GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

39th ESMO, Madrid, 26-30 Sept 2014
prIME Oncology Symposium

How Do You Measure Success? Recent Progress in Breast Cancer

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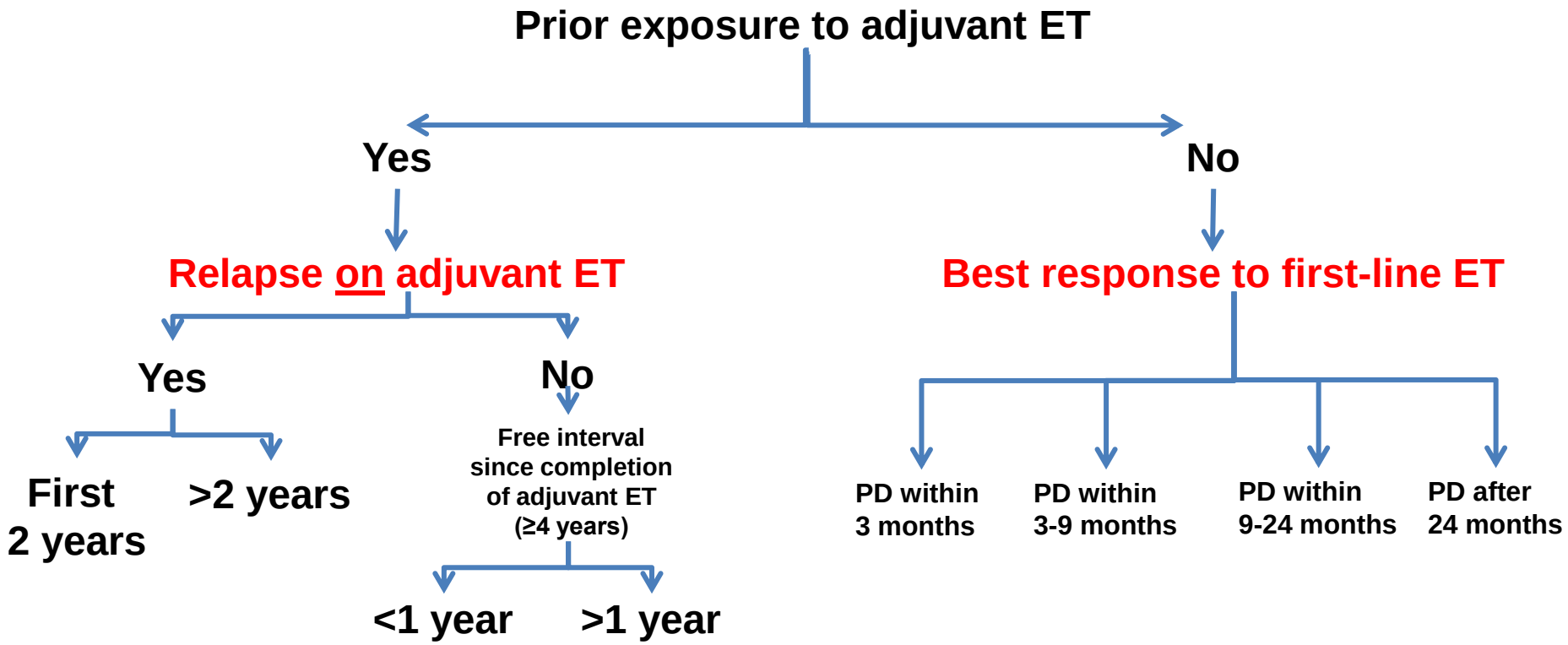
ULB Institut Jules Bordet réseau iris structuur Instituut

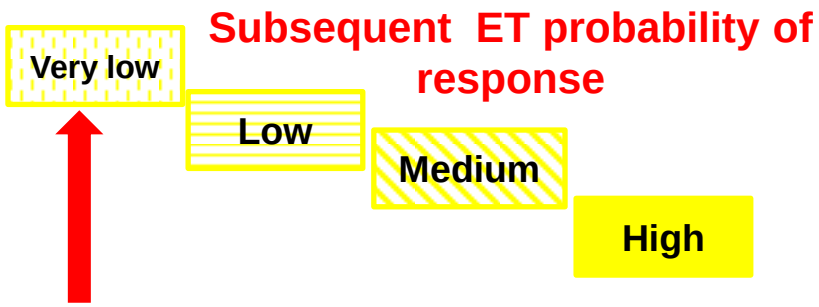
BIG Breast International Group

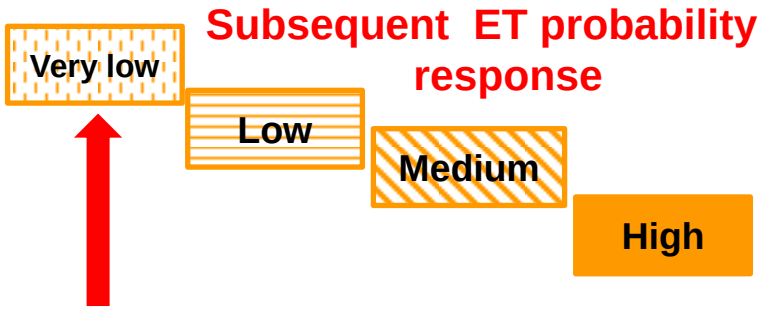
All our endocrine therapies fail… sooner or later, in view of the development of "ENDOCRINE RESISTANCE"

We have agreed on a definition of "endocrine resistance"!

ABC Consensus on the Definition of "Endocrine Resistance"



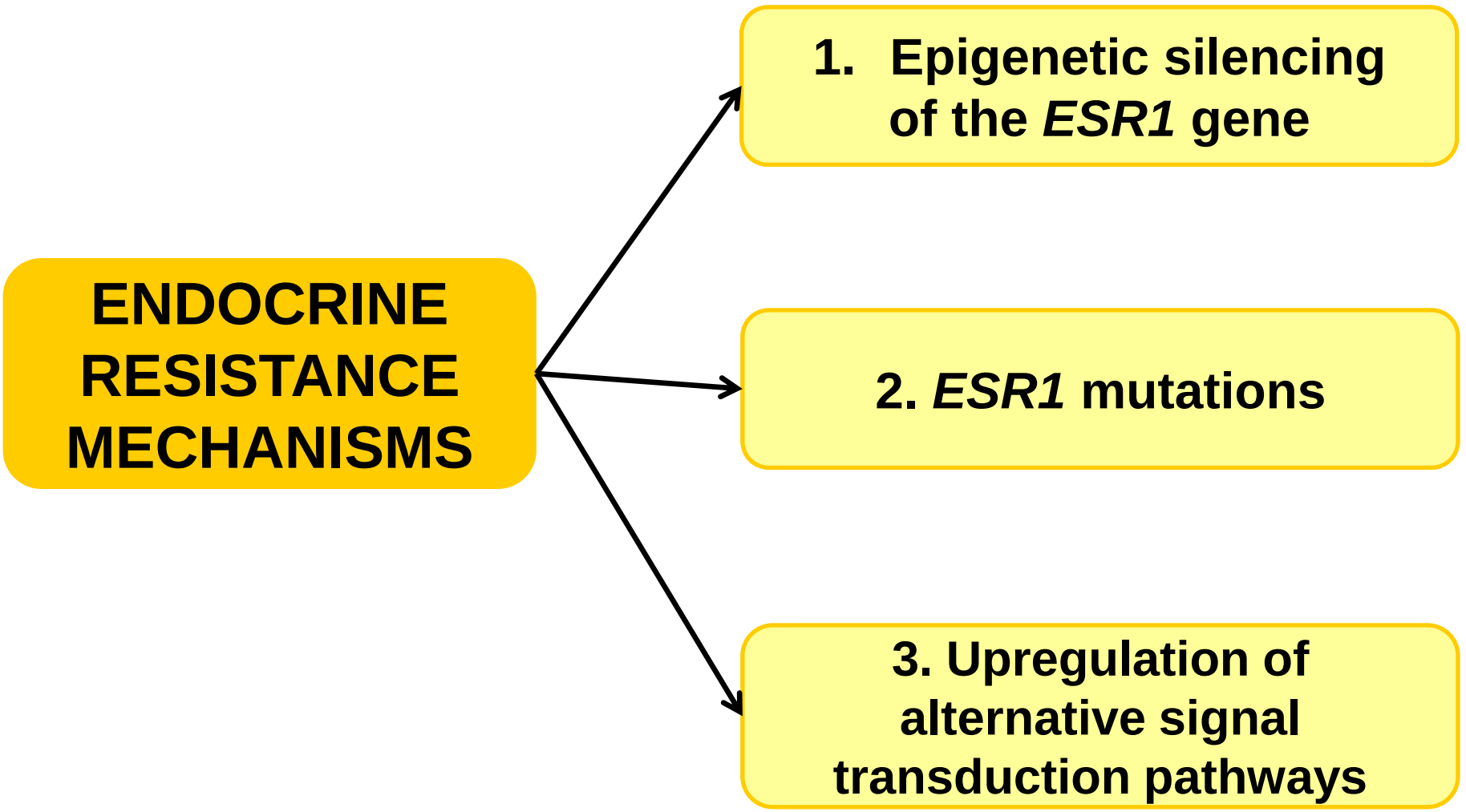




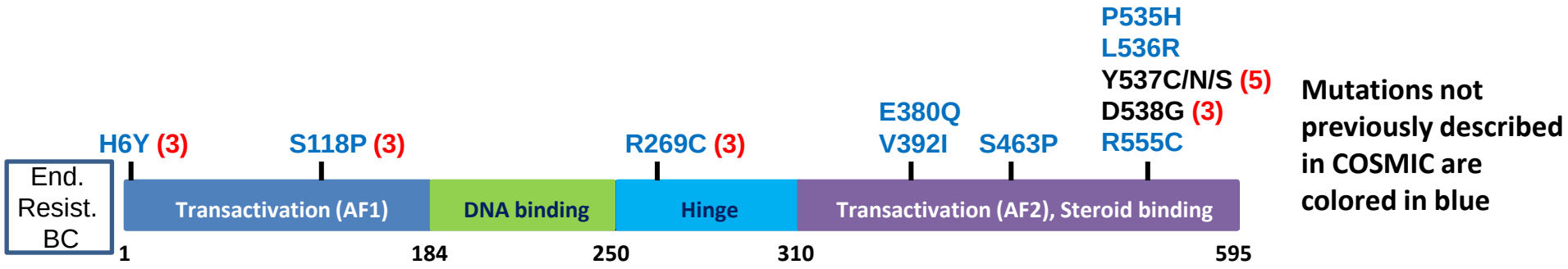
« ABC Lisbon » consensus definitions of primary endocrine resistance

ET, endocrine therapy

Endocrine-Resistant Breast Cancer



Mutations in Estrogen Receptor (ESR1) Are Enriched in Metastatic Samples Compared With Primary



