Future of targeted therapies in Breast Cancer

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02/2013

Molecular Breast Cancer : Active research (1)

- Understanding the heterogeneity of TNBC and looking for targets and new drugs
- Significant advances in HER2-targeted therapy (New agents, dual inhibition)
- Understanding the cross-talk between endocrine and growth factor receptors pathways and overcoming endocrine therapy resistance

Molecular Breast Cancer : Active research (2)

- Tumor microenvironment
  - Improve understanding of stromal – epithelial interaction
  - The role of leukocytes/macrophages seems important
  - Immunotherapy shows promise in early experiments
- Molecular imaging
  - Improved diagnosis, mapping tumor heterogeneity and (early) prediction of response/resistance to treatment

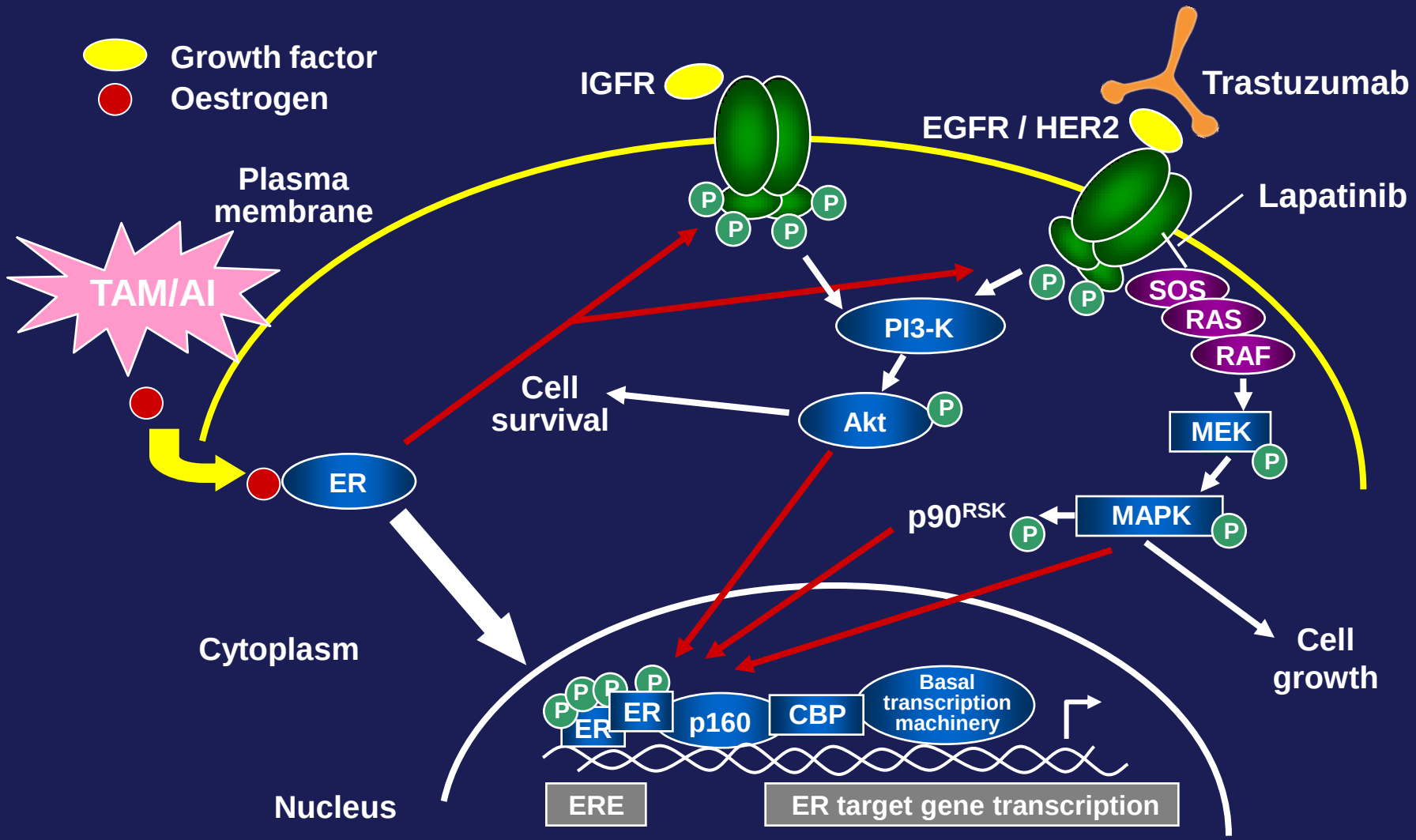
Luminal diseases

LUMINAL METASTATIC BREAST CANCER : AVAILABLE ENDOCRINE THERAPY

- **Tamoxifen**
- **Aromatase inhibitors**
  - **non steroidals (Anastrozole, Letrozole)**
  - **steroidal (Exemestane)**
- **Fulvestrant (500 mg > 250 mg)**
- **Progestatifs (Oestrogenes)**

- **Androgen synthesis inhibitor (Aberaterone): Phase II studies are ongoing**

Cross-talk between signal transduction and endocrine pathways (feedback loops!)



Adapted from Johnston 2005

Endocrine therapy + signal transduction inhibitors: Therapeutic breakthrough in HER2 disease (trastuzumab, lapatinib) and Everolimus-based endocrine therapy

HER2 inhibitor TRIALS

Arimidex ± trastuzumab	→ Positive results
Letrozole ± Lapatinib	→ Positive results

Everolimus (m-Tor inhibitor) TRIALS

Letrozole ± Everolimus (mTor inhibitor)	→ positive results*
Tamoxifen ± Everolimus (mTor inhibitor)	→ Positive trial
Exemestane ± Everolimus (mTor inhibitor)	→ Highly positive trial

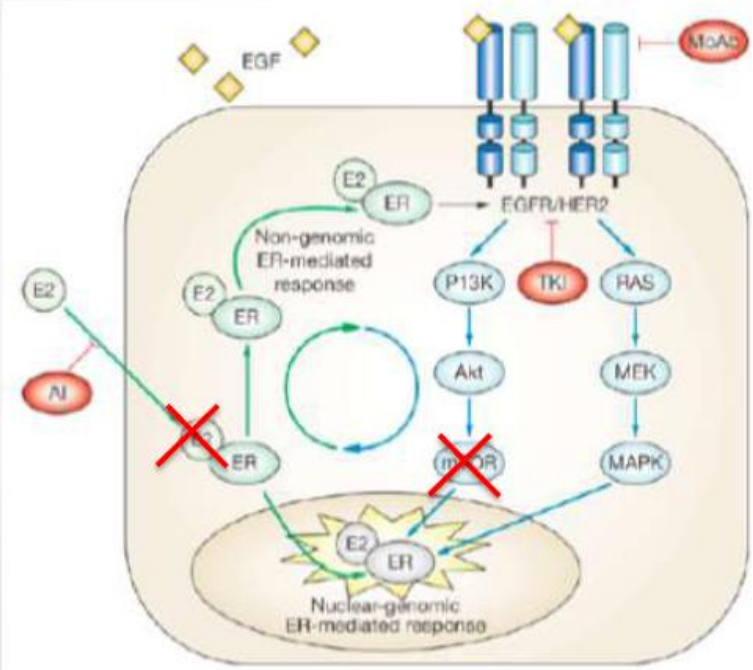
CDK inhibitor trial

Letrozole ± PD0332991 (CDK 4/6 inhibitor)	→ Positive trial

*Neoadjuvant trial

Endocrine therapy + Everolimus : Positive results

Dual inhibition of E2 and mTOR



From: Prat and Baselga *Nature Clinical Practice Oncology* (2008) **5**, 531-542

BOLERO-2: AI +/- mTOR inhibitor

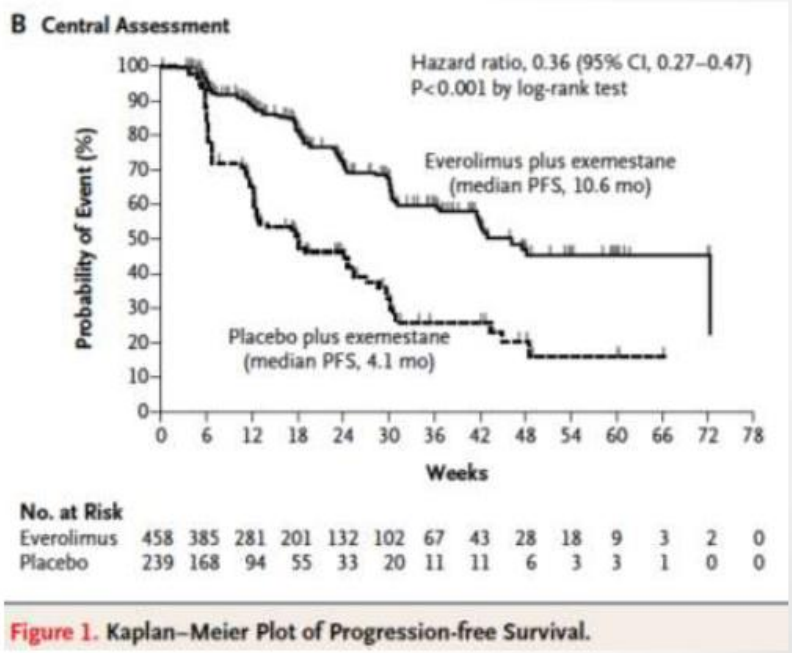
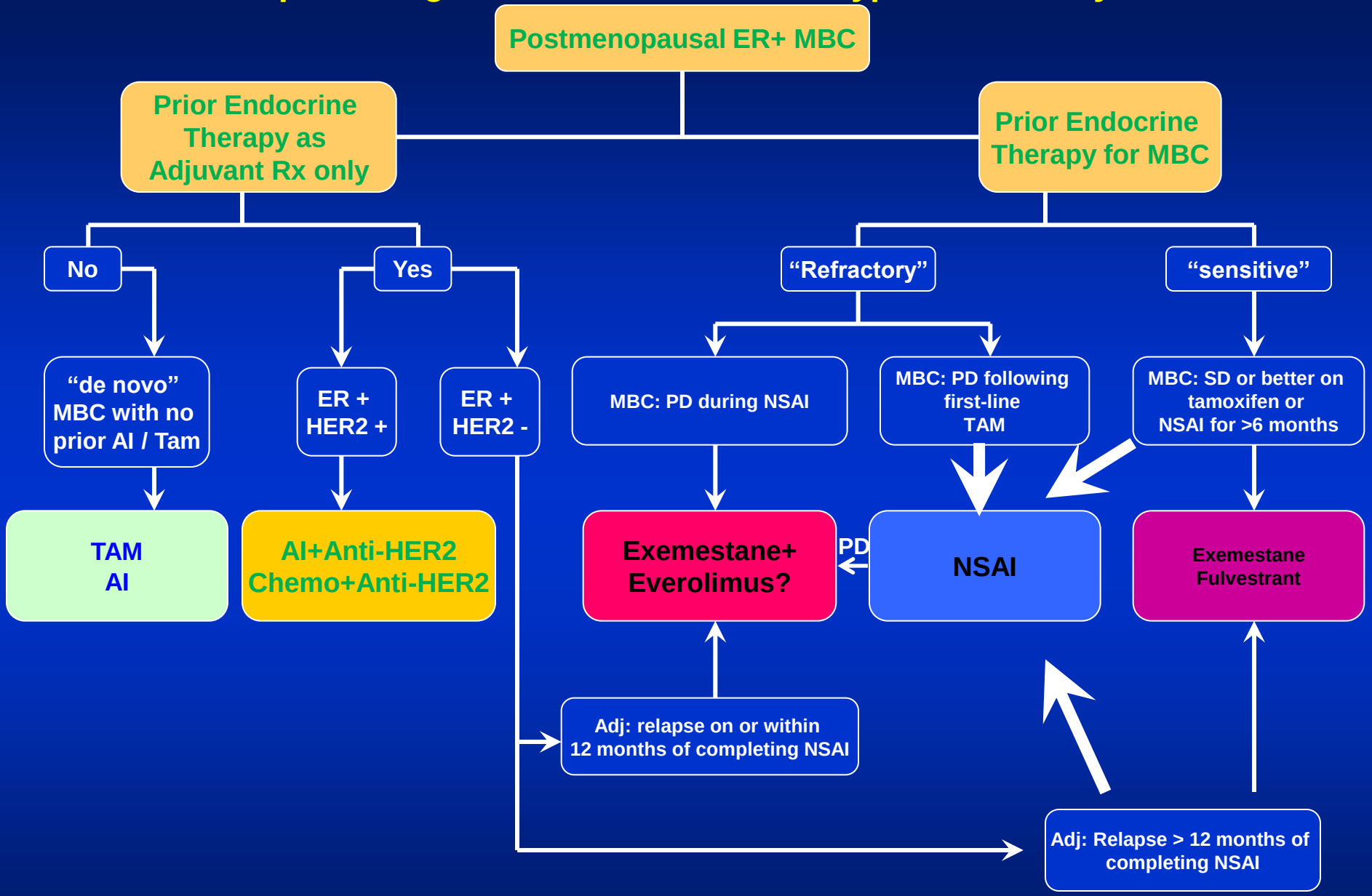


Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Baselga et al. NEJM 2011

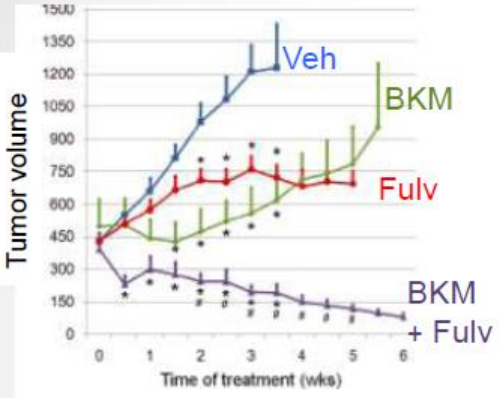
Therapeutic Algorithm For Luminal Subtype of MBC: My View



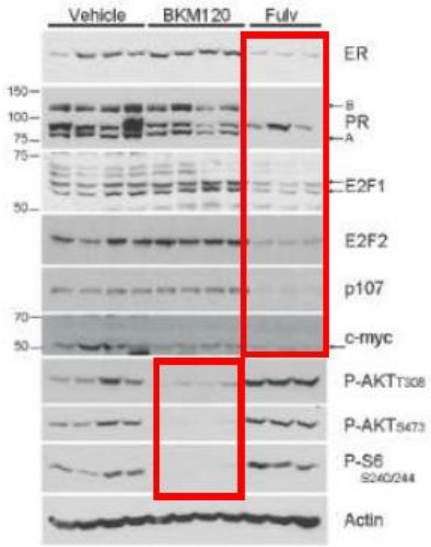
NSAI: Letrozole or Anastrozole acording to the previous NSAI

