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Fortschritte in der Behandlung des HER2-positiven metastasierten Mammakarzinoms mit Tucatinib

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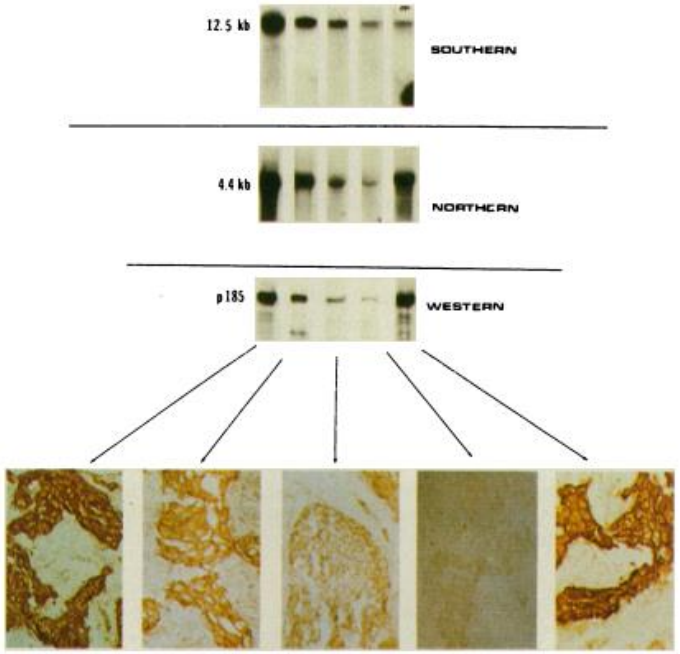
Conflict of Interest (COI)

- Forschungsunterstützung:
  - AstraZeneca, BioNTech, Eisai, Genentech, Myelo Therapeutics, Novartis, Pantarhei Bioscience, Pfizer, Pierre-Fabre, Roche
- Vortragsstätigkeit:
  - AstraZeneca, Eisai, Novartis, Pfizer, Roche, SeaGen
- Beratertätigkeit:
  - AstraZeneca, Celgene, Eisai, Lilly, Myelo Therapeutics, Novartis, Pantarhei Bioscience, Pfizer, Pierre-Fabre, Roche, SeaGen

