Novel Investigational Agents and Strategies

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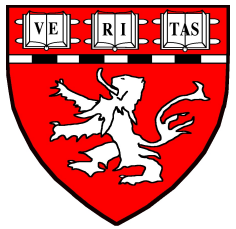


MGH 1811
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Objectives

- Understand mechanism of action of the next-generation selective estrogen receptor degraders (SERDs)
- Review completed and ongoing studies of oral SERDs as monotherapy as well as combination therapy for patients with ER-positive mBC
- Evaluate ongoing investigations of other novel agents and future directions in ER-positive mBC

Patient story:
Endocrine Therapy for HR+ Cancer

55 yo Female with :

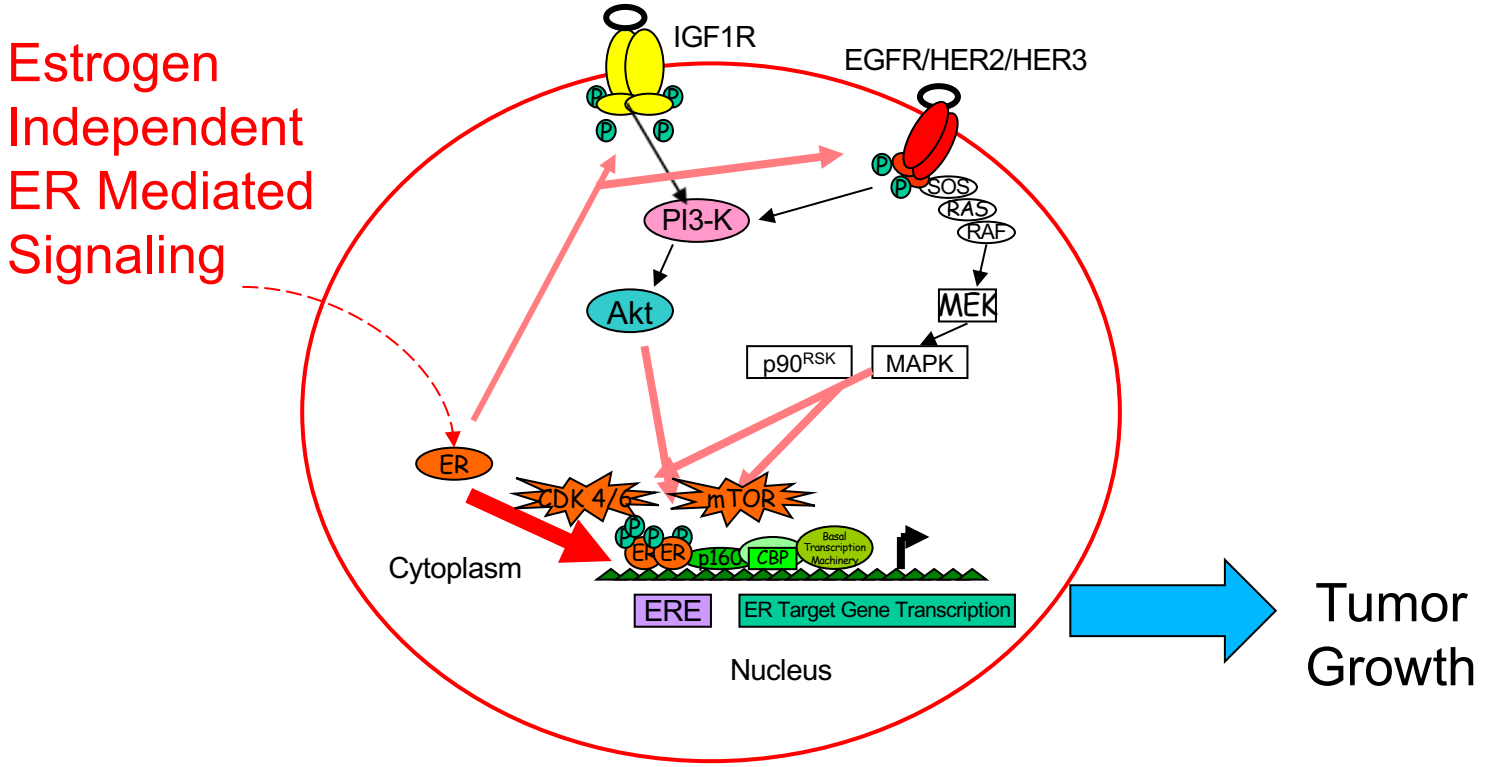
- 2005: HR+/HER2- breast cancer (localized)
- 2010: Completed adjuvant tamoxifen
- 2015: Disease recurrence (bone): Started Letrozole with CDK 4/6 inhibitor
- 2017: Disease progression (bone)

Which therapy would you consider next?

- Fulvestrant
- Fulvestrant + CDK 4/6 inhibitor
- Exemestane + everolimus
- Clinical Trial

ctDNA analysis revealed ESR1 mutation

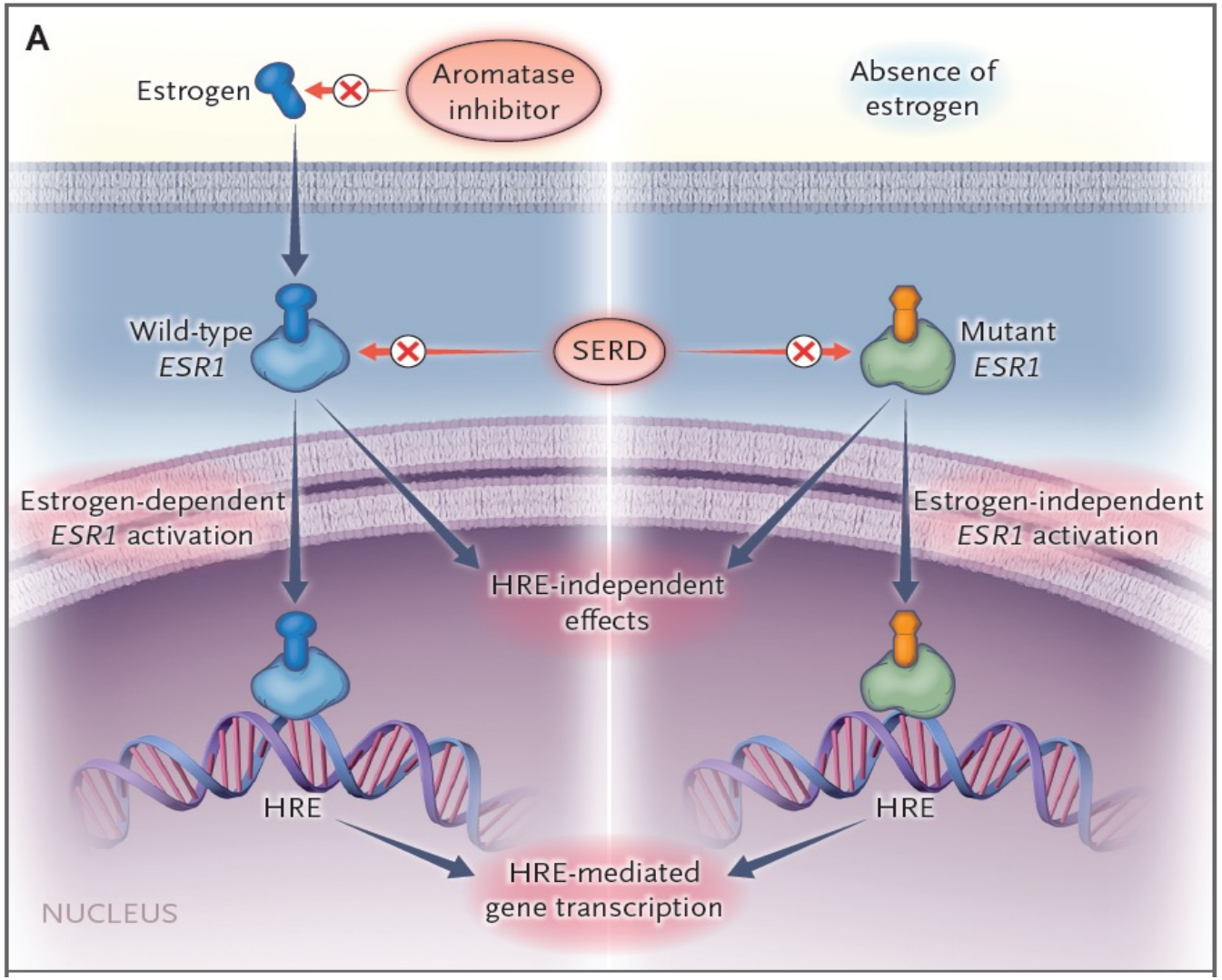
Endocrine Therapy Resistance: Potential Factors to Consider