BKM120 (Pan-PI3K inhibitor) and Fulvestrant synergistically inhibit tumor growth

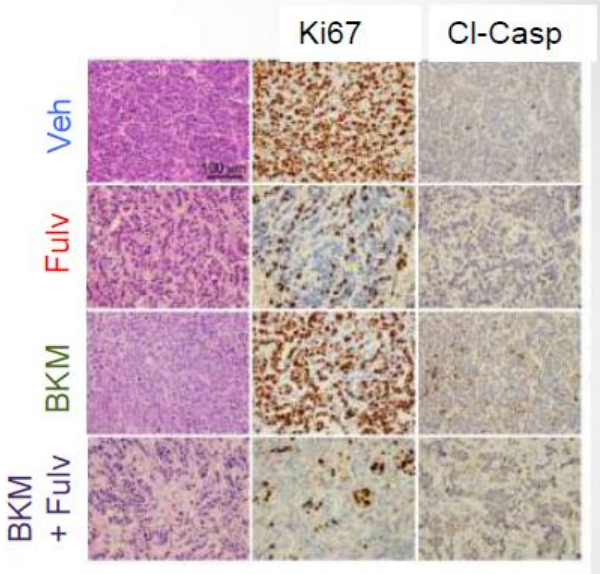
BKM120 and Fulv synergistically inhibit tumor growth

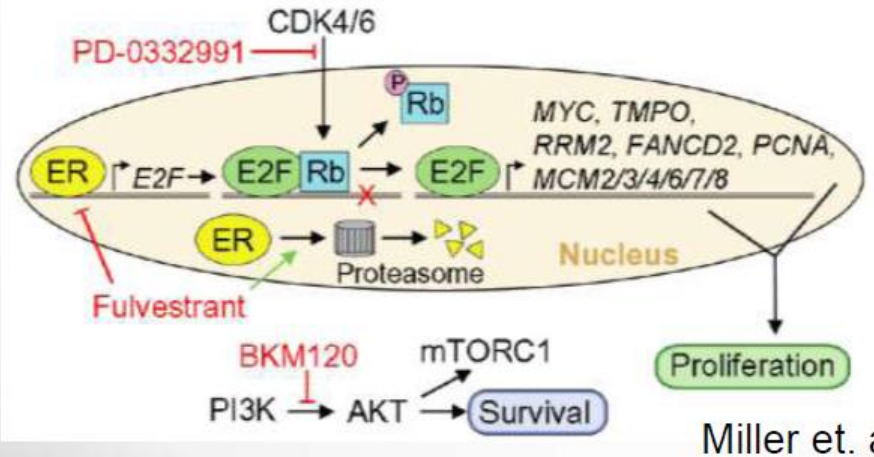


Signal independently



Fulv inhibits proliferation
BKM120 induces apoptosis



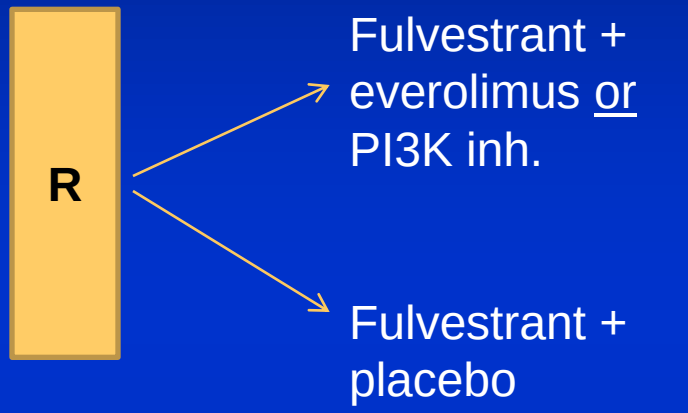


- Rationale for Fulv + PI3K inhibitors for overcoming AI resistance
- Potential for CDK4/6 inhibitors for combating AI resistance

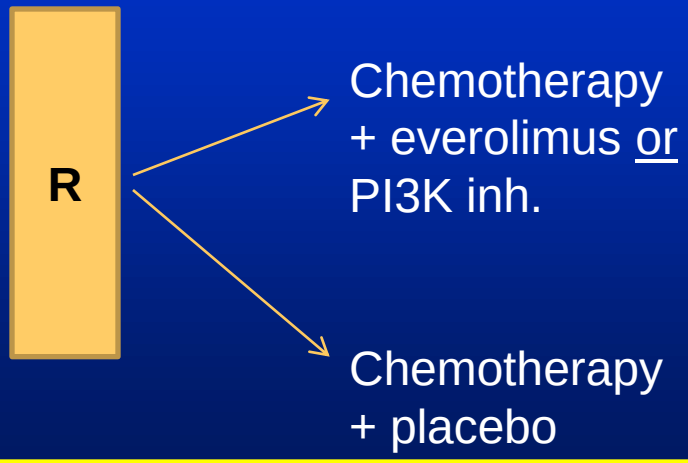
Miller et. al. Cancer Discov 2011 1(4): 338

Exemestane + Everolimus Progressing Patients : Is There Any Rationale to Keep « the Pressure » on the PI3K/mTOR Pathways ?!

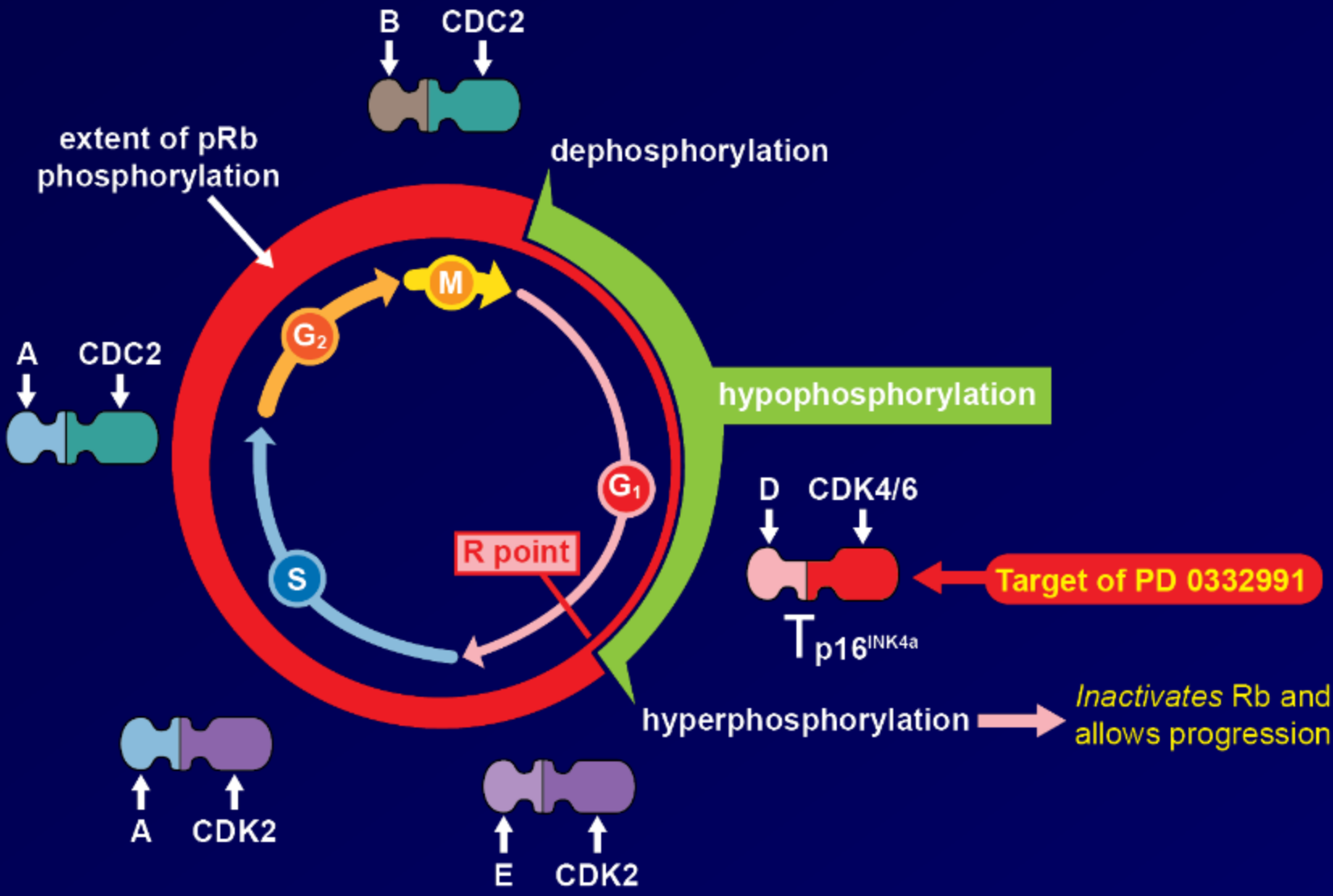
- **Pts progression on Exemestane + Everolimus**
- **Pts candidates for endocrine agents**



- **Pts progression on Exemestane + everolimus**
- **Pts candidates for chemotherapy**



Rb as Master-Regulator of the R-point



Abstract S1-6

Results of a Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (TRIO-18)

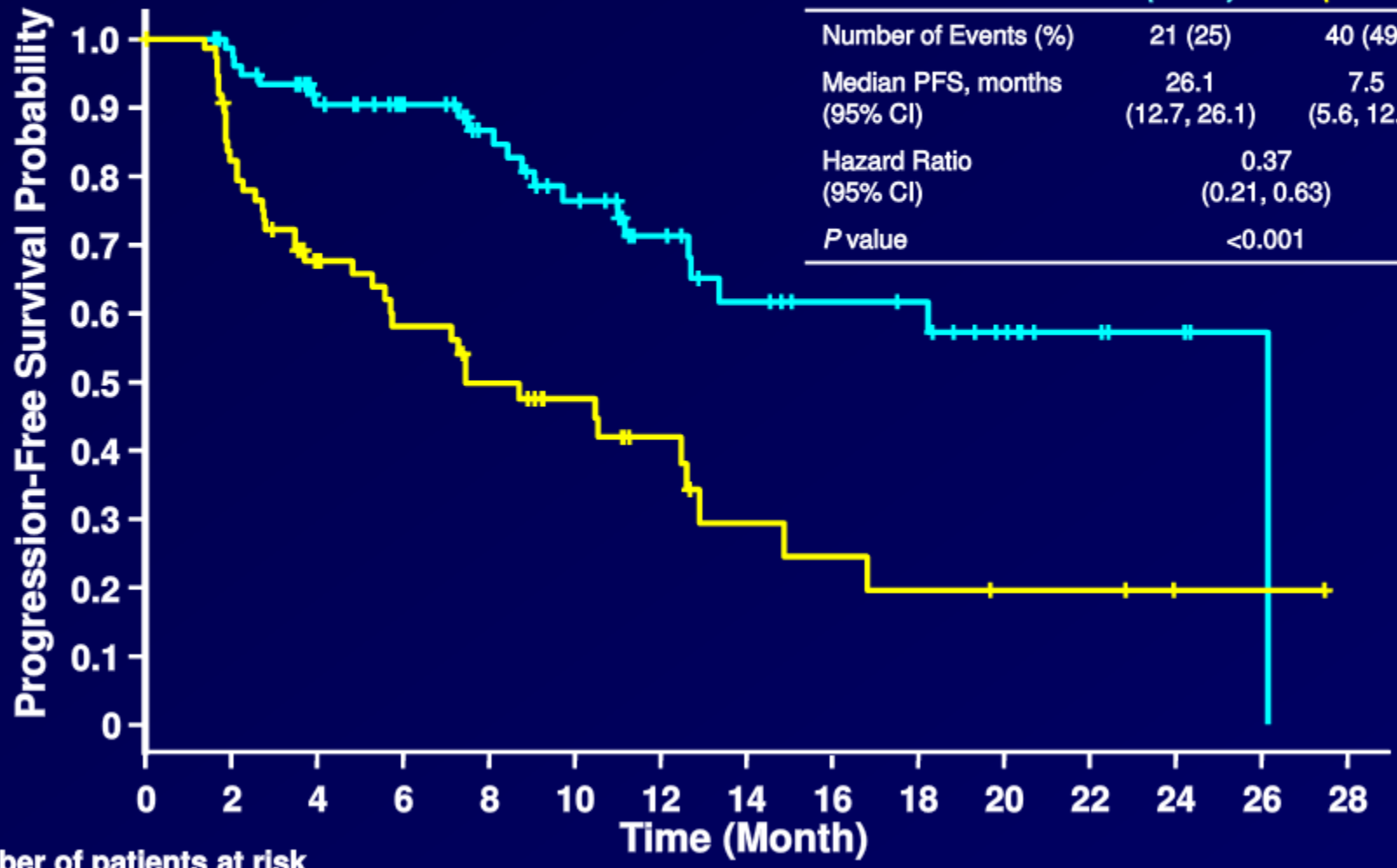
RS Finn,[1] JP Crown,[2] I Lang,[3] K Boer,[4] IM Bondarenko,[5] SO Kulyk,[6] J Ettl,[7] R Patel,[8] T Pinter,[9] M Schmidt,[10] Y Shparyk,[11] AR Thummala,[12] NL Voitko,[13] A Breazna,[14] ST Kim,[15] S Randolph,[15] DJ Slamon[1]

[1]University of California Los Angeles, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]Orszagos Onkologiai Intezet, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]University Hospital Mainz, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Henderson, NV, USA; [13]Kyiv City Clinical Oncology Center, Ukraine; [14]Pfizer Oncology, New York, NY, USA; [15]Pfizer Oncology, La Jolla, CA, USA

Presented at SABCS 2012; December 5, 2012; San Antonio, TX, USA

Progression-Free Survival

	PD 991 + LET (n = 84)	LET (n = 81)
Number of Events (%)	21 (25)	40 (49)
Median PFS, months (95% CI)	26.1 (12.7, 26.1)	7.5 (5.6, 12.6)
Hazard Ratio (95% CI)	0.37 (0.21, 0.63)	
P value	<0.001	



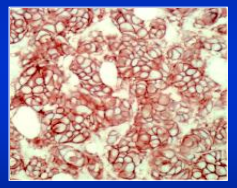
Number of patients at risk

PD991+LET	84	75	60	53	43	35	25	18	15	14	9	5	3	1
LET	81	57	38	29	22	17	11	6	5	4	3	3	1	1

HER-2 Positive Diseases

HER-2 OVEREXPRESSING METASTATIC BREAST CANCER: TOWARDS A CURE OF THIS DISEASE?

HER_2 OVEREXPRESSION



IHC

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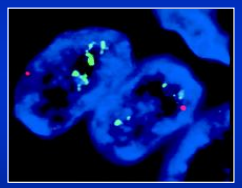
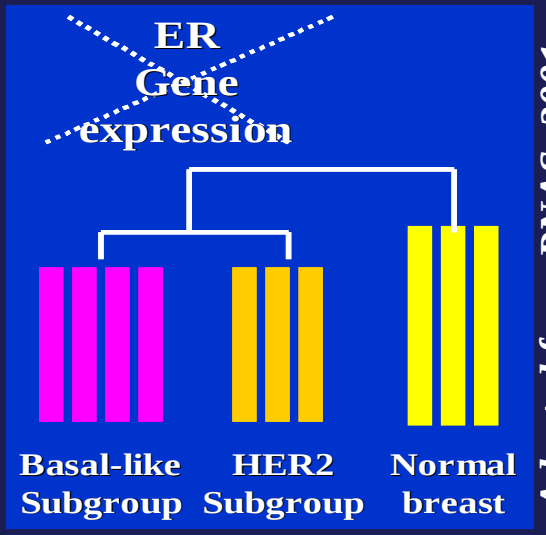
HER_2 AMPLIFICATION



FISH

A SEPARATE DISEASE ENTITY!



