

Year ⁱⁿ Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

**October 28, 2017, 8:00 AM – 4:00 PM
Orlando, Florida**

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Research
To Practice®



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Disclosures

Advisory Committee and Consulting Agreements	Amgen Inc, AstraZeneca Pharmaceuticals LP, Celgene Corporation, Eisai Inc, Genentech BioOncology, Lilly, Merck, Novartis, Pfizer Inc, Roche Laboratories Inc, Sanofi Genzyme, Takeda Oncology
Contracted Research	Merck



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Contracted Research	Amgen Inc, Eisai Inc, Genentech BioOncology, GlaxoSmithKline, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Roche Laboratories Inc
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Select Recently Approved Agents in Breast Cancer

Agent	Approval date	Indication
Ribociclib	3/13/17	HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with an AI as initial endocrine therapy
Neratinib	7/17/17	Adjuvant treatment of HER2-positive breast cancer after adjuvant trastuzumab
Abemaciclib	9/28/17	HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with fulvestrant after endocrine therapy or as monotherapy after endocrine therapy and chemotherapy for metastatic disease

Breast Cancer — Drs Rugo and O'Shaughnessy

HER2-Positive Disease

Genomic Assays to Guide Decisions in Early-Stage Breast Cancer

CDK4/6 Inhibitors in Breast Cancer

PARP Inhibitors in Patients with Germline BRCA Mutations and HER2-Negative Disease

Anti-PD-1/PD-L1 Checkpoint Inhibitors

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

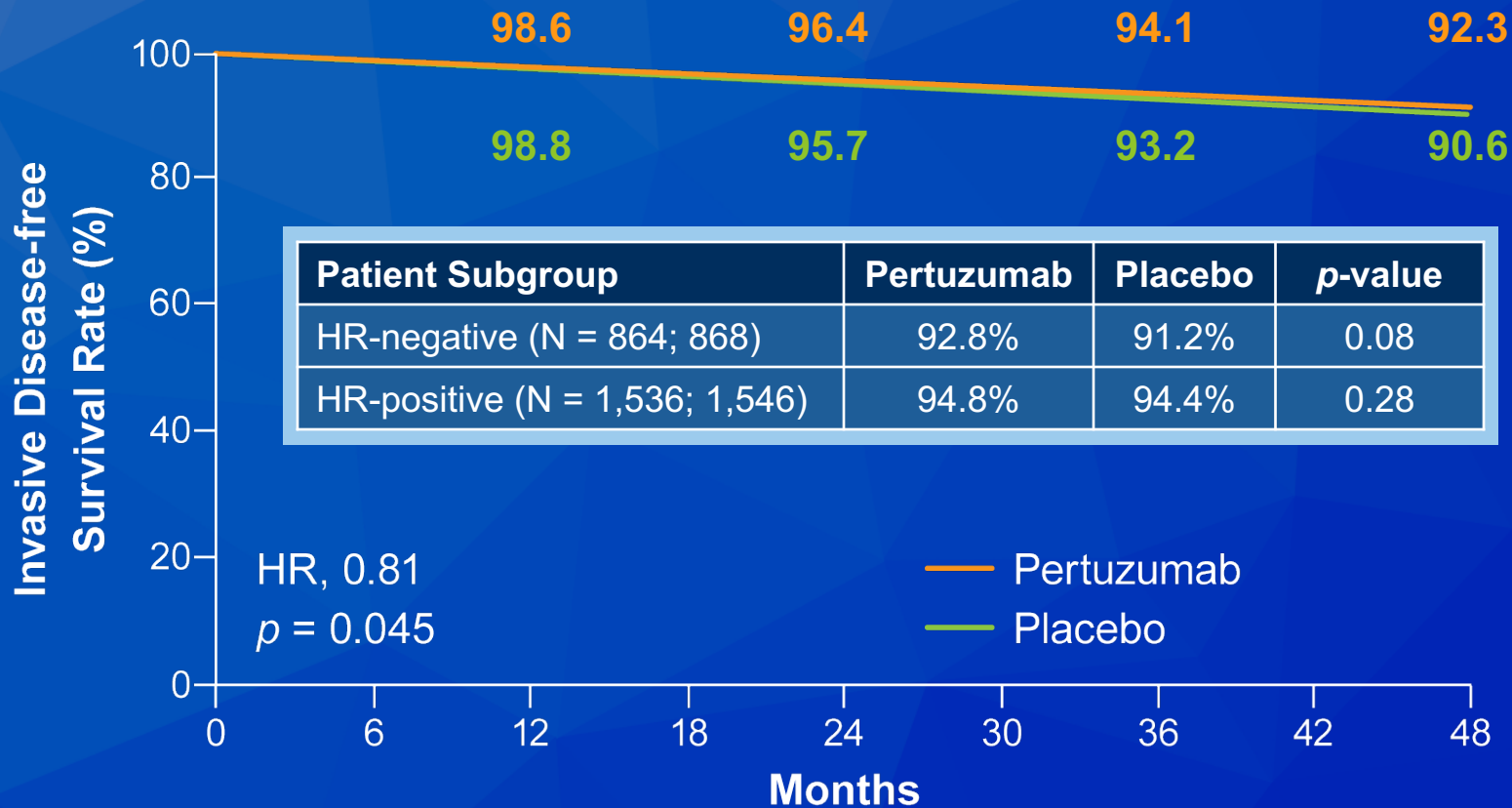
Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D., Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D., Istvan Lang, M.D., Christelle Levy, M.D., Denise A. Yardley, M.D., Jose Bines, M.D., Richard D. Gelber, Ph.D., Martine Piccart, M.D., and Jose Baselga, M.D.,
for the APHINITY Steering Committee and Investigators*

