Penn Medicine
Abramson Cancer Center

First Annual Review of Breast Cancer Highlights
from 2020 International Oncology Meeting

Updates on HER2 positive breast cancer

Hayley M. Knollman, MD

July 16, 2020

- Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.

- I have no disclosures

Outline

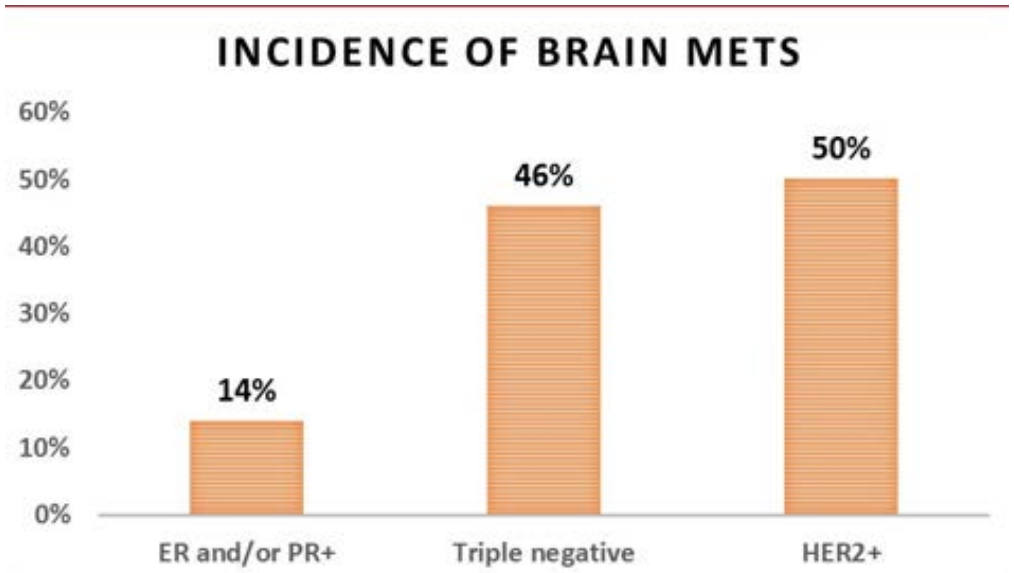
- HER2-CLIMB
- TRAIN-2

HER2-CLIMB

Abstract 1005: Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB).

Background

- Breast cancer has 2nd highest incidence of brain metastases among all cancers
- Risk and incidence of brain metastases varies depending on subtype
- Brain is frequently the first site of relapse in HER2 breast cancer patients treated with trastuzumab, whether given in adjuvant or metastatic setting
- Outcomes for patients with brain metastases remain poor
  - More treatment options needed
- Tucatinib is an oral TKI (recently FDA approved) that is highly selective for kinase domain of HER2 with minimal inhibition of EGFR
  - Diarrhea, PPE, n/v, fatigue, stomatitis, elevated LFTs
- HER2CLIMB first randomized trial to include patients with:
  - Untreated brain mets
  - Progressive brain mets post-local treatment



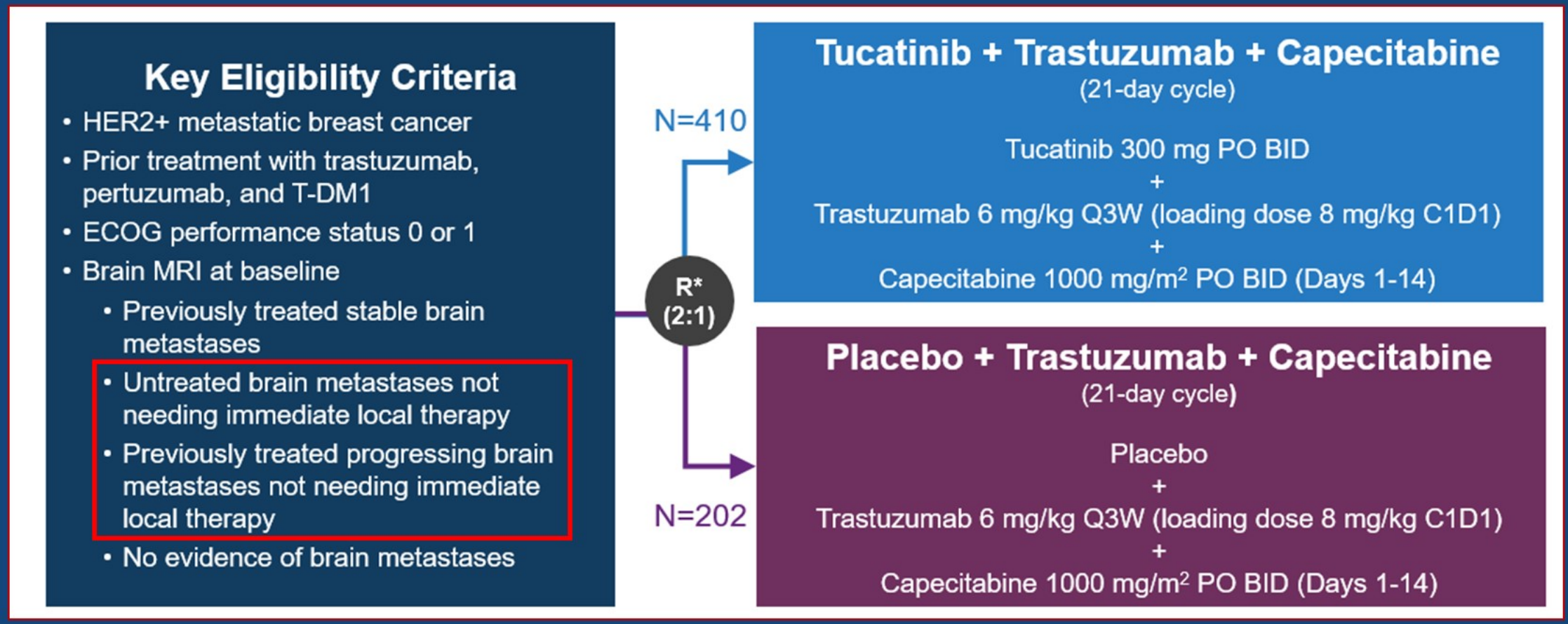
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

HER2CLIMB Trial design



RK Murthy et al SABCS 2019

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*	Overall Survival N=612	PFS by BICR in patients with brain metastases N=291
Risk of progression or death was reduced by **46%**	Risk of death was reduced by **34%**	Risk of progression or death was reduced by **52%**
95% CI: 0.42 to 0.71, P<0.001	95% CI, 0.50 to 0.88, P=0.005	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.

