ASOCIACIÓN DE ONCÓLOGOS CLÍNICOS DE CÓRDOBA

HOSPITAL PRIVADO UNIVERSITARIO DE CORDOBA

HER2CLIMB: Tucatinib plus Trastuzumab plus Capecitabine en Previously Treated HER2-Positive MBC With Brain Metastases

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INTRODUCTION

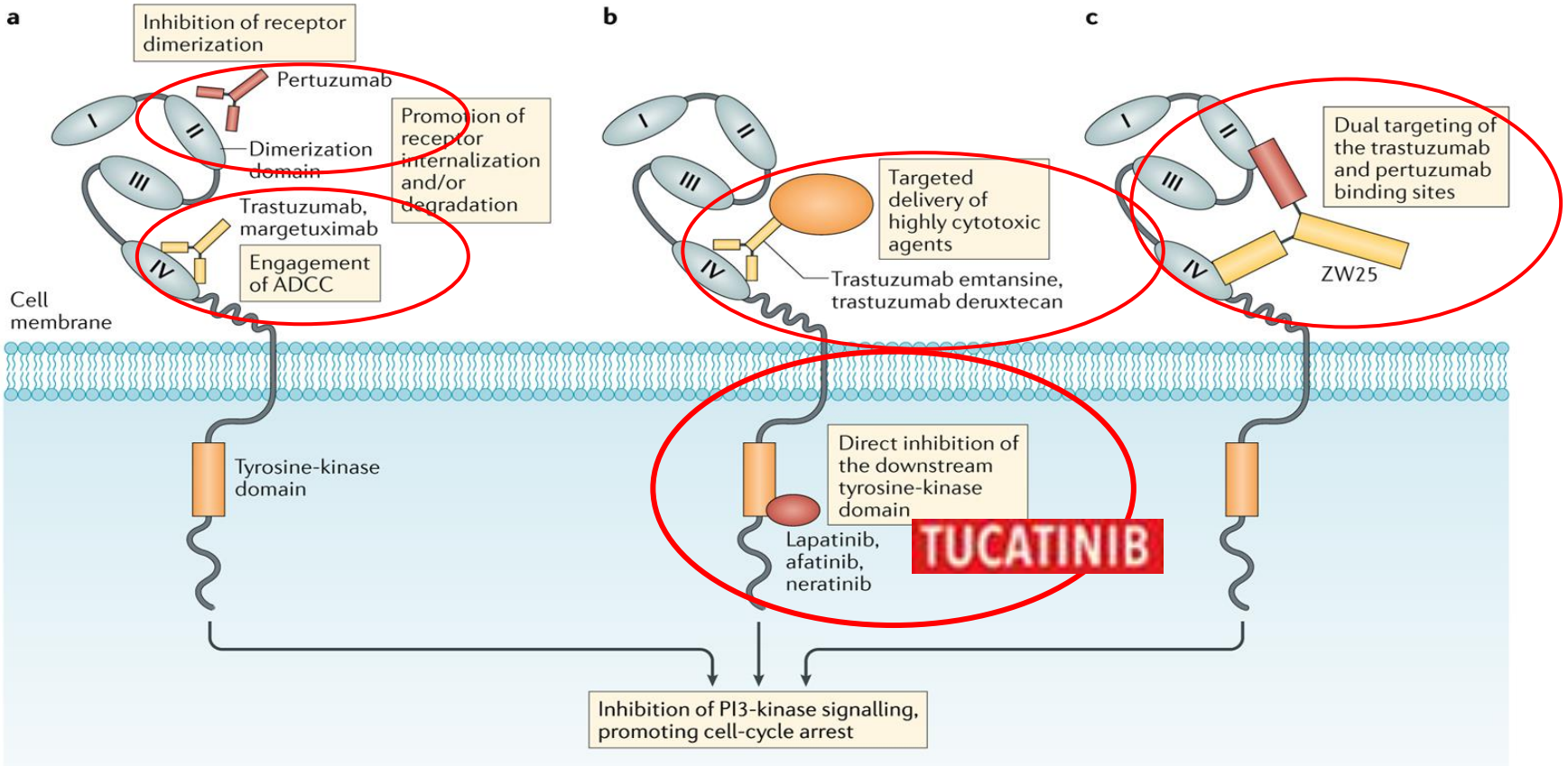
1. Up to 50% patients with MBC-HER2+ develop brain metastases (BMs) [1-5]
2. Initial therapy consists of locally directed therapy (surgical resection stereotactic radiosurgery, and/or whole-brain radiation therapy)[6]
3. The rate of intracranial progression within 6 to 12 months for this therapies [7-9]
4. Absence of randomized, prospective data of switching systemic agents at the time of brain progression. Guidelines, recommended the same treatment if have a estable systemic disease [6]

