CDK4/6 Inhibitor Therapie und wie danach in der metastasierten Situation weiter - PADMA

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AGAPLESION MARKUS KRANKENHAUS

Conflicts of Interest

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(1) Advisory Board (personal)

Agendia, Amgen, AstraZeneca, Becton and Dickinson, Biom'Up, Clearcut, Clovis, Daiichi Sankyo, Eisai, Exact Sciences, Gilead Sciences, Grünenthal, GSK, Lilly, MSD, Neodynamics, Novartis, Onkowissen, Organon, Pfizer, pfm medical, Pierre-Fabre, Roche, RTI Surgical, Saman Tree, Seagen, Sirius, Sysmex

(2) Lecture (personal)

Agendia, Amgen, art tempi, AstraZeneca, Clovis, Celgene, Connect Medica, Daiichi Sankyo, Eisai, Endomag, Exact Sciences, Gedeon Richter, Gilead Sciences, GSK, Hexal, I-Med-Institute, Jörg Eickeler, Laborarztpraxis Walther, Lilly, MCI, Medscape, Medtronic, MSD, Novartis, Onkowissen, Organon, Pfizer, pfm medical, Roche, RTI Surgical, Seagen, Sirius Medical, StreamedUp!, Sysmex, Viatris, Vifor, ZP Therapeutics

(3) Manuscript support (personal)

Amgen, Cairn Surgical, Clearcut, Clovis, Lilly, pfm medical, Organon, Roche, Servier

(4) Trial funding (institutional)

Endomag, Exact Sciences

(5) Industry study honoraria (institutional)

AstraZeneca, Biom'Up, Cairn Surgical, Celgene, Clearcut, Neodynamics, Novartis, pfm medical, RTI Surgical

Hintergrund

- **Internationale Leitlinien empfehlen seit mehreren Jahren eine endokrine Therapie (ET) mit CDK4/6i als Erstlinientherapie bei metastasiertem HR+/HER2- Brustkrebs (mBC).**

Hintergrund

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	Last Patient in	PFS HR (95% CI)	Medianes PFS CDK4/6|Placebo[a]	OS HR (95% CI)	Medianes OS CDK-Arm|Placebo[a]
MONALEESA-2 (N = 668)[1] Ribociclib + letrozole	Mar 2015	0.56 (0.43 – 0.72)	25.3 | 16.0	0.76 (0.63-0.93)	63.9 | 51.4
MONARCH 3 (N = 493)[2] Abemaciclib + NSAI	Nov 2015	0.54 (0.41-0.72)	28.2| 14.8	0.80 (0.63-1.01)	66.8 |53.7
PALOMA-2 (N = 666)[3] Palbociclib + letrozole	Jul 2014	0.58 (0.46-0.72)	24.8 | 14.5	0.956 (0.777-1.177)	53.9 | 51.2
MONALEESA-7 (N = 672)[4,5] Ribociclib + ET	Aug 2016	0.55 (0.44-0.69)	23.8 | 13.0	0.71 (0.54-0.95)	58.7 | 48.0
MONALEESA-3 (N = 726)[6,7] Ribociclib + fulvestrant	June 2016	0.593 (0.480-0.732)	20.5 | 12.8	0.72 (0.57-0.92)	53.7 | 41.5
MONARCH 2 (N = 669)[8,9] Abemaciclib + fulvestrant	Dec 2015	0.553 (0.449-0.681)	16.9 | 9.3	0.757 (0.606-0.945)	46.7 | 37.3
PALOMA-3 (N = 521)[10,11] Palbociclib + fulvestrant	Aug 2014	0.46 (0.36-0.59)	9.5 | 4.6	0.81 (0.64-1.03)	34.8 | 28.0

GBG
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[a] Based on the respective publication with the longest FU

1. Hortobagyi GN et al., N Engl J Med 2022;386:942-50. Hortobagyi GN, et al. N Engl J Med 2016;375:1738-48; Hortobagyi GN, et al. Ann Oncol. 2018;29:1541-1547; 2. Goetz M, et al.. J Clin Oncol. 2017;35(32):3638-3646. doi:10.1200/JCO.2017.75.61553. 3. Finn RS, et al. N Engl J Med. 2016;375(20):1925-1936 Johnston S, et al. NPJ Breast Cancer. 2019;5:5. doi:10.1038/s41523-018-0097-z. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174(3):719-729. 4. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915. 5. Im SA, et al. *N Engl J Med*. 2019;381(4):307-316. 6. Slamon DJ, et al. N Engl J Med. 2020;382:514-524. 7. Slamon DJ, Ann Oncol. 2021;32:1015-1024. 8. Sledge GW, et al. *JAMA Oncol*. 2019;6:116-124. 9. Sledge GW, et al. J Clin Oncol. 2017;35(25):2875-2884. 10. Cristofanilli M, et al. *Lancet Oncol*. 2016;17(4):425-439. 11. Turner NC, et al. *New Engl J Med*. 2018;379(2):1926-1936.

Hintergrund

- **Da keine prospektiven Daten zum Vergleich der ET mit der Standard-Chemotherapie in dieser Situation vorlagen, erhielten viele Patientinnen immer noch eine Chemotherapie als Erstlinientherapie für HR+/HER2- mBC.**

- **Die PADMA-Studie (NCT03355157; GBG 93) ist die erste prospektive, randomisierte, offene, multizentrische Phase-IV-Studie zum Vergleich von CDK4/6i + ET mit Standard-Monochemotherapie +/- Erhaltungs-ET als Erstlinientherapie bei Patientinnen mit Hochrisiko-mBC und einer Chemotherapie-Indikation.**

Hintergrund

	PALOMA-3[1]	PEARL[2,*]	Young-PEARL[3]
Erstlinie	22%	23%	**51%**
Zweitlinie	**43%**	**45%**	34%
≥ Drittlinie	35%	32%	15%
Vorher Chemo für MBC (Alle)	34%	29%	22%

*ohne Erhaltungstherapie nach Chemo

1 Turner NC et al. N Engl J Med 2015;373(3):209-219; I 2 Martin M et al. Ann Oncol. 2021 Apr;32(4):488-499; I
3 Lee J et al. et al. Cancer Res Treat. 2021 Jul;53(3):695-702

PADMA GBG 93 - Studiendesign

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PATIENTENPOPULATION:
N=150

- HR-positiv/HER2-negativ
- Weiblich oder männlich
- Indikation für Mono-Chemotherapie
- Keine vorherige Behandlung der metastasierten/rezidivierten Erkrankung
- Keine asymptomatische, nur die Knochen betreffende, oligo-metastatische Erkrankung
- Keine unkontrollierten/unbehandelten ZNS-Metastasen
- Lebenserwartung >6 Monate

R

1:1

Arm A: **Endokrine Therapie (ET) + Palbociclib**

Arm B: **Chemotherapie (CT) nach Wahl des Arztes ± ET-Erhaltungstherapie**

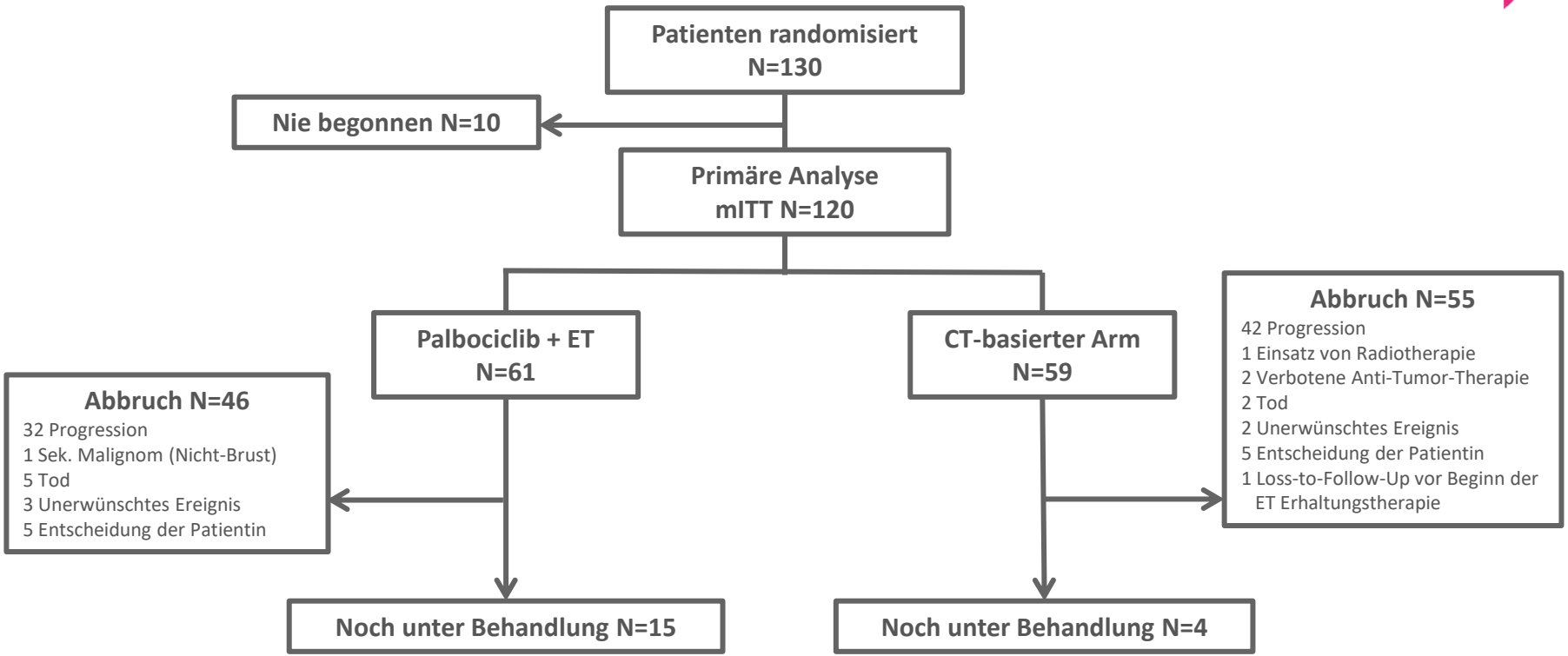
Stratifizierung:
- Endokrinresistent vs. endokrinsensitiv
- Symptomatische vs. asymptomatische metastatische Erkrankung

