Il paradigma terapeutico nel carcinoma mammario HER2-positivo alla luce dei nuovi farmaci disponibili: il ruolo del Tucatinib

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Topics

- **Tucatinib**
  - Efficacy (Overall/SNC)
  - Safety
- **Tucatinib in the Treatment Algorithm for HER2+ MBC**
- **Conclusions & Future perspectives**

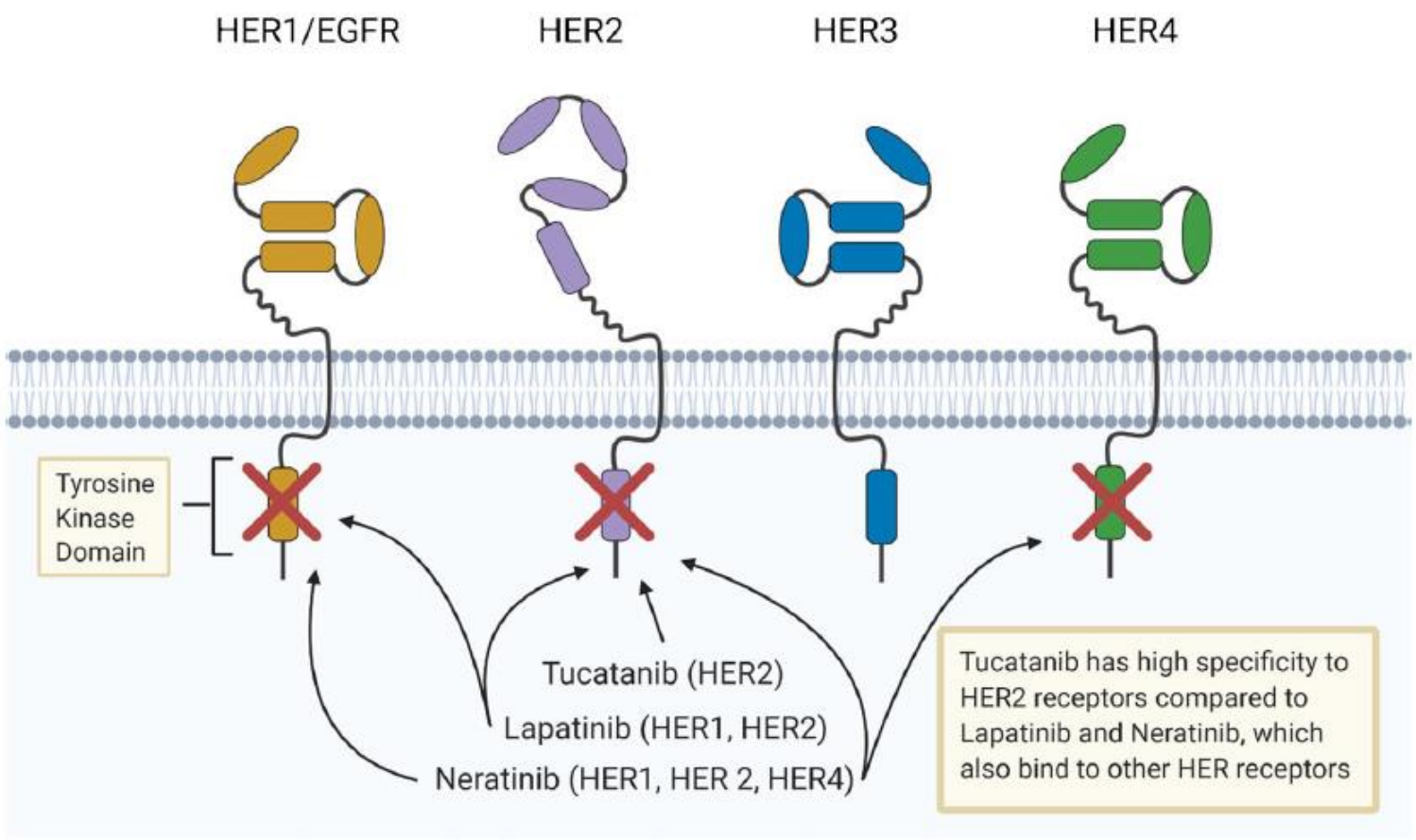
Tucatinib: Oral, HER2 Selective TKI

Tucatinib is an orally bioavailable, potent small molecule tyrosine kinase inhibitor (TKI) that is highly selective for HER2 without significant inhibition of EGFR (HER1).

- CNS penetration: high passive permeability (Normal brain and Brain Tumor).

Neratinib is an EGFR/2/4 inhibitor.

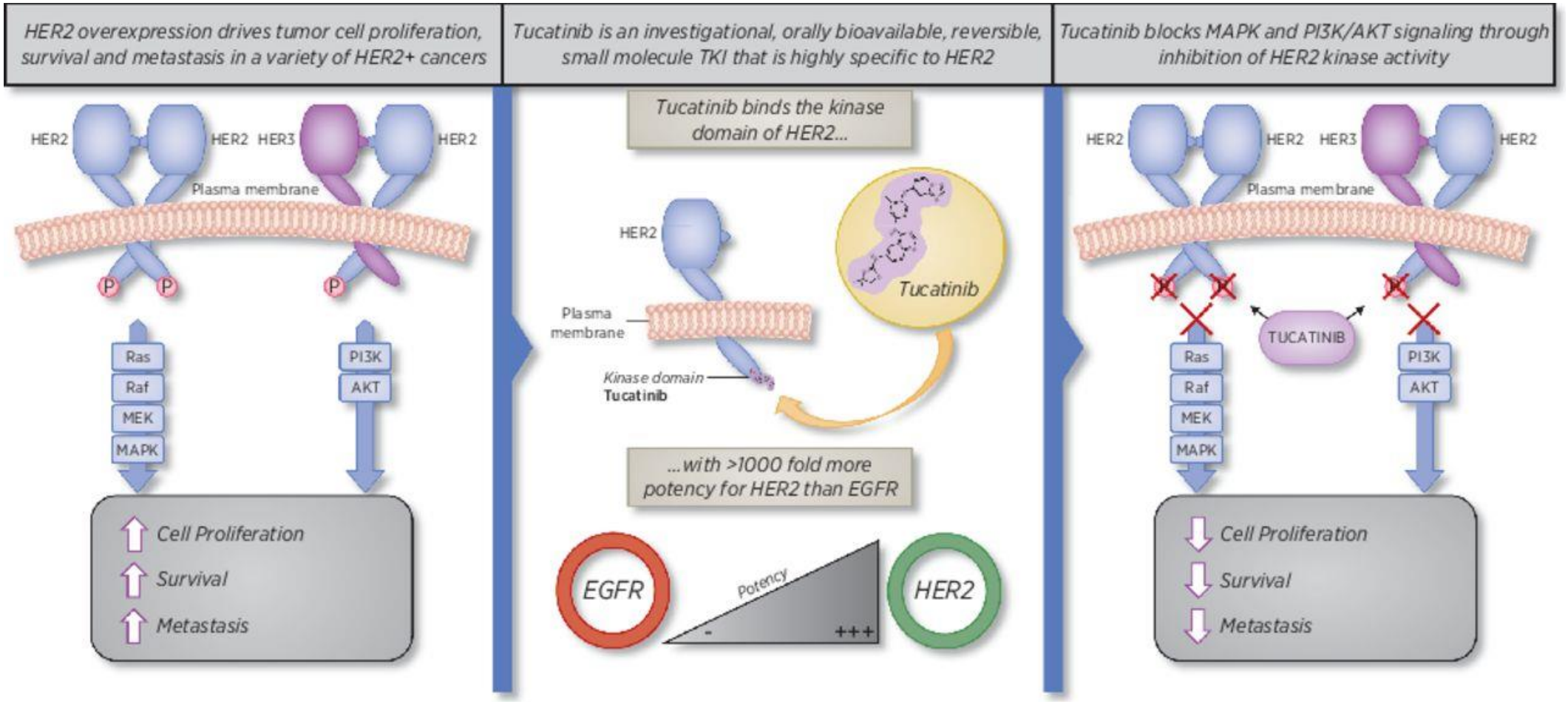
Lapatinib is an inhibitor of EGFR/HER2.



HER2 activation is mediated by homodimerization or heterodimerization with other EGFR family members, including EGFR or HER3.

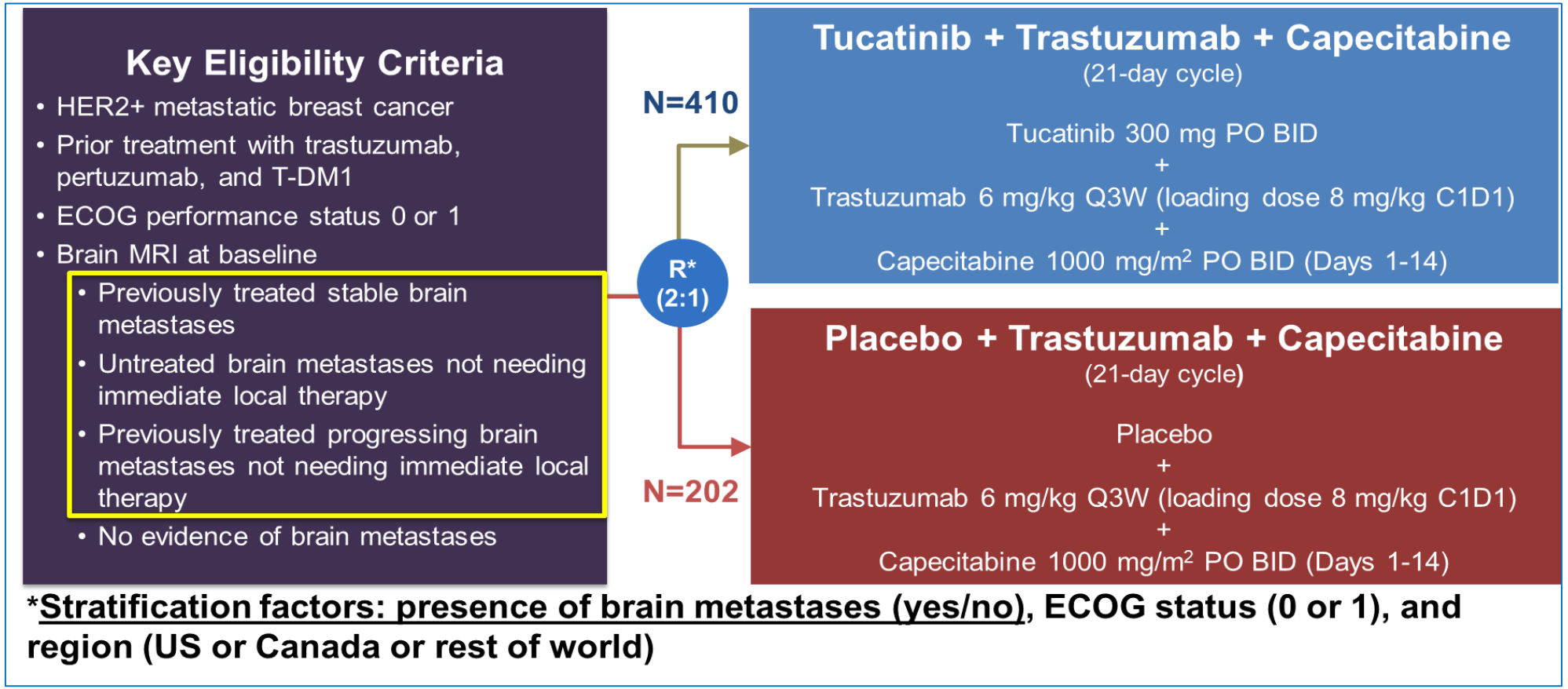
Dent SF et al, Current Oncology Reports 2021

