UI Health | UIC
UNIVERSITY OF ILLINOIS CANCER CENTER

Metastatic Interrogations and Recommendations

V.K. Gadi, MD PhD

Deputy Director, U of Illinois Cancer Center

October 19, 2024

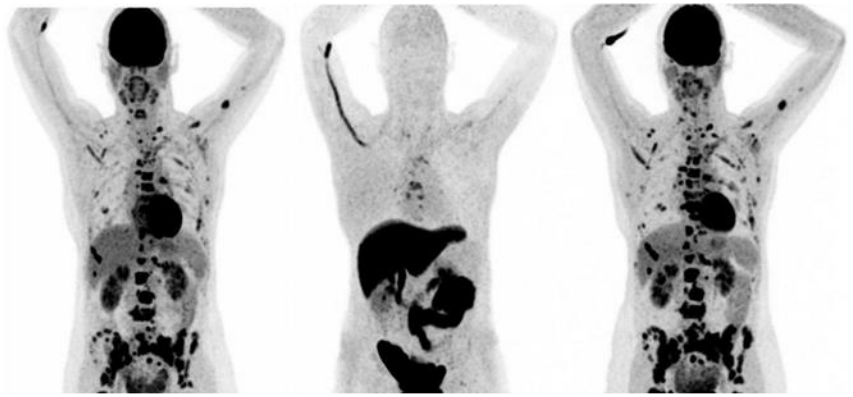
This is really a talk about markers

- Imaging
- Protein
- Genomics

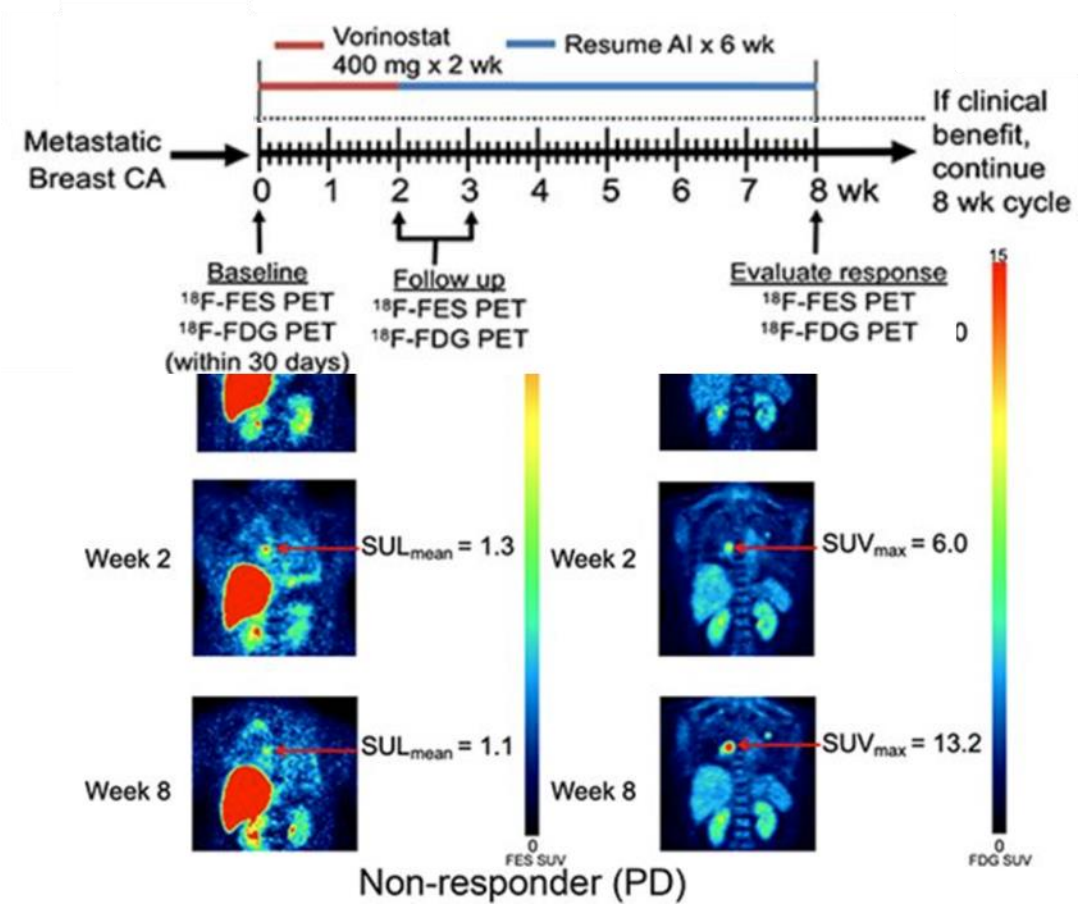
Imaging: some speculative stuff

FES PET: fluoroestradiol F^{18}

- FDA approval: 5.2020
- Distinguishes ER sensitive and insensitive lesions
- Addresses tissue heterogeneity
- $ESR1^{mut}$ appear endocrine sensitive

