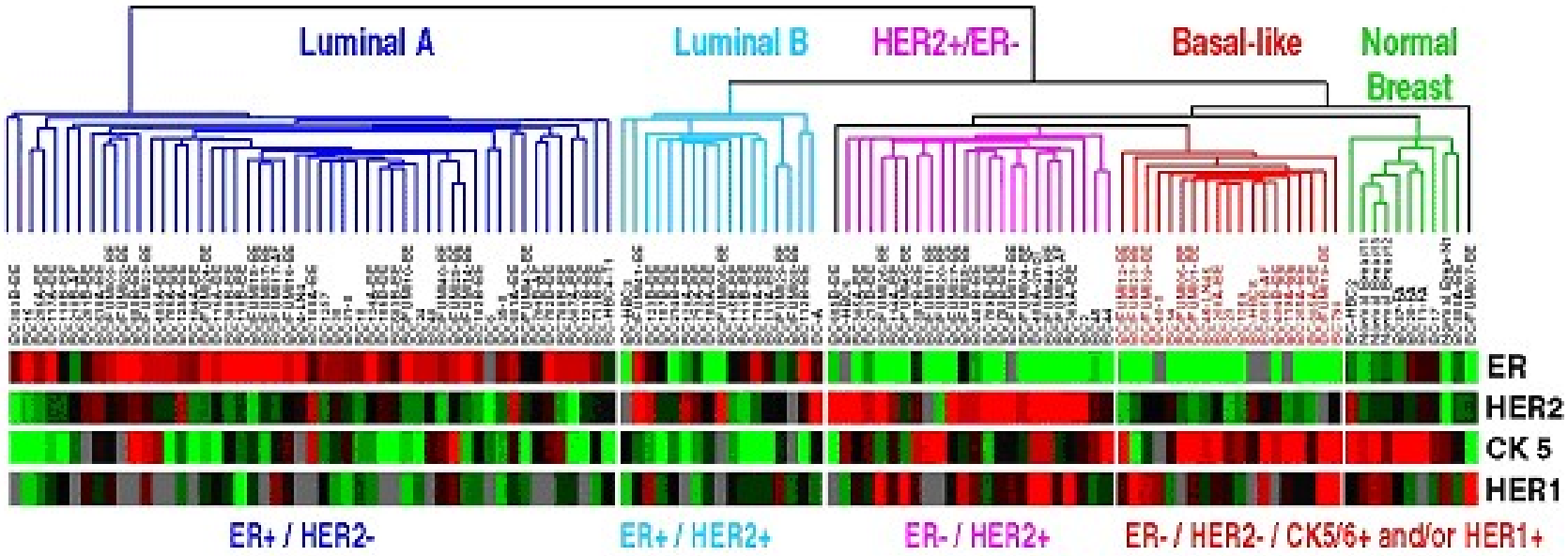
- In Italia nel 2020 stimati 55.000 nuovi casi (le stime per il 2021 non sono disponibili)
- Nel 2021 stimati 12.500 decessi
- Sopravvivenza netta a 5 anni dalla diagnosi 88%



D.A. Berry NEJM 2005

Gene expression array-identified subtypes of Breast Cancer

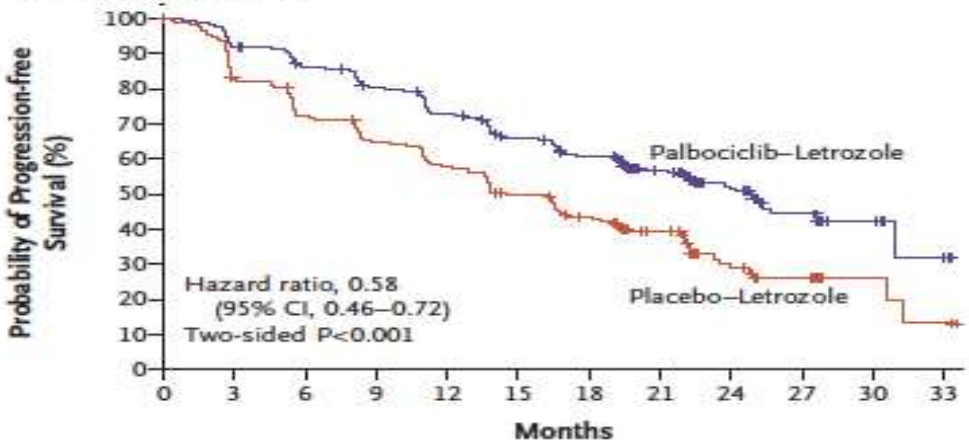
Unsupervised Hierarchical Clustering of Primary Breast Cancers



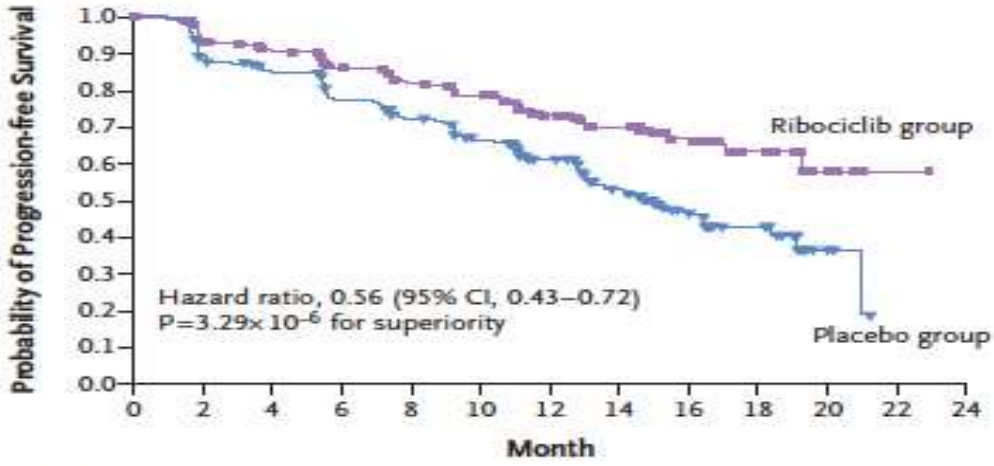
Perou *et al*. ***Nature*** 2000;406:747-52

MALATTIA LUMINALE

Investigator Assessment



No. at Risk												
Palbociclib–Letrozole	444	395	360	328	295	263	238	154	69	29	10	2
Placebo–Letrozole	222	171	148	131	116	98	81	54	22	12	4	2



No. at Risk													
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

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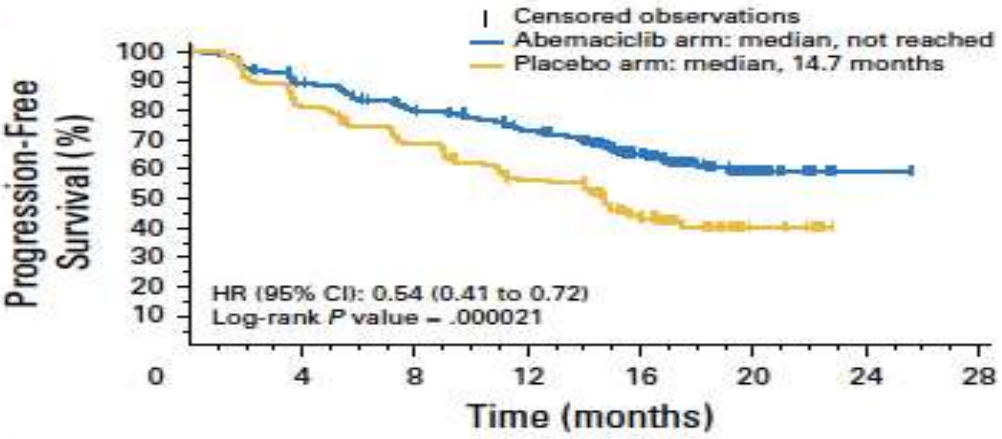


No. at risk:								
Abemaciclib arm	328	271	234	205	125	25	1	0
Placebo arm	165	127	105	82	45	7	0	0

Finn RS et al. N Engl J Med 2016
Hortobagyi GN et al. N Engl J Med 2016
Goetz MP et al. J Clin Oncol 2017

