Endocrine Resistance: Emerging Mechanisms and Therapies in Metastatic ER+ Breast Cancer

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Disclosures

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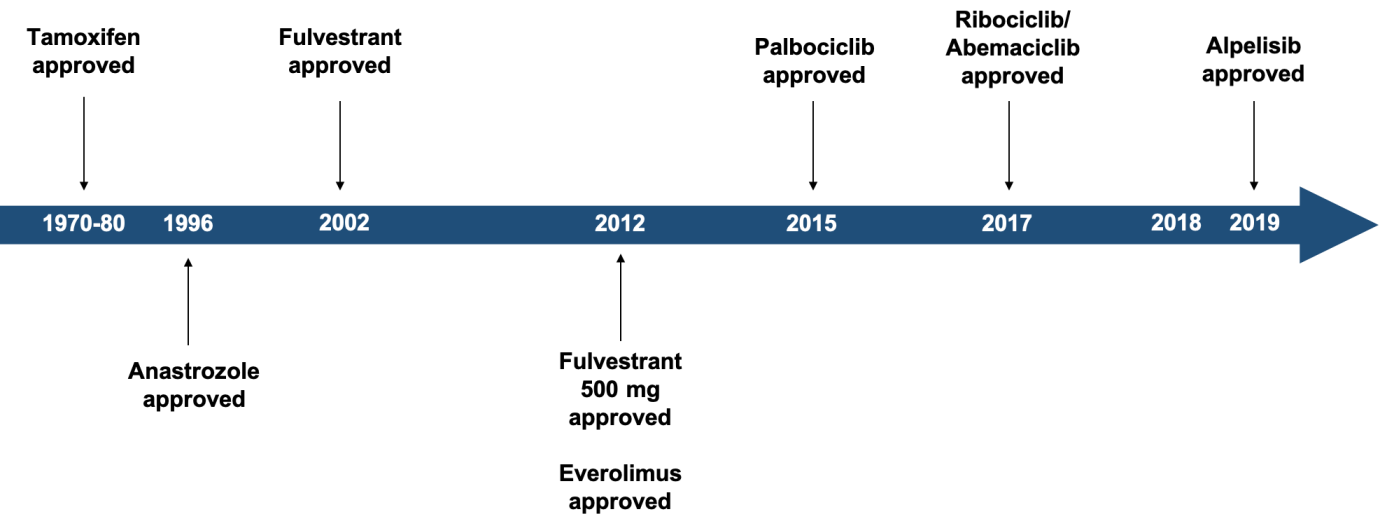
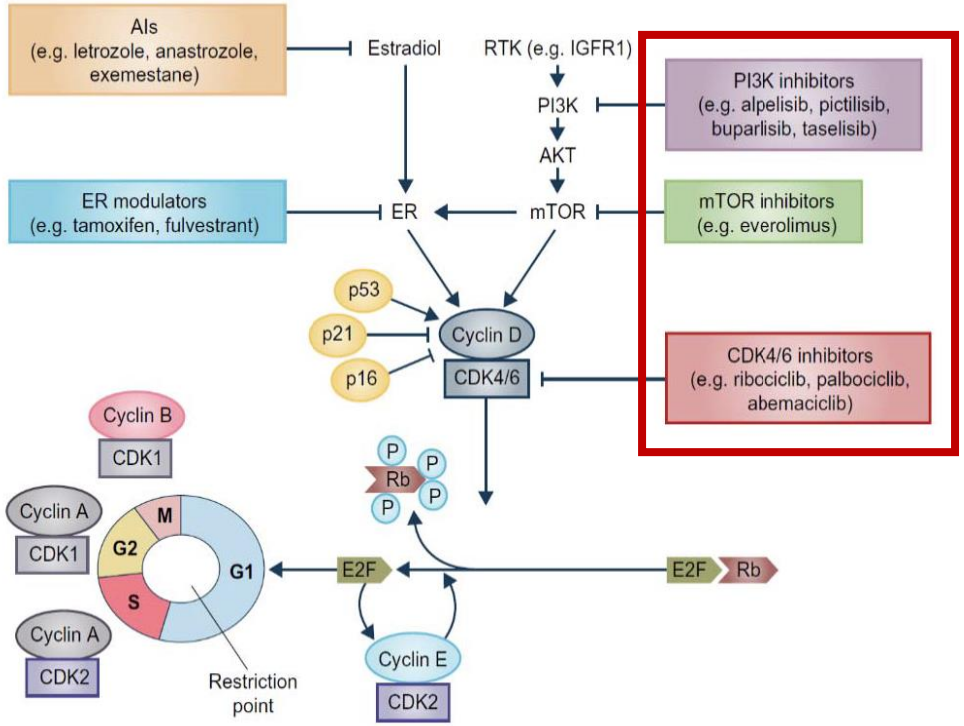
I will be discussing the off-label/investigational use of Selective Estrogen Receptor Degraders (SERDs), Neratinib, Erdafitinib, and Enobosarm.

The Landscape of HR+ MBC Treatment





References: 1. Jordan VC. Tamoxifen as the first targeted long-term adjuvant therapy for breast cancer. Endocr Relat Cancer. 2014;21(3):R235–R246. Published 2014 May 6. doi:10.1530/ERC-14-0092 2. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol. 1996;14(7):2000–2011. doi:10.1200/JCO.1996.14.7.2000 3. Morris C, Wakeling A. Fulvestrant ('Faslodex')--a new treatment option for patients progressing on prior endocrine therapy. Endocr Relat Cancer. 2002;9(4):267–276. 4. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337. doi:10.1093/jnci/djt337 5. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520–529. doi:10.1056/NEJMoa1109653 6. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373(3):209–219. doi:10.1056/NEJMoa1505270 7. Ribociclib Approved for Advanced Breast Cancer. Cancer Discov. 2017;7(5):OF3. doi:10.1158/2159-8290.CD-NB2017-043 8. FDA. FDA approves abemaciclib for HR-positive, HER2-negative breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-hr-positive-her2-negative-breast-cancer. Published September 28, 2017. Accessed July 18, 2019. 9. Hoy SM. Talazoparib: First Global Approval. Drugs. 2018;78(18):1939–1946. doi:10.1007/s40265-018-1026-z 10. 9. FDA. FDA approves alpelisib for metastatic breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer. Published May 24, 2019. Accessed July 18, 2019.

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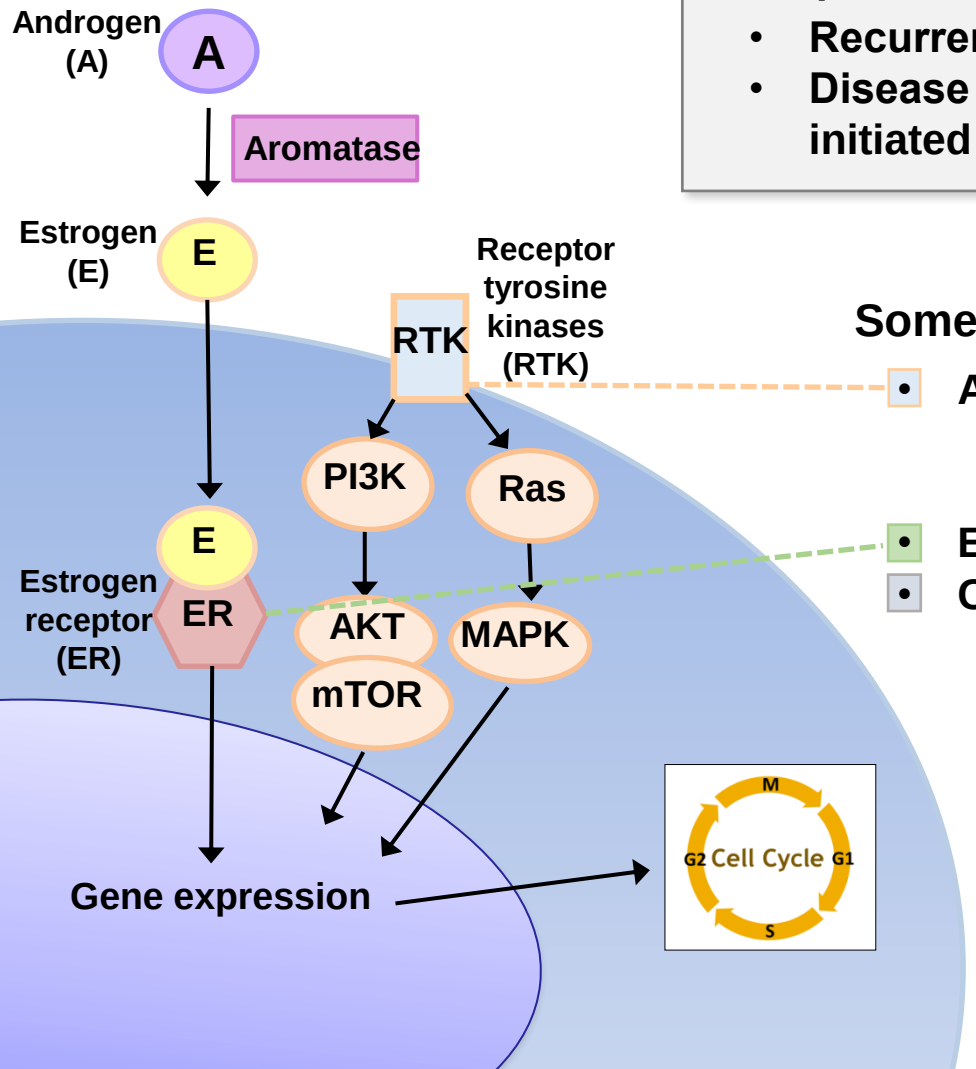
Tripathy et al., 2017

Acquired resistance to ET in HR+ BC



Acquired resistance is defined as:

- **Recurrence ≥ 2 years after initiation of adjuvant therapy**
- **Disease progression ≥ 6 months after endocrine therapy initiated in the metastatic setting**

Some ways acquired resistance may occur:

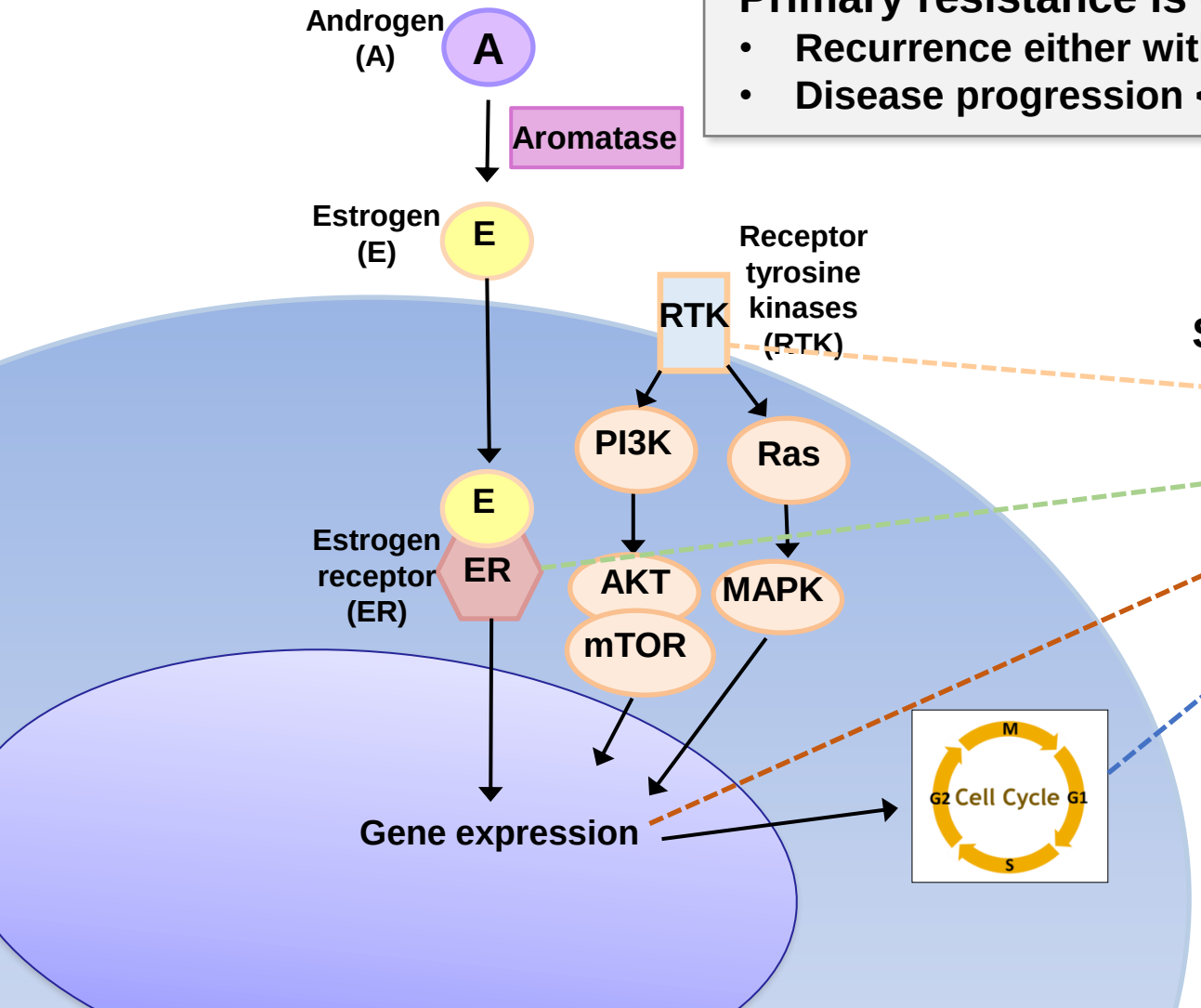
- **Activation of growth factor signaling pathways**
  - **PI3K/AKT/mTOR**
  - **MAPK/ERK**
- **ER mutations**
- **Changes in the tumor microenvironment**

Cardoso et al. Ann of Oncol 2017
Bachelot et al. JCO 2012
Bedard et al. Breast Cancer Res Treat 2008

Primary resistance to ET in HR+ BC

Primary resistance is defined as

- Recurrence either within 2 years of adjuvant therapy
- Disease progression < 6 months after treatment in the metastatic setting



Some ways primary resistance may occur:

- FGFR amplifications
- Loss of ERα
- Post-translational modification of ERα
- Expression of ER coactivation/corepression factors
- Cyclin D1 amplification or expression
- MYC amplification and overexpression

Cardoso et al. Ann of Oncol 2017
Bachelot et al. JCO 2012
Bedard et al. Breast Cancer Res Treat 2008

PFS in 1st and 2nd line treatment of HR+ MBC with CDK4/6 Inhibitors

	1st LINE TREATMENT				≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	MONALEESA-3
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control (pre-menopausal patients only)	Phase III placebo control	Phase III placebo control	Phase III placebo control
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	521	669	726
Primary Endpoint = PFS (CDK4/6 inhibitor + ET vs. ET)							
HR	0.58	0.56	0.54	0.55	0.46	0.55	0.59
Median PFS, months	24.8 vs 14.5 (10.3 mo)	25.3 vs 16 (9.3 mo)	28 vs 14.7 (13.3 mo)	23.8 vs 13 (10.8 mo)	9.5 vs 4.6 (4.9 mo)	16.4 vs 9.3 (7.1 mo)	20.5 vs 12.8 (7.7 mo)

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Cristofanilli et al, Lancet Oncology 2016; Finn et al, NEJM 2016; Hortobagyi et al, NEJM 2016; Tripathy et al, Lancet 2018; Sledge et al, JCO 2017; Goetz et al, JCO 2017; Slamon et al, JCO 2018; Llombart-Cussac et al, ASCO 2020

OS in 1st line treatment of HR+ MBC with CDK4/6 Inhibitors

	1st LINE TREATMENT			
	PALOMA-2	MONARCH-3	MONALEESA-2	MONALEESA-7
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control (pre-menopausal patients only)
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist
CDK4/6 Inhibitor	Palbociclib	Abemaciclib	Ribociclib	Ribociclib
Patients on study, n	666	493	668	672
OS (CDK4/6 inhibitor + ET vs. ET)				
HR	Not yet reported (Aug 2023?)	Not yet reported (Dec 2021?)	0.76	0.76
Median OS, months			63.9 vs 51.4	58.7 vs 40.9

Finn et al, NEJM 2016; Goetz et al, JCO 2017; Llombart-Cussac et al, ASCO 2020; Sledge et al, JAMA 2020; Hortobagyi et al, ESMO 2021

OS in 2nd line treatment of HR+ MBC with CDK4/6 inhibitors according to ET resistance

	≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT	1st LINE TREATMENT	2nd LINE TREATMENT
	PALOMA-3	MONARCH-2	MONALEESA-3	MONALEESA-3	MONALEESA-3
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control
Endocrine partner	Fulvestrant	Fulvestrant	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Abemaciclib	Ribociclib	Ribociclib	Ribociclib
Patients on study, n	521	669	726	365	361
OS (CDK4/6 inhibitor + ET vs. ET)					
Median OS, months	34.9 vs 28 (7 mo)	46.7 vs 37.3 (9 mo)	53.7 vs 41.5	NR vs 51.8	39.7 vs 33.7
HR	0.81	0.75	0.72	0.64	0.78
Primary resistance, early relapse, 2L	20.2 vs 26.2 (HR 1.14; NS)	38.7 vs 31.5 (HR 0.68)	35.6 vs 34 (HR 0.81)	___	___
Secondary resistance, sensitivity to prior therapy, 1 L	39.7 vs 29.7 (HR 0.72)	48.8 vs 40.7 (HR 0.78)	49.0 vs 41.8 (HR 0.73)	___	___

