Management of Residual Disease in Early-stage Breast Cancer

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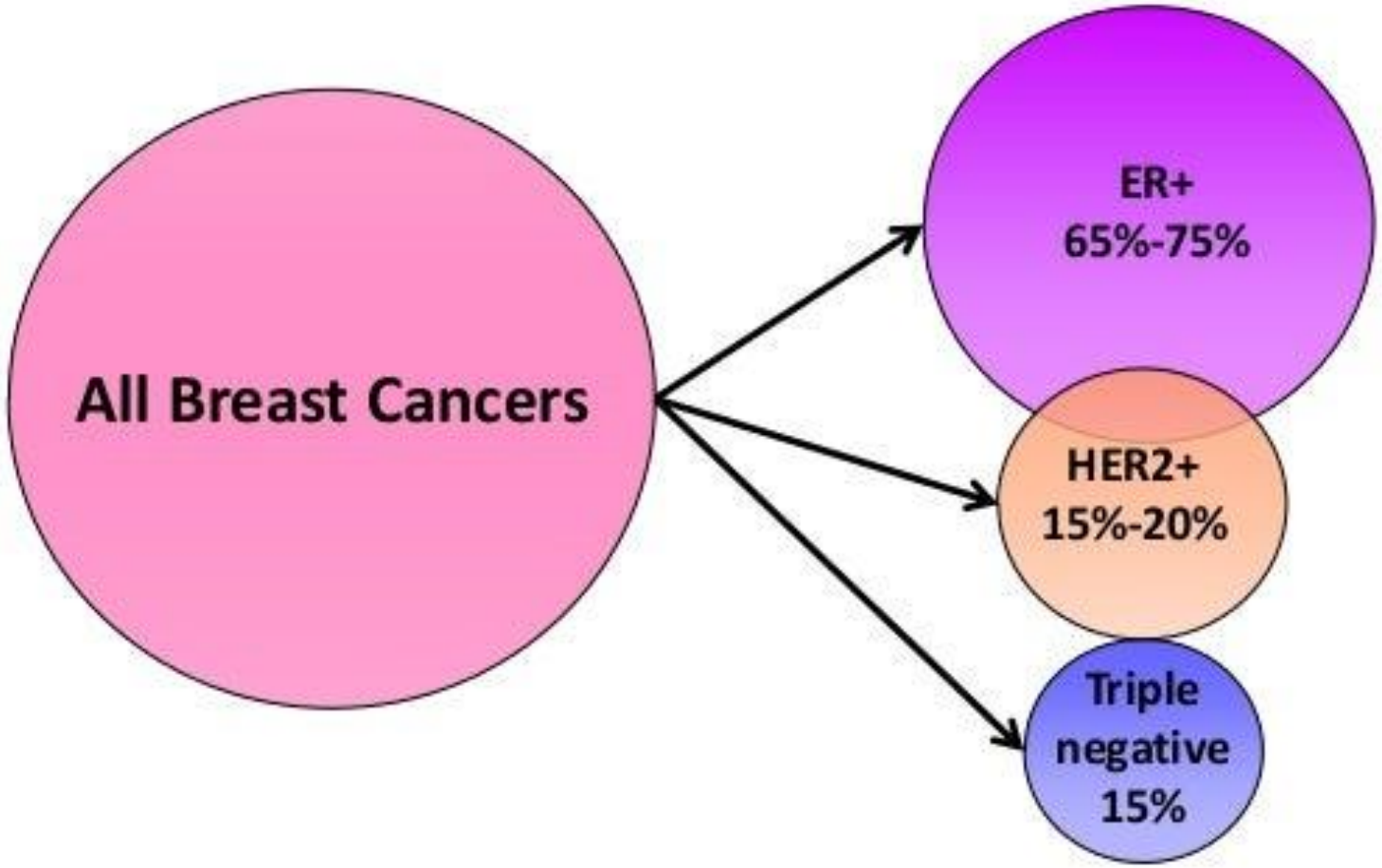
Invasive Breast Cancer Subsets Defined by IHC



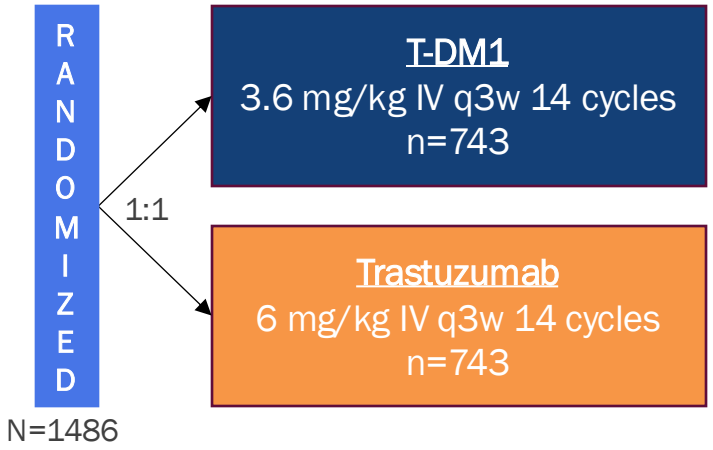
Burstein, Goldhirsch. St Gallen 2007.

Management of Residual Disease in HER2 Positive Breast Cancer

Final IDFS and Updated OS Results From the Phase 3 KATHERINE Trial of Adjuvant T-DM1 vs Trastuzumab in HER2+ EBC: Study Design and Patients

Key Eligibility Criteria

- HER2+ EBC diagnosis
- Prior neoadjuvant therapy consisting of minimum 6 cycles Chemo, minimum 9 weeks trastuzumab
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Updated analysis from 2018 primary analysis

Primary endpoint: IDFS
Secondary endpoints: IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL

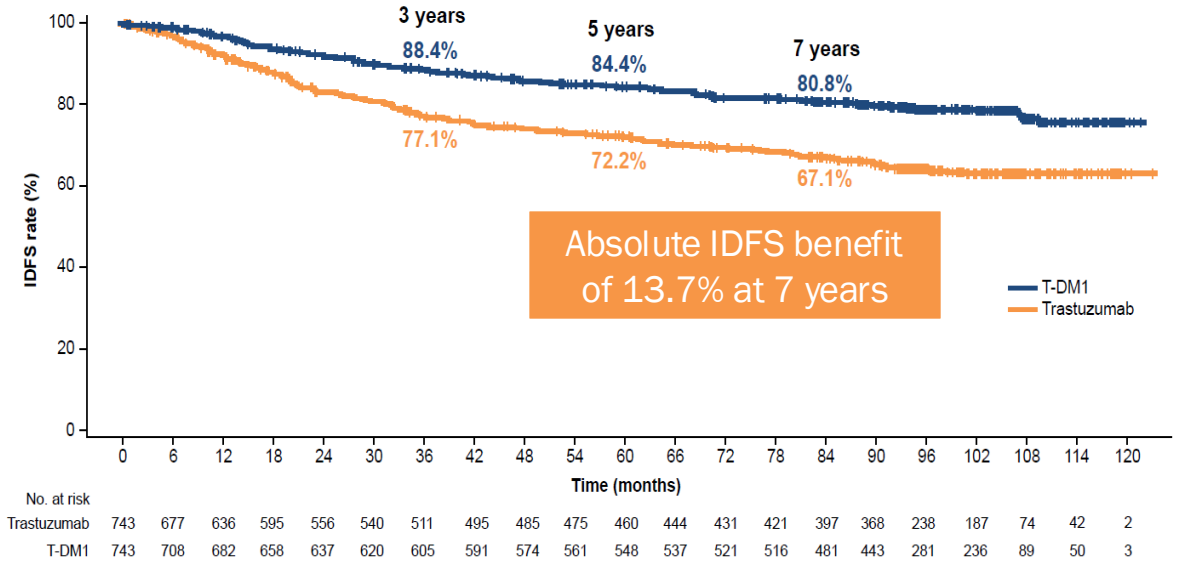
Patient Characteristics, n (%)		T-DM1 (n=743)	Trastuzumab (n=743)
Clinical stage at presentation[a]	cT1-3N0-1M0 (operable)	558 (75.1)	553 (74.4)
	cT4NxM0 or cTxN2-3M0 (inoperable)	185 (24.9)	190 (25.6)
HR+ (ER+ and/or PgR+)[a]		534 (71.9)	540 (72.7)
Preoperative HER2-directed therapy[a]	Trastuzumab alone	600 (80.8)	596 (80.2)
	Trastuzumab + other anti-HER2[b]	143 (19.2)	147 (19.8)
	Trastuzumab + pertuzumab	133 (17.9)	139 (18.7)
Pathological nodal status after preoperative therapy[a]	Node-positive	343 (46.2)	345 (46.4)
	Node-negative/not done	400 (53.8)	398 (53.6)
Prior anthracycline		579 (77.9)	564 (75.9)
Patient Disposition, n (%)		**T-DM1 (n=743)**	**Trastuzumab (n=743)**
Treated		740 (99.6)	720 (96.9)
Alive and on study		521 (70.1)	461 (62.0)
Discontinued study	With IDFS event reported	105 (14.1)	159 (21.4)
	Prior to IDFS event	117 (15.7)	123 (16.6)

[a] Key analysis stratification factors. [b] Non-pertuzumab HER2-directed agents included neratinib, afatinib, and lapatinib.

Loibl S, et al. SABCS 2023. Abstract GS03-12.

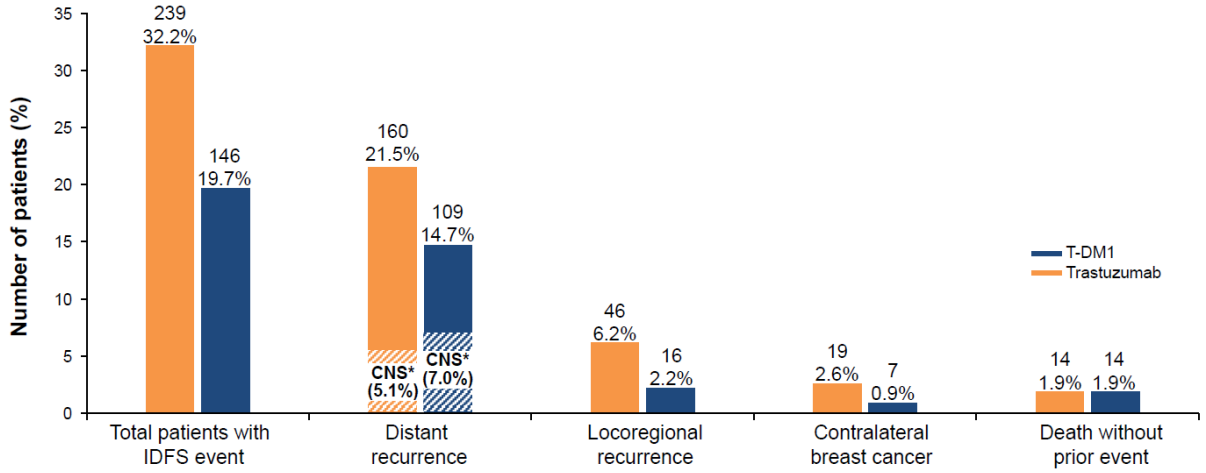
Final IDFS and Updated OS Results From the Phase 3 KATHERINE Trial of Adjuvant T-DM1 vs Trastuzumab in HER2+ EBC: IDFS

Final IDFS



IDFS	T-DM1 (n=743)	Trastuzumab (n=743)
Events, n (%)	146 (19.7)	239 (32.2)
Unstratified HR (95% CI)	0.54 (0.44-0.66)	
P value[a]	<0.0001	

Site of First Occurrence of an IDFS Event



- 8.4 years of median follow-up
- Compared with trastuzumab, patients treated with T-DM1 had 13.7% absolute IDFS benefit at 7 years

[a] *P* value for IDFS is now exploratory given the statistical significance was established at the primary analysis.

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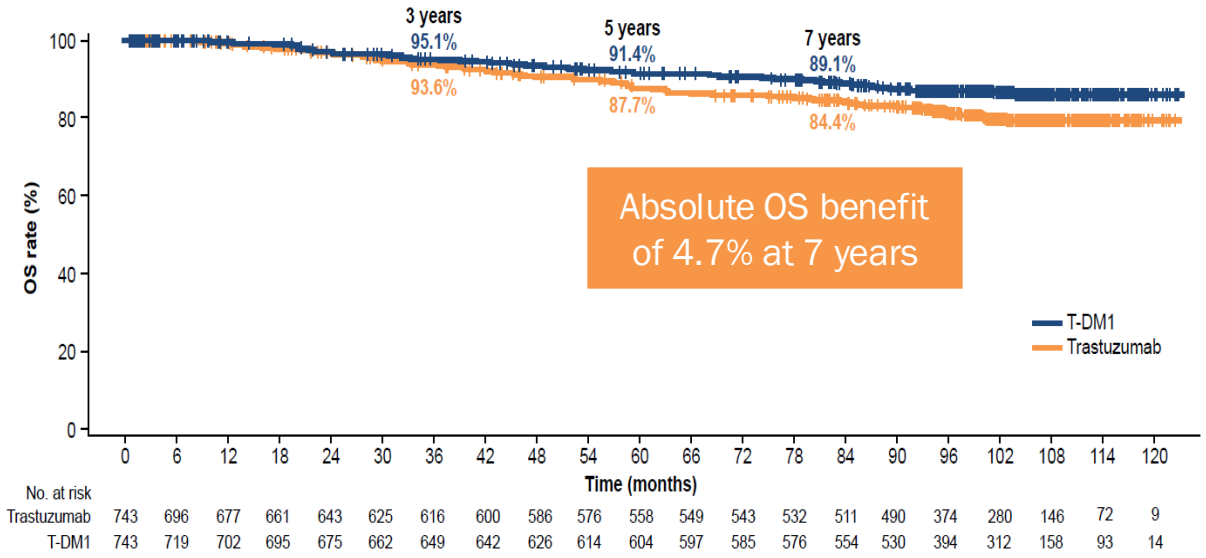
Final IDFS and Updated OS Results From the Phase 3 KATHERINE Trial of Adjuvant T-DM1 vs Trastuzumab in HER2+ EBC: OS

Second OS Interim Analysis



OS	T-DM1 (n=743)	Trastuzumab (n=743)
Events, n (%)	89 (12.0)	126 (17.0)
Unstratified HR[a] (95% CI)	0.66 (0.51-0.87)	
P value[a]	0.0027	

Summary of Deaths, n (%)	T-DM1 (n=743)	Trastuzumab (n=743)
Total number of deaths	89 (12.0)	126 (17.5)
Cause of death		
Breast cancer	70 (9.5)	108 (15.0)
AE	1 (0.1)	0
Other	18 (2.4)	18 (2.5)

- 8.4 years of median follow-up
- Compared with trastuzumab, patients treated with T-DM1 had:
  - 4.7% absolute OS benefit at 7 years
  - 34% lower risk of death

[a] Boundary for OS statistical significance HR <0.739 or *P* <0.0263.