New Engl J Med 2017; 377(2):122-31.

APHINITY trial: A randomized comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC).



APHINITY: Invasive Disease-Free Survival

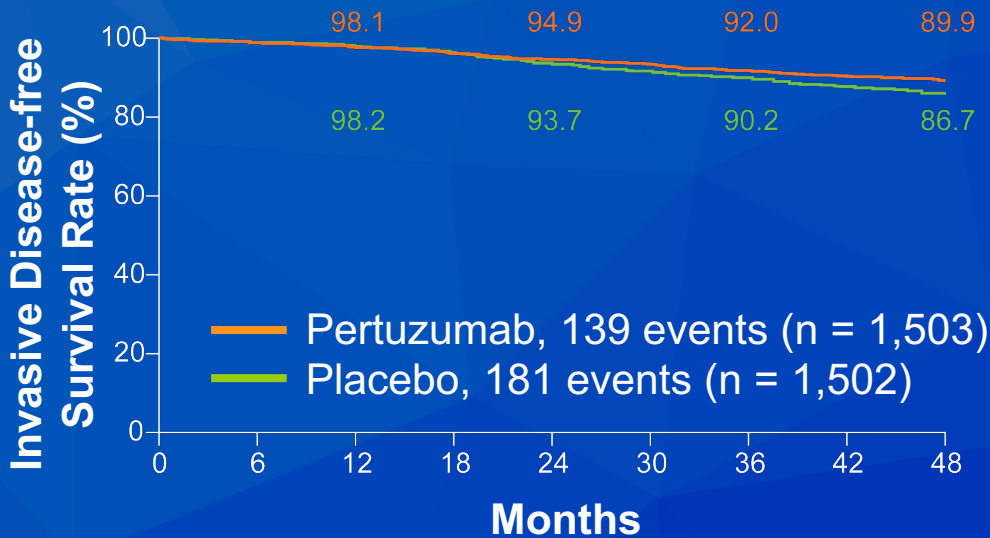


- Patients with node-positive or hormone receptor-negative disease derived the most benefit from pertuzumab
- Overall survival: no significant difference between arms (HR 0.89, $p = 0.47$)

Von Minckwitz G et al. *N Engl J Med* 2017;377(2):122-31. *Proc ASCO* 2017; Abstract LBA500.

