ESHOS SABCS 2022 Review: Genomic Update

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Disclosures

- Consulting/Advisory Board: Biovica, Eli Lilly,Foundation Medicine, Hologic, Pfizer, Puma Biotechnology, Veracyte
- Education/Speaking: Eli Lilly, Guardant Health, 2ndMD
- Institutional Research Support: Eli Lilly, Genentech, Nuvation Bio, Pfizer, Regor Therapeutics

ESHOS SABCS 2022 Review: Genomic Update

- Interrogating the genomic landscape of HER2 low disease
  - Bansal et al HER2-12; Tarantino et al HER2-05; Marra et al HER2-07

- Leveraging single cell genomics to predict tamoxifen response
  - Kim et al PD4-08

- Novel genomic insights in HR+ metastatic breast cancer
  - ESR1 mutations and clinical predictors in EMERALD
    - Bardia et al GS3-01
  - Clonal evolution and novel CDK4/6i resistance drivers
    - Guarducci et al GS3-07
  - Biomarkers to predict CDK4/6i benefit in PALLAS, PENELOPE-B, and beyond
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Genomic Landscape of HER2-Low Breast Cancer (I)

METHODS

Data Source: H2L breast tumors identified in the Caris Life Sciences database of >11,000 samples.

Outcomes:

- Mutations detected by DNA next-generation sequencing (NextSeq 592 gene panels or NovaSeq whole exome sequencing).
- PD-L1 IHC expression (SP142 IC ≥ 1%).
- Tumor mutational burden (TMB), total somatic mutations per-tumor (high ≥ 10 mutations per megabase).

PIK3CA mutation rate is higher in HR-/H2L vs. TNBC

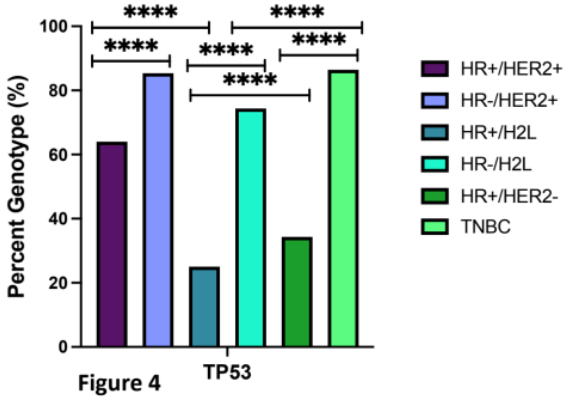


Figure 4

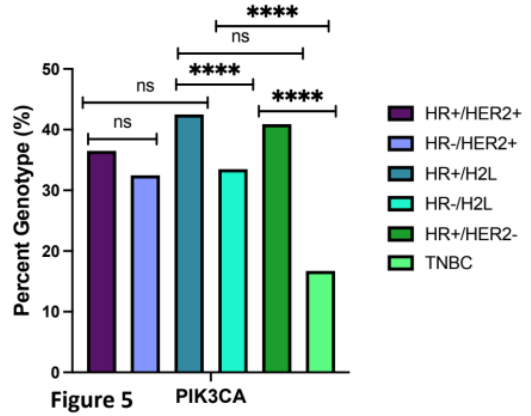
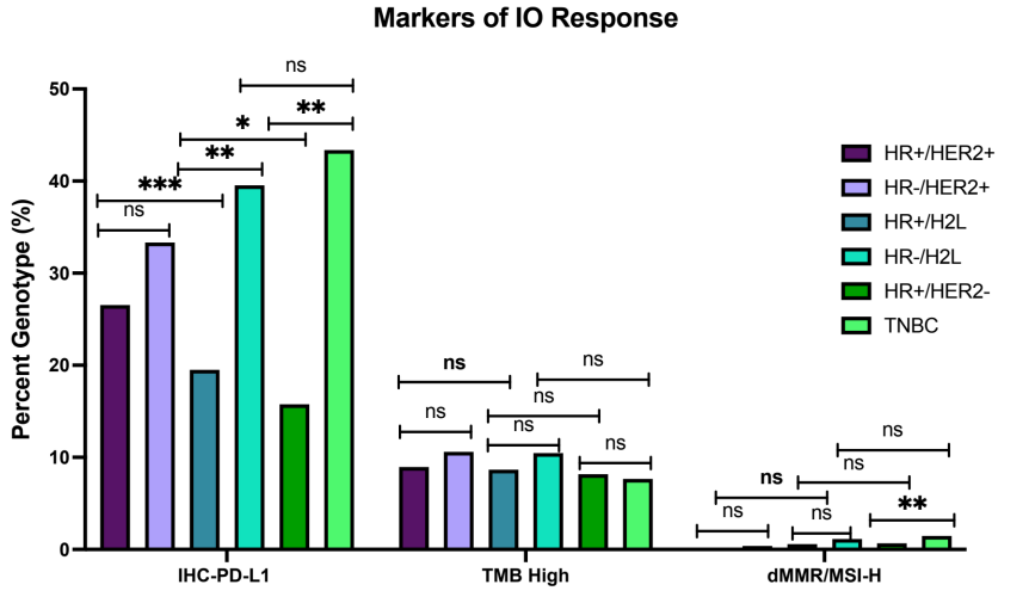


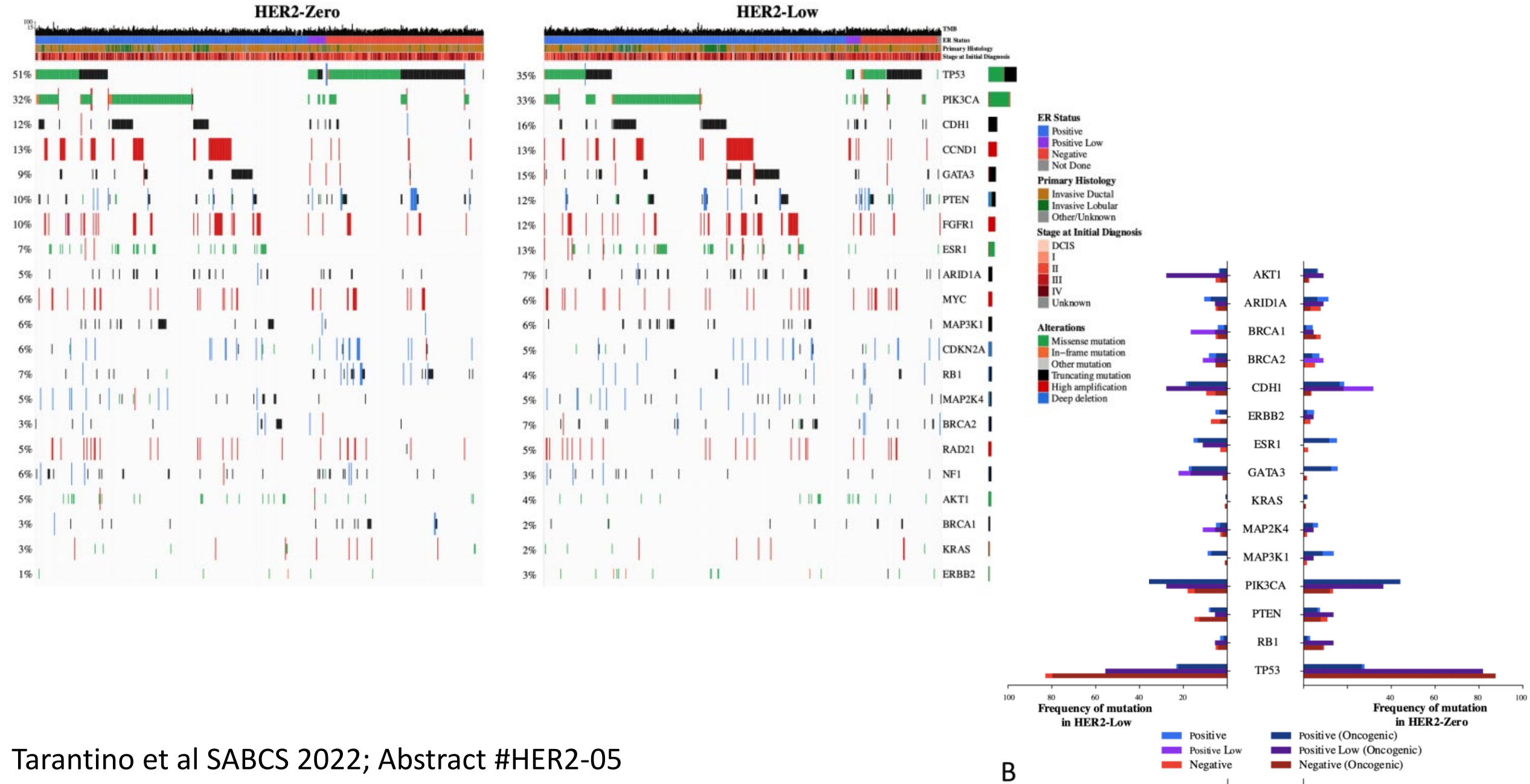
Figure 5

HR-/H2L similar to TNBC and are immune "hot" compared to HR+/H2L tumors



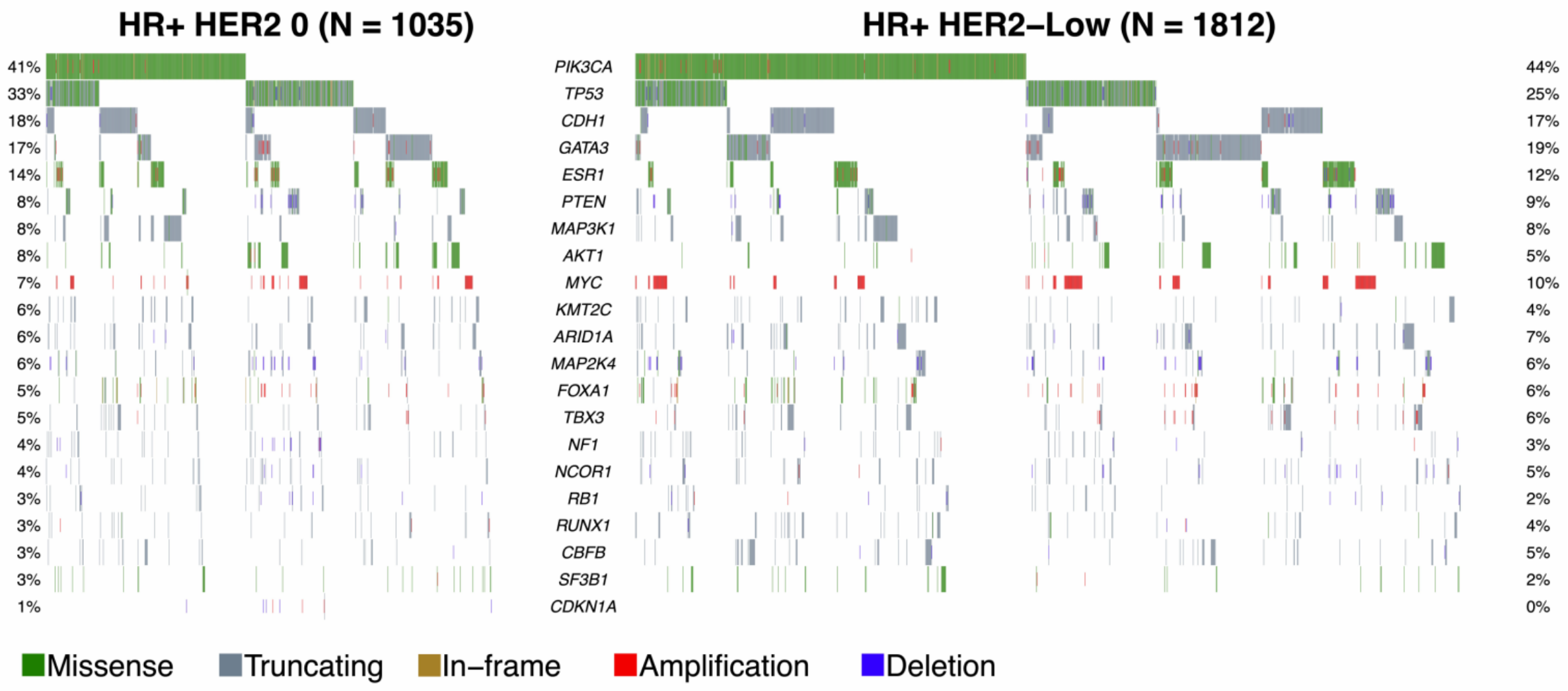
Bansal et al SABCS 2022, Abstract #HER2-12

Genomic Landscape of HER2-Low Breast Cancer (II)



Tarantino et al SABCS 2022; Abstract #HER2-05

Genomic Landscape of HER2-Low Breast Cancer (III)



Marra et al SABCS 2022; Abstract # HER2-07

Conclusions: Genomic Landscape of HER2-low Disease

- Across all 3 studies – HER2-low breast cancer did not appear to be a distinct genomic subset
  - PIK3CA mutations may be more common in HR-/HER2-low v TNBC
- Most differences were observed based upon ER+ v ER- expression
- Some genomic differences may occur when comparing HER2 IHC 1+ v 2+
- Better methods to quantify/define HER2-low are needed for clinical deployment

