Advancing Breast Cancer Treatment: Genomics and the Future of Precision Oncology

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BC CANCER
Provincial Health Services Authority

Disclosures

Advisory board: Astra Zeneca, Daiichi Sankyo, Eli Lilly, Gilead, Knight Therapeutics, Merck, Novartis, Pfizer, Roche, Seagen, TerSera

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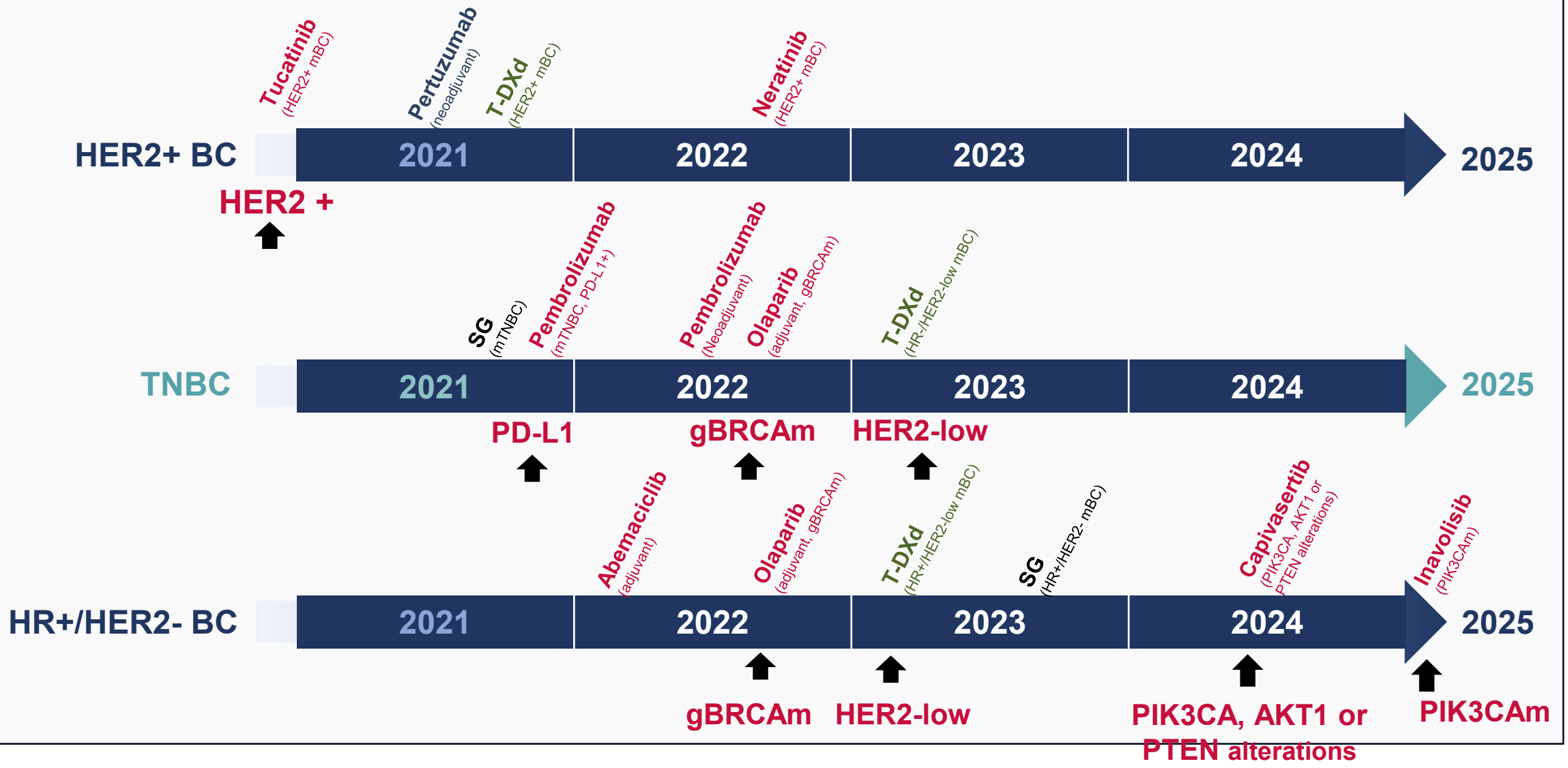
Objectives

1. Explore how genomic profiling informs personalized treatment decisions in metastatic breast cancer.
2. Review emerging innovations in genomics and their potential to shape the future of precision oncology in breast cancer care.
3. Discuss the practical, clinical and ethical considerations of integrating genomics into routine oncology practice.

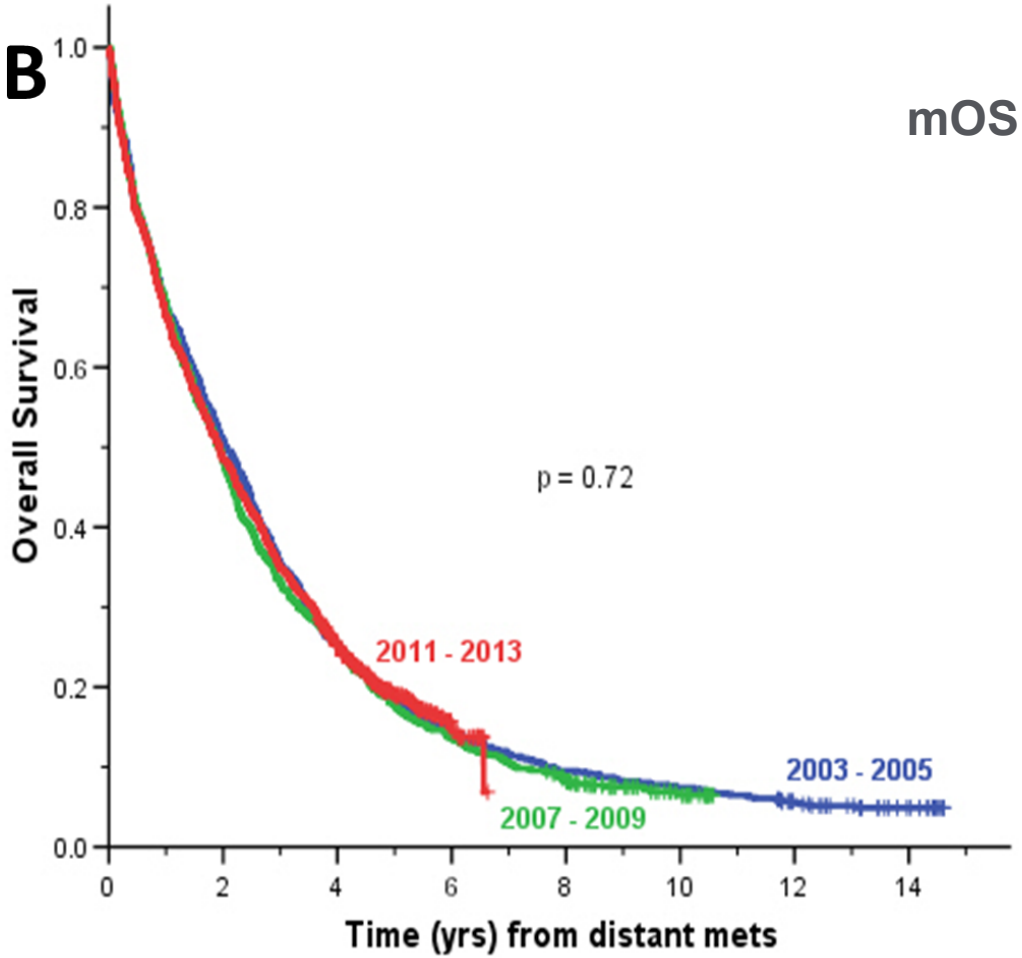
5 Years in Review - Health Canada Approvals



BC, breast cancer; gBRCAm, germline BRCA1/2-mutated; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer.

Survival for patients with metastatic ER+ breast cancer in British Columbia (2003-2013)

n=2440



mOS 1.96 years (95% CI 1.84-2.08)

LeVasseur et al. SABCS 2018.
Abstract P1-16-05.

Unmet needs for the HR+ population

Current treatment landscape and outcomes: mPFS*

*Based on data from Phase 3 registrational studies only

CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CT, chemotherapy; ET, endocrine therapy; HER2, human epidermal receptor 2; mBC, metastatic breast cancer; mo, month; mPFS, median progression-free survival.

1. Finn RS, et al. *N Engl J Med*. 2016;375:1925–1936; 2. Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541–1547; 3. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 4. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070 (suppl. appendix); 5. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 6. O'Shaughnessy J, et al. *JAMA Netw Open*. 2021;4:e214103; 7. O'Shaughnessy J, et al. *Cancer Res.* 2021;81(Suppl. 4):Abstract GS4-01; 8. Robert NJ, et al. *J Clin Oncol*. 2011;29:1252–1260; 9. Modi S, et al. *N Engl J Med*. 2022;387:9–20

