Breast Cancer Data Updates

European Society for Medical Oncology Breast Cancer (ESMO BC) 2025

May 14-17, 2025

Munich, Germany

Comparison of treatment related contacts and associated quality of life in patients with HR+/HER2- metastatic breast cancer treated in the PADMA Study

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*Clinical Research Collaboration**

*Padma study is sponsored by GBG (German Breast Group)

EM-DEU-plb-0172

PADMA (NCT03355157): Study Design[1]

Prospective, randomized, open-label, multicenter, phase 4 trial

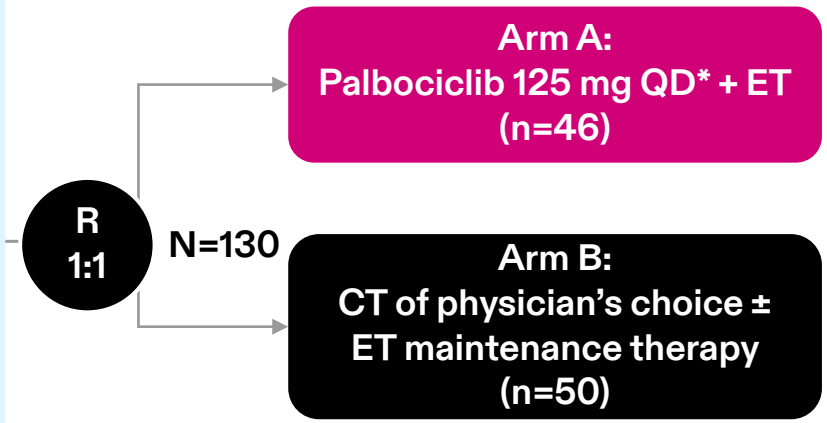
Objective: To compare CDK4/6 inhibitor + ET with standard monochemotherapy ± maintenance ET as first-line therapy in patients with high-risk mBC and a chemotherapy indication

Patient Population

- HR+/HER2- mBC
- Female or male
- Indicated for mono-CT
- No prior treatment for metastatic/relapsed disease
- No asymptomatic bone-only, oligometastatic disease
- No uncontrolled/untreated CNS metastases
- Life expectancy >6 months

Stratification

- Endocrine resistant vs endocrine sensitive
- Symptomatic vs asymptomatic metastatic disease



ET with palbociclib: AI or fulvestrant ± GnRHa
ET maintenance: tamoxifen, AI or fulvestrant ± GnRHa
CT: paclitaxel, capecitabine, epirubicin, or vinorelbine

Primary Endpoint

- TTF: defined as time from randomization to discontinuation of treatment due to disease progression, treatment toxicity, patient's preference, or death

Secondary Endpoints

- PFS
- OS
- Safety, tolerability, treatment adherence
- TFST and further time-to-event endpoints
- Patient-reported QoL
- DMTI: call tracking/geofencing with passive collection of information about frequency and duration of phone calls/visits to study site, respectively

Due to slow accrual, the study was stopped in 12/2023 with 130 patients (initial proposed sample size for randomization: 150) and 100 events without major loss of power with an accrual duration of 70 months and follow-up period of 8 months[4]

The PADMA trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in time to treatment failure with palbociclib + ET vs CT ± ET maintenance therapy.[1]
The PALOMA trials did not compare palbociclib + ET with monochemotherapy.[2,3]
Cross-trial comparisons are unreliable and likely to be confounded due to differences in study design and patient populations.

*Palbociclib was administered on days 1-21 of a 28-day cycle.
AI=aromatase inhibitor; CDK4/6=cyclin-dependent kinase 4/6; CNS=central nervous system; CT=chemotherapy; DMTI=Daily Monitoring of Treatment Impact; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; GnRHa=gonadotropin-releasing hormone agonists; HER=human epidermal growth factor receptor; HR=hormone receptor; mBC=metastatic breast cancer; OS=overall survival; PFS=progression-free survival; QD=once daily; QoL=quality of life; R=randomization; TFST=time to first subsequent treatment; TTF=time to treatment failure.

1. Loibl S, et al. SABCS 2024. Oral presentation LB1-03
2. Finn RS, et al. *N Engl J Med.* 2016;375:1925-1936
3. Turner NC, et al. *N Engl J Med.* 2015;373:209-219
4. Data on file

3
Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Methods (*Exploratory Analysis*)

Objective: To analyze the association of treatment regimens and treatment-related contacts (TRCs)* with healthcare systems, consecutive time burden, and the impact on QOL among patients with HR+/HER2- mBC who received palbociclib + ET or standard mono-CT ± subsequent maintenance ET

Methods†

Patients received smartphones to record TRCs, including:

- Number of phone calls (PCs)
- Investigator study site visits (SVs)

In addition, the following were assessed:

- Total time burden, travel-related financial burden, and environmental burden‡
- Differences in PCs and SVs related to QOL changes (FACT-B total score) from baseline to EOT§

*Defined as visits, calls, hospitalization, travel time, and travel costs.
†Longitudinal mixed-effects models analyzed changes in TRCs between arms.
‡Time and travel distance were calculated as distance between the study site and center of zip code of the patient's address.
§Differences in PC and SV related to quality-of-life changes (FACT-B total score) from baseline to EOT were considered by dividing TRC frequency in 2 groups (low/medium vs high) according to tertile distribution.
EOT=end of treatment; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast.

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Patient Characteristics (1 of 2)*

Characteristics	Palbociclib + ET (n=46)	CT-based (n=50)	Overall (N=96)
Age, years			
Median (range)	61.0 (42.0-85.0)	59.5 (31.0-80.0)	60.5 (31.0-85.0)
Menopausal status, n (%)			
Pre/perimenopausal	5 (10.9)	5 (10.0)	10 (10.4)
Postmenopausal	40 (87.0)	44 (88.0)	84 (87.5)
NA (male)	1 (2.2)	1 (2.0)	2 (2.1)
ECOG PS, n (%)			
0	35 (77.8)	32 (66.7)	67 (72.0)
>0	10 (22.2)	16 (33.3)	26 (28.0)
Missing	1	2	3

Characteristics	Palbociclib + ET (n=46)	CT-based (n=50)	Overall (N=96)
WHO BMI Class, kg/m^2			
Median (range)	27.2 (17.9-49.7)	16 (19.4-49.6)	26 (17.9-49.7)
HR status, n (%)†			
ER+, PgR-	11 (24.4)	9 (18.0)	20 (21.1)
ER+, PgR+	35 (75.6)	41 (82.0)	75 (78.9)
Missing	1	0	1
Tumor grading, metastasis, n (%)			
Grade 1	0 (0.0)	1 (5.9)	1 (3.3)
Grade 2	11 (84.6)	11 (64.7)	22 (73.3)
Grade 3	2 (15.4)	5 (29.4)	7 (23.3)
Missing	33	33	66

**P* values for between-group comparisons were >0.05 for all parameters. †If ER-PgR status was not available in patients with metastasis at primary diagnosis, ER and PgR status of primary breast cancer was considered.
BMI=body mass index; CT=chemotherapy; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; ET=endocrine therapy; HR=hormone receptor; NA=not applicable; PgR=progesterone receptor; WHO=World Health Organization.

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Patient Characteristics (2 of 2)*

Characteristics	Palbociclib + ET (n=46)	CT-based (n=50)	Overall (N=96)
Histological tumor type			
Ductal	36 (78.3)	38 (76.0)	74 (77.1)
Lobular	8 (17.4)	11 (22.0)	19 (19.8)
Other	2 (4.3)	1 (2.0)	3 (3.1)
Treatment setting at first diagnosis			
(Neo)adjuvant	31 (67.4)	30 (60.0)	61 (63.5)
De novo/metastatic	15 (32.6)	20 (40.0)	35 (36.5)

**P* values for between-group comparisons were >0.05 for all parameters.
CT=chemotherapy; ET=endocrine therapy.

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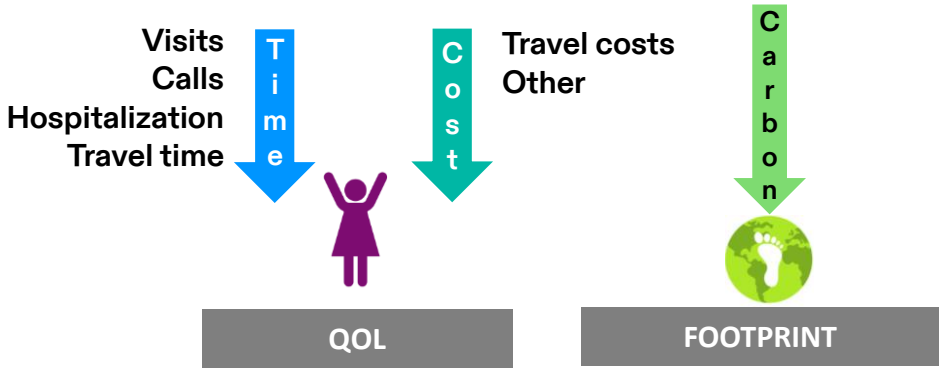
PADMA: Treatment-Related Contacts—Commute Details and Study Treatment

Treatment-Related Contacts as Burden



Patient Commute Details*

Category	Palbociclib + ET (n=46)	CT-based (n=50)	Overall† (N=96)
One-way distance to study center, km			
Median (range)	14.6 (2.6-132.9)	17.5 (2.7-124.0)	145.2 (2.6-132.9)
Time to study center for one way, min			
Median (range)	21.5 (6.0-79.0)	22.5 (7.0-109.0)	22.0 (6.0-109.0)

Study Treatment as Treated

Category	Palbociclib + ET (n=46)	CT-based (n=50)
Type of treatment of physician's choice CT, n (%)		
Capecitabine	—	34.0 (68.0)
Paclitaxel	—	15 (30.0)
Vinorelbine	—	1 (2.0)
Received ET maintenance after CT		11 (22.0)
Type of ET, n (%)		
Aromatase inhibitor	36 (78.3)	7 (14.0)
Tamoxifen	—	3 (6.0)
Fulvestrant	10 (21.7)	1 (2.0)

*The one-way distance and travel time were comparable between study arms.

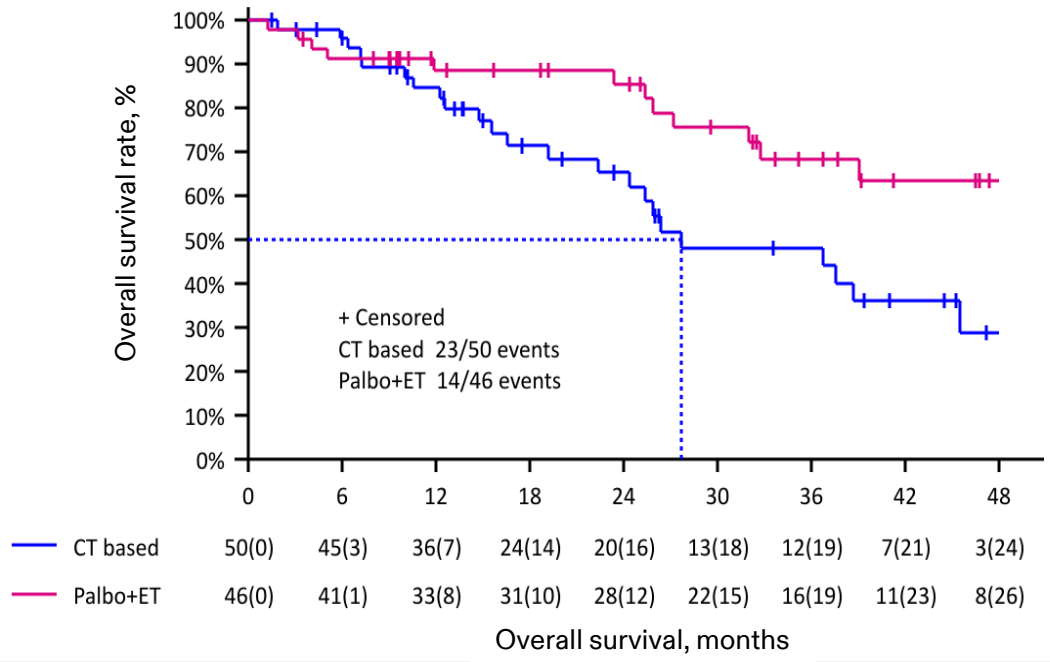
†*P* value for between-group comparisons were >0.05 for all parameters: One-way distance to study center, *P* = 0.722. Time to study center for one way, *P* = 0.761.

