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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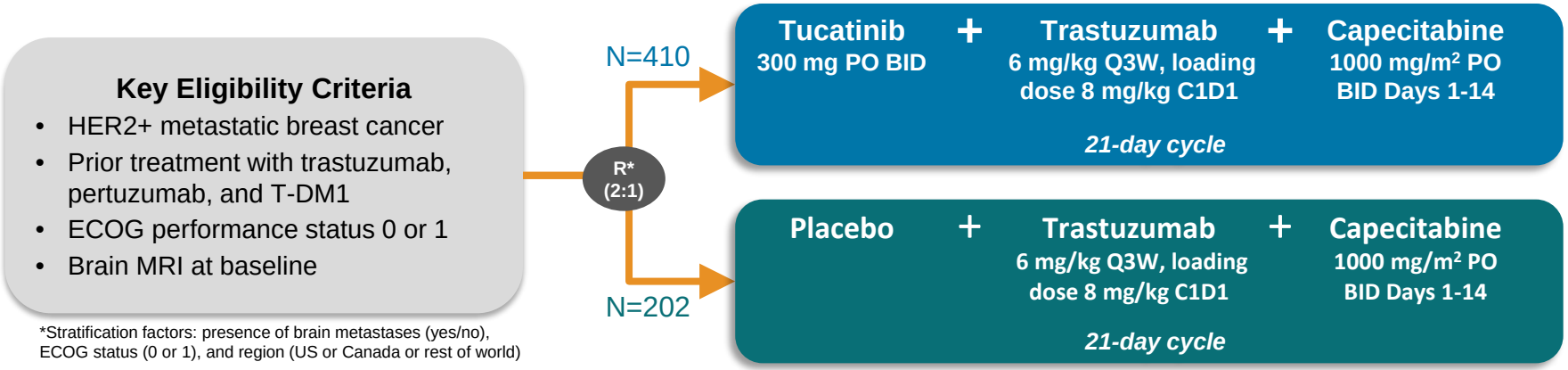
Background

- Up to half of patients with HER2+ metastatic breast cancer may develop brain metastases and effective and tolerable treatment options are needed.[1-4]
- Tucatinib is an oral TKI, recently approved by the FDA, that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.[5-6]

HER2CLIMB Randomized, Double-blind, Pivotal Trial



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

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TKI: tyrosine kinase inhibitor

HER2CLIMB Primary Analysis Results

- The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.
- Importantly, the secondary endpoint of PFS in patients with brain metastases was met.

