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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☆

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- Scientific Board in IBCSG; Membership/affiliation: LILT, FUV

Early prediction of endocrine responsiveness in ER+/HER2 negative MBC: Pilot study with 18F-fluoroestradiol (18F-FES) CT/PET

BACKGROUND

- 30-40% of ER+/HER2- MBC patients fail to achieve a durable response to ET.
- **18F-FES PET/CT** has been shown to represent an accurate diagnostic tool to determine ER status and it can be proposed as a valid alternative to biopsy of metastatic lesion.

In this trial, we evaluate 18F-FES PET/CT as a predictive tool for endocrine responsiveness in ER+ MBC.

AIM OF THE STUDY

Primary objective: to compare the efficacy of Ist line ET vs CT in pts with ER+/HER2- MBC and 18F-FES SUV<2 at basal PET/CT scan.

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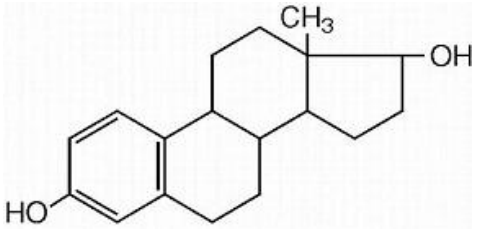
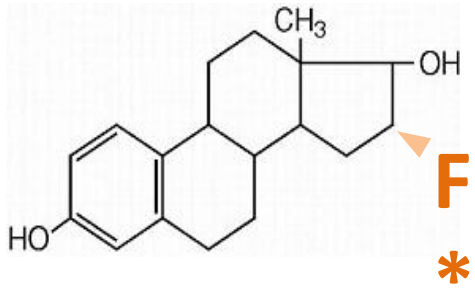
18F-Fluoro-Estradiol (FES)-PET/CT



Estradiol



FES

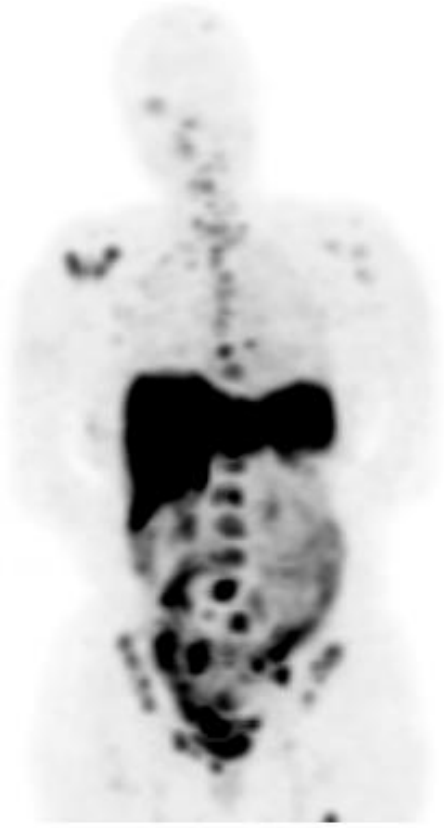


Table 1: FES Diagnostic Uses in the United States

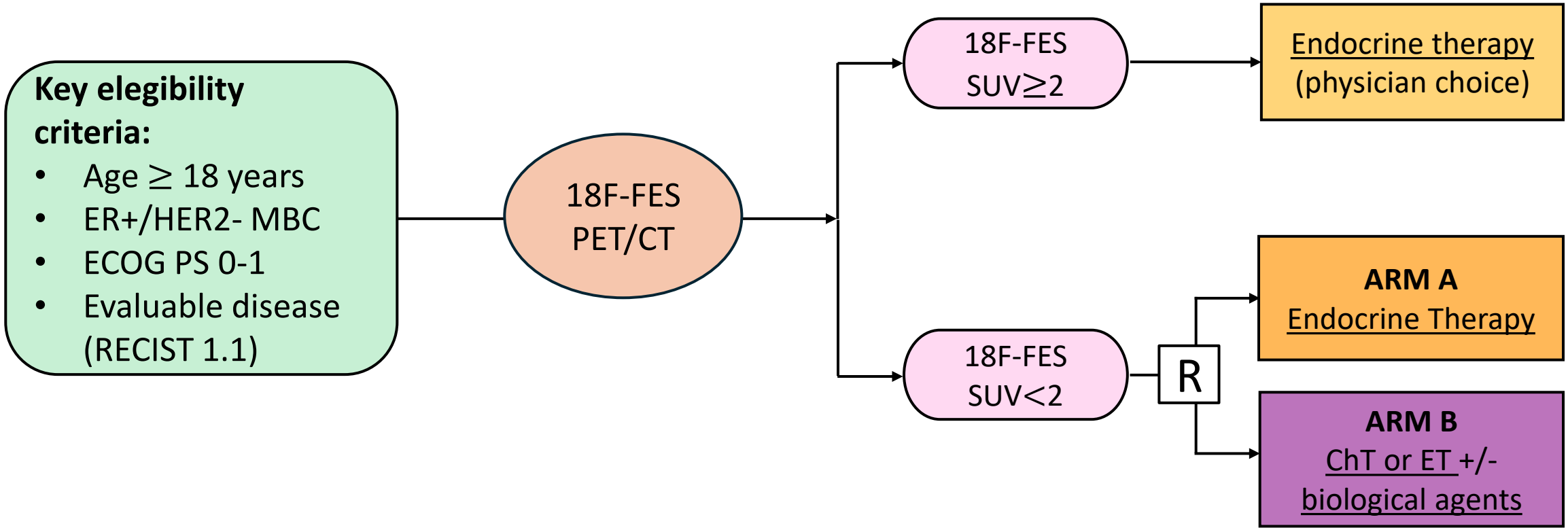
As an adjunct to biopsy, FES can be used as follows:
Select a biopsy target
Assess the burden of ER-positive disease
Clarify FDG-avid findings
Identify spatial and/or temporal ER heterogeneity
Possible future applications:
Predict response to systemic therapy
Demonstrate effective ER blockade by an ER antagonist
Initial staging of ER-positive breast cancer
Clinical use in other patient populations