INTRODUCTION

5. Patient with untreated or treated and progressing BMs, have excluded from most trials [10-11]

Recently reported [12-13]

- NERATINIB plus CAPECITABINE: ***CNS- PFS: 3.6 month***
- LAPATINIB +/- CAPECITABINE: ***CNS- PFS 5.5 vs 3.1* months**


a
Inhibition of receptor dimerization
Pertuzumab
Dimerization domain
Promotion of receptor internalization and/or degradation
Trastuzumab, margetuximab
Engagement of ADCC
Cell membrane
Tyrosine-kinase domain
b
Targeted delivery of highly cytotoxic agents
Trastuzumab emtansine, trastuzumab deruxtecan
Direct inhibition of the downstream tyrosine-kinase domain
Lapatinib, afatinib, neratinib
TUCATINIB
c
Dual targeting of the trastuzumab and pertuzumab binding sites
ZW25
I
II
III
IV
Inhibition of PI3-kinase signalling, promoting cell-cycle arrest

Pharmacodynamics and Pharmacokinetics

TUCATINIB [15]

Distribution: Vd: ~1,670 L.

Protein binding: 97.1%.

Metabolism: Primarily via CYP2C8, and to a lesser extent via CYP3A.

Half-life elimination: ~8.5 hours.

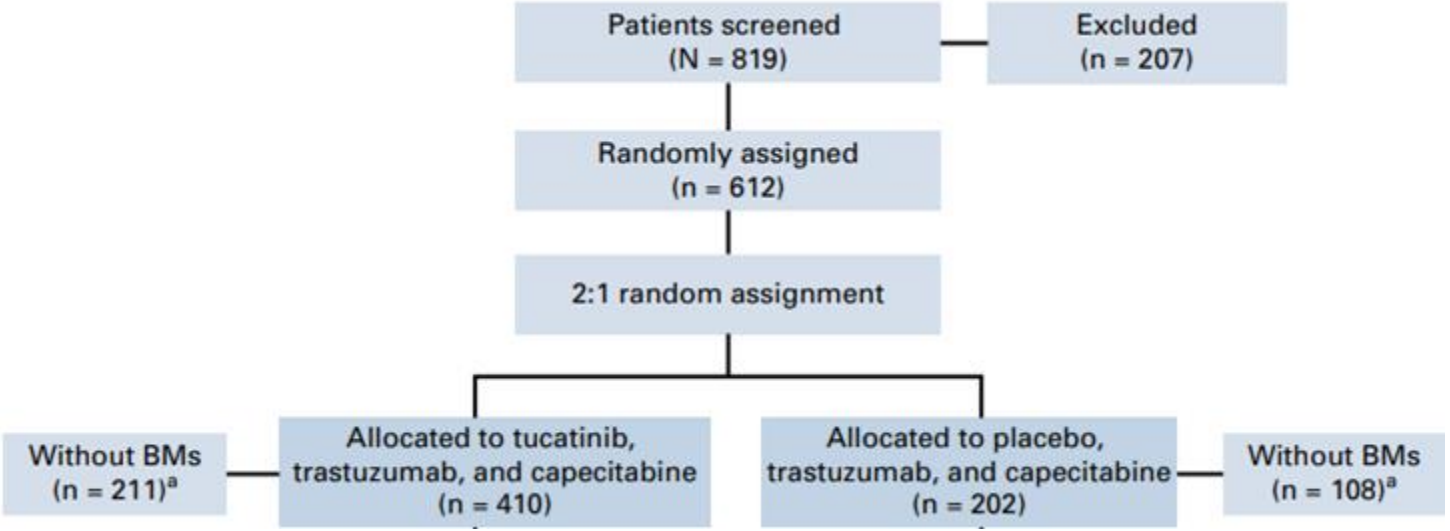
Time to peak: ~2 hours (range: 1 to 4 hours).

Excretion: Feces: ~86% (16% as unchanged drug); urine: 4.1%.

HER2CLIMB: Phase II Study Design

1. Randomized, double-blind, placebo-controlled, active comparator phase II trial at 155 sites in 15 countries (Feb-16 to May-19) median f/u: 14.0 mos
2. All patients had baseline MRI. **Included** previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.
3. Arm Tucatinib: Stratified by brain mets (yes vs no), ECOG PS (0 vs 1), and region (US or Canada vs rest of world)
4. ***Primary endpoint***: **PFS** (RECIST v 1.1) among first 480 patient
5. ***Secondary endpoints***: **OS, PFS in brain mets, ORR in patients with measurable disease, safety**

HER2CLIMB: Phase II Study Design



HER2CLIMB: Phase II Study Design

Patients with HER2+ MBC;
prior trastuzumab, pertuzumab,
and T-DM1; ECOG PS 0/1;
brain mets allowed*
(N = 612)

