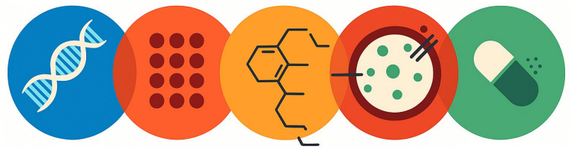
Molecularly Targeted Therapies For Breast Cancer



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Disclosures

Financial Relationship	Commercial Interest
Grant or research support	Guardant Health, Taiho, EMD Serono, Novartis, CPRIT, Sermonix, Edgewood Oncology, AstraZeneca, MediLink, Daiichi Sankyo
Paid consultant	NA
Membership on advisory committees or review panels	ASCO, ABIM, AstraZeneca, Sermonix, Eli Lilly
Employee	MD Anderson Cancer Center

Biomarkers of Interest in MBC

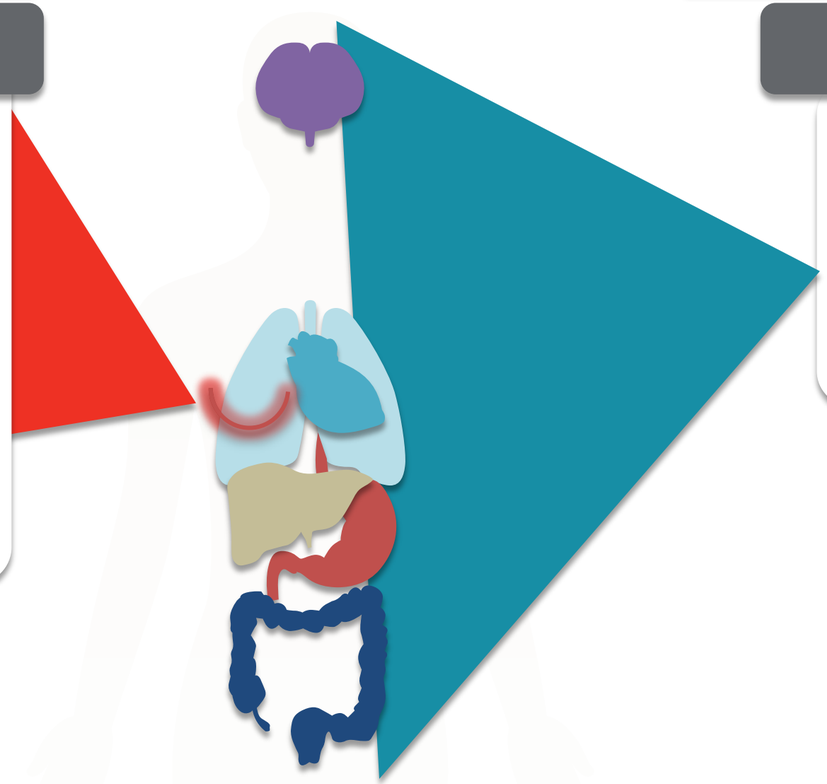
Breast cancer specific

Protein Biomarkers

ER
PR
HER2
PD-L1

Genomic Biomarkers

PIK3CA
ESR1
AKT1
PTEN
ERBB2
FGFR
BRCA1 / BRCA2
PALB2



Tumor agnostic

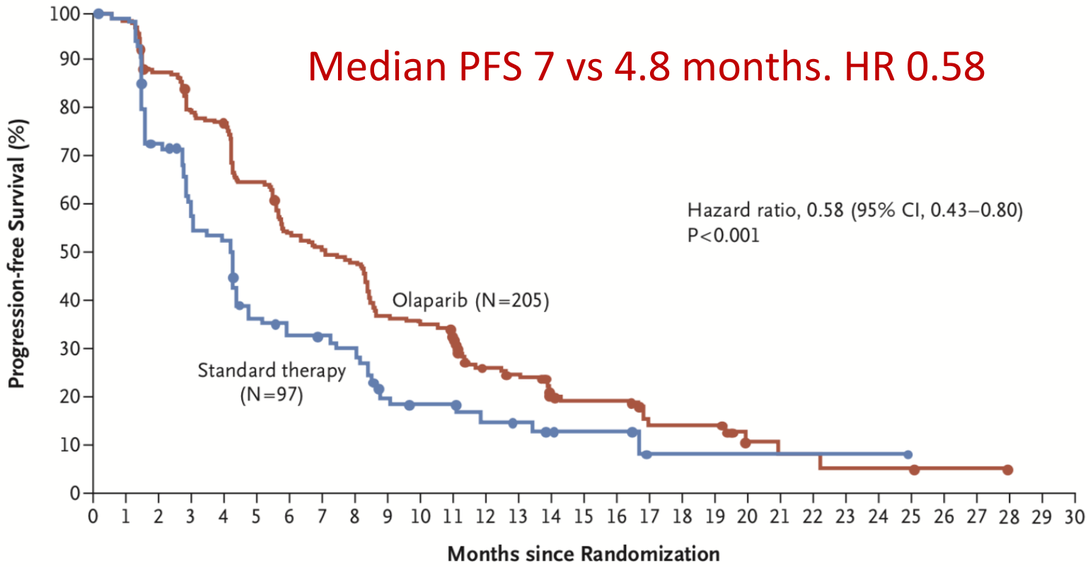
Genomic Biomarkers

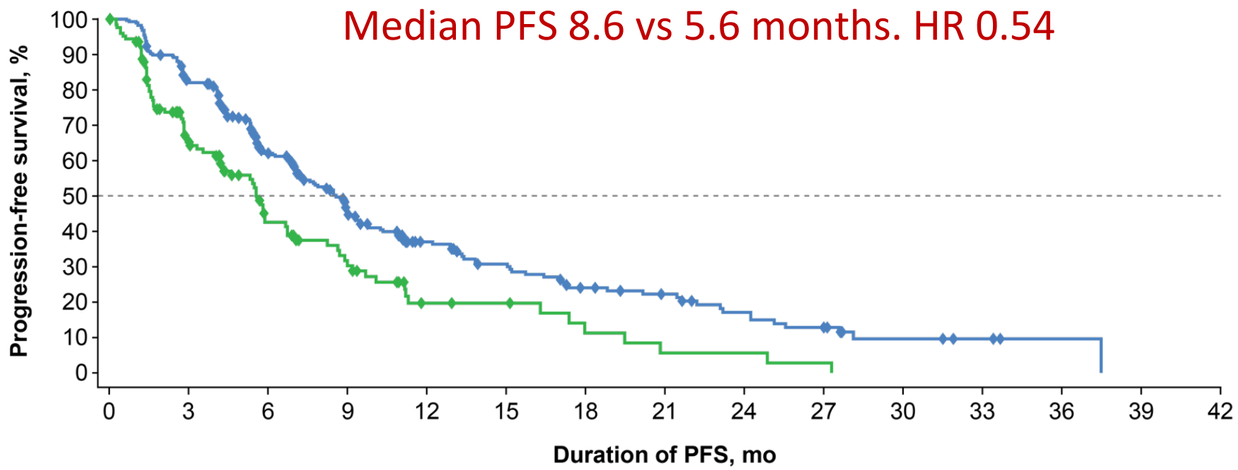
MSI-H / dMMR
TMB-H
RET
NTRK
BRAF V600E

Damodaran, S. Precisions Edge Webinar 2024

Germline BRCA1/2

PARP inhibition in g*BRCA*





OLAPARIB

- HER2–ve MBC
- No more than 2 prior chemo for MBC
- Olaparib vs TPC. ORR 60 vs 29%

TALAZOPARIB

- HER2–ve MBC
- No more than 3 prior chemo
- RR 63 vs 27%
- PFS 5.7 vs 1.6 in CNS mets

Robson et al. 2017 , Litton et al. 2018

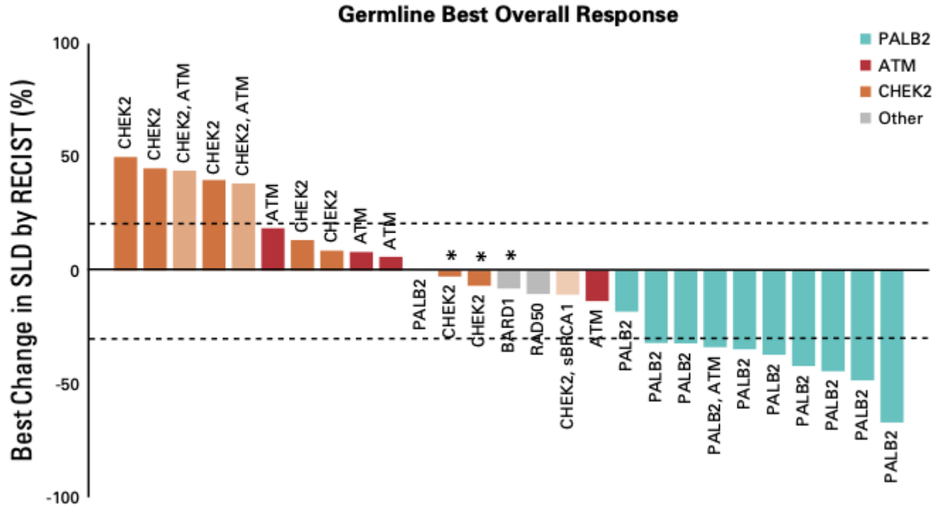
Beyond *gBRCA*…

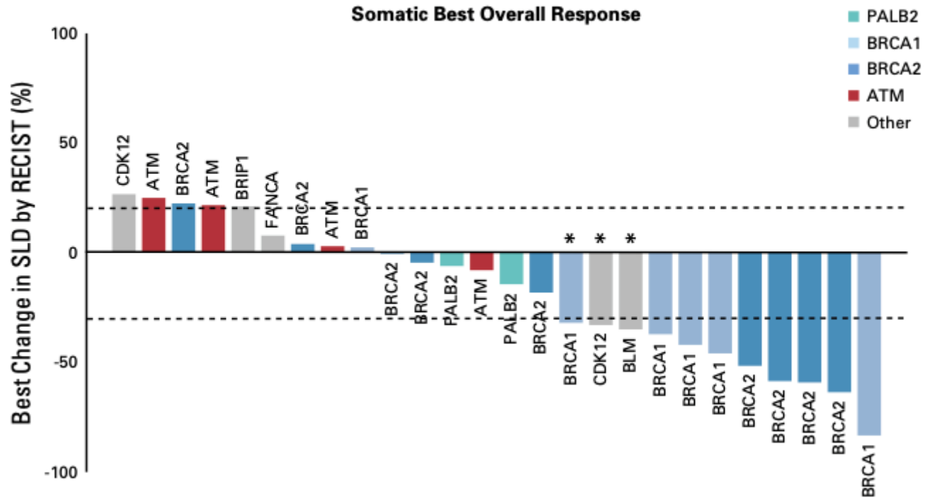
TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes

OLAPARIB

- Somatic pathogenic or likely PV, in *BRCA1/2*
- Germline or somatic *ATM, ATR, BAP1, BARD1, BLM, BRIP1, CHEK1, CHEK2, CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D, or WRN*
- Prior PARP or platinum refractory excluded

gPALB2 N=13	sBRCA1/2 N=17	ATM & CHEK2 N=17
• ORR 82% (CBR 100%) • PFS 13.3 months	• ORR 50% • PFS 6.3 months	• 0/13 germline • 0/4 somatic

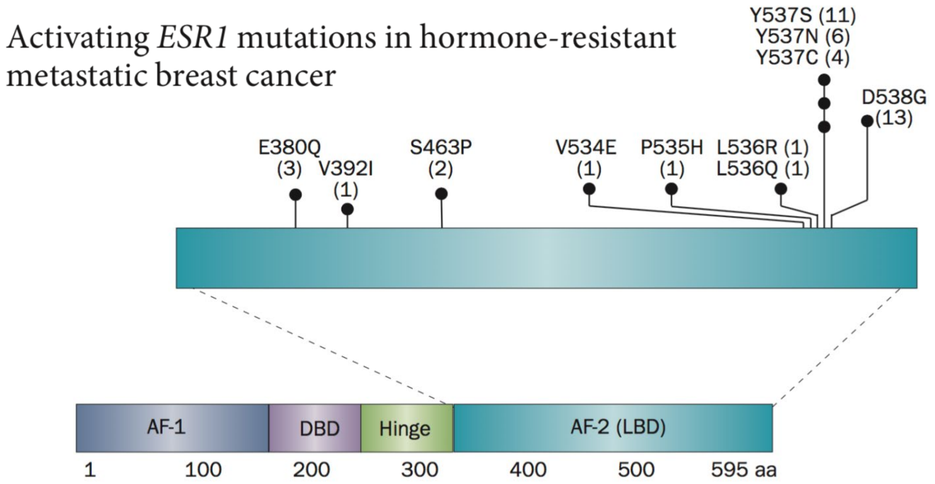


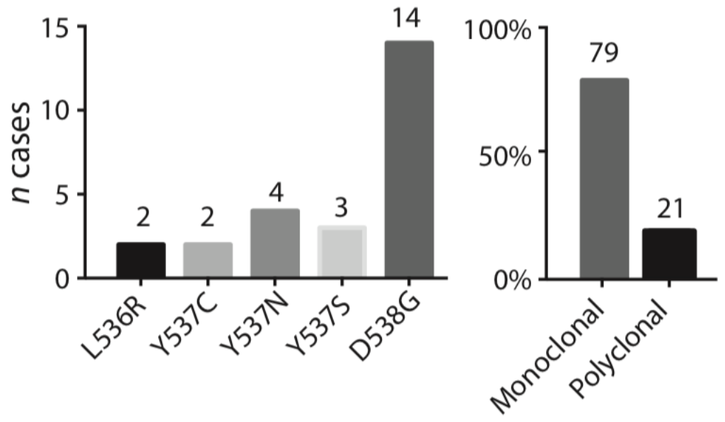


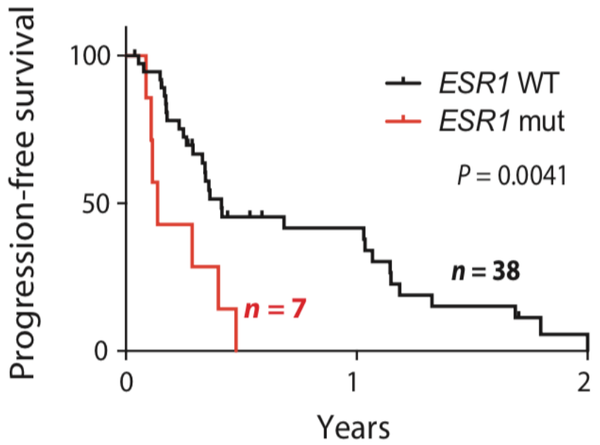
Tung N, et al.2020

ESR1

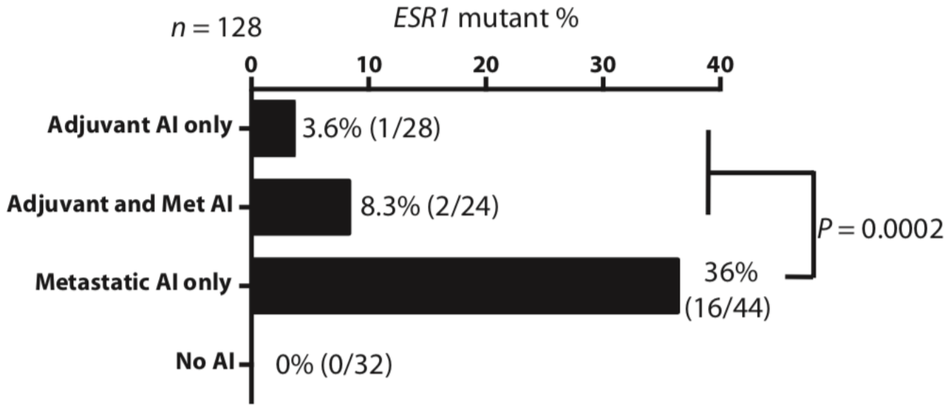
Acquired *ESR1* mutations in LBD mediates secondary endocrine resistance







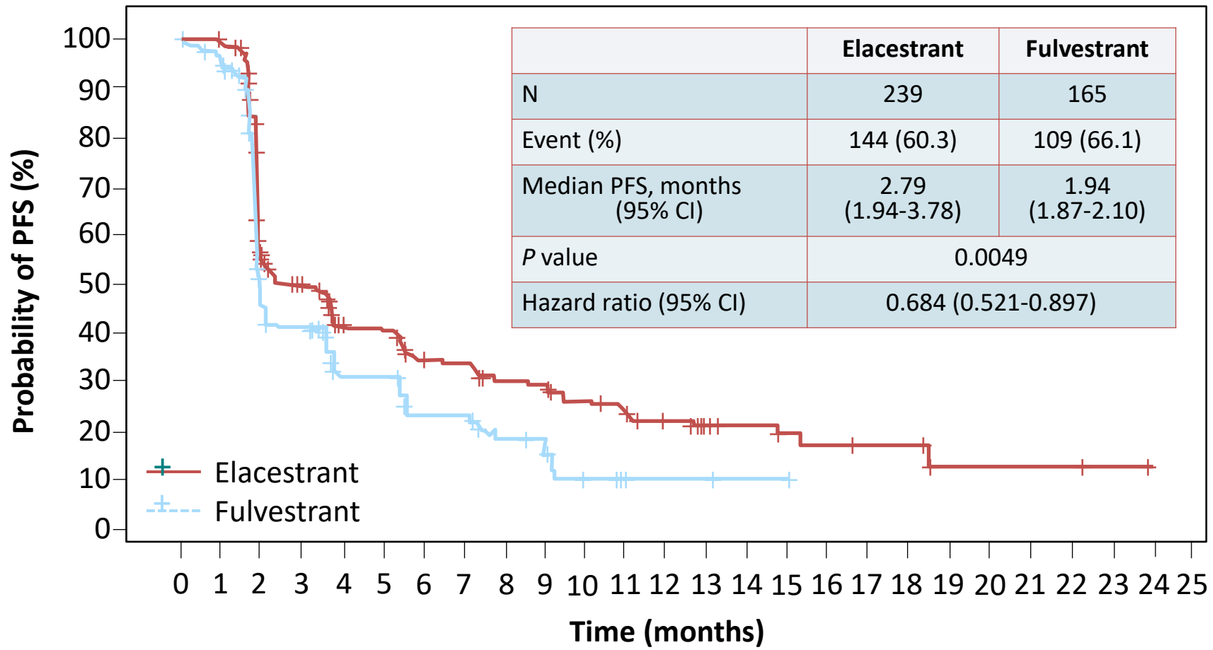
ESR1 mutations predict lack of sensitivity to AI