ET mit Palbociclib: AI oder Fulvestrant ± GnRHa
ET-Erhaltung: Tamoxifen, AI oder Fulvestrant ± GnRHa
CT: Paclitaxel, Capecitabin, Epirubicin oder Vinorelbin

Studienziele

- **Primärer Endpunkt:**
  - Zeit bis zum Therapie-Versagen (TTF), definiert als Zeit von der Randomisierung bis zum Abbruch der Behandlung aufgrund des Fortschreitens der Krankheit, der Toxizität der Behandlung, der Präferenz der Patientin oder Tod.
- **Sekundäre Endpunkte:**
  - Progressionsfreies Überleben (PFS)
  - Gesamtüberleben (OS)
  - Sicherheit, Verträglichkeit, Compliance
  - Zeit bis zur ersten Folgebehandlung (TFST)
  - Patient Reported QoL
  - Daily Monitoring of Treatment Impact (DMTI): Anrufverfolgung/Geofencing mit passiver Erfassung von Informationen über Häufigkeit und Dauer von Anrufen bzw. Besuchen im Studienzentrum

Studienbehandlung und Analysepopulation



Baseline Characteristics

	Palbociclib+ET N=61	CT-basiert N=59	Insgesamt N=120
Medianalter in Jahren (Range)	63 (42.0-85.0)	62 (31.0-80.0)	62 (31.0-85.0)
Postmenopausaler Status	54 (88.5%)	52 (88.1%)	106 (88.3%)
Lebermetastasen	28 (45.9%)	22 (37.3%)	50 (41.7%)
Endokrin resistent*	17 (27.9%)	21 (35.6%)	38 (31.7%)
Metastasierung bei Erstdiagnose	20 (33.3%)	24 (40.7%)	44 (37.0%)
Vorherige (neo)adjuvante CT	29 (47.5%)	25 (42.4%)	54 (45.0%)
HER2-low (IHC 1-2)**	41 (73.2%)	30 (58.8%)	71 (66.4%)
Analysierte Genmutation (Gewebe)***			
- PIK3CA	11 (18.0%)	16 (27.1%)	27 (22.5%)
- BRCA1/2	3 (4.9%)	4 (6.8%)	7 (5.8%)
- ESR1	1 (1.6%)	1 (1.7%)	2 (1.7%)

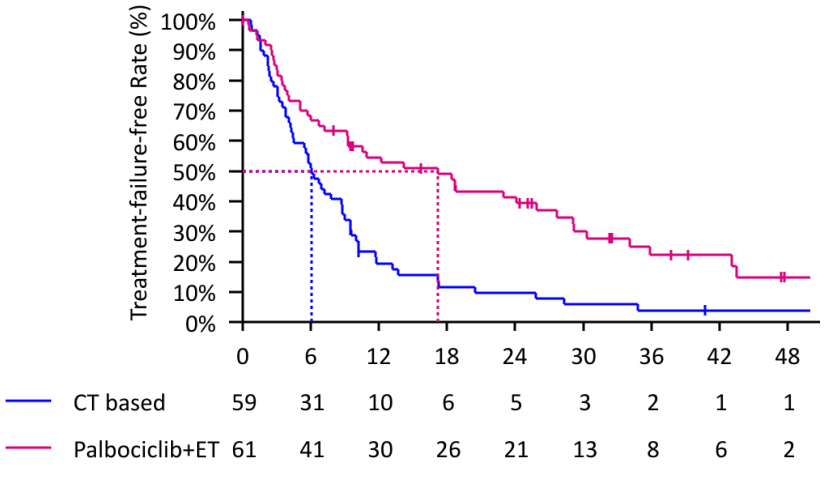
* Rückfall am oder innerhalb von 12 Monaten nach Ende der adjuvanten ET
** Von Metastasen (N=47), ansonsten, falls verfügbar, von der Erstdiagnose (N=24)
*** Getestet an 81 Patientinnen.

Studie Behandlung wie behandelt

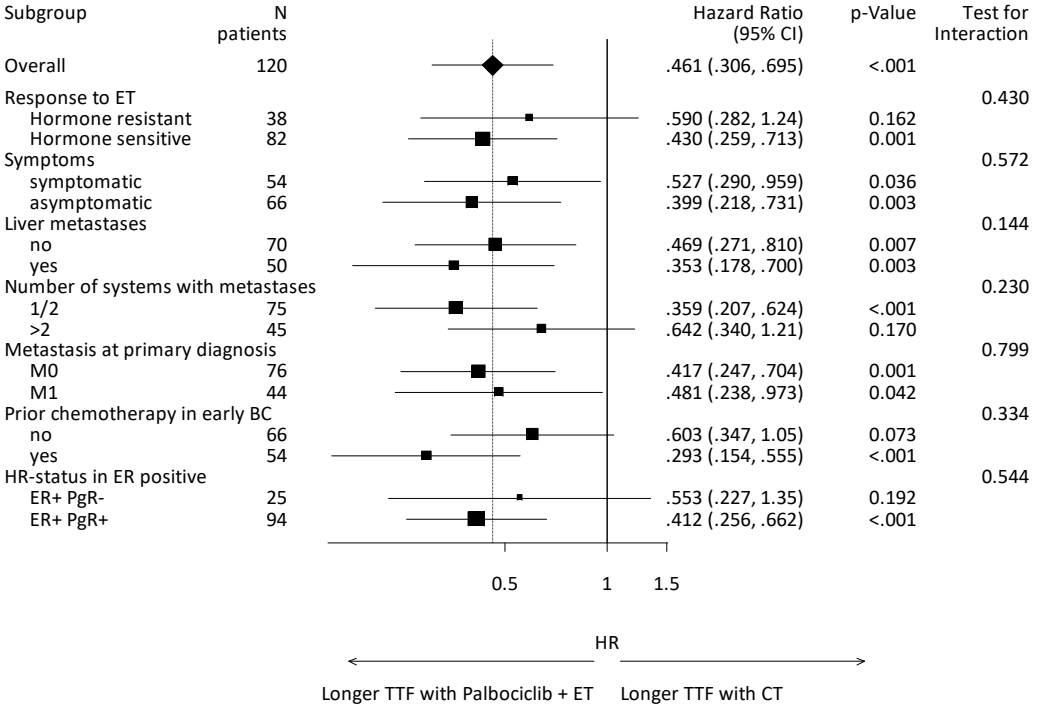
	Palbociclib+ET N=62*	CT-basiert N=58
Art der Behandlung nach Wahl des Arztes CT		
- Capecitabin	-	40 (69.0%)
- Paclitaxel		17 (29.3%)
- Vinorelbin		1 (1.7%)
ET-Erhaltung nach CT	-	13 (22.4%)
Typ der ET**		
- Aromatase-Hemmer	48 (77.4%)	9 (15.5%)
- Tamoxifen	-	3 (5.2%)
- Fulvestrant	14 (22.6%)	1 (1.7%)
Mediane Dauer Palbociclib oder CT, Wochen (Range)	51.0 (1.0-322.0)	19.5 (2.0-122.0)

* Eine Patientin, die dem CT-basierten Arm zugeordnet wurde, erhielt Palbociclib + ET.
** Prä- oder perimenopausale Frauen, die AI oder Fulvestrant erhielten, benötigten ein GnRH-Analogon oder eine Ovarialablation.

