BIOMARKERS IN BREAST CANCER

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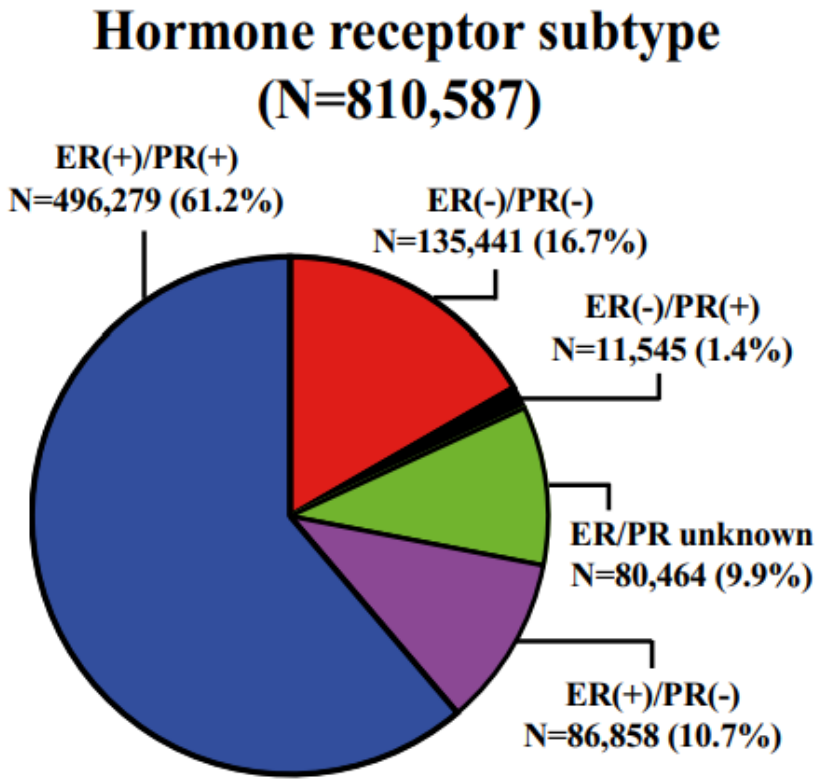
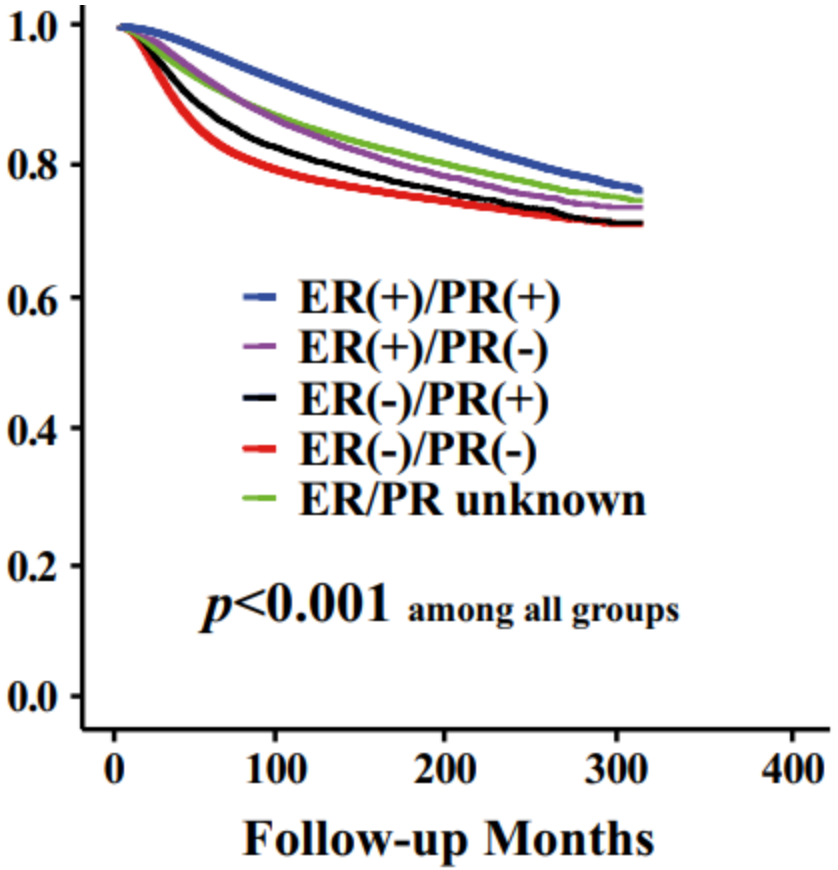
Biomarkers in breast cancer

- Traditional
  - Nodal status
  - Tumor Size
  - Tumor grade
  - ER, PR
  - HER2
- Molecular
  - Oncotype
  - MammaPrint
- Functional Imaging
  - Estrogen
  - HER2
- Predictive Markers
  - ESR1
  - ER, PR
  - HER2
  - PIK3/akt
- Potential Targets
  - ER, PR
  - HER2
  - Trop 2
  - HER3

Long-term prognostic Effect of hormone receptor subtype on breast cancer

810,587 women with operable invasive cancers from SEER with mean f/up of 94.2 months

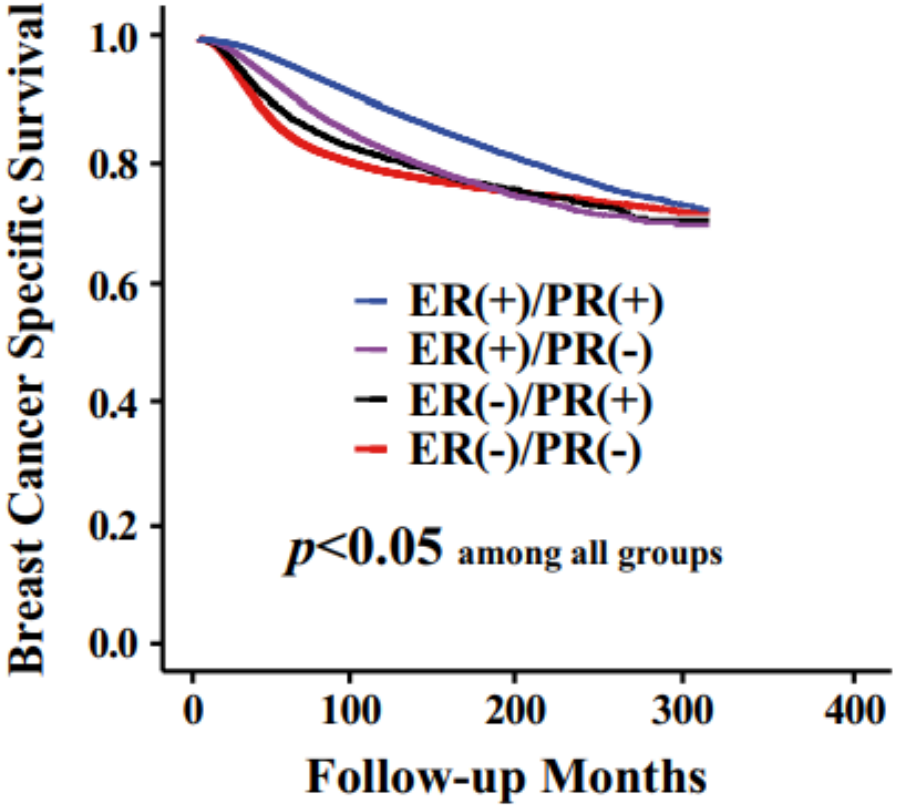




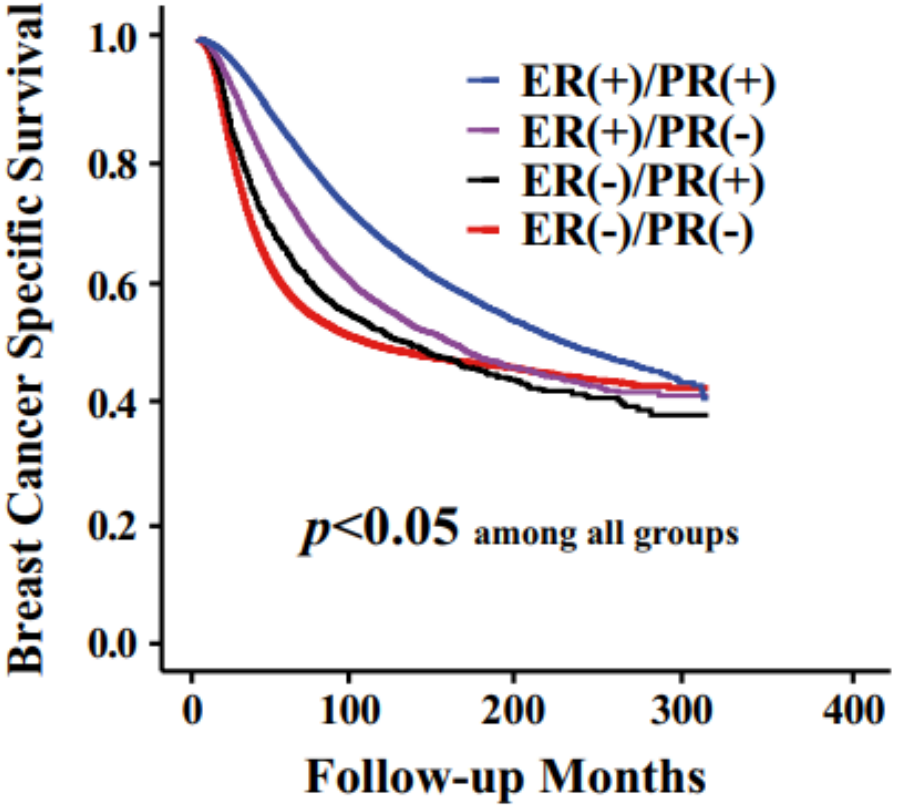
Hwang, Br Ca Res and Treat 202;179:139-151

Long-term prognostic Effect of hormone receptor subtype on breast cancer

810,587 women with operable invasive cancers from SEER with mean f/up of 94.2 months



Stage II (N=295,378)



Stage III (N=108,926)

Hwang, Br Ca Res and Treat 202;179:139-151

Significance of PR in Stage IV ER+ Breast Cancer Response to Tamoxifen

		% Response with PgR Level (fmol/mg)		
Patient Subset	Number	<10	10-99	≥ 100
All	342	43	53	64
ER < 50 fmol/mg	120	31	42	59
ER ≥ 50 fmol/mg	222	53	59	66

Ravdin, JCO 1992;10: 1284-1291

Nex Generation Sequencing directs subsequent therapy in HR+ disease

KEY ✓ Approved in Indication ~ Approved in Other Indication × Lack of Response

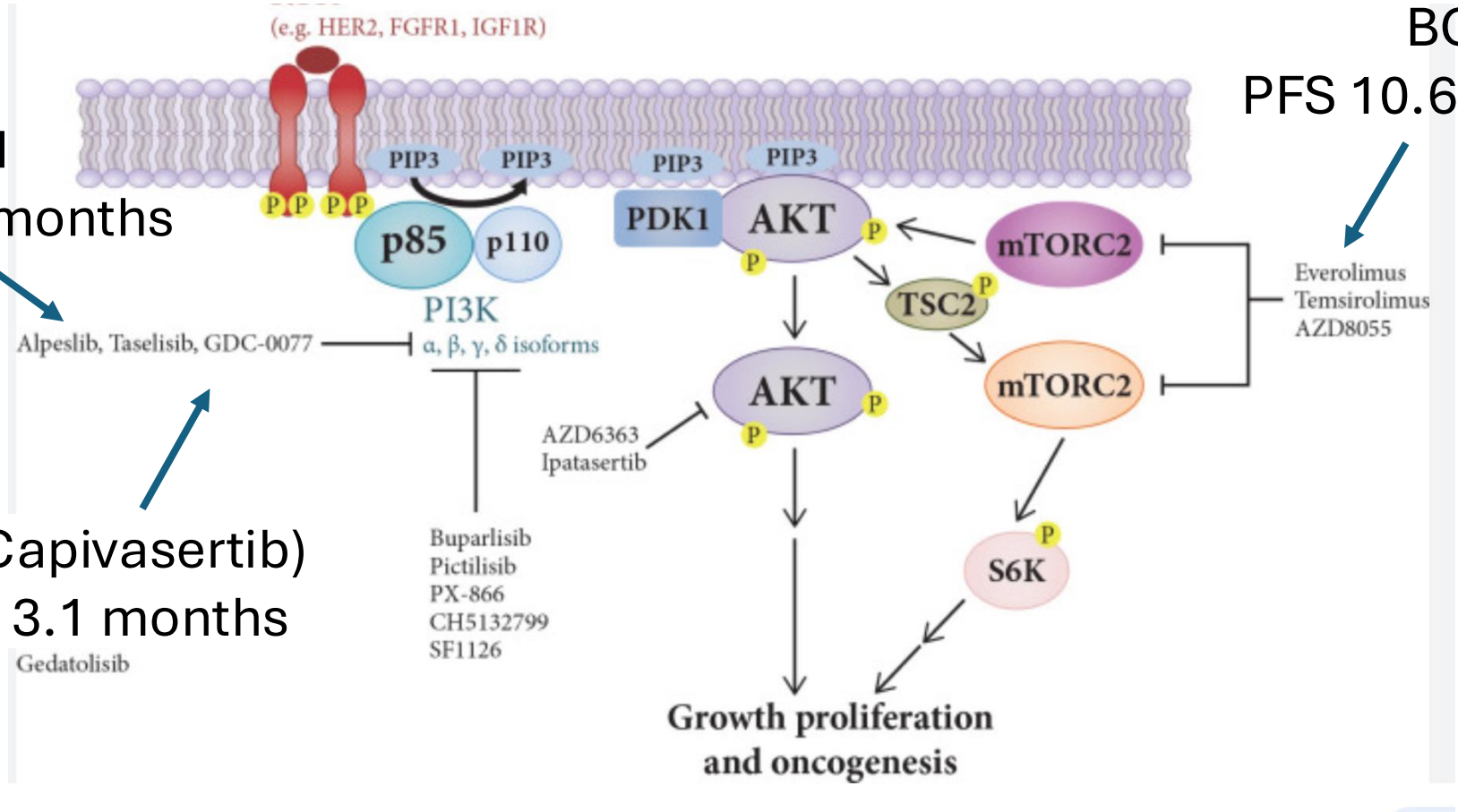
Detected Alteration(s) / Biomarker(s)		Associated FDA-approved therapies	Clinical Trial Availability	% ctDNA or Amplificati
PIK3CA	H1047R	✓ Alpelisib+fulvestrant, Capivasertib+fulvestrant	Yes	1.2%
AKT1	E17K	✓ Capivasertib+fulvestrant	Yes	0.5%
ATM	D2507D	Synonymous Alteration§	No (Synonymous)§	1.0%
BRCA2	H595P	None (VUS)§	None (VUS)§	0.6%
RIT1	R106Q	None (VUS)§	None (VUS)§	0.6%

