Predicting Response to Endocrine Therapy in Breast Cancer

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OSPEDALE DI RILIEVO NAZIONALE E DI ALTA SPECIALIZZAZIONE

Tailoring endocrine treatment in advanced Breast Cancer

- ≈ 70% of BC are ER sensitive, based on ER+ at diagnosis, on the primary tumor;
- Endocrine therapy not effective in all ER+ patients
- In MBC: clinical benefit rate = 50%.
- Early identification of ER+ MBC patients who are not going to respond might spare patients from ineffective therapies and unnecessary toxicities, while promoting the earlier use of more appropriate and active treatments.

Tailoring endocrine treatment in advanced Breast Cancer

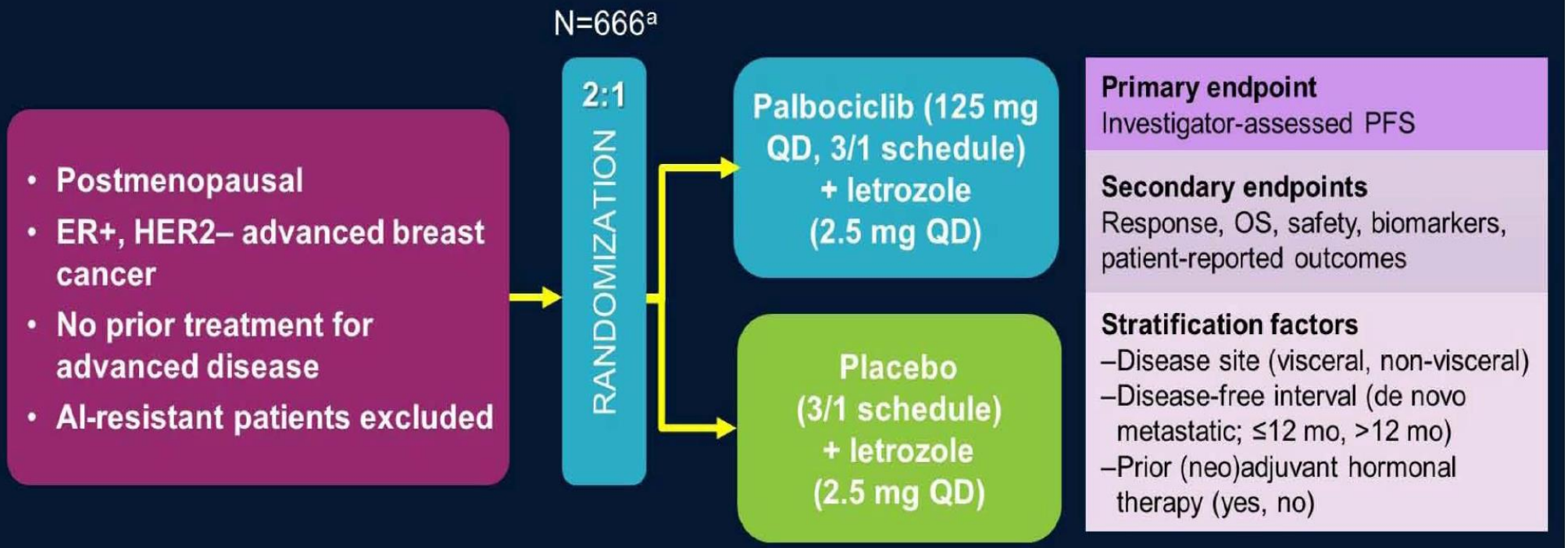
- lack of validated predictive biomarkers for ER+ tumors
- tumor lesions can express ER in a heterogeneous fashion.
- The continuous development of new compounds aimed to overcome endocrine resistance increases the complexity in the selection of patient's treatment.

Results from two Phase III trials testing CDK 4-6 inhibitors in the first-line treatment of HR+/HER-2 advanced breast cancer

-PALOMA 2

-MONA LEESA 2

PALOMA-2: Study Design (1008)[1]

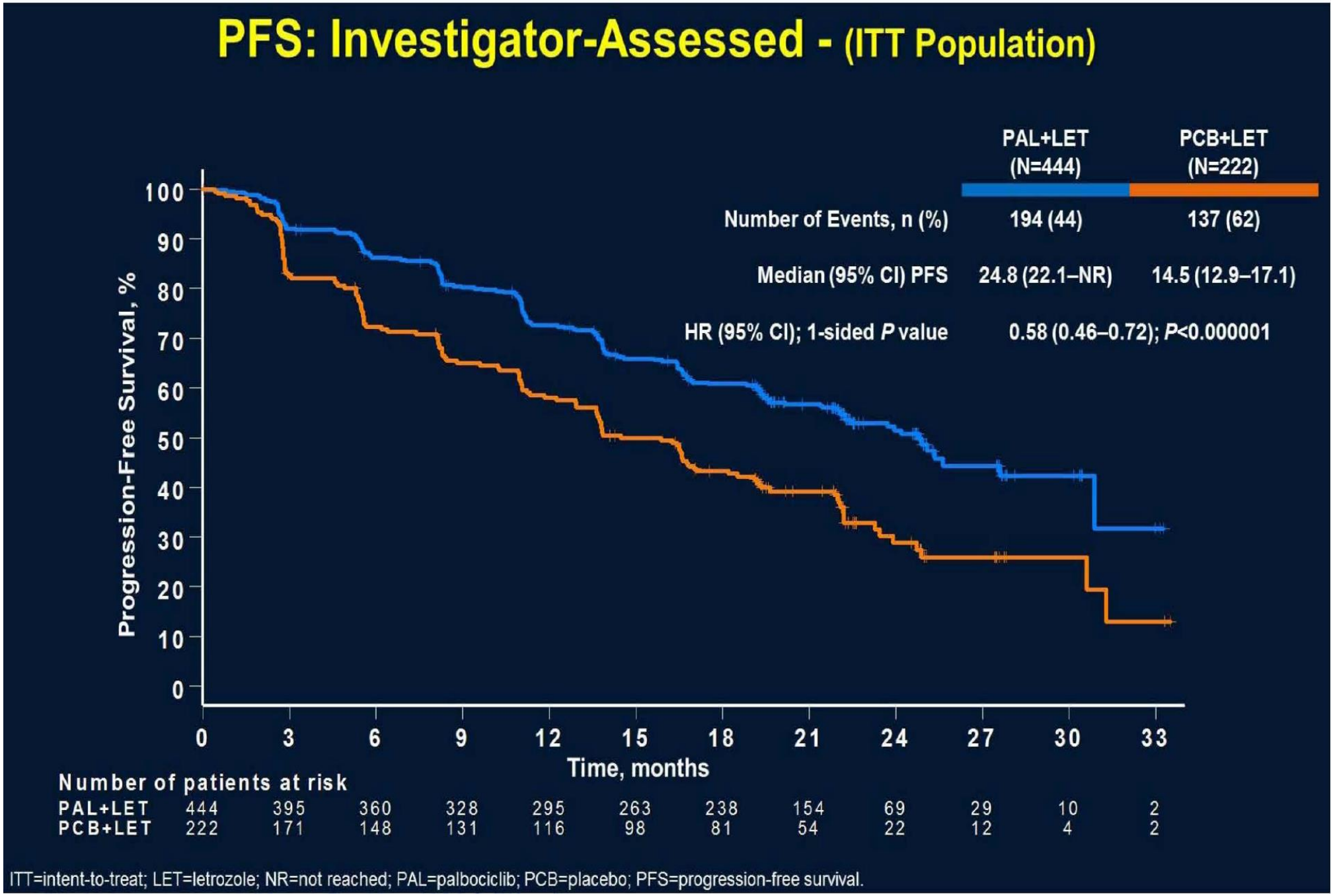


- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided α=0.025

  Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
- Blinded independent central review of efficacy endpoints performed as supportive analysis

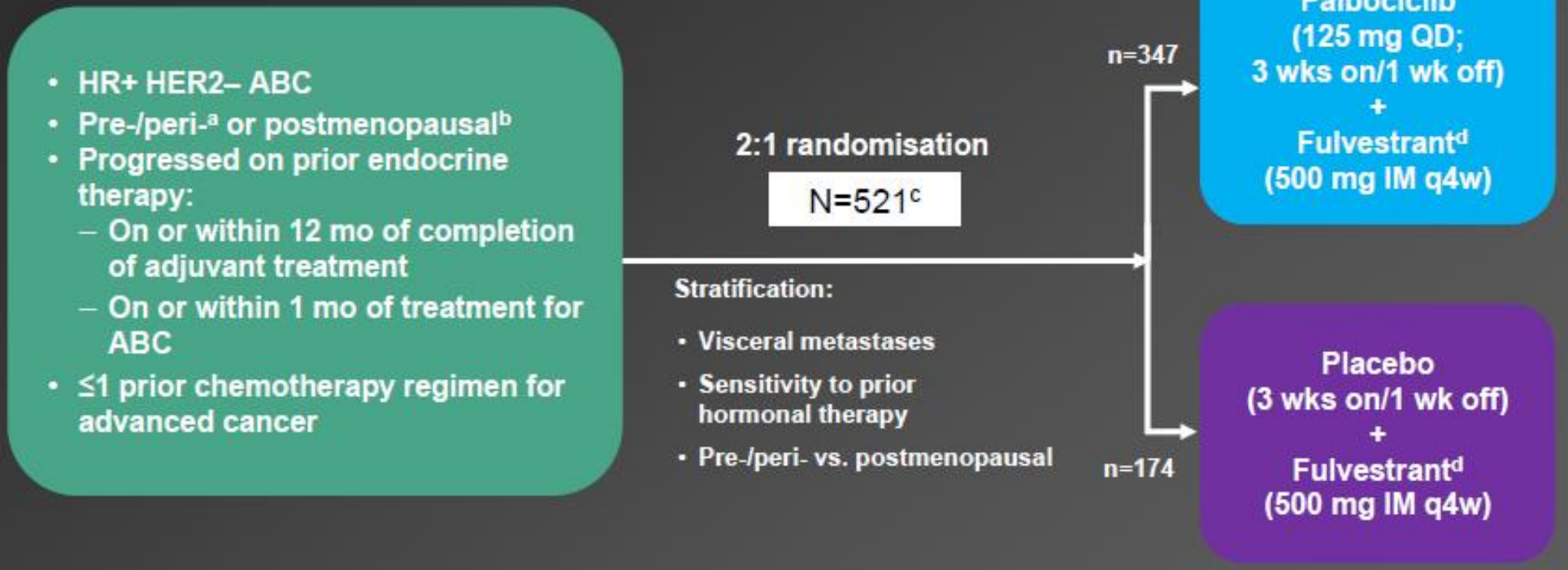
[a]Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

1.clinicaltrials.gov
NCT01740427



- NO Overall Survival benefit
- Approved FDA/EMA

PALOMA-3: Study design

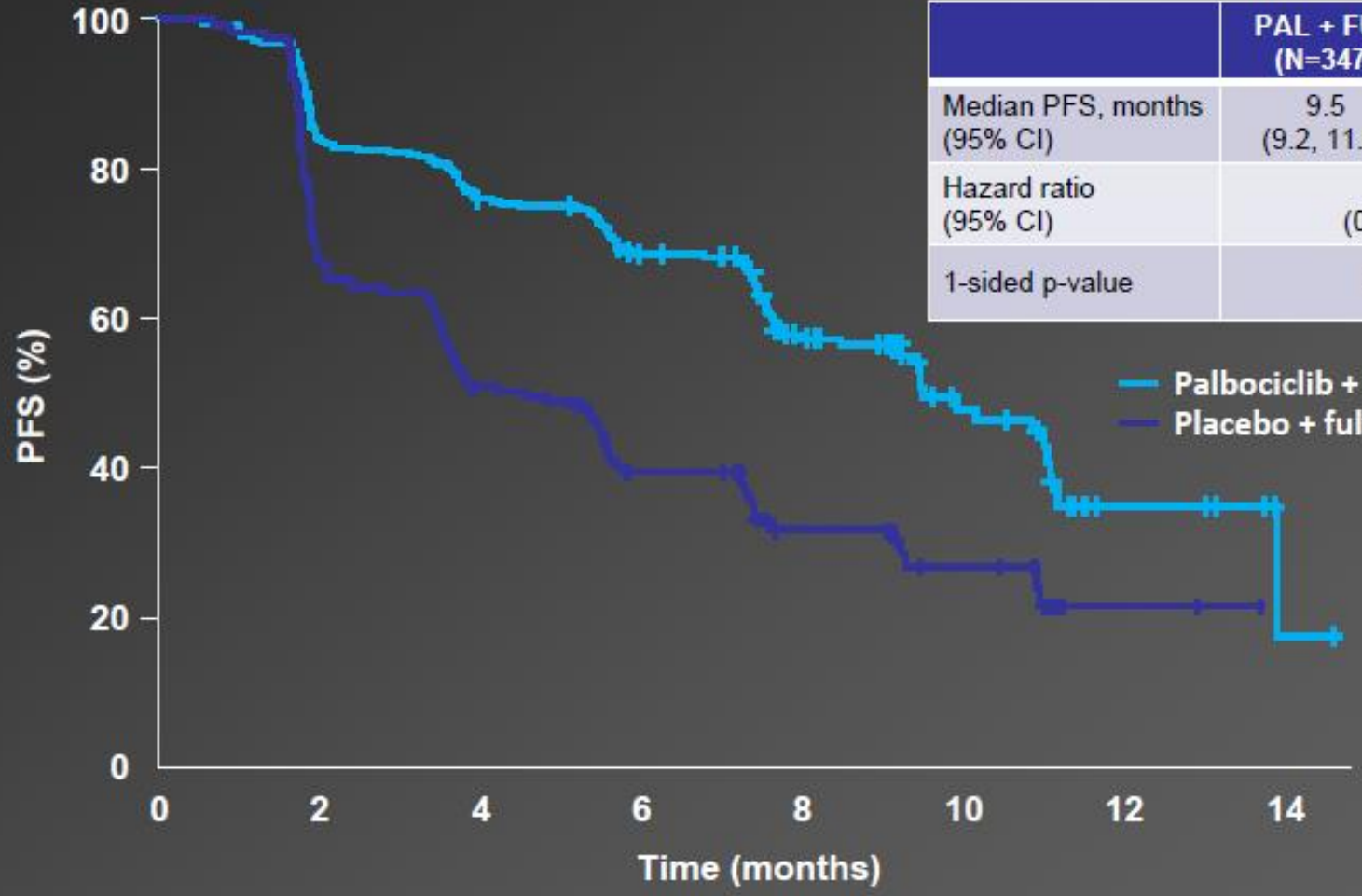


[a]All received goserelin.
[b]Must have progressed on prior endocrine therapy (pre-/perimenopausal) or aromatase inhibitor therapy (postmenopausal).
[c]Patients randomised.
[d]Administered on Days 1 and 15 of Cycle 1, then every 28 d.