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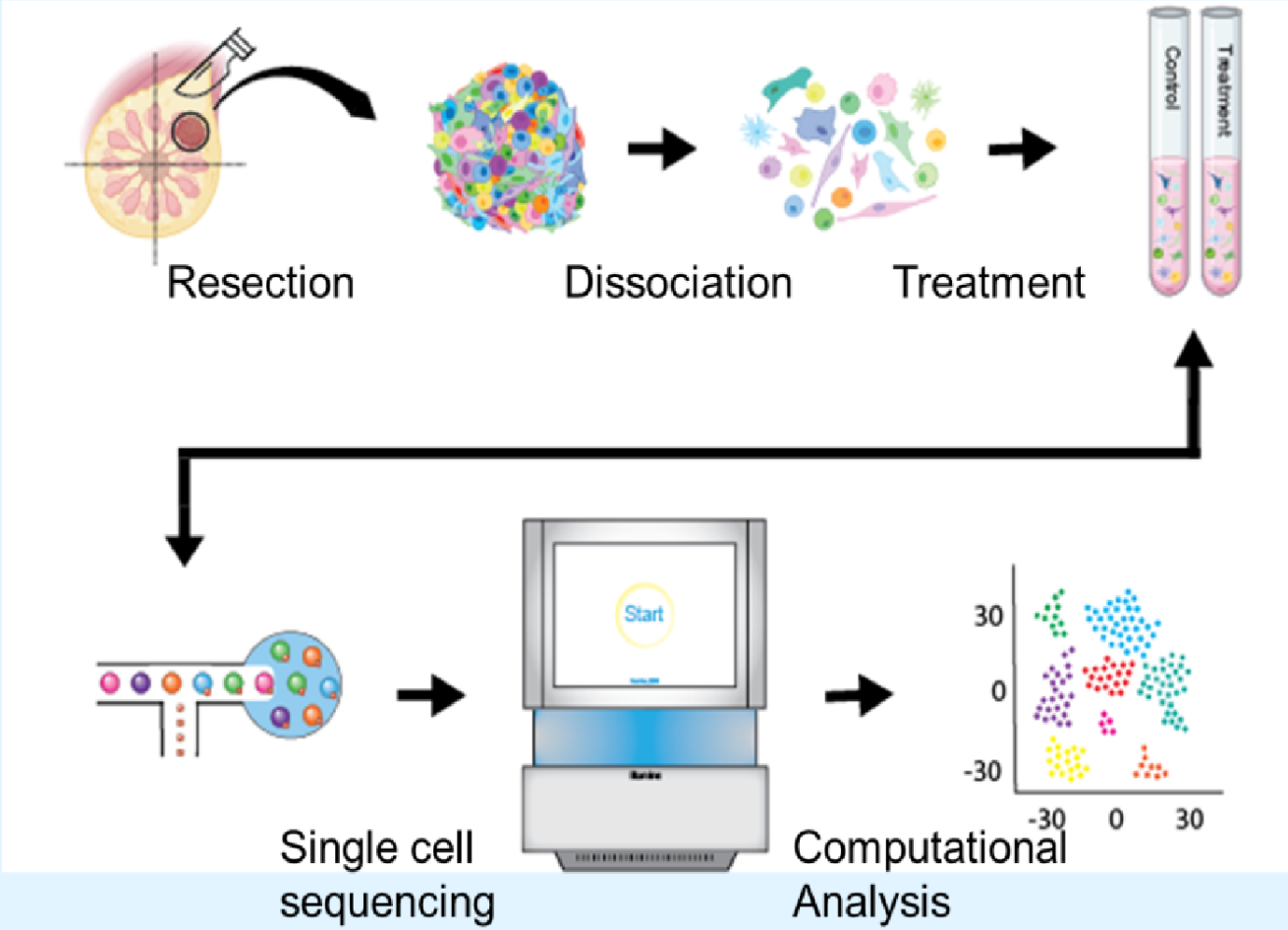
In ER+ breast cancer

Objectives:

1) To create an OR-to-lab pipeline to test treatment effect
2) To identify mechanisms of resistance/sensitivity to Tamoxifen

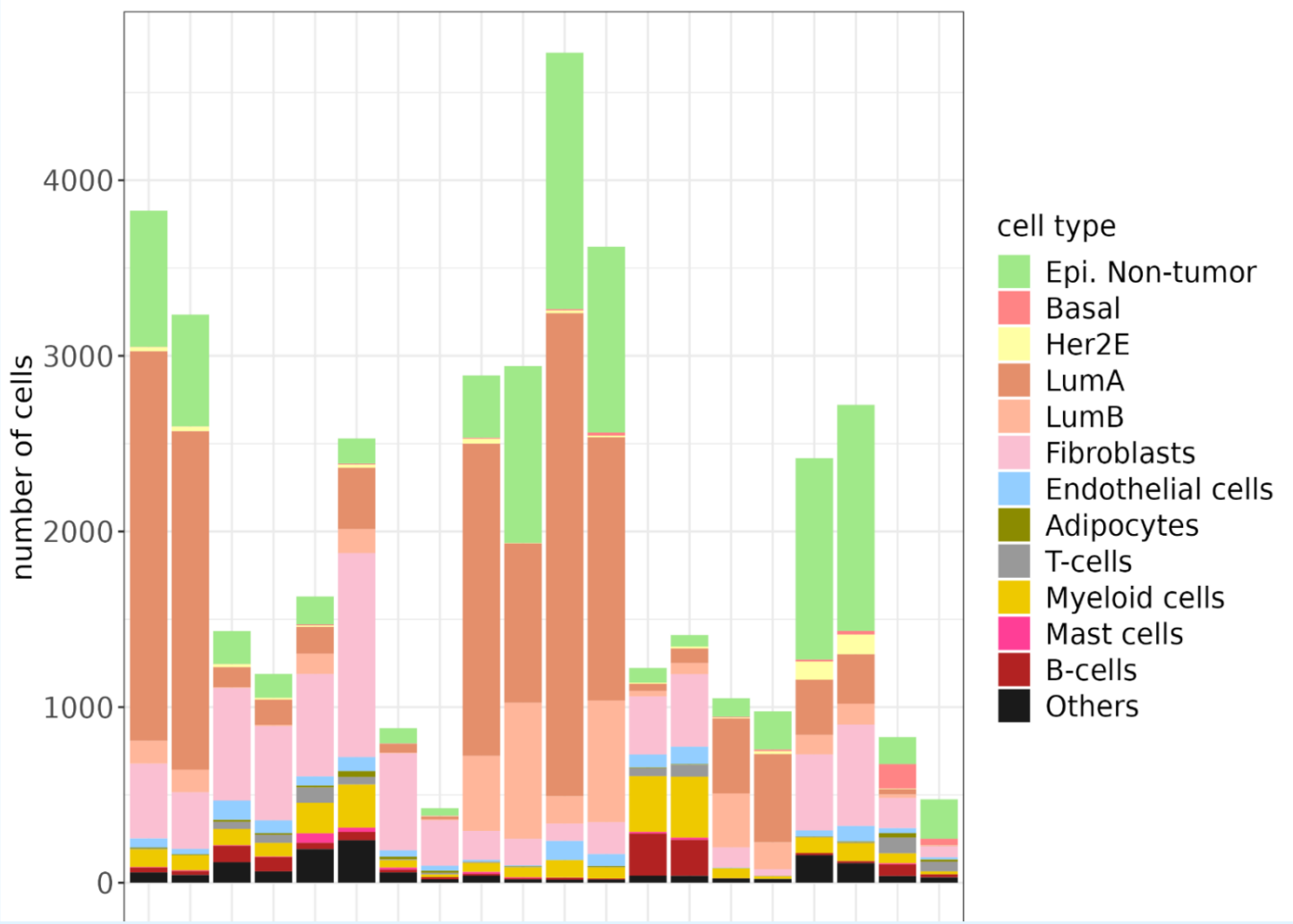


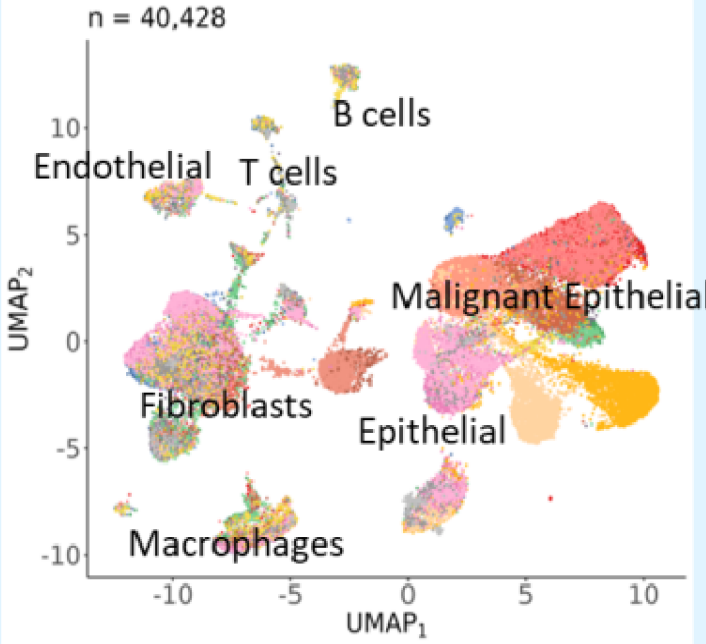
Patients (10 pts with ER+ BC)

Sample	Age	Histology	ER	PR	HER2	Grade	Stage	PAM50
Normal 1	**20**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Normal 2	**22**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tumor 1	**68**	IDC	100%	95%	2+ (FISH negative)	2	T1c N1a	LumA
Tumor 2	**44**	IDC	95%	65%	2+ (FISH negative)	2	T3 N1a	LumB
Tumor 3	**59**	IDC	90%	35%	2+ (FISH negative)	1	T2 N0	LumB
Tumor 4	**66**	ILC	100%	2%	1+	2	T3 N0 (i+)	LumA
Tumor 5	**71**	IDC	100%	5%	0	2	T1c N0	LumA
Tumor 6	**51**	ILC	95%	100%	1+	3	T1c N0	LumA
Tumor 7	**66**	IDC	95%	8%	1+	1	T1C N0	LumA
Tumor 8	**44**	IDC	90%	100%	0	3	T2 N1a	Her2
Tumor 9	**48**	IDC	95%	60%	0	3	T2 N0	LumB
Tumor 10	**22**	IDC	95%	80%	0	1	T2 N0	LumB

Kim et al SABCS 2022; Abstract # PD4-08

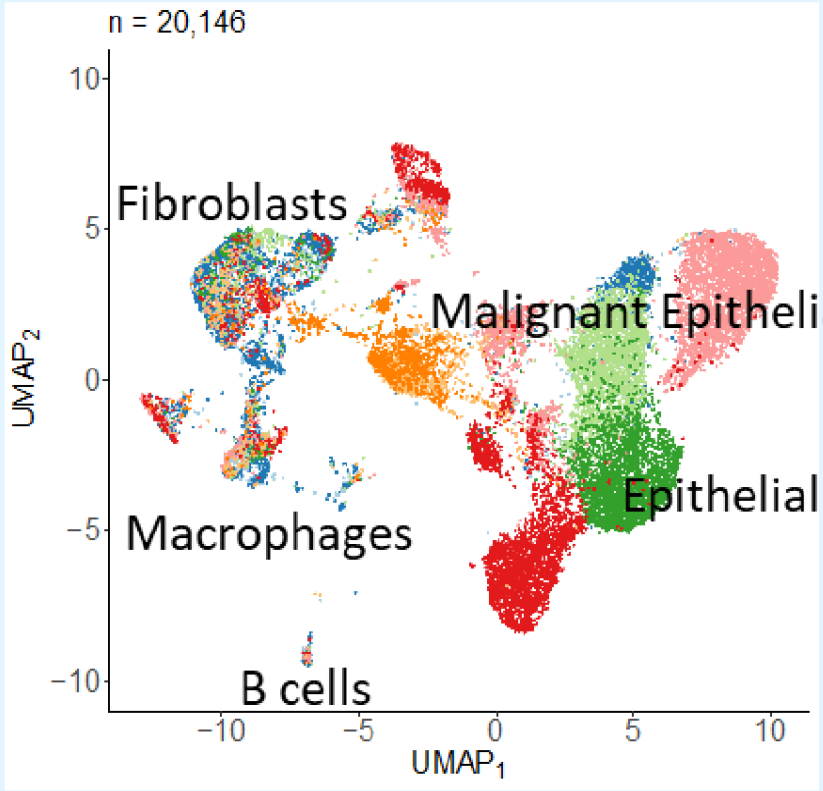
Patients (10 pts with ER+ BC)

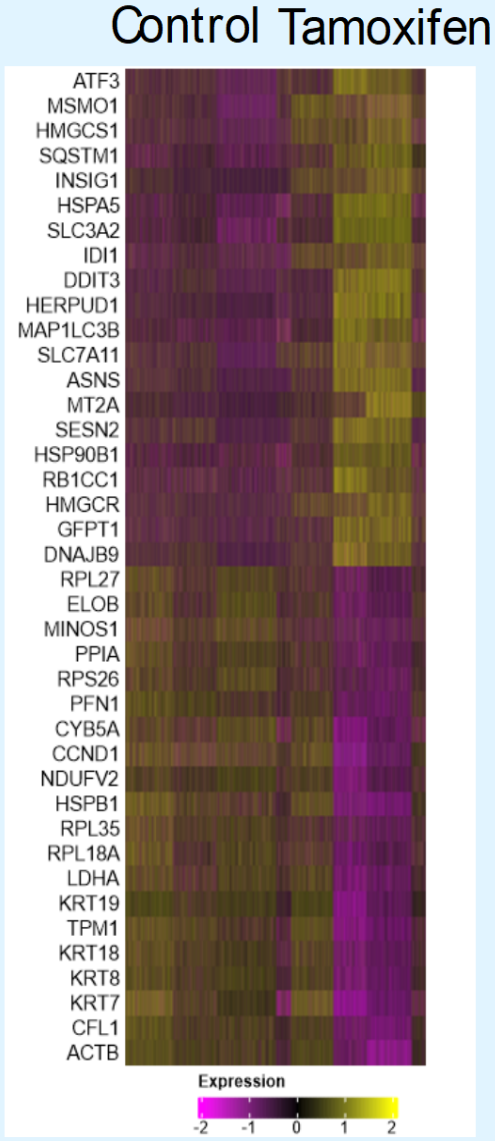




Only untreated/treated pairs with >500 tumor epithelial cells were further considered
➔ 4 untreated/treated pairs