PRESENTED BY: Nancy Lin, nlin@partners.org

Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Previously Treated HER2+ Metastatic Breast Cancer with Brain Metastases (HER2CLIMB)

Nancy U. Lin, Rashmi K. Murthy, Carey Anders, Virginia Borges, Sara Hurvitz, Sherene Loi, Vandana Abramson, Philippe L. Bedard, Mafalda Oliveira, Amelia Zelnak, Michael DiGiovanna, Thomas Bachelot, A. Jo Chien, Ruth O'Regan, Andrew Wardley, Volkmar Mueller, Lisa Carey, Suzanne McGoldrick, Grace An, Eric P. Winer

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

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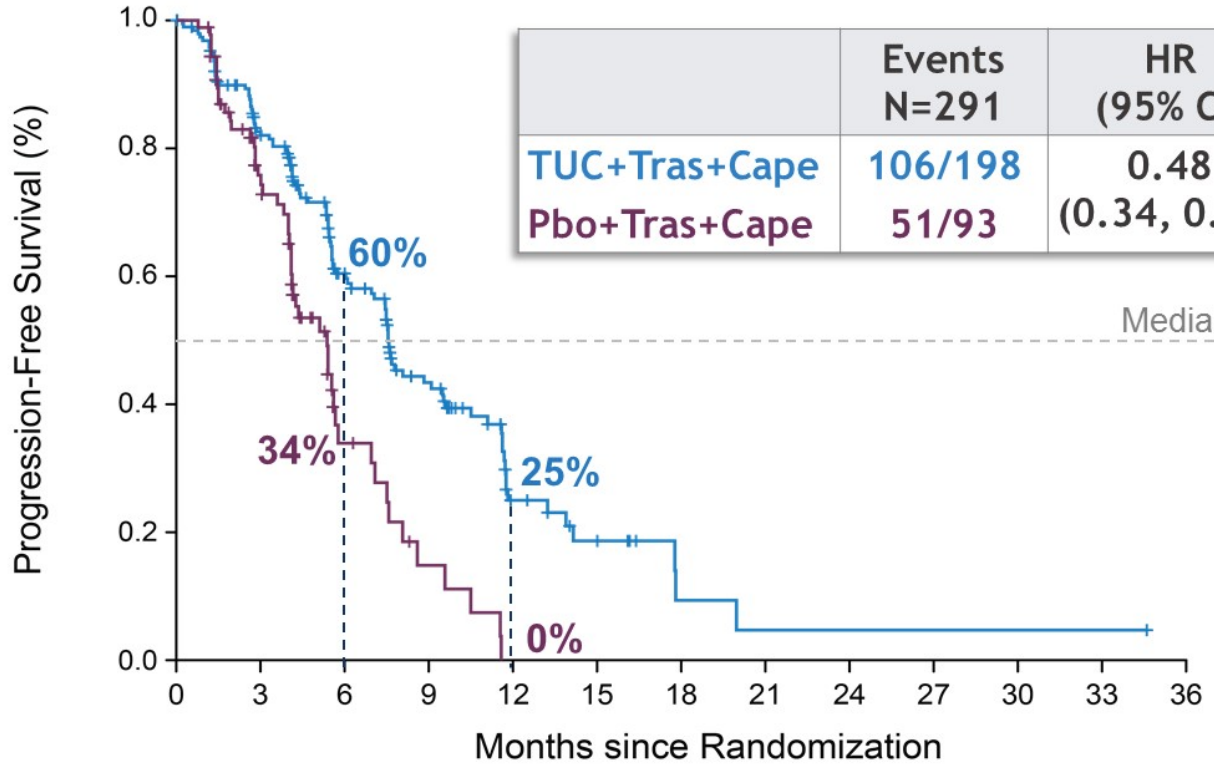
Progression-Free Survival* in Patients with Brain Metastases

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		

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 blinded independent central review) or death from any cause. Analysis does not include patients with dural lesions only.

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):

TUC+Tras+Cape	Pbo+Tras+Cape
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

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

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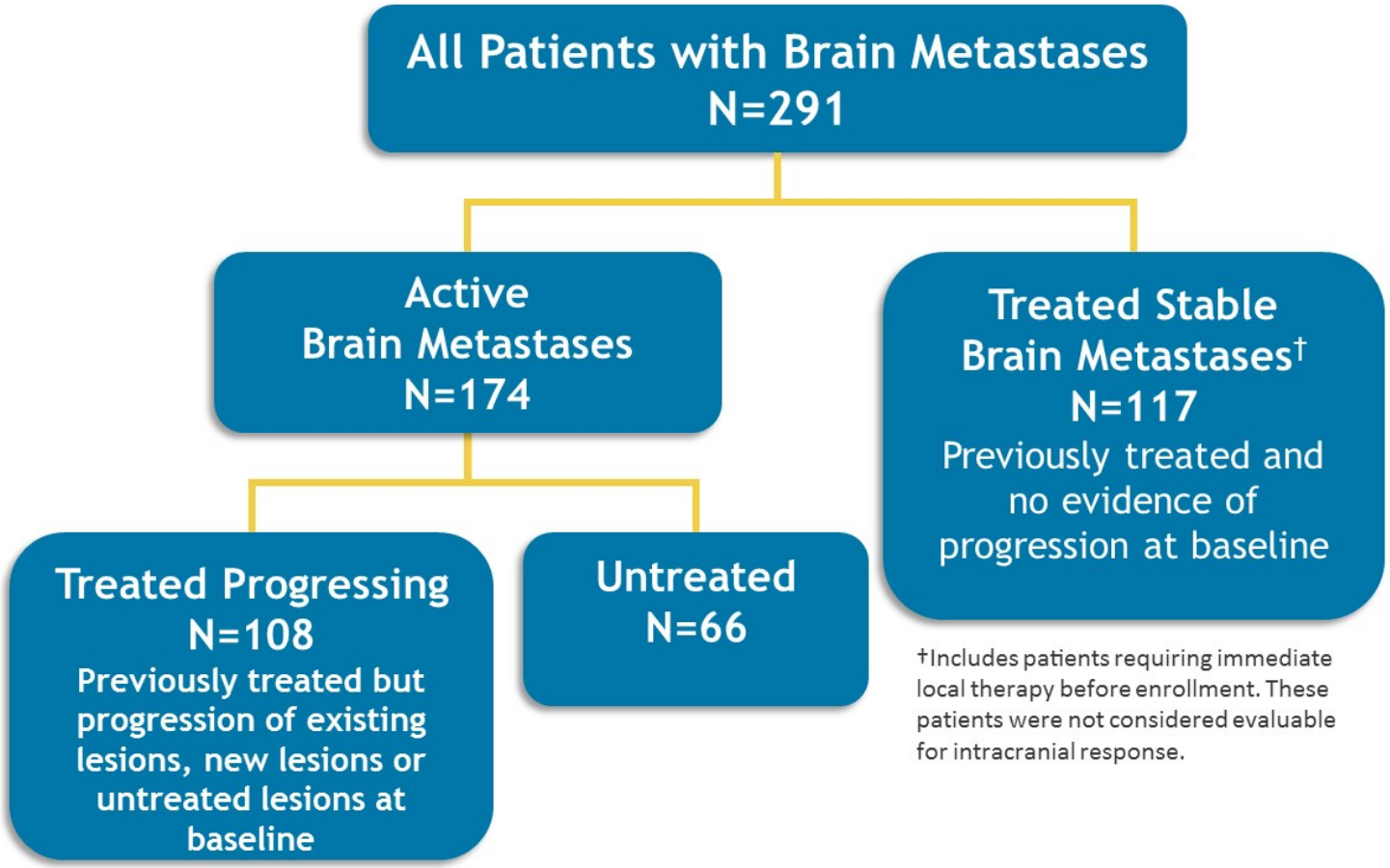
HER2CLIMB Analysis of Patients with Brain Metastases

- 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.