CT=chemotherapy; ET=endocrine therapy; QOL=quality of life.

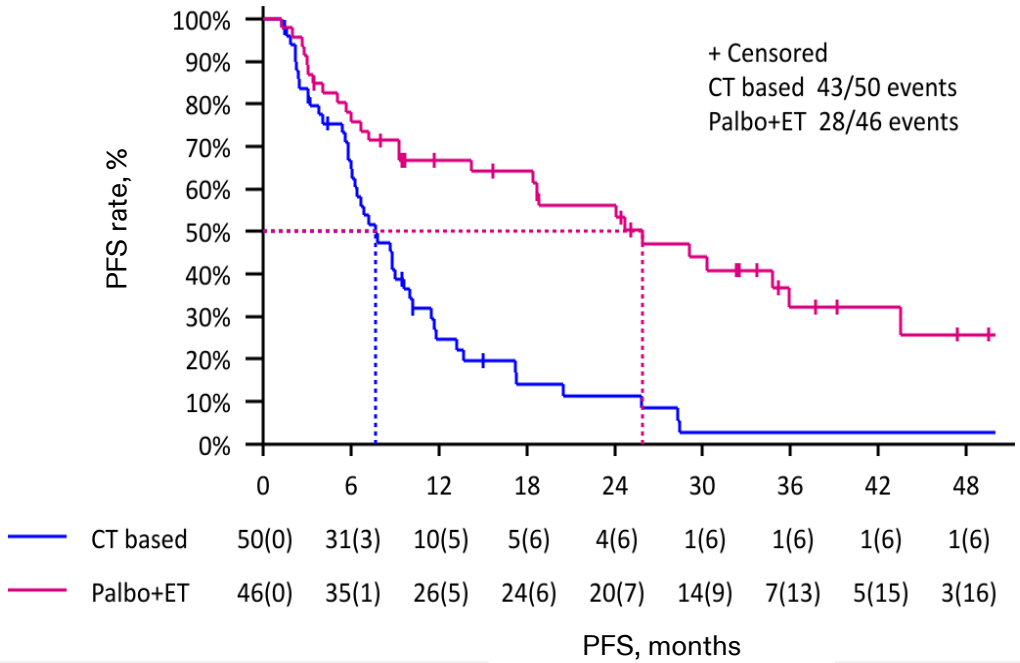
Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Survival and TRCs

OS



PFS



Consistent with the analysis in the entire cohort,[1,*] patients in this descriptive analysis had improved survival with palbociclib + ET vs CT-based treatment

***Data from 96 patients were available for the descriptive analysis of TRC until end of treatment.**

CT=chemotherapy; ET=endocrine therapy; OS=overall survival; Palbo=palbociclib; PFS=progression-free survival; TRC=treatment-related contact.

1. Loibl S, et al. SABCS 2024. Oral presentation LB1-03

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Comparison of TRC*

Characteristics	Palbociclib + ET (n=46)	CT-based (n=50)	*P* value
Number of phone calls/month			
Median (range)	0.0 (0.0-6.0)	0.0 (0.0-26.0)	0.646
Mean (SD)	0.8 (1.3)	1.7 (4.9)	0.589
Number of site visits/month			
Median (range)	1.0 (1.0-3.5)	1.0 (0.0-7.0)	0.030
Mean (SD)	1.5 (0.7)	2.0 (1.4)	0.072
Number of hospitalizations/month			
Median (range)	0.0 (0.0-3.0)	0.0 (0.0-1.0)	0.485
Mean (SD)	0.1 (0.5)	0.1 (0.2)	0.684
Number of total contacts (phone calls and site visits)/month			
Median (range)	1.0 (1.0-9.5)	2.0 (0.0-28.0)	0.045
Mean (SD)	2.2 (1.8)	3.7 (5.2)	0.045

Median TRC per month were lower in the palbociclib + ET group than in the CT group (1 vs 2, *P*=0.045)

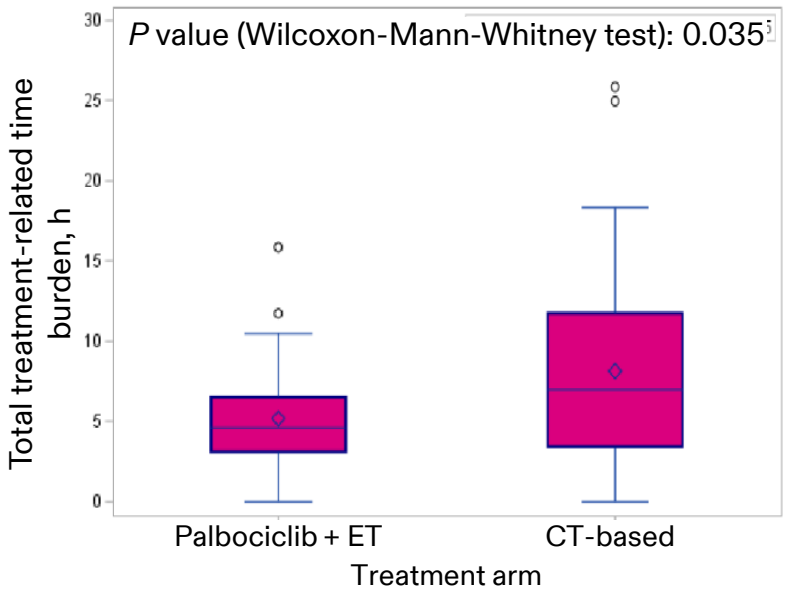
*Endpoints of TRC were mean/median normalized to the number of TRCs/month.
CT=chemotherapy; ET=endocrine therapy; SD=standard deviation; TRC=treatment-related contact.

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

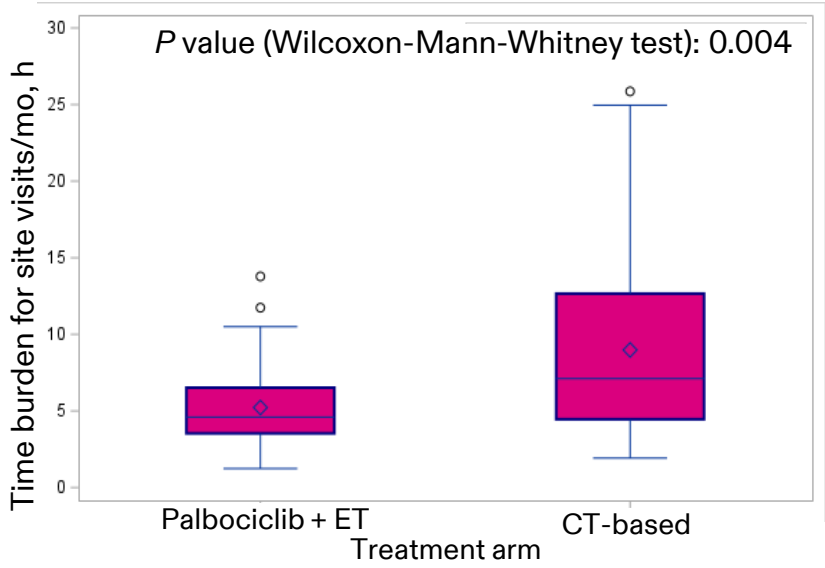
PADMA: Treatment-Related Contacts—Time-Related Time Burden

Time Burden

A. Total Treatment Time Burden/Month*



B. Time Burden of Outpatient Visits/Month



C. Ratio of PFS and Treatment Time Burden

	Palbociclib + ET N=46	CT-based N=49
PFS (brutto), mo	17.95	6.68
TRB until PFS, mo	0.20	0.10
PFS (netto), mo	17.75	6.58
Ratio of TRB on PFS, %	1.1	1.5

- Patients on palbociclib + ET had a lower time burden (Figure A), mainly due to less time spent at the site (Figure B, adjusted mean difference: -0.19 hours, *P*=0.009)
- The time burden was 1.1% of PFS in the palbociclib + ET group and 1.5% in the CT-based group (Figure C)

*Includes visits, travel, and phone calls.

CT=chemotherapy; ET=endocrine therapy; PFS=progression-free survival; TRB=treatment-related burden.