HER-2 alias c-erbB-2



Southern

Northern

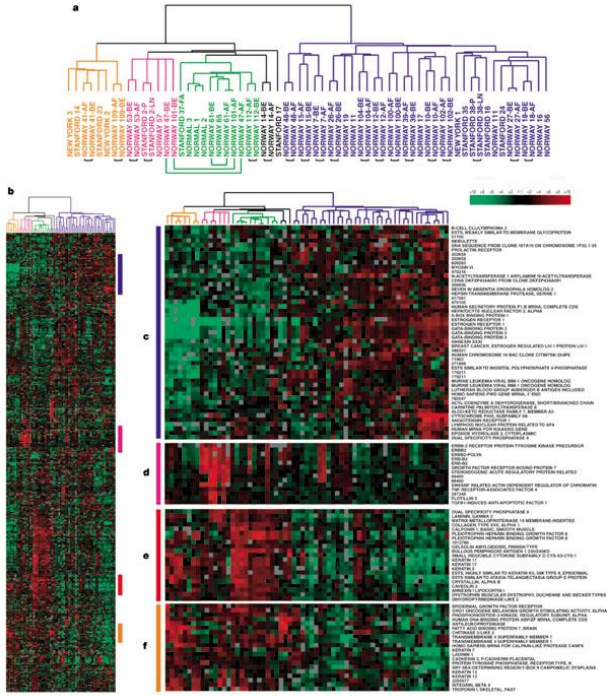
Western

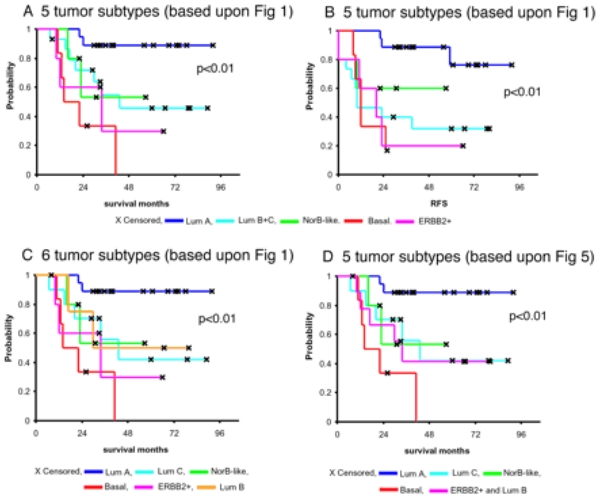
IHC

Slamon et al, Science 235: 177-182, 1987; Science 244: 707-712, 1989

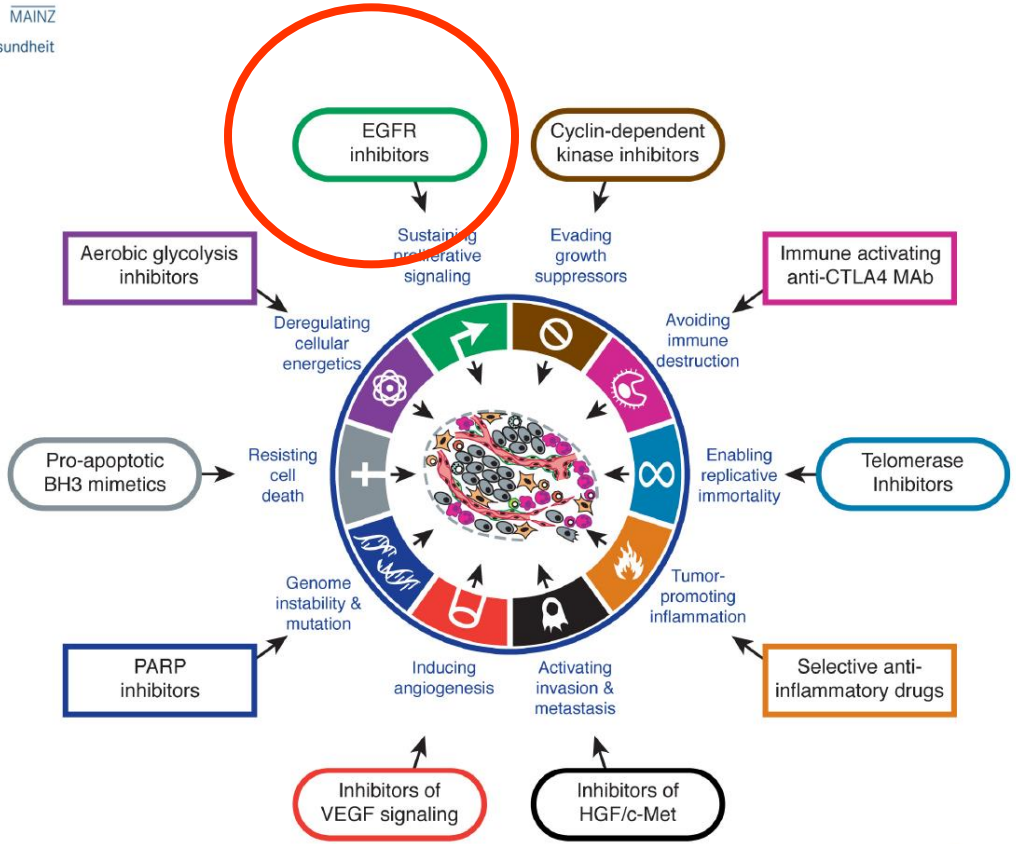
Molecular Portraits

-Basal-like
-Erb-B2
-Normal breast-like
-Luminal / ER+





Perou et al, Nature 406: 747-752, 2000
Sorlie et al, PNAS 98: 10869-10874, 2001



Hanahan and Weinberg, 2011

Cell PRESS

Hanahan & Weinberg, Cell 144: 646-674 , 2011

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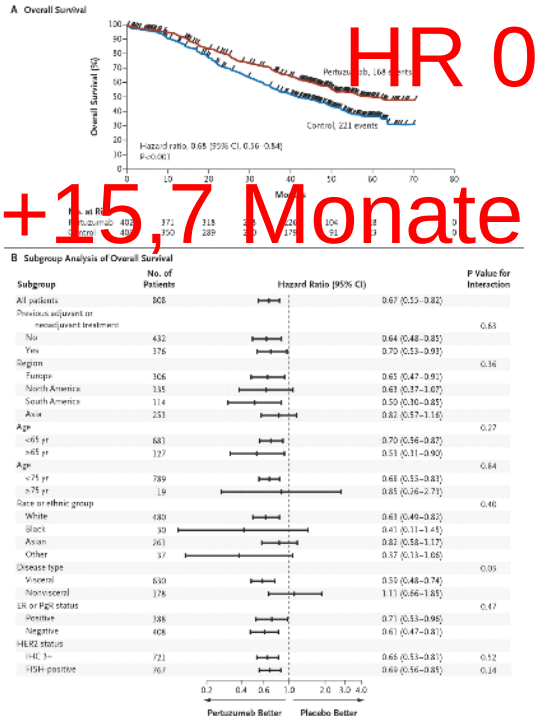
Therapiestandards HER2+ 2020?

CLEOPATRA – Pertuzumab / Trastuzumab



HR 0,68

+15,7 Monate

Swain et al, N Engl J Med 372:724-734, 2015

Erstlinientherapie beim HER2-pos. metastasierten Mammakarzinom

Guidelines Breast
Version 2020.1D

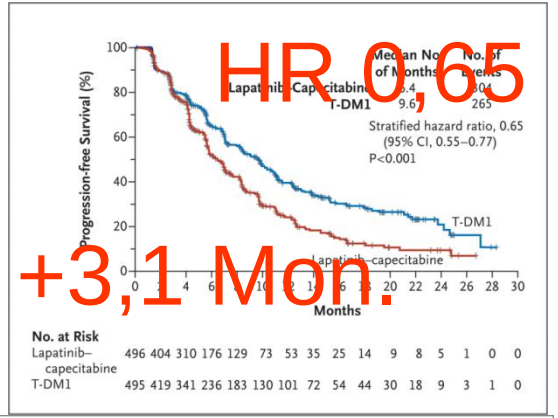
	Oxford		
	LoE	GR	AGO
▪ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
▪ Paclitaxel (weekly) + Trastuzumab + Pertuzumab	2b	B	++
▪ nab-Paclitaxel + Trastuzumab + Pertuzumab	3b[a]	C	+
▪ Vinorelbin + Trastuzumab + Pertuzumab	3b	B	+
▪ T-DM 1 (Rückfall innerhalb von 6 Monaten und nach Taxan und Trastuzumab)	2b	B	+
▪ 1st line Chemotherapie* + Trastuzumab	1b	B	+
▪ Trastuzumab mono	2b	B	+/-
▪ Taxan + Lapatinib	1b	B	+/-
▪ Taxan + Trastuzumab + Everolimus	1b	B	-
▪ Trastuzumab + Aromatase-Inhibitoren (ER+)	2b	B	+/-**
▪ Lapatinib + Aromatase-Inhibitoren (ER+)	2b	B	+/-**