- **Mutations are enriched in metastatic samples compared with primary samples**

ER mutations

Gene	Met With Variant	Met Without Variant	% Mets	Primary With Variant	Primary Without Variant	% Primary
ESR1	8	34	19.0	13	172	7.0

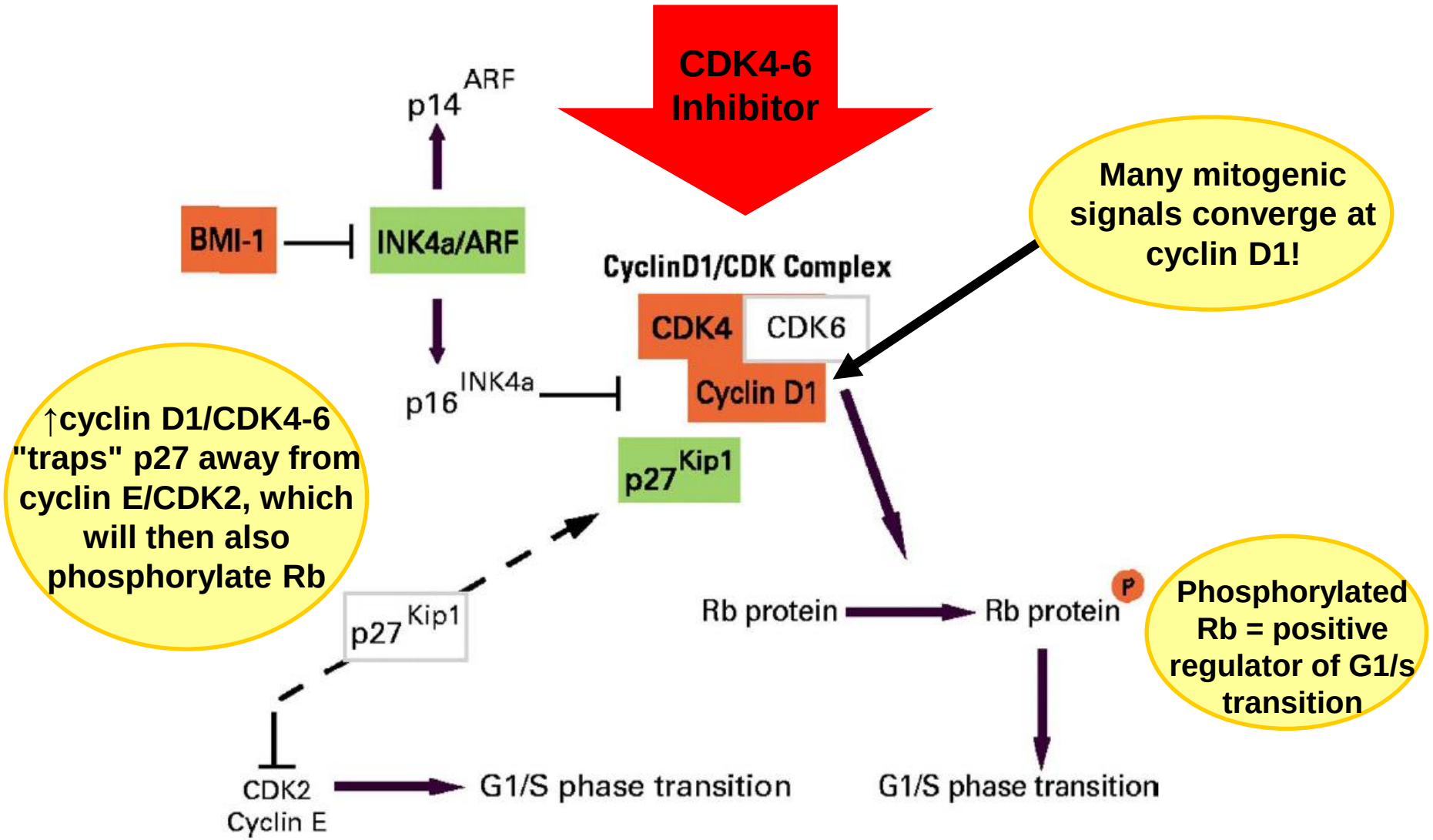
- Cluster of 11 mutations (between amino acids 535 and 538) in ligand-binding domain likely affect affinity and binding kinetics of estrogen
  - Example: *Y537S* mutant is constitutively active in the *absence* of ligand
- **Most of these mutations will ultimately lead to increased ER signaling, through constitutive, ligand-independent transactivation**

Lazennec G, et al. *Mol Endocrinol*. 1997;11(9):1375-1386.

Targeting the cell cycle progression downstream of the “activated” ER:

An efficient strategy for antagonizing constitutive ERα signaling ?

Role of CDK4 in Cell Cycle



Fernàndez V, et al. *J Clin Oncol.* 2005;23(26):6364-6369.

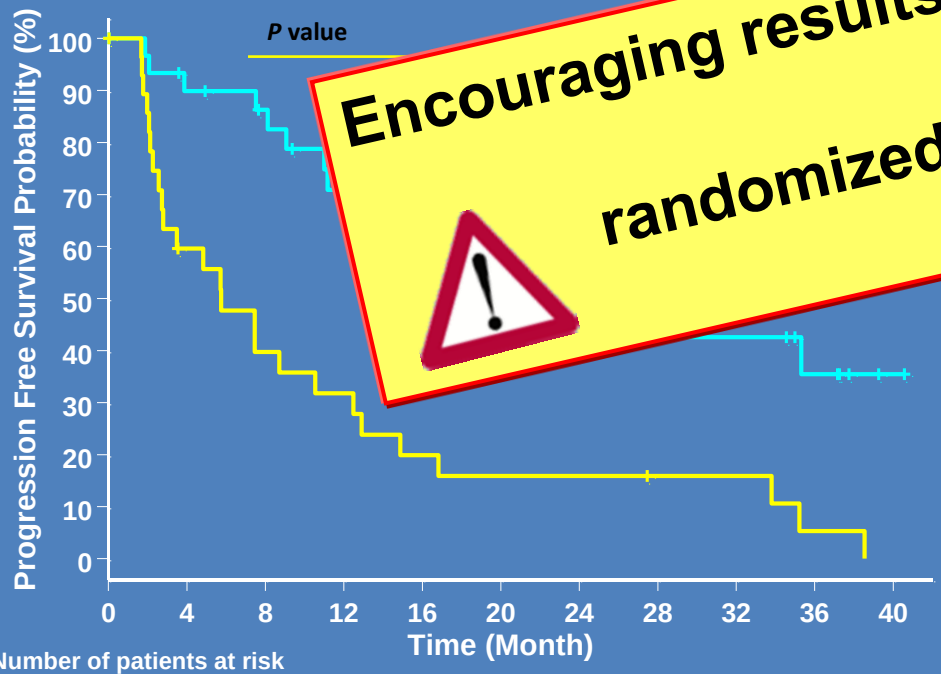
PALOMA-1 : Progression-Free Survival (ITT) Part 1 and Part 2

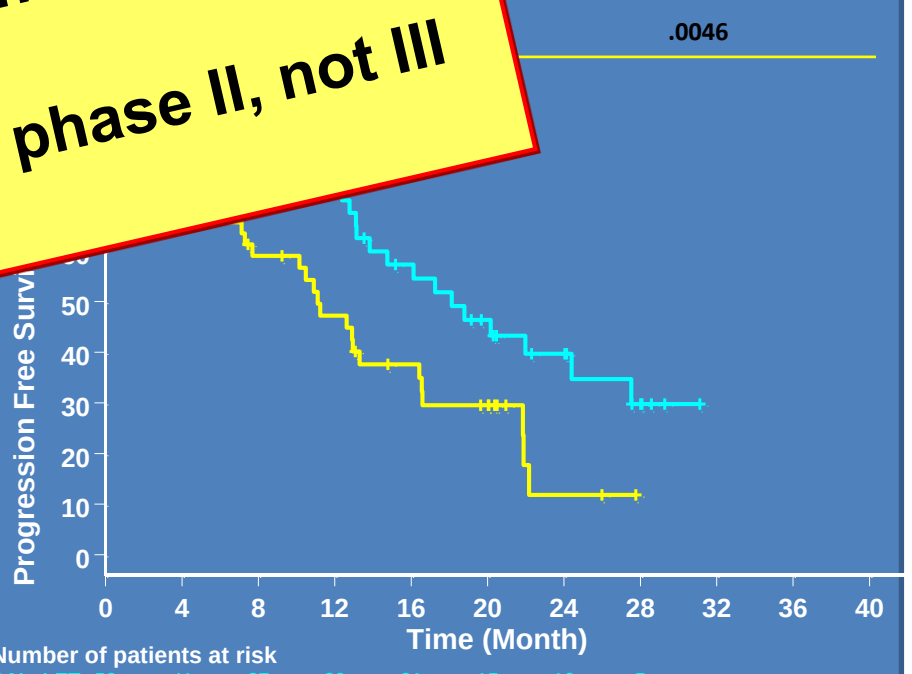
Part 1	PAL + LET (N = 34)	LET (N = 32)
Number of Events (%)	15 (44)	25 (78)
Median PFS, months (95% CI)	26.1 (11.2, NR)	5.7 (2.6, 10.5)
Hazard Ratio (95% CI)	0.299	
P value		

Part 2	PAL + LET (N = 50)	LET (N = 49)
Number of Events (%)	26 (52)	34 (69)
Median PFS, months (95% CI)	18.1 (13.1, 27.5)	11.1 (7.1, 16.4)
Hazard Ratio (95% CI)	0.508 (0.303, 0.853)	
P value	.0046	

Encouraging results… but

randomized phase II, not III





Finn RS, et al. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract CT101.