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

PFS by BICR in patients with brain metastases
N=291

Risk of progression or death was reduced by
52%

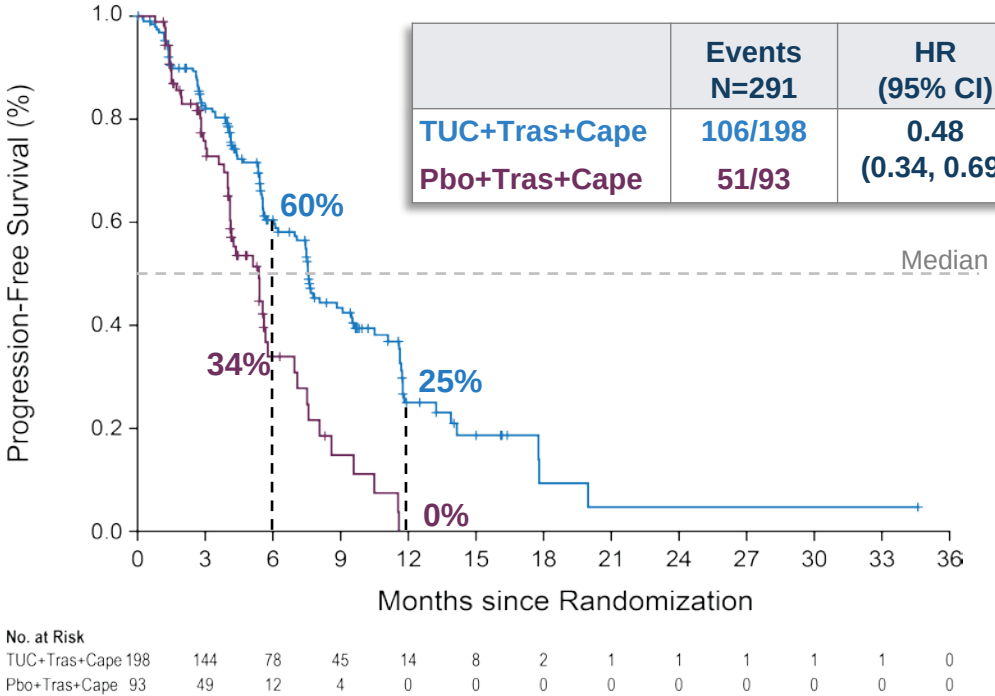
95% CI, 0.34 to 0.69, P<0.001

PFS: progression-free survival; BICR: blinded independent central review
*The primary endpoint of PFS was assessed in the first 480 patients enrolled.

Murthy RK, et al. *N Engl J Med* 2020;382:597-609.

Progression-Free Survival* in Patients with Brain Metastases

Alpha-controlled secondary endpoint in the HER2CLIMB trial



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.00001
Pbo+Tras+Cape	51/93		

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
25% (17, 34)	0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

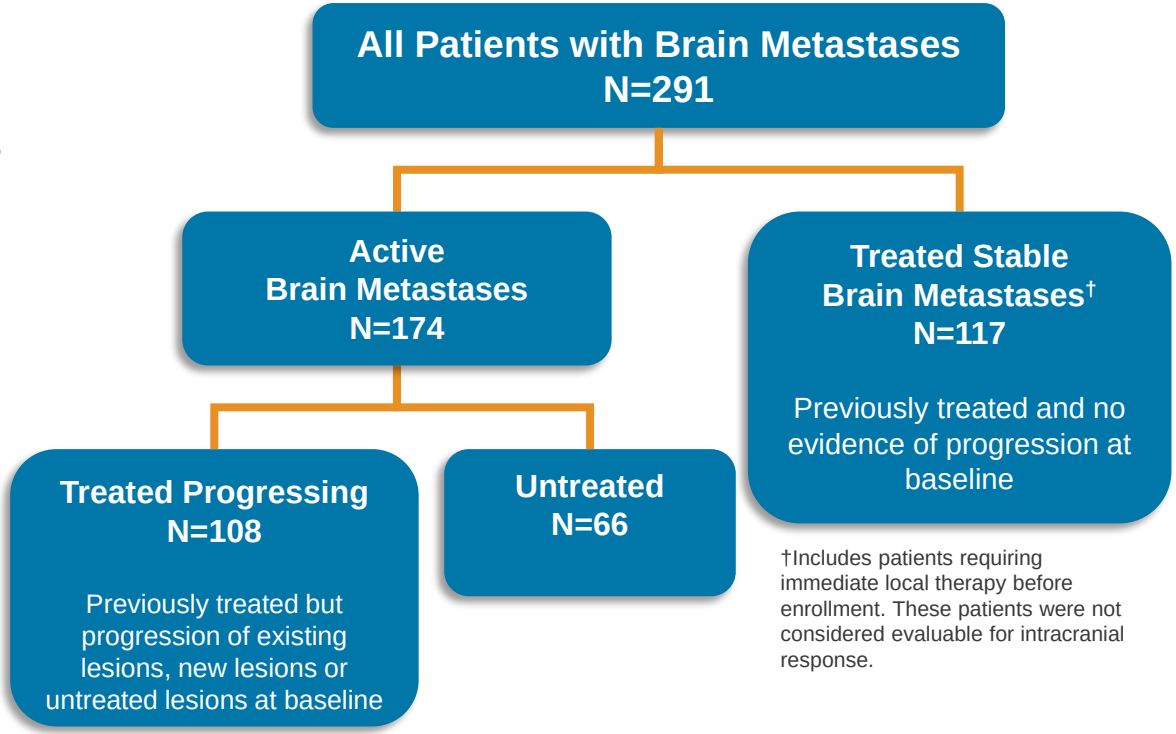
Prespecified efficacy boundary for PFS-brain metastases (P=0.0080) was met at the first interim analysis.
Data cut off: Sep 4, 2019

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

Murthy RK, et al. *N Engl J Med* 2020;382:597-609.