Dominant Pathways in HR+ HER2- Breast Cancer

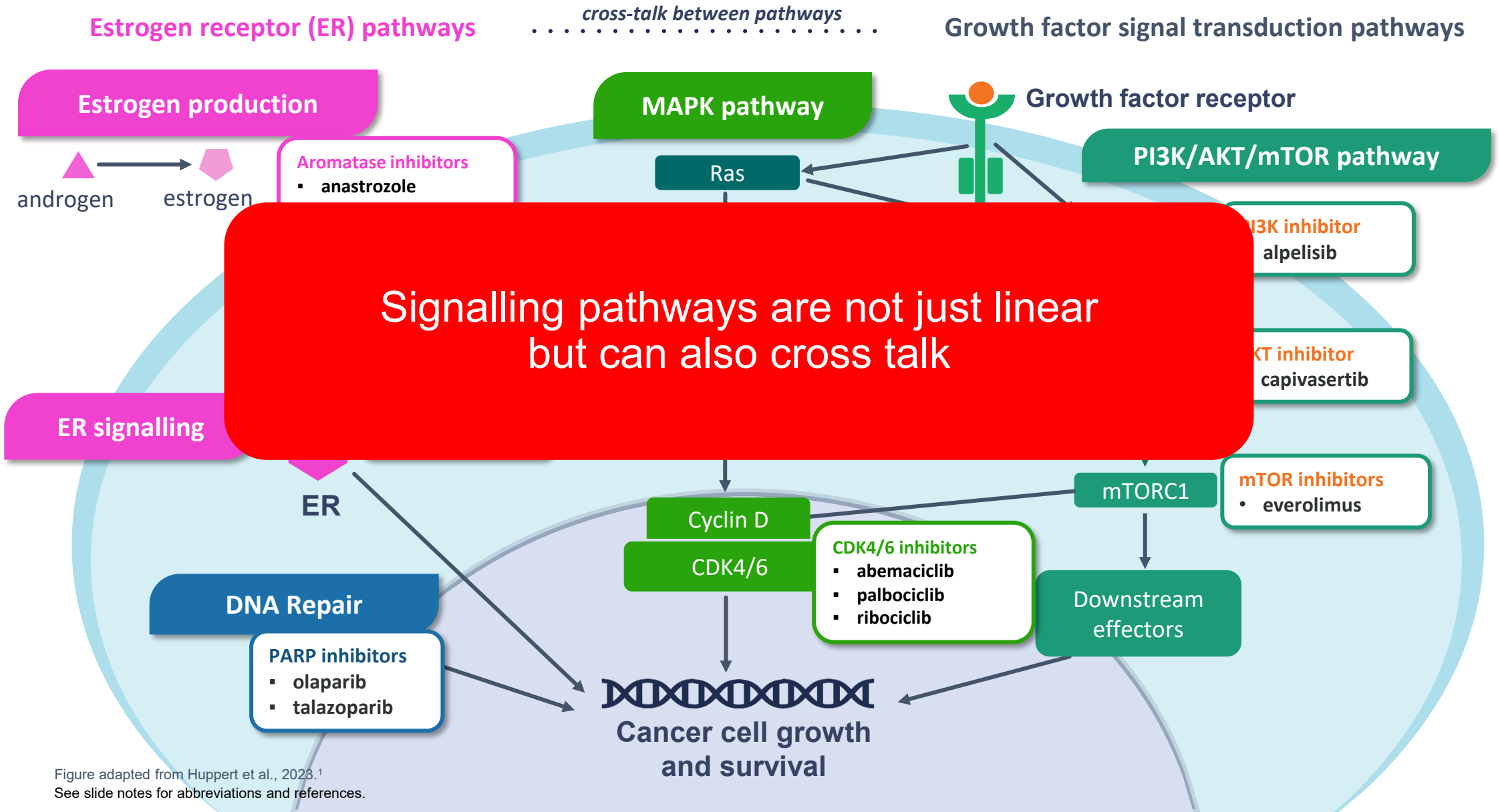


Figure adapted from Huppert et al., 2023.[1]
See slide notes for abbreviations and references.

Diagnostic Work-up and Staging of HR+/HER2– mBC

ESMO Clinical Practice Guidelines 2023

Newly Diagnosed or Recurrent mBC

Biopsy of metastatic lesion to confirm diagnosis → Reassess biomarkers:
- ER
- PgR
- HER2

→ HR+/HER2– mBC → Assessments:
- *PIK3CA*
- *gBRCAm*
- *gPALB2* (optional)

\+

Optional, if potential to guide available treatment:
- MSI
- TMB
- *NTRK*
- *ESR1*
- *sBRCAm*
- HER2-low

Progression after CDK4/6i + ET

Assessments:
- *sPIK3CA*
- *sESR1* (optional)
- *gBRCA**
- *gPALB2** (optional)

Staging

- History and physical examination
- Hematology, biochemistry
- Tumour markers
- CT chest and abdomen
- Bone scintigraphy (or PET-CT)
- Brain imaging (if symptomatic or according to subtype if presence of CNS metastases will alter choice of therapy)

Updates to Somatic Testing Recommendations (NCCN V1.2024)[3]

Diagnosis or Progression

Consider testing for variants in:
- *PIK3CA, AKT1,* and *PTEN* to identify candidates for 2L+ capivasertib
- *PIK3CA* to identify candidates for 2L+ alpelisib

Adapted from Gennari A, et al. and the ESMO Metastatic Breast Cancer Living Guideline v1.1. See slide notes for abbreviations.

* If not assessed previously.

1. Gennari A, et al. Ann Oncol. 2. ESMO Metastatic Breast Cancer Living Guideline | ESMO. May 2023. 3. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. Version 1.2024. Published online Jan. 25, 2024.

Mutation diagnostics in MBC: “Precision medicine” for targeted therapies

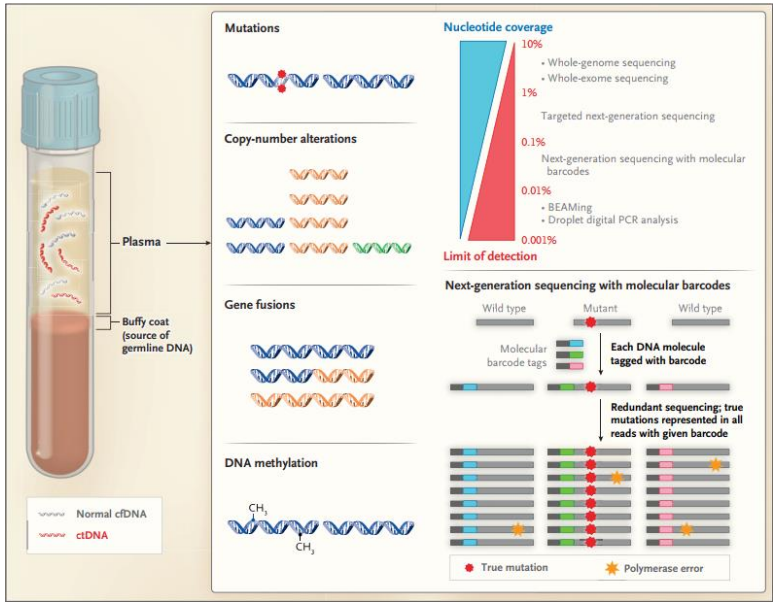
Altered genes	Therapeutic relevance	Gene region	Material	Oxford		
				LOE	GR	AGO
BRCA1/2	Olaparib Olapari			1b 2b	A B	++ +
PALB2	Olapari			2b	B	+
PIK3CA	Alpelisi		sma	1b	A	++
AKT1, PTEN, PI3KCA	Capivas		sma	1b	A	+
ESR1	Resistance against AI Response to elacestrant	Exons 4, 7 and 8	Metastases, plasma Metastases, plasma	2b 1b	B B	+ ++
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particularly secretory breast cancer	2a	B	+
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+

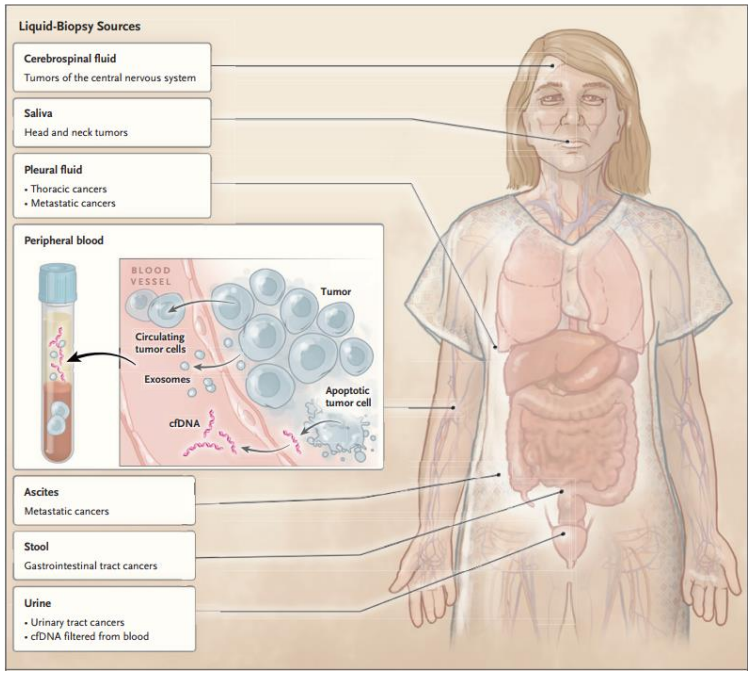
- There are now various predictive biomarkers in breast cancer
- Testing SHOULD BE standard in breast cancer
- Testing historically tied to drug funding in Canada

Available at: www.ago-online.de.

How Can We Assess Molecular Alterations?