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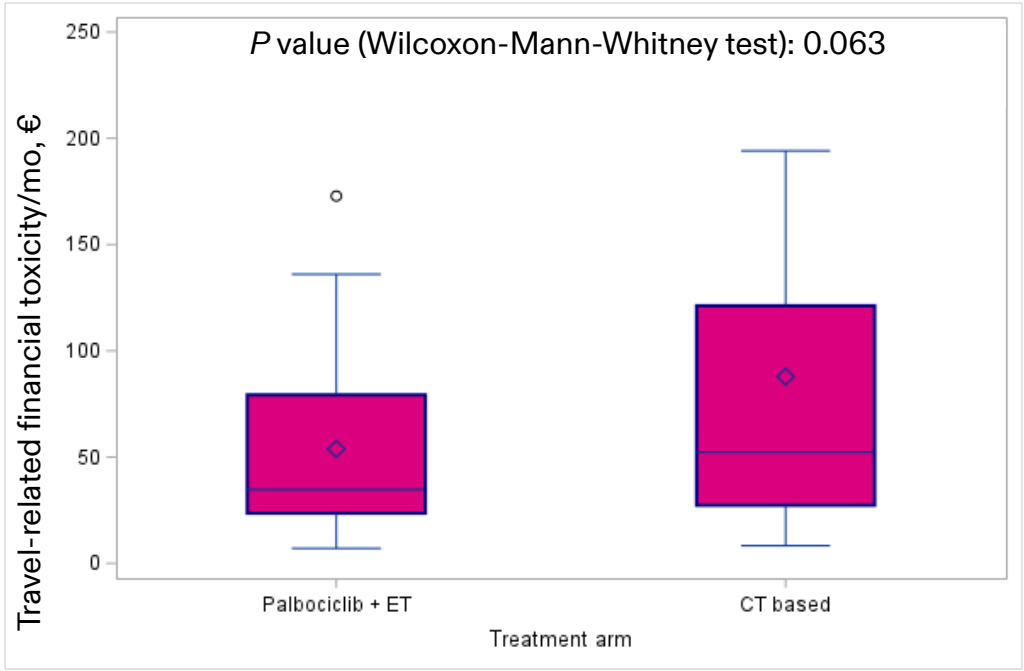
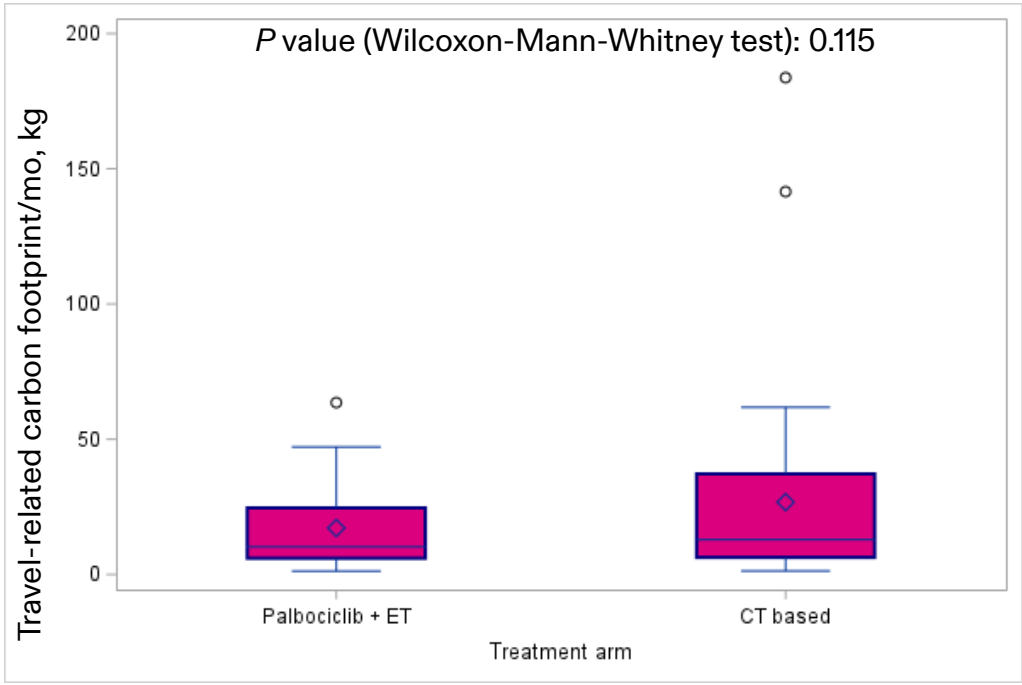
PADMA: Treatment-Related Contacts—Financial Burden & Travel Emissions

Monthly Travel-Related Financial Toxicity



Travel-Related Ecological Toxicity (Travel Emissions)



A trend was observed for a lower financial burden for palbociclib + ET (34.70 € vs 52.30 €/month; *P*=0.063), but no difference between arms in travel-related emissions

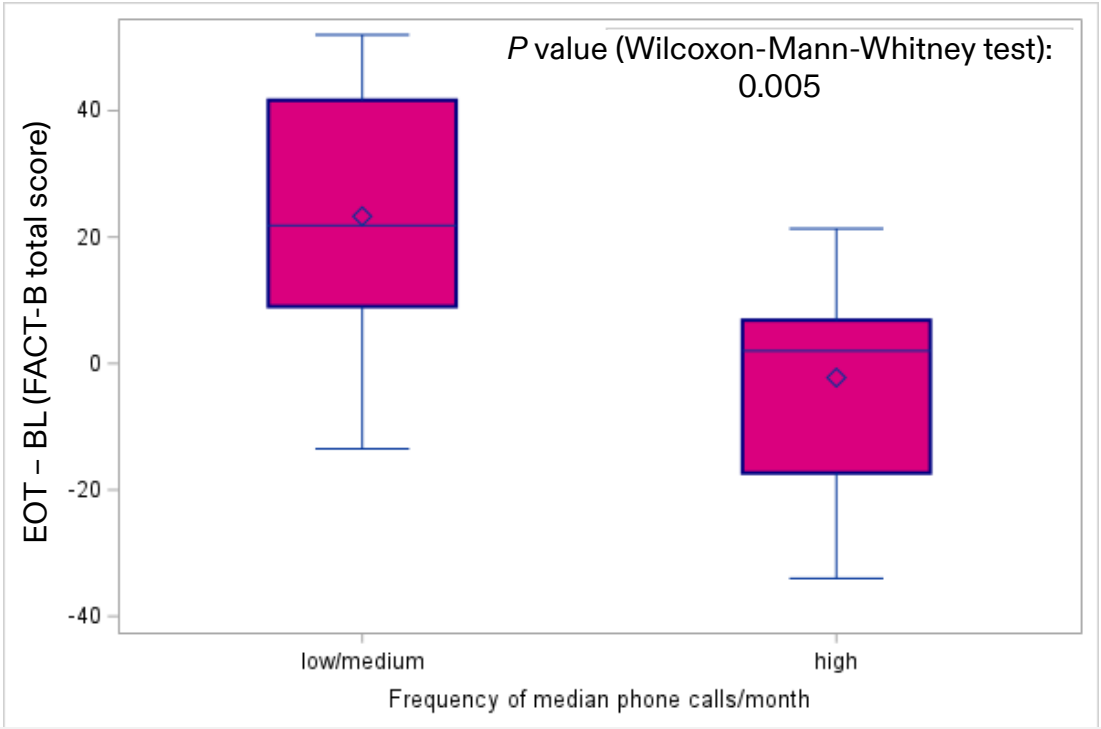
CT=chemotherapy; ET=endocrine therapy.

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

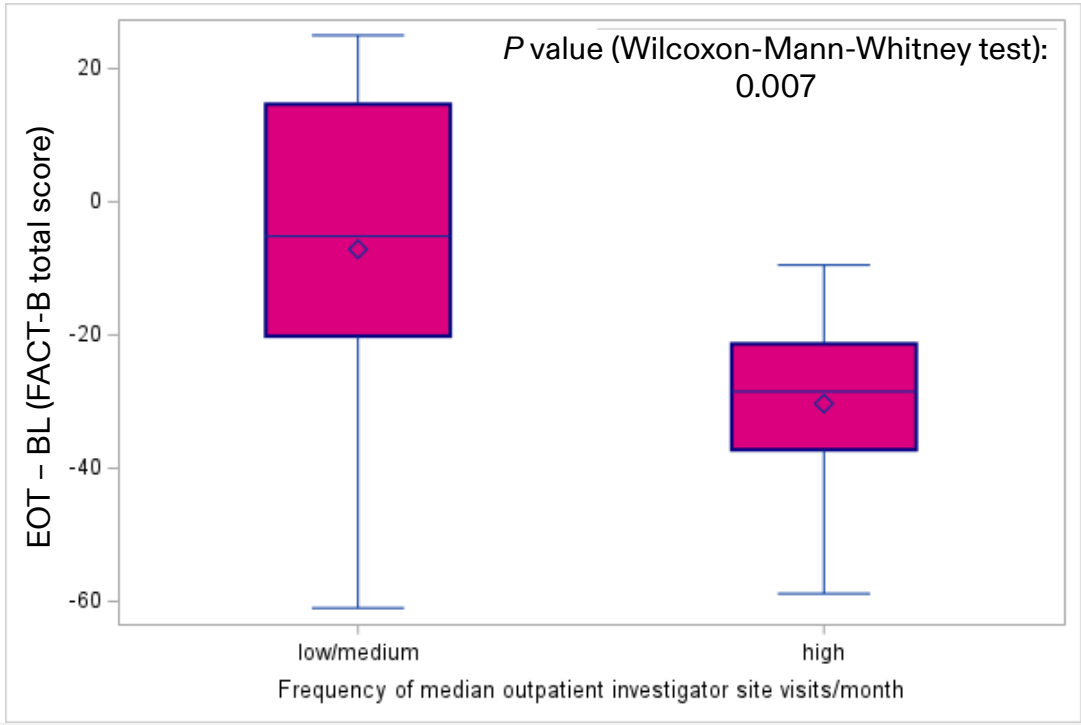
PADMA: Treatment-Related Contacts—Impact of TRCs on QOL

Changes in QOL

Change in QOL in Patients With Mean Low/Medium vs High Number of Phone Calls/Month*



Change in QOL in Patients With Mean Low/Medium vs High Number of Investigator Site Visits/Month†



A high number of site visits and phone calls was associated with a profound decrease in QOL by the FACT-B total score

*Cutoff: 0 phone calls per month. †Cutoff: 1.5 visits/month.

BL=baseline; EOT=end of treatment; FACT-B=Functional Assessment of Cancer Therapy—Breast; QOL=quality of life; TRC=treatment-related contact.

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

PADMA: Treatment-Related Contacts—Authors' Conclusions

- Patients on palbociclib + ET had a longer PFS and lower time burden of visits
  - A trend was observed toward a lower financial burden, but there was no difference in treatment travel emissions between the therapies with the given sample size
- Lower amounts of phone calls and site visits were associated with better QOL
- The results of these new patient-centric measures further support the use of palbociclib + ET as 1L treatment in patients with high-risk HR+/HER2- mBC

The PALOMA trials did not compare palbociclib + ET with monochemotherapy.[2,3]
Cross-trial comparisons are unreliable and are likely to be confounded due to differences in study design and patient populations.

1L=first-line; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PFS=progression-free survival; QOL=quality of life.

1. Lukac S, et al. ESMO BC 2025. Poster P323.
2. Finn RS, et al. *N Engl J Med.* 2016;375:1925-1936
3. Turner NC, et al. *N Engl J Med.* 2015;373:209-219

Lukac S, et al. Presented at ESMO BC; May 14-17; Munich, Germany. Poster P323.

Quality of life with first-line ET + palbociclib vs standard mono-chemotherapy in high risk HER2-/HR+ mBC and indication for chemotherapy in the PADMA study

Vesna Bjelic-Radisic, Marcus Schmidt, Marc Till, Julia Rey, Beate Rautenberg, Thomas Decker, Joachim Rom, Matthias Kögel, Kristina Lübbe, Axel Nacke, Sabine Seiler, Marianne Just, Volkmar Müller, Renu Buss-Steidle, Jürgen Terhaag, Christoph Mundhenke, Carsten Denkert, Johannes Holtschmidt, Sibylle Loibl

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*Clinical Research Collaboration**

*Padma study is sponsored by GBG (German Breast Group)

EM-DEU-plb-0172

PADMA: QOL—Methods *(Exploratory Analysis)*

Objective: To report patient well-being and quality of life from the PADMA trial

Methods

Two FACT-G–derived questions evaluated patient well-being

- Questions included “I am bothered with the side effects of treatment (GP5)” and “I am content with the quality of my life (GF7)”
- Data were collected daily via study cell phone or at study site visit

FACT-B evaluated patient QOL

- Data were collected at baseline, at each cycle for the first 6 months, and at every second cycle thereafter until EOT
    - Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or change in treatment regimen

Data were analyzed with a longitudinal mixed-effects model to account for repeated measures

EOT=end of treatment; QOL=quality of life.

Bjelic-Radisic V, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 310P.