Adapted from PNAS, 2001

NEW TREATMENT APPROACHES

Early use of trastuzumab

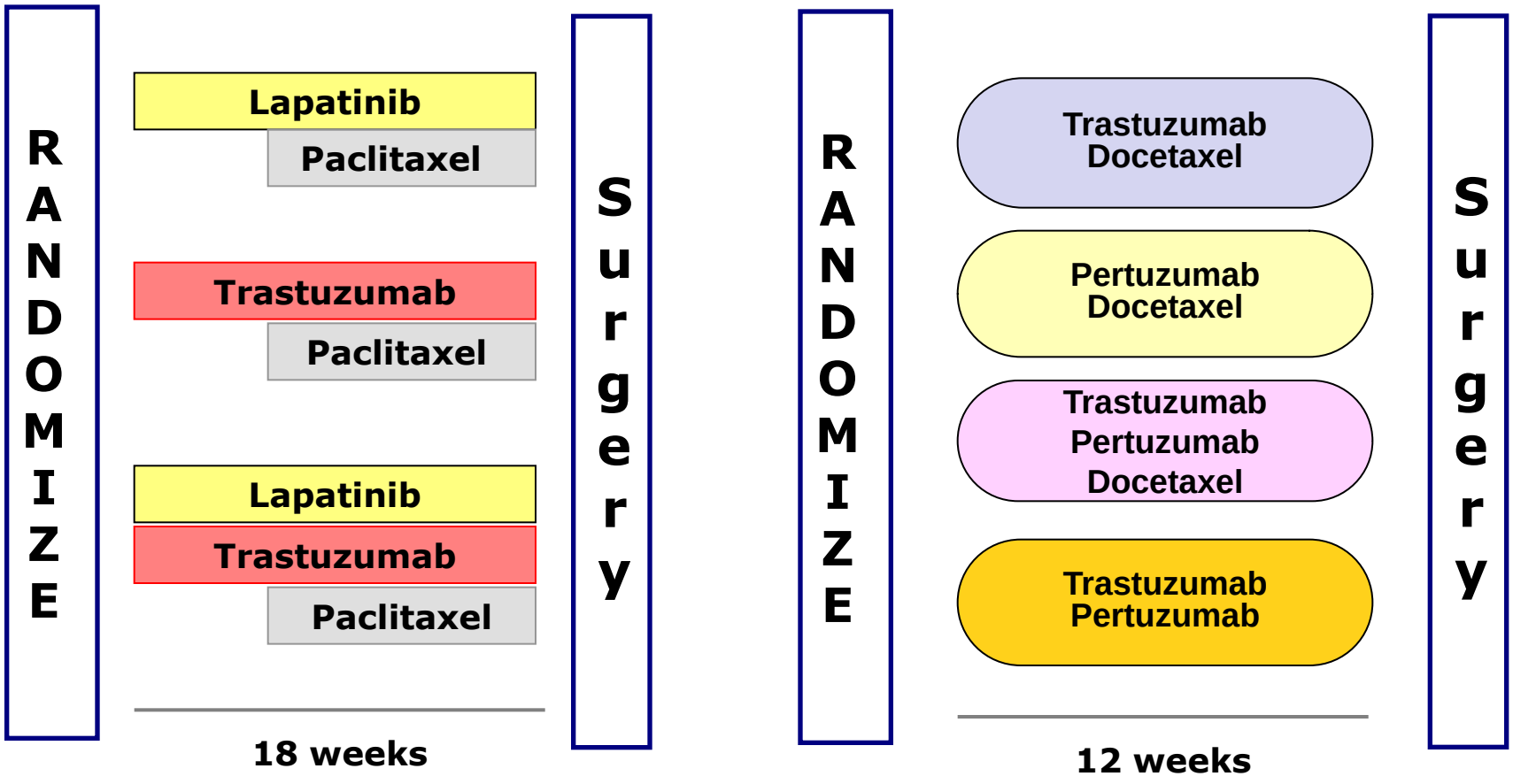
- **Alone** in selected women (ORR 14-25 %)
- **in combination with cytotoxics** (ORR > 50% !) or **hormonal agents**

Docetaxel + trastuzumab + bevacizumab

New HER-2 drugs (lapatinib, neratinib, afatinib, trastuzumab-DM1, pertuzumab, HSP90 inhibitors…)

Dual HER-2 inhibition + cytotoxics or endocrine agents

Dual Blockade with Taxanes in the Neoadjuvant Setting : NeoAltto and NeoSphere: Study Designs



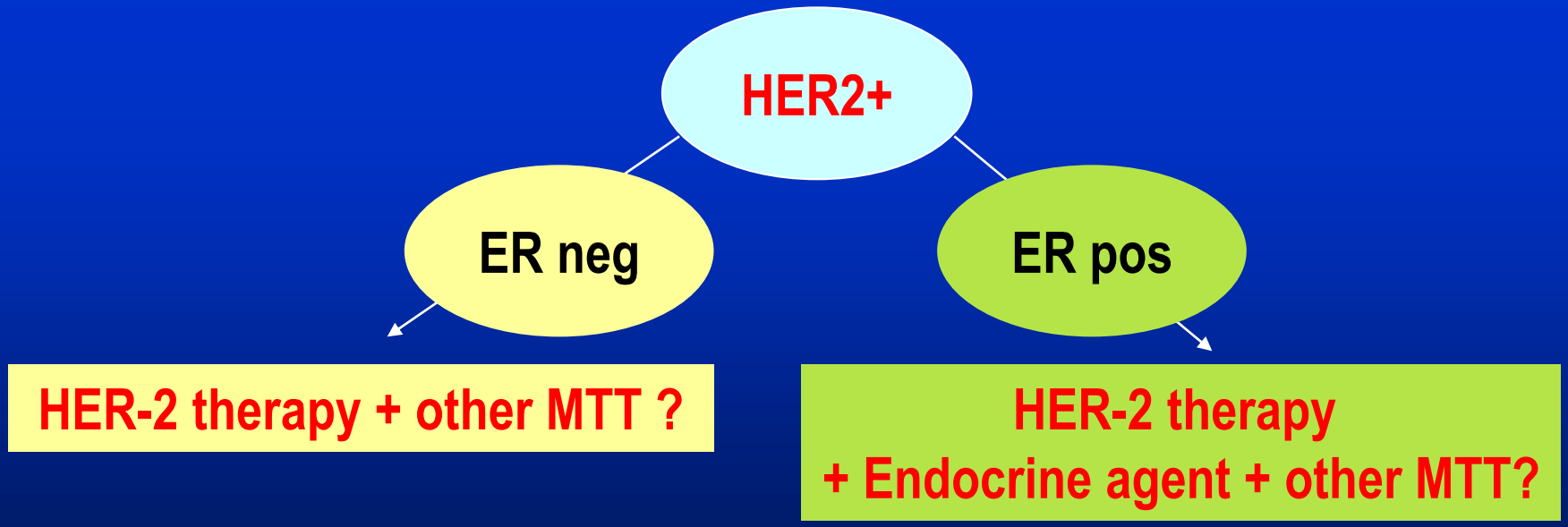
Neo-Altto **Neo-Sphere**

Pathologic CR Rates In NeoSphere

	Trast - Docetaxel	Pertuz – Docetaxel	Trast - Pertuz - Docetaxel	Trast - Pertuz
ITT (Overall)	29%	24%	46%	17%
ER-	37%	30%	63%	27%
ER+	20%	17%	26%	6%

The available data suggest significant molecular differences in HER2+ BC in relation to ER status

These differences may result in differing "pathway output dependency" and may have clinical research implications !



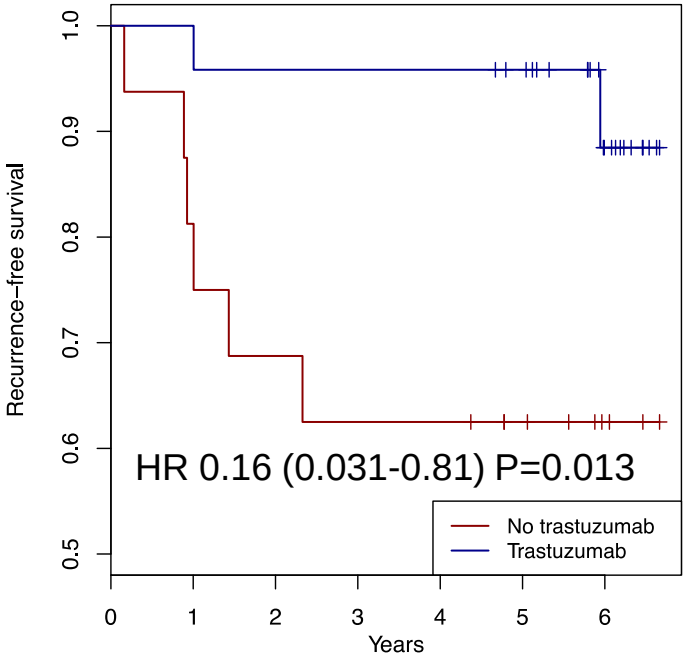
MTT: molecular-targeted therapy

Trastuzumab + Lapatinib or Pertuzumab (without chemotherapy): Main Message

Is it time to start thinking about to treat HER2 positive BC without chemotherapy !?
Role of biomarkers in the selection of patients!?

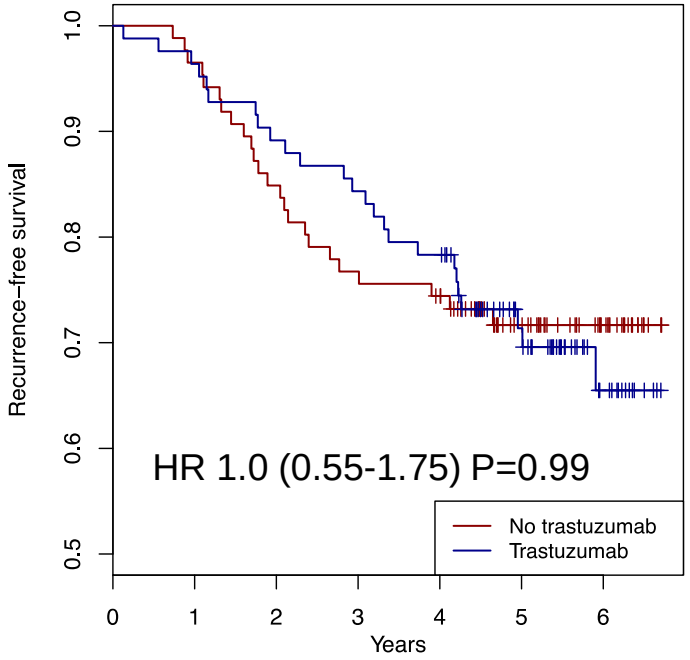
LYMPHOCYTIC INFILTRATION PREDICTS FOR TRASTUZUMAB RESPONSE IN THE FINHER TRIAL

LPBC



No. At Risk							
No trastuzumab	16	14	12	11	11	8	4
Trastuzumab	24	24	24	24	24	22	11

Non-LPBC



No. At Risk							
No trastuzumab	86	84	74	67	64	40	20
Trastuzumab	83	81	75	71	66	41	15

LPBC Significant interaction p value p=0.032

Interaction p value for Stromal-Ly as a continuous variable (10%) p=0.02

Courtesy Sherene LOI

FONDAZIONE MICHELANGELO

Roche

Adaptive immune system and immune checkpoints are associated with response to pertuzumab (P) and trastuzumab (H) in the NeoSphere study

Luca Gianni, Giampaolo Bianchini, Pinuccia Valagussa,
Anton Belousov, Marlene Thomas, Graham Ross, Lajos Pusztai

on behalf of the 'NeoSphere' study investigators

Results

Multivariate analysis with THP therapy

- A significant interaction was present between the ER status and IFNγ, PDL1 and CTLA4 (p=0.0003, p=0.025 and p=0.009 for the interaction term, respectively)

	ER neg		ER pos	
	OR (CI 95%)	p	OR (CI 95%)	p
PDL1	0.07 (0.01-0.60)	**0.016**		
IFNγ	9.63 (2.28-40.7)	**0.002**	0.11 (0.02-0.68)	**0.018**
CTLA4	0.03 (0.01-0.39)	**0.007**		
CD8A			5.97 (0.96-36.9)	*0.055*
Age (continuous)	1.05 (0.96-1.15)	0.26	0.88 (0.78-0.98)	**0.025**
LABC (vs non LABC)	1.61 (0.25-10.5)	0.616	NA	
IBC (vs non LABC)	5.58 (0.33-93.7)	0.232	NA	
cN1 (vs cN0)	0.82 (0.09-7.61)	0.861	0.36 (0.04-2.96)	0.346
PgR pos (vs neg)	0.11 (0.01-3.13)	0.199	0.09 (0.01-0.82)	**0.033**

DUAL HER-2 THERAPY IN THE (NEO)ADJUVANT SETTING : CONCLUSIONS (2013)

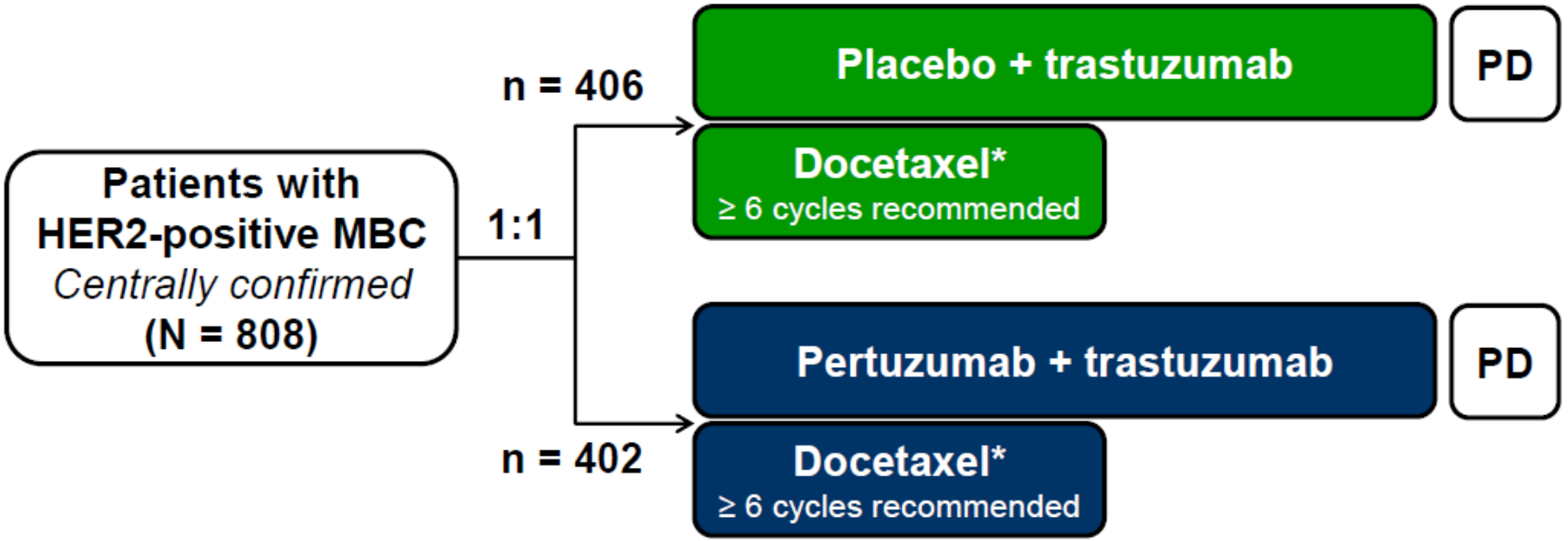
- Dual HER2 inhibitors + taxane :
  - Of interest in locally “bulky” disease !
  - Wide use await ALTTO and APHINITY trials data

