bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

Intro e place in therapy best papers nazionale

Disclosures:

La sottoscritta Sanò Maria Vita

in qualità di relatore

ai sensi dell’art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Pfizer, Novartis, Eli-lilly , Gilead , Istituto Gentili, Daiichi Sankyo, Astra Zeneca

Best paper nazionale 1

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

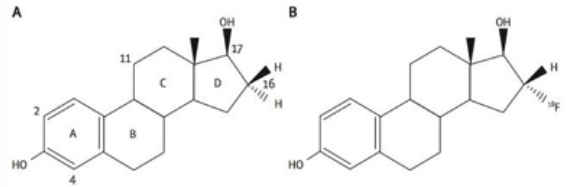
Early prediction of endocrine responsiveness in ER+/HER2-negative metastatic breast cancer (MBC): pilot study with ^{18}F-fluoroestradiol (^{18}F-FES) CT/PET☆

A. Gennari[1,2*], E. Brain[3], A. De Censi[4], O. Nanni[5], R. Wuerstlein[6], A. Frassoldati[7], J. Cortes[8,9], V. Rossi[2], M. Palleschi[10], J. L. Alberini[11], F. Matteucci[12], A. Piccardo[13], G. Sacchetti[14], H. Ilhan[15], F. D'Avanzo[2], B. Ruffilli[1], S. Nardin[16], M. Monti[5], M. Puntoni[17], V. Fontana[18], L. Boni[18] & N. Harbeck[6], on behalf of the ET-FES Collaborative Group†

Background

- ✓ Patients with metastatic HR positive breast cancer typically receive CDK4/6 inhibitor combined with endocrine therapy as their first-line treatment.
- ✓ While most patients see prolonged PFS, **some still experience rapid progression**.
- ✓ Endocrine resistance often stems from the **heterogeneity of ER expression**.
- ✓ Previously, we lacked methods to assess **whole-body ER levels** in advanced tumors.

18F-FES PET/CT : *Provides evaluation of whole-body ER expression*



- [18F]-fluoroestradiol (**18F-FES)** is a radiolabeledform of estrogen that binds to ER
- 18F-**FES- PET/CT** enables non-invasive assessment of **ER expression** and **heterogeneity** in ABC lesions.
- 18F-FES detects ER that is **functional** for ligand binding
- This information may guide therapy selection , potentially reducing the use of **ineffective endocrine therapies** in HR+/HER2- mBC.
- 18F-FES PET/TC is approved by the FDA as a diagnostic agent “for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

J Nucl Med. 2016 Aug;57(8):1269-75.
Clin Nucl Med. 2017 Jun;42(6):421-427.

Appropriate Use Criteria for Estrogen Receptor-Targeted PET Imaging with 18F-FES

SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

Clinical Scenarios for Breast Cancer

Scenario #	Description	Appropriateness	Score
1	Diagnosing primary breast cancer	Rarely Appropriate	2
2	Diagnosing malignancy of unknown primary when a biopsy is not feasible or is nondiagnostic	May be Appropriate	5
3	Routine staging of the primary tumor (T staging)	Rarely Appropriate	1
4	Routine staging of axillary nodes	Rarely Appropriate	3
5	Routine staging of extra-axillary nodes and distant metastases	May be Appropriate	5
6	Staging invasive lobular carcinoma and low-grade invasive ductal carcinoma	May be Appropriate	5
7	Assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy	May be Appropriate	5
8	Assessing ER status in lesions that are difficult to biopsy, or when biopsy is nondiagnostic	Appropriate	8
9	After progression of metastatic disease, for considering second line of endocrine therapy	Appropriate	8
10	At initial diagnosis of metastatic disease, for considering endocrine therapy	Appropriate	8
11	At initial diagnosis of primary breast cancer, for considering endocrine therapy	Rarely Appropriate	1
12	Measuring response to therapy	Rarely Appropriate	1
13	Detecting lesions in patients with suspected/known recurrent or metastatic breast cancer	May be Appropriate	5
14	Detecting ER status when other imaging tests are equivocal or suspicious	Appropriate	8

HR+ mBC current options

1st line, endocrine sensitive

Endocrine therapy (ET), with **AI + CDK4/6 inhibitor**

Median PFS: 24 mo. // Overall survival gain → PD

The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with ET for ABC patients vary according to the setting and drug.

They are the following, with the current available data and follow-up:

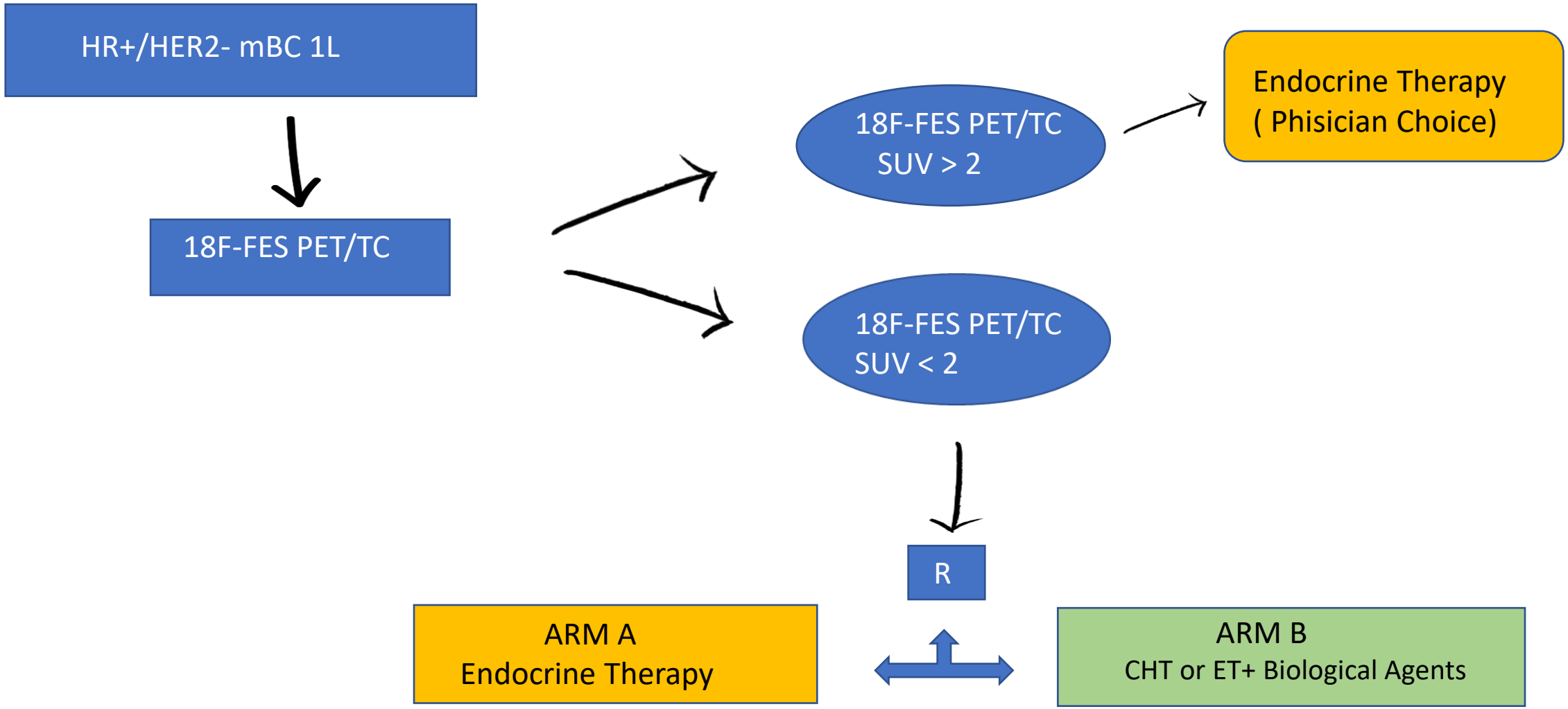
- Ribociclib + ET 1st line Pre-menopausal; ESMO-MCBS: 5
- Ribociclib + AI 1st line Post-menopausal; ESMO-MCBS: 4
- Palbociclib + AI 1st line; ESMO-MCBS: 3
- Abemaciclib + AI 1st line; ESMO-MCBS: 3