PADMA: QOL—Patient Characteristics (Safety Set)*

Characteristics	Palbociclib + ET (n=54)	CT-based (n=47)	Overall (N=101)
Age, y*			
Median (range)	62.5 (42.0-85.0)	60 (31.0-80.0)	62 (31.0-85.0)
Postmenopausal status			
n (%)	47 (87.0)	41 (87.2)	88 (87.1)
Endocrine resistant			
n (%)	16 (29.6)	14 (29.8)	30 (29.7)
Number of systems with metastases, n (%)			
1	12 (22.2)	10 (21.3)	22 (21.8)
2	24 (44.4)	17 (36.2)	41 (40.6)
3	12 (22.2)	13 (27.7)	25 (24.8)
≥4	6 (11.1)	7 (14.9)	13 (12.9)

Characteristics	Palbociclib + ET (n=54)	CT-based (n=47)	Overall (N=101)
Treatment setting at first diagnosis, n (%)			
Neoadjuvant	4 (7.4)	5 (10.6)	9 (8.9)
Adjuvant	34 (63.0)	22 (46.8)	56 (55.4)
Metastatic	16 (29.6)	20 (42.6)	36 (35.6)
HER2-low metastasis, n (%)			
HER2 0	9 (25.7)	10 (41.7)	19 (32.2)
HER2-low	26 (74.3)	14 (58.3)	40 (67.8)

The median time of therapy from baseline to EOT was longer in the palbociclib + ET arm than the CT-based arm (16.3 mo vs 6.4 mo)

*There were 120 patients included in the safety set (n=62 in the palbociclib + ET arm and n=58 in the CT-based arm). Of these patients, 101 (n=54 in the palbociclib + ET arm; n=47 in the CT-based arm) had a baseline and 1 further FACT-B assessment and were included in the exploratory QOL analyses.

CT=chemotherapy; EOT=end of treatment; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; HER2=human epidermal growth factor receptor 2; QOL=quality of life.

Bjelic-Radisic V, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 310P.

PADMA: QOL—FACT-B and FACT-G Minimal Clinically Important Difference (MCID)[1,2]

MCID is defined as "*the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management*"

These values are essential for interpreting the clinical relevance of observed changes, which should not rely solely on statistical significance

MCIDs for the FACT-B and FACT-G

Score	Scales included	MCID
FACT-B total	FWB + PWB + BCS + SWB + EWB	7-8 points
FACT-G total	FWB + PWB + SWB + EWB	5-6 points
FACT-B TOI	FWB + PWB + BCS	5-6 points

BCS=breast cancer scale; EWB=emotional well-being; FACT-B=Functional Assessment of Cancer Therapy—Breast; FACT-G=Functional Assessment of Cancer Therapy—General; FWB=functional well-being; PWB=physical well-being; SWB=social well-being; TOI=trial outcome index.

1. Bell ML, et al. *J Patient Rep Outcomes.* 2018;2:48.
2 Eton DT, et al. *J Clin Epidemiol.* 2004;57:898-910.

Bjelic-Radisic V, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 310P.

PADMA: QOL—FACT-G and FACT-B Scores

Results of QOL Scores and Indices

	Palbociclib + ET (n=54)*	CT-based (n=47)†	Repeated-measures mixed-effects model	
	Mean (SD)	Mean (SD)	$Mean_{adj}$	*P* value‡
FACT-G total score	81.2 (14.7)	72.3 (18.3)	4.11	**0.048**
FACT-B total score	108.1 (17.9)	97.5 (2.4)	3.66	0.097
FACT-B TOI	67.9 (12.7)	60.7 (15.5)	2.02	0.176
FACT-B physical well-being	22.2 (4.8)	19.7 (6.6)	1.31	**0.044**
FACT-B social well-being	21.7 (4.6)	21.0 (5.5)	0.11	0.545
FACT-B emotional well-being	18.5 (4.0)	15.8 (5.3)	1.92	**0.002**
FACT-B functional well-being	18.8 (5.3)	15.8 (6.3)	1.49	0.059

*Based on 906 assessments. †Based on 301 assessments.

‡*P* value only shown for treatment. The model includes baseline value as a random effect and treatment, time, and treatment by time as fixed effects; treatment *P* values are unadjusted and should be interpreted exploratively.

CI=confidence interval; CT=chemotherapy; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; FACT-G=Functional Assessment of Cancer Therapy—General; HR=hazard ratio; MCID=minimum clinically important difference; PAL=palbociclib; QOL=quality of life; SD=standard deviation; TOI=trial outcome index; TTD=time to deterioration.

Significant MCIDs for palbociclib + ET vs CT-based therapy

- FACT-B total score
- FACT-G total score
- FACT-B TOI

Significant adjusted mean difference for PAL + ET vs CT-based therapy

- FACT-G total score
- FACT-B physical well-being
- FACT-B emotional well-being

No significant differences

- GP5 ($mean_{adj}$: -0.18, *P*=0.123)
- GF7 ($mean_{adj}$: 0.13, *P*=0.461)
- TTD in FACT-B TOI of ≥5 points (HR=1.02; 95% CI, 0.61-1.70)

Bjelic-Radisic V, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 310P.

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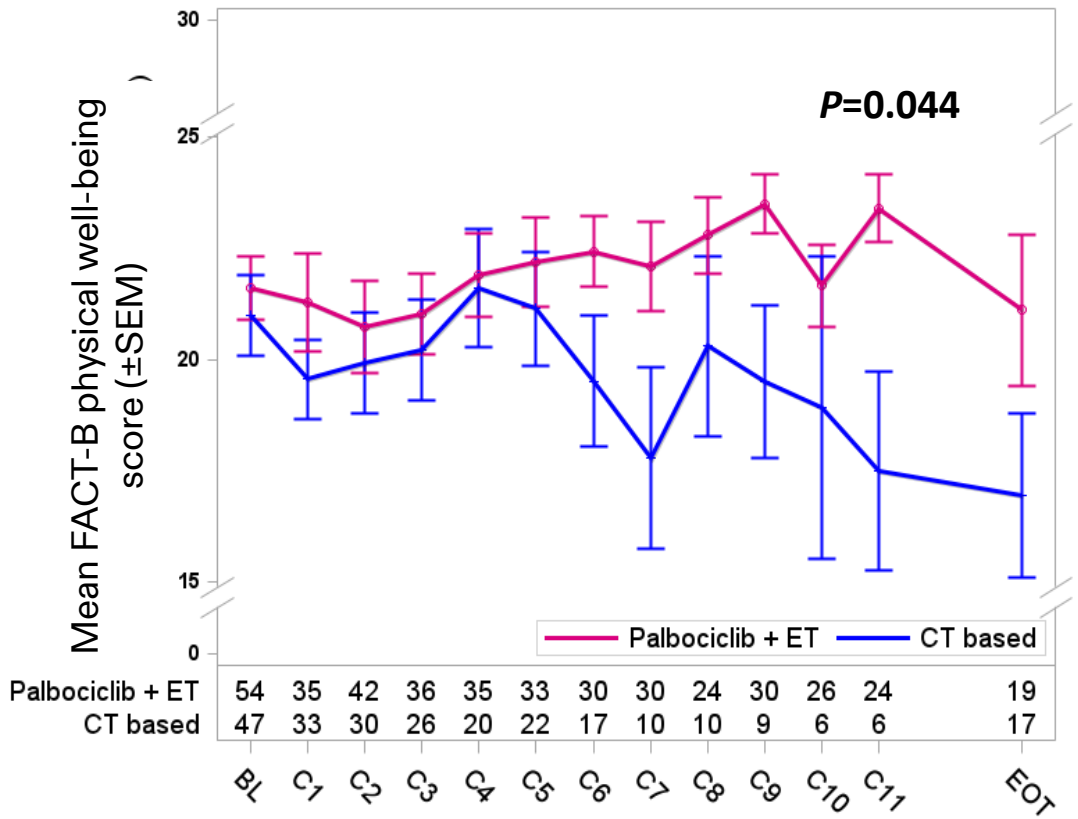
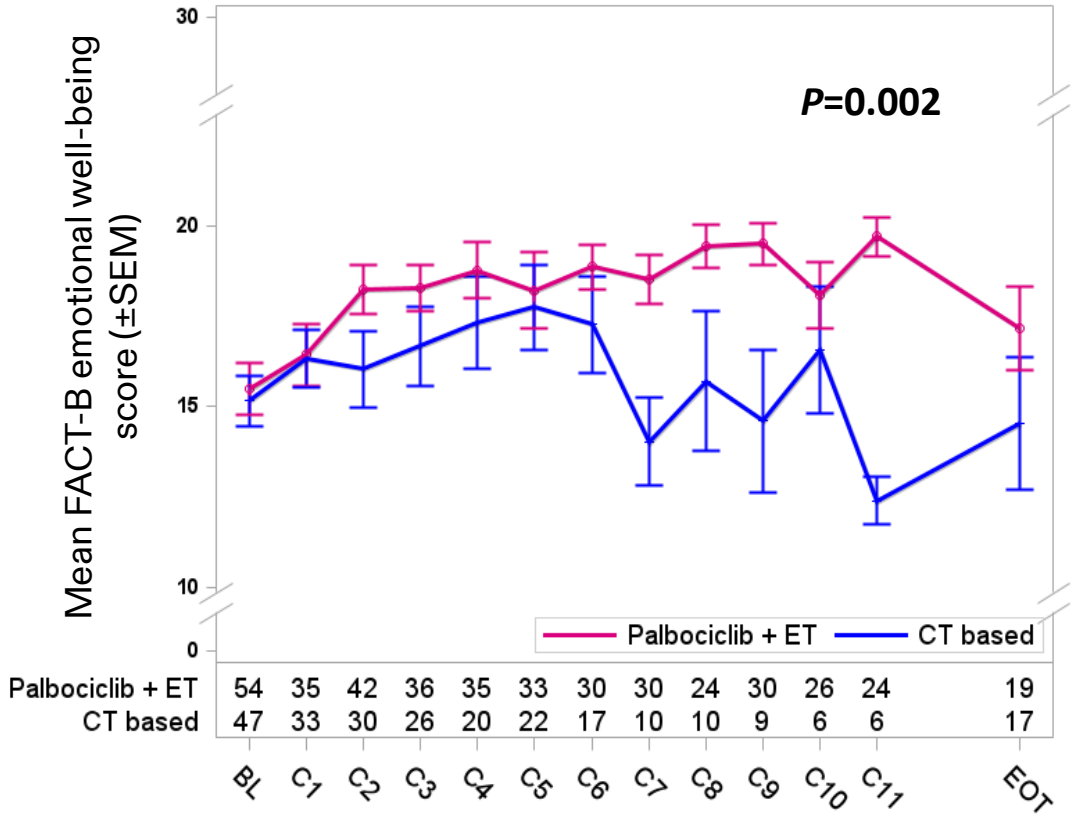
PADMA: QOL—FACT-B Physical and Emotional Well-Being Over Time

Physical Well-Being Over Time, per Treatment Arm



Emotional Well-Being Over Time, per Treatment Arm



Scores on the physical and emotional well-being scales were significantly better in the palbociclib + ET arm than the CT arm

BL=baseline; C=cycle; CT=chemotherapy; EOT=end of treatment; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; QOL=quality of life; SEM=standard error of the mean.