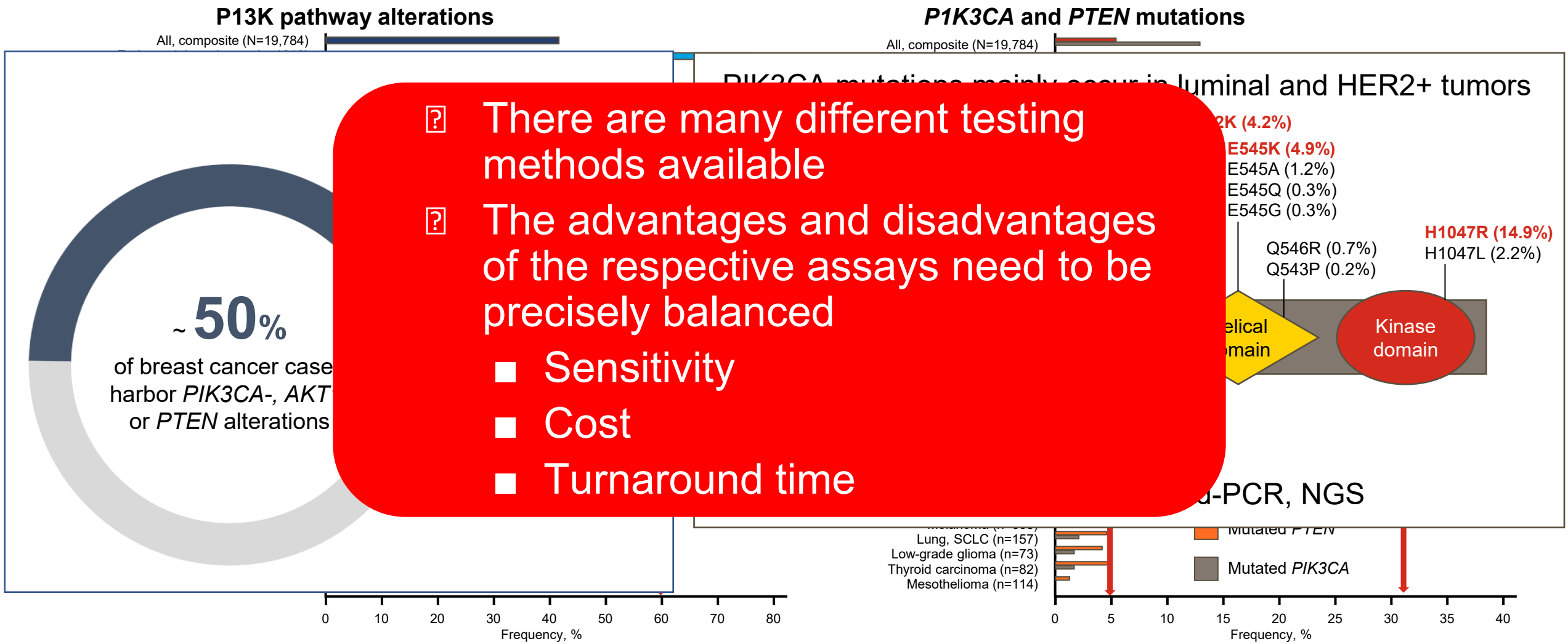
- Can assess
  - Tumor-tissue
  - “liquid-biopsy” such as changes in blood
    - ctDNA: circulating tumor DNA: part of DNA derived from tumors
- Next-Generation Sequencing (NGS): high-throughput sequencing platform
  - Multiple different platforms
    - Such as Illumina, IonTorrent
  - Can use different panels (few genes to hundreds of genes, whole exomes, whole genome) on tissue/other specimens.
    - FoundationOne ®, Oncomine – many panels, TSO 500
- ddPCR: checking for specific mutations in a gene via PCR





CORCORAN RB, CHABNER BA. APPLICATION OF CELL-FREE DNA ANALYSIS TO CANCER TREATMENT. *N ENGL J MED.* 2018;379(18):1754-1765.

Early Events - PI3K signaling pathway alterations



- There are many different testing methods available
- The advantages and disadvantages of the respective assays need to be precisely balanced
  - Sensitivity
  - Cost
  - Turnaround time

1. Millis SZ, et al. JAMA Oncol. 2016;2(12):1565-1573. 2. Miller TW, et al. Breast Cancer Res. 2011;13(6):224. 3. Martorana F, et al. Front Pharmacol. 2021; 12:662232.
4. Paplomata E, et al. Ther Adv Med Oncol. 2014;6(4):154-156. 5. Miricescu D, et al. Int J Mol Sci. 2020;22(1):173. 6. Cancer Genome Atlas Network. Nature. 2012;490(7418):61-70.
7. Chung JH, et al. Ann Oncol. 2017;28(11):2866-2873. 8. Kalinsky K, et al. Clin Cancer Res. 2009;15(16):5049–5059.

CAPItello-291: Capivasertib + fulvestrant in HR+, HER2- ABC

Objective

- To analyze the efficacy and safety of administering capivasertib in combination with fulvestrant vs placebo + fulvestrant in patients with HR+, HER2- locally advanced (inoperable) or metastatic BC

Key inclusion criteria

- HR+, HER2- ABC
- Men and pre/postmenopausal women
- PD with prior AI[a] or recurrence at ≤12 mo of EOT with adjuvant AI
- ET (≤2 lines) and CT (≤1 line)[a]
- Prior exposure to CDK4/6i[b] allowed
- No prior SERD, mTORi, PI3Ki or AKTi
- FFPE sample from primary/recurrent tumor

(N=708)

R 1:1

Capivasertib 400 mg BID 4 days on/3 days off + **fulvestrant** 500 mg C1 D1, 15 then q4w (n=355)

Stratification

- Prior CDK4/6i
- Presence of liver metastases
- Geographical region

Placebo + **fulvestrant** 500 mg C1 D1, 15 then q4w (n=353)

Primary endpoint

- PFS (investigator assessed; overall and AKT pathway-altered tumors)

Secondary endpoints

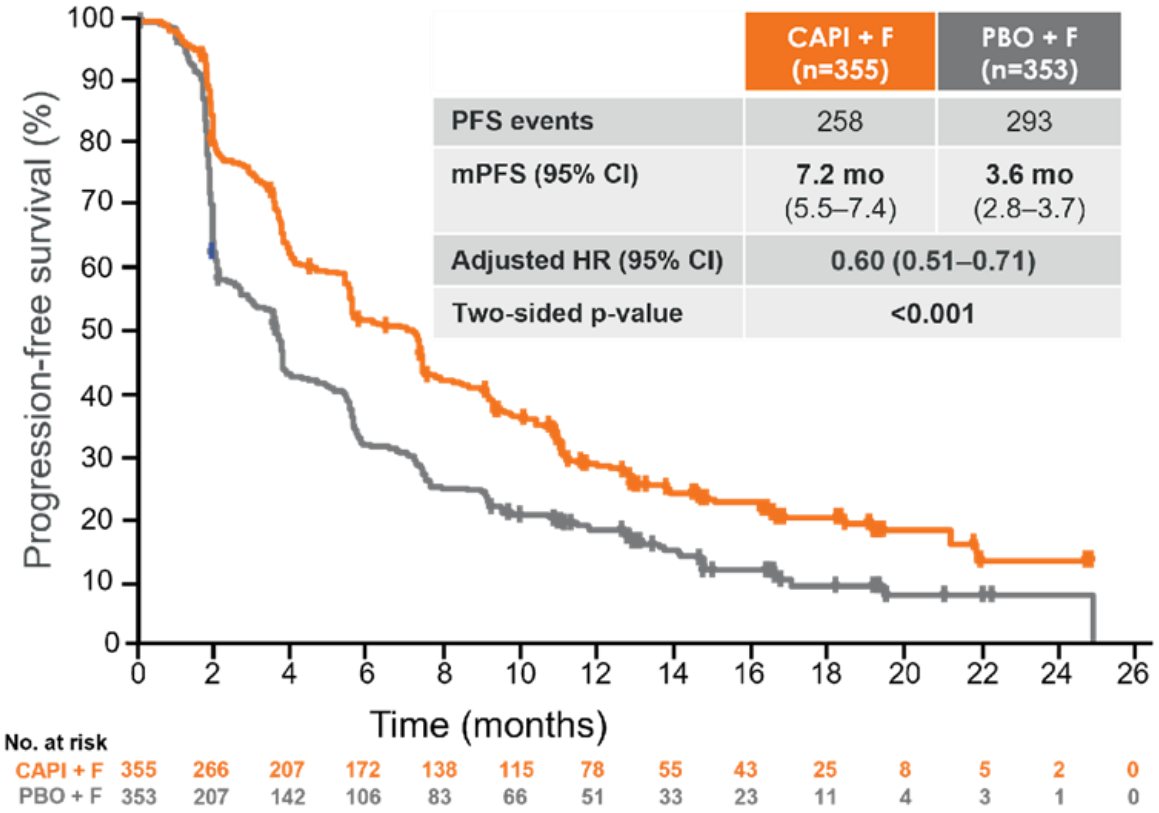
- OS, ORR (overall and AKT pathway-altered tumors)

[a]In the ABC setting. [b]Requirement of ≥51%.

1. Turner NC, et al. SABCS 2022. Abstract GS3-04. 2. Turner NC, et al. N Engl J Med. 2023;388(22):2058-2070.

CAPItello-291: Progression-free Survival

Overall Population

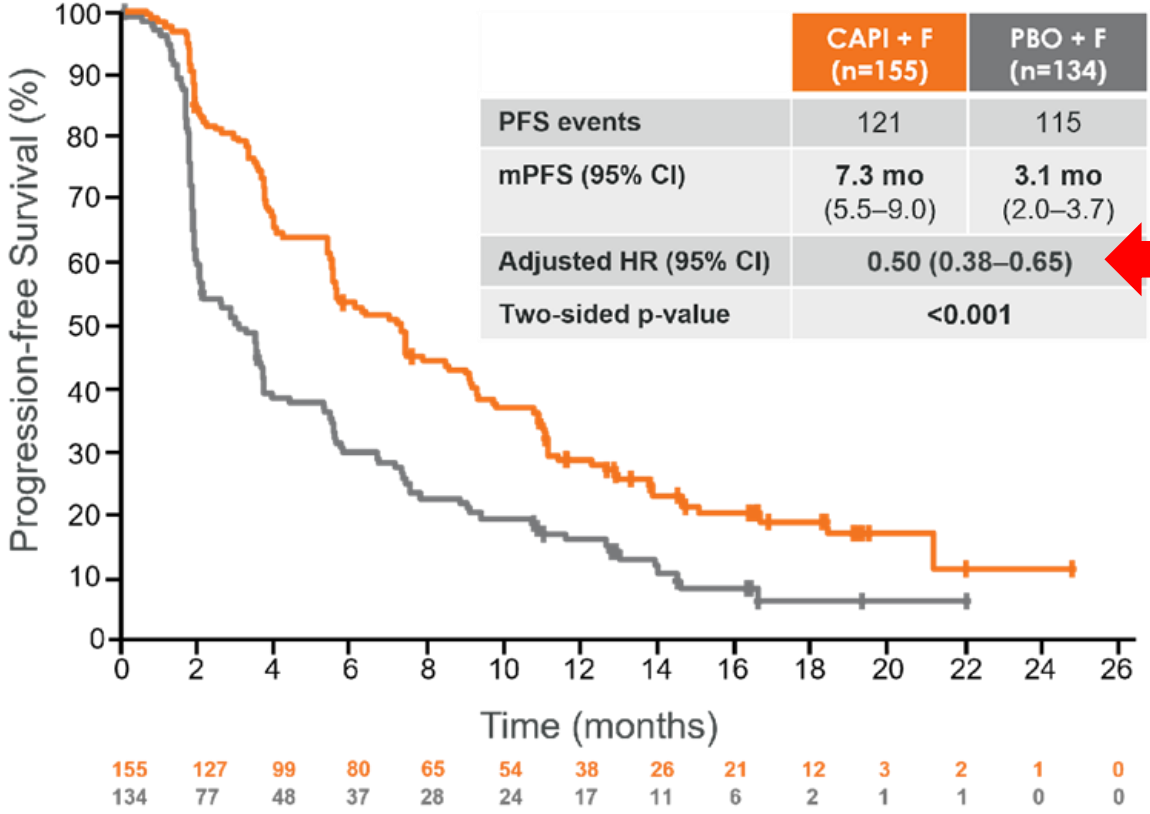


	CAPI + F (n=355)	PBO + F (n=353)
PFS events	258	293
mPFS (95% CI)	**7.2 mo** (5.5–7.4)	**3.6 mo** (2.8–3.7)
Adjusted HR (95% CI)	0.60 (0.51–0.71)	
Two-sided p-value	<0.001	

