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Personalized therapy in MBC: When and What?

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Disclosures

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What is needed in 2020 for a biomarker to guide personalized therapy?

1. The biomarker must be analytically validated in order to be reproductible, robust, precise and accurate (e.g., HR, HER2)
2. The biomarker must be able to divide a population of pts into different prognostic and/or treatment benefit groups (clinical validity) (e.g., TILs)
3. Clinical utility (e.g., BRCA 1/2, PDL1, PIK3CA)

Molecular Oncology in Breast Cancer: A Few Useful Biomarkers for personalized therapy

- HR+ (expression)
- ESR1 mutations
- HER2+ (amplification, mutations)
- PIK3CA (or AKT) mutations
- BRCA 1 and 2 mutations

Nine molecular subtypes of Breast Cancer with therapeutic implications

- ER+ and/or PgR+ (70% of pts)
- ER+ and/or PgR+ and PI3K-mutated (40% of pts)
- ER+ and/or PgR+ and HER-2+ (triple positive)
- ER+ and/or PgR+ and BRCA-mutated
- HER2+ and HR- ± BRCA-mutated
- TNBC + PD-L1 positive on IC (≥ 1%)
- TNBC ± BRCA mutations

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Therapeutic Approaches to tackle/delay Endocrine Resistance

- **Endocrine therapy combination (e.g., Anastrozole + fulvestrant): No biomarkers**
- **Maximizing sensitivity to endocrine therapy:**
  - **Strategies targeting CDK4/6 (no biomarkers)**
  - **Strategies to antagonize the growth factor pathways (mTor, PIK3CA, …)**
  - **Strategies targeting genomic alterations of ESR1**
  - **Strategies targeting the immune tolerance (PDL1 and/or TILs as biomarkers?)**
- **Antibody – drug conjugates (biomarker = target)**

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Use of CDK4/6 inhibitors in early setting (Δ~10 months) or later lines (Δ~5 months) significantly and consistently improved PFS, ORR, and more recently OS (HR = biomarkers)

	PALOMA-2[1]	MONALEESA-2[2]	MONARCH-3[3]	MONALEESA-7[4]	PALOMA-3[5]	MONARCH-2[6]	MONALEESA-3[7]
Study design	Phase III Placebo-controlled **1st-line** (n=666)	Phase III Placebo-controlled **1st-line** (n=668)	Phase III Placebo-controlled **1st-line** (n=493)	Phase III Placebo-controlled **1st-line** (n=672)	Phase III Placebo-controlled **≥2nd-line** (n=521)	Phase III Placebo-controlled **2nd-line** (n=672)	Phase III Placebo-controlled **1st or 2d line** (n=726)
Prior therapy	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior ET up to 1 CT **for ABC**	Prior ET up to 1 chemo **for ABC**	**No more than one ET No prior chemo for ABC**	**≤ 1 line of ET for ABC**
Endocrine therapy	Letrozole	Letrozole	NSAI	Tamoxifen NSAI/LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
HR PFS	**0.56**	**0.57**	**0.55**	**0.55**	**0.50**	**0.55**	**0.59**
Median PFS (mo)	27.6 vs 14.5	25.3 vs 16.0	NR vs 14.7	23.8 vs 13.0	11.2 vs 4.6	16.4 vs 9.3	20.5 vs 12.8
ESMO-MCBS	3	3	2	3	4	3 or 2	-

Cross-trial comparisons need to be taken with caution due to differences in trial design

ABC, Advanced Breast Cancer; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; LHRHa, luteinising hormone-releasing hormone agonist; NR, not reached; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival.

1. Rugo HS, et al. Presented at SABCS 2017; Abstract P5-21-03; 2. Hortobagyi G, et al. Presented at ASCO 2017. Abstract 1038; 3. Goetz MP, et al. *J Clin Oncol.* 2017;35:3638–3646; 4. Tripathy D, et al. Presented at SABCS 2017. Abstract GS2-05; 5. Turner NC, et al. Presented at SABCS 2016. Abstract P4-22-06; 6. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875–2884; 7. Slamon DJ, ASCO 2018

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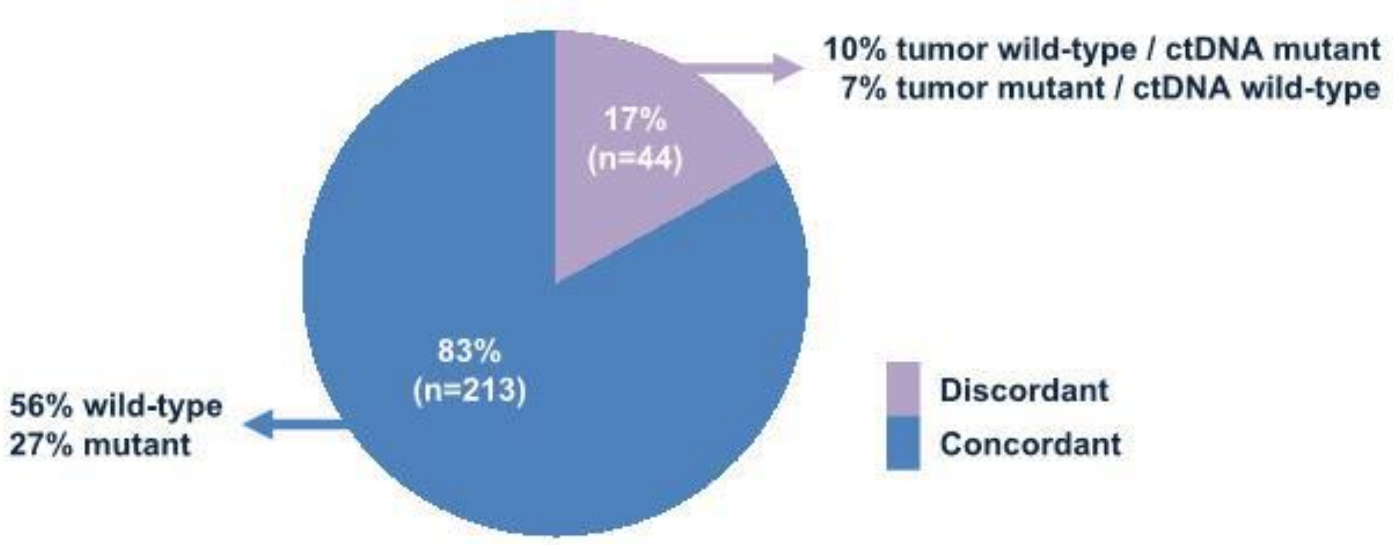
Strategies to antagonise the GF receptor pathway: PIK3CA Mutation as a Basis for Patient Selection

Good Concordance of PIK3CA Status in Tissue and ctDNA

- *PIK3CA* status was assessed in primary tumor tissue and matched ctDNA samples in 257 (59%) patients



ctDNA, circulating tumour DNA; GF, growth factor; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Di Leo A Lancet Oncol 2018 Jan;19(1):87-100.

