Impact of Tucatinib on Progression-Free Survival in Patients with HER2+ Metastatic Breast Cancer and Stable or Active Brain Metastases

Thomas Bachelot[1], Nancy U. Lin[2], Rashmi K. Murthy[3], Sara A. Hurvitz[4], Virginia Borges[5], Mafalda Oliveira[6], Catherine Oakman[7], Sarah Khan[8], Cynthia Lynch[9], Kelly Westbrook[10], Catherine Doyle[11], Mattea Reinisch[12], Marco Colleoni[13], Dennis Slamon[4], Gabriel N. Hortobagyi[3], Eric P. Winer[2], Suzanne McGoldrick[14], Xuebei An[14], Sibylle Loibl[15]

[1]Centre Léon Bérard, Lyon, France; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]UCLA Medical Center/Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [5]University of Colorado Cancer Center, Aurora, CO, USA; [6]Hospital Universitario Vall D'Hebron, Barcelona, Spain; [7]Sunshine Hospital, St. Albans, Victoria, Australia; [8]Nottingham University Hospitals NHS Trust, Nottingham, UK; [9]Cancer Treatment Centers of America – Phoenix, Goodyear, AZ, USA; [10]Duke University Medical Center, Durham, NC, USA; [11]Hopital du Saint-Sacrement, CHU de Quebec-Universite Laval, Quebec, Canada; [12]Kliniken Essen-Mitte - Evang. Huyssens-Stiftung, Essen, Germany; [13]Istituto Europeo di Oncologia, Milan, Italy; [14]Seattle Genetics, Bothell, WA, USA; [15]German Breast Group, Neu-Isenburg, Germany

Background

- Up to 50% of patients with HER2+ MBC will develop brain metastases and effective and tolerable treatment options are needed.[1-4]
  - These patients are frequently excluded from registrational trials
- Tucatinib is an oral TKI, recently approved in the US, Switzerland, Canada, Singapore, and Australia. Tucatinib is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.[5,6]
- The pivotal HER2CLIMB study compared tucatinib or placebo, in combination with trastuzumab and capecitabine, in patients with HER2+ MBC, with and without brain metastases, previously treated with trastuzumab, pertuzumab, and T-DM1.[7]
  - Enrolled a large percentage of patients (48%; 291/612) with brain metastases or history of brain metastases at baseline including previously untreated, treated stable, and treated progressing
  - HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis
  - Treatment with tucatinib in combination with trastuzumab and capecitabine was well tolerated and had a manageable safety profile

PFS by BICR
N=480

Risk of progression or death was reduced by

46%

95% CI: 0.42 to 0.71, P<0.001

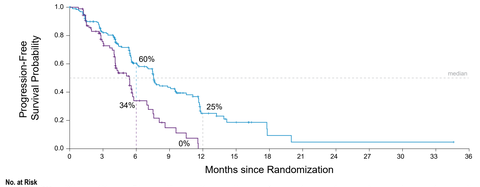
Overall Survival
N=612

Risk of death was reduced by

34%

95% CI: 0.50 to 0.88, P=0.005

Progression-Free Survival* per blinded independent central review (BICR) in Patients with Brain Metastases



No. at Risk													
TUC+Tras+Cape	198	144	78	45	14	8	2	1	1	1	1	1	0
Pbo+Tras+Cape	93	49	12	4	0	0	0	0	0	0	0	0	0

*PFS, defined as time from randomization to documented disease progression (assessed by BICR) or death from any cause. Analysis does not include patients with dural lesions only.