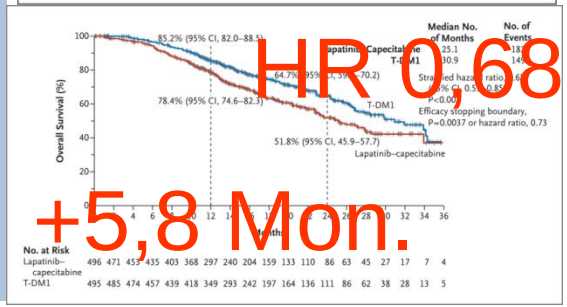
* Taxane; Vinorelbine; Paclitaxel/Carboplatin; Capecitabine/Docetaxel,

** siehe Kapitel „Endokrine +/- targeted Therapie“

EMILIA – T-DM1

- HER2+ nach Trastuzumab (n=991)
  - **T-DM1 vs. Lapatinib / Capecitabine**
- PFS
  - **9,6 vs. 6,4 Monate; HR 0,65**
- OS
  - **30,9 vs. 25,1 Monate; HR 0,68**
- Grad 3/4 Toxizitäten
  - 41 vs. 57%

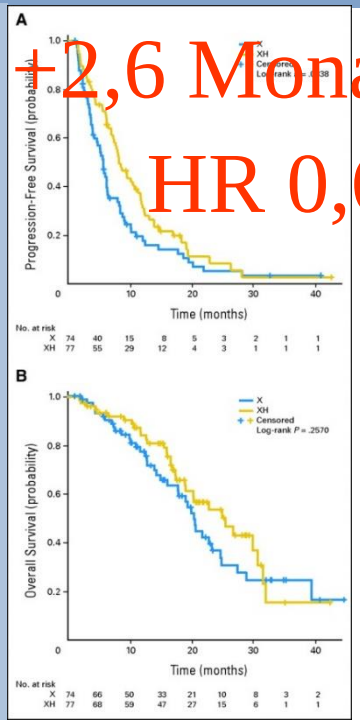




Verma et al, N Engl J Med 367:1783-1791, 2012

Treatment beyond progression

- HER2+ progredient unter Trastuzumab (n=156)
  - Capecitabine +/- Trastuzumab
- PFS: 5,6 vs. 8,2 Monate; HR 0,66
- OS: 20,4 vs. 25,5 Monate; HR 0,76 n.s.



+2,6 Monate

HR 0,66

von Minckwitz, J Clin Oncol 27:1999-2006, 2009

2nd line Therapie bei HER2-pos. mBC (nach Vorbehandlung mit Trastuzumab)

Guidelines Breast
Version 2020.1D

	Oxford LoE	Oxford GR	Oxford AGO
▪ T-DM 1	1b	A	++
▪ TBP: 2nd line Chemotherapie + Trastuzumab	2b	B	+
▪ BP: 2nd line Chemotherapie + Trastuzumab + Pertuzumab	5	D	+/-
▪ 2nd line Chemotherapie* + Trastuzumab + Pertuzumab (falls noch nicht gegeben)	5	D	+/-
▪ Taxane + Trastuzumab + Pertuzumab	5	D	+
▪ Capecitabin + Trastuzumab + Pertuzumab	1b[a]	B	+/-
▪ Capecitabin + Lapatinib	1b	B	+
▪ Trastuzumab + Lapatinib (HR neg. tumor)	2b	B	+

* e.g. Vinorelbin; Taxane/Carboplatin; Capecitabin/Docetaxel (Toxizität!)

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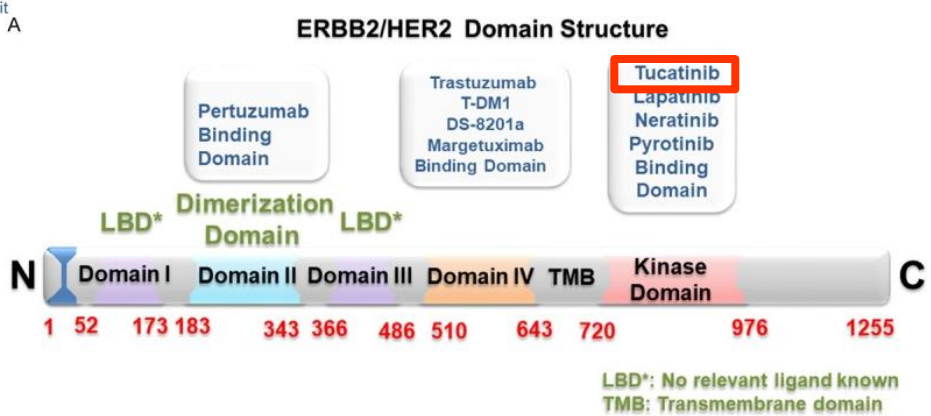
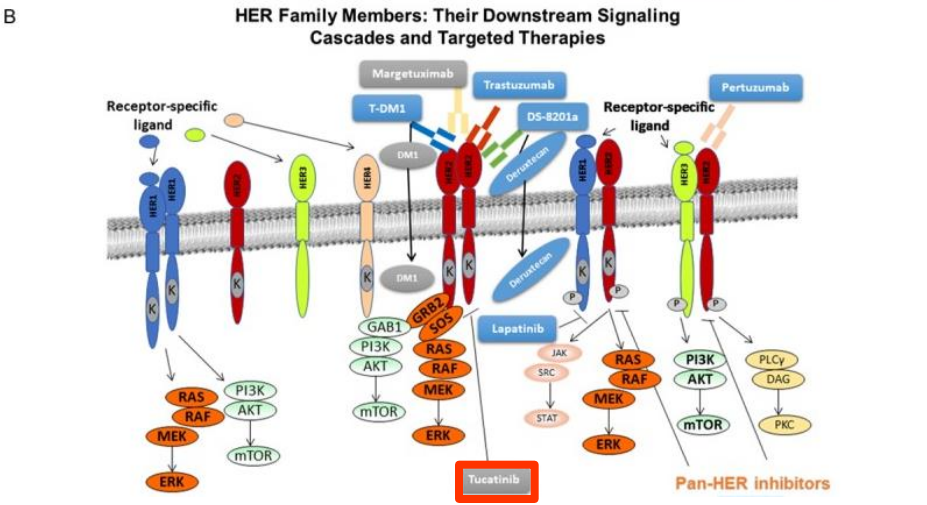
Was machen wir nach Trastuzumab / Pertuzumab und T-DM1?