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 202)

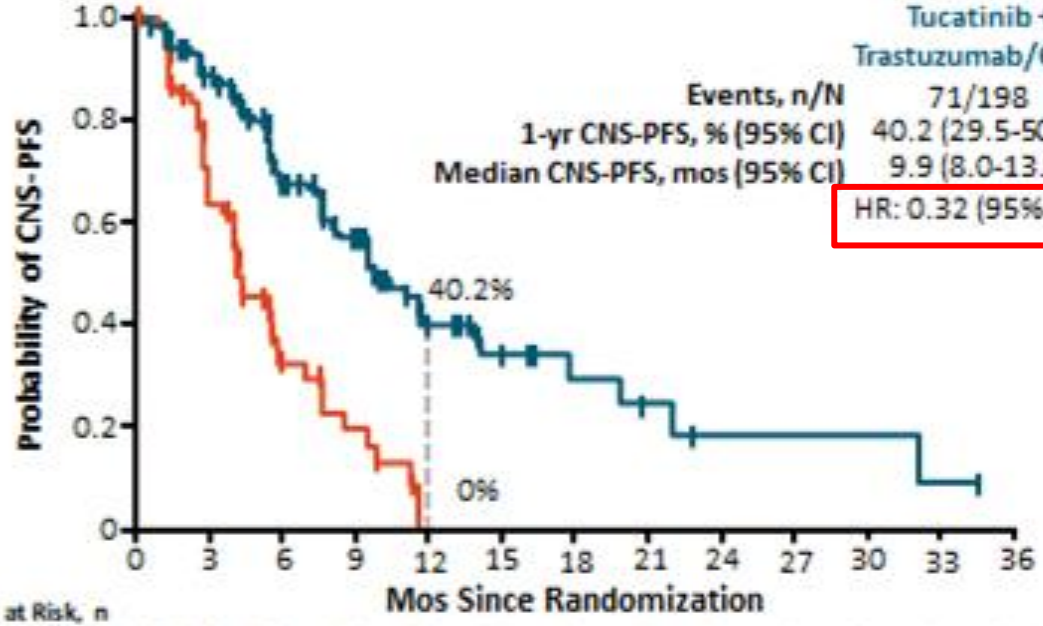
21days cycles

HER2CLIMB Intracranial Activity: Baseline Characteristics in Patients With Brain Metastases

Characteristic	Tucatinib + Trastuzumab/ Capecitabine (n = 198)	Placebo + Trastuzumab/ Capecitabine (n = 93)
Female, n (%)	197 (99.5)	92 (98.9)
Median age, yrs (range)	53 (22-75)	52 (25-75)
ECOG PS 0/1, n (%)	92 (46.5)/ 106 (53.5)	38 (40.9)/ 55 (59.1)
Metastatic (any location) at initial diagnosis, n (%)	77 (38.9)	39 (41.9)
▪ Non-CNS mets	192 (97.0)	90 (96.8)
Hormone receptor status, n (%)		
▪ ER and/or PgR positive	107 (54.0)	59 (63.4)
▪ ER and PgR negative	88 (44.4)	34 (36.6)

Characteristic, n (%)	Tucatinib + Trastuzumab/ Capecitabine (n = 198)	Placebo + Trastuzumab/ Capecitabine (n = 93)
Prior local therapy for brain mets		
▪ Radiotherapy	140 (70.7)	64 (68.8)
▪ WBRT	77 (38.9)	45 (48.4)
▪ Targeted	92 (46.5)	32 (34.4)
▪ Surgery	33 (16.7)	13 (14.0)
Brain met tx status at baseline		
▪ Treated, stable	80 (40.4)	37 (39.8)
▪ Treated, progressing	74 (37.4)	34 (36.6)
▪ Untreated	44 (22.2)	22 (23.7)

