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Tucatinib vs Placebo in Combination with Trastuzumab and Capecitabine for Patients with Locally Advanced Unresectable or HER2-Positive Metastatic Breast Cancer (HER2CLIMB): Outcomes by Hormone Receptor Status

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Background

- Tucatinib is a highly selective oral tyrosine kinase inhibitor of HER2 with minimal inhibition of epidermal growth factor receptor (EGFR).[1]
- The pivotal HER2CLIMB trial compared tucatinib (TUC) or placebo (Pbo), in combination with trastuzumab (Tras) and capecitabine (Cape), in patients with HER2+ metastatic breast cancer (MBC), with and without brain metastases, previously treated with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1).[2]
  - Enrolled a large percentage of patients (48%; 291/612) with history or presence of brain metastases at baseline
  - The addition of tucatinib resulted in clinically meaningful and statistically significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients with HER2+ MBC and was well tolerated with a manageable safety profile.
  - Tucatinib was approved by the FDA for patients with HER2+ MBC, including patients with brain metastases whose cancers have progressed on at least one prior anti-HER2 regimen in the metastatic setting.
- The impact of hormone receptor status in patients with HER2+ MBC, including those with brain metastases, is not well characterized.
- Here we present an exploratory analysis of outcomes in patients from the HER2CLIMB study by hormone receptor status.

HER2CLIMB Study Design

Key Eligibility Criteria

- HER2+ MBC
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline

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), Region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794[2]

- The primary endpoint was PFS (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 by blinded independent central review [BICR]) analyzed in the first 480 patients enrolled.
- Multiplicity-adjusted secondary efficacy endpoints were analyzed in the total population:
  - OS (n=612)
  - PFS in patients with brain metastases (RECIST v1.1 by BICR; n=291)
  - Confirmed ORR in patients with measurable disease (RECIST v1.1 by BICR; n=511)

Methods

- Patients with HER2+ MBC who were positive for either or both estrogen receptor and progesterone receptor (≥ 1%) were assigned to the hormone receptor (HR) "positive" (HR+) subgroup. Patients not meeting the above criteria were assigned to the HR "negative" (HR-) subgroup.
- PFS (RECIST v1.1 by BICR) was defined as time from randomization to disease progression or death from any cause.
  - PFS in the first 480 patients by HR status was a prespecified subgroup analysis
  - PFS in patients with brain metastases by HR status was a prespecified subgroup analysis
- OS was defined as time from randomization to death from any cause.
  - OS by HR status was a prespecified subgroup analysis
  - OS in patients with brain metastases by HR status was a post-hoc exploratory subgroup analysis
- Confirmed ORR in patients with measurable disease (RECIST v1.1 by BICR) by HR status was a post-hoc exploratory subgroup analysis.
- The Kaplan–Meier method was used to estimate PFS, median PFS, OS, and median OS, and 95% confidence intervals (CI) for the treatment groups by hormone receptor status. Cox proportional-hazards models, with stratification factors taken into account, were used to estimate hazard ratios and 95% confidence intervals.
- All P values in the analysis presented here are nominal.

Baseline Patient Characteristics

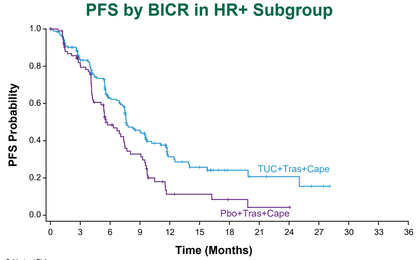
- Baseline demographics and disease characteristics in HR+/HR- subgroups were generally balanced between treatment arms.

		HR+		HR-	
		TUC+Tras+Cape (n=243)	Pbo+Tras+Cape (n=127)	TUC+Tras+Cape (n=167)	Pbo+Tras+Cape (n=75)
Age in years, median (range)		55.0 (22, 80)	54.0 (31, 82)	53.0 (32, 78)	53.0 (25, 78)
Female, n (%)		240 (98.8)	125 (98.4)	167 (100)	75 (100)
ECOG performance status, n (%)	0	121 (49.8)	64 (50.4)	83 (49.7)	30 (40.0)
	1	122 (50.2)	63 (49.6)	84 (50.3)	45 (60.0)
Stage IV at initial diagnosis, n (%)		95 (39.1)	51 (40.2)	48 (28.7)	26 (34.7)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2, 9)	4.0 (2, 10)	3.0 (2, 17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 8)	2.0 (1, 8)	3.0 (1, 13)
Presence/history of brain metastases, n (%)		107 (44.0)	59 (46.5)	91 (54.5)	34 (45.3)

PFS by HR Status in the Primary Endpoint Population

- PFS benefit was observed in patients in the tucatinib arm of the primary endpoint population regardless of hormone receptor status.