- Dual HER-2 therapy alone
  - Intensify translational research to help in the selection of patients candidates for dual HER-2 therapy without chemotherapy

HER2 Positive Metastatic Disease

- Dual HER2 inhibitor
- T-DM1

CLEOPATRA: Study design[1,2]

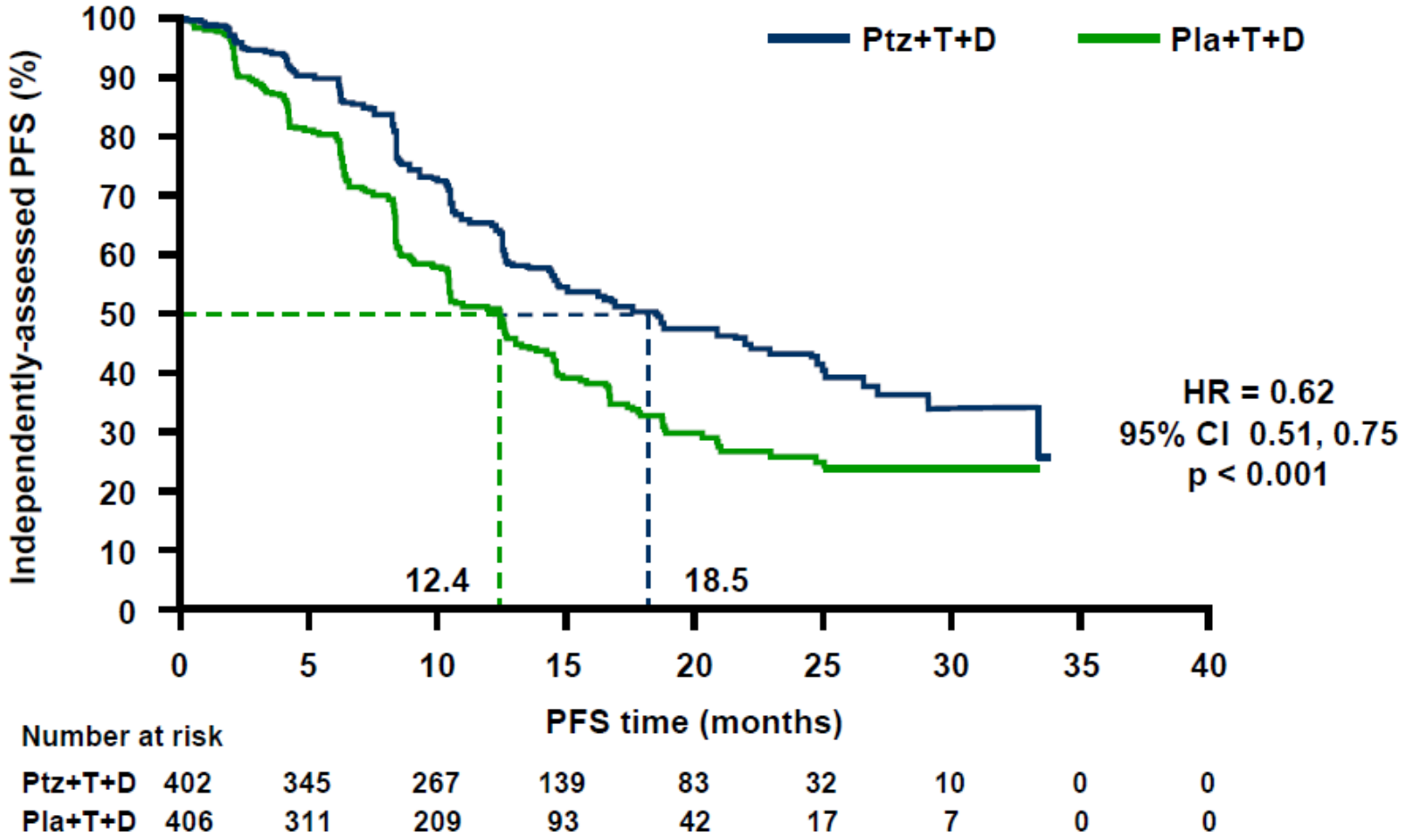


- Primary endpoint: Independently-assessed progression-free survival (PFS)
- Collection of tumor tissue (archival in >90%) and serum samples was mandatory
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion
HER2, human epidermal growth factor receptor 2; PD, progressive disease

1. Baselga J, *et al.* SABCS 2011 (Abstract S5-5);
2. Baselga J, *et al. N Engl J Med* 2012; **366:** 109–119.

CLEOPATRA: Significant improvement in median PFS[1,2] (and OS)[3] with pertuzumab



D, docetaxel; Ptz, pertuzumab; T, trastuzumab

1. Baselga J, *et al*. SABCS 2011 (Abstract S5-5);
2. Baselga J, *et al*. *N Engl J Med* 2012; **366:** 109–119;
3. Swain S, *et al*. SABCS 2012 (Poster P5-18-26).

Biomarker analyses in CLEOPATRA: A Phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC)

J Baselga,[1] J Cortés,[2] S-A Im,[3] E Clark,[4] A Kiermaier,[5] G Ross,[4] and S M Swain[6]

[1] *Memorial Sloan-Kettering Cancer Center, New York, NY;*
[2] *Department of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain;*
[3] *Department of Internal Medicine, Seoul National University College of Medicine, Korea;*
[4] *Roche Products Limited, Welwyn, United Kingdom;* [5] *F. Hoffmann-La Roche Limited, Basel, Switzerland;*
[6] *Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC*

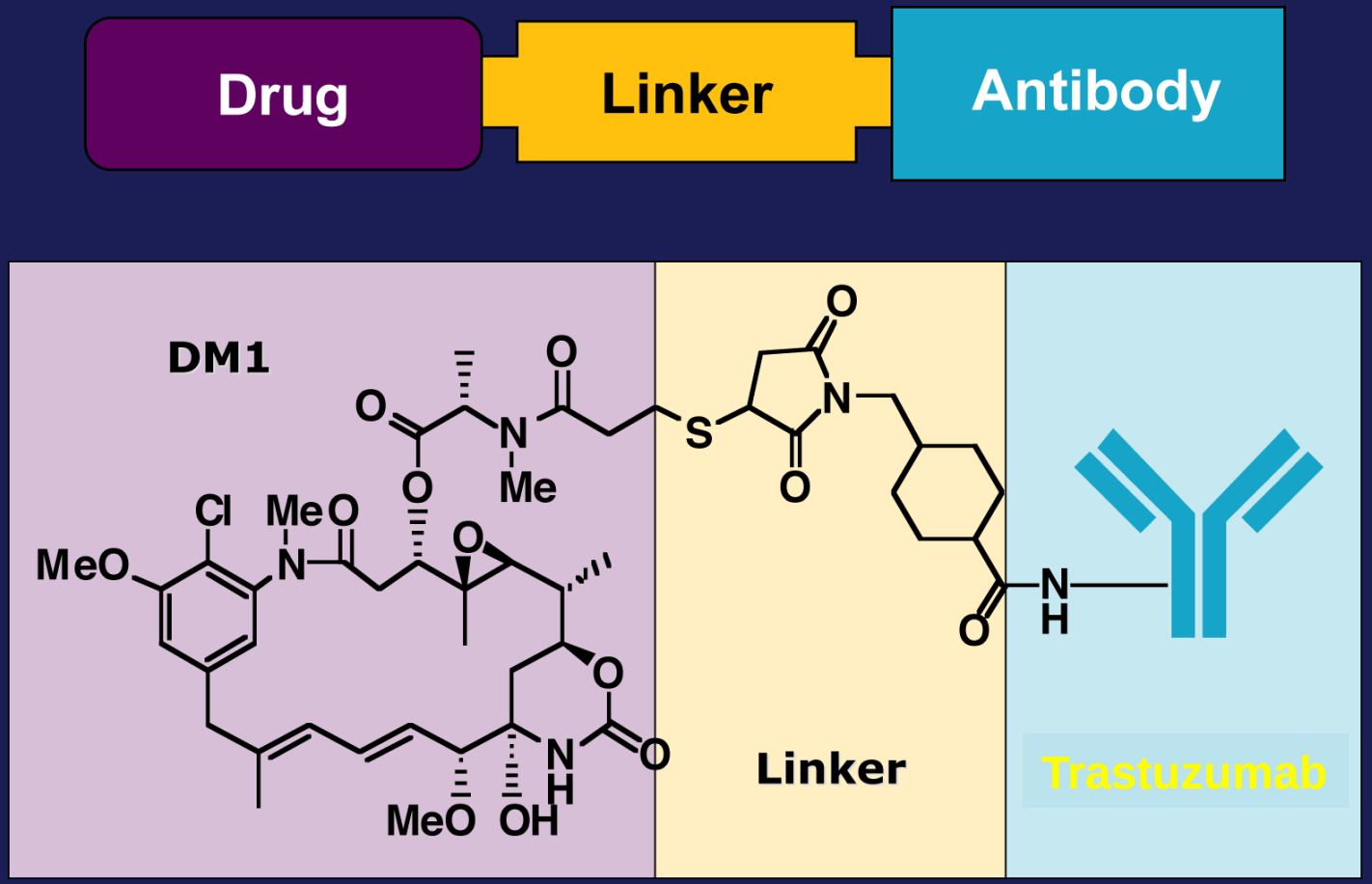
Shorter median PFS observed with mutated *PIK3CA* while treatment effect is maintained

	Pla+T+D			Ptz+T+D			
PIK3CA status	Patients, n	Events	Median, months	Patients, n	Events	Median, months	HR (95% CI)
Mut	90	63	8.6	86	45	12.5	0.64 (0.43, 0.93)
WT	191	101	13.8	190	83	21.8	0.67 (0.50, 0.89)
Overall	406	242	12.4	402	191	18.5	0.62 (0.51, 0.75)

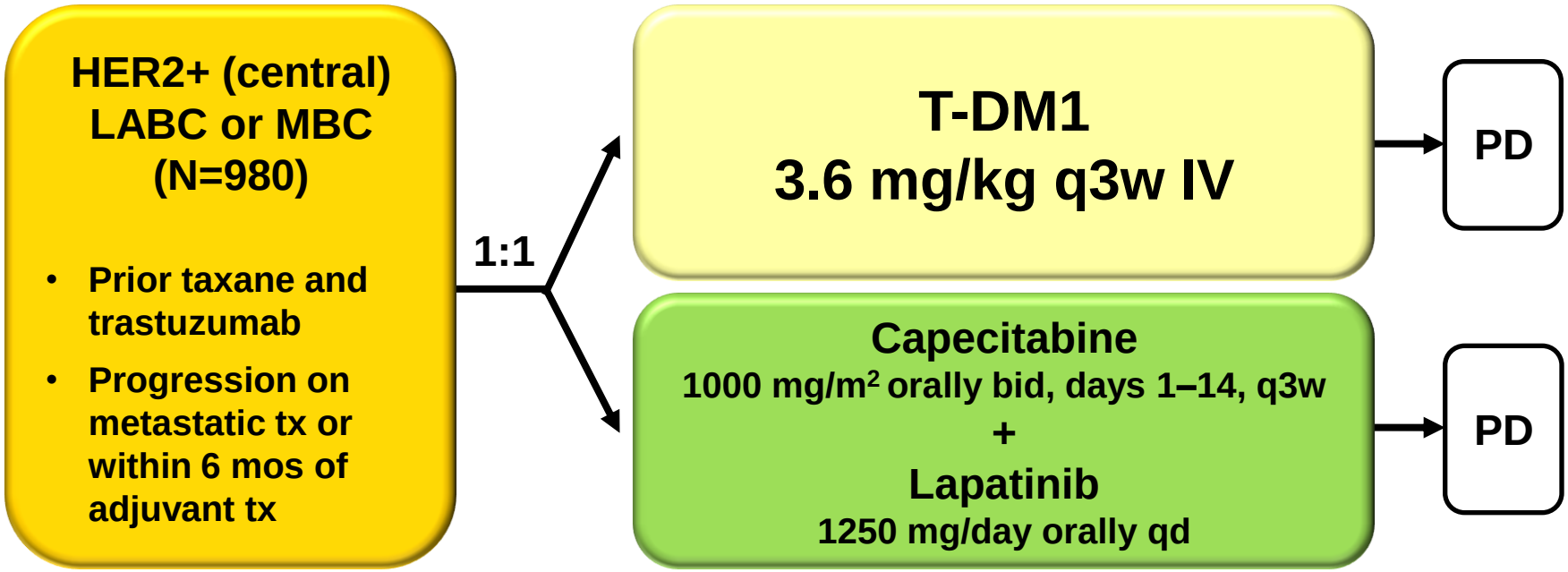
- The prognostic impact of *PIK3CA* mutations cannot be attributed to a specific mutation, nor to mutation(s) in a specific exon, based on the available dataset
  - 182 mutations detected overall (32%)
    - Exon 7: 12; exon 9: 39; exon 20: 131

