Klinikum rechts der Isar
Technische Universität München

TZM Highlights

2023 ASCO ANNUAL MEETING

Fortgeschrittenes Mammakarzinom

18.06.2023 Franziska Kotzur

Interessenskonflikte

Reisekostenerstattung: Pfizer, Daiichi, Lilly

Advisory Board: Novartis, Pfizer

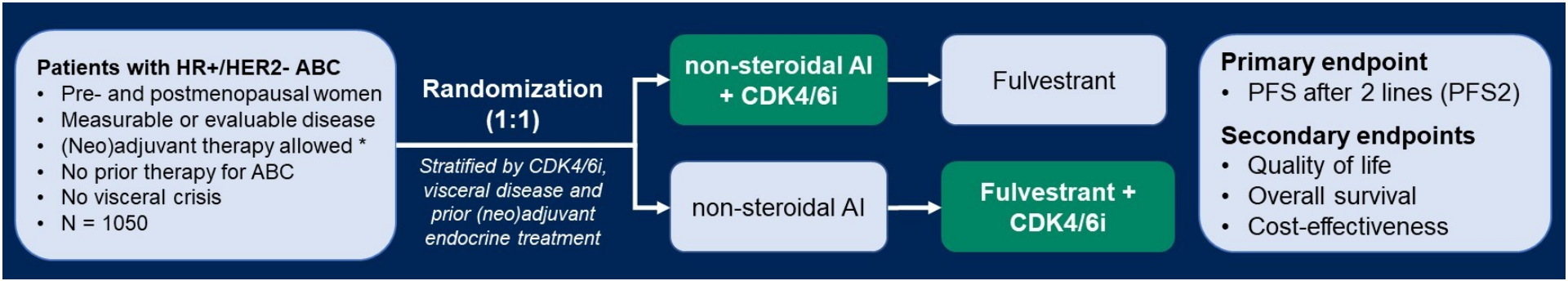
2023 ASCO® ANNUAL MEETING

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03)

Gabe Sonke, Annemiek van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid Swinkels, Hedwig Blommestein, Aart Beeker, Karin Beelen, Lisanne Hamming, Joan Heijns, Aafke Honkoop, Paul de Jong, Quirine van Rossum - Schornagel, Christa van Schaik - van de Mheen, Jolien Tol, Cathrien Tromp - van Driel, Suzan Vrijaldenhoven, Elise van Leeuwen - Stok, Inge Konings, Agnes Jager

SONIA

Studiendesign



- 1050 Pat., 72 Zentren in den Niederlanden
- Primärer Endpunkt PFS2:
  Zeit von Randomisierung bis Progress in der Zweitlinie

SONIA

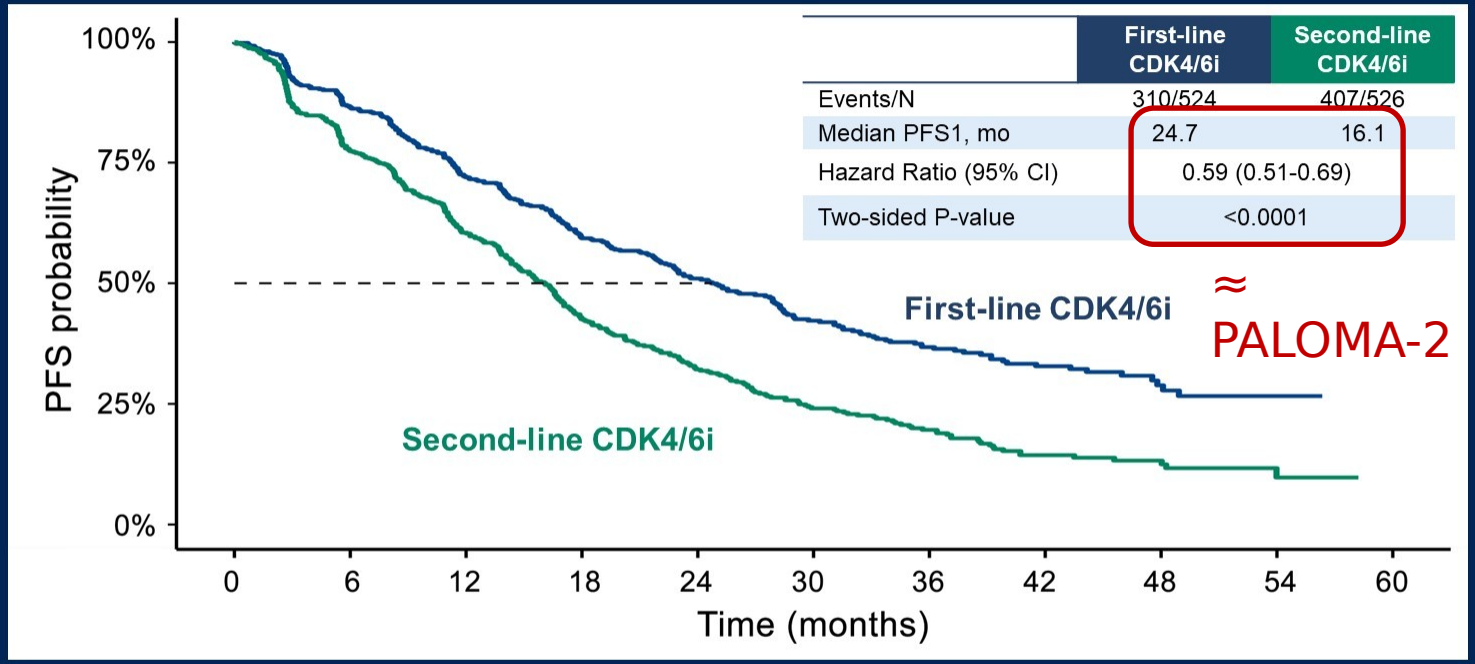
Baseline characteristics

		First-line CDK4/6i N=524	Second-line CDK4/6i N=526
Median age, years (range)		64 (24-88)	63 (25-87)
WHO PS, n (%)	0	257 (49)	257 (49)
	≥1	267 (51)	269 (51)
Menopausal status, n (%)	Pre- / perimenopausal	69 (13)	76 (14)
	Postmenopausal	455 (87)	450 (86)
Disease-free interval, n (%)	De novo	182 (35)	182 (35)
	≤24 months	96 (18)	98 (19)
	>24 months	246 (47)	246 (47)
Prior (neo)adjuvant therapy, n (%)	Chemotherapy	212 (40)	210 (40)
	Endocrine therapy	256 (49)	253 (48)
Metastatic site, n (%)	Visceral disease	291 (56)	292 (56)
	Bone-only disease	91 (17)	91 (17)
Measurable disease, n (%)		315 (60)	312 (59)
Type of CDK4/6i intended, n (%)	Palbociclib	479 (91)	479 (91)
	Ribociclib	42 (8)	44 (8)
	Abemaciclib	3 (1)	3 (1)

91% Palbociclib!