HER2CLIMB Intracranial Activity: CNS-PFS in All Patients With Brain Metastases



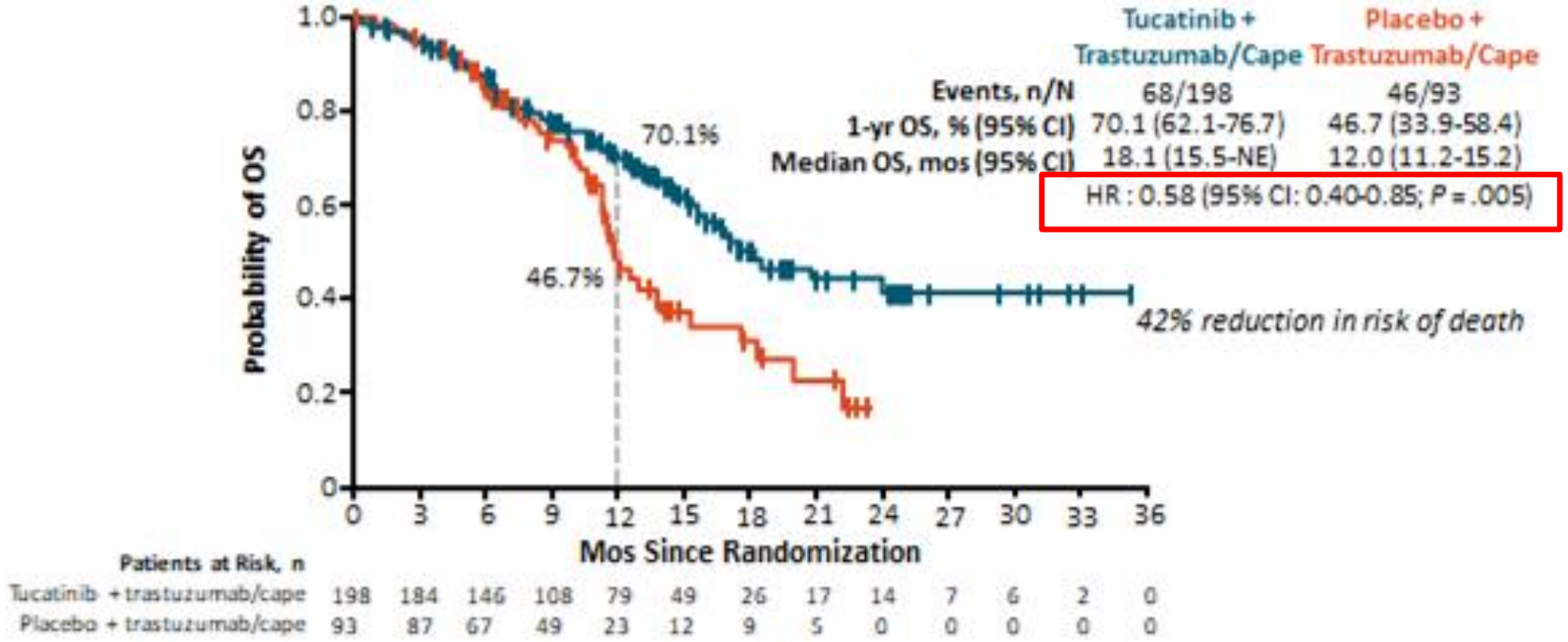
	Tucatinib + Trastuzumab/Cape	Placebo + Trastuzumab/Cape
Events, n/N	71/198	46/93
1-yr CNS-PFS, % (95% CI)	40.2 (29.5-50.6)	0
Median CNS-PFS, mos (95% CI)	9.9 (8.0-13.9)	4.2 (3.6-5.7)

HR: 0.32 (95% CI: 0.22-0.48; *P* < .00001)

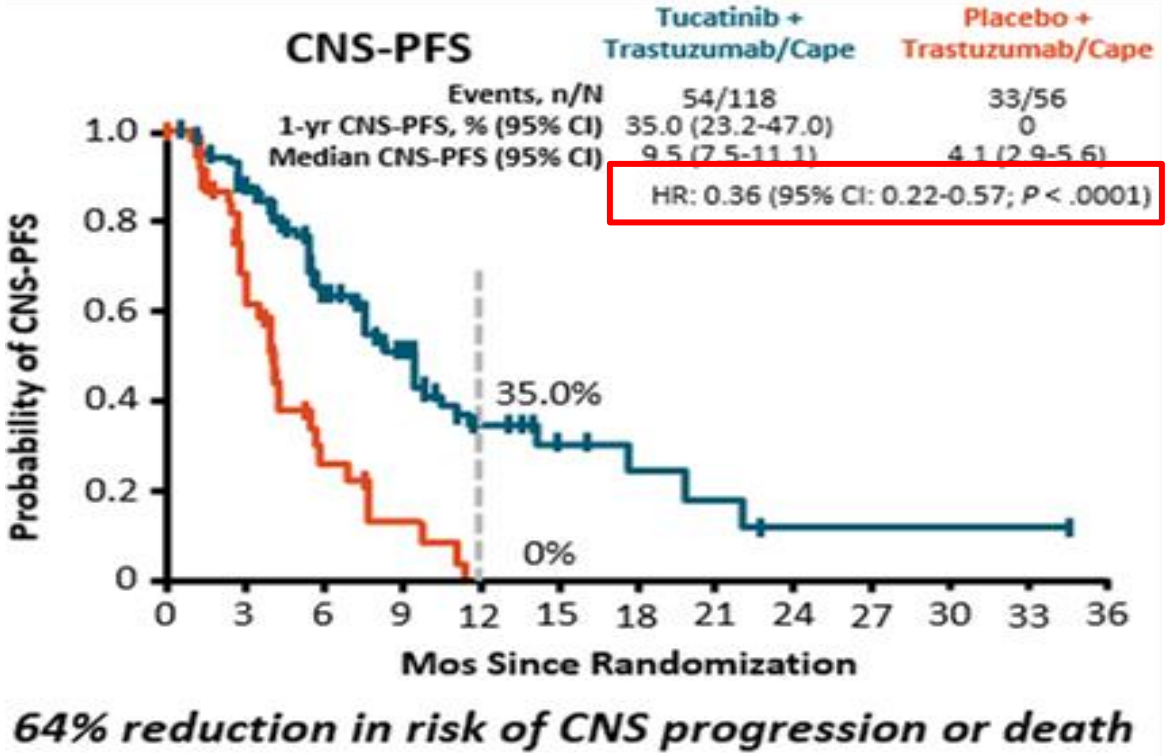
68% reduction in risk of CNS progression or death