Primärer Endpunkt, TTF

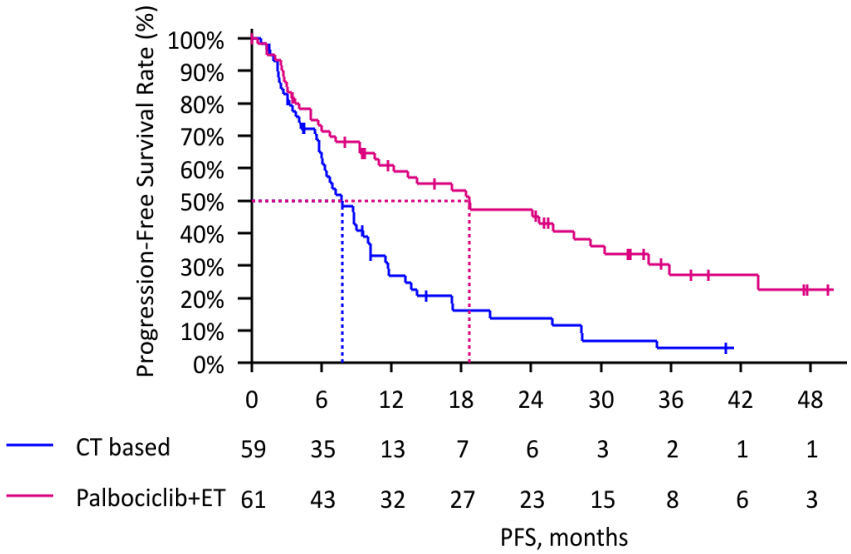


	Palbociclib + ET	CT
TTF Events, N (%)	45 (73.8)	55 (93.2)
Mediane TTF Monate	17.2	6.1
HR 0.46: 95% CI (0.31-0.69), p<0.001 (log-rank)		

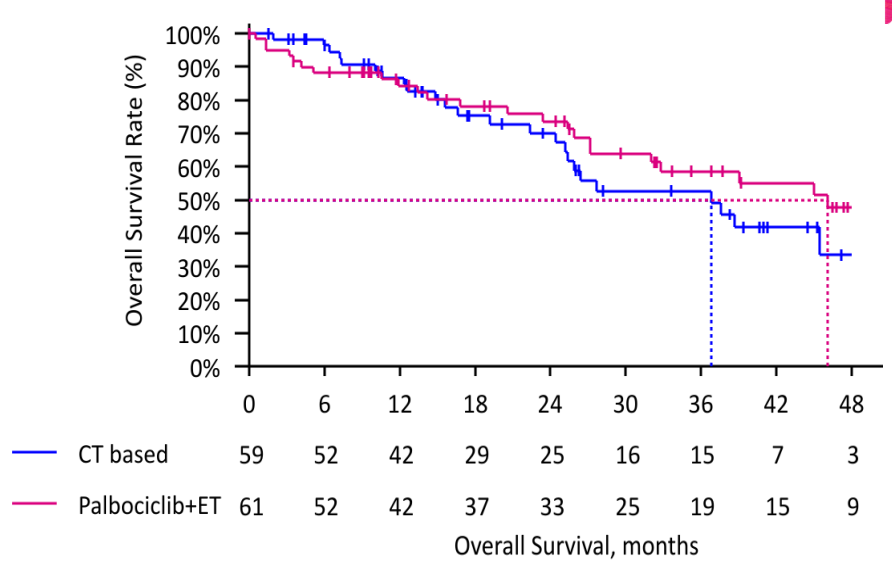


Medianes Follow-up von 36,8 (Range, 0-74,4) Monate

Sekundäre Endpunkte PFS, OS



	Palbociclib + ET	CT
PFS Events, N (%)	40 (65.6)	50 (84.7)
Mediane PFS Monate	18.7	7.8
HR 0.45 95% CI (0.29-0.70), p<0.001 (log-rank)		



	Palbociclib + ET	CT
OS Events, N (%)	25 (41.0)	24 (40.7)
Mediane OS Monate	46.1	36.8
Proportional Hazards können nicht angenommen werden		

Safety

Patientinnen mit behandlungsbedingten unerwünschten Ereignissen (TRAE)

	Palbociclib+ET N=62		CT-basiert N=58 N	
	Jeder Grad	Grad 3-4	Jeder Grad	Grad 3-4
Jede TRAE	60 (96.8%)	37 (59.7%)	55 (94.8%)	16 (27.6%)
Jede hämatologische TRAE	**60 (96.8%)**	**34 (54.8%)**	**34 (58.6%)**	**4 (6.9%)**
Jede nicht-hämatologische TRAE	51 (82.3%)	12 (19.4%)	54 (93.1%)	13 (22.4%)
Behandlungsbedingtes SAE	7 (11.3%)	5 (8.1%)	6 (10.3%)	6 (10.3%)
Behandlungsbedingter Tod	**1 (1.6%)**	-	0 (0.0%)	-

- **Hämatologische Toxizität signifikant höher im Palbociclib + ET-Arm im Vergleich zum CT-basierten Arm (96,8% vs. 58,6%; p<0,001). Vergleichbare nicht-hämatologische Toxizität.**
- **Ein behandlungsbedingter Todesfall (septischer Schock; Palbociclib + ET-Arm).**

Schlussfolgerungen

- **Die PADMA-Studie bei HR+/HER2- mBC mit hohem Risiko hat ihren primären Endpunkt (TTF) erreicht und zeigt eine statistisch signifikante und klinisch bedeutsame Verbesserung von TTF und PFS für Palbociclib + ET gegenüber Mono-CT (± ET-Erhaltungstherapie) als Erstlinientherapie**
  - Mediane TTF 17,2 vs. 6,1 Monate; HR 0,46, 95% CI (0,31-0,69), p<0,001
  - Medianes PFS 18,7 vs. 7,8 Monate; HR 0,45, 95% CI (0,29-0,70), p<0,001
- **Nach einer medianen Nachbeobachtungszeit von 36,8 Monaten gab es einen numerischen Trend für ein verbessertes OS für Palbociclib + ET 46,1 vs. 36,8 Monate**
- **Es wurden keine neuen Sicherheitssignale beobachtet**
- **Diese Ergebnisse untermauern die bestehenden internationalen Leitlinien, die den Einsatz von ET + CDK4/6i als Standard-Erstlinienbehandlung von Patientinnen mit HR+/HER2- mBC empfehlen.**

Danksagungen

- **Alle Patientinnen und ihre Familien, alle teilnehmenden Zentren und das IDMC**

Kooperierender Partner

Financial and Drug Support

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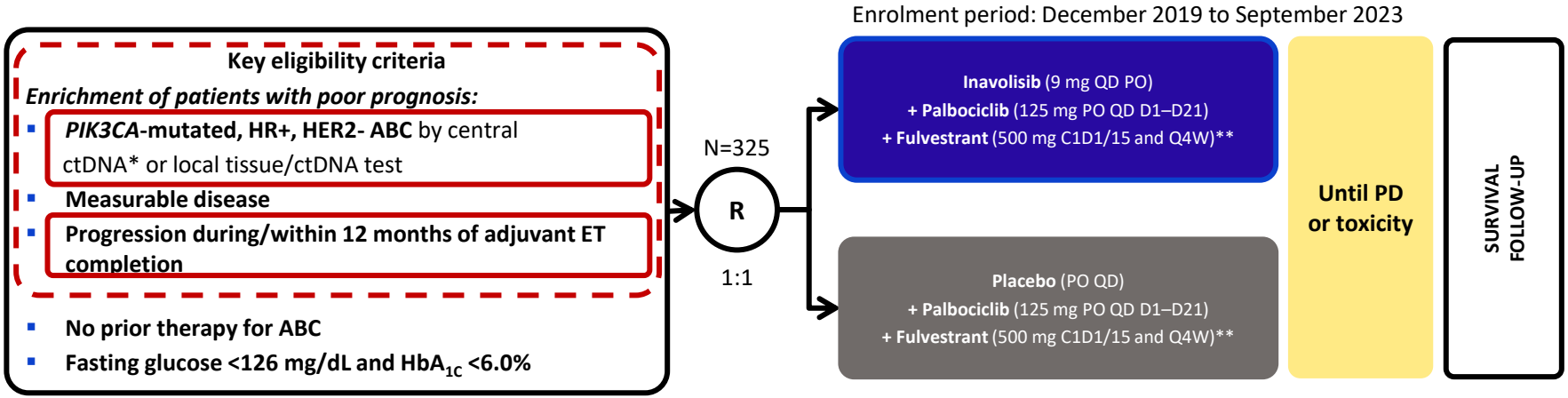
Kann man die Patientinnenselektion verbessern?