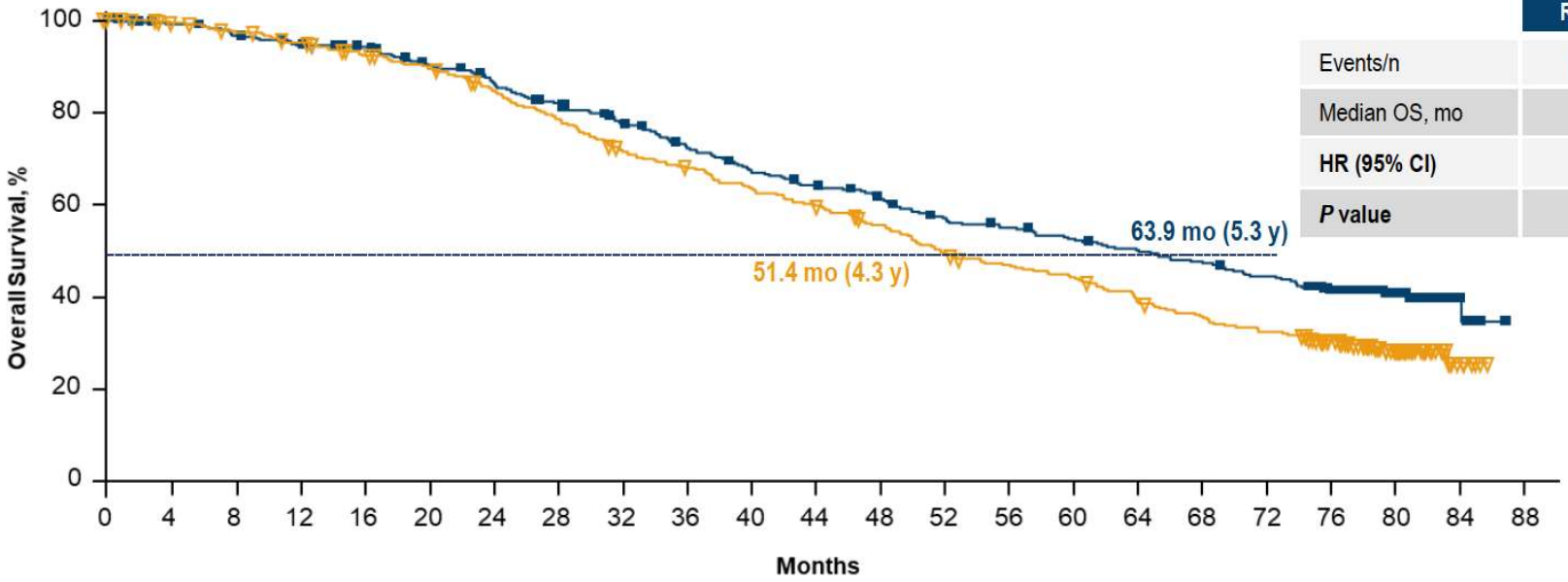
Focus on 1st line

	PALOMA-2		MONALEESA-2		MONARCH-3		MONALEESA-3		MONALEESA-7	
Setting	1st line		1st line		1st line		1st and 2nd line		1st and 2nd line	
ORR (%)	42.1	34.7	42.5	28.7	48.2	34.5	32.5	21.5	41	30
ORR meas disease (%)	55.3	44.4	54.5	38.8	59.2	43.8	40.9	28.7	51	36
PD (%)	NR		5.1	12.7	3.7	7.3	9.9	16.5	7	15
CBR (%)	OS (months)		Pending		63.9 vs 51.4		Pending		53.7 vs 41.5 NR vs 51.8 39.7 vs 33.7	NR vs 40.9	79	70
PFS (months)											23.8	13.8
HR	0.56		0.56		0.54		0.55		0.55	
Visceral involvement (%)	48.2	49.5	59	58.7	52.4	53.9	60.5	60.3	58	56
Previous CT (neo/adj) (%) Previous CT adv (%)	48 -	49.1 -	43.7 -	43.4 -	38.1 -	40 -	43.2 -	41.7 -	41 14	41 14
Previous ET (neo/adj) (%) Previous ET adv (%)	56.1	56.8	52.4	51.2	45.7	48.5	59.7 22.7	58.7 16.5	38 -	42 -

Finn RS et al. N Engl J Med 2016; Rugo H et al BCRT2019; Hortobagyi GN et al. N Engl J Med 2016; Ann Oncol 2018; ESMO 2021; Goetz MP et al. JCO 2017; Johnston NPJ Breast Cancer 2019; Slamon DJ JCO 2018 & NEJM 2020, ASCO 2021; Tripathy Lancet Oncol 2018; Im SA et al. NEJM, 2019

Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole



	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	**0.76 (0.63-0.93)**	
***P* value**	**.004**	

No. at risk																							
RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

The P value of .004 crossed the prespecified boundary to claim superior efficacy

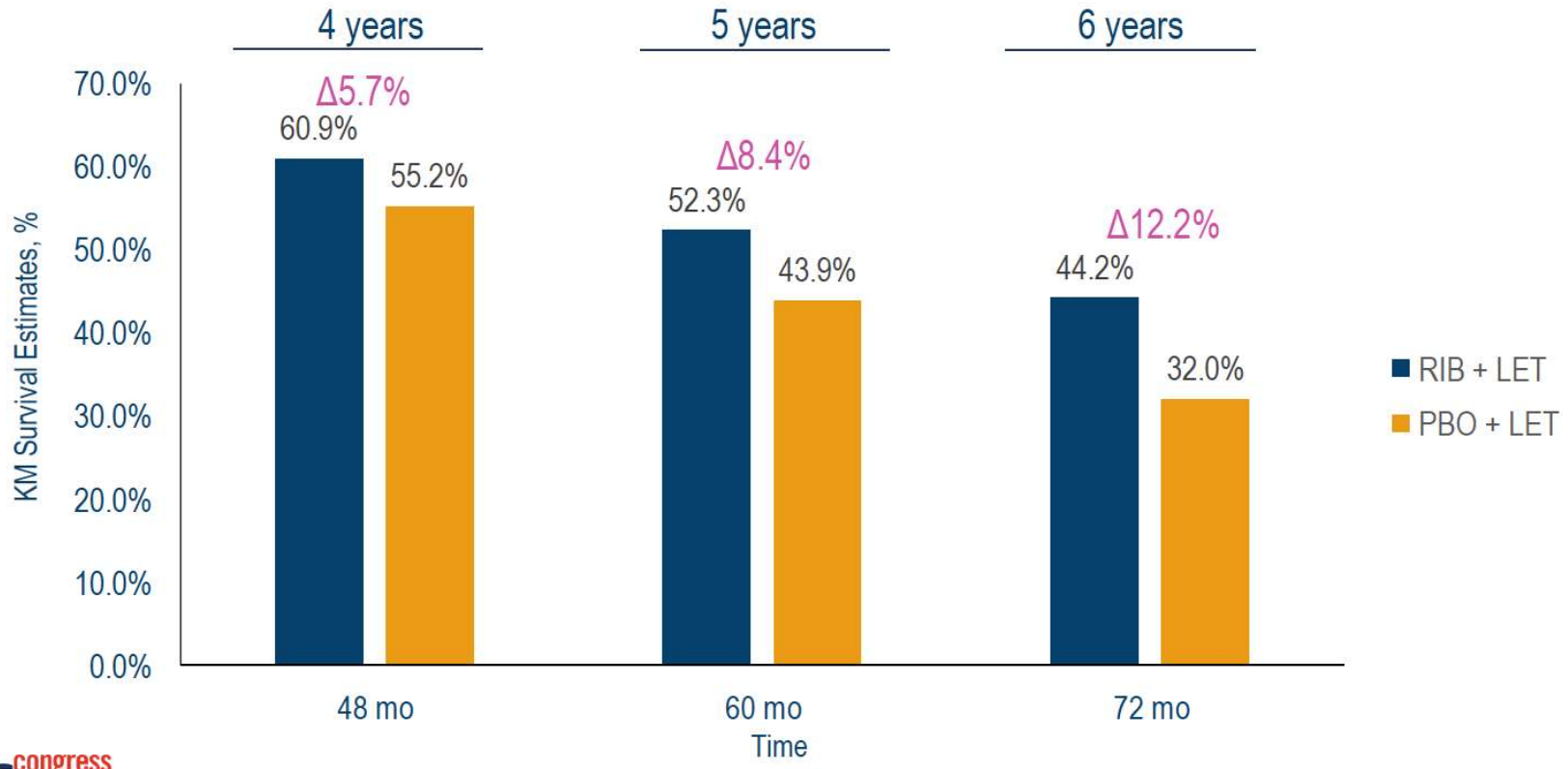
2021 ESMO congress

Gabriel N. Hortobagyi

HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

The OS benefit with ribociclib increased over time

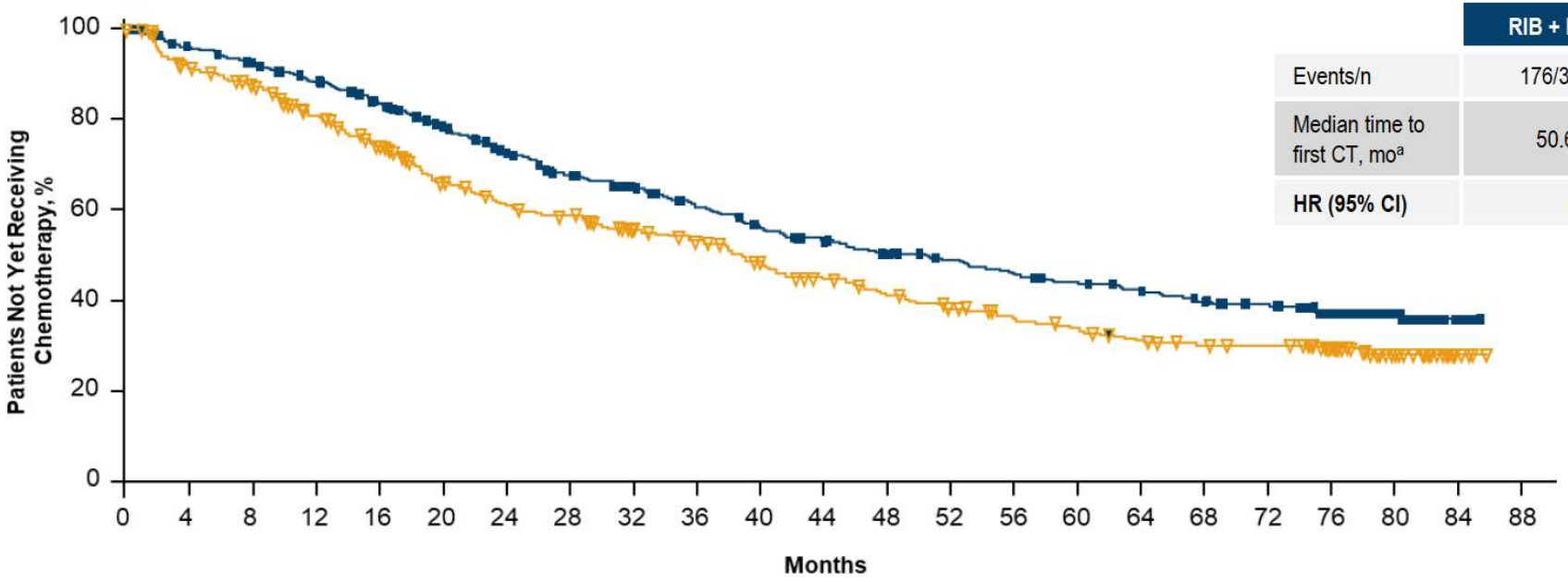
At 6 years, the survival rate of patients receiving ribociclib was 44.2%



Gabriel N. Hortobagyi

LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

Ribociclib delayed time to first chemotherapy by ≈ 1 year



	RIB + LET	PBO + LET
Events/n	176/334	200/334
Median time to first CT, mo[a]	50.6	38.9
HR (95% CI)	**0.74 (0.61-0.91)**	

No. at risk

RIB + LET	334	312	296	279	259	236	212	192	178	162	148	139	127	119	111	102	96	89	84	67	31	4	0
PBO + LET	334	302	283	254	224	194	175	166	150	140	123	110	98	87	77	72	64	59	57	43	25	5	0