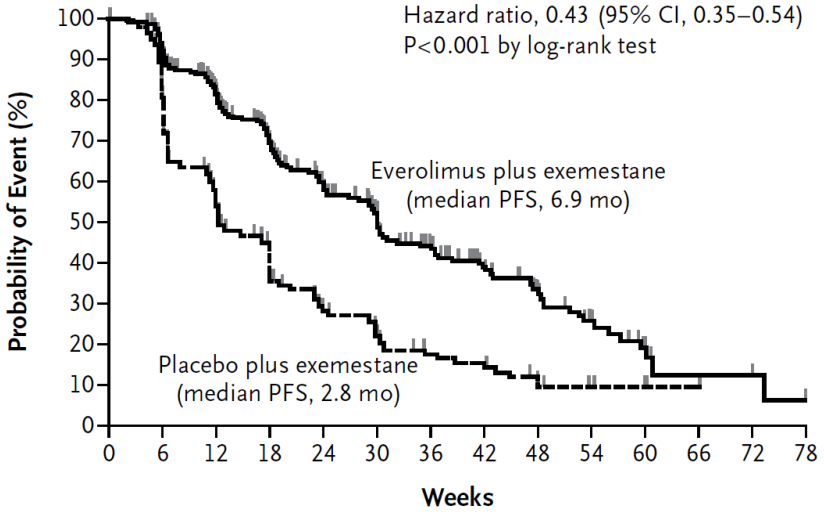
This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

Ongoing Phase III Studies Assessing CDK 4/6 Inhibition

PALOMA-2	Palbociclib + Letrozole vs. Letrozole For 1st Line Treatment Of Postmenopausal Women (NCT01740427)
PALOMA-3	Palbociclib + Fulvestrant vs. Fulvestrant + Placebo After Endocrine Failure (NCT01942135)
PEARL	Palbociclib + Exemestane vs. Capecitabine in Resistance to NSAI (NCT02028507)
MONARCH2	Fulvestrant With or Without Abemaciclib (LY2835219) (NCT02107703)
MONALEESA2	LEE011 in Combination With Letrozole (NCT01958021)

BOLERO-2 Study: Results

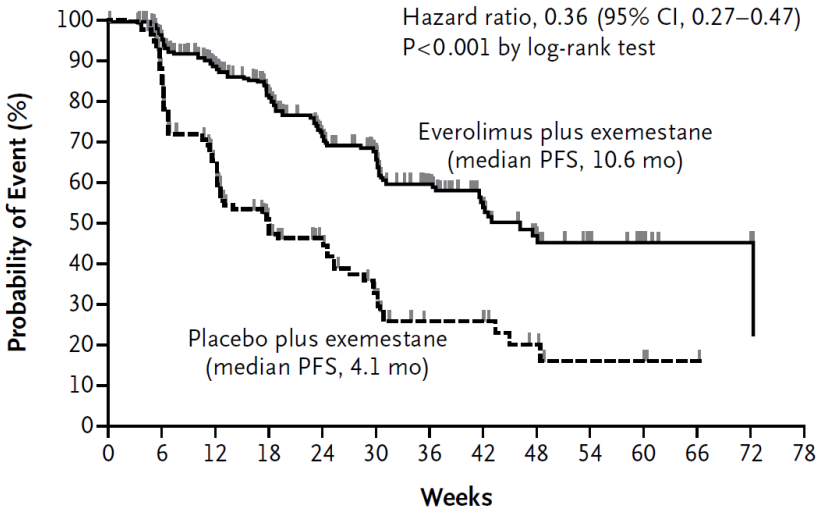
Local Assessment



No. at Risk

Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

Central Assessment



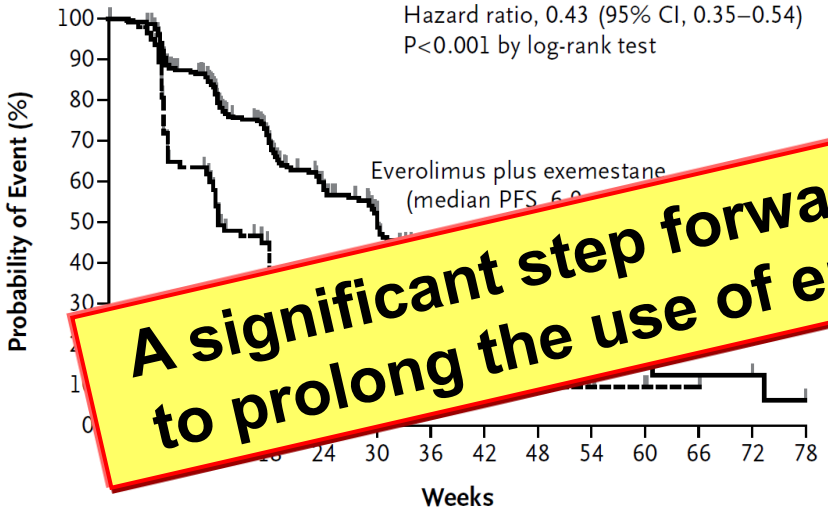
No. at Risk

Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2 Study: Results

Local Assessment



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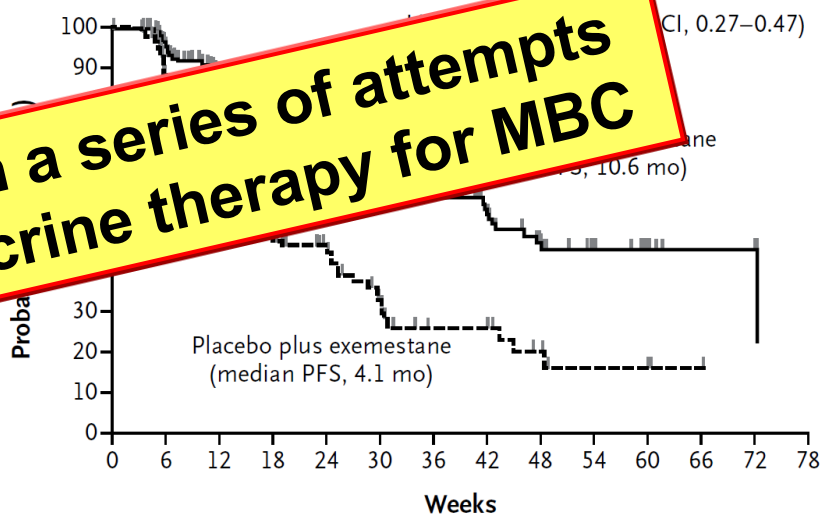

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Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

A significant step forward in a series of attempts to prolong the use of endocrine therapy for MBC

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2: Most Common G3/4 AEs

	Everolimus + Exemestane (N = 482), %			Placebo + Exemestane (N = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	56	8	0	11	1	0
Fatigue	33	3	<1	26	1	0
Dyspnea	18	4	0	9	1	<1
Anemia	16	5	1	4	<1	<1
Hyperglycemia	13	4	<1	2	<1	0
AST	13	3	<1	6	1	0
Pneumonitis	12	3	0	0	0	0

AE, Adverse Event; AST, Aspartate aminotransferase

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2: Most Common G3/4 AEs

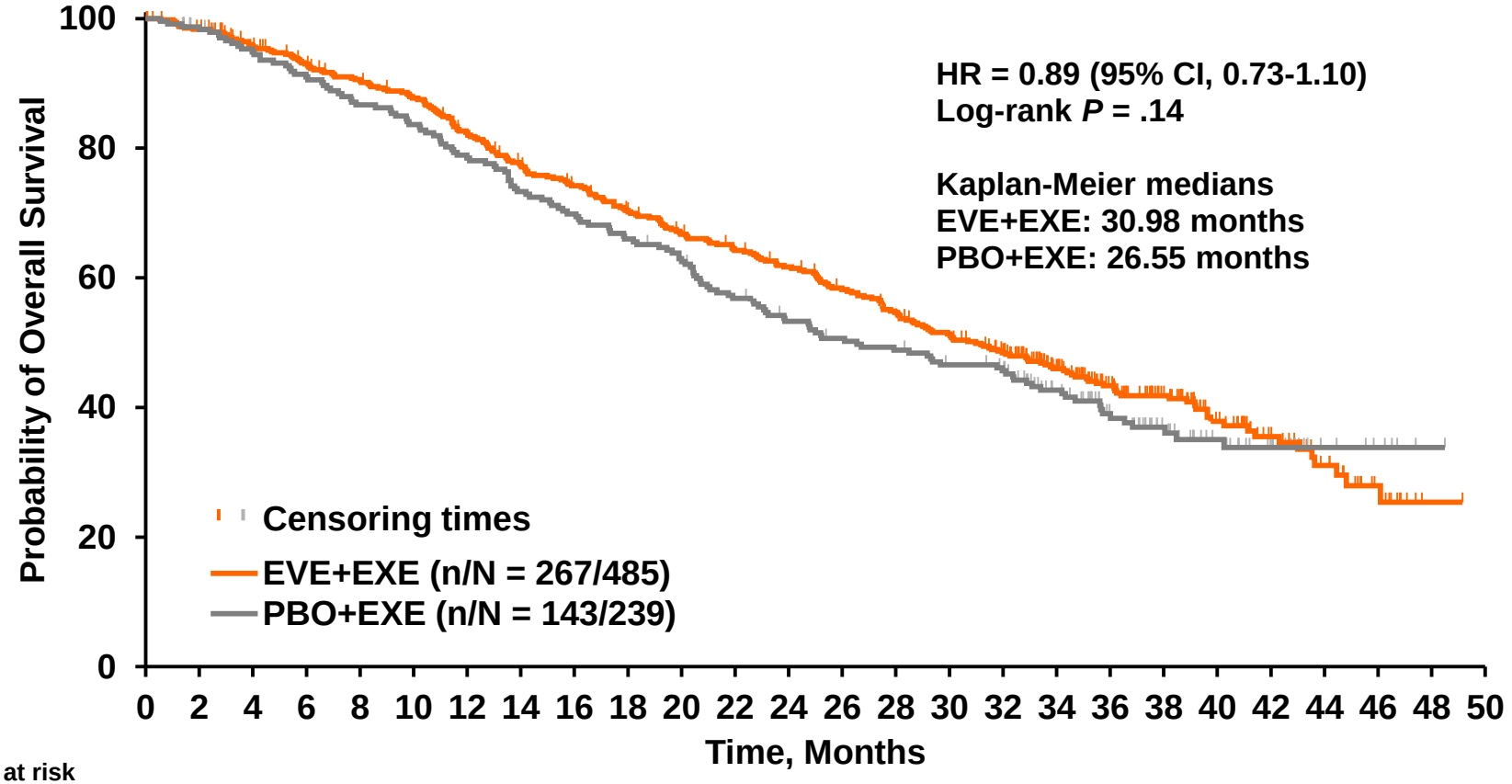
	Everolimus + Exemestane (N = 482), %			Placebo + Exemestane (N = 238), %		
	All Grades	Grade 3	Grade 4	All		4
Stomatitis	56	8			1	0
Fatigue				26	1	0
Dyspn			0	9	1	<1
	18	5	1	4	<1	<1
H ycemia	13	4	<1	2	<1	0
AST	13	3	<1	6	1	0
Pneumonitis	12	3	0	0	0	0

Discontinuation of treatment due to side effects : 19% vs 4%

AE, Adverse Event; AST, Aspartate aminotransferase

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2 (39-mo): Final OS Analysis



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 267 deaths (55%) in the EVE+EXE arm vs 143 deaths (60%) in the PBO+EXE arm

One-sided *P* value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.
CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Piccart M, et al. Presented at: 2014 European Breast Cancer Congress; 19-21 March 2014: Glasgow, Scotland. Abstract LBA1.