INAVO120 (Fulvestrant + Palbociclib ± Inavolisib)

Seit 10/2024 von der FDA zugelassen



Stratification factors

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

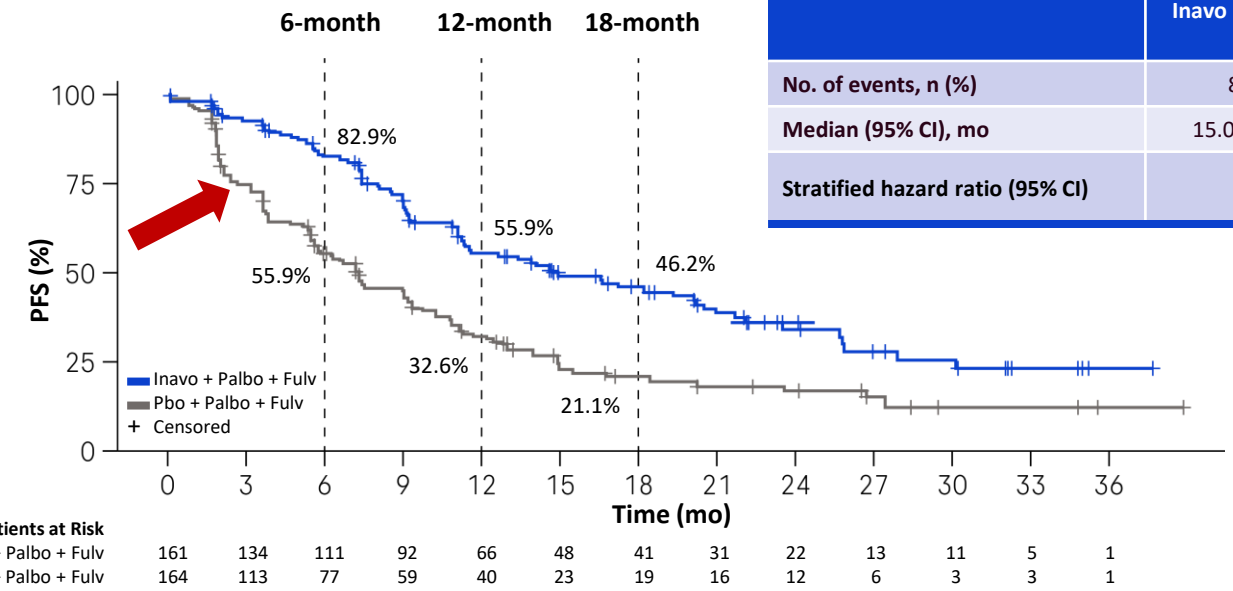
Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

*Central testing for PIK3CA mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu).
†Defined per 4th European School of Oncology (ESO) European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced B reast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre menopausal women received ovarian suppression.

[1]Cardoso F, et al. Ann Oncol 2018; 29:1634-1657.
Mod. Jhaveri K et al. SABCS 2023, General Session 3, Abstract No. GS03-13; Turner, N. et al. N Engl J Med 2024;391(17):1584-1596

INAVO120 (Fulvestrant + Palbociclib ± Inavolisib) – PFS



Patients at Risk

Inavo + Palbo + Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo + Palbo + Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)** ***p*<0.0001**	

Median follow-up:
21.3 months

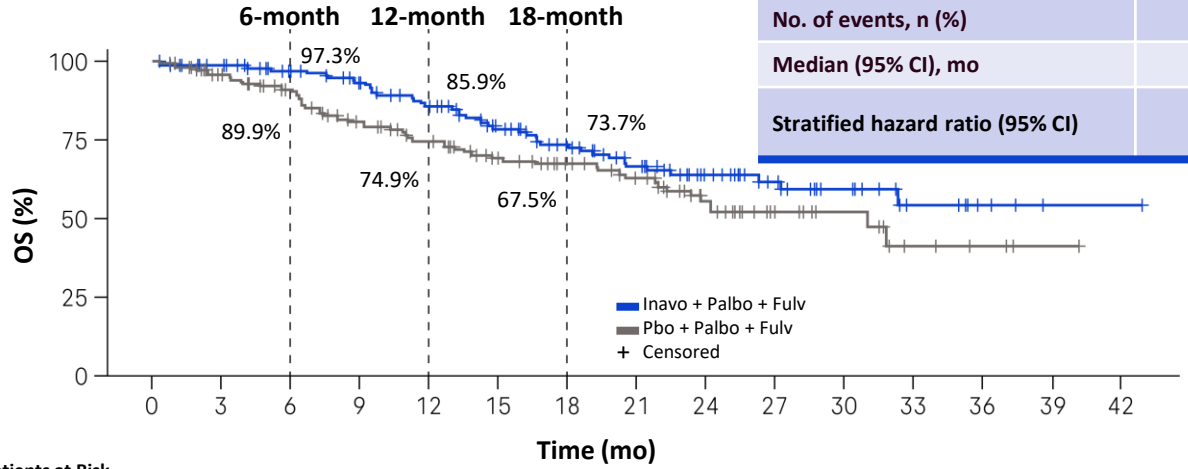
→ Kurzes PFS der Kontrollpopulation = Hochrisikokollektiv

→ Inavolisib verlängert signifikant und relevant das PFS

Mod. Jhaveri K et al. SABCS 2023, General Session 3, Abstract No. GS03-13; Turner, N. et al. N Engl J Med 2024;391(17):1584-1596

INAVO120 (Fulvestrant + Palbociclib ± Inavolisib) – OS

	Inavo + Palbo + Fulv (n=161)	Pbo + Palbo + Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified hazard ratio (95% CI)	0.64 (0.43, 0.97) *p*=0.0338	



Patients at Risk

Inavo + Palbo + Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo + Palbo + Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

Median follow-up:
21.3 months

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

→ Trend bezüglich verbessertem OS

Mod. Jhaveri K et al. SABCS 2023, General Session 3, Abstract No. GS03-13; Turner, N. et al. N Engl J Med 2024;391(17):1584-1596

INAVO120 (Fulvestrant + Palbociclib ± Inavolisib) – AEs

Patients with ≥1 AE, n (%)	Inavo+Palbo+Fulv (n=162)	Pbo+Palbo+Fulv (n=162)
All, n (%)	160 (98.8%)	162 (100%)
Grade 3–4 AE	143 (88.3%)	133 (82.1%)
Grade 5 AE*	6 (3.7%)	2 (1.2%)
Serious AE	39 (24.1%)	17 (10.5%)
AEs leading to discontinuation of treatment	11 (6.8%)	1 (0.6%)
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)
Palbociclib	8 (4.9%)	0
Fulvestrant	5 (3.1%)	0
AEs leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)
Palbociclib	125 (77.2%)	116 (71.6%)
Fulvestrant	52 (32.1%)	34 (21.0%)

AES were assessed per CTCAE V5
* None of the grade 5 AEs were reported as related to study treatment by investigators. The grade 5 AEs reported were cerebral hemorrhage; cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19 in the inavo+palbo+fulv arm and COVID-19 pneumonia and cardiac arrest in the pbo+palbo+fulv arm.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

Mod. Jhaveri K et al. SABCS 2023, General Session 3, Abstract No. GS03-13; Turner, N. et al. N Engl J Med 2024;391(17):1584-1596

Was kommt nach dem CDK4/6i?