No. at risk

CAPI + F	355	266	207	172	138	115	78	55	43	25	8	5	2	0
PBO + F	353	207	142	106	83	66	51	33	23	11	4	3	1	0

AKT Pathway-altered Population



	CAPI + F (n=155)	PBO + F (n=134)
PFS events	121	115
mPFS (95% CI)	**7.3 mo** (5.5–9.0)	**3.1 mo** (2.0–3.7)
Adjusted HR (95% CI)	0.50 (0.38–0.65)	
Two-sided p-value	<0.001	

	155	127	99	80	65	54	38	26	21	12	3	2	1	0
	134	77	48	37	28	24	17	11	6	2	1	1	0	0

PFS by subgroup in the overall population: CDK4/6i use	
Prior CDK4/6i (n=496)	HR, 0.59 (95% CI, 0.48–0.72)
CDK4/6-naïve (n=212)	HR, 0.64 (95% CI, 0.45–0.90)

Tick marks indicate censored data. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.
CAPI, capivasertib; F, fulvestrant. See speaker notes for full abbreviations; mPFS, median progression-free survival; PBO, placebo.

1. Turner NC, et al. *N Engl J Med.* 2023;388:2058-2070. DOI: 10.1056/NEJMoa2214131.

INAVO120: Inavolisib + palbociclib + fulvestrant in HR+, HER2-, PIK3CAm ABC

Objective

- To evaluate the efficacy and safety of inavolisib + palbociclib + fulvestrant in patients with PIK3CAm, HR+, HER2- ABC in the Phase 3 INAVO120 study

Key eligibility criteria

Enrichment of patients with poor prognosis:

- PIK3CAm, HR+, HER2- ABC by central ctDNA or local tissue/ctDNA test
- Measurable disease
- Progression during/within 12 months of adjuvant ET completion
- No prior therapy for ABC
- Fasting glucose <126 mg/dL and HbA1c <6.0%

(N=325)

R 1:1

Inavolisib 9 mg/day PO + **palbociclib** 125 mg/day PO D1–21 + **fulvestrant** 500 mg C1 D1/15 and q4w → PD/ toxicity

Stratification

- Visceral disease (yes vs no)
- Endocrine resistance (primary vs secondary)
- Region (North America/Western Europe; Asia; Other)

Placebo + **palbociclib** 125 mg/day PO D1–21 + **fulvestrant** 500 mg C1 D1/15 and q4w → PD/ toxicity

Primary endpoint

- PFS by investigator

Secondary endpoints

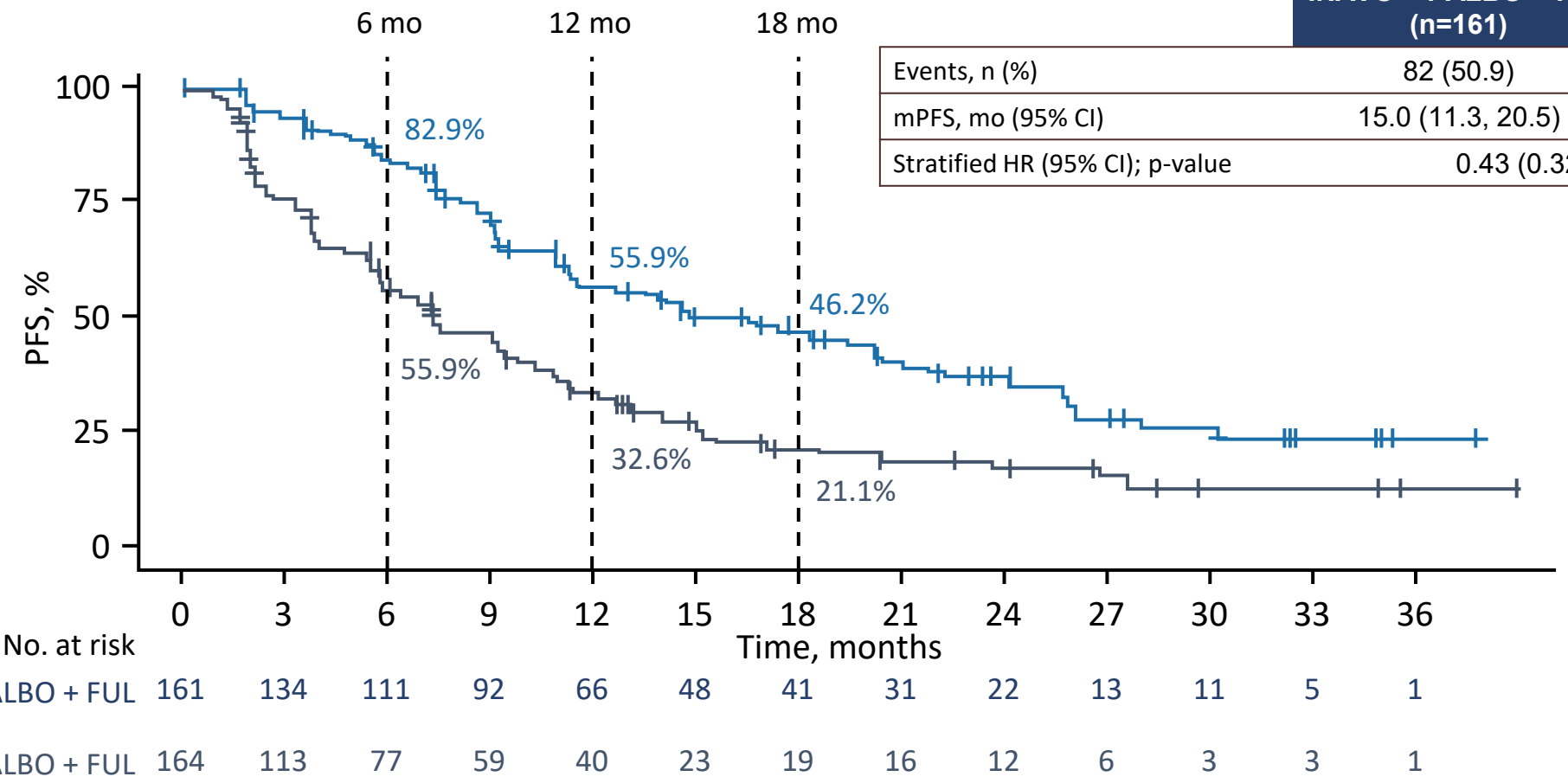
- OS, ORR, BOR, CBR, DoR, PROs

Enrolment period: December 2019 to September 2023.

1. Jhaveri KL, et al. SABCS 2023. Abstract GS03-12. 2. Turner NC, et al. N Engl J Med. 2024;391(17):1584-1596.

INAVO120: Inavolisib + palbociclib + fulvestrant in HR+, HER2-, PIK3CAm ABC

Progression-free survival (investigator assessed)



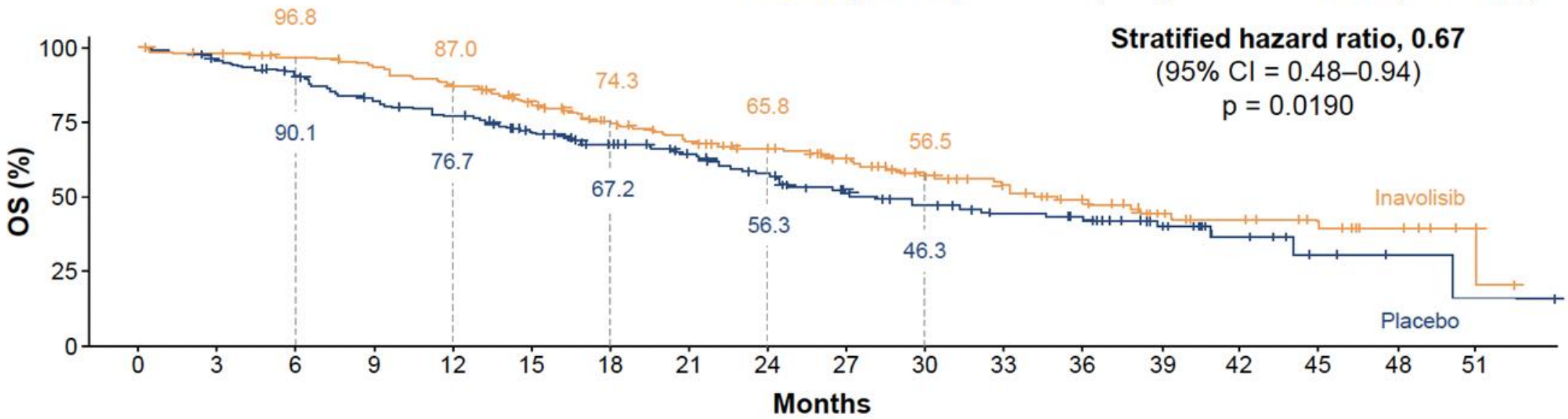
	INAVO + PALBO + FUL (n=161)	PBO + PALBO + FUL (n=164)
Events, n (%)	82 (50.9)	113 (68.9)
mPFS, mo (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified HR (95% CI); p-value	0.43 (0.32, 0.59); <0.0001	