Randomised Phase III double-blind trial at 144 centres in 17 countries (NCT01942135)

Turner NC, et al. N Engl J Med 2015;373:209–19;
Turner NC, et al. ASCO 2015 (Abstract LBA502);

PALOMA-3:
Updated investigator-assessed PFS (ITT)



	PAL + FUL (N=347)	PBO + FUL (N=174)
Median PFS, months (95% CI)	9.5 (9.2, 11.0)	4.6 (3.5, 5.6)
Hazard ratio (95% CI)	0.461 (0.360, 0.591)	
1-sided p-value	<0.000001	

Number of patients at risk

PAL+FUL	347	281	247	202	91	32	7	1
PBO+FUL	174	112	83	59	22	13	2	

Turner NC, et al. N Engl J Med 2015;373:209–19;
Turner NC, et al. ASCO 2015 (Abstract LBA502);

Tailoring endocrine treatment in advanced Breast Cancer

- The approval by FDA and EMA of everolimus and, more recently, by FDA /EMA of palbociclib first line of ER + MBC, disregard the size and duration of clinical benefit experienced by many of these patients with endocrine therapy alone.
- Everolimus and palbociclib retain a toxicity profile similar to that of commonly used chemotherapeutic agents: mucositis, fatigue and neutropenia
- High cost is likely to impact the sustainability of such agents on a large scale and in all countries.

New statement

ER POSITIVE / HER-2 NEGATIVE MBC

The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients, provided PFS benefit in a randomized phase 2 study. Results from the phase 3 trial (PFS and OS) are awaited before it can be considered as a recommended treatment option.

RE-WORDED AND RE-VOTED AFTER ASCO 2016

Note : The fact that palbociclib is commercially available and used in the US will be discussed in the manuscript

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Total # of votes: (43)

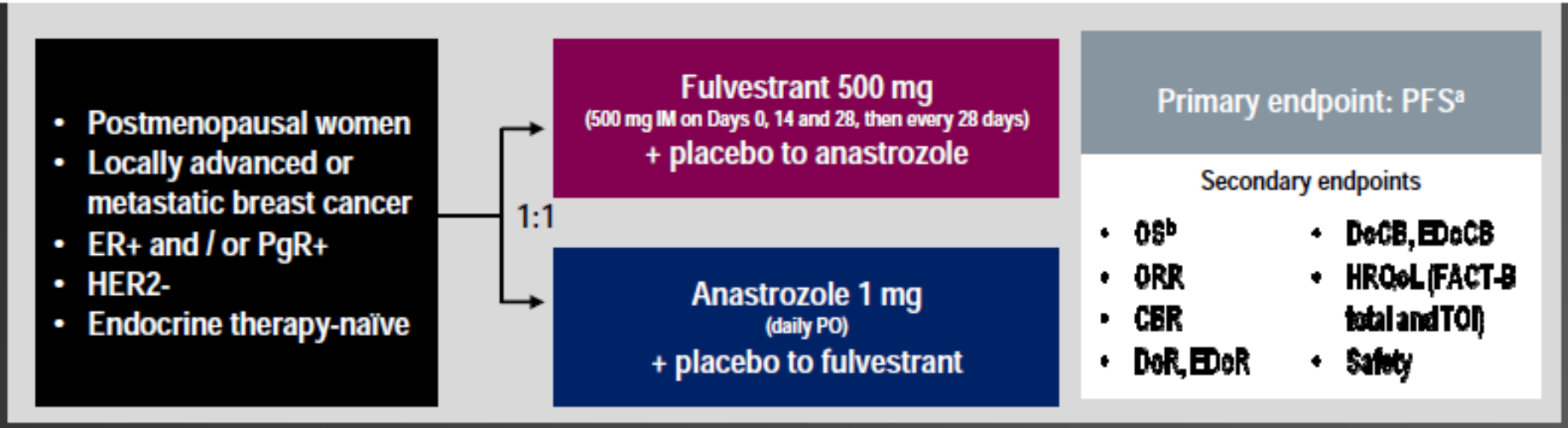
1.	YES:	51.1%	(22)
2.	NO:	39.5%	(17)
3.	ABSTAIN:	9.3%	(04)

ABC3 – ESMO Guidelines

GUIDELINE STATEMENT	LoE	Consensus
The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients (except patients relapsing < 12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available. OS results are still awaited. **ESMO MCBS: 3***	1 A	Voters: 37 Yes: 92% (34) Abstain: 3% (1)
The addition of CDK4/6 inhibitor palbociclib to Fulvestrant, beyond 1st line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal pts, an LHRH-agonist must also be used. At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue. **ESMO MCBS: 4***	1 B	Voters: 42 Yes: 86% (36) Abstain: 10% (4)

Ann Oncol, in press

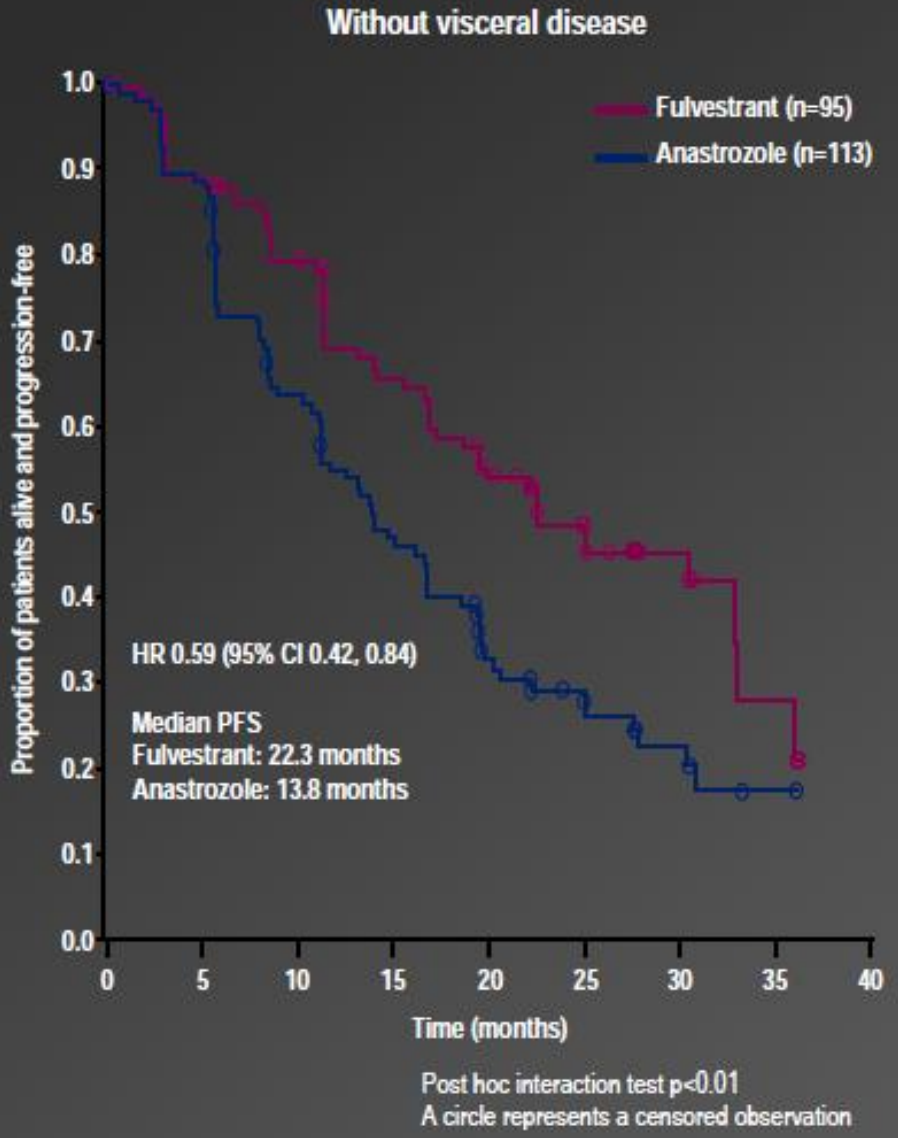
New data on endocrine therapy alone: the Falcon trial design

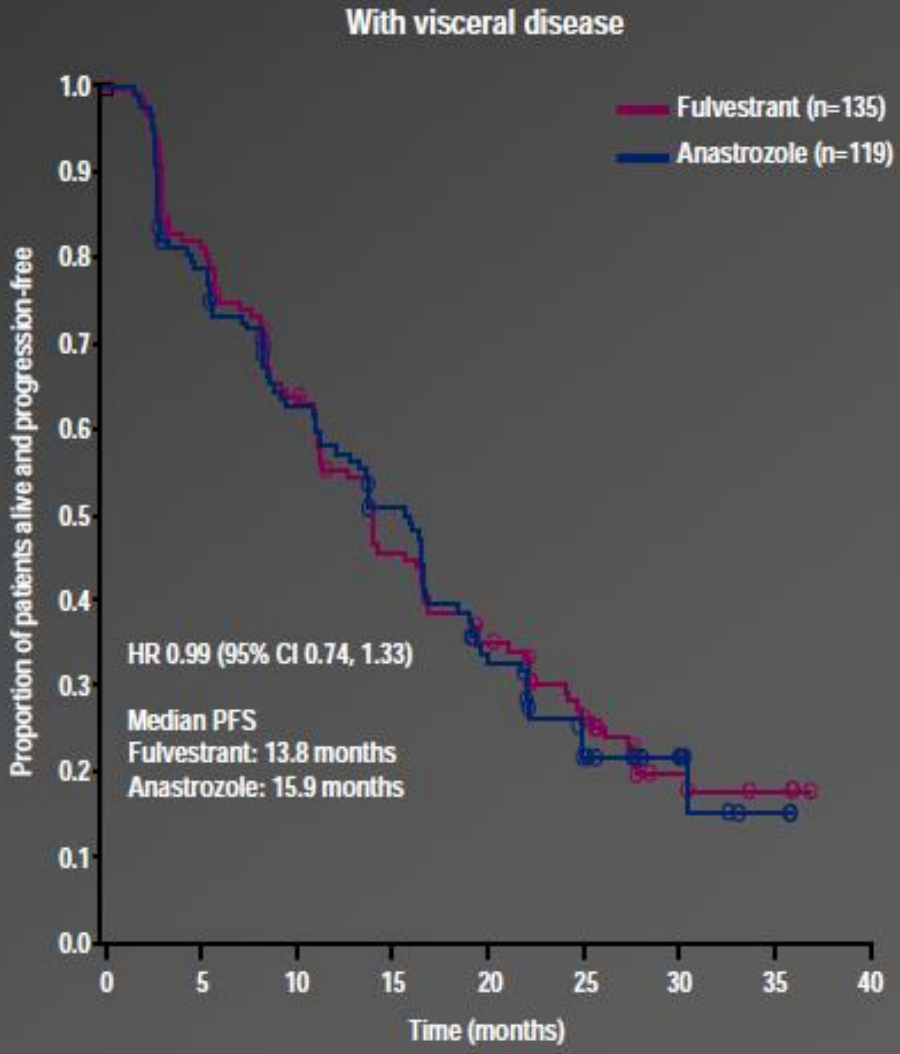


- Randomised, double-blind, parallel-group, international, multicentre study
- Follow-up for disease progression and survival
- Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test)
- Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease
- Subgroup analysis of PFS for pre-defined baseline covariates

Ellis MJ et al, proc Eur Soc Med Oncol meeting, October 2016 (abstr)

The Falcon trial: PFS results by visceral status





Post hoc interaction test p<0.01
A circle represents a censored observation

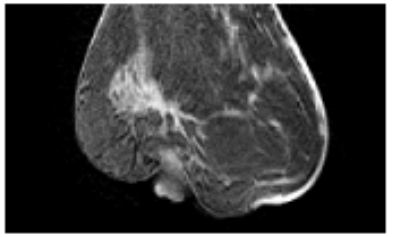
Ellis MJ et al, proc Eur Soc Med Oncol meeting, October 2016 (abstr)

Tailoring endocrine treatment in advanced Breast Cancer: Unmet Needs

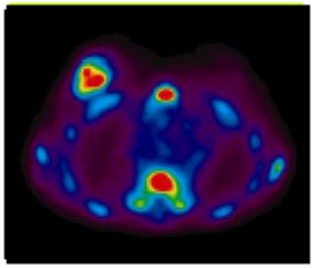
- Identification of pts likely to benefit from ET alone
  - Genomic analyses on ctDNA
  - Molecular Imaging of the Estrogen receptor «activity»

Anatomic versus Molecular Imaging

Anatomic Imaging



- size, shape, density
  - e.g. CT, MRI, echo- and mammography
- tumor response according to RECIST1.1 by changes in size after ~2 cycles
- bone metastases not measurable



