FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

UNIVERSITÀ DEGLI STUDI DI MILANO

IFOM

Metastatic luminal breast cancer

8 Marzo 2025

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Disclosures

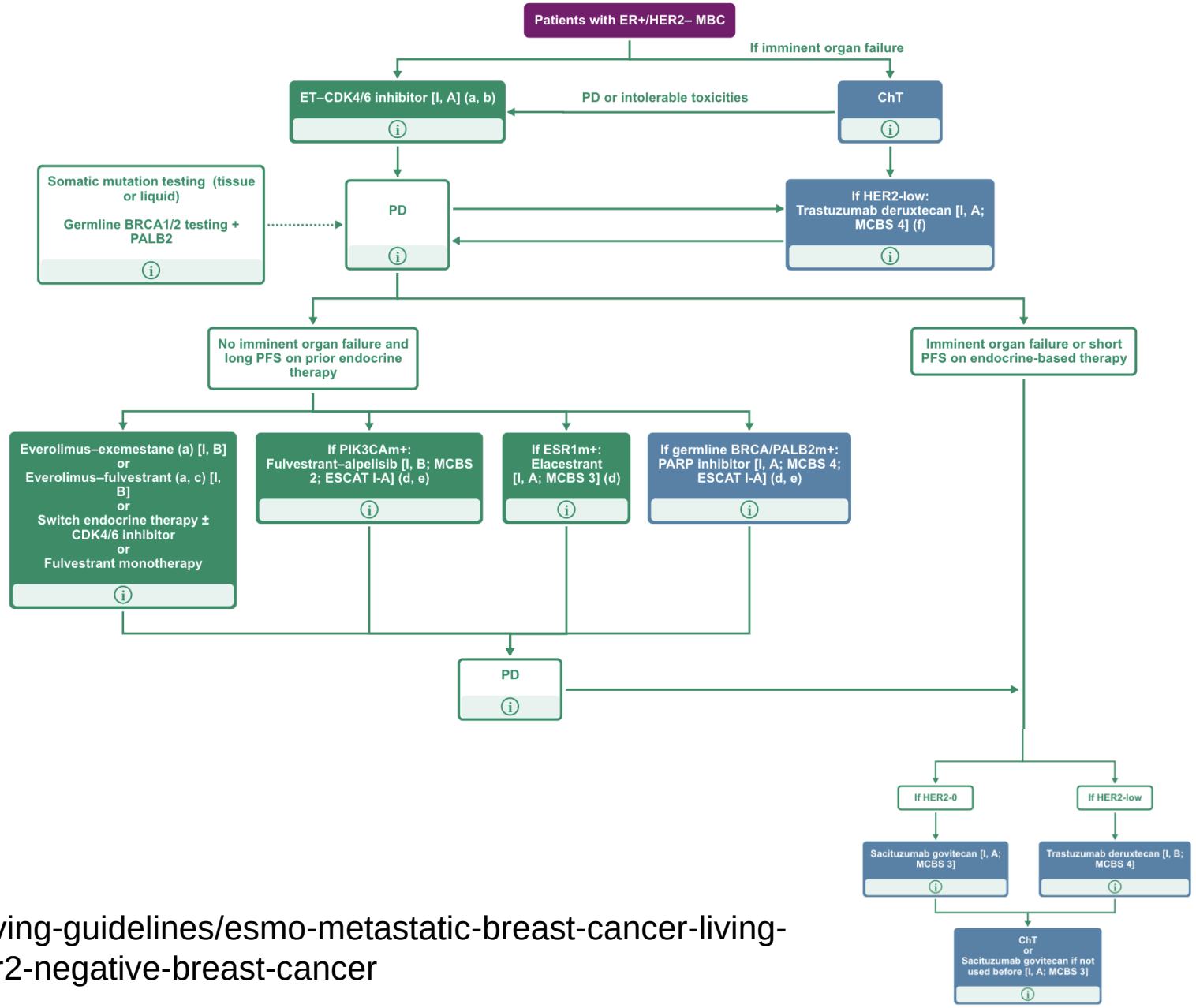
Consulting or Advisory role: Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, Astra Zeneca, Menarini Stemline

Honoraria as a Speaker: Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, Astra Zeneca, Menarini Stemline, MSD, Istituto Gentili, Accademia di Medicina

Research grants (to the Institution): AIRC, ERC, Roche, Giuliani Foundation, Ministero della Salute, Daiichi Sankyo/Astra Zeneca

ESMO Metastatic HR+/HER2- BC Living Guidelines

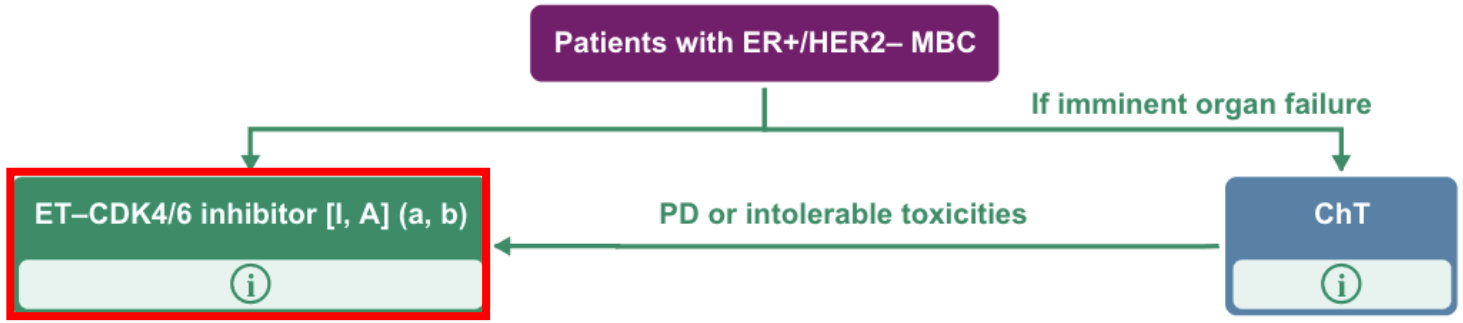
v1.1 - May 2023



https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

First-line treatment

v1.1 - May 2023



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SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 10–13, 2024
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Primary results of the randomised phase IV trial comparing first-line ET plus palbociclib vs standard mono-chemotherapy in women with high risk HER2-/HR+ metastatic breast cancer and indication for chemotherapy - PADMA study

Sibylle Loibl[1], Marc Thill[2], Julia Rey[1], Beate Rautenberg[3], Vesna Bjelic-Radisic[4,5], Thomas Decker[6], Joachim Rom[7], Matthias Kögel[8], Kristina Lübbe[9], Axel Nacke[10], Nader Hirmas[1], Marianne Just[11], Volkmar Müller[12], Renu Buss-Steidle[13], Jürgen Terhaag[14], Christoph Mundhenke[15], Carsten Denkert[16], Johannes Holtschmidt[1], Marcus Schmidt[17]

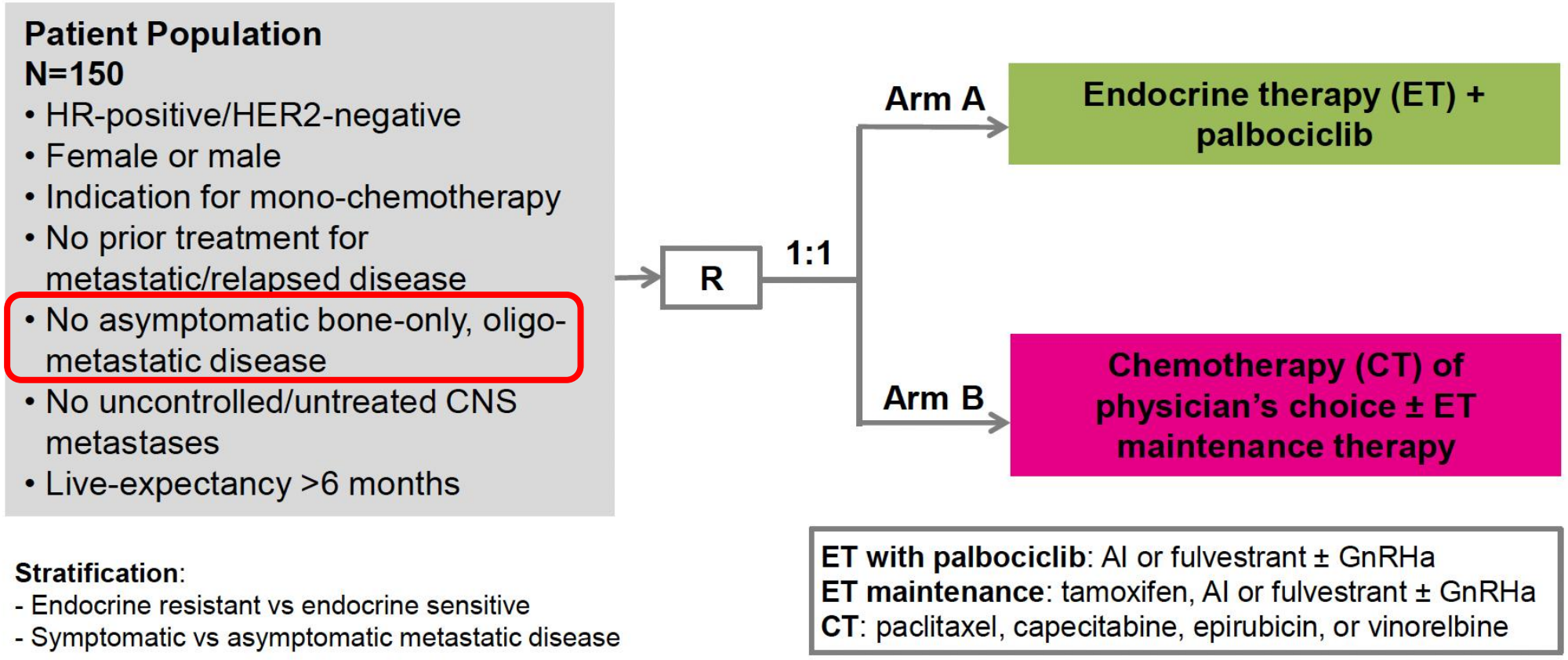
on behalf of the PADMA investigators

1 German Breast Group, Neu-Isenburg, Germany; 2 Agaplesion Markus Hospital, Frankfurt am Main, Germany; 3 Department of Obstetrics and Gynecology, Hospital Freiburg, Germany; 4 Helios University Clinic Wuppertal, Germany; 5 University Witten/Herdecke, Germany; 6 Oncology Ravensburg, Germany; 7 Hospital Höchst Frankfurt am Main, Germany; 8 Hospital Worms, Germany; 9 Diakovere Henriettenstift, Breast Center, Hannover, Germany; 10 Oncology Bad Neuenahr, Germany; 11 Oncology specialist practice Bielefeld, Germany; 12 University Hospital Hamburg-Eppendorf, Germany; 13 Helios Hospital Pforzheim, Germany; 14 MVZ Eggenfelden, Germany; 15 Department of Gynecology and Obstetrics, Hospital Hohe Warte, Bayreuth, Germany; 16 Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM) University Hospital Marburg, Germany; 17 Department of Obstetrics and Gynecology, University Medical Center Mainz, Germany

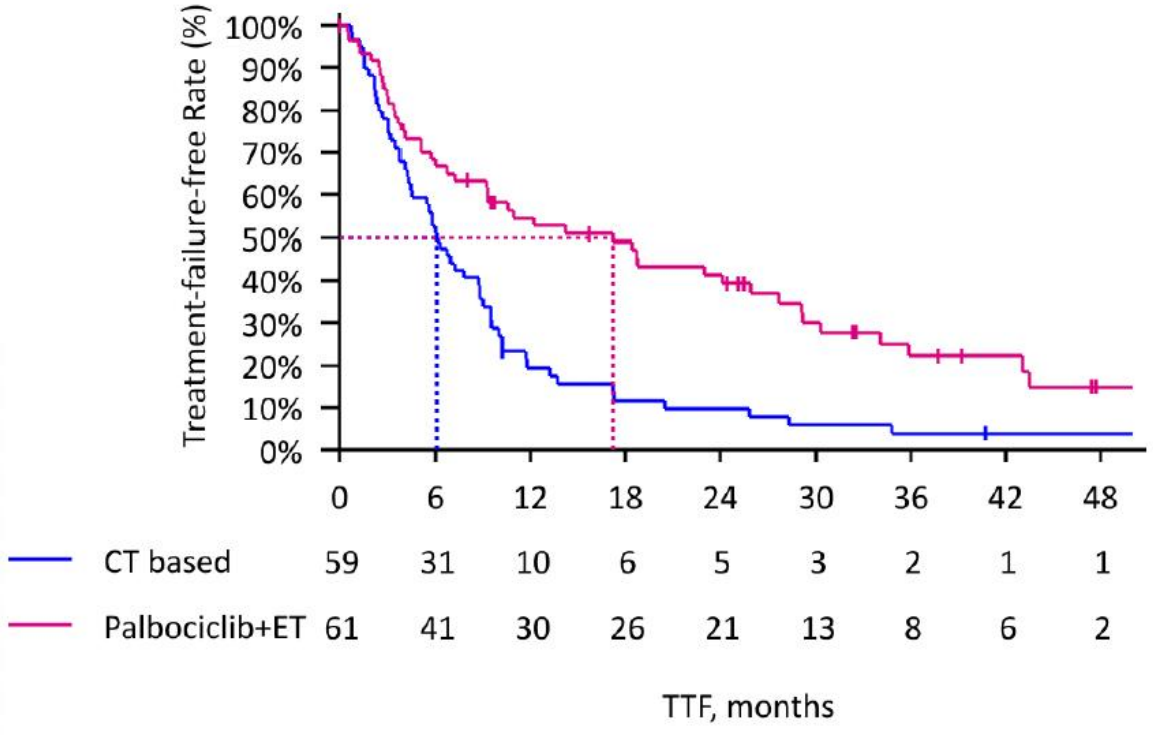
PADMA

GBG GERMAN BREAST GROUP

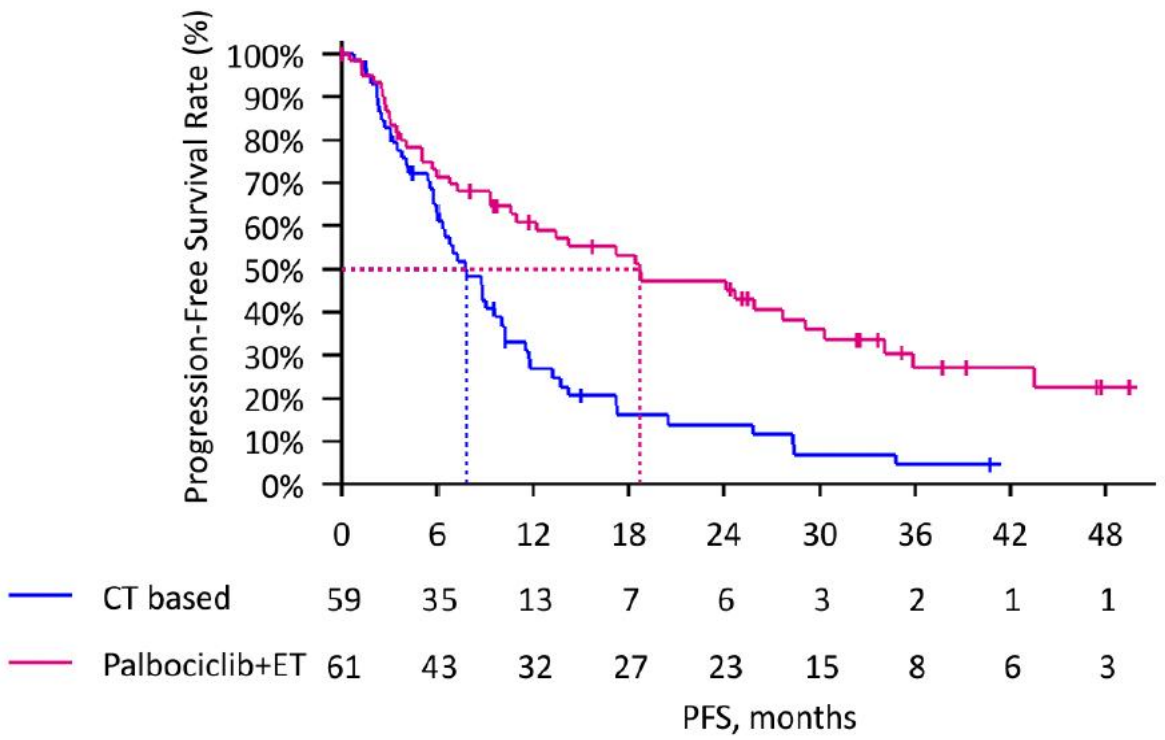
PADMA study design



First-line treatment ET plus palbociclib is more effective than first-line chemotherapy



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

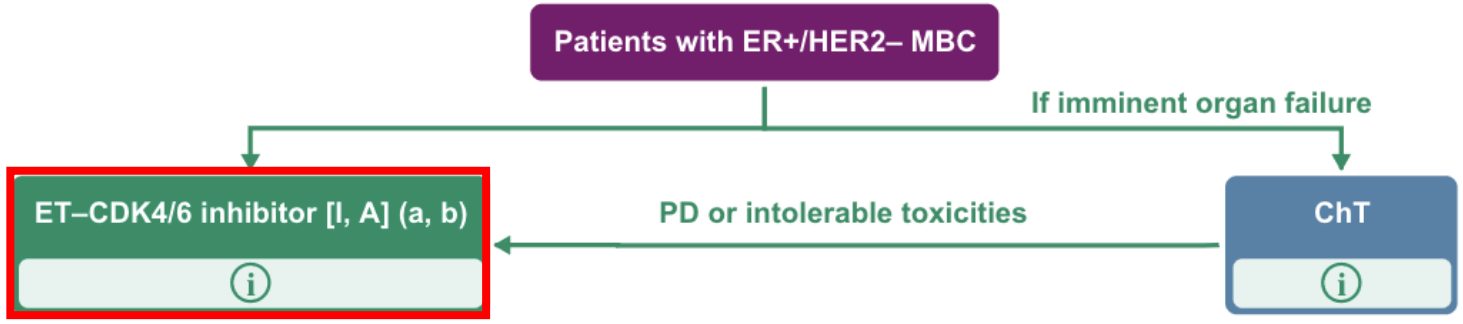


	Palbociclib + ET	CT
PFS events, N (%)	40 (65.6)	50 (84.7)
Median PFS months	18.7	7.8
HR 0.45 95% CI (0.29-0.70), p<0.001 (log-rank)		

Adapted from Loibl S et al. SABCS 2024

First-line treatment

v1.1 - May 2023



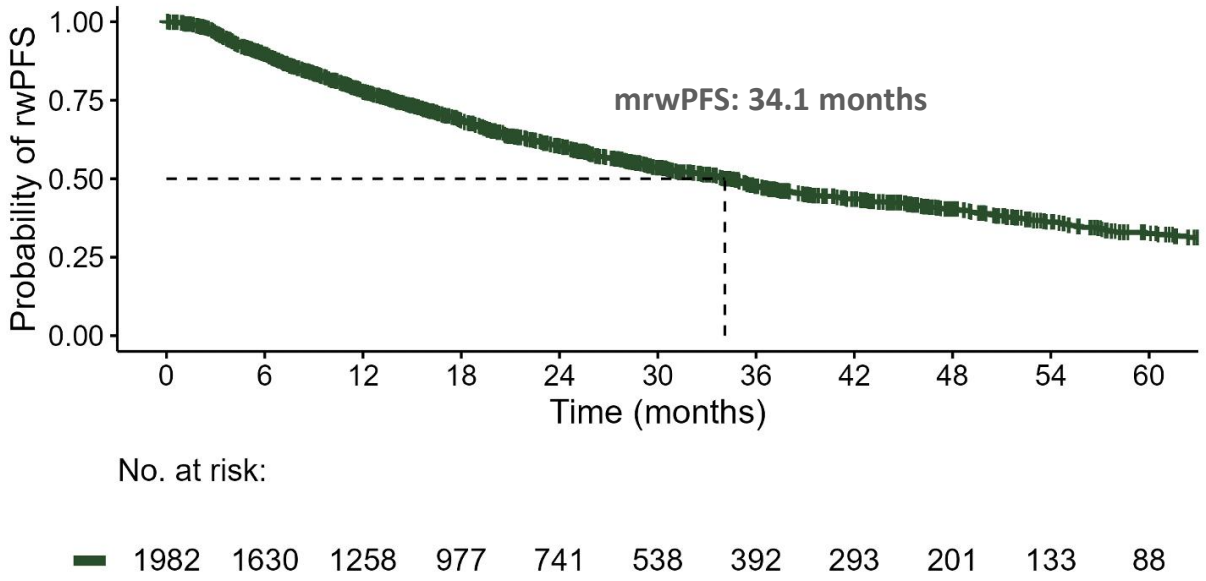
Current treatment landscape and outcomes: mPFS*

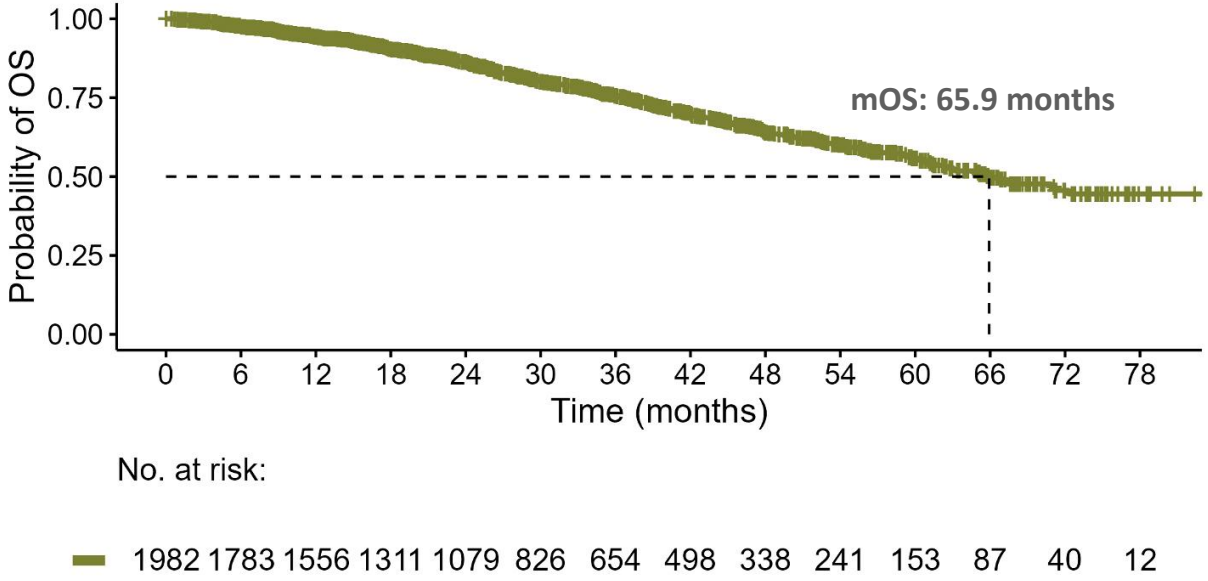
1L	ET + CDK4/6i	*No prior CDK4/6i*	24.8–28.2 mo[1–3]
2L+	ET + targeted therapies	*Prior CDK4/6i*	5.5 mo[4]
	ET monotherapy	*Prior CDK4/6i*	1.9–2.6 mo[4,5]
3L+	Single-agent CT	*Mostly CT naïve (mBC)*	6.2–7.1 mo[6–8]
	T-DXd (HER2-low)	*Prior ET and CT*	10.1 mo[9]

Adapted from G. Curigliano, ASCO 2024 meeting

https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

Patients with HR+/HER2- aBC spend more than half of their expected lifetime on ET+CDK4/6i therapy





PALMIRES-2

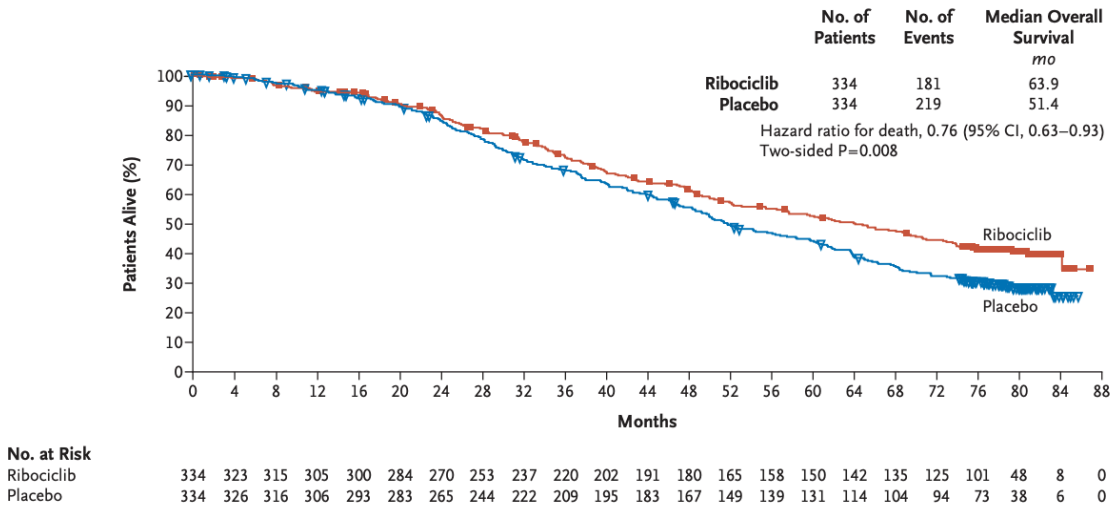
Manuscript under revision

[a] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).
[b] There is controversy on the choice of CDK4/6 inhibitor as there are no head to head comparisons between the agents and there are some differences in the study populations in the phase 3 randomized studies.
[c] In phase 3 randomized controlled trials, ribociclib + endocrine therapy have shown OS benefit in the first-line setting.
[d] Consider for disease progression on adjuvant endocrine therapy or with early disease relapse within 12 months of adjuvant endocrine therapy completion
[e] In phase 3 randomized controlled trials, fulvestrant + ribociclib or abemaciclib has shown OS benefit in the first-line setting
[f] In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown OS benefit in the second-line setting.
[g] If there is disease progression while on palbociclib, there are limited phase II data to support the use of ribociclib in the second line setting.
[h] If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PI3K-pathway inhibitor-containing regimen.
[i] If there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[j] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).
[k] A single study (S0226) in patients with HR-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression and OS. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.
[l] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

Note: All recommendations are category 2A unless otherwise indicated.