Median follow-up: 21.3 months

1. Jhaveri KL, et al. SABCS 2023. Abstract GS03-12. 2. Turner NC, et al. N Engl J Med. 2024;391(17):1584-1596.

INAVO120 key secondary endpoint: OS

	Deaths, n (%)	Median, months (95% CI)
Inavolisib (n = 161)	72 (44.7)	34.0 (28.4–44.8)
Placebo (n = 164)	82 (50.0)	27.0 (22.8–38.7)



Median follow-up: **34.2 months**

No. at risk																		
Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Improvement in median OS: 7 months. The prespecified boundary for statistical significance (p < 0.0469) was crossed

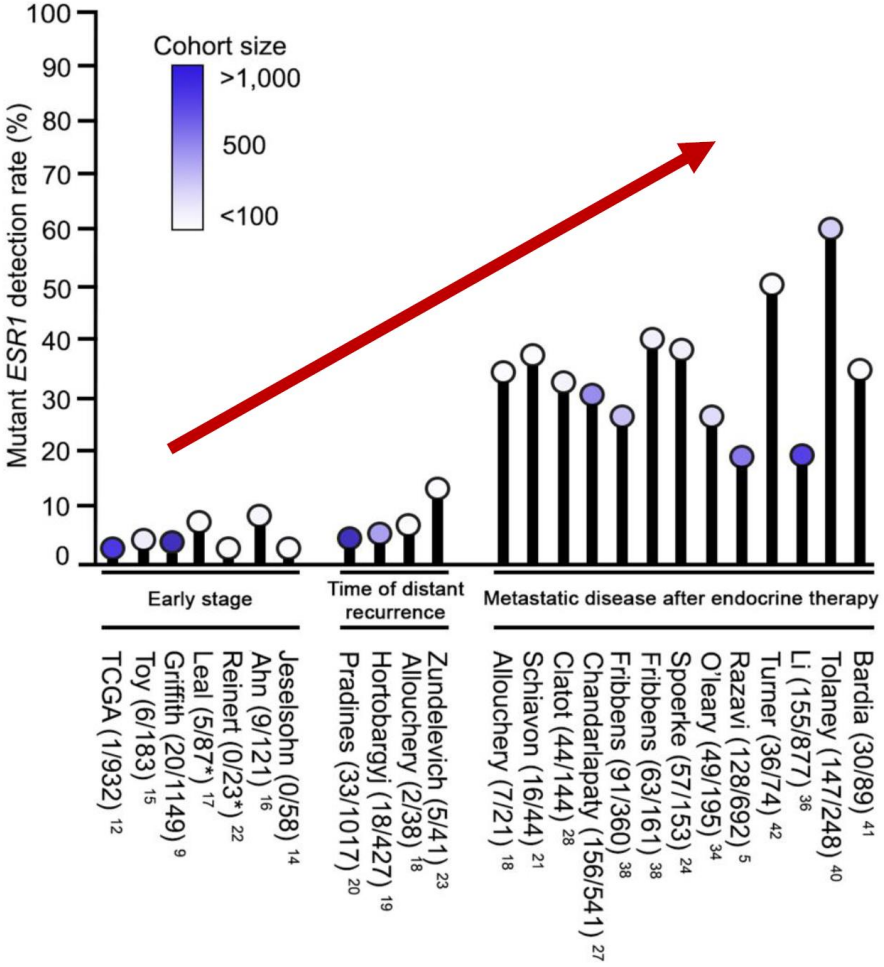
Data cutoff: November 15, 2024.
CI, confidence interval; OS, overall survival.

Acquired Resistance - ESR1 mutations

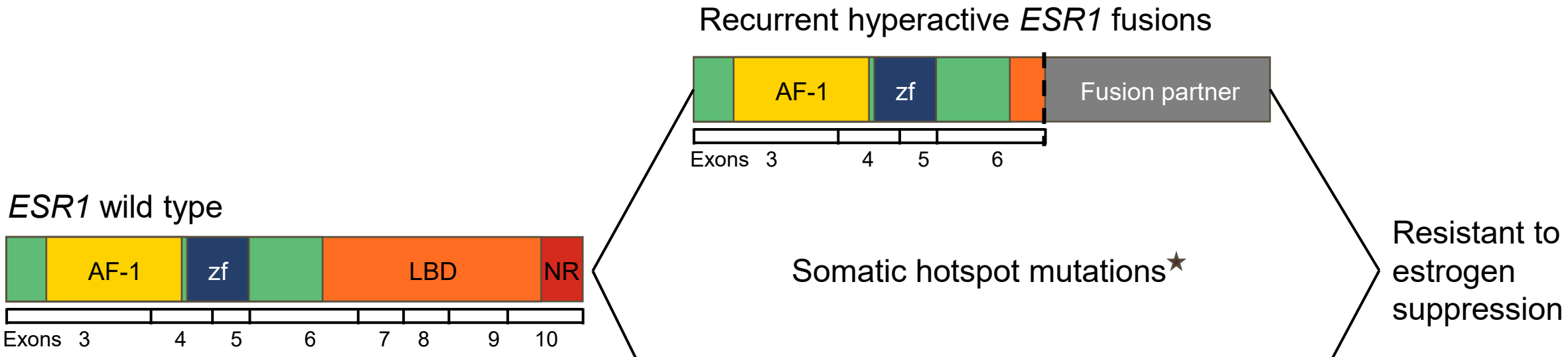
- Rare in **primary** tumors (**0–3%**)
- Relatively common in **metastatic** endocrine therapy-resistant breast cancer (**6–55%**)
- Prevalence depends on
  - Detection sensitivity
  - Prior endocrine therapy exposure
    - 5-10% at the time of diagnosis of metastatic disease
    - As high as 55% with multiple lines of endocrine therapy.

➢ Suggests selection of mutated clones through treatment

➢ Best to test upon progression of disease rather than primary or at diagnosis sample.



ESR1 alterations



- In breast cancer, different alterations can be found
- More than one alteration = worse prognosis
- ESR1 testing material: liquid biopsy

AF-1, activation function-1; LBD, ligand-binding domain; NR, nuclear receptor C-terminal; zf, zinc factor.

1. Piscuoglio S, et al. Ann Oncol. 2018;29(4):787-789. 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer. 3. Liao H, et al. Front Oncol. 2020;10:587671. 4. Fachinformation Orserdu Sept. 2023. 5. Bidard FC, et al. J Clin Oncol. 2022;40(28):3246-3256.

ctDNA testing in PADA-1 and EMERALD clinical trials

Clinical trial	EMERALD[1]	PADA-1[1]	EMBER-3[2]
SERD	Elacestrant	Fulvestrant	Imlunestrant
Assay	Guardant360® CDx	Custom assay	Guardant360® CDx
Platform	NGS	ddPCR	NGS
Reportable range	ESR1 missense mutations between codons 310 and 547	Hotspot codons 380, 536, 537 and 538	ESR1 missense mutations between codons 310 and 547
Multiplex analysis	Yes	Yes	Yes
LOD, %	0.3–1.1	0.0001	0.3–1.1

1. Venetis K, et al. Cancer Treat Rev. 2023;121:102642. 2. Jhaveri K, et al. N Engl J Med. 2024; doi: 10.1056/NEJMoa2410858.

ESR1 ctDNA testing – Methods

PCR-based techniques		NGS-based techniques	
Real-time quantitative (**qPCR**)			ed target analysis, with deep ng, barcoding, and rection
Droplet digital PCR (**ddPCR**)			formance targeted tegies
Beads, Emulsion, Amp and Magnetics (**BEAMing**)	complex workflow	deep sequencing (CAPP-Seq)	
		Safe sequencing system (Safe-Seq)	

Key Considerations:

- NGS allows broader genomic analysis, suitable for multiple oncogene targets
- PCR-based methods may be preferable based on cost, availability, and expertise

Venetis K, et al. Cancer Treat Rev. 2023;121:102642.