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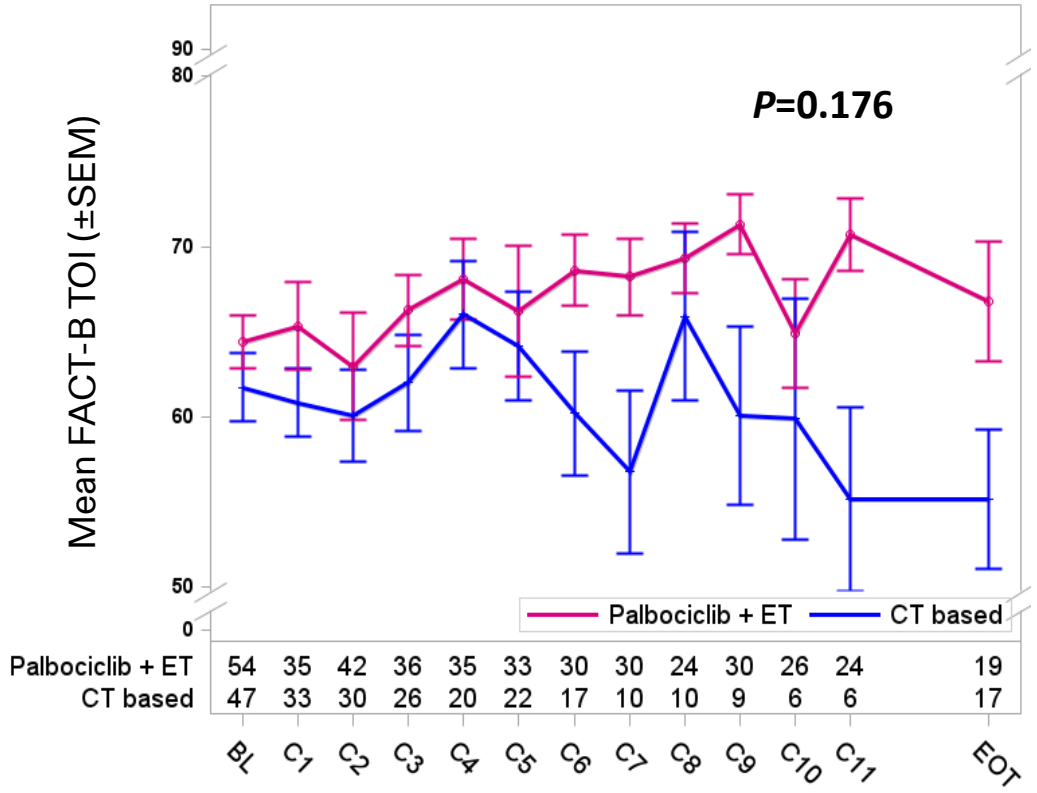
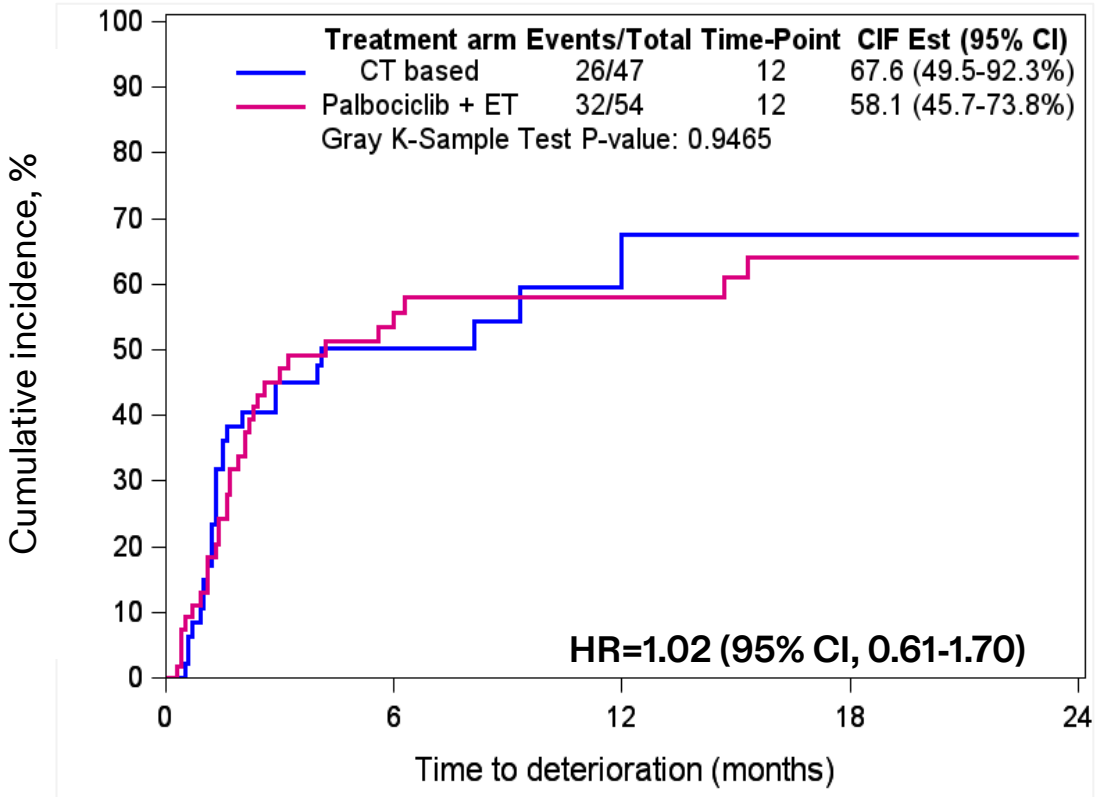
PADMA: QOL—FACT-B TOI and TTD

FACT-B TOI Score Over Time, per Treatment Arm



CUMULATIVE Incidence Function (CIF) Curve of TTD



There were no significant differences in the specific well-being regarding side effects and satisfaction with the QOL ($mean_{adj}$ for GP5: -0.18, *P*=0.123; for GF7: 0.13, *P*=0.461) or in TTD in FACT-B TOI of ≥5 points between treatment arms

BL=baseline; C=cycle; CI=confidence interval; CT=chemotherapy; EOT=end of treatment; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; HR=hazard ratio; QOL=quality of life; SEM=standard error of the mean; TOI=trial outcome index; TTD=time to deterioration.

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PADMA: QOL—Authors' Conclusions

- In this descriptive analysis, the palbociclib + ET combination showed a statistically significant improvement in QOL, particularly in physical and psychological domains, with significant MCIDs in FACT-B, FACT-G, and FACT-B TOI total scores, compared to mono-CT
- In addition to a statistically significant and clinically meaningful improvement in time to treatment failure and a significant PFS benefit in those receiving palbociclib + ET compared to those receiving mono-CT, the current results indicating improved QOL in the palbociclib + ET arm and further highlight the importance of ET + CDK4/6i as first-line therapy in HR+/HER2- MBC

The PALOMA trials did not compare palbociclib + ET with monochemotherapy.[1,2]
Cross-trial comparisons are unreliable and are likely to be confounded due to differences in study design and patient populations.

CDK4/6=cyclin-dependent kinase 4/6; CT=chemotherapy; ET=endocrine therapy; FACT-B=Functional Assessment of Cancer Therapy—Breast; FACT-G=Functional Assessment of Cancer Therapy—General; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; i=inhibitor; MBC=metastatic breast cancer; MCID=minimal clinically important difference; PFS=progression-free survival; QOL=quality of life; TOI=trial outcome index.

1. Finn RS, et al. *N Engl J Med.* 2016;375:1925-1936
2. Turner NC, et al. *N Engl J Med.* 2015;373:209-219

Bjelic-Radisic V, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 310P.

Real-world effectiveness of palbociclib in combination with an aromatase inhibitor in HR+/HER2– bone-only metastatic breast cancer

Adam Brufsky, Rachel M. Layman, Xianchen Liu, Benjamin Li, Lynn McRoy, Aaron Cohen, Melissa Estevez, Paul Cottu, Giuseppe Curigliano, Hope S. Rugo

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Pfizer-Sponsored Study

EM-DEU-plb-0172

RWE: Bone-Only Disease (Flatiron Health Database)—Study Design

Retrospective, observational study

Objective: To compare OS, rwPFS, and TTC of 1L palbociclib + AI versus AI alone in adult patients with HR+/HER2- MBC with bone-only disease in routine clinical practice in the US

Key Eligibility Criteria

- ≥18 years
- HR+/HER2- MBC with bone-only disease
- Initiated 1L treatment with PAL + AI or AI alone between February 2015 and June 2022 (index period)

N=974*

- **PAL + AI (n=538)** — Median follow-up: 31.9 mo
- **AI monotherapy (n=436)** — Median follow-up: 35.8 mo

Study data were from the Flatiron Health EHR-derived database MBC Enhanced Datamart, which represents a probabilistic sample of the overall Flatiron database, comprised of deidentified patient-level structured and unstructured data from ≈280 cancer clinics (≈800 sites of care), representing more than 3 million actively treated patients with cancer in the US

Clinical Outcomes†

- OS, rwPFS, TTC

Statistical Analysis

- Baseline demographics and disease characteristics were summarized via descriptive statistics
- sIPTW (**primary analysis**) was used to balance patient demographics and clinical characteristics
- 1:1 PSM was performed as a sensitivity analysis
- The weighted Cox proportional hazards model was used to compute hazard ratios and corresponding 95% CIs

Observational retrospective analyses cannot establish causality between treatments and outcomes.
Results are not intended to be compared with clinical trials and should be interpreted with caution in the context of the totality of evidence.

*5500 patients were randomly sampled from the EDM; of this sample, 5087 had 1L treatment data manually confirmed via abstraction, and 974 met inclusion criteria for this analysis.

†Patients were assessed from start of PAL + AI or AI to Dec 2022, death, or last medical activity. OS was defined as months from the start of PAL + AI or AI to death. rwPFS was months from start of PAL + AI or AI to death or disease progression, evaluated based on clinical assessment or radiographic scan/biopsy. TTC was months from start of PAL + AI or AI to subsequent chemotherapy.

1L=first-line; AI=aromatase inhibitor; CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; MBC=metastatic breast cancer; OS=overall survival; PAL=palbociclib; PSM=propensity score matching; rwPFS=real-world progression-free survival; sIPTW=stabilized inverse probability of treatment weighting; TTC=time to chemotherapy.

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RWE: Bone-Only Disease (Flatiron Health Database)—Patient Characteristics (1 of 4)

Characteristics	Unadjusted analysis			After sIPTW		
	PAL + AI (n=538)	AI alone (n=436)	Standard difference	PAL + AI (n=537)	AI alone (n=435)	Standard difference
Age at MBC diagnosis, y*						
Mean (SD)	64.8 (11.6)	70.1 (10.9)	−0.4785	66.9 (11.5)	67.7 (11.4)	−0.0705
Mean (IQR)	66 (15)	71 (16)	—	68 (17)	69 (17)	—
Age group, n (%)						
18-49 y	55 (10.2)	20 (4.6)	0.2165	41 (7.6)	31 (7.1)	0.0177
50-64 y	196 (36.4)	108 (24.8)	0.2551	168 (31.3)	136 (31.3)	0.0007
65-74 y	168 (31.2)	129 (29.6)	0.0356	164 (30.6)	134 (30.9)	−0.0052
75+ y	119 (22.1)	179 (41.1)	−0.4161	164 (30.5)	134 (30.7)	−0.0055
Sex, n (%)*						
Male	5 (0.9)	8 (1.8)	−0.0776	7 (1.3)	6 (1.4)	−0.0058
Female	533 (99.1)	428 (98.2)	—	530 (98.7)	429 (98.6)	—

*Variable used in propensity score estimation.

AI=aromatase inhibitor; IQR=interquartile range; MBC=metastatic breast cancer; PAL=palbociclib; RWE=real-world evidence; SD=standard deviation; sIPTW=stabilized inverse probability of treatment weighting.