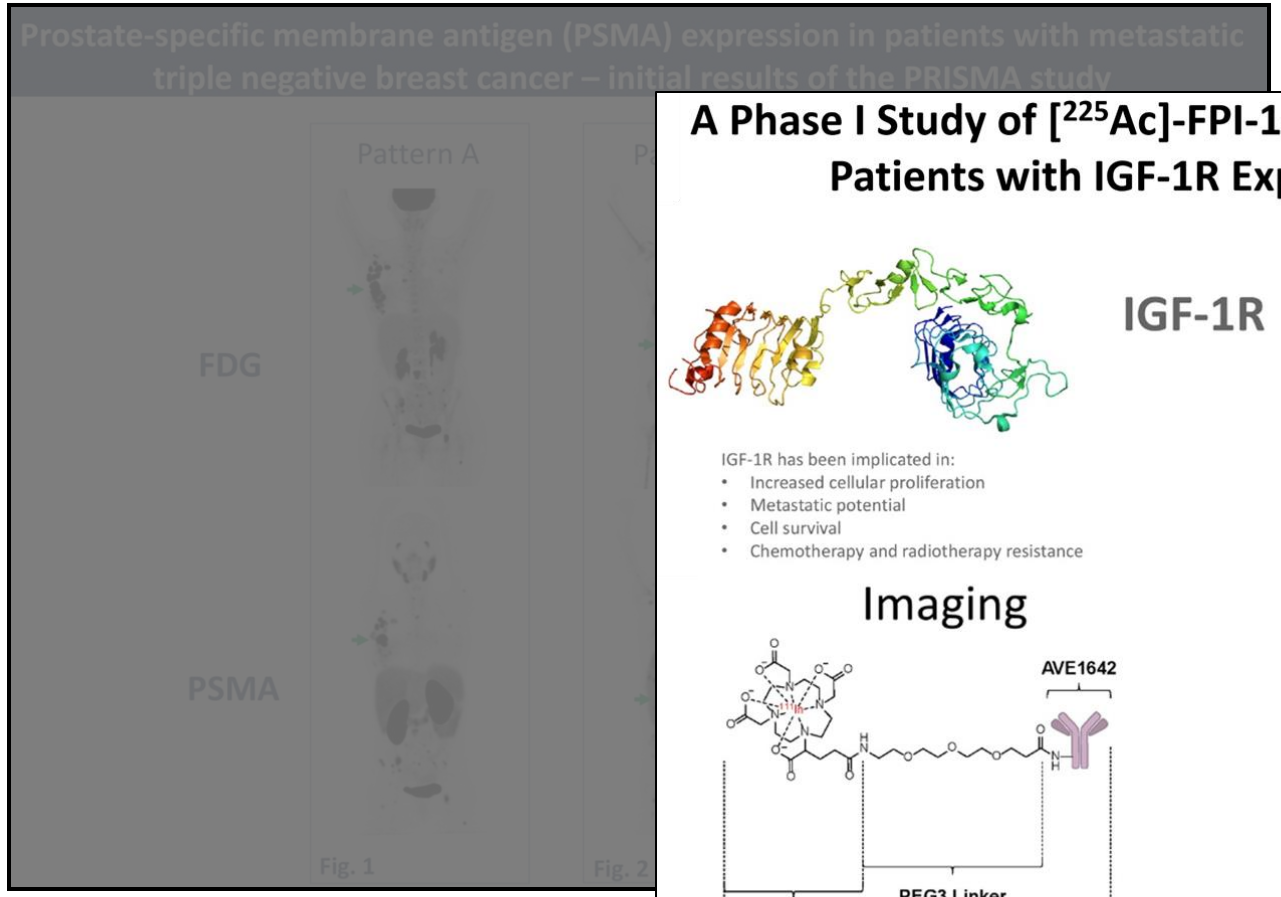


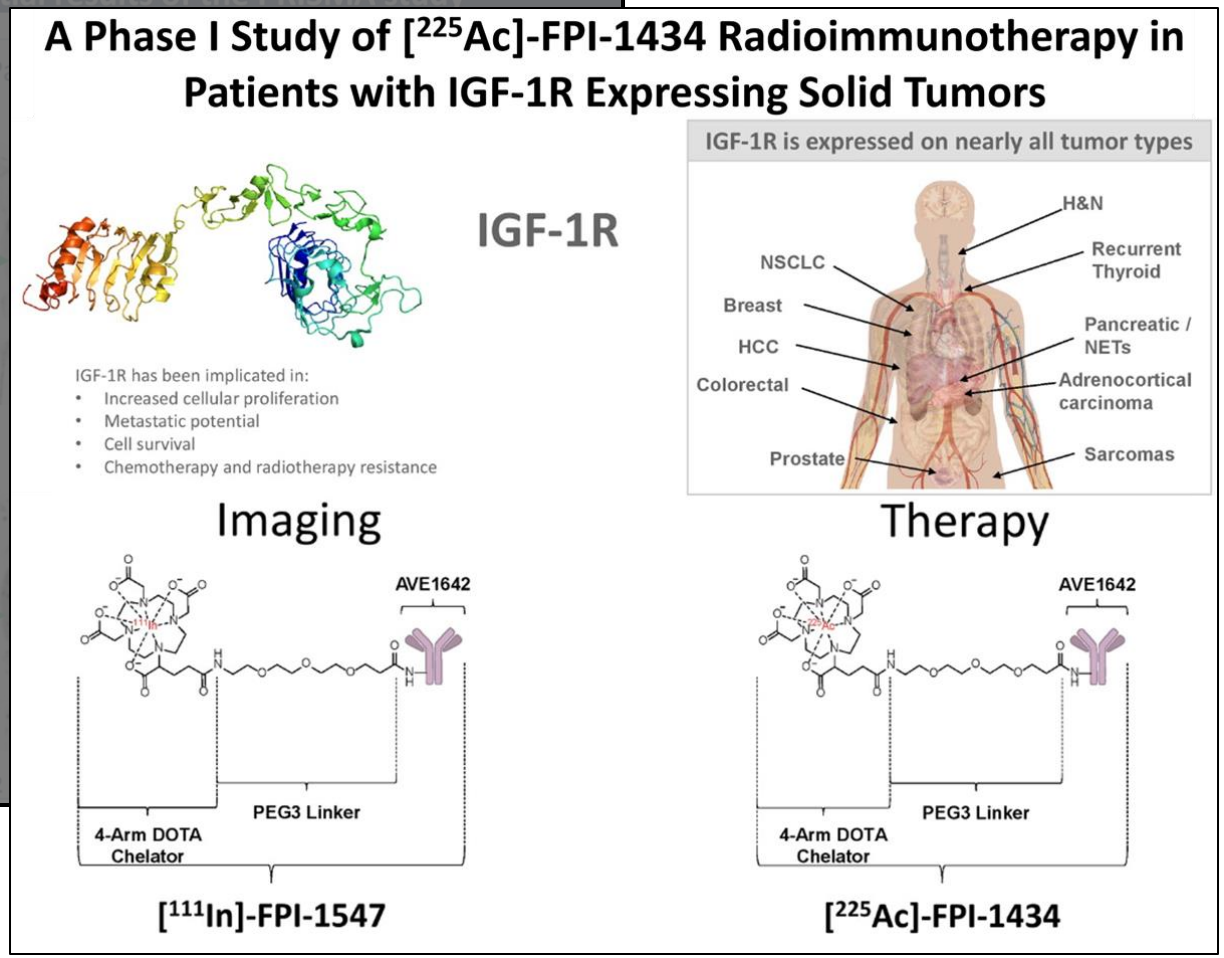
Boers, *Eur J Cancer* 2020



Peterson, *J Nucl Med* 2021

Theranostics for breast cancer?