Risk of progression or death was reduced by 52% in patients with brain metastases†

	Events	HR (95%CI)	P Value	One-year PFS (95% CI):	Median PFS (95% CI)
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.001	25% (17.0, 34.0)	7.6 months (6.2, 9.5)
Pbo+Tras+Cape	51/93			0%	5.4 months (4.1, 5.7)

Prespecified efficacy boundary for PFS-brain metastases (P=0.0080) was met at the first interim analysis. Data cut off: Sep 4, 2019

- In an exploratory analysis in patients with visceral metastases (n=455) the median OS was 18.1 months in the tucatinib arm vs 13.8 months in the placebo arm (HR=0.72; 95% CI: 0.53, 0.97; P=0.03).
- In an exploratory analysis in patients with brain metastases at baseline, tucatinib in combination with trastuzumab and capecitabine:[8]
  - Doubled the intracranial objective response rate (47% in the tucatinib arm vs 20% in the placebo arm; P=0.03)
  - Reduced the risk of intracranial progression or death by two thirds (HR=0.32; P<0.0001)
  - Reduced risk of death by nearly half (HR=0.58; P=0.005)
  - All assessments were done by investigator using RECIST 1.1 criteria

Abbreviations

BICR = blinded independent central review
BID = twice a day
BM = brain metastases
C1D1 = Cycle 1, Day 1
Cape = capecitabine
CI = confidence interval
CNS = central nervous system
DCR = disease control rate
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
HER2 = human epidermal growth factor receptor 2
HR = hazard ratio
MBC = metastatic breast cancer
MRI = magnetic resonance imaging
ORR = objective response rate
OS = overall survival
Pbo = placebo
PFS = progression free survival
PO = oral
Q3W = once every 3 weeks
RECIST = response evaluation criteria in solid tumors
SD = stable disease
T-DM1 = ado-trastuzumab emtansine or trastuzumab emtansine
TKI = tyrosine kinase inhibitor
Tras = trastuzumab
TUC = tucatinib

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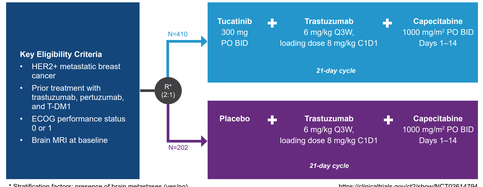
HER2CLIMB Study Design

HER2CLIMB Randomized, Double-Blind, Pivotal Trial
612 patients randomized 2:1 February 2016 to May 2019

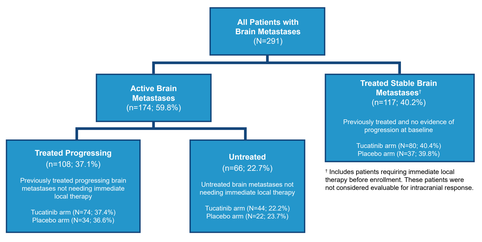


* Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

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

- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout

HER2CLIMB Analysis of Patients with Brain Metastases



† Includes patients requiring immediate local therapy before enrollment. These patients were not considered evaluable for intracranial response.

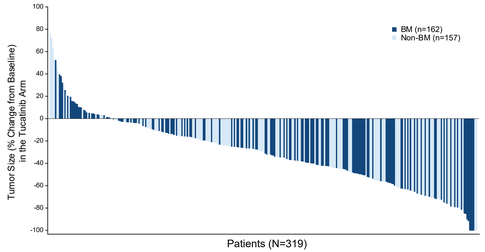
Methods

- OS was defined as time from randomization to death from any cause.
  - OS in patients with brain metastases was a prespecified subgroup analysis
  - Exploratory analysis of OS in patients who had best response of SD and by brain metastases subgroups are post-hoc
- PFS was defined as time from randomization to disease progression or death from any cause.
  - PFS by investigator in patients with brain metastases was a prespecified exploratory analysis
  - Exploratory analysis of PFS by investigator by brain metastases subgroups are post-hoc
- New brain lesion-free survival was defined as time from randomization to new lesion in the brain or death from any cause.
  - New brain lesion-free survival in all patients was an exploratory post-hoc analysis
- The Kaplan-Meier method was used to estimate PFS, OS, and new brain lesion-free survival time curves, median PFS, OS and new brain lesion-free survival, and 95% confidence intervals for the treatment groups. Cox proportional-hazards models, with stratification factors taken into account, were used to estimate hazard ratios and 95% confidence intervals.
- All P values are nominal.