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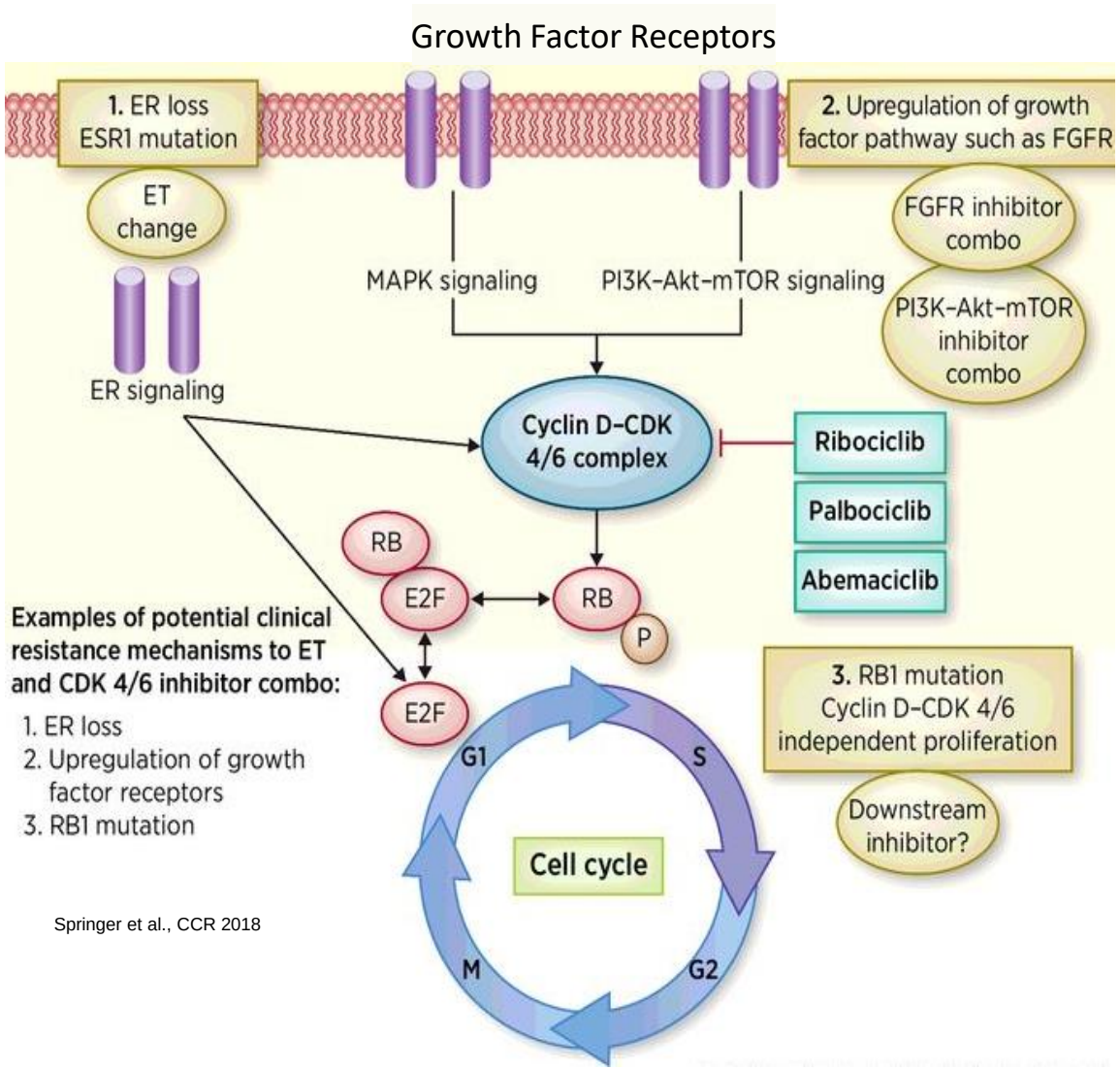
Im et al NEJM 2019 and SABCS 2020; Turner et al, NEJM 2018; Sledge et al, JAMA Oncol 2019; Slamon et al, JCO 2018 and ASCO 2021

Unanswered questions in CDK4/6i use:

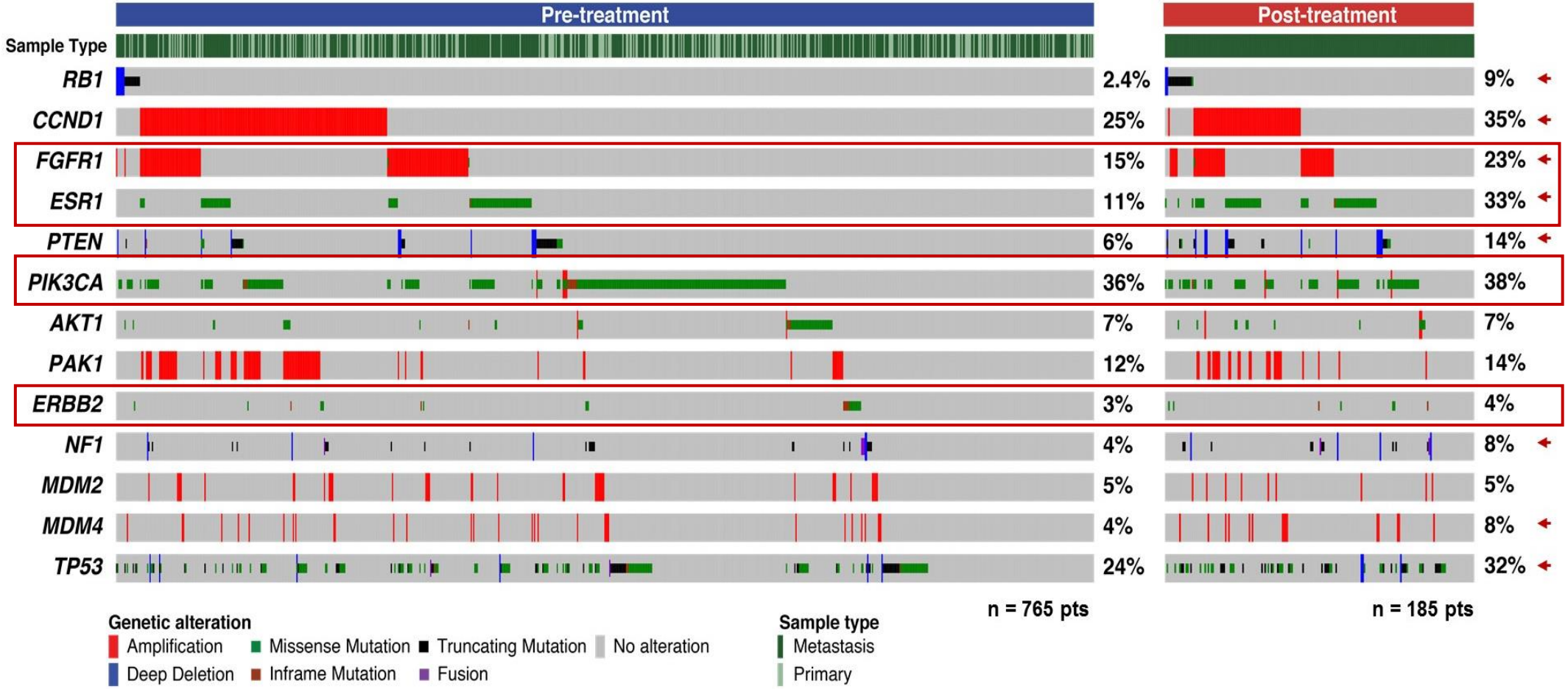
- Optimal sequencing (1st or 2nd line)?
- Biomarkers (other than ER/PR positivity) help selection of patients?
- What to do upon progression?
  - Mechanisms of resistance still under investigation
  - Several combination studies with novel agents (targeted therapies, immunotherapy, etc.) under way



Springer et al., CCR 2018

Biomarkers beyond ER/PR: Common genomic alterations in HR+ MBC

Mutations in Breast Cancer: comparison of pre- vs. post-CDK4/6i tumors



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Razavi et al, ASCO 2019

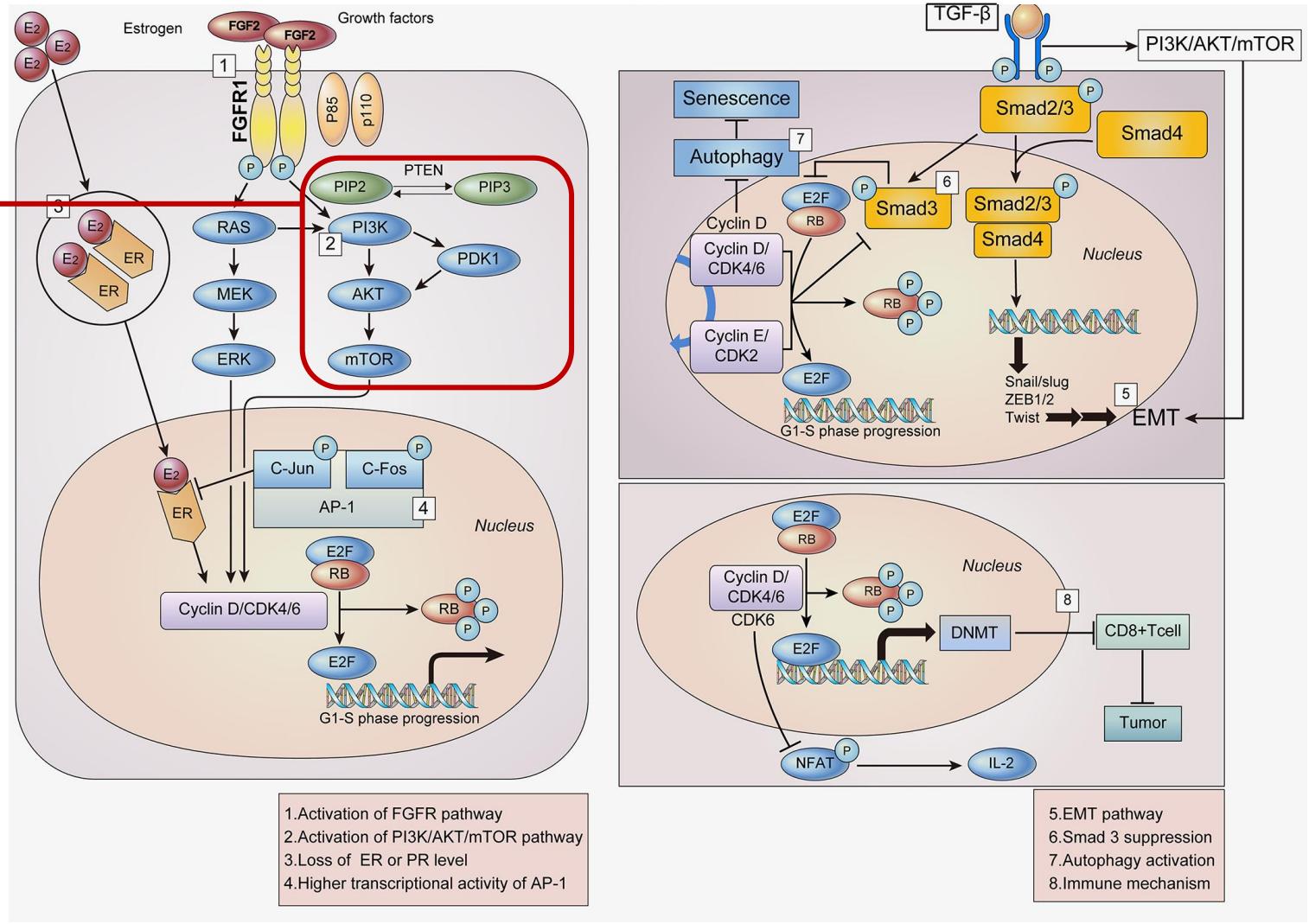
Mechanisms of resistance to ET and CDK4/6i: PI3K Pathway

Confers malignant transformation, tumor invasion, enhanced angiogenesis and survival, drug resistance

p110α oncogenic mutations:
37% Endometrial
30-40% Breast
25% Colon
13% Bladder

***PIK3CA* amplified:** 30% ovarian, lung

***PTEN* mutant/lost:**
TN breast, prostate, glioblastoma, melanoma, pancreatic, endometrial, ovarian, lung, head and neck, hepatocellular, thyroid



Pandey et al., IJC 2018

PFS and OS treatment of HR+ MBC with PI3K pathway inhibitors

	TAMRAD	HORIZON	BOLERO-2	prE102	SOLAR-1	BYLieve
Design	Phase II open label, ≥ 2nd line	Phase III placebo control, 1st line	Phase III placebo control, ≥ 2nd line	Phase II placebo control, ≥ 2nd line	Phase III placebo control, ≥ 2nd line, no prior CDK4/6i	Phase II open-label (indirectly compared to real world data) ≥ 2nd line post-CDK4/6i
Endocrine partner	Tamoxifen	Letrozole	Exemestane	Fulvestrant	Fulvestrant	Fulvestrant or Letrozole
PI3K Pathway Inhibitor	Everolimus	Temsirolimus	Everolimus	Everolimus	Alpelisib	Alpelisib
Patients on study, n	111	1112	724	131	341 with *PIK3CA*m (572 total)	127 with *PIK3CA*m
PFS (PI3K pathway inhibitor vs. control)						
Median PFS, months	8.6 vs 4.5	9 vs 8.9	7.8 vs 3.2	10.3 vs 5.1	11 vs 5.7	7.3 "vs" 3.7
HR	0.54	0.90	0.45	0.61	0.65	N/A
OS (PI3K pathway inhibitor vs. control)						
Median OS, months	Not reported	Not reported (most patients censored)	30.9 vs 26.5	28.3 vs 31.4	39.3 vs 31.4	N/A
HR	0.45	0.89	0.89	1.31	0.86	N/A

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Bachelot et al. JCO 2012; Wolff et al. JCO 2013; Baselga et al. NEJM 2012; Piccart et al. Annals of Onc 2014; Kornblum et al. JCO 2018; Andre et al. NEJM 2019; Andre et al. ESMO 2020; Rugo et al. ASCO 2020

Trials with PI3K pathways inhibitors addressing mechanisms of resistance to ET and CDK4/6i

Trial	Additional Agent/Strategy
TRINITI-1 NCT02732119	**mTOR inhibitor (Everolimus/ribociclib/ exemestane)**
PASTOR NCT02599714	**mTORC 1/2 inhibitor (Vistusertib)**
NCT02871791	**mTOR inhibitor (Everolimus/ palbociclib/ exemestane)**

Progression on CDK4/6 inhibitor and AI after ≥4 months as last therapy

- Ribociclib 300 mg/day
- Everolimus 2.5 mg/day
- Exemestane 25 mg/day

Moulder, AACR, 2018

Endpoint	Response (n=43)
Clinical Benefit	**39.5%**
Partial Response	**7%**

52% ribociclib dose reduction;
86% temporary interruption

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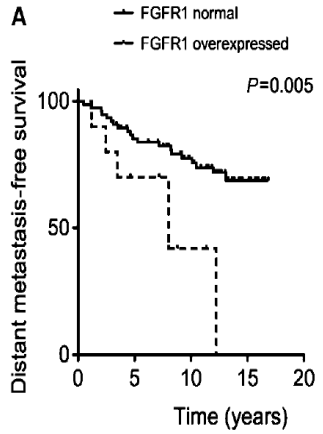
FGFR1 amplification correlates with early progression on endocrine therapy and CDK4/6 inhibition

FGFR1 amplification is an independent predictor of OS in ER+ BC treated with tamoxifen



Elbauomy Elsheiks et al. Breast Cancer Res 2003
Karlsson et al. Genes Chr Cancer 2011
Turner et al. Cancer Res 2010

MONALEESA-2 trial

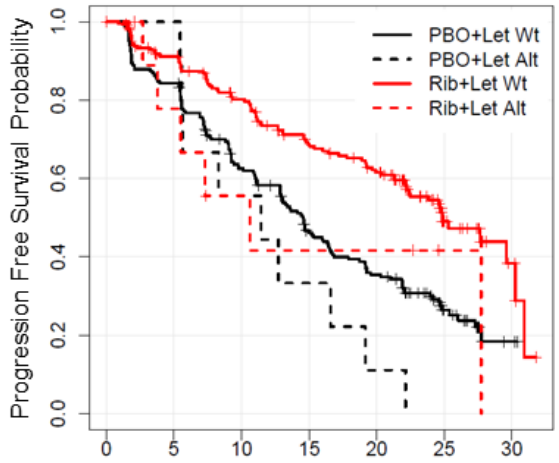
- Postmenopausal women with HR+/HER2– advanced breast cancer
- No prior therapy for advanced disease
- N = 668

Ribociclib (600 mg/day)
3 weeks on/1 week off
+
Letrozole (2.5 mg/day)
n = 334

Placebo
+
Letrozole (2.5 mg/day)
n = 334

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

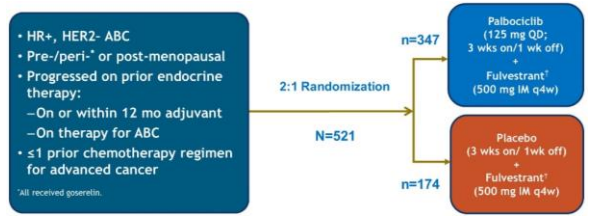
Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety



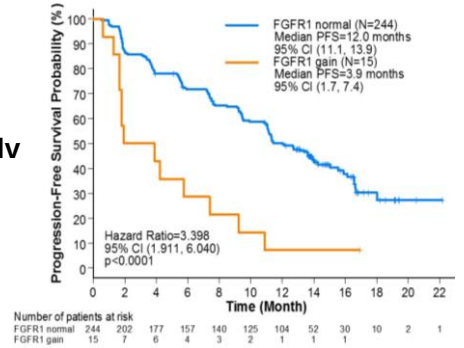
Group	*FGFR1/ZNF703* alteration	N	Median PFS	HR (95% CI)	*p*
Rib + Let	Wild-type	202	24.84	2.14 (0.93 – 4.94)	7.50e-0.2
	Amplified	**10**	**10.61**		
Plac + Let	Wild-type	205	14.59	1.61 (0.82 – 3.17)	1.70e-0.1
	Amplified	**10**	**11.43**		

Formisano et al. Nat Commun 2019

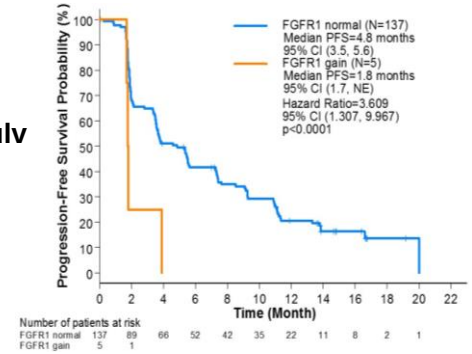
PALOMA-3 trial



Palbo + Fulv N=259



Plac + Fulv N=142



O'Leary et al ASCO 2019

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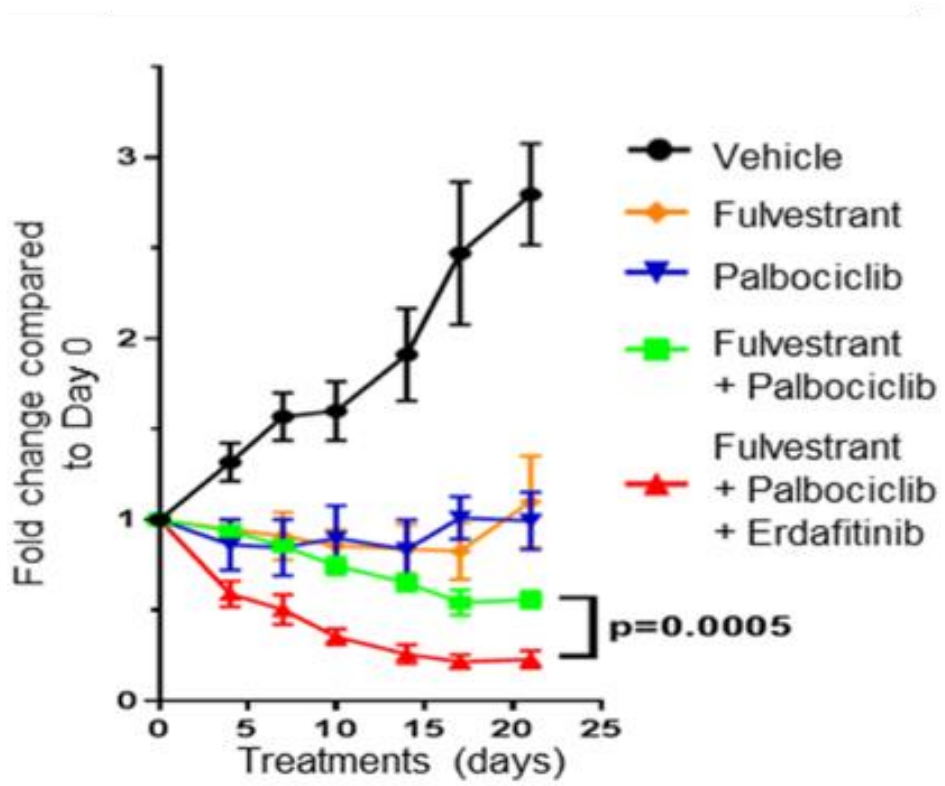
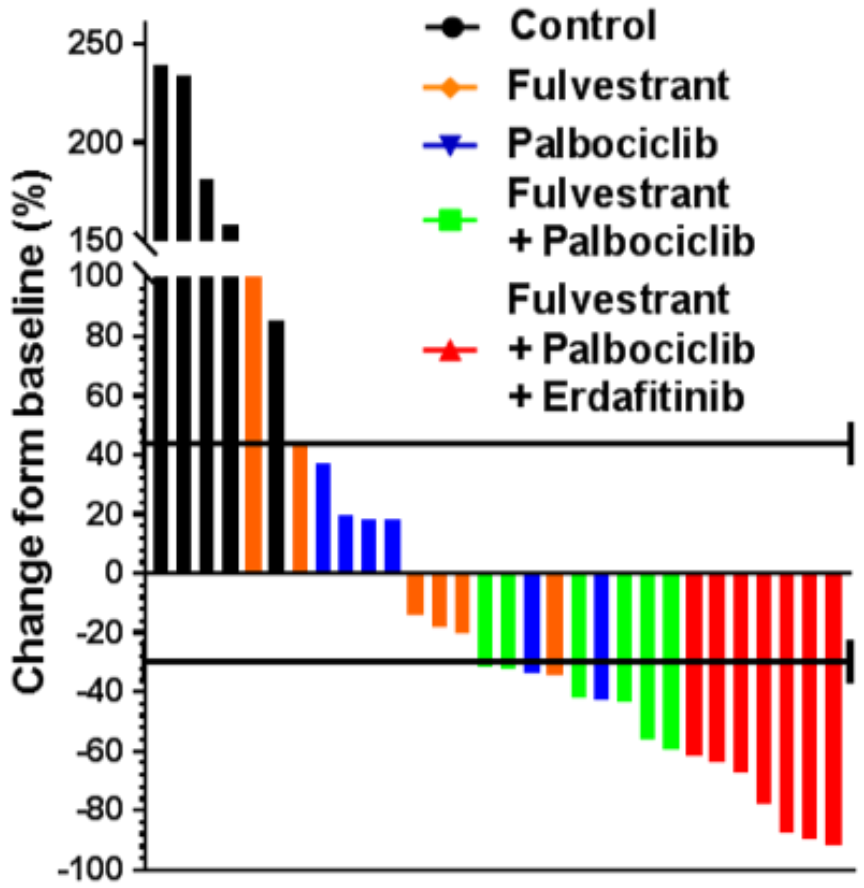
Triple therapy with fulvestrant/ palbociclib/ erdafitinib has potent activity against HR+/*FGFR1*-amplified PDXs





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Formisano et al, CCR 2017

Phase Ib/II trial of fulvestrant + CDK4/6i palbociclib + pan-FGFR TKI erdafitinib in *FGFR*-amplified/ HR+ MBC

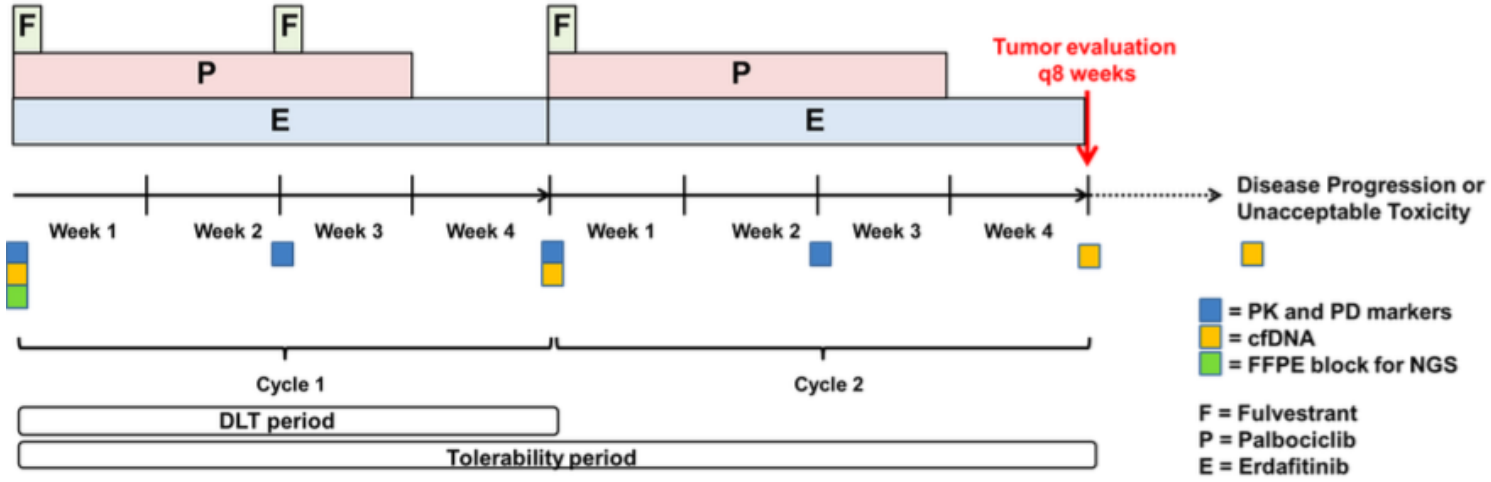
ASPIRE
Advancing Science Through Pfizer – Investigator Research Exchange

Phase Ib

Postmenopausal women with FGFR-altered/ER+/HER2– locally advanced or metastatic breast cancer that progressed on/after AI therapy
N ~ 32

FGFR inhibitor + CDK4/6 inhibitor + fulvestrant

Dose escalation: determination of MTD/ RP2D; PKs
Expansion: PD biomarkers



NCT03238196

- HR+/HER2 neg MBC
- *FGFR1 – 4* amplification
- Evaluable disease
- ≤ 2 lines chemotherapy
- Unlimited lines of ET, prior CDK4/6i allowed

1 cycle = 28 days			
Dose Level	Fulvestrant (IM q28 days)	Palbociclib (PO x 21/ 28 days)	Erdafitinib (PO daily)
1	500 mg	125 mg	6 mg
-1			5 mg
-2			4 mg

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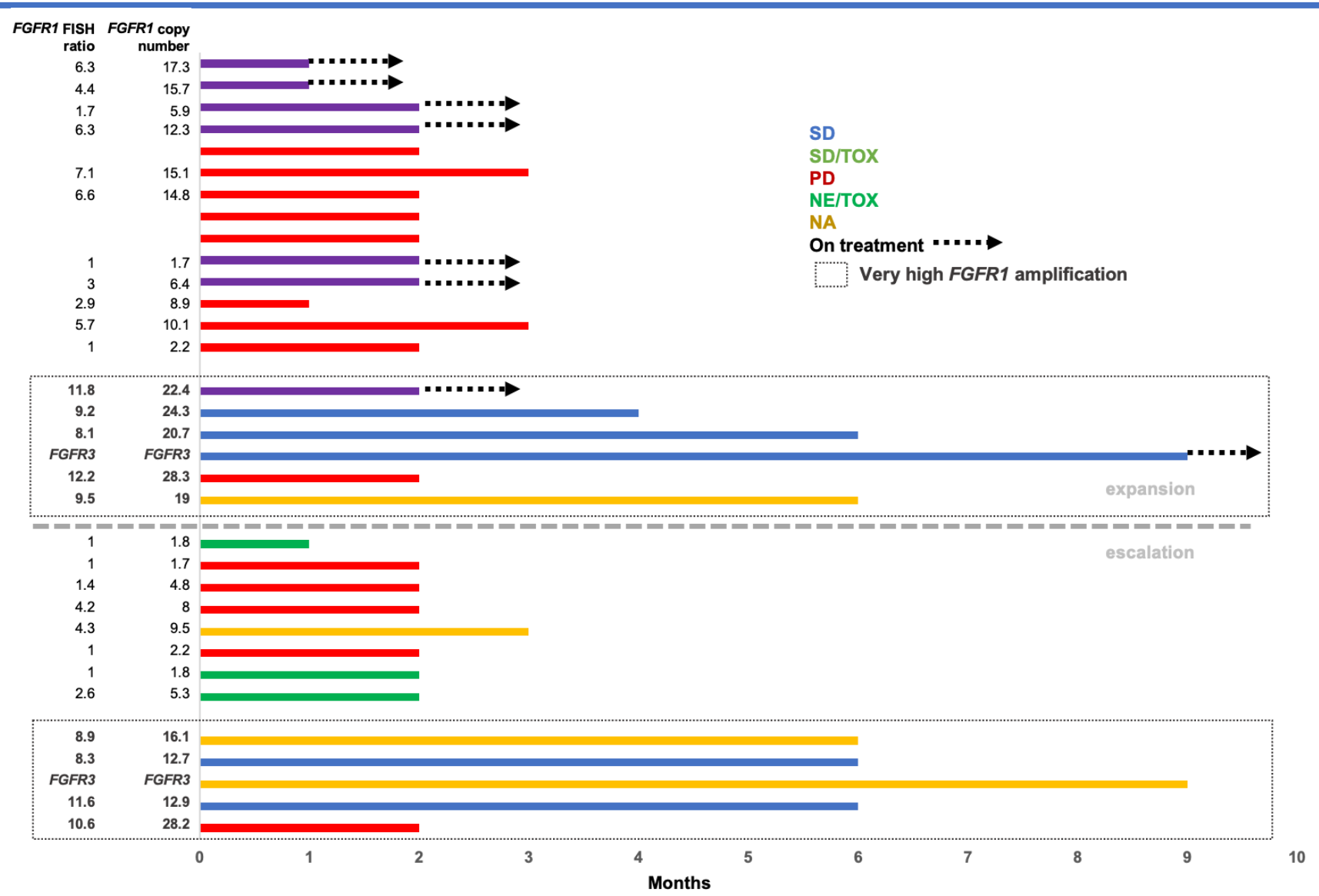
Mayer et al, SABCS 2020

Clinical outcomes based on *FGFR1* FISH amplification results



Mayer et al, SABCS 2020

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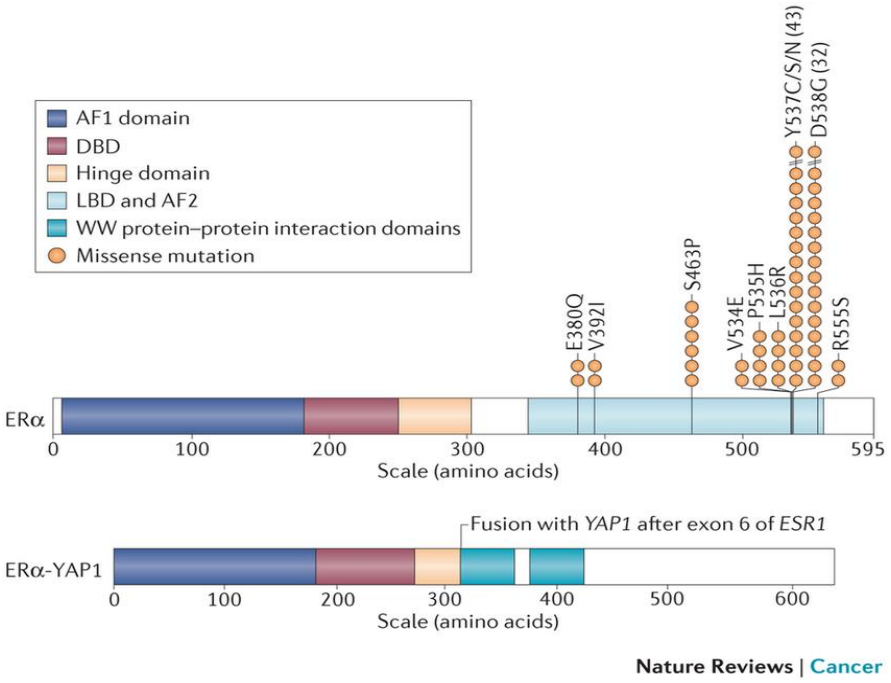
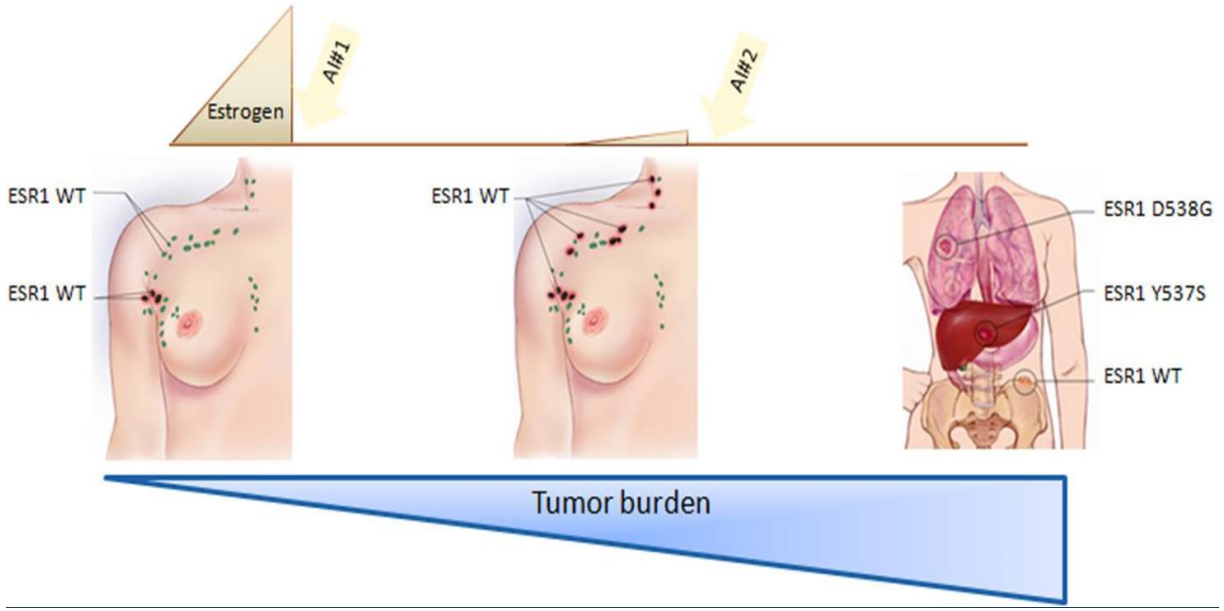
Targeting *ESR1* Mutations

