Adjuvant Therapy in Breast Cancer: State of the Art

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Objectives

- Hormone receptor positive
- Triple negative
- HER2 positive

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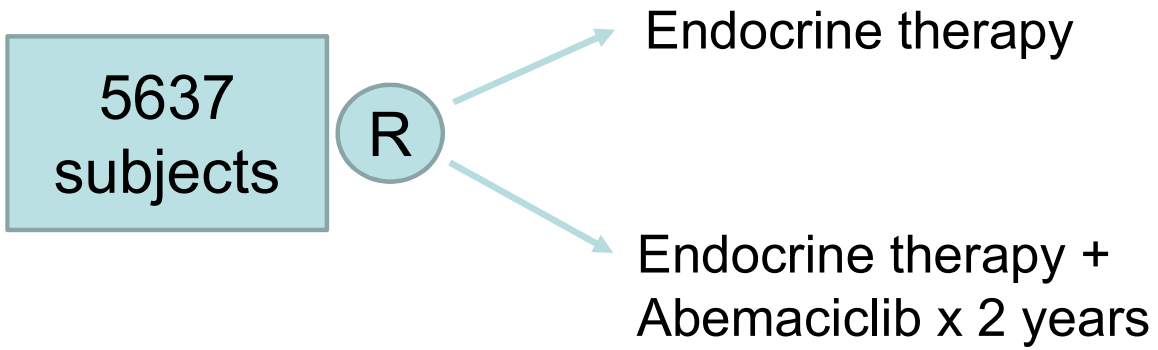
Cyclin 4/6 kinase inhibitors in MBC

Study	PALOMA 2 (palbociclib)	MONALEESA 2 (ribociclib)	MONALEESA 7 (ribociclib)	MONARCH 3 (abemaciclib)
Population	postmenopausal	postmenopausal	Pre/perimenopausal	postmenopausal
N	666	668	672	493
Prior chemotherapy for ABC?	No	No	$\leq$ 1	No
Median PFS (mos)	24.8 v 14.5	25.3 vs 16	23.8 vs 13	28.2 v 14.7
OS	Not reported	Not reported	Not reached v 40.9 mos	Not reported
References	Finn, et al, NEJM 2016	Hortabagyi, et al, NEJM 2016; Ann Onc 2018	Tripathy, et al, Lancet Onc 2018	Sledge, et al JCO 2017; Johnson et al, npjBreast Can 2019

monarchE

- HR+, HER2-
- > 4 positive LN or
- 1-3 positive LN and
  - T ≥5 cm
  - Grade 3
  - Central Ki-67 ≥20%



Johnson, et al, JCO 2020

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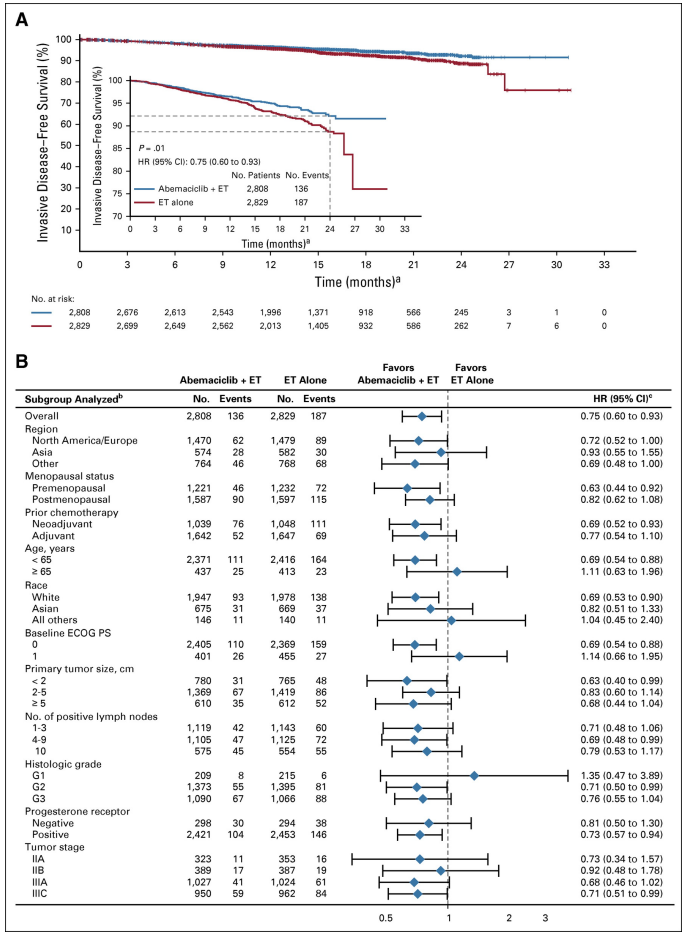