A



B



Kreutzfeld et al, Am J Cancer Res . 10:1045-1067, 2020

Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Previously Treated HER2+ Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB)

Rashmi K. Murthy, MD, Sherene Loi, MD, Alicia Okines, MD, Elisavet Paplomata, MD, Erika Hamilton, MD, Sara A. Hurvitz, MD, Nancy U. Lin, MD, Virginia Borges, MD, Vandana Abramson, MD, Carey Anders, MD, Philippe L. Bedard, MD, Mafalda Oliveira, MD, Erik Jakobsen, MD, Thomas Bachelot, MD, Shlomit S. Shachar, MD, Volkmar Mueller, MD, Sofia Braga, MD, Francois P. Duhoux, MD, Richard Greil, MD, David Cameron, MD, Lisa A. Carey, MD, Giuseppe Curigliano, MD, PhD, Karen Gelmon, MD, Gabriel Hortobagyi, MD, Ian Krop, MD, PhD, Sibylle Loibl, MD, Mark Pegram, MD, Dennis Slamon, MD, Maria Corinna Palanca-Wessels, MD, PhD, Luke Walker, MD, Wentao Feng, PhD, Eric P. Winer, MD

San Antonio Breast Cancer Symposium, San Antonio, Texas. December 11, 2019. Abstract GS1-01

HER2CLIMB Trial Design

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

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

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

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

*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

Key Baseline Demographics and Disease Characteristics

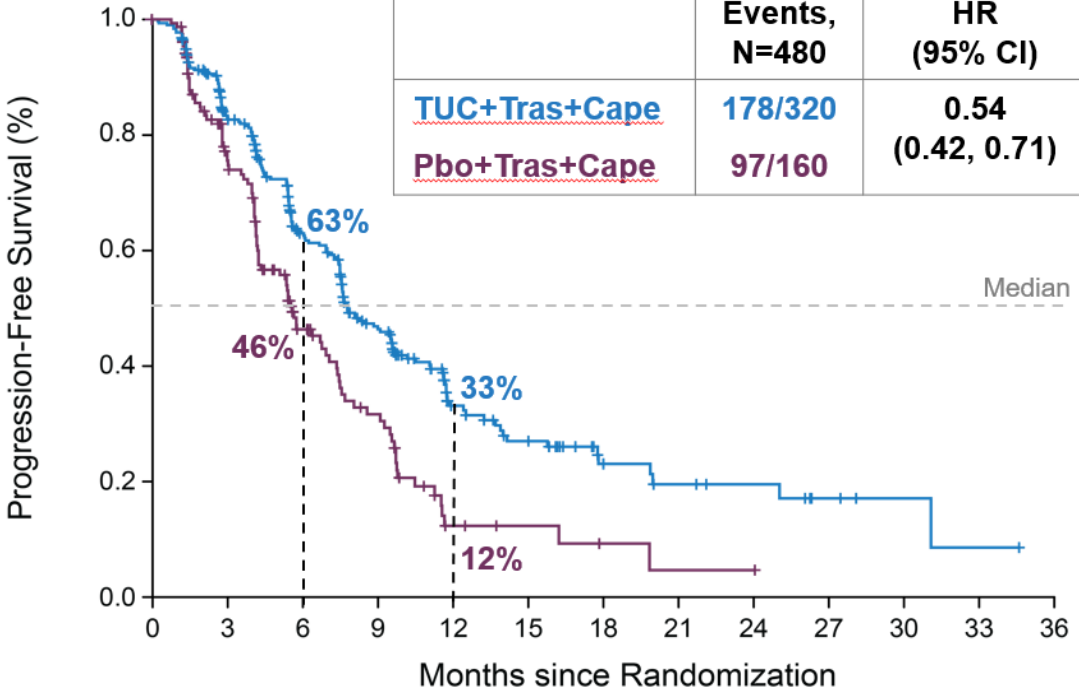
Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	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)
Presence/history of brain metastases		198 (48)	93 (46)
Treated, stable[a]		80 (40.4)	37 (39.8)
Untreated		44 (22.2)	22 (23.7)
Treated, progressing[a]		74 (37.4)	34 (36.6)

a. An error in programming logic resulted in the misclassification of some patients with treated and stable brain metastases at study entry. The numbers here have been corrected for accuracy (Murthy et al. N Engl J Med. 2020 [Supplement]).