PI3K/AKT/mTOR pathway

SOLAR 1
PFS 11 vs 5.7 months

BOLERO 2
PFS 10.6 vs 4.1 months

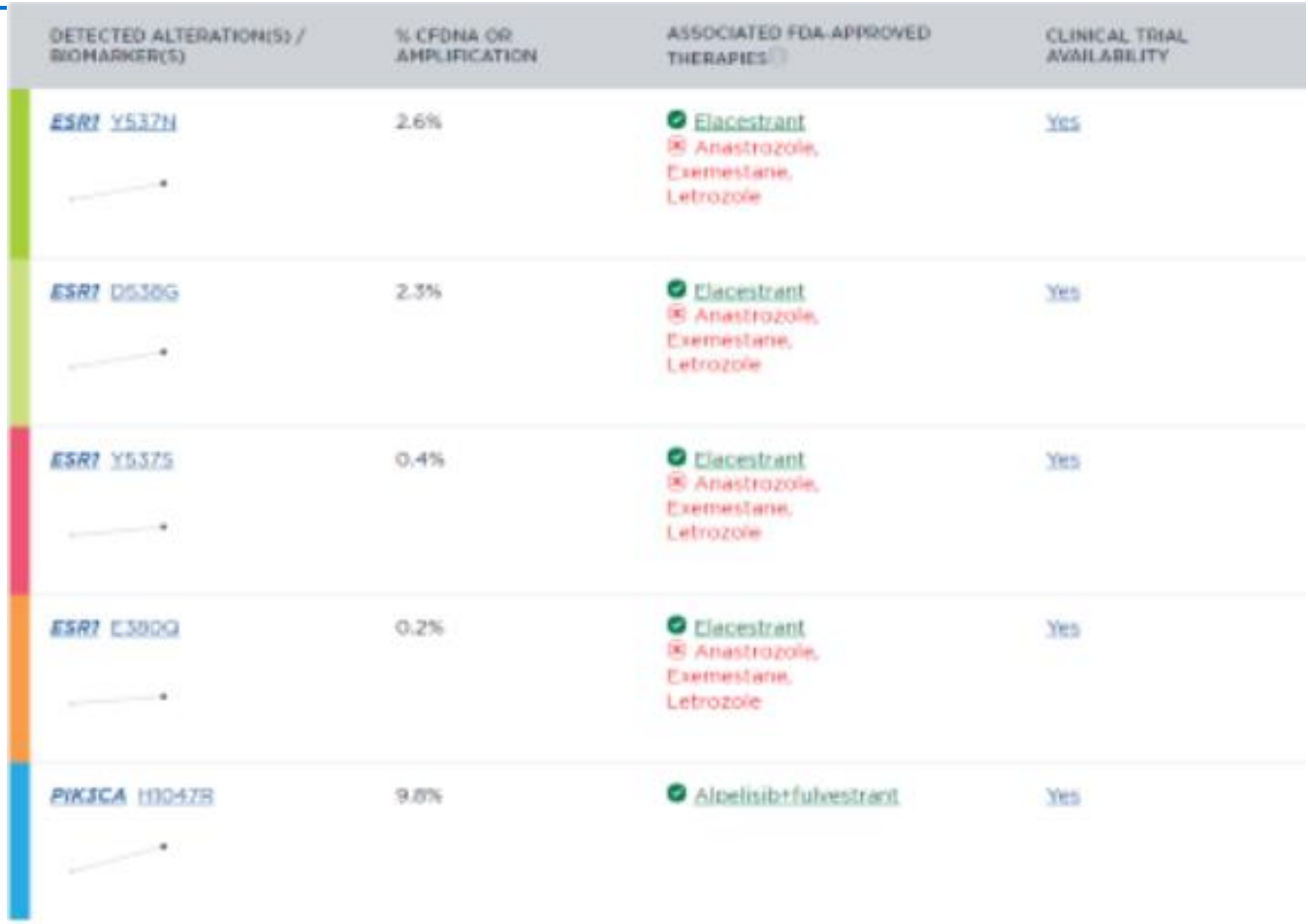
Capitello (Capivasertib)
PFS 7.3 vs 3.1 months



Baselga, NEJM 2012;366:520-526
Andre, NEJM 2019;380:1929-1940
Turner, NEJM 2023;388:2058-2070

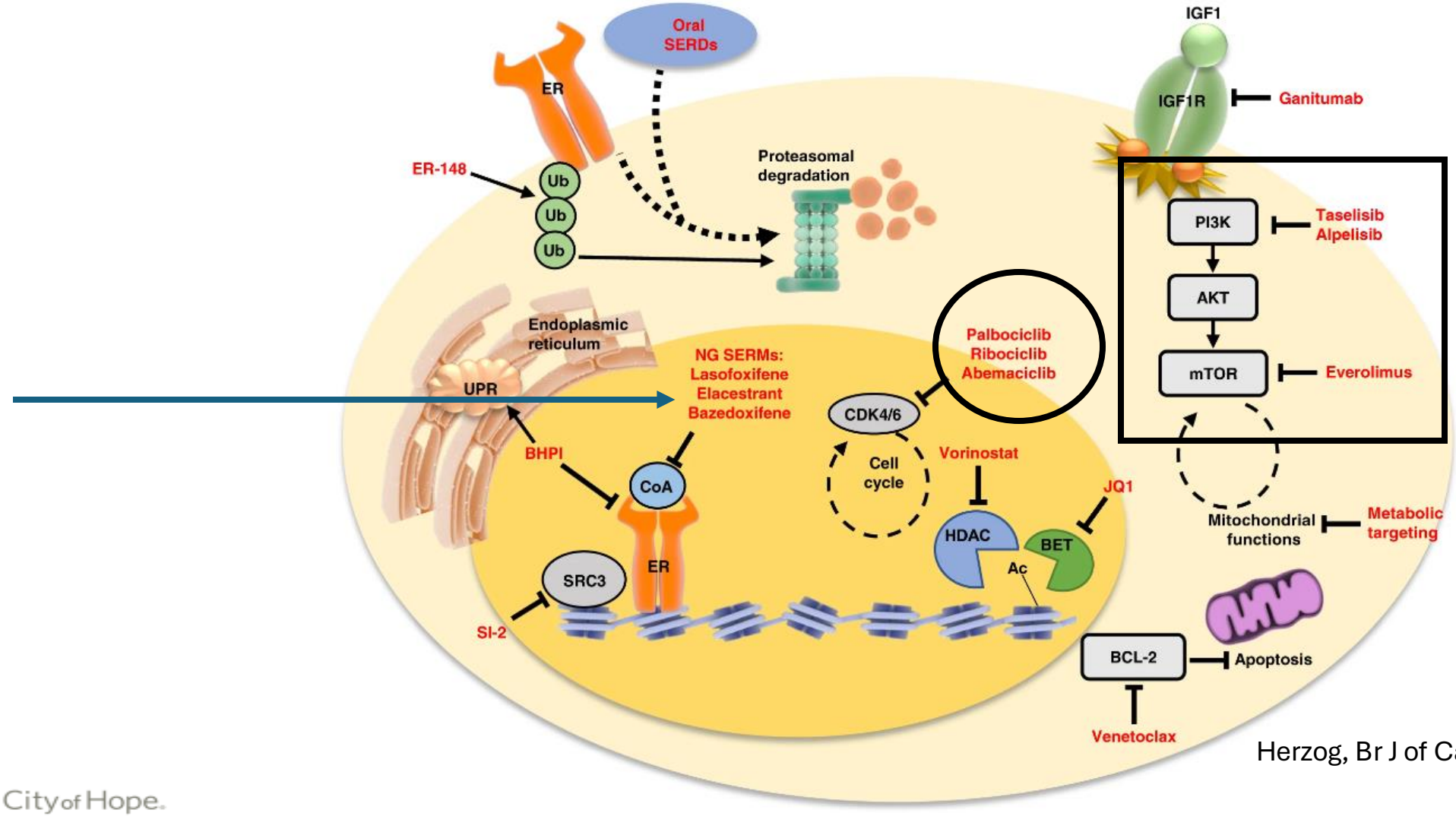
ESR1 mutations

- Are seldom present at diagnosis
- Likely to occur as a result of the “pressure” of therapy
- May predict for lack of efficacy of Ais
- Direct therapy to SERMs and SERDS



DETECTED ALTERATION(S) / BIOMARKER(S)	% CFDNA OR AMPLIFICATION	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIAL AVAILABILITY
ESR1 Y537N	2.6%	Elacestrant Anastrozole, Exemestane, Letrozole	Yes
ESR1 D538G	2.3%	Elacestrant Anastrozole, Exemestane, Letrozole	Yes
ESR1 Y537S	0.4%	Elacestrant Anastrozole, Exemestane, Letrozole	Yes
ESR1 E380Q	0.2%	Elacestrant Anastrozole, Exemestane, Letrozole	Yes
PIK3CA H1047R	9.8%	Alpelisib+fulvestrant	Yes