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Trials testing the 4 PIK3CA inhibitors in post-menopausal metastatic luminal breast cancer

Trial	Population: mBC HR+ HER2−	Endocrine therapy	Number of patients	Results
BELLE-2 (phase III)[51]	PD after AI (one line of chemotherapy in metastatic disease was allowed; design similar to that of PALOMA-3 trial)	Buparlisib + FVL versus FVL	1147	- Better mPFS in both PIK3CA mutated or wild-type • wild-type: mPFS increased from 4.5 to 6.8 months (hazard ratio 0.8; $P = 0.0033$) • mutated: mPFS increased from 4 to 6.8 months (hazard ratio 0.76; $P = 0.0014$) - Bad toxicity profile with 23% SAE in buparlisib group
BELLE-3 (phase III)[52]	PD after mammalian target of rapamycin (mTOR) inhibitor	Buparlisib + FVL versus FVL	432	- mPFS increased from 1.8 to 3.9 months (hazard ratio 0.67; $P = 0.00030$) - Significant toxicity profile with 22% SAE in buparlisib group
FERGI (part 2 of phase II)[53]	PD after AI (part 2 cohort including PI3KCA mutated tumors only)	Pictilisib + FVL versus FVL	61	- No statistically significant difference in mPFS - Significant toxicity profile with 36% of at least grade 3 AE and 5% SAE in pictilisib group
SANDPIPER (phase III)[54]	PD after AI (PIK3CA-mutated tumors only)	Taselisib (selective PI3K inhibitor) + FVL versus FVL	516	- mPFS increased from 5.7 to 7.4 months (hazard ratio 0.7; $P = 0.0037$) - Taselisib group: at least grade 3 AEs: 12% diarrhea, 10% hyperglycemia, 3% colitis, 2% stomatitis, and treatment discontinuation in 17%
SOLAR-1 (phase III)[37,38]	PD after AI with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor	Alpelisib (α-specific PI3K inhibitor) + FVL versus FVL	572	- mPFS increased from 5.7 to 11 months (hazard ratio 0.65; $P = 0.00065$) in mutated tumors - Alpelisib group: grade 3 AE: 32.7% hyperglycemia, 9.9% rash, and 6.7% diarrhea

AE, adverse event; AI, aromatase inhibitor; FVL, fulvestrant; HER2−, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; mBC, metastatic breast cancer; mPFS, median progression-free survival; PD, progression disease; SAE, serious adverse event.

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G. El Hachem, A. Gombos and A. Awada, F1000Res 2019

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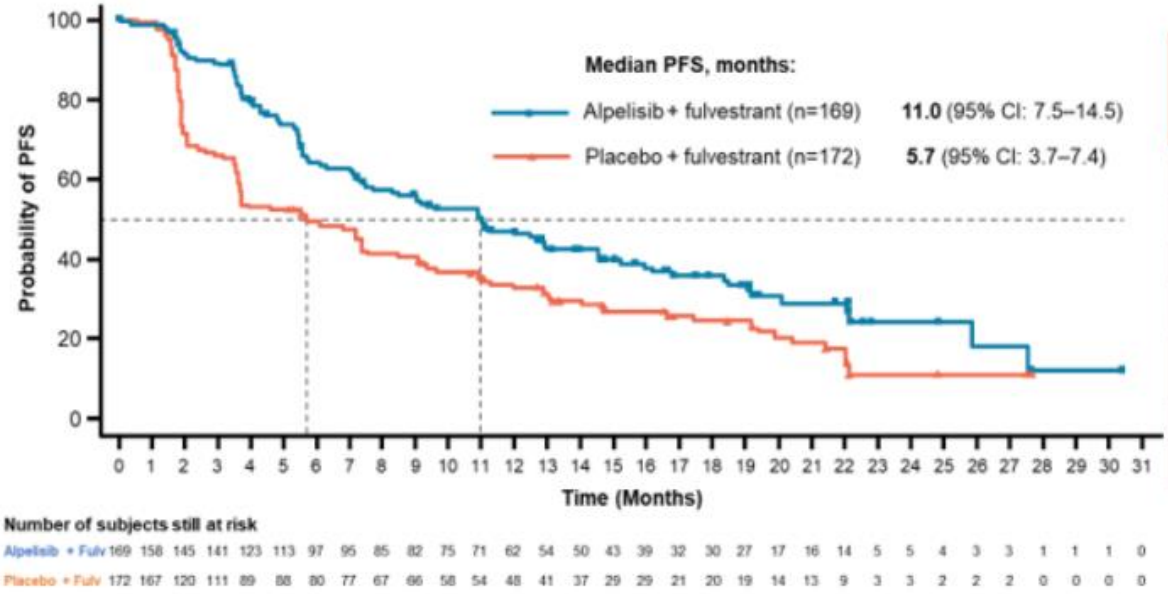
SOLAR-1 TRIAL: Fulvestrant ± Alpelisib for HR+, HER2- endocrine pretreated MBC

Primary endpoint: Locally assessed PFS in the *PIK3CA*-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

- The primary endpoint crossed the prespecified Haybittle–Peto boundary (one-sided p≤0.0199)

Double *PIK3CA* mutations in cis increase oncogenicity and sensitivity to PI3Kα inhibitors