Baseline characteristics were balanced between endpoint populations and treatment arms

Progression-Free Survival in the Primary Endpoint Population

	Events, N=480	HR (95% CI)	P Value
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		



No. at Risk

TUC+Tras+Cape	320	235	152	98	40	29	15	10	8	4	2	1	0
Pbo+Tras+Cape	160	94	45	27	6	4	2	1	1	0	0	0	0

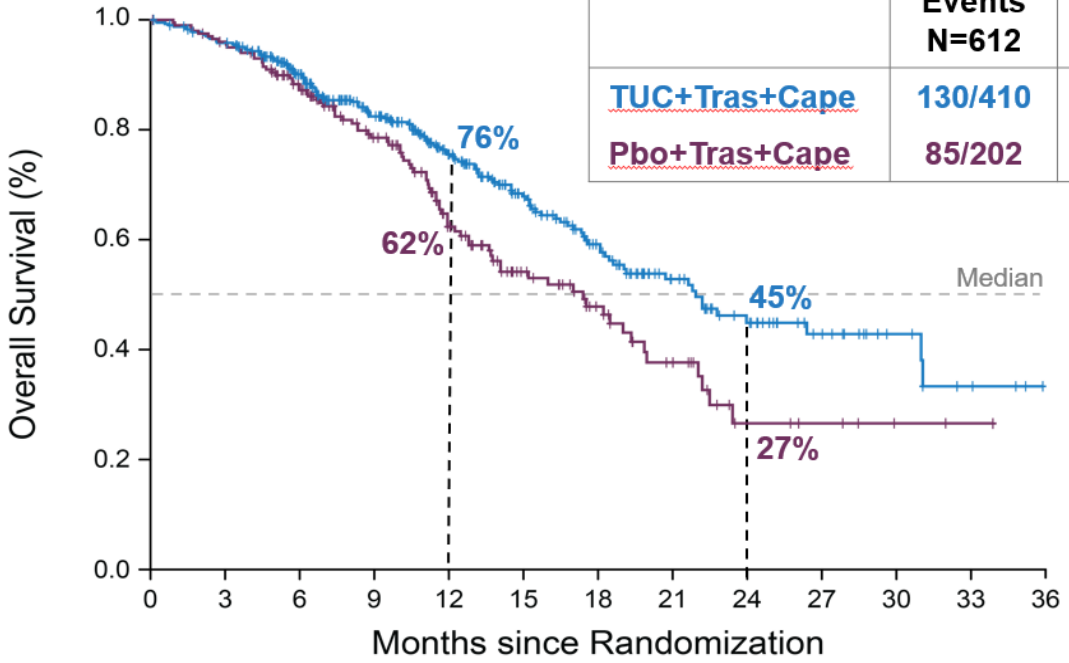
Risk of progression or death was reduced by 46% in the primary endpoint population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
33% (27, 40)	12% (6, 21)
Median PFS (95% CI):	
7.8 months (7.5, 9.6)	5.6 months (4.2, 7.1)

Prespecified efficacy boundary for PFS: P=0.05
Data cut off: Sep 4, 2019

Overall Survival in the Total Study Population

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		



No. at Risk

TUC+Tras+Cape	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo+Tras+Cape	202	191	160	119	77	48	32	19	7	5	2	1	0

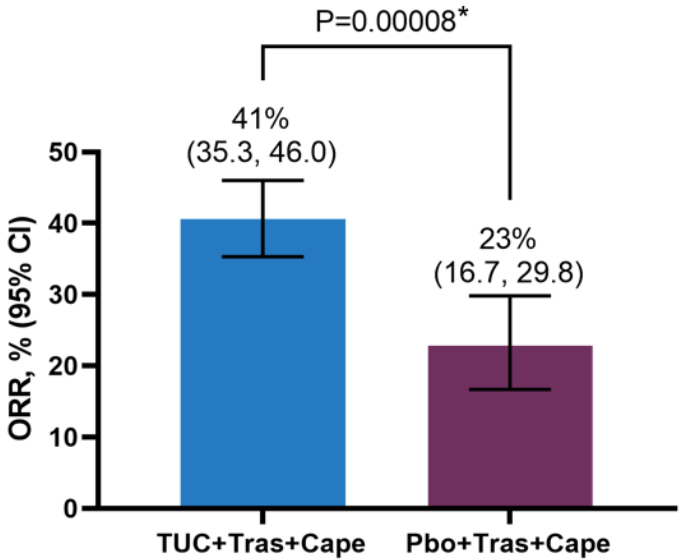
Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
45% (37, 53)	27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

Confirmed Objective Response Rate in the Total Study Population

Confirmed Objective Response Rate (RECIST 1.1, BICR)