Patients who don’t benefit from CDK4/6 inhibitors

	patients without clinical benefit	Early progressors
AI-naive		
PALOMA 2	**15%**	**NR**
MONARCH 3	**22%**	**4%**
MONALEESA 2	**20%**	**6%**
AI-pretreated		
PALOMA 3	**33%**	**17%**
MONARCH 2	**28%**	**9%**
AI-naive and AI-pretreated		
MONALEESA 3	**30%**	**10%**
MONALEESA 7	**21%**	**7%**

Finn NEJM 2016; 375: 1925-36; Goetz JClin Oncol 35:3638-3646; 2017; Hortobagyi NEJM 2016: 375: 1738-48; Cristofanilli Lancet Oncol 2016; 17: 425 39; Sledge JCO 2017; 35: 2875-84; Slamon JCO 2018; 36: 2465-72; Tripathy Lancet oncol 2018; 19: 904-15

ET-FES TRIAL


HR+/HER2- mBC 1L
18F-FES PET/TC
18F-FES PET/TC
SUV > 2
Endocrine Therapy
(Phisician Choice)
18F-FES PET/TC
SUV < 2
R
ARM A
Endocrine Therapy
ARM B
CHT or ET+ Biological Agents

Characteristics of patients at baseline

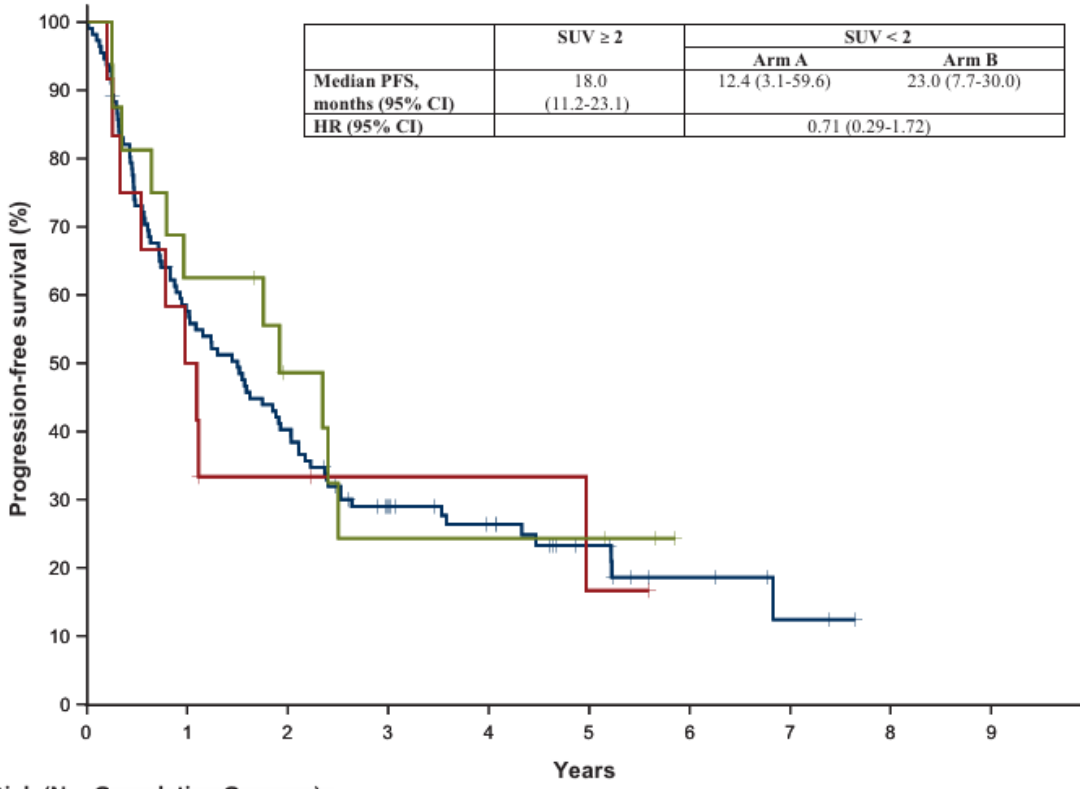
Table 1. Characteristics of the patients at baseline

Patients characteristics	Registered (n = 113) n (%)	Arm A (n = 13) n (%)	Arm B (n = 16) n (%)	Total (n = 142) n (%)
Median age (range), years	66 (36-90)	60 (38-79)	62 (38-87)	65 (36-90)
Menopausal status				
Pre/peri-menopausal	14 (12.4)	2 (15.4)	5 (31.3)	21 (14.8)
Post-menopausal	99 (86.6)	11 (84.6)	11 (68.7)	121 (85.2)
ECOG performance status				
0	89 (77.9)	10 (76.9)	14 (87.5)	113 (79.6)
1	24 (22.1)	3 (23.1)	2 (12.5)	29 (20.4)
Histology				
Ductal	84 (74.3)	12 (92.3)	11 (68.8)	107 (75.4)
Lobular	19 (16.8)	1 (7.7)	4 (25.0)	24 (16.9)
Other	10 (8.8)	—	1 (6.2)	11 (7.7)
Hormone receptor status				
Positive (>1%)	113 (100.0)	13 (100.0)	16 (100.0)	142 (100.0)
ER >50%	100 (88.5)	13 (100.0)	15 (93.7)	128 (90.1)
ER ≤ 50%	10 (8.9)	—	1 (6.3)	11 (7.8)
Missing	3 (2.6)	—	—	3 (2.1)
Disease-free interval				
DFI ≤ 24 months	11 (9.7)	1 (7.7)	1 (6.3)	13 (9.2)
DFI >24 months	75 (66.4)	9 (69.2)	14 (87.5)	98 (69.0)
NA[a]	27 (23.9)	3 (23.1)	1 (6.2)	31 (21.8)
Median (range), months	98.8 (0.3-360.3)	64.9 (4.2-196.3)	141.6 (2.8-272.3)	89.0 (0.3-360.3)
Metastatic *ab initio*	27 (23.9)	3 (23.1)	1 (6.2)	31 (21.8)
prior treatment				
Prior neo/adjuvant ChT	68 (60.2)	9 (69.2)	11 (68.8)	88 (62.0)
Prior adjuvant ET	78 (69.0)	8 (61.5)	13 (81.3)	99 (69.7)
Site of metastases				
Bone only	41 (36.3)	4 (30.8)	5 (31.3)	50 (35.2)
Bone + other	31 (27.4)	3 (23.1)	—	34 (23.9)
Visceral any	38 (33.6)	5 (38.5)	6 (37.5)	49 (34.5)
Soft tissue any	37 (32.7)	5 (38.5)	6 (37.5)	48 (33.8)
Other	8 (7.1)	1 (7.7)	1 (6.3)	10 (7.0)

ChT, chemotherapy; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; ER, estrogen receptor; NA, not applicable.