FIG 2. Invasive disease-free survival (IDFS). (A) Kaplan-Meier curves of IDFS and IDFS zoomed in to better visualize separation of the curves in the intent-to-treat population. (B) IDFS of patient subgroups. Hazard ratios (HRs) are stratified in overall population and unstratified in subgroups for abemaciclib plus endocrine therapy (ET) versus ET alone. HR estimates for IDFS are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. (a) Curves should not be interpreted beyond 24 months because of the limited follow-up. (b) If a subgroup consists of < 5% of randomly assigned patients, analysis within that subgroup was omitted. (c) The width of CIs in subgroups has not been adjusted for multiplicity; thus, the subgroup results are exploratory in nature. ECOG PS, Eastern Cooperative Oncology Group performance status.

Published in: Stephen R. D. Johnston; Nadia Harbeck; Roberto Hegg; Masakazu Toi; Miguel Martin; Zhi Min Shao; Qing Yuan Zhang; Jorge Luis Martinez Rodriguez; Mario Campone; Erika Hamilton; Joohyuk Sohn; Valentina Guarneri; Morihito Okada; Frances Boyle; Patrick Neven; Javier Cortés; Jens Huober; Andrew Wardley; Sara M. Tolaney; Irfan Cicin; Ian C. Smith; Martin Frenzel; Desirée Headley; Ran Wei; Belen San Antonio; Maarten Hulstijn; Joanne Cox; Joyce O'Shaughnessy; Priya Rastogi; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.20.02514

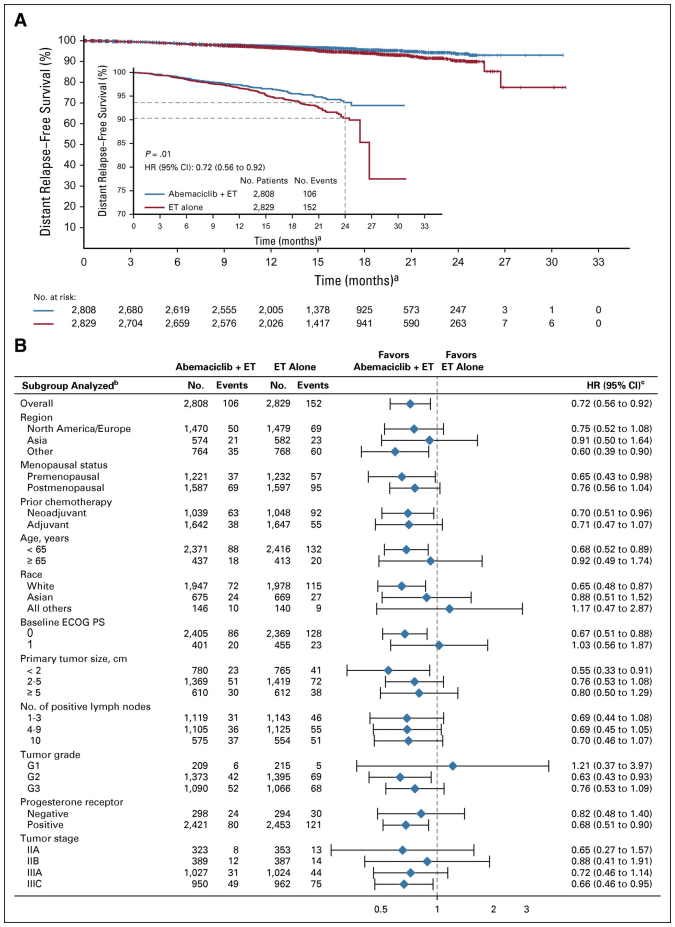

FIG 3. Distant relapse–free survival (DRFS). (A) Kaplan-Meier curves of DRFS and DRFS zoomed in to better visualize separation of the curves in the intent-to-treat population. (B) DRFS of patient subgroups. Hazard ratios (HRs) are stratified in overall population and unstratified in subgroups for abemaciclib plus endocrine therapy (ET) versus ET alone. HR estimates for DRFS are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. (a) Curves should not be interpreted beyond 24 months because of the limited follow-up. (b) If a subgroup consists of < 5% of randomly assigned patients, analysis within that subgroup was omitted. (c) The width of CIs in subgroups has not been adjusted for multiplicity; thus, the subgroup results are exploratory in nature. ECOG PS, Eastern Cooperative Oncology Group performance status.