Neil Vasan[1,2,3], Pedram Razavi[1,2]*, Jared L. Johnson[3]*, Hong Shao[1]*, Hardik Shah[4], Alesia Antoine[4], Erik Ladewig[1], Alexander Gorelick[1,5], Ting-Yu Lin[3], Eneda Toska[1], Guotai Xu[1], Abiha Kazmi[1], Matthew T. Chang[6], Barry S. Taylor[1,5,7], Maura N. Dickler[2,8], Komal Jhaveri[2], Sarat Chandarlapaty[1,2], Raul Rabadan[9], Ed Reznik[5,7], Melissa L. Smith[4,10], Robert Sebra[4,10,11], Frauke Schimmoller[6], Timothy R. Wilson[6], Lori S. Friedman[12], Lewis C. Cantley[3], Maurizio Scaltriti[1,13]†, José Baselga[1,2]†‡

Activating mutations in *PIK3CA* are frequent in human breast cancer, and phosphoinositide 3-kinase alpha (PI3Kα) inhibitors have been approved for therapy. To characterize determinants of sensitivity to these agents, we analyzed *PIK3CA*-mutant cancer genomes and observed the presence of multiple *PIK3CA* mutations in 12 to 15% of breast cancers and other tumor types, most of which (95%) are double mutations. Double *PIK3CA* mutations are in cis on the same allele and result in increased PI3K activity, enhanced downstream signaling, increased cell proliferation, and tumor growth. The biochemical mechanisms of dual mutations include increased disruption of p110α binding to the inhibitory subunit p85α, which relieves its catalytic inhibition, and increased p110α membrane lipid binding. Double *PIK3CA* mutations predict increased sensitivity to PI3Kα inhibitors compared with single-hotspot mutations.

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Vasan et al., Science 2019

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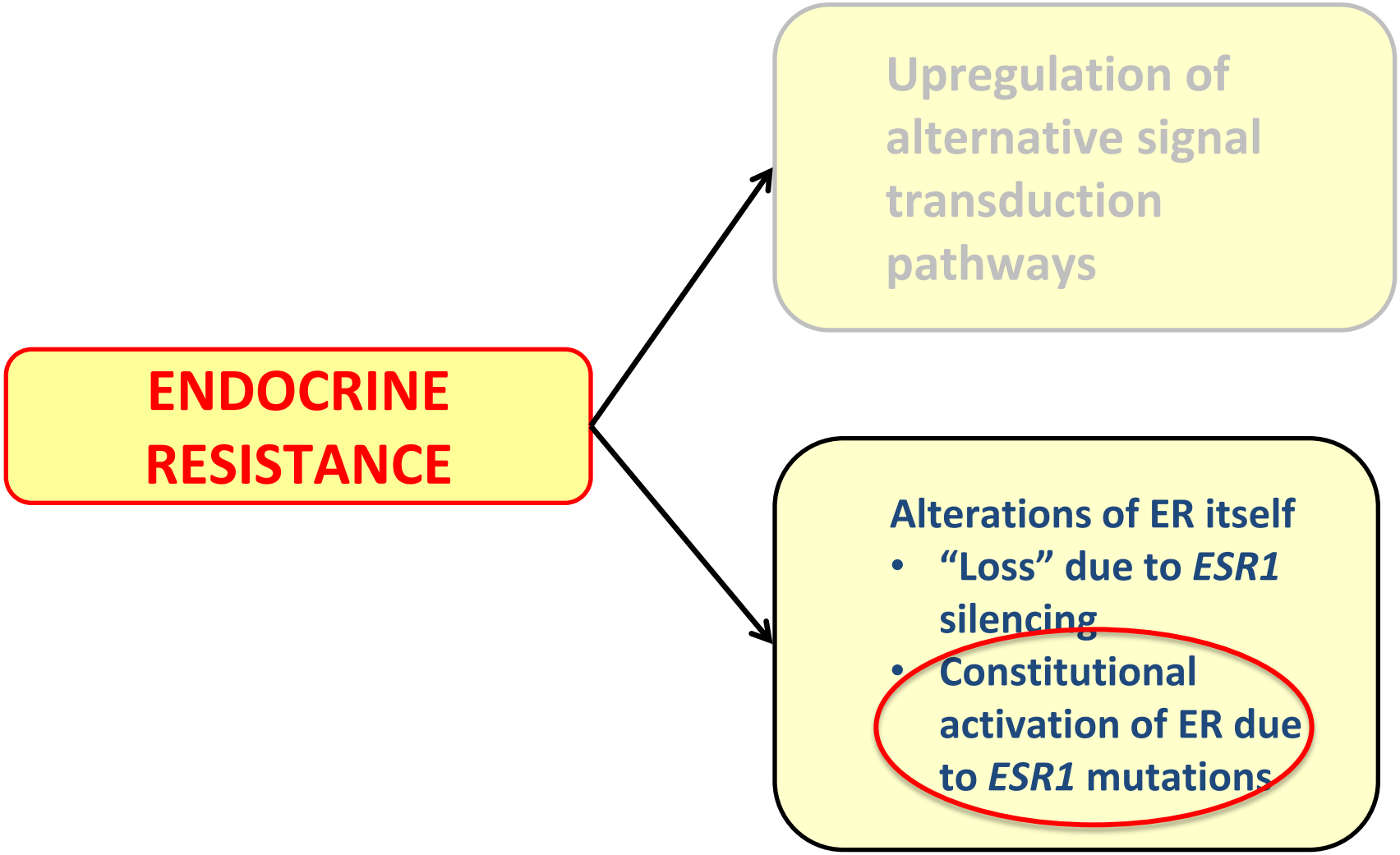
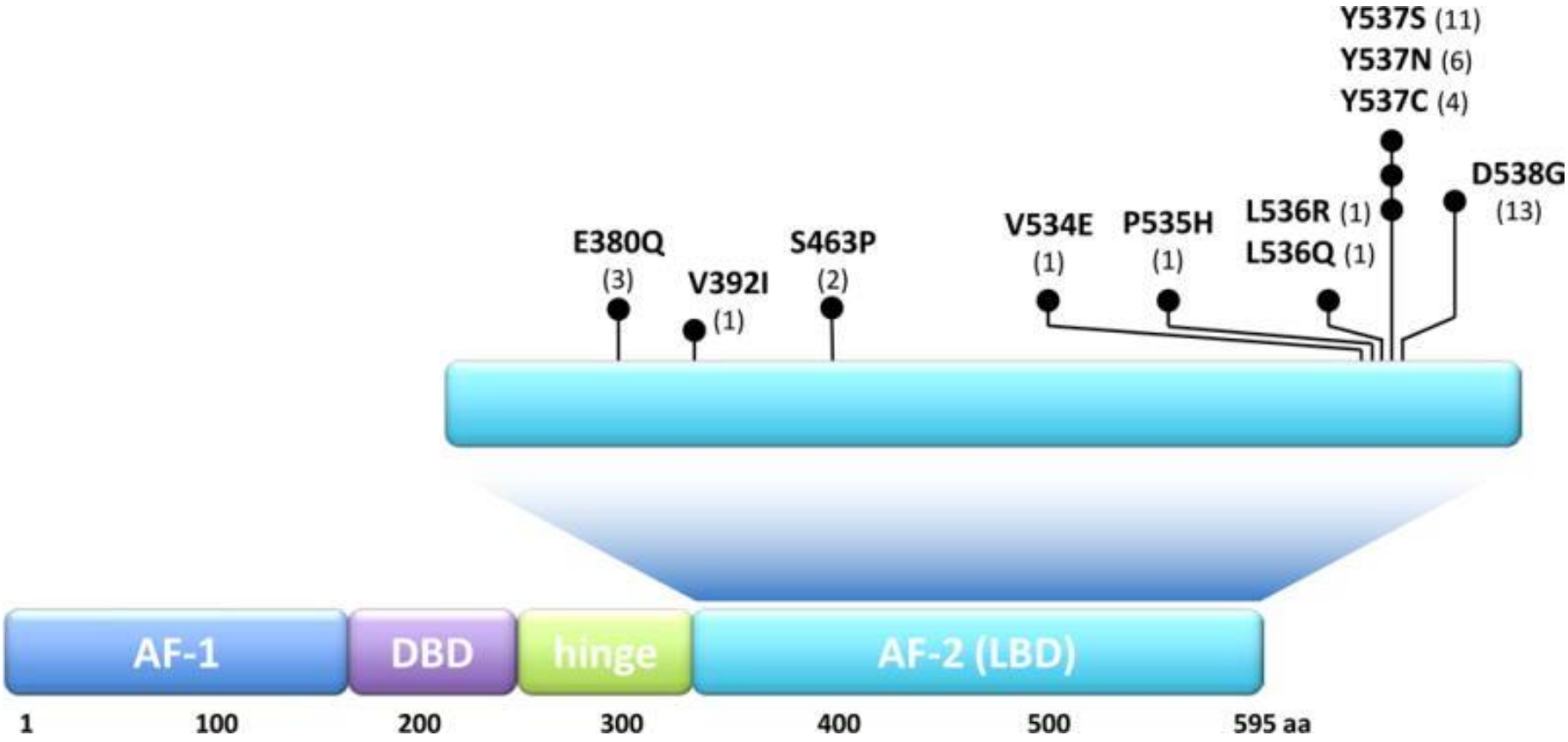
Strategies targeting genomic alterations in *ESR1*



