

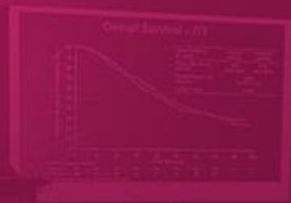
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REALIZAÇÃO



ctDNA in Breast Cancer: evidences and perspectives

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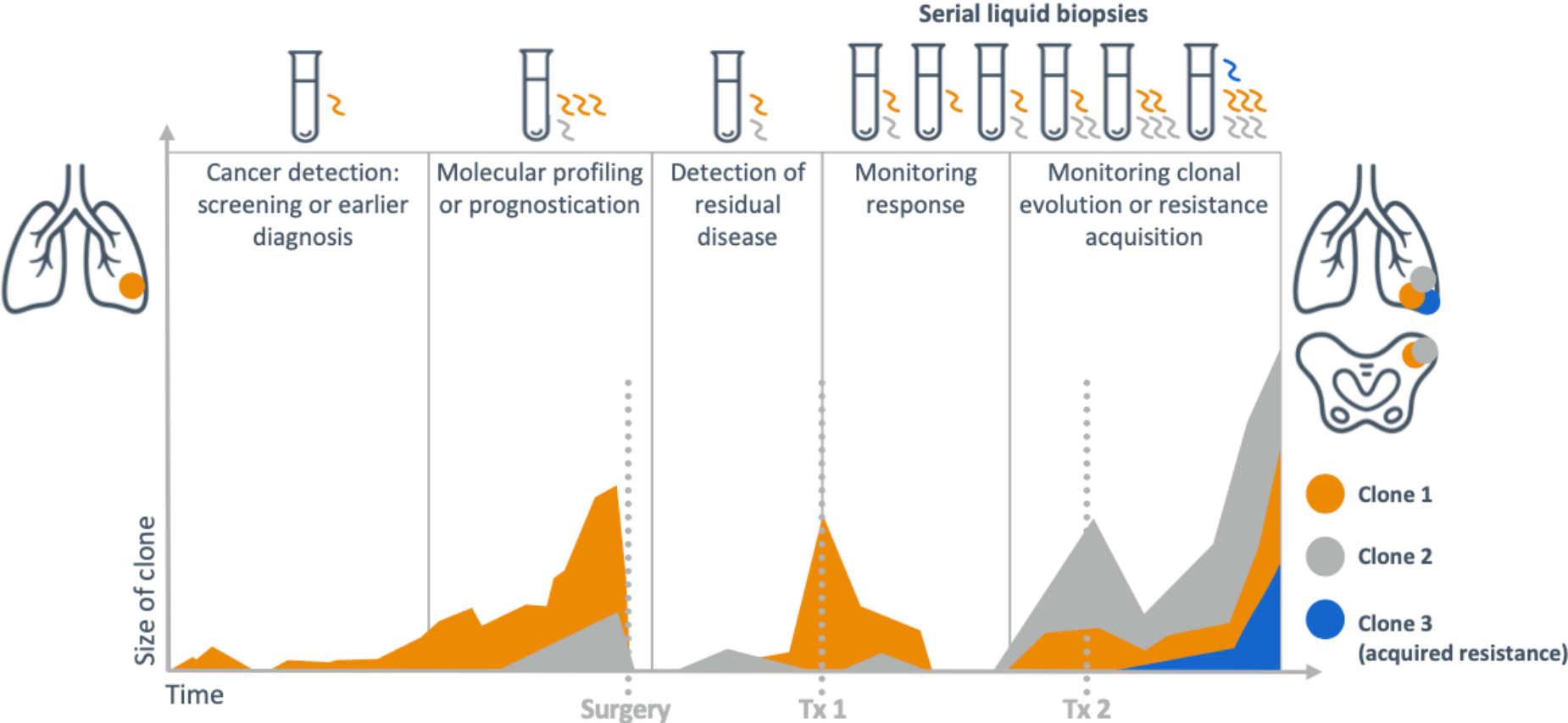
APOIO



CONFLICTS OF INTEREST

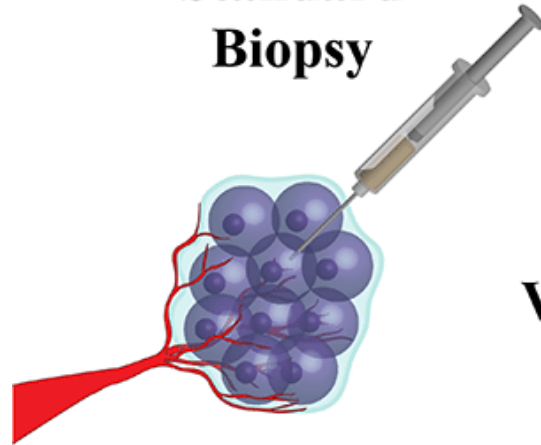
RD declares advisory role for Roche, Foundation Medicine, received a speaker's fee from Roche, Ipsen, Amgen, Servier, Sanofi, Libbs, Merck Sharp & Dohme, Lilly, AstraZeneca, Janssen, Takeda, Bristol Myers Squibb, GlaxoSmithKline, Gilead, research grants from Merck, Novartis, Daiichi-Sankyo, GlaxoSmithKline and AstraZeneca, and is investor in Trialing Health, S.L.

CLINICAL APPLICATION OF LIQUID BIOPSY



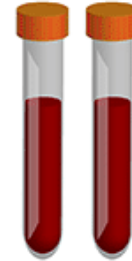
LIQUID BIOPSY ADVANTAGES

Standard Biopsy



VS.

Liquid Biopsy



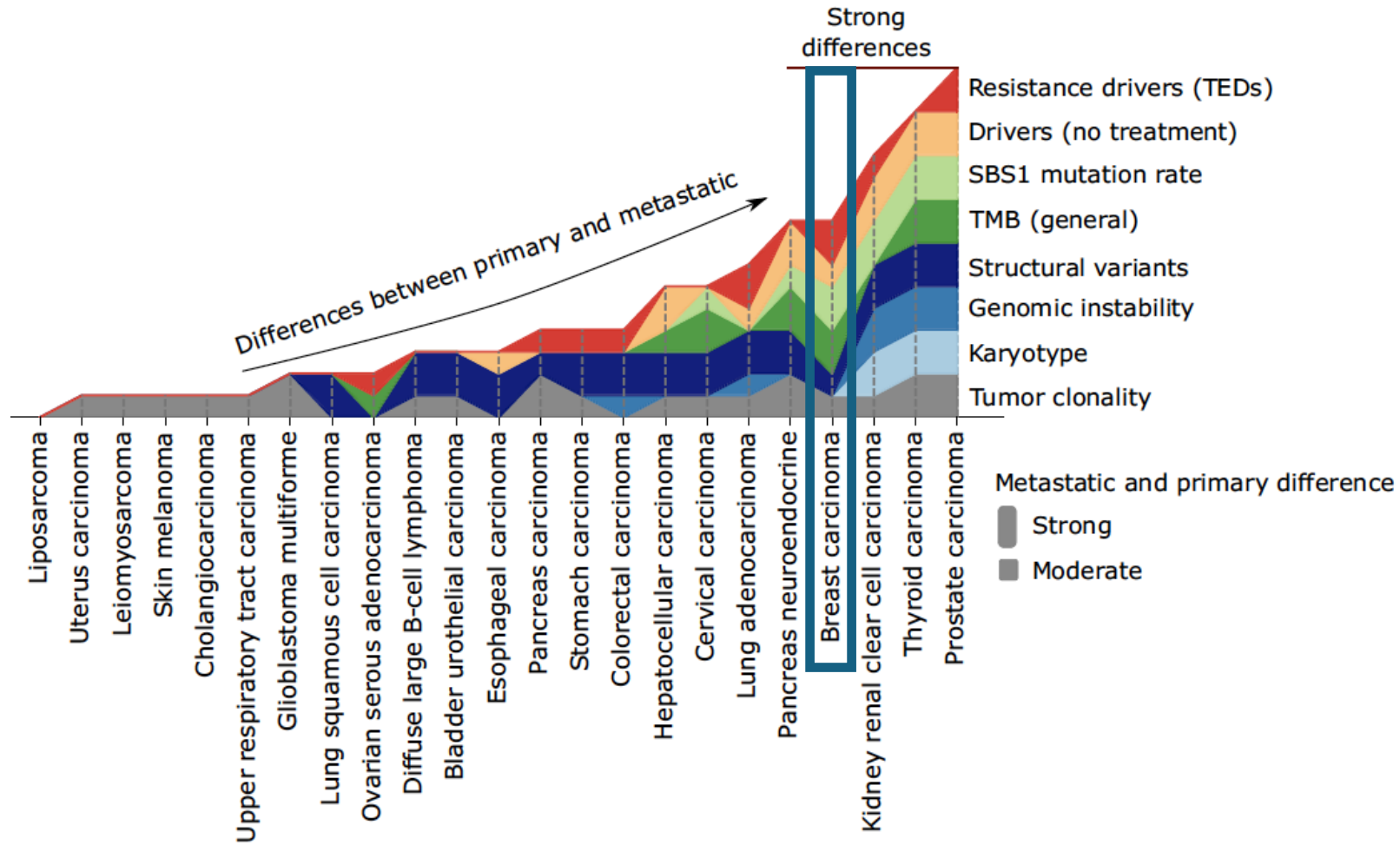
Time-Intensive Procedure
Localized Sampling of Tissue
Not Easily Obtained
Some Pain/Risk
Invasive

Paraffin quality may limit
large panel NGS

Quick
Comprehensive Tissue Profile
Easily Obtained
Minimal Pain/Risk
Minimally Invasive

ctDNA amount may be sufficient
to run large panel NGS

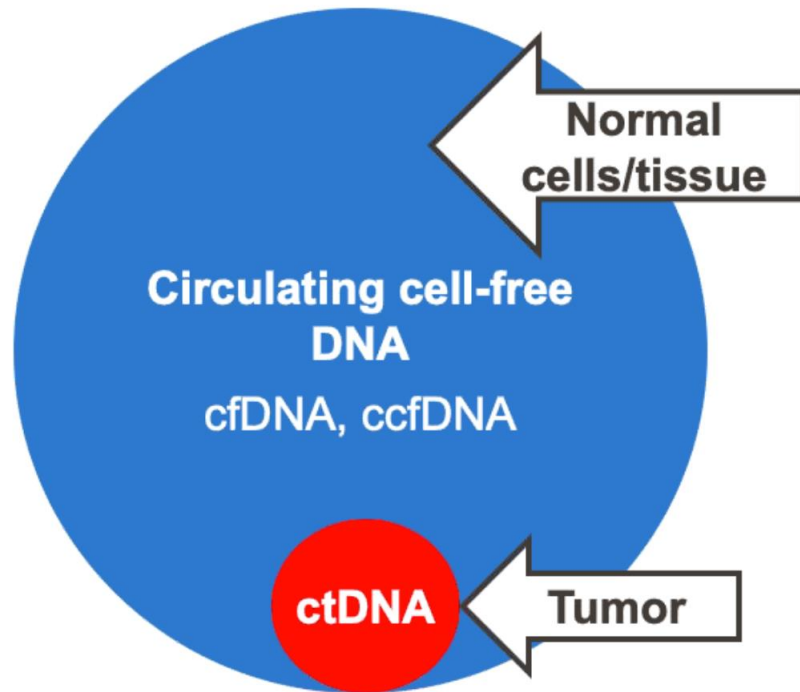
STRONG DIFFERENCES IN GENOMICS OF METASTATIC VERSUS PRIMARY BREAST CANCER



- > *ESR1* mutations
- > *PIK3CA* mutations
- > *AKT1* mutations
- > *PTEN* mutations
- > *RB1* mutations
- > *MYC/MDM4* amplifications
- > HRD
- > TMB