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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)

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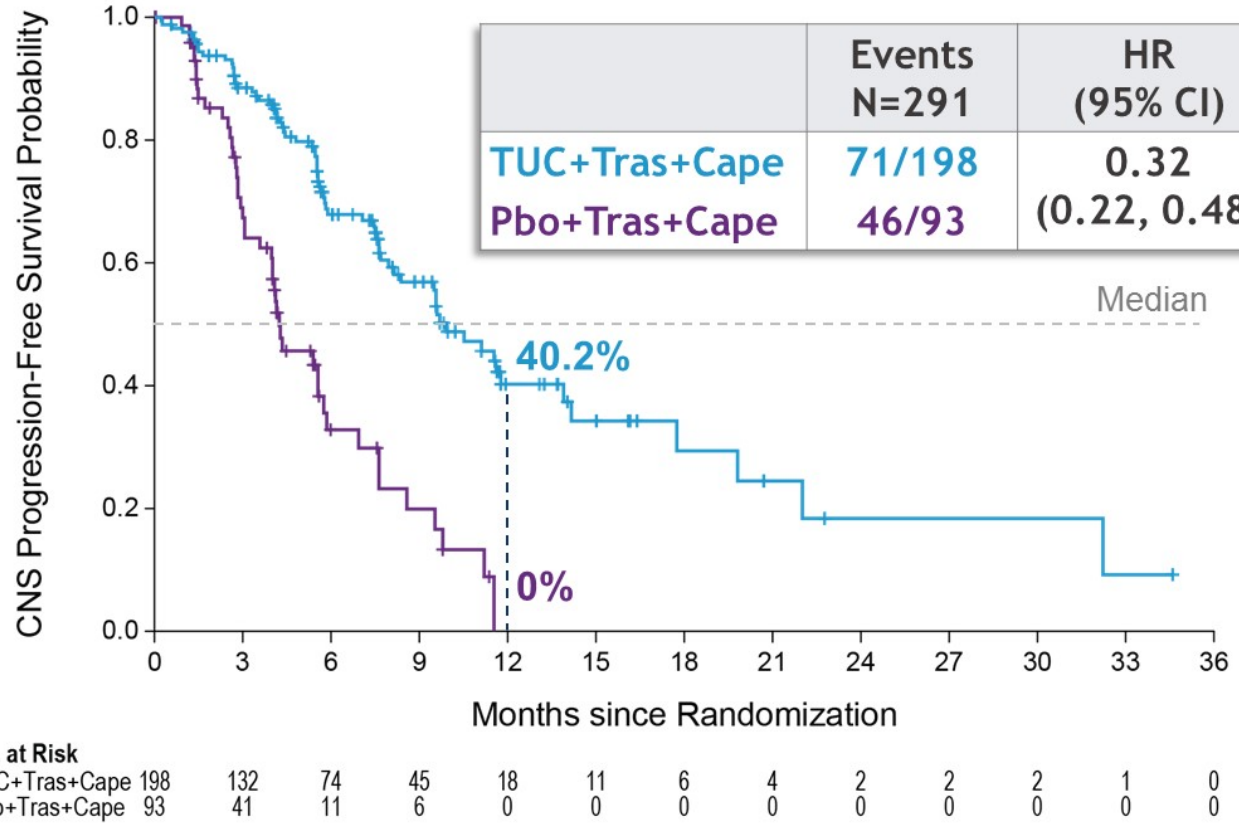
CNS-PFS Benefit in Patients with Brain Metastases



	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 40.2% (29.5, 50.6)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
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.

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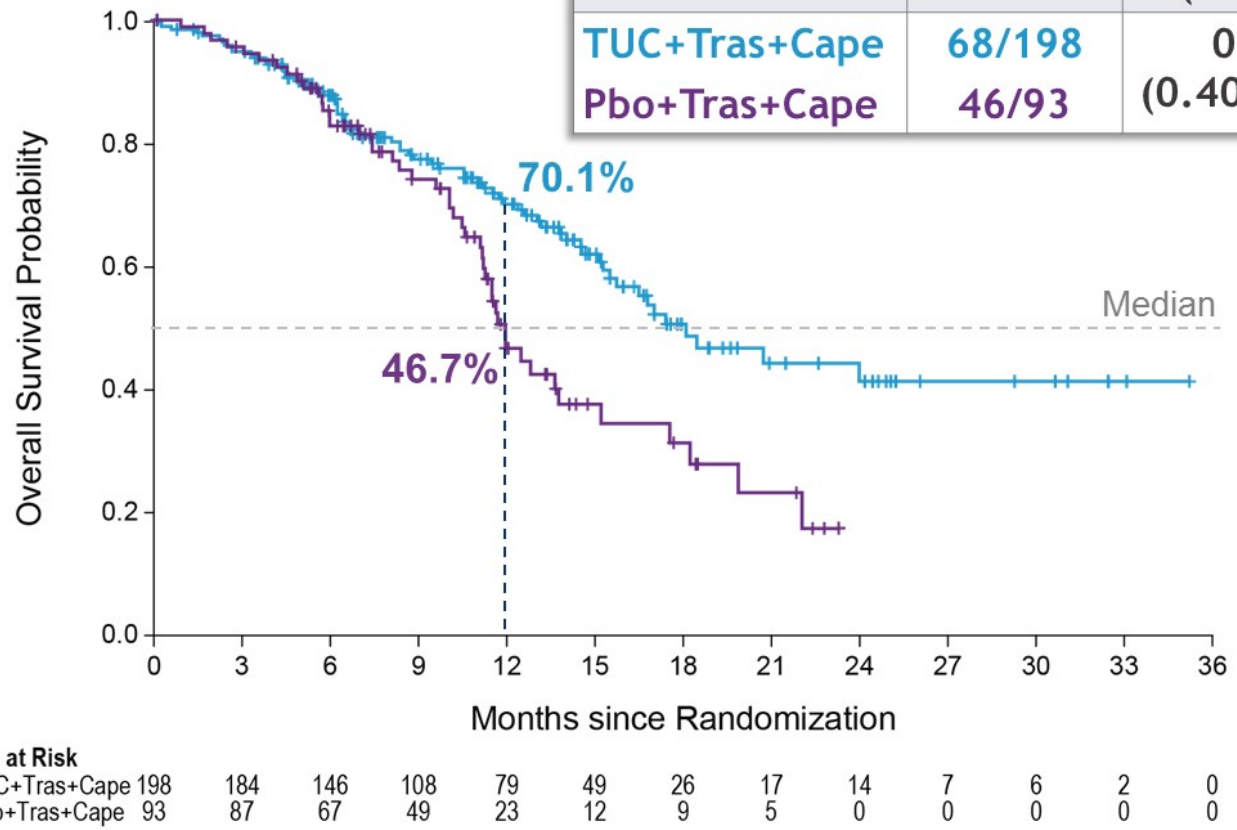
OS Benefit in Patients with Brain Metastases

	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	Pbo+Tras+Cape
70.1% (62.1, 76.7)	46.7% (33.9, 58.4)

Median OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
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.

