LIVING BEYOND
BREAST CANCER®

Newsflash: Updates from the 2025 ASCO Annual Meeting

ASCO 2025: Updates in Breast Cancer

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AT THE FOREFRONT
UChicago Medicine

Agenda

- Introduction to Clinical Trials
- Updates from ASCO 2025
  - HR+/HER2- disease: SERENA-6, VERITAC-02, TRADE
  - HER2+ disease: DESTINY BREAST-09
  - TNBC: ASCENT-04
- Is a Clinical Trial right for me?

FDA Approved Drugs

- Food and Drug administration is responsible for regulating prescription medications
- All drugs that are utilized today outside of clinical trials have gone through approval process

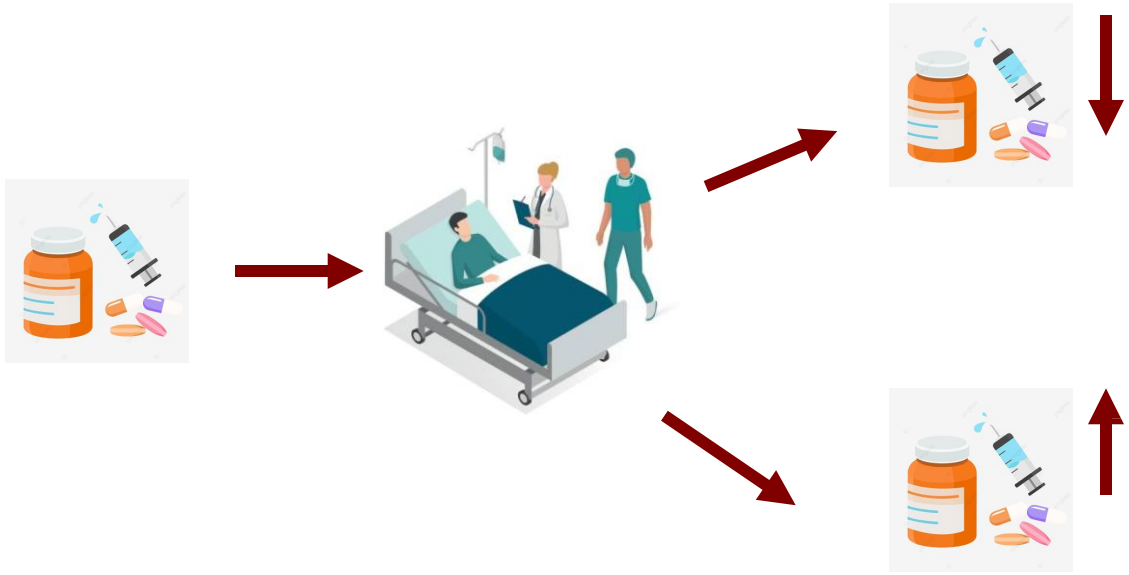
Clinical Trial Phases

EARLY STAGE BREAST CANCER: BEFORE SURGERY

Goals:

- Increase the likelihood that we significantly reduce or eradicate all cancer cells before surgery
- Find treatments that have less toxicity and side effects
- Find treatments that work in patients where traditional treatments have not

Early stage breast cancer: AFTER SURGERY

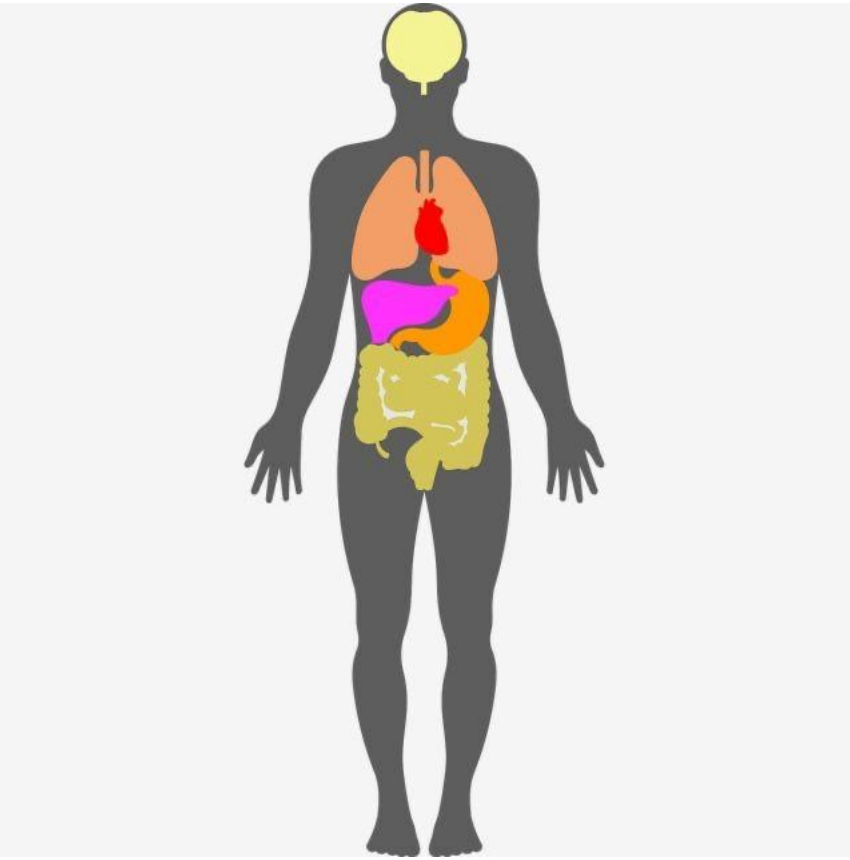


- Depending on a patient's response at surgery, we may want to give more or less medicine afterwards

Goals:

- Decrease patient's risk of cancer returning
- Match appropriate level of treatment with patient risk to reduce recurrence

Metastatic breast cancer



- Find treatments that have less toxicity and side effects
- Find treatments that are more effective than our current drugs and can extend a patient's life
- Understand how to use existing therapies in sequence for maximal benefit

SERENA-6

- Updates from ASCO 2025
  - HR+/HER2- disease: **SERENA-6**, VERITAC-02, TRADE
  - HER2+ disease: DESTINY BREAST-09
  - TNBC: ASCENT-04

2025 ASCO ANNUAL MEETING

SERENA-6

Camizestrant + CDK4/6 inhibitor for the treatment of emergent *ESR1* mutations during first-line endocrine-based therapy and ahead of disease progression in patients with HR+/HER2– advanced breast cancer: Phase 3, double-blind ctDNA-guided SERENA-6 trial

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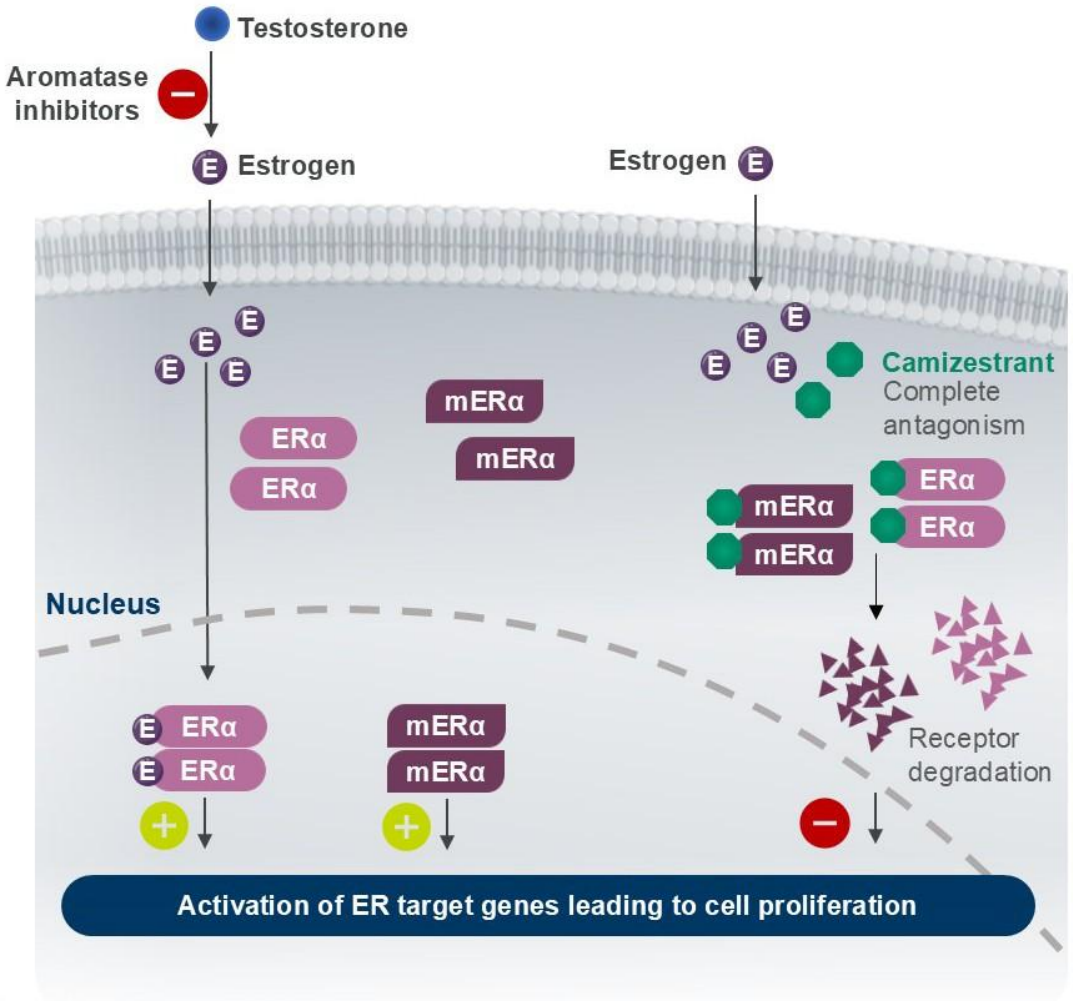
*Contributed equally

Background

- Approximately 70% of breast cancers are ER-positive and HER2-negative[1]
- ER is encoded by the *ESR1* gene. Hotspot *ESR1* mutations (*ESR1*m) lead to constitutive (estrogen-independent) activation of the ER
- *ESR1m* are rare (<5%) at diagnosis of ABC, but emerge during first-line AI + CDK4/6i, detected in ~40% of patients at disease progression[2–4]
- Camizestrant, the next-generation oral SERD and complete ER antagonist, was designed to inhibit and degrade mutant, as well as wildtype, ER[5,6]



ERα, estrogen receptor - alpha; HER2, human epidermal growth factor receptor 2; mERα, mutated estrogen receptor - alpha; SERD, selective estrogen receptor degrader.

1. National Cancer Institute: Cancer Stat Facts: Female Breast Cancer Subtypes. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html (Accessed April 22, 2025); 2. Bhave MA, et al. *Breast Cancer Res Treat* 2024;207:599–609; 3. Chaudhary N, et al. *NPJ Breast Cancer* 2024;10:15; 4. Bidard F-C, et al. *J Clin Oncol* 2022;40:3246–56; 5. Lawson M, et al. *Cancer Res* 2023;83:3989–4004; 6. Scott JS, et al. *J Med Chem* 2020;63:14530–59.

Background to the SERENA-6 study

- *ESR1* mutations can be detected in ctDNA liquid biopsies prior to progression on AI + CDK4/6i[1,2]
- In the open-label PADA-1 trial, switching to fulvestrant (a SERD) + palbociclib upon detection of *ESR1*m, ahead of disease progression, significantly improved PFS vs continuing AI + palbociclib[1]
- In the SERENA-2 study, camizestrant significantly improved PFS *vs* fulvestrant in pretreated ER-positive ABC including in patients with *ESR1*m[3]

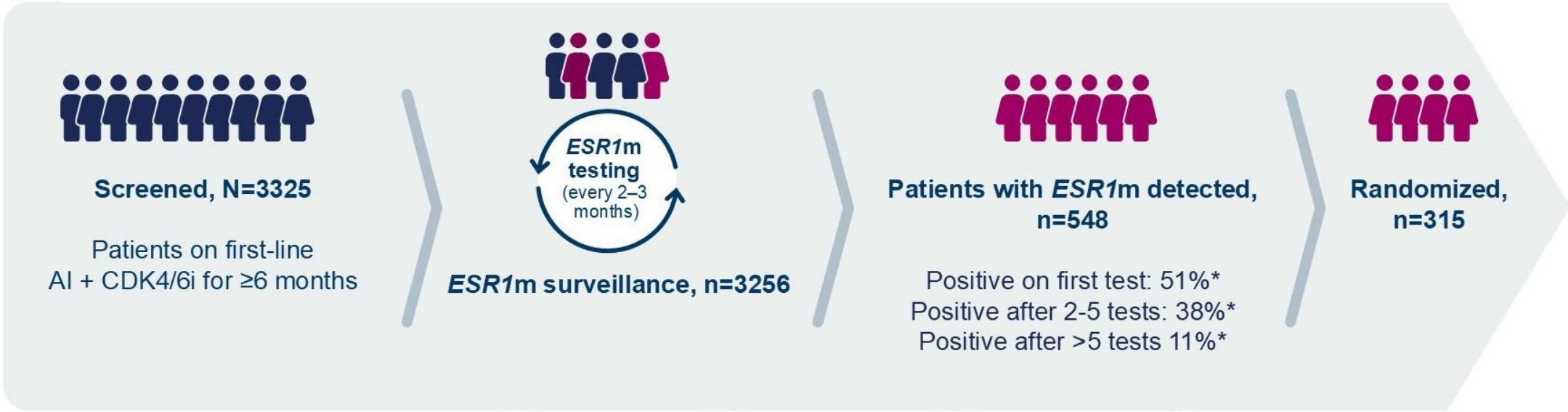
SERENA-6 tested the hypothesis that using camizestrant to treat emerging *ESR1*m ahead of disease progression, could extend the duration of benefit of first-line therapy

1. Bidard FC, et al. *Lancet Oncol* 2022;23:1367–77; 2. Fribbens C, et al. *Ann Oncol* 2018;29:145–53; 3. Oliveira M, et al. *Lancet Oncol* 2024;25:1424–39.