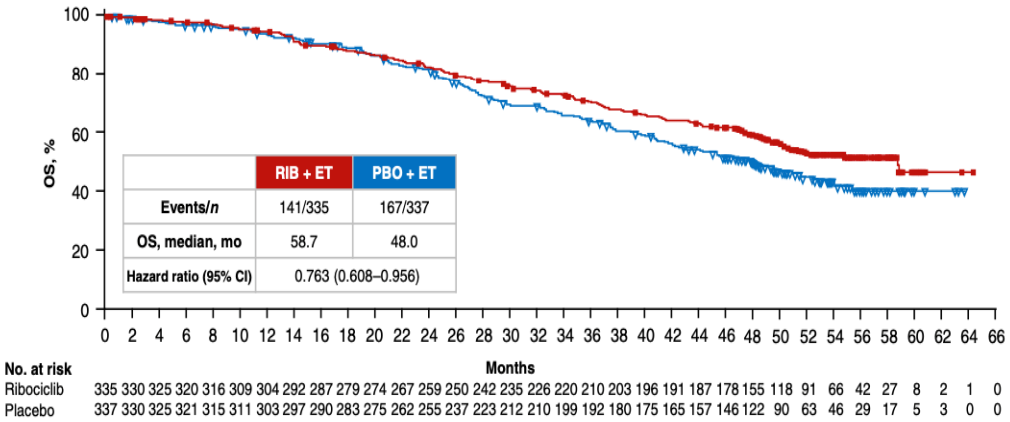
Ribociclib improves OS in both pre-menopausal and post-menopausal HR+/HER2- aBC patients

MONALEESA-2: post-menopausal; endocrine-sensitive



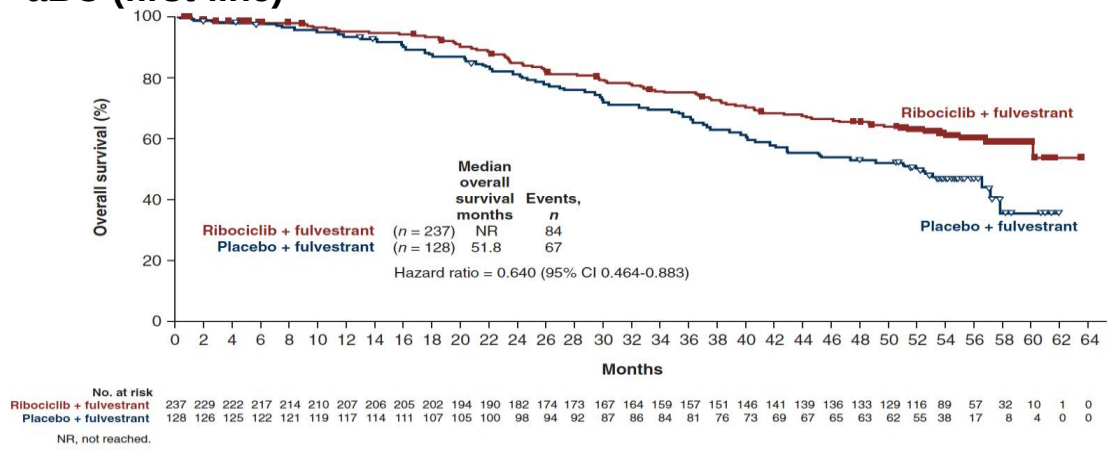
Hortobagyi GN et al. N Engl J Med 2022

MONALEESA-7: pre/peri-menopausal, endocrine sensitive/resistant



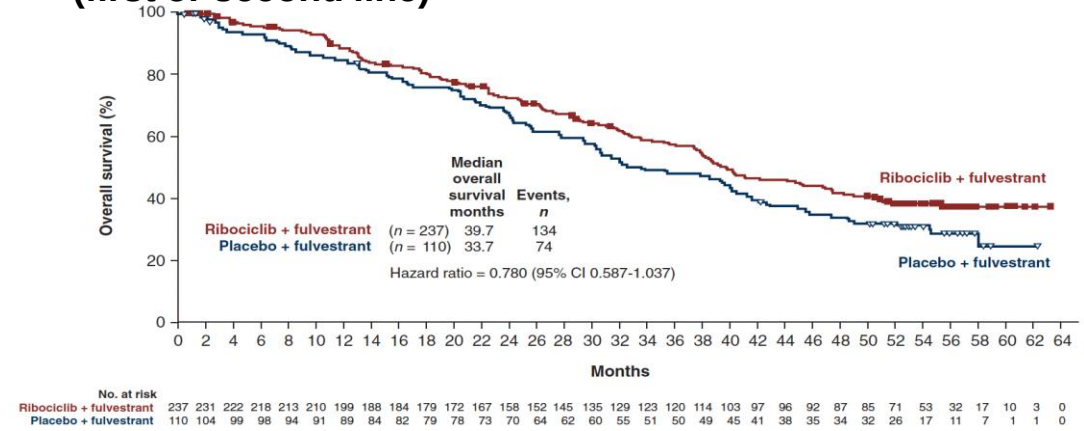
Lu YS et al. Clin Cancer Res 2022

MONALEESA-3: post-menopausal, endocrine sensitive/de novo aBC (first-line)



Slamon J et al. Ann Oncol 2021

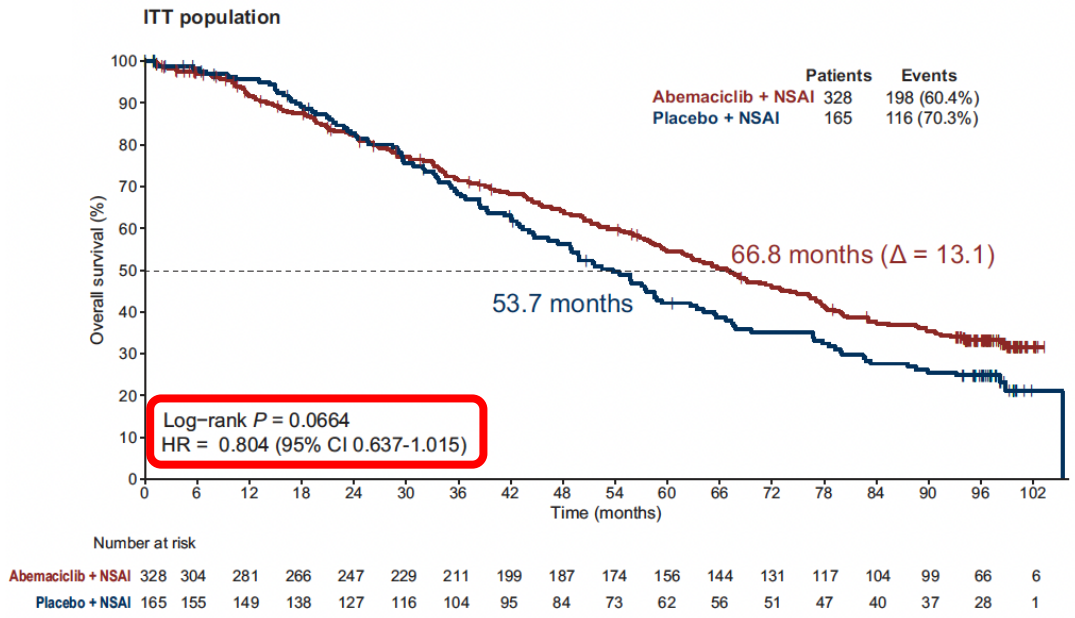
MONALEESA-3: post-menopausal, endocrine resistant (first or second line)



Slamon J et al. Ann Oncol 2021

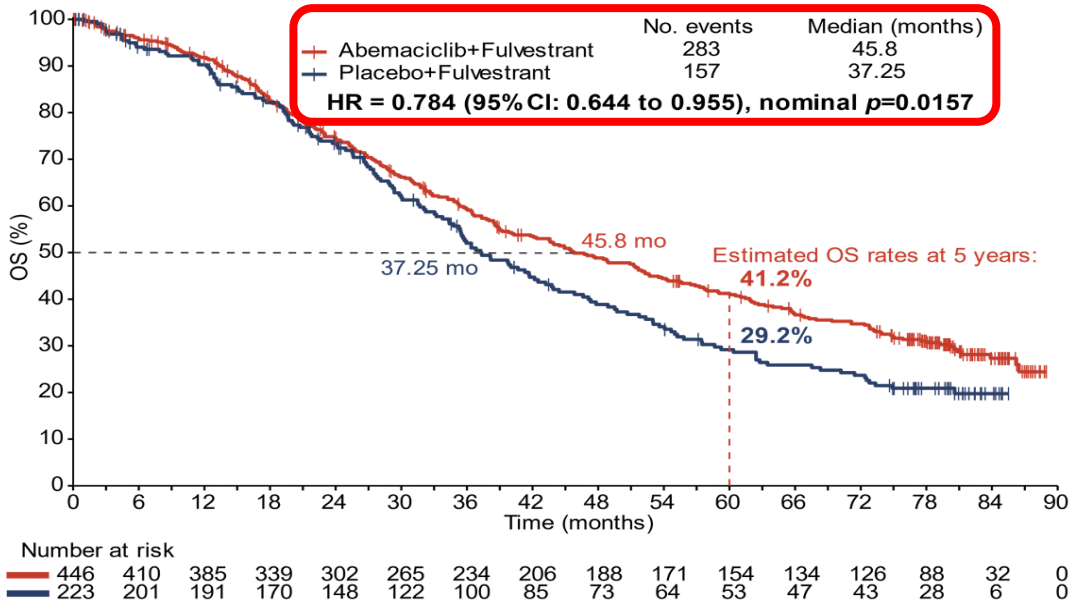
Abemaciclib resulted in clinically relevant OS improvement in pre-menopausal and post-menopausal HR+/HER2- aBC patients

MONARCH3: post-menopausal; endocrine-sensitive



Goetz MP et al. Ann Oncol 2024

MONARCH2: post-menopausal; endocrine-resistant



Sledge GW et al. SABCS 2022

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First-line treatment: novelties from 2024

- Real-world effectiveness comparison of first-line palbociclib, ribociclib or abemaciclib in combination with ET

- Inavolisib in combination with fulvestrant plus palbociclib in patients with endocrine-resistant, *PIK3CA*-mutated HR+/HER2- aBC

First-line treatment: novelties from 2024

- **Real-world effectiveness comparison of first-line palbociclib, ribociclib or abemaciclib in combination with ET**

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2024 ASCO ANNUAL MEETING

Comparison of antitumor efficacy of first-line Palbociclib, Ribociclib or Abemaciclib in patients with HR+/HER2- aBC: results of the multicenter, real-world, Italian study PALMARES-2

Vernieri C[1], Provenzano L[1], Giuliano M[2], Rizzo G[3], Toss A[4], Piras M[5], Sirico M[6], Tagliaferri B[7], Giordano M[8], Miliziano D[1], Generali D[9], Sartori D[10], Zambelli A[11], Gennari A[12], La Verde N[13], Pedersini R[14], Lambertini M[15], Botticelli A[16], Curigliano G[17], Dieci MV[18], PALMARES-2 study group

[1]Breast Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, [2] Department of Clinical Medicine and Surgery, University of Naples "Federico II", Napoli, Italy, [3] Department of Medical Oncology, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy, [4] Department of Medical Oncology, University of Modena and Reggio Emilia, Modena, Italy, [5] Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy, [6] Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, [7] Medical Oncology Unit, ICS Maugeri IRCCS, Pavia, Italy, [8] Oncology Unit, Sant'Anna Hospital, ASST Lariana, 22042 San Fermo della Battaglia, Italy, [9] Multidisciplinary Unit of Breast Pathology and Translational Research, Cremona Hospital, Cremona, Italy and University of Trieste, [10] Oncology Unit, AULSS 3, Mirano, Italy, [11] Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, [12] Medical Oncology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy, [13] Medical Oncology, ASST Fatebenefratelli Sacco, PO Luigi Sacco, Milan, Italy, [14] Medical Oncology Department, ASST Spedali Civili of Brescia, Brescia, Italy, [15] Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [16] Department of Radiological, Oncological and Pathological Science, Sapienza University of Rome, Rome, Italy, [17] European Institute of Oncology, IRCCS, Milan, Italy and University of Milano, [18] Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

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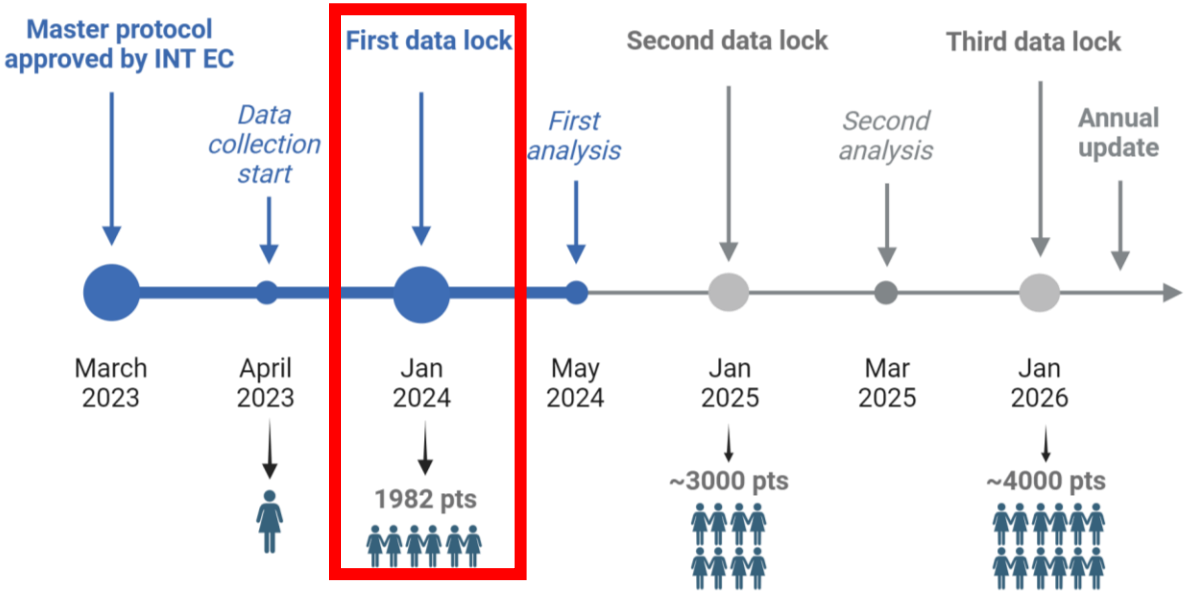
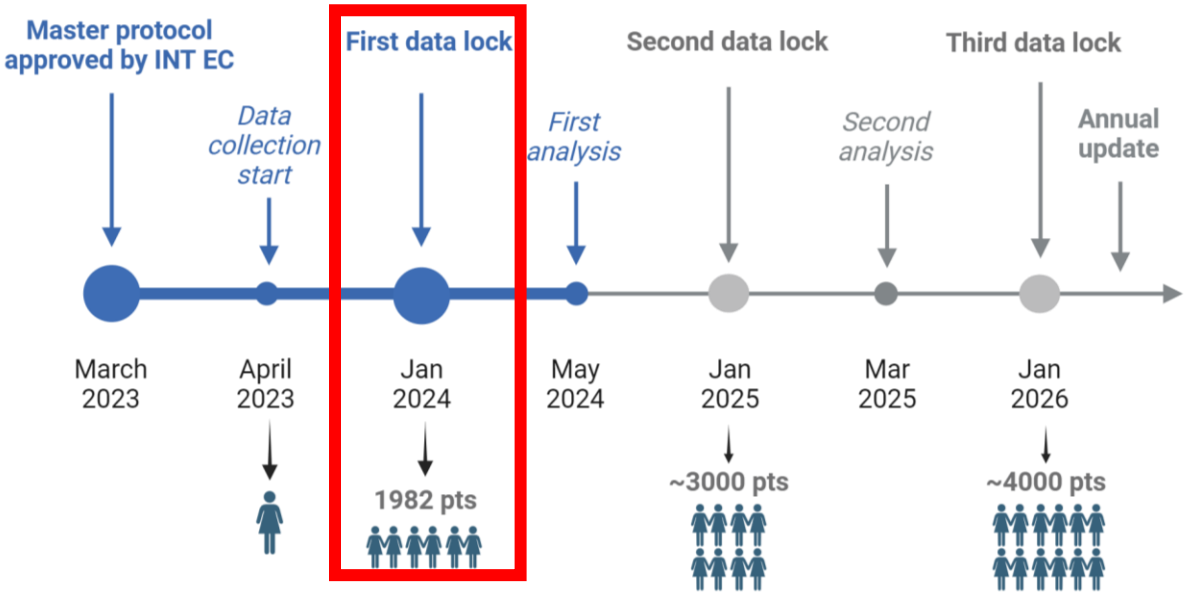
PALMARES-2 network and timeline

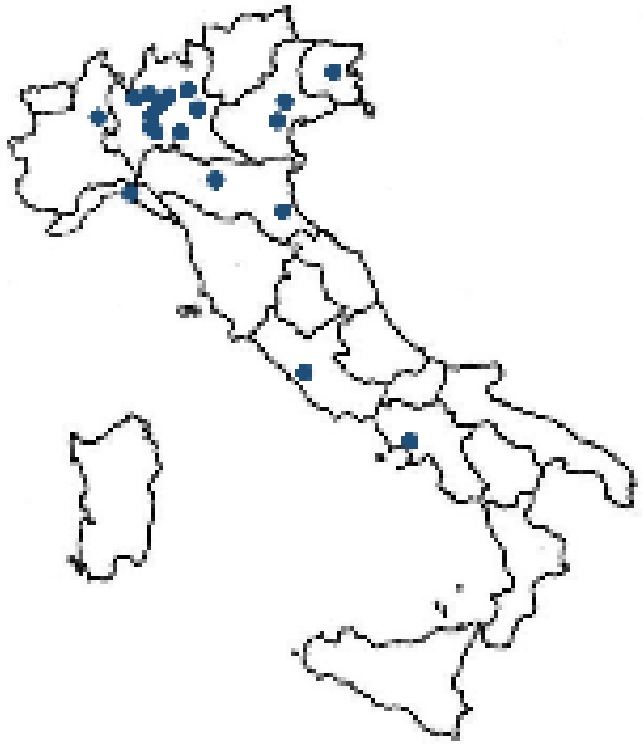


PALMARES-2

PALMARES-2 network and timeline



Participating centers (n=18)



Investigators

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G. Curigliano (IEO, Milan)
A. Botticelli (Umberto I, Rome)
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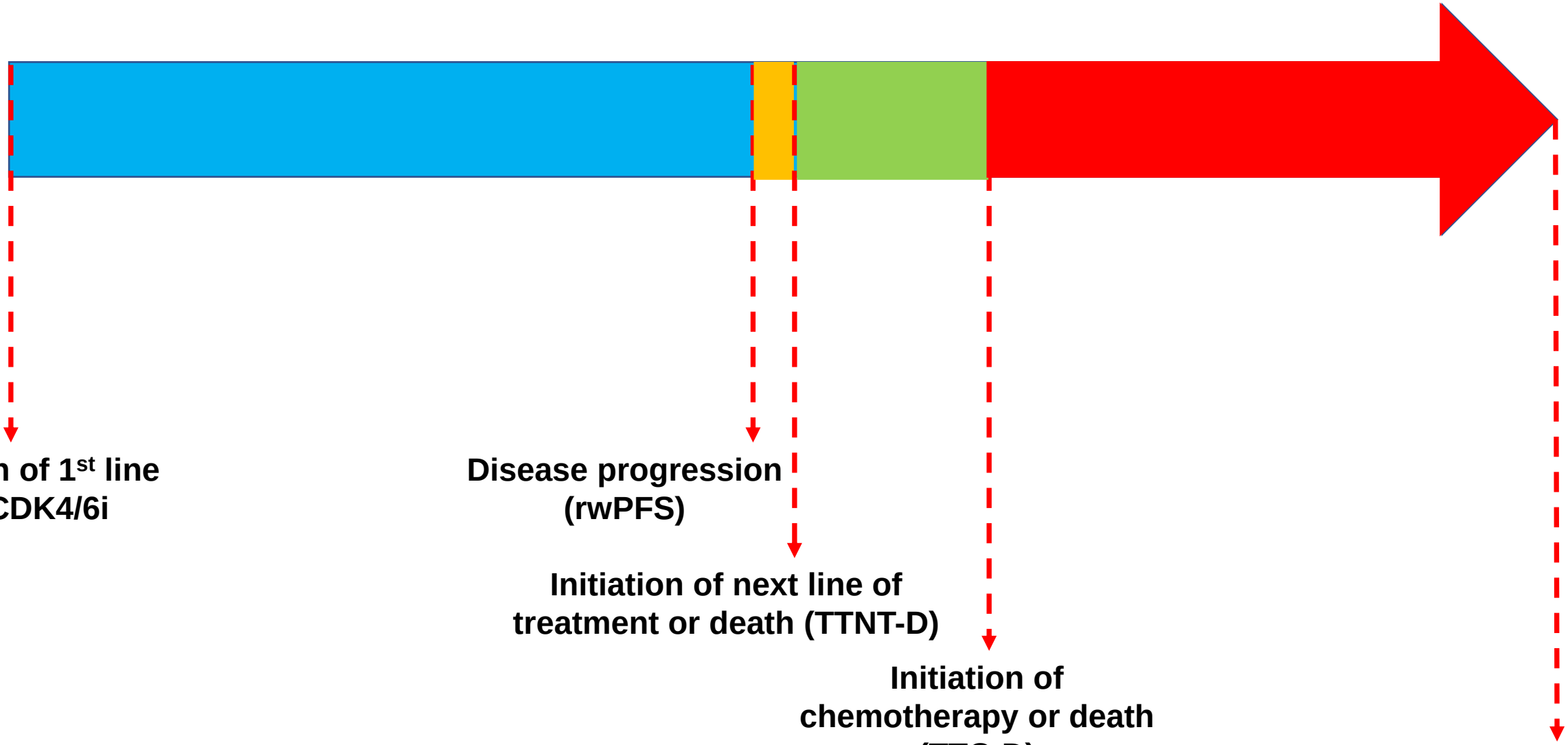
M Giordano (ASST Lariana, Como)
B. Tagliaferri (ICS Maugeri, Pavia)
D. Generali (ASST Cremona)
D. Sartori (ULSS 3 veneto)

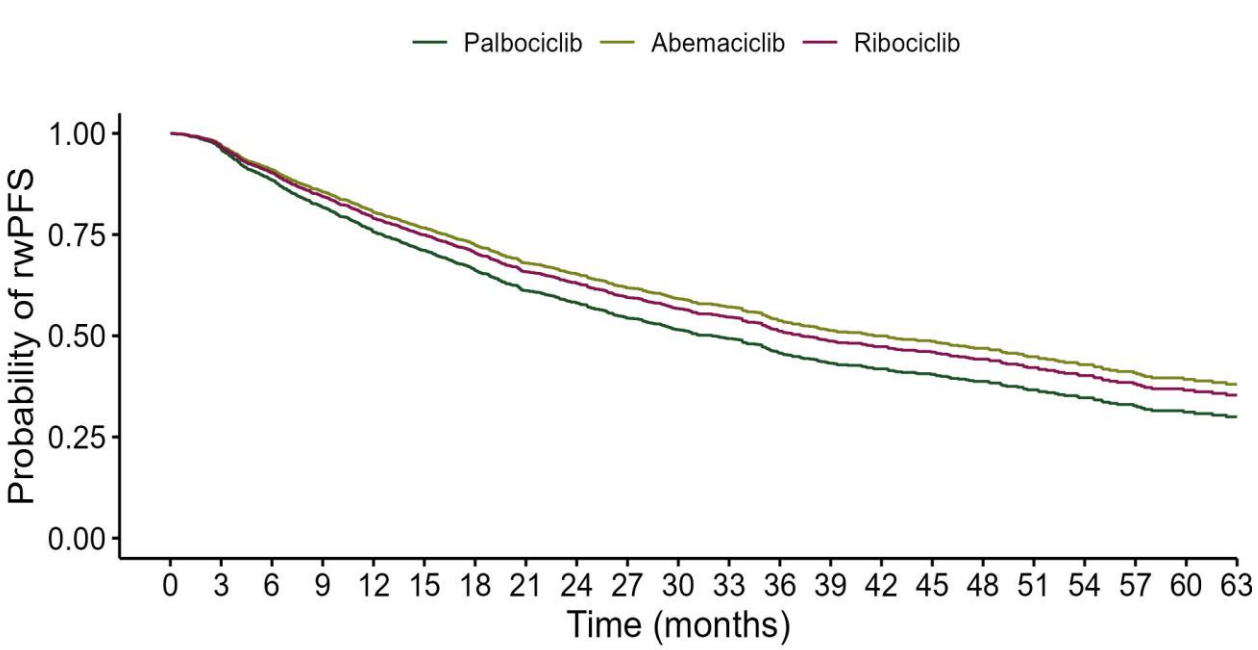
PALMARES-2

PALMARES-2 study endpoints

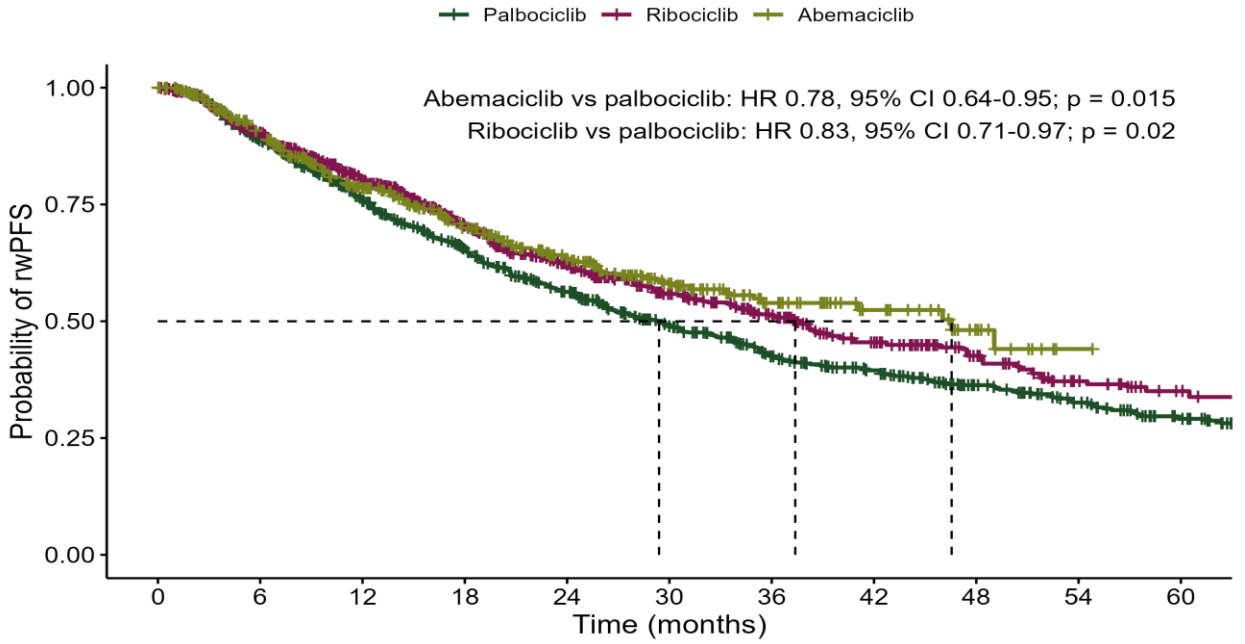


*OS: primary study endpoint

Ribociclib and abemaciclib are associated with better rwPFS when compared to palbociclib



Cox regression model adjusted curves

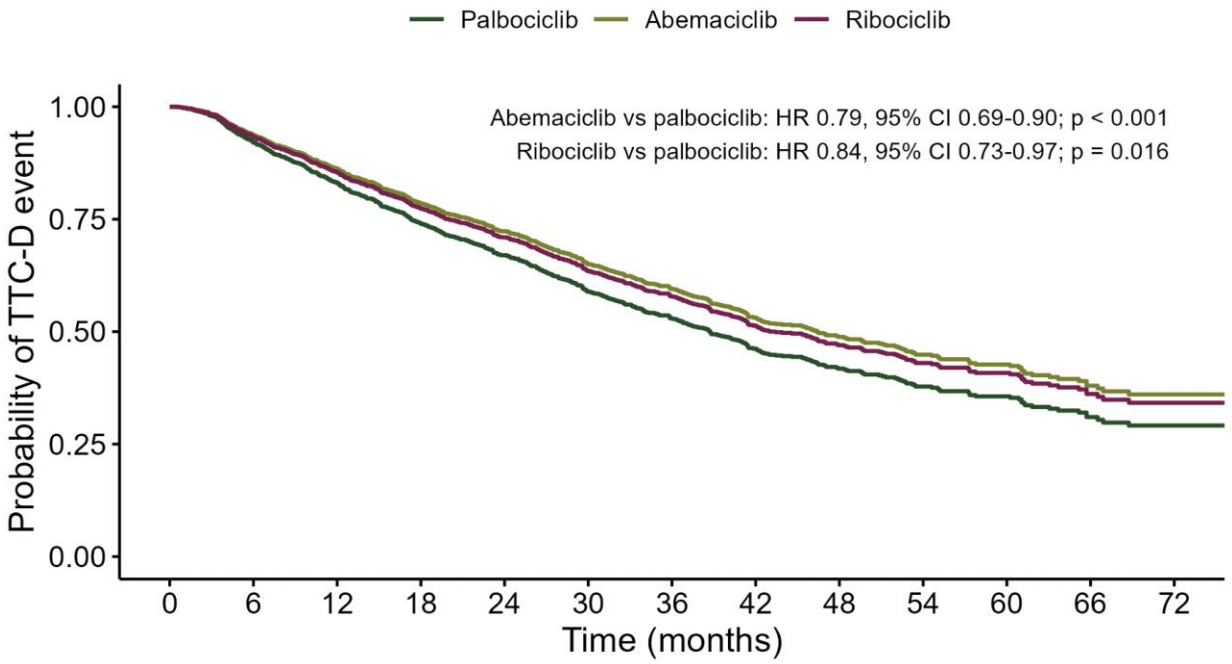


IPTW-based balancing of covariates

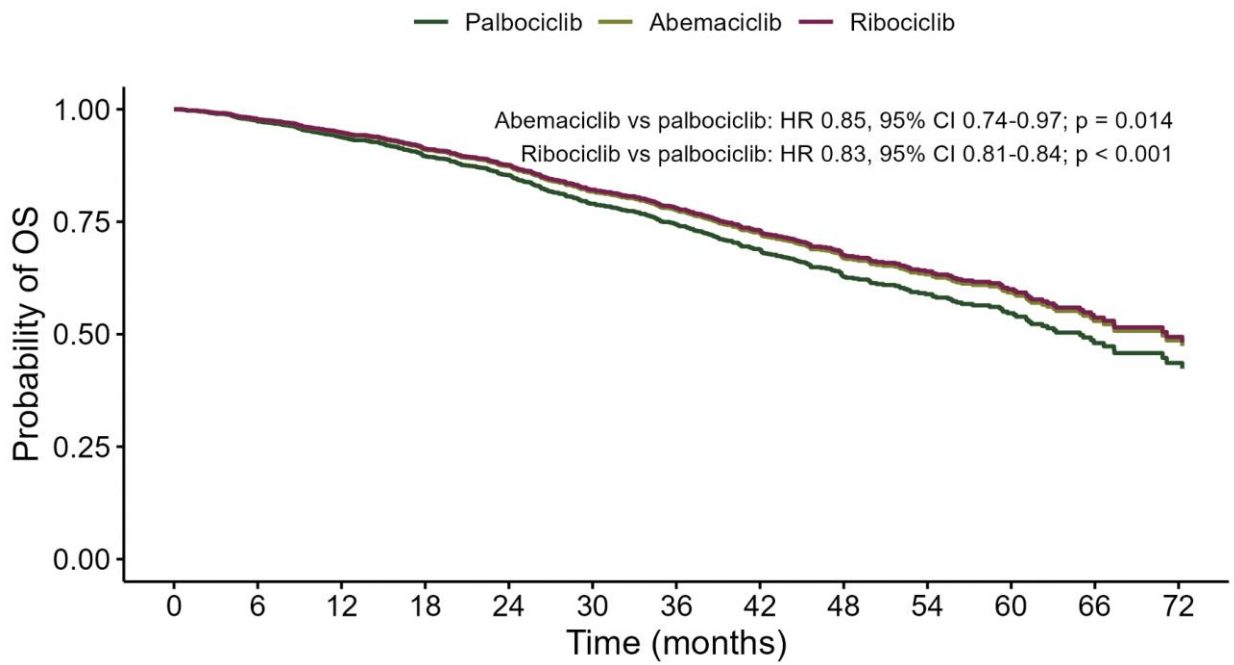
Vernieri C et al ASCO 2024 meeting
Manuscript under revision