- Patients in the PAL + AI group were younger than those in the AI-alone group
- Following sIPTW, baseline patient demographics and disease characteristics were well balanced between the 2 treatment groups

Observational retrospective analyses are not intended for direct comparisons to clinical trials.

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RWE: Bone-Only Disease (Flatiron Health Database)—Patient Characteristics (2 of 4)

Characteristics	Unadjusted analysis			After sIPTW		
	PAL + AI (n=538)	AI alone (n=436)	Standard difference	PAL + AI (n=537)	AI alone (n=435)	Standard difference
Race, n (%)*						
White	374 (69.5)	293 (67.2)	0.0498	367 (68.3)	297 (68.2)	0.0026
Black	43 (8.0)	45 (10.3)	−0.0808	48 (9.0)	40 (9.1)	−0.0047
Other†	121 (22.5)	98 (22.5)	0.0003	122 (22.7)	99 (22.7)	0.0003
Practice type, n (%)						
Academic	126 (23.4)	72 (16.5)	0.1734	113 (21.0)	92 (21.2)	−0.0053
Community	412 (76.6)	364 (83.5)	—	424 (79.0)	343 (78.8)	—
Insurance, n (%)						
Commercial + any other	182 (33.8)	163 (37.4)	−0.0743	193 (36.0)	155 (35.6)	0.0081
Commercial	193 (35.9)	123 (28.2)	0.1648	180 (33.6)	127 (29.3)	0.0935
Medicare	28 (5.2)	31 (7.1)	−0.0793	29 (5.4)	31 (7.1)	−0.0704
Medicaid	6 (1.1)	6 (1.4)	−0.0235	5 (1.0)	6 (1.3)	−0.0319
Other payer type	129 (24.0)	113 (25.9)	−0.0448	129 (24.0)	116 (26.7)	−0.0618

- Following sIPTW, baseline patient demographics and disease characteristics were well balanced between the 2 treatment groups

Observational retrospective analyses are not intended for direct comparisons to clinical trials.

*Variable used in propensity score estimation. †Other also includes Asian, Hispanic, or Latino.
AI=aromatase inhibitor; PAL=palbociclib; RWE=real-world evidence; sIPTW=stabilized inverse probability of treatment weighting.

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RWE: Bone-Only Disease (Flatiron Health Database)—Patient Characteristics (3 of 4)

Characteristics	Unadjusted analysis			After sIPTW		
	PAL + AI (n=538)	AI alone (n=436)	Standard difference	PAL + AI (n=537)	AI alone (n=435)	Standard difference
Disease stage at initial diagnosis, n (%)						
I	60 (11.2)	66 (15.1)	−0.1181	74 (13.7)	61 (14.1)	−0.0104
II	131 (24.3)	108 (24.8)	−0.0098	129 (24.1)	102 (23.5)	0.0135
III	75 (13.9)	68 (15.6)	−0.0467	79 (14.6)	65 (15.0)	−0.0097
IV	240 (44.6)	156 (35.8)	0.1808	216 (40.3)	175 (40.1)	0.0040
Not documented	32 (5.9)	38 (8.7)	−0.1063	39 (7.2)	32 (7.3)	−0.0025
ECOG PS, n (%)*						
0	189 (35.1)	111 (25.5)	0.2116	166 (31.0)	134 (30.9)	0.0022
1	132 (24.5)	98 (22.5)	0.0486	129 (24.0)	104 (23.9)	0.0030
≥2	67 (12.5)	70 (16.1)	−0.1032	73 (13.7)	60 (13.8)	−0.0041
Not documented	150 (27.9)	157 (36.0)	−0.1750	168 (31.3)	137 (31.4)	−0.0018

- Patients in the PAL + AI group had a higher proportion of patients with stage IV disease at diagnosis, and ECOG PS of 0 vs those in the AI alone group
- Following sIPTW, baseline patient demographics and disease characteristics were well balanced between the 2 treatment groups

Observational retrospective analyses are not intended for direct comparisons to clinical trials.

*Variable used in propensity score estimation.

AI=aromatase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; MBC=metastatic breast cancer; PAL=palbociclib; RWE=real-world evidence; sIPTW=stabilized inverse probability of treatment weighting.

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RWE: Bone-Only Disease (Flatiron Health Database)—Patient Characteristics (4 of 4)

Characteristics	Unadjusted analysis			After sIPTW		
	PAL + AI (n=538)	AI alone (n=436)	Standard difference	PAL + AI (n=537)	AI alone (n=435)	Standard difference
Number of metastatic sites, n (%)*,†						
1	518 (96.3)	416 (95.4)	0.0436	516 (96.2)	419 (96.2)	0.0005
2	20 (3.7)	20 (4.6)	—	20 (3.8)	17 (3.8)	—
≥3	0	0	—	0	0	—
Not documented	0	0	—	0	0	—
DFI in years, n (%)*,‡						
De novo	240 (44.6)	156 (35.8)	0.1808	216 (40.3)	175 (40.1)	0.0040
≤1	26 (4.8)	23 (5.3)	−0.0202	29 (5.4)	23 (5.4)	−0.0002
>1-5	83 (15.4)	105 (24.1)	−0.2187	103 (19.2)	86 (19.7)	−0.0117
>5	189 (35.1)	150 (34.4)	0.0153	188 (35.1)	151 (34.6)	0.0100
Not documented	0	2 (0.5)	−0.0960	0	1 (0.2)	−0.0642
NCI Comorbidity Index						
Mean (SD)	0.31 (0.5)	0.41 (0.6)	−0.2002	0.33 (0.5)	0.38 (0.6)	−0.0984

- Patients in the palbociclib + AI group had a higher proportion of patients with de novo MBC than those in the AI alone group
- Following sIPTW, baseline patient demographics and disease characteristics were well balanced between the 2 treatment groups

*Variable used in propensity score estimation. †Multiple metastases at the same site were counted as 1 site (eg, if a patient had 3 bone metastases in the spine, it was considered only 1 site). ‡Defined as the interval from initial breast cancer diagnosis to MBC diagnosis. AI=aromatase inhibitor; DFI=disease-free interval; MBC=metastatic breast cancer; NCI=National Cancer Institute; PAL=palbociclib; SD=standard deviation; sIPTW=stabilized inverse probability of treatment weighting.

Observational retrospective analyses are not intended for direct comparisons to clinical trials.

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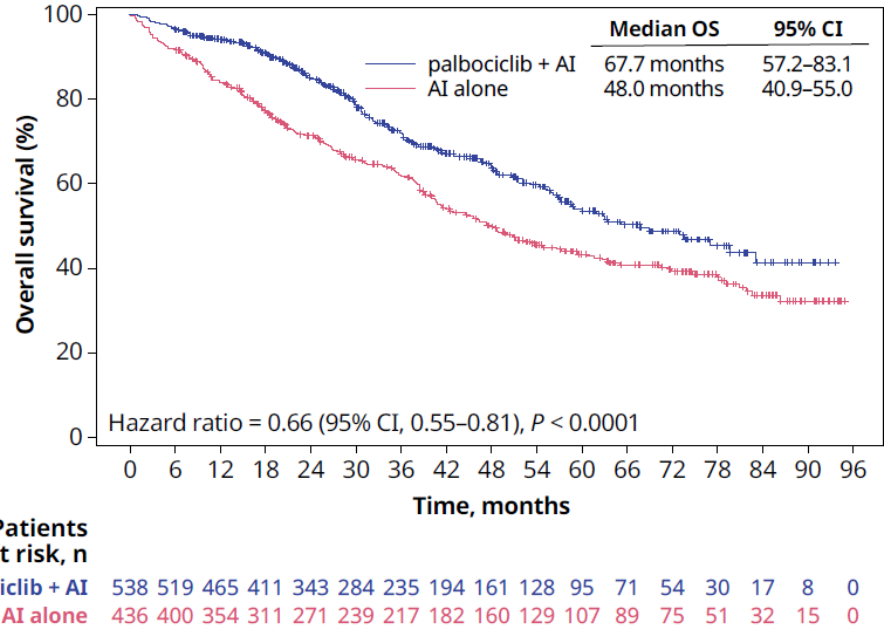
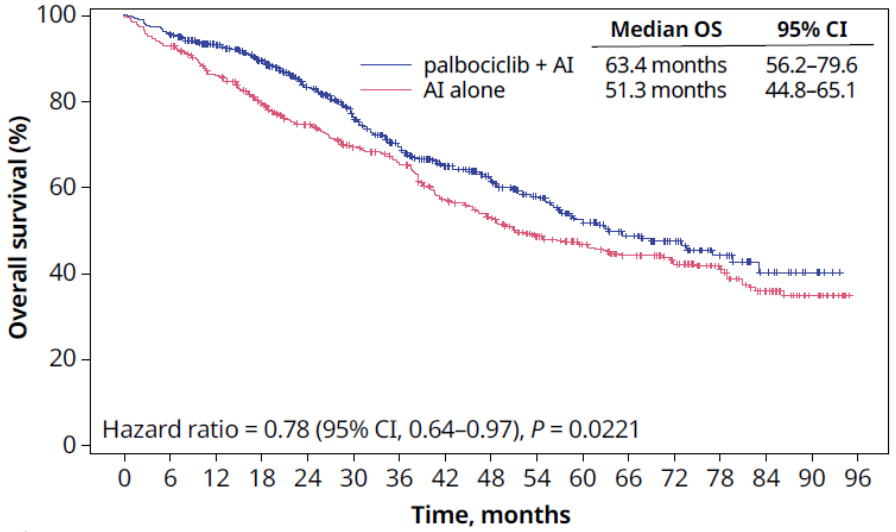
RWE: Bone-Only Disease (Flatiron Health Database)—Overall Survival

Unadjusted Analysis



Patients at risk, n																	
palbociclib + AI	538	519	465	411	343	284	235	194	161	128	95	71	54	30	17	8	0
AI alone	436	400	354	311	271	239	217	182	160	129	107	89	75	51	32	15	0

After sIPTW (Primary Analysis)



Patients at risk, n																	
palbociclib + AI	537	513	457	400	330	270	224	185	155	123	92	68	50	28	16	7	0
AI alone	435	405	361	320	283	253	229	188	167	138	116	98	80	55	34	15	0

- PAL + AI was associated with a significantly longer OS than AI alone, in both the unadjusted analysis (HR=0.66, *P*<0.0001) and after sIPTW (HR=0.78, *P*=0.0221), resulting in a 22% reduction in the risk of death in the primary analysis (sIPTW)*

Observational retrospective analyses cannot establish causality between treatments and outcomes.
Results are not intended to be compared with clinical trials and should be interpreted with caution in the context of the totality of evidence.

*PSM sensitivity analyses were similar to the primary sIPTW analysis. Data not shown. AI=aromatase inhibitor; CI=confidence interval; OS=overall survival; PAL=palbociclib; PSM=propensity score matching; RWE=real-world evidence; sIPTW=standardized inverse probability of treatment weighting.

