Updated Results of Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated HER2+ Metastatic Breast Cancer with and without Brain Metastases (HER2CLIMB)

Giuseppe Curigliano[1], Volkmar Mueller[2], Virginia Borges[3], Erika Hamilton[4], Sara Hurvitz[5], Sherene Loi[6], Rashmi Murthy[7], Alicia Okines[8], Elisavet Paplomata[9], David Cameron[10], Lisa A. Carey[11], Karen Gelmon[12], Gabriel Hortobagyi[7], Ian Krop[13], Sibylle Loibl[14], Mark Pegram[15], Dennis Slamon[5], Jorge Ramos[16], Wentao Feng[16], Eric Winer[13]

[1]Istituto Europeo di Oncologia, Milan, IRCCS and University of Milano, Italy; [2]Universitaetsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]University of Colorado Hospital, Aurora, CO, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology – Nashville, Nashville, TN, USA; [5]University of California, Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Peter MacCallum Cancer Centre, Melbourne, Australia; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]The Royal Marsden NHS Foundation Trust, London, UK; [9]Carbone Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, WI, USA; [10]Edinburgh Cancer Research Centre, Edinburgh, UK; [11]UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [12]British Columbia Cancer - Vancouver Centre, BC, Canada; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]German Breast Group, Neu-Isenburg, Germany; [15]Stanford Cancer Institute, Palo Alto, CA, USA; [16]Seagen Inc., Bothell, WA, USA

Background

- Tucatinib (TUC) is a highly selective HER2-directed tyrosine kinase inhibitor (TKI)[1] approved in multiple regions in combination with trastuzumab (Tras) and capecitabine (Cape) 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 metastatic)[2]
  - The trial enrolled patients with and without brain metastases at baseline, including those with active brain metastases
- HER2CLIMB met all primary* and alpha-controlled secondary endpoints at the time of the primary analysis:[2]
  - Risk of progression or death reduced by 46% in first 480 patients | risk of death reduced by 34% in total population | risk of progression or death in patients with brain metastases reduced by 52%
- Consistent benefit of tucatinib was observed across all pre-specified subgroups[2]

* The primary endpoint of PFS by blinded independent central review was assessed in the first 480 patients enrolled.

Methods

HER2CLIMB Trial Design

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 + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib
300 mg PO BID

Trastuzumab
6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine
1000 mg/m^2 PO BID (Days 1–14)

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

Placebo
+
Trastuzumab
6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine
1000 mg/m^2 PO BID (Days 1–14)

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

https://clinicaltrials.gov/ct2/show/NCT02614794

HER2CLIMB Unblinded Long-term Follow-up

- Protocol prespecified analysis ~2-years from the last patient randomized
- 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
- Data cut-off: 08 February 2021
- All P values are nominal

Assessments	Analysis Populations
• Overall survival • PFS per RECIST 1.1 by investigator assessment • Safety and tolerability of the tucatinib-trastuzumab-capecitabine and placebo-trastuzumab-capecitabine regimens	• OS and PFS by investigator assessment: all randomized patients (N=612) • Safety: all randomized patients who received at least one dose of study treatment (N=601)

PFS: progression-free survival; OS: overall survival

Acknowledgments

- 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
- Wendi Schultz, MS, and Michelle Ubowski, PharmD, of Seagen Inc., and Laurie LaRusso, MS, of Chestnut Medical Communications for writing support, which was funded by Seagen Inc.

References

1. Kulukian et al. Mol Cancer Ther. 2020;19:976-87.
2. Murthy RK, et al. N Engl J Med. 2020;382:597-609.

Disclosures: Dr. Curigliano reports consultancy from Bristol-Myers Squibb, Lilly, Novartis, Pfizer, Roche, Seagen Inc., Daichii Sankyo; employment at University of Milano, Istituto Europeo di Oncologia, IRCCS, Milano, Italy; and speaker's bureau participation for Lilly, Pfizer, Roche, Seagen Inc., Daichii Sankyo.

Results

Patient Disposition	TUC+Tras+Cape (N=410) n (%)	Pbo+Tras+Cape (N=202) n (%)
Pts randomized	410 (100)	202 (100)
Pts who received at least one dose of tucatinib/placebo	404 (98.5)	197 (97.5)
Pts on tucatinib/placebo[a]	35 (8.5)	1 (0.5)
Pts off tucatinib/placebo	369 (90.0)	196 (97.0)
Pts who never received tucatinib/placebo	6 (1.5)	5 (2.5)
Pts who crossed over	N/A	26 (12.9)
Pts on tucatinib after cross over	N/A	9 (4.5)
Pts off tucatinib after cross over	N/A	17 (8.4)
Pts in long-term follow-up	119 (29.0)	50 (24.8)
Pts off study	256 (62.4)	142 (70.3)
Reason for study discontinuation		
Death	229 (55.9)	136 (67.3)
Withdrawal of consent	22 (5.4)	5 (2.5)
Lost to follow-up	5 (1.2)	0
Physician decision	0	1 (0.5)

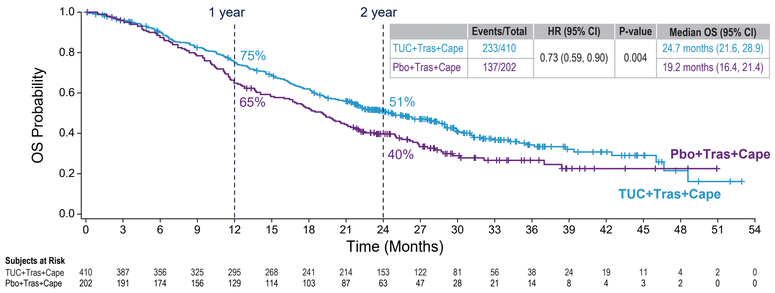
TUC: tucatinib; Pbo: placebo; Tras: trastuzumab; Cape: capecitabine

a. Original randomized treatment, not including cross-over

- In the tucatinib arm, 77% of patients who discontinued or never received tucatinib went on to receive subsequent therapies