Results

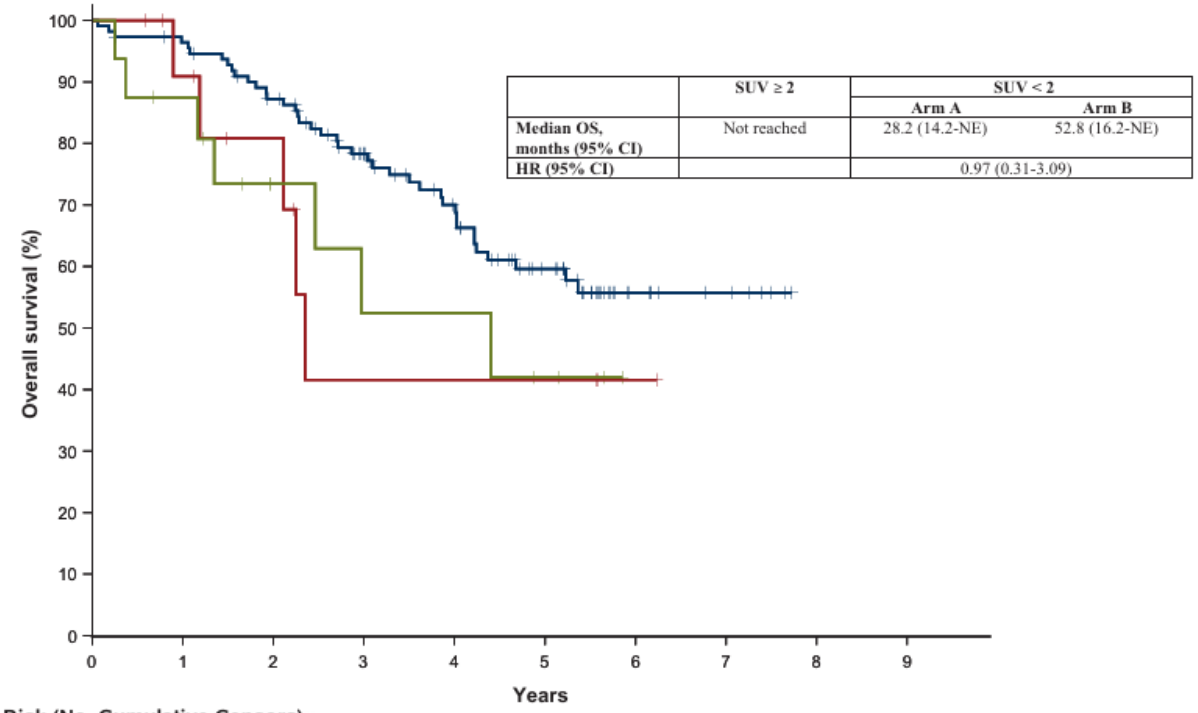
	SUV ≥ 2	SUV < 2	
		Arm A	Arm B
Median PFS, months (95% CI)	18.0 (11.2-23.1)	12.4 (3.1-59.6)	23.0 (7.7-30.0)
HR (95% CI)		0.71 (0.29-1.72)	



No. at Risk (No. Cumulative Censors)

Registered	113 (0)	63 (3)	44 (3)	26 (9)	19 (14)	11 (20)	5 (24)	2 (26)	0 (28)
Arm A	12 (0)	6 (0)	3 (1)	2 (2)	2 (2)	1 (2)	0 (3)		
Arm B	16 (0)	10 (0)	6 (2)	3 (2)	3 (2)	3 (2)	0 (5)		

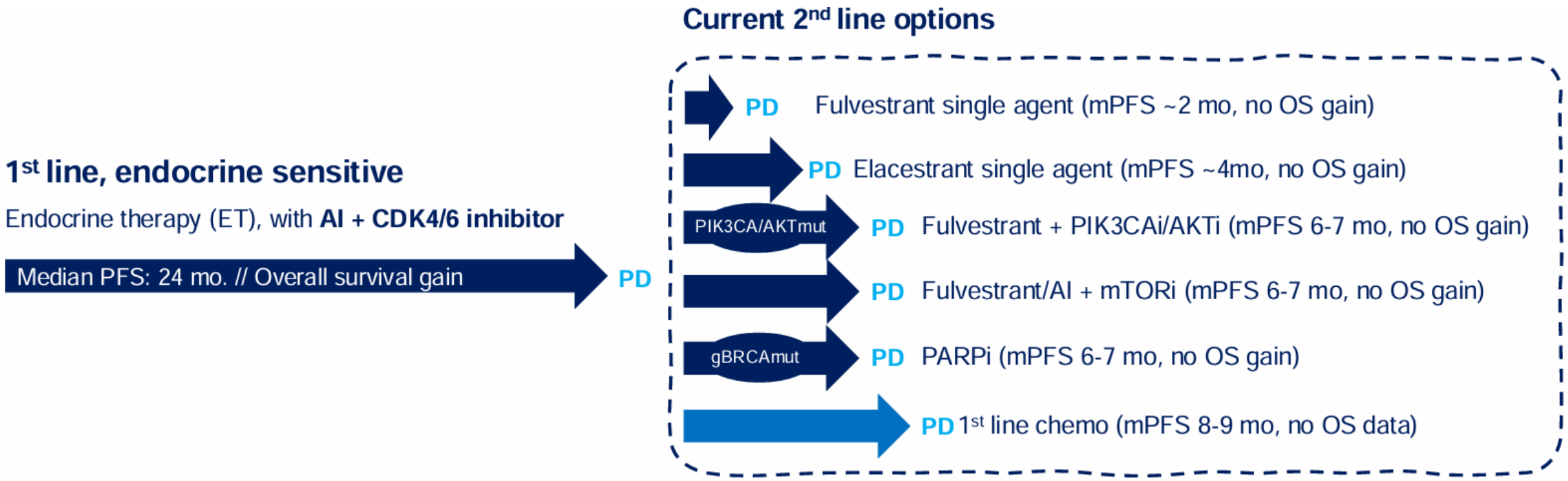
	SUV ≥ 2	SUV < 2	
		Arm A	Arm B
Median OS, months (95% CI)	Not reached	28.2 (14.2-NE)	52.8 (16.2-NE)
HR (95% CI)		0.97 (0.31-3.09)	



No. at Risk (No. Cumulative Censors)

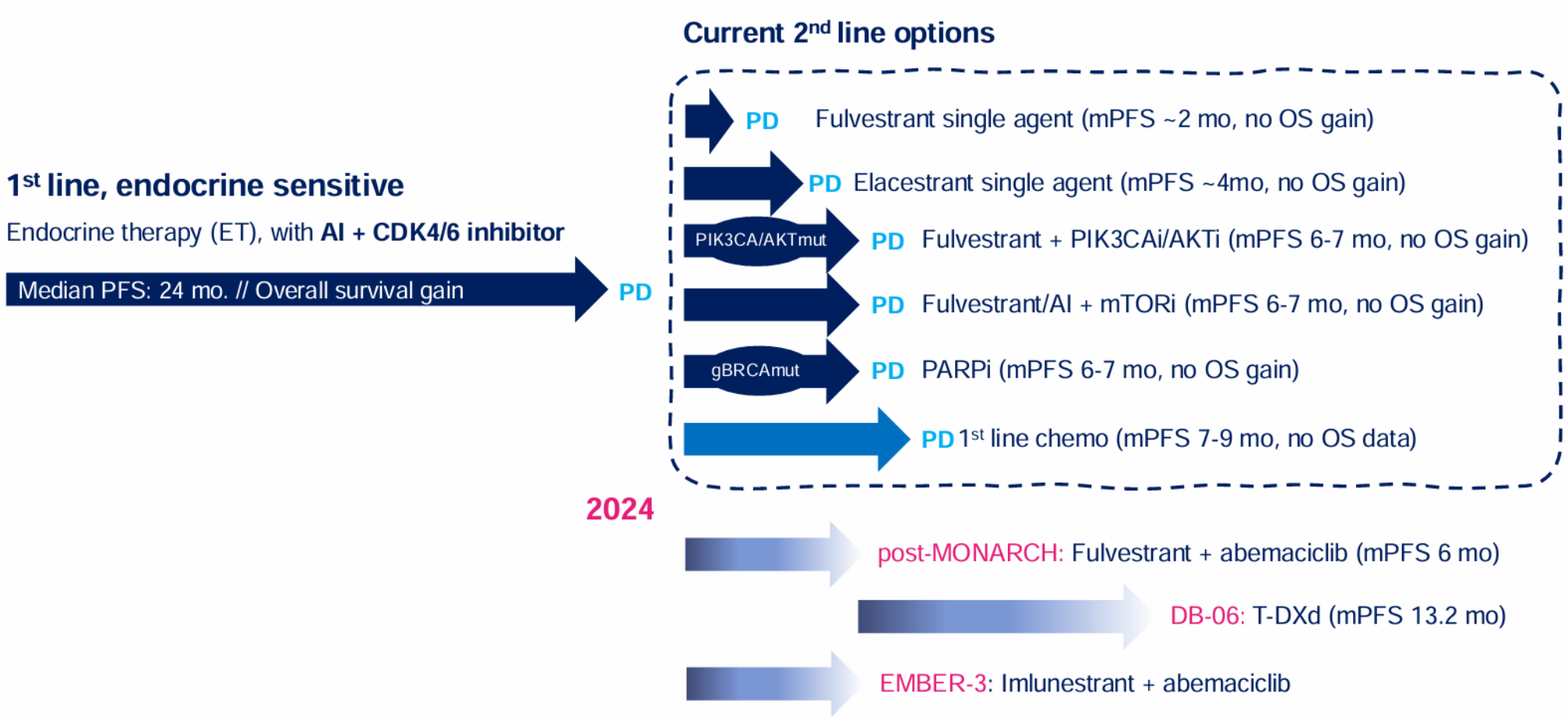
Registered	113 (0)	106 (3)	93 (6)	71 (19)	56 (27)	37 (38)	11 (62)	6 (67)	0 (73)
Arm A	13 (0)	10 (2)	7 (4)	3 (5)	3 (5)	3 (5)	1 (7)	0 (8)	
Arm B	16 (0)	13 (1)	7 (5)	5 (5)	5 (5)	3 (6)	0 (9)		

