

YIR On Demand Breast



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Disclosures

Contracted Research	Eisai Inc, Genentech BioOncology, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Plexxikon Inc, Roche Laboratories Inc
Paid Travel	Lilly, Mylan NV, Puma Biotechnology Inc

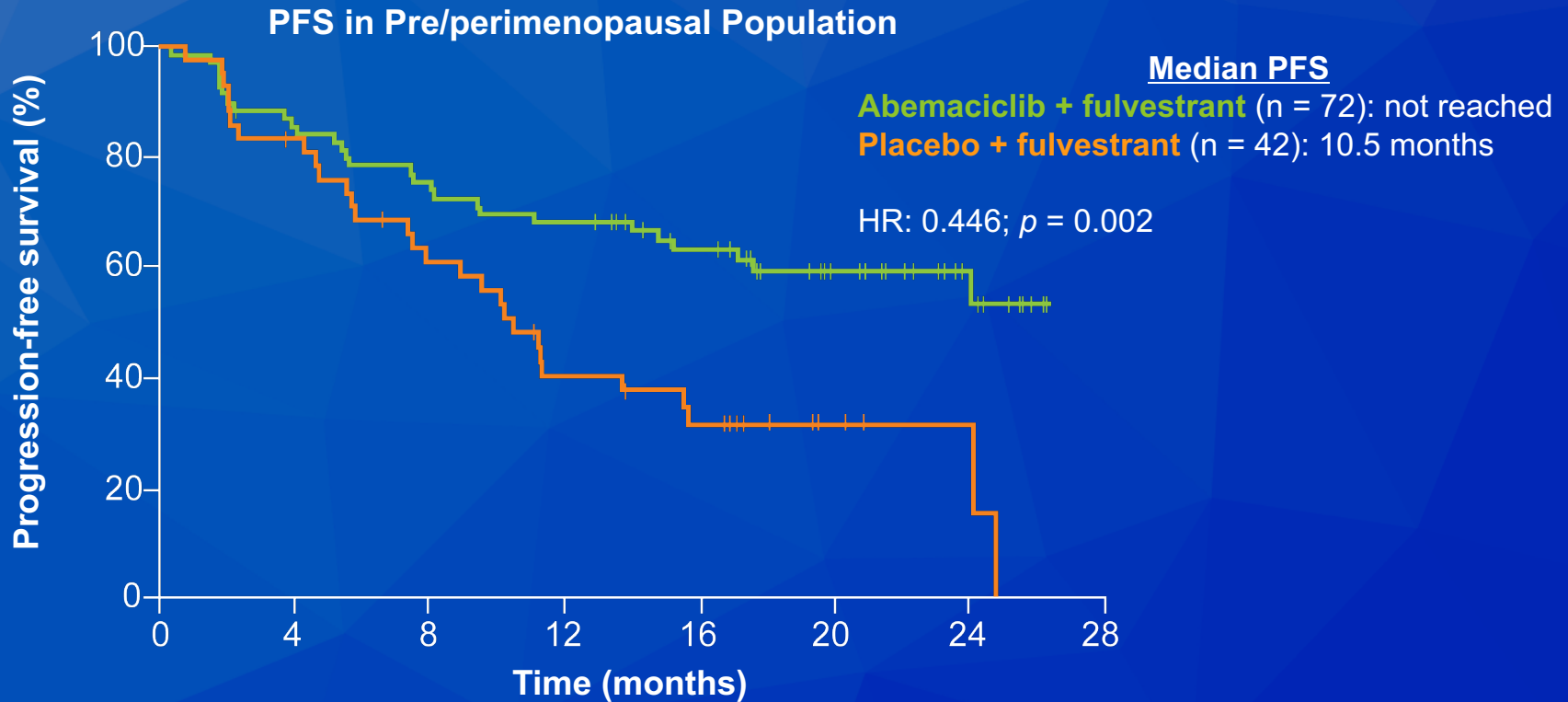
CDK4/6 Inhibitors in the Treatment of ER-Positive, HER2-Negative Breast Cancer (BC)

Abemaciclib for Pre/Peri-Menopausal Women with HR+, HER2-Advanced Breast Cancer

Neven P et al.

Proc ASCO 2018;Abstract 1002.

MONARCH 2: Investigator-Assessed PFS



	Abema + Fulv	Placebo + Fulv	HR (p-value)
Median PFS – ITT (n = 446; 223)	16.4 mo	9.3 mo	0.553 (<0.0000001)
Median PFS – Pre/perimenopausal with no prior AI (n = 62; 30)	Not reached	11.3 mo	0.451 (0.009)

AI = aromatase inhibitor

MONARCH 2: Select Treatment-Emergent Adverse Events

Adverse event (%)	Abema + Fulv (n = 71)				Placebo + Fulv (n = 42)			
	Any gr	Gr 2	Gr 3	Gr 4	Any gr	Gr 2	Gr 3	Gr 4
Diarrhea	87.3	31.0	11.3	0	23.8	2.4	0	0
Neutropenia	59.2	12.7	39.4	2.8	7.1	2.4	2.4	0
Leukopenia	43.7	21.1	16.9	0	4.8	2.4	0	0
Infections, infestations	43.7	36.6	1.4	0	26.2	16.7	4.8	0
Vomiting	32.4	7.0	1.4	0	7.1	0	2.4	0

- Diarrhea associated with abemaciclib was generally predictable (occurred early), manageable and reversible
- After protocol amendment to lower abemaciclib starting dose from 200 mg to 150 mg, no treatment discontinuations due to diarrhea were observed



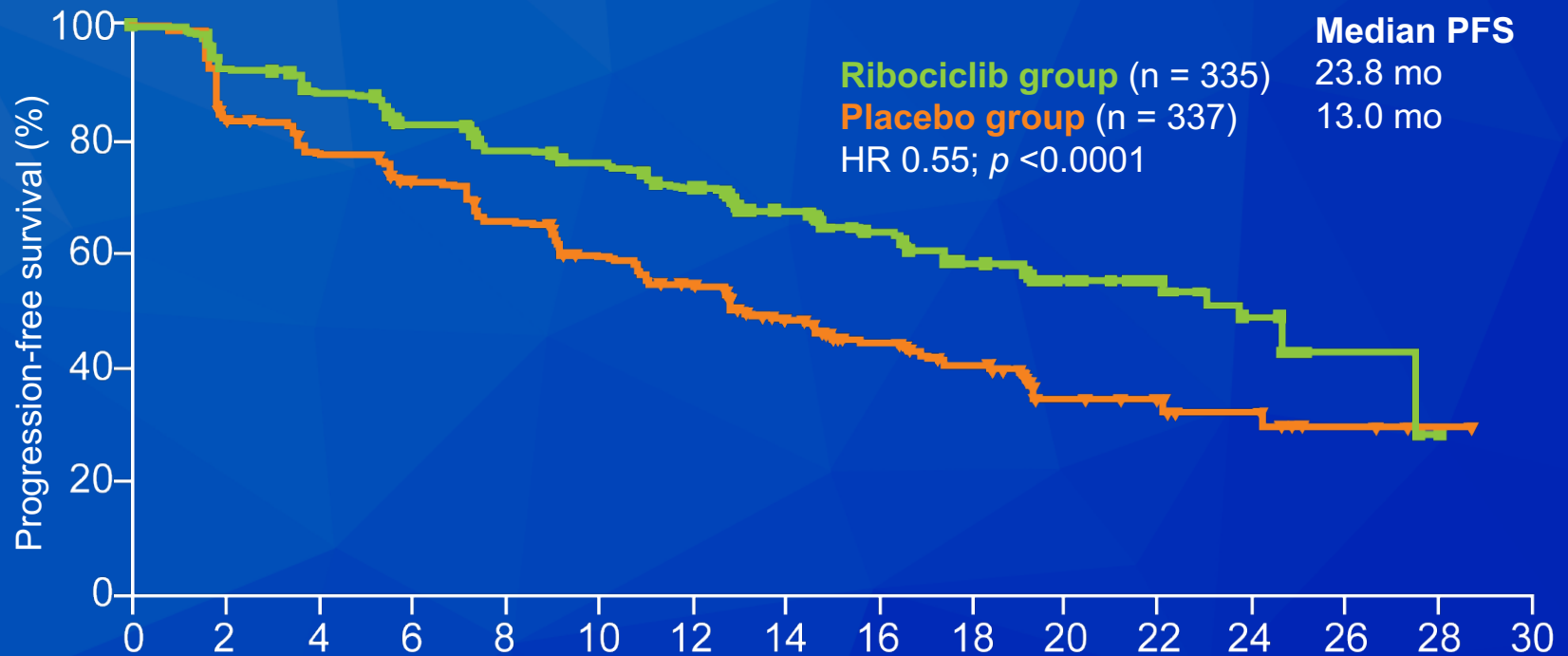
Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial

Debu Tripathy, Seock-Ah Im, Marco Colleoni, Fabio Franke, Aditya Bardia, Nadia Harbeck, Sara A Hurvitz, Louis Chow, Joohyuk Sohn, Keun Seok Lee, Saul Campos-Gomez, Rafael Villanueva Vazquez, Kyung Hae Jung, K Govind Babu, Paul Wheatley-Price, Michelino De Laurentiis, Young-Hyuck Im, Sherko Kuemmel, Nagi El-Saghir, Mei-Ching Liu, Gary Carlson, Gareth Hughes, Ivan Diaz-Padilla, Caroline Germa, Samit Hirawat, Yen-Shen Lu

Lancet Oncol 2018;19(7):904-15.

- Premenopausal women with HER2-negative breast cancer who were treatment naïve or had received up to 1 line of prior chemotherapy for advanced breast cancer
- 672 women were randomized 1:1 to ribociclib versus placebo, in combination with tamoxifen and goserelin or NSA and goserelin.

MONALEESA-7: Efficacy Summary



- ORR = 41% versus 30% for the ribociclib arm versus the placebo arm, respectively ($p = 0.00098$)
- OS data were immature at the time of analysis

MONALEESA-7: Select Adverse Events (≥5% of Patients)

Adverse event (%)	Ribociclib (n = 335)			Placebo (n = 337)		
	Gr 1-2	Gr 3	Gr 4	Gr 1-2	Gr 3	Gr 4
Neutropenia	15	51	10	4	3	1
Leukopenia	17	13	1	4	1	0
Elevated ALT	7	5	0	6	1	0
Elevated AST	8	4	0	8	1	0
Electrocardiogram QT prolonged	10	1	0	4	0	<1

- Dose reductions due to AEs (ribociclib vs placebo): 31% vs 5%

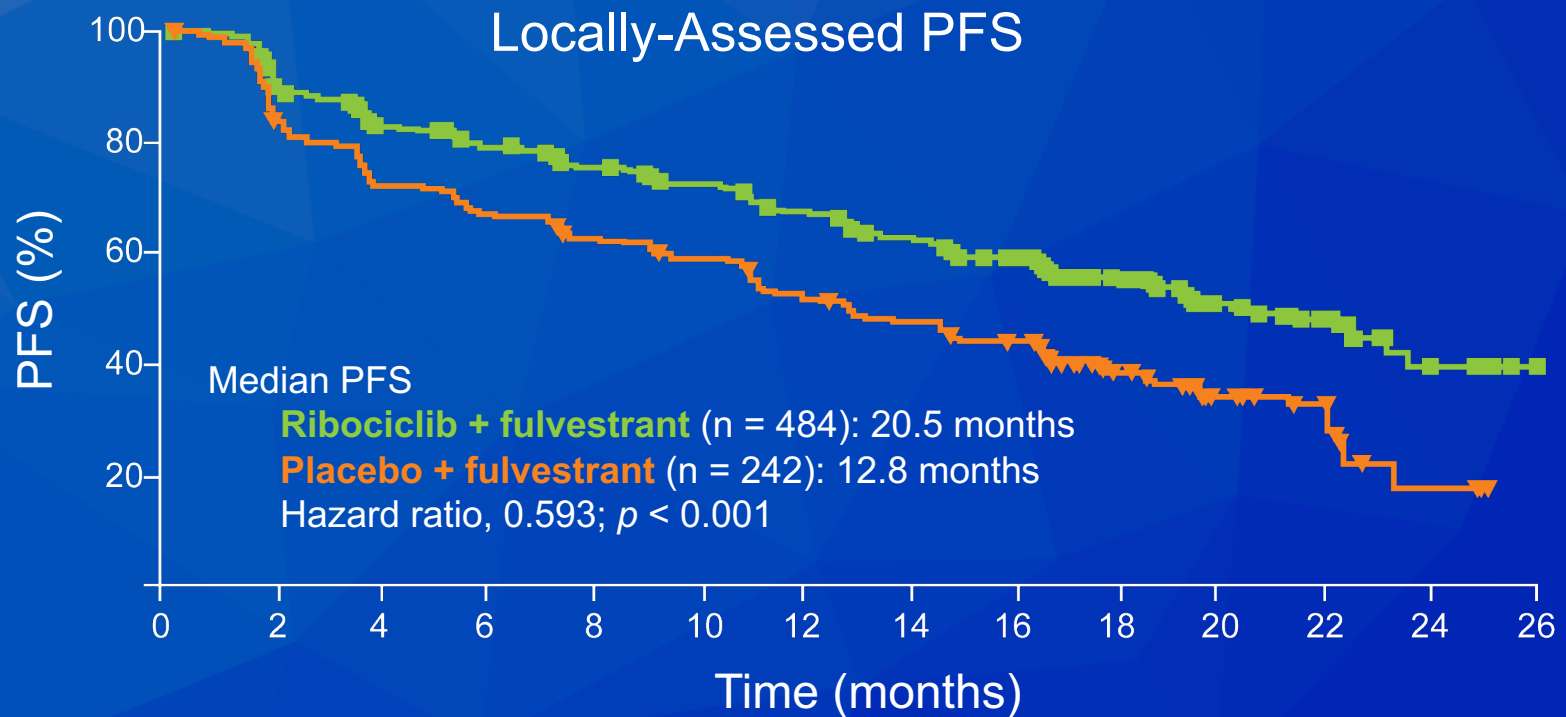
Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3

Dennis J. Slamon, Patrick Neven, Stephen Chia, Peter A. Fasching, Michelino De Laurentiis, Seock-Ah Im, Katarina Petrakova, Giulia Val Bianchi, Francisco J. Esteva, Miguel Martín, Arnd Nusch, Gabe S. Sonke, Luis De la Cruz-Merino, J. Thaddeus Beck, Xavier Pivot, Gena Vidam, Yingbo Wang, Karen Rodriguez Lorenc, Michelle Miller, Tetiana Taran, and Guy Jerusalem

Slamon DJ et al. *J Clin Oncol* 2018;36(24):2465-72.

- Postmenopausal women with HER2-negative breast cancer who were treatment naïve or had received up to 1 line of prior endocrine therapy for advanced breast cancer
- 726 women were randomized 2:1 to ribociclib plus fulvestrant or placebo plus fulvestrant.

