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Advanced Breast Cancer: are there new treatments on the horizon?

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Early breast cancer: Selected recently reported studies with clinical implications

Neoadjuvant

- HER-2 based therapy
- T-DM1 in HER-2+/HR+ disease
- Neoadjuvant therapy in TNBC (bevacizumab; carboplatin)

adjuvant

- Systemic therapy of luminal A disease
- Adjuvant denosumab
- Systemic therapy of stage I HER2+BC
- Outcome of BCIRG-006 trial (TCH) at 10y
- Emerging role of neratinib (TKI)
- Adjuvant capecitabine in patients with residual disease following neoadjuvant therapy (CREATE-X trial)

ADVANCED LUMINAL DISEASE : THERAPEUTIC ALGORITHM AND PERSPECTIVES

Luminal Diseases: Therapeutic Armamentarium in 2016
Clinical practice and advanced clinical research

- Tamoxifen
- NSAI (HER2-) [letrozole ± palbociclib*, anastrozole]
- NSAI (HER2+) [+ trastuzumab or lapatinib]
- Fulvestrant (500 mg) ± palbociclib* (CDK4/6 inhibitor)
- Exemestane ± everolimus (m-TOR inhibitor)
- Fulvestrant ± Buparlisib* (ct DNA PIK3CA mutant group)??

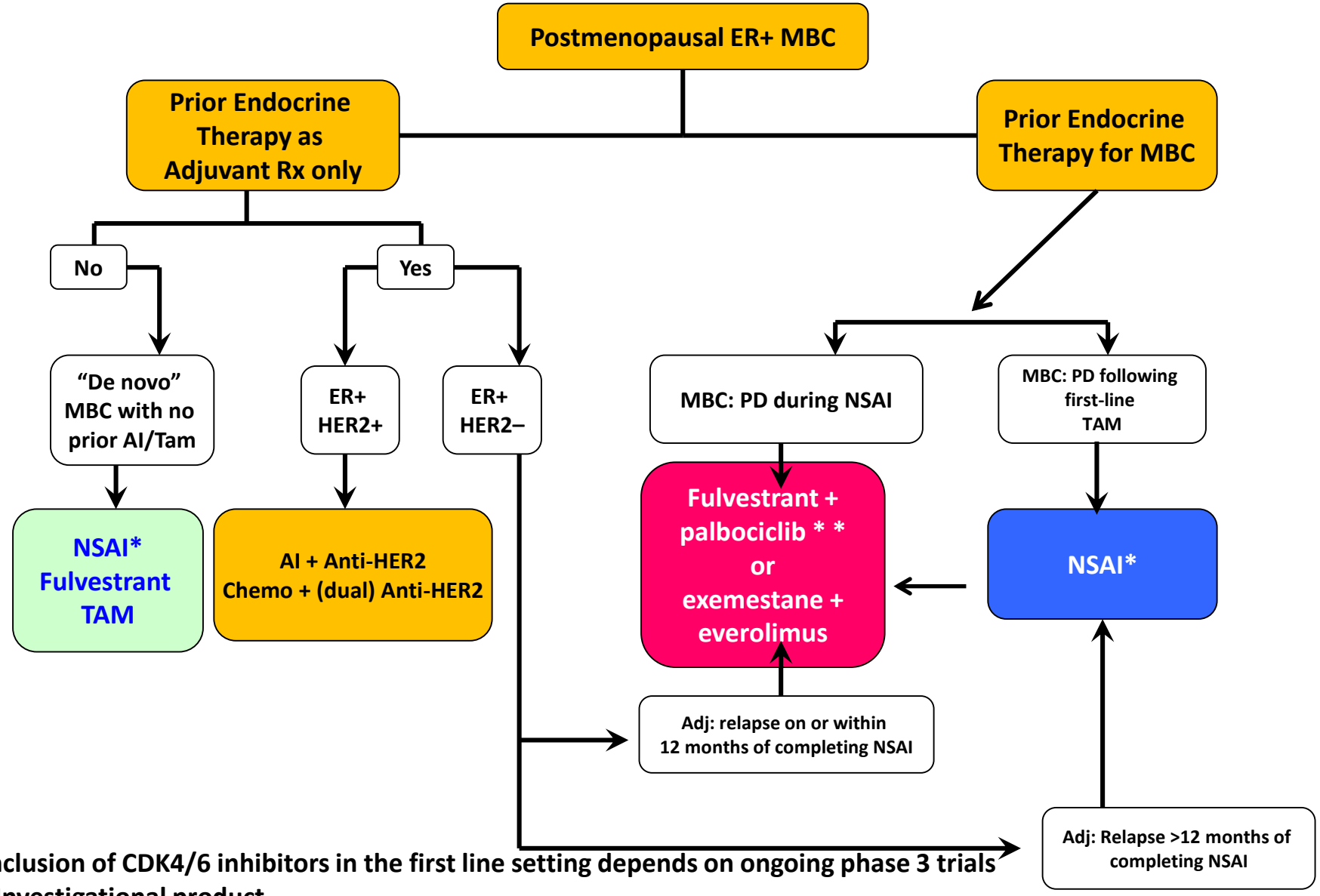
↓ PD

- Chemotherapy

*Investigational compound.

Several CDK4/ inhibitors are under active clinical investigation

Proposed Therapeutic Algorithm for Luminal Subtype after ASCO 2015 (A. Awada)



*Inclusion of CDK4/6 inhibitors in the first line setting depends on ongoing phase 3 trials

**Investigational product

NSAI: Letrozole or anastrozole according to the previous NSAI.

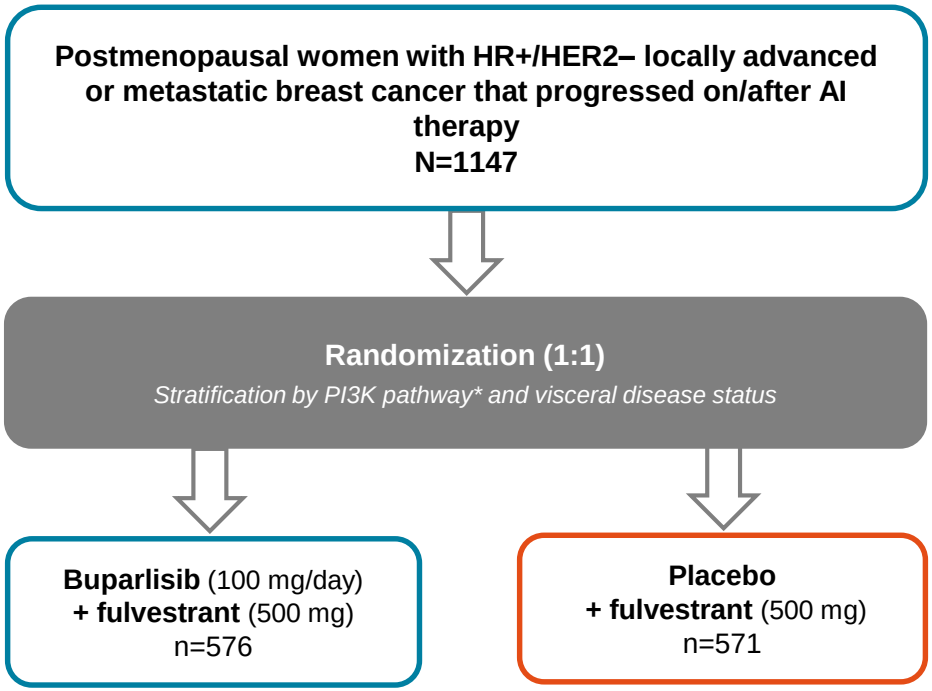
PERSPECTIVES

PIK3CA Status in Circulating Tumor DNA Predicts Efficacy of Buparlisib Plus Fulvestrant in Postmenopausal Women With Endocrine-resistant HR+/HER2– Advanced Breast Cancer: First Results From the Randomized, Phase III BELLE-2 Trial

José Baselga,[1] Seock-Ah Im,[2] Hiroji Iwata,[3] Mark Clemons,[4] Yoshinori Ito,[5] Ahmad Awada,[6] Stephen Chia,[7] Agnieszka Jagiełło-Gruszfeld,[8] Barbara Pistilli,[9] Ling-Ming Tseng,[10] Sara Hurvitz,[11] Norikazu Masuda,[12] Javier Cortés,[13] Michele De Laurentiis,[14] Carlos L. Arteaga,[15] Zefei Jiang,[16] Walter Jonat,[17] Soulef Hachemi,[18] Sylvie Le Mouhaër,[18] Emmanuelle Di Tomaso,[19] Patrick Urban,[20] Cristian Massacesi,[18] Mario Campone[21]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Aichi Cancer Center, Nagoya, Japan; [4]Ottawa Hospital Research Institute, Ottawa, Canada; [5]Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Institut Jules Bordet, Brussels, Belgium; [7]BC Cancer Agency, Vancouver, Canada; [8]Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology (MCMCC), Warsaw, Poland; [9]Ospedale di Macerata, Macerata, Italy; [10]Taipei Veterans General Hospital, Taipei, Taiwan; [11]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [12]National Hospital Organization Osaka National Hospital, Osaka, Japan; [13]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [14]Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [15]Vanderbilt-Ingram Cancer Center, Nashville, TN; [16]Beijing 307 Hospital of PLA, Beijing, China; [17]University Hospital Schleswig-Holstein, Kiel, Germany; [18]Novartis Pharma S.A.S., Paris, France; [19]Novartis Institutes for BioMedical Research, Cambridge, MA; [20]Novartis Pharma AG, Basel, Switzerland; [21]Institut de Cancérologie de l'Ouest – René Gauducheau Centre de Recherche en Cancérologie, Nantes, France

BELLE-2 Study Design and Endpoints



Primary Endpoints

- **PFS** in the main population (PI3K activated and non-activated, excluding status unknown*)
- **PFS** in the PI3K activated group* (*PIK3CA* mutation and/or PTEN loss in archival tissue)
- **PFS** in the full population (local assessment)

Key Secondary Endpoint

- **Overall survival**

Other Secondary Endpoints

- **Overall response rate**
- **Clinical benefit rate**
- **Safety, pharmacokinetics, quality of life**

Exploratory Endpoint

- **PFS** by ctDNA *PIK3CA* mutation status†

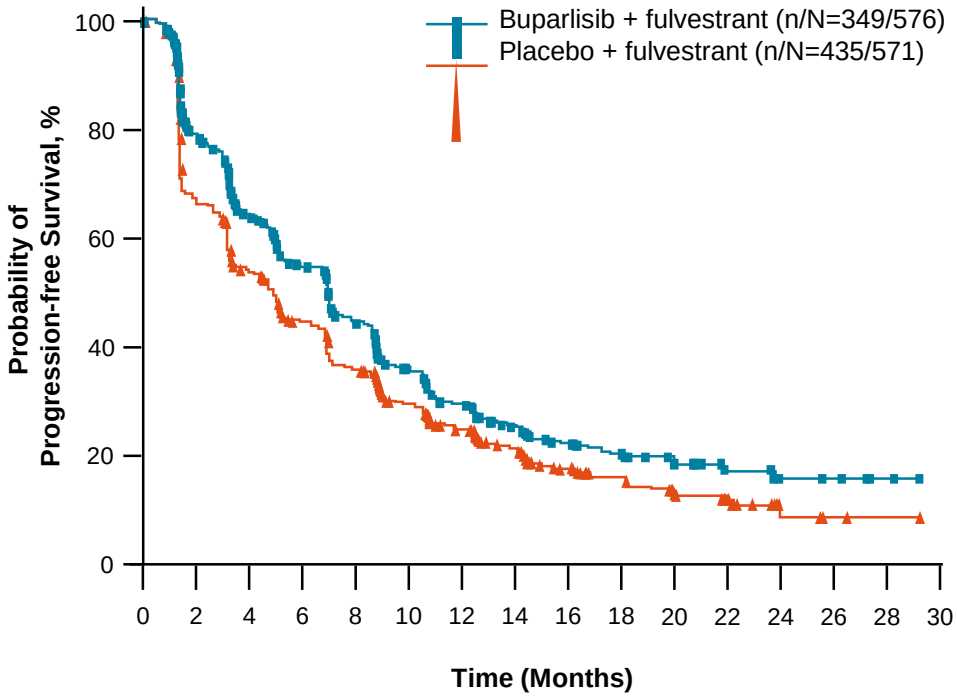
BELLE-2 Safety Profile Was Characterized by Hyperglycemia, Transaminitis, Rash, and Mood Disorders

	Buparlisib + Fulvestrant n=573			Placebo + Fulvestrant n=570		
Adverse event, %	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Total	**99.5**	**63.2**	**14.1**	**93.0**	**27.4**	**4.6**
Increased ALT	40.1	18.7	6.8	6.8	1.1	0
Increased AST	37.3	15.0	3.0	9.3	2.8	0
Hyperglycemia	43.1	15.2	0.2	7.7	0.2	0
Rash	32.1	7.7	0.2	6.3	0	0
Anxiety	22.3	5.2	0.2	8.2	0.9	0
Fatigue	31.9	4.9	0	23.9	1.6	0
Depression	26.2	3.7	0.7	8.9	0.4	0
Diarrhea	34.2	3.7	0	14.6	1.1	0
Asthenia	20.1	2.8	0	10.5	1.1	0
Stomatitis	21.6	2.1	0	6.5	0.5	0
Nausea	38.7	1.7	0	23.2	1.4	0
Decreased appetite	29.8	1.6	0	11.1	0.2	0

- **Serious adverse events occurred in 23.4% of patients in the buparlisib arm vs 15.8% in the placebo arm**
- **12 on-treatment deaths (2.1%) were reported in each arm in the full population, the majority due to disease progression**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

BELLE-2 Met the Primary Endpoint for Statistically Significant PFS Improvement (Δ 1,9 mo)



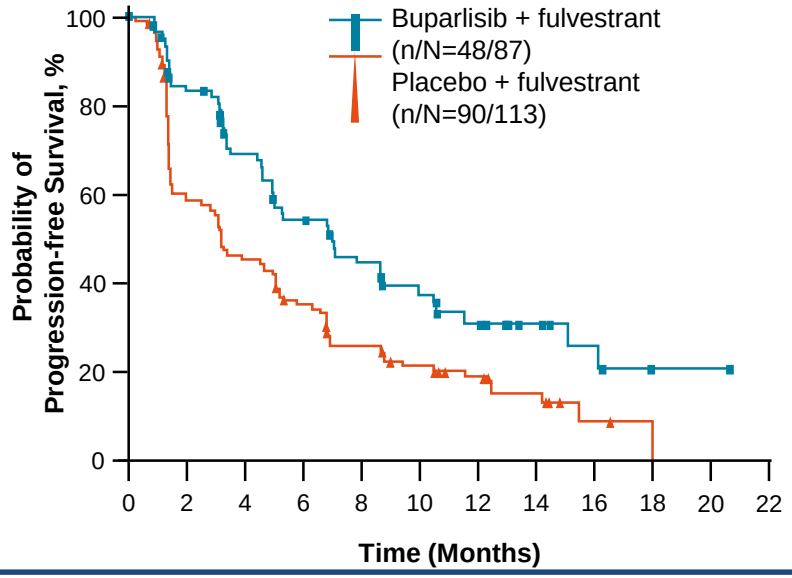
Full Population (N=1047)	Buparlisib + Fulvestrant n=576	Placebo + Fulvestrant n=571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided *P* value	<0.001	

- **Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population**
  - **At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm**