Note.—FES is currently FDA approved for detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

Peterson LM et al. *J Nucl Med*. 2008;49(3):367-374
Boers J et al. *Curr Oncol Rep*. 2020;22(8):85
O'Brien SR et al. *Radiographics*. 2023;43(3):e220143

ET-FES Study design

The ET-FES is a pilot, phase II, prospective, multicenter trial



ET-FES Study

- **Clinical validation trial:** phase II randomized comparative clinical trial with a diagnostic agent (18F-FES), whose primary aim is to identify endocrine resistant patients

- **Multicenter trial**
  - **Project coordinator:** Alessandra Gennari, Novara, IT
  - **Project partner:**
    - Dino Amadori, Meldola, IT
    - Javier Cortes, Barcelona, E
    - Nadia Harbeck, Munich, DE
    - Etienne Brain, St Cloud, FR

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ET-FES objectives

PRIMARY OBJECTIVE

- to compare the efficacy of first-line ET versus CT in patients with ER+/HER2-negative MBC and 18F-FES SUV<2 at basaline CT/PET scan.

PRIMARY ENDPOINT

- **DCR**, as defined by the proportion of patients who did not experience disease progression within 3 months of treatment → *due to low number of patients experiencing PD or death at 3 months*
- **Progression Free Survival (PFS)** and **Overall Survival (OS)**

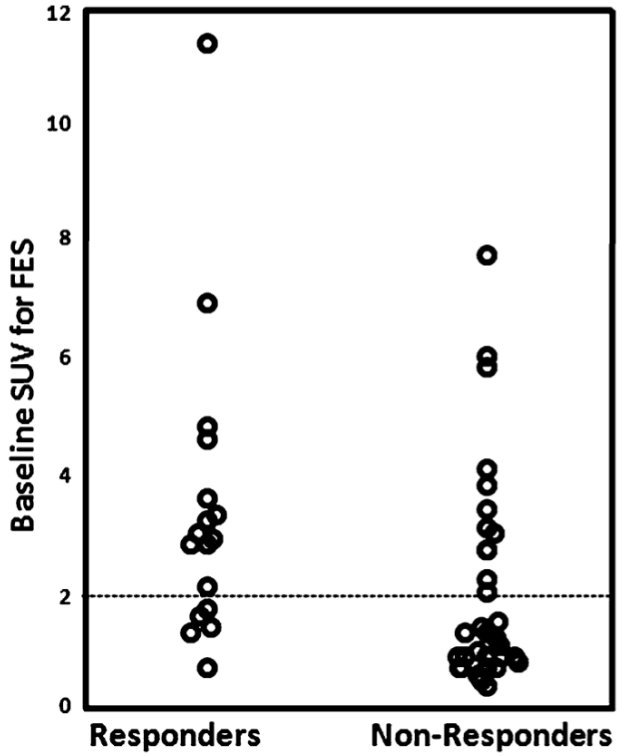
SECONDARY ENDPOINT

- Evaluating DCR with ET in patients with 18F-FES SUV≥2
- Comparing DCR with ET in patients with 18F-FES SUV≥2 with that of patients with 18F-FES<2
- Correlating ER expression in the primary tumor and overall 18F-FES uptake in metastases
- Assessing OS in all patients and by 18F-FES SUV value

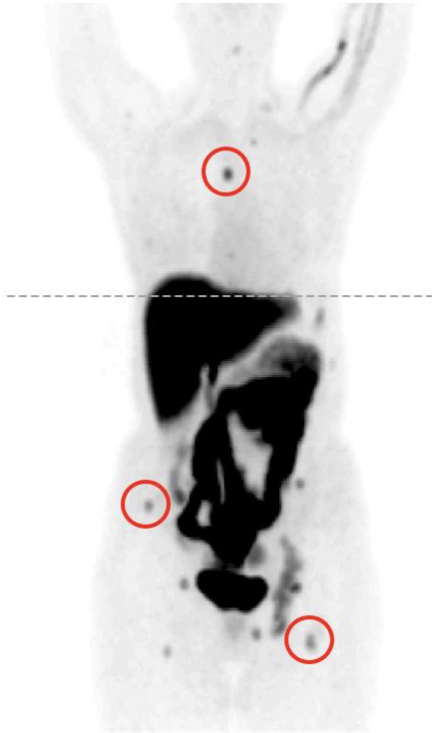
SUVmax

18F-FES SUV is normally distributed with a mean value = 2.

- **18-F FES SUV >2** → Responding patients
- **18F-FES SUV <2** → Non-responding patients



It was expected that ≈ 50% of the pts (n=110) show a 18F-FES SUV < 2 computed as the mean of values for up to the 3 largest tumor sites in the whole-body acquisition for each patient.