***ESR1* mutants favor formation of agonist conformation of Erα, enabling ligand-independent binding of co-activators = endocrine therapy (mainly tamoxifen and AI, fulvestrant a little less) resistance**





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Turner et al., 2016; Augusto et al., 2016

Several oral SERDs in HR+ MBC

Drug	Company	Completed Trials	Ongoing Trials
GDC-9545	Genentech		Phase I dose escalation and expansion as a single agent and + palbociclib
RAD-1901/ Elacestrant	Radius	Phase 1 dose escalation and expansion Phase 1B FES-PET study	Phase III study of single agent vs TPC
AZD-9496	Astra Zeneca	Phase I dose escalation and expansion	Window pre-op study compared to fulvestrant x 1 dose accrual completed
AZD-9833	Astra Zeneca		Phase I dose escalation and expansion as a single agent and + palbociclib
SAR-439859	Sanofi	Part A presented at ASCO 2019	Phase I/II dose escalation and expansion as a single agent and + palbociclib
LSZ102	Novartis	Phase I single agent data presented at SABCS 2018	Phase I/Ib: Single agent, + ribociclib, + alpelisib
G1T48	G1 Therapeutics		Phase I: Single agent dose escalation and expansion
ZN-C5	Zeno		Phase I/II dose escalation and expansion as a single agent and + palbociclib
LY3484356	Lilly		

AMEERA-1; a phase 1/2 study of Amcenestrant (SAR439859), an oral SERD, as monotherapy and in combination with other anti-cancer therapies, in postmenopausal women with HR+ MBC

Amcenestrant **monotherapy** at an RP2D of 400 mg once daily: PK, **safety, and antitumor activity, including *post hoc* analyses by prior therapy, and *ESR1* mutational status**

Key Inclusion Criteria - **heavily pre-treated, endocrine sensitive patient population**:

- Postmenopausal women with HR+ MBC
- Measurable disease and ≥ 6 months of prior ET in the advanced setting
- ≤ 3 (Part A) or ≤ 1 (Part B) chemotherapies in the advanced setting
- Prior mTORi and ≤ 1 prior CDK4/6i based therapy allowed

Linden et al., SABCS 2020

Heavily pre-treated patient population: Safety profile

Patient demographics and baseline characteristics

Amcenestrant ≥ 150 mg QD	Pooled Population (N = 62)
Median age, years (range)	63 (37–88)
ECOG PS, n (%)	
0	37 (59.7)
1	25 (40.3)
Prior advanced lines of therapy, median (range)	2 (1–8)
≥ 3 prior lines, n (%)	30 (48.4)
Type of prior therapy in advanced setting, n (%)	
SERD	29 (46.8)
SERM	18 (29.0)
Aromatase inhibitors	59 (95.2)
mTOR inhibitors	21 (33.9)
CDK4/6 inhibitors	39 (62.9)
Chemotherapy	26 (41.9)
Number of organs involved in metastatic disease, range	1–6
Visceral metastasis, n (%)	58 (93.5)

TRAEs occurring in ≥ 5% with Amcenestrant≥ 150 mg QD

	Pooled Population (N = 62)	
TRAEs, n (%)	All Grades	Grade ≥ 3
Any class	39 (62.9)	0
Hot flush	10 (16.1)	0
Constipation	6 (9.7)	0
Arthralgia	6 (9.7)	0
Decreased appetite	5 (8.1)	0
Vomiting	5 (8.1)	0
Diarrhea	5 (8.1)	0
Nausea	5 (8.1)	0
Fatigue	4 (6.5)	0

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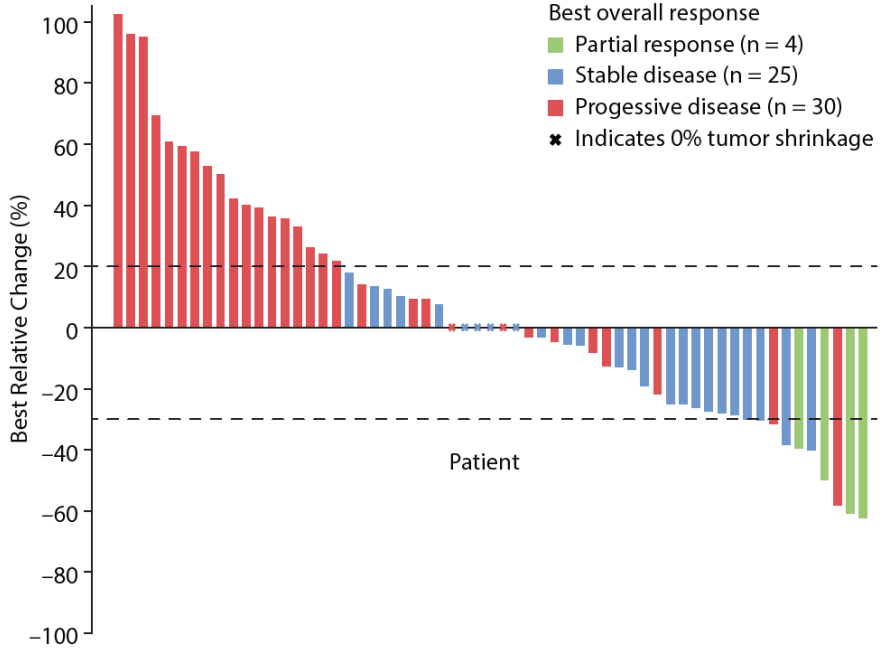
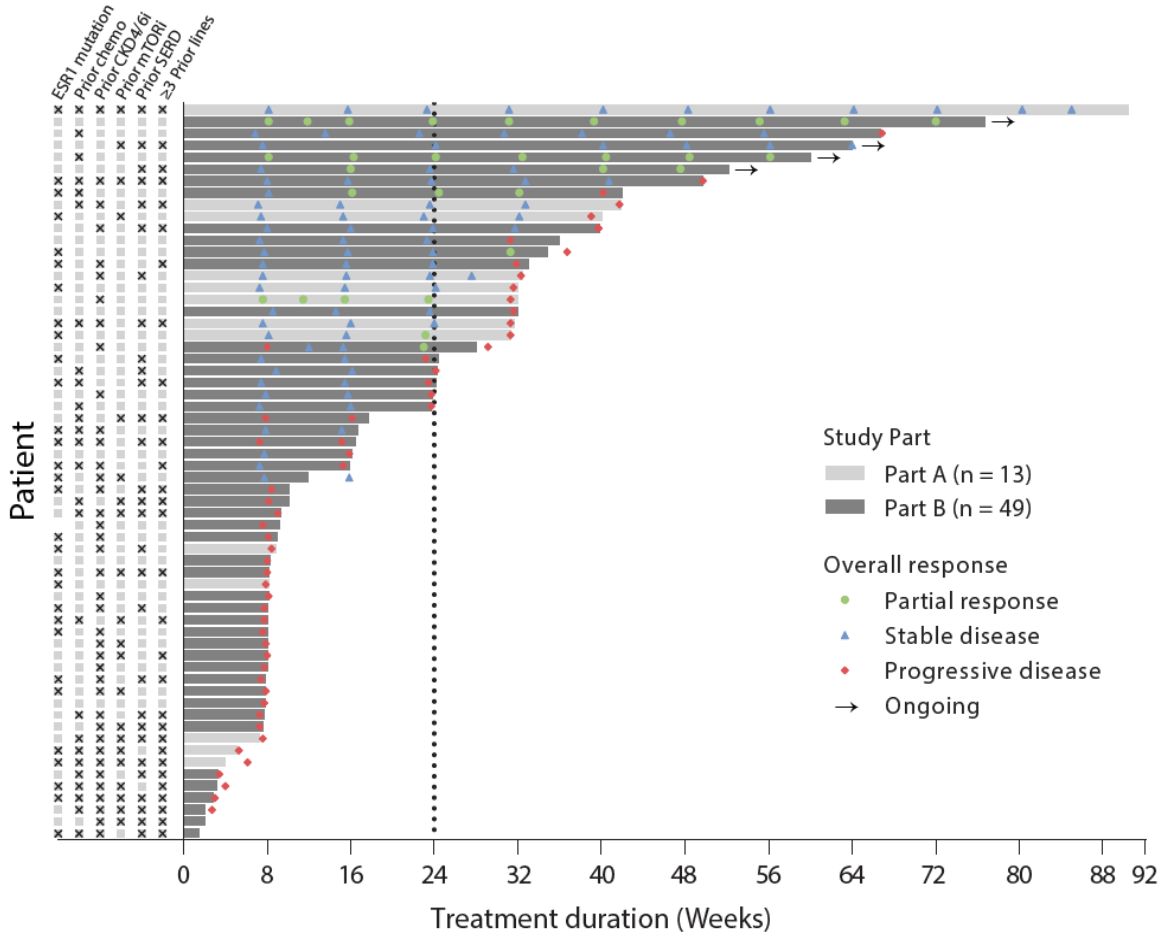
Linden et al., SABCS 2020

Response rates and duration of therapy

Response rates in evaluable patients defined by prior lines of therapy

	Pooled Population (A+B) (n = 59)	≤ 3 Prior Advanced Lines (n = 33)	Without Prior Targeted Therapy (n = 14)
Best overall response, n (%)			
CR	0	0	0
PR	5 (8.5)	5 (15.2)	3 (21.4)
SD	24 (40.7)	15 (45.5)	8 (57.1)
PD	30 (50.8)	13 (39.4)	3 (21.4)
ORR, n (%)	5 (8.5)	5 (15.2)	3 (21.4)
CBR, n (%)	20 (33.9)	14 (42.4)	9 (64.3)





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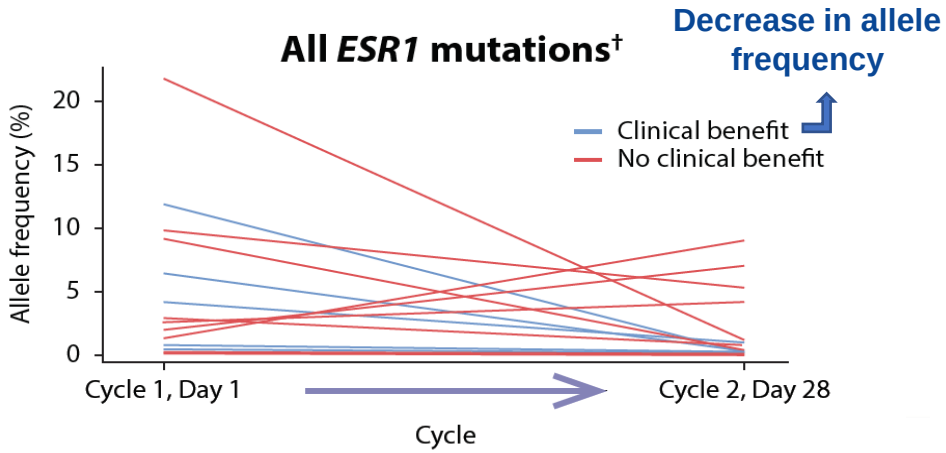
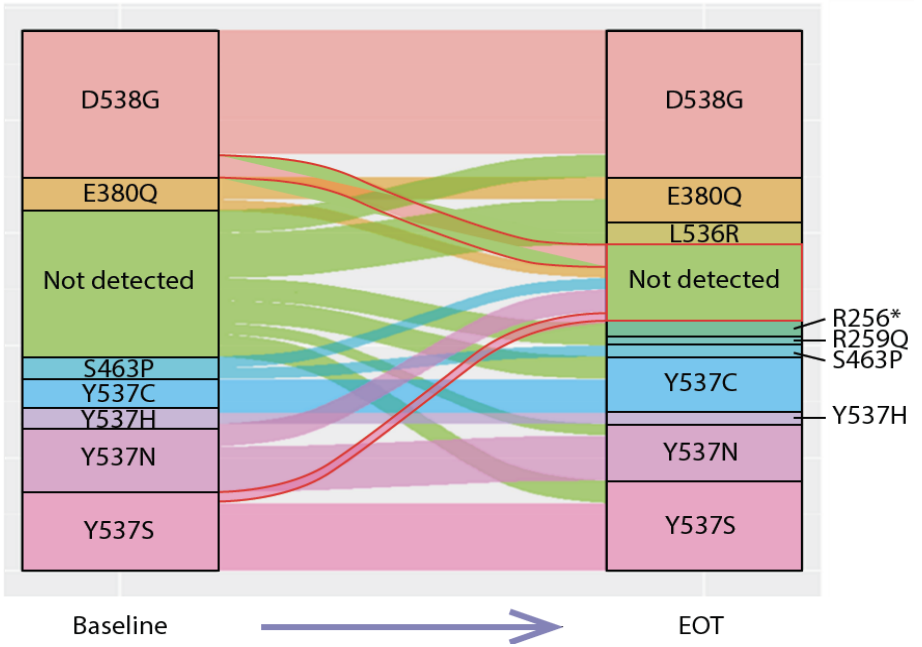
Linden et al., SABCS 2020

Clinical benefit and evolution of *ESR1* mutations in cfDNA over time

Clinical benefit (CB) rate in patients with available *ESR1* mutations at baseline

ESR1 Mutations	No CB (N = 22)	CB (N = 8)
D538G	13 (59.1%)	5 (62.5%)
E380Q	5 (22.7%)	0 (0.0%)
L536P	2 (9.1%)	0 (0.0%)
L536R	1 (4.5%)	0 (0.0%)
S463P	5 (22.7%)	1 (12.5%)
Y537C	4 (18.2%)	1 (12.5%)
Y537N	4 (18.2%)	3 (37.5%)
Y537S	4 (18.2%)	3 (37.5%)
L536H	0 (0.0%)	1 (12.5%)





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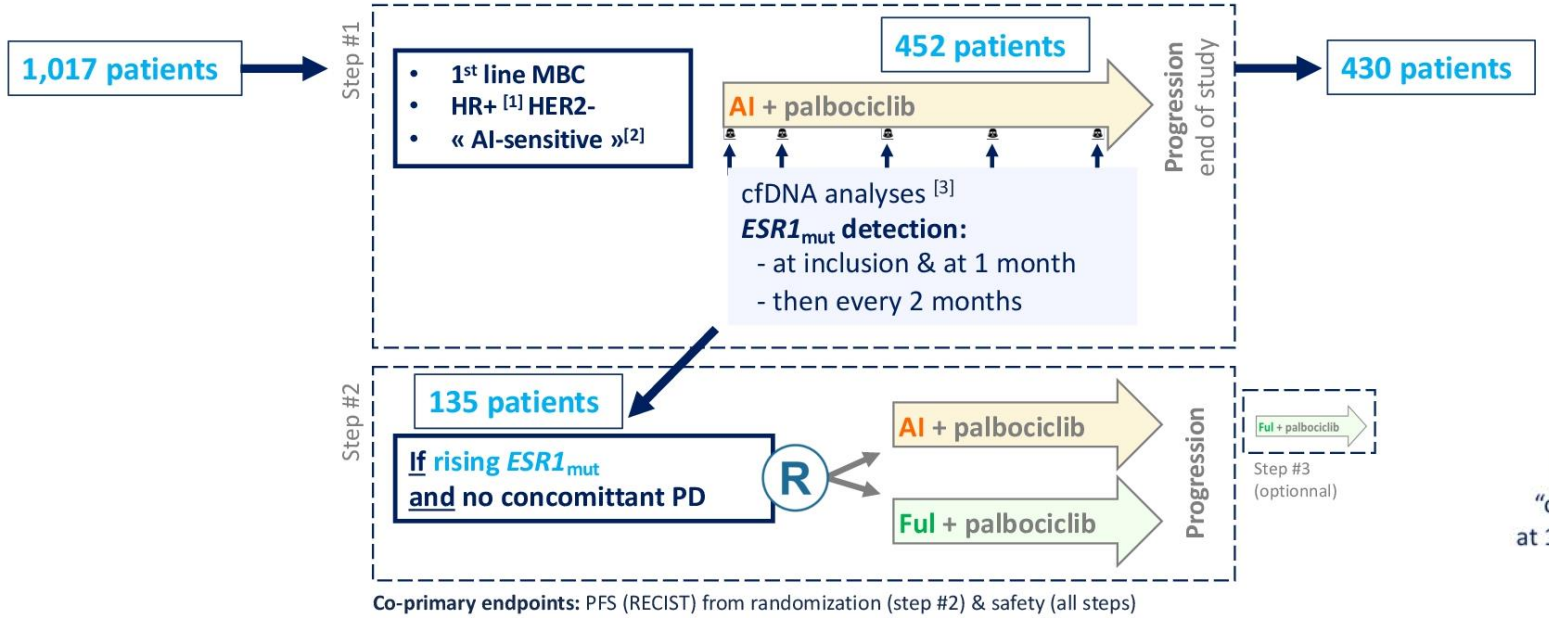
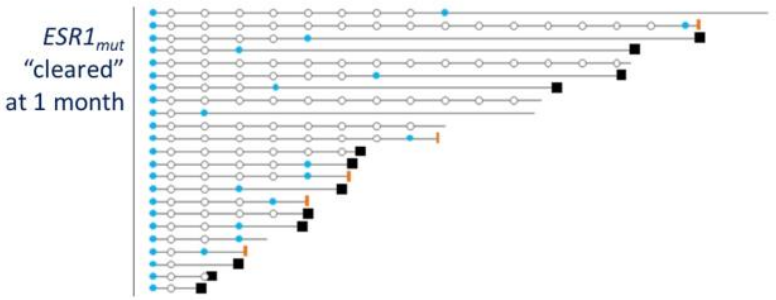
Linden et al., SABCS 2020