HER2CLIMB Analysis of Patients with Brain Metastases

- Brain MRI at baseline for all patients
- 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*



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

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

Exploratory Analyses of Intracranial Efficacy and Survival

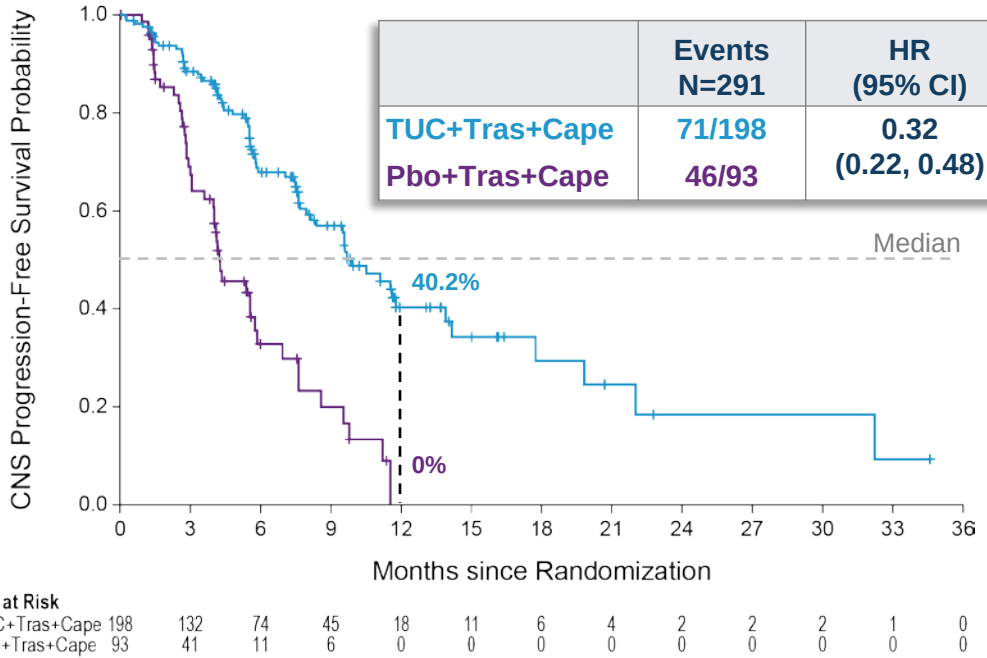
- Response and progression according to RECIST 1.1 for brain lesions only
- Analyses based on investigator assessment
- All patients with brain metastases
  - CNS-PFS: time from randomization to disease progression in the brain or death
  - OS: overall survival
- Patients with measurable intracranial (IC) disease
  - ORR-IC: confirmed intracranial objective response
  - DOR-IC: duration of intracranial response
- Patients who received CNS-directed local therapy and continued study treatment after isolated CNS progression*
  - Time from randomization to second progression or death
  - Time from first isolated CNS progression to second progression or death

*Note: First CNS progression was captured as a PFS event in the primary analysis. CNS: central nervous system.