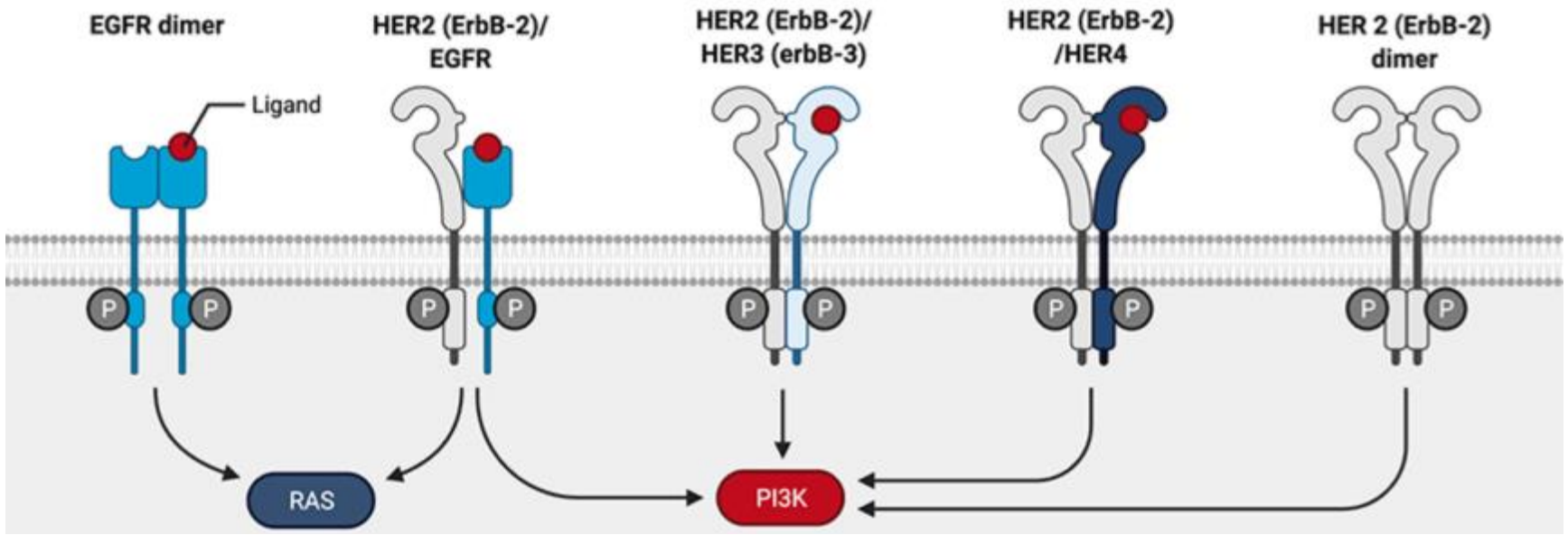


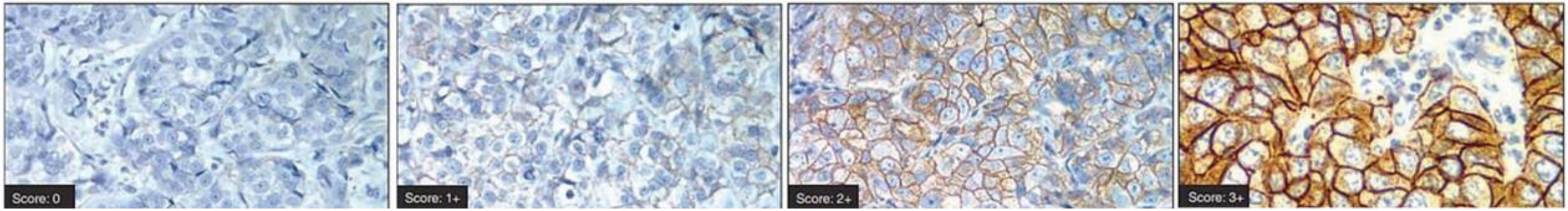


Valiant, ASCO 2019; NCT03746431

IHC

Modern *EGFR* Family





HER2 Is a Driver When . .

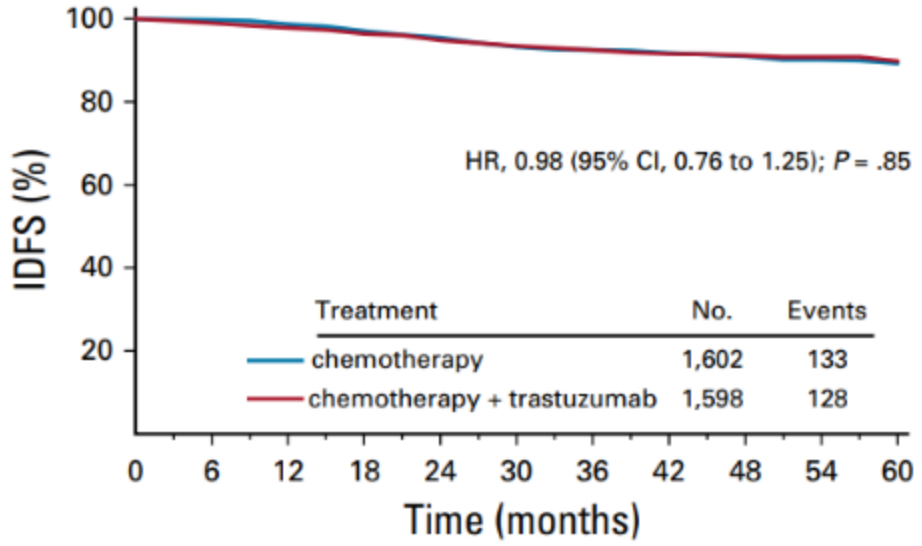
- HER2 is overexpressed (3+)
- HER2 is amplified

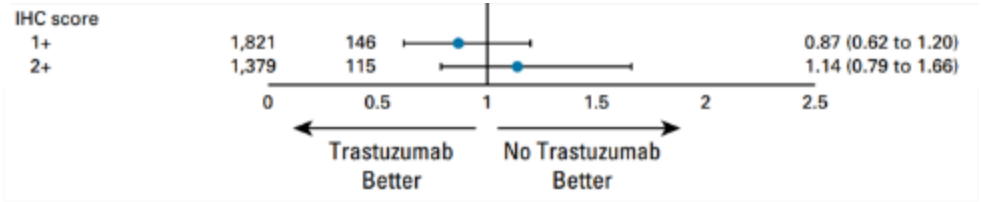
A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer

	HER2+ (n = 140)	HER2− (n = 89)
	Investigator review	Investigator review
Best response, n (%)		
CR	3 (2)	0
PR	3 (2)	0
SD	38 (27)	10 (11)
PD	85 (61)	76 (85)
Unknown	11 (8)	3 (3)
Response rate (CR or PR), % (95% CI)	4.3 (1.6, 9.1)	0.0 (0.0, 4.1)

Adapted from Burstein. *Ann Oncol*. 2008

NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2+





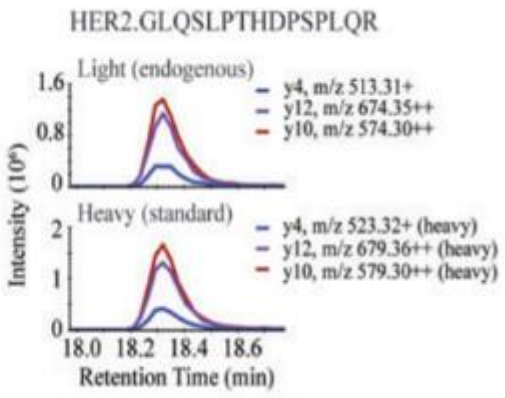
Adapted from Fehrenbacher. *J Clin Oncol* 2020

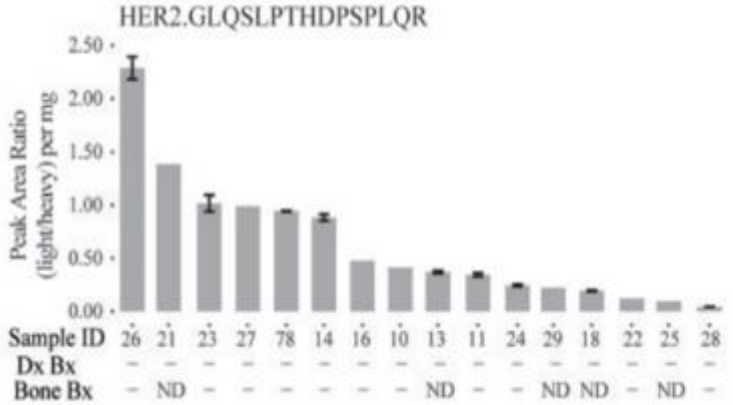
Path Workflow: HER2 After DESTINY-B04; -B06

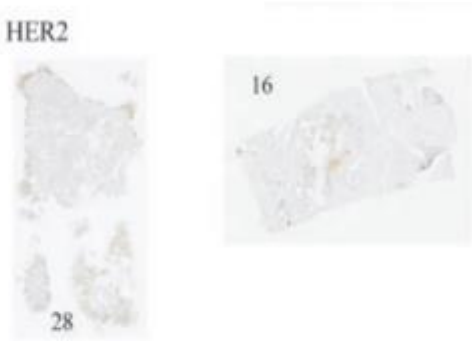
VK's thinking . . .

- Get tissue, HER2 (F)ISH preferred (NCCN, expert)
- Reflexively get HER2 IHC if (F)ISH negative
  - Know that some tissues are hard to process and some reports hard to interpret
  - HER2 0/1+ not reliable in non-breast tissue, esp. bone

Quantification of Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2 Protein Expression in Bone Biopsies by Targeted Mass Spectrometry without Acid Decalcification