Study	Frequency
FERGI	40%
SOFEA	40%
BOLERO-2	30%
Clatot	31%
PALOMA-3	25%

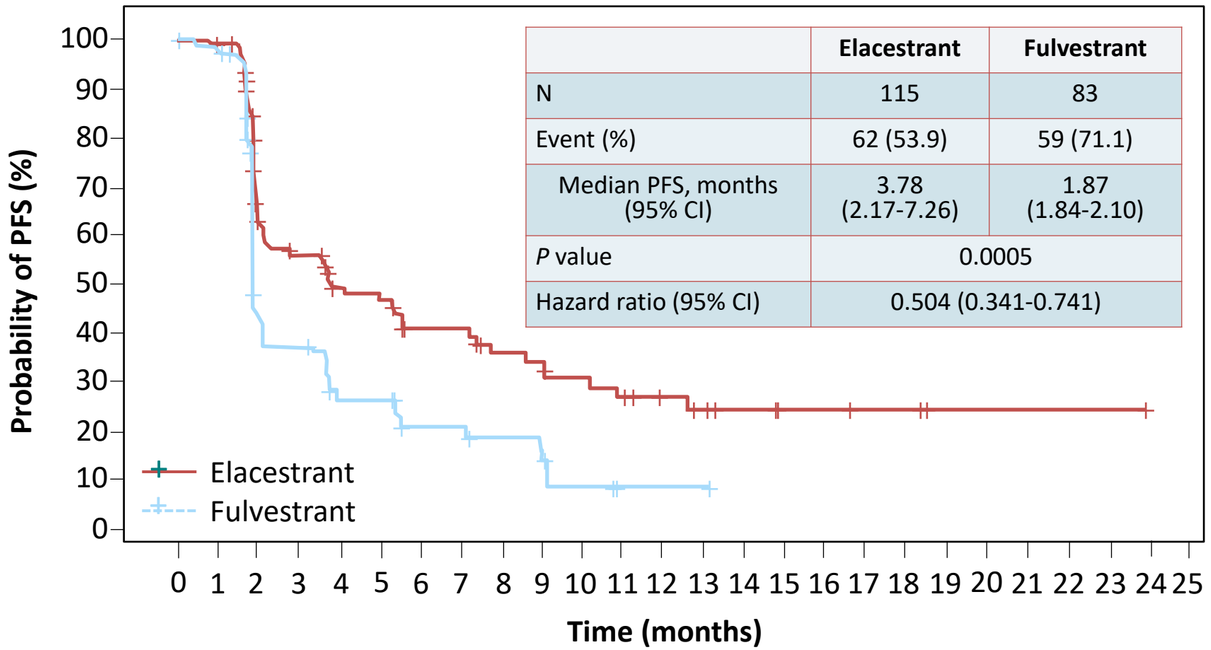
Jeselsohn et al. 2015, Robinson et al. 2013, Schiavon et al. 2015, Toy et al.2013

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)



	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2	0
Fulvestrant	165	62	33	21	14	5	2	1	0				



	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0
Fulvestrant	83	29	16	10	8	3	1	0					

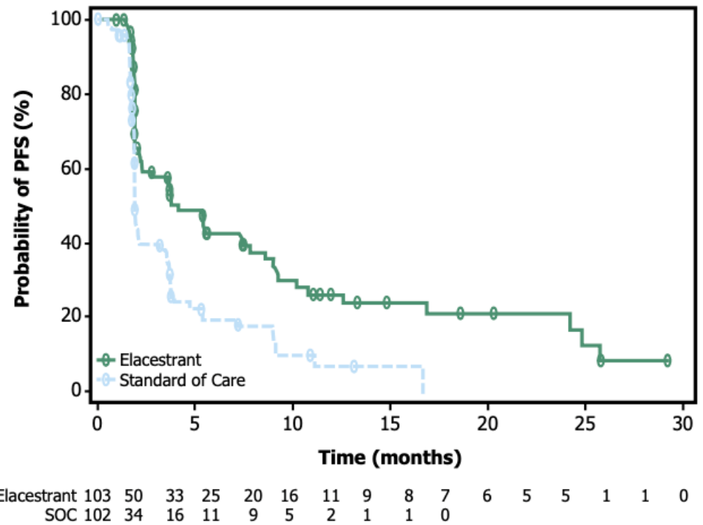
FDA Approved for patients with *ESR1* mutation following progression on at least one line of ET

Bardia A, et al. SABCS 2021

EMERALD

PFS by duration of prior CDK46I

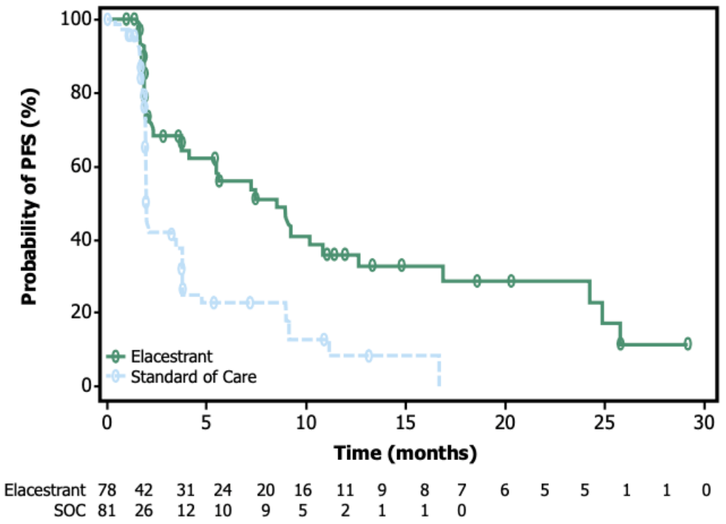
At least 6 mo CDK4/6i



Elacestrant	103	50	33	25	20	16	11	9	8	7	6	5	5	1	1	0
SOC	102	34	16	11	9	5	2	1	1	0						

	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)	

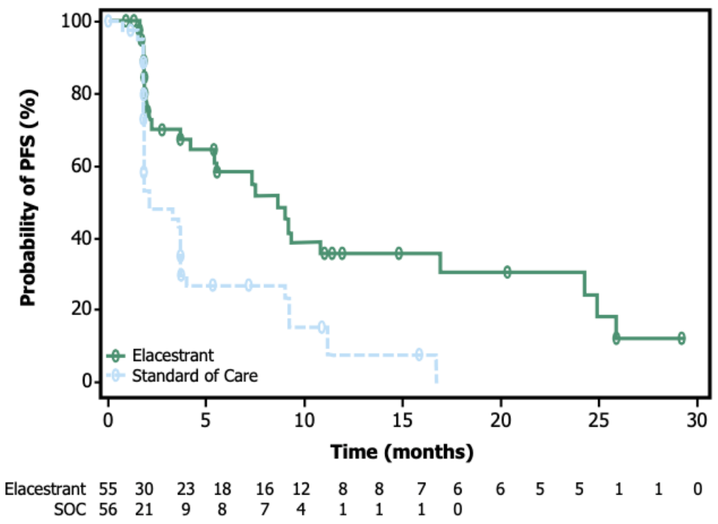
At least 12 mo CDK4/6i



Elacestrant	78	42	31	24	20	16	11	9	8	7	6	5	5	1	1	0
SOC	81	26	12	10	9	5	2	1	1	0						

	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	55	30	23	18	16	12	8	8	7	6	6	5	5	1	1	0
SOC	56	21	9	8	7	4	1	1	1	0						

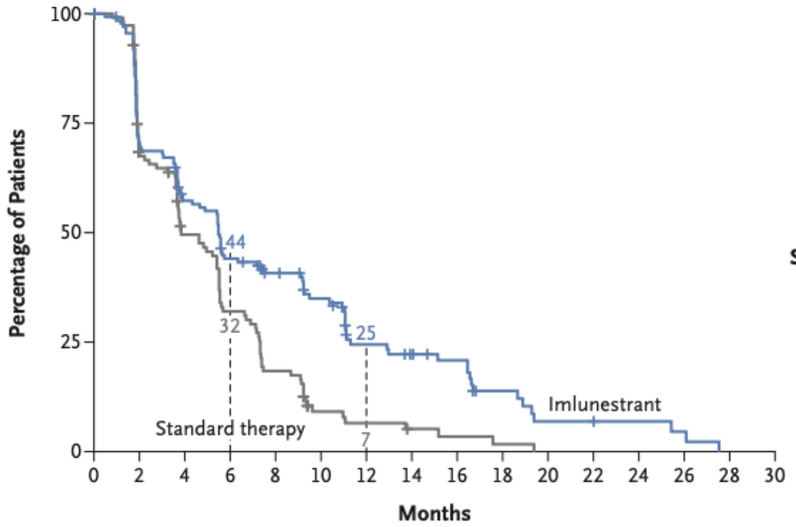
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Kaklamani V, et al. SABCS 2022

EMBER 3

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

A **Progression-free Survival among Patients with *ESR1* Mutations, Imlunestrant vs. Standard Therapy**

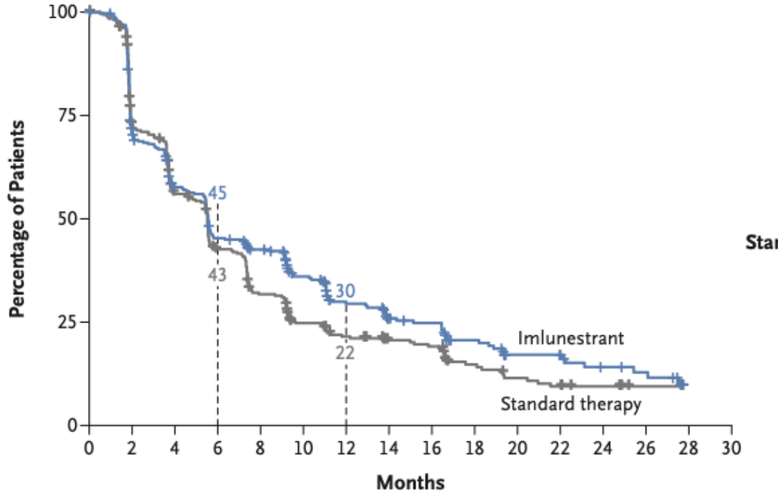


No. at Risk																
Imlunestrant	138	95	74	56	45	35	22	18	15	8	4	4	3	2	0	0
Standard therapy	118	74	51	33	19	7	5	3	2	1	0	0	0	0	0	0

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant	138	109	5.5 (3.9–7.4)
Standard Therapy	118	102	3.8 (3.7–5.5)

Difference in restricted mean survival time, 2.6 mo (95% CI, 1.2–3.9)
P<0.001

B **Progression-free Survival among All Patients, Imlunestrant vs. Standard Therapy**



No. at Risk																
Imlunestrant	331	225	173	135	118	89	62	47	43	30	20	19	13	10	0	0
Standard therapy	330	221	165	122	89	63	51	41	38	23	17	14	10	2	0	0

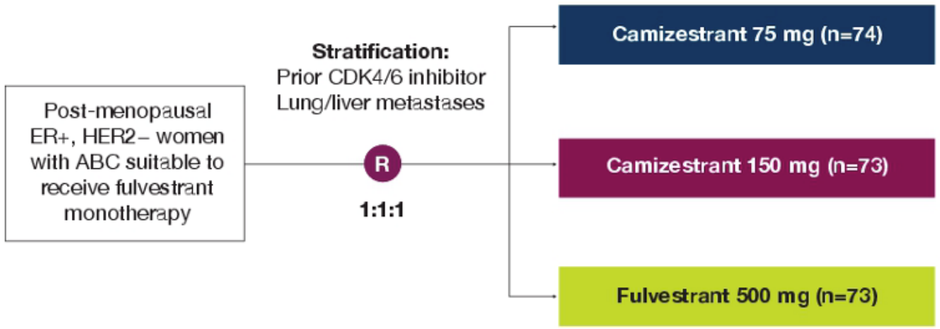
	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant	331	237	5.6 (5.3–7.3)
Standard Therapy	330	253	5.5 (4.6–5.6)

Hazard ratio for disease progression or death, 0.87 (95% CI, 0.72–1.04)
P=0.12

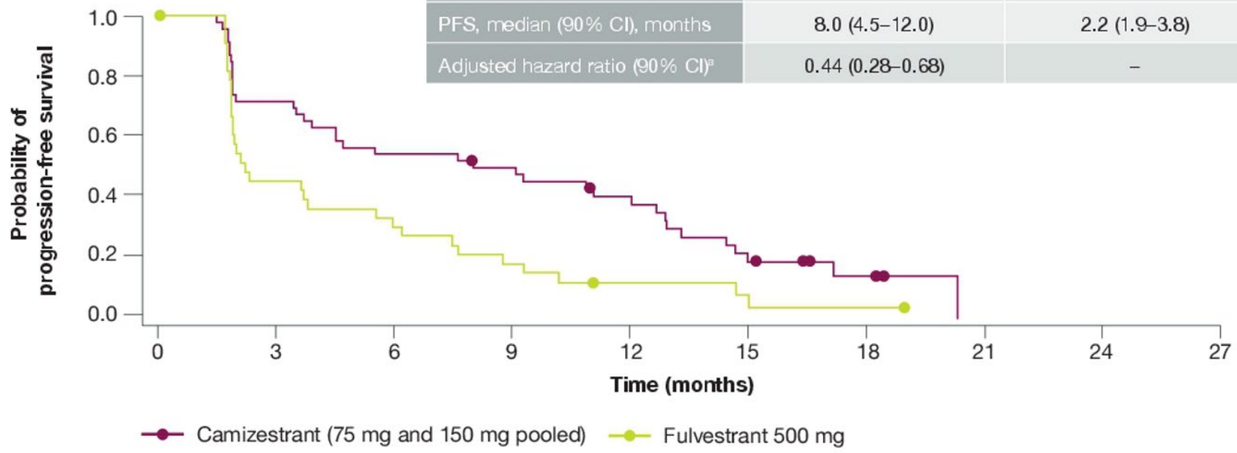
FDA Approved Sept 2025 for patients with *ESR1* mutation following progression on at least one line of ET

Jhaveri et al. 2024

SERENA-2



	Camizestrant 75 mg + 150 mg (n=48)	Fulvestrant 500 mg (n=35)
Events, n (%)	37 (77.1)	31 (88.6)
PFS, median (90% CI), months	8.0 (4.5–12.0)	2.2 (1.9–3.8)
Adjusted hazard ratio (90% CI)[a]	0.44 (0.28–0.68)	–



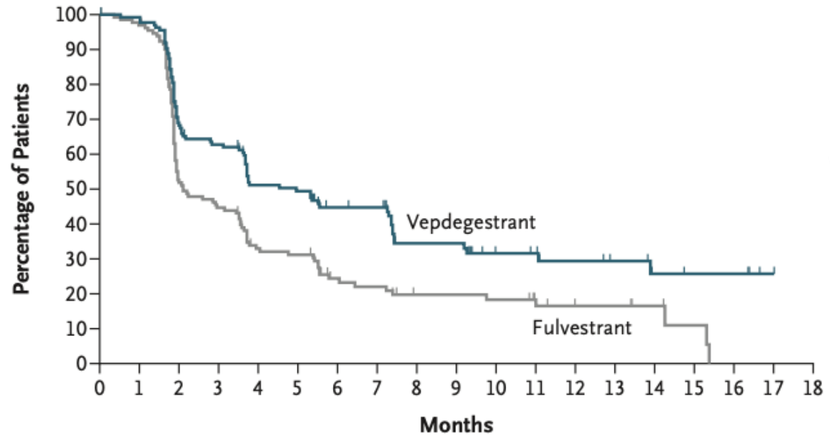
Efficacy measure	Camizestrant (75mg)	Camizestrant (150mg)	*Faslodex* (500mg)
Primary endpoint			
Overall population (n)	74	73	73
Median PFS (months)	7.2	7.7	3.7
Adjusted HR (90% CI)	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P-value	0.0124*	0.0161*	-
Prespecified sub-populations of interest			
ESR1m detected (n)	22	26	35
Median PFS (months)	6.3	9.2	2.2
Adjusted HR (90% CI)	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-
ESR1m not detected (n)	51	46	37
Median PFS (months)	7.2	5.8	7.2
Adjusted HR (90% CI)	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-

Oliviera, et al. 2022

VERITAC-2

Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer

A Progression-free Survival among Patients with *ESR1* Mutations



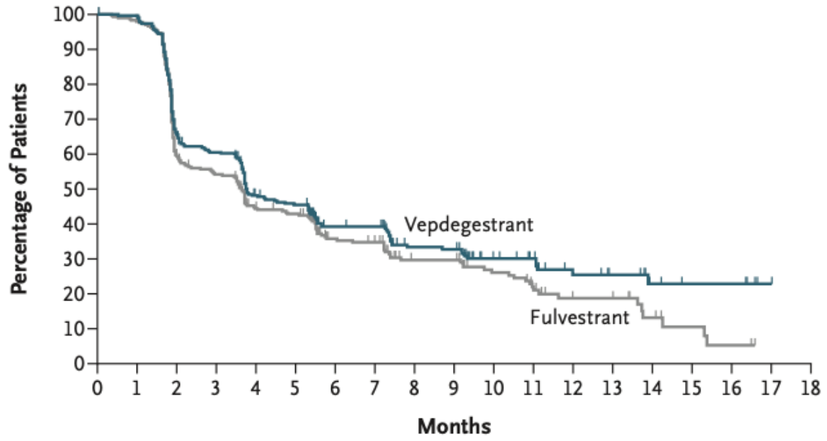
	No. of Events (%)	Median Progression-free Survival
		mo
Vepdegestrant (N=136)	82 (60.3)	5.0 (3.7–7.4)
Fulvestrant (N=134)	103 (76.9)	2.1 (1.9–3.5)

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.43–0.78)
P<0.001

No. at Risk

Vepdegestrant	136	134	89	80	58	56	41	40	24	24	16	15	11	9	6	5	5	2	0
Fulvestrant	134	128	66	56	37	35	21	19	12	14	13	10	6	6	4	2	0	0	0

B Progression-free Survival among All Patients Who Underwent Randomization



	No. of Events (%)	Median Progression-free Survival
		mo
Vepdegestrant (N=313)	198 (63.3)	3.8 (3.7–5.3)
Fulvestrant (N=311)	212 (68.2)	3.6 (2.6–4.0)