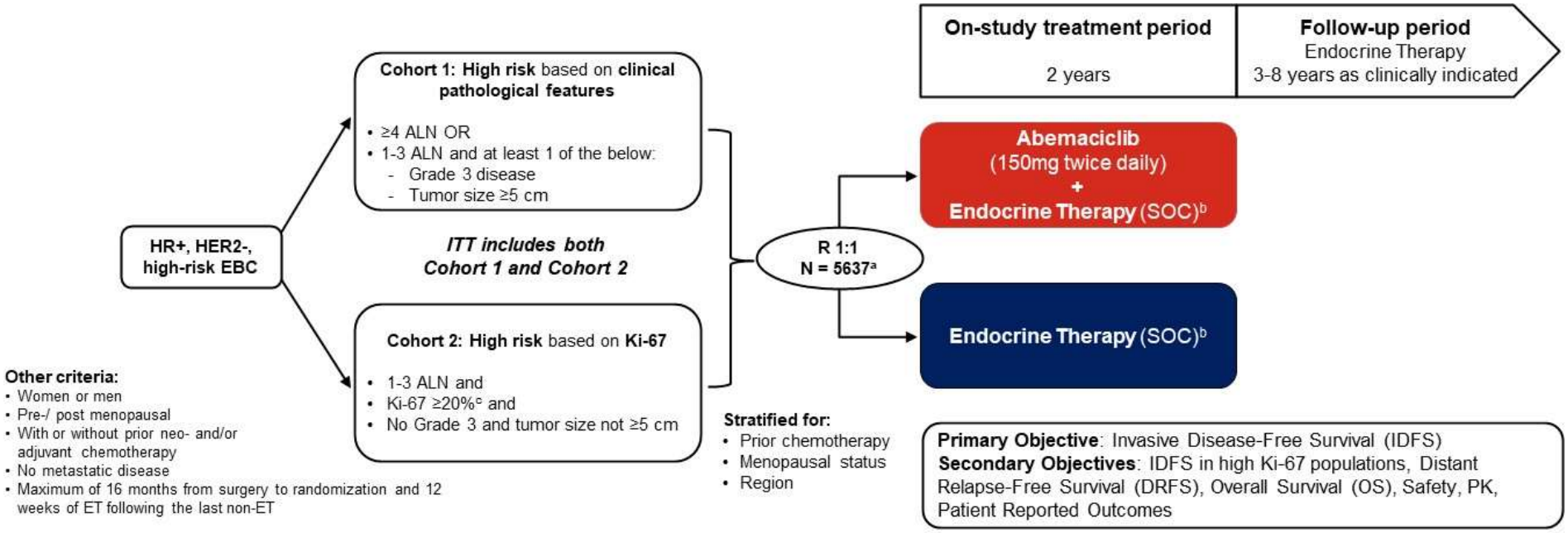
2021 ESMO congress

Gabriel N. Hortobagyi

CT, chemotherapy; HR, hazard ratio; LET, letrozole; PBO, placebo; RIB, ribociclib.

[a] Time to first chemotherapy was defined as the time from randomization to the start of the first chemotherapy following discontinuation of the study treatment.

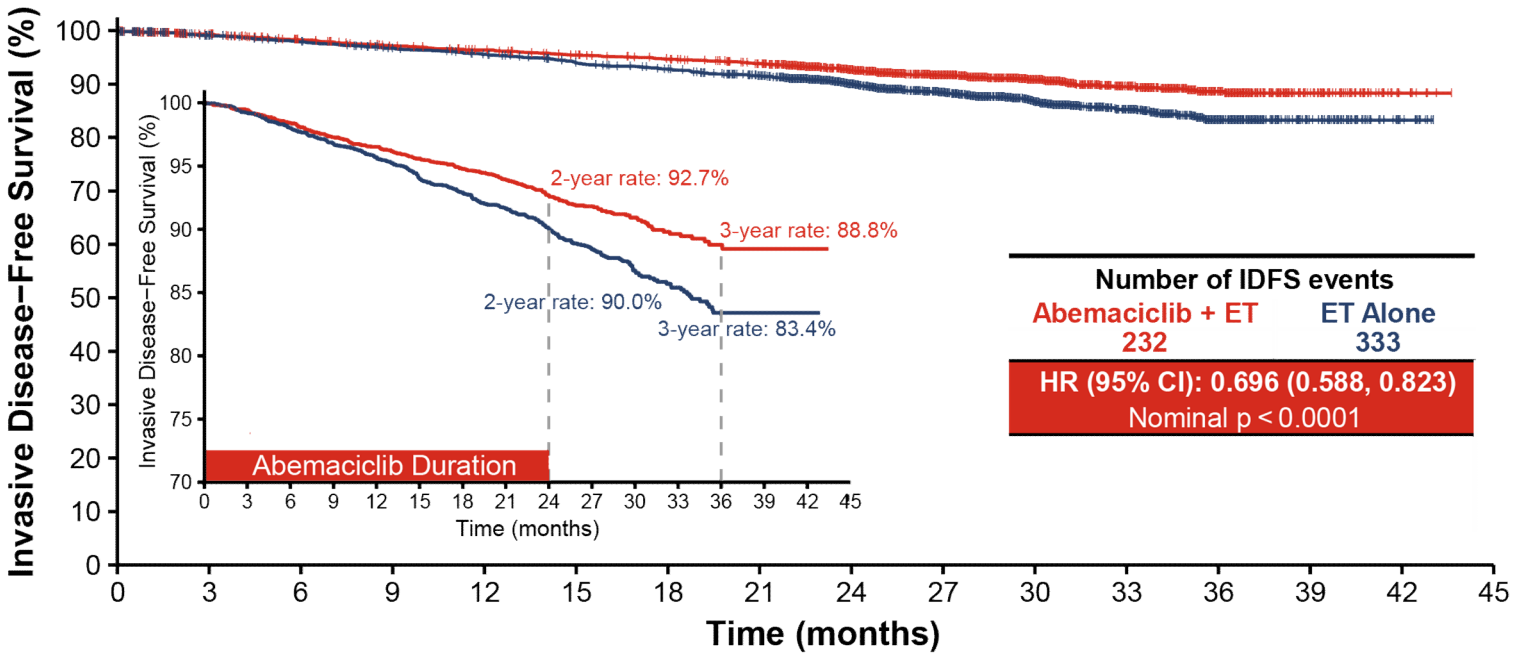
monarchE Study Design (NCT03155997)



[a]Recruitment from July 2017 to August 2019; [b]Endocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; [c]Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent

Abbreviations: ALN = positive axillary lymph nodes; CPF = clinicopathological features; HER2 = human epidermal receptor 2; HR = hormone receptor; ITT = intent-to-treat population; N = number of patients in the ITT population; R = randomized; SOC = standard of care

IDFS Benefit Maintained with Additional Follow-up in ITT population

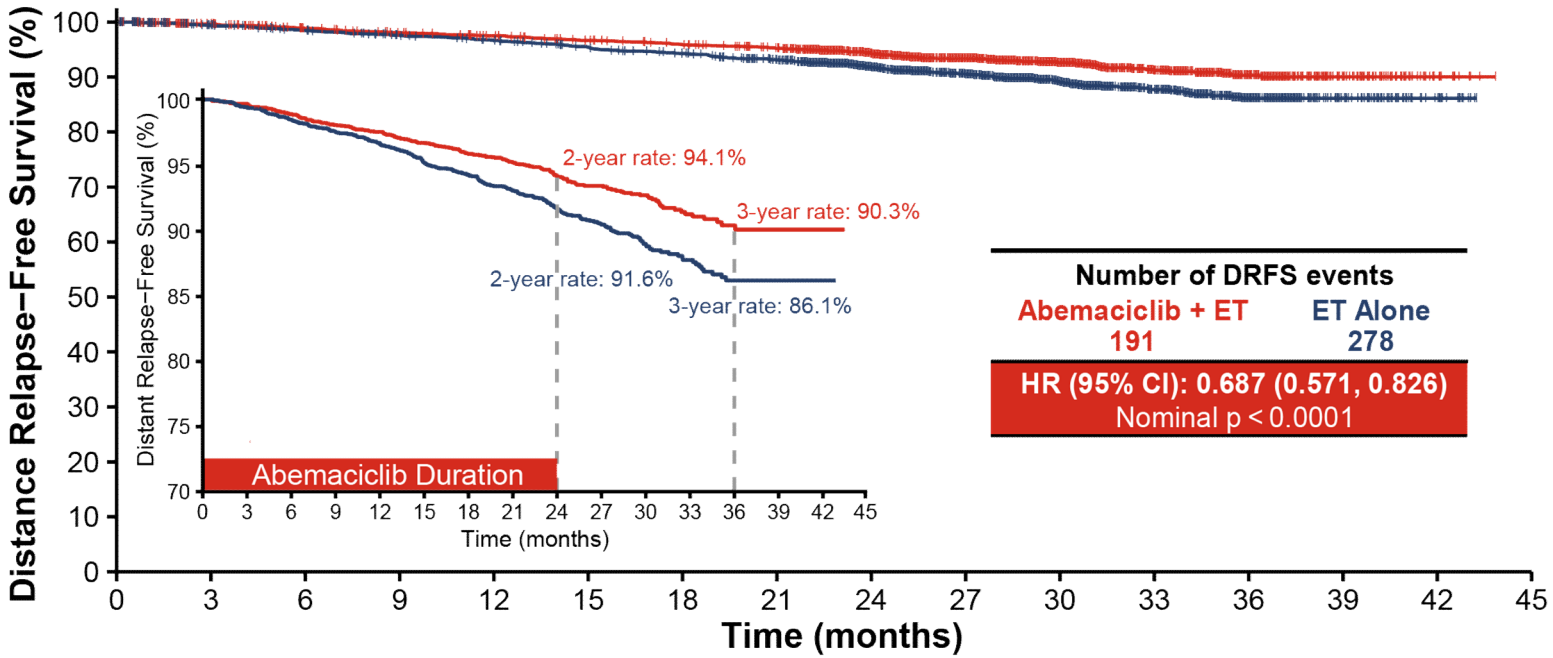


Number at risk																
Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET Alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

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.