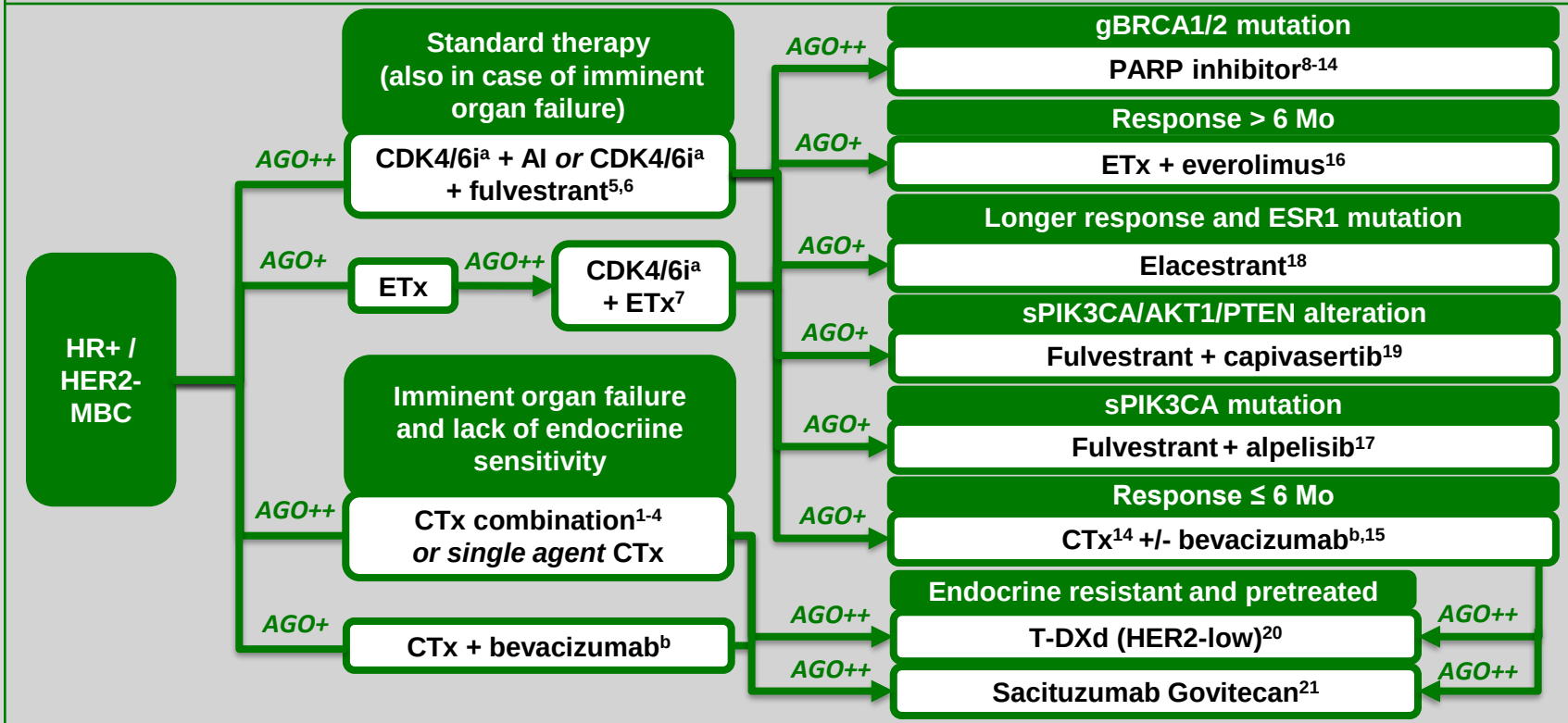
CDK4/6i beyond progression

	PostMONARCH	MAINTAIN	PACE	PALMIRA
N	368	119	166	198
CDK4/6i	Palbo → Abema (59%) Ribo → Abema (33%) Abema → Abema (8%)	Palbo → Ribo (86%) Ribo → Ribo (14%)	Palbo → Palbo (93%) Ribo → Palbo (4%) Abema → Palbo (3%)	Palbo → Palbo (100%)
Endocrine Therapy	AI → Fulvestrant (100%)	AI → Fulvestrant (83%) Fulvestrant → AI (27%)	AI → Fulvestrant (100%)	AI → Fulvestrant (88%) Fulvestrant → AI (12%)
Initial treatmend Duration > 12 month	71%	67%	78%	85%
Median PFS ET alone	5,3 Mo (3,7- 6,6)	2,76 Mo (2,66-3,25)	4,8 Mo (2,1-8,2)	4,2 Mo (3,5- 5,8)
Median PFS ET+ CDK4/6i beyond progression	6,0 Mo (5,6- 8,6)	5,29 Mo (3,02- 8,12)	4,6 Mo (3,6- 5,9)	4,2 Mo (3,5- 5,8)
HR	0,37	0,57	1,11	0,8
P-value	0,02	0,006	0,62 (ns)	0,206 (ns)

Kalinsky K et al. J Clin Oncol 2023; Mayer E et al. SABCS 2022; Lambart-Cussac A et al. ASCO 2023; Kalinsky K et al. ASCO 2024

HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

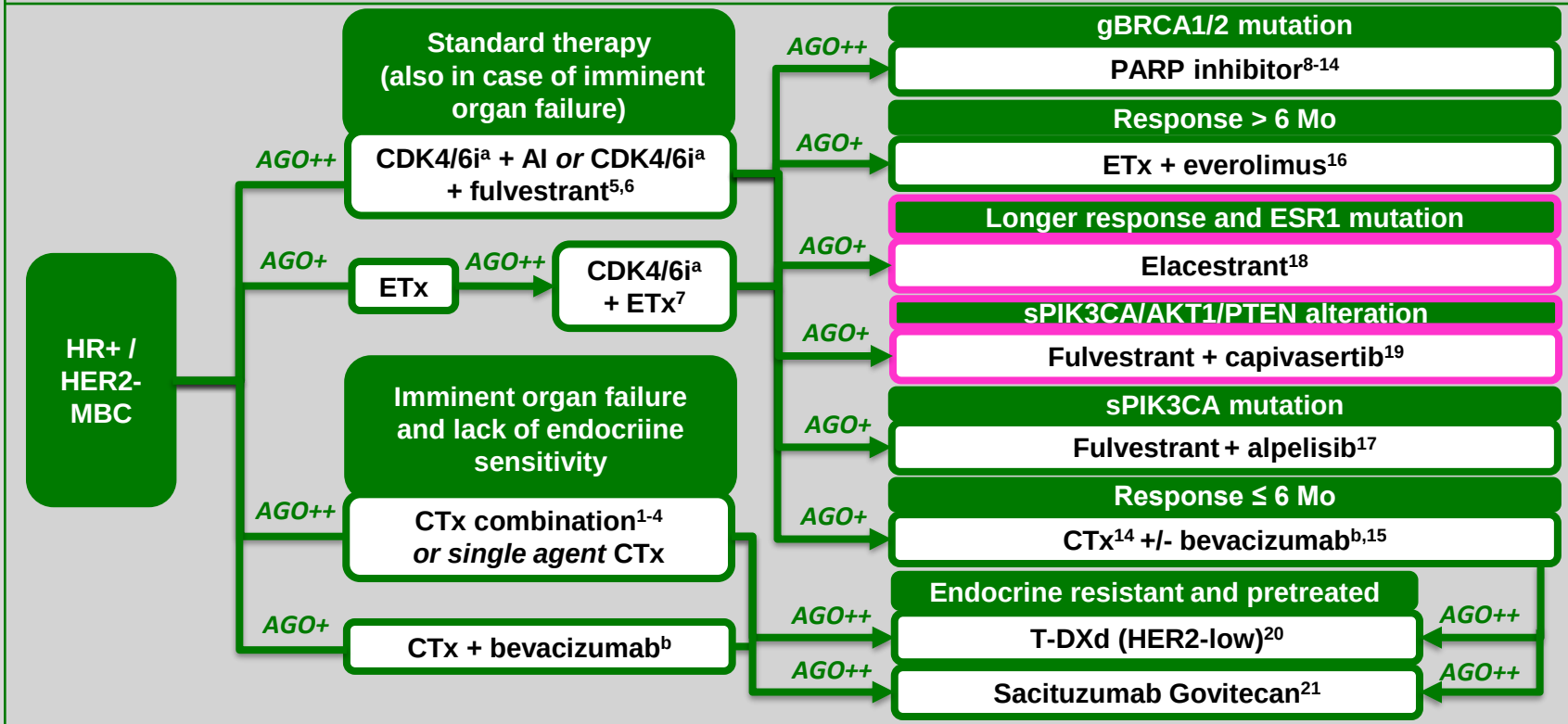
Guidelines Breast
Version 2024.1E



AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2 mutation, germ line BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mo, months; sPIK3CA mutation, somatic PIK3CA mutation; sPIK3CA/AKT1/PTEN alteration, somatic PIK3CA/AKT1/PTEN alteration; T-DXd, trastuzumab deruxtecan; [a] if premenopausal add ovarian function suppression; [b] bevacizumab + paclitaxel or + capecitabine.

HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

Guidelines Breast
Version 2024.1E



AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2 mutation, germ line BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mo, months; sPIK3CA mutation, somatic PIK3CA mutation; sPIK3CA/AKT1/PTEN alteration, somatic PIK3CA/AKT1/PTEN alteration; T-DXd, trastuzumab deruxtecan; [a] if premenopausal add ovarian function suppression; [b] bevacizumab + paclitaxel or + capecitabine.

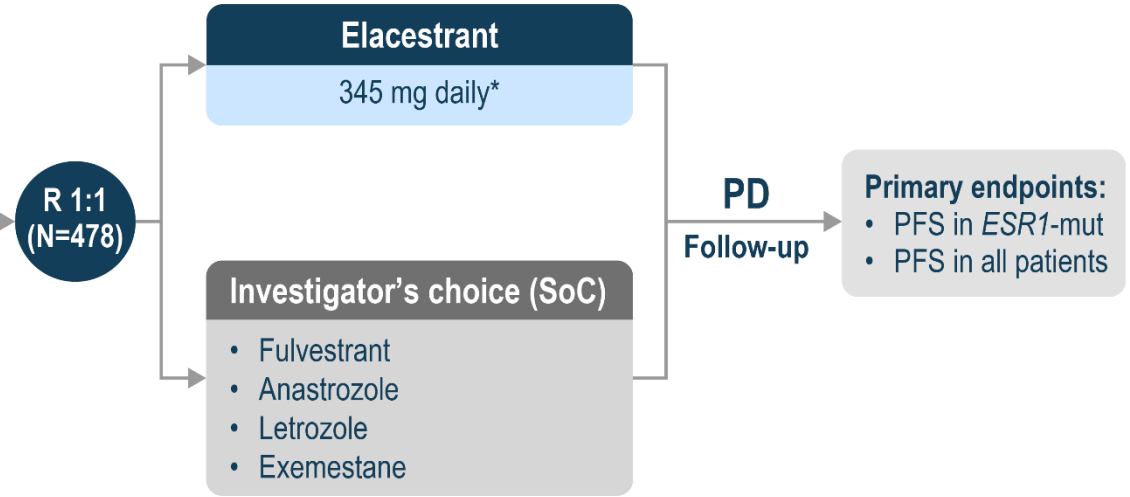
EMERALD: Phase 3 trial of elacestrant vs SoC endocrine therapy

100% of patients HAD received prior CDK4/6 inhibitor therapy

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER+/HER2−
- Progressed or relapsed on or after one or two lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

Stratification factors
- *ESR1* mutation status
- Presence of visceral metastases
- Prior treatment with fulvestrant

EMERALD study design

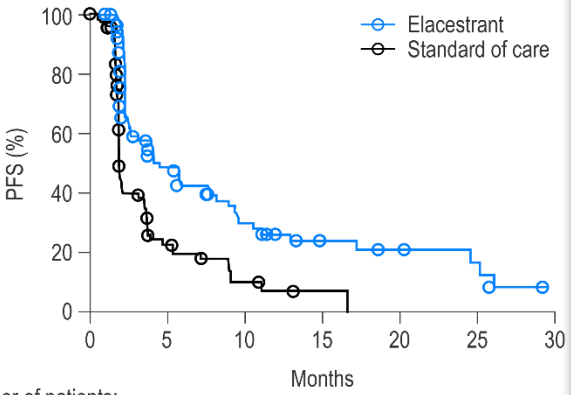


*345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride.

aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PD, progressive disease; PFS, progression-free survival; R, randomization; SoC, standard of care. Bidard FC et al. *J Clin Oncol* 2022;40:3246–3256.