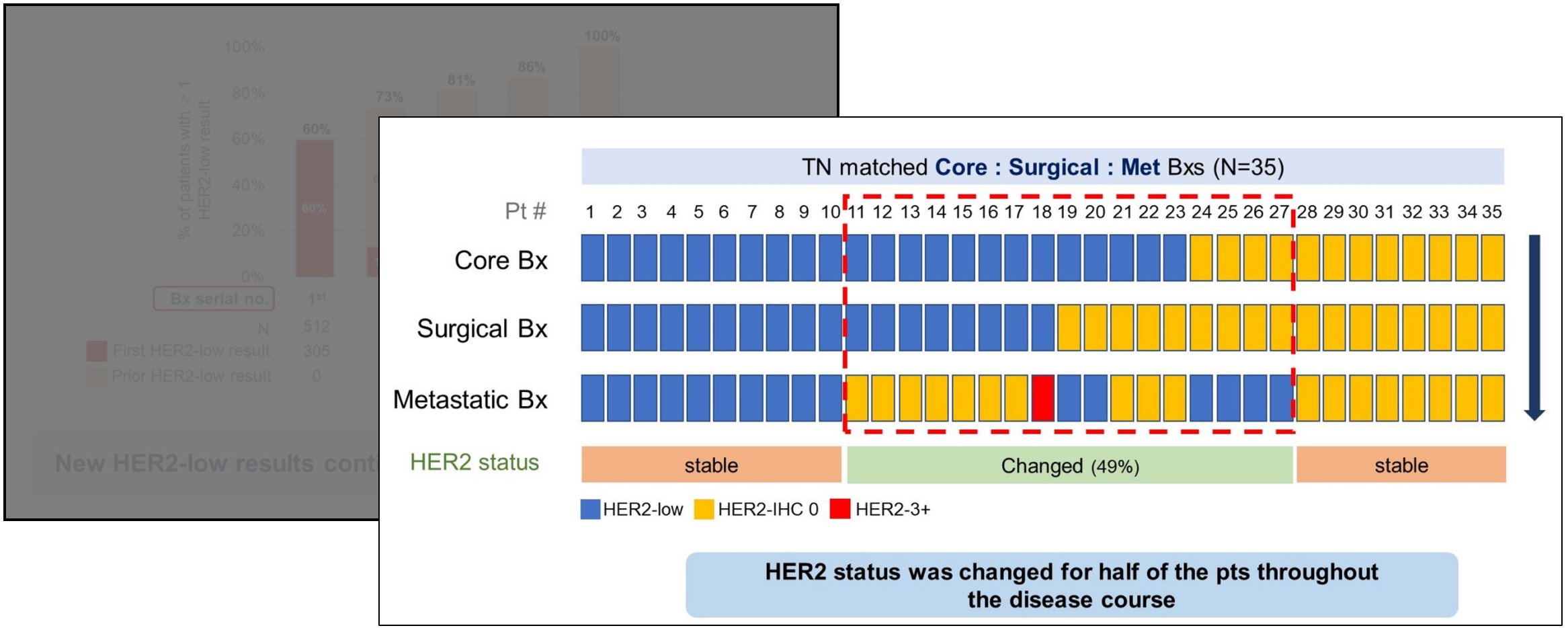






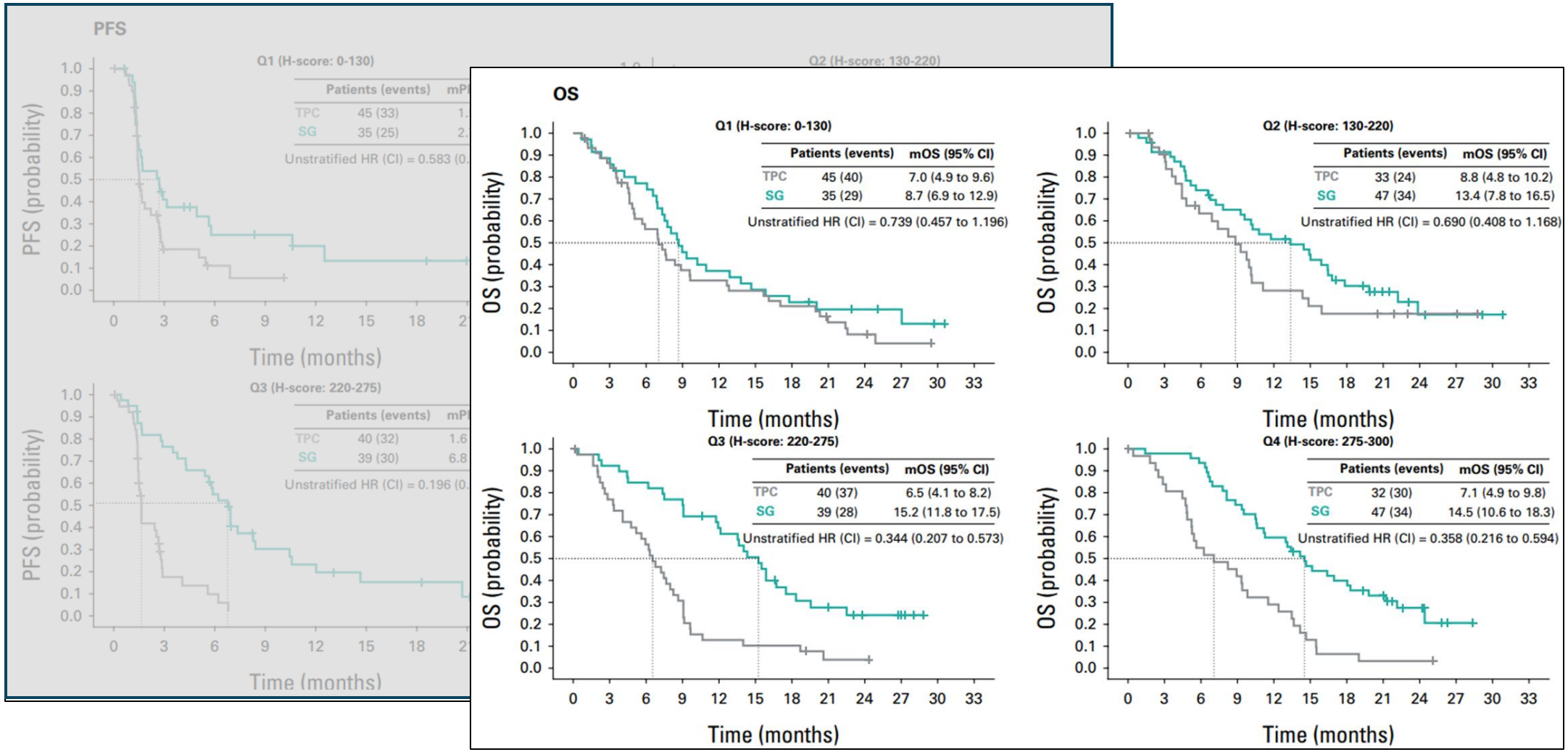
Schoenherr. *Clin Chem*. 2020

Dynamic HER2-low Status Among Patients With Triple Negative Breast Cancer (TNBC) – The Impact of Repeat Biopsies



Bar, ASCO 2023

Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple-Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression



Bardia, *JCO* 2024

Genomics: expression, mutations, immune-licensing

Where's gene expression profiling for MBC?