MONALEESA-3: Efficacy Summary



- ORR in all patients = 32.4% for the ribociclib + fulvestrant arm versus 21.5% for the placebo + fulvestrant arm ($p < 0.001$)
- At the first planned interim analysis, OS data were immature

MONALEESA-3: Select Adverse Events (≥15% of Patients)

Adverse event (%)	Ribociclib + Fulv (n = 483)			Placebo + Fulv (n = 241)		
	All gr	Gr 3	Gr 4	All gr	Gr 3	Gr 4
Neutropenia	69.6	46.6	6.8	2.1	0	0
Nausea	45.3	1.4	0	28.2	0.8	0
Fatigue	31.5	1.7	0	33.2	0.4	0
Leukopenia	28.4	13.5	0.6	1.7	0	0
Anemia	17.2	3.1	0	5.4	2.1	0

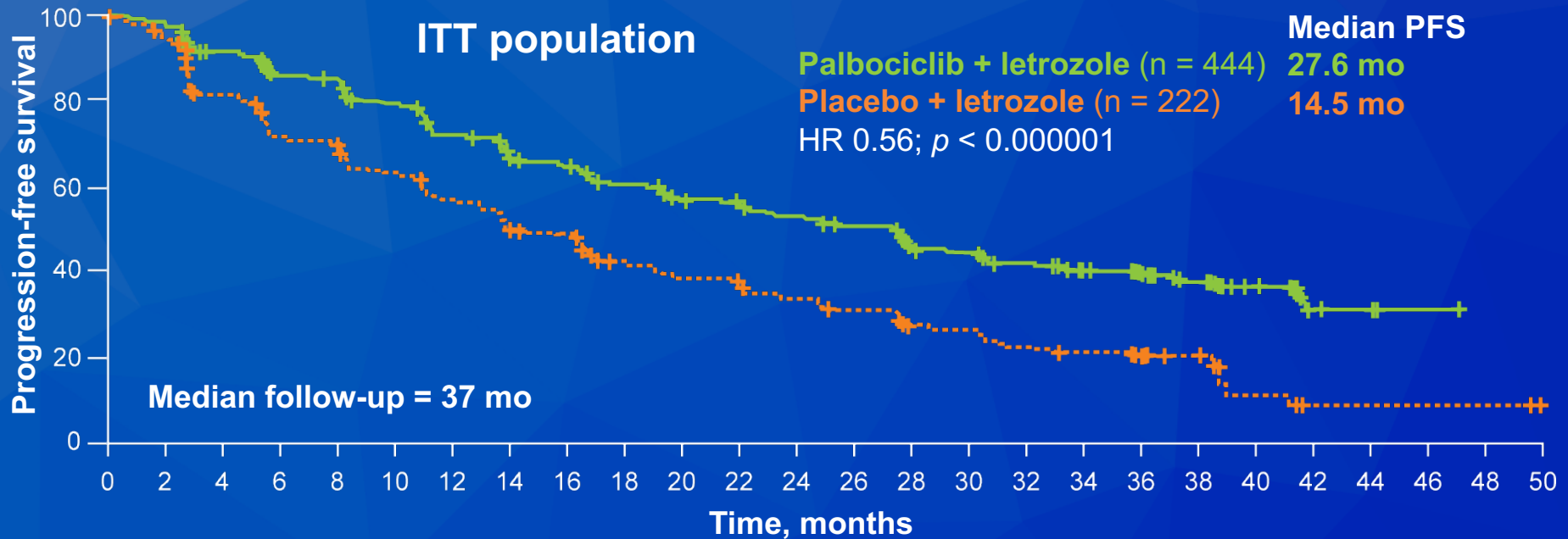
- QT interval prolongation (ribociclib vs placebo): 6.2% vs 0.8%
- Grade 3/4 elevated ALT/AST (ribociclib vs placebo): 8.5%/6.0% vs 1.2%/0
- Dose reductions due to AEs (ribociclib vs placebo): 33.1% vs 3.3%

Palbociclib plus Letrozole as First-Line Therapy in Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Efficacy and Safety Updates with Longer Follow-Up Across Patient Subgroups

Rugo HS et al.

San Antonio Breast Cancer Symposium
2017;Abstract P5-21-03.

PALOMA-2: Updated Investigator-Assessed PFS



Subgroup analysis of PFS	Palbo/let	Placebo/let	HR	p-value
Visceral disease + no prior ET	23.7 mo	13.9 mo	0.55	<0.005
Nonvisceral disease + no prior ET	36.2 mo	27.6 mo	0.59	<0.01
Bone-only disease	36.2 mo	11.2 mo	0.41	<0.0001
No bone-only disease	24.2 mo	14.5 mo	0.62	<0.0001
De novo metastatic disease	27.9 mo	22.0 mo	0.61	<0.005

All subgroups benefitted from the addition of palbociclib to letrozole

PALOMA-2: Select Treatment-Emergent AEs in >1% of Patients

	Palbociclib/letrozole (n = 444)		Placebo/letrozole (n = 222)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic				
Neutropenia	81.8%	69.1%	6.3%	1.4%
Leukopenia	40.3%	25.2%	2.3%	0
Anemia	26.4%	5.8%	9.5%	1.8%
Thrombocytopenia	19.6%	1.6%	1.4%	0
Nonhematologic				
Infection	62.6%	7.6%	45.0%	4.6%
Stomatitis	31.5%	1.1%	14.9%	0
Hyperglycemia	3.6%	0.7%	7.7%	0.9%
Pulmonary embolism	1.6%	1.5%	2.3%	2.4%

Genetic Landscape of Resistance to CDK4/6 Inhibition in Circulating Tumor DNA (ctDNA) Analysis of the PALOMA3 Trial of Palbociclib and Fulvestrant Versus Placebo and Fulvestrant

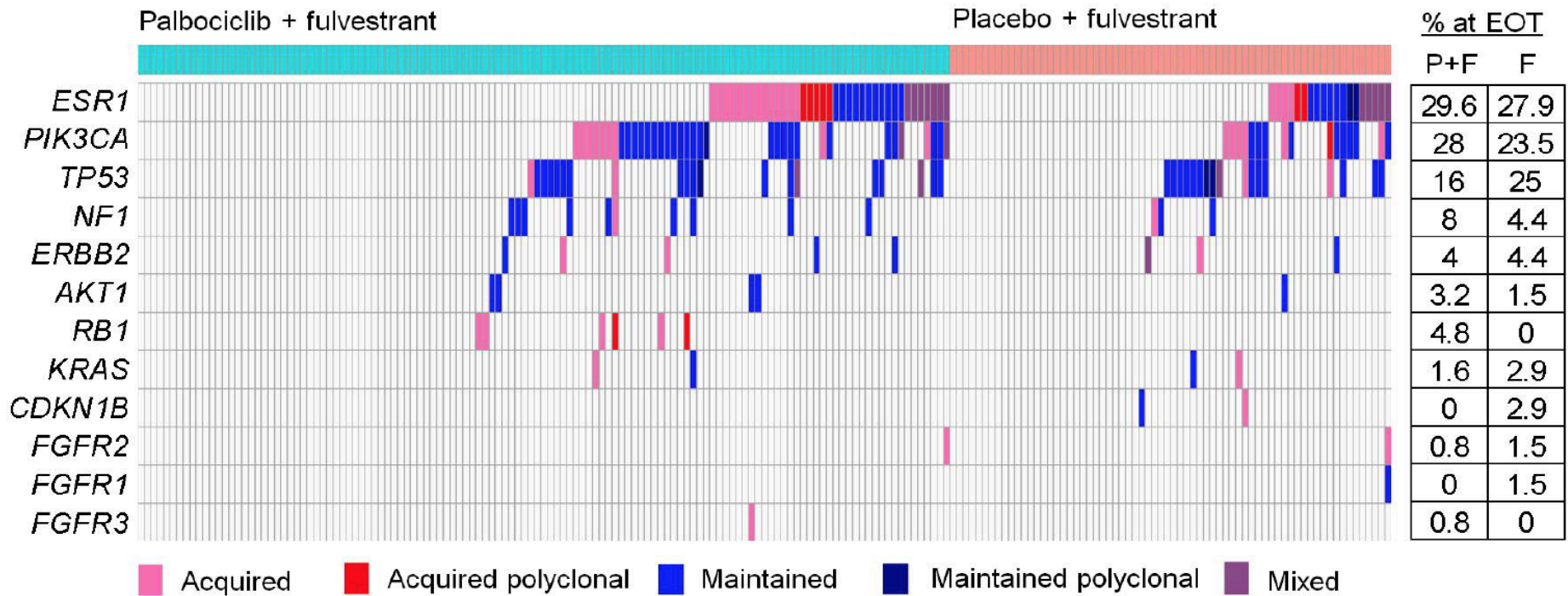
Turner NC et al.

Proc ASCO 2018;Abstract 1001.

PALOMA-3: Paired ctDNA Analysis Methods

- PALOMA-3 evaluated palbociclib + fulvestrant in women with HR-positive, HER2-negative advanced breast cancer who had experienced disease progression on prior endocrine therapy and received ≤ 1 chemotherapy for advanced breast cancer
- Plasma samples for ctDNA analysis were banked at baseline and at end of treatment (EOT): n = 125 palbociclib + fulvestrant arm; 68 fulvestrant alone arm
- A panel of 17 targetable driver and CDK4/6-related genes were analyzed by amplicon error-corrected sequencing
 - Coding exons: RB1, CDK4, CDK6, CDKN1A, CDKN1B, NF1 and TP53
 - Mutational hotspots: ERBB2, PIK3CA, AKT1, ESR1, FGFR1, FGFR2, FGFR3, KRAS, NRAS and HRAS

PALOMA-3: EOT Mutation Landscape



- Patients with at least 1 acquired mutation:
 - 35/125 (28%) palbociclib + fulvestrant arm
 - 15/68 (22.1%) fulvestrant alone arm

PALOMA-3: Mutation Analysis Summary

- RB1 mutations are enriched at EOT on the palbociclib/fulvestrant arm
 - No RB1 mutations were detected at baseline
 - 6/125 (4.8%) patients on palbociclib treatment had acquired an RB1 mutation (all truncating mutations) at EOT, but 0/68 patients on the fulvestrant alone arm had acquired a mutation
- PIK3CA mutations were acquired on both treatment arms
 - 9/125 (7.2%) patients on palbociclib treatment and 7/68 (10.3%) of patients on the fulvestrant alone arm had acquired mutations at EOT
- ESR1 mutations are both lost and acquired during treatment in both study arms
 - ESR1 Y537S mutation is likely selected by fulvestrant

mTOR Inhibitors and Anti-androgens for ER-Positive BC

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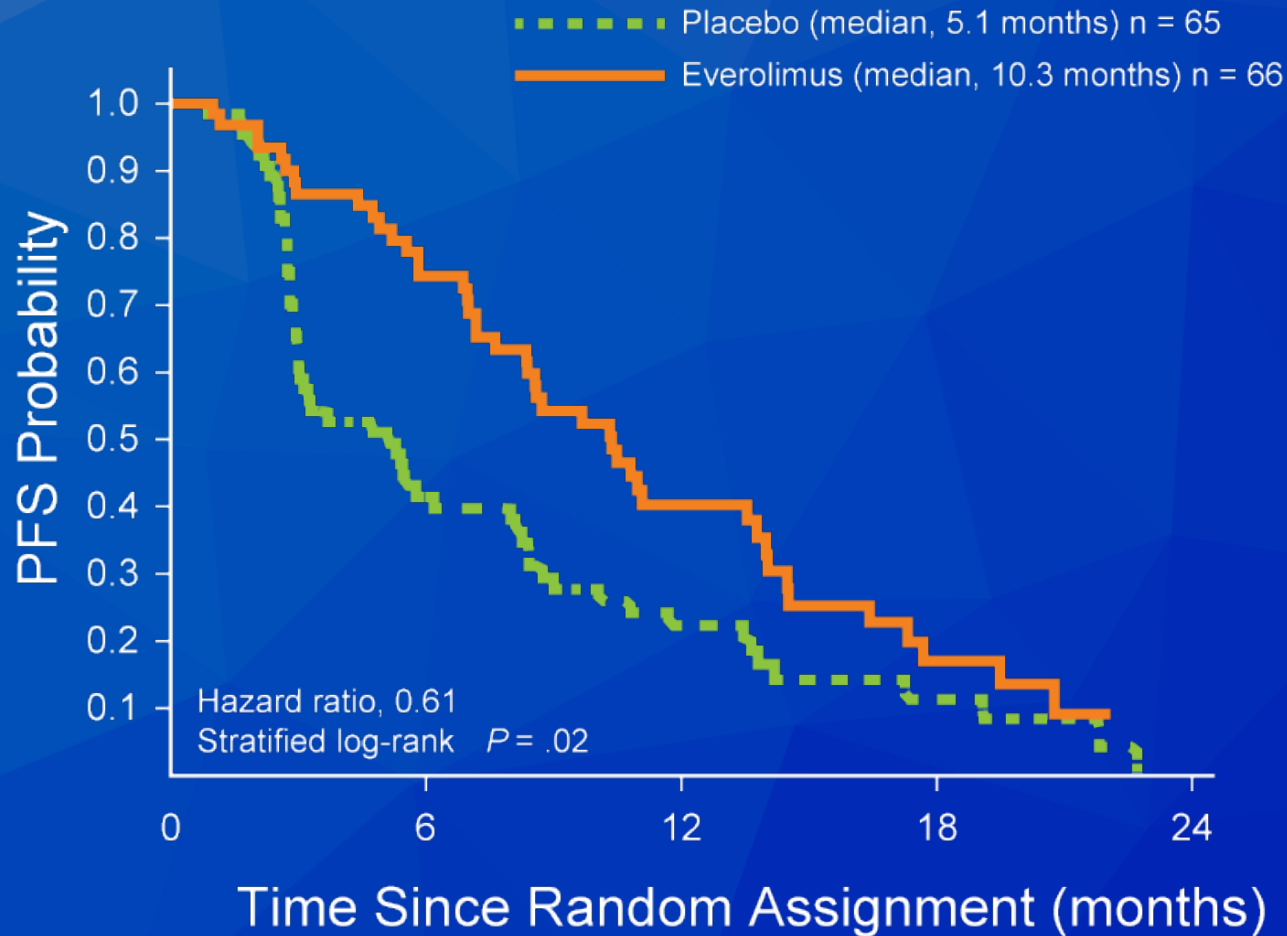
ORIGINAL REPORT

Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102

Noah Kornblum, Fengmin Zhao, Judith Manola, Paula Klein, Bhuvanewari Ramaswamy, Adam Brufsky, Phillip J. Stella, Brian Burnette, Melinda Telli, Della F. Makower, Puneet Cheema, Cristina I. Truica, Antonio C. Wolff, Gamini S. Soori, Barbara Haley, Timothy R. Wassenaar, Lori J. Goldstein, Kathy D. Miller, and Joseph A. Sparano

J Clin Oncol 2018;36(16):1556-63


PrE0102: Efficacy Summary



- There was no significant difference in OS ($p = 0.37$) or objective response rate ($p = 0.47$) between the study arms.

PrE0102: Select Treatment-Related Adverse Events

Adverse event (%)	Fulvestrant + everolimus (n = 64)				Fulvestrant + placebo (n = 65)			
	Any gr	Gr 2	Gr 3	Gr 4	Any gr	Gr 2	Gr 3	Gr 4
Oral mucositis	53	25	11	0	12	3	0	0
Rash	38	14	2	0	5	0	0	0
Hyperglycemia	19	3	3	0	5	0	0	0
Pneumonitis	17	6	6	0	0	0	0	0
Elevated AST	5	2	3	0	2	0	0	2



Research

JAMA Oncology | **Original Investigation**

Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer The BOLERO-6 Randomized Clinical Trial

Guy Jerusalem, MD, PhD; Richard H. de Boer, MBBS, FRACP; Sara Hurvitz, MD; Denise A. Yardley, MD; Elena Kovalenko, MD;
Bent Ejlersen, MD; Sibel Blau, MD; Mustafa Özgüroğlu, MD; László Landherr, PhD; Marianne Ewertz, MD;
Tetiana Taran, MD; Jenna Fan, MD, PhD; Florence Noel-Baron, PhD; Anne-Laure Louveau, MS; Howard Burris, MD

JAMA Oncol 2018;[Epub ahead of print].

BOLERO-6: Survival Analyses


Clinical endpoint	Everolimus (n = 103)	Everolimus + exemestane (n = 104)	Capecitabine (n = 102)
Median PFS*	6.8 mo	8.4 mo	9.6 mo
HR	0.74		—
	—	1.26	
Median OS	29.3 mo	23.1 mo	25.6 mo
HR	1.27		—
	—	1.33	

* A numerical PFS difference with capecitabine vs everolimus + exemestane should be interpreted cautiously owing to imbalances among baseline characteristics and potential informative censoring.

