ASCO Breast Cancer Updates

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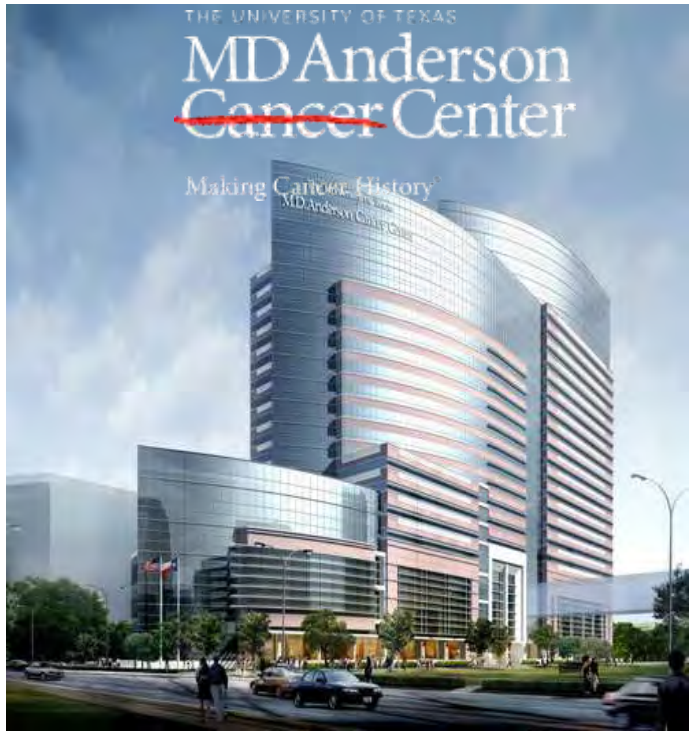


Disclosures:

Research Support: Novartis, Pfizer, Polyphor

Honoraria for Steering Committee Service: GSK, Novartis, Pfizer

Consulting: Genomic Health

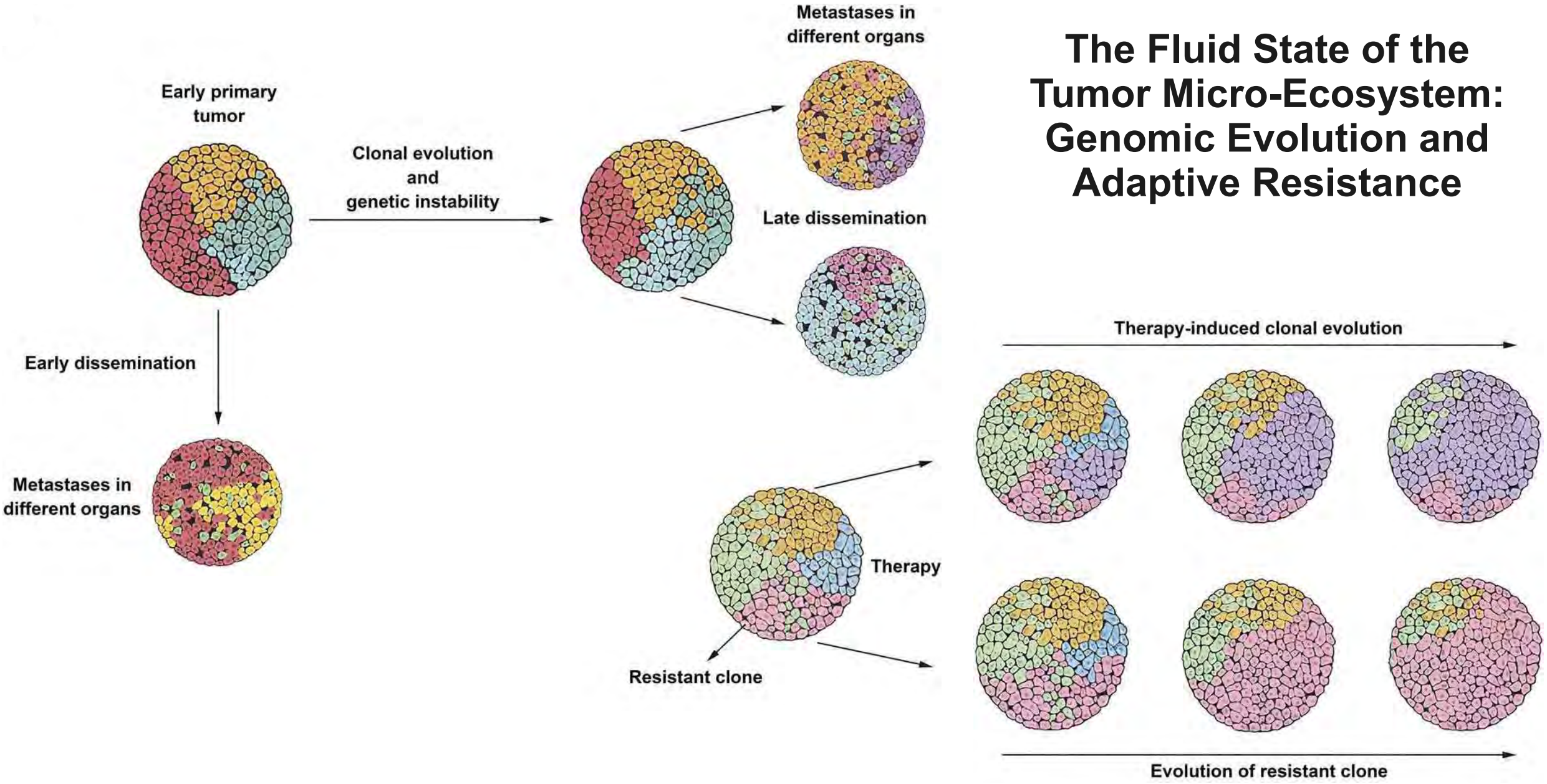
Progress in all Receptor Subtypes! – HR+, Triple Negative, HER+

- Improved Survival From CDK 4/6 Inhibitor Ribociclib
- Longer Time To Progression With AKT Inhibitor
- More Precise Decision-making For Adjuvant Chemotherapy

- Improved Survival From Immunotherapy – Checkpoint Inhibitor Atezolizumab

- Engineered HER2 Antibody Provides a Benefit Over Trastuzumab (Herceptin)
- Neratinib as a HER2 Kinase Inhibitor Partner With Capecitabine
- Longer Adjuvant Endocrine Therapy – When Does It Help?

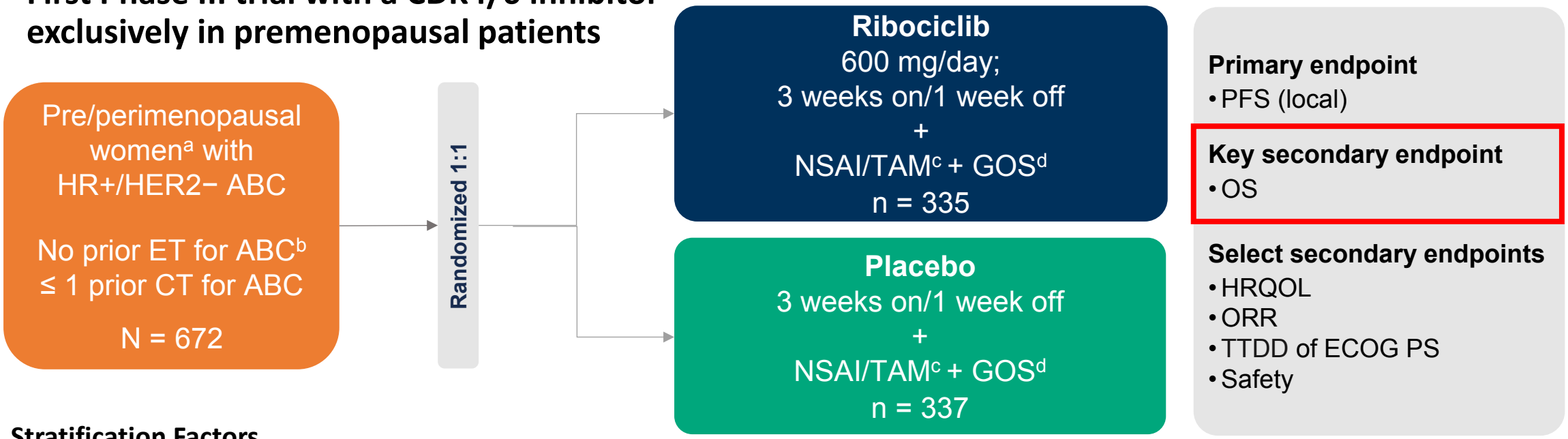
The Fluid State of the Tumor Micro-Ecosystem: Genomic Evolution and Adaptive Resistance



Santarpia L et al. The Oncologist 2016

MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients



Stratification Factors

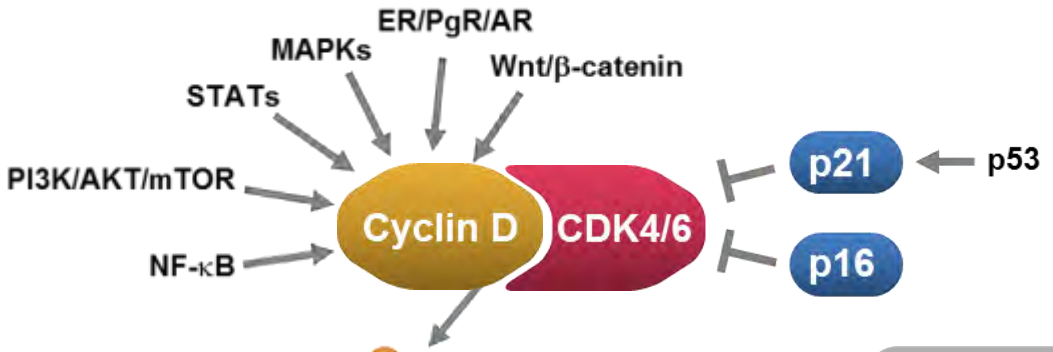
- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.

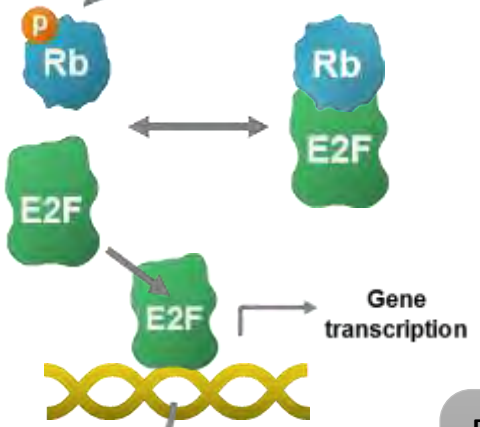
[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.

CDK4/6 Controls Cell Cycle Progression From G1 to S Phase by Regulating the Activity of Rb

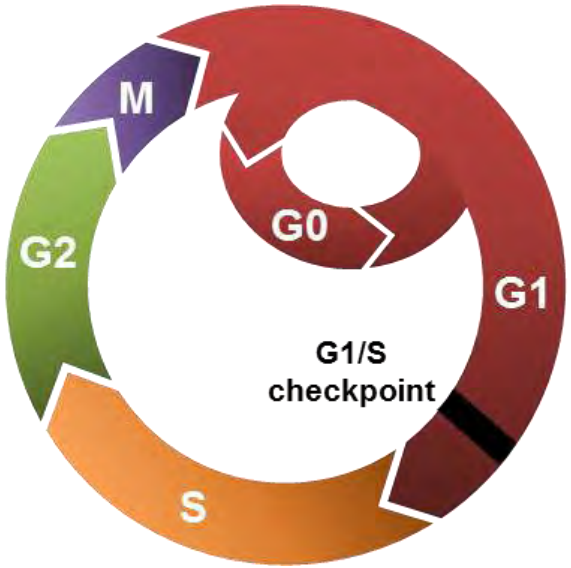
Synthesis of D-type cyclins (cyclin D1, D2, and D3) and association with CDK4/6 is initiated in response to mitogenic signaling pathways[1]



Active cyclin D–CDK4/6 phosphorylates Rb, decoupling Rb from E2F and allowing transcription of genes required for cell cycle progression[1]



Rb inhibits E2F-mediated transcription by binding to and sequestering E2F[2]

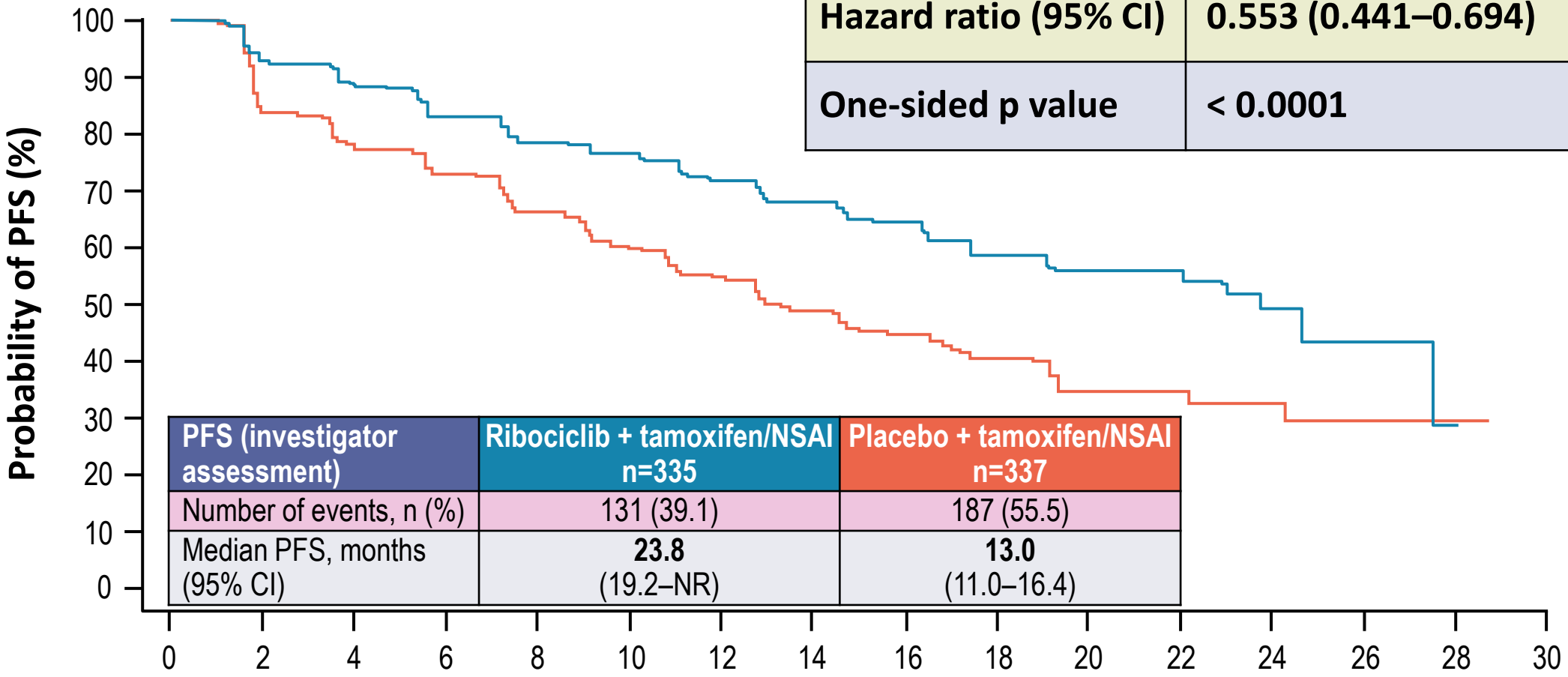


E2F activates transcription of genes necessary for S-phase entry and cell cycle progression[2]

1. Lange CA, et al. Endocr Relat Cancer. 2011
2. Rader J, et al. Clin Cancer Res 2013
Figure adapted from Lange CA, et al. Endocr Relat Cancer 2011

MONALEESA-7: Primary endpoint: PFS (investigator-assessed)

Hazard ratio (95% CI)	0.553 (0.441–0.694)
One-sided p value	< 0.0001



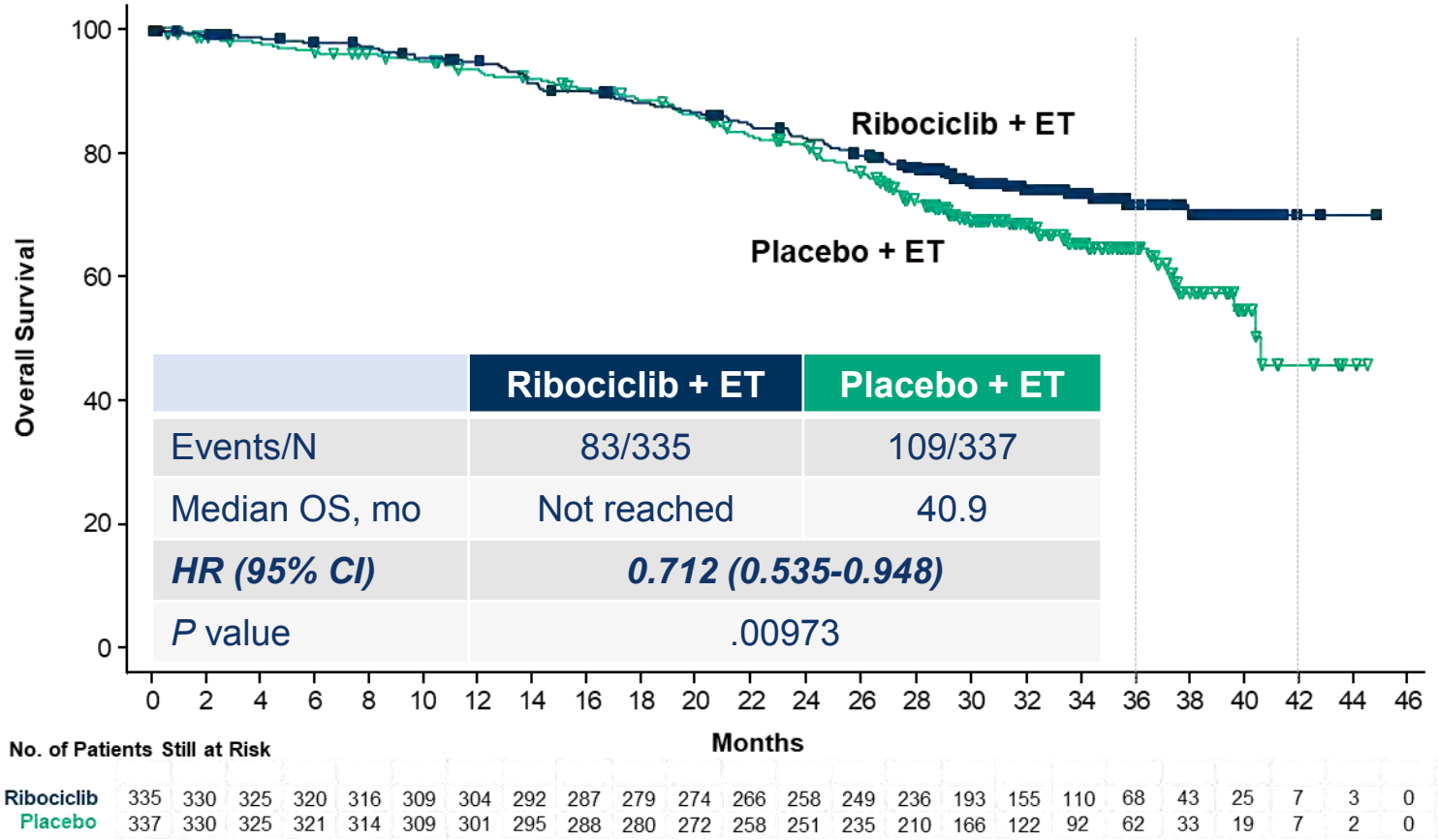
PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	**23.8** (19.2–NR)	**13.0** (11.0–16.4)