Tucatinib: Mechanism of Action



Kulukian et al. Mol Cancer Ther. 2020;19:976-87

HER2CLIMB Trial Design (Blinded Phase II) & Endpoints



Primary Endpoint Assessed (Primary Endpoint Population):

- PFS (RECIST 1.1 by Blinded Independent Central Review (BICR); N=480); power 90%, 288 events, **α=5%, HR=0.67**

Multiplicity-Adjusted Secondary Endpoints from the Total Population

- OS (N=612), power 80%, 361 deaths, **α=2%, HR=0.70**
- PFS in patients with brain metastases ($PFS_{BrainMets}$) (RECIST 1.1 by BICR; N=291), power 74%, 220 events, **α=3%, HR=0.67**
- Confirmed ORR in patients with measurable disease (RECIST 1.1 by BICR; N=511)

Murthy et al. N Engl J Med. 2020

Key Baseline Disease Characteristics

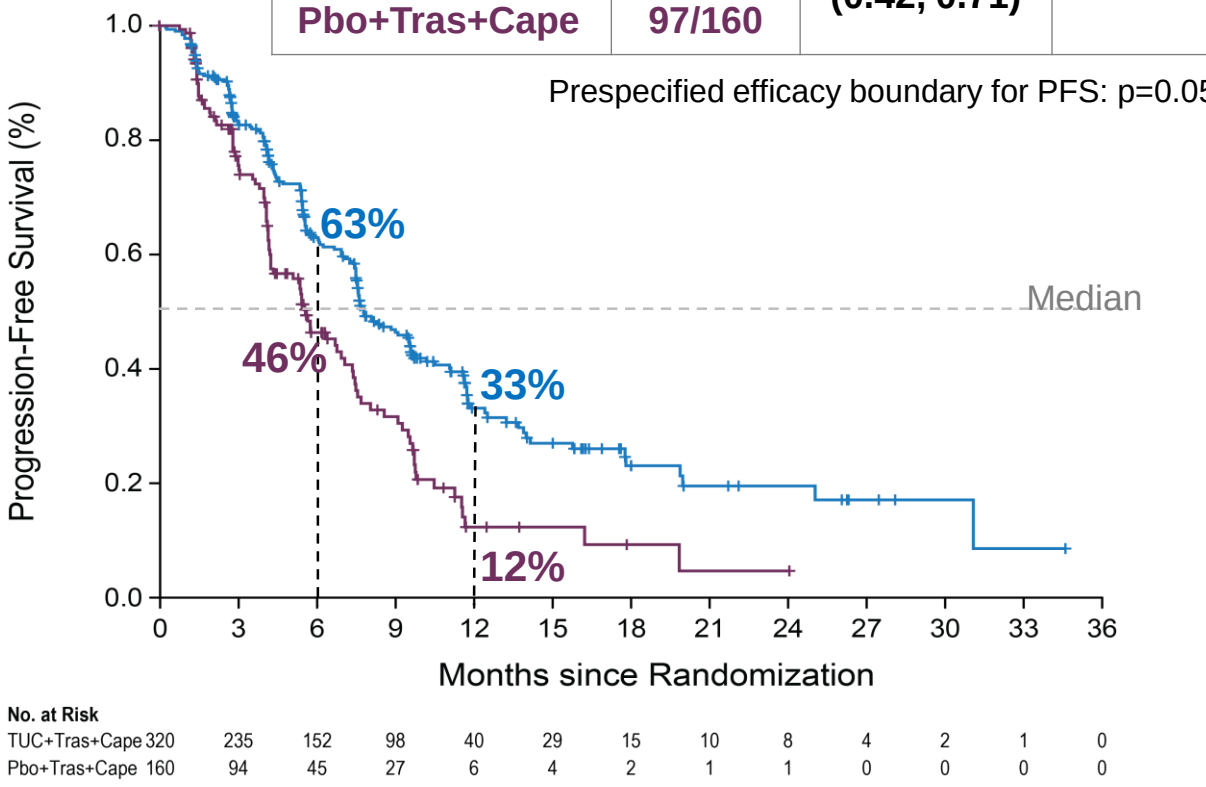
Characteristic, n (%)		Total Population, N=612	
		TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (38)
Hormone receptor status	ER and/or PR-positive	243 (59)	127 (63)
	ER and PR-negative	161 (39)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2, 17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Previous therapies	Trastuzumab	410 (100)	202 (100)
	Pertuzumab	409 (99.8)	201 (99.5)
	T-DM1	410 (100)	202 (100)
	Lapatinib	24 (5.9)	10 (5)
Patients with brain metastases or history of brain metastases at baseline		198 (48)	93 (46)

Murthy et al. N Engl J Med. 2020

PFS (by BICR, 480 Pts) & OS (ITT) – First Primary Analysis

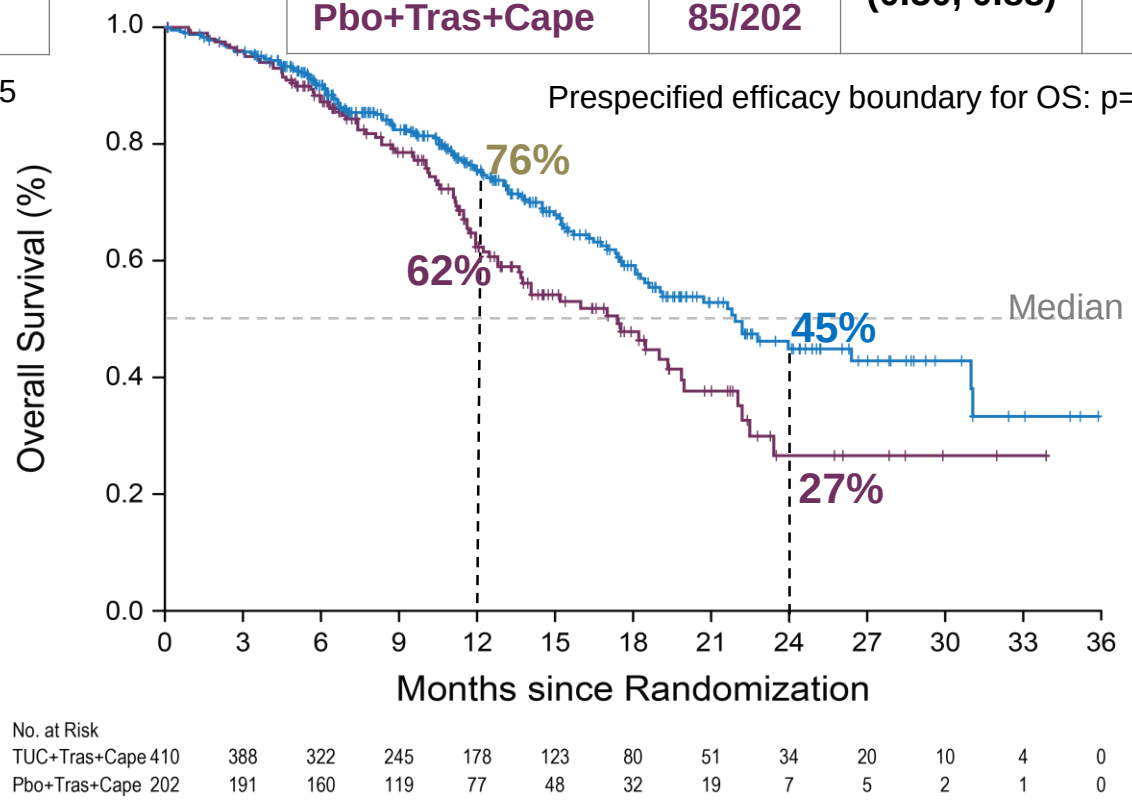
PFS

	Events/ Pts	HR (95% CI)	p Value
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.001
Pbo+Tras+Cape	97/160		



OS

	Deaths/ Pts	HR (95% CI)	p Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.005
Pbo+Tras+Cape	85/202		