PRESENTED BY: Nicholas Turner, MD, PhD

*ESR1*m surveillance during first-line AI+CDK4/6i

SERENA-6



Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans

Patients ongoing in surveillance when screening closed, n=1949

Discontinued (n=233) due to:
- Screen failure (n=200)
  - Concurrent disease progression (n=53)
  - Patient not meeting other eligibility criteria (n=48)
  - Reason not provided (n=99)
- Withdrew consent, lost to follow-up or unknown (n=33)

An estimate of the proportion of patients with emerging *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/(the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).

Number of tests to obtain a positive *ESR1*m test result based on n=521 patients who met all the eligibility criteria for the *ESR1m* surveillance step. Patients were screened for inclusion into the study from 264 sites in 23 countries.

Of the 3325 patients screened for inclusion, ctDNA from patient blood samples were tested for *ESR1*m using Guardant360CDx (Guardant Health, Redwood City, CA, US).

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SERENA-6 study design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1

N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Continuing AI (anastrozole/ letrozole) + CDK4/6i + placebo for camizestrant

Stratification factors

- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

Primary endpoint

PFS by investigator assessment (RECIST v1.1)

Secondary endpoints

- PFS2**
- OS**
- Safety
- Patient-reported outcomes

*Pre- or perimenopausal women, and men received a luteinizing hormone–releasing hormone agonist per clinical guidelines. **Key secondary endpoint.
OS, overall survival; PFS2, second progression-free survival; qd, once daily dose; R, randomized; RECIST, response evaluation criteria in solid tumors.

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Baseline characteristics

SERENA-6

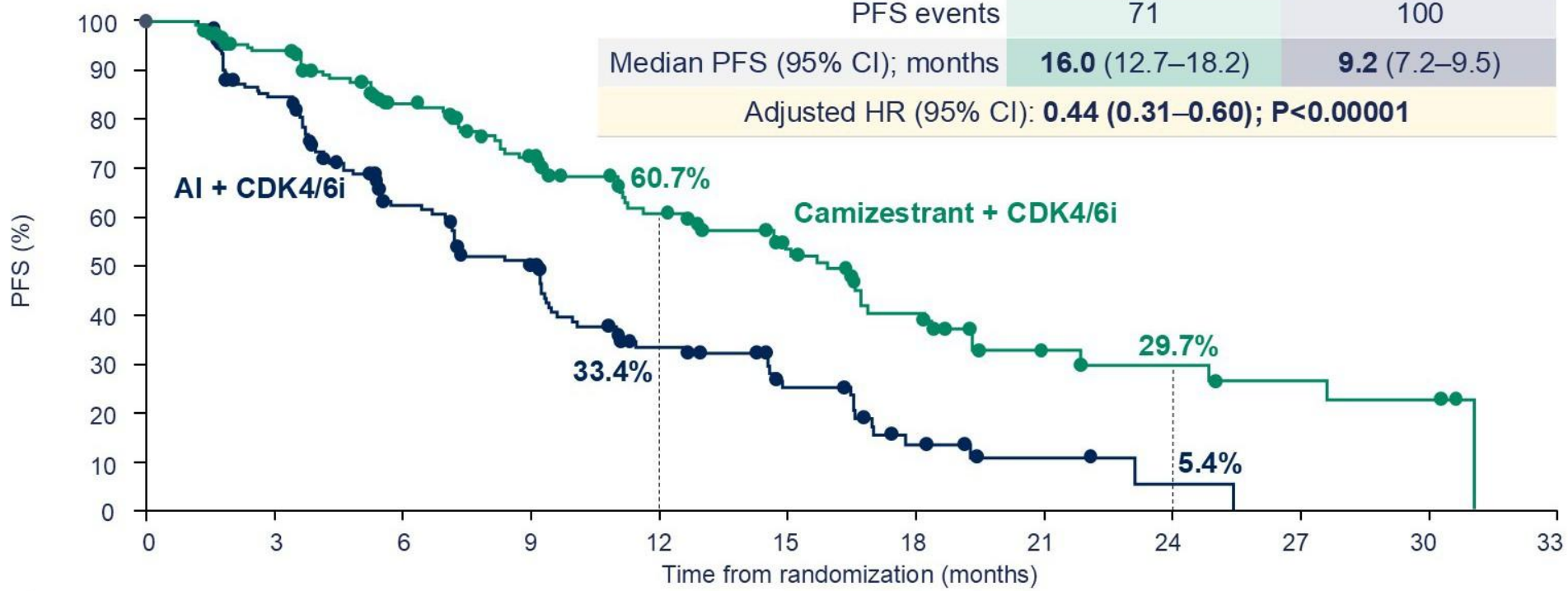
Characteristic		Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
Median age (range) — years		61.0 (29–81)	60.5 (35–89)
Female — n (%)		157 (100)	155 (98)
Race — n (%)	White	97 (62)	102 (65)
	Asian/other	39 (25) / 21 (13)	34 (22) / 22 (14)
Postmenopausal status — n (%)		123 (78)	127 (80)
ECOG performance-status score — n (%)*	0/1	107 (68) / 48 (31)	98 (62) / 56 (35)
Visceral metastases — n (%)†		66 (42)	71 (45)
Time of *ESR1*m detection — n (%)†	At first test	84 (54)	84 (53)
	At a subsequent test‖	73 (47)	74 (47)
	Median (range) – months	22 (4–95)	22 (6–96)
Time from initiation of AI + CDK4/6i to randomization — n (%)†	≥18 months	97 (62)	100 (63)
	<18 months	60 (38)	58 (37)
	Median (range) – months	23 (7–96)	23 (6–96)
CDK4/6i continued at randomization — n (%)†	Palbociclib	119 (76)	119 (75)
	Ribociclib	24 (15)	23 (15)
	Abemaciclib	14 (9)	16 (10)
Most common *ESR1*m at baseline — n (%)‡	D538G	70 (45)	82 (52)
	Y537S	61 (39)	60 (38)
	Y537N	29 (19)	25 (16)

*Data was missing for 2 patients in the camizestrant + CDK4/6i arm and 3 patients in the AI + CDK4/6i. One patient in the AI+CDK4/6i group had a score of 2, which was a protocol deviation. †Stratification factors. ‖Subsequent tests were performed every 2-3 months after the initial test. ‡Three most prevalent *ESR1*m detected of the 11 qualifying mutations. Patients may have had more than one *ESR1*m. ECOG, Eastern Cooperative Oncology Group.

Primary endpoint: Investigator-assessed PFS

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS events	71	100
Median PFS (95% CI); months	**16.0** (12.7–18.2)	**9.2** (7.2–9.5)
Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001**		



Number of patients at risk

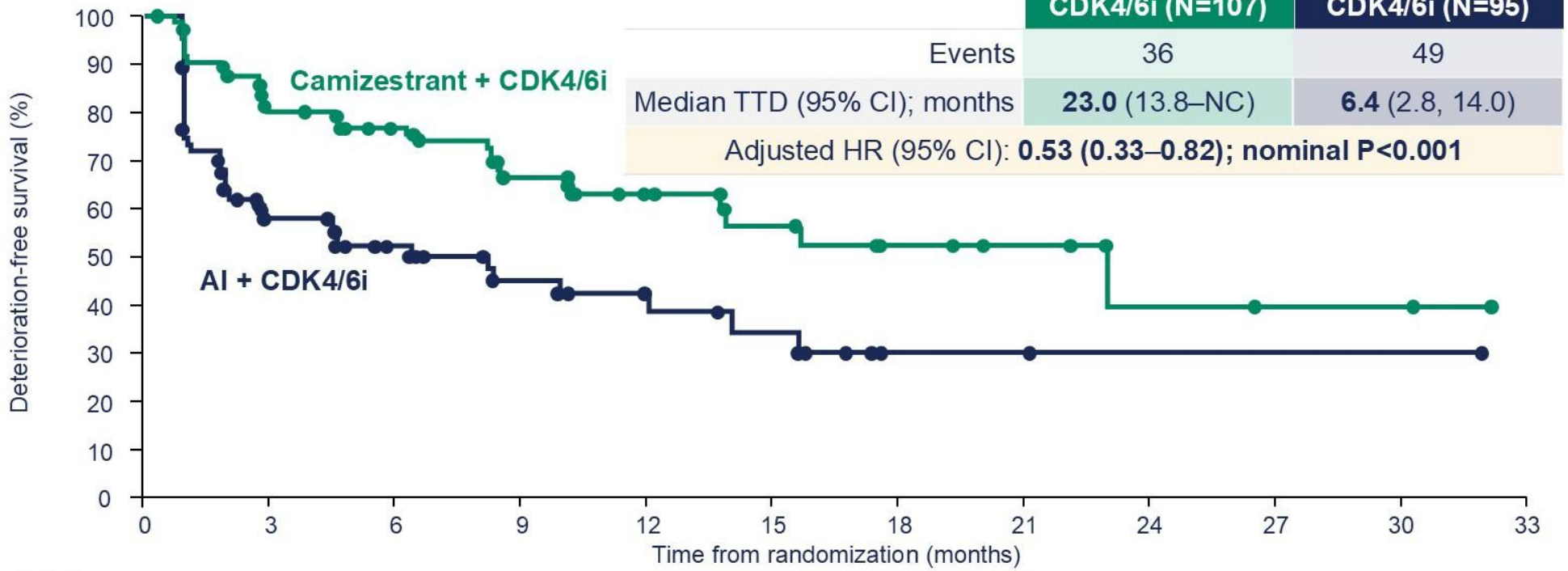
Camizestrant + CDK4/6i	157	138	105	82	55	41	26	11	9	7	6	0
AI + CDK4/6i	158	124	73	55	29	17	7	3	1	0	0	0

P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

Time to deterioration in global health status/quality of life

EORTC QLQ-C30

	Camizestrant + CDK4/6i (N=107)	AI + CDK4/6i (N=95)
Events	36	49
Median TTD (95% CI); months	**23.0** (13.8–NC)	**6.4** (2.8, 14.0)
Adjusted HR (95% CI): **0.53 (0.33–0.82); nominal P<0.001**		



Number of patients at risk

Camizestrant + CDK4/6i	107	72	59	40	24	16	9	6	3	2	2	0
AI + CDK4/6i	95	42	26	16	11	8	2	2	1	1	1	0

- Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i

Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 8 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (**EORTC QLQ-30**). Deterioration was defined as a decrease from baseline ≥16.6. HR was estimated using the Cox proportional hazard model stratified by time of *ESR1*m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥18 months). NC, not calculable; TTD, time-to-deterioration.

PRESENTED BY: Nicholas Turner, MD, PhD

Second progression-free survival (PFS2)

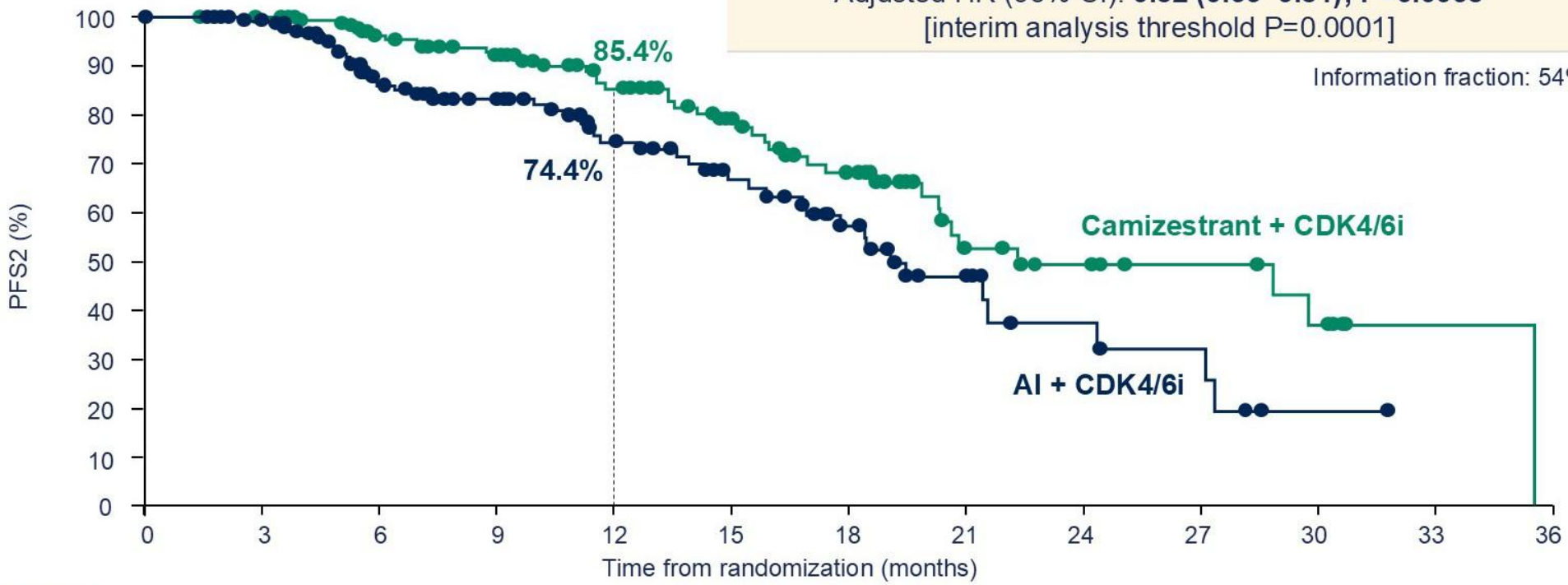
Key secondary endpoint

SERENA-6

	Camizestrant + CDK4/6i (N=157)	AI + CDK4/6i (N=158)
PFS2 events	38	47

Adjusted HR (95% CI): **0.52 (0.33–0.81); P=0.0038**
[interim analysis threshold P=0.0001]

Information fraction: 54%



Number of patients at risk

Camizestrant + CDK4/6i	157	146	120	103	74	55	39	17	12	9	6	1	0
AI + CDK4/6i	158	144	98	78	55	38	25	12	7	5	1	0	0

HR was estimated using the Cox proportional hazard model adjusted for stratification factors. Final PFS2 analysis will occur at 158 PFS2 events.