Tucatinib/Placebo Duration of Treatment	TUC+Tras+Cape (N=404)	Pbo+Tras+Cape (N=197)
Number of pts receiving at least one dose of tucatinib/placebo, n (%)	404 (100)	197 (100)
Duration of tucatinib/placebo exposure (months)		
Mean (SD)	10.2 (9.6)	6.1 (5.0)
Median	7.4	4.4
Min, Max	<0.1, 52.0	<0.1, 26.9

Overall Survival[a]

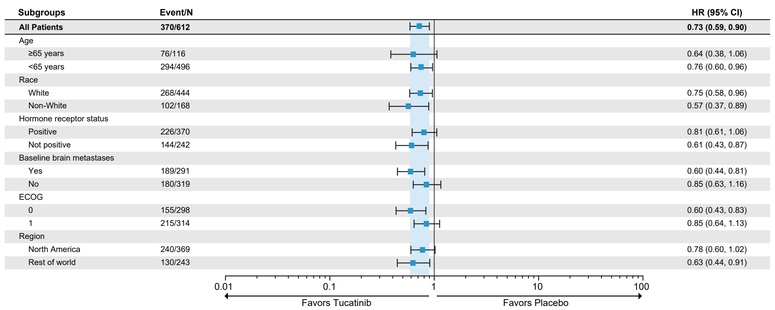


	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

a. Median overall study follow-up: 29.6 months

- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5 month improvement in median OS in the tucatinib arm compared to the placebo arm
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis

Overall Survival in Prespecified Subgroup Analyses



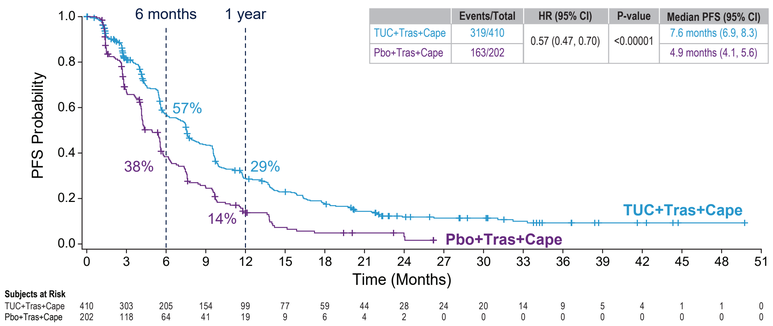
- OS benefit with tucatinib was generally consistent across patient subgroups

Overall Survival in an Exploratory Analysis in Patients with and without Visceral Metastases

	Patients with Visceral Metastases, n=455			Patients without Visceral Metastases, n=157		
	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)
TUC+Tras+Cape	0.70 (0.55, 0.89)	0.004	21.6 months (18.1, 25.6)	0.80 (0.48, 1.3)	0.36	32.9 months (27.7, 46.7)
Pbo+Tras+Cape			16.9 months (12.3, 19.4)			26.9 months (20.5, NE)

- Clinically meaningful improvement of OS was observed in patients with and without visceral metastases

PFS by Investigator Assessment



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	319/410	0.57 (0.47, 0.70)	<0.00001	7.6 months (6.9, 8.3)
Pbo+Tras+Cape	163/202			4.9 months (4.1, 5.6)

- PFS benefit with tucatinib was maintained with longer follow-up

Safety Summary

- Rate of treatment discontinuation remained low, similar to the primary analysis
- Tucatinib regimen continued to be safe and well-tolerated with longer follow-up

Treatment-Emergent Adverse Events (TEAEs)	TUC+Tras+Cape (N=404) n (%)	Pbo+Tras+Cape (N=197) n (%)
Any TEAE	401 (99.3)	191 (97.0)
Grade ≥3 TEAE	245 (60.6)	101 (51.3)
Any serious TEAE	123 (30.4)	58 (29.4)
TEAE leading to death	8 (2.0)	6 (3.0)
Pts who discontinued any study treatment due to TEAE	52 (12.9)	23 (11.7)
Pts who discontinued tucatinib/placebo due to TEAE	24 (5.9)	8 (4.1)
Pts who discontinued capecitabine due to TEAE	47 (11.6)	22 (11.2)
Pts who discontinued trastuzumab due to TEAE	17 (4.2)	7 (3.6)

Treatment-emergent AEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up through 30 days after the last dose of tucatinib or placebo.

Most Common Adverse Events (≥20% in the Tucatinib Arm)

- Rates of the most common adverse events remained stable with longer follow-up

	TUC+Tras+Cape (N=404) n (%)		Pbo+Tras+Cape (N=197) n (%)	
Preferred Term	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysaesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Conclusions

- Overall Survival 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
  - Overall Survival benefit also maintained across all prespecified subgroups
- Improvement in Overall Survival observed in patients with and without visceral metastases was clinically meaningful
- Progression-free survival benefit per investigator assessment was consistent with the primary analysis
- Tucatinib in combination with trastuzumab and capecitabine was well-tolerated with a low rate of discontinuation due to adverse events
  - Discontinuations due to adverse events were infrequent in both arms
  - Rates of liver lab abnormalities and diarrhea remained stable with longer follow-up
  - Safety profile was consistent with the primary analysis

Abstract No. 1043
American Society of Clinical Oncology Annual Meeting, Virtual Congress, June 4–8, 2021