BOLERO-6: Select Adverse Events

Adverse event, %	Everolimus (n = 103)		Everolimus + exemestane (n = 104)		Capecitabine (n = 102)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Stomatitis	46	5	49	9	25	7
Elevated γ -GGT	16	12	15	9	2	2
Elevated AST	14	8	15	7	9	1
Pneumonia	9	3	11	7	3	2
Hypertension	8	2	14	6	5	3
PPE syndrome	3	0	3	1	61	27

γ -GGT = gamma-glutamyl transferase; PPE = palmar-plantar erythrodysesthesia



Research

JAMA Oncology | **Original Investigation**

Everolimus Plus Endocrine Therapy for Postmenopausal Women With Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer A Clinical Trial

Melanie Royce, MD, PhD; Thomas Bachelot, MD; Cristian Villanueva, MD; Mustafa Özgüroğlu, MD; Sergio J. Azevedo, MD; Felipe Melo Cruz, MD; Marc Debled, MD; Roberto Hegg, MD; Tatsuya Toyama, MD; Carla Falkson, MD; Joon Jeong, MD; Vichien Srimuninnimit, MD; William J. Gradishar, MD; Christina Arce, BSc; Antonia Ridolfi, MSc; Chinjune Lin, MD; Fatima Cardoso, MD

JAMA Oncol 2018;4(7):977-84

BOLERO-4: Phase II Efficacy Summary for First- and Second-Line Everolimus plus Endocrine Therapy

Clinical endpoint	First-line everolimus + letrozole (n = 202)	Second-line everolimus + exemestane (n = 50)
Median PFS	22.0 mo	3.7 mo
Median OS	Not reached	Not reported
30-month OS	73.4%	Not reported
Overall response rate	45%	6.0%
Clinical benefit rate	74.3%	28.0%

BOLERO-4: Select Adverse Events

Adverse event, %	First-line everolimus + letrozole (n = 202)			Second-line everolimus + exemestane (n = 50)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Stomatitis	69	6	0	20	0	0
Hyperglycemia	29	3	1	NR	NR	NR
Rash	27	<1	0	NR	NR	NR
Hypertension	23	8	0	12	10	0
Elevated AST	19	1	<1	10	2	2
Pneumonitis	18	<1	0	NR	NR	NR

NR = not reported

Results from a Randomized Placebo-Controlled Phase 2 Trial Evaluating Exemestane ± Enzalutamide in Patients with Hormone Receptor-Positive Breast Cancer

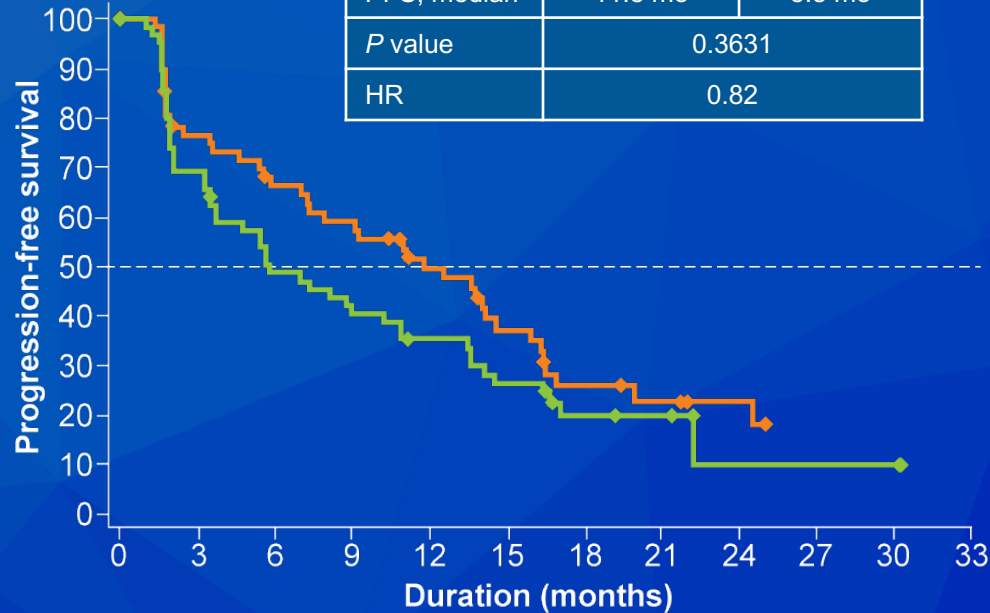
Krop I et al.

San Antonio Breast Cancer Symposium
2017;Abstract GS4-07.

Phase II Study of Enzalutamide (ENZA) + Exemestane (EXE) in Postmenopausal Women: PFS in ITT Population

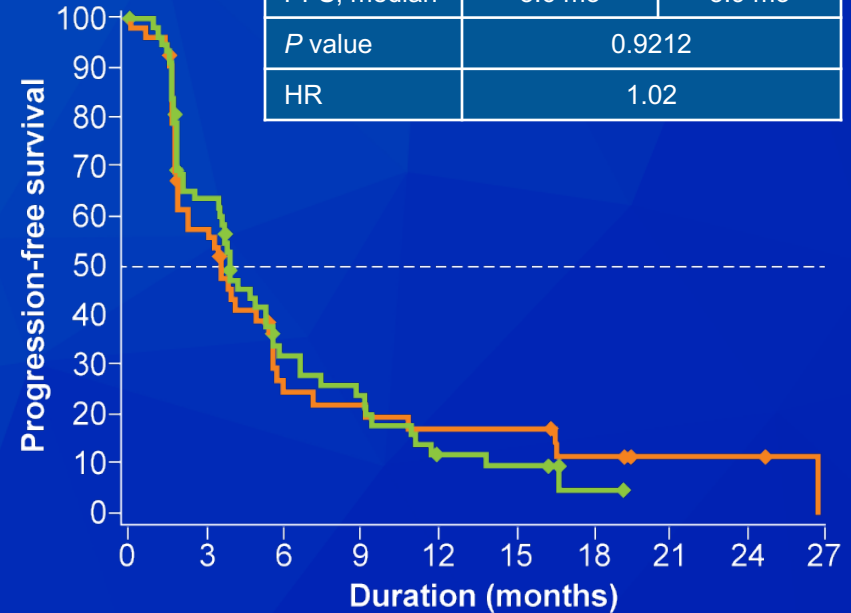
Cohort 1: No prior ET for advanced BC

	ENZA + EXE (N = 63)	PBO + EXE (N = 64)
PFS, median	11.8 mo	5.8 mo
<i>P</i> value	0.3631	
HR	0.82	



Cohort 2: One prior ET for advanced BC

	ENZA + EXE (N = 60)	PBO + EXE (N = 60)
PFS, median	3.6 mo	3.9 mo
<i>P</i> value	0.9212	
HR	1.02	



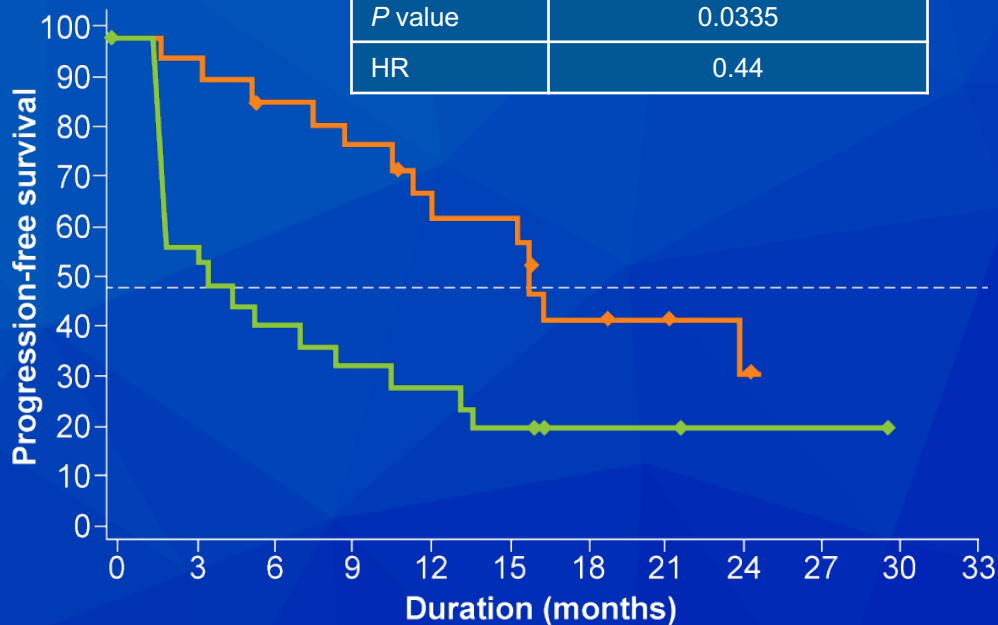
ET = endocrine therapy

Phase II Study of ENZA + EXE: PFS in Biomarker-Positive (Bkmr+) Subgroup of ITT Population

- Using tumor samples from patients with HR-positive breast cancer enrolled in the study, a gene signature-based biomarker indicating androgen receptor signaling predictive of response to ENZA was developed

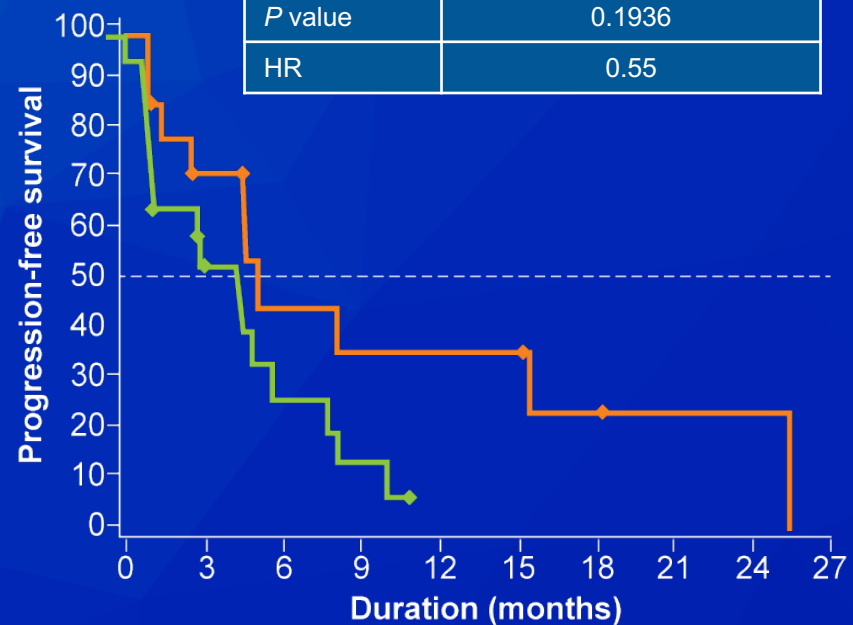
Cohort 1: No prior ET for advanced BC

	ENZA + EXE (N = 24)	PBO + EXE (N = 26)
PFS, median	16.5 mo	4.3 mo
P value	0.0335	
HR	0.44	



Cohort 2: One prior ET for advanced BC

	ENZA + EXE (N = 15)	PBO + EXE (N = 20)
PFS, median	6.0 mo	5.3 mo
P value	0.1936	
HR	0.55	



Phase II Study of ENZA + EXE: Treatment-Emergent Adverse Events (TEAEs) Summary

	Cohort 1: No prior ET for advanced BC		Cohort 2: One prior ET for advanced BC	
	ENZA + EXE (n = 62)	PBO + EXE (n = 63)	ENZA + EXE (n = 60)	PBO + EXE (n = 60)
Patients with ≥ 1 TEAE, no. (%)	59 (95.2)	58 (92.1)	58 (96.7)	53 (88.3)
TEAE Grade ≥ 3	20 (32.3)	15 (23.8)	22 (36.7)	12 (20.0)
TEAE leading to interruption	13 (21.0)	13 (20.6)	15 (25.0)	9 (15.0)
TEAE leading to discontinuation*	9 (14.5)	10 (15.9)	11 (18.3)	5 (8.3)
TEAE leading to death*	2 (3.2)	2 (3.2)	2 (3.3)	0 (0)
Serious TEAE	15 (24.2)	12 (19.0)	10 (16.7)	8 (13.3)

* The majority of TEAEs leading to death or discontinuation were due to disease progression

- Cohort 1 most common Grade ≥ 3 AEs with ENZA included: musculoskeletal chest pain, anxiety, dizziness, vomiting, diarrhea, nausea and fatigue
- Cohort 2 most common Grade ≥ 3 AEs with ENZA included: anemia, headache, fatigue, hot flush, vomiting, diarrhea and back pain

Adjuvant Therapy for BC

The NEW ENGLAND
JOURNAL *of* MEDICINE

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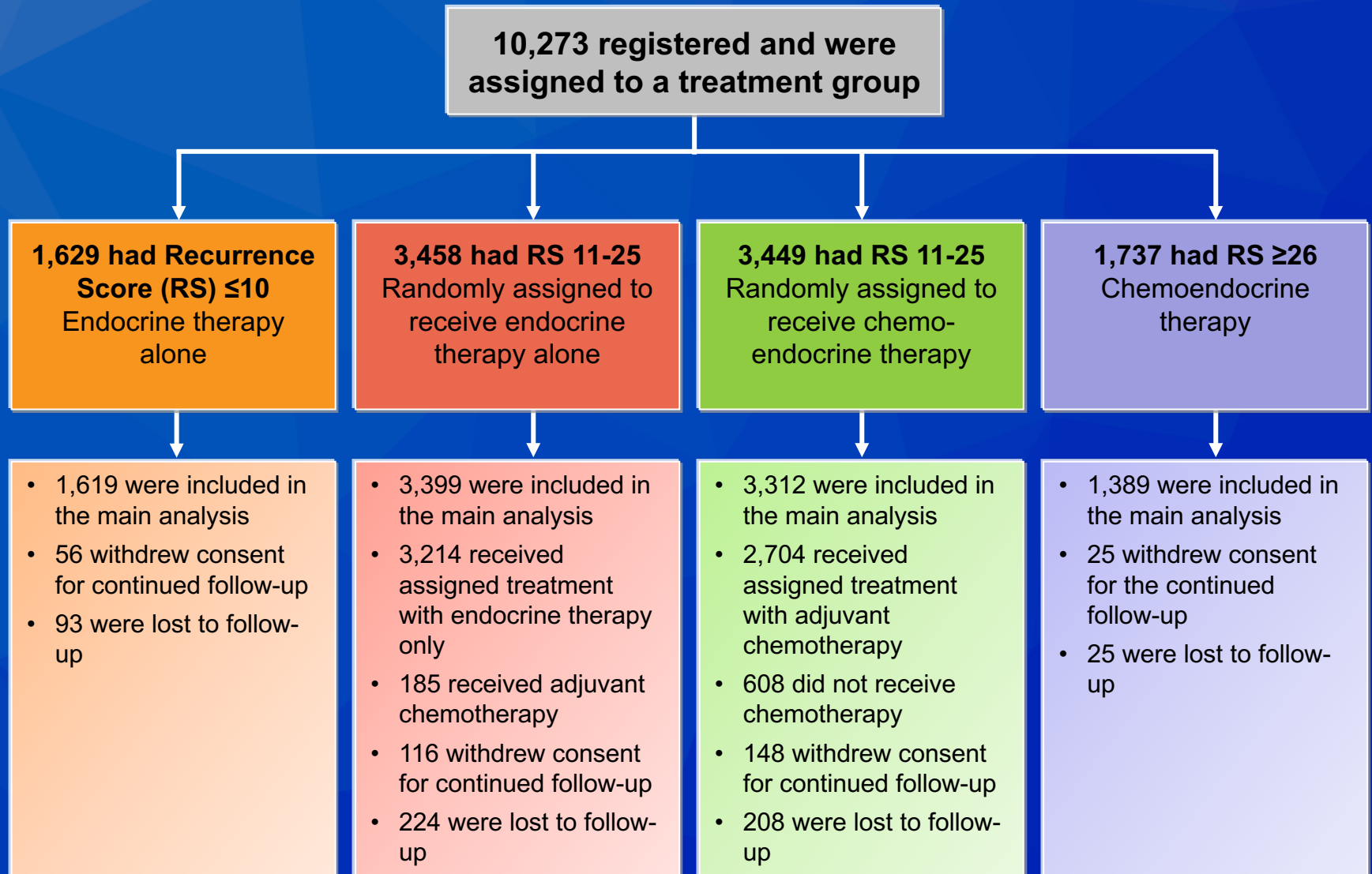
JULY 12, 2018

