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New drug development in metastatic breast cancer: from empirical to molecular approaches

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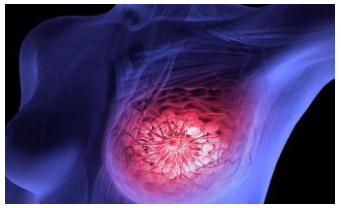
Disclosures

- Consulting: Boehringer Ingleheim, Macrogenics, Roche, Novartis, Amcure, Servier, G1 Therapeutics
- Honoraria: Synthon, Amgen, Novartis
- Travel grants: Amgen, MSD, Pfizer, Roche

Outline

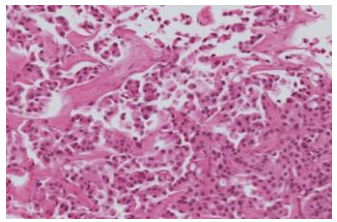
- Precision oncology strategies
- Targeting cancer epigenetics
- The advent of novel antibody-drug conjugates

AURORA Data Flow



Screening

- Locally relapsed BC or MBC with up to 1 line of systemic treatment

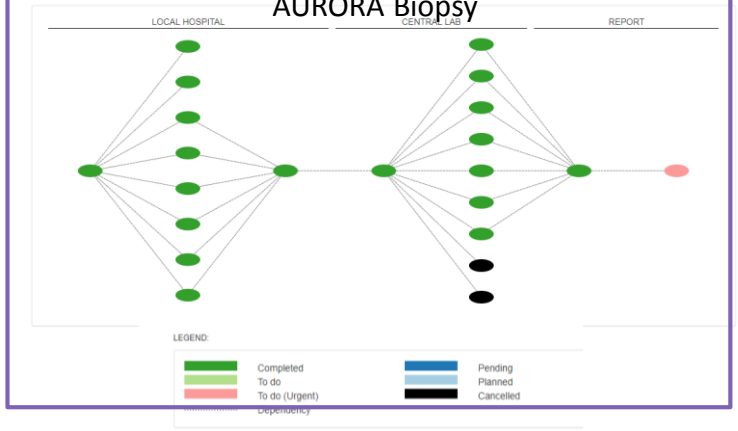


Central Lab evaluation

- Cellularity
- Histopathology

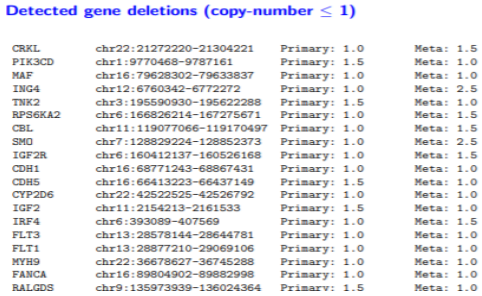
Informed consent, Registration and Samples collection

AURORA Biopsy



Molecular analysis

- Ion Torrent TGS (411 genes for tissue)
- Ion Torrent TGS (27 genes for ctDNA)
- Illumina, TrueSeq RNA seq
- OncoScan, FFPE, SNP/CNV



Detected gene deletions (copy-number ≤ 1)

CRKL	chr22:21272220-21304221	Primary: 1.0	Meta: 1.5
PIK3CD	chr1:9770468-9787161	Primary: 1.5	Meta: 1.0
MAF	chr16:79628302-79633837	Primary: 1.0	Meta: 1.0
ING4	chr12:6760342-6772272	Primary: 1.0	Meta: 2.5
TNK2	chr3:195590930-195622288	Primary: 1.5	Meta: 1.0
RPS6KA2	chr6:166826214-167275671	Primary: 1.0	Meta: 1.5
CBL	chr11:119077066-119170497	Primary: 1.0	Meta: 1.5
SMO	chr7:128829224-128852373	Primary: 1.0	Meta: 2.5
IGF2R	chr6:160412137-160526168	Primary: 1.0	Meta: 1.5
CDH1	chr16:68771243-68867431	Primary: 1.0	Meta: 1.0
CDH5	chr16:66413223-66437149	Primary: 1.5	Meta: 1.0
CYP2D6	chr22:42522525-42526792	Primary: 1.0	Meta: 1.0
IGF2	chr11:2154213-2161533	Primary: 1.5	Meta: 1.0
IRF4	chr6:393089-407569	Primary: 1.0	Meta: 1.5
FLT3	chr13:28578144-28644781	Primary: 1.0	Meta: 1.0
FLT1	chr13:28877210-29069106	Primary: 1.0	Meta: 1.0
MYH9	chr22:36678627-36745288	Primary: 1.0	Meta: 1.0
FANCA	chr16:89804902-89882998	Primary: 1.0	Meta: 1.0
RALGDS	chr9:135973939-136024364	Primary: 1.5	Meta: 1.0

Molecular advisory board
annotation of patient reports

MAB Output:
662 patient reports
1750 variants annotated

Feedback to clinician

- Consolidated MAB report
- « Advice » to clinicians

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Aftimos P et al. ESMO Breast 2019.

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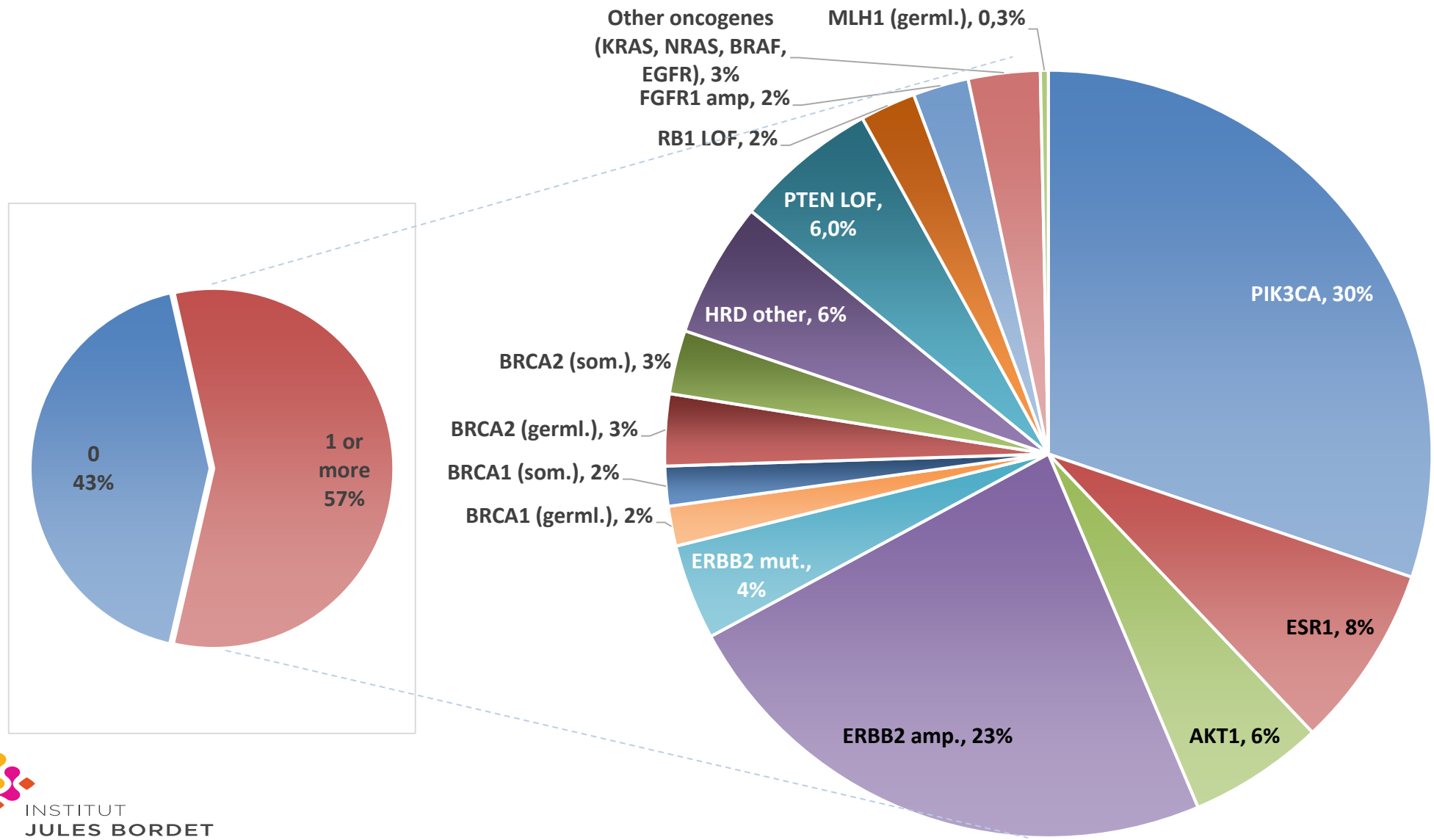
Potentially actionable molecular alterations



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Aftimos P et al. ESMO Breast 2019.

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Molecular screening of MBC: ready for daily practice?

	Readiness of use in clinical practice	ESCAT for alterations in breast cancer	Prevalence in the AURORA population
Tier I (I-A, I-B, I-C)	Targets ready for implementation in routine clinical decisions	**ERBB2 amplification** (IA), **germline BRCA1/2 mutations** (IA), **PIK3CA mutations** (IA), MSI (IC), TRK fusions (IC)	**149 (39.4%)**
Tier II (II-A, IIB)	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	**PTEN loss** (IIA), **ESR1 mutations** (IIA), **AKT1 mutations** (IIB), **ERBB2 mutations** (IIB)	**66 (17.5%)**
Tier III (III-A, III-B)	Clinical benefit previously demonstrated in other tumour type or for similar molecular targets	**Somatic BRCA1/2 mutations (IIIA), MDM2 amplification (IIIA), ERBB3 mutations (IIIB)**	13 (3.4%)
Tier IV (IV-A, IV-B)	Preclinical evidence of actionability	ARID1A/B, **ATM/ATR/PALB2**, **CDH1**, **IGF1R**, INPP4B loss**, MAP2K4/MAP3K1**, MT4, **MYC, NF1**, **PIK3R1**, RUNXB1/CBFB, SF3B1, **TP53** (IVA)	169 (44.7%)
Tier V	Evidence supporting co-targeting approaches		
Tier X	Lack of evidence of actionability	**CCND1 amplification, FGFR1 amplification**	15 (4%)

At least 1 alteration identified in 51.6% of patients.

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Aftimos P et al. ESMO Breast 2019.

Mateo J et al. Ann Oncol 2018.
Condorelli R et al. Ann Oncol 2019.

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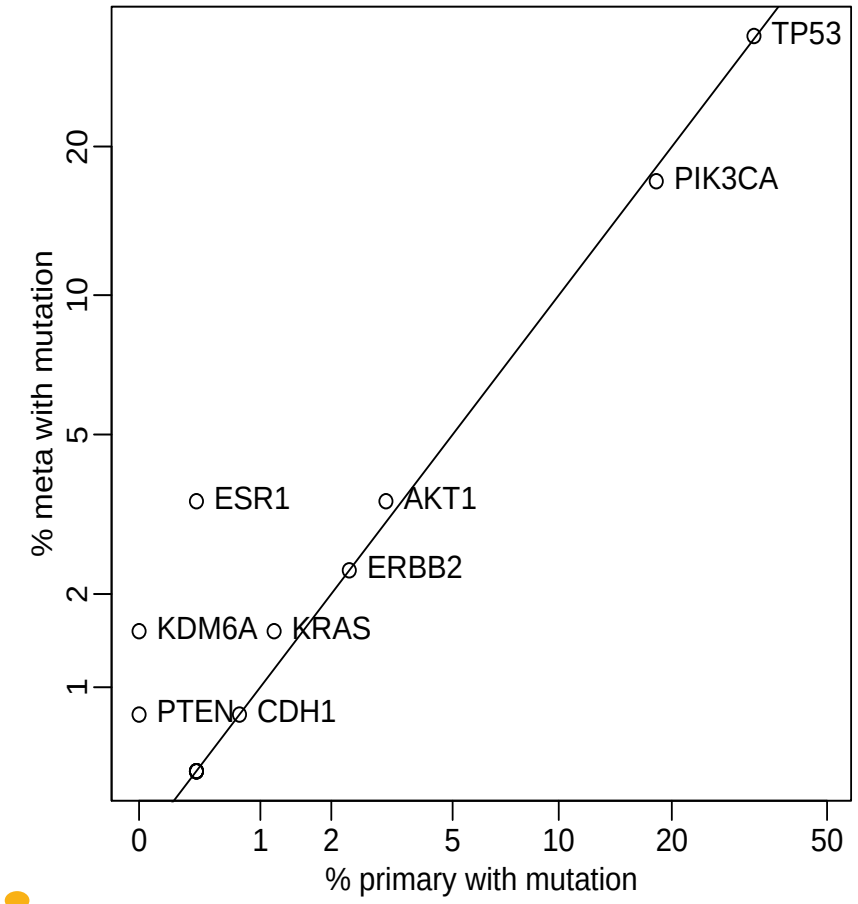
Single Nucleotide Variants based on TGS: Primary vs Metastases