ESR1 mutations detected through NGS or ddPCR

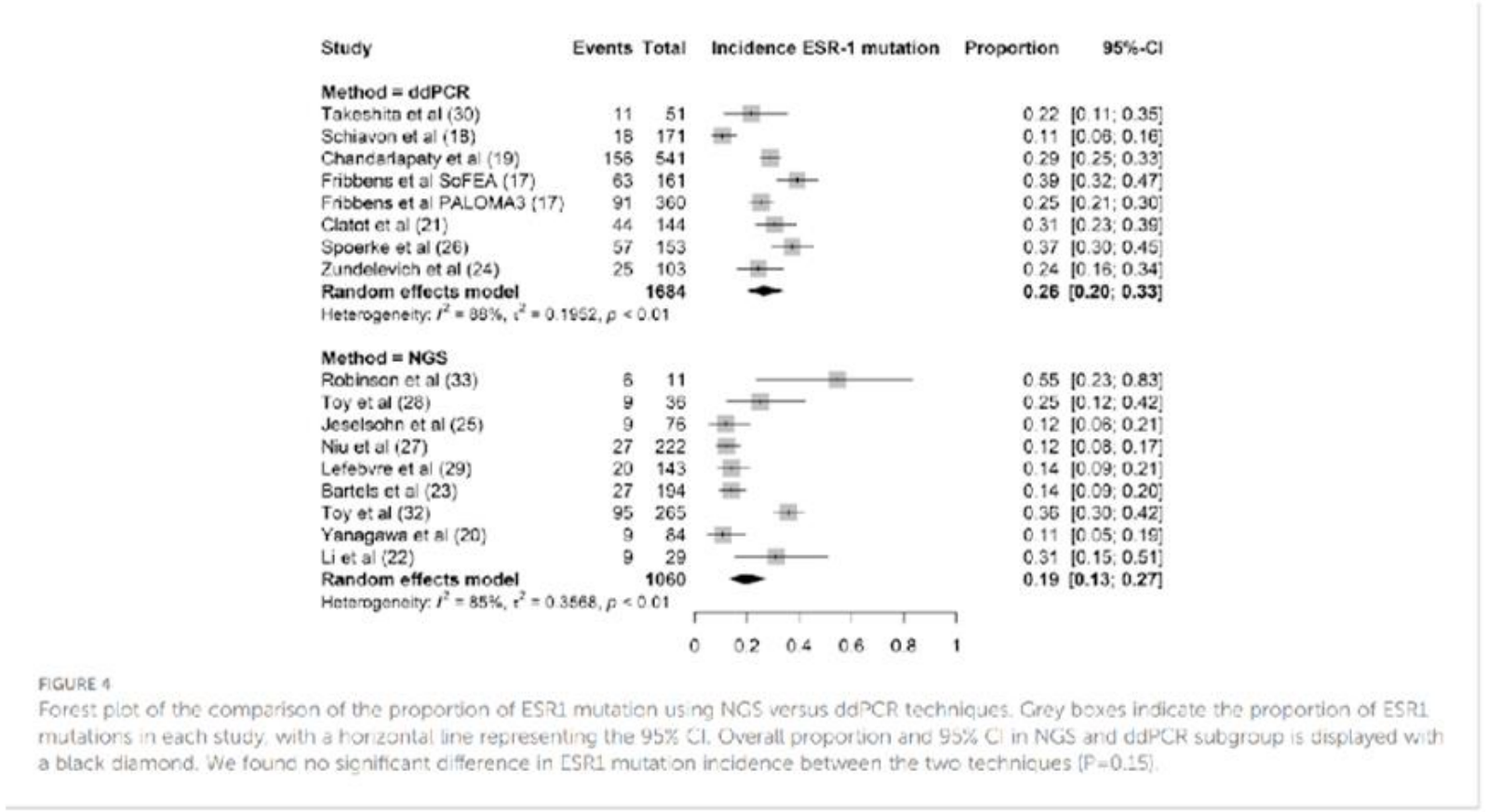


FIGURE 4
Forest plot of the comparison of the proportion of ESR1 mutation using NGS versus ddPCR techniques. Grey boxes indicate the proportion of ESR1 mutations in each study, with a horizontal line representing the 95% CI. Overall proportion and 95% CI in NGS and ddPCR subgroup is displayed with a black diamond. We found no significant difference in ESR1 mutation incidence between the two techniques (P=0.15).

Najim et al. 2023. Front Oncol. 13:1221773.

Co-alterations *ESR1* and PI3K/AKT pathway mutations

There are many combinations of different mutations in these two signaling pathways alone

Hilights the importance of choosing the right drug for the right patient at the right time

***ESR1*m and P13K/AKT pathway alterations co-occurrence in 1L (n=2154)**

*ESR1*m P13K/AKT alterations

35 (16.2%) 37 17.1% 81 (37.5%) 63 (29.2%)

***ESR1*m and P13K/AKT pathway alterations co-occurrence in 2L (n=269)**

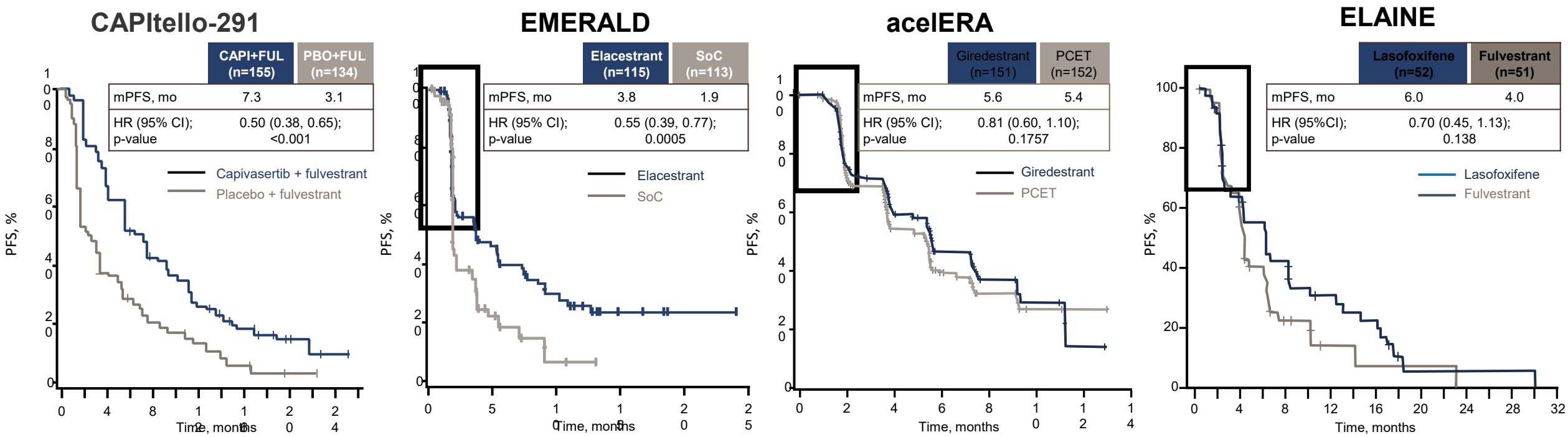
*ESR1*m P13K/AKT alterations

*PIK3CA*m *PTEN*m *AKT1*m *PTEN*loss

1020 (38.7%) 95 (3.6%) 67 (2.5%) 10 (0.4%) 0 (0%) 0 (0%) 128 (4.9%) 81 (3.1%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 33 (1.3%) 0 (0%) 0 (0%) 0 (0%) 1205 (45.7%)

Bhave et al. ASCO 2024.

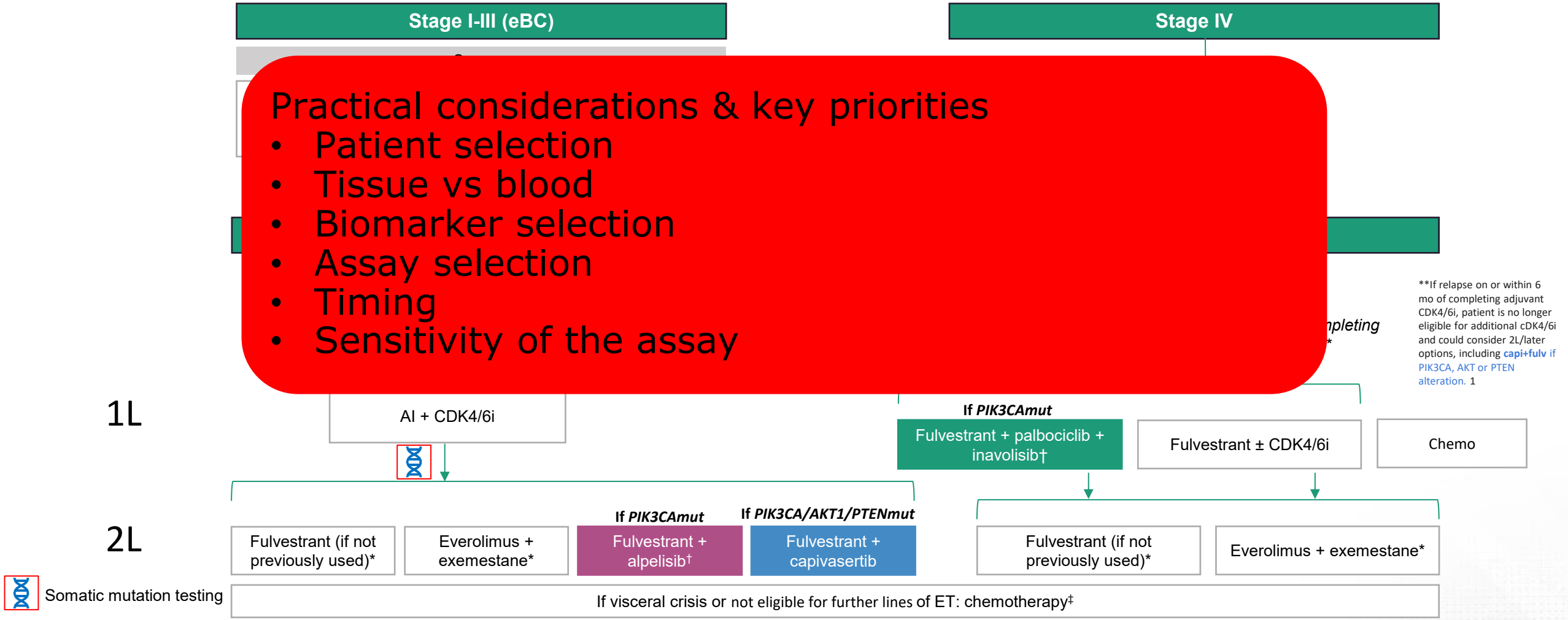
Significant proportion do not respond to endocrine therapy



- There will be considerable intracellular cross talk between the ER dependent and ER independent pathways of resistance
- Polyclonal resistance is a clinical challenge
- Tumors harboring ESR1 mutations may have subclones harboring concurrent genomic alterations that could mediate ER pathway independent resistance

Note: Cross-trial comparisons cannot be made unless substantiated by a head-to-head comparator trial(s).
Bidard FC et al, JCO 2022,,Martin M et al ESMO 2022, Goetz MP et al ESMO 2022.