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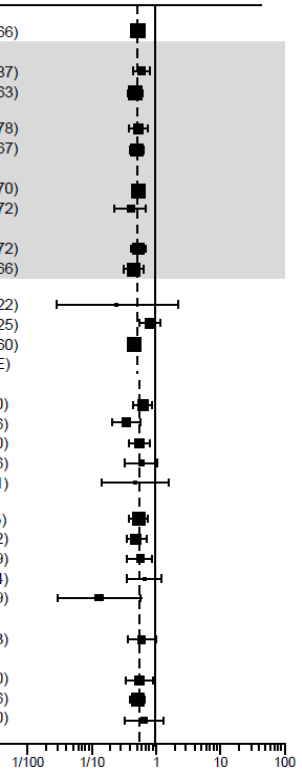
Final IDFS and Updated OS Results From the Phase 3 KATHERINE Trial of Adjuvant T-DM1 vs Trastuzumab in HER2+ EBC: Subgroup Analysis

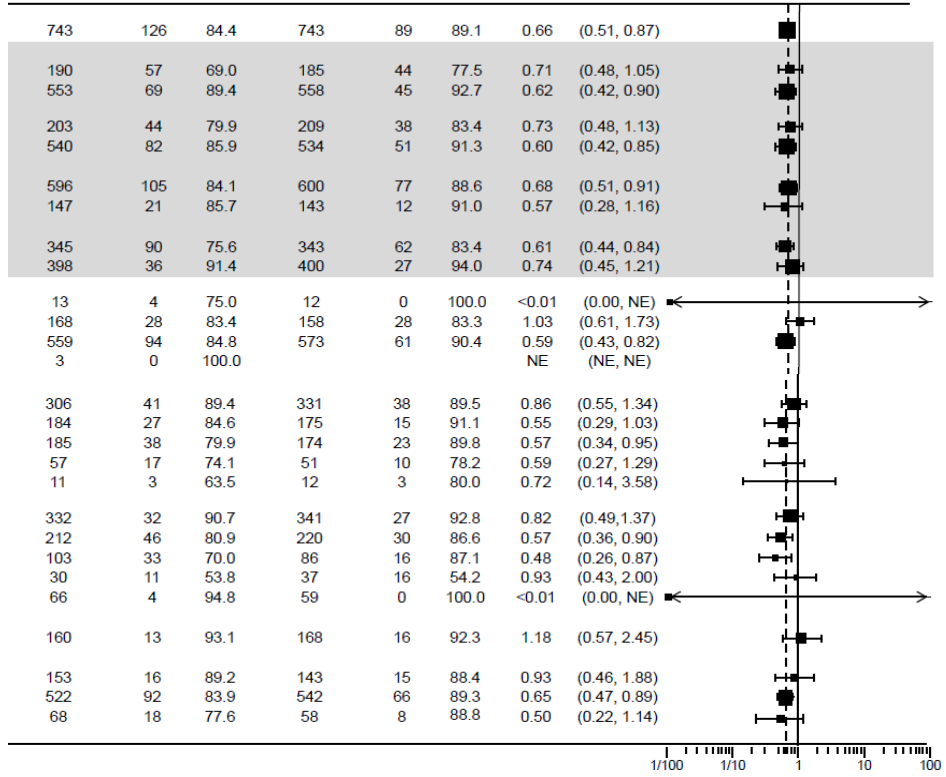
Subgroup Analysis: IDFS

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	n events	7-year IDFS	T-DM1 (n = 743) Patients per group	n events	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)
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)



Subgroup Analysis: OS

Trastuzumab (n = 743) Patients per group	n events	7-year OS	T-DM1 (n = 743) Patients per group	n events	7-year OS	Hazard ratio	95% CI
743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
190	57	69.0	185	44	77.5	0.71	(0.48, 1.05)
553	69	89.4	558	45	92.7	0.62	(0.42, 0.90)
203	44	79.9	209	38	83.4	0.73	(0.48, 1.13)
540	82	85.9	534	51	91.3	0.60	(0.42, 0.85)
596	105	84.1	600	77	88.6	0.68	(0.51, 0.91)
147	21	85.7	143	12	91.0	0.57	(0.28, 1.16)
345	90	75.6	343	62	83.4	0.61	(0.44, 0.84)
398	36	91.4	400	27	94.0	0.74	(0.45, 1.21)
13	4	75.0	12	0	100.0	<0.01	(0.00, NE)
168	28	83.4	158	28	83.3	1.03	(0.61, 1.73)
559	94	84.8	573	61	90.4	0.59	(0.43, 0.82)
3	0	100.0				NE	(NE, NE)
306	41	89.4	331	38	89.5	0.86	(0.55, 1.34)
184	27	84.6	175	15	91.1	0.55	(0.29, 1.03)
185	38	79.9	174	23	89.8	0.57	(0.34, 0.95)
57	17	74.1	51	10	78.2	0.59	(0.27, 1.29)
11	3	63.5	12	3	80.0	0.72	(0.14, 3.58)
332	32	90.7	341	27	92.8	0.82	(0.49,1.37)
212	46	80.9	220	30	86.6	0.57	(0.36, 0.90)
103	33	70.0	86	16	87.1	0.48	(0.26, 0.87)
30	11	53.8	37	16	54.2	0.93	(0.43, 2.00)
66	4	94.8	59	0	100.0	<0.01	(0.00, NE)
160	13	93.1	168	16	92.3	1.18	(0.57, 2.45)
153	16	89.2	143	15	88.4	0.93	(0.46, 1.88)
522	92	83.9	542	66	89.3	0.65	(0.47, 0.89)
68	18	77.6	58	8	88.8	0.50	(0.22, 1.14)



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Final IDFS and Updated OS Results From the Phase 3 KATHERINE Trial of Adjuvant T-DM1 vs Trastuzumab in HER2+ EBC: Safety and Summary

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

Authors' Conclusions

- After 8.4 years of median follow-up, patients with HER2+ EBC with residual invasive disease after neoadjuvant therapy treated with T-DM1 had sustained IDFS benefit and significantly improved OS in both the ITT and key subgroups
- No new safety issues emerged with longer follow-up, with rare cardiac toxicity across both arms
- T-DM1 is the first therapy to show improved survival post-surgery in this patient group
- Final OS analysis is ongoing

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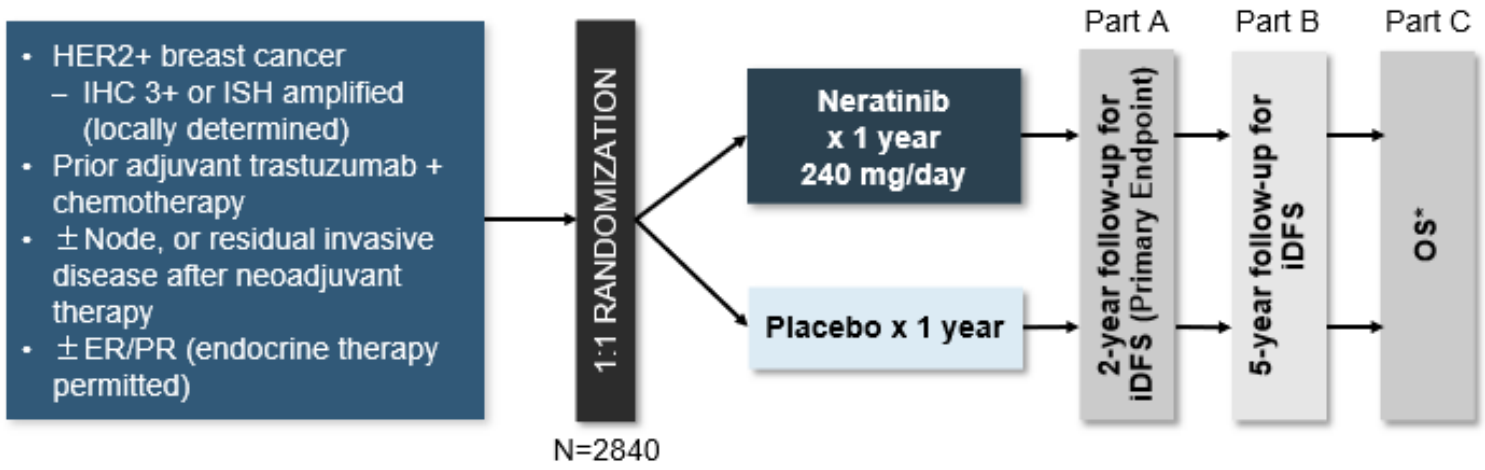
ExteNET: Study Design



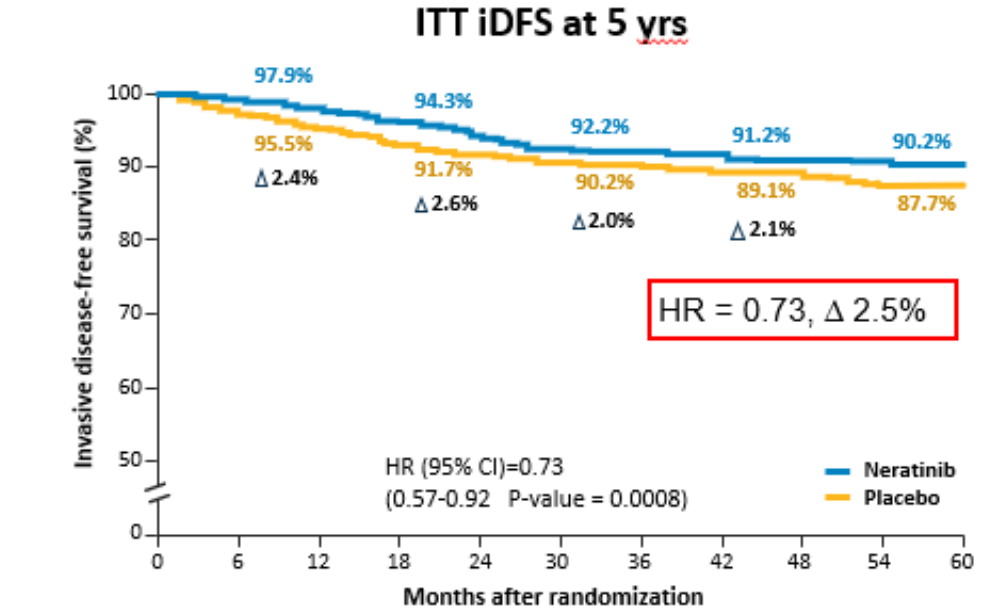
Primary endpoint:	invasive disease-free survival (iDFS)[1]
Secondary endpoints:	DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety[2]
Other analyses:	biomarkers, health outcome assessment (FACT-B, EQ-5D)[3]
Stratified by:	nodes 0, 1–3 *vs.* 4+, ER/PR status, concurrent *vs.* sequential trastuzumab[1]

In the ITT population, 24% of patients treated with neratinib and 27% of patients treated with placebo received prior neoadjuvant therapy.[2]

***An analysis of overall survival was performed after 248 events[2,4]**

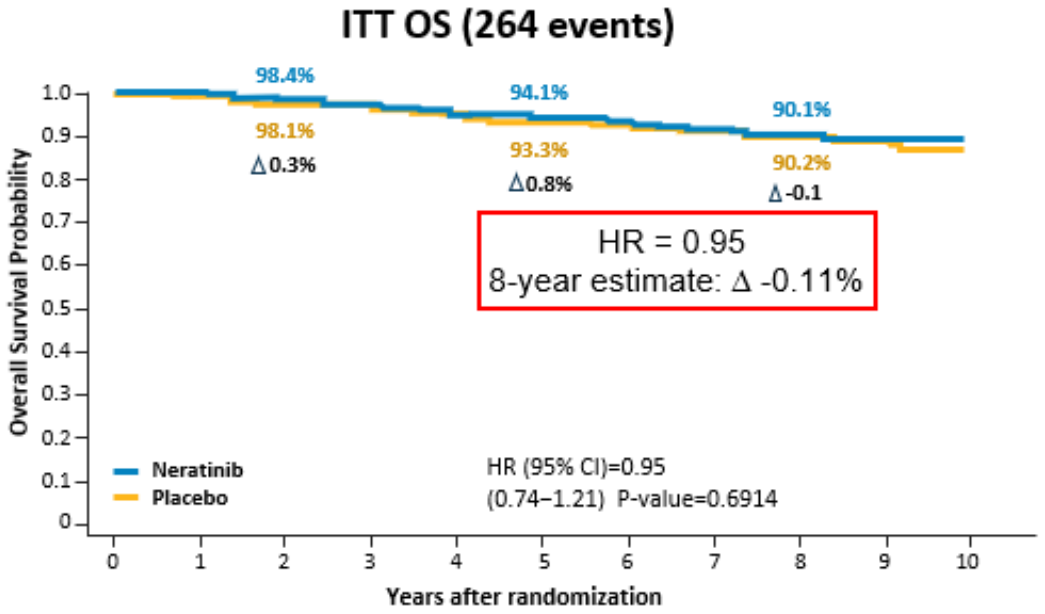
CNS = central nervous system; DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor 2; IHC = immunohistochemistry; ISH = in situ hybridization; ITT = intention-to-treat; OS = overall survival; PR = progesterone receptor.

ExteNET iDFS and OS Intent-To-Treat Population (N=2,840)



No. at risk

Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

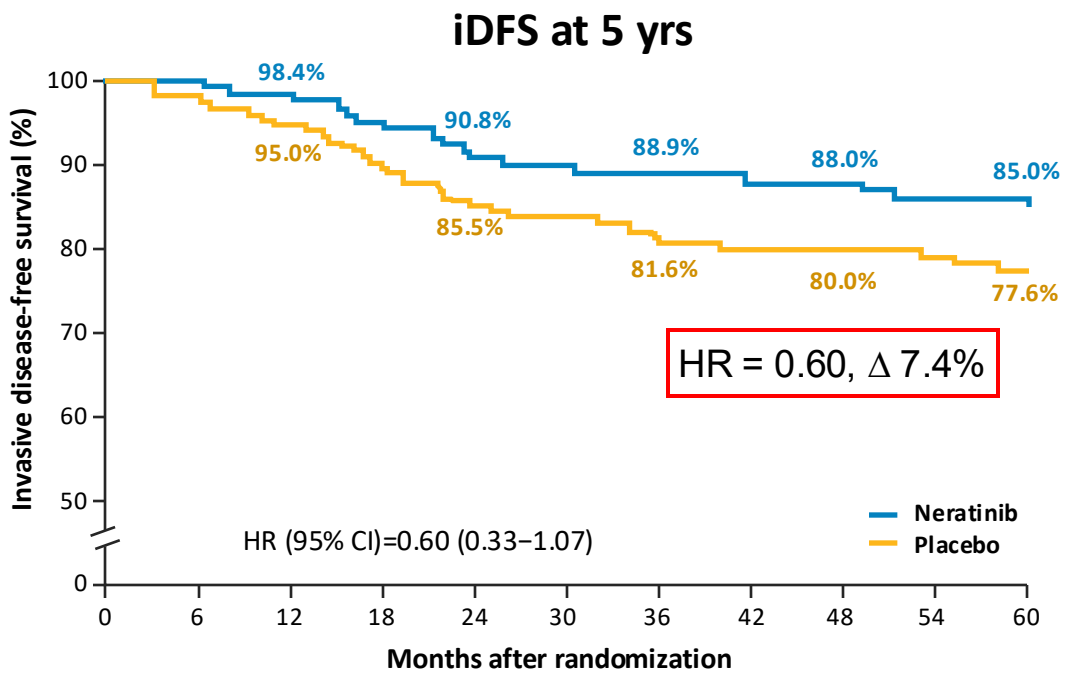


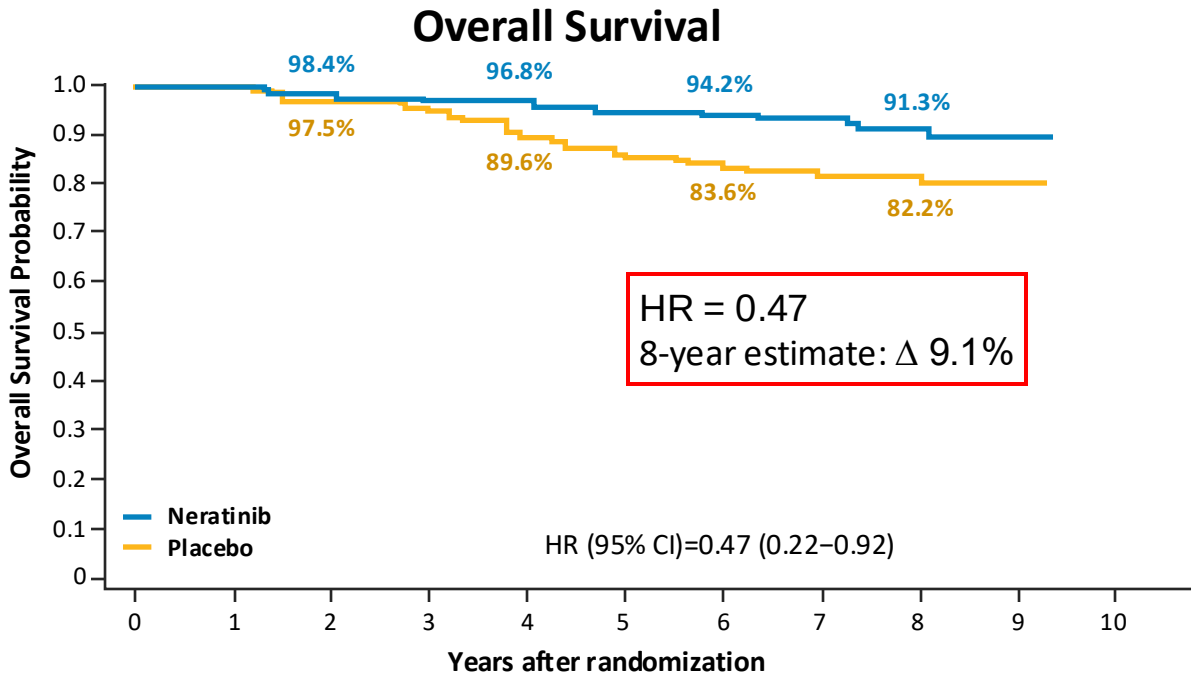
No. at risk

Neratinib	1420	1364	1309	1213	1118	1168	1123	1041	746	218	0
Placebo	1420	1384	1341	1249	1223	1199	1166	1086	796	221	0

Martin et al. *Lancet Oncol*. 2017;18(12):1688-1700.