ESR 1 mutation

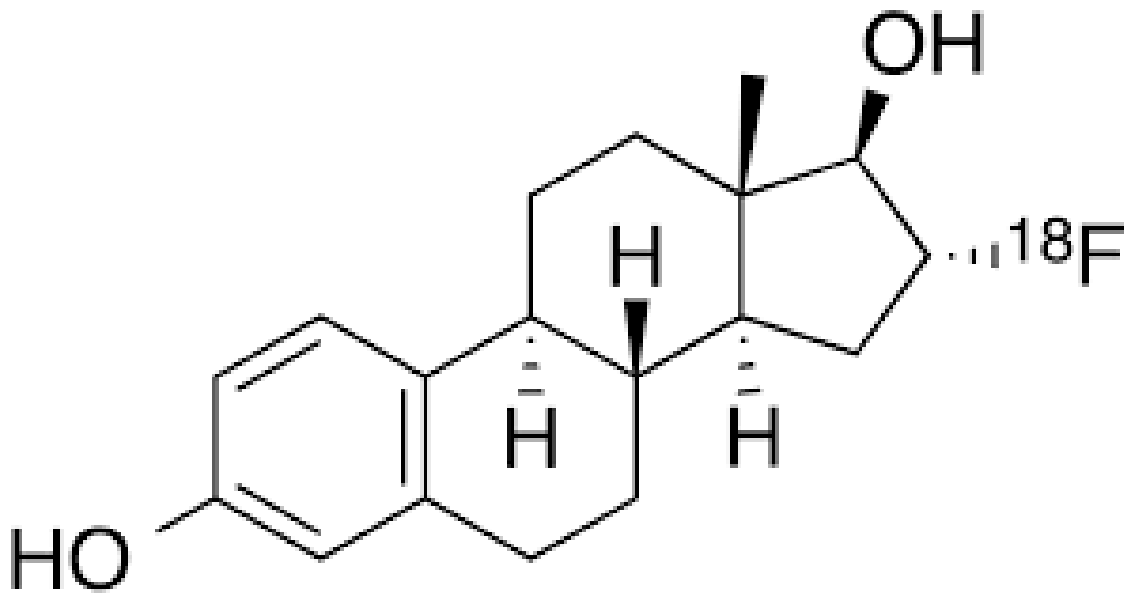


Herzog, Br J of Cancer 2022;126:174-186

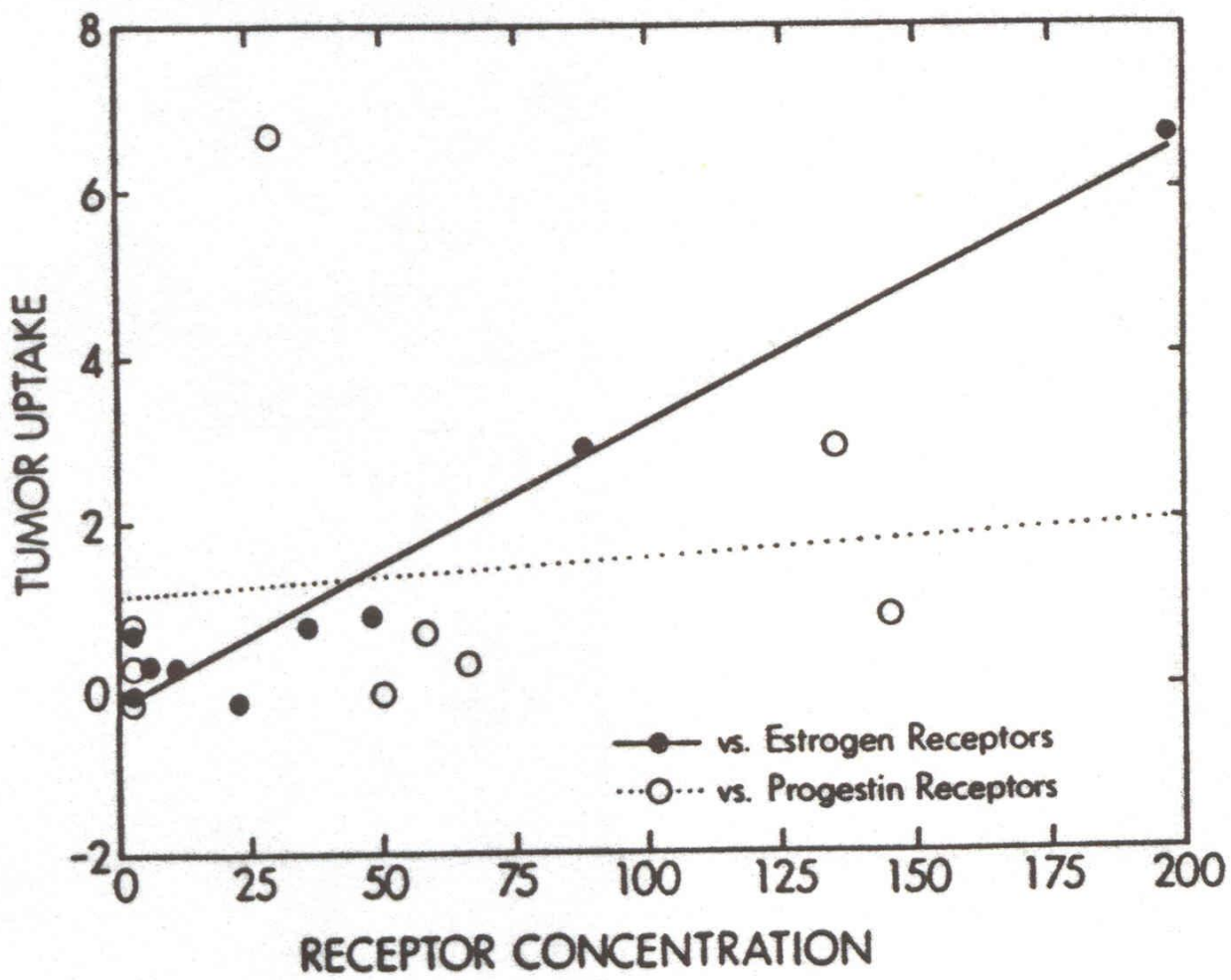
Functional Imaging

- Information about biologic activity
- Provides information about the entire patient
- Limited by lesion size

16α[18F]fluoro-17β-estradiol



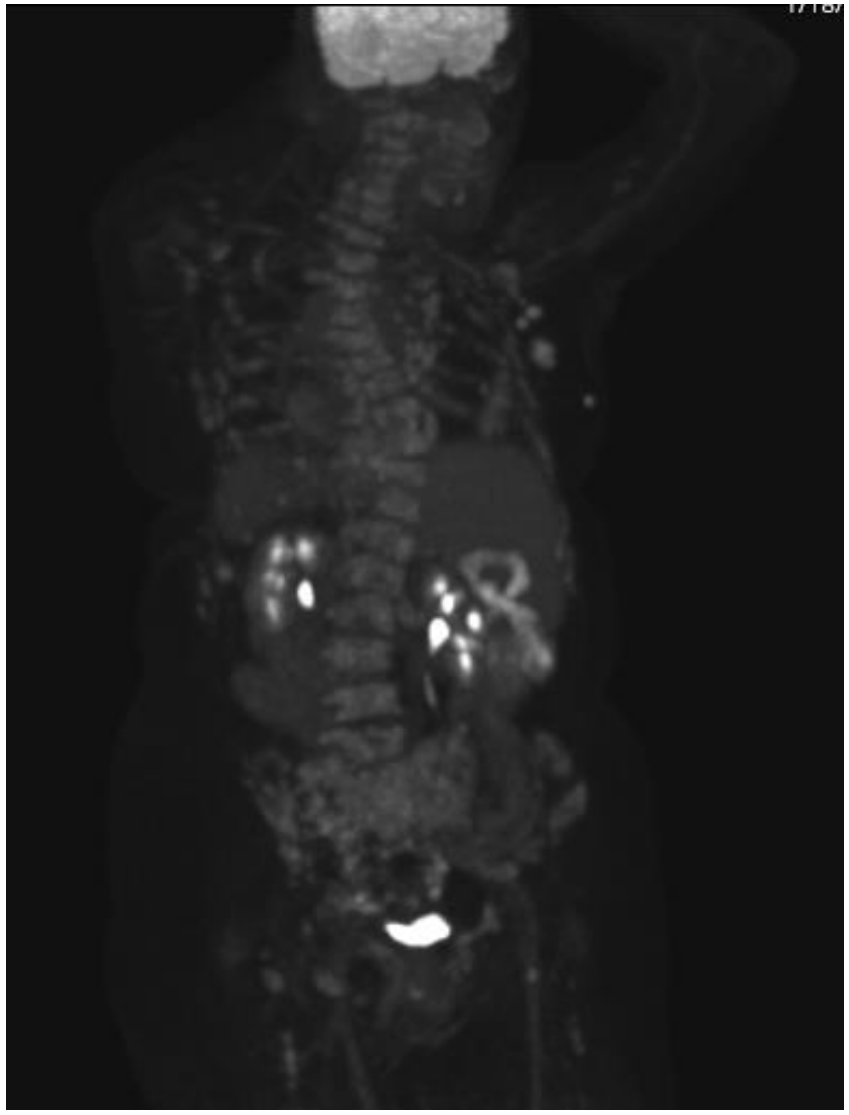
Relationship Between ^{18}F-FES-PET Uptake and Quantitative ER



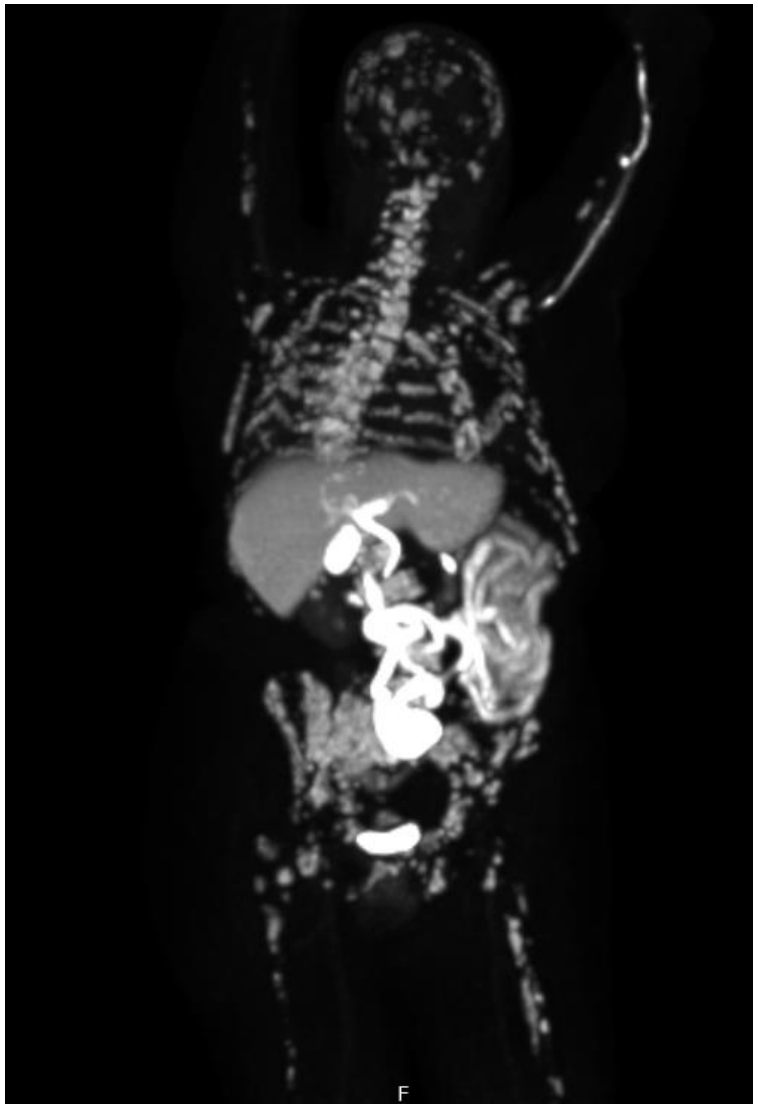
Wahl. Radiology 169;45-48, 1988

FES PET imaging

^{18}FDG



^{18}FES



Summary of ^{18}FES-PET Use

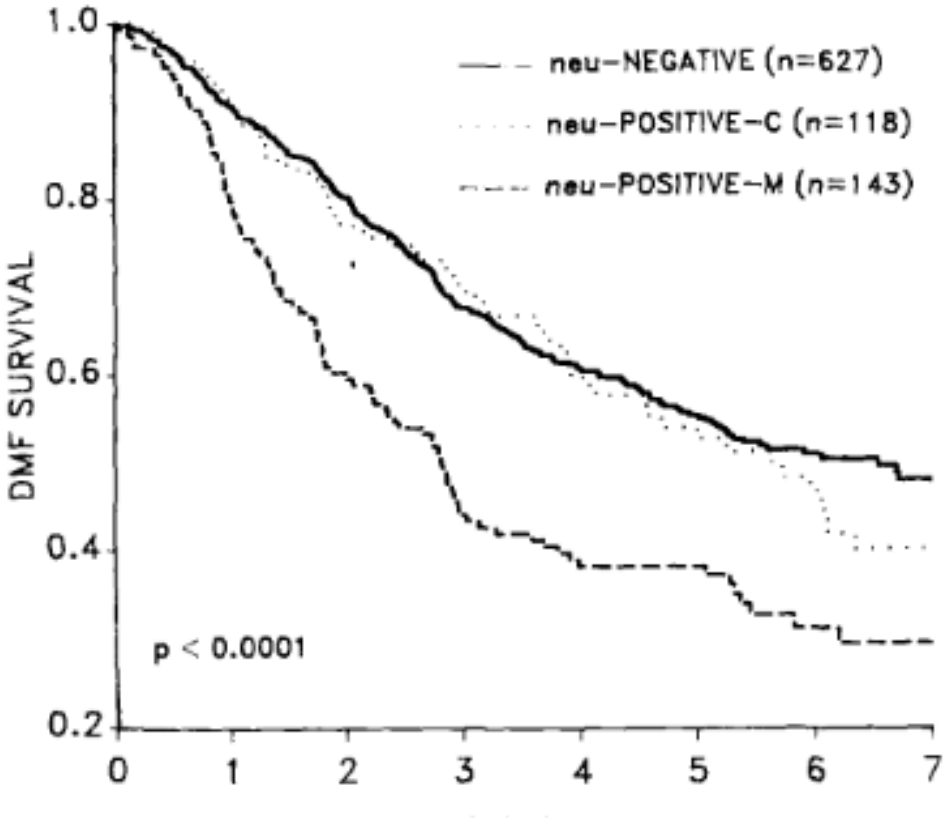
- Determine estrogen dependence when bx not possible
- Predict lack of response to endocrine therapy
- Identifies low grade disease

- Not helpful with liver metastases
- Not reliable in pts on SERD

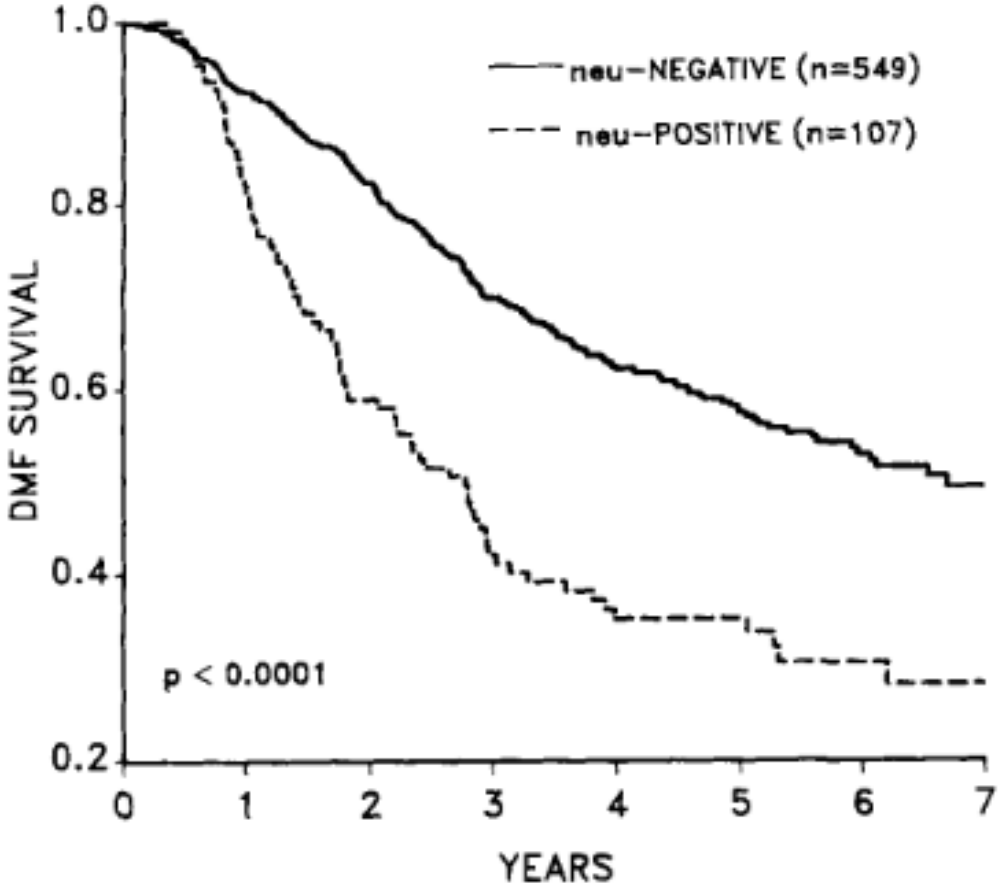

Her2-Positive
Breast Cancer

Prognostic significance of HER2/*Neu* oncoprotein expression in node-positive breast cancer