No. at risk

Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

Tripathy D, et al. Lancet Oncol 2018

Overall Survival



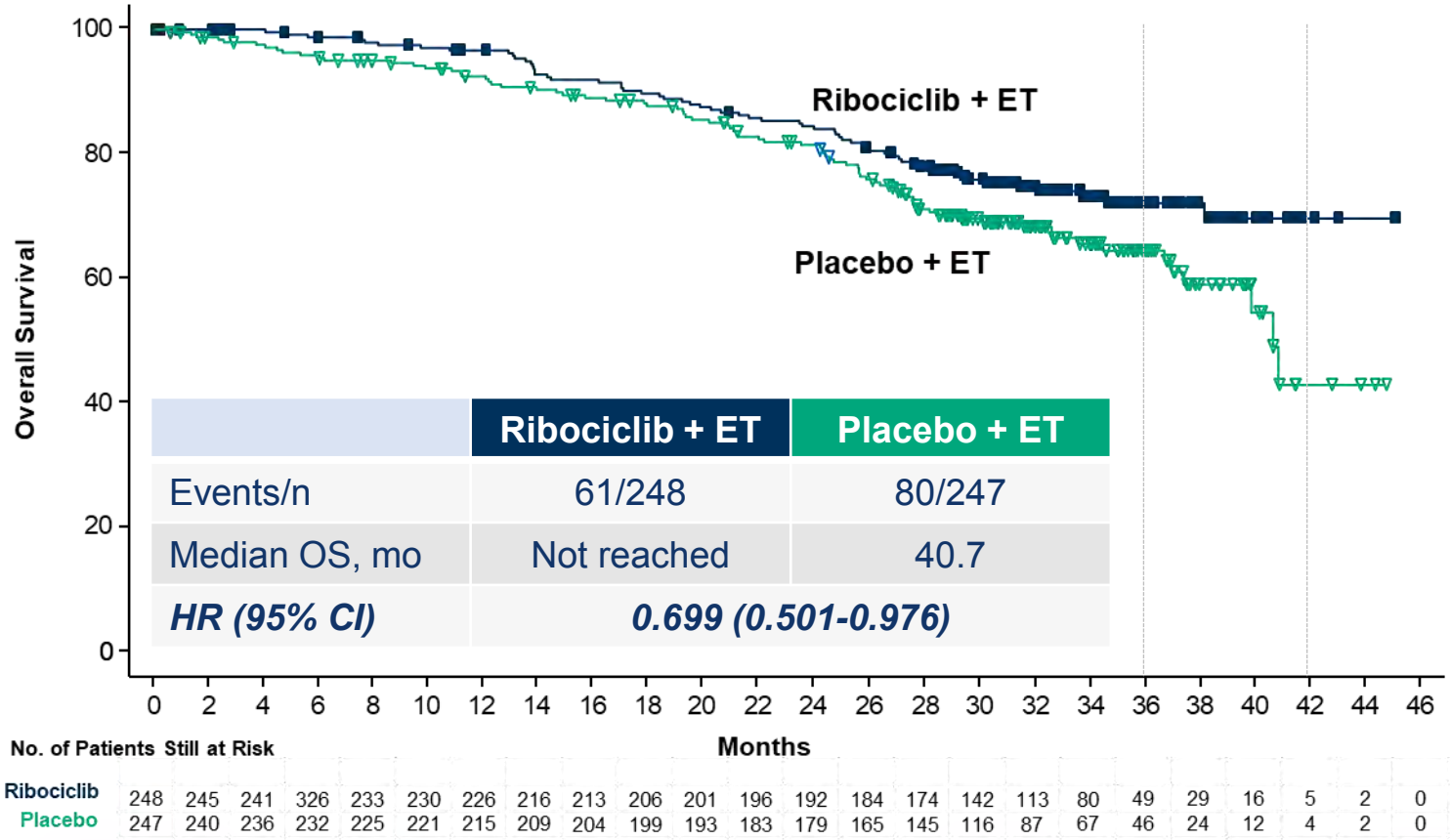
	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

Overall Survival in the NSAI Subgroup



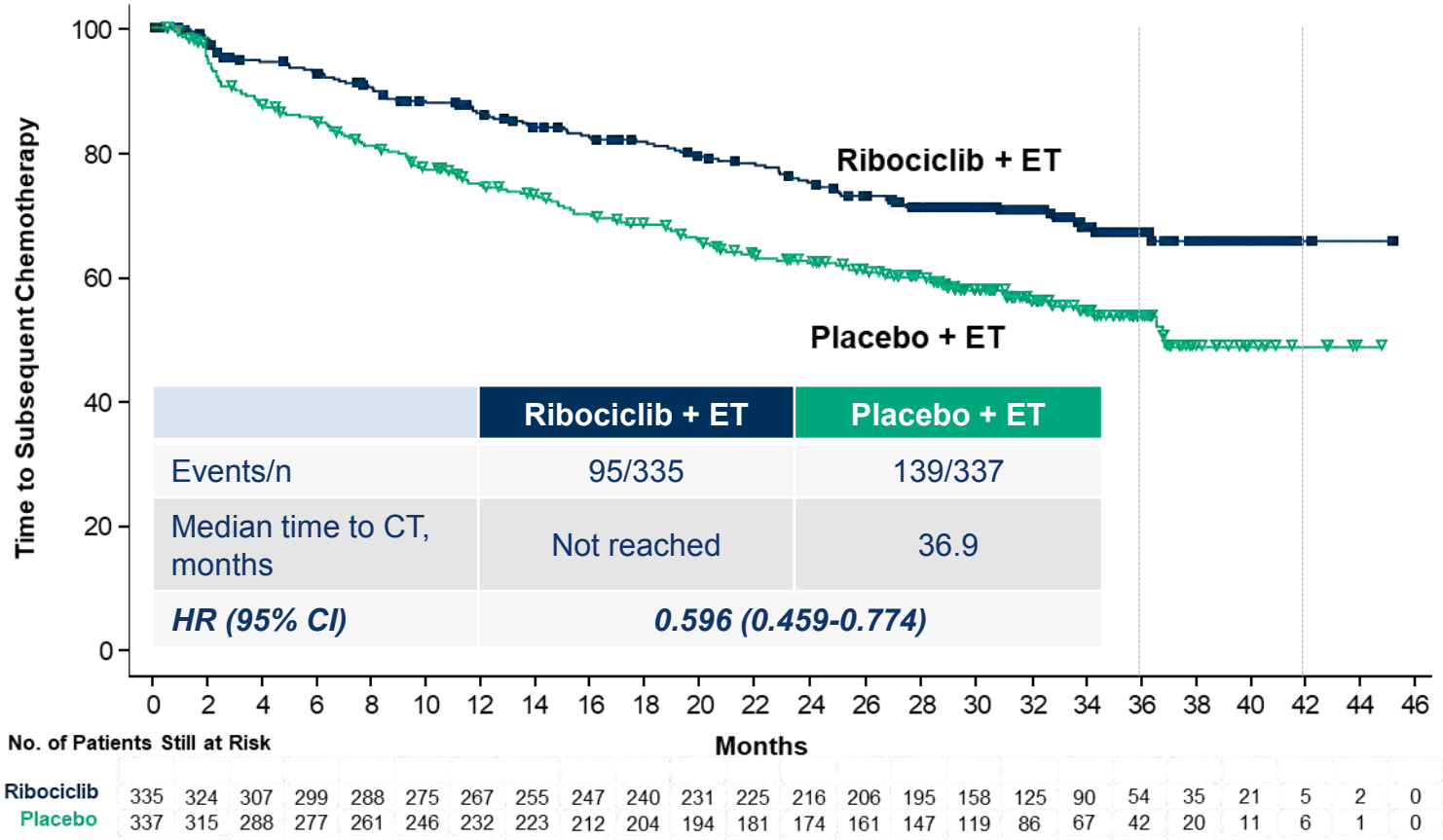
	Ribociclib + ET	Placebo + ET
Events/n	61/248	80/247
Median OS, mo	Not reached	40.7
HR (95% CI)	***0.699 (0.501-0.976)***	

- ≈ 30% relative reduction in risk of death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

Time to First Subsequent Chemotherapy

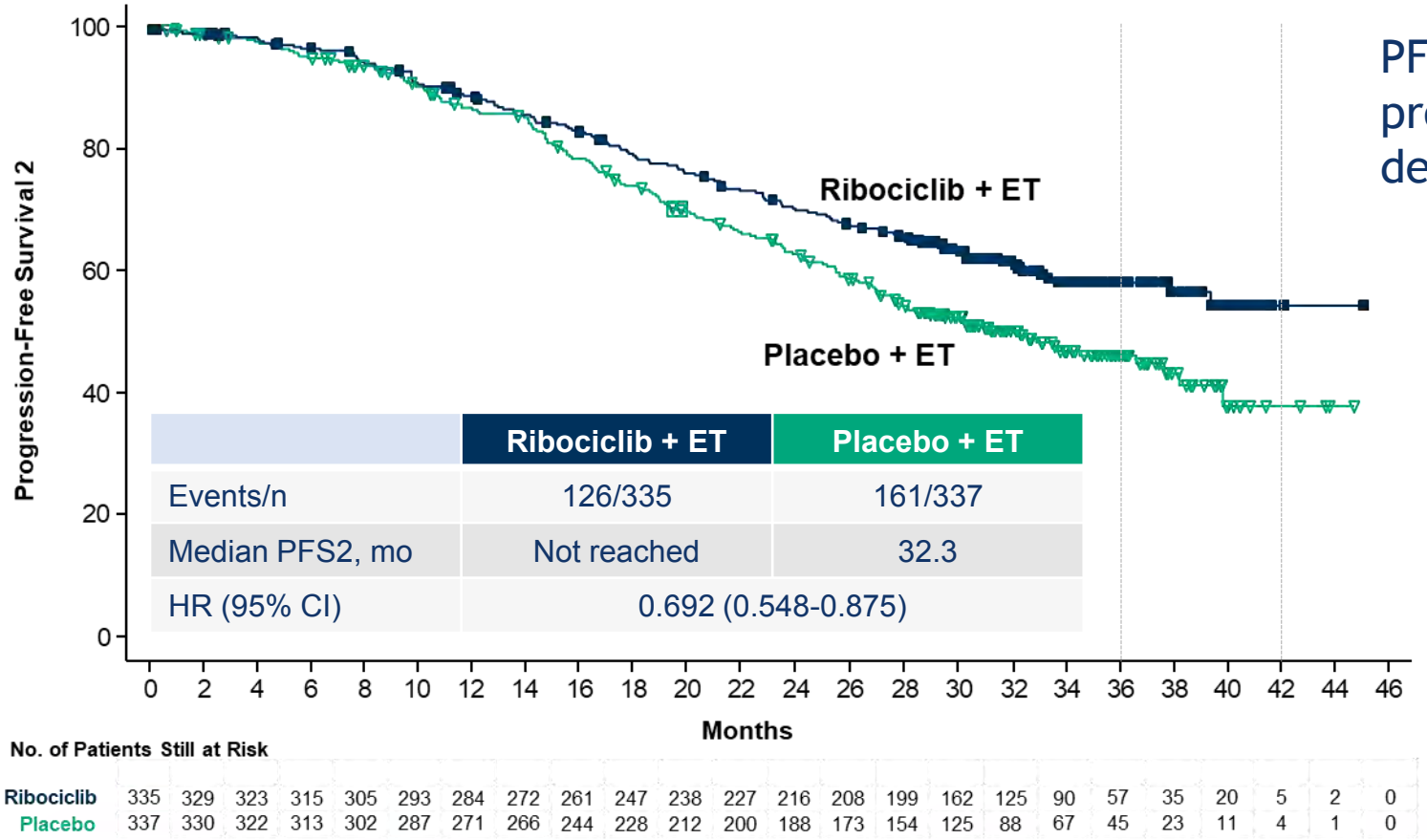


	Ribociclib + ET	Placebo + ET
Events/n	95/335	139/337
Median time to CT, months	Not reached	36.9
HR (95% CI)	***0.596 (0.459-0.774)***	

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

Progression-Free Survival 2



	Ribociclib + ET	Placebo + ET
Events/n	126/335	161/337
Median PFS2, mo	Not reached	32.3
HR (95% CI)	0.692 (0.548-0.875)	

PFS 2: time from randomization to progression on the next line of therapy or death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	58.4%	46.2%
42 months	54.6%	37.8%

Hematologic adverse events

Regardless of study treatment relationship

AEs ≥5% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	75.8	50.7	9.9	7.7	3.0	0.6
Leukopenia	31.3	13.1	1.2	5.6	1.2	0
Anemia	20.9	3.0	0	10.1	2.1	0
Thrombocytopenia	8.7	0.6	0.3	2.1	0.3	0.3

- Febrile neutropenia occurred in 2.1% of patients in the ribociclib arm vs 0.6% of patients in the placebo arm

Non-hematologic adverse events

Regardless of study treatment relationship

AEs ≥20% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hot flush	34.0	0.3	0	33.5	0	0
Nausea	31.6	0.6	0	19.6	0.3	0
Arthralgia	29.9	0.9	0	27.3	0.9	0
Fatigue	23.6	1.2	0	24.6	0	0
Headache	23.0	0	0	24.3	0.9	0
Diarrhea	20.3	1.5	0	18.7	0.3	0

- Post-baseline QTcF >480 msec, based on ECG data, occurred in 23 patients (6.9%) in the ribociclib arm vs 4 patients (1.2%) in the placebo arm
  - Post-baseline QTcF >500 msec occurred in 5 patients (1.5%) vs 1 patient (0.3%)
- Treatment discontinuation due to QT prolongation AEs occurred in 1 patient (0.3%) in the ribociclib arm vs 2 patients (0.6%) in the placebo arm
- QT prolongation events were not associated with clinical symptoms or arrhythmia

The Importance of the PI3K/AKT/mTOR Pathway in HR+ Breast Cancer

- The PI3K pathway is frequently altered in HR+ breast cancer and has been implicated in resistance to endocrine therapies[1,2]
- Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation, leading to hyperactivation of the PI3K pathway[3-5]
- PI3K signaling has been shown to promote estrogen-independent growth of ER+ breast cancer cells,[6,7] and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens[8]

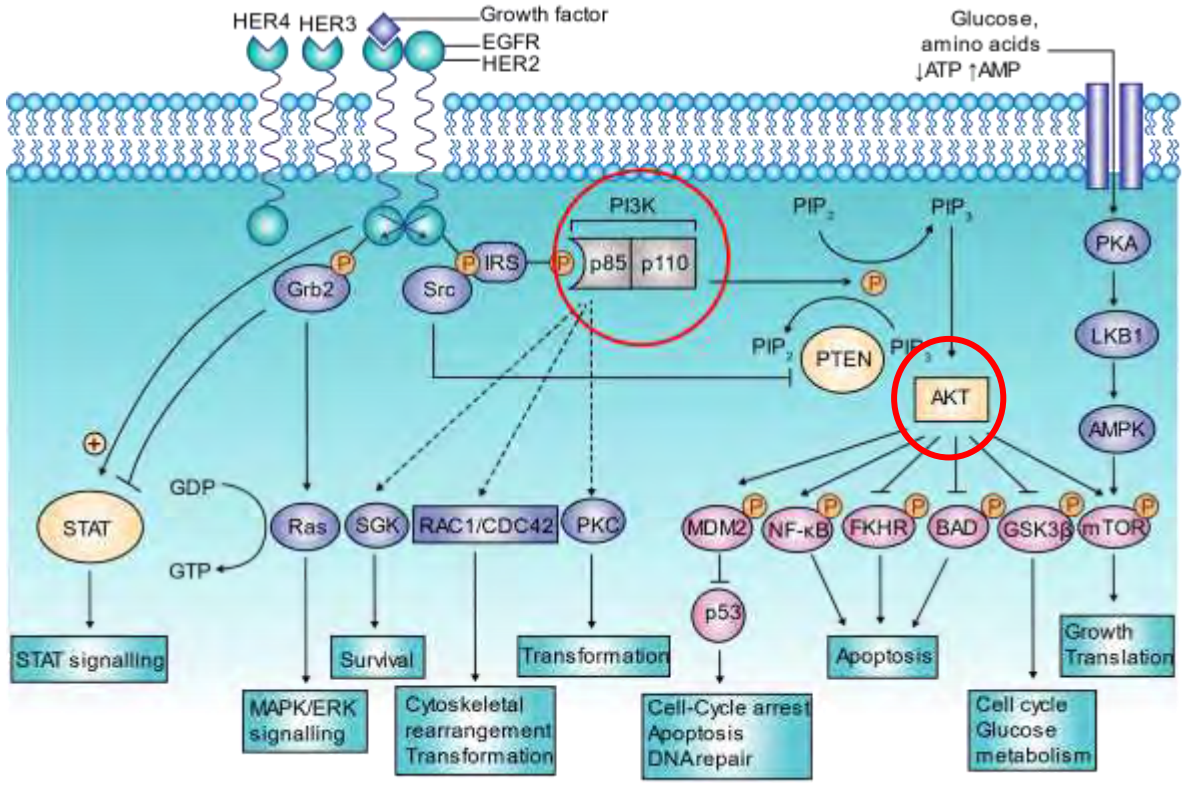


Figure reprinted by permission from Springer Nature: *Nature Reviews Drug Discovery*. Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery. Hennessy BT, et al. *Nat Rev Drug Discov*. 2005 Dec;4(12):988-1004. © 2005.

Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER positive breast cancer (FAKTION): A randomised, double-blind, placebo-controlled, phase II trial

Robert H Jones, Margherita Carucci, Angela Casbard, Rachel Butler, Fouad Alchami, Catherine Bale, Pavel Bezecny, Johnathan Joffe, Sarah Moon, Chris Twelves, Ramachadran Venkitaraman, Simon Waters, and Sacha J Howell

PI3K/AKT/PTEN pathway in ER positive Breast Cancer

- The PI3K/AKT/PTEN pathway is activated in approximately 50% of ER positive metastatic breast cancer[1-4]
  - PIK3CA activating mutation (30-45%)
  - PTEN loss/inactivation (3-8%)
  - AKT1 activating mutation (2-6%)

- Pre-clinically:
  - pathway activation leads to ligand independent activation of ER[5,6]
  - pathway inhibition leads to compensatory increase in ER-dependant transcription[7-9]

- There is a strong rationale for simultaneous targeting of the PI3K/AKT/PTEN and ER pathways

[1]TCGA. Nature 2012; 490: 61–70. [2]Stemke-Hale K et al. Cancer Res. 2008; 68:6084-91. [3]Hortobagyi et al. J Clin Oncol. 2016;34:419-26. [4] Baselga J et al. Lancet Oncol. 2017;18:904–916 [5] deGraffenried LA et al. Clin Cancer Res 2004; 10:8059–67. [6]Miller TW et al. J Clin Oncol 2011; 29:4452-61. [7]Bosch A et al. Sci Transl Med. 2015;7:283ra51, [8] Ribas R et al. Mol Cancer Ther. 2015;14:2035-48 [9]Toska E et al. Science. 2017;355:1324-1330.