ExteNET: No pCR Post Neoadjuvant Therapy HR+, ≤1 Year from Trastuzumab (N=295)





No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No. at risk

Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

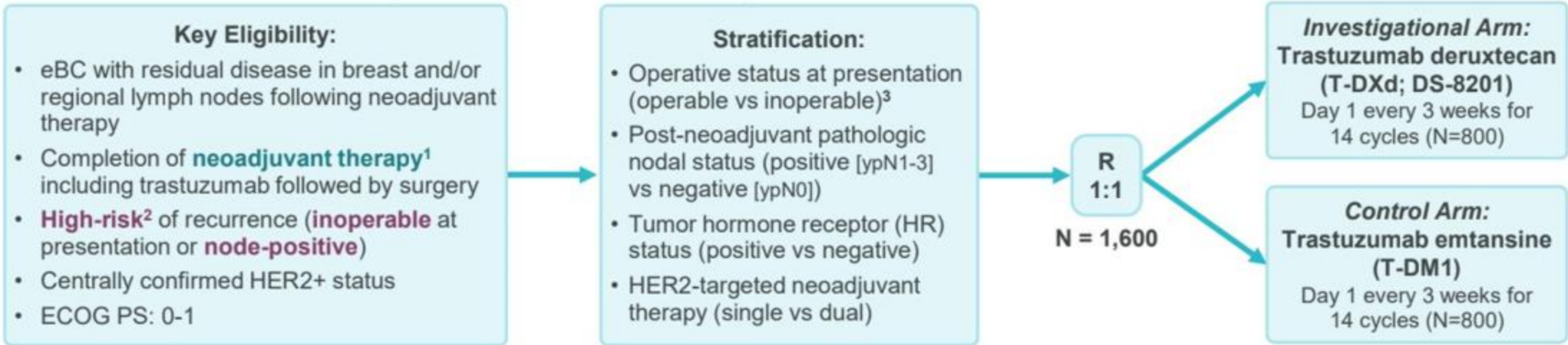
Chan A, et al. *Clin Breast Cancer*. 2021;21(1):80-91.e7.

Descriptive Analysis: Cumulative Incidence of CNS recurrences at first site of mets at 5 years HR+/≤1-year population (*n*=1334)

Subgroup	Cumulative Incidence of CNS recurrences at 5 years, %	
	Neratinib	Placebo
	%	%
All patients (*n*=1334)	0.7	2.1
Prior neoadjuvant therapy		
No (*n*=980)	0.7	1.5
Yes (*n*=354)	0.7	3.7
pCR status[1]		
No (*n*=295)	0.8	3.6
Yes (*n*=38)*	0	5

DESTINY-Breast05 (DS8201-A-U305) Study Design

T-DXd vs. T-DM1 in high-risk HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant therapy



[1] **Neoadjuvant therapy** to include at least 16 weeks of total systemic treatment in the preoperative setting, including:

- At least 9 weeks of HER2-targeted therapy including **trastuzumab** (±pertuzumab) and,
- At least 9 weeks of **taxane** therapy

[2] **High-risk definitions:**

- **Inoperable:** Inoperable breast cancer at presentation (prior to neoadjuvant therapy), defined as clinical stages T4,N0-3,M0 or T1-3,N2-3,M0
- **Node-positive:** Operable disease at presentation, defined as clinical stages T1-3,N0-1,M0, with axillary node positive disease (ypN1-3) following neoadjuvant therapy

[3] **Operative status at presentation** (prior to neoadjuvant therapy)**:**

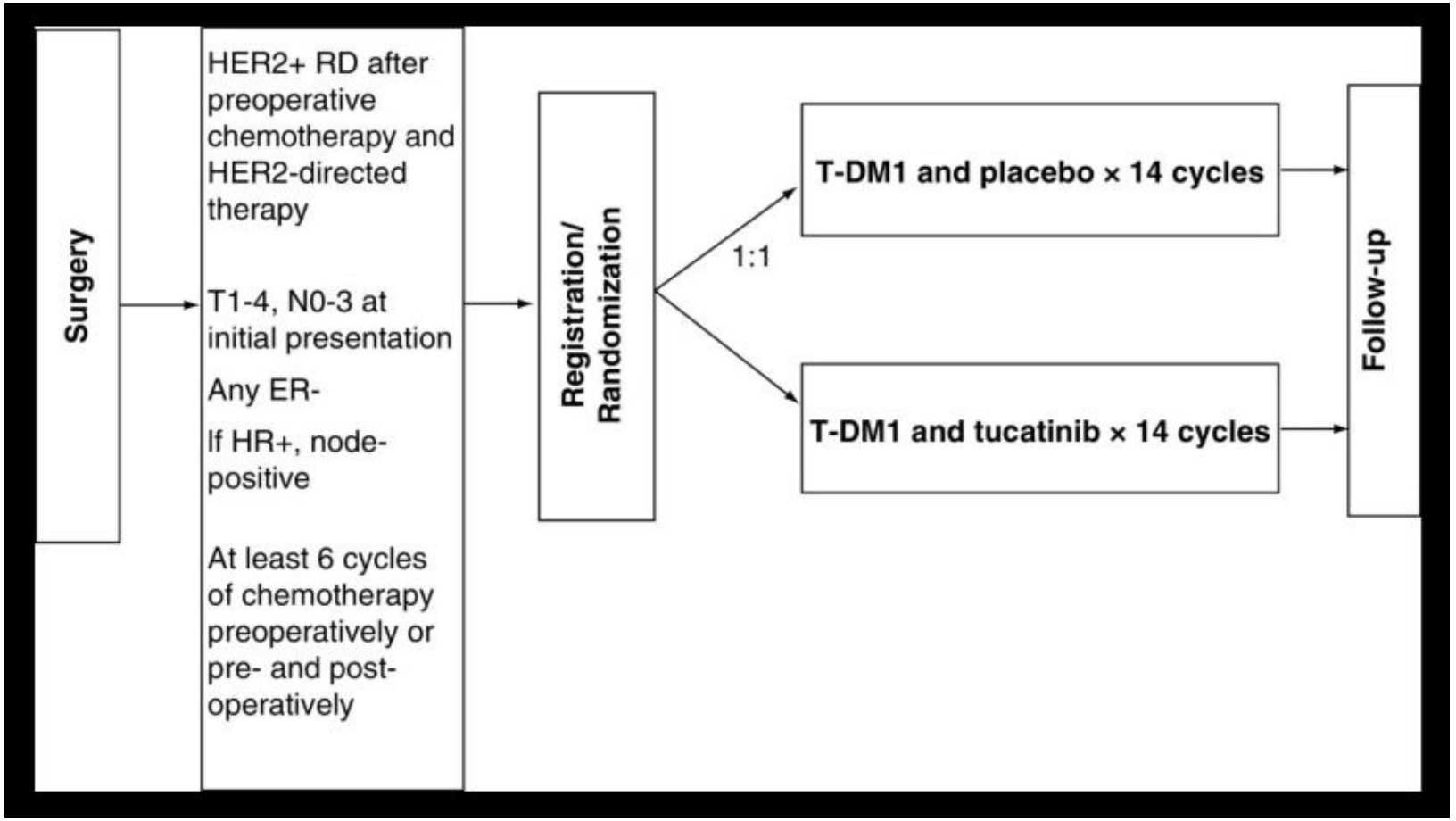
- **Operable:** clinical stages T1-3,N0-1,M0
- **Inoperable:** clinical stages T4,N0-3,M0 or T1-3,N2-3,M0

Additional Notes: Randomization within 12 weeks of surgery; adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines.

Endpoints:

- **Primary:**
  - **IDFS** (Invasive disease-free survival)
- **Secondary:**
  - **DFS** (Disease-free survival)
  - **DRFI** (Distant recurrence-free interval)
  - **BMFI** (Brain metastases-free interval)
  - **OS** (Overall survival)
  - **Adverse events**
- **Exploratory:**
  - **PROs** (Patient reported outcomes; QoL)
  - **Biomarkers** associated with efficacy/safety
  - **PK** associated with efficacy/safety

CompassHER2 RD Trial (recruiting)

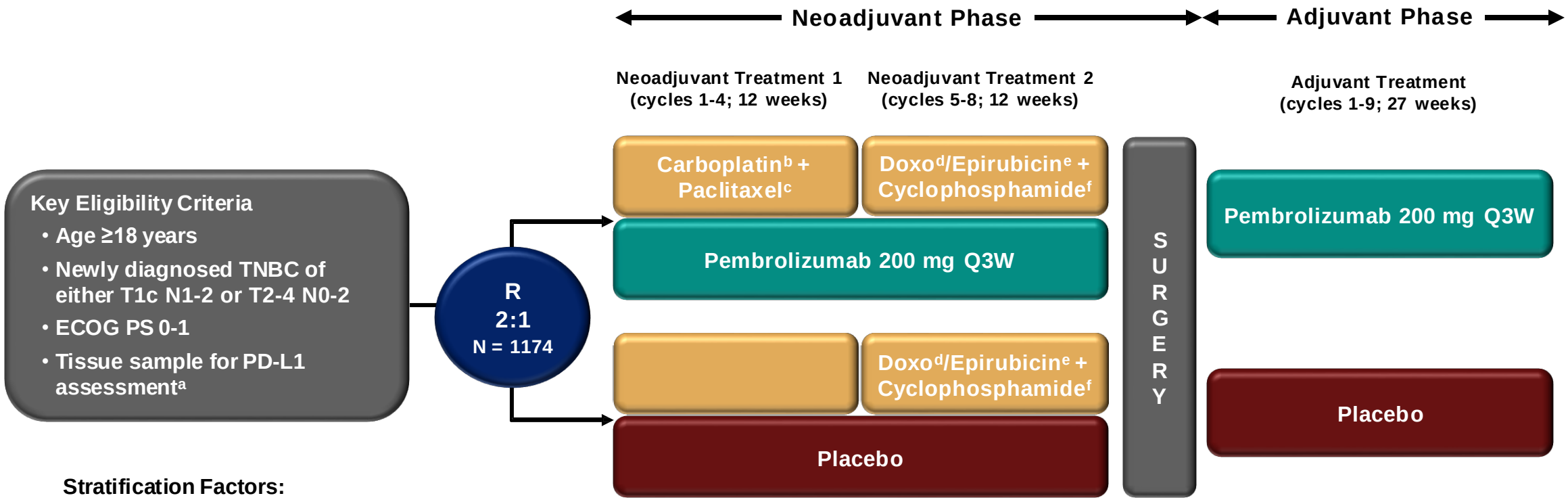


HER2+ Residual Disease Management Summary

- Data after 8 years of follow-up reveals that there is not only IDFS benefit to TDM 1 over trastuzumab in patients with residual disease after HER2 directed therapy but also a statistically significant improvement in overall survival
  - there is still no reduction in CNS events as first site of recurrence
- Among HR+/HER2+ patients who did not experience a pCR to NAC who receive extended adjuvant therapy with neratinib, there is a suggestion of both IDFS and OS benefit AND lower incidence of CNS metastasis as first site of recurrence
- Data from ongoing trials like Compass RD and destiny breast 05 will teach us if there are better mechanisms to reduce disease recurrence and CNS events in this high-risk population

Management of Residual Disease in Triple Negative Breast Cancer

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:

- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

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)

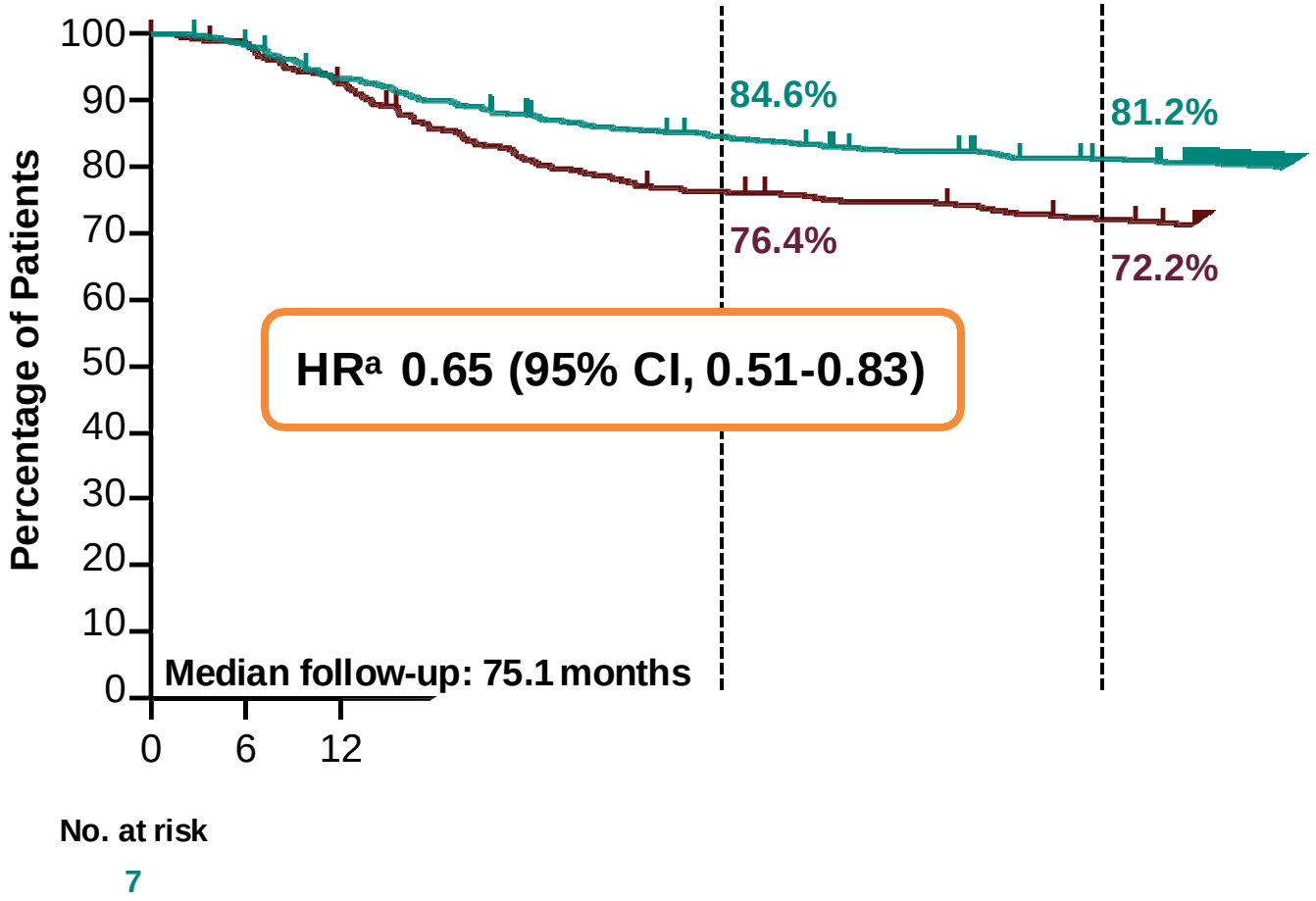
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Patients, N = 1174	
	Pembro + Chemo/Pembro N = 784	Placebo + Chemo/Placebo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1 CPS ≥1[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

[a]PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by the total number of tumor cells x 100). Data cutoff date: March 22, 2024.