SONIA

PFS1 Analyse

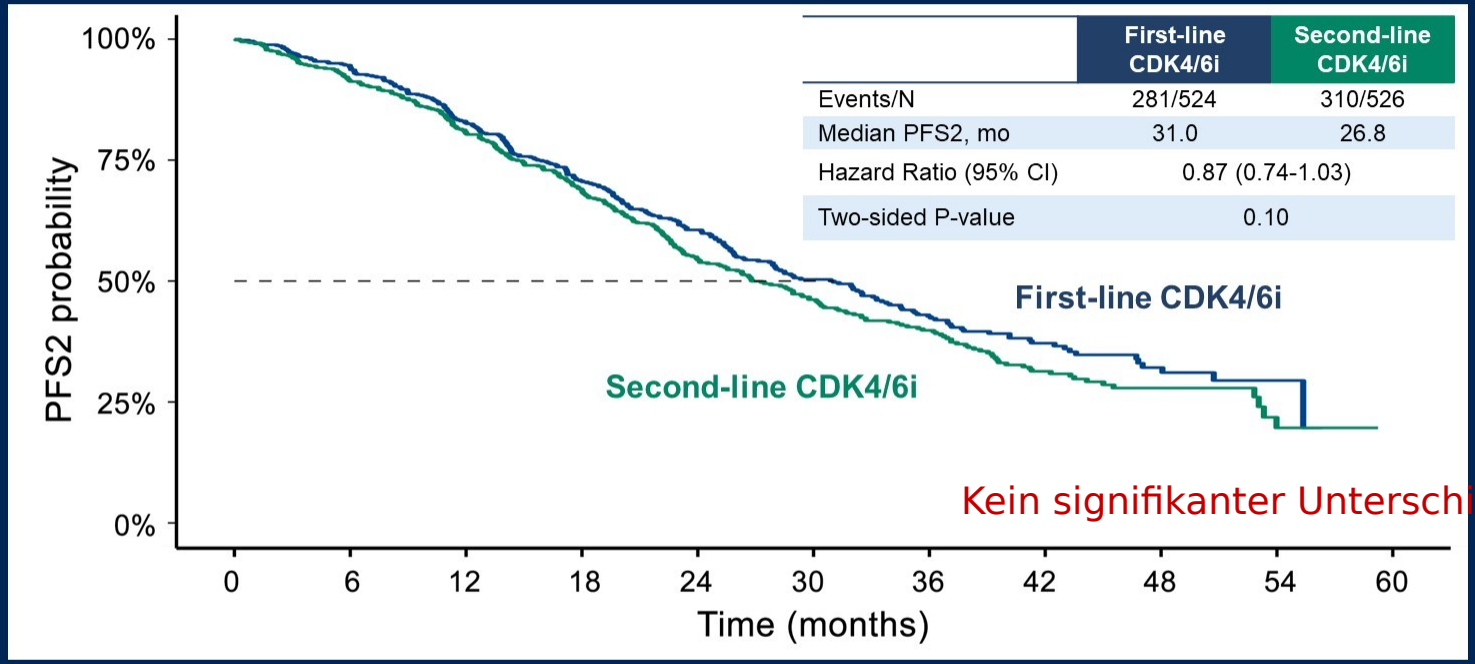


	First-line CDK4/6i	Second-line CDK4/6i
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

Numbers at risk (censored)											
First-line	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (210)
Second-line	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

SONIA

PFS2 Analyse: Zeit von Randomisierung bis Progress in der Zweitlinie



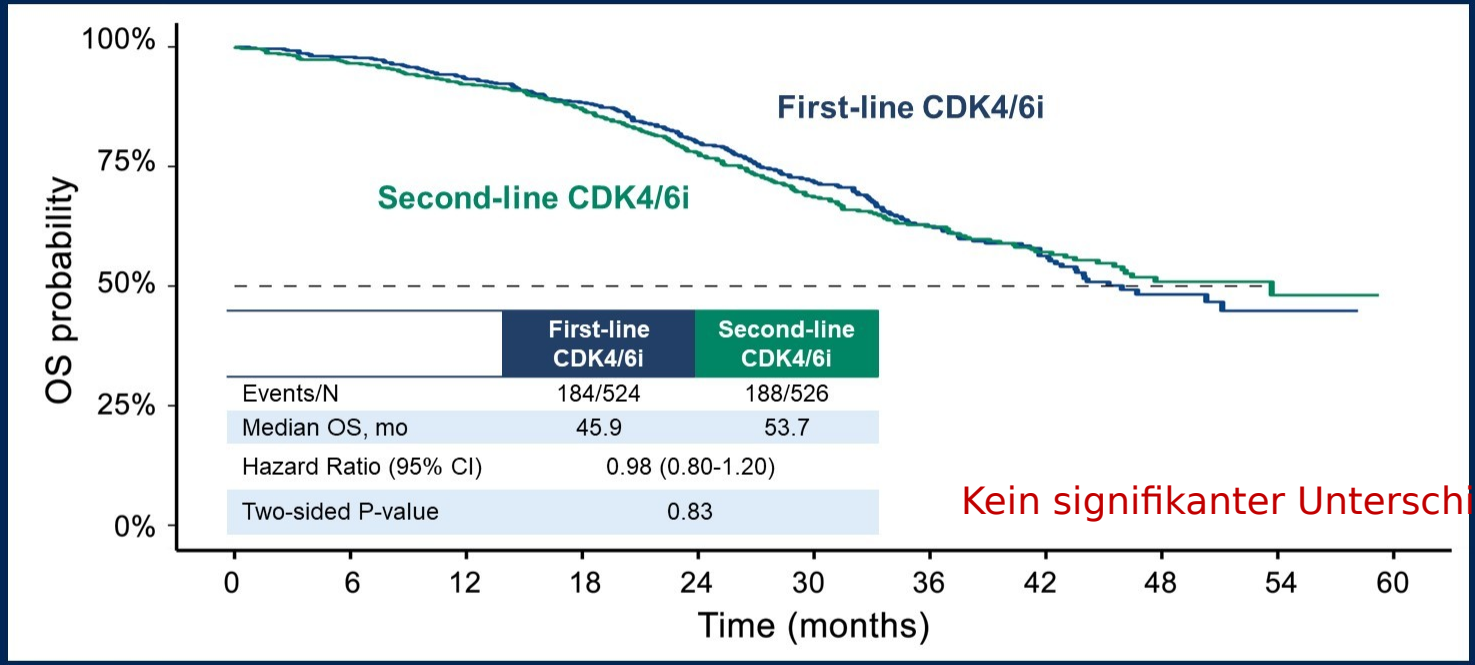
	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