Capivasertib (AZD5363) in ER positive breast cancer

- Capivasertib is a potent and selective inhibitor of Akt 1-3 isoforms[1]
- Synergistic activity seen with fulvestrant pre-clinically in endocrine sensitive and resistant models[1,2]
- Modest clinical activity seen with monotherapy in tumours with AKT1 (E17K) mutations[3] but minimal activity in tumours with PIK3CA mutations[4] ER+ MBC
- No effect in combination with paclitaxel chemotherapy in PIK3CA mutant ER+ MBC (BEECH)[5]
  - Co-treatment with endocrine therapy was not permitted

[1]Davies BR et al. Mol Cancer Ther 2012;11:873–87. [2]Ribas R et al. Mol Cancer Ther. 2015;14:2035-48. [3]Hyman DM et al J Clin Oncol. 2017;35:2251-2259. [4]Banerji U et al. Clin Cancer Res. 2018;24:2050-2059 [5]Turner NC et al Ann Oncol. 2019,

FAKTION Trial design

Phase 1b

3+3 design - fulvestrant 500mg q 4weeks + loading dose (LD) C1D15: Starting dose capivasertib 400mg bd 4 days on / 3 days off
N=9 SRC recommended not to dose escalate to established single agent dose 480mg bd 4 days on / 3 days off

Phase 2

Eligibility

- Post-menopausal women
- ER+/Her2- Metastatic or unresectable LABC
- Progression on AI for MBC/LABC **or** relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed

Exclusion

- Prior fulvestrant or PI3K/AKT/mTOR inhibitor therapy

N = 140

R

1:1

Fulvestrant 500mg q4weeks + LD
Capivasertib 400mg bd 4 days on / 3 days off from C1D15
N=69

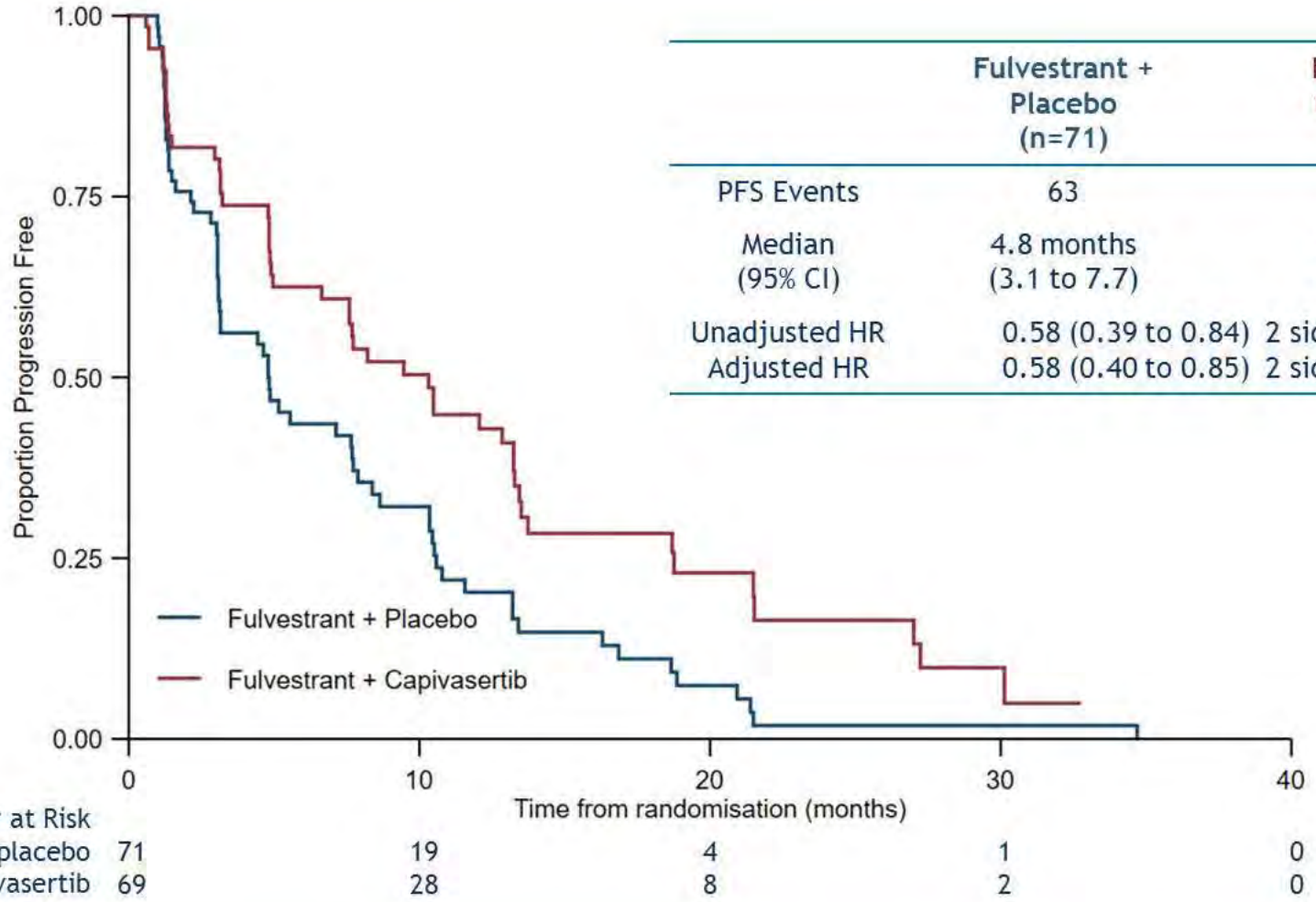
Fulvestrant 500mg q4weeks + LD
Placebo bd 4 days on / 3 days off from C1D15
N=71

Primary endpoint:
Investigator assessed PFS in the intent to treat (ITT) population

Secondary endpoints:

- Safety and toxicity
- Objective Response rate (ORR), Clinical Benefit Rate (CBR) and Overall Survival (OS) in ITT population
- PFS/ORR/CBR in PI3K/AKT/PTEN pathway activated vs non-activated tumours

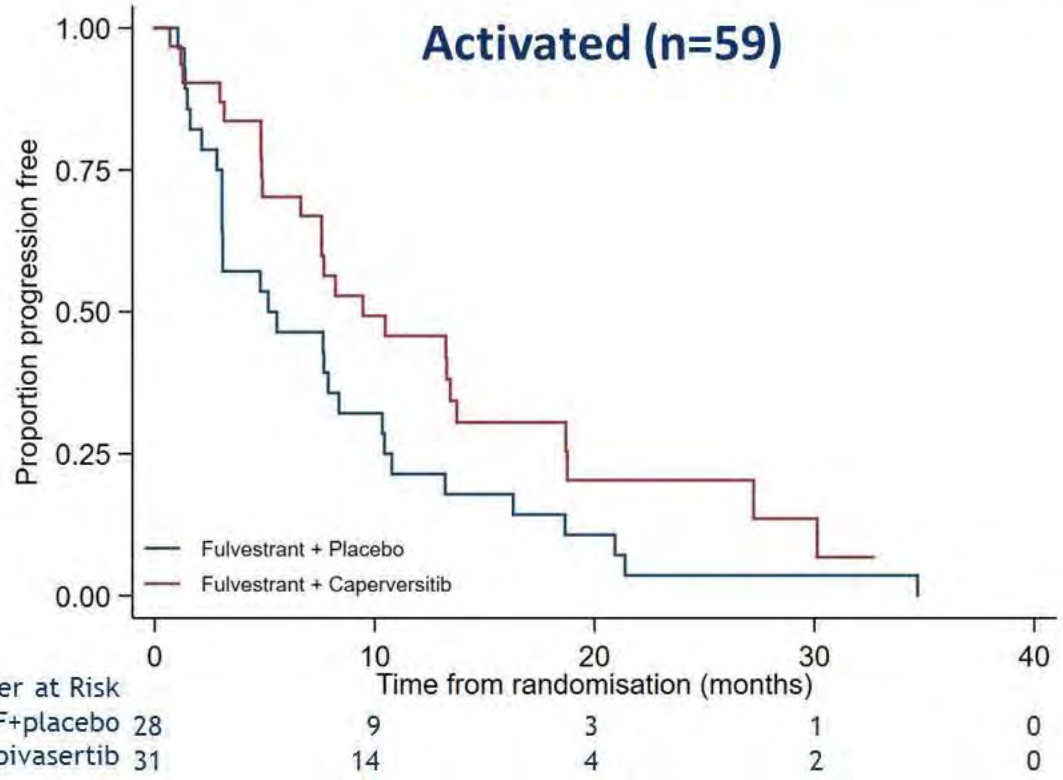
Progression Free Survival in the ITT population



	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
PFS Events	63	49
Median (95% CI)	4.8 months (3.1 to 7.7)	10.3 months (5.0 to 13.2)
Unadjusted HR	0.58 (0.39 to 0.84) 2 sided p = 0.004	
Adjusted HR	0.58 (0.40 to 0.85) 2 sided p = 0.005	

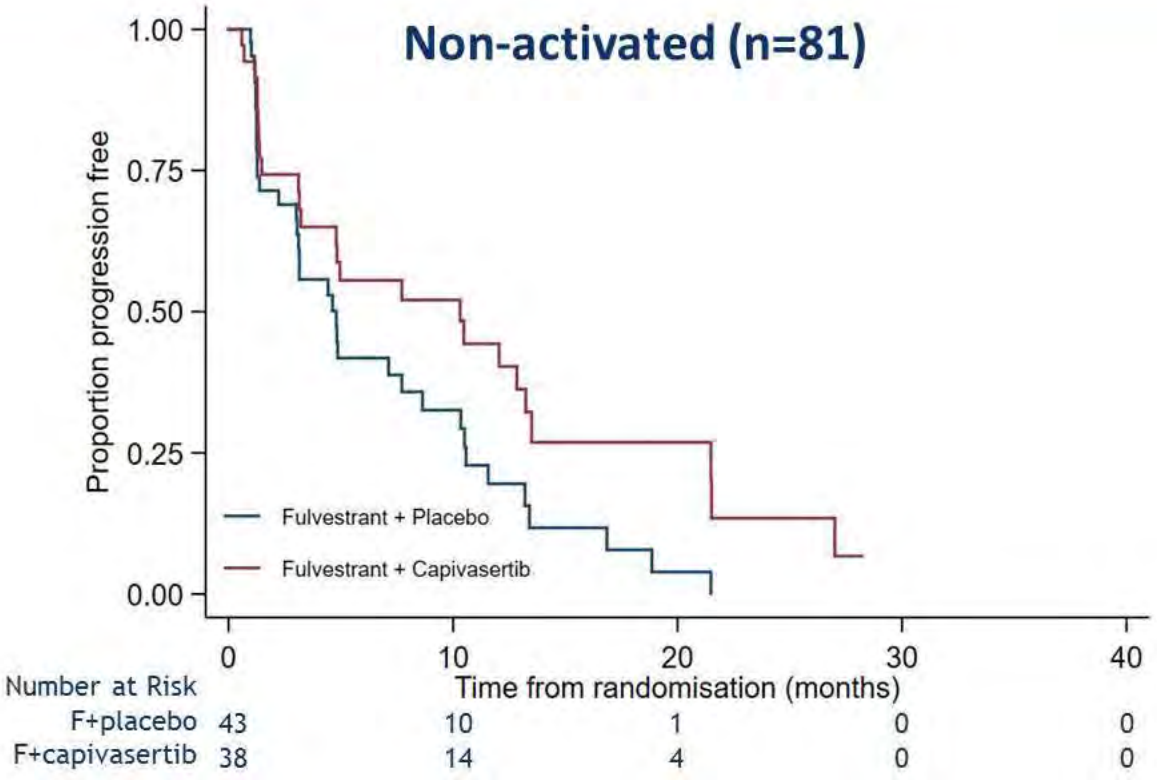
Progression Free Survival by PI3K/AKT/PTEN pathway activation status

Activated (n=59)



	Fulvestrant + Placebo (n=28)	Fulvestrant + Capivasertib (n=31)
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03)	2-sided p=0.064

Non-activated (n=81)



	Fulvestrant + Placebo (n=43)	Fulvestrant + Capivasertib (n=38)
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96)	2-sided p=0.035

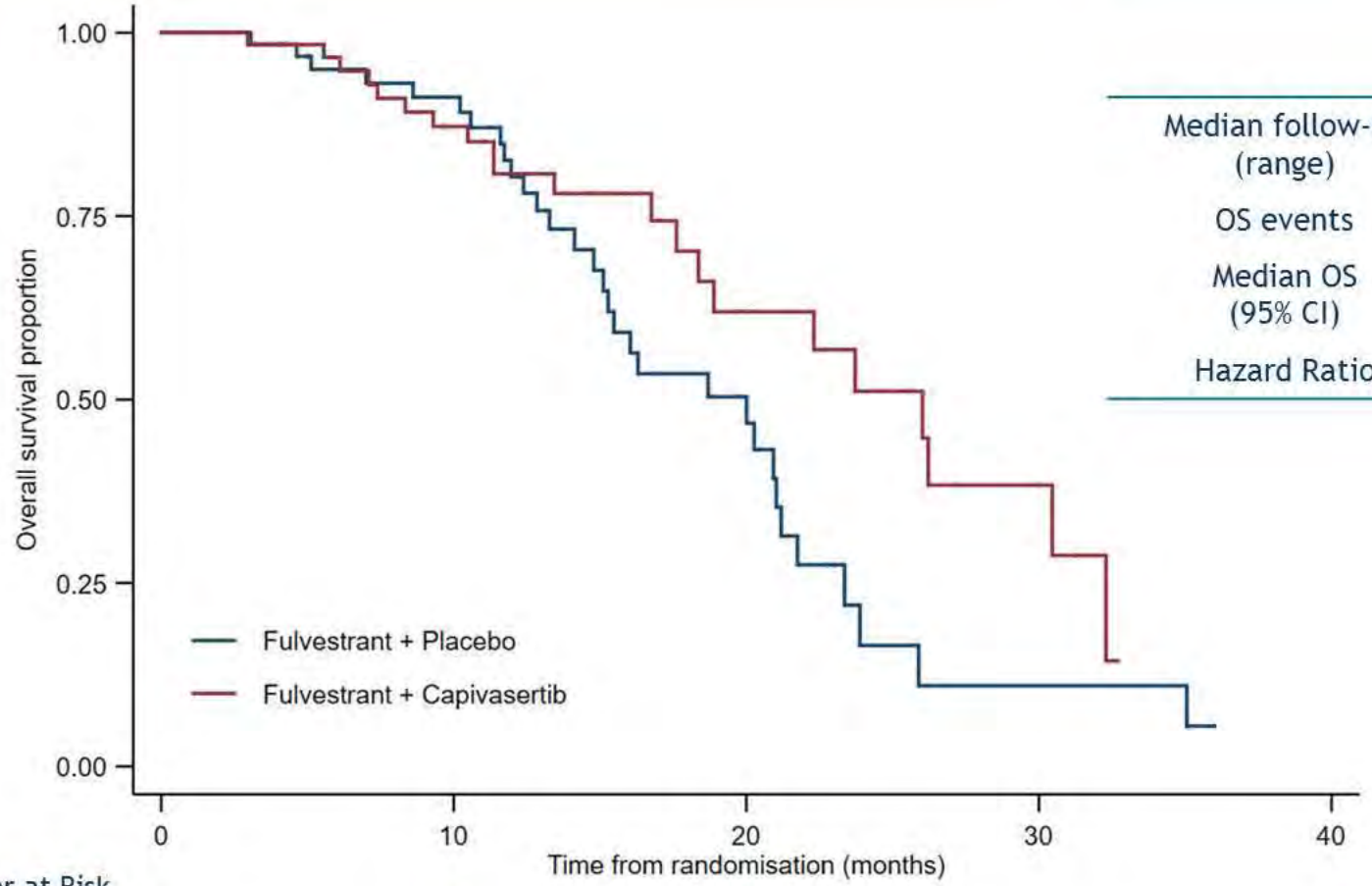
Objective Response Rates in those with measurable disease

	Fulvestrant + Placebo (n=50)	Fulvestrant + Capivasertib (n=49*)
Complete Response	0	0
Partial Response	6 (12%)	20 (41%)
Stable Disease	27 (54%)	17 (35%)
Progressive Disease	17 (34%)	10 (20%)
Objective Response Rate	6 (12%)	20 (41%)
Odds Ratio (95% CI)	5.17 (1.83 - 14.62) 2 sided p = 0.002	
Clinical Benefit Rate (CBR)	18 (36%)	27 (55%)
Odds Ratio (95% CI)	2.17 (0.97 - 4.87) 2 sided p = 0.061	
Median duration of response, months (IQR)	5.0 (2.8 - 7.3)	7.1 (3.8 - 9.9)

*2 patients missing data for objective response

CBR = stable disease for at least 6 months + objective response

Overall survival



Number at Risk					
F+placebo	71	19	4	1	0
F+capivasertib	69	28	8	2	0

	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
Median follow-up (range)	12.4 months (1.0 - 36.0)	11.8 months (1.7 - 32.7)
OS events	31	21
Median OS (95% CI)	20.0 months (15.1 - 21.2)	26.0 months (18.4 - 32.3)
Hazard Ratio	0.59 (0.34 to 1.05) 2-sided p=0.071	

37% data maturity

Notable adverse events affecting >10% of the study population

	Fulvestrant + Placebo (n=71)		Fulvestrant + Capivasertib (n=69)	
	All grades	CTCAE G3-5	All grades	CTCAE G3-5*
Any adverse event	67 (94%)	21 (30%)	69 (100%)	40 (58%)
Diarrhoea	25 (35%)	3 (4%)	56 (81%)	10 (14%)
Rash	13 (18%)	0	35 (51%)	14 (20%)
Hyperglycaemia	11 (16%)	0	29 (42%)	3 (4%)
Vomiting	15 (21%)	0	27 (39%)	2 (3%)
Nausea	36 (51%)	0	38 (55%)	0
Infections (composite term**)	13 (18%)	2 (3%)	26 (38%)	4 (6%)
Oral mucositis	5 (7%)	0	10 (14%)	0
Fatigue	41 (58%)	3 (4%)	40 (58%)	1 (1%)
Dizziness	1 (1%)	0	7 (10%)	0
Back pain	11 (16%)	0	17 (25%)	0

*2 patients died without progression on the Capivasertib arm: 1 with atypical chest infection and 1 with haemorrhage
** preferred terms falling under the Systems Organ Classification: infections and infestations

Other toxicities affecting >10%, but with similar distributions in each arm (or worse in placebo): abdominal pain; anorexia; arthralgia; non-cardiac chest pain; constipation; cough; dry mouth; dyspnea; extremity pain; flu symptoms; headache; injection site reactions; pain; pruritus; hot flashes.