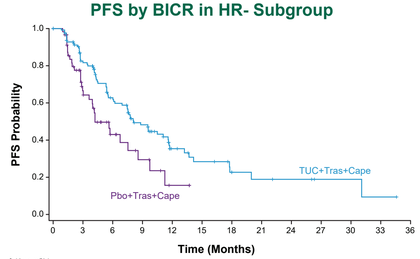
PFS by BICR in HR+ Subgroup



Risk of progression or death was reduced 42% in all HR+ patients in the TUC arm

	Events/Total	HR (95% CI)	P-value	One-year PFS (95% CI)	Median (95% CI)
TUC+Tras+Cape	106/190	0.58 (0.42, 0.80)	0.0008	31.3% (23.1, 39.9)	7.6 mo (7.4, 9.5)
Pbo+Tras+Cape	66/99			11.3% (4.6, 21.2)	5.6 mo (4.3, 7.4)

PFS by BICR in HR- Subgroup



Risk of progression or death was reduced 46% in all HR- patients in the TUC arm

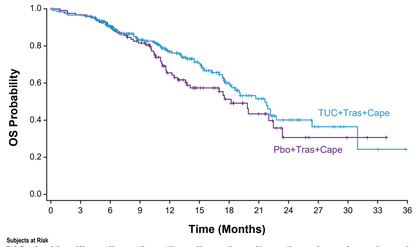
	Events/Total	HR (95% CI)	P-value	One-year PFS (95% CI)	Median (95% CI)
TUC+Tras+Cape	72/130	0.54 (0.34, 0.86)	0.008	35.4% (25.5, 45.6)	8.1 mo (7.0, 11.6)
Pbo+Tras+Cape	31/61			15.8% (3.7, 35.5)	4.2 mo (3.1, 8.6)

mo=months

OS by HR Status in the Total Study Population

- Clinically meaningful improvement of OS was observed in patients on the tucatinib arm regardless of hormone receptor status.

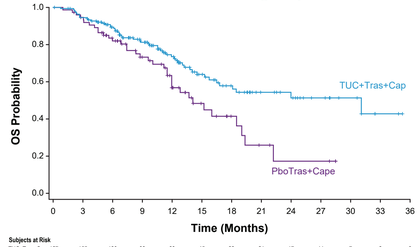
OS in HR+ Subgroup



Risk of death was reduced 15% in all HR+ patients in the TUC arm

	Events/Total	HR (95% CI)	P-value	Two-year OS (95% CI)	Median (95% CI)
TUC+Tras+Cape	78/243	0.85 (0.59, 1.23)	0.4	40.2% (29.1, 50.9)	21.7 mo (18.1, 26.4)
Pbo+Tras+Cape	51/127			30.7% (16.5, 46.1)	18.2 mo (13.6, 22.5)

OS in HR- Subgroup



Risk of death was reduced 50% in all HR- patients in the TUC arm

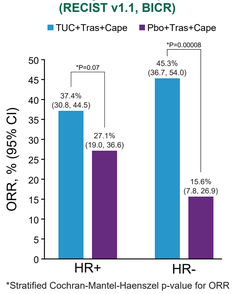
	Events/Total	HR (95% CI)	P-value	Two-year OS (95% CI)	Median (95% CI)
TUC+Tras+Cape	52/167	0.50 (0.31, 0.80)	0.003	51.3% (39.3, 62.1)	31.1 mo (16.5, –)
Pbo+Tras+Cape	35/75			17.3% (4.3, 37.6)	14.1 mo (11.5, 19.0)

- Of the HR+ patients who discontinued or never received tucatinib or placebo, 16% (n=23/172) in the tucatinib arm and 15% (n=16/108) in the placebo arm received one or more subsequent new hormonal therapies.

Confirmed ORR in Patients with Measurable Disease per BICR

- ORR was numerically higher in the tucatinib arm compared to the placebo arm regardless of hormone receptor status.

Confirmed Objective Response Rate (RECIST v1.1, BICR)



*Stratified Cochran-Mantel-Haenszel p-value for ORR

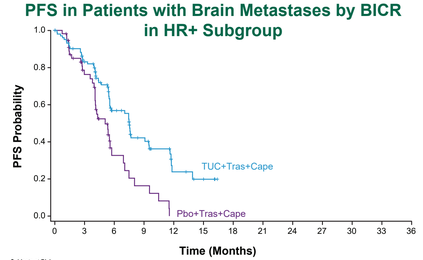
Response, n (%)	Patients with Measurable Disease (N=511)			
	HR+		HR-	
Best overall Response[a]	TUC+Tras+Cape (n=203)	Pbo+Tras+Cape (n=107)	TUC+Tras+Cape (n=137)	Pbo+Tras+Cape (n=64)
Complete response	1 (0.5)	2 (1.9)	2 (1.5)	0
Partial response	75 (36.9)	27 (25.2)	60 (43.8)	10 (15.6)
Stable disease	99 (48.8)	60 (56.1)	56 (40.9)	40 (62.5)
Progressive disease	16 (7.9)	13 (12.1)	11 (8.0)	11 (17.2)
Not evaluable	0	0	0	1 (1.6)
Not available[b]	12 (5.9)	5 (4.7)	8 (5.8)	2 (3.1)

a Confirmed Best overall response assessed per RECIST v1.1.
b Subjects with no post-baseline response assessments.