Kein signifikanter Unterschied

Numbers at risk (censored)											
First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (315)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)

SONIA

Overall Survival



	First-line CDK4/6i	Second-line CDK4/6i
Events/N	184/524	188/526
Median OS, mo	45.9	53.7
Hazard Ratio (95% CI)	0.98 (0.80-1.20)	
Two-sided P-value	0.83	

Kein signifikanter Unterschied

Numbers at risk (censored)											
First-line	524 (0)	510 (3)	485 (4)	427 (37)	324 (103)	240 (157)	171 (197)	104 (250)	42 (300)	7 (333)	0 (340)
Second-line	526 (0)	506 (2)	483 (2)	426 (32)	328 (89)	242 (139)	175 (186)	112 (236)	52 (287)	16 (322)	0 (338)

SONIA

Diskussion: Behandlungsdauer, Nebenwirkungen und Kosten

- Dauer der CDK4/6i-Behandlung: 24,6 Monate (Erstlinie) vs. 8,1 Monate (Zweitlinie)
- Typische Nebenwirkungen: Neutropenie, Leberfunktionsstörung, Anämie, Thrombopenie
- Bei Einsatz von CDK4/6i in der Erstlinie:
  - 42% höhere Inzidenz von AEs ≥ Grad 3 (wegen längerer Therapiedauer)
  - Höhere Behandlungskosten von ca. 200.000 € pro PatientIn
  - Keine signifikante Verbesserung von PFS2 oder OS

→ Einsatz in der Erstlinie überhaupt sinnvoll?

SONIA

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→ Einsatz in der Erstlinie überhaupt sinnvoll?

Nicht berücksichtigt: Kombinationstherapien in der Zweitlinie (Everolimus, Alpelisib, Capivasertib, anderer CDK4/6i, …)

2023 ASCO® ANNUAL MEETING

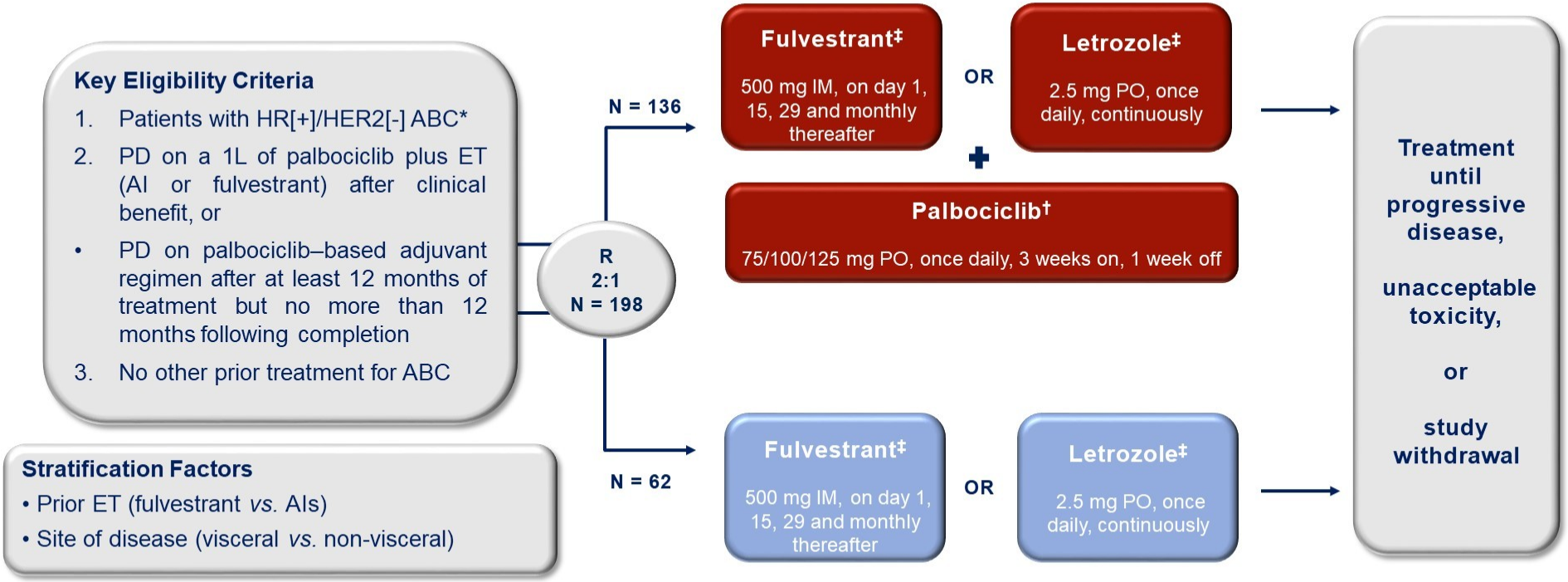
Second-line endocrine therapy with or without palbociclib maintenance in patients with HR[+]/HER2[-] advanced breast cancer: PALMIRA trial

Antonio Llombart-Cussac[1], Catherine Harper-Wynne[2], Antonia Perelló[3], Audrey Hennequin[4], Adela Fernández[5], Marco Colleoni[6], Vicente Carañana[7], Vanesa Quiroga[8], Jacques Medioni[9], Vega Iranzo[10], Duncan Wheatley[11], Sonia del Barco Berrón[12], Antonio Antón[13], Erion Dobi[14], Manuel Ruiz[15], Daniel Alcalá-López[16], Jhudit Pérez-Escuredo[17], Miguel Sampayo-Cordero[18], José Manuel Pérez-García[19], Javier Cortés[20]

1. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Hospital Arnau de Vilanova; FISABIO, Valencia, Spain. Universidad Católica de Valencia, Valencia, Spain; 2. Maidstone Hospital - Kent Oncology Centre, Maidstone, United Kingdom; 3. Hospital Universitari Son Espases, Palma de Mallorca, Spain; 4. Centre Georges François Leclerc, Dijon, France; 5. Institut Català d' Oncologia L'Hospitalet (ICO), Barcelona, Spain; 6. IEO, Instituto Europeo di Oncologia, IRCCS; Milan, Italy; 7. Hospital Arnau de Vilanova de Valencia, Valencia, Spain; 8. Institut Català d' Oncologia Badalona (ICO), Barcelona, Spain; 9. Hopital Europeen Georges Pompidou, Paris, France. University Paris Cite; 10. Consorci Hospital General Universitari de València, Valencia, Spain; Universitat de Valencia, Valencia, Spain; 11. Royal Cornwall Hospital NHS Trust, Cornwall, United Kingdom; 12. Institut Català d' Oncologia Girona (ICO), Girona, Spain; 13. Hospital Universitario Miguel Servet, Zaragoza, Spain; 14. Hôpital Jean Minjoz, Doubs, France; 15. Hospital Universitario Virgen del Rocío, Sevilla, Spain; 16. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; 17. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; 18. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; 19. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US; 20. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US. Universidad Europea de Madrid, Madrid, Spain.