Ribociclib and abemaciclib are associated with better TTC-D and OS when compared to palbociclib

TTC-D



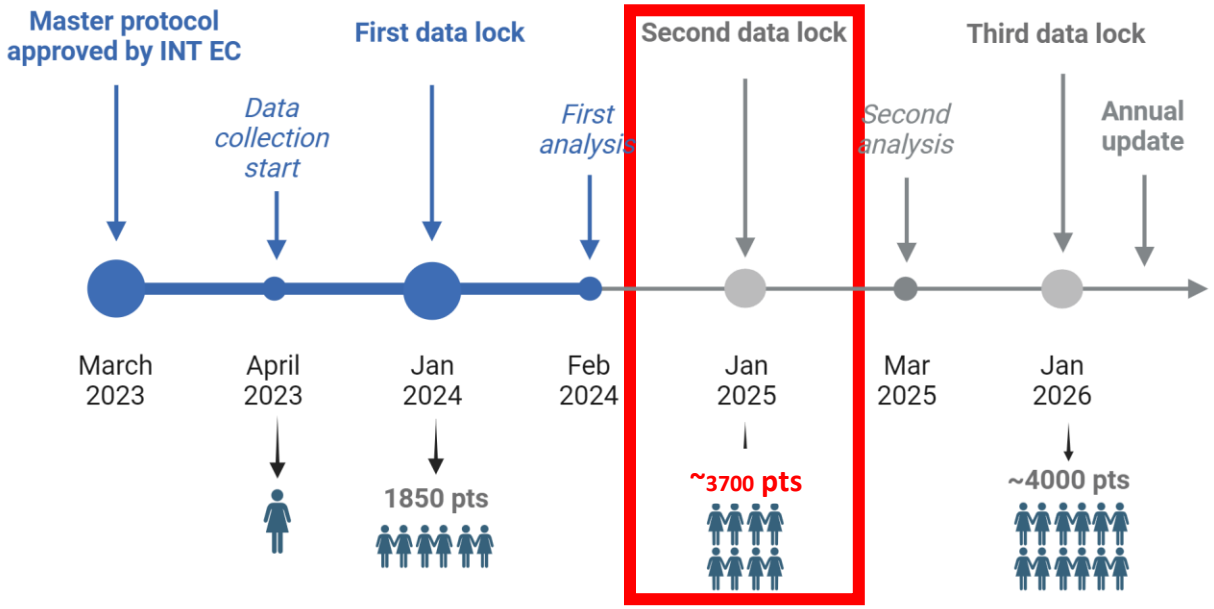
OS

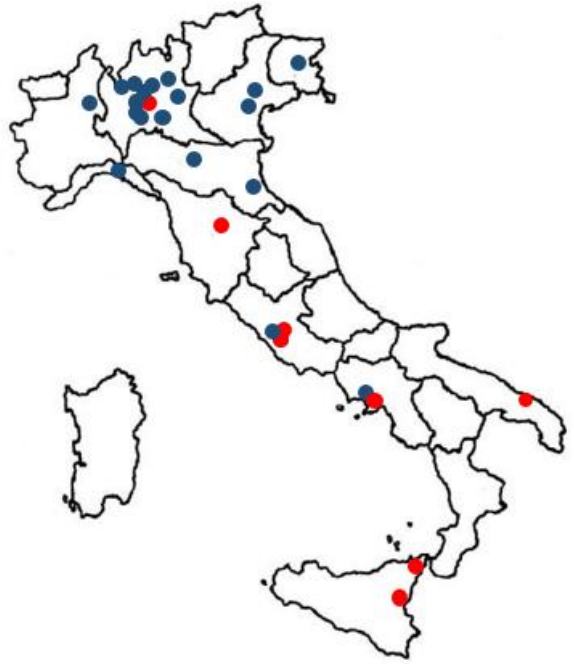


Data not mature yet

Vernieri C et al ASCO 2024 meeting
Manuscript under revision

Second PALMARES-2 study data lock





PALMARES-2

PALMARES-2 investigators

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D. Sartori (ULSS 3 veneto)
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O. Garrone (Ca' Granda Policlinico, Milan)
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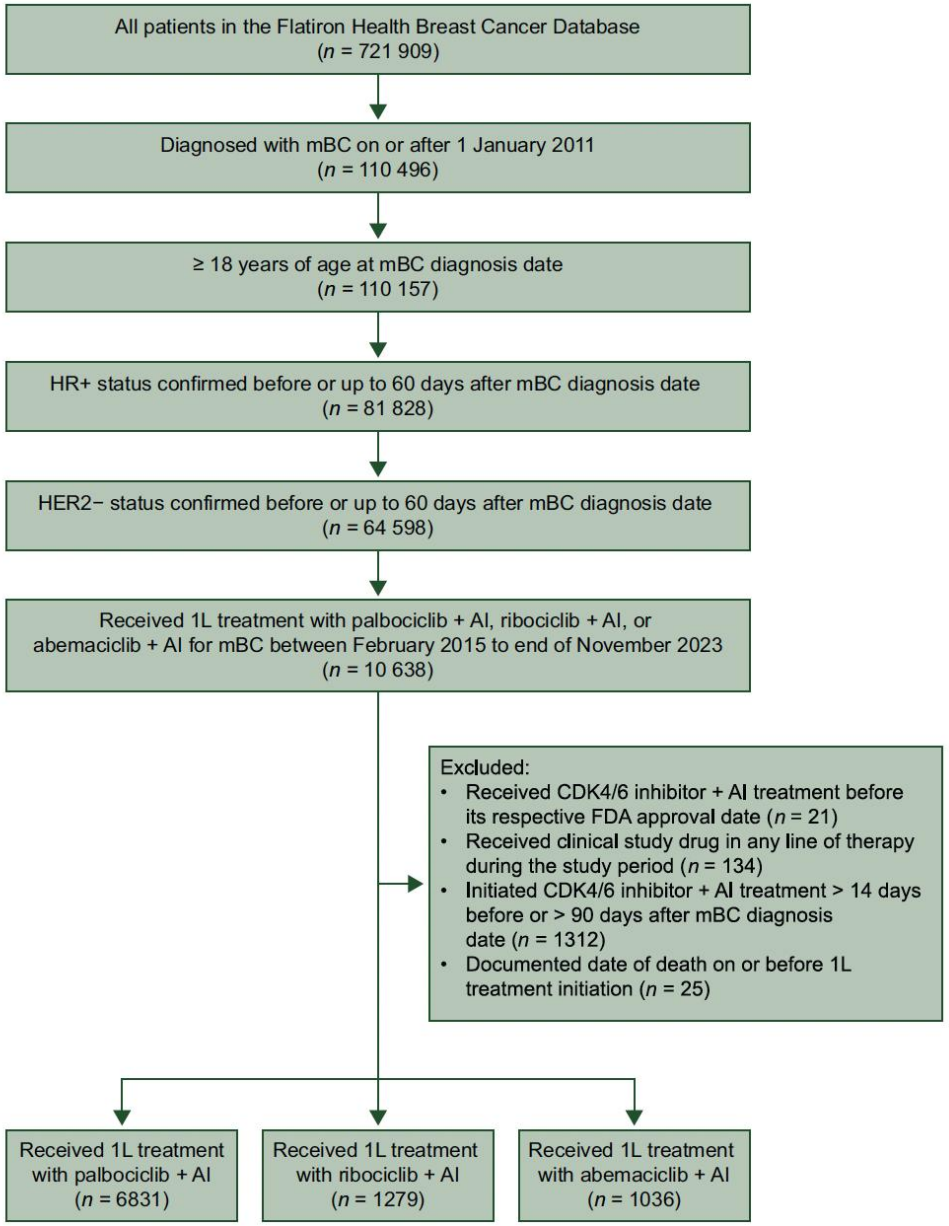
P. Vigneri (Humanitas, Catania)
G. Ricciardi (AO Papardo, Messina)

Mature TTC-D data will be presented at ASCO 2025 meeting

Mature OS data are expected for ASCO 2026 meeting

A large, retrospective OS comparison of first-line CDK4/6i in combination with AIs in patients with HR+/HER2- aBC



Adjustment methods:

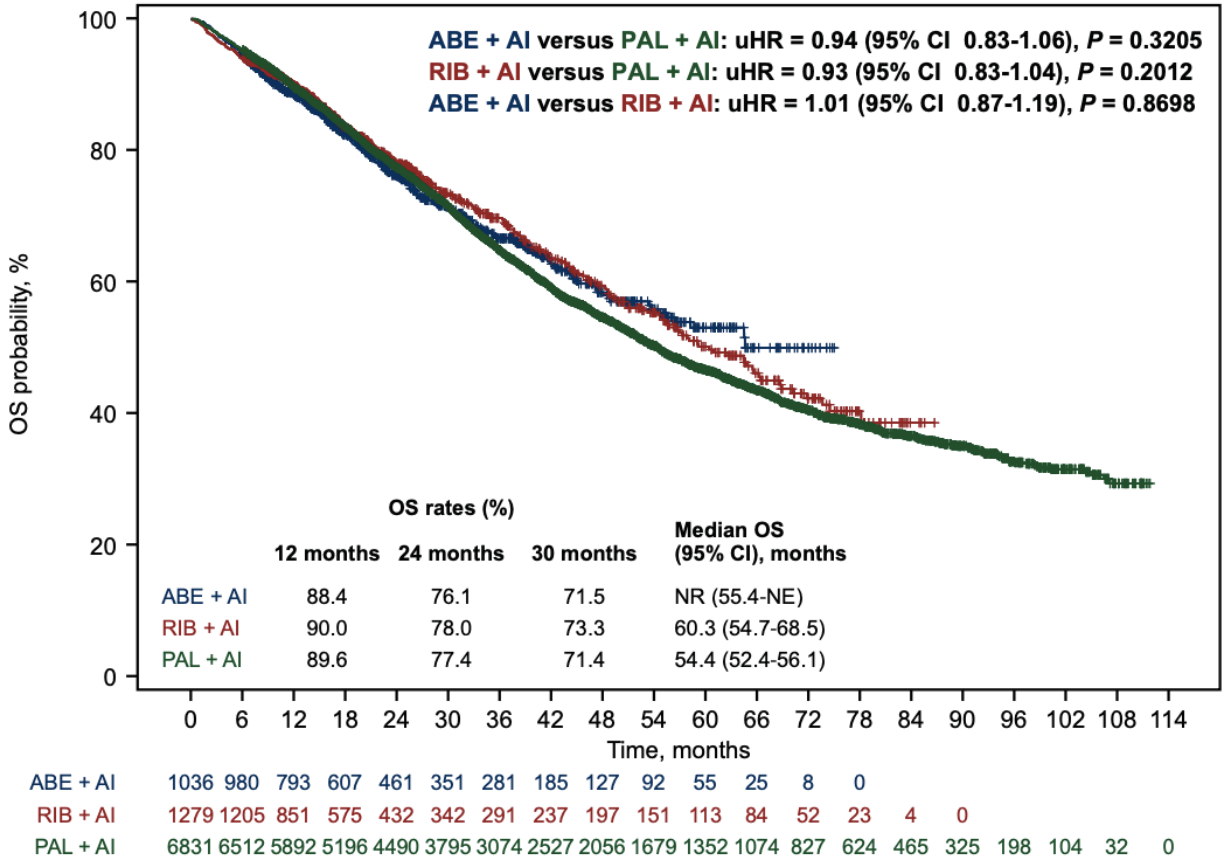
- sIPTW (stabilized inverse-probability-of-weighting)
- Cox proportional regression models

Adjustment covariates:

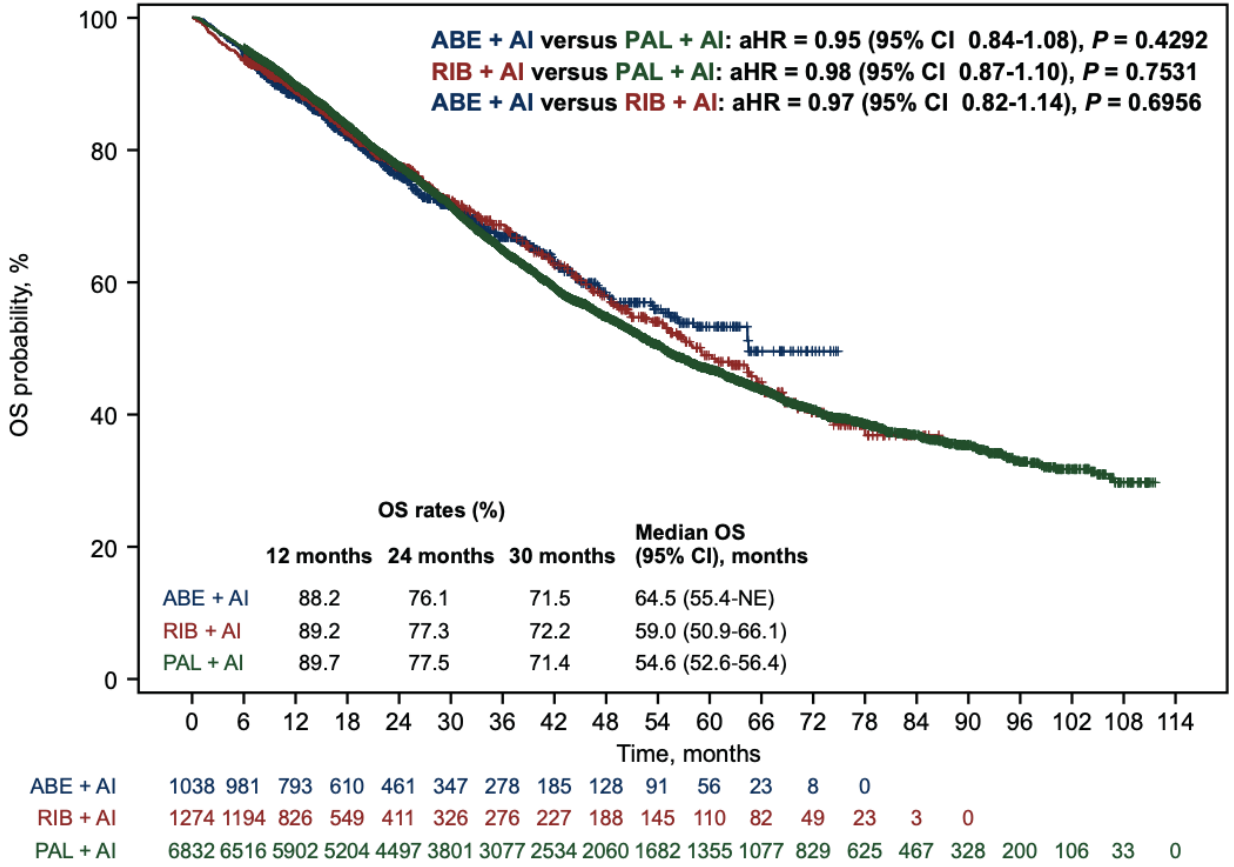
- Age
- Sex
- Practice type
- ECOG PS
- Disease stage at initial diagnosis
- Visceral metastasis
- Bone-only disease
- Number of disease sites
- Disease-free interval (from initial NC diagnosis to aBC diagnosis)

Rugo H et al SABCS 2024 meeting
Rugo H et al ESMO Open 2025

First-line palbociclib, ribociclib and abemaciclib are not associated with significantly different OS in a large US patient cohort (n=9146)



Unadjusted analysis



sIPTW

Rugo H et al SABCS 2024 meeting
Rugo H et al ESMO Open 2025

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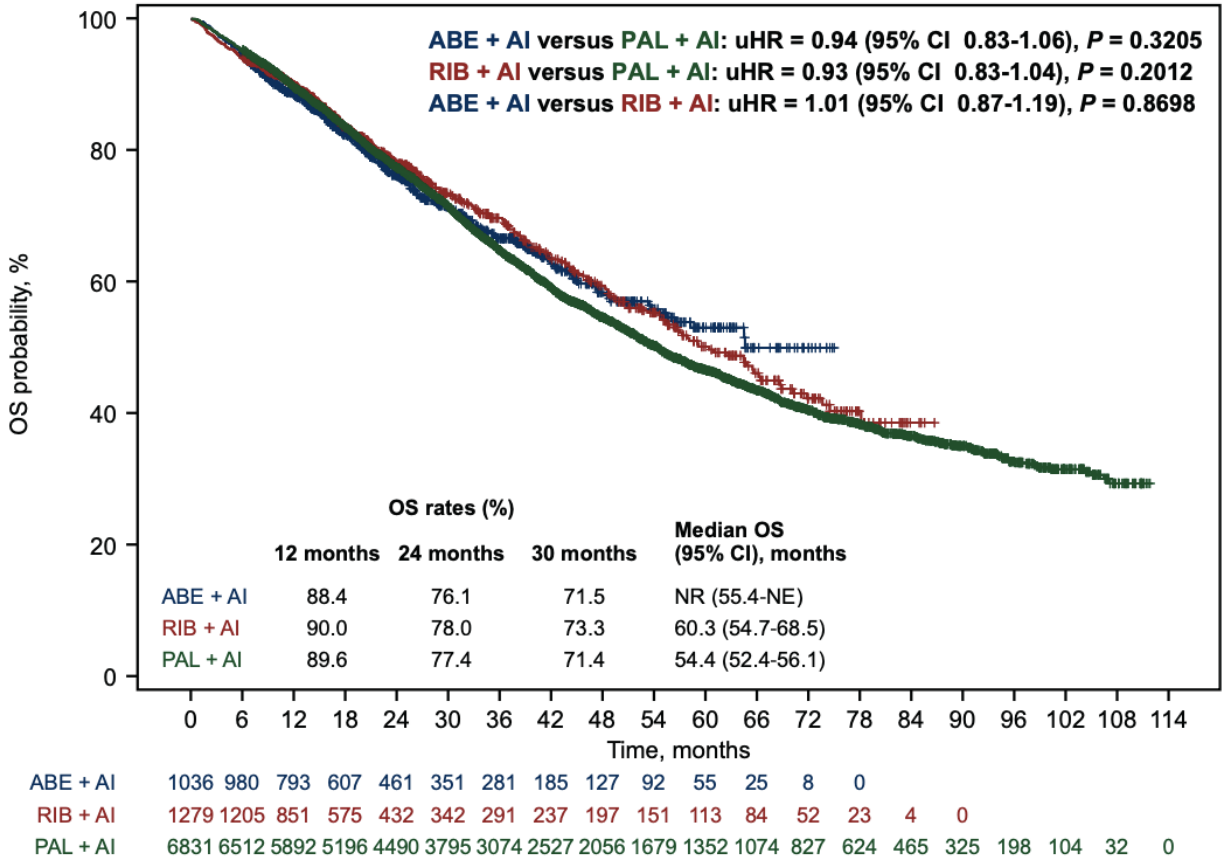
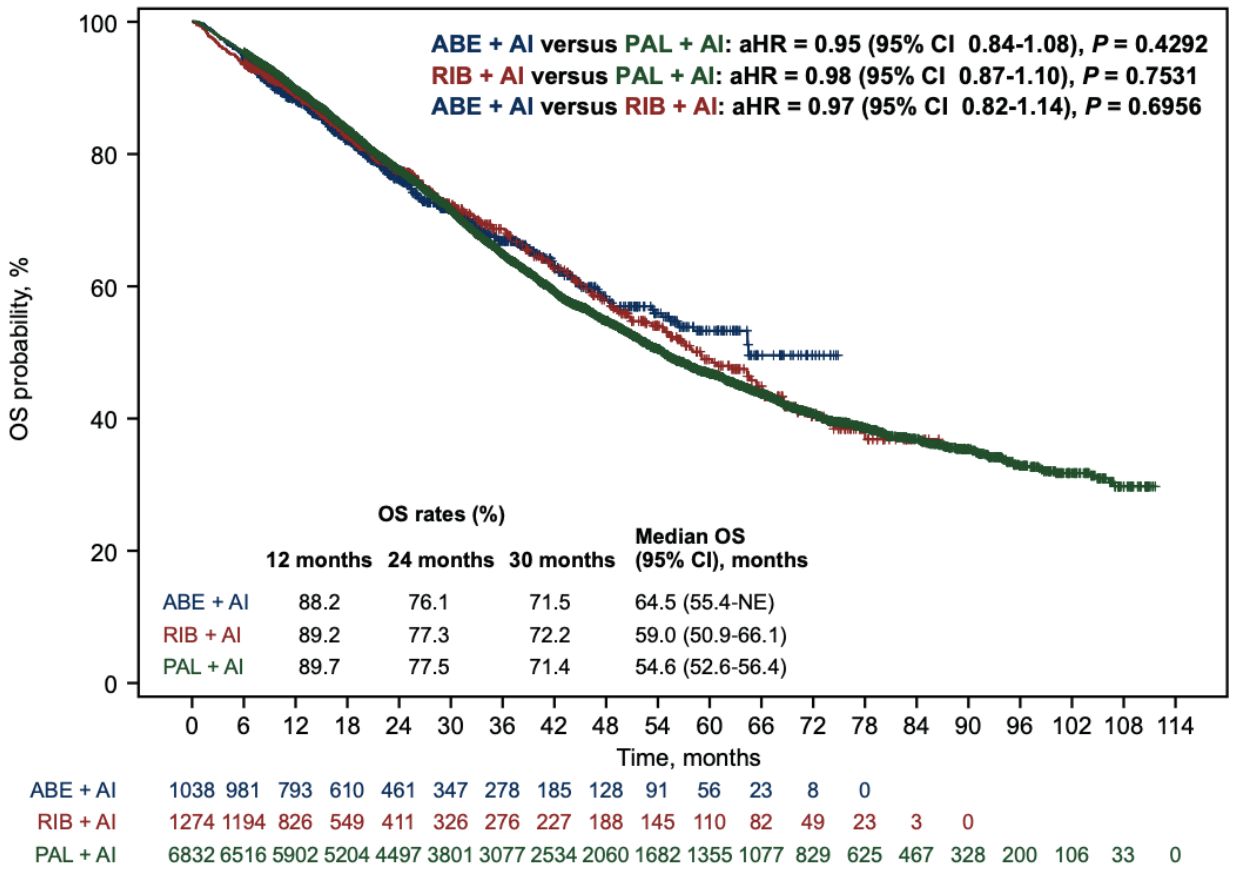


Unadjusted analysis



sIPTW

Results confirmed by multivariable analyses (Cox regression models)

- Ribociclib vs. palbociclib: aHR=0.94 (95% CI: 0.84-1.07; P=0.3216)
- Abemaciclib vs. palbociclib: aHR=0.94 (95% CI: 0.84-1.07; P=0.3603)
- Abemaciclib vs. ribociclib: aHR=1.00 (95% CI: 0.85-1.17; P=0.9851)

Rugo H et al SABCS 2024 meeting
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However…

- Imbalances in treatment assignment: palbociclib (n=6931), ribociclib (n=1279), abemaciclib (n=1036)
- Imbalances in median follow-up: palbociclib (33 months), ribociclib (16 months), abemaciclib (21 months)
- Crucial covariates were not used in multivariable models: endocrine sensitivity/resistance; adjuvant treatments; menopausal status; liver/lung metastases; ER/PgR expression; luminal A vs. B like disease; subsequent lines of therapy
- Only patients treated with concomitant aromatase inhibitors were included in this analysis (why?)
- Other clinically relevant endpoints, such as rwPFS, rwPFS2 and TTC, were not reported (because these data ”were not available”, as stated by the authors
- Due to the low number of patients at risk in the ribociclib and abemaciclib cohorts after month 30, point estimates beyond this timepoint were not stable

First-line treatment: novelties from 2024

- Real-world effectiveness comparison of first-line palbociclib, ribociclib or abemaciclib in combination with ET

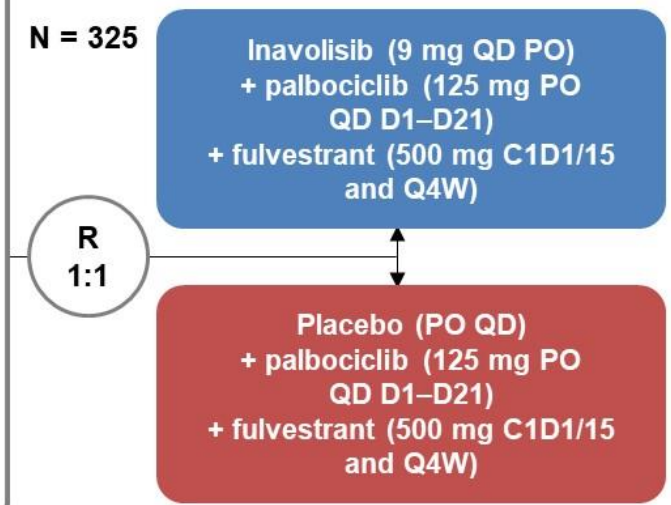
- **Inavolisib in combination with fulvestrant plus palbociclib in patients with endocrine-resistant, *PIK3CA*-mutated HR+/HER2- aBC**

INAVO120 study design[1]

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2– LA/mBC** by central ctDNA or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**
- **Fasting glucose <126 mg/dL (<7.0 mmol/L) and HbA1c <6.0% (< 42 mmol/mol)**



Statistical methods

- For efficacy endpoints and TTCD, hazard ratios were estimated using a Cox proportional hazard model with 95% CI and Kaplan–Meier methodology was used to estimate the medians with the Brookmeyer–Crowley method used for the 95% CI

Efficacy endpoints

- PFS by investigator
- OS
- ORR, BOR, CBR, DOR
- **Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)**
- **Time from randomization to first subsequent chemotherapy after treatment discontinuation**

Safety endpoints

Key selected AEs (hyperglycemia, diarrhea, rash, and stomatitis/mucosal inflammation)*

Patient-reported outcomes endpoints†

- **BPI-SF: TTCD in worse pain‡§**
- **EORTC QLQ-C30: mean change from baseline in HRQoL, physical functioning, and role functioning‖**
- **PRO-CTCAE: presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities**
- **An overall bother item: overall bother experienced due to side effects of treatment**

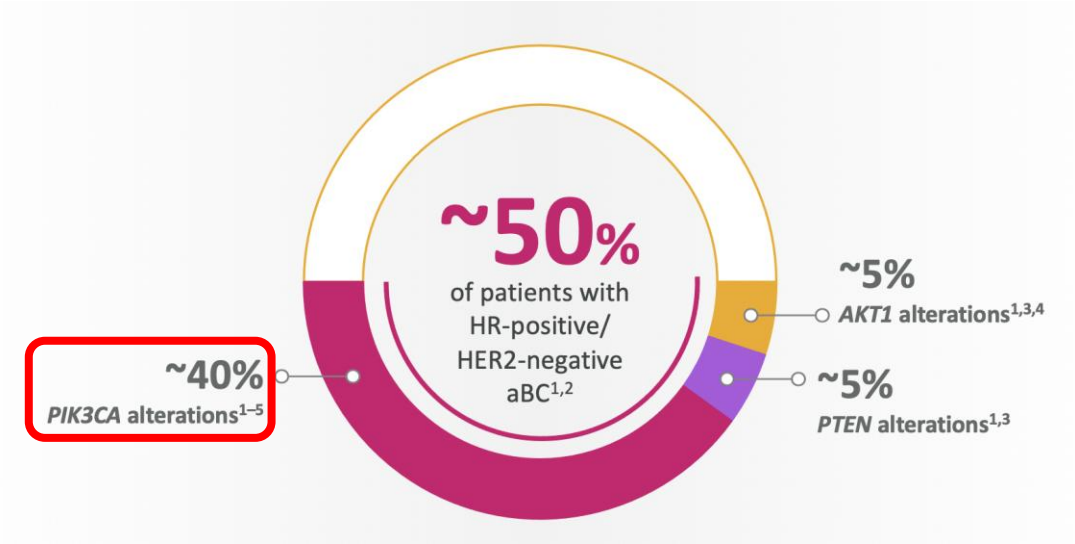
* Assessed using grouped terms; severity reported per National Cancer Institute CTCAE version 5.0. † Assessed at D1 of C1–3 then D1 of every other C thereafter (5, 7, 9, etc.), at treatment discontinuation, and every 3 months during survival follow-up; baseline completion rates in both arms were >90% for all assessments; post-baseline rates in both arms remain >80% through C15; <50% intent-to-treat sample remaining at C9 in the inavolisib arm versus C5 in the placebo arm. ‡ Type I error-controlled; hierarchically tested according to a prespecified fixed order of endpoints. § Defined as the time from randomization to the first documentation of a ≥2-point increase from baseline on the "worst pain" item held for at least two consecutive Cs, or an initial increase followed by death or treatment discontinuation within 3 weeks from the last assessment. ‖ A ≥10-point change was defined as a clinically meaningful difference.