Place of PI3K-Pathway Inhibitors in the Current Treatment Landscape for HR+, HER2- Breast Cancer[1-2]

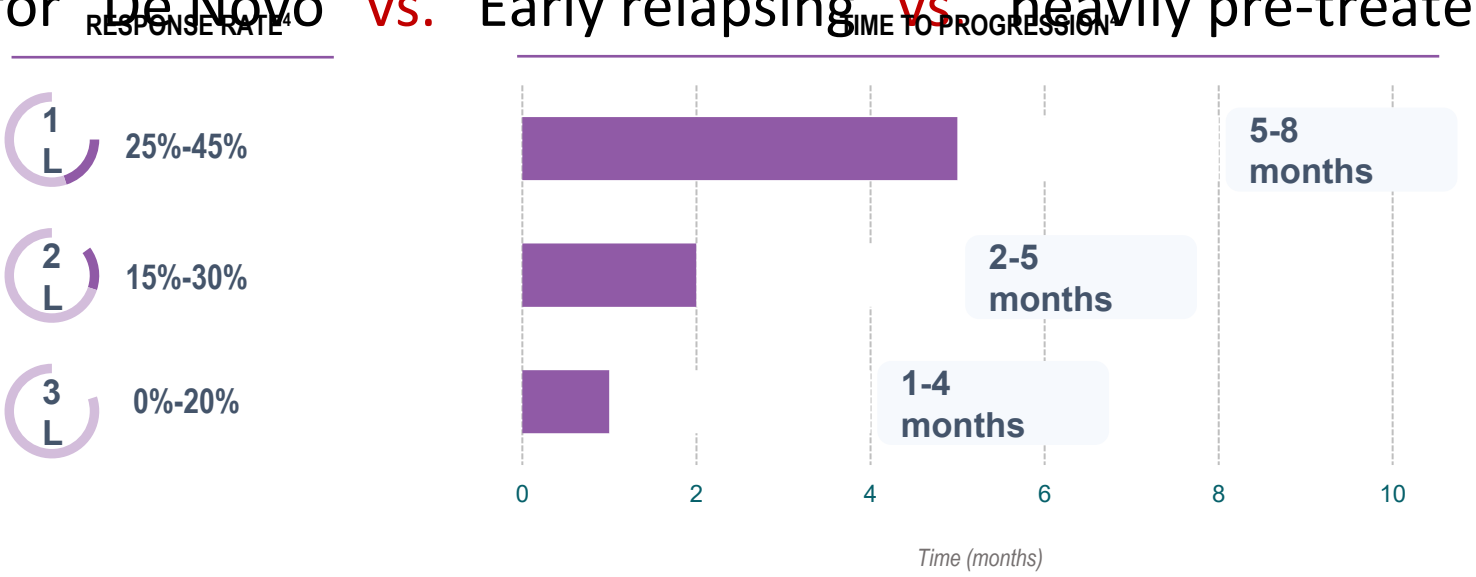


*Only funded in some provinces; †Not funded; ‡Chemotherapy might be the first choice if visceral crisis is suspected; after adequate response, other choices considered.
1L: first line; 2L: second line; AI: aromatase inhibitor; AKT: protein kinase B; BRCAmut: breast cancer gene (BRCA1, BRCA2) mutation; CDK4/6i: cyclin dependent kinase 4/6 inhibitor; CT: chemotherapy; eBC: early breast cancer; ET: endocrine therapy; mBC: metastatic breast cancer; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog.

1. CADTH Provisional Funding Algorithm. HR+, HER2- Breast Cancer. December 2024; 2. Jerzak et al. Curr Oncol. 2023;30:5425-47.

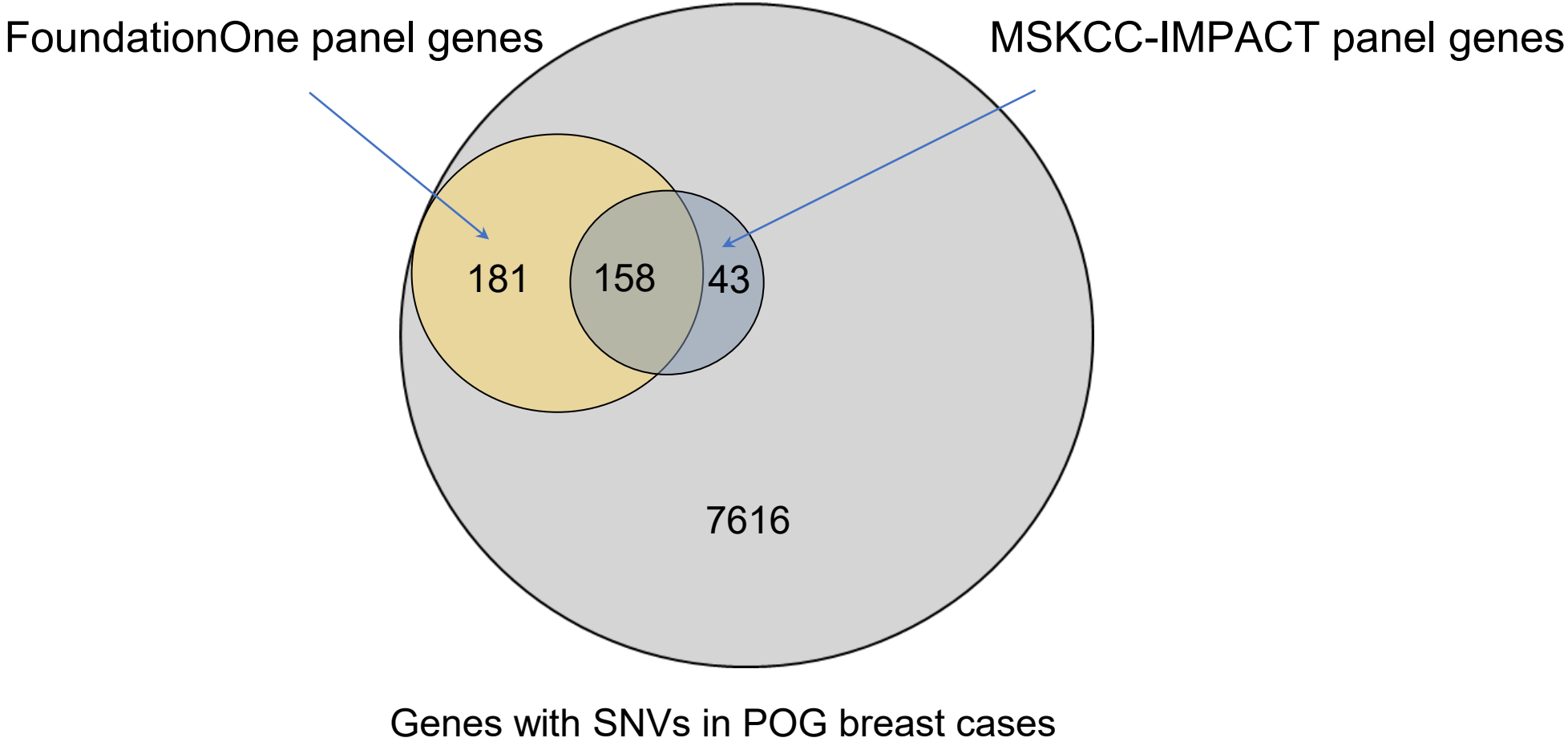
Triple Negative Breast Cancer (TNBC) – An Unmet Need

- For metastatic TNBC, current chemotherapeutic options are administered as rapid consecutive lines and are associated with poor long-term disease control and toxicities[1-3]
- Duration of treatment, response rates, and time to progression all diminish as line of chemotherapy increases[4]
- Variable course for “De Novo” vs. “Early relapsing” vs. ”heavily pre-treated first-line”



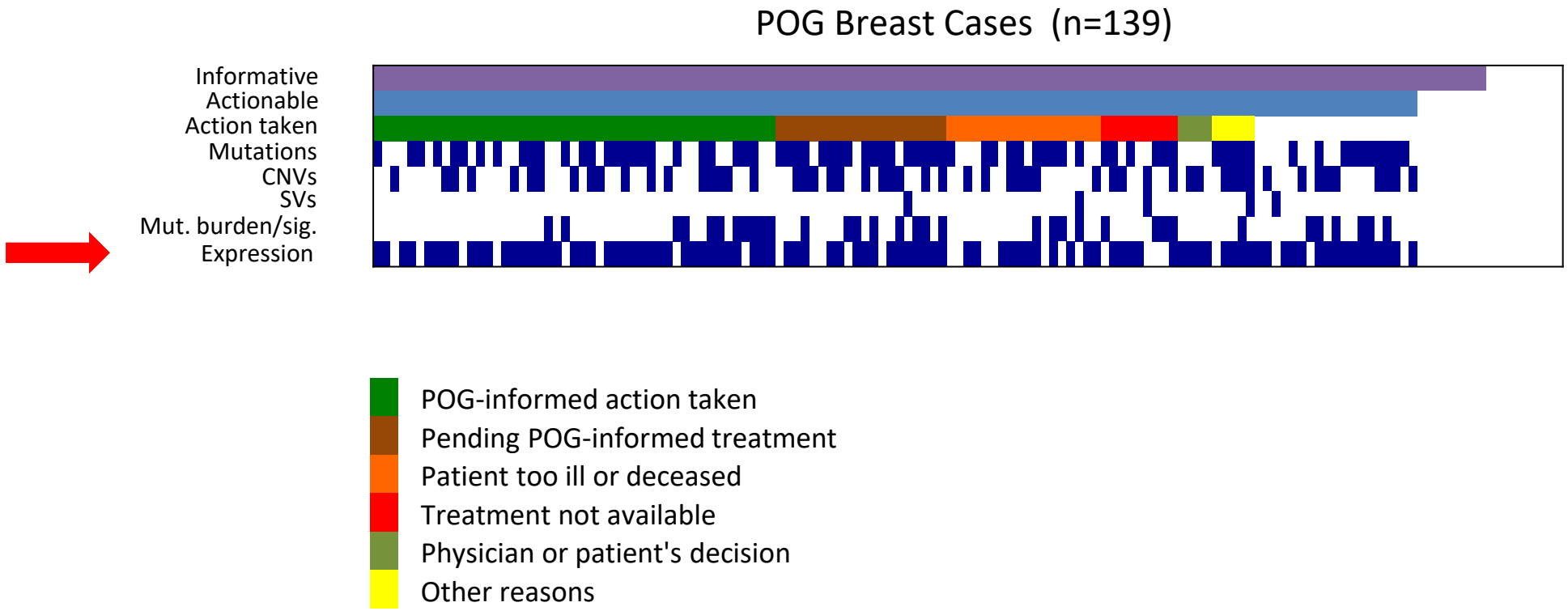
1. Loi S et al. *Proc Natl Acad Sci U S A.* 2013;110(27):11091–11096. 2. Rivera E, Cianfrocca M. *Cancer Chemother Pharmacol.* 2015;75(4):659–670. 3. Cortes J, Vidal M. *Breast Cancer Res Treat.* 2012;133(3):821–830. 4. Traina TA. Medscape Education Oncology. 2012. http://www.medscape.org/viewarticle/739390_transcript.