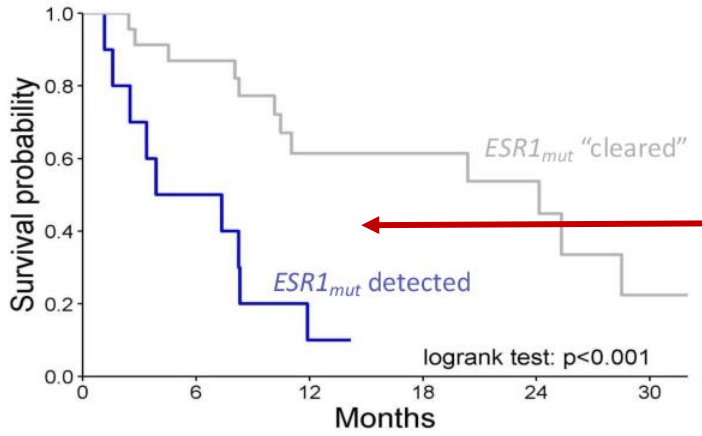
PADA-1 Study: *ESR1*mut and CDK4/6i



- Prevalence of ESR1 mutation in ctDNA at diagnosis of metastatic disease is 3.2% (33/1017)
  - 7.1% (19/267) if prior adjuvant with AI >12months ago
- "Clearance" of ESR1 mutation at 1 month in 23 of 33 patients



- **PFS to AI + Palbo:**
  - ESR_{WT}: 26.7m (N=973)
  - $ESR1_{mut}$ with clearance at 1 month: 24.1m (N=23)
  - Persistent $ESR1_{mut}$: 7.4m (N=10)



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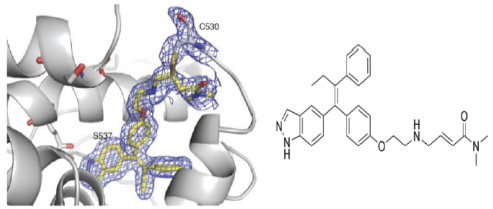
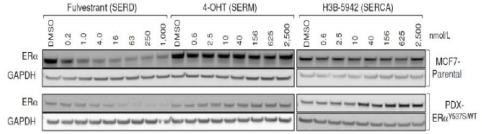
Wagle et al, ASCO 2020

Selective ER covalent antagonists (SERCAs) for the treatment of ERαwt and ERαmut breast CA

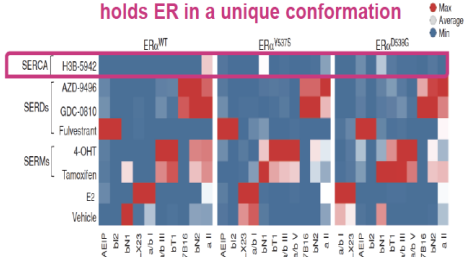
H3B-5942 engages C530 on ER wt and mutant



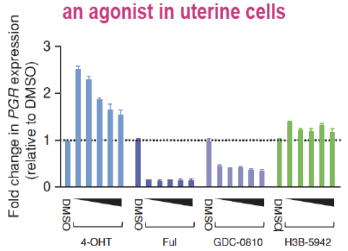
H3B-5942 is a non-degrader and stabilizes ER similar to tamoxifen



Conformation selective peptide probes shows H3B-5942 holds ER in a unique conformation



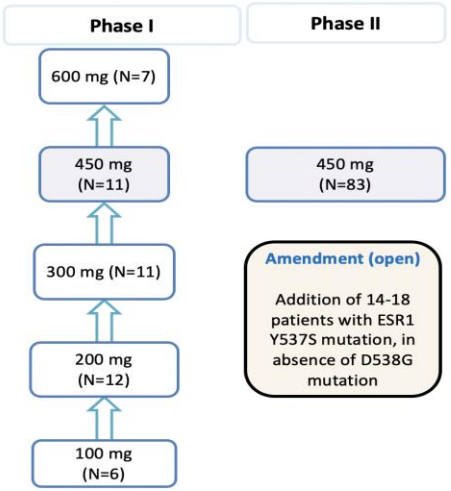
Unlike tamoxifen, H3B-5942 is not an agonist in uterine cells



Following medicinal chemistry optimization in this indazole series, H3B-6545 was discovered. H3B-6545 binds covalently to a cysteine residue at position 530 of both wild-type and the constitutively active mutant ERα proteins, including Y537S and D538G

***In vivo*, H3B-6545 demonstrated significant single agent anti-tumor activity in xenograft mouse models representing $ERα^{WT}$ and $ERα^{Y537S}$ breast cancer** (Smith et al. AACR 2017) **and in PDX breast cancer models including *ESR1*mut** (Korpal et al. SABCS 2017)

Phase I-II of oral H3B-6545 monotherapy trial



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Best Overall Response

Response	450 mg, N=72 n (%)
Complete response	0
Confirmed partial response	12 (17)
Stable disease	31 (43)
Progressive disease	27 (38)
Not evaluable	2 (3)
ORR (%) (95% confidence interval)[2]	17 (9, 27)
Median duration of response (mo) (min, max)	7.5 (3.5, 16.6)
Median time to response (mo) (min, max)	2.7 (1.6, 5.5)
Clinical benefit rate (CR + PR + SD≥23 weeks)	29 (40)

Best Overall Response by *ESR1* Subtype

Response	Clonal Y537S (N=10) n (%)	Clonal D538G (N=17) n (%)	Clonal Y537S or Clonal D538G (N=27) n (%)	Polyclonal Y537S and D538G (N=2) n (%)	Y537S and D538G Negatives (N=43) n (%)
Complete response	0	0	0	0	0
Confirmed partial response	3 (30)	0	3 (11)	0	9 (21)
Stable disease	4 (40)	10 (59)	14 (52)	1 (50)	16 (37)
Progressive disease	3 (30)	7 (41)	10 (37)	1 (50)	16 (37)
Not evaluable	0	0	0	0	2 (5)
Clinical benefit rate	6 (60)	6 (35)	12 (44)	1 (50)	16 (37)
Median PFS (mo)	7.3	5.4	5.4	3.5	3.8

Puyang et al., Cancer Disc 2018; Hamilton et al. ASCO 2021

Targeting *ESR1* Mutations with novel SERDs/ SERCAs

Several novel SERDs (e.g. rintodestrant; amcenestrant) and SERCAs (e.g. H3B-6545) are currently in clinical development with desirable clinical properties:

- **Oral** ✓
- **Good safety profile** ✓
- **Effective against *ESR1*mut and *ESR1*wt HR+ MBC** ✓
- **Better than fulvestrant ❓ Ongoing head-to-head comparisons with several SERDs**
- **Partner well with CDK4/6 and PI3K pathway inhibitors ❓**

Ongoing trials with expansion cohort combinations – could it circumvent resistance mechanisms such as *CCND1* variants?

***ESR1* mutation clearance in cfDNA: a new surrogate marker for ET +/- targeted therapy benefit?**

Androgen receptor (AR) in HR+ MBC

AR positivity (present in 70-95% of HR+ BC), but its role in HR+ BC depends on the tumor microenvironment as well as the relative levels of circulating estrogens and androgens

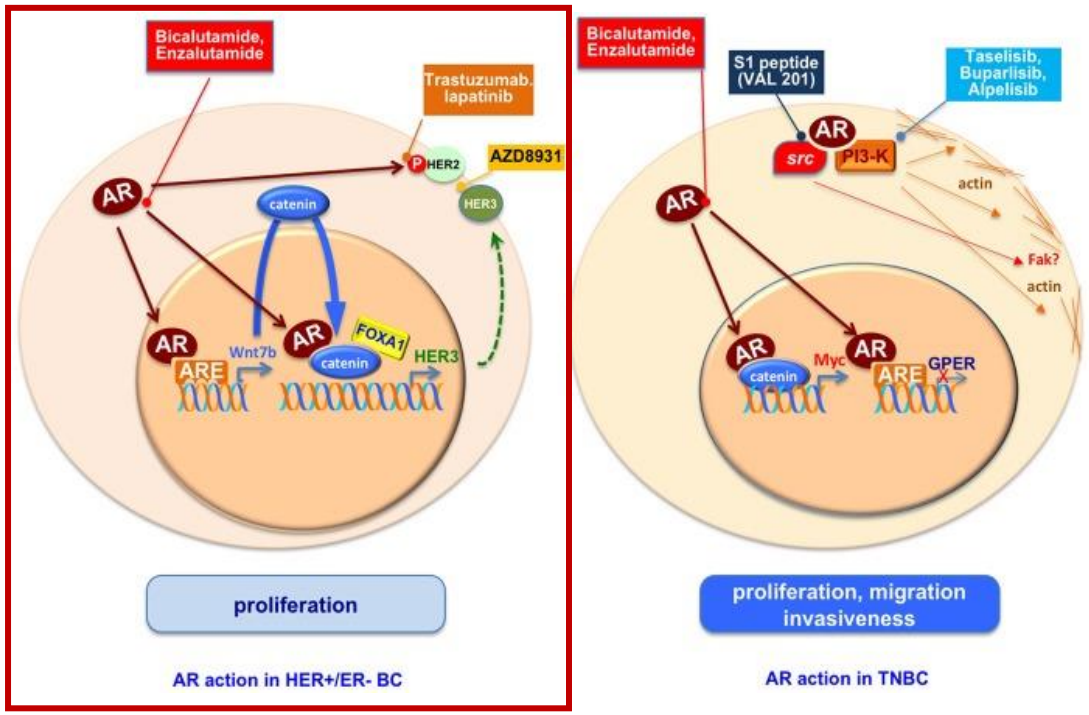
↓

AR expression is often associated with a favorable prognosis in HR+ BC, <u>but</u> many findings suggest that, in some instances, high levels of AR can contribute to the therapy-resistance

AR stimulates <u>or</u> inhibits cellular proliferation; promotes metastatization and resistence to therapies in <u>HR+ BC cells</u>

↓

These opposing actions in HR+ BC depend on the multitude of proteins interacting with AR!!



Giovanelli et al Front Endocrinol 2018
Michmerhuizen et al NPJ Breast Cancer 2020

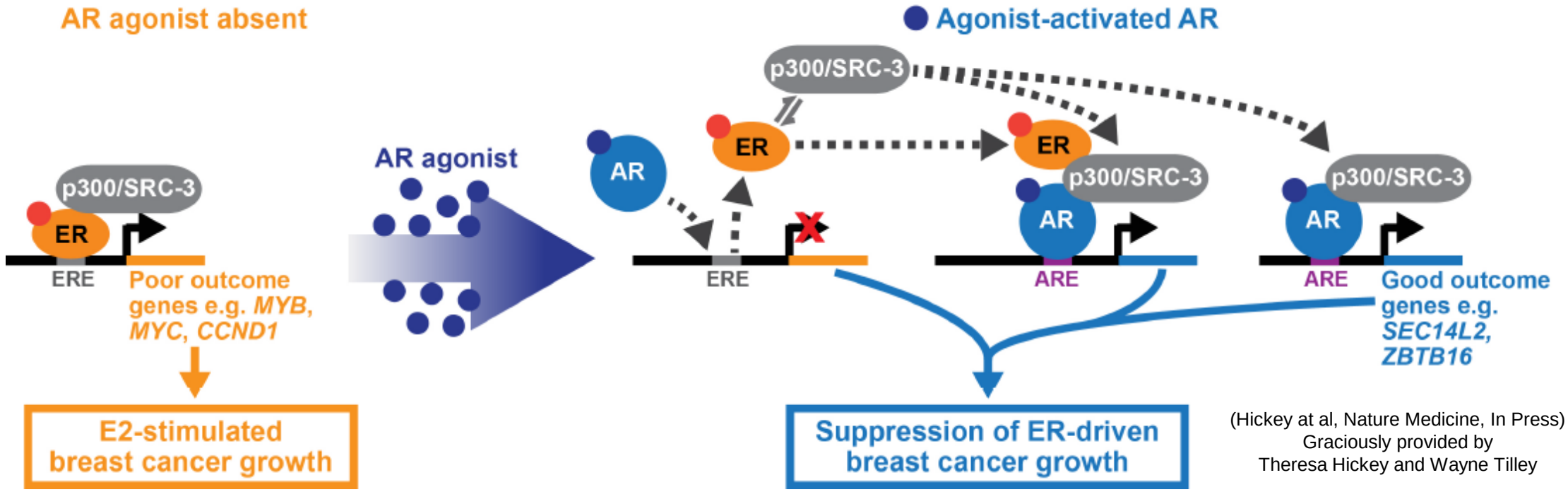
Selected trials targeting (blocking) AR in HR+ MBC

NCT number	Title	Arms	N	Clinical outcome		
NCT 02910050 Phase II	Bicalutamide plus aromatase inhibitors in ER+/AR+ MBC	Bicalutamide + AI	58	CBR (6 months): 16.7% SD: 3 pts (17%) PD: 15 pts (83%) PFS: 2.7 months (95% CI: 2.2–3.8 months)		
NCT 01597193 Phase I	Safety study of enzalutamide (MDV3100) in patients with MBC	Enzalutamide ± AI/SERD	101	MTD not yet reported. 160 mg enzalutamide: 22 patients, 3 AE 160 mg enzalutamide + 1 mg anastrozole: 20 patients, 1 AE 160 mg enzalutamide + 50 mg exemestane: 23 patients, 3 AEs 160 mg enzalutamide + 500 mg fulvestrant: 11 patients, 2 AEs		
NCT 02007512 Phase II	Efficacy and safety study of enzalutamide in combination with exemestane in patients with MBC	Enzalutamide +Exemestane vs. Placebo+ Exemestane	247	Without prior ET	Enzalutamide + Exemestane: PFS (ITT): 11.8 months (7.3–15.9) PFS (DX+): 16.5 months (11.0-NA) Exemestane: PFS (ITT): 5.8 months (3.5–10.9); PFS (DX+): 4.3 months (1.9–10.9)	Enzalutamide + Exemestane: CBR 24 weeks: 62% (49–74%) best objective response rate: 31% (17–48%) Exemestane: CBR 24 weeks: 45% (33–58%); best objective response rate: 19% (9–34%)
				With prior ET	Enzalutamide + Exemestane: PFS (ITT): 3.6 months (1.9–5.5) PFS (DX+): 6.0 months (2.3–26.7) Exemestane: PFS (ITT): 3.9 months (2.6–5.4); PFS (DX+): 5.3 months (1.8–6.7)	Enzalutamide + Exemestane: CBR 24 weeks: 20% (11–32%); best objective response rate: 10% (3–23%) Exemestane: CBR 24 weeks: 32% (20–45%); best objective response rate: 5% (0.6–16%)
NCT 01808040 Phase Ib	A Phase 1b study of TAK-700 in postmenopausal women with HR+ MBC	Orteronel	8	MTD not yet reported. Dose level 1: 300 mg (4 pts, 1 not evaluated) Dose level 2: 400 mg (3 pts) 1 patient with SD > 6 months 1 patient with SD for 3 months		

AR agonists as target for the treatment of HR+ MBC

AR agonists inhibit HR+ BC growth (pre-clinical data)

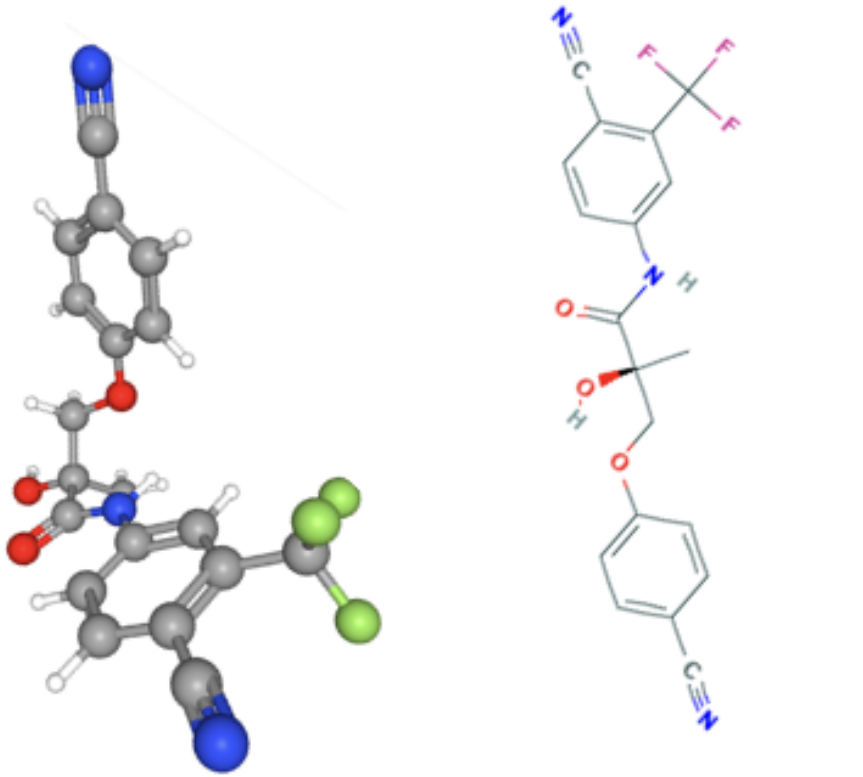
Model depicting the AR-mediated inhibition of ER function associated with anti-tumor activity