AE, adverse event; (LA/m)BC, (locally advanced/metastatic) breast cancer; BOR, best overall response; BPI-SF, brief pain inventory-short form; C, Cycle; CBR, clinical benefit rate; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; D, Day; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ET, endocrine therapy; HER2–, HER2-negative; HR+, hormone receptor-positive; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, time from randomization to next progression after discontinuing study treatment for PD, or death from any cause; PO, orally; PRO, patient-reported outcomes; Q4W, every 4 weeks; QD, once daily; R, randomized; TTCD, time to confirmed clinical meaningful deterioration.

1. Jhaveri KL, *et al.* SABCS 2023 (Abstract GS03-13).

Numbers…

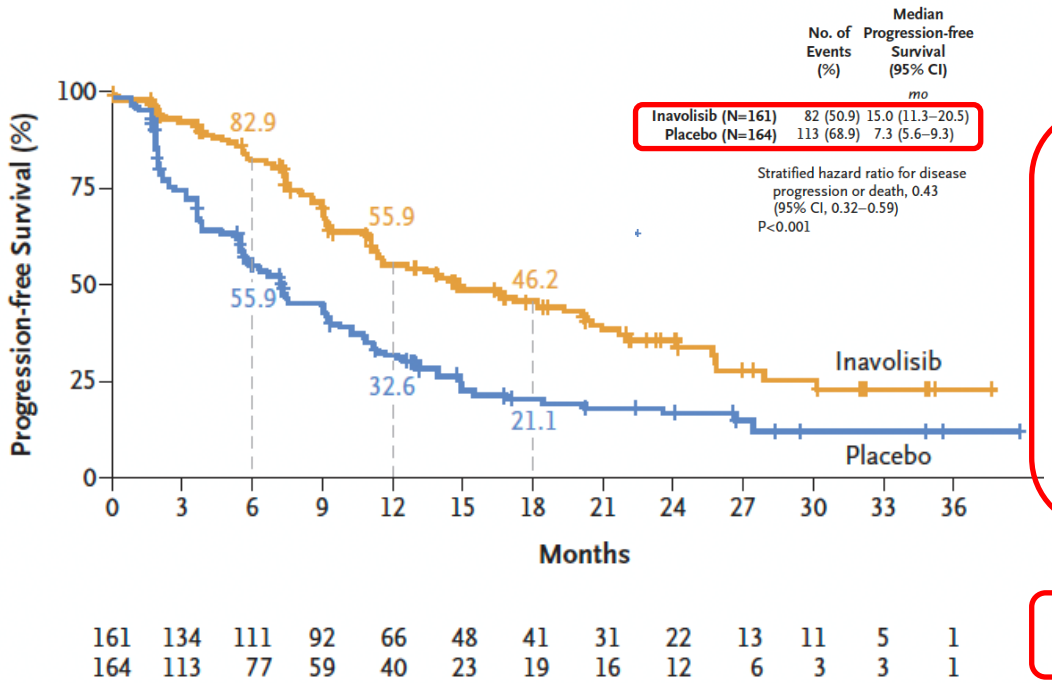
- About one third (33%) of HR+/HER2- aBC patients have endocrine-resistant disease
- About 40% of patients with HR+/HER2- aBC have *PIK3CA* tumor mutations



- **About 15% of all HR+/HER2- aBC have endocrine-resistant disease AND *PIK3CA* tumor mutations**

Inavolisib improves patient PFS regardless of type and sites of metastases, HR and menopausal status, ECOG PS

Progression-free survival

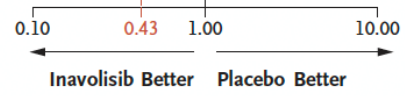


No. at Risk

Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1

B Analysis of Progression-free Survival in Key Subgroups

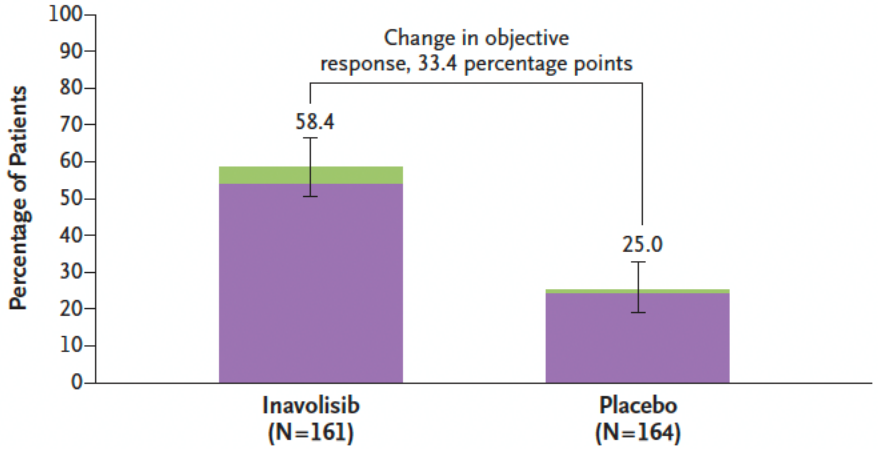
Subgroup	No. of Patients		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	Inavolisib	Placebo	Inavolisib	Placebo	
			mo		
All patients	161	164	15.0	7.3	0.50 (0.38–0.67)
Age					
<65 yr	136	130	16.6	7.2	0.44 (0.32–0.60)
≥65 yr	25	34	9.3	10.7	0.96 (0.50–1.83)
Geographic region					
Asia	56	58	14.6	5.8	0.40 (0.24–0.64)
North America or Western Europe	63	64	13.8	9.3	0.73 (0.47–1.15)
Other	42	42	21.0	5.6	0.40 (0.22–0.72)
ECOG performance-status score at baseline					
0	100	106	16.6	7.4	0.46 (0.32–0.66)
1	60	58	11.4	5.6	0.58 (0.36–0.92)
Menopausal status at randomization					
Premenopausal	65	59	20.1	6.5	0.35 (0.22–0.56)
Postmenopausal	91	104	13.4	7.5	0.64 (0.44–0.92)
Visceral disease					
No	29	36	25.8	7.4	0.43 (0.19–0.97)
Yes	132	128	13.8	7.2	0.51 (0.38–0.69)
Liver metastasis at enrollment					
No	84	73	24.2	11.3	0.56 (0.35–0.90)
Yes	77	91	11.0	5.6	0.48 (0.33–0.69)
No. of organs with metastases at enrollment					
1	21	32	20.2	7.4	0.35 (0.14–0.87)
2	59	46	18.2	7.4	0.47 (0.29–0.77)
≥3	81	86	14.1	7.3	0.55 (0.37–0.80)
Resistance to endocrine therapy					
Primary	53	58	11.4	3.7	0.39 (0.24–0.61)
Secondary	108	105	18.2	9.7	0.55 (0.38–0.80)
Hormone receptor status					
ER-positive, PR-negative	45	45	11.1	5.6	0.45 (0.27–0.76)
ER-positive, PR-positive	113	113	18.2	7.4	0.48 (0.34–0.68)
Previous endocrine therapy					
Aromatase inhibitor and tamoxifen	18	19	11.0	12.9	1.17 (0.42–3.24)
Aromatase inhibitor only	60	71	10.9	5.8	0.62 (0.41–0.94)
Tamoxifen only	82	73	21.0	7.4	0.38 (0.25–0.59)



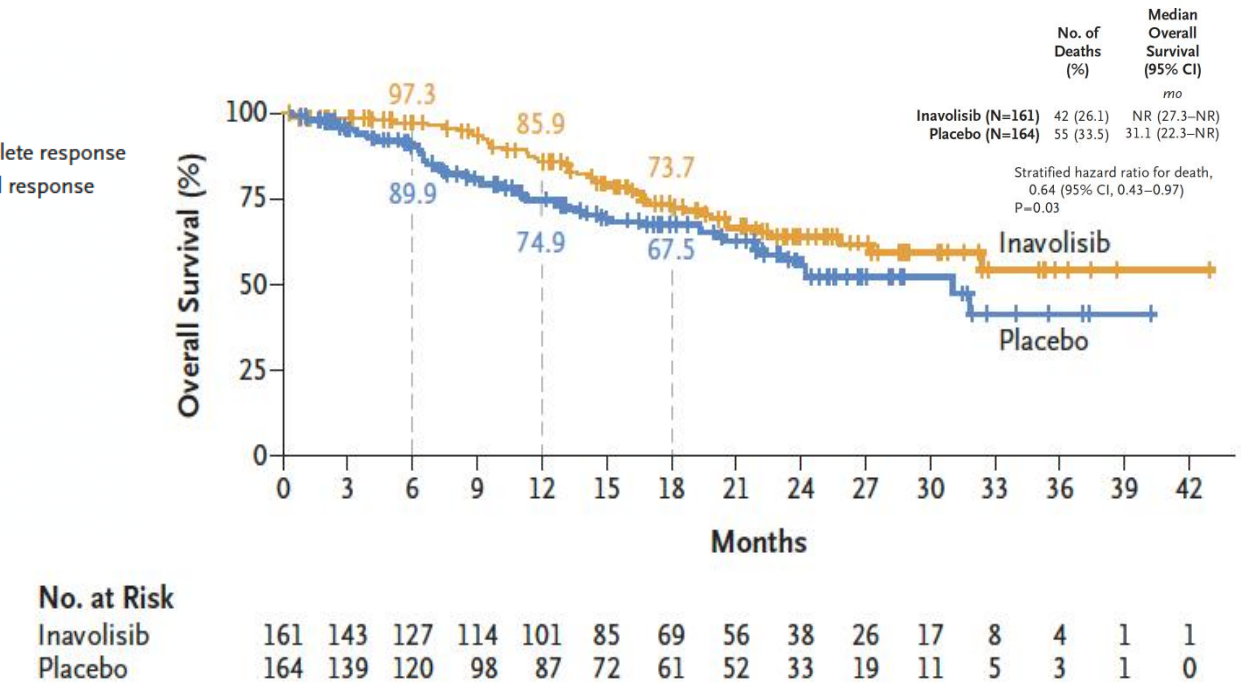
Turner NC et al. N Eng J Med 2024

Inavolisib also improves tumor responses and overall survival

Objective responses



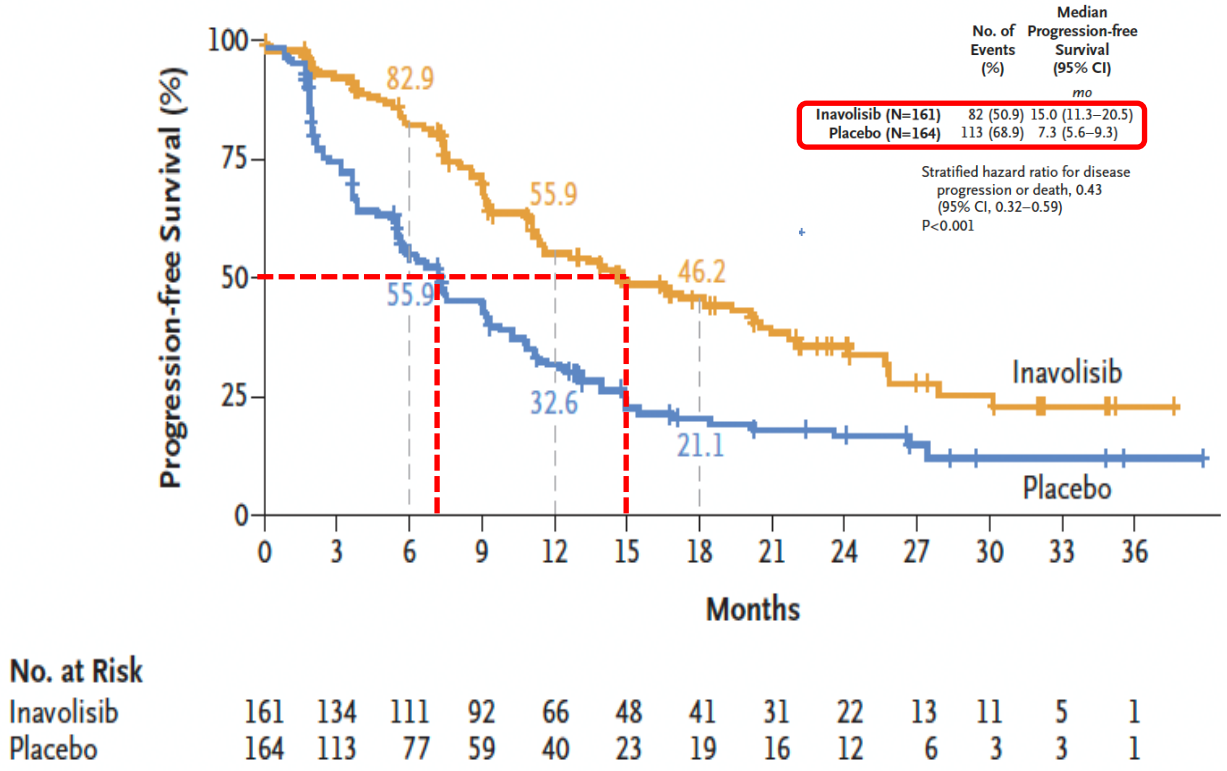
Overall survival



Turner NC et al. N Eng J Med 2024

PFS comparison of fulvestrant+abemaciclib vs. fulvestrant+ palbociclib+inavolisib in *PIK3CA*-mutated HR+/HER2- aBC patients

INAVO 120 trial



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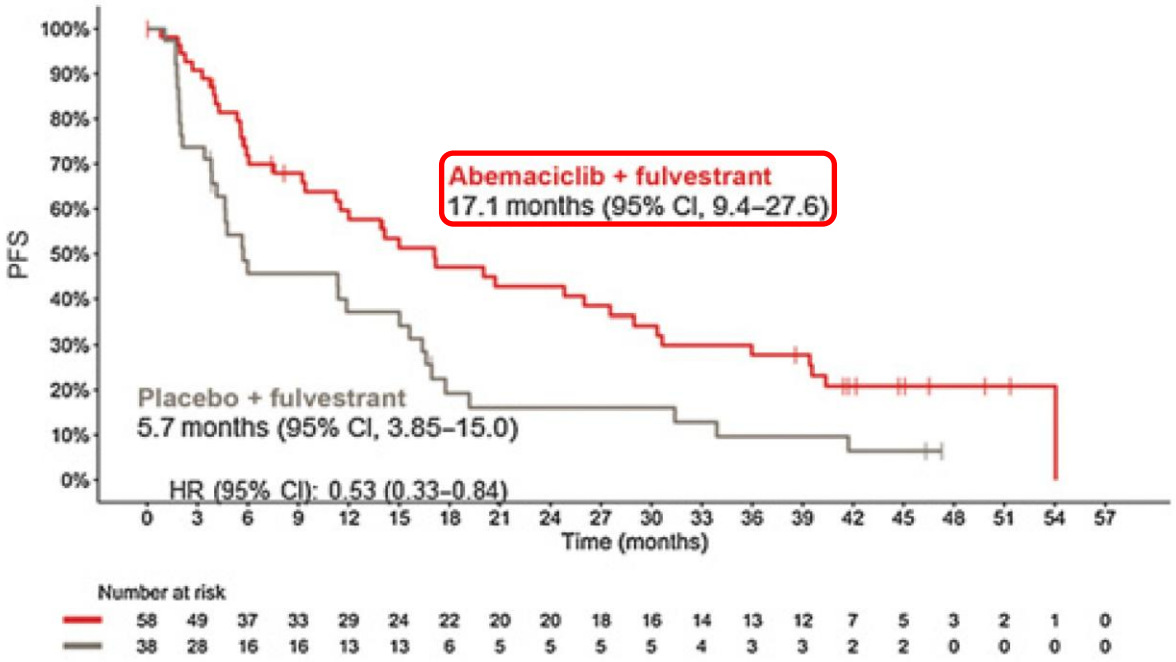
Turner NC et al. N Eng J Med 2024

MONARCH 2 trial *(PIK3CA-mut)*



Tolaney S.M. et al. Clin Cancer Res 2022

Some comments…

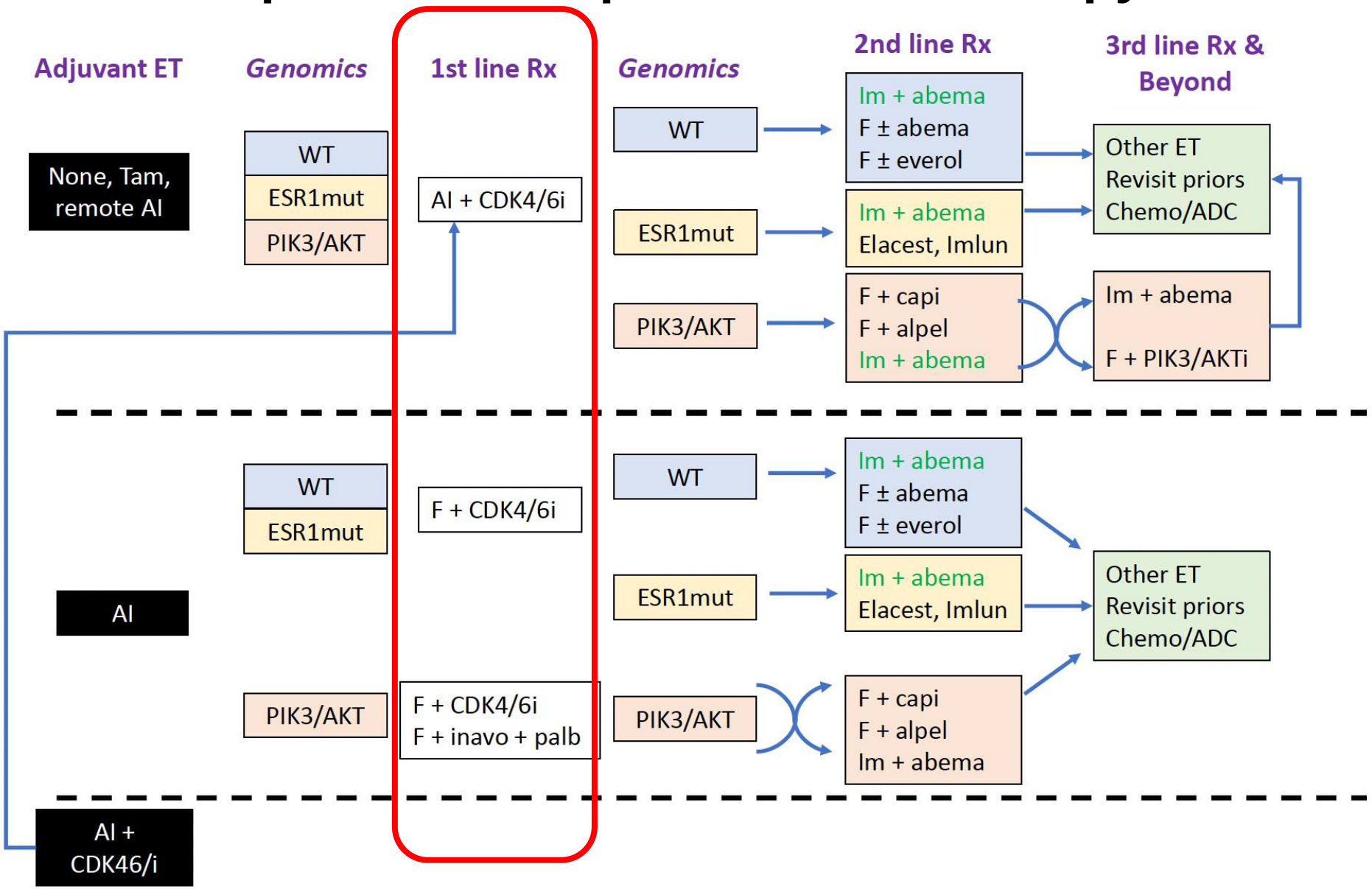
- Palbociclib is the the least effective CDK4/6i in patients with endocrine-resistant disease

- This limitation will become more and more important as the use of more potent CDK4/6i, namely ribociclib and abemaciclib, will increase in the adjuvant setting in the next years (based on the results o NATALEE and monarchE trials)

- We do not know whether a sequence of ET+CDK4/6i followed by ET+PI3K/AKT inhibitors (e.g., capivasertib; alpelisib) is more effective than a triplet treatment with ET+CDK4/6i+PI3K/AKTi

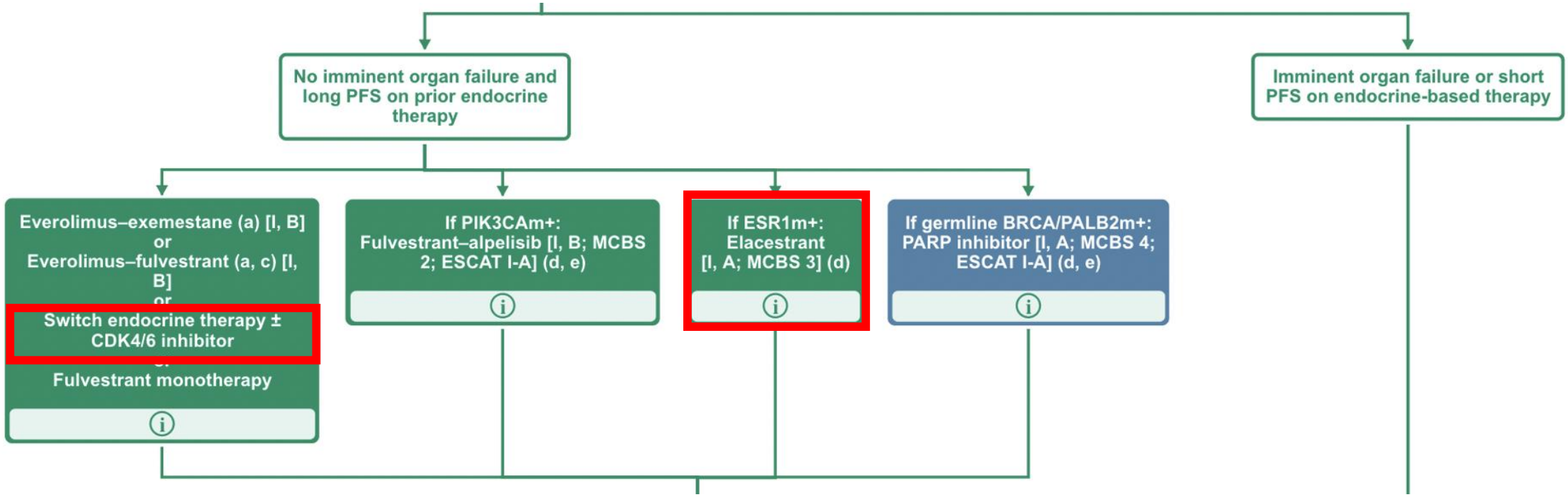
- The EMBER-3 trial provides the opportunity of using a second and more effective CDK4/6i, such as abemaciclib in combination with imlunestrant, as a second-line treatments in patients progressing on palbociclib-inavolisib-based therapy

Median PFS in recent RCTs of endocrine therapy: sub-analysis in patients with prior CDK4/6i therapy



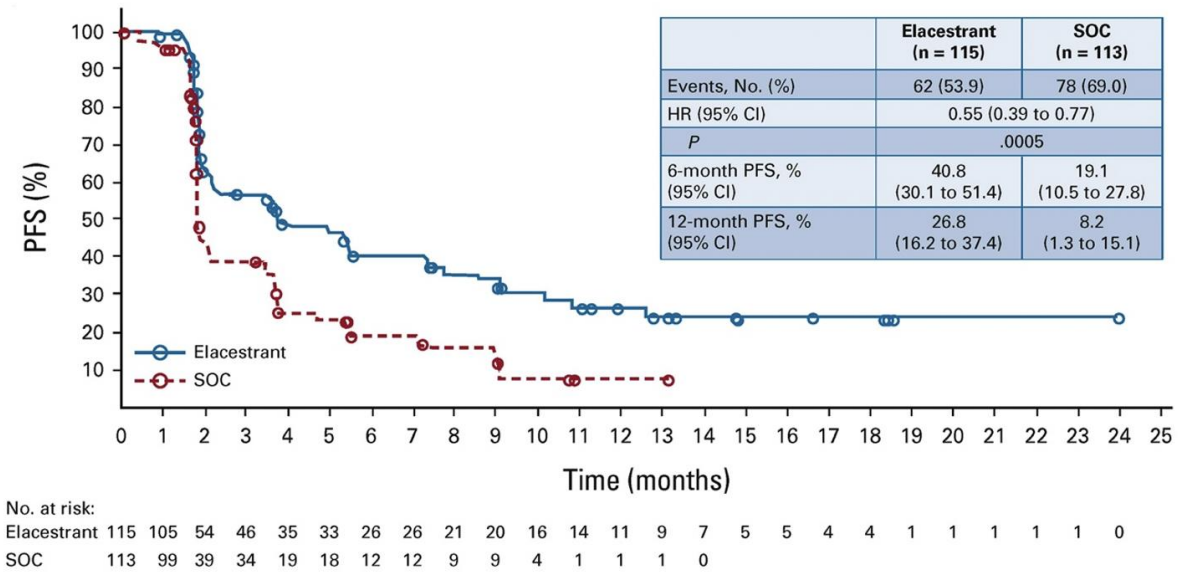
Adapted from Burstein HJ et a. SABCS 2024

Second-line treatment: *ESR1*-mutated tumors and CDK4/6i switch



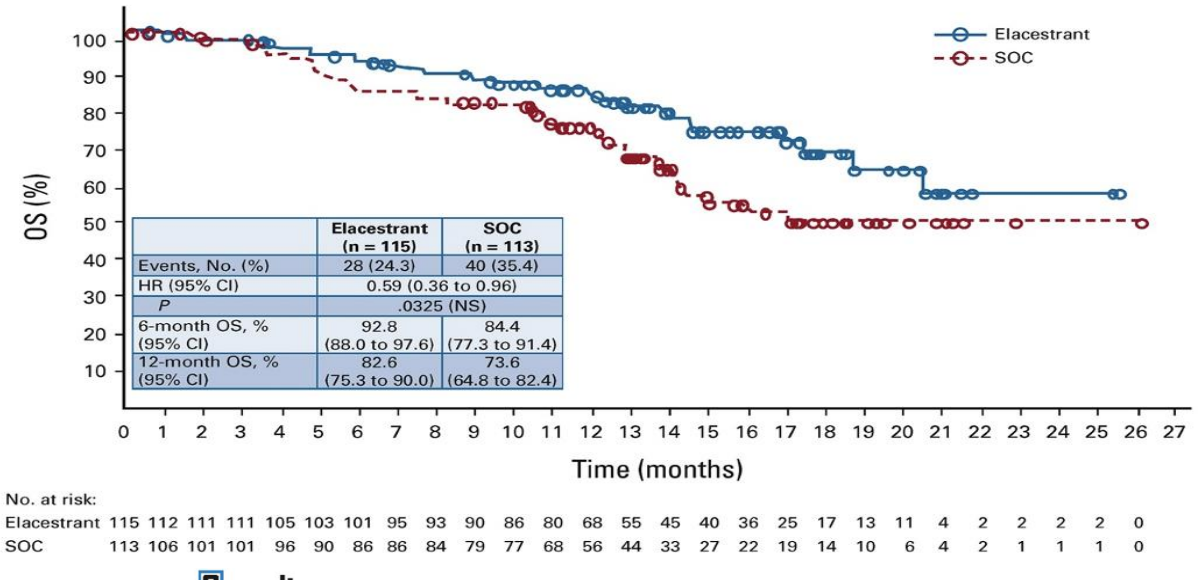
Elacestrant improved PFS and OS in HR+/HER2- aBC patient with *ESR1* mutations