- ER pathway is still active and disease progression due to estrogen-independent but estrogen-receptor mediated signaling….*ESR1* mutations…

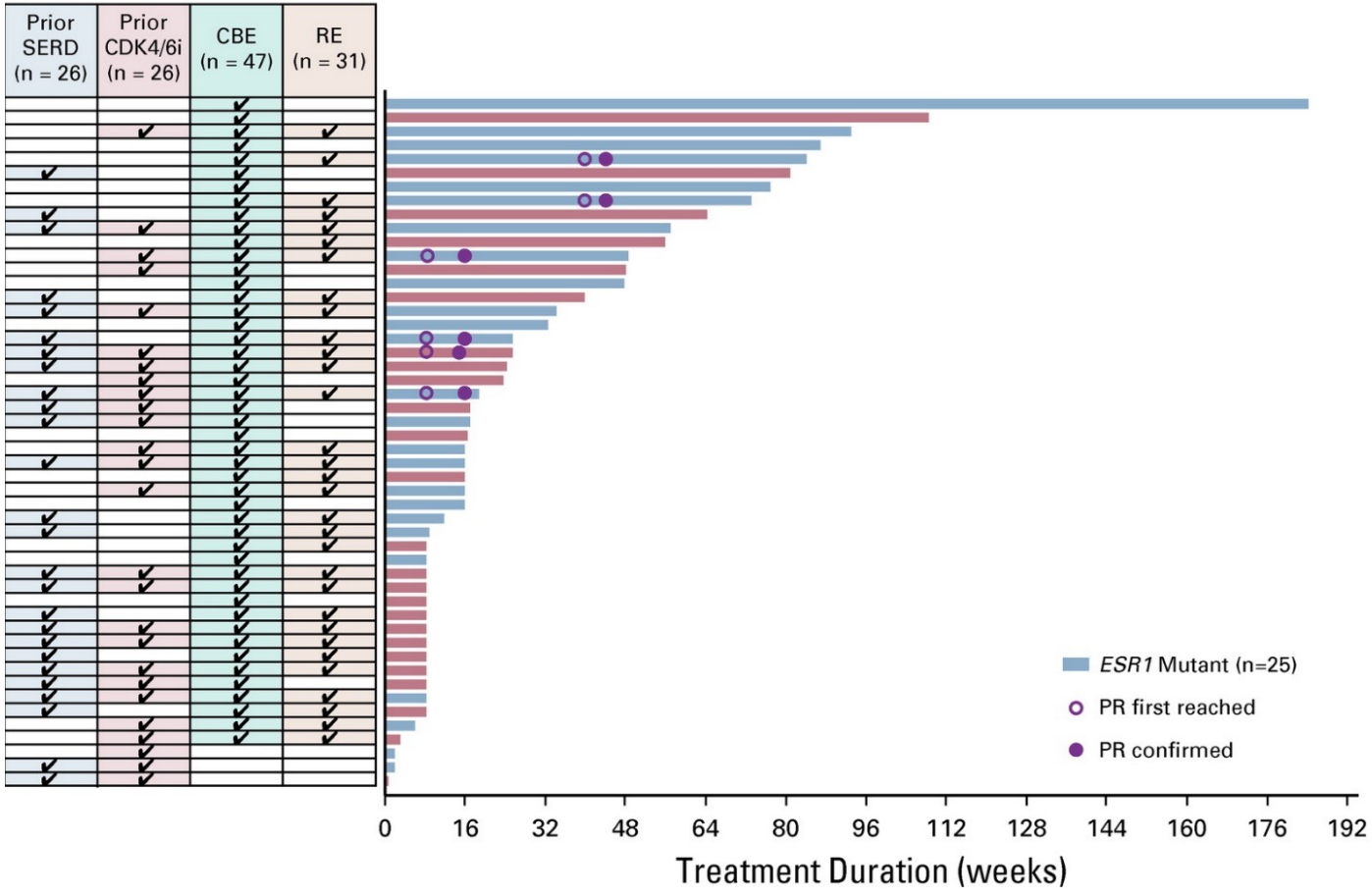
Adapted from Johnston ST. *J Natl Cancer Inst*. 2015;107(10).

ESR1 (Acquired) Mutations: Resistance to AI



Bardia A et al. NEJM. 2018.

Elacestrant Clinical Activity: CBR at 24 weeks 42.6%



- Median of 3 prior systemic therapies
  - 52% had previously received prior SERD
  - 52% had previously received CDK4/6 inhibitor therapy
  - 50% had ESR1 mutation

Bardia A et al. JCO. 2021.