DISCLOSURES: Study sponsored by Seattle Genetics, Inc. TB reports serving as an advisory board member, advisor, or consultant for AstraZeneca, MSD Oncology, Novartis, Pfizer, Rocher, and Seattle Genetics, institutional research grant/funding from AstraZeneca, Novartis, and Roche, and travel, accommodation, or expense support from AstraZeneca, Pfizer, and Roche.

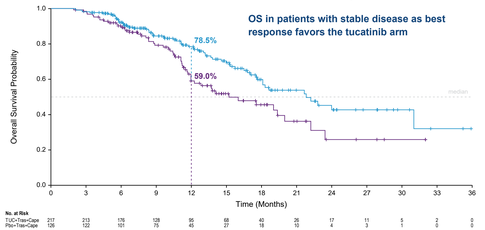
Results

Change in Tumor Size in the Tucatinib Arm Regardless of the Presence or Absence of Brain Metastases



- The DCR was 92% in the tucatinib arm and 85% in the placebo arm.

Survival Benefit in Patients with Stable Disease as Best Response



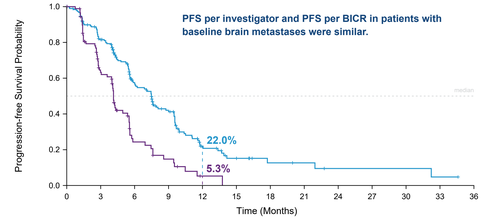
No. at Risk													
TUC+Tras+Cape	217	213	176	138	96	68	45	26	17	11	5	2	0
Pbo+Tras+Cape	126	122	101	79	45	27	18	13	4	3	1	0	0

Risk of death was reduced by 40% in the TUC arm in patients with stable disease (with and without brain metastases)

	Events	HR (95%CI)	P Value	One-year OS (95% CI):	Median OS (95% CI):
TUC+Tras+Cape	65/217	0.60 (0.41, 0.88)	0.007	78.5% (71.3, 84.0)	21.8 months (18.1, –)
Pbo+Tras+Cape	53/126			59.0% (48.2, 68.3)	15.2 months (12.0, 20.0)

Patients with Brain Metastases

PFS per Investigator Assessment in All Patients with Brain Metastases

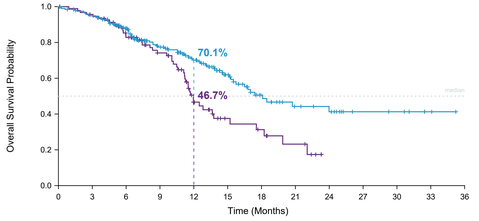


No. at Risk													
TUC+Tras+Cape	198	147	82	51	18	10	5	4	2	2	2	1	0
Pbo+Tras+Cape	93	50	13	7	1	0	0	0	0	0	0	0	0

Risk of progression or death was reduced by 55% in all patients with brain metastases in the TUC arm

	Events	HR (95%CI)	P Value	One-year PFS (95% CI):	Median PFS (95% CI):
TUC+Tras+Cape	124/198	0.45 (0.33, 0.62)	<0.001	22.0% (15.0, 29.8)	7.5 months (5.9, 8.8)
Pbo+Tras+Cape	67/93			5.3% (1.1, 14.6)	4.1 months (3.6, 5.4)

OS in All Patients with Brain Metastases



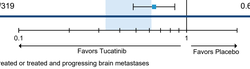
No. at Risk													
TUC+Tras+Cape	198	184	146	108	79	49	26	17	14	7	6	2	0
Pbo+Tras+Cape	93	87	67	49	23	12	9	5	0	0	0	0	0

Risk of death was reduced by 42% in all patients with brain metastases in the TUC arm[a]

	Events	HR (95%CI)	P Value	One-year OS (95% CI):	Median OS (95% CI):
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005	70.1% (62.1, 76.7)	18.1 months (15.5, –)
Pbo+Tras+Cape	46/93			46.7% (33.9, 58.4)	12.0 months (11.2, 15.2)