PFS: *ESR1*-mutated cohort



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

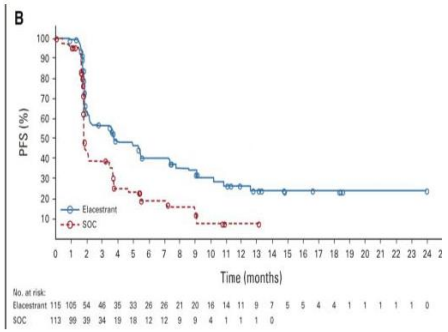
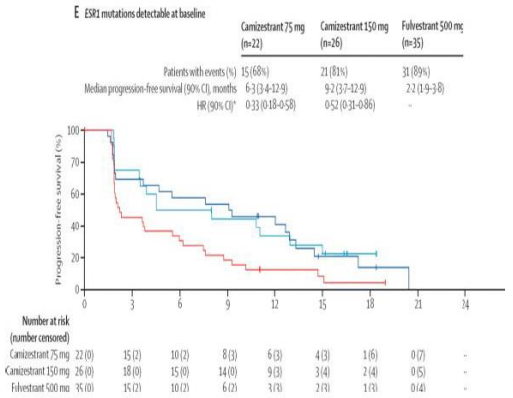
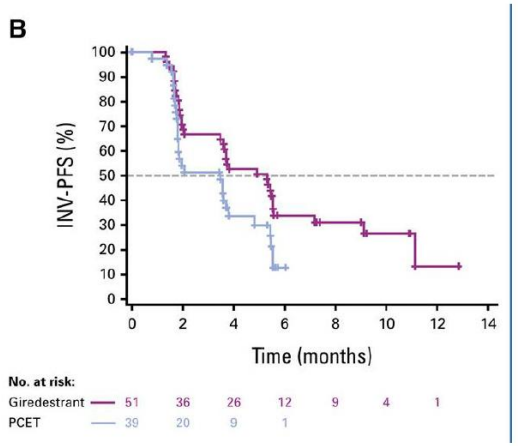
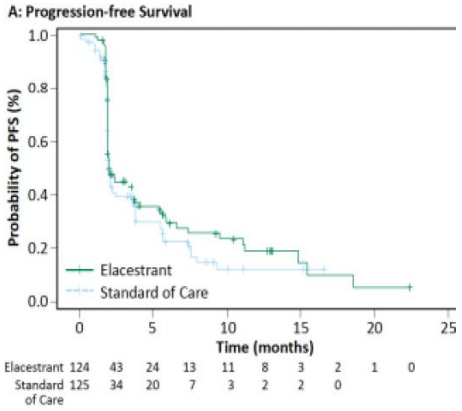
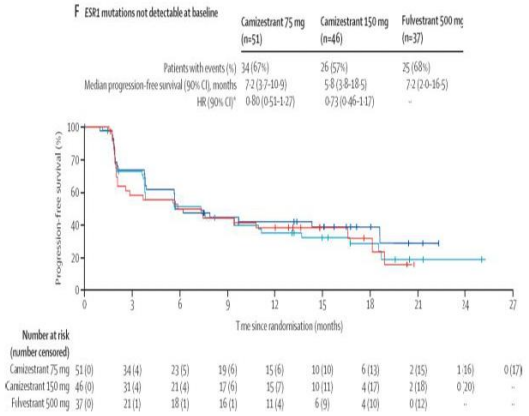
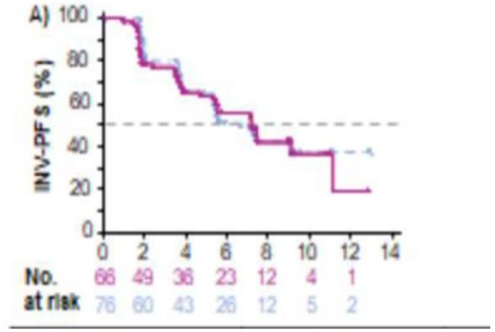
OS: *ESR1*-mutated cohort



	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	28 (24.3)	40 (35.4)
HR (95% CI)	0.59 (0.36 to 0.96)	
P	.0325 (NS)	
6-month OS, % (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS, % (95% CI)	82.6 (75.3 to 90.0)	73.6 (64.8 to 82.4)

Bidard FC et al. J Clin Oncol 2022

Benefit of oral SERDs vs. standard ET in *ESR1*-mutated and *ESR1*-wt tumors

	EMERALD SOC vs Elacestrant	SERENA-2 Fulv vs Camizestrant	acelERA PCET vs Giredestrant
***ESR1* mut**			
***ESR1* wt**			
	Bidard, FC et al. J Clin Oncol 2022;40:3246	Oliveira M, et al. Lancet Oncol 2024;25:1424	Martin M, et al. J Clin Oncol 2024;42:2149

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Imlunestrant, an Oral Selective Estrogen Receptor Degrader (SERD), as Monotherapy and Combined with Abemaciclib, for Patients with ER+, HER2- Advanced Breast Cancer (ABC), Pretreated with Endocrine Therapy (ET): Results of the Phase 3 EMBER-3 trial

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[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [2]University Hospitals Leuven, Leuven, Belgium; [3]Hospital María Curie, Buenos Aires, Argentina; [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [6]Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Brussels, Belgium; [7]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [8]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [9]Breast Center, Department of Obstetrics and Gynecology and CCC Munich, LMU University Hospital, Munich, Germany; [10]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [11]University of Milano, Milan, Italy and European Institute of Oncology, IRCCS, Milano, Italy; [12]Hospital Arnau de Vilanova, Valencia, Spain; [13]Garvan Institute of Medical Research and University of New South Wales, Darlinghurst, Sydney, New South Wales, Australia; [14]Hospital de Oncología, Centro Médico Nacional Siglo XXI, Ciudad de México, México; [15]Yonsei University College of Medicine, Seoul, Republic of Korea; [16]Mastology Department, Women's Health Hospital, São Paulo, Brazil; [17]Harbin Medical University Cancer Hospital, Harbin, China; [18]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [19]Division of Breast Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan; [20] Filios Alta Medicina SA de CV, Monterrey, Nuevo León, México; [21]Medical Oncology Department, Hospital Universitario Virgen del Rocío, Seville, Spain; [22] Department of Breast Surgery, Chiba Cancer Center Hospital, Chiba, Japan; [23]Eli Lilly and Company, Indianapolis, IN, USA; [24]Institut Curie and UVSQ/Paris-Saclay University, Paris and Saint-Cloud, France

24010150

EMBER-3 Study Design

ER+, HER2- ABC

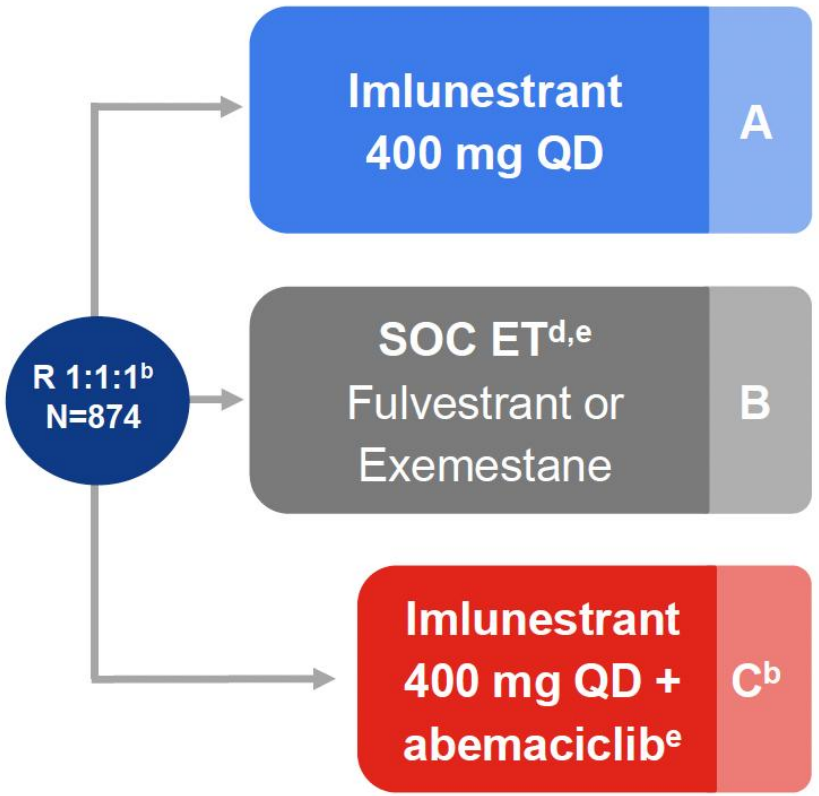
Men and Pre-[a]/Post-menopausal women

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.

Jhaveri KL et al. SABCS 2024
Jhaveri KL et al. N Engl J Med 2024

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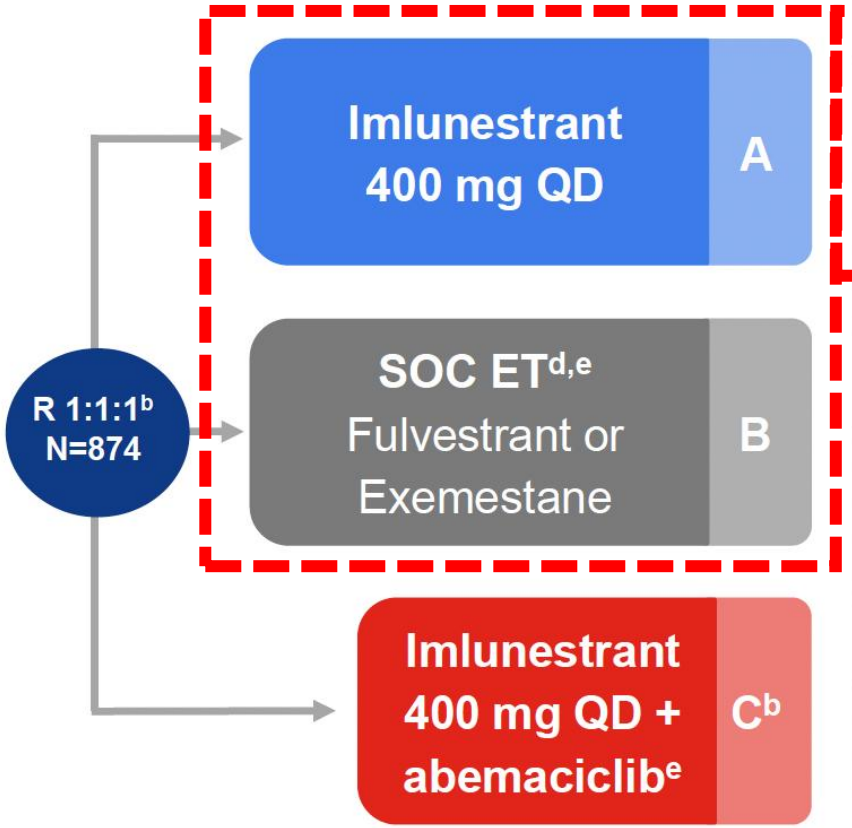
- Visceral metastases (Y/N)
- Region[c]



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.

Jhaveri KL et al. SABCS 2024
Jhaveri KL et al. N Engl J Med 2024

Patient characteristics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

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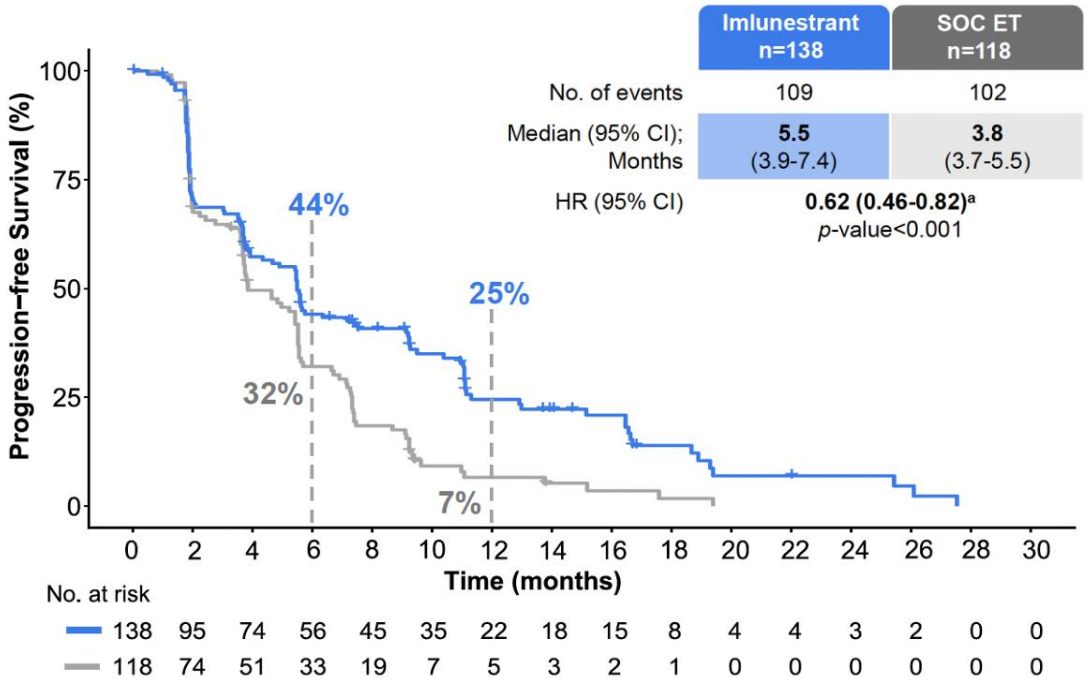
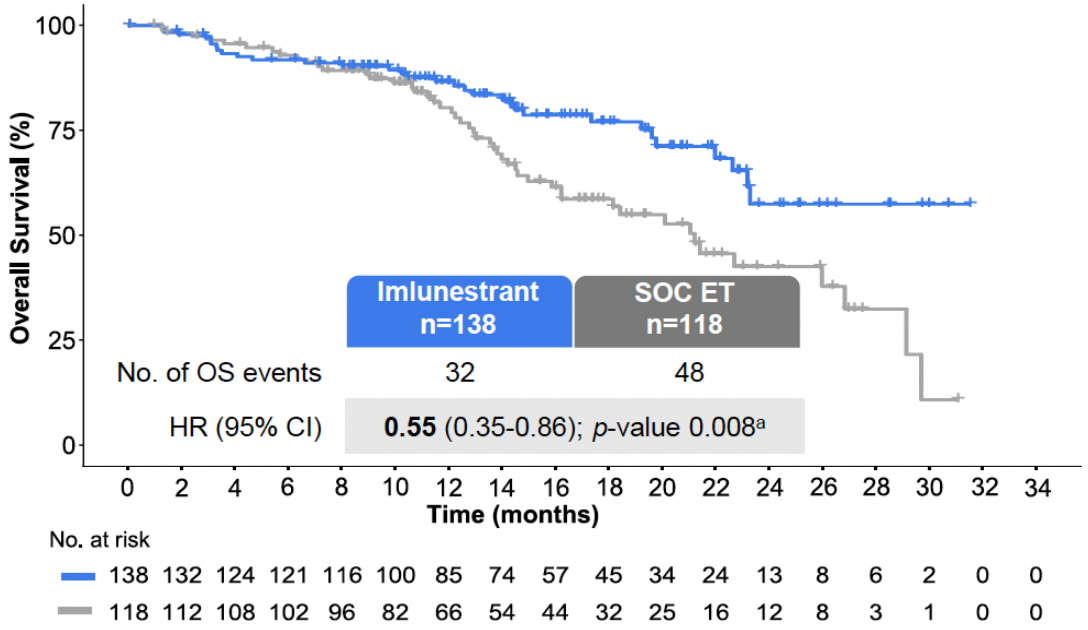
Imnulestrant improves PFS (primary endpoint) in patient with *ESR1*-mutated HR+/HER2- aBC

PFS: *ESR1*-mutated cohort



OS: *ESR1*-mutated cohort

(31% maturity)



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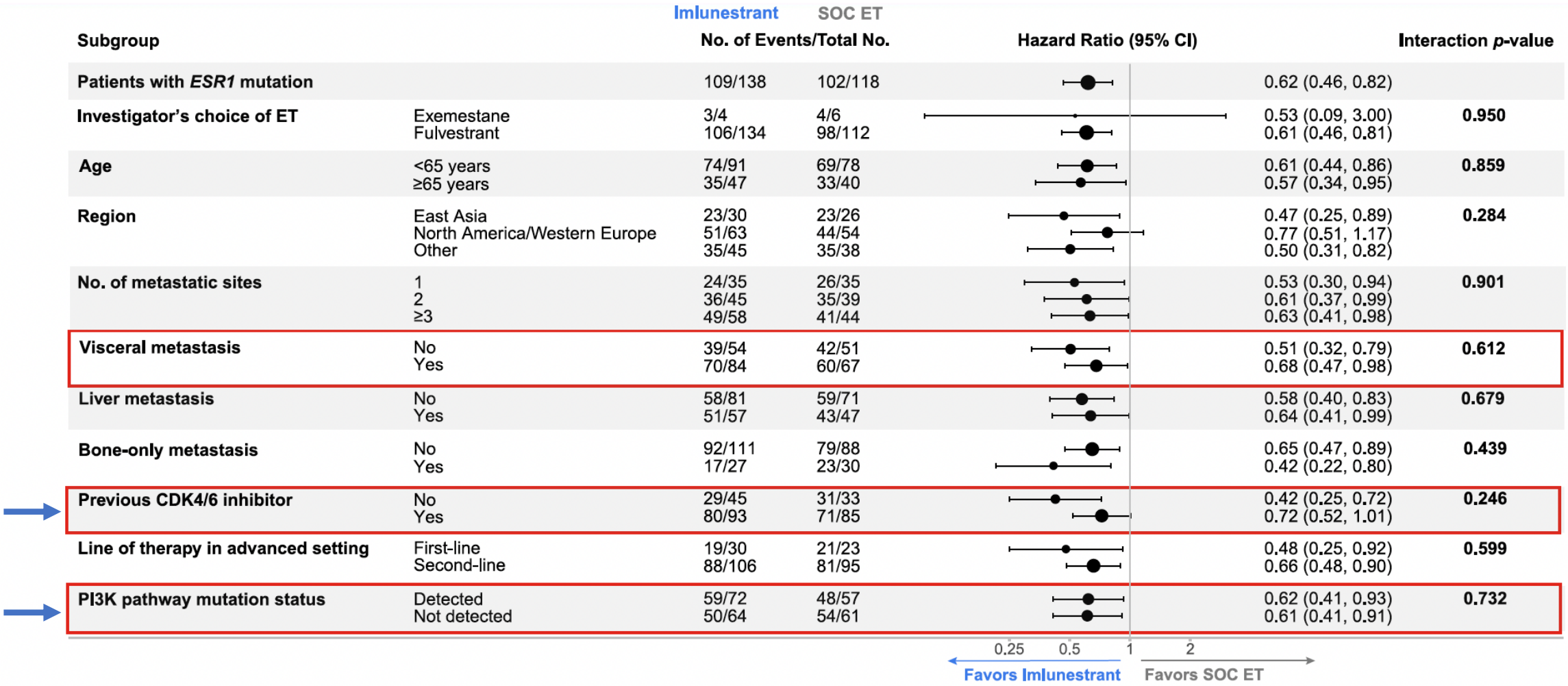
Imlunestrant improves PFS regardless of visceral metastases, previous CDK4/6i and PI3K pathway alterations



ET, endocrine therapy; SOC ET, standard of care endocrine therapy. First-line: most recent ET = adjuvant; Second-line: most recent ET = ABC. The total number of patients may not add up due to missing data in certain subgroups.

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Jhaveri KL et al. N Engl J Med 2024

Limitations of EMBER3 vs. EMERALD

- Only ~50% of patients received CDK4/6i for advanced disease
- Most patients treated with CDK4/6i received palbociclib (the least effective CDK4/6i)
- Subgroup PFS analysis in patients with *ESR1*-mutated tumors previously treated with CDK4/6i did not reach (yet?) statistical significance in favor of imlunestrant
- Lack of OS advantage in patients with *ESR1*-mutated tumors

EMBER-3 Study Design

ER+, HER2- ABC

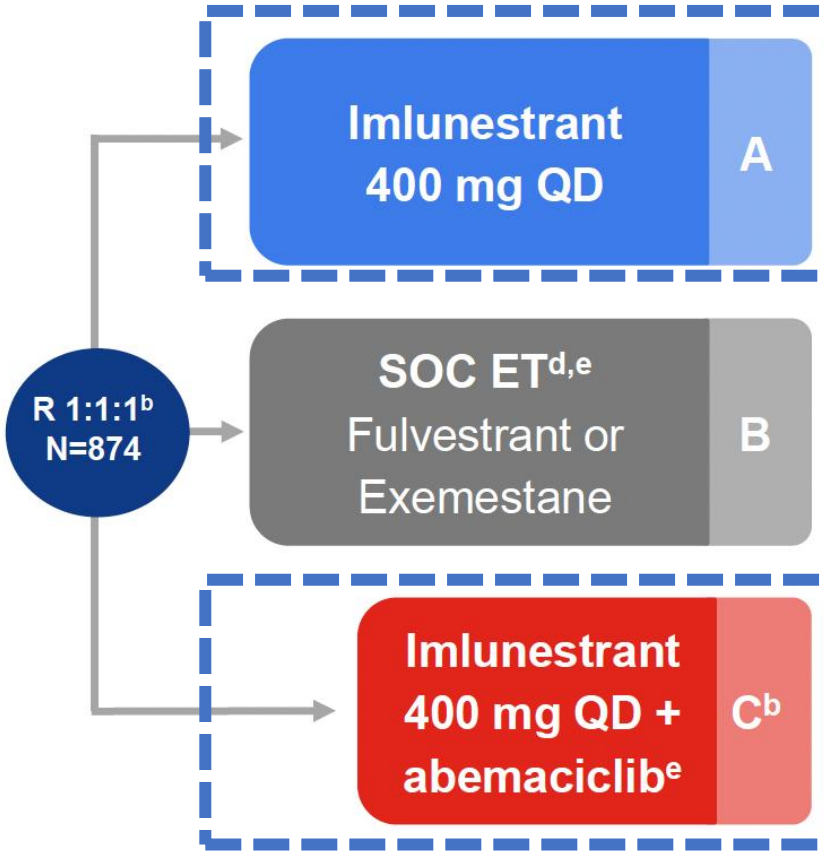
Men and Pre-[a]/Post-menopausal women

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]



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Jhaveri KL et al. SABCS 2024
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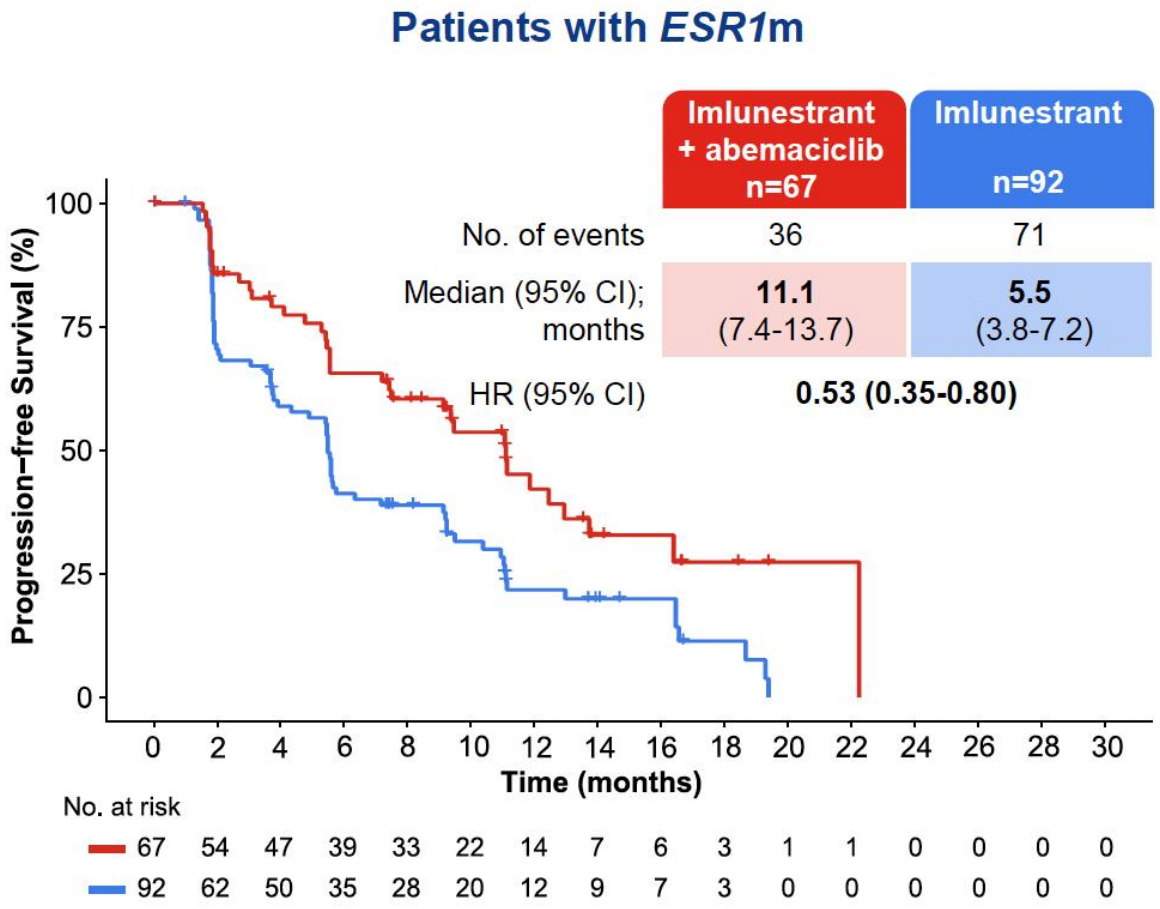
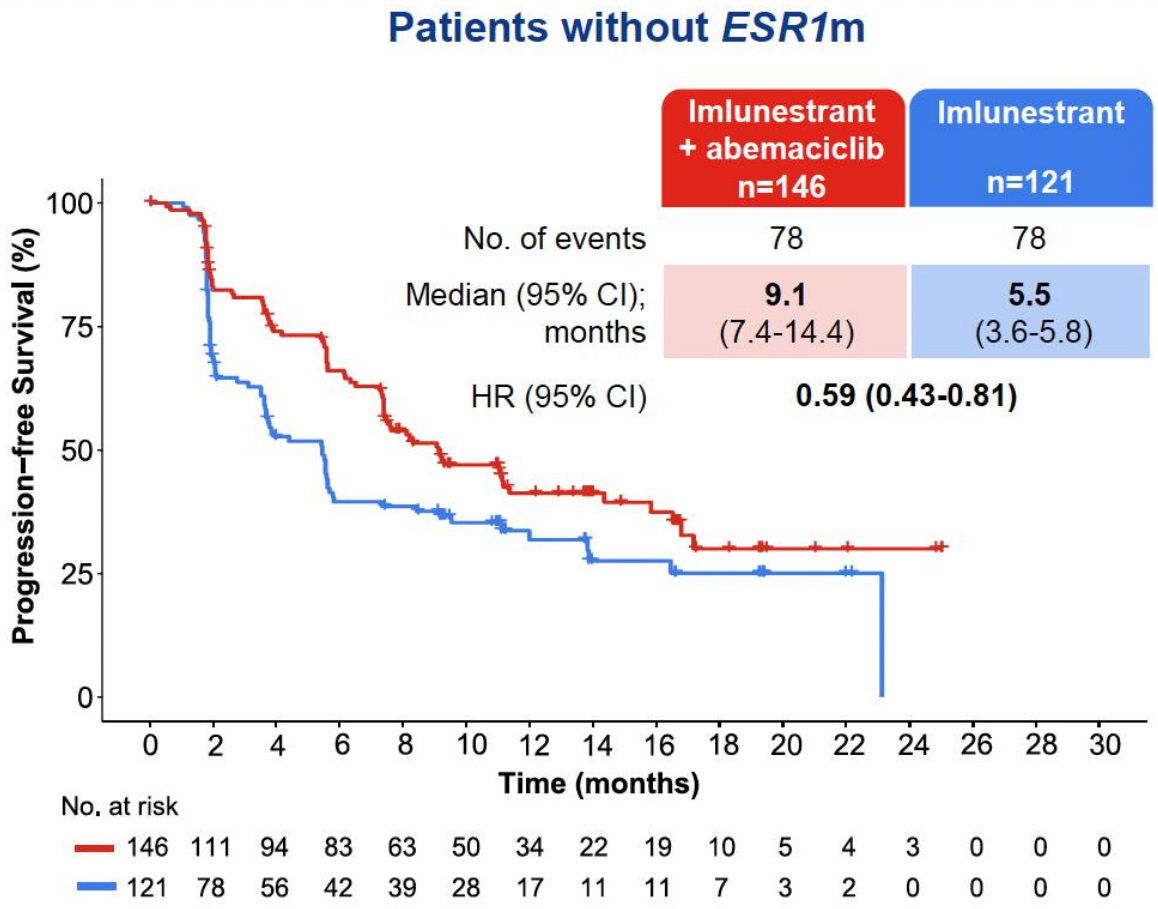
Imlunestrant plus abemaciclib is more effective than imlunestrant regardless of *ESR1* mutations