ER, oestrogen receptor; ESR1, oestrogen receptor 1 gene

The point mutations of ER reported in endocrine pretreated metastatic luminal breast cancers



AF-1, activation function-1; AF-2, activation function-2; DBD, DNA-binding domain; ER, oestrogen receptor; LBD, ligand-binding domain

Jeselsohn R, et al. *Nat Rev Clin Oncol* 2015;12:573-83

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Selected novel therapeutic strategies targeting genomic alterations in *ESR1*

Agent	Description	Results	Ongoing Studies
GDC-0810	Oral SERD	Activity in heavily pretreated ABC in phase I[1]	Phase I/II with palbociclib ongoing[2] Phase II vs fulvestrant ongoing with co-primary end point looking at response in *ESR1* mutants[3]
GDC-0927	Oral SERD	Phase I heavily pretreated. 42 patients with a CBR of 36%. Highly tolerable	
Elacestrant (RAD-1901)	Oral SERD	Phase I 22 heavily pretreated patients ORR 27.3%n mDoR 17.4 weeks. Highly tolerable	Phase I combining PET imaging to evaluate effect on oestrogen receptor expression/oestrogen binding[4]
AZD-9496	Oral SERD	Phase I with 45 patients with 4 having prolonged stable disease (12 months). Diarrhea, fatigue and nausea in more than 20% of patients	Ongoing Phase I studies
Endoxifen	Tamoxifen metabolite	Phase I[8] with 41 patients had a CBR of 26,3% including in patients with detectable ESR1 mutations and amplifications.	
Bazedoxifene	third generation SERM	Bazedoxifene: Inhibits proliferation of oestrogen-independent breast cancer cells in vitro and down-regulates ERα and cyclin D1[9]	Phase I/II in combination with palbociclib in MBC ongoing (NCT02448771)[10]

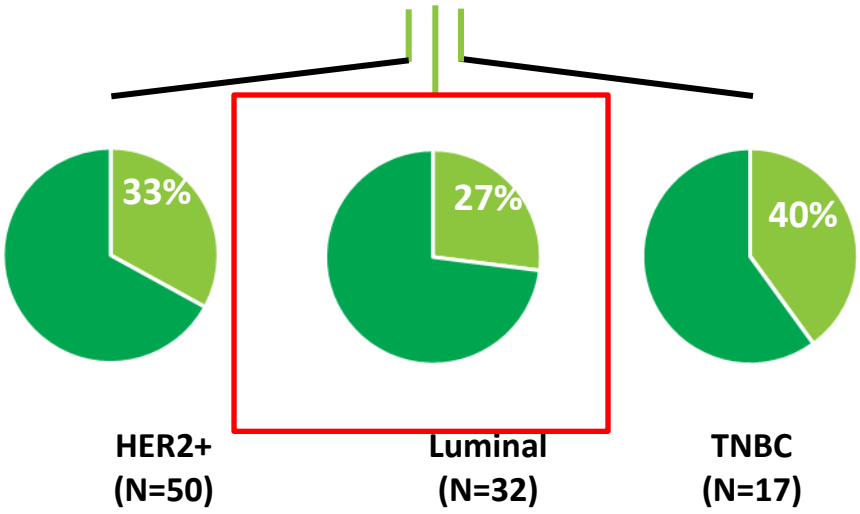
Investigational agents in this indication