Mut, mutated; WT, wild-type

“Anatomy” of Trastuzumab-DM1

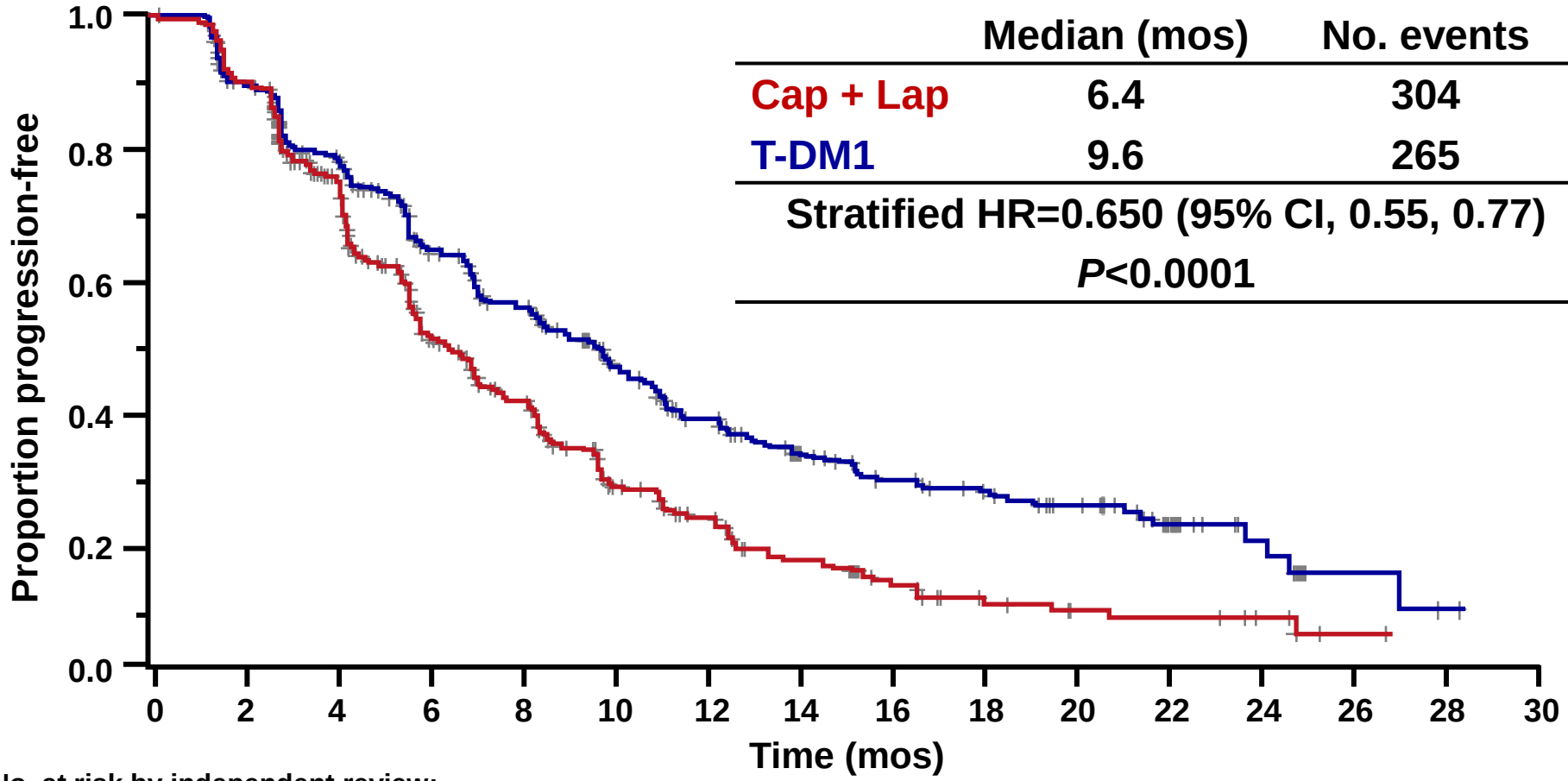


EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Progression-Free Survival by Independent Review



	Median (mos)	No. events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR=0.650 (95% CI, 0.55, 0.77)

P<0.0001

No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Unstratified HR=0.66 (*P*<0.0001).

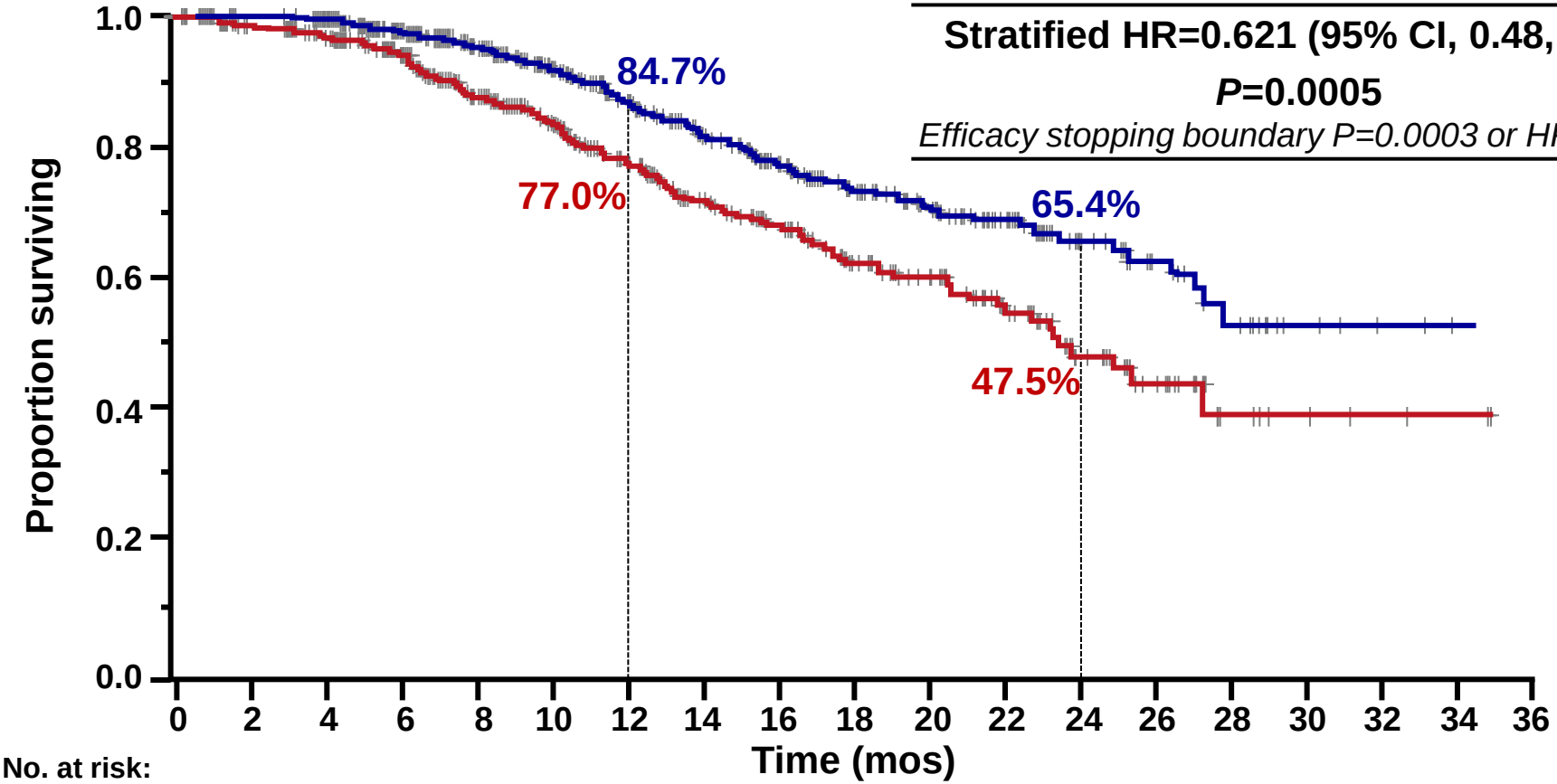
Overall Survival: Interim Analysis

	Median (mos)	No. events
Cap + Lap	23.3	129
T-DM1	NR	94

Stratified HR=0.621 (95% CI, 0.48, 0.81)

***P*=0.0005**

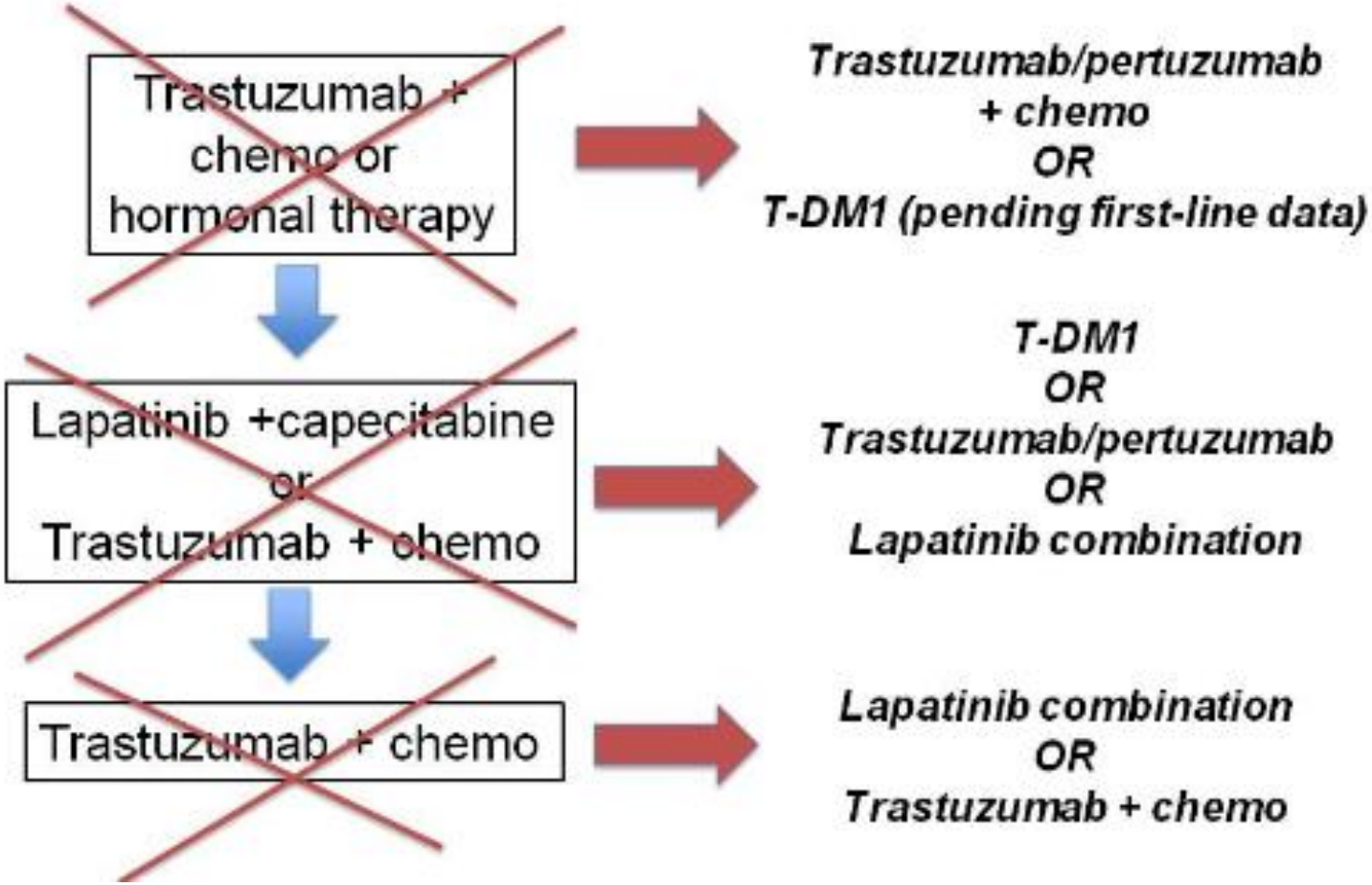
Efficacy stopping boundary P=0.0003 or HR=0.617



No. at risk:																			
Cap + Lap	496	469	438	364	296	242	195	155	129	97	74	52	31	17	7	3	2	1	0
T-DM1	495	484	461	390	331	277	220	182	149	123	96	67	46	29	16	5	2	0	0

Unstratified HR=0.63 (*P*=0.0005).
NR=not reached.

Evolving Algorithm for HER2+ Disease Through 3rd Line

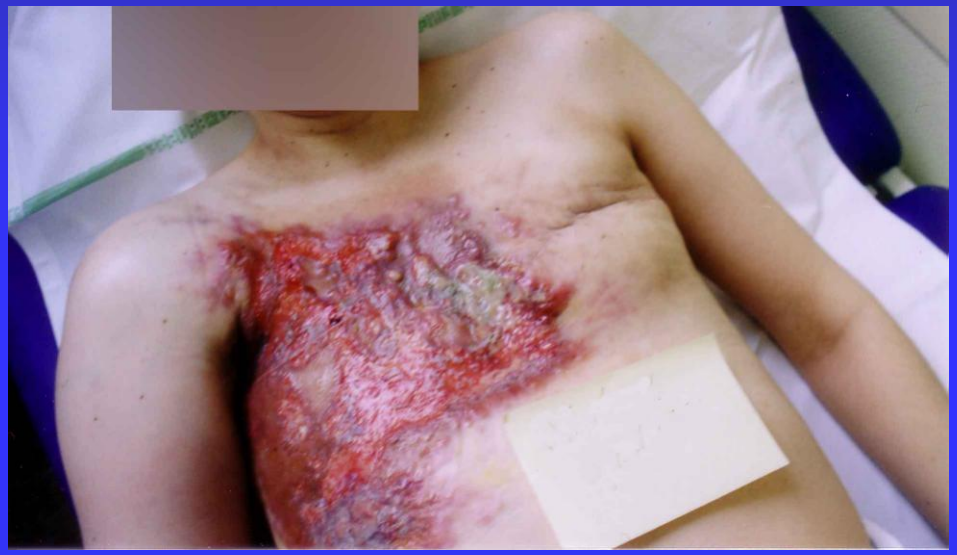


How Can We Improve Upon HER2 therapy + Chemotherapy For HER2 Positive Breast Cancer?

- **Better understand of HER-2 therapy sensitivity and resistance (biomarkers): difficult field**
- **The development of new anti-HER2 therapy overcoming the resistance : therapeutic breakthrough**
- **Characterize patients who may be candidates for different therapeutic strategies (e.g. chemotherapy alone, chemotherapy + biological or specific biological therapy alone)**

TNBC/Basal-like Diseases

POOR OUTCOME OF A "TRIPLE NEGATIVE" BREAST CANCER CLINICAL CASE



ER –
PgR –
HER-2 –
Ki67 80%
HER-1 +++

} "Triple Negative"

Progressive disease in spite of:
- FEC x 6
- Weekly paclitaxel
- Kinesin inhibitor
- Capecitabine
- Radiotherapy

Angiogenic and inflammatory pattern of the local recurrence !!!