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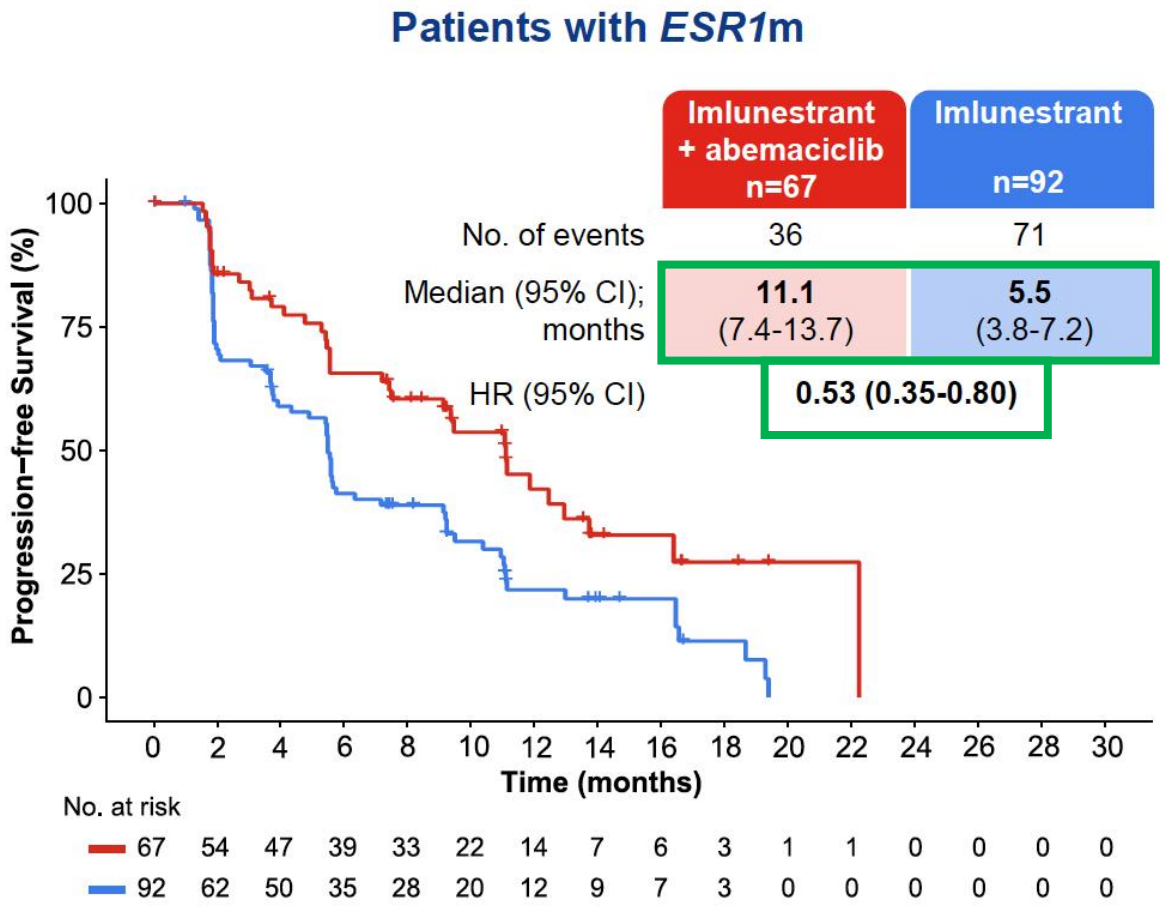
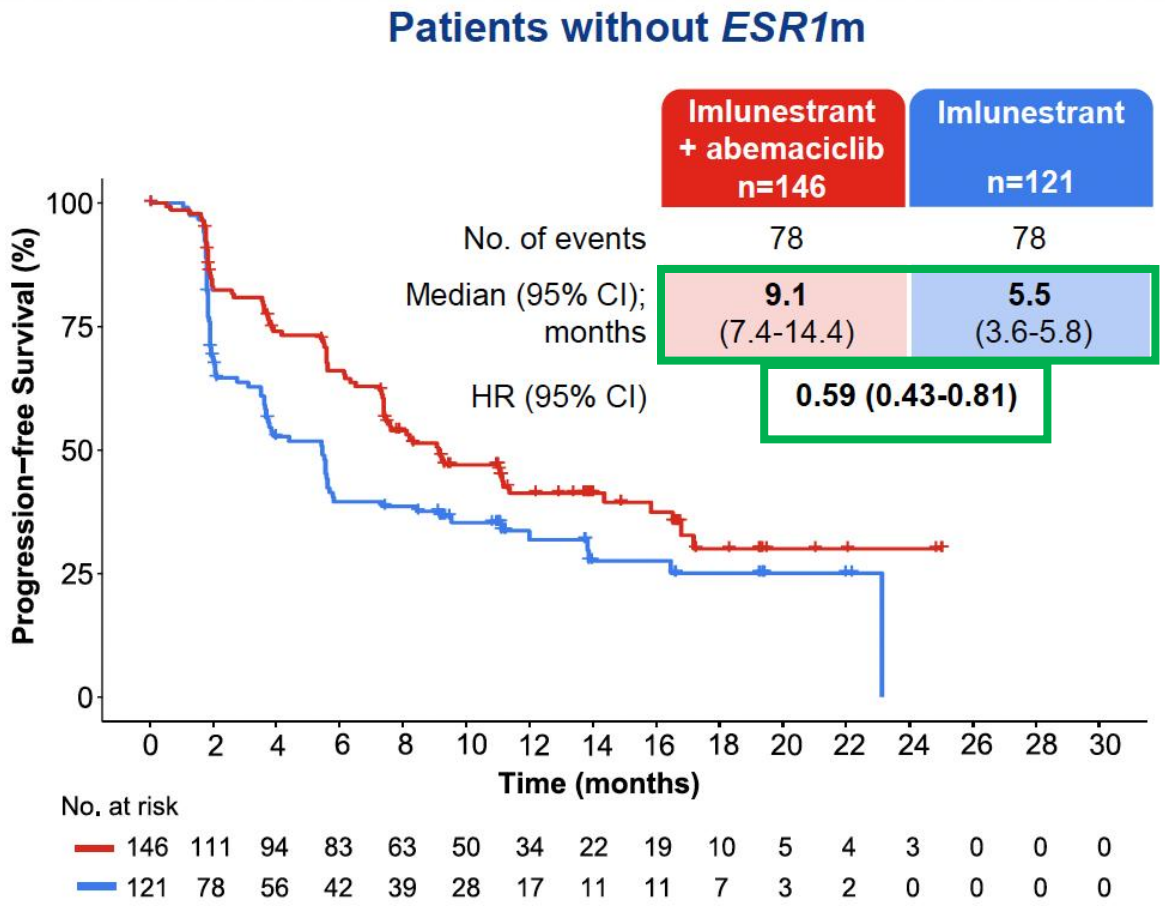
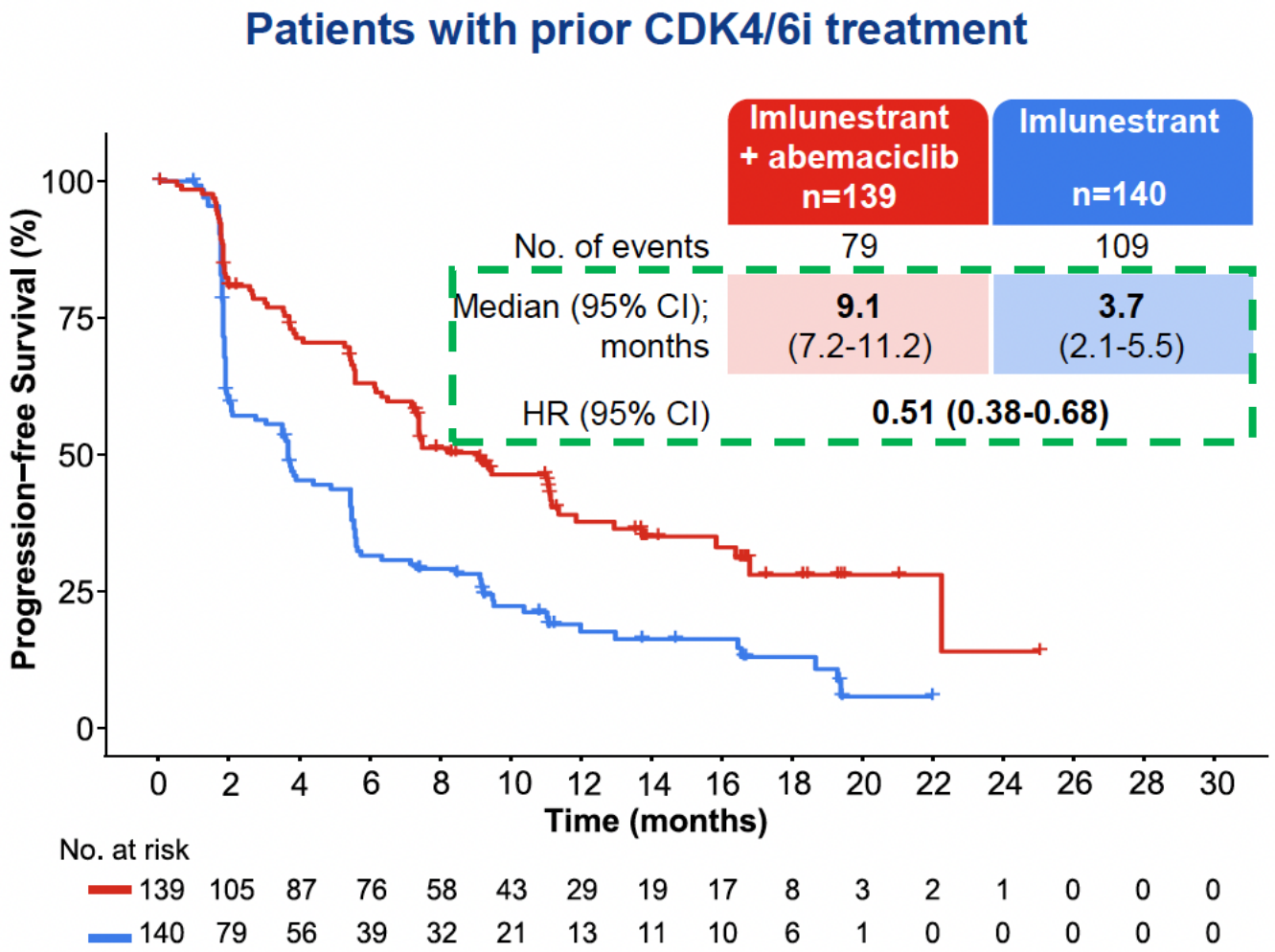




Jhaveri KL et al. SABCS 2024
Jhaveri KL et al. N Engl J Med 2024

Imlunestrant plus abemaciclib is associated with excellent clinical outcomes in patients previously treated with ET+CDK4/6i



Jhaveri KL et al. SABCS 2024
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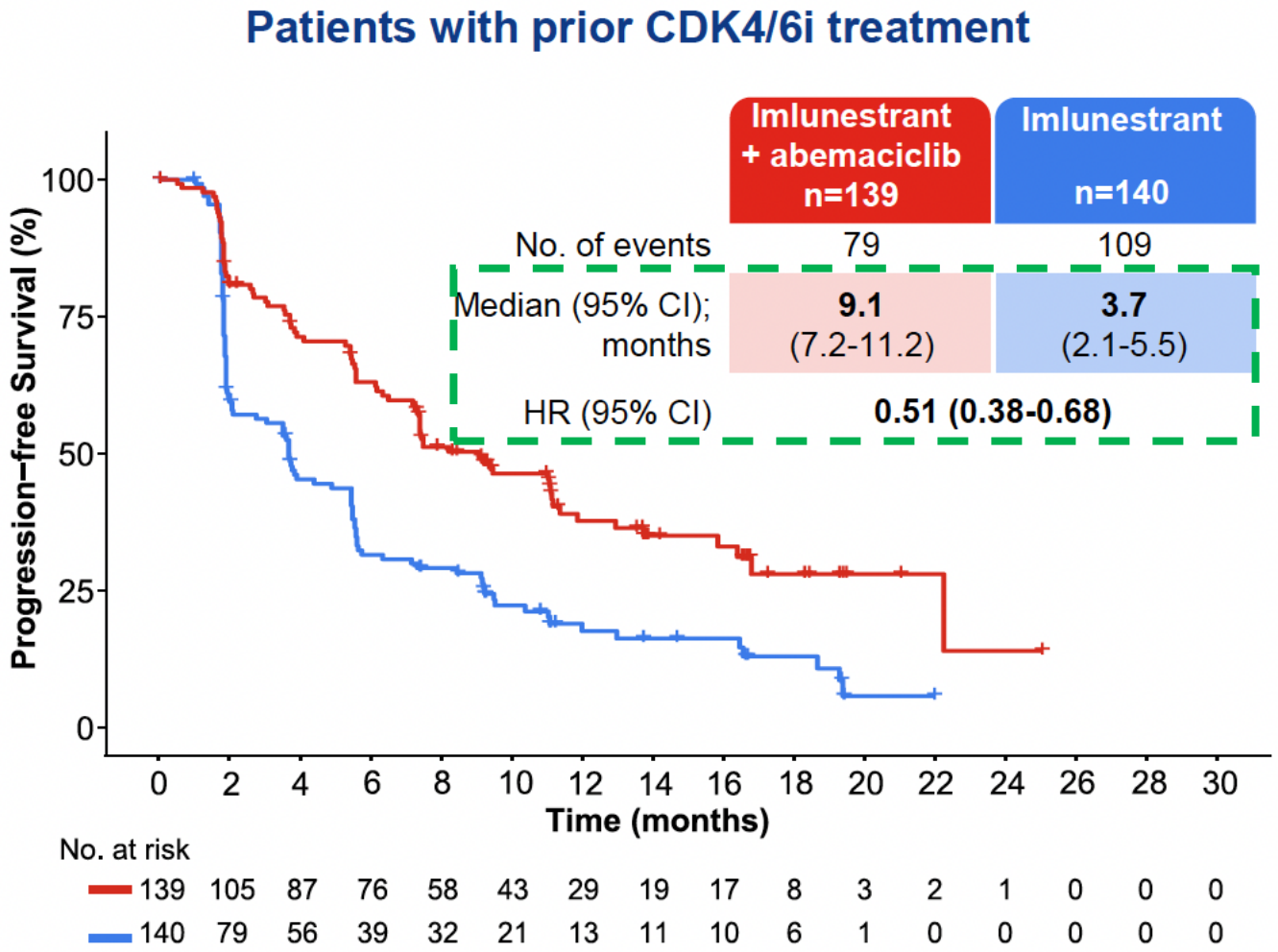
Clinically relevant PFS difference



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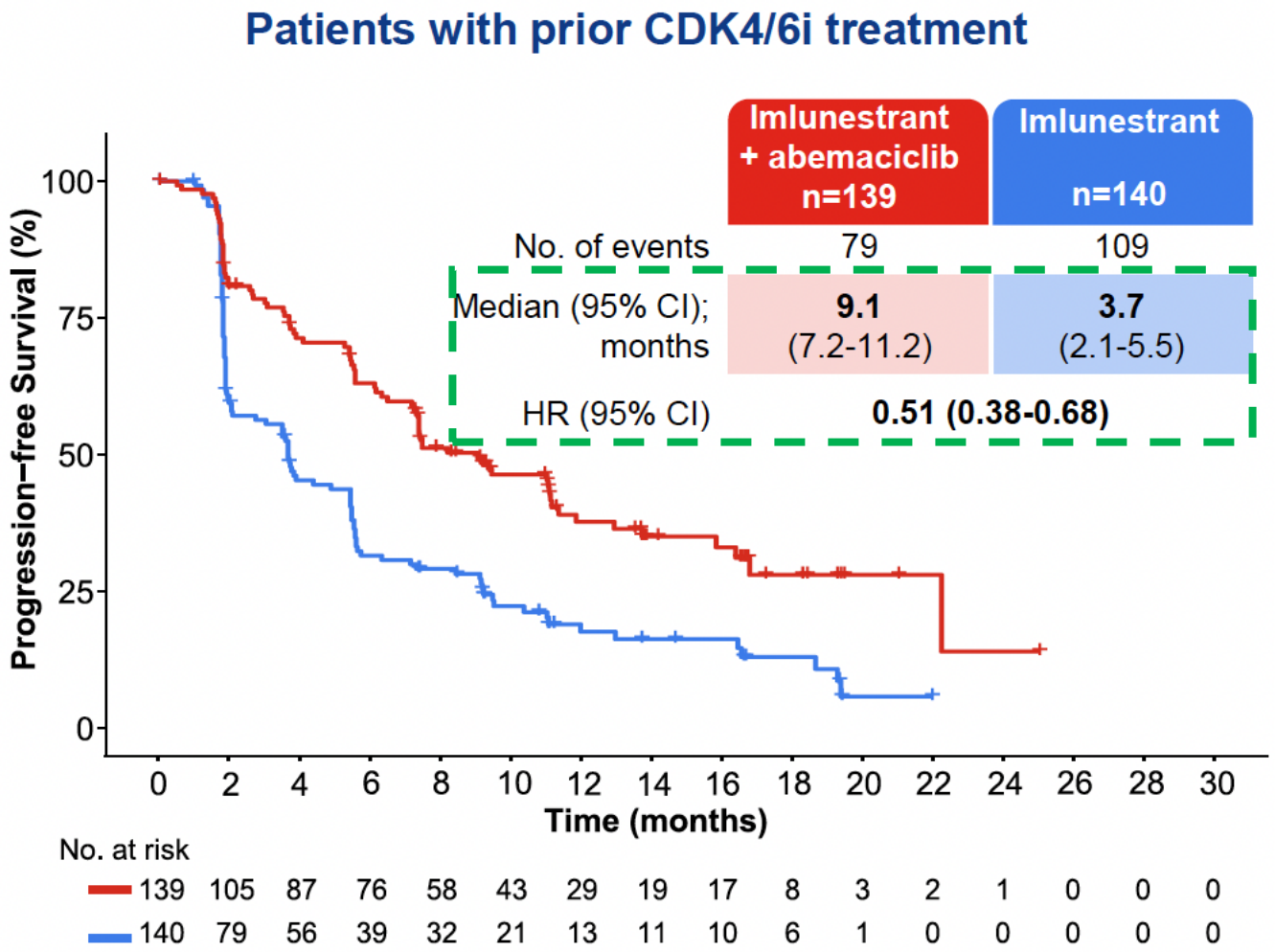

→ Clinically relevant PFS difference

→ Unknown impact of the type of prior CDK4/6i on imlunestrant+abemaciclib efficacy

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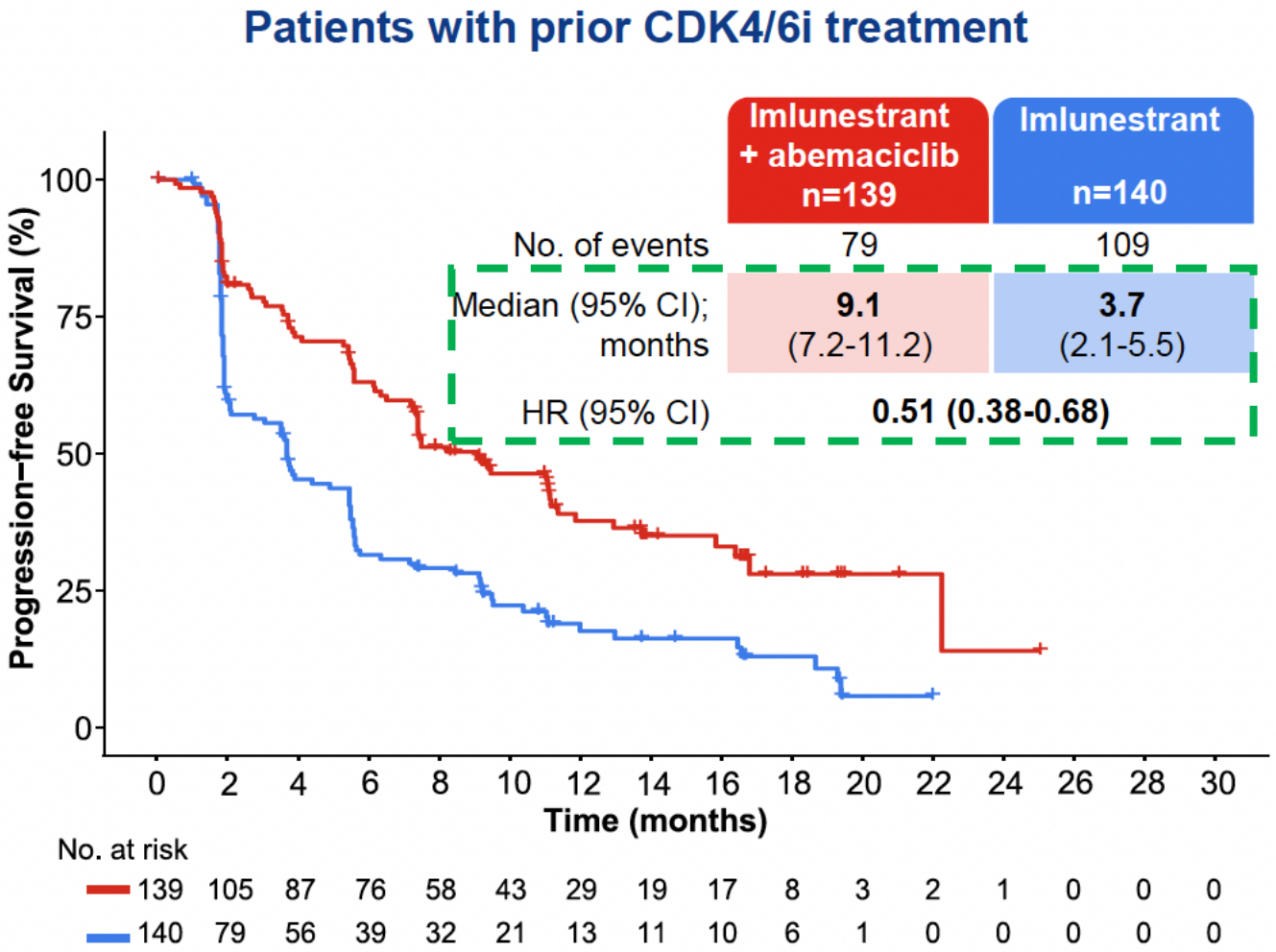

→ Clinically relevant PFS difference

→ Unknown impact of the type of prior CDK4/6i on imlunestrant+abemaciclib efficacy

→ Unknown predictive impact of *ESR1* status in CDK4/6i-pretreated patients

Jhaveri KL et al. SABCS 2024
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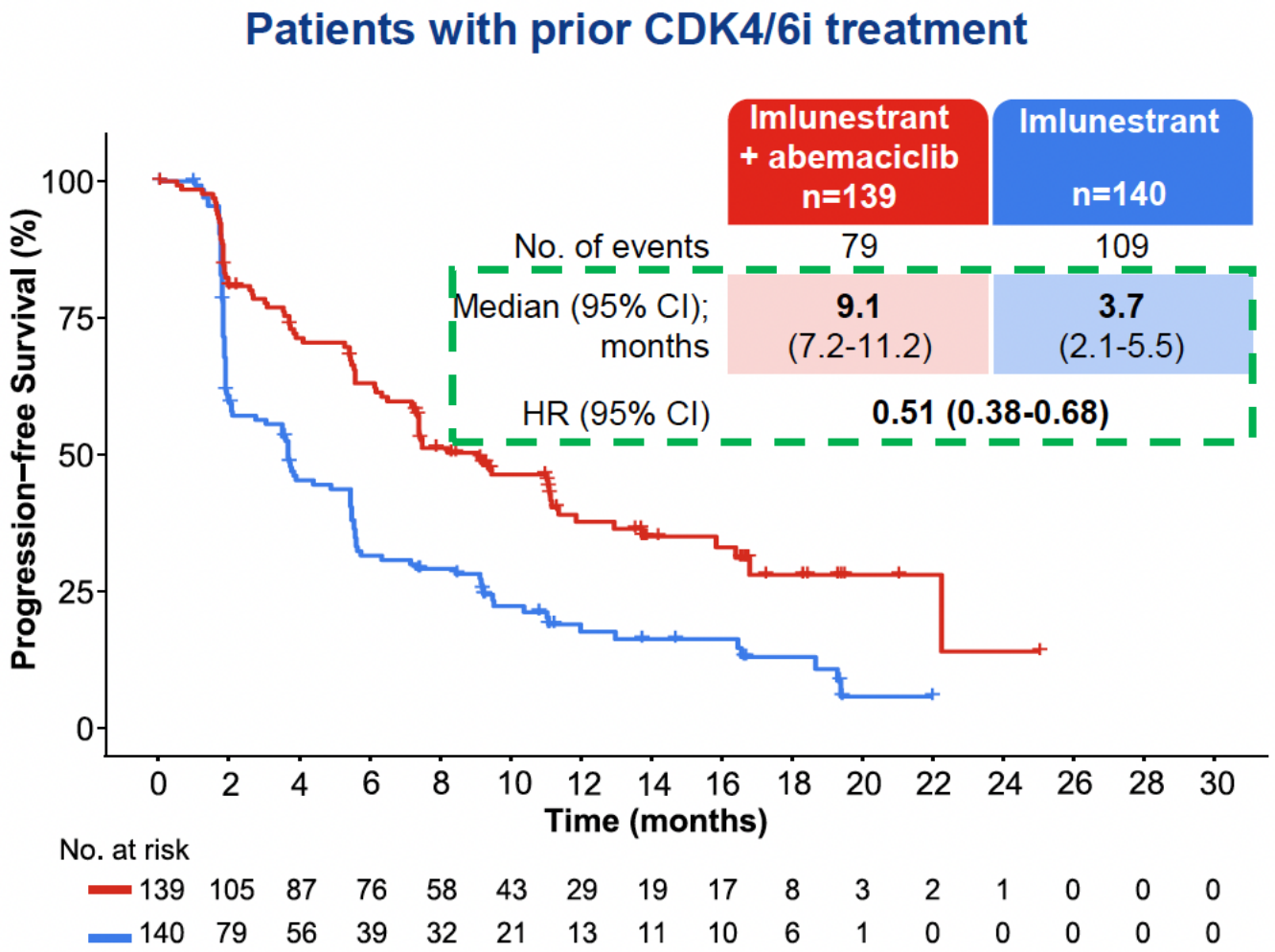