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TABLE 2. Recurrence Events

Recurrence Event	Abemaciclib + ET (n = 2,808)	ET Alone (n = 2,829)
IDFS events		
Total IDFS events	136	187
Patients with invasive disease, first occurrence	123	181
Local/regional recurrence	17	26
Distant recurrence	87	138
Contralateral recurrence	4	9
Second primary neoplasm	16	12
Death from any cause without invasive disease	13	6

TABLE 2. Recurrence Events

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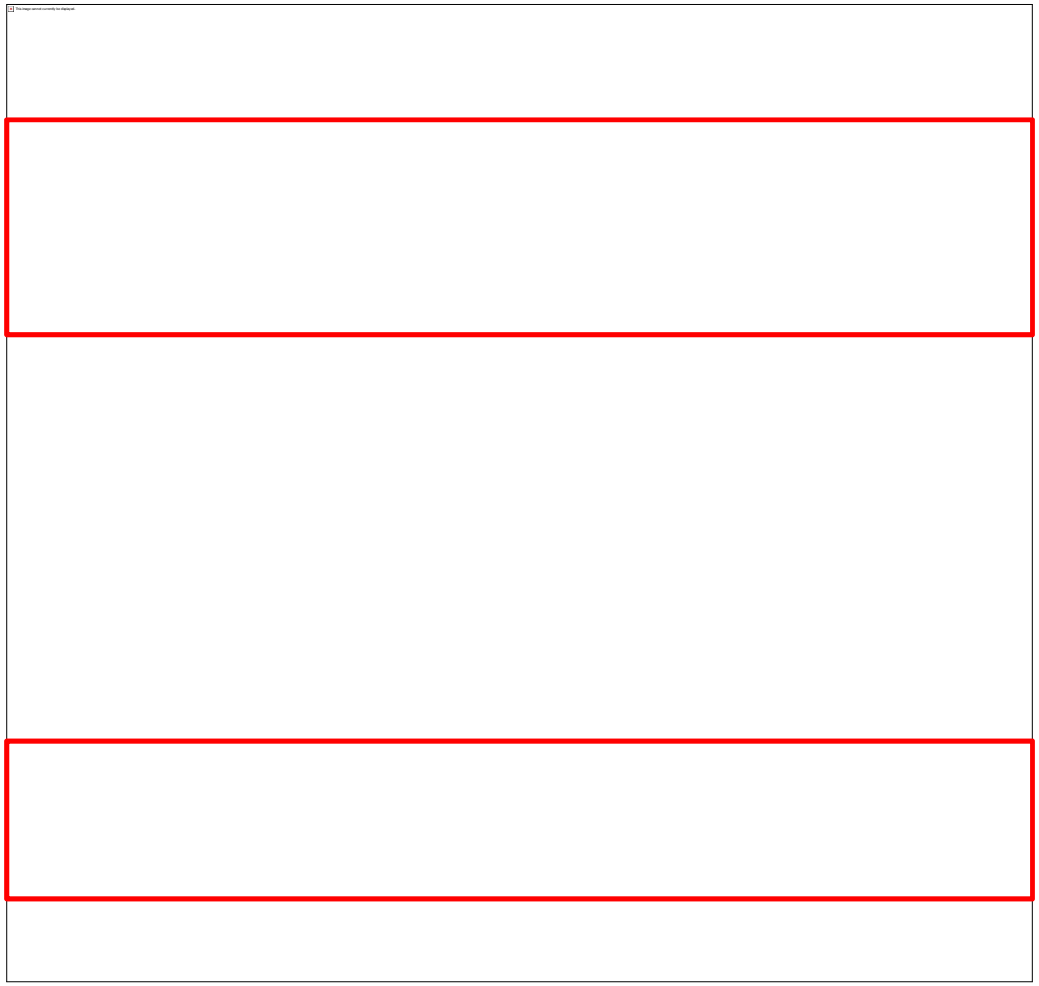
TABLE 3. Safety Table



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How does this change clinical practice?