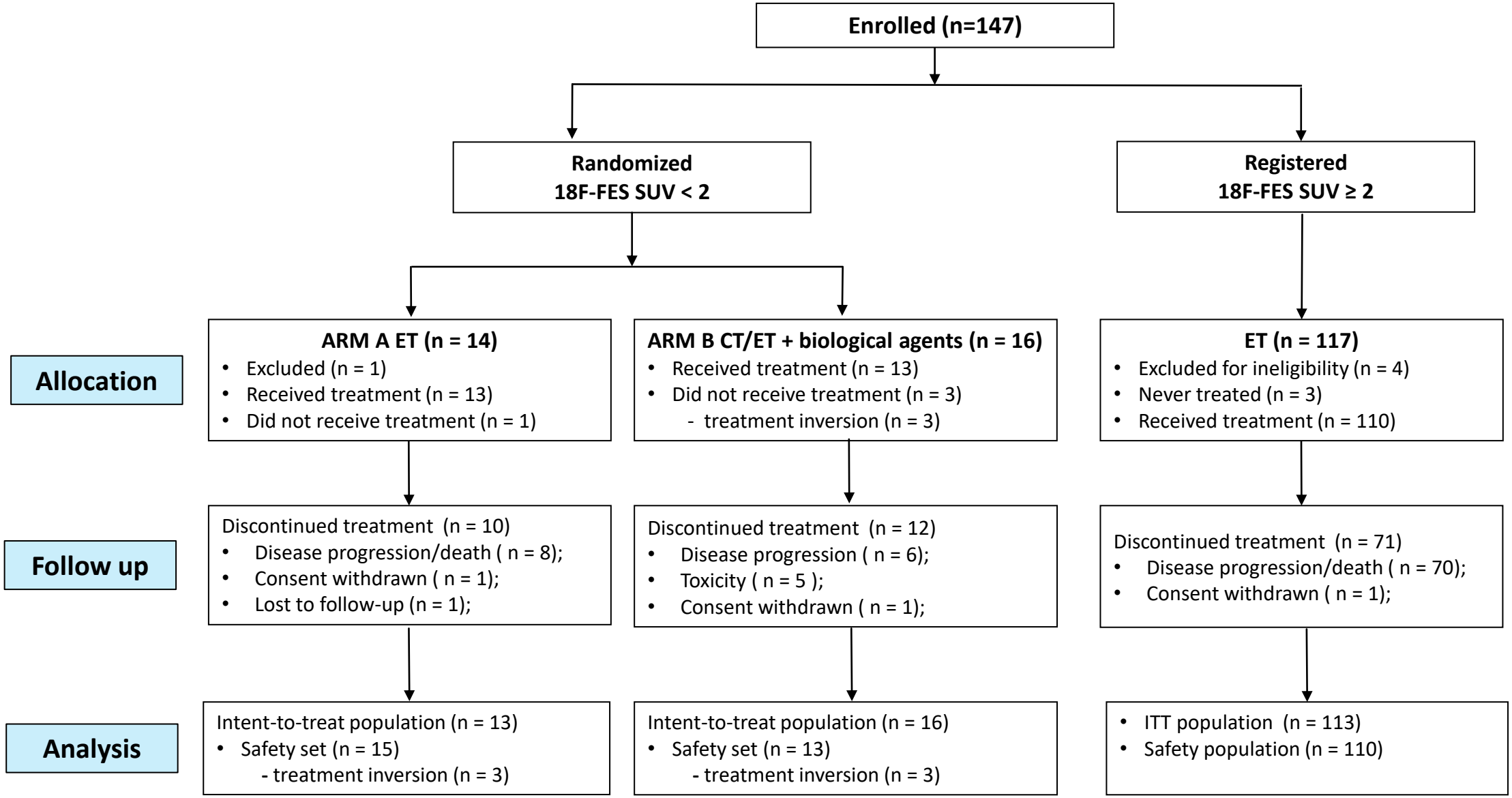


Contrast-enhanced-CT (CeCT) was used to draw ROIs on up to three of the largest tumor sites

SUVmax was computed as the mean of the values of the three largest tumor sites.