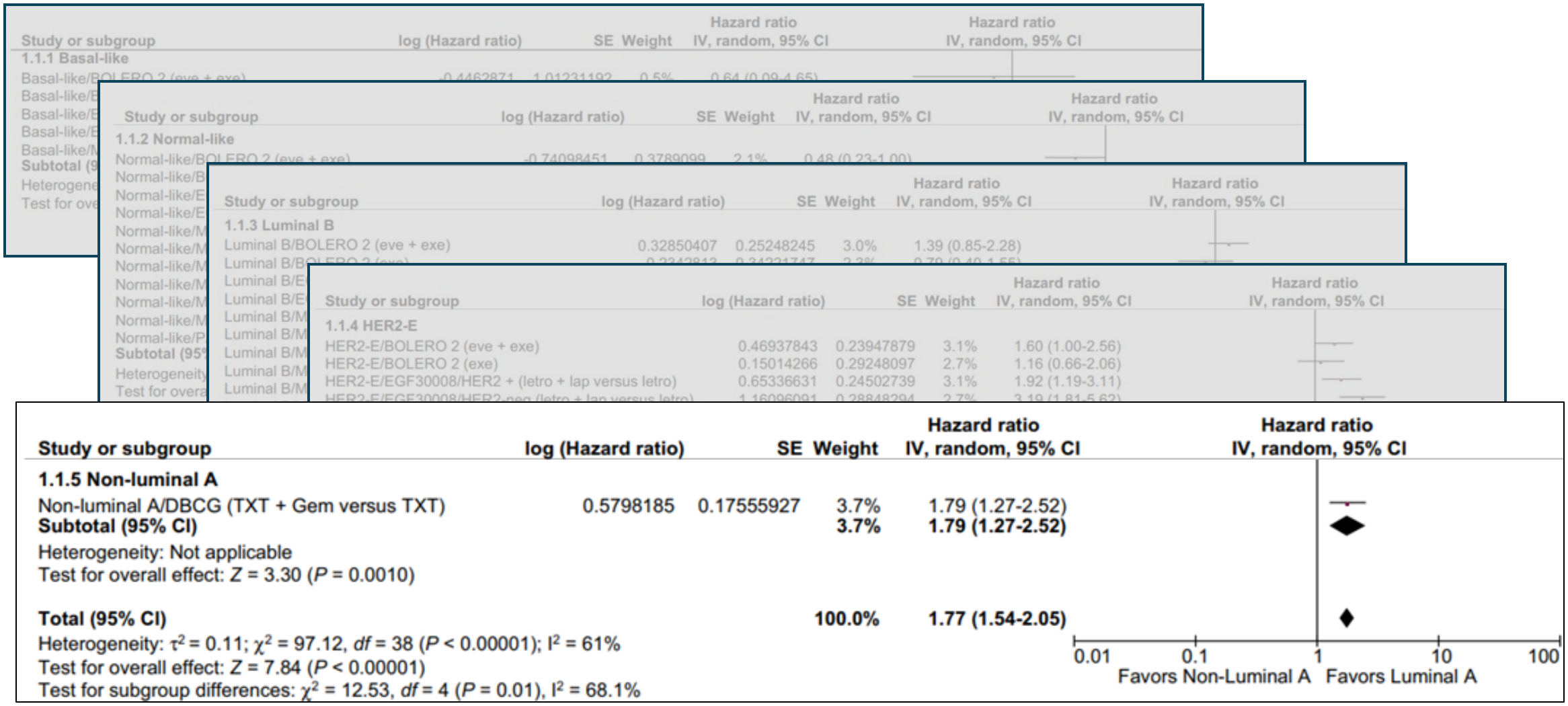
ORIGINAL RESEARCH

Prognostic value of intrinsic subtypes in hormone-receptor-positive metastatic breast cancer: systematic review and meta-analysis☆

Table 1. Characteristics of included studies

Study	Trial name	Population	Menopausal status	Trial type	Phase	Treatment	Line	Non-luminal A	Luminal A	Normal-like	Adjusted HR	Primary samples	Metastatic samples
Prat et al. *Oncologist*. 2019[32]	BOLERO2	HoR+/HER2-neg	Postmenopausal	Randomized	III	Everolimus + exemestane versus exemestane	≥1st	139	122	Included	No	80.7%	19.3%
Jørgensen et al. *Acta Oncol*. 2014[35]	DBCG	Mainly HoR+/HER2-neg	Mixed	Randomized	III	Docetaxel + gemcitabine versus docetaxel	1st-2nd	186	84	Not included	No	100%	0%
Prat et al. *JAMA Oncol*. 2016[16]	EGF30008	HoR+/HER2+ and neg	Postmenopausal	Randomized	III	Letrozole + lapatinib versus letrozole	1st	424	377	Included	No	80.6%	19.4%
Prat et al. *J Clin Oncol*. 2021[34]	MONALEESA 2	HoR+/HER2-neg	Postmenopausal	Randomized	III	Ribociclib + letrozole versus letrozole	1st	618	542	Included	Yes	72.0%	28.0%
Prat et al. *J Clin Oncol*. 2021[34]	MONALEESA 3	HoR+/HER2-neg	Postmenopausal	Randomized	III	Ribociclib + fulvestrant versus fulvestrant	1st-2nd			Included	Yes		
Prat et al. *J Clin Oncol*. 2021[34]	MONALEESA 7	HoR+/HER2-neg	Premenopausal	Randomized	III	Ribociclib + AI/TAM + GnRHa versus AI/TAM + GnRHa	1st			Included	Yes		
Ciruelos et al. *Clin Can Res*. 2020[25]	PATRICIA	HoR+/HER2+[a]	Postmenopausal	Non-randomized	II	Palbociclib ± letrozole + trastuzumab	3rd-5th	34	10	Included	No	54.2%	42.4%