Baseline Characteristics of HER2CLIMB Patients with Brain Metastases

		TUC+Tras+Cape (N=198)	Pbo+Tras+Cape (N=93)
Age (years), median (range)		53 (22, 75)	52 (25, 75)
Female, n (%)		197 (99.5)	92 (98.9)
ECOG PS, n (%)	0	92 (46.5)	38 (40.9)
	1	106 (53.5)	55 (59.1)
Histology, n (%)	ER and/or PR positive	107 (54.0)	59 (63.4)
	ER and PR negative	88 (44.4)	34 (36.6)
Metastatic (any location) at initial diagnosis, n (%)		77 (38.9)	39 (41.9)
Non-CNS metastatic disease		192 (97.0)	90 (96.8)
Prior local therapy for brain metastases	Prior radiotherapy	140 (70.7)	64 (68.8)
	Whole brain radiation	77 (38.9)	45 (48.4)
	Targeted radiation	92 (46.5)	32 (34.4)
	Prior surgery	33 (16.7)	13 (14.0)

CNS-PFS Benefit in Patients with Brain Metastases



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
40.2% (29.5, 50.6)	0%

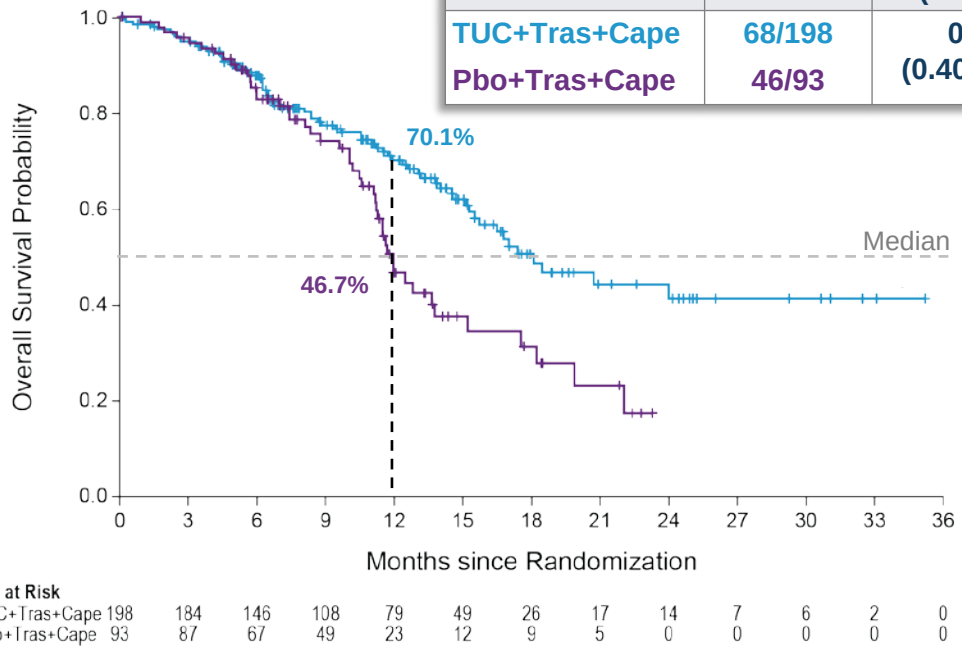
Median CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