T/FAC Neoadjuvant Response by PAM50 subtype

(12 weeks of paclitaxel followed by 4 cycles of FAC)

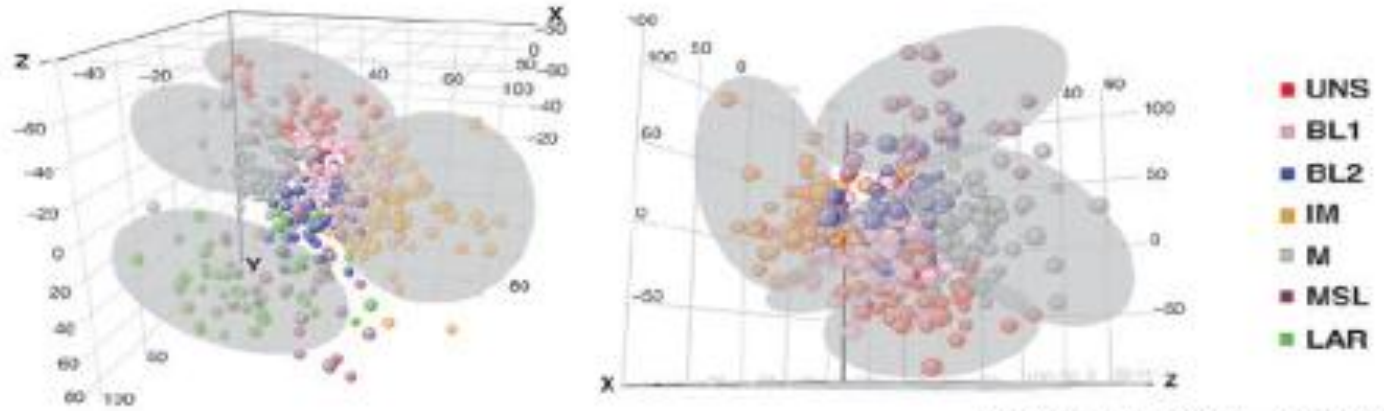
the overall pCR rate was 22%

T/FAC pathological complete response rates for PAM50 subtypes and the triple-negative classification

Classification	RD	pCR
Basal-like	11 (41%)	16 (59%)
HER2-enriched	17 (59%)	12 (41%)
LumA	36 (100%)	0 (0%)
LumB	22 (82%)	5 (18%)
Normal-like	13 (93%)	1 (7%)
Triple Negative	13 (50%)	13 (50%)
Any Positive	82 (80%)	20 (20%)
Triple Negative/Basal	6 (35%)	11 (65%)
Triple Negative/Non-Basal	7 (78%)	2 (22%)
Non-Triple Negative/Basal	4 (50%)	4 (50%)
Non-Triple Negative/Non-Basal	78 (83%)	16 (17%)

Parker et al. J Clin Oncol; 27:1160-1167 2009

Heterogeneity of TNBC



Lehmann et al, JCI 2011

- **Genomic instability common**
- **Multiple subsets with varying targets**
  - **Basal-like 1 and 2 – DNA damage response genes**
  - **Immunomodulatory**
  - **Mesenchymal and mesenchymal / stem cell – PI3K/mTOR pathway**
  - **LAR – androgen receptor signaling**

Targeting the androgen receptor (AR) in women with AR+ ER-/PR- metastatic breast cancer TBCRC011

Abstract #1006

Gucalp A, Tolaney S, Isakoff S, Ingle J, Liu MC, Carey L, Blackwell K, Rugo H, Nabell L, Forero A, Stearns V, Momen L, Gonzalez J, Akhtar A, Giri D, Patil S, Feigin K, Hudis CA, Traina TA

on behalf of

Translational Breast Cancer Research Consortium

ASCO Annual '12 Meeting

Bicalutamide Results : Patients with Clinical Benefit (5/24 = 21%)

Patients with clinical benefit on bicalutamide	AR%	ER%	PR%	HER2	Site of Testing	Site of Mets	Prior Therapy MBC/ LABC	DOR on Prior Therapy
#1	10-20	1	0	Neg	1º	LN	0	NA
#2	>80	3	0	Neg	Met	GI	0	NA
#3	>80	0	0	-/+	1º	Breast, LN	1	NR
#4	>90	0	0	Neg	1º	LN, Bone	1	158wk
#5	>50	0	0	Neg	1º	LN, Bone	1	15 wk

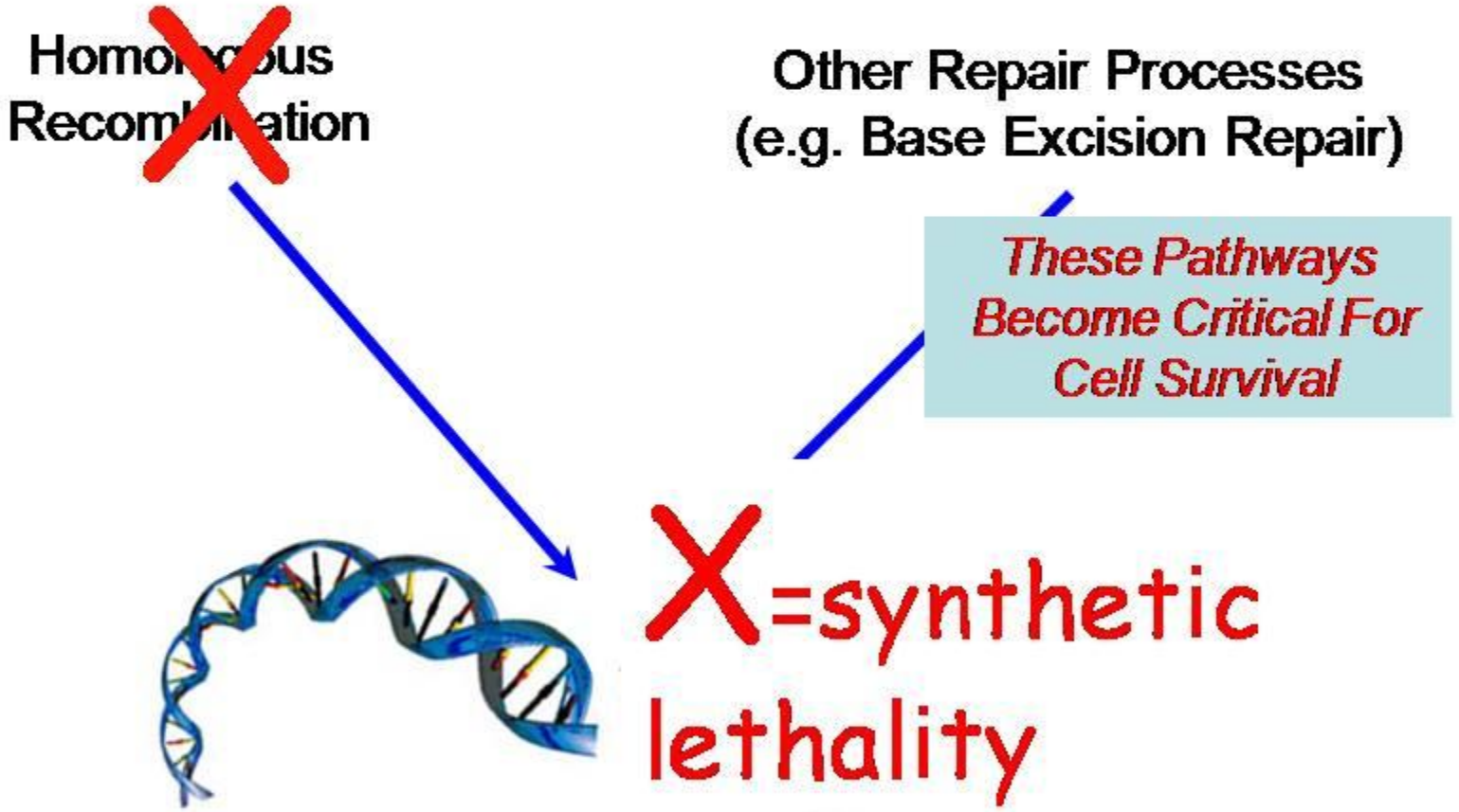
DOR duration of response;
NA not applicable; NR no response

Reported Studies Evaluating Cisplatin or Carboplatin for the Treatment of Patients With BRCA-Mutant Breast Cancer and/or TNBC

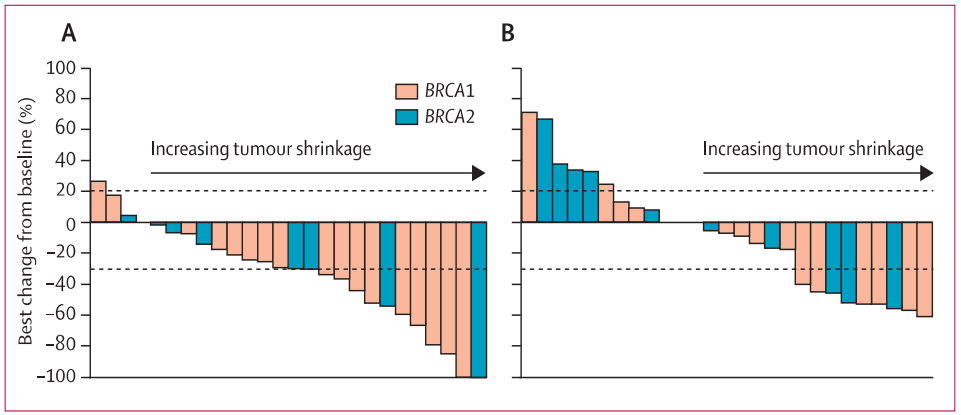
Study	Study Design	Population	No. of Patients	Treatment	Results
Byrski et al[22]	Retrospective-neoadjuvant	*BRCA1* mutant	102	CMF, n = 14; AC, n = 23; FAC, n = 28; AT, n = 25; cisplatin, n = 12	pCR: CMF, 7%; AC, 22%; FAC, 21%; AT, 8%; cisplatin, 83%
Byrski et al[22]	Pilot neoadjuvant	*BRCA1* mutant	10	Cisplatin	pCR: 90%
Gronwald et al[21]	Neoadjuvant phase II	*BRCA1* mutant	25	Cisplatin	pCR: 72%
Silver et al[24]	Neoadjuvant phase II	TNBC, n = 2 *BRCA1* mutant	28	Cisplatin	pCR: 22% (95% CI, 9% to 43%)
Alba et al[27]	Neoadjuvant randomized phase II	TNBC	94	EC × 4 → T *v* EC × 4 → T + carbo	pCR: EC × 4 → T, 30%; EC ×4 → T + carbo, 30%
Advanced setting					
Wang et al[25]	Phase II	First-line advanced TNBC	45	Cisplatin + gem	ORR: 62% (95% CI, 47.5% to 77%)
Bhattacharyya et al[26]	Randomized phase II	Second-line advanced TNBC	126	Metronomic CM (n = 66) *v* metronomic CM + cisplatin (n = 60)	ORR: metronomic CM, 30%; metronomic CM + cisplatin, 62%

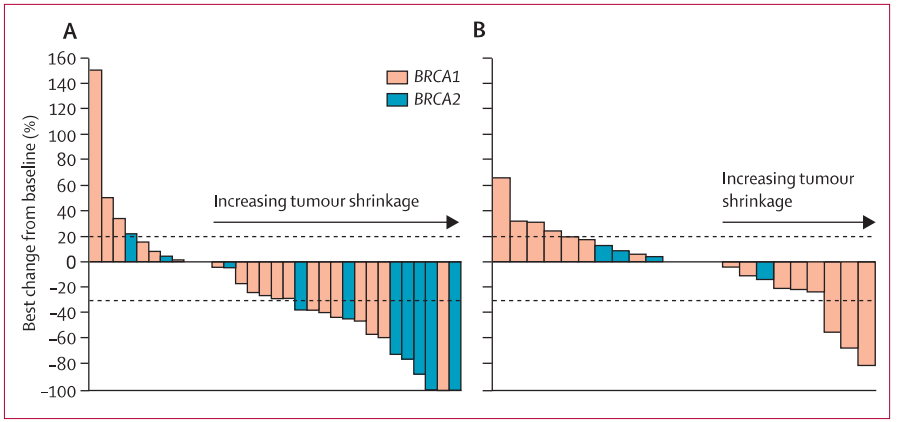
Metzger-Filho JCO 2012

Redundant Mechanisms of DNA Repair May Offer a Therapeutic Opportunity in Basal-like BRCA1-/- Breast and Ovarian Cancer



Olaparib demonstrated high efficacy in BRCA-mutated tumors





	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

BRCA-mutant breast cancer

	Olaparib 400 mg twice daily (n=33)	Olaparib 100 mg twice daily (n=24)
Objective response	11 (33%, 20–51)	3 (13%, 4–31)
Complete response	2 (6%, 2–20)	0
Partial response	9 (27%, 15–44)	3 (13%, 4–31)
Stable disease	12 (36%, 22–53)	7 (29%, 15–49)
Progressive disease	10 (30%, 17–47)	14 (58%, 39–76)
Duration of response (days)	290 (126–506)	269 (169–288)*

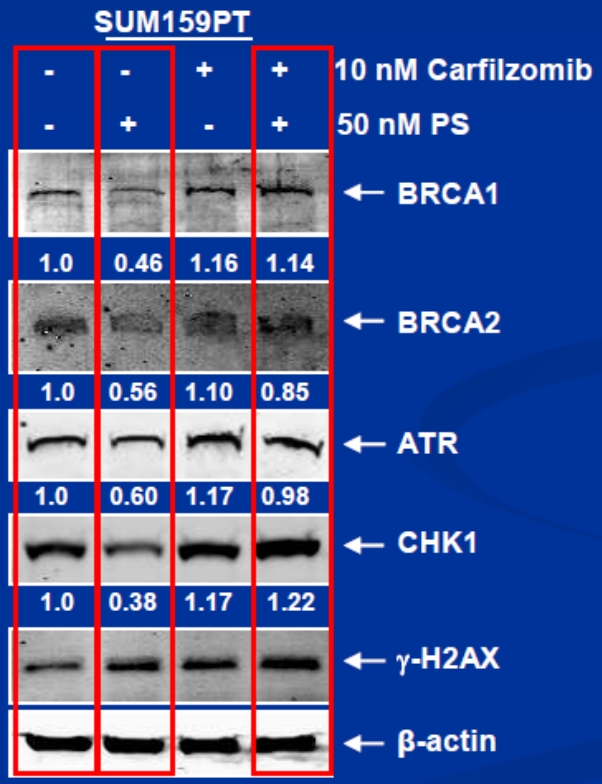
BRCA-mutant ovarian cancer

Tutt A et al, Lancet 2010
Audeh MW et al, Lancet 2010

Treatment with Histone Deacetylase Inhibitors Creates 'BRCAness' and Sensitizes Human Triple Negative Breast Cancer Cells to PARP Inhibitors and Cisplatin

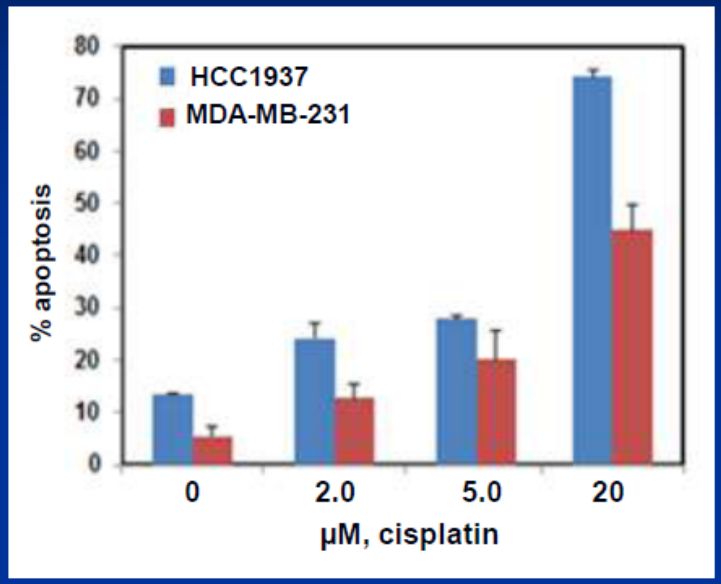
Kapil N. Bhalla, Rekha Rao,
Priyanka Sharma, Soumyasri Das Gupta,
Lata Chauhan, Shane Stecklein,
and Warren Fiskus

Treatment with HDAC inhibitor induces proteasomal degradation of BRCA1, BRCA2, ATR and CHK1