Potential Explanations for the Lack of a Survival Benefit in BOLERO-2

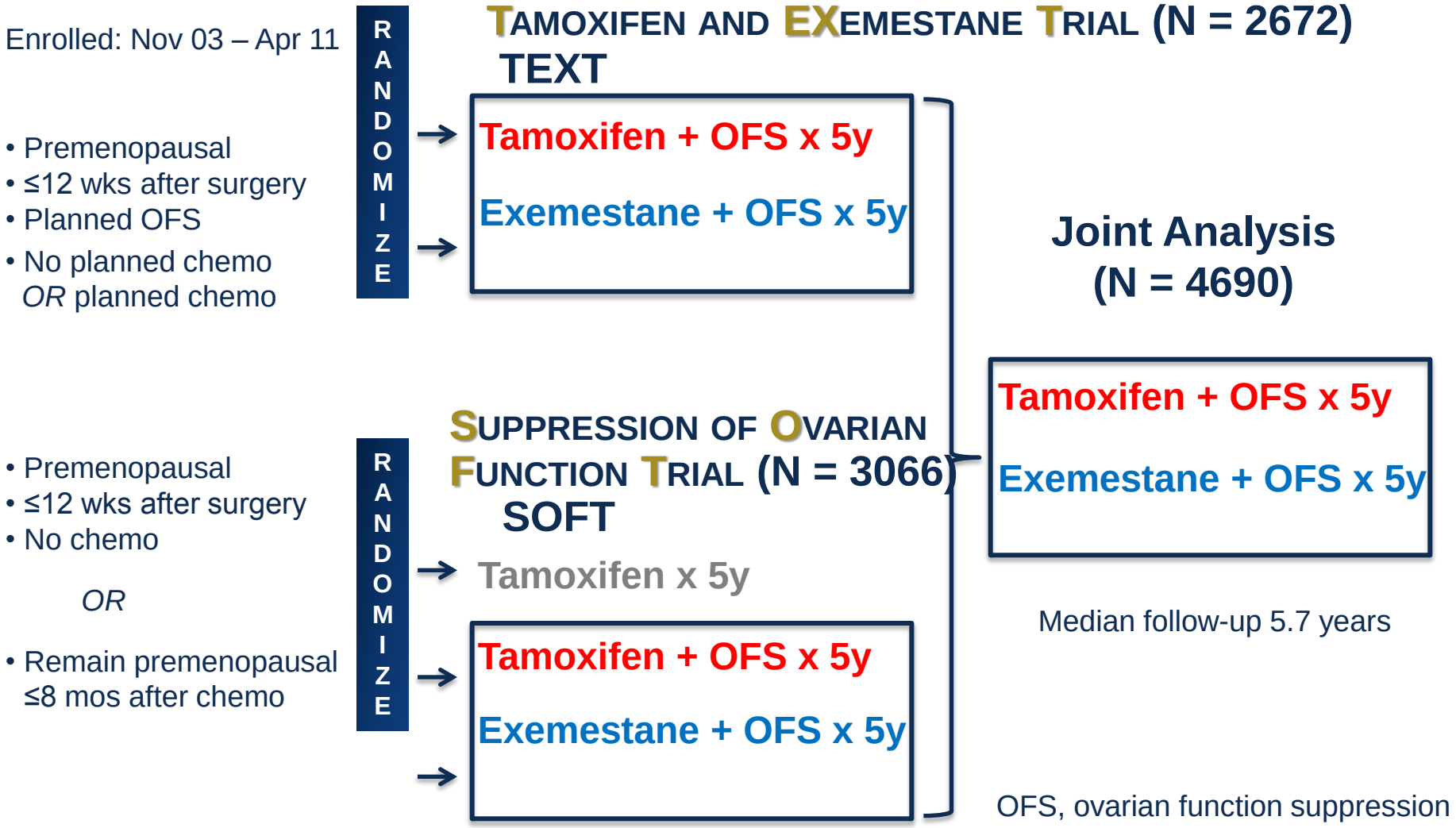
1. **The trial was not powered to detect a realistic OS gain of 4 to 6 months**

2. **A small inbalance in post-study salvage chemotherapy has been identified**

3. **Release of a negative intracellular feedback loop between mTORC-1 and IGF-1 could lead to "paradoxal" AKT activation and a possible impaired response to salvage therapies**

Progress in Endocrine Therapy Strategies for Premenopausal Women

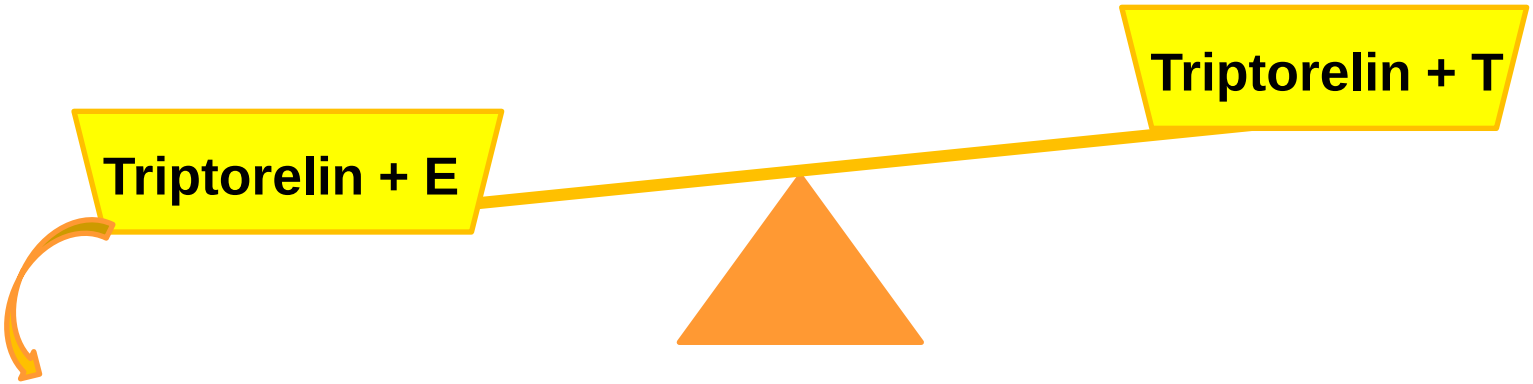
TEXT and SOFT Designs



Pagani O, et al. *J Clin Oncol*. 2014;32(5S): Abstract LBA1.

ASCO 2014 Breast Cancer Highlights

First Results of TEXT/SOFT Combined



	H.R.	
DFS	0.72	All significant
BCFI	0.66	
DDFI	0.78	
OS	1.14	Not (yet ?) significant

… but

Long accrual: 2003-2011
Heterogenous populations
Revised analysis plan needed
Results different from ABCSG12

Goserelin + A vs goserelin + T (3y)
(± zoledronic acid)
DFS HR 1.08 (0.81- 1.44)
OS HR 1.75 (1.08 - 2.83)

Pagani O, et al. *J Clin Oncol*. 2014;32(5S): Abstract LBA1.

First Results of TEXT/SOFT Combined

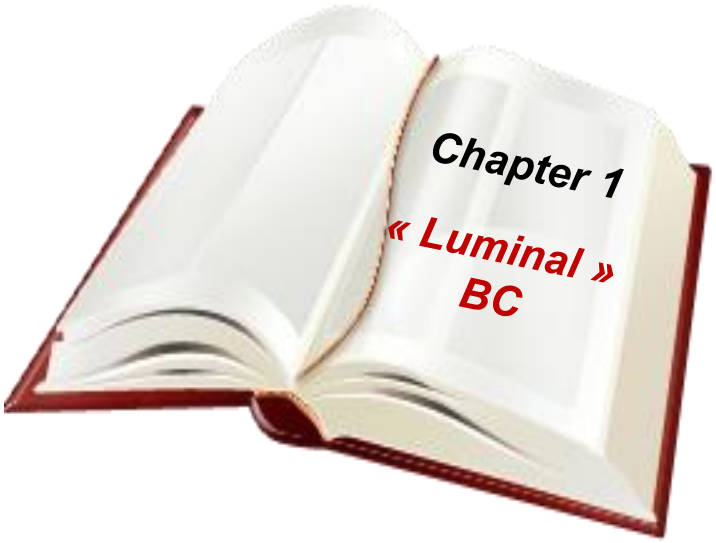
Absolute gain in 5y DFS of 3.8% to be balanced against grade 3 or 4 side effects

	E > T
Musculoskeletal	11% > 5%
Fractures	1.3% > 0.8%
Cardiac ischemia	0.3% > 0.1%
Dyspareunia	2.3% > 1.4%
Discontinuation of therapy	16% > 11%

	T > E
Thromboembolic events	1.9% > 0.8%

Pagani O, et al. *J Clin Oncol*. 2014;32(5S): Abstract LBA1.

Recent Progress in the Management of Breast Cancer



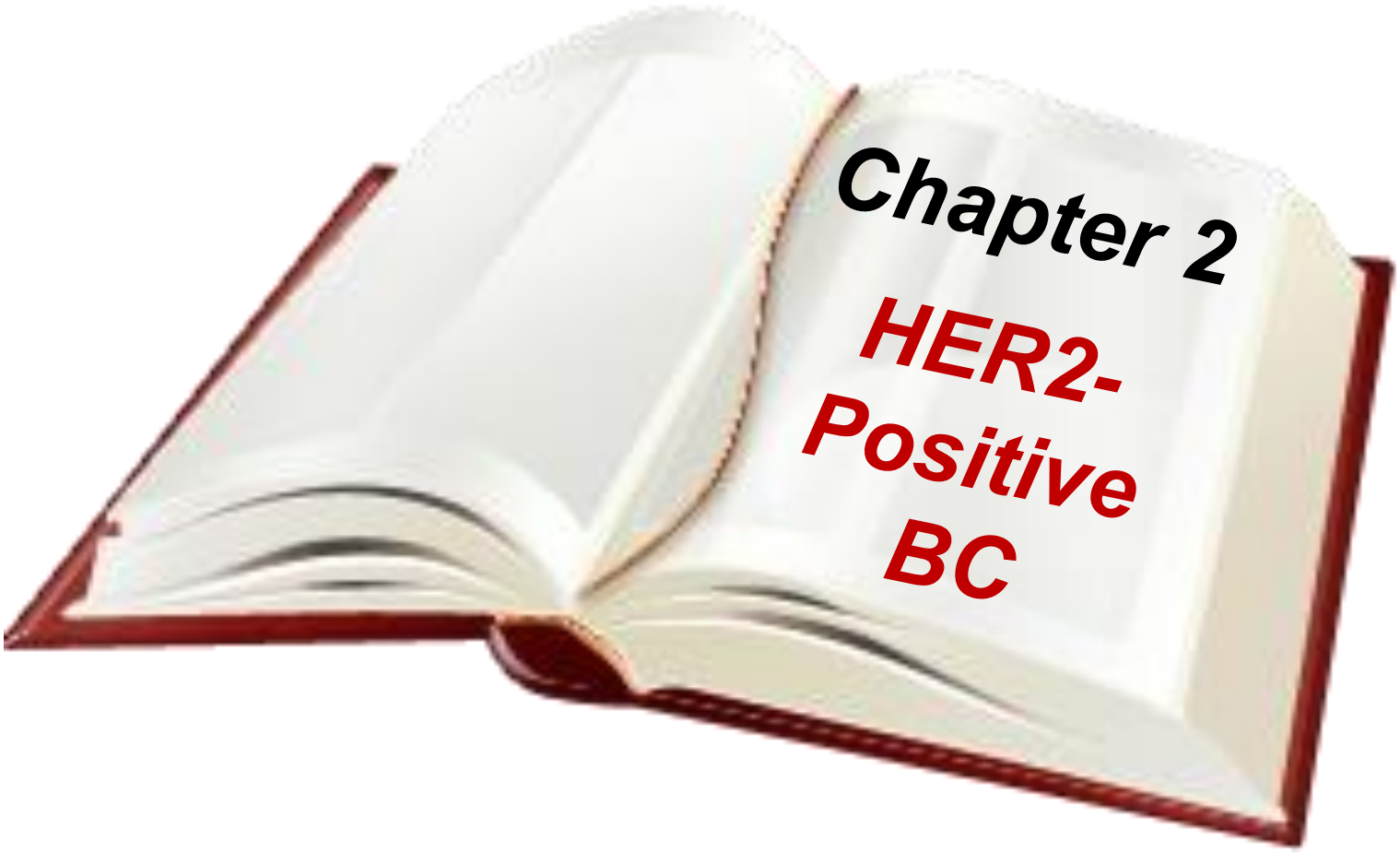
Progress ?