Conclusions

- The addition of capivasertib to fulvestrant more than doubles the PFS seen with fulvestrant alone in women with ER+ve Her2- MBC (median PFS 10.3m vs 4.8m; HR 0.58; p=0.004).
- The addition of capivasertib to fulvestrant significantly improves the ORR with a strong trend towards improved OS (median OS 20.0m vs 26.0m; HR 0.59).
- Capivasertib is deliverable in combination with fulvestrant, although ~1/3 of patients required dose reduction, predominantly for diarrhoea and rash.
- Tumour PI3K/AKT/PTEN pathway activation, defined as PIK3CA exon 9/20 hotspot mutation or PTEN null by IHC, does not appear to affect sensitivity to capivasertib in ER+ MBC.
    - Additional NGS analyses are ongoing to more comprehensively characterise tumours

Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer by age and the 21-gene recurrence score in TAILORx

Joseph A. Sparano, Robert J. Gray, Della F. Makower, Tracy G. Lively, Thomas J. Saphner, Maccon M. Keane, Henry L. Gomez, Pavan S. Reddy, Timothy F. Goggins, Ingrid A. Mayer, Deborah Toppmeyer, Adam Brufsky, Matthew P. Goetz, Daniel F. Hayes, Elizabeth C. Dees, Kathleen I. Pritchard, Charles E. Geyer Jr., John A. Olson, Kathy S. Albain, George W. Sledge,Jr

on behalf of the TAILORx Investigators

Canadian Cancer Trials Group

Alliance for Clinical Trials in Oncology

Federally Funded Research

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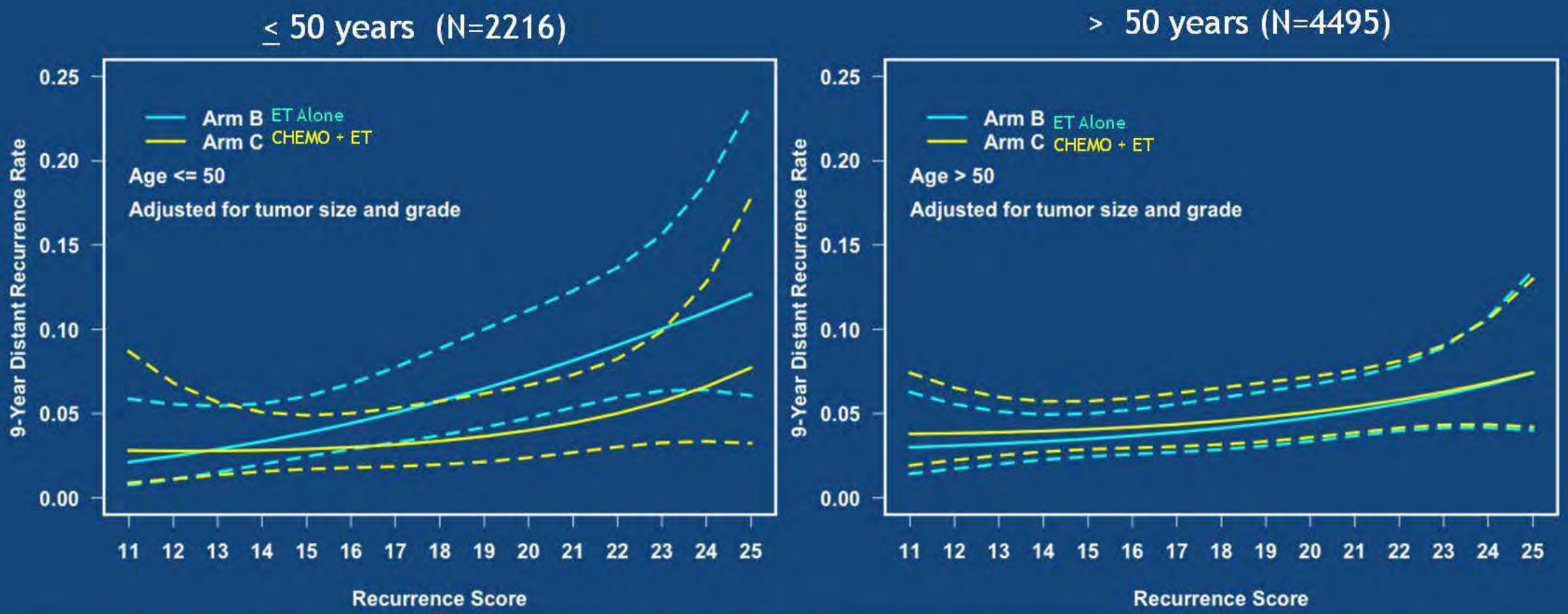
Background: Rationale for Integrating Genomic and Clinical Risk in Early Breast Cancer

- **Genomic risk – 21 gene recurrence score (RS) in HR+, HER2- early breast cancer**
  - Complementary prognostic information to pathologic features
    - Tumor size, grade, and nodal status
  - Predictive of large chemo benefit (RS > 25) or lack thereof (RS ≤ 25)
    - 3-way interaction - age, RS, and chemotherapy – resulting in an absolute chemo benefit in women ≤ 50 yrs & RS 16-20 (2%) or 21-25 (7%)
- **Clinical risk - pathologic features – tumor size, grade, and nodal status**
  - Prognostic - but doesn't correlate well with RS
- **Integration of genomic and clinical risk**
  - Potential for greater precision in prognosis & guiding use of adjuvant therapy

TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (</=50 vs. >50 Years)



RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade

Objectives and Methods: TAILORx Secondary Objective

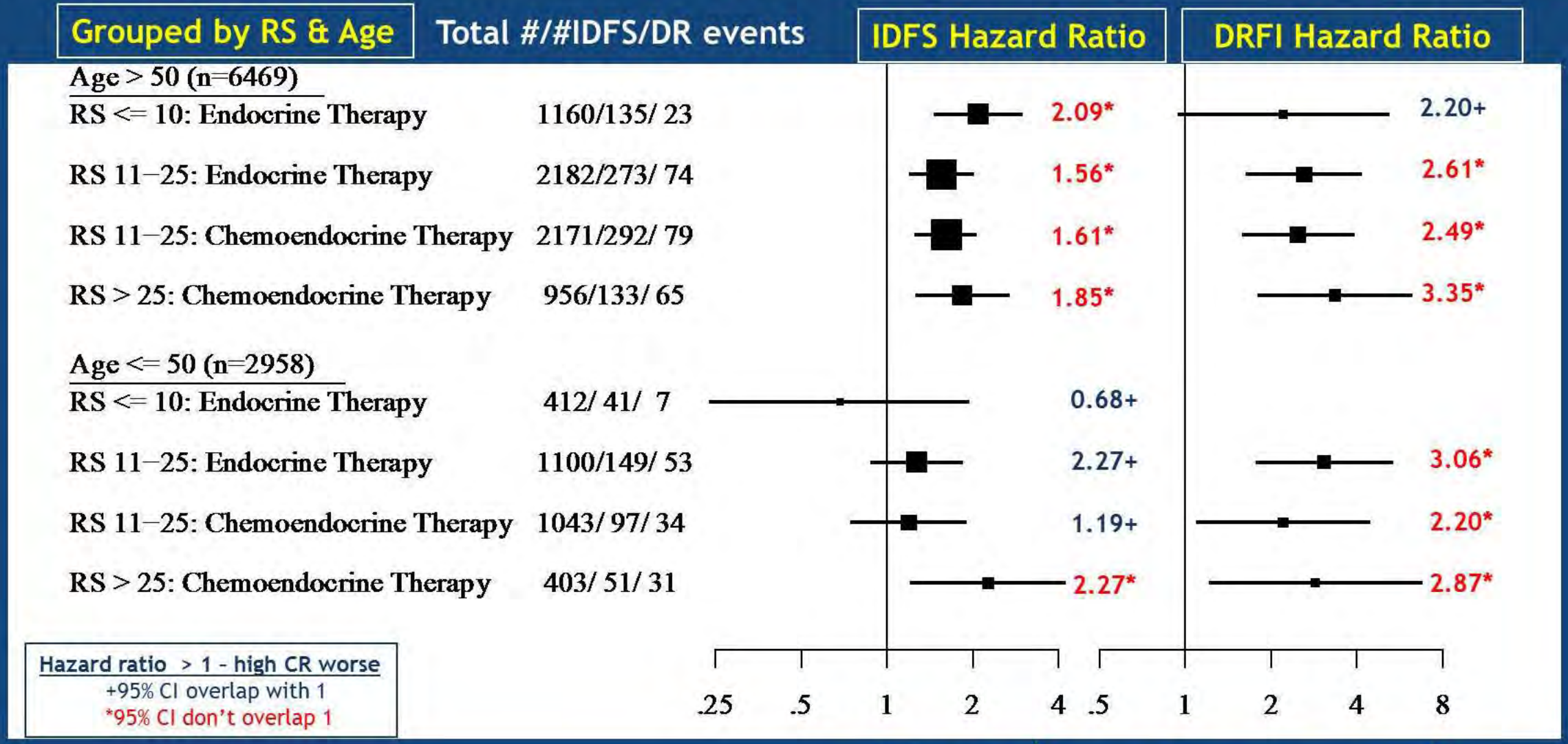
Objectives

- **Pre-specified secondary trial objective** "*…to … refine models that …use classical information (Adjuvant!) … in combination with genomic tests.*"
- **Binary clinical risk: low vs. high risk (MINDACT)**
  - Calibrated to > 92% 10-year BCSS for ET alone based on Adjuvant! (version 8.0)
  - **Low risk**
    - Tumor ≤ 1 cm & high grade
    - Tumor ≤ 2 cm & int. grade
    - Tumor ≤ 3 cm & low grade
  - **High risk** – not meeting low risk criteria
- **Exploratory objective**
  - Association between age and chemotherapy benefit in the RS 16-25 group

Methods

- Same ITT population previously reported in primary analysis (NEJM, 2018; ASCO Plenary, 2018)
- Event-free rates were estimated using the Kaplan-Meier method
- Hazard ratios estimated using partial likelihood analysis of the Cox proportional hazards model
- No corrections for multiple comparisons

Results: Impact of Clinical Risk (CR) on Prognosis by RS Group and Age



Results: Absolute Differences in 9-year Distant Recurrence Rate by Clinical Risk Stratified by Age, RS, and Chemotherapy Use

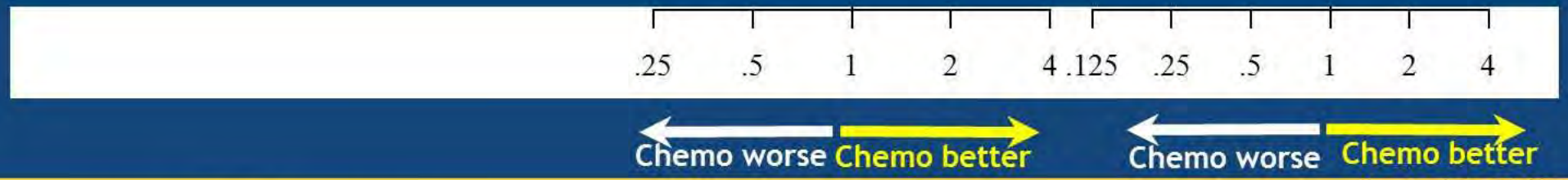
Parameter		Age > 50 Years (N=6469)
RS	Chemo	**Absolute Risk Difference:** High vs. Low Clinical Risk
0-10 (N=1572)	No (N=1572)	Δ +4.9 (±SE 3.5%)
11-25 (N=6496)	No (N=3282)	Δ +5.8% (±SE 2.0%)
	Yes (N=3214)	Δ +4.3% (±SE 1.6%)
26-100 (N=1359)	Yes (N=1359)	Δ +12.8% (±SE 4.5%)

Results: Absolute Differences in Distant Recurrence Rates by Chemo Use in Women ≤ 50 yrs & RS 16-25 Stratified by RS and Clinical Risk

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +1.6% (±SE 1.9%)
RS 21-25 (N=476)	Δ +6.5% (+SE 3.7%)

Results - Exploratory Analysis: Impact of Age and Menopausal Status on Chemotherapy Benefit for RS 16-25

Age & Menopausal Status	Total #/#IDFS/DR Events	IDFS Hazard Ratio	DRFI Hazard Ratio
Age <=40	203/ 35/12		
Age 41−45	441/ 51/21		
Age 46−50, Pre−Meno	630/ 69/33		
Age 46−50, Post−Meno	141/ 15/ 5		



Conclusions: Integrating Clinical and Genomic Risk in Breast Cancer to Guide Adjuvant Therapy

- **Clinical risk provides additional prognostic info to RS for distant recurrence**
  - In RS 11-25 group irrespective of chemo use – 2.5-3x relative, 5% absolute **Δ**
  - In RS 26-100 group treated with chemo + ET – 3x relative, 10% absolute **Δ**
- **Clinical risk did not provide predictive information for chemo benefit**
  - In RS 11-25 group treated with ET +/- chemo – *primary trial results unchanged*
  - For women ≤ 50 years and a RS 16-25, integrated risk distinguishes 50% who derive no chemo benefit from 50% who derive an absolute benefit of 6-9%
- **Absolute chemo benefit greatest if pre-menopausal & age 45-50 with RS 16-25**
  - Suggests absolute chemo benefit may be due to an endocrine effect
- **Integrated risk provides greater prognostic precision & may have clinical utility**
  - Superior to clinical or genomic features used individually

Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding Treatment in Women ≤ 50 Years

- **Low risk:** T ≤ 1 cm & high grade, ≤ 2 cm & int. grade, ≤ 3 cm & low grade
- **High risk:** not meeting low risk criteria

Integrated RS and Clinical Risk (CR)

Low Integrated Risk (58%)
< 5% Distant Recurrence

RS 0-10 & Any CR
(1.8% ±0.9%*) with tam#

RS 11-20 & Low CR
(3.2% ±1.2%*) with tam#

Tamoxifen alone adequate
No Chemotherapy

High Integrated Risk (31%)
> 10% Distant Recurrence

RS 16-25 & High CR
(14.7% ±3.1%*) with tam#
RS 21-25 & Low CR
(11.4% ± 3.9%) with tam#

OFS + AI
As Alternative to Chemo

RS 26-100 & High CR
(15.2% ±3.3%*) with tam# plus chemo

OFS + AI
Plus Chemotherapy

*Kaplan Meier estimates of 9-year distant recurrence rates
tamoxifen in 78% (including 35% who crossed over to an AI), or OFS +/- AI in 13%; 9% AI other

SOFT/TEXT: "...high recurrence risk ... experience improvement of 10%-15% in 5-year BCFI (with OFS/AI)..(whereas) Improvement minimal ...at lowest risk."
Regan et al. JCO 2016, PMID 27044936

IMpassion130: updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in previously untreated locally advanced or metastatic TNBC

Peter Schmid,[1] Sylvia Adams,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Carlos H. Barrios,[5] Hiroji Iwata,[6] Véronique Diéras,[7] Volkmar Henschel,[8] Luciana Molinero,[9] Stephen Y. Chui,[9] Amreen Husain,[8] Eric P. Winer,[10] Sherene Loi,[11] Leisha A. Emens[12]

[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2]New York University Langone Medical Center, New York, NY; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; [5]Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; [6]Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Genentech, Inc, South San Francisco, CA; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Peter MacCallum Cancer Centre, Melbourne, Australia; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA

Background

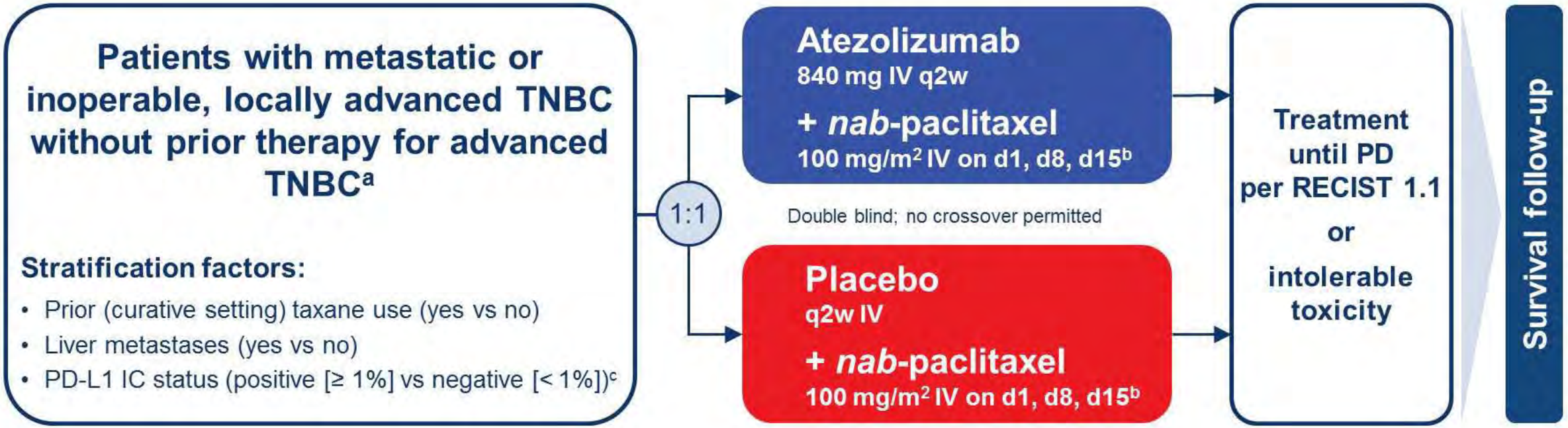
- Patients with mTNBC have a poor prognosis with SOC chemotherapy alone; the median OS is approximately 18 months[1-5]
- IMpassion130 is the first Phase III study of cancer immunotherapy in mTNBC to demonstrate clinical benefit in PD-L1+ patients[6]
- Clinically meaningful improvement in OS was observed in the PD-L1+ population at the first interim OS analysis (43% deaths in the ITT population)[6]
- We present the second interim OS analysis from IMpassion130 after 59% deaths in the ITT population

PD-L1+: PD-L1 on ≥ 1% of IC as percentage of tumor area assessed by VENTANA SP142 IHC assay.

IC, tumor-infiltrating immune cells.

1. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 2. Cardoso *Ann Oncol* 2018. 3. Bajaj *Ann Oncol* 2018. 4. Gobbini *Eur J Cancer* 2018. 5. Yardley *Ann Oncol* 2018. 6. Schmid *N Engl J Med* 2018.