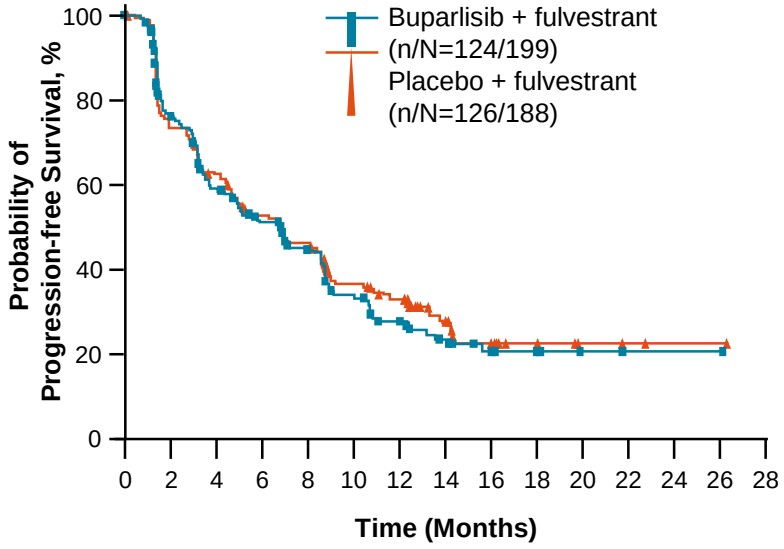
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Buparlisib and Fulvestrant Produced a Clinically Meaningful PFS Improvement (Δ 3,8 months) in Patients With ctDNA PIK3CA Mutations

ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	



ctDNA *PIK3CA* Non-mutant n=387	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	0.642	

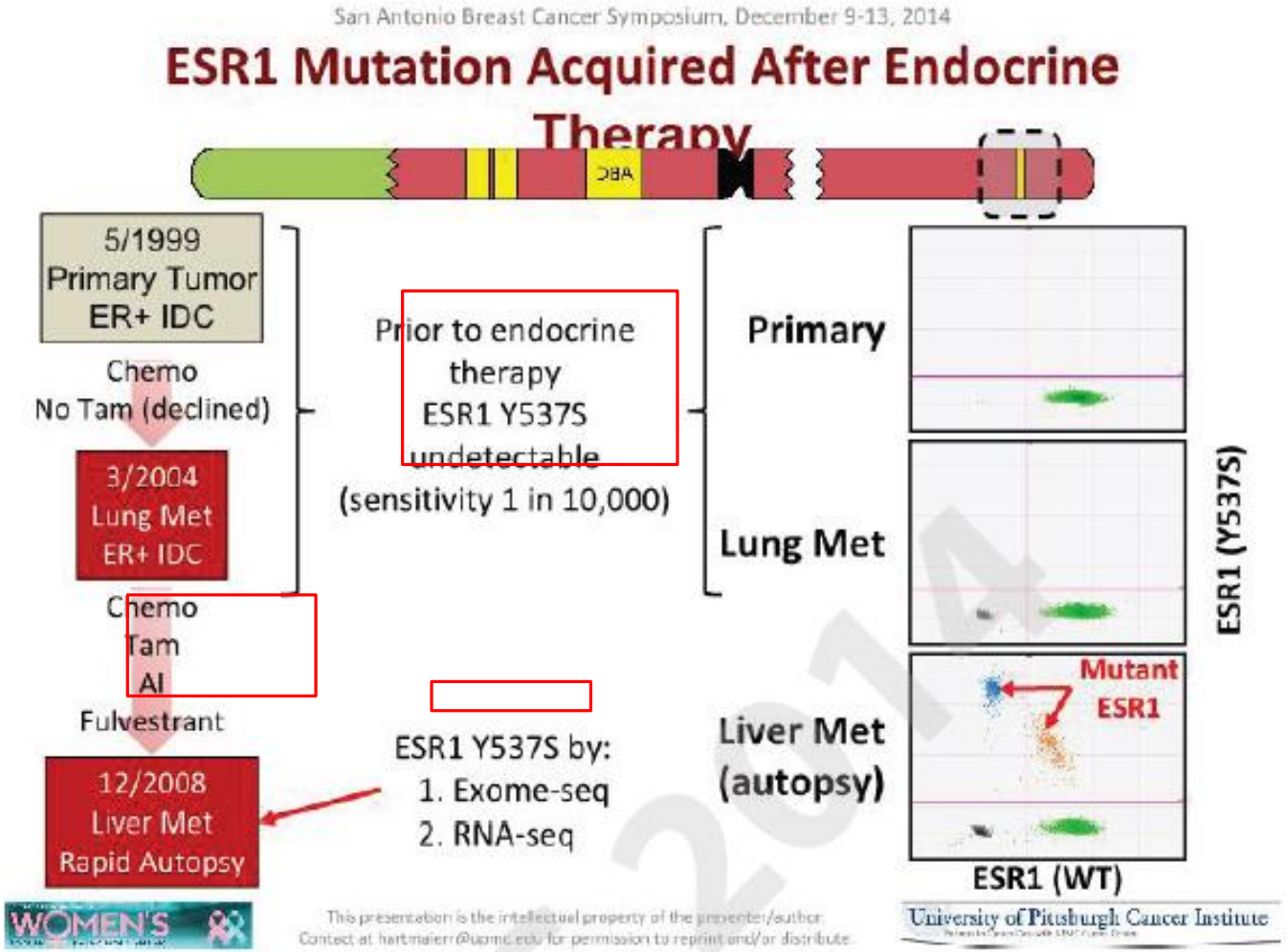


CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

Buparlisib and Fulvestrant Resulted in Higher Response Rates in the ctDNA PIK3CA Mutant Group

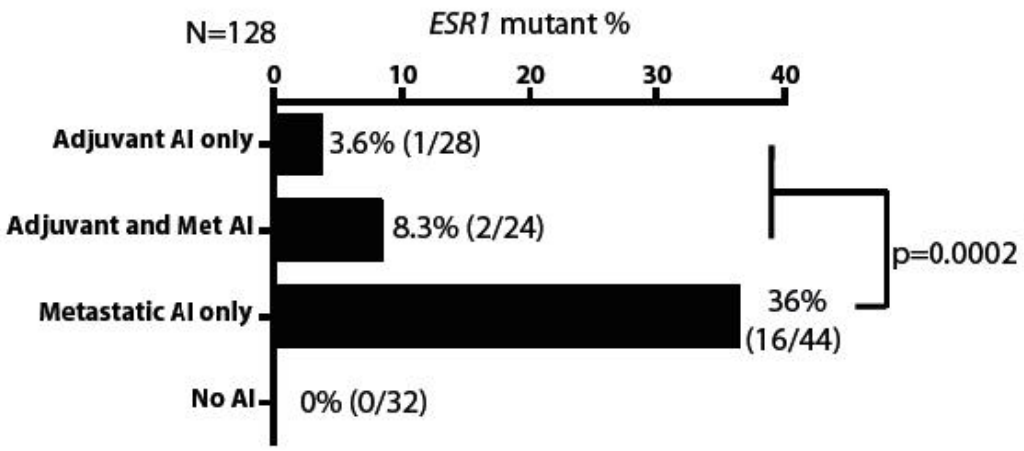
Efficacy Endpoint	*PIK3CA* Mutant (ctDNA)		*PIK3CA* Non-mutant (ctDNA)		PI3K Pathway Activated (Archival Tissue)	
	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188	Buparlisib + Fulvestrant n=188	Placebo + Fulvestrant n=184
ORR,* % (95% CI)	**18.4 (10.9–28.1)**	**3.5 (1.0–8.8)**	11.6 (7.5–16.8)	10.6 (6.6–16.0)	10.6 (6.6–16.0)	8.2 (4.6–13.1)
CBR,† % (95% CI)	**47.1 (36.3–58.1)**	**31.9 (23.4–41.3)**	42.7 (35.7–49.9)	50.0 (42.6–57.4)	40.4 (33.3–47.8)	40.8 (33.6–48.2)

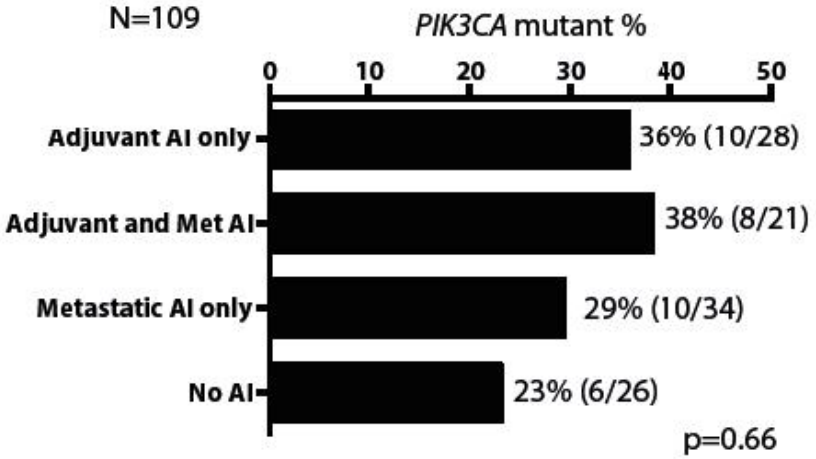
ESR1 Y537S mutation is undetectable in primary and metastatic disease before endocrine therapy



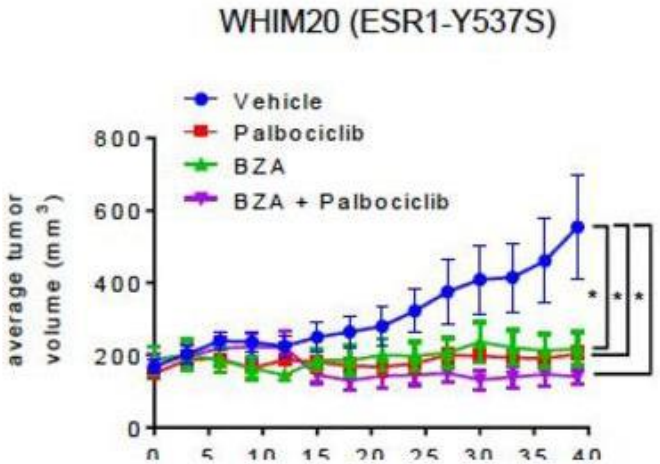
ESR1 mutations in metastatic AI resistant breast cancer

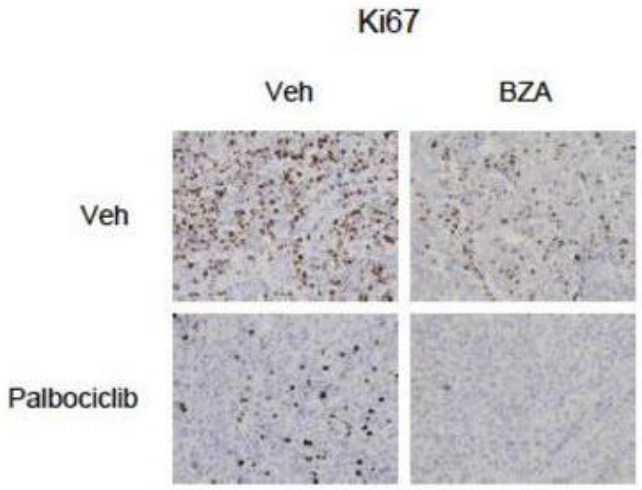
Timing of therapy influences evolution

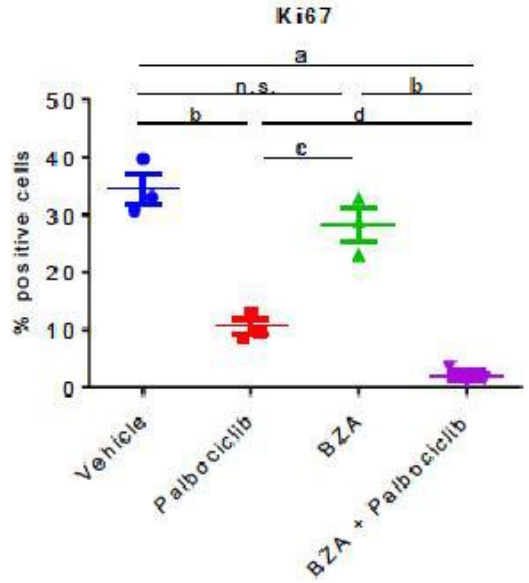




Antitumor activity of palbociclib and bazedoxifene in an ESR1-Y5375 mutant PDX







CDK 4/6 inhibitor Palbociclib and Bazedoxifene in an ESR1 mutant PDX

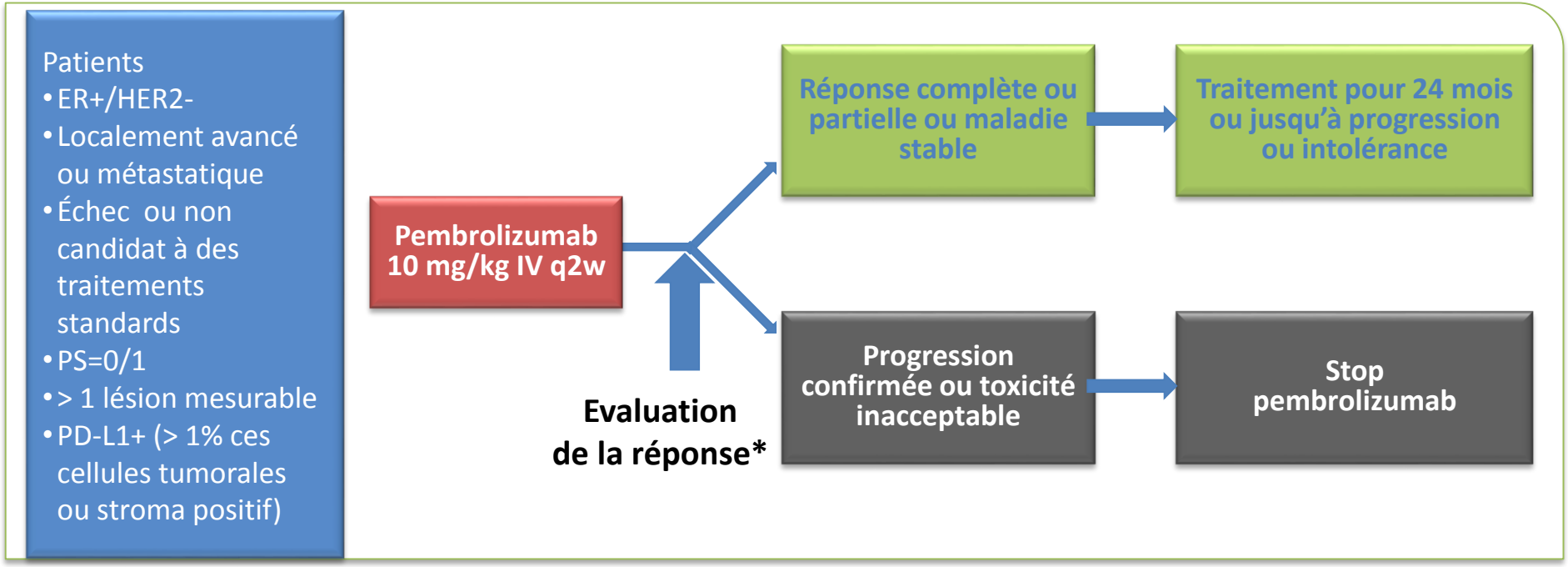
Wardell, Ellis et al Clin Cancer Res. 2015 May 19. pii: clincanres.0360.2015

