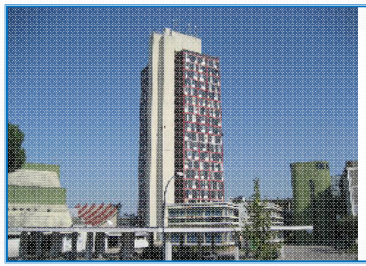
bjclub

breastJournalClub

Pearls from ESMO 2016



Mario Giuliano
Università degli Studi di Napoli Federico II

Napoli 10-11 Marzo 2017

ESMO 2016: the “record meeting”

- **ESMO 2016 has broken records of attendance**
  - 20.522 participants

- **1.640 studies presented, including 47 late-breaking trials**
  - A record number of research published in major medical journals such as NEJM, The Lancet Oncology and JAMA

- **Several practice-changing studies with positive results**
  - **ENGOT-OV16/NOVA** concerning landmark study for patients with recurrent ovarian cancer
  - **Keynote-024 and Keynote-021** presenting new immunotherapeutic options for advanced lung cancer
  - **Monaleesa 2** in HER2 negative advanced breast cancer
  - **EORTC 18071** with good survival results for patients with stage III melanoma
  - **Checkmate 141** study of patient reported outcomes in head and neck cancers

Pearls from ESMO 2016

Advanced Breast Cancer

- ER+ Disease
  - Single agent ET
  - Combination Strategies
    - CDK 4/6 inhibition
- HER2+ Disease
  - Trastuzumab biosimilars
- New Directions
  - New potential agents
  - New potential targets

Early Breast Cancer

- Neoadjuvant therapy
  - Interim results of neoMONARCH study
- Adjuvant therapy
  - Concurrent vs. sequential trastuzumab
- Molecular marker assays and patient outcome
- Identification of higher risk population

Pearls from ESMO 2016

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Early Breast Cancer

FALCON Trial

Study Design

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and/or PgR+
- Endocrine therapy-naïve

Stratification factors:

- Prior chemo for MBC
- Measurable disease
- Locally advanced vs. MBC

Fulvestrant 500 mg
(500 mg IM on days 0, 14, 28 then every 28 days)
+ Placebo

Anastrozole 1 mg + Placebo

Primary endpoint: PFS

Secondary: OS, ORR, CBR, DoR, DoCB, HRQol, Safety

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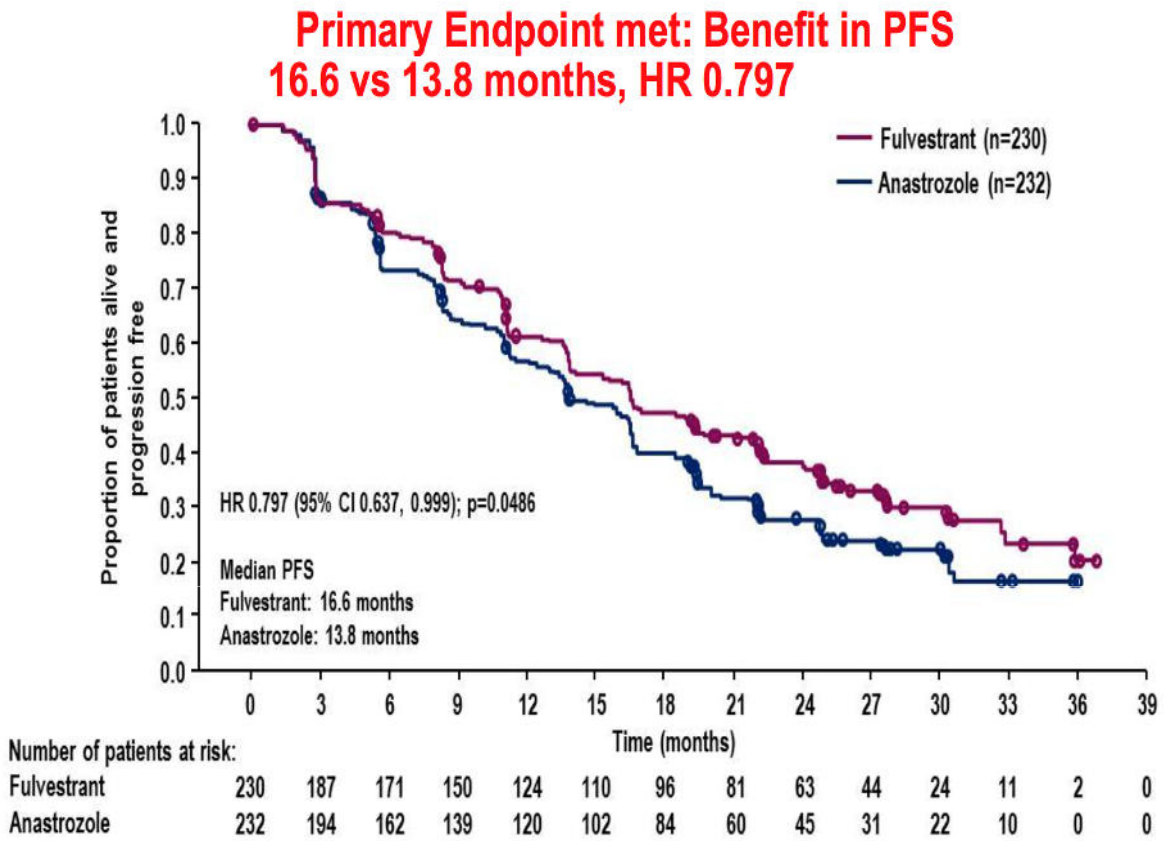
- N = 450 patients for 306 progression events;
- If true PFS HR was 0.69 this would provide 90% power at the 5% two-sided level (log-rank test)
- Subgroup analysis of PFS for pre-defined baseline covariates

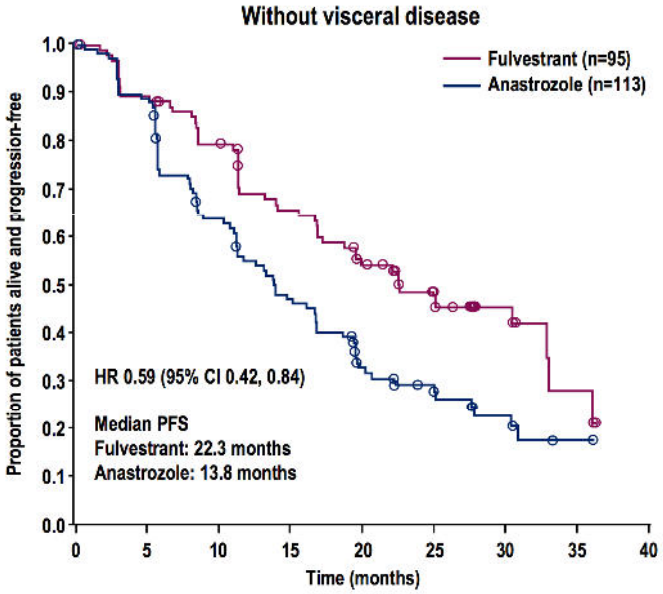
	Total (N=462)	
Any prior chemotherapy, n (%)	160	(34.6%)
Advanced disease	79	(17.1%)
Adjuvant / neoadjuvant	62 / 27	(13.4 %/ 5.8%)
Receptor status, n (%)		
ER+ / PgR+	354	(76.6%)
ER+ / PgR-	87	(18.8%)
Unknown	17	(3.7%)
Overall disease classification, n (%)		
Locally advanced disease	60	(13.0%)
Metastatic disease	402	(87.0%)
Visceral disease, n (%)	254	(55.0%)
Measurable disease, n (%)	389	(84.2%)

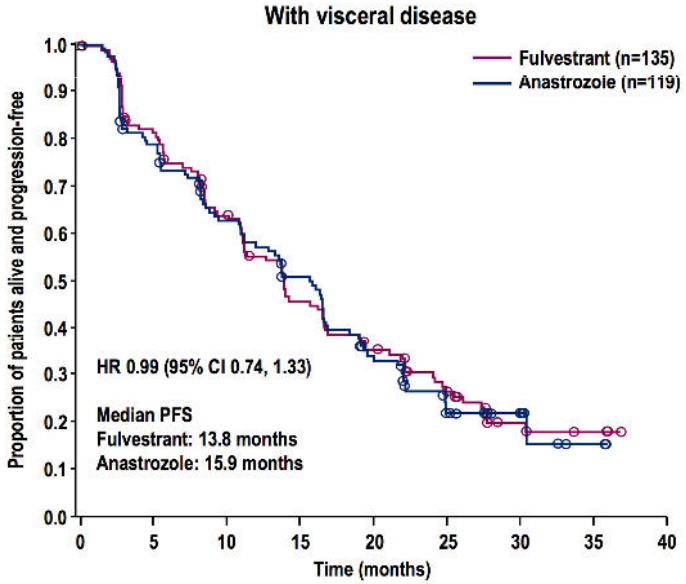
Ellis et Al., ESMO 2016

FALCON Trial

Results







Ellis et Al., ESMO 2016

Pearls from ESMO 2016

Advanced Breast Cancer

- **ER+ Disease**
  - Single agent ET
  - **Combination Strategies**
    - **CDK 4/6 inhibition**
- HER2+ Disease
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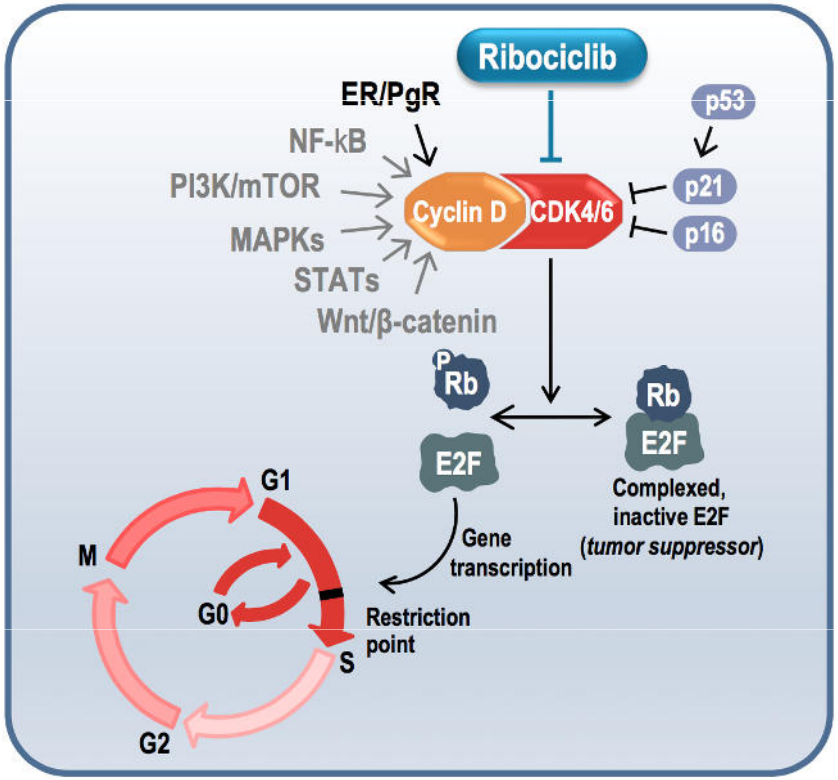
  - New potential agents
  - New potential targets

Early Breast Cancer

The Role of CDK4/6 in HR+ Breast Cancer



- Rb binding inactivates E2F, which regulates genes important for transition through the G1/S cell cycle restriction point[1,2]
- Phosphorylation of Rb by CDK4/6 leads to dissociation of E2F from Rb and cell cycle progression[1,2]
- Increased CDK4/6 activity driven by perturbations of other pathways is associated with endocrine therapy resistance[1,2]

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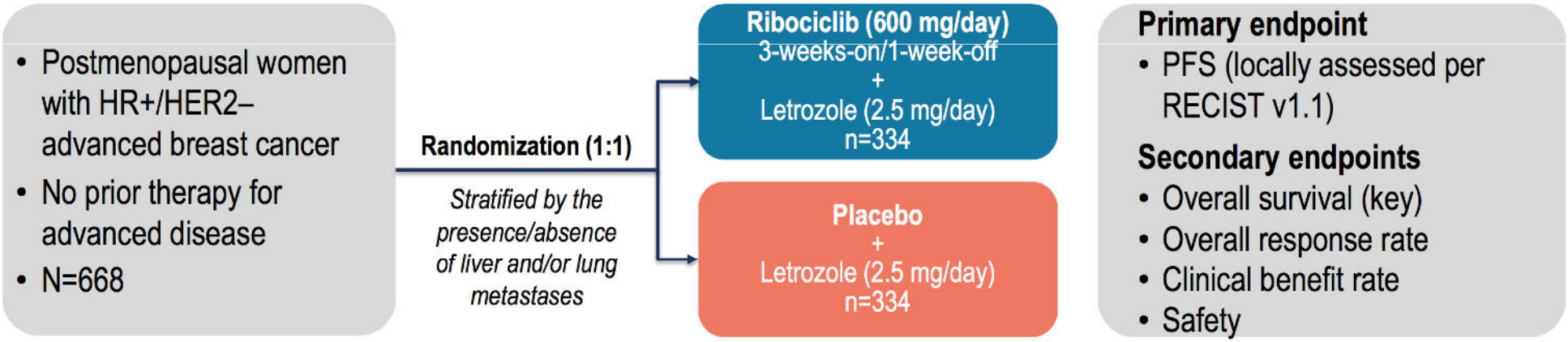
CDK, cyclin-dependent kinase; Rb, retinoblastoma.