4 tumor pairs (control/tamoxifen-treated)





- Down regulation of canonical GATA3 and E2 induced genes
- Upregulation of EGFR/MAPK, RAS, and HDAC target signatures

Kim et al SABCS 2022; Abstract # PD4-08

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GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Oral SERD Trial Landscape in Pretreated mBC

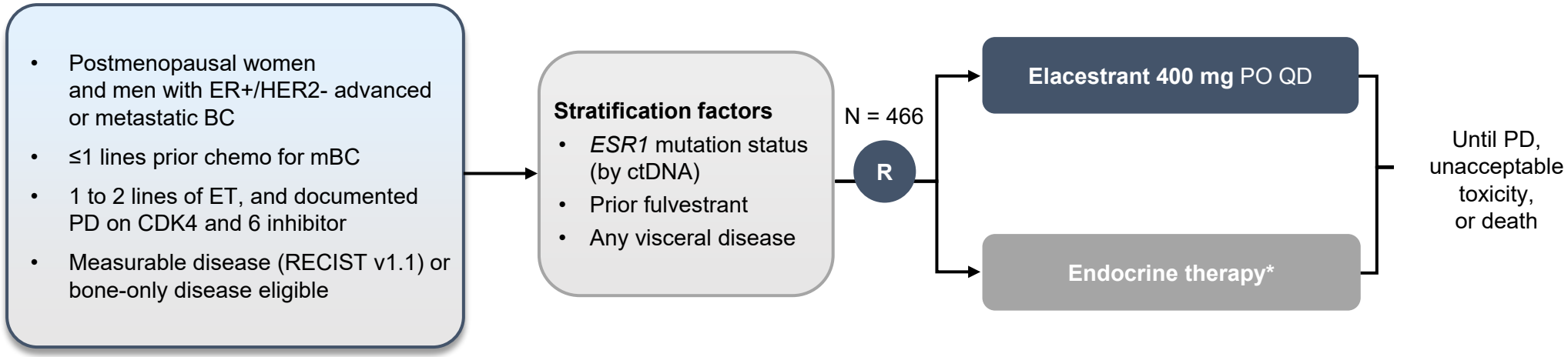
	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol.* 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

Bardia et al SABCS 2022; Abstract # GS3-01

Phase 3 EMERALD: Study Design

- Randomized, Open-Label Phase 3 Study



- **Primary endpoint:** PFS by BICR in all patients and in patients with mutant *ESR1*
  - Overall population (power ≥ 90% for HR of 0.667) or *ESR1*-mutated subset (power ≥ 80% for HR of 0.610) at an overall α level of 5%
- **Secondary endpoints:** OS, PFS by BIRC in patients with WT *ESR1*, PFS by investigator review, ORR, DoR, CBR, safety, PK, and QOL

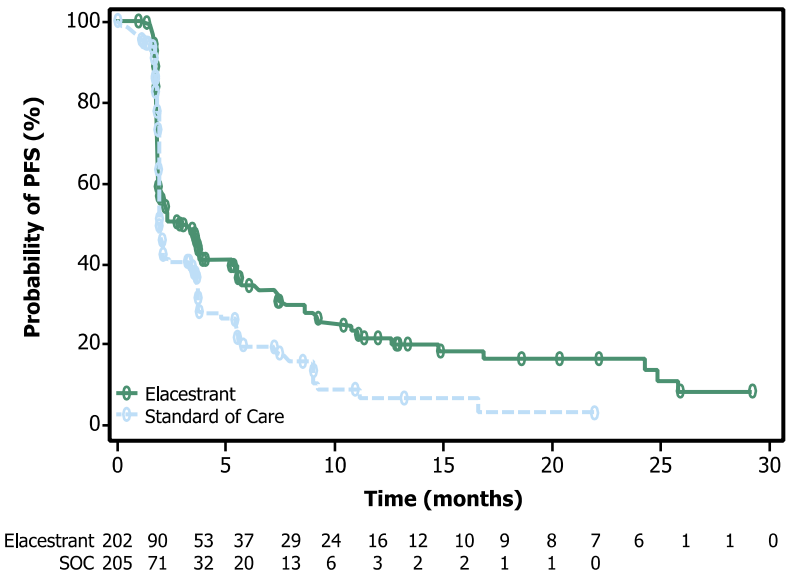
- *Investigator's choice of fulvestrant 500 mg IM on days 1 and 15 of cycle 1 and then on day 1 of 28-day cycles or an AI (continuous dosing of anastrozole 1 mg/day, letrozole 2.5 mg/day, or exemestane 25 mg/day).

BIRC, blinded independent review committee; CBR, clinical benefit rate; IM, intramuscular; PD, progressive disease; PK, pharmacokinetics; QOL, quality of life.

Bardia A, et al. J Clin Oncol. 2020;38(suppl): Abstract TPS1104.

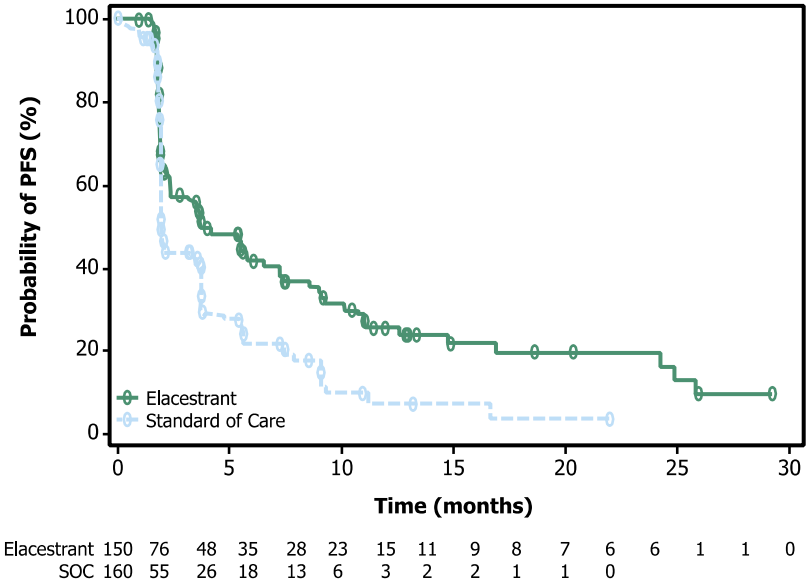
All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



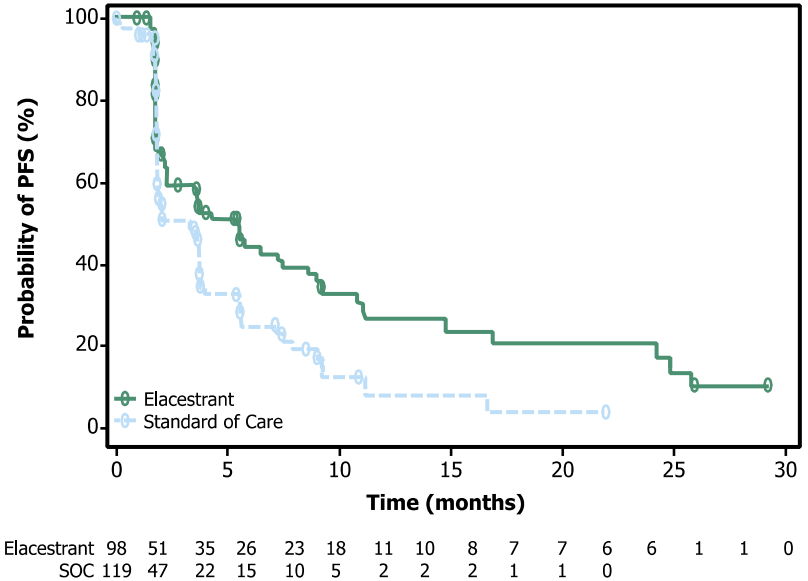
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i

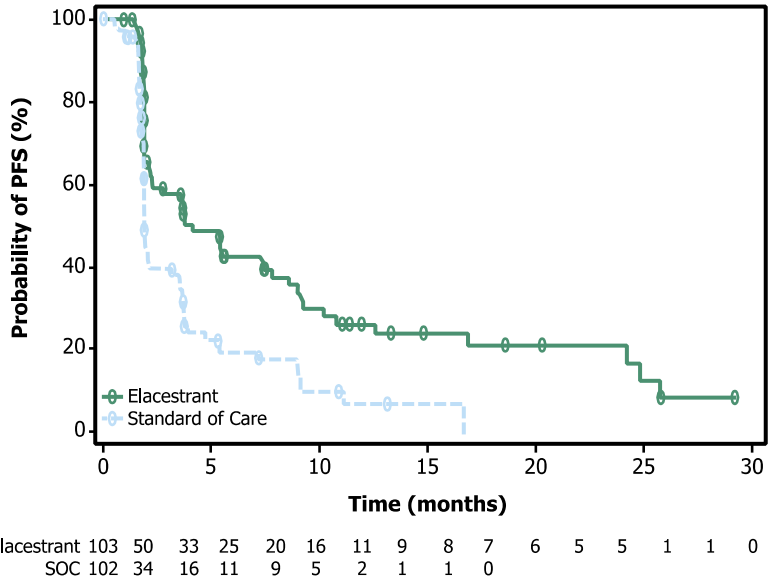


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Bardia et al SABCS 2022; Abstract # GS3-01

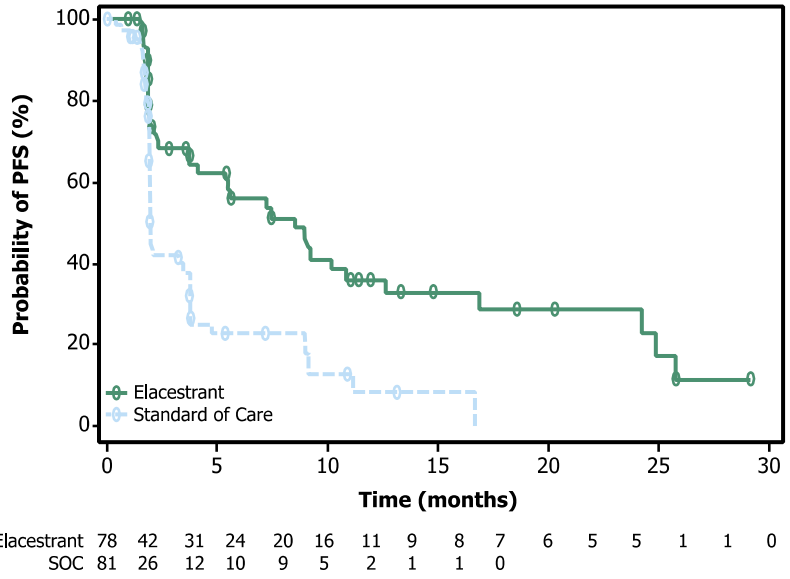
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



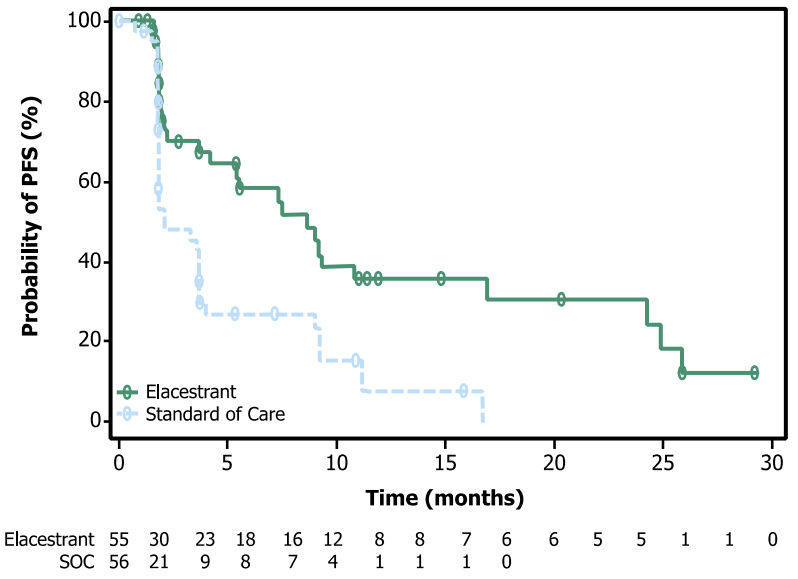
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia et al SABCS 2022; Abstract # GS3-01

Conclusions

- EMERALD is the only pivotal trial in 2nd/3rd-line mBC with 100% prior CDK4/6i usage.
- Duration of CDK4/6i was associated with PFS in the EMERALD trial. The longer the duration of prior CDK4/6i, the longer PFS on elacestrant as compared with SOC.
- This was even more pronounced in patients with *ESR1*-mut tumors, where patients who had at least 12 months of prior CDK4/6i duration achieved a mPFS of 8.6 months with elacestrant vs 2.1 months mPFS with SOC.
- No new safety signals were identified. Low-grade nausea was common in both treatment arms, but antiemetic usage was low with both oral drugs: 8% on elacestrant and 10.3% on AIs. There was no incidence of bradycardia.
- These results showed that elacestrant significantly prolongs PFS vs SOC with a low rate of adverse events.
- Elacestrant can become an important oral endocrine monotherapy agent in 2nd/3rd line as an alternative to combination therapies that are associated with challenging safety profiles.

