

UPDATE San Antonio Breast Cancer Symposium 2022

Metastasierte Mammakarzinom

Dr. Dirk Forstmeyer

Medizinische Klinik II

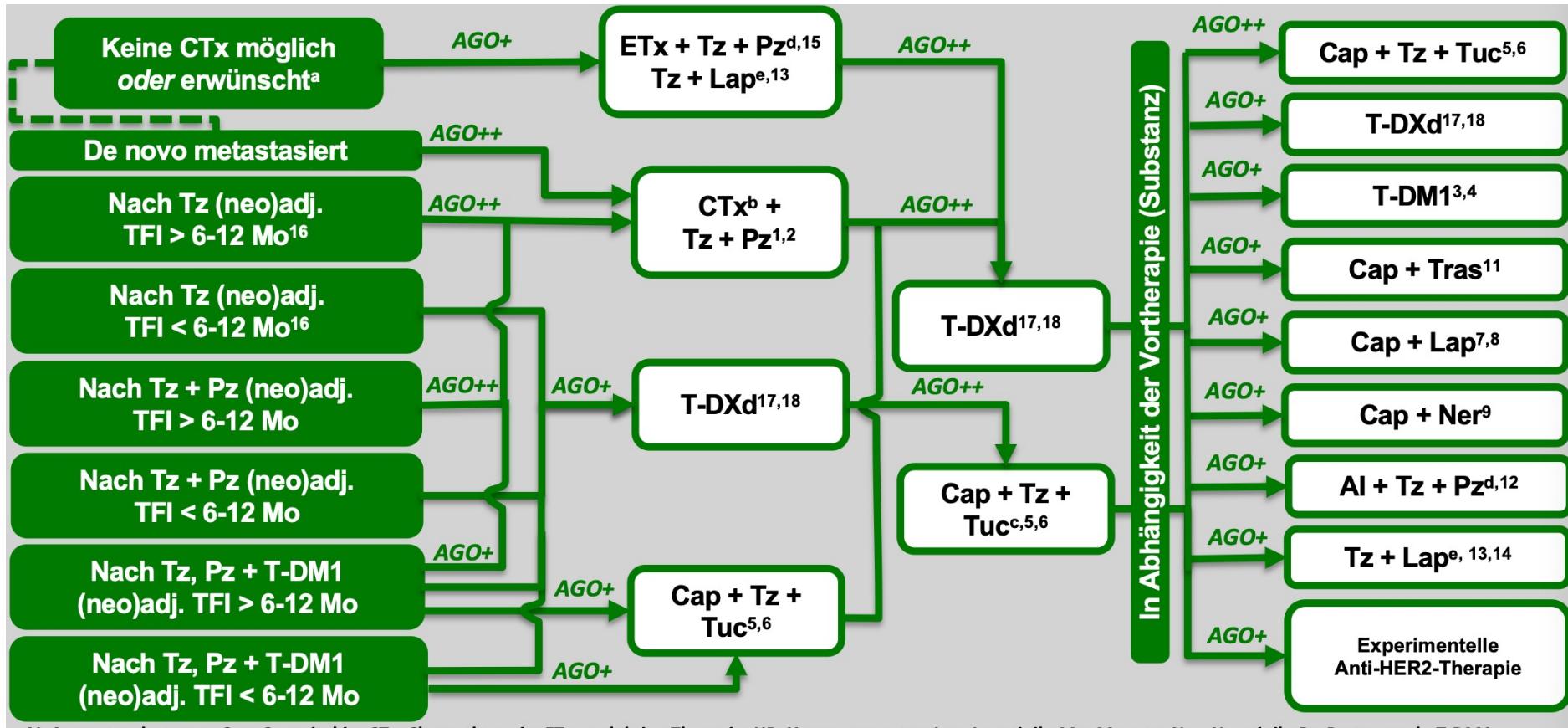
Klinik und Poliklinik für Internistische Onkologie, Gastroenterologie, Hepatologie, Pneumologie und Infektiologie



Universitätsklinikum Leipzig AÖR (2022): Dr. D. Forstmeyer

Metastasierte Her2-positive Mammakarzinom

Behandlungsalgorithmus Her2-positives metastasiertes Mammakarzinom



AI, Aromatasehemmer; Cap, Capecitabin; CTx, Chemotherapie; ETx, endokrine Therapie; HR, Hormonrezeptor; Lap, Lapatinib; Mo, Monate; Ner, Neratinib; Pz, Pertuzumab; T-DM1, Trastuzumab Emtansin; T-DXd, Trastuzumab Deruxtecan; TFI, treatment-free interval; Tuc, Tucatinib; Tz, Trastuzumab; ^a kein Überlebensvorteil, CTx in Erwägung ziehen; ^b Docetaxel (++), Paclitaxel (++), nab-Paclitaxel (+), Vinorelbine (+, nur sekundär metastasiert); ^c nur nach T-DM1; ^d nur HR pos; ^e nur HR neg

Therapiesequenz Her2-positives metastasiertes Mammakarzinom

1. Linie

Trastuzumab + Pertuzumab + Docetaxel

Chemotherapiepartner:

Docetaxel, Paclitaxel, nabPaclitaxel, Vinorelbine

Trastuzumab (+Pertuzumab) mit
endokriner Therapie für triple-positive
für hochselektionierte Patienten

2. Linie

Trastuzumab-Deruxtecan

Destiny-Breast-03 Phase III

Trastuzumab + Pertuzumab + Docetaxel
(falls nicht in der ersten Linie gegeben)

3. Linie

Trastuzumab-Deruxtecan (falls nicht 2. Linie)
Tucatinib/Trastuzumab/Capecitabin
Trastuzumab Emtansine (T-DM1)

Destiny-Breast – 01 Phase II
Destiny-Breast-02 Phase III

≥ 4. Linie

Neratinib + Capecitabin
Lapatinib + Capecitabin
Trastuzumab + Lapatinib
Trastuzumab + Chemotherapie
Trastuzumab + Vinorelbine + Everolimus

Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY-Breast02

Presentation ID: GS2-01

Ian Krop,^a Yeon Hee Park, Sung-Bae Kim, Giuliano Borges, Sercan Aksoy, Joaquin Gavila Gregori, Rebecca Roylance, Elgene Lim, Rinat Yerushalmi, Flora Zagouri, Francois P. Duhoux, Tanja Fehm, Toshimi Takano, Anton Egorov, Iris Wu, Jillian Cathcart, Changan Chu, Fabrice André

Destiny-Breast02 Studiendesign

Key eligibility criteria^a

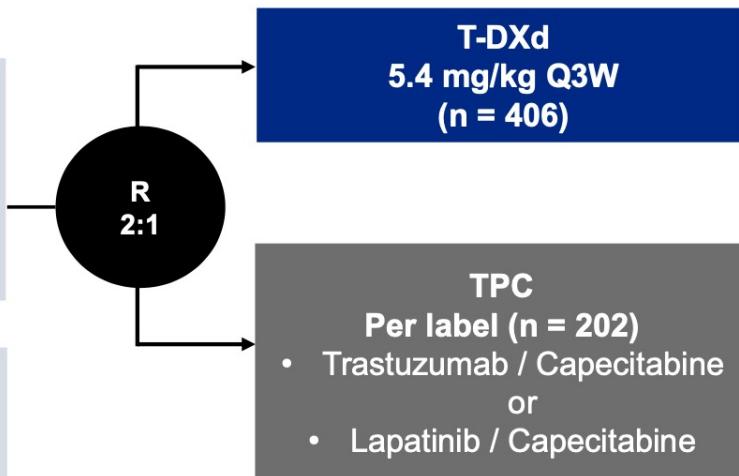
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

At data cutoff (June 30, 2022), the median duration of follow-up^d was:

- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm



Primary endpoint

- PFS (BICR^b)

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR^b)
- DoR (BICR^b)
- PFS (investigator)
- Safety

Exploratory endpoints

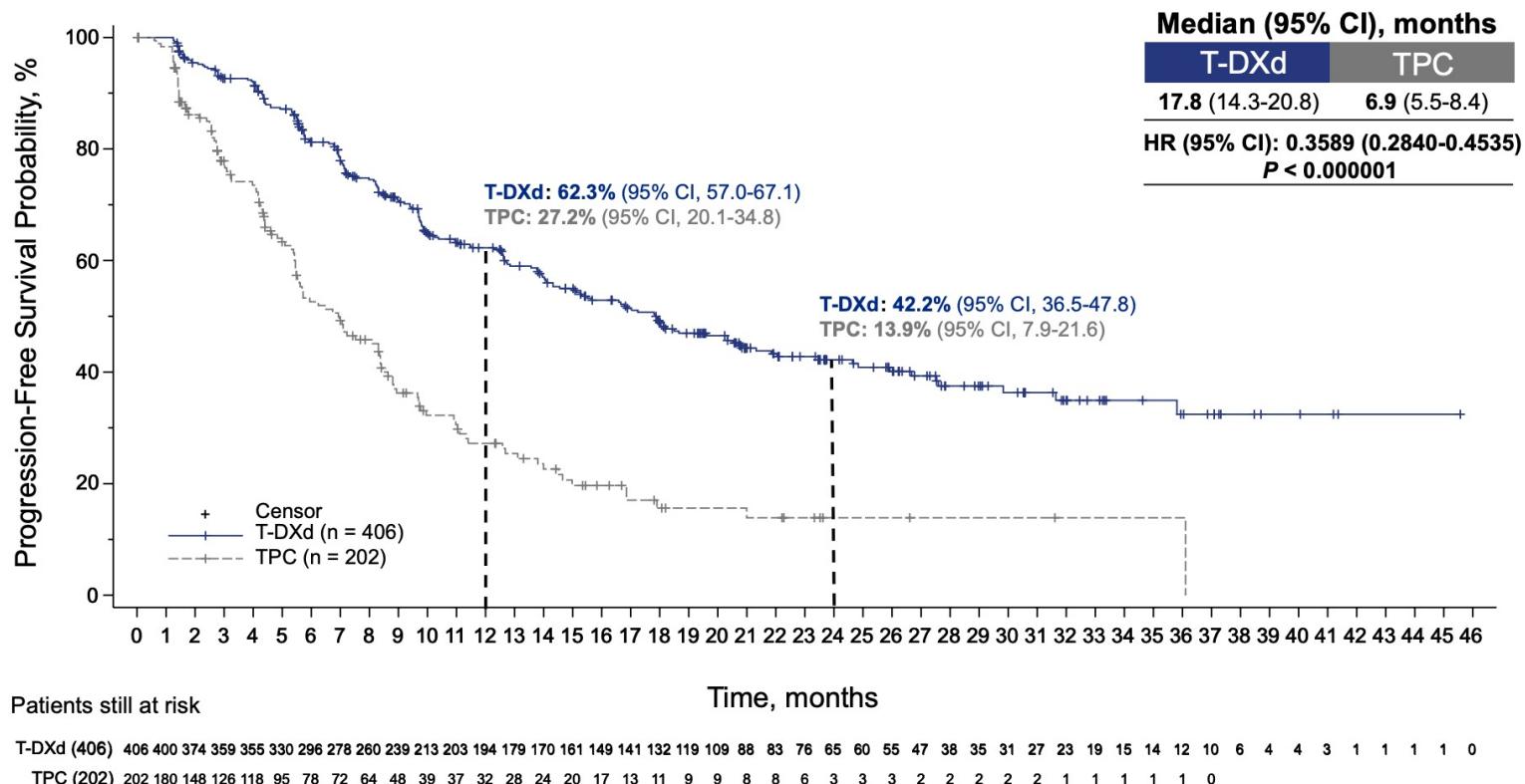
- CBR (BICR^b)
- PFS2^c (investigator)

Protocol-prespecified statistical analysis plan

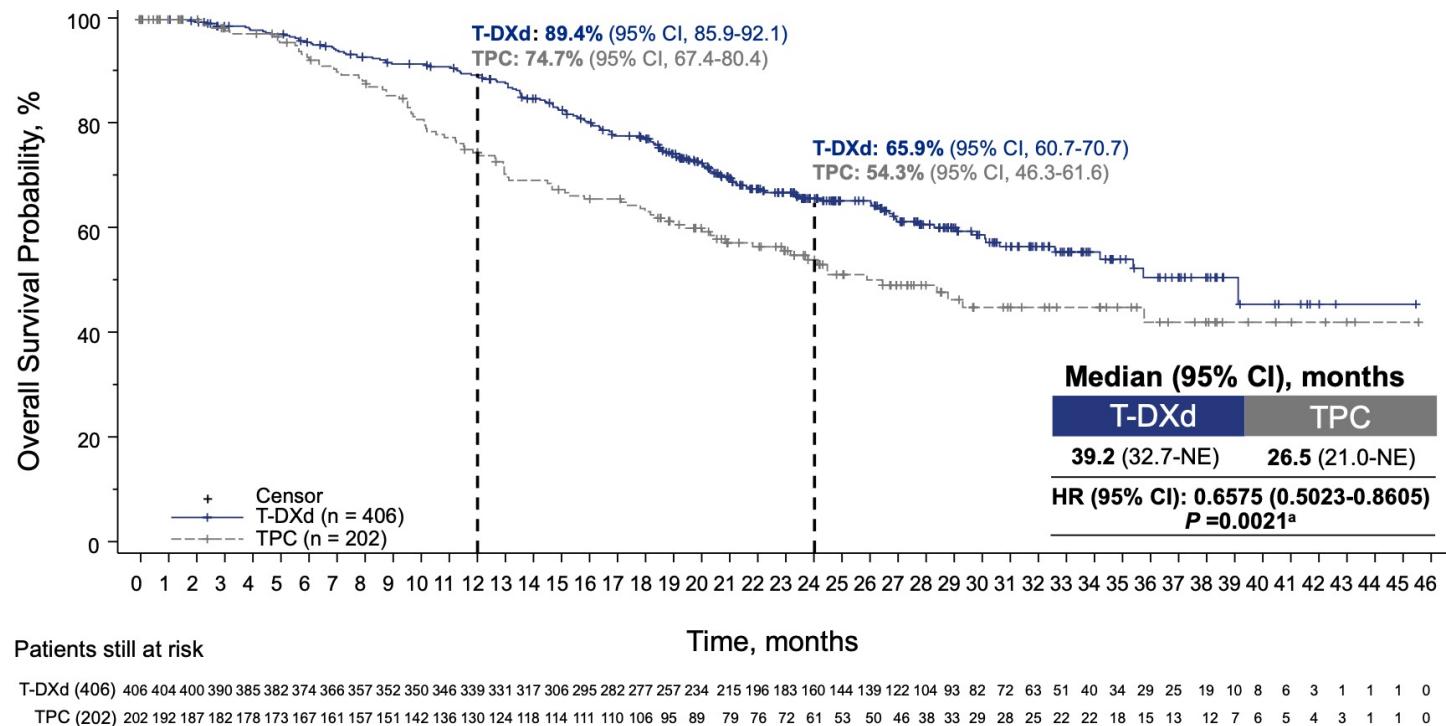
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