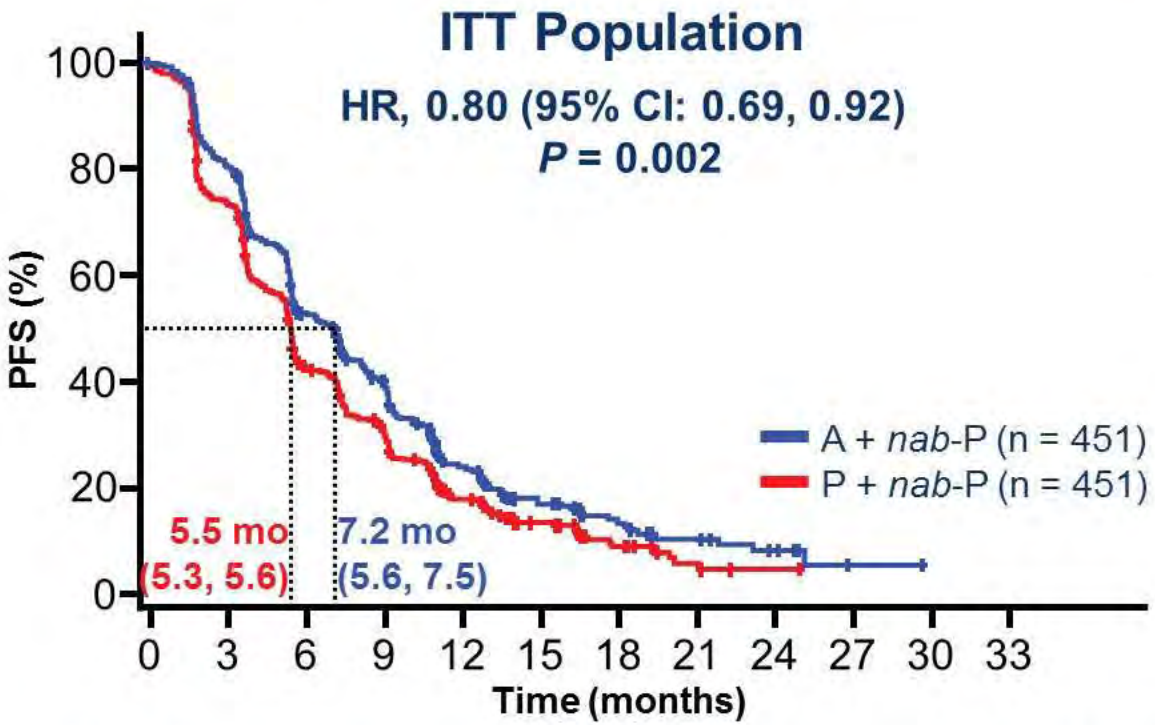
IMpassion130 Study Design

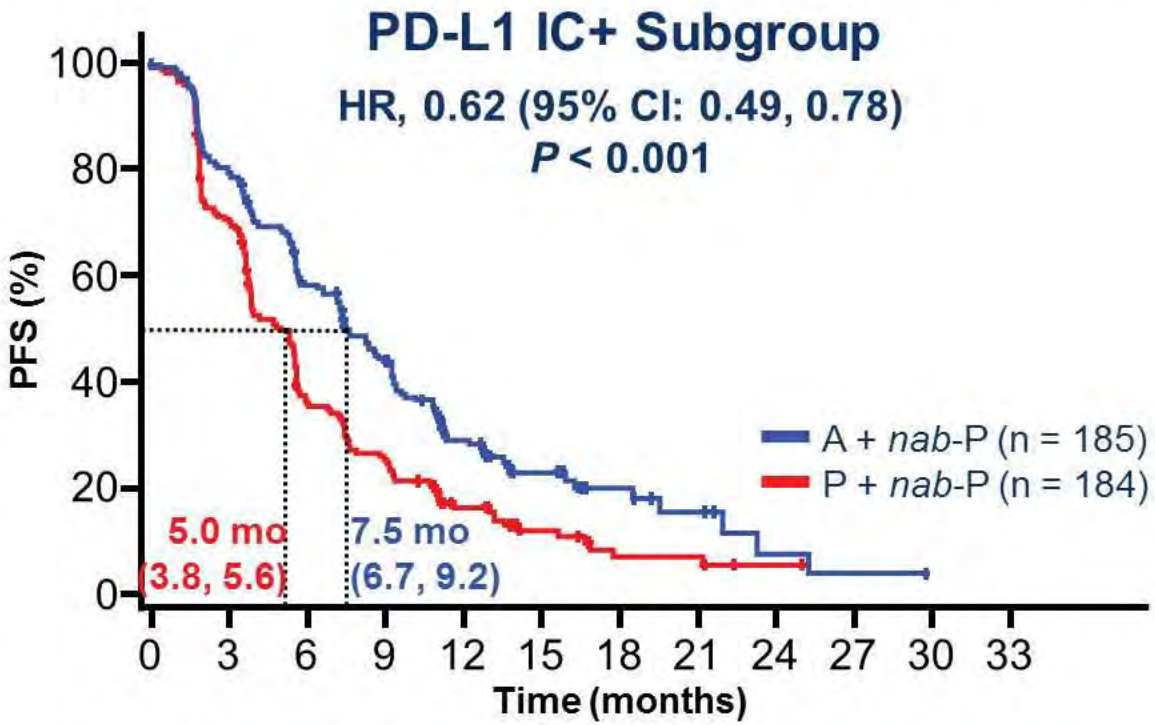


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



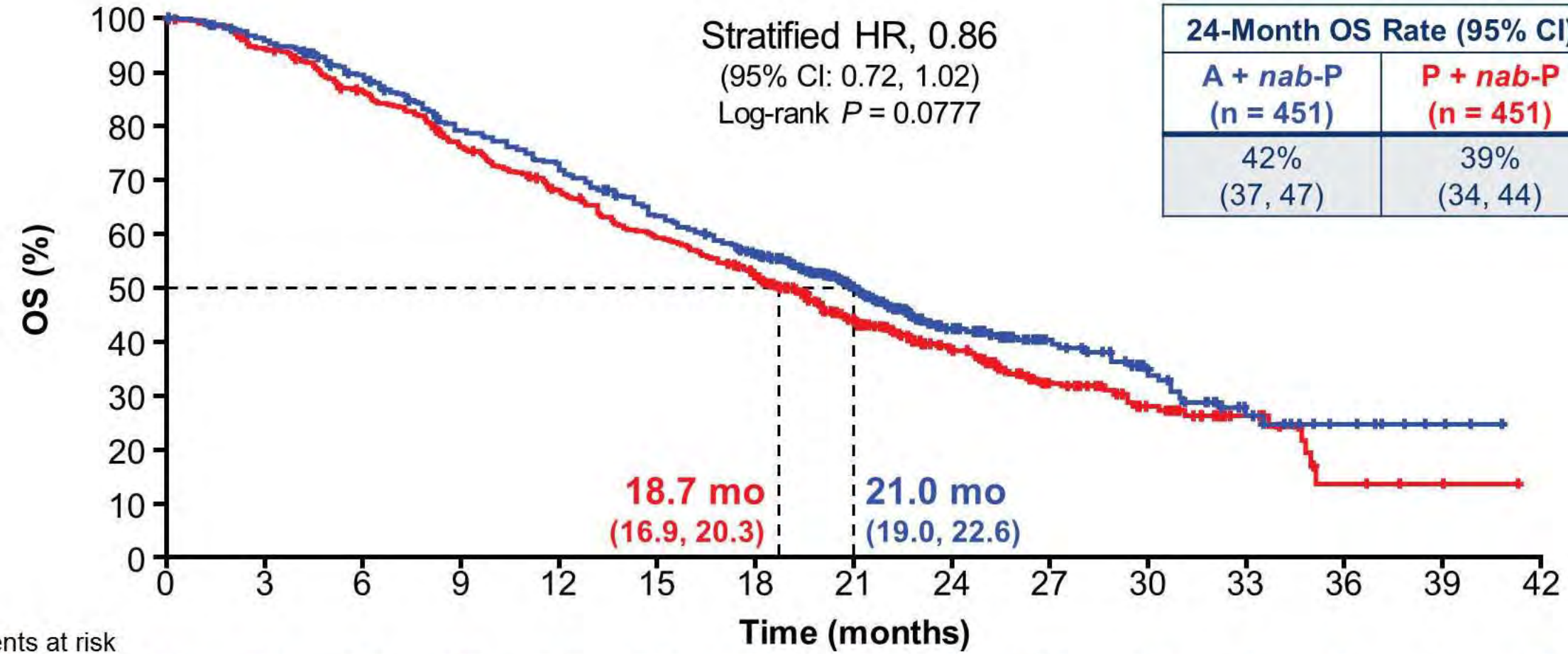


- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

1. Emens SABCS 2018. 2. Schmid *New Engl J Med.* 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

OS in ITT Population



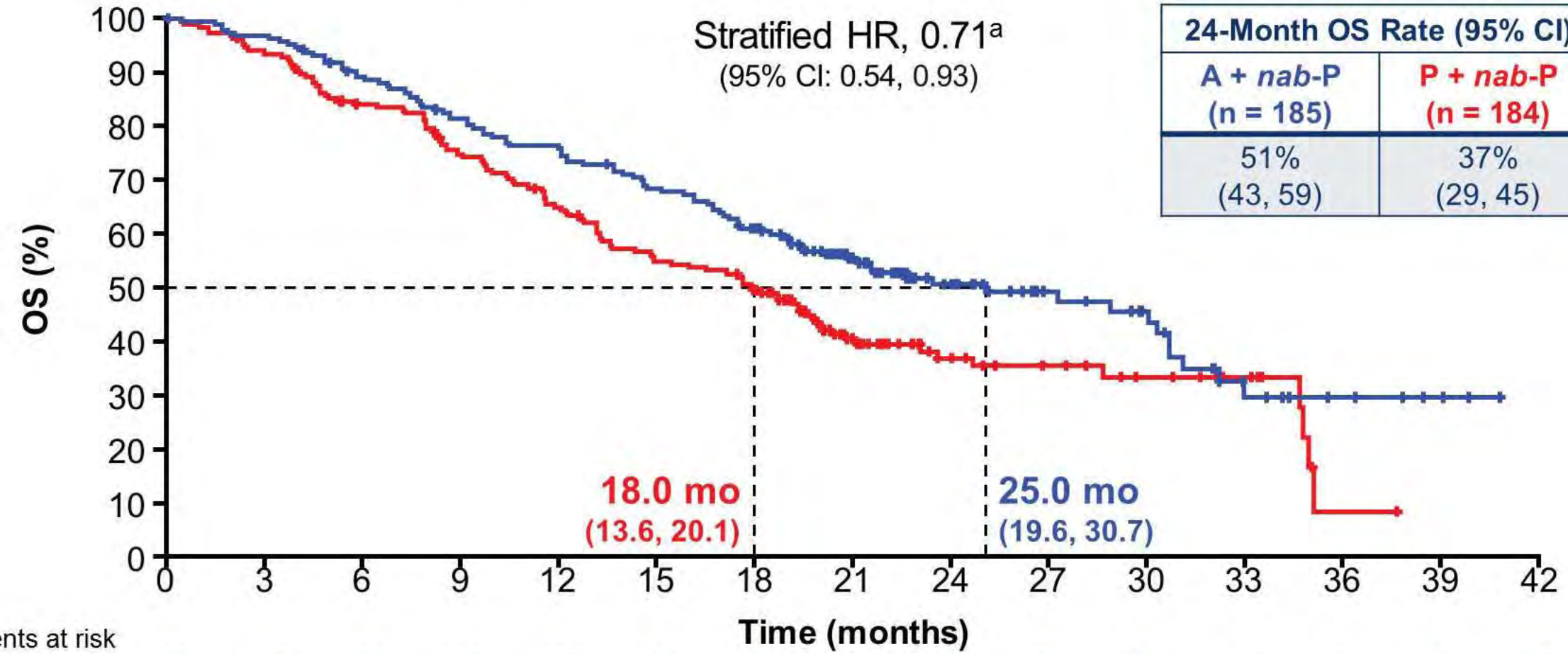
24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

OS in PD-L1+ Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 185)	P + *nab*-P (n = 184)
51% (43, 59)	37% (29, 45)

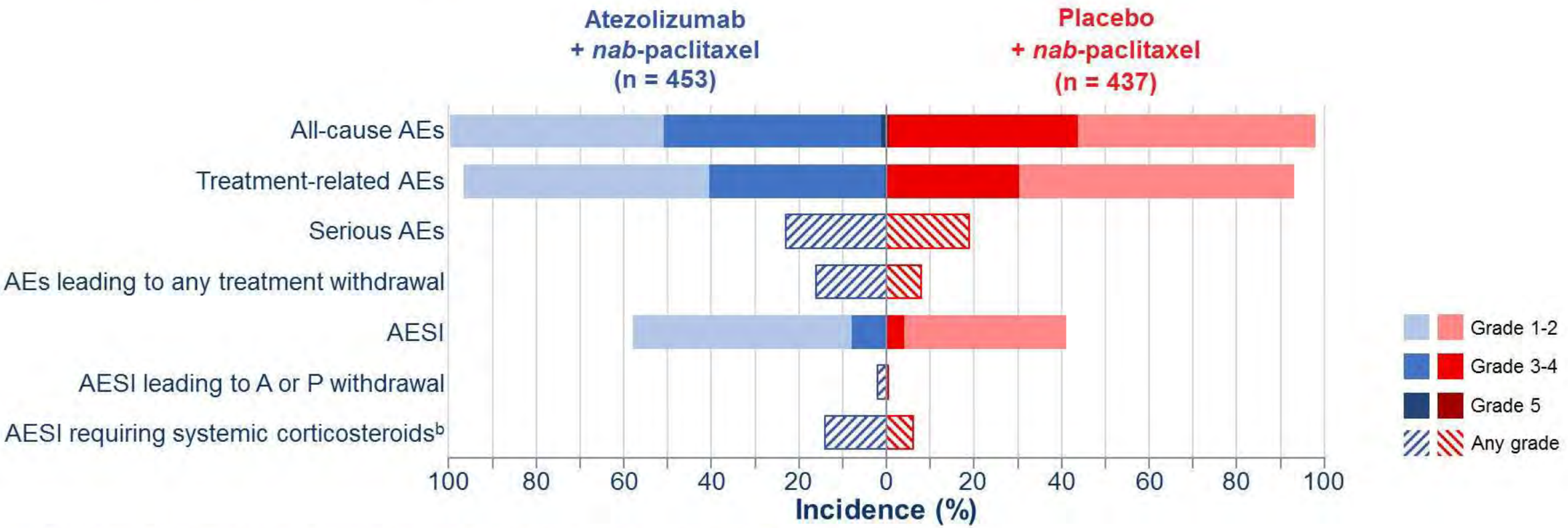
Patients at risk

A + *nab*-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

[a] Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.

Updated Safety Analysis[a]



- Safety data remain consistent with those previously published[1]
- **See poster #149 for further safety analysis details (Schneeweiss et al.) and poster #148 for patient-reported outcomes (Adams et al.)**

AESI, adverse events of special interest. Clinical data cutoff: September 3, 2018.
[a] Median follow-up 15.6 mo (4.5 months after primary PFS analysis). [b] Within 30 days of AESI onset. 1. Schmid et al. *N Engl J Med.* 2018.

Conclusions

- IMpassion130 is the first and only Phase III study to show the clinically meaningful benefit of first-line immunotherapy in mTNBC
- PD-L1 IC status predicts clinical benefit with atezolizumab + *nab*-paclitaxel
- Although not formally testable due to the pre-specified statistical analysis plan, a median OS improvement from 18 to 25 months was observed in the PD-L1+ population (HR, 0.71)
- Atezolizumab + *nab*-paclitaxel was well tolerated, with no cumulative toxicities and no new- or late-onset safety signals
- Atezolizumab + *nab*-paclitaxel sets a new benchmark as the first therapy to cross the 2-year landmark OS benefit in first-line therapy for PD-L1+ mTNBC
- Atezolizumab + *nab*-paclitaxel is approved by the FDA[1] and recommended for the treatment of patients with PD-L1 IC+ mTNBC in the NCCN[2] and AGO[3] guidelines

1. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019. 2. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 3. AGO Guidelines Breast Version 2019.1.

SOPHIA Primary PFS Analysis: A Phase 3 Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies

Hope S. Rugo, MD,[1] Seock-Ah Im, MD, PhD,[2] Gail S. Wright, MD, FACP, FCCP,[3] Santiago Escrivá-de-Romaní, MD,[4] Michelino De Laurentiis, MD, PhD,[5] Javier Cortes, MD, PhD,[6] Shakeela W. Bahadur, MD,[7] Barbara B. Haley, MD,[8] Raul H. Oyola, MD,[9] David A. Riseberg, MD,[10] Antonino Musolino, MD, PhD, MSc,[11] Fatima Cardoso, MD,[12] Giuseppe Curigliano, MD, PhD,[13] Peter A. Kaufman, MD,[14] Mark D. Pegram, MD,[15] Sutton Edlich,[16] Shengyan Hong, PhD,[16] Edwin Rock, MD, PhD,[16] William J. Gradishar, MD,[17] on behalf of the SOPHIA Study Group

[1]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Seoul National University Hospital Cancer Research Institute, Seoul, Korea; [3]Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; [4]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]National Cancer Institute Fondazione Pascale, Naples, Italy; [6]IOB Institute of Oncology, Madrid & Barcelona; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Bannerer MD Anderson Cancer Center, Gilbert, AZ, USA; [8]University of Texas Southwestern Medical Center, Dallas, TX, USA; [9]Northwest Georgia Oncology Centers, Marietta Cancer Center, Marietta, GA, USA; [10]Mercy Medical Center, Baltimore, MD, USA; [11]University Hospital of Parma, Parma, Italy; [12]Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; [13]University of Milano, European Institute of Oncology, Milan, Italy; [14]University of Vermont Cancer Center, Division of Hematology/Oncology, Burlington, VT, USA; [15]Stanford Women's Cancer Center, Palo Alto, CA, USA; [16]MacroGenics, Inc., Rockville, MD, USA; [17]Northwestern University, Chicago, IL, USA

Abstract #1000
PRESENTED AT: 2019 ASCO ANNUAL MEETING
#ASCO19

PRESENTED BY: Hope S. Rugo, MD

Persistent Unmet Need in HER2+ MBC After Anti-HER2 Therapy

- Current standard of care for HER2-positive MBC
  - First-line: trastuzumab and pertuzumab with chemotherapy[1-3]
  - Second-line: T-DM1[4,5]
- After the above therapies, there is no recognized standard of care
  - Subsequent therapies are poorly defined, including sequential chemotherapy with trastuzumab and/or lapatinib[6,7]
  - Continued anti-HER2 therapy after progression is generally preferred, in combination with chemotherapy[8-11]

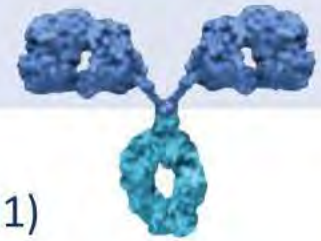
HER2=human epidermal growth factor receptor 2; MBC=metastatic breast cancer; T-DM1=ado-trastuzumab emtansine.

1. Baselga J, et al. *N Engl J Med.* 2012;366(2):109-119. 2. Swain SM, et al. *Lancet Oncol.* 2013;14(6):461-471. 3. Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734. 4. Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791. 5. Diéras V, et al. *Lancet Oncol.* 2017;18(6):732-742. 6. Giordano SH, et al. *J Clin Oncol.* 2018;36(26):2736-2740. 7. Cardoso F, et al. *Ann Oncol.* 2018;29(8):1634-1657. 8. von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006. 9. von Minckwitz G, et al. *Eur J Cancer.* 2011;47(15):2273-2281. 10. Geyer CE, et al. *N Engl J Med.* 2006;355(26):2733-2743. 11. Cameron D, et al. *Oncologist.* 2010;15(9):924-934.

