Applications for Community Oncology

SABCS Review

January 25, 2024

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer	HR+ Breast Cancer	HER2+ Breast Cancer
• ALEXANDRA/Impassion030 • KEYLYNK-009 • DESTINY-Breast08 • DEBBRAH	• PROSPECT • NRG Oncology/NSABP B-51/RTOG 1304 • IDEA • ADAPTcycle • INAVO120	• KATHERINE • HER2CLIMB-02 • Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

ALEXANDRA/Impassion030 Clinical Trial

Does the addition of atezolizumab to adjuvant chemotherapy benefit patients with stage II and stage III triple negative breast cancer?

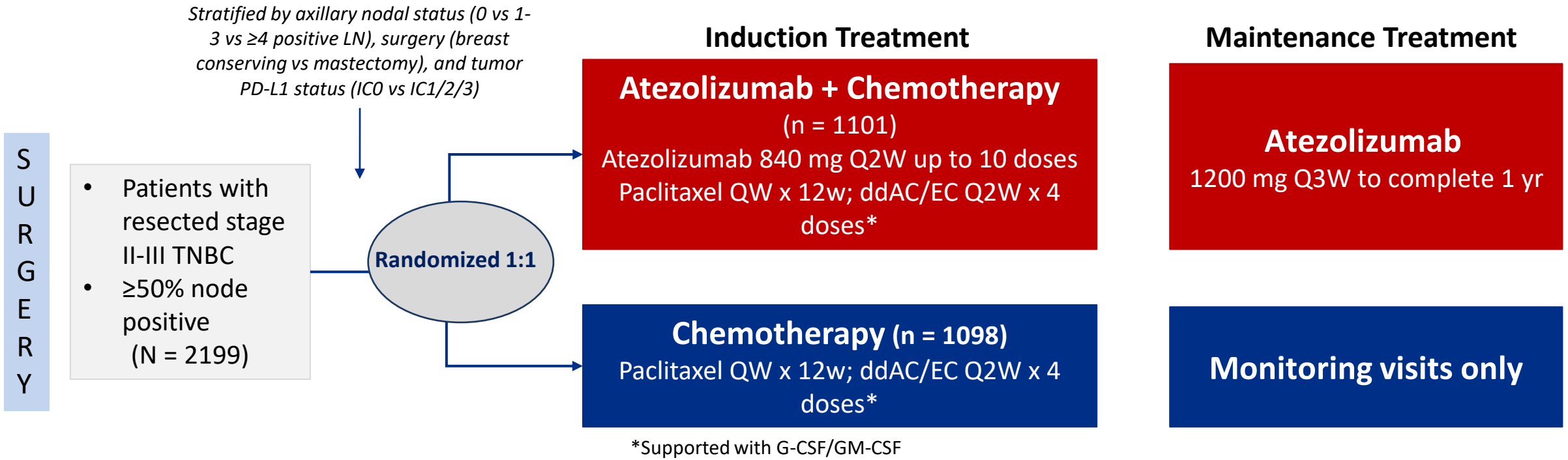
Interim analysis

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

Study Design: Randomized, open-label, Phase III trial



*Supported with G-CSF/GM-CSF

Primary End Point: iDFS in ITT population

Secondary Endpoints: iDFS in PD-L1–positive and node-positive subpopulations, iDFS including second primary nonbreast invasive cancer, OS, RFI, DRFI, DFS

SABCS 2023 Abstract GS01-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

Baseline Characteristics

Characteristic	Atezo + CT (n = 1101)	CT (n = 1098)
Median age, yr (range)	53 (24-86)	53 (23-79)
Race, n (%)		
• White	554 (50.3)	564 (51.4)
• Asian	423 (38.4)	401 (36.5)
• American Indian/Alaska Native	28 (2.5)	27 (2.5)
• Black	8 (0.7)	2 (0.2)
• Other/unknown	88 (8.0)	104 (9.5)
ECOG PS 0 | 1, %	80.6 | 19.4	81.5 | 18.5
Histology, n (%)		
• Ductal, NOS	823 (74.9)	793 (72.2)
• Lobular	39 (3.5)	54 (4.9)
• Metaplastic	50 (4.5)	46 (4.2)
• Other	211 (19.2)	241 (21.9)
Histologic grade at screening, n (%)		
• Well differentiated	60 (5.5)	75 (6.8)
• Moderately differentiated	205 (18.6)	233 (21.2)
• Poorly differentiated	686 (62.4)	653 (59.5)
• Anaplastic	3 (0.3)	3 (0.3)
• Unknown	146 (13.3)	134 (12.2)

Characteristic	Atezo + CT (n = 1101)	CT (n = 1098)
Primary tumor stage, n (%)		
• pT1-pT2	1024 (93.0)	1045 (95.2)
• pT3	71 (6.4)	51 (4.6)
• Other*	6 (0.5)	2 (0.2)
Axillary nodal status, n (%)		
• 0	577 (52.4)	573 (52.2)
• 1-3	390 (35.4)	390 (35.5)
• ≥4	134 (12.2)	135 (12.3)
AJCC stage at surgery, n (%)		
• II	935 (84.9)	940 (85.6)
• III	161 (14.6)	157 (14.3)
• Other†	5 (0.5)	1 (<0.1)
Breast-conserving surgery , %	47.6	47.6
Mastectomy, %	52.4	52.4
PD-L1: %		
• IC 0	28.7	28.8
• IC 1, 2, or 3	71.3	71.2

*Includes pT0, pTis, pT4, PT4b, and missing. †Includes stage I and missing.

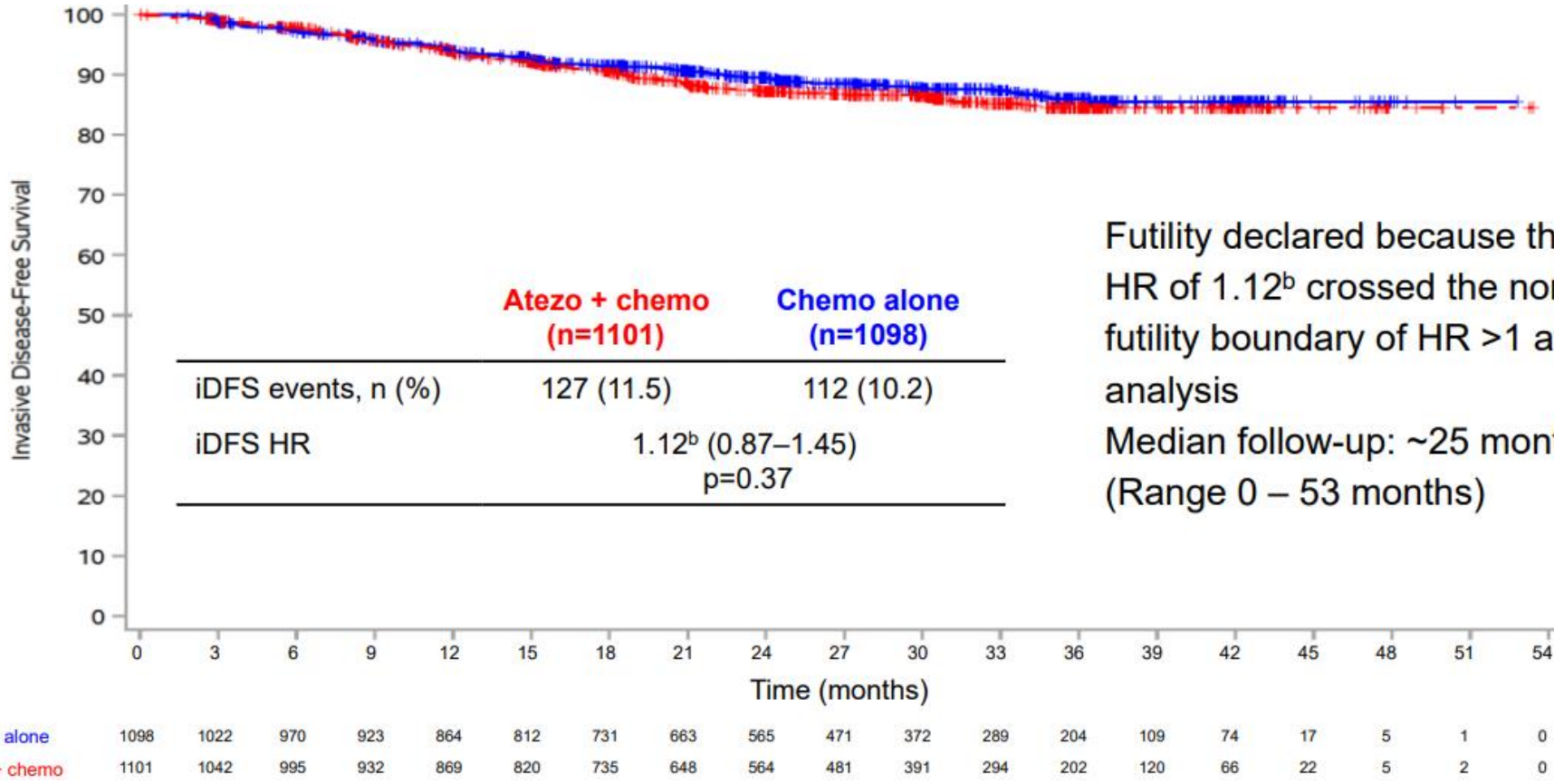
SABCS 2023 Abstract GS01-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

Primary Endpoint: iDFS[a] (ITT population)



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

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

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

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

SABCS 2023 Abstract GS01-03.

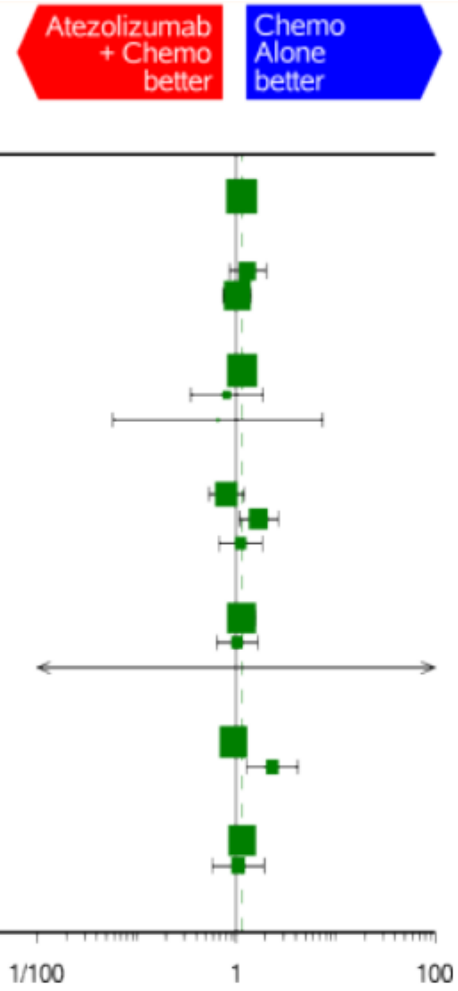
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

iDFS by Subgroup (ITT population)

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



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

SABCS 2023 Abstract GS01-03.

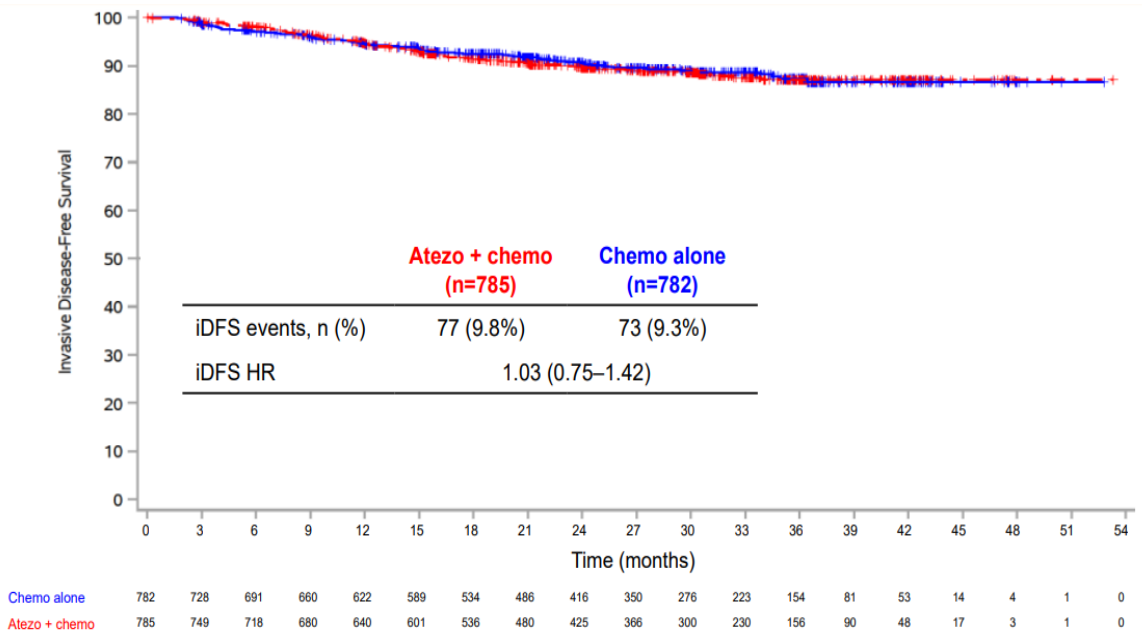
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

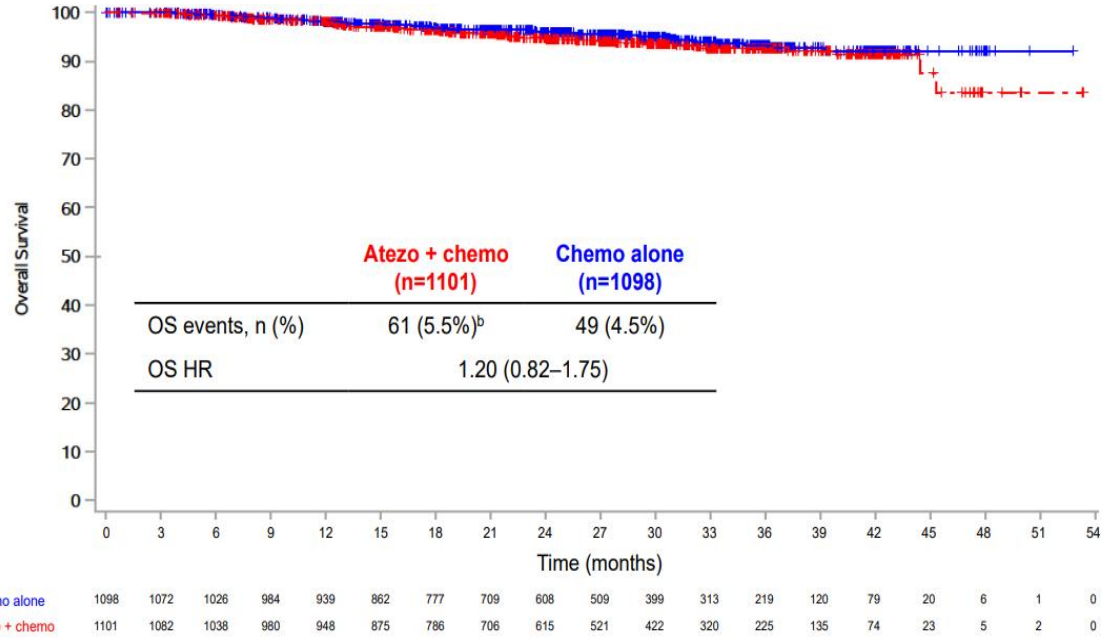
Secondary Endpoints

iDFS in the PD-L1+ subgroup (71%)



	Atezo + chemo (n=785)	Chemo alone (n=782)
iDFS events, n (%)	77 (9.8%)	73 (9.3%)
iDFS HR	1.03 (0.75–1.42)	

OS in the ITT population



	Atezo + chemo (n=1101)	Chemo alone (n=1098)
OS events, n (%)	61 (5.5%)[b]	49 (4.5%)
OS HR	1.20 (0.82–1.75)	

SABCS 2023 Abstract GS01-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

ALEXANDRA/Impassion030 Clinical Trial

Safety

Parameter	Atezolizumab + Chemotherapy (n = 1093)	Chemotherapy (n = 1084)
TEAEs, n (%)	1090 (99.7)	1073 (99.0)
TRAEs, n (%)		
• Any	1083 (99.1)	1066 (98.3)
• Grade 3/4	587 (53.7)	472 (43.5)
• SAEs	198 (18.1)	107 (9.9)
• Deaths	2 (0.2)	1 (<0.1)
AEs leading to any discontinuation, n (%)	185 (16.9)	60 (5.5)
AEs leading to discontinuation of: n (%)		
• Atezolizumab	144 (13.2)	0 (0)
• Epirubicin	30 (2.7)	12 (1.1)
• Doxorubicin	14 (1.3)	17 (1.6)
• Cyclophosphamide	43 (3.9)	30 (2.8)
• Paclitaxel	54 (4.9)	33 (3.0)

SABCS 2023 Abstract GS01-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ALEXANDRA/Impassion030 Clinical Trial

Safety

Parameter	Atezolizumab + Chemotherapy (n = 1093)	Chemotherapy (n = 1084)
Most frequent TEAEs (≥20%), any grade, %		
• Alopecia	66.1	65.2
• Nausea	49.8	47.5
• Anemia	36.8	37.5
• Fatigue	28.9	23.9
• ALT increased	26.3	21.4
• Diarrhea	25.4	17.2
• Neutrophil count decreased	24.7	23.3
• Rash	24.2	13.9
• Neutropenia	22.2	23.1
• AST increased	21.8	14.1
• Asthenia	21.2	21.3
• Constipation	20.6	18.5
• WBC count decreased	20.4	17.4

- Most frequent immune-mediated AEs in atezolizumab arm (≥5%): rash (42.7%), hepatitis (31.3%-32.8%), hypothyroidism (17.8%) were primarily low grade

SABCS 2023 Abstract GS01-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

ALEXANDRA/Impassion030 Clinical Trial

The addition of atezolizumab to adjuvant chemotherapy does not provide additional benefit to patients with early stage TNBC who have received primary surgery

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009

- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

KEYLYNK-009 Clinical Trial

Does pembrolizumab plus olaparib provide benefit for patients with untreated metastatic or locally recurrent inoperable TNBC who respond or have stable disease following pembrolizumab + chemotherapy induction?

© 2024 Cornerstone Specialty Network. All rights reserved.

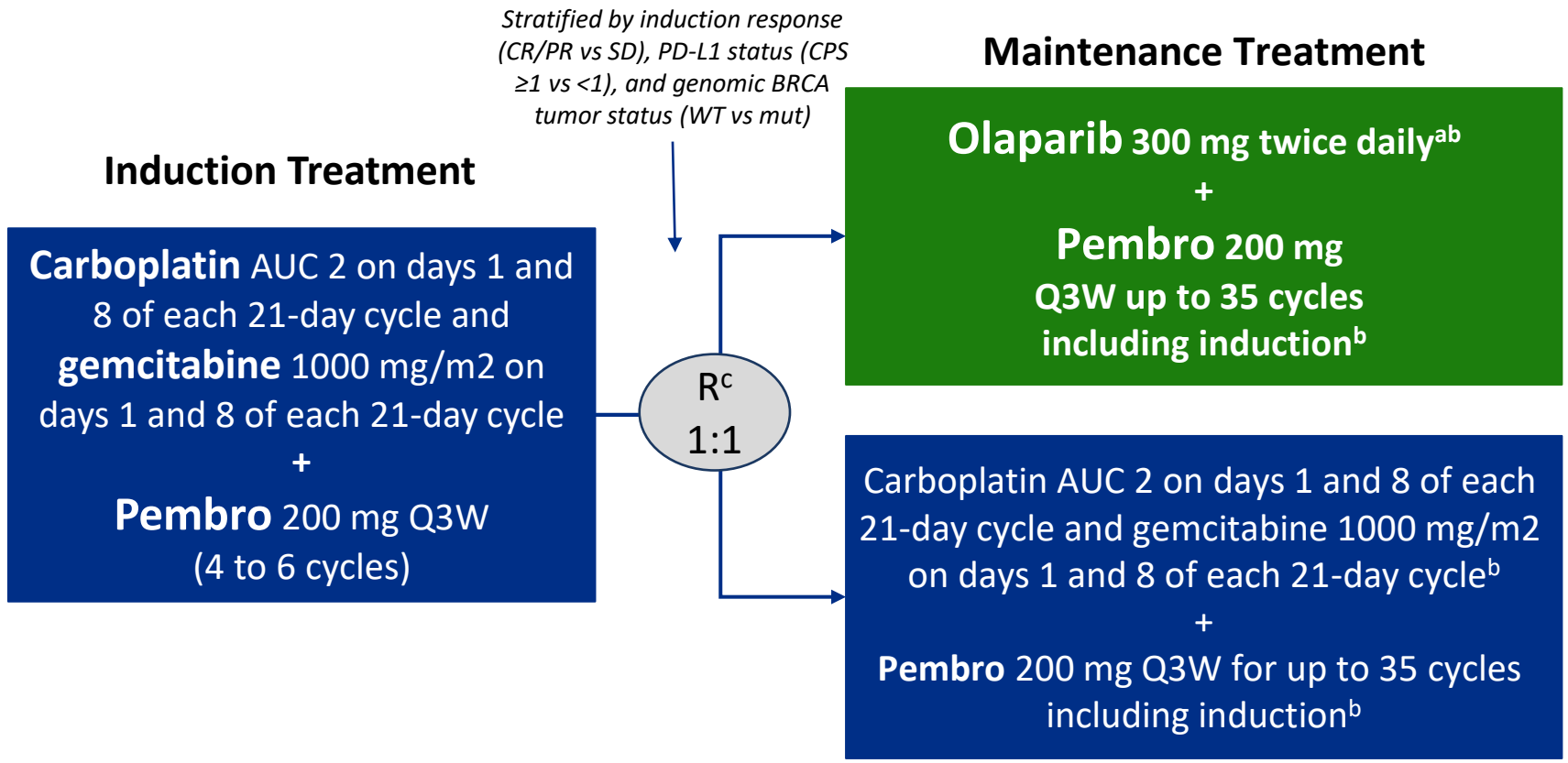
KEY DATA

KEYLYNK-009 Clinical Trial

Study Design: Randomized, open-label, Phase II trial

- Locally recurrent inoperable or metastatic TNBC not previously treated in the metastatic setting
- Measurable disease per RECIST v1.1 by local radiology review
- Interval between treatment with curative intent and recurrence ≥6 months
- Confirmed PD-L1 status

(N = 460)



aOlaparib was administered postinduction and given concurrently with pembrolizumab.
bUntil disease progression or unacceptable toxicity.
cITT population was determined from randomization (not from the time of enrollment).

Primary End Point: PFS according to RECIST v1.1 by BICR, OS (in ITT population)
Secondary Endpoints: PFS and OS in patients with tBRCAm or PD-L1 CPS ≥10, safety

SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KEYLYNK-009 Clinical Trial

Baseline Characteristics

Characteristic, n (%)	Pembrolizumab + Olaparib (n = 135)	Pembrolizumab + Chemotherapy (n = 136)
Median age, yr (range)	54 (25-82)	52 (30-80)
ECOG PS 1	48 (35.6)	45 (33.1)
Postmenopausal	96 (71.1)	94 (69.1)
PD-L1 status		
• CPS ≥1	106 (78.5)	105 (77.2)
• CPS <1	29 (21.5)	31 (22.8)
• CPS ≥10	65 (48.1)	65 (47.8)
• CPS <10	69 (51.1)	71 (52.2)
BRCA mutation	29 (21.5)	30 (22.1)
HRD ≥33	83 (61.5)	77 (56.6)

Characteristic, n (%)	Pembrolizumab + Olaparib (n = 135)	Pembrolizumab + Chemotherapy (n = 136)
Disease status		
• Metastatic, de novo	47 (34.8)	37 (27.2)
• Metastatic, recurrence	87 (64.4)	96 (70.6)
• Locally recurrent inoperable	1 (0.7)	3 (2.2)
Response at randomization		
• CR/PR	95 (70.4)	96 (70.6)
• Stable disease	39 (28.9)	40 (29.4)

SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

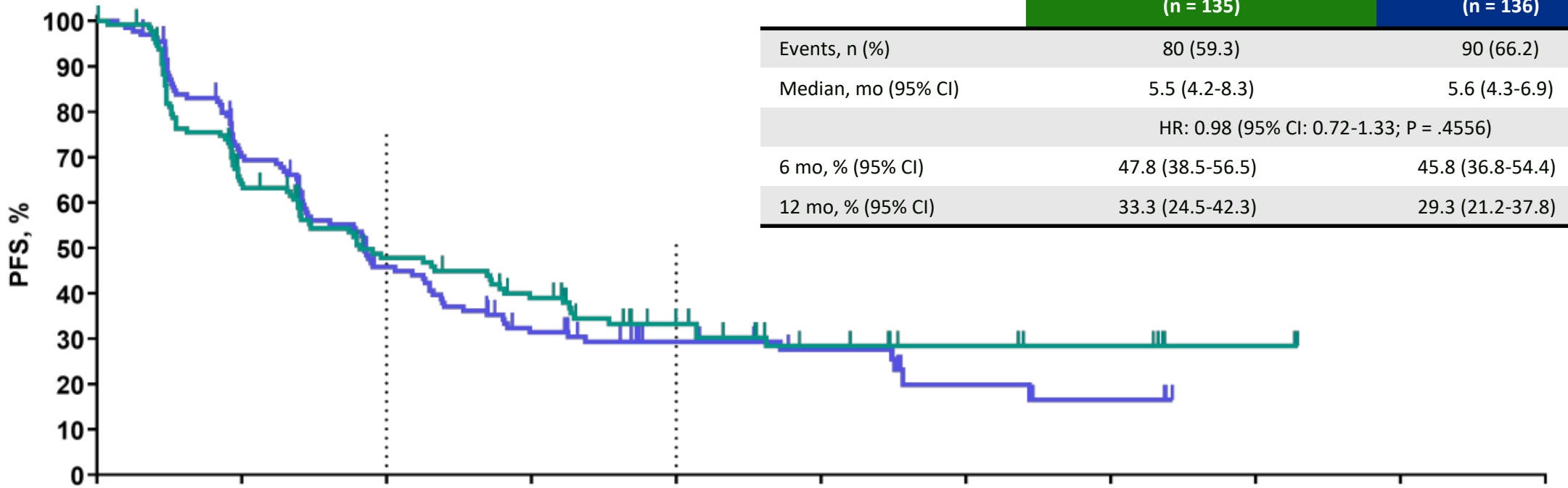
KEY DATA

KEYLYNK-009 Clinical Trial

Primary Endpoints

PFS per RECIST v1.1 by BICR in ITT Population

PFS by BICR (RECIST v1.1)	Pembrolizumab + Olaparib (n = 135)	Pembrolizumab + Chemotherapy (n = 136)
Events, n (%)	80 (59.3)	90 (66.2)
Median, mo (95% CI)	5.5 (4.2-8.3)	5.6 (4.3-6.9)
	HR: 0.98 (95% CI: 0.72-1.33; P = .4556)	
6 mo, % (95% CI)	47.8 (38.5-56.5)	45.8 (36.8-54.4)
12 mo, % (95% CI)	33.3 (24.5-42.3)	29.3 (21.2-37.8)



SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

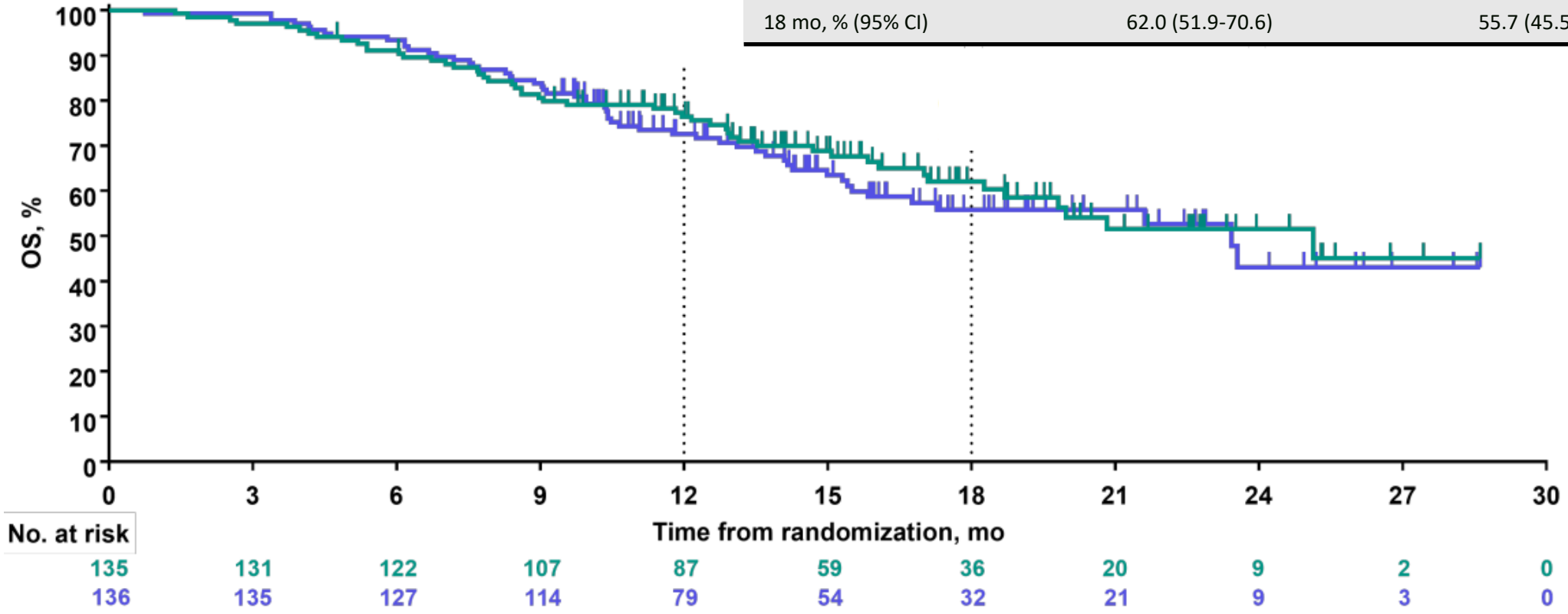
KEY DATA

KEYLYNK-009 Clinical Trial

Primary Endpoints

Estimates of OS: ITT Population

Estimated OS	Pembrolizumab + Olaparib (n = 135)	Pembrolizumab + Chemotherapy (n = 136)
Events, n (%)	50 (37.0)	54 (39.7)
Median, mo (95% CI)	25.1 (18.3-NR)	23.4 (15.8-NR)
	HR: 0.95 (95% CI: 0.64-1.40)	
12 mo, % (95% CI)	76.4 (68.2-82.8)	72.6 (64.0-79.4)
18 mo, % (95% CI)	62.0 (51.9-70.6)	55.7 (45.5-64.7)