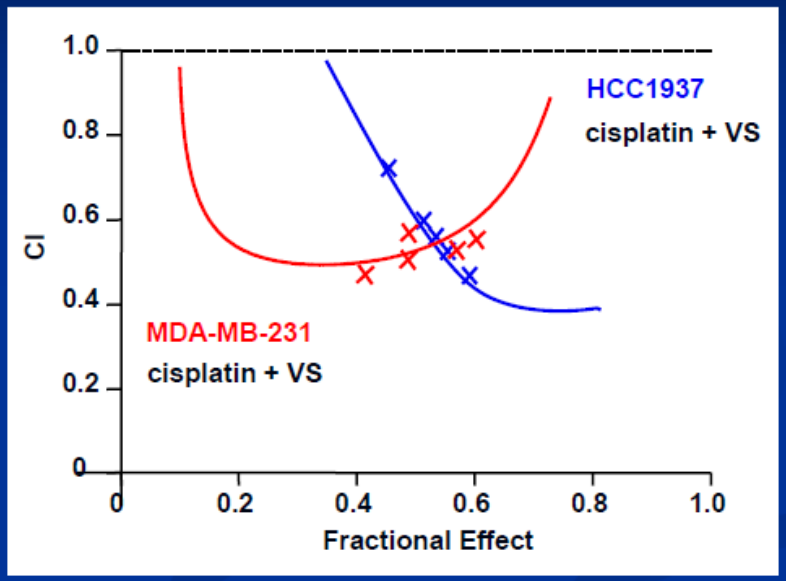


Co-treatment with vorinostat (VS) and cisplatin synergistically induces apoptosis of breast cancer cells

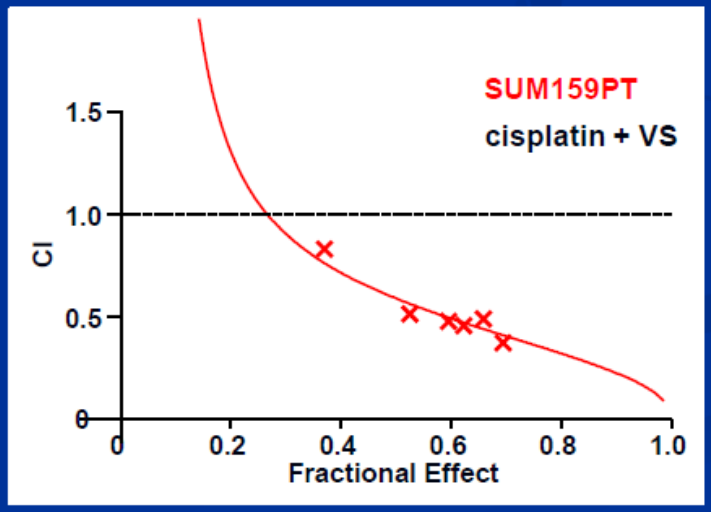
A



B



C



Basal-like/TNBC diseases : Conclusions

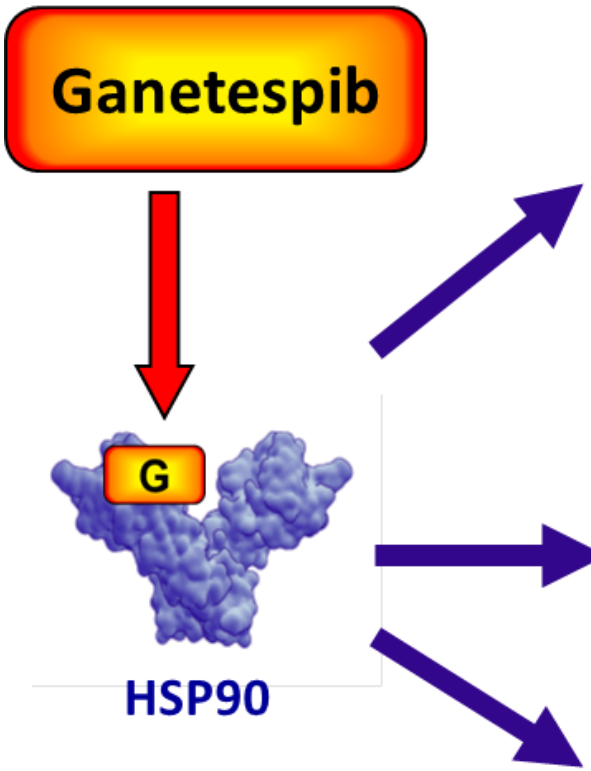
1. A group of TNBC benefits of standard chemotherapy

2. BRACA mutated : significant tumor response to cisplatin and PARP inhibitors (Olaparib)

3. Genomic era : better understanding of the tumor heteroneity and biology which might lead to new targets and new agents

New targets / Agents in Breast Cancer

HSP90 inhibitors : Degradation of oncogenic client proteins



Inhibition of chaperone leads to degradation of multiple client proteins; Hsp90 clients include key oncogenic drivers *[refs]*

Monotherapy applications

ALK, RAF, HER2, … → Oncogenic drivers

Combination therapy applications

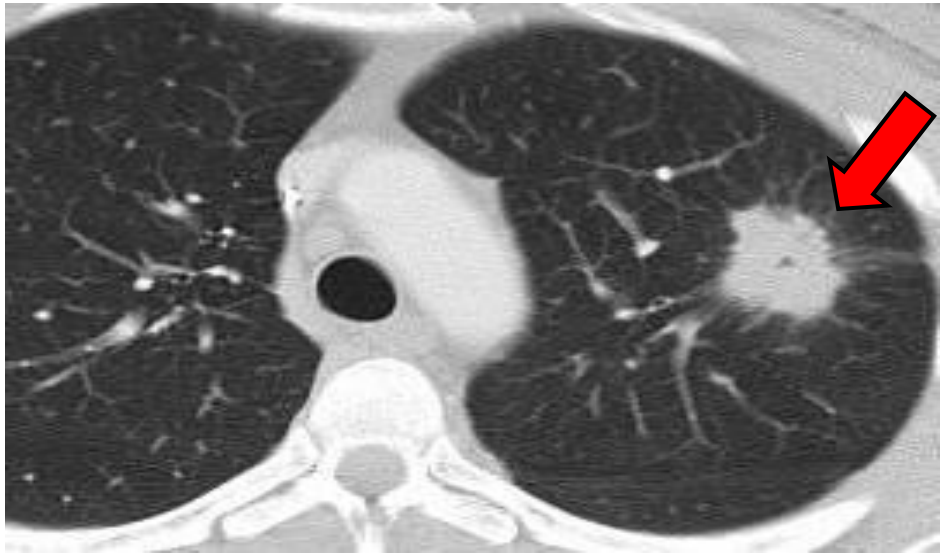
HIF-1α → Tumor aggressiveness
- Angiogenesis
- EMT
- Metastasis
- Immune evasion
- Chemo-resistance

DNA repair, cell cycle clients → Tumor recovery/ repair mechanisms

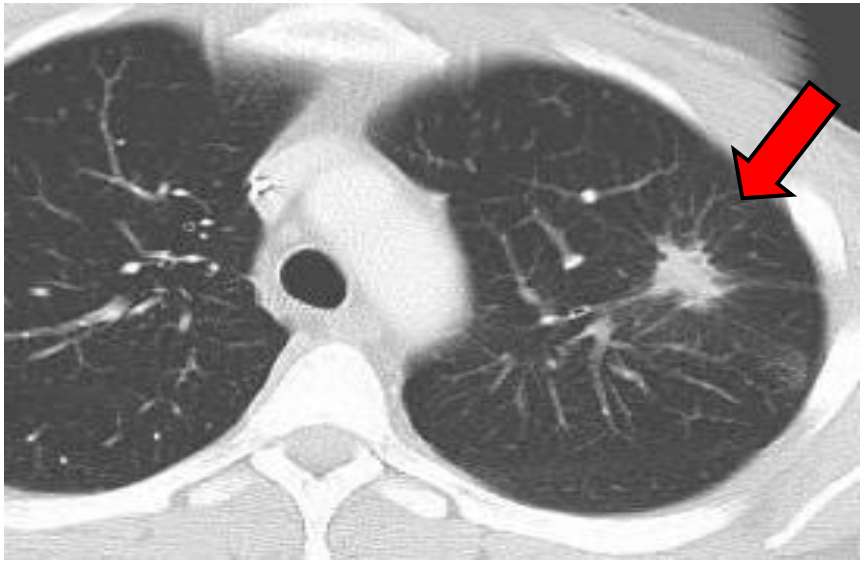
Ganestespib : Clinical activity in a TNBC patient

39 YO female – heavily pretreated: adriamycin+Cytoxan, Paclitaxel, chest wall RT, Avastin+Xeloda, Cisplatin, Xeloda (1 mo), cediranib+olaparib (3.5 mo)