VOL. 379 NO. 2

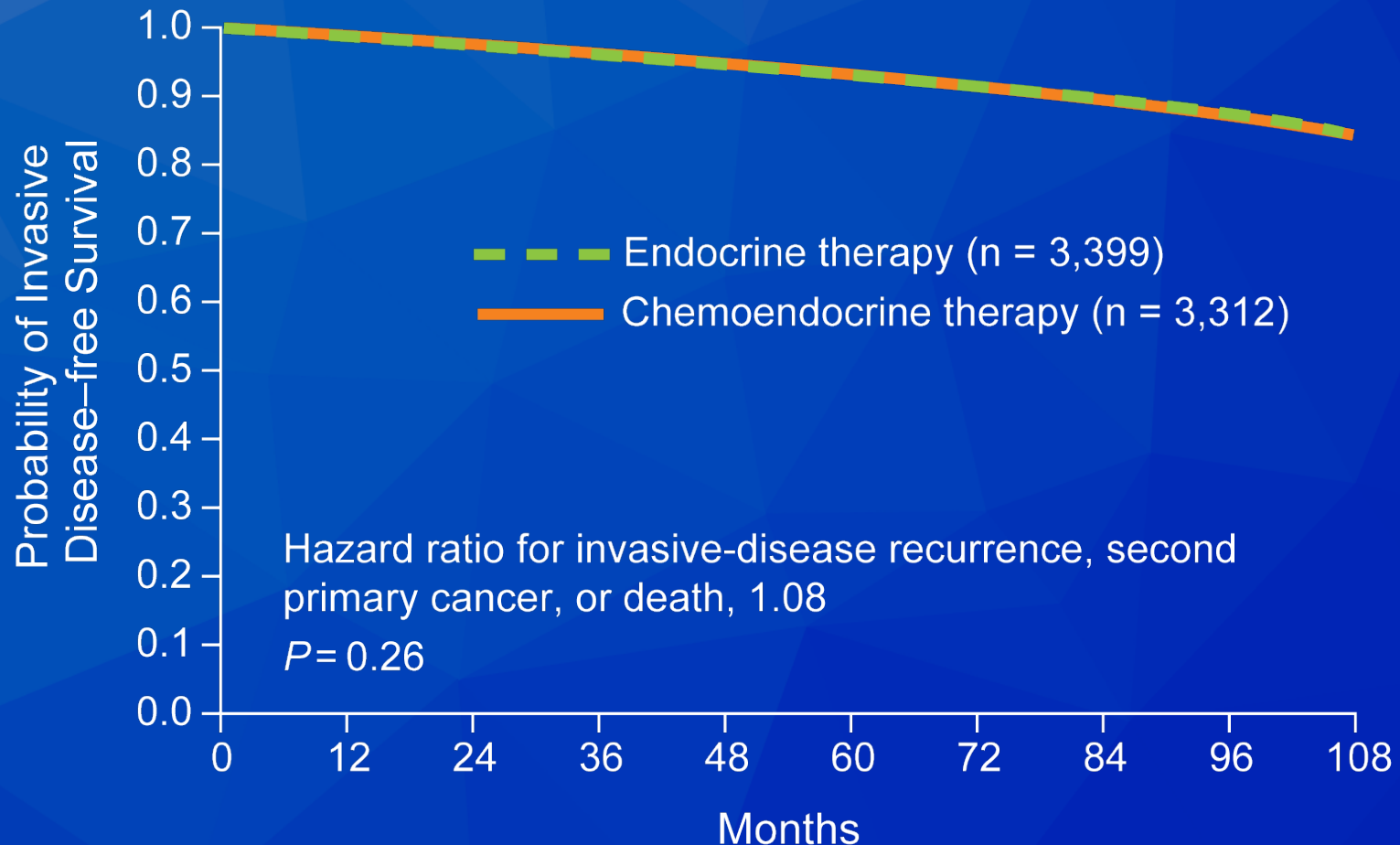
Adjuvant Chemotherapy Guided by a 21-Gene Expression
Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

TAILORx: Patient Disposition



TAILORx: Invasive Disease-Free Survival (IDFS) in RS 11-25 Cohort



- Primary endpoint of noninferiority of endocrine therapy alone to chemoendocrine therapy for IDFS was met

TAILORx: Estimated IDFS Rates According to RS and Assigned Treatment in ITT Population

	Rate at 5 years (%)	Rate at 9 years (%)
Score of ≤ 10 , endocrine therapy	94.0 \pm 0.6	84.0 \pm 1.3
Score of 11-25, endocrine therapy	92.8 \pm 0.5	83.3 \pm 0.9
Score of 11-25, chemoendocrine therapy	93.1 \pm 0.5	84.3 \pm 0.8
Score of ≥ 26 , chemoendocrine therapy	87.6 \pm 1.0	75.7 \pm 2.2

TAILORx: Estimated IDFS Rates According to RS and Assigned Treatment in Women Aged 50 Years or Younger

	Rate at 5 years (%)	Rate at 9 years (%)
Score of ≤ 10 , endocrine therapy	95.1 \pm 1.1	87.4 \pm 2.0
Score of 11-15, endocrine therapy	95.1 \pm 1.1	85.7 \pm 2.2
Score of 11-15, chemoendocrine therapy	94.3 \pm 1.3	89.2 \pm 1.9
Score of 16-20, endocrine therapy	92.0 \pm 1.3	80.6 \pm 2.5
Score of 16-20, chemoendocrine therapy	94.7 \pm 1.1	89.6 \pm 1.7
Score of 21-25, endocrine therapy	86.3 \pm 2.3	79.2 \pm 3.3
Score of 21-25, chemoendocrine therapy	92.1 \pm 1.8	85.5 \pm 3.0
Score of ≥ 26 , chemoendocrine therapy	86.4 \pm 1.9	80.3 \pm 2.9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D., Christina Davies, B.M., B.Ch., Carolyn Taylor, B.M., B.Ch., Ph.D., Paul McGale, Ph.D., Richard Peto, F.R.S., Kathleen I. Pritchard, M.D., Jonas Bergh, M.D., Ph.D., Mitch Dowsett, Ph.D., and Daniel F. Hayes, M.D., for the EBCTCG*

N Engl J Med 2017;377(19):1836-46.

Methods Summary

- Meta-analysis of 88 trials involving 62,923 women with ER-positive breast cancer:
 - At diagnosis, were aged <75 years, had T1 or T2 disease, fewer than 10 involved nodes and no distant metastases
 - Were disease free after 5 years of scheduled endocrine therapy
- The association of tumor characteristics such as diameter, nodal status and tumor grade with patient outcomes was assessed during the period from 5 to 20 years.

Association of Nodal Status and Tumor Size with Risk of Distant Recurrence

	Total (n)	Annual rate of distant recurrence		Cumulative risk from 5 to 20 years
		5 to <10 years	10 to 20 years	
Nodal involvement				
N0	28,847	1.0%	1.1%	15%
N1-3	25,292	1.9%	1.7%	23%
N4-9	8,784	3.9%	2.8%	38%
Tumor diameter in N0 only				
T1a or T1b: ≤1.0 cm	5,527	0.5%	0.8%	10%
T1c: 1.1-2.0 cm	13,875	0.8%	1.1%	14%
T2: 2.1-3.0 cm	6,700	1.5%	1.4%	19%
T2: 3.1-5.0 cm	2,745	1.7%	1.4%	20%

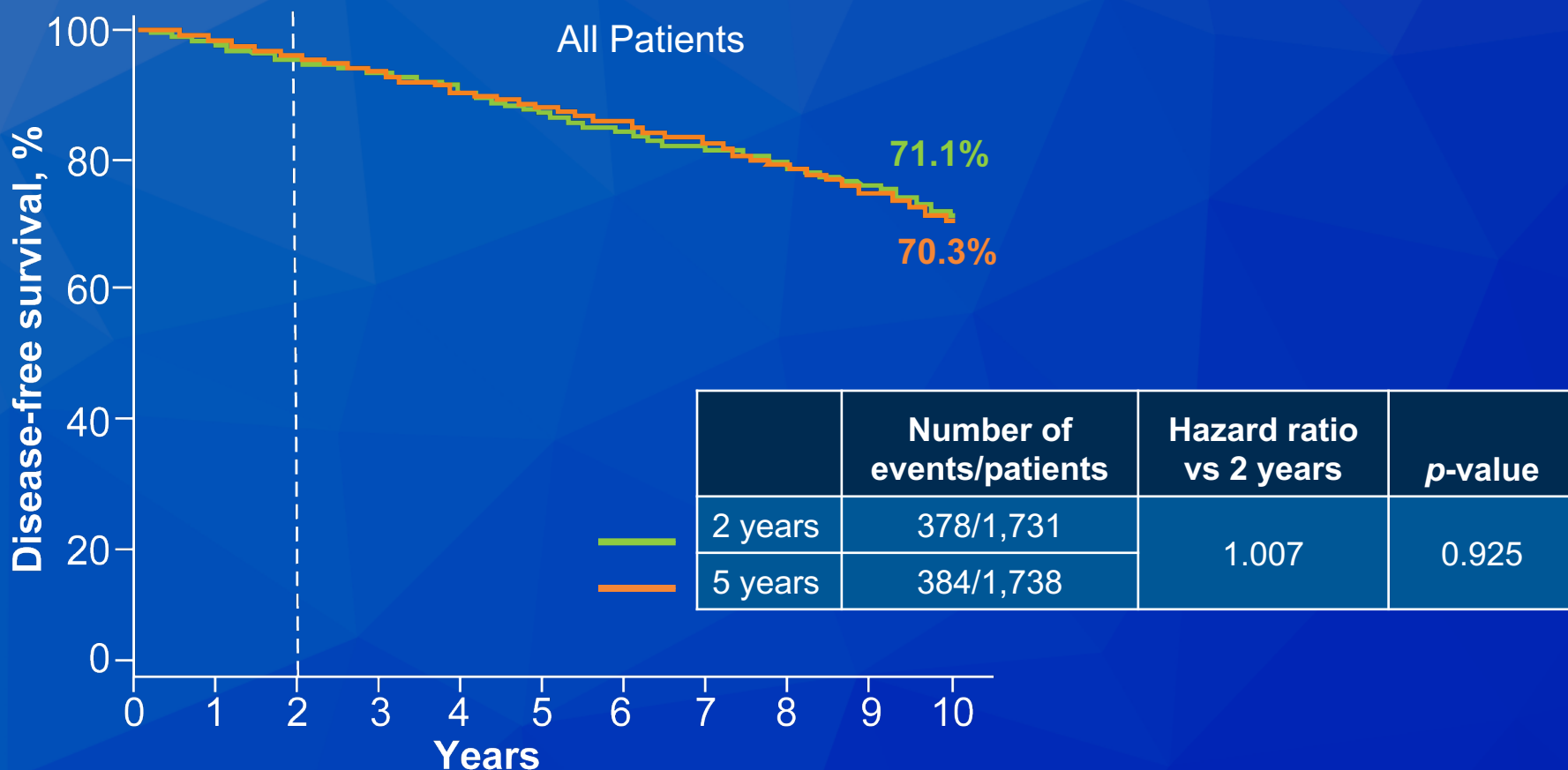
- There was a strong association of tumor grade and Ki-67 status with the risk of distant recurrence during years 0 to 5 but only a moderate association during years 5 to 20.

A Prospective Randomized Multi-Center Phase III Trial of Additional 2 versus Additional 5 Years of Anastrozole After Initial 5 Years of Adjuvant Endocrine Therapy – Results from 3,484 Postmenopausal Women in the ABCSG-16 Trial

Gnant M et al.

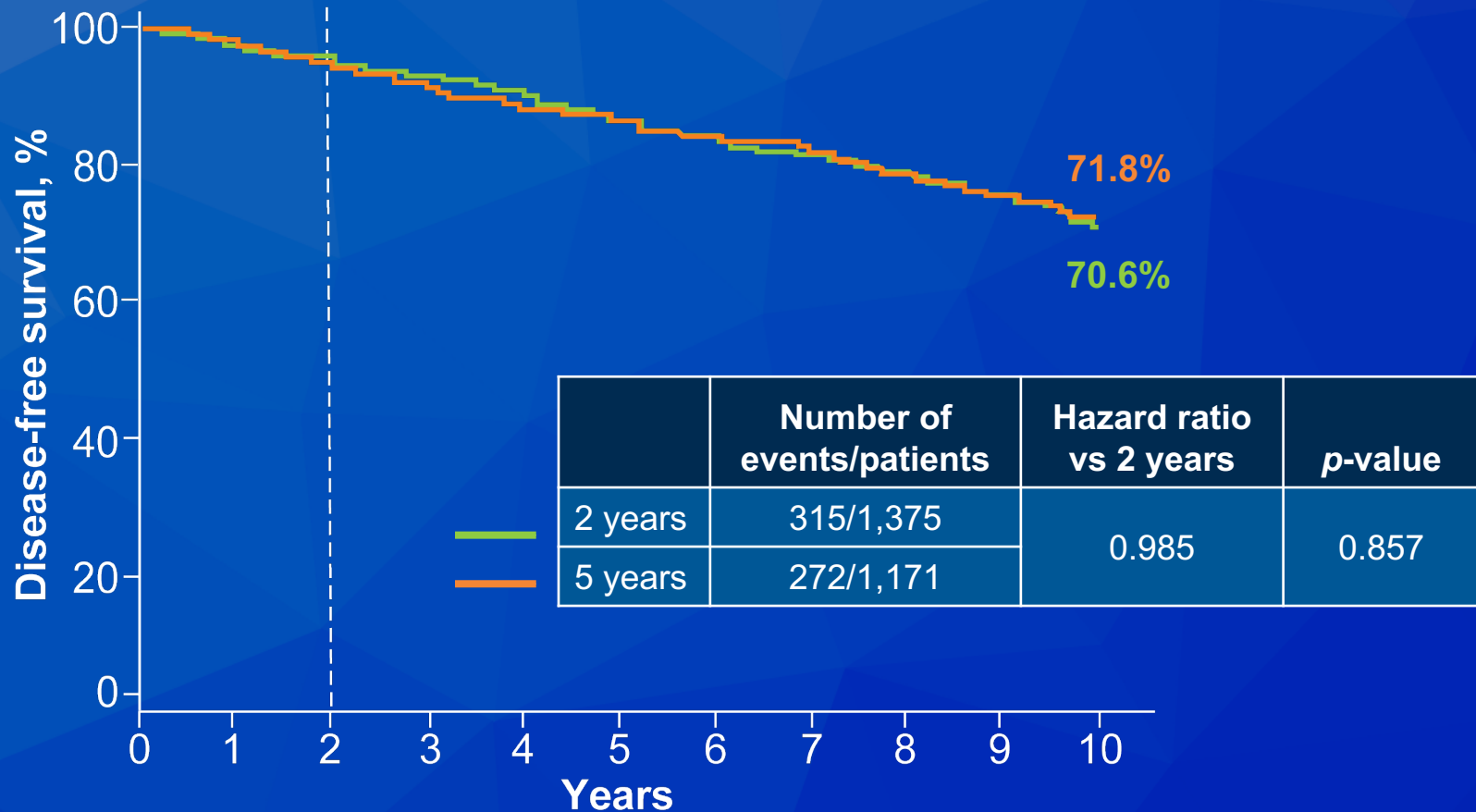
San Antonio Breast Cancer Symposium
2017;Abstract GS3-01.