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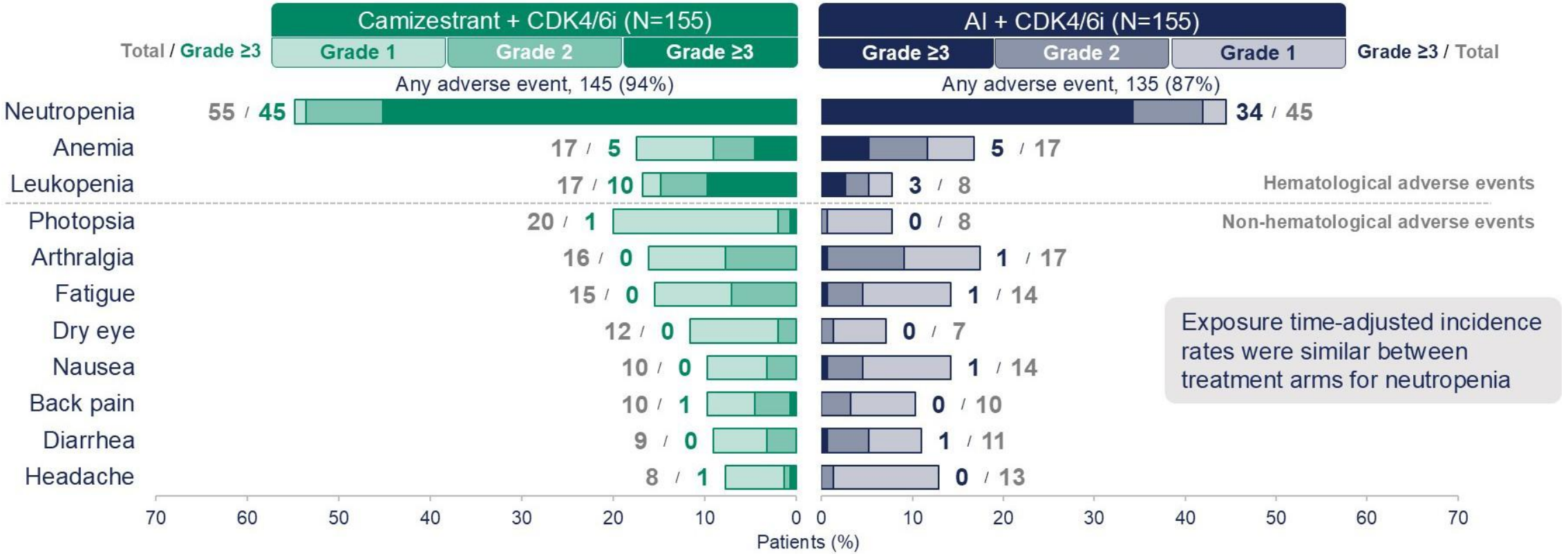
Adverse events (≥10% of patients)



Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities: If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity

Neutropenia is reported as a group term that includes neutropenia and decreased neutrophil count; anemia is reported as a group term that includes anemia and hemoglobin decreased; leukopenia is reported as a group term that includes leukopenia and white blood cell count decrease. Bradycardia and sinus bradycardia were reported in the camizestrant + CDK4/6i arm only, in 8 patients (5.2%) and 4 patients (2.6%), respectively. No (sinus) bradycardia AEs were grade ≥3, and none of these events required treatment discontinuation. Impact of visual effects was measured using the Visual Symptom Assessment Questionnaire.

Conclusions

- Switching AI to camizestrant with continuation of CDK4/6i, guided by the emergence of *ESR1* mutations during first-line therapy ahead of disease progression, significantly improved PFS in patients with HR+/HER2– ABC
- PFS benefit was consistent across the CDK4/6i and clinically relevant subgroups
- Camizestrant + CDK4/6i delayed time to deterioration in quality of life versus continuing AI + CDK4/6i, and was well tolerated with a very low rate of treatment discontinuations due to adverse events
- SERENA-6 is the first global registrational phase 3 study to demonstrate the clinical utility of ctDNA monitoring to detect and treat emerging resistance in breast cancer

The findings from SERENA-6 have the potential to become a new treatment strategy in oncology to optimize first-line patient outcomes

Ready for Prime Time?

- 548 out of 3256 patients had a positive test (16%)
- 43% of patients who had positive test declined to participate in study, suggesting reluctance to potentially continue on treatment that may not be controlling emerging mutations
- Lack of crossover to camizestrant in the control group, 10% of the control group received a different oral SERD
- Greater portion of patients received chemotherapy in the camizestrant group as next line therapy
- Overall survival data remains immature

VERITAC-02

- Updates from ASCO 2025
  - HR+/HER2- disease: SERENA-6, **VERITAC-02**, TRADE
  - HER2+ disease: DESTINY BREAST-09
  - TNBC: ASCENT-04

2025 ASCO ANNUAL MEETING

Vepdegestrant, a PROTAC ER Degrader, vs Fulvestrant in ER+/HER2- Advanced Breast Cancer: Results of the Global, Randomized, Phase 3 VERITAC-2 Study

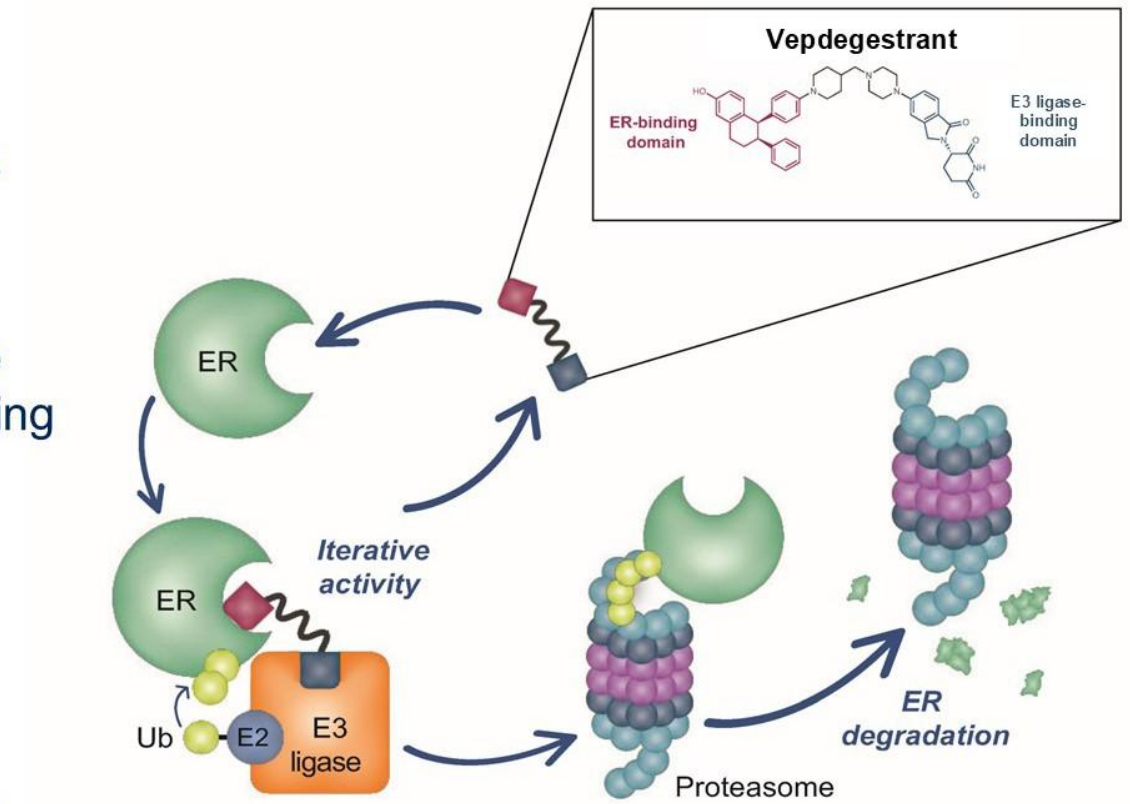
Erika P Hamilton[1], Michelino De Laurentiis[2], Komal Jhaveri[3], Xichun Hu[4], Sylvain Ladoire[5], Anne Patsouris[6], Claudio Zamagni[7], Jiuwei Cui[8], Marina Cazzaniga[9], Timucin Cil[10], Katarzyna Jerzak[11], Christian Fuentes[12], Tetsuhiro Yoshinami[13], Alvaro Rodriguez-Lescure[14], Olga Valota[15], Dongrui R Lu[16], Marcella Martignoni[15], Janaki Parameswaran[17], Xin Zhi[17], Mario Campone[18]

[1]Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [2]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Shanghai Cancer Center, Fudan University, Shanghai, China; [5]Centre Georges Francois Leclerc, Dijon, France; [6]Institut de Cancérologie de l'Ouest, Angers, France; [7]IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; [8]The First Hospital of Jilin University, Changchun, China; [9]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [10]Health and Science University, Adana City Hospital, Adana, Turkey; [11]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [12]Fundación Respirar, Buenos Aires, Argentina; [13]Graduate School of Medicine, Osaka University, Osaka, Japan; [14]Hospital General Universitario de Elche, Elche, Spain; [15]Pfizer, Inc., Milan, Italy; [16]Pfizer, Inc., San Diego, CA, USA; [17]Arvinas Operations, Inc., New Haven, CT, USA; [18]Institut de Cancérologie de l'Ouest Angers-Nantes, Angers, France

PRESENTED BY: Erika P Hamilton, MD

Background

- There is no established consensus for treatment of ER+/HER2- advanced breast cancer after progression on first-line ET[1]
- Fulvestrant, a SERD that is administered IM due to poor solubility,[2] has limited PFS benefit following disease progression on a CDK4/6i + ET[3,4]
- Vepdegestrant is a selective, oral PROTAC ER degrader that targets WT and mutant ER[5,6]
- In a first-in-human, phase 1/2 study (NCT04072952), vepdegestrant was well tolerated and demonstrated encouraging clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer[7]



Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; MOA=mechanism of action; PROTAC=PROteolysis TArgeting Chimera; SERD=selective estrogen receptor degrader; Ub=ubiquitin; WT=wild type.

1. Al Sukhun S, et l. *JCO Glob Oncol*. 2024;10:e2300285. 2. Nathan MR, Schmid P. Oncol Ther. 2017;5(1):17-29. 3. Lindeman GJ, et al. Clin Cancer Res. 2022;28(15):3256-67. 4. Bidard FC, et al. J Clin Oncol. 2022;40(28):3246-3256. 5. Békés M, et al. Nat Rev Drug Discov 2022;21(3):181-200. 6. Gough SM, et al. *Clin Cancer Res*. 2024;30(16):3549-3563. 7. Hurvitz SA, et al. SABCS. 2023; PO3-05-08. 8. Hamilton EP, et al. Futur Oncol. 2024;20(32):2447–55.

VERITAC-2: Global Phase 3 Trial of Vepdegestrant

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

Primary Endpoint:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

Data cutoff date: Jan 31, 2025
Clinicaltrials.gov: NCT05654623

[a]*ESR1*m status was assessed in ctDNA by Foundation Medicine, except in China, where Origmed testing was used.
AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; *ESR1*m=estrogen receptor 1 gene mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; ORR=objective response rate; OS=overall survival; PFS=progression-free survival, SERD=selective estrogen receptor degrader.