Bardia et al SABCS 2022; Abstract # GS3-01

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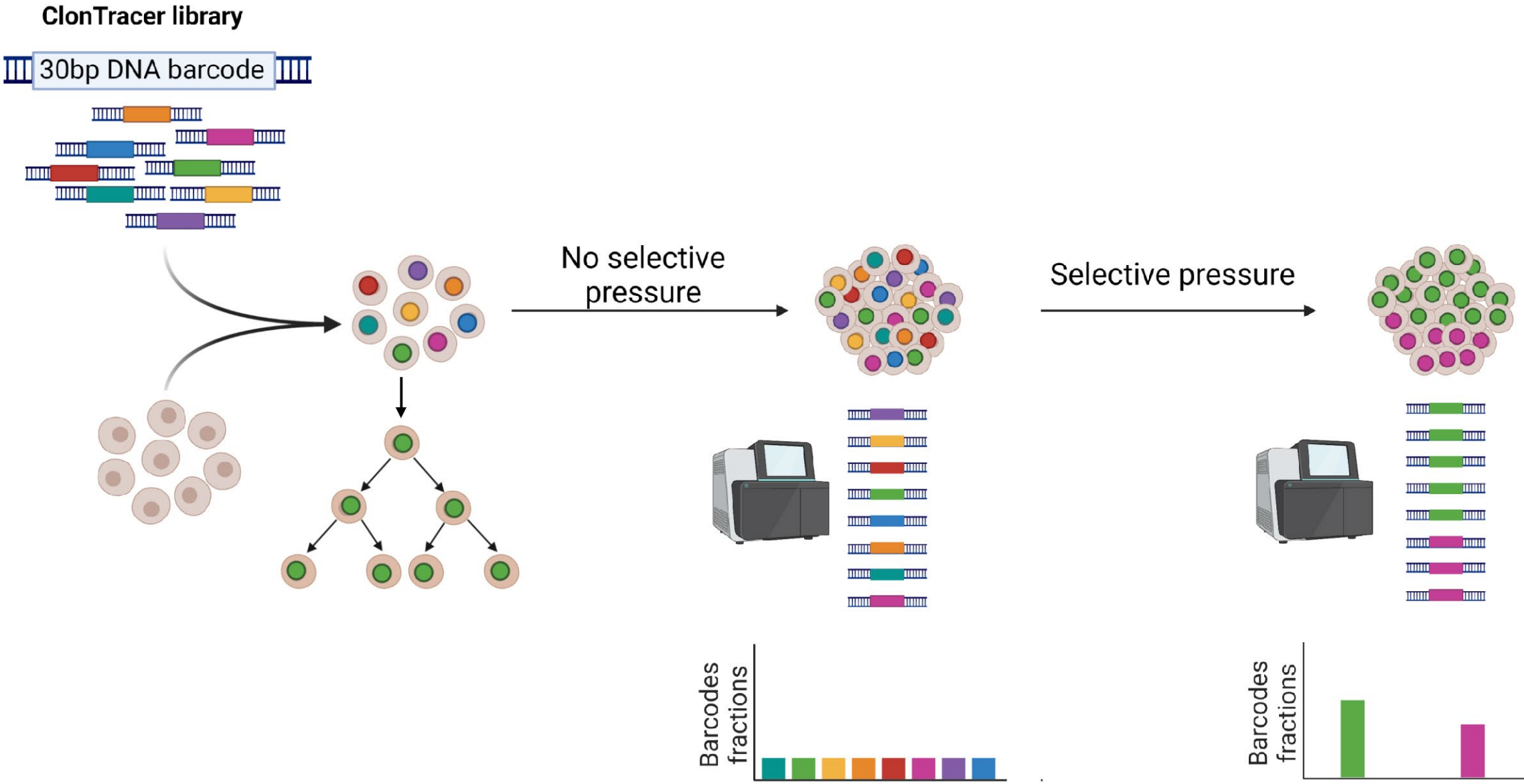
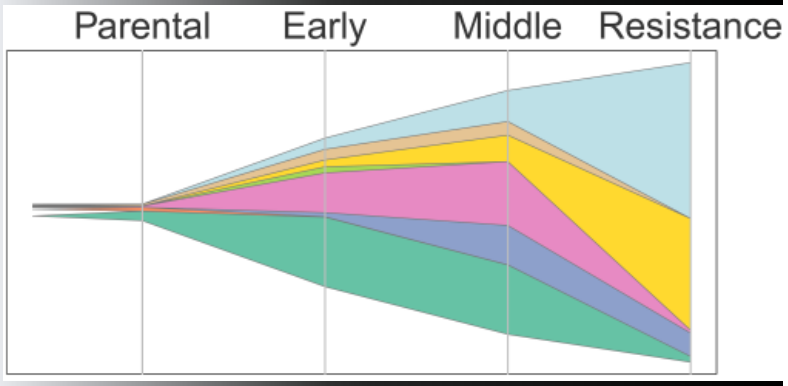
Methods



Guarducci et al SABCS 2022; Abstract # GS3-07

WT PalboR

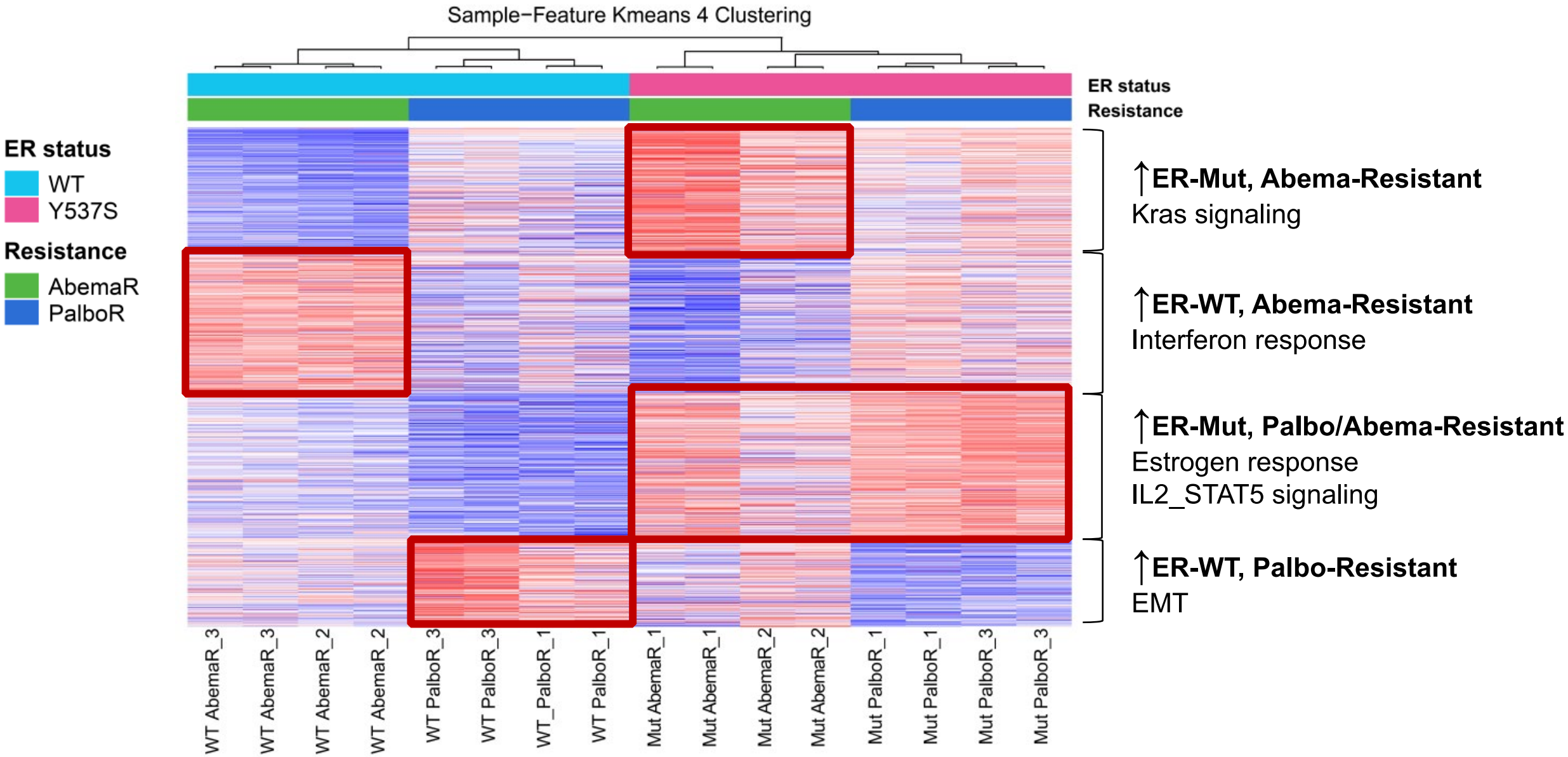
Mut PalboR



- In the AbemaR models the *ESR1* mutation leads to an earlier clonal selection, but it doesn't have a strong impact on the clonal diversity.

Guarducci et al SABCS 2022; Abstract # GS3-07

Transcriptional profile of Palbo/Abema-Resistant *ESR1*-Mutant and *ESR1*-WT MCF7 cells



Guarducci et al SABCS 2022; Abstract # GS3-07

Conclusions

- Resistance to CDK4/6i is likely due to the expansion of pre-existing resistant clones, suggesting that targeting resistance upfront could delay the acquisition of clinical resistance.

- Although the *ESR1*-mutant cells are sensitive to the CDK4/6i, the *Y537S ESR1* mutation shapes the clonal diversity and dynamics of the acquisition of resistance to CDK4/6i, more so to Palbociclib and to a lesser degree to Abemaciclib.

- The clonal selection and transcriptional changes during the acquisition of resistance to Palbociclib and Abemaciclib are different, especially in the *ESR1*-WT setting, highlighting the differences between these two CDK4/6i.

Guarducci et al SABCS 2022; Abstract # GS3-07

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Emerging Landscape of CDK4/6i Resistance

- CDK4/6 inhibitors provoke similar PFS benefits in 1st and 2nd line metastatic trials.
- Divergent outcomes with 1st line OS and in the adjuvant setting.

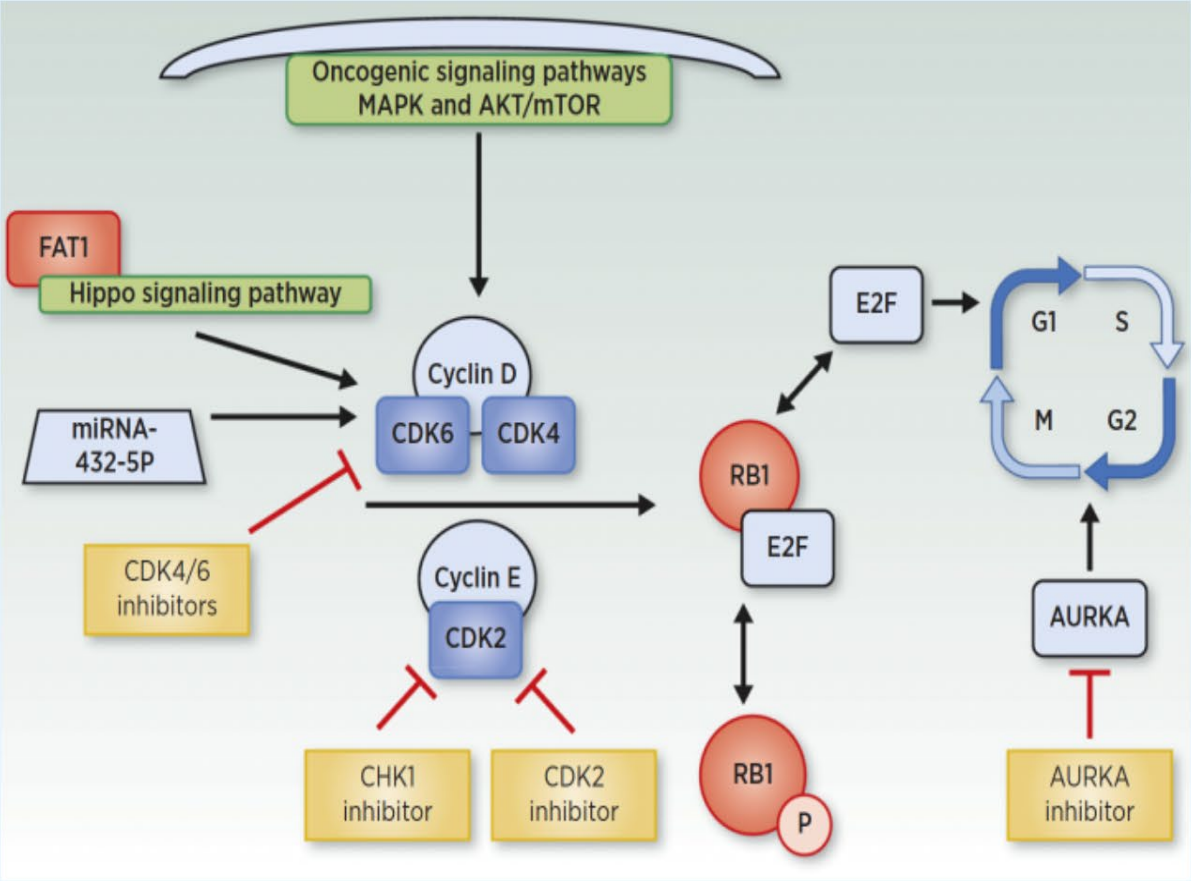
- Heterogeneous genomic/molecular mediators of CDK4/6i resistance.
  - No dominant resistance driver in large cohorts.
  - Diverse convergent cellular mechanisms of disruption/activation (eg. RB1, CDK6, AKT, etc).