Destiny-Breast02

Progressionsfreies Überleben



Destiny-Breast02 Gesamtüberleben



In the TPC arm

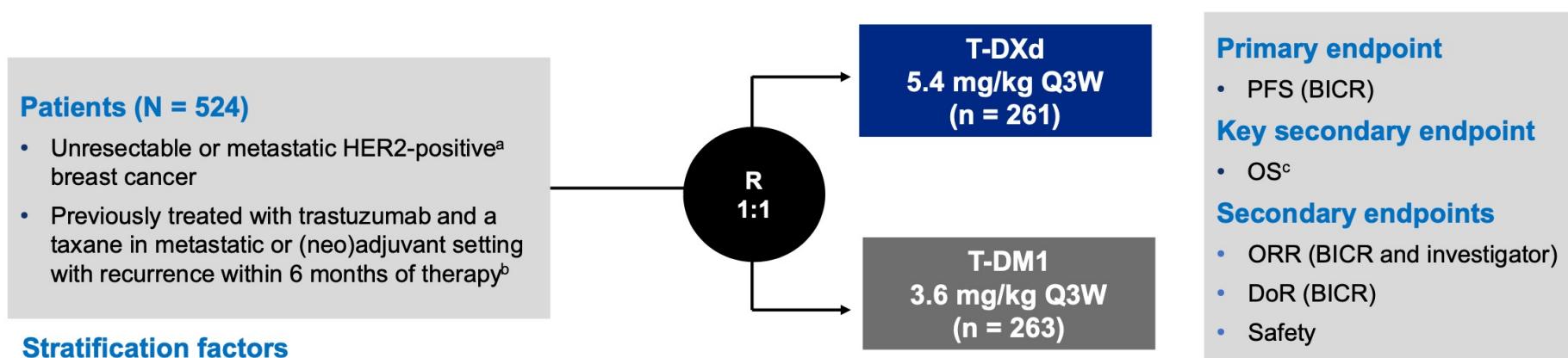
- 69.3% (140/202) of patients received a new systemic anticancer treatment
- 25.7% (52/202) of patients received T-DXd in the post-trial setting

Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results of the randomized, phase 3 study DESTINY-Breast03

Presentation ID: GS2-02

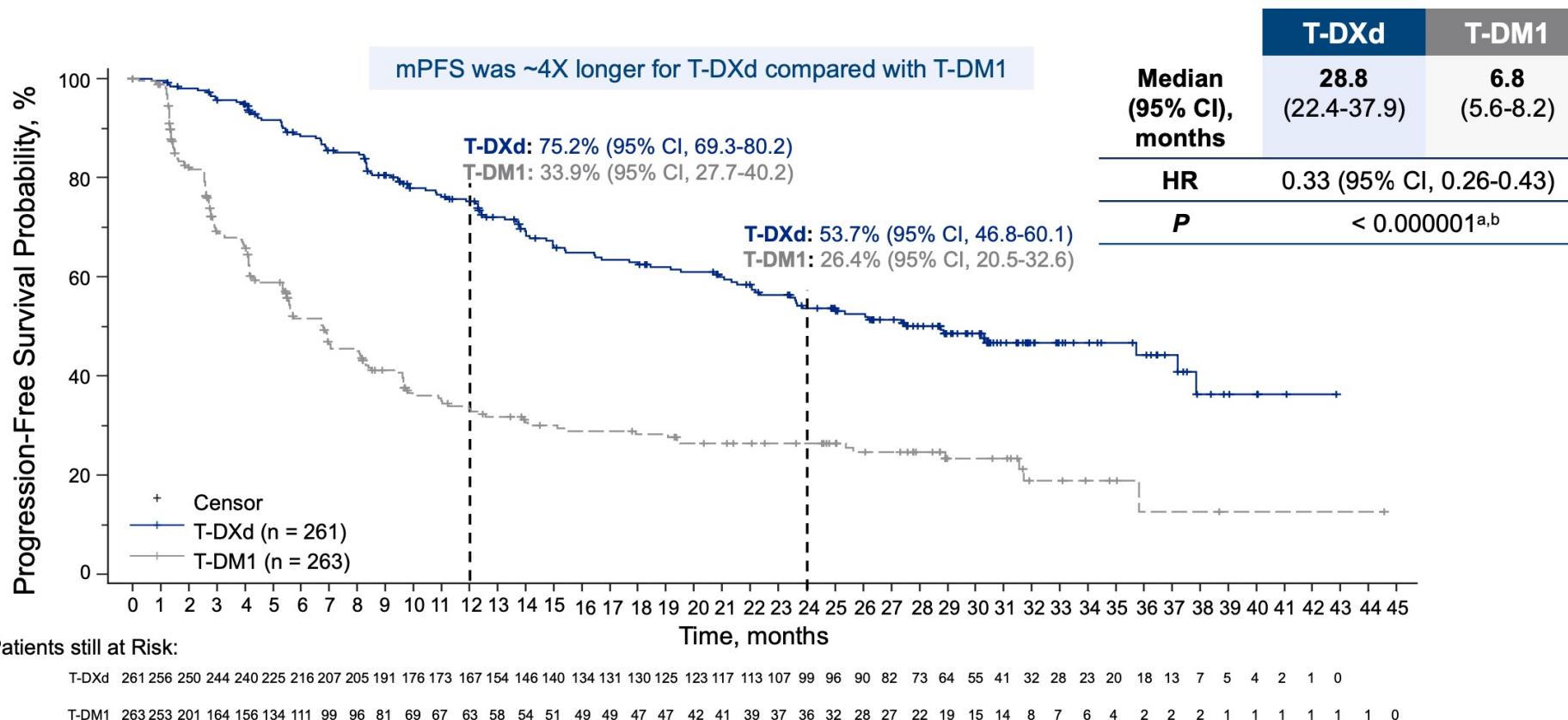
Sara A. Hurvitz,^a Roberto Hegg, Wei-Pang Chung, Seock-Ah Im, William Jacot, Vinod Ganju, Joanne Wing Yan Chiu, Binghe Xu, Erika Hamilton, Srinivasan Madhusudan, Hiroji Iwata, Sevilay Altintas, Jan-Willem Henning, Giuseppe Curigliano, José Manuel Perez-Garcia, Anton Egorov, Yali Liu, Jillian Cathcart, Shahid Ashfaque, Javier Cortés

Destiny-Breast03 – Studiendesign

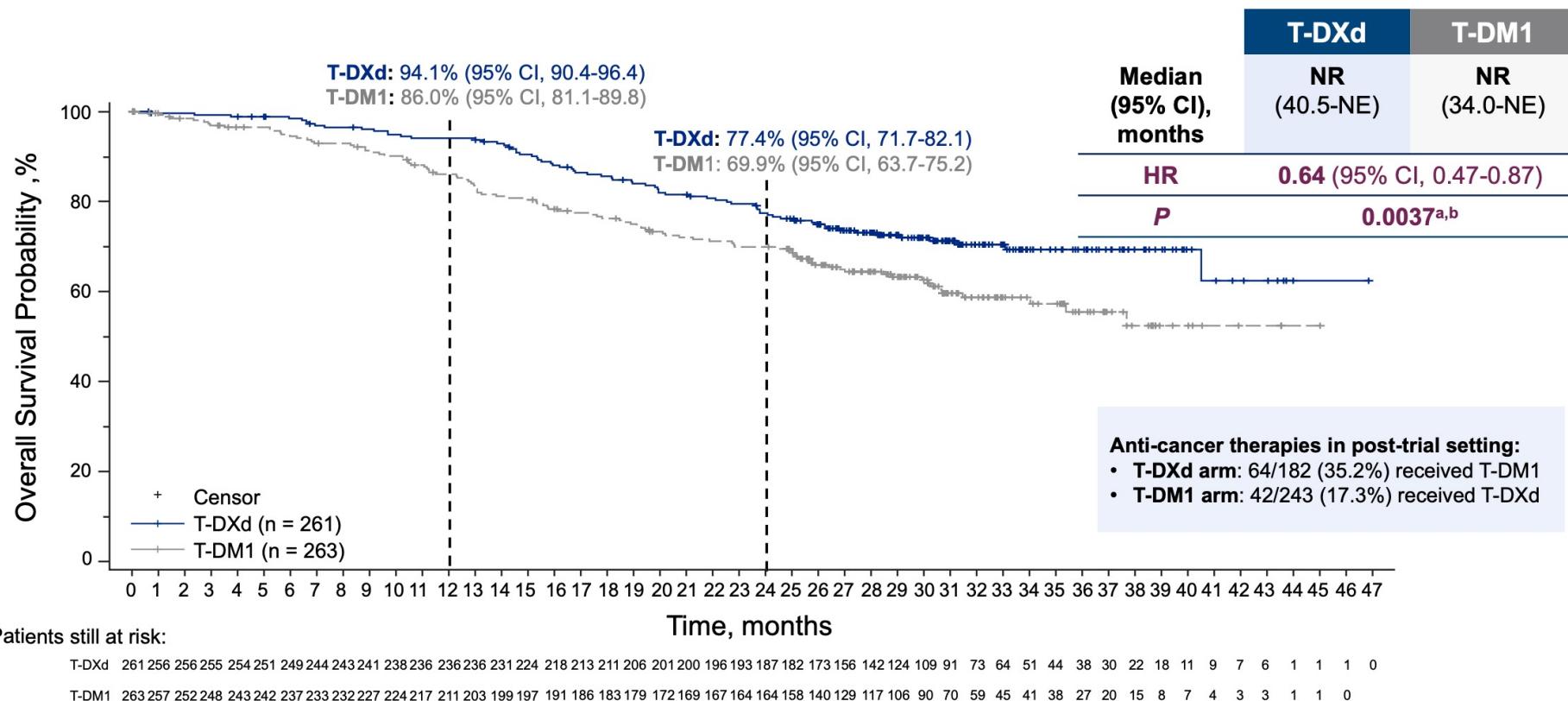


The prespecified OS interim analysis was planned with 153 events.^d
At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

Destiny-Breast03 Progressionsfreie Überleben



Destiny-Breast03 Gesamtüberleben



Therapiesequenz Her2-positives metastasiertes Mammakarzinom

1. Linie

Trastuzumab + Pertuzumab + Docetaxel

Destiny-Breast-09 Phase III ???

Chemotherapiepartner:
Docetaxel, Paclitaxel, nabPaclitaxel, Vinorelbine

Trastuzumab (+Pertuzumab) mit
endokriner Therapie für triple-positive
für hochselektionierte Patienten

2. Linie

Trastuzumab-Deruxtecan

Destiny-Breast-03 Phase III

Trastuzumab + Pertuzumab + Docetaxel
(falls nicht in der ersten Linie gegeben)

3. Linie

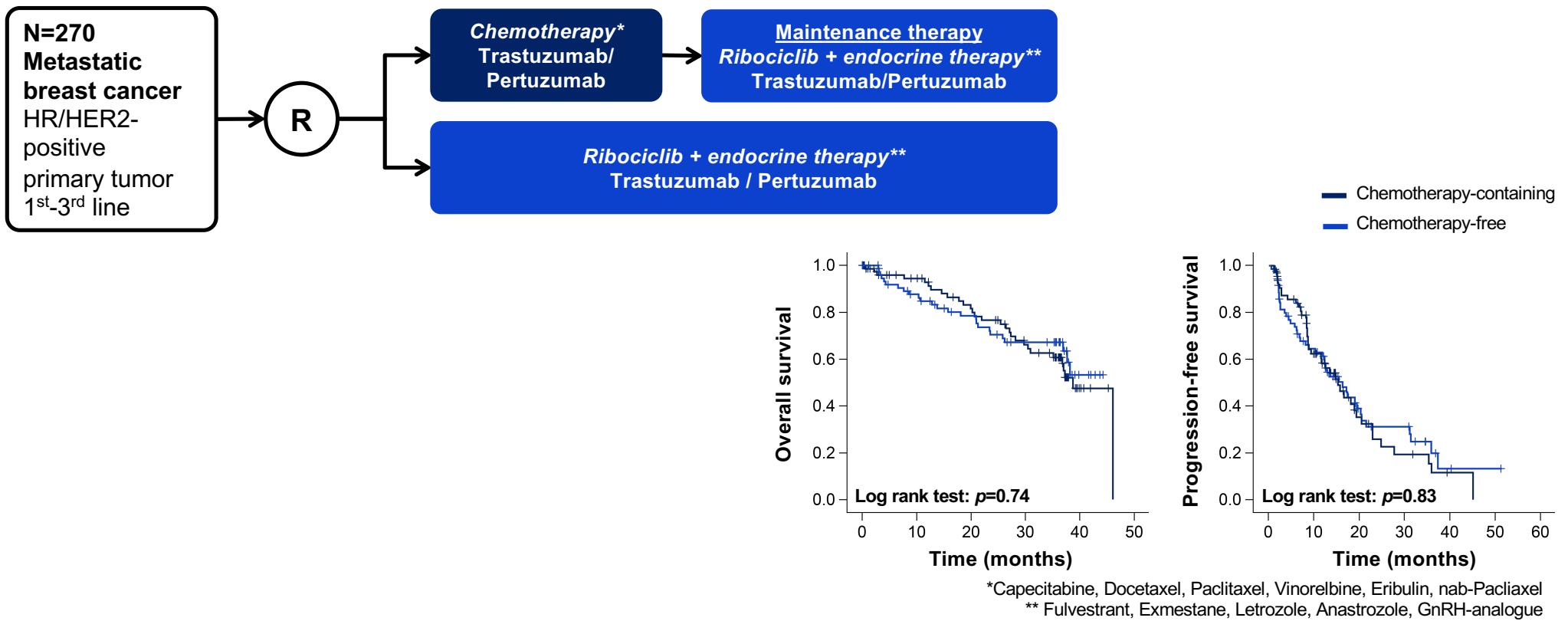
Trastuzumab-Deruxtecan (falls nicht 2. Linie)
Tucatinib/Trastuzumab/Capecitabin
Trastuzumab Emtansine (T-DM1)

Destiny-Breast – 01 Phase II
Destiny-Breast-02 Phase III

≥ 4. Linie

Neratinib + Capecitabin
Lapatinib + Capecitabin
Trastuzumab + Lapatinib
Trastuzumab + Chemotherapie
Trastuzumab + Vinorelbine + Everolimus