Dehdashti F et al. *Breast Cancer Res Treat*. 2009;113(3):509-517

ET-FES Consort Diagram



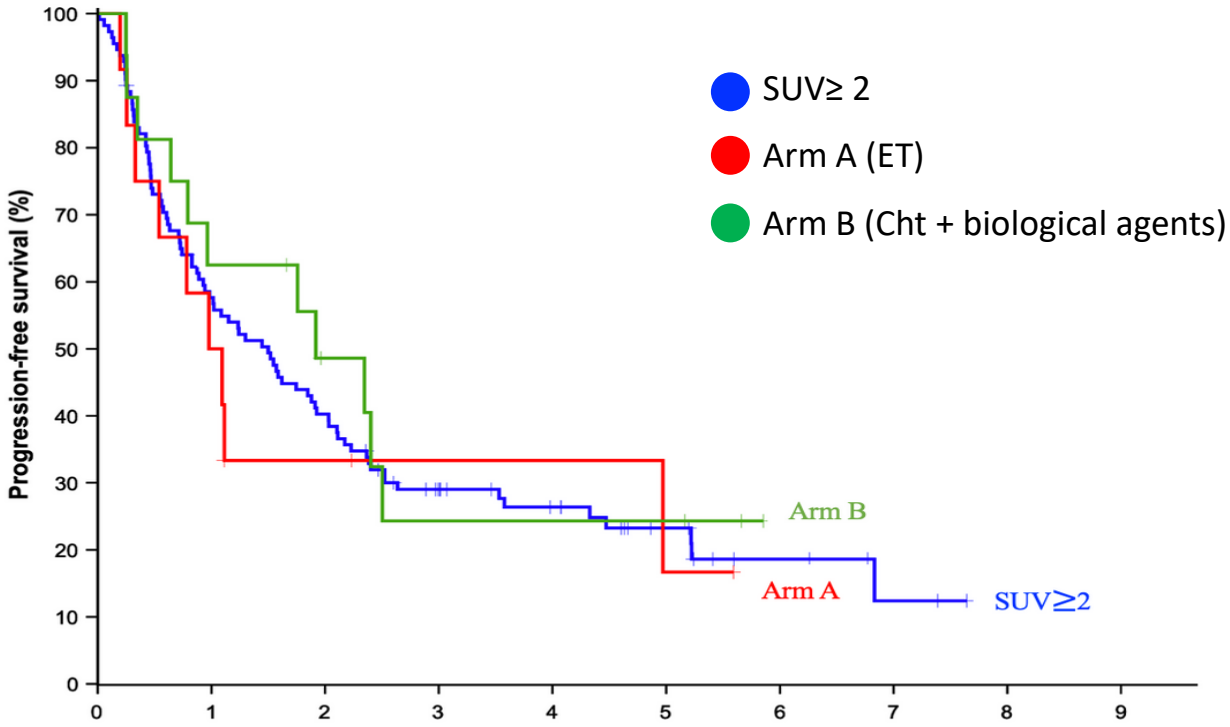
Baseline characteristics

Patients characteristics	Registered (n=113)	Arm A (n=13)	Arm B (n=16)	Total (n=142)
Median age (range) - yrs	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 PS				
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)
Hormone Receptor Status				
ER>50%	100 (88.5)	13 (100.0)	15 (93.7)	128 (90.1)
Disease-Free Interval				
DFI≤ 24 mos	11 (9.7)	1 (7.7)	1 (6.3)	13 (9.2)
DFI > 24 mos	75 (66.4)	9 (69.2)	14 (87.5)	98 (69.0)
Metastatic ab initio	27 (23.9)	3 (23.1)	1 (6.2)	31 (21.8)
Prior Treatment				
Prior Neo/Adjuvant CT	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)

Duration of Treatment and Efficacy

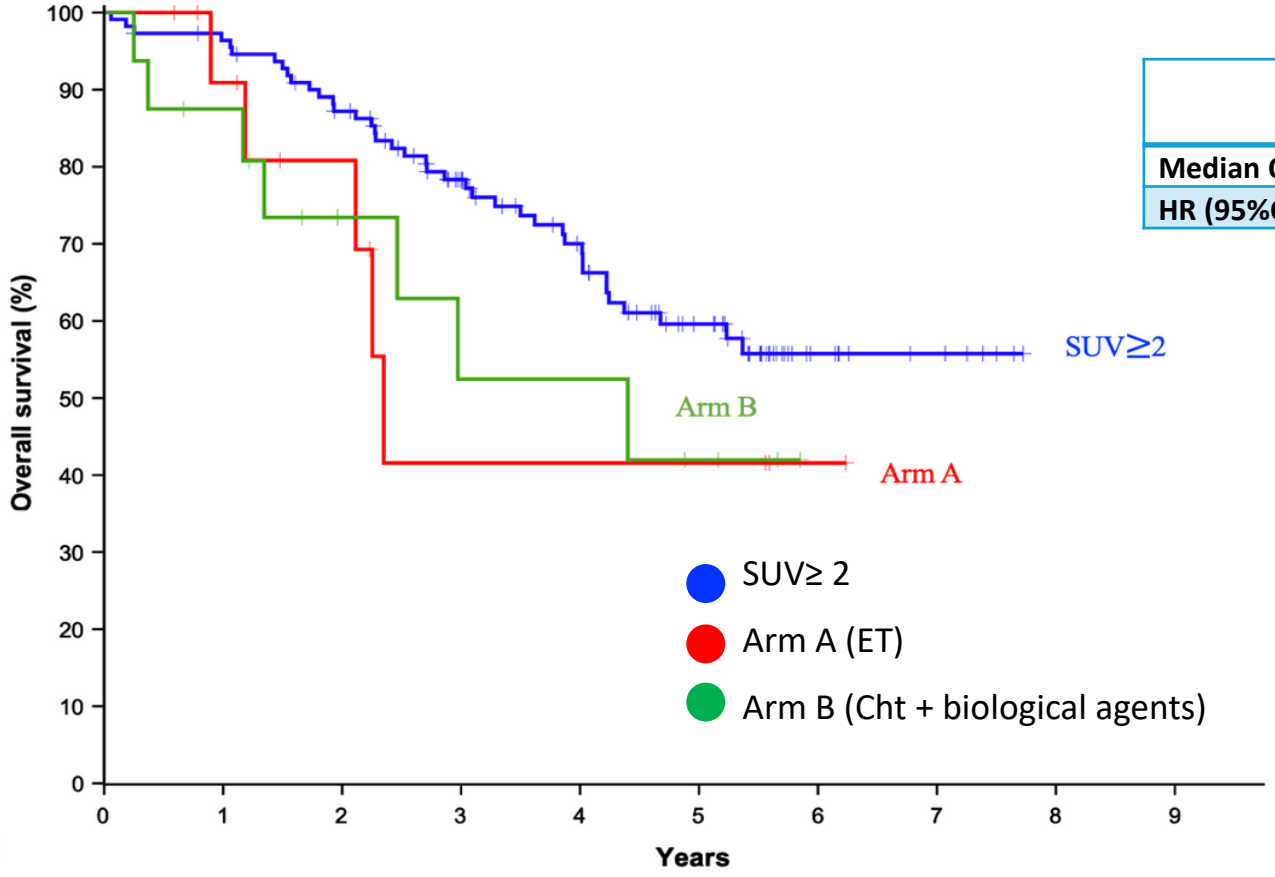
- Accrual period: April 25, 2015 to December 20, 2020
- Median follow up 62.4 months (IQR 36.2 - 68.4 months)
- At the cut-off date of 31 December 2023 104 patients (73.2%) had disease progression and 53 died (37.3%)
- At time of analysis, single agent ET was still ongoing in 39 patients with SUV > 2 (35.5%)