(Hickey at al, Nature Medicine, In Press)
Graciously provided by
Theresa Hickey and Wayne Tilley

[1]Birrell et al, J Steroid Biochem Mol Biol 52:459-67, 1995 | [2]Peters et al, Cancer Res 69: 6131-40, 2009 |[3]Hickey et al, Nature Medicine (In Press) | [4]Moinfar et al, Cancer 98:703–11, 2003 |[5]Hu et al, Clin Cancer Res 17:1867–74, 2011| [6]Ricciardelli et al, Clin Cancer Res 24:2328-41, 2018 |[7]Bronte et al, Transl Oncol 11: 950–956, 2018

Phase II trial of Enobosarm, a selective androgen receptor agonist, to target AR in women with advanced AR+/ER+ breast cancer



Chemical structure of Enobosarm

Enobosarm is a non-steroidal, selective androgen receptor agonist that inhibits AR+HR+ BC in cell lines/ PDX models of ET sensitive and resistant disease

- **Not a substrate for aromatase**
- **Anabolic on muscle; builds and heals bone**
- **Selective tissue activity (non-virilizing, no liver tox, no polycythemia)**
- **Extensive nonclinical and clinical package as it as been evaluated in 27 clinical trials in a total of 2,159 subjects (348 subjects dosed at ≥ 9mg)**

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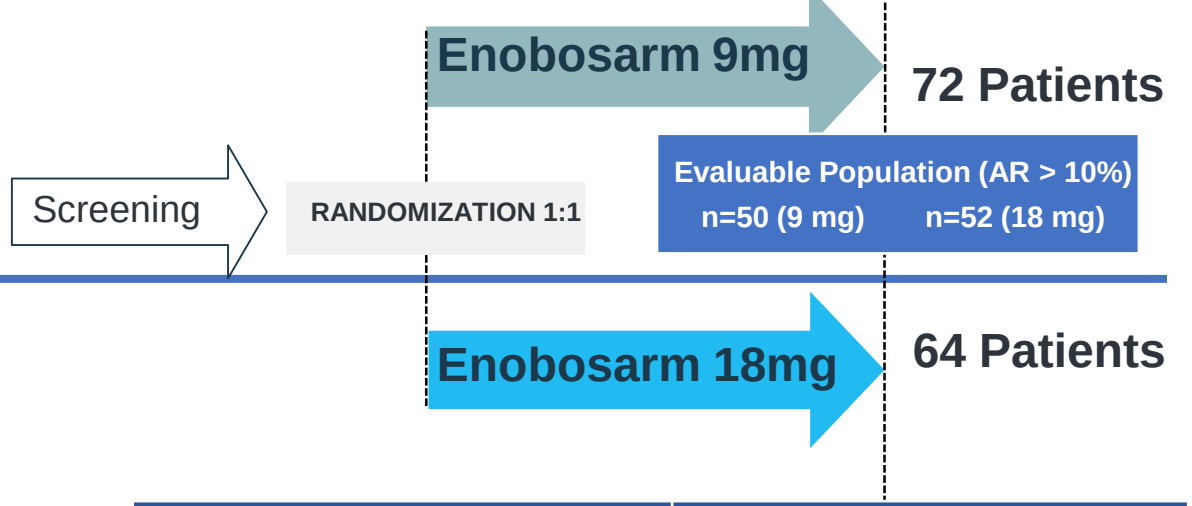
[1] Narayanan R et al. Mol Cell Endocrinol 2017|[2] Dalton JT et al. Curr Opin Support Palliat Care 7:345-351, 2013|[3]Kamrakova M et al Calcif Tissue Int 106:147-157,2020|[4] Hoffman DB et al. J Bone Metaab 37:243-255, 2019|[5] KearbeyJD et al Pharm Res 26:2471-2477, 2009| [6]Dobs AS et al. Lancet Oncol 14:335-45, 2013|[7]Hickey et al., Nature Medicine, in press. [8]Palmieri et al., SABCS 2020

Phase 2 (open label) clinical trial (G200802): aims to assess the efficacy (**CBR 1^{ary} endpoint**) and safety of Enobosarm 9 mg or 18 mg oral daily dose in a **heavily pretreated population of AR+(> 10%)/ ER+ MBC** patients who previously responded to endocrine treatment (adjuvant ET for ≥3 years, or most recent ET for MBC ≥ 6 months)



Demographics	9 mg cohort	18 mg cohort
Age (median), years (range)	60.5 (35-83)	62.5 (42-81)
Caucasian (%)	98.0	94.2
ECOG 0/1 (%)	60.0/40.0	53.8/42.3
Median months since initial diagnosis (range)	**110.0 (19-435)**	**86.0(15-323)**
Median months since metastatic diagnosis (range)	**34.3 (1-167)**	**27.4 (1-225)**
Central AR primary/metastatic (%)	52/44	57.7/40.4
Median % of cells staining AR+ (range)	53.4 (11-96)	51.4 (14-98)
AR status confirmed centrally (%)	94.0	86.5
Bone only non-measurable (%)	**38.0**	**32.7**
Prior chemotherapy (%)	**90.0**	**92.3**
Median prior lines of endocrine therapy	**3**	

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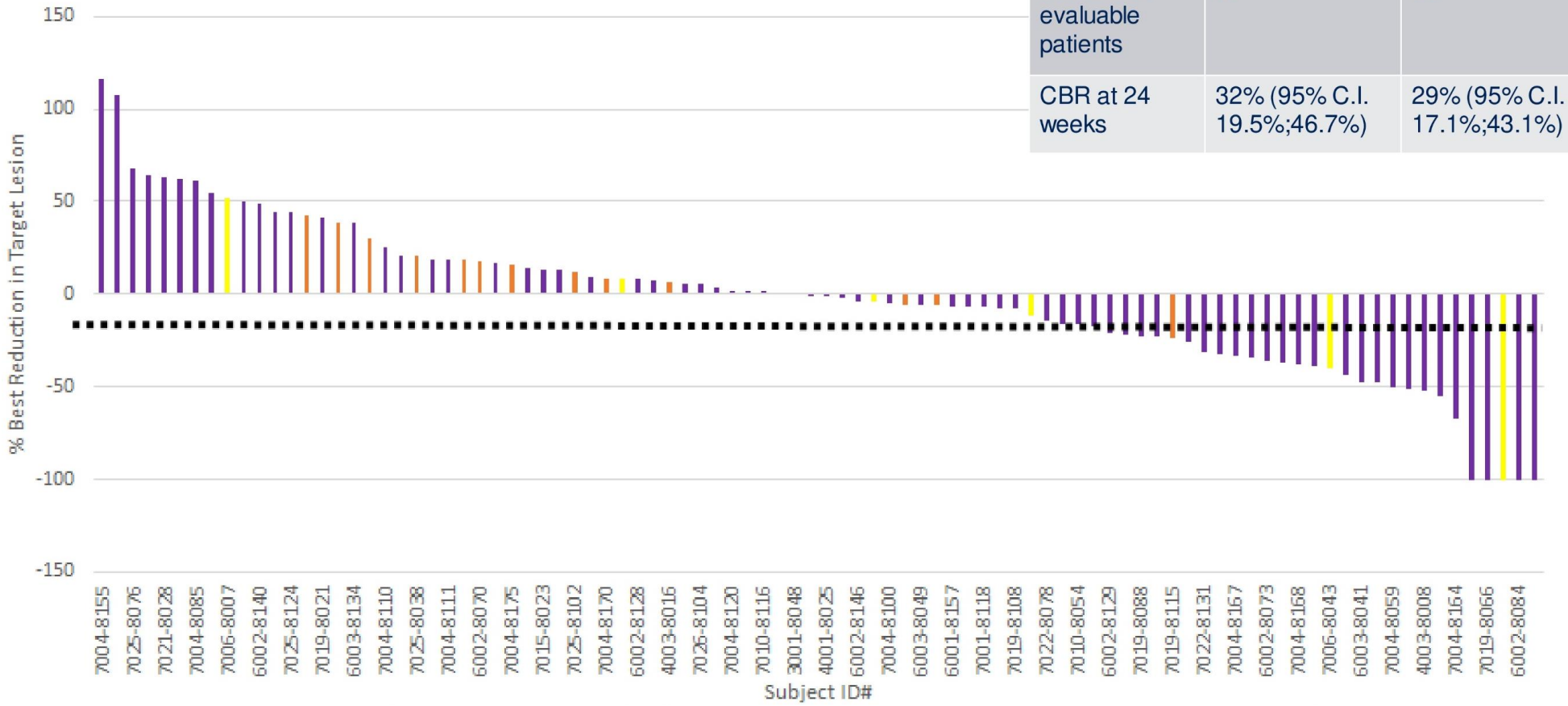
Anti-tumor efficacy: CBR

	9mg cohort	18mg cohort
Number of evaluable patients	50	52
CBR at 24 weeks	32% (95% C.I. 19.5%;46.7%)	29% (95% C.I. 17.1%;43.1%)



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Palmieri et al
ASCO 2021

AR blockers or AR agonists for HR+ MBC??

- Targeting of the AR as a monotherapy or in combination with other conventional therapies are increasingly being investigated in breast cancer ✓
- Novel AR agonists (monotherapy, e.g. enobosarm) have activity in heavily pre-treated (but ET sensitive) HR+ MBC ✓
- But is “ET + AR blocker” >, < or = as “AR agonist +/- ET” in HR+ MBC❓

Both strategies could work, as AR opposing actions could depend on clinical scenario and the multitude of proteins interacting with it in HR+ BC

ET-naïve patients with high AR mRNA levels, particularly in combination with low *ESR1* mRNA levels, may benefit from AR blocker (e.g. enzalutamide) with ET (e.g. exemestane)
(Krop et al CCR 2020)

ET-heavily pre-treated patients, especially with high AR mRNA levels and *ESR1* mut, may benefit from an AR agonist (e.g. enobosarm)
(Palmieri and Fuqua SABCS 2020)

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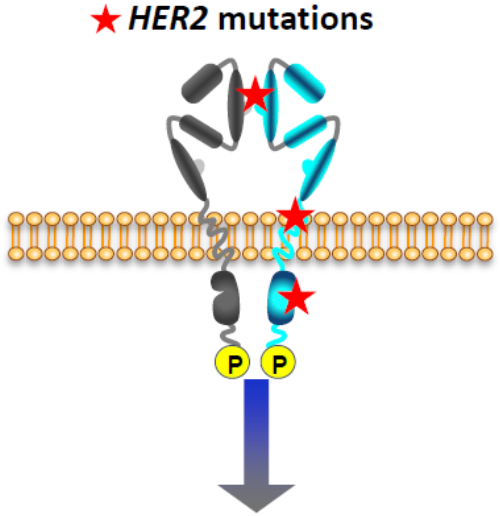
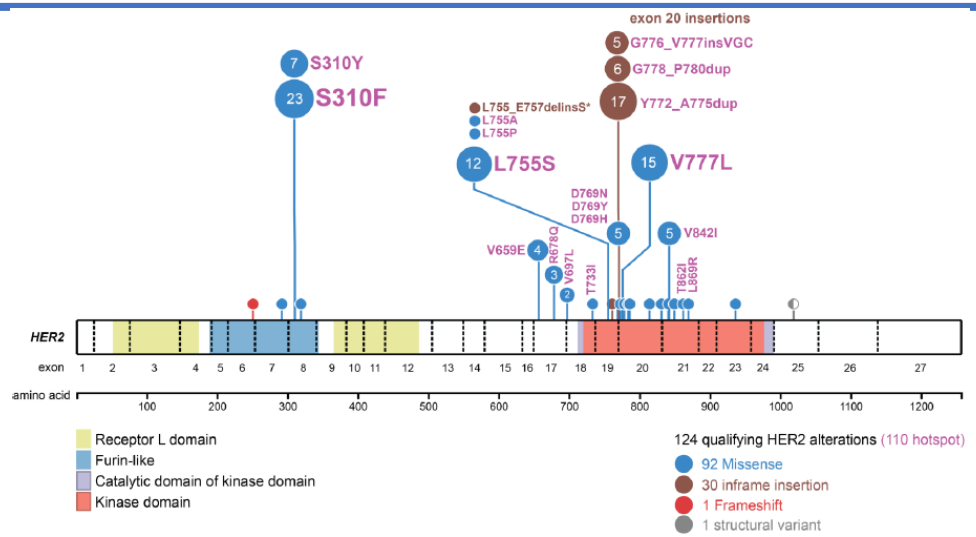
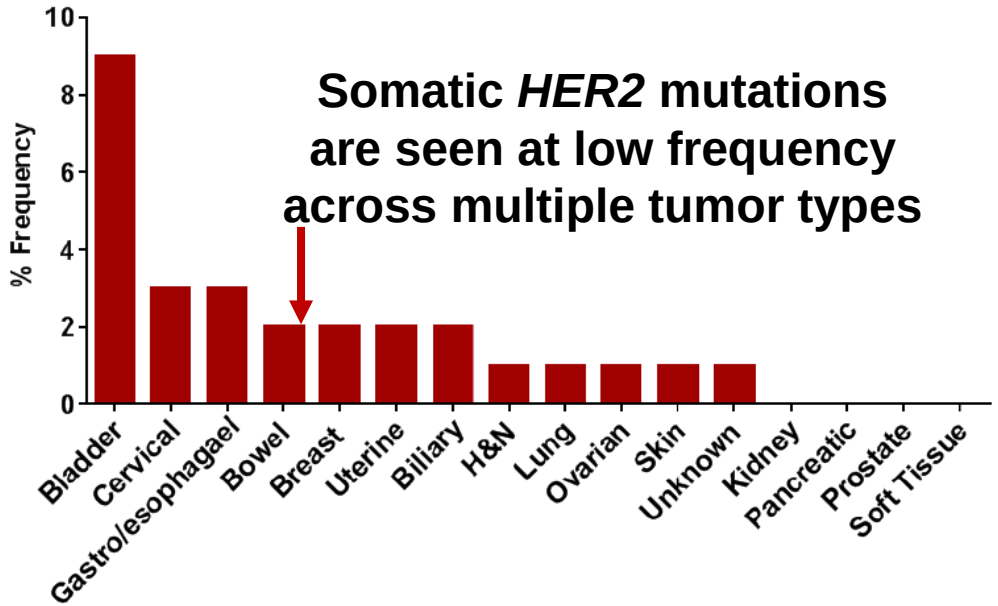
Targeting *HER2 (ERBB2)* Mutations



Activation of downstream signal transduction pathways and tumor growth survival





Somatic *HER2* mutations are seen at low frequency across multiple tumor types

Activating HER2 mutations result in constitutive kinase signaling, activation of growth promoting/ survival pathways, oncogenic transformation and enhanced tumor growth in preclinical models

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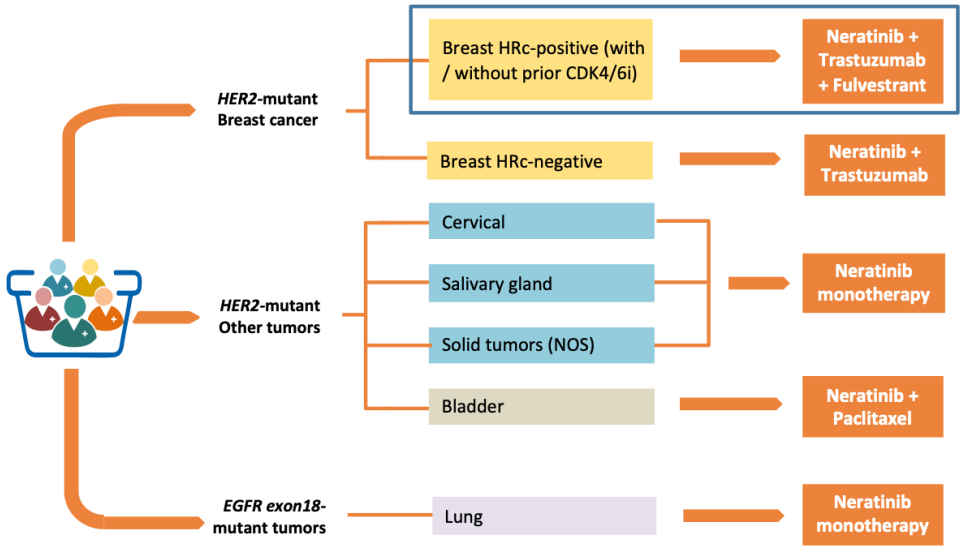
Neratinib Basket Trial (SUMMIT)



***EGFR or HER2* mutations**
(documented by local testing)

Primary endpoint
- Objective response rate at first post-baseline tumor assessment (ORR_{first})

Secondary endpoints
- ORR (confirmed)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Duration of Response (DOR)
- Safety (NCI CTCAE version 4.0)
- Biomarkers