DETECT V-Trial – Interims Analyse: Studiendesign & Ergebnisse

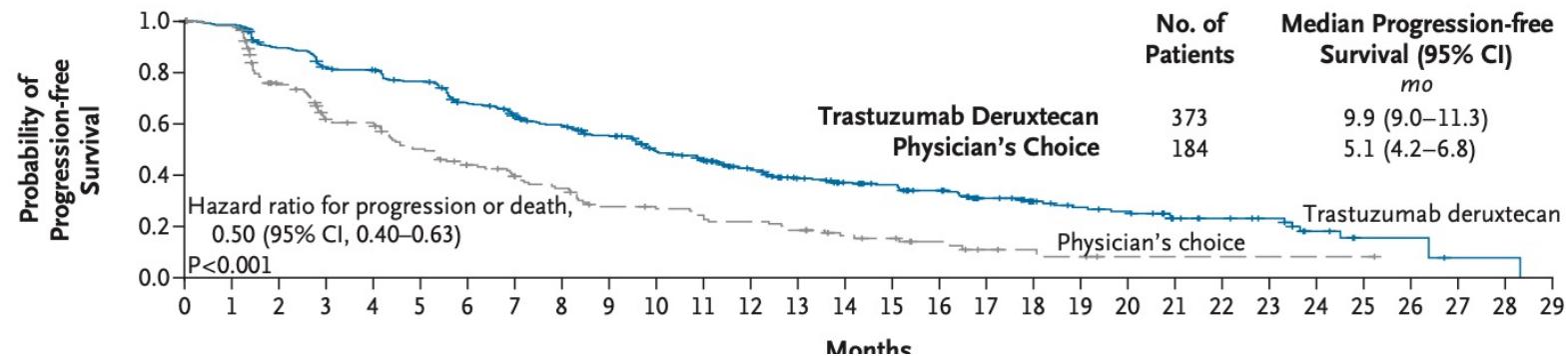


**Metastasiertes
Her2-low Mammakarzinom**

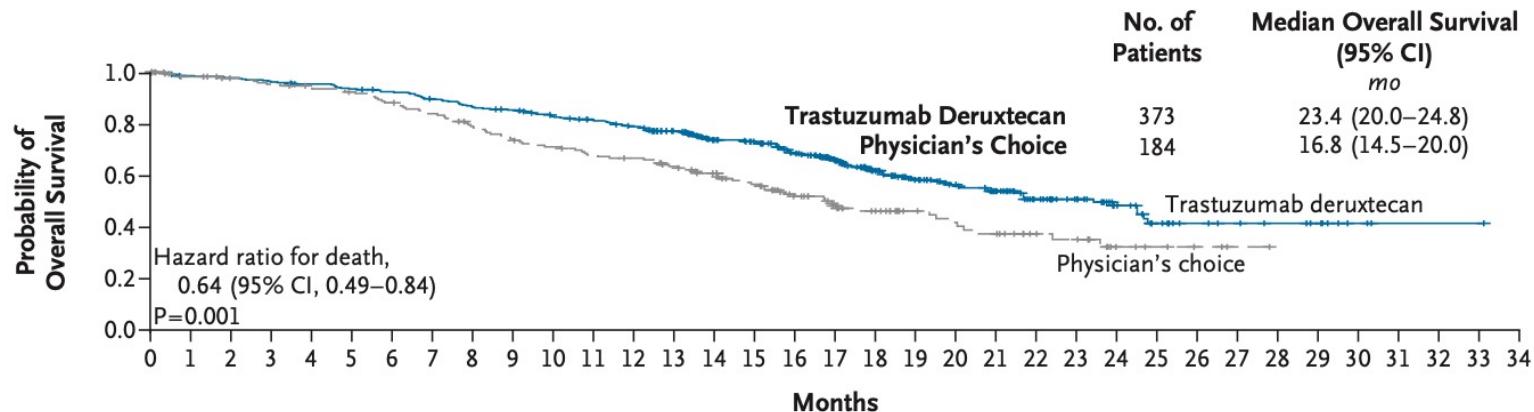
Destiny-Breast-04 (s.Modi, NEJM 2022)

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

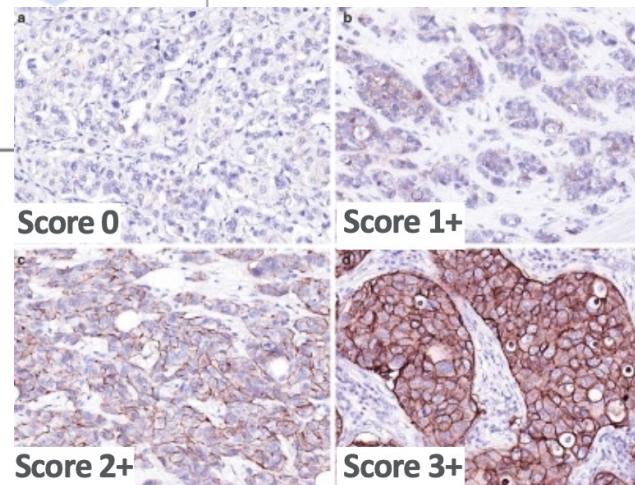
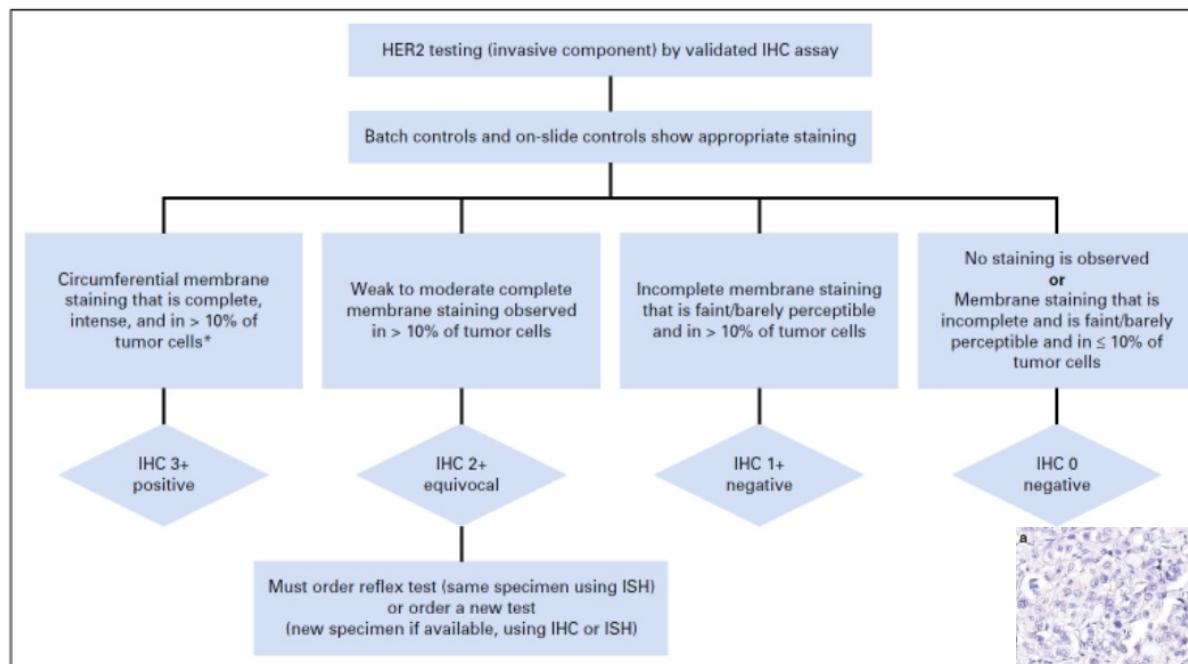
B Progression-free Survival among All Patients



D Overall Survival among All Patients



Nachweis der Her-2-Amplifikation



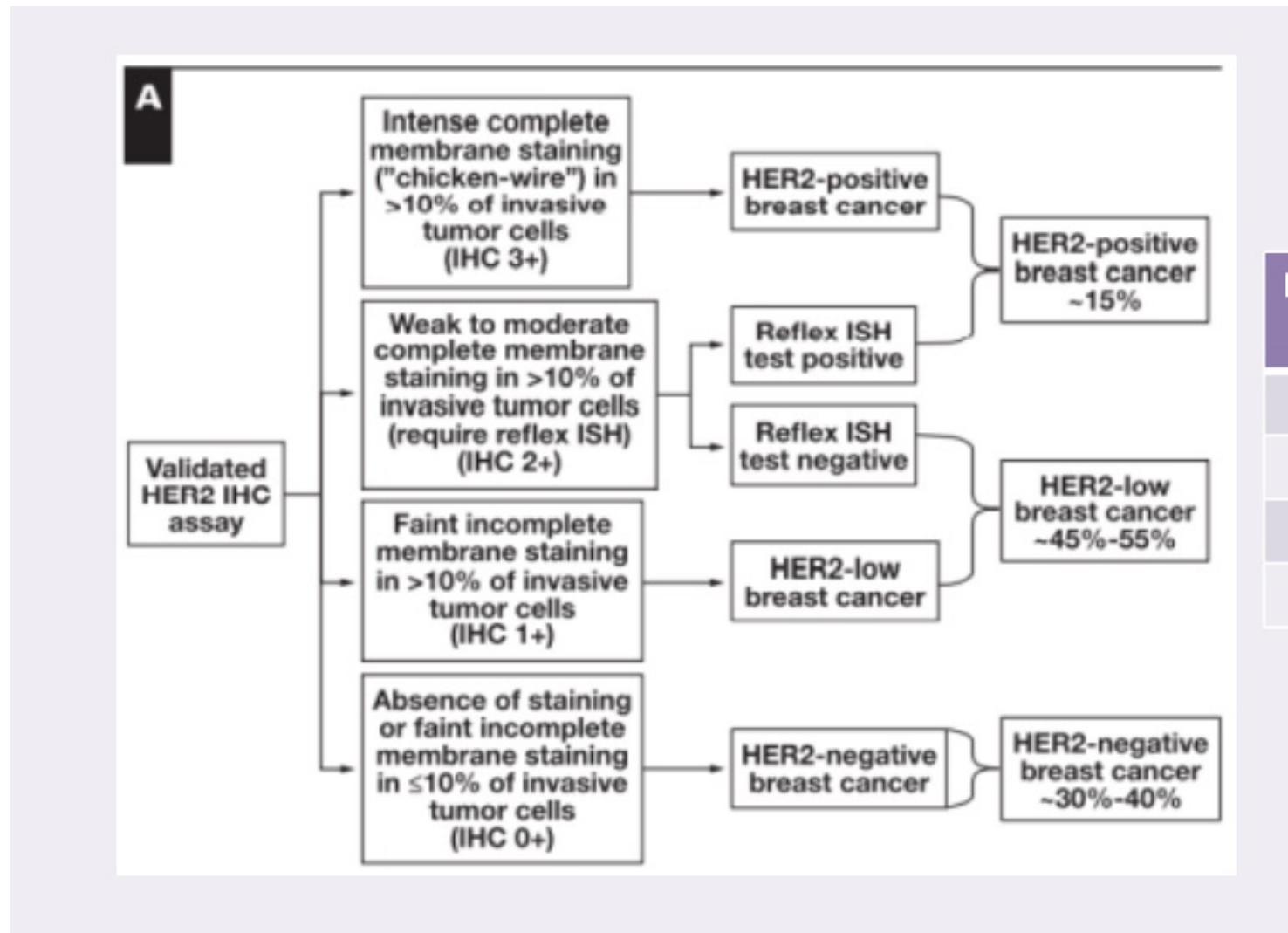
K.P. Siziopikou SABCS 2022

Übereinstimmung der Her2-Testung

- Fernandez et al (JAMA Oncol 2022)
 - Data from 1400 laboratories around the world; CAP HER2 survey, 80 HER2 cases
 - >90% agreement for Score 3+ and score 0
 - Lowest agreement between score 0 vs score 1+ (<70%)

K.P. Siziopikou SABCS 2022

Vorschlag einer neuen Klassifikation

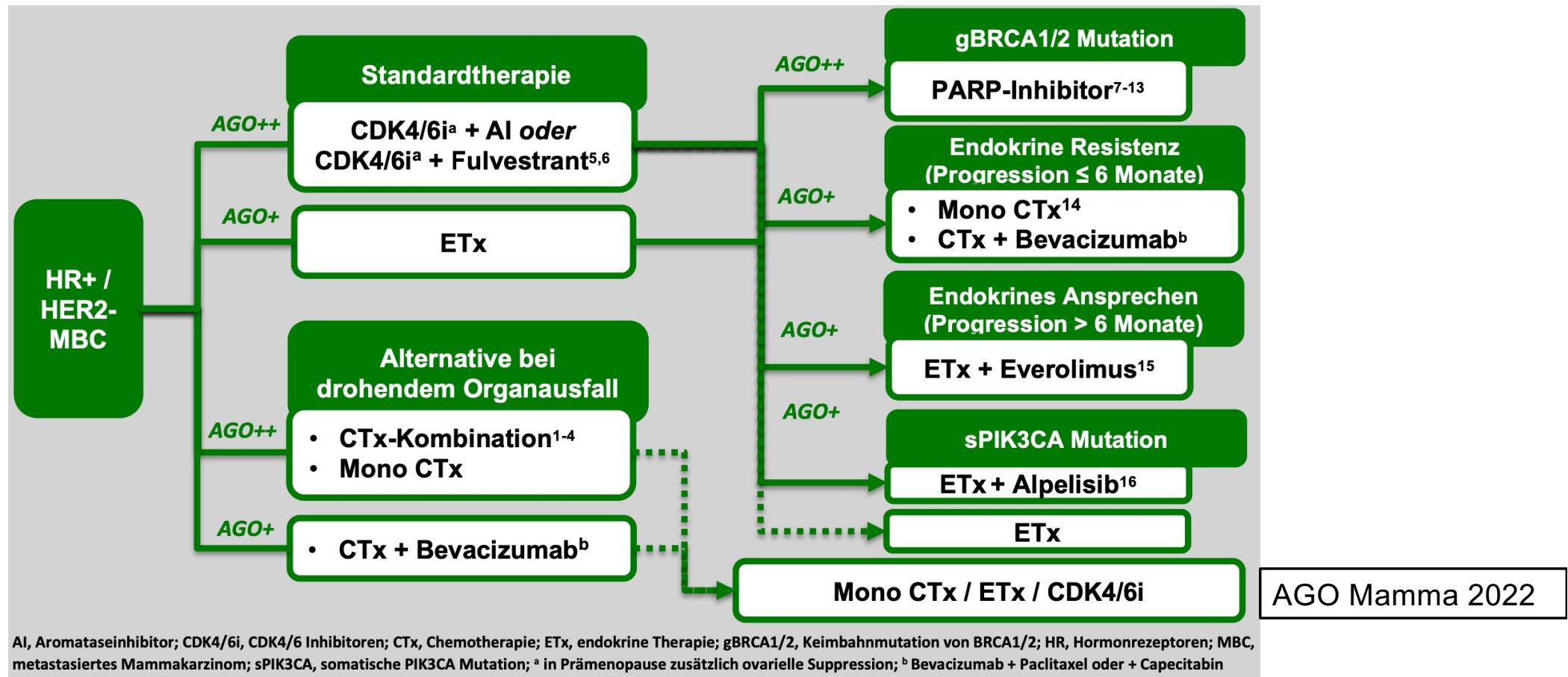


HER2 score	# cell surface receptors
0	20,000
1+	100,000
2+	500,000
3+	>2,000,000

K.P. Siziopikou SABCS 2022

Metastasierte Hormonrezeptor-positive Mammakarzinom

Behandlungsalgorithmus Hormonrezeptor-positives, Her2-negatives metastasiertes Mammakarzinom