- Cell cycle mediators and oncogenic signal transduction pathways.

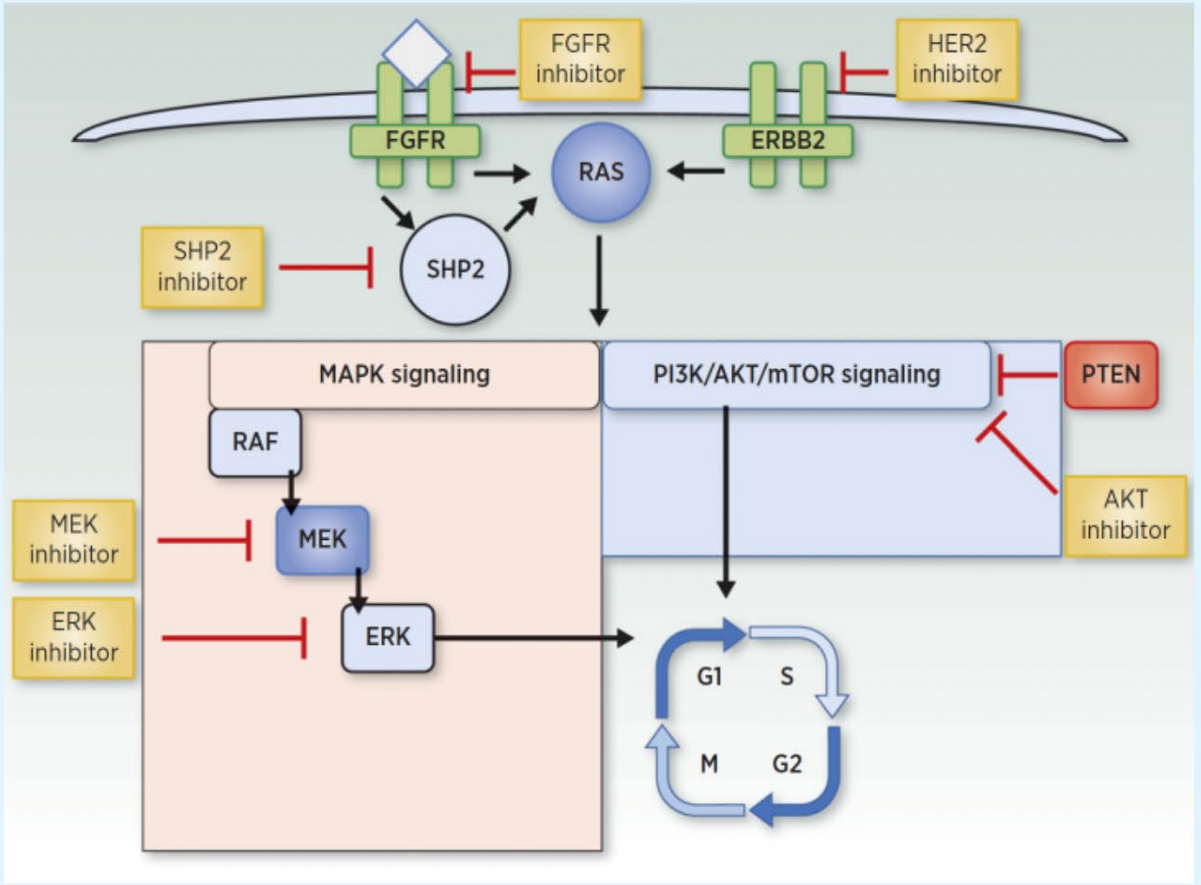
- Complex interplay between CDK4/6i and the immune system.

Resistance Drivers May Define New Therapeutic Targets

Cell-cycle mediators implicated in intrinsic and acquired resistance



Oncogenic signaling pathways and upstream tyrosine kinase receptors that mediate resistance



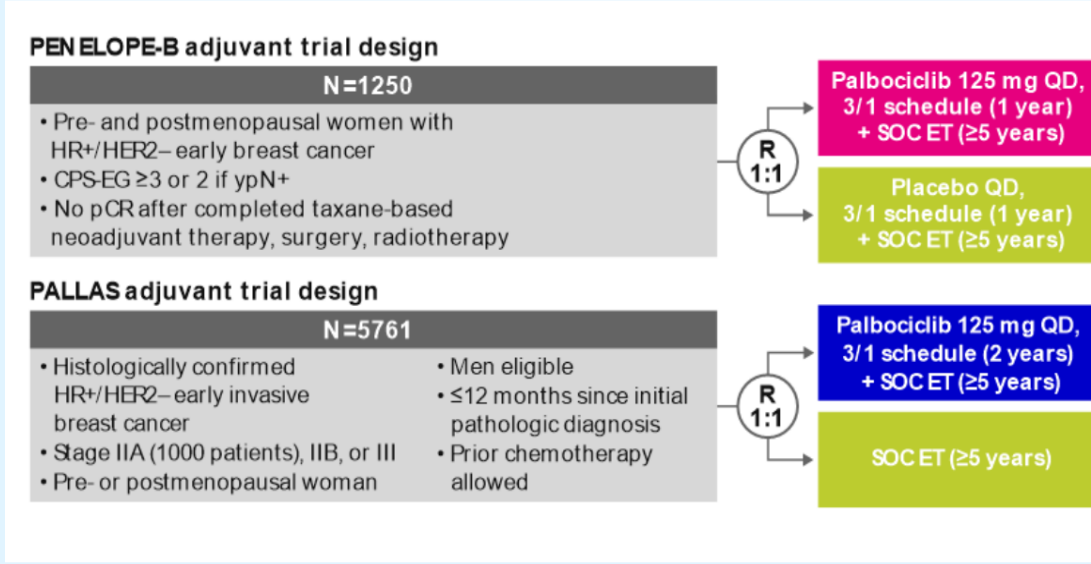
Lloyd MR et al CCR 2022

PD 17.05: Composite Biomarker for CDKi in PALLAS and PENELOPE-B

- Loibl, S et al

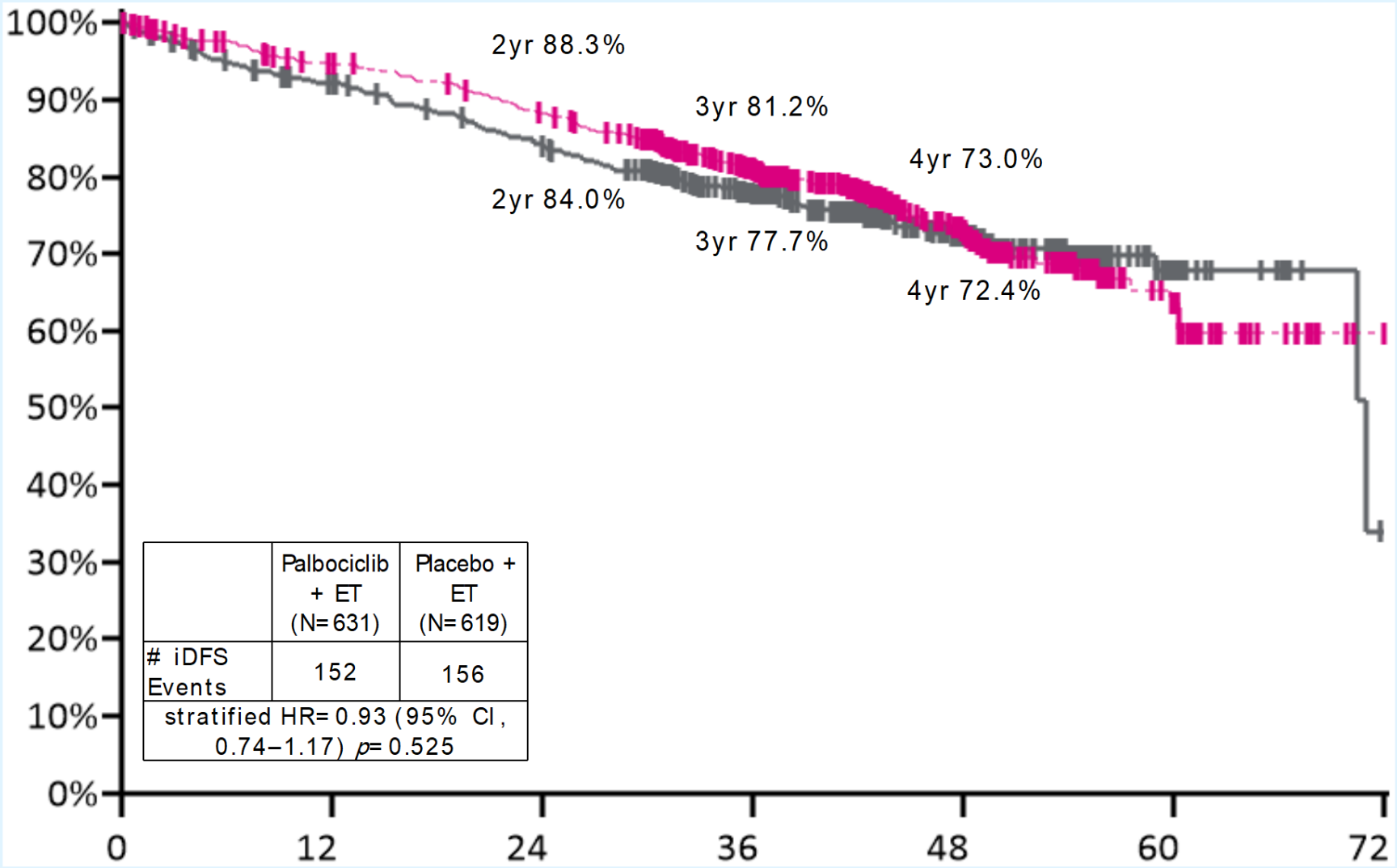
- Tissue analysis from PENELOPE-B (training set) and PALLAS (validation set)
- Composite biomarker developed with luminal subtype + ERBB2 expression + ER/PR status (based upon prior insights from PALOMA-2 and -3)
  - Biomarker positive = Luminal A + ERBB2-High and/or ER+/PR-
  - Biomarker negative = all others

- iDFS rates at 3y estimated
- Interaction between treatment and composite biomarker assessed



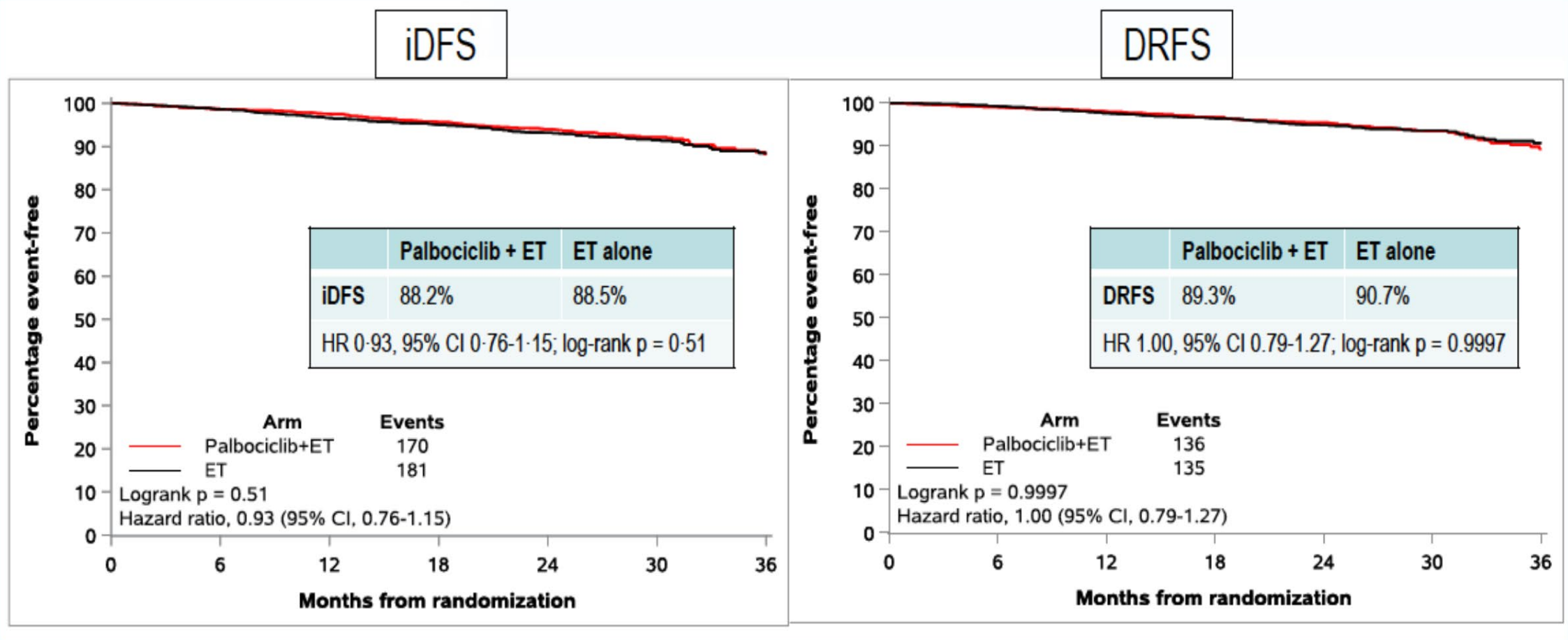
Loibl et al SABCS 2022; Abstract # PD17-05

PENELOPE-B



Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-153

PALLAS: Primary Endpoint iDFS



Mayer E, et al. *Lancet Oncol.* 2021; 22(2):212-222.