PRELIMINARY EFFICACY AND SAFETY OF PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH PD-L1–POSITIVE, ESTROGEN RECEPTOR-POSITIVE (ER+)/HER2-NEGATIVE ADVANCED BREAST CANCER ENROLLED IN KEYNOTE-028

RUGO HS ET AL. SABCS 2015 – S5-07

KEYNOTE-028 : pembrolizumab et cancer du sein RE+/HER2-

- **Design**



- **261 inclus - 248 analysés – 48 positifs pour PD-L1 - 25 traités**

*Evaluation de la réponse : toutes les 8 semaines pour les 6 premiers mois ; puis toutes les 12 semaines

Critère de jugement principal : taux de réponse globale (RECIST v1.1) et sécurité

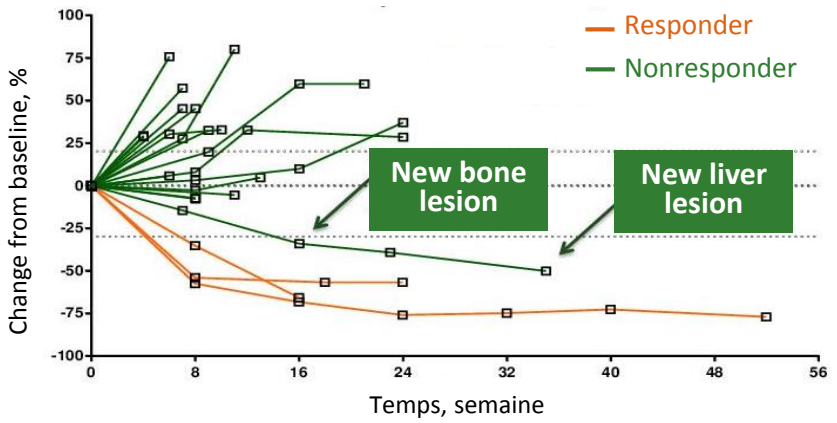
Critères de jugement secondaires : PFS, OS, durée de réponse

KEYNOTE-028 : pembrolizumab et cancer du sein RE+/HER2-

- **Activité anti-tumorale (RECIST 1.1)**

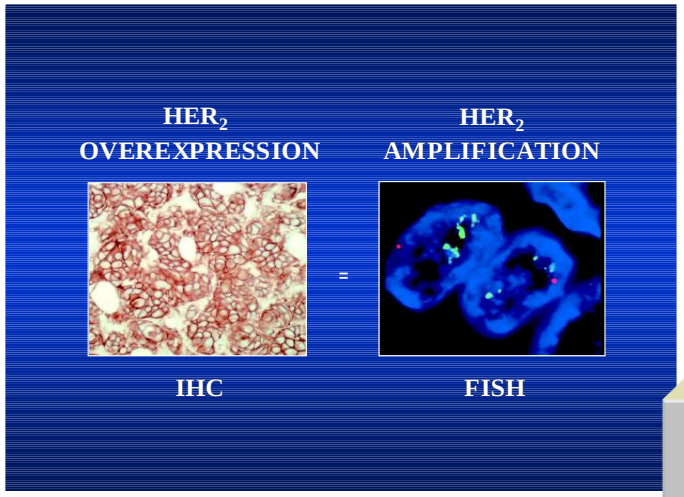
	n (%)	95% CI
Taux de réponse global	3 (12,0)	2,5 – 31,2
Réponse complète	0 (0,0)	0,0 – 13,7
Réponse partielle	3 (12,0)	2,5 – 31,2
Maladie stable	4 (16,0)	4,5 – 36,1
Bénéfice clinique	5 (20,0)	6,8 – 40,7
Maladie progressive	15 (60,0)	38,7 – 78,9
NE	3 (12,0)	2,5 – 31,2

Les réponses sont peu fréquentes mais semblent durables !



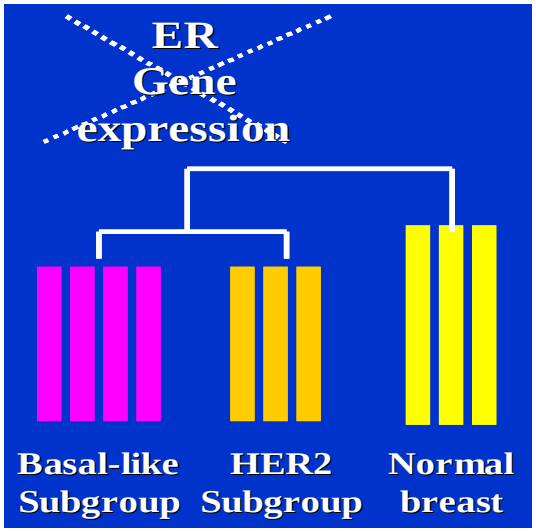
ADVANCED HER-2 DISEASE : THERAPEUTIC ALGORITHM AND PERSPECTIVES

HER2 POSITIF ADVANCED BREAST CANCER: TOWARDS A CURE?!



A SEPARATE DISEASE ENTITY!

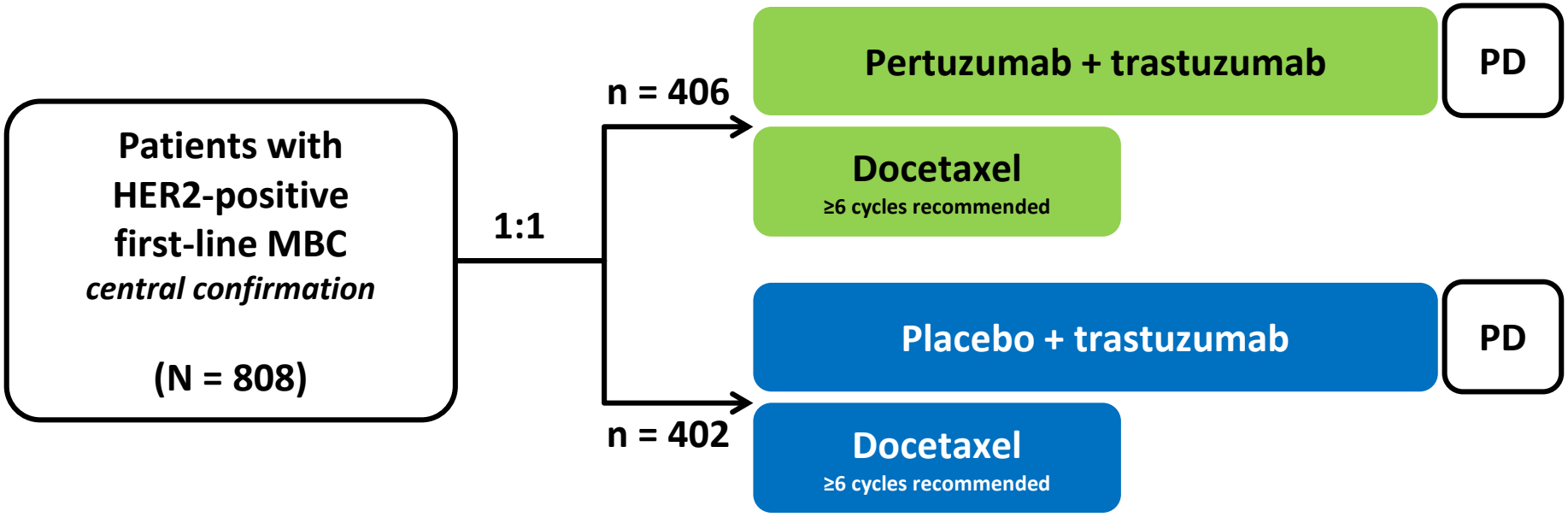
NEW TREATMENT APPROACHES



- **Trastuzumab in combination with cytotoxics or hormonal agents**
- **Lapatinib, trastuzumab-DM1, pertuzumab**
- **Dual HER2 inhibition + cytotoxics**
- **What's next? (neratinib? HER-2-TDB?)***

*Investigational compound

Phase III CLEOPATRA Trial: Docetaxel + Trastuzumab ± Pertuzumab in HER2-Positive First-Line MBC



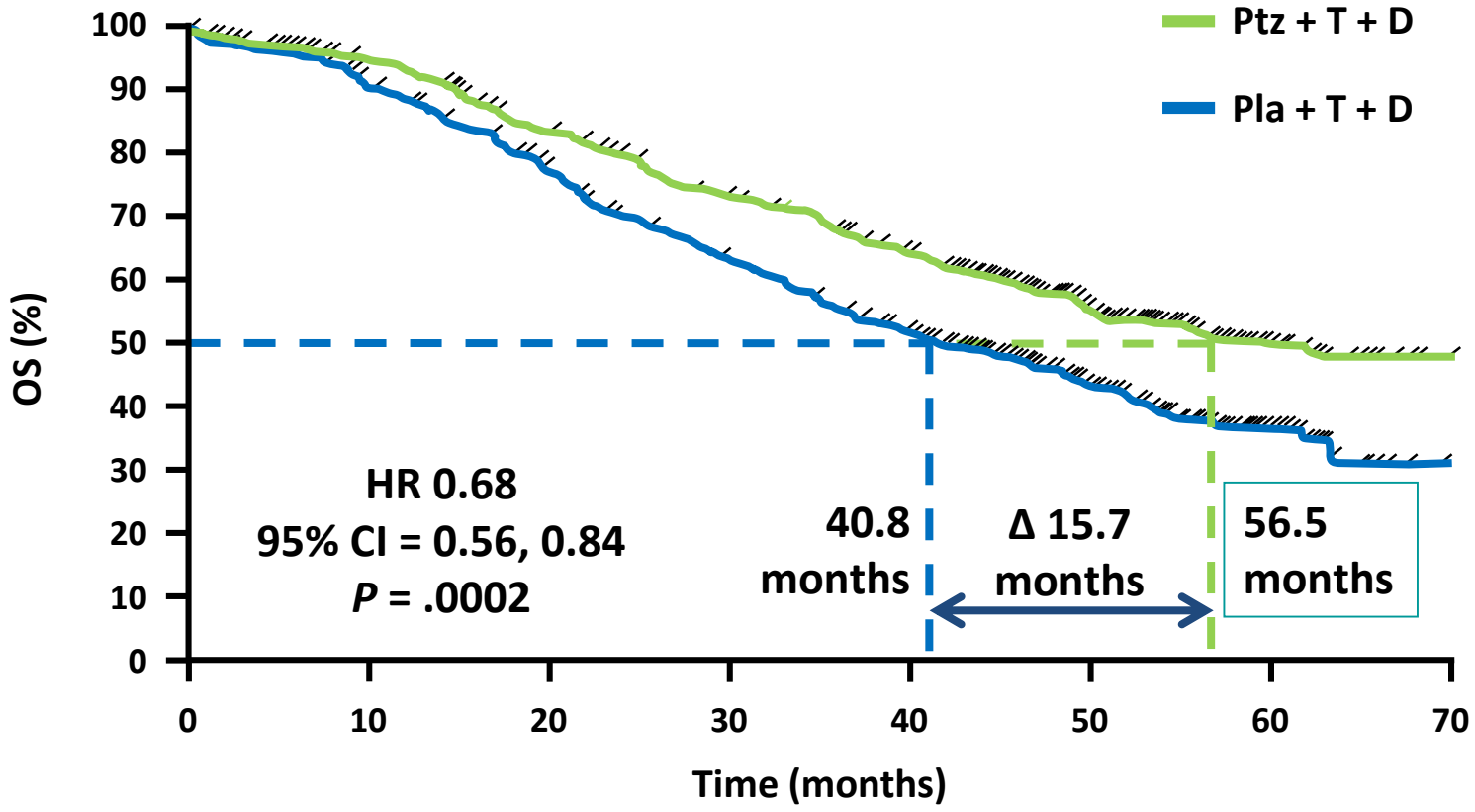
Primary endpoint: Independently assessed PFS

Secondary endpoints included Overall Survival; PFS by investigator assessment; Safety

Pertuzumab/Placebo: 840 mg loading dose, 420 mg q3w maintenance

Swain SM, et al. ESMO-ECCO 2014. Abstract 350O.

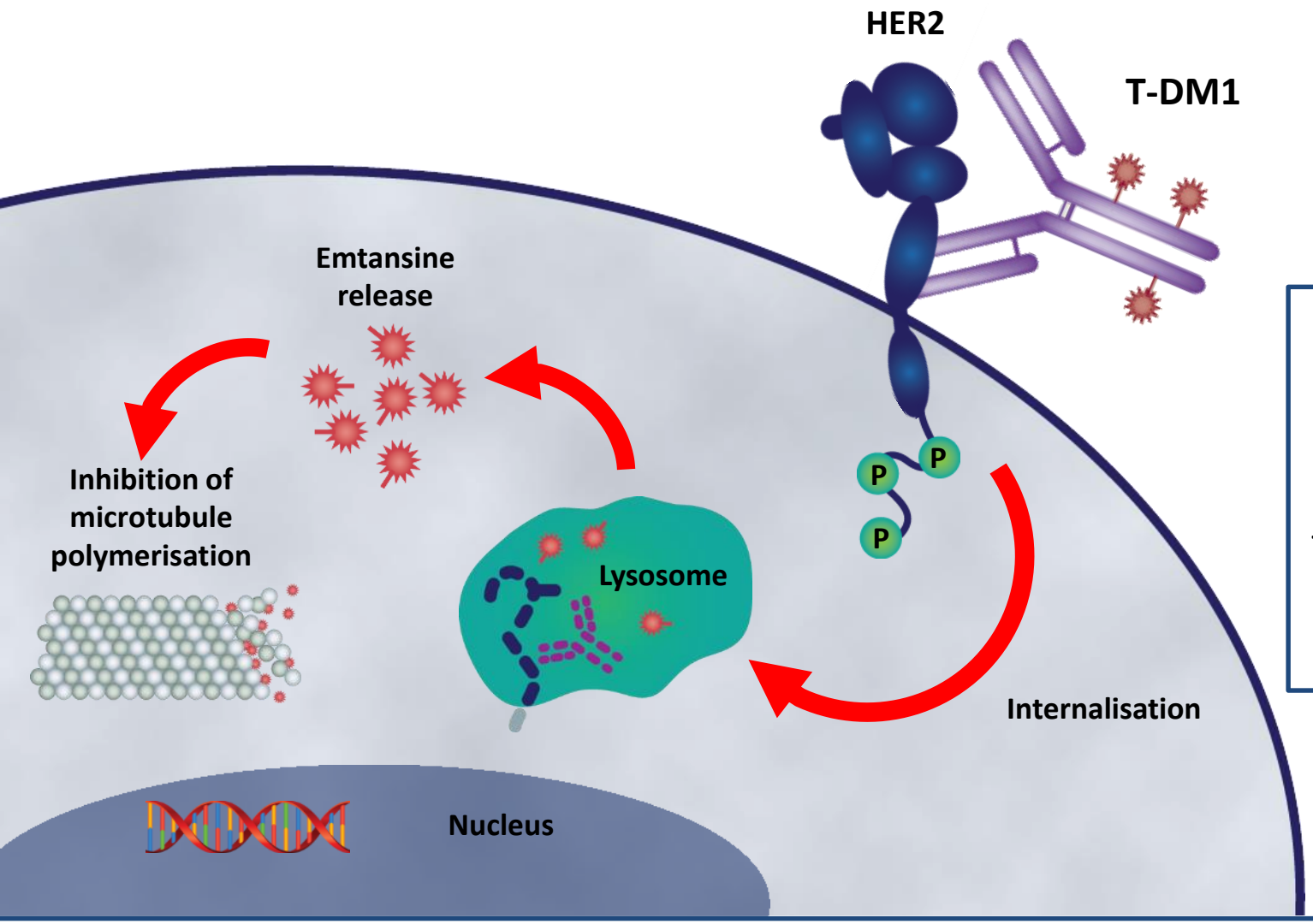
Patients on Pertuzumab plus Trastuzumab and Docetaxel Lived 15.7 Months Longer!!