Final analysis results: KM analysis of PFS



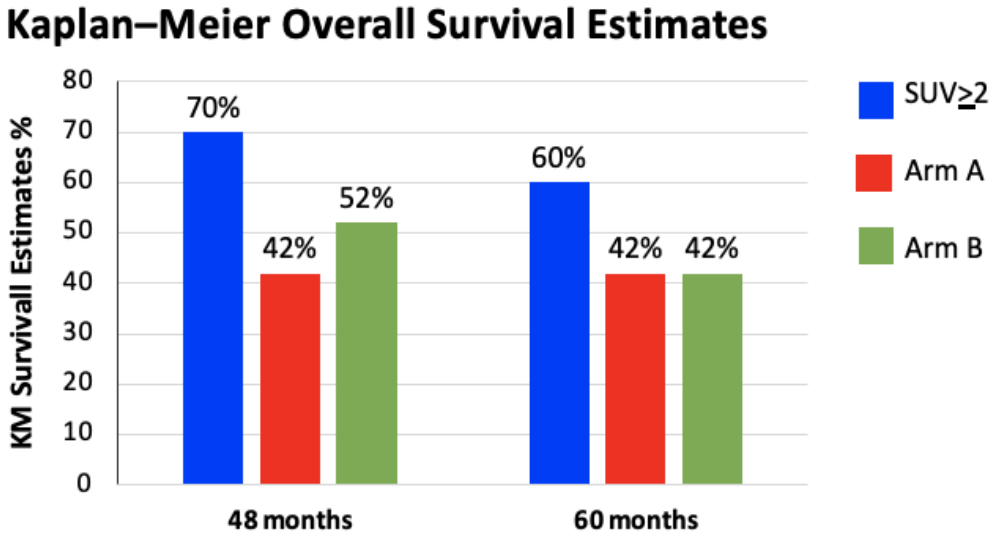
	18F-FES SUV≥2	SUV<2	
		Arm A	Arm B
Median PFS, mos (range, 95%CI)	18.0 (11.2-23.1)	12.4 (3.1 – 59.6)	23.0 (7.7 – 30.0)
HR (95%CI)		0.71 (0.29 – 1.72)	

Final analysis results: KM analysis of OS



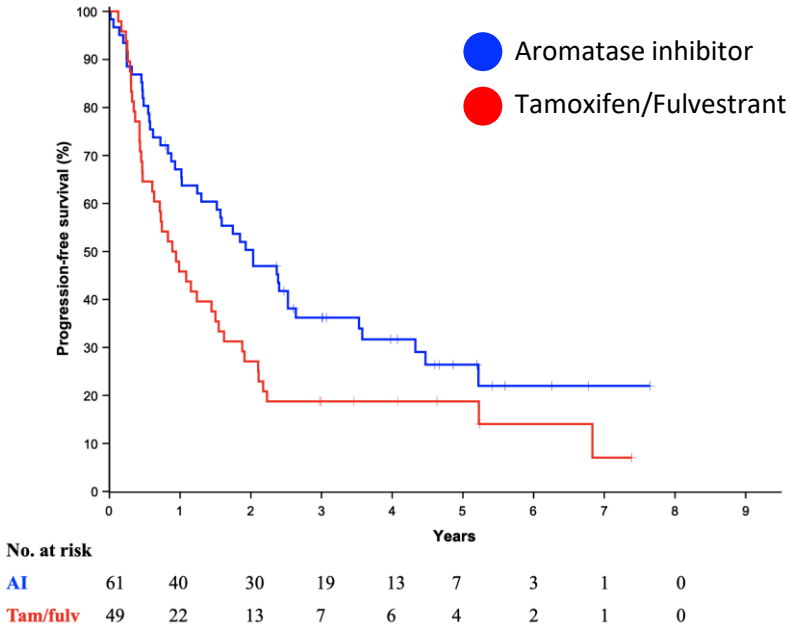
	18F-FES SUV≥2	SUV<2	
		Arm A	Arm B
Median OS, mos (range, 95%CI)	Not reached	28.2 (14.2 - NE)	52.8 (16.2 – NE)
HR (95%CI)		0.97 (0.31 – 3.09)	

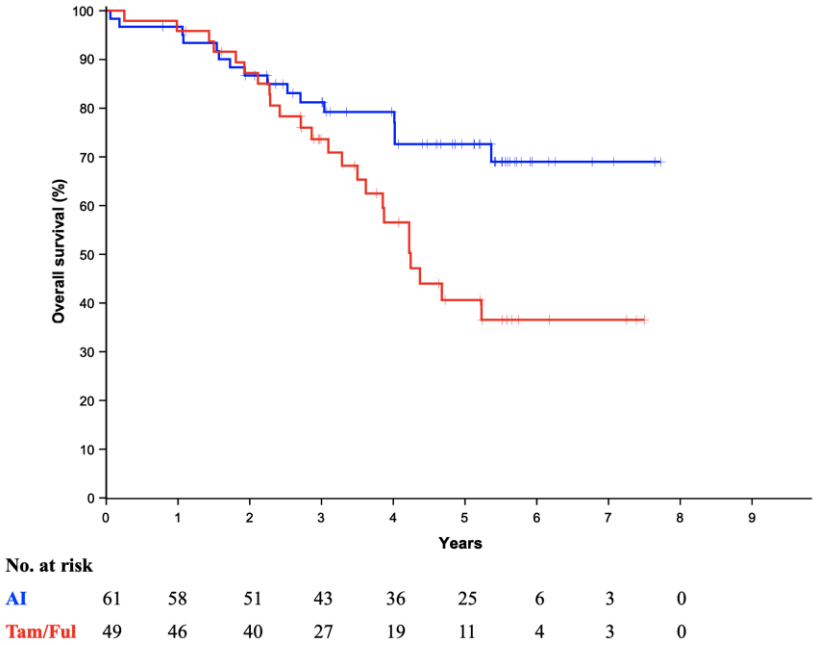
No. at risk									
SUV≥2	113	106	93	71	56	37	11	6	0
Arm A	13	10	7	3	3	3	1	0	
Arm B	16	13	7	5	5	3	0		