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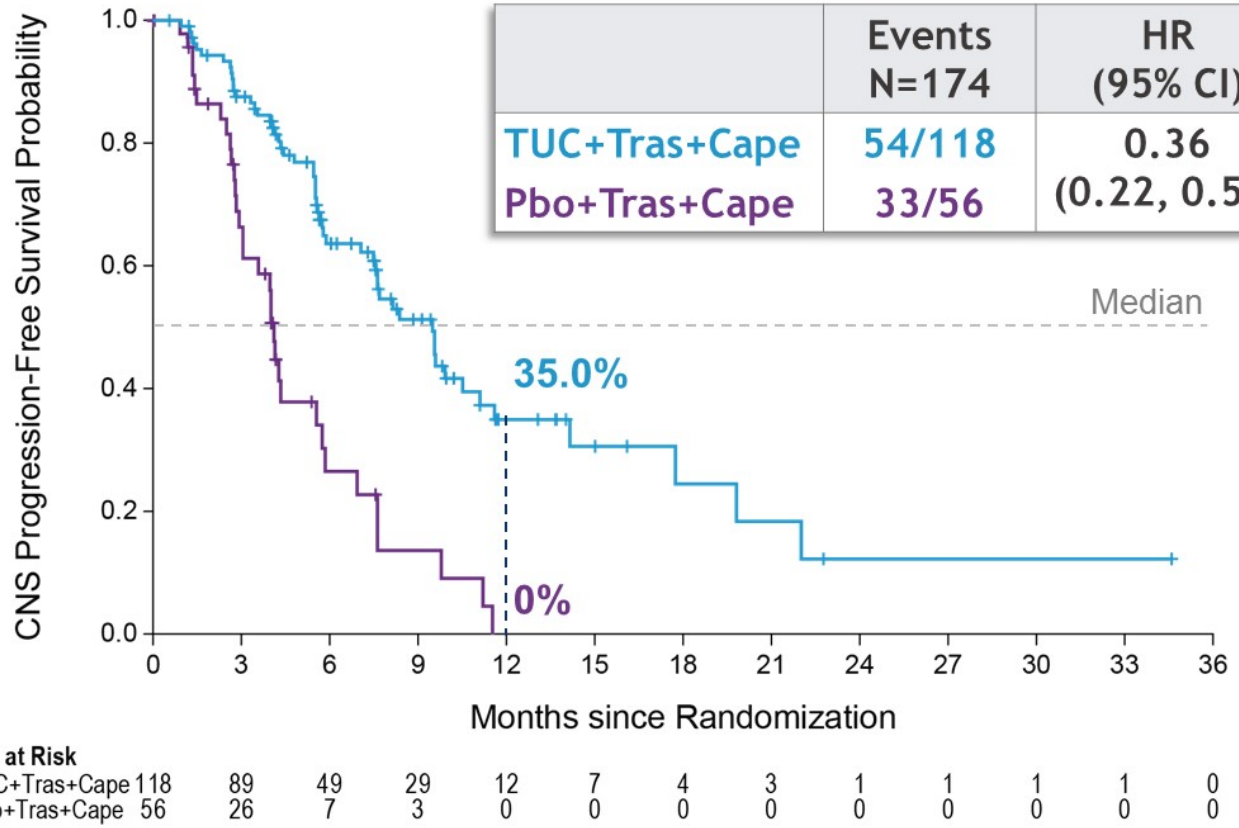
CNS-PFS Benefit in Patients with Active Brain Metastases



	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):	
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.

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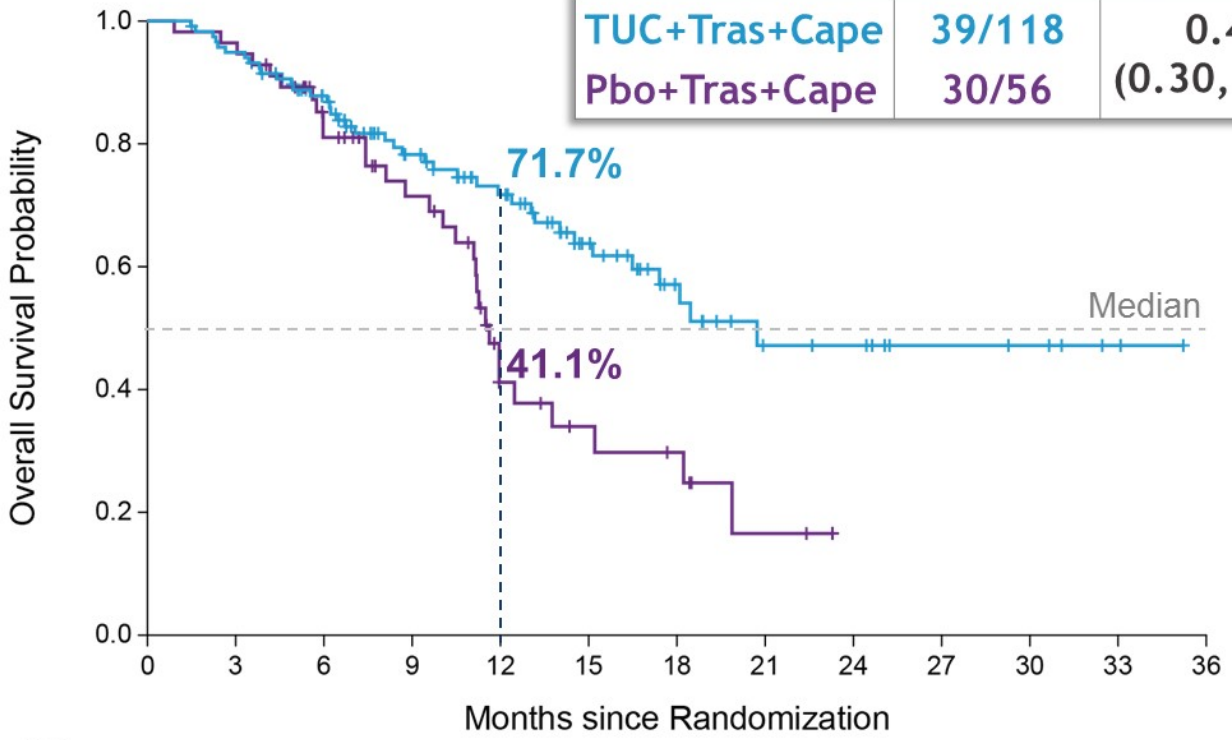
OS Benefit in Patients with Active Brain Metastases

	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):	
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.

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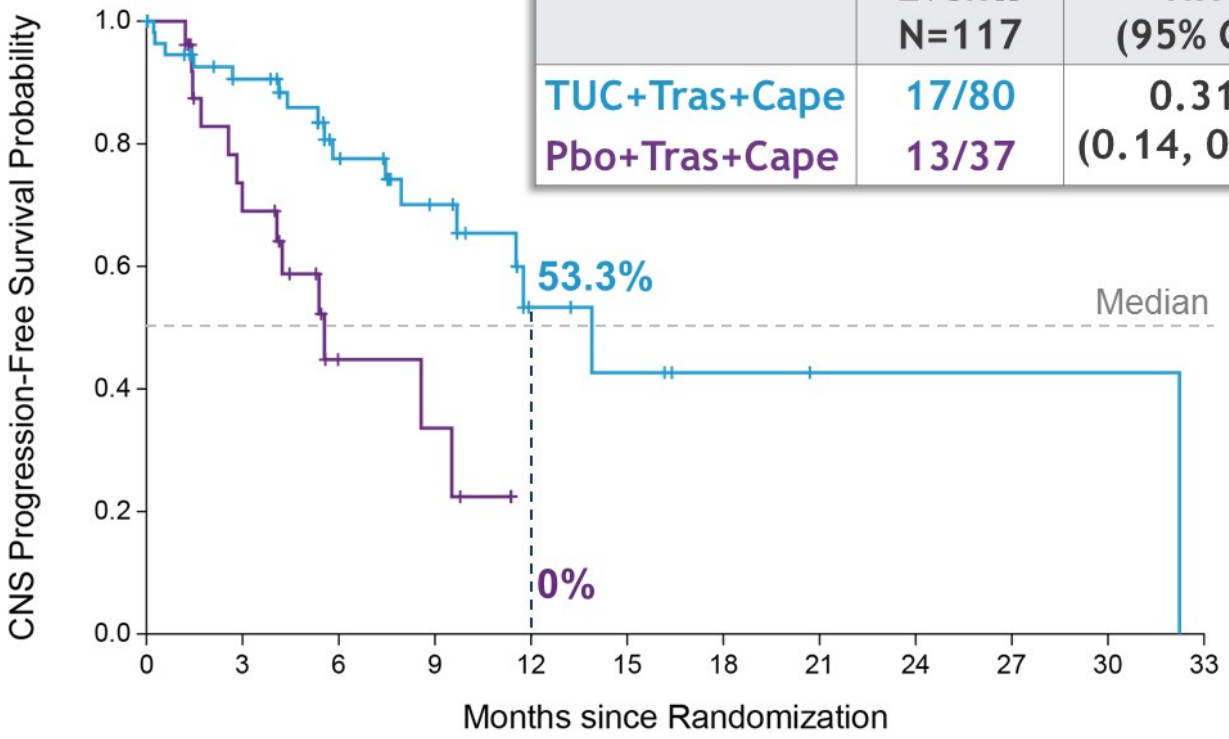
CNS-PFS Benefit in Patients with Stable Brain Metastases



	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 53.3% (31.4, 71.0)	Pbo+Tras+Cape 0%
Median CNS-PFS (95% CI):	
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.