TMB: tumor mutation burden
 HRD: homologous recombination deficiency

LIQUID BIOPSY TECHNICAL ASPECTS



cfDNA: cell free DNA

ctDNA: circulating tumor DNA
Half-life: < 2 hours

Tumor fraction: ctDNA/cfDNA
Ideal > 10%

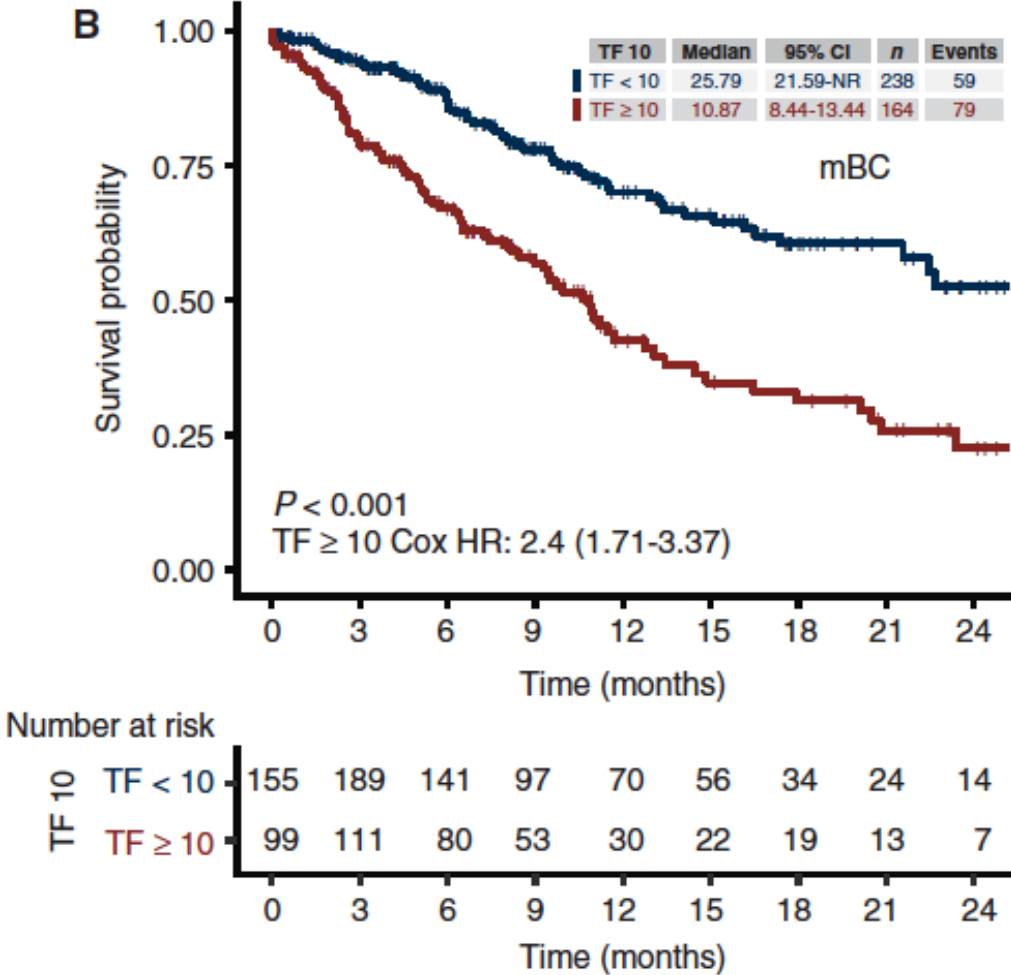
SOMETIMES REPORTED

VAF (variant allele frequency):
mutated allele/cfDNA
Commonly > 0.5%

REPORTED

LIQUID BIOPSY TUMOR FRACTION IS STRONG PROGNOSTIC FACTOR

Tumor Fraction (TF):
 surrogate of disease burden/
 independent prognostic factor

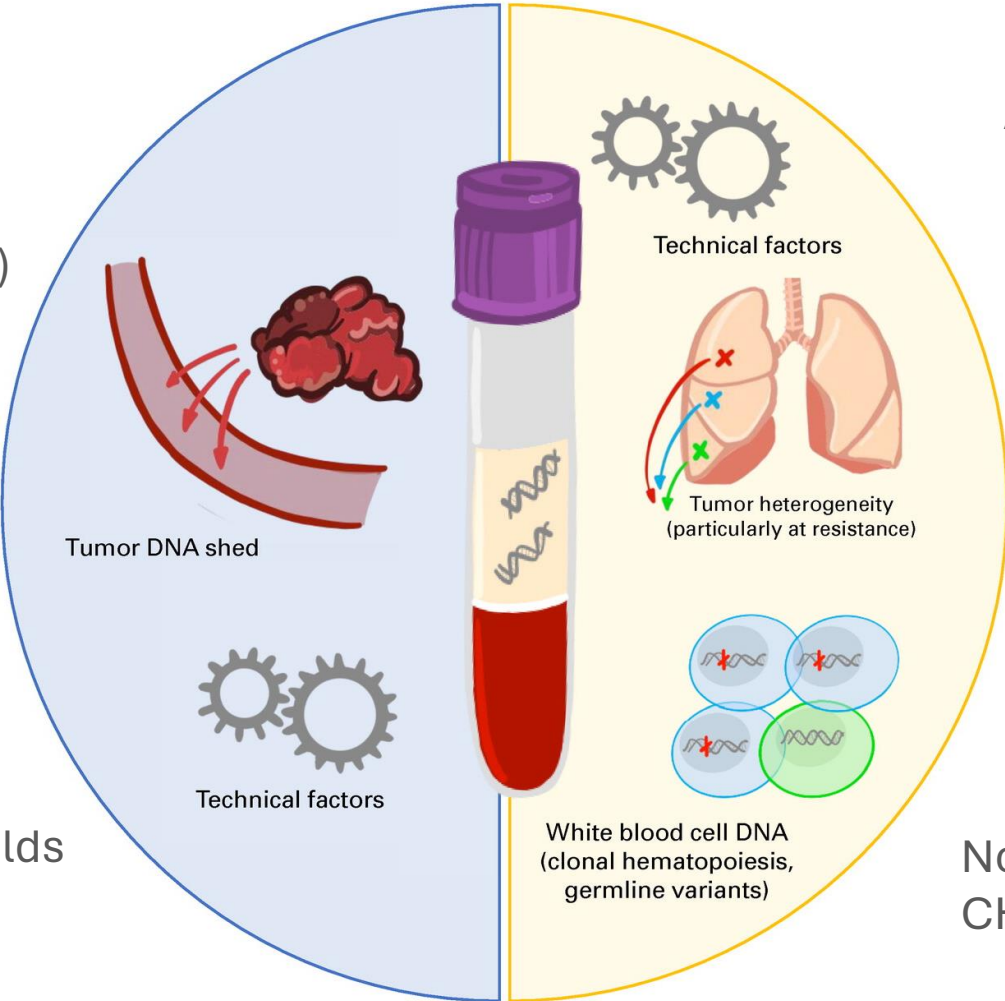


FALSE NEGATIVES AND POSITIVES WITH LIQUID BIOPSY

Timing of collection
(after start of new therapy)

Low tumor burden
(stable/responding disease)

False Negatives



Analytical issues
Bioinformatics thresholds

False Positives

Analytical issues
Bioinformatics thresholds
Complex variants
Subclonality

Non-cancerous somatic variants
CHIP – clonal hematopoeisis of indeterminate potential

2024 ESMO RECOMMENDATIONS FOR NGS IN BREAST CANCER

1. HR+/HER2- metastatic disease highest value
2. After resistance to endocrine therapy
3. Metastatic tissue or **liquid biopsy** highly recommended
4. In most patients tumor NGS can substitute germline BRCA1/2 testing

But false negatives in up to 10%

So if pre-test likelihood of germline is high, parallel testing is recommended



**ESMO RECOMMENDS
TO PERFORM TUMOUR
NGS IN PATIENTS WITH
ADVANCED BREAST
CANCER**



ESCAT – ESMO SCALE CLINICAL ACTIONABILITY MOLECULAR TARGETS

LEVEL I	Targets ready for implementation in routine clinical decisions given improved survival outcomes	Standard-of-care
LEVEL II	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	Clinical trial or registry preferred option
LEVEL III	Clinical benefit previously demonstrated in other tumour type or similar molecular targets	Clinical trial to be discussed as alternative
LEVEL IV	Pre-clinical evidence of actionability	Early clinical trials can be considered
LEVEL V	Evidence supporting co-targeting approaches	Clinical trials with combinations option
LEVEL X	Lack of evidence for actionability	Ignore

ESCAT – ESMO SCALE CLINICAL ACTIONABILITY MOLECULAR TARGETS

Level I	<i>ERBB2</i> ampl <i>PIK3CA</i> mut, <i>AKT1</i> mut, <i>PTEN</i> mut <i>ESR1</i> mut <i>BRCA1/BRCA2</i> mut (germline) MSI, <i>NTRK1-3</i> fus, <i>RET</i> fusion, <i>BRAF</i>^{V600E} mut, TMB high
Level II	<i>BRCA1/BRCA2</i> mut (somatic), <i>PALB2</i> mut (germline) <i>ERBB2</i> mut <i>CD274</i> (PDL1) ampl
Level III	<i>ATM</i> mut, <i>CHEK2</i> mut Others
Level IV	Multiple
Level X	<i>CDKN2A</i> mut, <i>CCND1</i> ampl, <i>FGFR1</i> ampl



**ESMO RECOMMENDS
TO PERFORM TUMOUR
NGS IN PATIENTS WITH
ADVANCED BREAST
CANCER**



VALUE OF COMPREHENSIVE GENOMIC PROFILING (BROAD NGS)

Increased sensitivity for driver mutations and critical for more complex alterations/signatures

PIK3CA H1047R
PIK3CA E545K

Oncogene hotspots



PIK3CA E726K
BRCA2 deletion

Oncogene non-hotspot
Oncogene complex alterations (indels)