PALMIRA

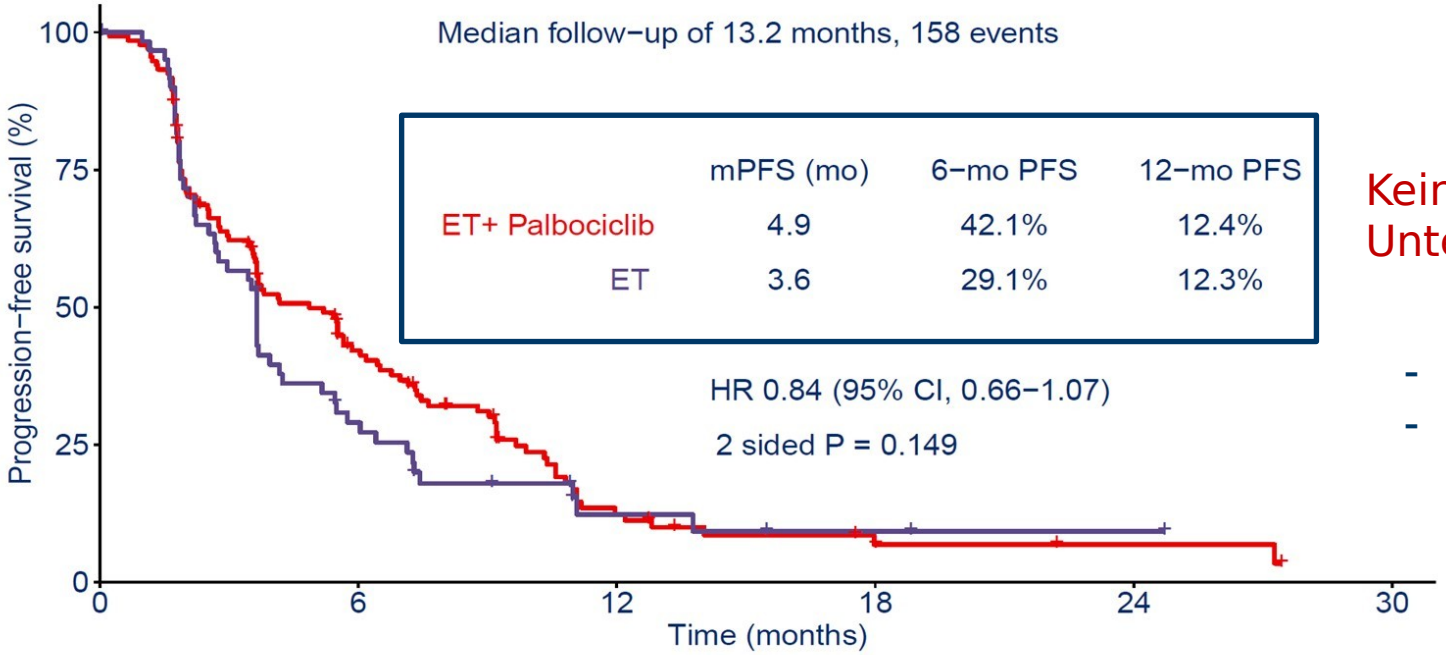
Studiendesign



1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2[-]: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

PALMIRA

Primärer Endpunkt: PFS (ITT Population)



	mPFS (mo)	6−mo PFS	12−mo PFS
ET+ Palbociclib	4.9	42.1%	12.4%
ET	3.6	29.1%	12.3%

Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

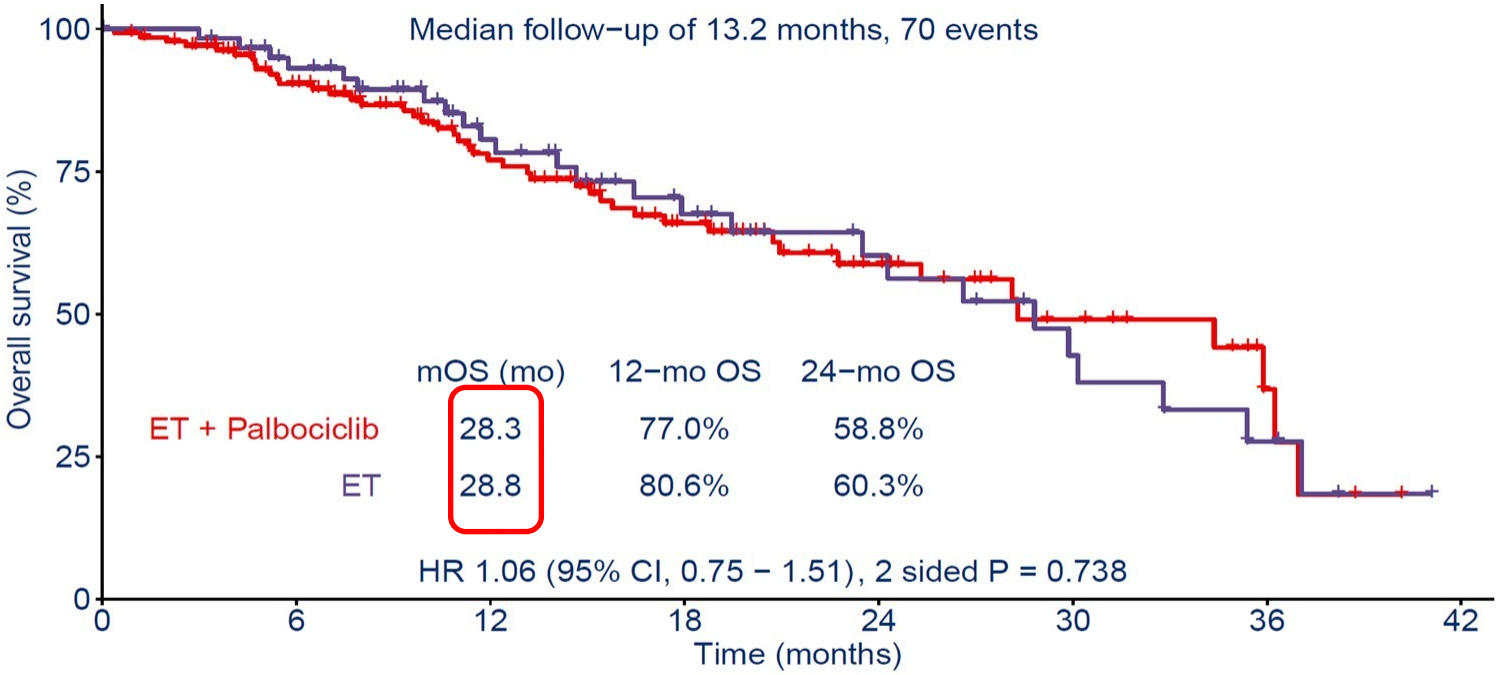
CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