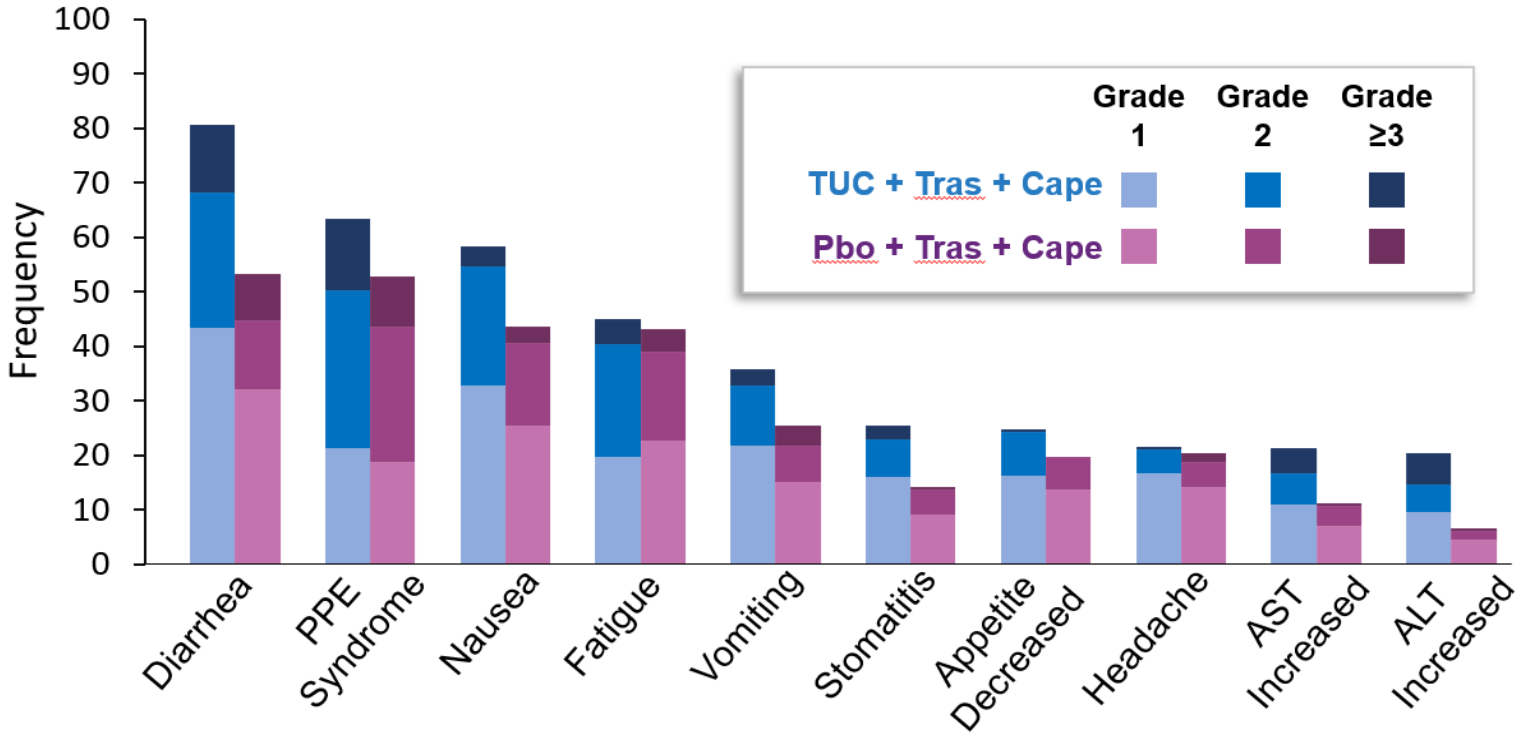


*Stratified Cochran-Mantel-Haenszel p-value for ORR

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)

a. Confirmed Best overall response assessed per RECIST 1.1
b. Patients with no post-baseline response assessments

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



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

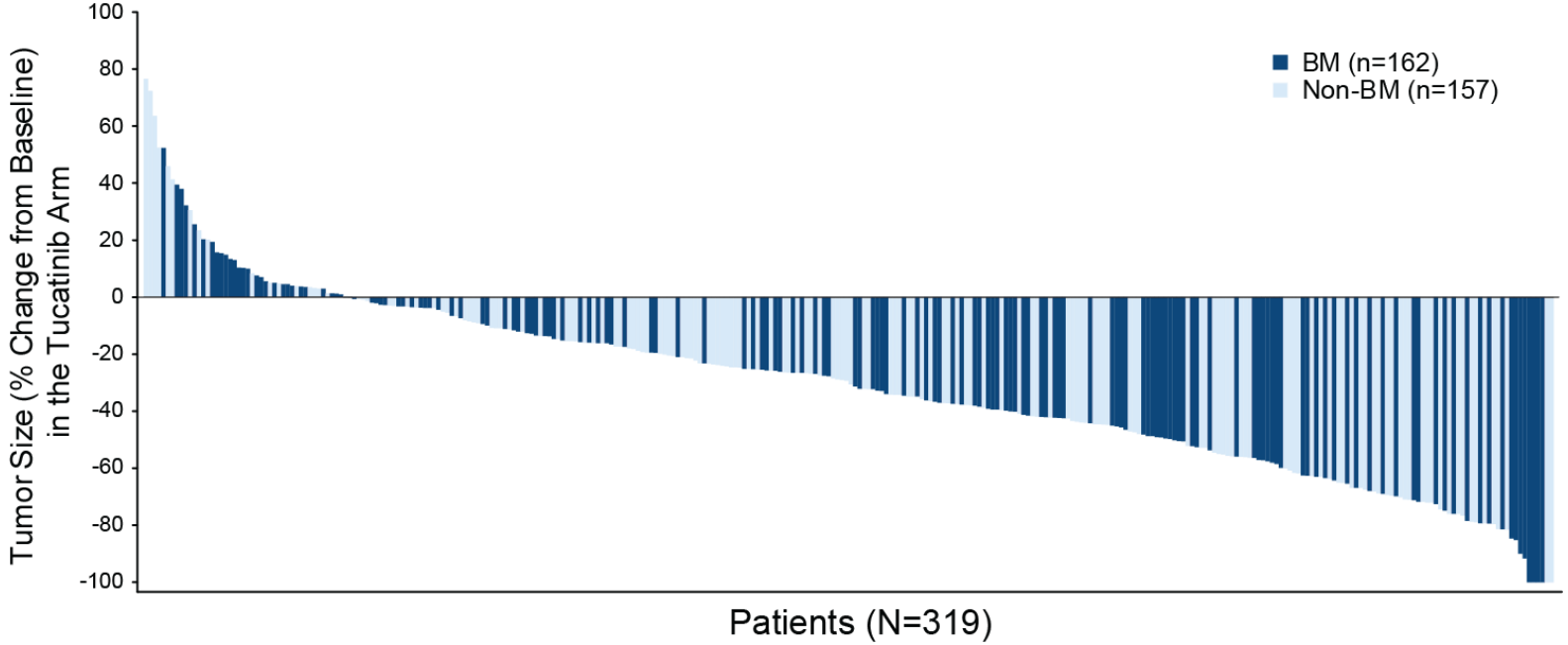
Summary

- Tucatinib in combination with trastuzumab and capecitabine:
  - Reduced the risk of death by a ~one third (HR=0.66, P=0.0048)
  - Reduced the risk of progression or death by ~half in all patients (HR=0.54, P<0.00001), including those patients with brain metastases (HR=0.48, P<0.00001)
  - Nearly doubled the confirmed objective response rate (41% vs 23%, P=0.00008)
- Tucatinib benefit across all subgroups was consistent with the overall outcome in the primary and secondary endpoints.
- Tucatinib in combination with trastuzumab and capecitabine was well tolerated.
  - Majority of adverse events were low-grade
  - Reversible elevations of liver enzymes, and diarrhea that was typically low grade and transient
  - Low rate of discontinuations due to adverse events