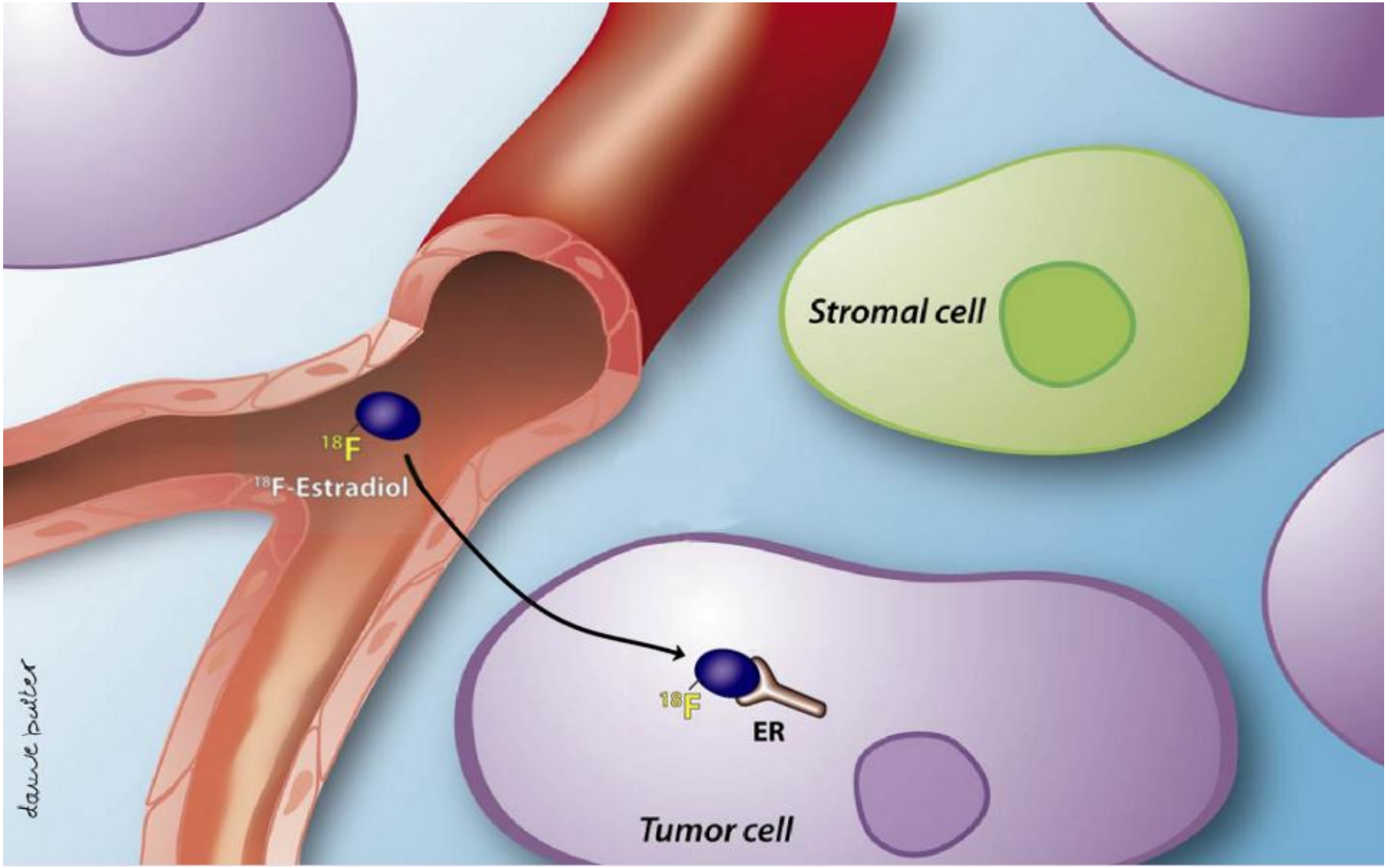
Molecular Imaging

- tumor biology *in vivo*
  - e.g. PET, SPECT, MRI
- tumor response by (early) changes in molecular processes

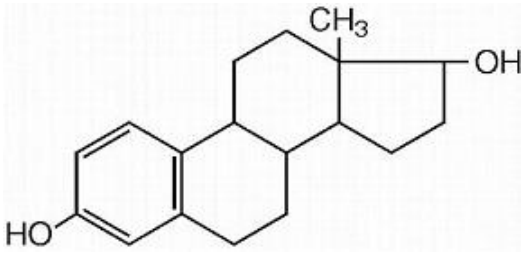
Why molecular imaging beyond FDG-PET

- To see target expression across lesions in a patient
- To see target conversion in a lesions over time
- To detect heterogeneity within lesions
- To see (heterogeneous) drug distribution
- To guide staging
- To guide surgery

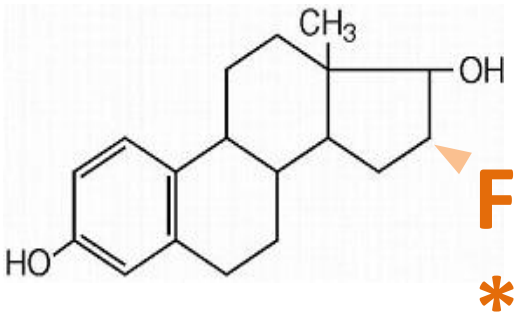
Visualization ER



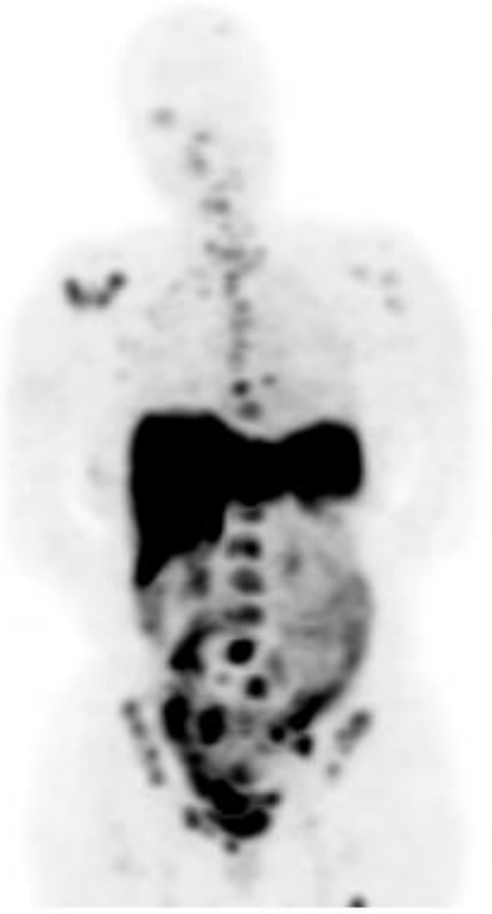
16α-[18F]-fluoro-17β-estradiol (FES)
PET tracer for ER imaging



Estradiol



FES



- Good correlation FES uptake & ER expression immunohistochemically
- FES tumor uptake predictive for response to anti-hormone therapy. Low FES uptake no response

Peterson et al, J Nucl Med 2008
Linden HM et al, J Clin Oncol 2006
Van Kruchten et al, Lancet Oncol 2013

Patients with history ER+ breast cancer: presenting with a diagnostic dilemma

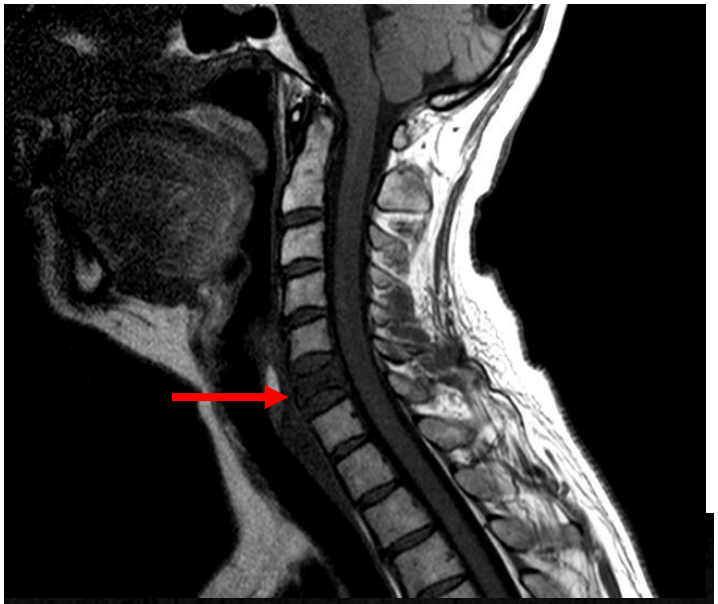
- 33 patients
- Number of lesions:
  - FES-PET: n = 398
  - Conventional imaging: n = 319

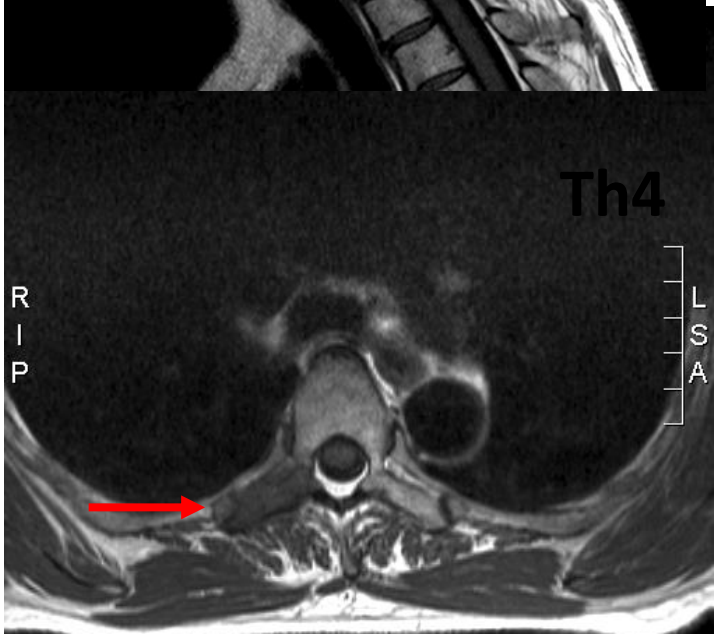
- FES-PET effect for patients
  - In 88% improved diagnostic understanding
  - in 48% change in therapy

Van Kruchten et al, J Nucl Med 2011

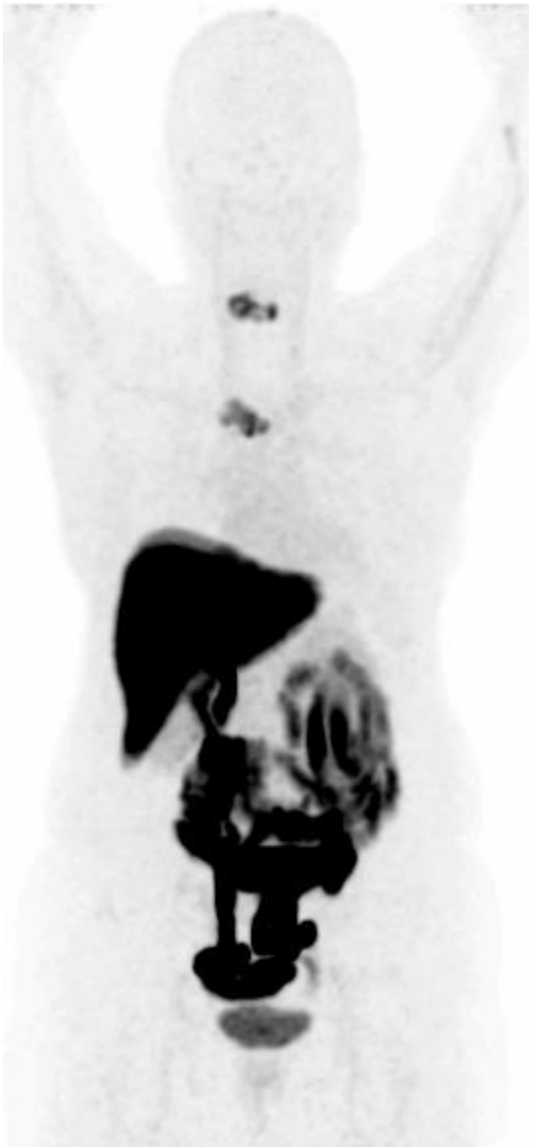
MRI suspicion of metastases C6 & Th4
4 years earlier small primary ER + breast tumor