Kein signifikanter Unterschied

- ORR: 4,4% vs 1,6
- Clinical Benefit Rate (CR,PR oder SD ≥24 Wochen: 41,9% vs 27,4%

PALMIRA

Overall Survival



Patients at risk, n (%)

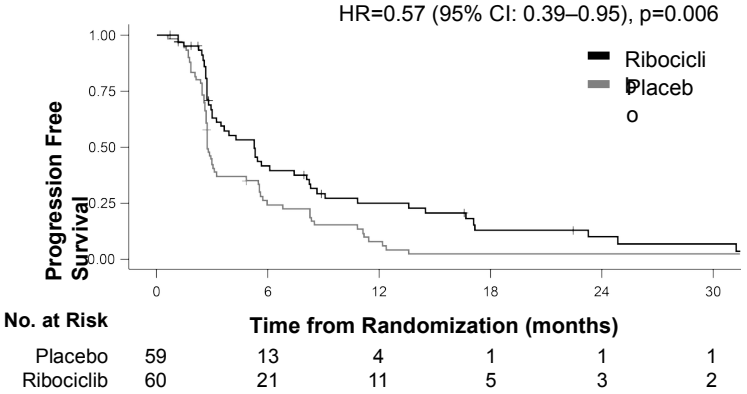
ET+Palbociclib	136 (100)	106 (78)	68 (50)	46 (34)	25 (18)	13 (10)	4 (3)	0 (0)
ET	62 (100)	52 (84)	35 (56)	23 (37)	15 (24)	9 (15)	4 (6)	0 (0)

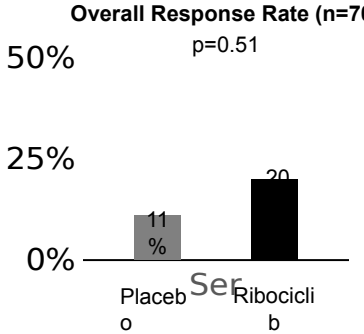
CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mOS: median Overall survival.

ASCO 2022: MAINTAIN (Kalinsky et al.)

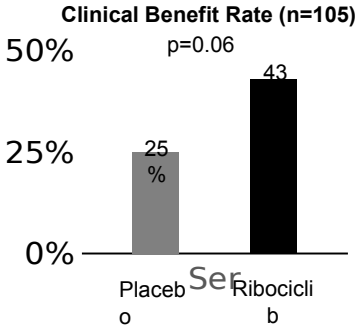
PFS (Primärer Endpunkt), ORR, CBR

	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66–3.25)	**5.29** (3.02–8.12)





	Placebo + ET (n=35)	Ribociclib + ET (n=35)
CR	0 (0%)	2 (6%)
PR	4 (11%)	5 (14%)
Median DOR (IQR) (mos)	14.8 (6.7–21.3)	18.8 (11.4–50.2)



	Placebo + ET (n=57)	Ribociclib + ET (n=49)
CR, PR, or SD ≥24 weeks	14 (25%)	21 (43%)

PFS signifikant verbessert

PALMIRA

Fazit:

- **Die Fortführung von Palbociclib „beyond progression“ führt nicht zu Verbesserung des PFS im Vergleich zur endokrinen Monotherapie**

- Wenn Fortführung CDK4/6i in der Zweitlinie, sollten sowohl die endokrine Therapie als auch der CDK4/6i gewechselt werden

2023 ASCO® ANNUAL MEETING

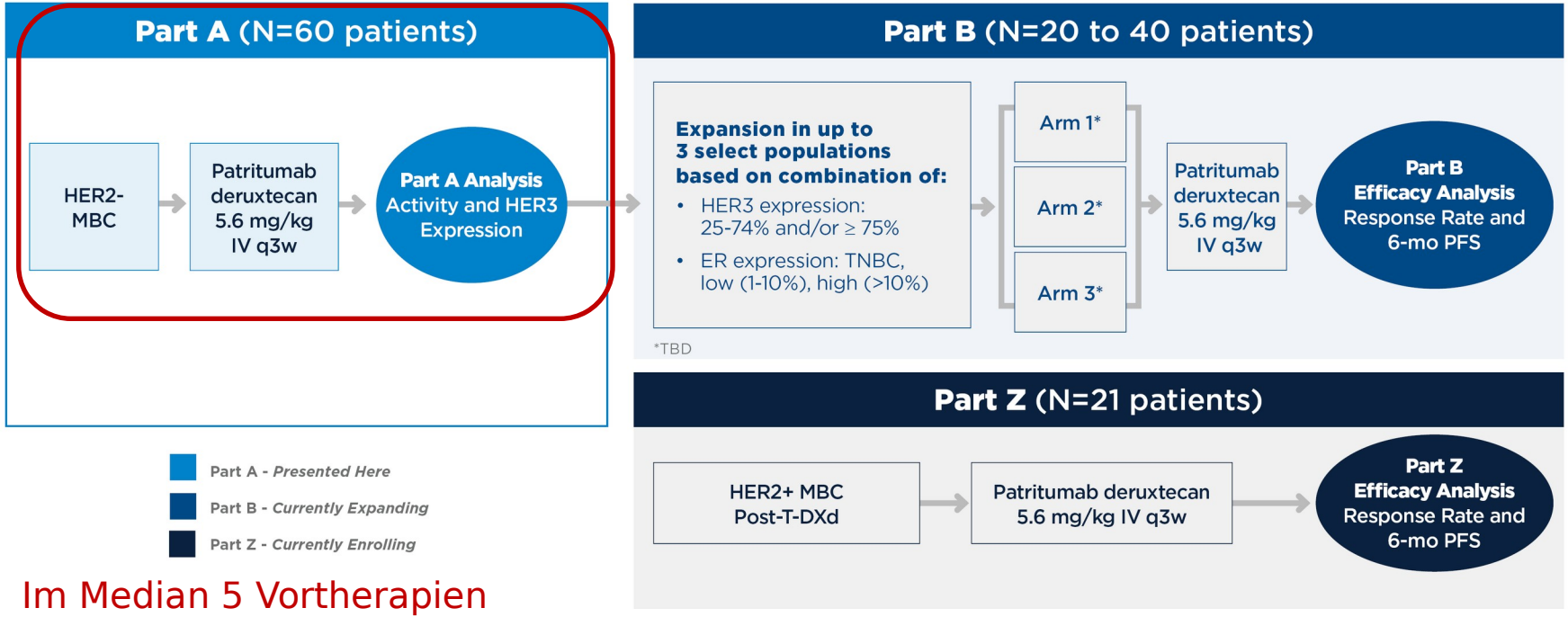
A Phase II Study of HER3-DXd in Patients with Metastatic Breast Cancer