Hazard ratio for disease progression or death, 0.83 (95% CI, 0.69–1.01)
P=0.07

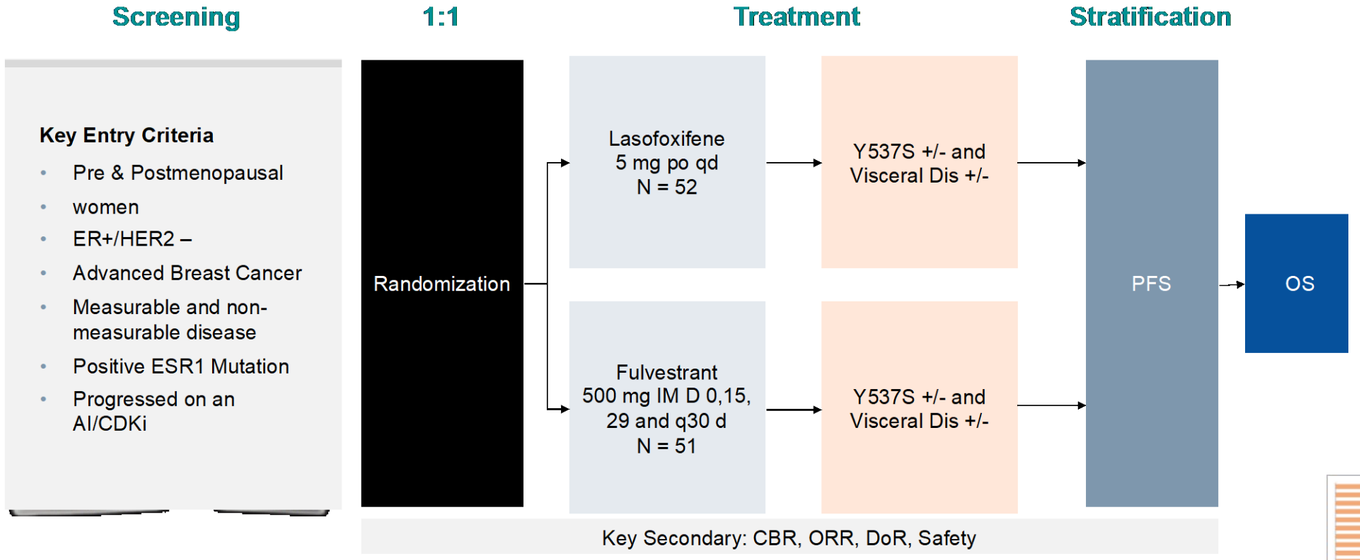
No. at Risk

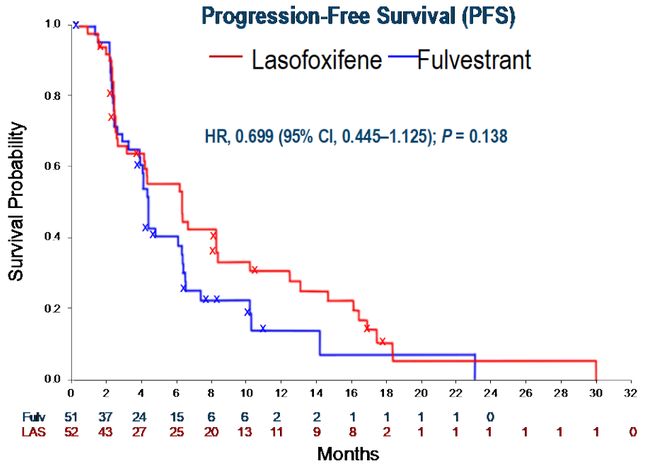
Vepdegestrant	313	307	199	180	126	118	84	82	56	55	34	29	17	13	8	6	6	2	0
Fulvestrant	311	297	173	154	115	109	70	66	47	47	33	24	14	14	7	4	2	0	0

Campone M, et al. 2025

ELAINE 1

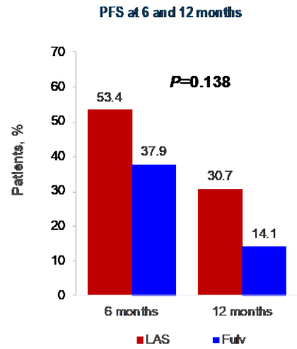
Open-label, randomized study of lasofoxifene (LAS) vs fulvestrant (Ful) for women with locally advanced/metastatic ER+/HER2- breast cancer (mBC), an estrogen receptor 1 (ESR1) mutation, and disease progression on aromatase (AI) and cyclin-dependent kinase 4/6 (CDK4/6i) inhibitors

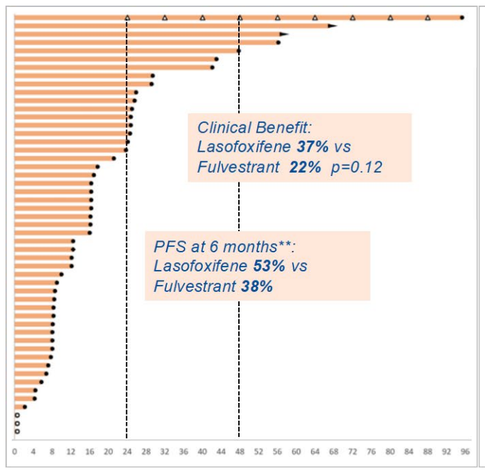


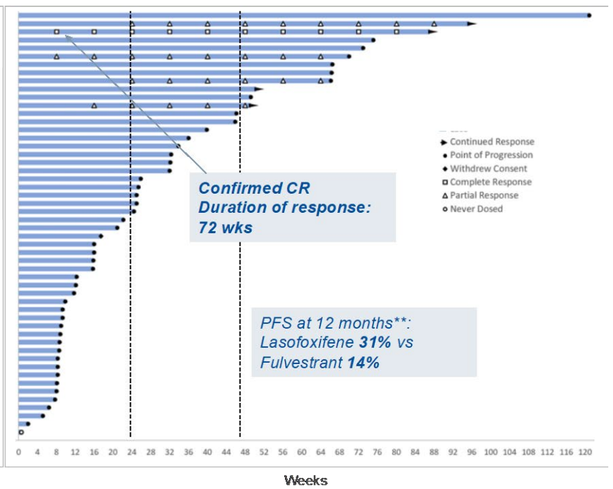


Median PFS

- LAS: 6.04 mos (2.82–8.04)
- Ful: 4.04 mos (2.93–6.04)







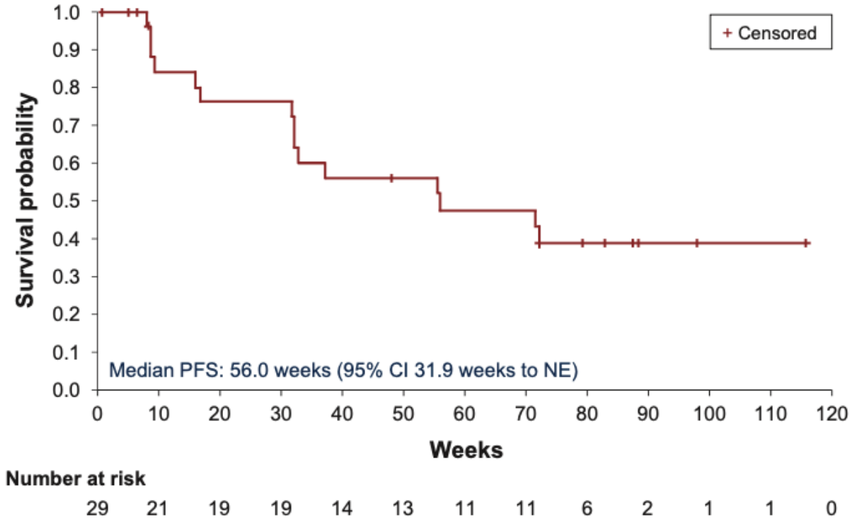
Goetz et al. ESMO 22

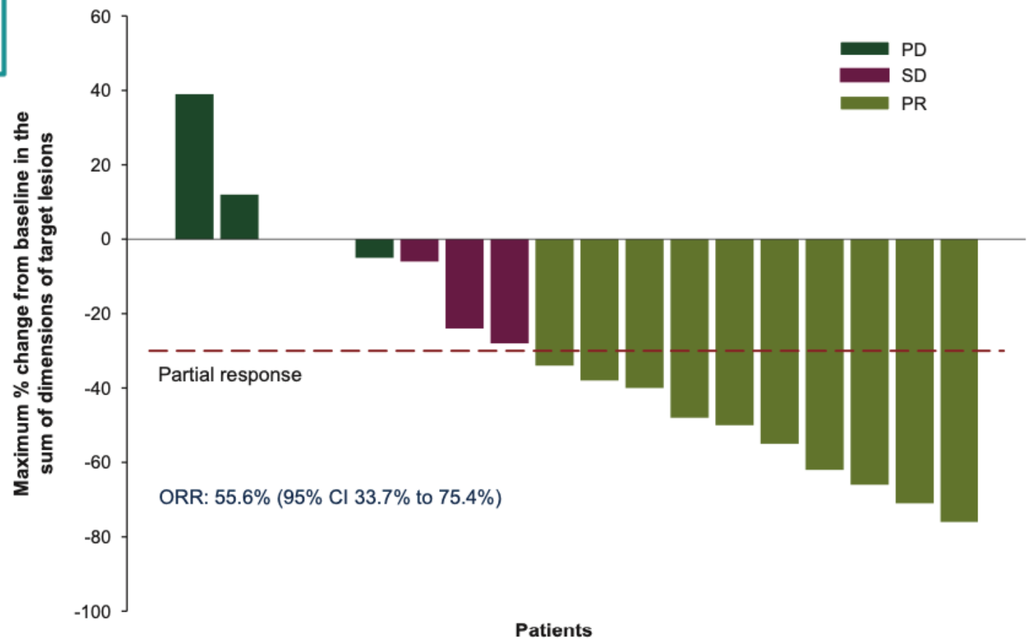
ELAINE2

Enrollment (full June 2021) N = 29

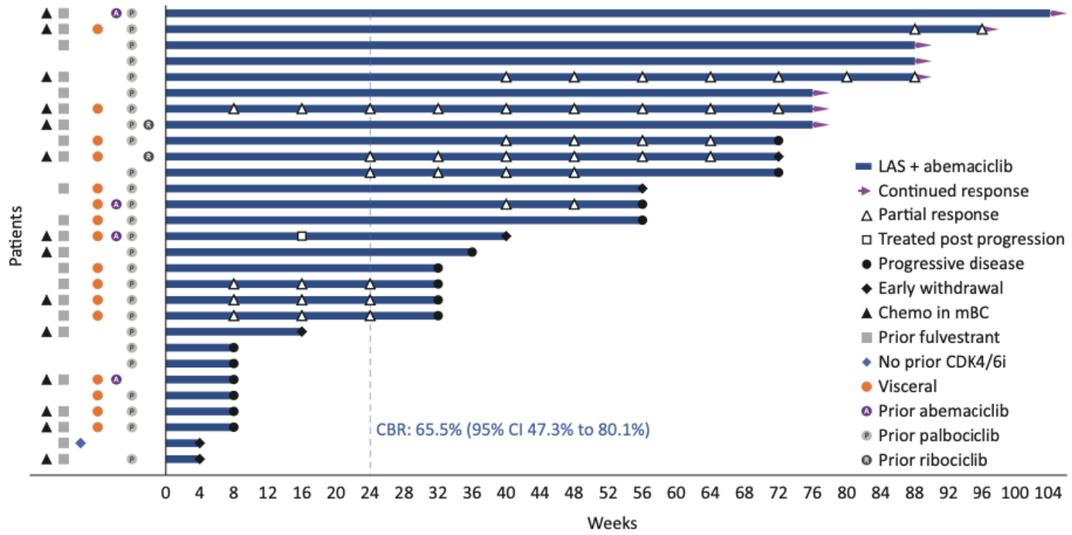
Lasofoxifene 5 mg oral QD plus **Abemaciclib**[32] 150 mg oral BID

Progression or withdrawal for any reason





Phase-3 ELAINE-3 in progress



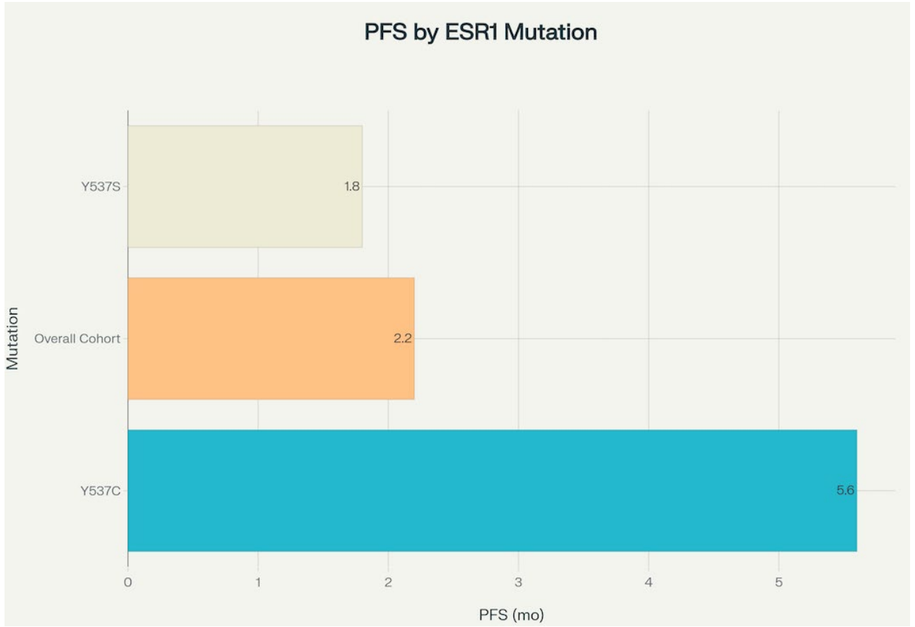
THE Elaine 2 STUDY

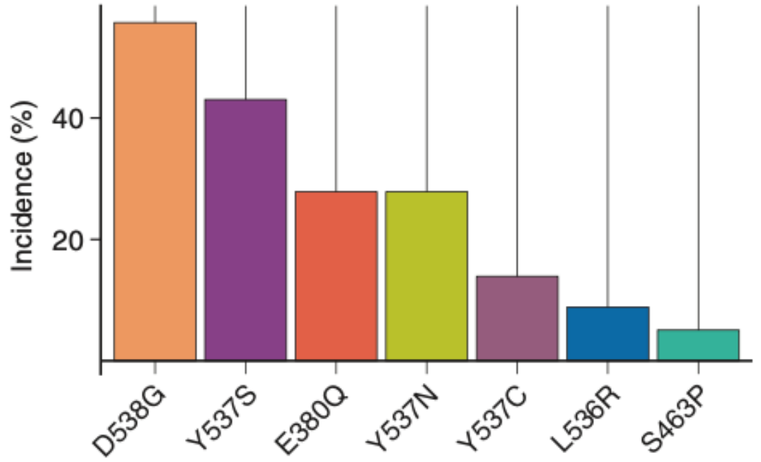
EVALUATING LASOFOXIFENE IN ESR1 MUTATIONS

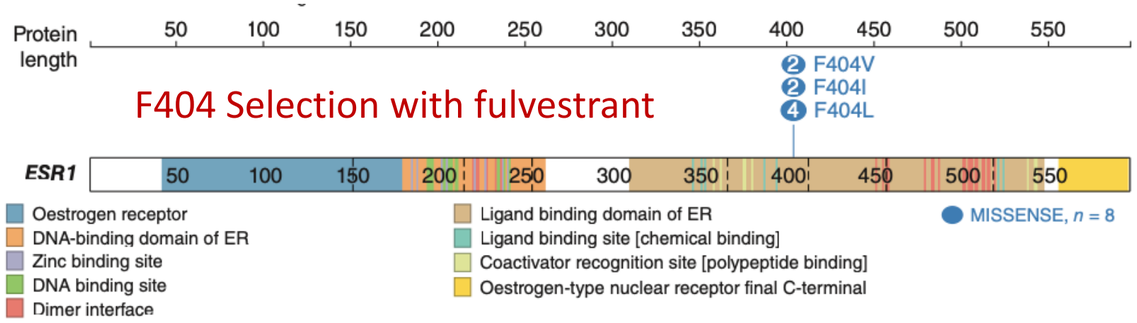
Damodaran, et al. 2023

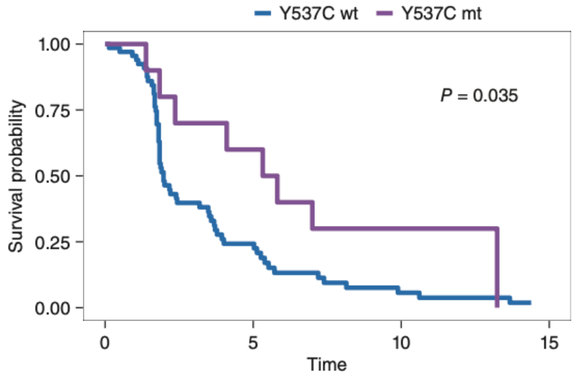
ESR1

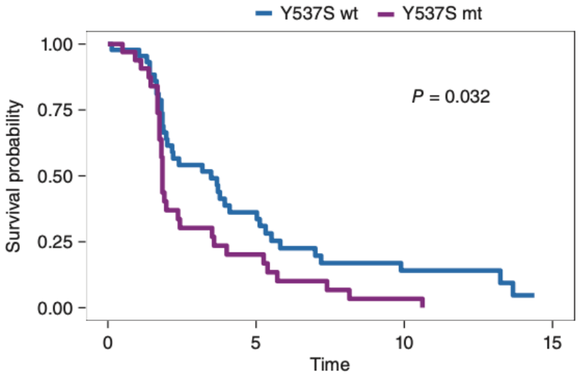
Differential sensitivity to fulvestrant









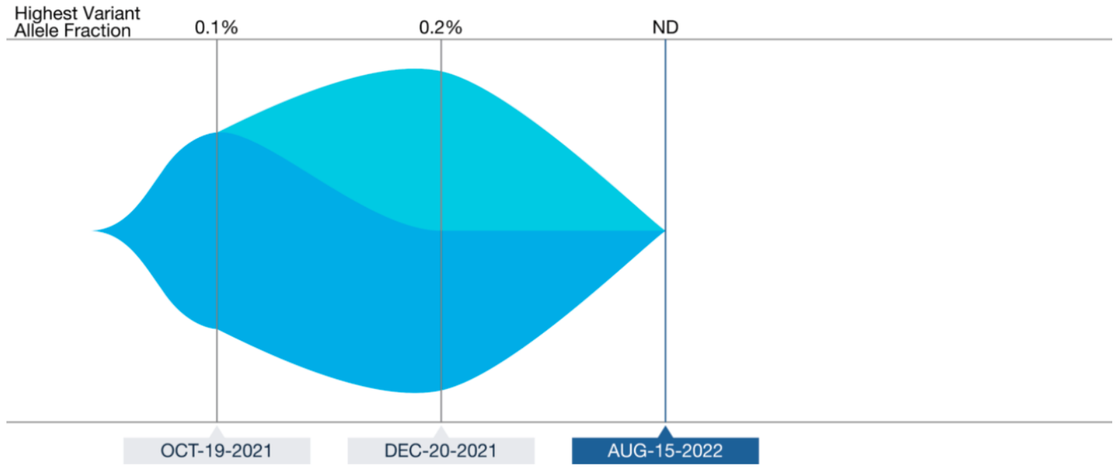


Kingston et al. 2024

ESR1

Evolving questions…

- Sub-clonal, low VAF and actionability ?
- Secondary mutations with novel SERDs
- Actionability of *ESR1* fusions ?
- Role of co-existing genomic alterations
- Role of non-LBD mutations