Patients at Risk, n													
Tucatinib + trastuzumab/cape	198	132	75	45	18	11	6	4	2	2	2	1	0
Placebo + trastuzumab/cape	93	41	11	6	0	0	0	0	0	0	0	0	0

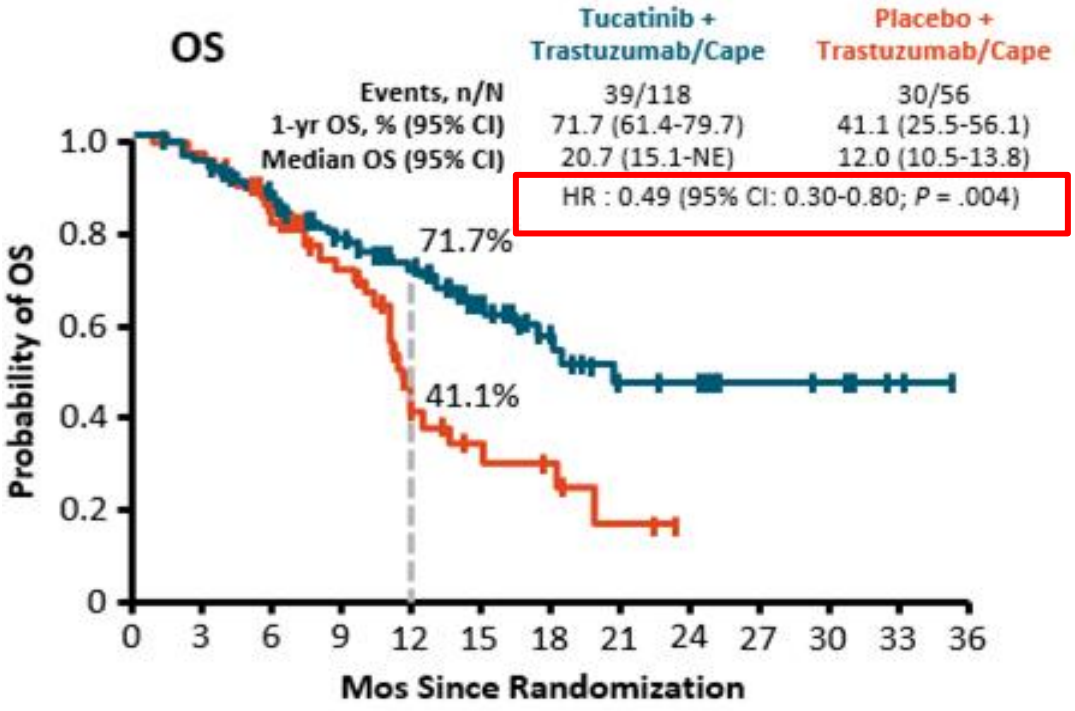
HER2CLIMB Intracranial Activity: OS in All Patients With Brain Metastases



HER2CLIMB Intracranial Activity: CNS-PFS in Patients With Active Brain Metastases