Phase 3 Study design (EMERALD)

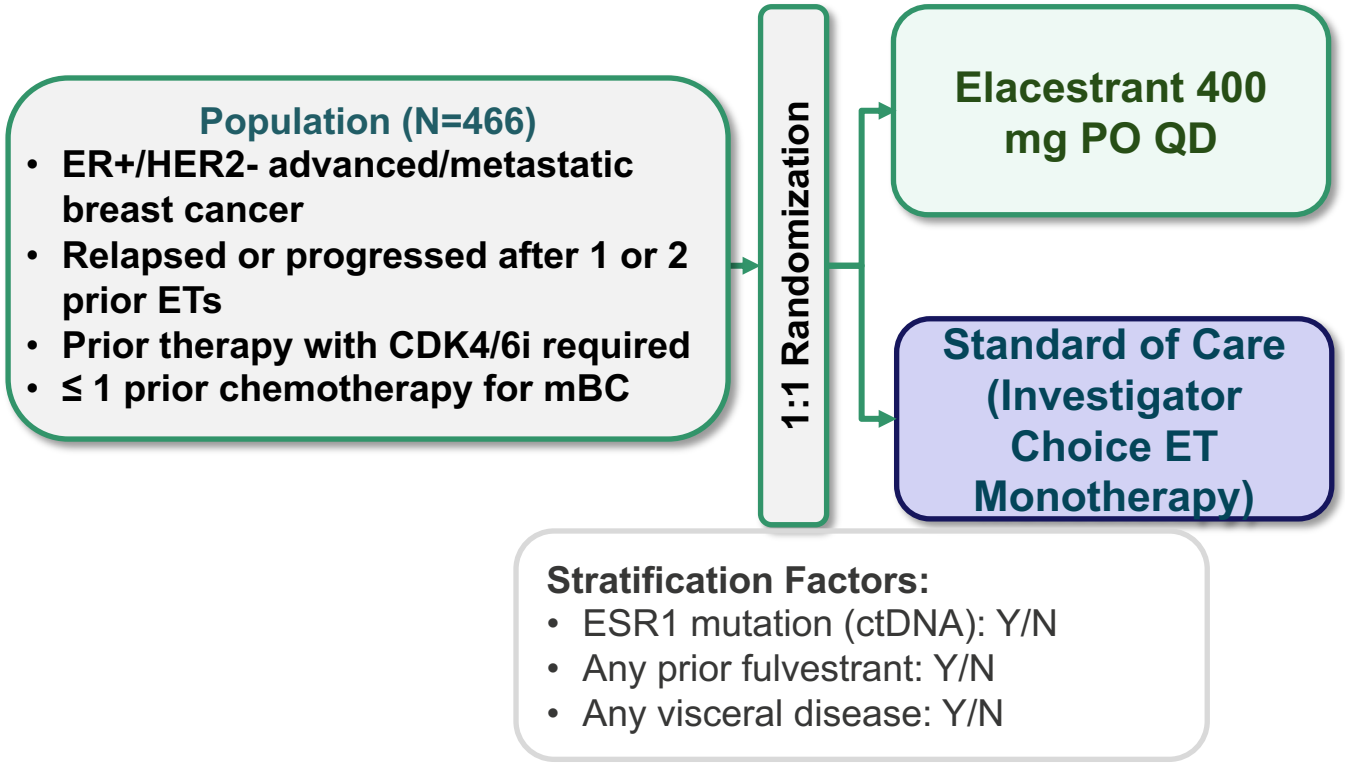
Indication: 2nd and 3rd adv/mBC (postmenopausal women and men) with PD on CDK4/6 inhibitor

Study: Randomized, open label, pivotal study in patients with ER+/HER2- advanced/metastatic breast cancer

Primary endpoint: Progression free survival (PFS)

- Tested in 2 populations*: All subjects and subset of subjects with ESR1 mutation

Comparator arm: Investigator choice of ET monotherapy with fulvestrant or an aromatase inhibitor (anastrozole, letrozole or exemestane)



Bardia A et al. Future Oncol. 2019.

Hot off the Press

10/20/21

Positive Phase 3 Topline Results from the EMERALD Trial Evaluating Elacestrant in Breast Cancer

- Study met both primary endpoints in patients with ER+/HER2- advanced or mBC
- Elacestrant becomes the first oral SERD with positive topline results in pivotal study as a monotherapy versus SoC for the treatment of ER+/HER2- advanced or mBC
- Elacestrant extended PFS in the overall population and the ESR1 mutation subgroup
- Plans for regulatory submissions in both the United States and Europe in 2022
- Data planned to be presented at the San Antonio Breast Cancer Symposium in December, 2021

The study was designed to evaluate elacestrant as a monotherapy versus the standard of care (SoC) for the treatment of ER+/HER2- advanced or metastatic breast cancer (mBC). There were two primary endpoints: progression-free survival (PFS) in the overall population and PFS in patients with tumors harboring estrogen receptor 1 (ESR1) mutations.

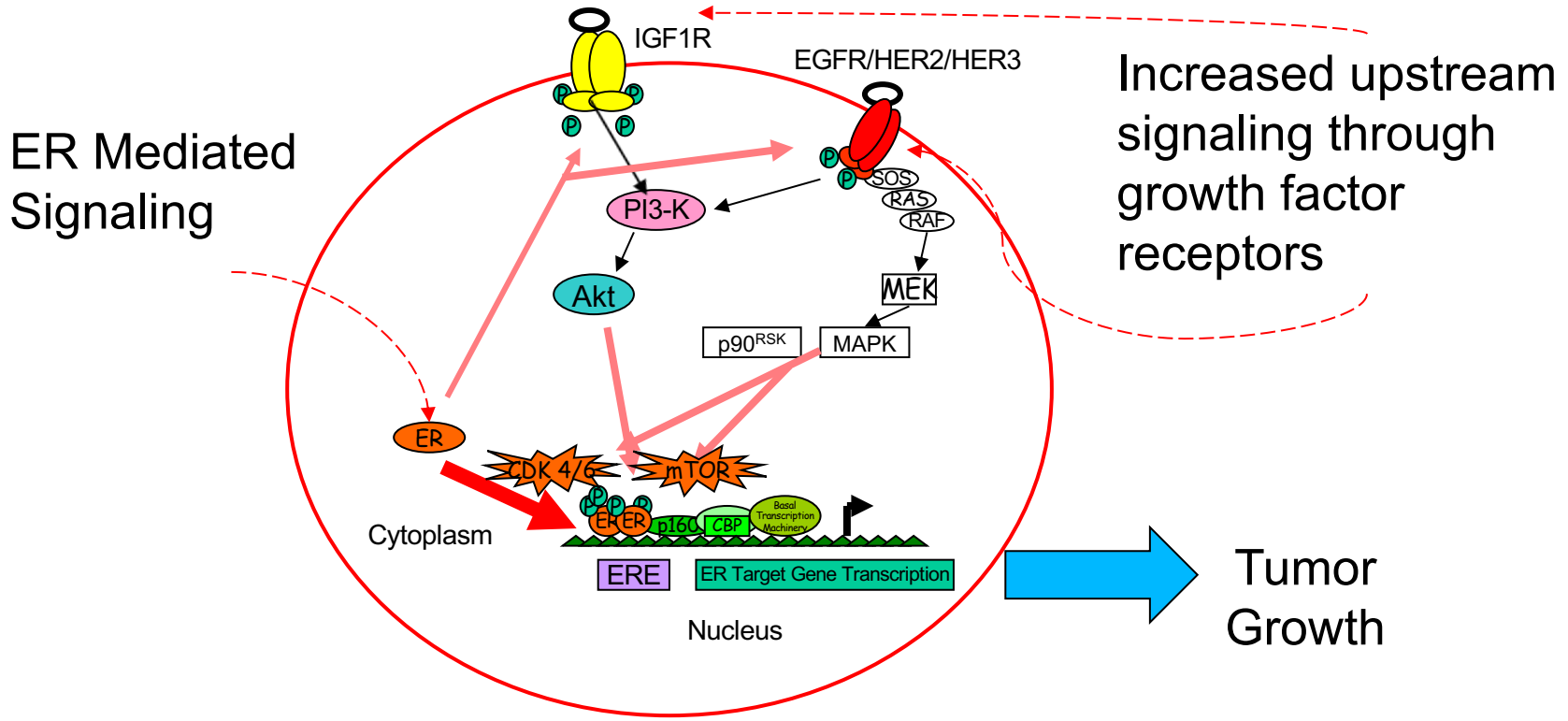
Results to be presented on Dec 8th, SABCS.