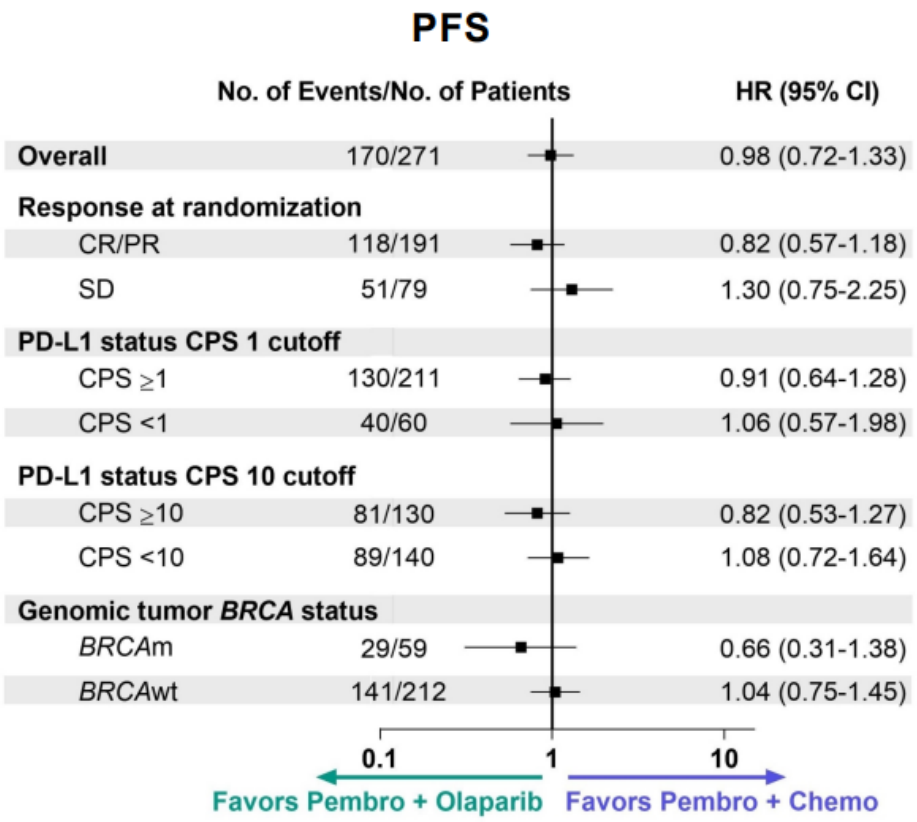


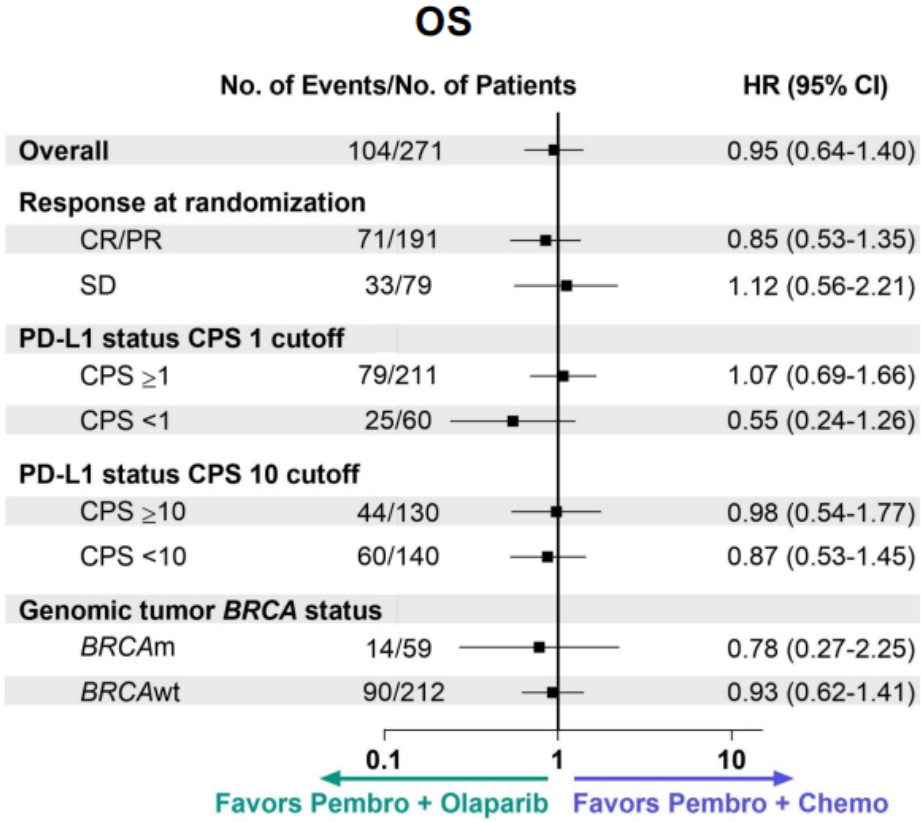
SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEYLYNK-009 Clinical Trial

PFS and OS in Key Patient Subgroups: ITT Population





SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KEYLYNK-009 Clinical Trial

Secondary Endpoints

PFS by BICR (RECIST v1.1)	Pembrolizumab + Olaparib	Pembrolizumab + Chemotherapy
PD-L1 CPS ≥10	**(n = 65)**	**(n = 65)**
Events, n (%)	36 (55.4)	45 (69.2)
Median, mo (95% CI)	5.7 (2.9-13.9)	5.7 (3.8-7.6)
	HR: 0.92 (95% CI: 0.59-1.43)	
6 mo, % (95% CI)	49.1 (35.7-61.2)	46.9 (33.9-58.8)
12 mo, % (95% CI)	40.7 (27.7-53.3)	30.9 (19.5-42.9)
tBRCAm	**(n = 29)**	**(n = 30)**
Events, n (%)	12 (41.4)	17 (56.7)
Median, mo (95% CI)	12.4 (8.3-NR)	8.4 (5.4-NR)
	HR: 0.70 (95% CI: 0.33-1.48)	
6 mo, % (95% CI)	84.4 (63.6-93.9)	61.1 (40.8-76.2)
12 mo, % (95% CI)	52.2 (30.0-70.4)	45.1 (25.9-62.6)

Estimated OS	Pembrolizumab + Olaparib	Pembrolizumab + Chemotherapy
PD-L1 CPS ≥10	**(n = 65)**	**(n = 65)**
Events, n (%)	22 (33.8)	22 (33.8)
Median, mo (95% CI)	NR (17.0-NR)	NR (15.5-NR)
	HR: 0.97 (95% CI: 0.53-1.76)	
12 mo, % (95% CI)	74.7 (61.9-83.7)	77.6 (65.1-88.2)
18 mo, % (95% CI)	62.4 (47.4-74.3)	59.1 (43.1-72.1)
tBRCAm	**(n = 29)**	**(n = 30)**
Events, n (%)	6 (20.7)	8 (26.7)
Median, mo (95% CI)	NR (17.1-NR)	23.4 (17.3-NR)
	HR: 0.81 (95% CI: 0.28-2.37)	
12 mo, % (95% CI)	96.6 (77.9-99.5)	82.9 (63.7-92.5)
18 mo, % (95% CI)	73.3 (45.9-88.4)	70.4 (45.5-85.5)

SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEYLYNK-009 Clinical Trial

Safety

AEs, n (%)	Pembrolizumab + Olaparib (n = 135)	Pembrolizumab + Chemotherapy (n = 136)
TRAEs		
• Any grade	114 (84.4)	128 (96.2)
• Grade 3-5	44 (32.6)	91 (68.4)
• Leading to treatment discontinuation	12 (8.9)	26 (19.5)
Immune-mediated AEs, infusion reactions		
• Any grade	26 (19.2)	31 (23.3)
• Grade 3-4	6 (4.4)	6 (4.5)
• Leading to treatment discontinuation	0	4 (3.0)

SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

KEYLYNK-009 Clinical Trial

- Pembrolizumab plus olaparib does not improve PFS or OS compared with pembrolizumab plus chemotherapy in patients with untreated metastatic or locally recurrent inoperable TNBC who respond or have stable disease following pembrolizumab plus chemotherapy induction
    - Small subpopulation of patients with t*BRCA*m showed trend toward improved PFS and OS with pembrolizumab plus Olaparib
- A lower incidence of treatment-related AEs was reported in patients receiving pembrolizumab plus olaparib compared to pembrolizumab plus chemotherapy

SABCS 2023 Abstract GS01-05.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEYLYNK-009 Clinical Trial

Maintenance pembrolizumab plus olaparib provides a chemotherapy-free option with similar efficacy and a more favorable safety profile for patients with metastatic triple negative breast cancer

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer	HR+ Breast Cancer	HER2+ Breast Cancer
• ALEXANDRA/Impassion030 • KEYLYNK-009 • DESTINY-Breast08 • DEBBRAH	• PROSPECT • NRG Oncology/NSABP B-51/RTOG 1304 • IDEA • ADAPTcycle • INAVO120	• KATHERINE • HER2CLIMB-02 • Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

DESTINY-Breast08 Clinical Trial

Does trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant provide benefit for patients with HER2-low HR+ advanced or metastatic breast cancer?

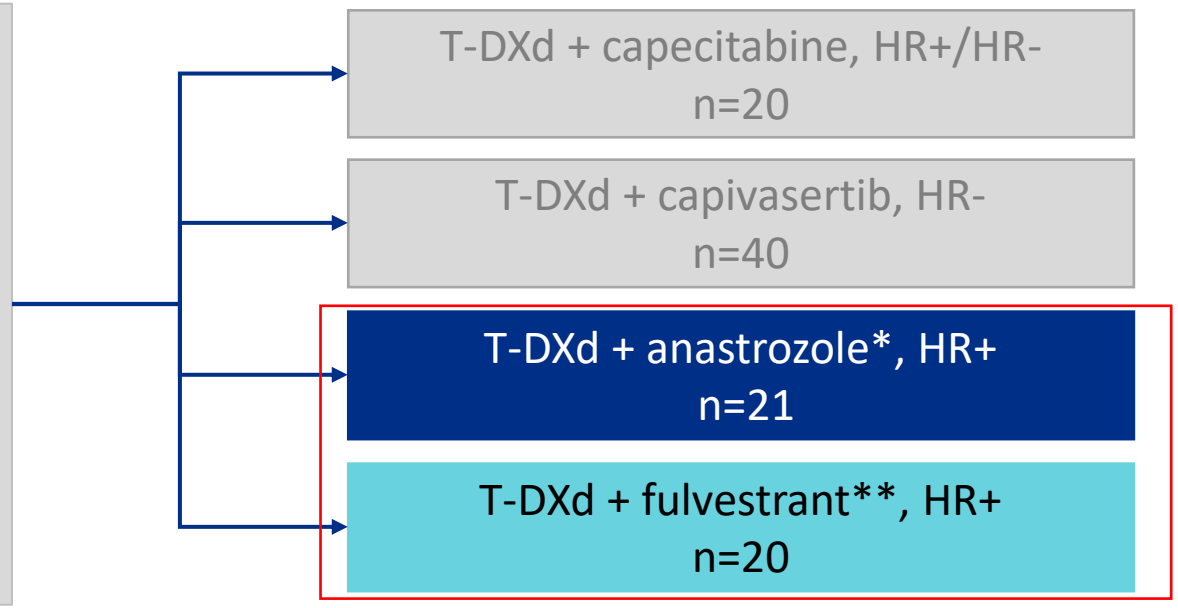
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DESTINY-Breast08 Clinical Trial

Study Design: Open-label, multicenter, dose-expansion, Phase Ib trial

- Locally assessed HER2-low (IHC 2+/ISH- HR+ advanced/mBC
- ≤ 1 prior treatment line of ET ± a targeted therapy (such as CDK4/6i, mTOR, or PI3K inhibitors) for metastatic BC allowed
- No prior chemotherapy in the metastatic setting allowed
- At least one measurable lesion per RECIST1.1
- ECOG PS 0-1



*T-DXd 5.4 mg/kg IV Q3W + anastrozole 1 mg daily
**T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg IM Q4W, with a 500 mg loading dose on Cycle 1, Day 15*

Primary End Point: Safety and tolerability, including AEs, AESIs, and SAEs
Secondary Endpoints: ORR, PFS, DOR (all evaluated by investigator per RECIST 1.1), and OS

SABCS 2023 Abstract RF02-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DESTINY-Breast08 Clinical Trial

Baseline Characteristics

Characteristic, n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Median age, yr (range)	55.0 (29.0 – 75.0)	65.5 (31.0–73.0)
Female, n (%)	21 (100.0)	20 (100.0)
Race, n (%)		
• Asian	11 (52.4)	12 (60.0)
• White	10 (47.6)	7 (35.0)
• Black or African	0	1 (5.0)
HER2 status, n (%)		
• IHC1+	16 (76.2)	13 (65.0)
• IHC2+/ISH-	5 (23.8)	7 (35.0)
HR status, n (%)		
• ER+/PR+	14 (66.7)	10 (50.0)
• ER+/PR-	7 (33.3)	9 (45.0)
• ER+ and PR missing	0	1 (5.0)
ECOG PS, n (%)		
• 0	12 (57.1)	17 (85.0)
• 1	8 (38.1)	3 (15.0)
• 2	1 (4.8)	0

Characteristic, n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Received no prior line of treatment for mBC, n (%)	7 (33.3)	6 (30.0)
Received a prior line as first line for mBC, n (%)	14 (66.7)	14 (70.0)
Median duration of follow up, months (range)	20.2 (4.9–24.8)	15.2 (2.2–22.6)
Treatment ongoing	6 (28.6)	7 (35.0)
Patients who discontinued both Ips	15 (71.4)	13 (65.0)
Patients who discontinued T-DXd	15 (71.4)	16 (80.0)
• AE	4 (19.0)	6 (30.0)
• Patient decision	0 (0)	4 (20.0)
• Objective disease progression	8 (38.1)	5 (25.0)
• Subjective disease progression	3 (14.3)	2 (10.0)
Patients who discontinued ET	15 (71.4)	13 (65.0)

- As of August 16, 2023, 6 patients (28.6%) in the T-DXd + ANA arm and 7 patients (35.0%) in the T-DXd + FUL arm were ongoing study treatment
- Disease progression was the leading reason for treatment discontinuation in both arms

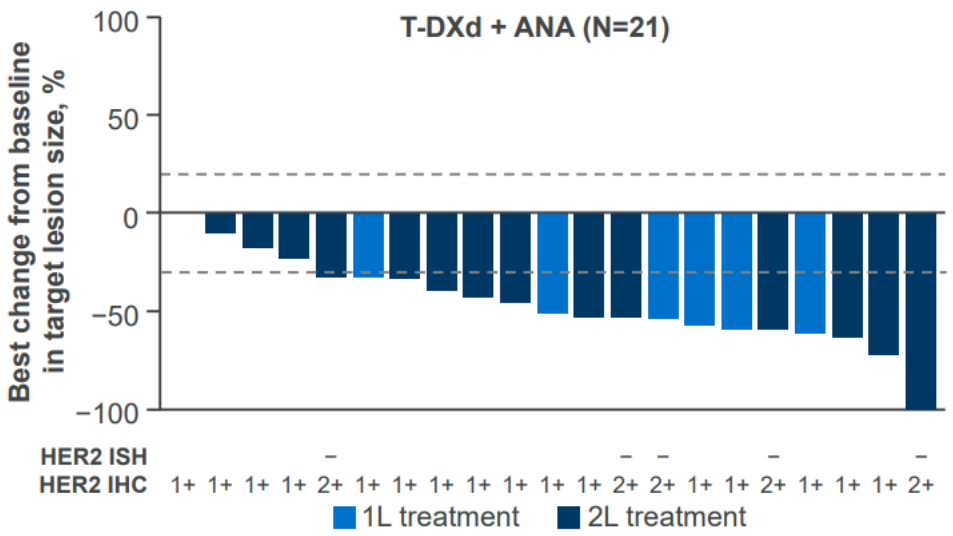
SABCS 2023 Abstract RF02-03.

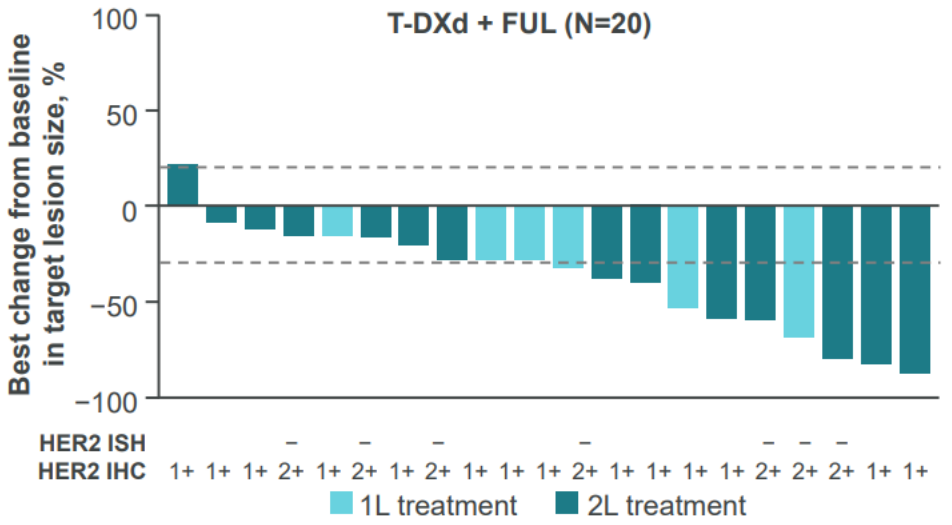
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DESTINY-Breast08 Clinical Trial

Efficacy





	T-DXd + ANA (N=21)
Confirmed ORR, % (95% CI)	**71.4** (47.8 - 88.7)
Unconfirmed ORR, % (95% CI)	76.2 (52.8 - 91.8)
Median DOR, months (95% CI)	**9.8** (6.7 - NE)
Total PFS events, n (%)	14 (66.7)
Median PFS, months (95% CI)	**13.4** (8.5 - 19.4)
• PFS rate at 6 months, % (95% CI)	80.7 (56.3 - 92.3)
• PFS rate at 12 months, % (95% CI)	50.4 (27.5 - 69.5)

	T-DXd + FUL (N=20)
Confirmed ORR, % (95% CI)	**40.0** (19.1 - 64.0)
Unconfirmed ORR, % (95% CI)	50.0 (27.2 - 72.8)
Median DOR, months (95% CI)	**NE** (4.1 - NE)
Total PFS events, n (%)	7 (35.0)
Median PFS, months (95% CI)	**NE** (5.6 - NE)
• PFS rate at 6 months, % (95% CI)	75.3 (46.4 - 90.0)
• PFS rate at 12 months, % (95% CI)	52.7 (25.0 - 74.4)

SABCS 2023 Abstract RF02-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DESTINY-Breast08 Clinical Trial

Safety

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Any AEs ≥ Grade 3	**10 (47.6)**	**11 (55.0)**
Any AEs ≥Grade 3 possibly related to either drug	7 (33.3)	10 (50.0)
AEs leading to dose interruptions of T-DXd	12 (57.1)	9 (45.0)
AEs leading to dose reduction of T-DXd	6 (28.6)	4 (20.0)
AEs leading to discontinuation of T-DXd	4 (19.0)	6 (30.0)
Any SAEs	4 (19.0)	4 (20.0)
AEs leading to death†	1 (4.8)	0
AESIs		
• Ejection fraction decreased‡	1 (4.8)	1 (5.0)
• Pneumonitis (adjudicated as ILD related to T-DXd), Grade	0	5 (25.0), all Grade 2

n (%)	T-DXd + ANA (N=21)	T-DXd + FUL (N=20)
Any Grade AEs	20 (95.2)	20 (100)
Any-grade AEs occurring in ≥30% of patients in either arm		
• Nausea	14 (66.7)	19 (95.0)
• Alopecia	9 (42.9)	10 (50.0)
• Fatigue	9 (42.9)	3 (15.0)
• Anemia	7 (33.3)	5 (25.0)
• COVID-19	7 (33.3)	5 (25.0)
• Decreased appetite	7 (33.3)	11 (55.0)
• Decreased weight	7 (33.3)	4 (20.0)
• Increased AST	7 (33.3)	4 (20.0)
• Neutropenia*	6 (28.6)	7 (35.0)
• Vomiting	6 (28.6)	7 (35.0)

- In the T-DXd + ANA arm, median actual treatment duration was 10.4 months (range 2.8–22.2) for T-DXd and 11.0 months (range 1.4–22.4) for ANA§
- In the T-DXd + FUL arm, median actual treatment duration was 6.3 months (range 1.4–21.9) for T-DXd and 8.3 months (range 1.8–22.5) for FUL§

*Grouped term including neutropenia and decreased neutrophil count events.
†Reported by investigator as related to disease and drug-induced pneumonitis; however, the ILD was not considered to be drug-induced by adjudication.
‡Both cases Grade 2 and resolved at DCO. §Total treatment duration, excluding drug interruptions and delays

SABCS 2023 Abstract RF02-03.

© 2024 Cornerstone Specialty Network. All rights reserved.

DESTINY-Breast08 Clinical Trial

T-DXd in combination with endocrine therapy may provide a beneficial additional option for patients with metastatic HER2-low breast cancer

Small data sets…more to come…

Awaiting results…T-DXd versus investigator's choice chemotherapy in HER2-low, HR+, metastatic breast cancer (DESTINY-Breast06)

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

DEBBRAH Clinical Trial

Does trastuzumab deruxtecan (T-DXd) provide benefit for patients with HER2+ or HER2-low advanced breast cancer and pathologically confirmed leptomeningeal carcinomatosis?

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DEBBRAH Clinical Trial

Study Design: multicohort, phase II trial

Cohort 5: international, open-label, single-arm, 5-cohort phase II trial

Cohort 1: HER2+ MBC with non-progressing brain mets after WBRT, SRS and surgery (N=8)

Cohort 2: HER2+ or HER2-low MBC with asymptomatic untreated brain mets (N=10)

Cohort 3: HER2+ MBC with progressing brain mets after WBRT, SRS and /or surgery (N=9)

Cohort 4: HER2-low MBC with progressing brain mets after WBRT, SRS and /or surgery (N=7)

Cohort 5

- Adults with HER2+/HER2-low MBC and LMC with positive CSF cytology findings
- If HER2+, prior taxane-based tx and ≥1 prior line of HER2-targeted tx for metastatic disease
- If HR-/HER2 low, ≥1 prior CT for metastatic disease
- If HR+/HER2 low, 1 prior line of ET and ≥1 prior CT for metastatic disease
- ECOG PS 0-2

(N = 7)

→ **Trastuzumab deruxtecan** 5.4 mg/kg IV on Day1 Q3W

Until PD, unacceptable toxicity, or withdrawal of consent

Primary endpoint, Cohort 5: OS
Secondary endpoints, **Cohort 5**: PFS, ORR, CBR, TTR, DoR, best percentage change in tumor burden, safety
Exploratory endpoints, Cohort 5: PROs; biomarkers in plasma, tissue, and/or CSF

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DEBBRAH Clinical Trial

Baseline Characteristics

Characteristic, n (%)	Cohort 5 (N = 7)
Median age, yr (range)	57 (42-69)
ECOG PS, n (%)	
• 0	3 (42.9)
• 1	2 (28.6)
• 2	2 (28.6)
Measurable systemic disease at BL, n (%)	n = 4
• Intracranial	1 (14.3)
• Extracranial	3 (42.9)
No. metastatic organ sites other than LMC, n (%)	
• <3	6 (85.7)
• ≥3	1 (14.3)
HER2 status, n (%)	
• Positive	3 (42.9)
• Low	4 (57.1)

Characteristic	Cohort 5 (N = 7)
HR status, n (%)	
• ER+ and/or PgR+	5 (71.4)
• ER- and PgR-	2 (28.6)
Median no. prior LoT for advanced disease (range)	4 (1-8)
Median duration of last prior tx, mo (range)	1.9 (0.7-15)
Prior systemic cancer tx, n (%)	
• Anti-HER2	3 (42.9)
• Chemotherapy	7 (100)
• Endocrine therapy	3 (42.9)

- No patient had received prior WBRT, SRS/SRT, or surgery for CNS disease
- All patients enrolled from Spanish sites

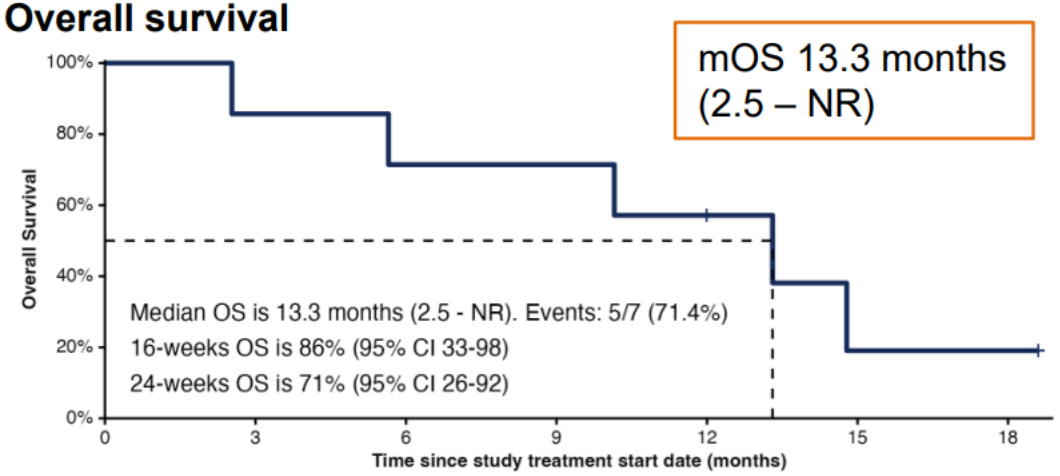
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

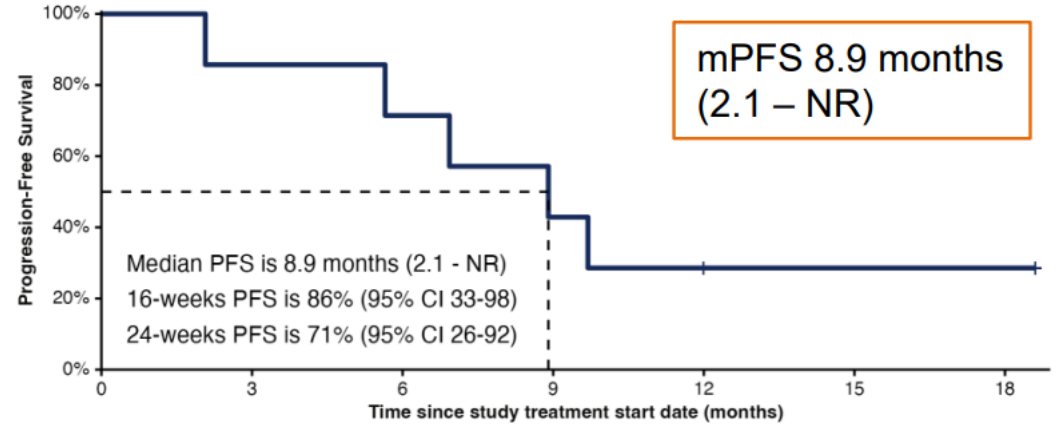
DEBBRAH Clinical Trial

Efficacy

Overall survival



PFS according to RANO-BM and RECIST v1.1



Outcome	Cohort 5 (N = 7)
OS (primary endpoint)	
Median OS, mo (95% CI)	**13.3** (2.5-NR; P <.001)
16-wk OS rate, % (95% CI)	86 (33-98)
24-wk OS rate, % (95% CI)	71 (26-92)
OS events, n/N (%)	5/7 (71.4)

PFS per RANO-BM and RECIST v1.1	
Median PFS, mo (95% CI)	**8.9** (2.1-NR)
16-wk PFS rate, % (95% CI)	86 (33-98)
24-wk PFS rate, % (95% CI)	71 (26-92)
PFS events, n/N (%)	5/7 (71.4)

SABCS 2023 Abstract PS11-05

© 2024 Cornerstone Specialty Network. All rights reserved.

DEBBRAH Clinical Trial

Efficacy: ORR and CBR

Outcome	Intracranial	Extracranial	All Lesions
Best overall response, n (%)	N = 7	N = 7	N = 7
• CR	1 (14.3)	0	0
• SD ≥24 wk	1 (14.3)	2 (28.6)	2 (28.6)
• SD <24 wk	0	0	0
• Non-CR/non-PD ≥24 wk	2 (28.6)	3 (42.9)	3 (42.9)
• Non-CR/non-PD <24 wk	1 (14.3)	0	1 (14.3)
• PD	0	1 (14.3)	1 (14.3)
• NE	2 (28.6)	1 (14.3)	0
ORR, n/N (%)	1/5 (20)	0/6 (0)	0/7 (0)
CBR, n/N (%)	4/5 (80)	5/6 (83.3)	5/7 (71.4)

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

DEBBRAH Clinical Trial

Safety

Related TEAEs in ≥15% of Patients, n (%)	Cohort 5, Patients (N = 7)	
	Any Grade	Grade 3
Any	7 (100)	3 (42.9)
Hematologic	4 (57.1)	1 (14.3)
• Anemia	3 (42.9)	0
• Thrombocytopenia	2 (28.6)	1 (14.3)
Nonhematologic	7 (100)	3 (42.9)
• Nausea	4 (57.1)	1 (14.3)
• Headache	3 (42.9)	0
• Fatigue	3 (42.9)	0
• Urinary tract infection	3 (42.9)	0
• Vomiting	3 (42.9)	0
• g-glutamyltransferase	2 (28.6)	1 (14.3)
• Constipation	2 (28.6)	0
• Diplopia	2 (28.6)	0
• Dizziness	2 (28.6)	0

No new safety signals identified:

- No cases of ILD/pneumonitis nor treatment related deaths were reported.