1. Hosford S, Miller T. *Pharmgenomics Pers Med* 2014;7:203–215; 2. Thangavel C, *et al. Endocr Relat Cancer* 2011;18:333–345;.

MONALEESA-2

Study Design



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio ≤0.56 and p<0.0000129

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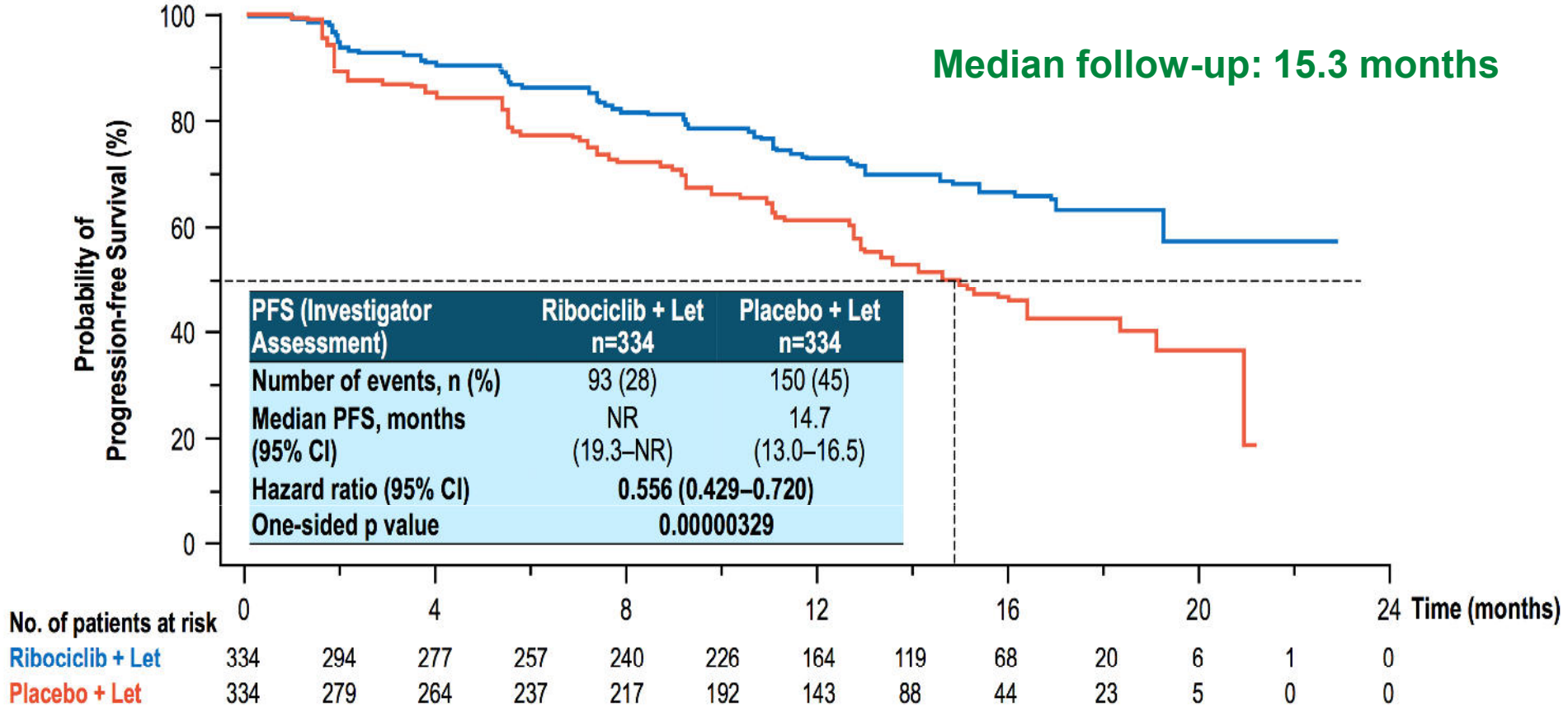
PFS, progression-free survival.
MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).

Hortobagyi G et al ESMO 2016 LBA 1

MONALEESA-2

Interim Analysis on Primary Endpoint



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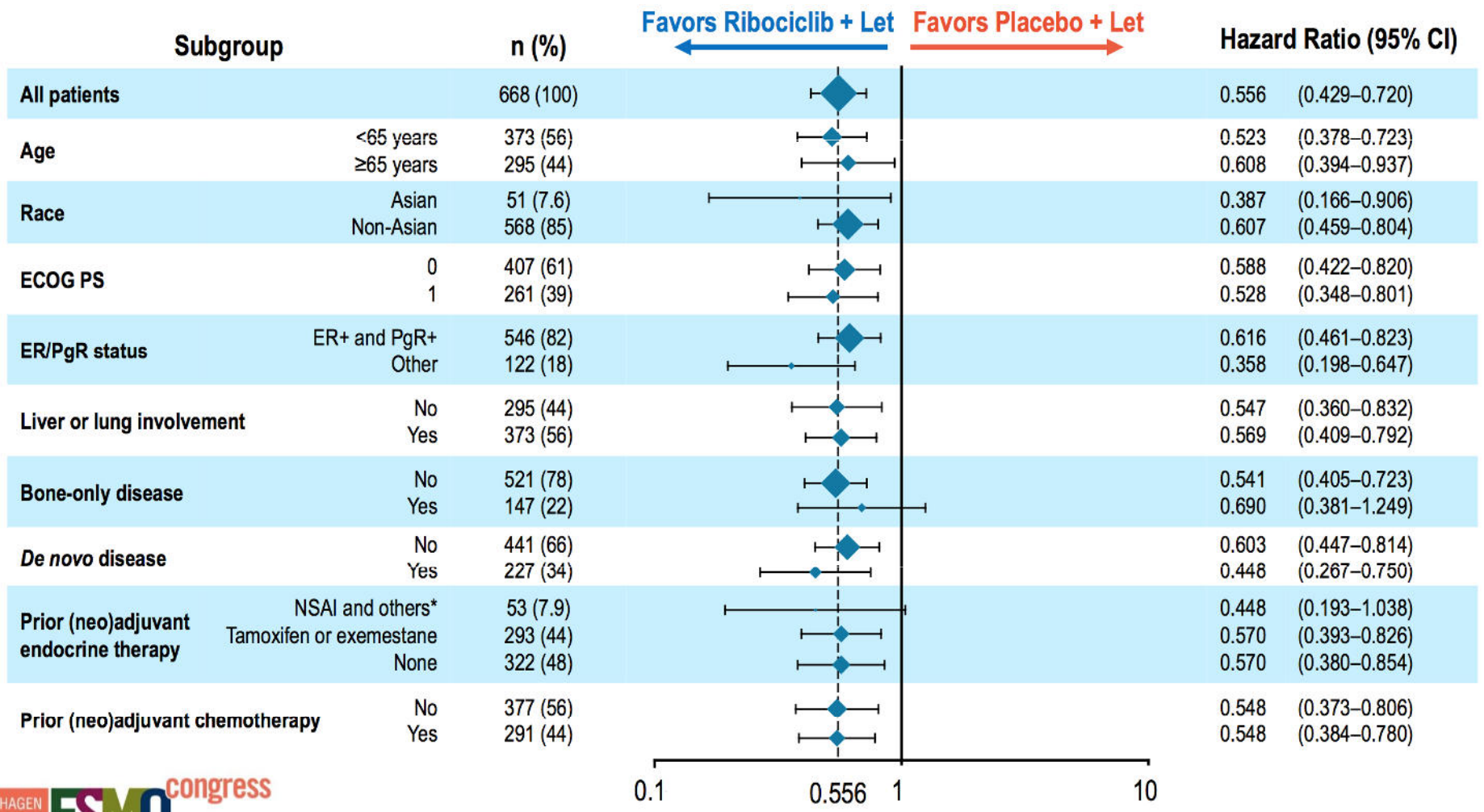
PFS results by independent central review: hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)

• Let, letrozole; NR, not reached.

Hortobagyi G et al ESMO 2016 LBA 1

MONALEESA-2

Subgroup Analysis



Subgroup		n (%)	Hazard Ratio (95% CI)
All patients		668 (100)	0.556 (0.429–0.720)
Age	<65 years	373 (56)	0.523 (0.378–0.723)
	≥65 years	295 (44)	0.608 (0.394–0.937)
Race	Asian	51 (7.6)	0.387 (0.166–0.906)
	Non-Asian	568 (85)	0.607 (0.459–0.804)
ECOG PS	0	407 (61)	0.588 (0.422–0.820)
	1	261 (39)	0.528 (0.348–0.801)
ER/PgR status	ER+ and PgR+	546 (82)	0.616 (0.461–0.823)
	Other	122 (18)	0.358 (0.198–0.647)
Liver or lung involvement	No	295 (44)	0.547 (0.360–0.832)
	Yes	373 (56)	0.569 (0.409–0.792)
Bone-only disease	No	521 (78)	0.541 (0.405–0.723)
	Yes	147 (22)	0.690 (0.381–1.249)
***De novo* disease**	No	441 (66)	0.603 (0.447–0.814)
	Yes	227 (34)	0.448 (0.267–0.750)
Prior (neo)adjuvant endocrine therapy	NSAI and others*	53 (7.9)	0.448 (0.193–1.038)
	Tamoxifen or exemestane	293 (44)	0.570 (0.393–0.826)
	None	322 (48)	0.570 (0.380–0.854)
Prior (neo)adjuvant chemotherapy	No	377 (56)	0.548 (0.373–0.806)
	Yes	291 (44)	0.548 (0.384–0.780)

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- NSAI, non-steroidal aromatase inhibitor.
- *Excludes patients who had received tamoxifen.