Erika P. Hamilton, MD[1,2]; Ololade Dosunmu, MD, MPH[1]; Mythili Shastry, PhD[1]; Lindsey Finney, MS[1]; Dalila Sellami, MD[3]; David Sternberg, MD, PhD[3]; Vance Wright-Browne, MD[4]; Deborah Toppmeyer, MD[5]; William R. Gwin III, MD[6]; J. Thaddeus Beck, MD, FACP[7]; Jennifer Cultrera, MD[8]; Nusayba A. Bagegni, MD[9]; Katia Khoury, MD[10]; Arielle Heeke, MD[11]; Yuan Yuan, MD, PhD[12]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Daiichi Sankyo, Inc., Basking Ridge, NJ; [4]Florida Cancer Specialists South, Fort Myers, FL; [5]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [6]University of Washington, Seattle, WA; [7]Highlands Oncology, Springdale, AR; [8]Florida Cancer Specialists North, St. Petersburg, FL; [9]Washington University, St. Louis, MO; [10]O'Neal Comprehensive Cancer Center at the University of Alabama, Birmingham, AL; [11]Levine Cancer Institute, Charlotte, NC; [12]City of Hope Comprehensive Cancer Center, Duarte, CA

BRE-354

Studiendesign

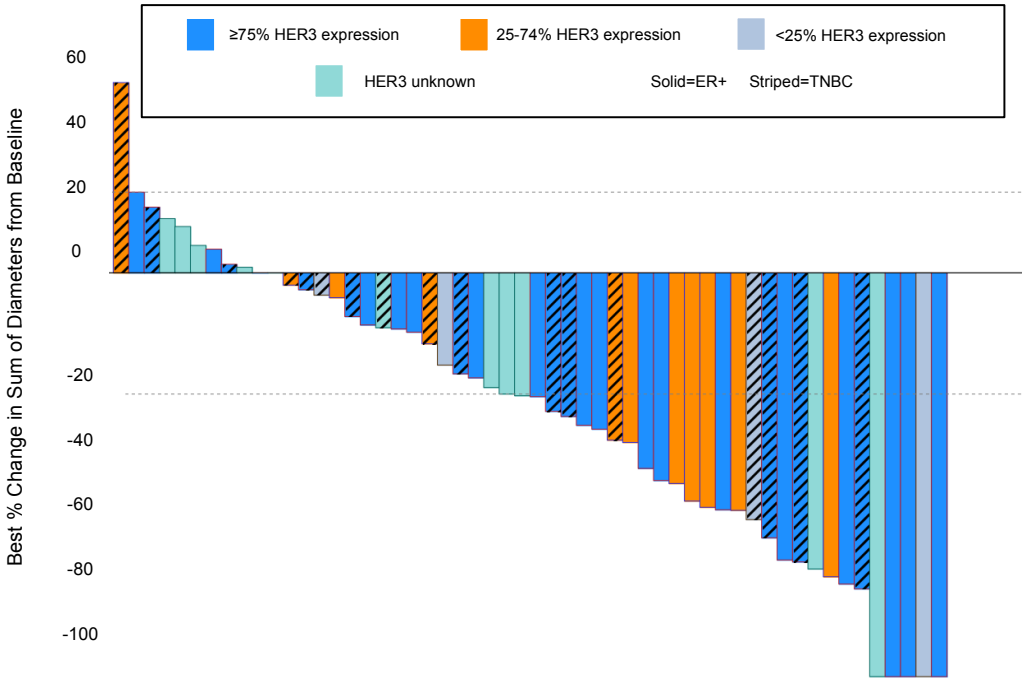


- Im Median 5 Vortherapien
- HER3-Expression:
  - ≥75%: 30/47 (64%)
  - 25-74%: 13/47 (28%)
  - <25%: 4/47 (8%)

BRE-354

Ansprechen nach HER3-Expression und klinischem Subtyp

Best Percent Change in Sum of Diameters from Baseline in Target Lesions



BRE-354

Ansprechen nach HER3-Expression und klinischem Subtyp

HER3-Expression ≥75%

	ER+ (N=16)	TNBC (N=11)
ORR, n (%)	**6 (37.5)**	**2 (18.2)**
95% CI	(15.2, 64.6)	(2.3, 51.8)
CBR, n (%)	**8 (50.0)**	**2 (18.2)**
95% CI	(24.7, 75.3)	(2.3, 51.8)
DoR ≥ 6 months, n (%)	**3 (50.0)**	**1 (50.0)**

All patients

	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	**12 (41.4)**	**4 (21.1)**
95% CI	(23.5, 61.1)	(6.1, 45.6)

HER3-Expression 25-74%

	ER+ (N=5)	TNBC (N=5)
ORR, n (%)	**3 (60.0)**	**1 (20.0)**
95% CI	(14.7, 94.7)	(0.5, 71.6)
CBR, n (%)	**3 (60.0)**	**2 (40.0)**
95% CI	(14.7, 94.7)	(5.3, 85.3)
DoR ≥ 6 months, n (%)	**1 (33.3)**	**0**

Ansprechen unabhängig vom Level der HER3-Expression

BRE-354

Sicherheitsprofil

Treatment-Related Adverse Events Occurring in ≥10% of Patients by Highest Reported Grade*