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

Swain SM, et al. ESMO-ECCO 2014. Abstract 350O.

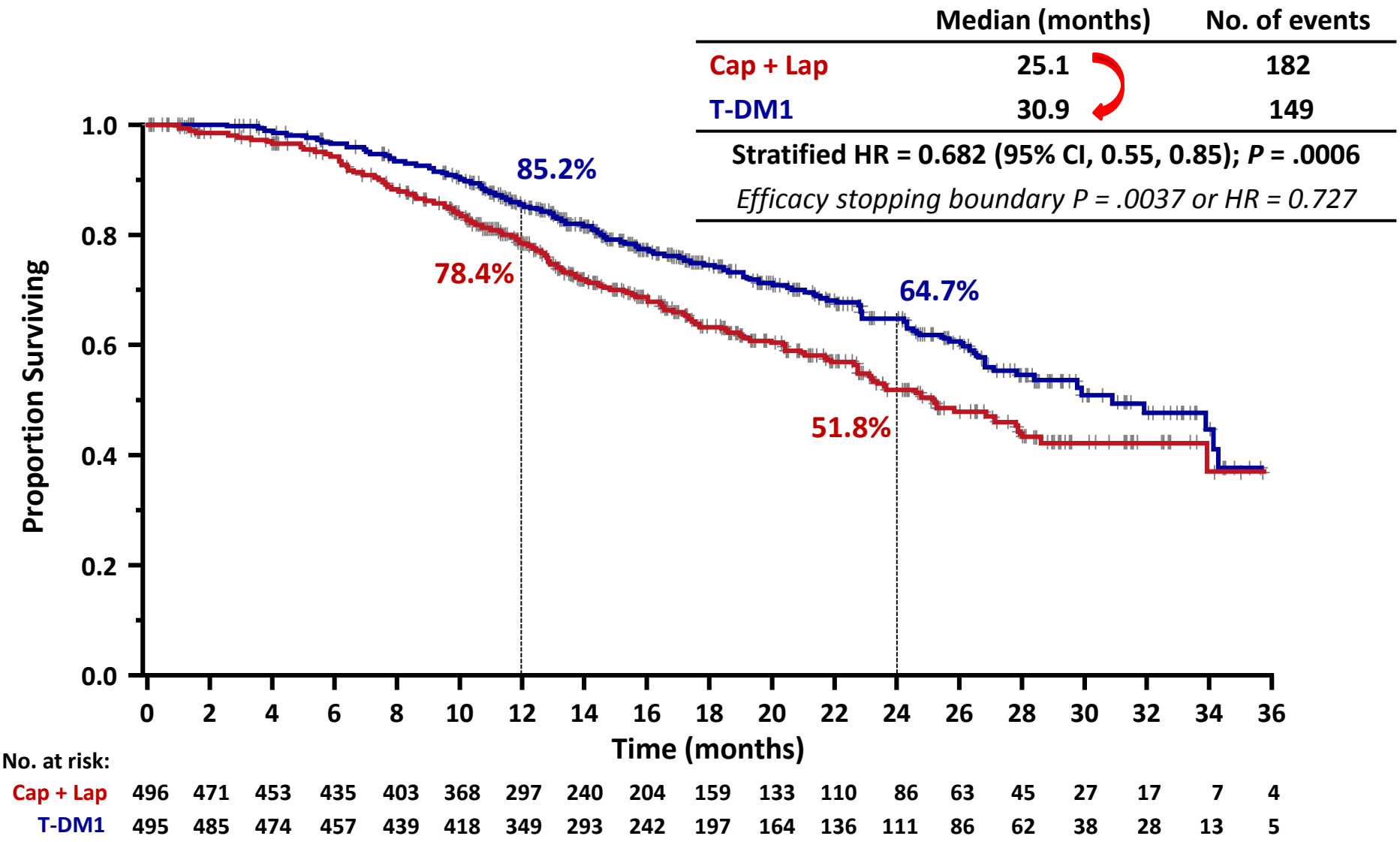
HER2 Therapy for Patients Resistant to Trastuzumab: T-DM1, A Targeted Chemotherapy!



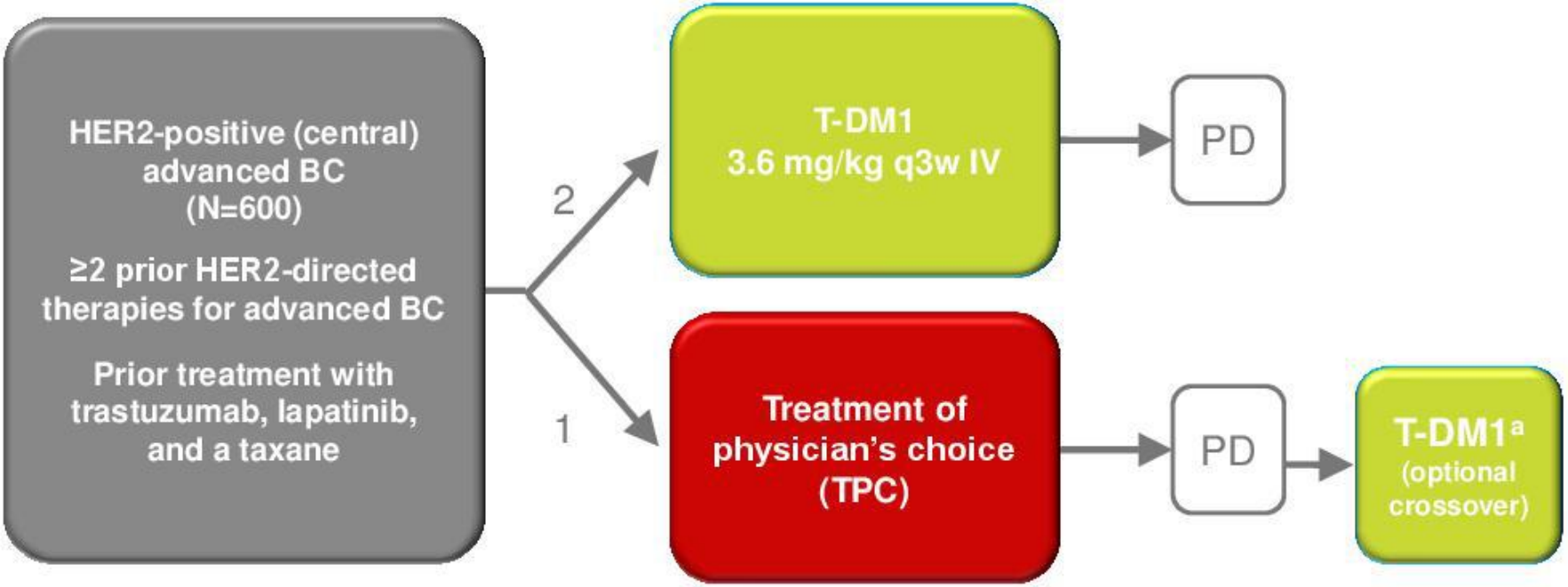
SYD 985: Another antibody drug conjugate targeting HER-2 (Van Herpen et al., ECC 2015)

LoRusso PM, et al. *Clin Cancer Res.* 2011;17(20):6437-6447

EMILIA Study: OS Was Significantly Improved with T-DM1 Treatment



TH3RESA STUDY



Stratification factors: World region, number of prior regimens for advanced BC, presence of visceral disease

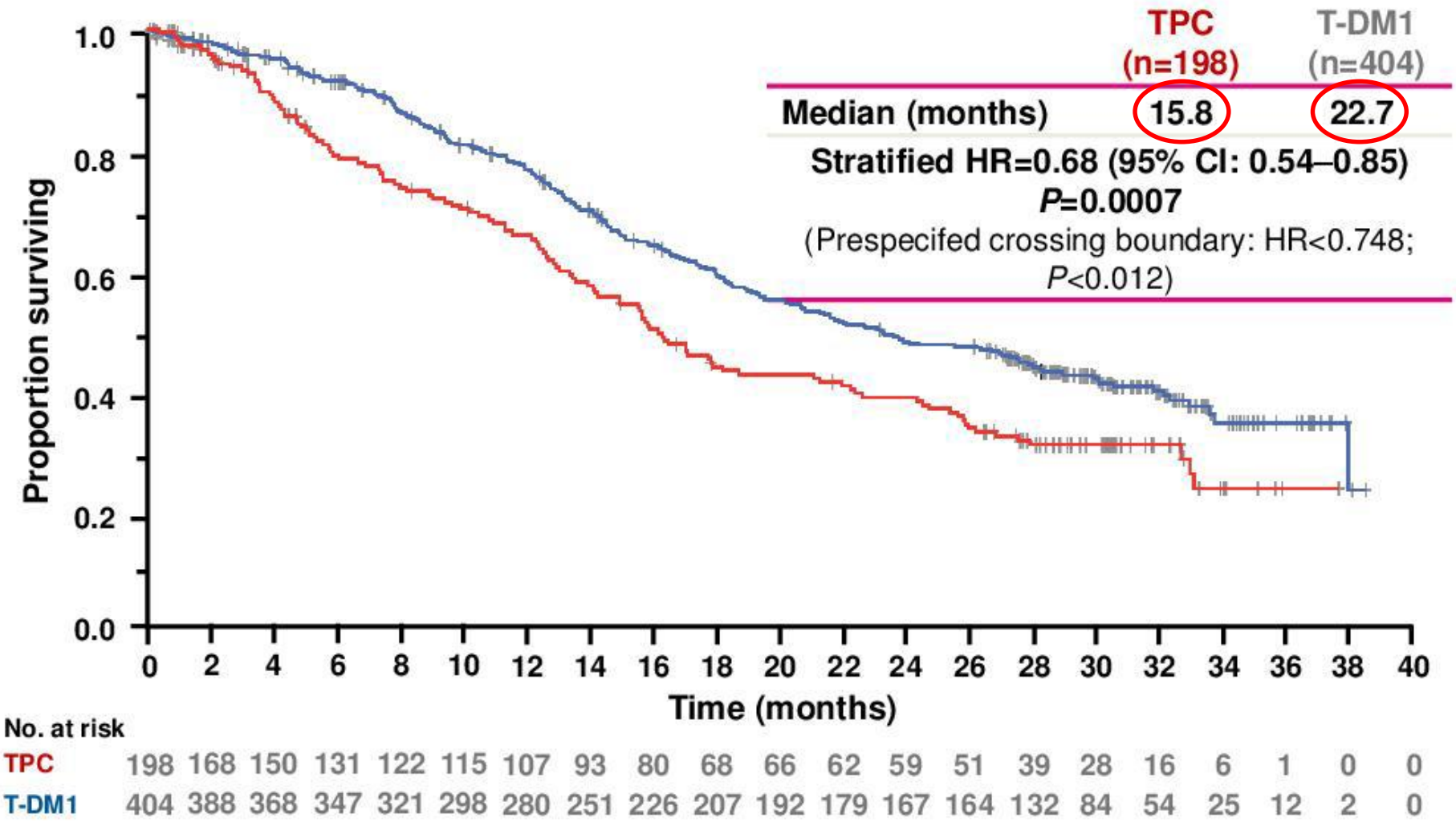
Co-primary endpoints: PFS by investigator and OS

Key secondary endpoints: ORR by investigator and safety

[a]First patient in: Sept, 2011. Study amended: Sept, 2012 following EMILIA 2nd interim OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.

Wildiers H et al. SABCS 2015, S05-05

TH3RESA


TPC (n=198)
T-DM1 (n=404)
Median (months) 15.8 22.7
Stratified HR=0.68 (95% CI: 0.54–0.85)
P=0.0007
(Prespecifed crossing boundary: HR<0.748; P<0.012)
Proportion surviving
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Time (months)
No. at risk
TPC 198 168 150 131 122 115 107 93 80 68 66 62 59 51 39 28 16 6 1 0 0
T-DM1 404 388 368 347 321 298 280 251 226 207 192 179 167 164 132 84 54 25 12 2 0

Neratinib

- Oral irreversible tyrosine kinase inhibitor of HER1, 2, 4

- Phase 2 trial (n=136) trastuzumab-pretreated cohort (66) – naïve (70)

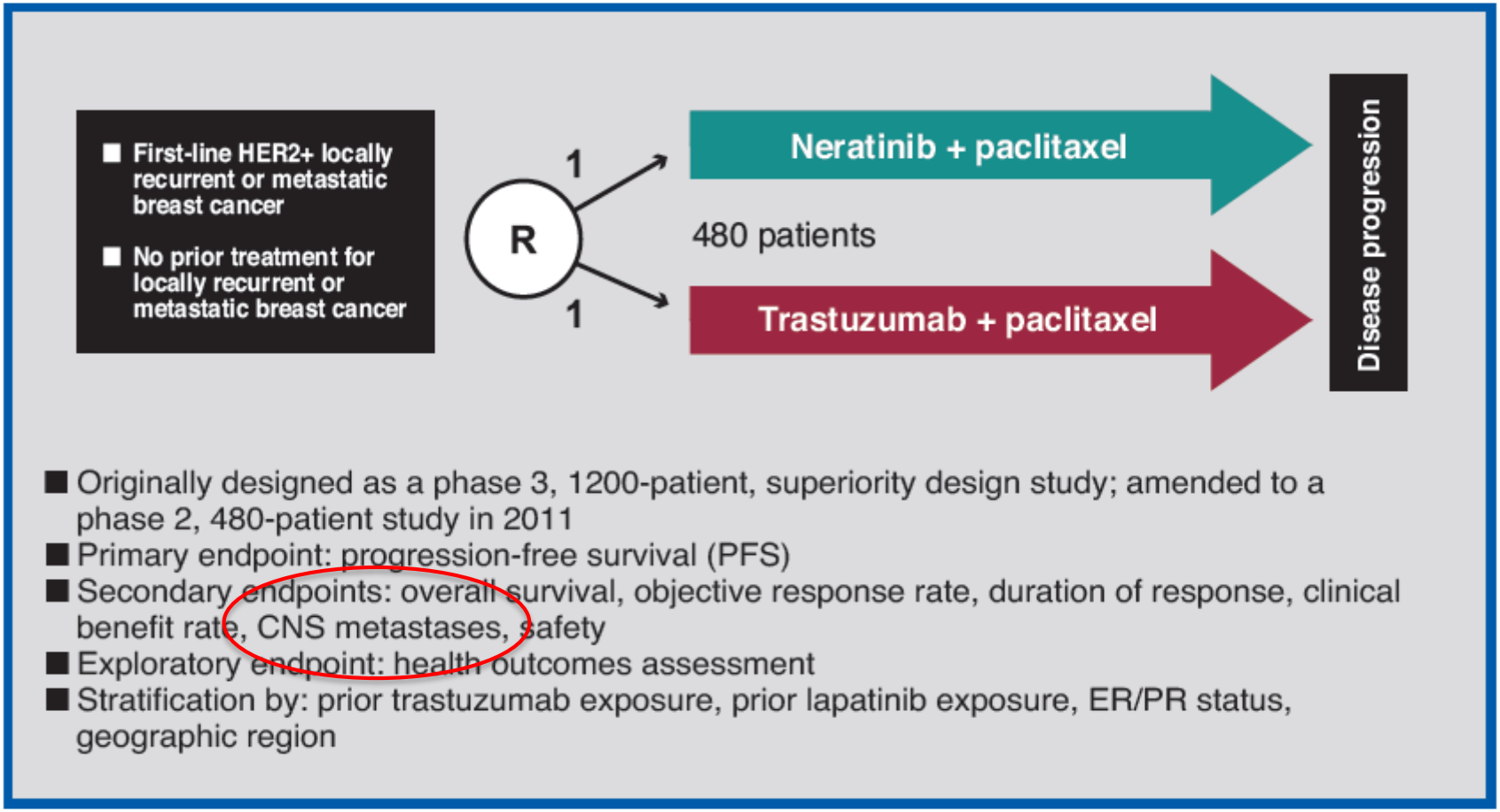
- - ORR: 24% & 56% respectively
- - 16-weeks PFS: 59% & 78% respectively