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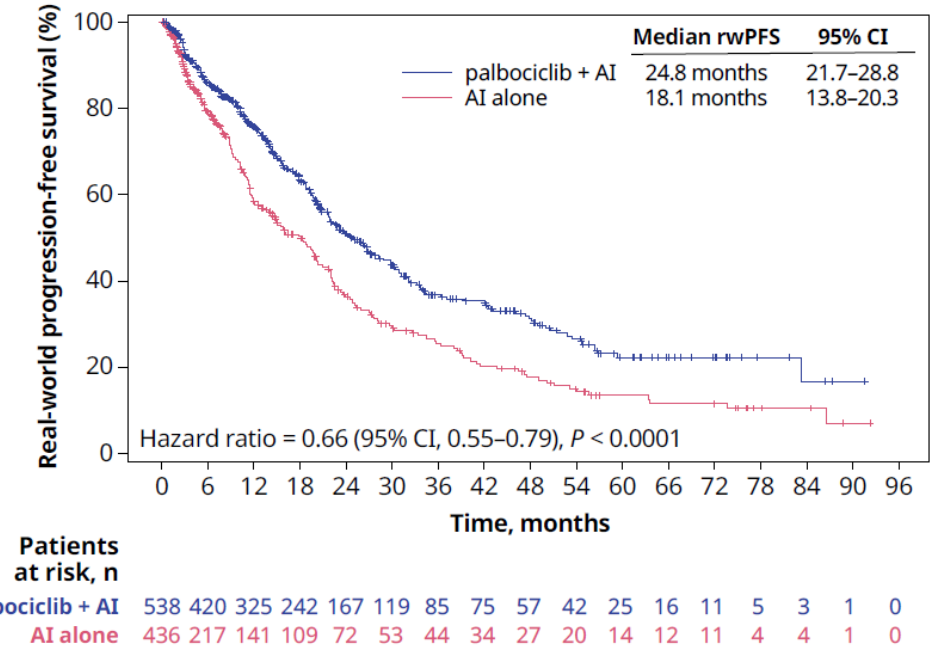
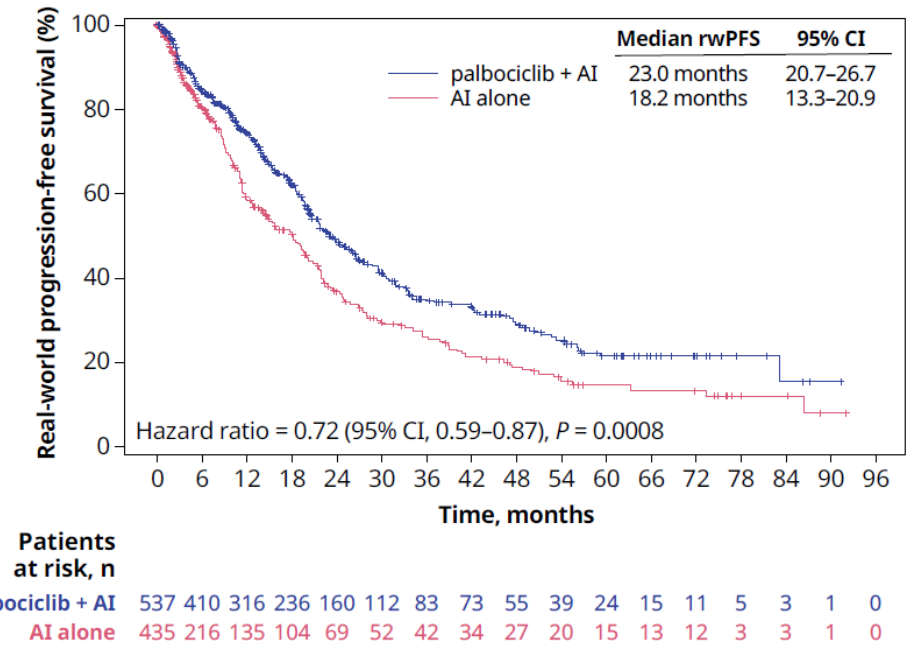
RWE: Bone-Only Disease (Flatiron Health Database)—rwPFS

Unadjusted Analysis



Patients at risk, n																
palbociclib + AI	538	420	325	242	167	119	85	75	57	42	25	16	11	5	3	1	0
AI alone	436	217	141	109	72	53	44	34	27	20	14	12	11	4	4	1	0

After sIPTW



Patients at risk, n																
palbociclib + AI	537	410	316	236	160	112	83	73	55	39	24	15	11	5	3	1	0
AI alone	435	216	135	104	69	52	42	34	27	20	15	13	12	3	3	1	0

- rwPFS was significantly longer with PAL + AI than with AI alone, in both the unadjusted analysis (HR=0.66, *P*<0.0001) and after sIPTW (HR=0.72, *P*=0.0008), resulting in a 28% reduction in the risk of disease progression after sIPTW*

Observational retrospective analyses cannot establish causality between treatments and outcomes.
Results are not intended to be compared with clinical trials and should be interpreted with caution in the context of the totality of evidence.

*PSM sensitivity analyses were similar to the primary sIPTW analysis. Data not shown.

AI=aromatase inhibitor; CI=confidence interval; PAL=palbociclib; PSM=propensity score matching; RWE=real-world evidence; rwPFS=real-world progression-free survival; sIPTW=standardized inverse probability of treatment weighting.

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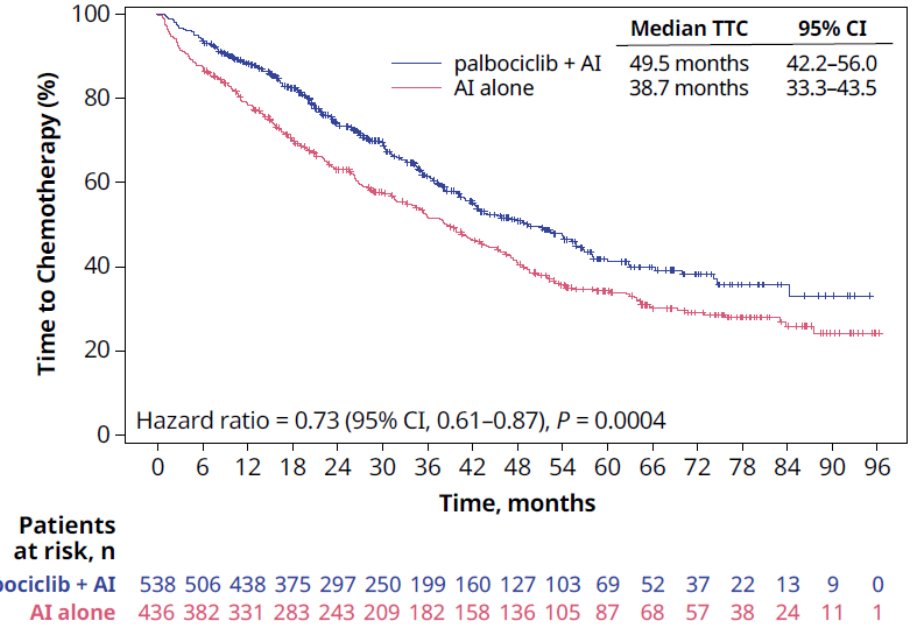
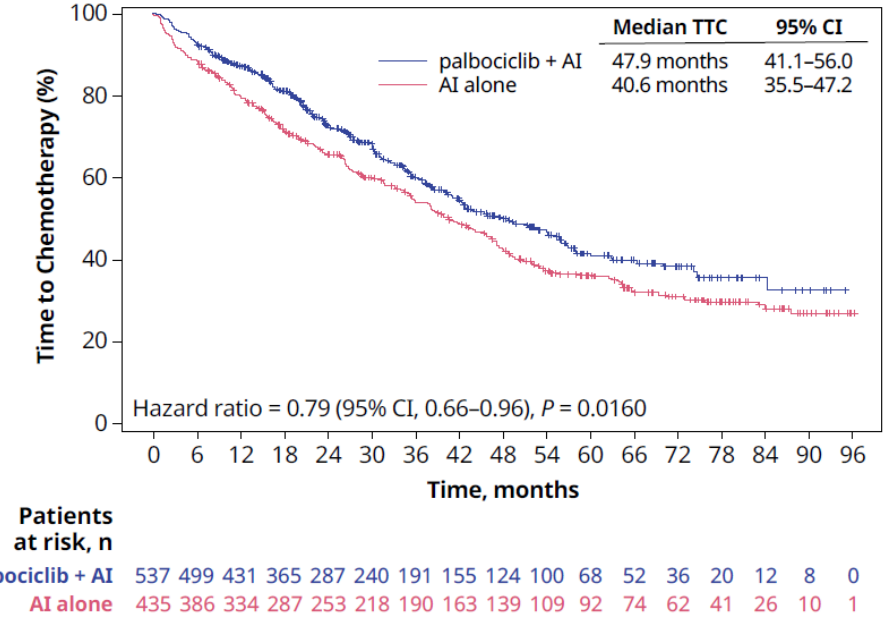
RWE: Bone-Only Disease (Flatiron Health Database)—Time to Chemotherapy

Unadjusted Analysis



Patients at risk, n																
palbociclib + AI	538	506	438	375	297	250	199	160	127	103	69	52	37	22	13	9	0
AI alone	436	382	331	283	243	209	182	158	136	105	87	68	57	38	24	11	1

After sIPTW



Patients at risk, n																
palbociclib + AI	537	499	431	365	287	240	191	155	124	100	68	52	36	20	12	8	0
AI alone	435	386	334	287	253	218	190	163	139	109	92	74	62	41	26	10	1

- PAL + AI was associated with a significantly longer median than AI alone, in both the unadjusted analysis (HR=0.73, *P*=0.0004) and after sIPTW (HR=0.79, *P*=0.0160), resulting in a 21% reduction in the risk of subsequent chemotherapy (sIPTW)*

Observational retrospective analyses cannot establish causality between treatments and outcomes.
Results are not intended to be compared with clinical trials and should be interpreted with caution in the context of the totality of evidence.

*PSM sensitivity analyses were similar to the primary sIPTW analysis. Data not shown.

AI=aromatase inhibitor; CI=confidence interval; PAL=palbociclib; PSM=propensity score matching; RWE=real-world evidence; sIPTW=standardized inverse probability of treatment weighting; TTC=time to chemotherapy.

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RWE: Bone-Only Disease (Flatiron Health Database)—Limitations

- Inherent to real-world databases, some variables might be incomplete, missing, or inaccurate
- Treatments were not randomly assigned; instead, they were selected for each patient according to the treating physician's clinical judgement and experience
- Disease progression was not evaluated according to a predefined schedule, nor were standardized clinical trial assessments used, such as the RECIST
  - As a result, rwPFS data relied on the treating physician's interpretation of pathology reports and scan results
- Due to the retrospective, observational design of this study, no causality between treatments and outcomes can be inferred
- sIPTW and PSM were used to balance patient characteristics between treatment groups, but the effect of unmeasured potential confounders could not be adjusted for in these analyses
- Since this analysis was based on data collected in the US, the results may not be generalizable to other patient populations

PSM=propensity score matching; RECIST=Response Evaluation Criteria in Solid Tumors; rwPFS=real-world progression-free survival; sIPTW=stabilized inverse probability of treatment weighting.

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RWE: Bone-Only Disease (Flatiron Health Database)—Authors' Conclusions

- First-line palbociclib + AI vs AI alone was significantly associated with prolonged OS, rwPFS, and TTC in patients with HR+/HER2- bone-only MBC in routine US clinical practice
- These findings support the use of first-line palbociclib in combination with ET for HR+/HER2- bone-only MBC

AI=aromatase inhibitor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; MBC=metastatic breast cancer; OS=overall survival; rwPFS=real-world progression-free survival; TTC=time to chemotherapy.

Brufsky A, et al. Presented at ESMO BC; May 14-17, 2025; Munich, Germany. Poster 319P.