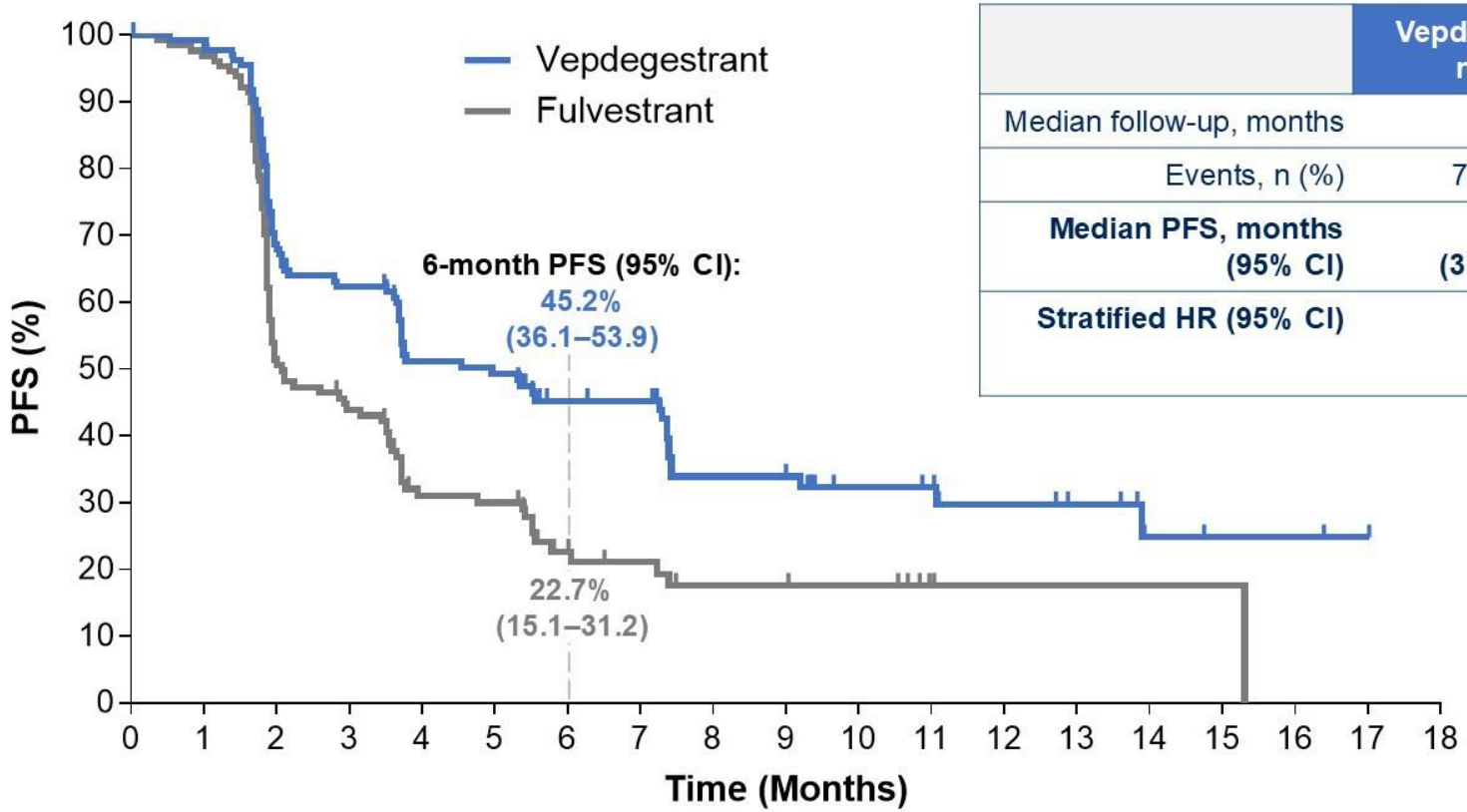
VERITAC-2: Baseline Characteristics

Characteristic	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Median age (range), y	60 (26–87)	60 (34–85)	60 (26–89)	60 (28–85)
Female, %	99	100	99	100
Postmenopausal, %	79	79	78	78
Race, %				
White	43	51	47	46
Black or African American	3	4	2	2
Asian	45	37	39	41
Unknown/NR	9	7	12	9
ECOG PS, %				
0	57	57	61	64
1	43	43	39	36
*ESR1*m, %[a]	100	100	43	43
Sites of disease, %				
Visceral disease	68	68	63	63
Liver metastasis	46	44	40	36
Bone-only disease	18	18	18	20

Characteristic, %	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Measurable disease[b]	71	75	71	71
Prior lines of therapy in advanced/metastatic setting[c]				
1	82	80	82	76
2	18	20	18[d]	23[d]
Prior endocrine therapy	100	100	100	100[e]
Aromatase inhibitor	99	100	99	99
SERM	15	16	16	20
Prior CDK4/6 inhibitor	100	100	100	100
Palbociclib	50	54	46	52
Ribociclib	38	28	36	31
Abemaciclib	16	25	20	21
Other[f]	1	5	4	4

CDK4/6=cyclin-dependent kinase 4/6; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*m=estrogen receptor 1 gene mutation; NR=not reported; SERD= selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.
[a]*ESR1*m status was assessed in pretreatment circulating tumor DNA. [b]Measurable disease assessed by blinded independent central review using Response Evaluation Criteria for Solid Tumors v1.1. [c]Disease progression during or within 12 months from the end of adjuvant therapy was counted as a line of therapy in the advanced/metastatic setting. [d]1 additional patient in the vepdegestrant group and 3 additional patients in the fulvestrant group received 3 prior lines of therapy. [e]1 patient received a prior SERD. [f]Other CDK4/6 inhibitors included birociclib, dalpiciclib, lerociclib.

VERITAC-2 Primary Endpoint: PFS by BICR in Patients With *ESR1*m



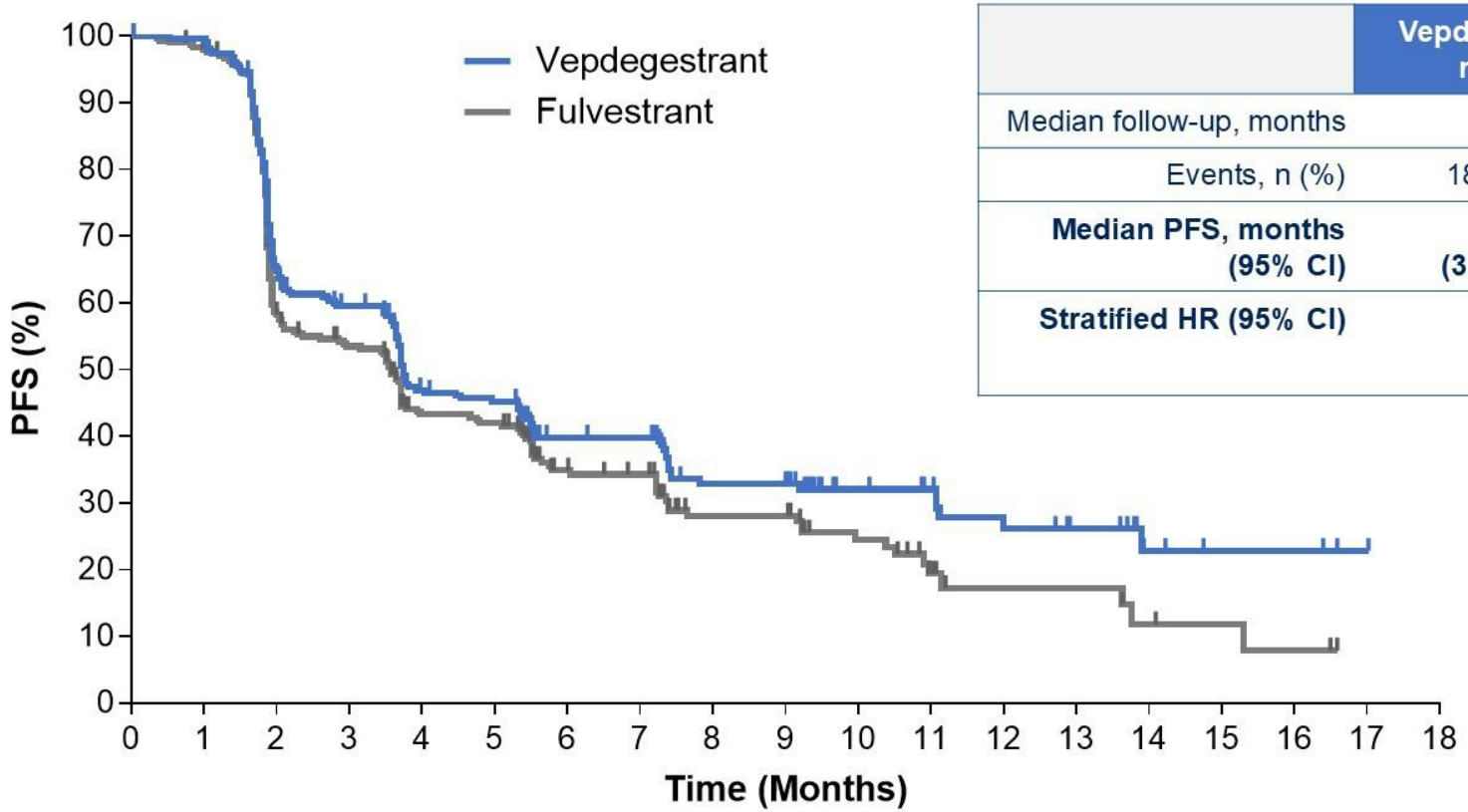
	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

No. at risk

Vepdegestrant	136	134	87	78	55	53	38	37	22	22	15	14	10	8	4	3	3	2	0
Fulvestrant	134	125	62	52	30	29	15	12	8	8	7	2	1	1	1	1	0	0	0

BICR=blinded independent central review; *ESR1m*=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

VERITAC-2 Primary Endpoint: PFS by BICR in All Patients



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	

No. at risk

Vepdegestrant	313	306	189	168	113	108	74	72	46	46	28	24	15	12	6	4	4	2	0
Fulvestrant	311	292	162	143	101	98	58	54	36	36	23	12	7	7	4	3	2	0	0

BICR=blinded independent central review; HR=hazard ratio; PFS=progression-free survival.

VERITAC-2: Safety and Tolerability (All Treated Patients)

Overview

TEAEs, %	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any grade	87	81
Grade ≥3	23	18
Serious	10	9
Leading to treatment discontinuation	3	1
Leading to dose reduction	2	NA
TRAEs, %		
Any grade	57	40
Grade ≥3	8	3

QT prolongation

- TEAEs: vepdegestrant,10%; fulvestrant, 1%
- A QT interval sub-study (n=88) confirmed a mild increase (11.1 ms) from baseline in mean QTcF, with upper 90% CI (13.7 ms) <20 ms,[f] **indicating no large QT-prolonging effect**

TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312)		Fulvestrant (n = 307)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue[a]	27	1	16	1
ALT increased[b]	14	1	10	1
AST increased[b]	14	1	10	3
Nausea	13	0	9	1
Anemia[b, c]	12	2	8	3
Neutropenia[d]	12	2[e]	5	1[e]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	5	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; QTcF=corrected QT interval using Fridericia's method; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.
[a]Includes fatigue and asthenia. [b]No between-group differences were observed for ALT/AST increases or anemia based on laboratory values. [c]Includes anemia, hemoglobin decreased, and iron deficiency anemia. [d]Includes neutropenia and neutrophil count decreased. No events led to dose reductions or treatment discontinuation in either treatment group. There were no events of febrile neutropenia in the vepdegestrant group and 1 event of grade 2 febrile neutropenia in the fulvestrant group. [e]1 patient with grade 4 event. [f]Based on a concentration-QTc population modeling analysis.

Conclusions

- Vepdegestrant is the first PROTAC to be evaluated in a phase 3 study
- Oral vepdegestrant demonstrated statistically significant and clinically meaningful improvement in PFS by BICR vs fulvestrant in patients with *ESR1*m ER+/HER2- advanced breast cancer
- OS analyses remain immature, and follow-up is ongoing
- Vepdegestrant demonstrated a favorable safety profile, evidenced by few AEs (<5%) leading to dose reduction or discontinuation

These results support vepdegestrant as a potential treatment option for previously treated *ESR1*m ER+/HER2- advanced breast cancer

AE=adverse event; BICR=blinded independent central review; ER=estrogen receptor; *ESR1*m=estrogen receptor 1 gene mutation; OS=overall survival; PFS=progression-free survival; PROTAC=PROteolysis TArgeting Chimera.

TRADE

- Updates from ASCO 2025
  - HR+/HER2- disease: SERENA-6, VERITAC-02, **TRADE**
  - HER2+ disease: DESTINY BREAST-09
  - TNBC: ASCENT-04

2025 ASCO ANNUAL MEETING

The TRADE Study: A Phase 2 Trial to Assess the Tolerability of Abemaciclib Dose Escalation in Early-Stage HR+/HER2- Breast Cancer

Erica L. Mayer[1], Dario Trapani[2], Se-Eun Kim[1], Meredith Faggen[1], Natalie Sinclair[1], Pedro Sanz-Altamira[1], Chiara Battelli[3], Shana Berwick[4], Steve Lo[5], Jose Acevedo[6], Sarah Sinclair[7], Alys Malcolm[1], Leticia Varella[1], Sarah Sammons[1], Susan Schumer[1], Philip D. Poorvu[1], Erin Wallace[1], Esther Pasternak[1], Nabihah Tayob[1], Sara M. Tolaney[1]

[1]Dana-Farber Cancer Institute, Boston MA;, [2]European Institute of Oncology, Milan; [3]New England Cancer Specialists, Portland ME; [4]Beth Israel Deaconess Medical Center, Boston MA; [5]Stamford Health, Stamford, CT; [6]Boston Medical Center, Boston MA; [7]Northern Light Health, Brewer ME.