Right Choice Trial

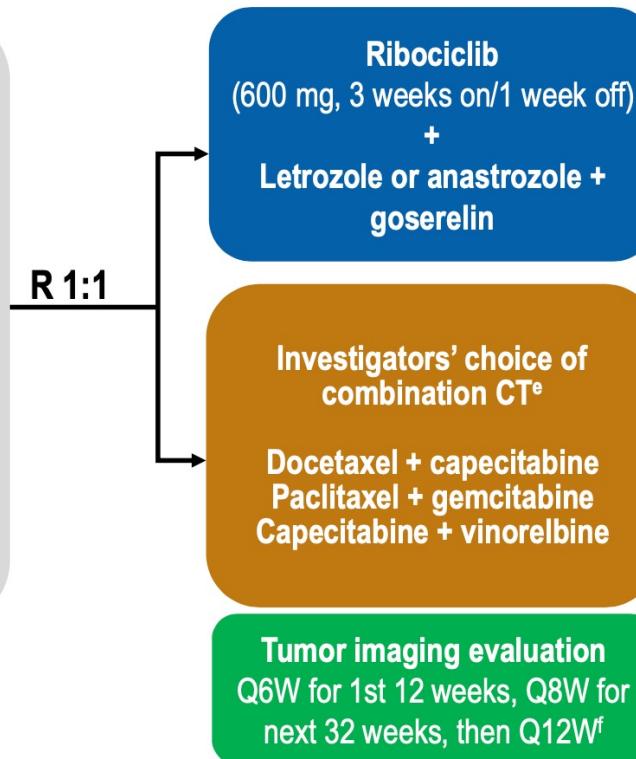
Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2- Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

Yen-Shen Lu,¹ Eznal Izwadi Bin Mohd Mahidin,² Hamdy Azim,³ Yesim Eralp,⁴ Yoon-Sim Yap,⁵ Seock-Ah Im,⁶ Julie Rihani,⁷ James Bowles,⁸ Teresa Delgar Alfaro,⁸ Jiwen Wu,⁹ Melissa Gao,⁸ Khemaies Slimane,⁸ Nagi El Saghir¹⁰

Right Choice Trial Studiendesign

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease^a
 - Symptomatic visceral metastases
 - Rapid disease progression or impending visceral compromise
 - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2^b
- Total bilirubin ≤ 1.5 ULN
- N = 222^c

Stratified by (1) the presence or absence of liver metastases and by (2) DFI^d < or ≥2 years



Primary endpoint

- PFS (locally assessed per RECIST 1.1)

Secondary endpoints

- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

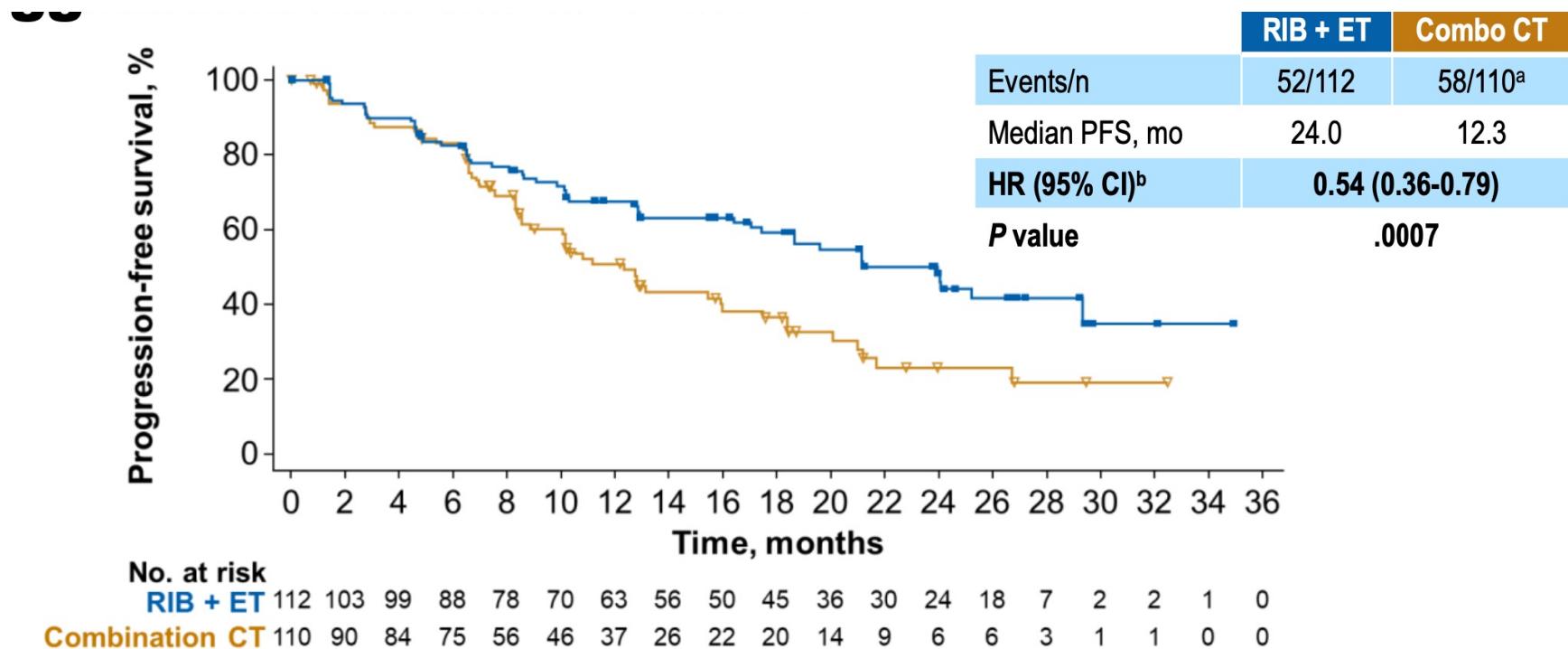
Exploratory endpoints

- Biomarker analyses
- Healthcare resource utilization

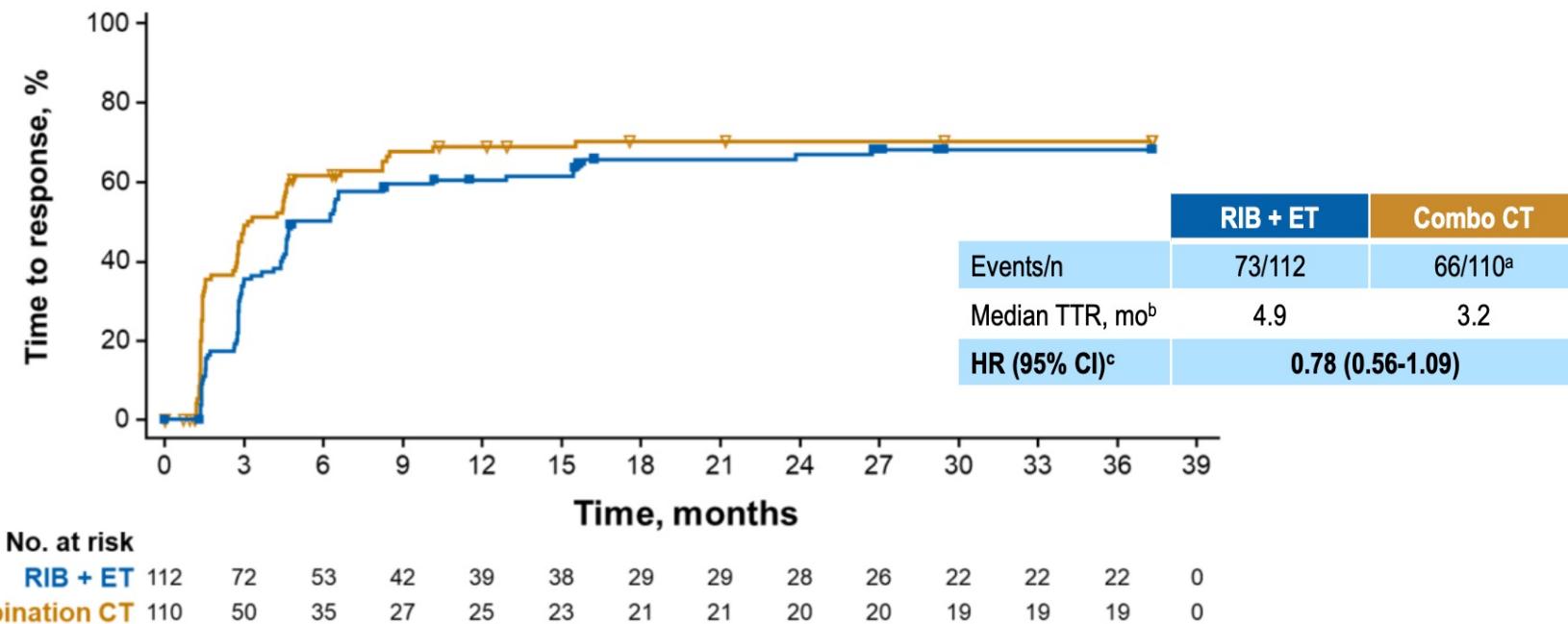
Right Choice Trial Patientencharakteristika

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110	Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0	Disease status		
≥40 years	80 (71.4)	72 (65.5)	De novo	71 (63.4)	73 (66.4)
Race^a			Visceral metastatic sites^b		
Asian	60 (53.6)	58 (52.7)	Liver	56 (50.0)	57 (51.8)
White	51 (45.5)	52 (47.3)	Lung	63 (56.3)	58 (52.7)
Histological grade			Liver or lung	89 (79.5)	85 (77.3)
Grade 1	10 (8.9)	16 (14.5)	Aggressive disease characteristic		
Grade 2	66 (58.9)	61 (55.5)	Rapid progression	23 (20.5)	18 (16.4)
Grade 3	35 (31.3)	29 (26.4)	Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
≥50% ER+	95 (84.8)	95 (86.4)	Symptomatic visceral metastases	74 (66.1)	76 (69.1)
PR+	99 (88.4)	102 (92.7)	Visceral crisis^c	61 (54.5)	55 (50.0)

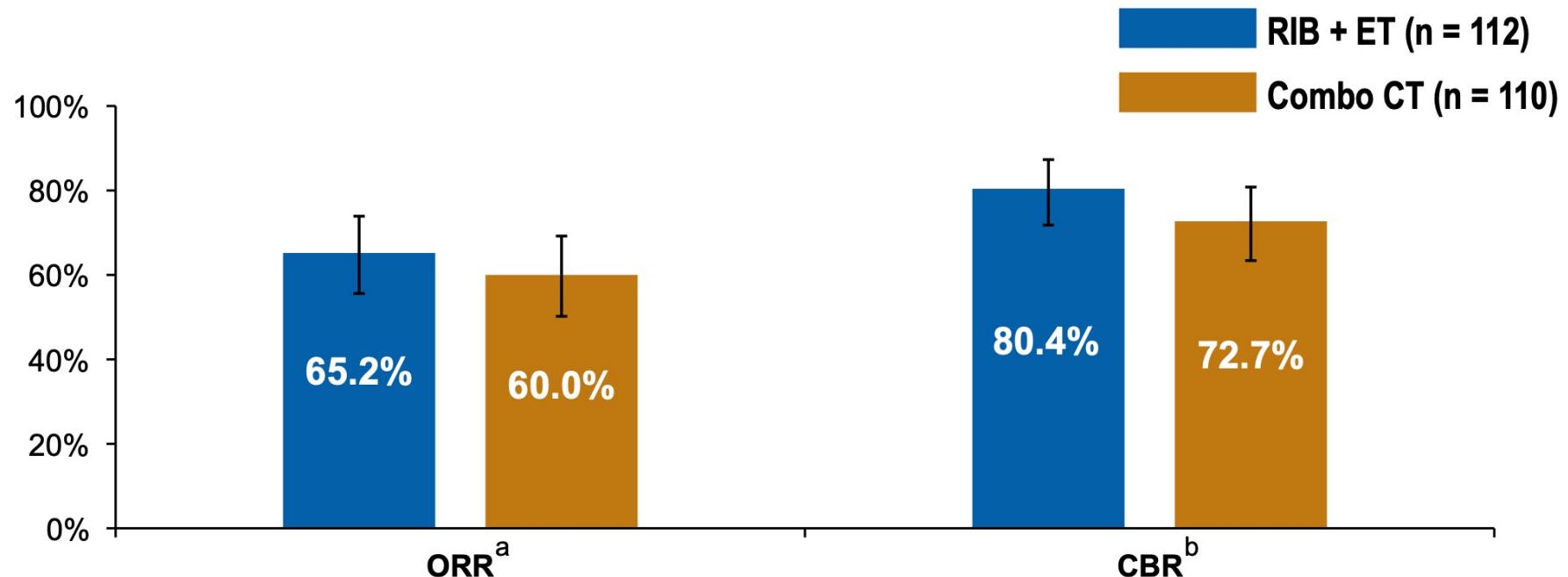
Right Choice Trial Progressionsfreies Überleben