HR+ mBC current options



F Cardoso et al, The Breast 2024

HR+ mBC : Current options



DESTINY-Breast06 study design and primary results

Phase 3, randomized, multicenter, open-label study[1,2]

Data cutoff: March 18, 2024

Patient population

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) **OR** HER2-ultralow (IHC 0 with membrane staining) status
- Chemotherapy naïve in the mBC setting

Prior lines of therapy

- ≥2 lines ET ± targeted therapy for mBC
  OR
- 1 line for mBC AND
  - Progression ≤6 mo of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 mo of starting adjuvant ET

R 1:1

T-DXd 5.4 mg/kg Q3W (n=436)

TPC (n=430)

Capecitabine, 59.8%; nab-paclitaxel, 24.4%; paclitaxel, 15.8%

HER2-low = 713
HER2-ultralow = 153

Baseline characteristics*

- Median age **58 years**; ECOG PS ≥1 **~42%**
- **De-novo mBC ~31%; liver metastases ~67%; visceral disease ~85%; primary endocrine resistance ~31%**

Primary endpoint

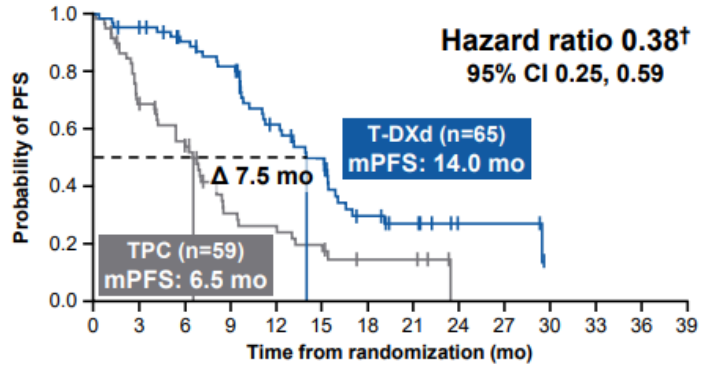
- PFS (BICR) in HER2-low
  - Median **13.2 mo T-DXd** vs **8.1 mo TPC** (hazard ratio 0.62; P<0.0001)†

Secondary endpoints

- PFS (BICR) in ITT (HER2-low + HER2-ultralow)
  - Median **13.2 mo T-DXd** vs **8.1 mo TPC** (hazard ratio 0.64; P<0.0001)‡
- OS
  - Data maturity ~40% at first IA; early trend favoring T-DXd in ITT
- **PFS2 (INV)**
- Safety and tolerability