PRESENTED BY: Erica L. Mayer, MD, MPH

TRADE: Background

- The **CDK4/6 inhibitor abemaciclib** is approved with adjuvant endocrine therapy for high-risk node positive hormone receptor positive (HR+) HER2- breast cancer
- This regimen reduces cancer recurrence, yet therapy **may be complicated by early toxicity**, limiting patient ability to maintain dose or continue medication
- Experiences with other targeted therapies suggest **initial dose escalation may reduce toxicity and discontinuation**
- **TRADE is a prospective, investigator-initiated single-arm, phase 2 study** evaluating whether an adjuvant abemaciclib dose-escalation strategy improves drug tolerability

Patient disposition in monarchE

Outcome in monarchE	By 12 weeks	Overall at 2 years
Discontinued abemaciclib for any reason	10%	30.6%
• Discontinued for adverse events	7%	18.5%
Required abemaciclib dose reduction	27%	43.4%

Rugo et al, Ann Oncol 2020

TRADE: Design

- HR-positive, HER2-negative, early breast cancer
- Adjuvant abemaciclib is indicated based on patient risk/stage

Screening

N=90

Adjuvant Endocrine Therapy

Abemaciclib 50mg BID	Abemaciclib 100mg BID	Abemaciclib 150mg BID
Days 1 – 14	Days 15 – 28	> 28 Days

→ **Endocrine Therapy + up to 2 years Abemaciclib**

Intra-patient dose escalation requirements: Absence of ongoing grade 3/4 or persistent grade 2 toxicity

Supportive care, including anti-diarrhea medication, provided as needed

PRIMARY ENDPOINT:

- **Composite Adverse Event Rate**: Discontinuation of adjuvant abemaciclib for any reason and/or inability to reach or maintain target dose of 150 mg BID by 12 weeks of therapy

SECONDARY ENDPOINTS:

- Treatment-emergent adverse effects, discontinuation / hold rates, incidence of grade ≥2 diarrhea, quality of life, adherence, dose intensity, correlative science

STATISTICAL DESIGN:

- **Experimental hypothesis**: **a dose-escalation schedule will significantly reduce the composite adverse event rate at 12 weeks from a baseline of 40%, based on monarchE**
- **Sample size**: 90 patients provides 92% power, against an alternative of 25%, with a 1-sided test at a significance level of 0.07, assuming drop-out rate of 10%

PRESENTED BY: Erica L. Mayer, MD, MPH

TRADE: Patient Characteristics

Treatment Exposure

- **90 patients** with stage II/III HR+/HER2- breast cancer were enrolled between **11/2023-10/2024** at DFCI main campus and regional sites
- **89 patients** are evaluable for the primary endpoint (1 excluded due to disease progression within 12 weeks)
- Median total duration on trial is 32.1 weeks; this report is a landmark analysis at the 12 week point for primary endpoint

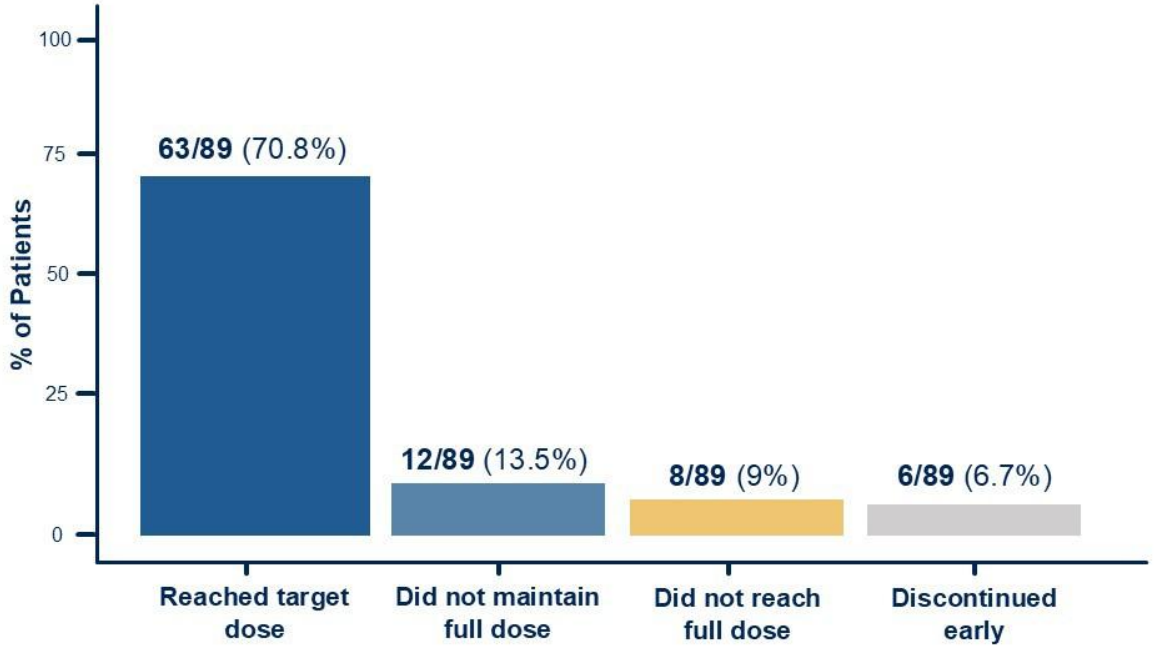
Patient Characteristics

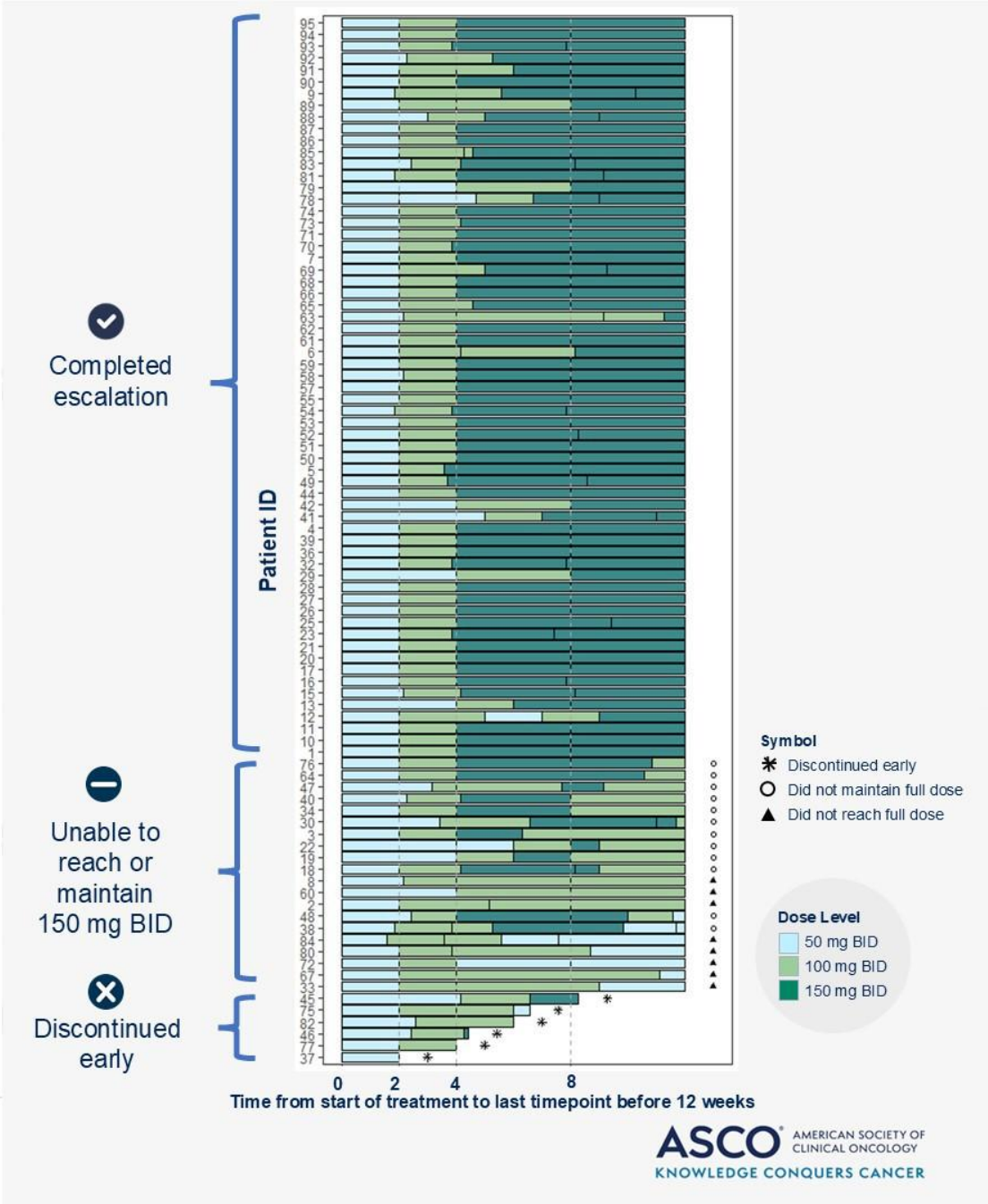
	N = 90, %
Age, median (range)	58 (24-78)
Race	
Asian	6 (6.7%)
Black/African American	4 (4.4%)
White	72 (80.0%)
Other	8 (8.9%)
Ethnicity	
Hispanic/Latino	3 (3.3%)
Stage	
II	45 (50.0%)
III	45 (50.0%)
Endocrine therapy at therapy initiation	
Aromatase Inhibitor only	75 (83.3%)
Aromatase Inhibitor and Ovarian Suppression	15 (16.7%)
Prior neo/adjuvant chemotherapy	56 (62.2%)
Prior adjuvant radiation	87 (96.7%)

TRADE: Primary Results

Of 89 evaluable patients, 26 (29.2%; 90% CI [21.3-38.2]; p=0.046) **met the primary endpoint at 12 weeks:**

- 12 (13.5%) for inability to maintain target dose of 150 mg BID
- 8 (9.0%) for inability to reach 150 mg BID
- 6 (6.7%) for early discontinuation (3 [3.4%] for toxicity)





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PRESENTED BY: Erica L. Mayer, MD, MPH

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TRADE: Conclusions

- The **TRADE study met its primary endpoint**, showing an initial dose escalation strategy for adjuvant abemaciclib allowed a greater number of patients (70.8%) to reach and maintain 150 mg BID dosing at 12-weeks than observed in monarchE (~ 60%).
- Early discontinuation was infrequent, and **93.3% were continuing therapy** at 12 weeks.
- A minority remained on therapy at lower doses, and were able to continue abemaciclib without discontinuation
- **An early dose escalation strategy could be considered when initiating adjuvant abemaciclib.**
- Further follow-up will assess long-term tolerability, dosing maintenance beyond 12 weeks, and correlative analyses.

DESTINY BREAST-09

- Updates from ASCO 2025
  - HR+/HER2- disease: SERENA-6, VERITAC-02, TRADE
  - HER2+ disease: **DESTINY BREAST-09**
  - TNBC: ASCENT-04

2025 ASCO ANNUAL MEETING

DESTINY Breast09

Trastuzumab deruxtecan (T-DXd) + pertuzumab vs taxane + trastuzumab + pertuzumab (THP) for first-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer: interim results from DESTINY-Breast09

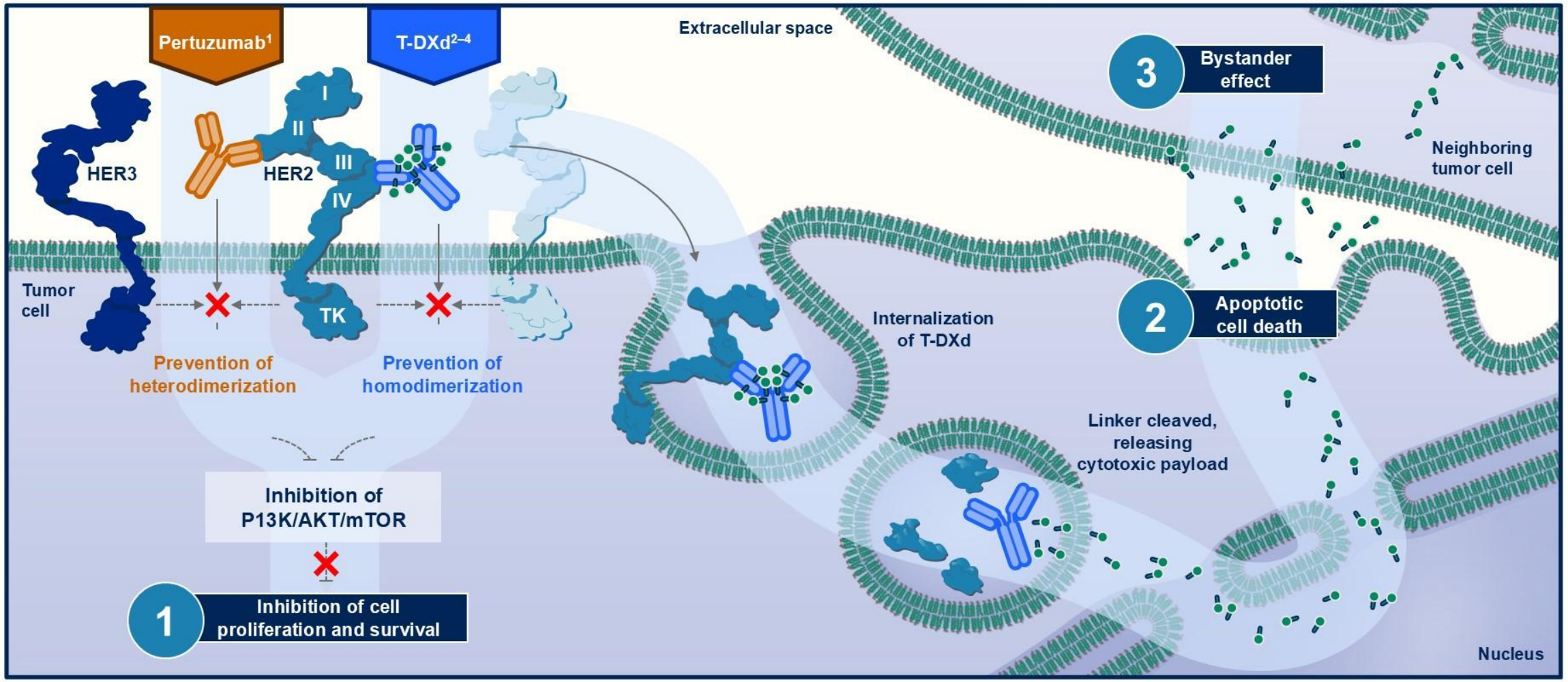
Sara M Tolaney, MD, MPH
Dana-Farber Cancer Institute, Boston, MA, US

Monday, June 2, 2025

Additional authors: Zefei Jiang, Qingyuan Zhang, Romualdo Barroso-Sousa, Yeon Hee Park, Mothaffar F Rimawi, Cristina Saura, Andreas Schneeweiss, Masakazu Toi, Yee Soo Chae, Yasemin Kemal, Mukesh Chaudhari, Toshinari Yamashita, Monica Casalnuovo, Michael A Danso, Jie Liu, Jagdish Shetty, Pia Herbolsheimer, Sibylle Loibl

On behalf of the DESTINY-Breast09 investigators

Rationale for combining pertuzumab with T-DXd



AKT, protein kinase B; HER2/3, human epidermal growth factor receptor 2/3; mTOR, mammalian target of rapamycin; P13K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TK, tyrosine kinase

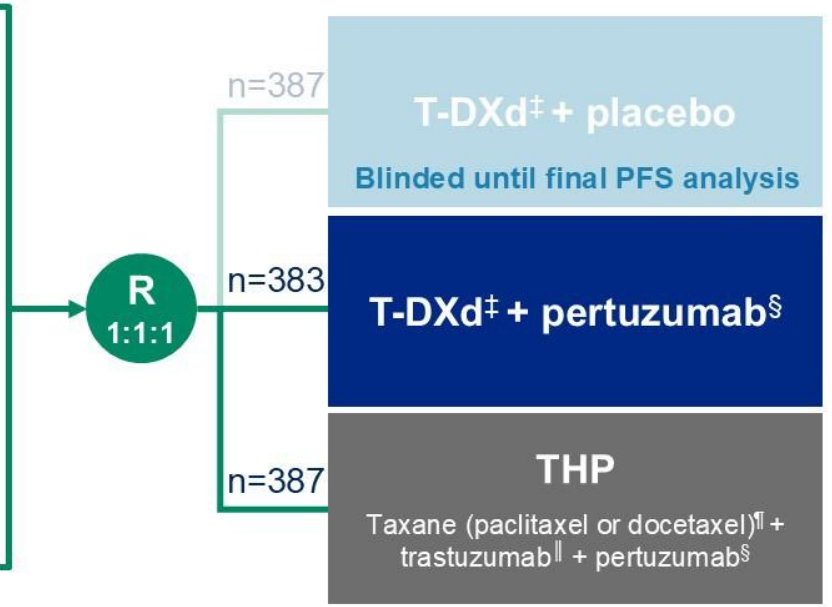
1. Nami B, et al. *Cancers (Basel)*. 2018;10:342; 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185; 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 4. Geng W, et al. *Eur J Pharmacol*. 2024:977:176725

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

Stratification factors

- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

At this planned interim analysis (DCO Feb 26, 2025), results are reported for the T-DXd + P and THP arms

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 mg/kg loading dose, then 6 mg/kg Q3W

a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DCO, data cutoff; DFI, disease-free interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; INV, investigator; mBC, metastatic breast cancer; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan

NCT04784715. Updated. May 6, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed May 29, 2025)

PRESENTED BY: Sara M Tolaney, MD, MPH

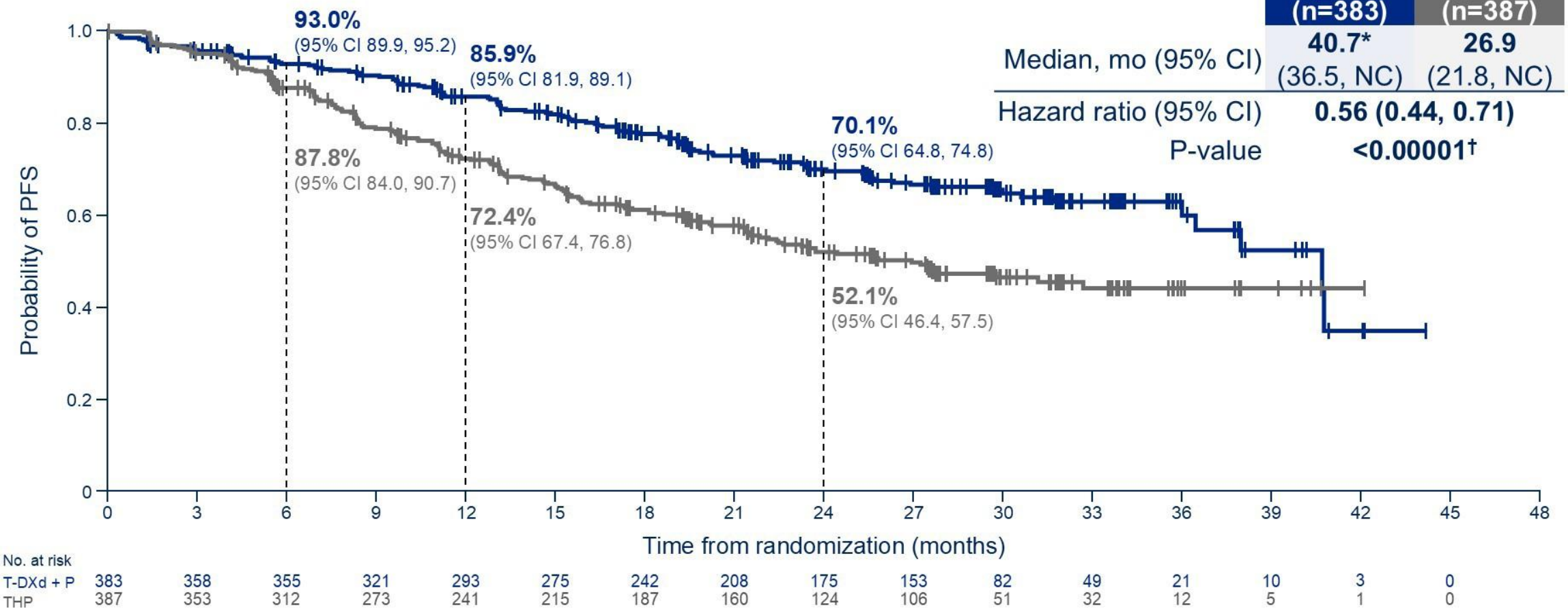
Patient demographics and key baseline characteristics

	T-DXd + P (n=383)	THP (n=387)
Age, median (range), years	54 (27–85)	54 (20–81)
Female, n (%)	383 (100)	387 (100)
Geographical region, n (%)		
Asia	188 (49.1)	191 (49.4)
Western Europe and North America	87 (22.7)	78 (20.2)
Rest of World	108 (28.2)	118 (30.5)
ECOG performance status, n (%)		
0 (normal activity)	256 (66.8)	246 (63.6)
1 (restricted activity)	127 (33.2)	141 (36.4)
HER2 score by central test, n (%)		
IHC 3+	318 (83.0)	315 (81.4)
IHC <3 / ISH+	62 (16.2)	71 (18.3)
IHC NR / ISH+	3 (0.8)	1 (0.3)
HR status, n (%)		
Positive*	207 (54.0)	209 (54.0)
Negative	176 (46.0)	178 (46.0)
De-novo disease at diagnosis, n (%)	200 (52.2)	200 (51.7)
***PIK3CA* mutations detected, n (%)**	116 (30.3)	121 (31.3)
Brain metastases, n (%)†	25 (6.5)	22 (5.7)
Visceral metastases, n (%)	281 (73.4)	268 (69.3)

*Defined as estrogen receptor–positive and/or progesterone receptor–positive (≥1%); †participants were eligible if they had brain metastases that were clinically inactive or treated/asymptomatic
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NR, not recorded; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS (BICR): primary endpoint

	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	



No. at risk

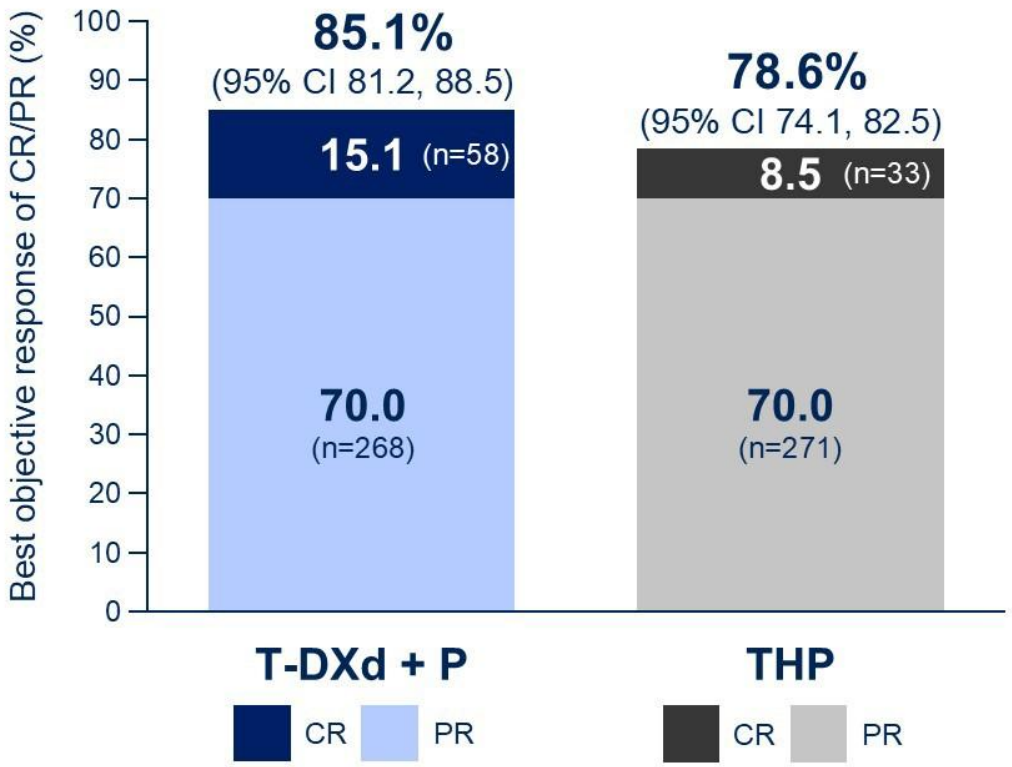
T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

ORR and DOR (BICR)

Confirmed ORR*

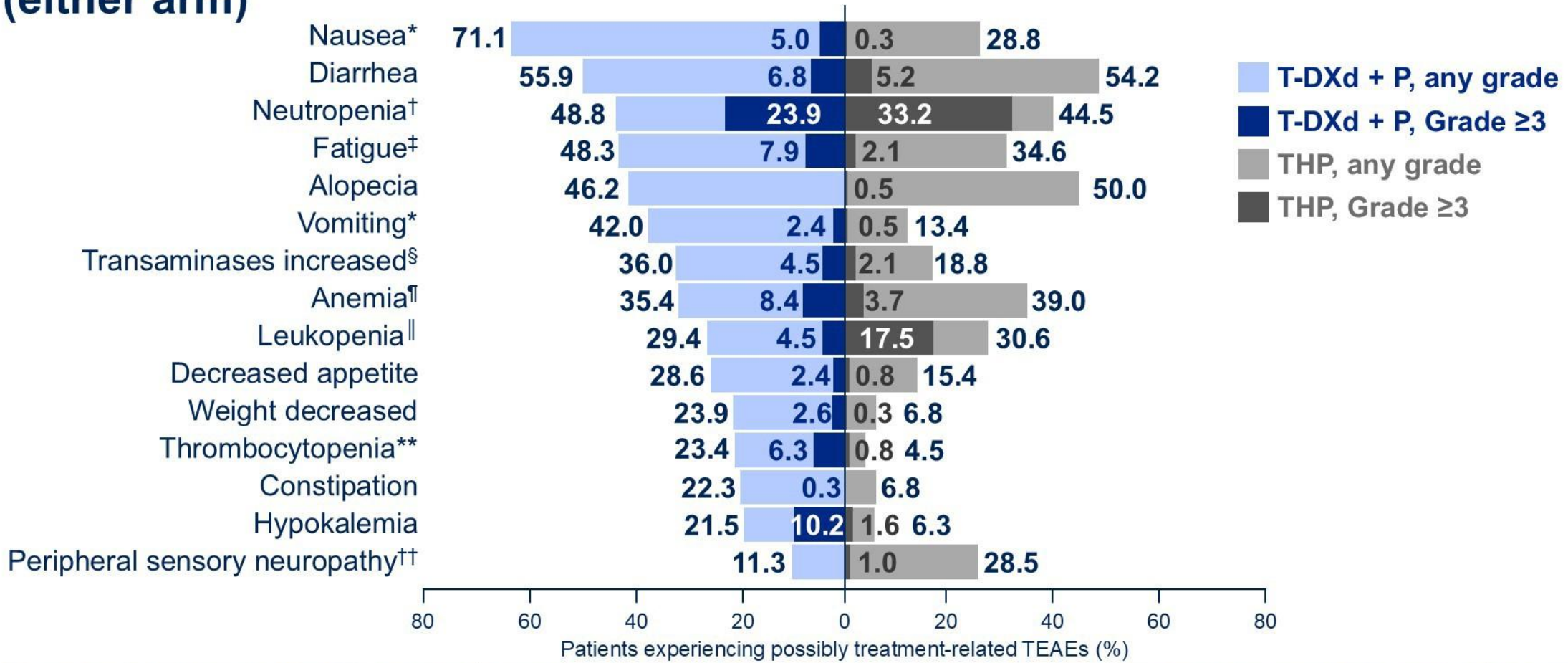


	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Possibly treatment-related (investigator assessed) TEAEs in ≥20% of patients (either arm)