Alterations in Tumor suppressors

NTRK1 fusion
TMB high
HRD positive

Fusions/ rearrangements

Genomic signatures

Decreasing utility of single
marker testing

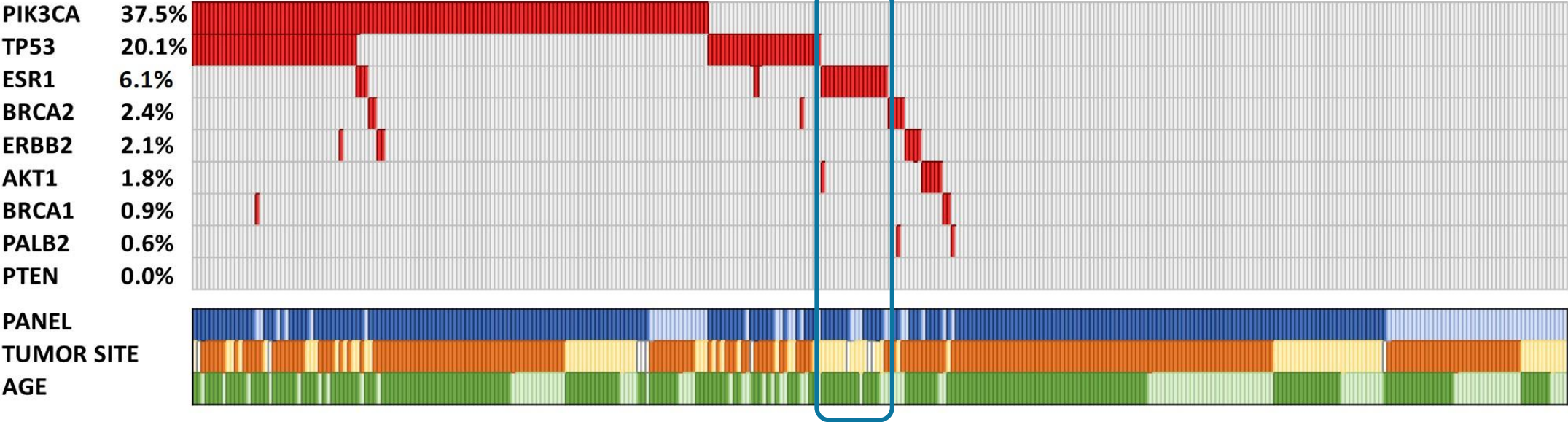
Increasing need for
comprehensive genomic profiling

TMB: tumor mutation burden

HRD: homologous recombination deficiency

PREVALENCE OF GENE DRIVERS IN HR+/HER2- BREAST CANCER TARGETED (SMALL NGS) PANEL

PATIENT SUPPORT PROGRAM

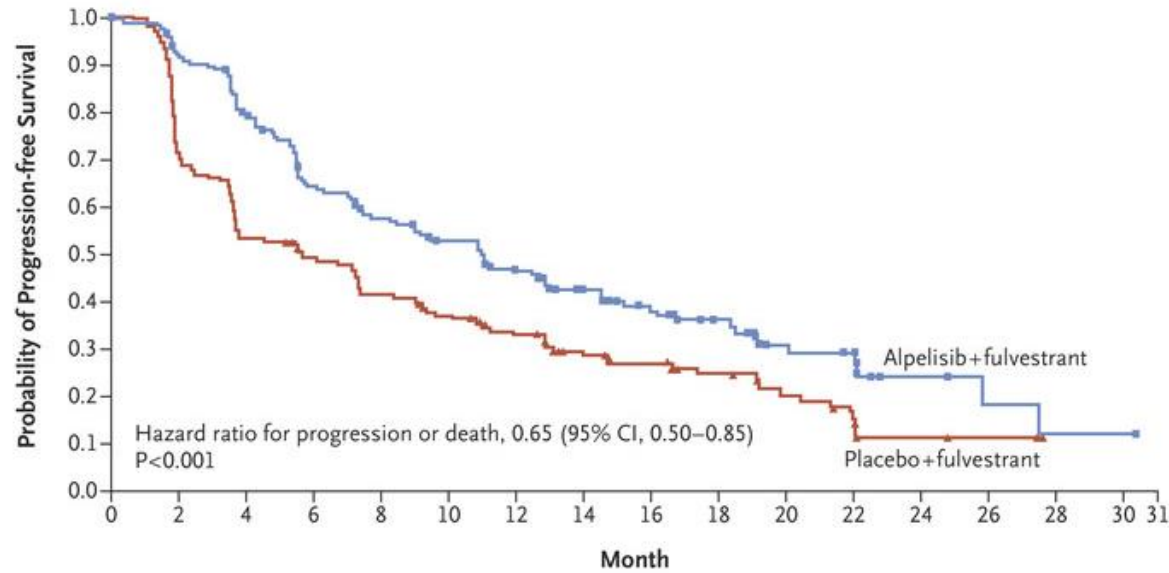


Source: Reinert et al, Frontiers Oncol in review

ESCAT LEVEL IA – *PIK3CA* mut (alpelisib + fulvestrant)

HR+/HER2- (30-40%)

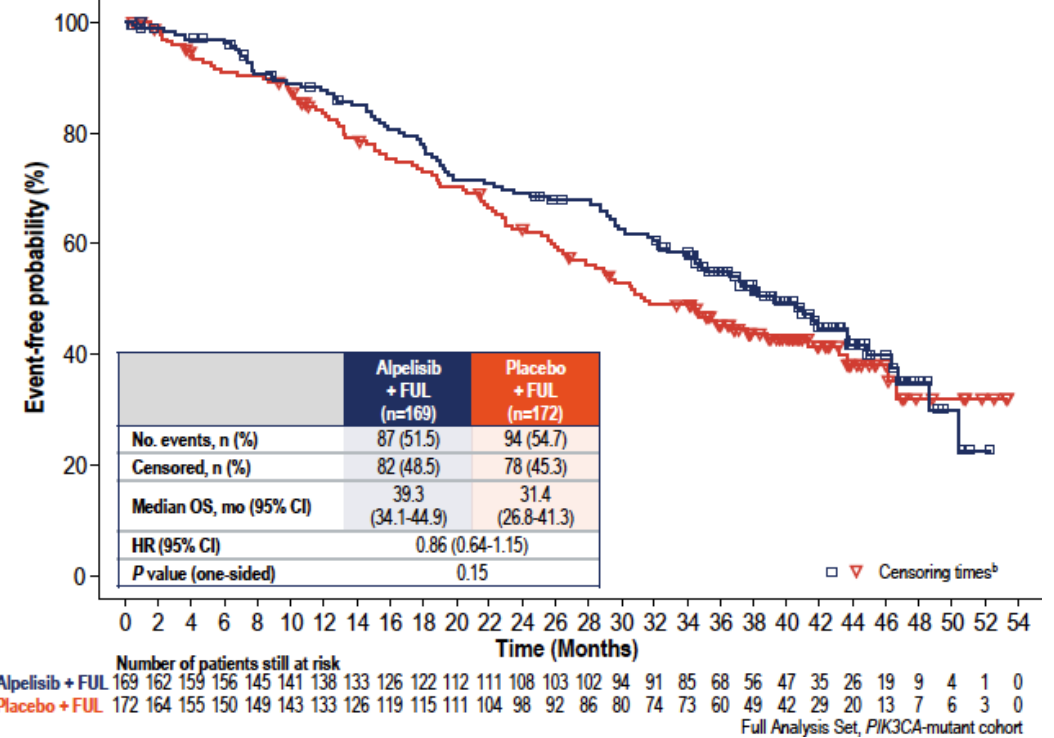
Progression-free survival



No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	31
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

Overall survival

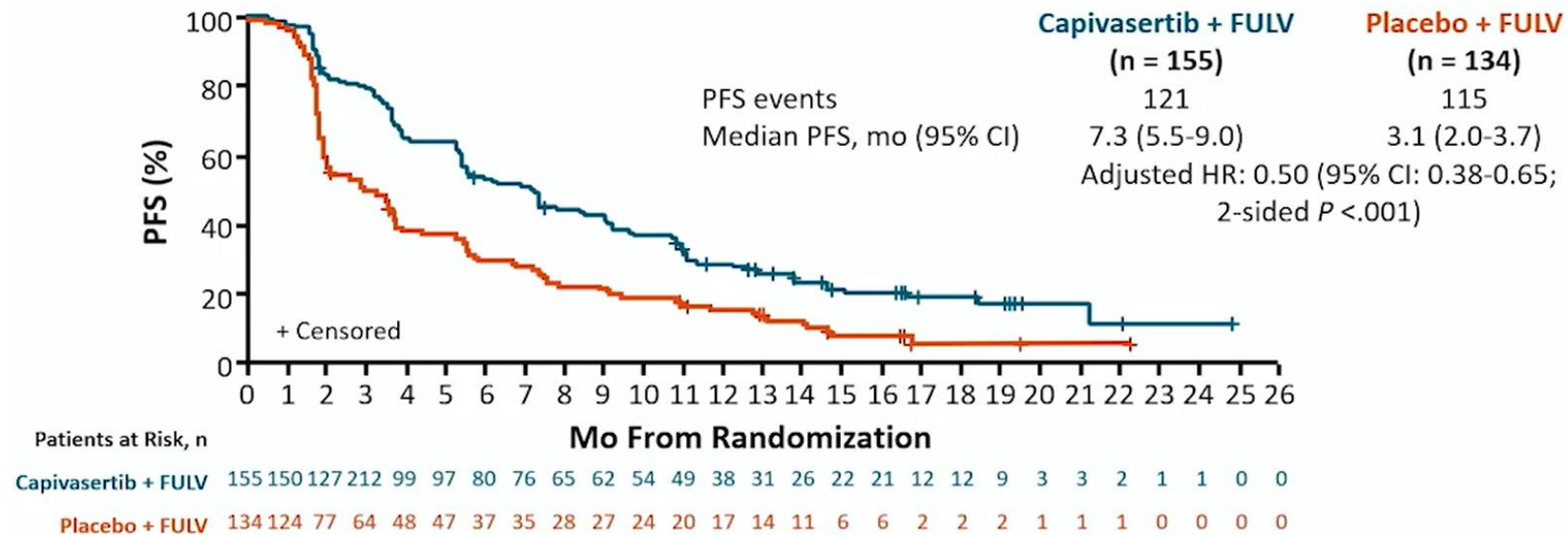


Up to 20% of activating *PIK3CA* mut are not hotspot variants (missed by hotspot panels)

ESCAT LEVEL IA – *PIK3CA*, *AKT1*, *PTEN* mut (capivasertib + fulvestrant)

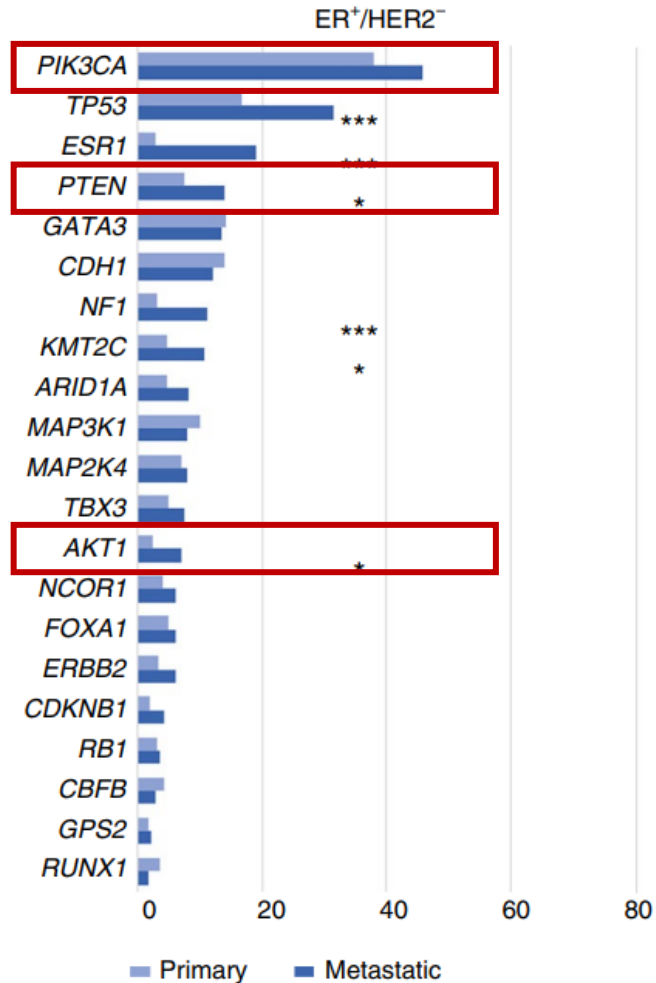
HR+/HER2- (30-40%)