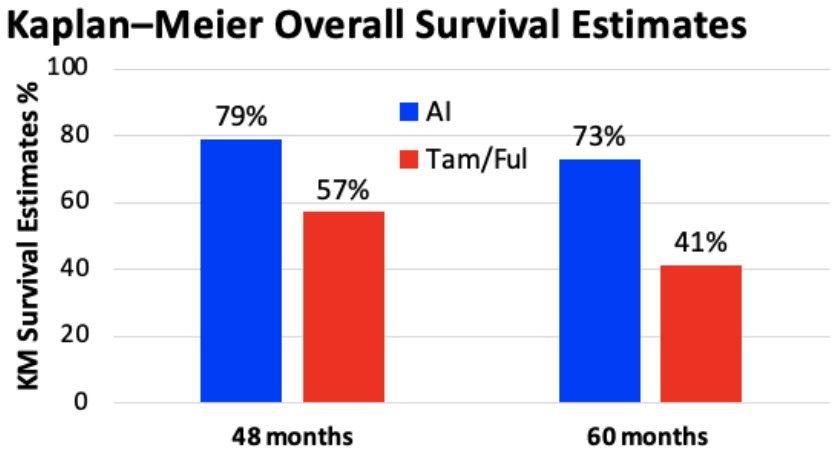


Final analysis results: KM analysis by ET

SUV ≥ 2	
Aromatase Inhibitors (AI)– no. (%)	**Fulvestrant/tam– no. (%)**
61 (55.5)	49 (44.5)







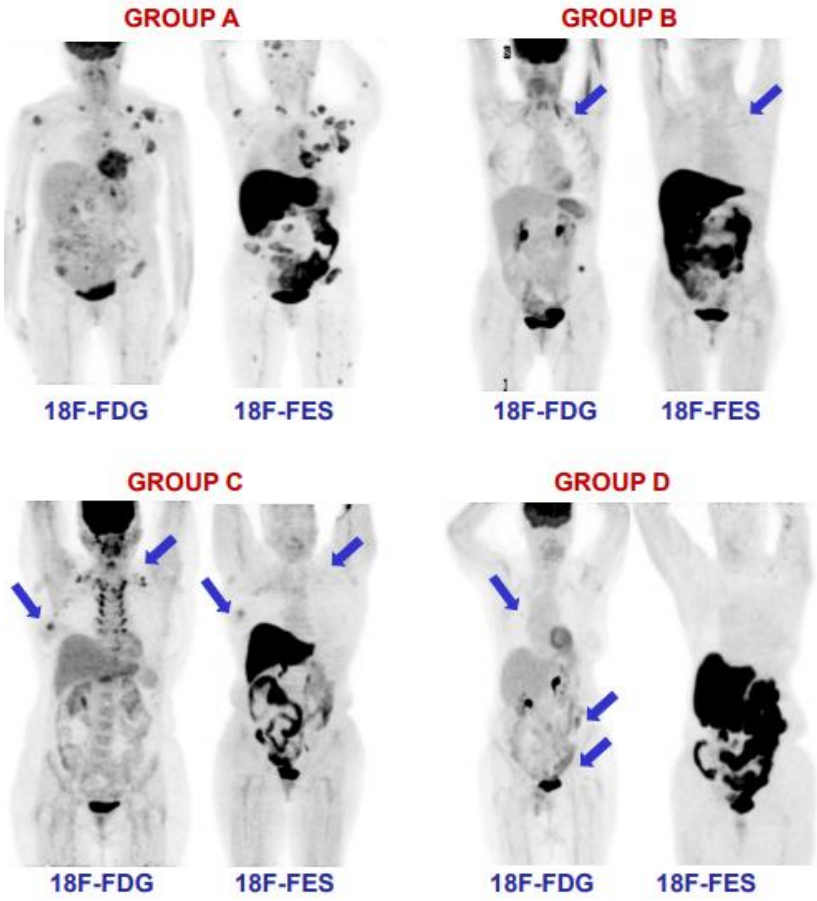
	AI	Fulvestrant/tam
12 mos (95%CI)	67.1 (53.8-77.4)	45.8 (31.4-59.1)
24 mos (95%CI)	50.3 (37.2-62.1)	27.1 (15.5-40.0)
HR (95%CI) - p	0.61 (0.40-0.95) p=0.026	

	AI	Fulvestrant/tam
48 mos, (95%CI)	79.2 (66.2-87.7)	56.6 (39.7-70.3)
60 mos (95%CI)	72.6 (58.5-82.6)	40.6 (24.5-56.1)
HR (95%CI) - p	0.45 (0.24-0.85) p=0.0011	

Heterogeneity between 18F-FES and 18F-FDG in ET-FES Study

PTS INCLUDED IN THE ANALYSIS	N° Pts	%
Group A 18F-FES & 18F-FDG ALL LESIONS 18F-FES POSITIVE	53/79	67.1%
Group B 18F-FES & 18F-FDG 50% OF LESIONS 18F-FES POSITIVE	11/79	13.9%
Group C 18F-FES & 18F-FDG 25% OF LESIONS 18F-FES POSITIVE	5/79	6.3%
Group D 18F-FES & 18F-FDG ALL LESIONS 18F-FES NEGATIVE	10/79	12.7%

Overall, 26/79 (33%) patients, with ER+ MBC had heterogeneous 18F-FES SUV uptake



The use of ET in discordant cases (B/C/D) was associated with a 79% increase in the risk of PD

- A Gennari et al, presented at ESMO 2017

Conclusions

ER+/HER2- MBC patients can be divided in two groups based on the overall endocrine sensitivity measured by 18F-FES SUV at different metastatic sites.