Hortobagyi G et al ESMO 2016 LBA 1

PALOMA-2

Biomarker Analysis

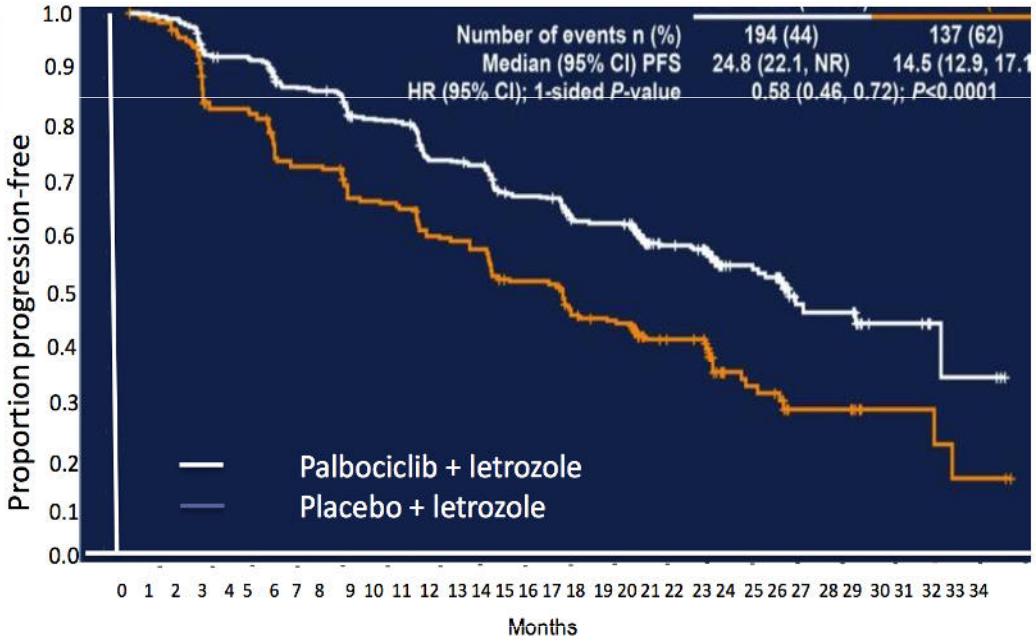
Postmenopausal ER+ HER2– advanced breast cancer with no prior treatment for advanced disease AI-resistant patients excluded N=666

RANDOMISE

2:1

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 md QD)

Placebo (3/1 schedule) + letrozole (2.5 mg QD)



- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: Response, OS, safety, biomarkers, PROs

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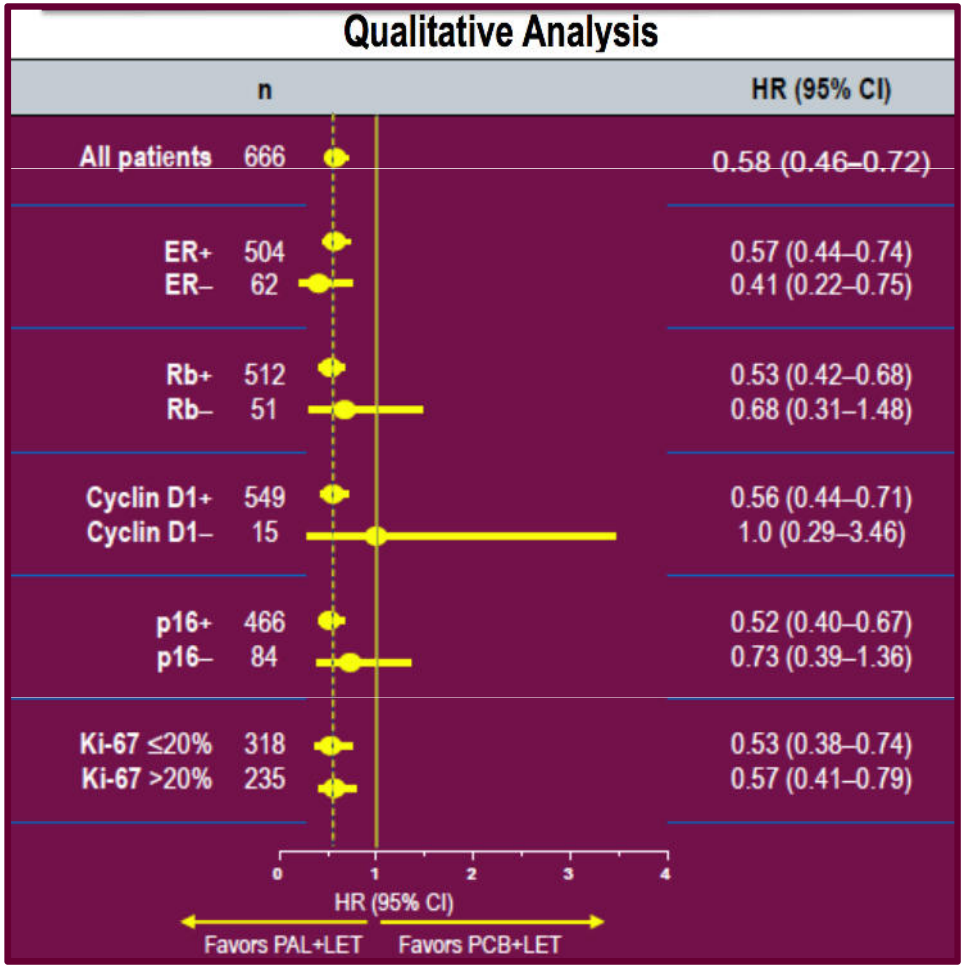
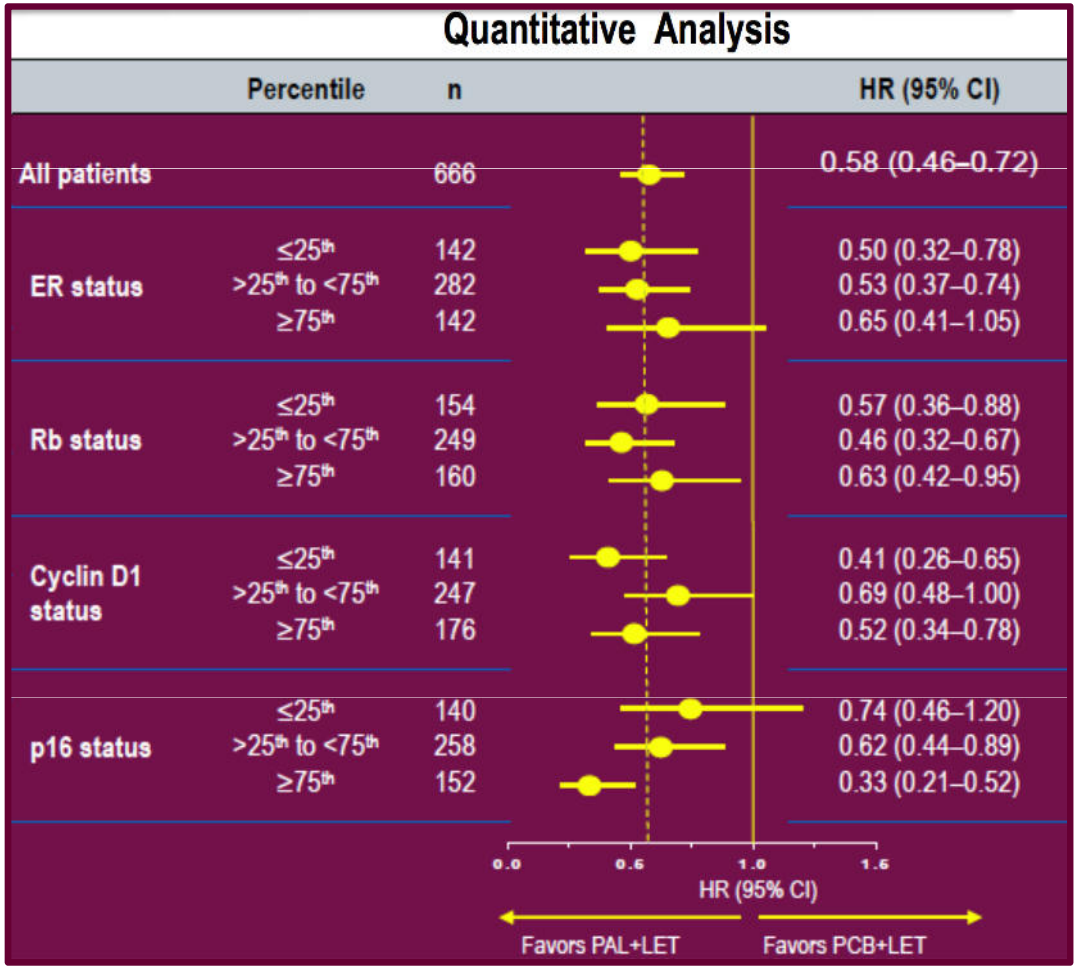
Finn R, et al. ASCO 2016, Abstract 504 (oral abstract)

PALOMA-2

Subgroup Analysis: PFS by biomarker





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HR=hazard ratio; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Finn R et al. ESMO 2016 LBA15

PALOMA-2

Impact of Palbociclib on Quality of Life

No significant differences between the treatment groups in change from baseline scores for Physical, Social/Family, Emotional, and Functional Well-Being were observed

Data consistent with PALOMA-3 (Annals Oncol)

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Rugo et al. ESMO 2016, 225PD

Pearls from ESMO 2016

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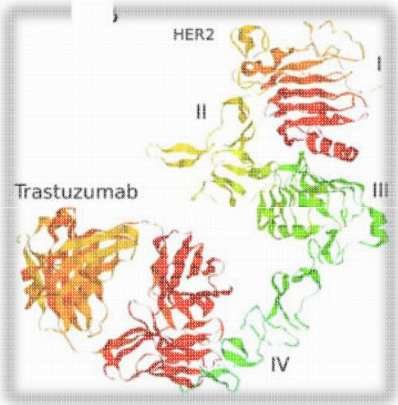
Early Breast Cancer

Biological Complexity of Monoclonal Antibodies

Intrinsic Complexity

- Size
- Structure
- Physiochemistry
- Heterogeneity

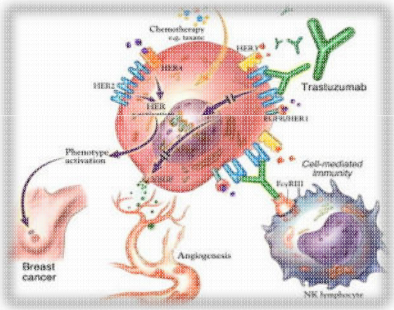


Additional Complexity

- Manufacturing process
- Formulation
- Handling
- Route of administration

Immunogenicity

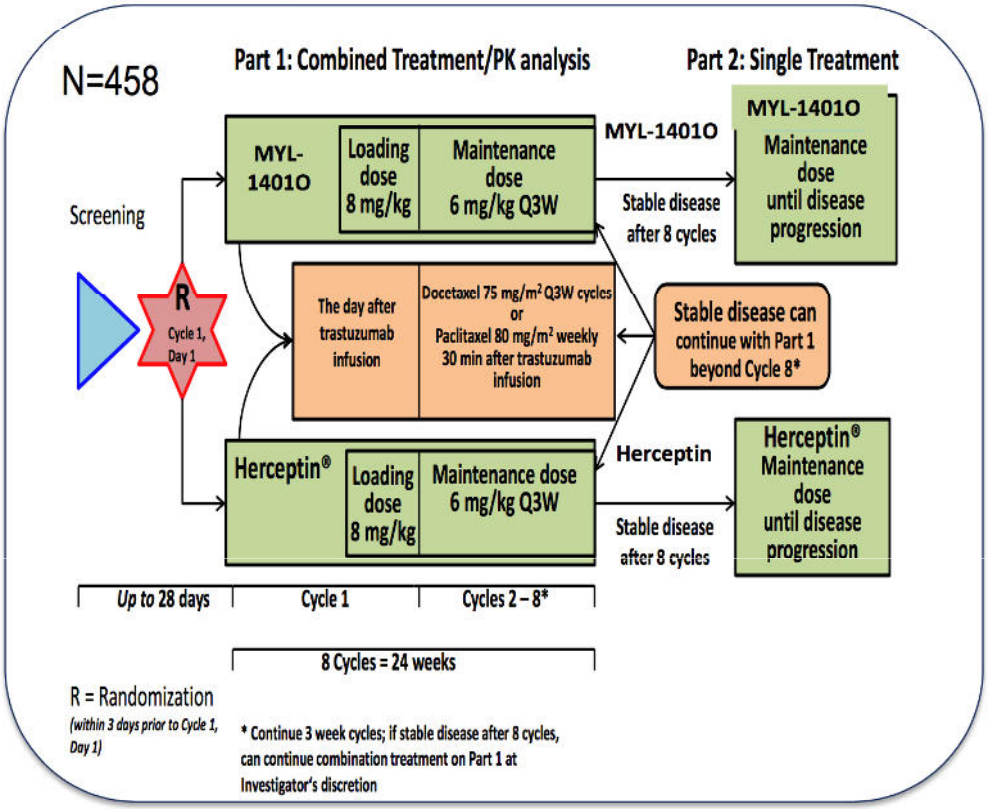
- Host related: genetic predisposition by MHC alleles, immunosuppression
- Product related: Structural properties, glycosylation, impurities, formulation, storage, aggregates



