Updated Results of Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Previously Treated HER2+ Metastatic Breast Cancer with Brain Metastases (HER2CLIMB)

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Abstract No. 858
San Antonio Breast Cancer Symposium
San Antonio, TX
December 7–10, 2021

Background

- Tucatinib is a highly selective HER2-directed tyrosine kinase inhibitor[1] approved in multiple regions in combination with trastuzumab and capecitabine for adult patients with metastatic HER2+ breast cancer.
- The HER2CLIMB trial evaluated tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for HER2+ metastatic breast cancer after progression on trastuzumab, pertuzumab, and T-DM1 in any setting (neoadjuvant, adjuvant, and/or metastatic).[2,3]
- HER2CLIMB enrolled patients with and without brain metastases at baseline, including those with active brain metastases.[2,4] In an exploratory efficacy analysis in patients with brain metastases at baseline, tucatinib in combination with trastuzumab and capecitabine reduced risk of intracranial progression or death by two thirds and reduced risk of death by nearly half.
- In a prespecified analysis ≈2 years from the last patient randomized, the OS benefit with tucatinib was maintained with an additional 15.6 months of follow-up (total of 29.6 months), with a 5.5-month improvement in median OS in the total population.[3]
  - Overall survival benefit was maintained across all prespecified subgroups, including those with brain metastases at baseline.
- We report updated results of exploratory efficacy analyses in patients with brain metastases from HER2CLIMB.

Methods

HER2CLIMB Trial Design[2,a]

Key Eligibility Criteria

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

R* (2:1)

N=410: **Tucatinib** 300 mg PO BID + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID (Days 1–14); *21-day cycle*

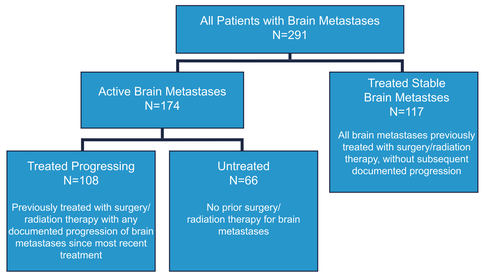
N=202: **Placebo** + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID (Days 1–14); *21-day cycle*

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

a HER2CLIMB met all primary and alpha-controlled secondary endpoints at the time of the primary analysis.

Prespecified Patient Subgroups[3]

- 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, 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.[a]



a These patients were included in the Treated Stable group for analysis.

Exploratory Analyses of Intracranial Efficacy and Survival

- Response and progression according to RECIST 1.1 for brain lesions only
- Analyses based on investigator assessment
- Data cut-off: 08 February 2021
  - Crossover from the placebo arm to receive tucatinib in combination with trastuzumab and capecitabine was permitted after the primary analysis.
  - First patient crossover: February 2020
  - Response assessments after crossover were not included in this report.
- All P-values are nominal.

Assessments	Analysis Populations
• OS • CNS-PFS[a] • ORR-IC • DOR-IC[b]	• OS and CNS-PFS: all patients with brain metastases (N=291) • ORR-IC and DOR-IC: patients with measurable intracranial disease (N=75)

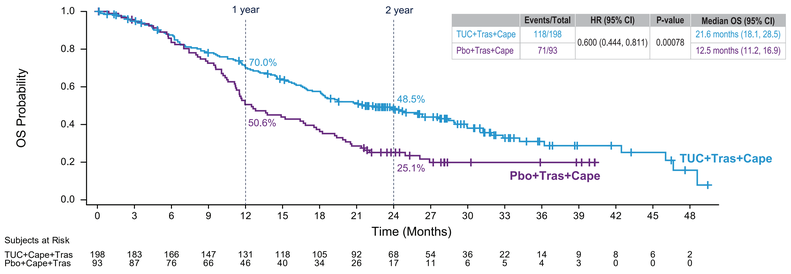
a Defined as time from random assignment to disease progression in the brain or death resulting from any cause, whichever occurred first
b Defined as time from first intracranial objective response to documented intracranial disease progression or death resulting from any cause, whichever occurred first