PFS by time to progression on 1L ET + CDK4/6i and endocrine resistance

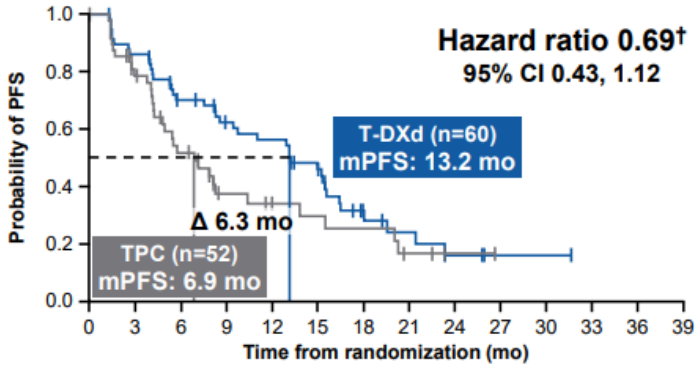
<6-mo 1L TTP*



Number at risk

T-DXd	65	61	53	47	32	25	12	8	3	3	0
TPC	59	38	30	14	12	9	4	4	0	0	0

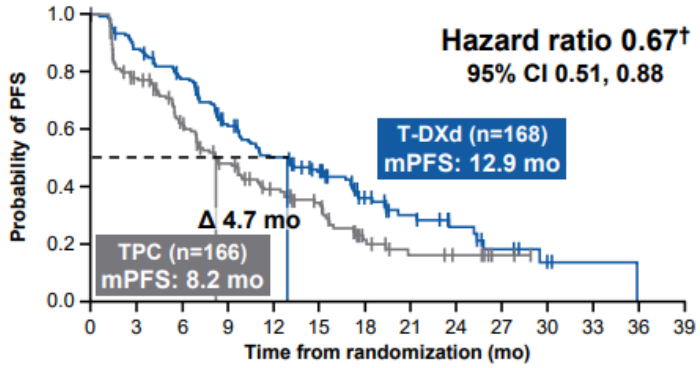
6–12-mo 1L TTP*



Number at risk

T-DXd	60	50	38	31	28	20	9	6	3	1	1	0
TPC	52	34	21	11	8	7	6	3	1	0	0	0

>12-mo 1L TTP*



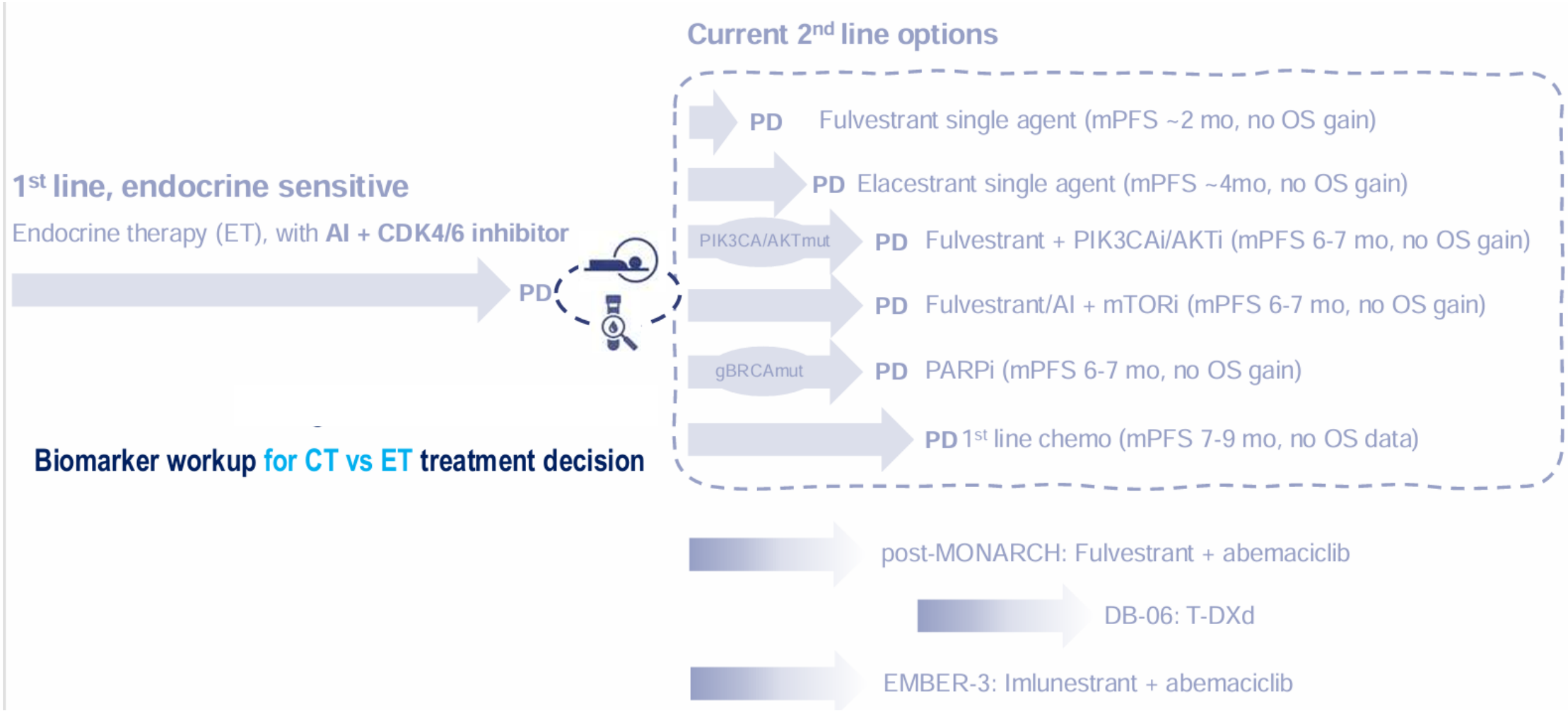
Number at risk

T-DXd	168	146	125	94	74	59	28	17	11	6	2	1	0
TPC	166	114	86	62	44	33	14	8	6	2	0	0	0

	Primary endocrine resistance‡		Secondary endocrine resistance‡	
	T-DXd (n=128)	TPC (n=140)	T-DXd (n=308)	TPC (n=288)
mPFS, mo (95% CI)	12.4 (10.3, 15.2)	6.6 (5.4, 7.4)	13.2 (12.0, 15.5)	9.5 (8.0, 11.1)
PFS hazard ratio (95% CI)	0.57 (0.42, 0.77)†		0.68 (0.55, 0.84)†	

T-DXd improved PFS vs TPC regardless of time to progression on 1L ET + CDK4/6i or type of endocrine resistance

HR+ mBC : Current options



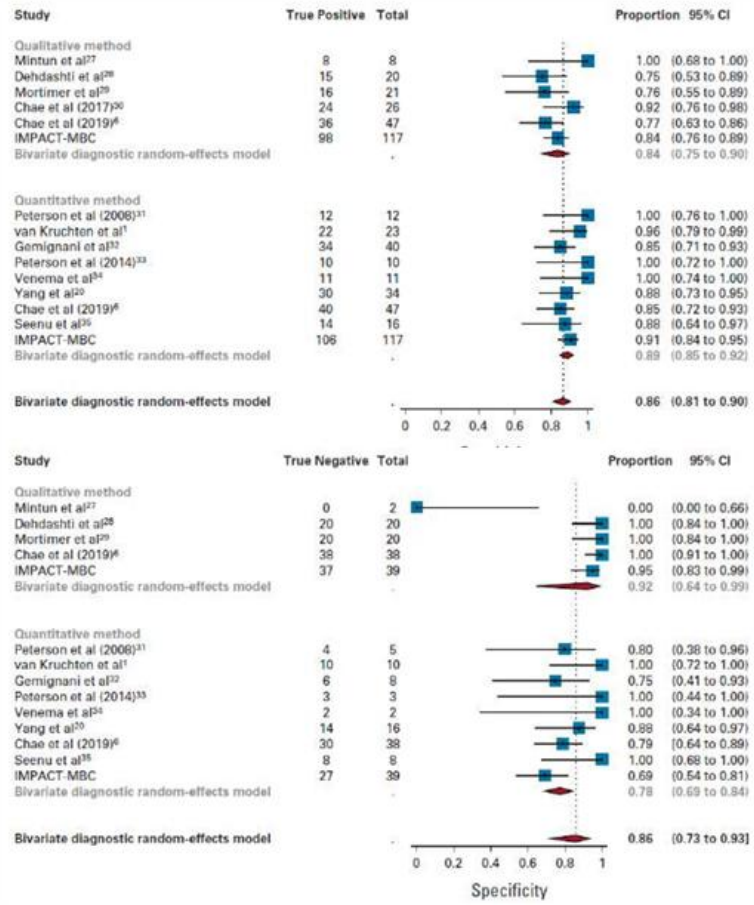
FLUORO-ESTRADIOL PET/CT

original reports

Clinical Validity of 16α-[18F] Fluoro-17β-Estradiol Positron Emission Tomography/Computed Tomography to Assess Estrogen Receptor Status in Newly Diagnosed Metastatic Breast Cancer

Jasper J.L. van Geel, MD[1]; Jorianne Boers, MD[1]; Sjoerd G. Elias, MD, PhD[2]; Andor W.J.M. Glaudemans, MD, PhD[3]; Erik F.J. de Vries, PhD[3]; Geke A.P. Hospers, MD, PhD[1]; Michel van Kruchten, MD, PhD[1]; Evelien J.M. Kuip, MD, PhD[4]; Agnes Jager, MD, PhD[5]; Willemien C. Menke-van der Houven van Oordt, MD, PhD[6]; Bert van der Vegt, MD, PhD[7]; Elisabeth G.E. de Vries, MD, PhD[1]; and Carolina P. Schröder, MD, PhD[6] on behalf of the IMPACT-Metastatic Breast Consortium

	Participants (n = 181)	
	ER IHC Status of the Biopsied Lesion	
Result	**Positive (n = 132)**	**Negative (n = 49)**
Whole-body [18F]FES-PET result		
Positive (n = 135)	125	10
Negative (n = 46)	7	39
Sensitivity	95 (89 to 97)	
Specificity	80 (66 to 89)	
PPV	93 (87 to 96)	
NPV	85 (72 to 92)	



➔ should detect accurately the ~**15-20%** of mBC pts with **ER loss** at time of progression

[18F]fluoroestradiol (FES) PET/CT to guide 2nd line treatment decision in patients with ER+ HER2- advanced breast cancer progressing on 1st line aromatase inhibitor and CDK4/6 inhibitor: early results of the ESTROTIMP trial

François-Clément Bidard[1,2], Romain-David Seban[1], Stephanie van de Ven[3], Sylvain Ladoire[4], Audrey Bellesoeur[2], Sandrine Parisse-Di Martino[5], Olivier Humbert[6], Thibaut Cassou-Mounat[7], Emmanuel Deshayes[8], Loic Djaileb[9], Khaldoun Kerrou[10], Eve Piekarski[11], Elise Deluche[12], Alexandre Cochet[4]

[1]Institut Curie, Saint Cloud, France; [2]Institut Curie, Paris, France; [3]GE HealthCare; [4]Centre George François Leclerc, Dijon, France; [5]Centre Léon Bérard, Lyon, France; [6]Centre Antoine Lacassagne, Nice, France; [7]IUCT-Oncopole Claudius Regaud Toulouse, France; [8]Institut du Cancer de Montpellier, France; [9]Centre Hospitalier Universitaire de Grenoble, France; [10]Hôpital Tenon, Paris, France; [11]Hôpital Américain, Paris, France; [12]Centre Hospitalier Universitaire de Limoges, France.