Joyce O'Shaughnessy

Benefit of DRFS Maintained with Additional Follow-up in ITT population



Number at risk																
Abemaciclib + ET	2808	2684	2629	2595	2566	2529	2497	2455	1990	1300	930	530	281	68	8	0
ET Alone	2829	2704	2660	2622	2591	2535	2499	2427	1955	1287	924	537	287	66	10	0

31.3% reduction in the risk of developing a DRFS event.
The absolute difference in DRFS rates between arms was 4.2% at 3 years.

Joyce O'Shaughnessy

Abemaciclib Treatment Effect Over Time

Analysis landmark	IDFS			DRFS		
	Events		Piecewise HR* (95% CI**)	Events		Piecewise HR* (95% CI**)
	Abemaciclib + ET	ET alone		Abemaciclib + ET	ET alone	
Year 0-1	93	116	0.795 (0.589, 1.033)	67	91	0.732 (0.520, 0.987)
Year 1-2	98	146	0.681 (0.523, 0.869)	85	129	0.675 (0.507, 0.875)
Year 2+	41	71	0.596 (0.397, 0.855)	39	58	0.692 (0.448, 1.032)

* Piecewise hazard ratio was estimated using piecewise exponential model to assess the yearly treatment effect size
** 95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

Increasing magnitude of IDFS and DRFS effect size from the first year to the second year, with maintained treatment benefit beyond the 2-year study treatment period.

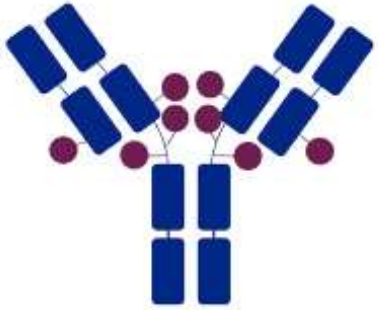
FDA approves abemaciclib with endocrine therapy for early breast cancer

On October 12,2021, the Food and Drug Administration approved abemaciclib (Verzenio,Eli Lilly and Company)with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

MALATTIA HER2+

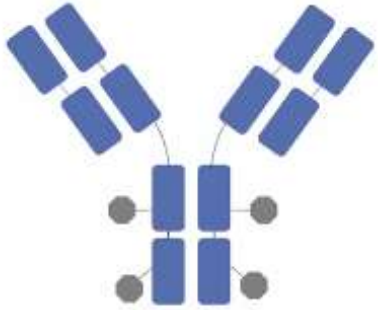
ADC Characteristic Differences Between T-DXd and T-DM1

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]



ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

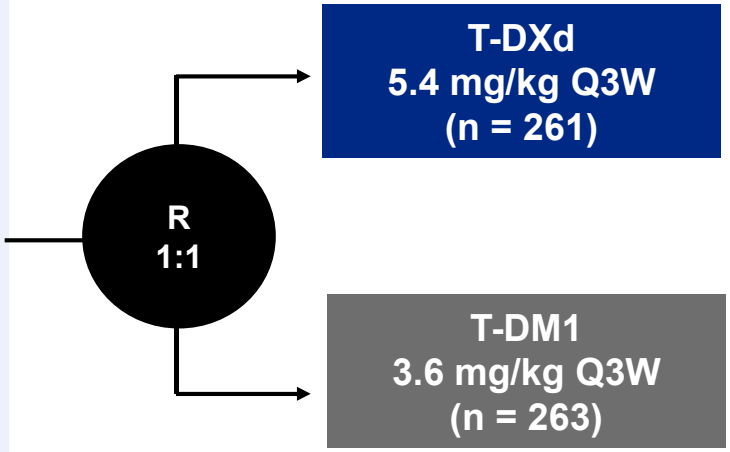
An open-label, multicenter study (NCT03529110)

Patients

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors

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



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)

- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

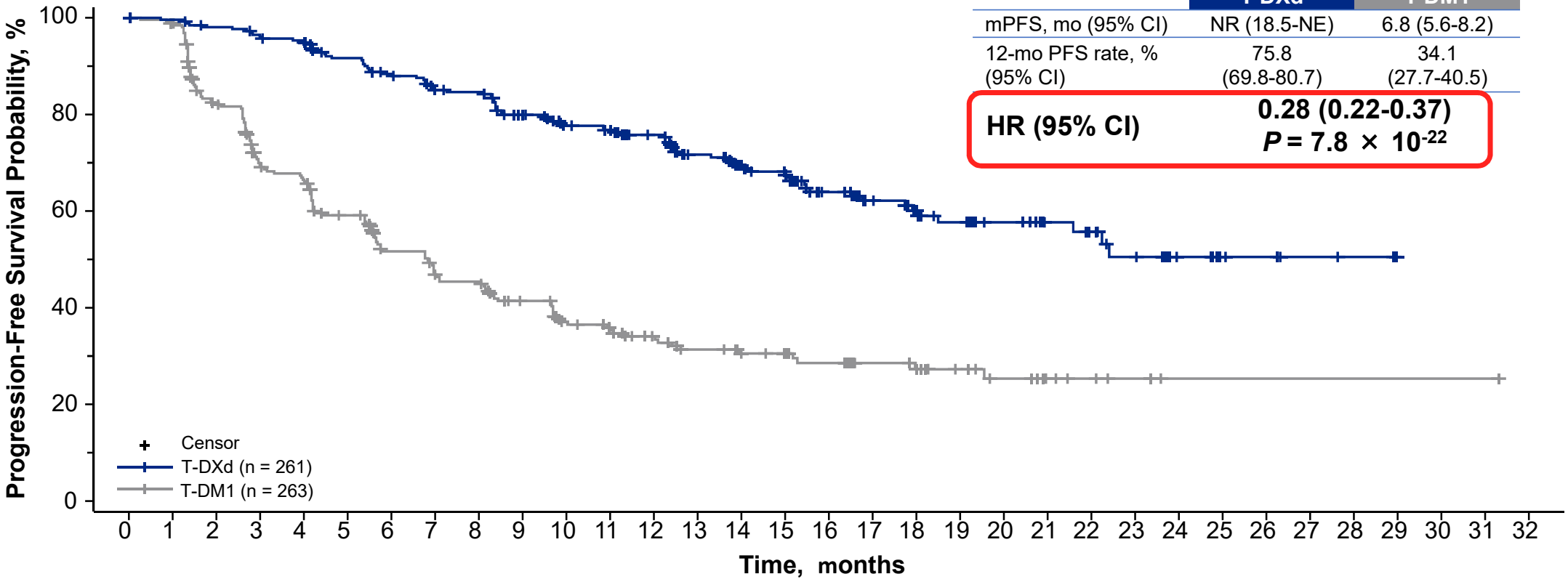
Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	**0.28 (0.22-0.37)**	
	P **= 7.8 × 10^{-22}**	



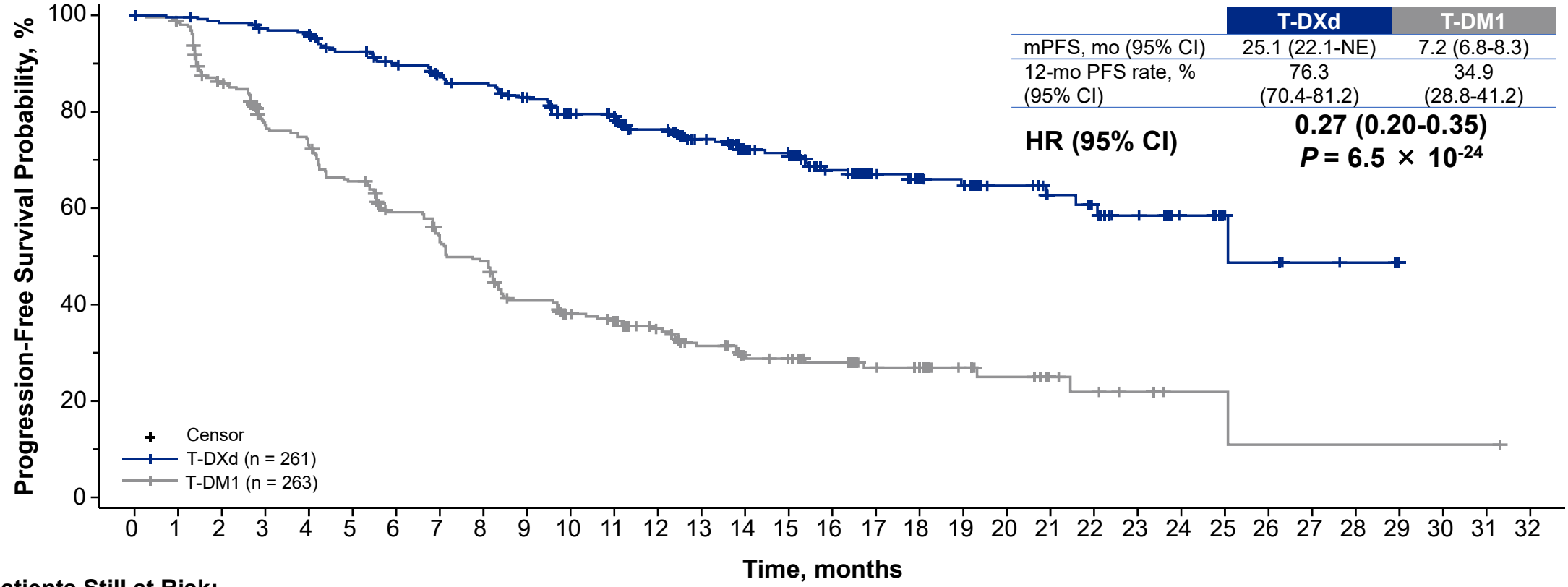
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0	
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

2021 ESMO congress

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

Secondary Endpoint: PFS by Investigator Assessment



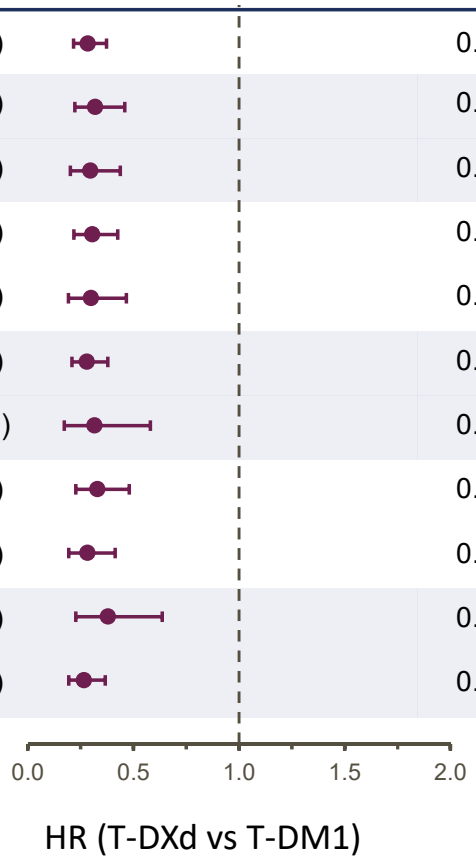
	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	**0.27 (0.20-0.35)**	
	***P* = 6.5 × 10^{-24}**	

Patients Still at Risk:

T-DXd (261)	261	256	252	247	244	230	221	209	205	195	179	176	158	140	120	113	85	64	53	48	37	31	27	20	11	7	5	3	2	0		
T-DM1 (263)	263	253	216	185	175	156	136	119	110	88	78	72	61	51	43	39	34	25	23	16	13	9	7	5	2	2	1	1	1	1	1	1	0

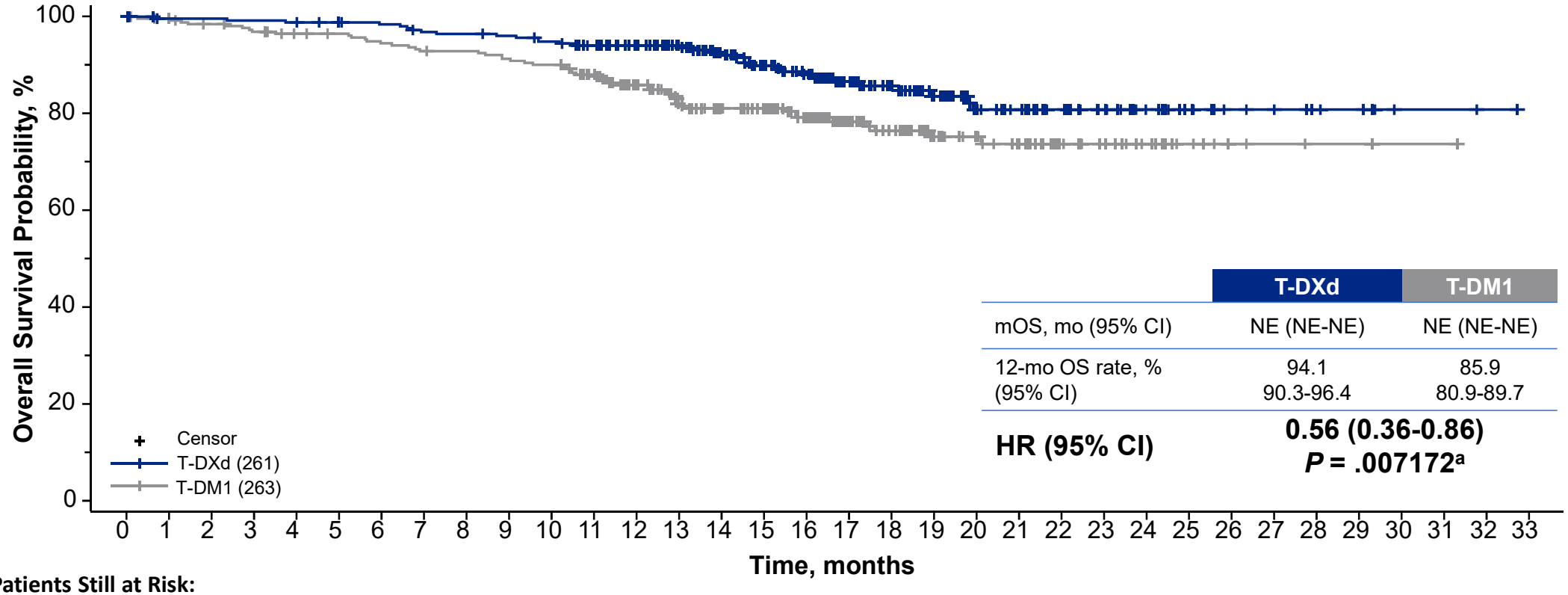
PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)



[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)** ***P* = .007172[a]**	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

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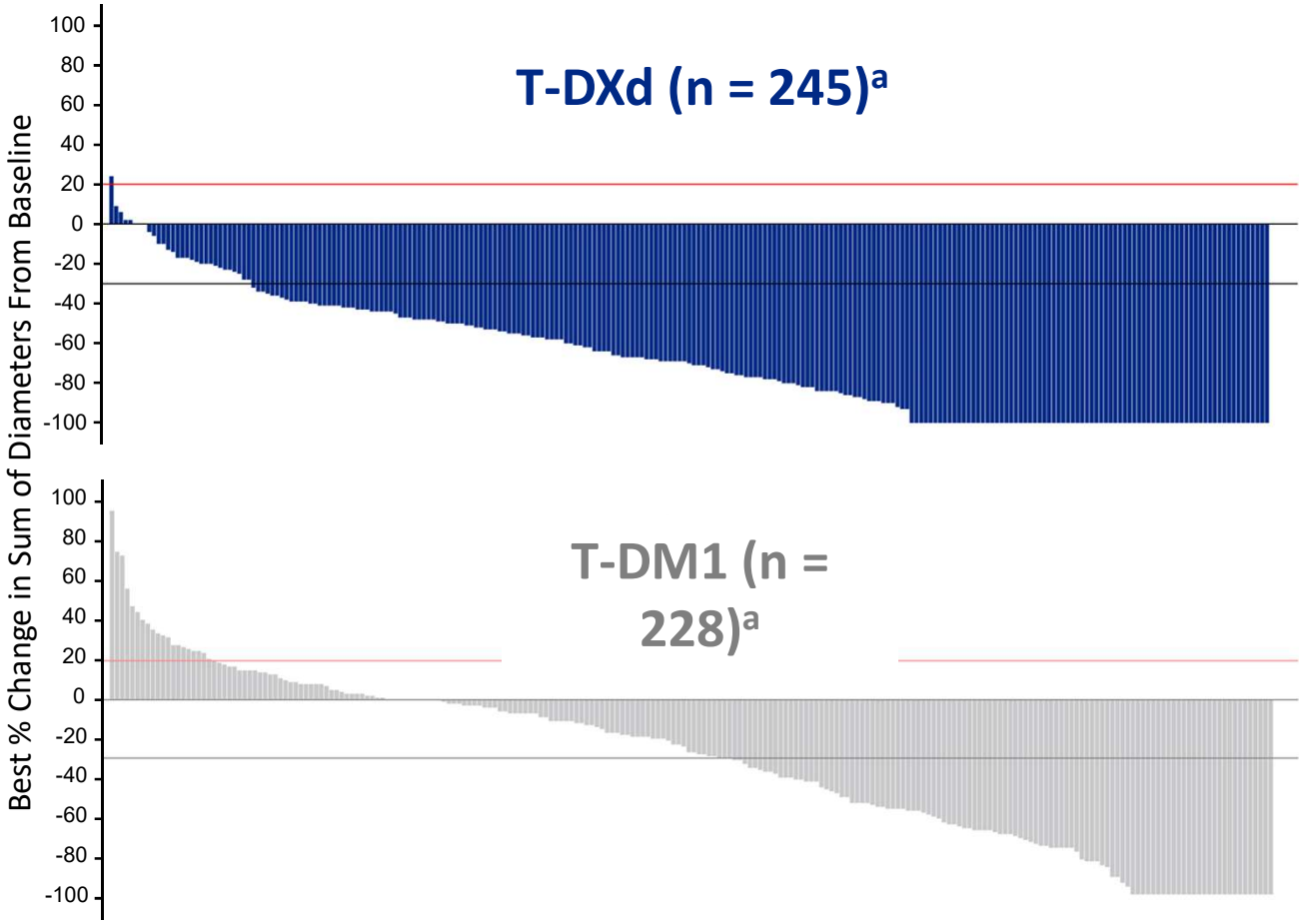
Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Confirmed ORR and Best Overall Response



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

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CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

Drug-Related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

ILD 10.5%

Most drug-related TEAEs were gastrointestinal or hematological in nature

Adverse events were managed according to the protocol.
[a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise. [f]Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%.

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

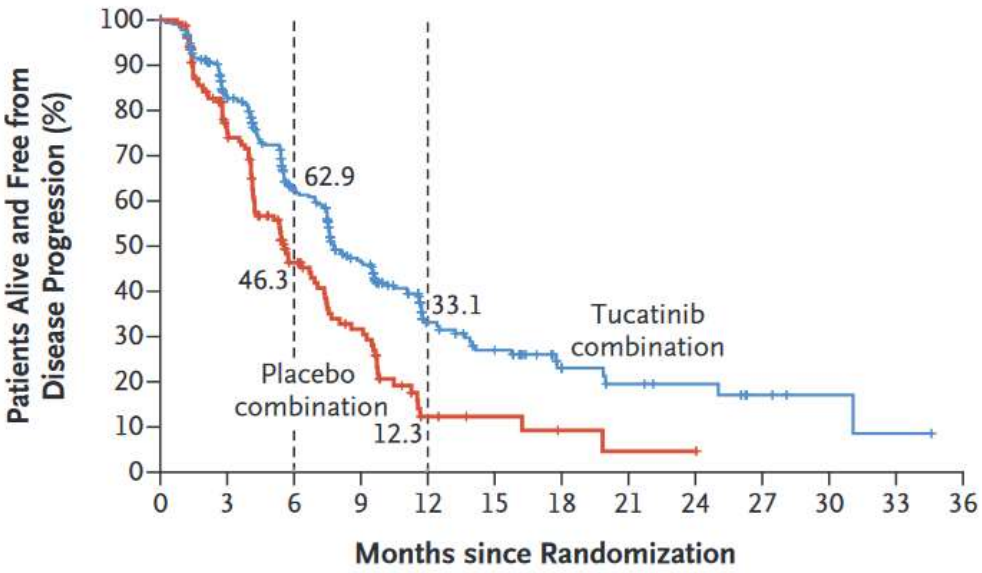
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

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

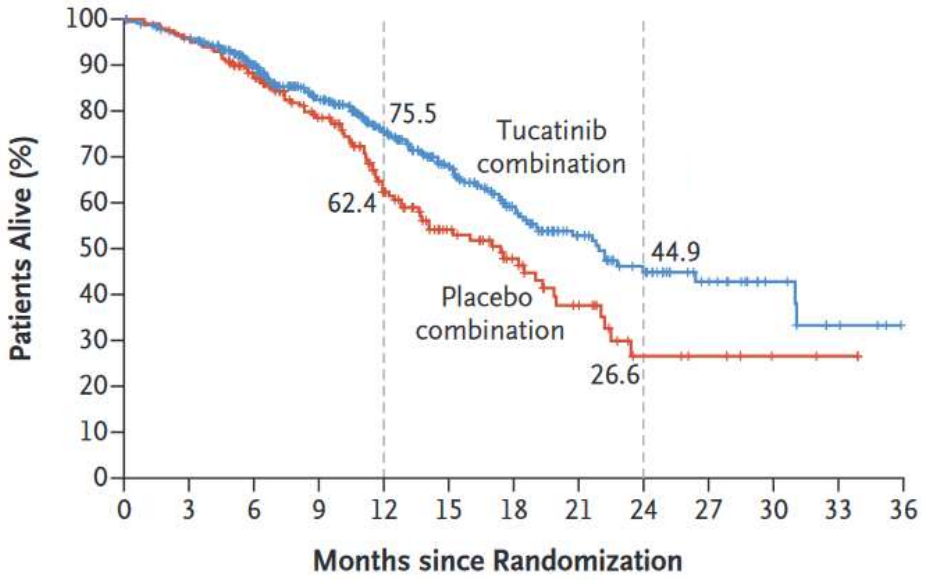
*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

HR+ ~60%; median previous lines of Tx 4; 100% received trast, pert and T-DM1

HER2CLIMB: PFS and OS results



	Events/pts	mPFS	HR (95%CI)
Tucatinib combination	178/320	7.8	
Placebo combination	97/160	5.6	0.54 (0.42-0.71)



	Events/pts	mOS	HR (95%CI)
Tucatinib combination	130/410	21.9	
Placebo combination	85/202	17.4	0.66 (0.50-0.88)

Murthy RK, et al. N Engl J Med 2020

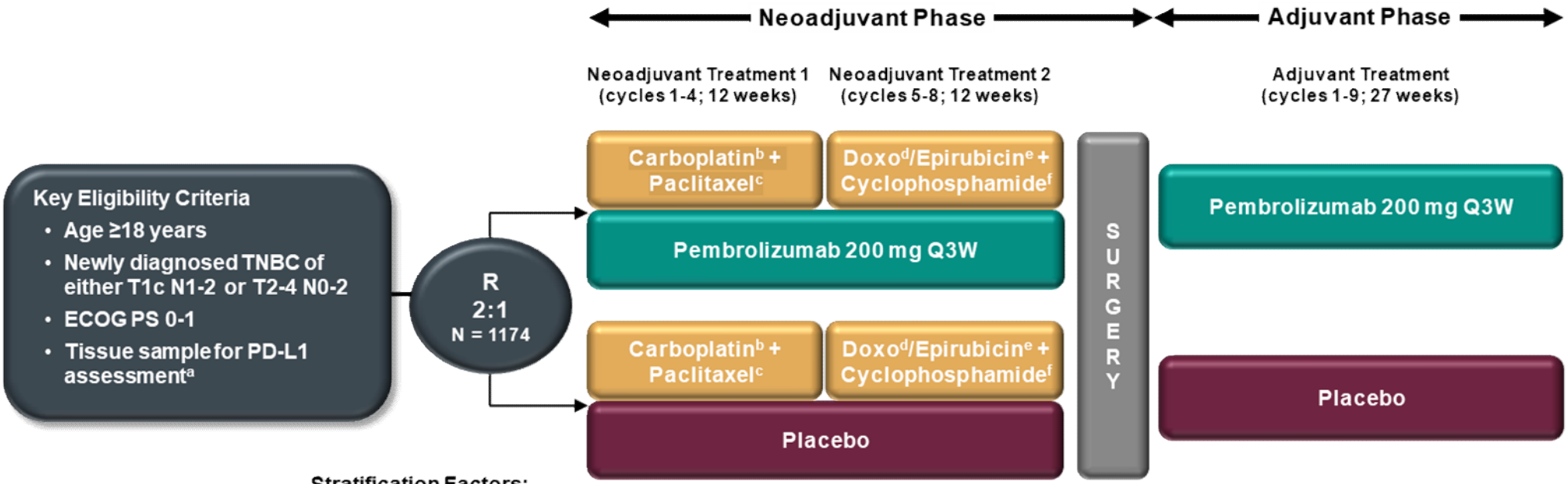
Outcome in patients with Brain Metastases

	Median survival Tucatinib	Median survival Placebo	1-yr survival Tucatinib	1-yr survival Placebo	HR (95% CI)
PFS	7.6	5.4	25%	0%	0.48 (0.34-0.69)
CNS-PFS	9.9	4.2	40.2%	0%	0.32 (0.22-0.48)
CNS-PFS active BM	9.5	4.1	35.0%	0%	0.36 (0.22-0.57)
CNS-PFS stable BM	13.9	5.6	53.3%	0%	0.31 (0.14-0.67)
OS	18.1	12.0	70.1%	46.1%	0.58 (0.40-0.85)
OS active BM	20.7	11.6	71.7%	41.1%	0.49 (0.30-0.80)
OS stable BM	15.7	13.6	67.6%	55.6%	0.88 (0.45-1.70)

Lin NU et al, J Clin Oncol 2020

MALATTIA Triplo negativa

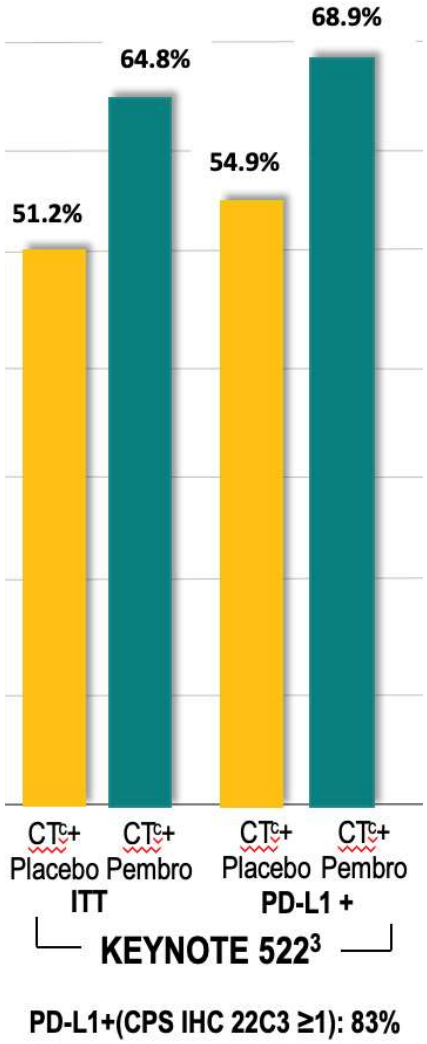
KEYNOTE-522 Study Design (NCT03036488)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

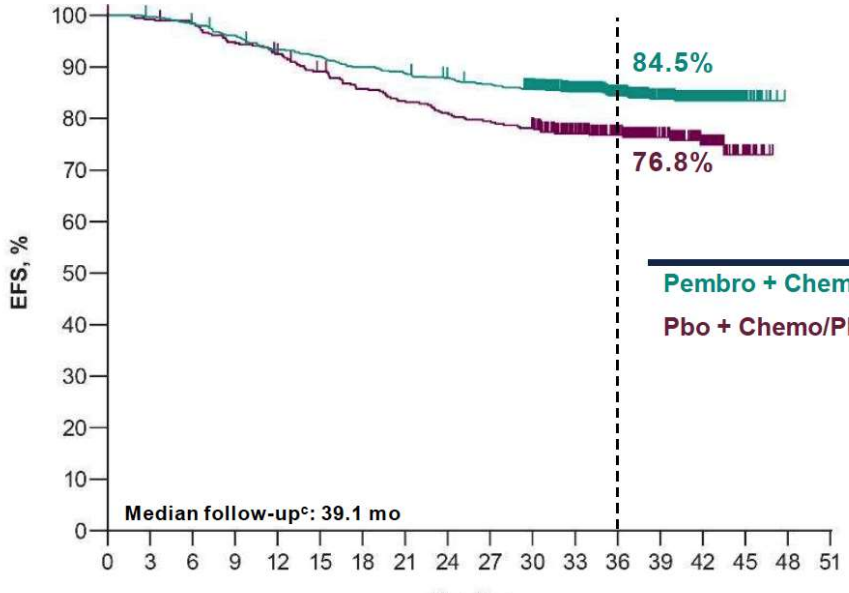
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m2 QW.
[d]Doxorubicin dose was 60 mg/m2 Q3W.
[e]Epirubicin dose was 90 mg/m2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m2 Q3W.



PD-L1+(CPS IHC 22C3 ≥1): 83%

Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

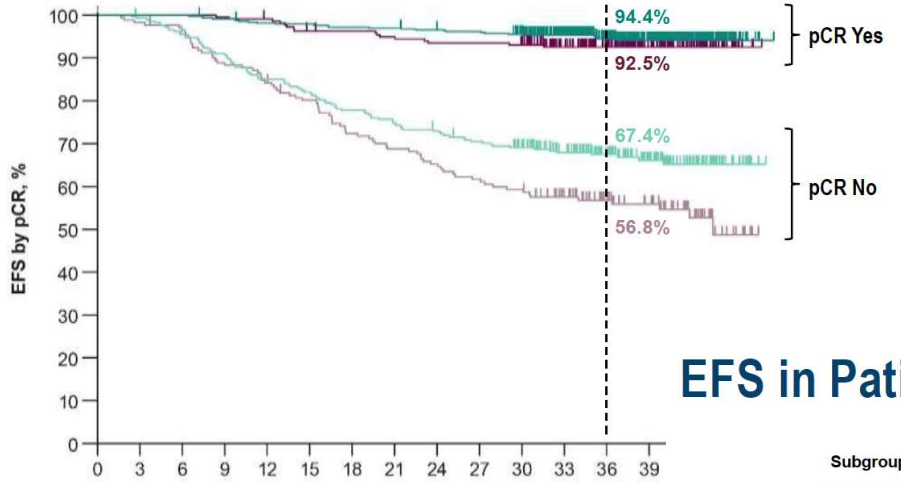
No. at Risk

Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Schmid P, ESMO Virtual Plenary 2021

EFS by pCR (ypT0/Tis ypN0)



No. at Risk														
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53

Data cutoff date: March 23, 2021.

EFS in Patient Subgroups

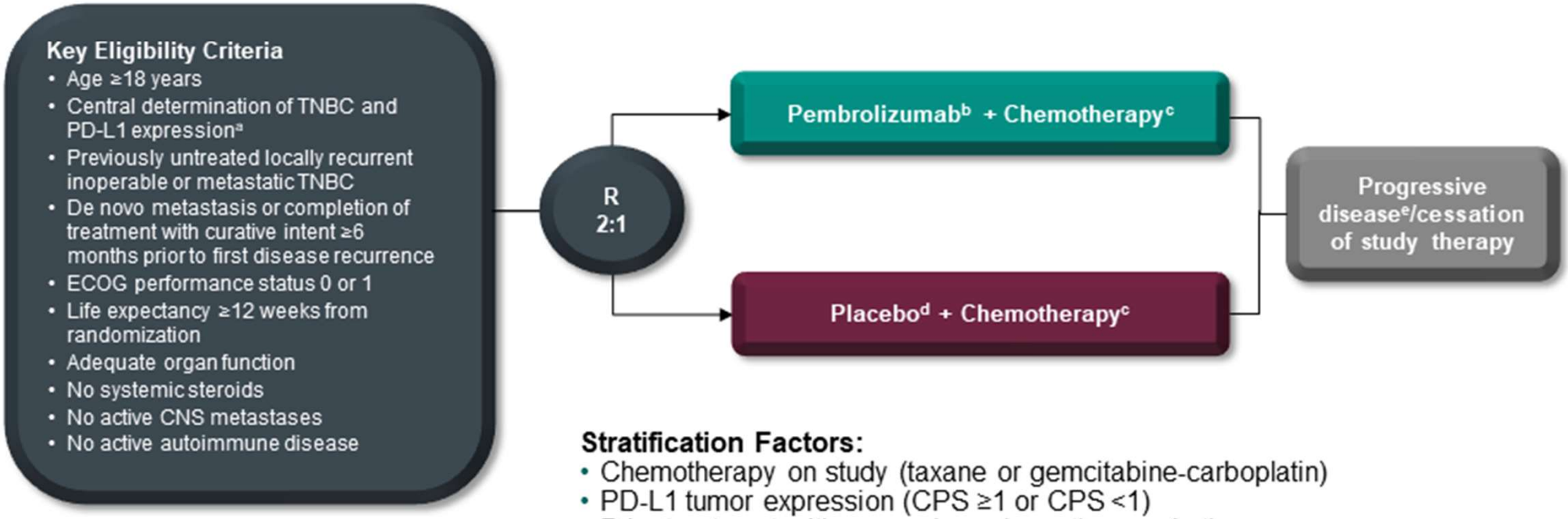
Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Pbo + Chemo/Pbo	Hazard Ratio (95% CI)
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Tumor size			
T1/T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36 to 0.73)
T3/T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55 to 1.28)
Carboplatin schedule			
Every 3 weeks	50/334 (15.0)	37/167 (22.2)	0.65 (0.42 to 0.99)
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42 to 0.86)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49 to 0.92)
Negative	25/128 (19.5)	25/69 (36.2)	0.48 (0.28 to 0.85)
Age category			
<65 years	103/700 (14.7)	79/342 (23.1)	0.61 (0.45 to 0.82)
≥65 years	20/84 (23.8)	14/48 (29.2)	0.79 (0.40 to 1.56)
ECOG PS			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45 to 0.80)
1	22/106 (20.8)	13/49 (26.5)	0.81 (0.41 to 1.62)

For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. Data cutoff date: March 23, 2021.

FDA D.I.S.C.O. Burst Edition: FDA approval of Keytruda (pembrolizumab) for high-risk early-stage triple-negative breast cancer

On July 26, 2021, the FDA approved pembrolizumab (brand name Keytruda) for high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYNOTE-355 Study Design (NCT02819518)



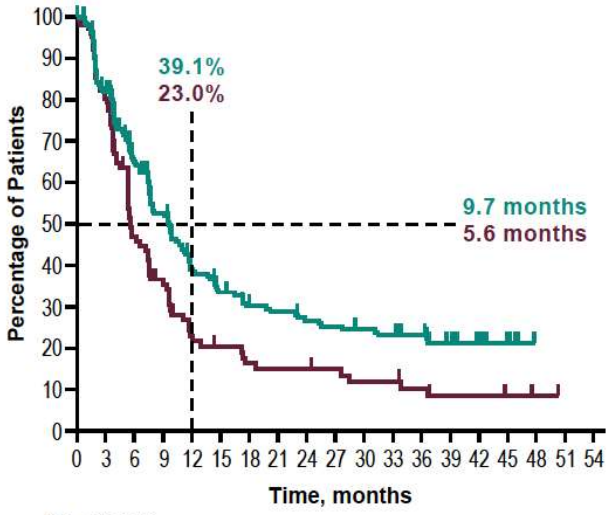
Stratification Factors:

- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumour sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). [c]Chemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days; Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days; Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days. [d]Normal saline. [e]Treatment may be continued until confirmation of progressive disease.

PFS PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



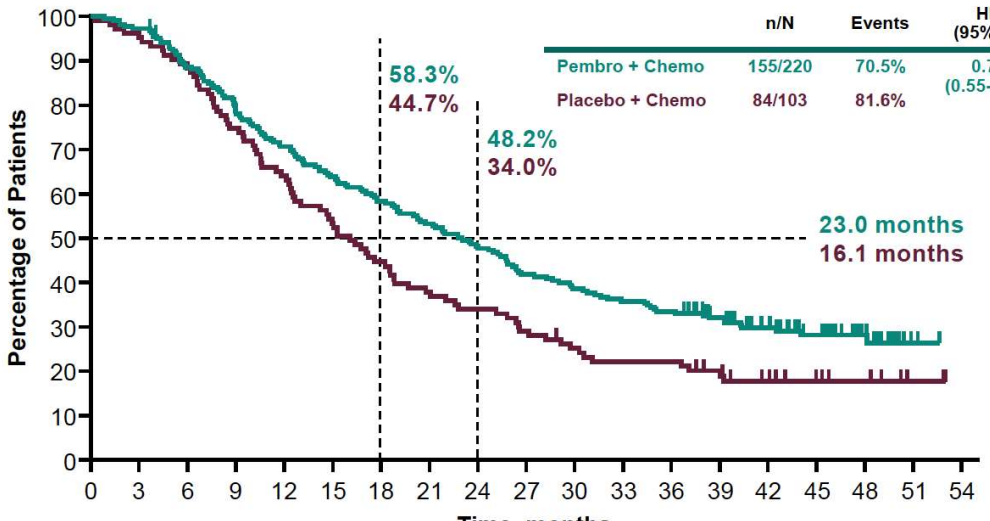
No. at risk

220	173	122	95	63	52	44	42	38	36	34	32	27	19	13	6	0	0	0
103	80	41	30	18	15	12	11	11	10	8	8	6	4	4	3	1	0	0

Data cutoff: June 15, 2021.

Overall Survival: PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

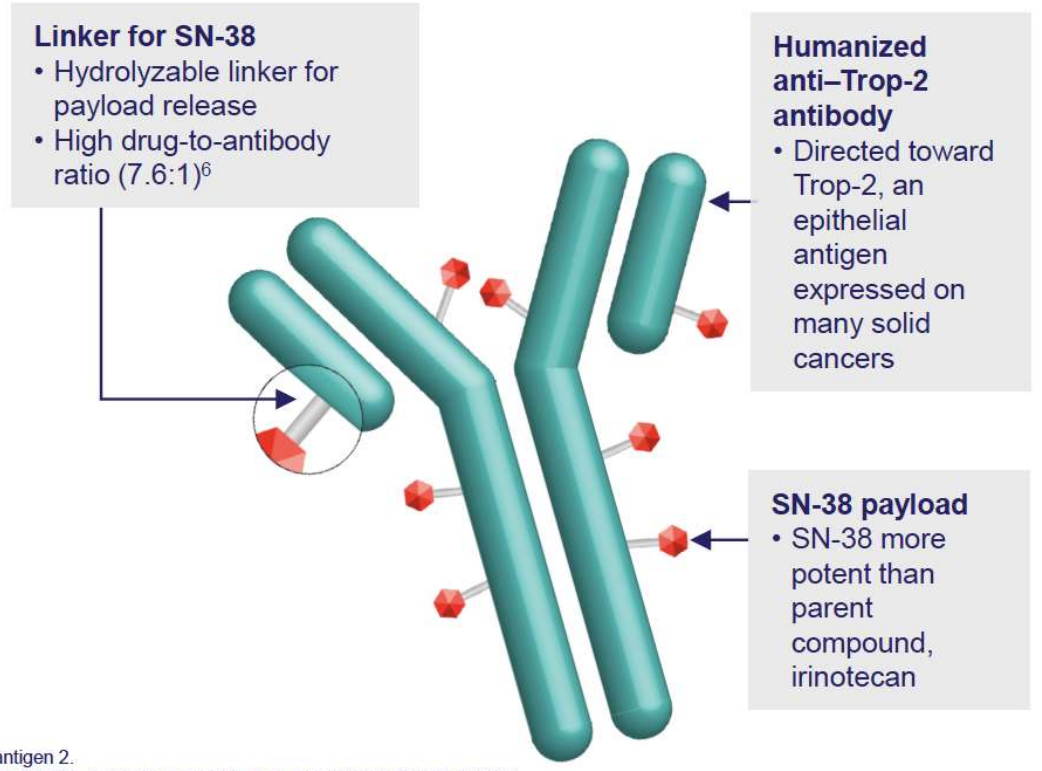
[a]Prespecified *P* value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

On 16 September 2021, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product pembrolizumab (Keytruda).