	Any grade (N=60) n (%)	Grade 3/4 (N=60) n (%)
Any Adverse Event (AE)	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased Appetite	8 (13.3)	0
Neutrophil Count Decreased**	7 (11.7)	3 (5.0)
White Blood Cell Count Decreased**	7 (11.7)	1 (1.7)

Treatment-Emergent Serious Adverse Events

Treatment-related SAEs	(N=60), n (%)
Interstitial Lung Disease†	1 (1.7)
Nausea/Vomiting	1 (1.7)
Pneumonitis	1 (1.7)
Thrombocytopenia	1 (1.7)
Unrelated SAEs	
Dyspnea	1 (1.7)
Pneumocystis jirovecii pneumonia	1 (1.7)
Pneumothorax	1 (1.7)

- Häufigste Nebenwirkungen: Übelkeit, Fatigue, Diarrhoe, Anämie, Alopezie
- Ein ILD/Pneumonitis-Fall, nach Data Cutoff Grad 5!

BRE-354

Fazit:

Patritumab Deruxtecan (HER3-DXd) zeigt vielversprechende Aktivität beim vorbehandelten HER2-negativen Mammakarzinom – unabhängig des Levels der HER3-Expression

2023 ASCO ANNUAL MEETING

Randomized Trial of Fixed Dose Capecitabine Compared to Standard Dose Capecitabine in Metastatic Breast Cancer: X-7/7 trial

Qamar Khan, Colleen Bohnenkamp, Taylor Monson, Holly Smith, Milind Phadnis, Vinay Raja, Manana Elia, Anne O'Dea, Gregory Crane, Mark Fesen, Lauren Nye, Maureen Sheehan, Robert Pluenneke, Raed Al-Rajabi, Joaquina Baranda, Anup Kasi, Richard McKittrick, Laura Mitchell, Stephanie LaFaver, Priyanka Sharma

X-7/7

Studiendesign

ELIGIBILITY

- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION

- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

153 Pat.

FD-7/7 Arm (N=80)

Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)

Capecitabine 1250* mg/m² PO BID x14 days followed by 7-day rest

**Physician had discretion to use alternative dosing of 1000 mg/m² PO BID (N=11)*

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit

ENDPOINTS

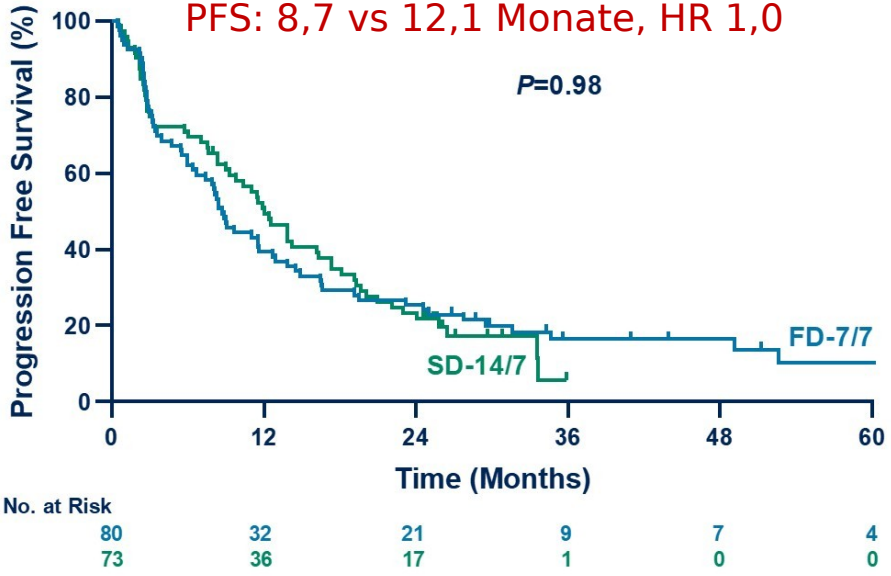
- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

Standard-Dosis bei uns: 1000 mg/qm BID!

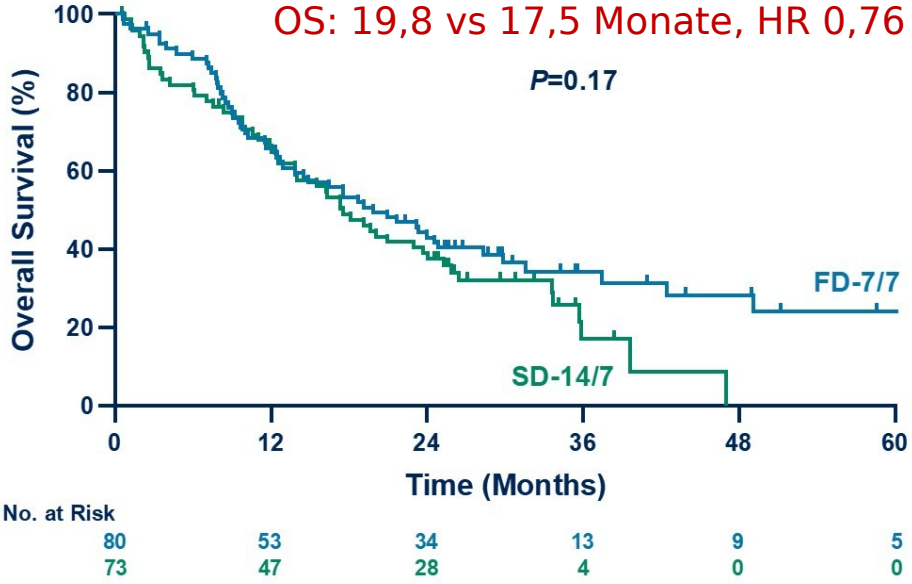
X-7/7

Progressionsfreies Überleben, Gesamtüberleben und ORR

PFS: 8,7 vs 12,1 Monate, HR 1,0



OS: 19,8 vs 17,5 Monate, HR 0,76



Response Rate	FD-7/7	SD-14/7	P-value
ORR	5/56 (8.9%)	9/46 (19.6%)	0.11

Kein signifikanter Unterschie

X-7/7

Toxizität

	FD-7/7 (N=80)	SD-14/7 (N=73)	P-Value
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	**2 (2.5)**	**15 (20.5)**	**0.0008**
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	**3 (3.8)**	**11 (15.1)**	**0.0019**
Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	**0**	**4 (5.48)**	**0.0001**
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	**17 (21.25)**	**20 (27.4)**	0.68