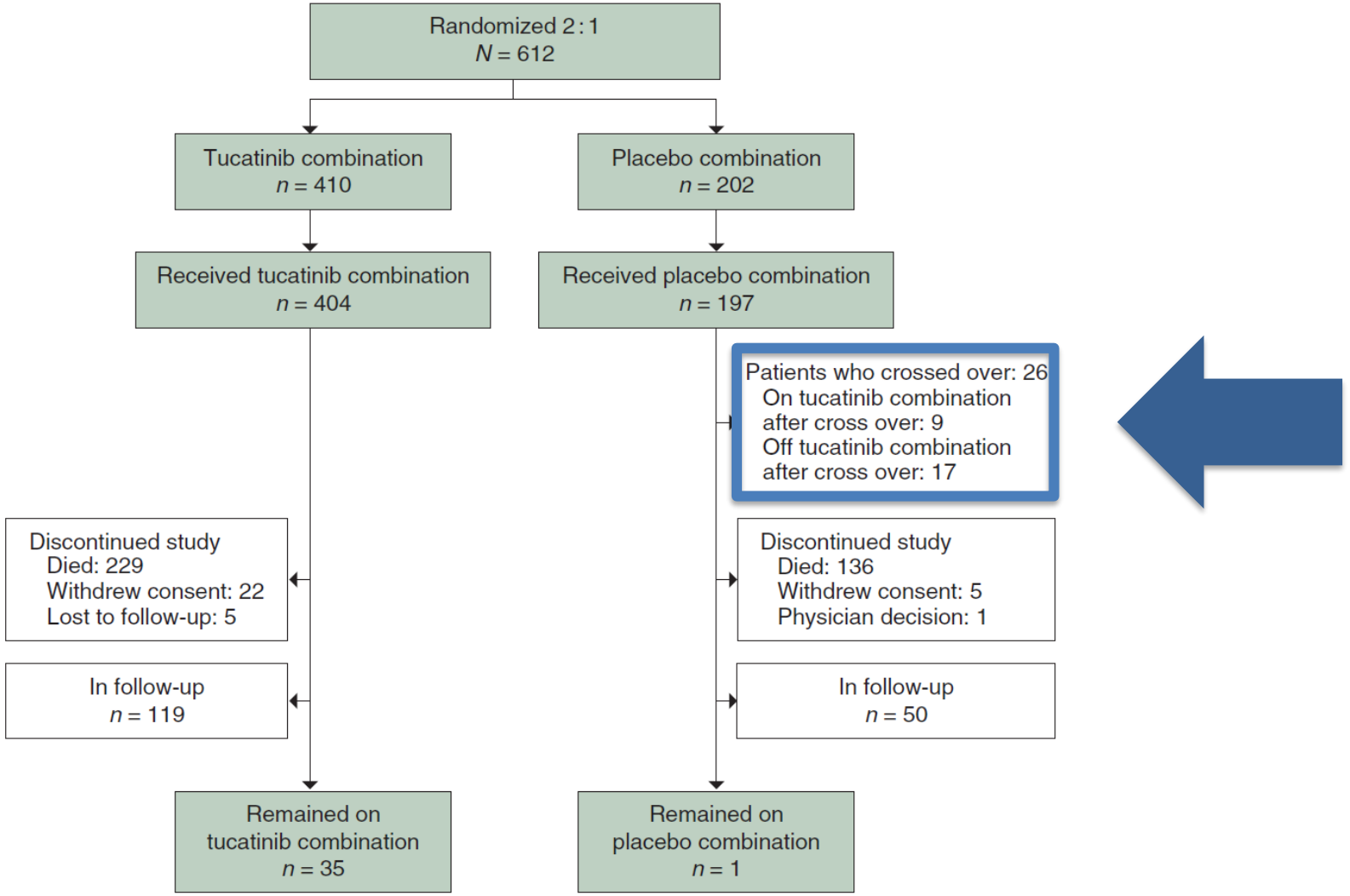


Median follow-up: 14 months

After the primary analysis, patients were unblinded and permitted to cross over from the placebo combination group to receive tucatinib in combination with trastuzumab and capecitabine.

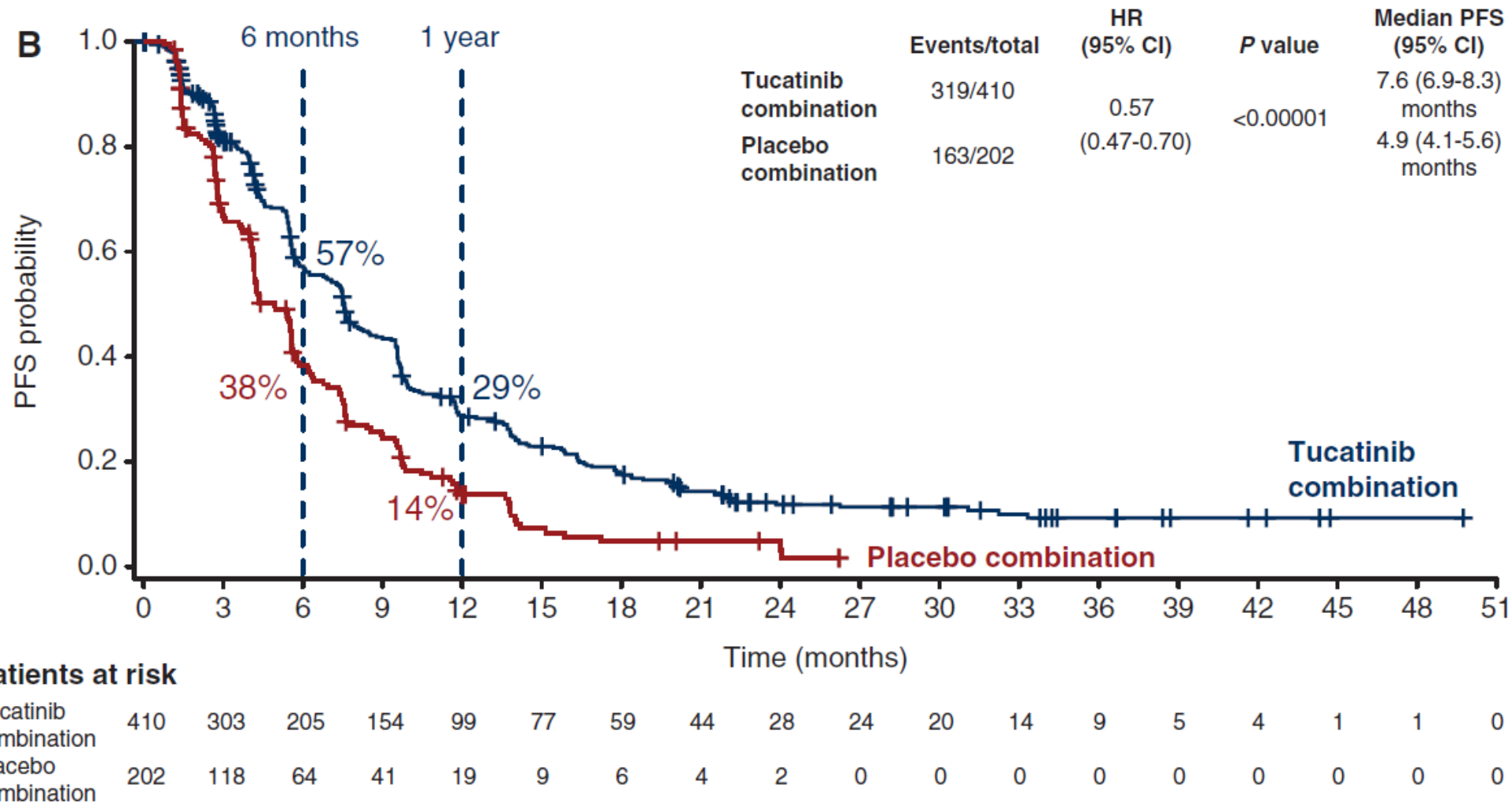
Murthy et al. N Engl J Med. 2020

HER2CLIMB Consort Diagram



Murthy et al. N Engl J Med. 2020

Updated PFS in the ITT Population (*after unblinding*)

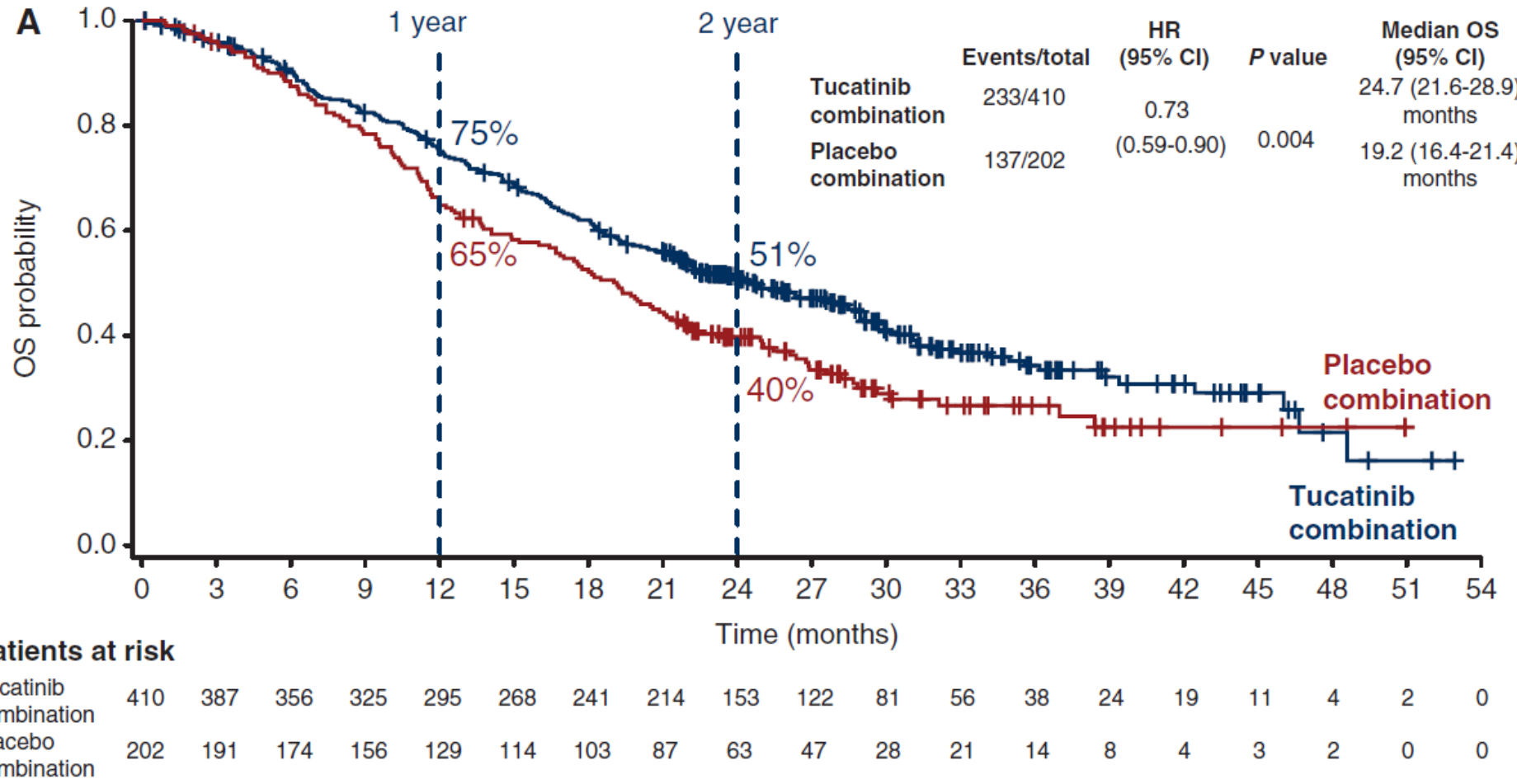


	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

Median OS follow-up: 29.6 months

Curigliano G et al, Ann Oncol 2021

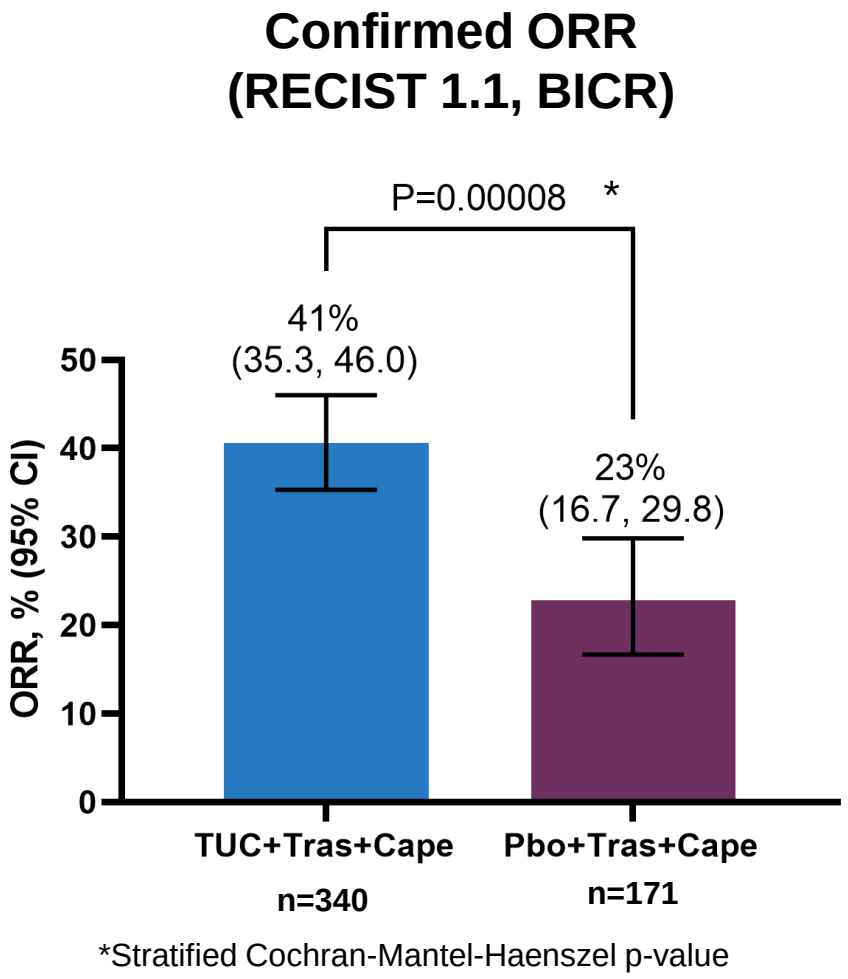
Updated OS in the ITT Population (*after unblinding*)



The OS analysis reported here was based on the ITT principle, i.e. patients were analyzed per randomization (regardless of cross-over).

Curigliano G et al, Ann Oncol 2021

Confirmed ORR by BICR (Measurable Disease)



*Stratified Cochran-Mantel-Haenszel p-value

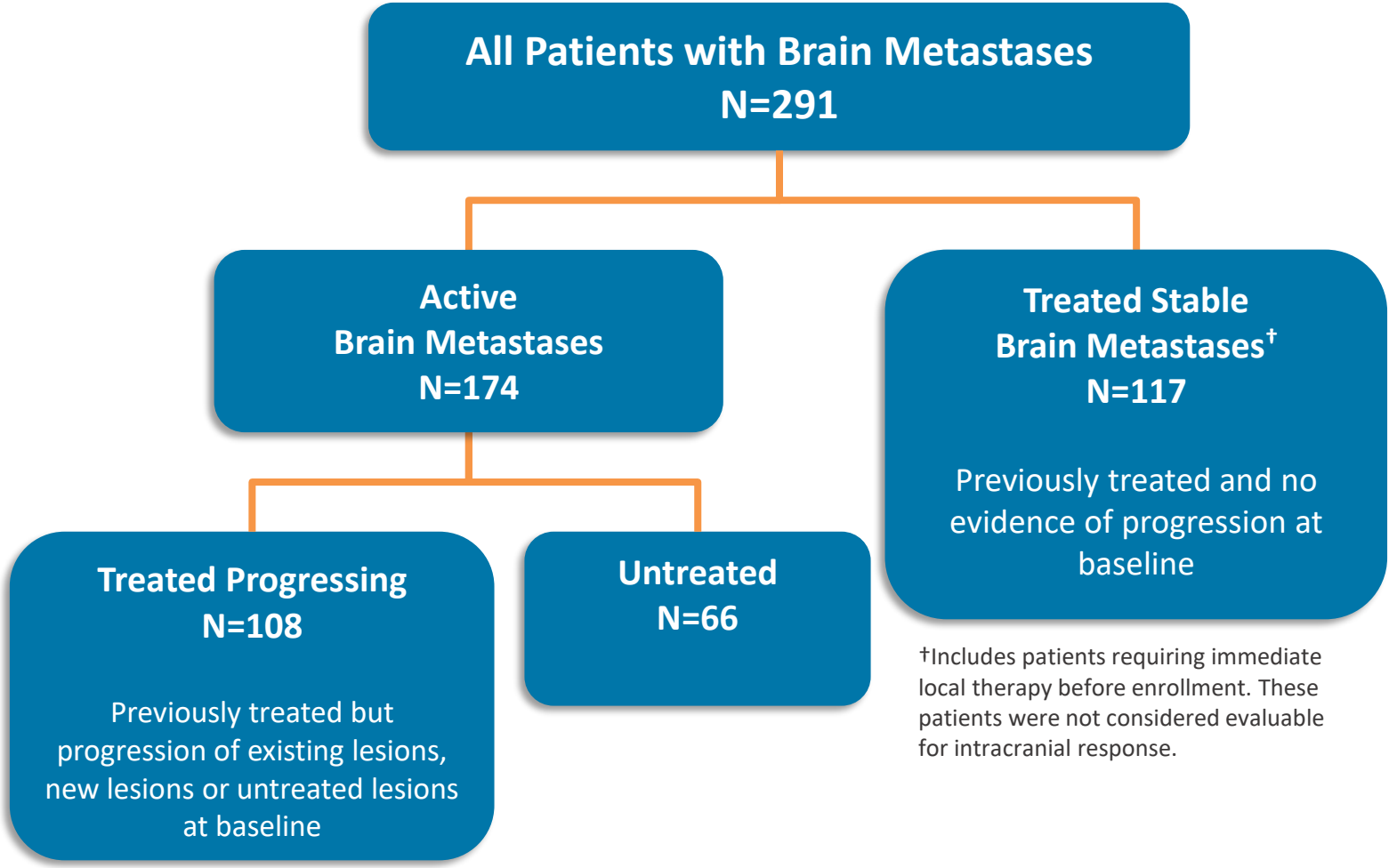
Response, n (%)	Patients with Measurable Disease N=511	
	TUC+Tras+Cape n=340	Pbo+Tras+Cape n=171
Best Overall Response[a]		
Complete response	3 (1)	2 (1)
Partial response	135 (40)	37 (22)
Stable disease	155 (46)	100 (59)
Progressive disease	27 (8)	24 (14)
Not evaluable	0	1 (1)
Not available[b]	20 (6)	7 (4)
Time to Response (months), median (min, max)[c]	1.4 (1.1, 9.7)	1.4 (1.2, 15.7)
Clinical Benefit Rate (CR+PR+SD >6 months)	60%	38%

a. Confirmed Best overall response assessed per RECIST 1.1
b. Patients with no post-baseline response assessments
c. Time to Response was an exploratory analysis

Murthy et al. N Engl J Med. 2020

HER2CLIMB: 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



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

Lin NU SABCS 2021

Baseline Characteristics of Patients with Brain Metastases

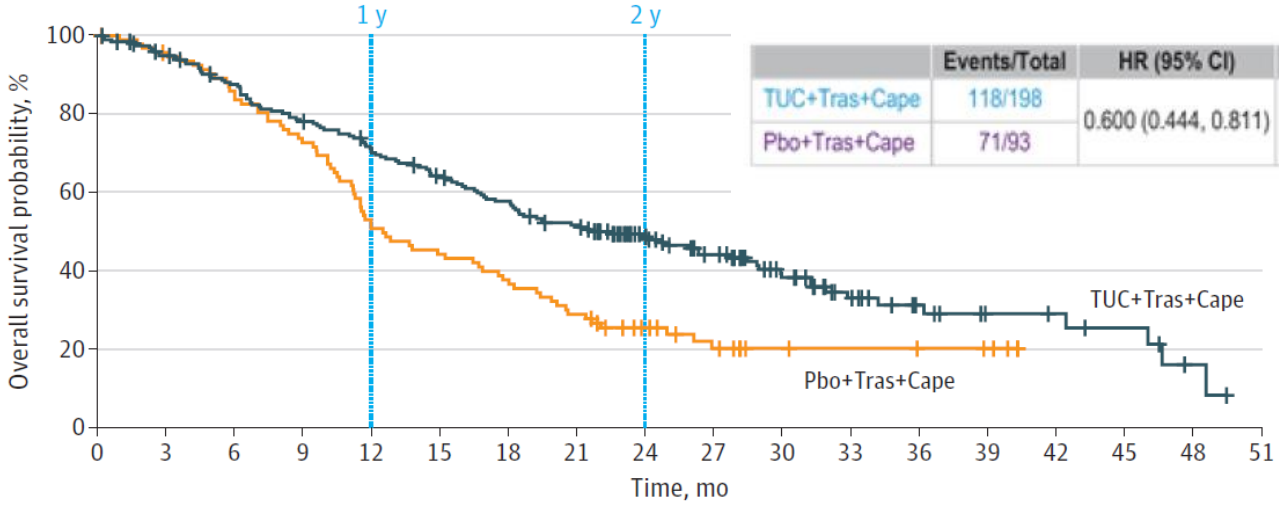
		TUC+Tras+Cape (N=198)	Pbo+Tras+Cape (N=93)
Age (years), median (range)		53 (22, 75)	52 (25, 75)
Metastatic (any location) at initial diagnosis, n (%)		77 (38.9)	39 (41.9)
Non-CNS metastatic disease		192 (97.0)	90 (96.8)
Treated, stable[a]		80 (40)	37 (40)
Treated, progressing[b]		74 (37)	34 (37)
Untreated[c]		44 (22)	22 (24)
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)

a. Previously treated with surgery or radiation, without subsequent documented progression of brain metastases.
b. Previously treated with surgery or radiation with any documented progression of brain metastases since most recent surgery or radiation treatment for brain metastases.
c. No prior surgery or radiation for brain metastases.

Lin NU SABCS 2021

OS, CNS-PFS & ORR for Patients with Brain Metastases

A Overall survival



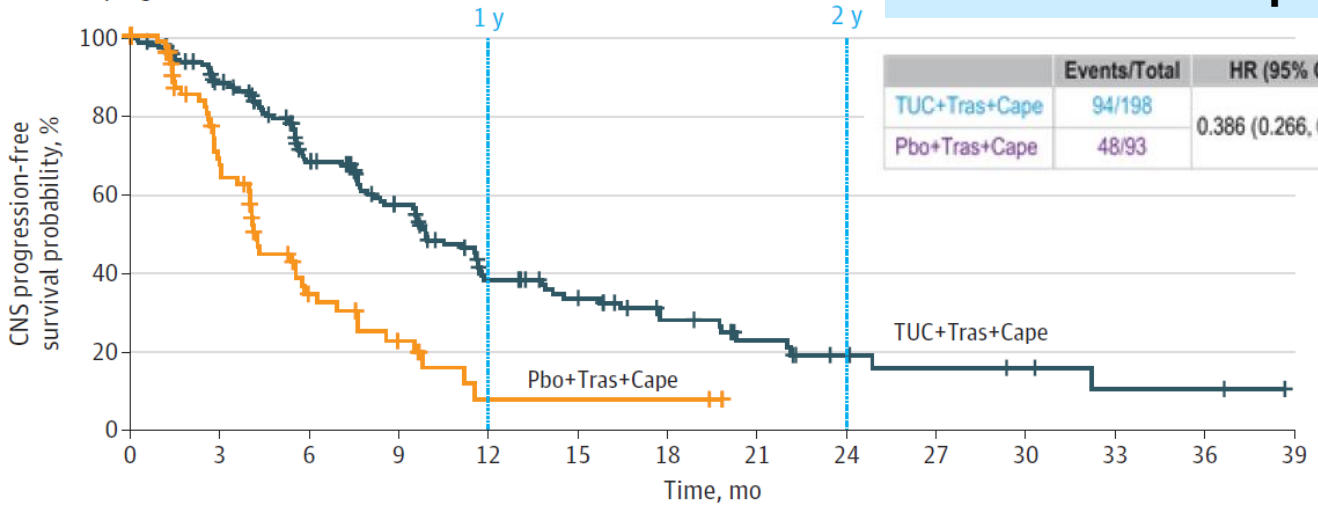
	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

No. at risk

TUC+Tras+Cape	198	183	166	147	131	118	105	92	68	54	36	22	14	9	8	6	2
Pbo+Tras+Cape	93	87	76	66	46	40	34	26	17	11	6	5	4	3	0	0	0

Median follow-up: 29.6 months

B Intracranial progression-free survival

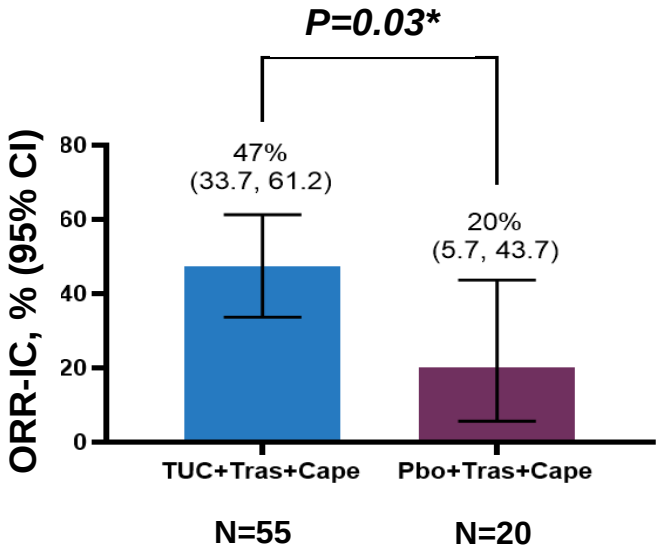


	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	94/198	0.386 (0.266, 0.559)	<0.00001	9.9 months (8.4, 11.7)
Pbo+Tras+Cape	48/93			4.2 months (3.6, 5.7)

No. at risk

TUC+Tras+Cape	198	132	91	65	37	29	19	12	7	5	4	2	2	0
Pbo+Tras+Cape	93	41	16	8	2	2	2	0	0	0	0	0	0	0

Confirmed Objective Response Rate (RECIST 1.1)



Lin NU et al. JAMA Oncology 2022

OS & CNS-PFS according to Subgroups

OS for Patients with Active Brain Metastases

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

OS for Patients with Treated Stable Brain Metastases

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	43/80	0.695 (0.416, 1.160)	0.16223	21.6 months (15.3, 42.4)
Pbo+Tras+Cape	25/37			16.4 months (10.6, 21.6)

CNS-PFS for All Patients with Brain Metastases by Subgroup

Subgroup	Treatment	Events	HR (95% CI)	P value	Median OS (95% CI)
Patients with active brain metastases	TUC+Tras+Cape	69/118	0.339 (0.215, 0.536)	<0.00001	9.6 months (7.6, 11.1)
	Pbo+Tras+Cape	35/56			4.0 months (2.9, 5.6)
Patients with treated stable brain metastases	TUC+Tras+Cape	25/80	0.406 (0.194, 0.850)	0.01	13.9 months (9.7, 24.9)
	Pbo+Tras+Cape	13/37			5.6 months (3.0, –)

Lin NU et al. JAMA Oncology 2022

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

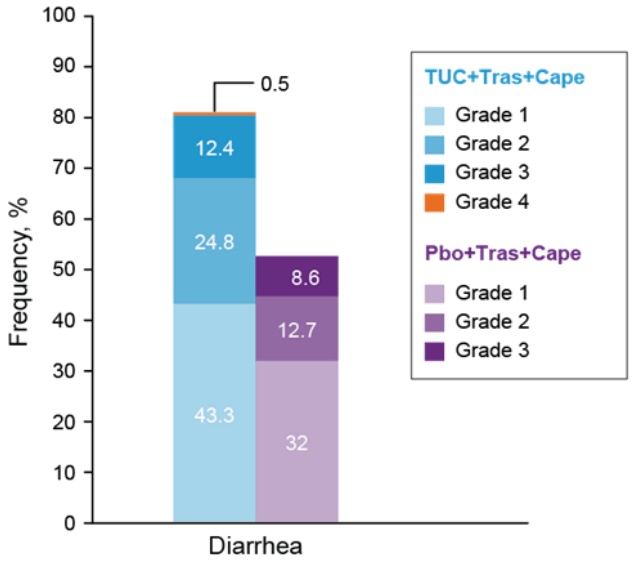
Adverse event	Tucatinib combination (*N* = 404) *n* (%)		Placebo combination (*N* = 197) *n* (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	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)

Murthy et al. N Engl J Med. 2020

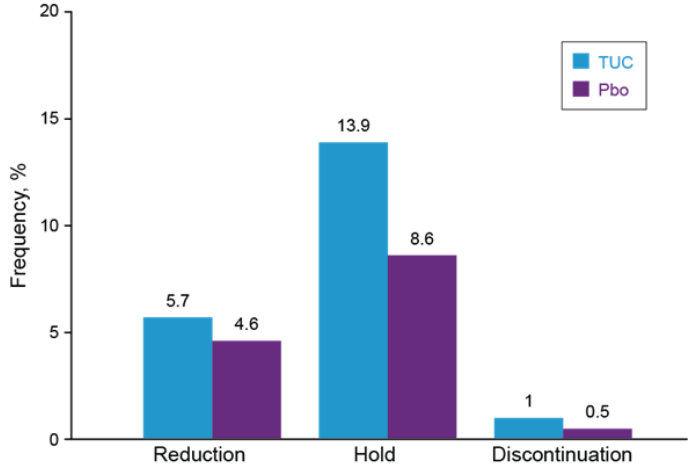
Key Safety Events: Diarrhea

- **Diarrhea was the most common AE observed in both arms, were primarily G1/2.**
  - **Serious AEs of diarrhea occurred in 4% of patients in the tucatinib arm and 3.6% of patients in the control arm.**
- **Most common modifications due to diarrhea were dose holds; treatment discontinuations were infrequent.**
- **Median time to diarrhea onset was 12 days (range, 1–420) in tucatinib arm and 22 days (range, 1–205) in placebo arm.**
- **Prophylactic antidiarrheals were not required per protocol.**
- **Antidiarrheal medications were used in 49.7% of cycles in the tucatinib arm and 39.8% of cycles in the placebo arm.**

Diarrhea by Severity



Tucatinib or Placebo Dose Modifications Due to Diarrhea

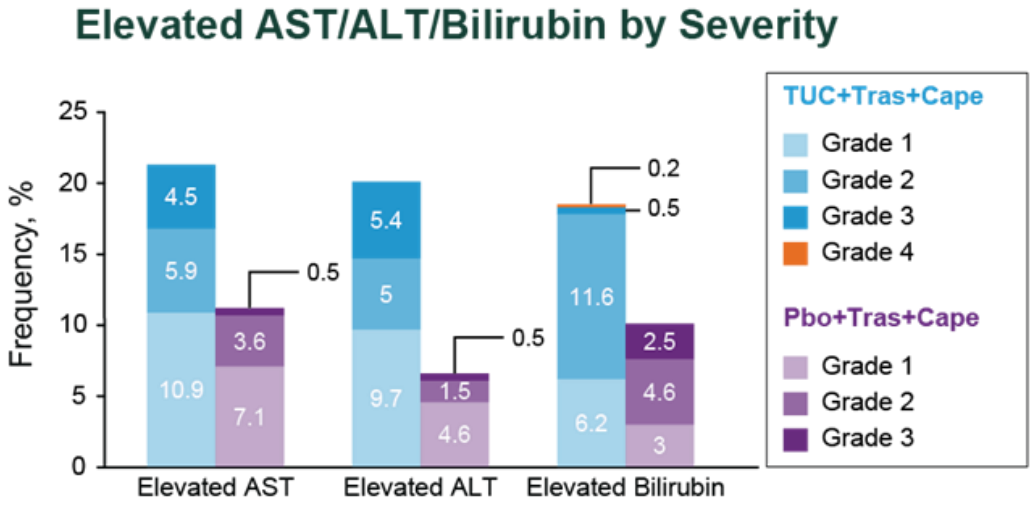


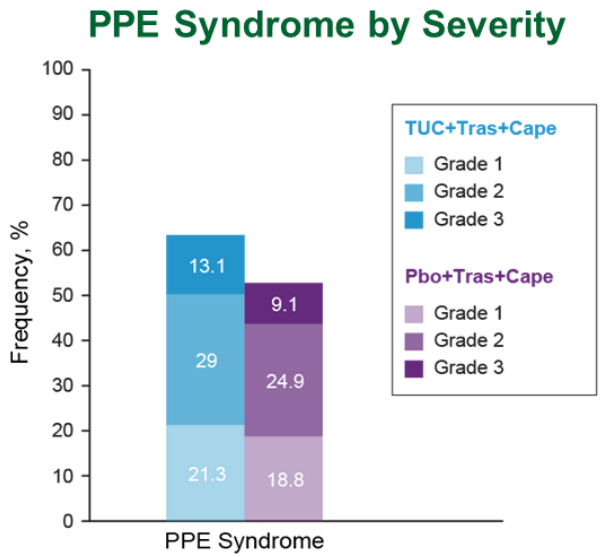
Okines A, et al. ASCO 2020

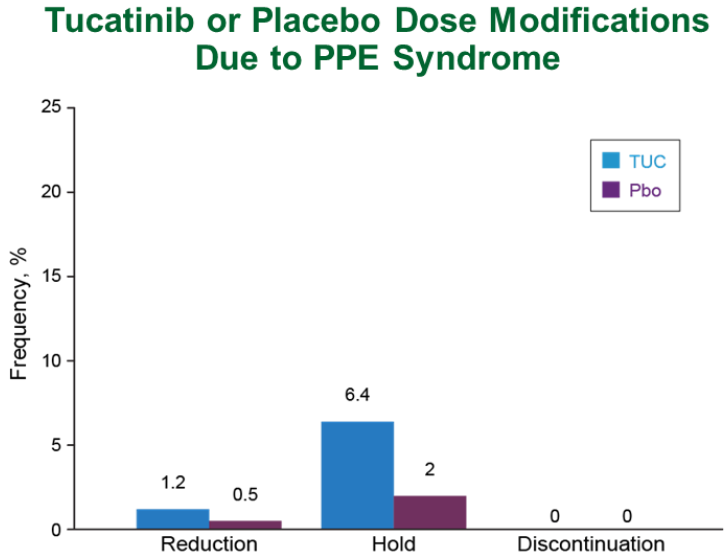
Key Safety Events: Elevated Liver Function Tests & PPE

- The incidence of elevated AST, ALT, and blood bilirubin was higher on the tucatinib arm (primarily G1/2, transient/manageable with dose modifications).
- Frequency of dose reductions and holds was higher on the tucatinib arm.
  - Treatment discontinuations due to elevated AST/ALT/bilirubin were infrequent.
- Median time to first onset: Cycles 1-2

- PPE events were common in both arms (primarily Grade 1-2), with manageable with dose modifications.
- Incidence of dose holds was higher in the tucatinib arm, with infrequent reductions/discontinuations.
  - The most common AE leading to capecitabine discontinuation on the tucatinib and placebo arms was PPE
- Median time to PPE: 33 days for tucatinib, 34.5 days for placebo



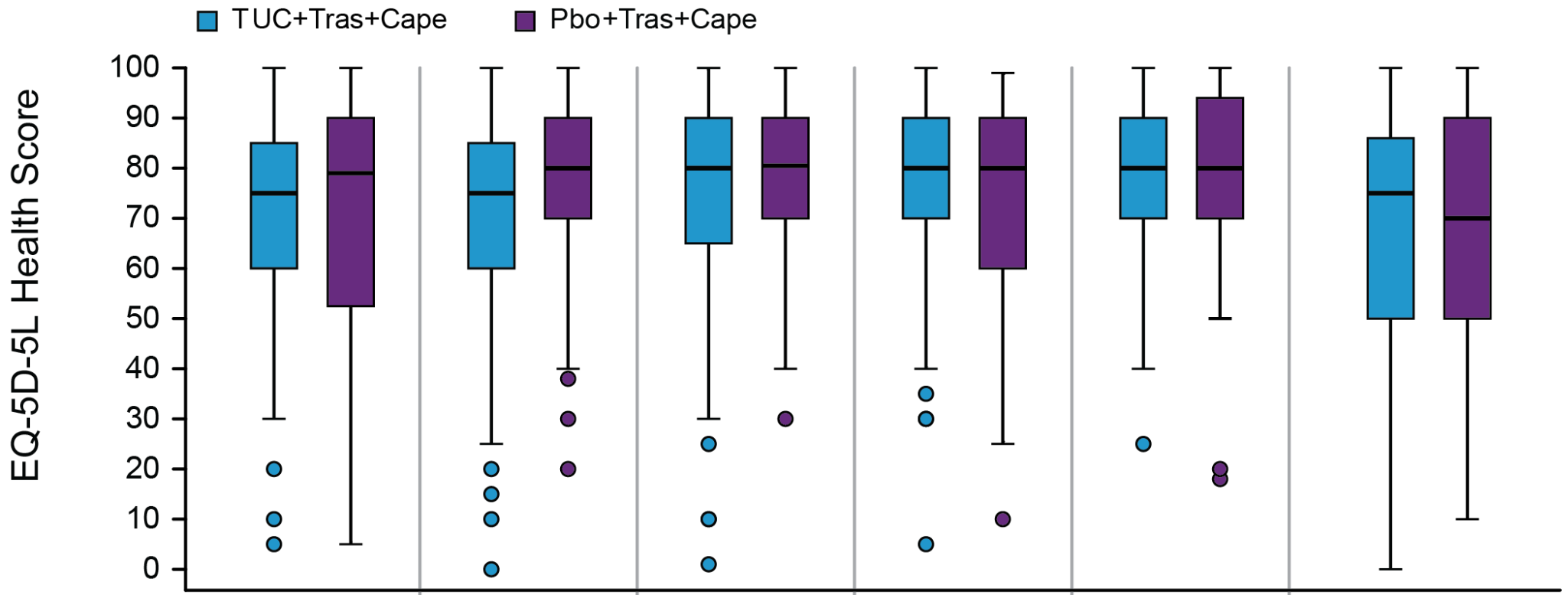




Okines A, et al. ASCO 2020

Overall HRQoL

HRQoL was maintained throughout treatment and was not different between treatment arms.



	Baseline	Cycle 3	Cycle 5	Cycle 7	Cycle 9	30 Day Follow Up
TUC+Tras+Cape (n/N)	217/217	183/200	157/194	134/182	90/178	76/188
Pbo+Tras+Cape (n/N)	112/112	91/102	70/88	54/84	39/83	45/93

Numerator is # of patients who completed the HRQoL survey in that cycle. Denominator is # of patients who completed the baseline survey and were still on treatment.

Mueller V, et al. ESMO 2020

HER2CLIMB: Summary

- Tucatinib in combination with trastuzumab and capecitabine in patients previously treated with trastuzumab, pertuzumab, and T-DM1:
  - Reduced the risk of death by a ~one third (HR=0.73, *p=0.004*)
  - Reduced the risk of progression or death by ~half in all patients (HR=0.57, *p<0.00001*), including patients with BM (OS benefit of 9.1 months)
  - Benefit across all subgroups was consistent
  - Nearly doubled the confirmed objective response rate (41% vs 23%)
  - Majority of adverse events were low-grade (Elevations of liver enzymes, and diarrhea typically transient)
  - Low rate of discontinuations due to adverse events

Tucatinib Approval

- On April 2020, the **FDA** issued approval to Tucatinib in combination with trastuzumab and capecitabine for adult patients with advanced unresectable or metastatic HER2+ BC, including those with BMs, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

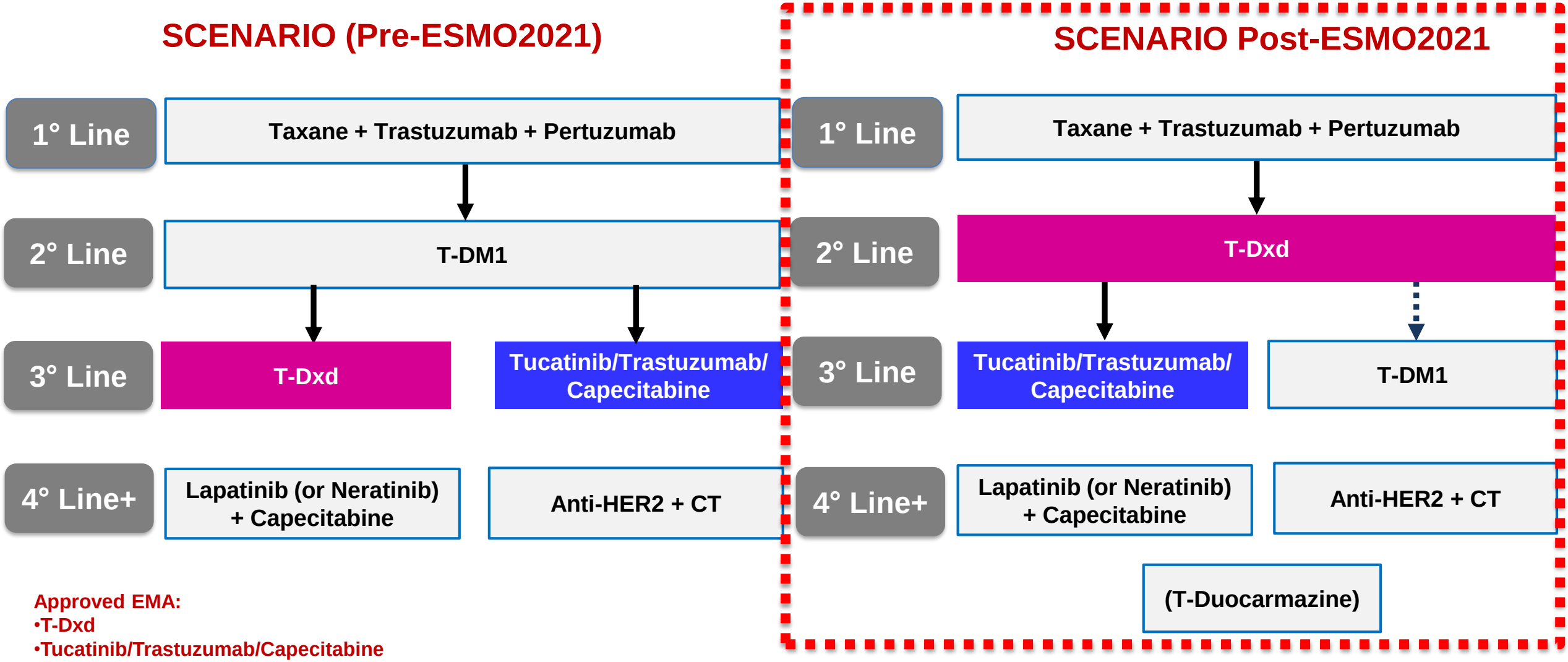
- On December 2020, the **EMA** Committee recommended the authorization for Tucatinib in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2+ locally advanced or metastatic BC who have received at least two prior anti-HER2 treatment regimens.

- On November 2022, the **AIFA** granted approval and reimbursement of Tucatinib for the treatment of adult patients with HER2+ locally advanced or metastatic BC who have received at least two prior anti-HER2 treatment regimens (excluding patients previously treated with capecitabine)

Topics

- **Tucatinib**
  - Efficacy (Overall/SNC)
  - Safety
- **Tucatinib in the Treatment Algorithm for HER2+ MBC**
- **Conclusions & Future perspectives**

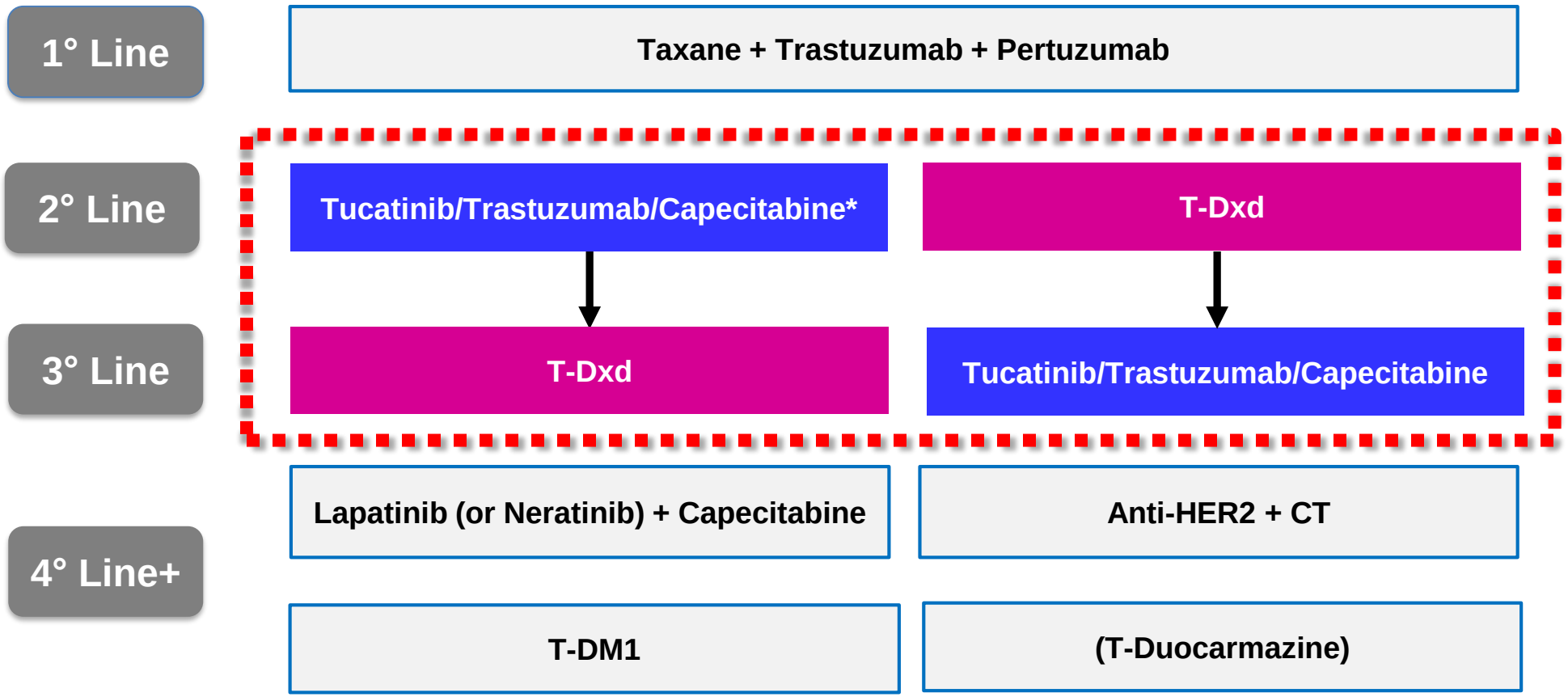
Potential Treatment Algorithm for HER2+ MBC



Approved EMA:
- **T-Dxd**
- **Tucatinib/Trastuzumab/Capecitabine**

Modified from ESMO Guidelines 2021 (Gennari A. et al., AO 2021)

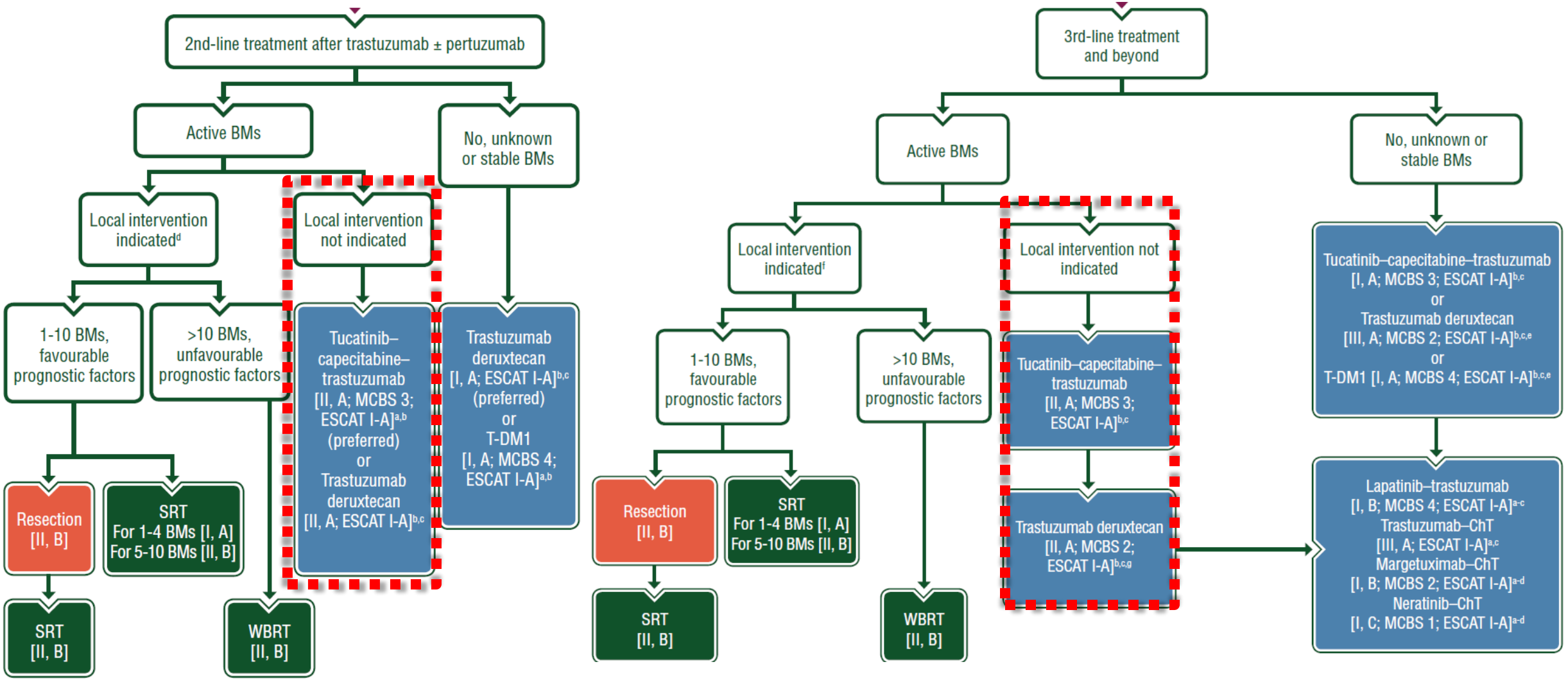
Potential Treatment Algorithm for HER2+ MBC with Brain Metastases



*N.B.: not approved

Modified from ESMO Guidelines 2021 (Gennari A. et al., AO 2021)

ESMO Guidelines for HER2+ MBC with Brain Metastases



ESMO Guidelines 2021 (Gennari A. et al., AO 2021)

DESTINY-Breast Trials: Brain Metastases (Stable/Treated) Subgroup

DESTINY-Breast01

Intent-to-Treat Analysis	CNS Subgroup (n=24)	All Patients (N=184)
Confirmed ORR by ICR	58.3% (n=14) (95% CI, 36.6%-77.9%)	60.9% (n=112) (95% CI, 53.4%-68.0%)

- T-Dxd demonstrated efficacy in patients who had stable, treated brain metastases at baseline that was similar to its efficacy in the overall population
  - Median DOR, 16.9 months
  - Median PFS, 18.1 months