↓

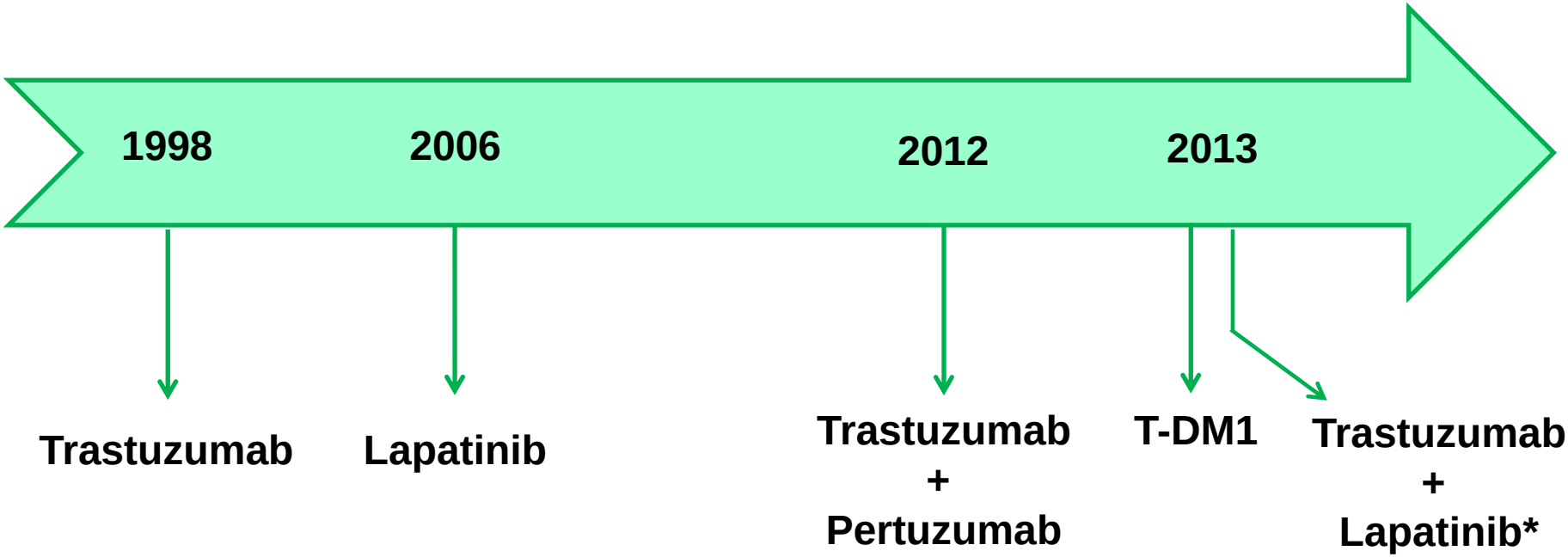
Yes

… but patient's preference will be key given side effects and lack of OS benefit

Recent Progress in the Management of Breast Cancer



Approval of New Drugs for the Treatment of HER2-Positive Metastatic Breast Cancer



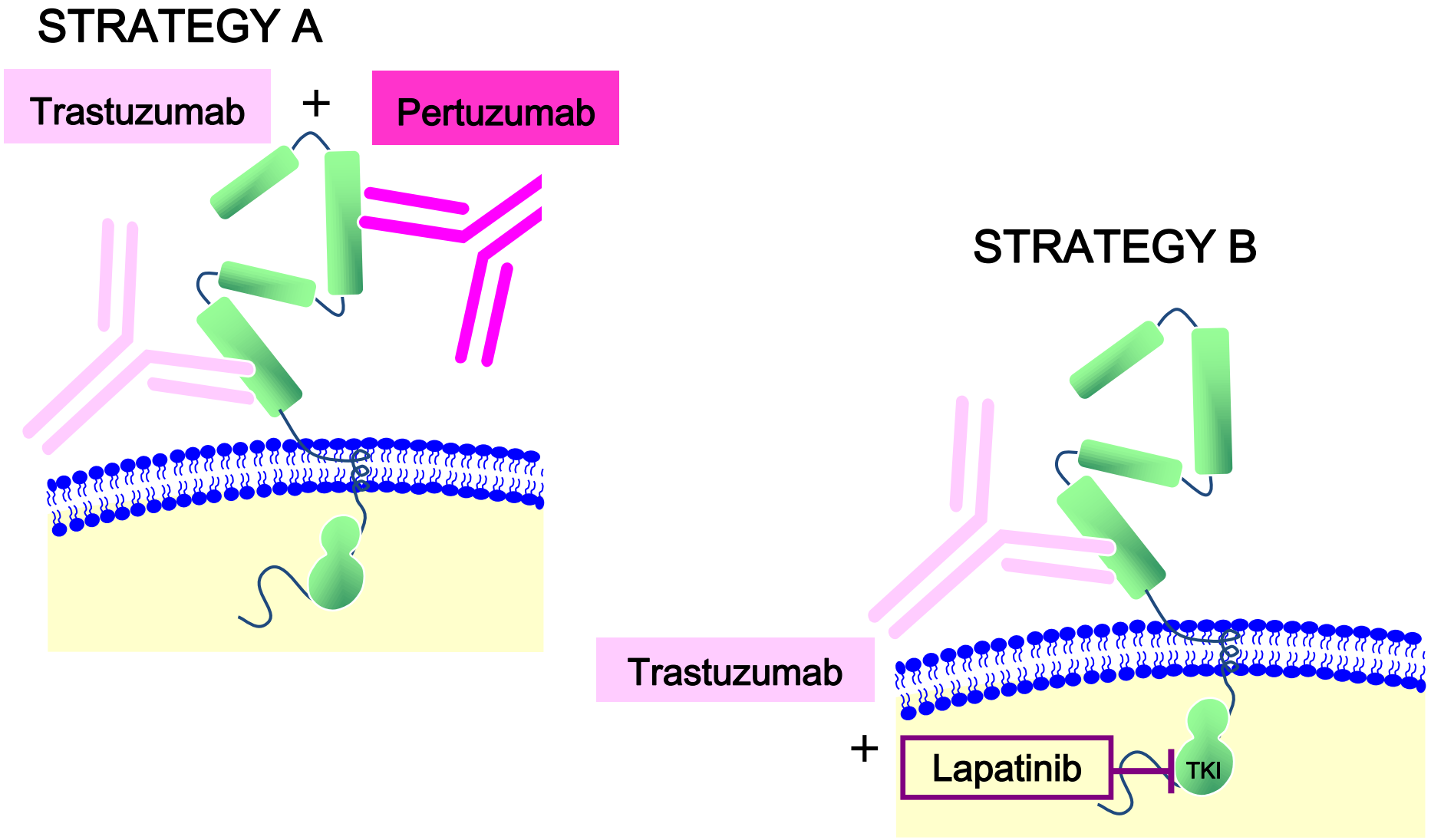
*EU only

Weaknesses of Approved Anti-HER2 Drugs

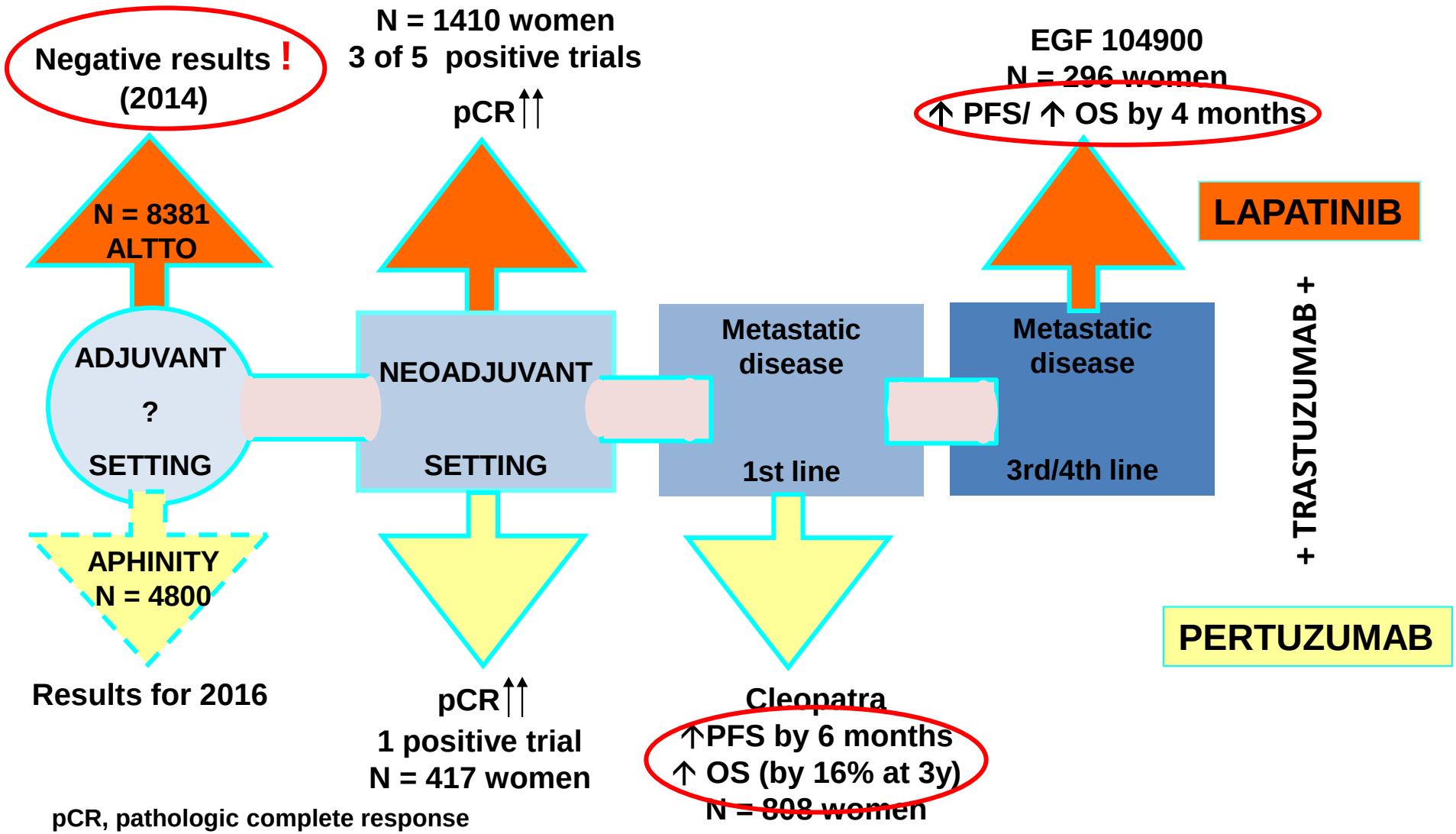
Drugs	WEAKNESSES
Trastuzumab	does not block heregulin-induced HER2-HER3 and HER2-HER4
Pertuzumab	does not block ligand-independent HER2-HER3
Lapatinib	allows "recovery" through HER3
T-DM1	spares HER2- cells within the tumor

Arteaga CL. Presented at: 2013 San Antonio Breast Cancer Conference; December 10-14, 2013; San Antonio, Texas.