- Very early follow up (med 15.5 months)
- Abemaciclib is not FDA approved in the adjuvant setting

- PALLAS trial found no difference in iDFS
- Neoadjuvant PALLET trial found no difference in response rate after 14 weeks of therapy

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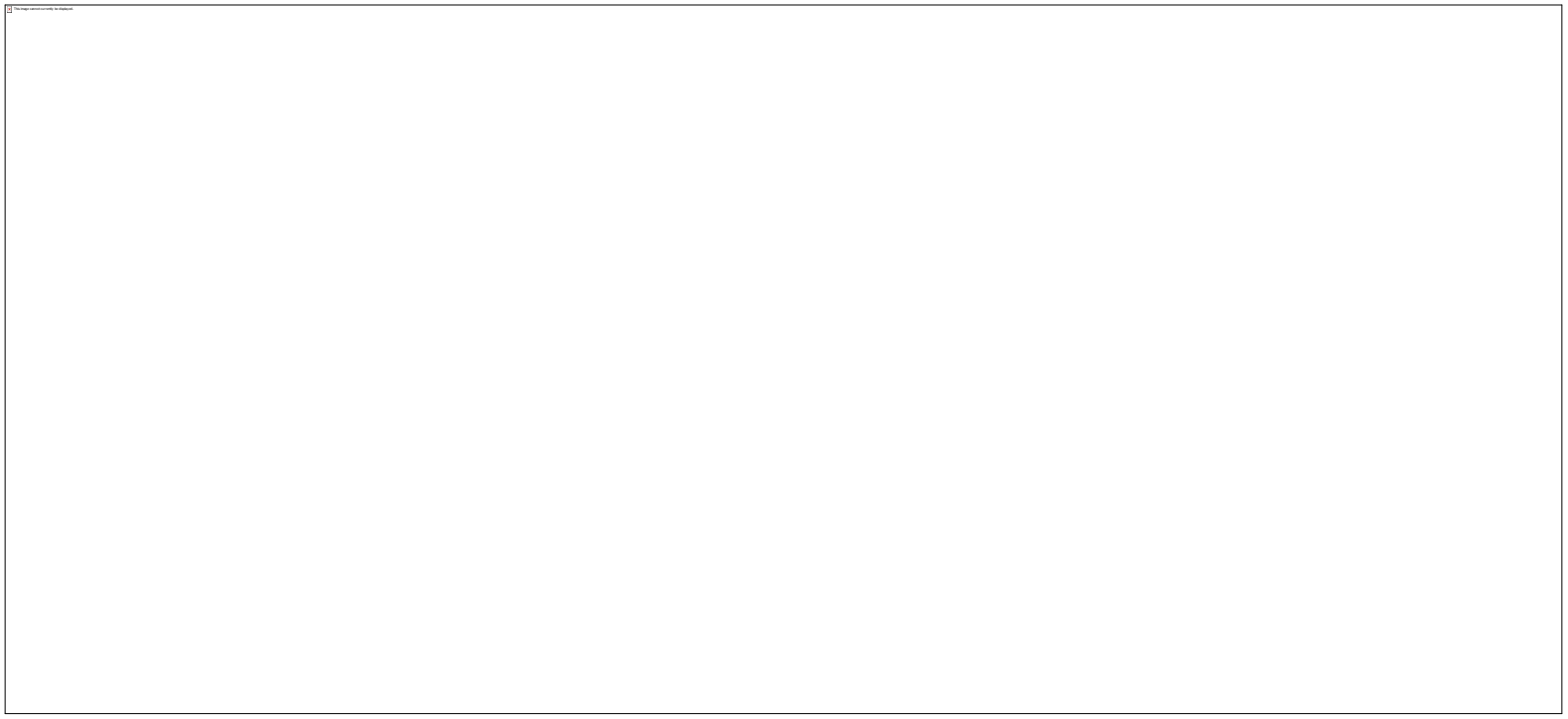
KEYNOTE-522



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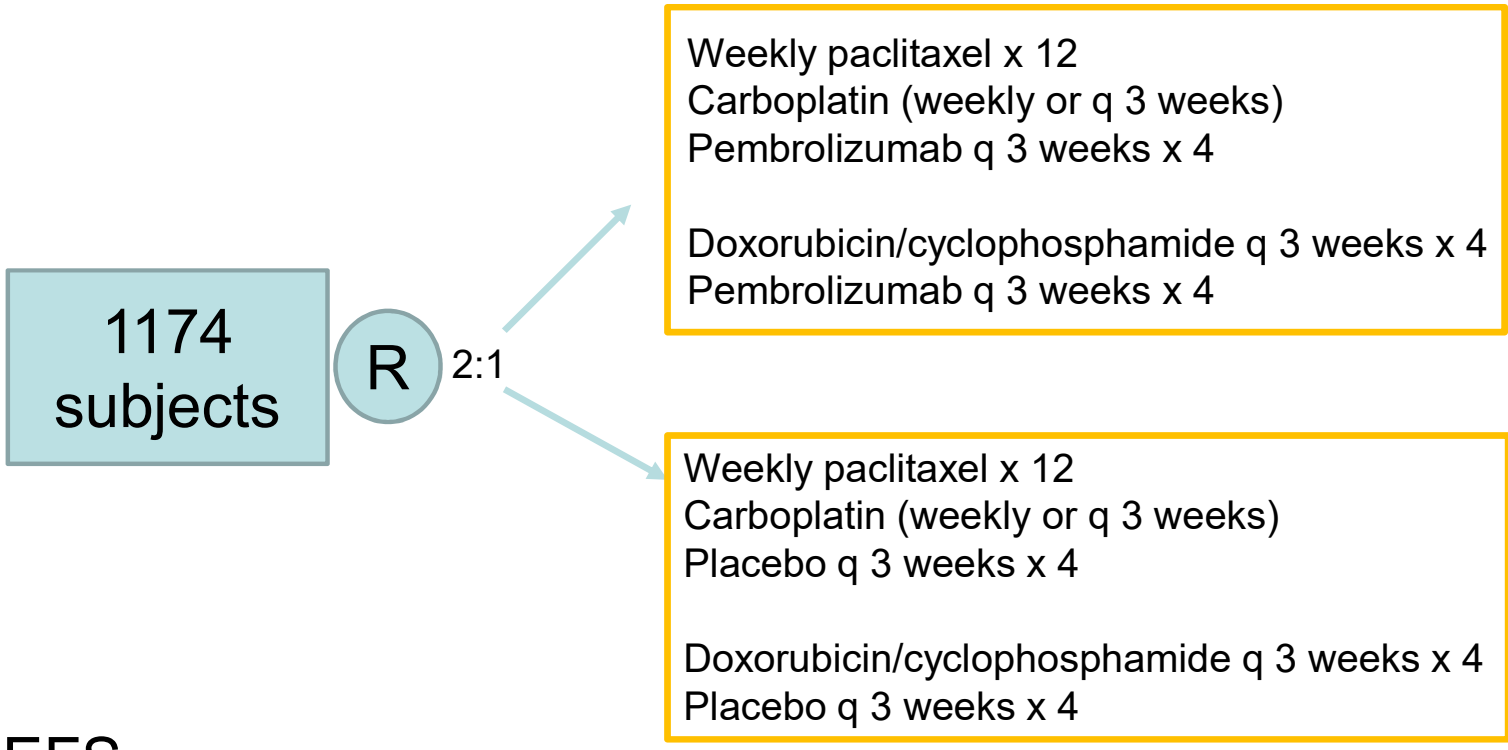
KEYNOTE-522

- HR-, HER2-
- T1c and N1-2 or
- T2-4 and N0-2



1º endpoints: pCR, EFS

Schmid, et al, NEJM, 2020

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Characteristics of the Patients at Baseline.

Schmid P et al. N Engl J Med 2020;382:810-821

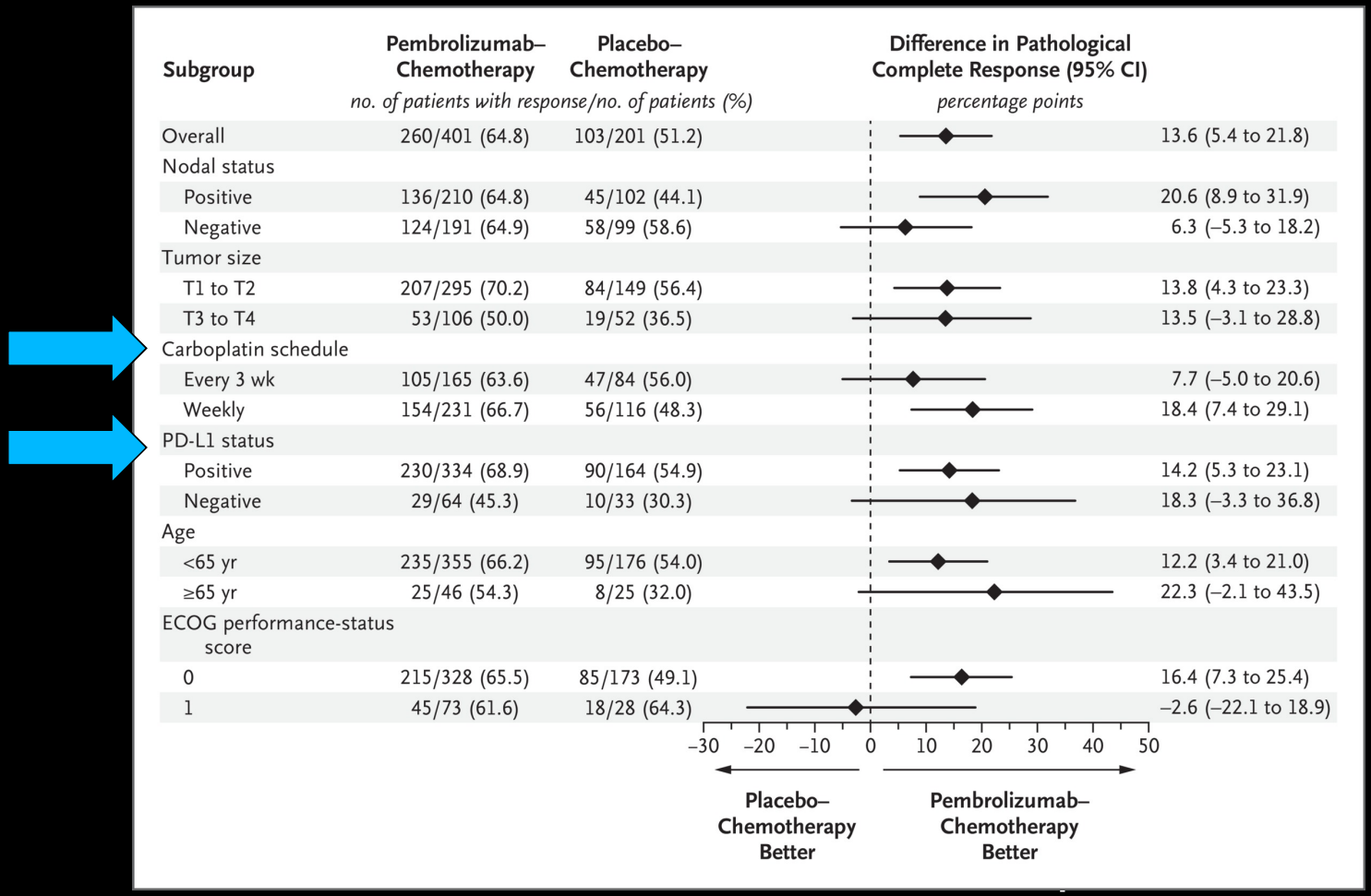
Pathological Complete Response, According to Pathological Stage.

Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

Schmid P et al. N Engl J Med 2020;382:810-821

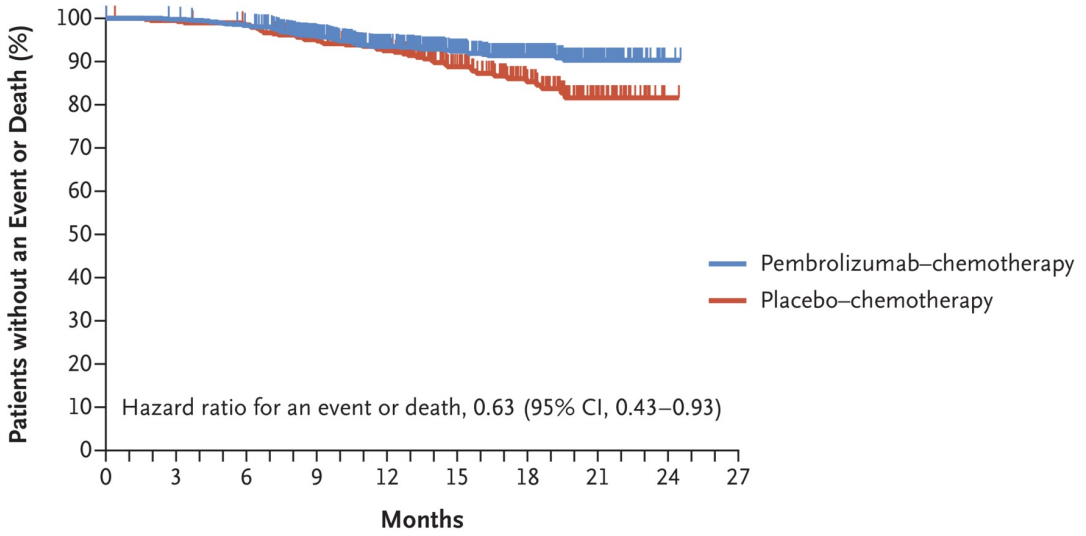
Subgroup Analysis of Difference in Percentages of Patients with a Pathological Complete Response (Stage ypT0/Tis ypN0).



Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in Pathological Complete Response (95% CI)
	no. of patients with response/no. of patients (%)		*percentage points*
Overall	260/401 (64.8)	103/201 (51.2)	13.6 (5.4 to 21.8)
Nodal status			
Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9 to 31.9)
Negative	124/191 (64.9)	58/99 (58.6)	6.3 (–5.3 to 18.2)
Tumor size			
T1 to T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3 to 23.3)
T3 to T4	53/106 (50.0)	19/52 (36.5)	13.5 (–3.1 to 28.8)
Carboplatin schedule			
Every 3 wk	105/165 (63.6)	47/84 (56.0)	7.7 (–5.0 to 20.6)
Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4 to 29.1)
PD-L1 status			
Positive	230/334 (68.9)	90/164 (54.9)	14.2 (5.3 to 23.1)
Negative	29/64 (45.3)	10/33 (30.3)	18.3 (–3.3 to 36.8)
Age			
<65 yr	235/355 (66.2)	95/176 (54.0)	12.2 (3.4 to 21.0)
≥65 yr	25/46 (54.3)	8/25 (32.0)	22.3 (–2.1 to 43.5)
ECOG performance-status score			
0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3 to 25.4)
1	45/73 (61.6)	18/28 (64.3)	–2.6 (–22.1 to 18.9)

Schmid P et al. N Engl J Med 2020;382:810-821

Kaplan–Meier Estimates of Event-free Survival, According to Trial Group in the Intention-to-Treat Population.



No. at Risk										
Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

Schmid P et al. N Engl J Med 2020;382:810-821

Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.

Table 3. Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

Schmid P et al. N Engl J Med 2020;382:810-821

How does this change clinical practice?

- While pCR improved, too early for EFS
- Muddies the picture regarding carboplatin and DFS

- Pembrolizumab is under review, but not yet FDA-approved in this setting

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KATHERINE

The NEW ENGLAND JOURNAL of MEDICINE

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Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

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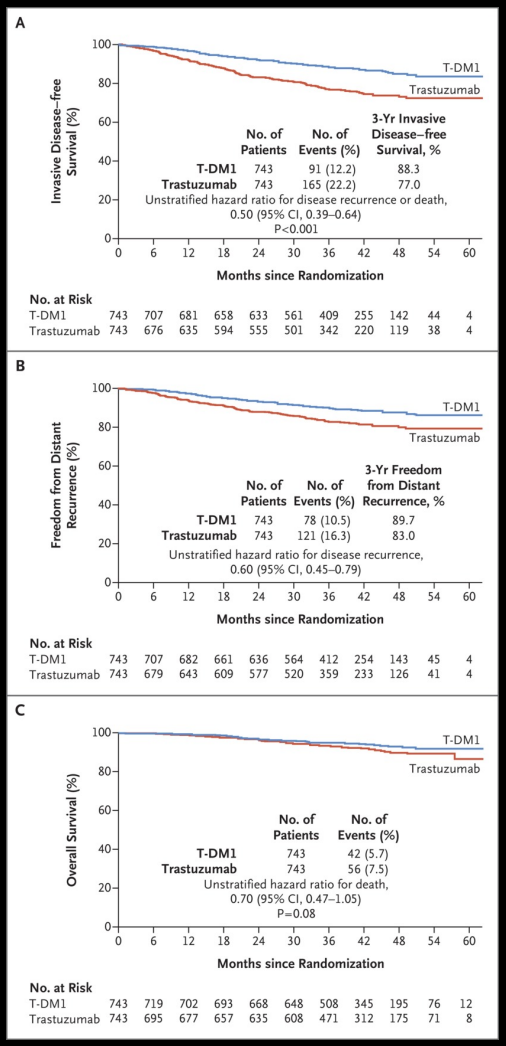
Demographic and Clinical Characteristics of the Patients at Baseline.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

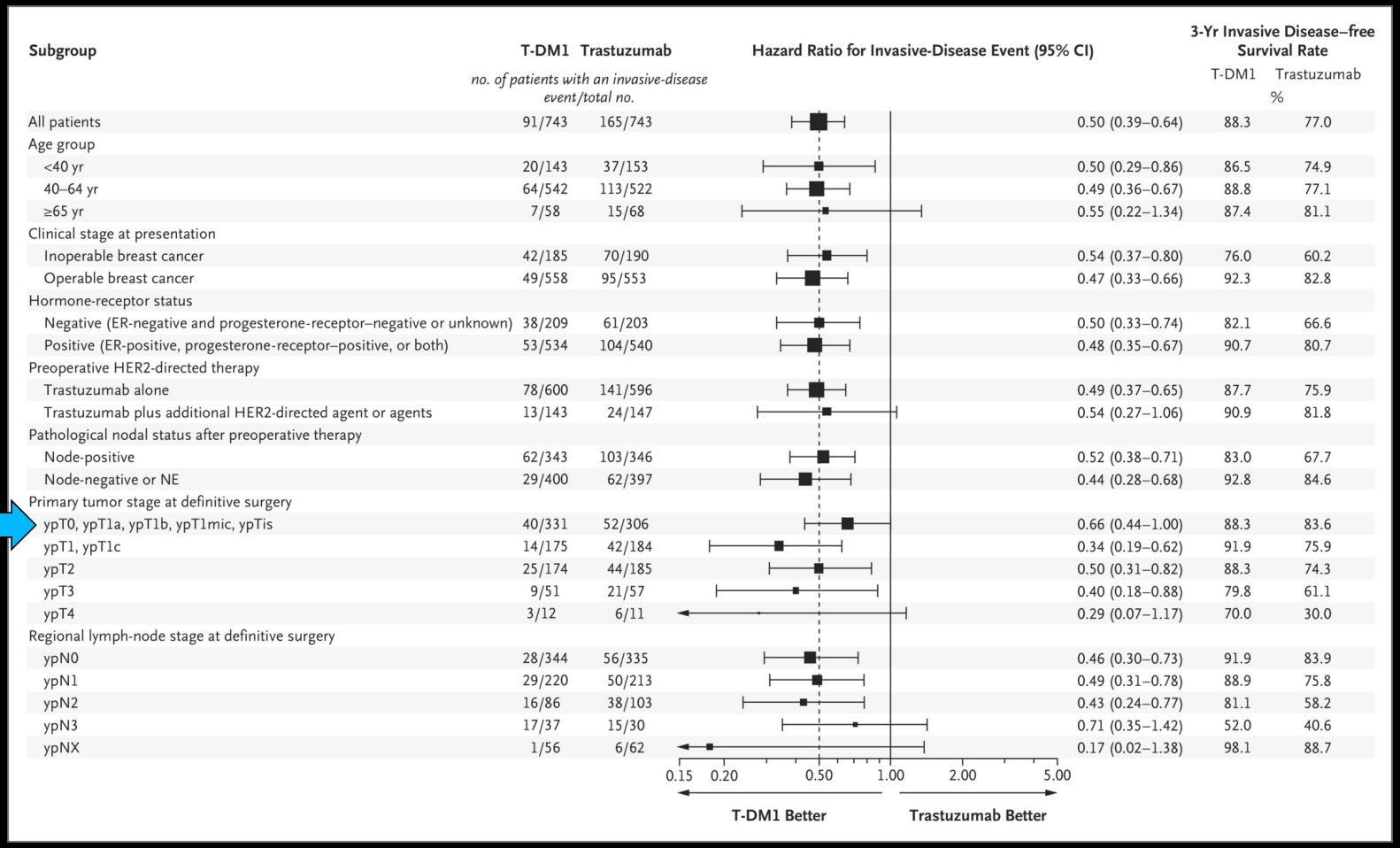
von Minckwitz G et al. N Engl J Med 2019;380:617-628

Kaplan–Meier Estimates of Survival in the Interim Analysis.



von Minckwitz G et al. N Engl J Med 2019;380:617-628

Subgroup Analysis of Invasive Disease–free Survival.



von Minckwitz G et al. N Engl J Med 2019;380:617-628

Summary of Adverse Events in the Safety Population.

Table 2. Summary of Adverse Events in the Safety Population.*

Event	Trastuzumab Group (N=720)	T-DM1 Group (N=740)
	no. of patients (%)	
Any adverse event	672 (93.3)	731 (98.8)
Grade ≥3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death†	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug‡	15 (2.1)	133 (18.0)
Grade ≥3 adverse event that occurred in ≥1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

von Minckwitz G et al. N Engl J Med 2019;380:617-628

How does this change clinical practice?

- Post-operative trastuzumab emtansine should be offered for residual disease

- Unclear role for adjuvant neratinib

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Questions?