Kinetics and determinants of *bESR1*^{mut} under AI and palbociclib in patients with HR+/HER2- mBC in the PADA-1 trial

Luc Cabel, Thomas Bachelot, Anne-Claire Hardy-Bessard, Barbara Pistilli, Florence Dalenc, Thibault de La Motte Rouge, Céline Callens, Renaud Sabatier, Jean-Sebastien Frenel, Sylvain Ladoire, Julien Grenier, Laetitia Stefani, Helene Vegas, Ivan Bieche, Suzette Delaloge, Anne Pradines, Jerome Lemonnier, Frédérique Berger, Francois-Clement Bidard

Presenting Author: Francois-Clement Bidard, MD, PhD
Institut Curie, Paris, France

Clinical Research Collaboration

EM-DEU-plb-0172

PADA-1: Study Design

Multicenter, international, open-label, controlled, phase 3 trial

Objective: Proof-of-concept, first-line academic CDK4/6i trial to detect[1,2] and target rising *ESR1*m before tumor progression to delay tumor progression and maximize exposure to CDK4/6i in patients with HR+/HER2- MBC

HR+: ER or PR ≥10% by IHC

Step 1

Patients (N=1017)
- 1L HR+/HER2- MBC
- AI sensitive

AI + palbociclib

b*ESR1*m detection*

Patients *ESR1*ND PD discontinued trial (n=395)

Step 2

b*ESR1*m detected† (n=283)

Rising *ESR1*m and synchronous PD → Discontinue trial (n=71)

Rising *ESR1*m and **no** synchronous PD (n=212‡) → Eligible for randomization → R
- AI + palbociclib mPFS=5.7 mo[3]
- Fulvestrant + palbociclib mPFS=11.9 mo[3]

Stratified HR=0.61[3]

Step #3 (optional)

Ful + palbociclib

mPFS=3.5 mo in selected pts

First evidence to support *ESR1*mut monitoring during the first-line
Understanding the kinetics of *ESR1*mut could help optimize *ESR1*mut screening§

*Screening for *ESR1*m occurred at inclusion/1 month, then every 2 months after. Screening for *ESR1*m was discontinued in step 1 once the target number of randomized patients was reached. 399 patients were either still on AI + palbociclib at time of *ESR1*mut screening discontinuation or dropped out. †*ESR1*mut detection rate was 41.9% (calculated as: 283 with *bESR1* detected/(1017 total patients – 339 dropped out or discontinued). ‡212 patients were eligible to randomize in step 2 in this analysis. In the primary analysis, 84 patients received palbociclib + AI and 88 patients received palbociclib + fulvestrant.[3] In the primary analysis, patients who received palbociclib + fulvestrant had a mPFS of 11.9 months vs 5.7 months for patients who received palbociclib + AI (stratified hazard ratio=0.61).[3] §Authors' conclusion.

1L=first-line; AI=aromatase inhibitor; b*ESR1*=*ESR1* in blood; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1; *ESR1*ND PD=patient with *ESR1*mut not detected and progressive disease; Ful=fulvestrant; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IHC=immunohistochemistry; m=mutation; MBC=metastatic breast cancer; mPFS=median progression-free survival; PD=progressive disease; PR=progesterone receptor; R=randomization.

1. Jeannot E, et al. *Oncogene*. 2020;39:2987-2995. 3
2. Callens C, et al. *Anal Chem*. 2022;94:6297-6303.
3. Bidard F-C, et al. *Lancet Oncol*. 2022;23:1367-1377.
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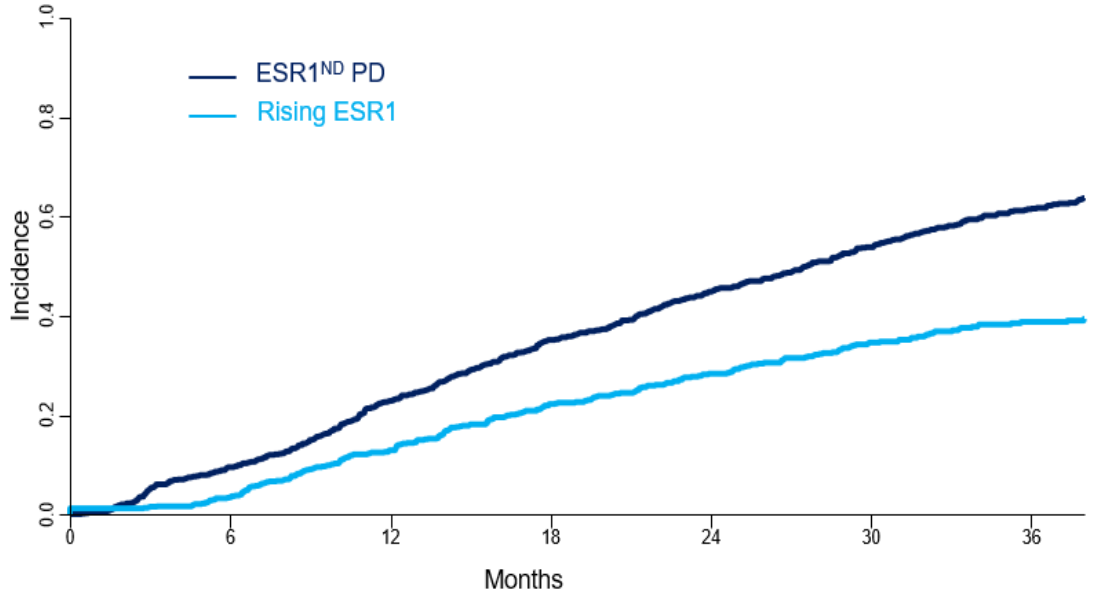
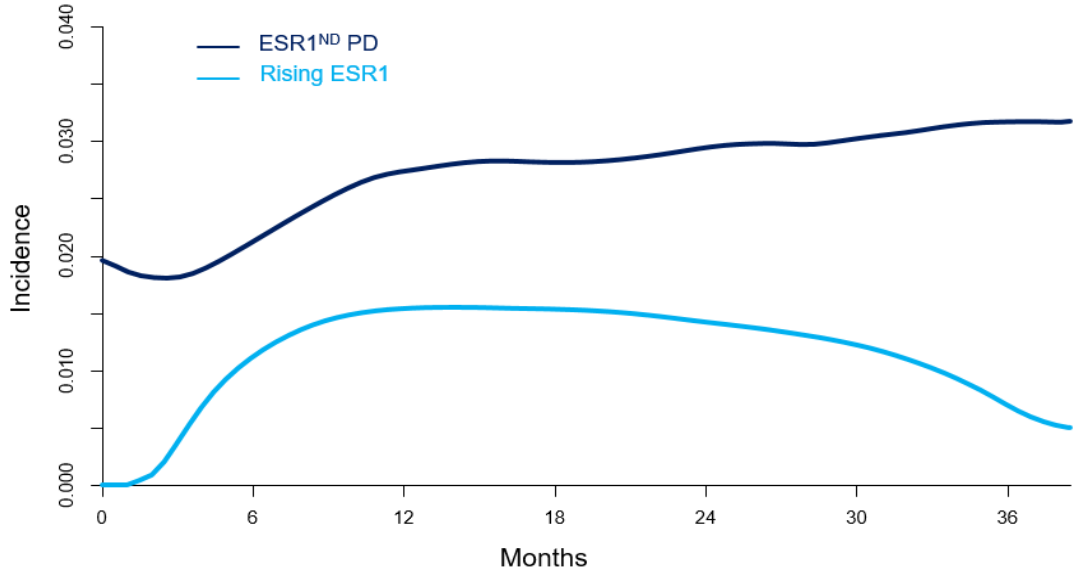
PADA-1: Cumulative and Instantaneous Incidence of *ESR1*m

Cumulative Incidence



Bell-shaped curve
Fewer mutations detected (vs *ESR1*ND PD) before 6 mo and after 30 mo

Instantaneous Incidence



Results compatible with the selection of a minor pre-existing mutant subclone, similar to emerging *KRAS*m kinetics in mCRC[1]

b*ESR1*=estrogen receptor 1 in blood; *ESR1*=estrogen receptor 1; *ESR1*ND PD=patient with *ESR1*mut not detected and progressive disease; *KRAS*=Kirsten rat sarcoma viral oncogene homolog; m=mutation; mCRC=metastatic colorectal cancer; PD=progressive disease.

1. Diaz LA, et al. *Nature.* 2012;486:537-540.

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PADA-1: Factors Modulating the Relative Incidence of *ESR1*m

Risk of *ESR1*m Being Detected vs *ESR1*ND PD

Multivariate analysis	**OR (95% CI)** >1 = increased incidence
Age, per +10 y	**0.79** (0.69-0.90)
ER % IHC, per +10%	**1.12** (1.01-1.26)
Sites of metastasis	
No bone metastasis	1
Bone + other site	**2.08** (1.30-3.38)
Bone only	**2.67** (1.52-4.76)
Elevated LDH at inclusion	**1.58** (1.10-2.27)

Explanatory Hypotheses

BC oncogenes is more dependent on high estrogen/high ER expression
Suggests an "oncogenic" addiction

Something specific about bone mets biology?
Or later detection of PD by imaging?
In-line with FALCON results

High tumor burden ➔ more ctDNA shed

BC=breast cancer; b*ESR1*m=estrogen receptor 1 mutation in blood; CI=confidence interval; ctDNA=circulating tumor DNA; ER=estrogen receptor; *ESR1*=estrogen receptor 1; *ESR1*ND PD=patient with *ESR1*mut not detected and progressive disease; IHC=immunohistochemistry; LDH=lactate dehydrogenase; mets=metastases; OR=objective response; PD=progressive disease.

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PADA-1: Factors Governing Synchronous PD vs non-PD When *ESR1*m is Detected

Risk of Synchronous PD vs Non-PD

Multivariate analysis	OR (95% CI) >1 = increased incidence of PD
Age, per +10 y	0.77 (0.60-0.90)
Tumor grade, 3 vs 1	2.56 (0.90-8.4)
Metastasis-free interval	
de novo stage IV	1
>3 years	6.61 (2.3-20.8)
Sites of metastasis	
No Bone	1
Bone + other	0.34 (0.16-0.75)
Bone only	0.21 (0.08-0.55)

Explanatory Hypotheses

Tumor growth kinetics/endocrine resistance

Limited sensitivity of imaging for PD in bone mets

Something specific about bone mets biology?

b*ESR1*m=estrogen receptor 1 mutation in blood; CI=confidence interval; *ESR1*=estrogen receptor 1; mets=metastases; OR=objective response; PD=progressive disease.

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PADA-1: Authors' Conclusions

- **Emergence of *ESR1*m during AI + CDK4/6i given in first-line**
  - Overall incidence of **≈40%** before or at progression, but incidence is **uneven over time** (bell-shaped curve)
  - Factors associated with *ESR1*m include **age, bone metastases, ER%**, and **baseline LDH**
  - **Interception** of *ESR1*m before PD is easier in MBC with **bone metastases** and **low proliferation**

➔ **These results may inform how to customize *ESR1*m monitoring in the first line***

- **Biologically**, results suggest that *ESR1* mutations are **selected** rather than acquired and reflect an **oncogenic addiction** to ER signaling

*Cross-validation is needed before implementation in routine practice.

AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1; LDH=lactate dehydrogenase; m=mutation; MBC=metastatic breast cancer; PD=progressive disease.

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