Serious unrelated TEAEs occurred in 4 (57.1%) of 7 patients, and 1 patient experienced a related serious TEAE (nausea, Grade 3)

© 2024 Cornerstone Specialty Network. All rights reserved.

DEBBRAH Clinical Trial

T-DXd shows promising activity in HER2+ and HER2-low patients with previously untreated, pathologically confirmed LMC

Small data set…more to come…

© 2024 Cornerstone Specialty Network. All rights reserved.

Managing Triple Negative Breast Cancer in Community Oncology

© 2024 Cornerstone Specialty Network. All rights reserved.

Guidelines for HER2-negative: preoperative/adjuvant

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g,1] ▸ Paclitaxel + carboplatin (various schedules) ▸ Docetaxel + carboplatin[g,1] (preoperative setting only)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

ALEXANDRA/Impassion030 has no impact on current standards of care

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

Guidelines for metastatic TNBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

Managing HR+, HER2-Low Breast Cancer in Community Oncology

© 2024 Cornerstone Specialty Network. All rights reserved.

Guidelines for metastatic HER2-Low

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

COMPARISON

DESTINY-Breast04 vs TROPiCS-02: Cross-study comparisons

HR+/ HER2-	DESTINY-Breast04		TROPiCS-02	
NCCN guideline or FDA approval in HR+ HER2- mBC	*Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy*		*Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease Preferred treatment option*	
Study Design	**T-DXd vs TPC**		**Sacituzumab Govitecan vs TPC**	
Inclusion Criteria	• HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable or metastatic BC • ≥1 ET if HR+ • **1-2 lines of chemotherapy** in the metastatic setting or recurrence ≤6 mo after adjuvant CT • Treated, stable brain metastases eligible		• Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression • At least 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)	
N of HR+ pts	331	163	272	271
Median PFS, months	**10.1**	5.4	**5.5**	4.0
	HR **0.51** (0.40-0.64) *P* < 0.0001		HR **0.66** (0.53-0.83) *P* = 0.0003	
Median OS, months	**23.9**	17.5	**14.4**	11.2
	HR **0.64** (0.48-0.86) *P* = 0.0028		HR **0.79** (0.65-0.96) *P* =0.02	
ORR, %	**52.9**	16.6	**21**	14
Median DoR, months	**10.7**	6.8	**8.1**	5.6

https://www.enhertuhcp.com/en/her2-low-breast

TRODELVY® (sacituzumab govitecan-hziy) | Official HCP Site (trodelvyhcp.com)

© 2024 Cornerstone Specialty Network. All rights reserved.

Sequencing of ADCs in HR+/HER2-low?

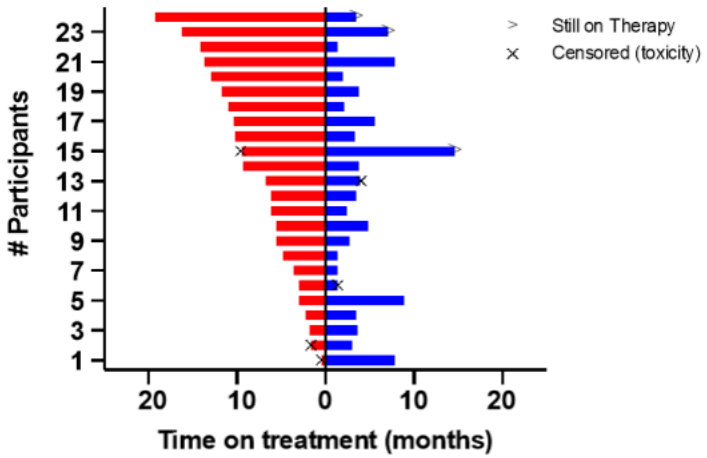
Multicenter, retrospective cohort study of the sequential use of the antibody drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

HR+/HER2-Low Efficacy Data (n=56)

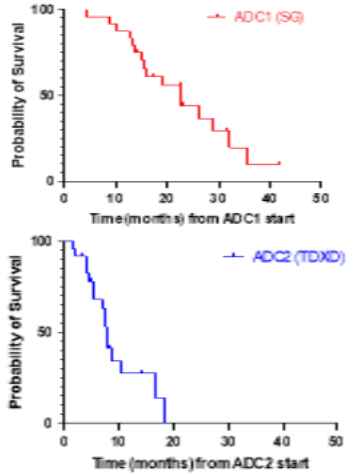
SG → T-DXd (n=24, 42.9%)

Intervening therapies between ADCs: 47.8%

rwPFS



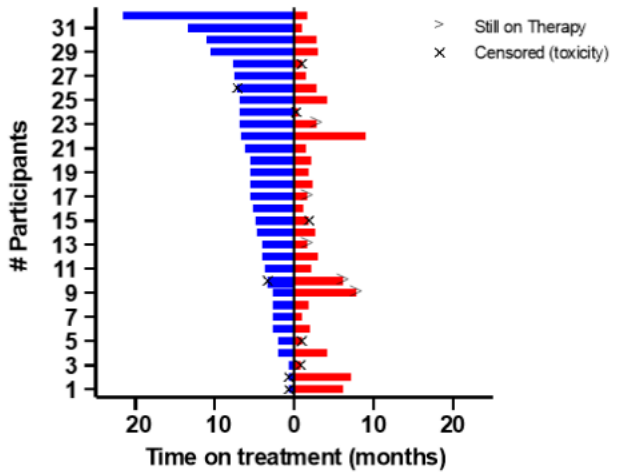
rwOS



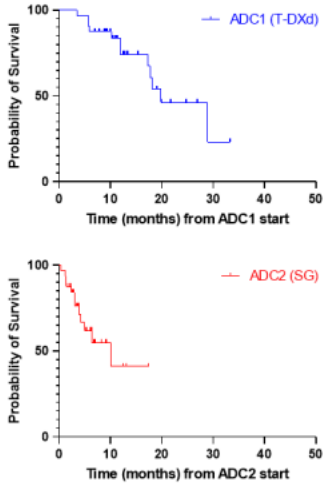
T-DXd → SG (n=32, 57.1%)

Intervening therapies between ADCs: 42.4%

rwPFS



rwOS



Regardless of ADC sequence, benefit observed with consistent toxicity profiles
Small study, more to come…

SABCS 2023 Abstract PS08-04

© 2024 Cornerstone Specialty Network. All rights reserved.

TROPION-Breast01

Study Design: Randomized, phase 3, open-label, global study

- HR-positive/HER2-negative BC[a] (HER2-negative defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1-2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

Randomization stratified by:
- *Lines of chemotherapy in unresectable/metastatic setting (1 vs 2)*
- *Geographic location (US/Canada/Europe vs ROW)*
- *Previous CDK4/6 inhibitor (yes vs no)*

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions[b]
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1-14 Q3W)
(n=367)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

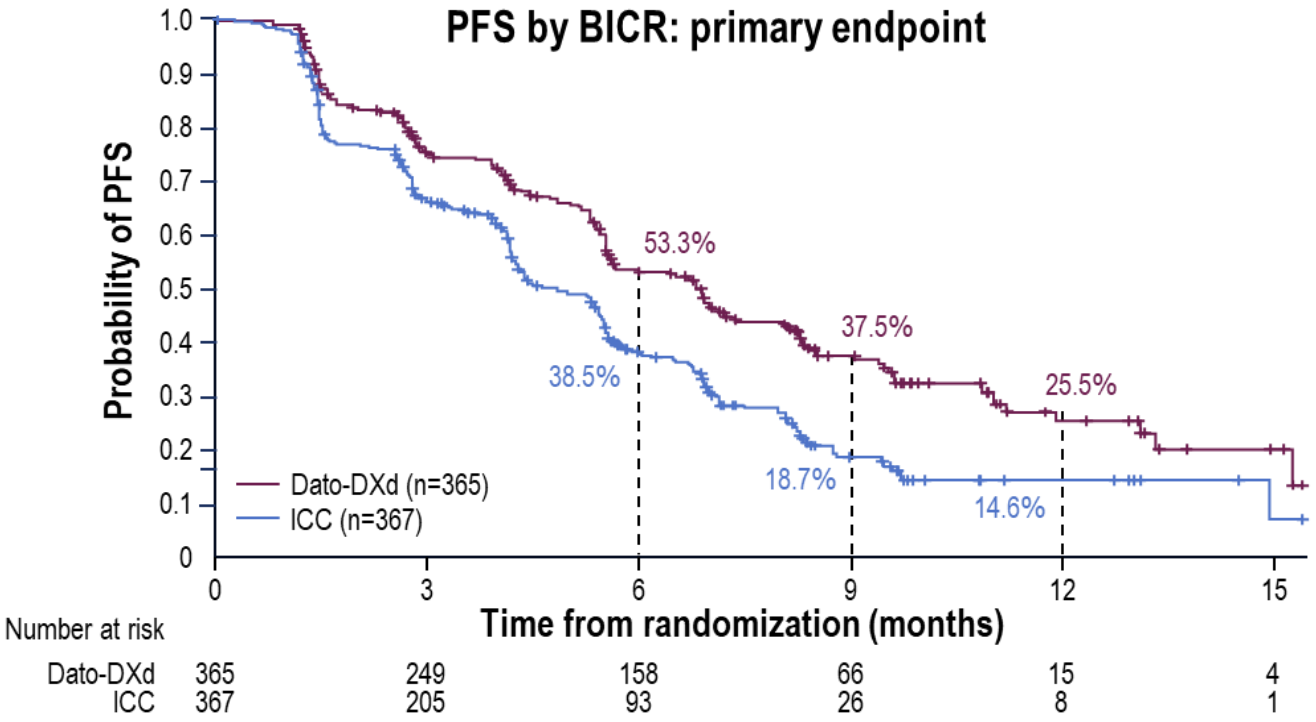
Endpoints:
- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

[a]Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines;
[b]ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W.

© 2024 Cornerstone Specialty Network. All rights reserved.

TROPION-Breast01

Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	**6.9** (5.7-7.4)	**4.9** (4.2-5.5)
Hazard ratio (95% CI)	**0.63 (0.52-0.76)**	
P value	<0.0001	

PFS by investigator assessment:

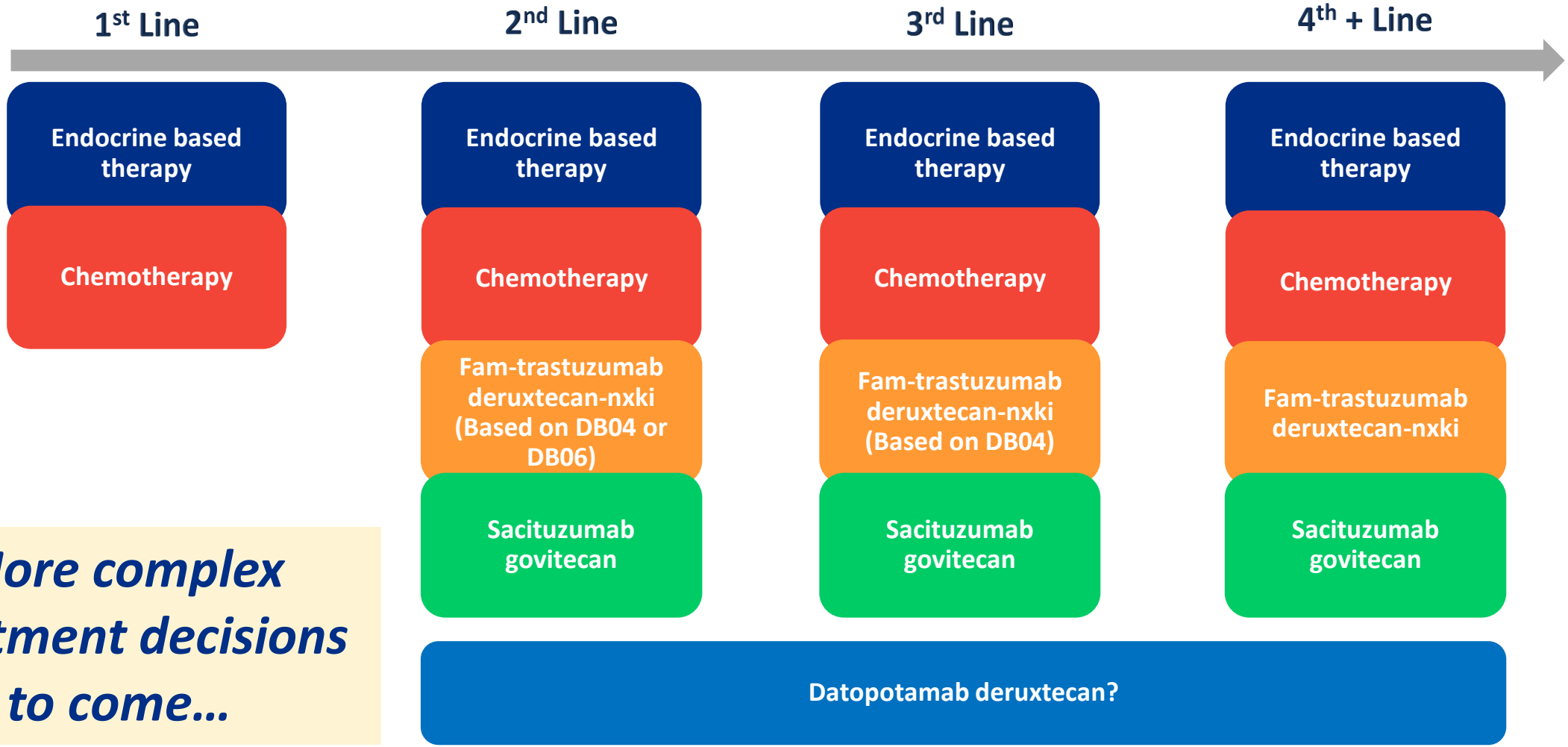
- Median 6.9 vs 4.5 months
- Hazard ratio **0.64** (95% CI, 0.53-0.76)

- OS data immature

ICC = investigator choice of single agent chemo

© 2024 Cornerstone Specialty Network. All rights reserved.

Future ADC treatment considerations HR+, HER2-low



More complex treatment decisions to come…

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009

- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

PROSPECT Clinical Trial

Does de-escalation of treatment by omission of radiotherapy benefit patients with early breast cancer?

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

PROSPECT Clinical Trial

Study Design: Cross-sectional, retrospective study, single site

- Prospective two-arm, non-randomized cohort study used MRI and pathology features to determine potential suitability for omission of RT
- Between May 17, 2011, and May 6, 2019, 443 patients with breast cancer underwent MRI
- Breast MRI in patients with apparently unifocal cT1N0 non-TNBC identified occult malignancy in 51/443 (11%)
- Those without high background enhancement on MRI and unifocal pT1N0 cancer were treated without RT
- Median time since diagnosis was 4.4 years

N=400

Group A
N=125
Underwent MRI
Omitted RT

Group B
N=102
Underwent MRI
Received RT

Group C
N=173
No MRI
Received RT

- Local recurrence rate when the 100th patient reached 5 years follow up was 1%
- There was a single distant recurrence in the entire cohort

Measures: Fear of Cancer Recurrence Inventory-SF (FCRI-SF); higher scores indicate more FCR (range 0-36)
HRQoL; breast cancer treatment outcomes scale (BCTOS); EORTC QLQ C30; EORTC BR23

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

PROSPECT Clinical Trial

Baseline Characteristics

Characteristics	Group A MRI, no RT	Group B MRI, RT	Group C No MRI, RT
Age, years (range)	66 (51-83)	65 (51-83)	63 (51-84)
Tumor size, mm (range)	**10** (3-20)	**13** (4-30)	**14** (1-30)
Months since diagnosis (range)	49 (14-109)	51 (13-118)	56 (12-120)
Neuroticism	22	23	23
Tertiary educated, n (%)	33 (26)	28 (28)	57 (33)
Partnered, n (%)	84 (67.2)	74 (72.5)	116 (67.1)

N (%)	Group A MRI, no RT	Group B MRI, RT	Group C No MRI, RT
Tumor Stage			
• T1a or T1b	73 (58.4)	31 (30.4)	53 (30.6)
• T1c	52 (41.6)	60 (58.8)	82 (47.4)
• T2	0 (0)	11 (10.8)	38 (22)
Nodal Stage			
• pN0	125 (100)	81 (79.4)	151 (87.3)
• pN1mi	0 (0)	8 (7.8)	9 (5.2)
• pN1	0 (0)	13 (12.7)	13 (7.5)
Tumor Grade			
• 1	62 (49.6)	30 (29.4)	39 (22.5)
• 2	56 (44.8)	56 (54.9)	93 (53.8)
• 3	7 (5.6)	16 (15.7)	37 (21.4)
• Not specified	0 (0)	0 (0)	4 (2.3)
Endocrine therapy	125 (100)	98 (96.1)	158 (91.3)

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

PROSPECT Clinical Trial

Quantitative Findings

	Group A MRI, no RT	Group B MRI, RT	Group C No MRI, RT	A-B-C P-value	A-BC, Mean (SD); p-value
Tumor size, mm (range)	**10** (3-20)	**13** (4-30)	**14** (1-30)	<0.001	
EORTC BR23, mean (SD)					
• Body image	89.73 (15.16)	85.62 (21.72)	84.15 (20.93)	0.049	84.70 (21.20); 0.007
• Breast symptoms	4.98 (9.72)	11.00 (13.13)	11.30 (16.18)	<0.001	11.19 (15.10); <0.001
• Arm symptoms	5.33 (11.16)	12.31 (17.68)	10.79 (17.99)	0.002	11.35 (17.86); <0.001
BCTOS, Median (IQR)					
• Cosmetic	1.38 (1.13-1.63)	1.63 (1.38-2.00)	1.75 (1.38-2.25)	<0.001	1.75 (1.38-2.25); <0.001
• Functions	1.00 (1.00-1.29)	1.00 (1.00-1.43)	1.00 (1.00-1.57)	0.011	1.00 (1.00-1.43); 0.003
• Breast Specific Pain	1.00 (1.00-1.67)	1.67 (1.00-2.33)	1.67 (1.00-2.00)	<0.001	1.67 (1.00-2.33); <0.001
• Sensation	1.00 (1.00-2.00)	2.00 (1.00-2.00)	2.00 (1.00-2.00)	<0.001	2.00 (1.00-2.00); <0.001
FCR, Median (IQR)					
• FCRI-SF	**11.00** (7.00-15.00)	**14.50** (9.75-18.00)	**14.00** (9.00-19.00)	**0.001**	**14.00** (9.00-18.00); <0.001
• Normal FCR <13, n (%)	77 (62)	36 (35)	69 (40)		
• Sub clinical FCR 13-21, n (%)	41 (33)	56 (55)	77 (45)		
• Clinical FCR ≥22, n (%)	7 (6)	10 (10)	27 (16)		
Decision regret, n (%)					
• Right decision to have MRI	**122 (97.60)**	94 (92.16)			
• Right decision to omit RT	**117 (93.6)**				

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

PROSPECT Clinical Trial

Breast cancer events at primary analysis when 100th patient reached 5 years of follow-up
Ipsilateral invasive recurrence rate (IIRR)

	Index cancer pathology	Radiotherapy given for index cancer	Timing of event	Subsequent event location	Subsequent event management	5-year IIRR (upper 95% CI, two-sided)*
Event 1	12 mm; grade 2; ER-positive, HER2-negative	No	4·5 years	Ipsilateral invasive	BCS, radiotherapy, systemic therapy	1·0% (5·4%)
Event 2	18 mm; grade 1; ER-positive, HER2-negative	No	7·5 years	Ipsilateral invasive	Total mastectomy and SNB, systemic therapy	NA
Event 3	20 mm; grade 2; ER-positive, HER2-positive	No	4·6 years	Ipsilateral regional	Axillary clearance, radiotherapy, systemic therapy	NA
Event 4	16 mm; grade 1; ER-positive, HER2-negative	No	5·0 years	Regional and distant	Systemic therapy	NA
Event 5	11 mm; grade 1; ER-positive, HER2-negative	No	4·5 years	Contralateral invasive	BCS and SNB, systemic therapy	NA
Event 6	7 mm; grade 2; ER-positive, HER2-negative	No	1·8 years	Contralateral DCIS	BCS and SNB	NA

Mann et al., TheLancet Published online Dec 5 2023; https://doi.org/10.1016/S0140-6736(23)02476-5

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

PROSPECT Clinical Trial

- Study time frame from 2011 to 2019
- Breast MRI identified additional cancers or areas of pre-cancer in 11% of the 443 patients
- After a median of 5 years follow up, the breast cancer local recurrence rate for the 201 patients treated on study without radiotherapy was a very low at 1%
    - Additionally, the recurrence rate of the entire cohort was very low
        - Only one patient experienced cancer recurrence around the body leading to a breast cancer-related death
        - Lower than would be expected in patients with this stage and type of breast cancer, suggesting that finding and treating the additional areas of cancer was important in preventing cancer recurrence

Mann et al, Primary results of ANZ 1002 : Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial (PROSPECT) following pre-operative breast MRI, a prospective two-arm cohort study. The Lancet; Published online Dec 5 2023; https://doi.org/10.1016/S0140-6736(23)02476-5

© 2024 Cornerstone Specialty Network. All rights reserved.

PROSPECT Clinical Trial

Omission of RT did not lead to increased fear of recurrence, resulted in a superior HRQoL and low recurrence rates, and should be factored into treatment decisions

MRI prior to breast surgery may identify some patients who can safely avoid radiotherapy as well as identify patients with additional areas of cancer for treatment

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009

- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Does loco-regional irradiation at presentation with biopsy-proven axillary node involvement provide benefit to patients who become pathologically node-negative after neoadjuvant chemotherapy?

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Study Design: Randomized, open-label phase III trial

Stratified by type of surgery (mastectomy vs lumpectomy), HR status (+/-), HER2 status (+/-), adjuvant chemotherapy (Y/N), and breast pCR status (Y/N)

- Patients with clinical T1-3, N1, M0 breast cancer
- Axillary LN+ by FNA or core needle biopsy
- Completed ≥8 wk of neoadjuvant chemotherapy (+ anti-HER2 therapy if HER2+)
- ypN0 by SLNB (≥2 nodes excised), ALND, or both after neoadjuvant chemotherapy
- Mastectomy or lumpectomy

(N = 1641)

R
1:1

No regional nodal irradiation (n = 821)
Breast radiation if breast-conserving surgery
No chest wall radiation if mastectomy

Regional nodal irradiation (n = 820)
Breast radiation if breast-conserving surgery
Chest wall radiation if mastectomy

Primary endpoint: IBCRFI (time from randomization to invasive local, regional, or distant recurrence, or death from breast cancer)

Secondary endpoints: LRRFI (locoregional recurrence without distant recurrence within 2 mo), DRFI, DFS, OS, toxicity

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Baseline Characteristics

Characteristic	No RNI (n = 821)	RNI (n = 820)
Median age, yr (range)	52	52
Age, %		
• ≤49 yr	40	41
• 50-59 yr	32	33
• ≥60 yr	28	26
Race, %		
• White	69	69
• Black	17	18
• Asian	8	6
• Unknown/other	6	6
Ethnicity, %		
• Not Hispanic/Latino/a	83	82
• Hispanic/Latino/a	14	14
• Other	3	3
Clinical tumor size, %		
• T1	21	21
• T2	59	61
• T3	20	18

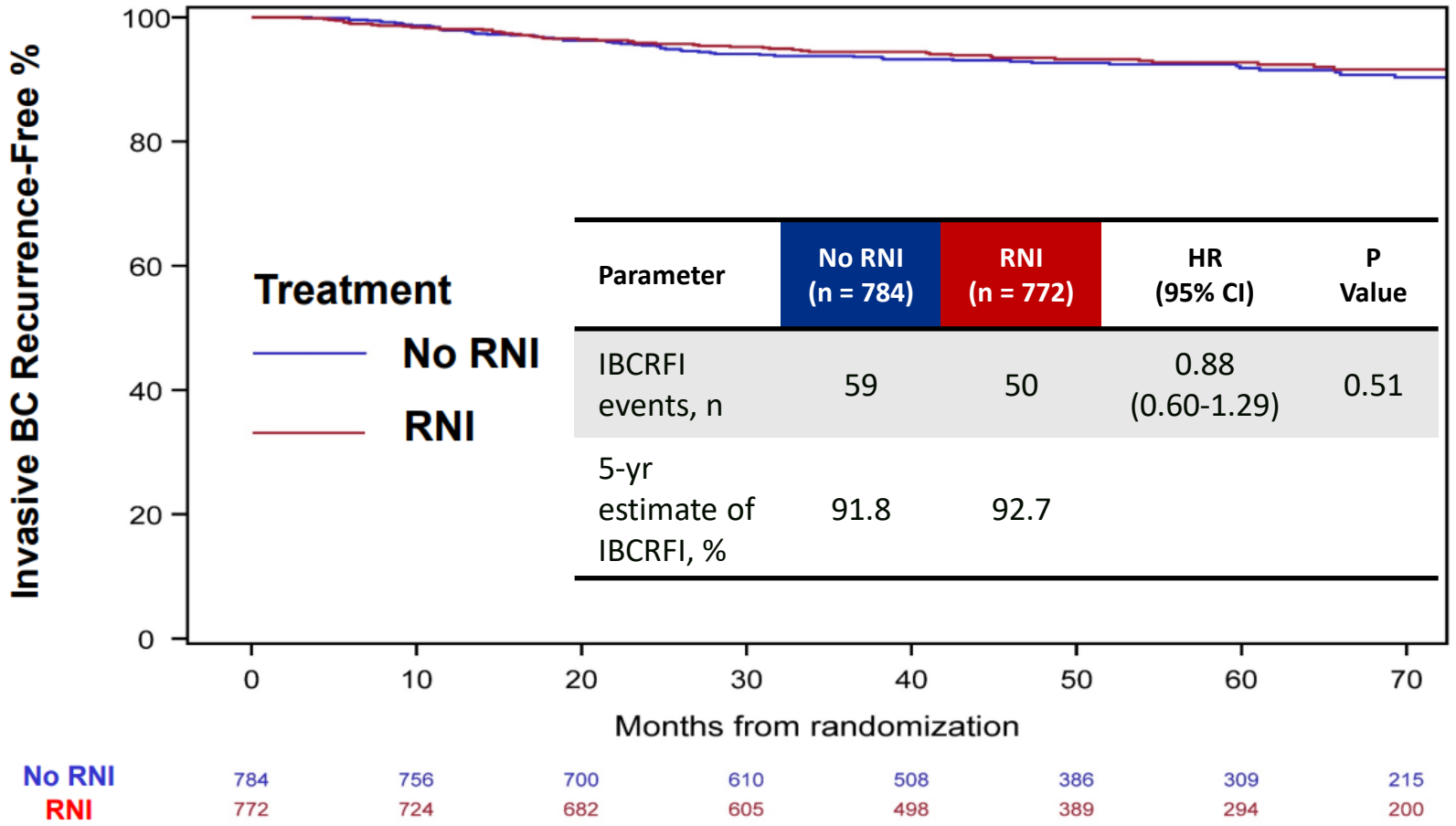
Characteristic, %	No RNI (n = 821)	RNI (n = 820)
Tumor subtype		
• TNBC	21	23
• ER+ and/or PgR+/HER2-	22	20
• ER- and PgR-/HER2+	25	24
• ER+ and/or PgR+/HER2+	31	33
Breast surgery		
• Lumpectomy	58	58
• Mastectomy	42	42
Axillary surgery		
• SLNB	55	56
• ALND (± SLNB)	45	44
pCR in breast		
• No	22	21
• Yes	78	79
Adjuvant chemotherapy		
• No	100	99
• Yes	<1	1

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Primary Endpoint: invasive breast cancer recurrence-free interval (IBCRFI)



Parameter	No RNI (n = 784)	RNI (n = 772)	HR (95% CI)	P Value
IBCRFI events, n	59	50	0.88 (0.60-1.29)	0.51
5-yr estimate of IBCRFI, %	91.8	92.7		

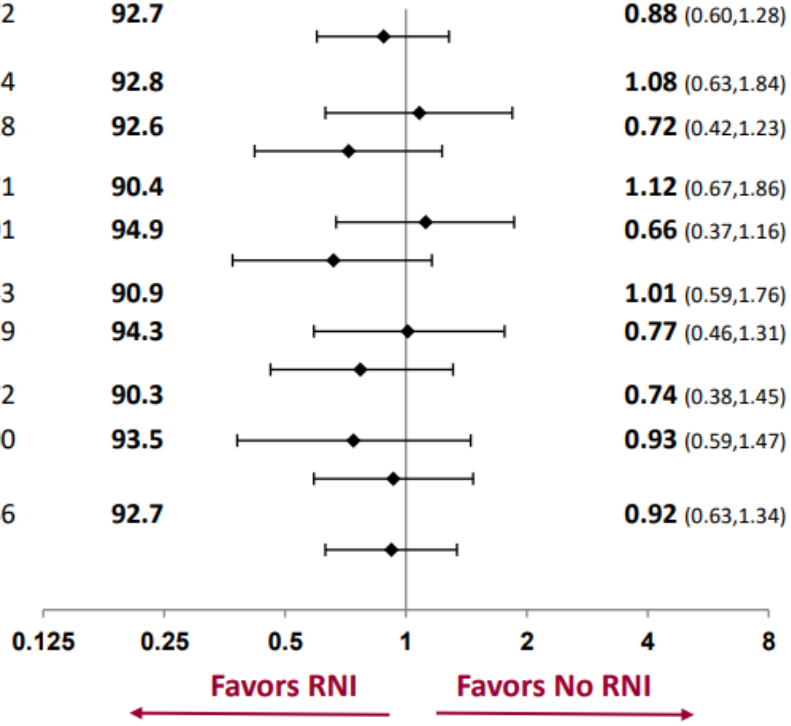
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Invasive breast cancer recurrence-free interval (IBCRFI) by Subgroups

		No RNI (n = 784)		RNI (n = 772)		HR (95% CI)	P Value
		(D/N)	5-y est (%)	(D/N)	5-y est (%)		
All patients		59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Surgery	Lumpectomy	26/454	**93.5**	28/454	**92.8**	**1.08** (0.63,1.84)	**0.28**
	Mastectomy	33/330	**89.5**	22/318	**92.6**	**0.72** (0.42,1.23)	
ER/PR	Negative	28/367	**91.7**	31/371	**90.4**	**1.12** (0.67,1.86)	**0.17**
	Positive	31/417	**92.1**	19/401	**94.9**	**0.66** (0.37,1.16)	
HER2	Negative	25/342	**92.6**	26/343	**90.9**	**1.01** (0.59,1.76)	**0.47**
	Positive	34/442	**91.3**	24/429	**94.3**	**0.77** (0.46,1.31)	
pCR breast	No	20/173	**87.8**	15/172	**90.3**	**0.74** (0.38,1.45)	**0.59**
	Yes	39/611	**93.0**	35/600	**93.5**	**0.93** (0.59,1.47)	
Adjuvant Chemotherapy	No	57/780	**92.1**	50/766	**92.7**	**0.92** (0.63,1.34)	
	Yes	2/4		0/6			