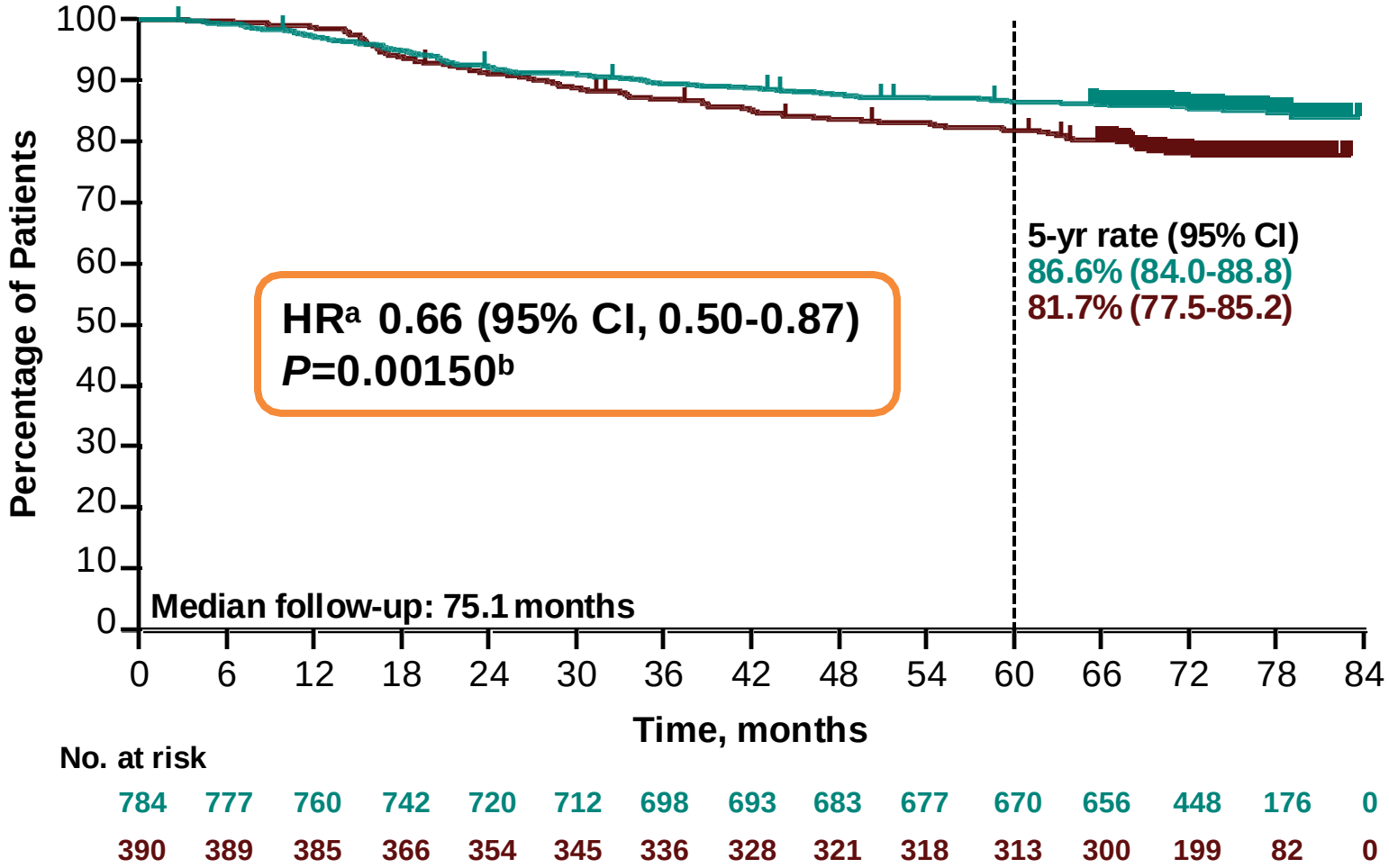
Updated Event-Free Survival



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

Key Secondary Endpoint: Overall Survival

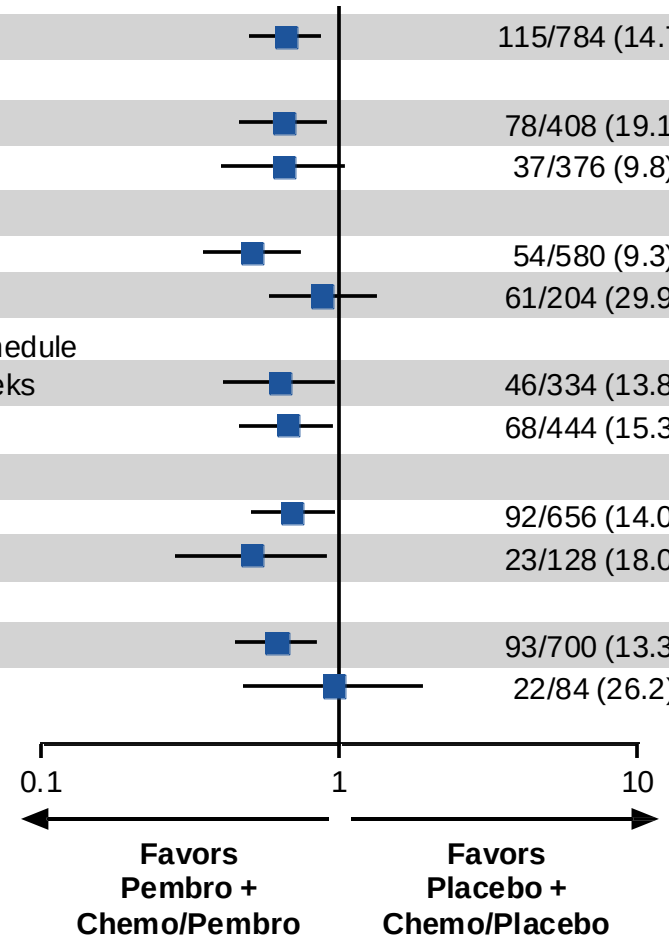


	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Data cutoff date: March 22, 2024.

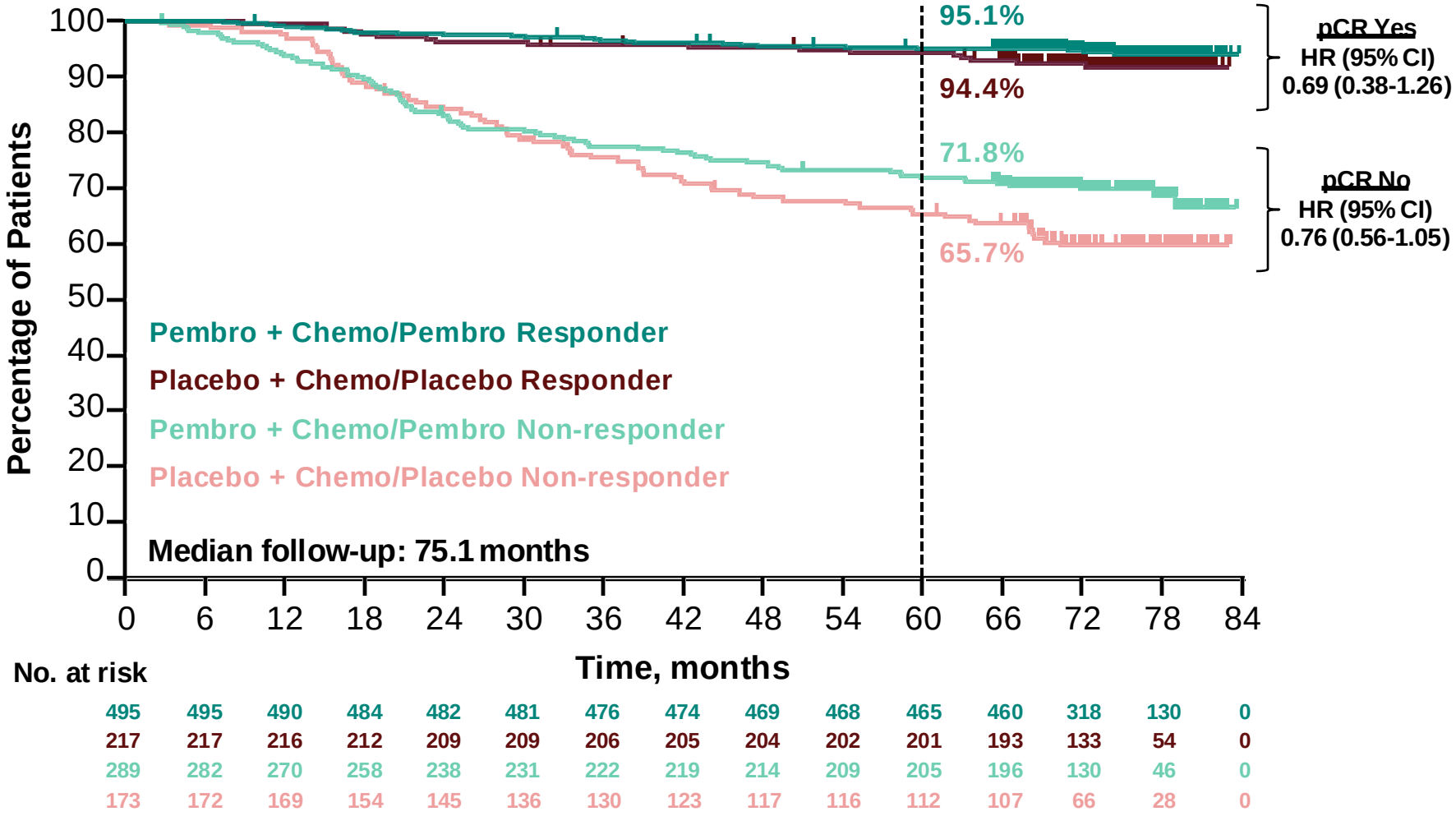
Overall Survival in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)



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. [a]Based on the small sample size and few events, results should be interpreted with caution. Data cutoff date: March 22, 2024.

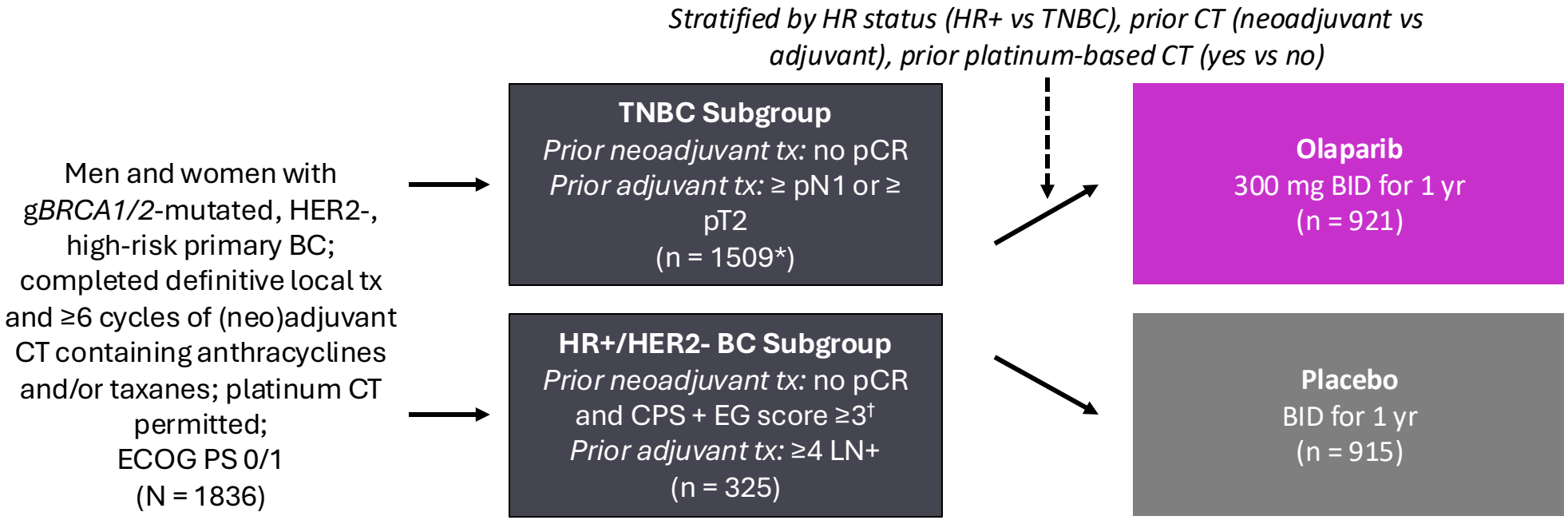
Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



This is a non-randomized subgroup analysis based on the post-treatment outcome of pCR and HRs should therefore be interpreted with caution. Data cutoff date: March 22, 2024.

OlympiA: Adjuvant Olaparib vs Placebo for BRCA1/2-Mutated, High-Risk HER2- eBC

- International, randomized, double-blind phase III trial



- **Primary endpoint:** iDFS
- **Secondary endpoints:** distant DFS, OS, safety

*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.
†Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

BC, breast cancer; BRCA, breast cancer gene; CPS +EG, estrogen receptor status and histologic grade; CT, chemotherapy; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EG, estrogen receptor status and histologic grade; HR, hormone receptor; LN, lymph node; pCR, pathologic complete response; PS, performance status; TNBC, triple-negative breast cancer; tx, treatment.

Geyer. Ann Oncol. 2022;33:1250. NCT02032823.

OlympiA: Baseline Patient Characteristics

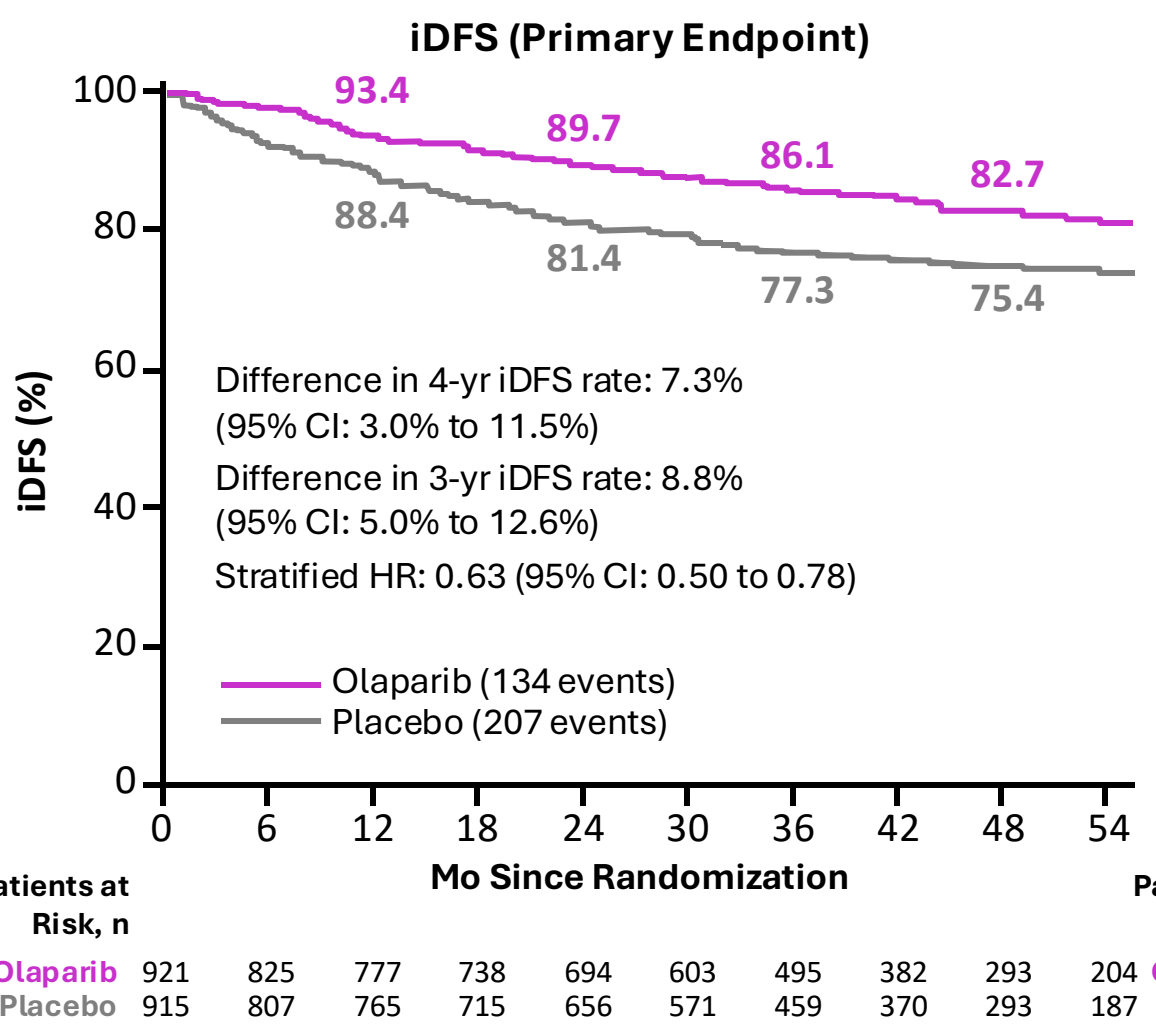
Characteristic, n (%)	Olaparib (n = 921)	Placebo (n = 915)
g*BRCA* mutation(s)*		
▪ *BRCA1*	656 (71.2)	669 (73.1)
▪ *BRCA2*	260 (28.2)	238 (26.0)
▪ *BRCA1* and *BRCA2*	2 (0.2)	5 (0.5)
Menopausal status (women only†)	n = 919	n = 911
▪ Premenopausal	572 (62.2)	553 (60.7)
▪ Postmenopausal	347 (37.8)	358 (39.3)
HR+/HER2-	168 (18.2)	157 (17.2)
TNBC	751 (81.5)	758 (82.8)
Concurrent ET (HR+ only), n/N (%)	146/168 (86.9)	146/157 (93.0)