Trastuzumab Biosimilar Studies

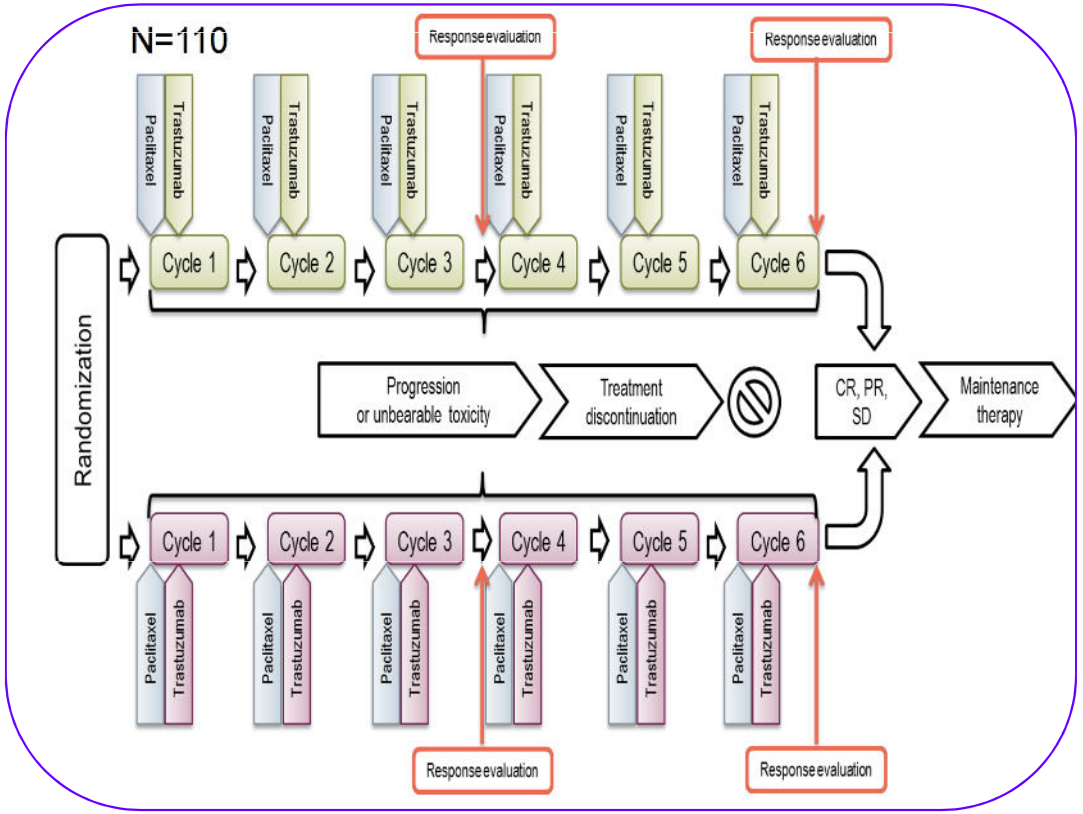
Design

Heritage Study – Trastuzumab MYL-1401O Biosimilar



Rugo H et Al., ESMO 2016. Abstract #LBA

Trastuzumab BCD-022 Biosimilar



Shustova M et Al., ESMO 2016. Abstract 224 PD

Trastuzumab Biosimilar Studies

Results

Heritage Study – Trastuzumab MYL-1401O Biosimilar

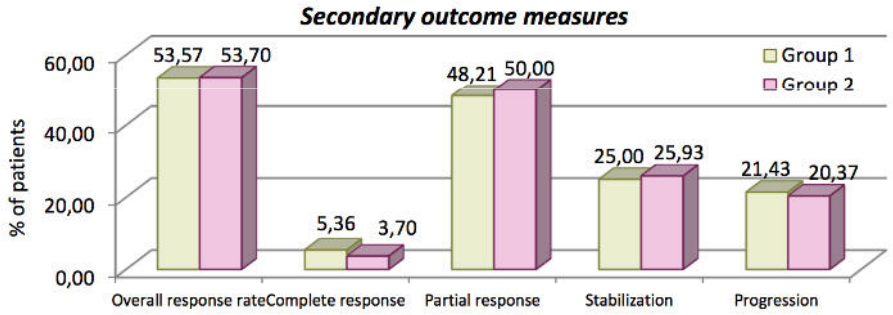
	MYL-1401O + Taxane N= 230	Herceptin + Taxane N= 228
Overall response rate n (%)	160 (69.6)	146 (64.0)
95% CI	(63.62, 75.51)	(57.81, 70.26)
Ratio of ORR: MYL-1401O/Herceptin (FDA)	1.09	
90% CI	(0.974, 1.211)	
95% CI	(0.954, 1.237)	
Difference in ORR: MYL-1401O-Herceptin (EMEA)	5.53	
90% CI	(-1.70, 12.69)	
95% CI	(-3.08, 14.04)	

Rugo H et Al., ESMO 2016. Abstract #LBA

Trastuzumab BCD-022 Biosimilar

Parameter	Group 1 (n = 54)		Group 2 (n = 56)		p
	n	% (95% CI)	n	% (95% CI)	
ORR	30	53,57 (40,70 - 65,98)	29	53,70 (40,60 - 66,31)	0,862[2]
Difference in ORR	-0,13% (-19,83% – 18,35%)				

[1] Yates-corrected Pearson's χ^2 test



Shustova M et Al., ESMO 2016. Abstract 224 PD

Pearls from ESMO 2016

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- **New Directions**
  - **New potential agents**
  - **New potential targets**

Early Breast Cancer

Phase II, PM01183 Monotherapy In Metastatic Breast Cancer

The University Of Sheffield.

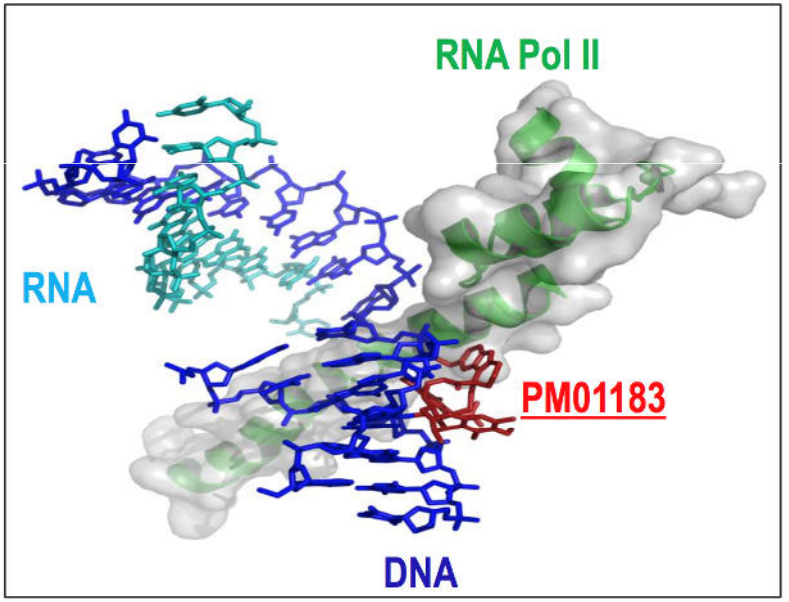
Lurbinectedin (PM01183) is a trabectedin analog:

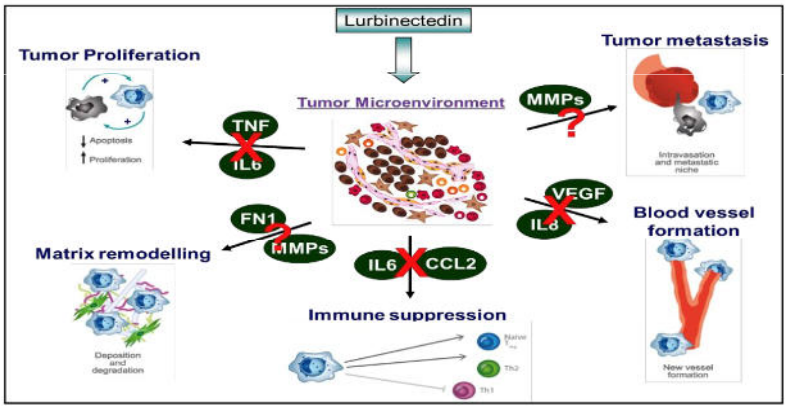
- Inhibits active transcription (RNA Pol II degradation) *(1)*:
  - Generates double strand DNA breaks
  - Affects tumor microenvironment

Deficient homologous recombination system favors PM01183-induced apoptosis *(2)*

Antitumor activity observed in patients resistant to platinum compounds *(3)*

Two Phase III trials are currently ongoing, one as a single agent in platinum resistant ovarian cancer, and one in combination with doxorubicin in 2nd line SCLC





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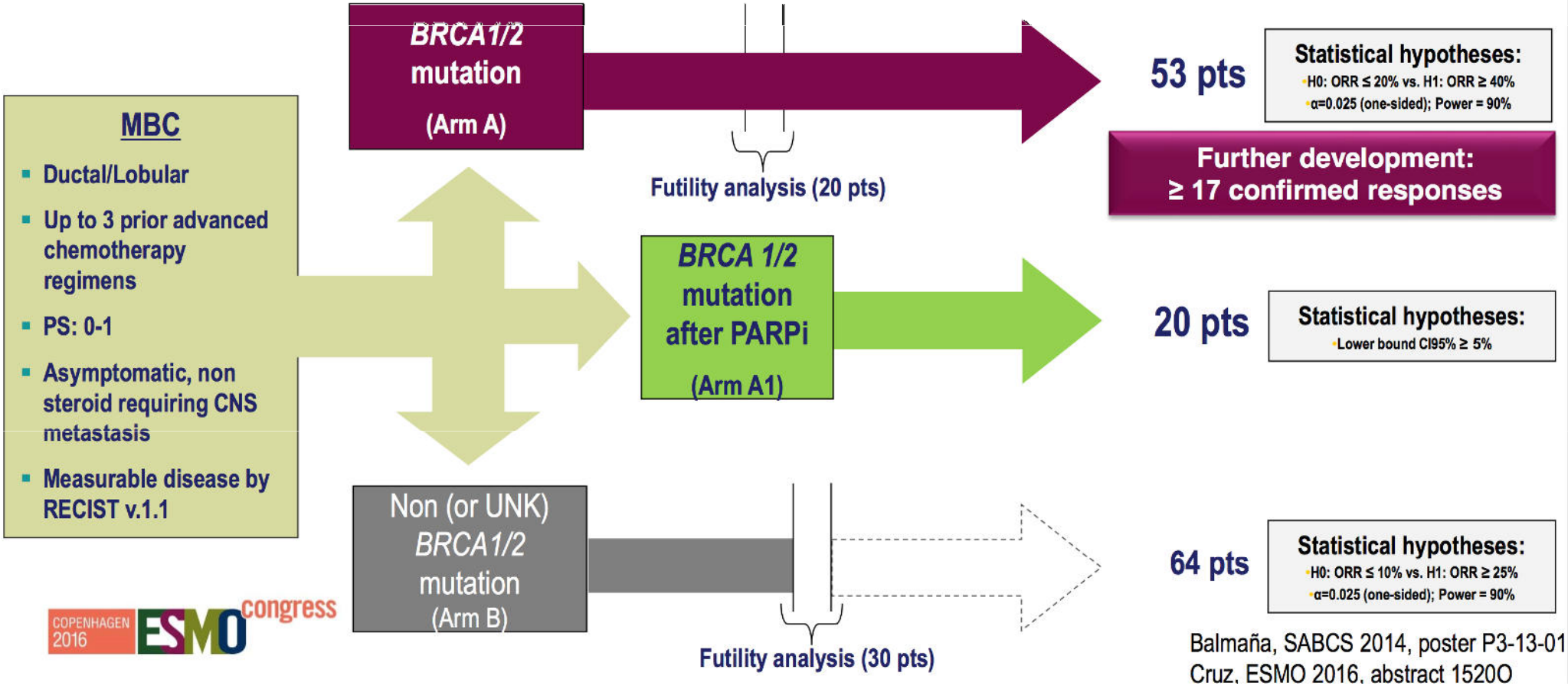
1. Santamaría G. et al, Mol Cancer Ther, 2016
2. Allavena P. et al, Proc AACR 2016
3. Poveda A. et al. ASCO 2014, oral presentation

Phase II, PM01183 Monotherapy In Metastatic Breast Cancer (MBC) – 7mg Flat Dose Amended To 3.5mg/m2

The University Of Sheffield.