Grade 3-4 toxicity:
27.4% in SD-14/7
11.3% in FD-7/7
p=0.02

Treatment Discontinuation:
28.7% in SD-14/7
7.5% in FD-7/7
p<0.0006

Dose Modification:
23.3% in SD-14/7
7.5% in FD-7/7
p=0.0063

Verträglichkeit im Fixed-Dose-7/7-Schema deutlich besser

2023 ASCO® ANNUAL MEETING

Randomized double-blind, placebo-controlled study of topical diclofenac in prevention of hand-foot syndrome in patients receiving capecitabine

The D-TORCH study

Akhil Santhosh[1], Akash Kumar[2], Raja Pramanik[1], Ajay Gogia[1], Winson Y. Cheung[3], Sameer Bakhshi[1], Atul Sharma[1], Chandra Prakash Prasad[4], Tushar Sehgal[5], Atul Batra[1]

[1]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India; [2]National Cancer Institute, All India Institute of Medical Sciences (AIIMS), New Delhi, India; [3]Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [4]Department of Medical Oncology (Lab), All India Institute of Medical Sciences, New Delhi, India; [5]Department of Laboratory Medicine, All India Institute of Medical Science (AIIMS), New Delhi, India;

D-TORCH

Studiendesign

Key eligibility criteria
> 18 years
ECOG Performance status 0-2
Breast or gastrointestinal cancer

Not receiving oral/topical NSAIDs
No known allergy to NSAIDs

Stratification
Sex
Monotherapy vs combination therapy

1:1

264 Pat.

Twice daily application of 1 g 1% topical diclofenac on both hands during four cycles capecitabine

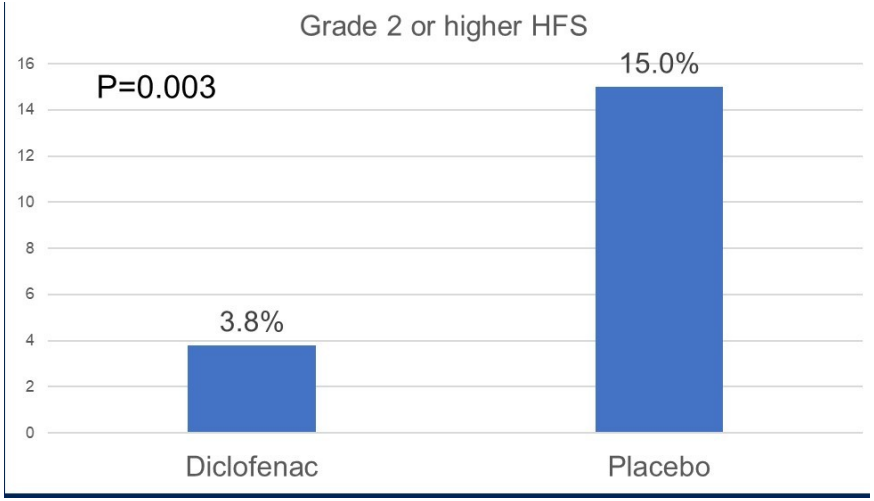
Twice daily application of matched placebo during four cycles capecitabine

Endpoints
> Grade 1 HFS (Primary)
All grade HFS
Time to HFS
Patient reported outcomes
Capecitabine dose modifications
Adverse events

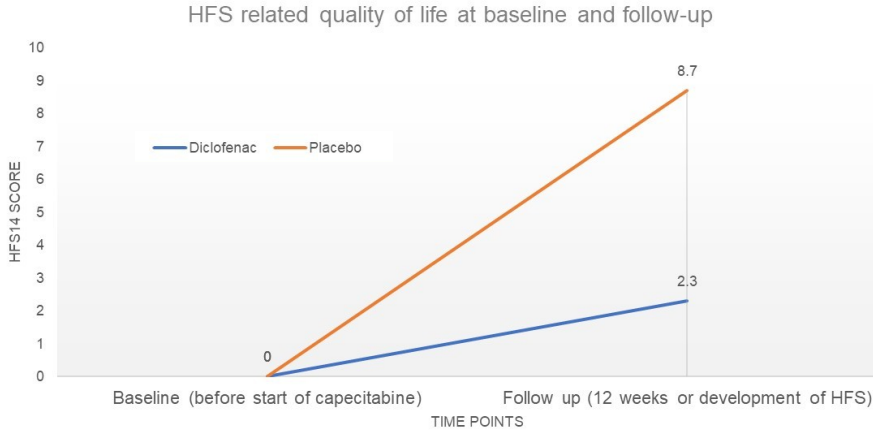
Treatment of HFS
Physician directed

D-TORCH

Ergebnisse



Cause of dose reduction	Diclofenac arm (n=130)	Placebo arm (n=133)
Hand foot syndrome	5 (3.8%)	**18 (13.5%)**
Mucositis	5 (3.8%)	10 (7.5%)
Diarrhoea	**8 (6.1%)**	8 (6.0%)
Myelosuppression	3 (2.3%)	5 (3.8%)
Total	21 (16.1%)	41 (30.8%)



- Weniger Hand-Fuß-Syndrom ≥ Grad 2
- Weniger Dosisreduktionen
- Bessere Lebensqualität

X-7/7 und D-TORCH

Fazit:

- **Capecitabin ist in fester Dosierung im 7/7-Schema verträglich und effektiv**

- **Diclofenac kann zur Prävention des Hand-Fuß-Syndroms eingesetzt werden**

Take Home Messages zum fortgeschrittenen Mammakarzinom

• In der **SONIA**-Studie war der Einsatz von CDK 4/6i in der Erstlinie bezüglich Wirksamkeit und Sicherheit dem Einsatz in der Zweitlinie nicht überlegen – allerdings ohne Berücksichtigung neuer Kombinationstherapien

• Die Fortführung von Palbociclib „beyond progression“ führt nicht zu Verbesserung des PFS im Vergleich zu endokriner Monotherapie (**PALMIRA**)

• Patritumab Deruxtecan (HER3-DXd) zeigt vielversprechende Aktivität beim vorbehandelten HER2− mBC (**ASCO 1004**)

• Capecitabin ist in fester Dosierung im 7/7-Schema verträglich und effektiv. Diclofenac wirkt präventiv gegen das Hand-Fuß-Syndrom (**X-7/7; D-TORCH**)

• Apps können zur Reduktion von Nebenwirkungen und Verbesserung der Lebensqualität unter onkologischer Therapie beitragen (**PreCycle**)

Klinikum rechts der Isar
Technische Universität München

Danke für die Aufmerksamkeit!