888 breast cancer from 1980-1986 (Quebec)

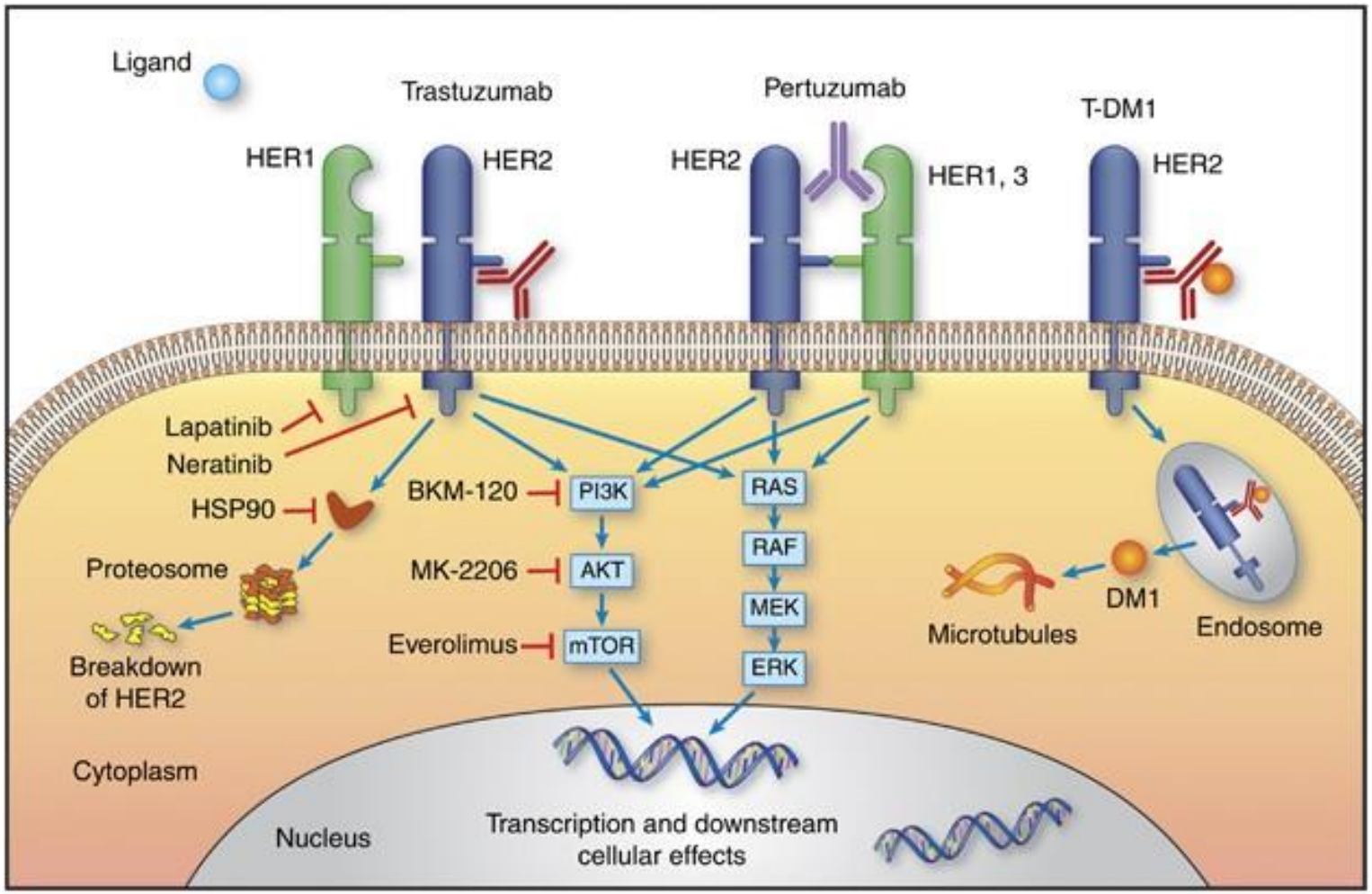


Membrane more important than cytoplasmic staining



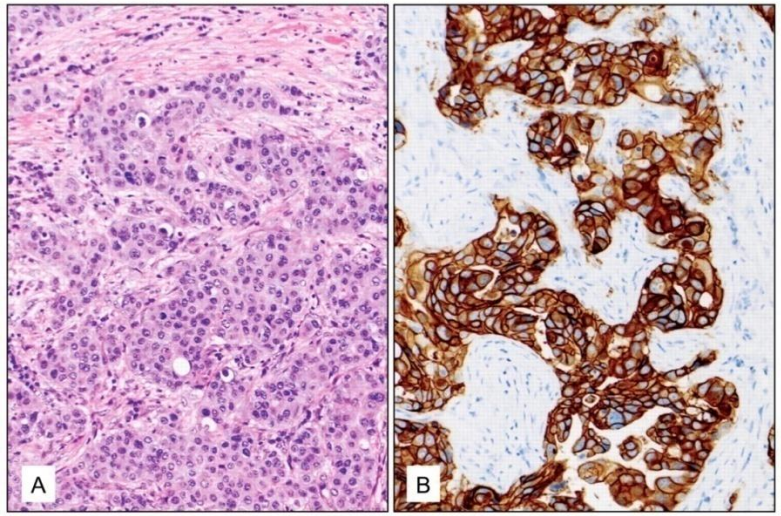
Tetu, Cancer 1994;73:2359-2365

HER2 as a target

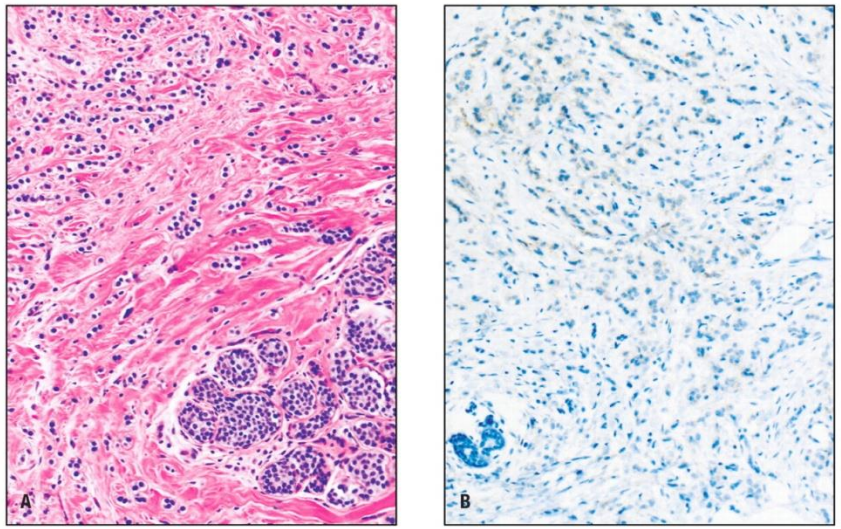


Singh, British J of Ca 2014;111:1888-1898

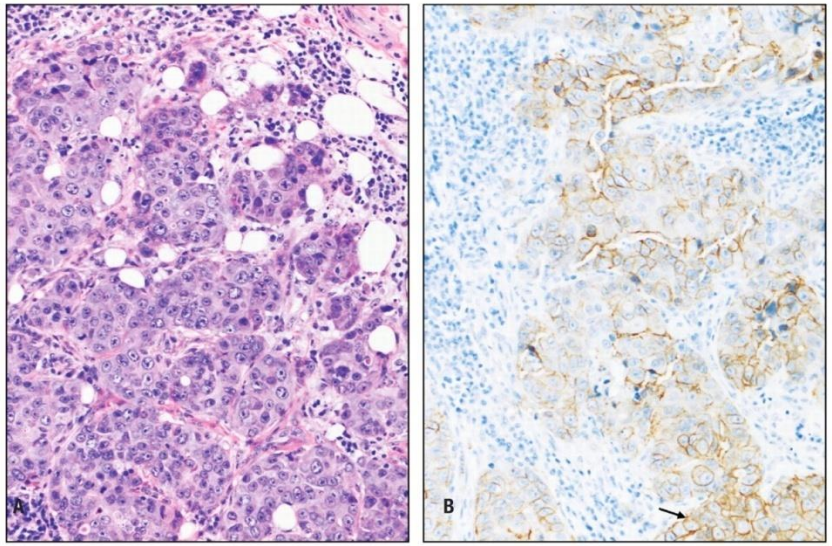
HER2 Assessment by Immunostaining



Positive 3+



Negative 0



Equivocal 2+

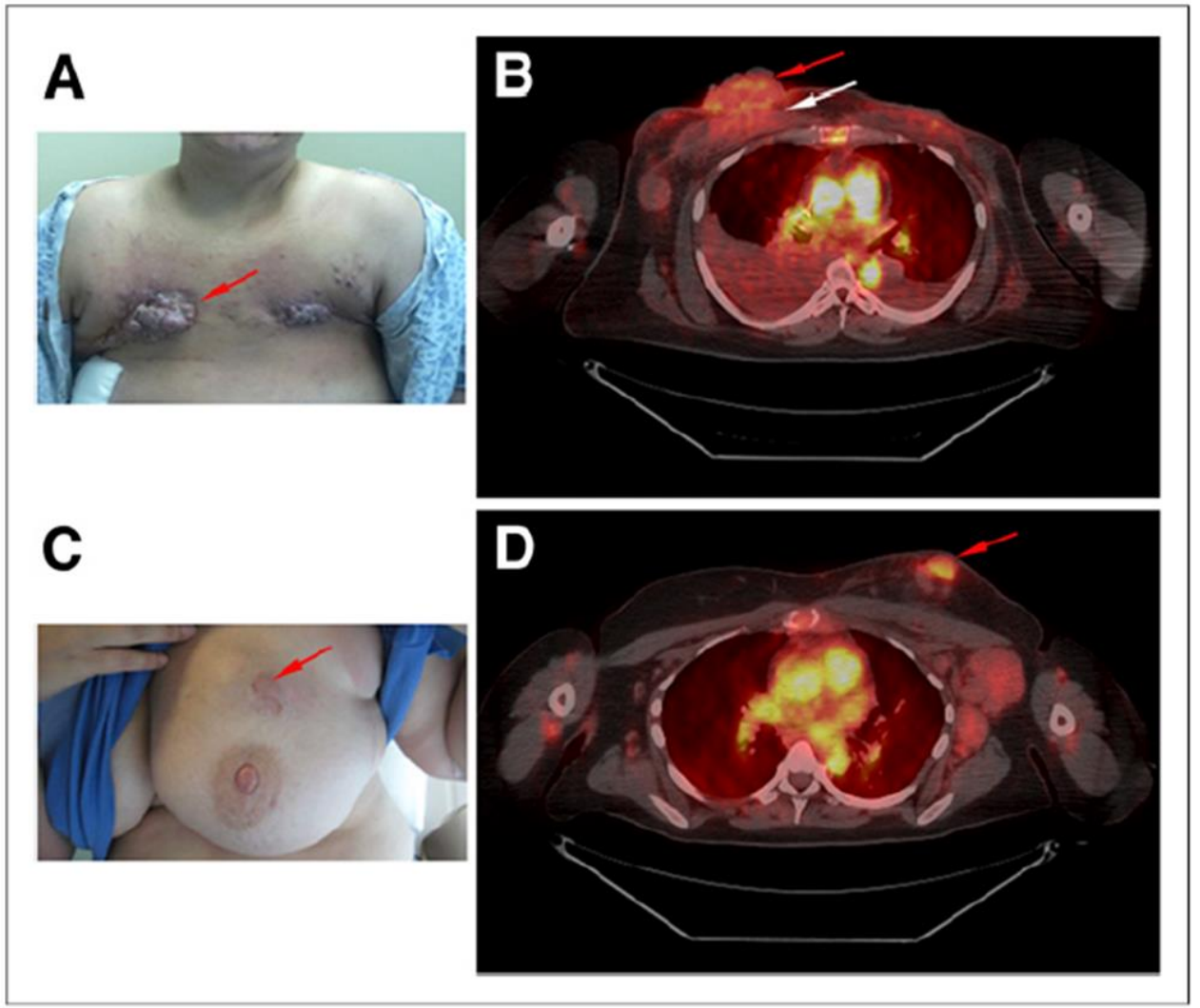
FISH

Hicks, Lab Medicine 2011:42:459-67

We have utilized ^{64}Cu-DOTA-Trastuzumab to image women with advanced breast cancer with HER2 1+, 2+, 3+

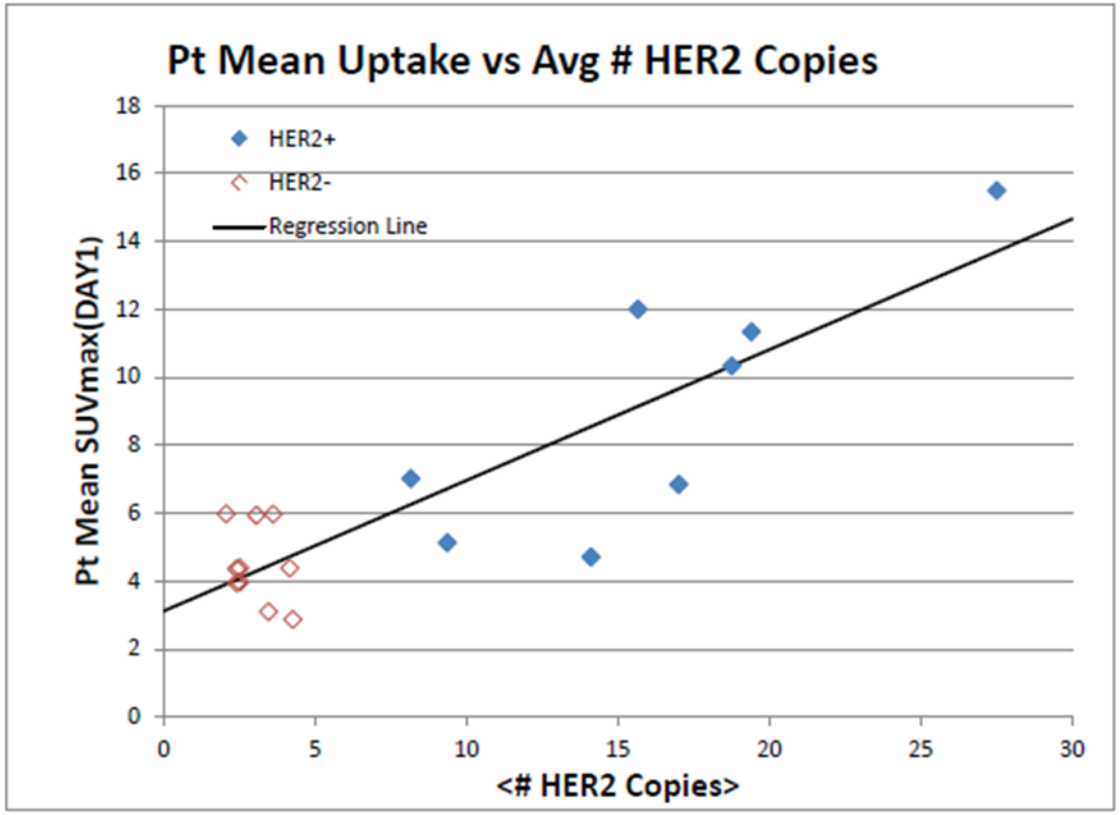
IHC 1+

IHC 3+



Mortimer, J Nucl Med 2018;59:38-43

Tumor uptake of ^{64}Cu-DOTA-Trastuzumab is highly correlated with HER2 gene amplification



CONCLUSION: Gene amplification explains high-side variability of tumor uptake.