- Neratinib (± endocrine therapy) seems to have antitumor activity in HER-2 mutated tumors (SABCS 2015)

Selected Studies of Neratinib, an Irreversible Pan HER Inhibitor in HER-2 + Advanced Breast Cancer

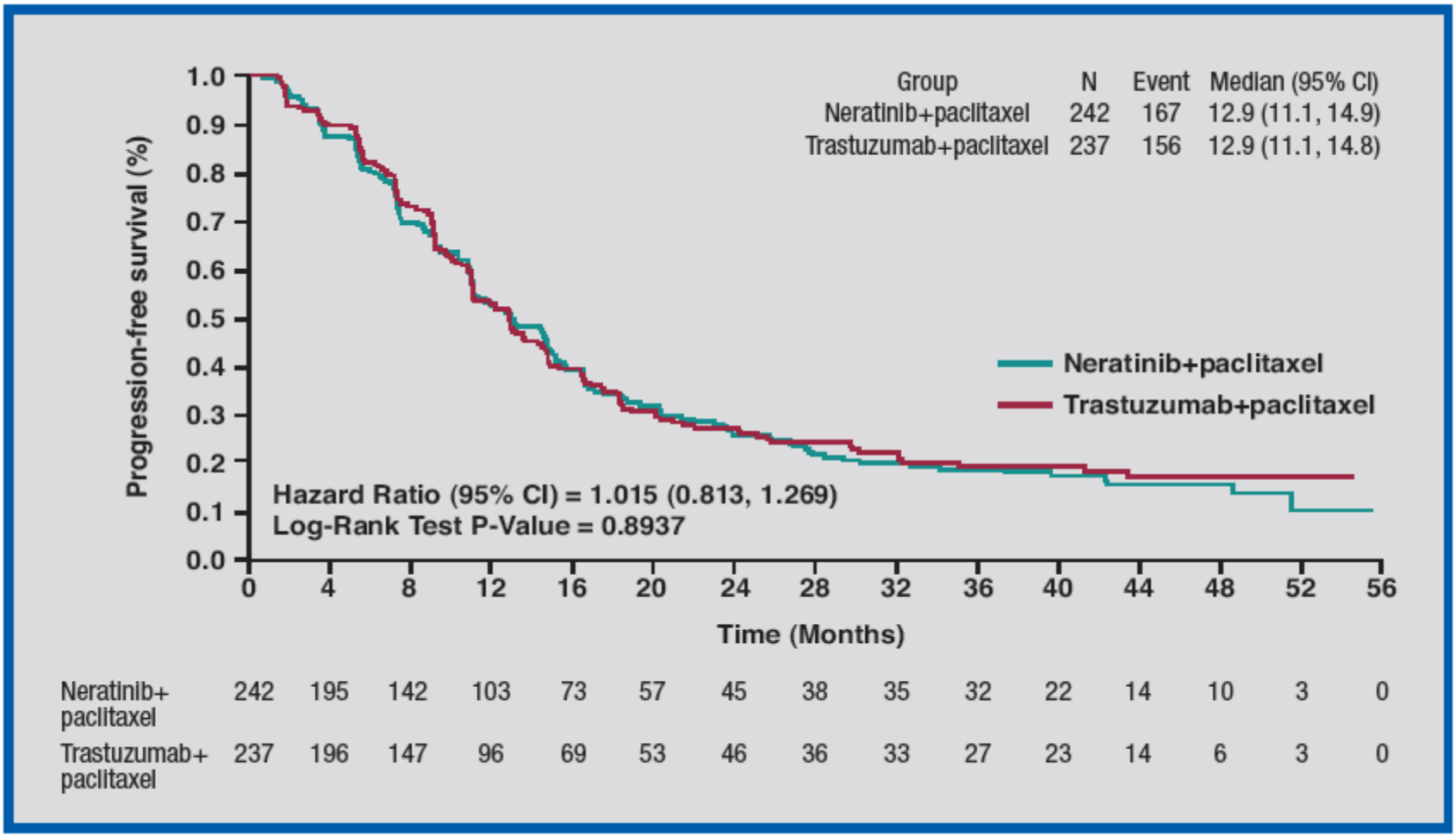
Author	Neratinib – based therapy	ORR
Burstein 2010	Neratinib (single agent, no prior trastuzumab)	56%
	Neratinib (single agent, prior trastuzumab)	24%
Saura 2014	Neratinib + Capecitabine (no prior Lapatinib)	64%
	Neratinib + Capecitabine (prior Lapatinib)	57%
Chow 2013	Neratinib + Paclitaxel (first-line)	73%
Swaby 2009	Neratinib + trastuzumab	27%
Jankowitz 2013	Neratinib + trastuzumab + Paclitaxel	38%

NEfERTT Trial: Study design



- Originally designed as a phase 3, 1200-patient, superiority design study; amended to a phase 2, 480-patient study in 2011
- Primary endpoint: progression-free survival (PFS)
- Secondary endpoints: overall survival, objective response rate, duration of response, clinical benefit rate, CNS metastases, safety
- Exploratory endpoint: health outcomes assessment
- Stratification by: prior trastuzumab exposure, prior lapatinib exposure, ER/PR status, geographic region

NEfERTT Trial: Kaplan-Meier estimate of progression-free survival

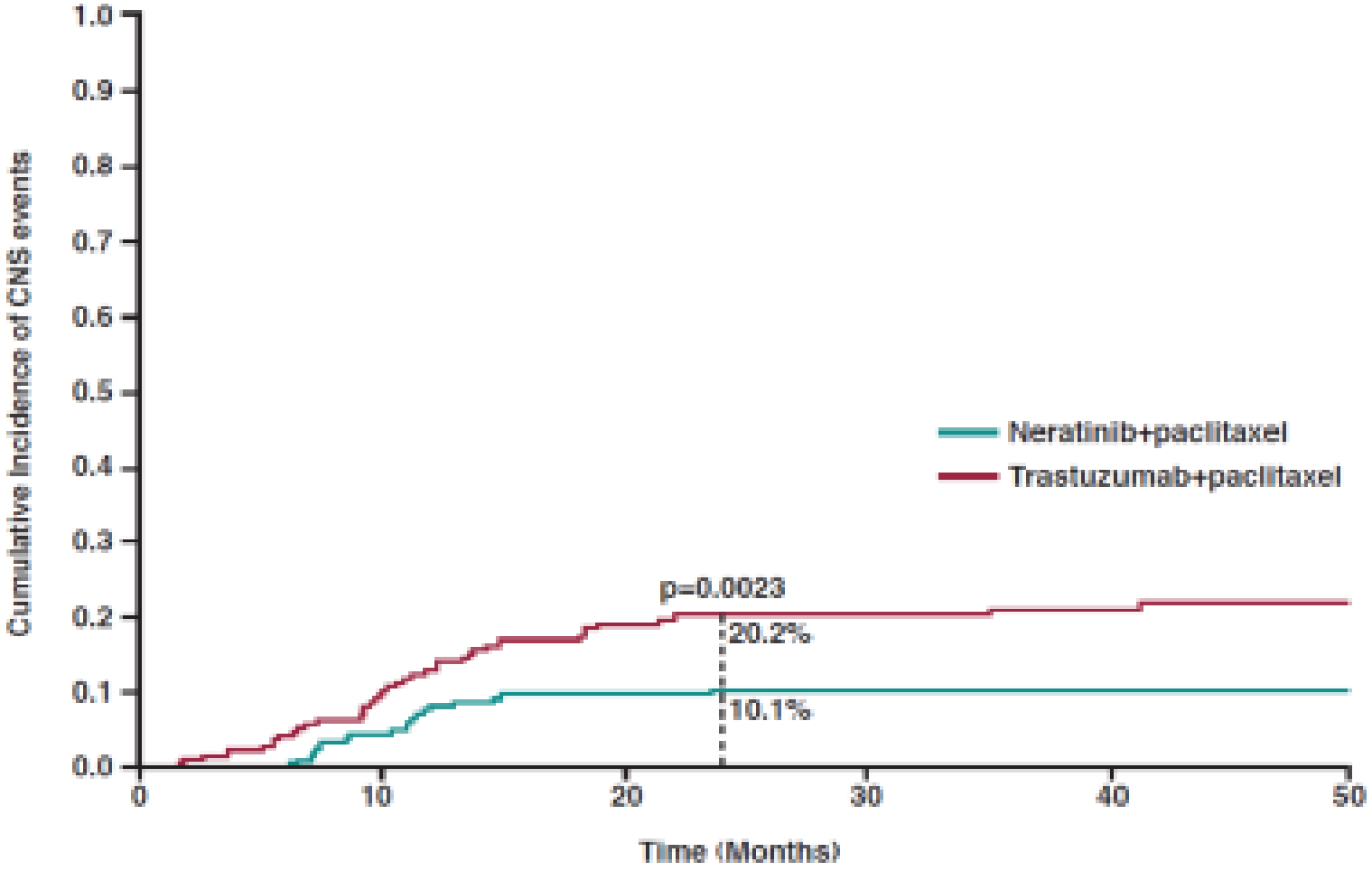


NEfERTT Trial: Efficacy Endpoints

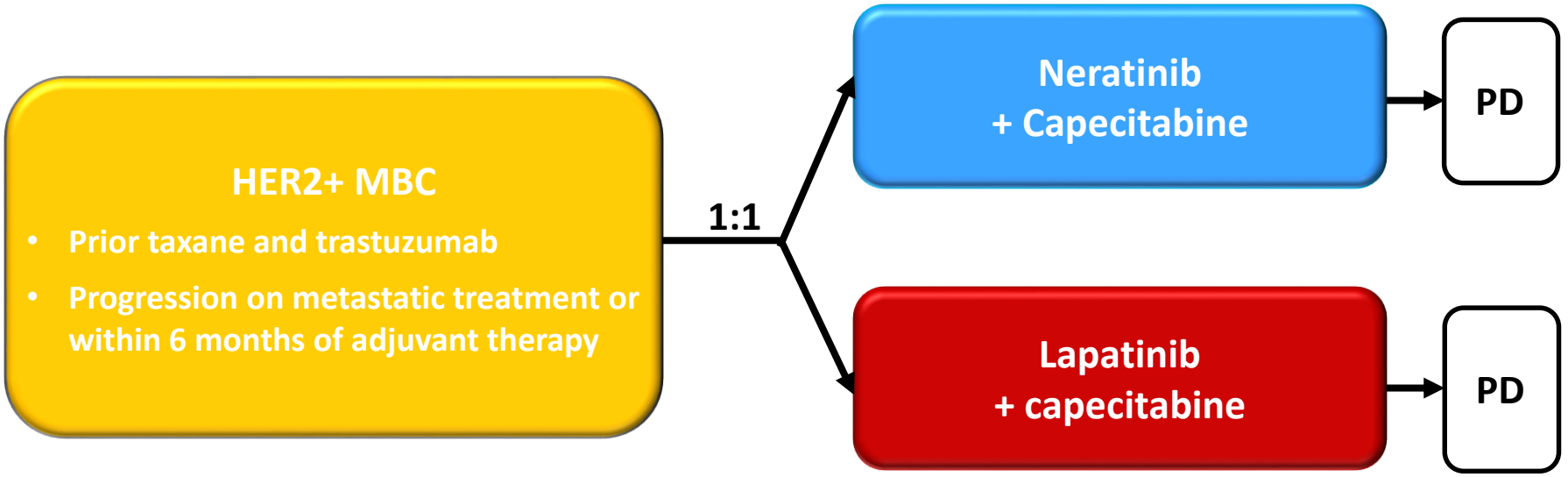
Variable	Neratinib + paclitaxel (n=242)	Trastuzumab + paclitaxel (n=237)	Hazard ratio (95% CI)	Difference (95% CI)	P value
Primary endpoint					
Patients with PFS event, n (%)	167 (69.0)	156 (65.8)	1.02 (0.81–1.27)	–	0.894*
Median PFS, months	12.9	12.9			
95% CI	11.1–14.9	11.1–14.8			
Secondary endpoints					
Patients with objective response, n (%)‡	181 (74.8)	184 (77.6)	–	–2.8 (–10.5–4.8)	0.522†
95% CI	68.8–80.1	71.8–82.8			
Complete response‡	4 (1.7)	9 (3.8)			
Partial response‡	177 (73.1)	175 (73.8)			
Patients with clinical benefit, n (%)	214 (88.4)	202 (85.2)	–	3.2 (–2.9–9.3)	0.236†
95% CI	83.7–92.2	80.1–89.5			
Median duration of response, months§	13.4	12.9	1.01 (0.78–1.32)	–	0.924*
95% CI	11.4–16.8	11.0–15.9			
Patients with symptomatic or progressive CNS events, n (%)	20 (8.3)	41 (17.3)	0.48 (0.29–0.79)∞	–	0.002
2-year Kaplan-Meier estimate of cumulative incidence of CNS events, %	16.3	31.2	0.45 (0.26–0.78)	–	0.0036

Awada et al ASCO 2015

NEfERTT Trial: Cumulative Incidence of CNS Events (reduced by 50% in the Neratinib arm)



Ongoing Phase III trial of Neratinib Plus Capecitabine versus Lapatinib Plus Capecitabine



Primary endpoint:

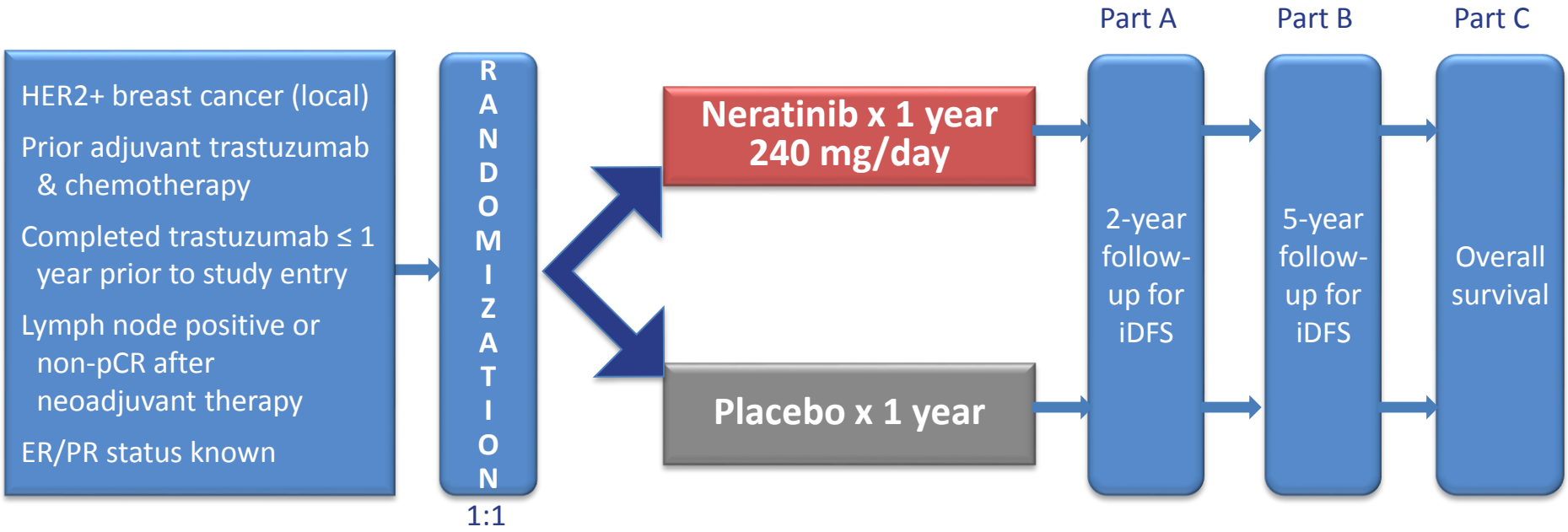
- **Independently assessed PFS**
- **OS**

Secondary endpoints:

- **Investigator Assessed PFS**
- **ORR**
- **CBR and CNS events**

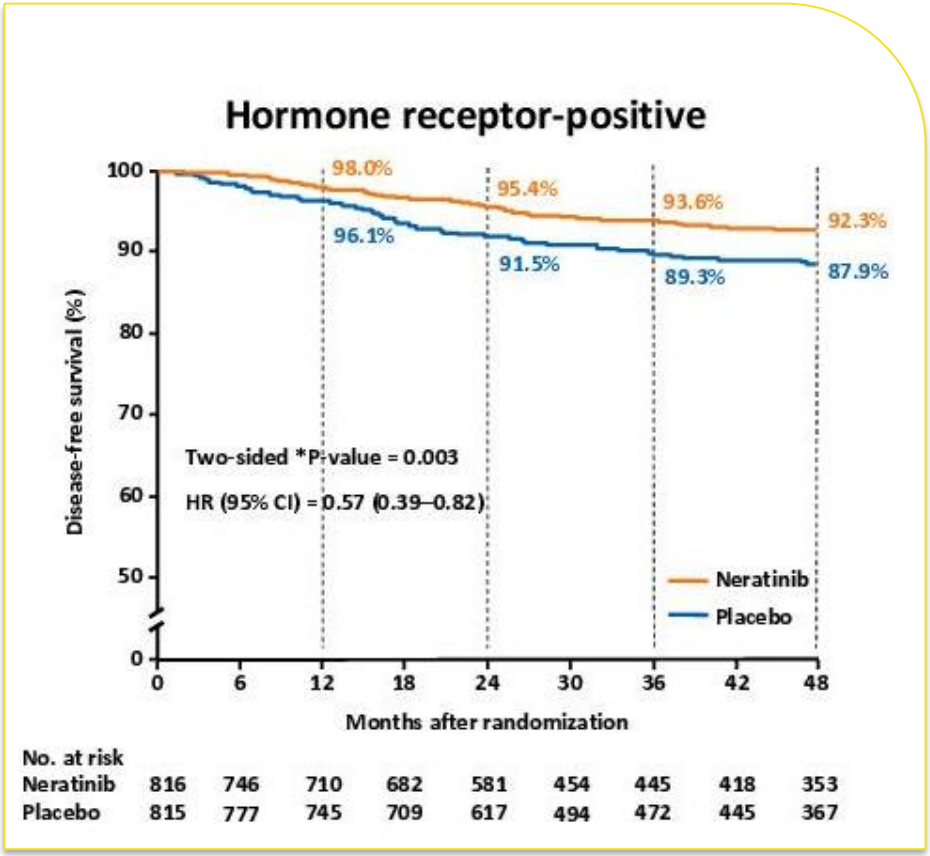
https://clinicaltrials.gov/ct2/show/NCT01808573

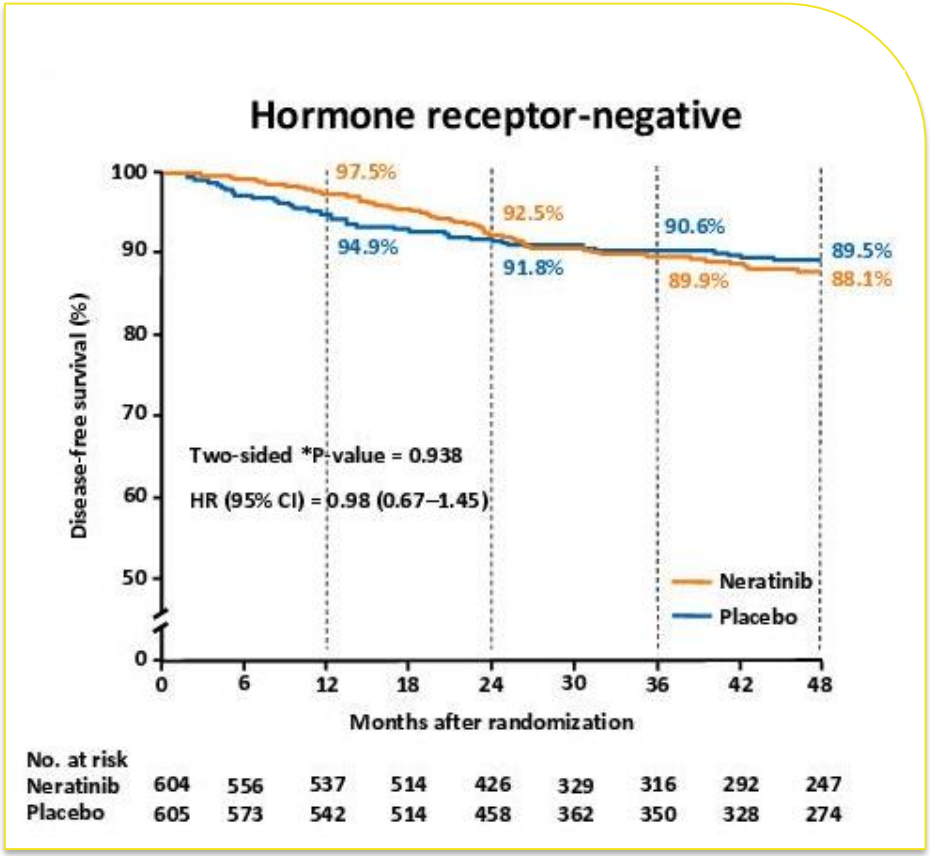
ExteNET : Schéma de l'étude



- **Primary analysis : invasive DFS (iDFS) in ITT population (n=2840)**
- **iDFS at 2 years : HR=0,67 (0,50-0,91); p=0,009**
  - **Hormone receptor-positive (n=1631 ; 57,4%); HR=0,51 ; *p=0,001***
  - **Centrally-confirmed HER2-positive 60% (n=1463 ; 51%) ; HR=0,51 ; *p=0,002***

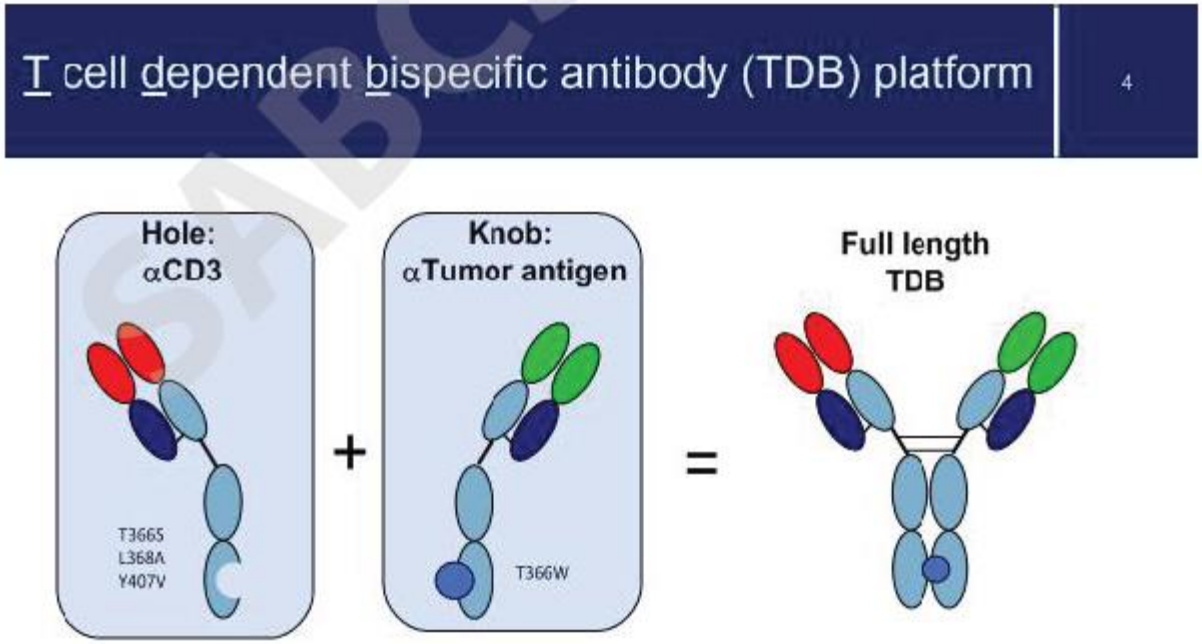
Analyse à 3 ans de l'iDFS selon le statut RH





**p-value descriptive*

Preclinical HER2-TDB: A promising agent targeting resistant HER-2+ BC

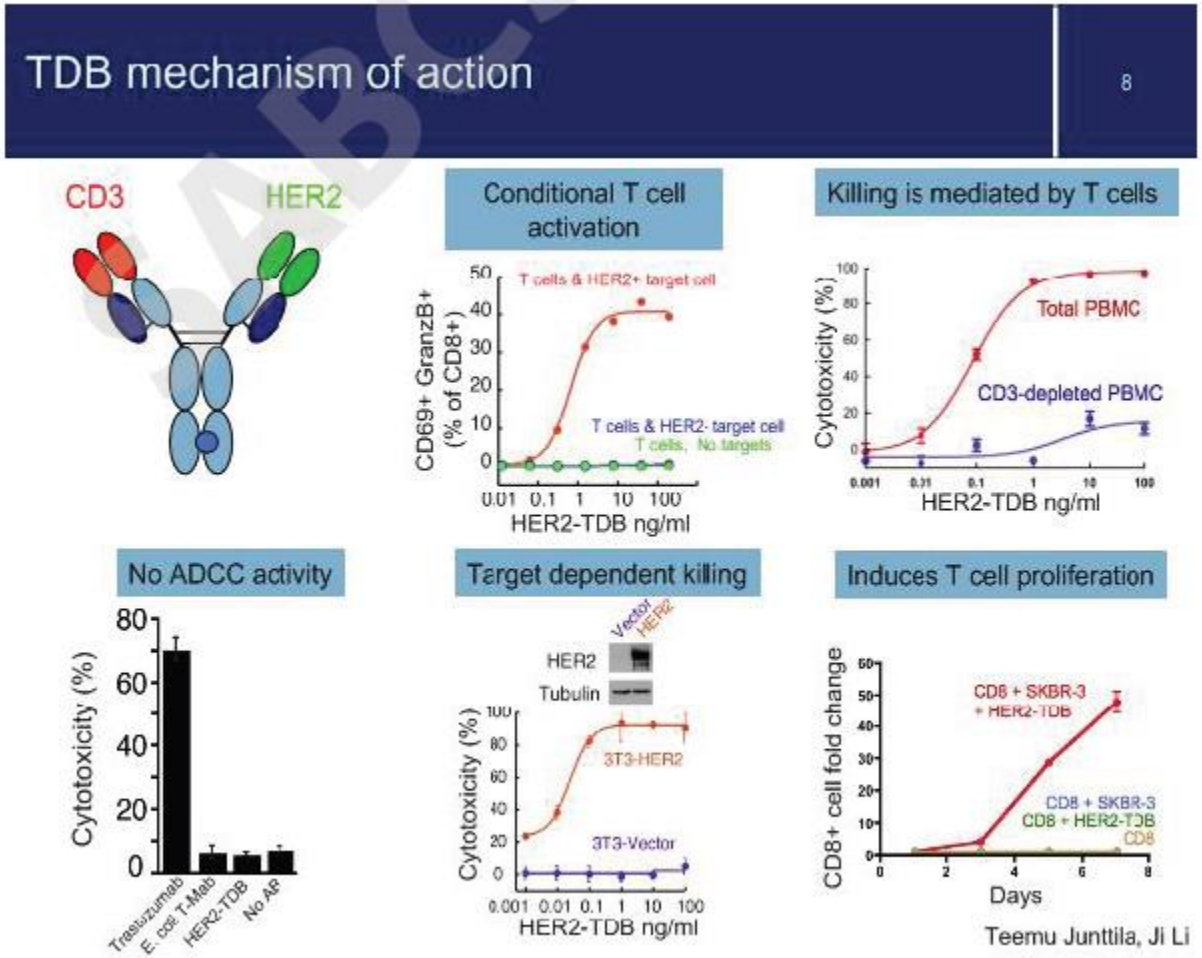


= IgG1 bispecific

- Produced using modular "knobs into holes" technology
- Effector functions removed (E. coli production / N297A)
- Minimal immunogenic potential
- PK is similar to conventional IgG1

Ridgeway...Carter. 1996 Prot. Engineering
Atwell...Carter. 1997 J. Mol Biol.