Right Choice Zeit bis zum Ansprechen



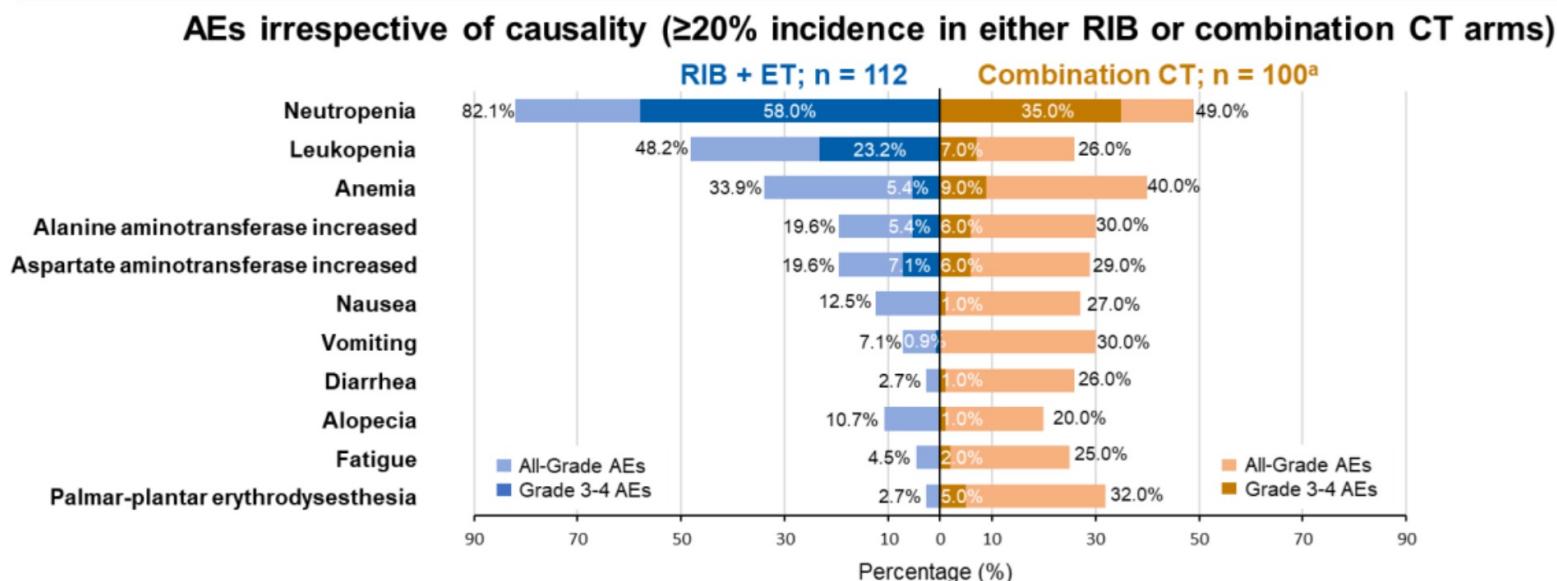
Right Choice Trial: Overall response rate Clinical Benefit Rate



- A sensitivity analysis^c confirmed the ORR and CBR findings in the safety set

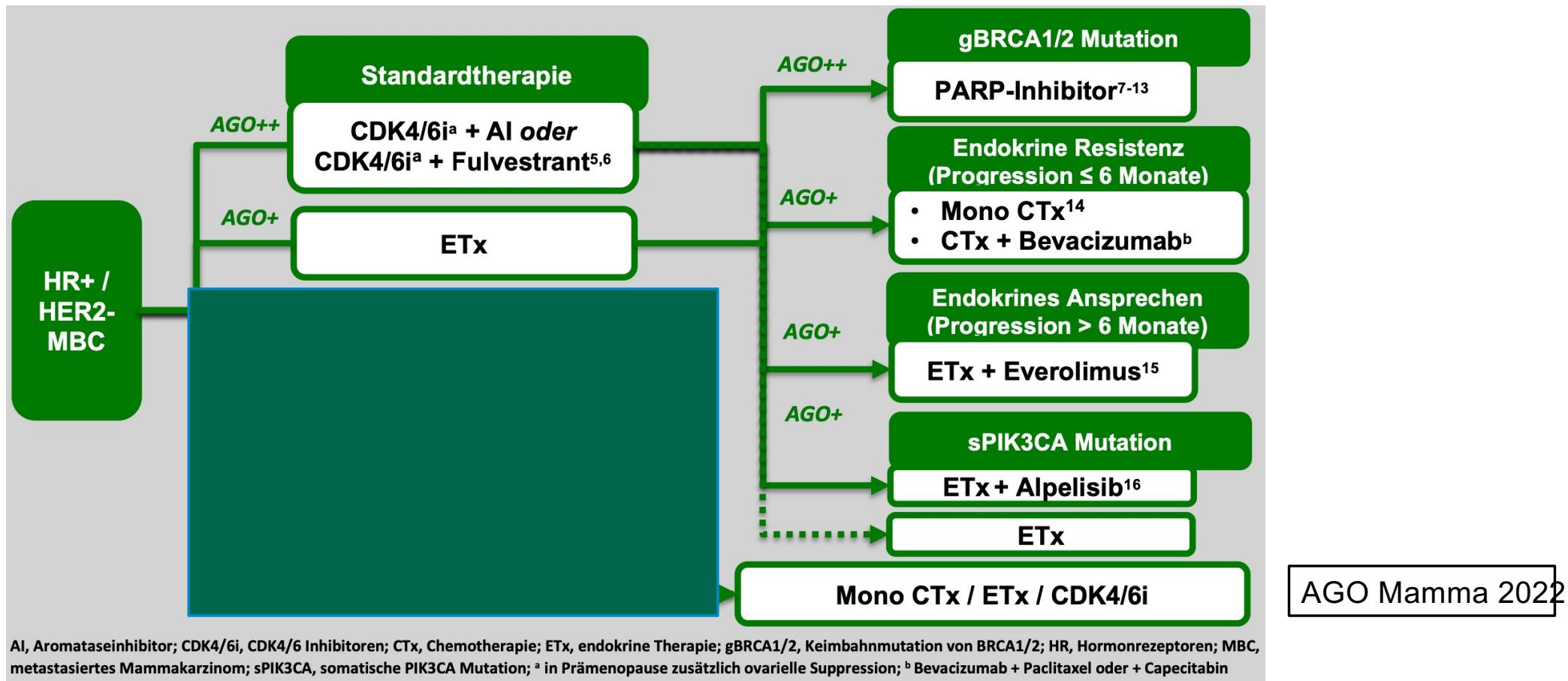
Fewer TRAEs with RIB + ET vs combination CT

n (%)	RIB + ET; n = 112		Combination CT; n = 100 ^a	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Total AEs	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
Treatment-related AEs leading to discontinuation ^b	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)



- Two patients (1.8%) in RIB arm^c and none in CT arm showed grade ≥ 3 QT prolongation

Behandlungsalgorithmus Hormonrezeptor-positives, Her2-negatives metastasiertes Mammakarzinom



Pooled analysis of post-progression treatments after first-line ribociclib + endocrine therapy in patients with HR+/HER2– advanced breast cancer in the MONALEESA-2, -3, and -7 studies

Erika Hamilton,¹ Laura Spring,² Peter A. Fasching,³ Sandra Franco,⁴ Richard De Boer,⁵ Javier Cortes,⁶ Kevin Kalinsky,⁷ Dejan Juric,² Aditya Bardia,² Sina Haftchenary,⁸ Agnes Lteif,⁹ Juan Pablo Zarate,⁹ Lili Cen,⁹ Patrick Neven¹⁰

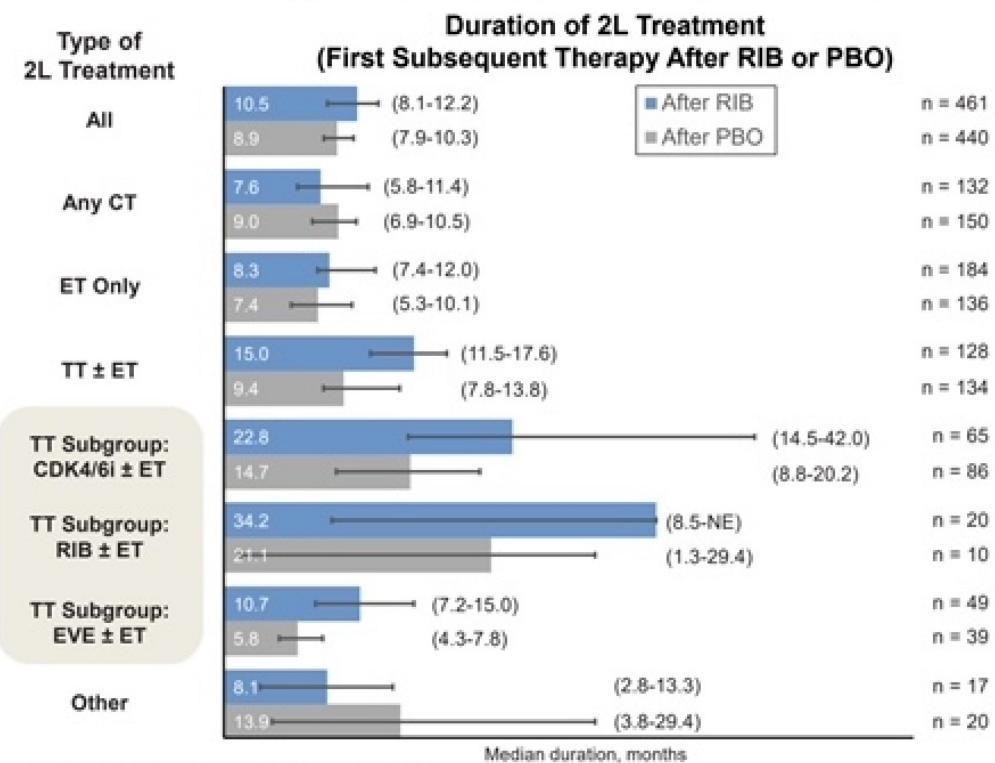
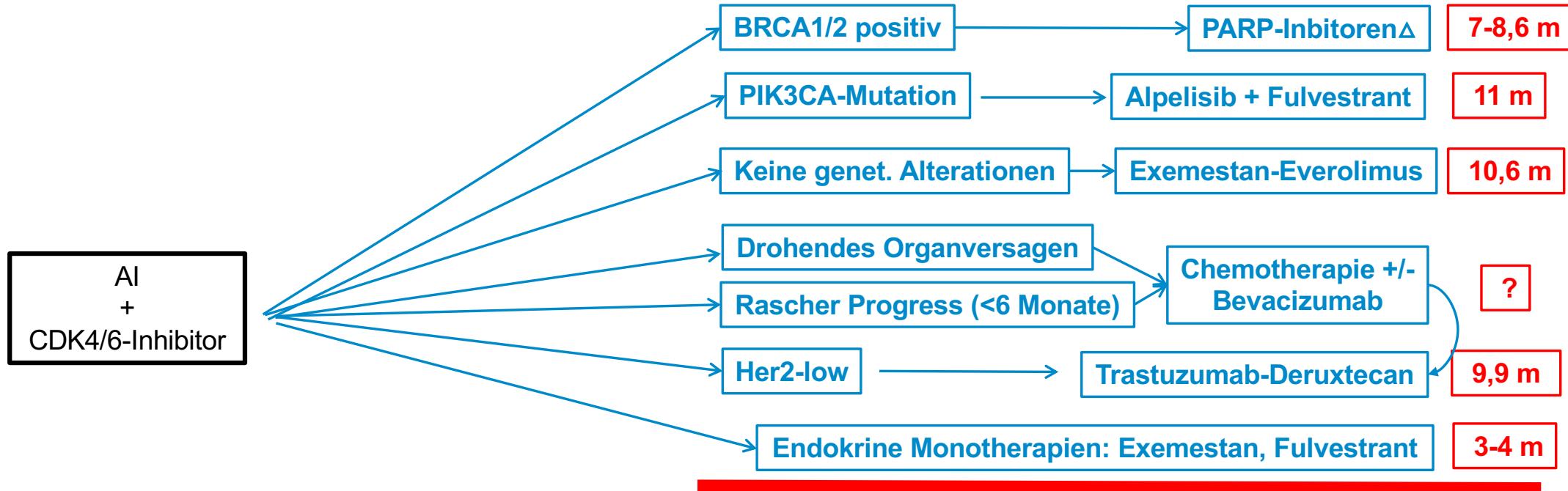


Table 3. Median OS After 1L RIB + ET, Grouped by Type of First Subsequent Therapy

	1L RIB + ET Followed by:			
	Any CT	ET Only	CDK4/6i	Targeted Therapy (Non-CDK4/6i)
Events/n	99/132	96/183	20/65	39/63
mOS, months	37.4	59.9	84.0	52.2
Hazard ratio vs CT (95% CI)		0.51 (0.38-0.69)	0.17 (0.10-0.30)	0.59 (0.40-0.89)

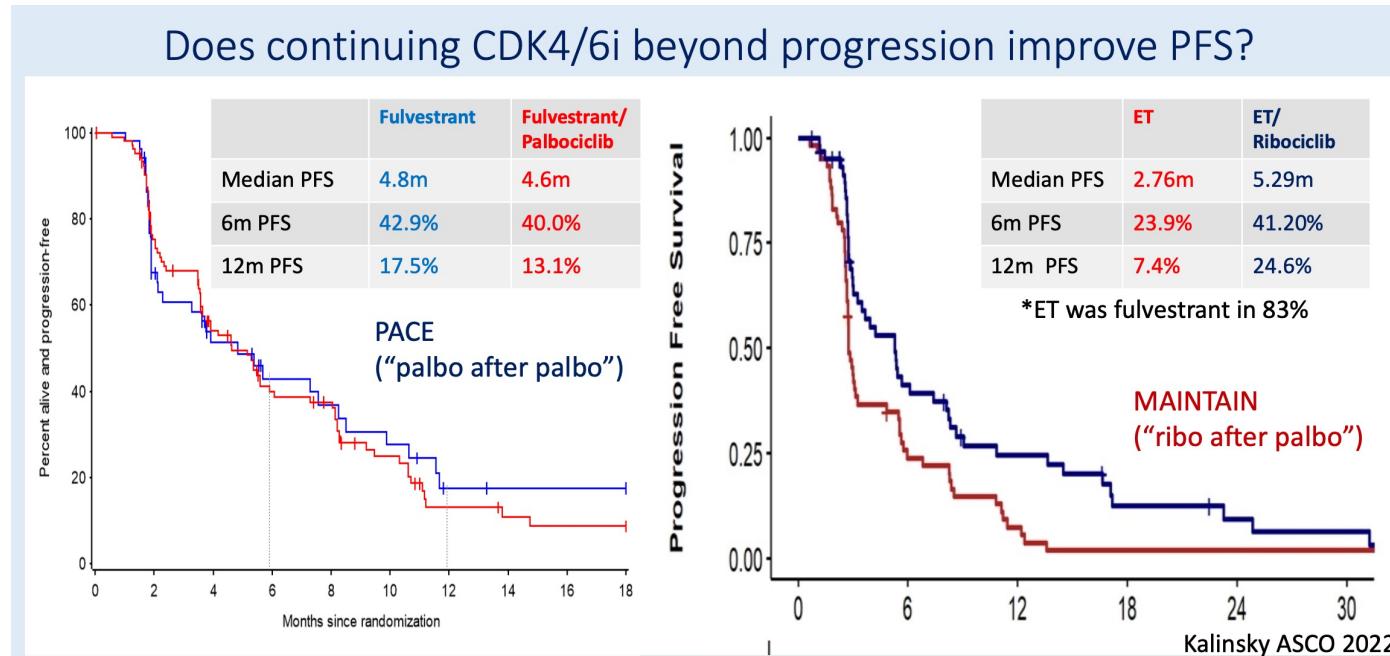
2.Therapielinie beim Hormonrezeptor-positives Mammakarzinom