Progression-free survival



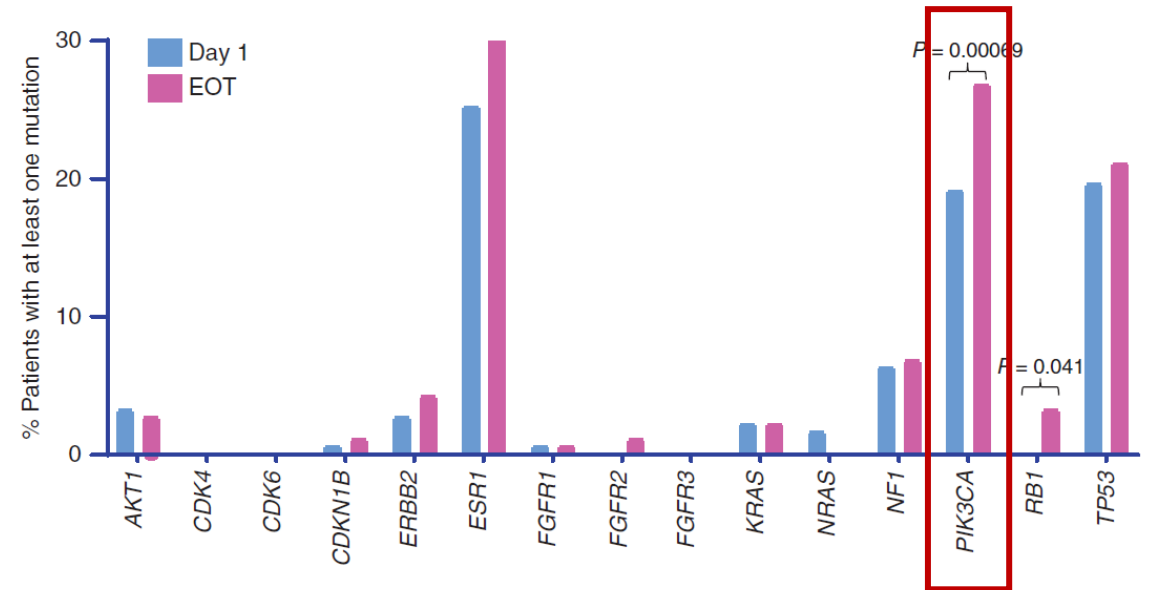
PIK3CA, PTEN mut – ENRICHED IN METASTATIC SAMPLES

Tissue NGS



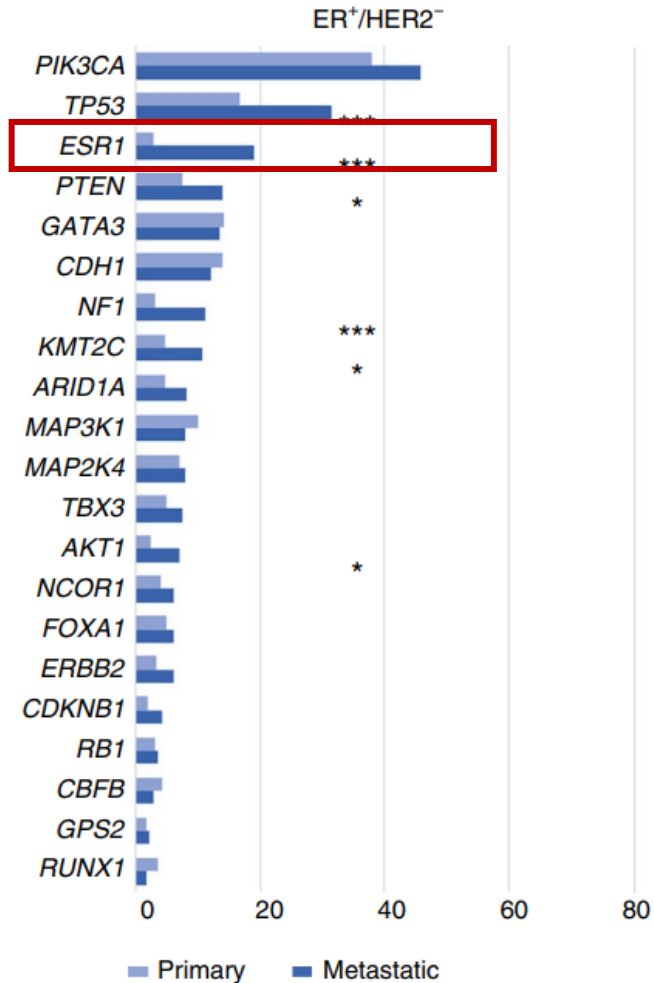
Liquid biopsy NGS

(progressing to AI, before or after CDKi)



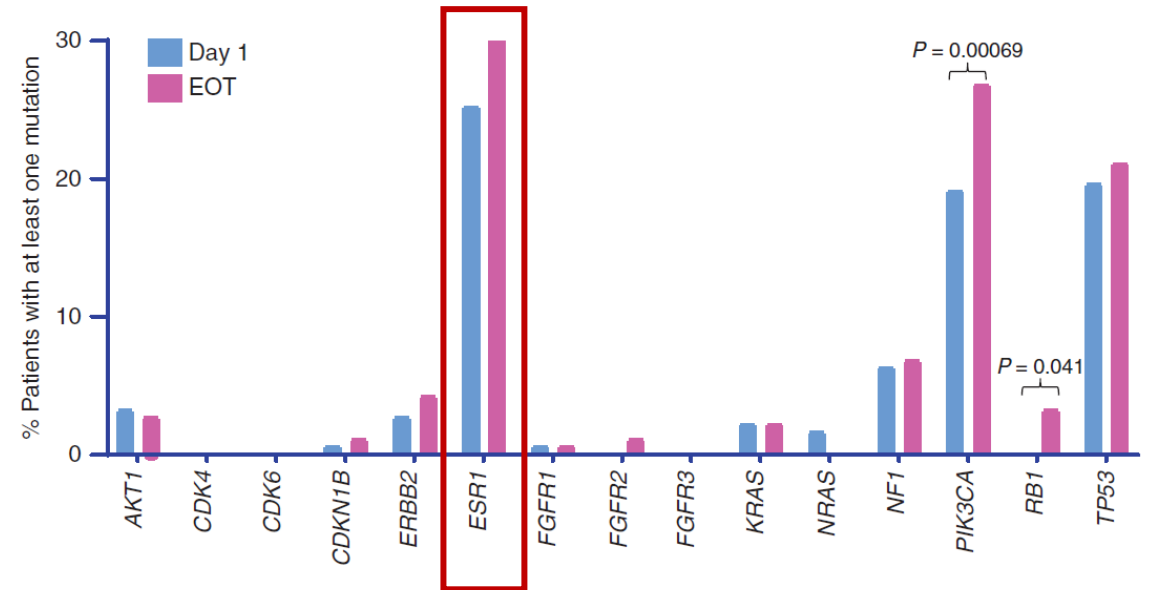
ESR1 mut – ENRICHED IN METASTATIC SAMPLES

Tissue NGS



Liquid biopsy NGS

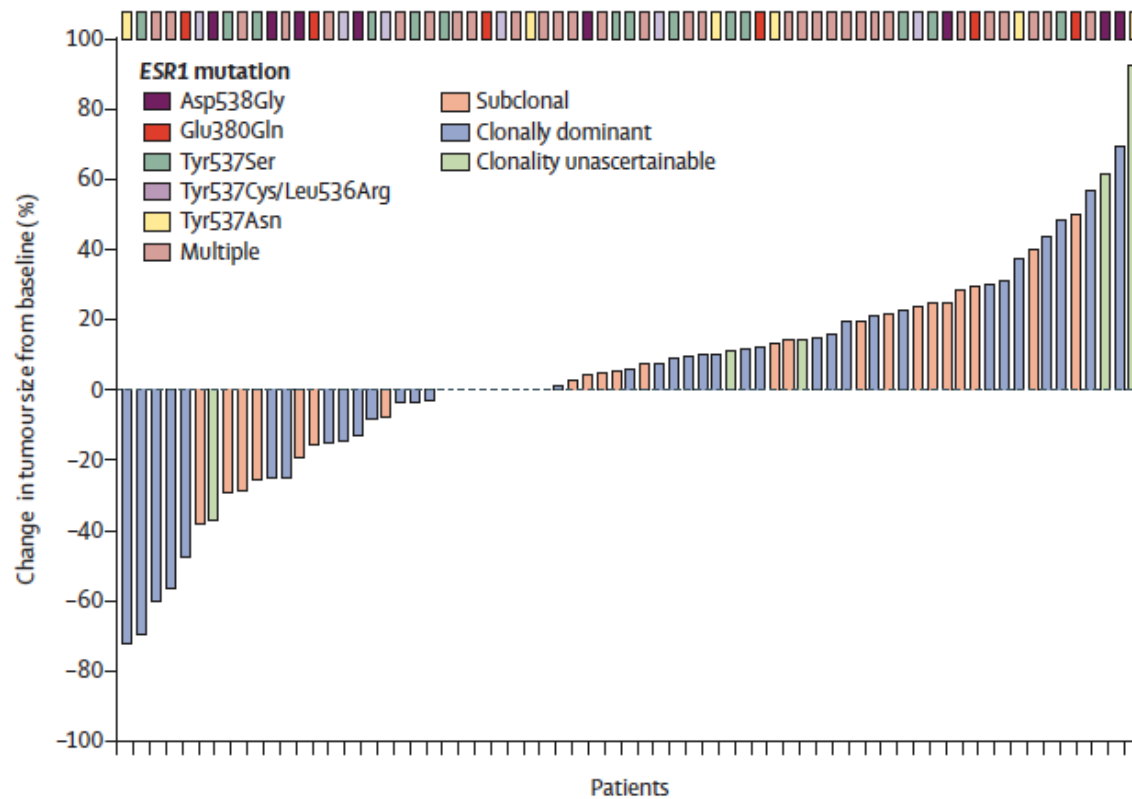
(progressing to AI, before or after CDKi)