ABC, advanced breast cancer; ESR1, oestrogen receptor 1 gene; ET, endocrine therapy; PET, positron emission tomography; SERDs, selective oestrogen receptor degraders

1. Dickler M, et al. AACR 2015 (Abstract CT231); 2. Clinicaltrials.gov: NCT01823835; 3. Clinicaltrials.gov: NCT02569801; 4. Clinicaltrials.gov: NCT02650817; 5. Weir HM, et al. *Cancer Res* 2016;76:3307-18; 6. Clinicaltrials.gov: NCT02248090; 7. Clinicaltrials.gov: NCT03236974 ; 8. Goetz MP et al JCO 2017; 9. Lewis-Wambi J. et al. *Mol Pharmacology* 2011;80:610-20; 10. Clinicaltrials.gov: NCT02448771

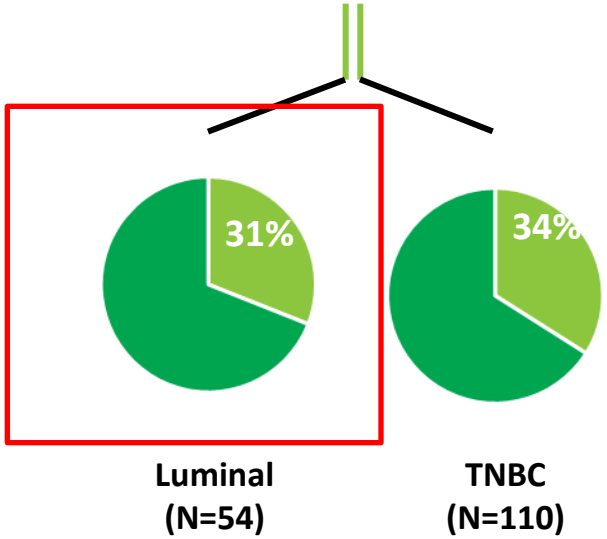
Antibody drug conjugates for ER+/HER2- Disease: Early Results (biomarker = target)

SYD 985
= trastuzumab-duocarmazine
with a protease cleavable linker



Ocular toxicity

Sacituzumab Govitecan
= an anti-Trop 2 SN38 ADC

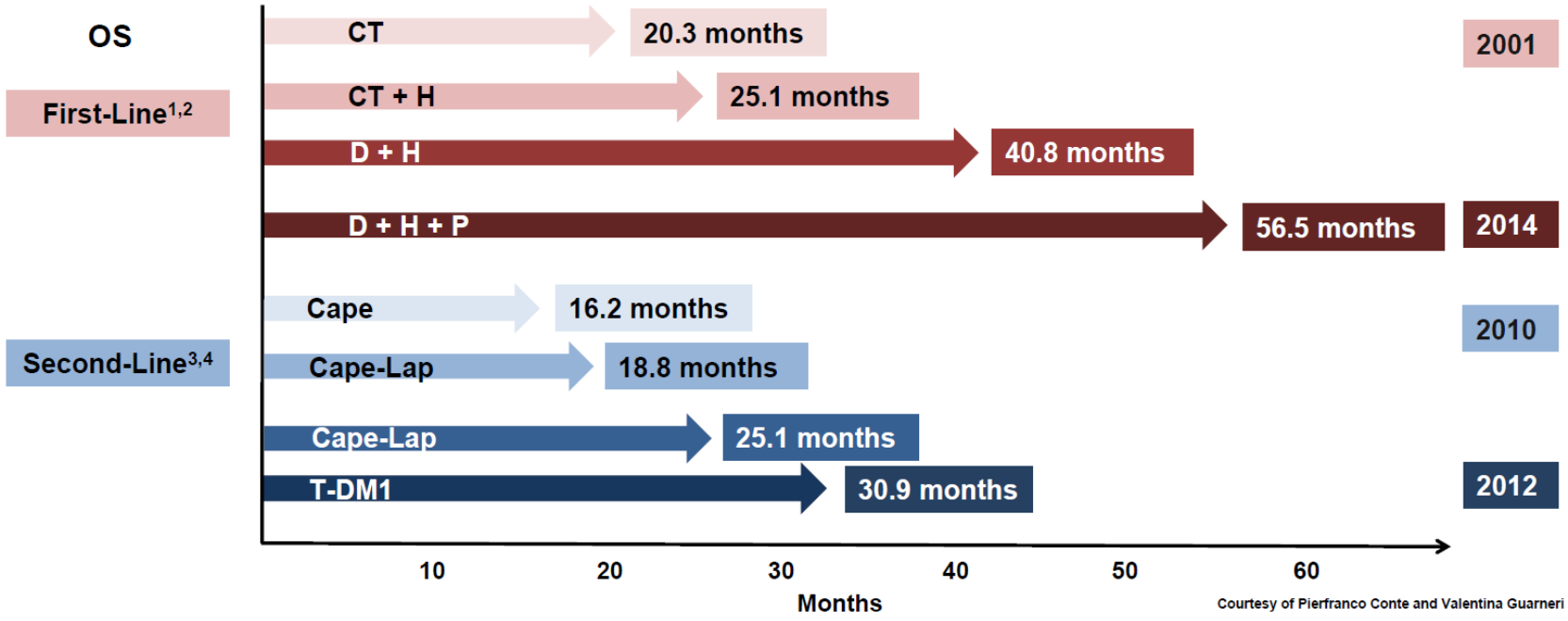


Neutropenia
Alopecia

Abst 1014 and 1004

Investigational agents in this indication

Treatment of HER2-positive MBC
Progress Over Time



Cape, capecitabine; CT, chemotherapy; D, docetaxel; H, trastuzumab; Lap, lapatinib; OS, overall survival; P, pertuzumab; T-DM1, trastuzumab emtansine

1. Slamon D, et al. *N Engl J Med.* 2001;15(1);344:783-792. 2. Swain S, et al. *N Engl J Med.* 2015;372(8):724-734. 3. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 4. Verma S, et al. *N Engl J* Med. 2012;367(19):1783-1791.