Margetuximab: Fc-engineered to Activate Immune Responses

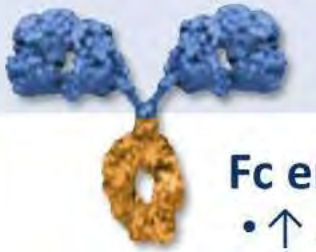
Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

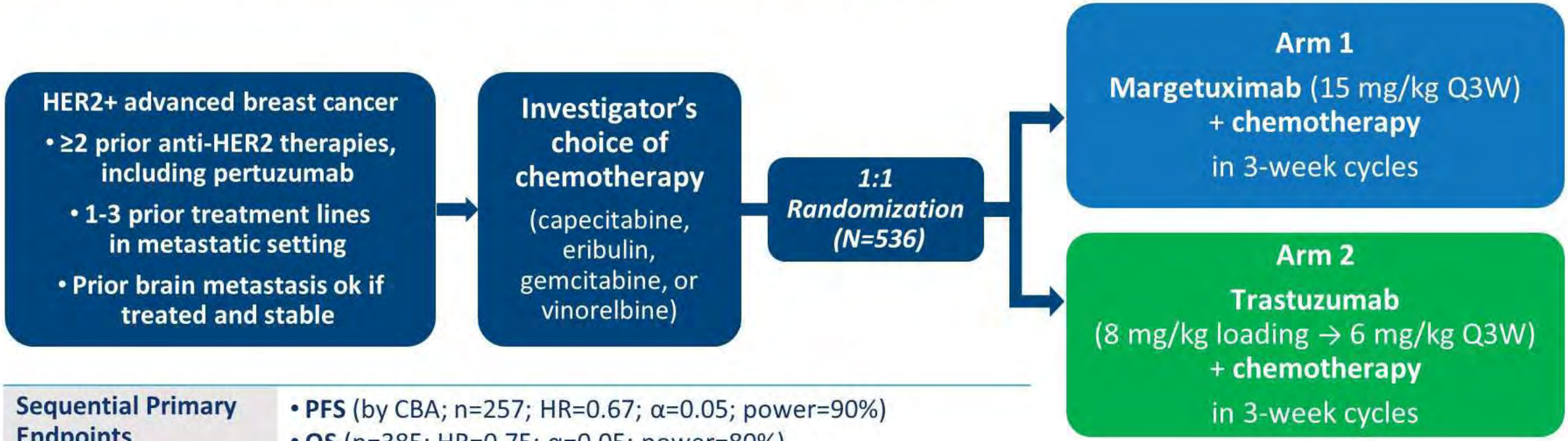
Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Study CP-MGAH22-04 (SOPHIA) Design[1,2]



Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

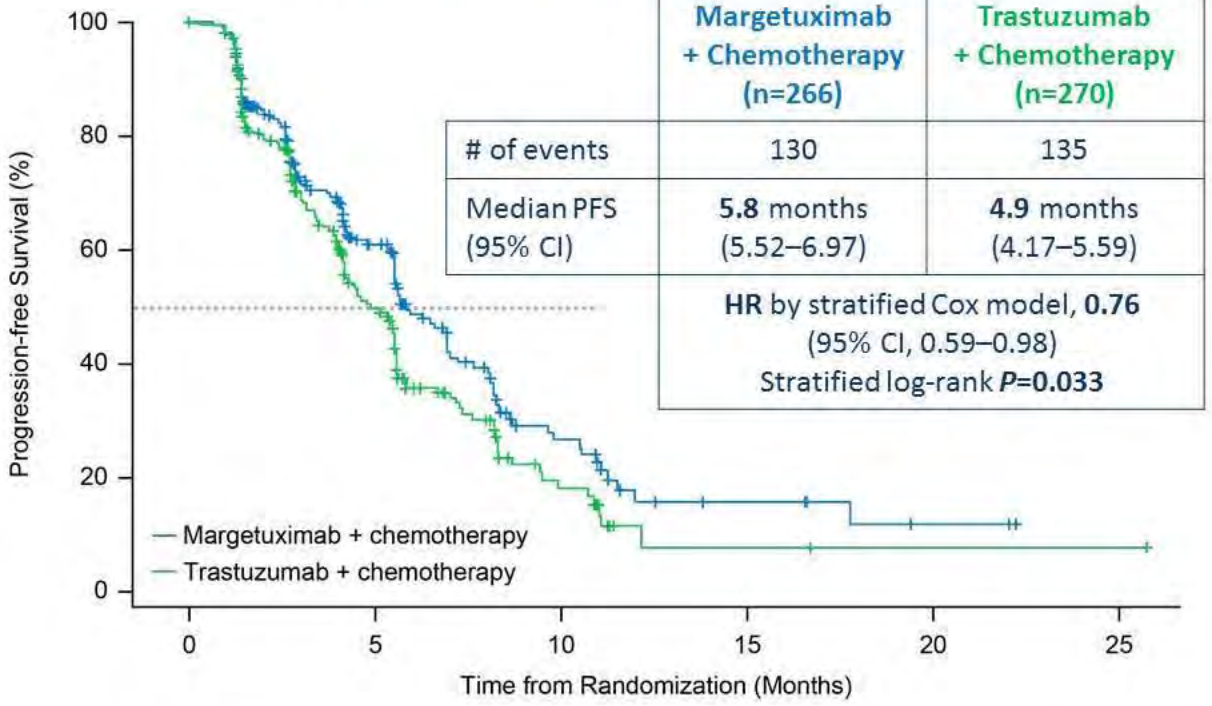
Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

PFS Analysis in ITT Population

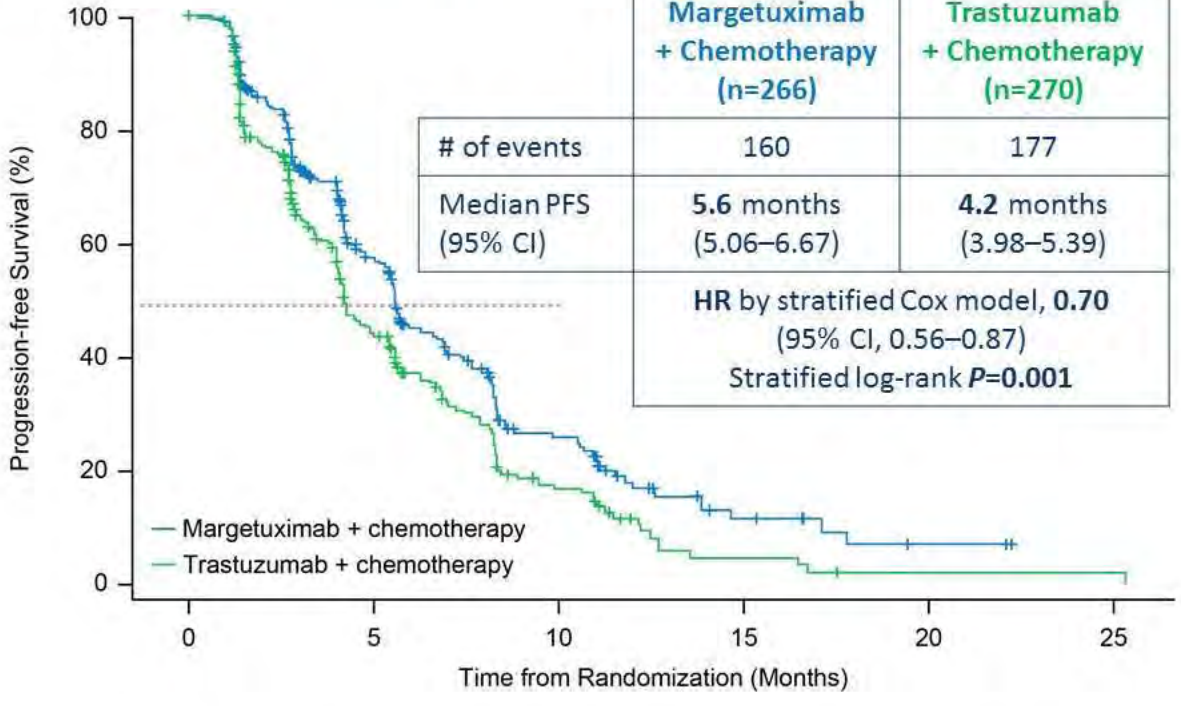
24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033**		

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

30% Risk Reduction of Disease Progression
Investigator Assessed (Secondary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	160	177
Median PFS (95% CI)	**5.6** months (5.06–6.67)	**4.2** months (3.98–5.39)
HR by stratified Cox model, **0.70** (95% CI, 0.56–0.87) Stratified log-rank ***P*=0.001**		

Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0	
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	1	0

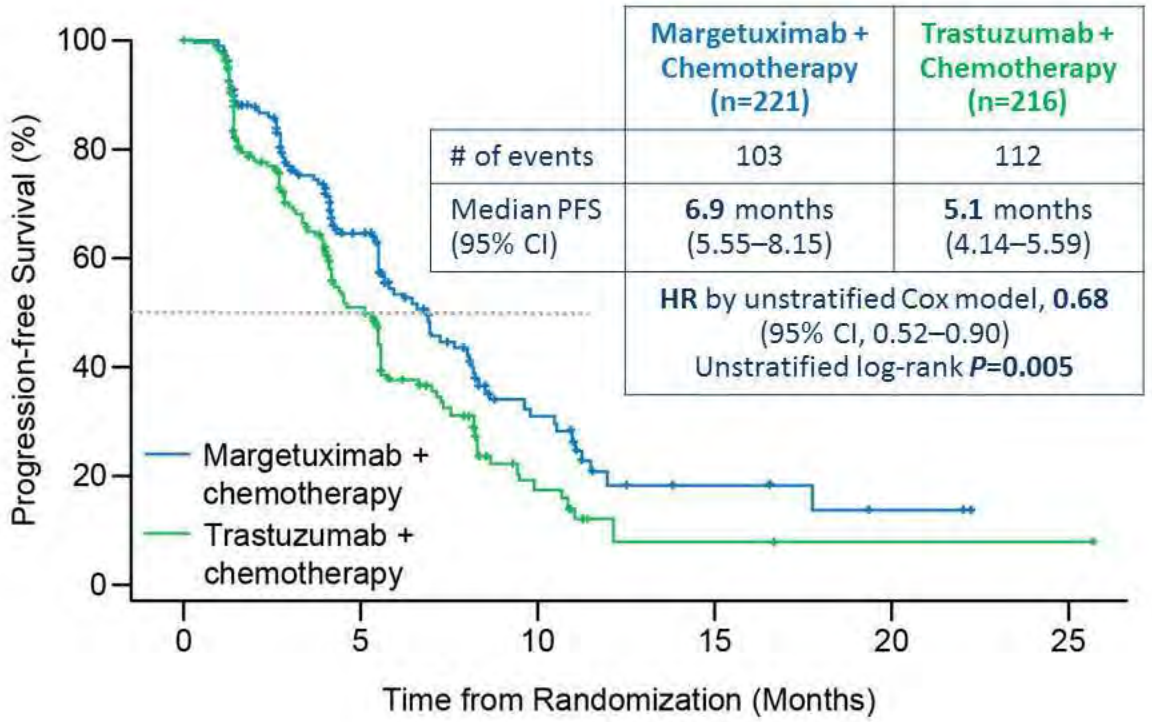
- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

Planned Exploratory PFS Analysis by CD16A Genotype, by CBA

506 patients genotyped (94%)

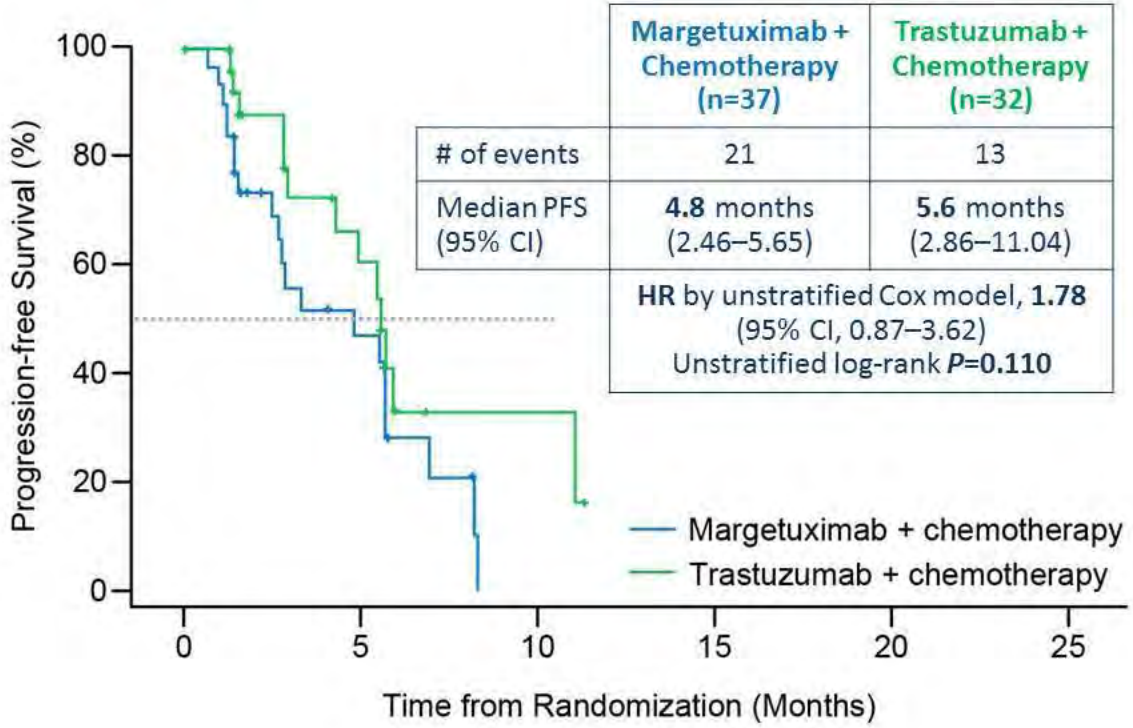
FF or FV, n=437 of 506 (86%)



	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)
HR by unstratified Cox model, **0.68** (95% CI, 0.52–0.90) Unstratified log-rank ***P*=0.005**		

Margetuximab	221	157	84	42	21	8	6	4	2	0	
Trastuzumab	216	129	62	30	11	2	2	1	1	1	1

VV, n=69 of 506 (14%)



	Margetuximab + Chemotherapy (n=37)	Trastuzumab + Chemotherapy (n=32)
# of events	21	13
Median PFS (95% CI)	**4.8** months (2.46–5.65)	**5.6** months (2.86–11.04)
HR by unstratified Cox model, **1.78** (95% CI, 0.87–3.62) Unstratified log-rank ***P*=0.110**		

Margetuximab	37	16	10	3	0	
Trastuzumab	32	18	10	2	2	0

Conclusions

- Margetuximab is a novel Fc-engineered HER2 targeted antibody that stimulates mechanisms of both innate and adaptive immunity
- In patients with HER2+ MBC progressing after trastuzumab, pertuzumab, chemotherapy, and T-DM1:
  - Margetuximab plus chemotherapy improved PFS (CBA: HR=0.76, *P*=0.033; Inv: HR=0.70, *P*=0.001), ORR, and CBR, compared with trastuzumab plus chemotherapy
- This is the first prospective analysis of CD16A genotype as predictor of efficacy from anti-HER2 therapy
  - Enhanced PFS benefit with margetuximab in low-affinity CD16A-158F carriers (HR=0.68, *P*=0.005)
- Acceptable safety, similar to trastuzumab[1]
  - Increased IRRs (primarily low grade) on margetuximab (13% vs 4%), managed with premedications
- Next milestone: second interim OS analysis, expected late 2019

.

IRR=infusion-related reaction. 1. Thompson LM, et al. *Oncologist*. 2014;19(3):228-234.

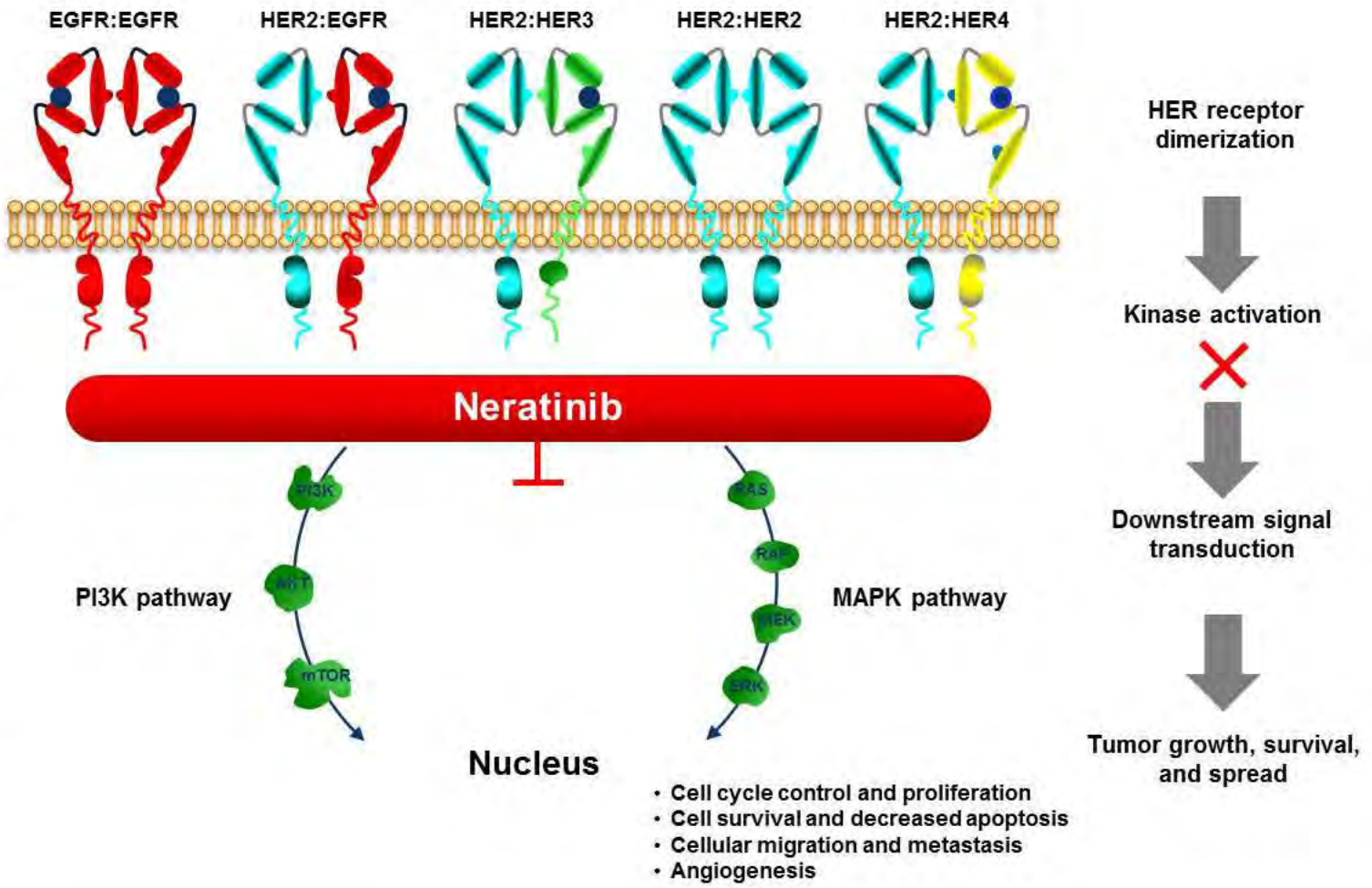
Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial

Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Sara A Hurvitz, Sung-Bae Kim, Beverly Moy, Suzette Delaloge, William Gradishar, Norikazu Masuda, Marketa Palacova, Maureen E Trudeau, Johanna Mattson, Yoon Sim Yap, Richard Bryce, Bin Yao, Judith Bebchuk, Kiana Keyvanjah, Adam Brufsky, NALA Investigators

Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Chi Mei Medical Centre, Tainan, Taiwan; Tri-Service General Hospital, Taipei, Taiwan; UCLA Hematology/Oncology Clinical Research Unit, Santa Monica, CA; University of Ulsan College of Medicine, Seoul, Republic of Korea; Massachusetts General Hospital Cancer Center, Boston, MA; Institut Gustave Roussy, Villejuif, France; Robert H Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; NHO Osaka National Hospital, Osaka, Japan; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Sunnybrook Health Sciences Centre, Toronto, ON; Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; National Cancer Centre Singapore, Singapore, Singapore; Puma Biotechnology Inc, Los Angeles, CA; Magee-Womens Hospital of UPMC, Pittsburgh, PA