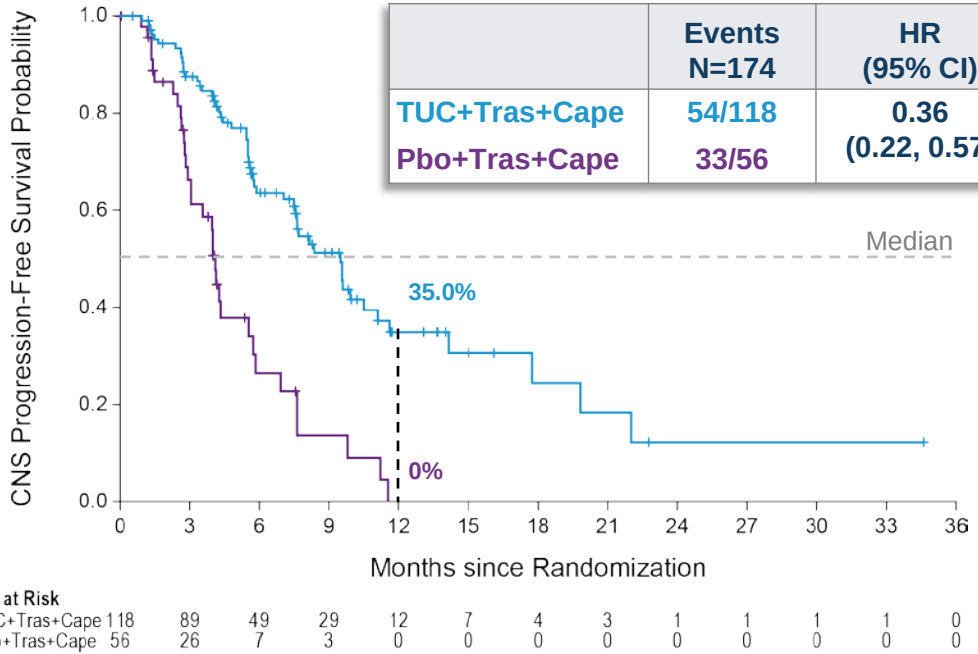
Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape 70.1% (62.1, 76.7)	Pbo+Tras+Cape 46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

CNS-PFS Benefit in Patients with Active Brain Metastases



	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	54/118	0.36 (0.22, 0.57)	<0.0001
Pbo+Tras+Cape	33/56		

Risk of CNS progression or death was reduced by 64% in patients with active brain metastases

One-year CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
35.0% (23.2, 47.0)	0%

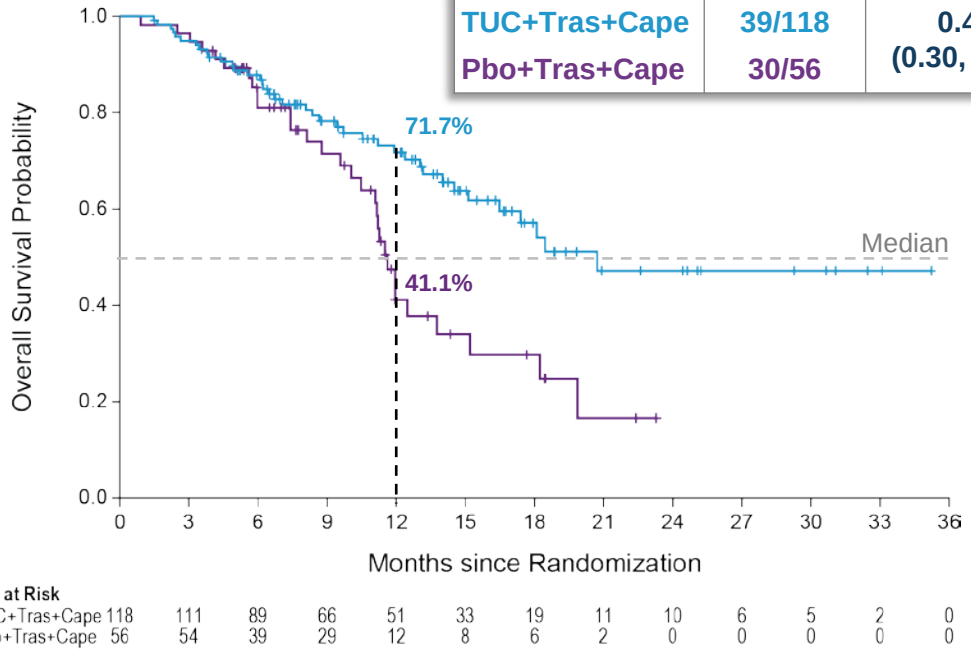
Median CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
9.5 months (7.5, 11.1)	4.1 months (2.9, 5.6)

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
71.7% (61.4, 79.7)	41.1% (25.5, 56.1)