PFS:



- Endokrine Vortherapie
- ESR1, PIK3CA, AKT/PTEN-Alterationen im Tumor
- BRCA1/2 Keimbahnmutation
- Ansprechens auf einen CDK 4/6-Inh. (\neq 12 Monate)

CDK4/6 Beyond Progression



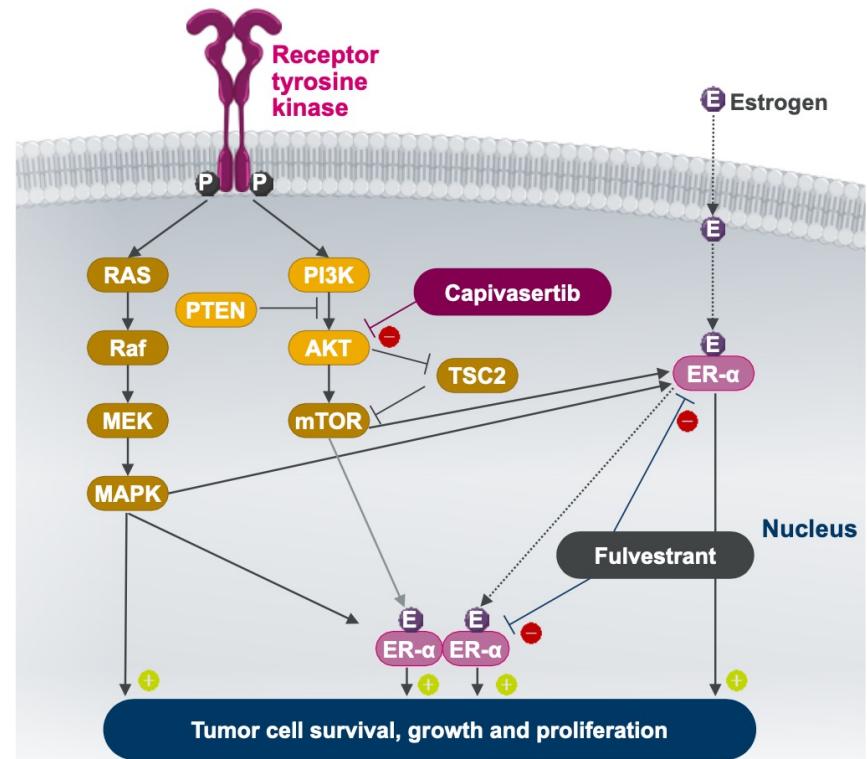
Study	Treatment	N
PALMIRA	ET +/- Palbociclib (after palbociclib)	198
EMBER-3	ET vs Imlunestrant vs Imlunestrant/Abemaciclib (after any CDK4/6i)	800
PostMONARCH	Fulvestrant +/- Abemaciclib (after any CDK4/6i)	350

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the Phase III CAPtello-291 trial

Nicholas C Turner,¹ Mafalda Oliveira,² Sacha Howell,³ Florence Dalenc,⁴ Javier Cortes,⁵ Henry Gomez,⁶ Xichun Hu,⁷ Komal Jhaveri,⁸ Sibylle Loibl,⁹ Serafin Morales Murillo,¹⁰ Zbigniew Nowecki,¹¹ Meena Okera,¹² Yeon Hee Park,¹³ Masakazu Toi,¹⁴ Lyudmila Zhukova,¹⁵ Chris Yan,¹⁶ Gaia Schiavon,¹⁶ Andrew Foxley,¹⁶ and Hope S Rugo¹⁷

CAPitello-291: Hintergrund

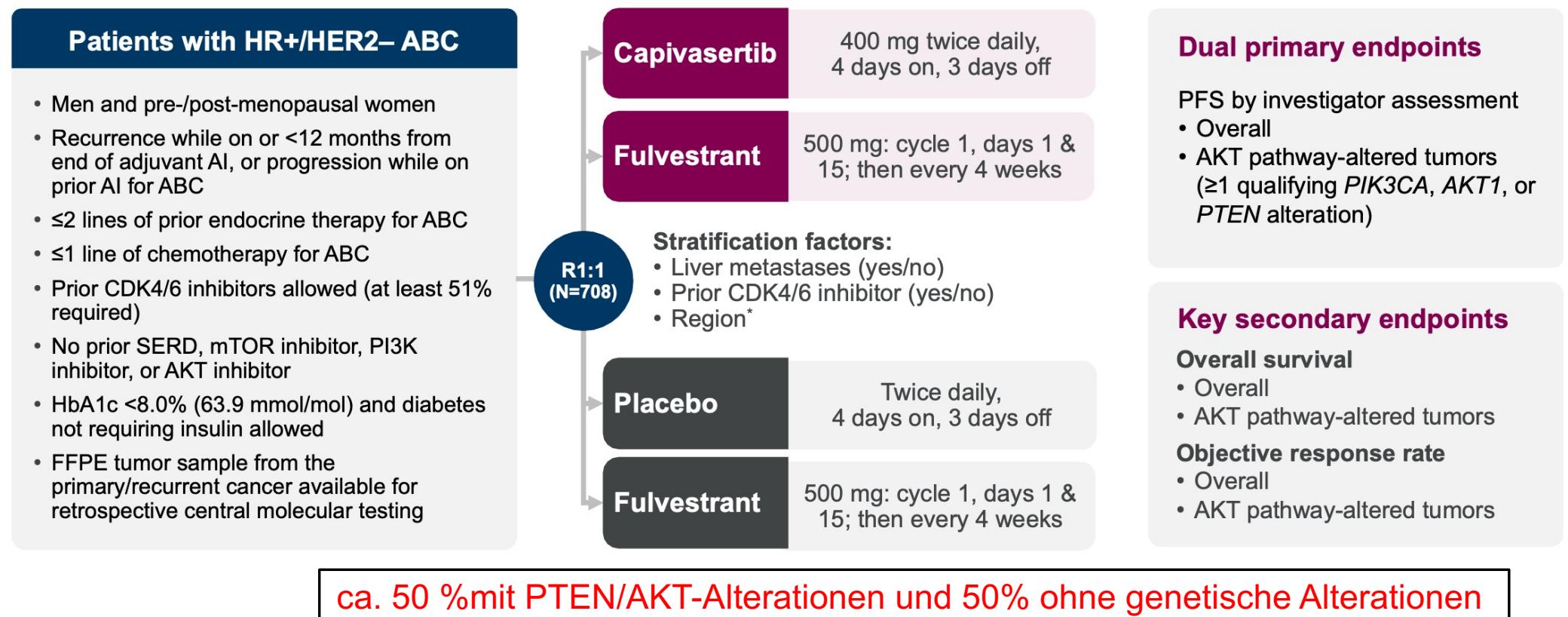
- AKT pathway activation occurs in many HR+/HER2–ABC through alterations in *PIK3CA*, *AKT1* and *PTEN*, but may also occur in cancers without those genetic alterations.^{1,2} AKT signalling is also implicated in the development of resistance to endocrine therapy²
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3)
- In the Phase II, placebo-controlled FAKTION trial³:
 - The addition of capivasertib to fulvestrant significantly improved PFS and OS in postmenopausal women with AI-resistant HR+/HER2–ABC in the overall population, with a more pronounced benefit in pathway altered tumours
 - No patients had received prior CDK4/6 inhibitors



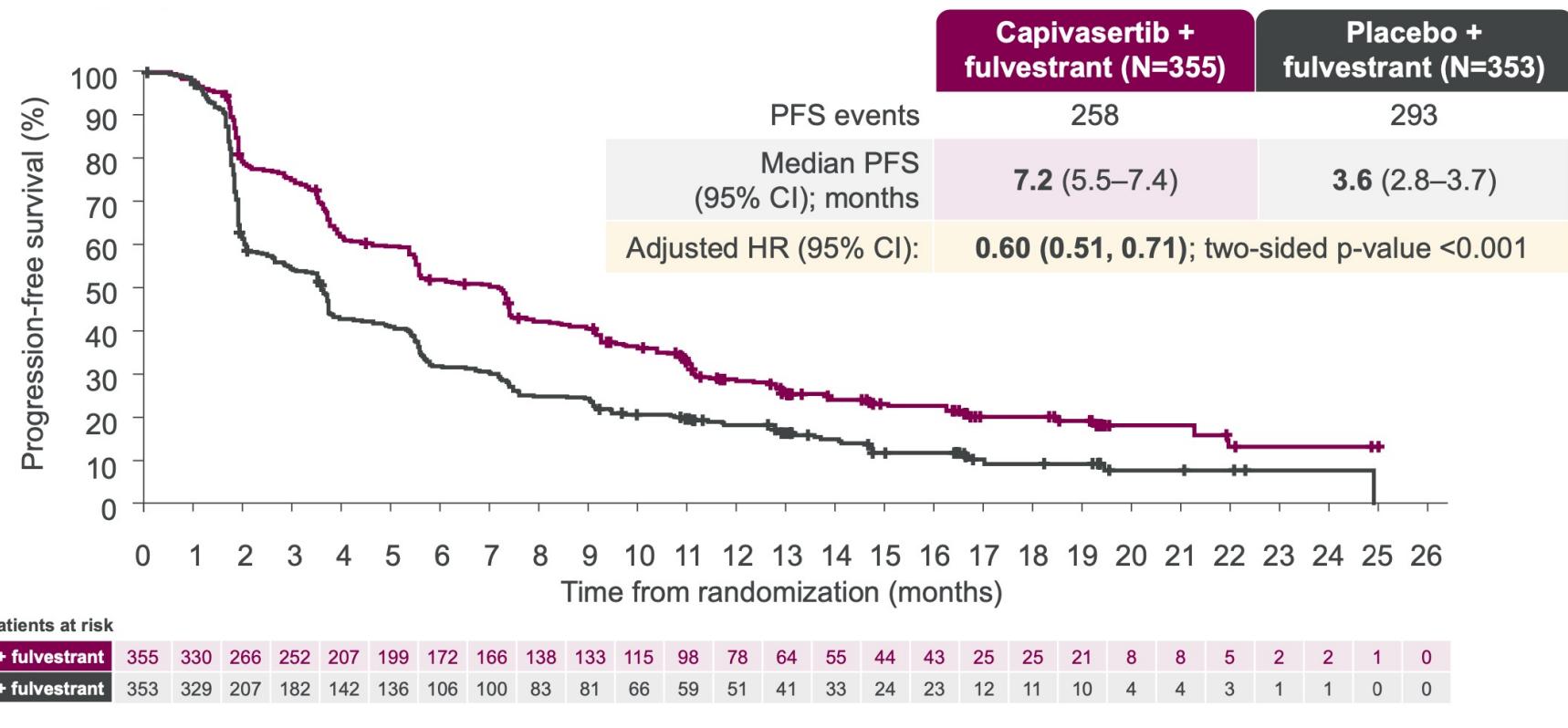
CAPtello-291

Studiendesign

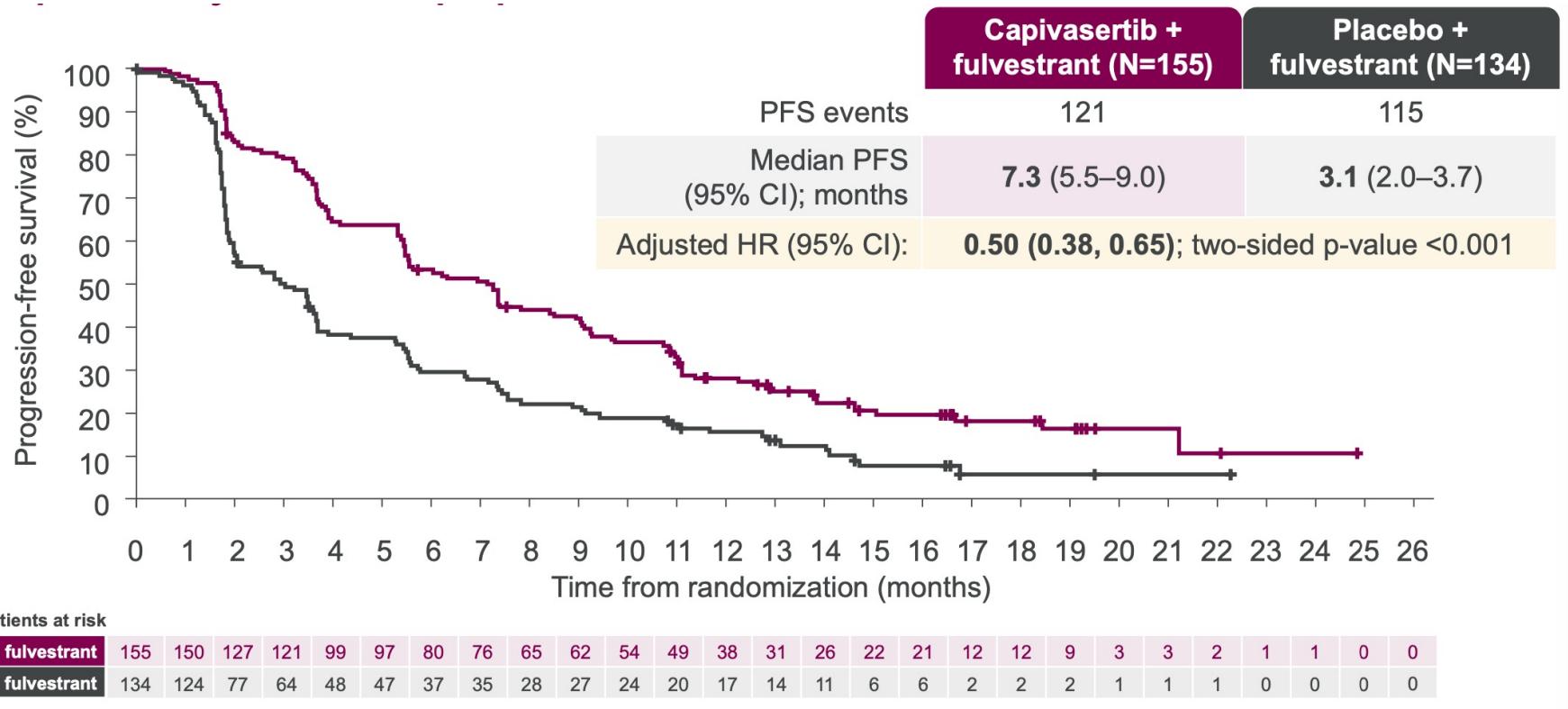
Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)