Neratinib: An irreversible pan-HER TKI

- Neratinib: pan-HER (HER1, 2, and 4) TKI
- Breadth of targets for neratinib in HER family of receptors (HER1, 2, and 4 for neratinib; HER1 and 2 for lapatinib)
- Neratinib binds irreversibly to HER1, 2, and 4; lapatinib binds reversibly



TKI, tyrosine kinase inhibitor

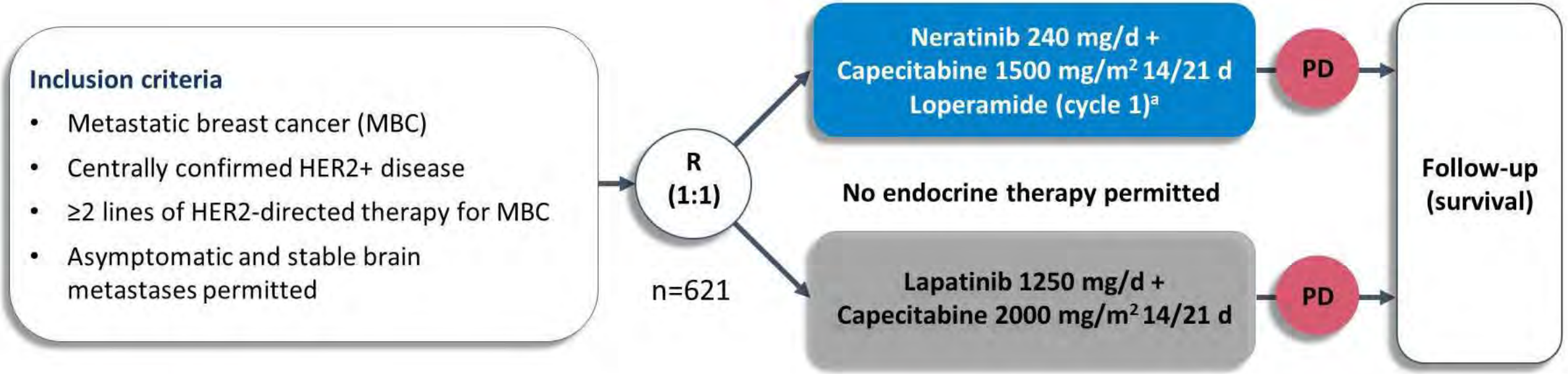
Rabindran et al. Cancer Res 2004
Neratinib US PI 2018

Clinical experience with neratinib

- **Extended adjuvant:** Approved by FDA and EMA based on reduced risk of recurrence of iDFS event with neratinib vs placebo in ExteNET[1]
- **Neoadjuvant:** Higher pCR rates with chemotherapy + neratinib vs chemotherapy + trastuzumab in patients with HER2+ breast cancer in I-SPY2[2]
- **Metastatic HER2+ disease:**
  - Study 2206: Promising efficacy with neratinib + capecitabine in trastuzumab-pretreated patients (recommended doses: neratinib 240 mg/d + capecitabine 1500 mg/m^2)[3]
  - NSABP FB-10: Evidence of efficacy with neratinib + T-DM1 in patients previously treated with trastuzumab + pertuzumab[4]
  - NEfERT-T: Delayed CNS progression with neratinib + paclitaxel in patients with HER2+ brain metastases[5]
  - TBCRC 022: Neratinib + capecitabine active against refractory brain metastases in patients with HER2+ brain metastases[6]

1. Martin et al. Lancet Oncol 2017; 2. Park et al. N Engl J Med 2016; 3. Saura et al. J Clin Oncol 2014
4. Abraham et al. J Clin Oncol 2018; 5. Awada et al. JAMA Oncol 2016; 6. Freedman et al. J Clin Oncol 2019

NALA study design



Stratification variables

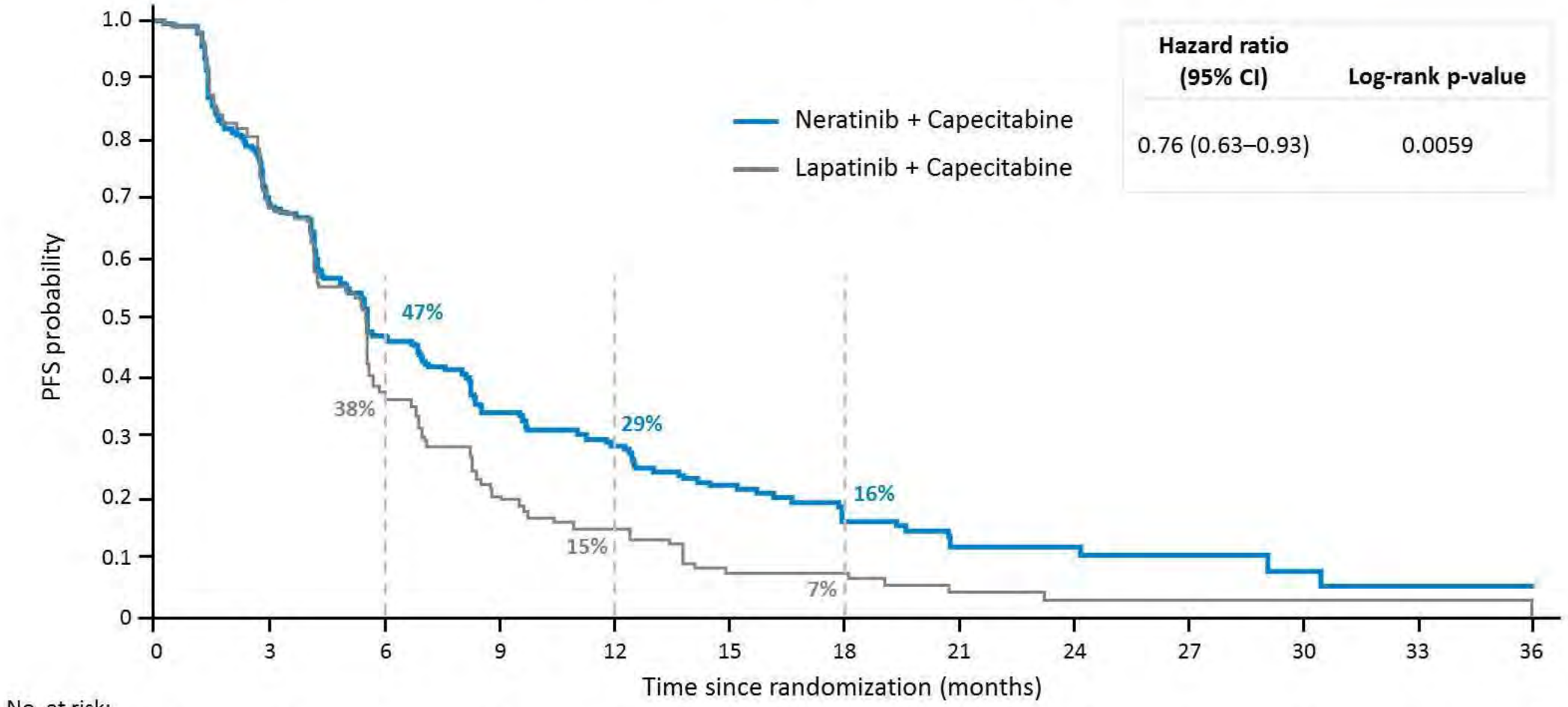
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

Centrally confirmed PFS (co-primary endpoint)

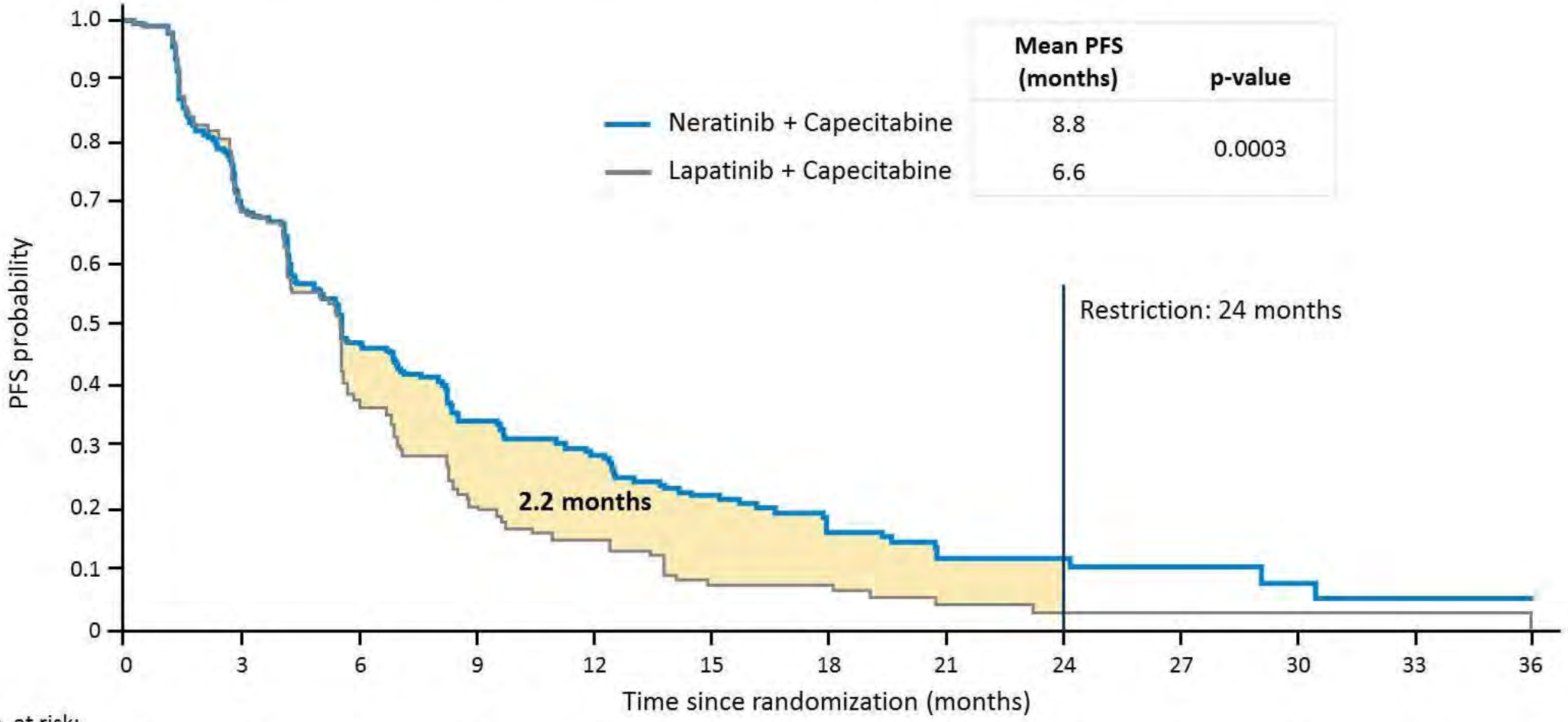


Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

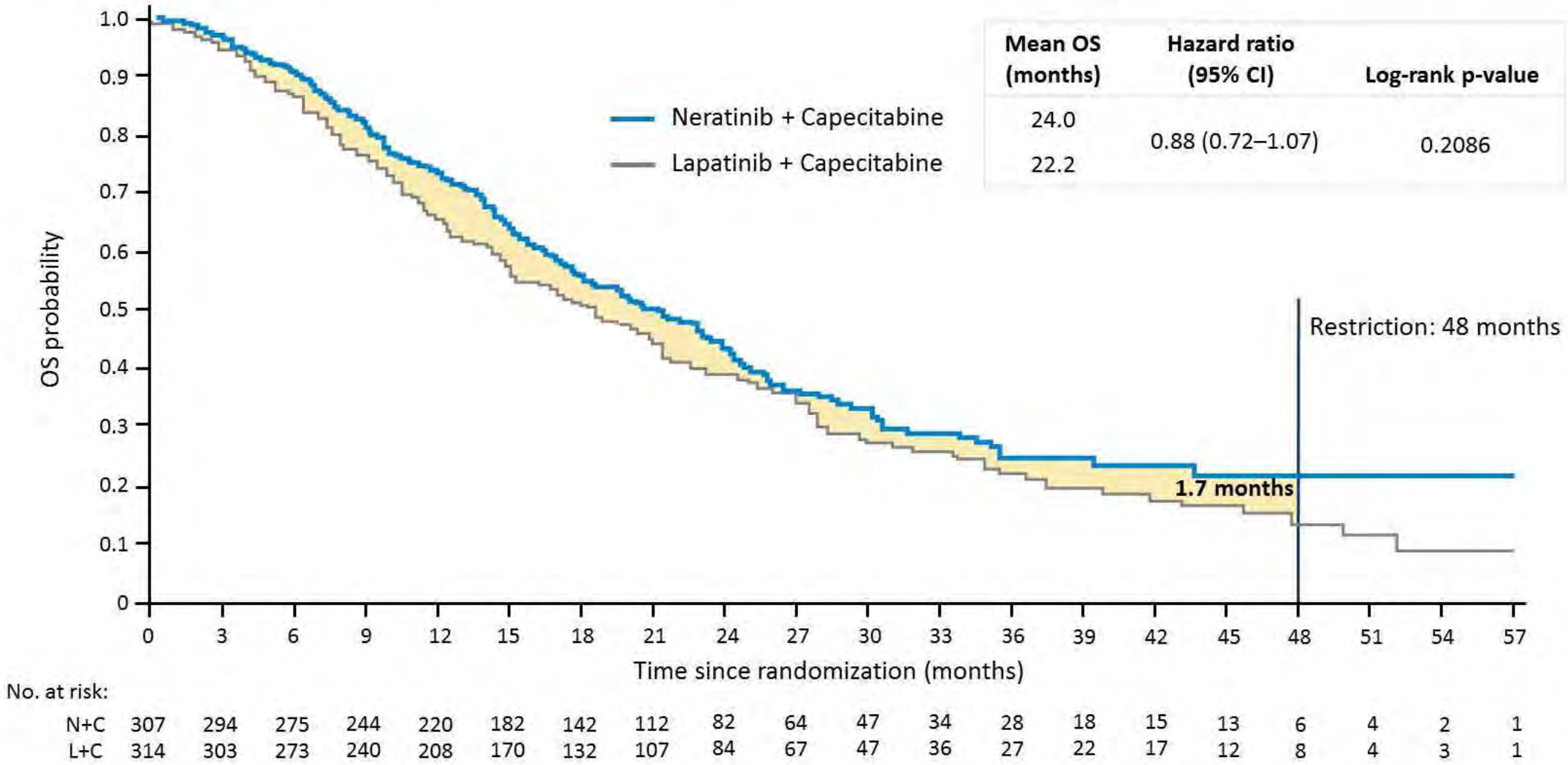
No. at risk:

N+C	307	183	113	69	54	35	20	13	9	7	3	2	2
L+C	314	183	82	39	24	9	8	3	2	2	2	2	1

Prespecified restricted means analysis – PFS



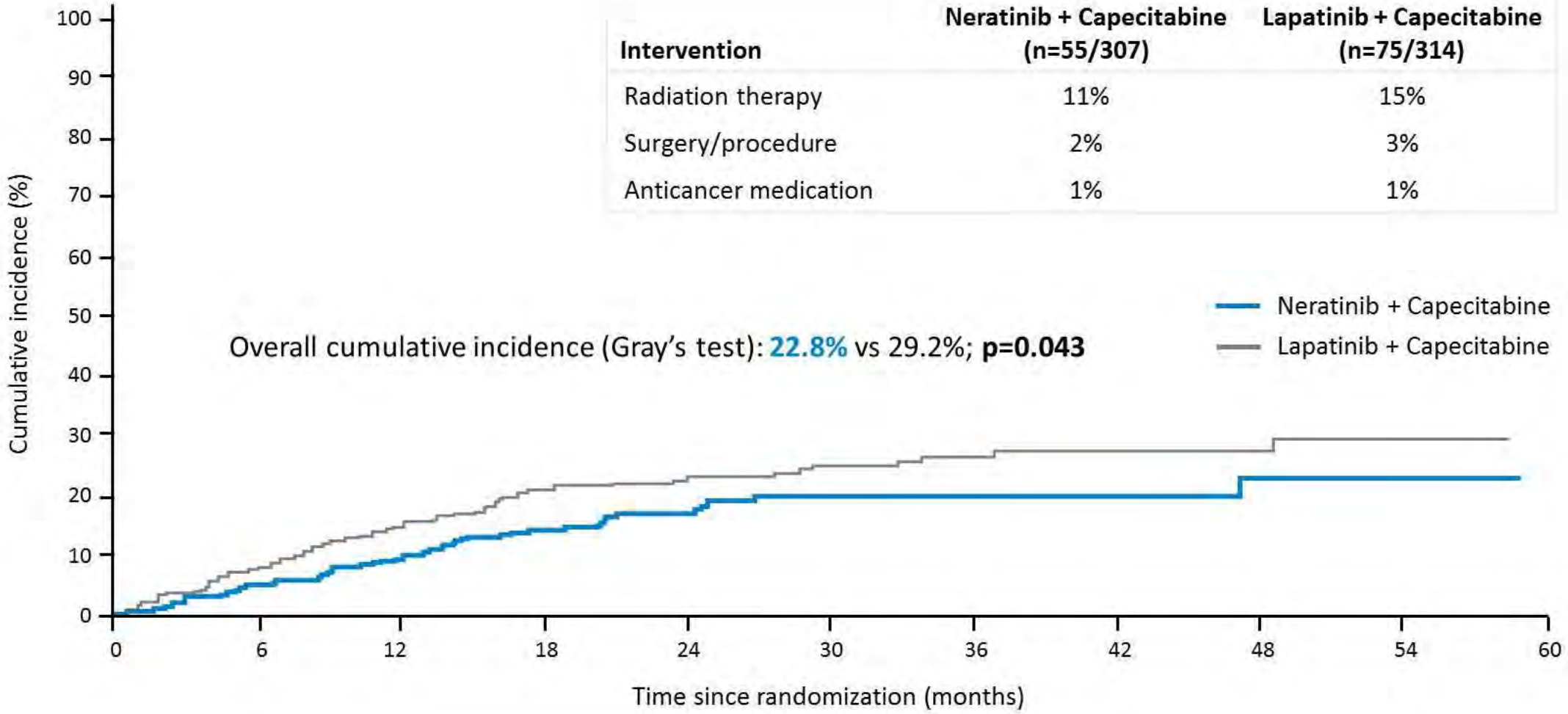
OS (co-primary endpoint)



Mean OS (months)	Hazard ratio (95% CI)	Log-rank p-value
24.0 22.2	0.88 (0.72–1.07)	0.2086