PD 17.05: Composite Biomarker for CDKi in PALLAS and PENELOPE-B

- Characteristics well balanced between analysis sets and ITT populations.
- Instrinsic subtypes similar between PALLAS and PENELOPE-B
  - Luminal A ~ 73%
- Benefit for palbociclib inclusion was identified in biomarker (+) subsets in both PALLAS and PENELOPE-B
- No benefit for palbociclib inclusion in biomarker (-)
- Treatment effect remained after adjusting for confounders in both study populations

Table 2. HTG-AIMS intrinsic molecular subtype distributions were similar between PENELOPE-B and PALLAS HTG Sets, as were the subtype prognostic profils [8] (data not shown)

Molecular Subtype (HTG-AIMS), n (%)	PENELOPE-B HTG Training Set	PALLAS HTG Validation Set
	Total (N=906)	Total (N=2085)
Basal-like	16 (1.8)	37 (1.8)
HER2-enriched	28 (3.1)	49 (2.5)
Luminal A	663 (73.2)	1516 (72.7)
Luminal B	64 (7.1)	172 (8.2)
Normal-like	135 (14.9)	311 (13.6)

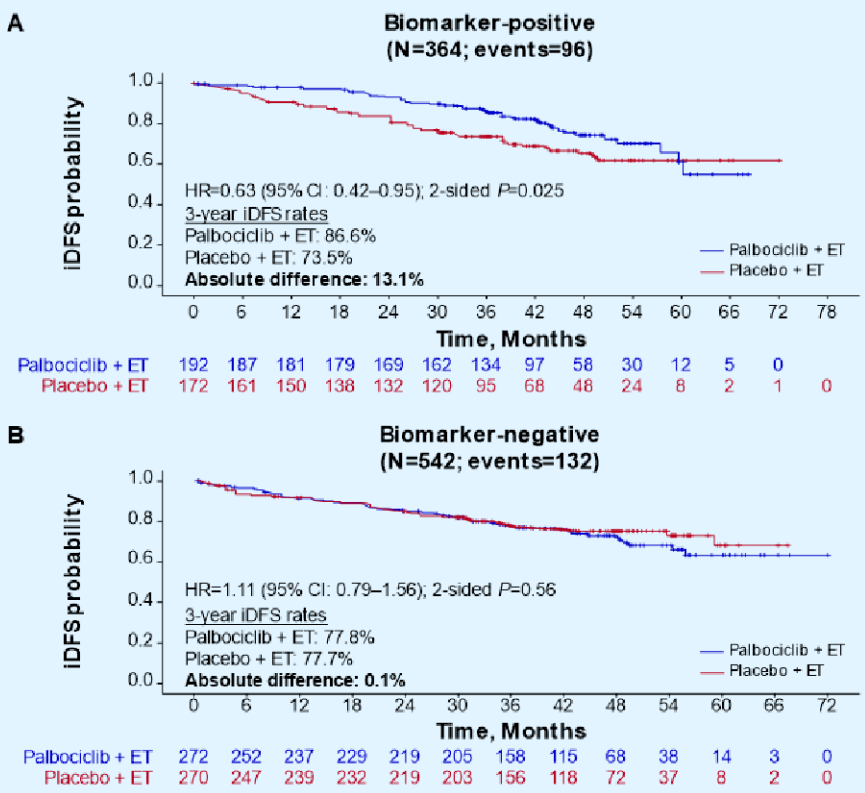
AIMS, absolute intrinsic molecular subtyping; HER2, human epidermal growth factor receptor 2.

Loibl et al SABCS 2022; Abstract # PD17-05

PD 17.05: Composite Biomarker for CDKi in PALLAS and PENELOPE-B

PENELOPE-B HTG TRAINING SET (N=906)

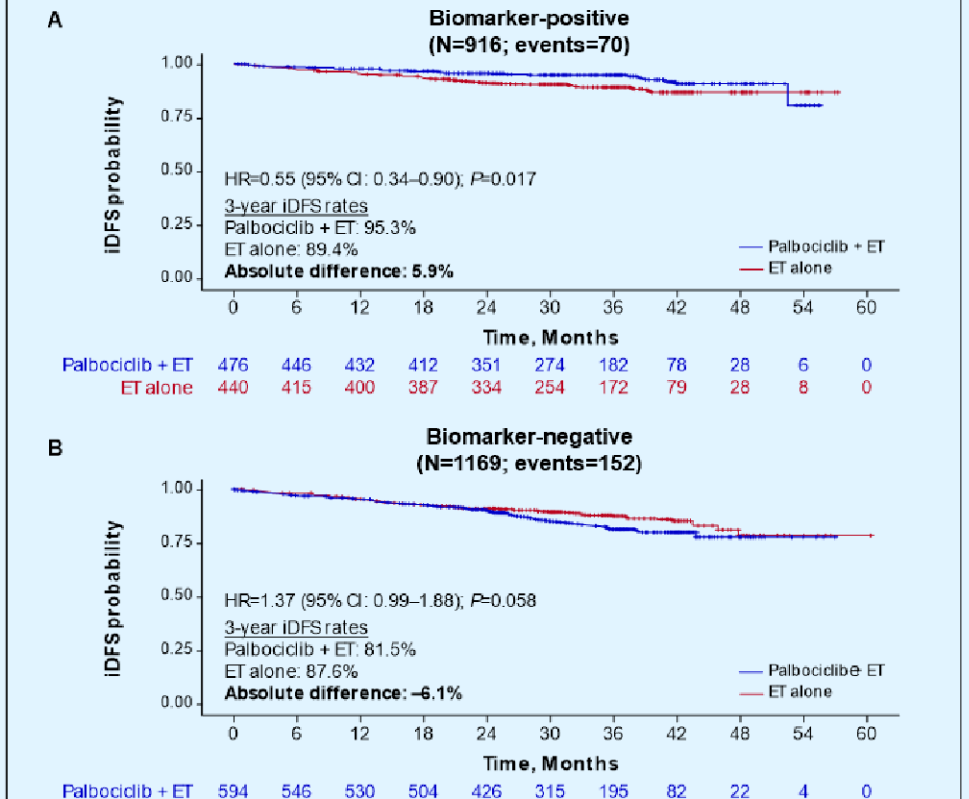
Figure 3. The biomarker-positive subgroup (composite of LumA with *ERBB2*-high and/or LumA ER+/PR–) demonstrated a preferential benefit from palbociclib + ET, which was not seen in the biomarker-negative subgroup (all other samples) of the PENELOPE-B HTG Training Set (interaction *P*=0.041)



CI, confidnce int er val ; ER, estr ogen receptor; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; LumA, luminal A; PR, progesterone receptor.

PALLAS HTG VALIDATION SET (N=2085)

Figure 4. Independent validation of the biomarker with tumor samples from the PALLAS HTG Validation Set confire d si gni fica t bene f i t f om palbociclib + ET in the biomarker-positive subgroup, but not in the biomarker-negative subgroup (interaction *P*=0.0022)



CI, confidnce int er val ; ET , endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival.

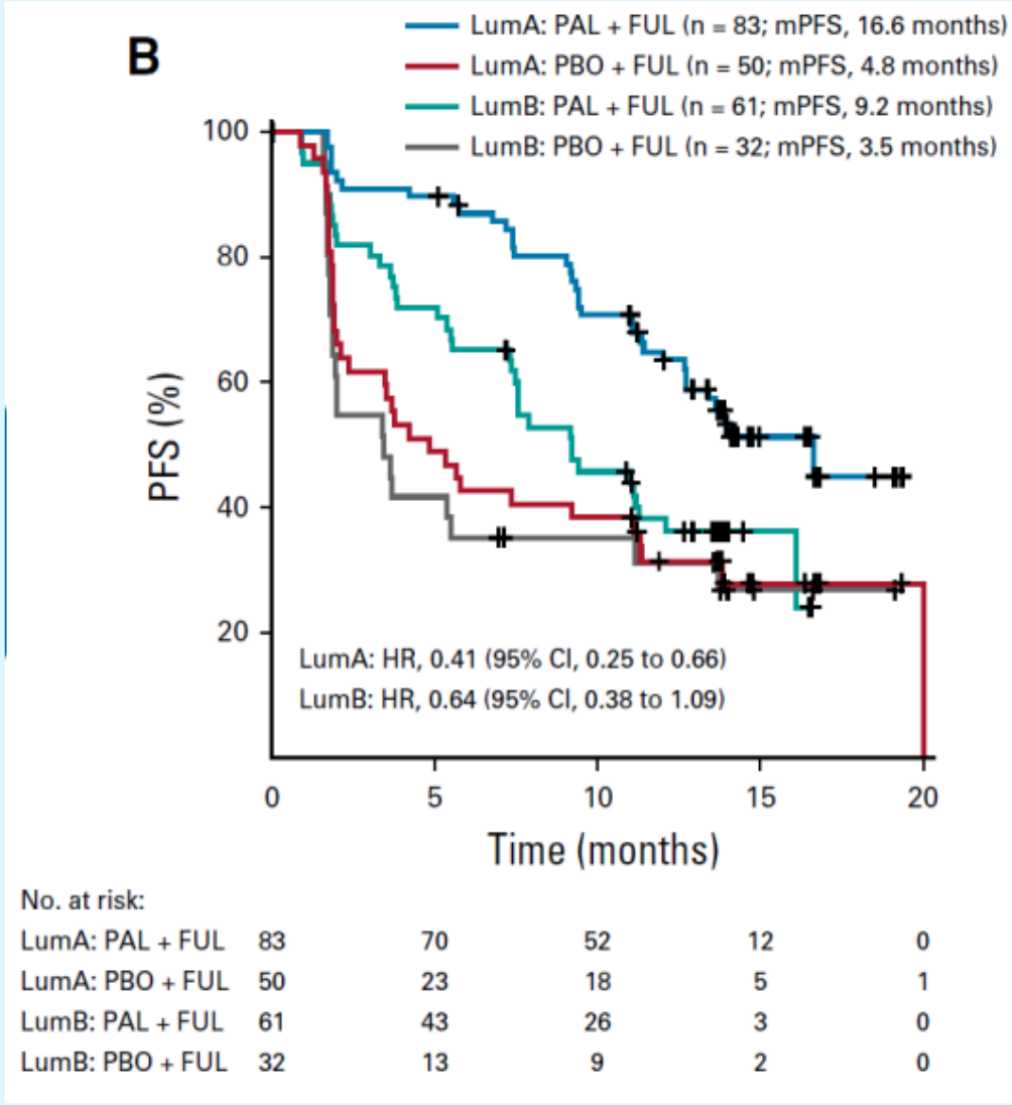
Loibl et al SABCS 2022; Abstract # PD17-05

PD 17.05: Composite Biomarker for CDKi in PALLAS and PENELOPE-B

- Key question related to potential subgroups that might benefit from adjuvant palbociclib given negative study results.
- How much of this finding is driven by intrinsic subtype alone? Luminal A v Luminal B/Basal/HER2-enriched
- Does intrinsic subtype itself reflect underlying genomic/molecular mediators of resistance?
  - Eg. RB1 alterations in basal, CCNE upregulation in Luminal B etc
- Why are PALLAS/PENELOPE-B negative while MonarchE is positive?
  - Drug-related factors vs. study design/population/drug administration
  - NATALEE and insights from ribociclib in this setting

Intrinsic Subtype and CDK4/6i Resistance

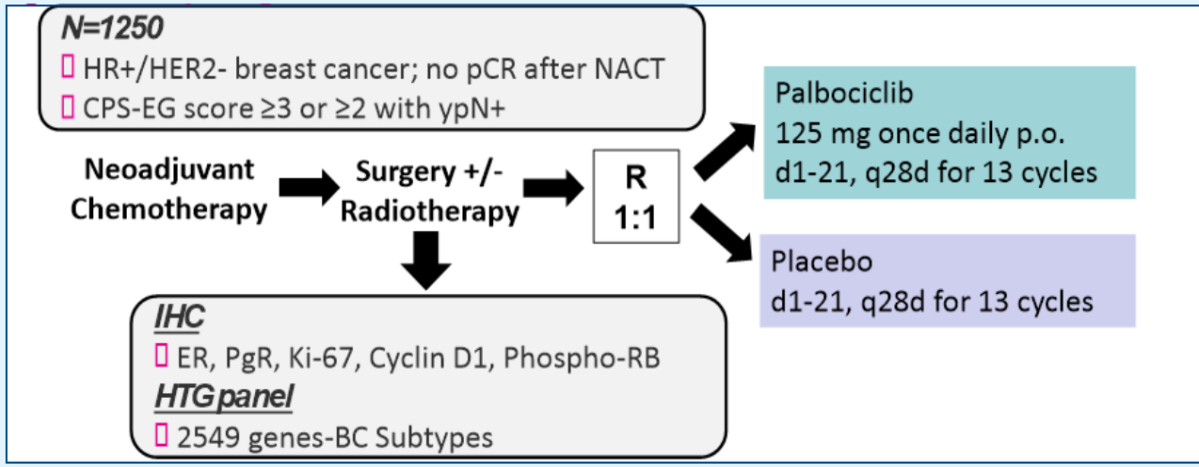
- CCNE1 emerged as a key predictor of drug benefit in PALOMA-3.
- Luminal B tumors derived less benefit, and had higher CCNE1 mRNA expression levels (vs. luminal A tumors).