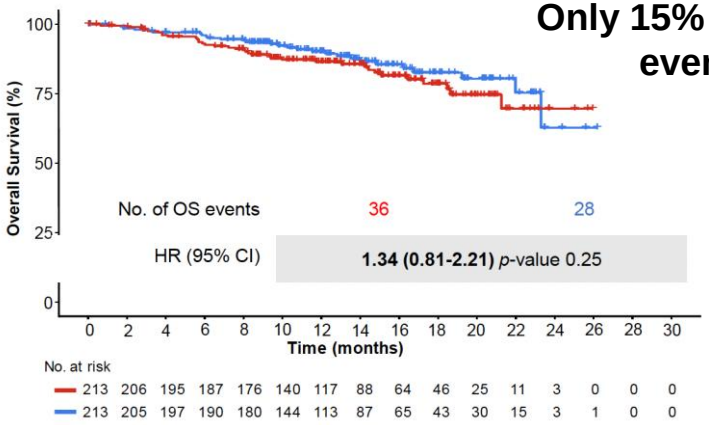
→ Clinically relevant PFS difference

→ Unknown impact of the type of prior CDK4/6i on imlunestrant+abemaciclib efficacy

→ Unknown predictive impact of *ESR1* status in CDK4/6i-pretreated patients

→ Unknown impact of imlunestrant + abemaciclib on OS

Only 15% of death events



2024 ASCO ANNUAL MEETING

Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the Phase 3 postMONARCH trial

Kevin Kalinsky[1], Giampaolo Bianchini[2], Erika P. Hamilton[3], Stephanie L. Graff[4], Kyong Hwa Park[5], Rinath Jeselsohn[6], Umut Demirci[7], Miguel Martin[8], Rachel M. Layman[9], Sara Hurvitz[10], Sarah Sammons[11], Peter A. Kaufman[12], Montserrat Munoz[13], Ling-Ming Tseng[14], Holly Knoderer[15], Bastien Nguyen[15], Yanhong Zhou[15], Elizabeth Ravenberg[15], Lacey M. Litchfield[15], Seth A. Wander[16]

[1]Winship Cancer Institute at Emory University, Atlanta, GA, USA, [2]IRCCS Ospedale, San Raffaele, Milan, Italy, [3]Sarah Cannon Research Institute, Nashville, TN, USA, [4]Lifespan Cancer Institute, Warren Albert School of Medicine, Brown University, Providence, RI, USA , [5]Korea University Anam Hospital, Korea University, Seoul, South Korea, [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [7]Memorial Ankara Hospital, Ankara, Turkey, [8]Hospital General Universitario Gregorio Maranon, Universidad Complutense, Madrid, Spain, [9]MD Anderson Cancer Center, University of Texas, Houston, TX, USA, [10]Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA, [11]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [12]University of Vermont Medical Center, Burlington, VT, USA, [13]Hospital Clinic i Provincial, Barcelona, Spain,[14]Taipei Veterans General Hospital, Taipei, Taiwan,[15]Eli Lilly and Company, Indianapolis, IN, USA, [16]Massachusetts General Hospital, Harvard University, Boston, MA, USA

PRESENTED BY: Kevin Kalinsky, MD, MS

postMONARCH study design

Eligibility

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:
- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC

Randomization 1:1

N = 368

Abemaciclib + Fulvestrant

Placebo + Fulvestrant

Primary Endpoint:
Investigator-Assessed PFS

Secondary Endpoints:
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

Stratification Factors:
- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY assay

Kalinsky K et al. ASCO 2024

Patient characteristics

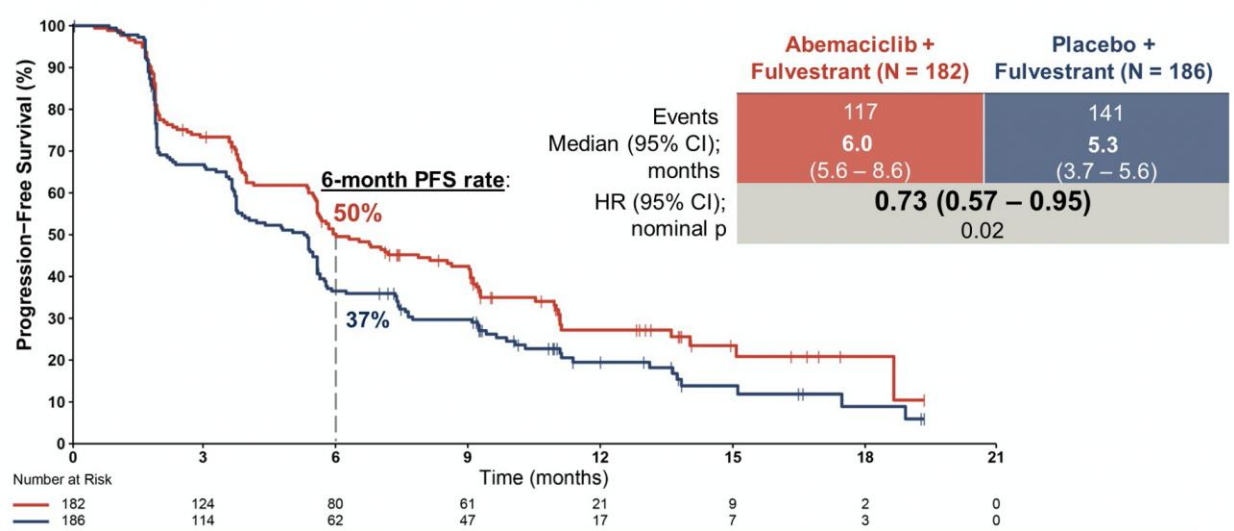
		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestrant N=186 (%)
Age	Median (range)	58 (27, 86)	61 (28, 85)
	< 65 years	69	63
	≥ 65 years	31	37
Gender	Female	99	100
ECOG	0	57	58
	1	43	43
Region	Other (includes EU)	73	72
	Asia	12	13
	USA	15	15
Race	White	82	82
	Asian	12	15
	Black/African American	4	2
Ethnicity	Not Hispanic/Latino	74	77
	Hispanic/Latino	15	15
HR Status	ER+	100	99
	PR+	70	81

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8
Prior CDK4/6i Duration	≥12 months*	71	77
	<12 months^	29	22
Median Prior CDK4/6i Duration (mo; range)#	All	19 (2, 110)	21 (3, 87)
	Palbociclib	19	23
	Ribociclib	15	18
	Abemaciclib	26	21

Adapted from Kalinsky K et al. ASCO 2024

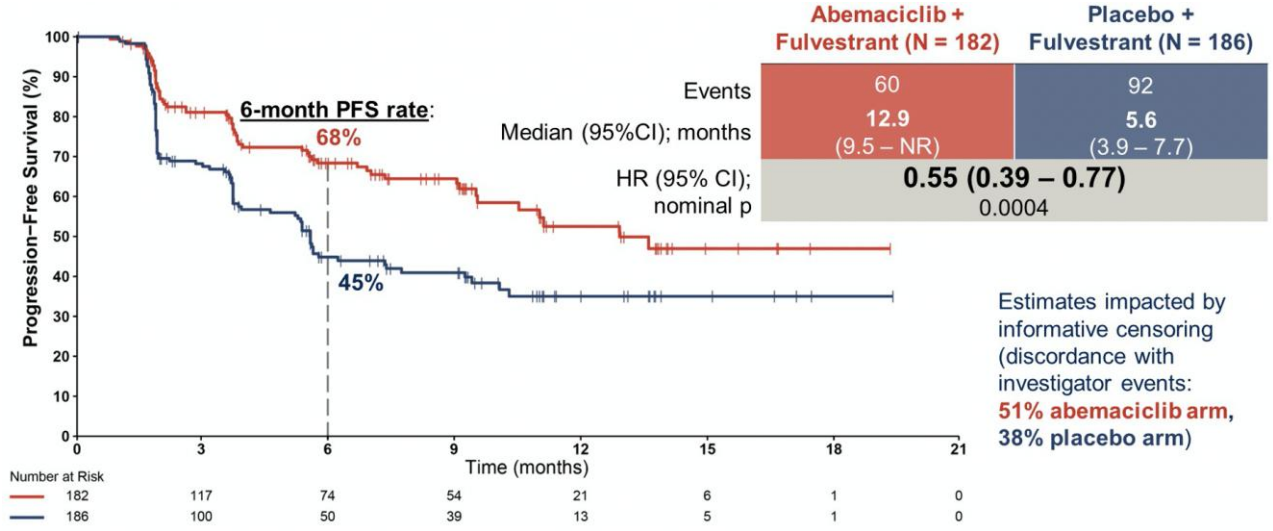
Fulvestrant plus abemaciclib improves PFS when compared to fulvestrant after prior CDK4/6i (mostrly palbociclib or ribociclib)

Investigator-assessed PFS



Abemaciclib: 27% reduction in PFS risk

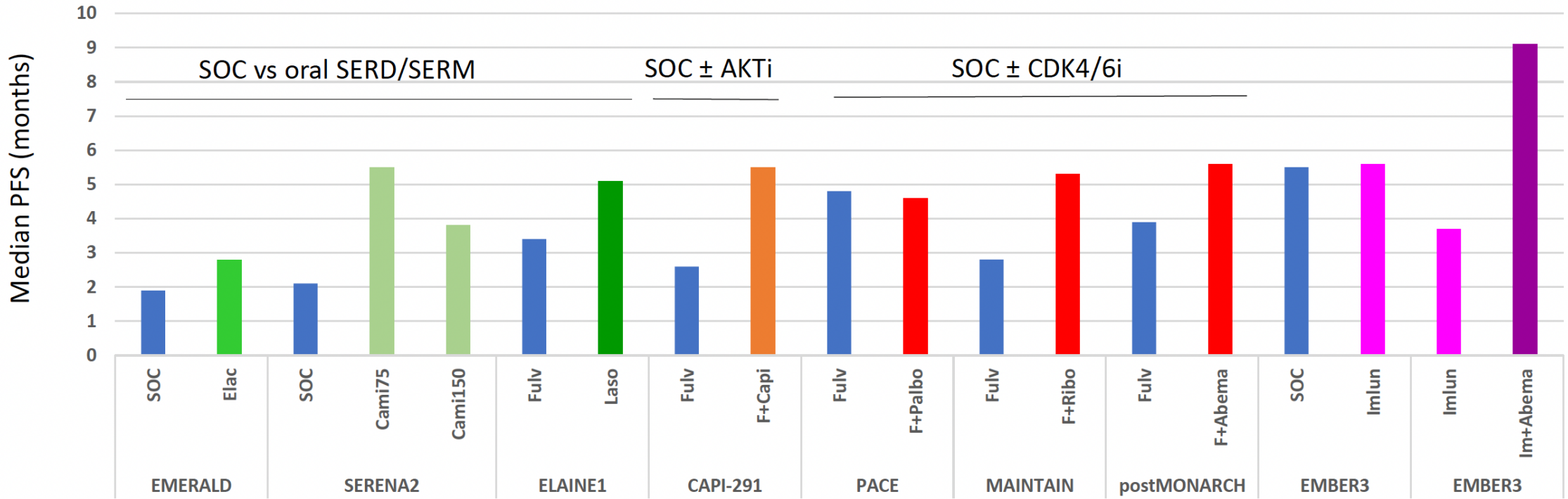
Blinded-independent central review (BICR)



Abemaciclib: 45% reduction of BICR PFS risk

Adapted from Kalinsky K et al. ASCO 2024

Median PFS in recent RCTs of endocrine therapy: sub-analysis in patients with prior CDK4/6i therapy



*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

Adapted from Burstein HJ et a. SABCS 2024

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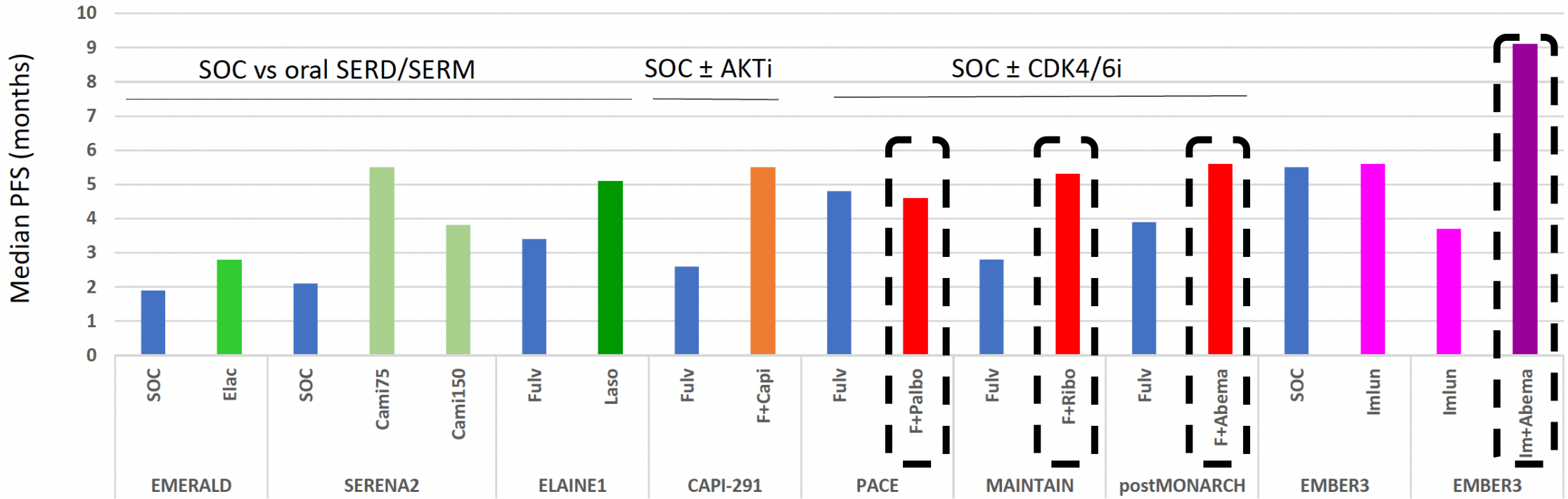

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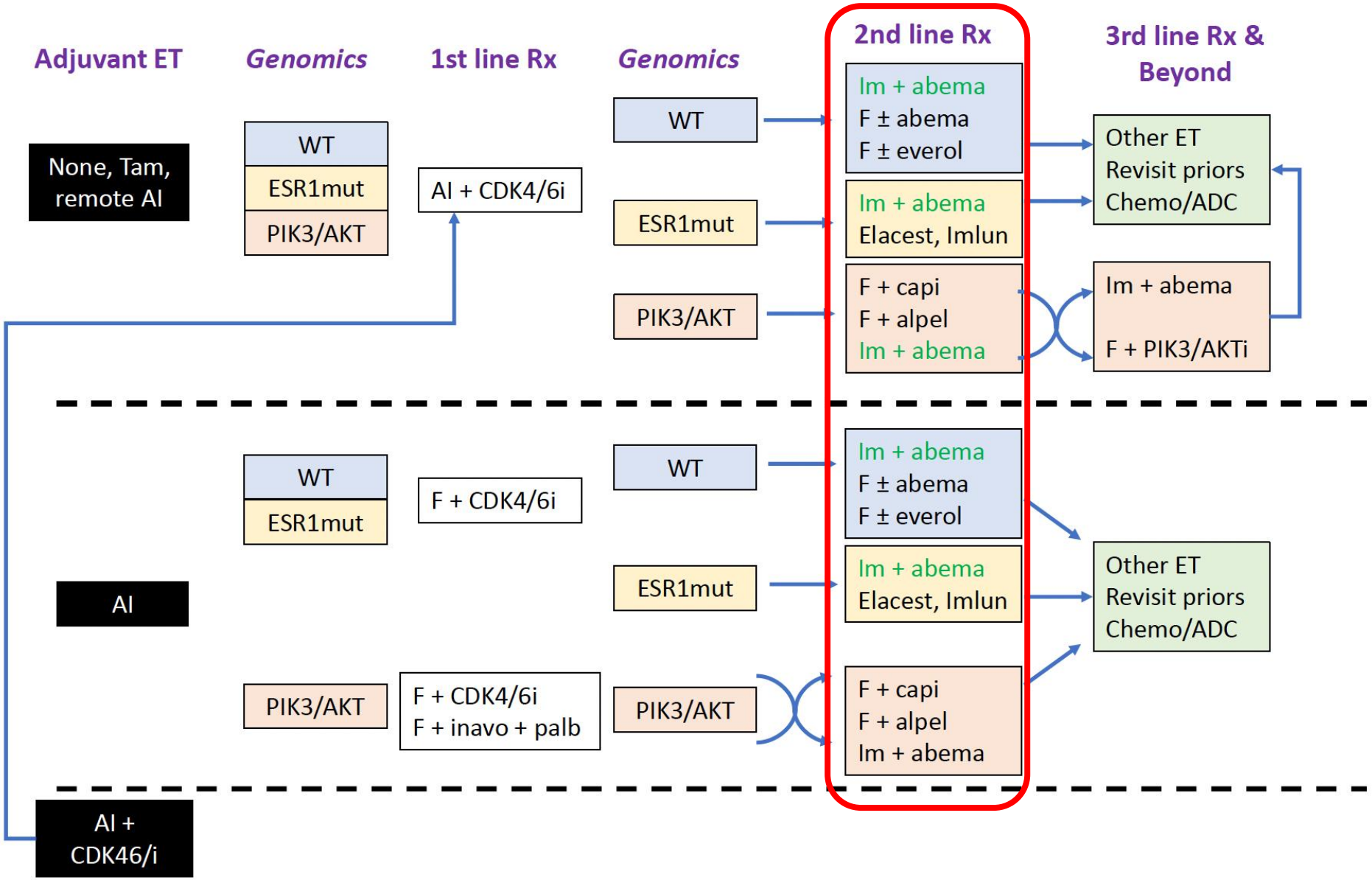
Adapted from Burstein HJ et a. SABCS 2024

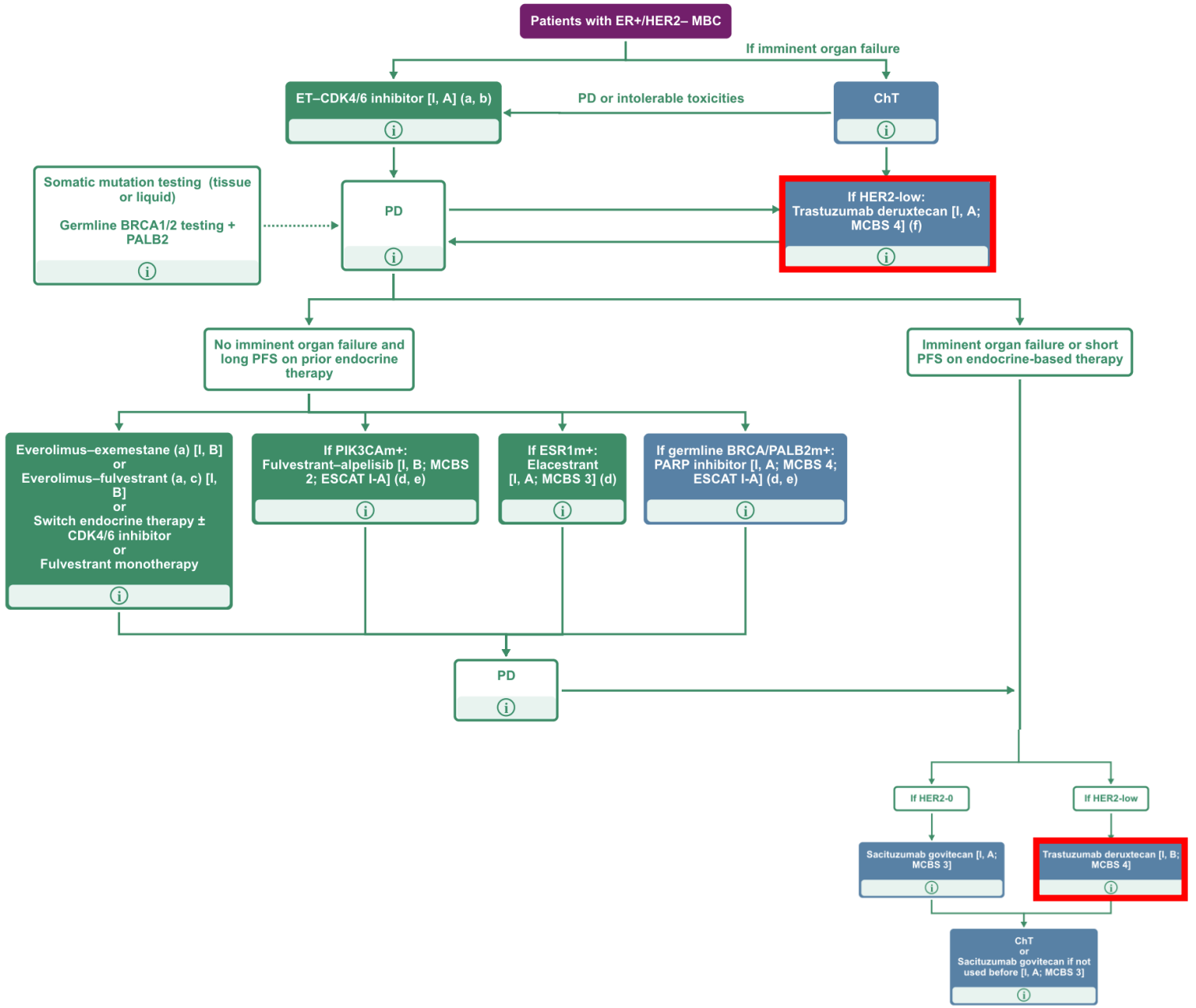
Imlunestrant + abemaciclib could become a preferred second-line treatment option regardless of tumor genomics and endocrine sensitivity



Adapted from Burstein HJ et a. SABCS 2024

Subsequent lines of therapy

v1.1 - May 2023



2024 ASCO ANNUAL MEETING

DESTINY BREAST06

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06

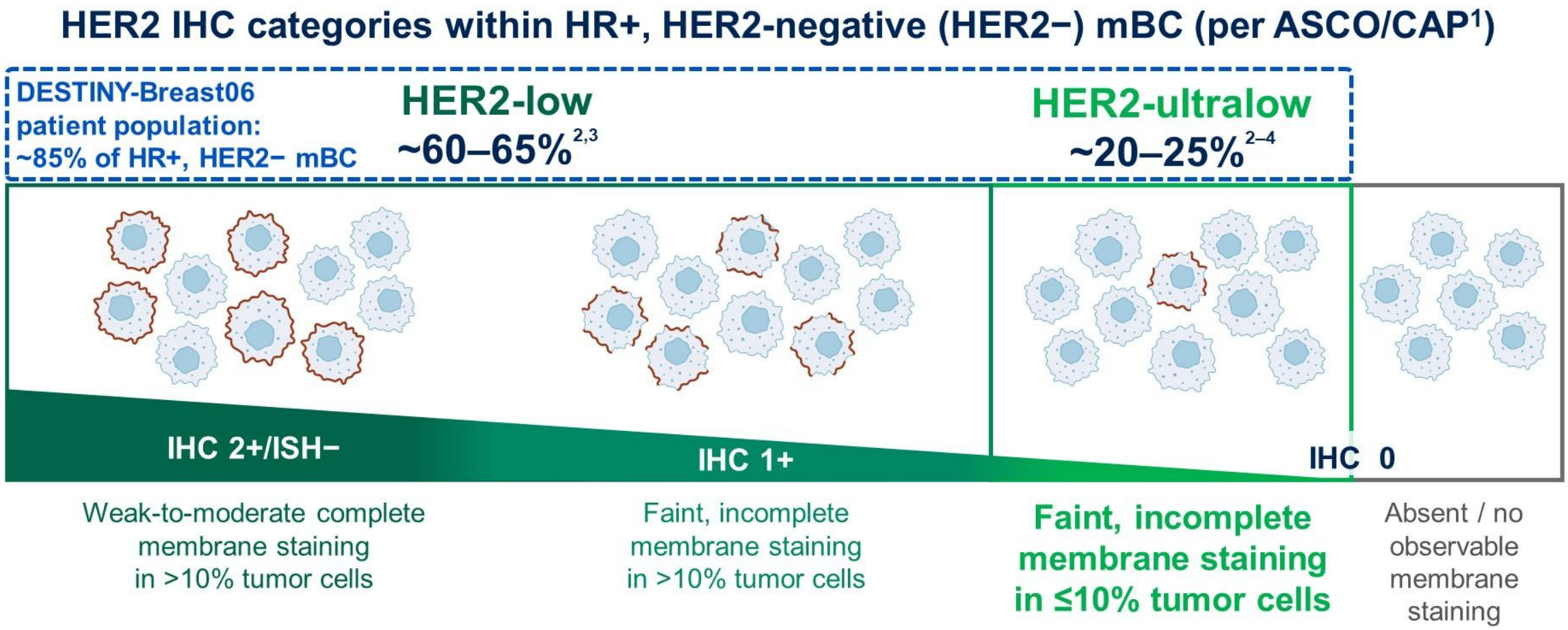
Giuseppe Curigliano
European Institute of Oncology, IRCCS, Milan, Italy;
Department of Oncology and Hematology-Oncology, University of Milan, Italy

Sunday, June 2, 2024

Additional authors: Xichun Hu, Rebecca Dent, Kan Yonemori, Carlos H Barrios, Joyce A O'Shaughnessy, Hans Wildiers, Qingyuan Zhang, Seock-Ah Im, Cristina Saura, Laura Biganzoli, Joohyuk Sohn, Christelle Lévy, William Jacot, Natasha Begbie, Jun Ke, Gargi Patel, Aditya Bardia

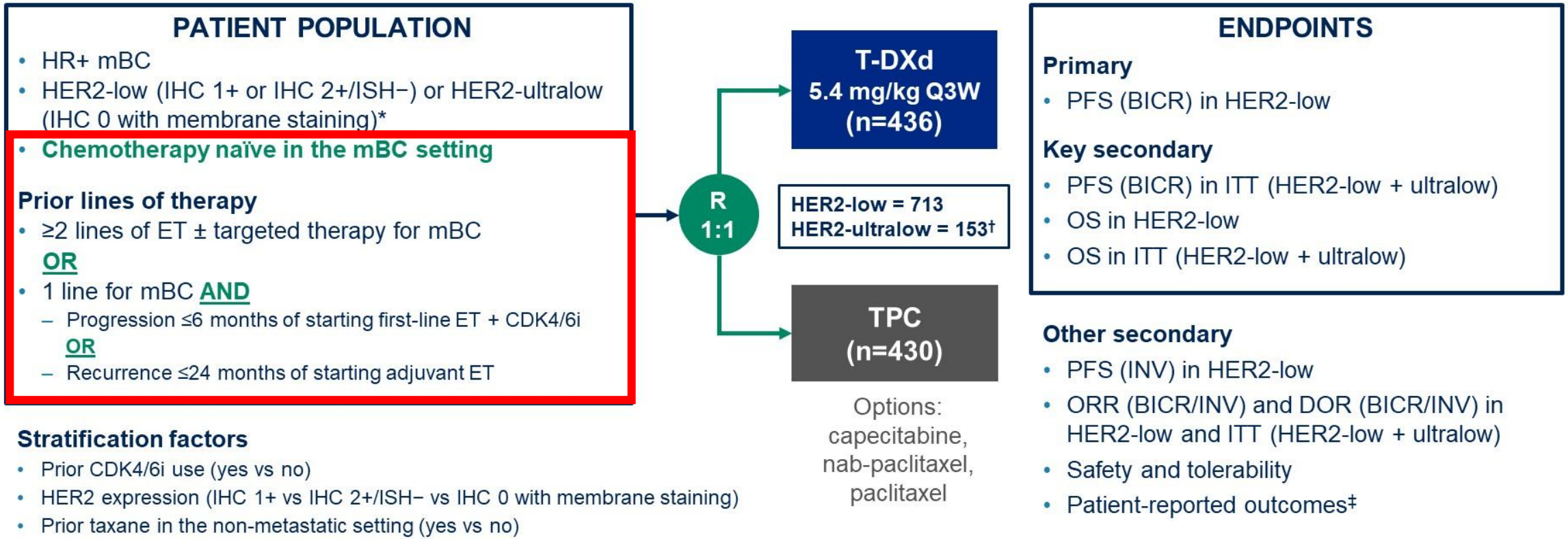
On behalf of the DESTINY-Breast06 investigators