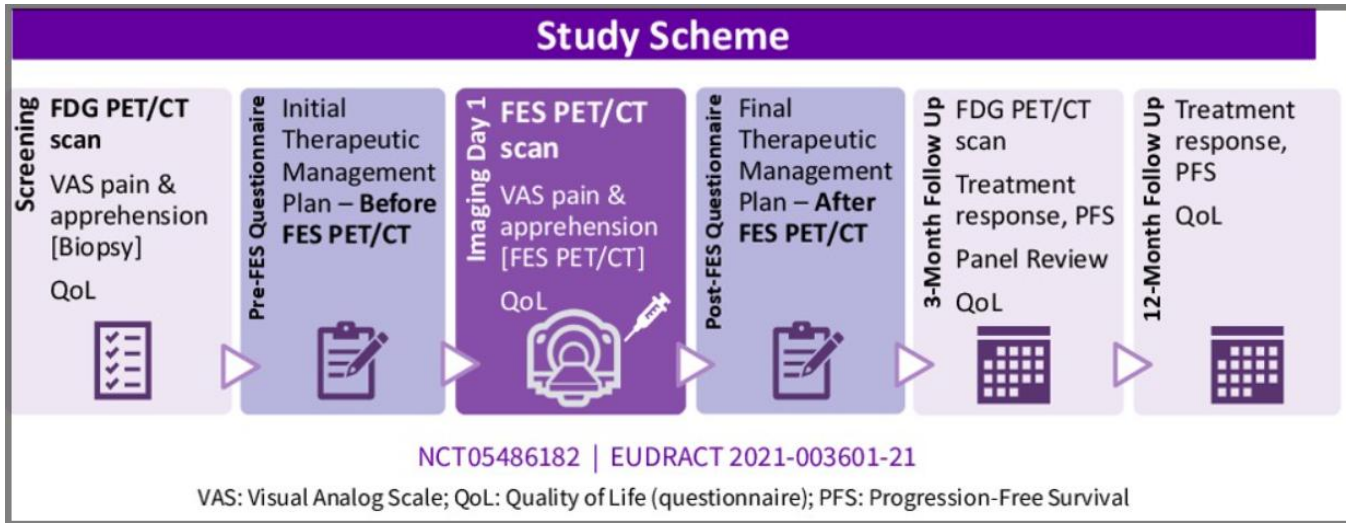
PS11-02

San Antonio Breast Cancer Symposium
December 10-13, 2024

Study Design

- ESTROTIMP is an ongoing multicenter, single arm, Phase IV clinical trial in France, prospectively enrolling 152 patients after disease progression on 1st line AI+CDK4/6i. (Re)biopsy at time of progression was not a requirement for enrollment.
- Purpose of ESTROTIMP is to **document the impact of FES PET/CT on therapeutic management** in patients who have already undergone standard of care [18F]fluorodeoxyglucose (FDG) PET/CT, using a before/after comparison.
- **Before FES PET/CT:** Treating oncologists prospectively record their planned therapeutic management before FES PET/CT. Patients score pain and apprehension for biopsy, recalling their most recent biopsy.
- **After FES PET/CT:** Treating oncologists record their final therapeutic management incorporating FES PET/CT results (local read, compared with FDG PET/CT results). Note: therapeutic decisions are left up to the oncologists, **the protocol does not mandate management changes based on FES PET/CT results.** Patients are followed to document PFS achieved for this treatment line. Patients score pain and apprehension for FES PET/CT.
- Primary endpoint is the impact of FES PET/CT as measured by **% of changes in therapeutic management** after FES PET/CT as compared to before FES PET/CT. Key secondary endpoints (not reported here) include FES PET/CT parameters associated with change in management, 2nd line PFS, and QoL. A retrospective matched cohort of 152 pts without FES PET/CT will be used to compare 2nd line PFS.
- We present the results of a planned interim analysis of the first 30 patients evaluable for the primary endpoint.

Study Scheme



NCT05486182 | EUDRACT 2021-003601-21

VAS: Visual Analog Scale; QoL: Quality of Life (questionnaire); PFS: Progression-Free Survival

[^{18}F]fluoroestradiol (FES) PET/CT to guide 2nd line treatment decision in patients with ER+ HER2- advanced breast cancer progressing on 1st line aromatase inhibitor and CDK4/6 inhibitor: early results of the ESTROTIMP trial

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PS11-02

San Antonio Breast Cancer Symposium
December 10-13, 2024

ER Expression Heterogeneity

- 11/30 patients (36.7%) had ≥1 FES negative lesion(s) when comparing FES with FDG PET/CT imaging results (local read by investigators)

	Interim Analysis Population (N=30)
All lesions ER-positive (FES uptake in all lesions)	19 (63.3%)
Mixed ER-positive/negative lesions (FES uptake in some but not other lesions)	7 (23.3%)
All lesions ER-negative (no FES uptake in any lesions)	4 (13.3%)

ER = Estrogen Receptor; FES = [^{18}F]fluoroestradiol.

In 17 of 19 patients without changes in therapeutic management, treating physicians indicated that FES PET/CT helped confirm the initial plan.

- In 2 patients, treating physicians decided not to change from 2nd line endocrine therapy despite the presence of FES-negative lesions; FDG PET/CT showed progressive disease at 3-month follow up in both patients.

Conclusions

- ESTROTIMP is the first trial to prospectively document the clinical utility of FES PET/CT to inform therapeutic management in patients with CDK4/6i-resistant ER-positive/HER2-negative ABC, where there is a strong unmet need for predictive biomarkers.

Impact on Therapeutic Management Decision

Therapeutic management was changed based on incorporation of FES PET/CT results in 11/30 pts (36.7%)

	Interim Analysis Population (N=30)
Patients with therapeutic management change	
Number of patients (%)	11 (36.7%)
Confidence interval [1]	16.0; 61.6
p-value [2]	0.0002
Number of patients with	
Treatment modifications (compared to initial plan before FES PET/CT)	9 (30.0%)
Addition of endocrine therapy (e.g., initial plan did not include endocrine therapy and final plan did)	3
Withdrawal of endocrine therapy (e.g., initial plan did include endocrine therapy and final plan did not)	3
Change in endocrine therapy (e.g., different molecule / dose)	1
Change in other systemic therapy	1
Addition of radiotherapy	1
Diagnostic modifications (compared to initial plan before FES PET/CT)	5 (16.7%)
Scheduling of biopsy	1
Addition of diagnostic test	1
Not specified	3
Follow-up modifications (compared to initial plan before FES PET/CT)	0 (0%)

[1] 99% two-sided Exact (Clopper-Pearson) confidence interval – per statistical analysis plan for the interim analysis.
[2] p-value from two-sided Exact test (vs pre-specified futility threshold : change rate of 10%)
A patient can be counted in more than 1 type of modification (treatment, diagnostic, follow-up).
The protocol did not mandate any therapeutic management changes based on FES PET/CT results.

18F- FES PET/TC : Place in therapy

- **18F-FES PET/TC** in the **baseline diagnostic work-up** of ER+/HER2- MBC allows the identification of a subset of patients classified as endocrine resistant based on a mean SUV , where the upfront administration of first-line tailored therapy can improve outcomes.
- **18F- FES PET /CT** can help to assess HR status in lesions that are difficult to biopsy
- **18F-FES PET/CT** is a helpful tool to **inform therapeutic management decisions** in patients with progression of ER+/HER2- ABC on endocrine based therapy

Best paper nazionale 2

Intermediate clinical endpoints in early-stage breast cancer: an analysis of individual patient data from the Gruppo Italiano Mammella and Mammella Intergruppo trials

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Background

- Improving the **overall survival (OS)** of patients with cancer should be considered the **main goal** of anticancer treatments

- In randomised trials (RCTs), OS definition (i.e., the elapsed time from randomisation to death) is unique and OS is the **preferred endpoint for regulatory purposes**.