Oral SERD in ER+ MBC: Current Development Status

Company	Drug name	Current Development Status
Radius Health Menarini Group	*Elacestrant (RAD-1901)*	*Phase 3*
Genentech	Giredestrant (GDC-9545)	Phase 2/3
Sanofi	Amcenestrant (SAR439859)	Phase 2/3
G1 Therapeutics	Rintodestrant (G1T48)	Phase 2
Astra Zeneca	Camizestrant (AZD9833)	Phase 2/3

Need to be careful with cross-study comparisons –
Differences in prior lines of Rx, endocrine sensitivity, tumor biology

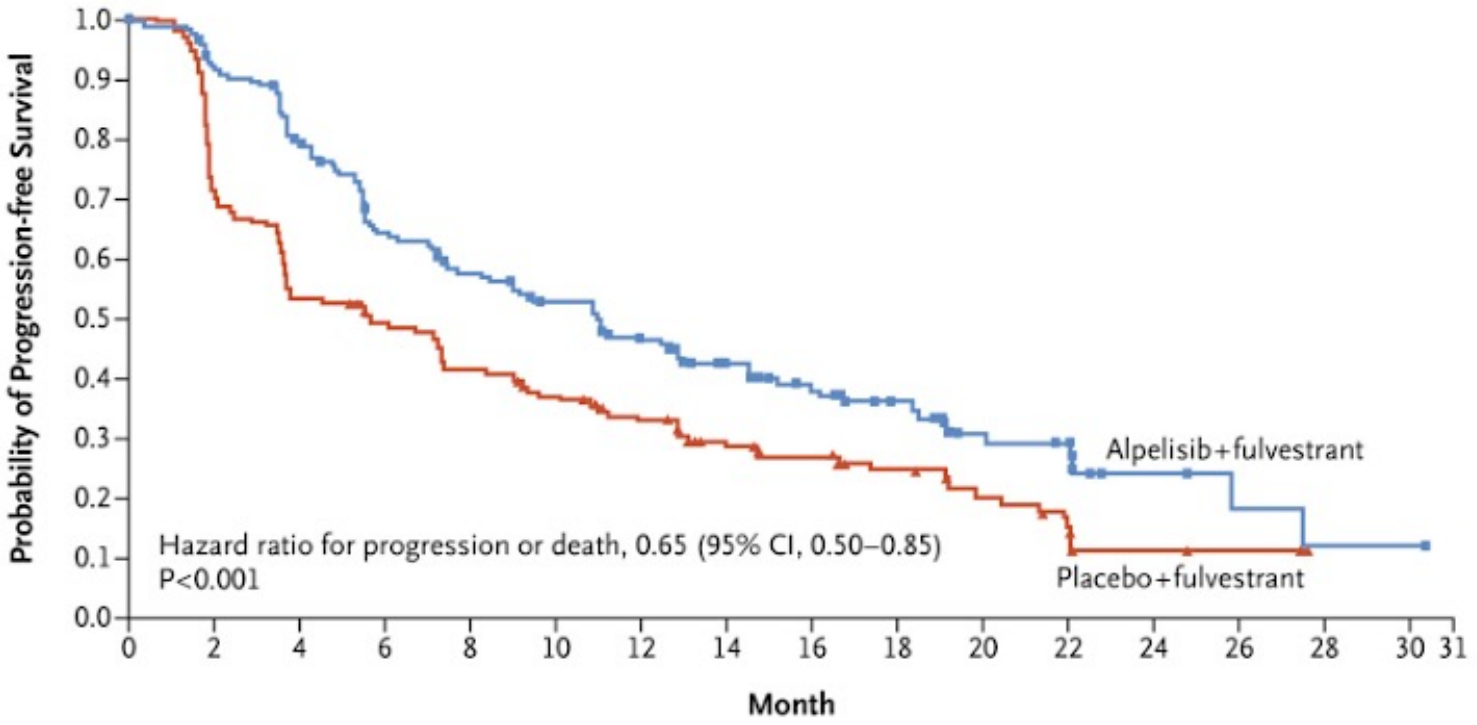
Optimal Biological Effect Does Not Guarantee Clinical Efficacy



Endocrine Therapy with 100% ER Pathway Inhibition would have limited impact on a tumor that is ER-pathway independent

Adapted from Johnston ST. J Natl Cancer Inst. 2015.