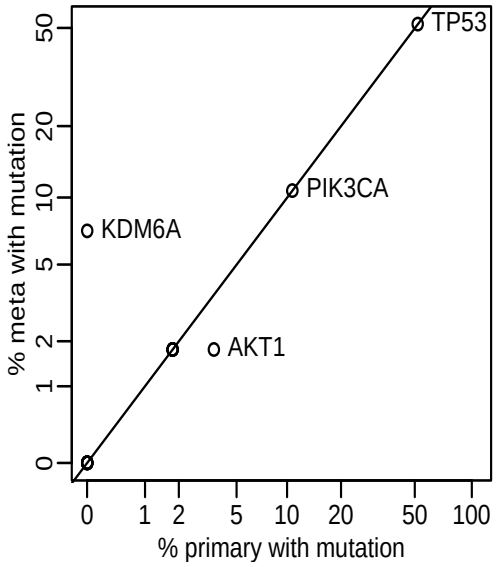
All patients



N= 258

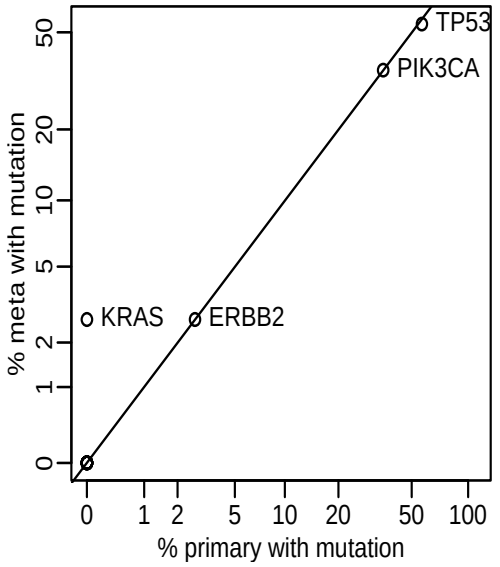
No change in truncal mutations but an enrichment in resistance mechanisms such as ESR1, PTEN and MAPK pathway genes

TNBC



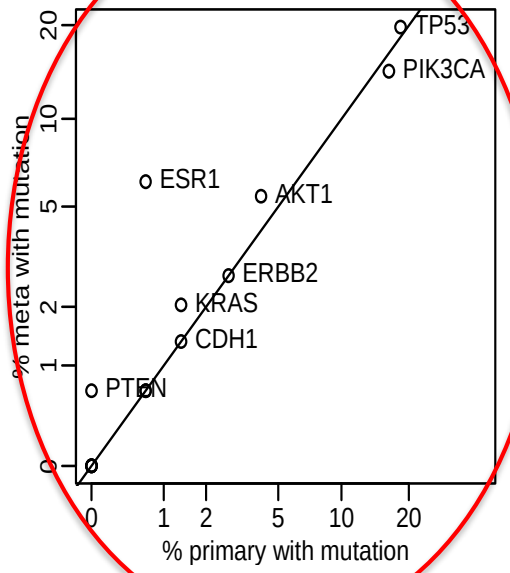
N= 56

HER2+



N=37

ER+



N=147

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Aftimos P et al. ESMO Breast 2019.

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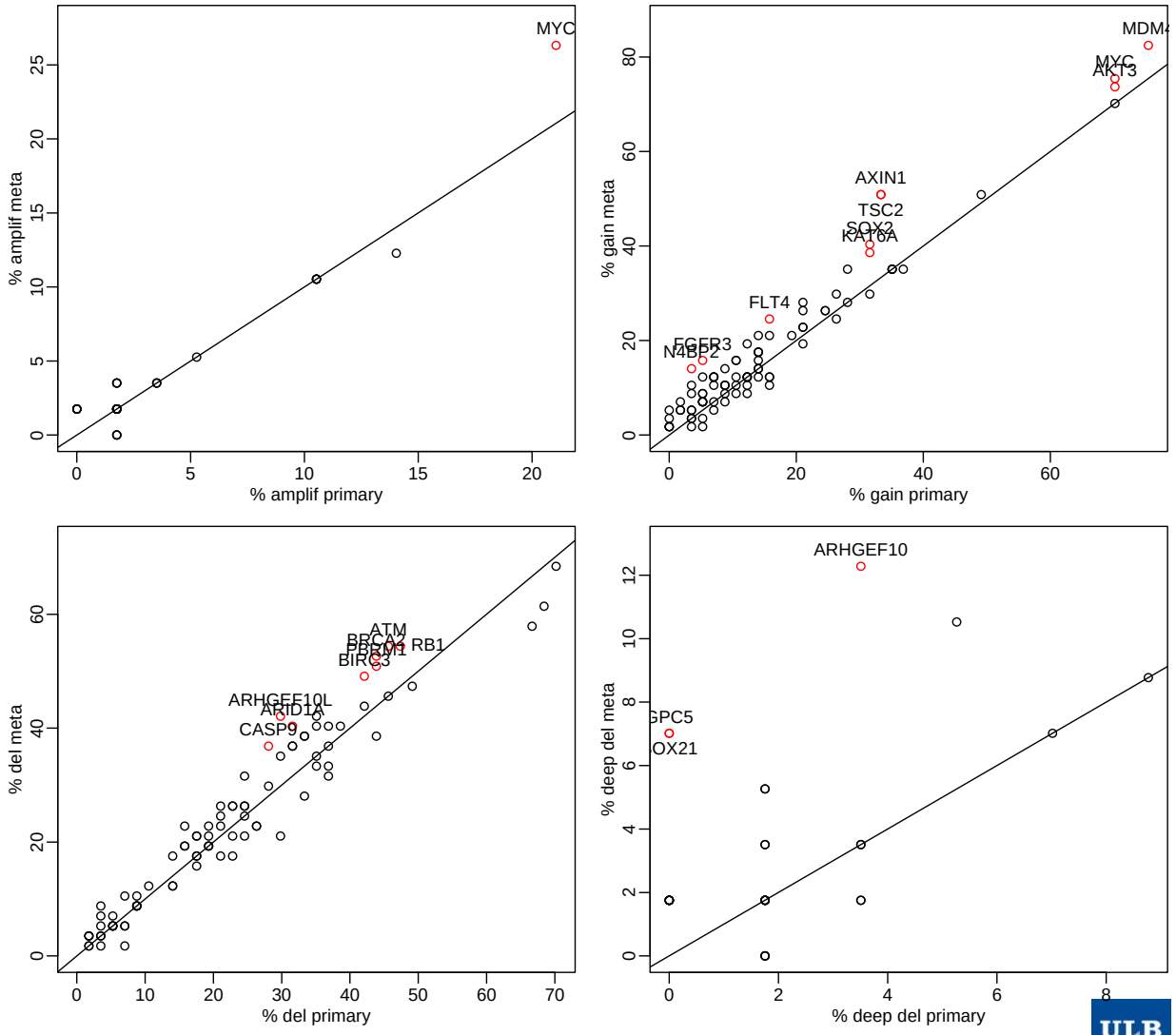
Copy Number Alterations: Primary vs Metastases (N=57)

CN gains (**KAT6A, MYC**) and CN losses (**RB1**) in genes promoting endocrine resistance

CN gains in genes promoting cell cycle arrest evasion (**MDM4**), treatment resistance via DNA repair (**AKT3**)

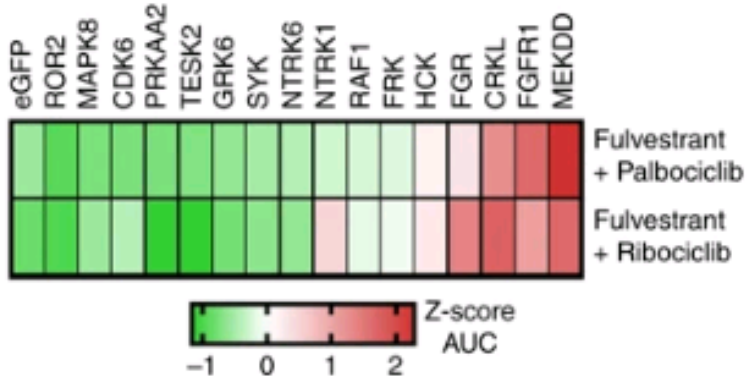
CN losses in **ARID1A** is correlated with microsatellite instability, a mutator phenotype and PD-L1 expression [1]

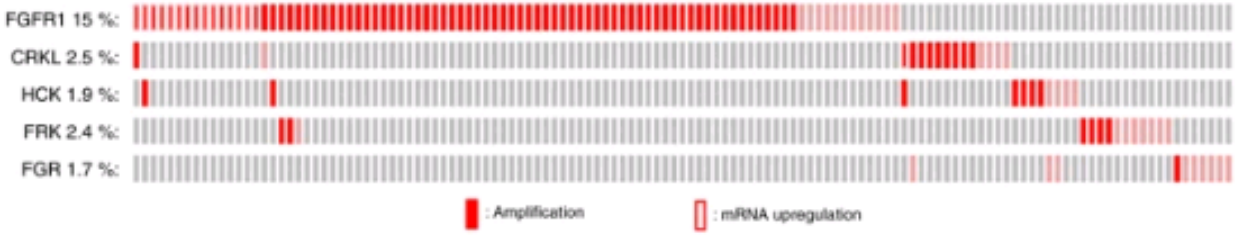


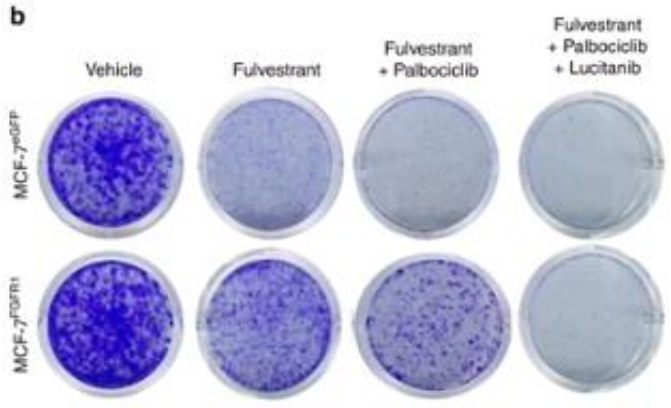
[1]Shen J et al. Nature Medicine 2018.

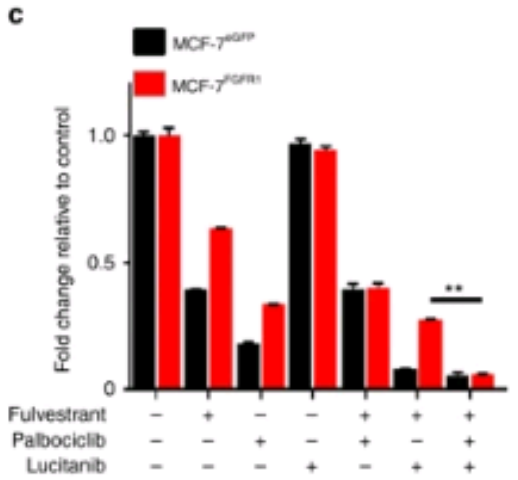
Aftimos P et al. ESMO Breast 2019.

Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer









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Formisano L et al. Nature Comm 2019.