MRI

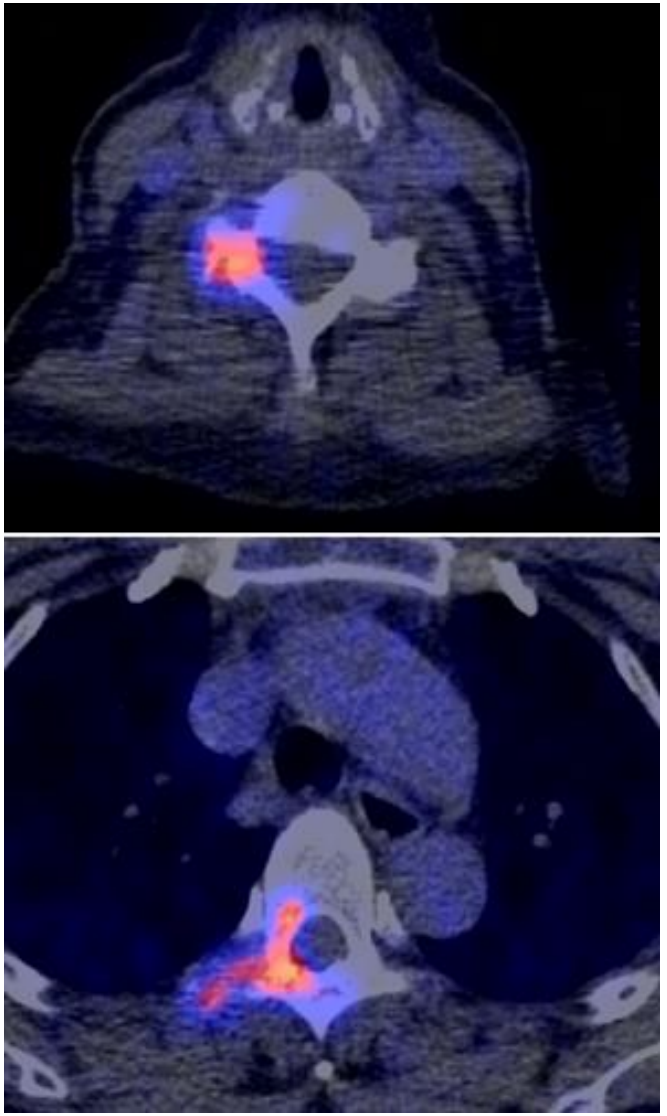




FES-PET

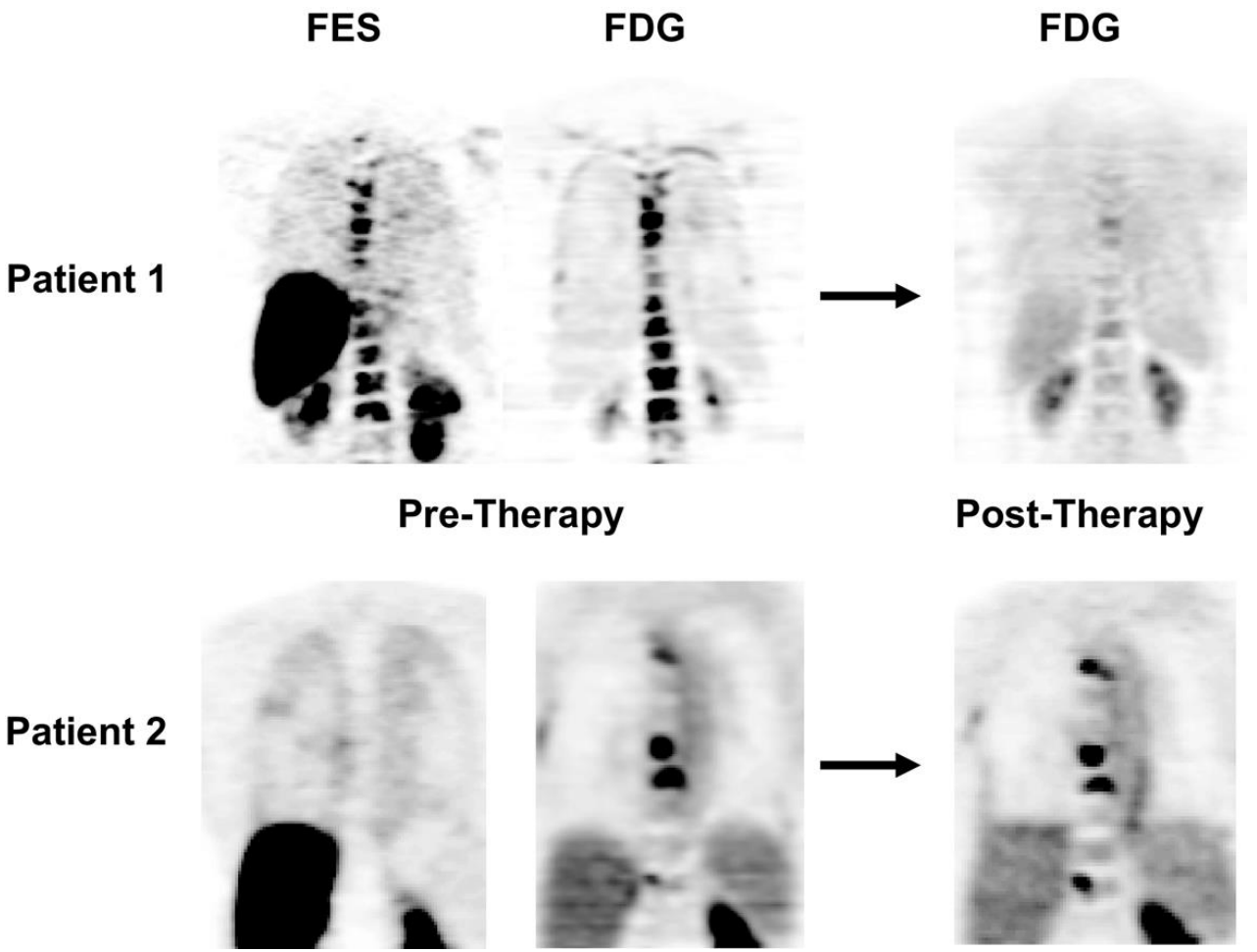


FES-PET/MRI



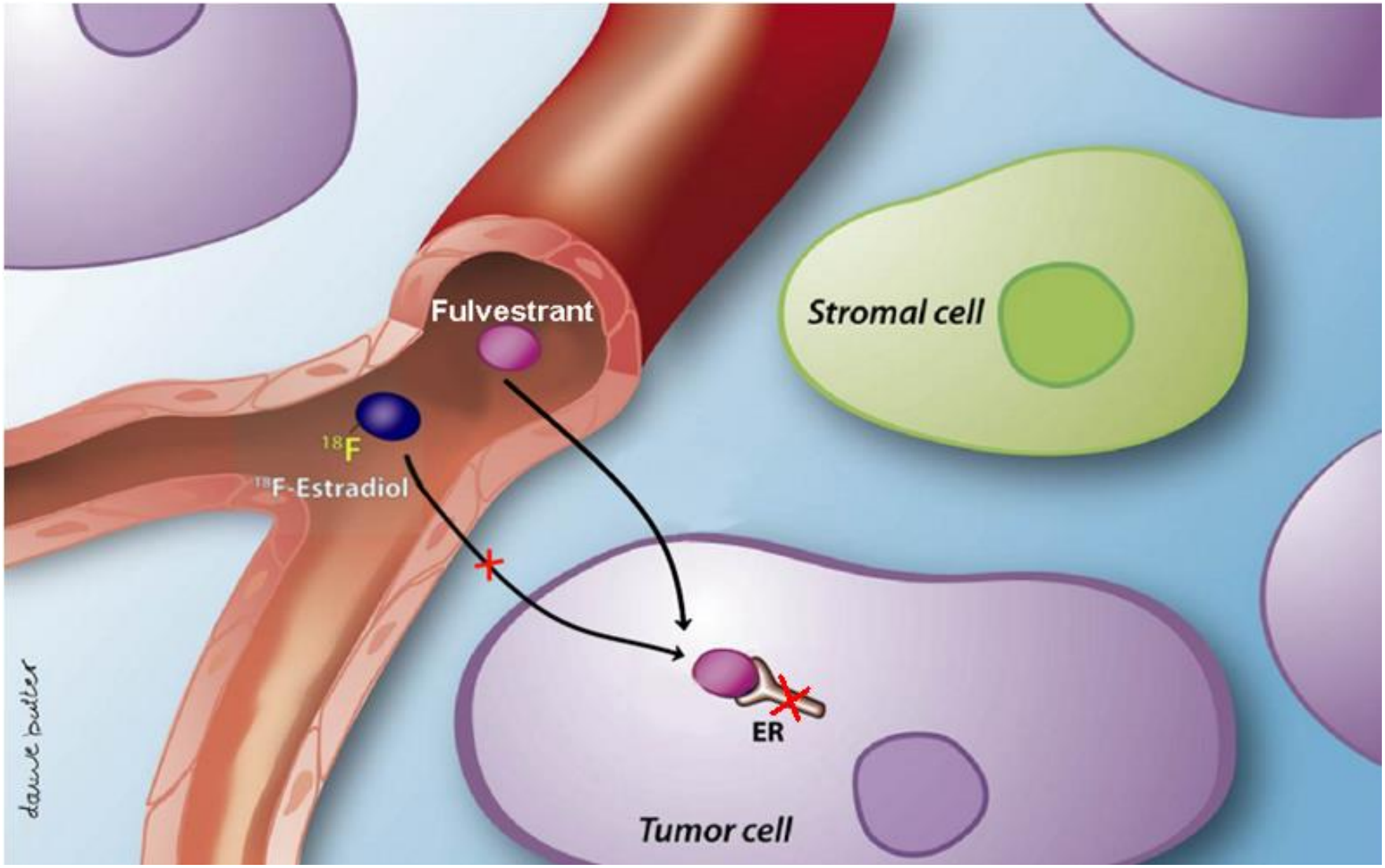
Van Kruchten et al, J Nucl Med 2011

Response to Endocrine Therapy
FES vs FDG



18F-Fluoroestradiol

Monitoring fulvestrant effects on tumor ER

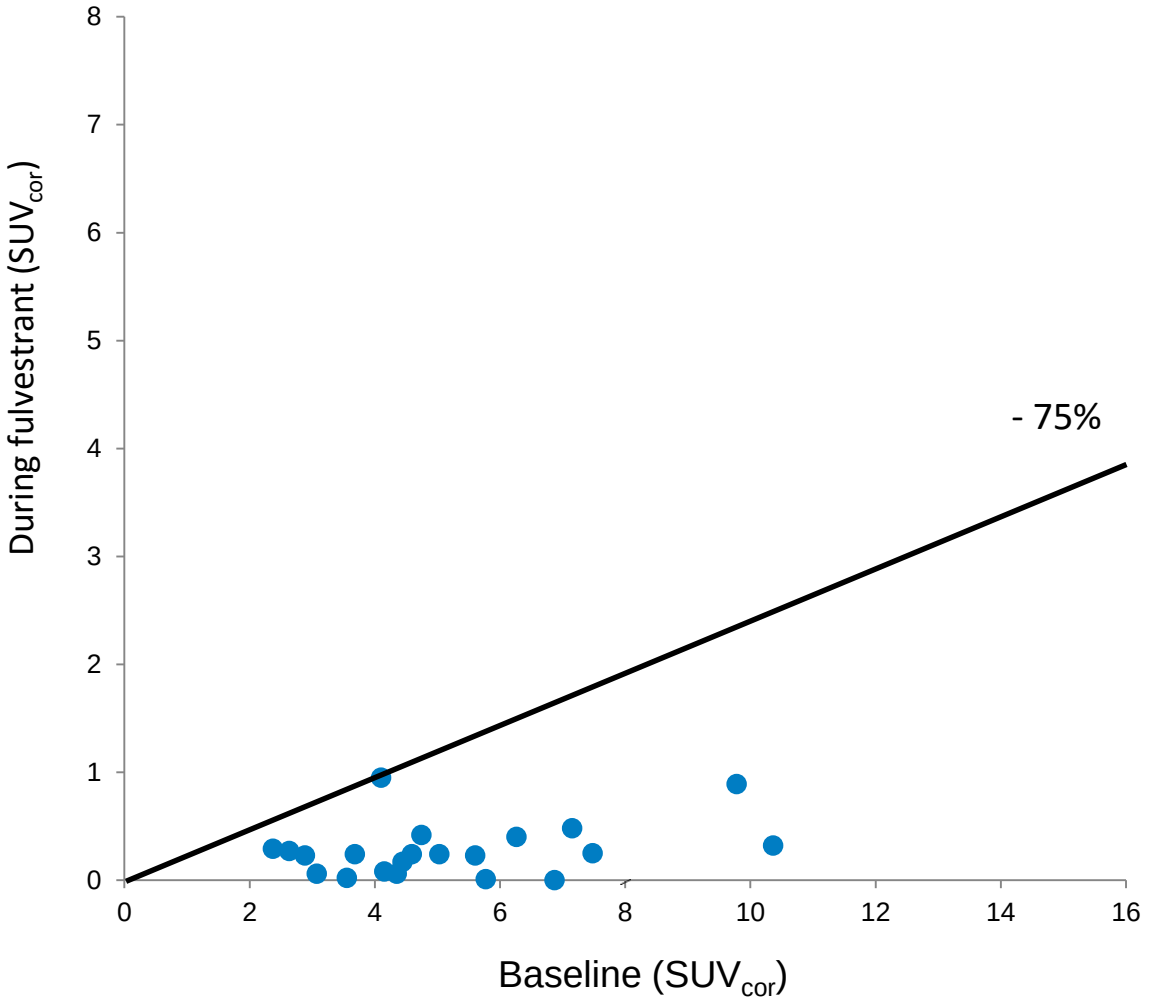


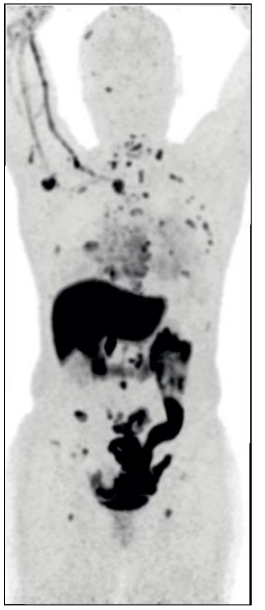
Monitoring effects of fulvestrant on tumor ER

- Fulvestrant leads to blockade and degradation of tumor ER-expression
- Optimal fulvestrant dose currently considered
  - 500 mg im/ 4 weeks + ‘loading dose’ day 14
- Trial with serial FES-PET before and during fulvestrant (days 0, 28 and 84)