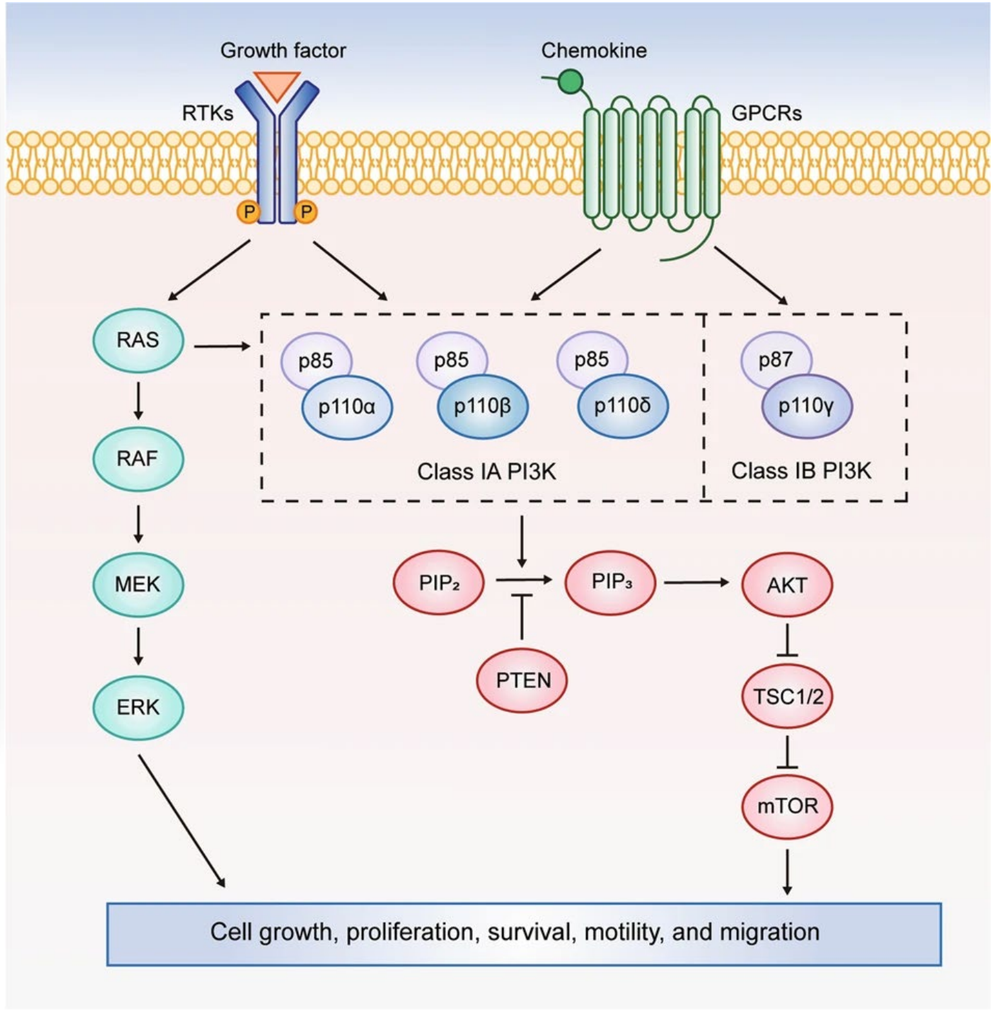
Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
ESR1 E380Q	ND	0.1% 0.2% ND
ESR1 Y537C	ND	ND 0.2% ND

Veeraraghavan et al.2014 Holst et al.2007

PI3K/AKT/MTOR Pathway

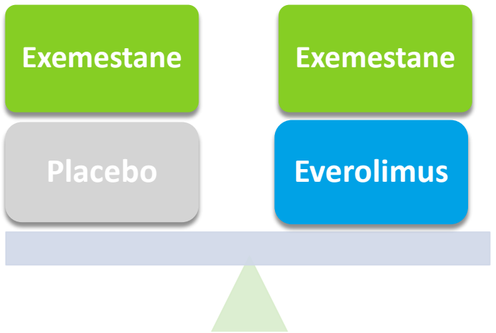
- The PI3K/AKT/mTOR pathway is one of the most frequently activated signaling pathways in cancers
- Critical for regulating cell growth, survival, metabolism
- Aberrant activation contributes to tumor growth, metastasis and drug resistance

The PI3K/AKT/mTOR signaling pathway in cancer



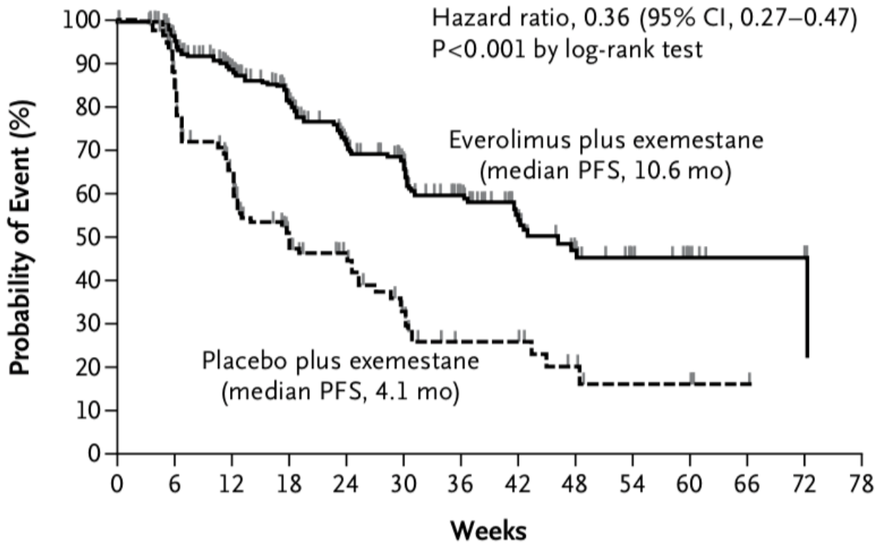
Sun and Meng, 2020

Everolimus



BOLERO-2

- Prior progression on NSAI
- No OS benefit
- With Fulvestrant (PFS 10.3 vs 5.1 months)
- *PIK3CA* mutations did not predict activity



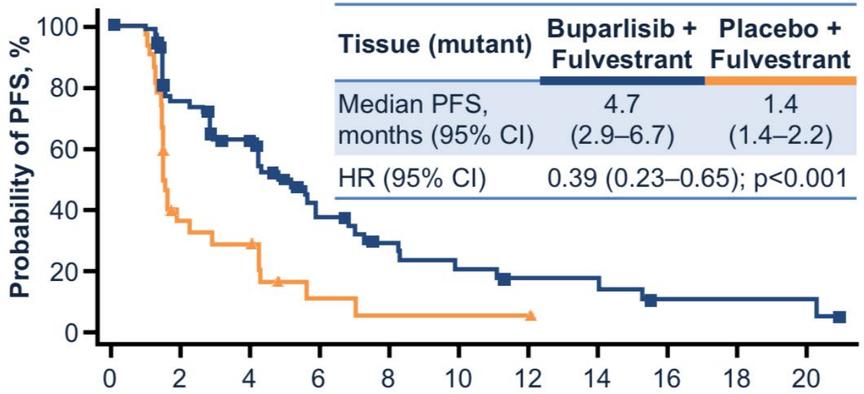
PIK3CA status	Treatment	*n*	Events	Median PFS, months (95% CI)	Hazard ratio (95% CI)
WT	EVE + EXE	188	132	7.36 (6.77–9.69)	0.43 (0.34–0.56)
	PBO + EXE	124	111	2.96 (2.76–4.17)	
MT	EVE + EXE	169	123	6.90 (5.55–8.31)	0.37 (0.27–0.51)
	PBO + EXE	69	60	2.69 (1.51–4.11)	
H1047R	EVE + EXE	95	65	7.59 (5.59–9.76)	0.37 (0.24–0.56)
	PBO + EXE	43	38	4.04 (1.51–4.70)	
E545K/ E542K	EVE + EXE	74	58	5.59 (4.14–7.82)	0.30 (0.18–0.51)
	PBO + EXE	26	22	2.22 (1.38–2.76)	

Baselga J. et al. 2012; Hortobagyi et al. 2015; Moynahan et al. 2017

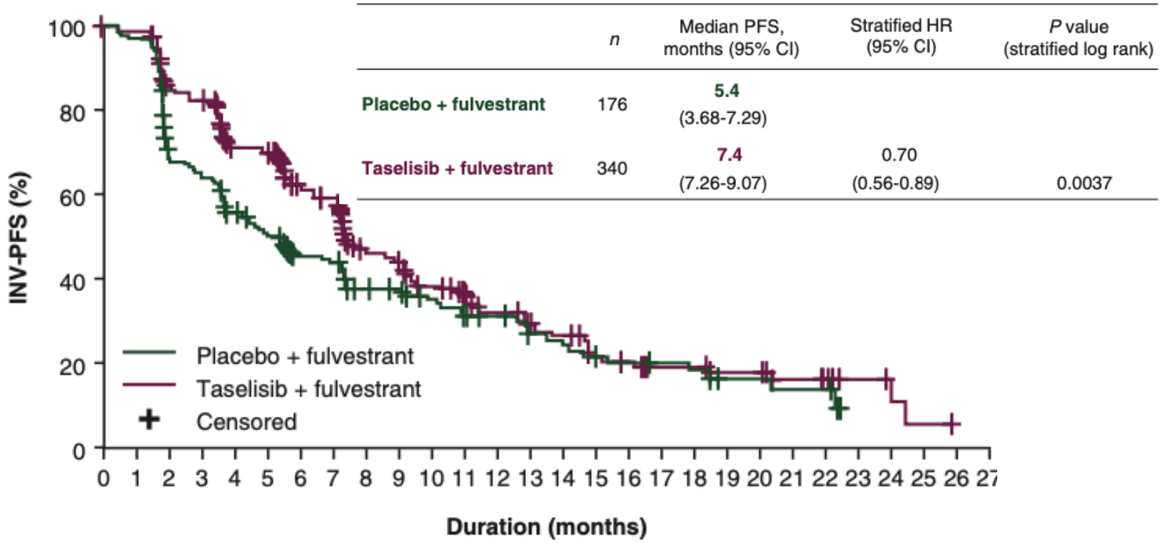
PIK3CA

Primary tumor tissue (PCR) N=321

PIK3CA mutant: 34%



Tissue (mutant)	Buparlisib + Fulvestrant	Placebo + Fulvestrant
Median PFS, months (95% CI)	4.7 (2.9–6.7)	1.4 (1.4–2.2)
HR (95% CI)	0.39 (0.23–0.65); p<0.001	



	n	Median PFS, months (95% CI)	Stratified HR (95% CI)	*P* value (stratified log rank)
Placebo + fulvestrant	176	5.4 (3.68-7.29)		
Taselisib + fulvestrant	340	7.4 (7.26-9.07)	0.70 (0.56-0.89)	0.0037

BELLE-3

- Phase-3 for ER +ve MBC
- Progressed on endocrine therapy or mTOR inhibitor (2:1)
- PFS improvement in *PIK3CA*
- AE - LFT elevation, hyperglycemia, HTN

SANDPIPER

- ER +ve MBC, recurrence on AI, No prior everolimus
- Post menopausal, *PIK3CA* mutation positive
- Significant toxicity, frequent interruptions

Di Leo et al. 2018; Baselga ASCO 2018

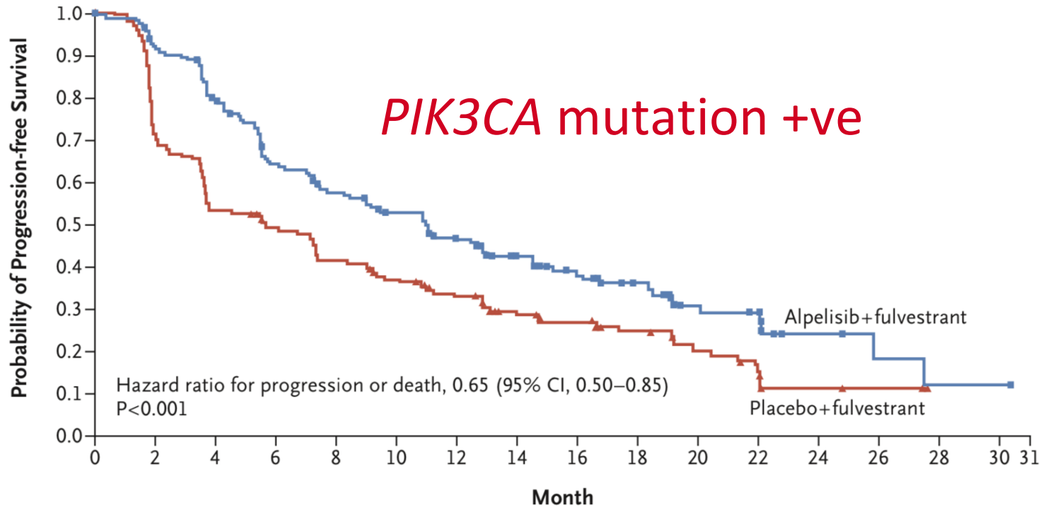
PIK3CA

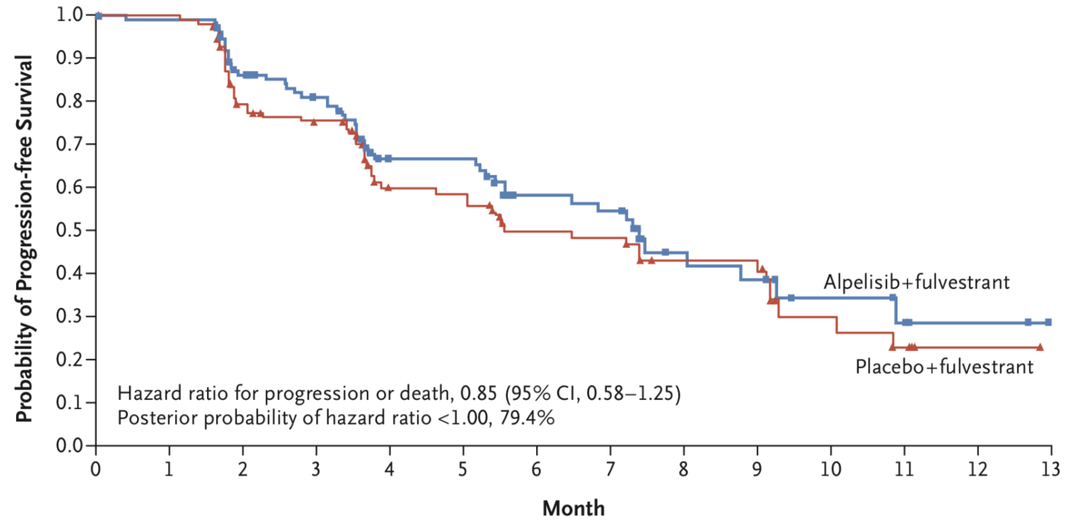
Alpelisib plus Fulvestrant vs. Fulvestrant

SOLAR-1

- ER +ve MBC, Recurrence on prior AI
- Alpha selective isoform inhibitor
- *PIK3CA* mutation +ve
- Primary endpoint – PFS 11 vs 5.7 months (HR 0.65). ORR 36% vs 16%
- Activity in both exon 9 and exon 20 mutations
- G3 hyperglycemia 33%, 10% rash, 7% diarrhea

FDA Approval May 2019

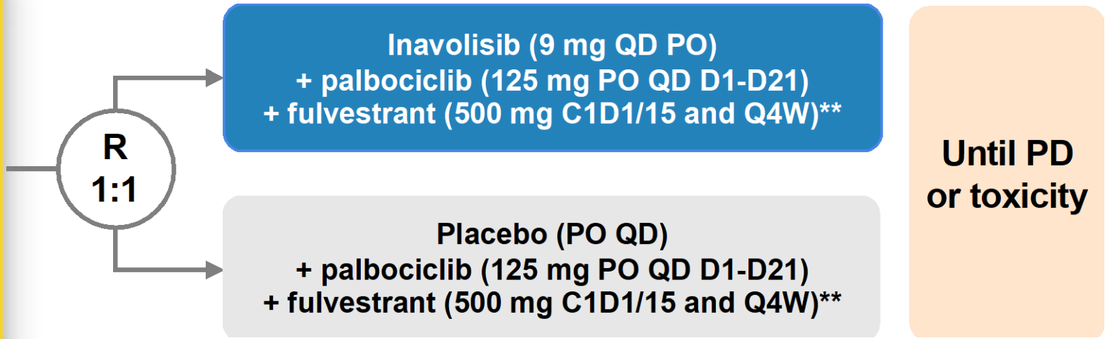


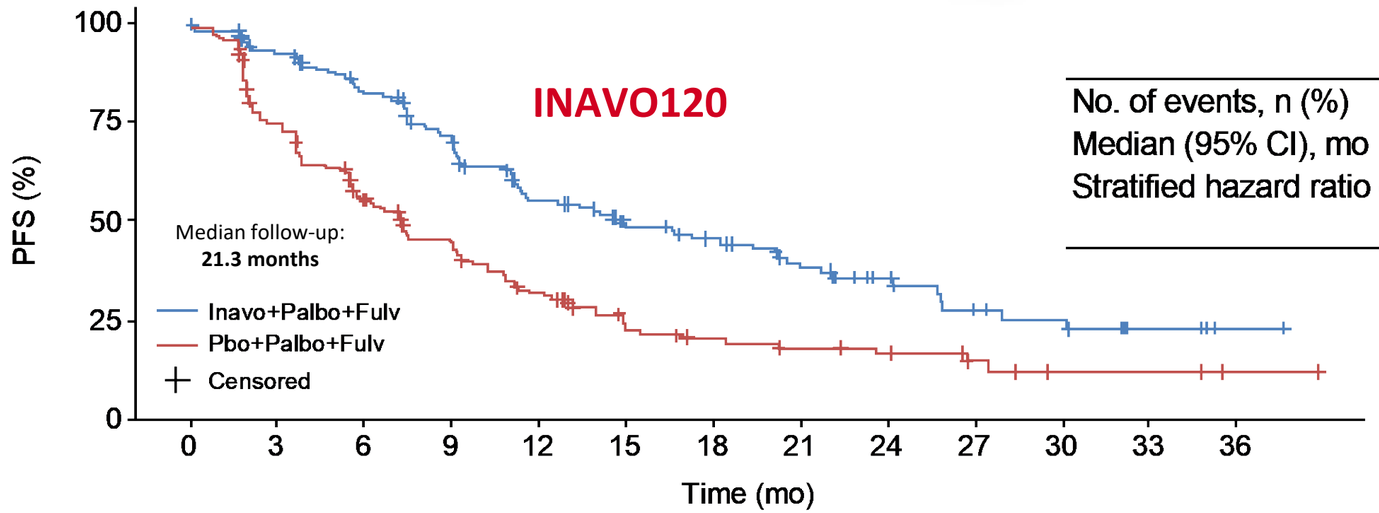


Andre et al. 2019

INAVO120

- Inavolisib, highly potent, selective inhibitor that also promotes the degradation of *mPIK3CA*
- *PIK3CA*-mutated, HR+, HER2- ABC
- Recurred on or within 12 months of adjuvant ET
- No prior therapy for ABC, fasting glucose <126 mg/dL and HbA1C <6.0%
- PFS 15 vs.7.3 mos; ORR 58.4 vs. 25%