- However, showing **OS improvements** in RCTs usually require the inclusion of a **substantial number** of **patients** and **long- term follow-up data**

- In the **early stage breast cancer** setting, **intermediate clinical endpoints** (ICEs), such as disease-free-survival (DFS)or invasive-DFS (iDFS), are frequently used as *primary endpoint* in RCTs and **OS** is often included as *secondary endpoint*.

Results

ICE	Outcome-level surrogacy (OS and ICE are correlated irrespective of treatment)				Trial-level surrogacy (treatment effects on both end points are correlated)	
	Correlation at the patient level		Regression of 8-year OS rate v 5-year ICE rate by trial, Arm, and nodal status (No. of units = 16)		Regression of Log (HR)-OS v Log (HR)-ICE by trial and nodal status (No. of units = 8)	
	No. of events out of 6612 patients included	Kendall's τ (95% CI)	No. of events out of 7718 patients included	R^2 (95% CI)	R^2 (95% CI)	Regression equation
DFS	1450	0.73 (0.72–0.75)	1855	0.92 (0.79–0.95)	0.54 (0.00–0.76)	$Log\ (HR)_{OS} = -0.158 + 0.666*Log\ (HR)_{DFS}$
DDFS	1211	0.80 (0.79–0.82)	1566	0.92 (0.79–0.95)	0.67 (0.05–0.83)	$Log\ (HR)_{OS} = -0.110 + 0.811*Log\ (HR)_{DDFS}$
RFS	1204	0.80 (0.79–0.82)	1558	0.94 (0.83–0.96)	0.66 (0.04–0.82)	$Log\ (HR)_{OS} = -0.109 + 0.756*Log\ (HR)_{RFS}$
DRFS	1082	0.85 (0.84–0.86)	1413	0.94 (0.84–0.96)	0.67 (0.05–0.83)	$Log\ (HR)_{OS} = -0.082 + 0.791*Log\ (HR)_{DRFS}$
IBCFS	1325	0.77 (0.75–0.78)	1707	0.94 (0.84–0.96)	0.49 (0.00–0.74)	$Log\ (HR)_{OS} = -0.147 + 0.617*Log\ (HR)_{IBCFS}$
RFI	900	0.71 (0.69–0.73)	1206	0.95 (0.87–0.97)	0.49 (0.00–0.74)	$Log\ (HR)_{OS} = -0.114 + 0.531*Log\ (HR)_{RFI}$
DRFI	767	0.76 (0.74–0.78)	1048	0.94 (0.85–0.97)	0.53 (0.00–0.75)	$Log\ (HR)_{OS} = -0.090 + 0.539*Log\ (HR)_{DRFI}$
BCFI	1030	0.67 (0.65–0.69)	1365	0.95 (0.85–0.97)	0.29 (0.00–0.63)	$Log\ (HR)_{OS} = -0.158 + 0.400*Log\ (HR)_{BCFI}$

DFS, disease-free survival; HR, hazard ratio; ICE, intermediate clinical end point; OS, overall survival; DDFS distant disease-free survival; RFS, recurrence-free survival; DRFS, distant relapse-free survival; RFI, recurrence-free interval; DRFI, distant recurrence-free interval; BCFI, breast cancer-free interval; IBCFS, invasive breast cancer-free survival.

Table 2: **Two-condition surrogacy analysis among patients with hormone-receptor positive/HER2-negative breast cancer.**

This study provides **evidence supporting** the use of all intermediate clinical endpoints, except for BCFI, defined by STEEP criteria v2.0, as **primary endpoint** in breast cancer adjuvant trials

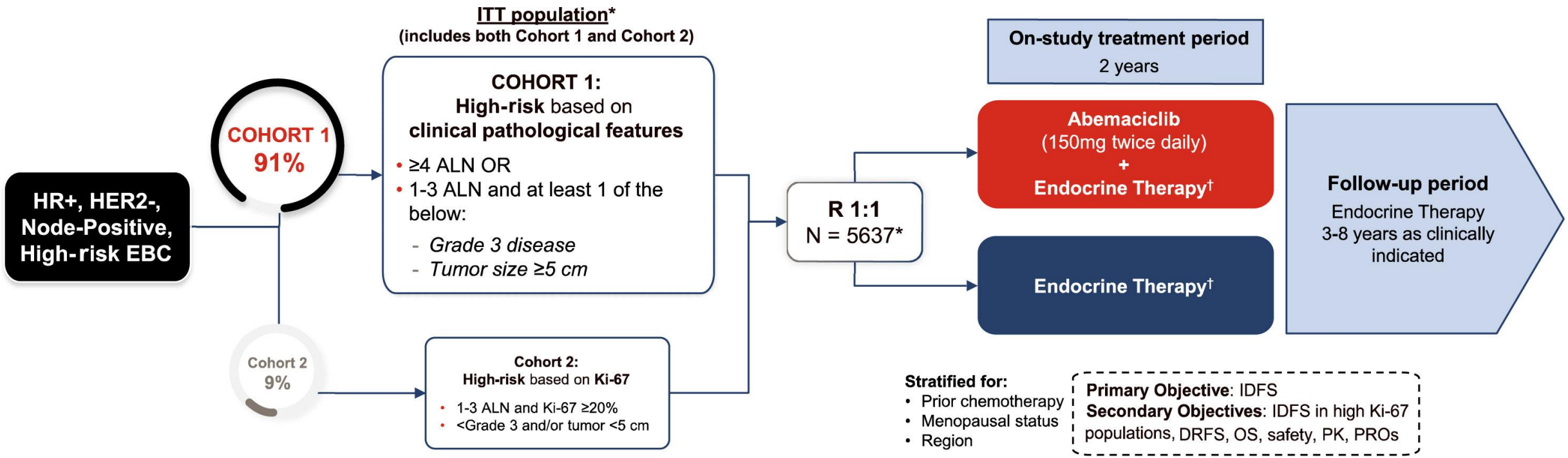
Treatment of Early-Stage, HR+/HER2- Breast Cancer

The goal of adjuvant treatment is to optimize OS

- **Endocrine therapy**
  - Tamoxifen
  - Aromatase inhibitors
  - Ovarian Suppression (LHRH analogs) in high-risk prememopausal women
- **Chemotherapy**
  - Benefit depends on risk for recurrence and biology of the disease (genomic platforms)
- **Targeted agents**
- **Adiuvant CDK 4/6i :** Abemaciclib (monarchE)

  Ribociclib (Natalee)