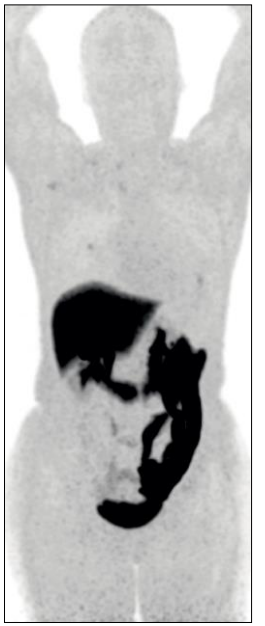
Van Kruchten et al, Cancer Disc 2015

Excellent blockade FES uptake during fulvestrant



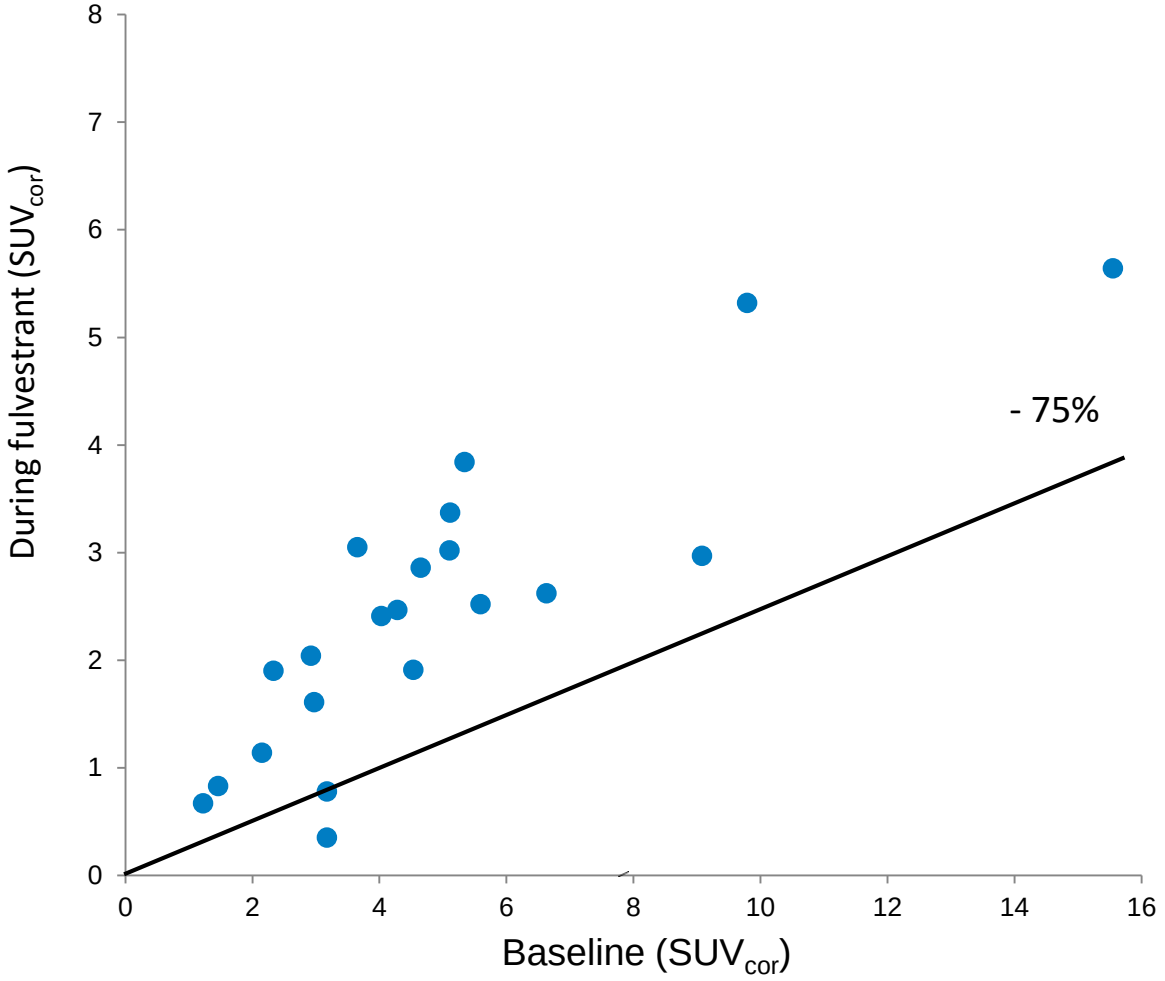


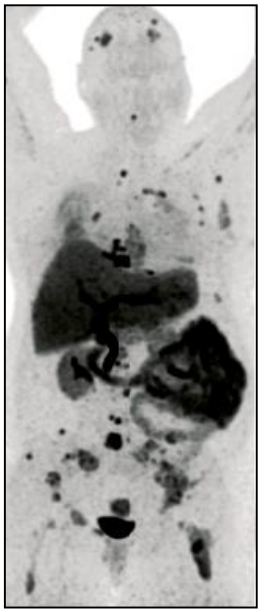
Baseline



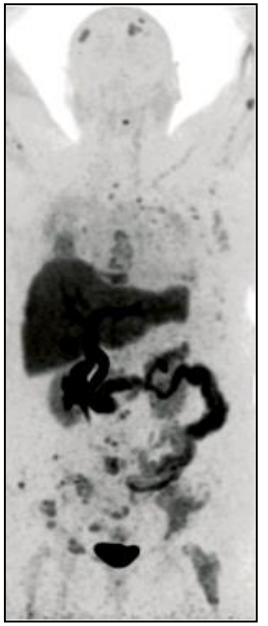
Day 28

Bad blockade FES uptake during fulvestrant



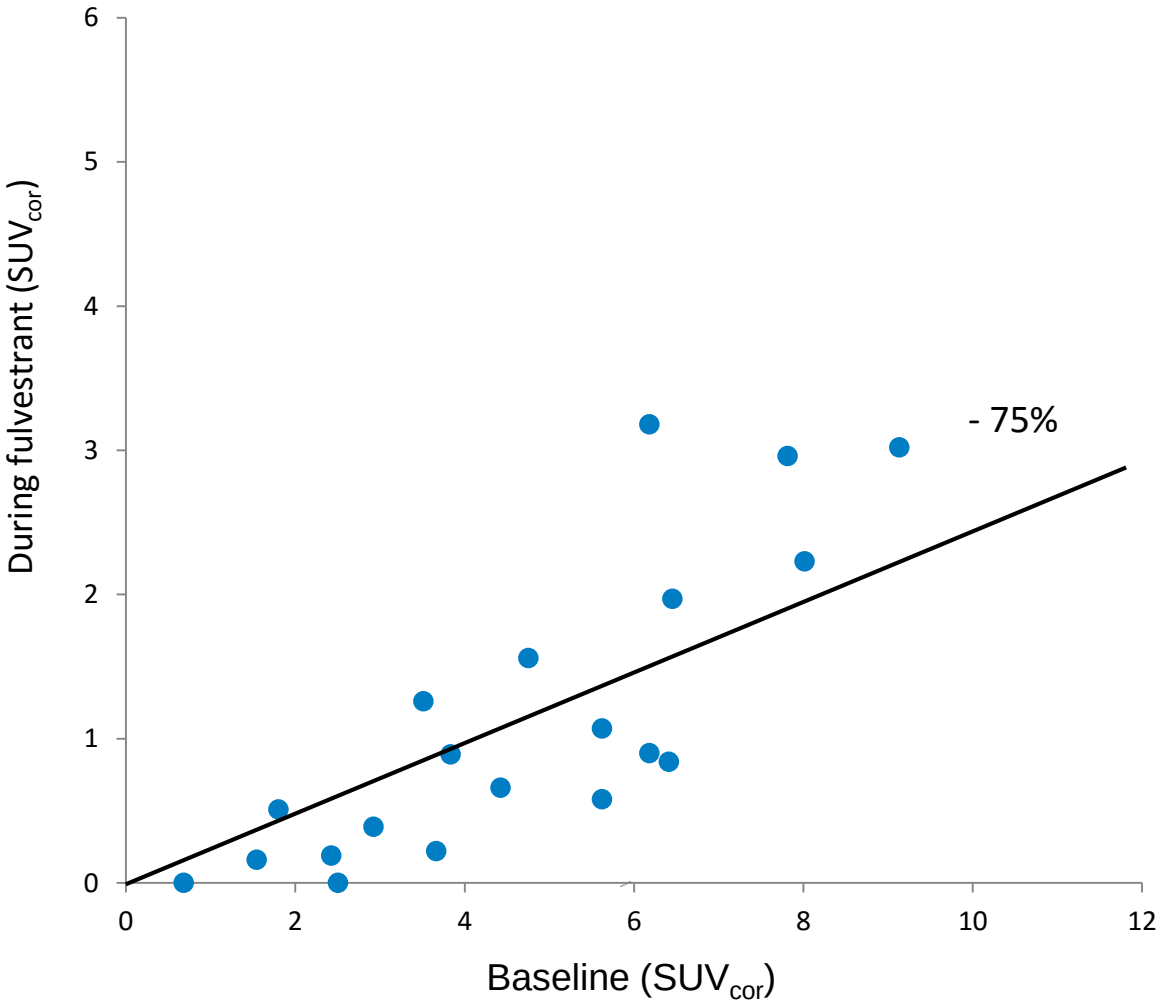


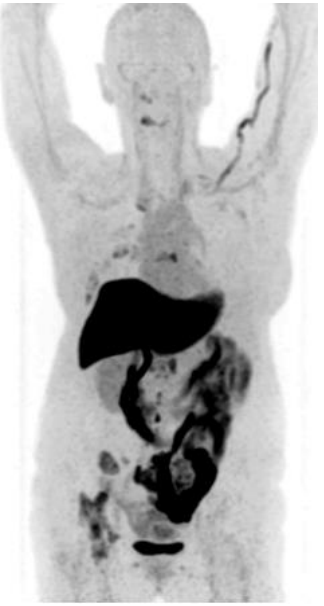
Baseline



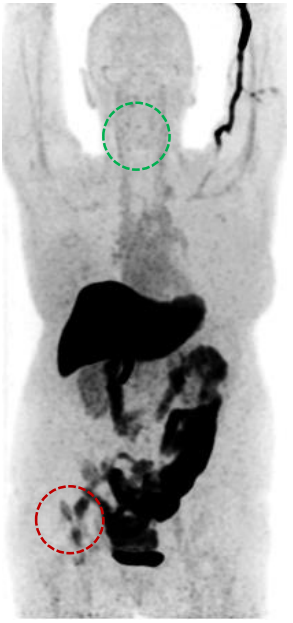
Day 28

Heterogenous blockade FES uptake during fulvestrant



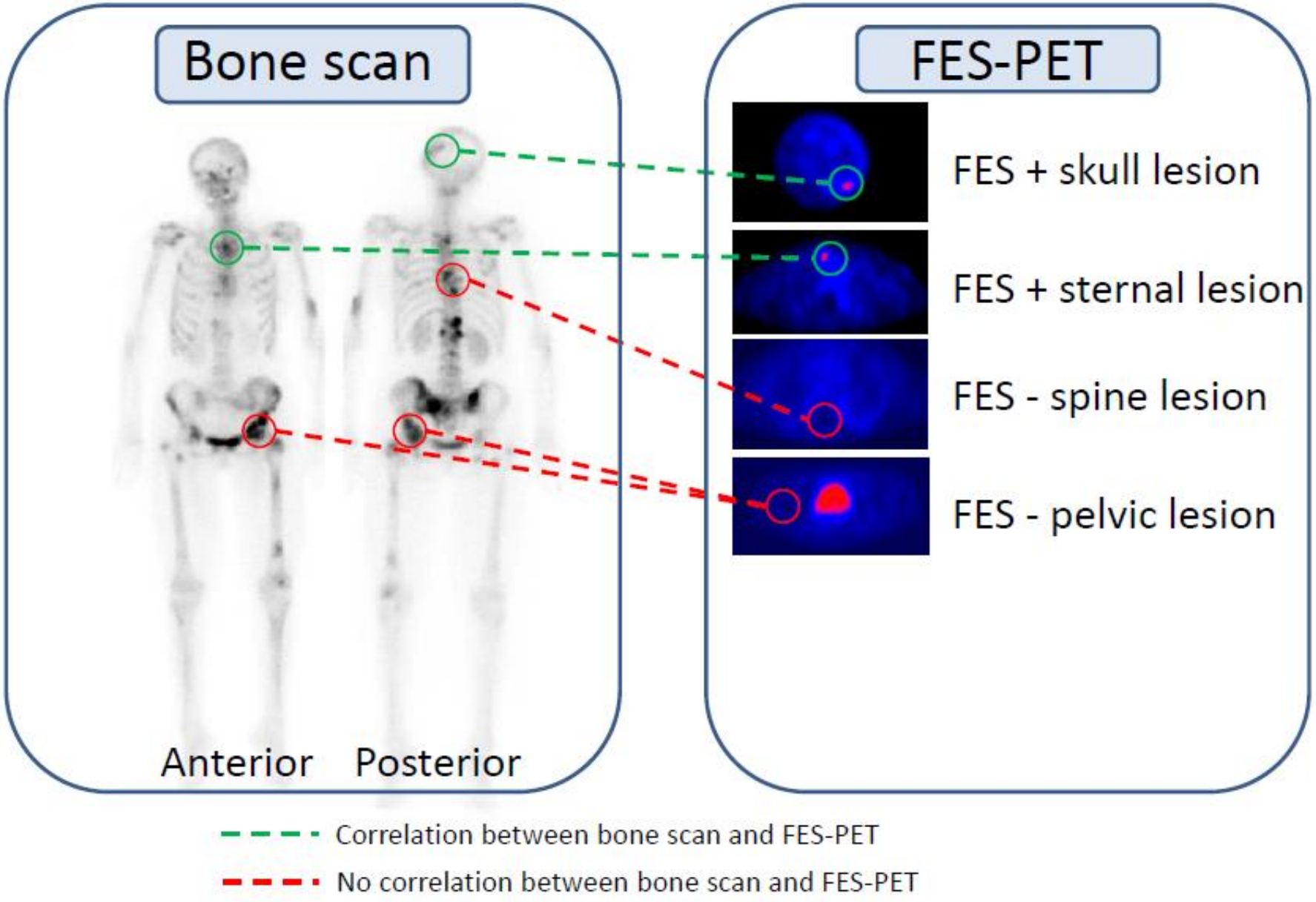


Baseline

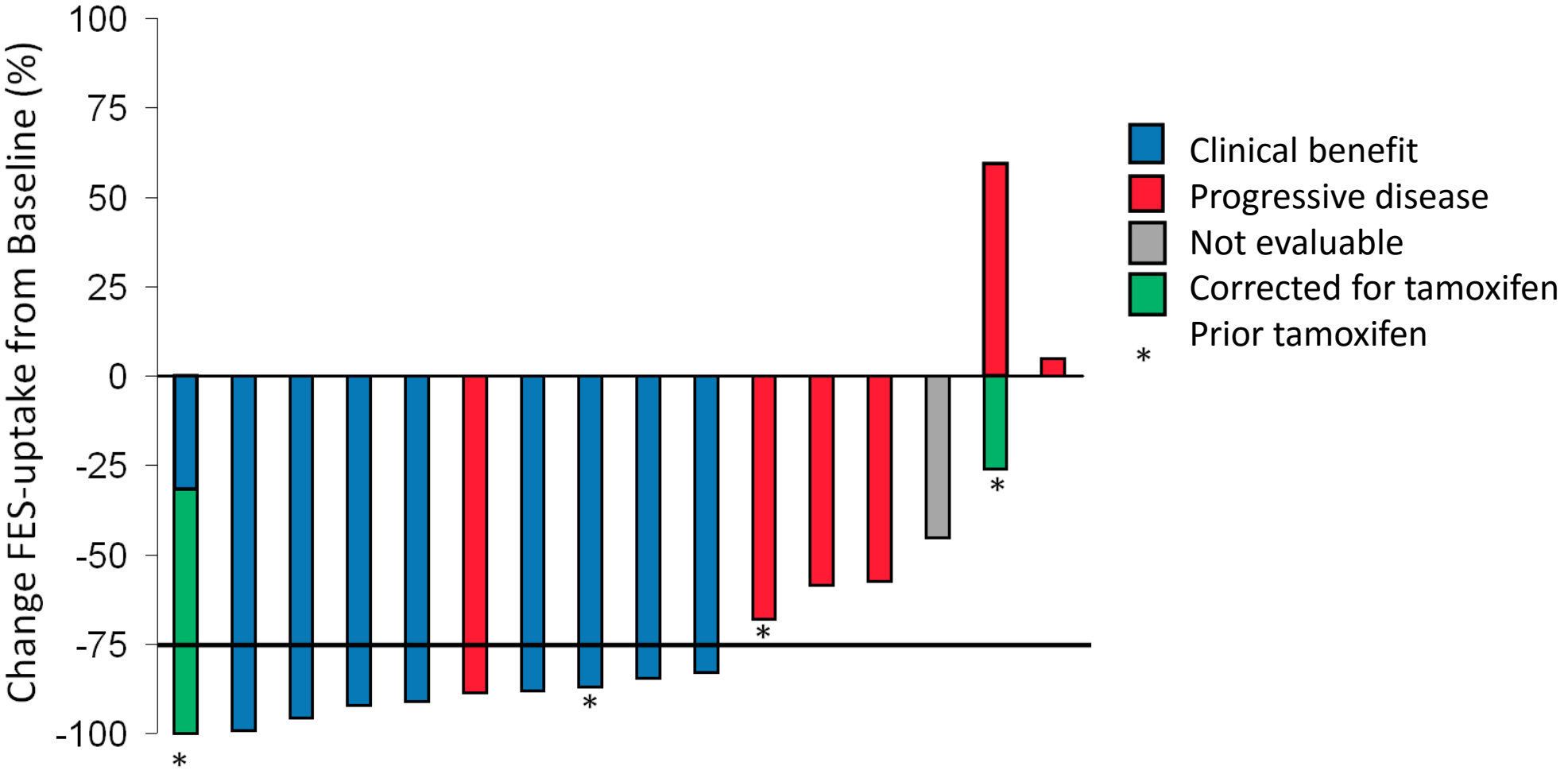


Day 28

Intra-patient heterogeneity



Waterfall plot: Changes in tumor FES-uptake before & during fulvestrant (day 28) of all patients

