Applications for Community Oncology

SABCS Review

January 13, 2022

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KEY QUESTION

HR+ Breast Cancer

What role may new SERMs/SERDs play in the treatment of patients with HR+ breast cancer?

Should ESR1 mutation monitoring become standard?

Testing of palbociclib as adjuvant therapy for HR+ eBC

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2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01
- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB
- MA.32A

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CLINICAL QUESTION

EMERALD Clinical Trial

Will use of elacestrant, an investigational oral selective estrogen receptor degrader (SERD) benefit pts with ER+/HER2- advanced or metastatic BC following tumor progression on prior endocrine and CDK4/6 inhibitor therapy?

KEY DATA

EMERALD Phase 3 Clinical Trial: Comparing a new oral SERD vs hormonal SOC

Inclusion Criteria

- Men and postmenopausal women with advanced or metastatic breast cancer
- ER+[a], HER2-
- Progression or relapse on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6 inhibitor
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

Stratification factors:

- ESR1-mutation status
- Prior treatment with fulvestrant
- Presence of visceral metastases

R 1:1
N = 477[b]

Elacestrant
400mg daily[c]
N=239

Investigators choice (SOC):
Fulvestrant, Anastrozole, Letrozole, or Exemestane
N=238

Primary Endpoints:

- PFS in all patients
- PFS in pts with mESR1[d]

Secondary Endpoint:

- Overall survival

[a] ER+ tumor with ≥ 1% staining by IHC; [b]Recruitment from Feb 2019 to Oct 2020; [c]Protocol-defined dose reductions permitted; Blinded Independent Central Review. [d]ESR1-mutation status was determined by ctDNA analysis using the Guardant360 assay; Restaging CT scans every 8 weeks

Stats: ≥90% power to evaluate a PFS hazard ration (HR) of 0.667 in all pts and ≥80% power for a PFS HR of 0.610 in the mESR1 subset

Bardia. SABCS 2021. Abstr GS2-02.

KEY DATA

EMERALD Clinical Trial

PFS by Independent Review Committee for All Patients (ITT)

	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3%)	156 (65.5%)
Median PFS (months)	**2.79**	**1.91**
***P* value**	0.0018	
Hazard Ratio (95% CI)	**0.697** (0.552 – 0.880)	
PFS rate at 6 months (95% CI)	**34.3%** (27.2 – 41.4%)	**20.4%** (14.1 – 26.7%)
PFS rate at 12 months (95% CI)	**22.3%** (15.2 – 29.4%)	**9.4%** (4.0 – 14.8%)

Bardia. SABCS 2021. Abstr GS2-02.

KEY DATA

EMERALD Clinical Trial

PFS by IRC for Pts with Tumors Harboring *mESR1*

	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9%)	78 (69.0%)
Median PFS (months)	**3.78**	**1.87**
***P* value**	0.0005	
Hazard Ratio (95% CI)	**0.546** (0.387 – 0.768)	
PFS rate at 6 months (95% CI)	**40.8%** (30.1 – 51.4%)	**19.1%** (14.1 – 26.7%)
PFS rate at 12 months (95% CI)	**26.8%** (16.2 – 37.4%)	**8.2%** (1.3 – 15.1%)

Bardia. SABCS 2021. Abstr GS2-02.

KEY DATA

EMERALD Clinical Trial: OS Interim Analysis

OS for All Patients

	Elacestrant	SOC
N	239	238
Event (%)	70 (29.3%)	79 (33.2%)
Median PFS (months)	NC	NC
***P* value**	0.0821	
Hazard Ratio (95% CI)	**0.751** (0.542 – 1.038)	

OS for Pts with Tumors Harboring *mESR1*

	Elacestrant	SOC
N	115	113
Event (%)	28 (24.3%)	40 (35.4%)
Median PFS (months)	NC	16.95
***P* value**	0.0325	
Hazard Ratio (95% CI)	**0.592** (0.361 – 0.958)	

Note: Final analysis with mature data is expected to take place in late 2022/early 2023

Bardia. SABCS 2021. Abstr GS2-02.

KEY DATA

EMERALD Clinical Trial: Safety Summary

	Elacestrant N=237, n (%)	Standard of Care		
		Total N=229, n (%)	Fulvestrant N=161, n (%)	AI N=68, n (%)
Number of pts with at least 1 TEAE	218 (92.0)	197 (86.0)	144 (89.4)	53 (77.9)
Any treatment-related TEAE (TRAE)	150 (63.3)	100 (43.7)	72 (44.7)	28 (41.2)
Any Grade 3 or 4 TRAE	17 (7.2)	7 (3.1)	5 (3.1)	2 (2.9)
Any Fatal TRAE (Grade 5)	0	0	0	0
Any serious TRAE	3 (1.3)	0	0	0
Any TRAE leading to dose reduction	6 (5.2)	0	0	0
Any TRAE leading to discontinuation	8 (3.4)	2 (0.9)	1 (0.6)	1 (1.5)

TEAE: treatment-emergent adverse event leading to discontinuation of elacestrant or SOC were infrequent in both arms (6.35 and 4.4%, respectively)
Nausea was the most common TEAE experienced by 35% of pts taking elacestrant vs 18.8% of pts receiving SOC.

Bardia. SABCS 2021. Abstr GS2-02.

SUMMARY

EMERALD Clinical Trial: the New Oral SERD Led to Better Outcomes than Hormonal SOC

- Elacestrant extended PFS versus SOC in the overall population and the m*ESR1* subgroup
  - Elacestrant is associated with a 32% reduction in the risk of progression or death for ITT population, and 50% for those harboring m*ESR1*
- OS interim analysis shows a trend favoring elacestrant over SOC in the overall population and in the m*ESR1* subgroup
- Elacestrant was well tolerated with a safety profile consistent with other ETs
- Next steps and impact of *ESR1* mutation testing:
  - Elacestrant has received fast-track designation with plans for regulatory submissions in both the United States and Europe in 2022
  - Benefit observed for pts with or without m*ESR1* tumors (measured by plasma ctDNA)

Bardia. SABCS 2021. Abstr GS2-02.

EMERALD Clinical Trial

Elacestrant is the first oral SERD with positive results in a pivotal study as a monotherapy vs hormonal SOC for the treatment of ER+/HER2- advanced or mBC

More to come, including review and potential approval by regulatory agencies…

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CLINICAL QUESTION

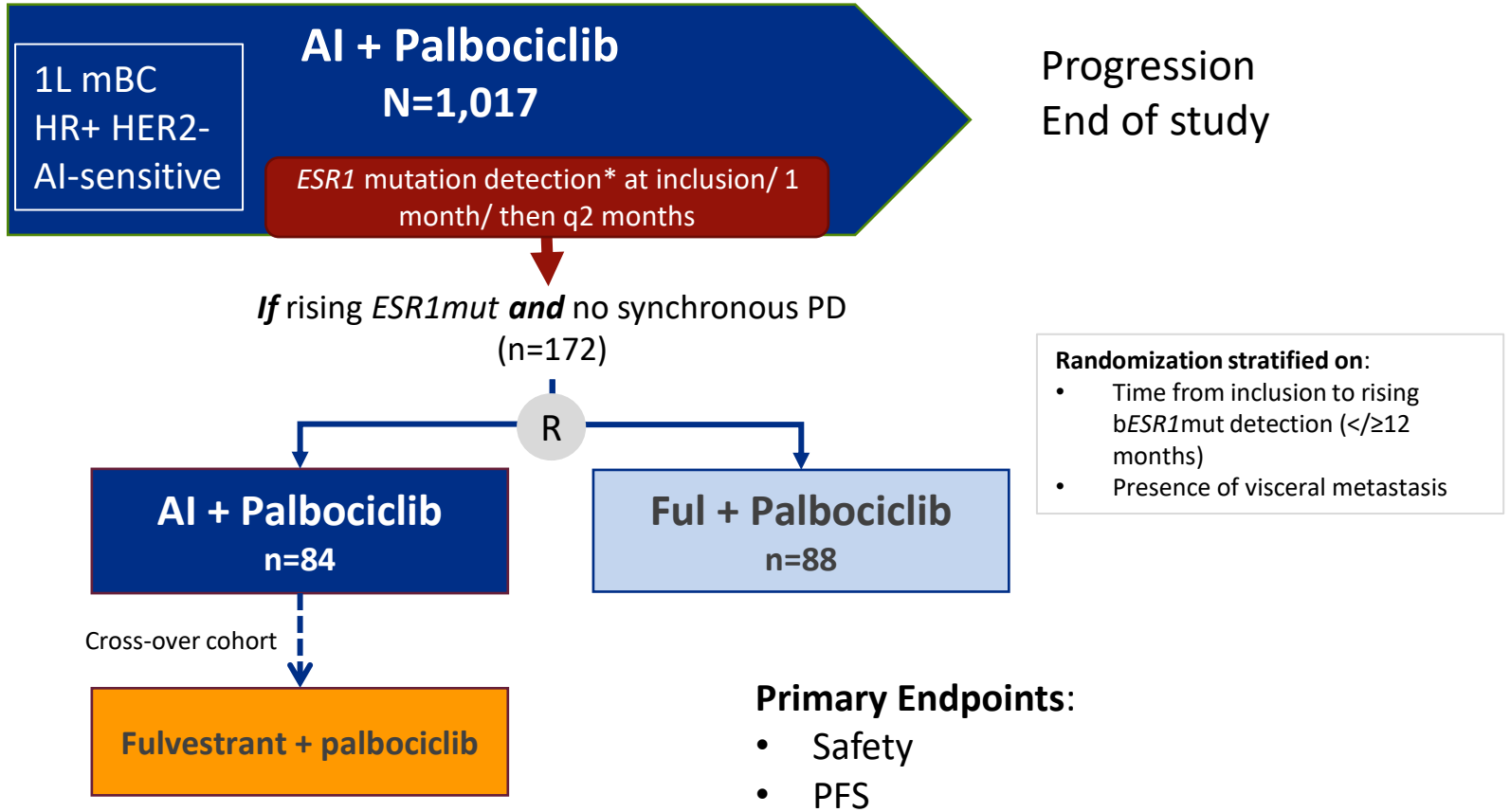
PADA-1 Clinical Trial

Will switching to fulvestrant on detection of *ESR1* mutation by ctDNA (vs continuing AI) plus CDK4/6 inhibitor in 1L setting prevent or delay progression in pts with HR+/HER2- mBC?

KEY DATA

PADA-1 Phase 3 Clinical Trial: testing hormonal selection (continuing AI vs switching to fulvestrant, both with palbociclib, after asymptomatic detection of m*ESR1* in mBC)

Inclusion Criteria
- PS 0 – 2
- HR+ (>10%) HER2- mBC
- No relapse under /<12 m from adjuvant AI
- No prior systemic therapy for mBC
- Adequate organ function
- Absence of visceral crisis
- Measurable or evaluable disease



Randomization stratified on:
- Time from inclusion to rising b*ESR1*mut detection (</≥12 months)
- Presence of visceral metastasis

Premenopausal women received LH-RH agonist during therapy

ESR1mut monitoring with ddPCR
- Targets E380, P535, L536, Y537, D538 mutations
- >12,000 samples analyzed in real time

Primary Endpoints:
- Safety
- PFS

Secondary Endpoint:
- PFS after cross over

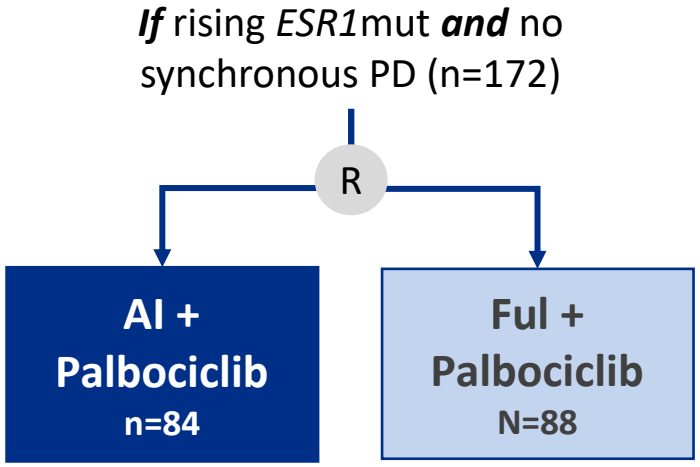
**ESR1* mutation detectable in blood by cell-free circulating DNA analysis*

Bidard. SABCS 2021. Abstr GS3-05.

KEY DATA

PADA-1 Clinical Trial

Patient Demographics



	AI + PAL N (%)	FUL + PAL N (%)
Total number of pts	84	88
Age at inclusion		
Median (range)	60 (30 – 80)	62 (23 – 88)
Prior adjuvant AI therapy		
Yes	31 (37%)	30 (34%)
No	53 (63%)	58 (66%)
Metastatic sites		
Bone only	19 (23%)	19 (22%)
Visceral	41 (49%)	42 (48%)
Non-visceral ± bone	24 (29%)	27 (31%)
Time to rising *bESR1mut*		
< 12 months	29 (35%)	34 (39%)
≥ 12 months	55 (65%)	54 (61%)
PS ECOG at randomization		
PS 0	51 (61%)	50 (57%)
PS 1 – 2	33 (39%)	38 (43%)

Bidard. SABCS 2021. Abstr GS3-05.

KEY DATA

PADA-1 Clinical Trial: Primary analysis: PFS after randomization

	AI + PAL	FUL + PAL
Median PFS, months	**5.7**	**11.9**
	95% CI (3.9 – 7.5)	95% CI (9.1 – 13.6)
HR (95% CI)	**0.63** (0.45 – 0.88)	
P value	0.007	
Stratified HR (95% CI)	0.61 (0.43 – 0.86)	
P value	0.005	

Median follow-up 26 months (range: 0 – 36); N=136 PFS events

Bidard. SABCS 2021. Abstr GS3-05.

SUMMARY

PADA-1 Clinical Trial

- mPFS doubled by switching from AI+PAL to FUL+PAL with *mESR1* detection
  - Cross-over cohort did not achieve the same clinical benefit
- Demonstrates potential clinical utility of *mESR1* monitoring in blood and potential optimization of endocrine therapy partner for CDK4/6 inhibitor
- No new safety signals
- *But study was small, and data should be corroborated*

Bidard. SABCS 2021. Abstr GS3-05.

PADA-1 Clinical Trial

By monitoring mESR1 and switching from AI to fulvestrant as soon as detectable while maintaining CDK4/6 inhibition, may delay or prevent progression and should be considered a treatment strategy for patients with HR+/ HER2- mBC.

But study was too small to reach conclusions

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CLINICAL QUESTION

PALLAS Clinical Trial

Does the additional of palbociclib to adjuvant ET improve outcomes, compared to ET alone, for patients with HR+/HER2- early breast cancer?