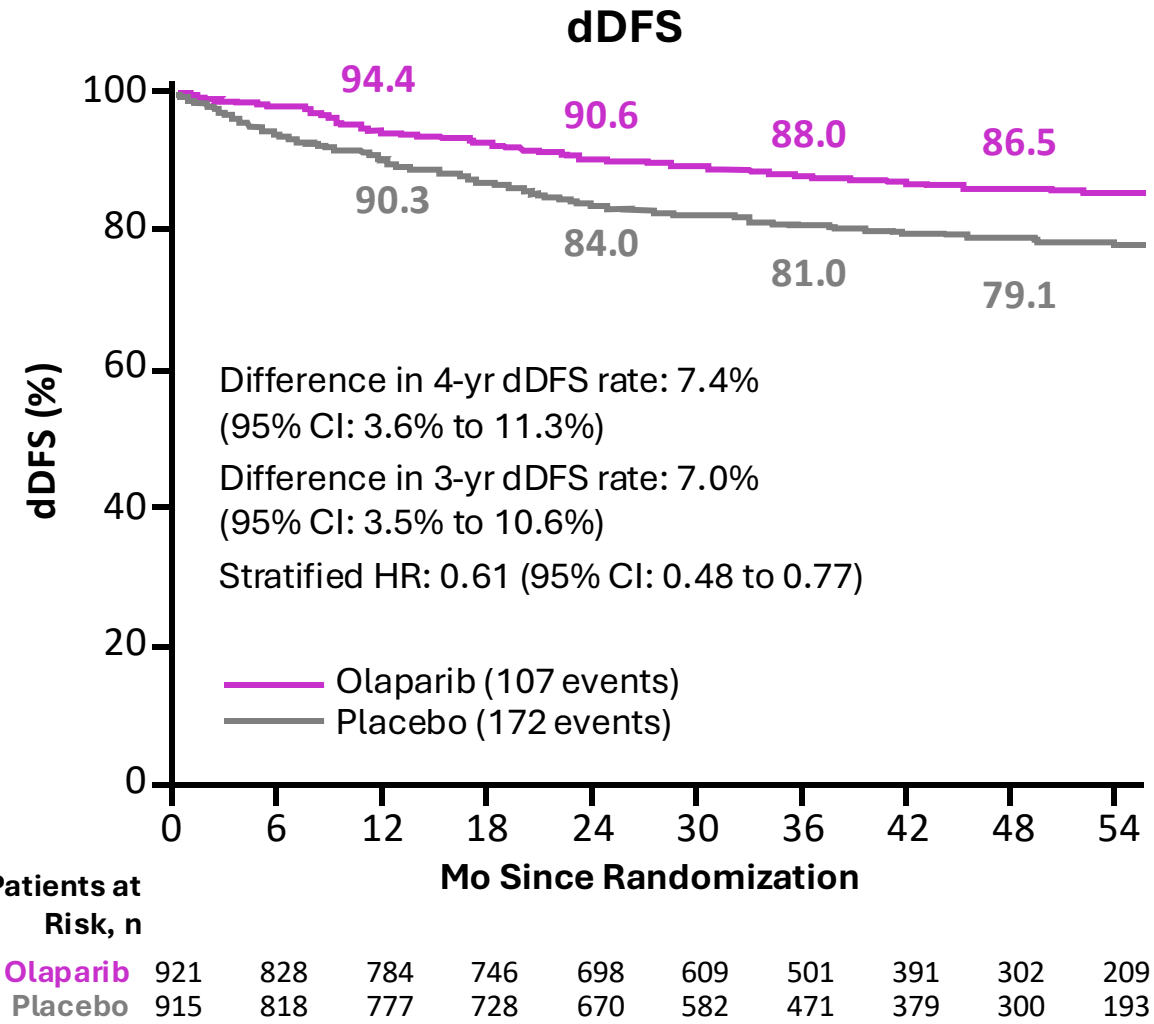
*Data missing for n = 1 in olaparib arm. †Trial enrolled 6 men.

BRCA 1/2, breast cancer gene 1 and 2; ET, endocrine therapy; gBRCA, germline BRCA; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

Geyer. Ann Oncol. 2022;33:1250. NCT02032823.

OlympiA: Second Interim Analysis of iDFS and dDFS





Patients at Risk, n										
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

Patients at Risk, n										
Olaparib	921	828	784	746	698	609	501	391	302	209
Placebo	915	818	777	728	670	582	471	379	300	193

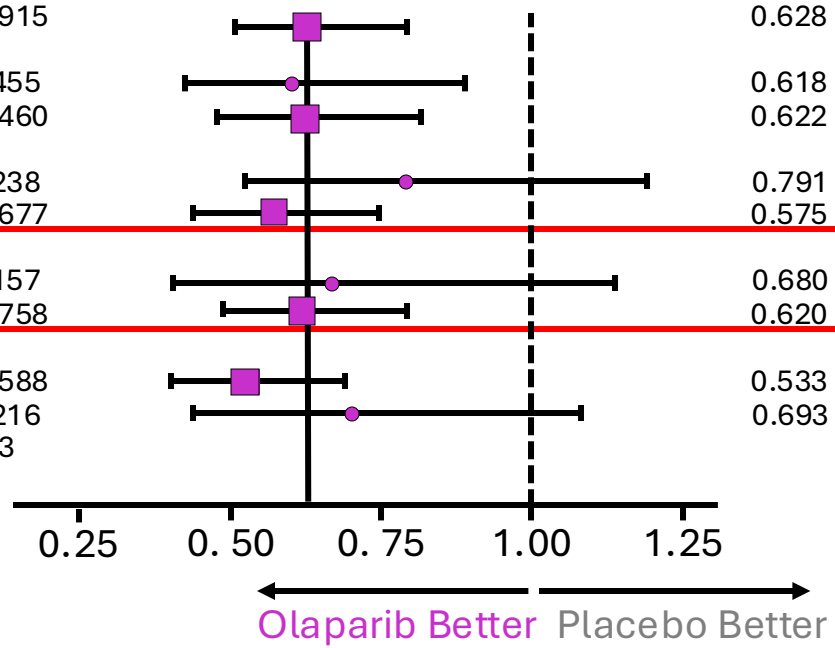
Median follow-up: 3.5 yr

CI, confidence interval; dDFS, distant disease-free survival; HR, hazard ratio; iDFS, invasive disease-free survival.

Geyer. Ann Oncol. 2022;33:1250. NCT02032823.

OlympiA: Subgroup Analysis of iDFS

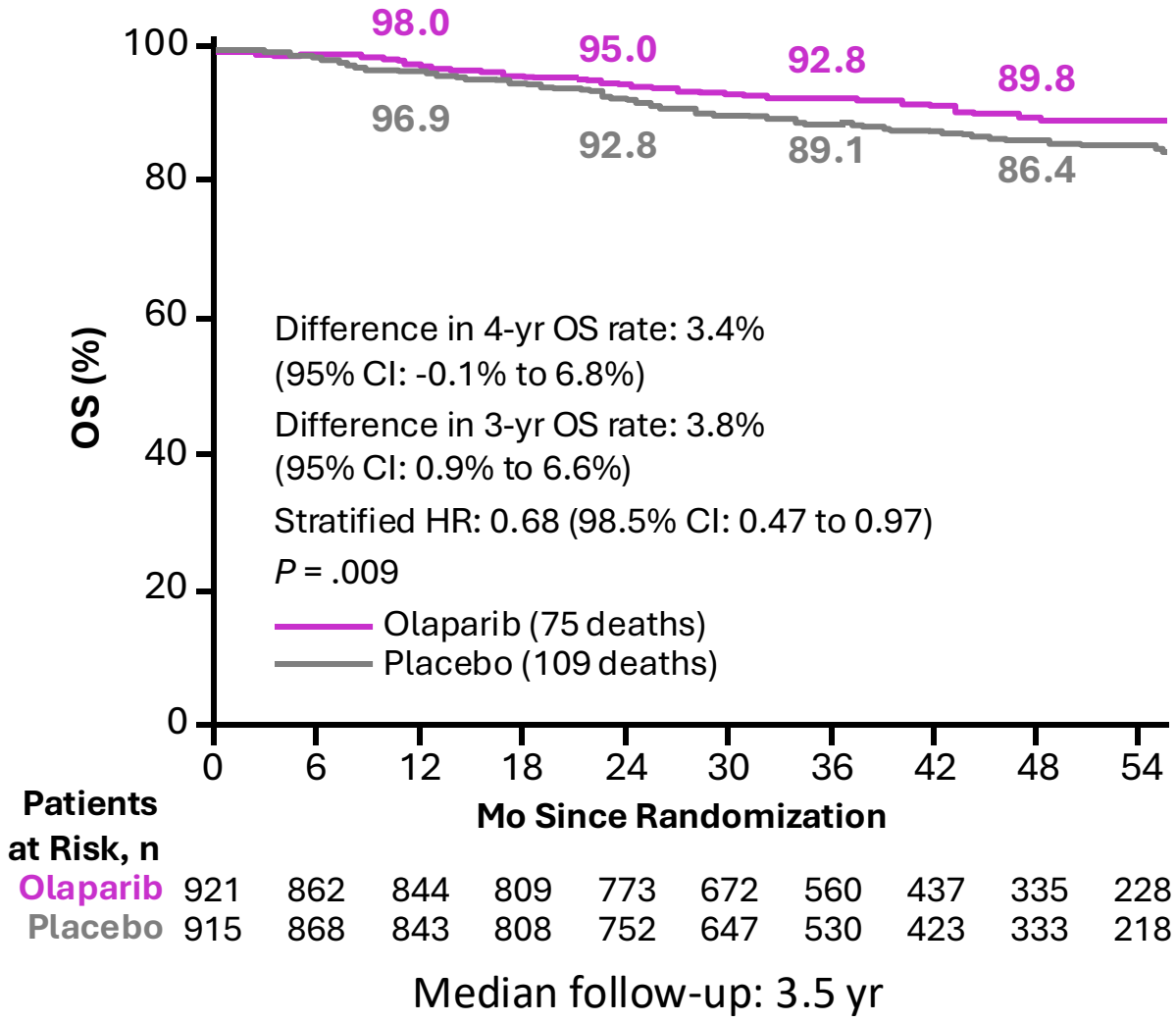
Subgroup	Olaparib	Placebo	Stratified Hazard Ratio for iDFS (95% CI)	4-Yr iDFS, %		*P* Value for Heterogeneity
	No. Patients With Event/Total No.			*Olaparib*	*Placebo*	
All patients	134/921	207/915	0.628 (0.504-0.779)	82.7	75.4	
Prior chemo						.977
Adjuvant	46/461	75/455	0.618 (0.425-0.888)	88.3	83.0	
Neoadjuvant	88/460	135/460	0.622 (0.473-0.813)	77.0	67.6	
Prior platinum						.197
Yes	42/247	51/238	0.791 (0.523-1.187)	77.8	76.2	
No	92/674	156/677	0.575 (0.443-0.742)	84.4	75.2	
HR status						.754
HR+/HER2-	25/168	34/157	0.680 (0.402-1.134)	80.1	76.6	
TNBC	109/751	173/758	0.620 (0.487-0.787)	83.1	75.2	
BRCA						.615
BRCA1	83/579	149/588	0.533 (0.406-0.695)	83.6	72.4	
BRCA2	34/235	44/216	0.693 (0.440-1.082)	80.6	78.1	
BRCA1 and *BRCA2*	0/2	0/3	NC	NC	NC	



BRCA1/2, breast cancer gene 1 and 2; iDFS, invasive disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NC, not calculated; TNBC, triple-negative breast cancer; tx, treatment.

Geyer. Ann Oncol. 2022;33:1250. NCT02032823.

OlympiA: Second Interim Analysis of OS

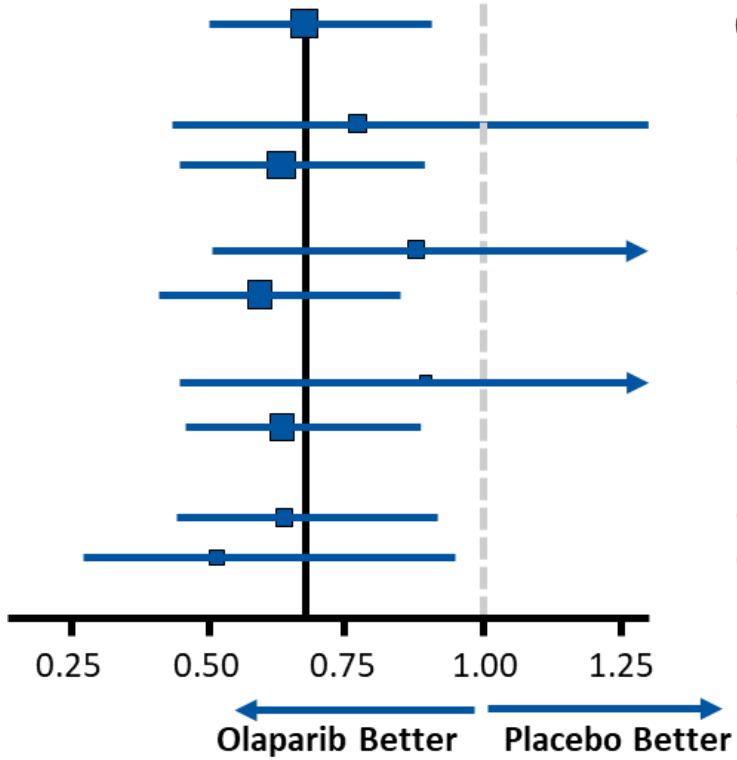


HR, hazard ratio; OS, overall survival.

Geyer CE, et al. *Ann Oncol*. 2022;33:1250-1268.

OlympiA: OS Analysis by Subgroup

Subgroup	Olaparib	Placebo	Stratified Hazard Ratio for Overall Survival (95% CI)	4-Yr Overall Survival, %		*P* Value for Heterogeneity
	Patients Who Died, n/N			Olaparib	Placebo	
All patients	75/921	109/915	0.678 (0.503-0.907)	89.8	86.4	
Prior chemo						.543
▪ Adjuvant	22/461	28/455	0.783 (0.444-1.365)	93.4	93.9	
▪ Neoadjuvant	53/460	81/460	0.638 (0.449-0.900)	86.0	78.5	
Prior platinum						.236
▪ Yes	27/247	29/238	0.882 (0.520-1.491)	85.7	83.9	
▪ No	48/674	80/667	0.601 (0.417-0.855)	91.2	87.2	
HR status						.381
▪ HR+/HER2-	16/168	17/157	0.897 (0.449-1.784)	88.1	86.3	
▪ TNBC	59/751	92/758	0.640 (0.459-0.884)	90.1	86.3	
BRCA						.845
▪ *BRCA1*	49/579	75/588	0.643 (0.446-0.918)	89.5	84.9	
▪ *BRCA2*	16/235	28/216	0.521 (0.276-0.951)	92.1	85.3	
▪ *BRCA1* and *BRCA2*	0/2	0/3	NC	NC	NC	

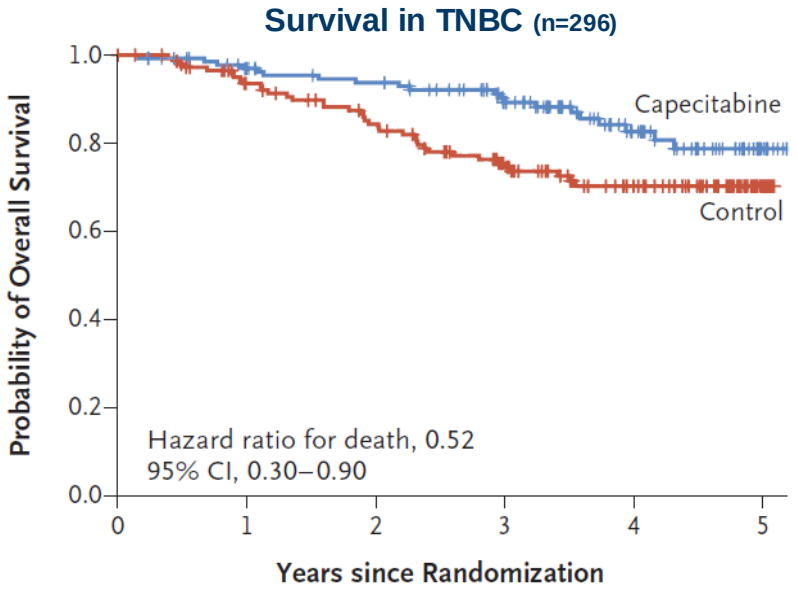


BRCA1/2, breast cancer gene 1 and 2; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NC, not calculated; OS, overall survival; TNBC, triple-negative breast cancer.