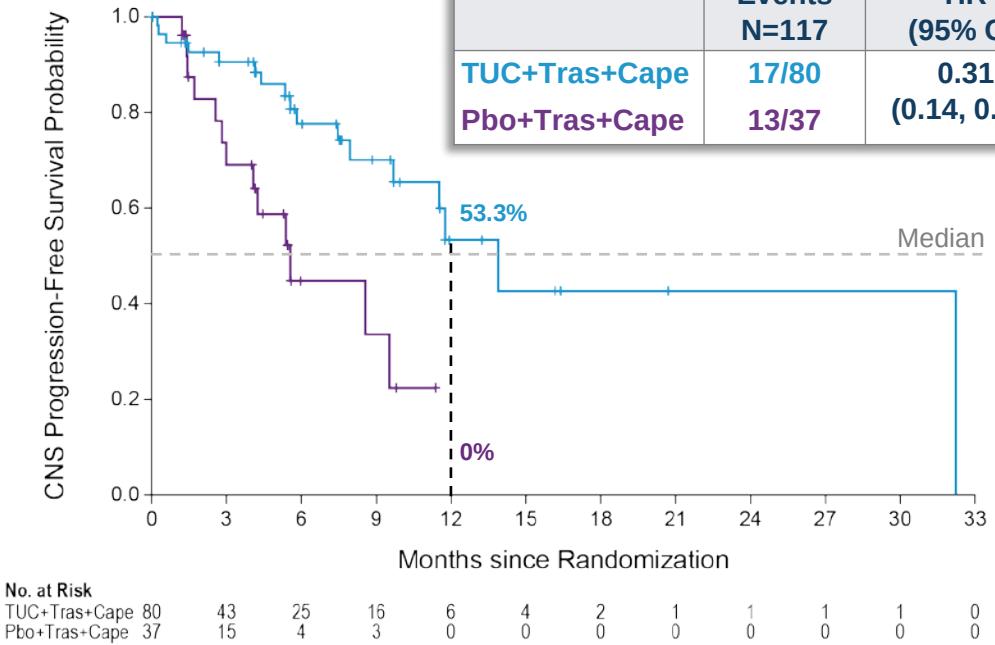
Median OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

CNS-PFS Benefit in Patients with Stable Brain Metastases



	Events N=117	HR (95% CI)	P Value
TUC+Tras+Cape	17/80	0.31 (0.14, 0.67)	0.002
Pbo+Tras+Cape	13/37		

Risk of CNS progression or death was reduced by 69% in patients with stable brain metastases

One-year CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
53.3% (31.4, 71.0)	0%

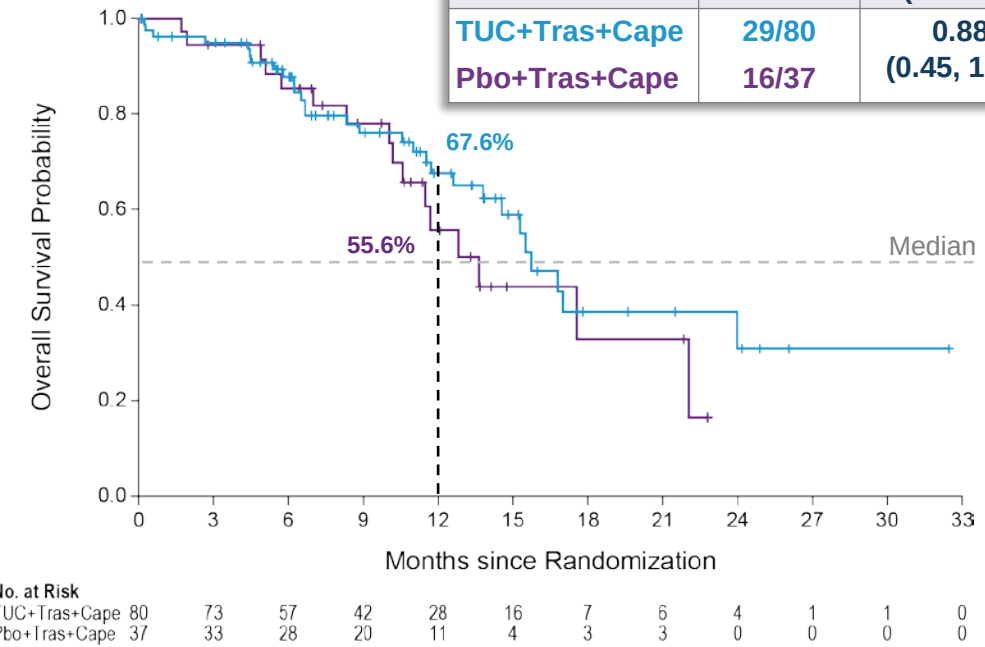
Median CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
13.9 months (9.7, 32.2)	5.6 months (3.0, 9.5)