KEY DATA

PALLAS Phase 3 Clinical Trial: testing the addition of palbociclib to hormonal therapy

Stratification factors:
- Stage (IIA vs IIB/III)
- Chemo (yes/no)
- Age (≤50 vs >50)
- Geographic region (US vs Europe vs other)

Inclusion Criteria
- Stage II-III HR+/HER2-
- Completion of prior surgery, +/- chemo, RT
- Within 12 months of diagnosis, within 6 months of starting adjuvant ET
- FFPE tumor block submitted and received at biorepository

N=5,600

R 1:1

Endocrine treatment plus Palbociclib x 2 years
(125 mg qd, 3 weeks on 1 week off)

N=2884

Endocrine treatment
(Aromatase inhibitor or tamoxifen, +/- LHRH agonist; duration: at least 5 years)

N=2887

Primary Endpoints:
- Invasive Disease-Free Survival (iDFS) using STEEP criteria

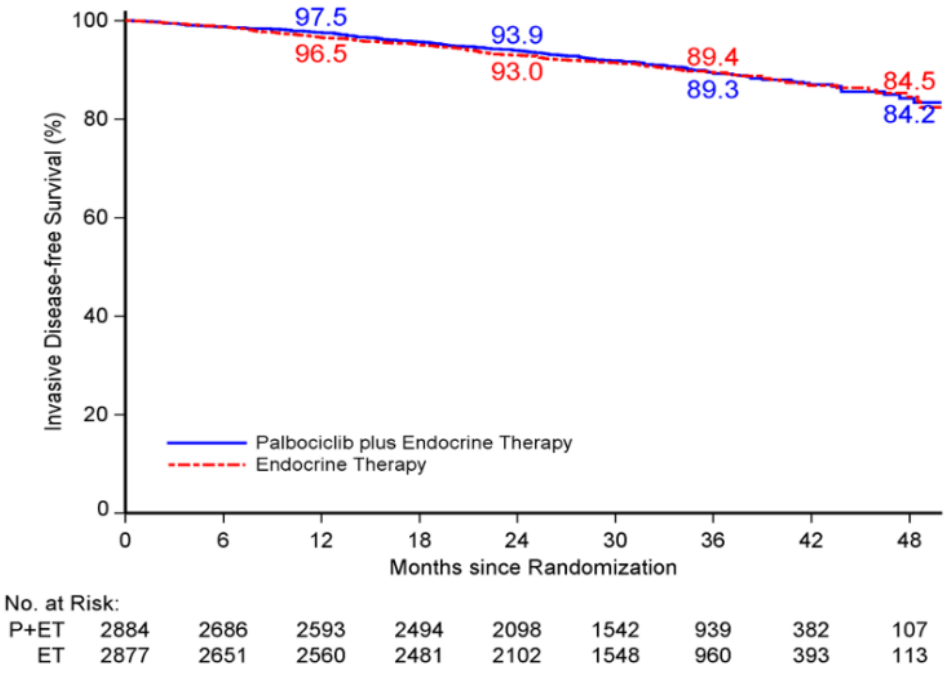
Secondary Endpoints:
- iDFS excluding second cancers of non-breast origin (iBFS)
- Distant recurrence-free survival (DRFS)
- Locoregional recurrence-free survival (LRFS)
- Overall survival (OS)
- Safety

Analyses:
First IA (futility): 167 events
Second IA (efficacy and futility): 313 events
Final analysis: 469 events

KEY DATA

PALLAS Clinical Trial

Primary Endpoint: iDFS



	Palbociclib +ET	ET alone
iDFS @ 4 years	84.2%	84.5%

HR 0.96

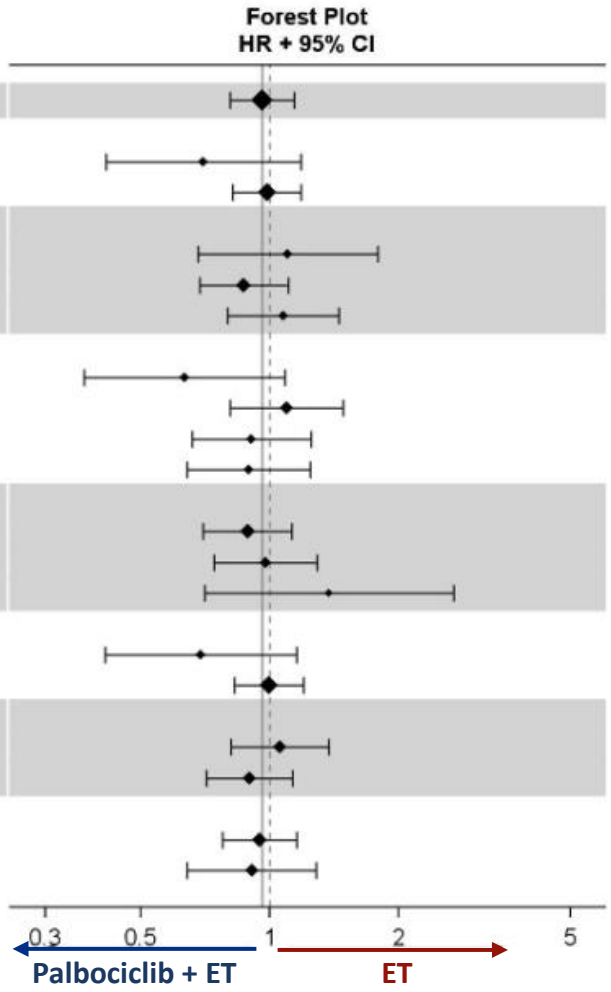
95% CI 0.81-1.14; log-rank p = 0.65

- At a median follow-up of 31 months, no significant difference in 4-year iDFS was observed
- 253 vs 263 iDFS events with no difference in event categories (distant recurrences, second primaries, local, regional, contralateral, deaths without recurrence)

PALLAS Clinical Trial

Primary Endpoint: iDFS in Subgroups

Subgroup	Palbociclib+ET Events / N	ET Events / N	HR (95% CI)
All patients	253 / 2884	263 / 2877	0.96 (0.81 - 1.14)
Anatomic Staging			
I/IIA	23 / 513	36 / 519	0.70 (0.41 - 1.18)
IIB/III	230 / 2370	227 / 2358	0.98 (0.82 - 1.18)
T-Stage			
T0/T1/Tis/TX	36 / 558	31 / 501	1.10 (0.68 - 1.78)
T2	127 / 1603	149 / 1636	0.87 (0.69 - 1.10)
T3/T4	90 / 722	83 / 740	1.07 (0.80 - 1.45)
N-Stage			
N0	21 / 365	36 / 385	0.63 (0.37 - 1.08)
N1	86 / 1431	80 / 1411	1.09 (0.81 - 1.48)
N2	73 / 700	78 / 709	0.91 (0.66 - 1.25)
N3	73 / 386	69 / 372	0.89 (0.64 - 1.24)
Grading			
G1/G2	129 / 1926	150 / 1971	0.89 (0.70 - 1.12)
G3	105 / 836	97 / 769	0.98 (0.74 - 1.29)
GX	19 / 122	16 / 137	1.37 (0.71 - 2.67)
Neo/adjuvant Chemotherapy			
No	24 / 499	37 / 507	0.69 (0.41 - 1.15)
Yes	229 / 2384	226 / 2370	0.99 (0.83 - 1.20)
Age group			
<=50	116 / 1310	109 / 1304	1.05 (0.81 - 1.37)
>50	137 / 1573	154 / 1573	0.90 (0.71 - 1.13)
Clinical Risk			
high risk	194 / 1711	193 / 1673	0.95 (0.77 - 1.15)
low risk	59 / 1171	70 / 1204	0.91 (0.64 - 1.28)



SUMMARY

PALLAS Clinical Trial

- The addition of palbociclib to adjuvant ET did not prolong iDFS compared to ET alone in patients with stage II-III HR+/HER2- breast cancer
  - No subgroups of patients were identified as gaining benefit from adjuvant Palbociclib; limited by small number of events

- Benefits observed with palbociclib in the metastatic setting did not translate into the earlier adjuvant setting

Why are the PALLAS results (palbociclib) different from monarchE (abemaciclib)?

Unclear…

PALLAS Clinical Trial

The additional of palbociclib to adjuvant ET does not improve outcomes, compared to ET alone, for patients with HR+/HER2- early breast cancer

Q & A

HR+ Breast Cancer

KEY QUESTION

Triple Negative Breast Cancer

Is there a role for an ADC Trop-2 inhibitor in TNBC?

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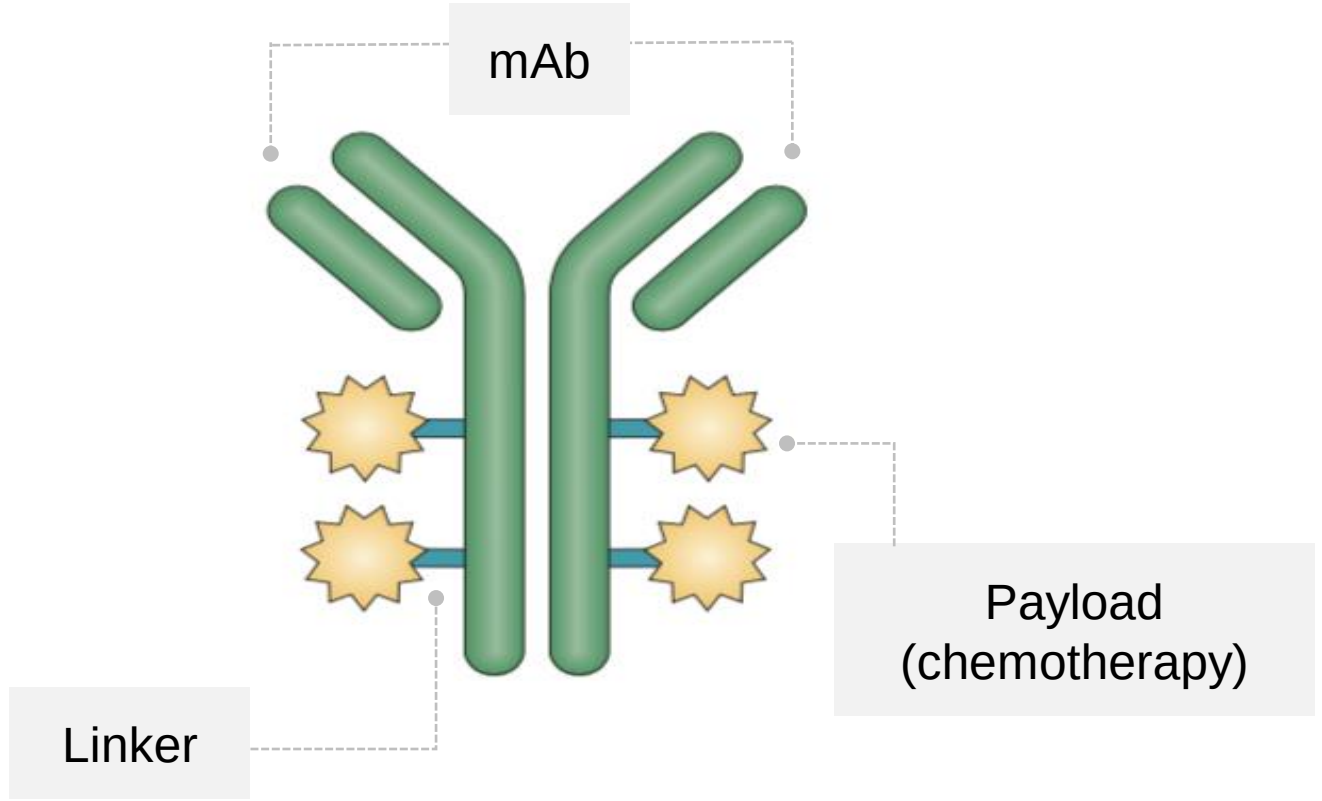
Antibody Drug Conjugates (ADCs)

- ADCs are a class of cancer therapies that combine antigen specificity and potent cytotoxicity in a single molecule
- Offer increased therapeutic index of anticancer agents

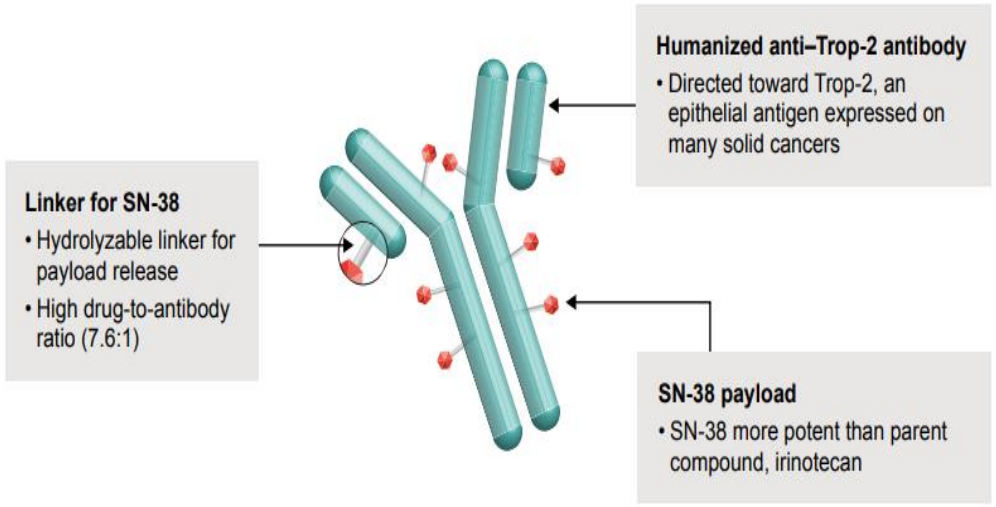
Structure of ADC



Drago JZ, Modi S, Chandarlapaty S. Nature Reviews Clinical Oncology 18 (6), 327-344, 2021

Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis, which has led to development of various ADCs

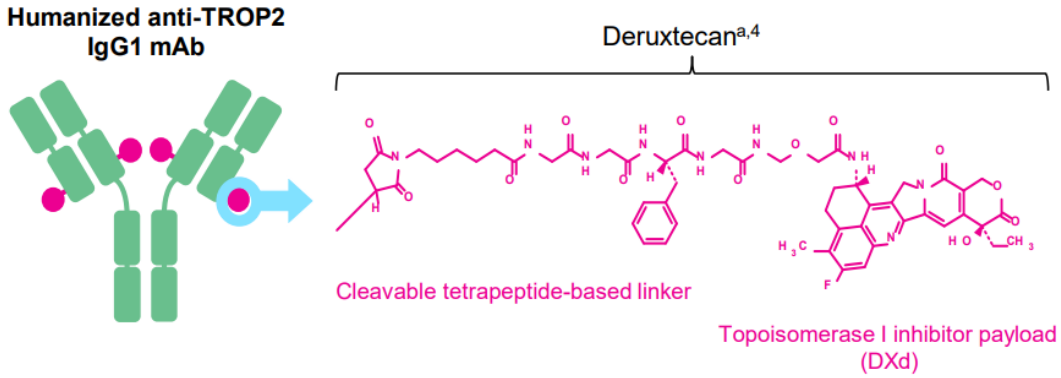
Sacituzumab Govitecan (SG) Antibody Drug Conjugate



Datopotamab Deruxtecan (Dato-DXd) Antibody Drug Conjugate

3 components:

- Humanized anti-TROP2 IgG1 monoclonal antibody attached to:
- Topoisomerase I inhibitor payload, as exatecan derivative, via
- A tetrapeptide-based cleavable linker



[a]Image is for illustration purposes only; 4. Krop I, et al. SABCS 2019; [abstract GS1-03]

CLINICAL QUESTION

ASCENT Clinical Trial

Does the use of Sacituzumab Govitecan improve quality of life, clinical outcomes for black pts (12% of study population), and outcomes for pts on post-progression therapy with advanced or mTNBC that has relapsed?