Results

Disposition of HER2CLIMB Patients with Brain Metastases

Patient Disposition	TUC+Tras+Cape (N=198) n (%)	Pbo+Tras+Cape (N=93) n (%)
Patients randomized	198 (100)	93 (100)
Patients who received ≥1 dose of TUC or Pbo	194 (98.0)	91 (97.8)
Patients on TUC or Pbo	11 (5.6)	1 (1.1)
Patients off TUC or Pbo	183 (92.4)	90 (96.8)
Patients who never received TUC or Pbo	4 (2.0)	2 (2.2)
Patients who crossed over	NA	9 (9.7)
Patients on TUC after cross over	NA	4 (4.3)
Patients off TUC after cross over	NA	5 (5.4)
Patients in long-term follow-up	56 (28.3)	15 (16.1)
Patients off study	131 (66.2)	73 (78.5)
Reason for study discontinuation		
Death	116 (58.6)	70 (75.3)
Withdrawal of consent	14 (7.1)	3 (3.2)
Lost to follow-up	1 (0.5)	0

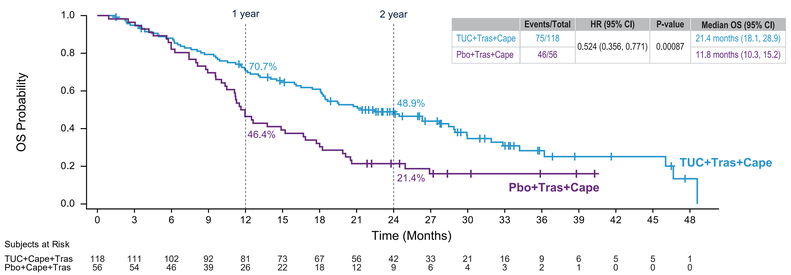
OS for All Patients with Brain Metastases



	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)

- OS benefit with tucatinib was improved with additional follow-up. Median OS was 9.1 months longer in the tucatinib arm compared with the control arm in all patients with brain metastases.
  - Previously reported, median OS was 6.1 months longer in tucatinib arm compared with control arm in all patients with brain metastases (18.1 vs 12.0 months)[4]

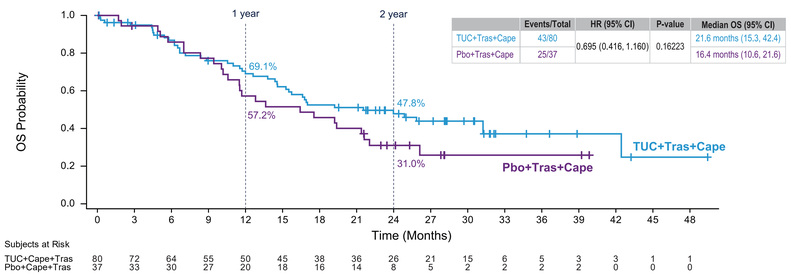
OS for Patients with Active Brain Metastases



	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 in the tucatinib arm compared with the control arm in patients with active brain metastases.

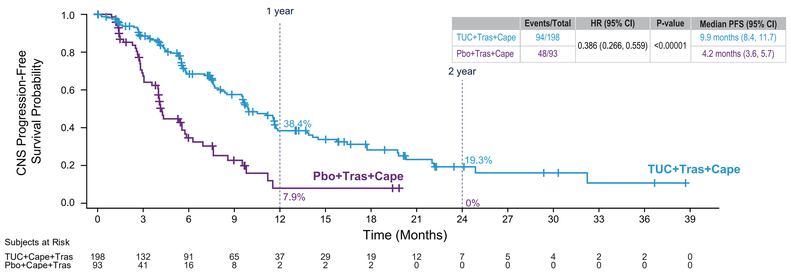
OS for Patients with Treated Stable Brain Metastases



	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 in the tucatinib arm compared with the control arm in patients with treated stable brain metastases.

CNS-PFS for All Patients with Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	94/198	0.386 (0.266, 0.559)	<0.00001	9.9 months (8.4, 11.7)
Pbo+Tras+Cape	48/93			4.2 months (3.6, 5.7)

- CNS-PFS benefit with tucatinib was maintained with longer follow-up in all patients with brain metastases.