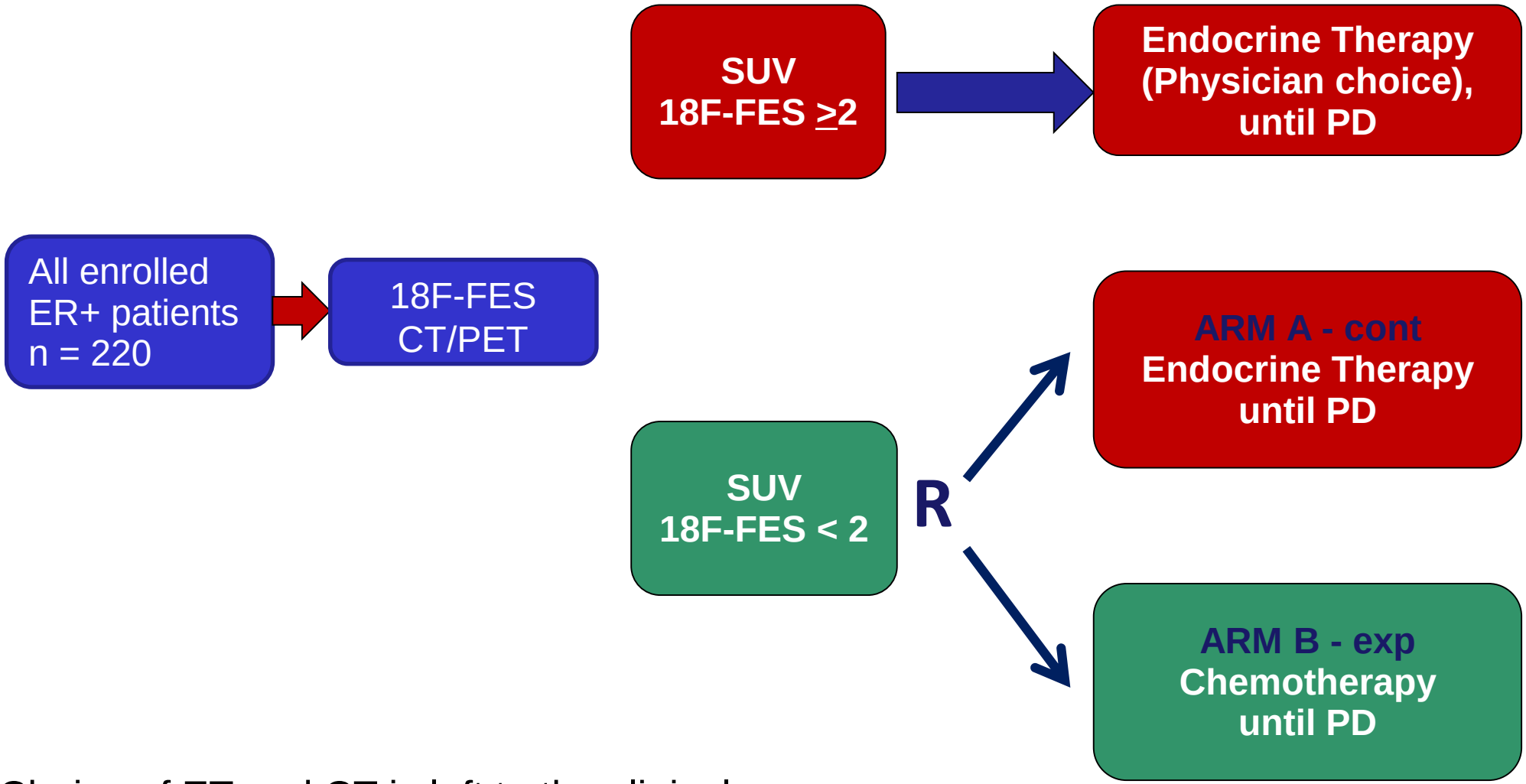


Van Kruchten et al, Cancer Disc 2015

TRANSCAN
ERA-NET on Translational Cancer Research

ET-FES Project

TRANSCAN



Choice of ET and CT is left to the clinical judgment of the treating physician, according to local clinical practice.

Ente Ospedaliero Ospedali Galliera Genova

ET-FES: Partners

1. **Partner # 1:** Project Coordinator Alessandra Gennari, Genova, IT
2. **Partner # 2:** Dino Amadori, Meldola, FC, IT
3. **Partner # 3:** Javier Cortes, Barcelona, E
4. **Partner # 4:** Nadia Harbeck, Munich, DE
5. **Partner # 5:** Etienne Brain, St Cloud, FR

ET-FES Project Development

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

2.Translational study: this will include the evaluation of estrogen-related genes on primary tumor and biopsies of metastatic sites. Expression data will then be correlated with 18F-FES Uptake results.

ET-FES Italian Extension: funded by the Italian Association for Cancer Research

• 90 patients with the same characteristics will be enrolled by 7 additional italian centers

• All study procedures will be the same

• Tumor sample collection at baseline is mandatory

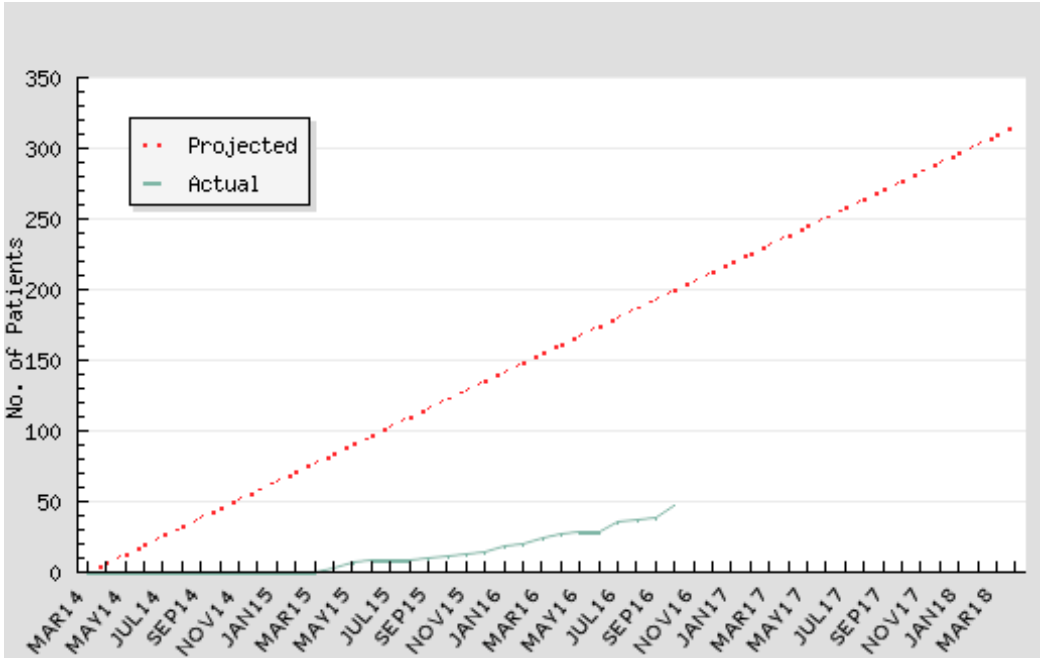
Primary objective:

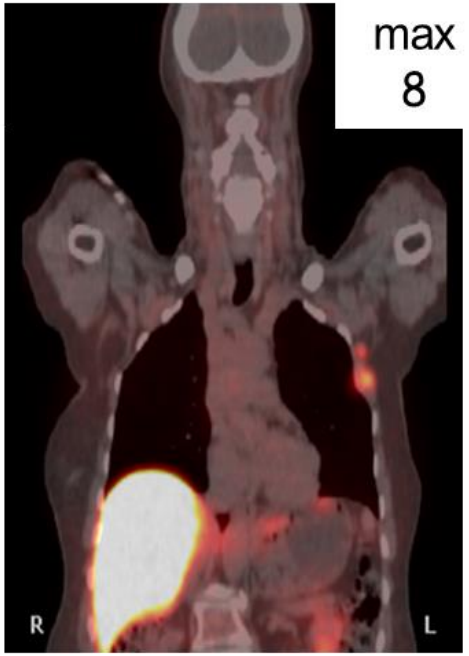
- to assess tumor biology (centralised ER assessment, PgR, HER2/3, steroid co-receptor activators SRCs family

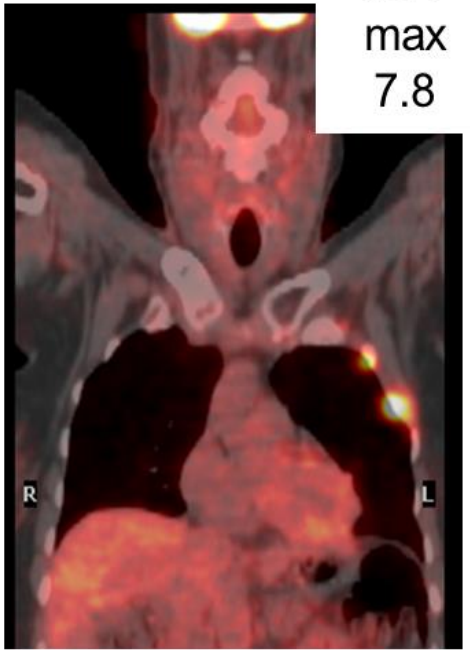
ET-FES Study Accrual

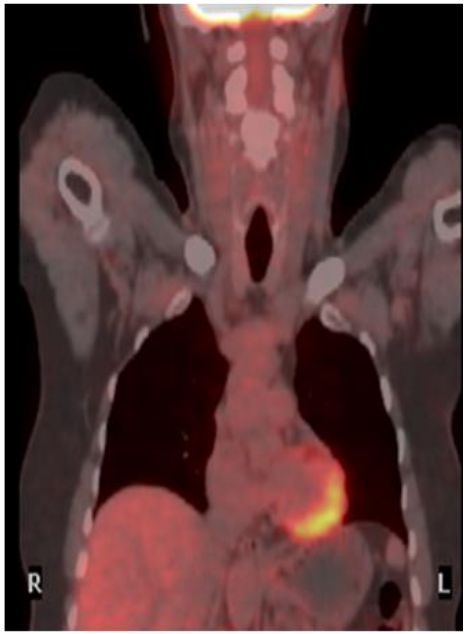
1. EO Galliera, Genoa, IT 19
2. IRCCS-IRST Meldola, IT 15
3. Institute Curie, St Cloud, FR 15
4. VHIO, SP 0
5. University Munich, DE NA