Dual HER2 Blockade



Dual HER2 Blockade: Results As of 2014



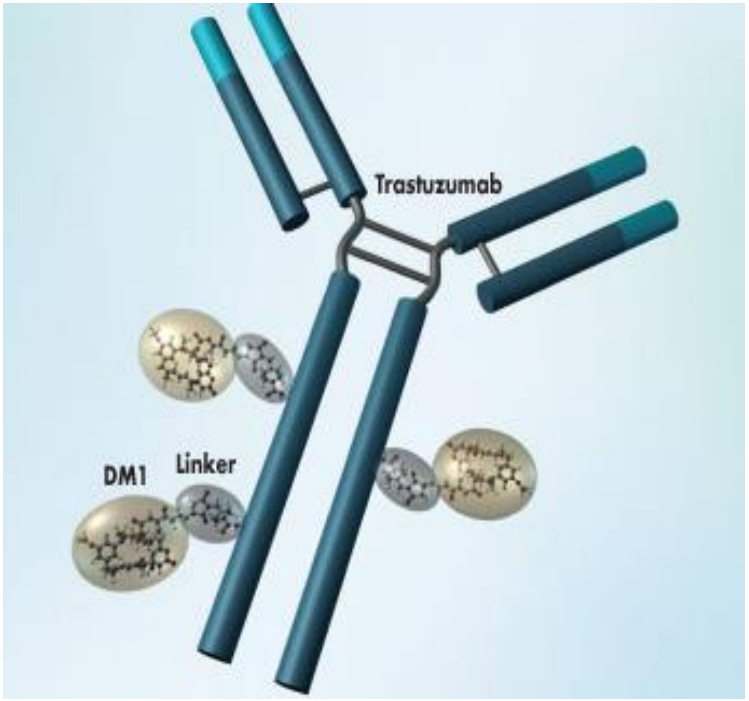
pCR, pathologic complete response

ASCO 2014

Comparison	Assumptions	Result (HR, 97.5% CI, P-value)
L + T vs. T	Test superiority in intention-to-treat (ITT) population at alpha = **0.025**	0.84 (0.70, 1.02), p = **0.048**
T→ L vs. T	Test non-inferiority in per protocol population (PPP) at alpha = **0.025**	0.93 (0.76, 1.13), p = **0.044**

Trastuzumab-DM1 in HER2+ MBC

Trastuzumab-DM1 → **Antibody Drug Conjugate (ADC)**



DM1 — **Maytansine (inhibitor of microtubule assembly)**

- **Potency > vincristine or vinblastine**
- **Maximal exposure of HER2+ tumors**
- **Minimal exposure of normal tissues**
- **Antitumor properties of trastuzumab**

Lewis-Phillips GD, et al. *Cancer Res. 2008;*68(22):9280-9290.

TDM1 Randomized Clinical Trials in Advanced HER2-Positive BC

Current "standard of care" therapies in advanced disease

Taxane + Trastuzumab → Capecitabine + Lapatinib → Other Chemotherapies + Trastuzumab

TDM1 becoming the treatment of choice for all…!

? Superiority of TDM1 or TDM1 + P

Superiority of TDM1

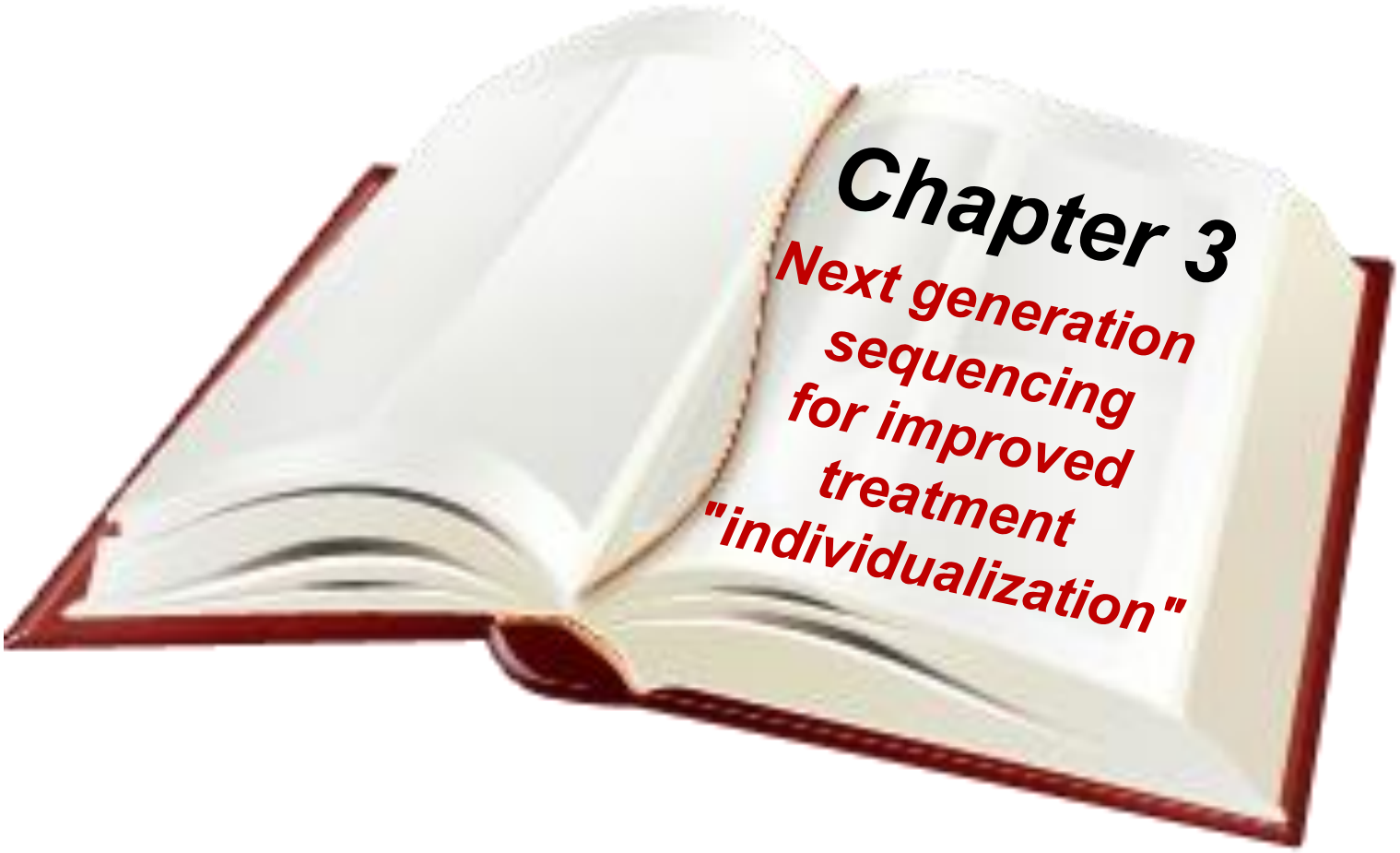
Superiority of TDM1

(MARIANNE study) (EMILIA study) (TH3RESA study)

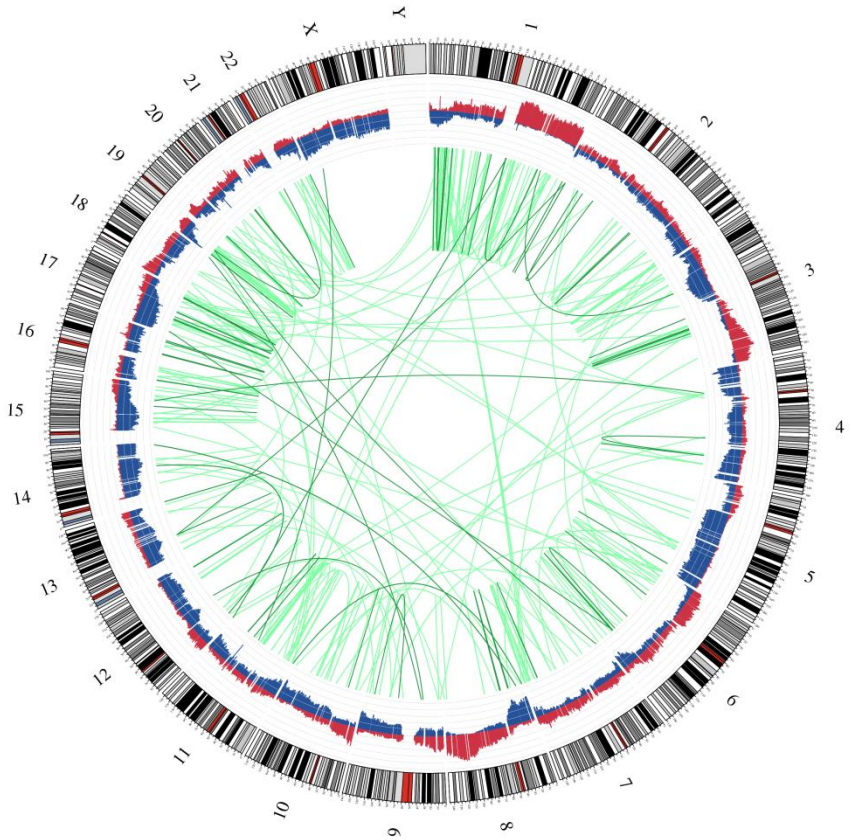
With excellent quality of life!