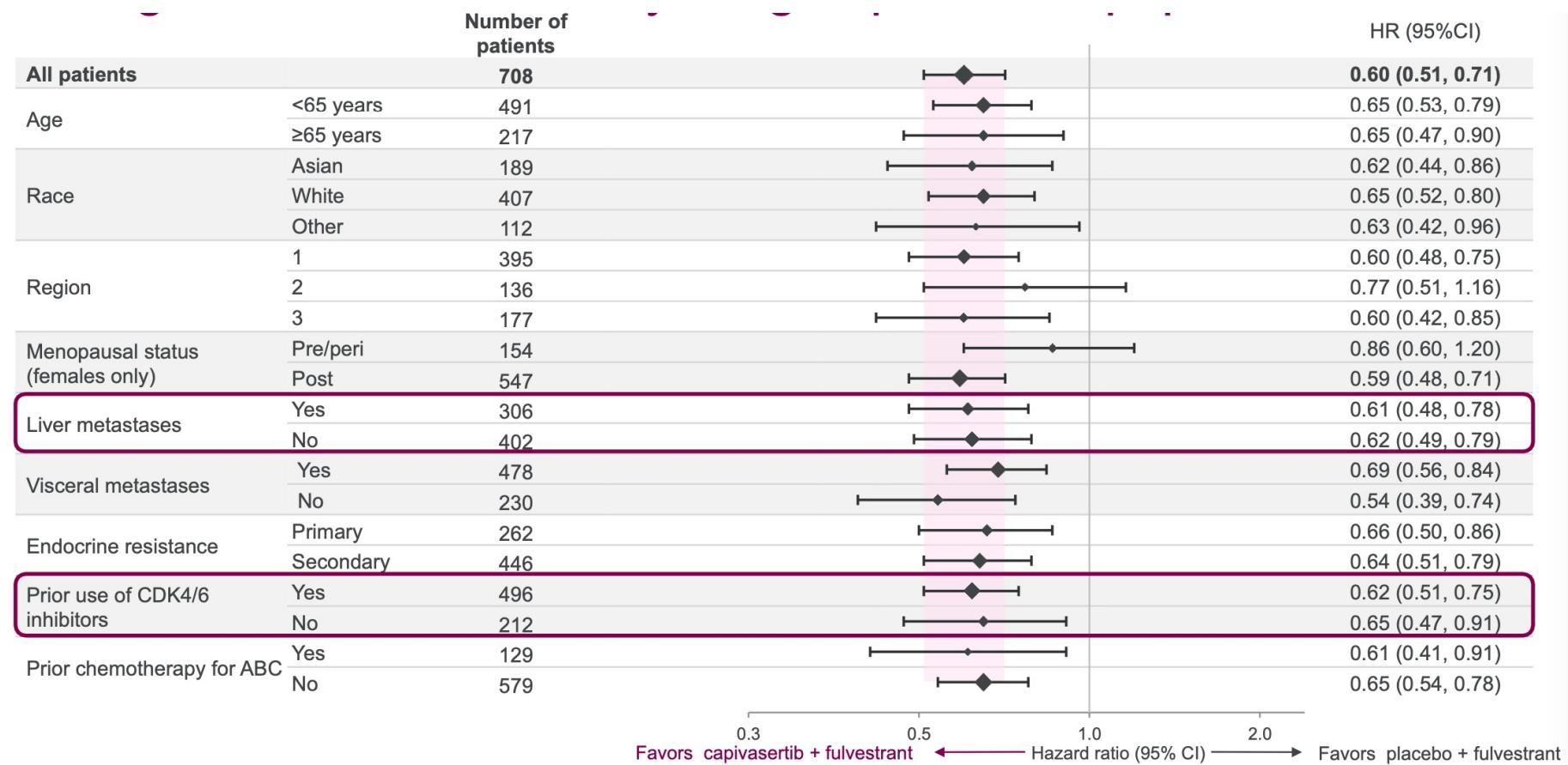
CAPtello-291 Progressionsfreies Überleben Gesamtpopulation



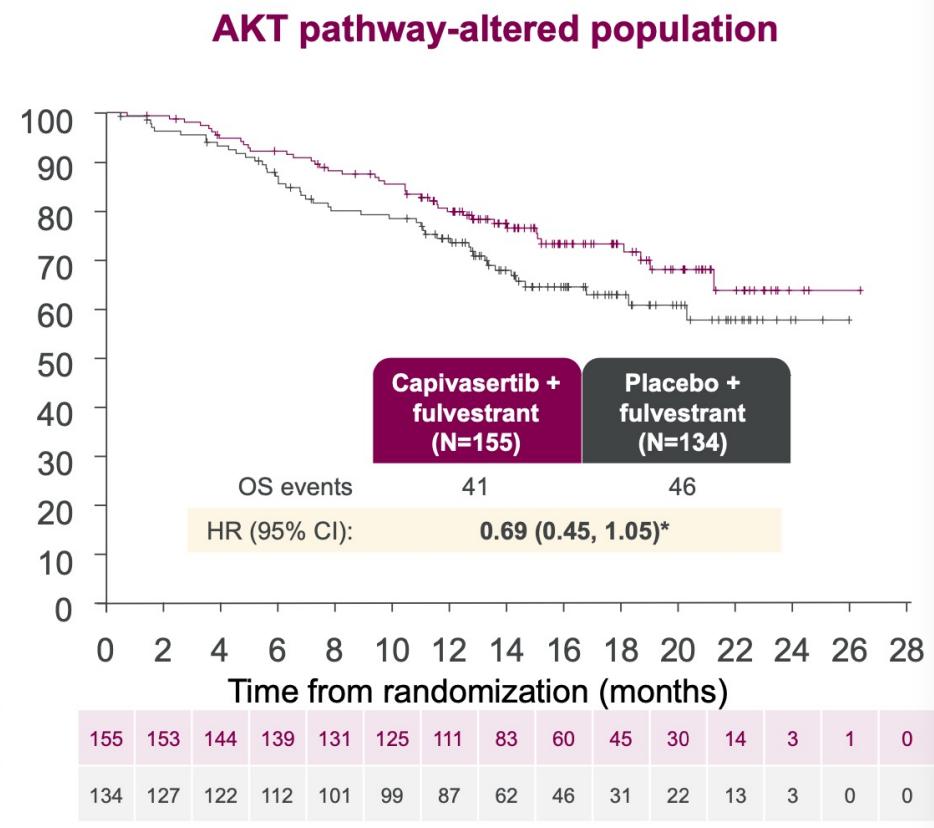
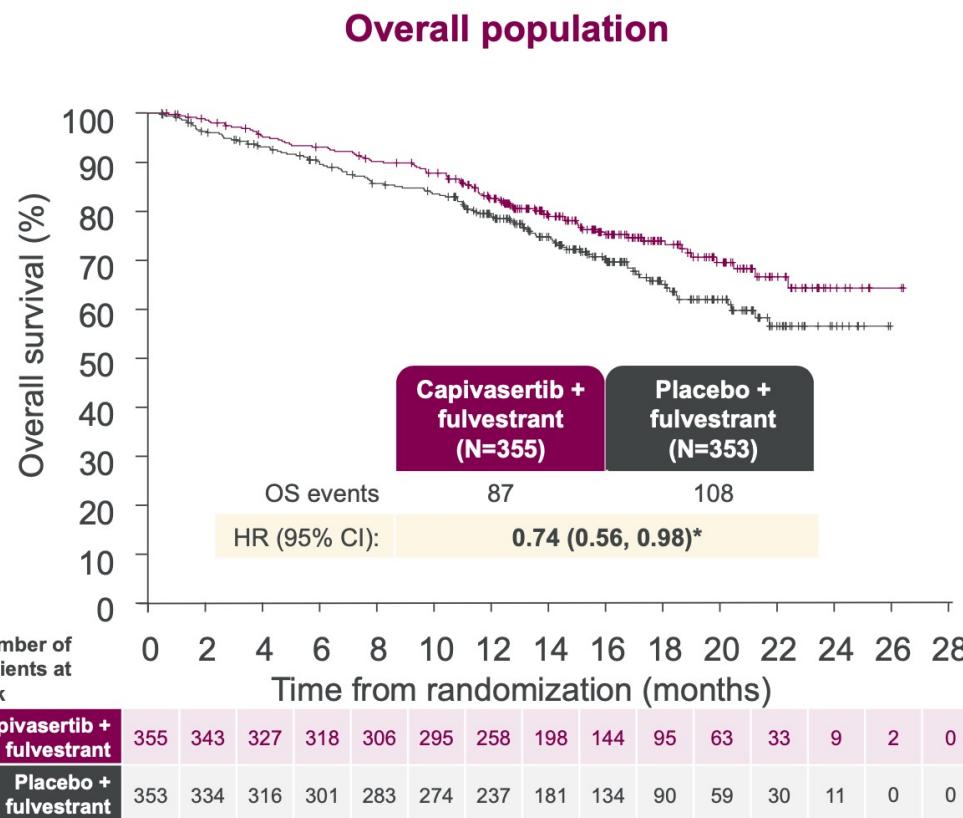
CAPItello-291: AKT-Signalweg- alteriert



CAPItello-291 Subgruppenanalyse

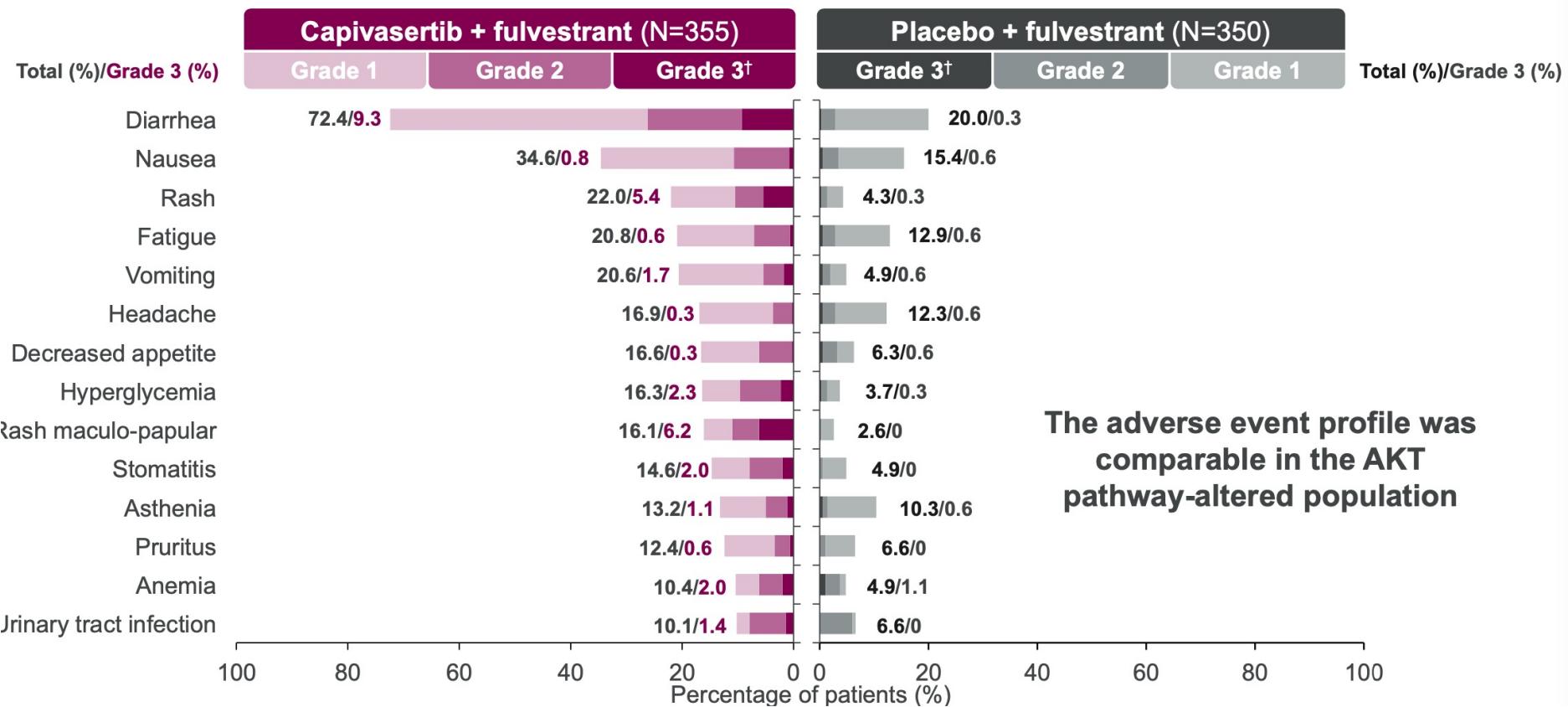


CAPtello-291 Gesamtüberleben



CAPtello-291 Toxizitäten

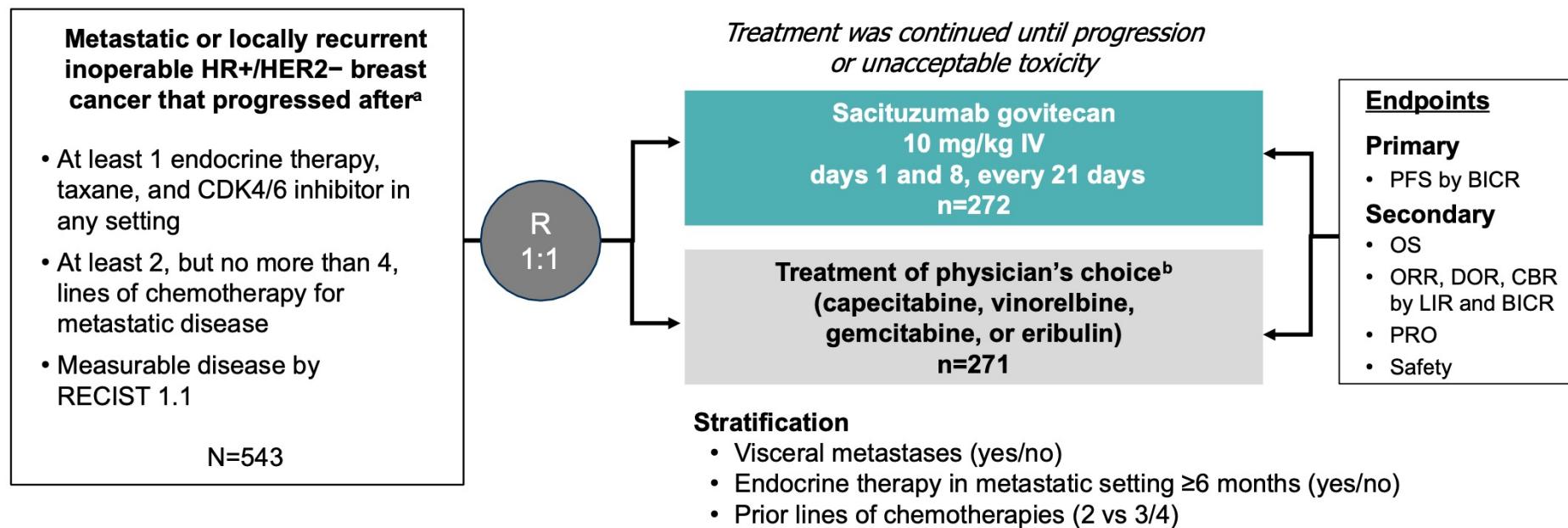
Adverse events (>10% of patients) – overall population