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

OS in Patients with Stable Brain Metastases

	Events N=117	HR (95% CI)	P Value
TUC+Tras+Cape	29/80	0.88 (0.45, 1.70)	0.70
Pbo+Tras+Cape	16/37		



Risk of death was reduced by 12% in patients with stable brain metastases

One-year OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
67.6% (53.8, 78.0)	55.6% (34.1, 72.6)

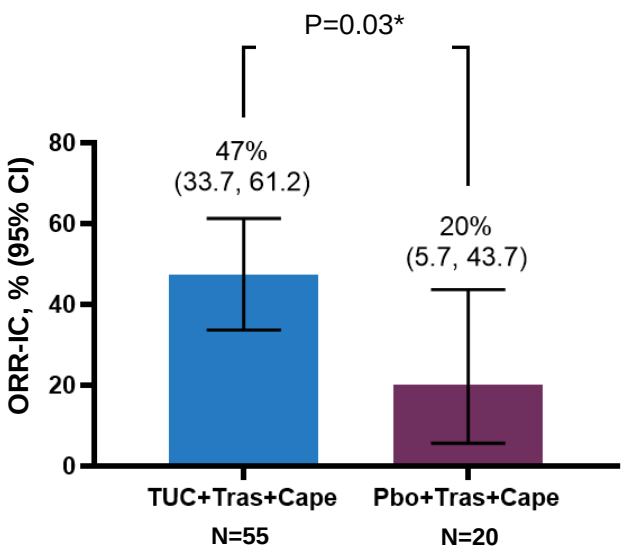
Median OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
15.7 months (13.8, NE)	13.6 months (10.2, 22.0)

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)