Turner NC, et al. *J Clin Oncol*. 2019;37(14):1169-1178

PD 17.06: IHC and Determinants of Clinical Response in PENELOPE-B

- Knudsen, E et al
- PENELOPE-B did not show improvement with palbociclib+ ET in high-risk, early breast cancer s/p neoadjuvant chemotherapy.
- Immunohistochemical markers interrogated in samples from n= 1250 patients.
- IHC3 score = ER + PR + Ki67; CCND1; phospho-RB1; intrinsic subtypes
- Regression models used to explore impact of these variables on overall outcomes and CDKi benefit.



Knudsen et al SABCS 2022; Abstract # PD17-06

PD 17.06: IHC in PENELOPE-B

- IHC3 high ~ worse iDFS
- No correlation with CDKi
- Luminal A + IHC3 low had improved outcomes with CDKi
- IHC3 status was not predictive in Luminal B/HER2/Basal groups

Figure 2. Prognostic significance of IHC3: **(A)** Patients with IHC3 score high had a worse iDFS compared to patients with IHC3 score low (MVA HR 2.29 95%CI [1.79-2.93], p<0.0001). **(B)** IHC3 was not predictive.

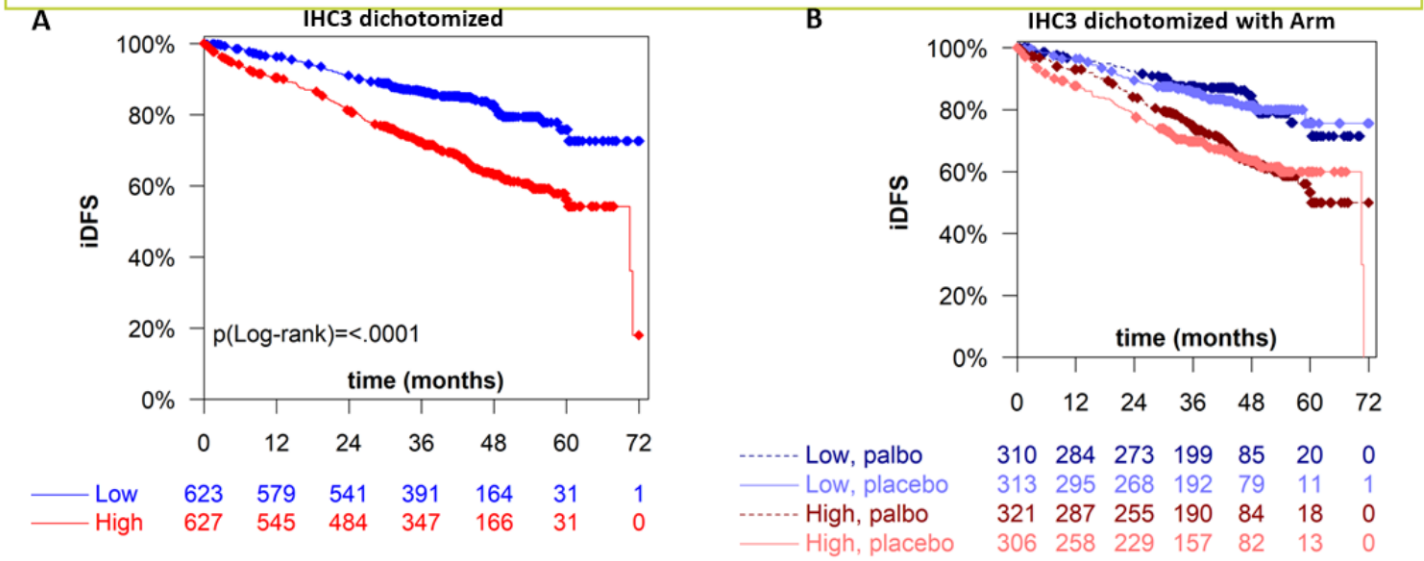
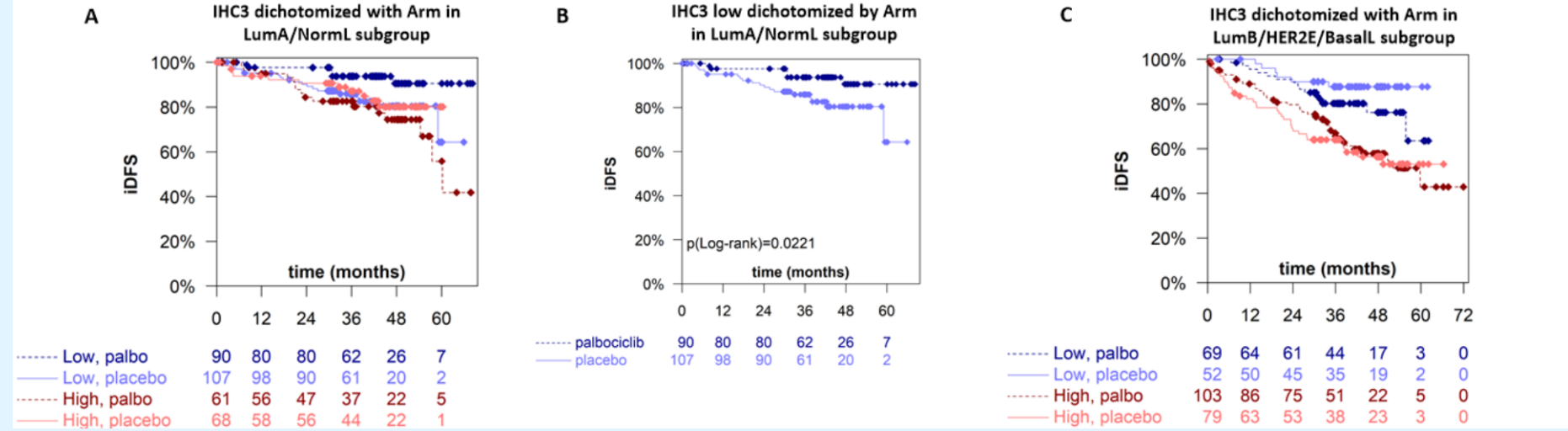


Figure 3. Predictive significance of IHC3 in luminal A/normal like tumors: **(A/B)** Patients with luminal-A/normal-like tumors (Pre-NACT AIMS) and IHC3 low had an improved iDFS with the addition of palbociclib to ET (MVA HR 0.35 95%CI (0.14-0.90), test for interaction p=0.01). **(C)** Patients with luminal-B/HER2/Basal tumors (Pre-NACT AIMS) IHC3 was not predictive.

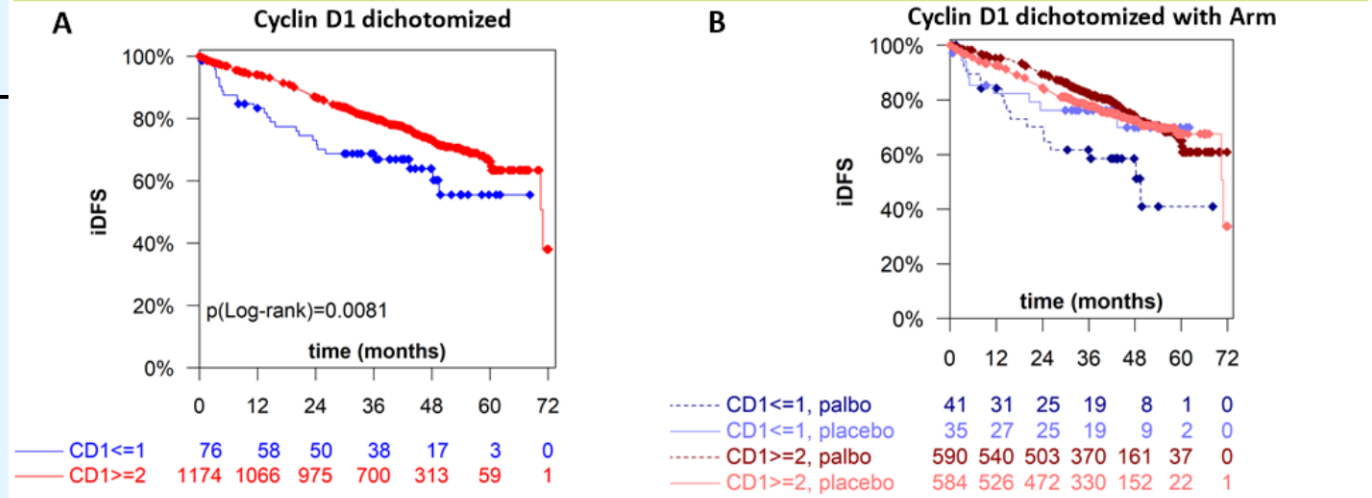


Knudsen et al SABCS 2022; Abstract # PD17-06

PD 17.06: IHC in PENELOPE-B

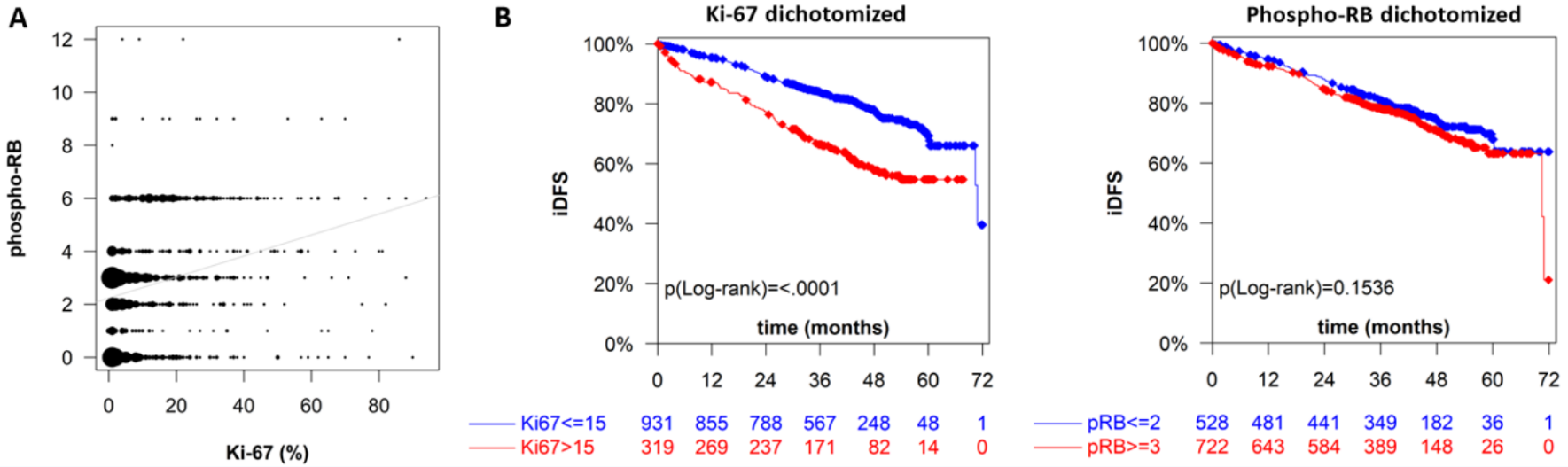
- CCND1 high ~ better iDFS
- No correlation with CDKi

Figure 4. Prognostic significance of Cyclin D1: **(A)** Cyclin D1>1 is prognostic for iDFS (MVA HR 0.62 95%CI [0.41-0.94], p=0.023), LRRFI (MVA HR 0.30 95%CI (0.15-0.63), p=0.001) and OS (MVA HR 0.50 95%CI [0.28-0.89], p=0.019). Similar results when Cyclin D1 was analysed as continuous variable (not shown). **(B)** Cyclin D1>1 has no predictive value.



- Ki67 associated with higher pRB1
- Ki67 high ~ worse iDFS
- pRB1 – no correlation to outcomes

Figure 5. Role of phospho-RB and Ki67: **(A)** Bubble chart illustrating the correlation between Ki-67 and phospho-RB from resection samples (Spearman correlation coefficient 0.324, p<0.0001). The area of each bubble is proportional to the number of patients. The gray line denotes a linear regression model. **(B)** Ki-67, but not phospho-RB is prognostic at the cut-off points employed in PenelopeB.