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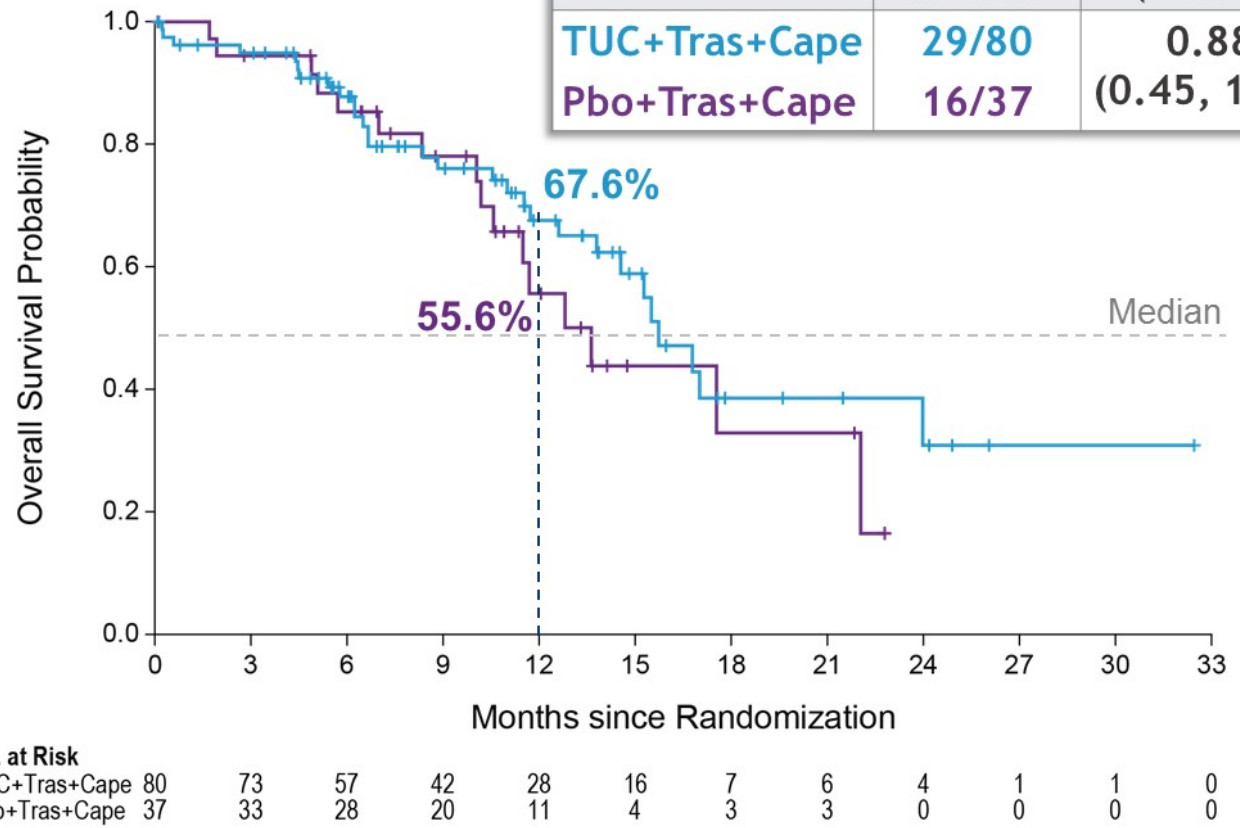
OS in Patients with Stable Brain Metastases

	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.

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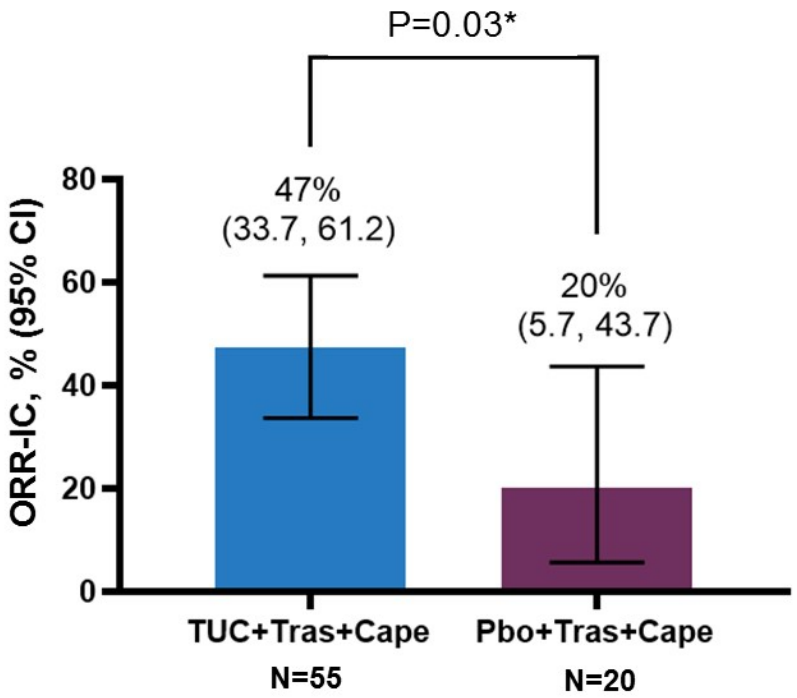
Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

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).

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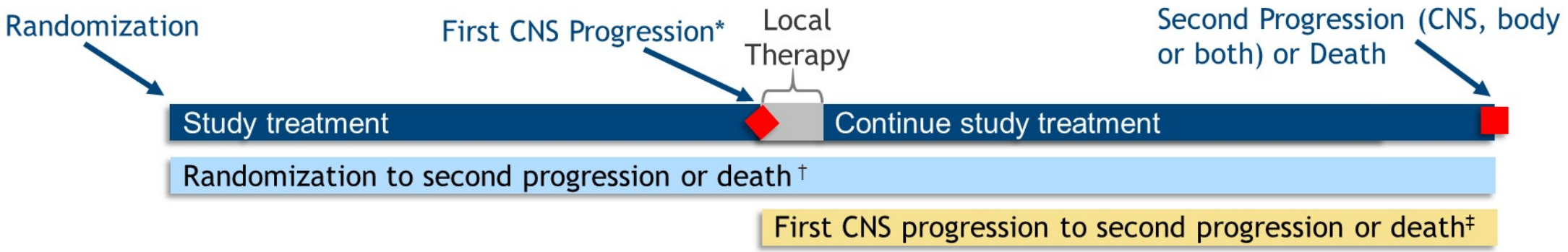
PFS in Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



	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.

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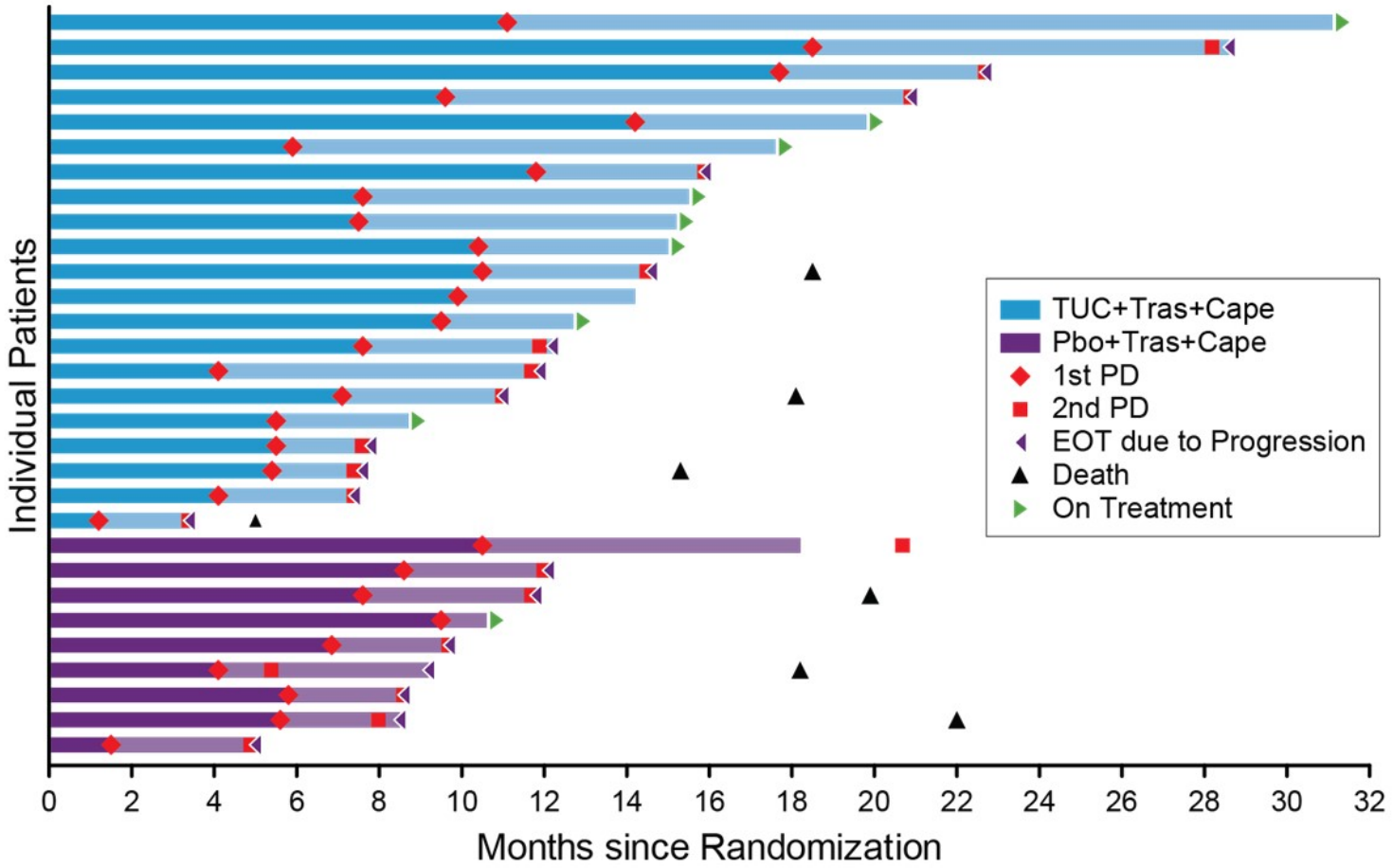
Duration on Treatment for Patients with Isolated Progression in the Brain Who Continued with Assigned Study Treatment



PD: progressive disease; EOT: end of treatment

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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 the 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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Journal of Clinical Oncology®

rapid communications

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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Thoughts/Future directions

- Timing of drugs with CNS activity
  - Use earlier to prevent development of mets?
- More study of tucatinib after first CNS progression
- Future trials should have broader eligibility criteria to ensure real-world population derive benefit
  - Patients with brain metastases is unmet need
- Leptomeningeal disease

TRAIN-2

Abstract 501: Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2-positive breast cancer (TRAIN-2): A randomized phase III trial.

Background

- Optimal chemotherapy backbone for dual HER2-blockade in neoadjuvant setting for early stage breast cancer is unknown
- Overlap of cardiotoxicity with trastuzumab and anthracyclines
  - Anthracycline-free regimens have been assessed
  - HOWEVER - Trials directly comparing anthracycline-containing regimens & anthracycline-free regimens are rare
- Role of anthracyclines in era of dual HER2 blockade is unknown
- TRAIN study – single arm, neoadjuvant
  - Weekly paclitaxel, trastuzumab, carboplatin
  - 43% of 108 patients achieved pathCR
  - <5% febrile neutropenia, and no LV dysfunction
- TRAIN-2:
  - Multicenter (Netherlands), phase III
  - Designed to directly compare efficacy & safety of anthracycline-containing chemo regimen (FEC x 3 → paclitaxel, carboplatin, trastuzumab x 6) with anthracycline-free chemo regimen of same duration (paclitaxel, carboplatin, trastuzumab x 9 cycles) in combination with HP in both groups

van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630-1640. doi:10.1016/S1470-2045(18)30570-9

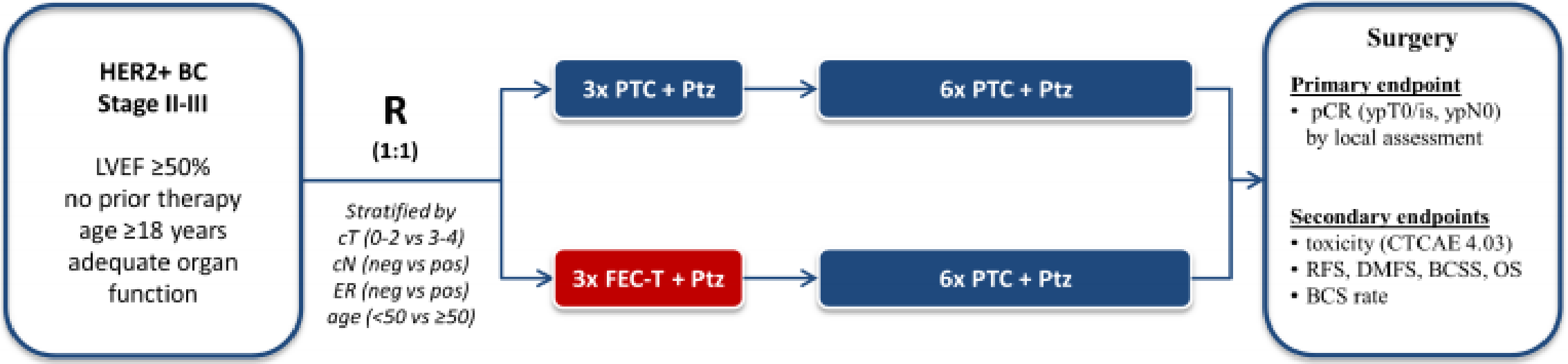
THE LANCET
Oncology
Volume 19, Issue 12, December 2018, Pages 1630-1640

Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, Ingrid A Mandjes, Inge Kemper, Vincent O Dezentjé, Irma M Oving, Aafke H Honkoop, Lidwine W Tick, Agnes J van de Wouw, Caroline M Mandigers, Laurence J van Warmerdam, Jelle Wesseling, Marie-Jeanne T Vrancken Peeters, Sabine C Linn, Gabe S Sonke, on behalf of the Dutch Breast Cancer Research Group (BOOG)

van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630-1640. doi:10.1016/S1470-2045(18)30570-9

Supplementary figure 1. **Study design**



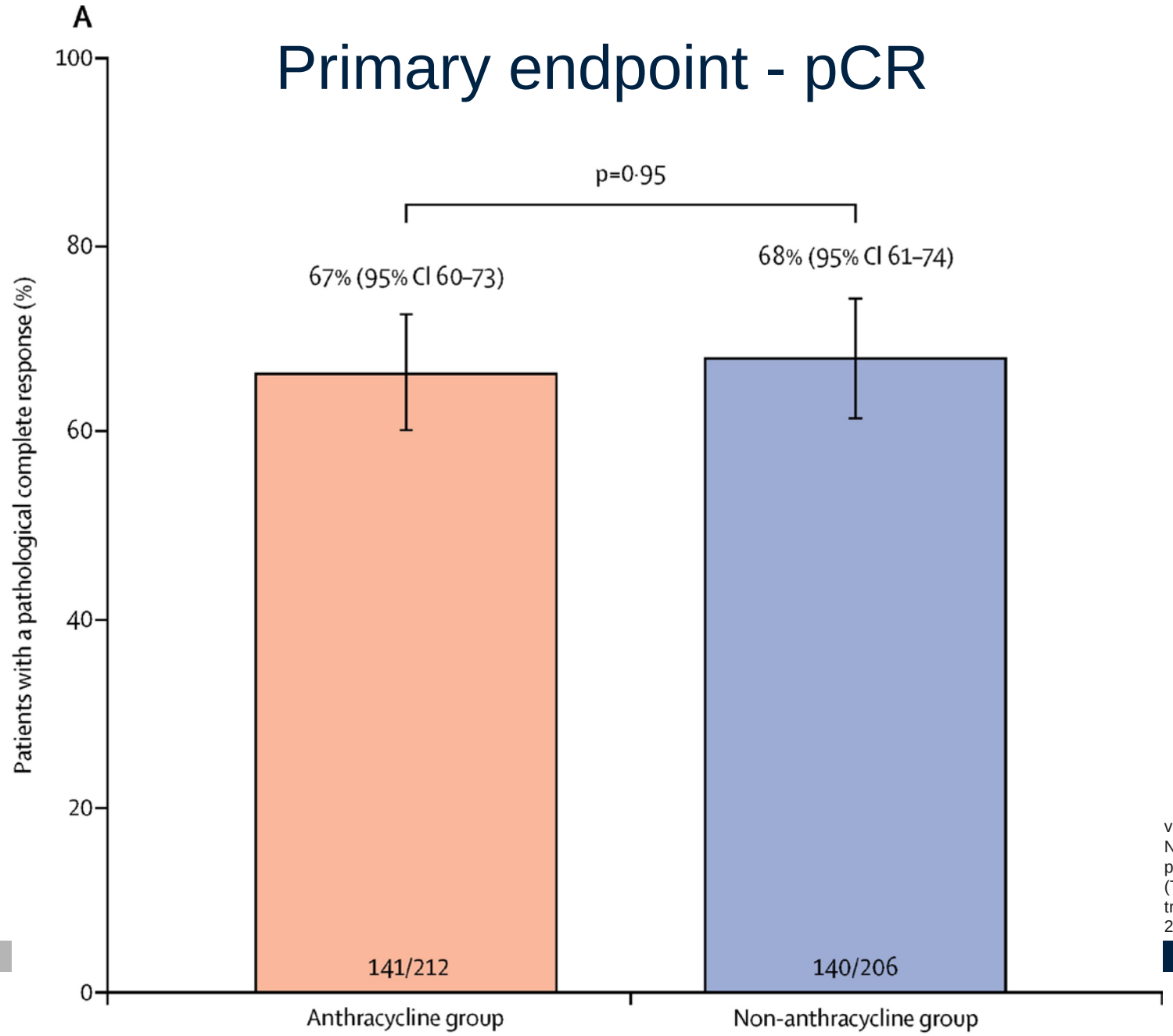
Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumours

PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m^2; T = trastuzumab 6mg/kg (loading dose 8mg/kg);
C = carboplatin AUC = 6mg·min/ml (alternatively, AUC=3mg·min/ml day 1 and day 8); Ptz = pertuzumab, 420mg (loading dose 840mg)

FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m^2; E = epirubicin 90mg/m^2; C = cyclophosphamide 500mg/m^2;
T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)

van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(12):1630-1640. doi:10.1016/S1470-2045(18)30570-9

Primary endpoint - pCR



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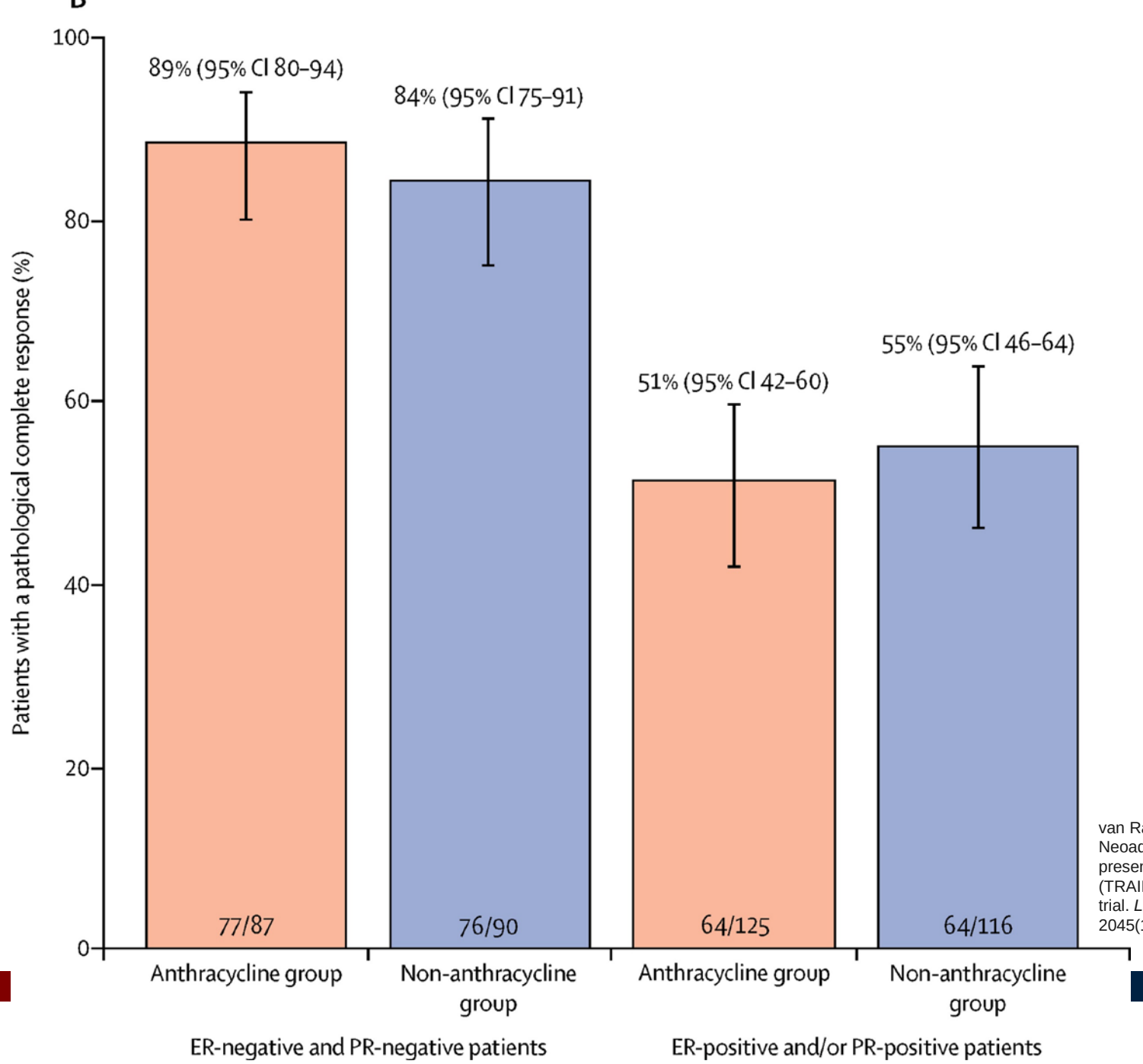