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INDICATION

ASCENT Clinical Trial

April 22, 2020

The FDA granted accelerated approval to Sacituzumab govitecan-hziy (Trodelvy®) for adult patients with metastatic triple negative breast cancer who received at least two prior therapies for metastatic disease

April 7, 2021

The FDA granted **regular approval** to sacituzumab govitecan (Trodelvy®) for patients with 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**

September 27, 2021

The updated NCCN Guidelines include sacituzumab govitecan-hziy (Trodelvy®) as a **preferred regimen** for the treatment of adult patients with metastatic triple-negative breast cancer (TNBC) who received at least two prior therapies, with **at least one line for metastatic disease**

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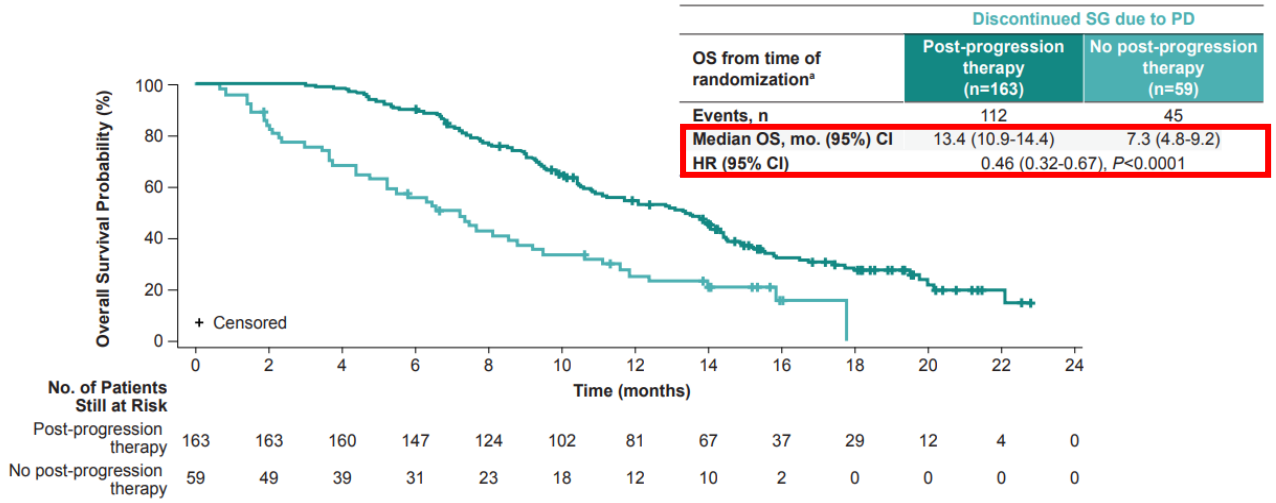
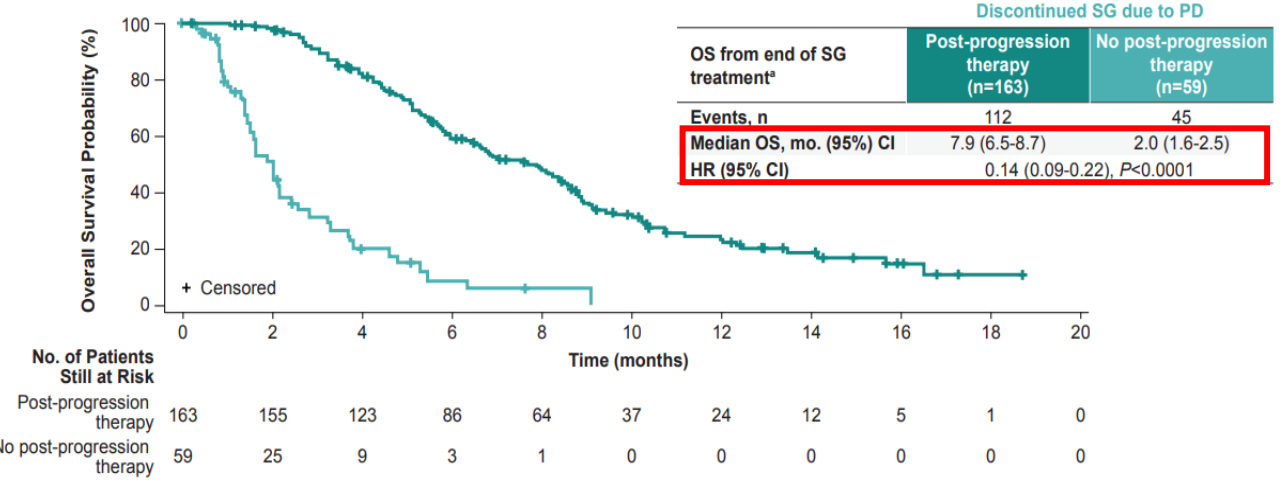
KEY DATA

ASCENT: Post hoc subgroup analysis of post-progression treatment and OS for pts who discontinued SG due to Prog Disease during the ASCENT trial



OS from time of randomization[a]	Discontinued SG due to PD: Post-progression therapy (n=163)	Discontinued SG due to PD: No post-progression therapy (n=59)
Events, n	112	45
Median OS, mo. (95% CI)	13.4 (10.9-14.4)	7.3 (4.8-9.2)
HR (95% CI)	0.46 (0.32-0.67), *P*<0.0001	



OS from end of SG treatment[a]	Discontinued SG due to PD: Post-progression therapy (n=163)	Discontinued SG due to PD: No post-progression therapy (n=59)
Events, n	112	45
Median OS, mo. (95% CI)	7.9 (6.5-8.7)	2.0 (1.6-2.5)
HR (95% CI)	0.14 (0.09-0.22), *P*<0.0001	

- The ASCENT trial enrolled 529 patients, 267 (50%) were randomized to receive SG and of those 222 (83%) discontinued treatment due to PD
- Following SG discontinuation,163 of the 222 patients (73%) received post-progression therapy
  - Common post-SG therapies included eribulin (32%), carboplatin (15%), capecitabine (15%), and atezolizumab (7%)
- Median OS from time of randomization:
  - **13.4 vs 7.3** months
  - (HR, 0.46; 95% CI, 0.32-0.67; P<0.0001)
- Median OS from end of SG treatment:
  - **7.9 vs 2.0** months
  - (HR, 0.14; 95% CI, 0.09-0.22; P<0.0001)
- Pts who received eribulin, carboplatin, atezolizumab, or capecitabine, as post-progression therapy following SG had similar median OS

SABCS 2021 Poster P5-16-01, P5-16-07, P5-16-15

SUMMARY

ASCENT Clinical Trial

- Efficacy and safety results from subgroup analysis is consistent with the overall study population
- SG clinical responders (extended PFS and OS compared to TPC) also benefit the most from maintained or improved HRQoL
- Neutropenia and diarrhea remain a concern but are manageable
  - Active monitoring and early intervention; dose reduction, premedication or concomitant medication

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SUMMARY

ASCENT Clinical Trial

Further studies initiated:

- Clinical trial collaboration with Merck to evaluate Trodelvy® (sacituzumab govitecan-hziy) in combination with KEYTRUDA® (pembrolizumab) in pts with first-line metastatic TNBC
  - Saci-IO TNBC: Randomized Phase II Study of Sacituzumab Govitecan With or Without Pembrolizumab in PD-L1-negative mTNBC
- SASCIA: Phase III postneoadjuvant study evaluating sacituzumab govitecan in primary HER2- breast cancer pts with high relapse risk after standard neoadjuvant treatment
  - Not open in the US
- TROPiCS-02: Phase III study of sacituzumab govitecan (IMMU-132) versus treatment of physician's choice (TPC) in pts with HR+, HER2- metastatic breast cancer (MBC) who have failed at least two prior chemotherapy regimens
  - Study to read out soon

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ASCENT Clinical Trial

Sacituzumab govitecan (Trodelvy®) provides benefit irrespective of race, on receipt of further systemic therapy post-SG, and maintains or improves health-related QoL for patients with relapsed or refractory mTNBC

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CLINICAL QUESTION

TROPION-PanTumor01 Clinical Trial

Will the use of Dato-DXd benefit patients with advanced or metastatic TNBC that has relapsed?

KEY DATA

TROPION-PanTumor01 Clinical Trial

Study Design: Phase 1 study in pts with relapsed or refractory metastatic solid tumors

Key Eligibility Criteria

- Relapsed of refractory advanced or metastatic solid tumors
- Unselected for TROP2 expression
- Age ≥18 (USA) or ≥ 20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST version 1.1
- Stable, treated brain metastases allowed

NSCLC
(0.27 to 10 mg/kg IV Q3W)

TNBC
8 mg/kg (n=2); 6 mg/kg (n=42)

- 31 (70%) discontinued
  - 30 (68%) had disease progression
  - 1 (2%) had as adverse event
- 13 (30%) treatment ongoing

HR+/HER2- Breast Cancer

Other tumor types
(including SCLC, bladder, gastric, esophageal)

Primary Objectives
- Safety
- Tolerability

Secondary Objectives
- Efficacy
- Pharmacokinetics
- Antidrug antibodies

Data cutoff: July 30, 2021

Last patient enrolled Apr 2021; median follow-up: 7.6 mo (range 4-13 mo)

Krop. SABCS 2021 (Abstract #GS1-05).

KEY DATA

TROPION-PanTumor01 Clinical Trial: Baseline Characteristics

Patient Characteristics	TNBC (n=44)
Age, Median (range), years	53 (32 – 82)
Country n (%)	
USA / Japan	31 (70) / 13 (30)
ECOG PS, n (%)	
0 / 1	18 (41) / 26 (59)
De novo metastatic, n (%)	
Yes / No	14 (32) / 30 (68)
Brain metastases, n (%)	5 (11)
Prior therapies in met. setting median (range), n	3 (1 – 10)
≥2 prior lines of therapy, n (%)	30 (68)
Previous systemic treatment, n (%)	
Taxanes	40 (91)
Platinum-based chemotherapy	23 (52)
Immunotherapy	19 (43)
PARPi	7 (16)
Topo I inhibitor-based ADC*	13 (30)

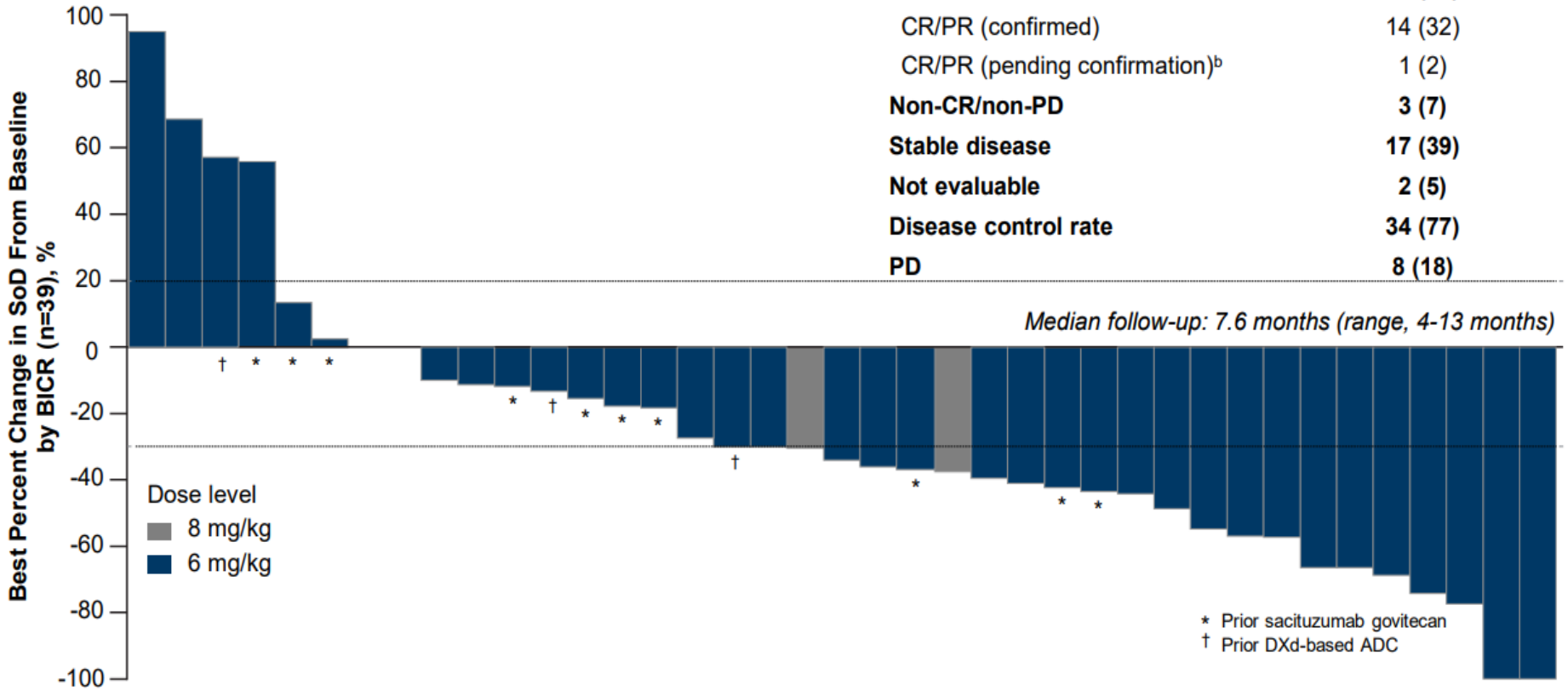
* Includes Sacituzumab govitecan (n=10); trastuzumab deruxtecan (n=2); patritumab deruxtecan (n=1)

Krop. SABCS 2021 (Abstract #GS1-05).

KEY DATA

TROPION-PanTumor01 Trial: Anti-tumor Responses by BICR

All patients with TNBC



Patients, n (%)[a]	All Patients (n=44)
ORR	**15 (34)**
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	**3 (7)**
Stable disease	**17 (39)**
Not evaluable	**2 (5)**
Disease control rate	**34 (77)**
PD	**8 (18)**

[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at the data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.
[b] Includes patients with an unconfirmed response but are ongoing treatment.