Investigational agents

Activity of new HER2 directed tyrosine kinase inhibitors

Agent	Target	Phase of development	Systemic activity of combination therapy	Activity in the CNS of combination therapy
Lapatinib	HER1/HER2	Approved	RR:22%[1],PFS:8.4 mo[1] (capecitabine)	RR:66%[2](capecitabine)
Neratinib	HER1/HER2/HER4	Phase 3 (NALA)	RR:57%-64%*[25], PFS: 40-36w**[25] (capecitabine)	RR:49%[3](capecitabine)
Tucatinib	HER2	Phase 3 (HER2 Climb)	RR:61%[56], PFS:7.8 mo[56] (capecitabine+trastuzumab)	RR:42% [56](capecitabine +trastuzumab)
Pyrotinib	HER1/HER2	Phase 3	RR: 78.5%[58], PFS: 18 mo[58] (Capecitabine)	NA
Poziotinib	HER1/HER2/HER4	Phase 2	RR: 25.5 mo[59], PFS: 4 mo[59] (monotherapy)	NA

[1]Geyer et al NEJM, 2006, [2]Bachelot et al, Lancet Oncol 2013, [25]Saura et al, ASCO, 2014, [3]Freedman et al, ASCO 2017, [56] Murthy et al, Lancet Oncol 2018, [58]Xu B et al, SABCS 2017, [59]Park et al, IJC, 2018
*, ** : according to prior lapatinib exposure or not

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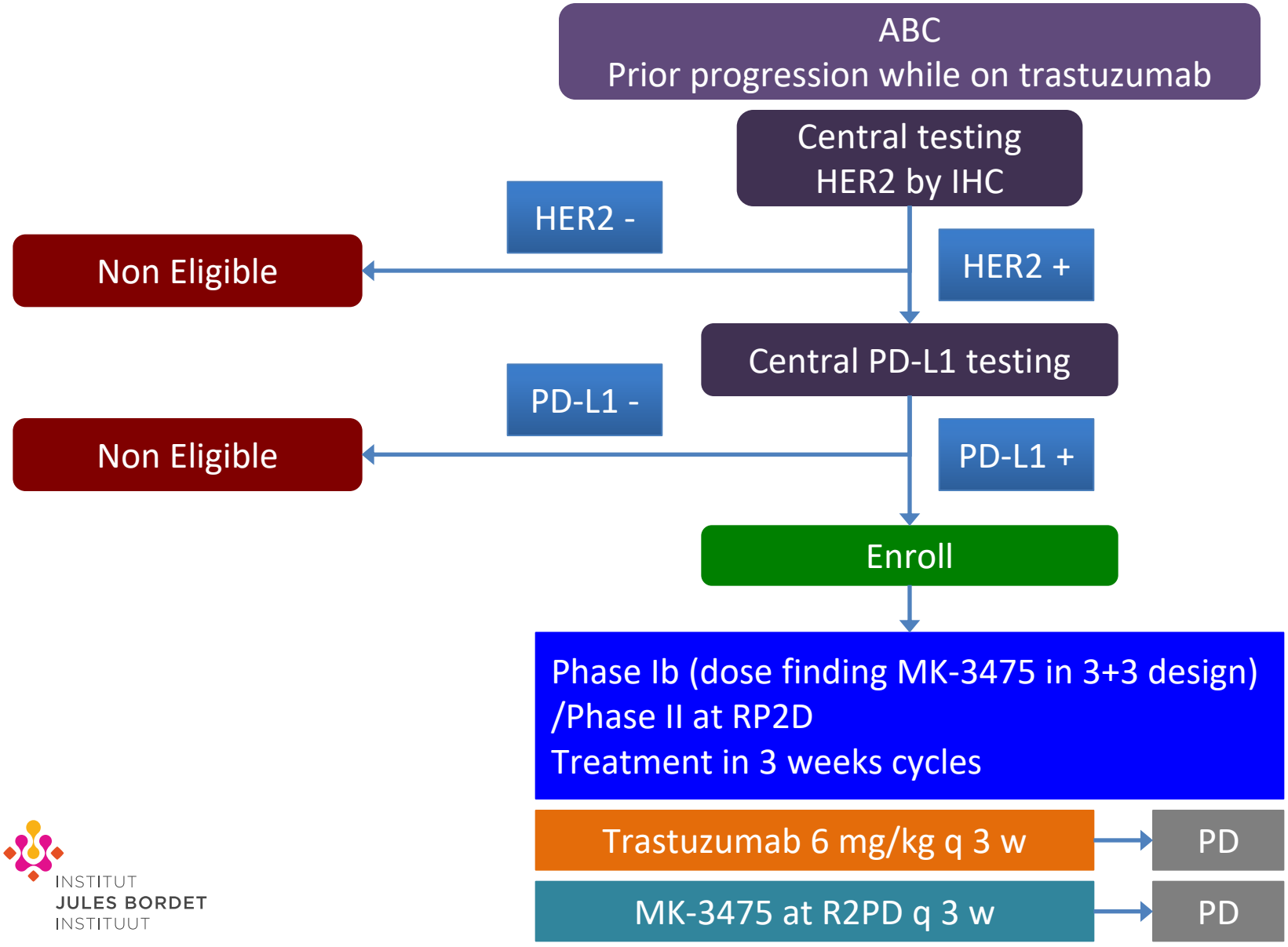
New Antibody drug conjugates (ADCs) targeting HER2 (including HER2 low expressors!)

Agent	Target	Phase of development	Initial Phase I Results	Main Side Effects
DS8201a[1]	Humanized HER2 antibody + topoisomerase-I inhibitor exatecan	Ongoing phase II (DESTINY-Breast01) and III (NCT03529110)	RR: 64.2% PFS:10.4 mo. (heavily pre-treated patients)	Gastrointestinal, haematological and ILD
SYD985[2]	Trastuzumab + duocarmazine	Ongoing phase III (TULIP)	RR: 33%[2] PFS: 9.4 mo.	Ophthalmologic effects (conjunctivitis and keratitis)
RC48- ADC[3]	HER2 antibody + MMAE	Ongoing phase II (NCT03500380)	RR: 36.7%	Transaminases elevations Neutropenia

[1] Iwata H et al. J Clin Oncol. 2018, [2] Saura C et al. J Clin Oncol. 2018, [3] Xu B et al. J Clin Oncol. 2018

PANACEA TRIAL DESIGN: IMMUNE + HER-2 THERAPY



Metastatic breast cancer: Immune (Pembrolizumab) + HER-2 therapy (trastuzumab)