PFS by Investigator in Brain Metastases Subgroups

Subgroups	Event/N	HR (95% CI)
All Brain Metastases	191/291	0.45 (0.33, 0.62)
Patients with Active Brain Metastases[a]	120/174	0.38 (0.25, 0.58)
Previously Treated, Progressing	73/108	0.36 (0.21, 0.63)
Previously Untreated	47/66	0.47 (0.24, 0.92)
Patients with Stable Brain Metastases	71/117	0.56 (0.33, 0.96)
Patients without Brain Metastases	208/319	0.64 (0.48, 0.85)

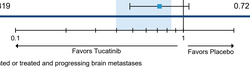


a Active brain metastases is defined as patients with untreated or treated and progressing brain metastases

- PFS benefit was observed in all patients regardless of presence or absence of brain metastases.

OS in Brain Metastases Subgroups

Subgroups	Event/N	HR (95% CI)
All Brain Metastases	114/291	0.58 (0.34, 0.85)
Patients with Active Brain Metastases[a]	69/174	0.49 (0.30, 0.80)
Previously Treated, Progressing	41/108	0.49 (0.25, 0.94)
Previously Untreated	28/66	0.49 (0.22, 1.07)
Patients with Stable Brain Metastases	45/117	0.88 (0.45, 1.70)
Patients without Brain Metastases	101/319	0.72 (0.48, 1.08)

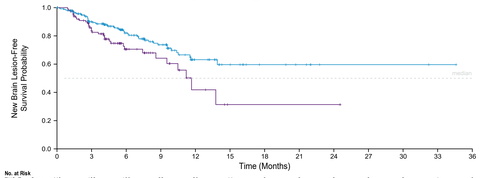


a Active brain metastases is defined as patients with untreated or treated and progressing brain metastases

- OS benefit was observed in all patients regardless of presence or absence of brain metastases.

Time to New Brain Lesions or Death in Patients (with or without Brain Metastases)

New Brain Lesion-Free Survival per Investigator Assessment



No. at Risk													
TUC+Tras+Cape	410	182	105	66	25	14	8	6	2	2	2	1	0
Pbo+Tras+Cape	202	77	31	17	5	1	1	0	1	0	0	0	0

Risk of developing new CNS lesions or death was reduced by 48% in all patients with or without brain metastases in the TUC arm

	Events	HR (95%CI)	P Value	Median new brain lesion-free survival (95% CI):
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005	Not reached (13.9, –)
Pbo+Tras+Cape	33/202			11.7 months (9.5, –)

- For this analysis, the rate of new brain lesions in all patients was lower in the tucatinib arm (n=25/410; 6.1%) compared to the placebo arm (n=19/202; 9.4%) and the rate of death was similar between arms (n=27/410; 6.6% in the tucatinib arm and n=14/202; 6.9% in the placebo arm).
- The incidence of new brain lesions while on study treatment in patients without brain metastases at baseline was lower in the tucatinib arm (n=3/211; 1.4%) compared to the placebo arm (n=2/108; 1.9%).

Conclusions

- Tucatinib is the first TKI to demonstrate prolonged OS in patients with HER2+ MBC regardless of the presence or absence of brain metastases in a randomized, controlled trial.
  - Patients with SD as a best response in the tucatinib arm had a clinically meaningful improvement in OS.
- Treatment with tucatinib in combination with trastuzumab and capecitabine resulted in better disease control in patients with or without brain metastases compared to the placebo arm.
- OS and PFS benefit of tucatinib in patients with baseline brain metastases was seen across all brain metastases subgroups.
- In all HER2CLIMB patients, tucatinib reduced the risk of developing new brain lesions or death by nearly half.
  - New brain lesions in patients without baseline brain metastases were rare.
- These results further demonstrate that tucatinib in combination with trastuzumab and capecitabine is an active regimen for patients with HER2+ MBC, with or without brain metastases, previously treated with trastuzumab, pertuzumab, and T-DM1.

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