Overall Accrual: 49 pts









^{18}F-FDG PET/CT

^{18}F-FES PET/CT

ET

^{18}F-FDG PET/CT

ET +CT

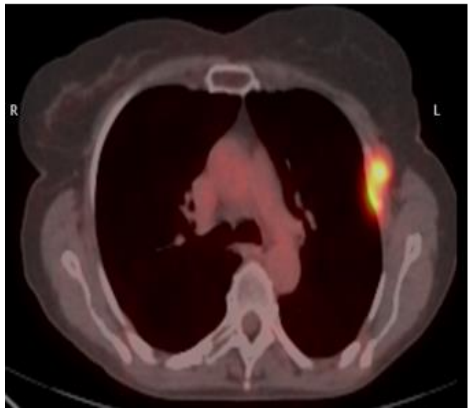
^{18}F-FDG PET/CT

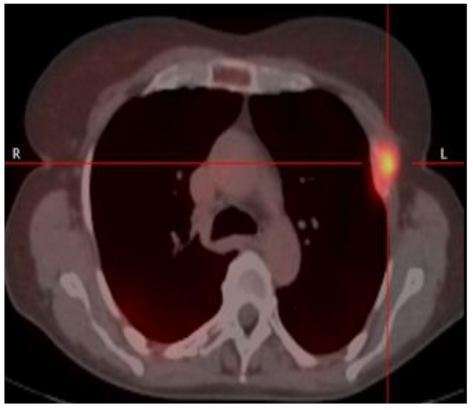
04/05/2015

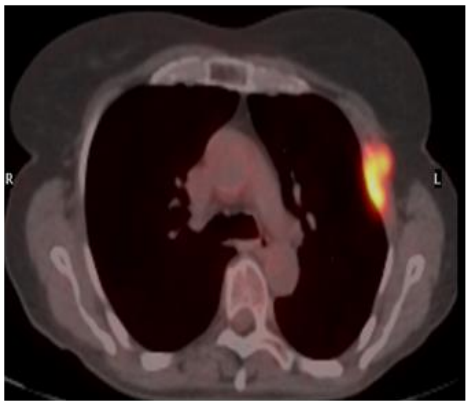
06/05/2015

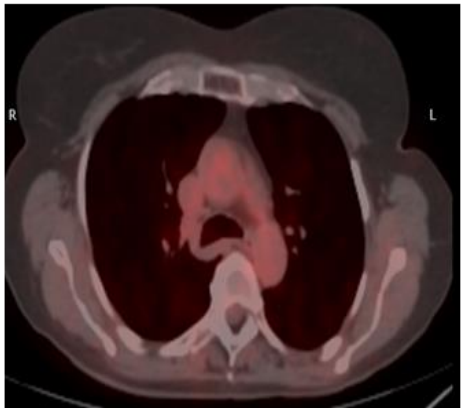
11/08/2015

01/08/2016

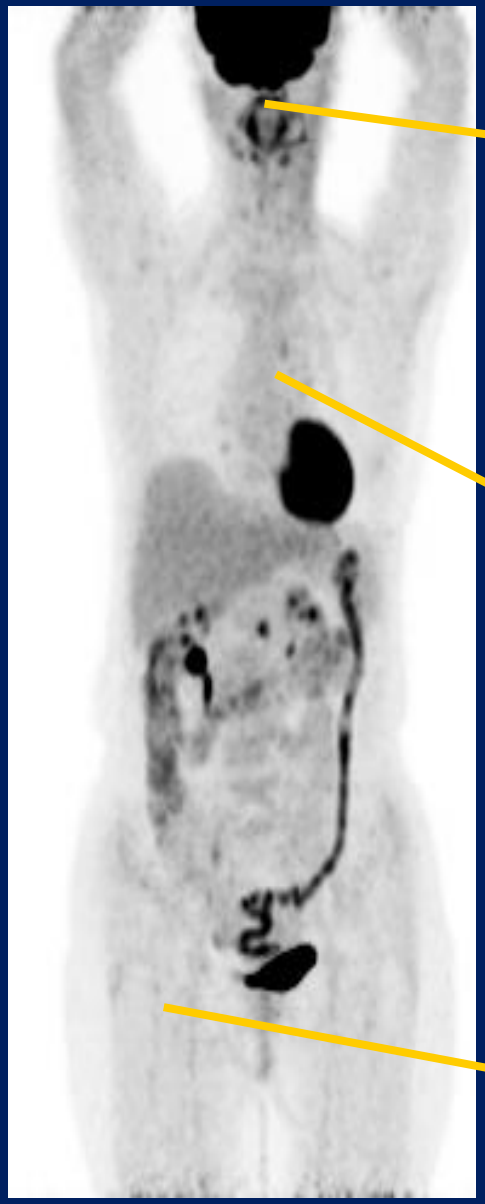


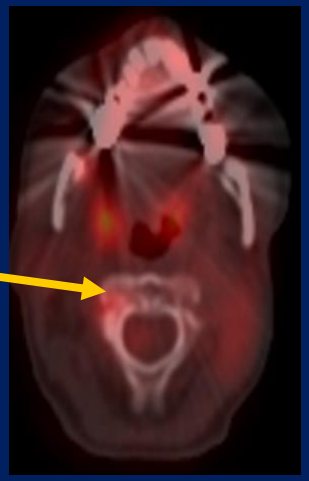


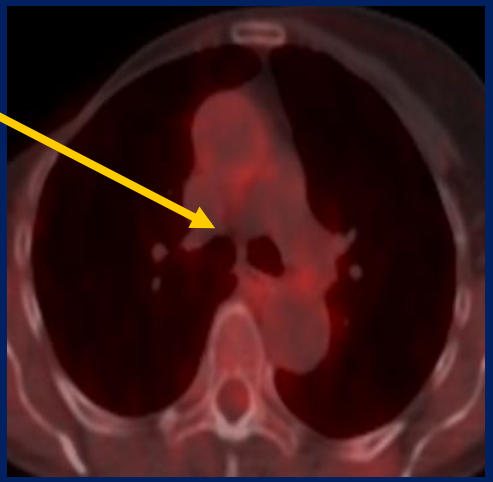


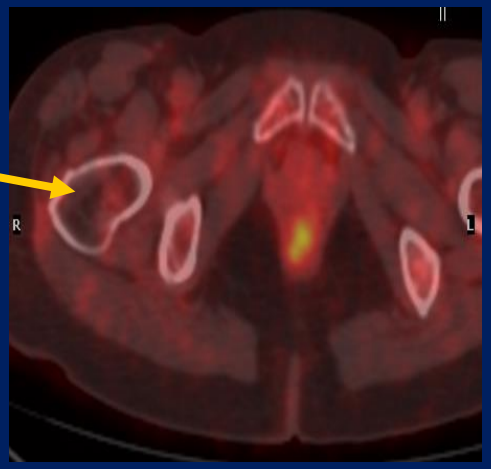


SUV max 2



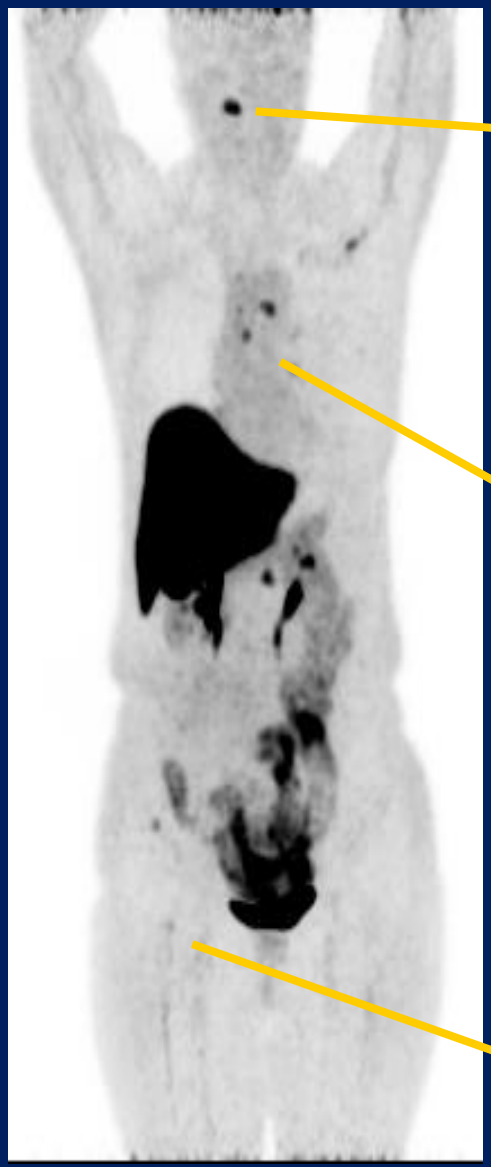


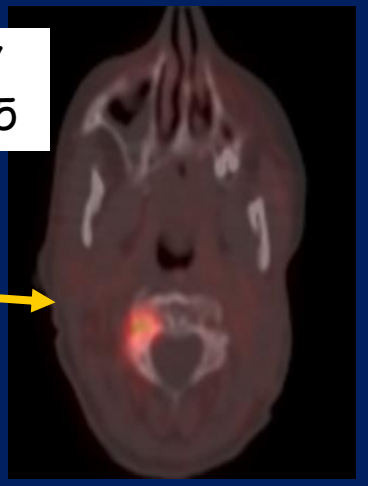


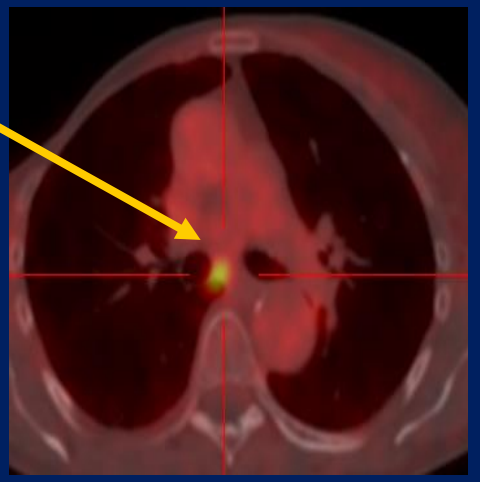


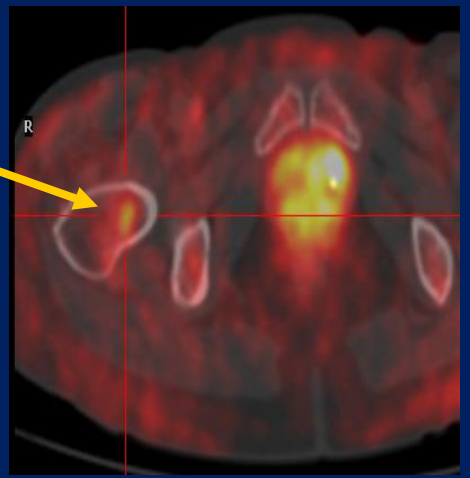
^{18}F-FDG PET/CT

SUV max 5

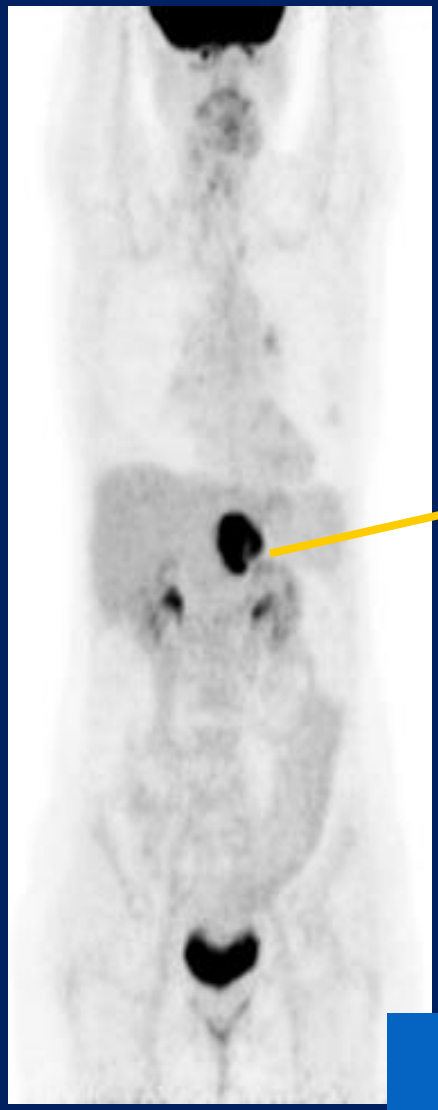


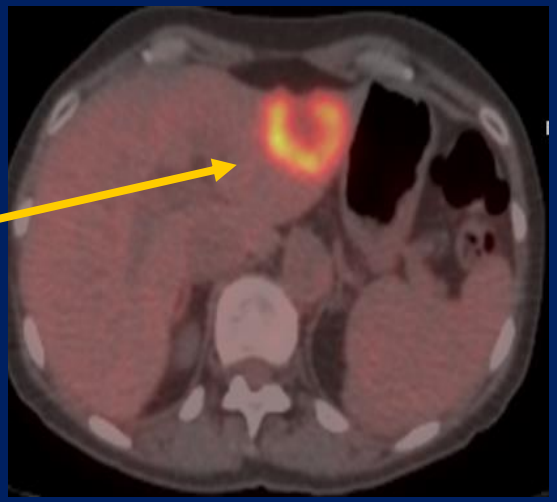




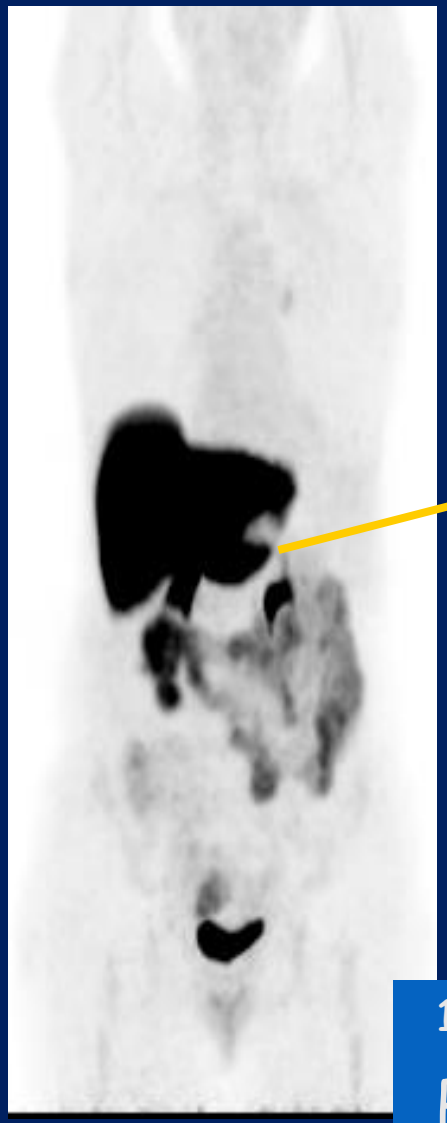


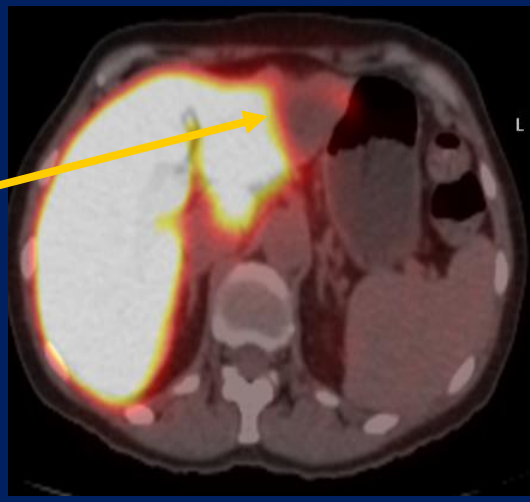
^{18}F-FES PET/CT