	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59)**	
	p<0.0001	

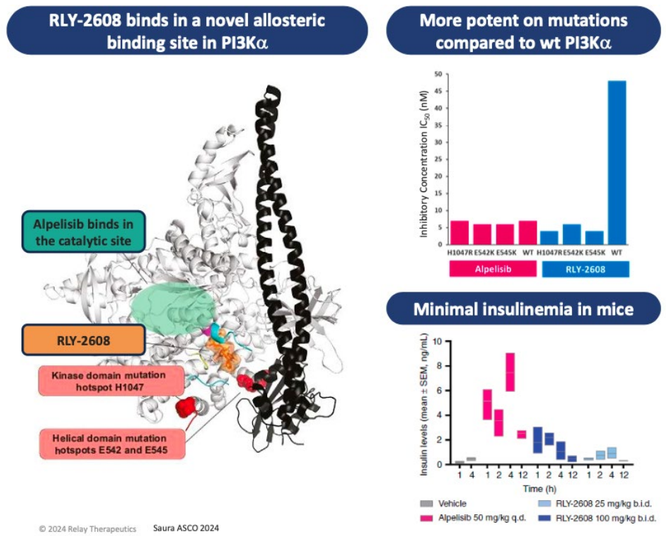
Jhaveri et al. SABCS 23

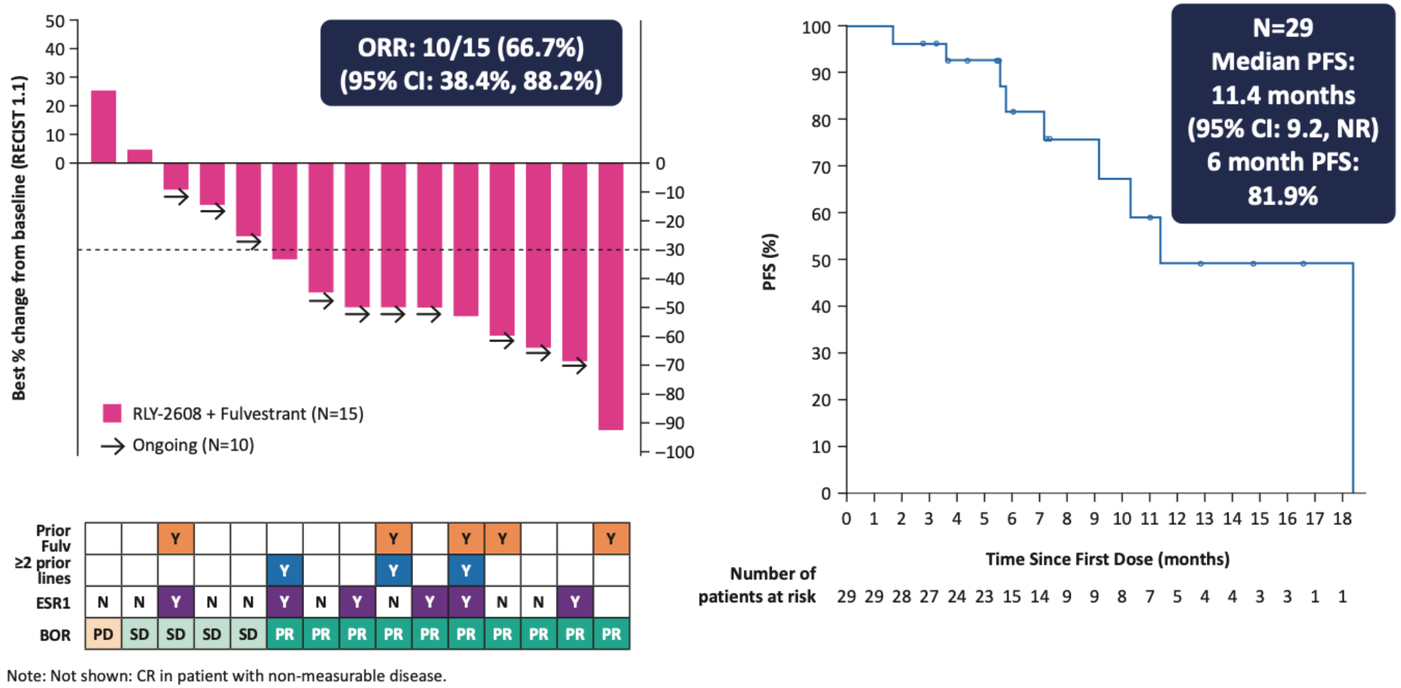
Next gen agents…

Mutant Selective Allosteric
- LOXO 783, OKI-219 (H1047R)

Pan-Mutant Selective Allosteric
- RLY-2608, STX-478, RLY-5836

Covalent Inhibitor
- TOS-358





Note: Not shown: CR in patient with non-measurable disease.

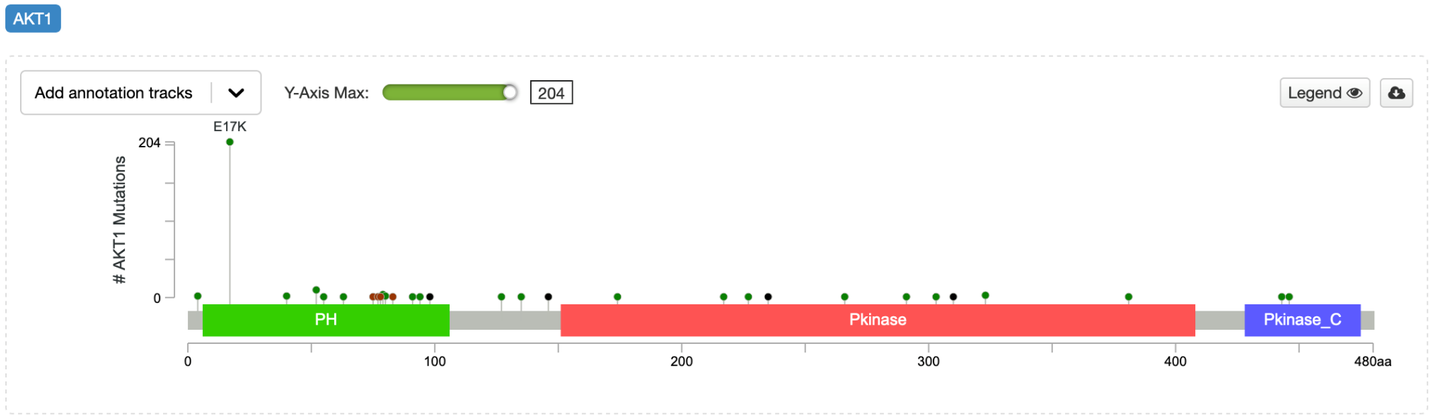
Saura et al. 2024

AKT1

A transforming mutation in the pleckstrin homology domain of AKT1 in cancer

John D. Carpten[1], Andrew L. Faber[2], Candice Horn[2], Gregory P. Donoho[2], Stephen L. Briggs[3], Christiane M. Robbins[1], Galen Hostetter[1], Sophie Boguslawski[2], Tracy Y. Moses[1], Stephanie Savage[1], Mark Uhlik[2], Aimin Lin[4], Jian Du[2], Yue-Wei Qian[4], Douglas J. Zeckner[2], Greg Tucker-Kellogg[5], Jeffrey Touchman[1], Ketan Patel[5], Spyro Mousses[6], Michael Bittner[1], Richard Schevitz[3], Mei-Huei T. Lai[2], Kerry L. Blanchard[2] & James E. Thomas[2]

- Downstream of PI3K
- Mutations primarily in E17K
- Important role in metabolism, cell survival, drug resistance
- ~ 5% primarily in HR positive



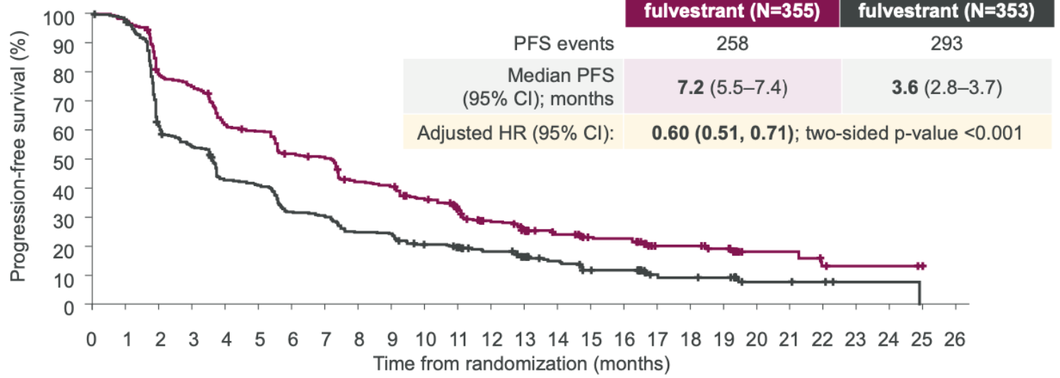
Carpten et al.2007

CAPItello-291

CAPItello-291

- 80% Received one line of ET, 70% CDK4/6 inhibitor. 19% prior chemo for MBC
- AE – Diarrhea, nausea, fatigue, hyperglycemia, rash
- Benefit seen in prior CDK4/6 inhibitors and visceral mets
- ORR 29 vs 10% in PI3K pathway altered

Dual-primary endpoint: Investigator-assessed PFS in the overall population

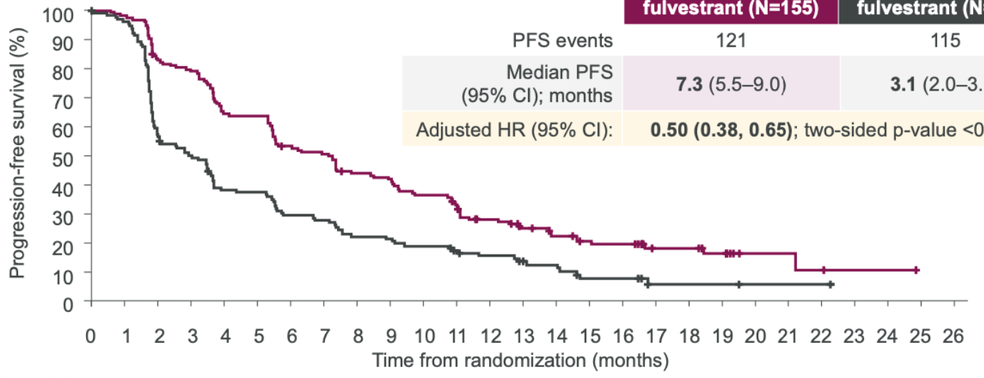


	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population



	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

FDA Approved – Nov 2023 for patients with *PIK3CA/ AKT1/PTEN* alterations

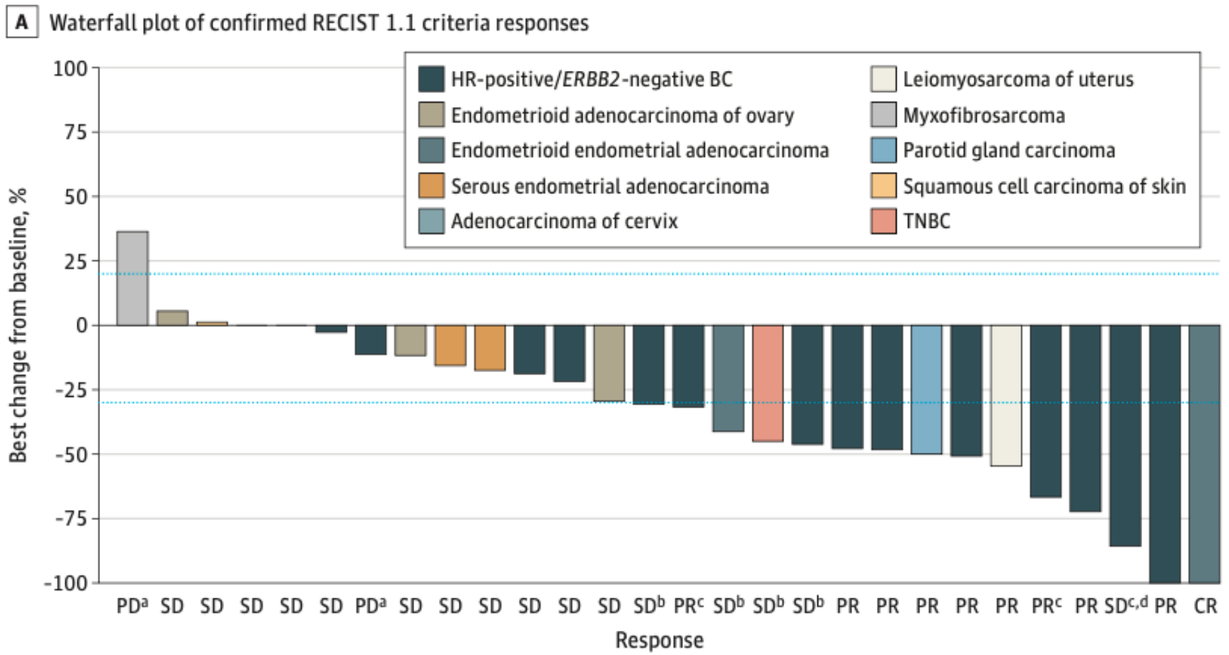
Turner, et al. 2022

AKT1 NCI MATCH

Effect of Capivasertib in Patients With an *AKT1 E17K*-Mutated Tumor
NCI-MATCH Subprotocol EAY131-Y Nonrandomized Trial

NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL

Tumor type	No. (%)
Breast carcinoma	18/35 (51)
HR positive/*ERBB2* (formerly *HER2*) negative	15 (43)
TNBC	3 (9)
Gynecologic	11/35 (31)
Endometrioid endometrial adenocarcinoma	4 (11)
Endometrioid adenocarcinoma of the ovary	3 (9)
Serous endometrial adenocarcinoma	2 (6)
Leiomyosarcoma of the uterus	1 (3)
Adenocarcinoma of the cervix	1 (3)
Other	
Adenocarcinoma of the pancreas	1 (3)
Myxofibrosarcoma	1 (3)
Oncocytic carcinoma of the parotid gland	1 (3)
Squamous cell carcinoma of the skin	1 (3)
Squamous cell lung carcinoma	1 (3)
Squamous cell and urothelial carcinoma of the kidney pelvis	1 (3)

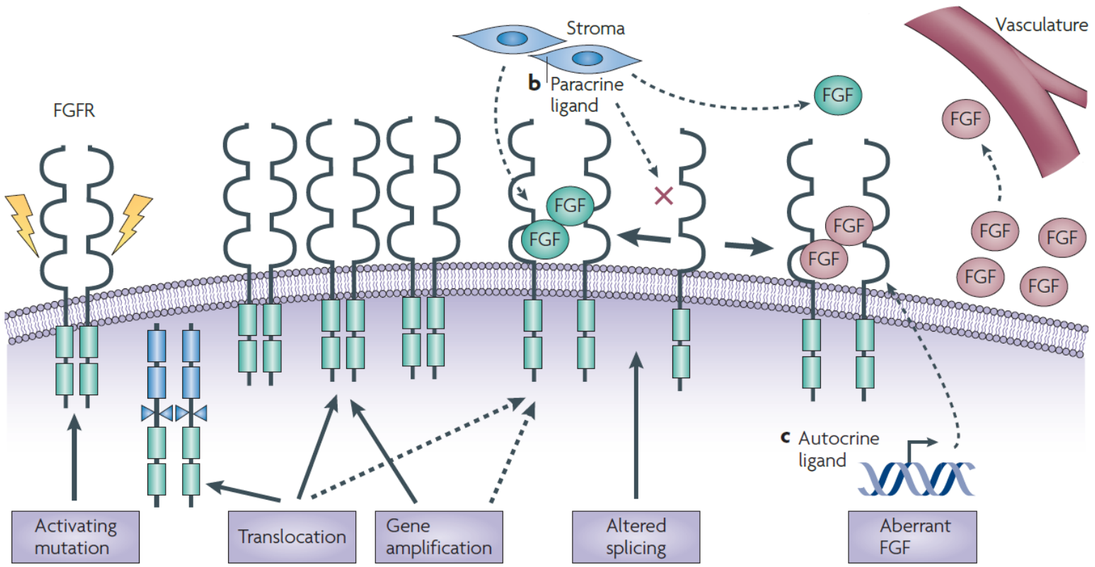


Kalinsky, et al. 2020

FGFR

- Play essential roles in mediating cell proliferation, migration, and survival
- Four different receptors – FGFR1, FGFR2, FGFR3 and FGFR4 with 22 known ligands
- Deregulation of FGFR signaling pathway recognized in multiple cancers including breast, bladder, CCA, and lung cancers
- *FGFR1* amplification /overexpression observed in ~10% of HR+/HER2−ve breast cancer and associated with endocrine resistance with poor prognosis
- *FGFR1* amplifications often coexist with 11q amplification (*CCND1, FGF3/4/19*)
- *FGFR2* amplification observed in 4% TNBC

Aberrant FGFR Signaling



Amplifications

SNV

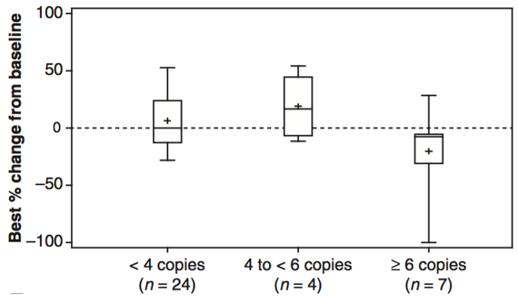
Fusion

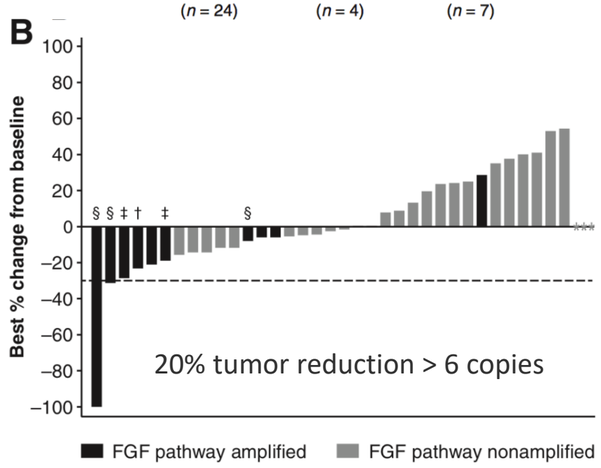
Turner and Grose, 2010; Jang et al. 2012, Turner et al. 2010