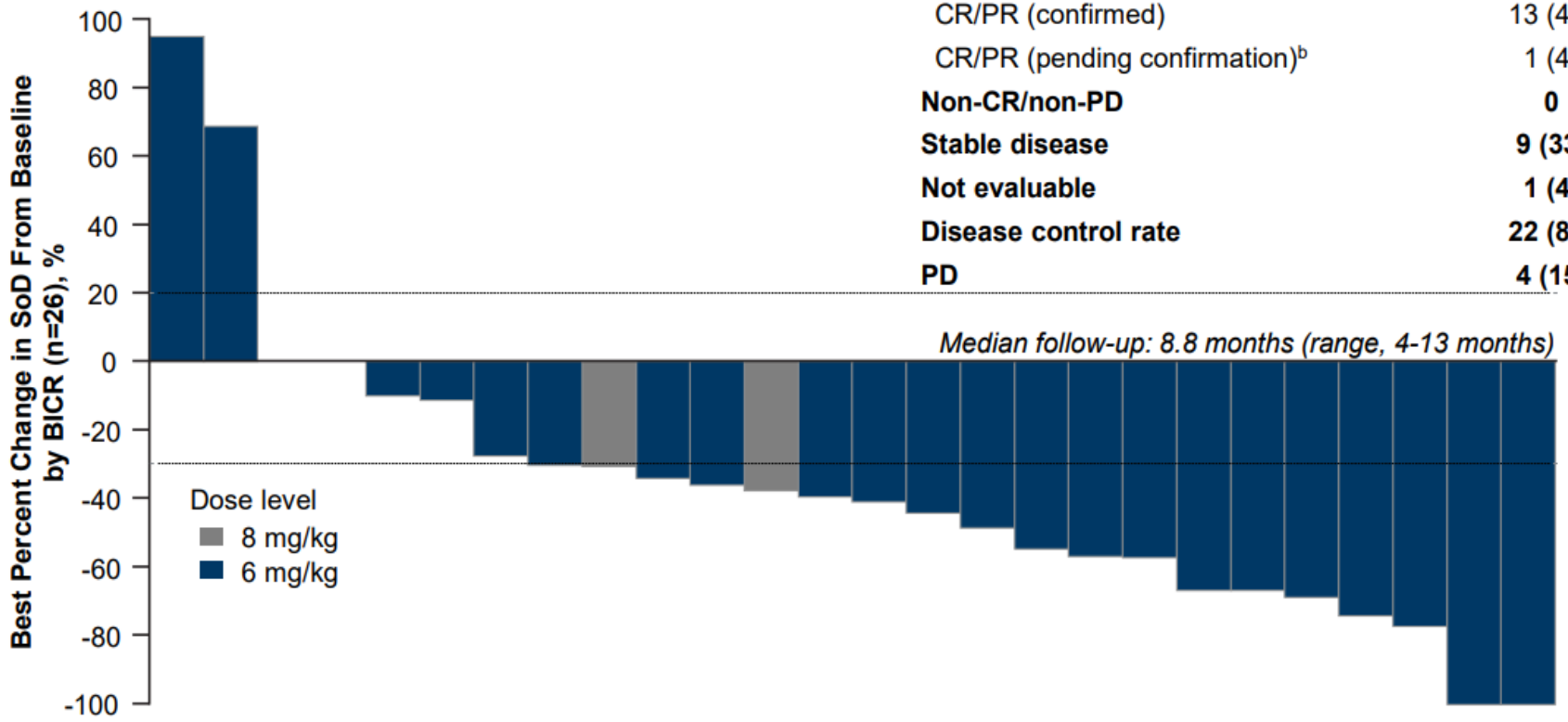
Krop. SABCS 2021 (Abstract #GS1-05).

KEY DATA

TROPION-PanTumor01 Trial: Anti-tumor Responses by BICR

Patients with TNBC without prior Topo I inhibitor-based ADC

Patients, n (%)[a]	SG/DXd Naïve Patients with Measurable Disease at BL (n=27)
ORR	**14 (52)**
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[b]	1 (4)
Non-CR/non-PD	**0**
Stable disease	**9 (33)**
Not evaluable	**1 (4)**
Disease control rate	**22 (81)**
PD	**4 (15)**



[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 1 patient at the data cutoff.
[b] Includes patients with an unconfirmed response but are ongoing treatment.

Krop. SABCS 2021 (Abstract #GS1-05).

SUMMARY

TROPION-PanTumor01 Data in TNBC: Summary and Next Steps

- In a heavily pretreated pts with TNBC treated in this dose escalation study, the ORR by BICR was 34% in *all* patients
  - 52% in pts with measurable disease at baseline who were treatment naïve to Topo I inhibitor-based ADC therapies

- Manageable safety profile with no new safety signals

- Further studies initiated:
  - BEGONIA (arm 7): Phase 2 of Dato-DXd plus durvalumab for TNBC
    - Durvalumab (1120 mg) + Dato-DXd (6 mg/kg) IV every 3w. Part 1 of 30 pts: safety run-in (n=6) to identify the recommended phase 2 dose (RP2D), and detect an efficacy signal for part 1 expansion. Once the RP2D has been established, a futility analysis will be performed with an option to expand the cohort to an additional 27 pts if expansion criteria are met. The primary endpoint for part 1 is ORR. Tumors will be assessed every 6 weeks per RECIST v1.1. Kaplan-Meier analysis will be used for PFS and OS. PD-L1 and TROP2 expression will be assessed by IHC.

  - TROPION-Breast01 (NCT05104866): phase 3 trial in HR+/HER- breast cancer of single Dato-DXd vs single agent chemo after 1-2 chemos for mTNBC

Krop. SABCS 2021 (Abstract #GS1-05).

TROPION-PanTumor01 Clinical Trial

Dato-DXd has the potential to provide an additional option for patients with relapsed or refractory mTNBC

KEY QUESTION

Triple Negative Breast Cancer

Can subset analysis help identify patients with Triple Negative Breast Cancer that will benefit from immunotherapy in the (neo)adjuvant and metastatic setting?

2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01

- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB

- MA.32A

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CLINICAL QUESTION

KEYNOTE-522 Clinical Trial

Does use of pembrolizumab in combination with chemotherapy in the neoadjuvant setting, followed by pembrolizumab as a single agent in the adjuvant setting improve outcomes for all subgroups of patients with early TNBC?

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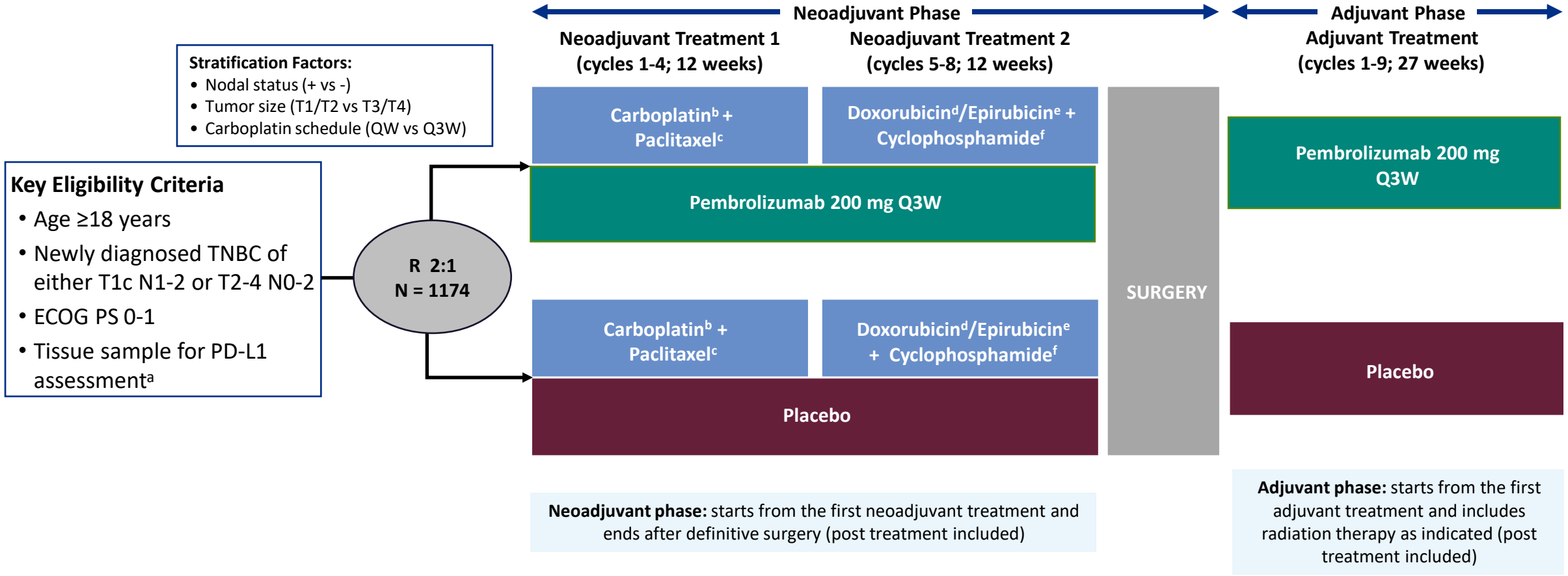
KEY DATA

KEYNOTE-522 Clinical Trial

Study Design: Phase 3 multicenter study



[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose AUC 5 q3w or AUC 1.5 qw. [c]Paclitaxel dose was 80 mg/m^2 qw. [d]Doxorubicin dose 60 mg/m^2 q3w.
[e]Epirubicin dose 90 mg/m^2 q3w. [f]Cyclophosphamide dose 600 mg/m^2 q3w.
Ref. Schmit et al. ESMO Virtual Plenary July 2021

KEYNOTE-522 Clinical Trial

Study Design: Endpoints

- Primary Endpoints
  - pCR (ypTo/Tis ypNO) assessed by local pathologist in ITT population
  - EFS assessed by investigator in ITT population

- Secondary Endpoints
  - pCR by alternative definitions (ypTo ypNO and ypTO/Tis)
  - OS
  - pCR, EFS, and OS in the PD-L1 – positive population
  - Safety in all treated populations

- **Exploratory Analyses**
  - **EFS sensitivity analyses**
  - **EFS in patient subgroups**

Prespecified sensitivity and subgroup analyses were performed to assess the robustness and consistency of the primary EFS result

Schmid. SABCS 2021 Abstract #GS1-01.

KEY DATA

KEYNOTE-522 Clinical Trial

Primary and Sensitivity Analyses Definitions of EFS

Analysis	Local PD precludes definitive surgery	Local Recurrence	Distant PD	Distant recurrence	Death from any cause	Positive margin at last surgery	Second primary cancer (non-breast)	Second Primary breast cancer	New anticancer therapy for metastatic disease
Primary	X	X	X	X	X	X	X		
Sensitivity									
1*	X	X	X	X	X	X	X		
2	X	X	X	X	X	X	X		X
3	X	X	X	X	X		X		
4	X	X	X	X	X				
5	X	X	X	X	X	X	X	X	

*In the primary analysis, patients who did not experience an event at the time of data analysis were censored at the date they were last known to be alive and event free. Sensitivity analysis 1 uses alternative censoring rules: events after 2 consecutive mussed disease assessments or initiation of post surgery new anti-cancer therapy were censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessments and initiation of post-surgery new anti-cancer therapy; if no events before new anti-cancer therapy, patients were censored at last disease assessment before initiation of post-surgery new anti-cancer treatment.

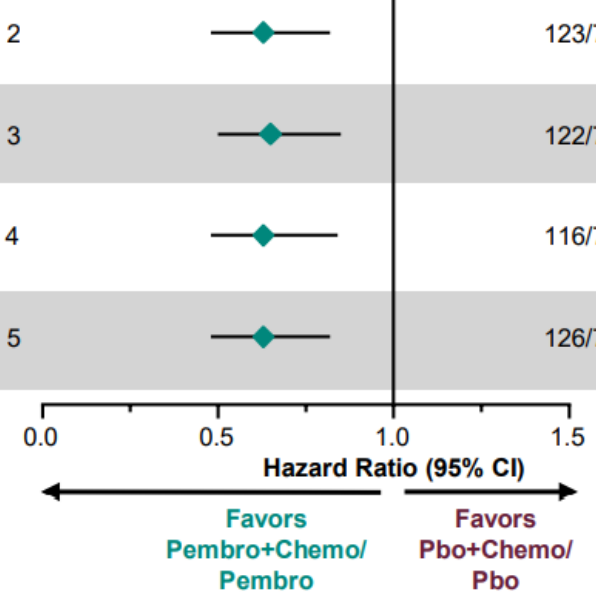
Schmid. SABCS 2021 Abstract #GS1-01.

KEY DATA

KEYNOTE-522 Clinical Trial

EFS Sensitivity Analyses

EFS Analyses	No. of events/no. of patients (%) Pembro+Chemo/Pembro	Pbo+Chemo/Pbo	Hazard Ratio (95% CI)[a]
Primary analysis	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Sensitivity analyses			
Analysis 1	112/784 (14.3)	84/390 (21.5)	0.64 (0.48 to 0.84)
Analysis 2	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Analysis 3	122/784 (15.6)	90/390 (23.1)	0.65 (0.50 to 0.85)
Analysis 4	116/784 (14.8)	88/390 (22.6)	0.63 (0.48 to 0.84)
Analysis 5	126/784 (16.1)	95/390 (24.4)	0.63 (0.48 to 0.82)



[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

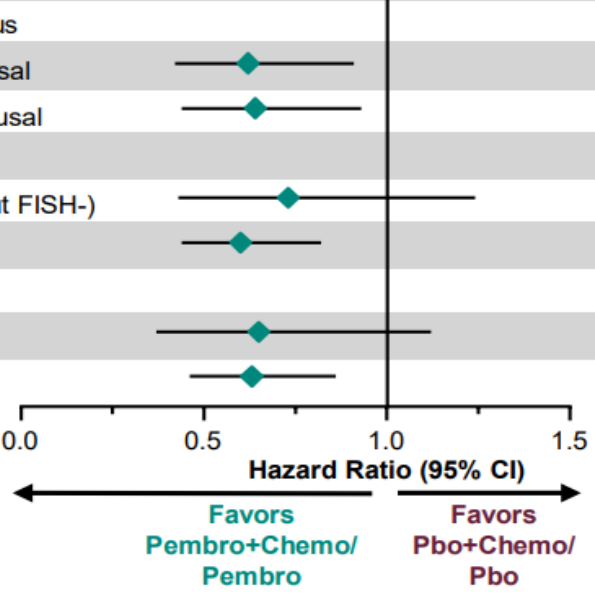
Schmid. SABCS 2021 Abstract #GS1-01.