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Balmaña, SABCS 2014, poster P3-13-01
Cruz, ESMO 2016, abstract 1520O

Response Data For Specific Subpopulations

The University Of Sheffield.

	Prior Platinum		BRCA		Hormone Status		Prior Chemo	
	No (n: 27)	Yes (n: 27)	1 (n: 31)	2 (n: 23)	Triple Negative (n: 33)	HR+ (n: 21*)	0-1 (n: 31)	2-3 (n: 23)
ORR (95% CI)	**56%** (35.3-55.6)	**26%** (11.1-25.9)	**26%** (11.9-25.8)	**61%** (38.5-60.9)	**36%** (13.3-27.3)	**48%** (38.4-81.9)	**52%** (33.1-69.9)	**26%** (10.2-48.4)
Duration of Response (95% CI)	**10.2 m** (3.0-13.5)	**5.9 m** (2.8-12.8)	**6.6 m** (2.8-12.8)	**6.7 m** (3.4-13.5)	**7.7 m** (2.8-12.8)	**6.7 m** (2.8-13.4)	**8.5 m** (3.0-12.8)	**3.4 m** (2.8-20.5)
Disease control rate	25 (93%)	19 (70%)	23 (74%)	22 (96%)	26 (79%)	19 (90%)	27 (87%)	18 (78%)
Clinical benefit (CR+PR+SD ≥ 3 mo)	19 (70%)	14 (52%)	14 (45%)	19 (83%)	29 (88%)	14 (67%)	21 (68%)	12 (52%)

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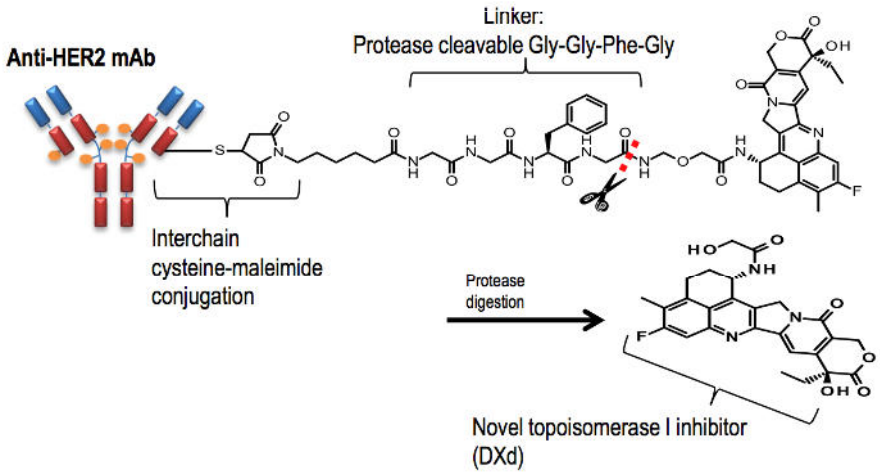
* Including 2 patients also HER-2 +

Balmana J et al. ESMO 2016 Abstract 2230

Single Agent Activity Of Her2 Antibody Drug-Conjugate DS-8201A

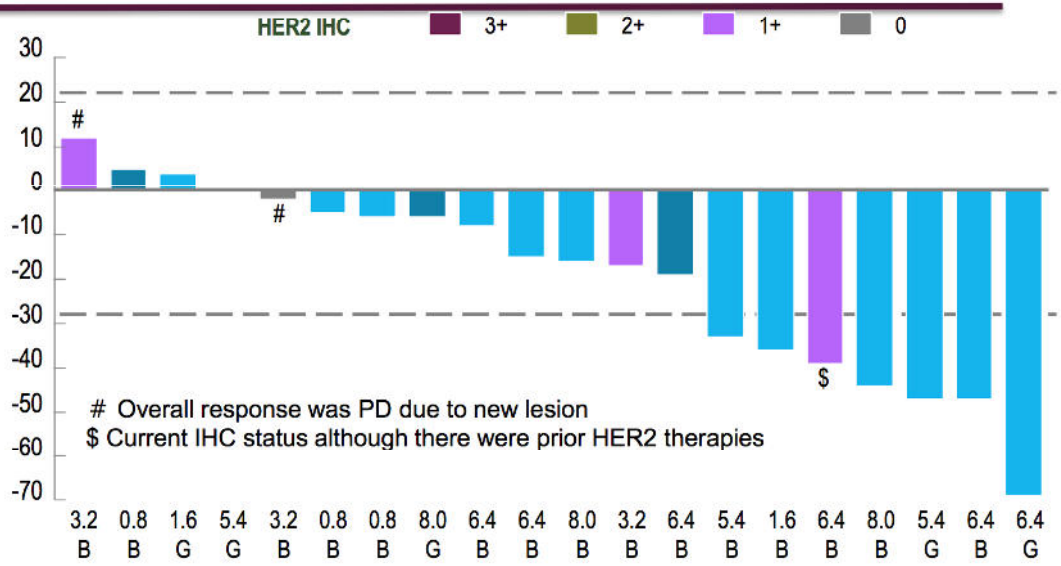
The University Of Sheffield.

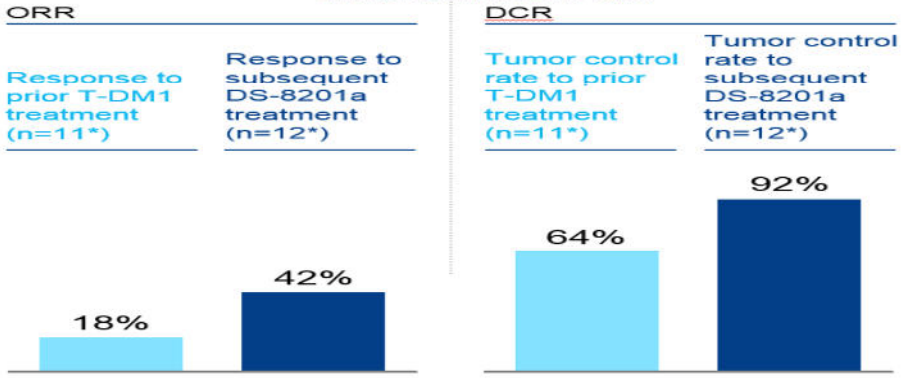
Structure of DS-8201a compared with T-DM1



	DS-8201a	T-DM1
Antibody	Anti-HER2 Ab	Trastuzumab
Payload	Topoisomerase I inhibitor (DXd)	Tubulin inhibitor (DM1)
DAR*	7-8	3.5

* DAR: Average drug-to-antibody Ratio





Tamura K et al. ESMO 2016 Abstract LBA 17

Pathways Altered In Breast Carcinomas

The University Of Sheffield.

N=8564

	ERBB Pathway	Hormone Therapy Resistant (*ESR1* Mut)	HR Deficient	IO Sensitive	PI3K/AKT/mTOR Pathway	FGFR Pathway	CDK Pathway	Other Kinases
Total Cases	1294	796	1266	419	4375	2650	2685	630
% Total Cases	15%	9%	15%	5%	51%	31%	31%	7%
Unique Cases	274	109	309	48	1442	226	231	87
% Unique Cases	3%	1%	4%	1%	17%	3%	3%	1%
Therapy Examples	Trastuzumab, Pertuzumab, Afatinib, Lapatinib, Neratinib	*[Fulvestrant, Tamoxifen]*	Olaparib	Pembrolizumab, Nivolumab, Atezolizumab, Ipilumumab	Everolimus, Temsirolimus	Pazopanib, Ponatinb	Palbociclib	Sorafenib, Regorafenib, Dabrafenib, Vemurafenib, Crizotinib, Cabozantinib, Sunitinib

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Ross JR et al. ESMO Abstract 229PD

Pearls from ESMO 2016

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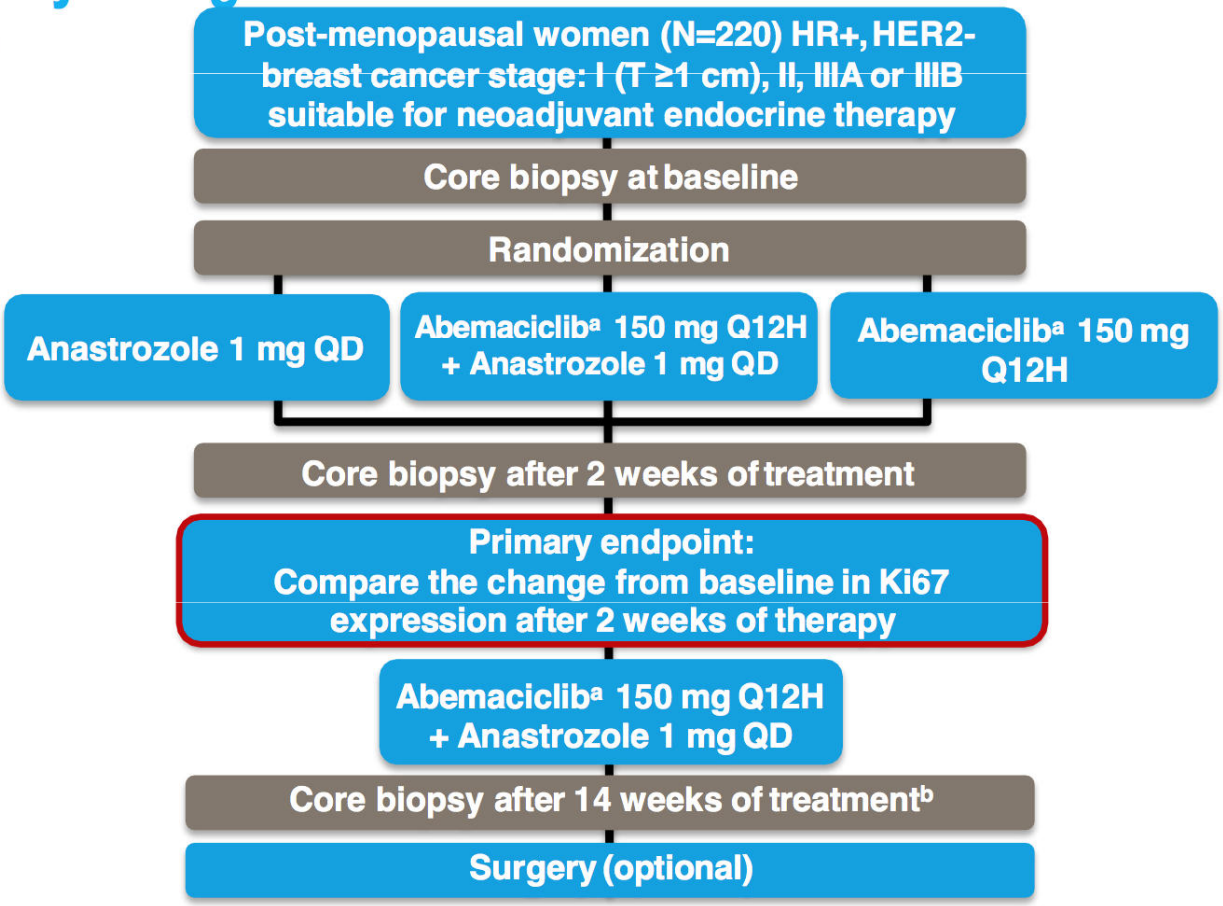
- **Neoadjuvant therapy**
  - **Interim results of neoMONARCH study**
- Adjuvant therapy
  - Concurrent vs. sequential trastuzumab
- Molecular marker assays and patient outcome
- Identification of higher risk population