Keytruda, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) in adults whose tumours express PD-L1 with a combined positive score (CPS) ≥10 and who have not received prior chemotherapy for metastatic disease.

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

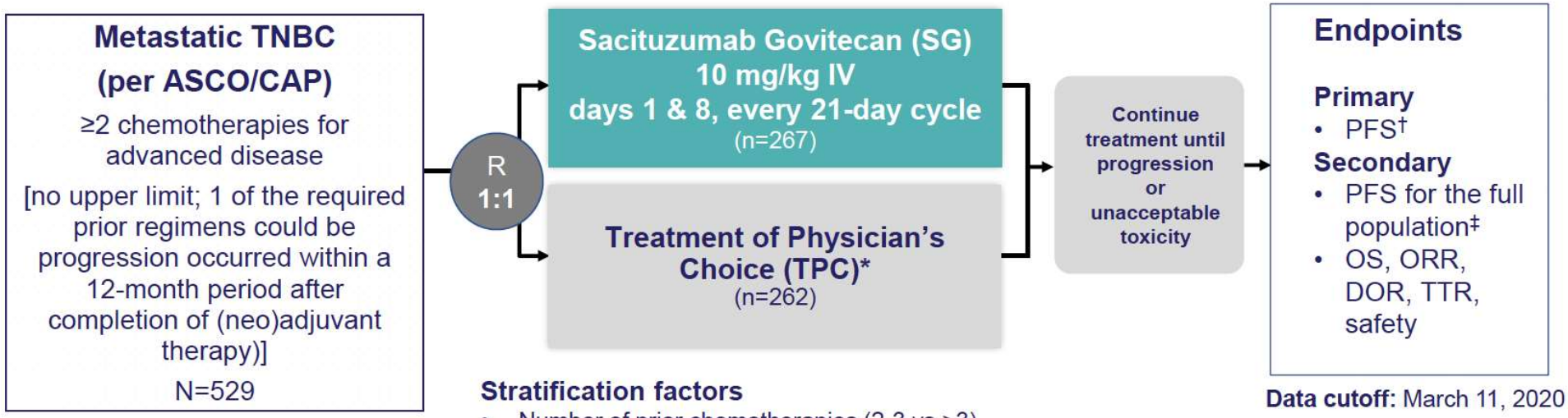
- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]



ADC, antibody–drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol*. 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One*. 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem*. 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget*. 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

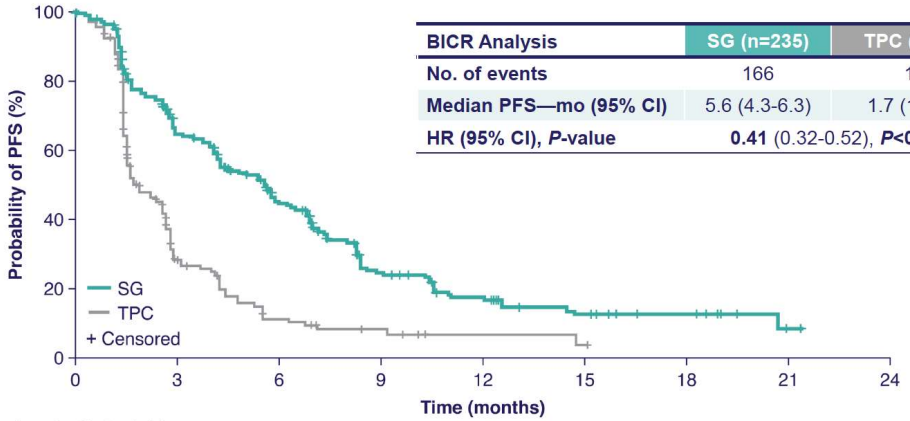
Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Progression-Free Survival (BICR Analysis)



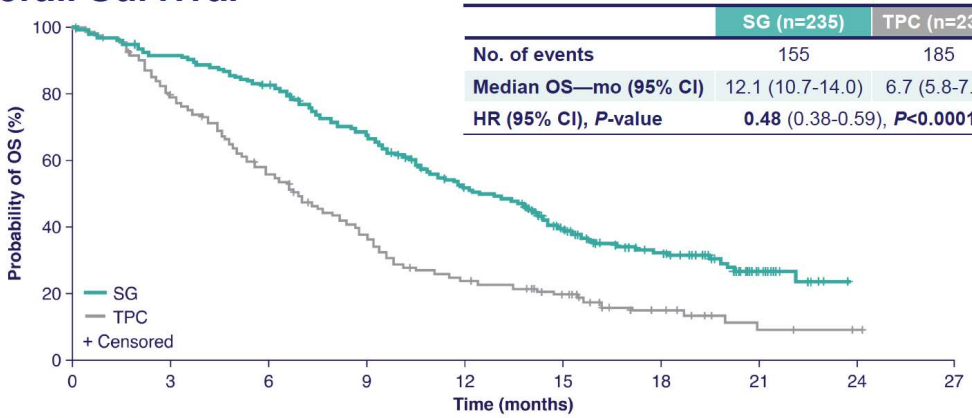
BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Number of patients at risk

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

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Survival



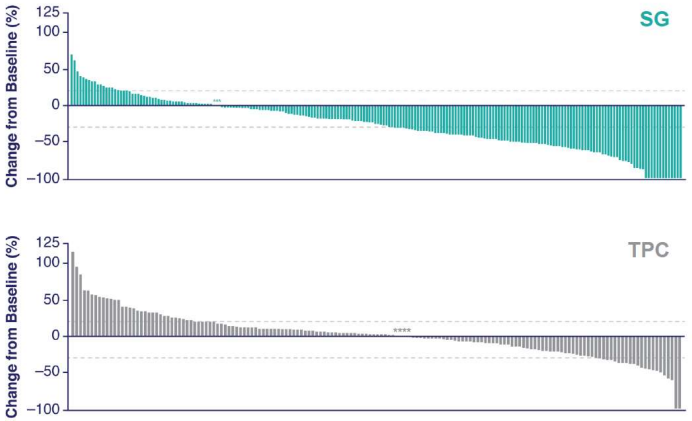
	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Number of patients at risk

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

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Response and Best Percent Change From Baseline in Tumor Size



	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
P-value	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
P-value	**<0.0001**	
Median DOR —mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
P-value	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

Mutazione BRCA1 e BRCA2

OLAPARIB rimborsato in monoterapia per il trattamento di pazienti con carcinoma mammario localmente avanzato o metastatico HER2-, HR- e con mutazione di BRCA1 o BRCA2, pretrattate con antracicline, taxani e platino nel setting neo/adiuvante o metastatico.

TALAZOPARIB rimborsato in monoterapia per il trattamento di pazienti con carcinoma mammario localmente avanzato o metastatico HER2-, e con mutazione di BRCA1 o BRCA2, pretrattate con antracicline e/o taxani nel setting neo/adiuvante o metastatico.
Le pazienti con malattia HR+ devono essere state precedentemente trattate con terapia endocrina e devono aver ricevuto un inibitore delle chinasi ciclino-dipendenti.
Le pazienti con malattia HR- devono essere state precedentemente pretrattate con chemioterapia a base di platino.

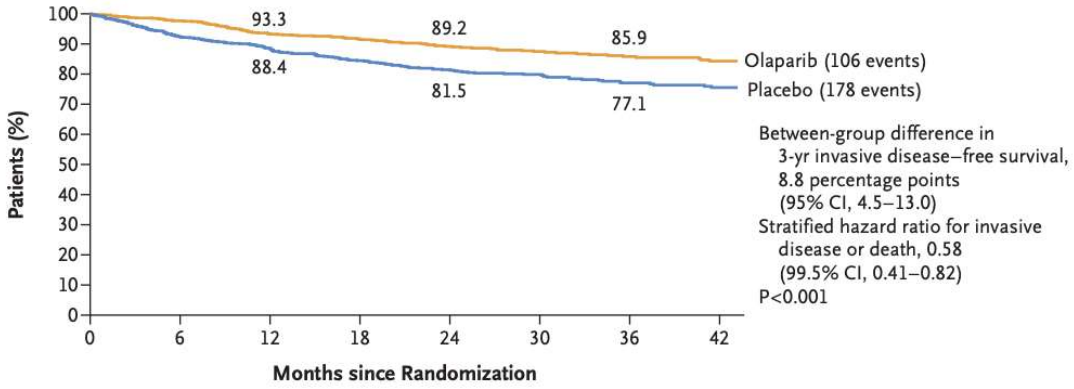
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

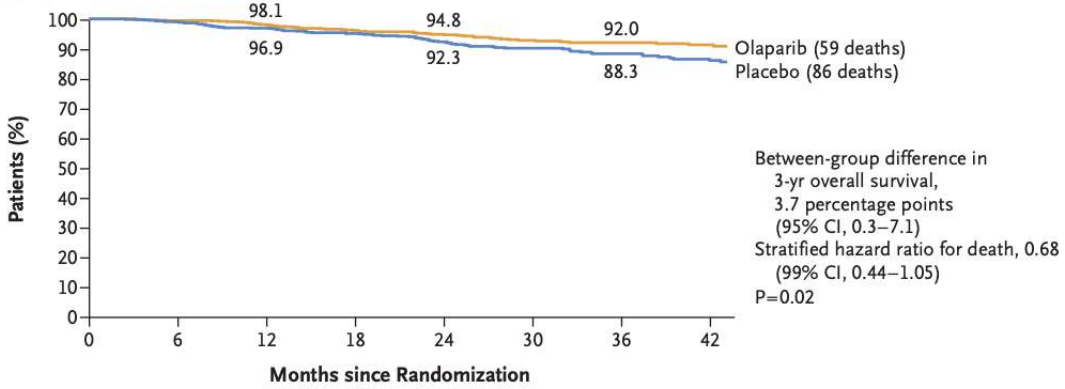
Invasive Disease–free Survival



No. at Risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Overall Survival



No. at Risk

Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

Conclusioni

- Programmi di screening
- Terapie adiuvanti
- Caratterizzazione molecolare
- Nuovi farmaci
- Multidisciplinarietà
- Presa in carico