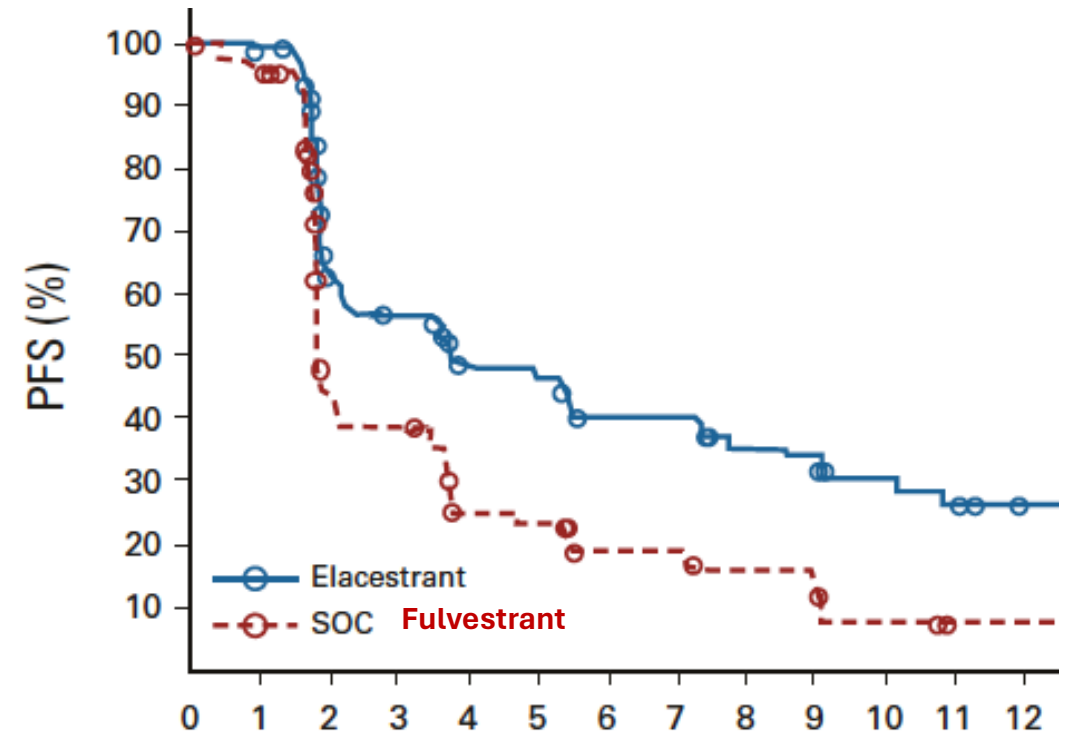
ESCAT LEVEL IA – ESR1 mut (fulvestrant, elacestrant)

HR+/HER2- (20-30%)

Fulvestrant (extended dose) (PlasmaMatch)

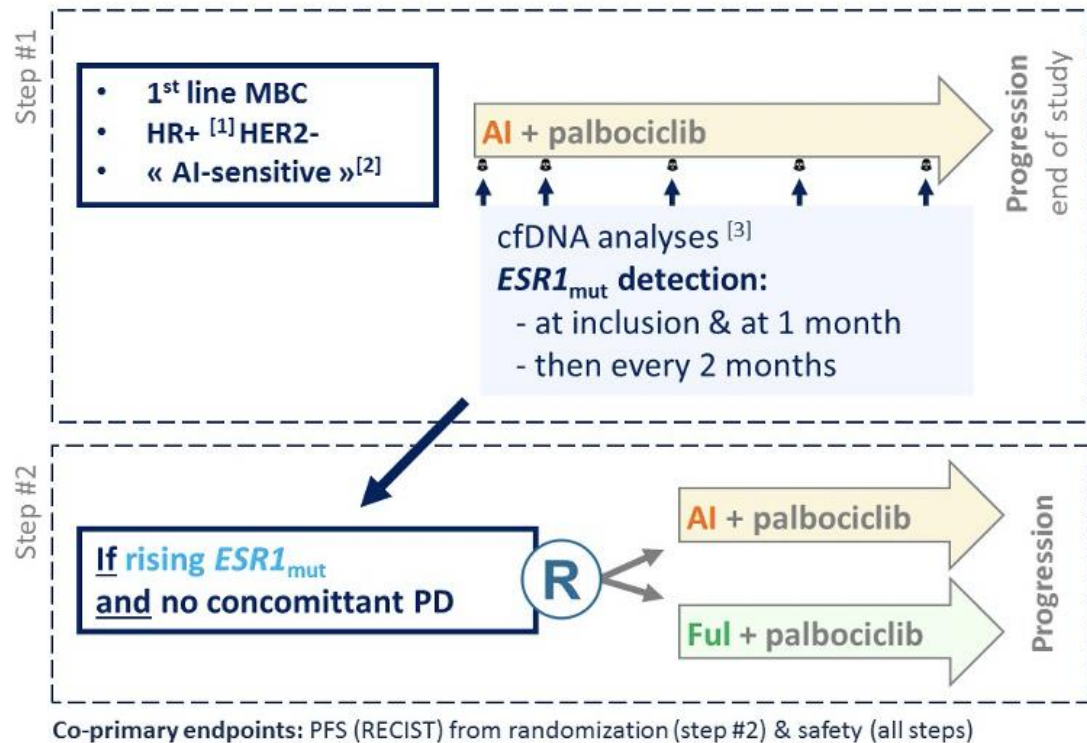


Elacestrant



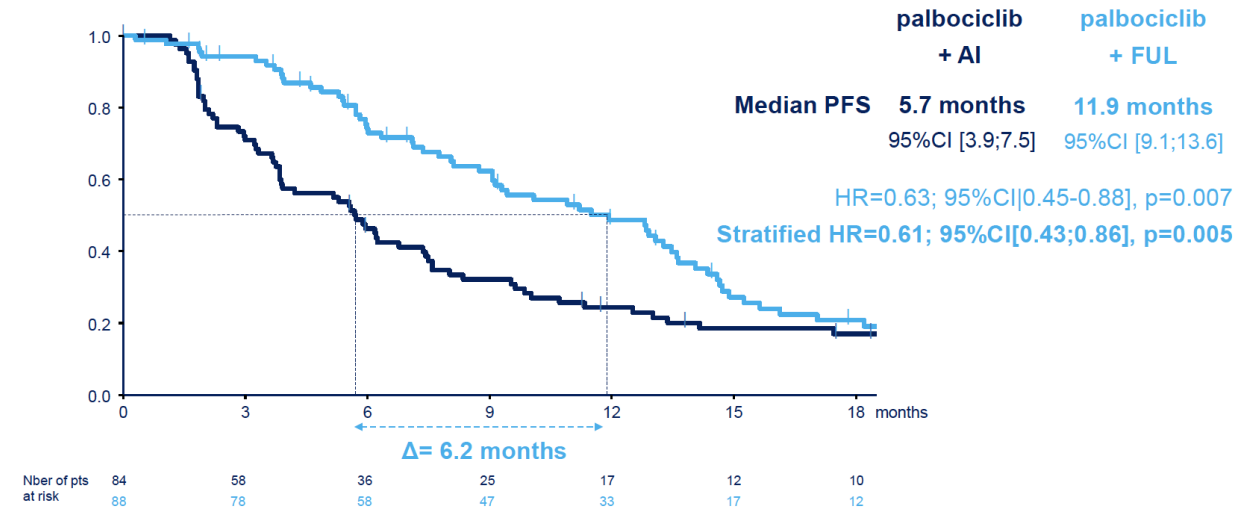
ESCAT LEVEL IA – ESR1 mut (fulvestrant)

HR+/HER2- (20-30%)