Personalized Oncogenomics Program in BC
Whole Genome vs Gene Panels in Breast Cancer (n=139)



LeVasseur et al. ASCO 2019.

RNA/DNA support for Actionable Findings



LeVasseur et al. ASCO 2019.

MRD monitoring can detect recurrence prior to radiological detection

- MRD detection is strongly associated with disease recurrence[1]
- Might allow for identification of individuals at highest risk of metastatic recurrence, for whom escalated therapies may have the greatest potential benefit[2]
- Recurrence can be detected in the blood by MRD ≥7 months before it is radiologically evident[2,3]

Current and Potential Uses of ctDNA in EBC[4]

- **Complement mammography**
- **Pan-cancer detection**

- **Prognostication**
- **Treatment escalation or de-escalation**

- **Early relapse detection**
- **Treatment escalation**

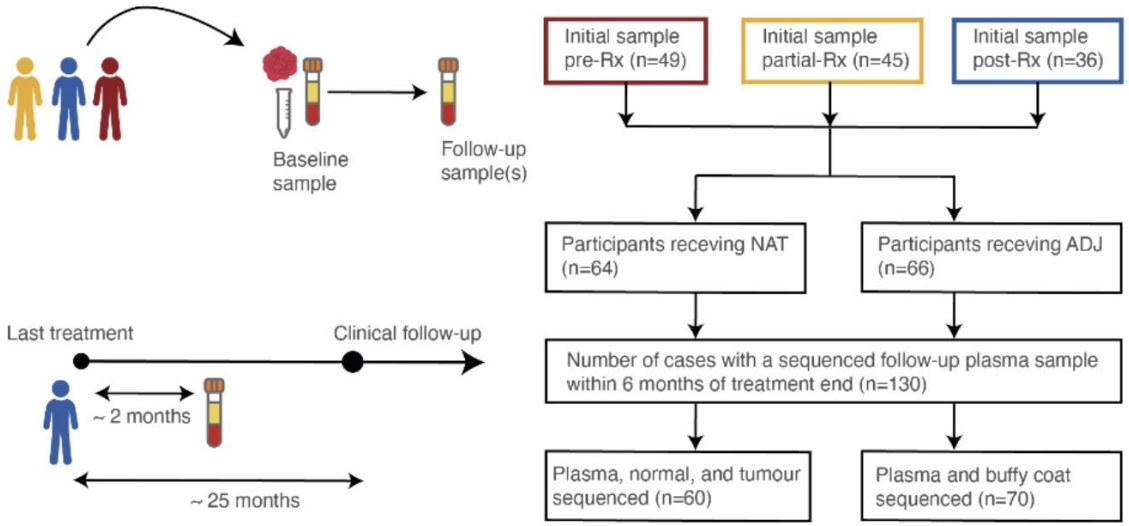
Figure adapted from Panet et al with permission.[4]

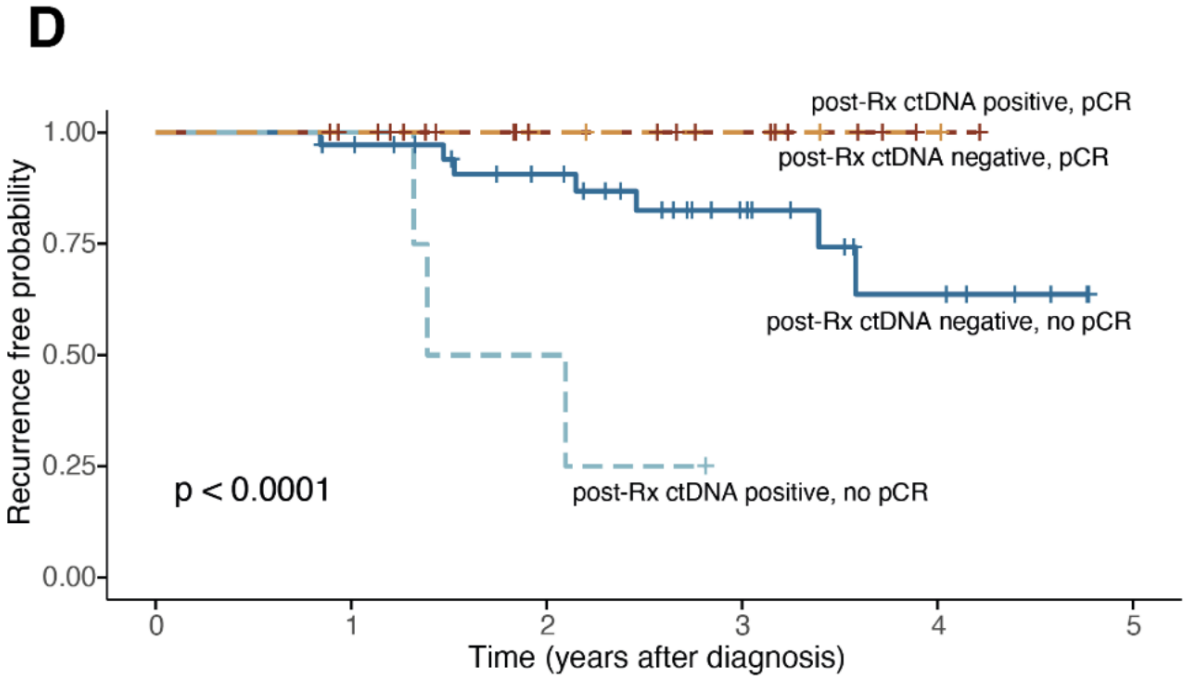
Trial	Treatment
ZEST (phase 3)[5]	**Niraparib in patients with ctDNA+, BRCA-mutated BC or TNBC**
c-TRAK-TN (phase 2)[6]	**Pembrolizumab in patients with ctDNA+ TNBC**
LEADER (phase 2)[7]	**Ribociclib in patients with ER+ disease**
KAN-HER2 MRD (phase 2)[8]	**Neratinib + ado-trastuzumab emtansine in patients with HER2+ MRD**
DARE (phase 2)[9]	**Adjuvant SOC or palbociclib + fulvestrant in patients with ER+ HER2− disease**

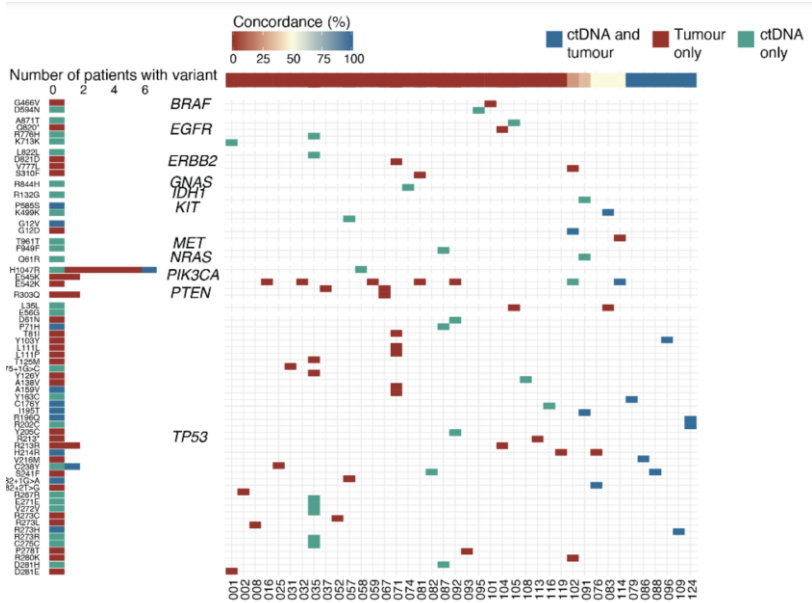
BC, breast cancer; ctDNA, circulating tumor DNA; EBC, early breast cancer; ER, endocrine receptor; HER2, human epidermal growth factor receptor 2; MRD, minimal residual disease; SOC, standard of care; TNBC, triple-negative breast cancer.

References: 1. Medford AJ et al. *Clin Cancer Res.* 2023;29(22):4540-4548. **2.** Cescon DW et al. *Front Oncol.* 2022;11:667397. **3.** Spring LM et al. *npj Breast Cancer.* 2025;11:2. **4.** Panet F et al. *npj Breast Cancer.* 2024;10:50. **5.** Clinicaltrials.gov. NCT04915755. Accessed March 3, 2025. https://clinicaltrials.gov/study/NCT04915755 **6.** Clinicaltrials.gov. NCT03145961. Accessed March 3, 2025. https://clinicaltrials.gov/study/NCT03145961 **7.** Clinicaltrials.gov. NCT03285412. Accessed March 3, 2025. https://clinicaltrials.gov/study/NCT03285412 **8.** Clinicaltrials.gov. NCT05388149. Accessed March 3, 2025. https://clinicaltrials.gov/study/NCT05388149 **9.** Clinicaltrials.gov. NCT04567420. Accessed March 3, 2025. https://clinicaltrials.gov/study/NCT04567420

ctDNA in Early Stage TNBC







- Added value for response monitoring and prognosis in TNBC
- 7.7% had detectable residual disease with a hotspot panel
- positive ctDNA within 7 months of treatment completion were at risk of reduced progression free survival

Zaikova et al. npj Breast Cancer 2024

Even with precision medicine & novel therapeutics on the horizon, challenges remain

- Equitable access to broad scale testing
- Overcoming drug resistance
- Optimizing and personalizing therapeutics
  - There is no reliable blood-based monitoring after curative intent therapy
  - Radiographic evaluation is performed only in response to symptoms

Exploring new targeted treatment options, improving drug delivery, combining drug classes and earlier implementation of effective screening strategies are potential future research directions for breast cancer

CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

References: 1. Garg P et al. *Cancers*. 2024;16(13)2478. **2.** Wang X et al. *Cancer Gene Ther*. 2024;31:1283-1291. **3.** Cao LQ et al. *Front Pharmacol*. 2024;15:1340764. **4.** Huang J et al. *Int J Mol Med*. 2022;50(4):128. **5.** Medford AJ et al. *Clin Cancer Res*. 2023;29(22):4540-4548.

Questions

BC CANCER

Provincial Health Services Authority