CNS-PFS for All Patients with Brain Metastases by Subgroup

Subgroup	Treatment	Events	HR (95% CI)	P-Value	Median PFS (95% CI)
Patients with active brain metastases	TUC+Tras+Cape	69/118	0.339 (0.215, 0.536)	<0.00001	9.6 months (7.6, 11.1)
	Pbo+Tras+Cape	35/56			4.0 months (2.9, 5.6)
Patients with treated stable brain metastases	TUC+Tras+Cape	25/80	0.406 (0.194, 0.850)	0.01	13.9 months (9.7, 24.9)
	Pbo+Tras+Cape	13/37			5.6 months (3.0, –)

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

- DOR-IC was nearly 3-fold higher in the tucatinib arm compared with the control arm for patients with brain metastases.

	TUC+Tras+Cape (N=55)	Pbo+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[a], months (95% CI)	8.6 (5.5, 10.3)	3.0 (3.0, 10.3)

a Calculated using the complementary log-log transformation method (Collet, 1994)

Conclusions

- With an additional 15.6 months of follow-up (total 29.6 months), tucatinib in combination with trastuzumab and capecitabine resulted in an improved OS benefit of 9.1 months in patients with brain metastases.
  - The regimen resulted in a 9.6-month improvement in median OS in patients with active brain metastasis.
  - The regimen resulted in a 5.2-month improvement in median OS in patients with treated stable brain metastasis.
- At follow-up, DOR-IC was nearly 3-fold higher in the tucatinib arm compared to the control arm for patients with brain metastases.
- Tucatinib treatment continued to show clinically meaningful benefit in CNS-PFS, representing a delay in progression in the brain.
- This analysis demonstrates that tucatinib in combination with trastuzumab and capecitabine is an active regimen for active and stable brain metastases in patients with HER2+ metastatic breast cancer.

Abbreviations

BID: twice a day; C1D1: Day 1 of chemotherapy treatment cycle 1; Cape: capecitabine; CNS: central nervous system; CNS-PFS: time from randomization to disease progression in the brain or death; CR: confirmed response; DOR-IC: duration of intracranial response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HER2+: human epidermal growth factor receptor 2 positive; HR: hazard ratio; MRI: magnetic resonance imaging; NA: not applicable; ORR-IC: confirmed intracranial objective response rate; OS: overall survival; Pbo: placebo; PFS: progression-free survival; PO: orally; Q3W: every 3 weeks; R: randomization; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; T-DM1: trastuzumab emtansine; PR: partial response; Tras: trastuzumab; TUC: tucatinib

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Acknowledgements

- To all patients who participated in this trial and their families
- To investigators and research staff at all HER2CLIMB clinical sites
- To members of the Independent Data and Safety Monitoring Committee
- This study is sponsored by Seagen Inc., Bothell, WA, USA in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Ind., Kenilworth, NJ, USA.
- The authors thank Irene Park, PhD and Wendi Schultz, MS of Seagen Inc., Bothell, WA, USA for providing medical writing support/editorial support, which was funded by Seagen Inc., Bothell, WA, USA in accordance with Good Publication Practice (GPP3) guidelines.

Disclosures

NUL has received royalty from UptoDate; received consulting fees from Pfizer, AstraZeneca, Daiichi-Sankyo, Seagen Inc., Olema Pharmaceuticals, Prelude Pharmaceuticals, Affinia Therapeutics, Denali Therapeutics, and Aleta BioPharma; and has participated in contracted research with Merck, Genentech, Pfizer, Seagen Inc., AstraZeneca, and Zion Pharma Limited. EW has received consulting fees from Carrick Therapeutics, G1 Therapeutics, Genentech/Roche, Gilead, GlaxoSmithKline, Jounce, Leap, Lilly, Seagen Inc., Syros Pharma,and Zymeworks; has received honoraria from Genentech/Roche and Genomic Health; has participated in contracted research with AstraZeneca and Genentech; and has received other support from InfiniteMD.

JR and WF are employees and have ownership interest in Seagen.