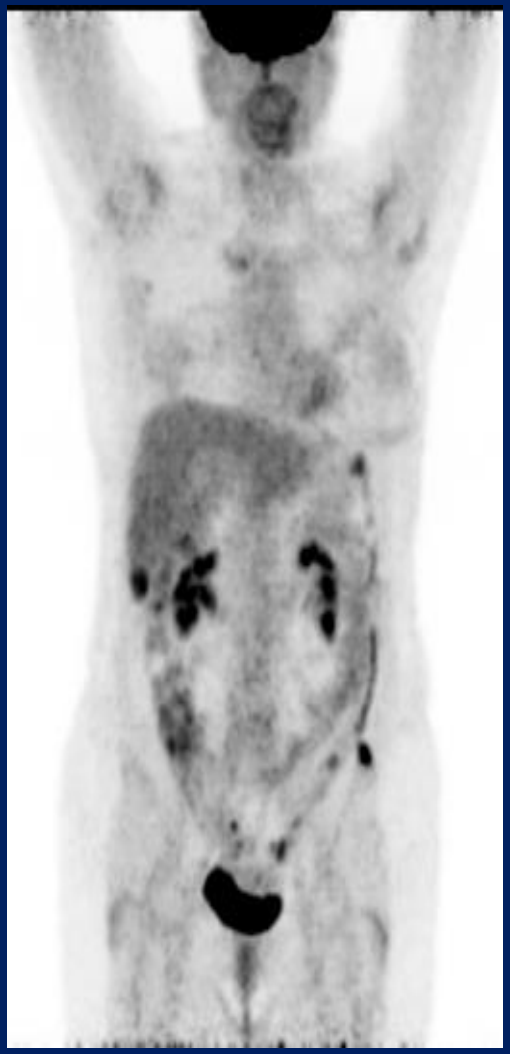


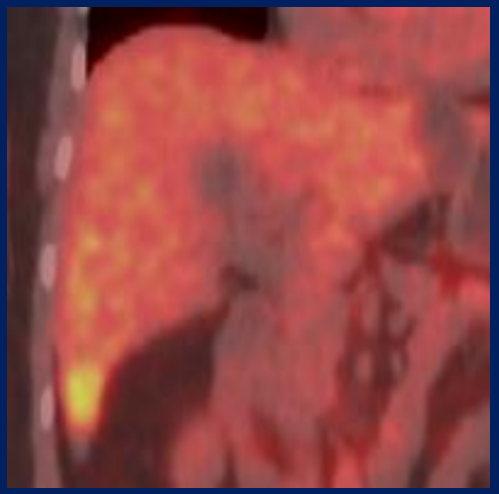
^{18}F-FDG
PET/CT

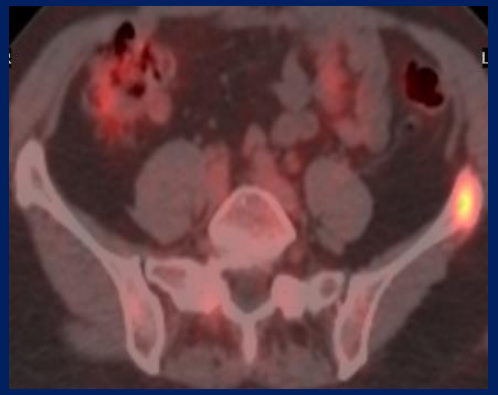




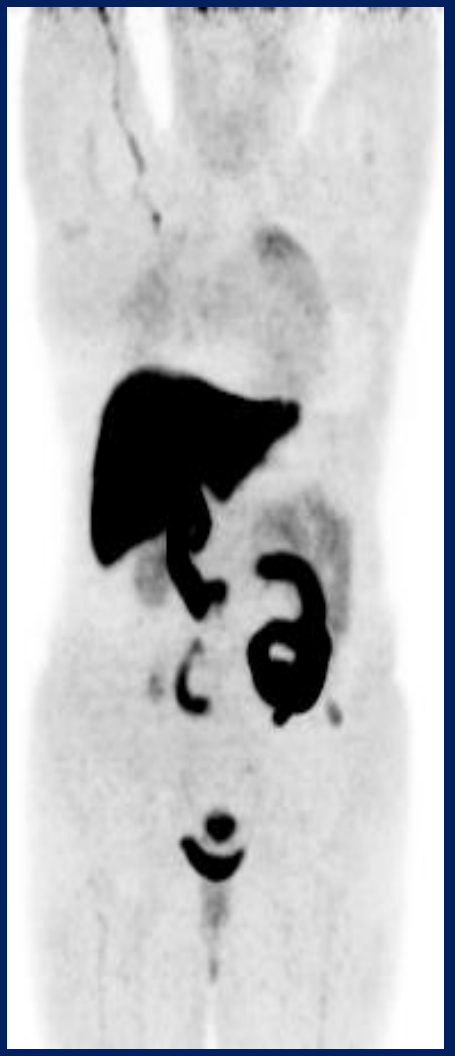
^{18}F-FES
PET/CT

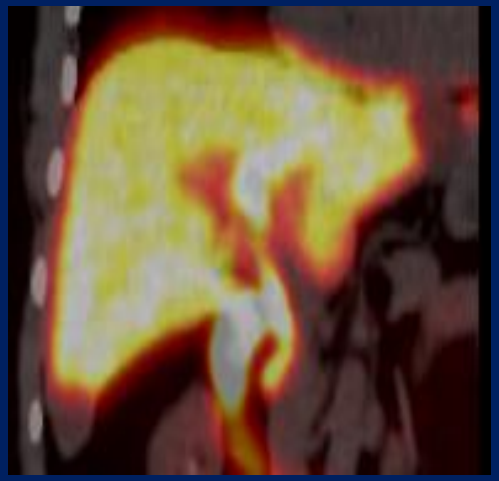


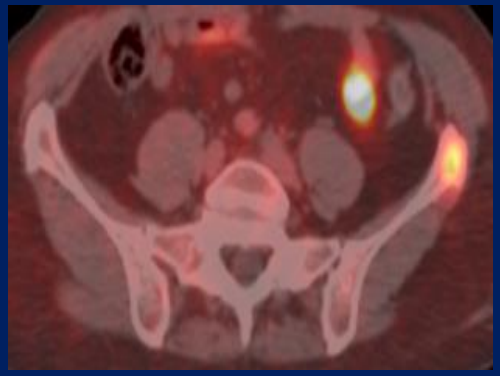




^{18}F-FDG
PET/CT







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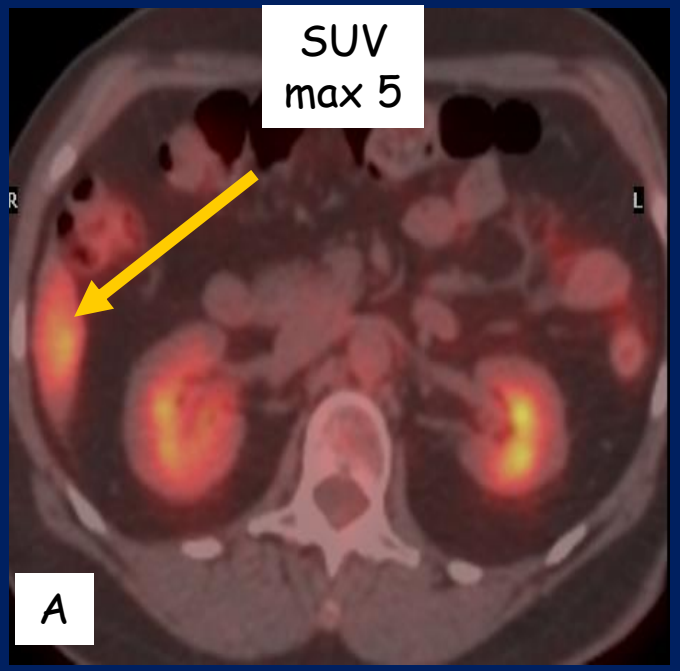
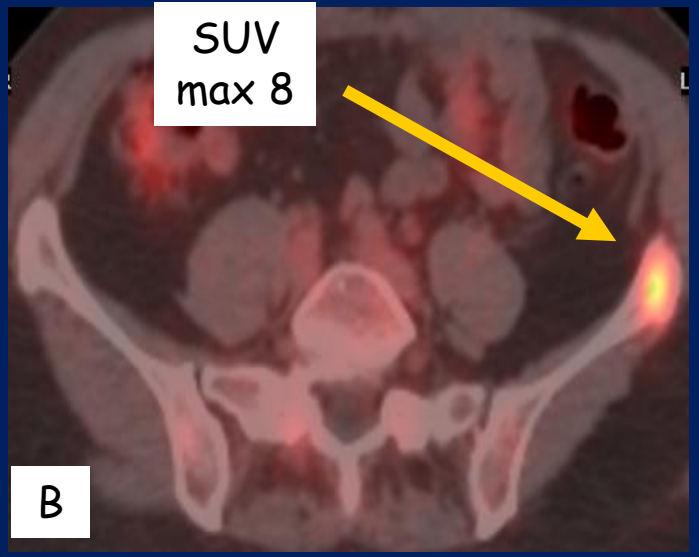
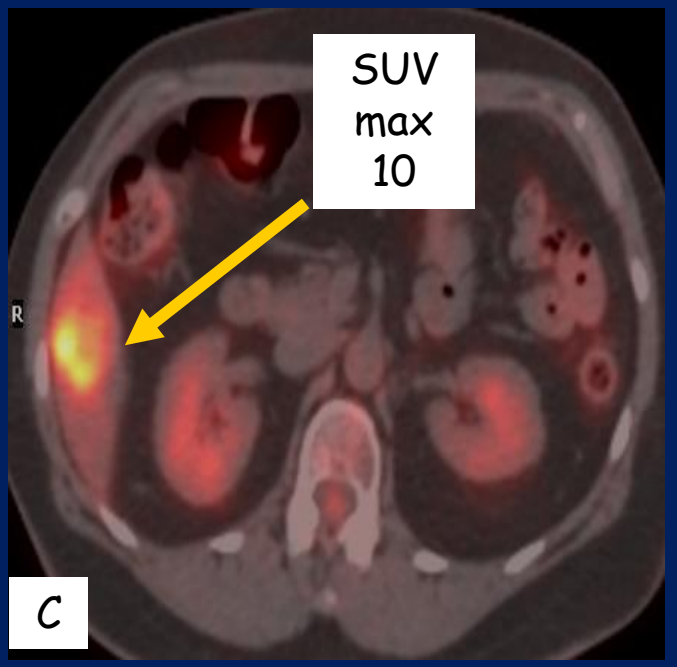
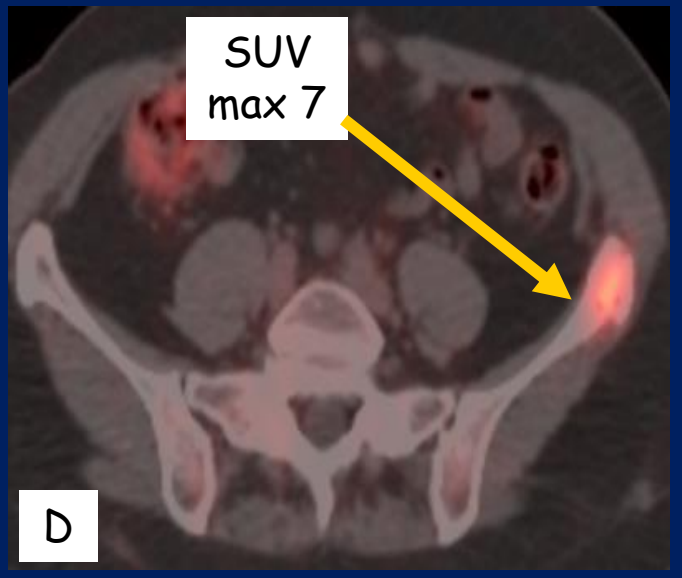








^{18}F-FDG PET/CT pre therapy

^{18}F-FDG PET/CT post therapy

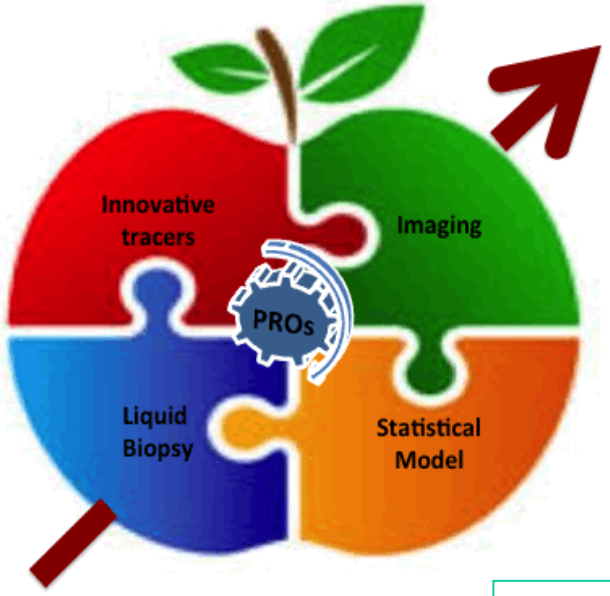
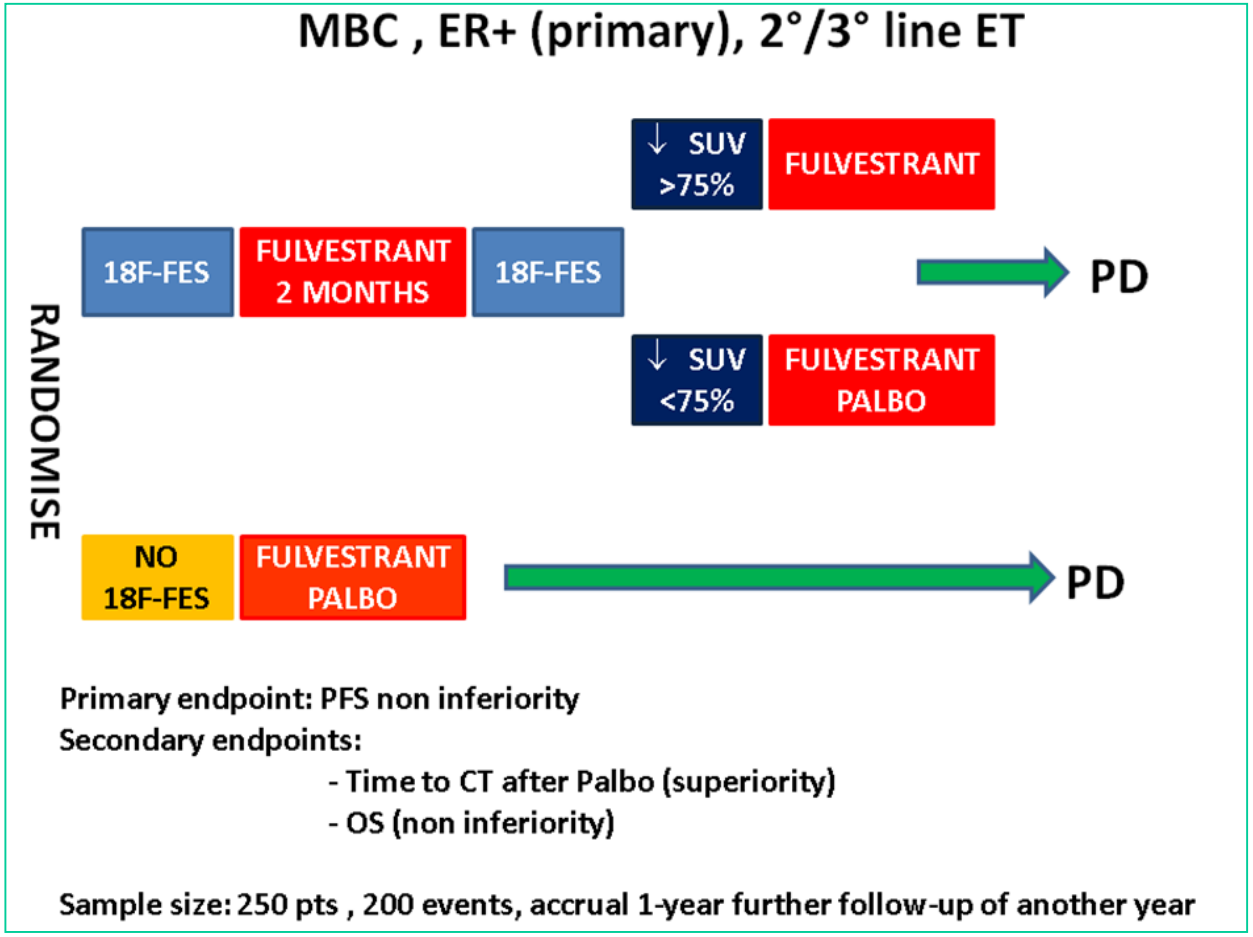


Figure 1 NEWTON stratification concept

NEWTON 2.0

Innovative Approach To Breast Cancer Endocrine Treatment Tailoring Through Personalized Molecular Imaging And Genomic Analysis



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