18F-FES CT/PET may be used as a **predictive tool** of efficacy of ET to assess overall endocrine sensitivity

Endocrine sensitive patients (SUV max ≥2) treated with single agent ET have a **prolonged overall survival** (60% alive at 5 years)

In endocrine sensitive patients **PFS and OS related to the use of AI was significantly higher than ER directed agents (fulvestrant or tamoxifen)**

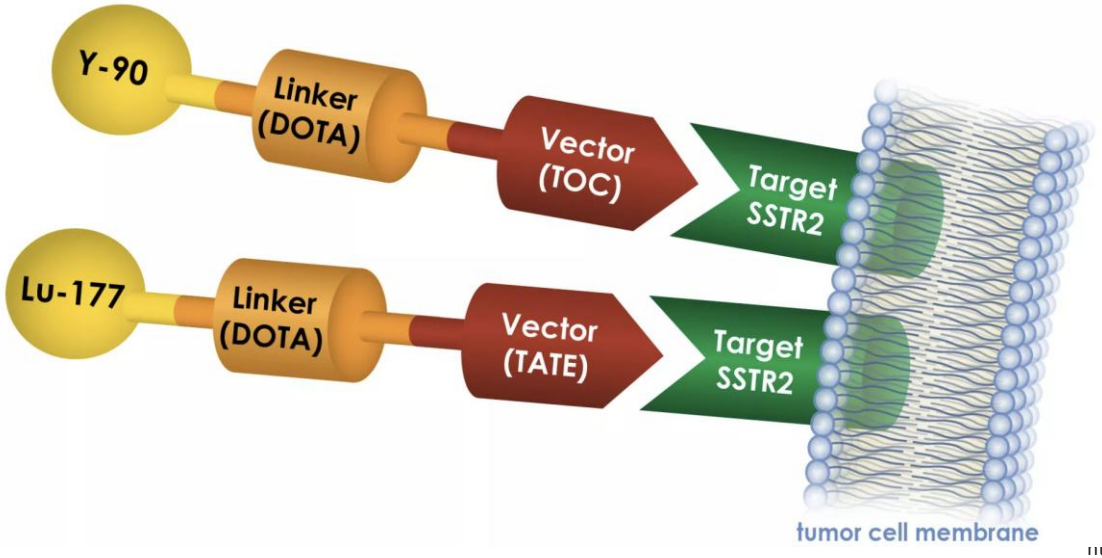
18F-FES CT/PET can be used as a **complementary method to biopsy**

WHAT IS THERANOSTICS?
for medical oncologists

THERANOSTICS is a combination of the terms **THERA**peutics and diag**NOSTICS**. Theranostics is the term used to describe the combination of using one radioactive tracer to identify (diagnose) with NM techniques (e.g. SPECT, PET) a target and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.

Two phases:

1) Diagnostic phase
2) Therapeutic phase



https://uihc.org/health-topics/what-theranostics

Lutetium-177–PSMA-617 for CT pretreated mCRPC

VISION prostate specific membrane antigen

Eligibility

- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted SOC planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Adequate major organ and bone marrow function
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

~87% of patients scanned met the VISION imaging criteria for PSMA-positive mCRPC

2:1

- **Protocol-permitted SOC + ^{177}Lu-PSMA-617**
  7.4 GBq (200 mCi) every 6 weeks
  4 cycles, increasable to 6 cycles
- **Protocol-permitted SOC alone**

Treatment → Follow-up → Final analysis

Alternate primary endpoints

- Radiographic progression-free survival
- Overall survival

Key secondary endpoints

- Time to first symptomatic skeletal event
- RECIST v1.1 overall response rate
- RECIST v1.1 disease control rate

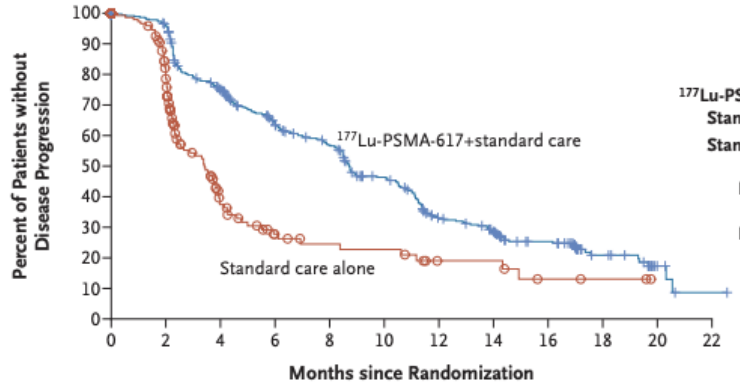
Other secondary endpoints

- Safety and tolerability
- Biomarkers including PSA
- Health-related quality of life and pain
  - FACT-P
  - Brief Pain Inventory – Short Form
  - EQ-5D-5L