Re-defining the biology of HR+/HER2 BC



Adapted from G. Curigliano, ASCO 2024 meeting

DESTINY Breast06 study design



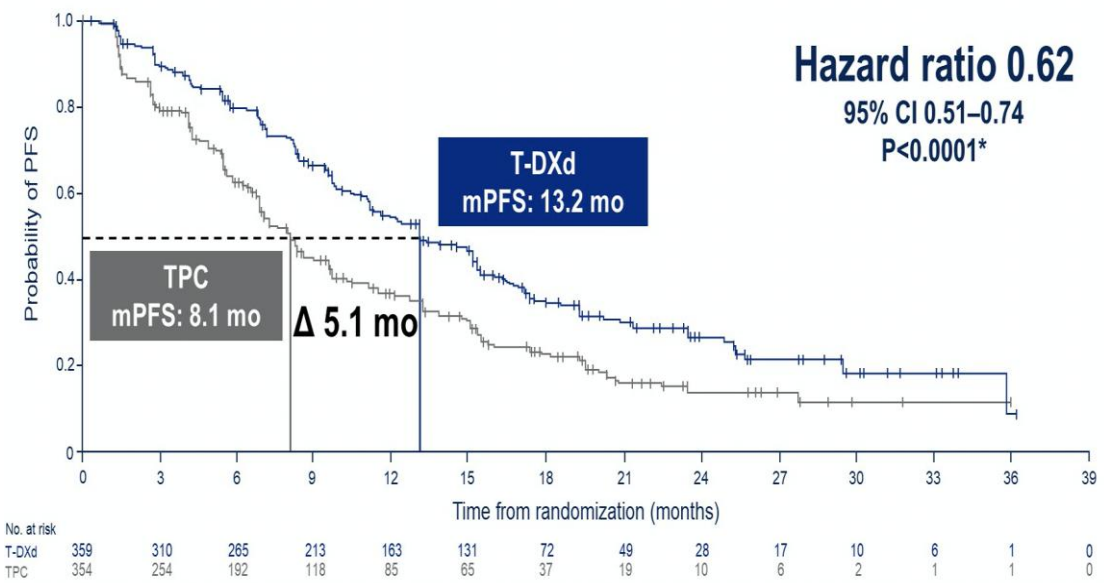
Adapted from G. Curigliano, ASCO 2024 meeting

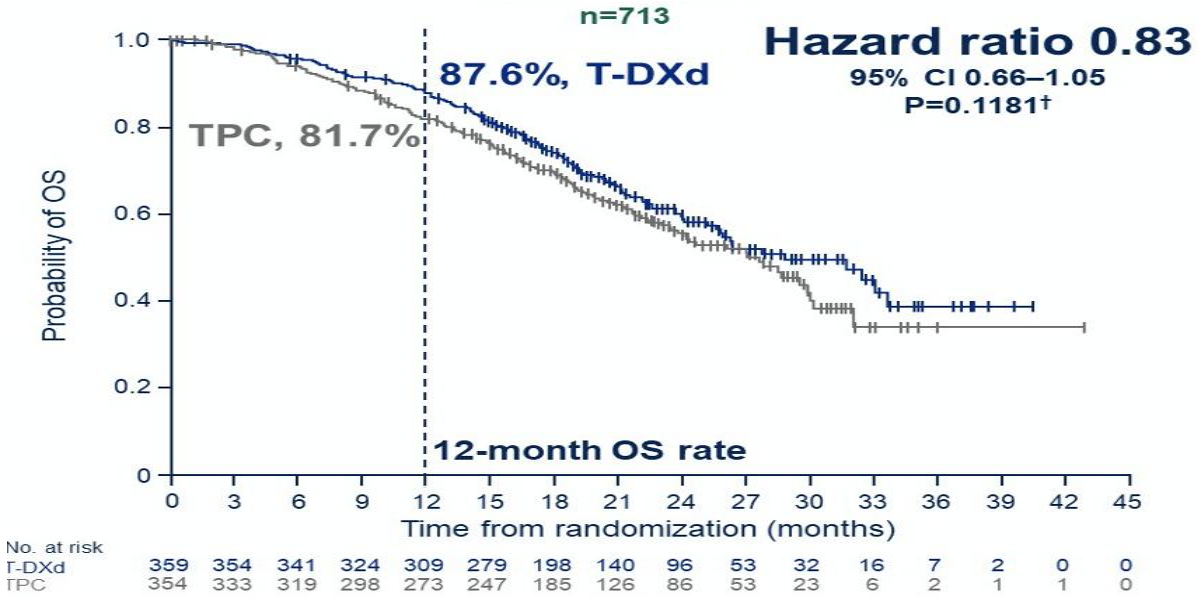
The majority of patients (~two thirds) received 2 lines of endocrine therapy

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
<6 months on first-line ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies, n (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with other targeted therapy†	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Adjuvant/neoadjuvant setting‡						
Prior therapies, n (%)						
ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

Adapted from G. Curigliano, ASCO 2024 meeting

T-DXd improves PFS when compared to physician choice therapy in patients with HER2-low disease, with a trend towards improved OS

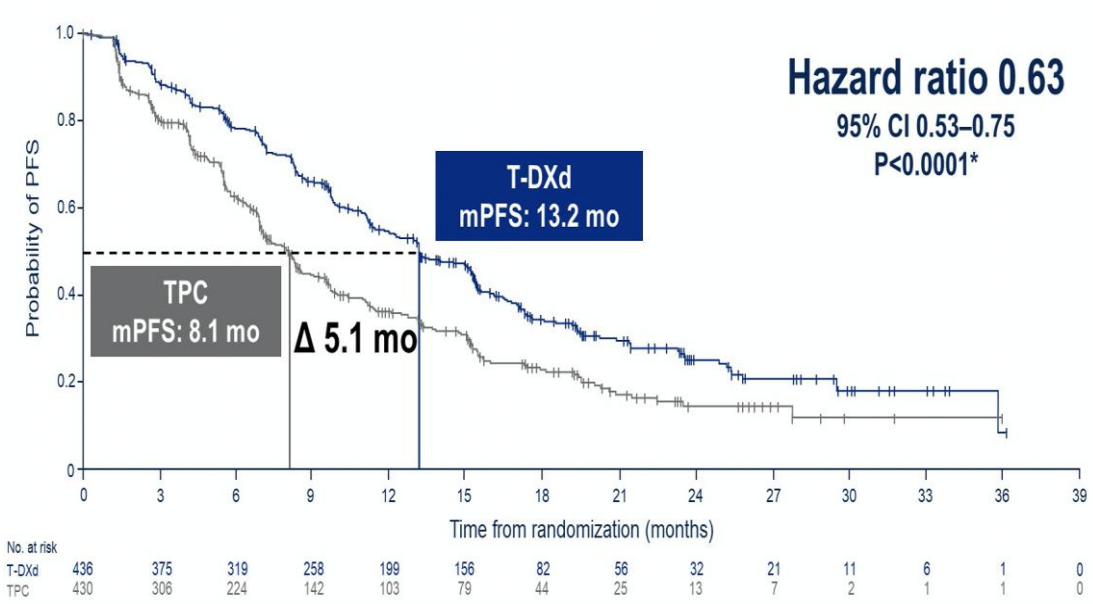


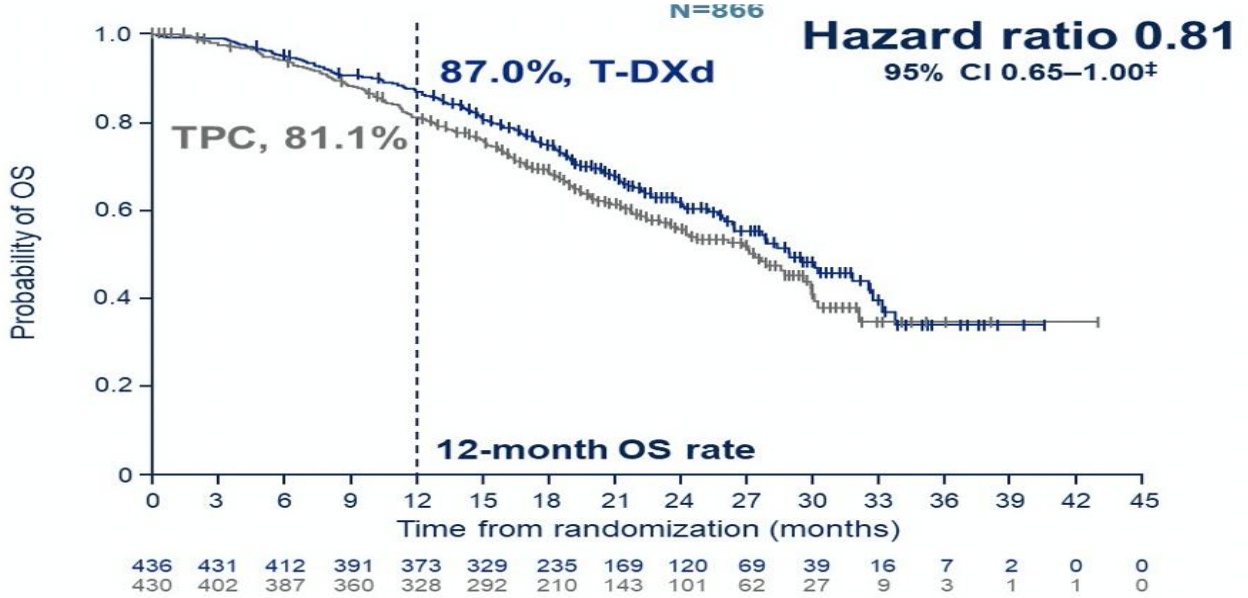


OS data: ~40% maturity

Adapted from G. Curigliano, ASCO 2024 meeting

T-DXd improves PFS when compared to physician choice therapy in ITT patients (HER2-low/ultra-low), with a trend towards improved OS



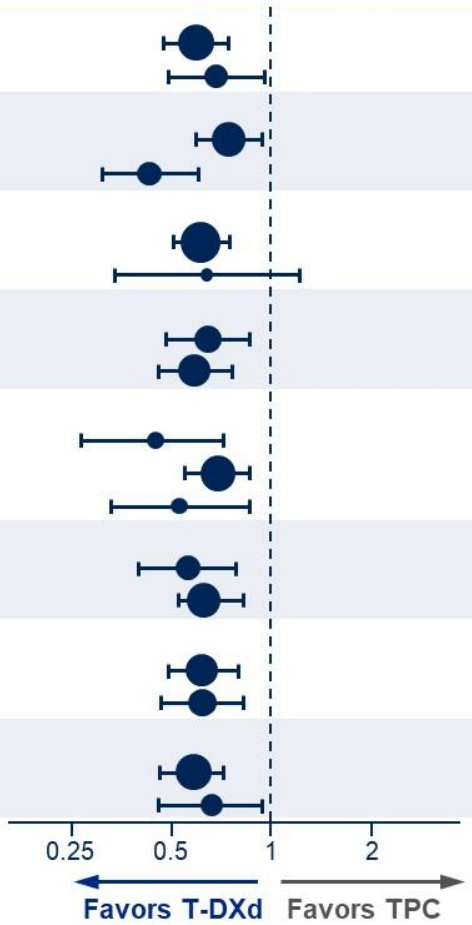


OS data: ~40% maturity

Adapted from G. Curigliano, ASCO 2024 meeting

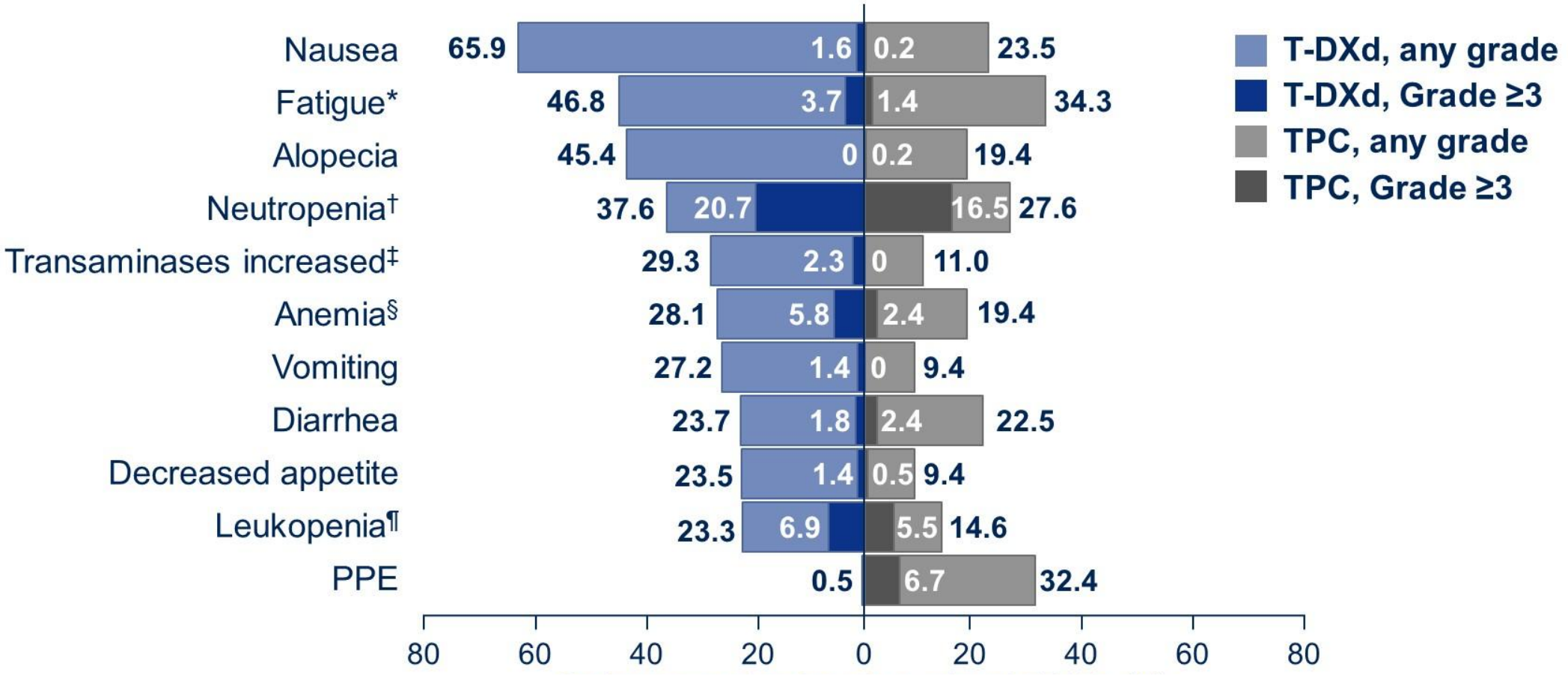
T-DXd improves PFS in all clinically relevant subgroups

	No. of events / no. of patients		mPFS (95% CI), months		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Age					
<65 years	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 years	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 status*					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+/ISH−	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Prior CDK4/6i					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Prior taxane use (adjuvant/neoadjuvant setting)					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
Number of prior lines of ET (metastatic setting)					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Choice of chemotherapy†					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes (Nab-paclitaxel + paclitaxel)	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)



Adapted from G. Curigliano, ASCO 2024 meeting

T-DXd is associated with higher rates of adverse events when compared to chemotherapy



Adapted from G. Curigliano, ASCO 2024 meeting

TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; FISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary:** included PFS (investigator assessed) PFS2, TFST, TSST, ORR, DCR at 12 weeks, DoR, PROs, and safety

Randomisation stratified by:

- **Lines of chemotherapy** in inoperable/metastatic setting (1 vs 2)
- **Geographic location** (USA/Canada/Europe vs other geographic regions)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
†ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W.
CDK4/6, cyclin-dependent kinase 4/6; D, day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FISH, fluorescent in-situ hybridisation; IHC, immunohistochemistry; IV, intravenous; PD, progressive disease; PFS2, time to second progression or death; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

1. Bardia A, et al. Future Oncol 2024;20:423–36.

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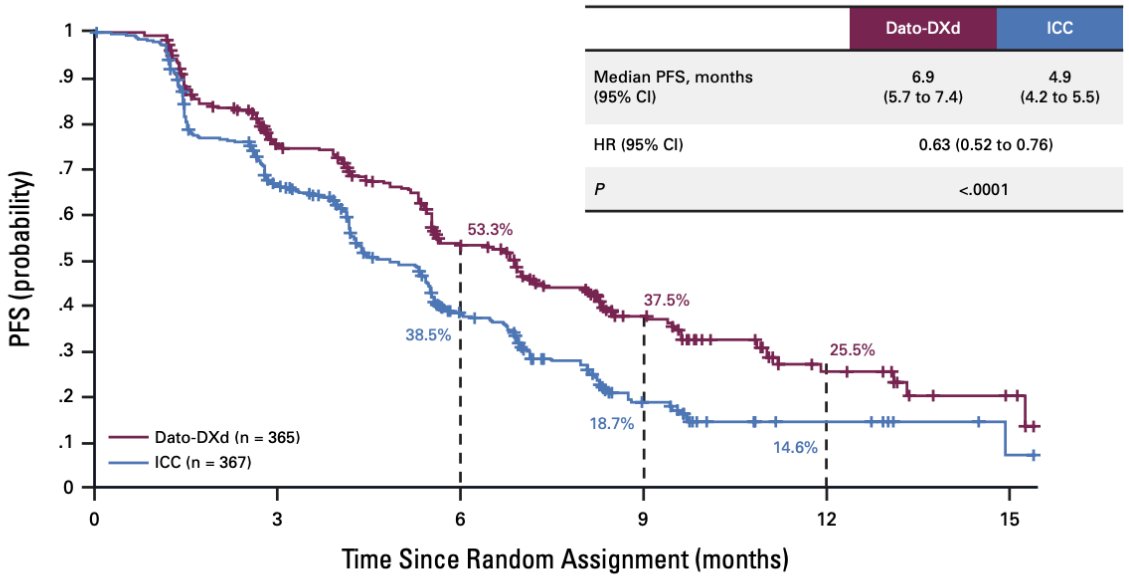
1. Bardia A, et al. Future Oncol 2024;20:423–36.

Dato-DXd improves patient PFS when compared to physician choice chemotherapy regardless of clinically relevant covariates

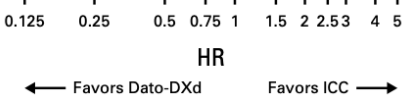


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7 to 7.4)	4.9 (4.2 to 5.5)
HR (95% CI)	0.63 (0.52 to 0.76)	
P	<.0001	

Number at risk

Dato-DXd	365	249	158	66	15	4
ICC	367	205	93	26	8	1

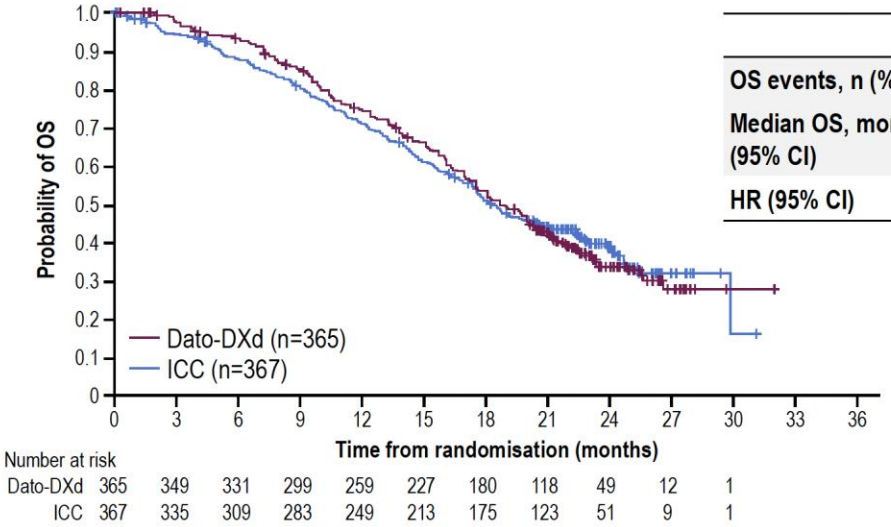
		No. of events/N (%) Dato-DXd	ICC	HR (95% CI)
All patients		212/365 (58.1%)	235/367 (64%)	0.63 (0.52 to 0.76)
No. of previous lines of chemotherapy	1	128/229 (55.9%)	145/225 (64.4%)	0.65 (0.51 to 0.83)
	2	84/135 (62.2%)	90/141 (63.8%)	0.60 (0.45 to 0.81)
Geographic region	The United States, Canada, Europe	110/186 (59.1%)	112/182 (61.5%)	0.62 (0.48 to 0.81)
	Other geographic regions	102/179 (57%)	123/185 (66.5%)	0.66 (0.50 to 0.85)
Previous use of the CDK4/6 inhibitor	Yes	177/304 (58.2%)	192/300 (64%)	0.62 (0.50 to 0.76)
	No	35/61 (57.4%)	43/67 (64.2%)	0.73 (0.46 to 1.14)
Previous use of the CDK4/6 inhibitor	≤12 months	95/151 (62.9%)	92/136 (67.6%)	0.61 (0.45 to 0.81)
	>12 months	82/153 (53.6%)	100/164 (61%)	0.61 (0.45 to 0.82)
Previous use of endocrine therapy in the metastatic setting	<6 months	23/40 (57.5%)	34/49 (69.4%)	0.58 (0.34 to 0.99)
	≥6 months	161/282 (57.1%)	174/277 (62.8%)	0.62 (0.50 to 0.77)
Previous use of taxanes and/or anthracyclines	Taxanes alone	54/91 (59.3%)	59/85 (69.4%)	0.61 (0.42 to 0.89)
	Anthracyclines alone	19/24 (79.2%)	20/28 (71.4%)	0.48 (0.24 to 0.93)
	Both taxanes and anthracyclines	117/204 (57.4%)	129/211 (61.1%)	0.69 (0.54 to 0.89)
	Neither taxanes nor anthracyclines	22/46 (47.8%)	27/43 (62.8%)	0.45 (0.24 to 0.81)
Age at random assignment, years	<65	163/274 (59.5%)	190/295 (64.4%)	0.64 (0.52 to 0.79)
	≥65	49/91 (53.8%)	45/72 (62.5%)	0.65 (0.43 to 0.97)
Race	Asian[a]	88/146 (60.3%)	101/152 (66.4%)	0.70 (0.52 to 0.93)
	Non-Asian	109/187 (58.3%)	119/183 (65%)	0.59 (0.45 to 0.76)
Brain metastases at baseline	Yes	26/35 (74.3%)	15/23 (65.2%)	0.73 (0.39 to 1.42)
	No	186/330 (56.4%)	220/344 (64%)	0.62 (0.51 to 0.75)
ECOG PS	0	119/197 (60.4%)	136/220 (61.8%)	0.73 (0.57 to 0.94)
	1	91/165 (55.2%)	98/145 (67.6%)	0.52 (0.38 to 0.69)



Bardia A et al. J Clin Oncol 2024

Dato-DXd does not result in OS improvement when compared to chemotherapy

Overall survival

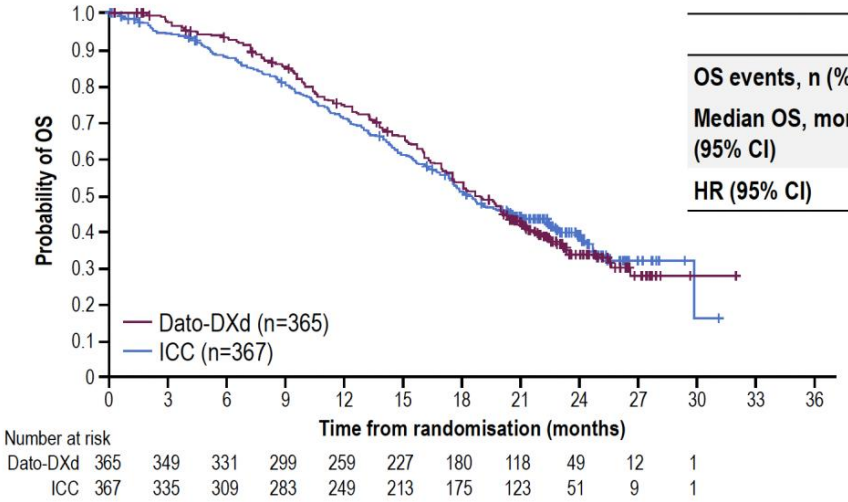


	Dato-DXd	ICC
OS events, n (%)	223 (61)	213 (58)
Median OS, months (95% CI)	18.6 (17.3–20.1)	18.3 (17.3–20.5)
HR (95% CI)	1.01 (0.83–1.22)	

- Maturity: 59.6%
- Median follow-up: 22.8 months
- Protocol prespecified OS sensitivity analysis based on the stratification factors according to the eCRF*: **HR 0.99 (95% CI: 0.82–1.20)**

Data cutoff: 24 July 2024. Pre-specified P-value boundary for OS analysis: α=0.0427.
*Mis-stratification between interactive response technology (where data entered could not be changed by the site) and eCRF (where data could be corrected by sites) was <5%.
eCRF, electronic case report form.

Overall survival adjusted for subsequent ADCs



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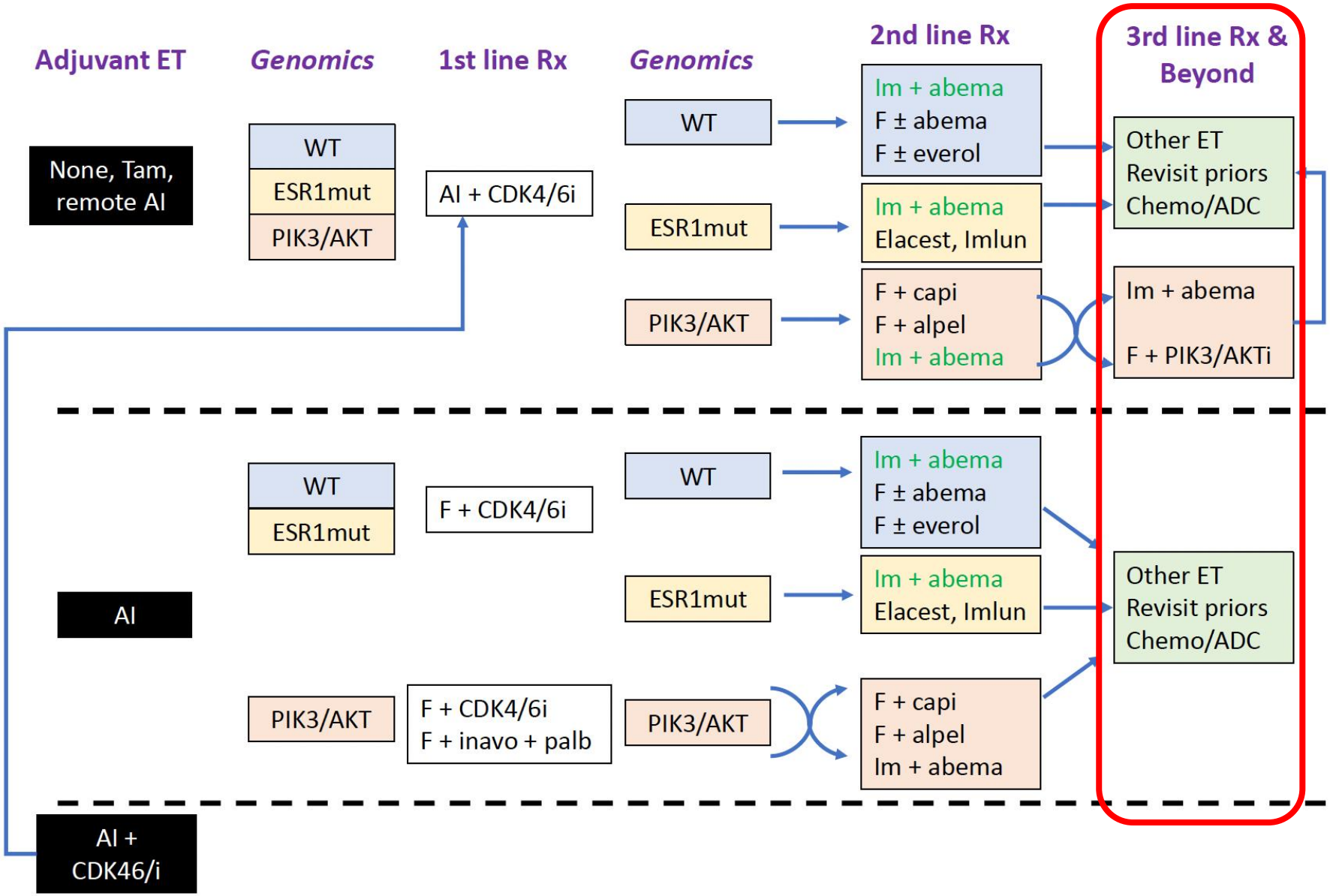
Imlunestrant + abemaciclib could become a preferred second-line treatment option regardless of tumor genomics and endocrine sensitivity



T-DXd: 0-2 prior lines of ChT (DB04; DB06) in 65-85% of pts (HER2-low/ultralow)

Dato-DXd (?): 1-2 prior lines of ChT (Tropion-B01)

SG: 2-4 prior lines of ChT in 100% of pts (TROPiCS02)

Adapted from Burstein HJ et a. SABCS 2024

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IFOM

Thank you for your attention!

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