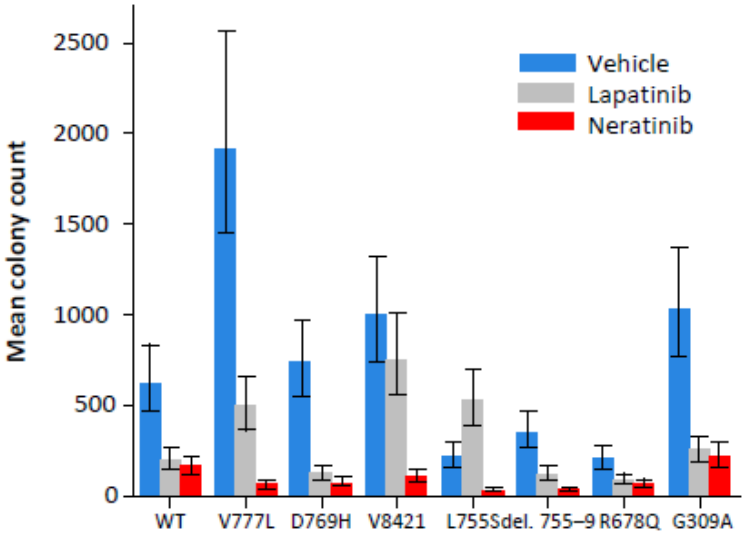
Simon 2-stage design
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments
- RECIST v1.1 (primary criteria)

Statistical methods
- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI

Key inclusion criteria
- Histologically confirmed cancers for which no curative therapy exists
- Documented *EGFR exon 18* or *HER2* mutation (identified by genomic sequencing)
- ECOG status of 0 to 2
- RECIST 1.1 evaluable disease (measurable or non-measurable disease): if RECIST non-measurable, evaluable by other accepted criteria

Key exclusion criteria
- Prior treatment with any pan-HER TKI (eg, lapatinib, afatinib, dacomitinib, neratinib, tucatinib, poziotinib)
- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding



Prior therapies	Safety evaluable patients (n=51)
Patients with prior treatment for locally advanced/metastatic disease, n (%)	46 (90.2)[a]
Median number of prior therapies (range)	4 (1–10)
Prior endocrine therapy, n (%)	
Prior aromatase inhibitor	35 (68.6)
Prior fulvestrant	36 (70.6)
Prior tamoxifen	4 (7.8)
Prior chemotherapy, n (%)	35 (68.6)
Prior HER2 antibody-directed therapy, n (%)	2 (3.9)[a]
Prior CDK4/6 inhibitor, n (%)	30 (58.8)
Prior PIK3CA inhibitor, n (%)	4 (7.9)
Prior mTOR inhibitor, n (%)	15 (29.4)

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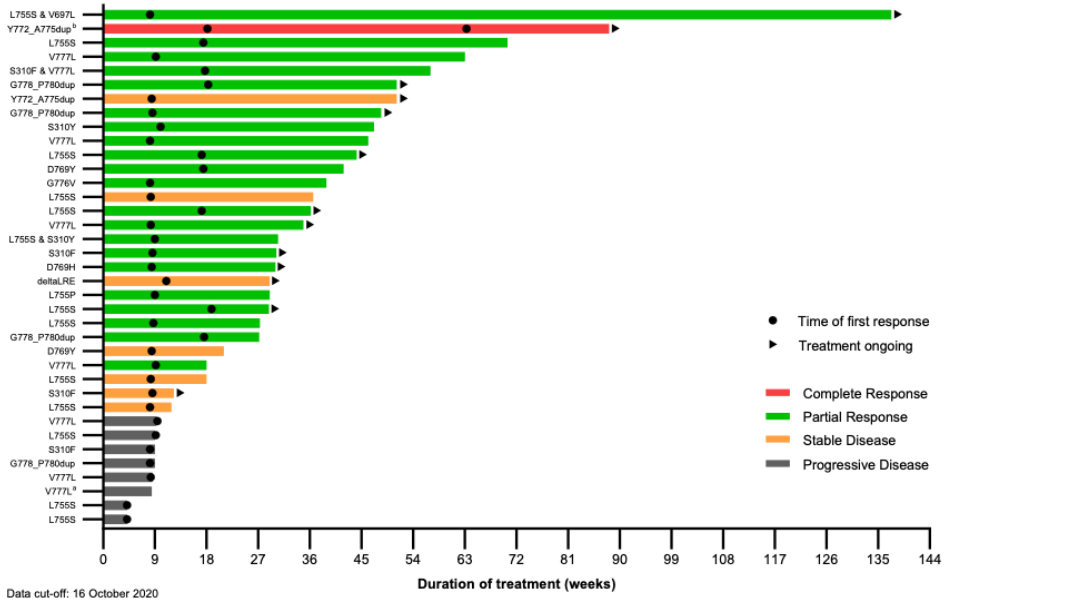
Hyman *et al. Nature* 2018; Jhaveri et al SABCS 2020

Neratinib Basket Trial (SUMMIT) Responses

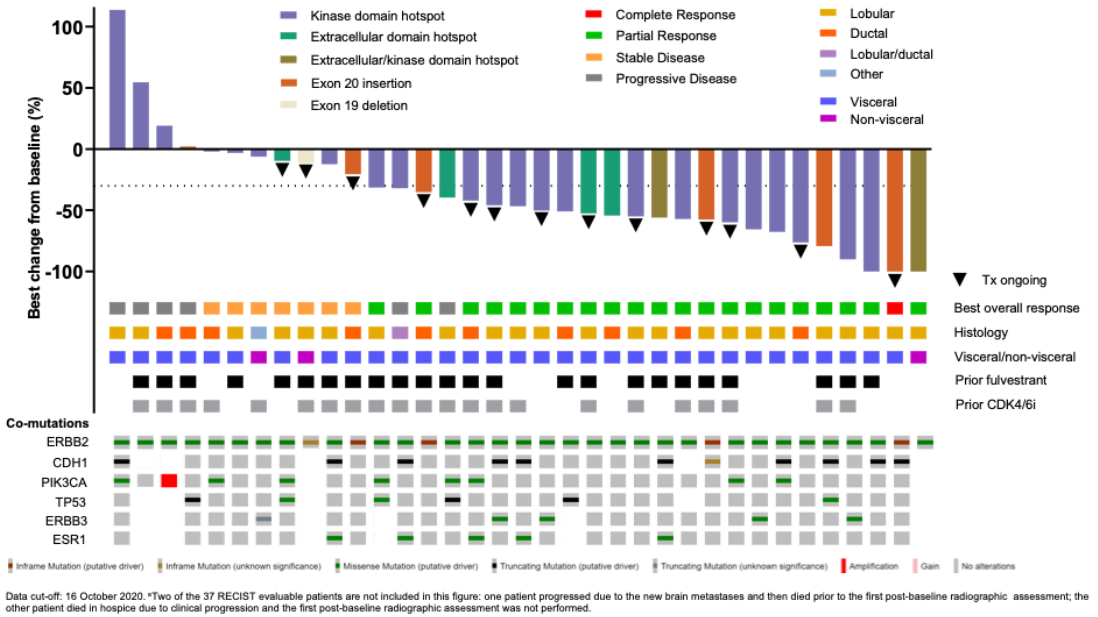
Duration of treatment and best response (RECIST evaluable, n=37)



Data cut-off: 16 October 2020

[a]This patient died in hospice due to clinical progression prior to the first post-baseline tumor response assessment; [b] This patient had first partial response at week 18 and first complete response at week 63.

Change in tumor size and characteristics (n=35)[a]



Data cut-off: 16 October 2020. *Two of the 37 RECIST evaluable patients are not included in this figure: one patient progressed due to the new brain metastases and then died prior to the first post-baseline radiographic assessment; the other patient died in hospice due to clinical progression and the first post-baseline radiographic assessment was not performed.

The combination of neratinib + fulvestrant + trastuzumab demonstrated encouraging clinical activity in heavily pre-treated *HER2*-mutant, HR+, *HER2*-non-amplified MBC, including patients who had previously received either fulvestrant and/or CDK4/6 inhibitor-based therapies: **ORR 45.9%**; median DoR 10.9 months; **median PFS 8.3 months**

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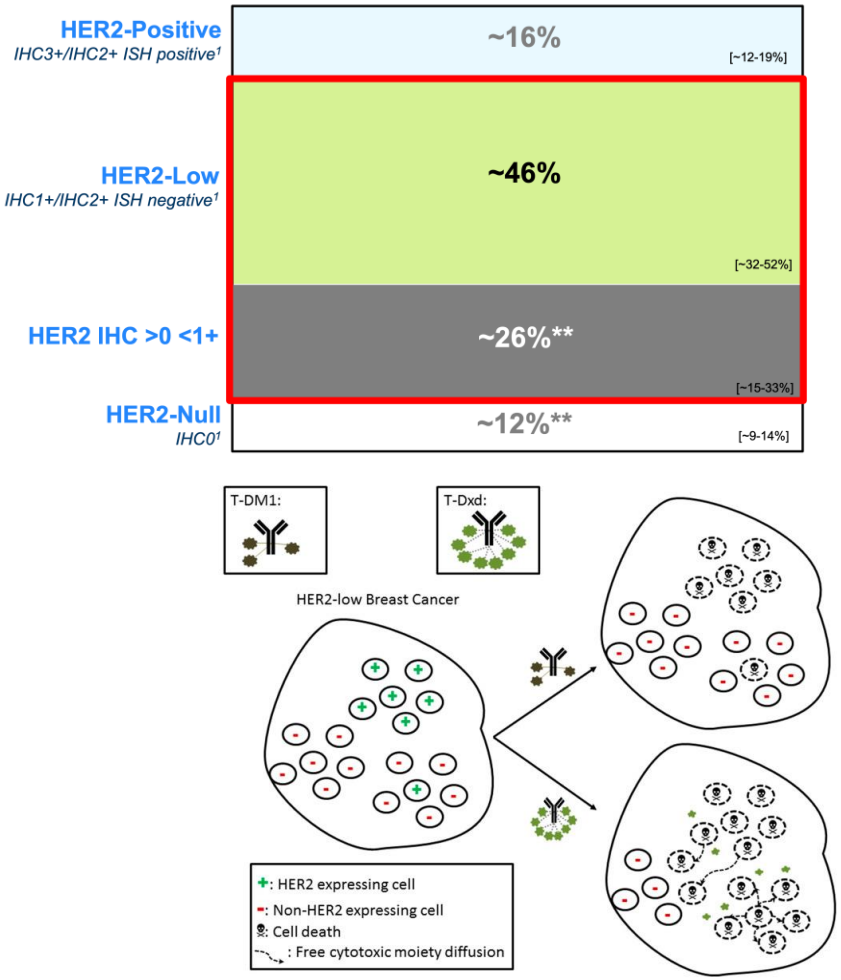
Hyman *et al. Nature* 2018; Jhaveri et al SABCS 2020

HER2-low HR+ breast cancer



Comparison of trastuzumab–emtansine (T-DM1) vs. trastuzumab–duocarmazine (SYD–986) vs. trastuzumab–deruxtecan (T-Dxd).

Antibody-Drug Conjugate	T-DM1	SYD-986	T-Dxd
HER2 targeting vehicle	Trastuzumab	Trastuzumab	Trastuzumab
Linker	Non-cleavable	Cleavable	Cleavable
Drug–antibody ratio	3.5:1	2.8:1	8:1
Cytotoxic moiety	Maytansine derivative	Seco-DUBA	Exatecan derivative
Cytotoxic moiety MoA	Antimicrotubule (mitotic poison)	Alkylating agent	Topoisomerase I inhibitor
Diffusible cytotoxic moiety?	✗	✗	✓
Bystander killing effect?	✗	✓	✓
Targets HER2-positive or homogenous tumors?	✓	✓	✓
Targets HER2-low or heterogeneous tumors?	✗	✓	✓

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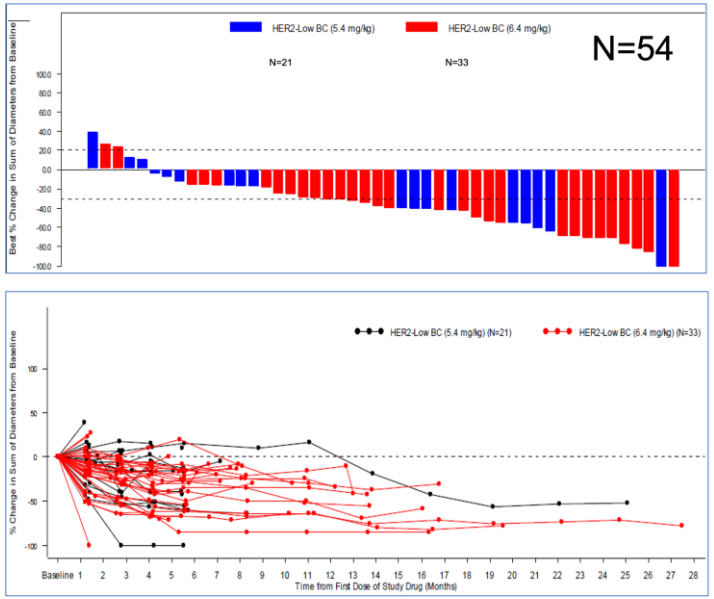
1. Trail, et al. Pharmacol Ther. V181 p126-142 (2018). **2.** Marcoux et al. Protein Sci. v24 p1210-1223 (2015). **3.** Nakada et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. **4.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **5.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046 **6.** Eiger D, et al. Cancers 2021 **7.** Iwata et al. J Clin Oncol 2018

Antibody-conjugates and bi-specific Abs in HER2-low tumors

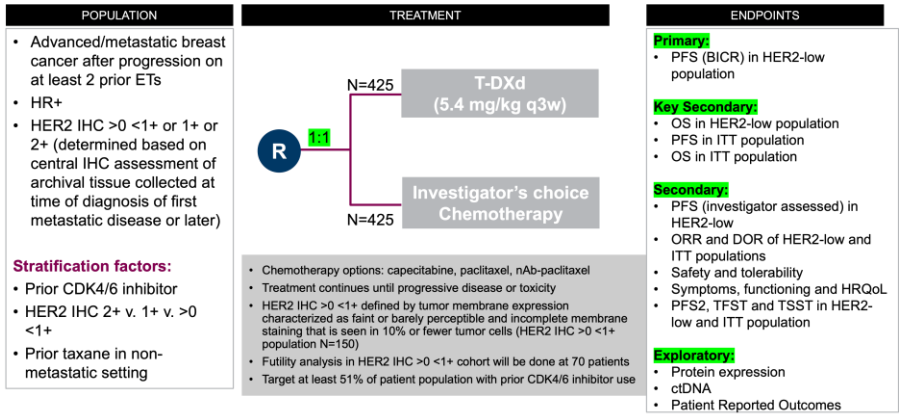
Trastuzumab deruxtecan J-101 Phase I trial

Subgroup	ORR by BICR (all doses)	mDoR	mPFS
HR+ (n = 47)	**40.4%**	**10.4m (-,-)**	**13.4m (-,-)**
IHC 2+ (n = 26)*	38.5%	-	13.4m (-,-)
IHC 1+ (n = 28)*	35.7%	8.8m (-,-)	7.6m (-,-)
Prior CDK4/6i (n = 16)	43.8%	-	10.2m (-,-)

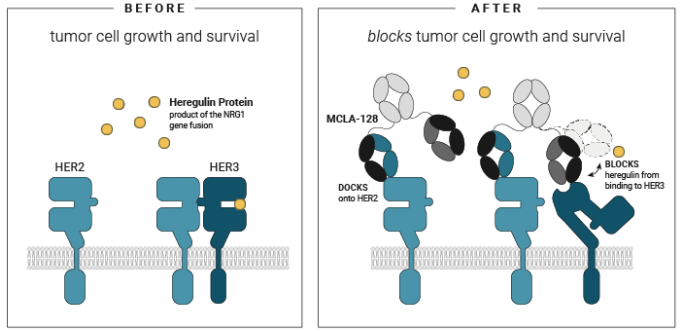
DCO: Feb 2019
*Note: n=7 HR(-) patients included within IHC2+/1+ (1 response) included in waterfall/spider plots

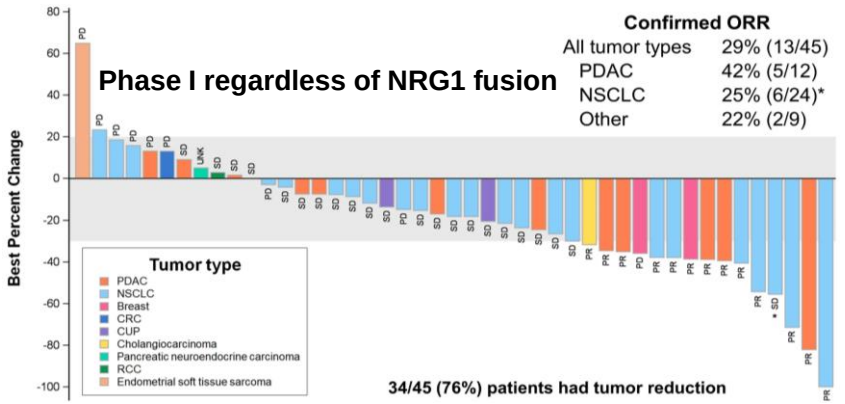


DESTINY-06 Phase III trial



Zenocutuzumab (MCLA-128)