NeoMONARCH

Study Design

neoMONARCH: Phase II study design

- Abemaciclib 150 mg BID is tolerable when dosed on a continuous schedule with endocrine therapy[1]
- The most common adverse event has been diarrhea
  - Typically occurred within the first 7 days of treatment
  - Manageable with use of loperamide or dose reduction
- Loperamide was administered prophylactically for the first 28 days then at discretion of investigator



[1]Patnaik A et al. *Cancer Discovery* 2016;6:740-5

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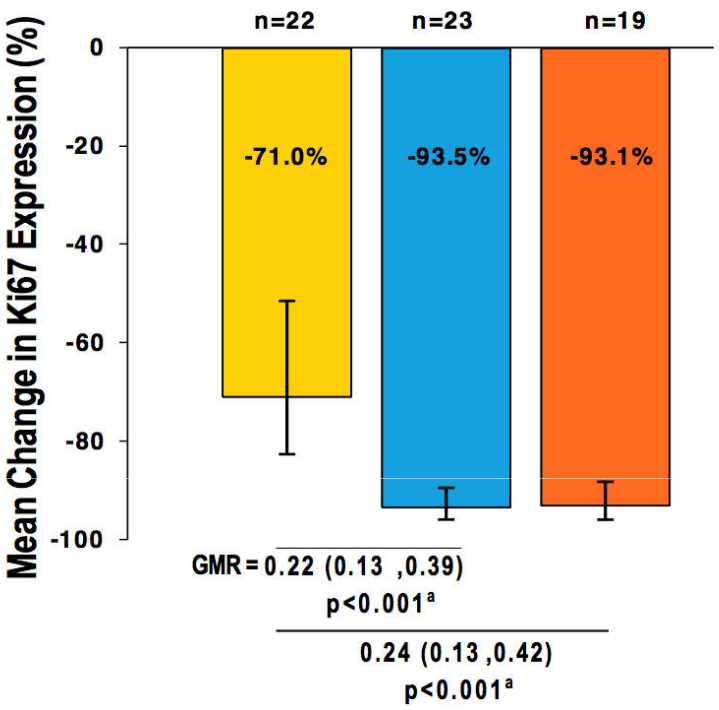
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; Q12H = every 12 hours; QD = once daily
[a]Participants receive loperamide with each dose of abemaciclib
[b]Participants who experience benefit following 14 weeks may remain on neoadjuvant therapy for up to 8 additional weeks

NeoMONARCH

Change in Ki67

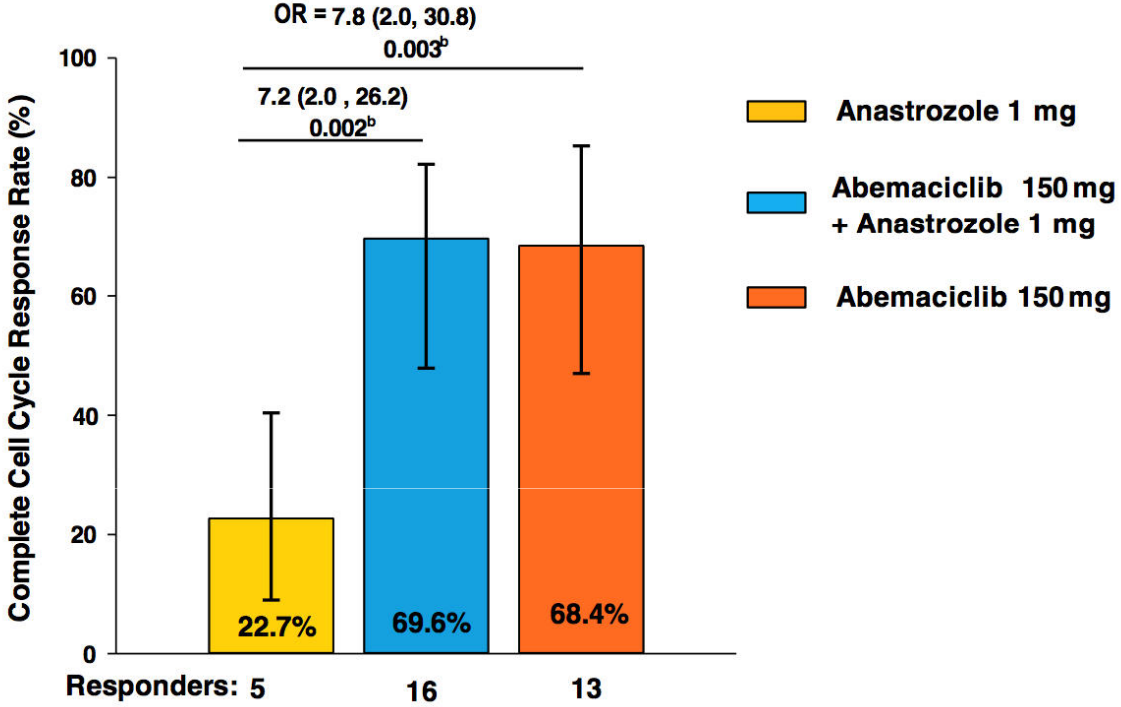
- Study met the boundary for statistical significance at the interim analysis (boundary p <0.03)

Geometric Mean Change



Complete Cell Cycle Arrest

Ki67 index <2.7% at 2 weeks



Abbreviations: GMR = geometric mean ratio, OR = odds ratio

[a]Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value. p-values are based on a one-sided hypothesis test from a linear model with treatment, PR status (positive versus negative/unknown) and tumor size (<2 cm versus ≥2 cm and <5 cm versus ≥5 cm) as fixed effects.

[b]A responder is identified as a patient with a ln(Ki67) value of less than 1. Odds ratio (OR), 2-sided 90% CI, p value. p-value is calculated by Fisher's Exact test of a one-sided hypothesis.

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Pearls from ESMO 2016

Advanced Breast Cancer

- ER+ Disease
  - Single agent ET
  - Combination Strategies
    - CDK 4/6 inhibition
- HER2+ Disease
  - Trastuzumab biosimilars
- New Directions
  - New potential agents
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Early Breast Cancer

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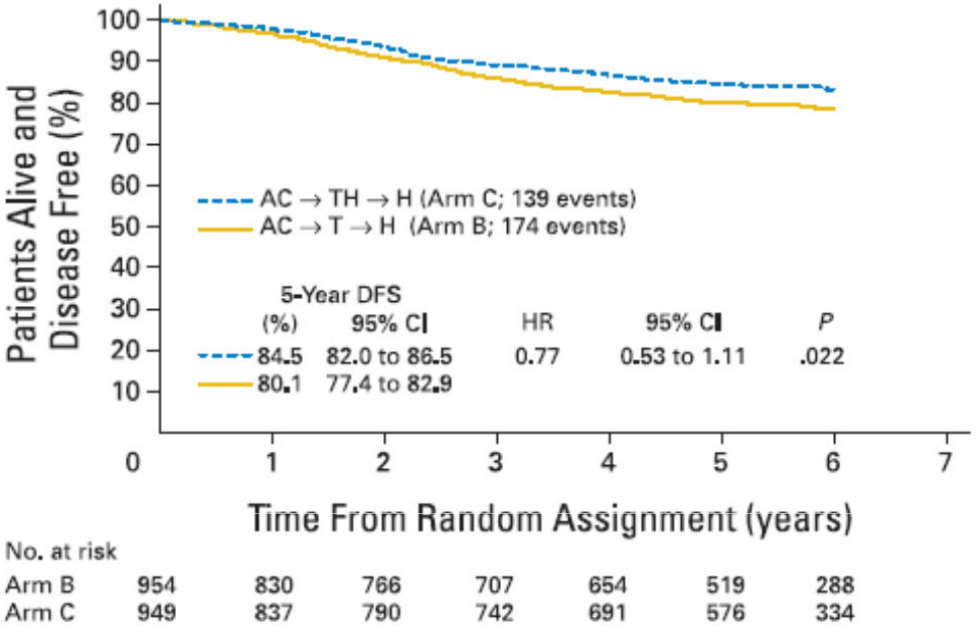
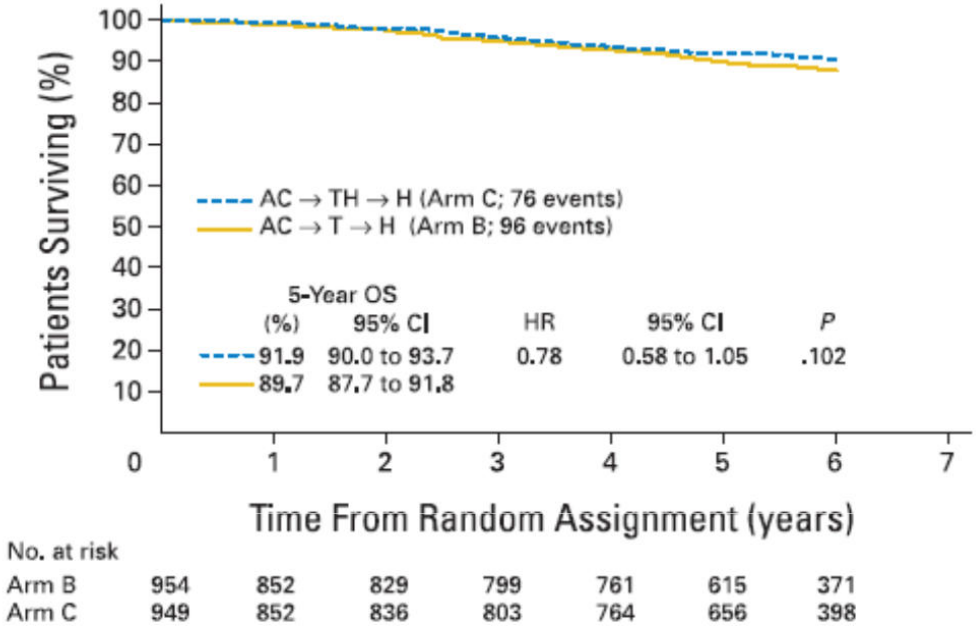
Sequential vs. Concurrent Trastuzumab in EBC

NCCTG Trial





The P value (.02) did not cross the prespecified O'Brien-Fleming boundary (.00116) for the planned interim analysis

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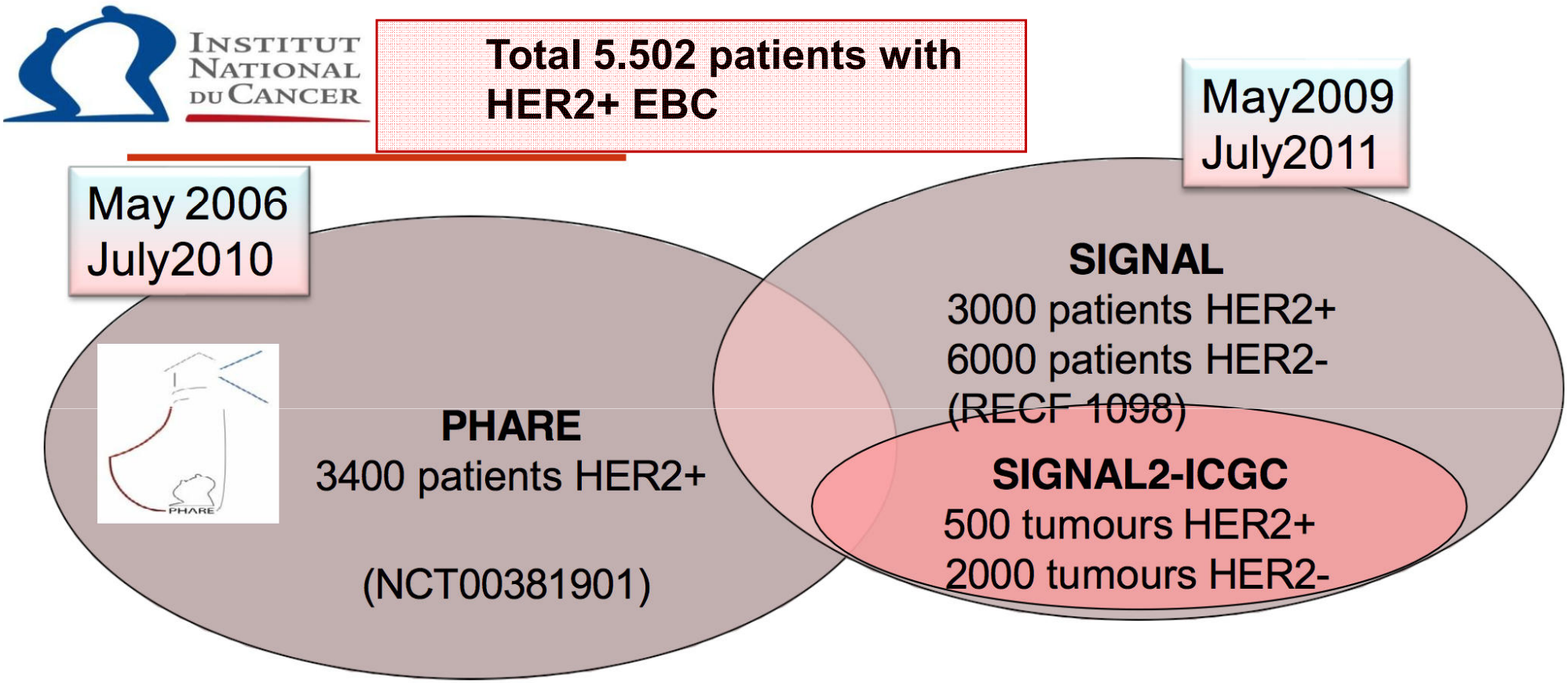
J Clin Oncol 29:4491-4497, 2011