REMAINING QUESTION: What causes the variability about the regression line?
E.g., the 2 patients with avg # of HER2 copies closest to 15 vary nearly 3-fold in mean uptake, which could well make the difference between response & non-response.

^{64}cu-DOTA-trastuzumab PET Imaging ,to predict response to TDM1 in Advanced HER2+ Breast Cancer

Eligibility

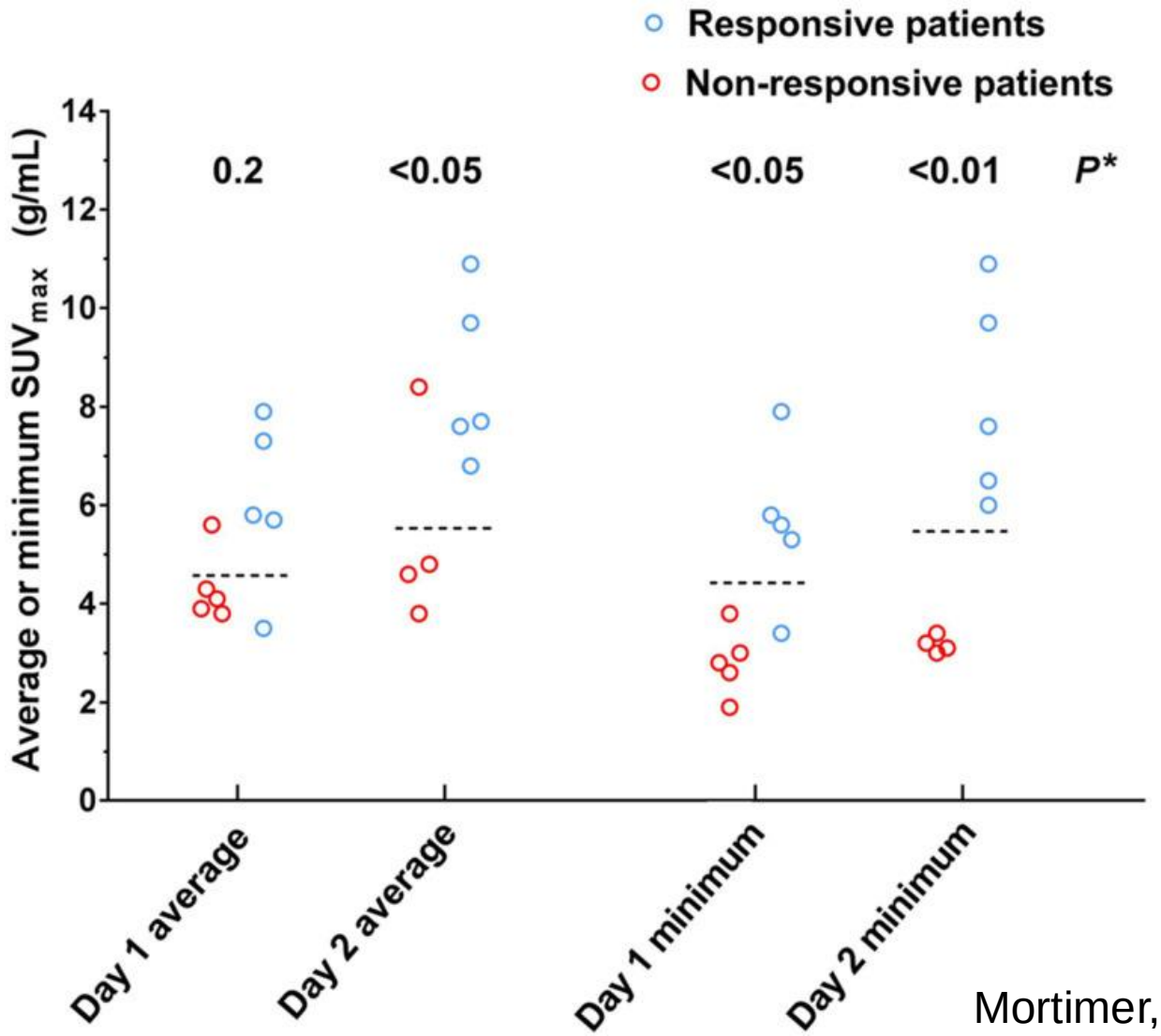
- Women with locally advanced or metastatic disease
- Biopsy confirmed HER2 +
- Planned treatment with TDM1
- No prior HER2 directed therapy for > 21 days

Baseline	Study Day 0	Study D 1 and 2
^{18}FDG-PET/CT	Trastuzumab 45 mg IV	^{64}Cu-trastuzumab PET/CT