TDB mechanism of action: T cell activation and profileration



HER2-TDB kills T-DM1 resistant cells

11

Resistance mechanisms of T-DM1

-Increased expression of drug efflux pumps

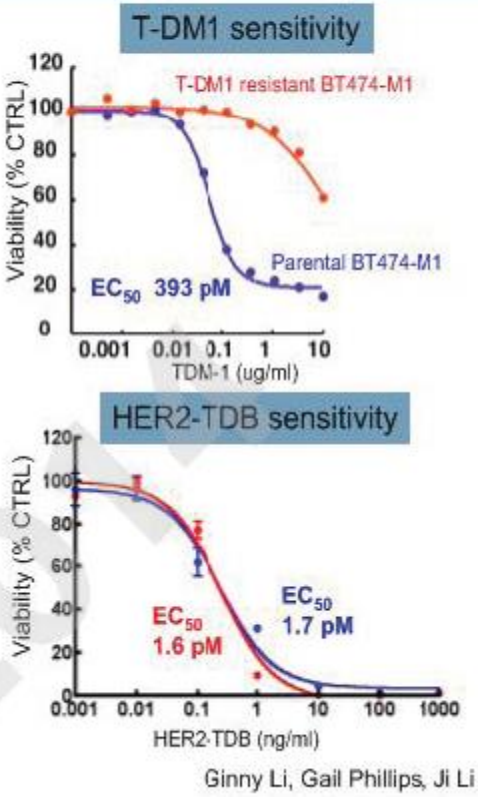
-Reduced HER2 expression

-Parallel growth factor signaling

-Up-regulated pro-survival signals

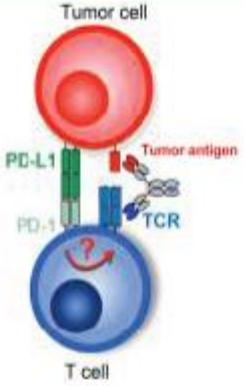
↑Bcl-2 ↓PTEN ↑DUSP6 ↑DARPP32

Gail Phillips lab

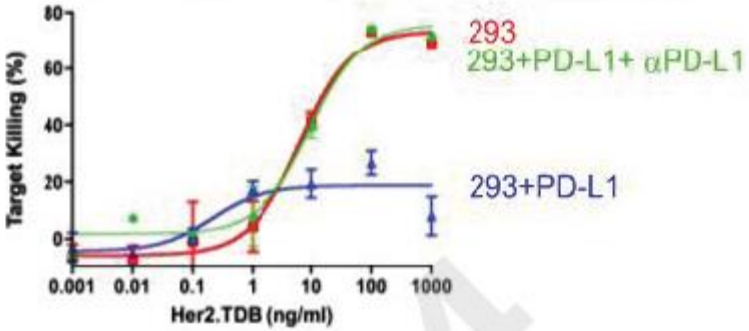


Ginny Li, Gail Phillips, Ji Li

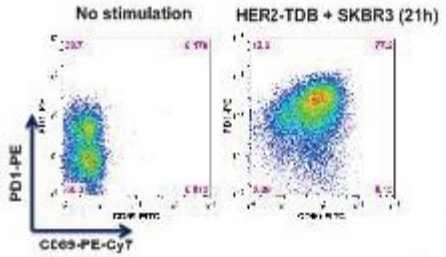
PD-L1 expression by tumor cell may affect TDB activity



PD-L1-expression in target cells inhibits TDB activity



TDB induces PD-1 in human T cells



- Potential diagnostic for TDB activity
- Mechanistic rationale for combining HER2-TDB with anti-PD-L1

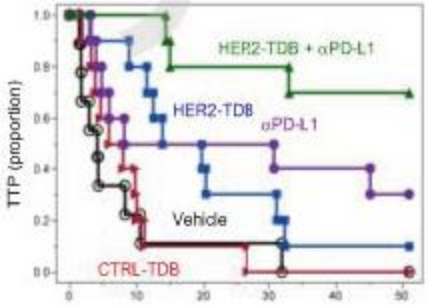
Ji Li

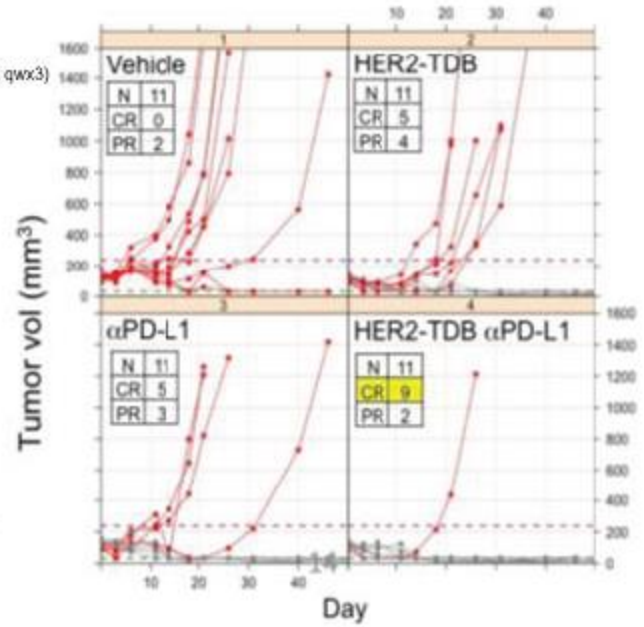
HER2-TDB anti-PDL1 combination is effective in treatment of CT26-HER2 tumors

Tumor Model: CT26-HER2

a-PDL1: 25A1 (DANA, tiwx3)

HER2-TDB: 4D5-SP34 (mIgG2a DANG, qwx3)





Combination of TDB and anti-PD-L1:

- Enhanced inhibition of tumor growth
- Increased response rates
- Durable responses

Robyn Clark, Maria Hristopoulos, Klara Totpal, Teemu Junttila

TNBC/Basal-Like Diseases

Paclitaxel/FAC Neoadjuvant Response by PAM50 Subtype: A Significant PCR (50%–65%) in a Subgroup of Patients

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

Bevacizumab (B) in Metastatic Breast Cancer: Phase III Studies Showed ORR and PFS Improvement but No OS Benefit

TNBC patients seemed to benefit most

Study	Treatment	Line of Therapy	N° of Pts	RR (%)	mPFS (mo)	mOS (mo)
US Study	Paclitaxel +/- B	First	722	37 vs 21	11.8 vs 5.9	26.7 vs 25.2
AVADO	Docetaxel +/- B[1]	First	736	64 vs 55 vs 46	9 vs 8.1 (7.5 mg/kg) 10 vs 8.1 (15 mg/kg)	31.9 vs 30.8 vs 30.2
RIBBON 1	[2]Chemo +/- B	First	1237	Taxane/anthra 51 vs 38 Capecitabine 35 vs 24	Taxane/anthra 10.7 vs 8.3 Capecitabine 9.8 vs 6.2	Taxane/anthra 25.2 vs 23.8 Capecitabine 29 vs 21.2
RIBBON 2	[3]Chemo +/- B	Second	684	39.5 vs 29.6	7.2 vs 5.1	NA

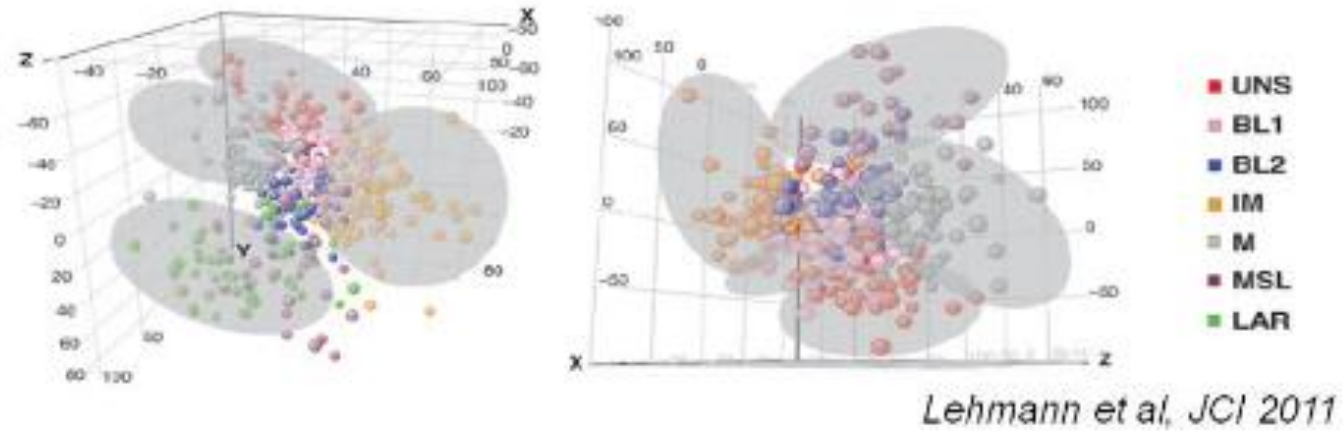
[1]Beva 7.5 or 15 mg/kg q3w.

[2]Capecitabine or taxane or anthracycline.

[3]Taxane or gemcitabine or capecitabine or vinorelbine

Seddon et al. *J Oncol Pharm Pract December 2014 20: 433-444*.

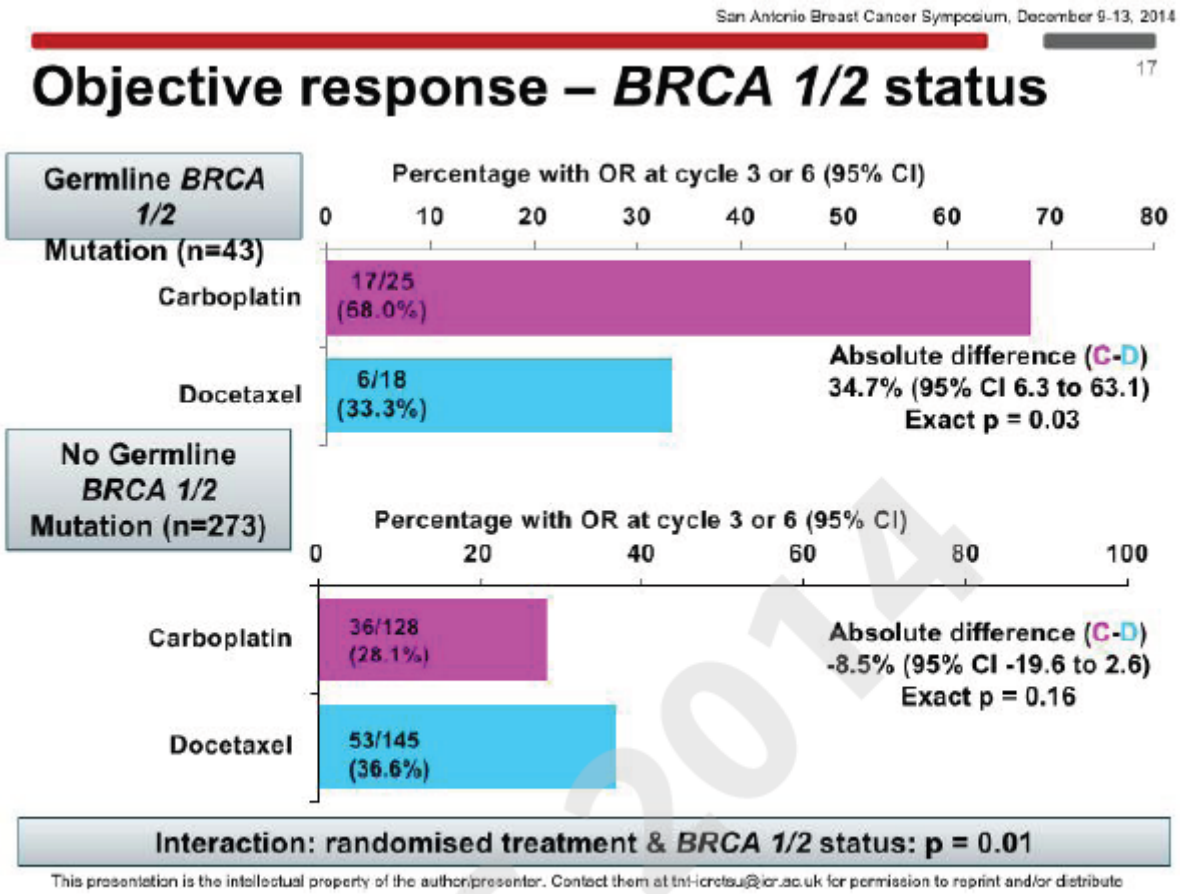
Heterogeneity of TNBC: An Opportunity for New Agents?!



Lehmann et al, JCI 2011

- Genomic instability common
- Multiple subsets with varying targets
  - Basal-like 1 and 2 – DNA damage response genes (Platinum, PARP inhibitors)
  - Immunomodulatory (checkpoint inhibitors)
  - Mesenchymal and mesenchymal/stem cell – PI3K/mTOR pathway
  - LAR – androgen receptor signaling (Enzalutamide)

TNT Trial: Patients with BRCA1 or BRCA2 Mutation Experience Significantly Greater Objective Response with Carboplatin than Docetaxel



Results from a Phase 2 Study of Enzalutamide, an Androgen Receptor (AR) Inhibitor, in Advanced AR+ Triple-Negative Breast Cancer (MDV3100-11)

Tiffany A. Traina, Kathy Miller, Denise A. Yardley, Joyce O'Shaughnessy, Javier Cortes, Ahmad Awada, Catherine Kelly, Maureen Trudeau, Peter Schmid, Luca Gianni, Laura Garcia-Estevez, Rita Nanda, Foluso Ademuyiwa, Stephen Chan, Joyce L. Steinberg, Martha Blaney, Iulia Cristina Tudor, Hirdesh Uppal, Amy Peterson, Clifford A. Hudis

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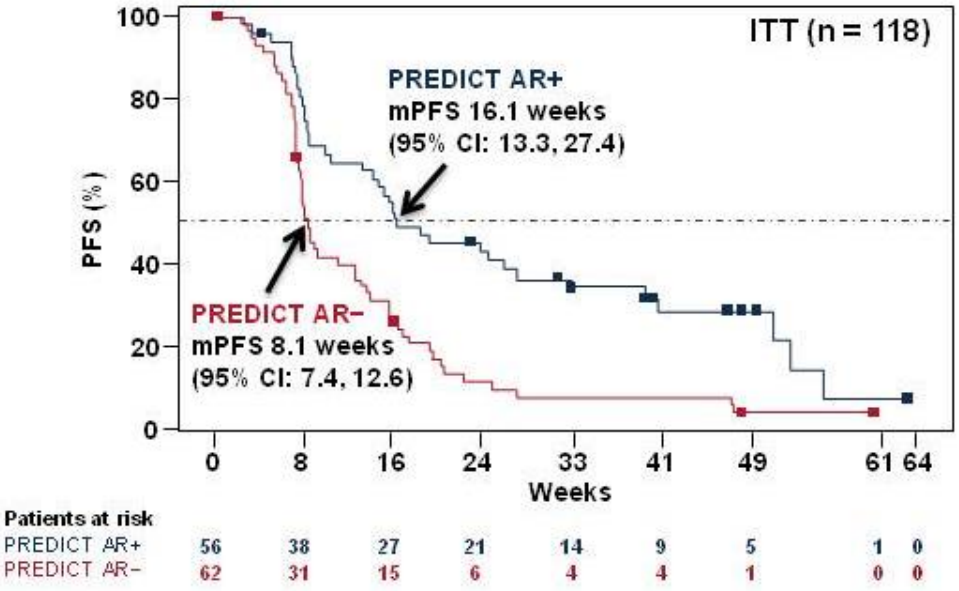
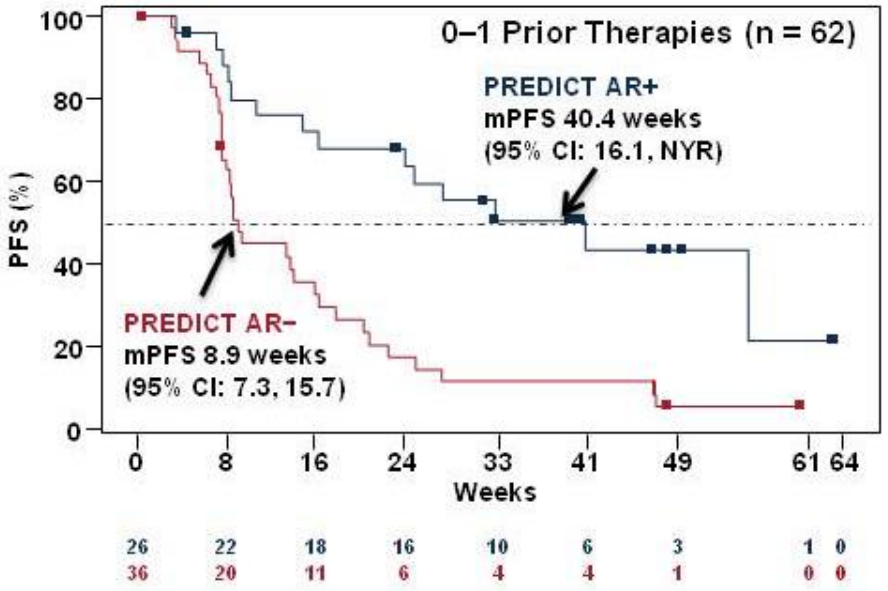
Progression-Free Survival in TNBC Patients on Enzalutamide and According to PREDICT AR Status