*Antiemetic prophylaxis was recommended but not mandated by protocol; †neutropenia (grouped term) includes: neutropenia and neutrophil count decreased; ‡fatigue (grouped term) includes: fatigue, asthenia, malaise, and lethargy; §transaminases increased (grouped term) includes: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increase; ¶anemia (grouped term) includes: anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ‖leukopenia (grouped term) includes: leukopenia and white blood cell count decreased; **thrombocytopenia (grouped term) includes: platelet count decreased and thrombocytopenia; ††peripheral sensory neuropathy (grouped term) includes: neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy
P, pertuzumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; THP, taxane + trastuzumab + pertuzumab

PRESENTED BY: Sara M Tolaney, MD, MPH

Conclusions

- T-DXd + P demonstrated a **statistically significant and clinically meaningful PFS benefit** by BICR vs THP, which was consistently observed across subgroups
  - Hazard ratio of **0.56** vs THP (**P<0.00001**)
  - Median PFS was **40.7 months (T-DXd + P)** vs **26.9 months (THP)**
- Median DOR of **>3 years with T-DXd + P**, with CRs in **15.1% (T-DXd + P)** vs **8.5% (THP)**
- Early OS data suggest a positive trend favoring T-DXd + P, with a supportive hazard ratio of **0.60** for PFS2
- T-DXd + P safety data were **consistent with known profiles of individual treatments**

PFS by BICR

44%

Reduction in risk of disease progression or death with T-DXd + P vs THP

T-DXd + P demonstrated a statistically significant and clinically meaningful PFS benefit vs THP and may represent a new first-line standard of care for patients with HER2+ a/mBC

a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; CR, complete response; DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PRESENTED BY: Sara M Tolaney, MD, MPH

ASCENT-04

- Updates from ASCO 2025
  - HR+/HER2- disease: SERENA-6, VERITAC-02, TRADE
  - HER2+ disease: DESTINY BREAST-09
  - TNBC: **ASCENT-04**

2025 ASCO ANNUAL MEETING

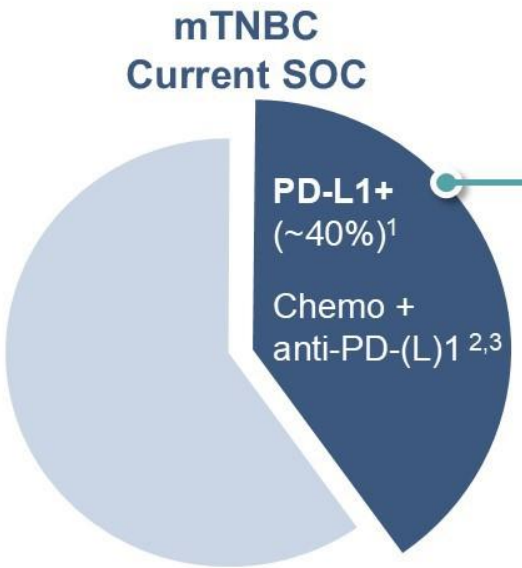
Sacituzumab Govitecan Plus Pembrolizumab vs Chemotherapy Plus Pembrolizumab in Patients With Previously Untreated, PD-L1 Positive, Advanced or Metastatic Triple-Negative Breast Cancer: Primary Results From the Randomized, Phase 3 ASCENT-04/KEYNOTE-D19 Study

Sara M Tolaney[1], Evandro de Azambuja[2], Kevin Kalinsky[3], Sherene Loi[4], Sung-Bae Kim[5], Clinton Yam[6], Bernardo Rapoport[7,8], Seock-Ah Im[9], Barbara Pistilli[10], Wassim McHayleh[11], David W Cescon[12], Junichiro Watanabe[13], Manuel Alejandro Lara Banuelas[14], Ruffo Freitas-Junior[15], Javier Salvador Bofill[16], Maryam Afshari[17], Dianna Gary[17], Lu Wang[17], Catherine Lai[17], Peter Schmid[18]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B) and Université Libre de Bruxelles (ULB), Brussels, Belgium; [3]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]The Medical Oncology Centre of Rosebank, Clinical and Translational Research Unit (CTRU), Saxonwold, South Africa; [8]Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [9]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [10]Department of Cancer Medicine, Gustave Roussy, Villejuif, France; [11]AdventHealth Cancer Institute, Orlando, FL, USA; [12]Princess Margaret Cancer Centre, UHN, Toronto, Canada; [13]Juntendo University Graduate School of Medicine, Tokyo, Japan; [14]Oncology Center of Chihuahua, Chihuahua, Mexico; [15]CORA – Advanced Center for Diagnosis of Breast Diseases, Federal University of Goiás, Goiânia, Brazil; [16]Medical Oncology Department, Hospital Universitario Virgen del Rocio, Seville, Spain; [17]Gilead Sciences, Inc., Foster City, CA, USA; [18]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK

PRESENTED BY: Sara M Tolaney, MD, MPH

Unmet Need in Previously Untreated, PD-L1+, Locally Advanced Unresectable or Metastatic TNBC



Remaining unmet need

- Median PFS observed in prior studies of chemotherapy in combination with immune checkpoint inhibitors was 7.5-9.7 months[1, 4]; most patients still experience disease progression[5-7]
- About half of the patients treated for 1L mTNBC do not receive 2L treatment[5]

Rationale for this study

- SG is the only Trop-2–directed ADC with demonstrated OS benefit in multiple phase 3 studies; it is approved for 2L+ mTNBC and pre-treated HR+/HER2- mBC in multiple countries[8,9]
- Early studies have observed improved anti-tumor effects when immunotherapy is combined with ADCs[10]

We present the primary results from the global, randomized, phase 3 ASCENT-04/KEYNOTE-D19 study of SG + pembro vs chemo + pembro in previously untreated, PD-L1+, locally advanced unresectable or metastatic TNBC

1L, first line; 2L(+), second line (and further); ADC, antibody drug conjugate; chemo, chemotherapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; PFS, progression-free survival; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; SG, sacituzumab govitecan SOC, standard of care.

1. Cortes J, et al. *N Engl J Med*. 2022;387(3):217-226. 2. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V4.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed April 22, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Schmid P, et al. *N Engl J Med*. 2018;379(22):2108-2121. 5. Punie K, et al. *Oncologist*. 2025;30(3).*ePublished*. 6. Skinner KE, et al. *Future Oncol*. 2021;18(8):931-941. 7. Geurts V, Kok M. *Curr Treat Options Oncol*. 2023;24(6):628-643. 8. TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; March 2025. 9. TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. County Cork, Ireland: Gilead Sciences Ireland UC; August 2023. 10. Nicolo E, et al. *Cancer Treat Rev*. 2022;106:102395.

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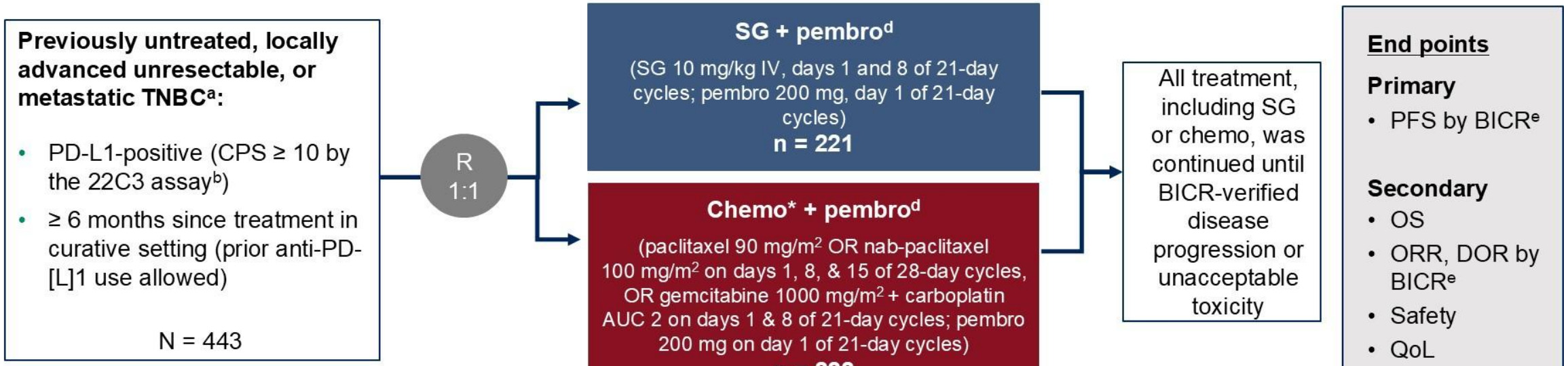
ASCENT-04/KEYNOTE-D19 Study Design



Stratification factors:

- De novo mTNBC[c] vs recurrent within 6 to 12 months from completion of treatment in curative setting vs recurrent > 12 months from completion of treatment in curative setting
- US/Canada/Western Europe vs the rest of the world
- Prior exposure to anti-PD-(L)1 (yes vs no)

ClinicalTrials.gov identifier: NCT05382286.
[a]TNBC status determined according to standard American Society of Clinical Oncology-College of American Pathologists criteria. [b]Dako, Agilent Technologies. [c]Up to 35% de novo mTNBC. [d]Pembro was administered for a maximum of 35 cycles. [e]Per RECIST v1.1.
AUC, area under the curve; BICR, blinded independent central review; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; QoL, quality of life; R, randomized; RECIST v1.1; Response Evaluation Criteria in Solid Tumors, version 1.1; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TTR, time-to-response.

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Demographics and Baseline Characteristics

ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Female sex, n (%)	221 (100)	222 (100)
Median age, (range) yr	54 (23-88)	55 (27-82)
≥ 65 yr, n (%)	58 (26)	57 (26)
Race or ethnic group,[a] n (%)		
White	139 (63)	118 (53)
Asian	43 (19)	63 (28)
Black	13 (6)	11 (5)
Other/not specified	26 (12)	30 (14)
Geographic region, n (%)		
US/Canada/Western Europe	85 (38)	85 (38)
Rest of the world[b]	136 (62)	137 (62)
ECOG PS at baseline,[c] n (%)		
0	156 (71)	154 (69)
1	65 (29)	67 (30)
Curative treatment-free interval, n (%)		
De novo	75 (34)	75 (34)
Recurrent within 6-12 mo	40 (18)	40 (18)
Recurrent > 12 mo	106 (48)	107 (48)

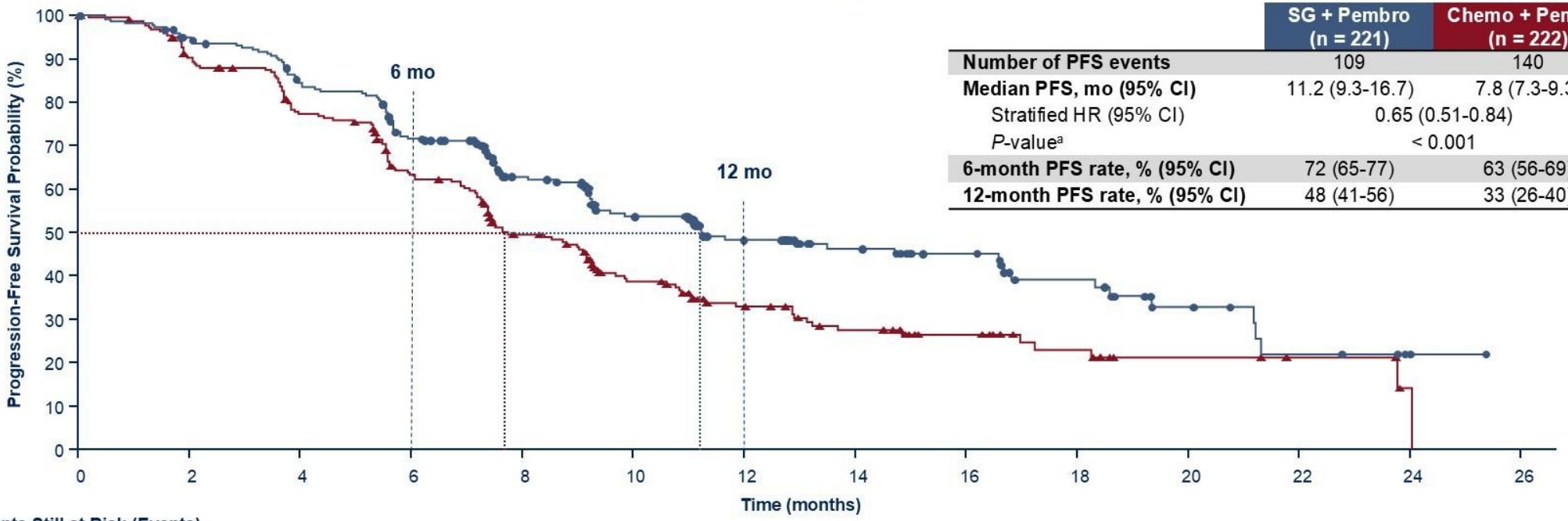
ITT Population	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
PD-L1 CPS ≥ 10,[d] n (%)	221 (100)	222 (100)
Metastatic sites, n (%)		
Lymph node	159 (72)	154 (69)
Lung	111 (50)	95 (43)
Bone	61 (28)	45 (20)
Liver	55 (25)	57 (26)
Brain	8 (4)	6 (3)
Other[e]	81 (37)	71 (32)
Chemo selected prior to randomization,[f] n (%)		
Taxane	116 (52)	114 (51)
Gemcitabine/carboplatin	105 (48)	108 (49)
Prior anti-PD-(L)1 therapy,[g] n (%)	9 (4)	11 (5)

Data cutoff date: March 3, 2025.