Conclusion

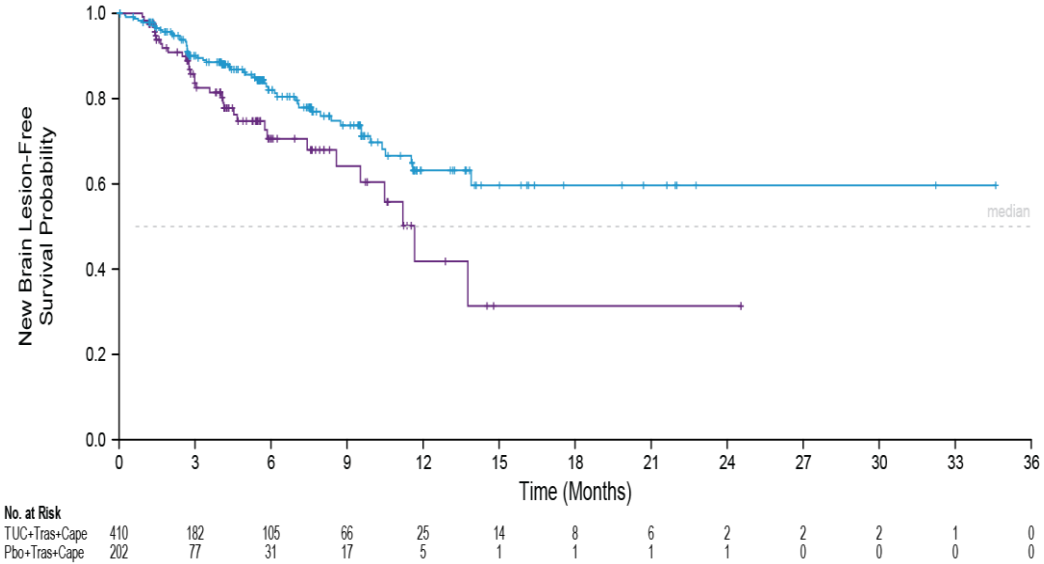
- In patients previously treated with trastuzumab, pertuzumab, and T-DM1, tucatinib in combination with trastuzumab and capecitabine significantly improved PFS and OS.
- The tolerability profile and low discontinuation rate allows for continued HER2 inhibition until progression in heavily pre-treated patients.
- HER2CLIMB is the first randomized trial completed in patients with HER2+ metastatic breast cancer that included patients with untreated or previously treated, progressing brain metastases.
- Tucatinib in combination with trastuzumab and capecitabine has the potential to become a new standard of care in this population with and without brain metastases.

Änderung des Tumordurchmessers unter Tucatinib



Bachelot et al, ESMO 2020

Zeit bis Auftreten neuer Hirnmetastasen

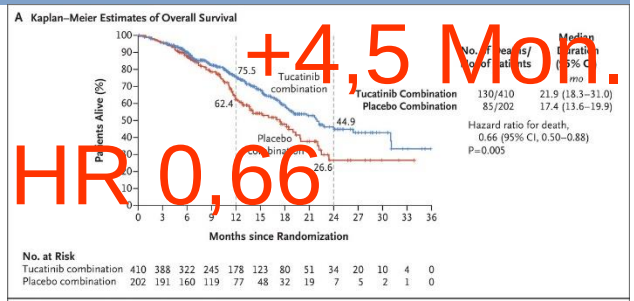


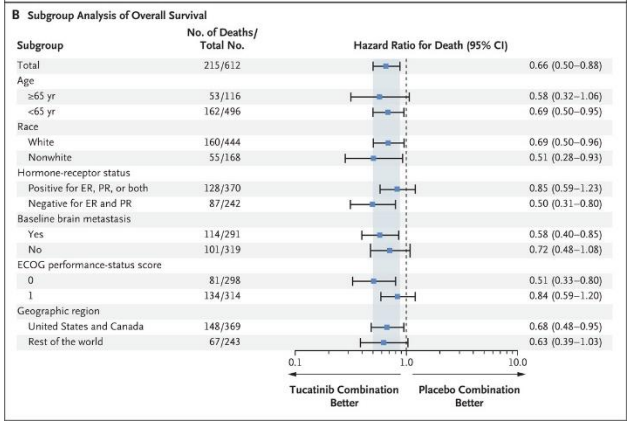
Risk of developing new CNS lesions or death was reduced by 48% in all patients with or without brain metastases in the TUC arm				
	Events	HR (95%CI)	P Value	Median new brain lesion-free survival (95% CI):
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005	Not reached (13.9, –)
Pbo+Tras+Cape	33/202			11.7 months (9.5, –)

Bachelot et al, ESMO 2020

HER2CLIMB – Tucatinib (Pivotal Trial)

- HER2+ metastasiert (n=612)
  - Ausgedehnt vorbehandelt u.a. T-DM1
  - Trastuzumab/Capecitabine **+/- Tucatinib**
- PFS: HR 0,54; +2,2 Monate
- **OS: HR 0,66; +4,5 Monate**
- **Hirnmetastasen**
  - **PFS: HR 0,48; +2,2 Monate**
- Grad 3/4 Diarrhoe: 12,9% vs. 8,6%
- Studienabbruch: 5,7% vs. 3%