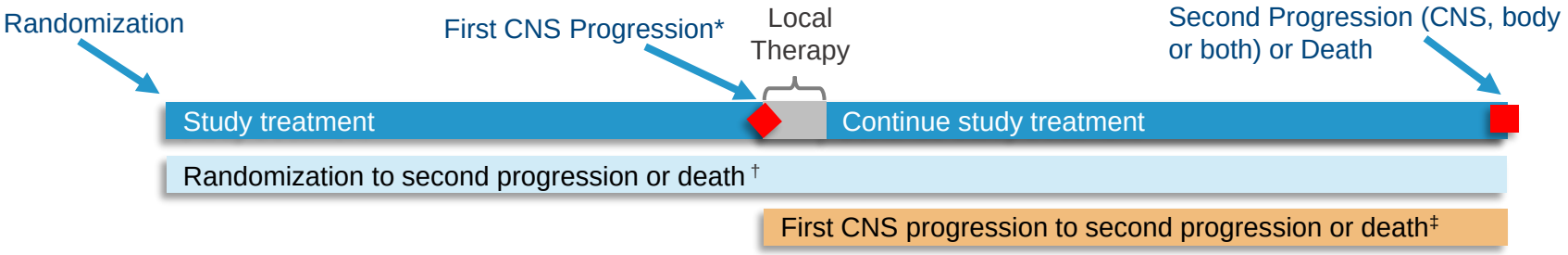


*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

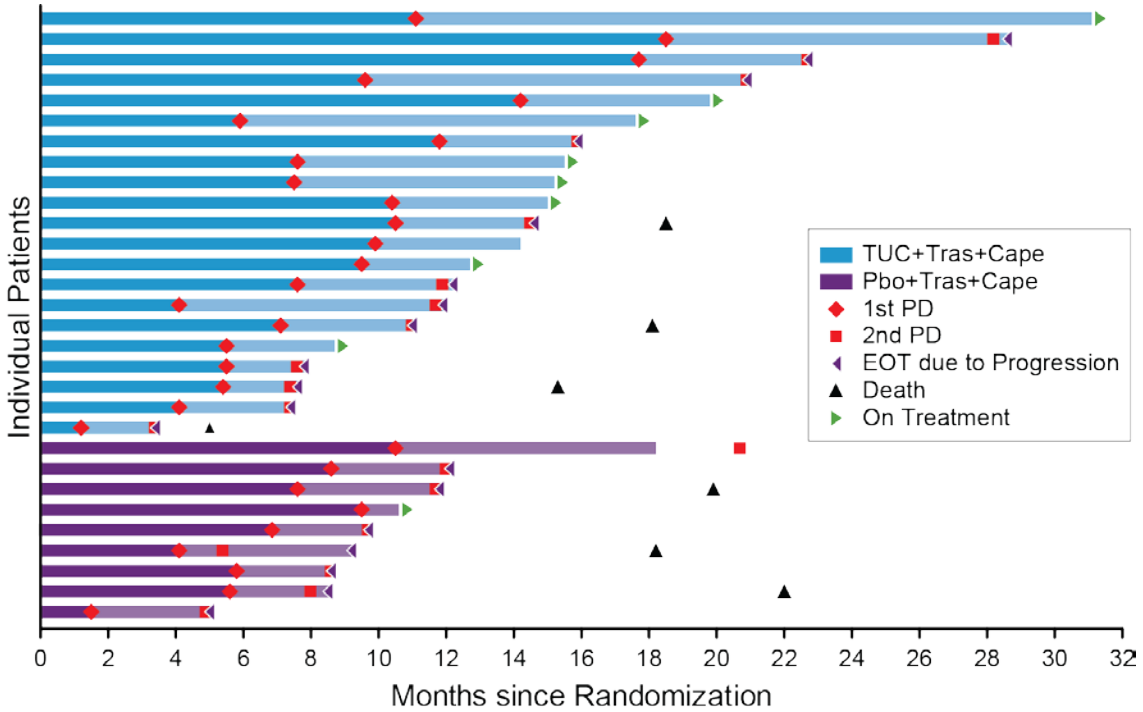
PFS in Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



	Median time from randomization to second progression or death	HR	Median time from first CNS progression to second progression or death	HR
TUC+Tras+Cap N=21	15.9 months (11.7, 28.2)	0.292 (0.11, 0.77) P=0.009	7.6 months (3.9, 11.3)	0.332 (0.13, 0.85) P=0.02
Pbo+Tras+Cap N=9	9.7 months (4.9, 12.0)		3.1 months (1.2, 4.1)	

*Note: First CNS progression was captured as a PFS event in the primary analysis.
† Time from randomization to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.
‡Time from first isolated CNS progression to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

Duration on Treatment for Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



PD: progressive disease; EOT: end of treatment

Conclusions

- The addition of tucatinib to trastuzumab and capecitabine doubled the intracranial response rate, reduced the risk of CNS progression or death by two-thirds, and reduced the risk of death by nearly half.
- The CNS-PFS results represent a delay in progression in the brain.
- Tucatinib is the first TKI to demonstrate prolongation of overall survival in patients HER2+ MBC with brain metastases in a randomized, controlled trial.
- These results together with HER2CLIMB primary analysis demonstrate that this is an active regimen for intracranial and extracranial disease in patients with HER2+ MBC.

TKI: tyrosine kinase inhibitor

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Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

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