PREDICT AR+ mPFS 3.7 months



PREDICT AR+ mPFS 9.3 months

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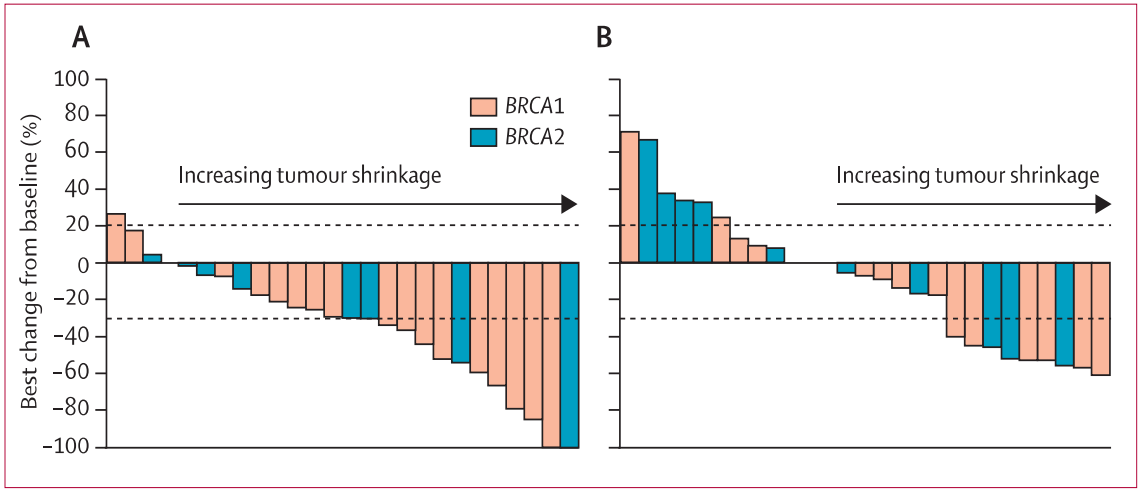
Olaparib, a PARP Inhibitor, Demonstrated Significant Efficacy in BRCA-Mutated Tumours



	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).

Several PARPi are under clinical investigation including in the adjuvant setting

BRCA-mutant breast cancer

Tutt A, et al. *Lancet.* 2010;376(9737):235-244; Audeh MW, et al. *Lancet*. 2010;376(9737):245-251.

Anti-PD-(L)1 Monotherapy

Agent		No of patients	ORR (95% CI)	PD-(L)1+	Author
Atezolizumab	Anti-PD-L1	21	n.a.	19% (5-42)	Emens LA AACR 2015
Avelumab	Anti-PD-L1	58	8.6% (2.9-19)	33%	Dirix L et al. S1-04 2015
Pembrolizumab	Anti-PD-1	27	n.a.	18.5%	Nanda R et al. SABCS 2014

Anti-PD-L1 -Combination

Atezolizumab Combination with nab-Paclitaxel (Phase I expansion)

Table 3. Summary of Best Overall Responses by RECIST v1.1

Best Overall Response	1L (n = 9)	2L (n = 8)	3L+ (n = 7)	All Patients N = 24
Confirmed ORR (95% CI)[a]	66.7% (29.9, 92.5)	25% (3.2, 65.1)	28.6% (3.7, 71.0)	41.7% (22.1, 63.4)
ORR (95% CI)[a]	88.9% (51.7, 99.7)	75.0% (34.9, 96.8)	42.9% (9.9, 81.6)	70.8% (48.9, 87.4)
CR	11.1%	0	0	4.2%
PR	77.8%	75.0%	42.9%	66.7%
SD	11.1%	25.0%	28.6%	20.8%
PD	0	0	28.6%	8.3%

Table 5. Objective Response Rate by PD-L1 Expression Level[a]

	IC0 (n = 7)	IC1/2/3 (n = 9)	Unknown (n = 8)
ORR (95% CI)	57.1% (18.4, 90.1)	77.8% (40.0, 97.2)	75% (34.9, 96.8)
CR	0	0	12.5%
PR	57.1%	77.8%	62.5%
SD	42.9%	22.2%	0
PD	0	0	25%

[a] Including investigator-assessed unconfirmed responses.

Adams S SABCS 2015

BEACON: A Phase 3 Open-label, Randomized, Multicenter Study of Etirinotecan Pegol (EP) versus Treatment of Physician's Choice (TPC) in Patients With Locally Recurrent or Metastatic Breast Cancer Previously Treated With an Anthracycline, a Taxane, and Capecitabine

Edith A. Perez, Ahmad Awada, Joyce O'Shaughnessy, Hope Rugo, Chris Twelves, Seock-Ah Im, Carol Zhao, Ute Hoch, Alison L. Hannah, Javier Cortes

BEACON

BREAST CANCER OUTCOMES WITH NKTR-102

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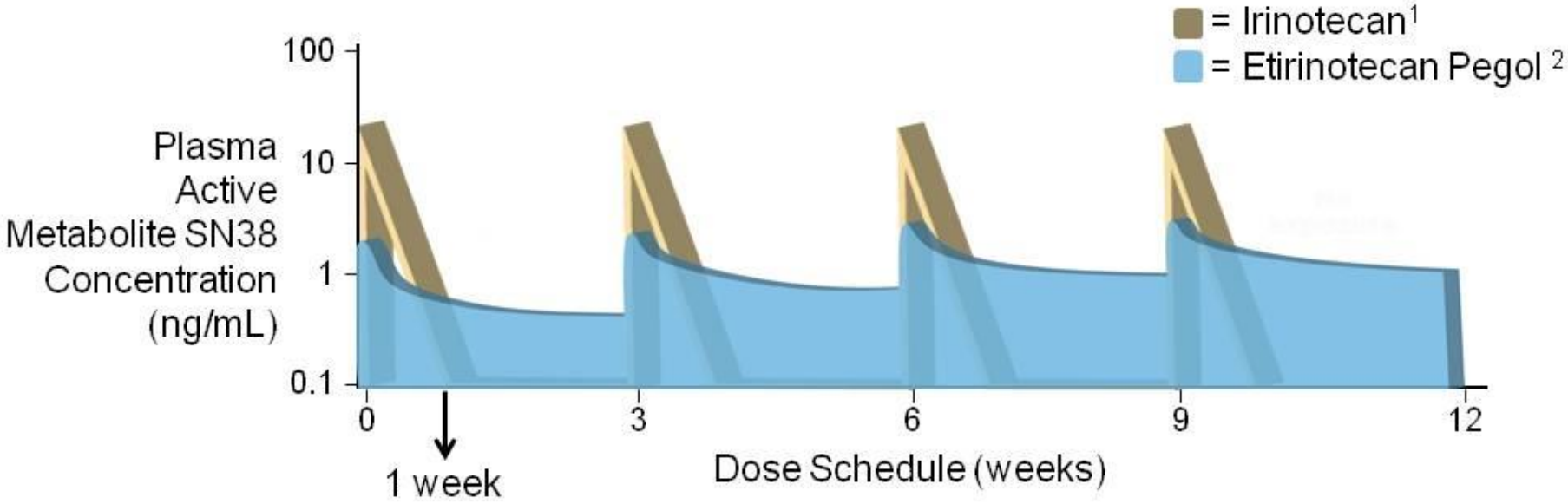
Comparative Pharmacokinetics of SN38: Irinotecan vs Etirinotecan Pegol

Etirinotecan Pegol's design results in low initial peak and sustained concentrations of active topoisomerase 1 inhibitor



1. Xie et al. *J Clin Oncol.* 2002;20:3293-3301
2. Jameson et al. *Clin Cancer Res.* 2013;19:268-78

BEACON Phase 3 Study Design

Locally recurrent or metastatic breast cancer (n=852)

- Prior treatment with anthracycline, a taxane, and capecitabine
- ECOG PS 0-1
- 2-5 prior chemotherapies for advanced disease
- Stable brain mets allowed

R

Single-Agent Etirinotecan Pegol
145 mg/m^2 every 3 weeks
(n=429)

Single-Agent Treatment of Physician's Choice (TPC)
Docetaxel, eribulin, gemcitabine, ixabepilone, *nab*-paclitaxel, paclitaxel or vinorelbine
(n=423)

Primary Endpoint
- Overall Survival

Secondary Endpoints
- PFS, ORR, CBR, DoR, HRQoL

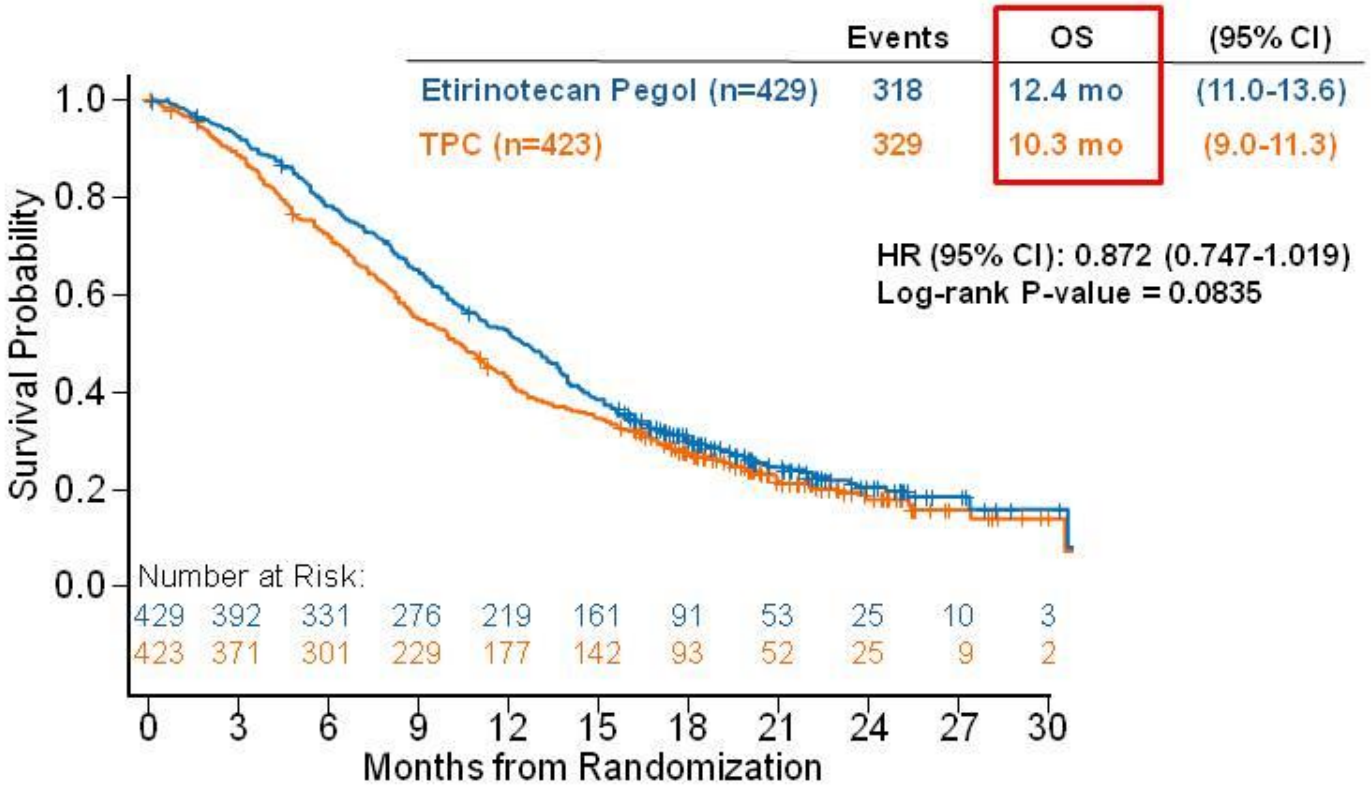
Exploratory Endpoints
- PD Markers in CTC, others

Stratification:
- Geographic region
- Prior eribulin use
- Receptor status

135 centers in US, Canada, Belgium, France, Germany, Italy, Korea, Russia, Spain, The Netherlands, UK

Enrollment: Dec 2011 – Aug 2013
Event cutoff: Dec 2014

Primary Efficacy Endpoint: Overall Survival



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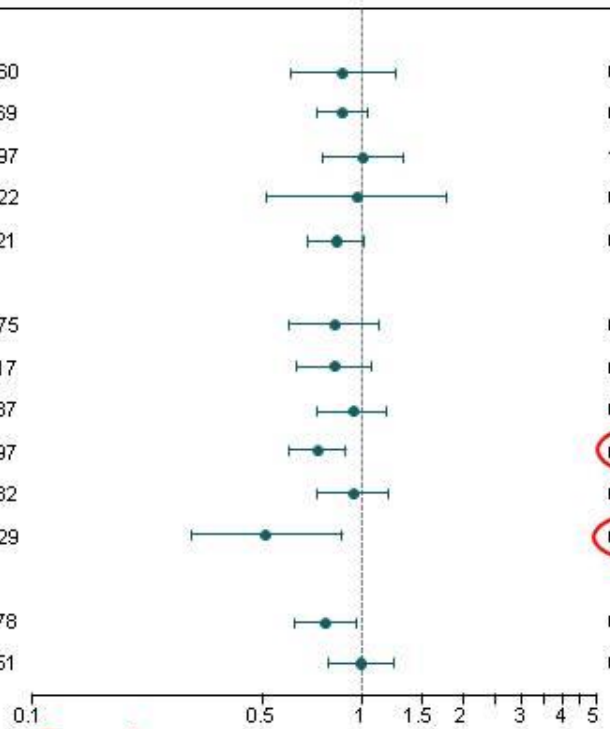
Pre-planned OS Subgroup Analyses

Subgroup	N	EP # Events	N	TPC # Events	HR (95% CI)	EP Median	TPC Median
Prior Eribulin							
Y	71	59	72	60	0.87 (0.60, 1.25)	11.0	8.0
N	358	259	351	269	0.87 (0.73, 1.03)	12.8	10.9
TNBC	119	102	117	97	1.00 (0.76, 1.32)	9.8	8.8
HER2+	30	19	32	22	0.96 (0.52, 1.78)	8.6	11.6
HR+	295	208	290	221	0.83 (0.69, 1.00)	13.6	11.0
Prior Regimens							
≥ 5	117	91	94	75	0.82 (0.60, 1.11)	11.9	9.7
4	142	101	153	117	0.82 (0.63, 1.07)	13.6	9.7
≤ 3	170	126	176	137	0.92 (0.72, 1.17)	12.1	11.5
Liver Metastasis	229	179	227	197	0.73 (0.59, 0.89)	10.9	8.3
Lung Metastasis	155	121	168	132	0.93 (0.73, 1.20)	12.0	10.4
Brain Metastasis	36	31	31	29	0.51 (0.30, 0.86)	10.0	4.8
Sites Involved							
> 2	201	158	202	178	0.77 (0.62, 0.95)	10.6	8.6
≤ 2	228	160	221	151	0.98 (0.78, 1.22)	13.3	12.6



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INSTITUT
JULES BORDET

Thank you