FGFR Targeting

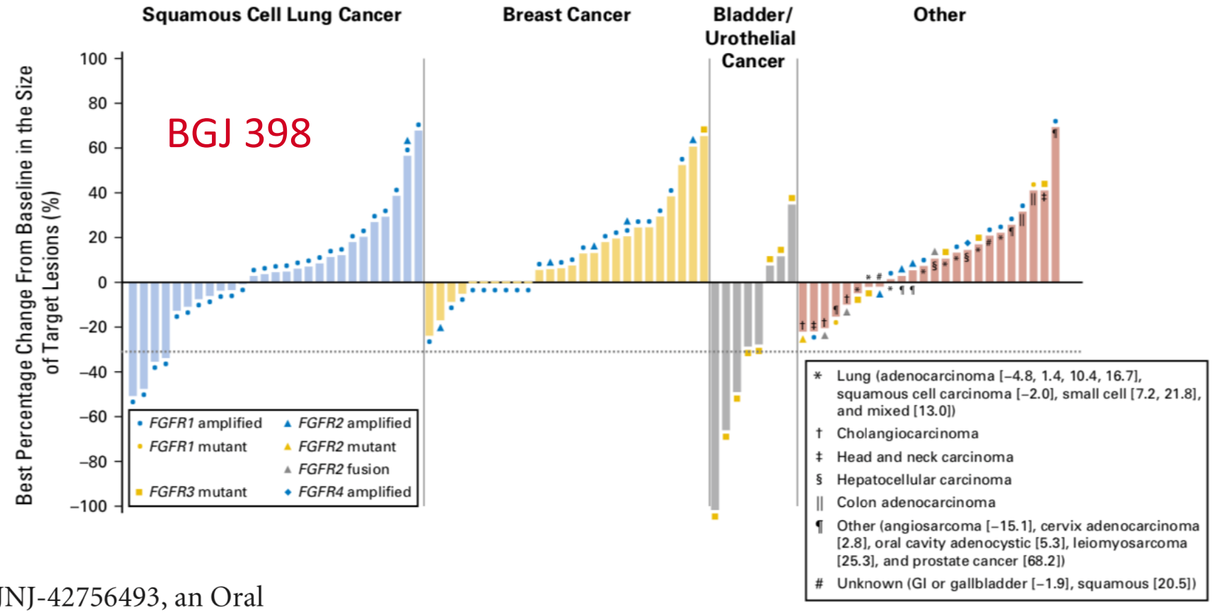
Single agent FGFR inhibitor activity

Dovitinib

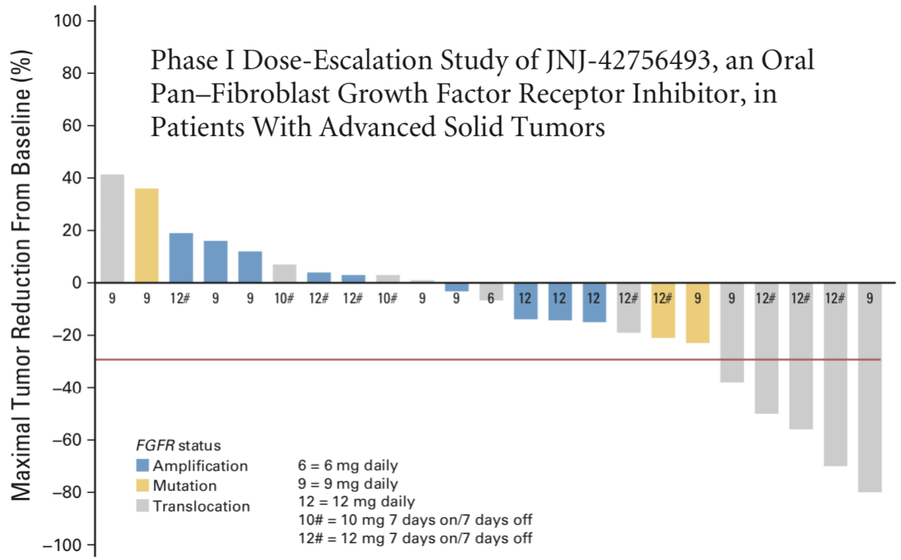




BGJ 398



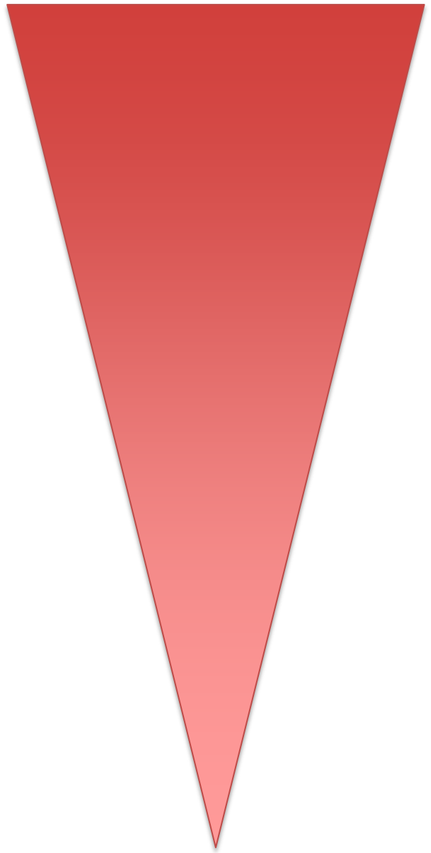
Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan–Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors



Andre et al. 2013, Nogova et al. 2016, Tabernero et al. 2015

Targeting FGFR

Actionability

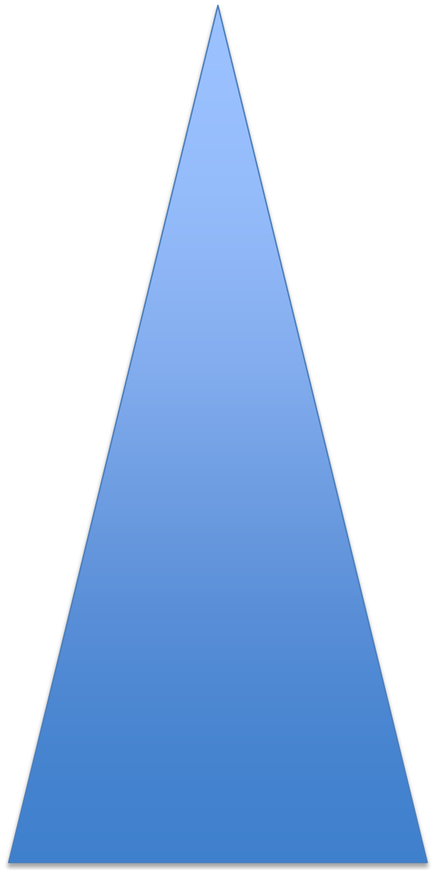


Fusions

SNVs

CNVs

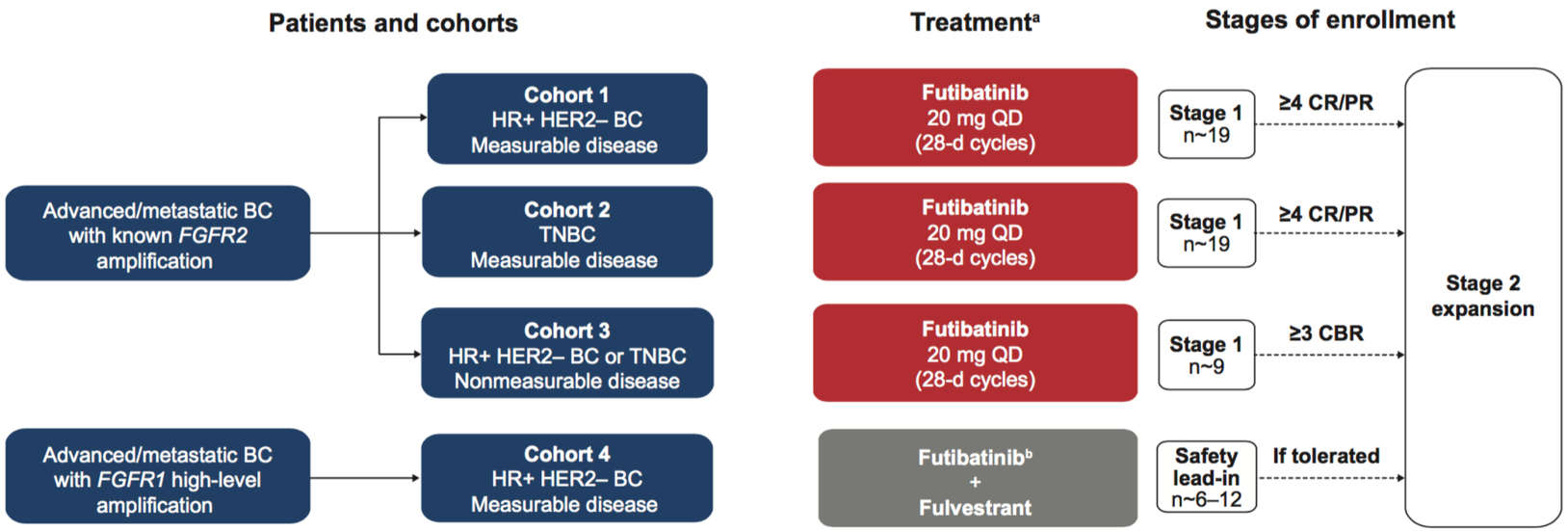
Prevalence



14% FGFR1 CNV, 2.3% FGFR2 CNV

Futibatinib (TAS 120) in MBC

- Futibatinib (TAS-120) a potent, highly selective irreversible, FGFR1–4 inhibitor
- *FGFR2* CNV or *FGFR1* with high copy number CN ≥ 10



Futibatinib (TAS 120) in MBC

Patients
- HR+/HER2− MBC

Futibatinib PO
every 28 days
trant 500 mg IM

Primary endpoint
- 6-month PFS rate

Secondary endpoints
- ORR, CBR, PFS,OS

Patients
- Advanced or metastatic TNBC
- Locally confirmed *FGFR2* amplification

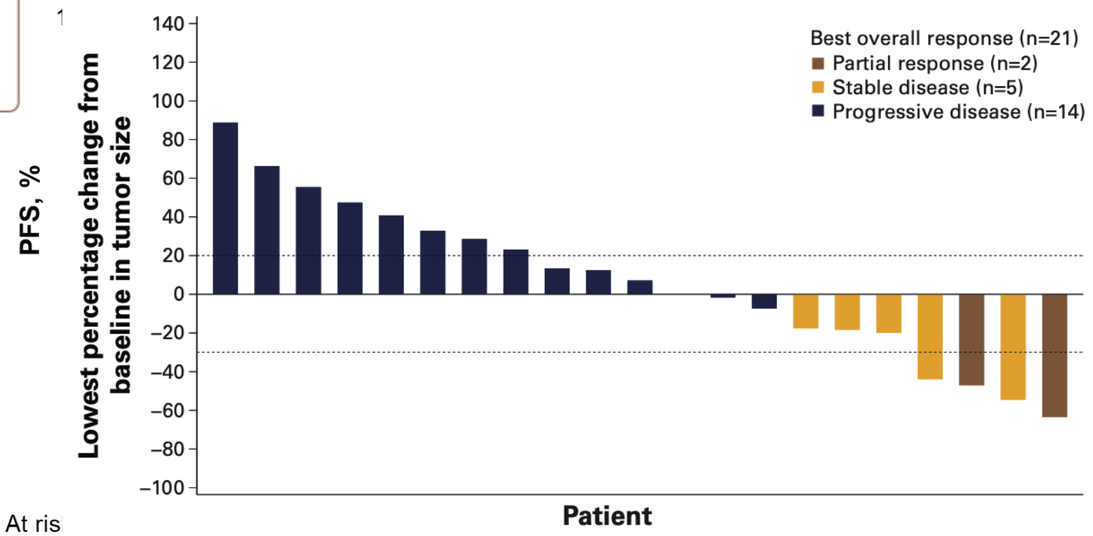
Futibatinib
20 mg orally
QD, continuously
(28-day cycles)

Primary endpoint
- ORR

Secondary endpoint
- CBR
- 6-month PFS
- PFS
- DOR
- OS
- Safety profile

Confirmed best response, n (%)

	Patients (N=21)
Confirmed best overall response, n (%)	
CR	0
PR	2 (9.5)
SD	5 (23.8)
PD	14 (66.7)
ORR, % (95% CI)	9.5 (1.2, 30.4)
CBR, % (95% CI)[a]	23.8 (8.2, 47.2)
Median DOR, months (range)	3.38 (3.1–3.7)
Median time to response, months (range)	2.7 (1.8–3.6)

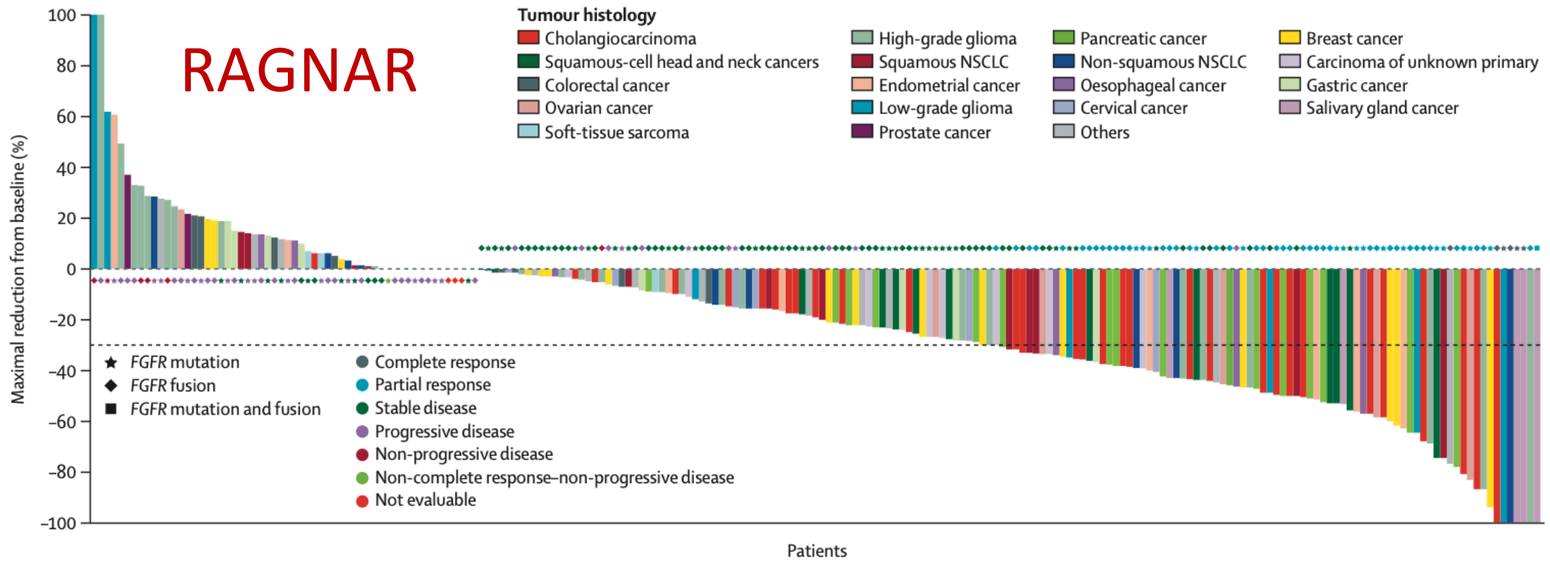


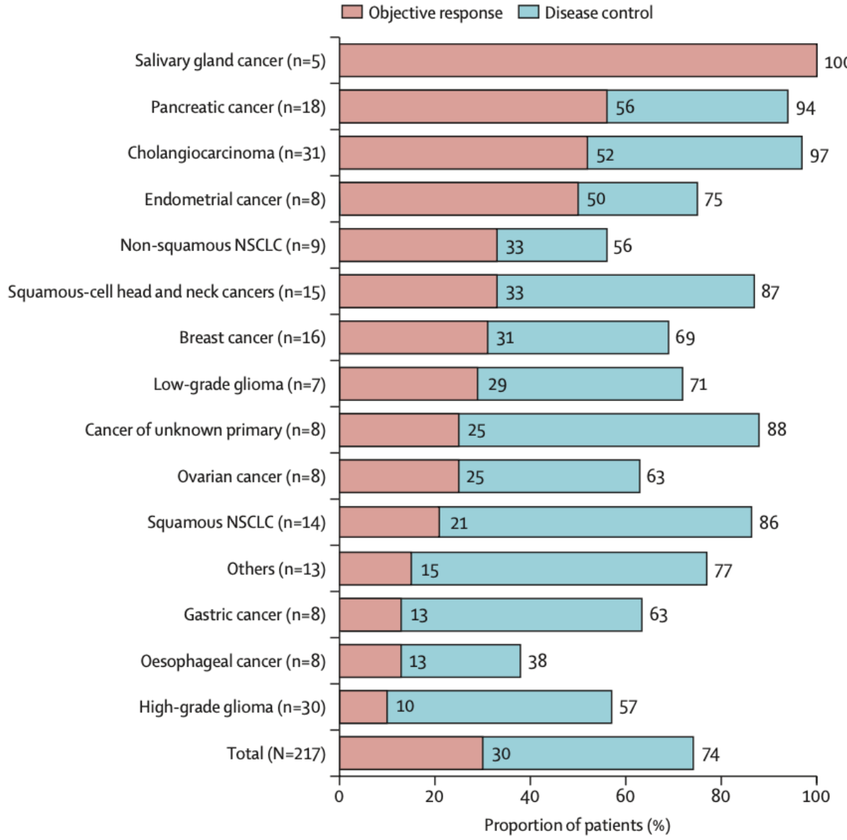
At ris

Damodaran et al 2023; Giordano et al. 2023

Erdafitinib

Histology Agnostic, FGFR1–4 alterations (mutations or fusions)





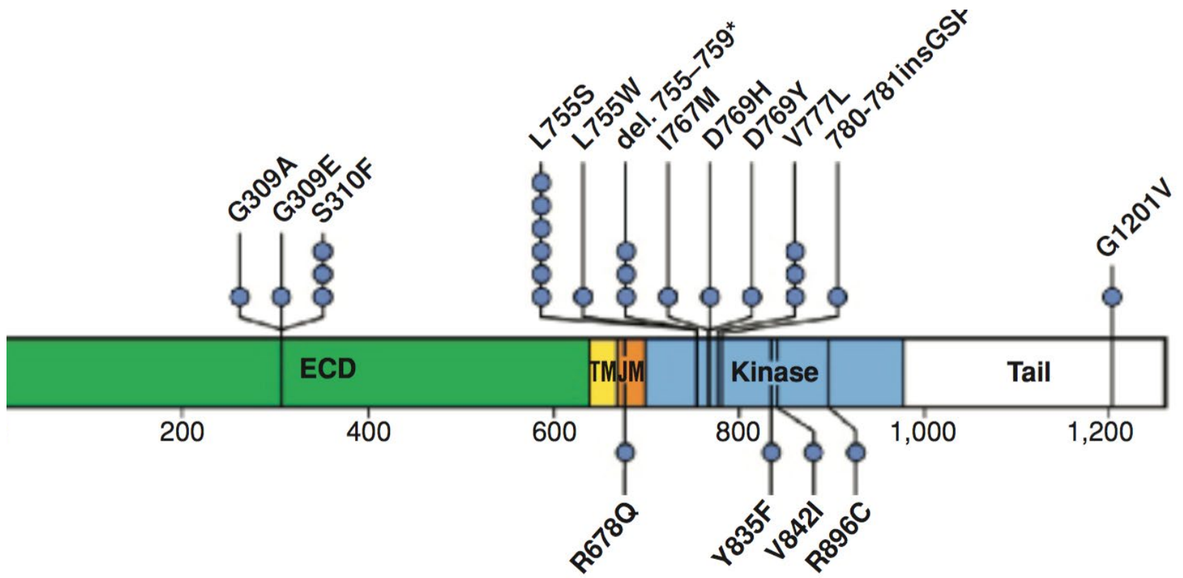
Responses in FGFR2/3 mutants. Erdafitinib endorsed by NCCN (2B)