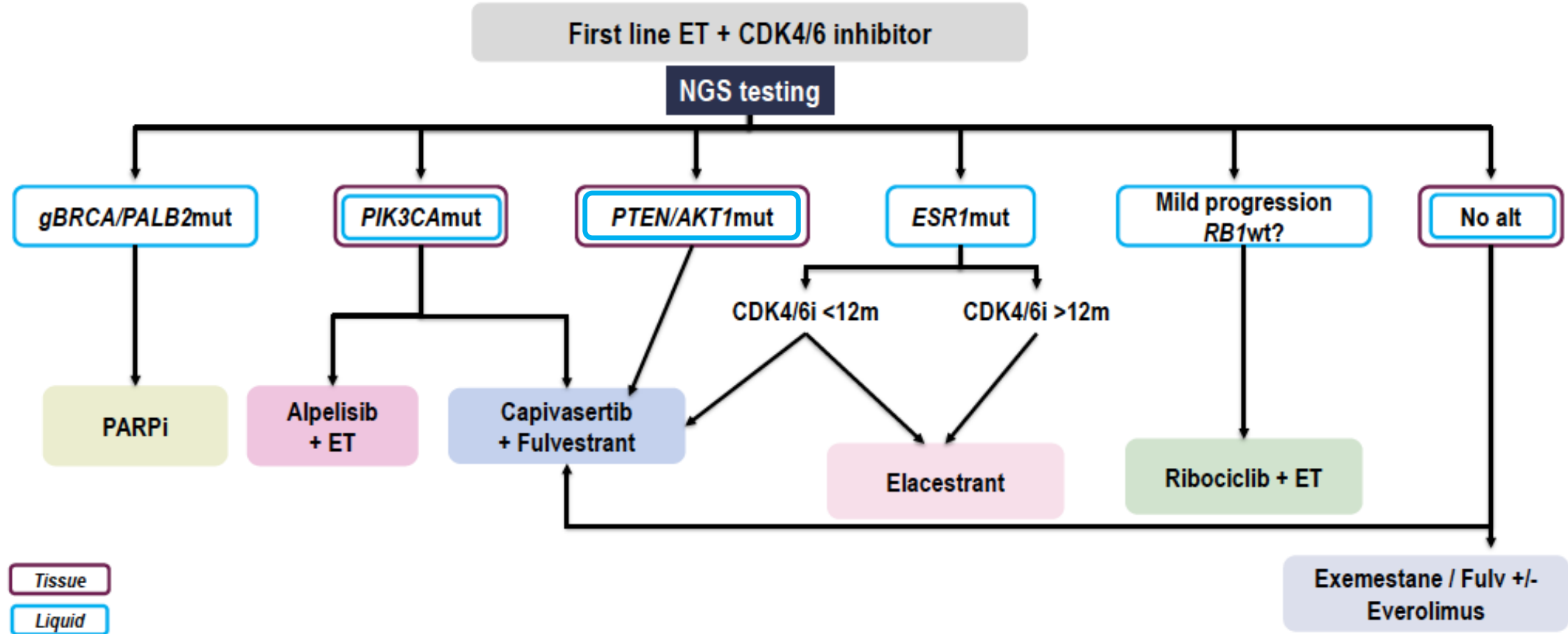
Progression-free survival

Median FU in step #2: 26 months (range: 0-36m); N=136 PFS events



Source: Bidard et al, 2022

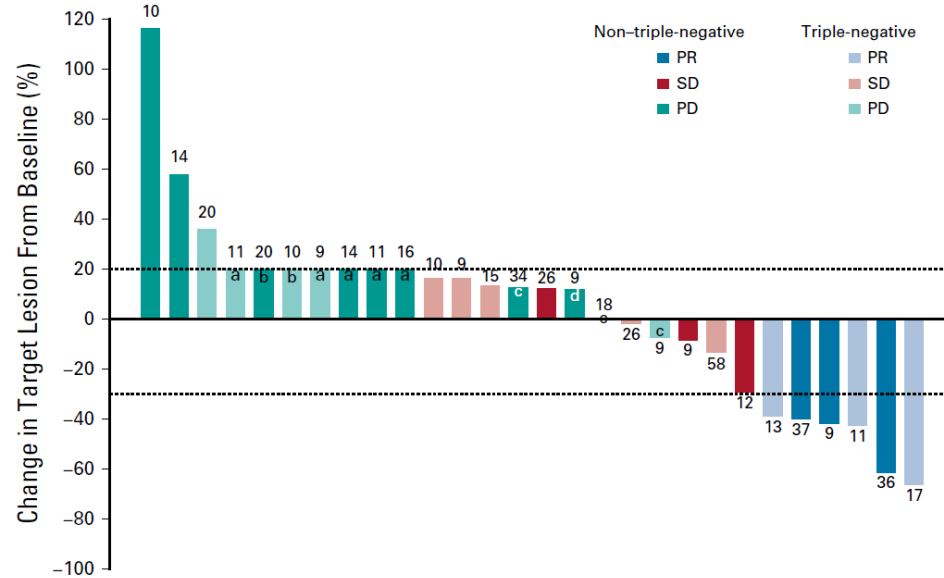
TREATMENT ALGORITHM BASED ON BROAD NGS PANEL IN HR+/HER2- BREAST CANCER



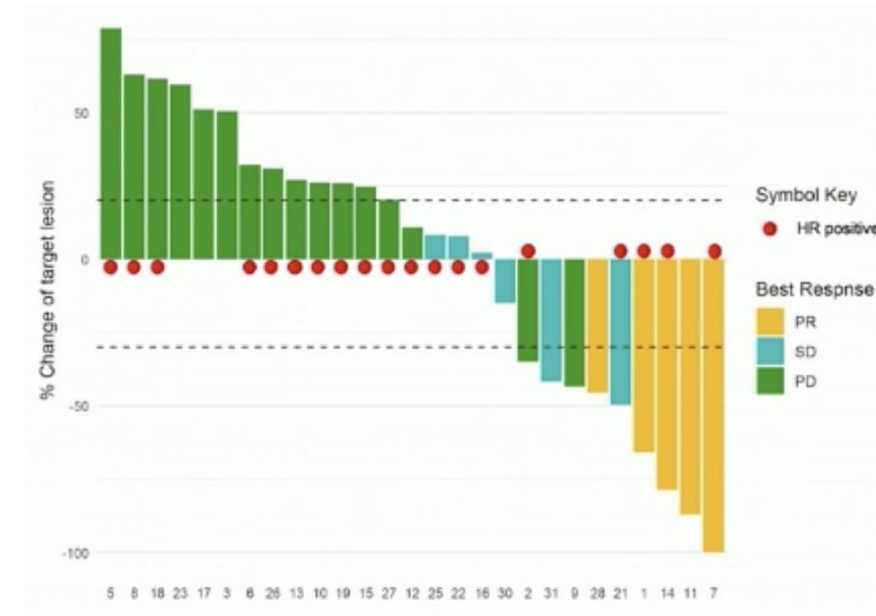
ESCAT LEVEL IC – TMB high (immunotherapy)

HER2 neg (5-10%)

Pembrolizumab



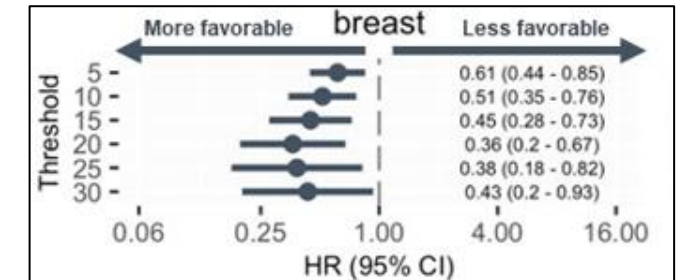
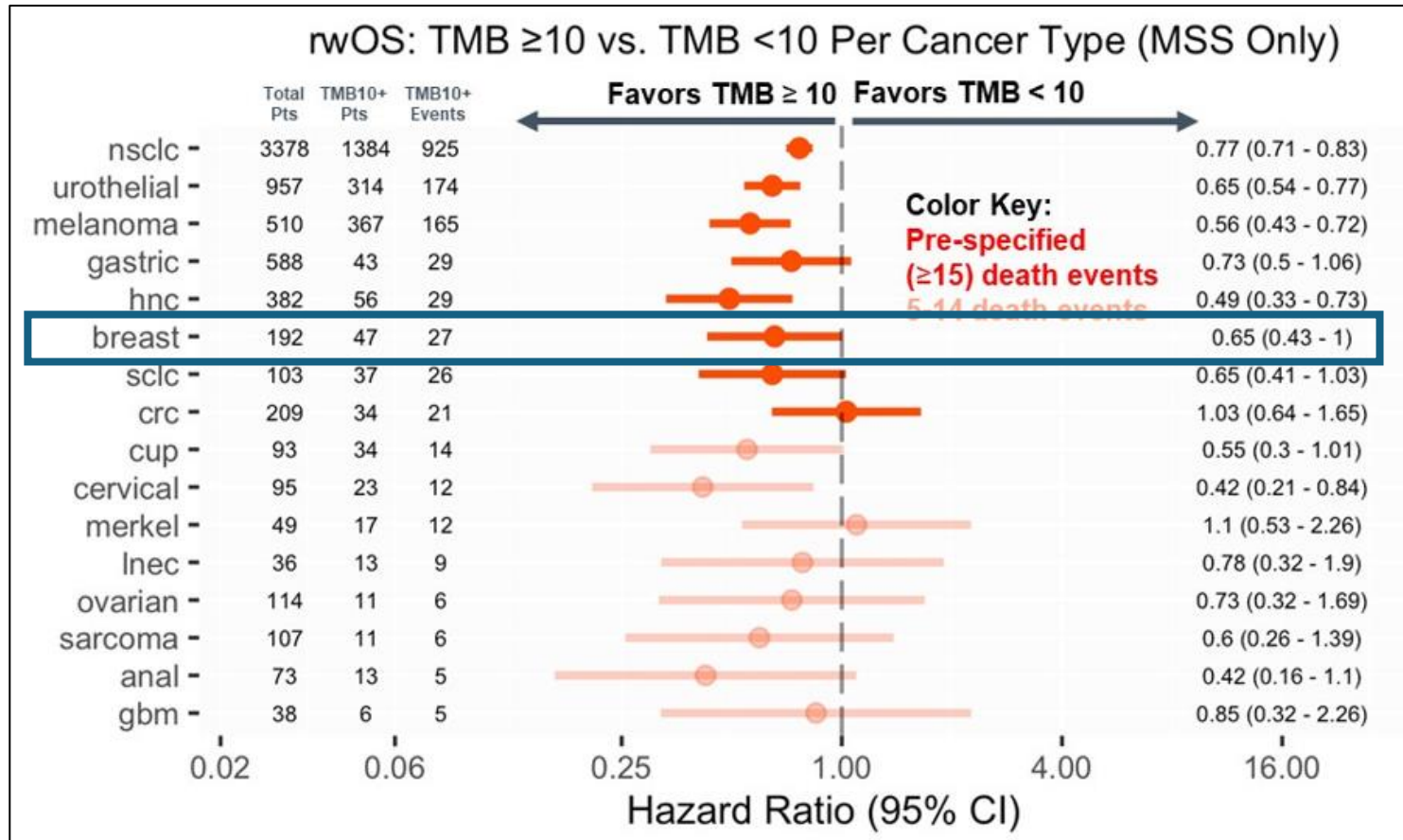
Nivolumab + ipilimumab



Favor broad NGS panel (ideally >1.5 Mb) and validated assay (exome sequencing and/or FOne CDx comparison)

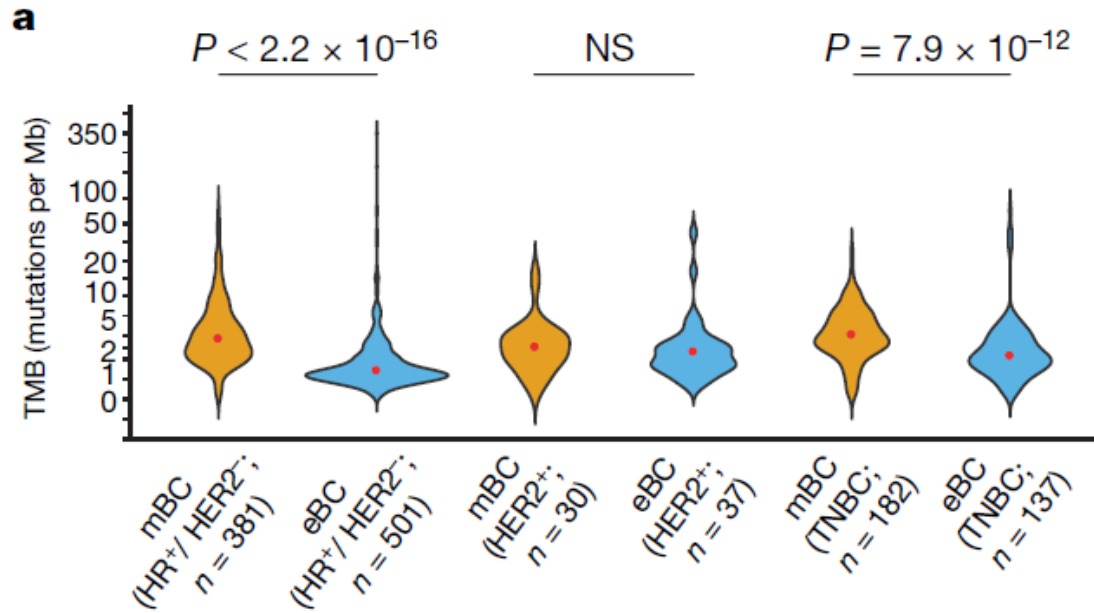
ESCAT LEVEL IC – TMB high (immunotherapy)

HER2 neg (5-10%)



TMB high – ENRICHED IN METASTATIC SAMPLES

HER2 neg (5-10%)



Primary tissue (HR+/HER2-): 2%
Metastatic biopsies (HR+/HER2-): 7%

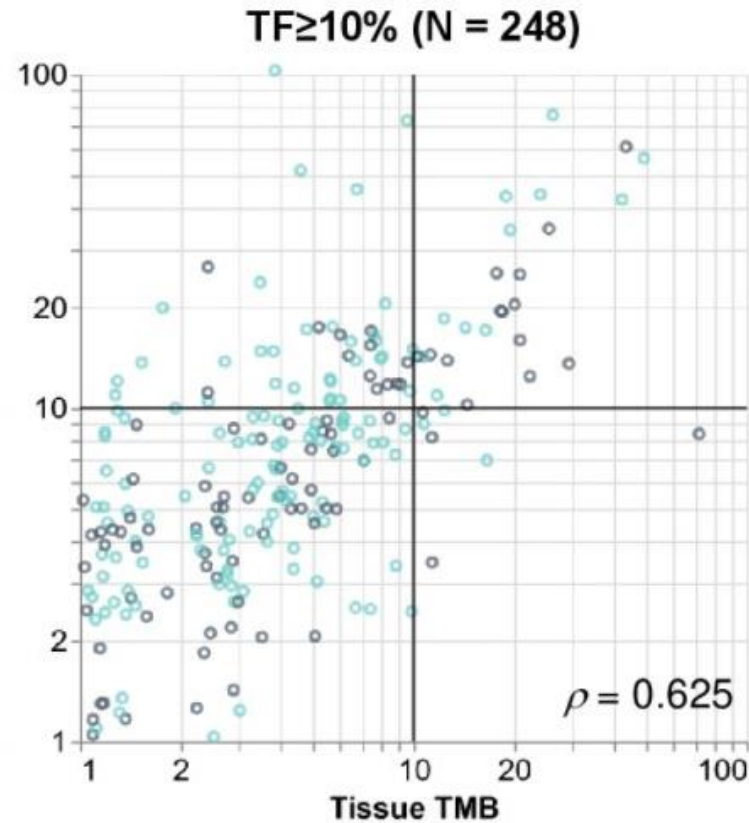
Primary tissue (lobular): 5%
Metastatic biopsies (lobular): 19%