Side effects: ↑ live function tests, thrombocytopenia

Recent Progress in the Management of Breast Cancer



Directing “Personalized Therapy” on the Basis of “Genetic Tumor Markers”

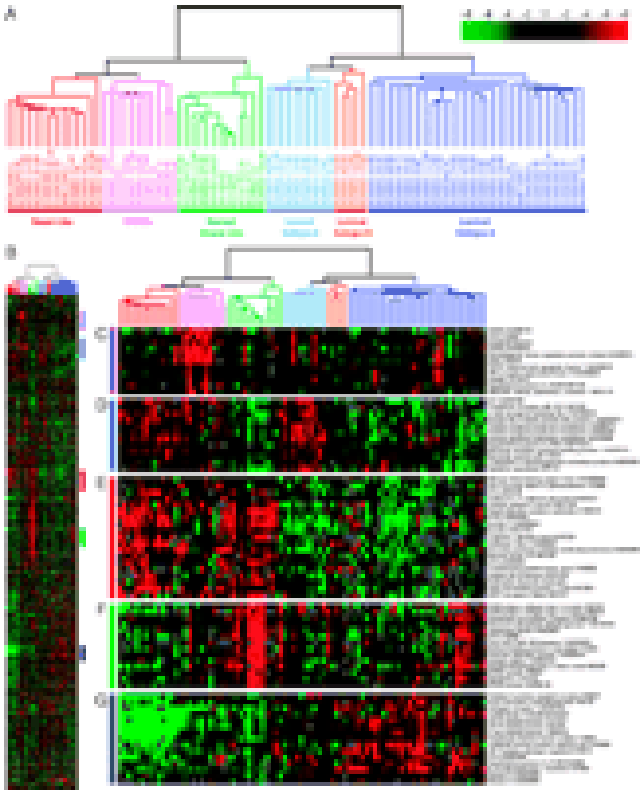


Mutations

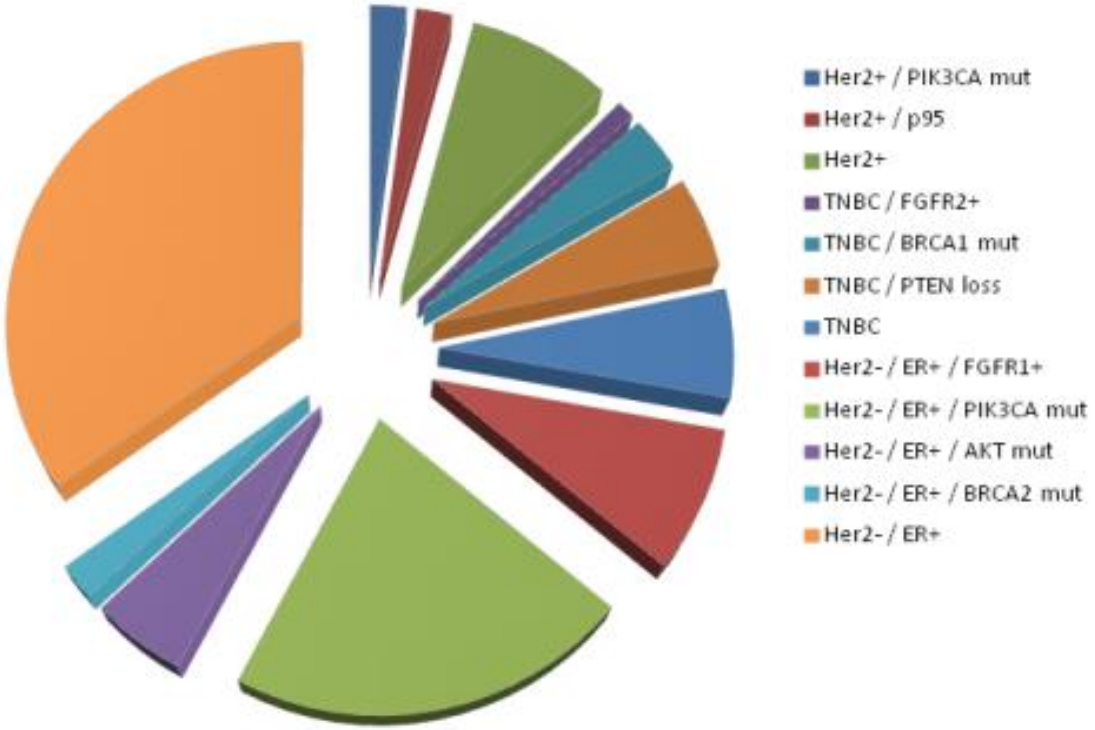
Copy n°changes

Rearrangements

→ **NEXT GEN SEQUENCING**



BC Is a Mixture of Several RARE, "ORPHAN" Molecular Entities



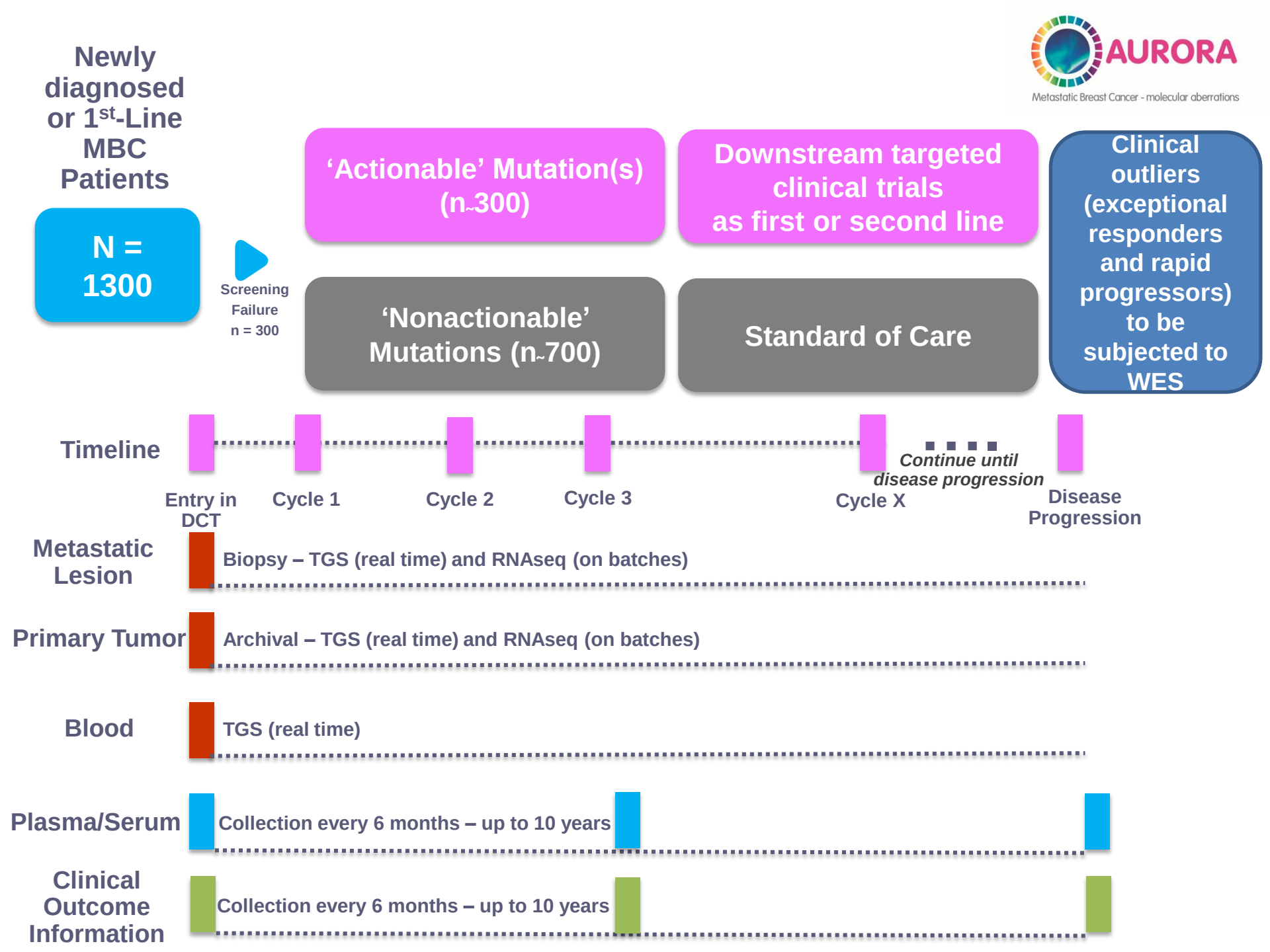
Towards molecular segmentation!

More challenges in identifying a homogenous population

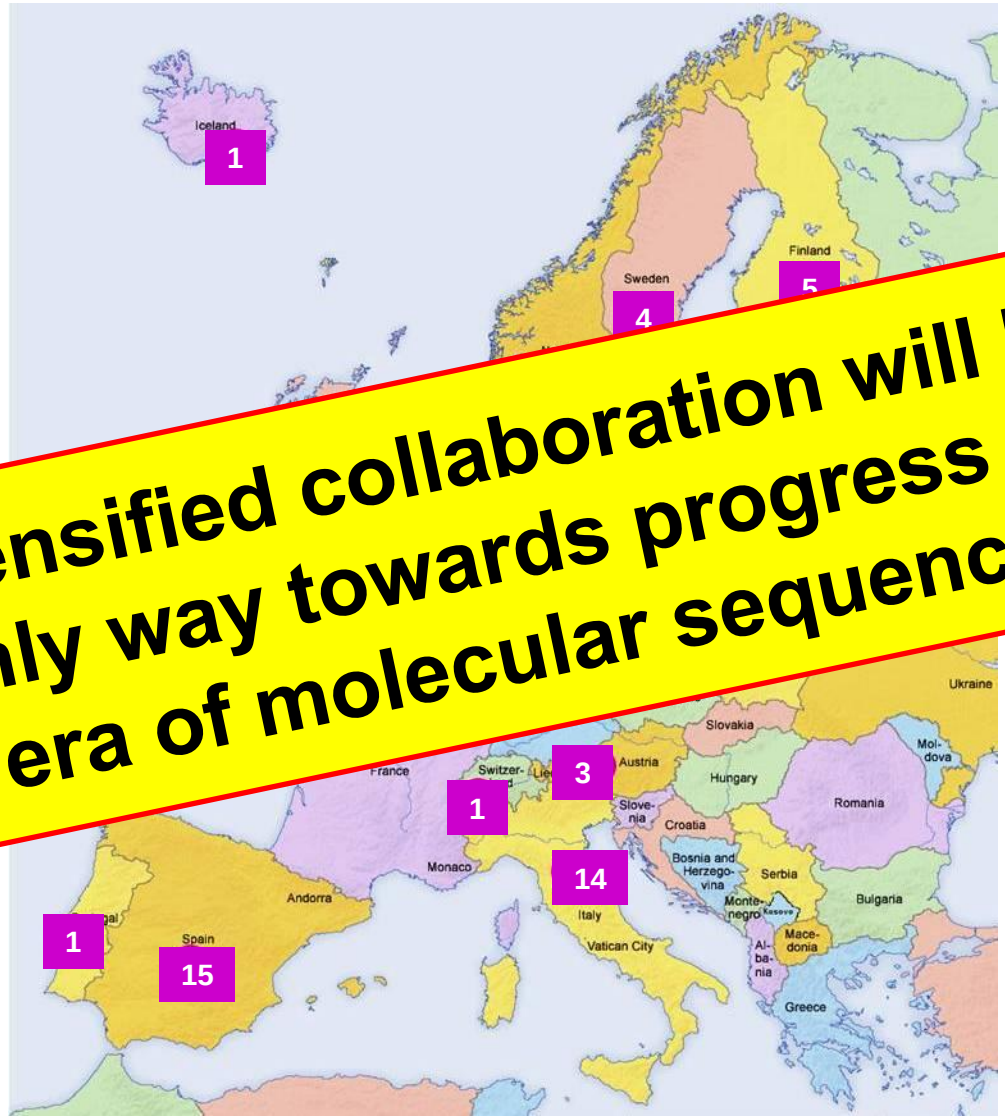
2014-2017
BIG's Program for MBC

The "AURORA initiative for advanced BC"