Pant et al. 2023

HER2

SNV

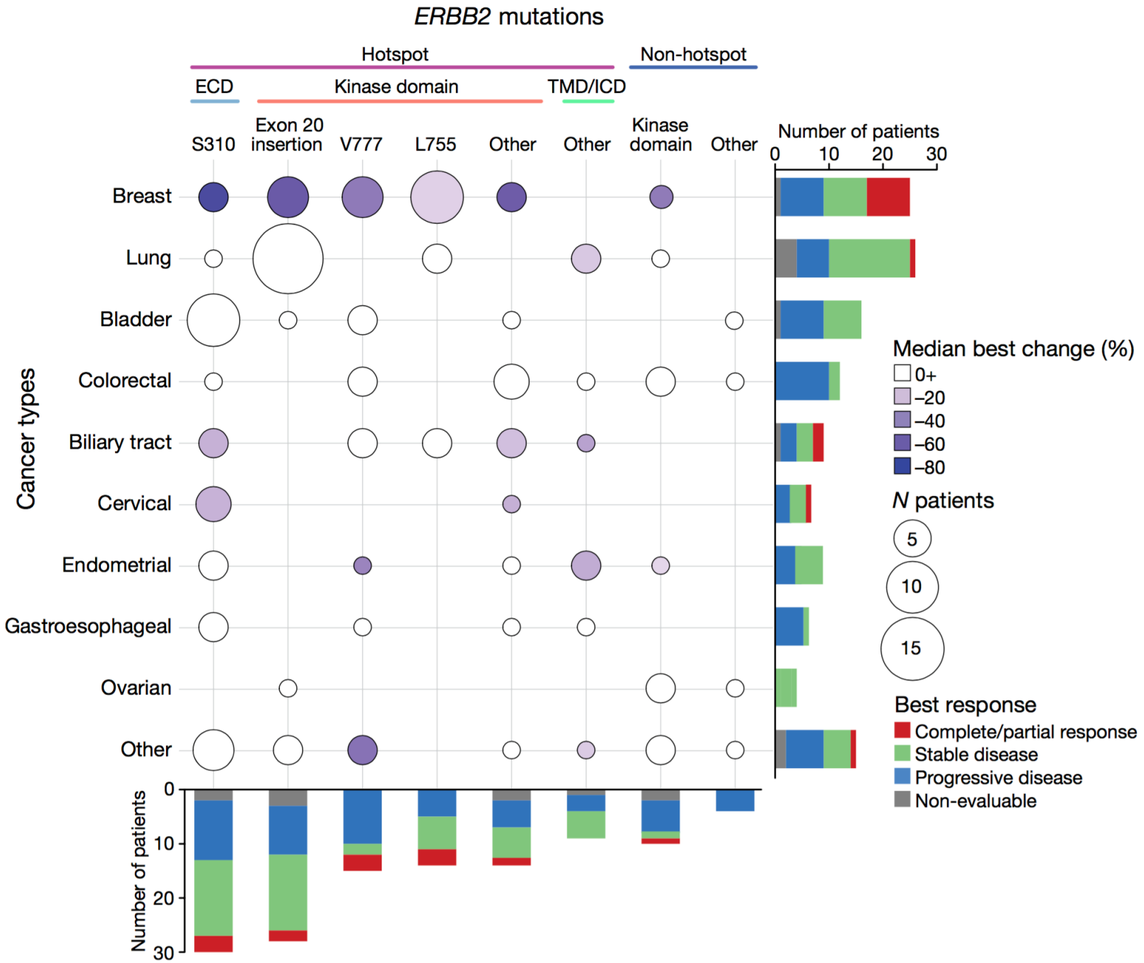
- ERBB2(HER2) mutations observed in ~2 % of breast cancers. Common in ILC
- Typically, exclusive with ERBB2 amplification
- Can affect binding to mAB (pertuzumab)
- Variants predict differential sensitivity or response to HER2 agents (e.g. neratinib vs lapatinib for L755S)

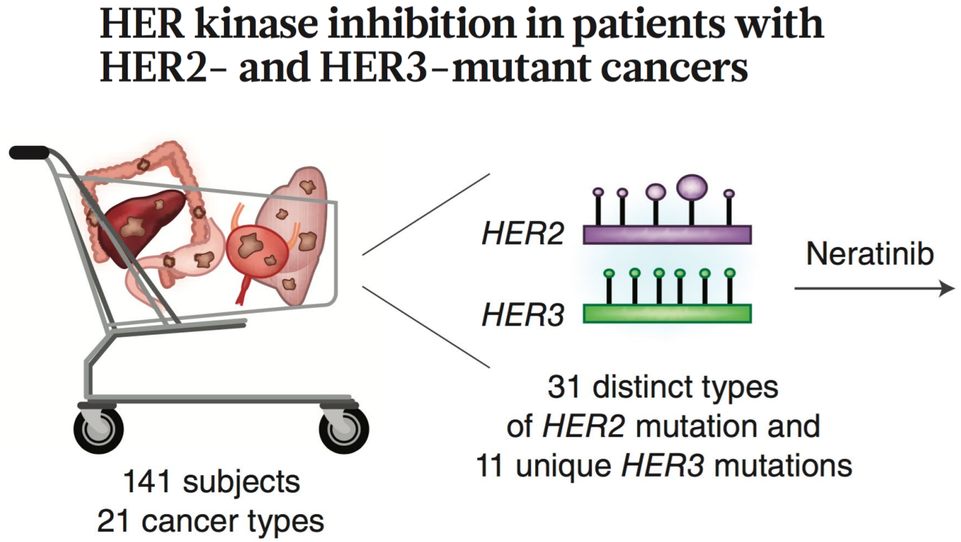


Bose et al. 2012

HER2

SUMMIT Basket Trial - Neratinib





Breast - RR:32% (8/25), 6 ER positive

Hyman et al. 2018

HER2

***HER2*-mutant MBC**

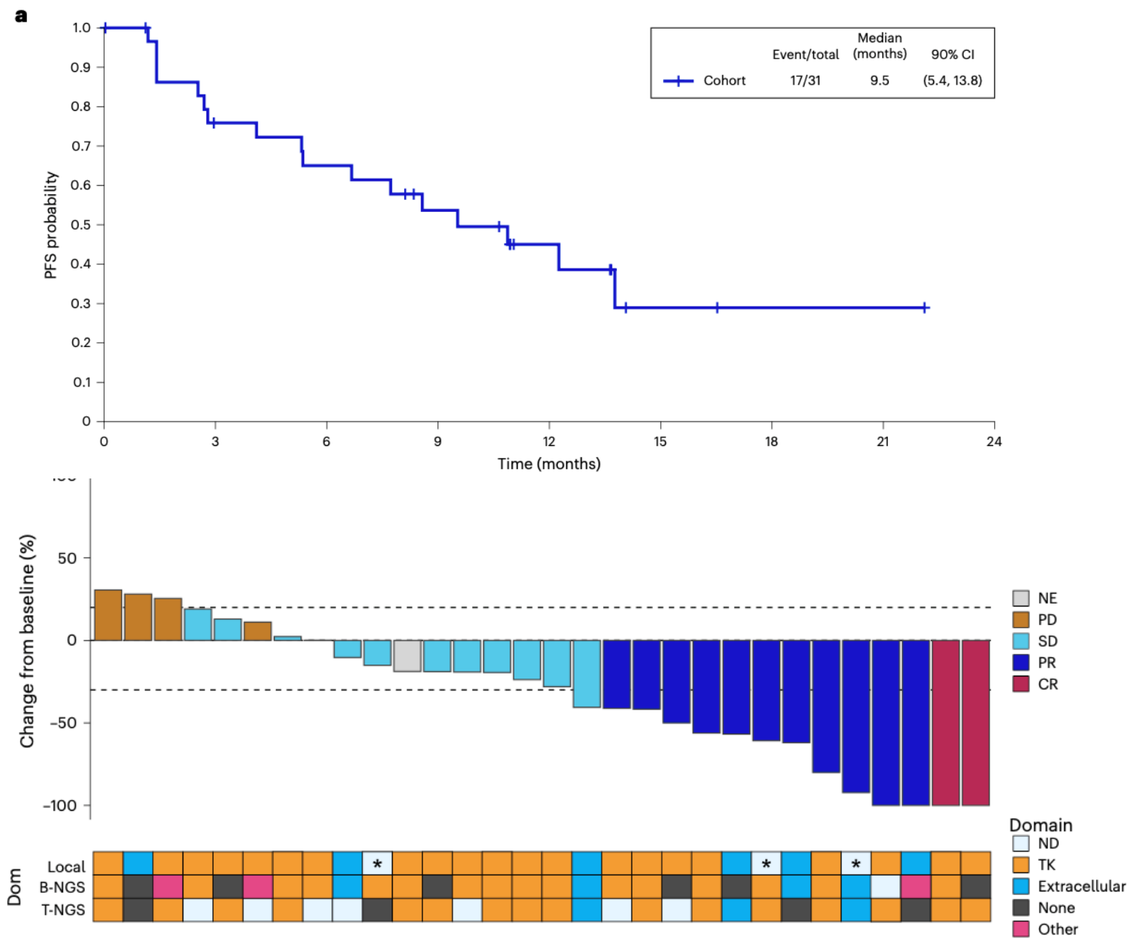
MBC cohort	Treatment assignment	ORR
HR+/HER2-negative MBC (with prior CDK4/6i) **Non-randomized**	**Neratinib + Fulvestrant + Trastuzumab**	**12/26 (46.2%)**
HR+/HER2-negative MBC (with prior CDK4/6i) **Randomized** (R 1:1:1)	**Neratinib + Fulvestrant + Trastuzumab**	**2/7 (28.6%)**
	Fulvestrant + Trastuzumab	**0/7 (0%)** → PD → N+T+F
	Fulvestrant	**0/7 (0%)** → PD → N+T+F
Triple-negative breast cancer	**Neratinib + Trastuzumab**	**2/7 (0%)**

Jhaveri K, et al. SABCS 2021

HER2 SNV

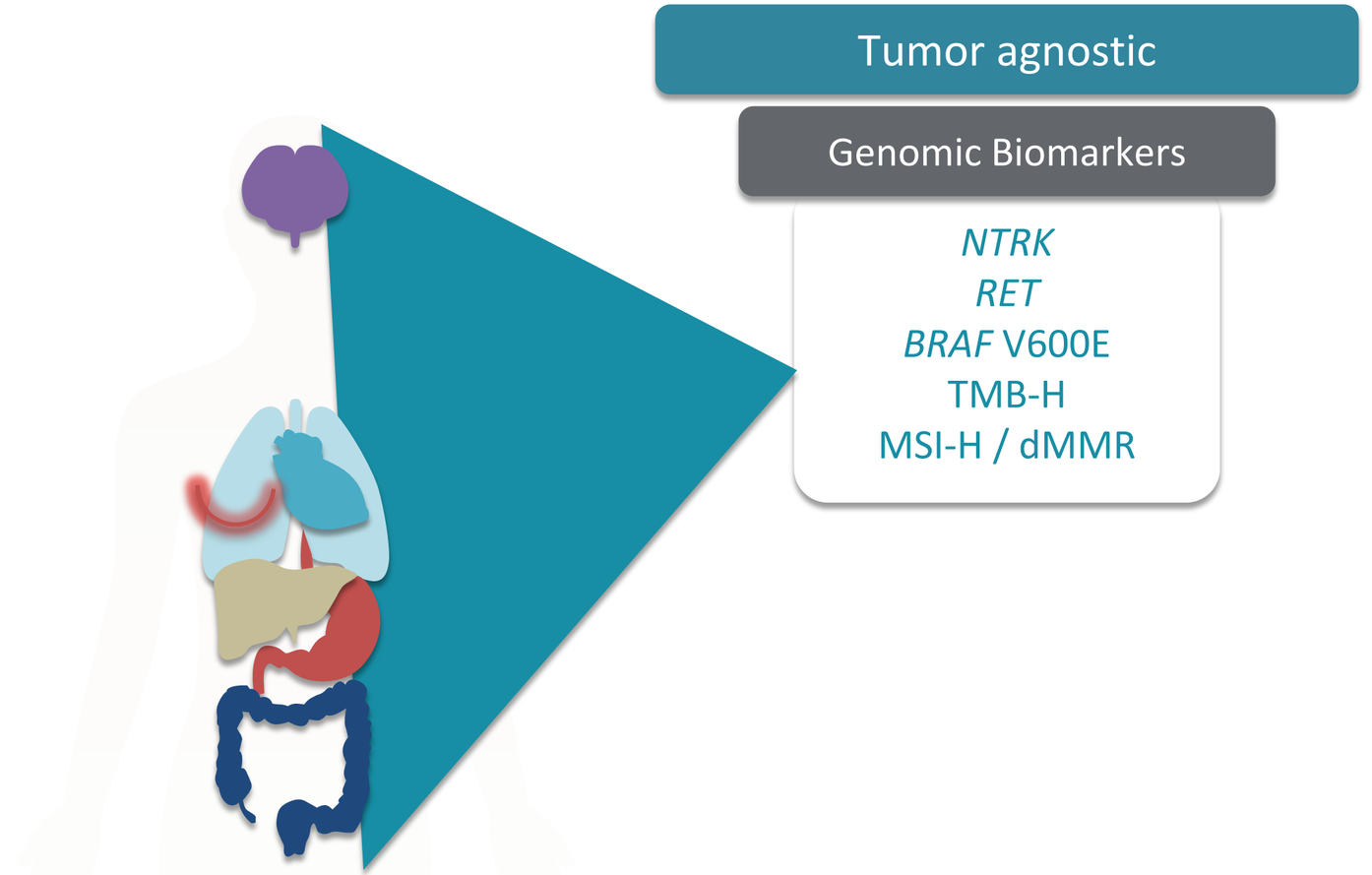
Tucatinib and trastuzumab in HER2-mutated metastatic breast cancer: a phase 2 basket trial

	Total (*N*=31)
Best overall response[a], *n* (%)	
CR	2 (6.5)
PR	11 (35.5)
SD	12 (38.7)
PD	4 (12.9)
Not available[b]	2 (6.5)
cORR, *n* (%)	13 (41.9)
90% CI[c] for cORR	(26.9, 58.2)
Median duration of objective response[d] (months) (90% CI)[c]	12.6 (4.7, –)
Disease control rate[e], *n* (%)	25 (80.6)
90% CI[c] for disease control rate	(65.3, 91.2)
Median PFS (months) (90% CI)[f]	9.5 (5.4, 13.8)
Median OS (months) (90% CI)[f]	20.1 (15.9, –)



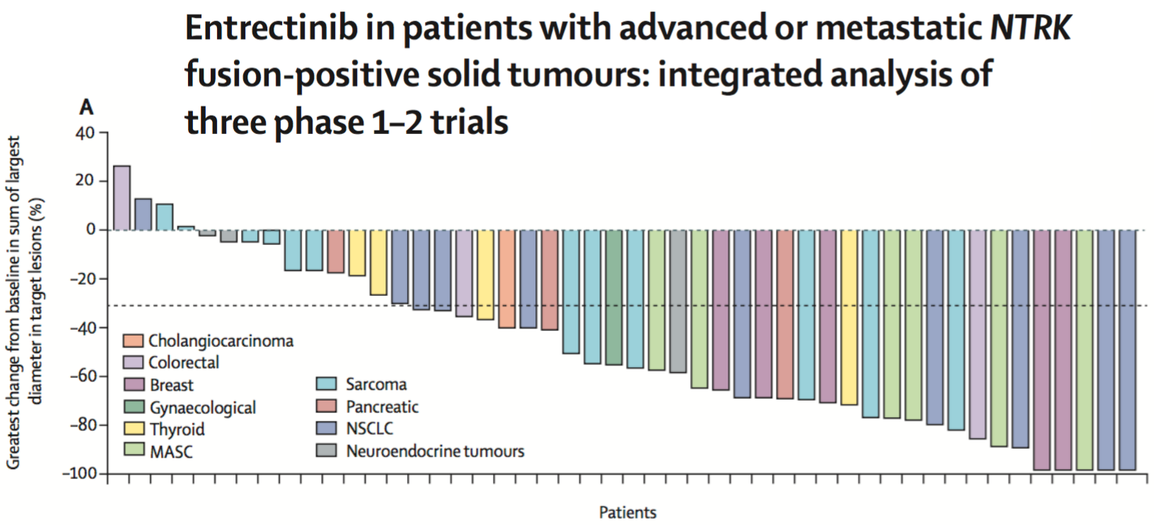
Okines et al. 2025

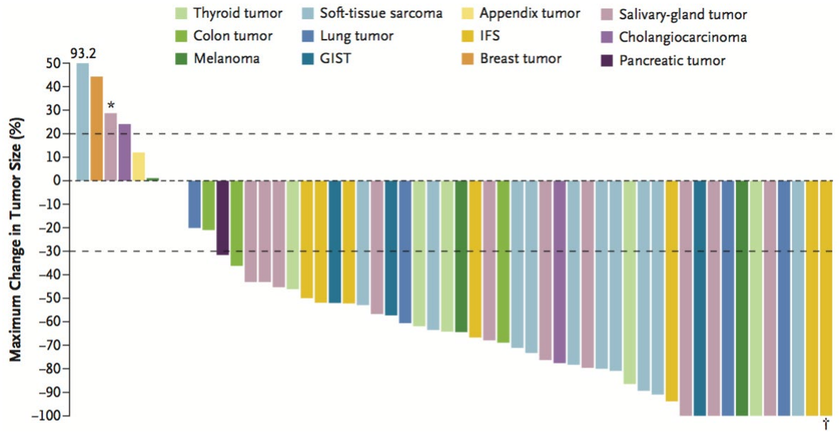
Tumor agnostic biomarkers



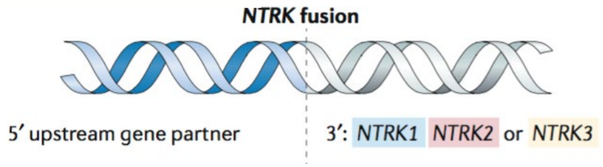
Damodaran, S. Precisions Edge Webinar 2024

NTRK





Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children



- Present in < 1% of breast cancers, in TNBC
- Pathognomonic in secretory breast cancer (ETV6-NTRK3)
- Typically associated with low TMB and MSI-S

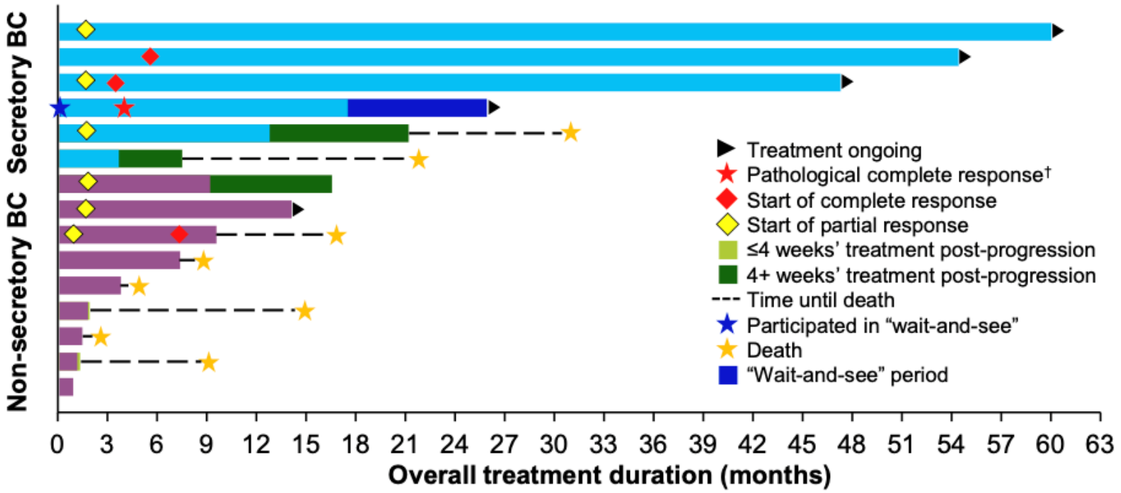
Larotrectinib, Entrectinib, Repotrectinib approved for *NTRK* gene fusion-positive solid tumors