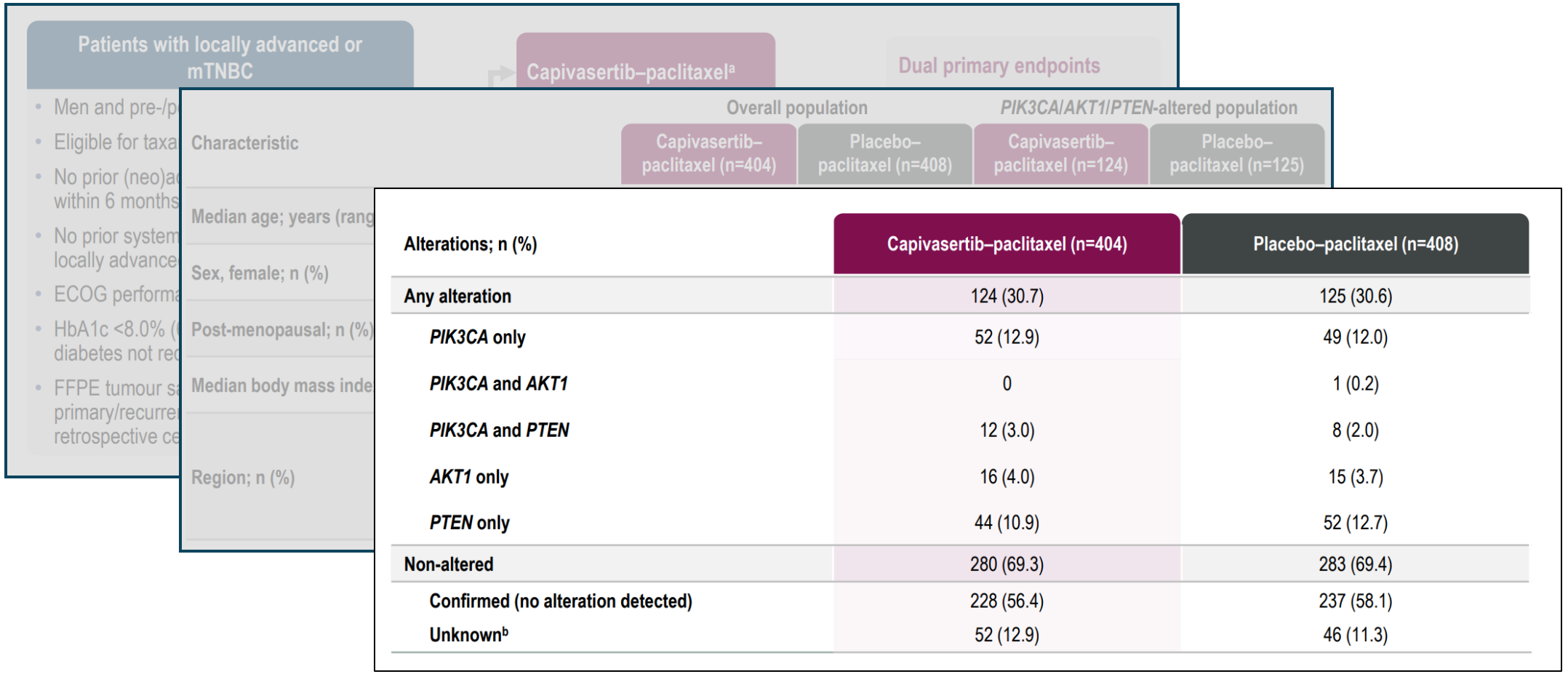
Schettini, *ESMO Open* 2023


Study or subgroup
log (Hazard ratio)
SE
Weight
Hazard ratio IV, random, 95% CI
Hazard ratio IV, random, 95% CI
1.1.1 Basal-like
1.1.2 Normal-like
Normal-like/BOLERO 2 (eve + exe) -0.74098451 0.3789099 2.1% 0.48 (0.23-1.00)
1.1.3 Luminal B
Luminal B/BOLERO 2 (eve + exe) 0.32850407 0.25248245 3.0% 1.39 (0.85-2.28)
1.1.4 HER2-E
HER2-E/BOLERO 2 (eve + exe) 0.46937843 0.23947879 3.1% 1.60 (1.00-2.56)
HER2-E/BOLERO 2 (exe) 0.15014266 0.29248097 2.7% 1.16 (0.66-2.06)
HER2-E/EGF30008/HER2 + (letro + lap versus letro) 0.65336631 0.24502739 3.1% 1.92 (1.19-3.11)
1.1.5 Non-luminal A
Non-luminal A/DBCG (TXT + Gem versus TXT) 0.5798185 0.17555927 3.7% 1.79 (1.27-2.52)
Subtotal (95% CI) 3.7% 1.79 (1.27-2.52)
Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)
Total (95% CI) 100.0% 1.77 (1.54-2.05)
Heterogeneity: τ² = 0.11; χ² = 97.12, df = 38 (P < 0.00001); I² = 61%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: χ² = 12.53, df = 4 (P = 0.01), I² = 68.1%
0.01
0.1
1
10
100
Favors Non-Luminal A
Favors Luminal A

NCCN: Nucleic Acid Biomarkers

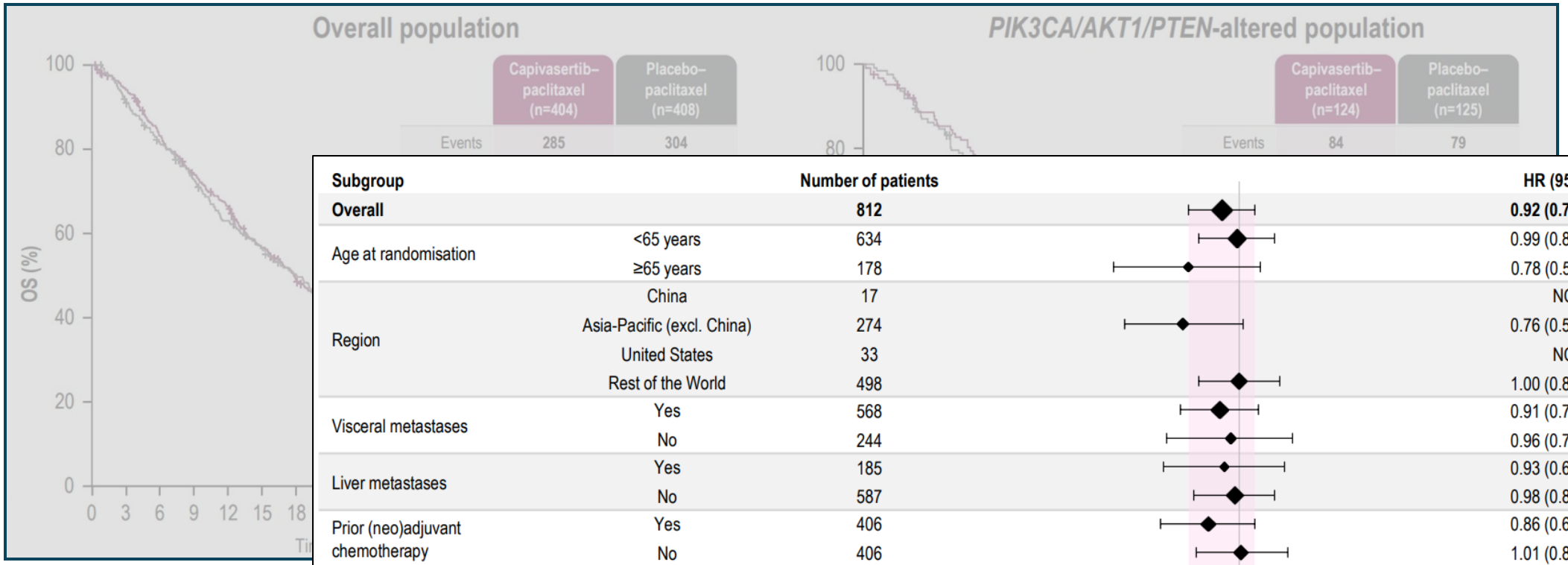
Subtype	Biomarker	NGS	PCR	Other
ER+/HER2-	ESR1	✓	✓	
ER+/HER2-	PIK3CA/AKT/mTOR/PTEN	✓	✓ (PIK3CA)	
ER(any)/HER2-	HER2 TK	✓	?	
Any	BRCA1/BRCA2/PALB2 mut	?		Germline
Any	TMB > 10mut/Mb	✓	?	
Any	MSI-H	✓		MMR by IHC
Any	NTRK Fusion	✓	✓	✓ (FISH)
Any	RET Fusion	✓		
Any	Somatic BRCA1/BRCA2 mut	✓		

Capivasertib + paclitaxel as first-line treatment of metastatic triple-negative breast cancer: the CAPItello-290 Phase 3 trial