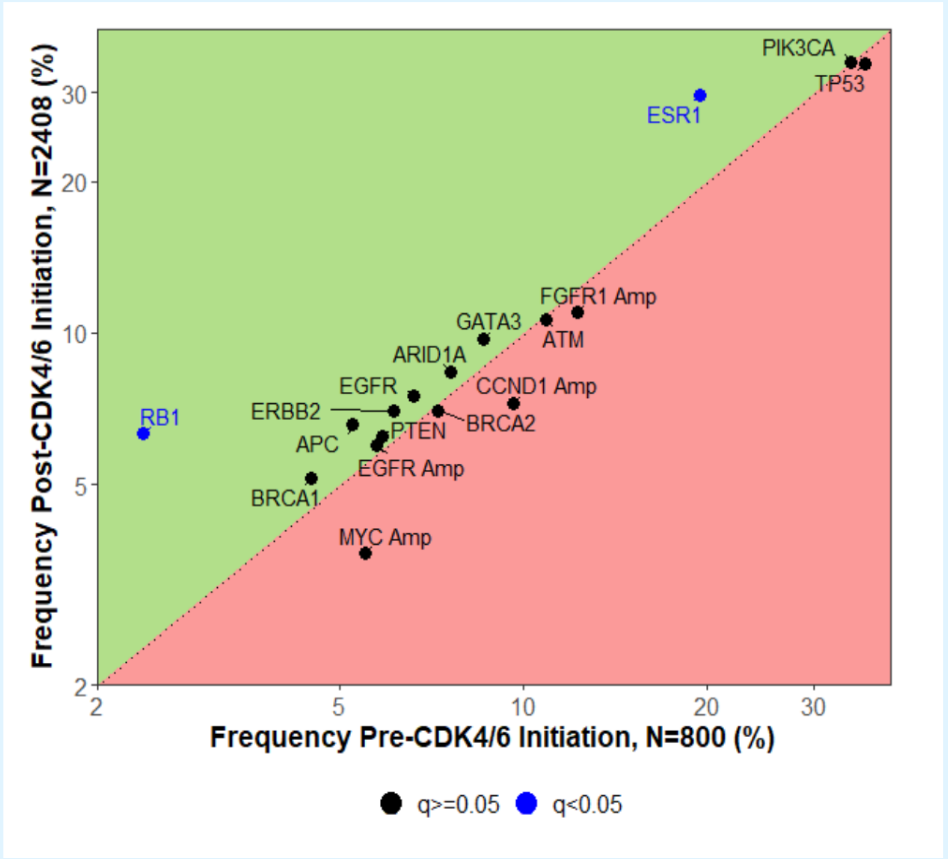
PD 17.06: IHC and Determinants of Clinical Response in PENELOPE-B

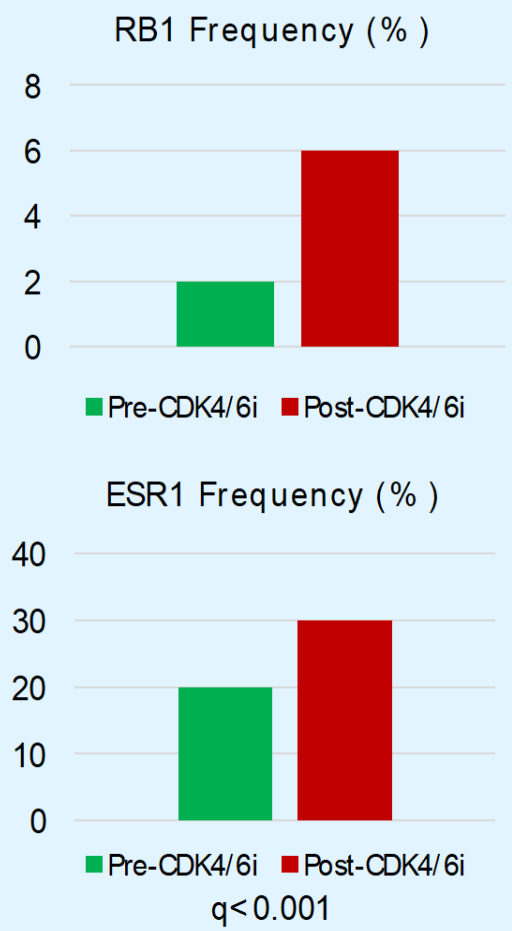
- Robust analysis of multiple IHC readouts and instrinsic tumor subtype.
- Multiple metrics correlate with overall prognosis (IHC3, Ki67, CCND1), but limited utility in predicting potential palbociclib benefit.
- IHC3-low + Luminal A high-risk early breast cancer may be a subgroup that can benefit from adjuvant palbociclib.
  - Again highlights the importance/potential of intrinsic subtype in predicting CDK4/6i benefit.
  - Validation and further exploration of this subgroup will be critical – PALLAS dataset?
- Given divergent results between PALLAS, PENELOPE-B, and MonarchE – can translational datasets guide therapy selection?

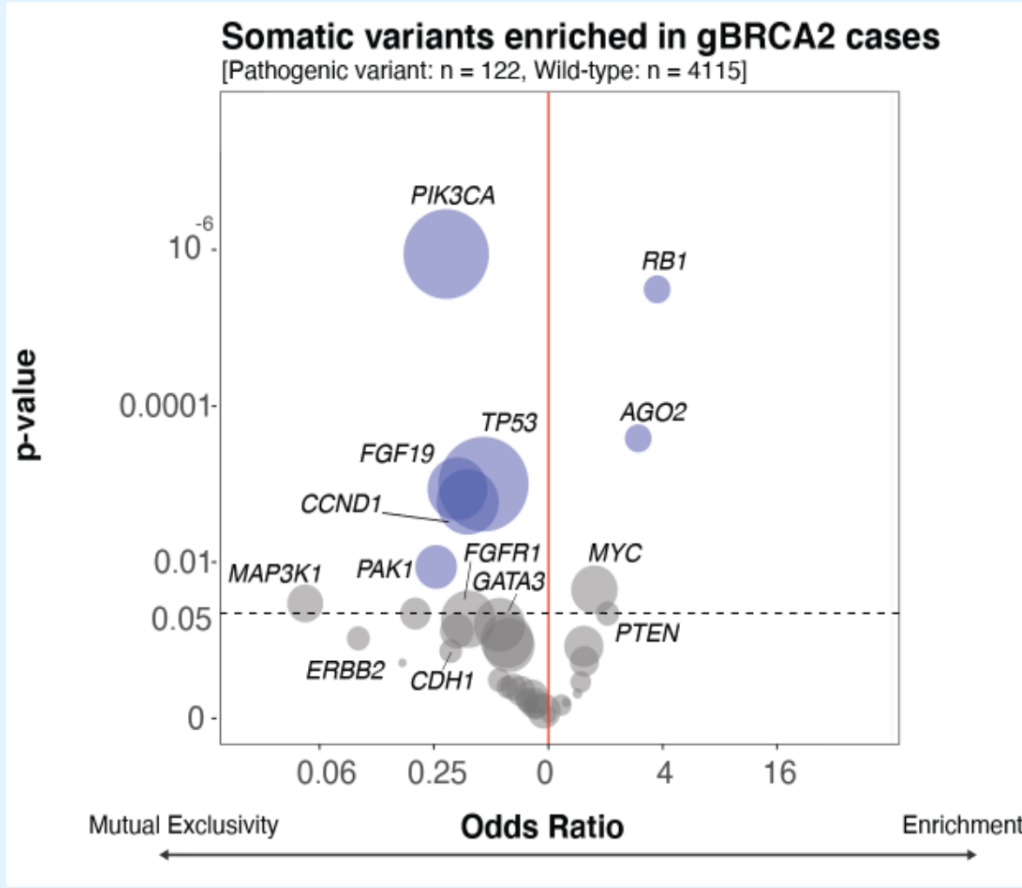
Distinct Approaches to Biomarker Discovery

- What is the optimal approach to discovery, interrogation, and validation of potential biomarkers or genomic signatures?
- Broad, unbiased analyses of large datasets to extract alterations which correlate with outcome/drug response?
- Smaller, biased assessment for previously identified targets with prior preclinical/clinical validation?
- Which data sets are optimal? Prospective large clinical trials? Real-world clinical/genomic databases? Smaller retrospective institutional cohorts?

Distinct Approaches to Biomarker Discovery - Unbiased







Safanov et al SABCS 2021
Wander SA et al ASCO 2022

Distinct Approaches to Biomarker Discovery - Biased

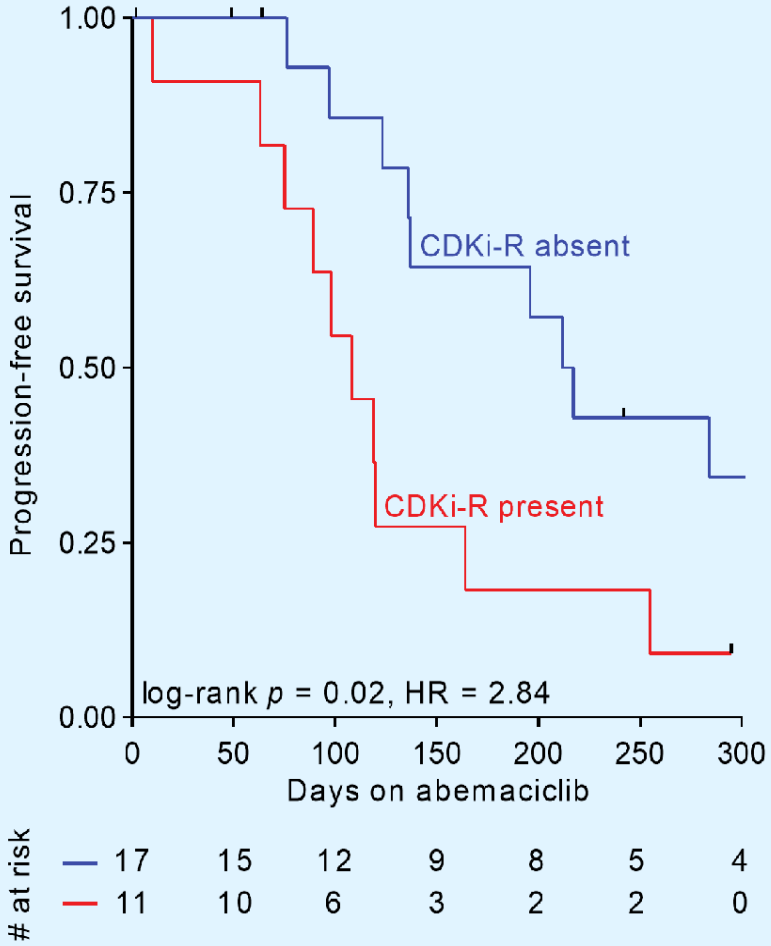


Table 1. Established CDK4/6i resistance genes.

Gene	Alteration	Patients	Cells	Xenografts
AKT1	amp, gof	Wander et al. 2020 (3)	Wander et al. 2020 (3)	
AURKA	amp	Wander et al. 2020 (3)	Wander et al. 2020 (3)	
CCNE1	amp	O'Leary et al. 2021 (32)	Herrera-Abreu et al. 2016 (23)	
CCNE2	amp	Wander et al. 2020 (3)	Wander et al. 2020 (3); Herrera-Abreu et al. 2016 (23)	
ERBB2	gof	Wander et al. 2020 (3)	Nayar et al. 2019 (8)	
FAT1	lof	Li et al. 2018 (4)	Li et al. 2018 (4)	
FGFR1	amp, gof	O'Leary et al. 2021 (32); Formisano et al. 2019 (12); Drago et al. 2019 (13)	Mao et al. 2020 (9); Mouron et al. 2021 (10); Formisano et al. 2019 (12); Drago et al. 2019 (13)	Formisano et al. 2019 (12)
FGFR2	amp, gof	Wander et al. 2020 (3); Formisano et al. 2019 (12)	Mao et al. 2020 (9)	
KRAS	gof	Wander et al. 2020 (3); Raimondi et al. 2021 (11)	Wander et al. 2020 (3)	
PTEN	lof	O'Leary et al. 2021 (32)	Costa et al. 2020 (6)	
RB1	lof	Wander et al. 2020 (3); Li et al. 2018 (4); Condorelli et al. 2018 (21); O'Leary et al. 2018 (22)	Wander et al. 2020 (3)	Herrera-Abreu et al. 2016 (23)

- Subset of ESR1m patients from a retrospective study exploring Abemaciclib utility after Palbociclib progression.
- For patients receiving Abemaciclib after Palbociclib, ESR1 mutation did not correlate with clinical benefit
- CDKi-R genes were a powerful predictor of Abemaciclib benefit in this cohort (RB1, FGFR, AKT, PTEN, FAT1, CCNE1/2, AURKA, ERBB2, KRAS)

Brett JO et al SABCS 2021; manuscript in revision

Distinct Approaches to Biomarker Discovery

Unbiased:

- Larger data sets
- Less clinical annotation/insight
- No prior bias from preclinical efforts
- Challenging to extract multiple drivers

- Potential for novel discovery

Biased:

- Smaller data sets
- Deep clinical annotation and insight
- Based upon preclinical/clinical rationale
- Ability to pool multiple genomic/molecular drivers

- More likely to succeed given prior target validation?

Abstracts today with diverse approaches – can we coordinate and consolidate findings moving forward?

ESHOS SABCS 2022 Review: Genomic Update
Summary and Future Directions

- HER2-low breast cancer does not appear to define a distinct genomic entity.
- Single cell sequencing can define distinct molecular subpopulations and provide insight into drug response in vitro (and potentially in vivo).
- Elacestrant response may be maximal in ESR1m patients with longer prior CDK4/6i response.
- Abemaciclib and palbociclib resistance may occur via distinct genomic and molecular pathways.
- Genomic profiling (and molecular phenotype) may help identify patient populations that derive benefit from adjuvant palbociclib.
- Biomarker discovery efforts need to leverage relative strengths/weaknesses of biased and unbiased approaches.