Sequential and concomitant adjuvant trastuzumab in HER2+ EBC

Results from the SIGNAL/PHARE prospective cohort



Pivot et al, ESMO 2016

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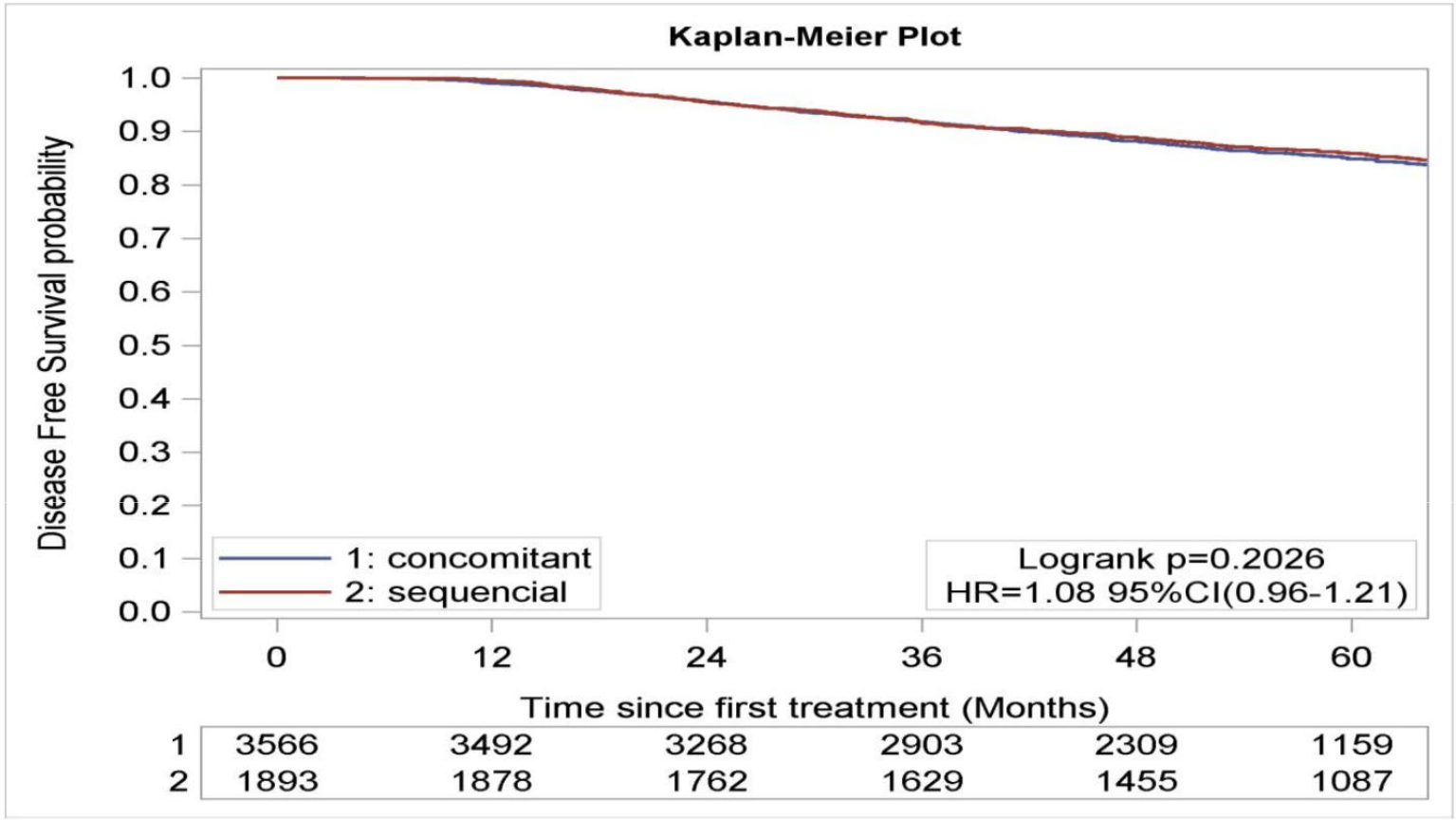

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FIRST PROSPECTIVELY-DESIGNED OUTCOME STUDY IN ESTROGEN RECEPTOR (ER)+ BREAST CANCER (BC) PATIENTS (PTS) WITH N1MI OR 1-3 POSITIVE NODES IN WHOM TREATMENT DECISIONS IN CLINICAL PRACTICE INCORPORATED THE 21-GENE RECURRENCE SCORE (RS) RESULT

S.M. Stemmer, et al.

Abstract: 3040

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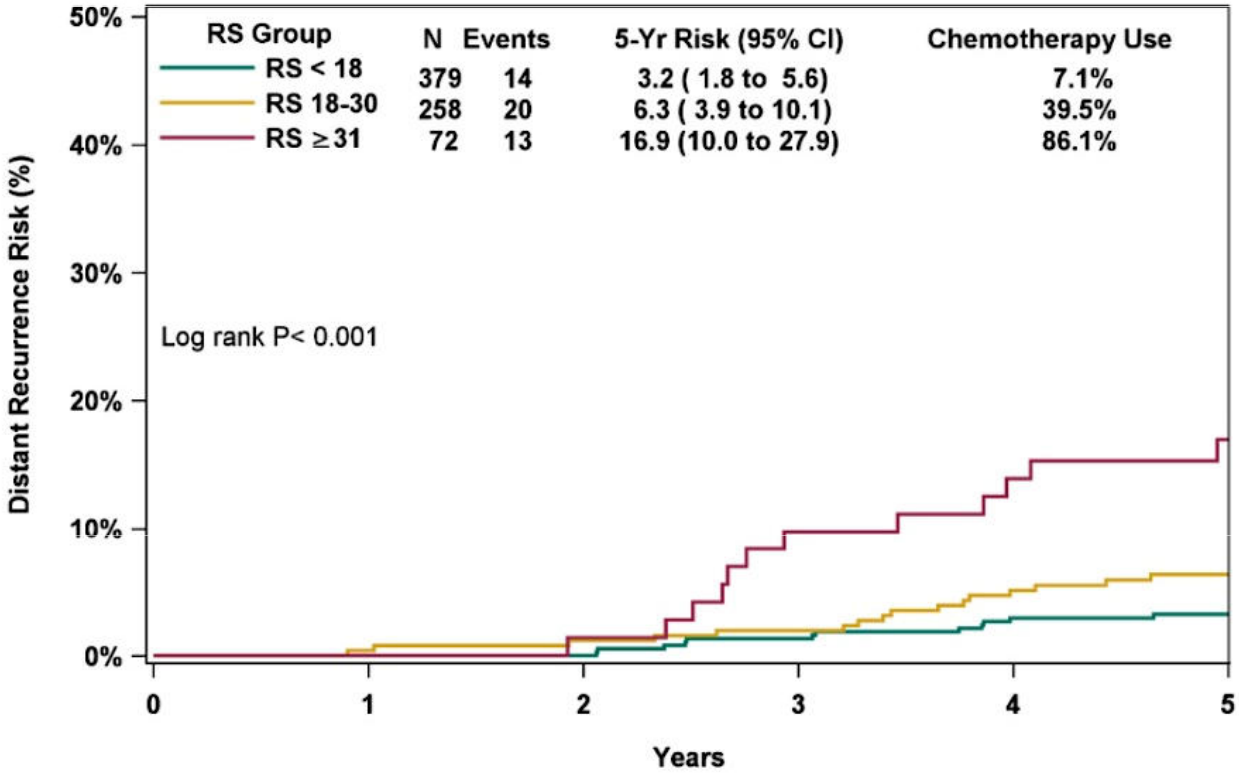
Risk of Distant Recurrence by RS Group



- **The overall number of patients with distant recurrence by RS risk group (Low/Intermediate/High): 14/379, 20/258, 13/72, respectively**
- **The rate of distant recurrence in the low RS group was 3.2% within 5 years compared to 16,9% for the high RS group**

Stemmer SM et Al., ESMO 2016. Abstract 3040

BREAST CANCER-SPECIFIC SURVIVAL IN PATIENTS WITH LYMPH NODE-POSITIVE HORMONE RECEPTOR POSITIVE INVASIVE BREAST CANCER AND 21-GENE RECURRENCE SCORE RESULTS IN THE SEER DATABASE

D.P. Miller, et al.

Abstract: 4013

esmo.org

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5-year Breast Cancer-specific Survival (95% CI), by RS Group and Number of Positive Lymph Nodes – Total N=6,768

	RS <18 (N=3,919; 23.8% CT Use*)		RS 18-30 (N=2,380; 49.0% CT Use*)		RS ≥31 (N=469; 77.0% CT Use*)	
# Positive Nodes	n	5-y BCSS	n	5-y BCSS	n	5-y BCSS
Micrometastases	1,644	98.9% (97.4%, 99.6%)	998	99.1% (97.9%, 99.6%)	178	84.0% (74.1%, 90.4%)
1	1549	99.4% (98.4%, 99.8%)	893	95.9% (92.6%, 97.7%)	178	93.3% (85.2%, 97.0%)
2	458	97.1% (91.3%, 99.0%)	268	97.8% (91.4%, 99.4%)	45	87.0% (54.4%, 96.9%)
3	139	95.1% (87.0%, 98.2%)	104	87.2% (65.2%, 95.7%)	29	89.8% (63.5%, 97.5%)
4+	129	92.8% (73.5%, 98.2%)	117	83.9% (69.5%, 91.9%)	39	65.4% (40.9%, 81.8%)

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*Chemotherapy (CT) use reported as 'yes' (vs. 'no/unknown')