Fulvestrant and Alpelisib: SOLAR-1

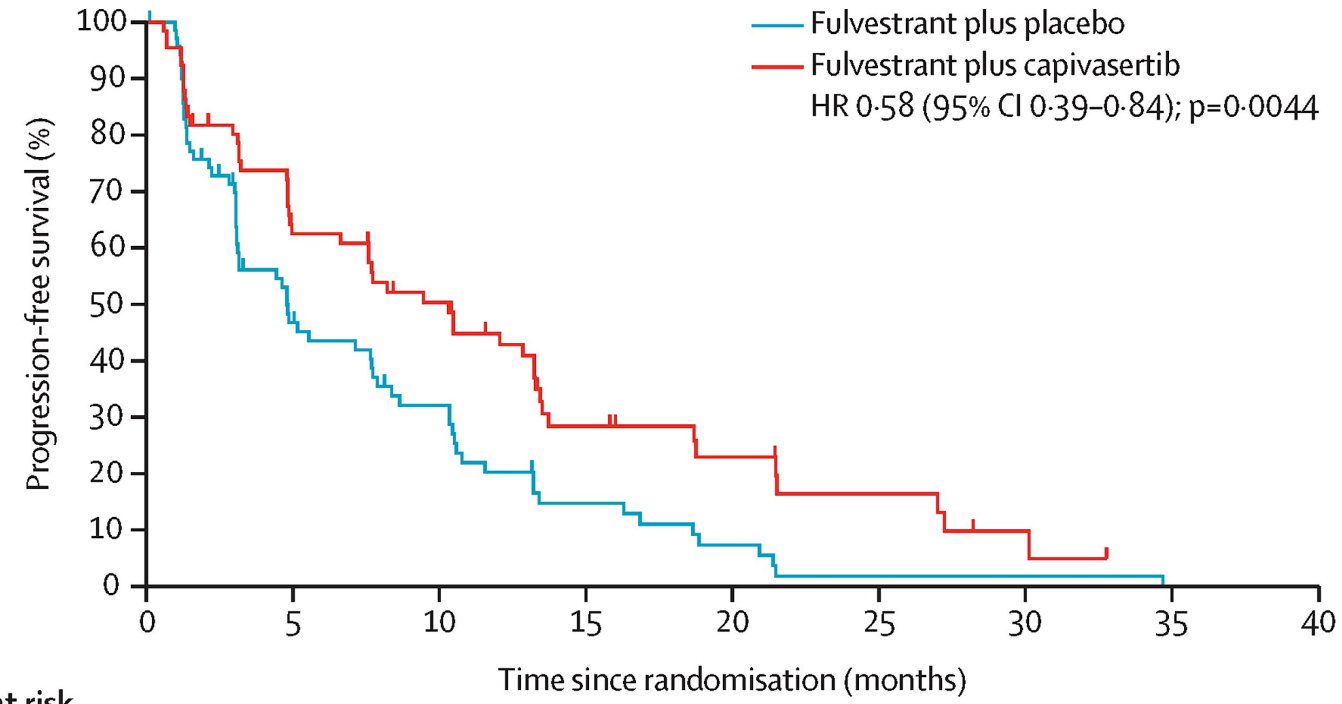


No. at Risk																
Alpelisib+fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo+fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

Improvement in PFS with PI3K Inhibitor for PIK3CA mutant MBC → FDA Approved

Andre F et al. New Engl J Med. 2019.

Fulvestrant and AKT inhibitor: FAKTION

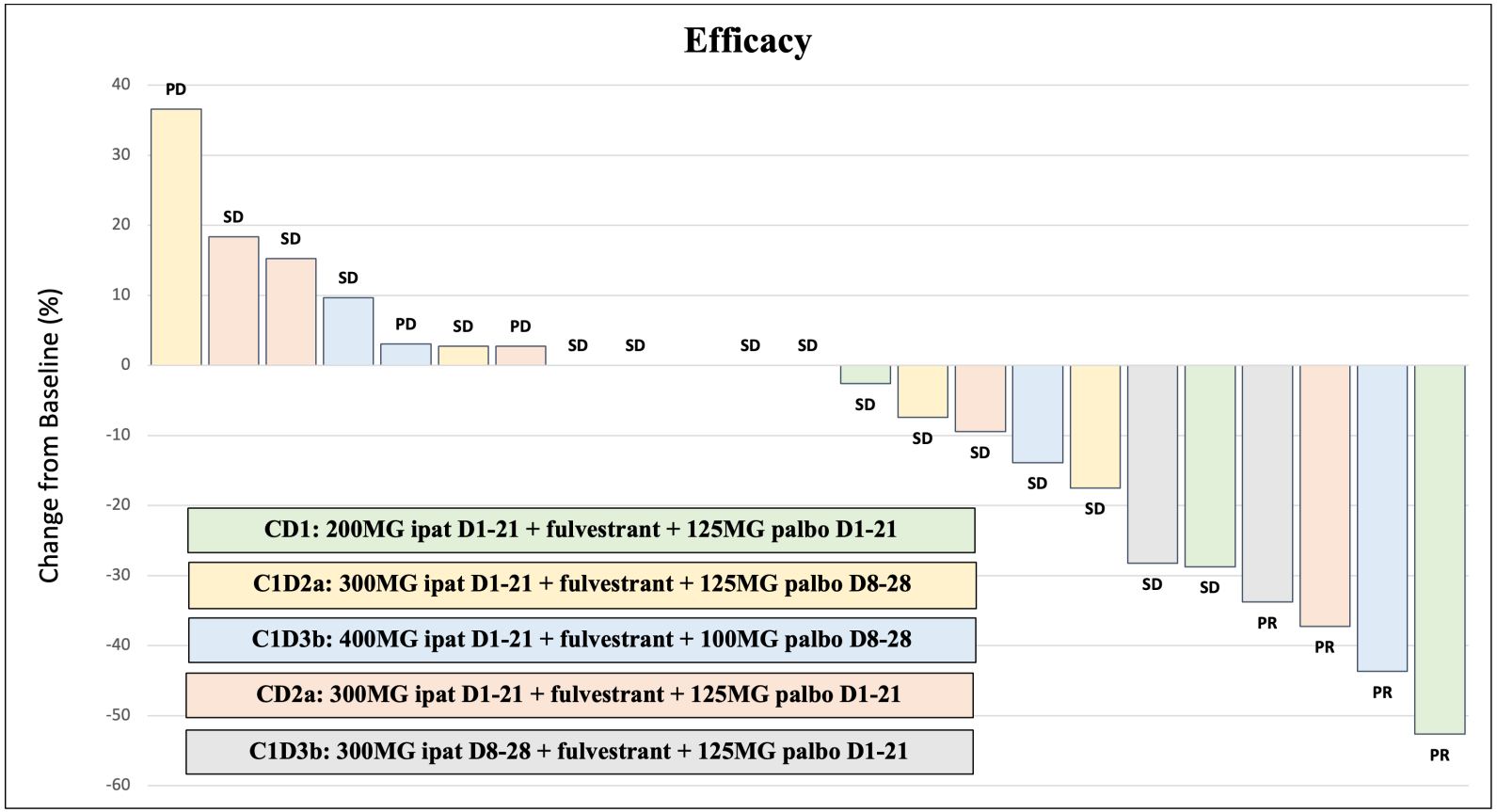


Number at risk (number censored)									
Fulvestrant plus placebo	71 (0)	29 (6)	19 (7)	8 (8)	4 (8)	1 (8)	1 (8)	0 (8)	0 (8)
Fulvestrant plus capivasertib	69 (0)	38 (7)	28 (10)	13 (14)	8 (17)	5 (18)	2 (19)	0 (20)	2 (20)

Improvement in PFS with AKT Inhibitor for HR+ MBC → Phase 3 Trial Ongoing

Jones RH et al. Lancet Oncol. 2020.

Fulvestrant and AKTi and CDK 4/6i: TAKTIC



Triplet therapy feasible with preliminary evidence of clinical activity → Further eval needed

Wander S et al. SABCS. 2021.