EMERALD: Duration of prior CDK4/6 inhibitor therapy is positively associated with mPFS in patients with ESR1 mutations

At least 6 months of prior CDK4/6i

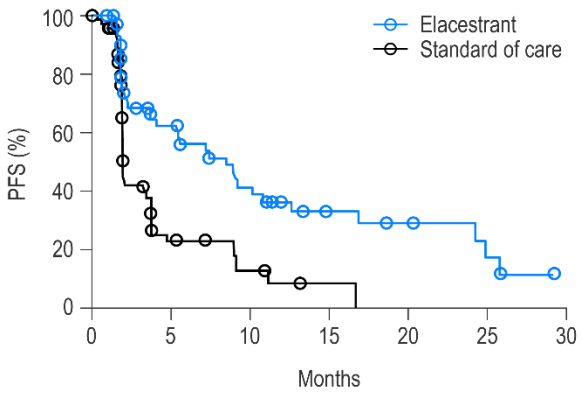


Number of patients:

Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SoC	102	34	16	11	9	5	2	1	1	0						

	Elacestrant	SoC
mPFS, months (95% CI)	**4.14** (2.20–7.79)	**1.87** (1.87–3.29)
PFS rate at 12 months, % (95% CI)	**26.02** (15.12–36.92)	**6.45** (0.00–13.65)
HR (95% CI)	**0.517** (0.361–0.738)	

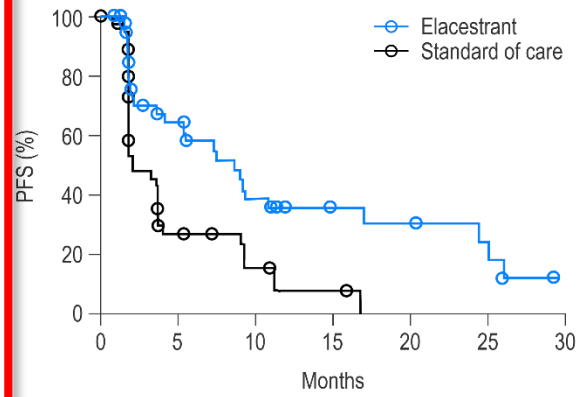
At least 12 months of prior CDK4/6i



	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0
	81	26	12	10	9	5	2	1	1	0						

	Elacestrant	SoC
mPFS, months (95% CI)	**8.61** (4.14–10.84)	**1.91** (1.87–3.68)
PFS rate at 12 months, % (95% CI)	**35.81** (21.84–49.78)	**8.39** (0.00–17.66)
HR (95% CI)	**0.410** (0.262–0.634)	

At least 18 months of prior CDK4/6i



	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0
	56	21	9	8	7	4	1	1	1	0						

	Elacestrant	SoC
mPFS, months (95% CI)	**8.61** (5.45–16.89)	**2.10** (1.87–3.75)
PFS rate at 12 months, % (95% CI)	**35.79** (19.54–52.05)	**7.73** (0.00–20.20)
HR (95% CI)	**0.466** (0.270–0.791)	

Results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; HR, hazard ratio; mPFS, median PFS; PFS, progression-free survival; SoC, standard of care.
Bardia A et al. SABCS 2022. Abstract GS3-01.

EMBER-3 – Study Design

ER+, HER2-ABC

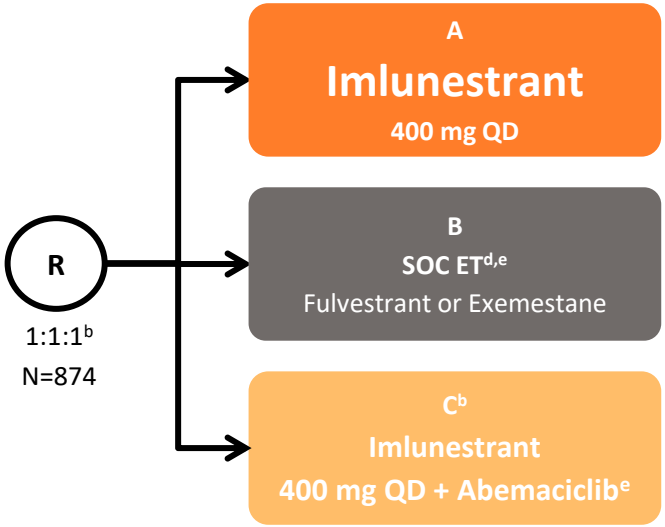
Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC**: Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs. B in patients with *ESR1*m[g]
- A vs. B in all patients
- C vs. A in all[h] patients

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

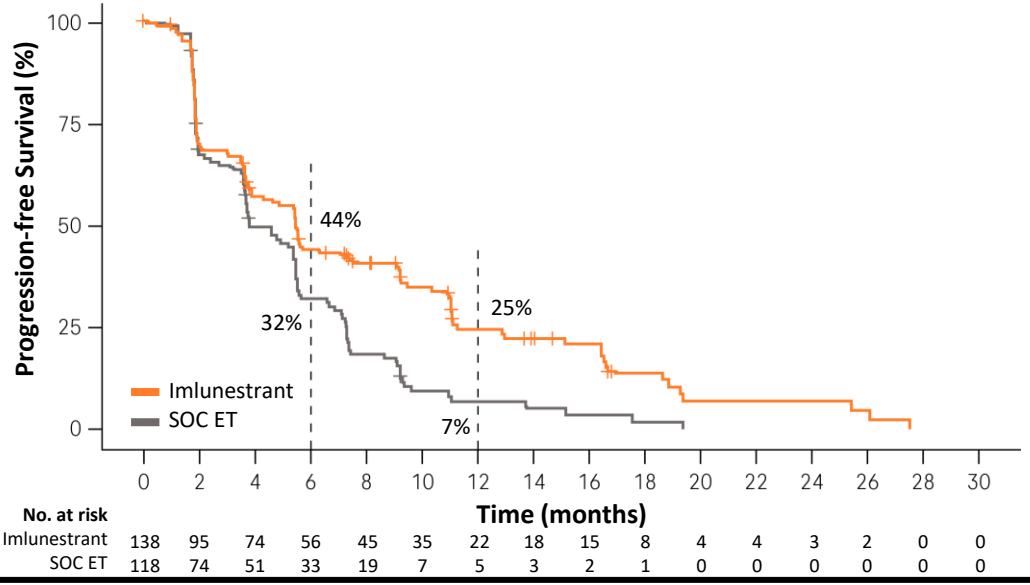
- PFS and OS for C vs. B in all[h] patients

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a]A GnRH agonist was required in men and premenopausal women; [b]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c]East Asia vs. United States/European Union vs. others; [d]Investigator's choice; [e]Labeled dose; [f]Scans every 8 weeks for the first 12 months, then every 12 weeks; [g]*ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h]Analysis conducted in all concurrently randomized patients

Mod. Jhaveri KL et al. SABCS 2024, General Session 1, Abstract No. GS1-01

EMBER-3 – Primary Endpoint: Imlunestrant vs. SOC ET

Investigator-assessed PFS in Patients with *ESR1*m



	Imlunestrant (n=138)	SOC ET (n=118)
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9–7.4)	**3.8** (3.7–5.5)
HR (95% CI)	**0.62 (0.46–0.82)**[a] *p*-value<0.001	

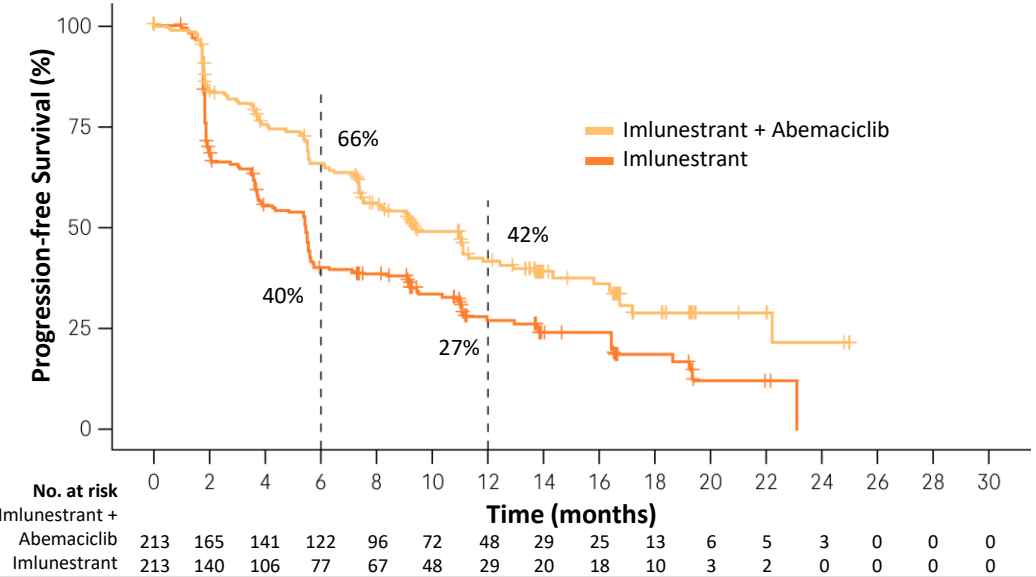
Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; RMST, restricted mean survival time; SOC ET, standard of care endocrine therapy. The median follow-up was 16.7 months in the Imlunestrant arm and 13.8 months in the SOC ET arm. [a]Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RMST at 19.4 months was 7.9 months (95% CI 6.8–9.1) in the Imlunestrant arm vs. 5.4 months (95% CI 4.6–6.2) in the SOC ET arm [difference 2.6 months (1.2–3.9)].