Miller DP et Al., ESMO 2016. Abstract 4013

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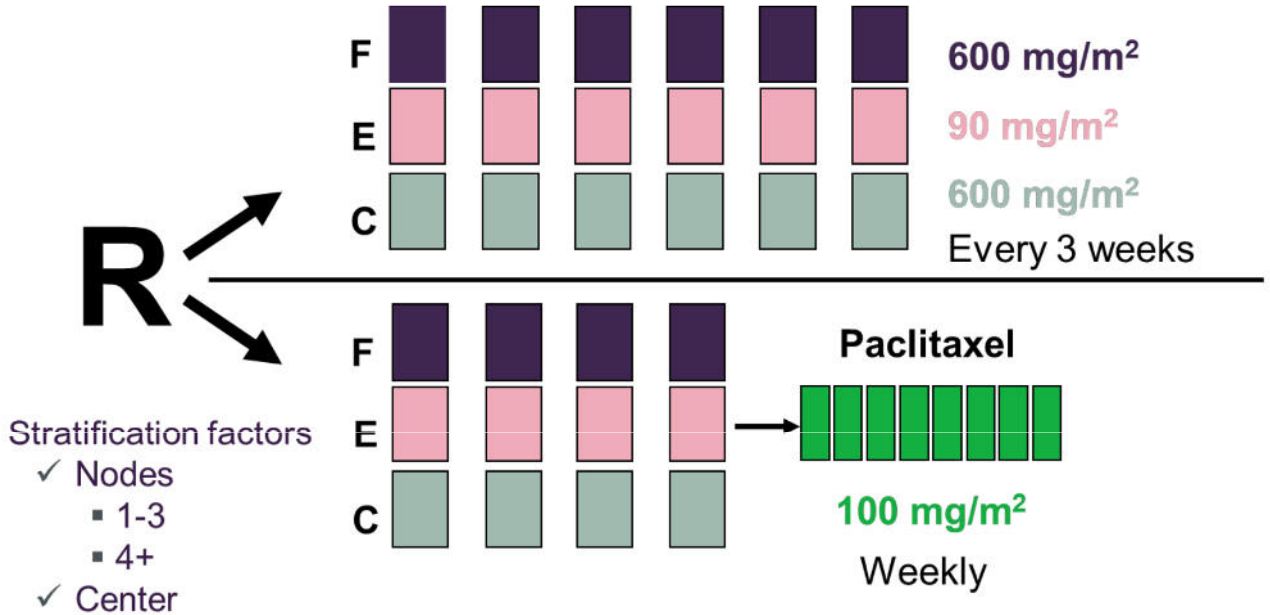
Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

Study design

GEICAM spanish breast cancer group



Stratification factors
- ✓ Nodes
  - 1-3
  - 4+
- ✓ Center
- ✓ Menopausal status

dNLR expression

✓ The dNLR was constructed as follows (1):

$$\text{dNLR} = \frac{\text{neutrophil count}}{\text{white cells} - \text{neutrophil count}} \quad (10^9/\text{L})$$

Ocana A., ESMO 2016. Abstract 3576

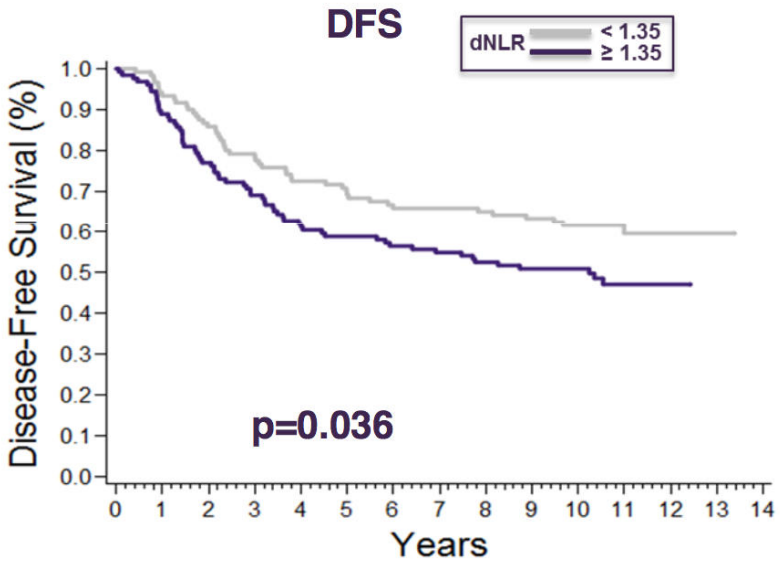
Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

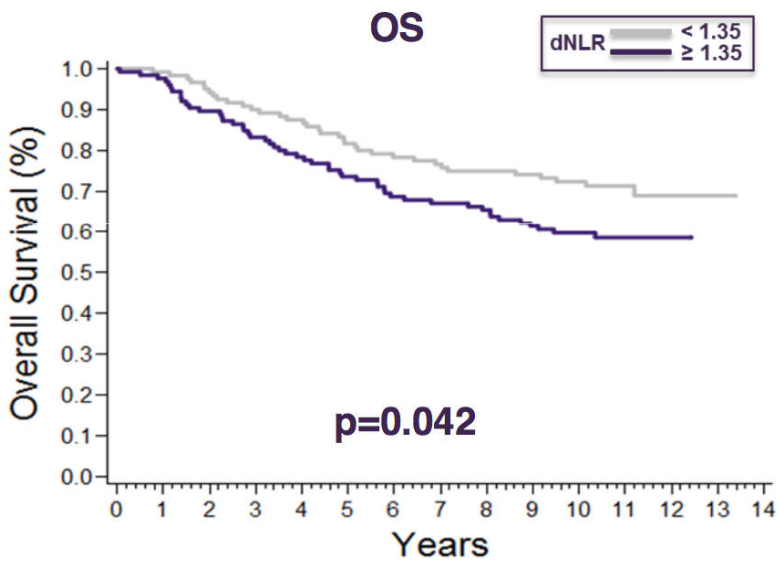
Association of dNLR with outcome

By PAM50 subtypes (Luminal A, Luminal B, HER2-enriched, Basal-like)

GEICAM spanish breast cancer group

- ✓ **For the non luminal subgroups (HER2-enriched, basal-like), elevated levels of dNLR (median cut-off) were associated with worse prognosis regardless of treatment arm.**





Ocana A., ESMO 2016. Abstract 3576

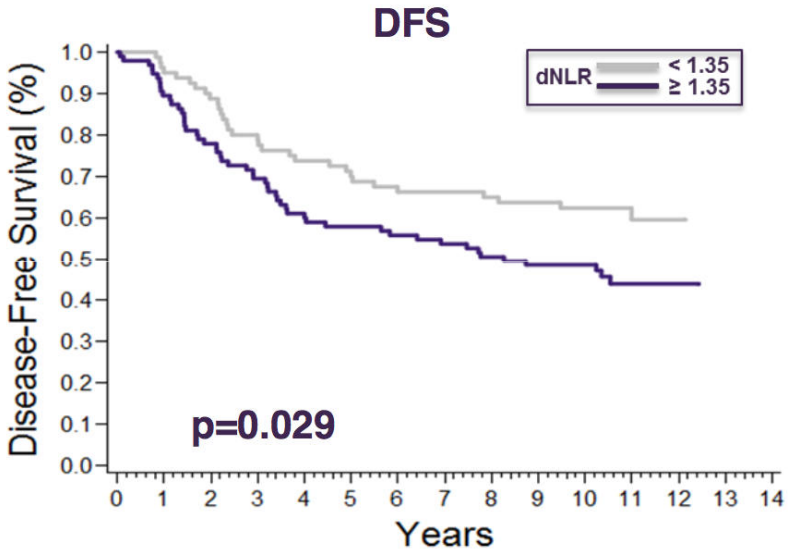
Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

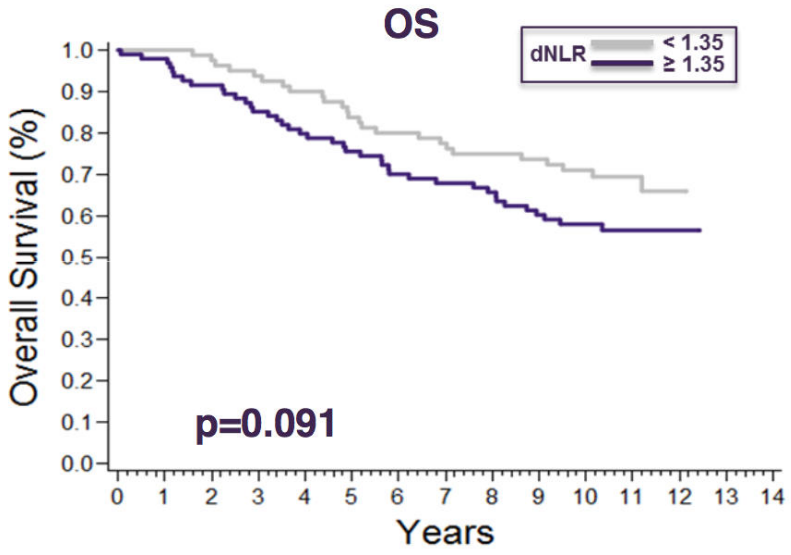
Association of dNLR with outcome

GEICAM spanish breast cancer group

By PAM50 subtypes

- ✓ **For the HER2-enriched subgroup, elevated dNLR was significantly associated with DFS and non-significantly associated with OS regardless of treatment arm.**





Ocana A., ESMO 2016. Abstract 3576

GESTATIONAL BREAST CANCER: DISTINCTIVE MOLECULAR AND CLINICO-EPIDEMIOLOGICAL FEATURES. GEICAM/2012-03 STUDY

J. de la Haba, et al.

Abstract: 3679

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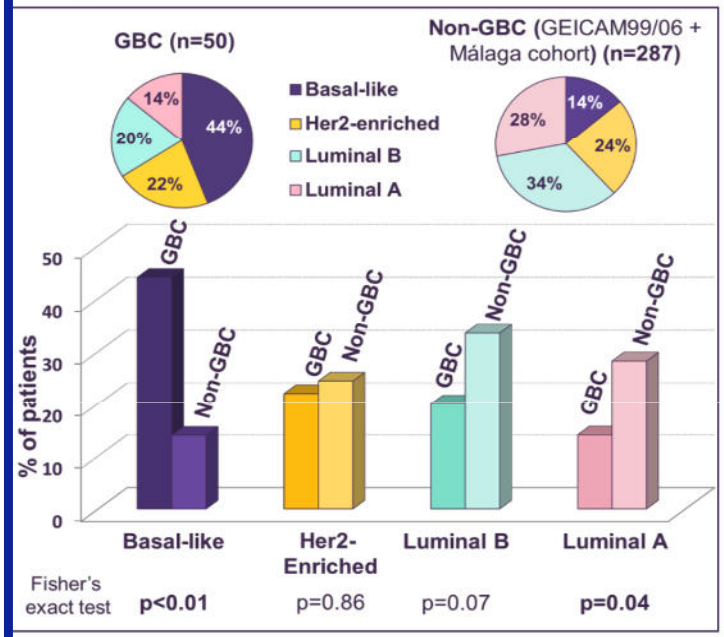
Gestational BC: Distinctive Molecular and Clinico-Epidemiological Features

GEICAM/2012-03 Study

GEICAM/2012-03 Results

✓ GBC patients showed a more aggressive clinico-pathological profile.



Patient characteristics and treatment types n (%)		GBC	Non-GBC		
		GEICAM/2012-03	Alamo III	GEICAM/9906	Málaga
Mean age at diagnosis		35	37	37	37
Negative HR		30 (**43**)	330 (**24**)	33 (**16**)	27 (**28**)
Tumor size (T2-T4)		51 (**76**)	787 (**56**)	176 (**60**)	84 (**92**)
Grade 3		38 (**63**)	479 (**40**)	121 (**44**)	38 (**47**)
High Ki67 (≥20%)		33 (**89**)	209 (**61**)	46 (**22**)	60 (**65**)
Family history of BC		32 (**47**)	296 (**25**)	NA	NA
Mean age at first partum		31	26	NA	NA
First therapy	CT*	Neoadj.: 34 (**49**) Adj.: 29 (**42**) 1st line ABC: 5 (**7**)	Neoadj.: 202 (**14**) Adj.: 1106 (**75**) 1st line ABC: 54 (**4**)	Adj.: 293 (**100**)	Neoadj.: 96 (**100**)
	Only HT	1 (**1**)	68 (**4**)	0	0
	No systemic therapy	1 (**1**)	43 (**3**)	0	0

treatment; Neoadj.: Neoadjuvant treatment; ABC: Advanced Breast Cancer. *CT combined or not with HT or targeted therapy.

✓ Intrinsic subtypes in GBC were 44% Basal-like, 22% Her2-enriched, 20% Luminal B and 14% Luminal A.

✓ Basal-like phenotype was enriched (44% *vs* 14%, p<0.01) and Luminal (A+B) phenotype was less prevalent (34% *vs* 62%, p<0.01), being more evident in Luminal A than in Luminal B cases.

CONCLUSIONS: Our study suggests that GBC patients have tumors of a particularly aggressive biology, with a higher rate of basal-like subtypes and a lower proportion of luminal subtypes compared to non-GBC patients of similar age.

de la Haba J., ESMO 2016. Abstract 3679