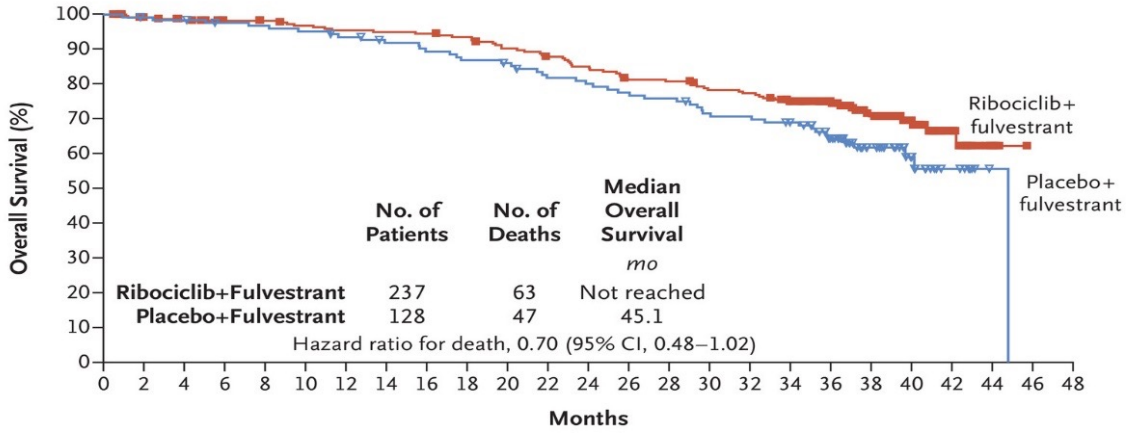
How about 1st line?

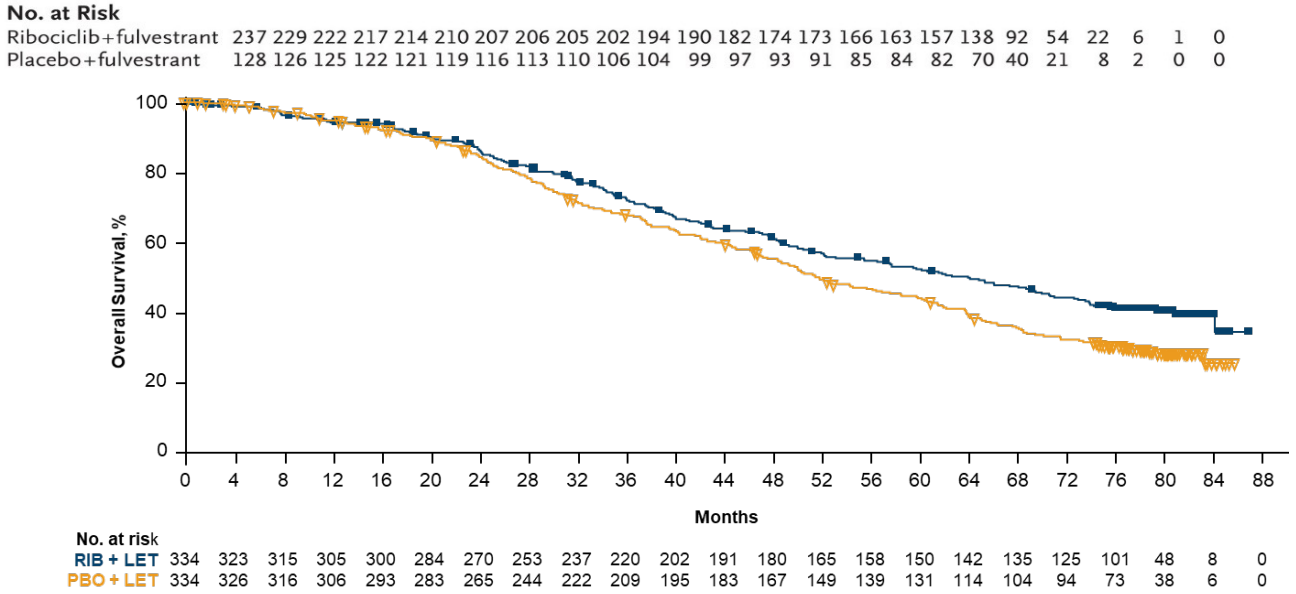
CDK4/6i Combination Studies in 1st Line

	MONALEESA-3[1] (N = 483)	PALOMA- 2[2] (N = 230)	MONALEESA-2[3] (N = 334)	MONARCH-3[4] (N = 328)	MONALEESA-7[5] (N = 672)
Menopausal Status	Postmenopausal	Postmenopausal	Postmenopausal	Postmenopausal	Premenopausal
Treatment Lines	*De novo* **1st and 2nd line** Relapse or progression to ET	*De novo* 1st line	*De novo* 1st line	*De novo* 1st line	*De novo* 1st line
Patient Selection (as per previous treatment)	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
	Recurrence >12 m after (neo) adj **ET** completion w/o ABC treatment	Recurrence >12 m after (neo) adj **NSAI** completion w/o ABC treatment	Recurrence >12 m after (neo) adj **NSAI** completion w/o ABC treatment	Recurrence >12 m after (neo) adj **ET** completion	Recurrence >12 m after (neo) adj **ET** completion
	Recurrence on (neo) adjuvant ET or ≤12 m of adj w/o ABC treatment		Recurrence on (neo) adjuvant tamoxifen or ≤12 m of adj tamoxifen		Recurrence on (neo) adjuvant ET or ≤12 m
Prior Treatment	No Chemo for ABC allowed	No Chemo for ABC allowed	No Chemo for ABC allowed	No Chemo for ABC allowed	≤1L Chemo allowed for ABC
Randomization	2:1	2:1	1:1	2:1	1:1
PS	0-1	0-2	0-1	0-1	0-1
Stratification	Liver and/or lung Prior endocrine therapy (treatment naive vs up to 1 line)	Visceral disease DFI (de novo, ≤12m and >12 m) Prior neo-adj ET (Y/N)	Lung and/or liver (Y/N)	Visceral; bone only; other Prior neo/adj (AI; no ET or other)	Liver or lung (Y/N) Previous CT for ABC (Y/N) Endocrine combination partner (TAM or NSAI)

Slamon D et al. New Engl J Med 2019; Finn RS et al. N Engl J Med 2016; Hortobagyi GN et al. N Engl J Med 2016; Goetz MP et al. J Clin Oncol. 2017; Tripathy D et al. Lancet Oncol. 2018.