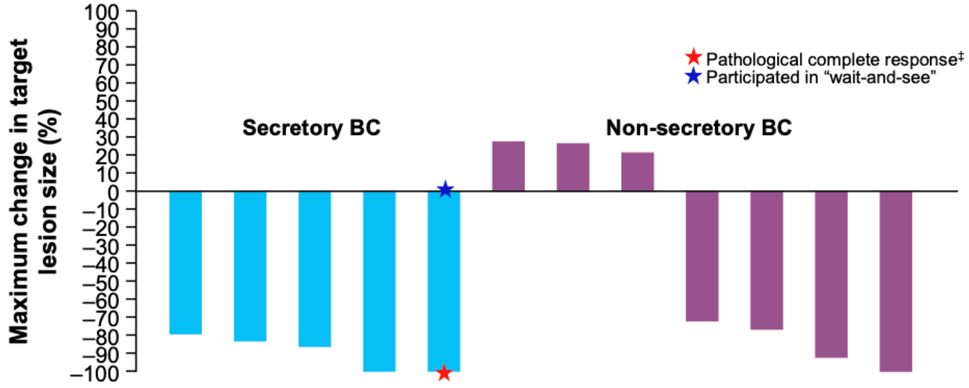
Cocco et al. 2018, Doebele et al.2020, Drilon et al. 2020

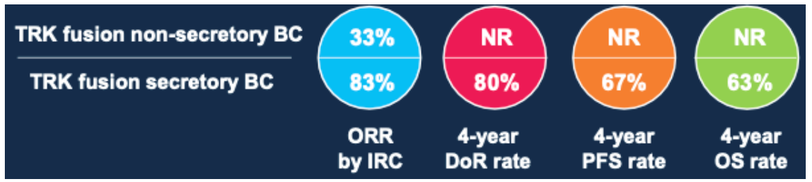
NTRK Targeting

Larotrectinib NTRK Fusion BC

Efficacy	Non-secretory BC (n=10)	Secretory BC (n=6)	Total (N=16)
IRC-eligible patients, n	9	6	15
ORR, % (95% CI)	**33 (7–70)**	**83 (36–100)**	**53 (27–79)**
Best overall response, n (%)			
Complete response	1 (11)	2 (33)	3 (20)
Pathological complete response†	0 (0)	1 (17)	1 (7)
Partial response	2 (22)	2 (33)	4 (27)
Stable disease	2 (22)	1 (17)	3 (20)
Progressive disease	3 (33)	0 (0)	3 (20)
Not evaluable	1 (11)	0 (0)	1 (7)







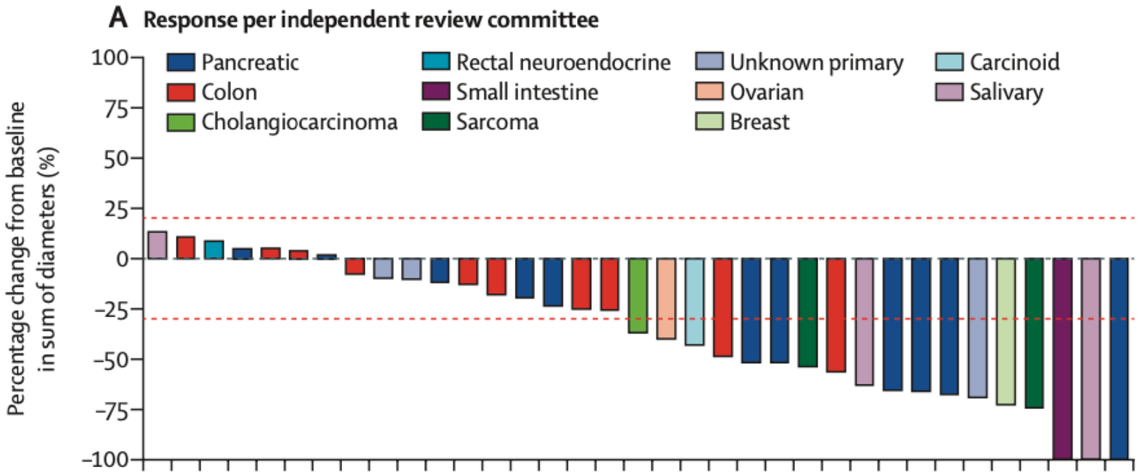
ORR was 53% (95% confidence interval 27–79), Treatment duration ranged from 0 to 60+ months.

Souza et al. 2024

RET

	Number of patients per primary diagnosis	Independent review committee assessment		Investigator assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)	Objective response rate (95% CI)	Median duration of response, months (IQR)
All *RET* fusion-positive solid tumour types	41	43·9% (28·5–60·3)	24·5 (9·2–NR)	43·9% (28·5–60·3)	18·4 (9·8–22.6)
Pancreatic	11	54·5% (23·4–83·3)	NR (NR–NR)	55·5% (23·4–83·3)	NR (12·0–NR)
Colon	10	20·0% (2·5–55·6)	9·4 (5·6–13·3)	30·0% (6·7–65·3)	9·2 (3·7–9·8)
Salivary	4	50·0% (6·8–93·2)	NR (5·7–NR)	25·0% (0·6–80·6)	5·7 (5·7–5·7)
Unknown primary	3	33·3% (0·8–90·6)	9·2–9·2	33·3% (0·8–90·6)	9·2 (NR–NR)
Breast	2	100·0% (15·8–100·0)	17·3 (17·3–17·3)	100·0% (15·8–100·0)	18·4 (18·4–18·4)

- Tumor agnostic approval based on LIBRETTO study. RR 100%, DOR ~ 18 months
- *RET* alterations ~ 1.2% in breast cancers
- Primarily in ER -ve tumors



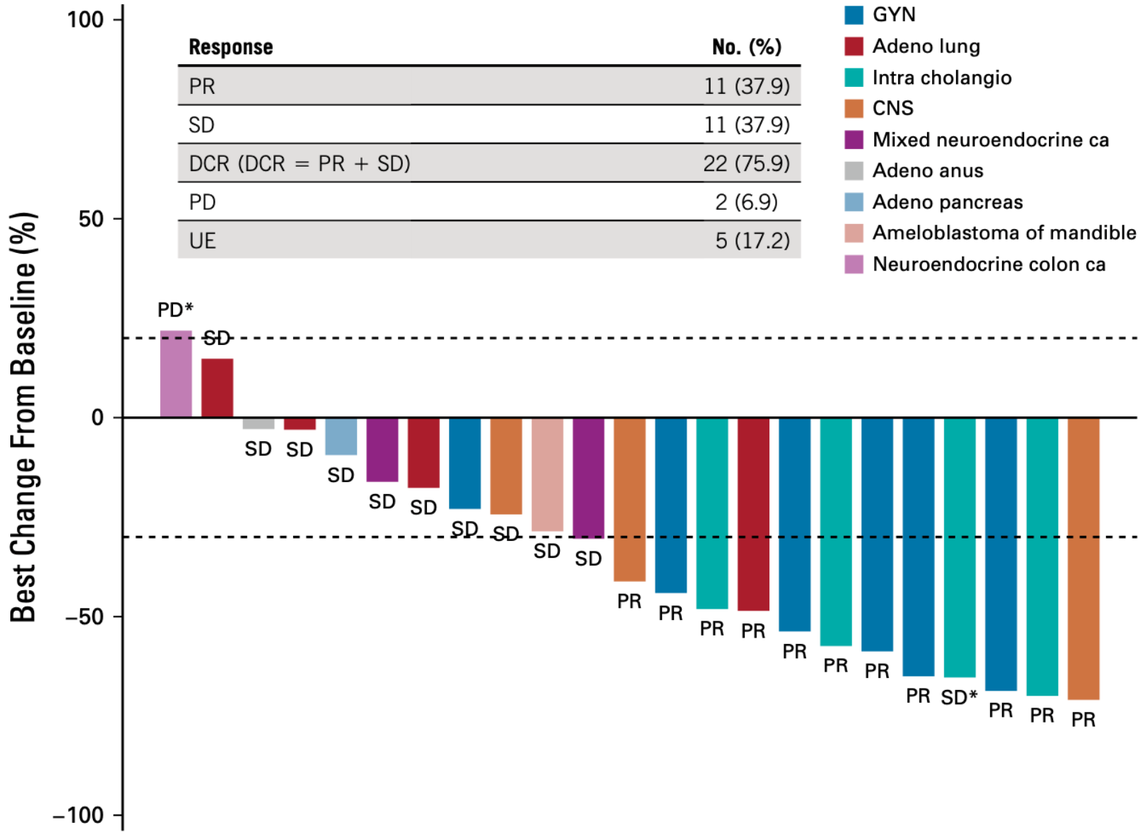
Paratala et al. 2018; Subbiah et al 2022

BRAF V600E

- Very uncommon in BC; < 1%
- Predominance in TNBC?
- Case reports with clinical response, CR, prolonged SD
- Approval only for V600E

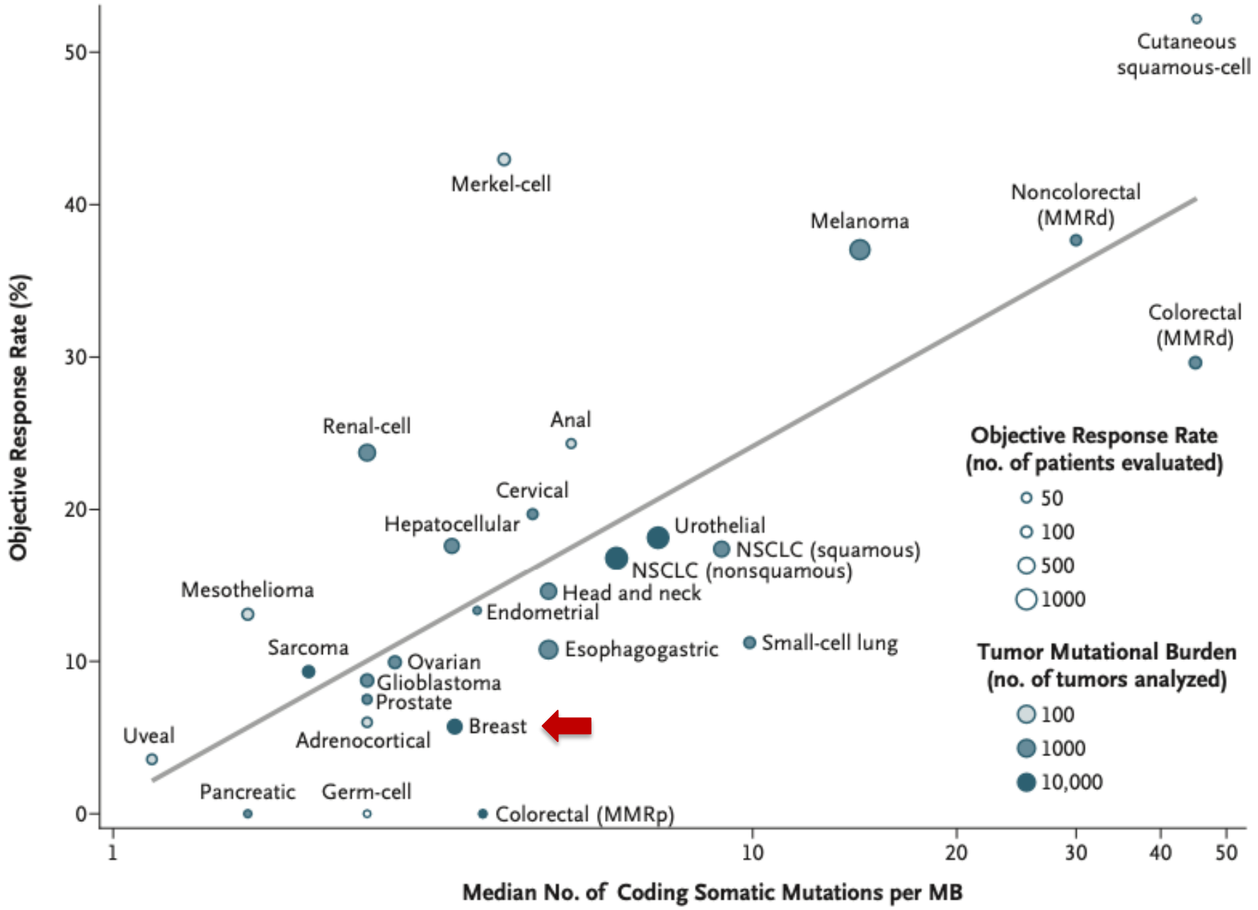
Dabrafenib and Trametinib in Patients With Tumors With *BRAF*^{V600E} Mutations: Results of the NCI-MATCH Trial Subprotocol H

Response	No. (%)
PR	11 (37.9)
SD	11 (37.9)
DCR (DCR = PR + SD)	22 (75.9)
PD	2 (6.9)
UE	5 (17.2)



Salama et al. 2020

Tumor Mutational Burden



Correlation with neoantigen load and elevated TMB and potentially enhanced ICI efficacy across solid tumors

Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 / Anti–PD- L1 Therapy

Yarchoan et al 2017

TMB

- Pembrolizumab approval based on KN study
- ORR 29% with 4% CR
- FDA approval TMB ≥ 10
- High TMB (≥ 10) ~ 5% of breast cancers

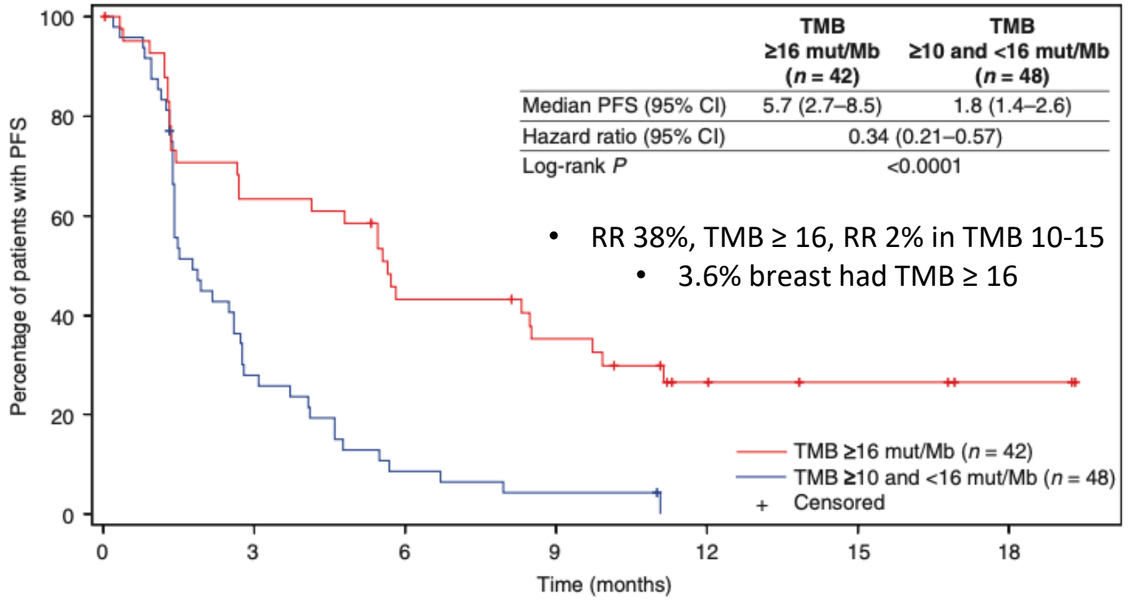
- *Is TMB ≥ 10 optimal threshold for breast cancers?*

Caveats…

- Heterogeneity in TMB assessment (non-synonymous, depth, matched g/normal)
- More of continuous than categorial variable
- WES gold standard. Panel based TMB correlates with WES if panel ~ 1MB
- Plasma TMB threshold?

Pembrolizumab in Patients With Metastatic Breast Cancer With High Tumor Mutational Burden: Results From the Targeted Agent and

Atezolizumab Treatment of Tumors with High Tumor Mutational Burden from MyPathway, a Multicenter, Open-Label, Phase IIa Multiple Basket Study



	TMB ≥16 mut/Mb (*n* = 42)	TMB ≥10 and <16 mut/Mb (*n* = 48)
Median PFS (95% CI)	5.7 (2.7–8.5)	1.8 (1.4–2.6)
Hazard ratio (95% CI)	0.34 (0.21–0.57)	
Log-rank *P*	<0.0001	

- RR 38%, TMB ≥ 16, RR 2% in TMB 10-15
- 3.6% breast had TMB ≥ 16

Friedman et al. 2021; Barrosa-Sousa et al 2020; Alva et al. 2021

MSI

MSI/dMMR

- MMR – MLH1, MSH2, MSH6, PMS2
- Low prevalence in BC, < 1%
- 6718 patients, 0.63% had MSI-H tumor. With median alteration of 11 in MSI-H vs 3 in MSS
- Tend to have high TMB and genomic instability

Overall prevalence of MSI-H across all solid tumors is estimated ~ 14%

Pembrolizumab (Keytruda) and Dostarlimab (Jemperli) approved for dMMR

Neelima et al 2022; Marabelle et al. 2020

Precision Agents in Breast Cancer

	Gene	Alteration	Prevalence	Agents
Breast Specific	***HER2***	Amplification	20%	Trastuzumab, pertuzumab, margetuximab, T-DXD, T-DM1, lapatinib, neratinib, tucatinib
	ESR1	Mutation	30-35%	Elacestrant, Imlunestrant
	PIK3CA	Mutation	30-40%	Capivasertib, Inavolisib, Alpelisib
	PTEN/AKT1	Loss/Mutation	8/5%	Capivasertib
	BRCA 1/2	Inactivating (germline)	5%	Olaparib, Talazoparib
Tumor Agnostic	***BRAF***	Mutation (V600E)	<1%	Dabrafenib and trametinib
	NTRK	Fusion / Translocation	<1%	Larotrectinib, Entrectinib, Repotrectinib
	RET	Fusion / Translocation	<1%	Selpercatinib
	TMB-H	TMB ≥ 10	5-7%	Pembrolizumab
	MMR	Microsatellite instability/ MMR-H	<1%	Pembrolizumab, Dostarlimab
NCCN	*BRCA1/2*	Inactivating (somatic)	6-8%	Olaparib
	FGFR1/2/3	Mutations/Fusions	2-3%	Erdafitinib
	HER2	Mutations	2-8%	Neratinib, trastuzumab, fulvestrant
	PALB2	Inactivating (germline)	~ 1%	Olaparib

Thank You!

- Biomarker testing is an integral part of therapeutic decision making in breast cancers
- Tumor genomic sequencing is standard of care for patients with MBC
- Utility depends on context of genomic alterations and available matching therapies
- Focus on next generation agents (mutant specific inhibitors) and rational combinatorial therapies