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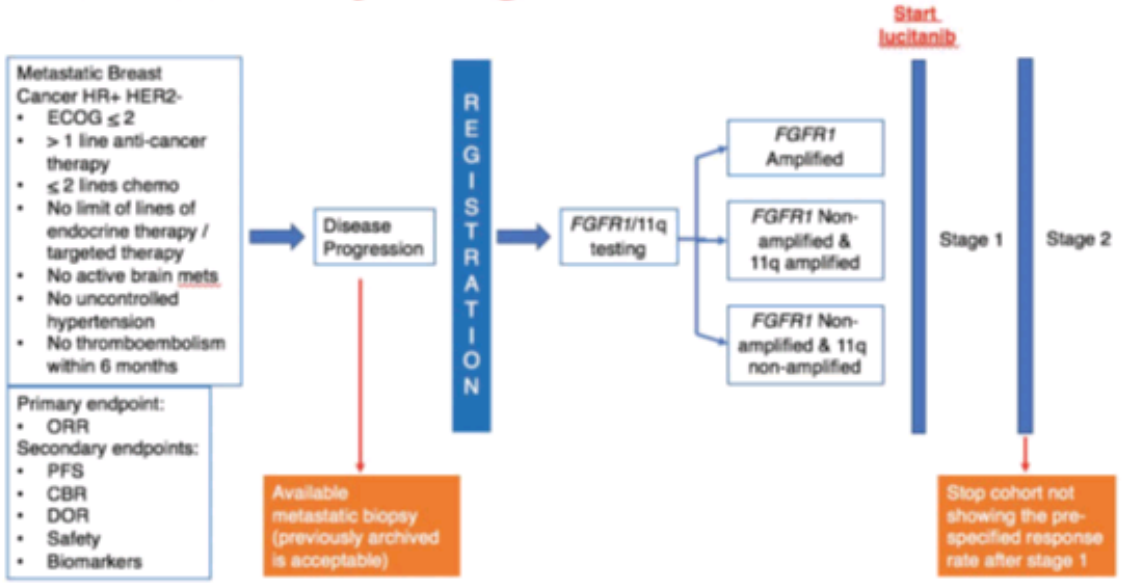
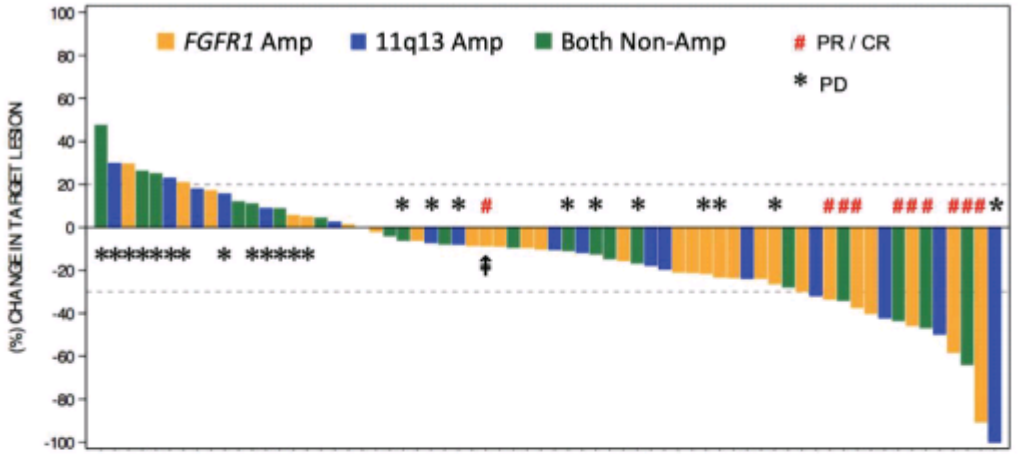
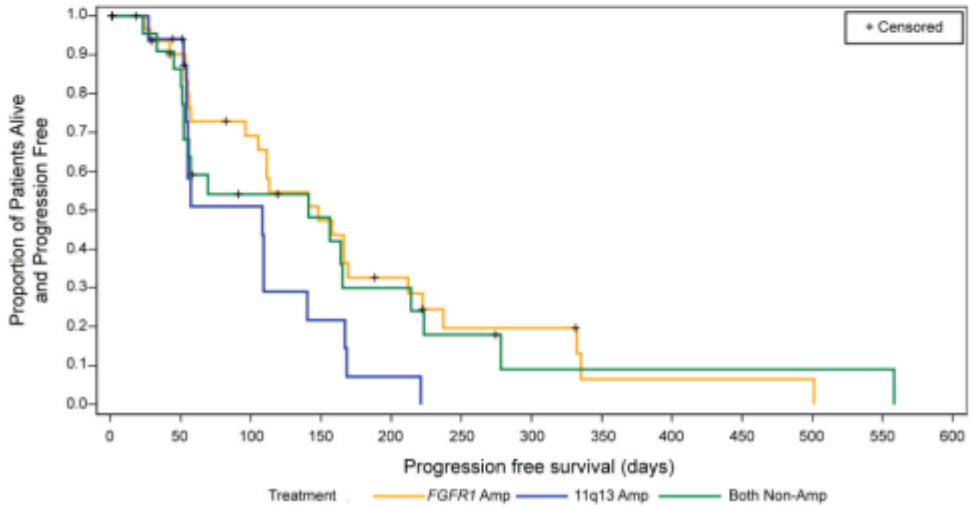
Lucitanib in ER+/HER2- MBC

FINESSE: Study Design

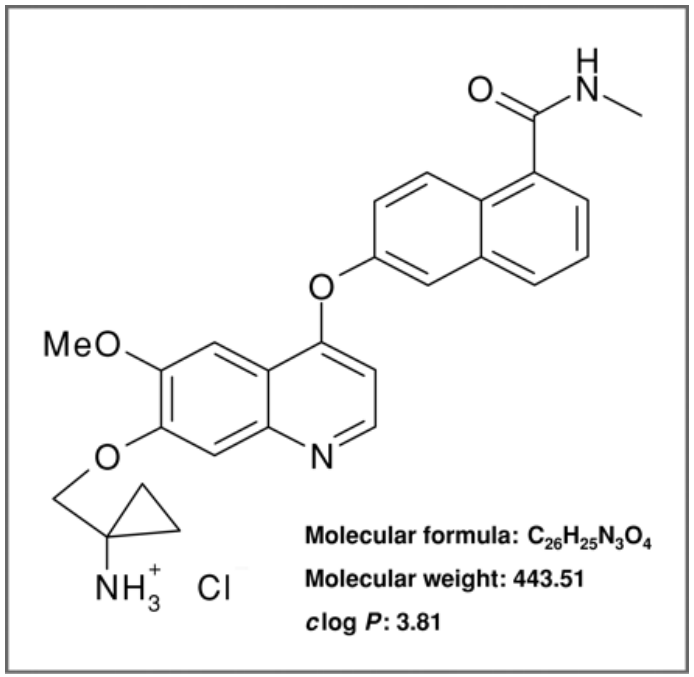






Hui R et al. CCR 2019.

A need for a new generation of targeted drugs



Lucitanib potently and selectively inhibits **VEGF receptor (VEGFR)-1, -2, and -3** and FGF receptor (FGFR)-1 and -2 kinases in the nanomolar range.

	Cohort 1 *FGFR1* Amp (n = 32)		Cohort 2 11q13 Amp (n = 18)		Cohort 3 Both Non-Amp (n = 26)		All (n = 76)	
	n	%	n	%	n	%	n all grades (grade 3-4)	% all grades (grade 3-4)
Hypertension	28	88	14	78	24	92	66 (50)	87 (66)
Hypothyroidism	20	63	4	22	10	39	34 (0)	45 (0)
Nausea	14	44	2	11	9	35	25 (1)	33 (1)
Proteinuria	12	38	6	33	6	23	24 (0)	32 (0)
Fatigue	15	47	3	17	5	19	23 (3)	30 (4)
Diarrhoea	12	38	4	22	7	27	23 (1)	30 (1)
Headache	9	28	2	11	7	27	18 (0)	24 (0)
Asthenia	7	22	3	17	6	23	16 (2)	21 (3)
AST increased	11	34	2	11	2	8	15 (1)	20 (1)
ALT increased	10	31	2	11	2	8	14 (2)	18 (3)
Vomiting	6	19	2	11	5	19	13 (0)	17 (0)
Thrombocytopenia	6	19	1	6	5	19	12 (2)	16 (3)
Reduced Appetite	6	19	1	6	5	19	12 (0)	16 (0)
GGT increased	5	16	3	17	3	12	11 (6)	15 (8)
Abdominal pain	6	19	1	6	3	12	10 (0)	13 (0)
Abdominal pain upper	5	16	2	11	3	12	10 (0)	13 (0)
ALP increased	4	13	2	11	1	4	7 (1)	9 (1)
Myalgia	2	6	2	11	2	8	6 (1)	8 (1)

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Bello E et al. Cancer Res 2011.

Hui R et al. CCR 2019.

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The NEW ENGLAND JOURNAL of MEDICINE

Erdafitinib for Urothelial Carcinoma

MULTICENTER, OPEN-LABEL, PHASE 2 STUDY

210

Patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations

Erdafitinib

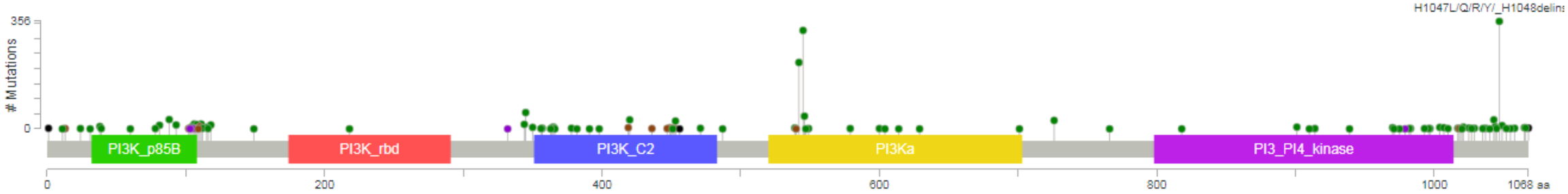
Dose-Selection Phase		Selected Regimen
10 mg/day (intermittently) (N = 33)	6 mg/day (continuously) (N = 78)	8 mg/day (continuously) (N = 99)

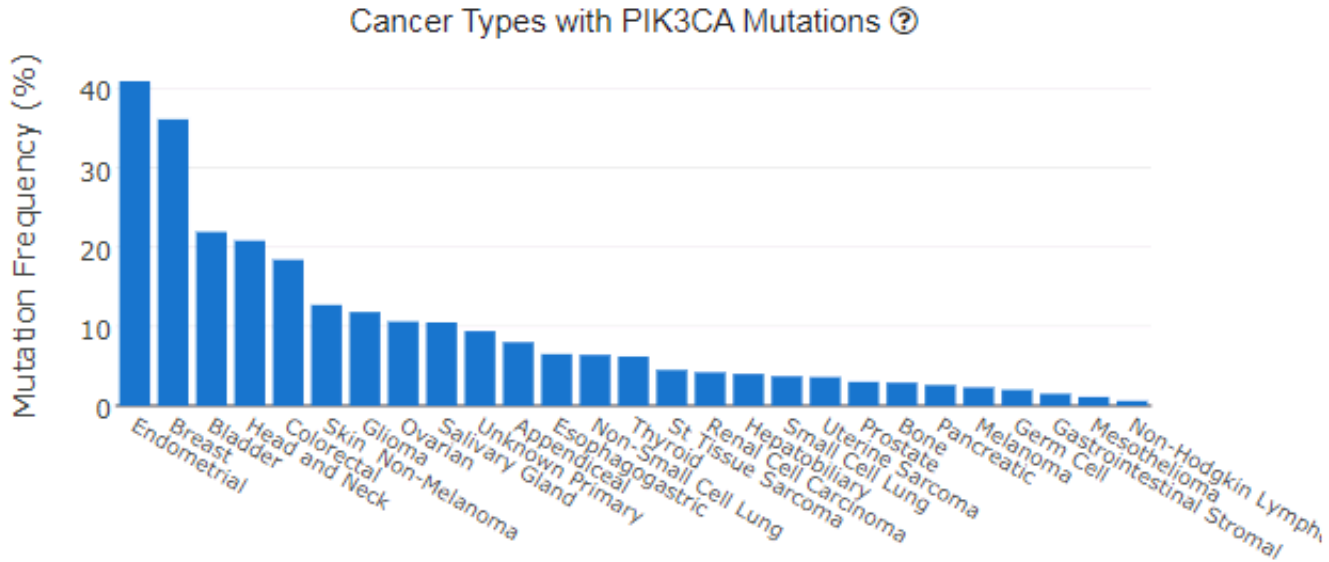
Interim analysis completed and regimen selected

Rate of confirmed response	40% (95% CI, 31–50)
Grade ≥3 adverse events	67%

Y. Loriot et al. 10.1056/NEJMoa1817323

PIK3CA is an actionable oncogene





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OncoKB based on Zehir A et al. Nat Med 2017.