KEY DATA

KEYNOTE-522 Clinical Trial

EFS Subgroup Analyses

EFS Analyses	No. of events/no. of patients (%) Pembro+Chemo/Pembro	Pbo+Chemo/Pbo	Hazard Ratio (95% CI)
Primary analysis	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Overall disease stage			
Stage II	65/590 (11.7)	54/291 (18.6)	0.60 (0.42 to 0.86)
Stage III	54/194 (27.8)	39/98 (39.8)	0.68 (0.45 to 1.03)
Menopausal status			
Pre-menopausal	60/438 (13.7)	47/221 (21.3)	0.62 (0.42 to 0.91)
Post-menopausal	63/345 (18.3)	46/169 (27.2)	0.64 (0.44 to 0.93)
HER2 status			
2+ by IHC (but FISH-)	32/188 (17.0)	24/104 (23.1)	0.73 (0.43 to 1.24)
0-1+ by IHC	91/595 (15.3)	69/286 (24.1)	0.60 (0.44 to 0.82)
LDH			
>ULN	29/149 (19.5)	23/80 (28.8)	0.65 (0.37 to 1.12)
≤ULN	93/631 (14.7)	69/309 (22.3)	0.63 (0.46 to 0.86)



[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Schmid. SABCS 2021 Abstract #GS1-01.

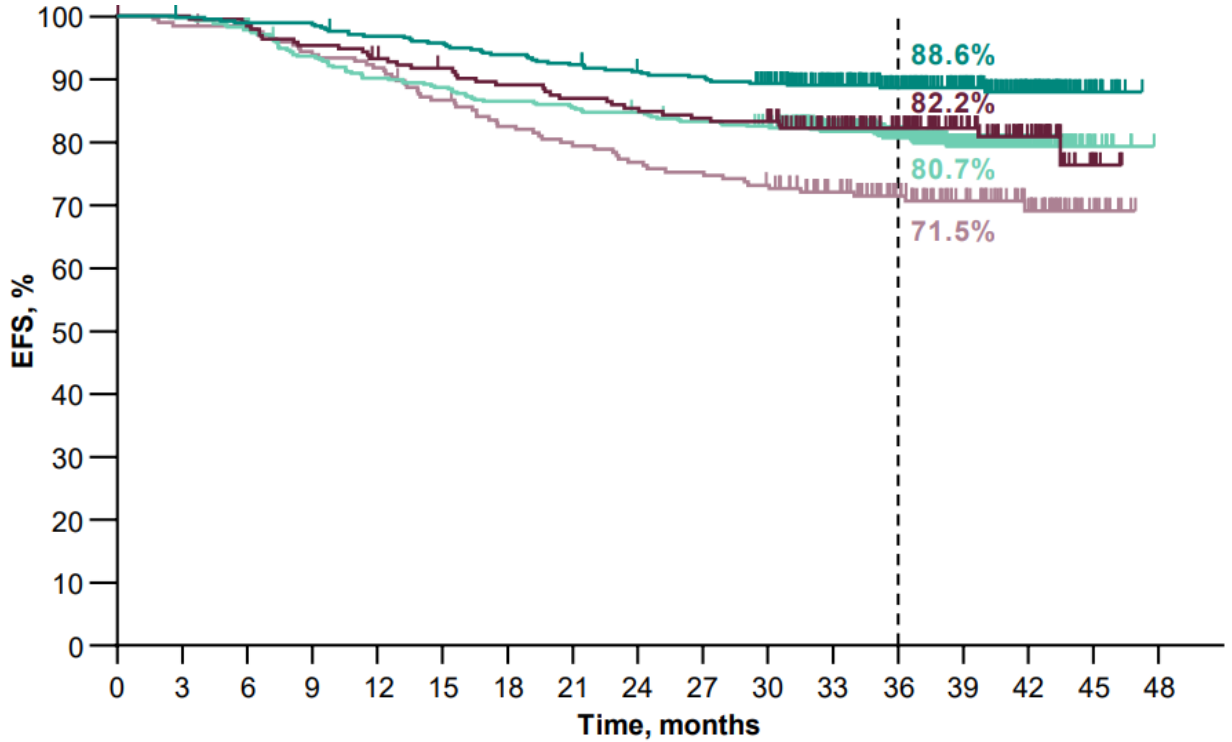
KEY DATA

KEYNOTE-522 Clinical Trial

EFS by Nodal Status

Node Negative	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.4%	0.58 (0.37-0.91)
Pbo+Chemo/Pbo	18.6%	

Node Positive	Events	HR (95% CI)
Pembro+Chemo/Pembro	19.6%	0.65 (0.46-0.91)
Pbo+Chemo/Pbo	29.1%	



No. at risk																	
Pembro+Chemo/Pembro, Node Negative	376	374	371	371	362	358	351	345	338	335	322	272	212	151	81	16	0
Pbo+Chemo/Pbo, Node Negative	194	193	190	184	179	174	169	165	162	159	157	131	101	71	39	7	0
Pembro+Chemo/Pembro, Node Positive	408	407	398	380	366	360	351	347	343	336	330	279	221	152	84	12	0
Pbo+Chemo/Pbo, Node Positive	196	193	192	184	179	168	159	154	148	145	140	119	94	69	44	10	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Schmid. SABCS 2021 Abstract #GS1-01.

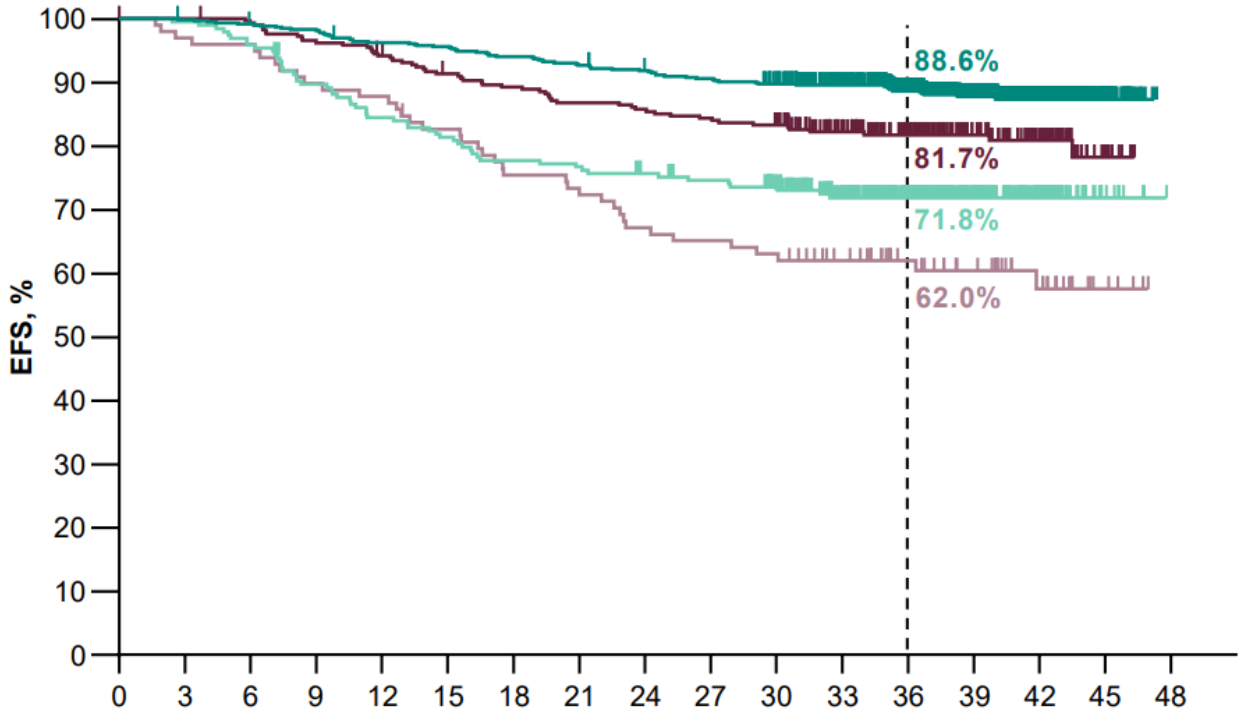
KEY DATA

KEYNOTE-522 Clinical Trial

EFS by Overall Disease Stage

Stage II	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.7%	0.60 (0.42-0.86)
Pbo+Chemo/Pbo	18.6%	

Stage III	Events	HR (95% CI)
Pembro+Chemo/Pembro	27.8%	0.68 (0.45-1.03)
Pbo+Chemo/Pbo	39.8%	



No. at risk																	
Pembro+Chemo/Pembro, Stage II	590	588	583	578	565	561	552	544	536	529	515	434	345	243	126	20	0
Pbo+Chemo/Pbo, Stage II	291	290	287	279	271	261	255	248	245	241	236	197	156	109	63	12	0
Pembro+Chemo/Pembro, Stage III	194	193	186	173	163	157	150	148	145	142	137	117	88	60	39	8	0
Pbo+Chemo/Pbo, Stage III	98	95	94	88	86	80	73	71	65	63	61	53	39	31	20	5	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Schmid. SABCS 2021 Abstract #GS1-01.

SUMMARY

KEYNOTE-522 Clinical Trial

- Neoadjuvant pembrolizumab added to chemotherapy, followed by adjuvant pembrolizumab resulted in a statistically significant and improvement in EFS
  - Prespecified EFS sensitivity analyses shows a robust treatment benefit for previously untreated non-metastatic TNBC
  - Benefit is consistent across a broad selection of prespecified patient subgroups, including those defined by nodal status and overall disease stage
  - EFS improvement was seen in both PD-L1-positive and PD-L1-negative subsets, and did not differ by the chosen schedule of carboplatin administration.

- The absolute EFS benefit from the addition of pembrolizumab was larger in patients who failed to achieve pCR with NACT (67% versus 57%) than in those who achieved pCR (94% versus 92%).

- The addition of pembrolizumab to NACT raised the overall pCR rate from 51% to 65%, and improvements in pCR rates were seen in both PD-L1-positive and PD-L1-negative cancers.

- No new safety concerns

Schmid. SABCS 2021 Abstract #GS1-01.

KEYNOTE-522 Clinical Trial

Use of pembrolizumab with chemotherapy in the neoadjuvant setting followed by single agent pembrolizumab in the adjuvant setting provides benefit for patients with high-risk, early stage triple negative breast cancer

2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01
- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB
- MA.32A

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CLINICAL QUESTION

KEYNOTE-355 Clinical Trial

Does the use of pembrolizumab in combination with chemotherapy in the 1L setting continue to benefit patients with metastatic TNBC based on additional PD-L1 expression analysis?

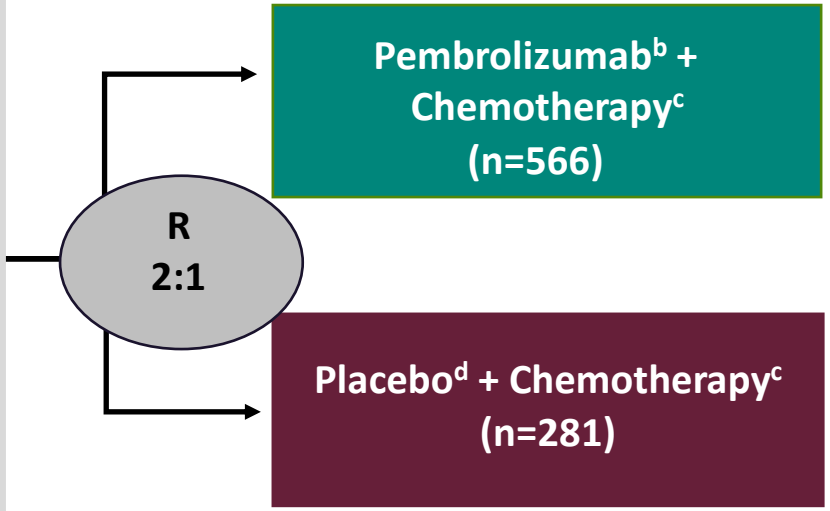
KEY DATA

KEYNOTE-355 Clinical Trial

Study Design: Phase 3 study

Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥ 1 or CPS < 1)
- Prior treatment with same class chemotherapy in the neo/adjuvant setting

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥ 6 months prior to first disease recurrence
- ECOG status 0 or 1
- Life expectancy of 12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS mets
- No active autoimmune disease
- N=847



In this analysis, outcomes in subgroups of patients by additional CPS cut-offs were assessed

Primary Endpoints: PFS, OS
Secondary Endpoints: ORR, DOR, DCR, safety

[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumor sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg IV q3w. [C]PChemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 every 28 days; Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days; Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days. [d]Normal saline.
Ref. Schmit et al. ESMO Virtual Plenary July 2021

KEY DATA

KEYNOTE-355 Clinical Trial

Baseline characteristics: ITT

Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastasis	168 (29.7)	84 (29.9)
<12 months	125 (22.1)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Prevalence of Additional PD-L1 CPS Subgroups

	Pembro + Chemo	Placebo + Chemo
CPS <1	24.9%	24.9%
CPS 1-9	36.2%	38.4%
CPS 10-19	14.1%	13.9%
CPS ≥ 20	24.7%	22.8%

Cortes. SABCS 2021 Abstract # GS1-02.

KEY DATA

KEYNOTE-355 Clinical Trial

Overall Survival in Additional PD-L1 CPS Subgroups

Population	Treatment (n/N)	Median OS, mo	Events	HR (95% CI)
ITT	**Pembro + CT** (460/566)	17.2	81.3%	0.89 (0.76-1.05)
	Placebo + CT (238/281)	15.5	84.7%	
PD-L1 CPS <1	**Pembro + CT** (124/141)	16.2	87.9%	0.97 (0.72 – 1.32)
	Placebo + CT (61/70)	14.7	87.1%	
PD-L1 CPS 1 -9	**Pembro + CT** (181/205)	13.9	88.3%	1.09 (0.85 – 1.40)
	Placebo + CT (93/108)	15.5	86.1%	
PD-L1 CPS 10-19	**Pembro + CT** (56/80)	**20.3**	**70.0%**	**0.71 (0.46 – 1.09)**
	Placebo + CT (33/39)	**17.6**	**84.6%**	
PD-L1 CPS ≥ 20	**Pembro + CT** (99/140)	**24.0**	**70.7%**	**0.72 (0.51 – 1.01)**
	Placebo + CT (51/64)	**15.6**	**79.7%**	

Data cutoff: June 15, 2021

Cortes. SABCS 2021 Abstract # GS1-02.