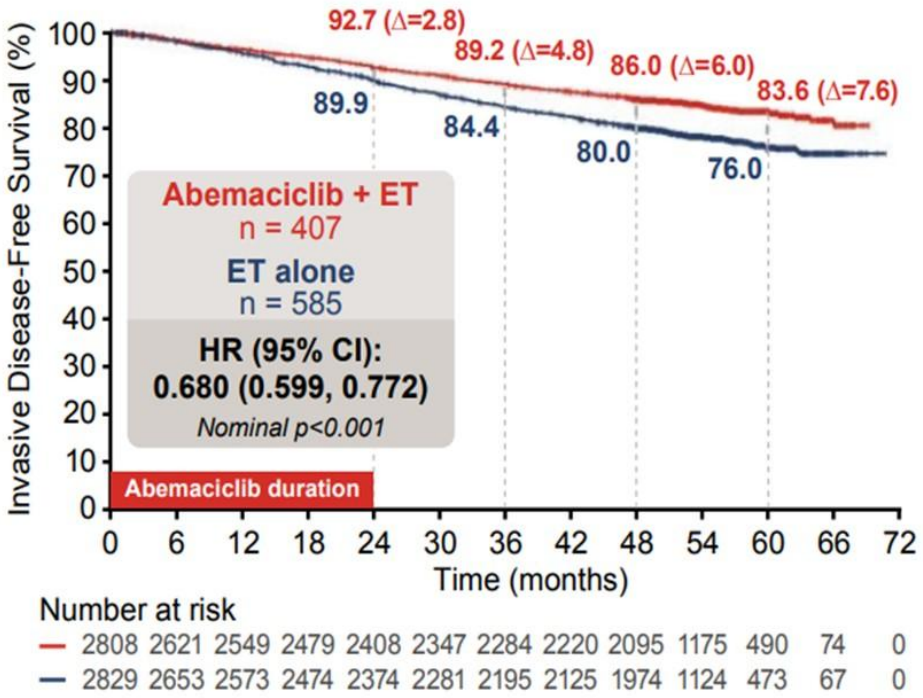
monarchE Study Design



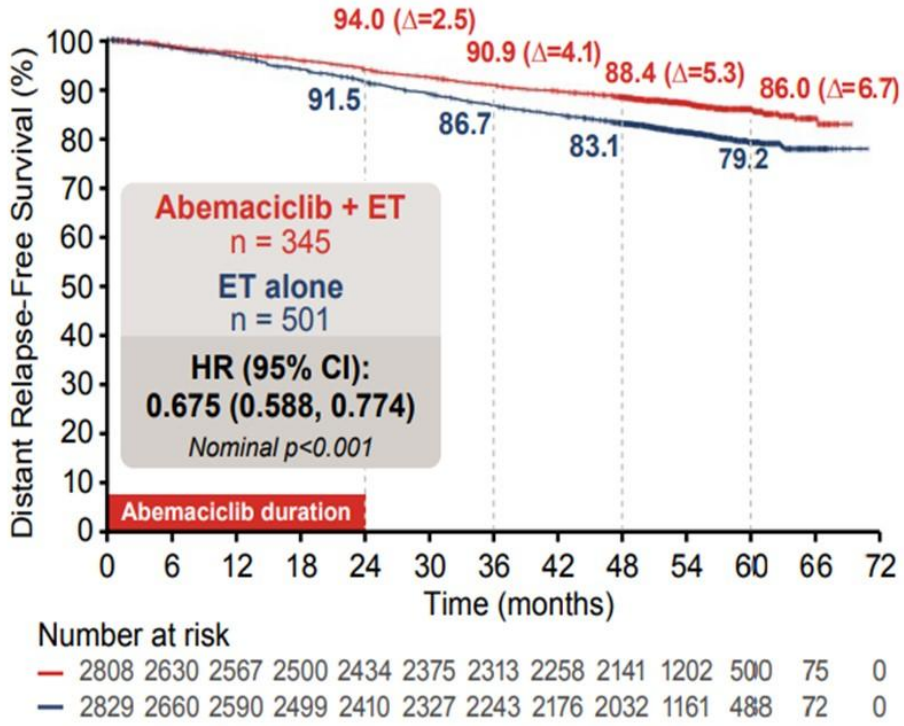
*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

monarchE- Sustained benefit at 5 years

5 years IDFS Benefit in ITT



5 years DRFS Benefit in ITT



Benefit of adjuvant abemaciclib exists regardless of Ki67 status

Rastogi P, et al. JCO. 2024

NATALEE Study Design[1-3]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N=5101[b]

R 1:1[c]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

Primary End Point
– iDFS using STEEP criteria

Secondary End Points
– Recurrence-free survival
– Distant disease–free survival
– OS
– PROs
– Safety and tolerability
– PK

Exploratory End Points
– Locoregional recurrence–free survival
– Gene expression and alterations in tumor ctDNA/ctRNA samples

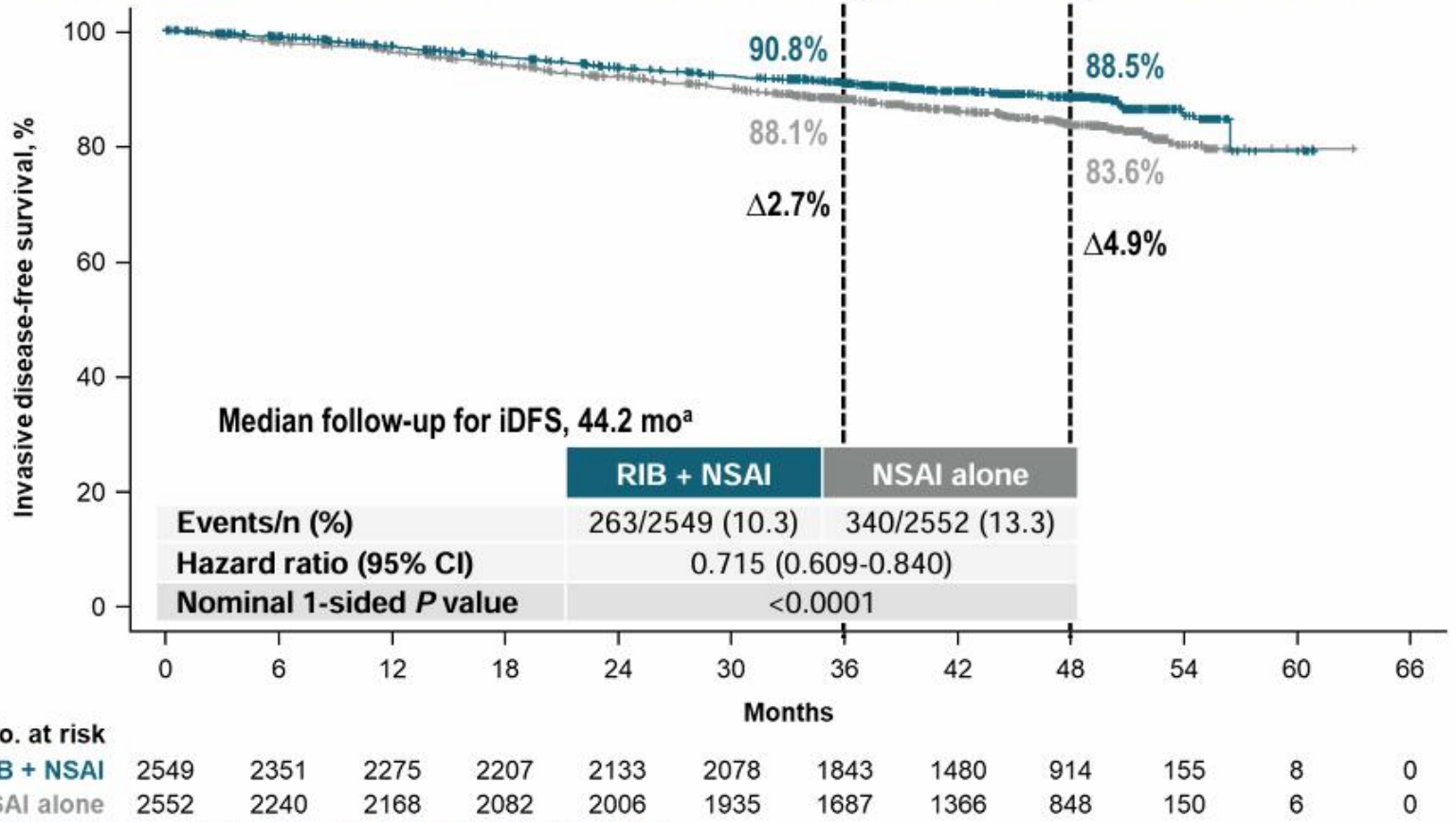
Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.

iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment



iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

Peter A. Fasching

Place in therapy

- Because demonstrating an improvement in overall survival in RCTs requires the inclusion of a substantial number of patients and long-term follow-updata , using ICEs in the RCTs is highly attractive with reduced number of patients and length of follow up.

- However, changes in ICEs should be able to predict changes in overall survival.

- This study provides **evidence supporting the use** of all intermediate clinical endpoints, except for BCFI, defined by STEEP criteria v2.0, as **primary endpoint** in breast cancer adjuvant trials


Grazie