TMB high – TISSUE vs. LIQUID BIOPSY

FOne CDx

Concordance: 86%

HER2 neg (5-10%)



Time between collection	N	ρ
○ <90 days	98	0.758
○ \geq 90 days	150	0.590

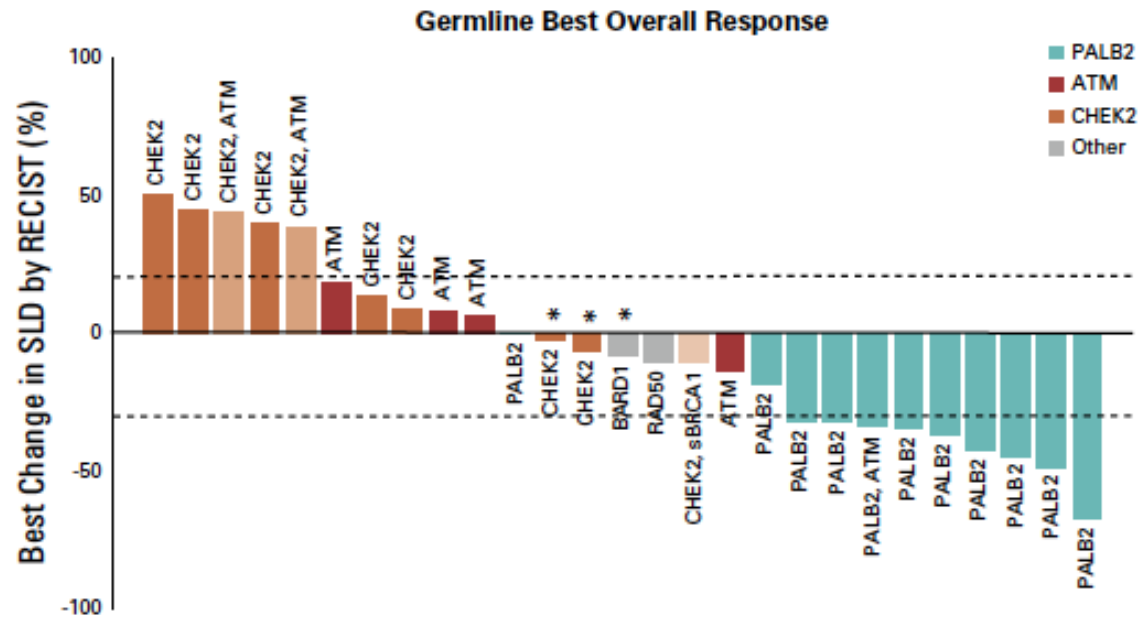
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Level III	<i>ATM</i> mut, <i>CHEK2</i> mut Others
Level IV	Multiple
Level X	<i>CDKN2A</i> mut, <i>CCND1</i> ampl, <i>FGFR1</i> ampl

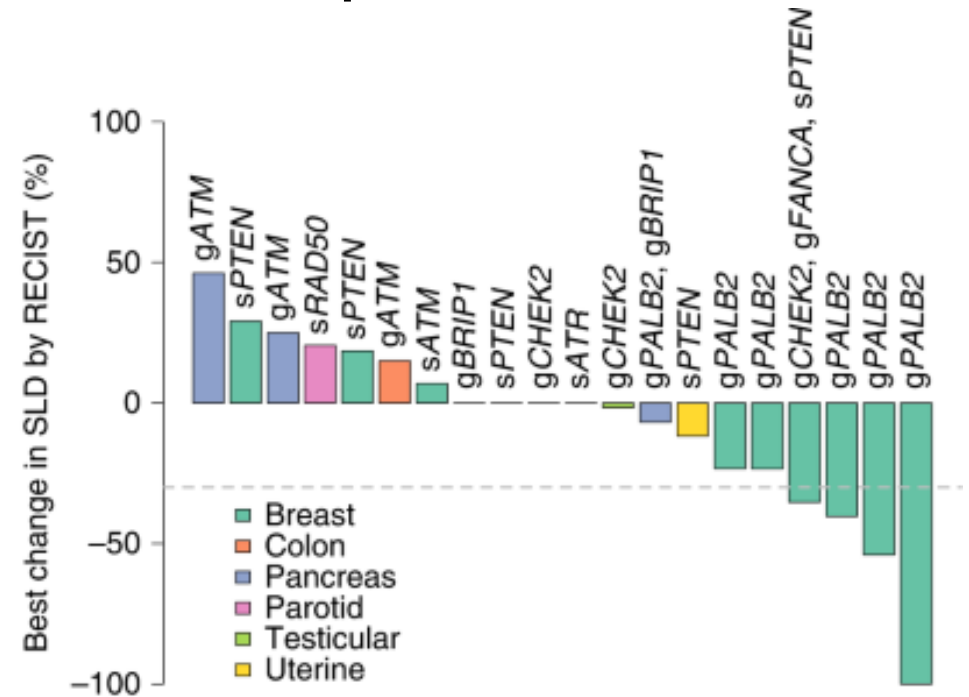
ESCAT LEVEL IIB – gPALB2 mut (olaparib, talazoparib)

HER2 neg (2%)

Olaparib



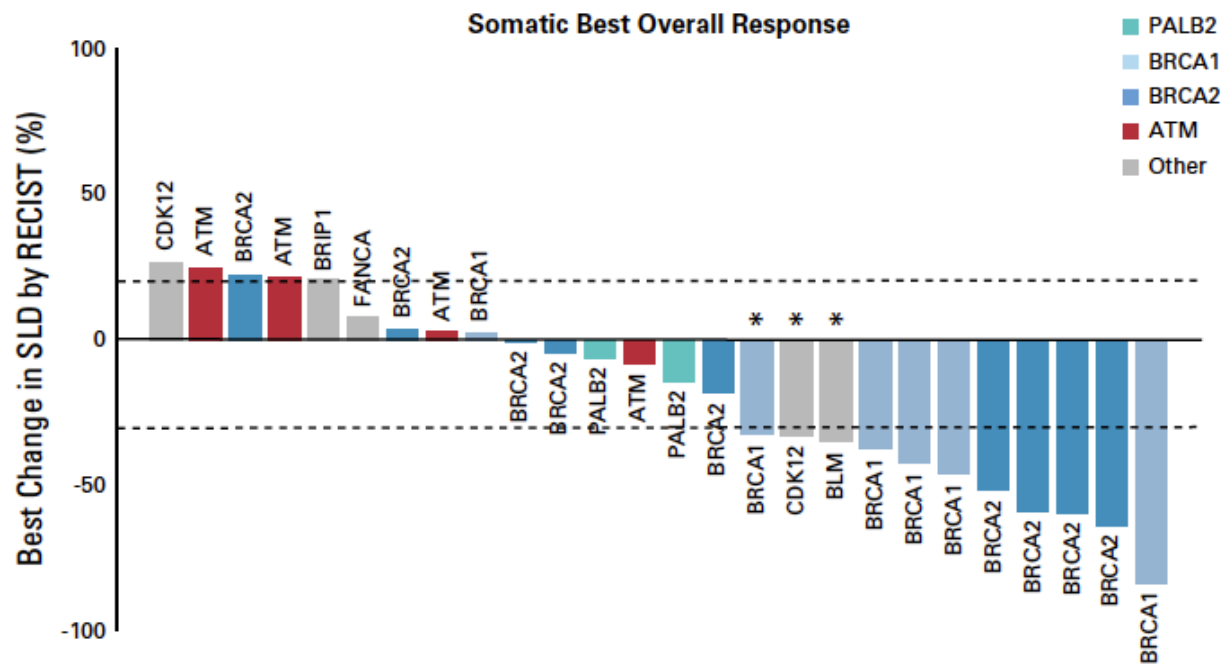
Talazoparib



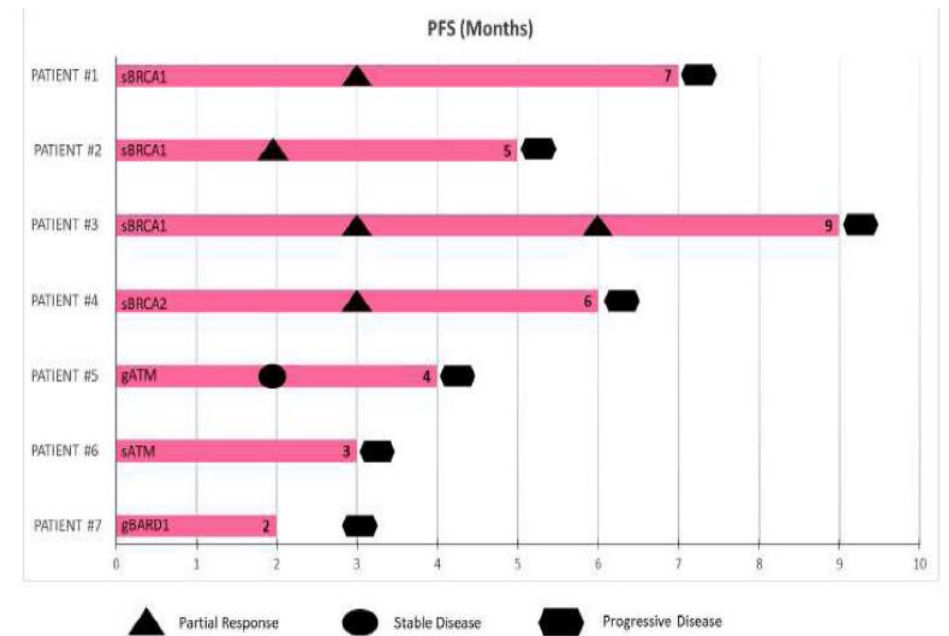
ESCAT LEVEL IIB – BRAC1/2 somatic mut (olaparib)

HER2 neg (3%)

Olaparib



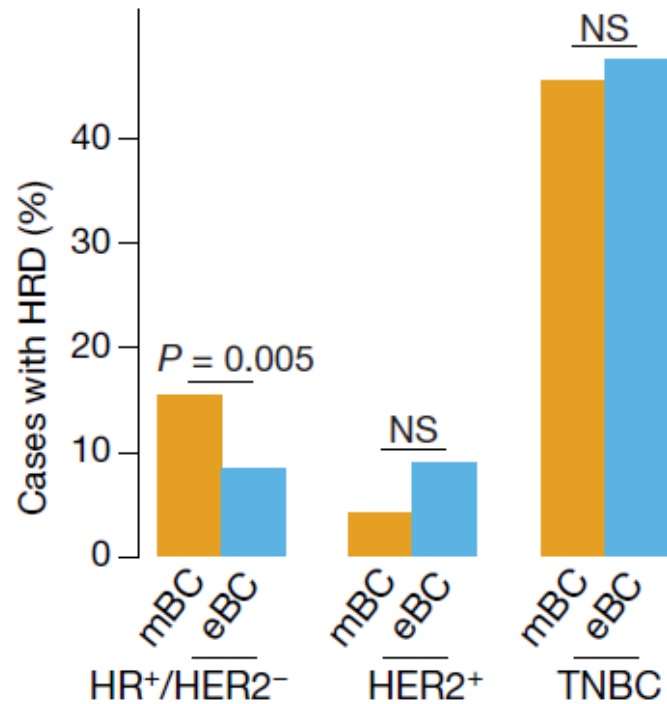
Enriched in metastatic lesions, HR+ and TNBC.