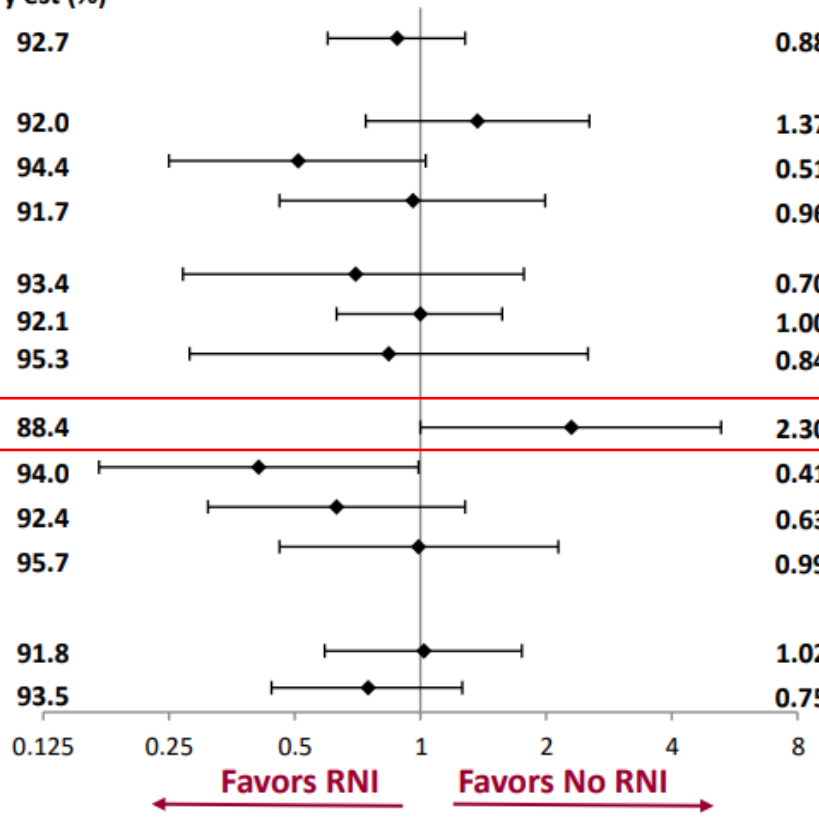
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Invasive breast cancer recurrence-free interval (IBCRFI) by Exploratory Subgroup Analysis

		No RNI (n = 784)		RNI (n = 772)		HR (95% CI)	P Value
		(D/N)	5-y est (%)	(D/N)	5-y est (%)		
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Age	<=49	18/311	**92.8**	24/312	**92.0**	**1.37** (0.74,2.54)	0.09
	50-59	25/257	**90.4**	12/254	**94.4**	**0.51** (0.25,1.03)	
	>= 60	16/216	**92.4**	14/206	**91.7**	**0.96** (0.46,1.99)	
Race	Black	11/135	**92.6**	8/140	**93.4**	**0.70** (0.27,1.77)	0.69
	White	40/543	**91.6**	36/533	**92.1**	**1.00** (0.63,1.57)	
	Other	8/106	**91.8**	6/99	**95.3**	**0.84** (0.28,2.52)	
	Triple-negative	8/169	**95.0**	19/188	**88.4**	**2.30** (1.00,5.25)	0.037
Tumor Subtype	ER/PR+/HER2-	17/173	**90.5**	7/155	**94.0**	**0.41** (0.17,0.99)	
	ER/PR-/HER2+	20/198	**88.8**	12/183	**92.4**	**0.63** (0.31,1.28)	
	ER/PR+/HER2+	14/244	**93.3**	12/246	**95.7**	**0.99** (0.46,2.14)	
Axillary Surgery	Axil +/- SLNB	27/357	**92.0**	25/338	**91.8**	**1.02**	
	SLNB alone	32/427	**91.5**	25/434	**93.5**	**0.75**	



© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Secondary Endpoints

Parameter	No RNI (n = 784)	RNI (n = 772)	HR (95% CI)	P Value
Isolated LRRFI events, %	11*	4†	0.37 (0.12-1.16)	0.088
• 5-yr estimate of LRRFI, %	98.4	99.3		
DRFI events, n	48	46	1.00 (0.67-1.51)	0.99
• 5-yr estimate of DRFI, %	93.4	93.4		
DFS events, n	83	85	1.06 (0.79-1.44)	0.69
• 5-yr estimate of DFS, %	88.5	88.3		

	(n = 802)	(n = 800)	HR (95% CI)	P Value
OS events, n	45	49	1.12 (0.75-1.68)	0.59
• 5-yr estimate of OS, %	94.0	93.6		

*2 local, 8 regional, and 1 locoregional. †All local.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Safety

AE, %	No RNI (n = 800)	RNI (n = 759)
Grade 0/1	58.0	37.2
Grade 2	35.4	52.3
Grade 3	6.5	10.0
Grade 4	0.1	0.5
Radiation Dermatitis: Grade 3	3.3	5.7

- No study-related deaths

SABCS 2023 Abstr GS02-07

© 2024 Cornerstone Specialty Network. All rights reserved.

NRG Oncology/NSABP B-51/RTOG 1304 Clinical Trial

Adjuvant regional nodal irradiation is not associated with 5-year benefit

Downstaging involved axillary nodes with neoadjuvant chemotherapy can optimize adjuvant radiotherapy use without adversely affecting oncologic outcomes

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

IDEA Clinical Trial

Does endocrine therapy without radiotherapy after breast-conserving surgery benefit postmenopausal patients aged 50-69 with genomically-selected favorable Stage 1 breast cancer?

Individualized Decisions for Endocrine therapy Alone
5-year outcomes

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

IDEA Clinical Trial

Study Design: Prospective multicenter cohort trial

First to use genomic assay and consider younger post-menopausal patients

- Postmenopausal women aged 50-69 years with unifocal breast cancer that was pT1 and pN0, on the basis of sentinel node evaluation or axillary dissection
- Surgical margins were required to be 2 mm or wider after BCS
- ER-positive, PR-positive, and HER2-negative
- Oncotype DX 21-gene recurrence score ≤18
- Zubrod performance status 0-2
- No previous radiotherapy to the breast region, bilateral disease or a previous personal history of breast cancer, have any previous malignancy other than non-melanoma skin cancer unless no evidence of disease for over 5 years, or be a known carrier of a mutation that predisposes toward breast cancer development including BRCA-1 and BRCA-2

→

- Single-arm trial of radiotherapy omission
- 5 years of endocrine therapy and 10 years of surveillance on study
- Primary end point was the rate of locoregional recurrence 5 years after breast conserving surgery (BCS)

200 patients enrolled over 3.3 years (June 2015-October 2018); 186 patients with clinical follow-up of at least 56 months

Primary analysis conducted 5 years after last patient enrolled completed surgery

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

IDEA Clinical Trial

Baseline Characteristics

Characteristic	
Age, years	
• Mean (SD)	62 (4.9)
• Median (IQR)	63 (58-66)
Age Group, N (%)	
• 50-59	60 (30)
• 60-69	140 (70)
Zubrod PS, N (%)	
• 0	175 (87.5)
• 1	25 (12.5)
MRI at the time of diagnosis, N (%)	66 (33)
Imaging evidence beyond primary site of tumor, N (%) No | Yes	188 (94) | 12 (6)
Histology	
• Ductal	169 (84.5)
• Lobular	20 (10)
• Mixed	4 (2)
• Mucinous	3 (1.5)
• Tubular	4 (2)

Characteristic	
Oncotype DX 21-gene assay recurrence score	
• Mean (SD)	**11.2 (4.8)**
• Median (IQR)	**12 (8-15)**
Tumor size, mm	
• Mean (SD)	10 (4.6)
• Median (IQR)	9 (7-13)
Nodal status, N (%)	
• Node-negative without ITCs	199 (99.5)
• ITCs, no cluster >0.2 mm	1 (0.5)
Tumor grade, N (%)	
• Grade 1	85 (42.5)
• Grade 2	109 (54.5)
• Grade 3	6 (3)
No lymphovascular invasion, N (%)	171 (85.5)
ER + | PR+ | HER2-	100% | 100% | 100%

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

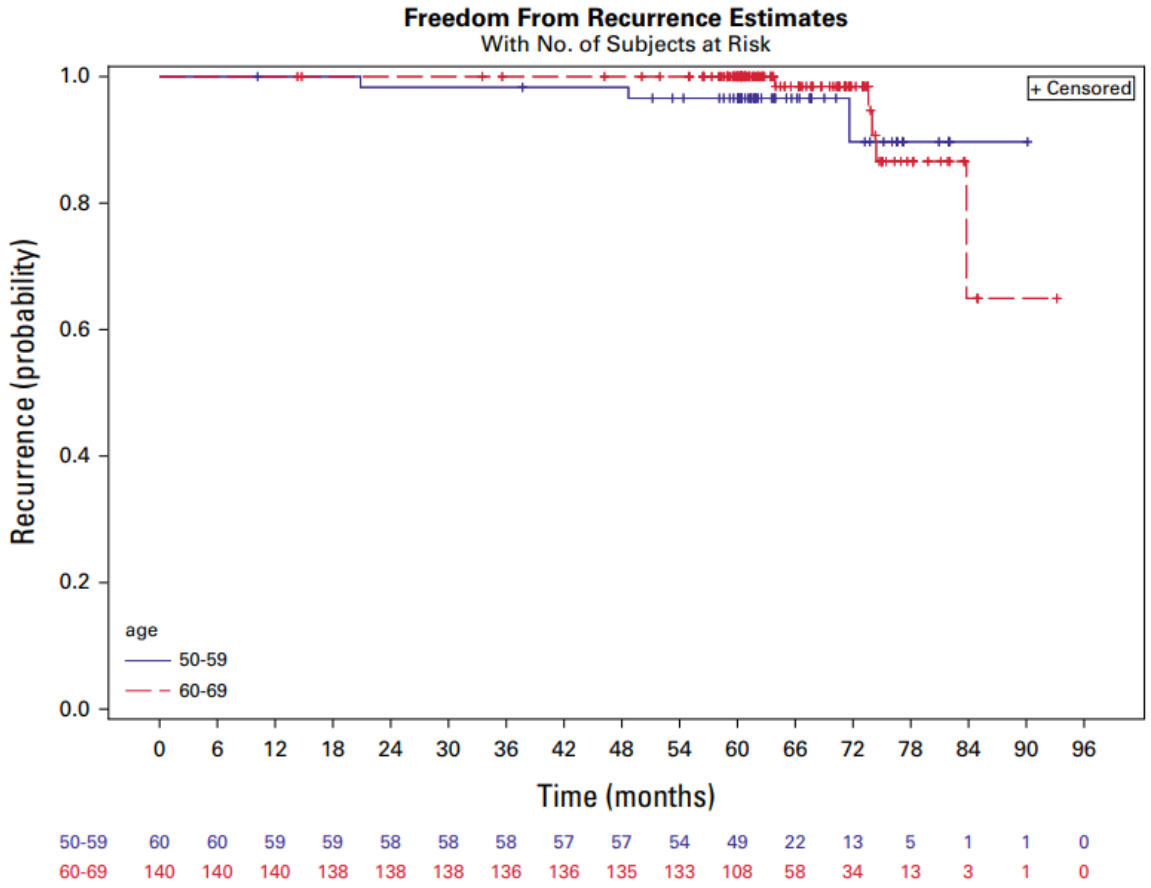
IDEA Clinical Trial

Results

Among the 186 patients with clinical follow-up of at least 56 months:

- **Overall and breast cancer-specific survival rates at 5 years were both 100%**
- **5-year freedom from any recurrence was 99% (95% CI, 96%- 100%)**
- Only 2 pts had recurrences before 5 years (isolated ipsilateral axillary recurrence at 21 months, IBE at 49 months)
- 6 additional pts recurred later than 5 years after BCS (5 IBEs, 1 IBE plus regional recurrence)
- No distant recurrences were observed
- Overall, 169 patients were compliant with endocrine therapy
  - Both patients who recurred before 5 years were compliant
  - 3/6 who recurred later than 5 years were compliant

Freedom from recurrence in relation to age cohort



Median follow up 5.2 years

© 2024 Cornerstone Specialty Network. All rights reserved.

IDEA Clinical Trial

Using a genomic assay in combination with clinical and biologic features for treatment selection (ET without RT) can result in very low risk of recurrence including for postmenopausal patients younger than 60 years

Risk-benefit of receiving RT should be considered in light of recent advances

More to come…NRG BR007: Randomized Trial Evaluating De-escalation of Breast Radiation (DeBRa)

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

ADAPTcycle Clinical Trial

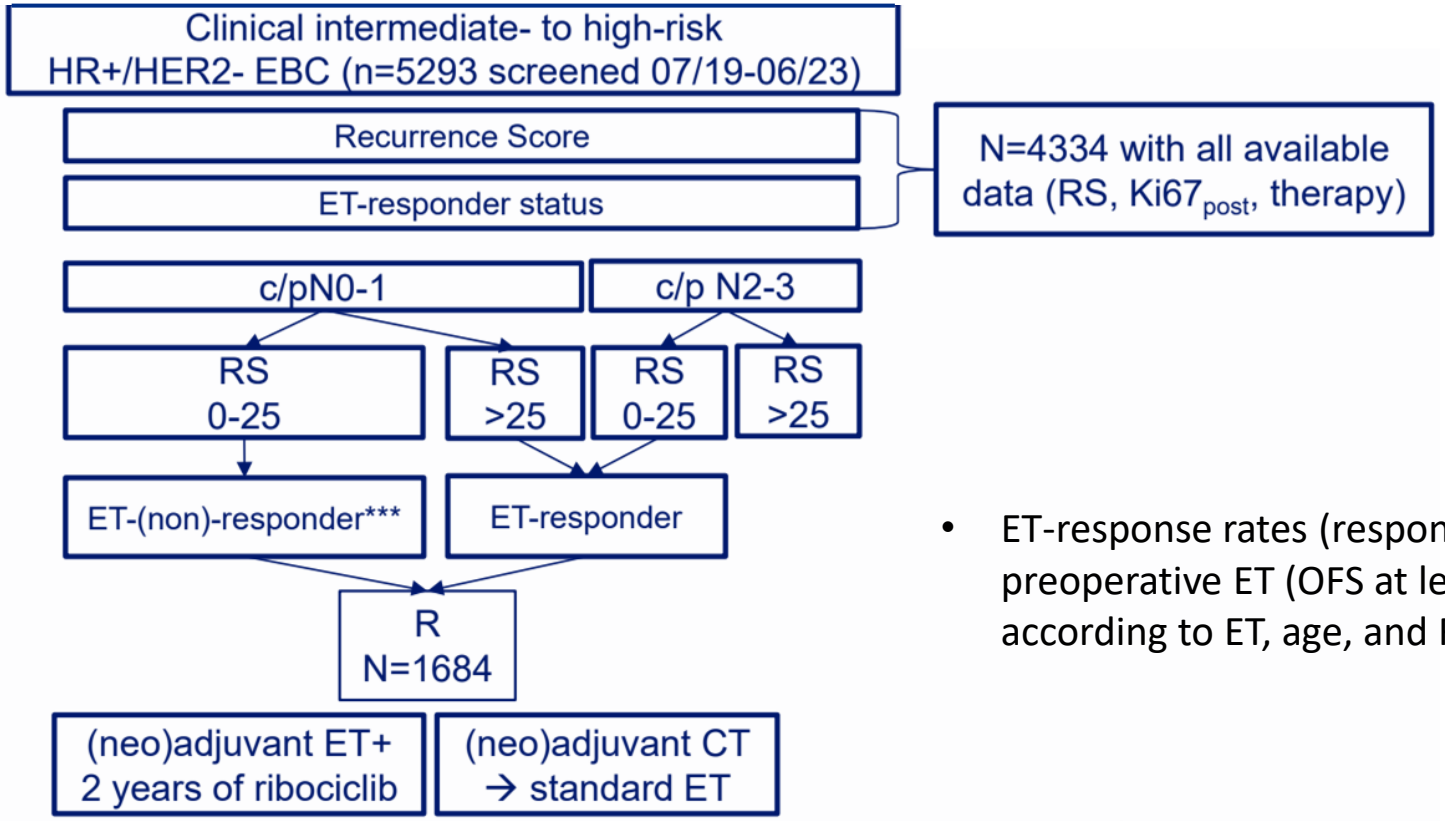
Does age and ovarian function suppression (OFS) impact endocrine response to short preoperative ET for patients with HR+/HER2- early breast cancer?

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ADAPTcycle Clinical Trial

Study Design: multicenter trial



- Central Ki67, ER, PR, HER2 assessment
  - Ki67: Consensus of semiquantitative (by 2 pathologists) and quantitative measurements, about 62% surgical samples

- ET-response rates (responder: Ki67post ≤ 10% after short 2-4-week preoperative ET (OFS at least 4 weeks)) analyzed in subgroups according to ET, age, and Recurrence Score (RS)

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ADAPTcycle Clinical Trial

Baseline Characteristics

	Overall n=4334	≤50 years and premenopausal n=1368	>50 years or postmenopausal n=2966
Median age (years, min/max)	56 (22-87)	45	61
Postmenopausal	2576 (59.4%)		2576 (86.9%)
Pre-ET: AI	2488 (57.4%)		2477 (83.5)
TAM	1162 (26.8%)	799 (58.4%)	363 (12.2%)
TAM+OFS	293 (6.8%)	**255 (18.6%)**	38 (1.2%)
AI+OFS	391 (9.1%)	**314 (22.9%)**	88 (3.0%)
ET-responders	1423 (63.0%)	**659 (48.2%)****	2155 (72.7%)
RS (median/min/max)	20 [0-80]	21.0 [0, 74]	20 [0-80]
-RS>25	1169 (32.8%)	374 (33.9%)	795 (32.3%)
c/pT2-4:	2336 (54.6%)	808 (59.2%)	1558 (52.6%)
c/pN+	1211 (28%)	378 (27.7%)	833 (28.2%)
G3	1759 (42.1%)	550 (42.0%)	1209 (42.2%)

	Overall n=4334	≤50 years and premenopausal n=1368	>50 years or postmenopausal n=2966
KI67*	25	25	25
ER by IHC*	100	100	100
PR by IHC*	90	90	90
HER2-low	3100 (74.5%)	956 (73%)	2144 (75.1%)
ER by RT-PCR* [min/max]	9.9 [3.7, 12.5]	9.2 [4.6, 11.9]**	10.3 [3.7, 12.5]
PR by RT-PCR* [min/max]	7.4 [3.2, 10]	7.6 [3.2, 10]	7.2 [3.2, 10]
HER2 by RT-PCR* [min/max]	9.4 [7.6, 13]	9.4 [7.6, 13]	9.4 [7.6, 11.5]

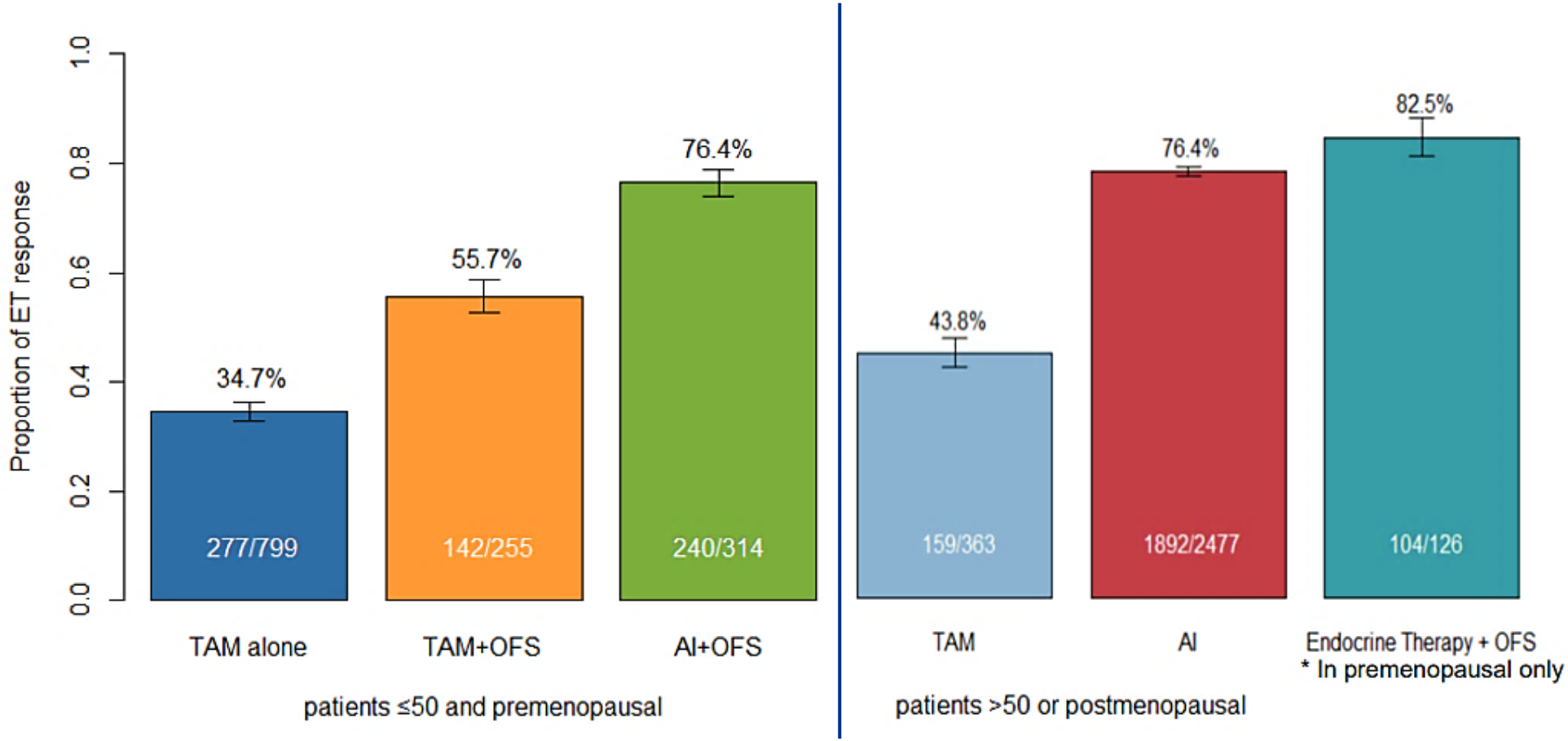
*median, **significant

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ADAPTcycle Clinical Trial

ET-response (Ki67 post ≤10%) - all patients



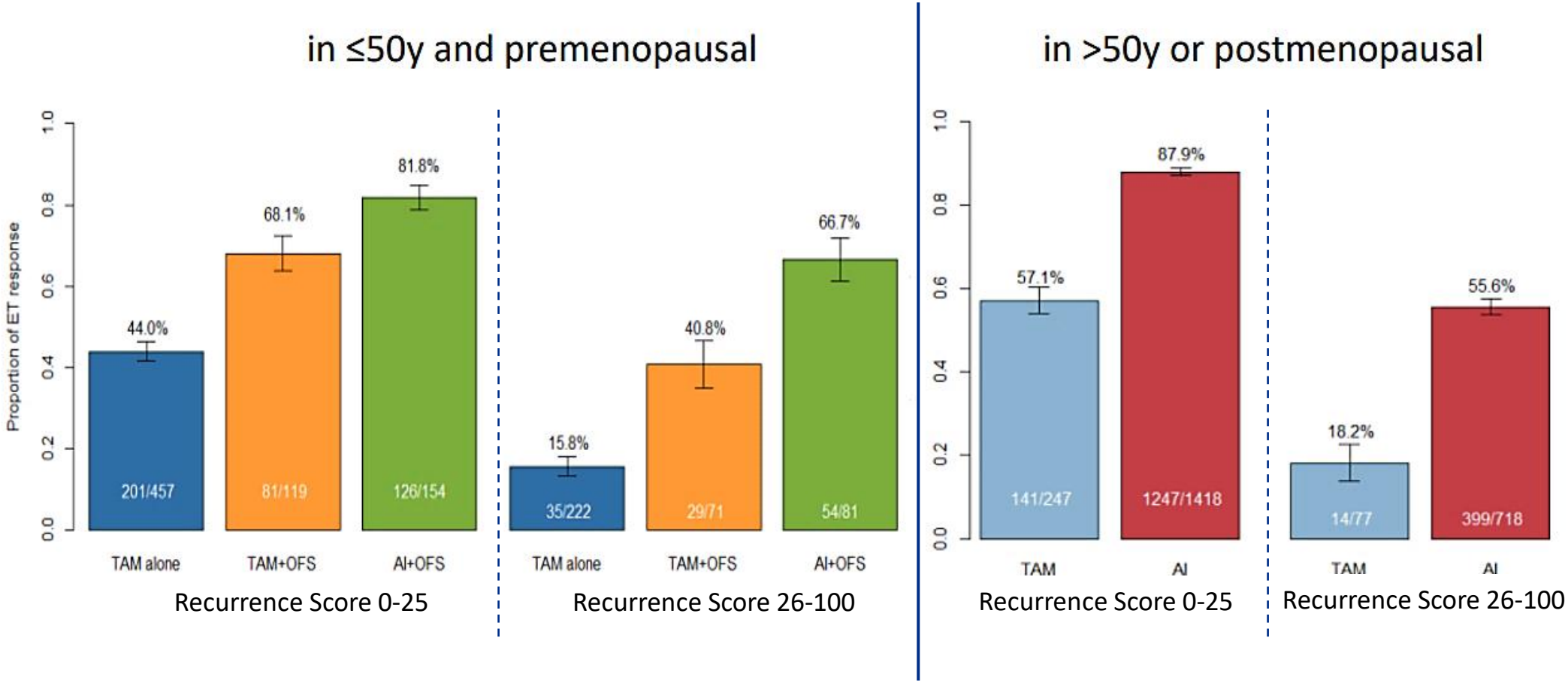
Note: In the ADAPT trial ET-response rate of 40.1% (TAM) in the premenopausal population of endocrine responders; ET-response rate of 81.5% (AI) in the postmenopausal population

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

ADAPTcycle Clinical Trial

ET-response rates and Recurrence Score

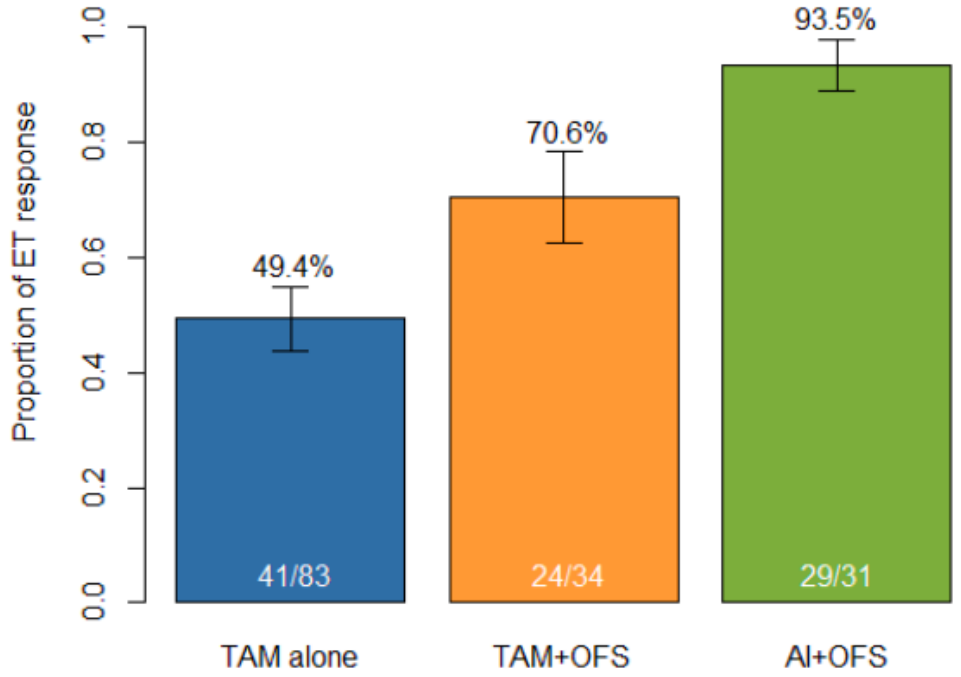


© 2024 Cornerstone Specialty Network. All rights reserved.

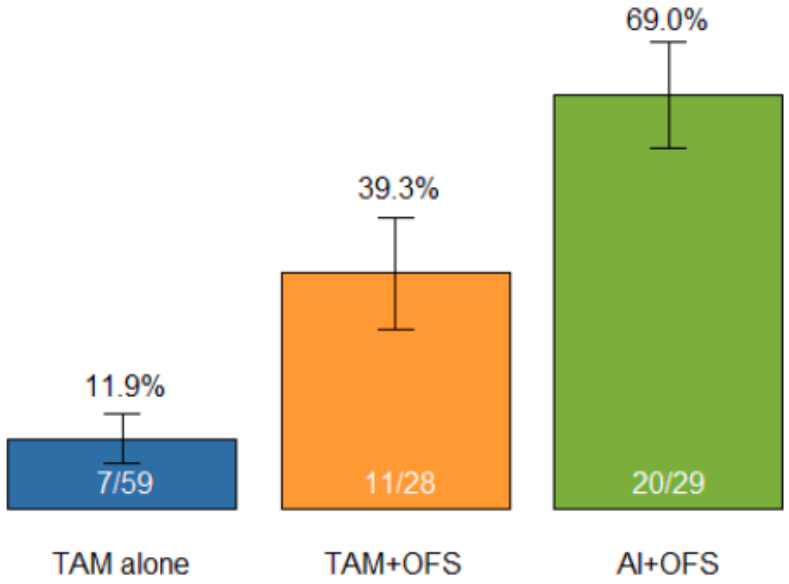
KEY DATA

ADAPTcycle Clinical Trial

ET-response rates and Recurrence Score in ≤ 40 years (premenopausal)



Recurrence Score 0-25



Recurrence Score 26-100

© 2024 Cornerstone Specialty Network. All rights reserved.

ADAPTcycle Clinical Trial

ET-response - all patients

Characteristics	OR (95% CI)	*P*-value
Treatment		
• TAM	0.19 (0.14 – 0.24)	<0.001
• AI	1.00	
• TAM + OFS*	0. 62 (0.42 – 0.93)	0.02
• AI + OFS*	2.00 (1.33 – 2.99)	0.001
Age		
• ≤ 50	1.00	
• >50	1.71 (1.32 – 2.22)	<0.001
Recurrence Score (cont. per 10%)	0.58 (0.53 – 0.64)	<0.001
Ki67 at baseline (cont. per 10%)	0.62 (-.56 – 0.67)	<0.001
Estrogen receptor (cont. per 10%)	1.10 (1.03 – 1.18)	0.004

*in premenopausal pts, irrespective of age

If RT-PCR data were used:
the same factors are predictive, but in addition:
HER2 OR 1.33 (1.17 – 1.51)

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

ADAPTcycle Clinical Trial

- ADAPTcycle screening cohort (n=4,334) confirms ADAPT ET-response rates
- Adding OFS to TAM or AI substantially improves ET-response in premenopausal patients
  - Adding OFS to AI substantially improves ET-response in premenopausal patients rates comparable to AI-treated postmenopausal pts
- ADAPTcycle follow-up will demonstrate impact of ET-response (with and w/o OFS) on survival
- Based on ADAPT and ADAPTcycle, optimal ET (type / duration) for ET-response assessment:
  - 2-4w AI in postmenopausal pts
  - 4w GnRH and AI (started simultaneously) in premenopausal pts

© 2024 Cornerstone Specialty Network. All rights reserved.

ADAPTcycle Clinical Trial

Endocrine therapy plus ovarian suppression can generate high response rates in patients with hormone receptor-positive early breast cancer regardless of age

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

INAVO120 Clinical Trial

Does inavolisib in combination with palbociclib and fulvestrant provide benefit for patients with PIK3CA-mutated, HR+, HER2- locally advanced or metastatic breast cancer?

Inavolisib is an investigational, highly potent and selective PI3Kα inhibitor

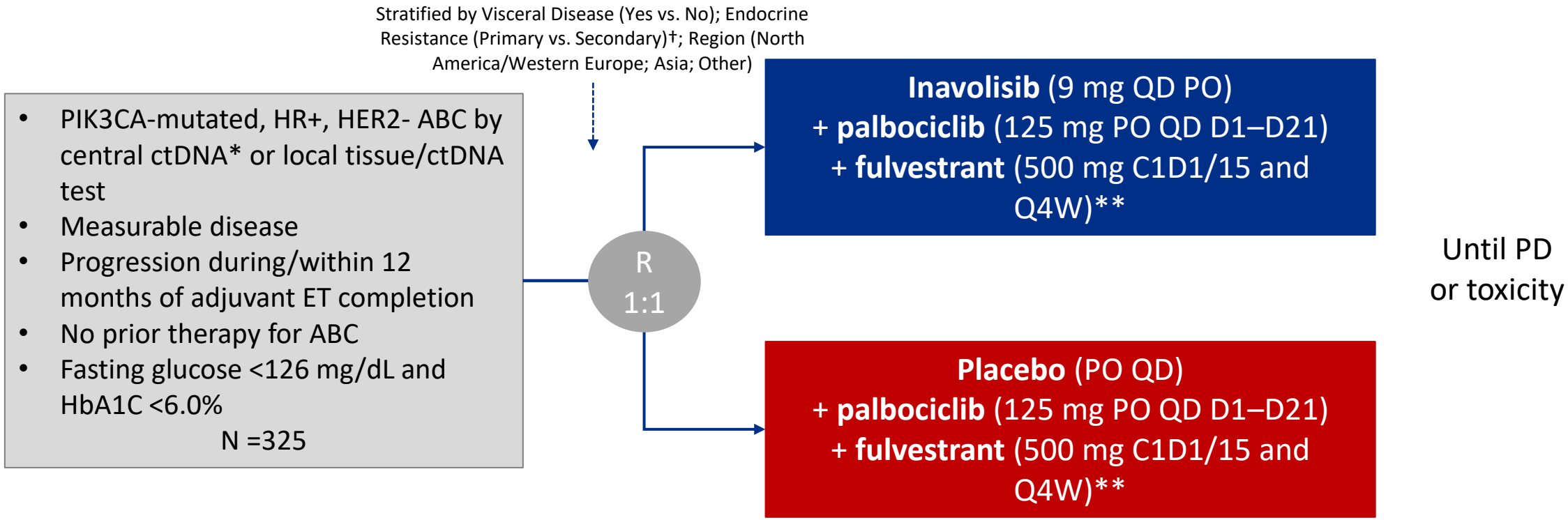
cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Study Design: Randomized, double-blind, placebo-controlled, Phase 3 study



Primary endpoint: PFS by Investigator

Secondary endpoints: OS‡, ORR, BOR, CBR, DOR, PROs

Enrollment period: December 2019 to September 2023

Central testing for PIK3CA mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu).
† Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.
1 Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.
‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis;
** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, et al. Ann Oncol 2018;29:1634–1657.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Baseline Characteristics

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Age (year)		
Median	53.0	54.5
Min–Max	27–77	29–79
Sex, n (%)		
Female	156 (96.9)	163 (99.4)
Race, n (%)		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG PS, n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance , n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. ** Endocrine resistance was defined per 4th ESO–[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

© 2024 Cornerstone Specialty Network. All rights reserved.

INAVO120 Clinical Trial

Prior Therapy

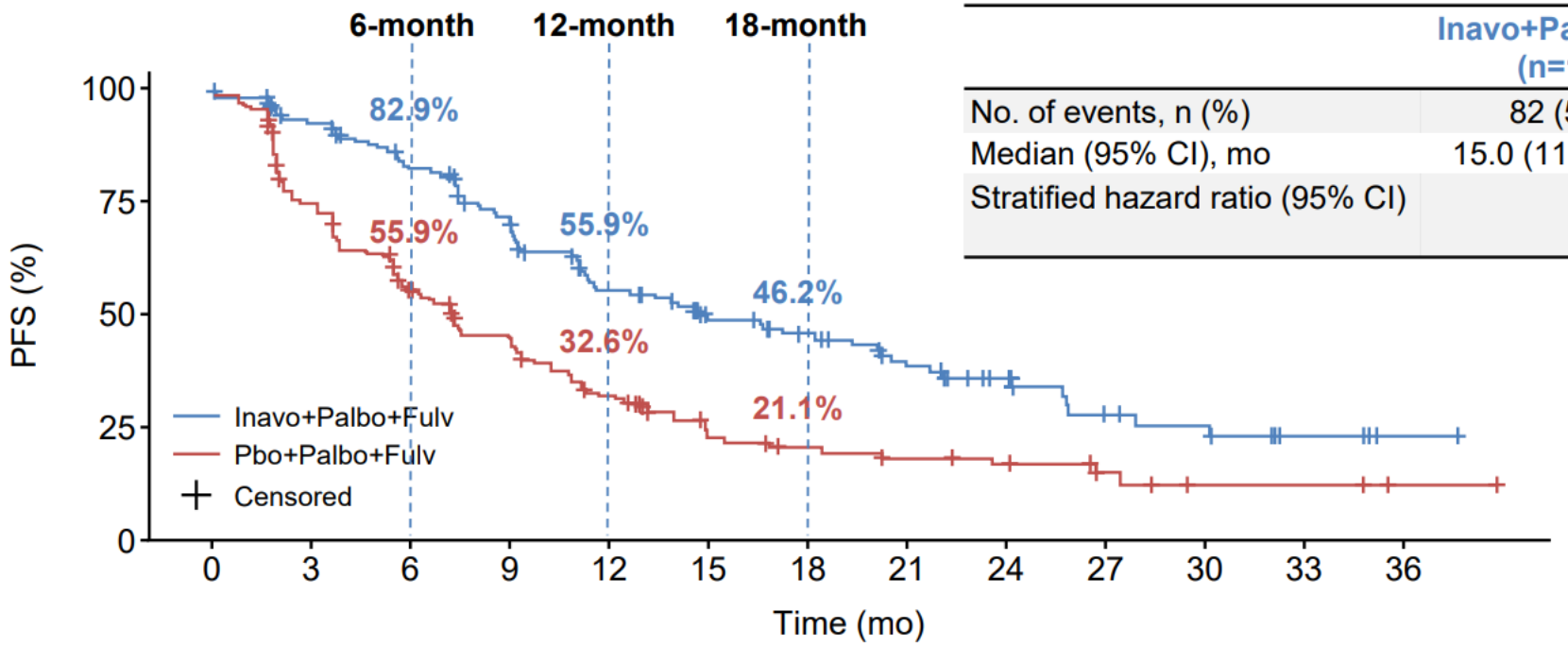
	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	132 (82.0)	137 (83.5)
Prior (neo)adjuvant endocrine therapy, n (%)		
Yes	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Prior adjuvant CDK4/6 inhibitor, n (%)		
Yes	3 (1.9)	1 (0.6)

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Primary Endpoint: PFS by investigator



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

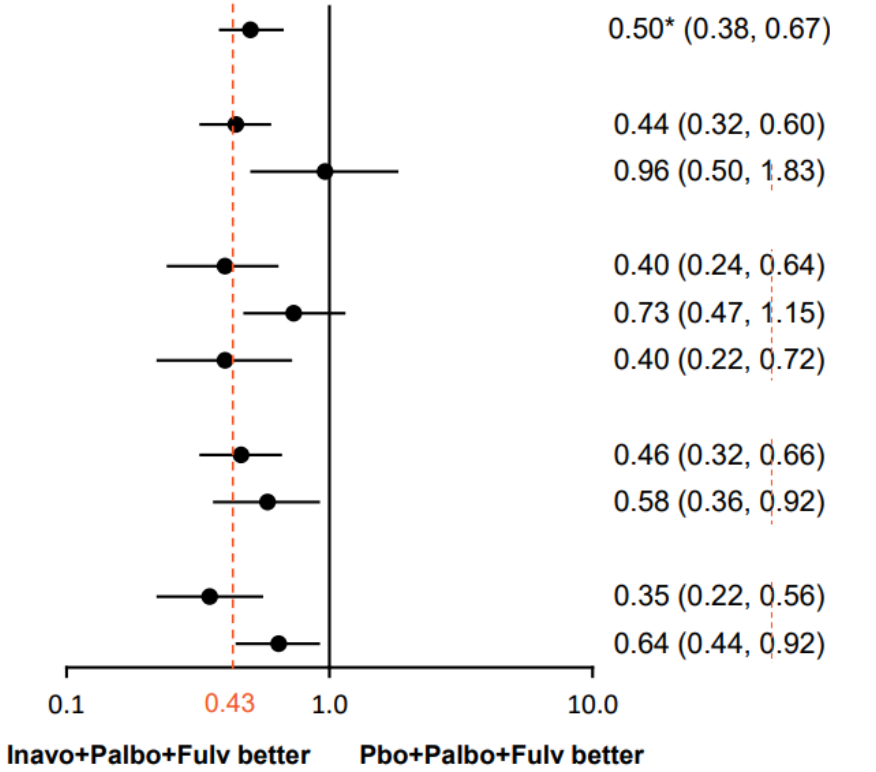
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Primary Endpoint: PFS by subgroups (1/2)

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Age, years					
<65	136	16.6	130	7.2	0.44 (0.32, 0.60)
≥65	25	9.3	34	10.7	0.96 (0.50, 1.83)
Region					
Asia	56	14.6	58	5.8	0.40 (0.24, 0.64)
North America/Western Europe	63	13.8	64	9.3	0.73 (0.47, 1.15)
Other	42	21.0	42	5.6	0.40 (0.22, 0.72)
ECOG PS at baseline					
0	100	16.6	106	7.4	0.46 (0.32, 0.66)
1	60	11.4	58	5.6	0.58 (0.36, 0.92)
Menopausal status at randomization					
Premenopausal	65	20.1	59	6.5	0.35 (0.22, 0.56)
Post-menopausal	91	13.4	104	7.5	0.64 (0.44, 0.92)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Fulv, fulvestrant; Inavo, inavolisib; mo, months, Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

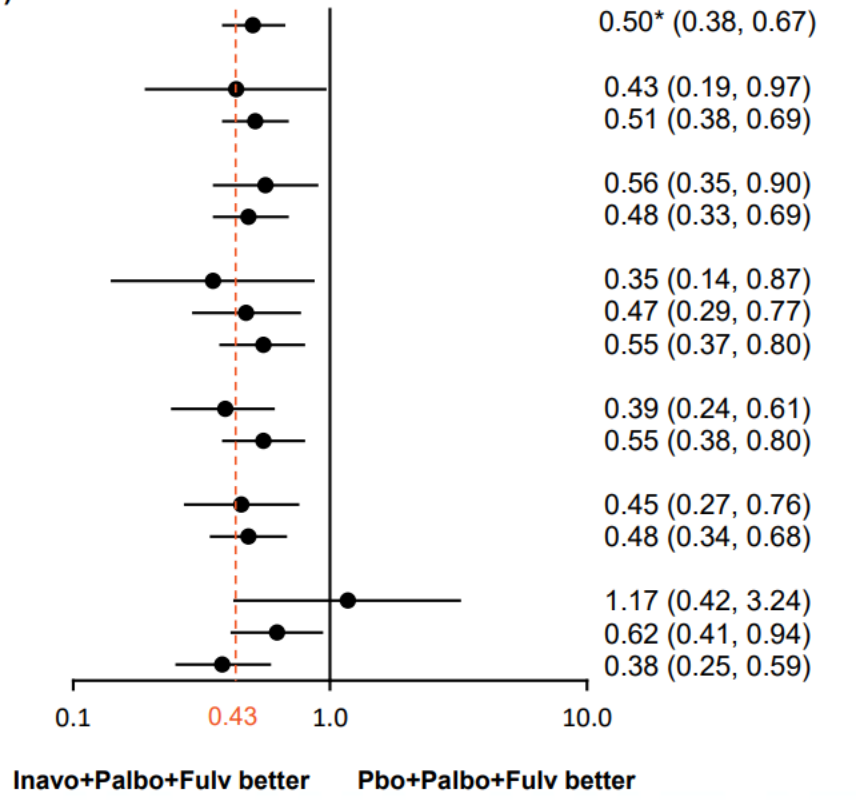
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Primary Endpoint: PFS by subgroups (2/2)

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Visceral disease					
No	29	25.8	36	7.4	0.43 (0.19, 0.97)
Yes	132	13.8	128	7.2	0.51 (0.38, 0.69)
Liver metastasis at enrollment					
No	84	24.2	73	11.3	0.56 (0.35, 0.90)
Yes	77	11.0	91	5.6	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment					
1	21	20.2	32	7.4	0.35 (0.14, 0.87)
2	59	18.2	46	7.4	0.47 (0.29, 0.77)
≥3	81	14.1	86	7.3	0.55 (0.37, 0.80)
Endocrine resistance					
Primary	53	11.4	58	3.7	0.39 (0.24, 0.61)
Secondary	108	18.2	105	9.7	0.55 (0.38, 0.80)
HR status					
ER+/PgR-	45	11.1	45	5.6	0.45 (0.27, 0.76)
ER+/PgR+	113	18.2	113	7.4	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy					
Aromatase inhibitor and tamoxifen	18	11.0	19	12.9	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	10.9	71	5.8	0.62 (0.41, 0.94)
Tamoxifen only	82	21.0	73	7.4	0.38 (0.25, 0.59)



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

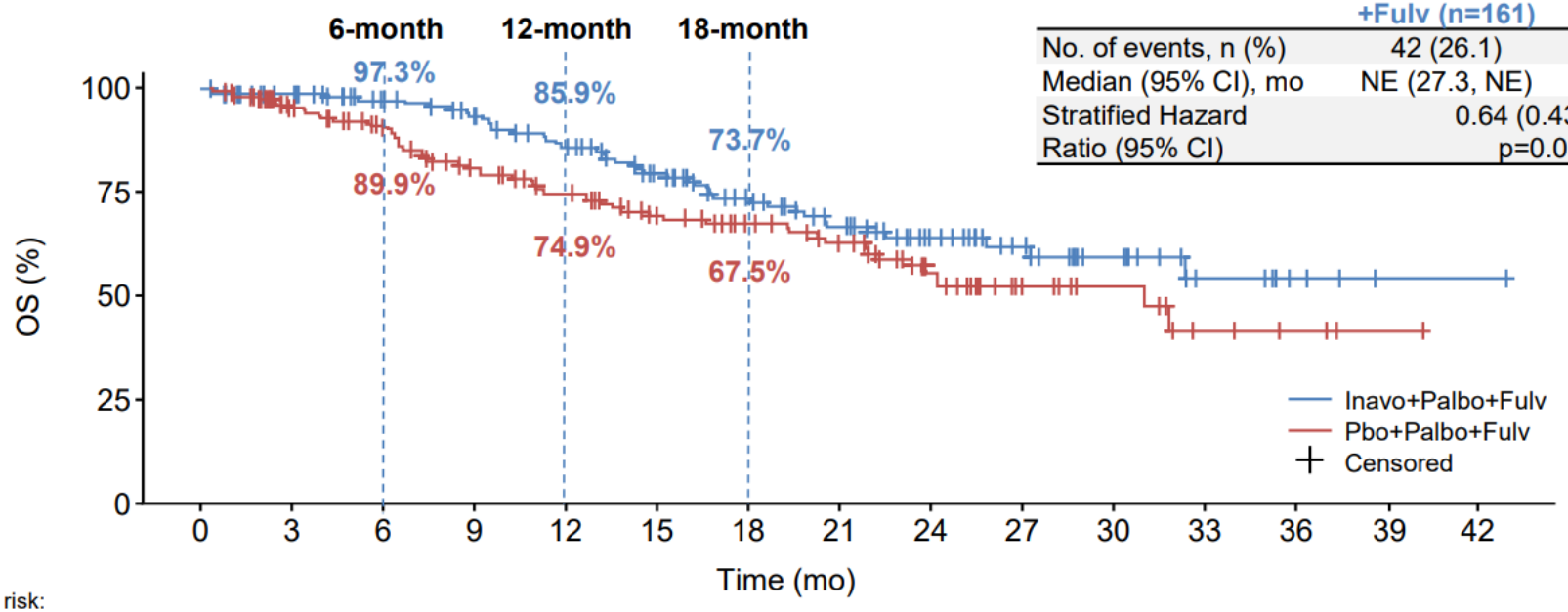
CI, confidence interval; ER, estrogen receptor; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival; PgR, progesterone receptor.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Secondary Endpoint: Overall Survival



	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	

Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

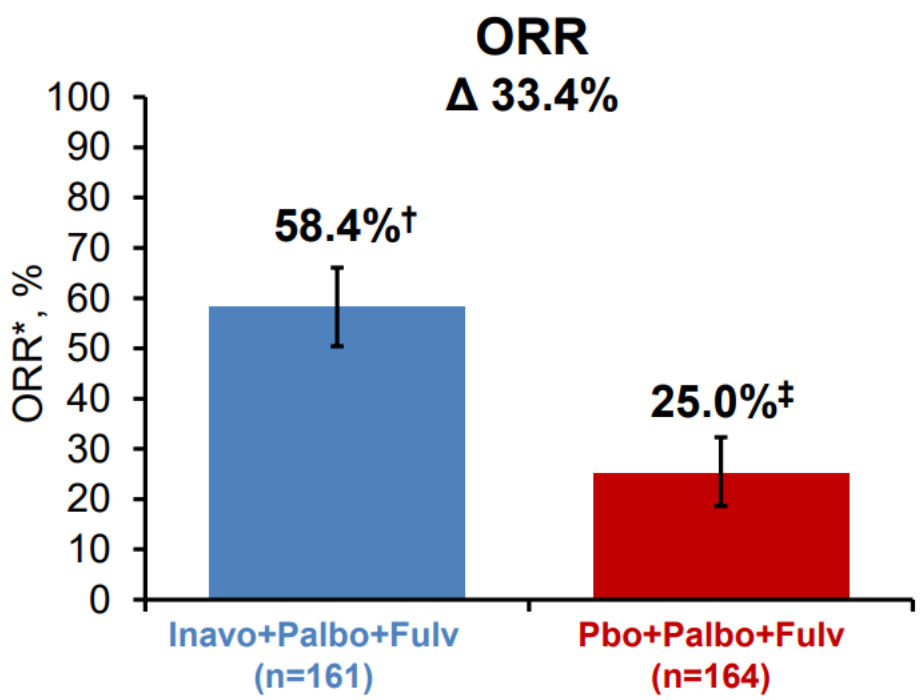
SABCS 2023 Abstr GS03-13

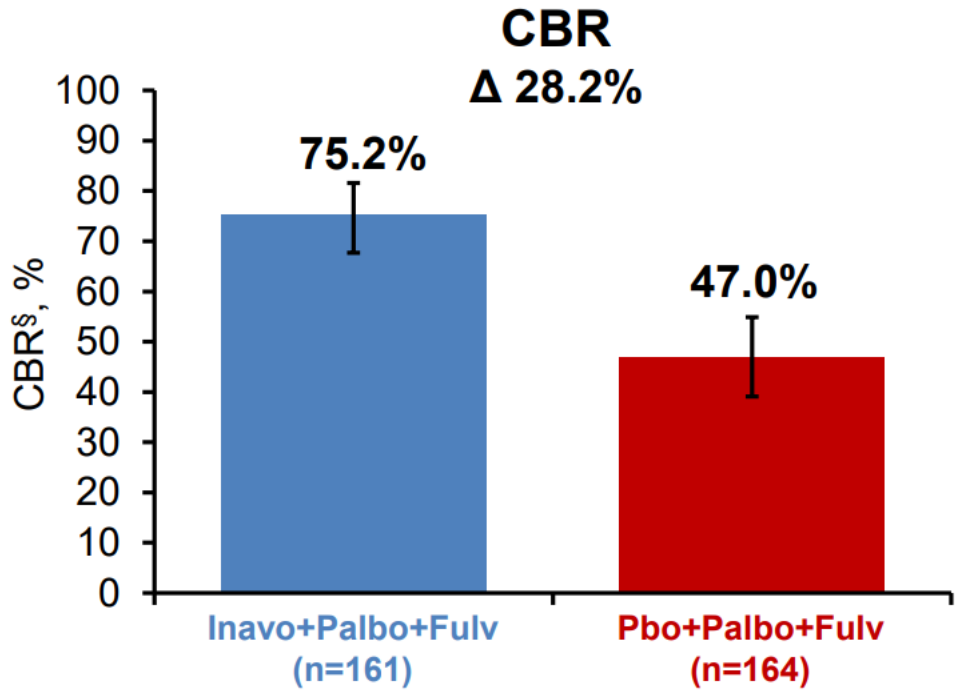
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Secondary Endpoint: ORR and Clinical Benefit Rate





* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

SABCS 2023 Abstr GS03-13

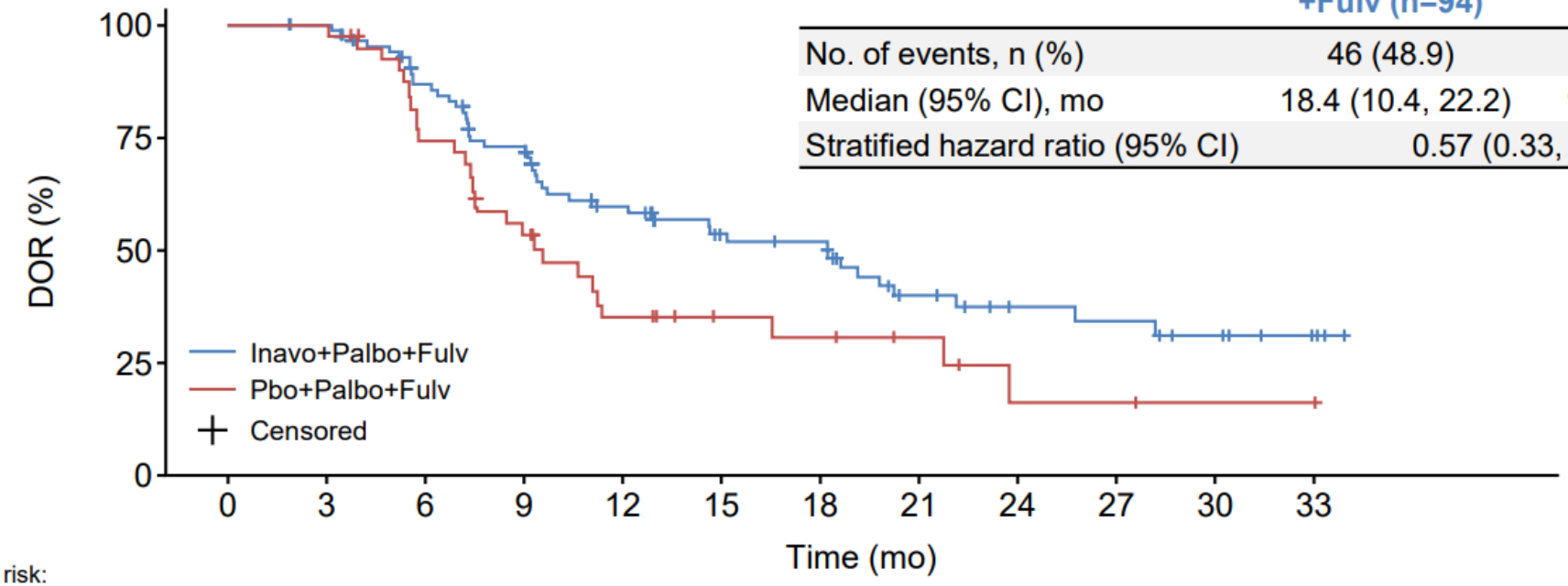
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Secondary Endpoint: DOR

	Inavo+Palbo +Fulv (n=94)	Pbo+Palbo+Fulv (n=41)
No. of events, n (%)	46 (48.9)	27 (65.9)
Median (95% CI), mo	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
Stratified hazard ratio (95% CI)	0.57 (0.33, 0.99)	



Patients at risk:

Inavo+Palbo+Fulv	94	89	71	58	43	32	29	17	12	11	7	3
Pbo+Palbo+Fulv	41	41	29	21	12	8	7	5	2	2	1	1

Median follow-up:
21.3 months

SABCS 2023 Abstr GS03-13

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Safety

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

AES were assessed per CTCAE V5

* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage; cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

INAVO120 Clinical Trial

Safety

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

INAVO120 Clinical Trial

- Addition of inavolisib to palbociclib + fulvestrant demonstrated a statistically significant and clinically meaningful improvement in PFS in patients with PIK3CA-mutated, HR+, HER2- advanced breast cancer who recurred on or within 12 months of adjuvant ET
  - Median PFS more than doubled from 7.3 to 15.0 mo, with a stratified hazard ratio of 0.43 (95% CI 0.32, 0.59; $p<0.0001$)

- Trend towards improved OS at first interim analysis: stratified hazard ratio 0.64 (95% CI 0.43, 0.97)

- Inavolisib + palbociclib + fulvestrant had a manageable safety profile, consistent with the safety profiles of the individual drugs with no new safety signals and with a low discontinuation rate

© 2024 Cornerstone Specialty Network. All rights reserved.

INAVO120 Clinical Trial

Triplet therapy (inavolisib in combination with palbociclib and fulvestrant) may represent a new standard of care for patients with PIK3CA-mutated, HR+, HER2- advanced Breast Cancer

More to come…

© 2024 Cornerstone Specialty Network. All rights reserved.

Managing HR+ Breast Cancer in Community Oncology

© 2024 Cornerstone Specialty Network. All rights reserved.