KEY DATA

KEYNOTE-355 Clinical Trial

Progression-Free Survival in Additional PD-L1 CPS Subgroups

Population	Treatment (n/N)	Median OS, mo	Events	HR (95% CI)
ITT	**Pembro + CT** (406/566)	7.5	71.7%	0.82 (0.70-0.98)
	Placebo + CT (217/281)	5.6	77.2%	
PD-L1 CPS <1	**Pembro + CT** (107/141)	6.3	75.9%	1.09 (0.78 – 1.52)
	Placebo + CT (51/70)	6.2	72.9%	
PD-L1 CPS 1 -9	**Pembro + CT** (155/205)	5.7	75.6%	0.85 (0.65 – 1.11)
	Placebo + CT (85/108)	5.6	78.7%	
PD-L1 CPS 10-19	**Pembro + CT** (50/80)	**9.9**	**62.5%**	**0.70 (0.44 – 1.09)**
	Placebo + CT (31/39)	**7.6**	**79.5%**	
PD-L1 CPS ≥ 20	**Pembro + CT** (94/140)	**9.2**	**67.1%**	**0.62 (0.44 – 0.88)**
	Placebo + CT (50/64)	**5.4**	**78.1%**	

Data cutoff: June 15, 2021

Cortes. SABCS 2021 Abstract # GS1-02.

SUMMARY

KEYNOTE-355 Clinical Trial

- Overall, there was a modest improvement in median PFS with the addition of pembrolizumab
  - Pembrolizumab added to chemotherapy resulted in statistically significant improvement in PFS and OS versus chemotherapy alone for the 1L treatment of PD-L1 CPS ≥10 metastatic TNBC
- Results stratified according to CPS suggest that benefit is limited to those with CPS ≥10, in whom the addition of pembrolizumab to chemotherapy improved median PFS by approximately two months
- Although there were also improvements in PFS among those with CPS ≥1, this improvement may have been driven by those with CPS scores ≥10
- No new safety concerns

Based on the additional subgroup analysis CPS ≥ 10 is a reasonable cut-off to determine the population of patients with metastatic TNBC that would benefit from pembrolizumab + chemotherapy

Cortes. SABCS 2021 Abstract # GS1-02.

KEYNOTE-355 Clinical Trial

Adding pembrolizumab to chemotherapy in the 1L setting should be considered as a new standard of care treatment regimen for patients with locally recurrent or metastatic TNBC whose tumors express PD-L1 (CPS ≥10)

Q & A

Triple Negative Breast Cancer

KEY QUESTION

HER2+ Breast Cancer

Should patients with HER2+ stable versus active brain metastases be managed differently?

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2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01

- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB

- MA.32A

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CLINICAL QUESTION

DESTINY-Breast03 Clinical Trial

Does the use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 2L setting benefit pts with HER2+ stable brain metastases, when compared with T-DM1?

Subset analysis

KEY DATA

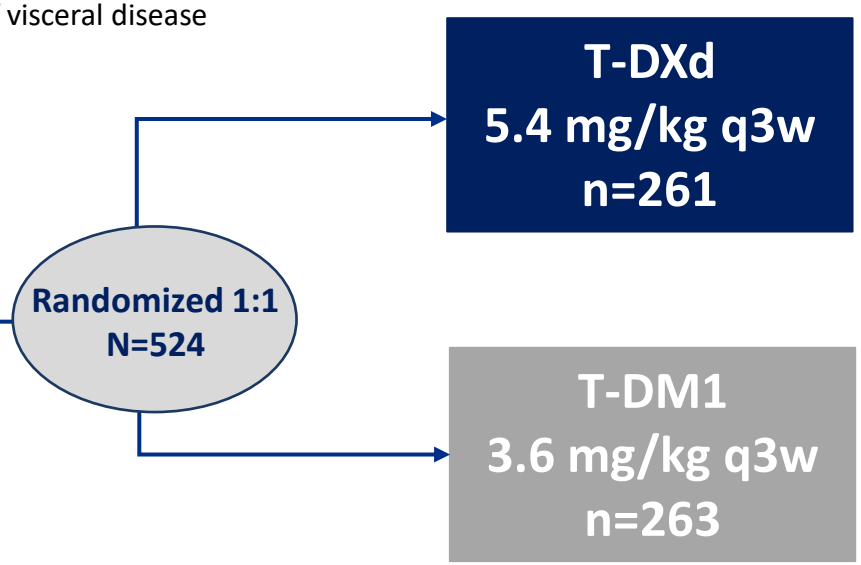
DESTINY-Breast03 Clinical Trial

Study Design: Randomized Phase 3 open-label, multicenter study

Stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease

Inclusion Criteria

- Unresectable or metastatic HER2+* BC
- Previously treated with trastuzumab and taxane in advanced or metastatic setting^
- Could have clinically stable, previously treated brain metastases
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment



*HER2 IHC3+ or IHC2+/ISH+ based on central confirmation
^Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

- **Primary End Point:** PFS (Blinded ICR)
- **Secondary Endpoints:** OS, ORR (BIDR and investigator), DOR (BICR), PFS (investigator), safety

At the time of data cutoff (May 21, 2021), 125 (48.6%) T-DXd patients and 214 (82.0%) T-DM1 patients had discontinued treatment; Median follow up of 15.9 months

Brain mets were measured at baseline by CT or MRI and lesions were monitored throughout the study for pts with a known history of brain mets. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 wk must have elapsed between the end of whole brain radiotherapy and study enrollment.

Hurvitz. SABCS 2021 (Abstract #GS3-01).

KEY DATA

DESTINY-Breast03 Clinical Trial

Baseline Characteristics

	Randomized to T-DXd (n=261)	Randomized to T-DM1 (n=263)
Age, Median (range), years	54.3 (27.9 – 83.1)	54.2 (20.2 – 83.0)
Female, %	99.6	99.6
• Europe	20.7	19.0
• **Asia**	**57.1**	**60.8**
• North America	6.5	6.5
• Rest of World	15.7	13.7
HER2 Status (IHC, %)		
• 3+	89.7	88.2
• 2+ (ISH amplified)	9.6	11.4
• 1+ / not evaluable /not examined	0.4 / 0.4 / 0	0 / 0.4 / 0
ECOG PS, %: 0 / 1 / missing	59.0 / 40.6 / 0.4	66.5 / 33.1 / 0.4
Hormone Receptor, %: +ve / -ve	50.2 / 49.8	51.0 / 49.0
History of Brain Mets, %	62 (23.8%)	52 (19.8%)
Brain Mets at baseline*, n (%)	**43 (16.5%)**	**39 (14.8%)**
Visceral Disease, %	70.5	70.3
Prior treatment for mBC (%)	92.0	89.0
Prior lines of therapy, (%) 0-1 I ≥ 2	50.6 I 49.4	47.9 I 52.1
Prior cancer therapy, trastuzumab, (%)	99.6	99.6
Prior cancer therapy, pertuzumab, (%)	**62.1**	**60.1**

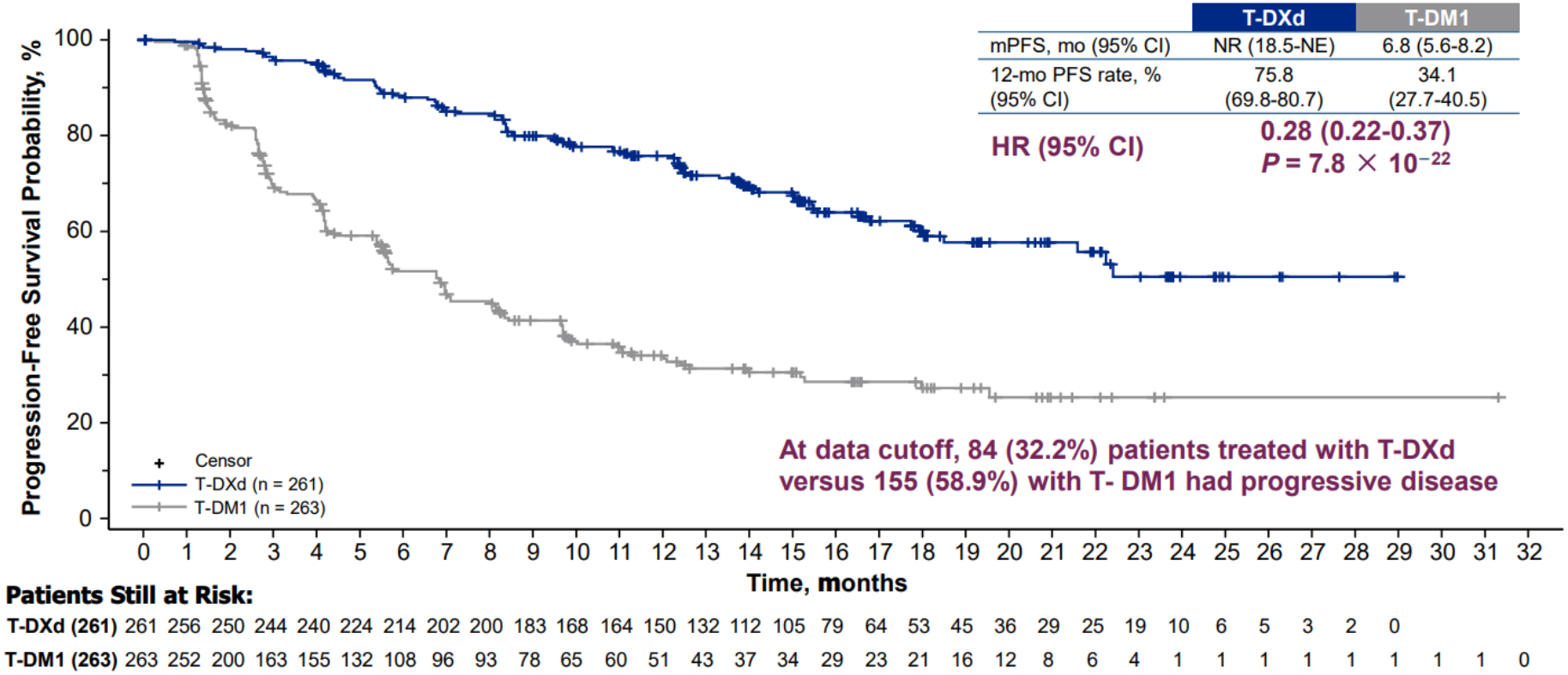
Note: *Only patients with brain mets at baseline on imaging

Hurvitz. SABCS 2021 (Abstract #GS3-01).

KEY DATA

DESTINY-Breast03 Clinical Trial

Previously Reported Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Median PFS follow up for T-DXd was 15.5 months (range 15.1 – 16.6) and for T-DM1 was 13.9 months (range 11.8 – 15.1)

NR, not reached; NE, not evaluable

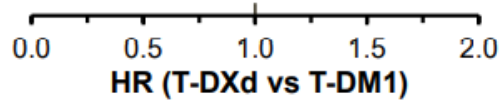
Hurvitz. SABCS 2021 (Abstract #GS3-01).

KEY DATA

DESTINY-Breast03 Clinical Trial

PFS in Key Subgroups

		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone receptor status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior pertuzumab treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior lines of therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Patients with BM	Yes (n = 82)	22/43	27/39	15.0 (12.5-22.2)	3.0 (2.8-5.8)	0.2465 (0.1341-0.4529)
	No (n = 442)	65/218	131/224	NE (22.4-NE)	7.1 (5.6-9.7)	0.2971 (0.2199-0.4014)



[a]Rapid progressors on (neo)adjuvant therapy were included; Line of therapy does not include endocrine therapy
BM = brain mets at baseline only; NE = not evaluable/not reached

Hurvitz. SABCS 2021 (Abstract #GS3-01).

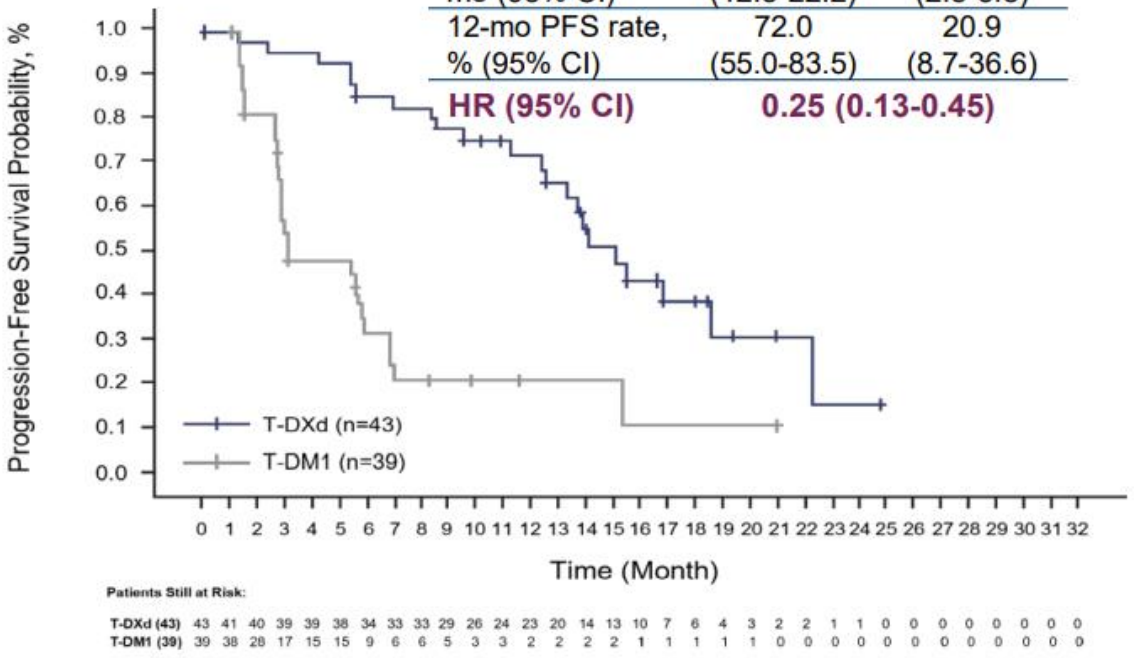
KEY DATA

DESTINY-Breast03 Clinical Trial

PFS for Patients With and Without Brain Mets

Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	0.25 (0.13-0.45)	

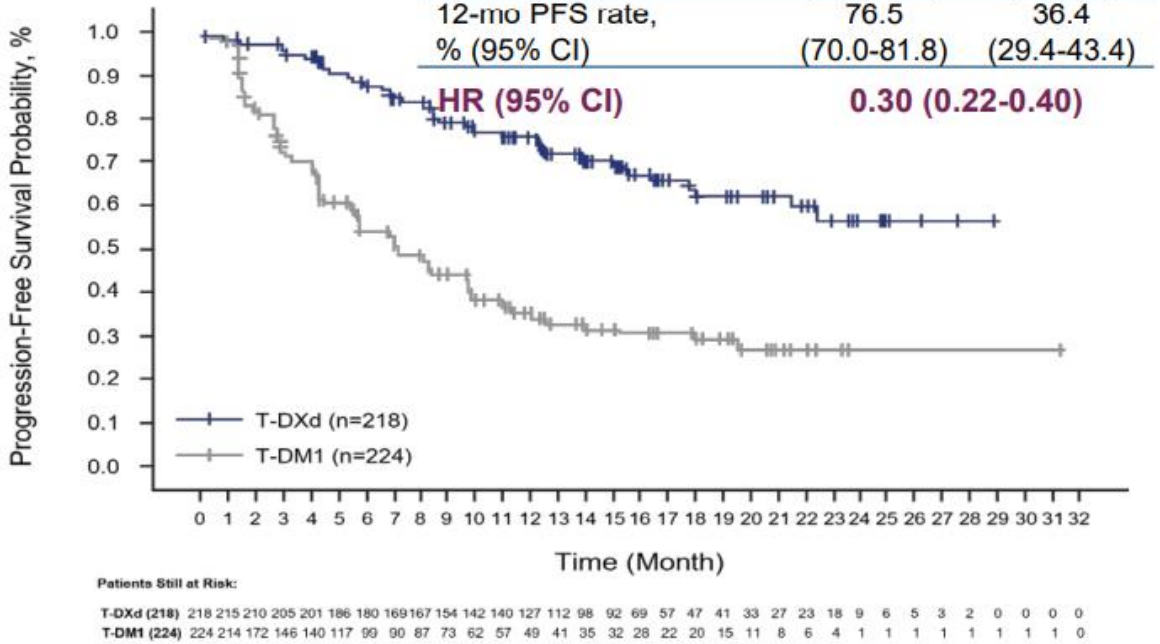


At data cutoff, in pts **with brain mets** at baseline, PD (any time point, any type) was observed

- In **21/43** (~49%) treated with T-DXd vs **27/39** (~69%) with T-DM1
  - In the brain*, in 9/21 treated with T-DXd vs 11/27 with T-DM1

No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	0.30 (0.22-0.40)	



At data cutoff, in pts **without brain mets** at baseline, PD (any time point, any type) was observed

- In **63/218** (~29%) treated with T-DXd vs **128/224** (~57%) with T-DM1
  - In the brain*, in 4/63 treated with T-DXd vs 1/128 with T-DM1

Note: *patients with PD in the brain may also have had progression elsewhere (not specified)

NE = not evaluable/not reached

Hurvitz. SABCS 2021 (Abstract #GS3-01).