Geyer CE, et al. *Ann Oncol*. 2022;33:1250-1268.

Can postoperative Capecitabine improve cure rates in patients with residual disease after preoperative chemotherapy?

Yes, in TNBC



Masuda N, et al. *N Engl J Med*. 2017;376:2147–2159.; Tutt et al, NEJM 2021

TNBC Residual Disease Management Summary

- Neoadjuvant pembro + chemo followed by adjuvant pembro resulted in a statistically significant and clinically meaningful improvement in OS compared with neoadjuvant chemo alone in patients with previously untreated, high-risk, early-stage TNBC
- Neoadjuant therapy with the Keynote 522 regimen continues to show a clinically meaningful improvement in EFS compared to chemo alone after 6 years median follow-up
- Among patients with BRCA associated high-risk breast cancer, adjuvant Olaparib offers IDFS and OS benefit
- Studies are ongoing to determine potential targeted options based on ctDNA in this high-risk population. Vaccine trials also underway

Management of Residual Disease in HR+ Breast Cancer

Summary of CDK4/6i Trials in EBC: Design

	PENELOPE-B[1-3]	PALLAS[4-6]	monarchE[7-9]	NATALEE[10-12]
CDK4/6i	Palbociclib	Palbociclib	Abemaciclib	Ribociclib
Design	Phase III, randomized, placebo-controlled	Phase III, randomized, open-label	Phase III, randomized, open-label	Phase III, non-randomized, open-label
Sample size	1250	5796	5637	5101
Study population	High risk	Stages II-III	High risk	Stages II-III
Details of combination therapy	1 year (125 mg, 3 weeks on/ 1 week off × 13 cycles) + ET for ≥5 years	2 years (125 mg, 3 weeks on/ 1 week off × 26 cycles) + ET for ≥5 years	2 years (150 mg, continuous dosing × 26 cycles) + ET for ≥5 years	3 years (400 mg, 3 weeks on/ 1 week off) + ET for ≥5 years
Duration of CDK4/6i treatment	1 year	2 years	2 years	3 years
First results reported	December 2020	September 2020	September 2020	June 2023
Primary endpoint	IDFS			

monarchE and PENELOPE-B enrolled patients with higher risk of recurrence than in NATALEE or PALLAS

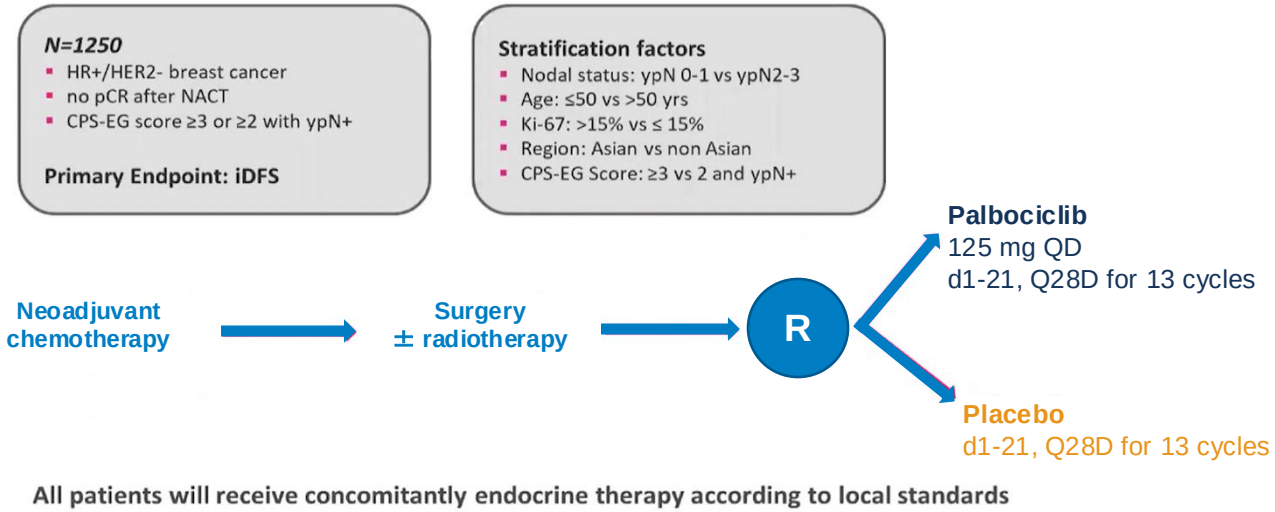
Abemaciclib was dosed continuously vs intermittent dosing with palbociclib and ribociclib

Palbociclib duration was 1 or 2 years, abemaciclib was 2 years, and ribociclib was 3 years

Note: This table is not intended as a head-to-head trial comparison. Cross-trial comparison of efficacy, tolerability, and safety cannot be made.
References are included in slide notes section.

PENELOPE-B: Palbociclib + Endocrine Therapy in HR+/HER2- With Residual Disease After Neoadjuvant Chemo + Surgery

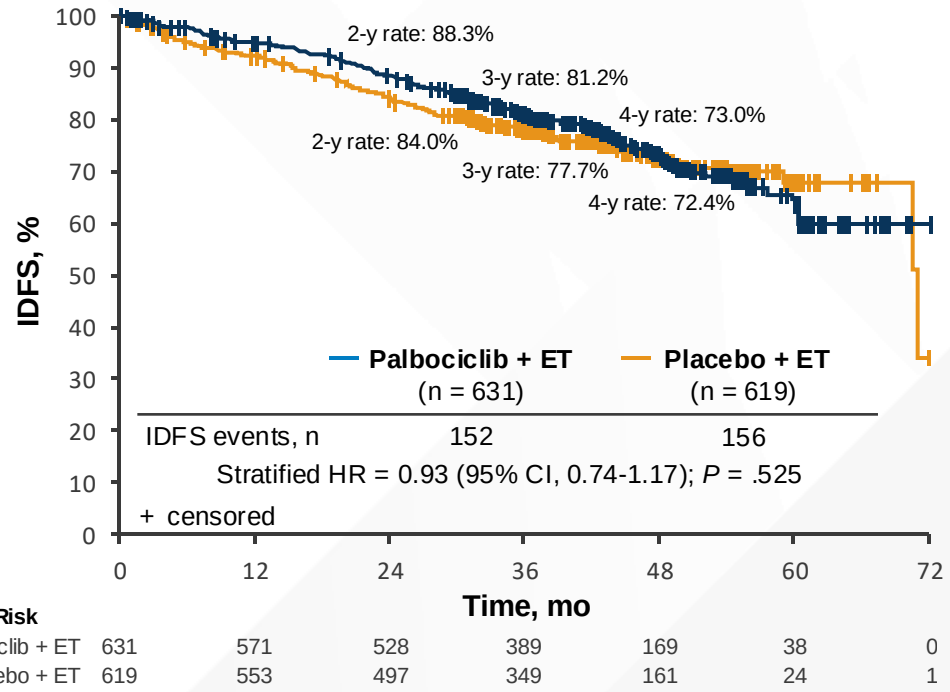
Study Design



All patients will receive concomitantly endocrine therapy according to local standards

IDFS

Median follow-up 42.8 mo



No. at Risk							
Palbociclib + ET	631	571	528	389	169	38	0
Placebo + ET	619	553	497	349	161	24	1

- The most frequent AEs in the palbociclib arm were hematologic in nature (any grade: neutropenia 95.7%, leukopenia 99.2%, thrombocytopenia 56.6%, anemia 73.9%)
- Most common related serious adverse events were infections and vascular disorders
- 2 deaths in palbociclib arm (not related to study drug), 6 deaths in placebo arm

Slide courtesy of Joyce A. O'Shaughnessy, MD.

Loibl S, et al. *J Clin Oncol*. 2021;39(14):1518-1530.

AE, adverse events; CPS-EG, clinical pathological staging-estrogen receptor grading; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; IDFS, invasive disease-free survival; Ki67, antigen Kiel 67; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; QD, once per day; R, randomized.

monarchE: Study Design[1,2]

Eligibility

- HR+/HER2– high-risk EBC
- Women (regardless of menopausal status) or men
- Underwent definitive surgery of the primary breast tumor
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on clinical pathological features (91% of pts)

- ≥4 ALNs, or
- 1-3 ALNs and ≥1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on Ki-67 (9% of pts)

- 1-3 ALN
- Tumor size <5 cm and grade <3
- Ki-67 ≥20%[3,a]

Randomized 1:1

N=5637

Abemaciclib 150 mg bid + ET[b]

On-study treatment period: *2 years*
Follow-up period: *ET 3-8 years as clinically indicated*

ET[b]

Node-Positive Criteria:
- **Stage 1** + Grade 3 disease
- **Stage 2** + Grade 3 disease and/or tumor size 5 cm
- **Stage 3**

Stratified for:
- Prior CT: neo(adjuvant) vs none
- Menopausal status[d]
- Region: NA/EU vs Asia vs other

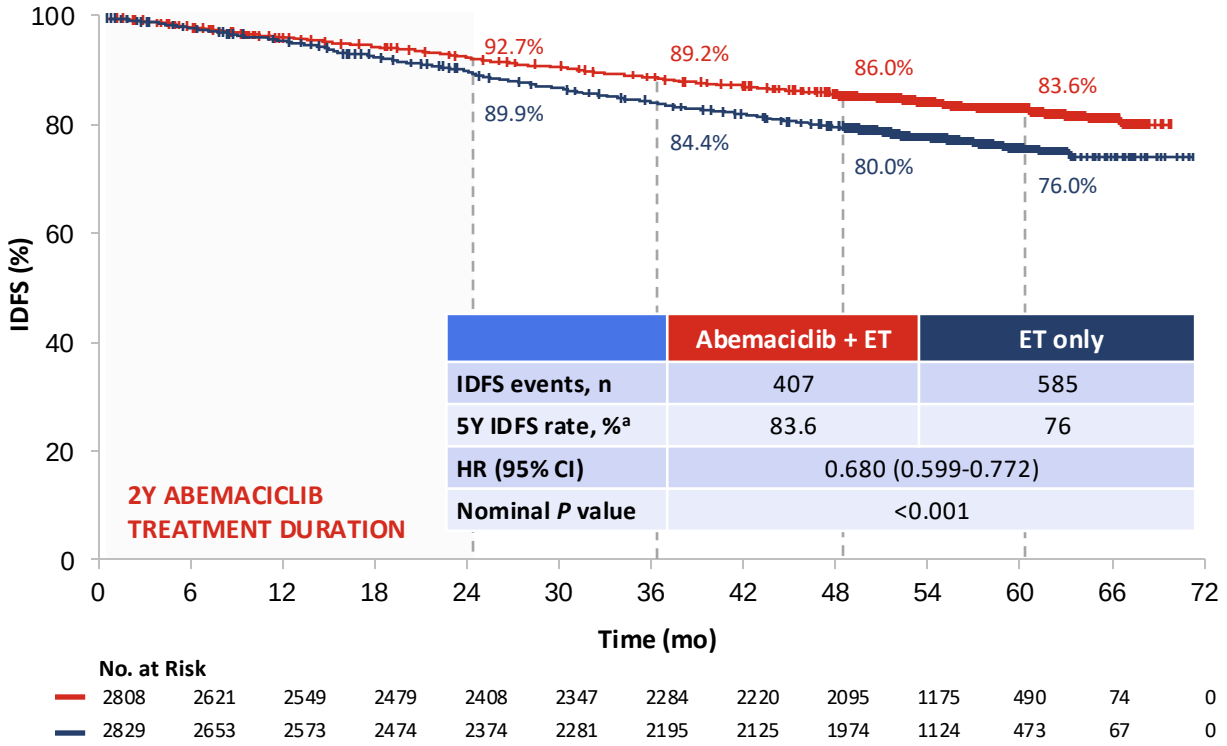
Primary Objective: IDFS
Secondary Objectives:
IDFS in high Ki-67 index, DRFS, OS, safety, PK, PROs

[a] Ki-67 expression was centrally assessed in all patients with suitable untreated breast tissue via IHC during the study screening period. Cohort 1 was not required to submit a tissue sample prior to randomization, but a sample was requested, where available, to support Ki-67 analyses. Cohort 2 had to submit an untreated tissue sample for Ki-67 analysis to determine eligibility.[3]
[b] ET includes antiestrogen agents (eg, tamoxifen) or aromatase inhibitors ± a gonadotropin-releasing hormone agonist.

1. Harbeck N, et al. *Ann Oncol*. 2021;32(12):1571-1581. 2. ClinicalTrals.gov. Accessed October 28, 2021. https://clinicaltrials.gov/ct2/show/NCT03155997 3. Johnston SRD, et al. *J Clin Oncol*. 2020;38(34):3987-3998.

monarchE Data at 54 Month Median Follow-Up: IDFS

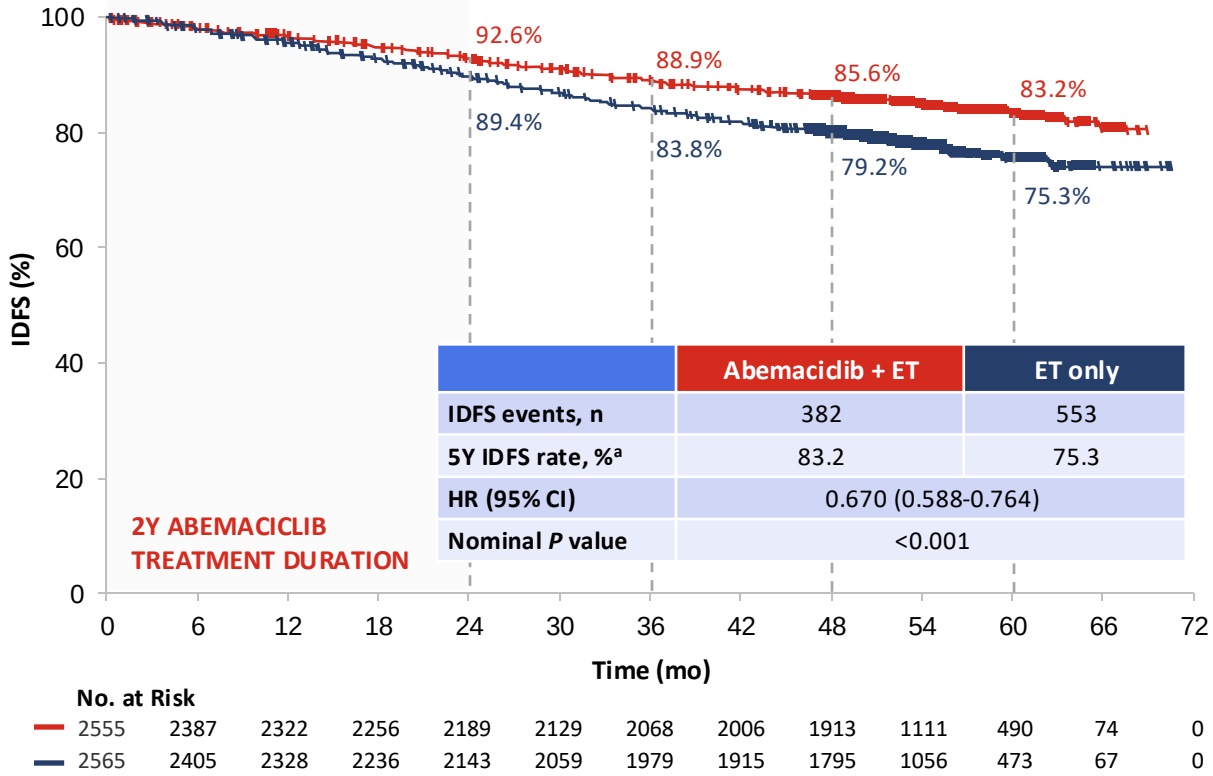
IDFS of ITT



	Abemaciclib + ET	ET only
IDFS events, n	407	585
5Y IDFS rate, %[a]	83.6	76
HR (95% CI)	0.680 (0.599-0.772)	
Nominal *P* value	<0.001	

The IDFS benefit was maintained in the ITT population, with an absolute improvement of 7.6% at 5 years compared with 2- and 3-year DRFS rates of 2.8% and 4.8% respectively

IDFS of Cohort 1[b]



	Abemaciclib + ET	ET only
IDFS events, n	382	553
5Y IDFS rate, %[a]	83.2	75.3
HR (95% CI)	0.670 (0.588-0.764)	
Nominal *P* value	<0.001	

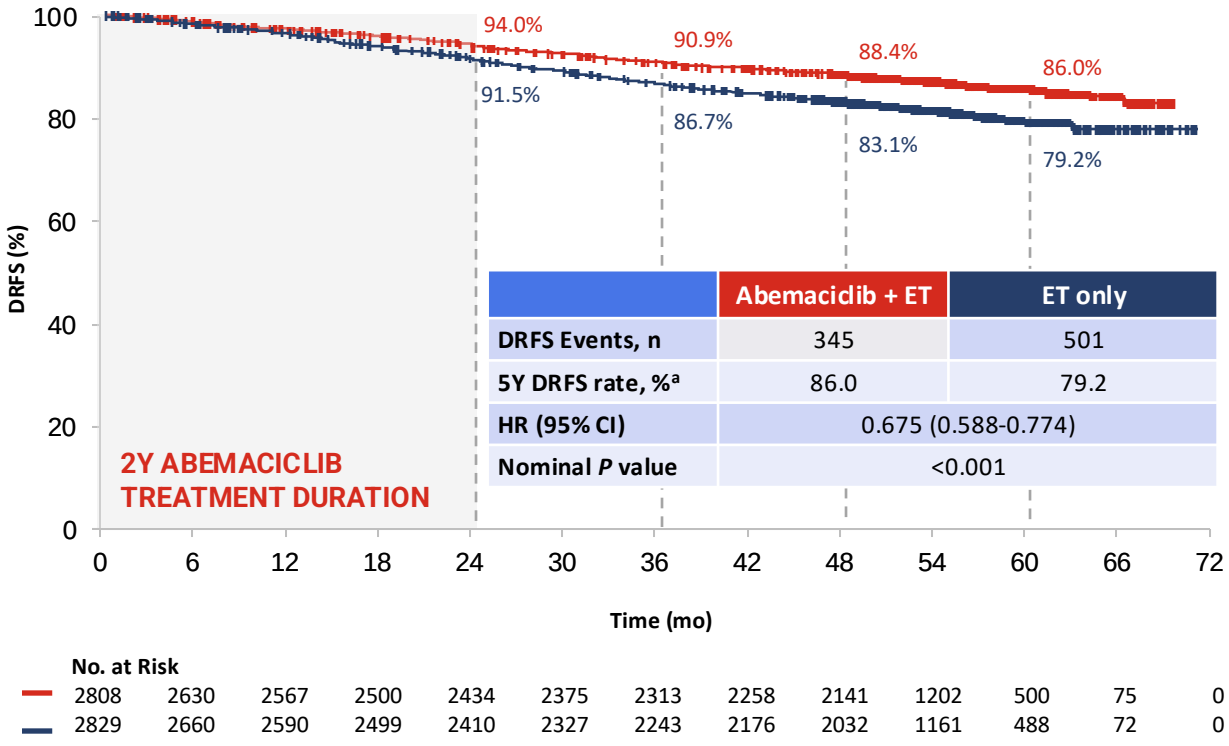
The IDFS benefit was maintained in the Cohort 1 subpopulation, with an absolute improvement of 7.9% at 5 years compared with 2- and 3-year IDFS rates of 3.2% and 5.1% respectively

[a] mFU of 54mo. [b] Statistical significance was achieved in the Cohort 1 High Ki-67 population at the primary outcome analysis. This population was the basis of approval by the FDA.

Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

monarchE Data at 54 Month Median Follow-Up: DRFS

DRFS of ITT



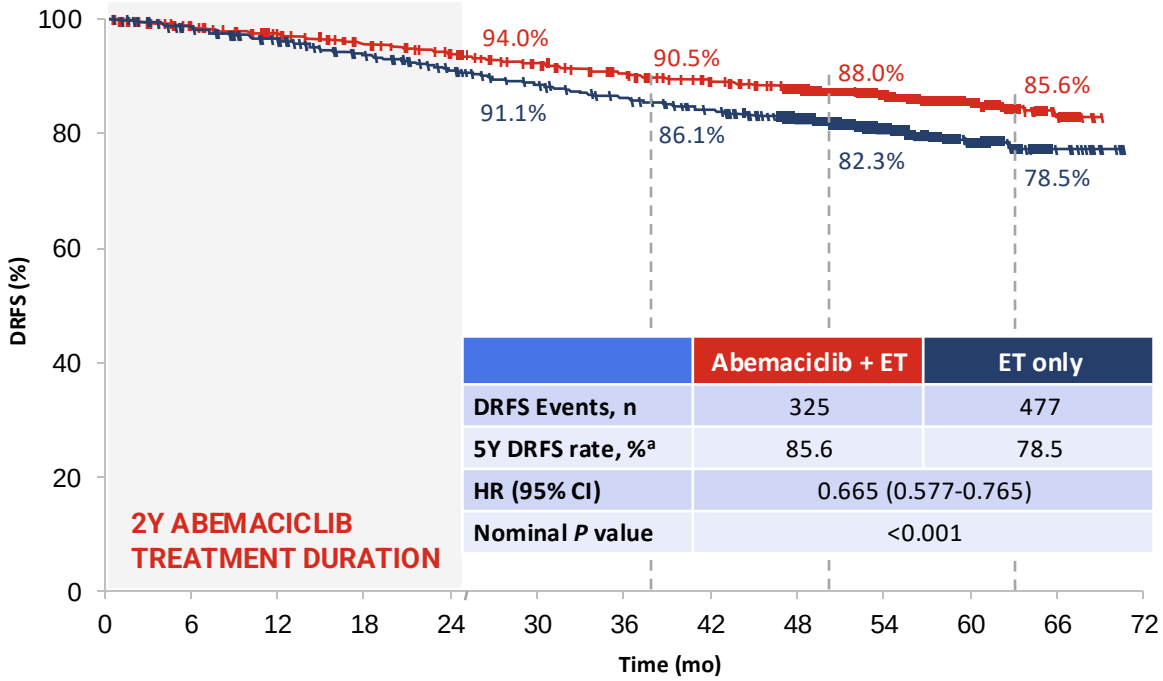
	Abemaciclib + ET	ET only
DRFS Events, n	345	501
5Y DRFS rate, %[a]	86.0	79.2
HR (95% CI)	0.675 (0.588-0.774)	
Nominal *P* value	<0.001	

No. at Risk

2808	2630	2567	2500	2434	2375	2313	2258	2141	1202	500	75	0
2829	2660	2590	2499	2410	2327	2243	2176	2032	1161	488	72	0

The DRFS benefit was sustained in the ITT population, with an absolute improvement of 6.7% at 5 years compared with 2- and 3-year DRFS rates of 2.5% and 4.1% respectively

DRFS of Cohort 1[b]



	Abemaciclib + ET	ET only
DRFS Events, n	325	477
5Y DRFS rate, %[a]	85.6	78.5
HR (95% CI)	0.665 (0.577-0.765)	
Nominal *P* value	<0.001	

No. at Risk

2555	2396	2339	2274	2213	2155	2095	2040	1953	1136	500	75	0
2565	2412	2345	2259	2177	2102	2023	1960	1849	1092	488	72	0

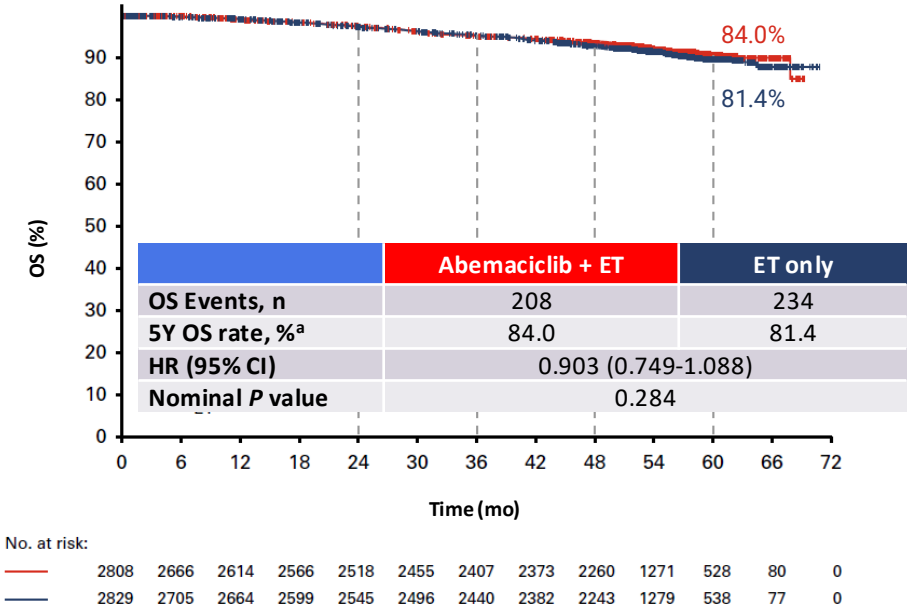
The DRFS benefit was maintained in the Cohort 1 subpopulation, with an absolute improvement of 7.1% at 5 years compared with 2- and 3-year IDFS rates of 2.9% and 4.4% respectively

[a] mFU of 54mo. [b] Statistical significance was achieved in the Cohort 1 High Ki-67 population at the primary outcome analysis. This population was the basis of approval by the FDA.

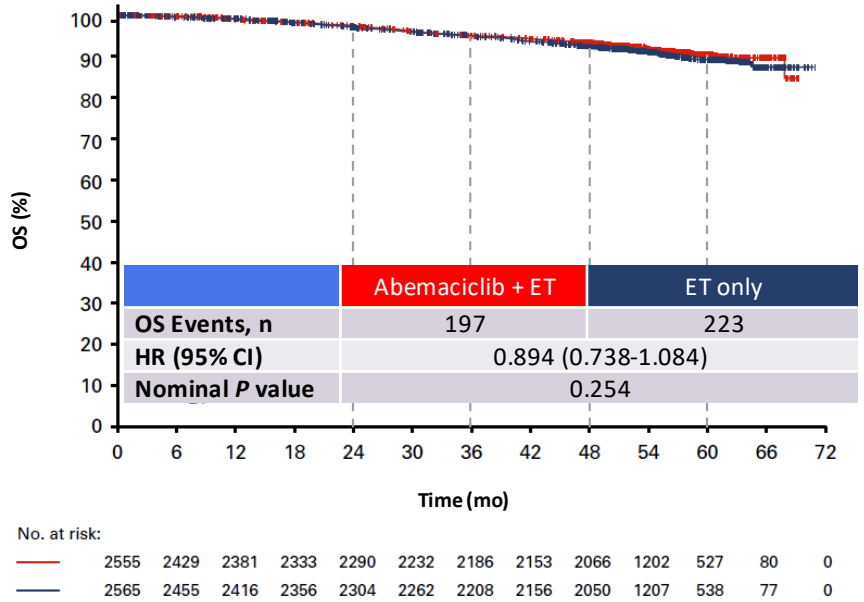
Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993.

monarchE Data at 54 Month Median Follow-Up: OS

OS of ITT



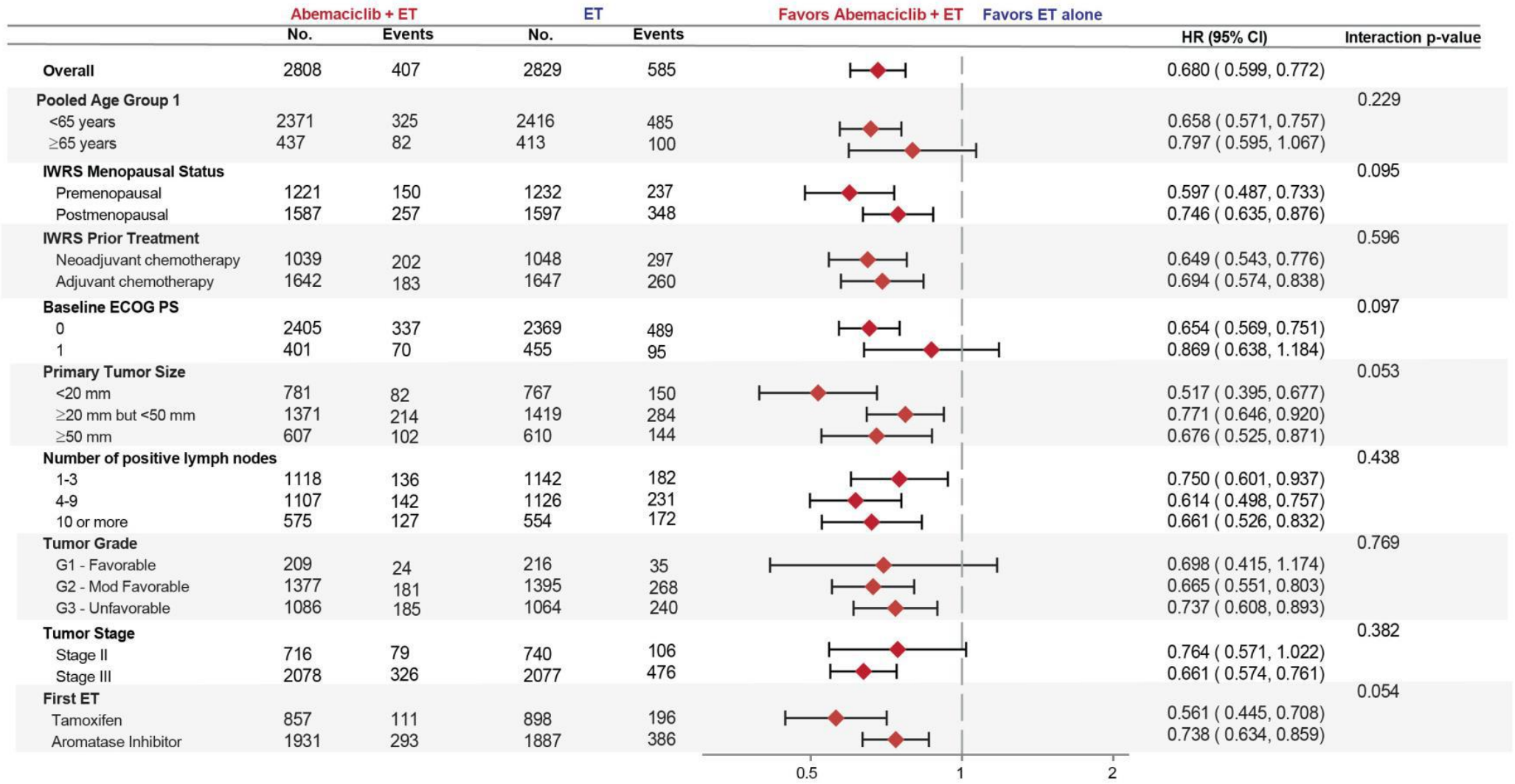
OS of Cohort 1[a]



The abemaciclib + ET arm was associated with fewer deaths but statistical significance was not reached.
OS data remain immature and continued follow-up is ongoing

[a] mFU of 54 months.
Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993.