TDM1 3.6 mg/kg IV Q3w until disease progression

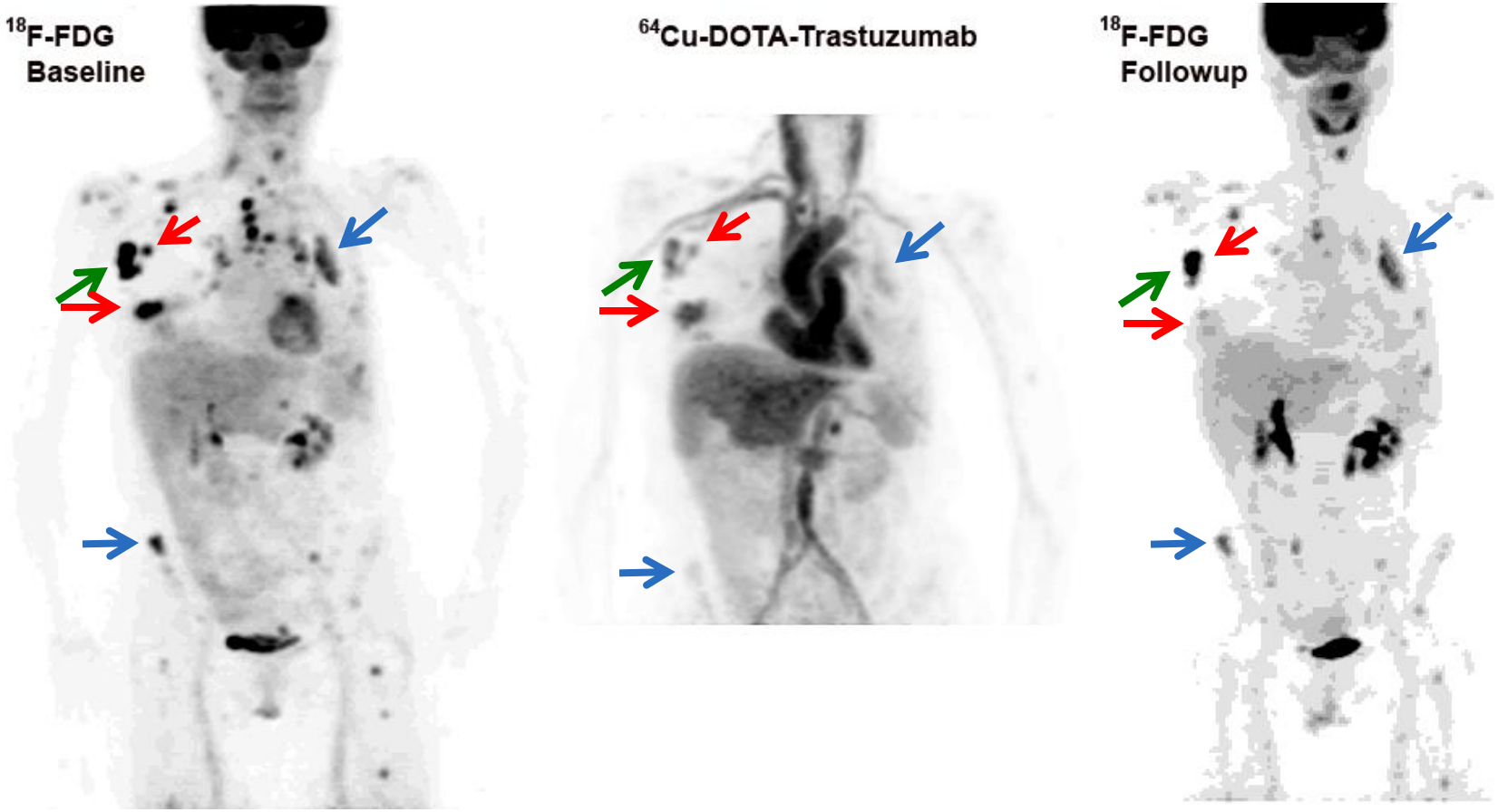
Restaging every 6 weeks

64Cu-DOTA –trastuzumab PET to predict response to TDM1 in advanced breast cancer



Mortimer, J Nucl Med 2022;63:1145-48

Mixed Trastuzumab Uptake and Response



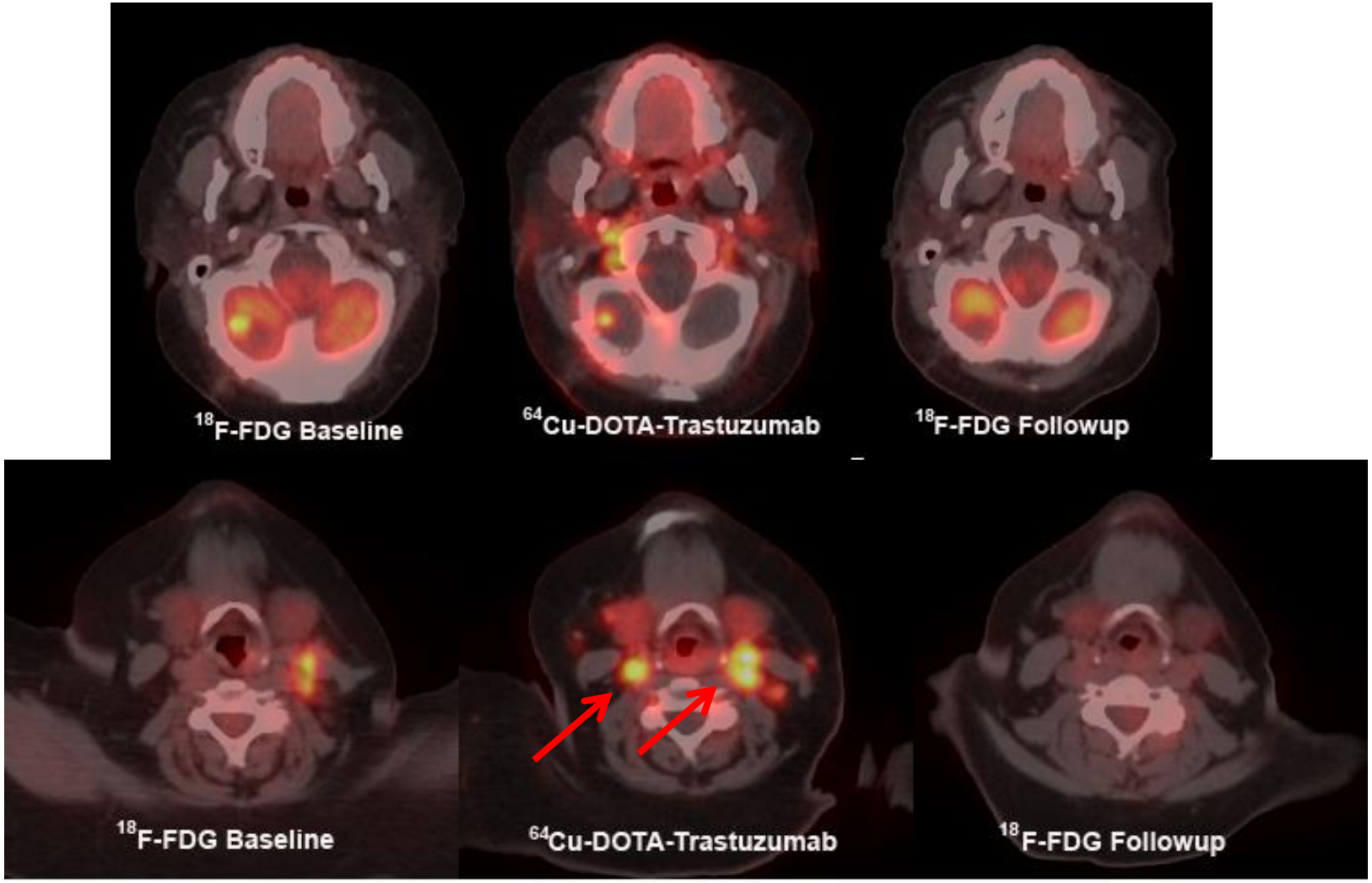
responding lesion

non-responding lesion

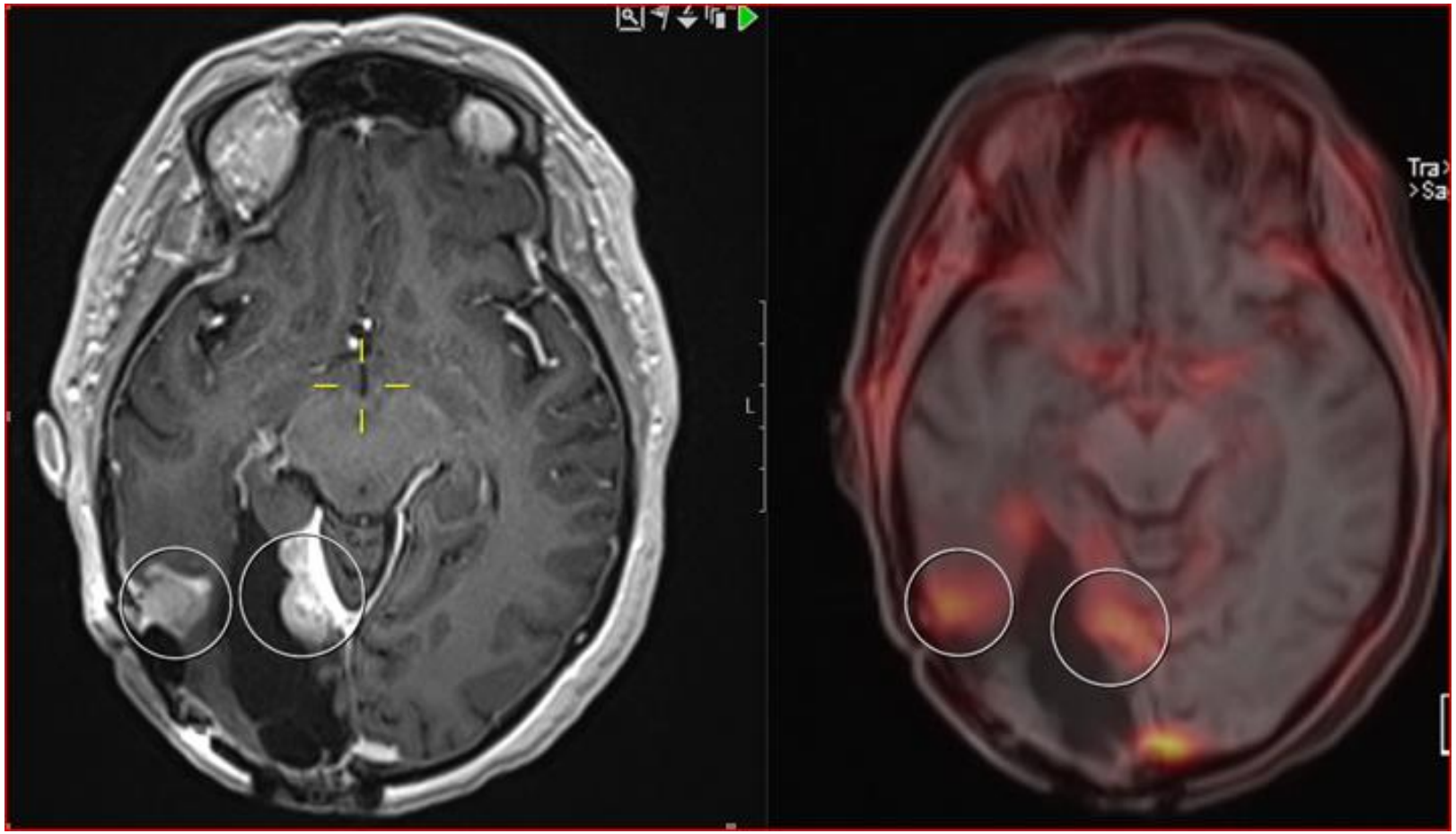
lesion with mixed response

Mortimer, J Nuc Med 2019;60:23

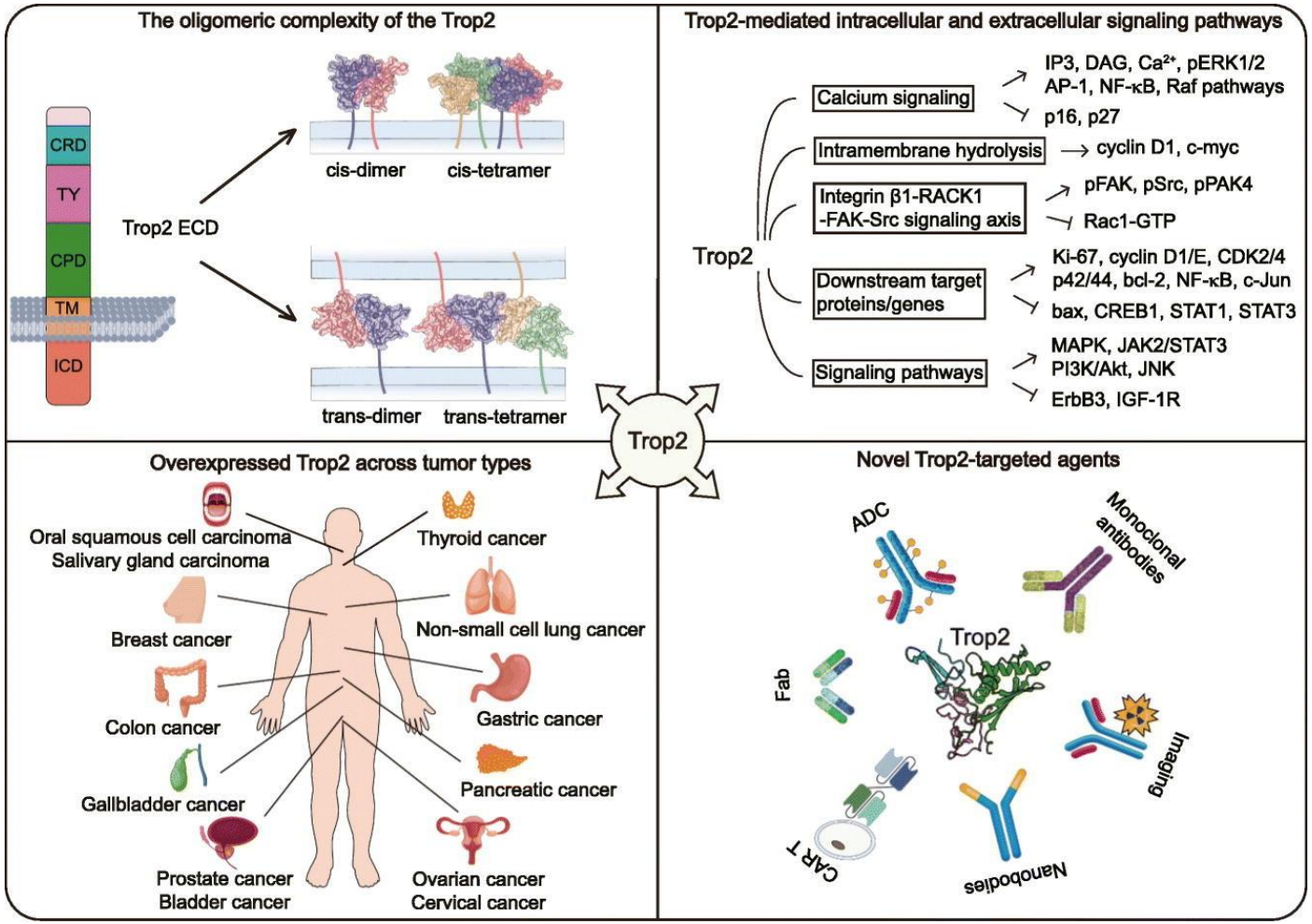
^{64}cu-DOTA-trastuzumab PET Uptake in brain



Currently studying ^{64}cu-DOTA-trastuzumab PET to predict for CNS response to trastuzumab-deruxtecan