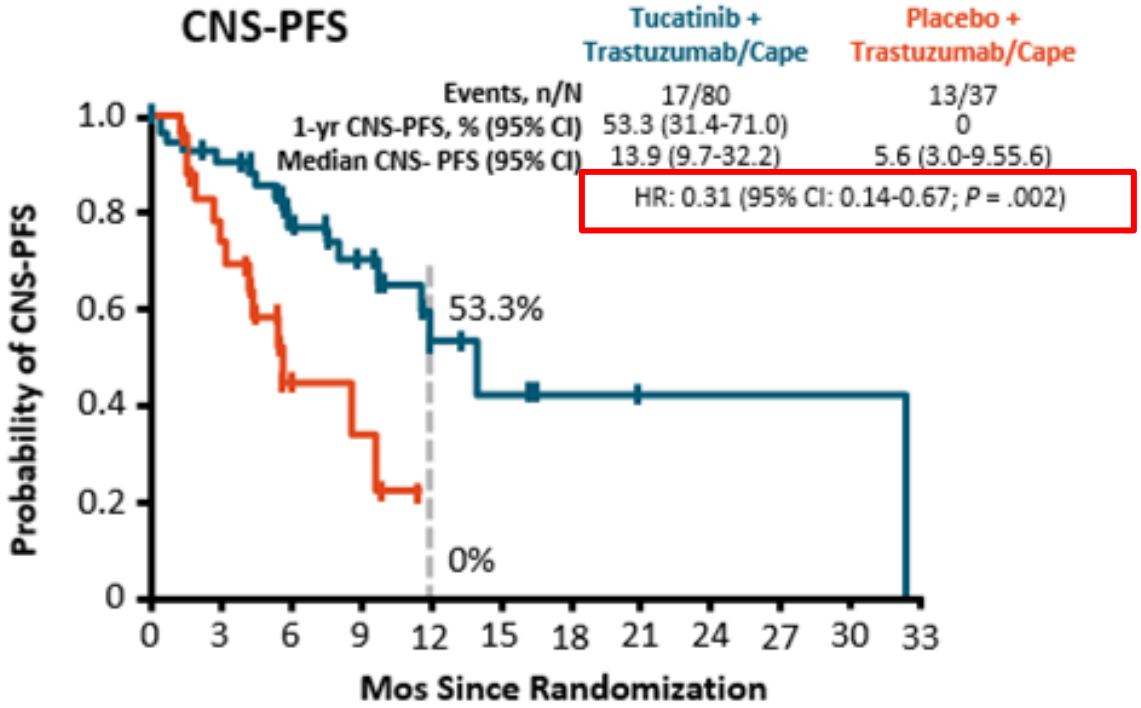


HER2CLIMB Intracranial Activity: OS in Patients With Active Brain Metastases



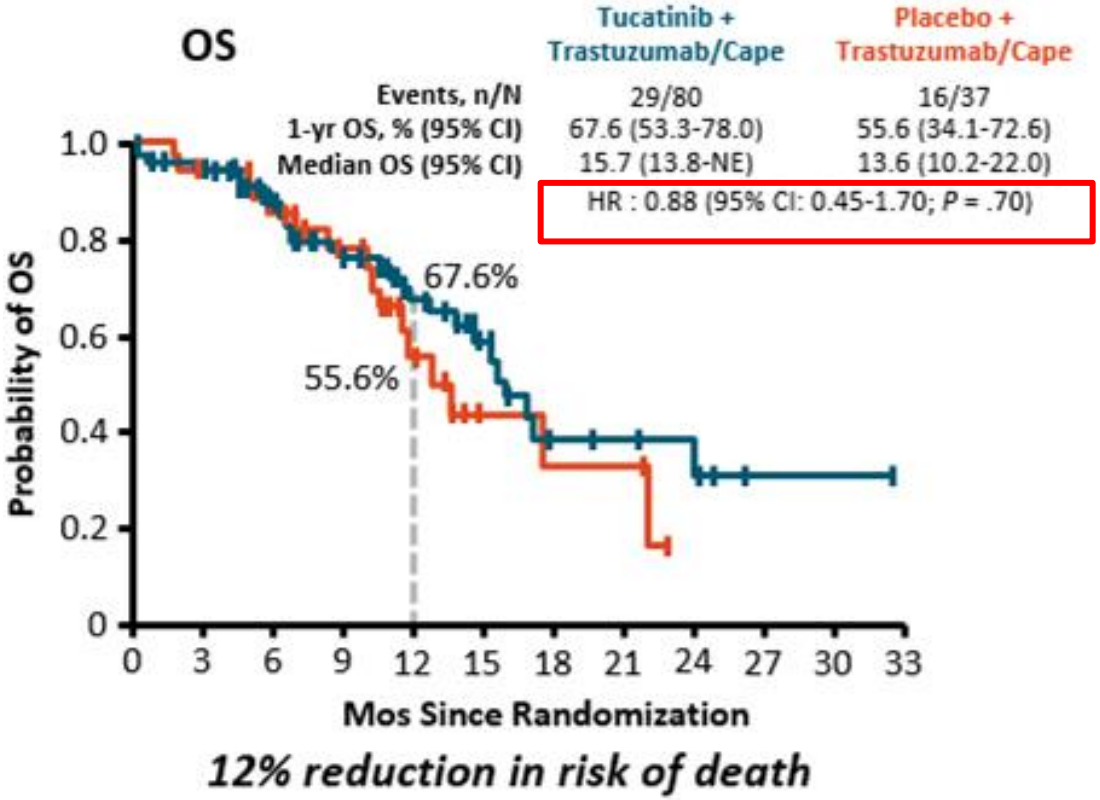
51% reduction in risk of death

HER2CLIMB Intracranial Activity: CNS-PFS in Patients With Stable Brain Metastases