2021 ESMO congress Karim Fizazi

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P, Functional Assessment of Cancer Therapy – Prostate; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care

Imaging-Based Progression-free Survival



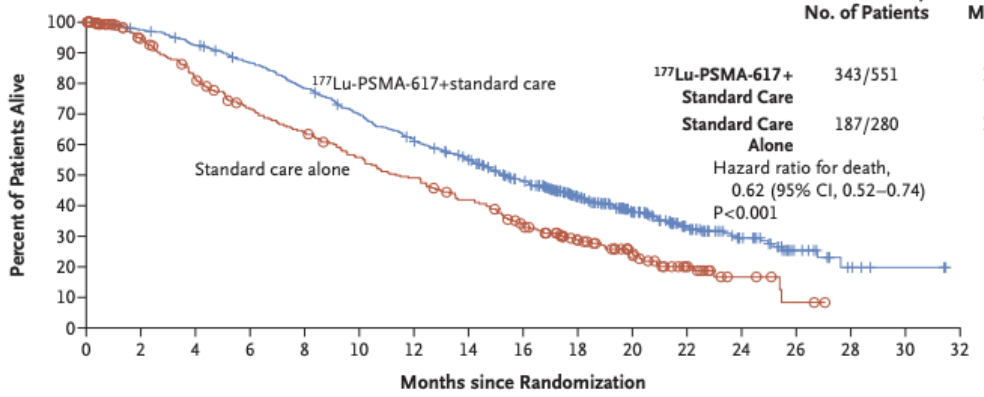
	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	254/385	8.7
Standard Care Alone	93/196	3.4

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29–0.57)
P<0.001

No. at Risk

^{177}Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

Overall Survival



	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617+ Standard Care	343/551	15.3
Standard Care Alone	187/280	11.3

Hazard ratio for death, 0.62 (95% CI, 0.52–0.74)
P<0.001

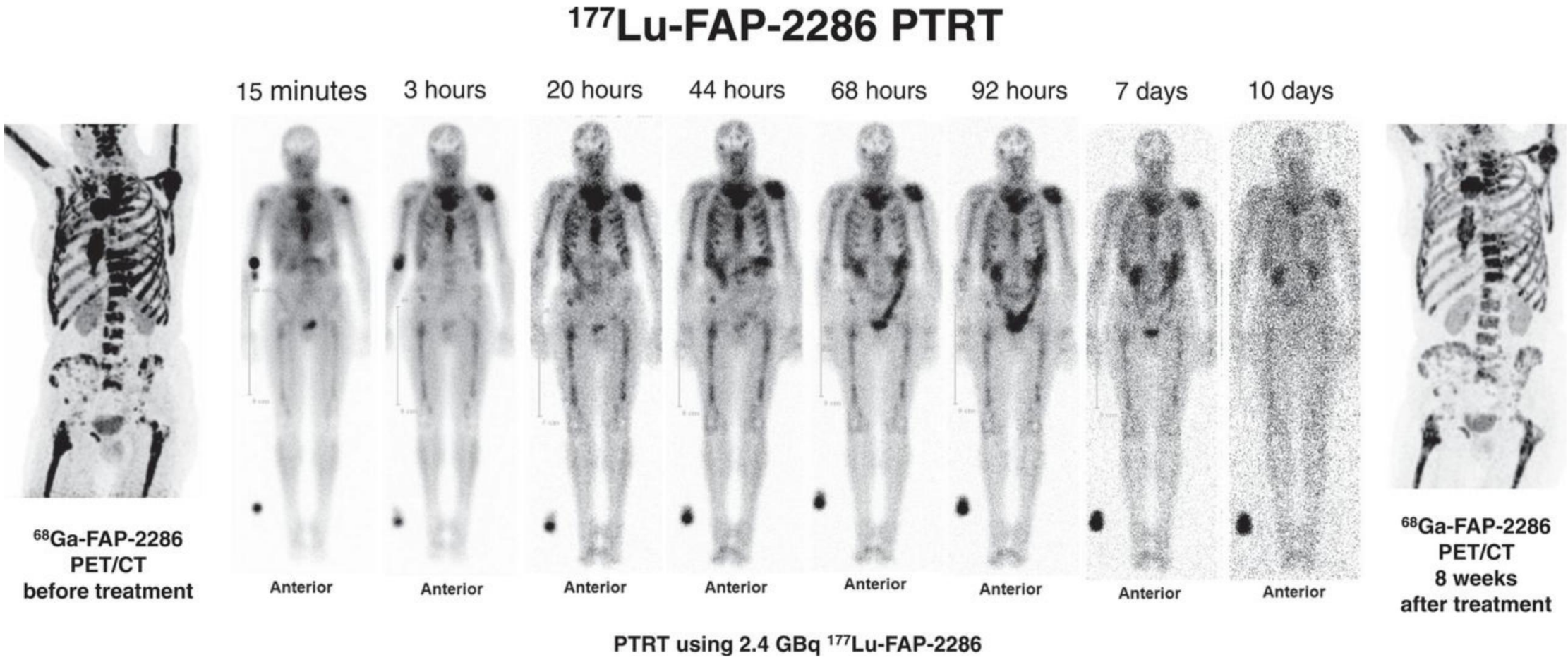
No. at Risk

^{177}Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Sartor O et al. *N Engl J Med*. 2021;385(12):1091-1103

THERANOSTICS IN BREAST CANCER

Fibroblast Activation Protein (FAP) is a promising target for diagnosis and therapy of numerous malignant tumors. FAP-2286 is the conjugate of a fap-binding peptide, which can be labeled with radionuclides for th



Baum RP et al. *J Nucl Med*. 2022;63(3):415-423

Thank you

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