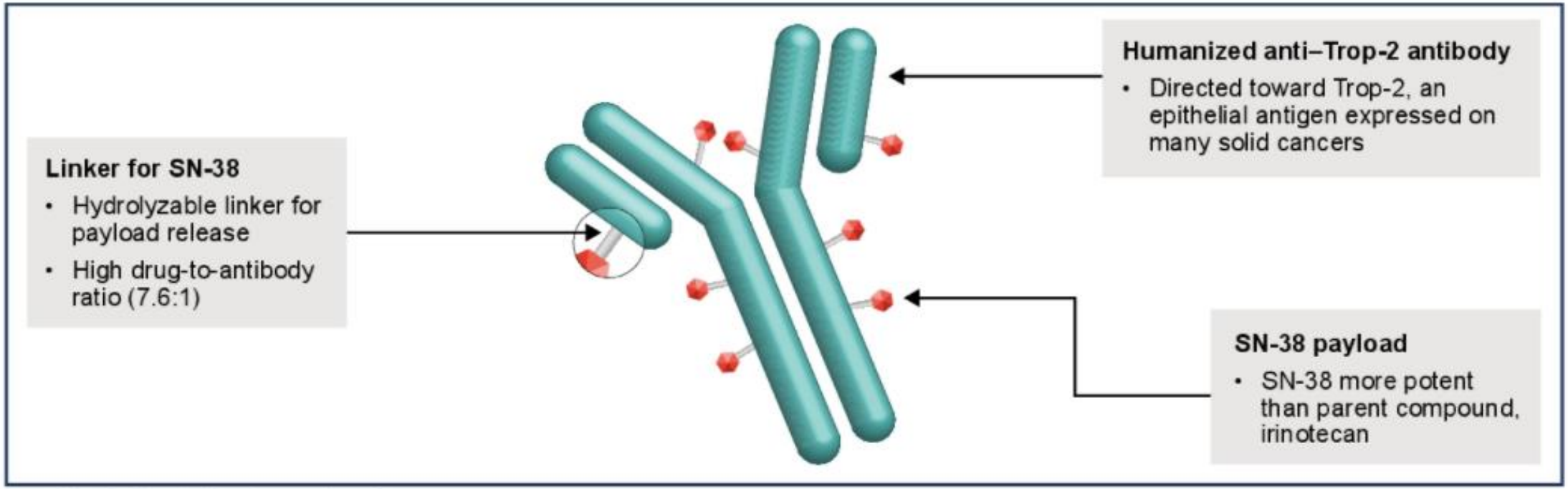


TROP2 and Cancer



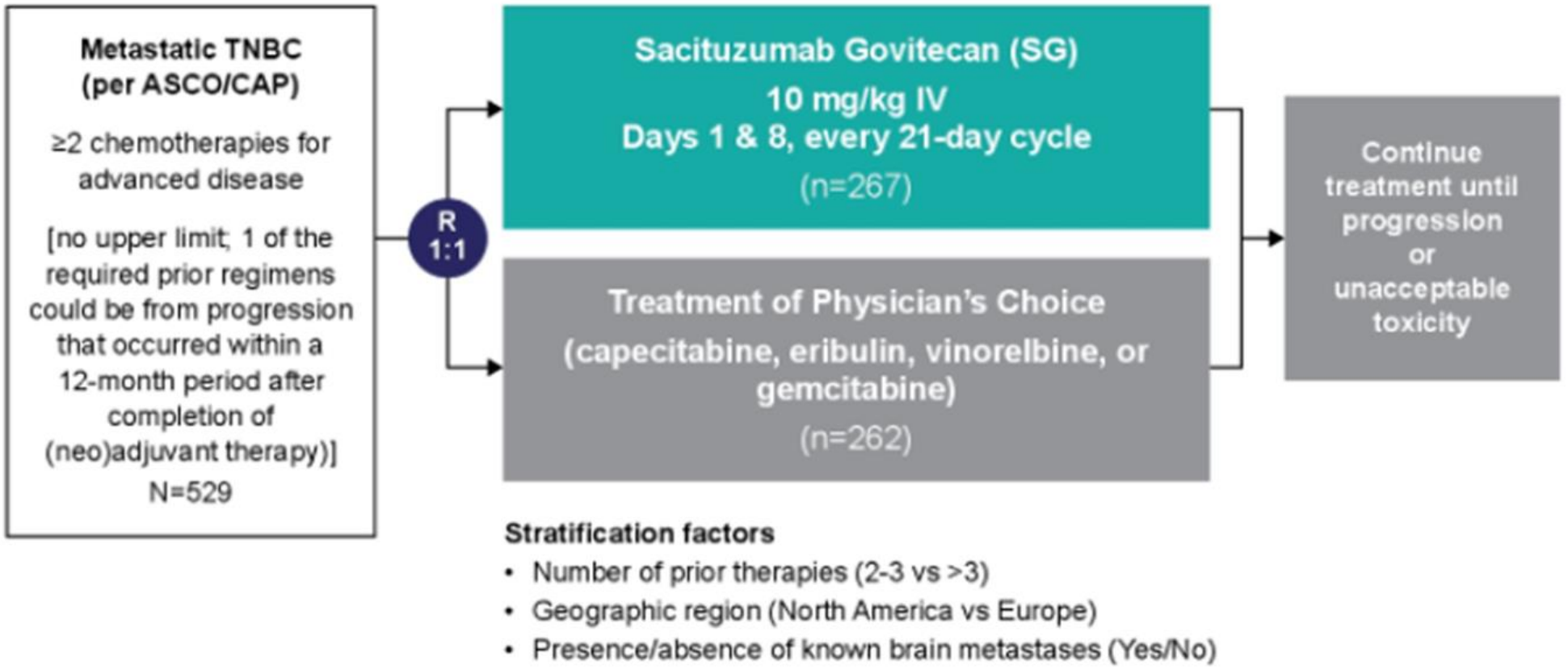
Liu, Pharm and Ther 2022: 108296

Sacituzumab is approved in advanced HR+/HER2- and TNBC

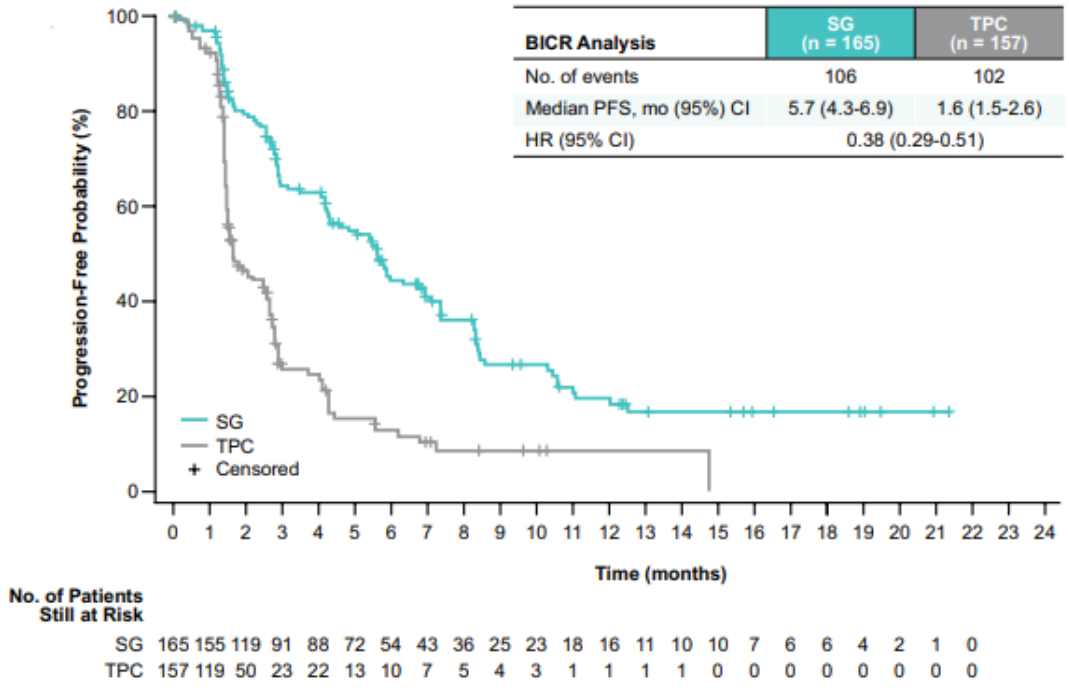


Trop-2, trophoblast cell surface antigen 2.

Sacituzumab as second line therapy in Triple Negative Breast Cancer



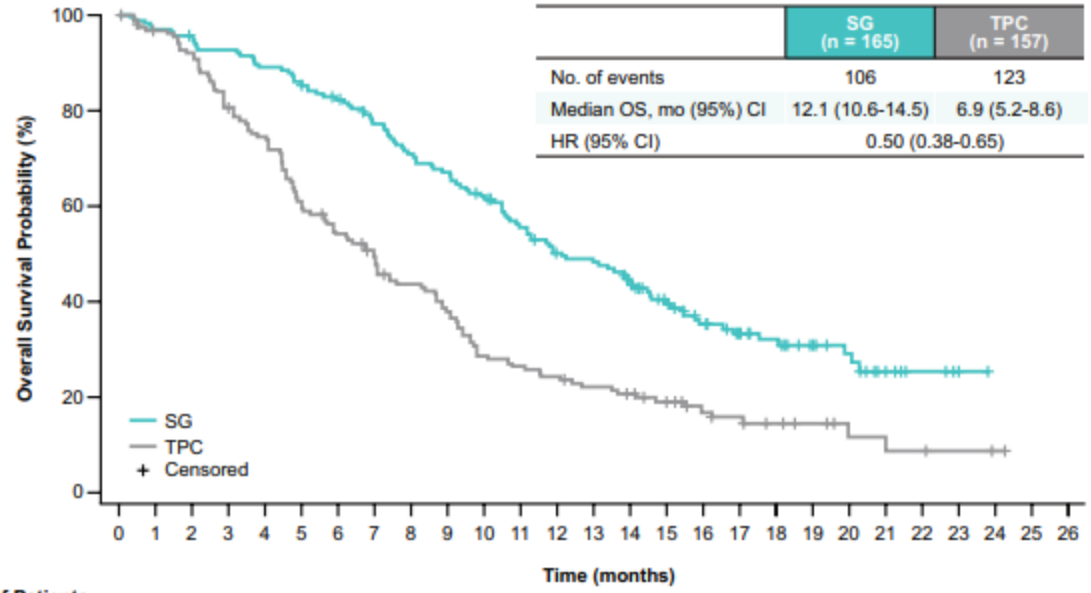
Sacituzumab as second line therapy in Triple Negative Breast Cancer



BICR Analysis	SG (n = 165)	TPC (n = 157)
No. of events	106	102
Median PFS, mo (95% CI)	5.7 (4.3-6.9)	1.6 (1.5-2.6)
HR (95% CI)	0.38 (0.29-0.51)	

No. of Patients Still at Risk

SG	165	155	119	91	88	72	54	43	36	25	23	18	16	11	10	10	7	6	6	4	2	1	0
TPC	157	119	50	23	22	13	10	7	5	4	3	1	1	1	1	0	0	0	0	0	0	0	0



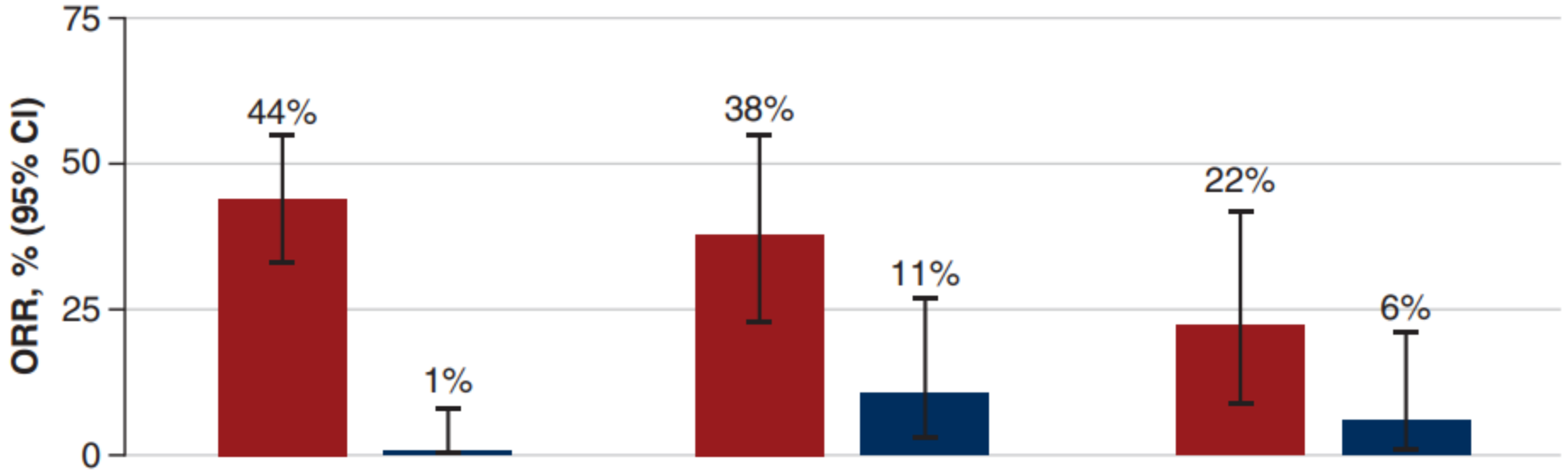
	SG (n = 165)	TPC (n = 157)
No. of events	106	123
Median OS, mo (95% CI)	12.1 (10.6-14.5)	6.9 (5.2-8.6)
HR (95% CI)	0.50 (0.38-0.65)	

No. of Patients Still at Risk

SG	165	160	155	151	145	138	132	122	112	106	96	85	75	72	63	50	39	30	26	20	16	8	4	1	0	0
TPC	157	144	137	119	109	88	79	69	61	53	40	37	34	30	27	22	15	12	9	7	4	3	3	2	1	0

O'Shaughnessy, Br Ca Res and Treat 2022;195:127-139

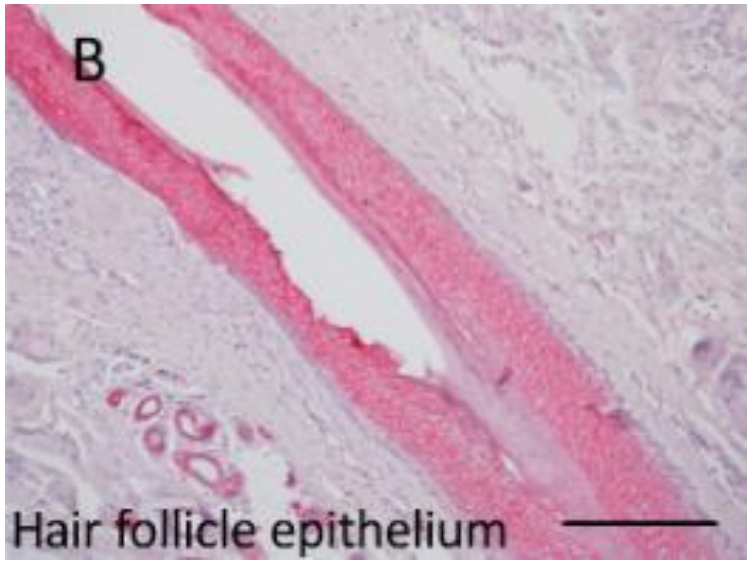
Response by TROP2 expression from ASCENT trial of sacituzumab govitecan versus chemotherapy in TNBC

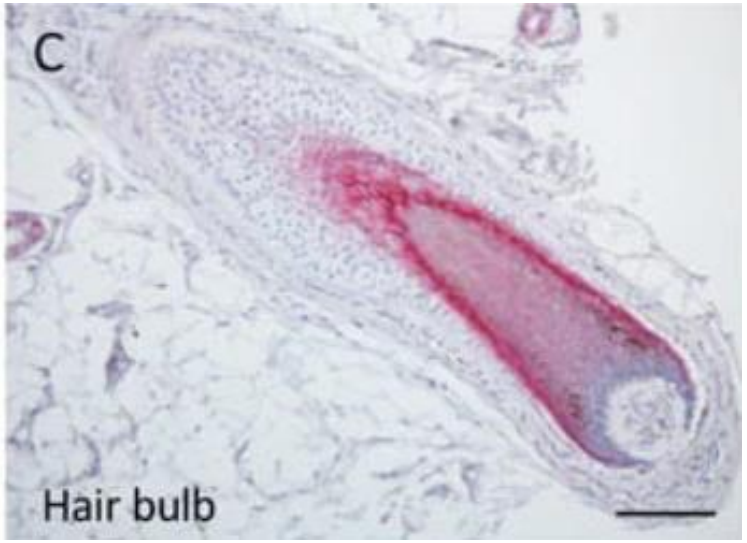


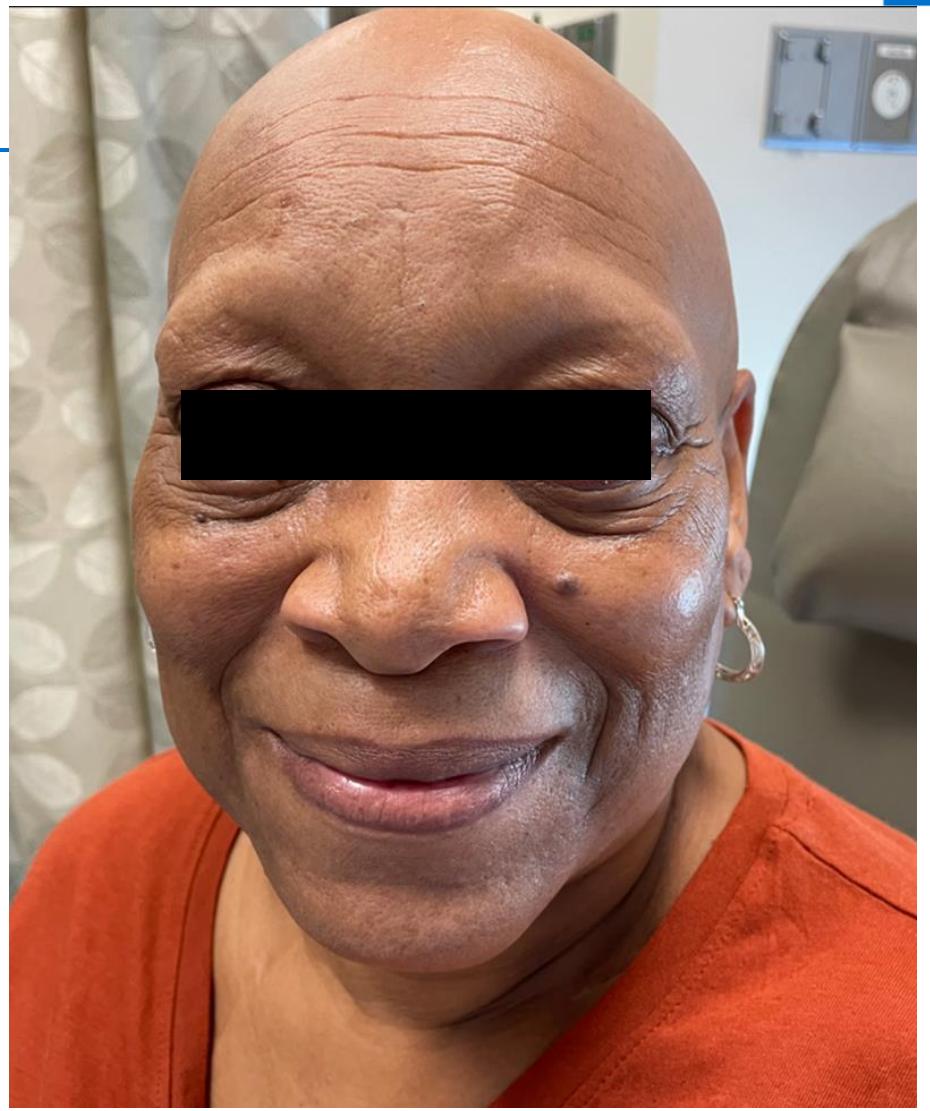
	Trop-2 high H-score: >200-300 (*n* = 157)		Trop-2 medium H-score: 100-200 (*n* = 74)		Trop-2 low H-score: 0 to <100 (*n* = 59)	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
ORR, % (*n*)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Bardia, Annals of Oncol 2021;32: 1148-1156