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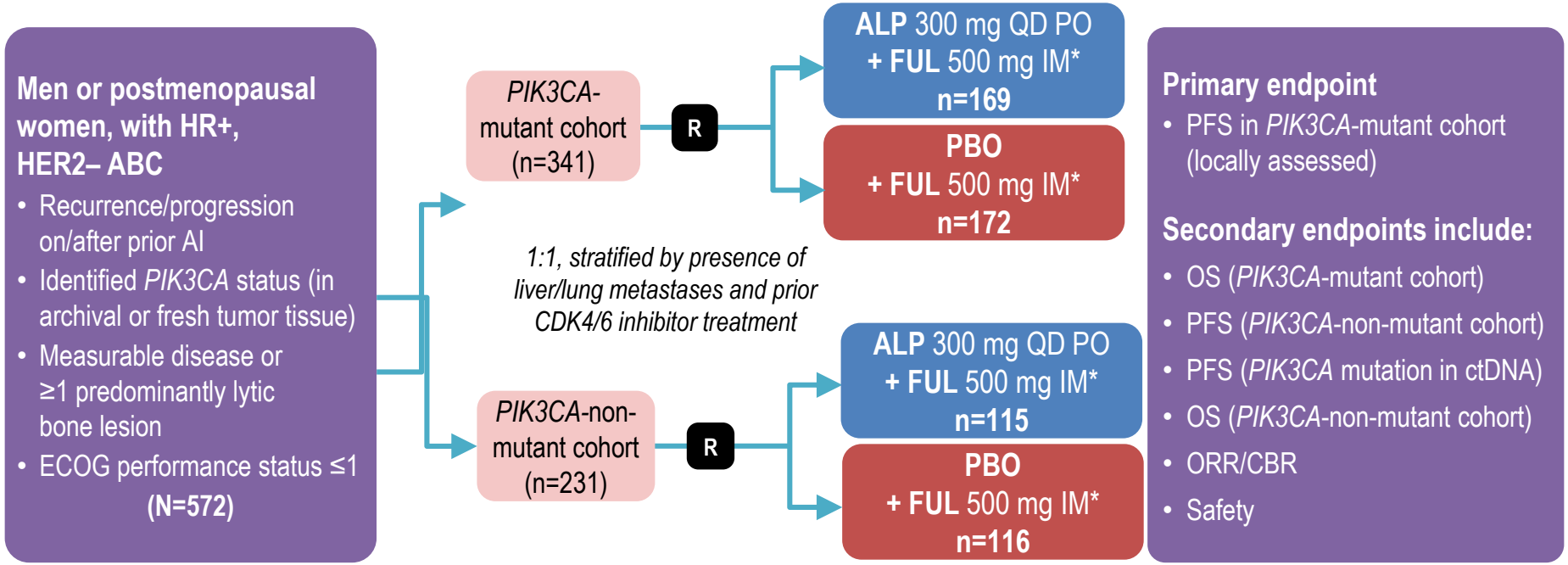
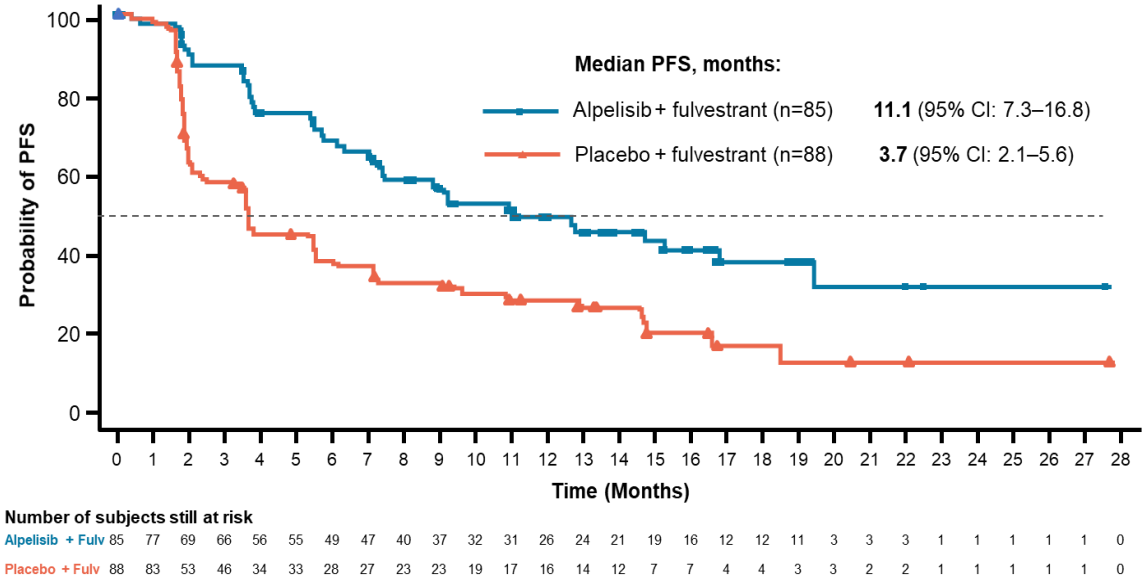
SOLAR-1: A Phase III randomized, controlled trial (NCT02437318)



- *Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28 day cycles.

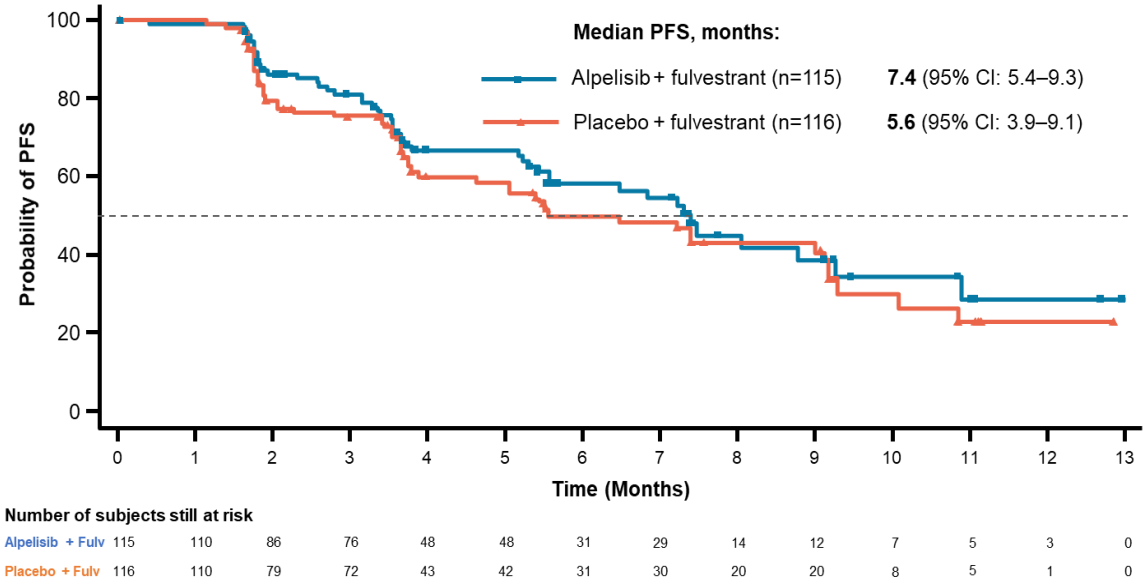
SOLAR-1: Alpelisib proof of concept and regulatory approval

PIK3CA-mutated



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=85)	Placebo + fulvestrant (N=88)
Number of PFS events, n (%)	43 (50.6)	63 (71.6)
Median PFS (95% CI)	11.1 (7.3–16.8)	3.7 (2.1–5.6)
HR (95% CI)	0.48 (0.32–0.71)	

PIK3CA WT



Data cut-off: Dec 23, 2016	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Number of PFS events, n (%)	49 (42.6)	57 (49.1)
Median PFS (95% CI)	7.4 (5.4–9.3)	5.6 (3.9–9.1)
HR (95% CI)	0.85 (0.58–1.25)	

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André F et al. ESMO 2018.

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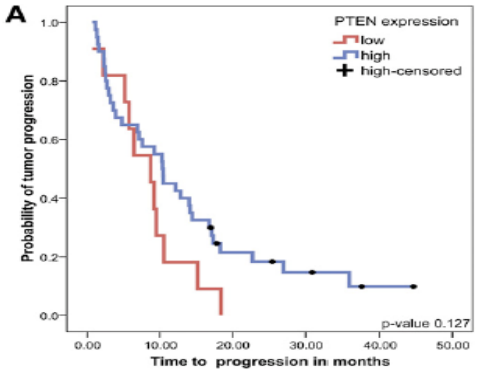
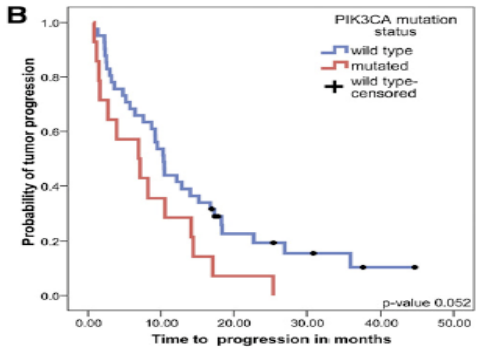
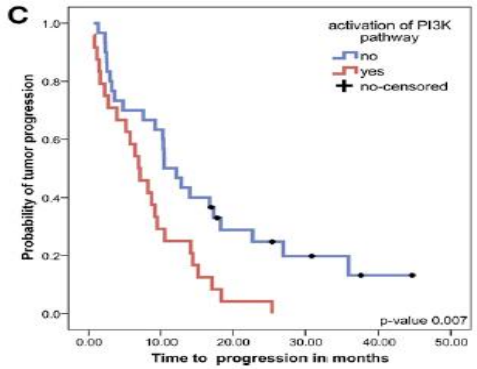
PI3K-AKT-mTOR and Trastuzumab Resistance