Mod. Jhaveri KL et al. SABCS 2024, General Session 1, Abstract No. GS1-01

EMBER-3 – Primary Endpoint: Imlunestrant + Abemaciclib vs. Imlunestrant

Investigator-assessed PFS in All Patients



	Imlunestrant + Abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5–11.9)	**5.5** (3.8–5.6)
HR (95% CI)	**0.57 (0.44–0.73)** *p*-value <0.001	

Imlunestrant + Abemaciclib led to a 43% reduction in the risk of progression or death over Imlunestrant alone in all patients

CI, confidence interval; HR, hazard ratio. [a]Efficacy analyses confined to the Imlunestrant population concurrently randomized to Imlunestrant + Abemaciclib treatment arm. The median follow-up was 13.5 months in the Imlunestrant + Abemaciclib arm and 13.7 months in the Imlunestrant arm.

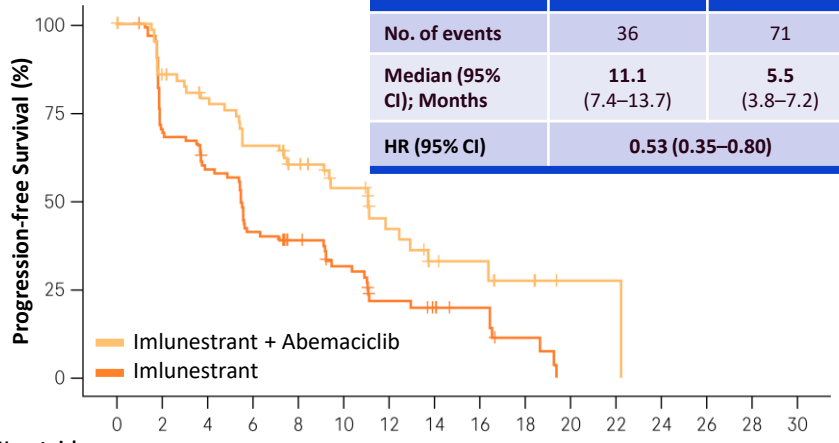
Mod. Jhaveri KL et al. SABCS 2024, General Session 1, Abstract No. GS1-01

EMBER-3 – Primary Endpoint: Imlunestrant + Abemaciclib vs. Imlunestrant

Investigator-assessed PFS by *ESR1*m status

Patients with *ESR1*m

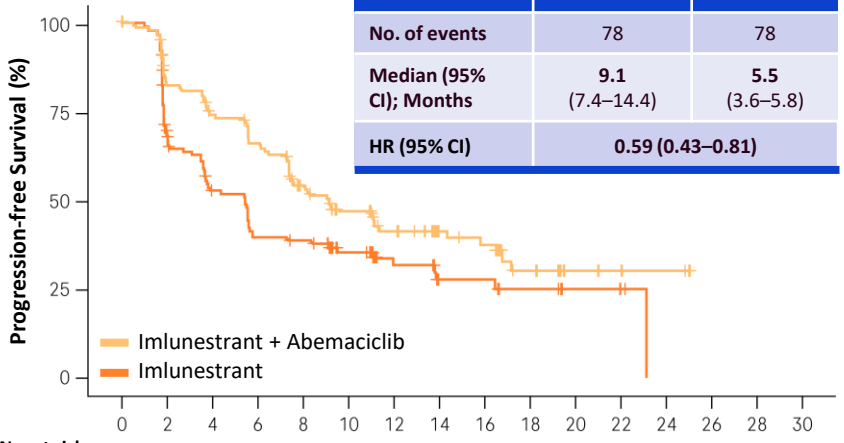
	Imlunestrant + Abemaciclib n=67	Imlunestrant n=92
No. of events	36	71
Median (95% CI); Months	**11.1** (7.4–13.7)	**5.5** (3.8–7.2)
HR (95% CI)	**0.53 (0.35–0.80)**	



No. at risk																
Imlunestrant + Abemaciclib	67	54	47	39	33	22	14	7	6	3	1	1	0	0	0	0
Imlunestrant	92	62	50	35	28	20	12	9	7	3	0	0	0	0	0	0

Patients without *ESR1*m

	Imlunestrant + Abemaciclib n=146	Imlunestrant n=121
No. of events	78	78
Median (95% CI); Months	**9.1** (7.4–14.4)	**5.5** (3.6–5.8)
HR (95% CI)	**0.59 (0.43–0.81)**	



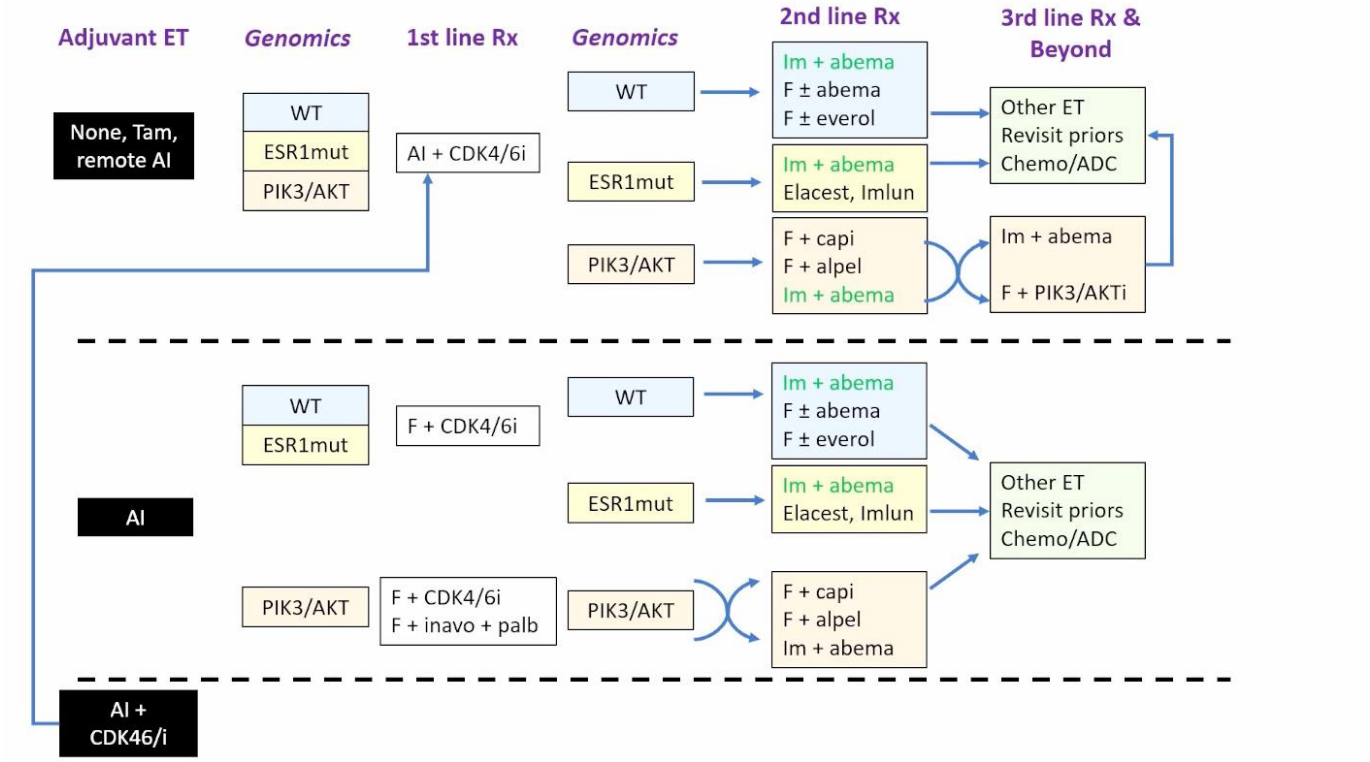
No. at risk																
Imlunestrant + Abemaciclib	146	111	94	83	63	50	34	22	19	10	5	4	3	0	0	0
Imlunestrant	121	78	56	42	39	28	17	11	11	7	3	2	0	0	0	0

Consistent benefit of Imlunestrant + Abemaciclib regardless of *ESR1*m status

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival. Patients without *ESR1*m status (Imlunestrant + Abemaciclib, n=1; Imlunestrant, n=7).

Mod. Jhaveri KL et al. SABCS 2024, General Session 1, Abstract No. GS1-01

Wie passt die SERD/CDK4/6i-Combo in einen Algorithmus?