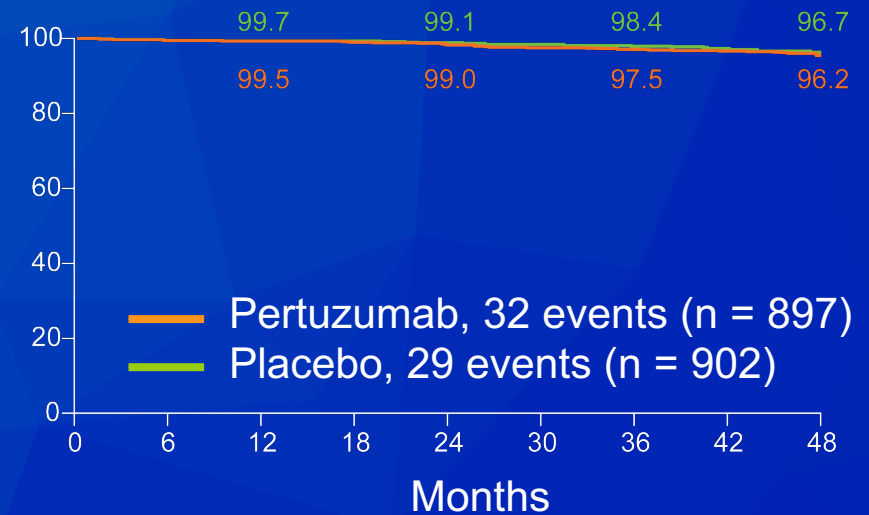
APHINITY: Three-Year Invasive Disease-Free Survival By Nodal Status

Node-Positive



Unstratified hazard ratio, 0.77
P = 0.02

Node-Negative



Unstratified hazard ratio, 1.13
P = 0.64

APHINITY: Safety Summary

	Pertuzumab n = 2,364	Placebo n = 2,405
Grade \geq 3 AEs	64.2%	57.3%
Neutropenia	16.3%	15.7%
Febrile neutropenia	12.1%	11.1%
Decreased neutrophil count	9.6%	9.6%
Diarrhea	9.8%	3.7%
Anemia	6.9%	4.7%
Primary cardiac events	0.7%	0.3%

Editorial — Dr Rugo

The addition of pertuzumab to standard trastuzumab and taxane chemotherapy as first-line therapy for HER2+ metastatic breast cancer in the CLEOPATRA trial resulted in a marked improvement in both progression free and overall survival (PFS, OS) and generated great enthusiasm about the potential of double antibody therapy to improve outcome for patients with HER2+ early stage disease. Improved pathologic complete response rates with a similar combination in the NEOSPHERE study further fueled this enthusiasm, leading to the phase III APHINITY trial, which randomized 4,805 women with centrally confirmed HER2+ early stage breast cancer to receive chemotherapy (78% anthracycline based) plus trastuzumab and either pertuzumab or placebo.

Editorial — Dr Rugo (continued)

As we have seen in a number of recent adjuvant trials, the population had overall lower risk disease compared to neoadjuvant trial patients; 64% had hormone receptor positive disease, and ~37% had node negative disease.

The addition of pertuzumab improved invasive disease free survival (IDFS) by a small margin (absolute difference of 1.7%, MR 0.81, p -value 0.045), but patients fared much better than expected at the 3 year IDFS mark (91.8% vs 89.2%). The absolute difference in distant DFS was 1.1%. Interestingly, the main impact of pertuzumab appeared to be in patients with node positive disease (3.2% absolute difference in IDFS, HR 0.77, $p = 0.019$), and in those with hormone receptor negative tumors (2.3% absolute difference in IDFS, HR 0.76, $p = 0.085$).

Editorial — Dr Rugo (continued)

Overall, pertuzumab was well tolerated with the primary toxicity being diarrhea (grade ≥ 3 9.8%, increasing to 18% when combined with docetaxel/carboplatin/trastuzumab). How do these data apply to the clinic? Pertuzumab clearly improves response, but understanding where double antibody therapy is optimally used in the adjuvant setting is going to require more follow-up data from the APHINITY trial. APHINITY also treated with one year of pertuzumab; the optimal duration has yet to be defined. We know that 12 weeks of paclitaxel and one year of trastuzumab in stage I, node negative, HER2+ disease was associated with excellent outcome at 7 years of follow-up.