- **Results**
  - PD-L1+ cohort (n=46):
    - ORR: 15.2% (CI 7–27%)
    - No progression at 6 mo: 24% (CI 14–36%)
    - Median PFS: 2.7 mo
    - Median duration of disease control: 11.1 mo
  - PD-L1– cohort (n=12)
    - ORR: 0%
- **Stromal TILs (sTILs) from metastatic biopsy**
  - sTILs ≥5% present in 41% of PD-L1+ cohort
  - ORR 39% (sTILs+) versus 5% (sTILs–)
- **Toxicity:** 2/58 with grade III/IV pneumonitis

Loi S, et al. Presented at SABCS 2017; Abstract GS2-06

Tumors harboring HER2 mutations: SUMMIT Efficacy Data

Efficacy	Neratinib Monotherapy (n = 24)	Neratinib + Fulvestrant (n = 12)
ORR at 8 weeks, n	8	5
CR	2	2
PR	6	3
ORR (95% CI)	33.3 (15.6, 35.3)	41.7 (15.2, 72.3)
Clinical benefit, n	10.0	7.0
Clinical benefit rate (95% CI)	41.7 (21.1, 63.4)	58.3 (27.7, 84.8)
Median PFS, months (95% CI)	3.5 (1.9, 4.3)	3.7 (2.1, 6.7)

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Hyman DM, et al. AACR. Abstract PD2-08.

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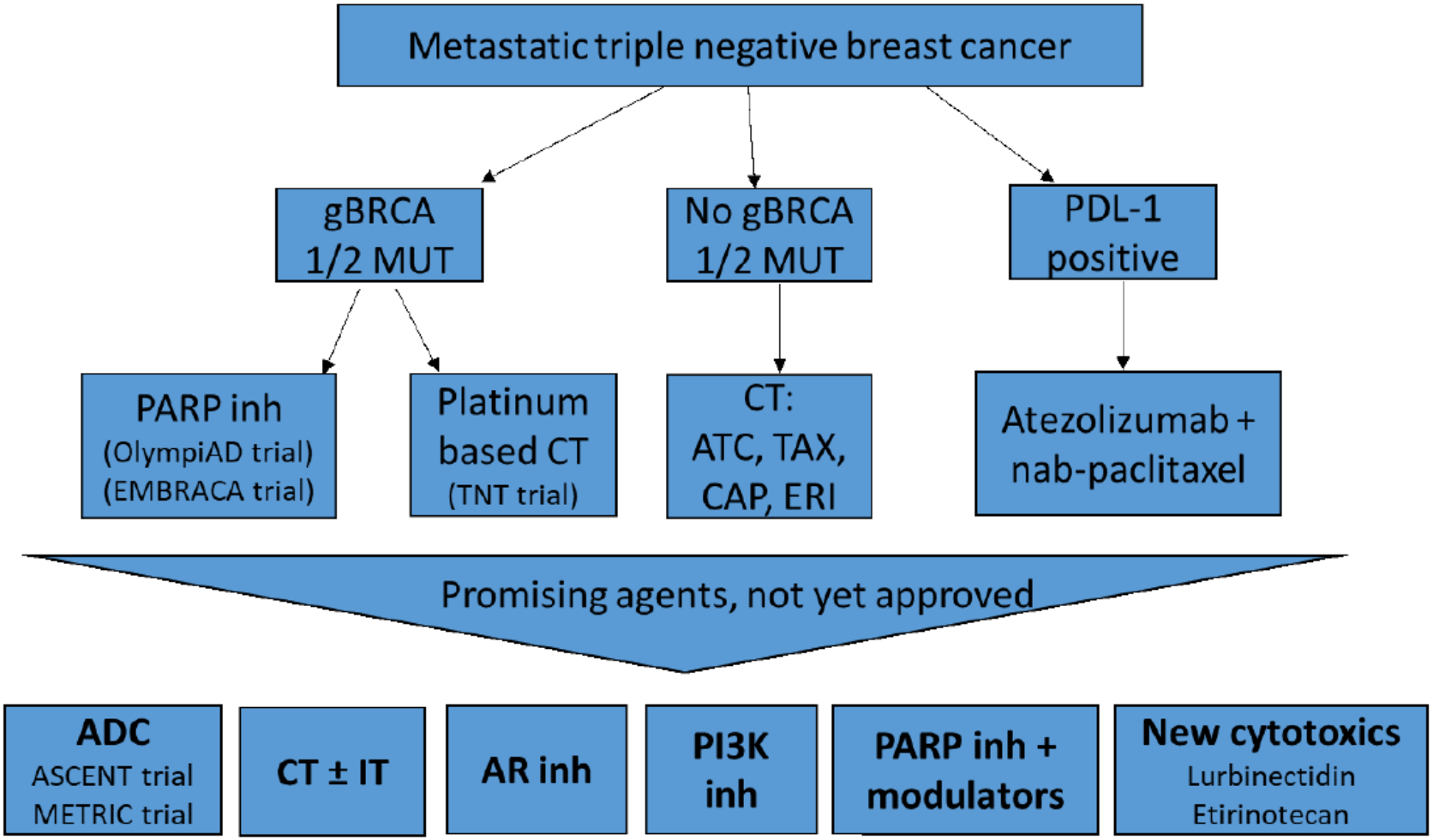
Current standard-of-care treatments in metastatic triple-negative breast cancer and future perspective