NCCN Guidelines for Breast Cancer

Principles of radiation therapy

RT with Preoperative or Adjuvant Systemic Therapy

- In patients treated with preoperative systemic therapy, adjuvant RT is based on the maximal disease stage (ie, clinical stage, pathologic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathology results after preoperative systemic therapy.
- Sequencing of RT with systemic therapy:
  - It is common for RT to follow chemotherapy when chemotherapy is indicated. However,
    - CMF (cyclophosphamide/methotrexate/fluorouracil) and RT may be given concurrently, or CMF may be given first.
    - Capecitabine is typically given after completion of RT.
    - Olaparib should be given after completion of RT.
  - Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred. Endocrine therapy may be delivered concurrently with RT or started after the completion of RT.
  - Adjuvant HER2-targeted therapy ± endocrine therapy may be delivered concurrently with RT

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

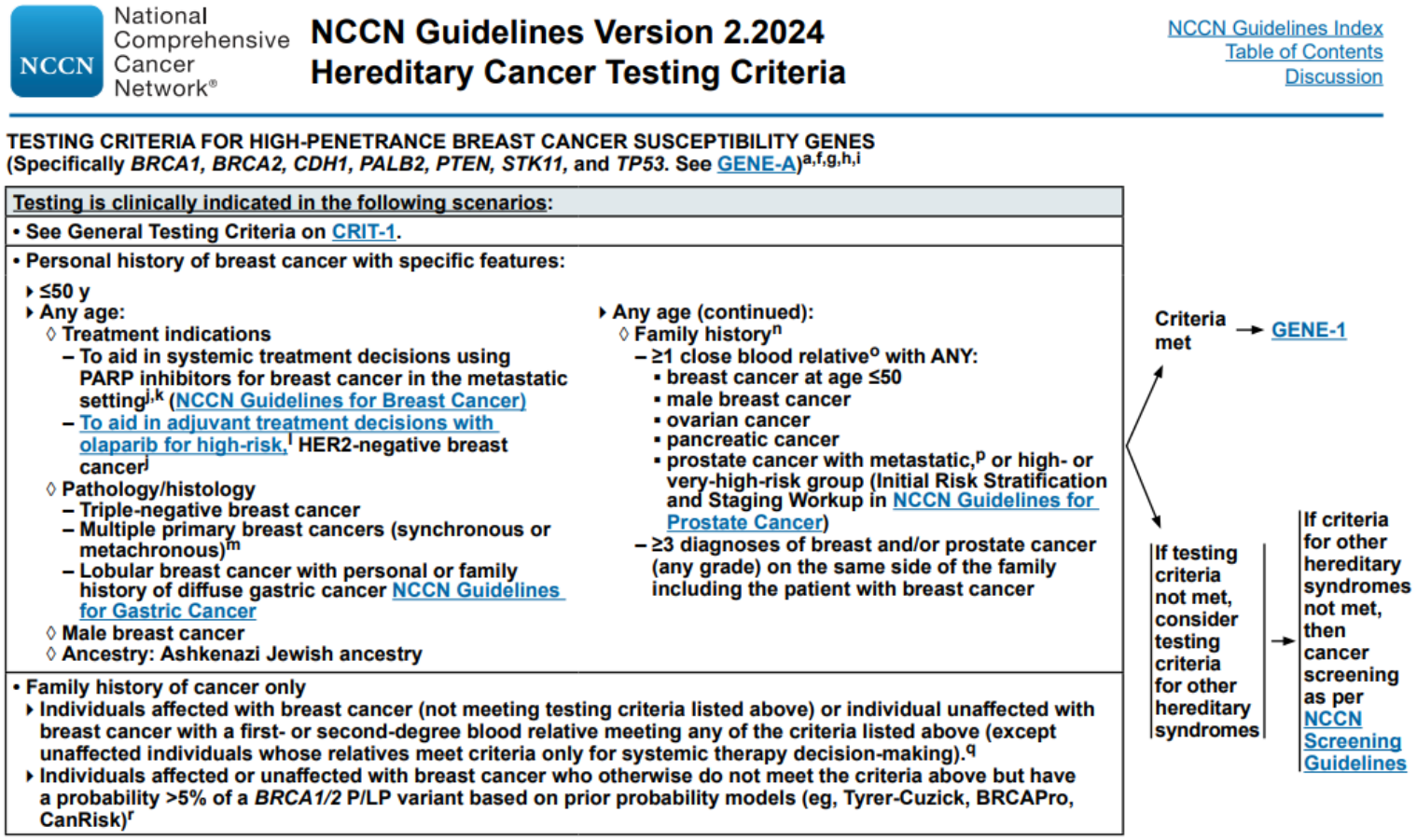
HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g,1] ‣ Paclitaxel + carboplatin (various schedules) ‣ Docetaxel + carboplatin[g,1] (preoperative setting only)

breast.pdf (nccn.org)

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

Breast Cancer Susceptibility Gene Testing



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Hereditary Cancer Testing Criteria

NCCN Guidelines Index
Table of Contents
Discussion

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,f,g,h,i]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[m]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer NCCN Guidelines for Gastric Cancer
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - ◊ Family history[n]
      - – ≥1 close blood relative[o] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history of cancer only
  - Individuals affected with breast cancer (not meeting testing criteria listed above) or individual unaffected with breast cancer with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[q]
  - Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[r]

Criteria met → GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

NCCN Guidelines for Breast Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA* or AKT1/PTEN-activating mutations, see additional targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and/or Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
  - For *ESR1* mutated tumors, see BINV-Q (6)
- Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Addtional targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal[m,n] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

NCCN Guidelines for Breast Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[x]	*PIK3CA/AKT1/PTEN* activating mutations	NGS	Capivasertib + fulvestrant	Category 1	Preferred second- or subsequent-line therapy in select patients[x]
HR-positive/ HER2-negative[y]	*ESR1* mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other recommended regimen
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[z] Entrectinib[z]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[aa,bb] Dostarlimab-gxly[cc]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[aa,bb]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[dd]	Category 2A	

[v] For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[w] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[x] In adult patients with PIK3CA/AKT1/PTEN activating mutations after disease progression or recurrence after one or more prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

KATHERINE Clinical Trial

Updated long term data from the KATHERINE study:
Impact of post neoadjuvant T-DM1 vs Trastuzumab

Does adjuvant ado-trastuzumab emtansine versus trastuzumab for residual invasive HER2-positive early breast cancer provide benefit after neoadjuvant chemotherapy and HER2-targeted therapy?

cornerstone specialty network™

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

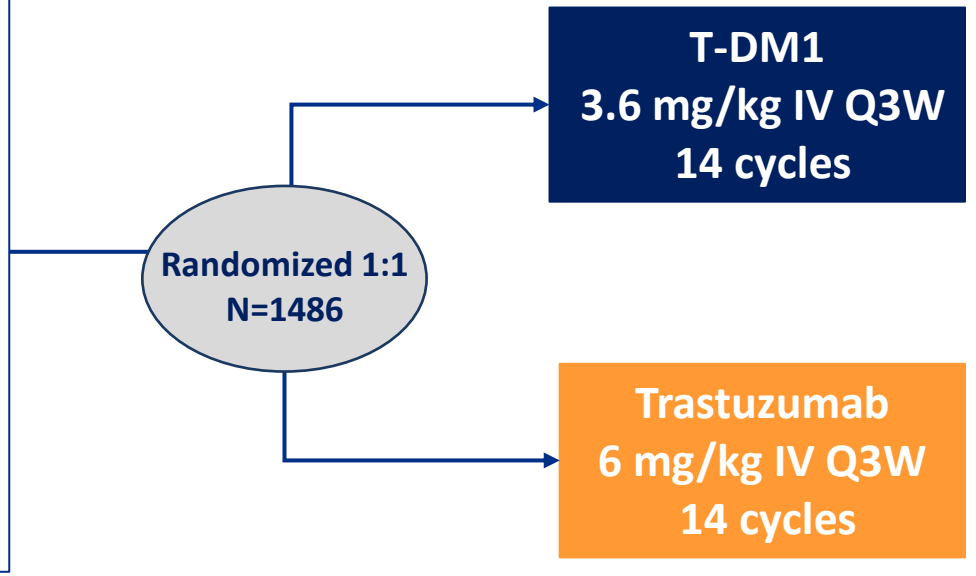
KATHERINE Clinical Trial

Study Design: Phase III trial

Stratified by clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

Prior neoadjuvant therapy consisting of:

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



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

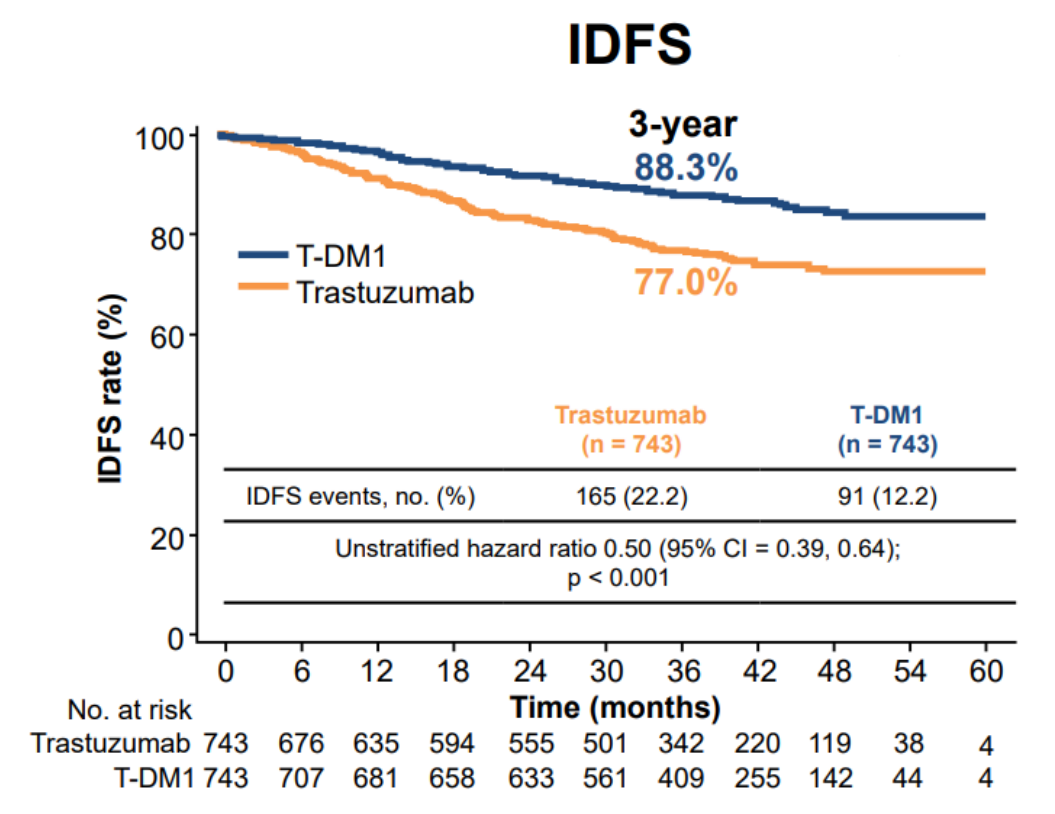
Data cutoff: October 5, 2023

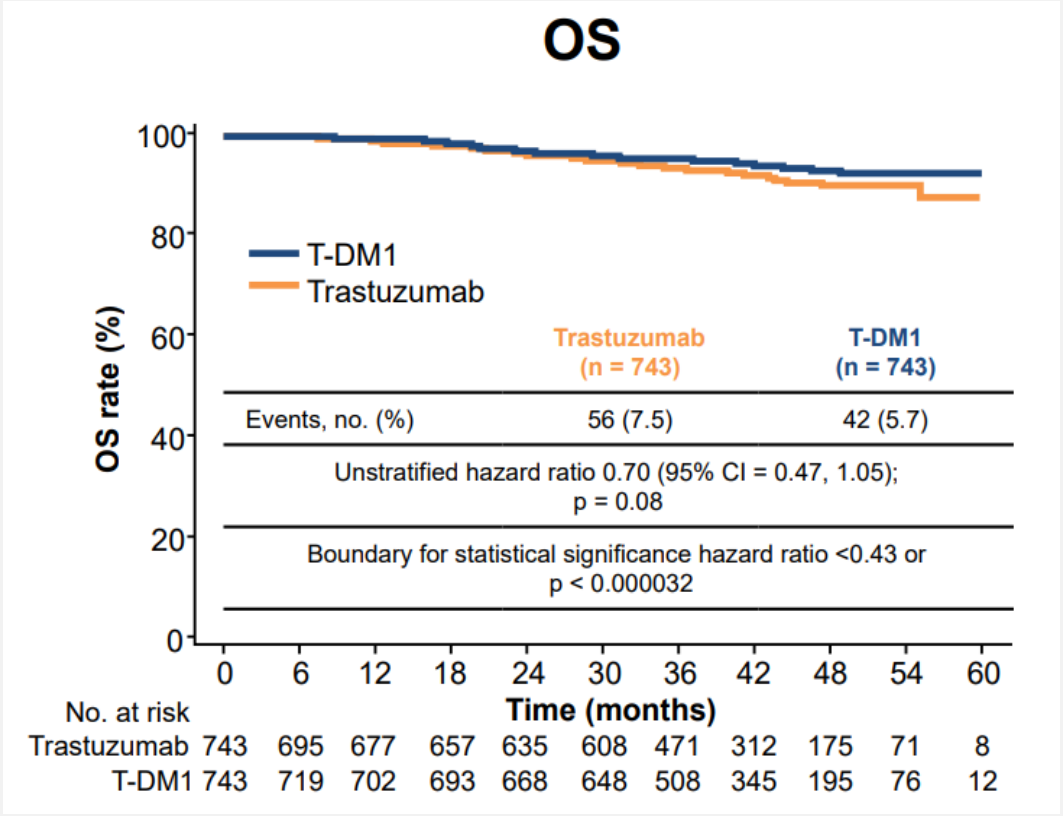
Primary End Point: IDFS
Secondary Endpoints: IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial: Primary Analysis 2018





SABCS 2023 Abstract GS03-12

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial: 2023 SABCS updated data

Patient Disposition

	T-DM1 (n=743)	Trastuzumab (n=743)
Randomized, ITT, n	743	743
Treated, n	740	720
Alive and on study, n (% ITT)	541 (70.1)	461 (62.0)
Discontinued from study, n (%)		
• With IDFS event reported	105 (14.1)	159 (21.4)
• Prior to IDFS event*	117 (15.7)	123 (16.6)

Reasons include:
- withdrawal by subject, 88 (11.8%) in the trastuzumab arm and 77 (10.4%) in the T-DM1 arm;
- lost to follow-up, 28 (3.8%) in the trastuzumab arm and 30 (4.0%) in the T-DM1 arm;
- other, 7 (0.9%) in the trastuzumab arm and 5 (0.7%) in the T-DM1 arm;
- physician decision, 0 in the trastuzumab arm and 5 (0.7%) in the T-DM1 arm.

Baseline Characteristics

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

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

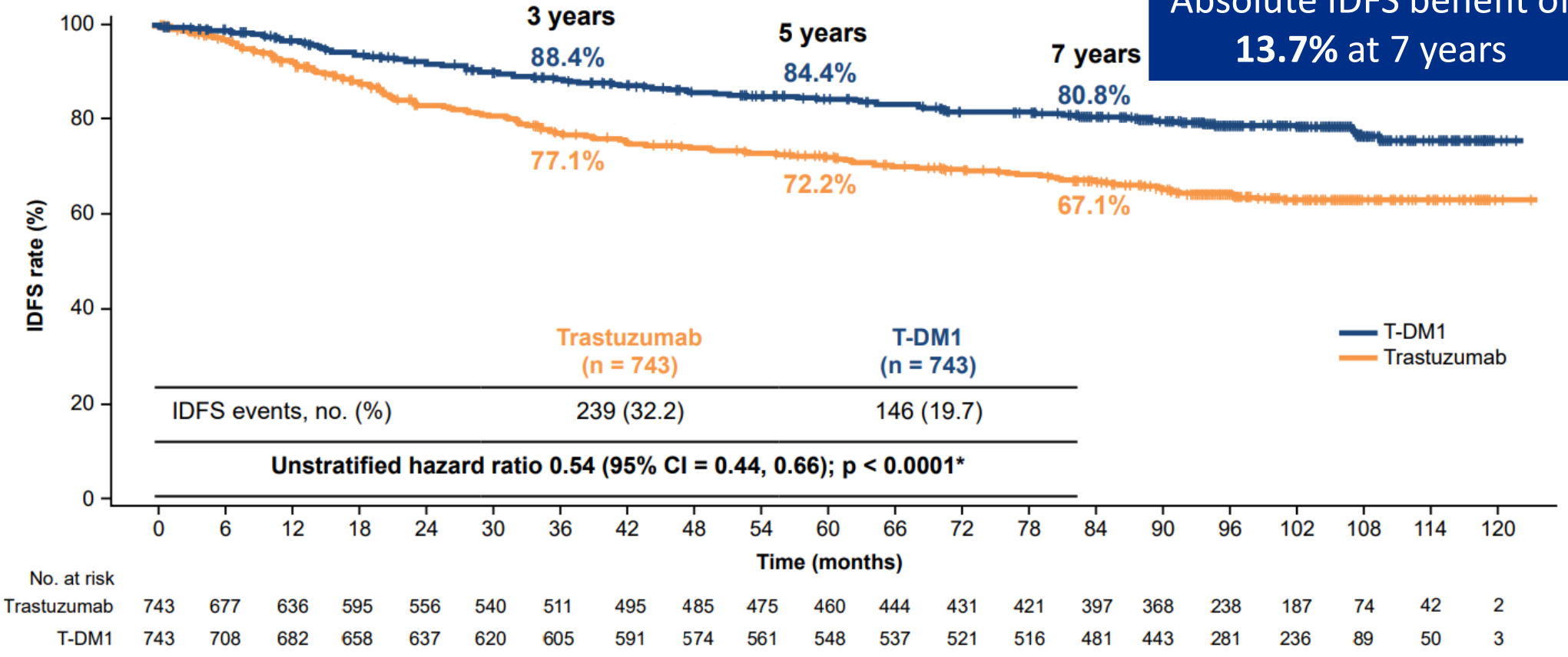
KATHERINE Clinical Trial

2023 SABCS updated data

IDFS Final Analysis

- Median follow-up 8.4 years (101 months)

Absolute IDFS benefit of 13.7% at 7 years



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.

SABCS 2023 Abstract GS03-12

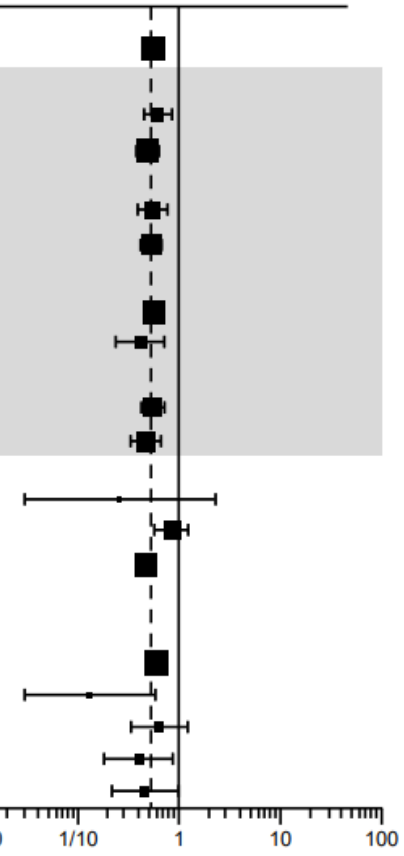
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

IDFS Final Analysis by Subgroups

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



SABCS 2023 Abstract GS03-12

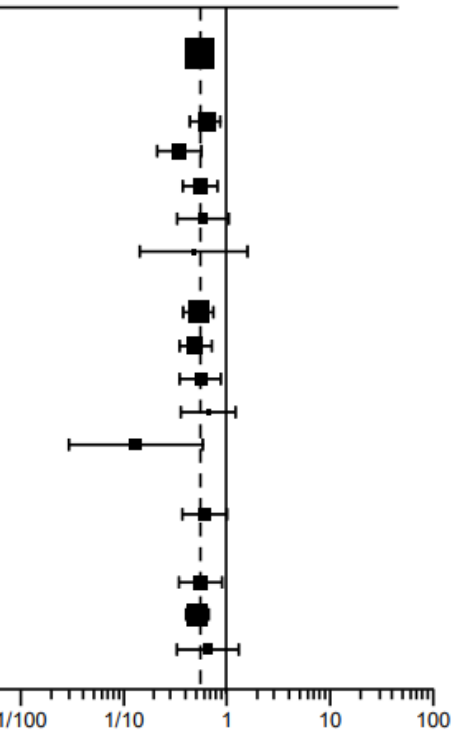
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

IDFS Final Analysis by Subgroups

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



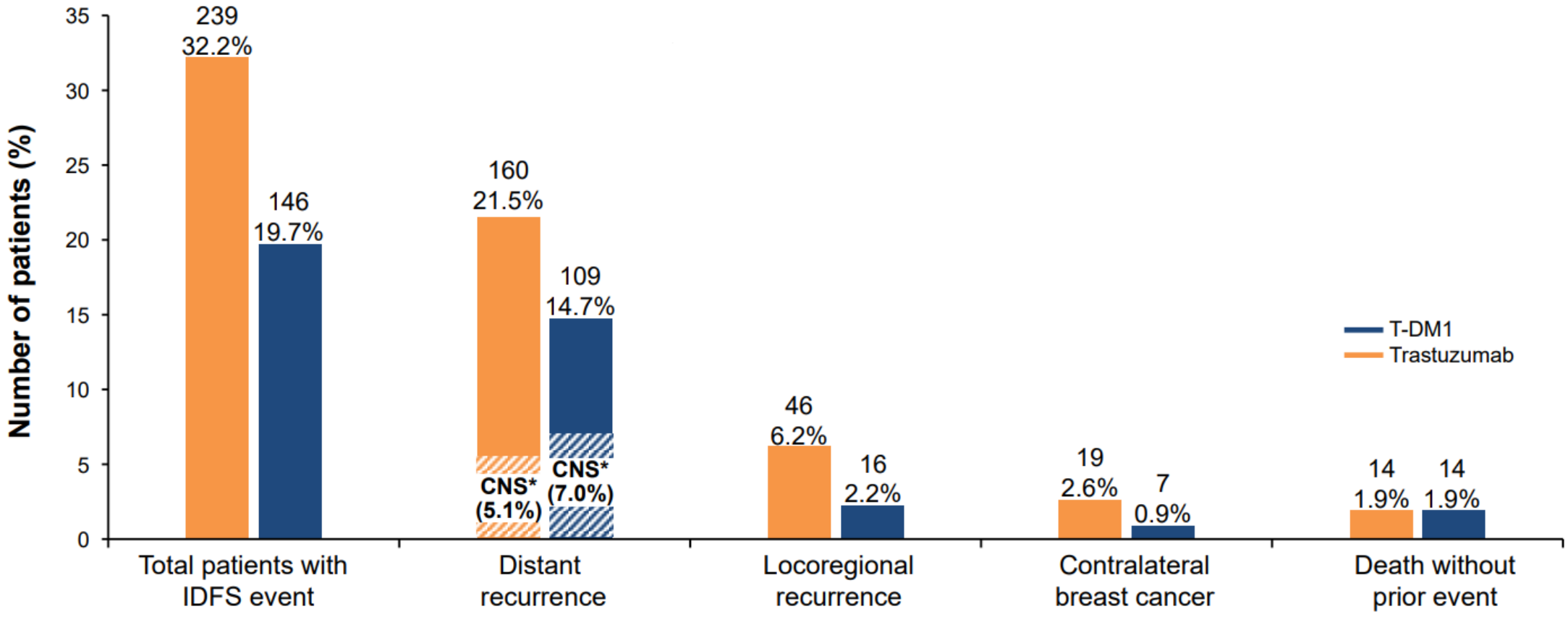
SABCS 2023 Abstract GS03-12

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

Site of first occurrence of an IDFS event



* CNS metastases as component of distant recurrence (isolated or with other sites)

SABCS 2023 Abstract GS03-12

© 2024 Cornerstone Specialty Network. All rights reserved.

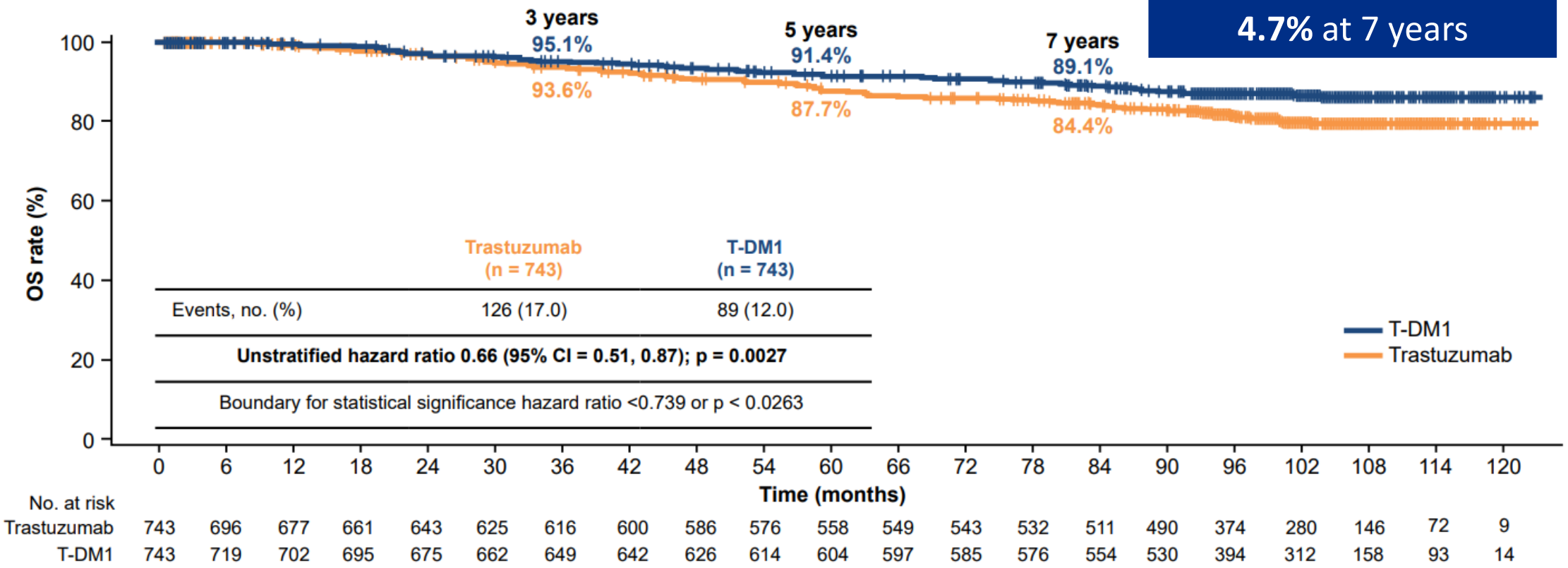
KEY DATA

KATHERINE Clinical Trial

2nd OS Interim Analysis

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

Absolute OS benefit of 4.7% at 7 years



SABCS 2023 Abstract GS03-12

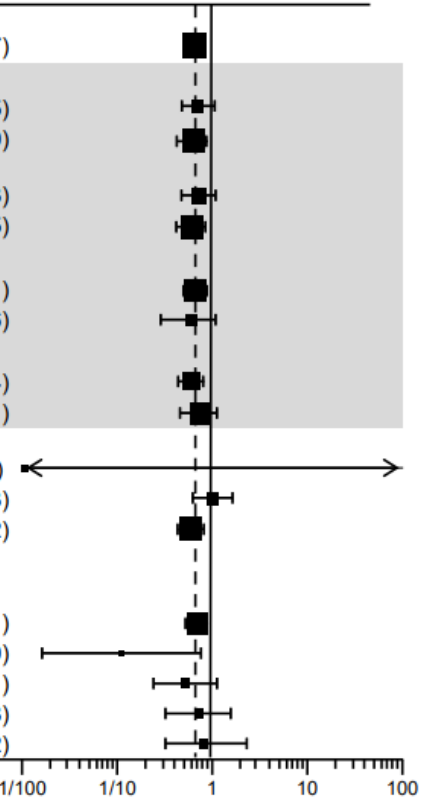
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

2nd OS Interim Analysis by Subgroups

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
All	1486	743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
Clinical stage at presentation									
Inoperable	375	190	57	69.0	185	44	77.5	0.71	(0.48, 1.05)
Operable	1111	553	69	89.4	558	45	92.7	0.62	(0.42, 0.90)
Hormone receptor status									
Negative (ER-negative and PgR-negative/-unknown)	412	203	44	79.9	209	38	83.4	0.73	(0.48, 1.13)
Positive (ER- and/or PgR-positive)	1074	540	82	85.9	534	51	91.3	0.60	(0.42, 0.85)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	105	84.1	600	77	88.6	0.68	(0.51, 0.91)
Trastuzumab plus additional HER2-directed agent(s)	290	147	21	85.7	143	12	91.0	0.57	(0.28, 1.16)
Pathologic nodal status after preoperative therapy									
Node-positive	688	345	90	75.6	343	62	83.4	0.61	(0.44, 0.84)
Node-negative/not done	798	398	36	91.4	400	27	94.0	0.74	(0.45, 1.21)
Central HER2 status by IHC									
0/1+	25	13	4	75.0	12	0	100.0	<0.01	(0.00, NE)
2+	326	168	28	83.4	158	28	83.3	1.03	(0.61, 1.73)
3+	1132	559	94	84.8	573	61	90.4	0.59	(0.43, 0.82)
Unknown	3	3	0	100.0				NE	(NE, NE)
Race									
White	1081	530	80	86.3	551	64	89.0	0.72	(0.52, 1.01)
Black or African American	40	19	8	73.3	21	1	94.1	0.10	(0.01, 0.80)
Asian	129	64	15	78.0	65	9	90.0	0.53	(0.23, 1.21)
American Indian or Alaska Native	86	50	14	68.9	36	8	78.8	0.75	(0.31, 1.78)
Other or multiple or unknown	150	80	9	89.3	70	7	92.3	0.87	(0.32, 2.32)



SABCS 2023 Abstract GS03-12

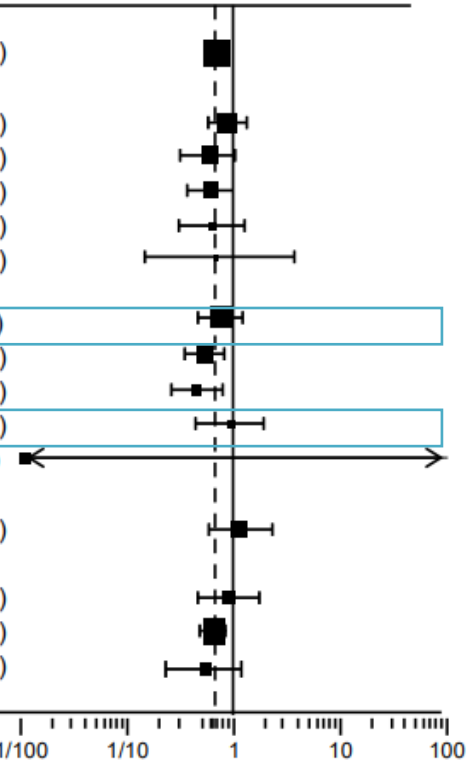
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

2nd OS Interim Analysis by Subgroups

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
All	1486	743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
Primary tumor stage (at definitive surgery)									
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	306	41	89.4	331	38	89.5	0.86	(0.55, 1.34)
ypT1, ypT1c	359	184	27	84.6	175	15	91.1	0.55	(0.29, 1.03)
ypT2	359	185	38	79.9	174	23	89.8	0.57	(0.34, 0.95)
ypT3	108	57	17	74.1	51	10	78.2	0.59	(0.27, 1.29)
ypT4*	23	11	3	63.5	12	3	80.0	0.72	(0.14, 3.58)
Regional lymph node stage (at definitive surgery)									
ypN0	673	332	32	90.7	341	27	92.8	0.82	(0.49,1.37)
ypN1	432	212	46	80.9	220	30	86.6	0.57	(0.36, 0.90)
ypN2	189	103	33	70.0	86	16	87.1	0.48	(0.26, 0.87)
ypN3	67	30	11	53.8	37	16	54.2	0.93	(0.43, 2.00)
ypNX	125	66	4	94.8	59	0	100.0	<0.01	(0.00, NE)
Residual disease ≤1 cm with negative axillary lymph nodes									
ypT1a, ypT1b or ypT1mic and ypN0	328	160	13	93.1	168	16	92.3	1.18	(0.57, 2.45)
Age group (years)									
<40	296	153	16	89.2	143	15	88.4	0.93	(0.46, 1.88)
40–64	1064	522	92	83.9	542	66	89.3	0.65	(0.47, 0.89)
≥65	126	68	18	77.6	58	8	88.8	0.50	(0.22, 1.14)



SABCS 2023 Abstract GS03-12

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

Follow-up medications after IDFS events (ITT)

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

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

KATHERINE Clinical Trial

Related AEs during the post-treatment period*

Patients, n (%) with ≥1:	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 disorders	5 (0.7)	5 (0.7)
• Nervous system disorders	4 (0.5)	0
• Hepatobiliary disorders	2 (0.3)	0
• Metabolism and nutrition disorders	2 (0.3)	0
• Skin and subcutaneous tissue disorders	2 (0.3)	0
Serious AE	**2 (0.3)**	**4 (0.6)**
• Cardiac disorders	0	3 (0.4)
• Hepatobiliary disorders	2 (0.3)	0
• Vascular disorders	0	1 (0.1)
Grade ≥3 AE	**3 (0.4)**	**3 (0.4)**
• Cardiac disorders	1 (0.1)	3 (0.4)
• Hepatobiliary disorders	2 (0.3)	0

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

KATHERINE Clinical Trial

- After 8.4 years (101 months) median follow-up, T-DM1 significantly improved OS in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy
  - Hazard ratio **0.66** (95% CI 0.51, 0.87), p = 0.0027
  - 7-year OS rates: 89.1% (T-DM1) vs 84.4% (trastuzumab), a difference of 4.7%
- IDFS benefit of T-DM1 was sustained in the ITT population with longer follow-up with a hazard ratio of **0.54** (95% CI 0.44, 0.66) as well as in key subgroups
  - 7-year IDFS rates: 80.8% (T-DM1) vs 67.1% (trastuzumab), a difference of 13.7%
- No new safety issues emerged with longer follow-up
  - Cardiac toxicity was rare in both arms
- Follow-up is ongoing for the final OS analysis

© 2024 Cornerstone Specialty Network. All rights reserved.

KATHERINE Clinical Trial

Use of T-DM1 improves survival compared to trastuzumab post-surgery in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

CLINICAL QUESTION

HER2CLIMB-02 Clinical Trial

Does tucatinib in combination with trastuzumab emtansine (T-DM1) provide benefit for patients with previously treated HER2-positive metastatic breast cancer?

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

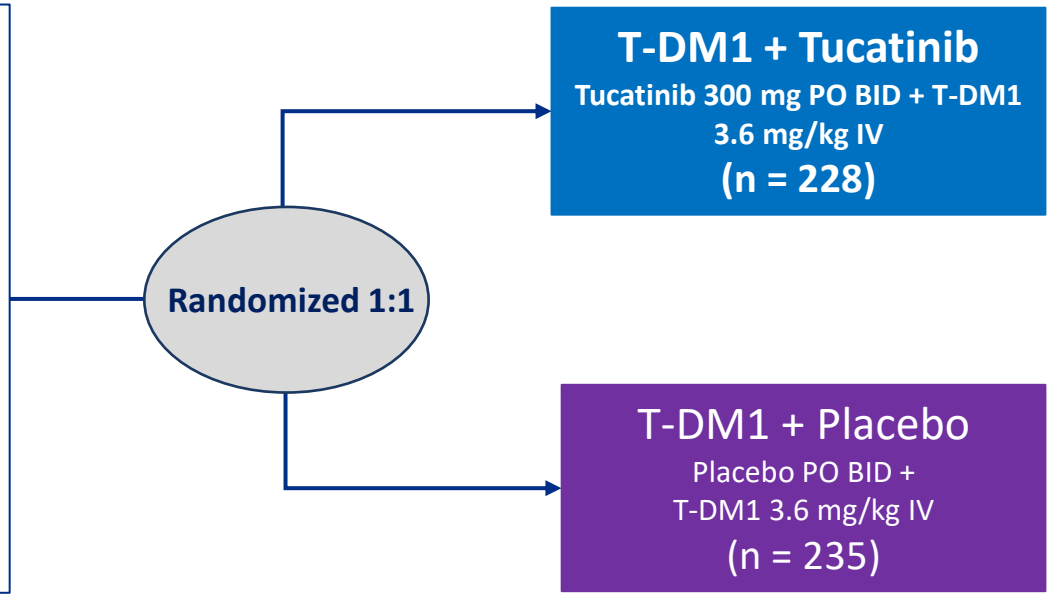
HER2CLIMB-02 Clinical Trial

Study Design: Randomized, double-blind, placebo-controlled, phase III trial

Stratified by line of tx for metastatic disease (1L vs other), hormone receptor status (positive vs negative), brain mets (yes vs no), ECOG PS (0 vs 1)

- Patients with HER2+ LA/MBC
- Progression on prior trastuzumab + taxane in any setting
- Previous treatment with tucatinib, afatinib or T-DXd, lapatinib and neratinib (if received within 12 mo of study tx), and pyrotinib (for recurrent or MBC) not allowed
- ECOG PS 0/1
- Brain mets allowed*

(N = 463)



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05.

The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.

*Previously treated stable, progressing, or untreated brain mets not requiring immediate local therapy.

Median follow up: 24.4 mo

Primary End Point: PFS (RECIST v1.1 by investigator) 90% power with ~331 events for HR: 0.70 at 2-sided α = 5%
Secondary Endpoints: OS, PFS and OS in patients with brain mets, cORR (per RECIST v1.1)

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Baseline Characteristics

Characteristic	T-DM1 + Tucatinib (n = 228)	T-DM1 + Placebo (n = 235)
Median age, yr (range)	55.0 (26-83)	53.0 (27-82)
Female, n (%)	226 (99.1)	235 (100)
Geographic region, n (%)		
• North America	105 (46.1)	93 (39.6)
• Europe/Israel	53 (23.2)	77 (32.8)
• Asia-Pacific	70 (30.7)	65 (27.7)
Hormone receptor, n (%)		
• Positive	137 (60.1)	140 (59.6)
• Negative	91 (39.9)	95 (40.4)
ECOG PS, n (%)		
• 0	137 (60.1)	141 (60.0)
• 1	91 (39.9)	94 (40.0)
Stage at initial diagnosis, n (%)*		
• 0-III	120 (52.6)	130 (55.3)
• IV	103 (45.2)	98 (41.7)

Characteristic	T-DM1 + Tucatinib (n = 228)	T-DM1 + Placebo (n = 235)
Presence or history of brain mets, n (%)	99 (43.4)	105 (44.7)
• Active	50 (21.9)	57 (24.3)
• Treated stable	49 (21.5)	48 (20.4)
No brain mets, n (%)†	129 (56.6)	130 (55.3)
Prior lines of systemic tx in metastatic setting		
• Median (range)	1 (0-8)	1 (0-6)
• 0, n (%)	29 (12.7)	33 (14.0)
• 1, n (%)	146 (64.0)	150 (63.8)
• 2, n (%)	36 (15.8)	31 (13.2)
• ≥3, n (%)	17 (7.5)	21 (8.9)
Received prior pertuzumab tx, n (%)	202 (88.6)	214 (91.1)
Received prior anti-HER2 TKIs, n (%)	3 (1.3)	5 (2.1)

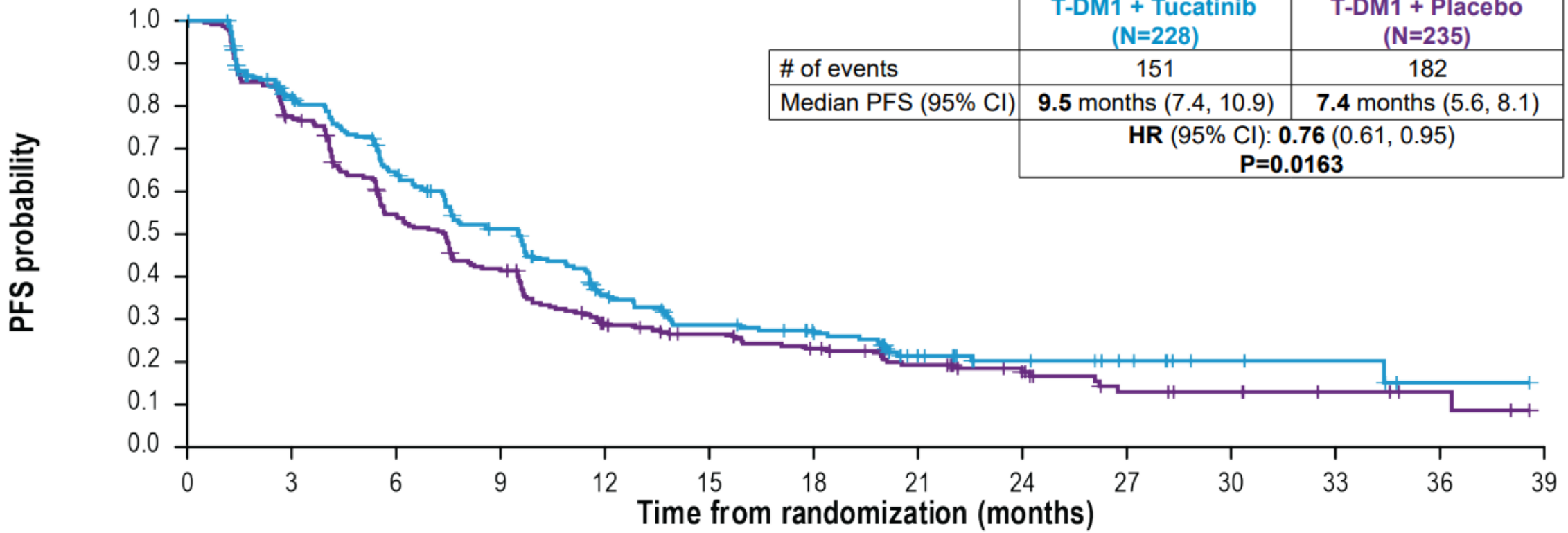
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Progression-Free Survival

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



Patients at risk

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

SABCS 2023 Abstract GS01-10

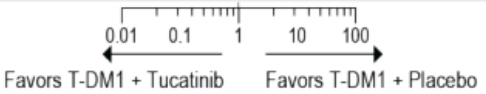
© 2024 Cornerstone Specialty Network. All rights reserved.

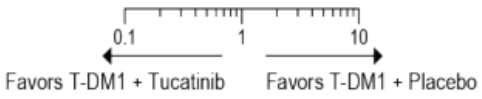
KEY DATA

HER2CLIMB-02 Clinical Trial

Progression-Free Survival by Subgroups

	T-DM1 + Tucatinib (N=228) Events/N	T-DM1 + Placebo (N=235) Events/N	Hazard Ratio with 95% CI
ITT Analysis	151/228	182/235	0.76 (0.61, 0.95)
Baseline brain metastasis			
Yes	70/99	85/105	0.64 (0.46, 0.89)
No	80/127	97/130	0.88 (0.65, 1.19)
Line of treatment for metastatic disease			
First	16/26	21/28	0.51 (0.23, 1.12)
Other	135/202	161/207	0.79 (0.63, 1.00)
ECOG performance status			
0	86/137	109/141	0.66 (0.49, 0.89)
1	65/91	73/94	0.91 (0.65, 1.28)
Hormone receptor status			
Positive	85/137	107/140	0.75 (0.56, 1.01)
Negative	66/91	75/95	0.82 (0.58, 1.15)
Region			
North America	68/105	69/93	0.88 (0.62, 1.26)
Europe/Israel	36/53	57/77	0.75 (0.46, 1.20)
Asia-Pacific	47/70	56/65	0.74 (0.49, 1.12)
Age			
<65 years	126/186	155/201	0.80 (0.62, 1.02)
≥65 years	25/42	27/34	0.61 (0.33, 1.11)
Race			
White	68/101	76/102	0.79 (0.55, 1.13)
Asian	45/66	58/65	0.73 (0.49, 1.11)
Others	38/61	48/68	0.79 (0.48, 1.28)
Initial diagnosis			
0-III	81/120	100/130	0.72 (0.53, 0.99)
IV	67/103	79/98	0.77 (0.55, 1.08)
Prior pertuzumab			
Yes	137/203	166/214	0.78 (0.62, 0.99)
No	14/25	16/21	0.74 (0.29, 1.87)





ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

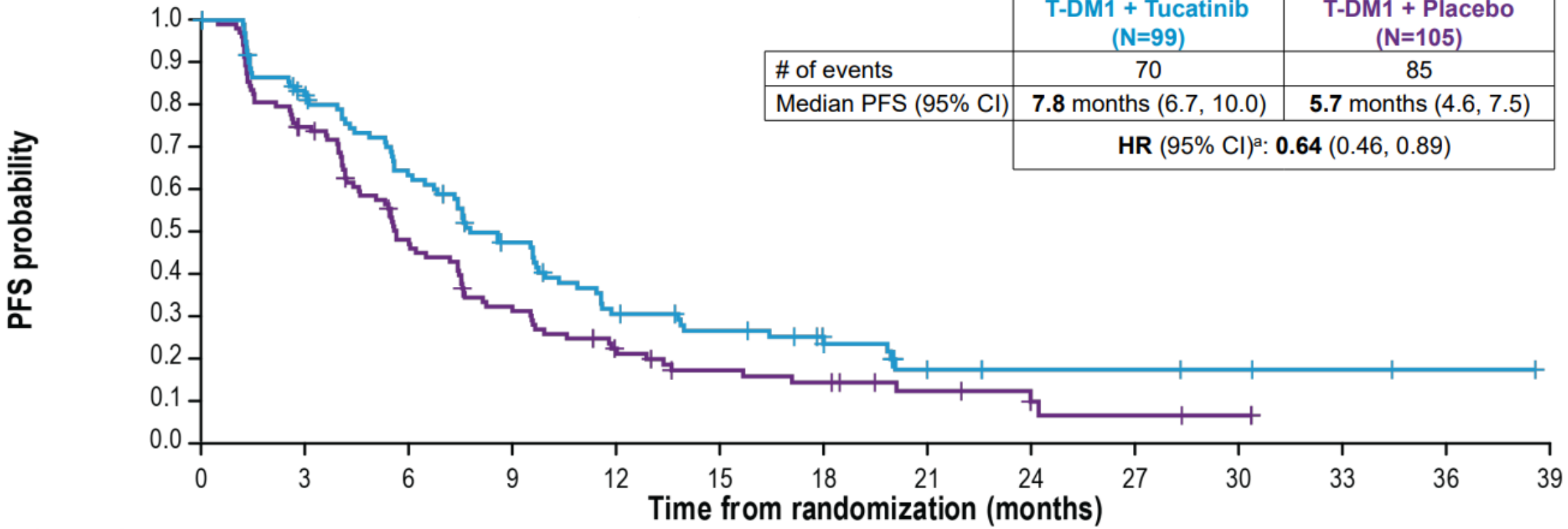
© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Progression-Free Survival in Patients with Brain Metastases

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



Patients at risk

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

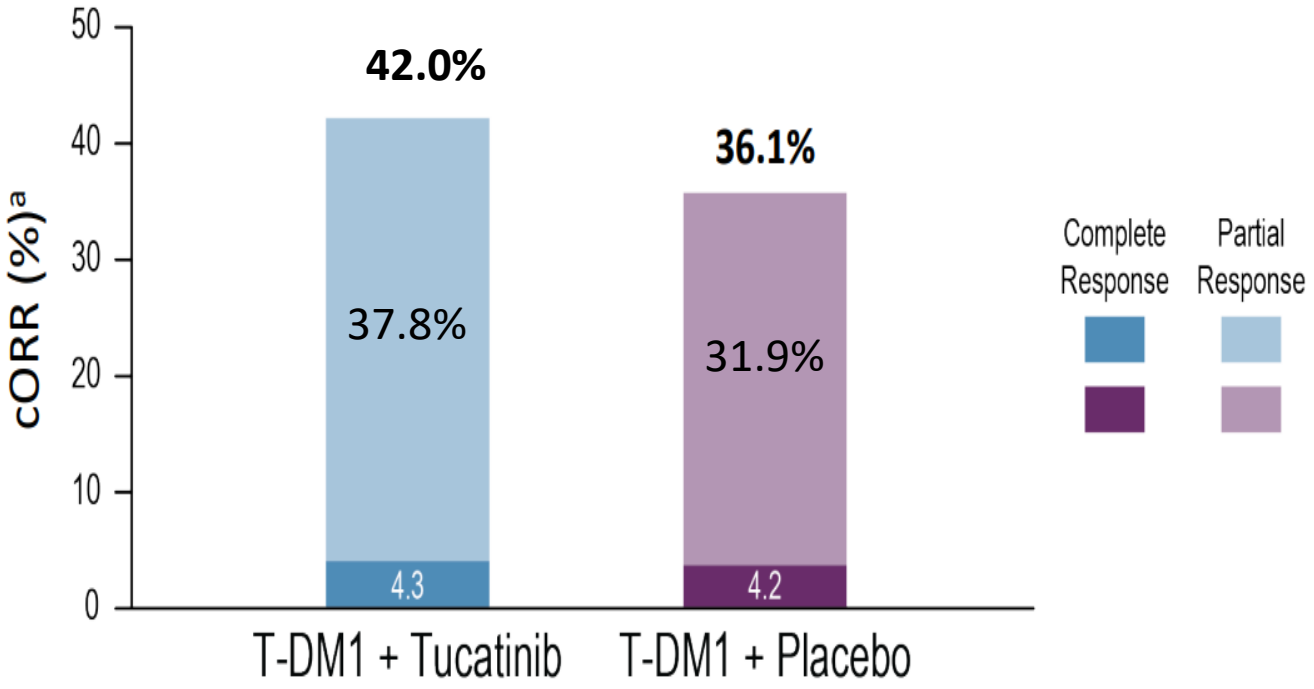
SABCS 2023 Abstract GS01-10

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Confirmed ORR



Median duration of tucatinib or placebo treatment:

- 7.4 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

Median duration of T-DM1 treatment:

- 7.5 months for T-DM1 + Tucatinib and 6.2 months for T-DM1 + Placebo

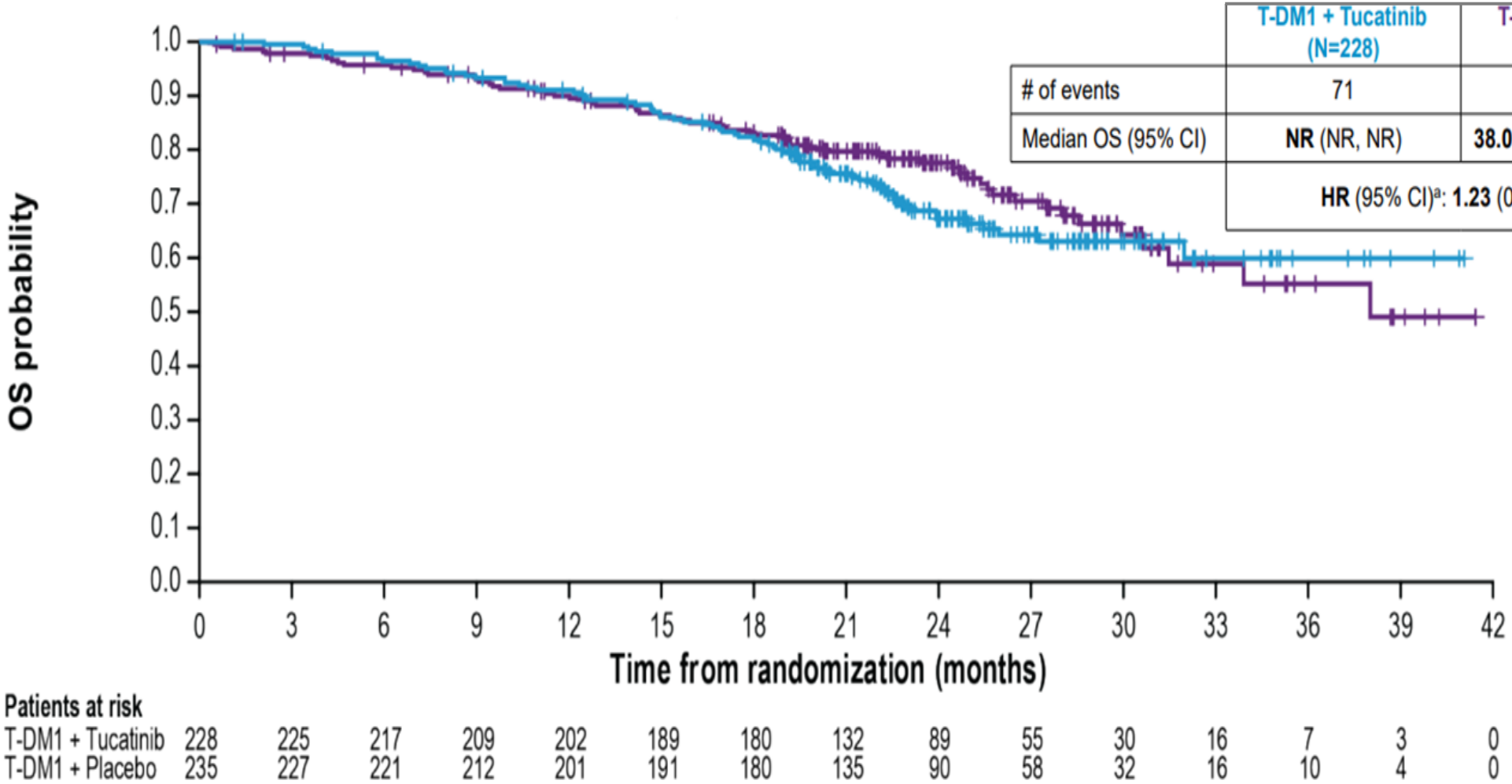
SABCS 2023 Abstract GS01-10

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Overall Survival



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

SABCS 2023 Abstract GS01-10

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Subsequent Therapies

	T-DM1 + Tucatinib (n = 228)	T-DM1 + Placebo (n = 235)
Patients who have discontinued or never received study treatment, n (%)	188 (82.5)	206 (87.7)
Patients who received ≥1 subsequent anticancer systemic therapy, n (%)	150 (79.8)	168 (81.6)
Median subsequent lines of therapies (range)	2.0 (1-13)	2.0 (1-15)
Subsequent therapies, n (%)		
• T-DXd	93 (49.5)	101 (49.0)
• Chemotherapy	76 (40.4)	81 (39.3)
• Trastuzumab	60 (31.9)	51 (24.8)
• Tucatinib	29 (15.4)	28 (13.6)
• T-DM1	25 (13.3)	22 (10.7)

SABCS 2023 Abstract GS01-10

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

HER2CLIMB-02 Clinical Trial

Safety

TEAEs, n (%)	T-DM1 + Tucatinib (n = 231)	T-DM1 + Placebo (n = 233)
Any grade	230 (99.6)	233 (100)
Grade ≥3	159 (68.8)	96 (41.2)
Serious TEAEs	70 (30.3)	52 (22.3)
Leading to death	3 (1.3)	2 (0.9)
Leading to discontinuation of tucatinib or pbo	40 (17.3)	16 (6.9)
Leading to discontinuation of T-DM1	47 (20.3)	26 (11.2)

Most common TEAE (≥2%) leading to discontinuation of tucatinib or placebo was
- increased ALT (2.6% vs 0%)

Most common TEAEs (≥2%) leading to discontinuation of T-DM1 (with tucatinib vs placebo) were:
- Increased ALT (2.2% vs 0%)
- Thrombocytopenia (2.2% vs 0%)
- Interstitial lung disease (0% vs 2.1%)

TEAEs in ≥20% of Patients, %	T-DM1 + Tucatinib (n = 231)		T-DM1 + Placebo (n = 233)	
	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3
Nausea	61.9	3.5	47.3	2.1
Diarrhea	51.9	4.8	25.7	0.9
Fatigue	42.8	6.1	34.3	3.0
Vomiting	35.1	1.7	15.1	2.1
Increased AST	19.4	16.5	16.7	2.6
Increased ALT	18.1	16.5	14.6	2.6
Headache	34.6	1.3	38.2	0.9
Epistaxis	33.8	0.4	19.3	0.4
Decreased appetite	32.9	0.9	21.8	0.9
Constipation	25.9	0.9	32.6	0.4
Pyrexia	22.9	0.9	14.6	0
Arthralgia	23.0	0.4	24.9	2.1

© 2024 Cornerstone Specialty Network. All rights reserved.

HER2CLIMB-02 Clinical Trial

AEs of Special Interest

Dose Modifications Due to Hepatic TEAEs, n (%)	T-DM1 + Tucatinib (n = 231)	T-DM1 + Placebo (n = 233)
Tucatinib or placebo dose holds	76 (32.9)	26 (11.2)
Tucatinib or placebo dose reduction	46 (19.9)	12 (5.2)
Tucatinib or placebo discontinuation	16 (6.9)	5 (2.1)
T-DM1 discontinuation	18 (7.8)	5 (2.1)

Dose Modifications Due to Diarrhea, n (%)	T-DM1 + Tucatinib (n = 231)	T-DM1 + Placebo (n = 233)
Tucatinib or placebo dose holds	9 (3.9)	2 (0.9)
Tucatinib or placebo dose reduction	9 (3.9)	1 (0.4)
Tucatinib or placebo discontinuation	1 (0.4)	0
T-DM1 discontinuation	0	0

Hepatic TEAEs

- Grade ≥3 hepatic TEAEs greater in T-DM1 + Tucatinib arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
- No Hy's law cases were identified
- 85% of all-grade hepatic TEAEs in T-DM1 + Tucatinib arm resolved or returned to grade 1, with median of 22 days to resolution

Diarrhea

- Grade ≥3 events reported in 4.8% of T-DM1 + Tucatinib arm and 0.9% of T-DM1 + Placebo arm
- No grade ≥4 events were reported in either arm

© 2024 Cornerstone Specialty Network. All rights reserved.

SUMMARY

HER2CLIMB-02 Clinical Trial

- In primary analysis of phase III HER2CLIMB-02 trial in patients with previously treated HER2-positive LA/MBC, combination T-DM1 + tucatinib significantly improved median PFS vs T-DM1 + placebo
  - Median PFS: 9.5 mo vs 7.4 mo; HR: 0.76 (95% CI: 0.61-0.95; *P* = 0.0163)
  - PFS benefit was consistent across prespecified subgroups
  - Improved median PFS for patients with brain mets (7.8 mo vs 5.7 mo; HR: 0.64)
  - OS data immature at data cutoff

- Safety profile was consistent with previous reports from tucatinib and T-DM1, with more frequent hepatic events in combination arm that were generally manageable and reversible

© 2024 Cornerstone Specialty Network. All rights reserved.

HER2CLIMB-02 Clinical Trial

Use of tucatinib in combination with T-DM1 provides benefit to patients with HER2+ locally advanced or metastatic breast cancer, compared to T-DM1 alone, regardless of brain metastases

© 2024 Cornerstone Specialty Network. All rights reserved.

2023 SABCS Key Studies

Triple negative and HER2-low Breast Cancer

- ALEXANDRA/Impassion030
- KEYLYNK-009
- DESTINY-Breast08
- DEBBRAH

HR+ Breast Cancer

- PROSPECT
- NRG Oncology/NSABP B-51/RTOG 1304
- IDEA
- ADAPTcycle
- INAVO120

HER2+ Breast Cancer

- KATHERINE
- HER2CLIMB-02
- Zanidatamab

© 2024 Cornerstone Specialty Network. All rights reserved.

Zanidatamab Clinical Trial

Does zanidatamab in combination with palbociclib and fulvestrant (phase 2 trial) provide benefit to patients with HER2-positive metastatic breast cancer?

Zanidatamab is an investigational HER2 targeted bispecific antibody

cornerstone specialty network™

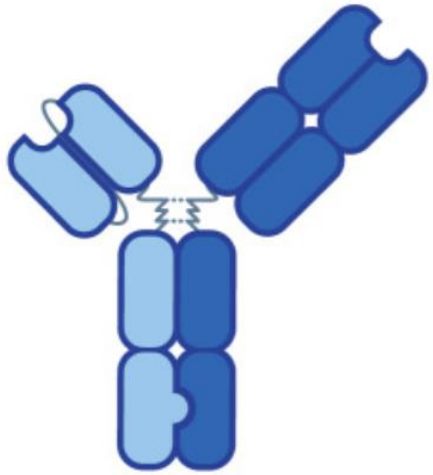
© 2024 Cornerstone Specialty Network. All rights reserved.