KEY DATA

DESTINY-Breast03 Clinical Trial

Confirmed ORR across Patient Subgroups

		T-DXd (n = 261)	T-DM1 (n = 263)		
		No. of Patients With Confirmed CR/PR	No. of Patients With Confirmed CR/PR	ORR, % (95% CI) ■ T-DXd ■ T-DM1	Difference of T-DXd vs T-DM1, % (95% CI)
All patients		208/261	90/263	79.7 / 34.2	45.5 (37.6-53.4)
Hormone receptor status	Positive (n = 272)	104/133	43/139	78.2 / 30.9	47.3 (36.1-58.4)
	Negative (n = 248)	103/126	47/122	81.7 / 38.5	43.2 (31.5-55.0)
Prior pertuzumab treatment	Yes (n = 320)	129/162	52/158	79.6 / 32.9	46.7 (36.5-56.9)
	No (n = 204)	79/99	38/105	79.8 / 36.2	43.6 (30.5-56.7)
Visceral disease	Yes (n = 384)	151/195	55/189	77.4 / 29.1	48.3 (39.1-57.6)
	No (n = 140)	57/66	35/74	86.4 / 47.3	39.1 (23.6-54.6)
Prior lines of therapy[a]	0-1 (n = 258)	99/132	45/126	75.0 / 35.7	39.3 (27.3-51.2)
	≥2 (n = 266)	109/129	45/137	84.5 / 32.8	51.6 (40.9-62.4)
Patients with BM	Yes (n = 82)	29/43	8/39	67.4 / 20.5	46.9 (25.6-68.3)
	No (n = 442)	179/218	82/224	82.1 / 36.6	45.5 (36.9-54.1)

BM, brain metastasis; CR, complete response; ORR, objective response rate; PR, partial response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Hurvitz. SABCS 2021 (Abstract #GS3-01).

DESTINY-Breast03 Clinical Trial

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis, n (%)							
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Overall	**T-DXd** (n=257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
	T-DM1 (n=261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)
Asia subgroup	**T-DXd** (n=147)	5 (3.4)	10 (6.8)	1 (0.7)	0	0	16 (10.9)
	T-DM1 (n=159)	3 (1.9)	1 (0.6)	0	0	0	4 (2.5)
Non-Asia subgroup	**T-DXd** (n=110)	2 (1.8)	8 (7.3)	1 (0.9)	0	0	11 (10.0)
	T-DM1 (n=102)	1 (1.0)	0	0	0	0	1 (1.0)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXD

Hurvitz. SABCS 2021 (Abstract #GS3-01).

SUMMARY

DESTINY-Breast03 Clinical Trial

- Clinically meaningful and statistically significant improvement in PFS and ORR compared to T-DM1 overall and across patient subgroups
- Benefit in patients with and without brain mets; T-DXd resulted in greater efficacy compared to T-DM1
  - With brain mets mPFS: 15 vs 3 months for T-DXd vs T-DM1
  - Without brain mets mPFS: Not reached vs 7.1 months T-DXd vsT-DM1
- Continue to be aware of and monitor for ILD/pneumonitis

***October 4, 2021**: The U.S. Food and Drug Administration (FDA) has granted ENHERTU® (fam-trastuzumab deruxtecan-nxki) Breakthrough Therapy Designation (BTD) in the U.S. for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer who have received one or more prior anti-HER2-based regimens.*

***NCCN Guidelines updated November 24, 2021**: ENHERTU® (fam-trastuzumab deruxtecan-nxki) is now a category 1 preferred regimen in the second line metastatic setting; may also be considered in the first line setting as an option for select patients (i.e., those with rapid progression within 6 months of (neo)adjuvant therapy)*

Hurvitz. SABCS 2021 (Abstract #GS3-01).

DESTINY-Breast03 Clinical Trial

Use of fam-trastuzumab deruxtecan-nxki (T-DXd, ENHERTU®) in the 2L setting is a standard of care for patients with HER2+ metastatic breast cancer including patients with stable brain metastases

2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01

- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB

- MA.32A

CLINICAL QUESTION

HER2CLIMB Clinical Trial

Does a TKI-based regimen improve outcomes in the 3L setting for pts with HER2+ mBC with stable vs active brain metastases?

HER2CLIMB Clinical Trial

Tucatinib- vs Placebo-based Regimen

- Updated exploratory efficacy analyses in patients with brain metastases

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status of 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain mets
  - Untreated not needing immediate local therapy
  - Previously treated progressing brain mets not needing immediate local therapy
  - No evidence of brain mets

*Stratification factors: presence of brain metastases (yes/no), ECOG performance status (0 or 1), and region (US or Canada or rest of world)

R* 2:1

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
21 day cycle
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
21 day cycle
(n = 202)

Assessments

- OS, CNS-PFS, ORR-IC, DOR-IC

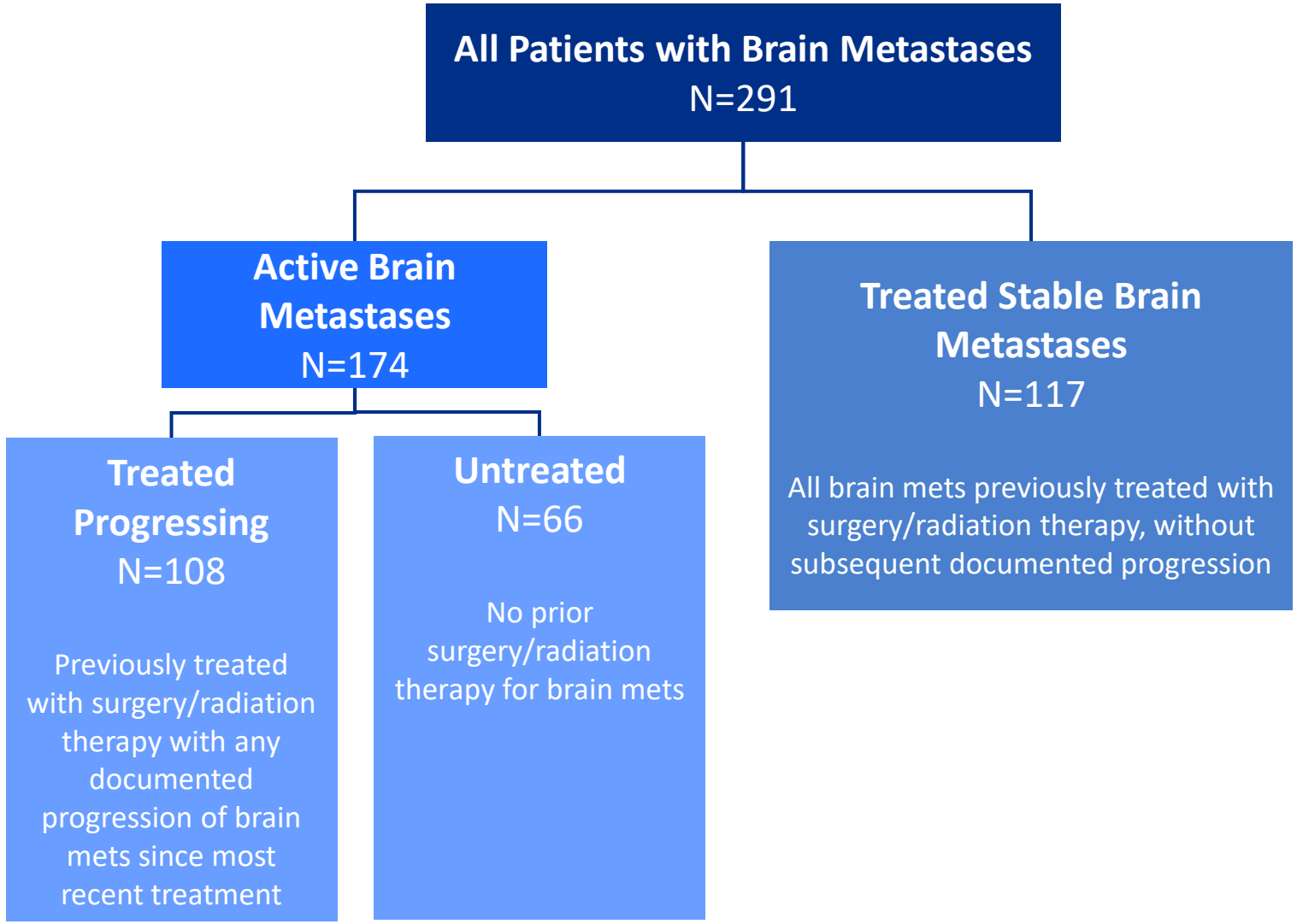
Analysis Populations

- OS and CNS-PFS: all patients with brain mets (N=291)
- ORR-IC and DOR-IC: patients with measurable intracranial disease (N=75)

HER2CLIMB Clinical Trial

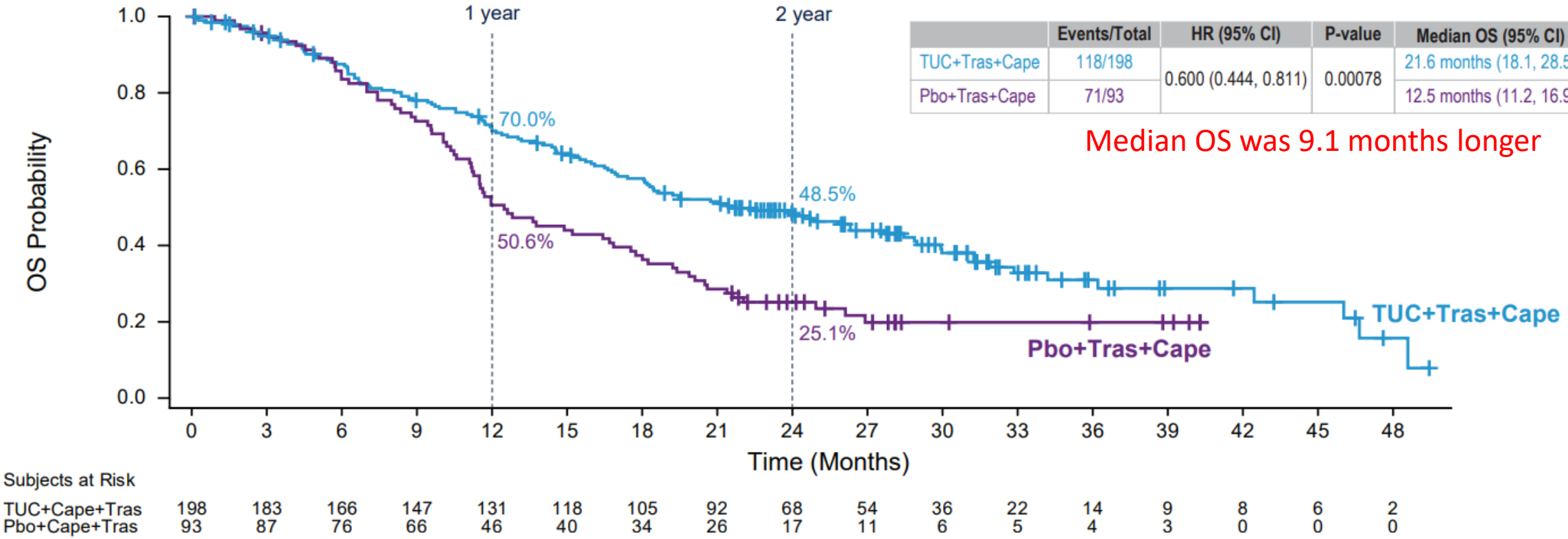
Prespecified Patient Subgroups

- Brain MRI were evaluated at baseline for all patients
- Brain MRI were evaluated for patients with brain metastases every 6 weeks for the first 24 weeks, and every 9 weeks thereafter
- Patients with brain metastases requiring local therapy were not eligible. Those who required immediate local therapy during screening could be eligible after washout. Those patients were included in the Treated Stable group for analysis