ABCESG-16: Disease-Free Survival (DFS)



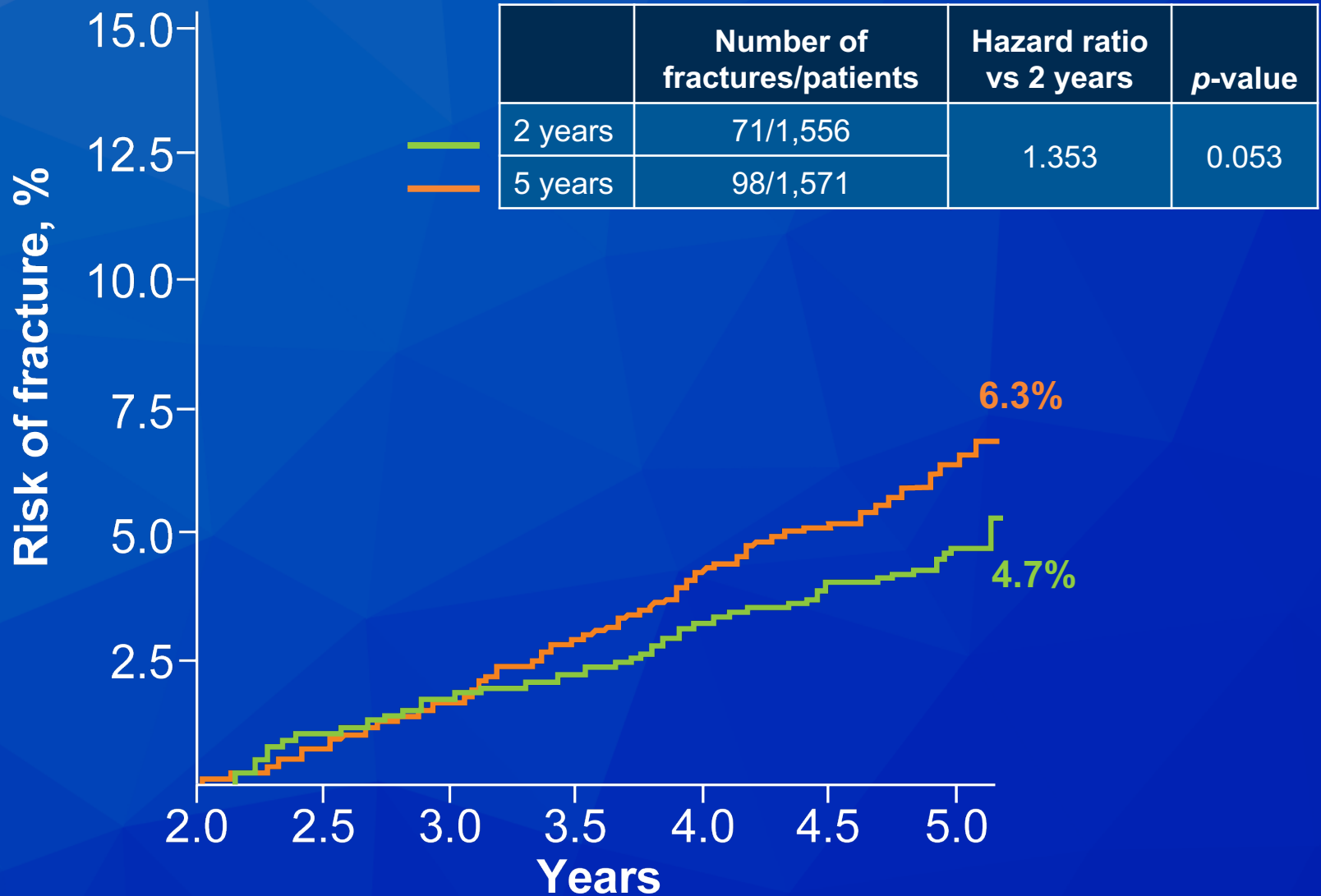
- No difference was observed between an additional 2 versus additional 5 years of anastrozole for:
 - Overall survival
 - Time to second primary cancer
 - Time to contralateral breast cancer

ABCSG-16: DFS in Adherent Patients Only



- No difference was observed between an additional 2 versus additional 5 years of anastrozole for:
 - Time to contralateral breast cancer
 - Time to second primary cancer

ABCSG-16: Fractures



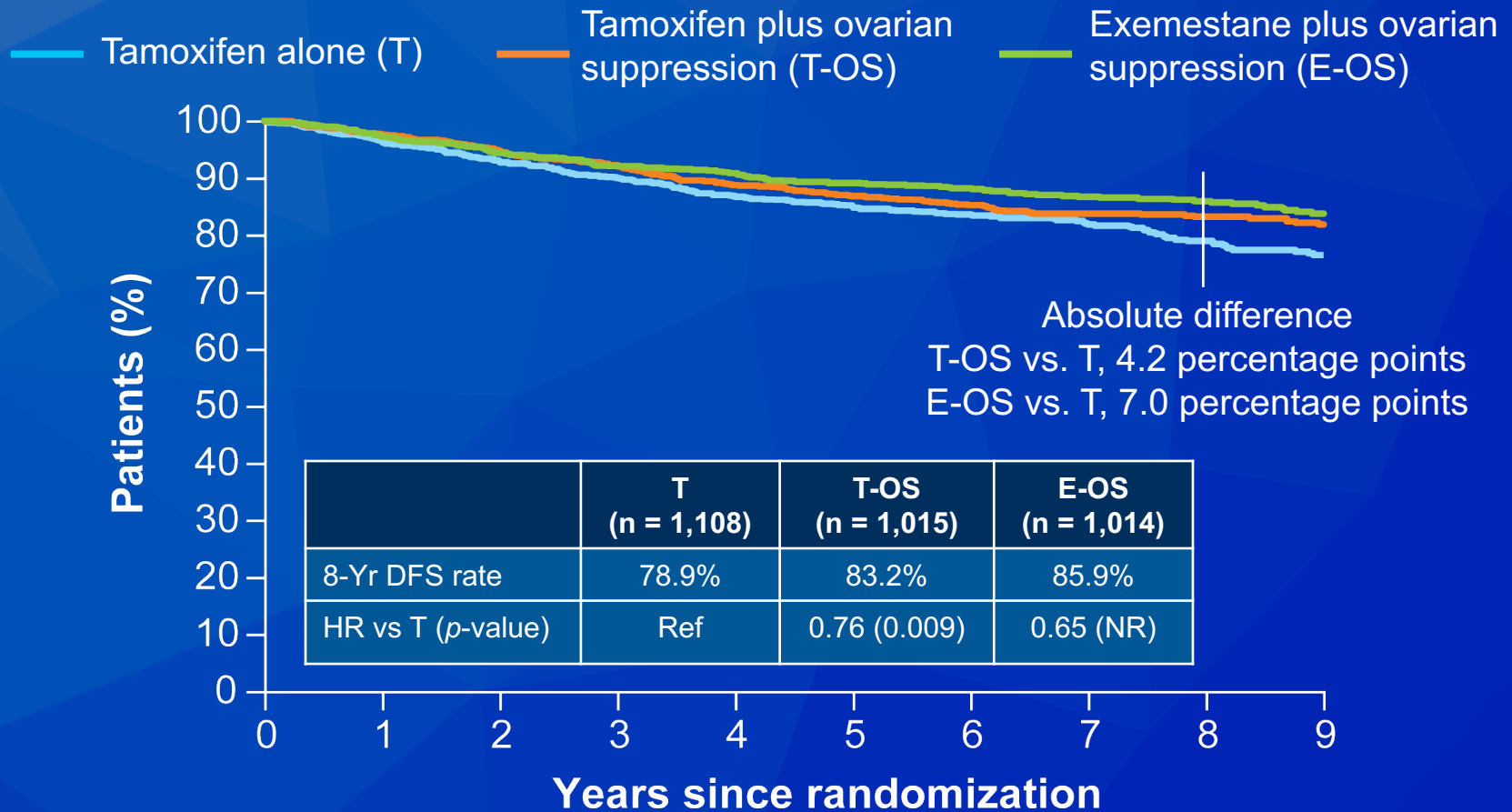
ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H.L. Gómez, C. Tondini, E. Ciruelos, H.J. Burstein, H.R. Bonnefoi, M. Bellet, S. Martino, C.E. Geyer, Jr., M.P. Goetz, V. Stearns, G. Pinotti, F. Puglisi, S. Spazzapan, M.A. Climent, L. Pavesi, T. Ruhstaller, N.E. Davidson, R. Coleman, M. Debled, S. Buchholz, J.N. Ingle, E.P. Winer, R. Maibach, M. Rabaglio-Poretti, B. Ruepp, A. Di Leo, A.S. Coates, R.D. Gelber, A. Goldhirsch, and M.M. Regan, for the SOFT and TEXT Investigators and the International Breast Cancer Study Group*

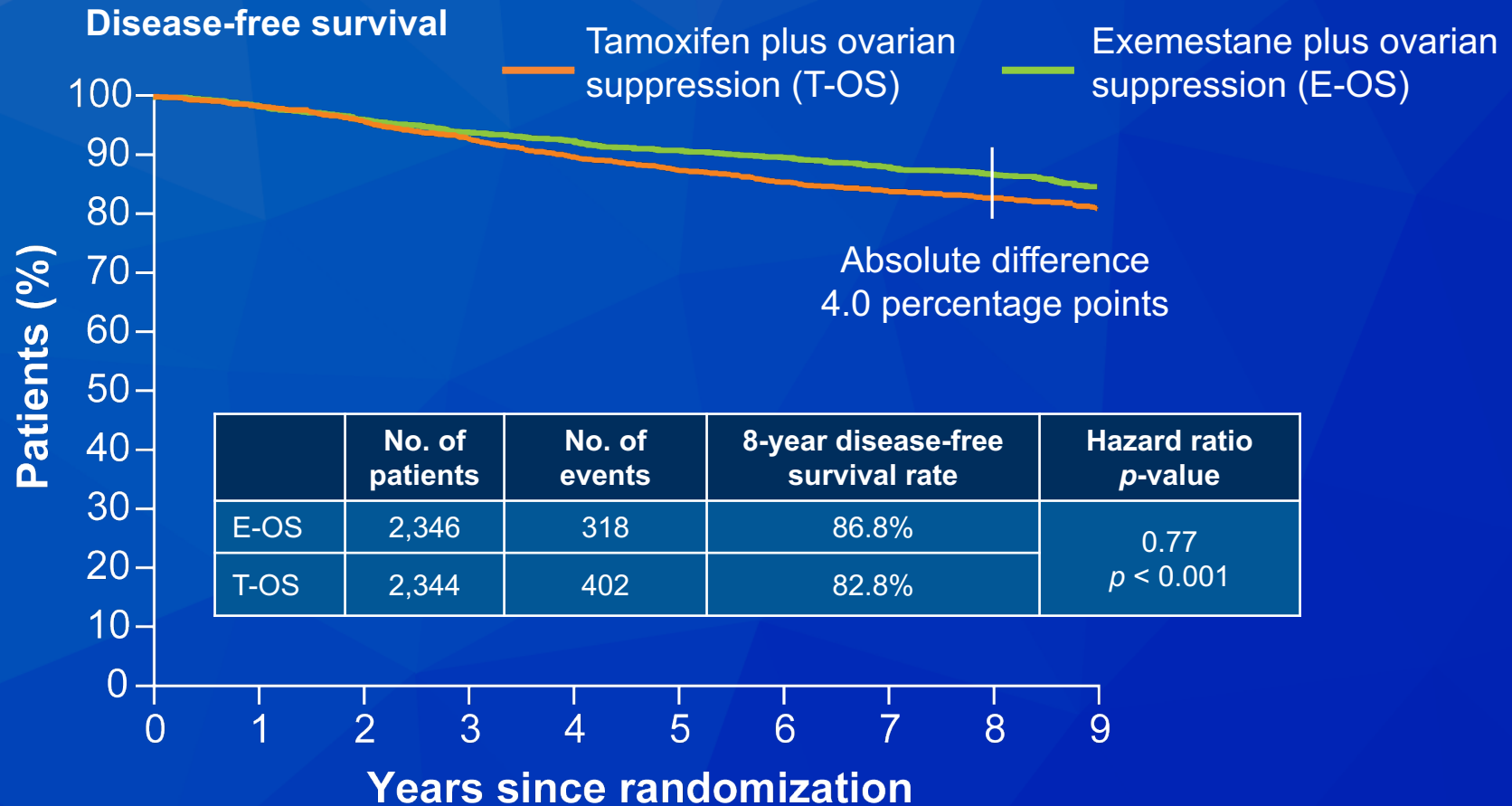
N Engl J Med 2018;379(2):122-37.

SOFT: DFS in All Patients (Median Follow-Up of 8 Years)



- 8-year overall survival rates were significantly higher with the addition of ovarian suppression to tamoxifen compared to tamoxifen alone (93.3% vs 91.5%, $p = 0.01$)

SOFT and TEXT (Combined): DFS in All Patients (Median Follow-Up of 9 Years)



- There was no statistically significant difference in 8-year overall survival observed with tamoxifen plus ovarian suppression compared to exemestane plus ovarian suppression (93.3% vs 93.4%, *p* = 0.84)

DFS for Patients with HER2-Negative Breast Cancer

SOFT trial	8-Yr DFS	HR
Tamoxifen-OS (n = 868)	82.8%	0.83
Tamoxifen alone (n = 860)	79.9%	
Exemestane-OS (n = 858)	88.0%	0.60
SOFT and TEXT (combined)		
Tamoxifen-OS (n = 2,024)	82.7%	0.70
Exemestane-OS (n = 2,011)	88.1%	

SPECIAL ARTICLE

De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

G. Curigliano^{1*†}, H. J. Burstein^{2†}, E. P. Winer², M. Gnant³, P. Dubsy^{3,4}, S. Loibl⁵, M. Colleoni¹, M. M. Regan⁶, M. Piccart-Gebhart⁷, H.-J. Senn⁸ & B. Thürlimann⁹, on behalf of the Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017

¹Breast Cancer Program, Istituto Europeo di Oncologia, Milano, Italy; ²Breast Oncology Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; ³Department of Surgery, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria; ⁴Klinik St. Anna, Luzern, Switzerland; ⁵German Breast Group, Neu-Isenburg, Germany; ⁶Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; ⁷Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; ⁸Tumor and Breast Center ZeTuP, St. Gallen; ⁹Breast Center, Kantonsspital St. Gallen, St. Gallen, Switzerland

Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017

F. André¹⁰, J. Baselga¹¹, J. Bergh¹², H. Bonnefoi¹³, S. Y. Brucker¹⁴, F. Cardoso¹⁵, L. Carey¹⁶, E. Ciruelos¹⁷, J. Cuzick¹⁸, C. Denkert¹⁹, A. Di Leo²⁰, B. Ejlertsen²¹, P. Francis²², V. Galimberti¹, J. Garber², B. Gulluoglu²³, P. Goodwin²⁴, N. Harbeck²⁵, D. F. Hayes²⁶, C.-S. Huang²⁷, J. Huober²⁸, K. Hussein²⁹, J. Jassem³⁰, Z. Jiang³¹, P. Karlsson³², M. Morrow¹¹, R. Orecchia¹, K. C. Osborne³³, O. Pagani³⁴, A. H. Partridge², K. Pritchard³⁵, J. Ro³⁶, E. J. T. Rutgers³⁷, F. Sedlmayer³⁸, V. Semiglazov³⁹, Z. Shao⁴⁰, I. Smith⁴¹, M. Toi⁴², A. Tutt⁴³, G. Viale^{44,45}, T. Watanabe⁴⁶, T. J. Whelan⁴⁷ & B. Xu⁴⁸

St Gallen's Panel Favored Several Interventions in Multiple Fields of Treatment

- Surgery:
 - Acceptance of 2-mm margins for DCIS, the resection of residual cancer (but not baseline extent of cancer) in women undergoing neoadjuvant therapy
 - Acceptance of sentinel node biopsy after neoadjuvant treatment of many patients
 - The preference for neoadjuvant therapy in HER2-positive and triple-negative, Stage II and III breast cancer
- Radiation therapy:
 - Favored escalating radiation therapy with regional nodal irradiation in high-risk patients, while encouraging omission of boost in low-risk patients.

St Gallen's Panel Favored Several Interventions in Multiple Fields of Treatment

- Genetics:
 - Endorsed gene expression signatures that permit avoidance of chemotherapy in many patients with ER-positive breast cancer.
- Adjuvant therapy:
 - For women with higher-risk tumors, the Panel escalated recommendations for adjuvant endocrine treatment to include ovarian suppression in premenopausal women and extended therapy for postmenopausal women.
 - However, low-risk patients can avoid these treatments.
- Bone-modifying therapy:
 - Recommended bisphosphonate use in postmenopausal women to prevent breast cancer recurrence.

Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Neelima Denduluri, Mariana Chavez-MacGregor, Melinda L. Telli, Andrea Eisen, Stephanie L. Graff, Michael J. Hassett, Jamie N. Holloway, Arti Hurria, Tari A. King, Gary H. Lyman, Ann H. Partridge, Mark R. Somerfield, Maureen E. Trudeau, Antonio C. Wolff, and Sharon H. Giordano

J Clin Oncol 2018;36(23):2433-43.