Endocrine therapy + CDK 4/6i: OS improvement





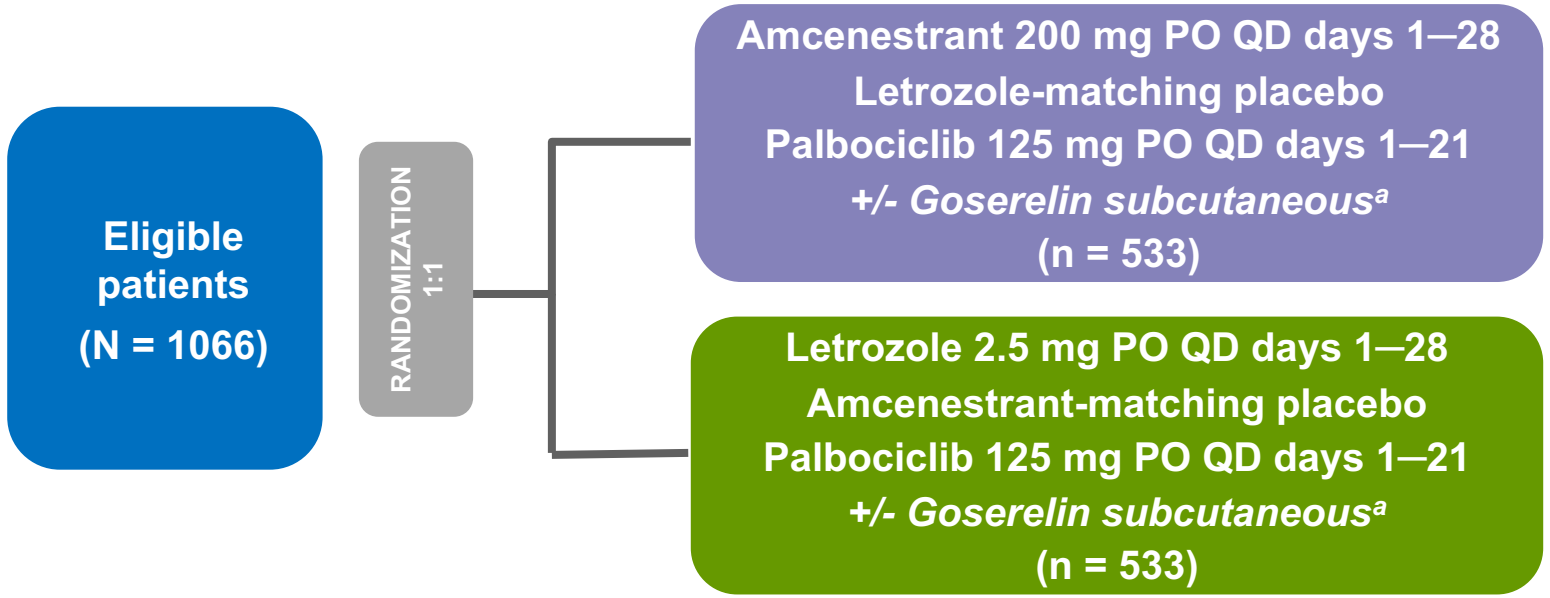
Combination with Fulvestrant

Combination with Aromatase inhibitor

What is the best endocrine therapy backbone?

Slamon D et al. *NEJM*. 2019; Hortobagyi G et al ESMO 2021.

AI vs oral SERD (with CDK 4/6i): AMEERA-05



Treatment until:

- **Disease progression**
- **Unacceptable toxicity**
- **Participant's request to stop treatment**
- **Investigator's decision**

Stratification factors:

- **De novo metastatic disease: Yes or No**
- **Postmenopausal woman: Yes or No**
- **Visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement: Yes or No**

[a] + for men and pre-/peri-menopausal women
PO, oral administration; QD, once daily.

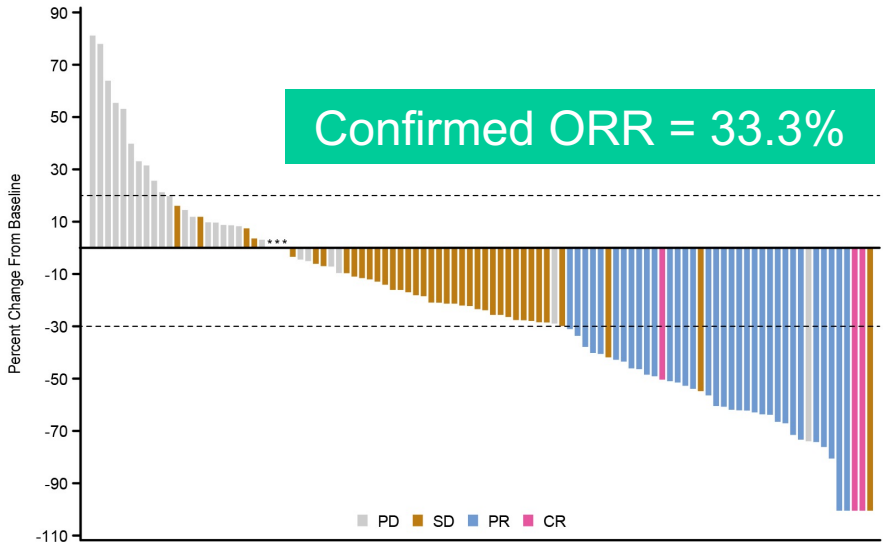
Similar trials with:

- *Giredestrant*
- *Camizestrant*

How about other drugs?

Sacituzumab Govitecan: First-in-class trop2 ADC

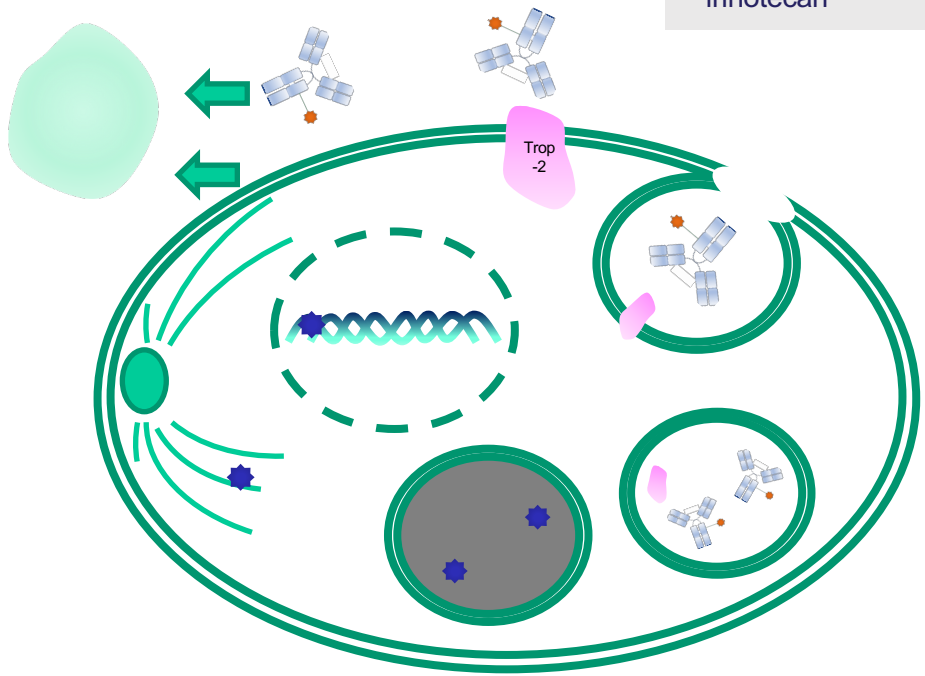
- SG is distinct from other ADCs
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC



Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)

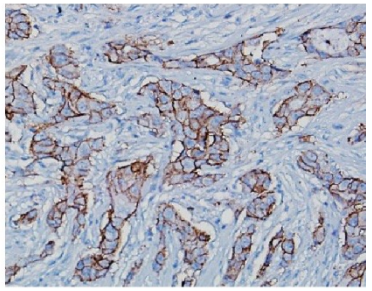
Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