TROP2 expression in normal skin







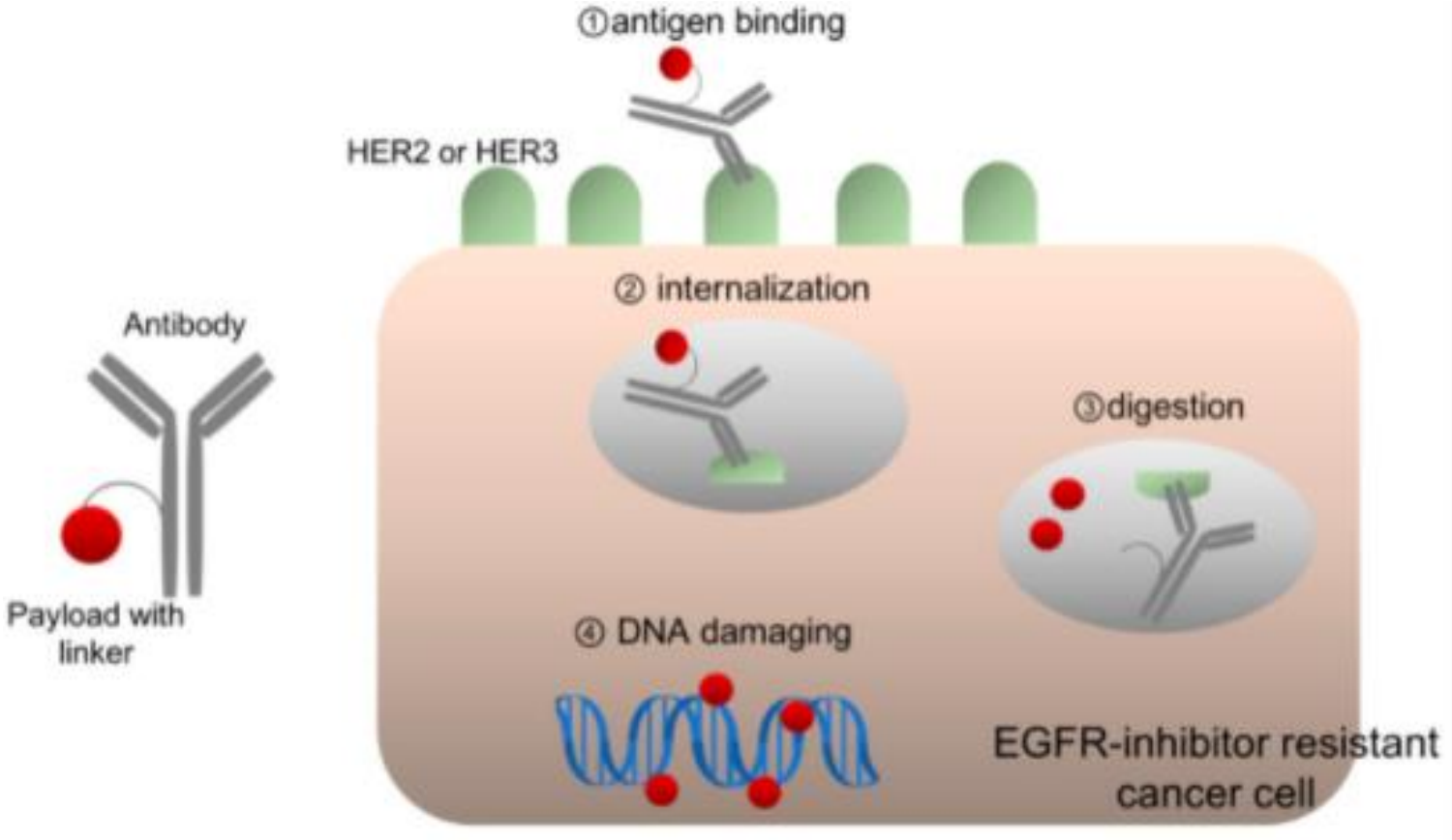
City of Hope

Ito, Int J Mol Sci 2021;22: 7706

Antibody Drug Conjugates in Breast Cancer

	Target		
Payload	HER2	TROP2	HER3
Maytansine Derivative	TDM1		
Deruxtecan	TDXd	Datopotomab	Patritumab
SN38		Sacituzumab	

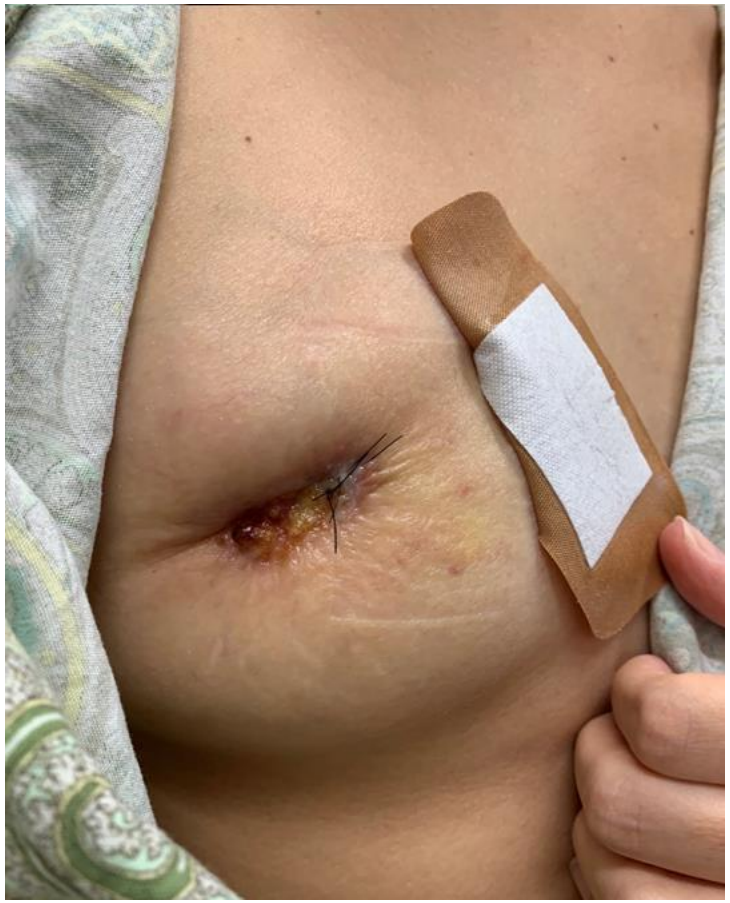
Patritumab deruxtecan



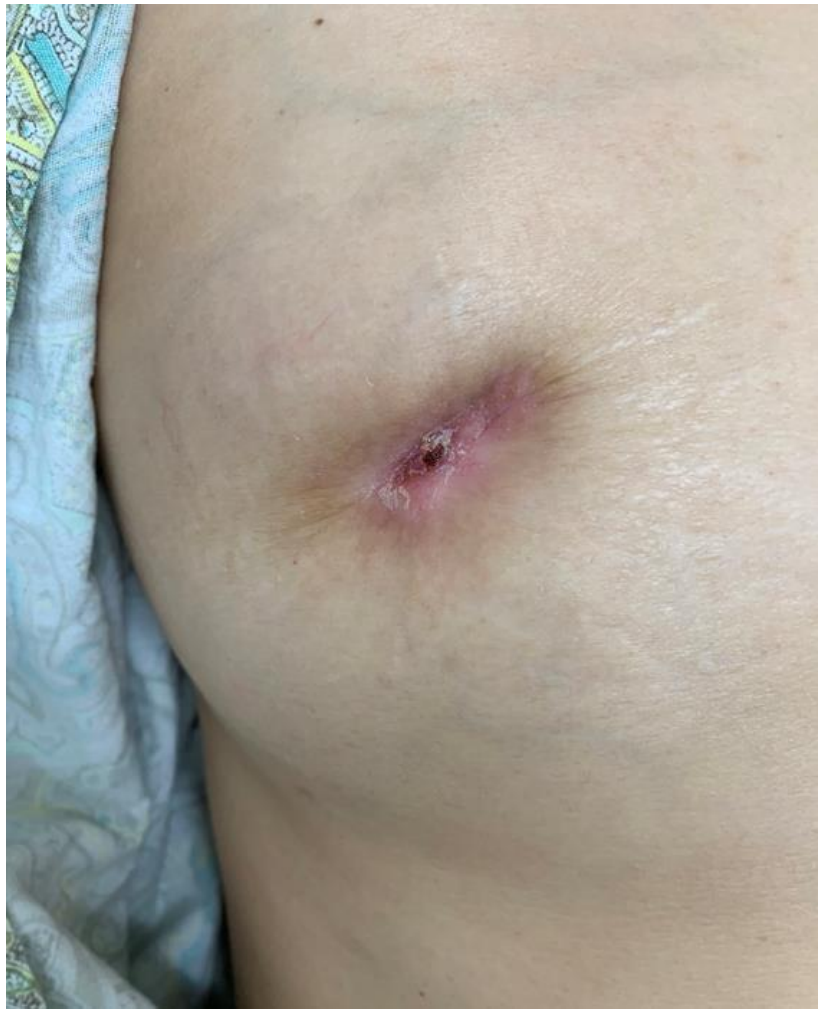
Yonesaka, Cancers 2021;13(5), 1047

Patritumab Deruxtecan

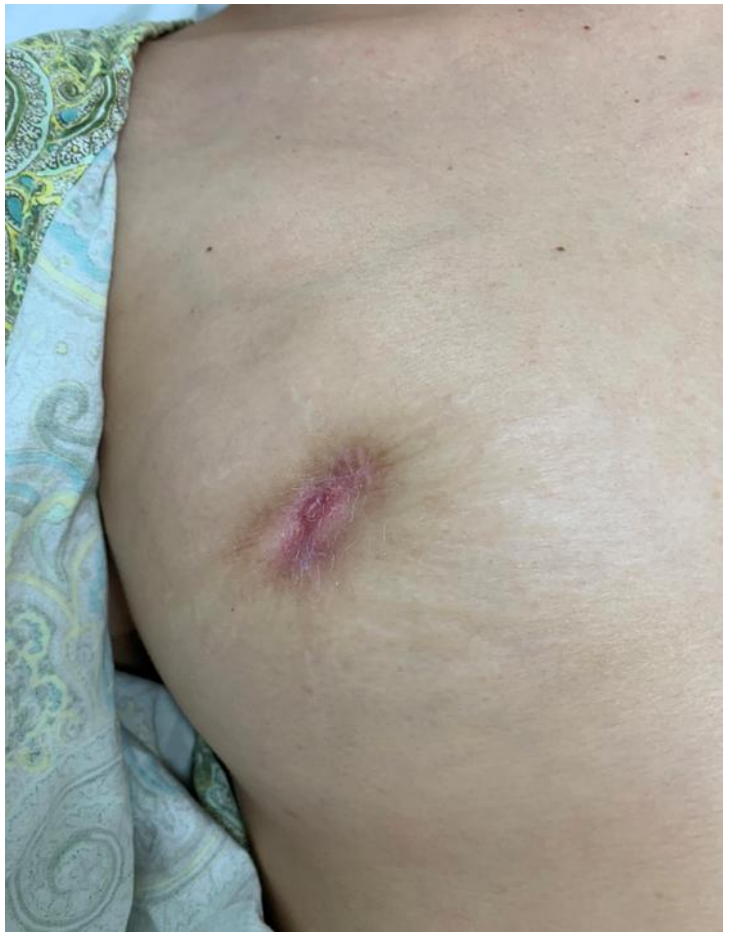
10/26/21 PREtreatment



11/23/21 PRE-Cycle 2



1/4/22 PRE-Cycle 3



Patritumab deruxtecan Phase I/II study in metastatic breast cancer

	HR+/HER2-	TNBC	HER2+
Number	113	53	14
ORR	30.1%	22.6%	42.9%
PFS	7.4 months	5.5 months	11 months

Dose Limiting Toxicity - GI and Hematologic
Responses seen in high and low HER3 expression

Krop, J Clin Onc 2023;41:5550-5560

Olaparib in MBC with Germline mutations
TBCRC 048

	g*PALB2* Cohort 1a (n=24)	s*BRCA* Cohort 2a (n=30)
Age – median (range)- yrs	53 (26-86)	63 (28-86)
Subtype*		
ER+ HER2-neg	79%	77%
TNBC	13%	13%
HER2+	8%	10%
BRCA1	----	50%
BRCA2	----	50%
# lines chemo in metastatic setting- (median, range)	0 (0-2)	1 (0-3)
Prior platinum	4%	10%

* Subtype of primary tumor

Gene	ORR (90% CI)
g*PALB2* (n=11)	82% (48%-98%)
s*BRCA* (n=16)	50% (25%-75%)
ATM, *CHEK2* (n=18)	0%

Tung, ASCO 2024

Thoughts about biomarkers in breast cancer

- Important in directing therapy
- May provide prognostic information
- May predict for toxicity
- Limited by sampling
- Functional imaging provides pharmacokinetic information
  - In assessing response, the threshold for efficacy or lack thereof is likely to be different for every agent and disease site