Ganetespib monotherapy



Baseline

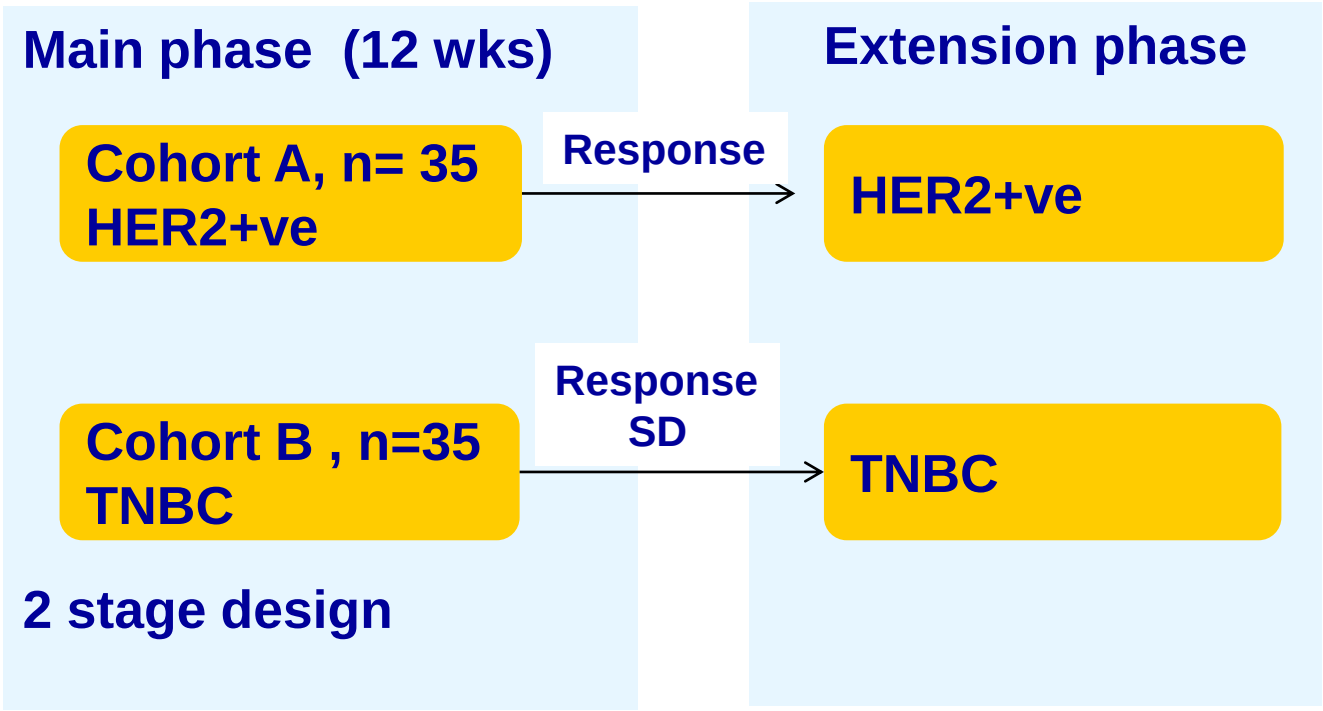


Week 16

JFriedland et al, SABCS, 2011, P3-17-05

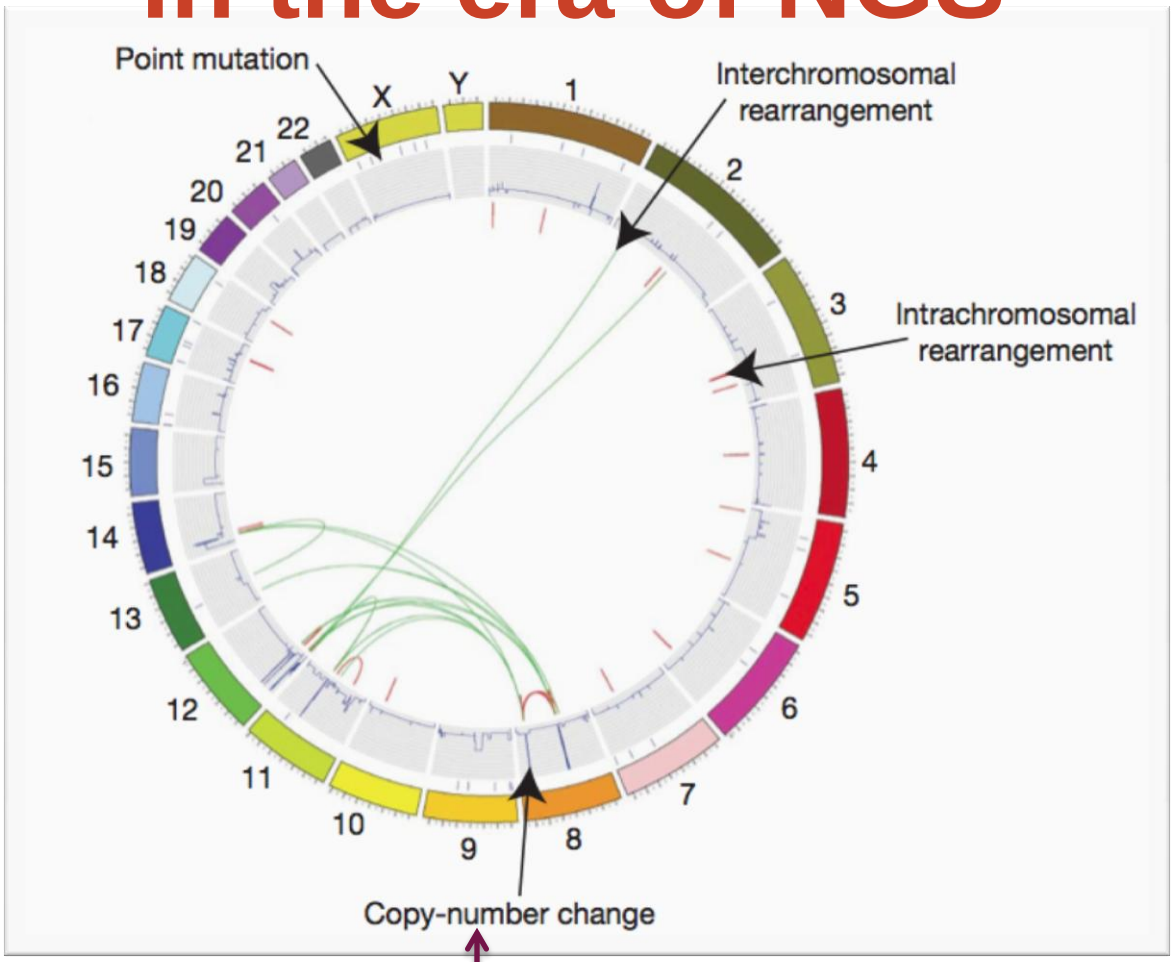
Ganestespib : ENCHANT study design

MBC
1st line setting !!
IBC (1st and 2nd) line
PS 0-1
Prior adjuvant Rx



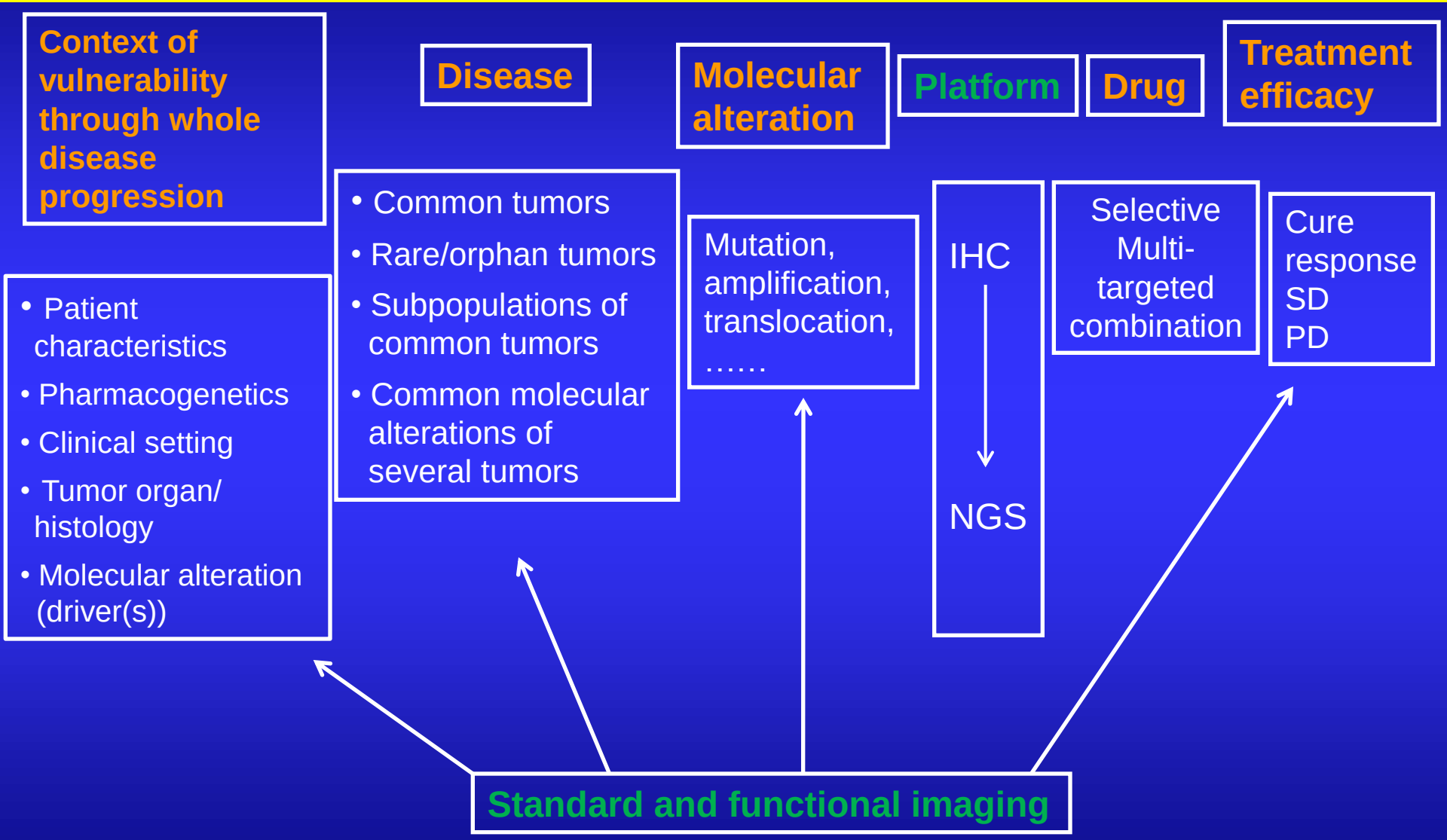
Ganetespib monotherapy150mg/m^2 twice weekly for 3 weeks and 1 week off (PET/CT before treatment and on d18 of first cycle)

Getting familiar with “circus plots” in the era of NGS



Genomic « landscape » of the tumor

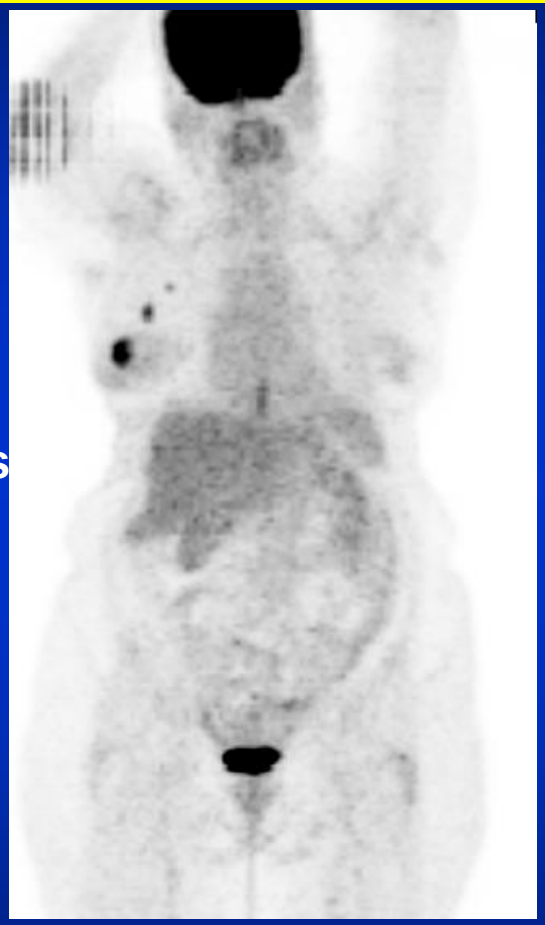
Matching patient / tumor / molecular aberration / test-platform / drug: The basis for individualized oncology



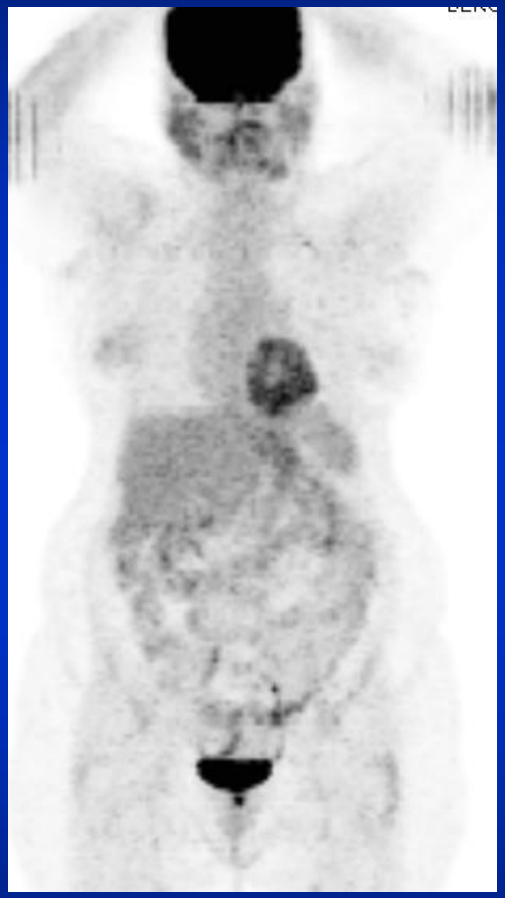
Molecular/Functional imaging

Anti HER2 therapy for 2 weeks : a “dramatic” early response in the neoAltto trial

Primary Tumor +
2 Lymph Node Mets



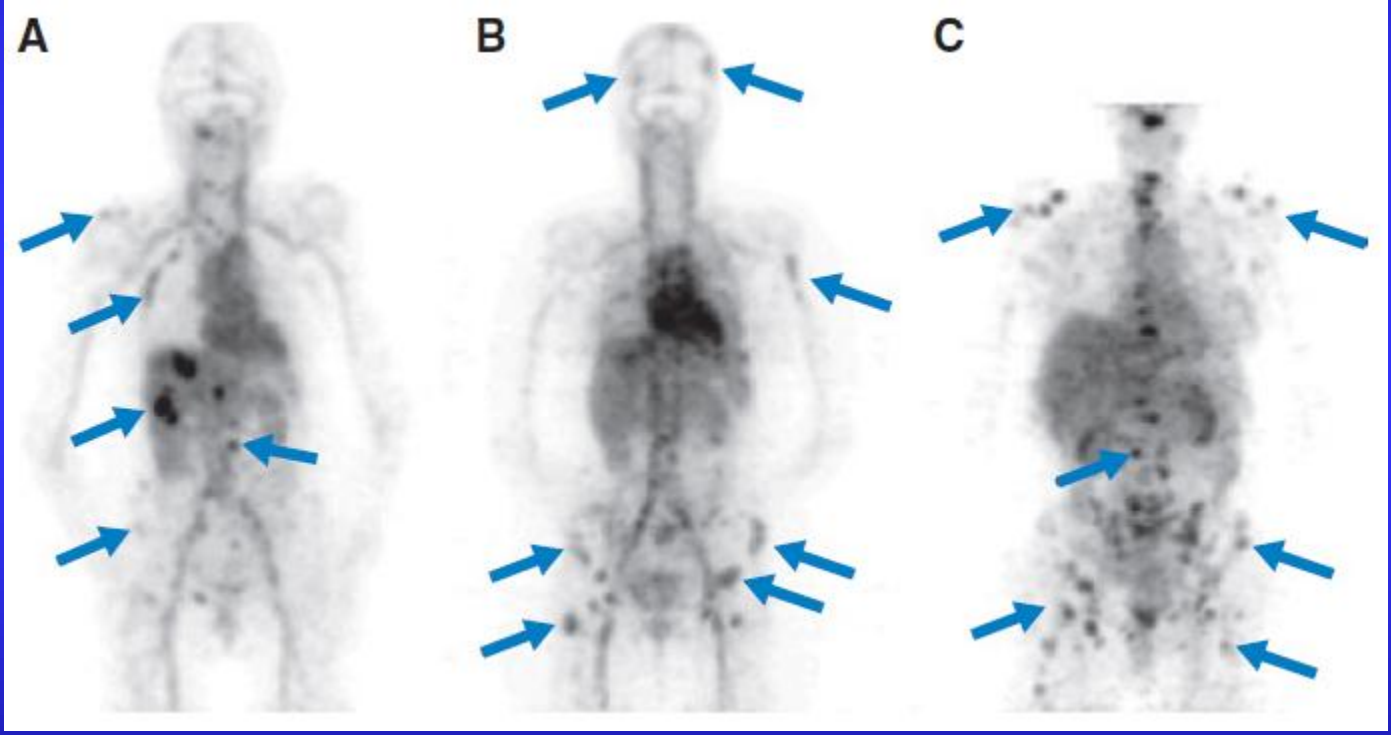
Baseline



After 2 weeks

FDG PET-CT images

Zirconium-89-trastuzumab localizes to HER-2 expressing tumors (and heart) : Mapping HER-2 heterogeneity ?



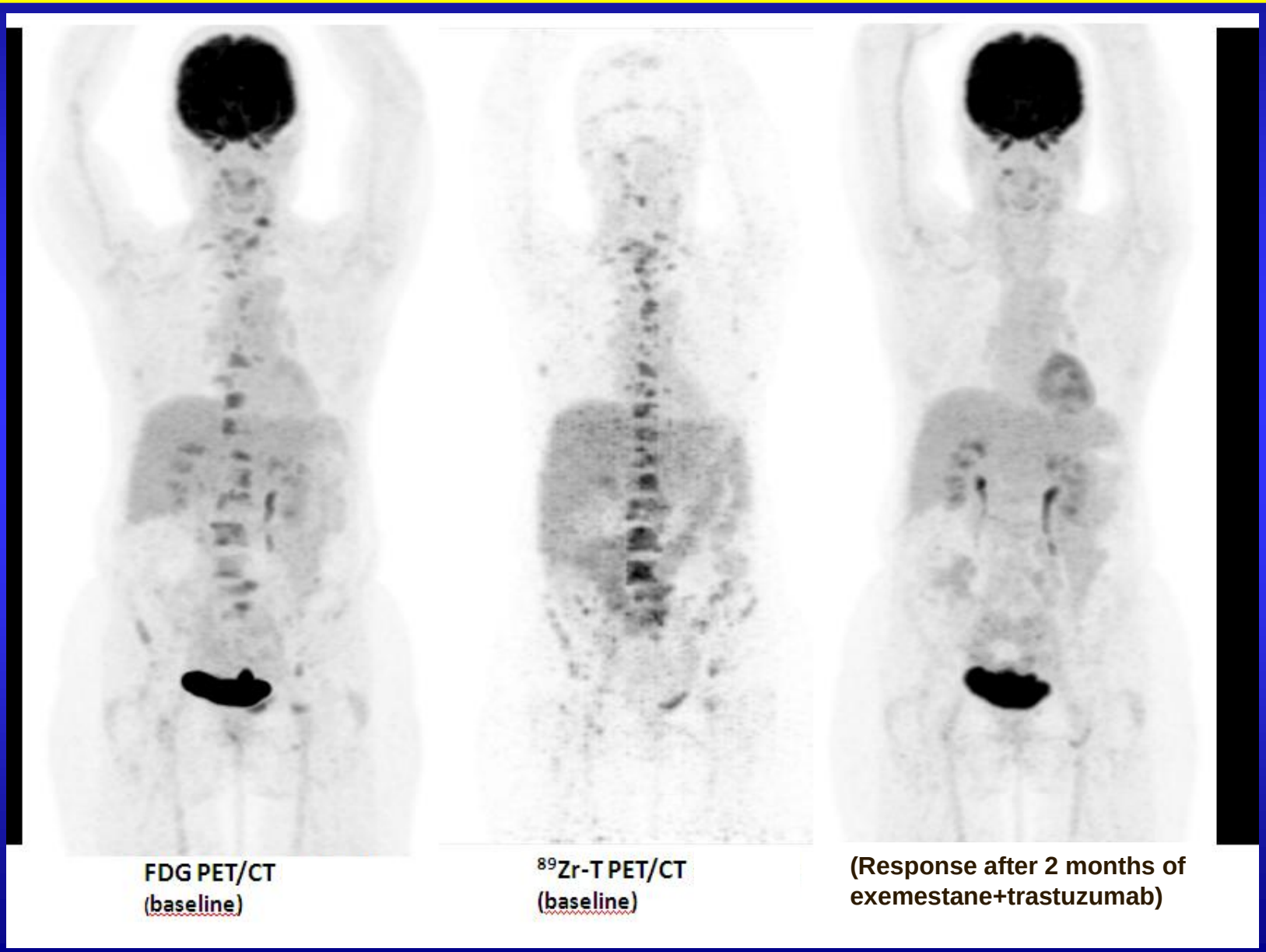
Bone & liver metastases

Bone metastases
Heart uptake

Massive bone metastases

S.M Knowles, JCO, 2012

FDG PET/CT and ^{89}Zr-Trastuzumab PET/CT in a patient (ER+/HER-2+) with bone metastases responding to therapy



FDG PET/CT (baseline)

^{89}Zr-T PET/CT (baseline)

(Response after 2 months of exemestane+trastuzumab)

THANK YOU