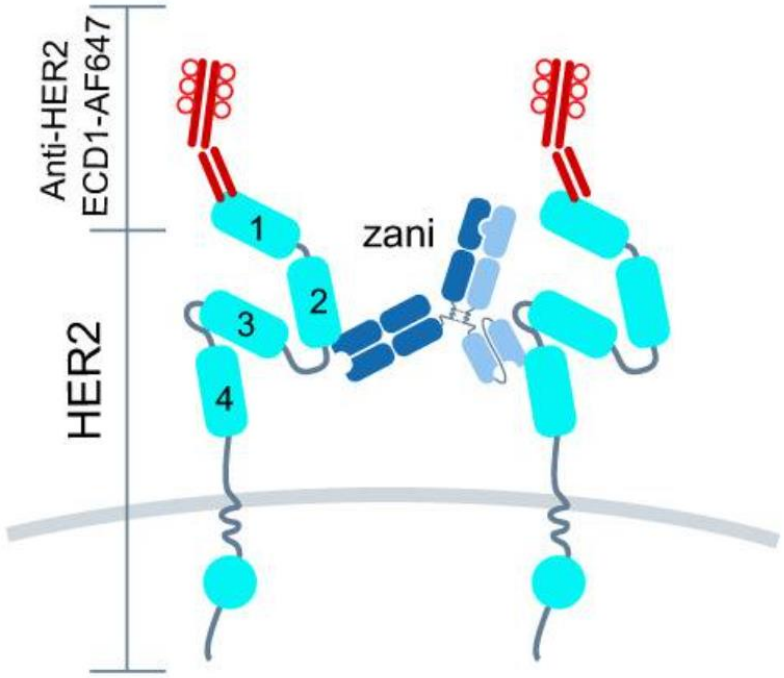
KEY DATA

Zanidatamab Clinical Trial

Zanidatamab is a humanized, biparatopic, immunoglobulin 1 (IgG1)-like Ab with an scFv (light blue) that binds the juxtamembrane ECD4 of HER2 and a Fab (dark blue) that binds the ECD2 dimerization domain of HER2, the same domains targeted by trastuzumab and pertuzumab, respectively, leading to:

- Receptor crosslinking, clustering, internalization, and downregulation
- Inhibition of tumor cell signaling and proliferation by preventing HER2 dimerization
- Immune-mediated antitumor effects including antibody- dependent cellular cytotoxicity and phagocytosis, and complement-dependent cytotoxicity





Zanidatamab is a bispecific antibody that simultaneously binds two non-overlapping extracellular domains of HER2 (biparatopic binding)

Weisser NE, et al. Nat Commun. 2023;14(1):1394

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Study Design: Single arm phase IIa trial

- Unresectable, locally advanced and/or metastatic HER2+ HR+ BC
- Enrollment based on local HER2 assess ment (reassessed using central testing)
- ECOG PS ≤1
- Prior treatment with trastuzumab, pertuzumab, and TDM1 were required
- No prior treatment with CDK4/6 inhibitor(s)
- Previously treated, stable brain metastases allowed

Zanidatamab[a]
20 mg/kg IV Q2W
+
Palbociclib
125 mg PO daily (day 1-21)
+
Fulvestrant
500 mg IM Q4W[b]

Tumor assessments Q8W

- Part 1 of the study evaluated safety and was previously reported (n=45);
- No zanidatamab-related DLTs occurred and the RDs for part 2 were identified[c]

Primary End Point: *Part 1*: Safety
Part 2: PFS at 6 mo (PFS6)

Secondary Endpoints: ORR, DCR, DOR, PFS, OS
Select exploratory endpoints: PAM50 subtyping

Enrollment completed November 2022 (data extracted August 2023)

[a]Mandatory infusion-related reaction prophylaxis (acetaminophen, diphenhydramine, and corticosteroids [hydrocortisone or dexamethasone]).
[b]After loading doses of 500 mg IM on days 1, 15, 28.
[c]One DLT of grade 4 neutropenia lasting >7 days occurred and was related to palbociclib.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Baseline Characteristics

	All Patients (N=51)	ccHER2+ (n=32)	non-ccHER2+ (n=19)
Median age (range), years	54 (36-77)	55 (36-75)	54 (39-77)
Female sex, n (%)	49 (96)	31 (97)	18 (95)
Race, n (%)			
White	42 (82)	30 (94)	12 (63)
Asian	2 (4)	1 (3)	1 (5)
Other	7 (14)	1 (3)	6 (32)
ECOG PS, n (%)			
0	25 (49)	18 (56)	7 (37)
1	26 (51)	14 (44)	12 (63)
HER2 and HR status: local testing, n (%)	51 (100)		
	32 (63)	32 (100)	0 (0)
HER2+: central testing	51 (100)	32 (100)	19 (100)
HR+: local testing only			
Prior history of brain metastases, n (%)	9 (18)	8 (25)	1 (5)
Prior systemic anticancer therapy regimens: metastatic setting, n (%)	51 (100)	32 (100)	19 (100)
Median # of prior regimens (range)	4 (1-12)	4 (1-12)	4 (2-10)

	All Patients (N=51)	ccHER2+ (n=32)	non-ccHER2+ (n=19)
Prior endocrine therapy: metastatic setting, n (%)	37 (73)	21 (66)	16 (84)
Median # of prior regimens (range)	1 (0-5)	1 (0-5)	1 (0-3)
Prior fulvestrant therapy: any setting, n (%)	11 (22)	6 (19)	5 (26)
Prior HER2-targeted therapy: any setting, n (%)	51 (100)	32 (100)	19 (100)
Median (range)	4 (2-6)	4 (1-10)	3 (2-8)
Trastuzumab	51 (100)	32 (100)	19 (100)
T-DM1	50 (98)	31 (97)	19 (100)
Pertuzumab	42 (82)	26 (81)	16 (84)
Lapatinib	14 (27)	9 (28)	5 (26)
Tucatinib	13 (25)	11 (34)	2 (11)
T-DXd	12 (24)	8 (25)	4 (21)
Neratinib	2 (4)	2 (6)	0 (0)
Margetuximab	1 (2)	1 (3)	0 (0)

HER2 central testing: 32 patients were HER2+ (centrally confirmed HER2+[ccHER2+]), 18 HER2− (positive with local assessment), and 1 patient had missing data

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Efficacy

	All Patients (n=51)	ccHER2+ Subset (n=32)	non-ccHER2+ Subset (n=19)
PFS6, n (%) [95% CI]	34 (**67**) [52, 79]	22 (**69**) [50, 84]	12 (**63**) [38, 84]
Median PFS, months [95% CI]	12 (8, 15)	15 (9, 17)	8 (4, 9)
cORR, n (%) [95% CI][a]	16 (35) [21, 50]	14 (48) [29, 68]	2 (10) [1, 33]
cBOR, n (%)[a]			
• CR	3 (6)	3 (10)	0 (0)
• PR	13 (28)	11 (38)	2 (12)
• SD	26 (56)	13 (45)	13 (76)
• PD	4 (9)	2 (7)	2 (12)
Disease Control Rate, n (%) [95% CI]	42 (91) [79, 98]	27 (93) [77, 99]	15 (88) [64, 98]
Median Duration of Response, months[b]	15 (12, 25)	14 (11, 25)	NE (7, NE)[c]

- Median (range) follow-up time: 16 (2-32) months
- Median (range) duration of zanidatamab treatment: 8 (1-30) months

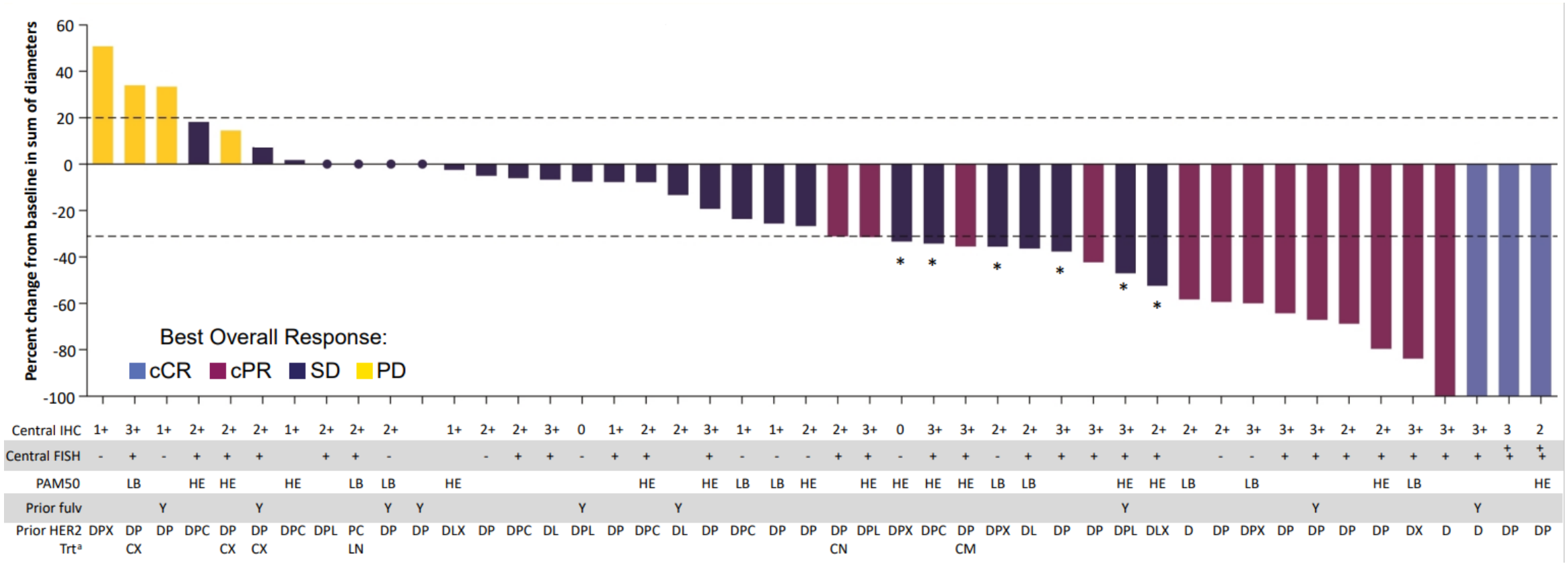
aEvaluated in patients with measurable disease (n=46 all patients; n=29 ccHER2+ subset; n=17 non-ccHER2+ subset.
bEvaluated in patients with a CR or PR (n=16 all patients; n=14 ccHER2+ subset; n=2 non-ccHER2+ subset).
cMedian DOR was 7.1 and 24.1 months for the 2 patients with a response in the non-ccHER2+ subset.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Response Rate



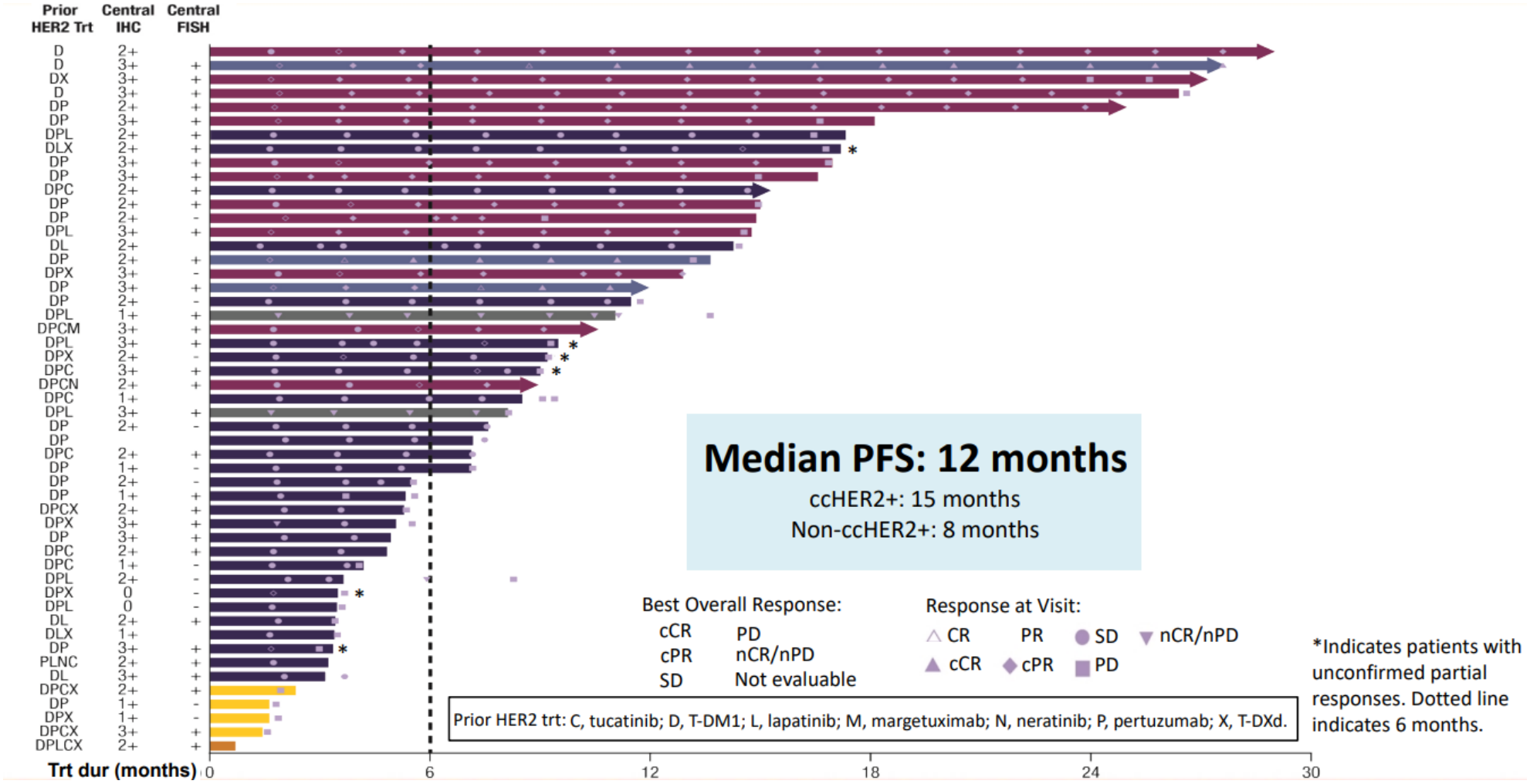
Prior HER2 trta: C, tucatinib; D, T-DM1; L, lapatinib; M, margetuximab; N, neratinib; P, pertuzumab; X, T-DXd.
PAM50 subtype: HE, HER2-enriched; LB, luminal B.
*Indicates patients with unconfirmed partial responses.
Dotted lines indicate - 30% and +20% change in tumor size. aAll patients received prior trastuzumab and taxane.

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Treatment Duration and PFS



SABCS 2023 Abstract LBO1-04

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Efficacy by PAM50 Subtype

- 29 patients (57%) had PAM50 subtyping available: 3% basal-like; 55% HER2-enriched; 41% Luminal B

	All Patients With PAM50 Subtyping (n=29)	Basal-Like (n=1)[a]	HER2-Enriched (n=16)	Luminal B (n=12)
PFS6, n (%) [95% CI]	**19 (66) [46, 82]**	**1 (100) [2, 100]**	**10 (62) [35, 85]**	**8 (67) [35, 90]**
Median PFS, months [95% CI]	9 (7, 14)	6 (NE, NE)	9 (4, 15)	12 (3, 24)
cORR, n (%)[b]	**7 (28)**	**0**	**4 (27)**	**3 (30)**
cBOR, n (%)[b]				
• CR	1 (4)	0	1 (7)	0
• PR	6 (24)	0	3 (20)	3 (30)
• SD	16 (64)	0	10 (67)	6 (60)
• PD	2 (8)	0	1 (7)	1 (10)
Disease Control Rate, n (%) [95% CI][b]	**23 (92) [74, 99]**	**0**	**14 (93) [68, 100]**	**9 (90) [56, 100]**
Median Duration of Response, months[c]	**22 (12, NE)**	**0**	**13 (12, NE)**	**NE (22, NE)**

cBOR, confirmed best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2+, human epidermal growth factor receptor 2 positive; PD, progressive disease; PFS, progression-free survival; PFS6, progression-free survival at 6 months; PR, partial response; SD, stable disease

aThis patient did not have measurable disease. bEvaluated in patients with measurable disease (n=25 all patients with PAM50 subtyping; n=15 HER2-enriched; n=10 luminal B). cEvaluated in patients with CR or PR (n=7 all patients with PAM50 subtyping; n=4 HER2-enriched; n=3 luminal B).

© 2024 Cornerstone Specialty Network. All rights reserved.

KEY DATA

Zanidatamab Clinical Trial

Safety

	Patients (N=51)	
	Any Grade	Grade 3 or 4
Any TRAE, n (%)	51 (100)	34 (67)
Serious TRAE, n (%)	1 (2)	1 (2)
TRAE in >20% of patients and/or grade 3 TRAE in ≥2 patients, n (%)		
Diarrhea	41 (80)	7 (14)
Nausea	20 (39)	1 (2)
Stomatitis	19 (37)	1 (2)
Neutrophil count decreased/neutropenia	30 (59)	27 (53)
Anemia	15 (29)	5 (10)
Vomiting	13 (25)	1 (2)
Asthenia	12 (24)	0 (0)
Thrombocytopenia	8 (16)	3 (6)
Hypomagnesemia	5 (10)	2 (4)
Hypokalemia	4 (8)	2 (4)
Treatment-related AESI, n (%)		
Ejection fraction decreased	6 (12)	1 (2)[a]
Infusion-related reaction	2 (4)	0 (0)

aEvent ongoing at the time data was extracted

- AEs requiring discontinuation of drug
  - All treatments: 1 patient (grade 1 asthenia)
  - Palbociclib treatment: 2 patients (1 had gr ade 3 diarrhea and 1 had grade 3 transam inases increased)
- One serious TRAE (transaminases increased) was reported (event resolved)
- AEs led to a dose reduction of zanidatamab in 4 patients
- 14 deaths (none related to treatment)
  - 12 due to disease progression
  - 1 due to an unrelated TEAE of COVID-19
  - 1 cause unknown (causality pending)

© 2024 Cornerstone Specialty Network. All rights reserved.

Zanidatamab Clinical Trial

Efficacy and safety results of Zanidatamab in combination with palbociclib and fulvestrant supports further investigation as a potential novel chemotherapy-free treatment option for previously treated patients with HER2+ HR+ mBC

Not yet approved, small n, more to come…

© 2024 Cornerstone Specialty Network. All rights reserved.

Managing HER2+ Breast Cancer in Community Oncology

© 2024 Cornerstone Specialty Network. All rights reserved.

Guidelines for HER2+ BC: preoperative/adjuvant

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[h] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[k]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[i] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[j] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	**Other Recommended Regimens:** • AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m².
[c] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
[h] Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.
[i] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.
[j] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[k] Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences in those with node positive disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-L
2 OF 9

Version 5.2023, 12/05/23 © 2023 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.

- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[k]

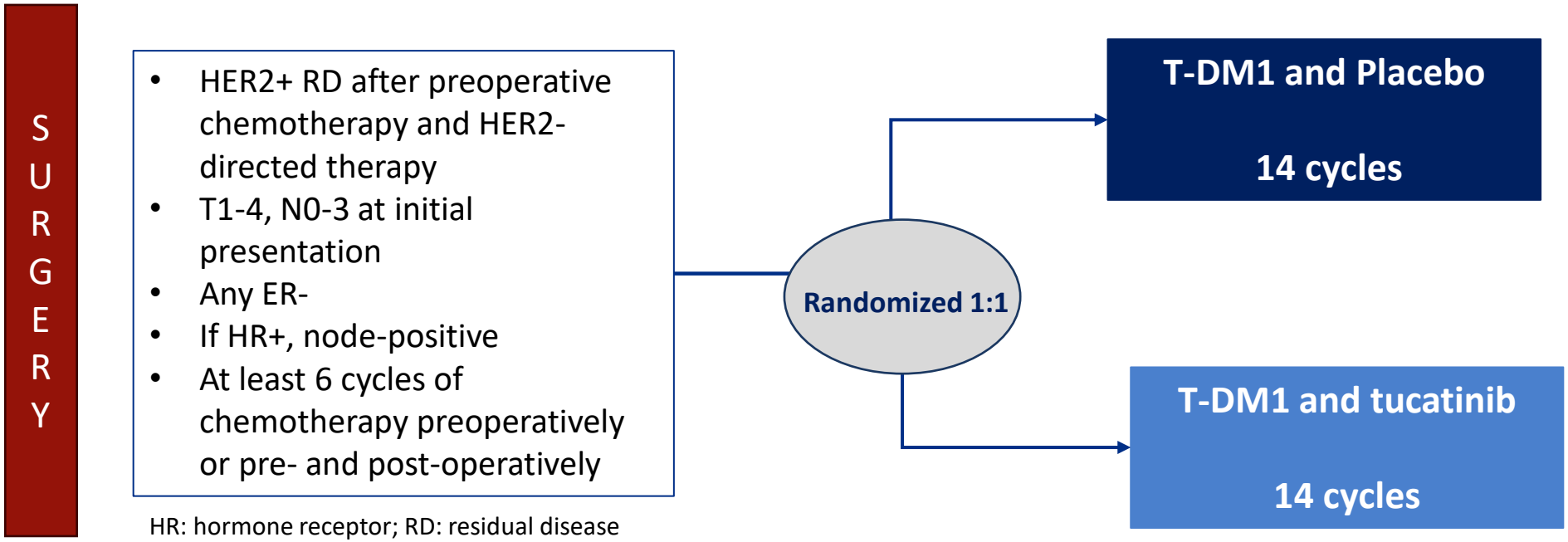
© 2024 Cornerstone Specialty Network. All rights reserved.

ONGOING TRIALS

CompassHER2 RD Clinical Trial

Alliance A011801 (compassHER2 RD): postneoadjuvant T-DM1 + tucatinib/placebo in patients with residual HER2-positive invasive breast cancer

Study Design: ongoing prospective, multicenter, Phase III randomized trial



HR: hormone receptor; RD: residual disease
If indicated, patients will also receive radiation therapy and/or endocrine therapy per standard of care guidelines.

Primary End Point: Invasive disease-free survival (iDFS)
Secondary Endpoints: Overall survival (OS), breast cancer free survival (BCFS), distant recurrence-free survival (DRFS), disease-free survival (DFS), and brain metastases-free survival (BMFS)

Future Oncol. 2021 Sep; 17(34): 4665–4676.

© 2024 Cornerstone Specialty Network. All rights reserved.

ONGOING TRIALS

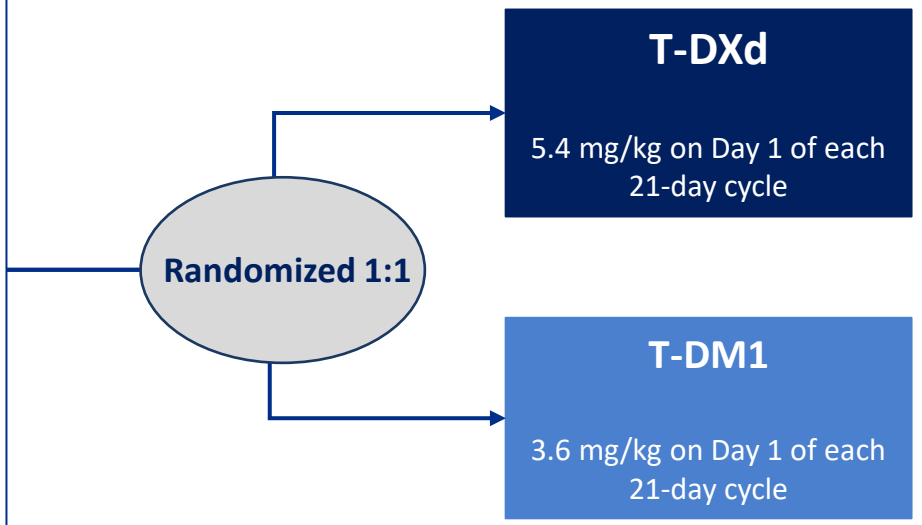
DESTINY-Breast05 Clinical Trial

A Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in High-risk HER2-positive Participants With Residual Invasive Breast Cancer Following Neoadjuvant Therapy

Study Design: Ongoing, Multicenter, Randomized, Open-Label, Active-Controlled Phase III Study

Stratified by: Operative status at disease presentation, prior to neo-adjuvant therapy (operable vs inoperable); Tumor hormone receptor status (positive vs negative); Post-neo-adjuvant therapy pathologic nodal status (positive vs negative); HER2 targeted neo-adjuvant therapy approach (single vs dual)

- Pathologically documented HER2-positive and histologically confirmed invasive BC
- Clinical stage at disease presentation: T1-4, N0-3, M0; patients presenting with T1N0 tumors are not eligible
- Patients defined as high-risk based on inoperable cancer at disease presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) or operable at presentation (clinical stages T1-3, N0-1, M0) with positive pathological node status (ypN1-3) after neo-adjuvant therapy.
- Completion of neoadjuvant systemic therapy, including taxane-based chemotherapy and HER2-directed treatment prior to surgery*



Primary End Point:
Invasive disease-free survival (iDFS) by investigator assessment

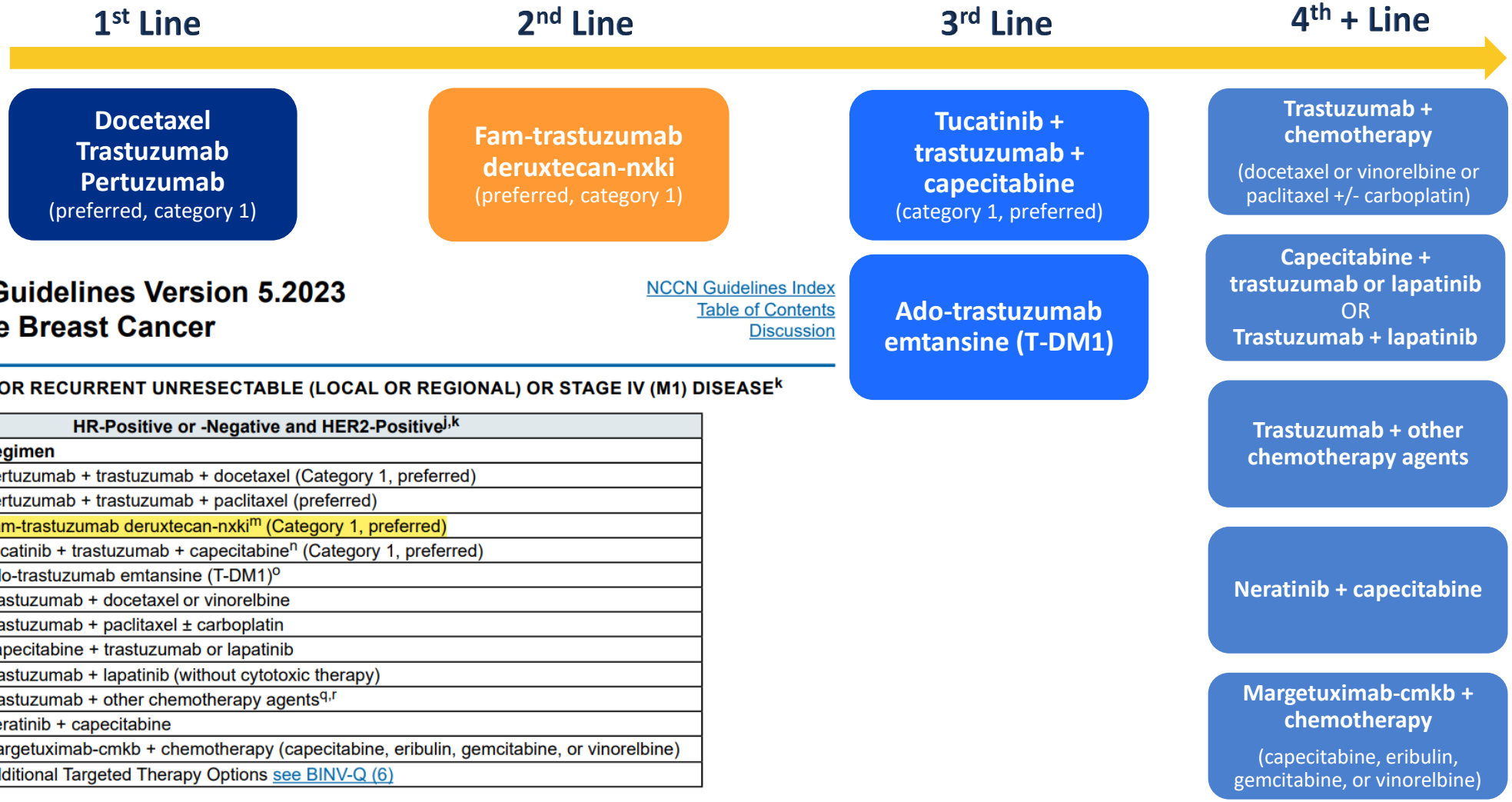
Secondary Endpoints:
Overall survival (OS), disease-free survival (DFS) by investigator, and safety

*Systemic therapy must consist of at least 6 cycles of neoadjuvant therapy with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab (± pertuzumab) and at least 9 weeks of taxane-based chemotherapy to be completed prior to surgery. Patients may have received an anthracycline as part of neoadjuvant therapy in addition to taxane chemotherapy.

ClinicalTrials.gov ID NCT04622319

© 2024 Cornerstone Specialty Network. All rights reserved.

Guidelines for HER2+ metastatic BC



National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

[m] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.

[o] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.

© 2024 Cornerstone Specialty Network. All rights reserved.

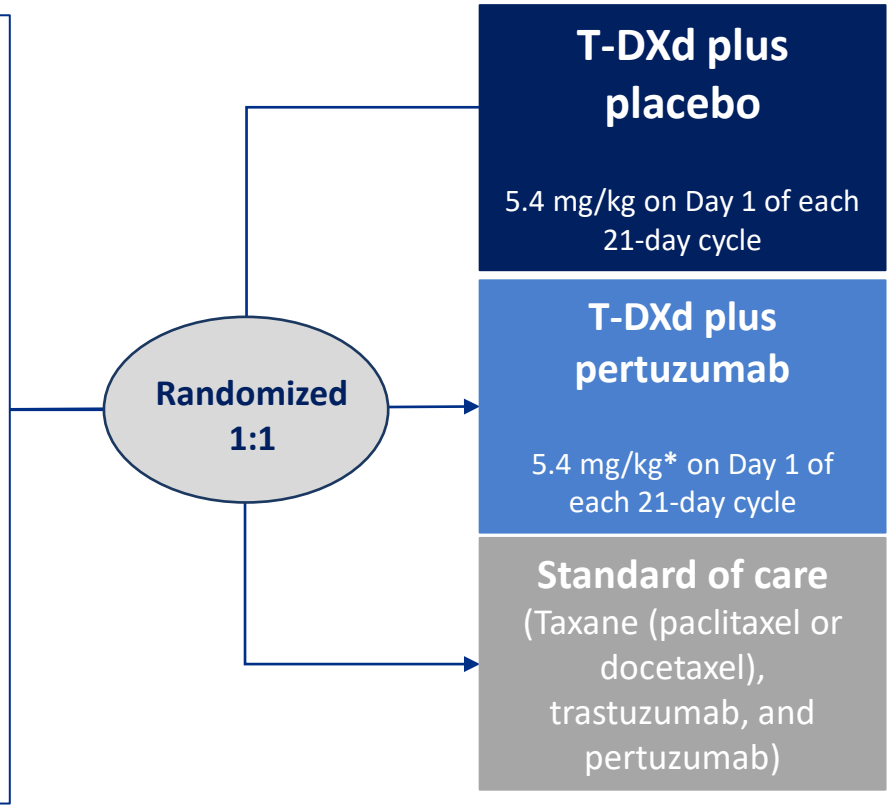
ONGOING TRIALS

DESTINY-Breast09 Clinical Trial

Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive, First-line Metastatic Breast Cancer

Study Design: Ongoing, global head-to-head Phase III Study

- Pathologically documented breast cancer that:
  - is advanced or metastatic
  - is locally assessed and prospectively centrally confirmed as HER2-positive (IHC3+ or ISH+)
  - is documented by local testing as hormone receptor (HR)-positive or HR-negative disease in the metastatic setting
- No prior chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer or only 1 previous line of endocrine therapy in the metastatic setting. Participants who have received chemotherapy or HER2-targeted therapy in the neo-adjuvant or adjuvant setting are eligible if > 6 months from treatment to metastatic diagnosis.
- Has protocol-defined adequate organ and bone marrow function
- ECOG performance status 0 or 1



Primary End Point:
Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) assessment

Secondary Endpoints:
Progression Free Survival (PFS) by Investigator assessment, Overall survival (OS), ORR, DoR, PFS2 and safety/tolerability

*Correction: presented dose was incorrectly shown as 3.6 mg/kg; actual dose of T-DXd is 5.4 mg/kg

ClinicalTrials.gov ID NCT04622319

© 2024 Cornerstone Specialty Network. All rights reserved.