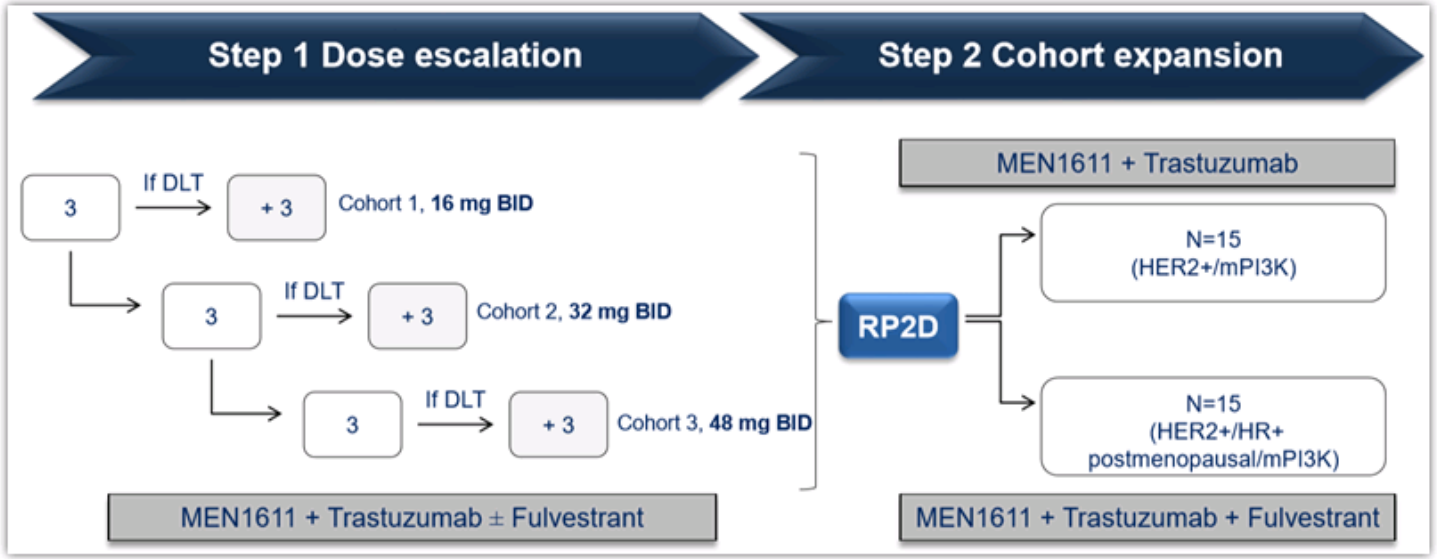




Berns K et al. Cancer Cell 2007

B·PRECISE·01

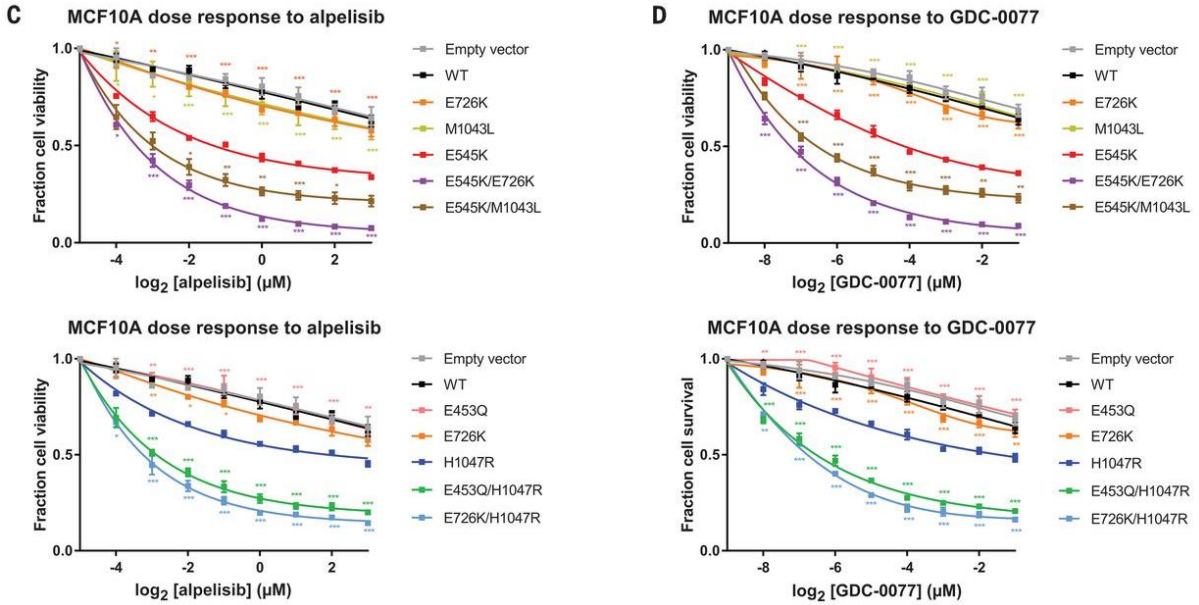
BREAST-A PI3K INHIBITOR WITH TARGETED COMBINATIONS IN SOLID TUMORS TREATMENT

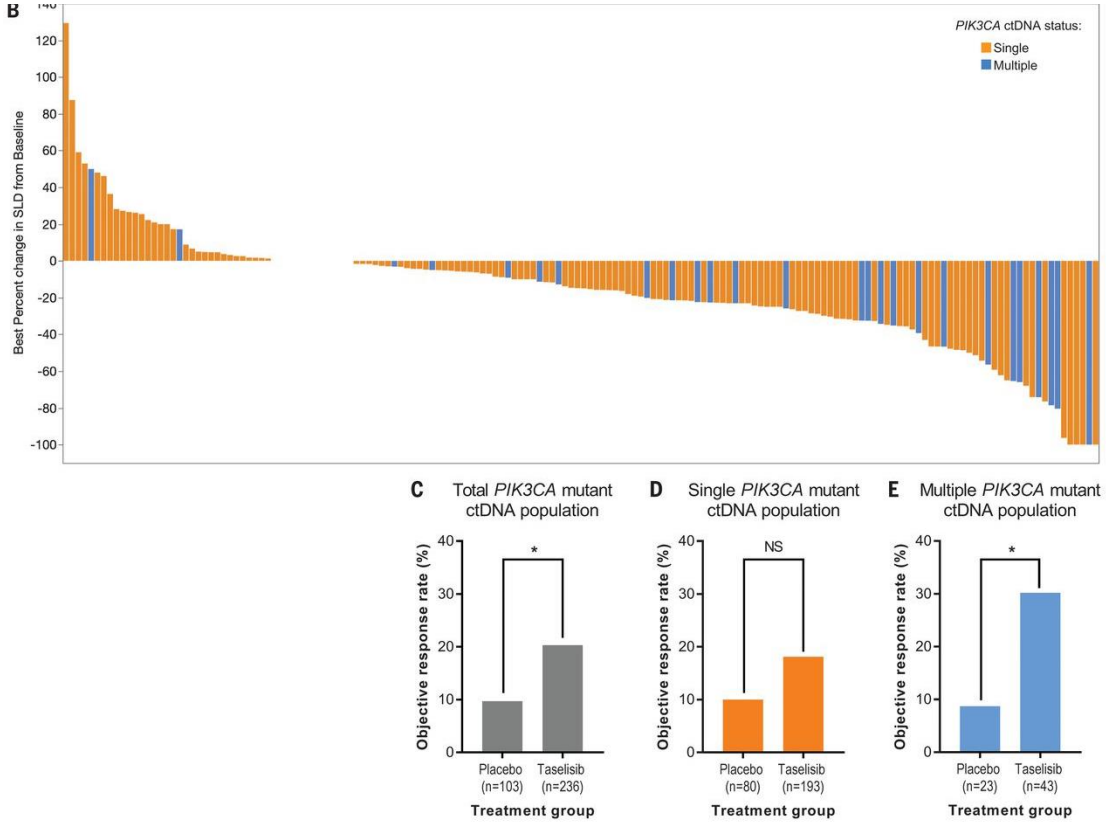


NCT03767335

Piccart M et al. ASCO 2019.

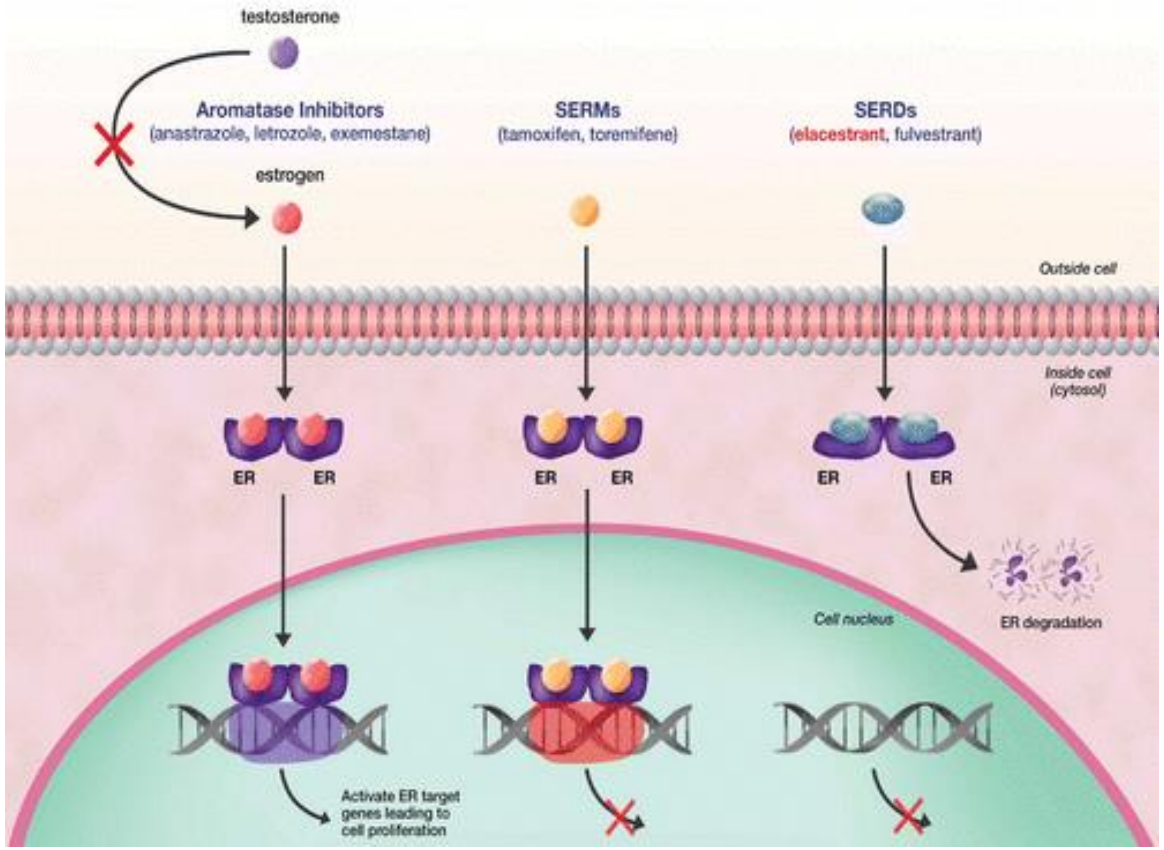
Double PIK3CA mutations and the concept of « super-oncogene »





Vasan N et al. Science 2019.

Selective Estrogen Receptor Degraders (SERDs)



Also G1T48, LSZ102, SAR439859, AZD9833, GDC-9545

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Bardia A et al. Future Oncology 2019

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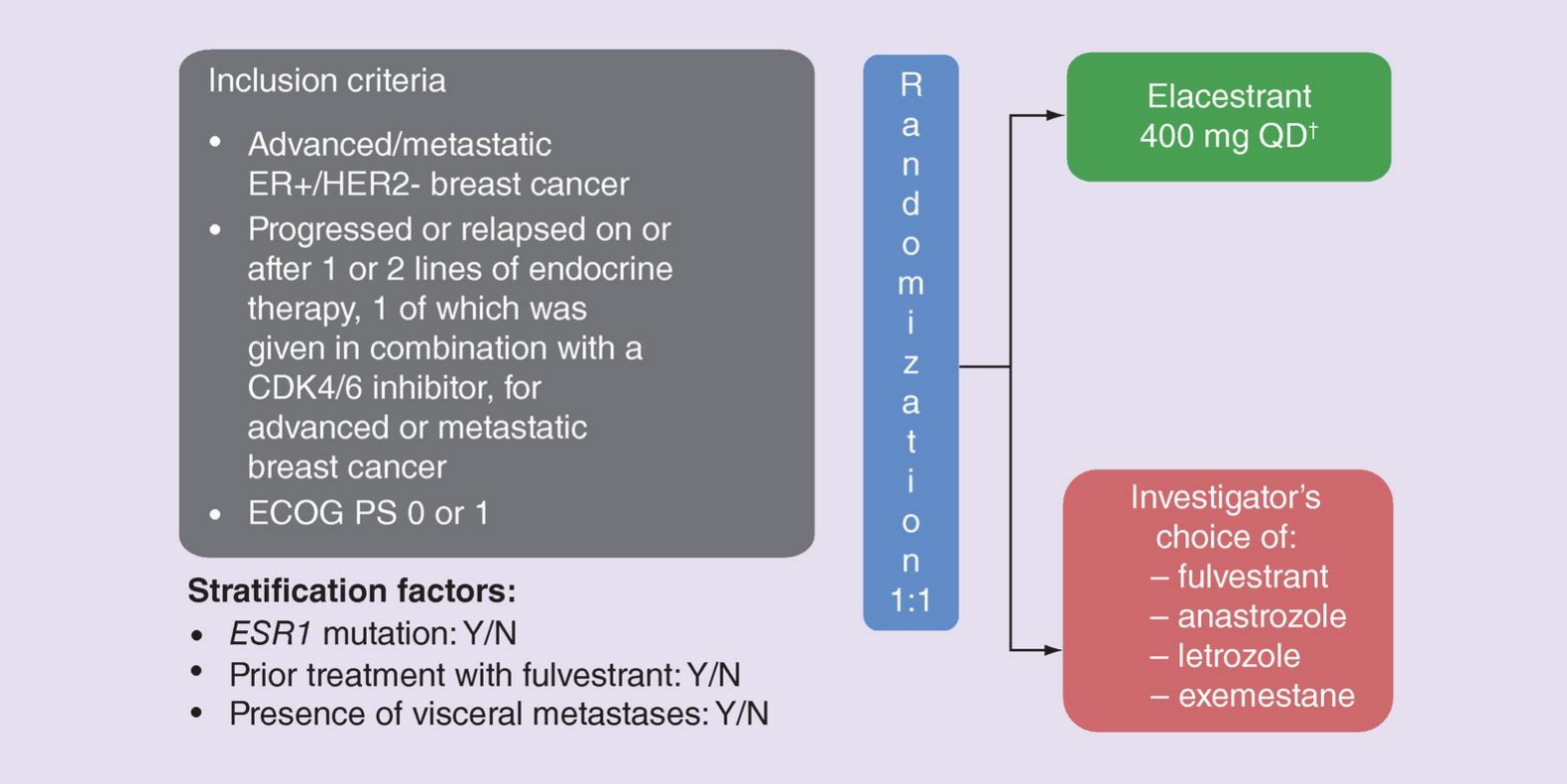
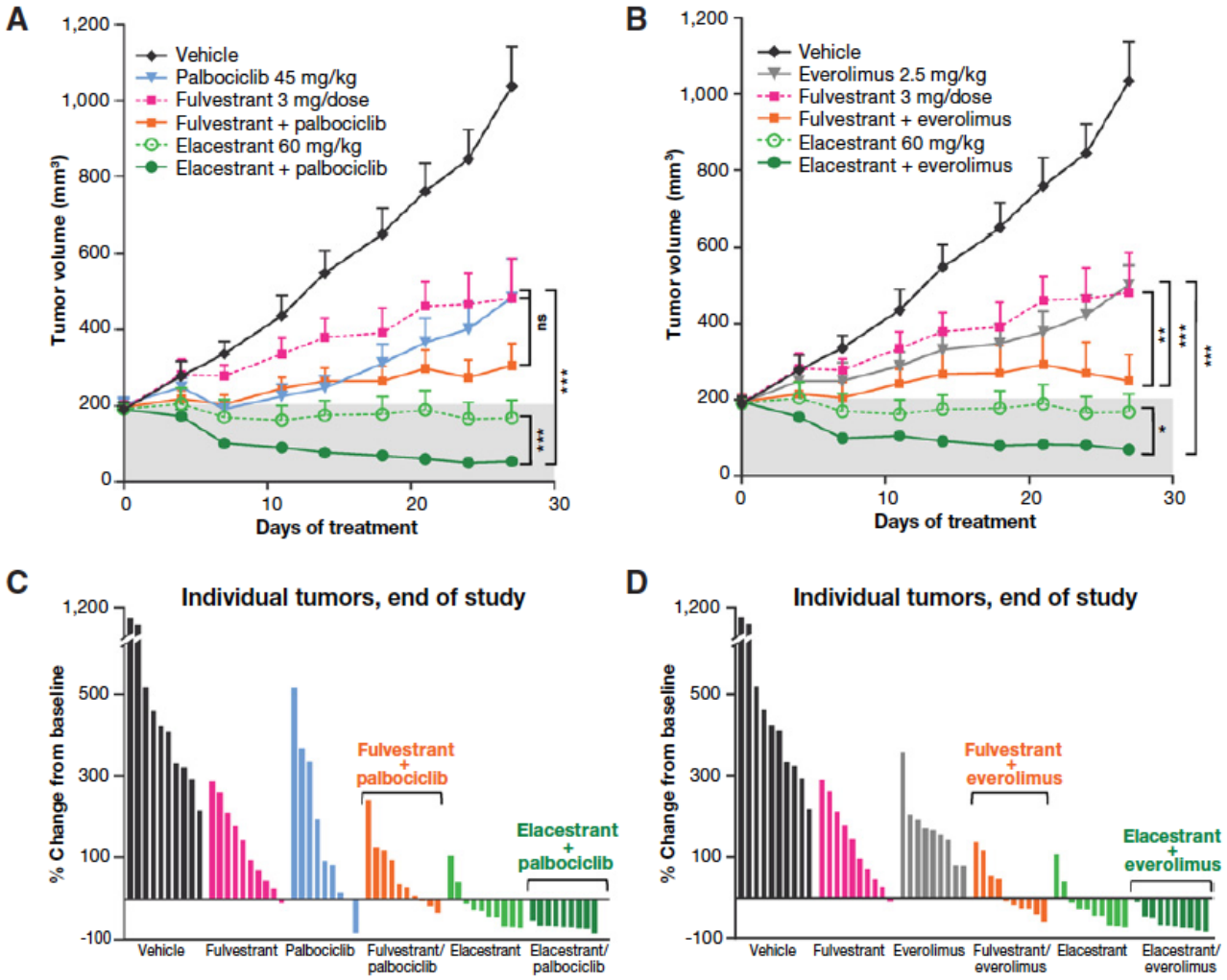
EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer



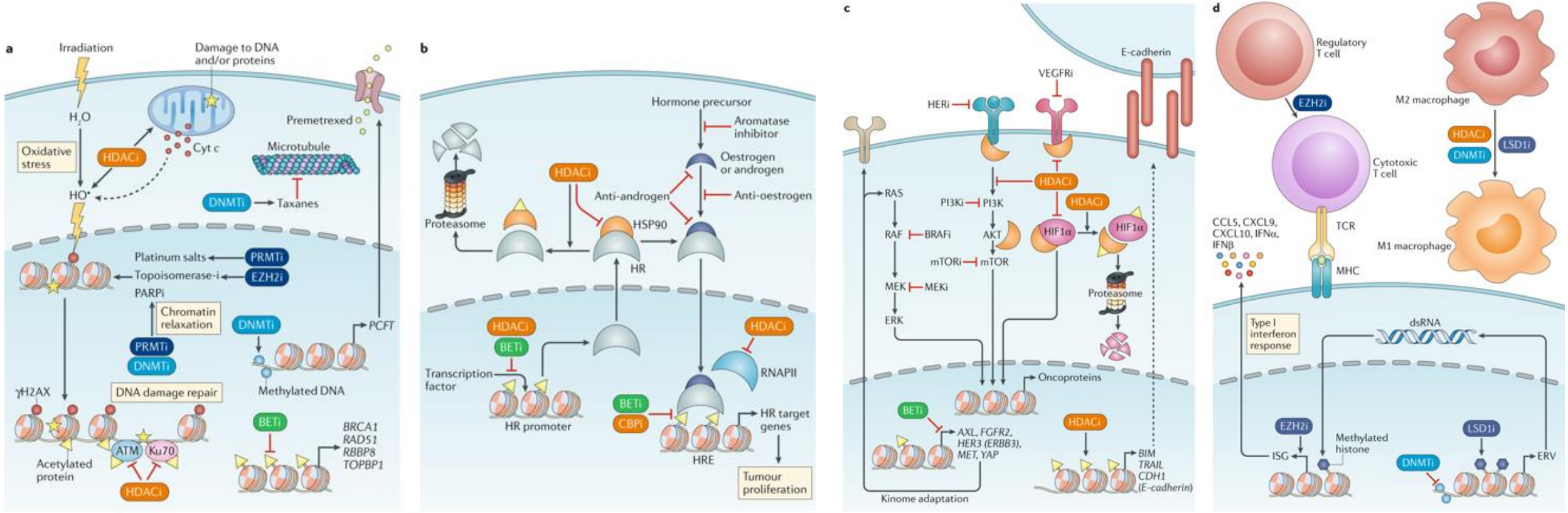
Bardia A et al. Future Oncology 2019

Promise as combination therapy



Bihani T et al. Clin Can Res 2017.

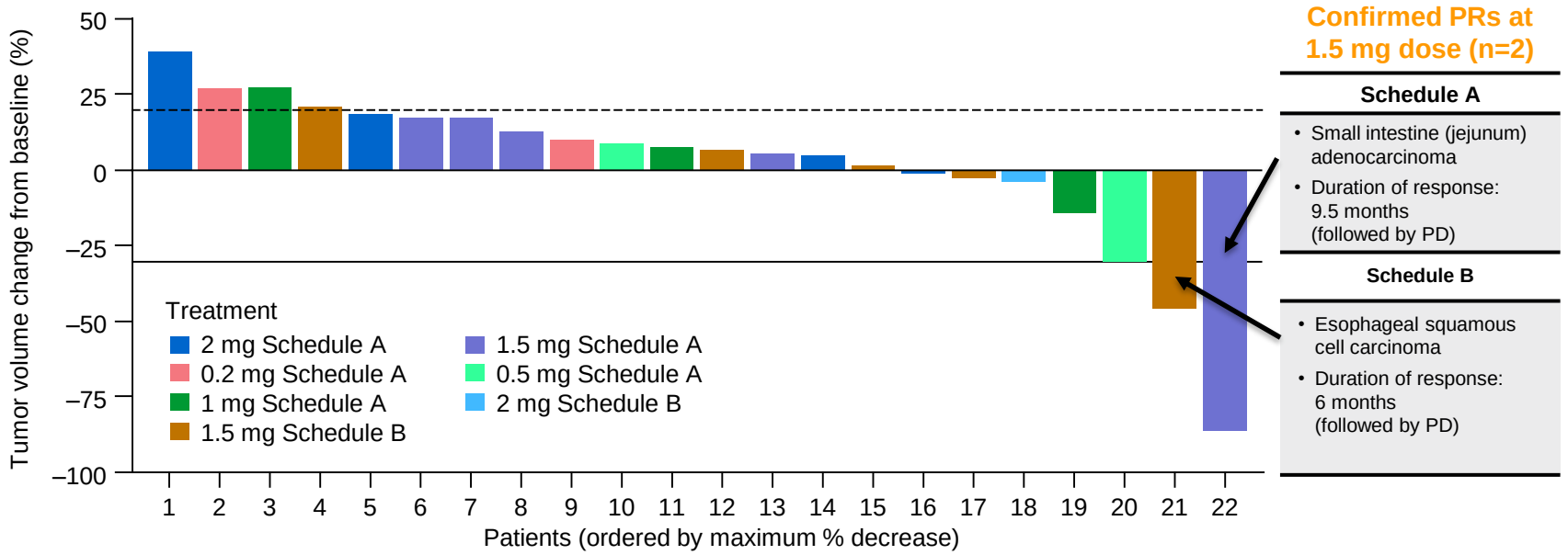
A variety of combinations based on epigenetics-targeting drugs



Morel D et al. Nat Rev Clin Oncol 2019.

Tumor responses

- Overall*, 3 patients had a PR (2 were confirmed) and 9 had SD†



Confirmed PRs at 1.5 mg dose (n=2)

Schedule A

- Small intestine (jejunum) adenocarcinoma
- Duration of response: 9.5 months (followed by PD)

Schedule B

- Esophageal squamous cell carcinoma
- Duration of response: 6 months (followed by PD)

*22 patients were evaluable according to RECIST 1.1; †SD lasted for >10 cycles in one patient. PD, progressive disease

CANCER

Repression of BET activity sensitizes homologous recombination–proficient cancers to PARP inhibition

Article

Cancer Cell

BRD4 Inhibition Is Synthetic Lethal with PARP Inhibitors through the Induction of Homologous Recombination Deficiency

Report

Cell Reports

BET Bromodomain Inhibition Synergizes with PARP Inhibitor in Epithelial Ovarian Cancer

Breast International Group

CLINICAL STUDY PROTOCOL	
TITLE	A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer
INVESTIGATIONAL NEW DRUG NUMBER	141108
EUDRACT NUMBER	
STUDY DRUG	ZEN003694
PROTOCOL NUMBER	ZEN003694-004
SPONSOR	Zenith Epigenetics Ltd.

48mg Zen-3694 1mg tala (3+3)

Simon Two Stage Part 1
RP2D 48mg ZEN-3694 + 1mg talazoparib

End Simon 2-stage, n=20

(12/20)

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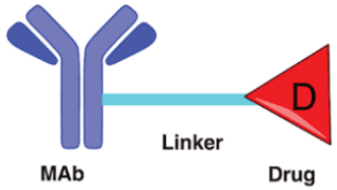
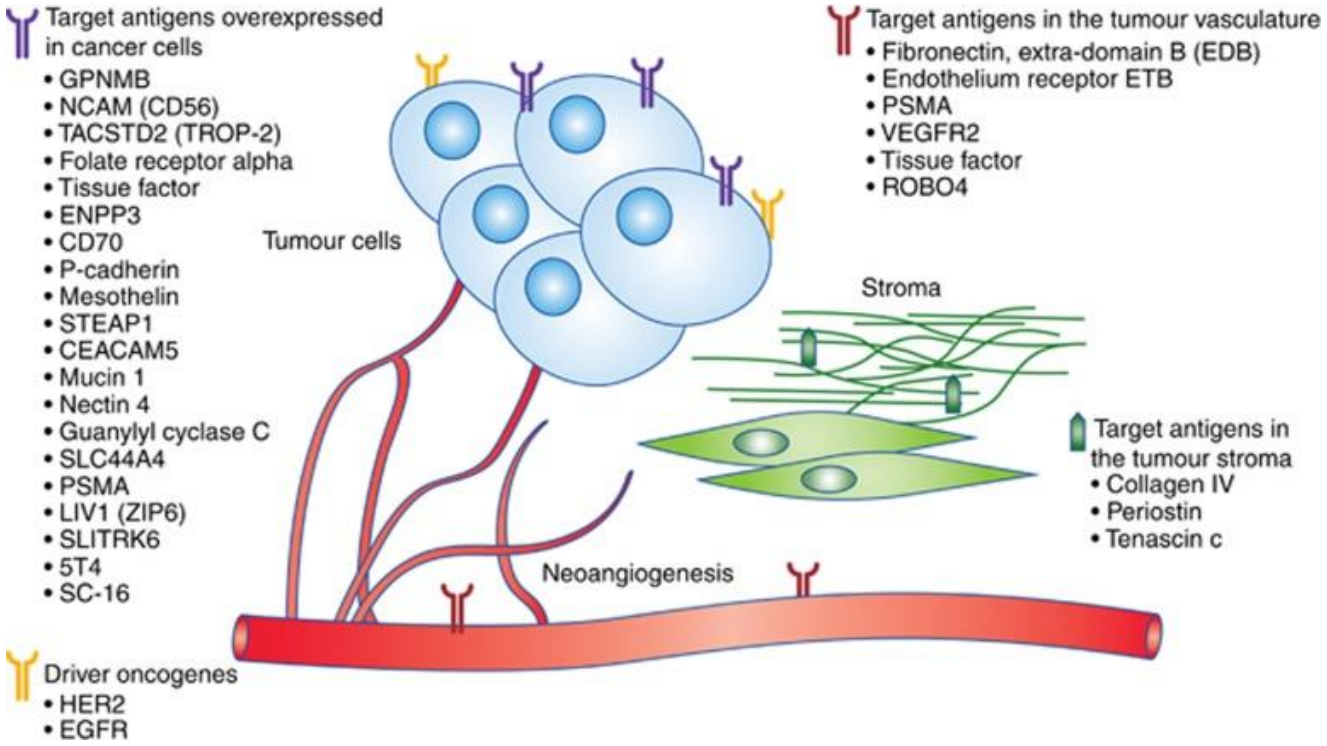
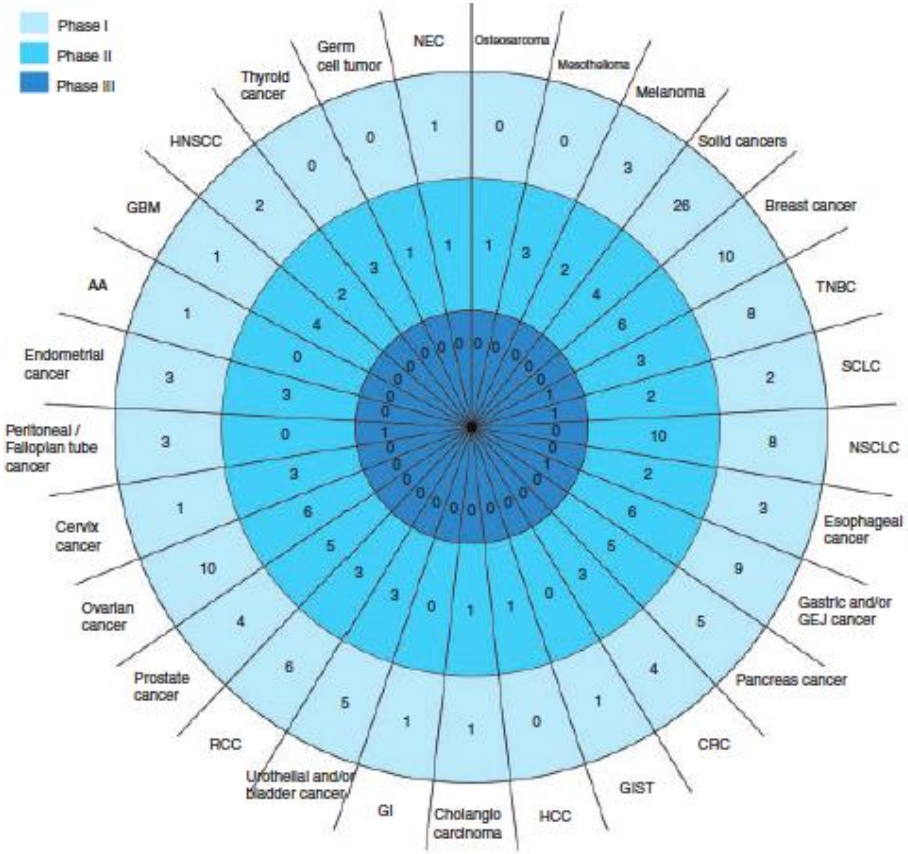
The ADC approach