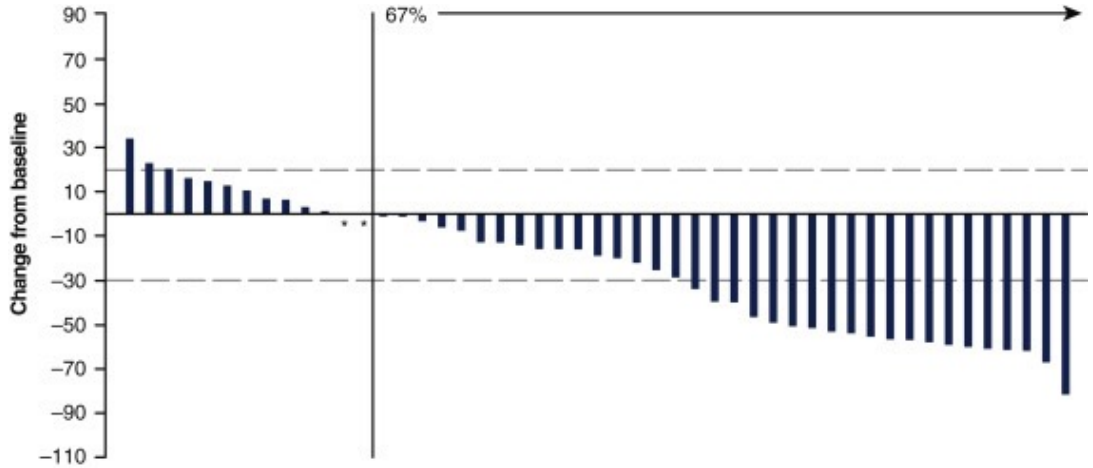


Bardia A et al. NEJM. 2019; Nagayama, A, et al. Target Oncol. 2017

Clinical activity not restricted to TNBC: HR+ MBC



Confirmed ORR = 31.5%



TROPICS-02 Phase 3 Trial

Patients with MBC who are HR+/HER2- based on ASCO/CAP criteria and who have progressed on or after:

- At least 1 endocrine therapy, taxane, and CDK4/6
- At least 2, but no more than 4, lines of chemotherapy in the metastatic setting
- Measurable disease by RECIST 1.1

- Estimated primary completion: November 2021

N=400

1:1 randomization

Sacituzumab govitecan
10 mg/kg IV day 1 & 8, every 21 days

Treatment of physician choice
(capecitabine, vinorelbine, gemcitabine, and eribulin)

Stratification:

- Visceral metastases (Y/N)
- Endocrine therapy in the metastatic setting >6 months (Y/N)
- 2 vs 3/4 prior lines of chemotherapies

Primary Endpoints

- PFS: Hazard ratio and associated CI estimated using Cox proportional-hazards model
- ORR: 2-sided 95% CIs calculated by Clopper-Pearson exact method

Secondary Endpoints

- OS, DOR, safety

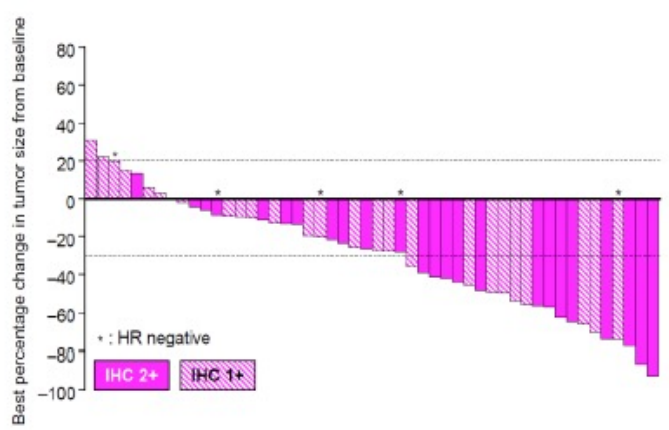
Exploratory

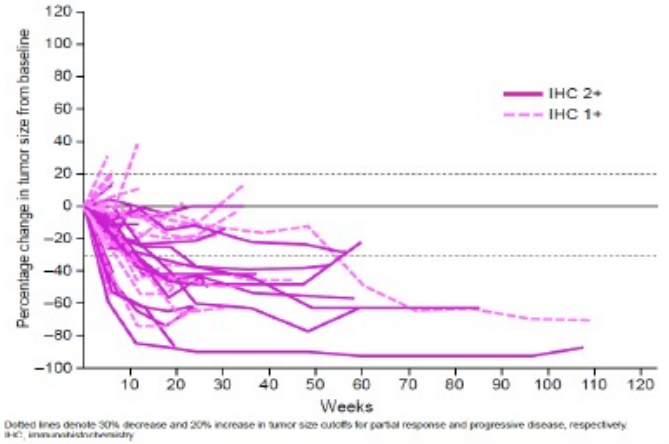
- Biomarkers, QoL

Similarly, enrollment in TROPION-PanTumor01: Dato-DXd HR+ Breast Cancer Cohort

Kalinsky K et al. Ann Oncol. 2020
Rugo H et al. ASCO 2020.

Trastuzumab Deruxtecan (T-DXd): HER2 Low Tumors





	Confirmed ORR	mDoR	mPFS
All (N = 51)	44.2% (N=43)	9.4m	7.6m
IHC 2+ (n = 24)	54.5% (N=22)	11.0m	13.6m
IHC 1+ (n = 27)	33.3% (N=21)	7.9m	5.7m
HR+ (n = 45)	47.4% (N=38)	11.0m	7.9m
Prior CDK4/6 inhibitor (n = 15)	33.3% (N=12)	NR	7.1m

Ongoing phase 3 trials evaluating trastuzumab deruxtecan for HR+/HER2 low MBC

Modi S et al. J Clin Oncol. 2020.

ADCs to target MBC: Multiple Agents in Development

Drug	Target
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1
Patritumab deruxtecan (U3-1402)	HER3
Datopotamab deruxtecan (DS-1062)	Trop-2
AVID100	EGFR
BA3021	ROR2
SAR6658	CA6
SAR408701	CEA-CAM5

Conclusions

- Endocrine therapy is the mainstay of management of patients with HR+ MBC.

- Tumor progression in HR+ MBC could be due to:
  - estrogen-independent estrogen-receptor mediated signaling due to genomic alterations such as ESR1 mutations – could respond to additional ER-directed therapy such as SERDs.

  - estrogen-independent and estrogen-receptor independent signaling – need for combination therapy.

Conclusions

- There are several oral SERDs in clinical development for HR+ metastatic breast cancer, alone and in combination therapy with other targeted therapies, including CDK 4/6, PI3K, and AKT inhibitors.
- There are multiple ADCs in development to target antigens overexpressed in MBC, including ER+ disease, including trastuzumab deruxtecan and sacituzumab govitecan.
- Additional studies evaluating efficacy of ADCs alone and in combination with other targeted therapies as well as other indications in breast cancer could redefine the molecular classification of breast cancer

Thank you for your attention