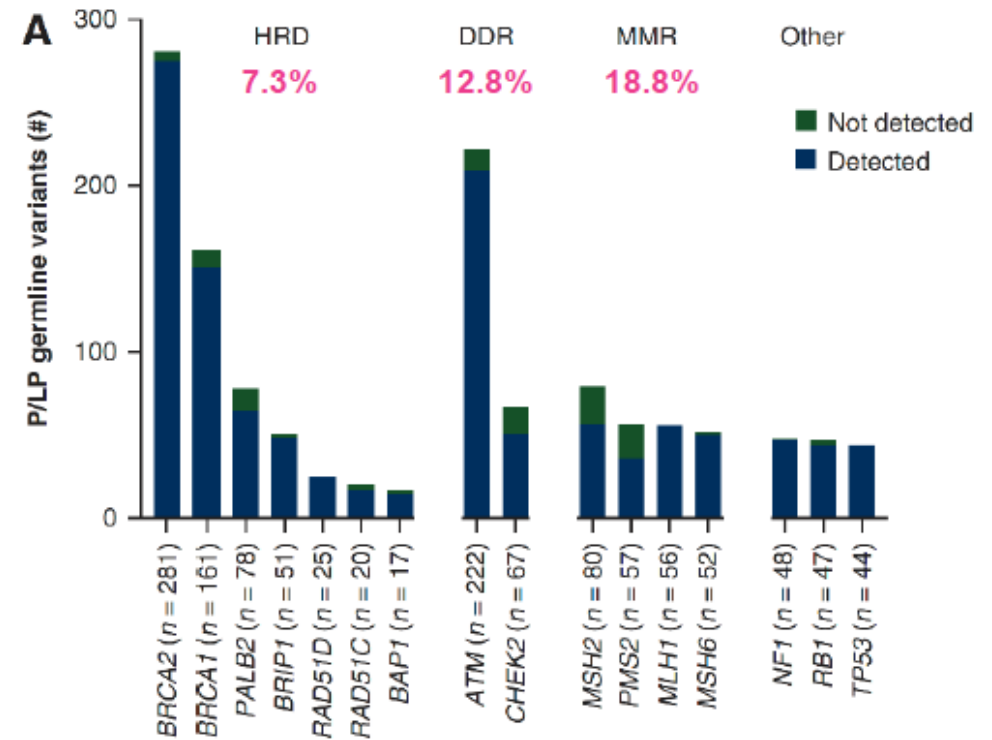
Hom Recomb Deficiency (HRD) – ENRICHED IN METASTATIC SAMPLES BUT GERMLINE TESTING IS GOLD-STANDARD

HR+/HER2- (10-15%)

Primary-metastasis heterogeneity



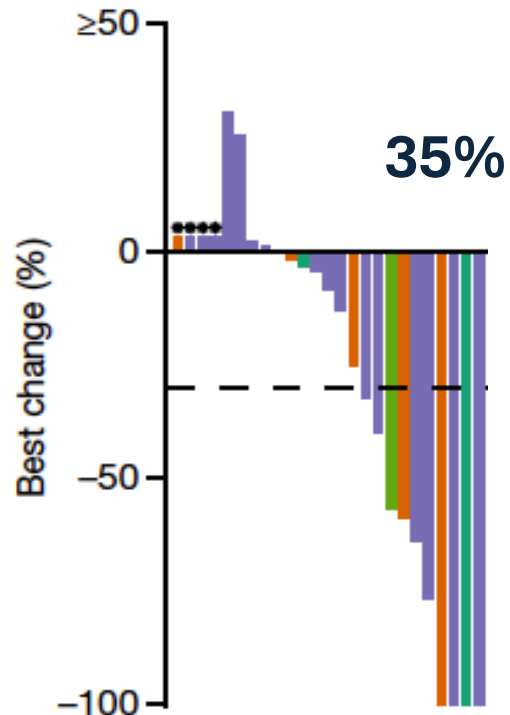
False negative in tumor-only NGS panel



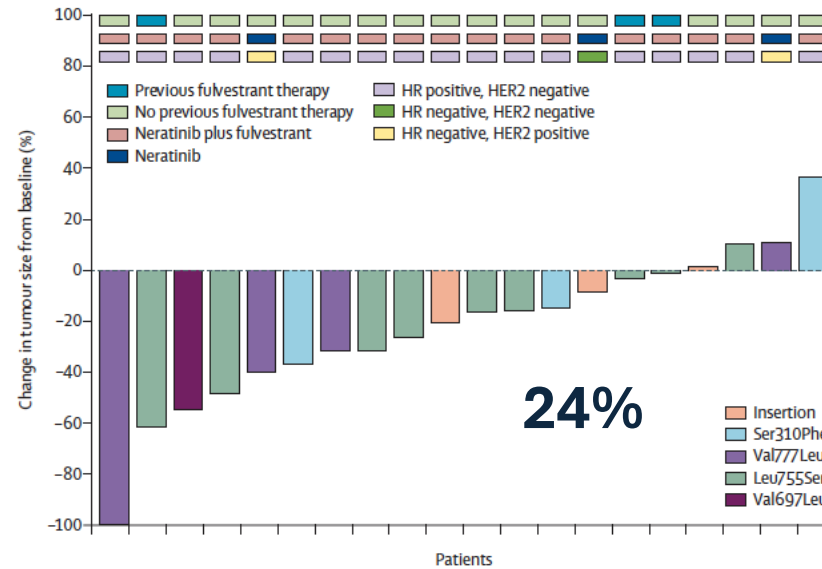
ESCAT LEVEL IIB – ERBB2 mut (neratinib, trastuzumab deruxtecan)

HER2 neg (3%)

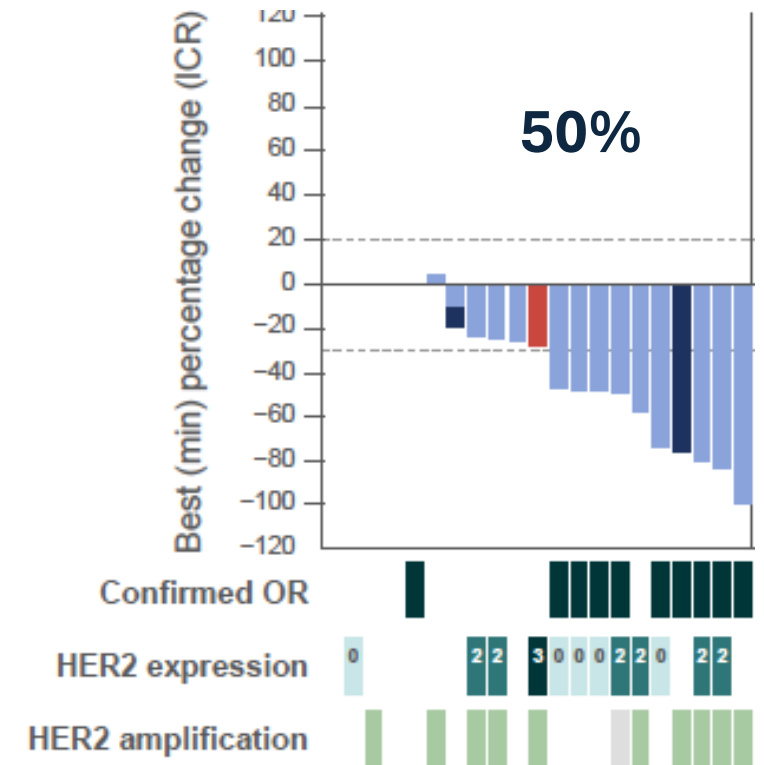
Neratinib



Neratinib (PlasmaMatch)



Trastuzumab deruxtecan



BROAD NGS PANEL IN HER2 NEGATIVE METASTATIC BREAST CANCER

HR positive:

PIK3CA, *AKT1*, *PTEN* mut
emergence of *ESR1* mut
BRCA1/BRCA2 mut
ERBB2 mut
TMB high, others

TNBC:

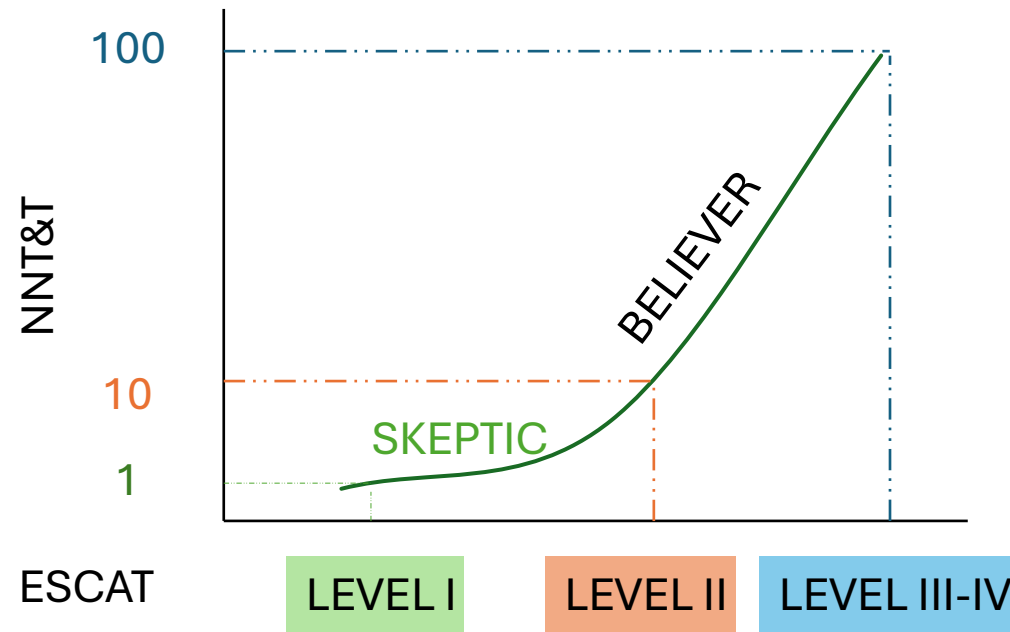
BRCA1/BRCA2 mut
ERBB2 mut
TMB high, others

Secretory breast cancer & rare histologies:

NTRK1-3 fusions, other fusions

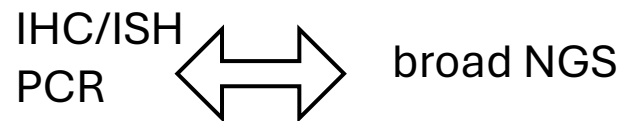
- ✓ **Metastatic lesions or liquid biopsy ideal**
- ✓ **Parallel germline sequencing has added value**

NUMBER NEEDED TO TEST AND TREAT (NNT&T) FOR BENEFIT



Favorable Precision Medicine ecosystem

Regulatory approval (test + drug)
Clinical trials



CONCLUSIONS

- Continuous progress in genomically-guided targeted therapies in breast cancer.
- 1 in 10 patients with HER2 neg breast cancer will have direct benefit from broad NGS panels)
- Guarantee access to high-quality molecular diagnostics.
From IHC/FISH to broad NGS panels and liquid biopsies.

False negative liquid biopsy: complex variants in tumor suppressor genes and fusions
False positive liquid biopsy: CHIP (TP53, others) and TMB high

- Liquid biopsy is recommended test in HR+/HER2- metastatic breast cancer after 1L CDK inh
- Germline sequencing has added value (up to 10% false negative BRCA1/2)