Jerusalem G et al, ESMO Breast Cancer 2020

DESTINY-Breast03

- For patients with stable brain metastases at baseline (n=82), median PFS was 15.0 months for T-Dxd vs 3.0 months for T-DM1 (HR 0.25)
- ORR was 67.4% (4.7% CR, 62.8% PR) for T-Dxd vs 20.5% (0% CR, 20.5% PR) for T-DM1
- Intracranial ORR was 63.9% (27.8% CR, 36.1% PR) for T-Dxd vs 33.4% (2.8% CR, 30.6% PR) for T-DM1

Hurvitz, SABCS 2021

T-DXd Trials in pts with Brain Metastases (including Active)

DS8201- DEBBRAH STUDY

Trastuzumab-deruxtecan (5.4 mg/kg) every 3 weeks until disease progression or unacceptable toxicity

A Multicenter, Open-Label, Single-Arm, Multicohort Phase II Clinical Trial of Trastuzumab Deruxtecan (DS-8201a) in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced Breast Cancer with Brain Metastases and/or Leptomeningeal Carcinomatosis

Step 1: Single cohort

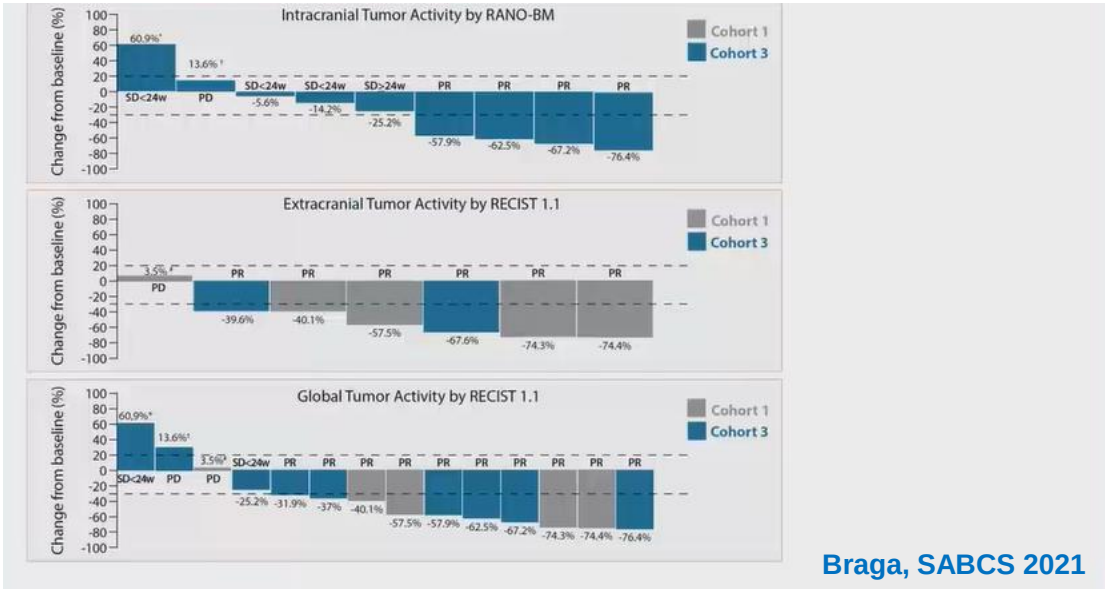
HER2-positive MBC pts with stable CNS Disease

8 patients

Step 2: 4 Cohorts

- *Cohort 2: HER2[3+] or [+low] with untreated BM* — 10 pts
- *Cohort 3: HER2[3+] & BM progression after local treatment* — 7 pts
- *Cohort 4: HER2[+low] & BM progression after local treatment* — 7 pts
- *Cohort 5: HER2[3+] or [+low] & meningeal carcinomatosis.* — 7 pts

Primary Objective: 16 weeks CNS PFS



Braga, SABCS 2021

TUXEDO- 1 Phase 2 Trial

HER2+ MBC with newly diagnosed or progressive brain metastases N=15 → Trastuzumab Deruxtecan 5.4mg/kg IV q3wk

Primary endpoint: CNS Response Rate

- **Intracranial response rate by RANO-BM was 73.3% (95% CI 48.1–89.1%) (11/15 patients; 2 patients in CR (13.3%); 9 patients in PR (60%)).**

Bartsch R, Nature Medicine 2022

DESTINY-Breast12

Study Design and Population

Patient population (N≈500)

- HER2-positive advanced or metastatic breast cancer
- Absence or presence of BM at baseline
- ≤2 prior lines of therapy in the metastatic setting

T-DXd 5.4 mg/kg q3w

- Cohort 1 (n≈250): absence of BM at baseline
- Cohort 2 (n≈250): presence of BM at baseline

Topics

- **Tucatinib**
  - Efficacy (Overall/SNC)
  - Safety
- **Tucatinib in the Treatment Algorithm for HER2+ MBC**
- **Conclusions & Future perspectives**

Conclusions: HER2CLIMB Pros and Cons (1)

- **Tucatinib in combination with trastuzumab and capecitabine represents a new treatment option for HER2+ MBC patients previously treated with ≥ anti-HER2 regimens.**

- **HER2CLIMB is the first randomized trial that 1) included patients with untreated or previously treated, progressing BM (traditionally excluded from enrollment in clinical trials) 2) demonstrated an OS benefit for these patients.**
  - **Although the strategy to define it as phase II was determined by the formal absence of a phase II following the phase 1b, HER2CLIMB has appropriate end-points for phase III, unblind design, and power to derive conclusions.**

- **Tucatinib may be offered to patients with BM (without symptoms) after progression on ≥1 anti-HER2 lines (ASCO Recommendation 2022). In this cases, local therapy may be delayed until evidence of intracranial progression.**

Conclusions: HER2CLIMB Pros and Cons (2)

- **The occurrence of BMs is frequent in HER2+, with at least half of patients developing BMs.**
  - **These results are applicable to patients whereas MRI is considered as a standard staging tool. Are these data supporting MRI as the standard for all HER2+ patients in routinary clinical practice?**
  - **ASCO Recommendation for MRI in non-symptomatic patients: Evidence Quality LOW; Strength: WEAK.**

- **At the time HER2CLIMB was designed, no single regimen was considered the standard of care for patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and T-DM1.**
  - **Capecitabine-Trastuzumab is not a common regimen in EU routinary clinical practice (risk of indirectness), whereas capecitabine-lapatinib is currently adopted. Nevertheless, such last regimen is not supported by any data after T-DM1.**

- **On the basis of the rapid switch of T-DXd in earlier lines, Tucatinib-capecitabine-trastuzumab is to be considered a valuable option for treatment after T-DXd.**
  - **Are HER2CLIMB data likely to be reproducible after patients have progressed during T-DXd?**
  - **Future Role for T-Dxd? First Line? (Destiny-Breast09) Other settings?**
  - **New combos with Tucatinib are under development**

Selected Ongoing Trials with Tucatinib

HER2CLIMB-02: A Randomized Phase 3 Trial of Tucatinib Plus T-DM1 vs T-DM1

Key eligibility criteria

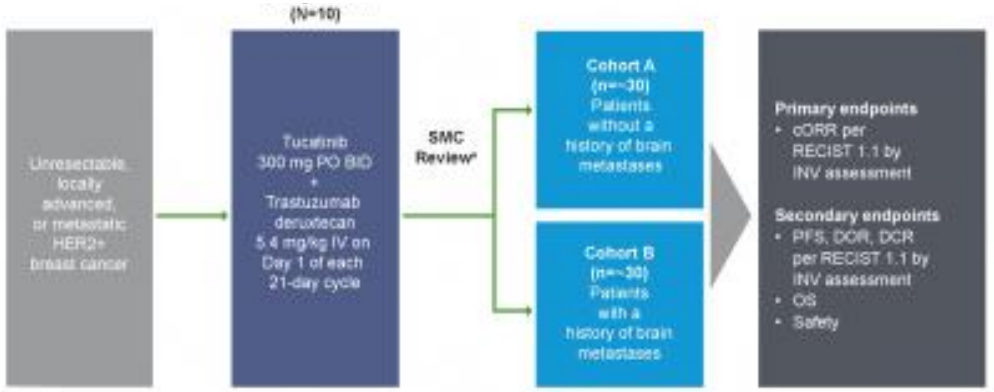
- HER2-positive mBC
- Prior trastuzumab and taxane (pertuzumab permitted)
- Patients with or without brain metastases

Randomized 1:1
n = 460

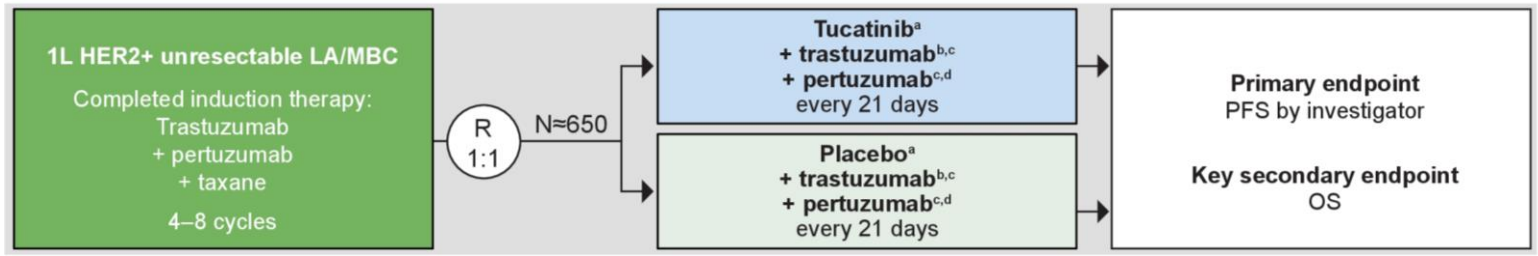
- Tucatinib (300 mg orally twice a day) + T-DM1 (3.6 mg/kg IV once every 3 weeks)
- Placebo (orally twice a day) + T-DM1 (3.6 mg/kg IV once every 3 weeks)

HER2CLIMB-04 - A Study of Tucatinib Plus Trastuzumab Deruxtecan in HER2+ Breast Cancer

Primary end point: PFS



- HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib or placebo in combination with trastuzumab plus pertuzumab as maintenance therapy in the 1L setting for patients with unresectable LA or metastatic HER2+ breast cancer following SOC induction therapy



NCT03501979

A Phase II Non-randomized Study to Assess the Safety and Efficacy of the Combination of Tucatinib and Trastuzumab and Capecitabine for Treatment of Leptomeningeal Metastases in HER2 Positive Breast Cancer

Thank you for your attention