Phase II trial in HR+, HER2 low (IHC 1+/IHC 2+ with negative FISH) MBC, who had progressed on a CDK4/6i and up to 3 lines of ET, with ≤ 2 chemotherapy regimens in the metastatic setting (N=48): DCR was 45% (90% CI 32-59) with 2 pts having unconfirmed PR and 19 pts SD

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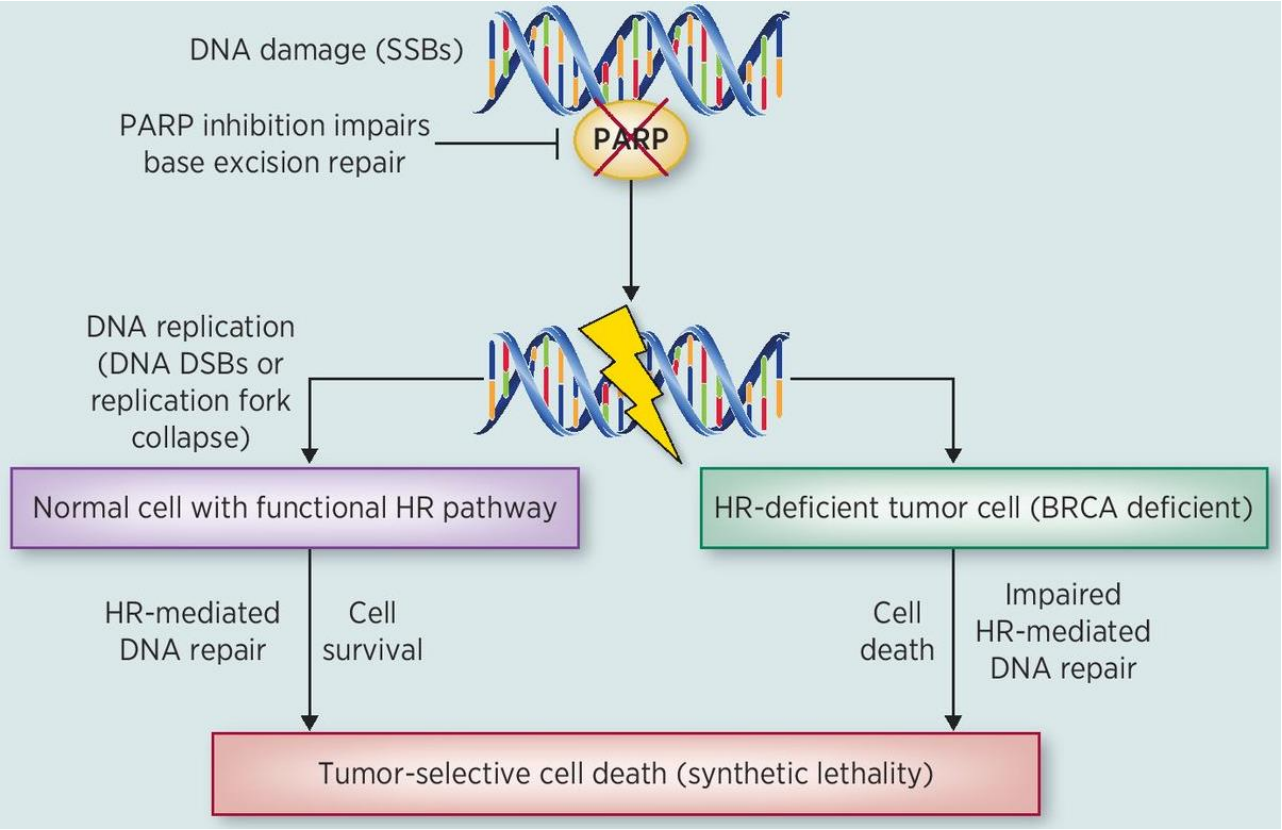
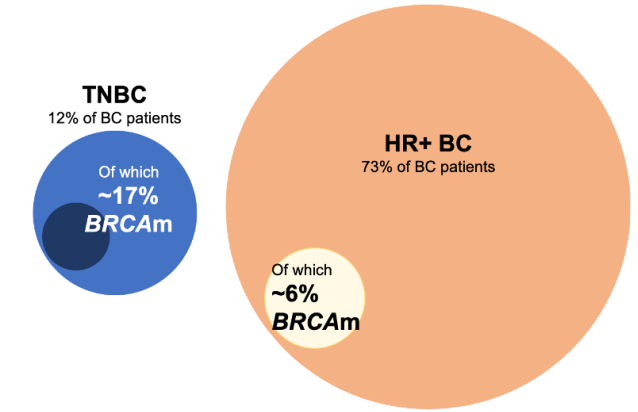
Iwata et al. J Clin Oncol 2018; Geuijen et al. Cancer Cell 2018; Pistilli et al. ASCO2020; Schram et al. ASCO2021

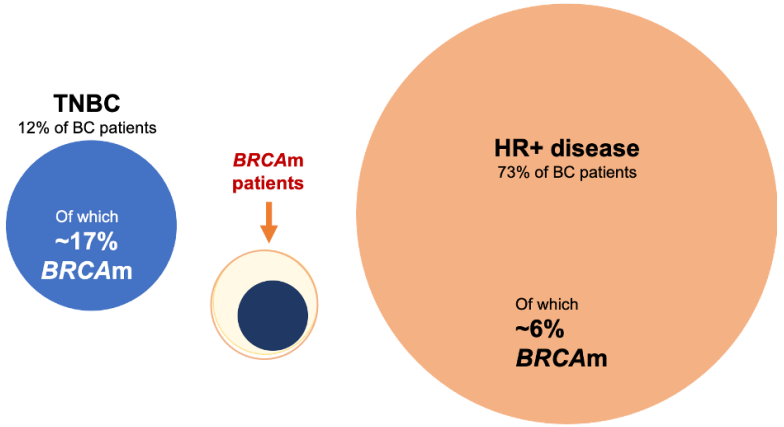
Targeting *BRCA* Mutations in HR+ MBC



A higher proportion of TNBC patients have *BRCA*m than HR+ BC patients



However, due to the relative prevalence, the majority of *BRCA*m are found in HR+ BC patients rather than TNBC



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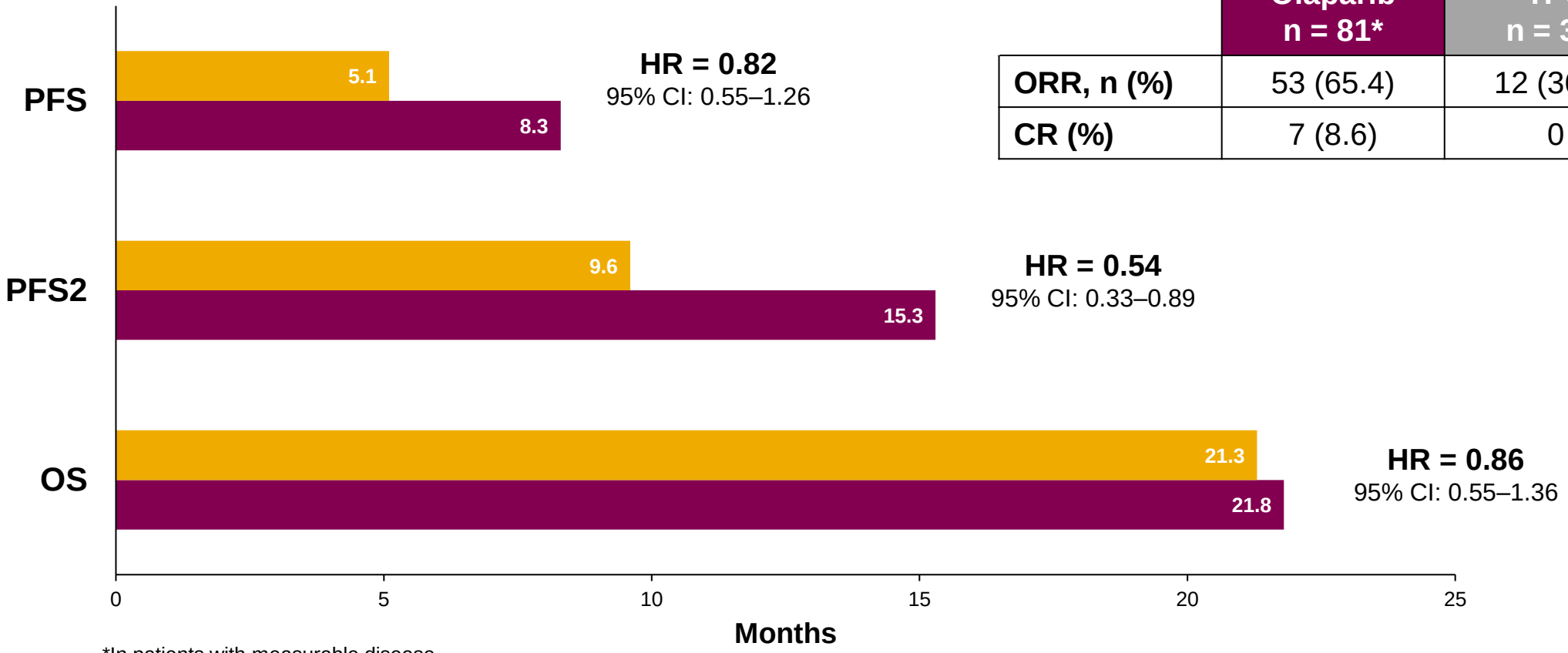
Winter C, et al. *Ann Oncol* 2016

OlympiAD: PFS and OS in HR+ MBC



	Olaparib n = 81*	TPC n = 33*
ORR, n (%)	53 (65.4)	12 (36.4)
CR (%)	7 (8.6)	0

*In patients with measurable disease.
The OlympiAD study was not powered to identify differences in treatment effect between subgroups, and any differences observed here are hypothesis-generating.

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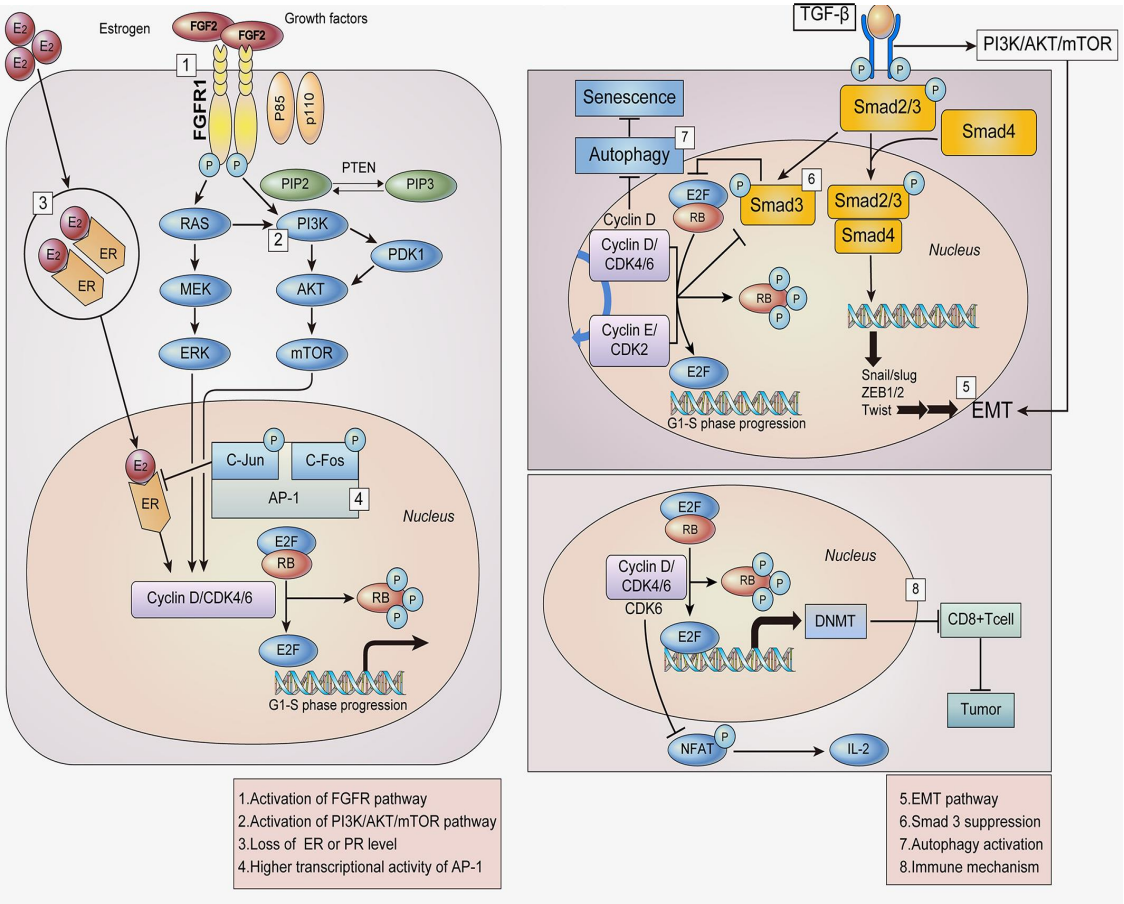
Senkus, et al. *EBCC 2018.* Poster PB-002; Robson M, et al. *Ann Oncol* 2019

Novel therapeutic options in HR+ BC: where are we going?



***BRCA* mutations - PARP inhibitors**

***ESR1* mutations - Novel SERDs, SERCAs**

***HER2* mutations - Neratinib + ET**

AR overexpression - AR blockers/agonists + ET

HER2-low – T-deruxtecan

CDK2/7/9 inhibitors + ET?

FGFR inhibitors + ET?

AuroraK inhibitors + ET?

BCL2 inhibitors + ET?

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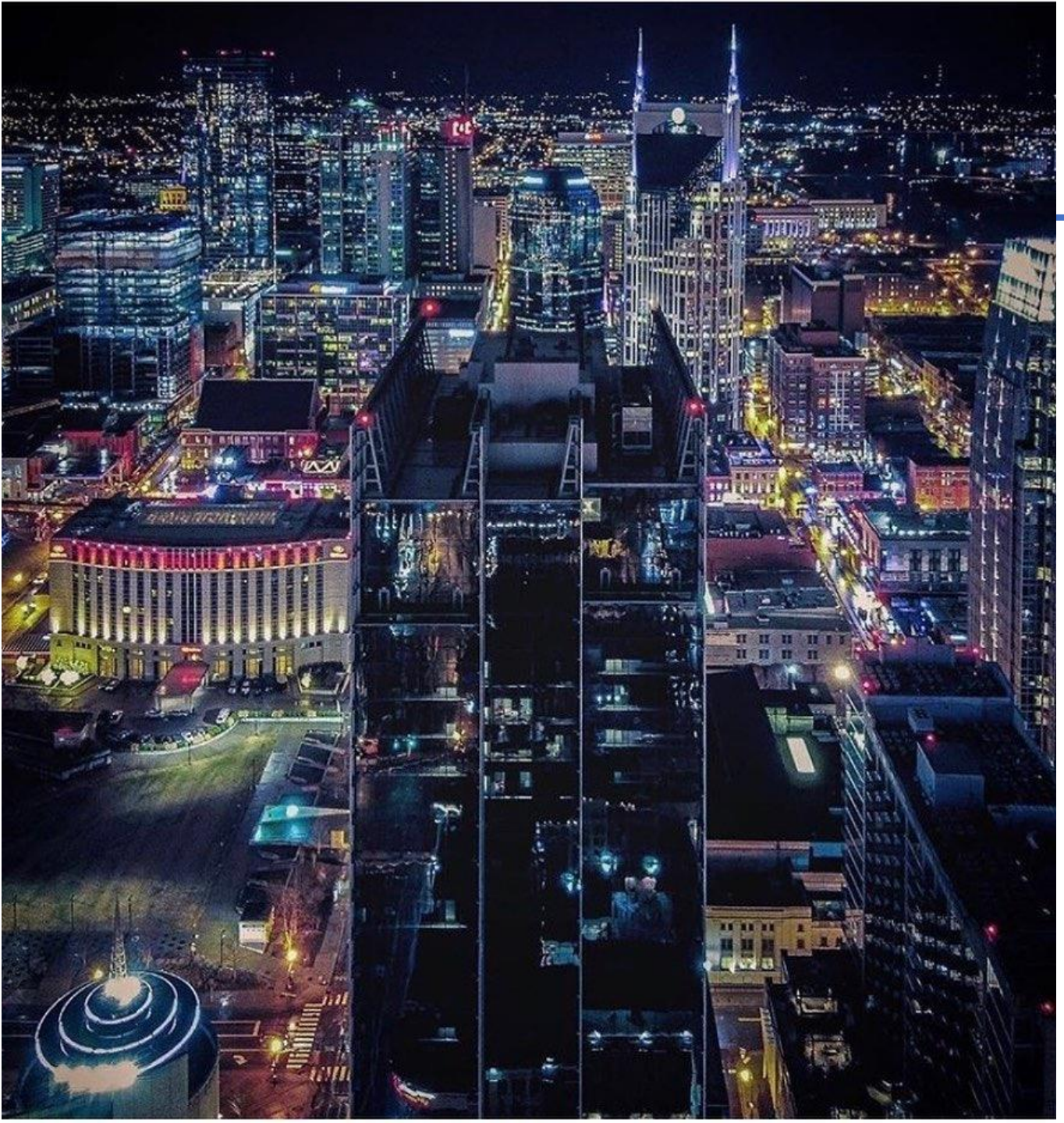
Pandey et al, IJC 2018



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QUESTIONS?