monarchE IDFS Subgroup Analysis

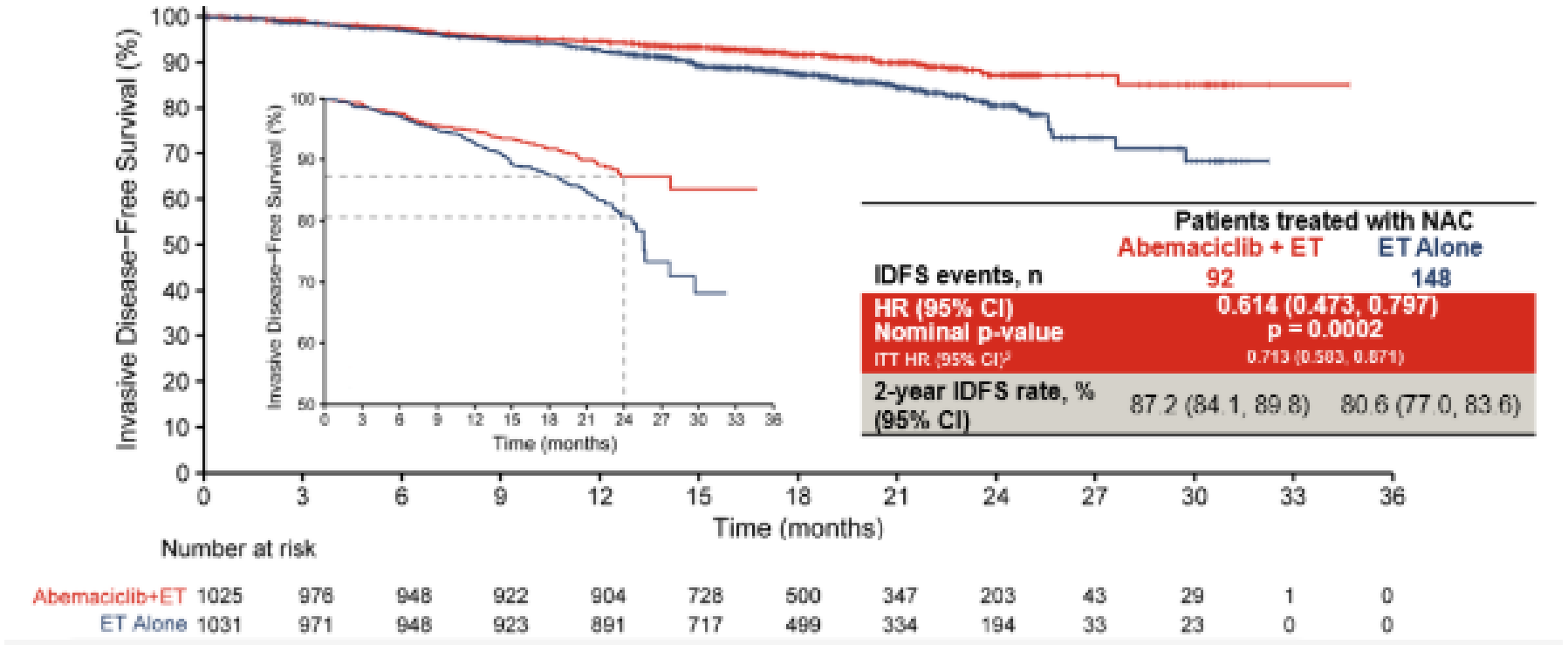


	Abemaciclib + ET No.	Abemaciclib + ET Events	ET No.	ET Events	HR (95% CI)	Interaction p-value
Overall	2808	407	2829	585	0.680 (0.599, 0.772)	
Pooled Age Group 1						0.229
<65 years	2371	325	2416	485	0.658 (0.571, 0.757)	
≥65 years	437	82	413	100	0.797 (0.595, 1.067)	
IWRS Menopausal Status						0.095
Premenopausal	1221	150	1232	237	0.597 (0.487, 0.733)	
Postmenopausal	1587	257	1597	348	0.746 (0.635, 0.876)	
IWRS Prior Treatment						0.596
Neoadjuvant chemotherapy	1039	202	1048	297	0.649 (0.543, 0.776)	
Adjuvant chemotherapy	1642	183	1647	260	0.694 (0.574, 0.838)	
Baseline ECOG PS						0.097
0	2405	337	2369	489	0.654 (0.569, 0.751)	
1	401	70	455	95	0.869 (0.638, 1.184)	
Primary Tumor Size						0.053
<20 mm	781	82	767	150	0.517 (0.395, 0.677)	
≥20 mm but <50 mm	1371	214	1419	284	0.771 (0.646, 0.920)	
≥50 mm	607	102	610	144	0.676 (0.525, 0.871)	
Number of positive lymph nodes						0.438
1-3	1118	136	1142	182	0.750 (0.601, 0.937)	
4-9	1107	142	1126	231	0.614 (0.498, 0.757)	
10 or more	575	127	554	172	0.661 (0.526, 0.832)	
Tumor Grade						0.769
G1 - Favorable	209	24	216	35	0.698 (0.415, 1.174)	
G2 - Mod Favorable	1377	181	1395	268	0.665 (0.551, 0.803)	
G3 - Unfavorable	1086	185	1064	240	0.737 (0.608, 0.893)	
Tumor Stage						0.382
Stage II	716	79	740	106	0.764 (0.571, 1.022)	
Stage III	2078	326	2077	476	0.661 (0.574, 0.761)	
First ET						0.054
Tamoxifen	857	111	898	196	0.561 (0.445, 0.708)	
Aromatase Inhibitor	1931	293	1887	386	0.738 (0.634, 0.859)	

Harbeck N, et al. ESMO 2023. Abstract LBA17.

IDFS in Patients Who Received NAC in monarchE

Prespecified subgroup analysis of patients receiving NAC prior to enrollment in monarchE



- 38.6% reduction in risk of developing IDFS event in abemaciclib + ET arm for patients who received NAC
- 2-year IDFS rate in the abemaciclib + ET arm was 87.2% v. 80.6% in the ET only arm
- 6.6% difference in IDFS

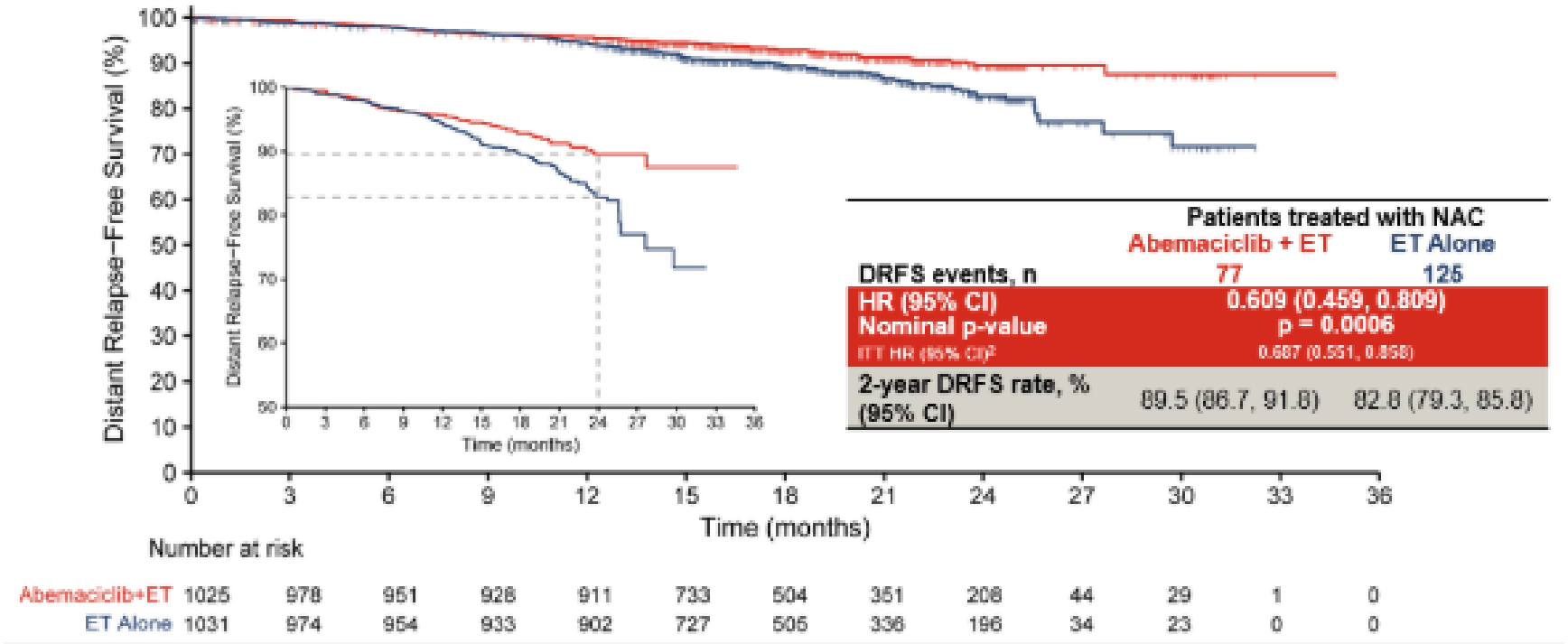
Figure 2 description: In the subgroup of patients treated with neoadjuvant chemotherapy prior to monarchE, 92 invasive disease-free survival events occurred out of 1025 patients in the abemaciclib treatment group, and 148 events occurred out of 1031 patients in the endocrine therapy only group. This resulted in a clinically meaningful improvement in invasive disease-free survival with a hazard ratio of 0.614 and 95% confidence interval of 0.473 to 0.797 with nominal p=.0002. The 2-year invasive disease-free survival rates were 87.2% in the abemaciclib plus endocrine therapy arm and 80.6% in the endocrine therapy only arm corresponding to a 6.6% absolute improvement. Note: in the intent-to-treat population, the hazard ratio for invasive disease-free survival was 0.713 with a 95% confidence interval of 0.583 to 0.871.

[2] Harbeck N, Rastogi P, Martin M, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol*. 2021;32(12):1571-1581. DOI: 10.1016/j.annonc.2021.09.015.

Abbreviations: ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; ITT = intent to treat; NAC = neoadjuvant therapy.

DRFS in Patients Who Received NAC in monarchE

Prespecified subgroup analysis of patients receiving NAC prior to enrollment in monarchE



- 39.1% reduction in risk of developing distant metastases in the abemaciclib + ET arm for patients who received NAC
- 2-year DRFS rate in the abemaciclib + ET arm was 89.5% v. 82.8% in the ET only arm
- 6.7% difference in IDFS

Figure description: In the subgroup of patients treated with neoadjuvant chemotherapy prior to monarchE, 77 distant relapse-free survival events occurred out of 1025 patients in the abemaciclib treatment group, and 125 events occurred out of 1031 patients in the endocrine therapy only group. This resulted in a clinically meaningful benefit in distant relapse-free survival with a hazard ratio of 0.609 and 95% confidence interval of 0.459 to 0.809 with nominal p=.0006. The 2-year distant relapse-free survival rates were 89.5% in the abemaciclib plus endocrine therapy arm and 82.8% in the endocrine therapy only arm corresponding to a 6.7% absolute improvement. Note: in the intent-to-treat population, the hazard ratio for distant relapse-free survival was 0.687 with a 95% confidence interval of 0.551 to 0.858.

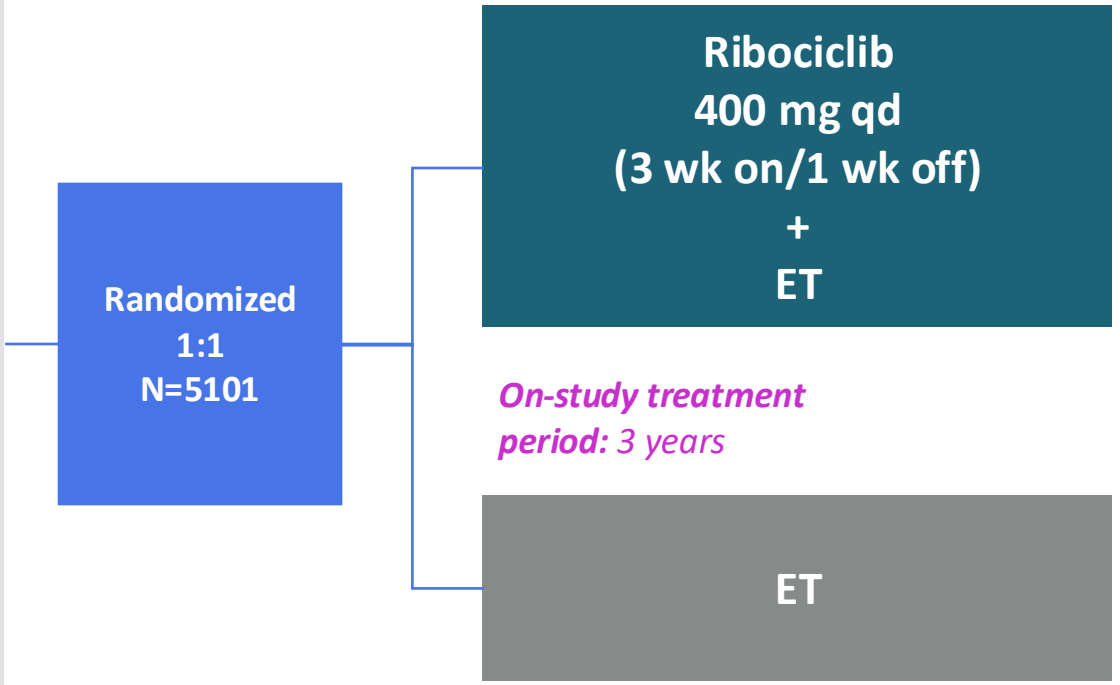
[2] Harbeck N, Rastogi P, Martin M, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol*. 2021;32(12):1571-1581. DOI: 10.1016/j.annonc.2021.09.015.

Abbreviations: DRFS = distant relapse-free survival; ET = endocrine therapy; HR = hazard ratio; ITT = intent to treat; NAC = neoadjuvant chemotherapy.

NATALEE: Study Design[1,2]

Eligibility

- Adult patients with HR+/HER2– EBC
- Prior ET allowed up to 12 months
- Anatomical stage IIA[a]
  - N0 with:
    - Grade 2, evidence of high risk:
      - Ki67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26
      - High risk via genomic risk profiling
    - Grade 3
  - N1
- Anatomical stage IIB[a]
  - N0 or N1
- Anatomical stage III
  - N0, N1, N2, or N3



Stratified for:

- Anatomical stage: II vs III
- Menopausal status: men and premenopausal women vs postmenopausal women
- Prior (neo)adjuvant chemotherapy: yes vs no
- Geographic location: North America/Western Europe/Oceania versus rest of world

Primary endpoint: IDFS

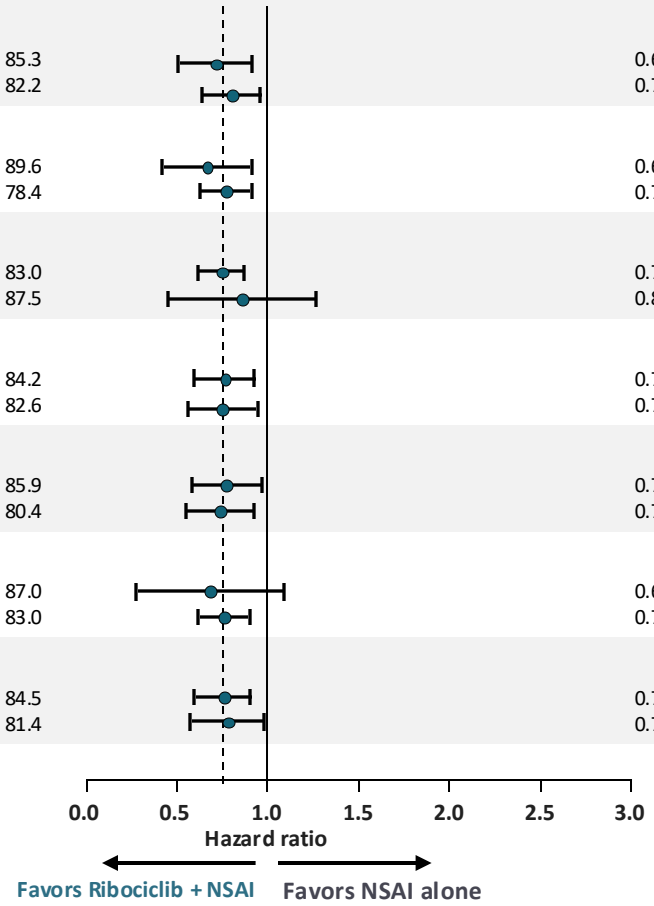
Secondary endpoints: RFS, DDFS, OS, QoL, PK

[a] Enrollment of patients with stage II disease capped at 40%.

1. ClinicalTrals.gov. Accessed October 28, 2021. https://clinicaltrials.gov/ct2/show/NCT03701334
2. Slamon D, et al. *N Engl J Med.* 2024;390(12):1080-1091.

NATALEE: IDFS Across Key Prespecified Subgroups

Subgroup	Ribociclib + NSAI		NSAI alone		Hazard ratio	95% CI
	Events/n	4Y IDFS rate, %	Events/n	4Y IDFS rate, %		
Menopausal Status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC Stage						
Stage II	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior Chemotherapy						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 Status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal Status[b,c]						
N0	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994



The IDFS benefit with ribociclib + NSAI across subgroups was consistent with that observed in the ITT population

[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Fasching PA, et al. ESMO 2024. Abstract LBA13.

CDK 4/6 Inhibitors in Adjuvant Setting

- In monarchE, the patients who received NAC were associated with increased risk of recurrence compared to the ITT population*
  - The 2-year IDFS rate in the control arm indicated a higher risk of recurrence compared to the ITT population
  - The 2-year IDFS rate in the control arm also suggested a risk of recurrence comparable to other trials investigating use of CDK 4 6 inhibitors for adjuvant treatment of patients with HR+, HER2- EBC that receive NAC
- CDK 4/6 inhibitors continue to show significant reduction in risk of disease recurrence for patients with high-risk HR+ EBC
- OS data from both monarchE and NATALEE remain immature
- CK4/6 inhibitor use in the adjuvant setting is firmly established as a standard of care for high risk patients regardless of pathologic response

*Martin M, Hegg R, Kim SB, et al. Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). *Journal of Clinical Oncology*. 2021;39(15 suppl):517. American Society of Clinical Oncology abstract 517. https://doi.org/10.1200/JCO.2021.39.15_suppl.517