Trojan horse





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Diamantis N et al. Br J Cancer 2016.

Moek KL et al. Ann Oncol 2017.

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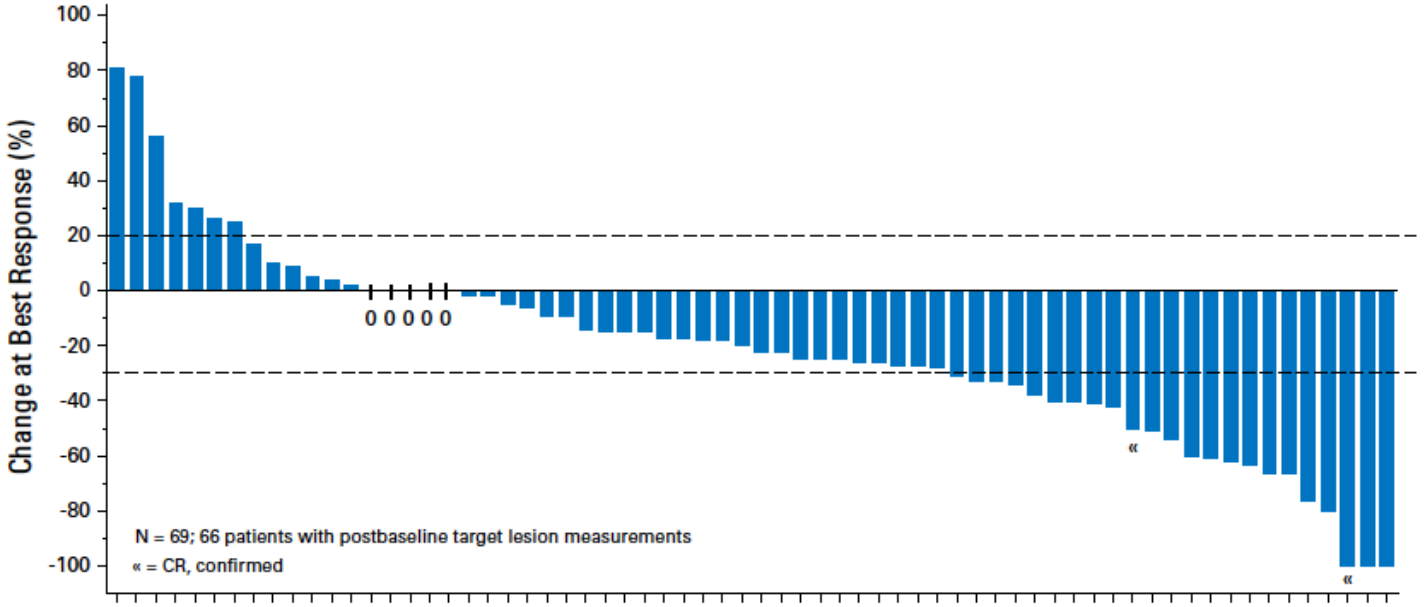
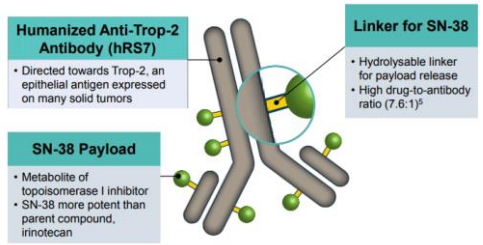
Sacituzumab Govitecan (anti-Trop 2 ADC) in heavily pretreated metastatic TNBC





Bardia A et al. J Clin Oncol 2017.

Compound	Indication	Research / Preclinical	Phase 1	Phase 2	Phase 3	Approval
Sacituzumab govitecan (IMMU-132)	mTNBC (3L+)				Re-submit BLA	
	mTNBC (3L) – ASCENT					
	Urothelial (3L) – TROPHY U-01					
	HR+/HER2– mBC					
	CPI combo (mBC / mUC / mNSCLC)					
	PARPi combo (mBC / mUC / ovarian)					
	Basket (mNSCLC / H&N / mSCLC / endometrial / HCC)					

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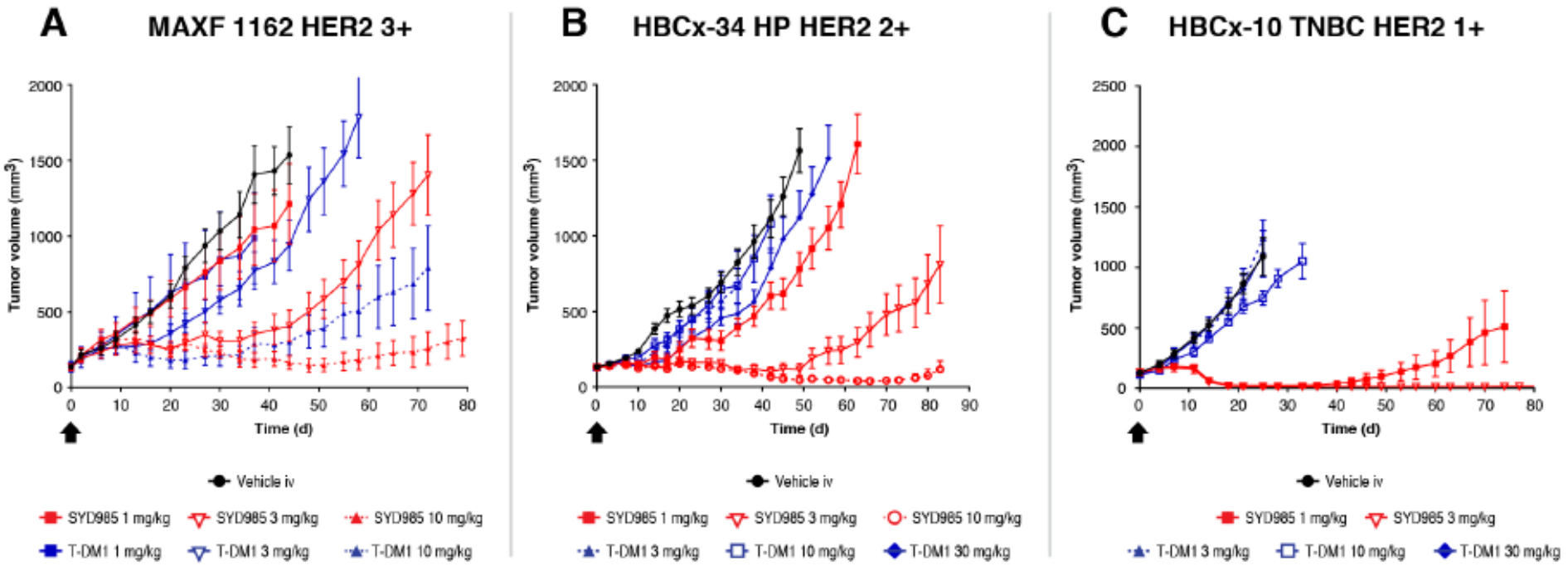
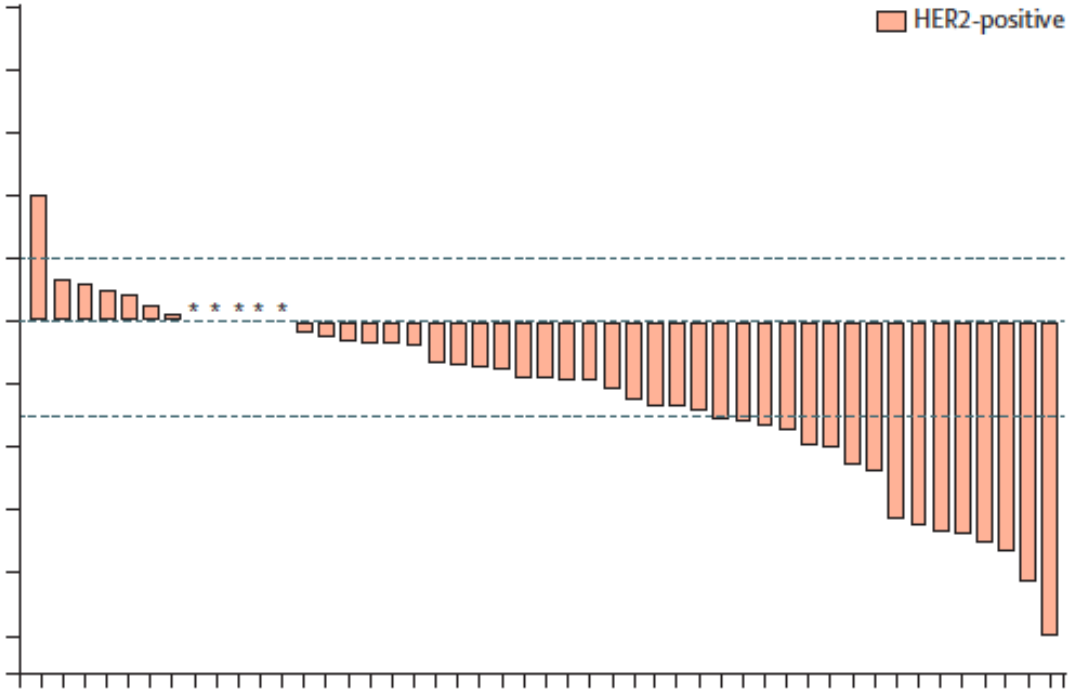
SYD985 vs T-DM1 in the pre-clinical setting



Van der Lee et al. Mol Ther 2015.

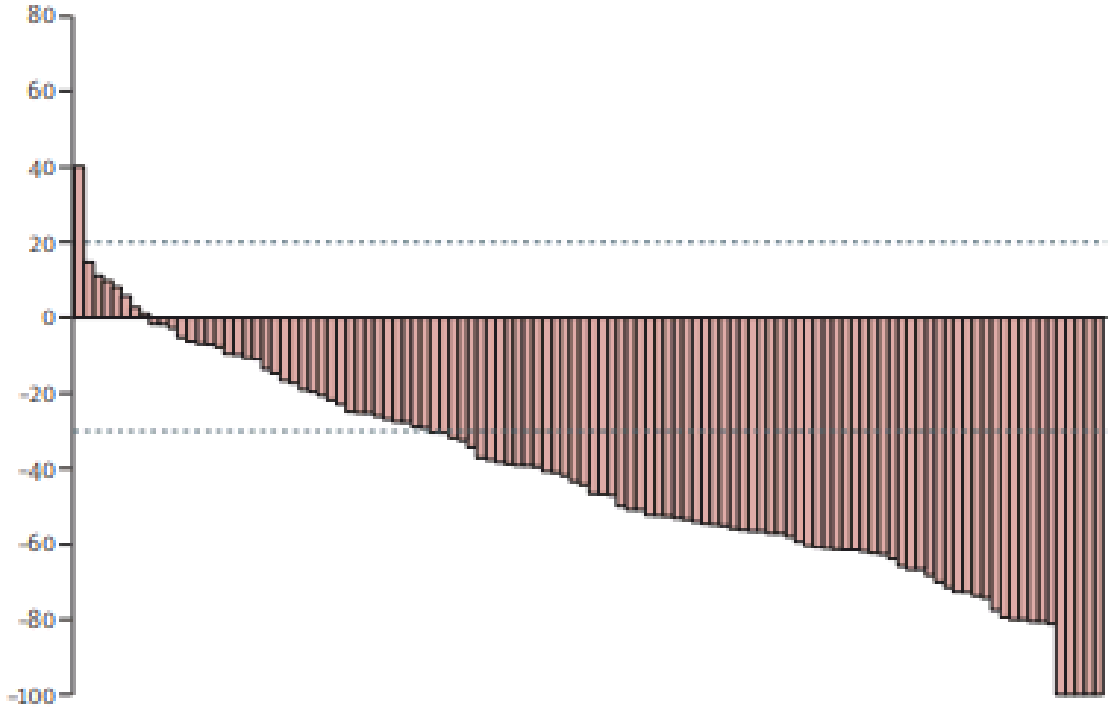
Novel ADCs in heavily pretreated HER2+ MBC

Trastuzumab Duocarmazine (SYD985)



ORR = 33%
PFS = 7.6 months

Trastuzumab Deruxtecan (DS-8201)



ORR = 59.5%
PFS = 22.1 months

3 ongoing phase 3 trials
NCT03262935
NCT03523585
NCT03529110

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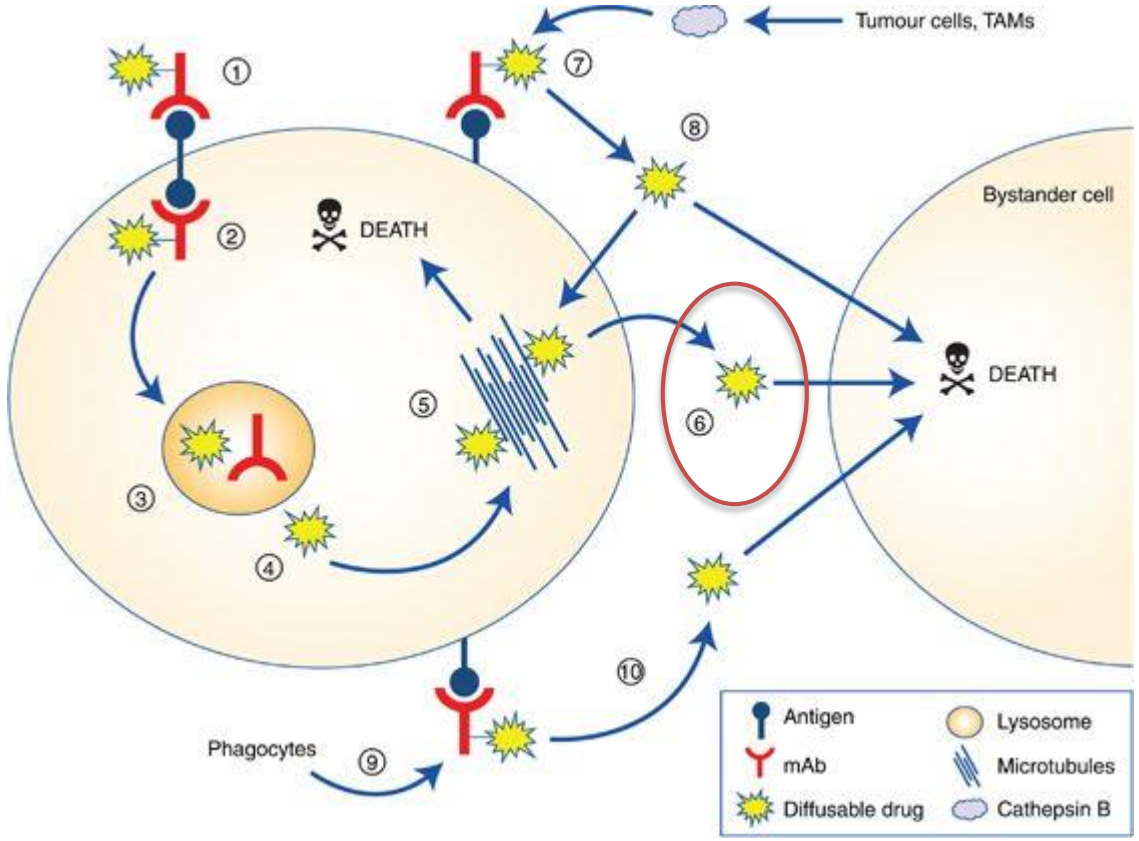
Banerji U et al. lancet Oncol 2019
Tamura K et al. Lancet Oncol 2019

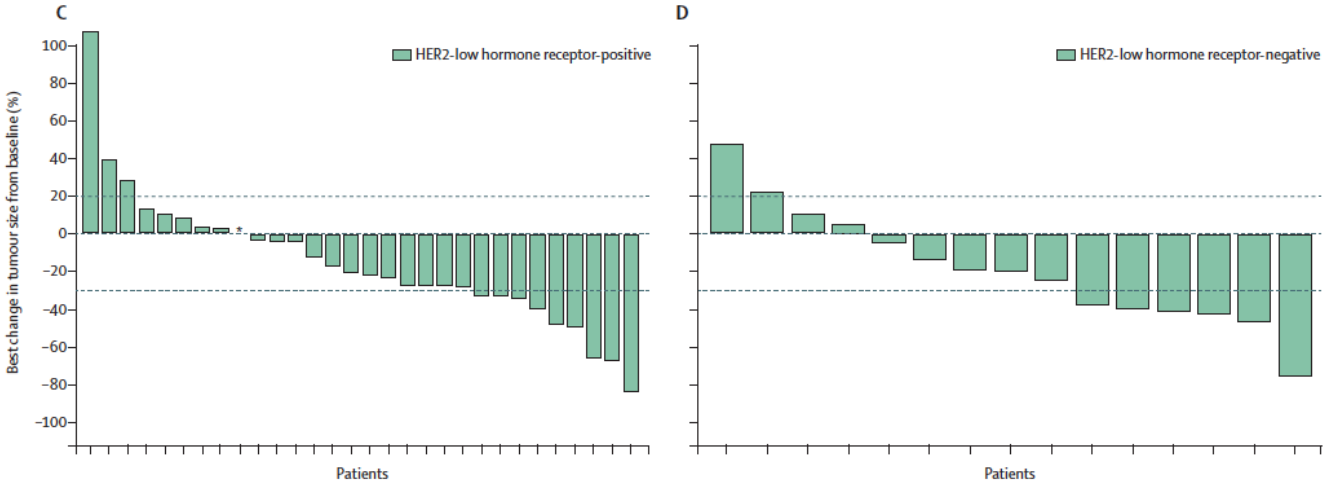
Bystander killing: anti-HER2 ADCs in HER2- (low) breast cancer



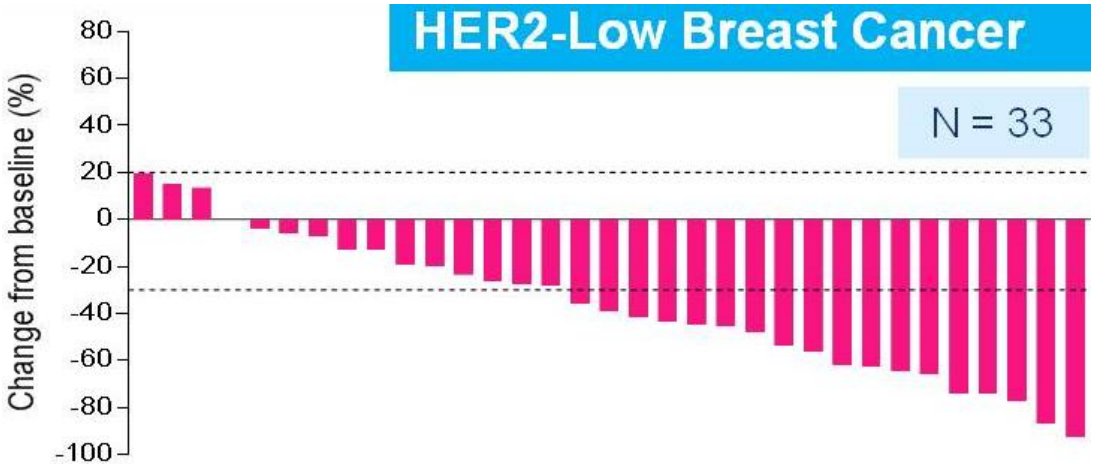
Staudacher A et al. Br J Cancer 2017.

Novel anti-HER2 ADCs and the concept of HER2-low

Trastuzumab Duocarmazine (SYD985)



Trastuzumab Deruxtecan (DS-8201)



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Banerji U et al. Lancet Oncol 2019
Hiroji Iwata et al. 2018 ASCO Annual Meeting.

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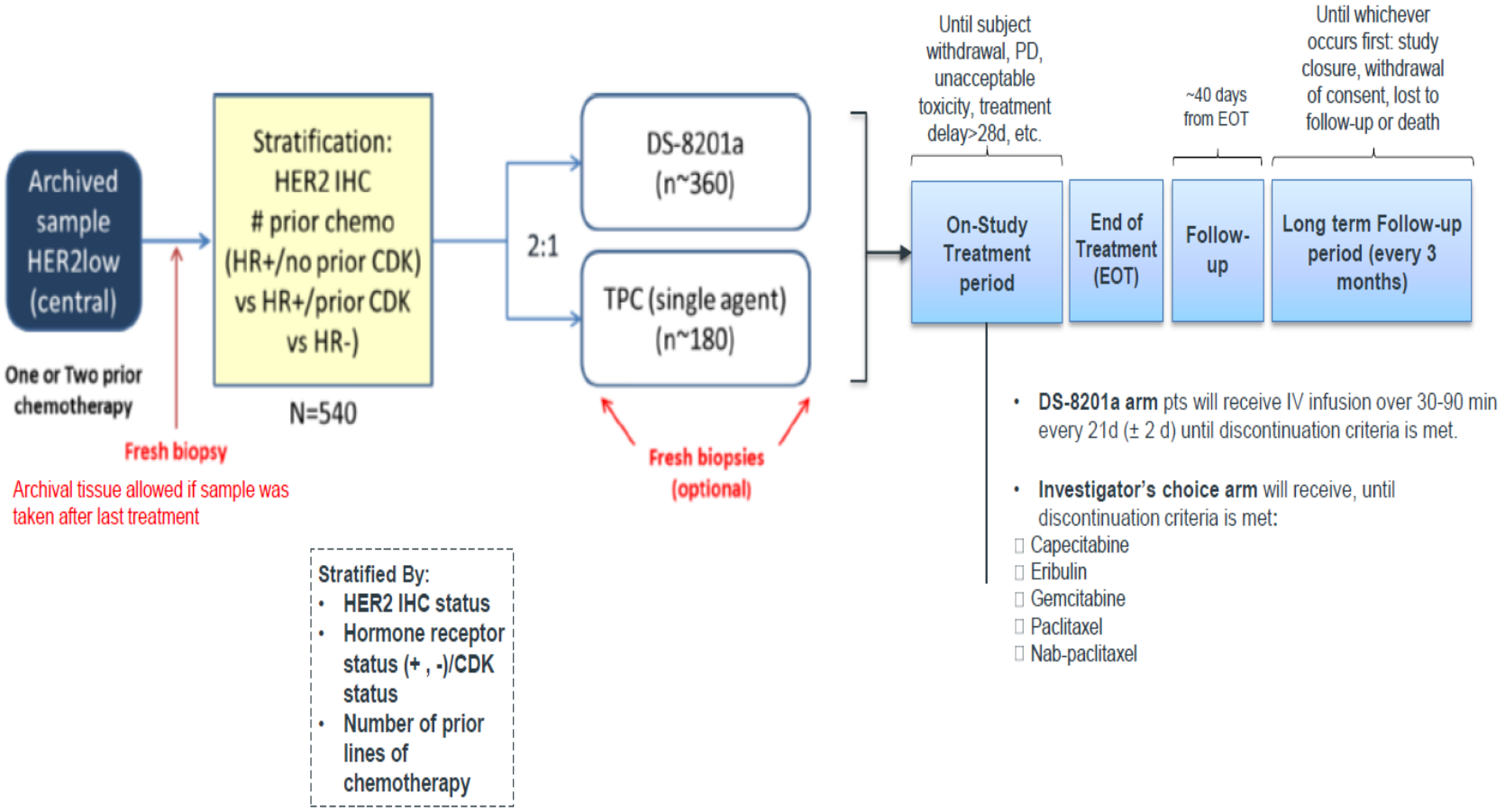
DESTINY-Breast04 randomized phase 3 trial in HER2-low MBC



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Let’s interact… twitter @aftimosp

Clinical trial referrals: trials.ijbctcu@bordet.be

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