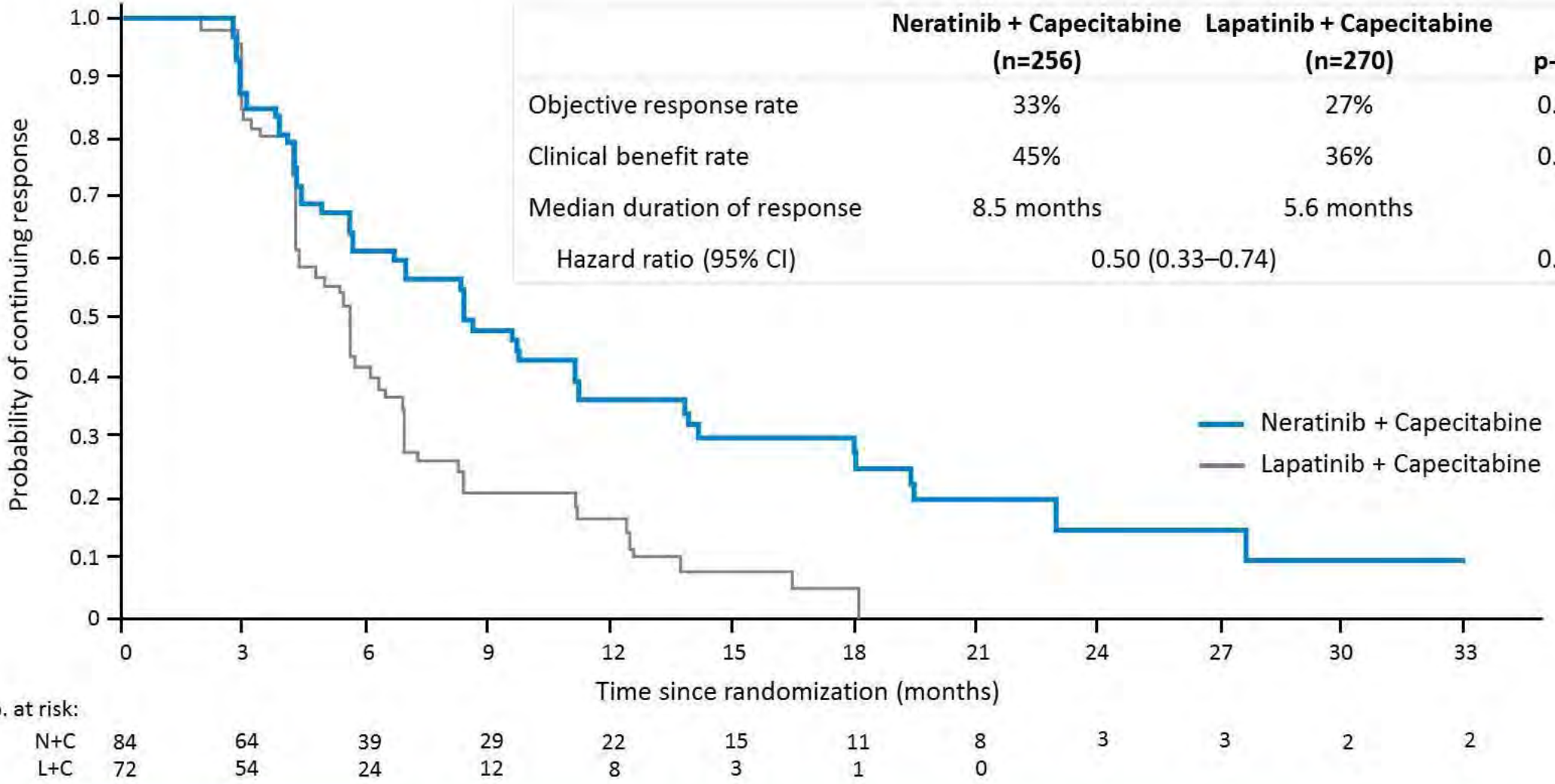
Time to intervention for CNS metastases

Intervention	Neratinib + Capecitabine (n=55/307)	Lapatinib + Capecitabine (n=75/314)
Radiation therapy	11%	15%
Surgery/procedure	2%	3%
Anticancer medication	1%	1%



Response rate and duration of response

	Neratinib + Capecitabine (n=256)	Lapatinib + Capecitabine (n=270)	p-value
Objective response rate	33%	27%	0.1201
Clinical benefit rate	45%	36%	0.0328
Median duration of response	8.5 months	5.6 months	
Hazard ratio (95% CI)	0.50 (0.33–0.74)		0.0004



Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AE, %	100	61	99	60
Diarrhea	83	24*	66	13*
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuation due to treatment-emergent AEs: N+C: 10.9%; L+C: 14.5%

*No Grade 4 diarrhea

Conclusions

- NALA met its primary objective: N+C superior to L+C in ≥3L HER2+ MBC
  - Significant PFS benefit favoring N+C: HR=0.76; p=0.0059
  - Numerical improvement in OS favoring N+C: HR=0.88; p=0.2086
- Fewer patients required intervention for symptomatic CNS metastases with N+C (p=0.043), suggestive of a delay in CNS progression
  - Consistent with results from previous neratinib studies[1,2]
- Duration of response significantly improved with N+C: HR=0.50; p=0.0004
- No new safety signals seen. Discontinuations due to diarrhea 2.3% with N+C and a median cumulative duration of grade 3 diarrhea of 4 days
- Trial results suggest N+C is an effective option for treating progressive HER2+ MBC

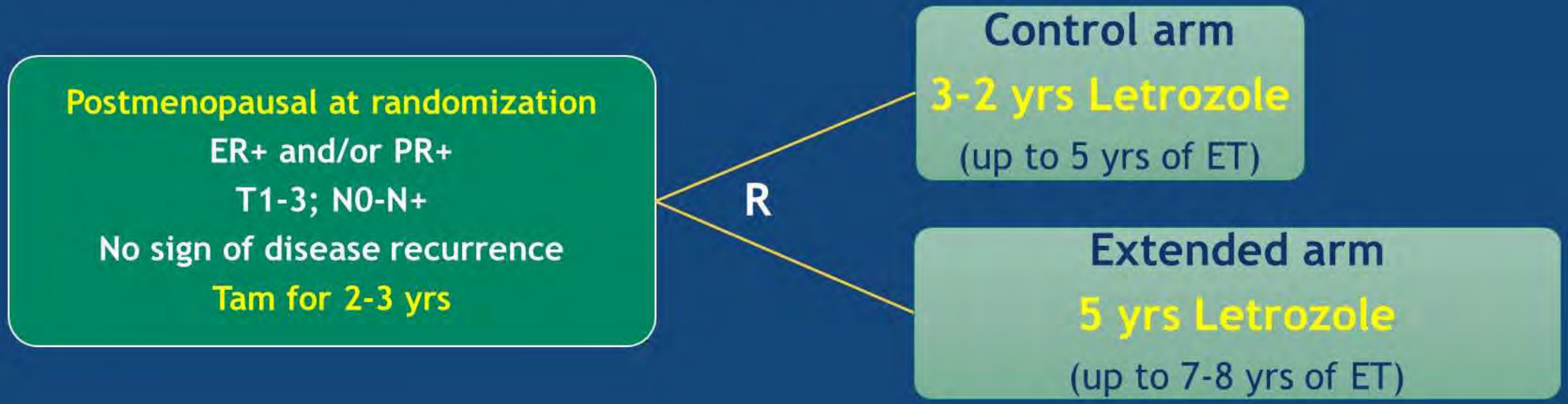
1. Awada et al. JAMA Oncol 2016; 2. Martin et al. Lancet Oncol 2017

Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: A randomized, phase III study of the Gruppo Italiano Mammella (GIM)

Lucia Del Mastro[1,2], Mauro Mansutti[3], Giancarlo Bisagni[4], Riccardo Ponzone[5], Antonio Durando[6], Laura Amaducci[7], Alessandra Fabi[8], Antonio Fassoldati[9], Andrea Michelotti[10], Antonio Pazzola[11], Enrichetta Valle[12], Giovanni Sanna[13], Stefania Gori[14], Sabino De Placido[15], Ornella Garrone[16], Michela Donadio[6], Paolo Bruzzi[2], Claudia Bighin[2], Matteo Lambertini[1,2], Francesca Poggio[2] **on behalf of the Gruppo Italiano Mammella (GIM)**

1. DIMI, University of Genova; 2. Ospedale Policlinico San Martino, Genova; 3. ASIU Udine University Hospital; 4. Azienda USL/IRCCS Reggio Emilia; 5. Candiolo Cancer Institute, Torino; 6. Città della Salute e della Scienza ASO S. Anna, Torino; 7. Dipartimento oncologico Ospedale Faenza; 8. Regina Elena National Cancer Institute, Roma; 9. Ferrara University Hospital, Ferrara; 10. Ospedale S. Chiara, Pisa; 11. Ospedale Civile SS Annunziata; Sassari; 12. Ospedale Oncologico A. Businco, Cagliari; 13. Azienda Ospedaliera Universitaria; Sassari; 14. Ospedale Sacro Cuore Don Calabria, Negrar; 15. Università Federico II, Napoli; 16. S. Croce e Carlo Teaching Hospital, Cuneo

GIM4 Study Design



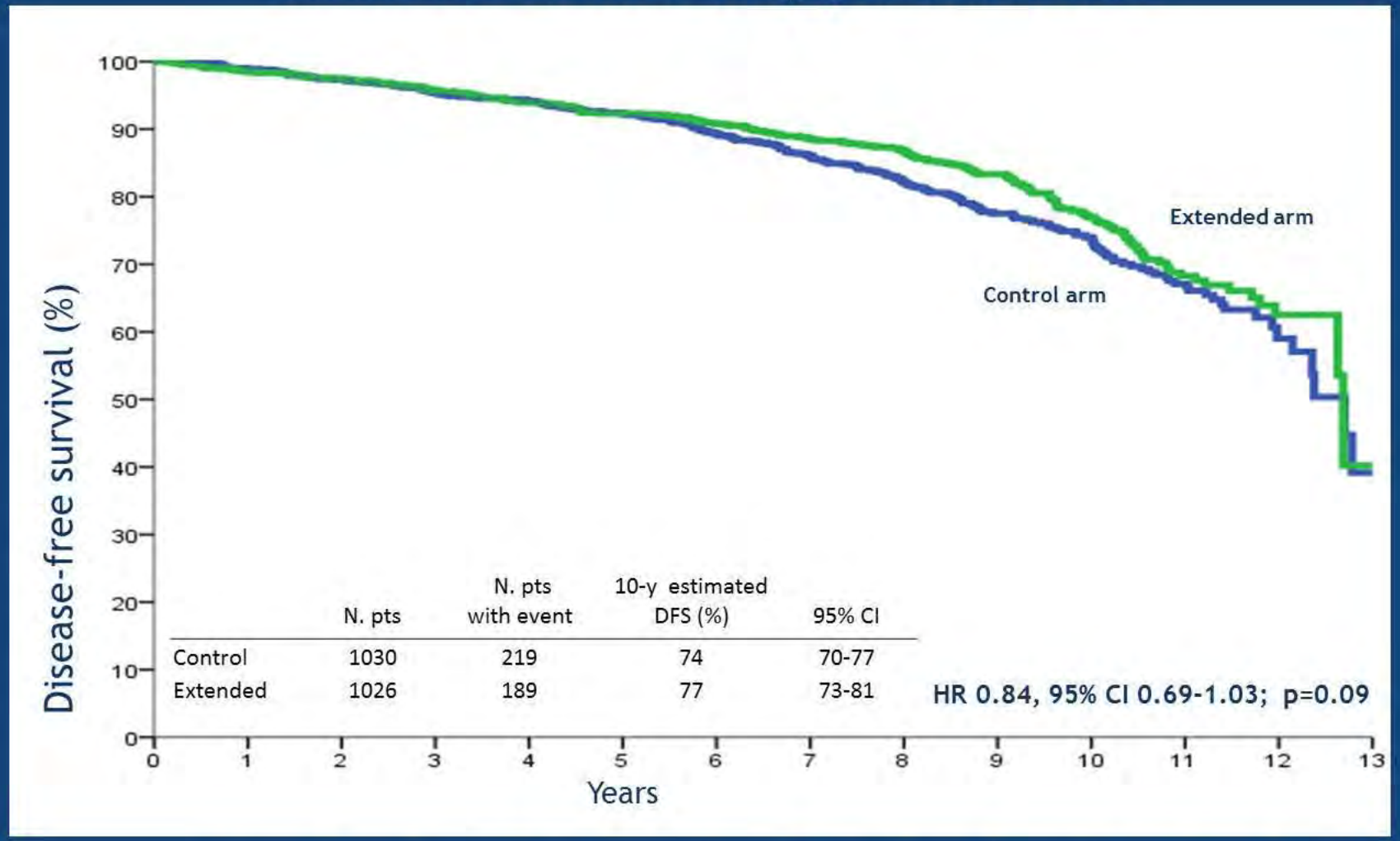
N=2056
Recruitment in 64 centres in Italy (GIM group), 2005-2010
Median follow-up: 10.4 years (IQR 8.8-11.4)

ClinicalTrials.gov: NCT01064635; EudraCT: 2005-001212-44

Treatment compliance

	Control arm 2-3 year letrozole (n=1030)	Extended arm 5-year letrozole (n=1026)
Treatment completed	779 (76%)	582 (57%)
Median duration of letrozole (IQR), years	2.4 (1.9 -2.8)	5.0 (2.4-5)
Early treatment discontinuation	251 (24%)	444 (43%)
Toxicity	87 (8%)	133 (13%)
Patient refusal	37 (4%)	96 (9%)
Primary disease event	35 (3%)	65 (6%)
Not begun	27 (3%)	35 (3%)
Other	65 (6%)	115 (11%)

Disease-Free Survival - ITT population. N=2056



	N. pts	N. pts with event	10-y estimated DFS (%)	95% CI
Control	1030	219	74	70-77
Extended	1026	189	77	73-81

Number at risk

		1	2	3	4	5	6	7	8	9	10	11	12	13
Control	1030	999	967	919	873	805	731	611	485	332	236	135	35	5
Extended	1026	990	963	917	875	814	739	636	512	397	254	120	38	3

Median follow up: 10.4 years

DFS first events by treatment

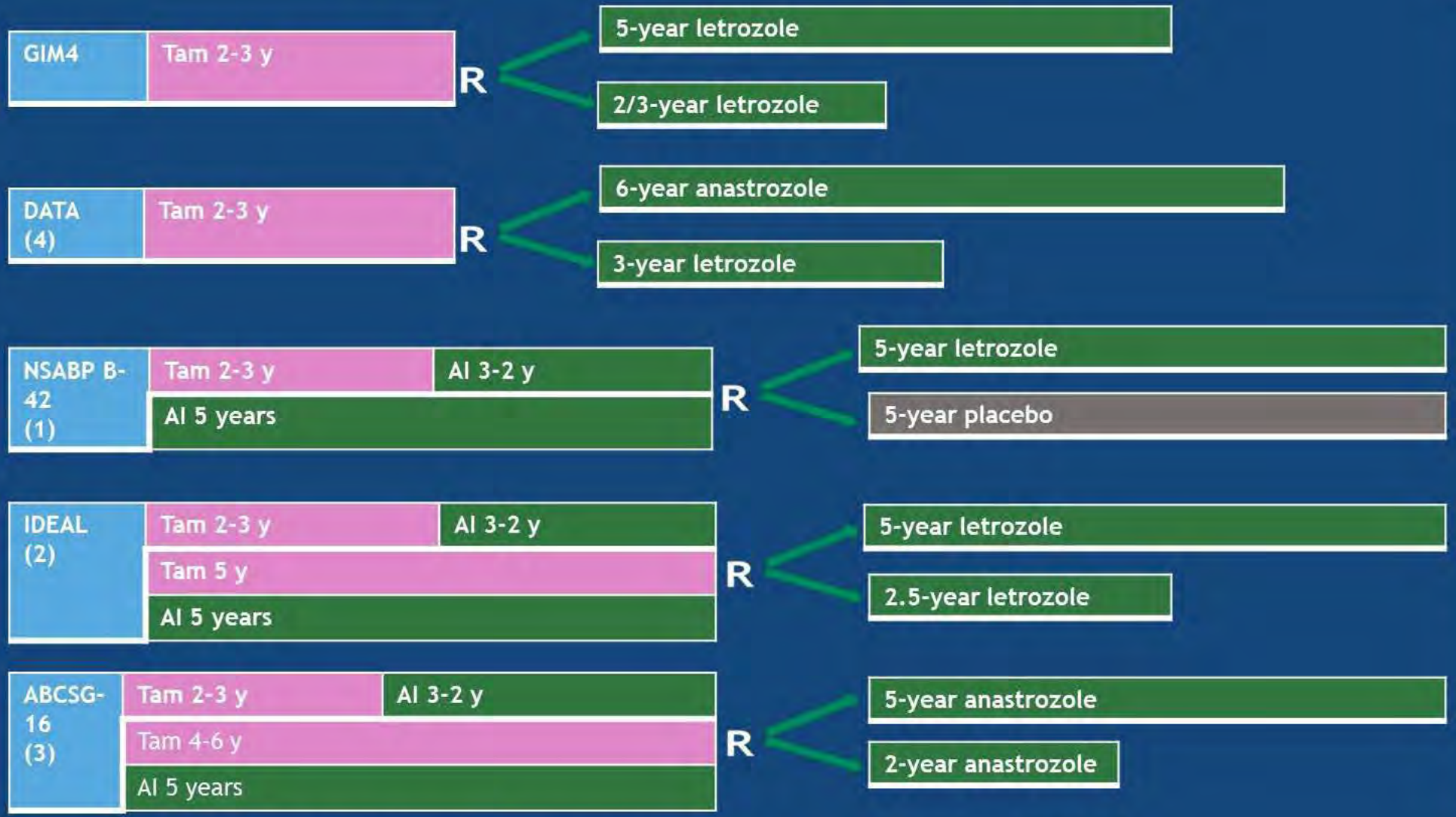
	Control arm 2-3-year letrozole (n=1030)		Extended arm 5-year letrozole (n=1026)	
First event	n.	%	n.	%
Distant recurrence	77	7.5	69	6.7
Local recurrence	28	2.7	21	2.0
Second primary cancer	65	6.3	57	5.5
Breast	36	3.5	31	3.0
Non -breast	29	2.8	26	2.5
Death without recurrence	49	4.8	42	4.1
Total first events	219	21.2	189	18.4

Selected side effects

	Control arm 2-3-year letrozole (n=983)		Extended arm 5-year letrozole (n=977)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Arthralgia	263 (27%)	22 (2%)	311 (32%)	29 (3%)
Myalgia	65 (7%)	7 (1%)	95 (10%)	9 (1%)
Hot flashes	119 (12%)		127 (13%)	
Alopecia	31 (3%)		35 (4%)	
Osteoporosis	47 (5%)[a]		81 (8%)[b]	
Bone fractures	5 (<1%)		9 (1%)	
Hypercholesterolemia	32 (3%)		22 (2%)	
Hypertension	7 (1%)		19 (2%)	
Cardiovascular event	1 (<1%)		6 (1%)	

a. 103 pts (10%) and b. 79 pts (8%) had baseline osteoporosis

Extended adjuvant AI studies



ET duration, years	HR DFS
5 vs 7/8	0.81 (0.65-1.00)
5/6 vs 8/9	0.79 (0.62-1.02)
5 vs 10	0.85 (0.62-1.02)
7.5 vs 10	1.007 (0.87-1.16)
7 vs 10	0.92 (0.74-1.16)

1. Mamounas; Lancet Oncol. 2019; 20:88-99; 2. Blok; J Natl Cancer Inst 2018; 110:40-48; 3. Gnant; SABCS 2017;
2. 4. Tjan-Heijnen ; Lancet Oncol 2017; 18:1502-11