Murthy et al, N Engl J Med 382:597-609, 2020

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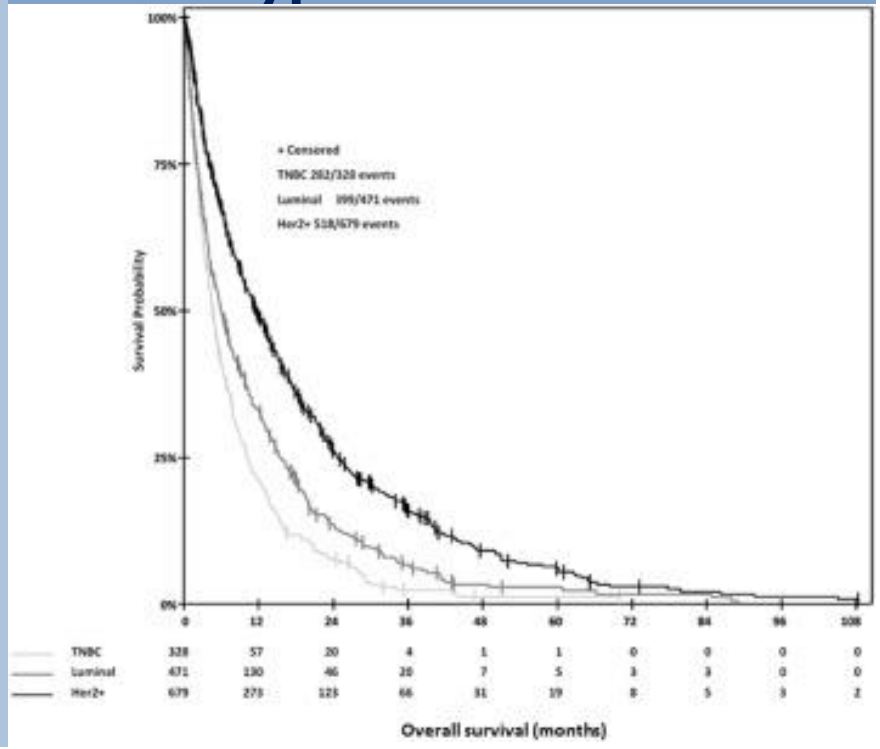
Hirnmetastasen beim fortgeschrittenen HER2-positiven Mammakarzinom?

BMBC – Überleben bei Hirnmetastasen nach molekularem Subtyp

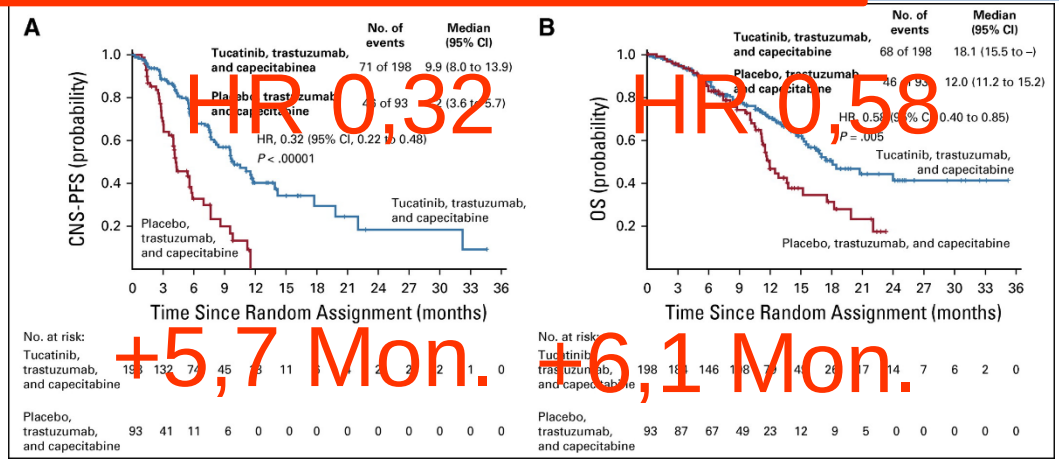
- Mammakarzinom mit Hirnmetastasen (n=1712)
- OS: 7,4 Monate
  - HER2+ 11,6 Monate
    - **mit anti-HER2 Therapie 17,1 Monate**
    - ohne anti-HER2 Therapie 7,2 Monate
  - Luminal-like 5,9 Monate
  - TNBC 4,5 Monate
- „…poor in triple-negative and HR-positive/HER2-negative patients. “



Witzel et al, Eur J Cancer 102:1-9, 2018

HER2CLIMB – Hirnmetastasen

- HER2+ mit Hirnmetastasen (n=291)
  - ZNS-PFS: HR 0,32; +5,7 Monate
  - **ZNS-OS: HR 0,58; +6,1 Monate**
  - ZNS-ORR: 47,3% vs. 20%
- Effektiv bei **stabilen und aktiven Hirnmetastasen**



HR 0,32

HR 0,58

+5,7 Mon.

+6,1 Mon.

Lin et al, J Clin Oncol 38:2610-2619, 2020

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Fortschritte in der Behandlung des HER2-positiven metastasierten Mammakarzinoms mit Tucatinib?

Eine wichtige neue Option – nicht nur bei Hirnmetastasen!

Tucatinib Zulassung durch EMA am 12-2-21

TUKYSA wird angewendet **in Kombination mit Trastuzumab und Capecitabin** zur Behandlung von Patienten mit **lokal fortgeschrittenem oder metastasiertem HER2-positivem Brustkrebs**, die zuvor **mindestens 2 gegen HER2 gerichtete Behandlungsschemata** erhalten haben.

Fachinformation Tucatinib, Februar 2021, DE-TUP-21-109-MT

Guidelines Breast
Version 2020.1D

Save the Date:
Update virtuell am 27. Februar 2021
https://www.ago2021.de

FORSCHEN
LEHREN
HEILEN