69% reduction in risk of CNS progression or death

HER2CLIMB Intracranial Activity: OS in Patients With Stable Brain Metastases



HER2CLIMB Intracranial Activity: ORR in Patients With Active Brain Metastases and BL CNS Lesions

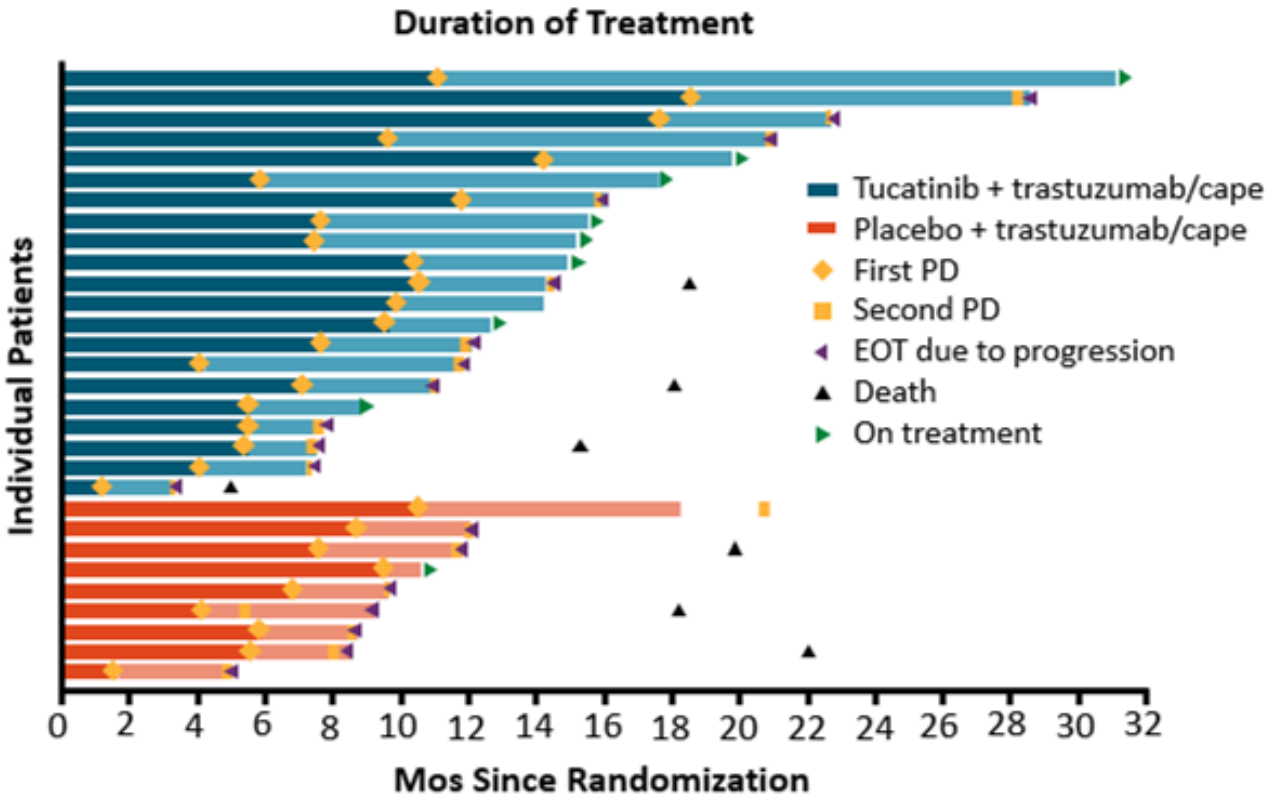
Response	Tucatinib + Trastuzumab/ Capecitabine (n = 55)	Placebo + Trastuzumab/ Capecitabine (n = 20)
Intracranial ORR, % (95% CI)	47 (33.7-61.2)*	20 (5.7-43.7)*
Best overall intracranial response, n (%)		
▪ CR	3 (5.5)	1 (5.0)
▪ PR	23 (41.8)	3 (15.0)
▪ SD	24 (43.6)	16 (80.0)
▪ PD	2 (3.6)	0
▪ Not available	3 (5.5)	0
Objective response of confirmed CR or PR, n	26	4
Duration of intracranial response, mos (95% CI)	6.8 (5.5-16.4)	3.0 (3.0-10.3)

*P = .03

HER2CLIMB Intracranial Activity: Outcomes With Isolated CNS Progression and Ongoing Assigned Study Tr

PFS in Patients With Isolated CNS Progression*	Tucat Trastuz Capeci (n =
Median time from randomization to 2nd progression or death, mos (95% CI)	15.9 (11
HR (95% CI)	0.2
Median time from 1st CNS progression to 2nd progression or death, mos (95% CI)	7.6 (3.
HR (95% CI)	0.3

*Patients were permitted to remain on stud



Adverse Reactions

Incidences reported for combination therapy with trastuzumab and capecitabine. Comparator: Placebo + trastuzumab + capecitabine.