Recommendations from ASCO 2018 Focused Guideline Update

1. Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease at surgery after standard anthracycline- and taxane-based preoperative therapy may be offered up to 6 to 8 cycles of adjuvant capecitabine
2. Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy for patients with high-risk, early-stage, HER2-positive breast cancer
3. Clinicians may use extended adjuvant therapy with neratinib to follow trastuzumab for patients with early-stage, HER2-positive breast cancer. Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used

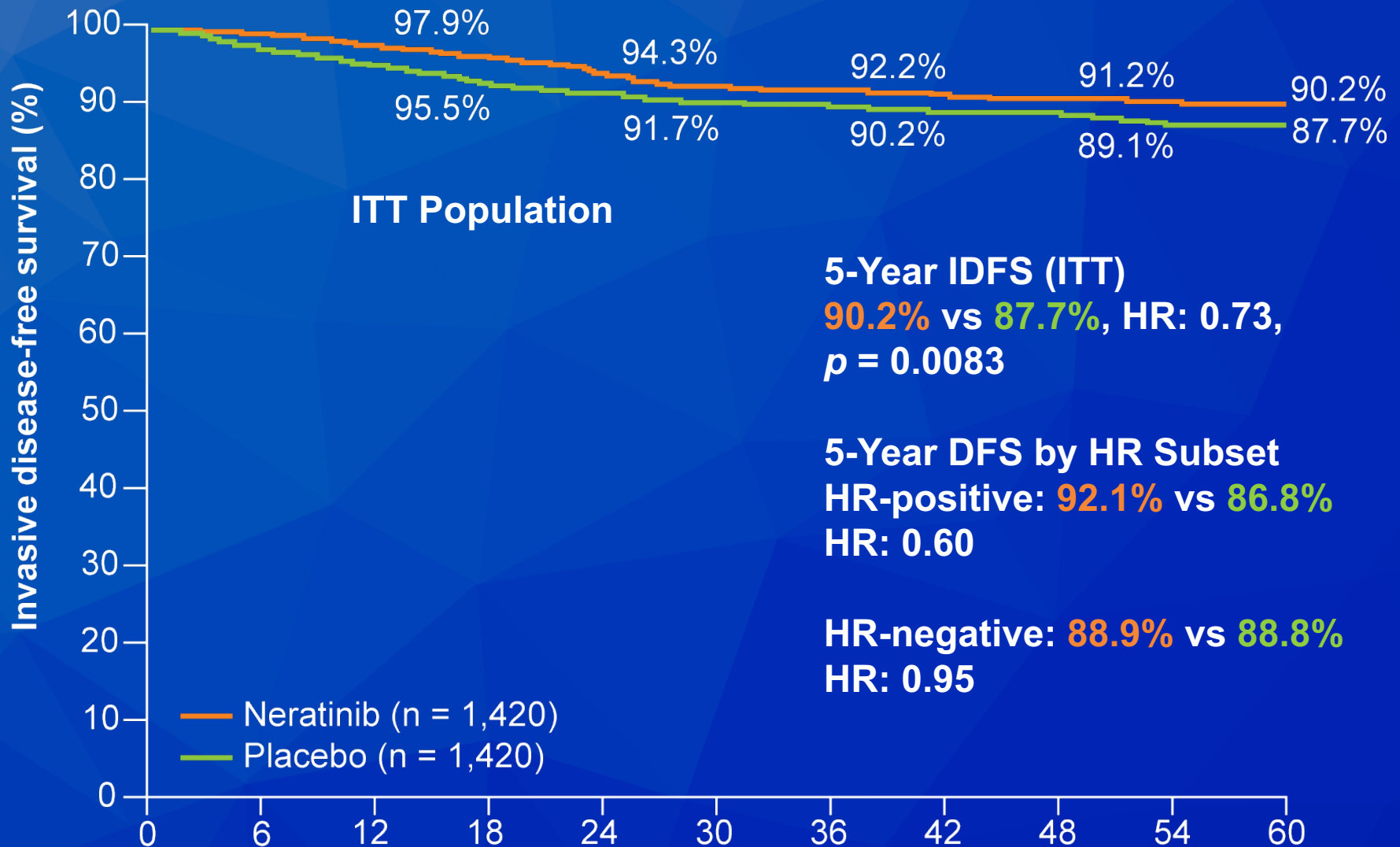


Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

*Miguel Martin, Frankie A Holmes, Bent Ejlersen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group**

Lancet Oncol 2017;18(12):1688-700.

ExteNET: Invasive Disease-Free Survival (IDFS)



PARP Inhibitors for Advanced Disease

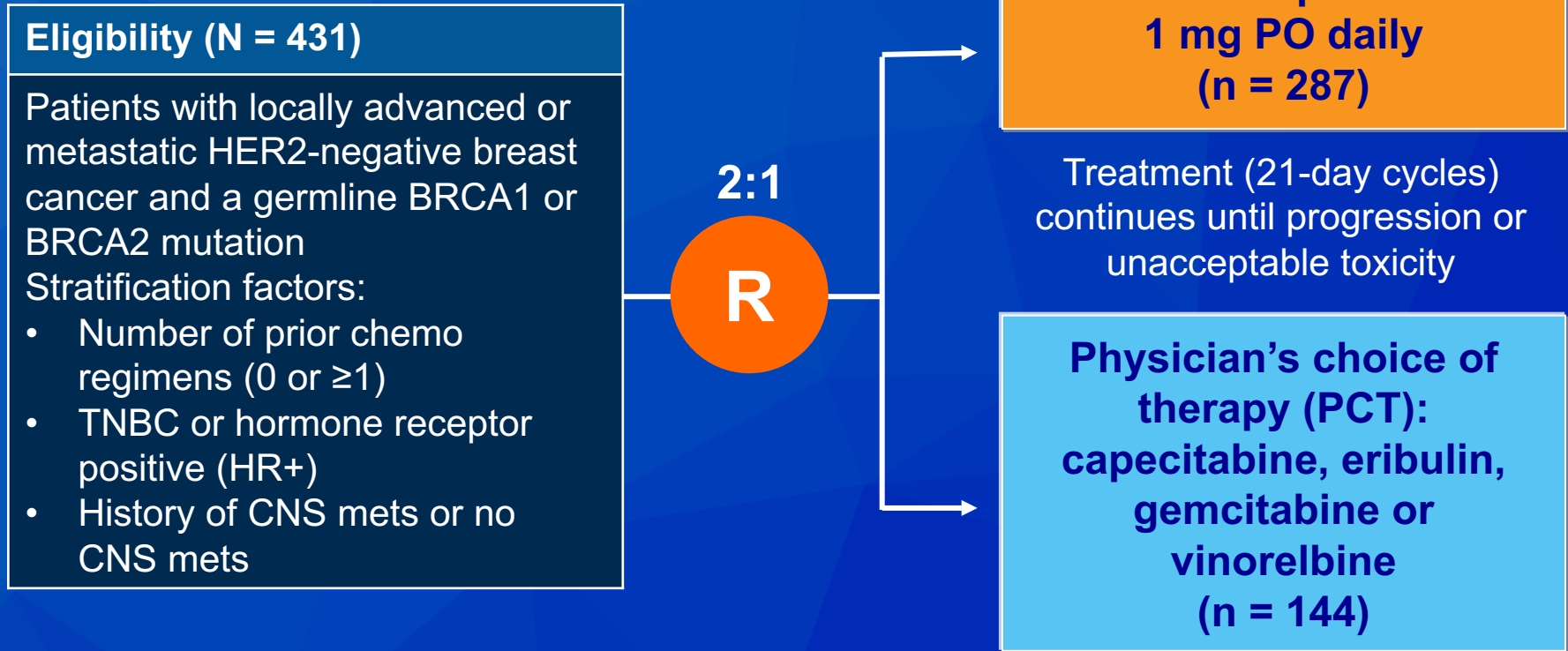
ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

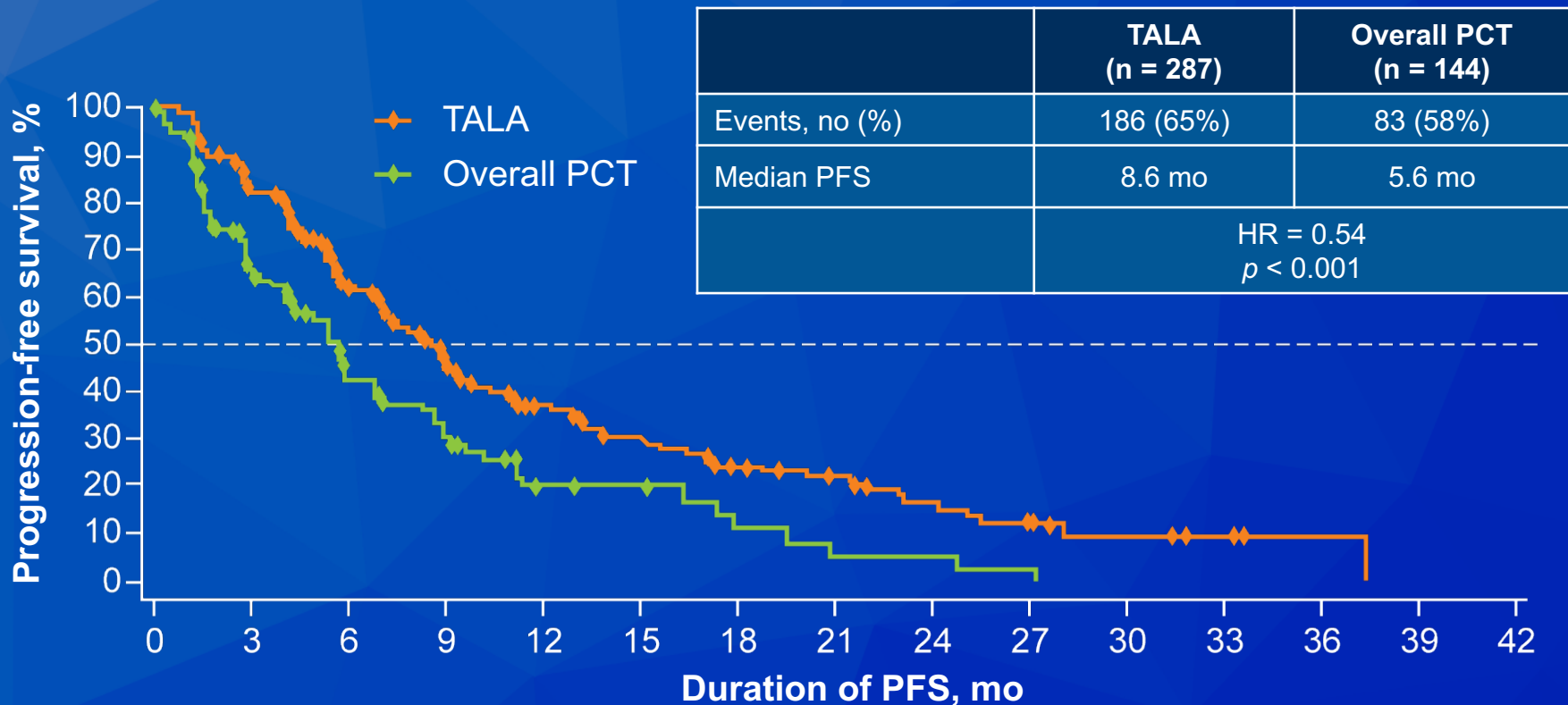
Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.

N Engl J Med 2018;379(8):753-63.

EMBRACA: Phase III Trial Design



EMBRACA: Primary Endpoint PFS by Blinded Central Review



- In all clinically relevant subgroups, the risk of disease progression was lower with talazoparib than standard therapy.
 - Prior exposure to platinum agents was the only factor resulting in a 95% confidence interval with an upper bound exceeding 1.0

Litton JK et al. *N Engl J Med* 2018;379(8):753-63; Litton J et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

EMBRACA: Grade 3/4 Adverse Events

Adverse event, %	Talazoparib (n = 286)		Overall PCT (n = 126)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	38.5	0.7	4.0	0.8
Neutropenia	17.8	3.1	19.8	15.1
Vomiting	2.4	0	1.6	0
Diarrhea	0.7	0	5.6	0
Nausea	0.3	0	1.6	0
Palmar-plantar erythrodysesthesia syndrome	0.3	0	2.4	0

Litton JK et al. *N Engl J Med* 2018;379(8):753-63; Litton J et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

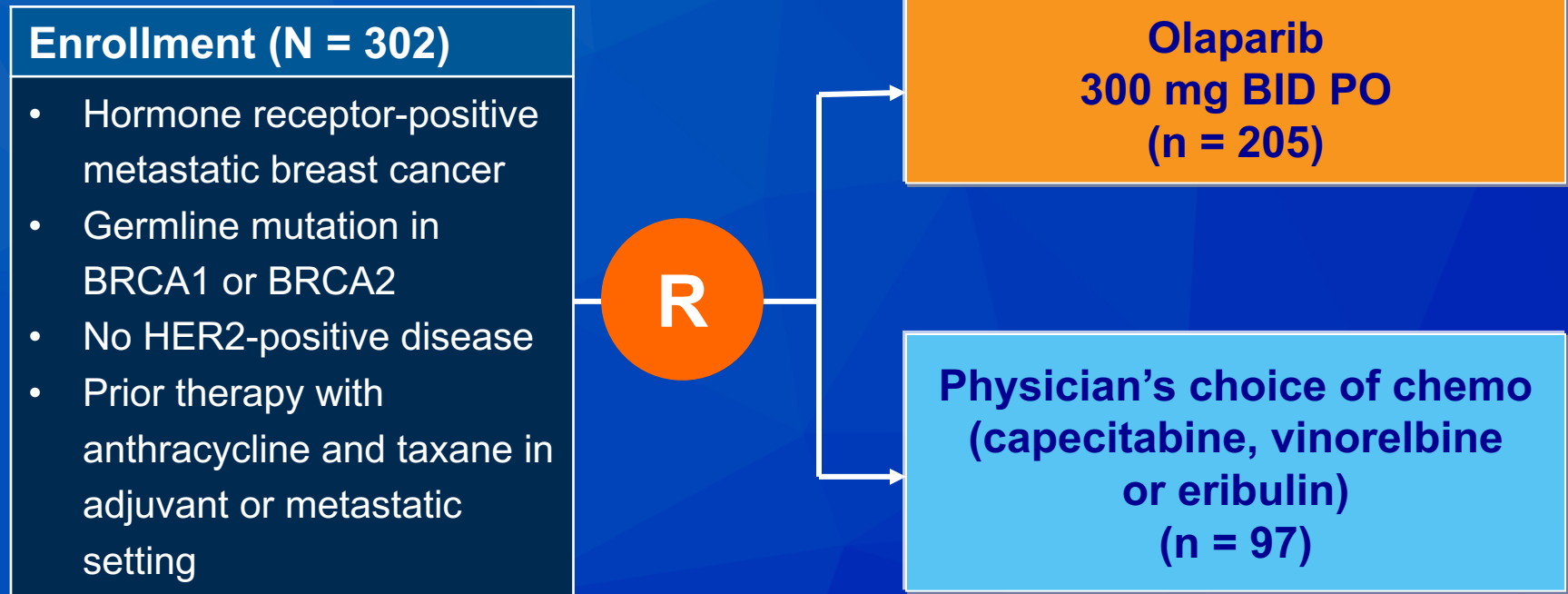
ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D.,
Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D.,
Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D.,
Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D.,
Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

N Engl J Med 2017;377(6):523-33.

OlympiAD: Phase III Trial Design



Primary endpoint: Progression-free survival

OlympiAD: Survival and Response Rates

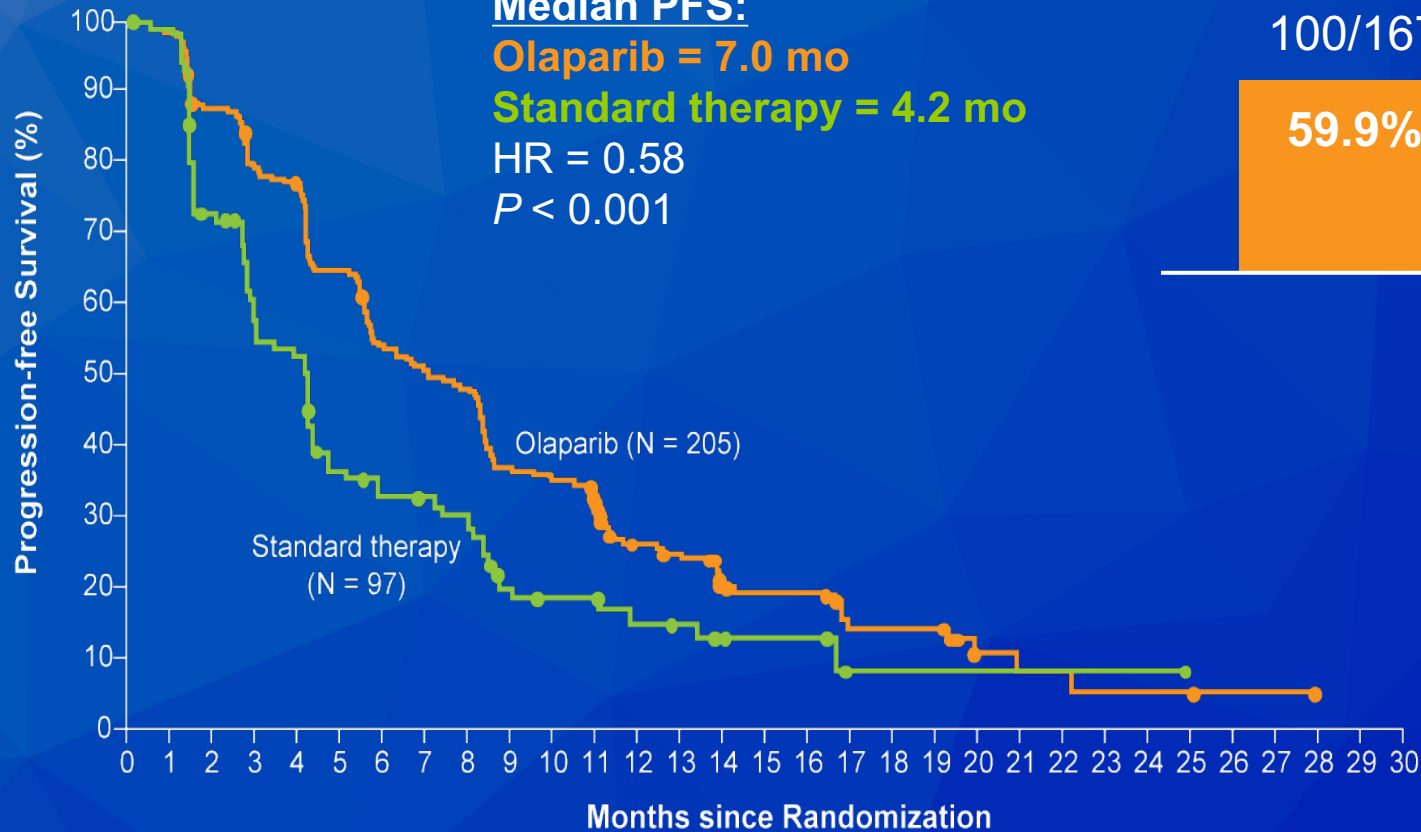
Median PFS:

Olaparib = 7.0 mo

Standard therapy = 4.2 mo

HR = 0.58

$P < 0.001$



- Overall survival did not differ significantly between groups ($p = 0.57$)

OlympiAD: Select Adverse Events (AEs)

	Olaparib (n = 205)		Standard therapy (n = 91)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia*	40%	16%	26%	4%
Neutropenia†	27%	9%	50%	26%
Nausea	58%	0%	35%	1%
Vomiting	30%	0%	15%	1%
Dose reduction due to AE	25%	NA	31%	NA
Treatment interruption or delay due to AE	35%	NA	28%	NA
Treatment discontinuation due to AE	5%	NA	8%	NA

* Anemia, decreased hemoglobin level, decreased hematocrit, decreased red-cell count and erythropenia; † Febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count and neutropenic infection

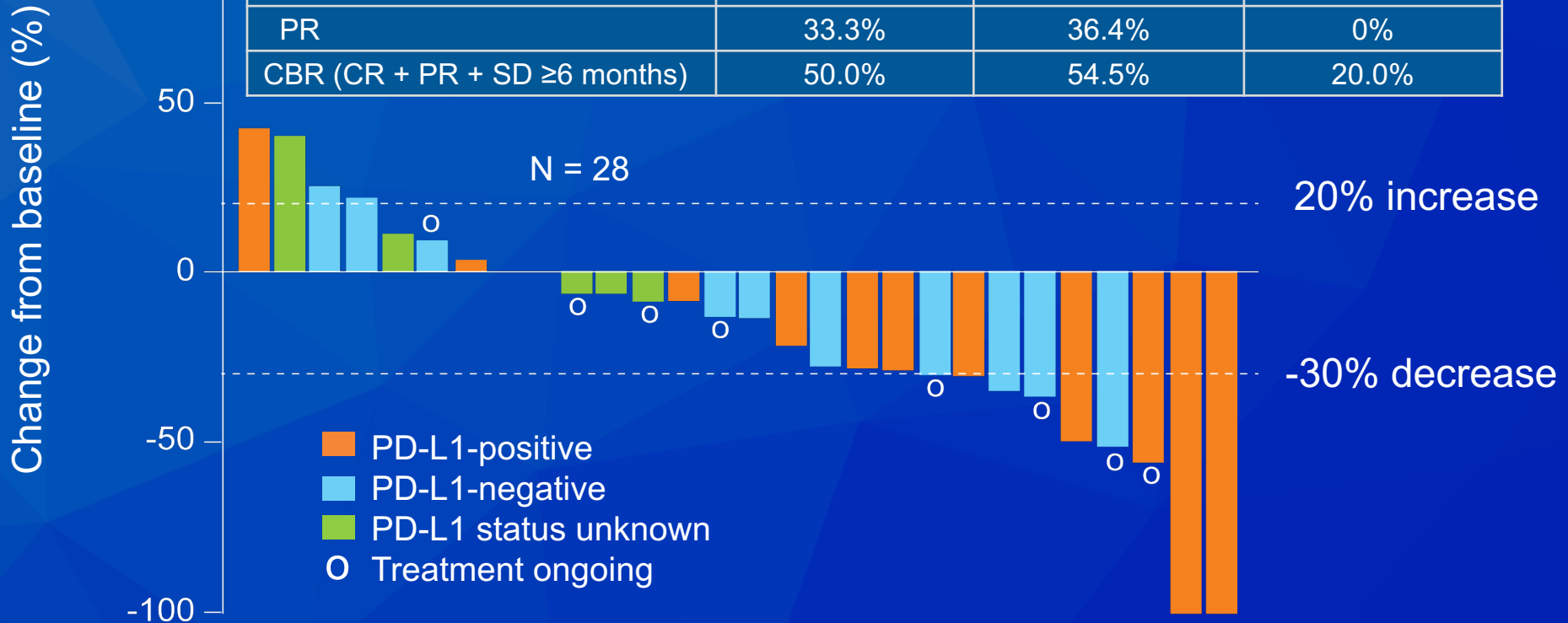
Role of Immune Checkpoint Inhibitors

**Updated Efficacy, Safety, & PD-L1
Status of Patients with HR+,
HER2- Metastatic Breast Cancer
Administered Abemaciclib plus
Pembrolizumab**

Tolaney SM et al.
Proc ASCO 2018;Abstract 1059.

Abemaciclib/Pembrolizumab: Response Summary by PD-L1 Status

Investigator-assessed response (N = 28)	PD-L1-positive (n = 12)	PD-L1-negative (n = 11)	PD-L1 unknown (n = 5)
Confirmed ORR	33.3%	36.4%	0%
CR	0%	0%	0%
PR	33.3%	36.4%	0%
CBR (CR + PR + SD ≥6 months)	50.0%	54.5%	20.0%



- Baseline PD-L1 status was not predictive for response in patients who received treatment for up to 24 weeks

Abemaciclib/Pembrolizumab: Select AEs

Event (N = 28)	All grades n (%)	Grade 1-2 n (%)	Grade 3 n (%)
Diarrhea	22 (78.6)	19 (67.9)	3 (10.7)
Neutropenia	11 (39.3)	3 (10.7)	8 (28.6)
Pruritus	11 (39.3)	11 (39.3)	0 (0.0)
Vomiting	8 (28.6)	7 (25.0)	1 (3.6)
Abdominal pain	7 (25.0)	6 (21.4)	1 (3.6)
Pneumonitis	2 (7.1)	2 (7.1)	0 (0.0)
Acute kidney injury (renal failure)	2 (7.1)	2 (7.1)	0 (0.0)
Colitis	1 (3.6)	1 (3.6)	0 (0.0)

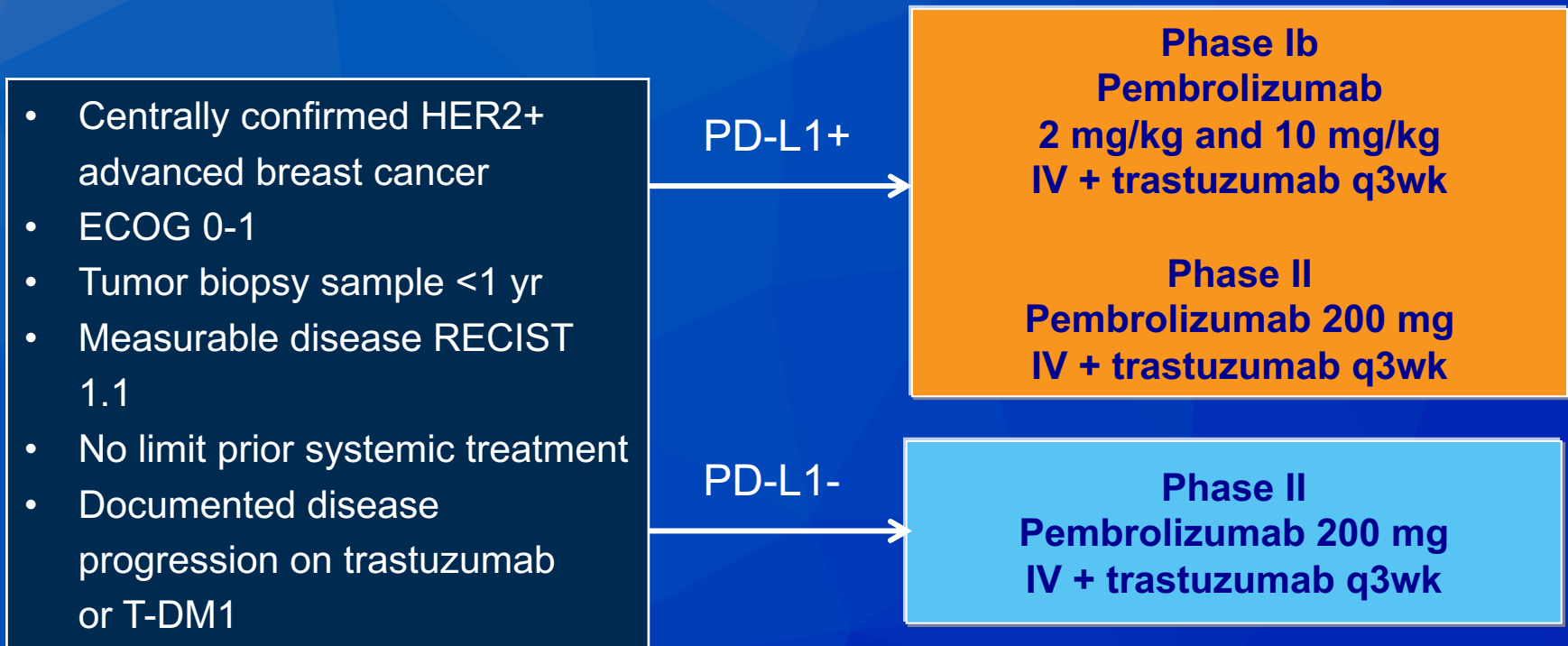
The combination of abemaciclib and pembrolizumab demonstrated a manageable safety profile.

Phase Ib/II Study Evaluating Safety and Efficacy of Pembrolizumab and Trastuzumab in Patients with Trastuzumab Resistant HER2-Positive Metastatic Breast Cancer: Results from the PANACEA (IBCSG 45-13/BIG 4-13/KEYNOTE-014) Study

Loi S et al.

San Antonio Breast Cancer Symposium
2017;Abstract GS2-06.

PANACEA: Phase Ib/II Study Design



Screening

- IBCSG Central Pathology Office
 - HER2 IHC and ISH
 - ER status
 - % stromal tumor-infiltrating lymphocytes (sTILs)
- PD-L1 central assessment

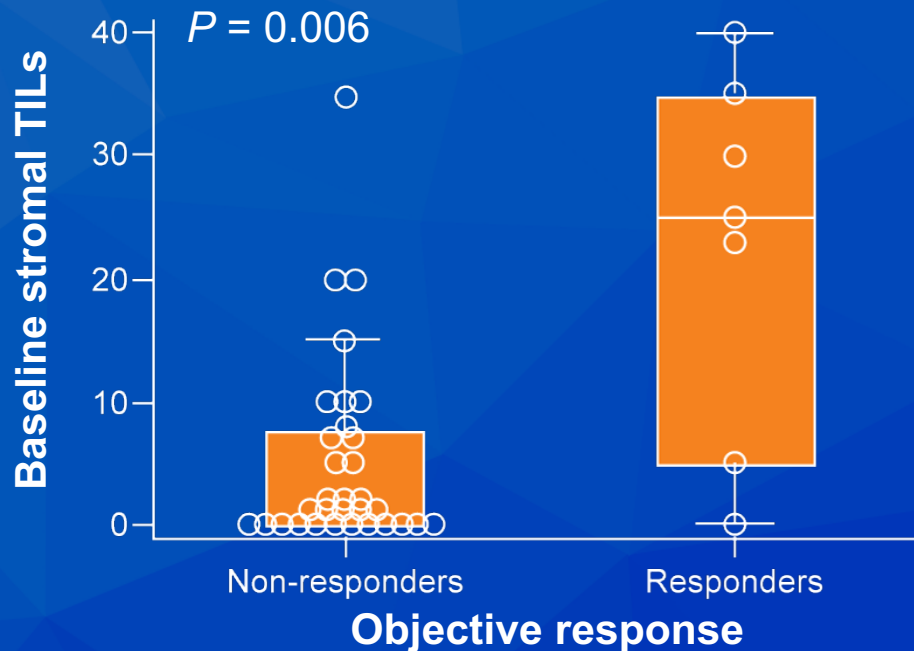
PANACEA: Response Rates to Pembrolizumab and Trastuzumab by PD-L1 status

	PD-L1-positive Phase II n = 40	PD-L1-negative Phase II n = 12
ORR, n (%)	6 (15%)	0 (0%)
DCR, n (%)	10 (25%)	0 (0%)
Best overall response, n (%)		
Complete response	1 (2.5%)	—
Partial response	5 (12.5%)	—
Stable disease	7 (17.5%)	2 (16.7%)
Progressive disease	25 (62.5%)	9 (75.0%)
Not evaluable	2 (5.0%)	1 (8.3%)

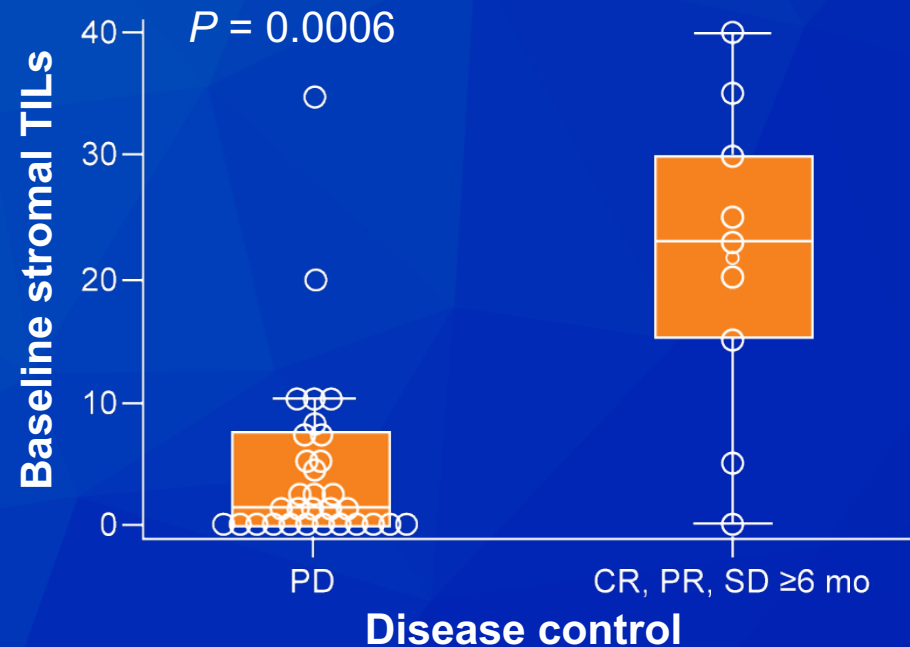
- Pembrolizumab + trastuzumab in trastuzumab-resistant HER2-positive metastatic breast cancer met its primary endpoint in the PD-L1-positive cohort
- No response observed in patients with PD-L1-negative disease

PANACEA: Baseline sTILs by Response and Disease Control in PD-L1-Positive Cohorts