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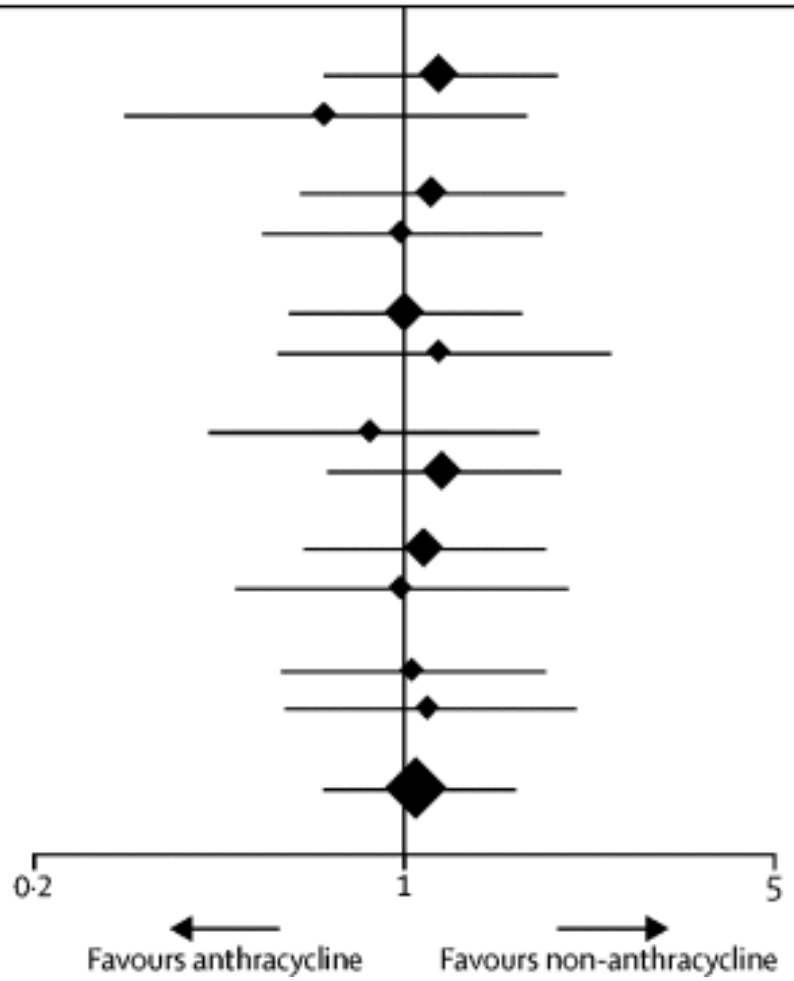
	Anthracycline group (n=212)	Non-anthracycline group (n=206)	Odds ratio (95% CI)
Hormone receptor status			
ER-positive and/or PR-positive	64/125 (51%)	64/116 (55%)	1·17 (0·71–1·95)
ER-negative and PR-negative	77/87 (89%)	76/90 (84%)	0·71 (0·30–1·68)
Age			
<50 years	79/116 (68%)	78/110 (71%)	1·14 (0·65–2·01)
≥50 years	62/96 (65%)	62/96 (65%)	1·00 (0·55–1·81)
Tumour stage			
0–2	96/141 (68%)	99/145 (68%)	1·01 (0·61–1·66)
3–4	45/71 (63%)	41/61 (67%)	1·18 (0·58–2·43)
Node status			
Negative	59/79 (75%)	54/75 (72%)	0·87 (0·43–1·78)
Positive	82/133 (62%)	86/131 (66%)	1·19 (0·72–1·96)
Disease stage			
II	89/133 (67%)	98/142 (69%)	1·10 (0·66–1·83)
III	52/79 (66%)	42/64 (66%)	0·99 (0·49–1·99)
Tumour grade			
1–2	65/102 (64%)	66/102 (65%)	1·04 (0·59–1·85)
3	68/98 (69%)	66/72 (72%)	1·12 (0·60–2·09)
All patients	**141/212 (67%)**	**140/206 (68%)**	**1·07 (0·71–1·61)**



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TRAIN-2 – 3 year follow up

- 438 patient (219/arm) were randomized and evaluable for long-term efficacy
- Median follow up of 48.8 months
- 23 EFS (event-free survival) events in FECT-PTC-PTz-arm (anthracycline-containing) vs. 21 in PTC-Ptz-arm (HR 0.90; 95% CI 0.5 – 1.63)
- 3 year EFS estimates were 92.7% (anthracyline-containing arm) vs. 93.6%
- 3 year OS estimates were 97.7% (anthracyline-containing arm) vs. 98.2%
  - Results irrespective of hormone receptor & nodal status
- LVEF decline >10% and <50% more common in anthracyline-containing arm (8.6 vs. 3.2%).
- Two patients in anthracyline-containing arm developed acute leukemia
- No other new safety concerns seen

Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2-positive breast cancer (TRAIN-2): A randomized phase III trial. Anna van der Voort, Mette S. van Ramshorst, Erik D. van Werkhoven, Ingrid A. Mandjes, Inge Kemper, Annelie J. Vulink, Irma M. Oving, Aafke H. Honkoop, Lidwine W. Tick, Agnes J. van de Wouw, Caroline M. Mandigers, Laurence J. C. van Warmerdam, Jelle Wesseling, Marie-Jeanne T.F.D Vrancken Peeters, Sabine C. Linn, Gabe S. Sonke, and on behalf of the Dutch Breast Cancer Group (BOOG). Journal of Clinical Oncology 2020 38:15_suppl, 501-501

TRAIN-2 – 3 year follow up

- Conclusions:

3 year follow up confirms results of primary outcome that anthracyclines do not improve efficacy and are associated with clinically relevant toxicity

A neoadjuvant carboplatin-taxane-based regimen with dual HER2-blockade can be considered in all stage II-III patients with breast cancer, regardless of hormone receptor & nodal status

Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2-positive breast cancer (TRAIN-2): A randomized phase III trial. Anna van der Voort, Mette S. van Ramshorst, Erik D. van Werkhoven, Ingrid A. Mandjes, Inge Kemper, Annelie J. Vulink, Irma M. Oving, Aafke H. Honkoop, Lidwine W. Tick, Agnes J. van de Wouw, Caroline M. Mandigers, Laurence J. C. van Warmerdam, Jelle Wesseling, Marie-Jeanne T.F.D Vrancken Peeters, Sabine C. Linn, Gabe S. Sonke, and on behalf of the Dutch Breast Cancer Group (BOOG). Journal of Clinical Oncology 2020 38:15_suppl, 501-501


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