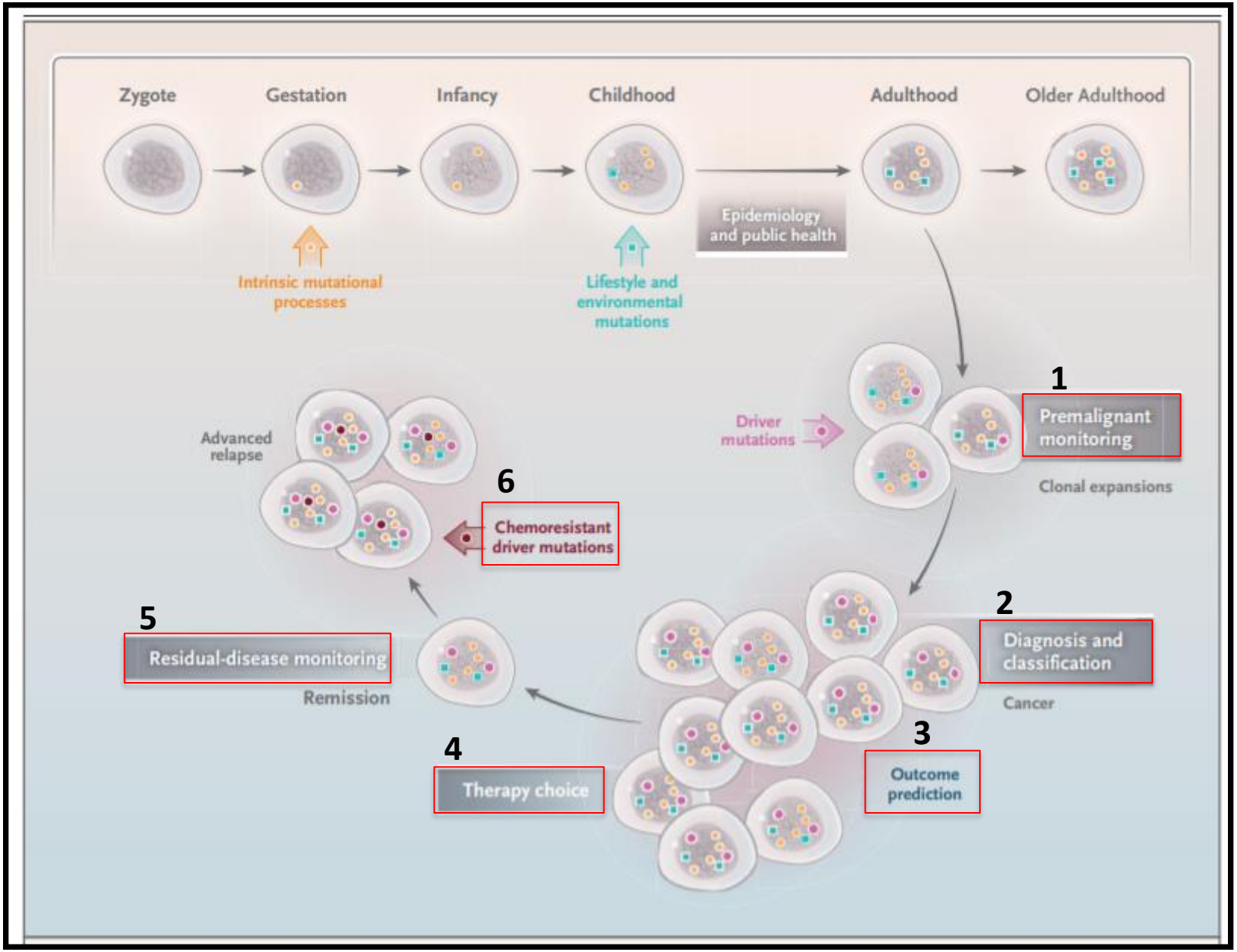
El Hachem, Gombos, Awada, 2019

Insights from Studying the cancer genome

Somatic	Germline
Genetic driver mutation	Drug metabolism (e.g., DPD)
Mutational signature	Familial cancer risk (e.g., BRCA)
Chromosomal aberration	
Cancer neoantigens	
Tumor heterogeneity	

Nangalia J et al., NEJM 2019, 381(22)

Genome Sequencing opportunities for cancer management



Nangalia J et al., NEJM 2019, 381(22)

Frequency (%) of selected somatic mutations and copy number changes in TCGA (2014)

Gene	Breast
Selected somatic mutations	
AKT	2.4
BRAF	0.6
BRCA1	3
BRCA2	4.3
EGFR	0.8
FGFR1	0
FGFR2	0.8
FGFR3	0.2
HRAS	0
IDH1	0.2
IDH2	0
KIT	1
KRAS	0.8
NF1	2.8
NF2	0.4
NRAS	0
PIK3CA	35.1
PIK3R1	2.6
PTCH1	1.2
PTEN	3.6
SMO	0.4
TSC1	0.6
TSC2	0.4

Gene	Breast
Copy number changes	
ERBB2	12.9
FGFR1	10.7
FGFR2	1.7
FGFR3	0.3
MET	NA
PIK3CA	3.7

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Meric-Bernstam et al., JNCI J Natl Cancer Inst 2015

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Limits to personalize cancer medicine (1)

1. Technical issues such as inadequate tumor specimens
2. Intratumor heterogeneity (← single agent with wide range of targets vs combination!?); Role of ctDNA?!
3. Limited access to targeted agents both within and outside clinical trials

Tannock et al., NEJM 2016

Limits to personalize cancer medicine (2)

4. Most molecular targeted agents provide only partial inhibition of signaling pathways
5. Cancer cells have an almost universal capacity to develop resistance
6. Substantial cost (molecular analysis ↓ but cost of therapy ↑)

Tannock et al., NEJM 2016

In summary:
Biomarkers and Personalized therapy of Luminal disease

- ER expression
- PgR expression

} [endocrine therapy + CDK4/6 inhibitors]

- PIK3CA mutations (←Alpelisib)
- BRCA 1/2 mutations (← Olaparib, Talazoparib)

- -

- Androgen receptor??

In summary: Biomarkers and Personalized therapy of TNBC

- PDL1 expression on IC (← Atezolizumab)
- BRCA 1/2 mutations (← Olaparib, Talazoparib)

- HRD/Other DNA damage response abnormalities (e.g., ATR, ...)? (← PARP inhib. ± other agents?)
- TILs?
- AKT mutations? (← Ipatasertib or Capivasertib?)
- Androgen receptor?

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In summary:
Biomarkers and Personalized therapy of HER2 disease

- HER2 amplification (high vs low expression!)
- HER2 mutation (← Neratinib)

- TILs?
- PIK3CA? (← MEN1611?)
- PDL1?

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In summary:
Biomarkers and Personalized therapy for BC
agnostic subtypes

- PDL1
- NTRK (secretory tumors,...) (← Larotrectinib, ..)
- MSI (← checkpoints inhibitors)
- BRCA 1/2 mutations (← PARP inhibitors)

Thank you !

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