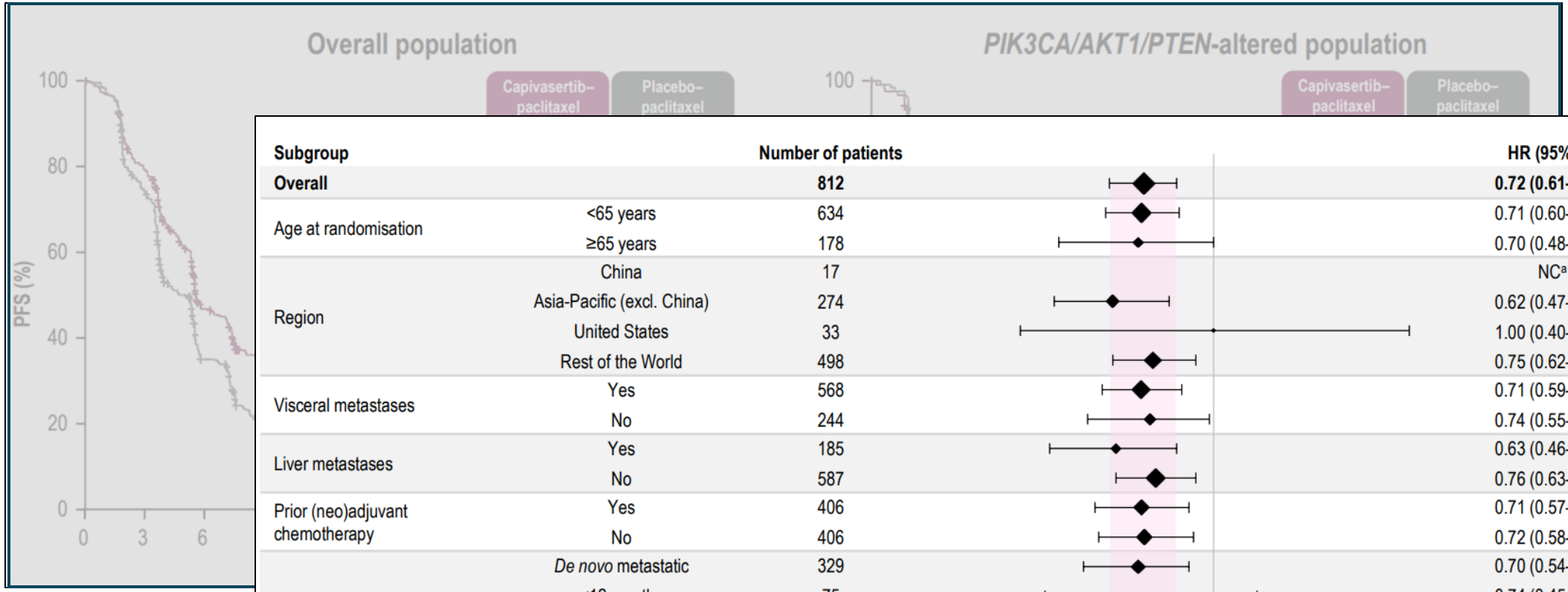


Alterations; n (%)	Capivasertib–paclitaxel (n=404)	Placebo–paclitaxel (n=408)
Any alteration	124 (30.7)	125 (30.6)
***PIK3CA* only**	52 (12.9)	49 (12.0)
PIK3CA* and *AKT1	0	1 (0.2)
PIK3CA* and *PTEN	12 (3.0)	8 (2.0)
***AKT1* only**	16 (4.0)	15 (3.7)
***PTEN* only**	44 (10.9)	52 (12.7)
Non-altered	280 (69.3)	283 (69.4)
Confirmed (no alteration detected)	228 (56.4)	237 (58.1)
Unknown[b]	52 (12.9)	46 (11.3)

McArthur, ESMO 2024



Subgroup		Number of patients	HR (95% CI)
Overall		**812**	**0.92 (0.78–1.08)**
Age at randomisation	<65 years	634	0.99 (0.82–1.19)
	≥65 years	178	0.78 (0.54–1.11)
Region	China	17	NC[a]
	Asia-Pacific (excl. China)	274	0.76 (0.57–1.02)
	United States	33	NC[a]
	Rest of the World	498	1.00 (0.82–1.22)
Visceral metastases	Yes	568	0.91 (0.75–1.10)
	No	244	0.96 (0.70–1.30)
Liver metastases	Yes	185	0.93 (0.69–1.25)
	No	587	0.98 (0.80–1.19)
Prior (neo)adjuvant chemotherapy	Yes	406	0.86 (0.68–1.08)
	No	406	1.01 (0.81–1.27)
Disease-free interval[b]	*De novo* metastatic	329	0.97 (0.75–1.25)
	<12 months	75	0.95 (0.58–1.59)
	≥12–<24 months	163	0.65 (0.45–0.92)
	≥24 months	155	1.02 (0.74–1.39)
PD-L1 status	Positive	126	0.71 (0.47–1.08)
	Negative	362	0.94 (0.74–1.19)
	Unknown	324	1.02 (0.79–1.32)



Subgroup		Number of patients	HR (95% CI)
Overall		**812**	**0.72 (0.61–0.84)**
Age at randomisation	<65 years	634	0.71 (0.60–0.85)
	≥65 years	178	0.70 (0.48–1.00)
Region	China	17	NC[a]
	Asia-Pacific (excl. China)	274	0.62 (0.47–0.81)
	United States	33	1.00 (0.40–2.53)
	Rest of the World	498	0.75 (0.62–0.92)
Visceral metastases	Yes	568	0.71 (0.59–0.86)
	No	244	0.74 (0.55–0.98)
Liver metastases	Yes	185	0.63 (0.46–0.84)
	No	587	0.76 (0.63–0.92)
Prior (neo)adjuvant chemotherapy	Yes	406	0.71 (0.57–0.89)
	No	406	0.72 (0.58–0.91)
Disease-free interval	*De novo* metastatic	329	0.70 (0.54–0.89)
	<12 months	75	0.74 (0.45–1.23)
	≥12–<24 months	163	0.72 (0.51–1.02)
	≥24 months	155	0.69 (0.51–0.93)
PD-L1 status	Positive	126	0.58 (0.38–0.87)
	Negative	362	0.88 (0.69–1.11)
	Unknown	324	0.62 (0.48–0.80)

Interrogations:

- Imaging – guide treatment selection
- IHC – beyond the usual…
  - HER2 testing
  - PD testing
  - MMR
- Nucleic Acids
  - Relatively few actionable markers
  - ctDNA – the new CA15.3, CEA, etc?