HER2CLIMB Clinical Trial

OS for All Patients with Brain Metastases



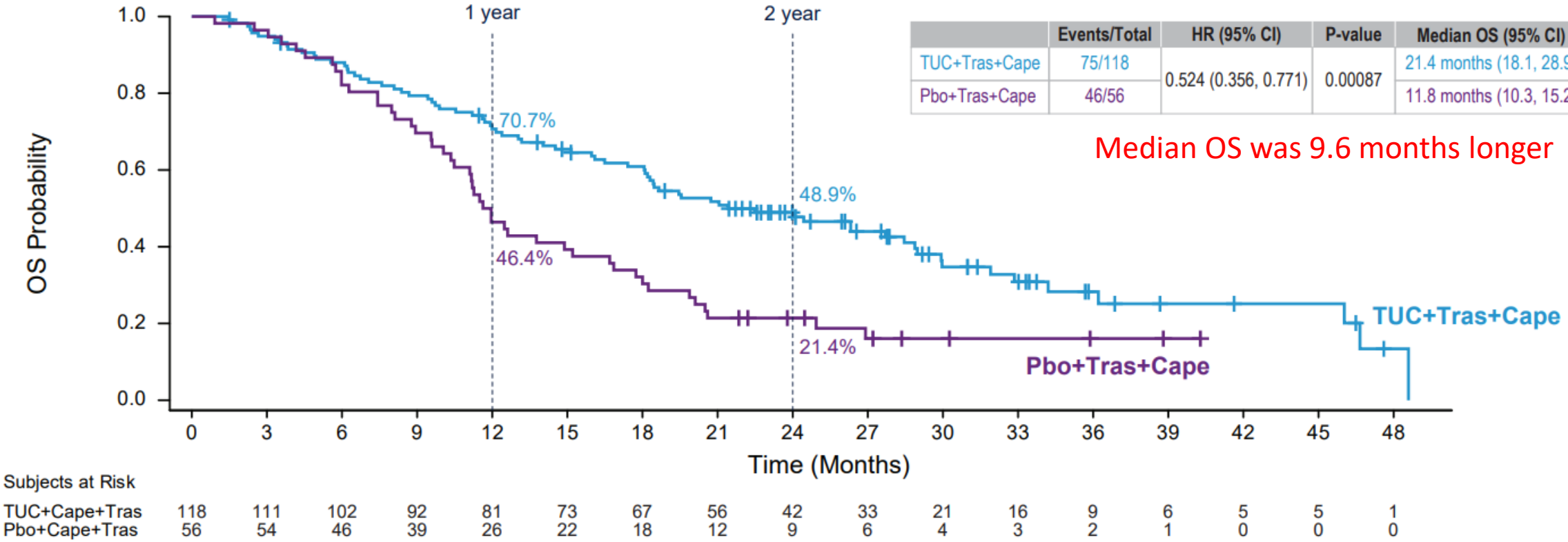
	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

Median OS was 9.1 months longer

Note: OS benefit improved with additional follow-up. Previously reported median OS in all patients with brain mets was 18.1 vs 12.0 months in tucatinib arm vs control arm

HER2CLIMB Clinical Trial

OS for Patients with Active Brain Metastases

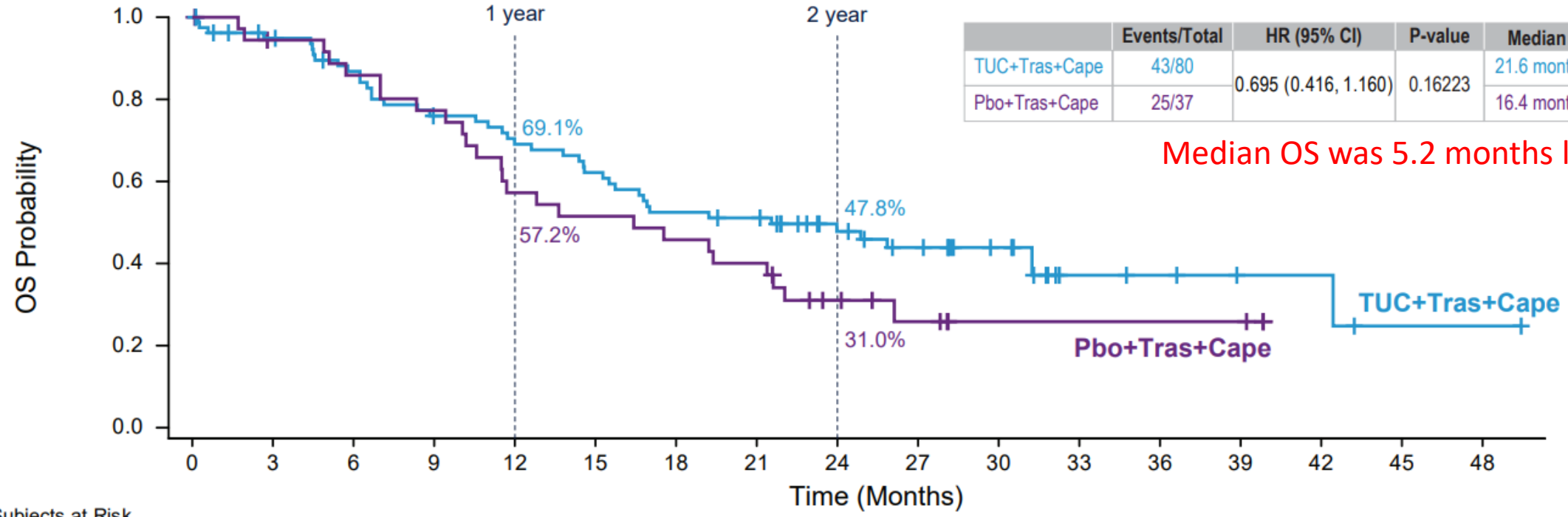


	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

Median OS was 9.6 months longer

HER2CLIMB Clinical Trial

OS for Patients with Treated, Stable Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	43/80	0.695 (0.416, 1.160)	0.16223	21.6 months (15.3, 42.4)
Pbo+Tras+Cape	25/37			16.4 months (10.6, 21.6)

Median OS was 5.2 months longer

HER2CLIMB Clinical Trial

CNS-PFS for Patients with Brain Metastases

Group	Treatment	Events	Median PFS (95% CI)	HR (95%CI)	P-Value
All Patients with Brain Mets	TUC+Tras+Cape	94/198	9.9 months (8.4 – 11.7)	**0.386** (0.266 – 0.559	<0.00001
	Pbo+Tras+Cape	48/93	4.2 months (3.6 – 5.7)		
Patients with Active Brain Mets	TUC+Tras+Cape	69/118	9.6 months (7.6 – 11.1)	**0.339** (0.215-0.536)	<0.00001
	Pbo+Tras+Cape	35/56	4.0 months (2.9 – 5.6)		
Patients with Treated Stable Brain Mets	TUC+Tras+Cape	25/80	13.9 months (9.7 – 24.9)	**0.406** (0.194 – 0.850)	0.01
	Pbo+Tras+Cape	13/37	5.6 months (3.0 -)		

HER2CLIMB Clinical Trial

ORR-IC and DOR-IC in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

	TUC+Tras+Cape N=55	Placebo+Tras+Cape N=20
Patients with Objective Response of Confirmed CR or PR, n	26	4
Confirmed ORR-IC, % (95%CI)	47.3 (33.7 – 61.2)	20.0 (5.7 – 43.7)
DOR-IC, months (95% CI)	8.6 (5.5-10.3)	3.0 (3.0 – 10.3)

DOR-IC was almost 3-fold higher in the tucatinib arm vs the control arm

SUMMARY

HER2CLIMB Clinical Trial

- With an additional 15.6 months of follow up (29.6 months total), tucatinib in combination with trastuzumab and capecitabine resulted in an improved OS benefit
  - 9.1 month improvement in all patients with brain metastases
  - 9.6-month improvement in median OS in patients with active brain metastasis
  - 5.2-month improvement in median OS in patients with treated stable brain metastasis

- Tucatinib treatment continued to show clinically meaningful benefit in CNS-PFS, representing a delay in progression in the brain

KEY DATA

DESTINY-Breast03 and HER2CLIMB

Study Design	DESTINY-Breast03		HER2CLIMB	
Trial	**Phase III** • Unresectable or metastatic HER2+ breast cancer • Previously treated with trastuzumab and taxane in advanced or metastatic setting		**Phase III** • HER2+ metastatic breast cancer • Prior treatment with trastuzumab, pertuzumab, *and* T-DM1	
Brain Mets Inclusion Criteria	• Could have clinically stable, treated brain mets • ≥2 weeks between end of whole brain radiotherapy and study enrollment		• Previously treated, stable brain mets • Untreated, not needing immediate local therapy • Previously treated, progressing brain mets not needing immediate local therapy • No evidence of brain mets	
Trial Design	**T-DXd** (n=261)	**T-DM1** (n=263)	**Tucatinib** + Trastuzumab + Capecitabine (n = 410)	**Placebo** + Trastuzumab + Capecitabine (n = 202)
# of stable, treated brain mets	**43**	**39**	Total brain mets 291 (n=174 active; **n= 117 treated, stable**)	
			80	**37**
mPFS (stable, treated brain mets)	**15.0** months (12.5 – 22.2)	3.0 months (2.8 – 5.8)	**13.9** months (*CNS-PFS*) (9.7 – 24.9)	5.6 months (*CNS-PFS*) (3.0 -)
Hazard Ratio	**0.25** (0.134 – 0.453)		**0.406** (0.194 – 0.850)	
Confirmed IC-ORR (CR or PR)	**63.9%** (n=23/36)	33.4% (n=12/36)	**47.3%** (n=26/55)	20.0% (n=4/20)

HER2CLIMB Clinical Trial

Tucatinib-based regimen in the 3L setting demonstrated clinical benefit in patients with HER2+ metastatic breast cancer with active and stable brain metastases

2021 SABCS Key Studies

HR+ Breast Cancer

- EMERALD
- PADA-1
- PALLAS

Triple Negative Breast Cancer

- ASCENT
- TROPION-PanTumor01
- KEYNOTE-522
- KEYNOTE-355

HER2+ Breast Cancer

- DESTINY-Breast03
- HER2CLIMB
- MA.32A

cornerstone specialty network™

MA.32 Clinical Trial

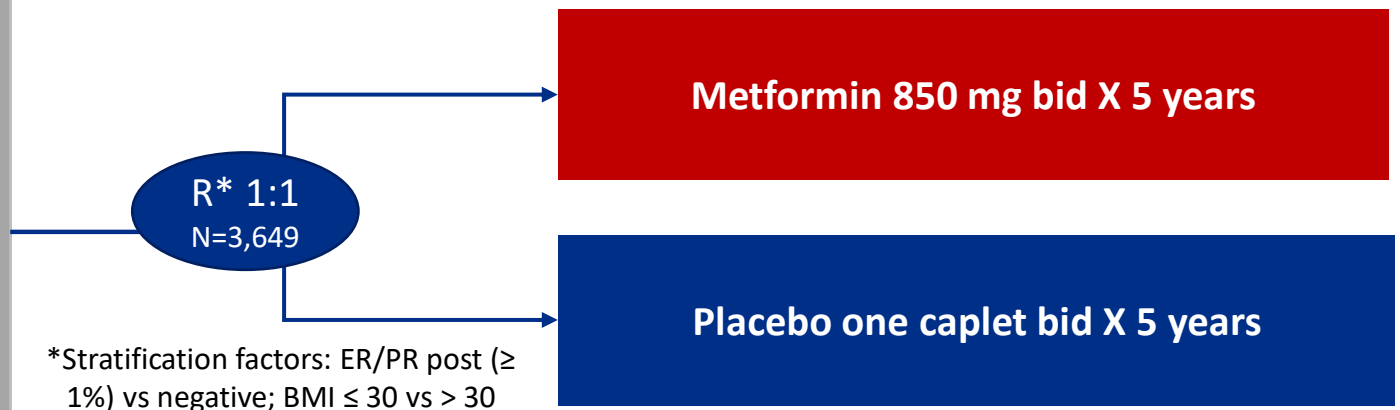
Does use of metformin benefit patients in early-stage breast cancer?

MA.32 Clinical Trial

Study Design

Population

- 18-74 years of age
- Invasive BS dx within 1 year, excised with negative margins
- T1c-T3, N0-N3, M0 (if T1cN0 ≥ 1 of: high grade/Ki67/oncotype RS, ER/PR-/HER2+)
- Standard BC therapy
- Not diabetic, FBS ≤ 7 mmol/L =126 mg/dl
- Adequate heart, liver, kidney function
- ≤ 3 ETOH drinks/day, no hx lactic acidosis



*Stratification factors: ER/PR post (≥ 1%) vs negative; BMI ≤ 30 vs > 30 kg/m2; HER2 positive vs negative; Chemo, any vs none

- **Primary analysis**: ER/PR positive breast cancer regardless of HER2 status
- **Follow-up of the futility result**: ER/PR negative breast cancer (regardless of HER2 status)
- **Exploratory analysis**: HER2 positive breast cancer (regardless of ER/PR status)

Goodwin. SABCS 2021 (Abstract #GS1-08).

KEY DATA

MA.32 Clinical Trial

Primary analysis:

ER/PR positive breast cancer (regardless of HER2 status)

Outcome	HR	95%CI	P (2 tail)
IDFS	1.01	0.84 – 1.21	0.93
OS	1.10	0.86 – 1.41	0.47
Distant DFS	0.99	0.80 – 1.23	0.95
BCFI	0.98	0.08 – 1.20	0.87
iBCFS	0.98	0.80 – 1.20	0.83

ER/PR negative breast cancer (regardless of HER2 status)

Outcome	HR	95%CI	P (2 tail)
iDFS	1.01	0.79 – 1.30	0.92
OS	0.89	0.64 – 1.23	0.46

IDFS: invasive disease-free survival; OS: overall survival; Distant DFS: distant disease-free survival; BCFI: breast cancer-free interval; IBCFS: invasive breast cancer-free survival; SNP single-nucleotide polymorphism

Exploratory analysis:

HER2 positive breast cancer (regardless of ER/PR status)

- Treated with chemo + trastuzumab +/- metformin for 24 weeks

	Outcome	HR	95%CI	P (2 tail)
All HER2+	**IDFS**	**0.64**	0.43 – 0.95	0.026
	OS	**0.53**	0.30 – 0.98	0.038
HER2+ with SNP CA/CC	**IDFS**	**0.51**	0.31 – 0.83	0.0067
	OS	**0.35**	0.17-0.73	0.0031
HER2+ with SNP AA	**IDFS**	1.32	0.58 – 2.96	0.51
	OS	2.15	0.56 – 8.36	0.26

HER2+ with SNP CA/CC: HER2+ patients who had at least one *C* allele of a prespecified *ATM*-associated single-nucleotide polymorphism (SNP); pts with at least one *C* allele associated with metformin benefit in diabetes

HER2+ with SNP AA: HER2+ patients who had no *C* allele of a prespecified *ATM*-associated single-nucleotide polymorphism (SNP): pts with the AA genotype had no evidence of benefit with metformin in diabetes

Goodwin. SABCS 2021 (Abstract #GS1-08).

SUMMARY

MA.32 Clinical Trial

- The addition of metformin to standard therapy did not improve outcomes in moderate/high risk HR+ or HR- breast cancer
  Metformin should not be used as a breast cancer treatment in these populations

- The addition of metformin to standard therapy in moderate/high risk HER2+ breast cancer suggests a beneficial effect (notably in patients with at least one C allele of the rs11212617 snp, associated with metformin benefit on glucose control in diabetes)
  - Further study required

Goodwin. SABCS 2021 (Abstract #GS1-08).

Q & A

HER2+ Breast Cancer

Thank you