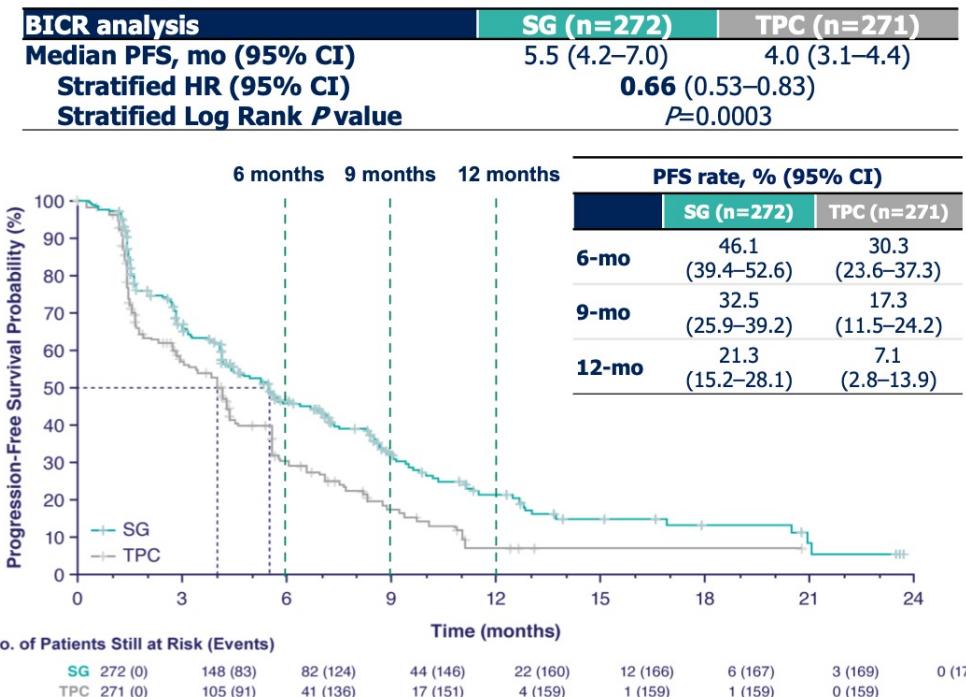
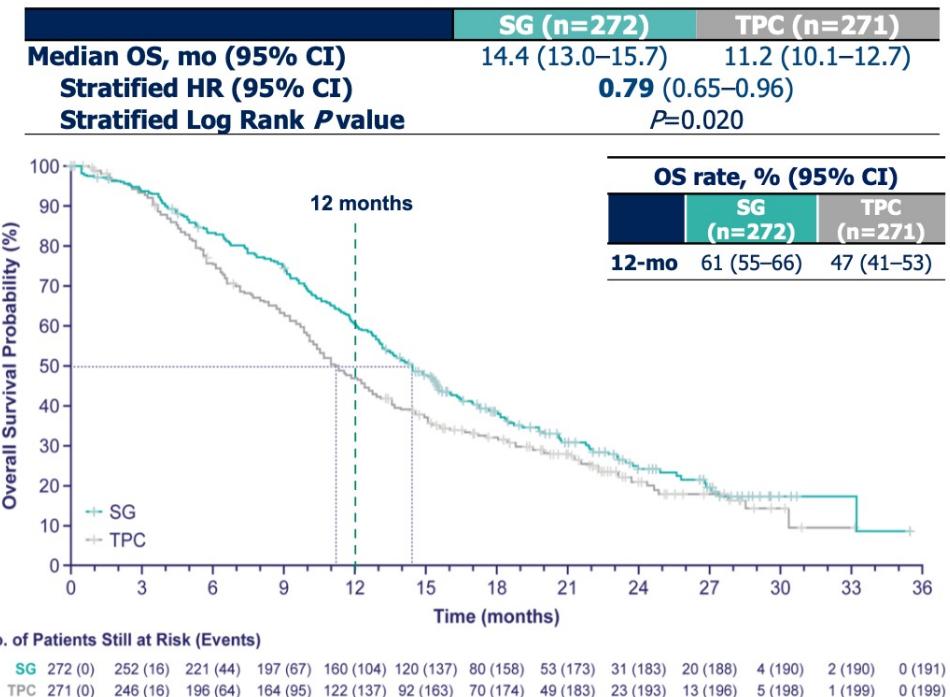


Sacituzumab Govitecan vs Treatment of Physician's Choice: Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients With HR+/HER2– Metastatic Breast Cancer

Hope S. Rugo,¹ Aditya Bardia,² Frederik Marmé,³ Javier Cortes,⁴ Peter Schmid,⁵ Delphine Loirat,⁶ Olivier Trédan,⁷ Eva Ciruelos,⁸ Florence Dalenc,⁹ Patricia Gómez Pardo,¹⁰ Komal L. Jhaveri,¹¹ Monica Motwani,¹² Oh Kyu Yoon,¹² Hao Wang,¹² Wendy Verret,¹² Sara M. Tolaney¹³

TROPiCS-02 Studiendesign



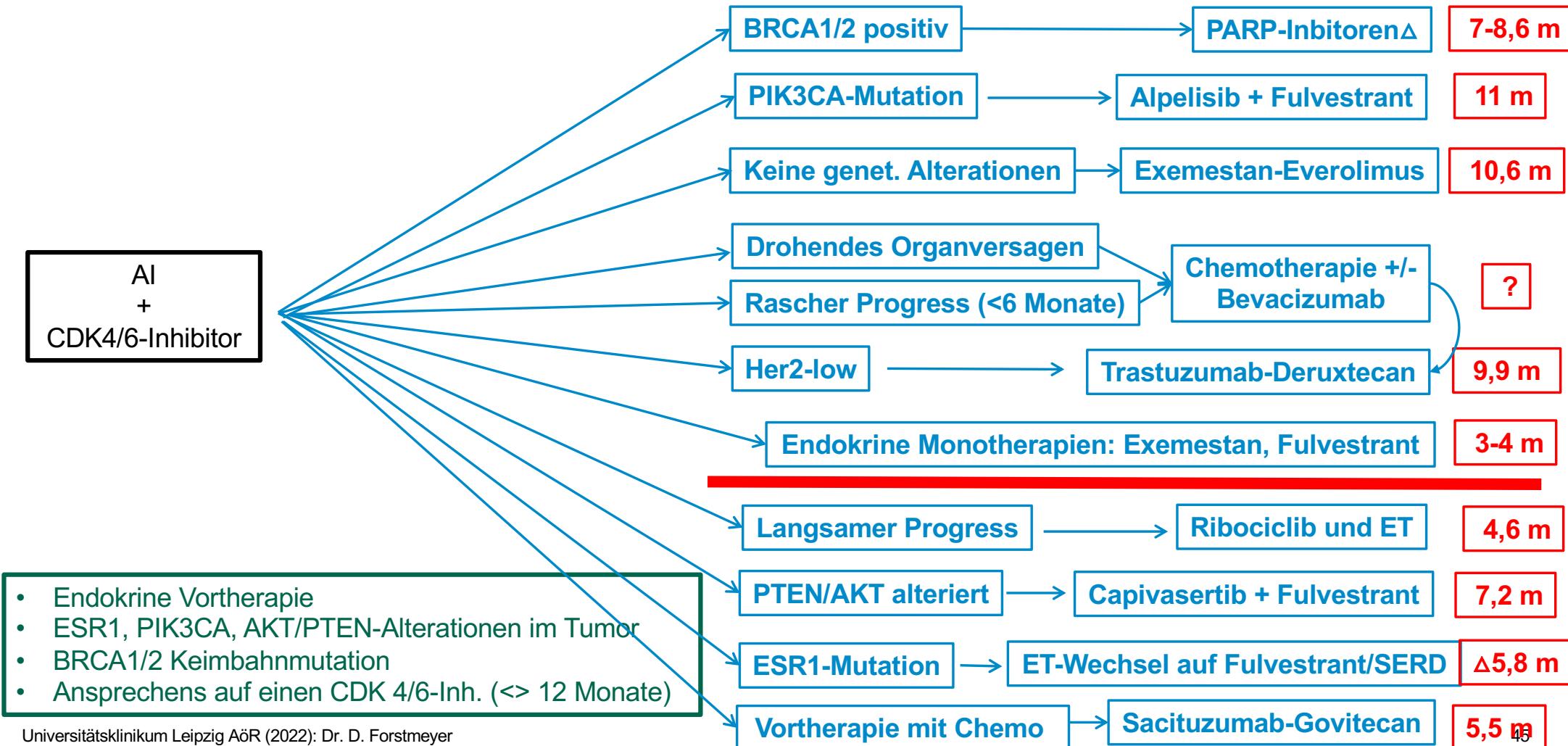
PFS¹OS²

Orale SERD-Studienlandschaft

	EMERALD¹	SERENA-2²	EMBER-3³	AMEERA-3⁴⁻⁶	acelERA⁶⁻⁹
Treatment	Elacestrant	Camizestrant	Imlunestrant +/- abemaciclib	Amcenestrant	Giredestrant
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	Required (100%)	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	YES	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	YES	YES	NO	YES	YES
Data readout	Positive (Registrational)	Positive (Non-Registrational)	Ongoing	Negative	Negative

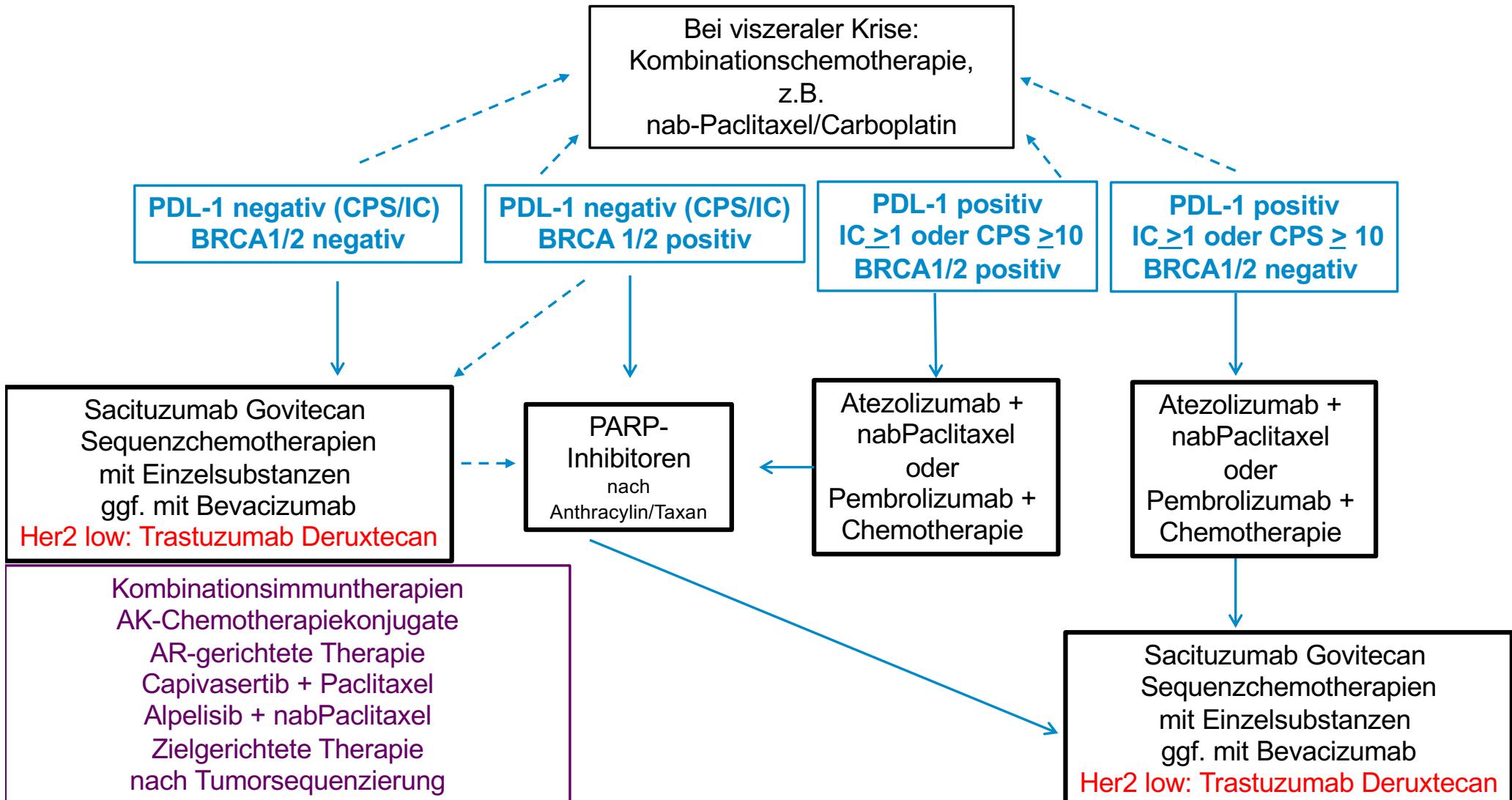
2.Therapielinie beim Hormonrezeptor-positives Mammakarzinom

PFS:



Metastasierte Triple-negative Mammakarzinom

Therapiesequenz Triple-negatives metastasiertes Mammakarzinom



**Vielen Dank für Ihre
Aufmerksamkeit**



Universitätsklinikum Leipzig AöR (2022): Dr. D. Forstmeyer



**NETZWERK
ONKOLOGISCHE
SPITZENZENTREN**