[a]As reported by the patients; "other" includes American Indian or Alaska Native, other, and not permitted. [b]Rest of the world includes Argentina, Australia, Brazil, Chile, Czech Republic, Hong Kong, Hungary, Israel, Japan, Malaysia, Mexico, Poland, Singapore, South Africa, South Korea, Taiwan, and Turkey. [c]One patient in the chemo + pembro group had an ECOG PS ≥ 2. [d]PD-L1 status assessed using the PD-L1 IHC 22C3 assay (Dako, Agilent Technologies) at the time of enrollment. [e]Other metastatic sites includes pleura, pleural effusion, skin, soft tissue, chest wall, and muscle. [f]Actual chemo received was consistent with what was selected prior to randomization; however, two patients were randomized but did not receive treatment. [g]While 20 patients were included in the stratified subgroup of prior exposure to anti-PD-(L)1 therapy (yes) per the IRT system, only 6 patients received prior treatment with anti-PD-(L)1 agents per the clinical database.

Chemo, chemotherapy; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; PARPi, poly ADP-ribose polymerase inhibitor; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; SG, sacituzumab govitecan.

Progression-Free Survival by BICR



	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Number of PFS events	109	140
Median PFS, mo (95% CI)	11.2 (9.3-16.7)	7.8 (7.3-9.3)
Stratified HR (95% CI)	0.65 (0.51-0.84)	
P-value[a]	< 0.001	
6-month PFS rate, % (95% CI)	72 (65-77)	63 (56-69)
12-month PFS rate, % (95% CI)	48 (41-56)	33 (26-40)

No. of Patients Still at Risk (Events)

SG + Pembro	221 (0)	202 (11)	174 (33)	142 (59)	105 (75)	78 (89)	58 (96)	42 (98)	34 (99)	22 (103)	11 (106)	6 (109)	2 (109)	0 (109)
Chemo + Pembro	222 (0)	191 (21)	159 (48)	123 (76)	88 (102)	59 (120)	40 (128)	29 (134)	21 (135)	13 (137)	7 (138)	4 (138)	1 (139)	0 (140)

SG + pembro demonstrated statistically significant and clinically meaningful improvement in PFS vs chemo + pembro by BICR analysis, with a 35% reduction in risk of disease progression or death

Data cutoff date: March 3, 2025.
[a]Two-sided *P*-value from stratified log-rank test.
BICR, blinded independent central review; chemo, chemotherapy; HR, hazard ratio; PFS, progression-free survival; pembro, pembrolizumab; SG, sacituzumab govitecan.

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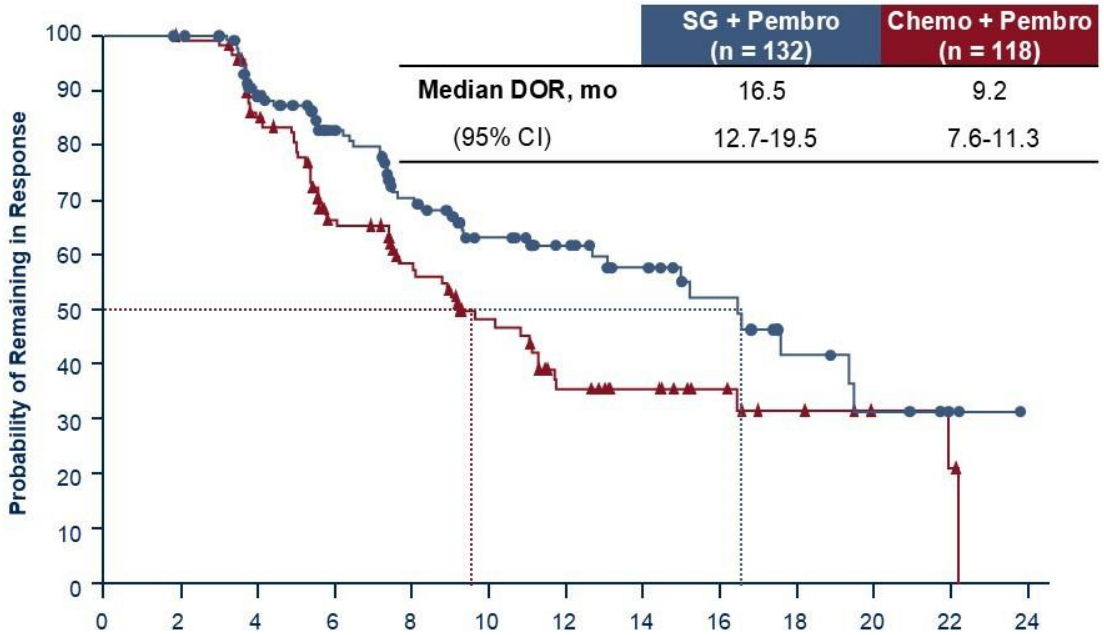
Tumor Responses and Duration of Response by BICR

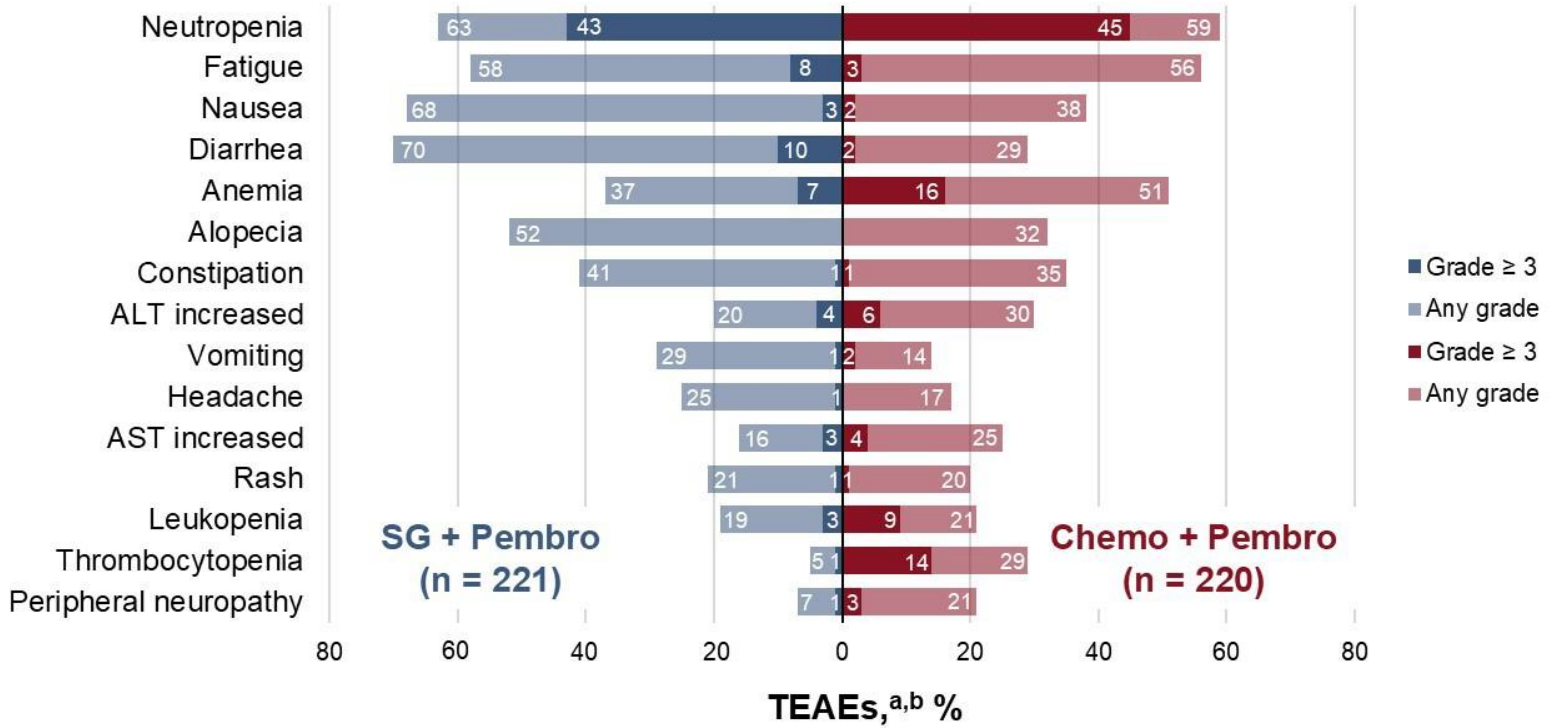
Variable	SG + Pembro (n = 221)	Chemo + Pembro (n = 222)
Objective response rate[a] (95% CI), %	60 (52.9-66.3)	53 (46.4-59.9)
Stratified odds ratio (95% CI)	1.3 (0.9-1.9)	
Best overall response, n (%)		
Complete response	28 (13)	18 (8)
Partial response	104 (47)	100 (45)
Stable disease	70 (32)	70 (32)
Stable disease ≥ 6 months	23 (10)	29 (13)
Progressive disease	9 (4)	26 (12)
Not evaluable	10 (5)	8 (4)
Time to response,[b] median (range), months	1.9 (1.0-9.3)	1.9 (1.1-11.4)



A substantially longer duration of response and a higher overall response rate (including an increased complete response rate) was observed for SG + pembro vs chemo + pembro

Data cutoff date: March 3, 2025.
[a]Objective response rate is defined as the proportion of patients who achieved a best overall response of complete response/partial response; [b]Time to response (months) = (date of first documented complete or partial response - date of randomization + 1)/30.4375.
BICR, blinded independent central review; DOR, duration of response; mo, months; pembro, pembrolizumab; SG, sacituzumab govitecan.

Most Common Adverse Events (≥20% in any group)



The AEs observed are consistent with the known profiles of both SG and pembro

TEAEs were defined as any adverse events that began or worsened on or after the first dose date of study drug up to 30 days (or up to 90 days for SAEs) after the last dose date of study drug or the initiation of subsequent anticancer therapy (including crossover treatment), whichever occurred first. Data cutoff date: March 3, 2025.
[a]TEAEs were included if they occurred in ≥ 20% of patients in either arm. [b]Combined preferred terms of Neutropenia includes neutrophil count decreased, Leukopenia includes white blood cell count decreased, Anemia includes hemoglobin decreased and red blood cell count decreased, Thrombocytopenia includes platelet count decreased, Fatigue includes asthenia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; chemo, chemotherapy; pembro, pembrolizumab; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.

Conclusions

- ASCENT-04/KEYNOTE-D19 is the first randomized, phase 3 study to evaluate the efficacy and safety of an ADC/checkpoint inhibitor combination for first-line treatment of patients with PD-L1+[a] mTNBC
- SG + pembro led to a statistically significant and clinically meaningful improvement in PFS vs chemo + pembro (median 11.2 vs 7.8 months; HR, 0.65; 95% CI, 0.51-0.84; $P < 0.001$)
  - PFS benefit was observed across prespecified subgroups
- OS data are immature, but an early trend in improvement was observed
- ORR was higher (including an increased complete response rate), and responses were more durable with SG + pembro vs chemo + pembro
- The safety profile of SG + pembro was consistent with the established profiles of either agent; no additive toxicity was observed

Results from ASCENT-04/KEYNOTE-D19 support the use of SG + pembro as a potential new standard of care for patients with previously untreated, PD-L1+, locally advanced unresectable or metastatic TNBC

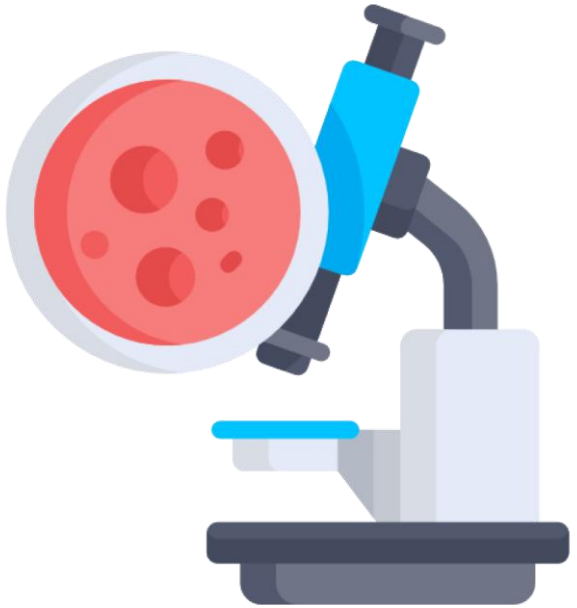
Data cutoff date: March 3, 2025
[a]CPS ≥ 10 per IHC 22C3 assay (Dako, Agilent Technologies).
ADC, antibody drug conjugate; chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; HR, hazard ratio; IHC, immunohistochemistry; mTNBC; metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer.

Is a Clinical Trial Right for Me?

- Talk to your oncologist!
  - Is there a clinical trial that you can suggest for me?
  - Can you provide me additional information about this trial?
  - How often will I have to be seen?
  - What are the side effects I may experience on this trial?
  - Does this trial include a placebo? Will I get one?
  - What costs are covered by the trial?

www.ClinicalTrials.gov or www.BreastCancerTrials.org

Blood, stool, and tissue collection



We can collect blood, stool, and tissue either once or even at multiple time points to better understand how cancers change over time and react to our therapies.

Quality of life

- Fertility
- Sexual Function
- Long-Term Side Effects
- Emotional Well-Being
- Mental Health
- Financial Toxicity
- Diet
- Exercise
- Family

Thank you.