Baseline sTILs and ORR



Baseline sTILs and DCR



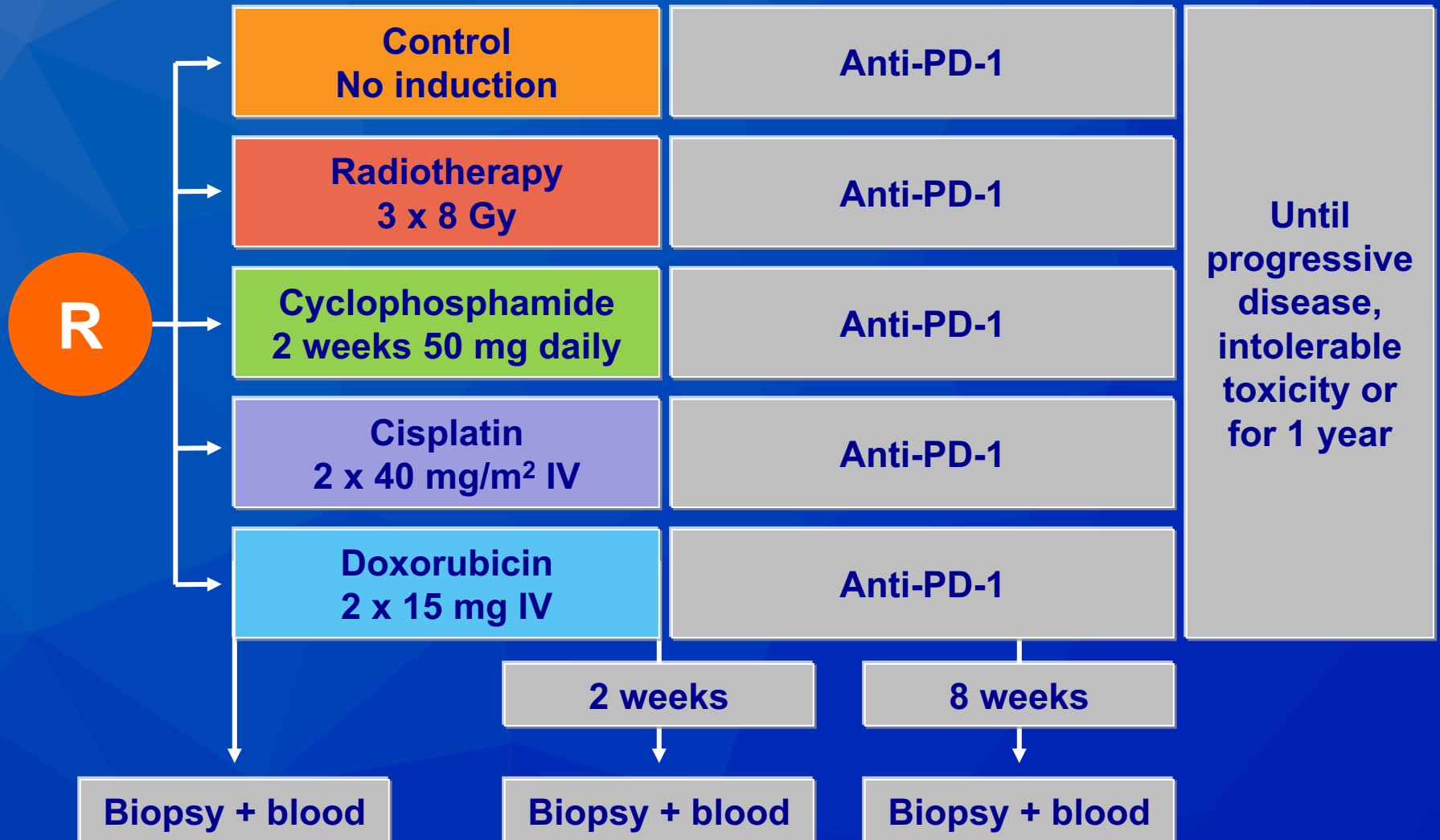
- Higher sTILs were associated with better response and disease control in PD-L1-positive cohorts
- For patients with sTILs $\geq 5\%$: ORR 39%, DCR 47%

Adaptive Phase II Randomized Trial of Nivolumab After Induction Treatment in Triple Negative Breast Cancer (TONIC trial): Final Response Data Stage I and First Translational Data

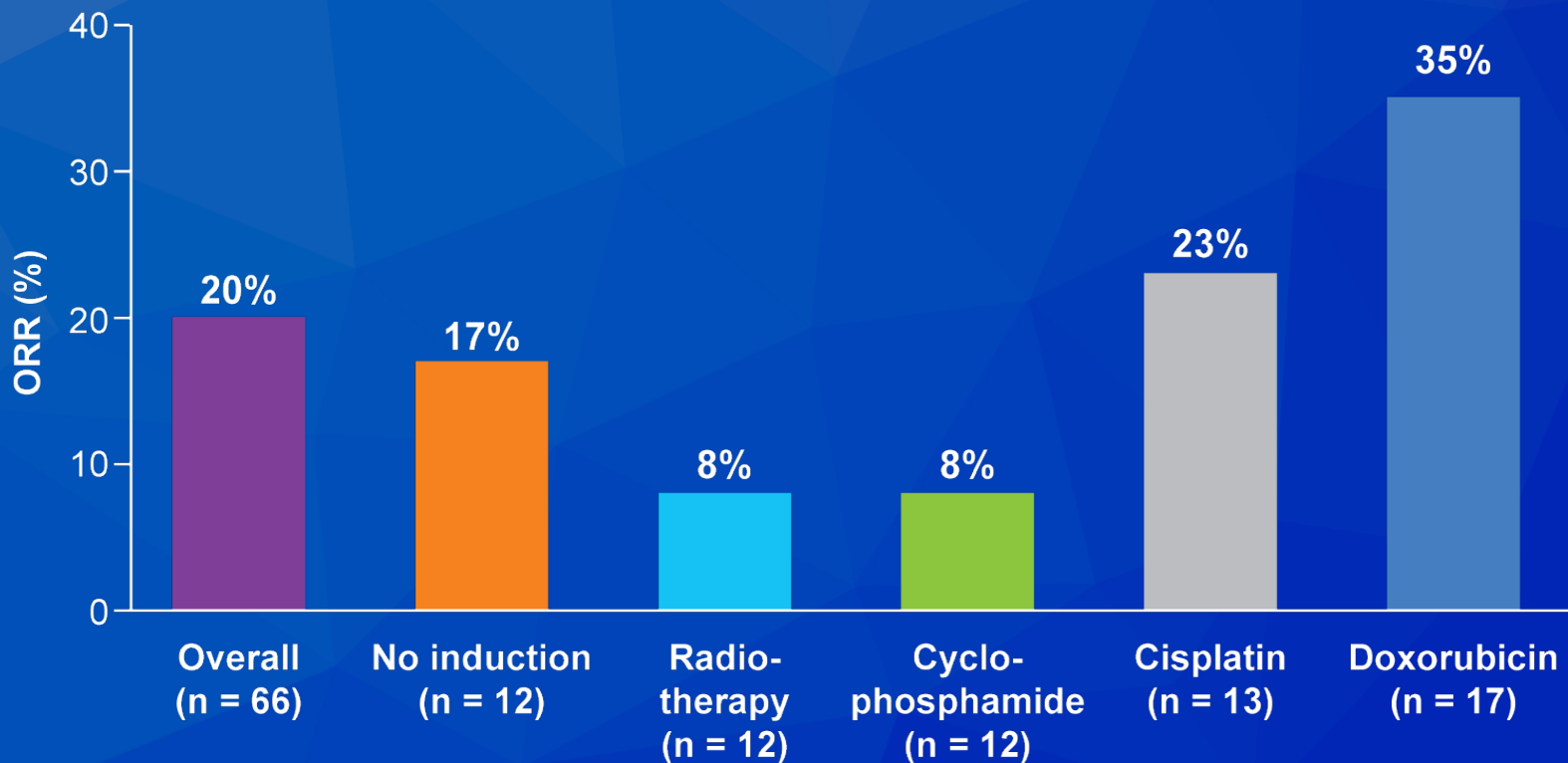
Kok M et al.

Proc ASCO 2018;Abstract 1012.

TONIC: Phase II Trial Design Schema



TONIC: Efficacy of Induction + Nivolumab per Cohort



Induction with doxorubicin or cisplatin may result in:

- Increased likelihood to respond to nivolumab
- Upregulation of gene signatures associated with response to anti-PD-1 therapy
- Increased T cells and T cell clonality

Phase 1b/2 Study to Evaluate Eribulin Mesylate in Combination with Pembrolizumab in Patients with Metastatic Triple-Negative Breast Cancer

Tolaney SM et al.
San Antonio Breast Cancer Symposium
2017;Abstract PD6-13.

ENHANCE 1: Response to Eribulin Mesylate in Combination with Pembrolizumab

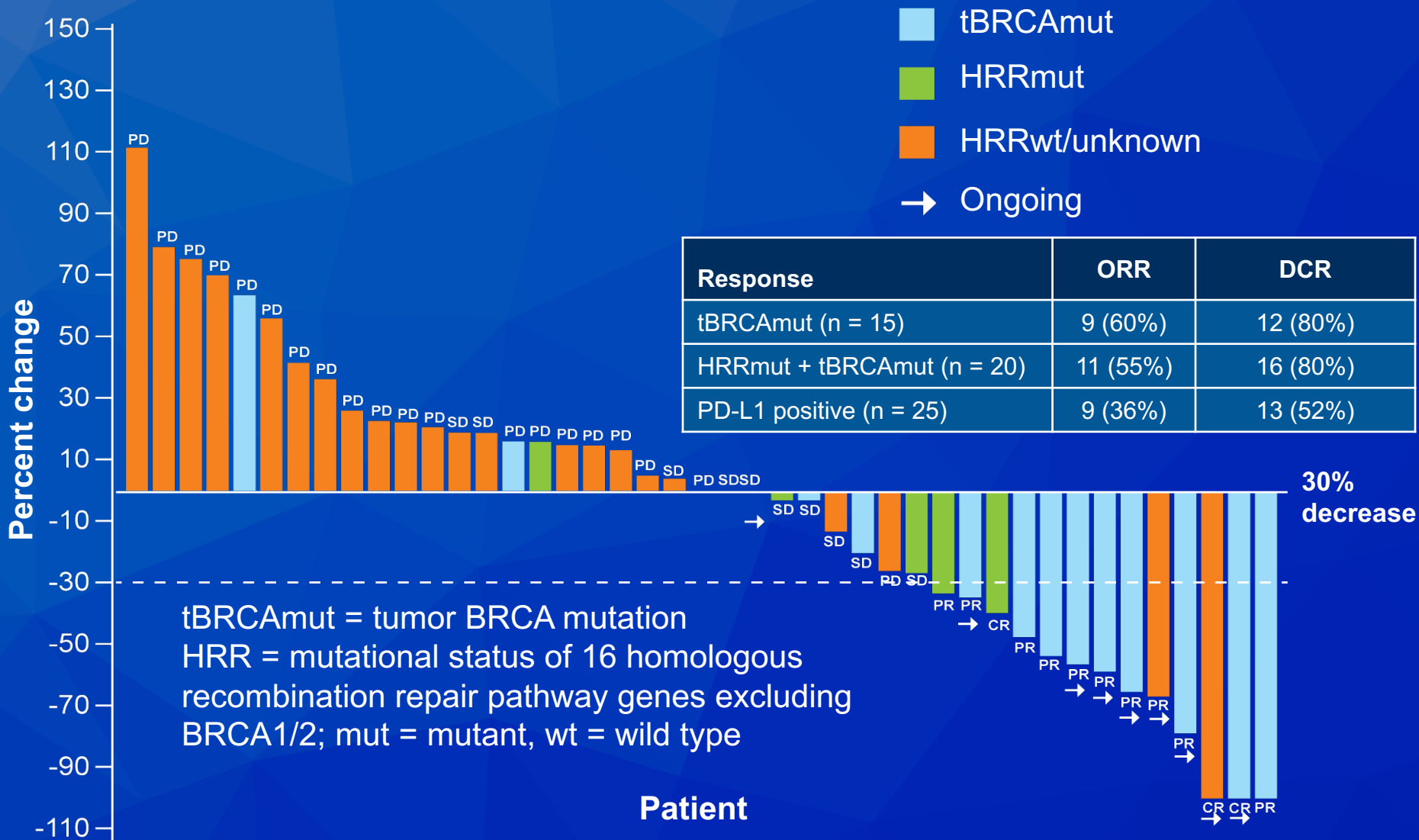
	Overall (N = 82)	No prior chemo in metastatic setting (N = 48)	1-2 prior lines of chemo in metastatic setting (N = 34)
ORR, n (%)	21 (26)	12 (25)	9 (27)
CBR, n (%)	25 (31)	13 (27)	12 (35)
DCR, n (%)	46 (56)	28 (58)	18 (53)
Median PFS, mo	4.1	4.1	3.9
Median OS, mo	NE	17.7	NE

TOPACIO/Keynote-162: Niraparib + Pembrolizumab in Patients (pts) with Metastatic Triple-Negative Breast Cancer (TNBC), a Phase 2 Trial

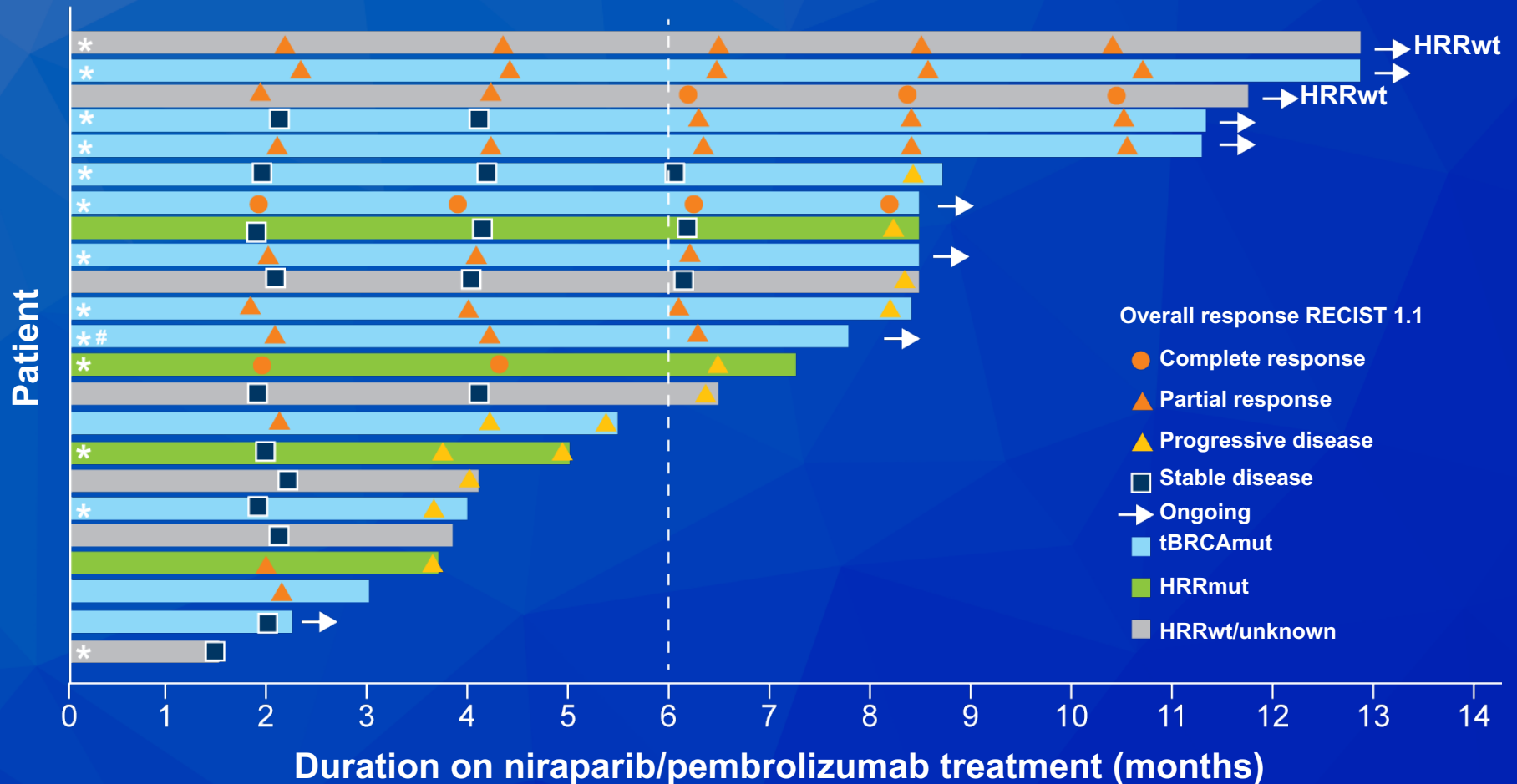
Vinayak S et al.

Proc ASCO 2018;Abstract 1011.

TOPACIO/Keynote-162: Best Overall Response and Objective Response Rate (ORR)



TOPACIO/Keynote-162: Durable Clinical Benefit Extends Beyond tBRCAmut



- Durable responses observed irrespective of BRCA1/2 or PD-L1 status or prior platinum exposure with the highest ORR in pts with BRCAmut disease