Goals: build a longitudinal map of the clonal evolution of BC diseases that interrogates the primary tumor as well as the metastases and accelerates new target drug development across Europe


AURORA
Metastatic Breast Cancer - molecular aberrations
Newly diagnosed or 1st-Line MBC Patients
N = 1300
Screening Failure n = 300
'Actionable' Mutation(s) (n~300)
'Nonactionable' Mutations (n~700)
Downstream targeted clinical trials as first or second line
Standard of Care
Clinical outliers (exceptional responders and rapid progressors) to be subjected to WES
Timeline
Entry in DCT
Cycle 1
Cycle 2
Cycle 3
Cycle X
Continue until disease progression
Disease Progression
Metastatic Lesion
Biopsy – TGS (real time) and RNAseq (on batches)
Primary Tumor
Archival – TGS (real time) and RNAseq (on batches)
Blood
TGS (real time)
Plasma/Serum
Collection every 6 months – up to 10 years
Clinical Outcome Information
Collection every 6 months – up to 10 years

Participating Countries in AURORA (N= 15)

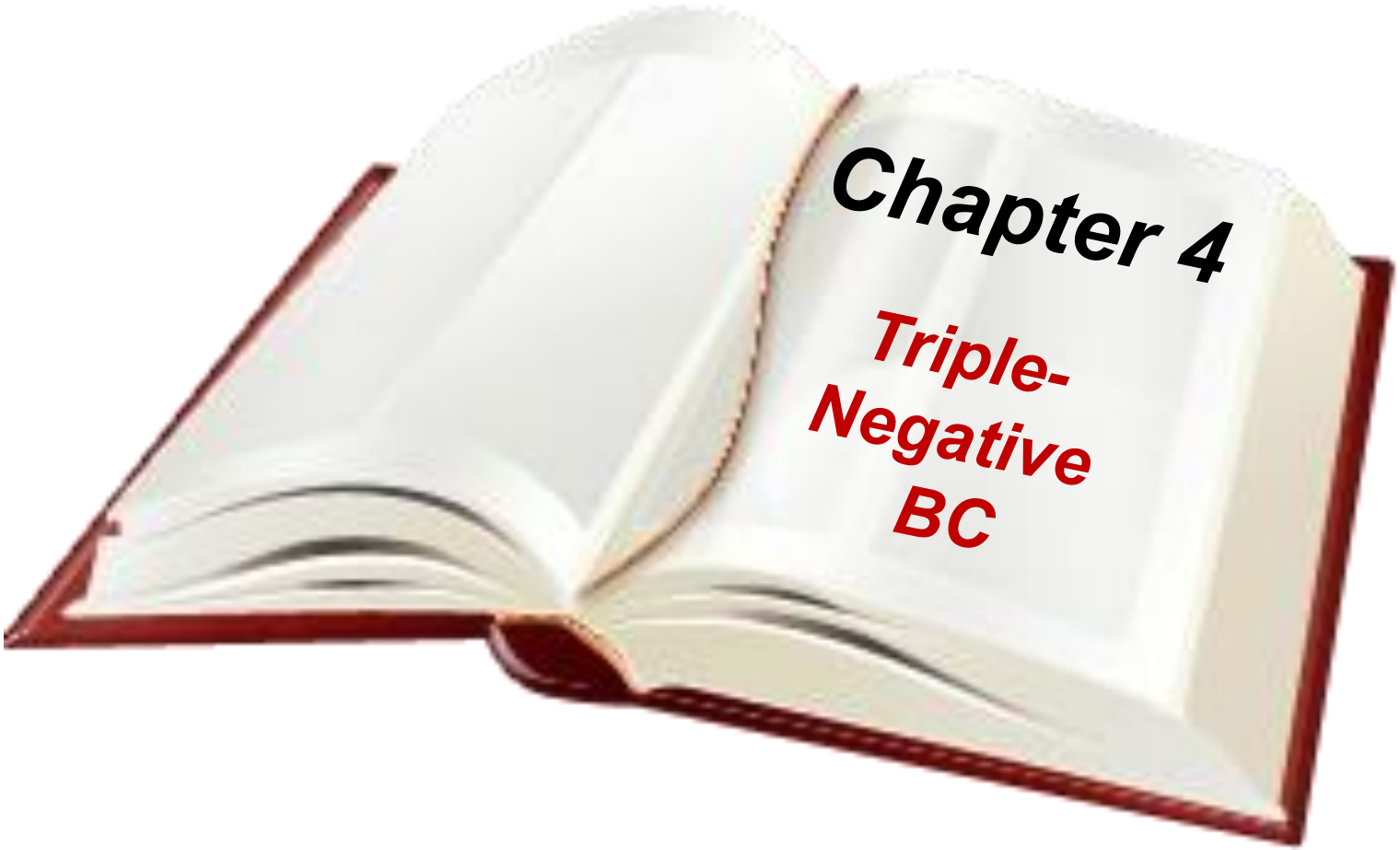


Intensified collaboration will be the only way towards progress in the era of molecular sequencing !

countries

AURORA
Metastatic Breast Cancer - molecular aberrations

Recent Progress in the Management of Breast Cancer



Olaparib Data in Breast Cancer

➢Tutt et al 2010; Ph II monotherapy olaparib in patients with *BRCA1 or BRCA2* mutations and with advanced breast cancer (doses; 100 mg BD or 400 mg BD); Median 3 prior lines of chemotherapy**. ORR for 400 mg BD 41% (11/27)**

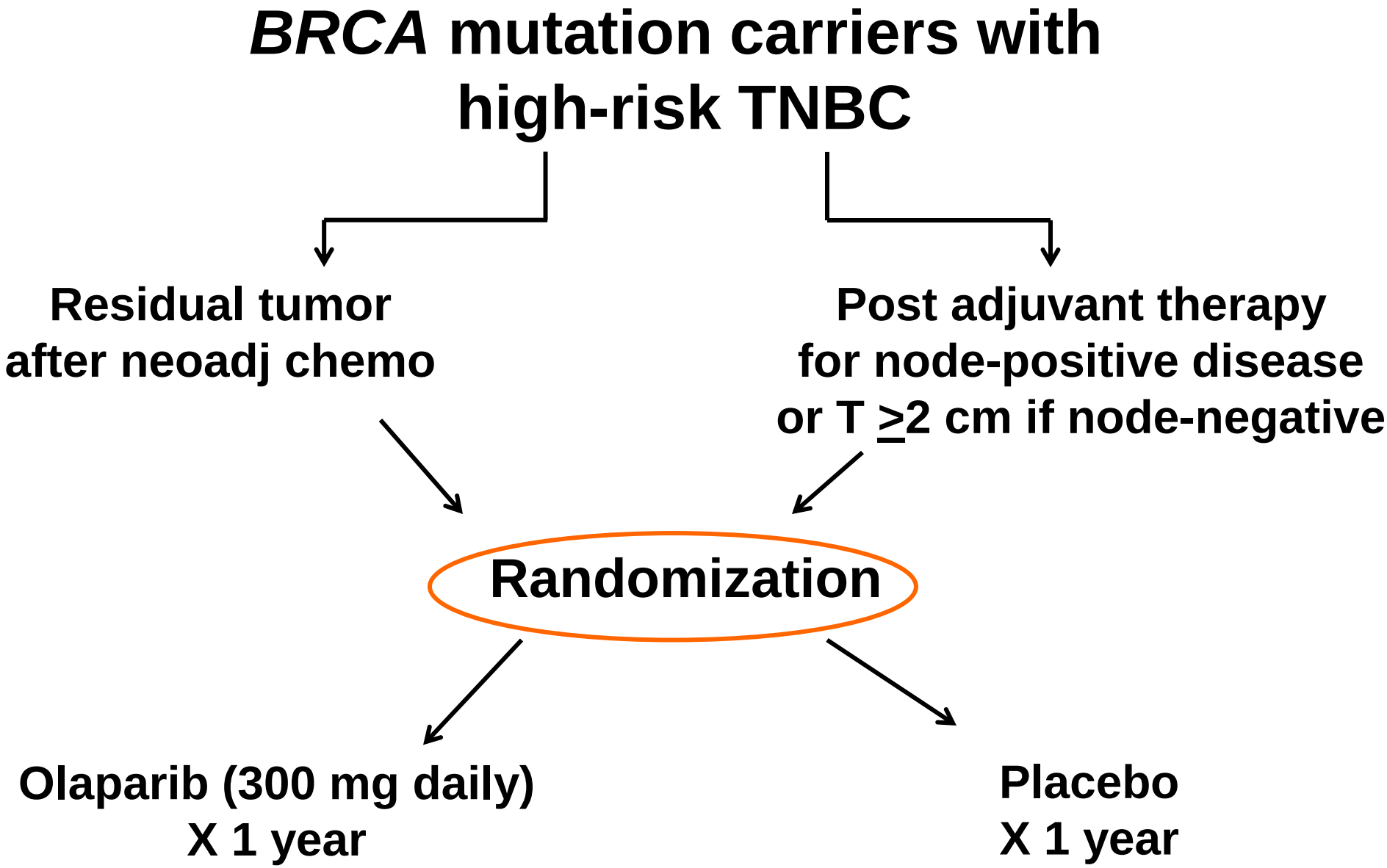
➢Gelmon et al 2011; Ph II monotherapy olaparib in patients with *BRCA1 or BRCA2* mutations and with advanced breast cancer or ovarian cancer (dose 400 mg BD). Median 3 prior lines of chemotherapy overall – breast cancer patient more heavily pretreated. **No RECIST responses for breast cancer patients – 38.5% had SD**

➢Kauffman et al 2013; Ph II monotherapy olaparib in patients (multiple tumors) with *BRCA1 or BRCA2* mutations (dose 400 mg BD). 62 breast cancer patients with median number of 6 prior lines of chemo. **ORR for breast cancer patients = 12.9% (8/62); At 4 mo, disease control in 37% (23/62)**

"OlympiA" is currently open in the adjuvant setting: Olaparib for BRCAg TNBC

This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

Flow Chart - OlympiA Study Design



GRACIAS!

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions