ASCO 2022 Updates – Spotlight on Breast Cancer

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Disclosures

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- Many of the slides are courtesy of clinicaloptions.com or were adapted from them, tailored to the objectives of this talk.

Presentation Outline and Learning Objectives

- Early-Stage Disease
  - Update on KEYNOTE-522
- Advanced Stage Disease
  - MAINTAIN trial
  - DB-04
  - TROPiCS-02
  - PALOMA-2
- Local Therapy
  - LUMINA

1. Understand the importance of the residual cancer burden on breast cancer outcomes and considerations for escalation of adjuvant therapy in triple negative disease.

2. Know the findings of practice-changing and potentially practice-changing trials in the advanced disease setting.

3. Be familiar with concepts in de-escalation of local therapy for low-risk breast cancer.

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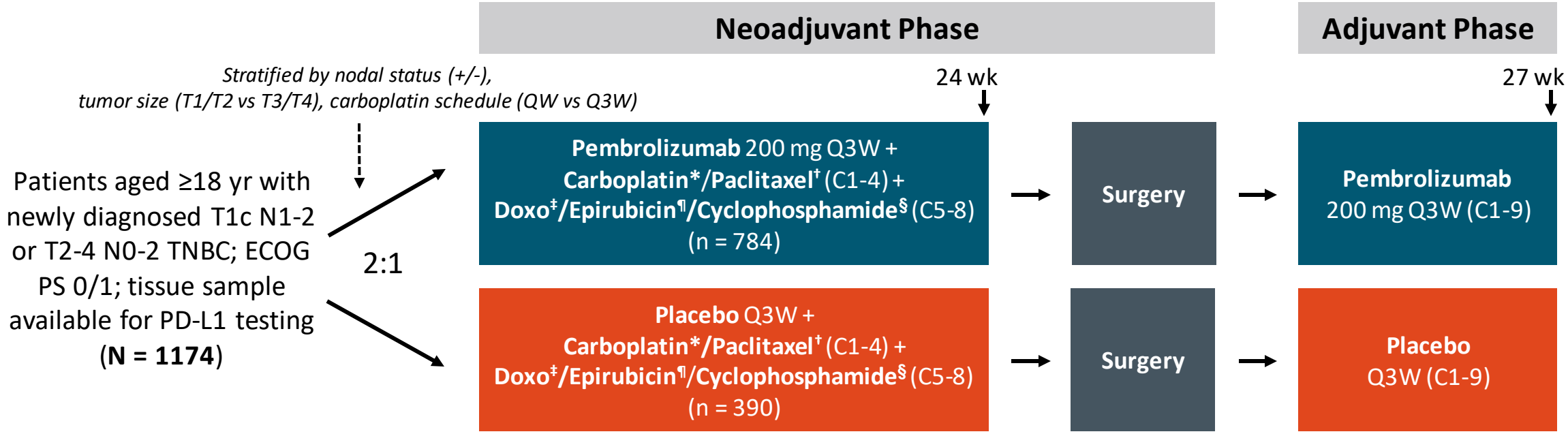
Early-Stage Disease

Updates to KEYNOTE-522

KEYNOTE-522: Study Design

- Randomized, placebo-controlled phase III trial
  - Median f/u: 39.1 mo (range: 30.0-48.0); data cutoff: March 23, 2021



- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS (PD-L1+), safety, QoL
- **Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR**

*AUC 5 Q3W or AUC 1.5 Q1W.
†80 mg/m^2 Q1W.
‡60 mg/m^2 Q3W.
¶90 mg/m^2 Q3W.
§600 mg/m^2 Q3W.

Pusztai. ASCO 2022. Abstr 503. NCT03036488.

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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)	

* Patients were considered to have not had a response if they did not receive trial medication, discontinued trial treatment and continued neoadjuvant treatment with drugs in categories not specified by the trial before definitive surgery (regardless of the surgical outcome), discontinued trial treatment for reasons that precluded definitive surgery, or had missing data with respect to pathological complete response for any reason. According to the current staging criteria of the American Joint Committee on Cancer and assessment by the local pathologist at the time of definitive surgery after completion of neoadjuvant systemic therapy, patients with pathological stage ypT0/Tis ypN0 have no residual invasive cancer in the complete resected breast specimen and all sampled regional lymph nodes, those with stage ypT0 ypN0 have no residual invasive and in situ cancer in the complete resected breast specimen and all sampled regional lymph nodes, and those with stage ypT0/Tis have no invasive cancer in the breast, irrespective of ductal carcinoma in situ or nodal involvement. CI denotes confidence interval.

† The estimated treatment difference is based on the Miettinen and Nurminen method, stratified according to nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and administration of carboplatin (once weekly or once every 3 weeks).

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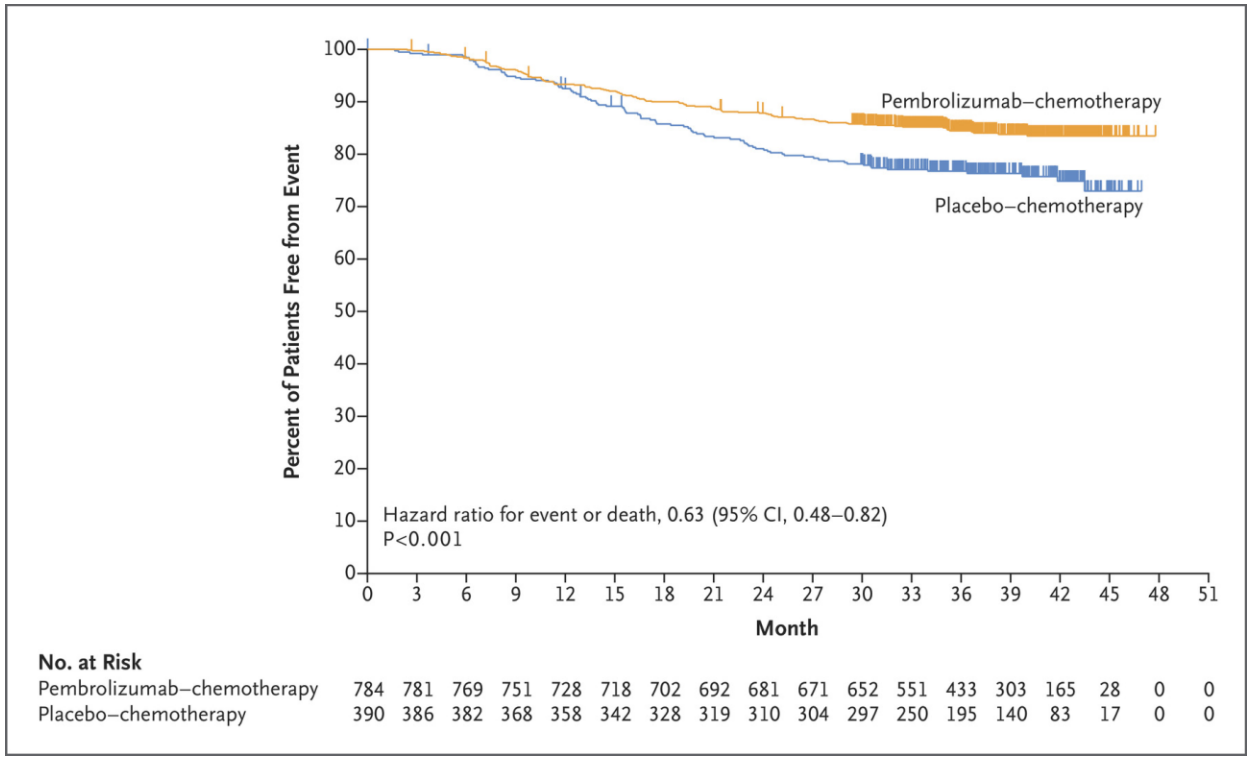
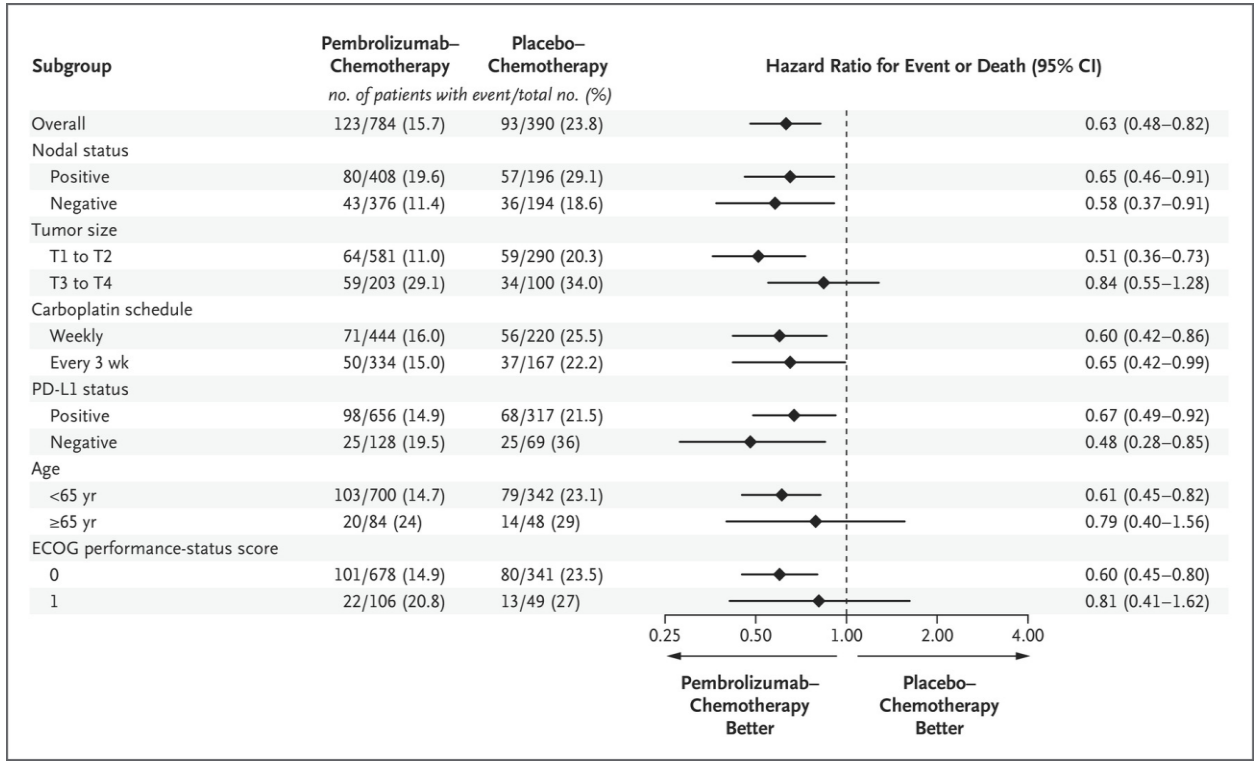
pCR rate was 68.9% (230 of 334 patients) among those who received pembrolizumab–chemotherapy and 54.9% (90 of 164 patients) among those who received placebo–chemotherapy in the **PD-L1–positive population**. It was 45.3% (29 of 64 patients) among those who received pembrolizumab–chemotherapy and 30.3% (10 of 33 patients) among those who received placebo–chemotherapy in the **PD-L1–negative population**.

Schmid P et al. NEJM 2020





The estimated event-free survival at 36 months was 84.5% (95% CI, 81.7 to 86.9) in the pembrolizumab–chemotherapy group and 76.8% (95% CI, 72.2 to 80.7) in the placebo–chemotherapy group; the median event-free survival was not reached in either group.

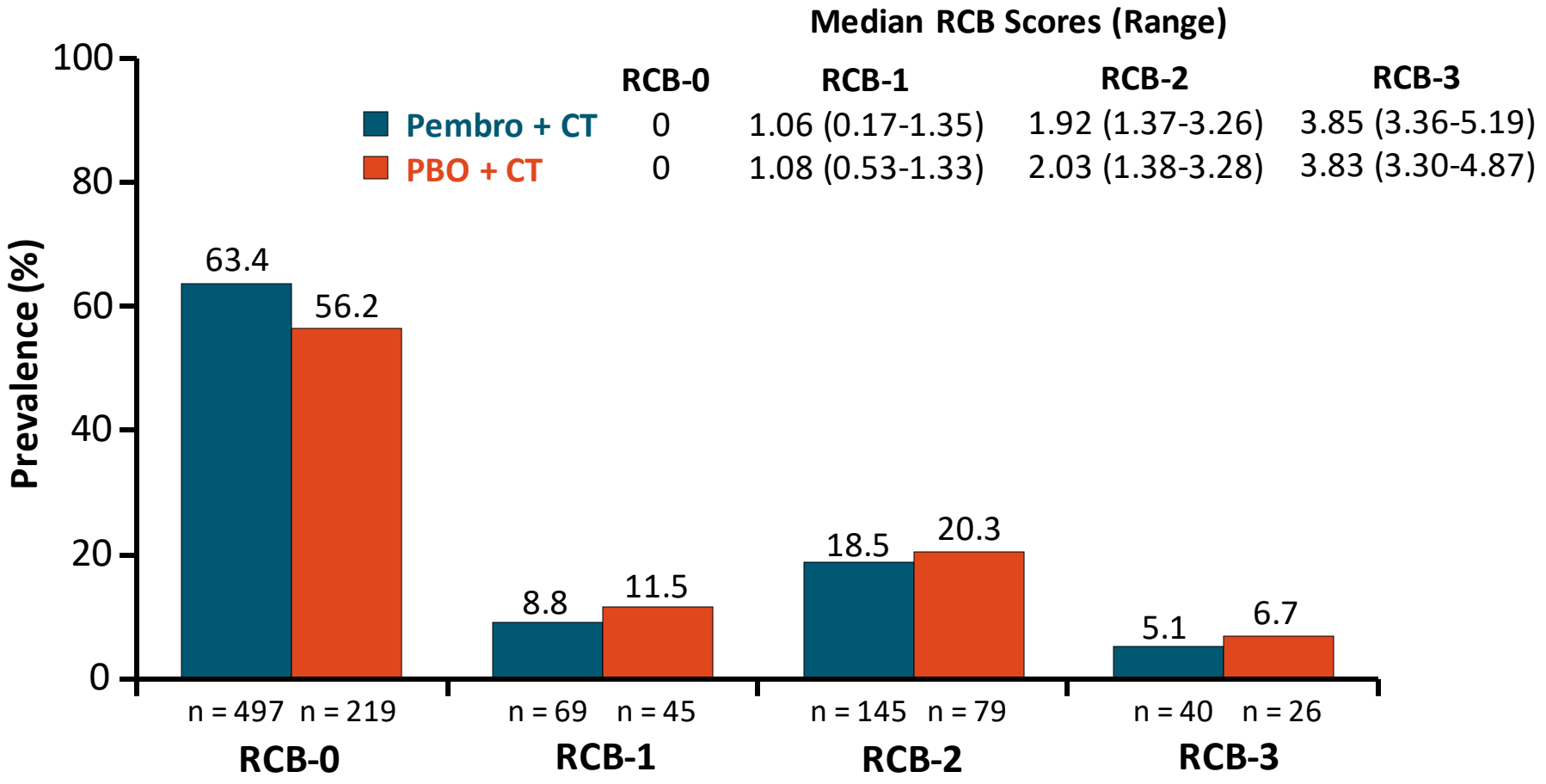
Schmid P et al. NEJM 2022

ASCO update – EFS by RCB *exploratory analysis

- RCB = residual cancer burden
- Composite measure of pathological tumor size, % cellularity, and nodal involvement
- RCB 0-3 depending on amount of residual disease with pCR=RCB 0
- We know from large retrospective series that survival outcomes decrease as RCB increases, especially in TNBC and HER2+ subtypes

Symmans WF et al JCO 2017

KEYNOTE-522 Exploratory Analysis: Prevalence of Residual Cancer Burden Categories (ITT)



n = 54 (4.6%) missing RCB categorical data; n = 33 (4.2%) in pembrolizumab arm, n = 21 (5.4%) in PBO arm.

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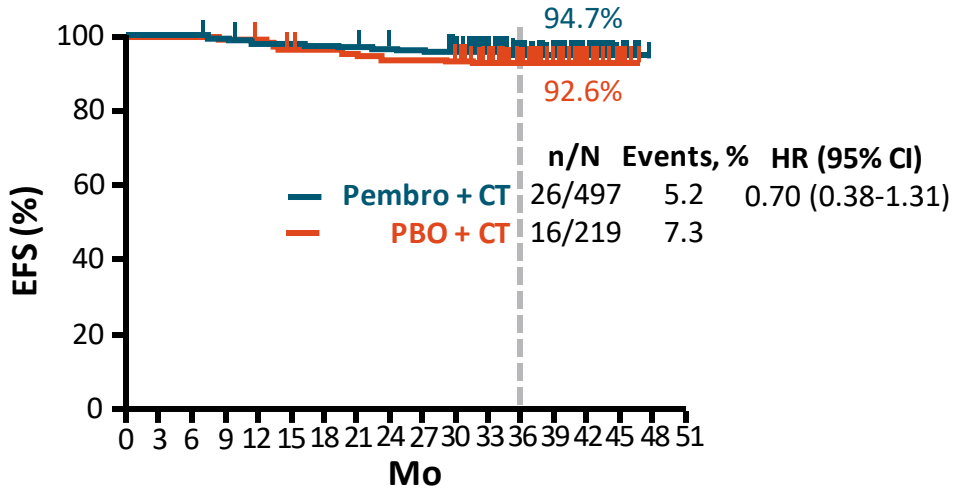
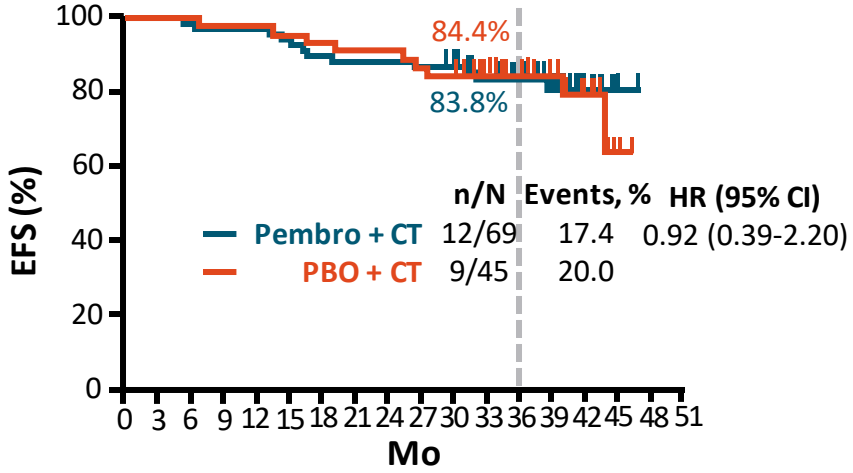
KEYNOTE-522 Exploratory Analysis: EFS by RCB Category

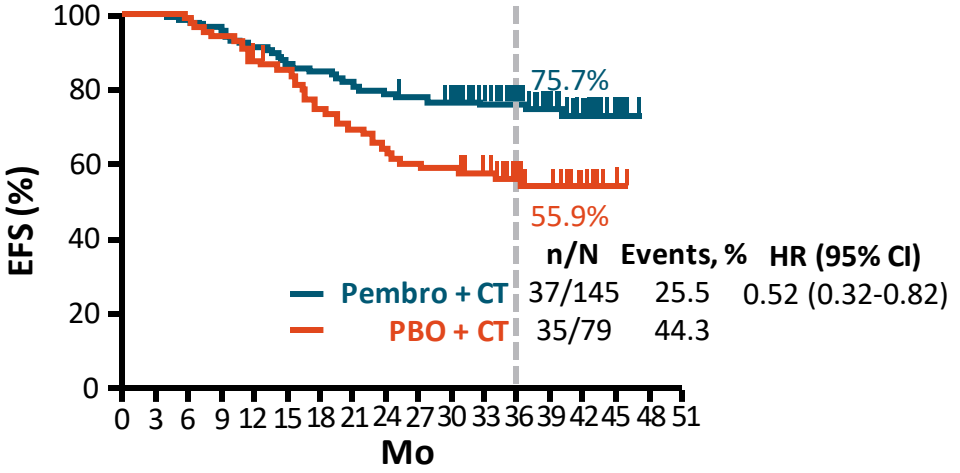
EFS in RCB-0



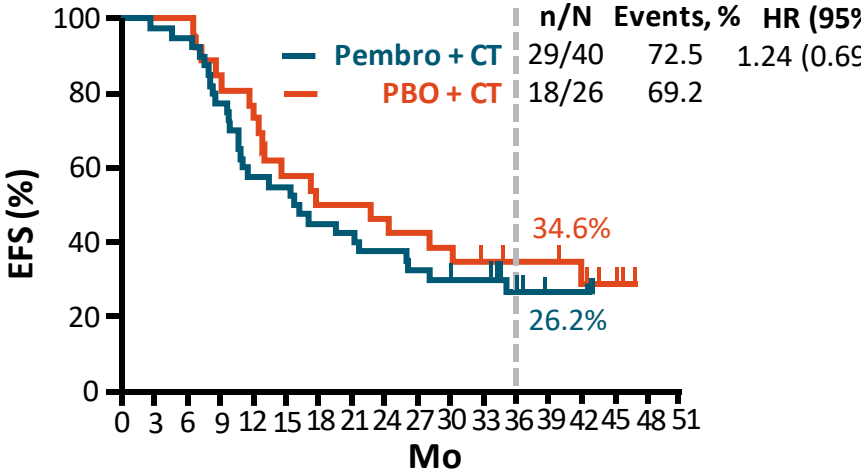
EFS in RCB-1



EFS in RCB-2



EFS in RCB-3



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KEYNOTE-522 Exploratory Analysis: Conclusions

- Prespecified exploratory analysis indicates that higher RCB score associated with worse EFS in patients with early-stage TNBC
  - Independent of treatment group
- Compared with placebo, neoadjuvant pembrolizumab added to chemotherapy was associated with higher pCR rate (RCB-0) and fewer patients in higher RCB categories
- Addition of pembrolizumab to chemotherapy reduced EFS events in most RCB categories, with largest benefit in RCB-2 category
- Investigators conclude that pembrolizumab has EFS benefit even in patients who do not achieve pCR, suggesting a contribution from adjuvant therapy

Pusztai. ASCO 2022. Abstr 503.

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KEYNOTE-522: Changes in clinical practice

- None but very interesting exploratory analysis given that there are risks with immunotherapy and perhaps patients with RCB-0 and maybe RCB-1 do not benefit from adjuvant pembrolizumab.
- Perhaps those with RCB-2 and –3 should get pembrolizumab + capecitabine or other targeted therapy.

Advanced Stage Disease

DESTINY-Breast04: Phase III Study of T-DXd vs CT for HER2-Low MBC

- Multicenter, randomized, open-label, active-controlled phase III trial

Stratified by HER2-low status (IHC1+ vs IHC2+ and ISH-), no. of prior lines of CT for metastatic disease (1 vs 2), HR status (HR+ [with vs without previous CDK4/6 inhibitor] vs HR-)

Patients with HER2-low (IHC1+ or IHC2+/ISH-) unresectable or metastatic BC; 1-2 lines of CT in the metastatic setting or recurrence ≤6 mo after adjuvant CT; ≥1 ET if HR+; treated, stable brain metastases eligible
(N = 557)

2:1

T-DXd 5.4 mg/kg Q3W
(n = 373)

CT*
(n = 184)

*Treatment of physician's choice: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

- **Primary endpoint:** PFS in HR+ patient population (by BICR)
- **Key secondary endpoints:** PFS (all patients), OS in HR+ and in all patients, PFS by investigator, ORR, DoR, efficacy in HR- patient population

Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;[Epub].

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DESTINY-Breast04: Baseline Characteristics

Characteristic	HR+ Patients		All Patients	
	T-DXd (n = 331)	CT (n = 163)	T-DXd (n = 373)	CT (n = 184)
Median age, yr (range)	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
▪ Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
▪ Asia	128 (39)	60 (37)	147 (39)	66 (36)
▪ North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
▪ 1+	193 (58)	95 (58)	215 (58)	106 (58)
▪ 2+/ISH-	138 (42)	68 (42)	158 (42)	78 (42)
ECOG PS, n (%)				
▪ 0	187 (57)	95 (58)	200 (54)	105 (57)
▪ 1	144 (44)	68 (42)	173 (46)	79 (43)
HR, n (%)				
▪ Positive	328 (99)	162 (99)	333 (89)	166 (90)
▪ Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;[Epub].

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DESTINY-Breast04: Prior Therapies

Prior Therapy	HR+ Patients		All Patients	
	T-DXd (n = 331)	CT (n = 163)	T-DXd (n = 373)	CT (n = 184)
Median lines of systemic therapy,* n (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
No. of prior lines of systemic therapy*, n (%)				
▪ 1	23 (7)	14 (9)	39 (10)	19 (10)
▪ 2	85 (26)	41 (25)	100 (27)	53 (29)
▪ ≥3	223 (67)	108 (66)	234 (63)	112 (61)
Median lines of chemotherapy,* n (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
No. of prior lines of chemotherapy*, n (%)				
▪ 0	1 (0.3)	1 (0.6)	1 (0-3)	1 (0.5)
▪ 1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
▪ 2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
▪ ≥3	3 (0.9)	0	6 (1.6)	0
Median lines of ET,* n (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
No. of prior lines of ET,* n (%)				
▪ 0	28 (8)	17 (10)	60 (16)	34 (18)
▪ 1	105 (32)	49 (30)	108 (29)	51 (28)
▪ 2	110 (33)	53 (33)	115 (31)	54 (29)
▪ ≥3	88 (37)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)	259 (78)	132 (81)	279 (75)	140 (76)
▪ CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

*In metastatic setting.

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;[Epub].

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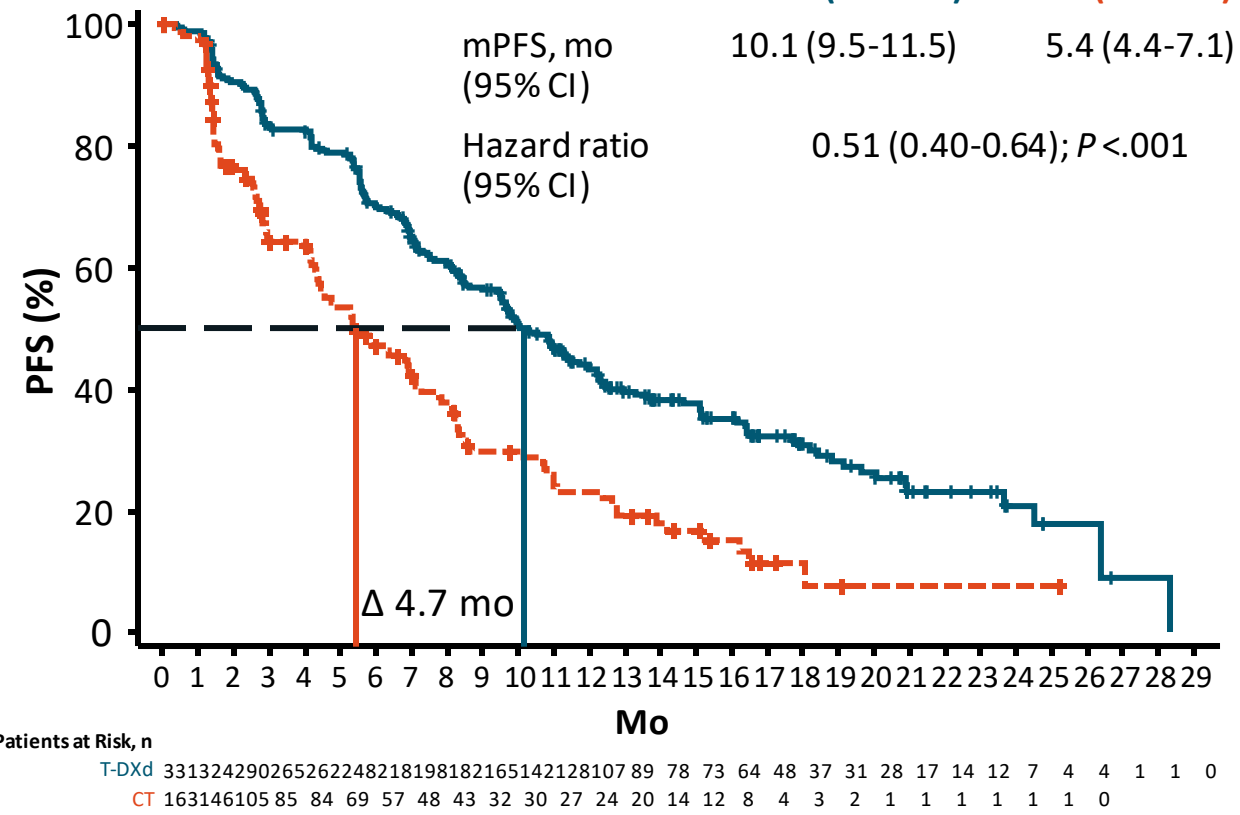
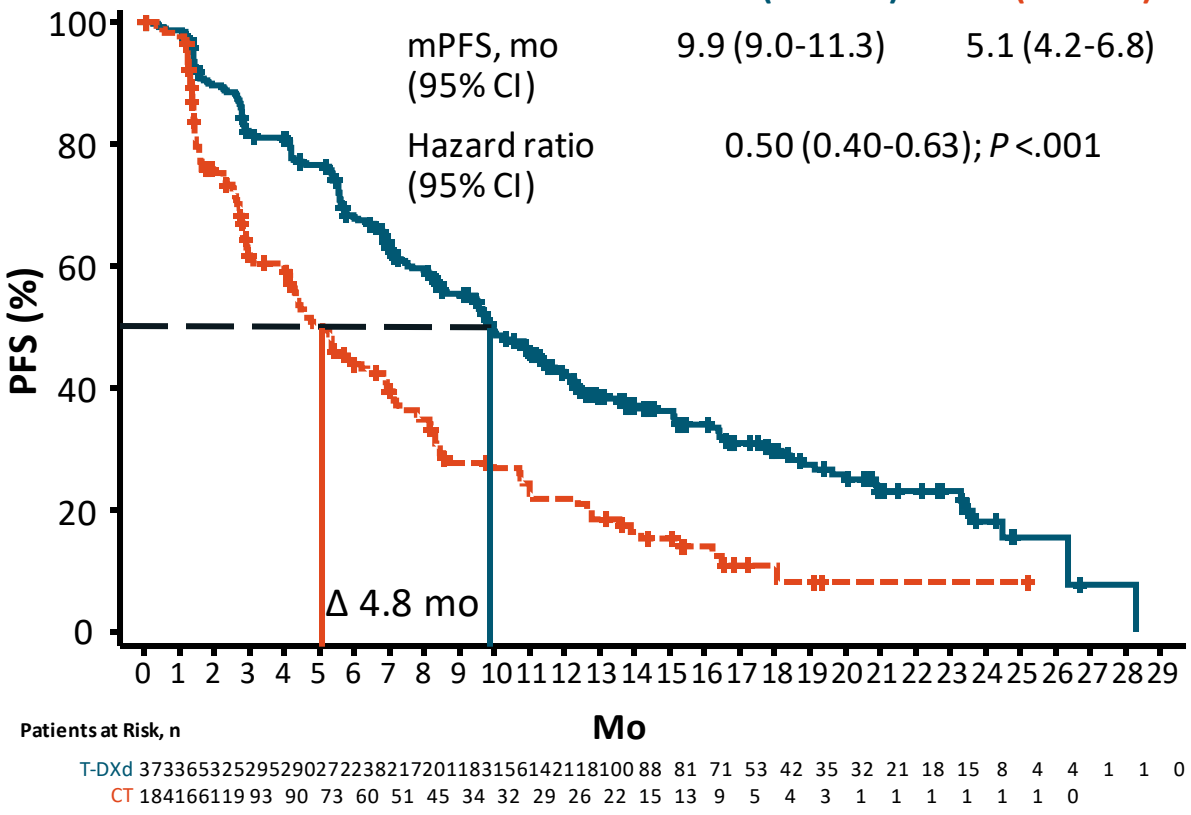
DESTINY-Breast04: PFS

Patients With HR+ Disease



All Patients



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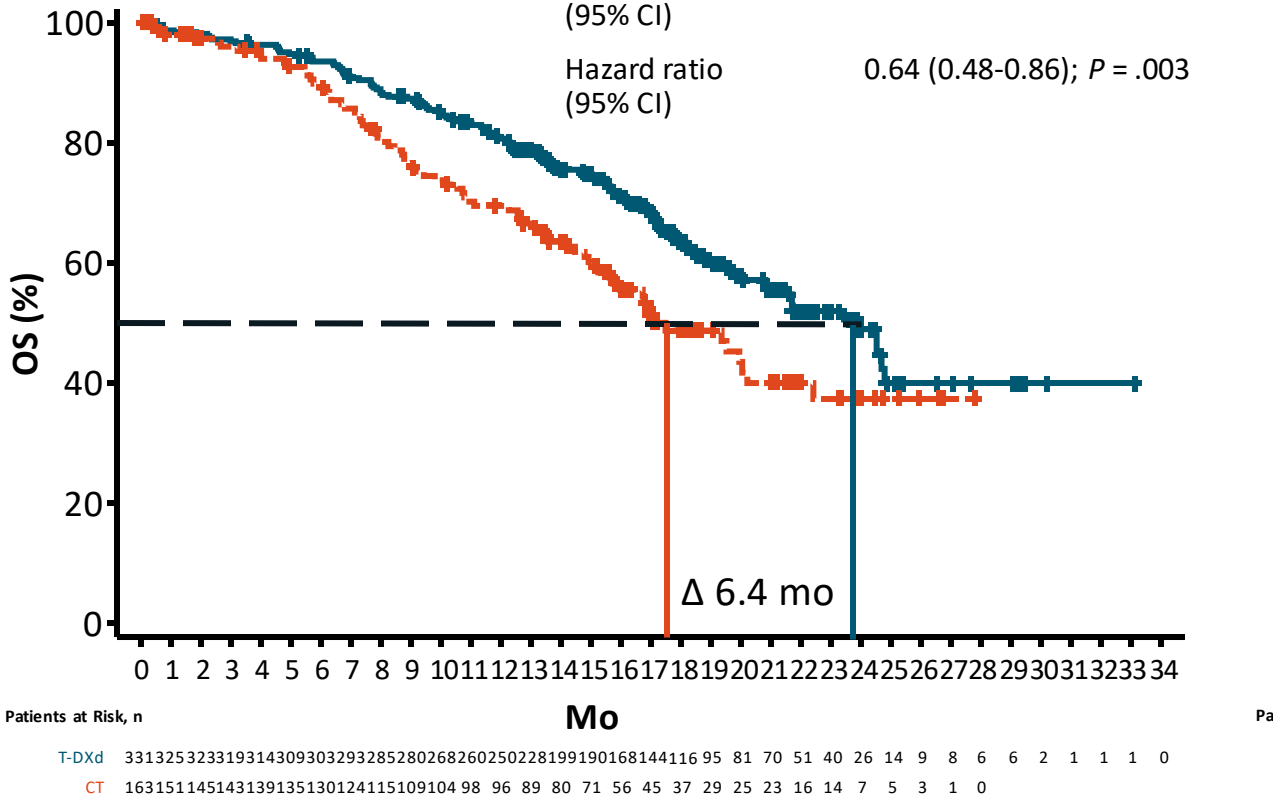
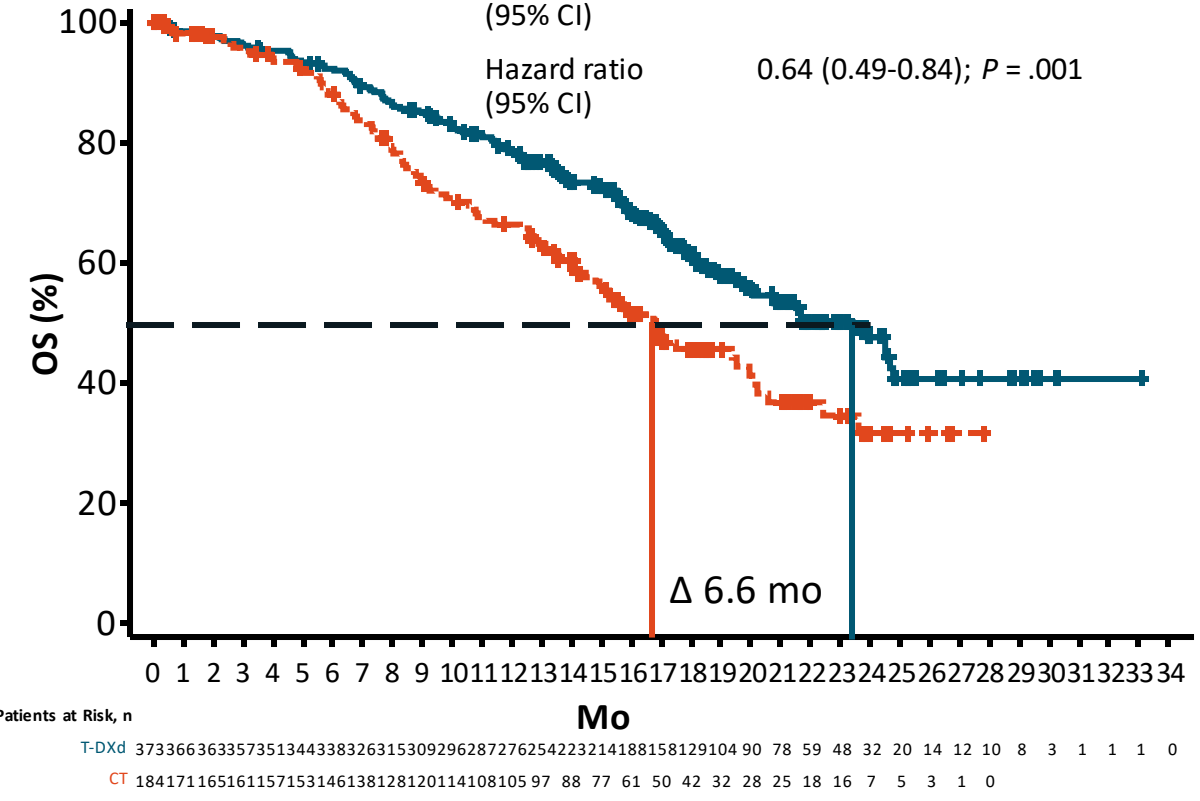
DESTINY-Breast04: OS

Patients With HR+ Disease



All Patients



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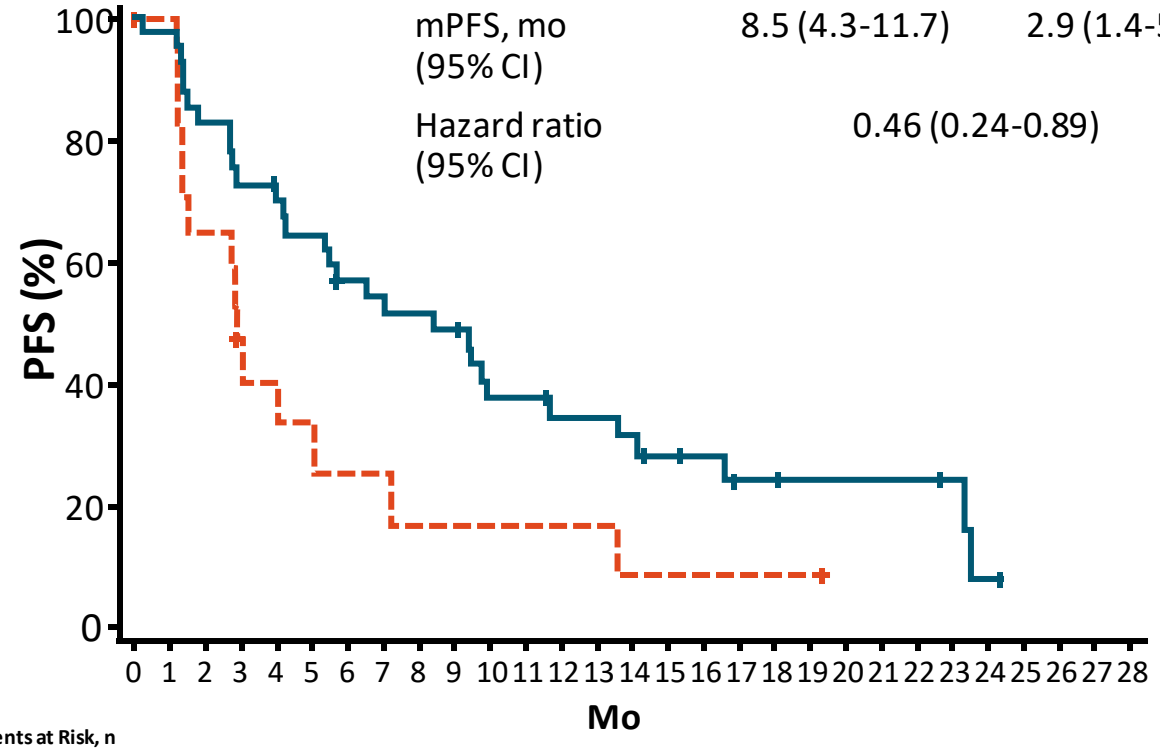
DESTINY-Breast04: Exploratory Analysis of PFS and OS in HR- Patients

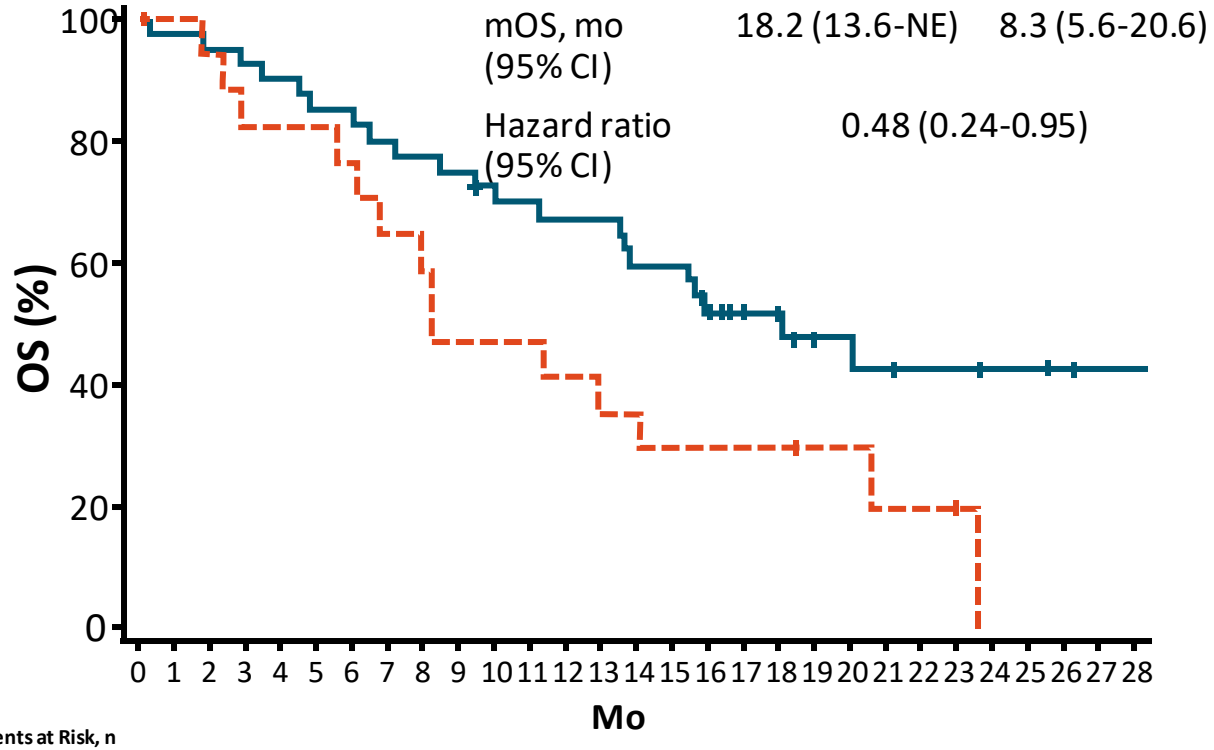
PFS



Patients at Risk, n

T-DXd	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0
CT	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0					

OS



Patients at Risk, n

T-DXd	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
CT	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;[Epub].

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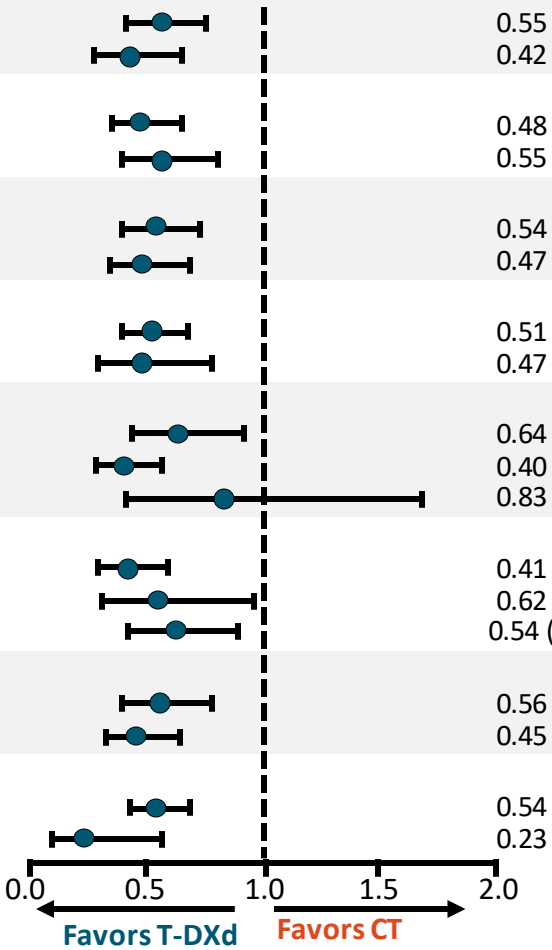
DESTINY-Breast04: PFS by Subgroup in HR+ Patients

	No. of Events/No. of Patients		Median Progression-free Survival, mo (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	CT	T-DXd	CT	
Prior CDK 4/6 Inhibitors					
▪ Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
▪ No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
▪ IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
▪ IHC 2+/ISH-	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy in the metastatic setting					
▪ 1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
▪ ≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
▪ <65 yr	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
▪ ≥65 yr	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
▪ White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
▪ Asian	83/131	54/66	11.0 (8.4-13.6)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
▪ Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
▪ Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
▪ Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
▪ North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30—0.97)
ECOG performance status					
▪ 0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
▪ 1	95/144	55/58	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
▪ Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
▪ No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



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DESTINY-Breast04: Safety

Safety Outcome	T-DXd (n = 371)	CT (n = 172)
Median treatment duration, mo (range)	8.2 (0.2-33.3)	3.5 (0.3-17.6)
TEAEs, n (%) ▪ Grade ≥3	369 (100) 195 (53)	169 (98) 116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuation	60 (16)	14 (8)
TEAEs associated with dose interruption	143 (39)	72 (42)
TEAEs associated with dose reduction	84 (23)	66 (38)
TEAEs associated with death	14 (4)	5 (3)

Drug-Related TEAEs, % (in ≥20% of Patients)	T-DXd (n = 371)		CT (n = 172)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	73.0	4.6	23.8	0
Fatigue	47.7	7.5	42.4	4.7
Alopecia	38	0	33	0
Vomiting	34.0	1.3	9.9	0
Neutropenia	33.2	13.7	51.2	40.7
Anemia	33.2	8.1	22.7	4.7
Decreased appetite	28.6	2.4	16.3	1.2
Thrombocytopenia	23.7	5.1	9.3	0.6
Transaminases increased	23.5	3.2	22.7	8.1
Leukopenia	23.2	6.5	31.4	19.2
Diarrhea	22.4	1.1	18.0	1.7
Constipation	21.3	0	12.8	0

- LV dysfunction in 17 (4.6%) with T-DXd
- Incidence of ILD/pneumonitis with T-DXd: 45 patients (12.1%), including 13 (3.5%) grade 1, 24 (6.5%) grade 2, 5 (1.3%) grade 3, and 3 (0.8%) grade 5 events

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022;[Epub].

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DESTINY-Breast04: Changes in clinical practice

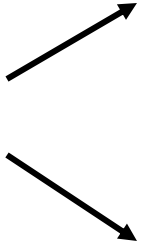
- In patients with previously treated unresectable or metastatic HER2-low breast cancer, trastuzumab deruxtecan significantly improved survival vs physician's choice of chemotherapy
  - Median PFS 9.9 vs 5.1 mo: HR: 0.50; *P* <.001
  - Median OS 23.4 vs 16.8 mo: HR: 0.64; *P* = .001
- Based on these results, patients with HER2-low disease should receive TDxd as standard of care after 1-2 lines of chemotherapy.
- Calls into question how we determine HER2 positivity and the importance recognizing tumor heterogeneity, especially in the context of agents like TDxd which have a higher chemotherapy payload and unique linker molecule that confers a bystander effects on cells with low or no HER2 positivity.
- Concordance between local and central review of HER2 has not been reported, and we know that there are inter-observer discrepancies. Also not clear why the target population was HR+ and if some "triple negative" patients need to be reclassified into some other new cate

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022.

MAINTAIN: Study Design

- Multicenter, randomized, placebo-controlled phase II trial

Adults with ER and/or PR ≥1%; HER2- MBC and progression on ET and CDK4/6i; ≤1 CT line for MBC; ECOG PS 0 or 1; postmenopausal (or premenopausal with GnRH agonist); stable brain metastases allowed
(N = 120)



Ribociclib 600 mg QD 3 wk on, 1 wk off
+ Switch ET*
(n = 60)

Placebo + Switch ET*
(n = 59)

*Patients with progression on AI for MBC and no prior fulvestrant received fulvestrant. After protocol amendment, patients who progressed on prior fulvestrant received exemestane.

- **Primary endpoint:** PFS (locally assessed per RECIST v1.1)
- **Key secondary endpoints:** ORR, CBR, safety, tumor response

Kalinsky. ASCO 2022. Abstr LBA1004.

Slide credit: clinicaloptions.com

MAINTAIN: Baseline Characteristics

Characteristic	Ribociclib (n = 60)	Placebo (n = 59)
Female, n (%)	60 (100)	58 (99)
Median age, yr (IQR)	55 (48-67)	59 (52-65)
Race/ethnicity, n (%)		
▪ White	46 (77)	42 (71)
▪ Black	5 (8)	8 (14)
▪ Asian	5 (8)	2 (3)
▪ Other	4 (7)	7 (12)
ECOG PS, n (%)		
▪ 0	40 (67)	38 (64)
▪ 1	20 (33)	21 (36)
De novo metastasis at diagnosis,* n (%)	21 (35)	32 (54)
Visceral metastases, n (%)	36 (60)	35 (59)
Bone disease only, n (%)	13 (22)	9 (15)
≥2 prior ET for MBC, n (%)	11 (18)	11 (19)
CT for MBC, n (%)	4 (7)	7 (12)

Characteristic	Ribociclib (n = 60)	Placebo (n = 59)
Prior CDK4/6i, n (%)		
▪ Palbociclib	52 (87)	51 (88)
▪ Ribociclib	6 (10)	8 (14)
▪ Abemaciclib	2 (3)	0 (0)
Median duration of prior CDK4/6i, mo (IQR)	15.5 (12-21)	17 (11-23.5)
Prior CDK4/6i duration, n (%)		
▪ ≤12 mo	18 (30)	21 (36)
▪ >12 mo	42 (70)	38 (64)
Prior CDK4/6i in metastatic setting, n (%)	60 (100)	59 (100)
Subsequent therapy after progression on CDK4/6i, n (%)	1 (2)	6 (10)

*P = .035.

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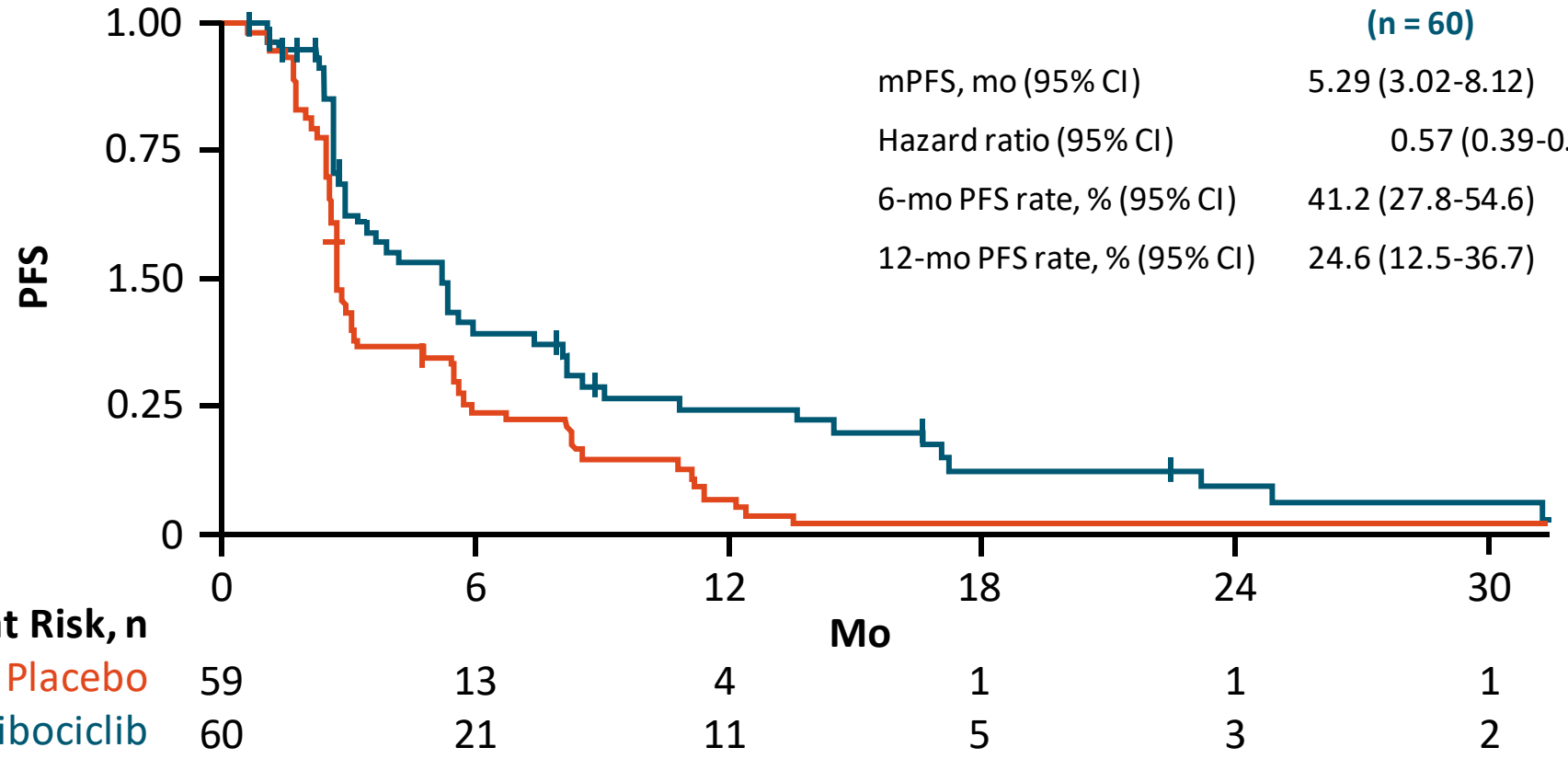
MAINTAIN: PFS



	Ribo + ET (n = 60)	Placebo + ET (n = 59)
mPFS, mo (95% CI)	5.29 (3.02-8.12)	2.76 (1.66-3.25)
Hazard ratio (95% CI)	0.57 (0.39-0.95); *P* = .006	
6-mo PFS rate, % (95% CI)	41.2 (27.8-54.6)	23.9 (12.8-35)
12-mo PFS rate, % (95% CI)	24.6 (12.5-36.7)	7.4 (0.4-14.3)

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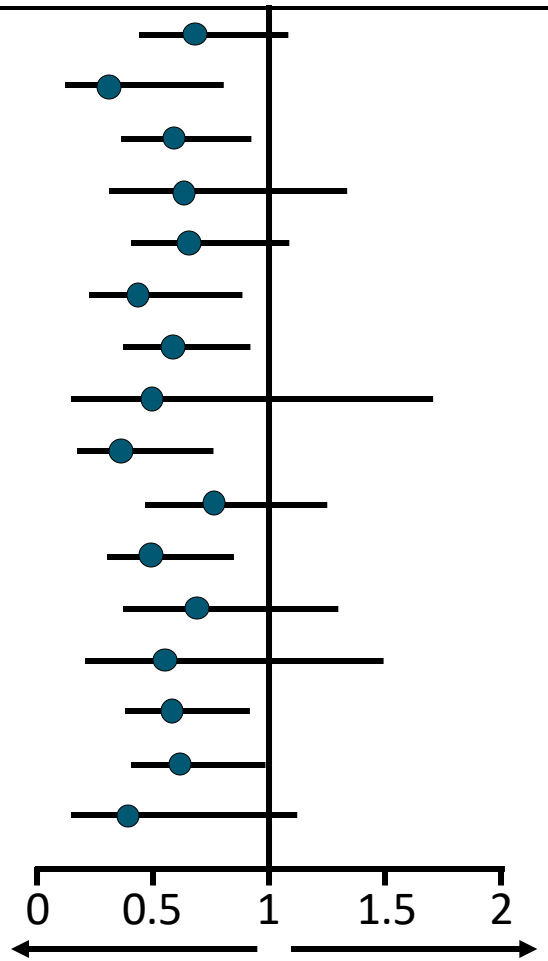
MAINTAIN: PFS by Subgroup

Subgroup	N	HR (95% CI)
Age ≤65	87	0.68 (0.43-1.06)
Age >65	32	0.31 (0.12-0.80)
Race White	88	0.58 (0.36-0.92)
Race Non-white	31	0.63 (0.30-1.33)
ECOG 0	78	0.66 (0.40-1.07)
ECOG 1	41	0.43 (0.21-0.87)
Prior Palbociclib	103	0.58 (0.38-0.90)
Prior Ribociclib	14	0.50 (0.15-1.70)
Duration Prior CDK 4/6 ≤12	39	0.36 (0.17-0.74)
Duration Prior CDK 4/6 >12	80	0.76 (0.47-1.24)
Visceral Disease Yes	71	0.49 (0.29-0.83)
Visceral Disease No	48	0.69 (0.37-1.29)
Bone Disease Yes	22	0.54 (0.20-1.49)
Bone Disease No	97	0.58 (0.38-0.90)
Prior Endocrines Mets Setting <2	97	0.62 (0.40-0.96)
Prior Endocrines Mets Setting ≥2	22	0.39 (0.14-1.12)



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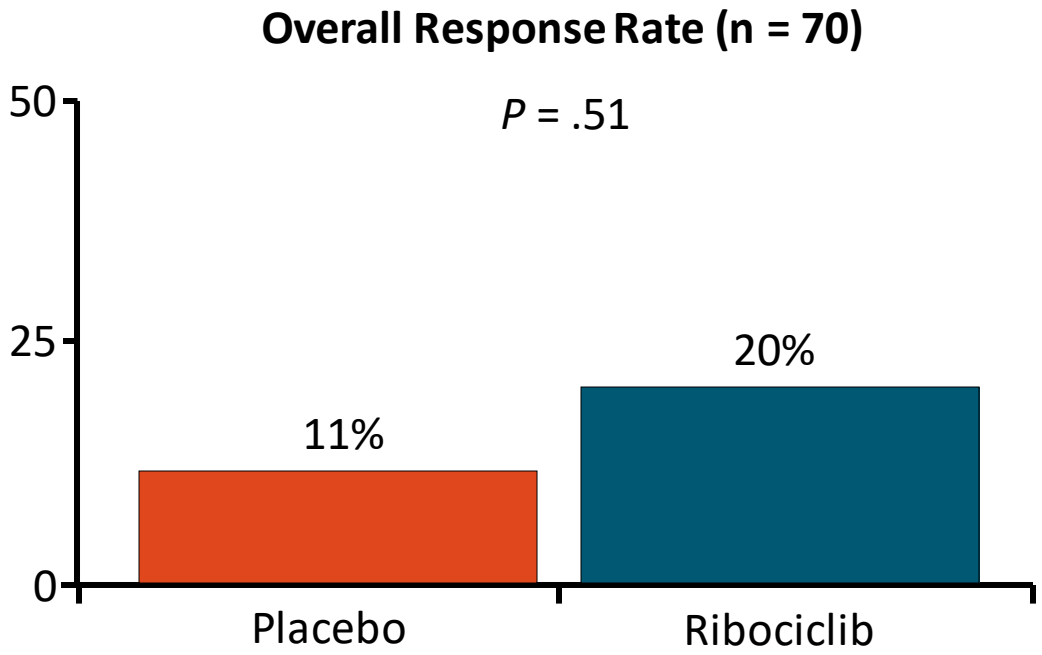
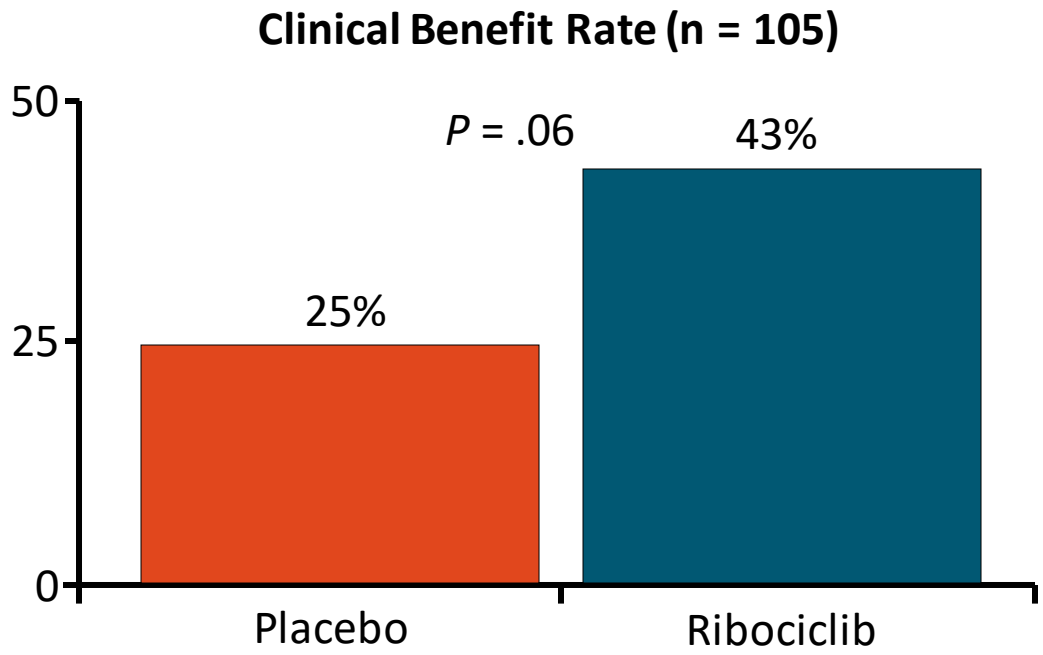
MAINTAIN: Responses





Characteristic	Placebo (n = 35)	Ribociclib (n = 35)
CR, n (%)	0 (0)	2 (6)
PR, n (%)	4 (11)	5 (14)
Median DoR, mo (IQR)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Characteristic	Placebo (n = 57)	Ribociclib (n = 49)
CR/PR/SD ≥24 wk, n (%)	14 (25)	21 (43)

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MAINTAIN: TRAEs

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

- Treatment-related deaths (n = 3)—ribociclib arm: 1 sepsis, neutropenia, and disease progression and 1 with pneumonia without fever or neutropenia; placebo: 1 with pneumonia without fever or neutropenia

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MAINTAIN: Changes in clinical practice

- None today, but certainly more trials with similar results would be practice changing.
  - PACE – randomized phase 2 trial for patients with progression on an ET and any CDK 4/6 inhibitor in the metastatic setting, and/or relapse/progression during or within 12 months of completion of an endocrine and CDK4/6 inhibitor regimen in the adjuvant setting.
    - Randomized to fulvestrant, fulvestrant + palbociclib, or fulvestrant, palbociclib, and avelumab
  - PostMONARCH - phase 3, global randomized, double-blind, placebo-controlled study for patients with disease progression on treatment with a prior CDK4/6 inhibitor + an aromatase inhibitor as initial therapy for ABC or recurrence on/after treatment with a CDK4/6 inhibitor plus ET in the adjuvant setting.
    - Eligible patients are randomized 1:1 to receive abemaciclib 150 mg twice daily or placebo, plus fulvestrant.

Kalinsky. ASCO 2022. Abstr LBA1004.

TROPiCS-02: Background

- Sacituzumab govitecan is a first-in-class Trop-2–directed ADC
  - Approved by FDA for patients with triple-negative MBC after ≥2 previous therapies (≥1 for metastatic disease)
  - Activity in pretreated HR+/HER2- MBC reported in IMMU-132-01 phase I/II trial[2]
- TROPiCS-2 compared sacituzumab govitecan vs physician's choice of treatment for patients with HR+/HER2- MBC after previous treatment with ET, CDK4/6 inhibitors, and CT[3]

Kalinsky. Ann Oncol. 2020;31:P1709. 3. Rugo. ASCO 2022. Abstr LBA1001.

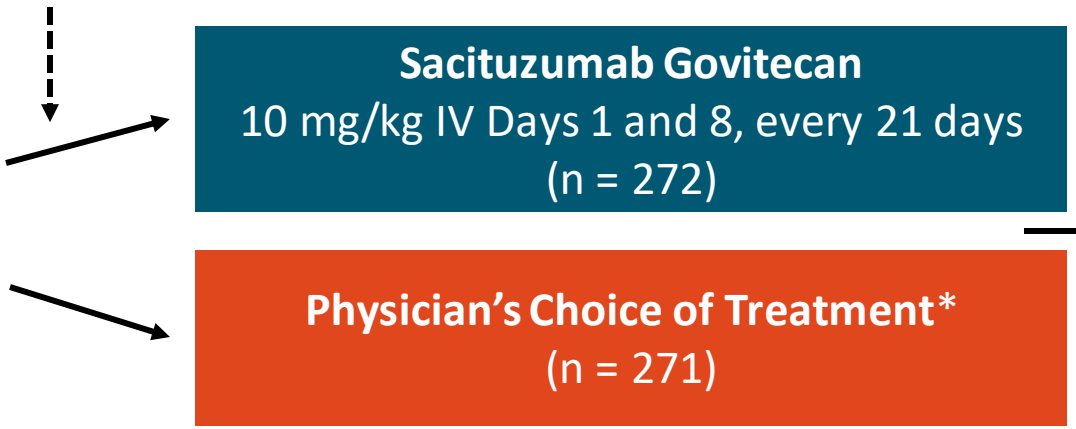
Slide credit: clinicaloptions.com

TROPiCS-02: Study Design

- Randomized, multicenter, open-label phase III study

Stratification by visceral metastases (yes vs no), ET in metastatic setting ≥6 mo (yes vs no), prior therapy lines (2 vs 3/4)

Patients with metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression after ≥1 ET, taxane, and CDK4/6 inhibitor in any setting; 2-4 previous lines of CT for metastatic disease (neo/adjuvant therapy qualified as a prior line of CT if disease recurred within 12 mo); measurable disease by RECIST v1.1
(N = 543)



*Capecitabine, vinorelbine, gemcitabine, or eribulin.

- **Primary endpoint:** PFS (BICR)
- **Secondary endpoints:** OS, ORR, DoR, CBR (LIR and BICR), PRO, safety

Rugo. ASCO 2022. Abstr LBA1001.

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TROPiCS-02: Baseline Characteristics

Characteristic	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Female, n (%)	270 (99)	268 (99)
Median age, yr (range)	57 (29-86)	55 (27-78)
▪ <65 yr, n (%)	199 (73)	204 (75)
▪ ≥65 yr, n (%)	73 (37)	67 (25)
Race/ethnicity, n (%)		
▪ White	184 (68)	178 (66)
▪ Black	8 (3)	13 (5)
▪ Asian	11 (4)	5 (2)
▪ Other or not reported	69 (25)	75 (28)
ECOG PS, n (%)		
▪ 0	116 (43)	126 (46)
▪ 1	156 (57)	145 (54)
Visceral mets at BL, n (%)	259 (95)	258 (95)
Liver mets, n (%)	229 (84)	237 (87)
De novo MBC, n (%)	78 (29)	60 (22)

Characteristic	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median time from MBC diagnosis to randomization, mo (range)	48.5 (1.2-243.8)	46.6 (3.0-248.8)
Prior CT in neo/adjuvant setting, n (%)	173 (64)	184 (68)
Prior ET use in MBC setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
▪ ≤12 mo	161 (59)	166 (61)
▪ >12 mo	106 (39)	102 (38)
▪ Unknown	5 (2)	3 (1)
Median prior CT regimens for MBC, n (range)	3 (0-8)	3 (1-5)

Rugo. ASCO 2022. Abstr LBA1001.

Slide credit: clinicaloptions.com

TROPiCS-02: PFS by BICR

BICR Analysis	Sacituzumab Govitecan (n = 272)		Physician's Choice (n = 271)
Median PFS, mo (95% CI) ▪ Stratified hazard ratio (95% CI) ▪ Stratified log-rank *P* value	5.5 (4.2-7.0)	0.66 (0.53-0.83) .0003	4.0 (3.1-4.4)
6-mo PFS, % (95% CI)	46.1 (39.4-52.6)		30.3 (23.6-37.3)
9-mo PFS, % (95% CI)	32.5 (25.9-39.2)		17.3 (11.5-24.2)
12-mo PFS, % (95% CI)	21.3 (15.2-28.1)		7.1 (2.8-13.9)

- PFS benefit associated with sacituzumab govitecan observed across subgroups, including:
  - Patients with ≥3 prior CT regimens for metastatic disease
  - Patients with visceral metastases
  - Patients aged ≥65 yr

Rugo. ASCO 2022. Abstr LBA1001.

Slide credit: clinicaloptions.com

TROPiCS-02: OS in ITT Population

OS in ITT Population (First Planned Interim Analysis)	Sacituzumab Govitecan (n = 272)		Physician's Choice (n = 271)
Median OS, mo (95% CI)	13.9 (12.7-15.4)		12.3 (10.8-14.2)
▪ Stratified hazard ratio (95% CI)		0.84 (0.67-1.06)	
▪ Stratified log-rank *P* value		.14	
Events, n	149		144

- OS data not mature at this analysis
- Follow-up is ongoing

Rugo. ASCO 2022. Abstr LBA1001.

Slide credit: clinicaloptions.com

TROPiCS-02: Safety Summary

Safety Outcome, n (%)	Sacituzumab Govitecan (n = 268)	Physician's Choice (n = 249)
Grade ≥3 TEAE	198 (74)	149 (60)
TEAEs leading to d/c	17 (6)	11 (4)
TEAEs leading to dose delay	178 (66)	109 (44)
TEAEs leading to dose reductions	89 (33)	82 (33)
TE SAEs	74 (28)	47 (19)
TEAEs leading to death ▪ Treatment related	6 (2) 1 (<1)*	0 0

*Treatment-related TEAE leading to death included septic shock due to neutropenic colitis.

- Most common TE SAEs (≥2%):
  - Sacituzumab govitecan: diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), neutropenic colitis (2%)
  - Physician's choice: febrile neutropenia (4%), pneumonia (2%), nausea (2%), dyspnea (2%)

Rugo. ASCO 2022. Abstr LBA1001.

Slide credit: clinicaloptions.com

TROPiCS-02: Conclusions and changes in practice

- In patients with HR+/HER2- advanced breast cancer previously treated with ET, CDK4/6 inhibitors, and ≥2 CT regimens for metastatic disease, sacituzumab govitecan improved PFS vs physician's choice treatment
  - Median PFS by BICR: 5.5 vs 4.0 mo (hazard ratio: 0.66; 95% CI: 0.53-0.83; *P* = .0003)
- OS data not yet mature
- Safety of sacituzumab govitecan manageable and consistent with previous data
- HRQoL higher with sacituzumab govitecan (*P* = .005)
  - Delayed worsening of fatigue and global health status
- Investigators concluded that sacituzumab govitecan should be considered as a potential treatment option in heavily pretreated patients with HR+/HER2- MBC

Rugo. ASCO 2022. Abstr LBA1001.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS Analysis: Background

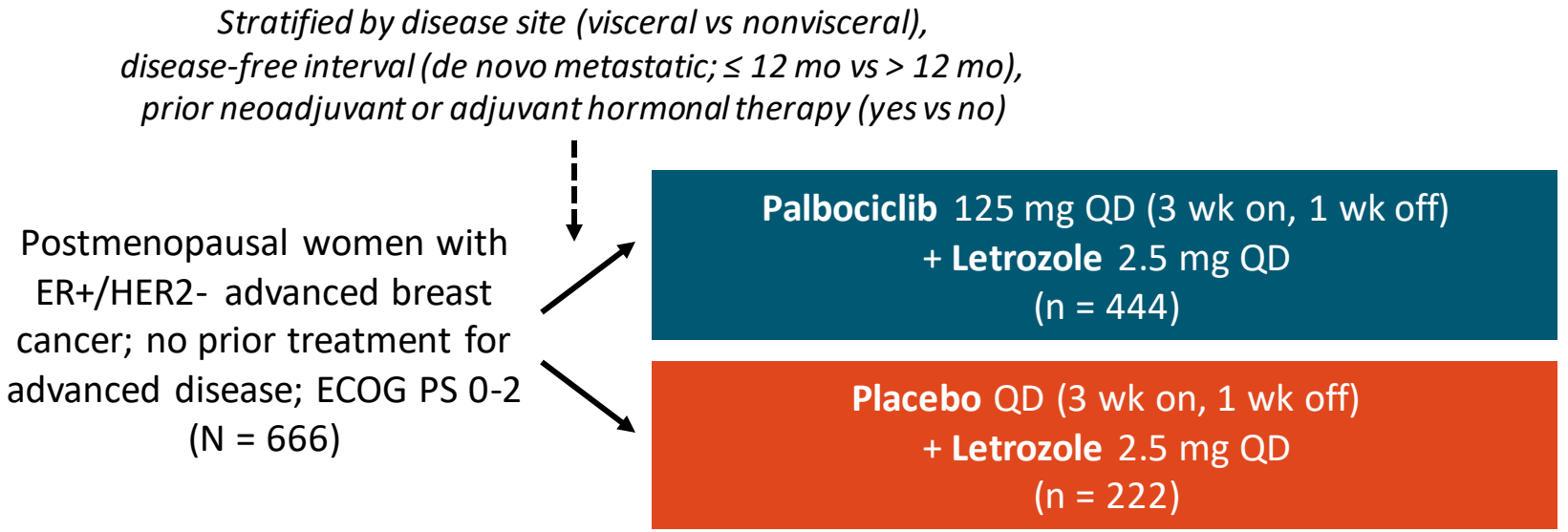
- Palbociclib: CDK4/6 inhibitor approved by FDA for ER+/HER2- advanced breast cancer in combination with an AI as initial therapy for postmenopausal women or with fulvestrant after PD following ET
  - PALOMA-1: open-label, randomized phase II study reported 10-mo PFS increase with palbociclib + letrozole vs letrozole alone (HR: 0.49; *P* = .0004)[1]
- PALOMA-2: randomized, double-blind phase III trial comparing first-line palbociclib + letrozole vs placebo + letrozole in ER+/HER2- advanced breast cancer
  - Primary analysis: median PFS of 24.8 mo with palbociclib + letrozole vs 14.5 mo with placebo + letrozole (HR: 0.58; *P* <.001)[2]
- Current study reports final OS analysis of PALOMA-2, completed after median follow-up of 90 mo[3]

1. Finn. Lancet Oncol. 2015;16:25. 2. Finn. NEJM. 2016;375:1925. 3. Finn. ASCO 2022. Abstr LBA1003.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS Analysis: Study Design

- Multicenter, international, double-blind, randomized phase III trial



- **Primary endpoint**: PFS by investigator*
- **Secondary endpoints:** OS,* response, safety, biomarkers, patient-reported outcomes

*PFS: Study powered to detect ~44% increase in median PFS from 9 mo (placebo) to 13 mo (palbociclib), assuming HR 0.69 favoring palbociclib (90% power to detect 1-sided α = 0.025).
OS: Assuming median OS 34-46 mo (placebo), 390 events needed to detect HR ≤0.74 (80% power to detect 1-sided α = 0.025).

Finn. ASCO 2022. Abstr LBA1003.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS Analysis: Baseline Characteristics

Characteristic	Palbociclib + Letrozole (n = 444)	Placebo + Letrozole (n = 222)
Median age, yr (range)	62 (30-89)	61 (28-88)
ECOG PS, %		
▪ 0/1/2	257 (58)/178 (40)/9 (2)	102 (46)/117 (53)/3 (1)
Disease site, %		
▪ Visceral	214 (48)	110 (50)
▪ Nonvisceral	230 (52)	112 (50)
Disease-free interval, %		
▪ >12 mo from end of adjuvant to recurrence	179 (40)	93 (42)
▪ ≤12 mo from end of adjuvant to recurrence	98 (22)	48 (22)
▪ De novo metastatic	167 (38)	81 (37)
Prior endocrine therapy, %		
▪ Yes	250 (56)	126 (57)
▪ No	194 (44)	96 (43)
Prior systemic treatment, %		
▪ None	167 (38)	81 (37)
▪ Chemotherapy	213 (48)	109 (49)
▪ Endocrine therapy	250 (56)	126 (57)

Finn. ASCO 2022. Abstr LBA1003.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS Analysis: OS in ITT Population

Outcome	Palbociclib + Letrozole (n = 444)	Placebo + Letrozole (n = 222)	HR (95% CI)
Planned ITT Analysis* Median OS in ITT population, mo (95% CI)	53.9 (49.8-60.8)	51.2 (43.7-58.9)	0.956 (0.777-1.777); *P* = .3378
Post Hoc Sensitivity Analysis Median OS (excluding patients with missing survival data†), mo (95% CI)	51.6 (46.9-57.1)	44.6 (37.0-52.3)	0.869 (0.706-1.069)
Median duration of treatment, mo	22.0	13.8	--
Discontinued study treatment, n (%)	399 (90)	217 (98)	--
Median time to chemotherapy, mo (95% CI)	38.1 (34.1-42.2)	29.8 (24.7-34.8)	0.730 (0.607-0.879)

*Median follow-up: 90 mo.

†Survival data missing in 13% of patients in palbociclib arm vs 21% in placebo arm.

PALOMA-1 and PALOMA-2 Combined OS Analysis	Palbociclib + Letrozole (n = 444)	Placebo + Letrozole (n = 222)	HR (95% CI)
ITT Analysis Median OS, mo (95% CI)	51.8 (47.8-56.9)	46.8 (38.8-52.3)	0.934 (0.780-1.120)
Subgroup With DFI >12 Mo Median OS, mo (95% CI)	64.0 (49.2-73.4)	44.6 (37.0-53.2)	0.736 (0.551-0.982)

Finn. ASCO 2022. Abstr LBA1003.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS Analysis: Conclusions

- In postmenopausal patients with ER+/HER2- advanced breast cancer, addition of palbociclib to frontline letrozole significantly extended PFS and ORR[1]
- In this final OS analysis, OS was not significantly increased among patients randomized to receive palbociclib[2]
  - Median OS >50 mo obtained in both treatment arms
- Safety profile of palbociclib + letrozole maintained with long-term use
- Investigators suggest that a high number of patients with missing survival data, particularly in placebo arm, limit interpretation of OS data in this trial

1. Finn. NEJM. 2016;375:1925. 2. Finn. ASCO 2022. Abstr LBA1003.

Slide credit: clinicaloptions.com

PALOMA-2 Final OS: Changes in clinical practice

- Palbociclib is not my first choice for 1L treatment in HR+ metastatic disease.
- MONALEESA-2 did show an OS advantage with ribociclib.
  - Ribociclib + letrozole showed a significant OS benefit as compared with placebo + letrozole. Median OS was 63.9 months (95% confidence interval [CI], 52.4 to 71.0) with ribociclib + letrozole and 51.4 months (95% CI, 47.2 to 59.7) with placebo + letrozole (HR for death, 0.76; 95% CI, 0.63 to 0.93; two-sided P=0.008).
  - Awaiting for MONARCH-3 OS data
  - Still appropriate to look at toxicity profile and individual patient characteristics

Local Therapy

LUMINA: Local Recurrence With Omission of Radiotherapy After Breast-Conserving Surgery in T1N0 Luminal A Breast Cancer

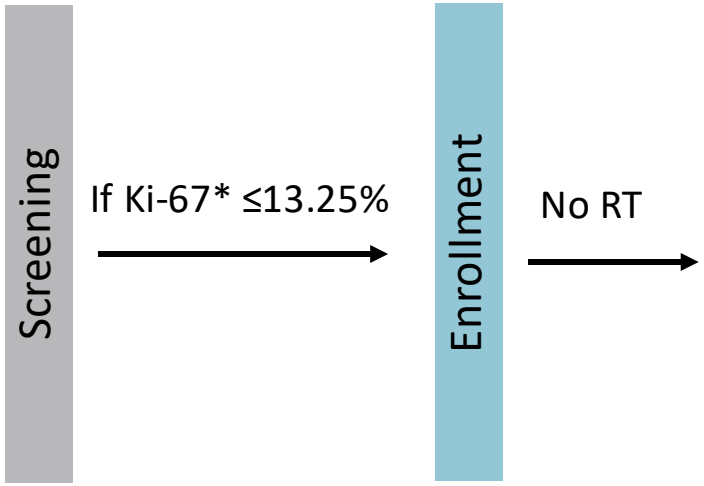
LUMINA: Background

- As screening and treatment advances have reduced the risk of local recurrence, there is growing interest in identifying low-risk patients for whom RT may be omitted
  - Intrinsic subtype based on biomarkers may be prognostic for local recurrence, with the lowest risk of local recurrence associated with the luminal A subtype
- The LUMINA trial prospectively evaluated the use of clinical pathologic factors and luminal A subtype to identify patients at very low risk of local recurrence after BCS for whom RT may be omitted.

1. Majeed. Adverse Effects of Radiation Therapy. 2021. 2. Voduc. JCO. 2010;28:1684. 3. Whelan. ASCO 2022. Abstr LBA501.

LUMINA: Study Design

Patients aged ≥55 yr with invasive ductal T1N0 luminal A* breast cancer treated with BCS and ET† alone for ≥5 yr, margins ≥1 mm, grade 1/2, without multifocal/ multicentric tumor, >25% DCIS, or lymphatic vascular invasion (N = 500)



*ER ≥1%, PgR >20%, HER2 negative, Ki-67 ≤13.25% as assessed at central laboratory.
†Aromatase inhibitor or tamoxifen for ≥5 yr.

Follow-up

- Every 6 mo for first 2 yr, then yearly
- Yearly mammogram
- Probability of LR estimated using cumulative incidence function with death as competing risk
- ITT analysis planned at median follow-up of 5 yr

- **Primary outcome:** LR (any invasive or non-invasive event)
- **Secondary outcomes:** contralateral breast cancer, any recurrence, DFS and OS

1. Whelan. ASCO 2022. Abstr LBA501

Slide credit: clinicaloptions.com

LUMINA: Baseline Characteristics

Characteristic	All Patients (N = 500)
Mean age, yr	67
▪ 55 to <65, n (%)	200 (40)
▪ 65 to <75, n (%)	242 (48)
▪ ≥75, n (%)	58 (12)
Mean tumor size, cm	1.1
▪ <0.5, n (%)	40 (8)
▪ 0.51-1.0, n (%)	216 (43)
▪ 1.1-2.0, n (%)	244 (49)
Tumor grade, n (%)	
▪ 1	330 (66)
▪ 2	170 (34)
Endocrine therapy, n (%)	
▪ Tamoxifen	200 (41)
▪ Aromatase inhibitor	292 (59)

Whelan. ASCO 2022. Abstr LBA501.

Slide credit: clinicaloptions.com

LUMINA: Local Recurrence Events

Outcome	Total Events at 5 Yr	5-Yr Rate (90% CI)
Local recurrence	10	2.3 (1.3-3.8)
Contralateral breast cancer	8	1.9 (1.1-3.2)
Any recurrence	12	2.7 (1.6-4.1)
DFS	47*	89.9 (87.5-92.2)
OS	13†	97.2 (95.9-98.4)

*23 second primary nonbreast cancer.
†1 death from breast cancer.

Whelan. ASCO 2022. Abstr LBA501.

Slide credit: clinicaloptions.com

LUMINA: Conclusions

- Women defined as having a low-risk of recurrence (age ≥55 yr with T1N0, grade 1/2 luminal A breast cancer following BCS with endocrine therapy alone) had a low 5-yr local recurrence rate of 2.3%
  - This rate satisfied the prespecified boundary
- The investigators concluded that these patients could be considered as candidates for the omission of radiation therapy after BC.

Whelan. ASCO 2022. Abstr LBA501.

Take-home points

- Practice-changing studies:
  - DESTINY-Breast04 --> Use of TDxd for patients with HER2-low metastatic breast cancer
  - PALOMA-2 --> Reconsider use of palbociclib for 1st line; consider using ribociclib
  - Consider omission of adjuvant radiation in patients meeting criteria for LUMINA, although this was not a randomized trial
    - We know from CALGB 9343 and PRIME-II that older women (70 and 65 yo, respectively) with HR+ node-negative low-risk breast cancer do not benefit from adjuvant radiation with regard to overall survival
    - One other concern with omission of adjuvant radiation is subsequent compliance with endocrine therapy.

Thank you!