Burstein H, EMBER-3 discussion, SABC 2024

CAPItello-291: Studiendesign

22. ASM FRANKFURT /MAIN

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

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

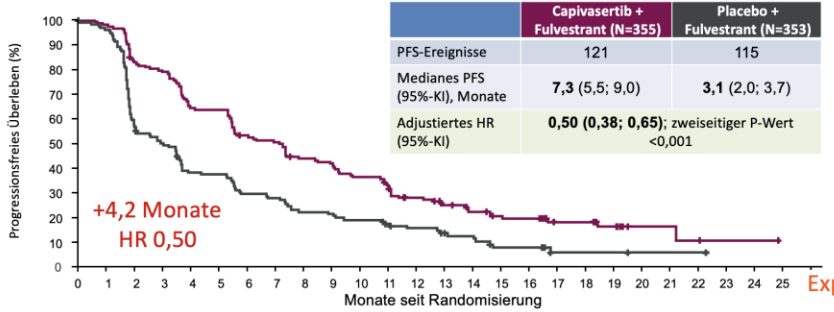
HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.

ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.

Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered and non-altered population

Dualer primärer Endpunkt: PFS* der Population mit AKT-Signalweg-Alteration

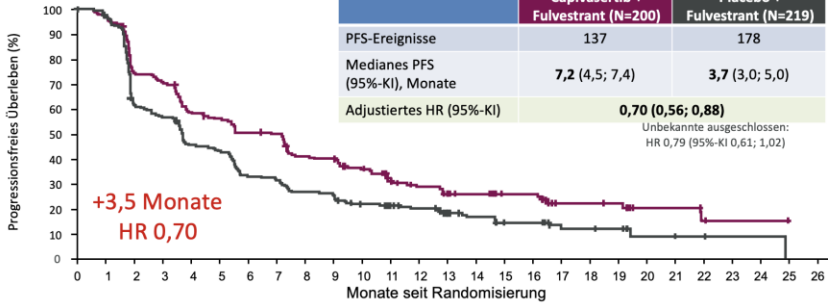


	Capivasertib + Fulvestrant (N=355)	Placebo + Fulvestrant (N=353)
PFS-Ereignisse	121	115
Medianes PFS (95%-KI), Monate	**7,3** (5,5; 9,0)	**3,1** (2,0; 3,7)
Adjustiertes HR (95%-KI)	**0,50 (0,38; 0,65)**; zweiseitiger P-Wert <0,001	

Patient:innenanzahl																								
Capivasertib + Fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0
Placebo + Fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0

+ steht für eine zensierte Beobachtung. Das HR wurde anhand des Cox-Proportional-Hazard-Modells geschätzt, das nach dem Vorhandensein von Lebermetastasen und der vorherigen Anwendung eines CDK4/6-Inhibitors stratifiziert wurde. *Nach Einschätzung des Prüfarztes/der Prüfärztin.

Explorative Analyse: PFS* der Population ***ohne*** Alteration (inkl. Unbekannt**)



	Capivasertib + Fulvestrant (N=200)	Placebo + Fulvestrant (N=219)
PFS-Ereignisse	137	178
Medianes PFS (95%-KI), Monate	**7,2** (4,5; 7,4)	**3,7** (3,0; 5,0)
Adjustiertes HR (95%-KI)	**0,70 (0,56; 0,88)** Unbekannte ausgeschlossen: HR 0,79 (95%-KI 0,61; 1,02)	

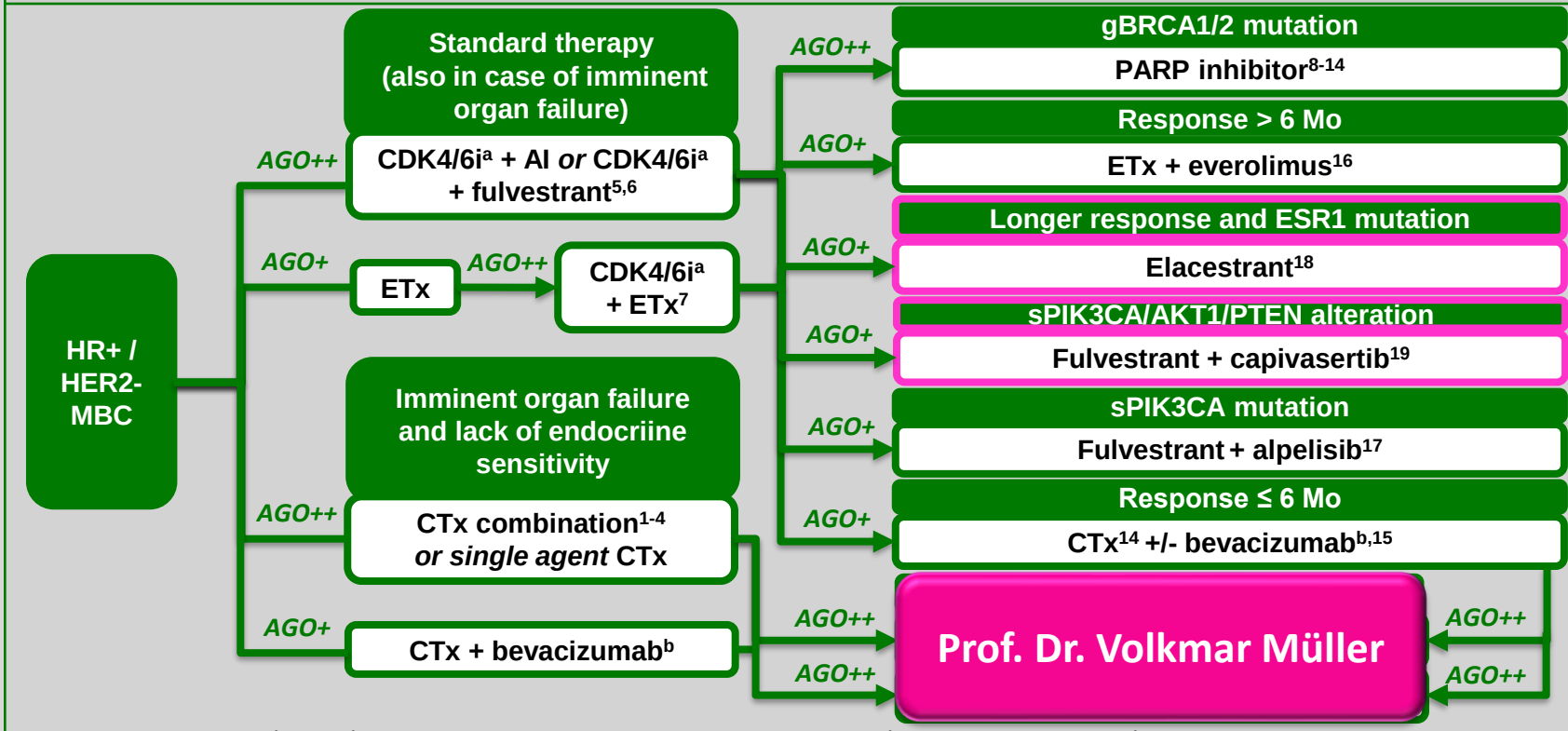
Patient:innenanzahl																								
Capivasertib + Fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + Fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

+ steht für eine zensierte Beobachtung. *Nach Einschätzung des Prüfarztes/der Prüfärztin. **Patient:innen ohne gültige NGS-Ergebnisse. Das HR wurde anhand des Cox-Proportional-Hazard-Modells geschätzt, das nach dem Vorhandensein von Lebermetastasen und der vorherigen Anwendung eines CDK4/6-Inhibitors stratifiziert wurde

In Deutschland seit 01.10.2024 zugelassen!

HR-positive/HER2-negative Metastatic Breast Cancer: Strategies

Guidelines Breast
Version 2024.1E



AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; CTx, chemotherapy; ETx, endocrine therapy; gBRCA1/2 mutation, germ line BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mo, months; sPIK3CA mutation, somatic PIK3CA mutation; sPIK3CA/AKT1/PTEN alteration, somatic PIK3CA/AKT1/PTEN alteration; T-DXd, trastuzumab deruxtecan; [a] if premenopausal add ovarian function suppression; [b] bevacizumab + paclitaxel or + capecitabine.

Fazit

- **PADMA mit statistisch signifikanter Verbesserung des PFS und der TTF gegnüber Mono-CTx in der 1st L**
- **Bessere Selektion durch PIK3CAmt -> Inavolisib +Palbociclib + Fulvestrant**
- **CDK4/6i nach CDK4/6i möglich, aber nur wenn sowohl der CDK4/6i als auch die ET gewechselt wird**
- **Verschiedene neue zugelassene Therapieoptionen mit:**
  - Elacestrant bei ESR1mt und längerem Ansprechen auf CDK4/6i
  - Capivasertib bei PIK3CA/AKT1/PTEN-Alteration
- **Zukünftige Therapieoptionen:**
  - SERD + CDK4/6i (EMBER-3 mit Imlunestrant, aber auch ELEVATE mit Elacestrant)

Heilung durch Innovation, Kompetenz und Partnerschaft – führend in der Brustkrebs-Forschung

GBG
GERMAN BREAST GROUP

22. Annual Scientific Meeting 06. – 07. März 2025