>10%:

Dermatologic: Palmar-plantar erythrodysesthesia (63%), skin rash (20%)

Endocrine & metabolic: Decreased serum magnesium (40%), decreased serum phosphate (57%), decreased serum potassium (36%), decreased serum sodium (28%), weight loss (13%)

Gastrointestinal: Abdominal pain (≥20%), decreased appetite (25%), diarrhea (81% [comparator: 53%]; severe diarrhea: 4%), nausea (58% [comparator: 44%]), stomatitis (32% [comparator: 21%]); grade 3: 3% [comparator: 0.5%]), vomiting (36% [comparator: 25%])

Hematologic & oncologic: Anemia (21%; grade 3: 4%)

Hepatic: Hepatotoxicity (42% [comparator: 24%]), increased serum alanine aminotransferase (46% [comparator: 27%]; severe hepatotoxicity: >5x ULN: 8%), increased serum alkaline phosphatase (26%), increased serum aspartate aminotransferase (43% [comparator: 25%]; severe hepatotoxicity: >5x ULN: 6%), increased serum bilirubin (47% [comparator: 30%])

Nervous system: Fatigue (≥20%), headache (≥20%), peripheral neuropathy (13%; grade 3: <1%)

Neuromuscular & skeletal: Arthralgia (15%)

Renal: Increased serum creatinine (14% to 33%)

Respiratory: Epistaxis (12%)

HER2CLIMB Intracranial Activity: Conclusions

1. Tucatinib plus Trastuzumab/capecitabine demonstrated statistically significant and clinically meaningful improvements BMs. ORR, CNS-PFS, and OS
    a. 68% reduction in risk of CNS progression, 42% reduction in risk of death
    b. CNS-PFS and OS ***benefit observed in patients with active*** brain mets

1. Current study is first RCT to report a TKI leading to prolonged OS in patients with HER2+ MBC and brain mets

1. This regimen is active against intracranial and extracranial disease in HER2+ MBC

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References

1. Bendell JC, Domchek SM, Burstein HJ, et al: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 97:2972-2977, 2003

2. Brufsky AM, Mayer M, Rugo HS, et al: Central nervous system metastases in patients with HER2-positive metastatic breast cancer: Incidence, treatment, and survival in patients from registHER. Clin Cancer Res 17:4834-4843, 2011

3. Leyland-Jones B: Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J Clin Oncol 27:5278-5286, 2009

4. Olson EM, Najita JS, Sohl J, et al: Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the posttrastuzumab era. Breast 22:525-531, 2013

5. Pestalozzi BC, Holmes E, de Azambuja E, et al: CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: A retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 14:244-248, 2013

6. Ramakrishna N, Temin S, Chandarlapaty S, et al: Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: ASCO clinical practice guideline update. J Clin Oncol 36:2804-2807, 2018

7. Patchell RA, Tibbs PA, Regine WF, et al: Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. JAMA 280: 1485-1489, 1998

8. Kocher M, Soffietti R, Abacioglu U, et al: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. J Clin Oncol 29:134-141, 2011

References

9. Mahajan A, Ahmed S, McAleer MF, et al: Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: A single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 18:1040-1048, 2017 [Errata: Lancet Oncol 18:e433, 2017; Lancet Oncol 18:e510, 2017]

10. US Food and Drug Administration: Cancer Clinical Trial Eligibility Criteria: Brain Metastases—Guidance for Industry. https://www.fda.gov/media/121317/ download

11. Costa R, Gill N, Rademaker AW, et al: Systematic analysis of early phase clinical studies for patients with breast cancer: Inclusion of patients with brain metastasis. Cancer Treat Rev 55:10-15, 2017

12. Freedman RA, Gelman RS, Anders CK, et al: TBCRC 022: A phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol 37:1081-1089, 2019

13. Lin NU, Dieras V, Paul D, et al: Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 15: ´ 1452-1459, 2009

14. Otto Metzger-Filho , William Thomas Barry , Ian E. Krop , et al. - Phase I dose-escalation trial of ONT-380 in combination with trastuzumab in participants with brain metastases from HER2+ breast cancer- JCO- 2017 - 32, no. 15_suppl.

15. Tukysa (tucatinib) [información de prescripción]. Bothell, WA: Seattle Genetics Inc; Abril 2020