PFS by HR Status in Patients with Baseline Brain Metastases

- PFS benefit favoring the tucatinib arm was observed in patients with brain metastases regardless of hormone receptor status.

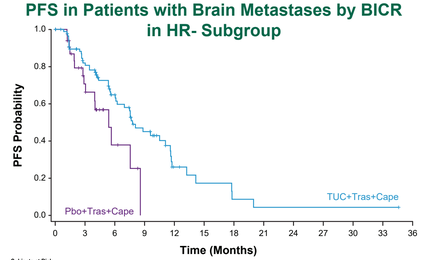
PFS in Patients with Brain Metastases by BICR in HR+ Subgroup



Risk of progression or death was reduced 52% in all HR+ patients with brain metastases in the TUC arm

	Events/Total	HR (95% CI)	P-value	One-year PFS (95% CI)	Median (95% CI)
TUC+Tras+Cape	56/107	0.48 (0.31, 0.75)	0.0008	23.8% (12.6, 37.0)	7.5 mo (5.6, 8.5)
Pbo+Tras+Cape	36/59			0%	5.1 mo (4.1, 5.7)

PFS in Patients with Brain Metastases by BICR in HR- Subgroup



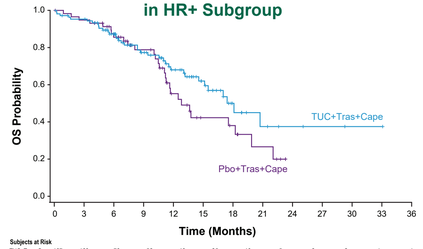
Risk of progression or death was reduced 50% in all HR- patients with brain metastases in the TUC arm

	Events/Total	HR (95% CI)	P-value	One-year PFS (95% CI)	Median (95% CI)
TUC+Tras+Cape	32/91	0.37 (0.19, 0.70)	0.001	44.1% (28.7, 58.4)	18.5 mo (14.5, –)
Pbo+Tras+Cape	18/34			0%	11.5 mo (8.8, 15.2)

OS by HR Status in Patients with Baseline Brain Metastases

- OS was numerically improved in patients with brain metastases in the tucatinib arm in both hormone receptor subgroups.

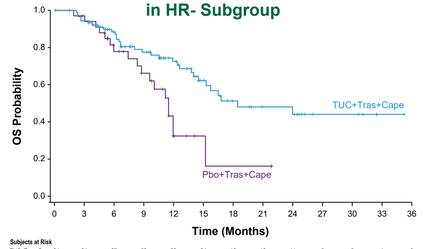
OS in Patients with Brain Metastases in HR+ Subgroup



Risk of death was reduced 24% in all HR+ patients with brain metastases in the TUC arm

	Events/Total	HR (95% CI)	P-value	Two-year OS (95% CI)	Median (95% CI)
TUC+Tras+Cape	36/107	0.76 (0.46, 1.26)	0.3	37.5% (19.5, 55.5)	18.1 mo (14.6, –)
Pbo+Tras+Cape	28/59			0%	12.8 mo (11.2, 18.2)

OS in Patients with Brain Metastases in HR- Subgroup



Risk of death was reduced 63% in all HR- patients with brain metastases in the TUC arm

	Events/Total	HR (95% CI)	P-value	Two-year OS (95% CI)	Median (95% CI)
TUC+Tras+Cape	18/34	0.37 (0.19, 0.70)	0.001	0%	11.5 mo (8.8, 15.2)

Conclusions

- Tucatinib is the first tyrosine kinase inhibitor to demonstrate prolonged OS in patients with and without brain metastases with HER2+ MBC in a randomized, controlled trial.[2]
  - HER2CLIMB was not powered to detect a difference in outcomes by hormone receptor status; however, the hazard ratios for both HR+ and HR- subgroups reveal a consistent benefit in OS for patients treated with tucatinib, trastuzumab, and capecitabine.
- Tucatinib in combination with trastuzumab and capecitabine demonstrate clinically meaningful improvements in PFS regardless of hormone receptor status in patients with HER2+ MBC, with and without brain metastases.
- The observed benefit of tucatinib regardless of hormone receptor status was consistent with the overall outcome in the HER2CLIMB primary analysis and demonstrate that tucatinib in combination with trastuzumab and capecitabine is an active regimen in patients with HER2+ MBC.

References

1. Kulukian A, et al. Molecular Cancer Therapeutics. 2020; 19(4): 976-987.
2. Murthy RK, et al. N Engl J Med. 2020; 382:597-609.

Seagen