Editorial — Dr Rugo (continued)

For now, it would seem prudent to use pertuzumab in the neoadjuvant setting, and in the adjuvant setting for high risk disease. Whether a year of therapy or a shorter duration is required will not be addressed by APHINITY. The good news is that patients with HER2+ disease are doing well, with a 4 year IDFS from standard therapy of 90.6%. Now we need to figure out who needs more therapy, as we clearly have effective options.

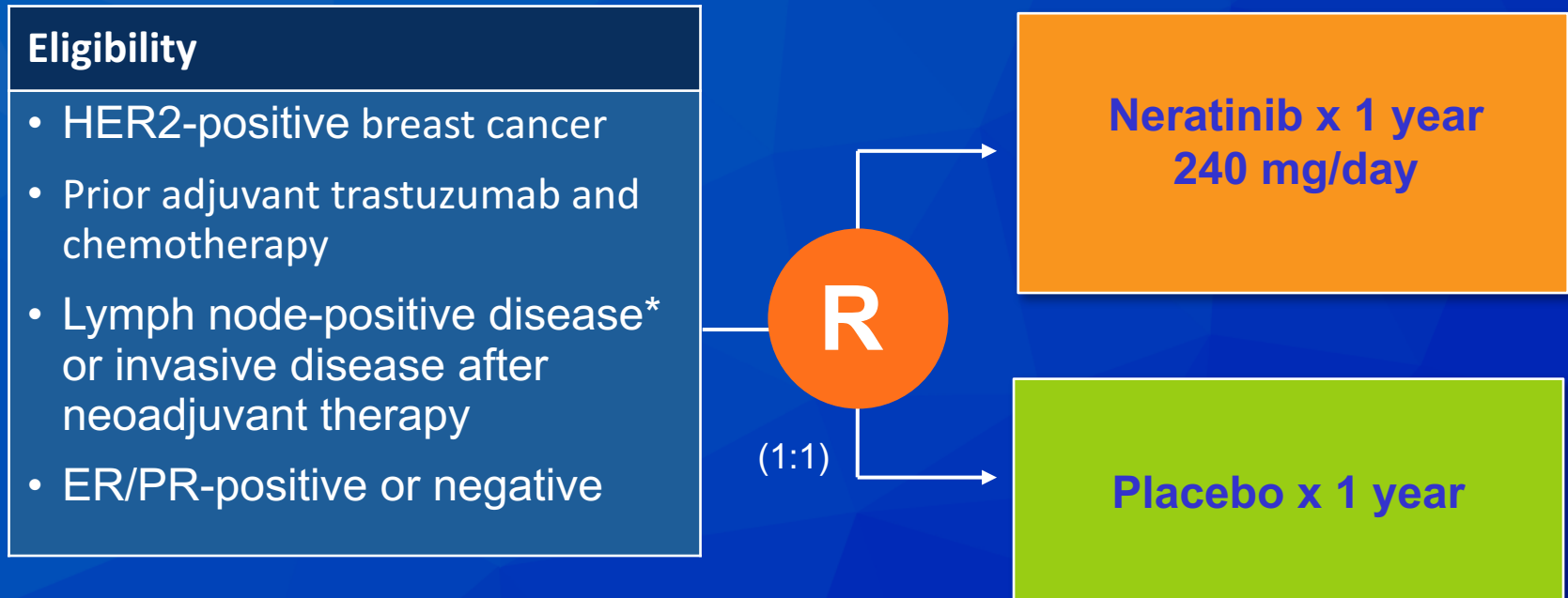
Neratinib after trastuzumab (T)-based adjuvant therapy in early-stage HER2+ breast cancer (BC): 5-year analysis of the phase III ExteNET trial

Martin Jimenez M et al.
Proc ESMO 2017;Abstract 1490.



ExteNET Phase III Schema

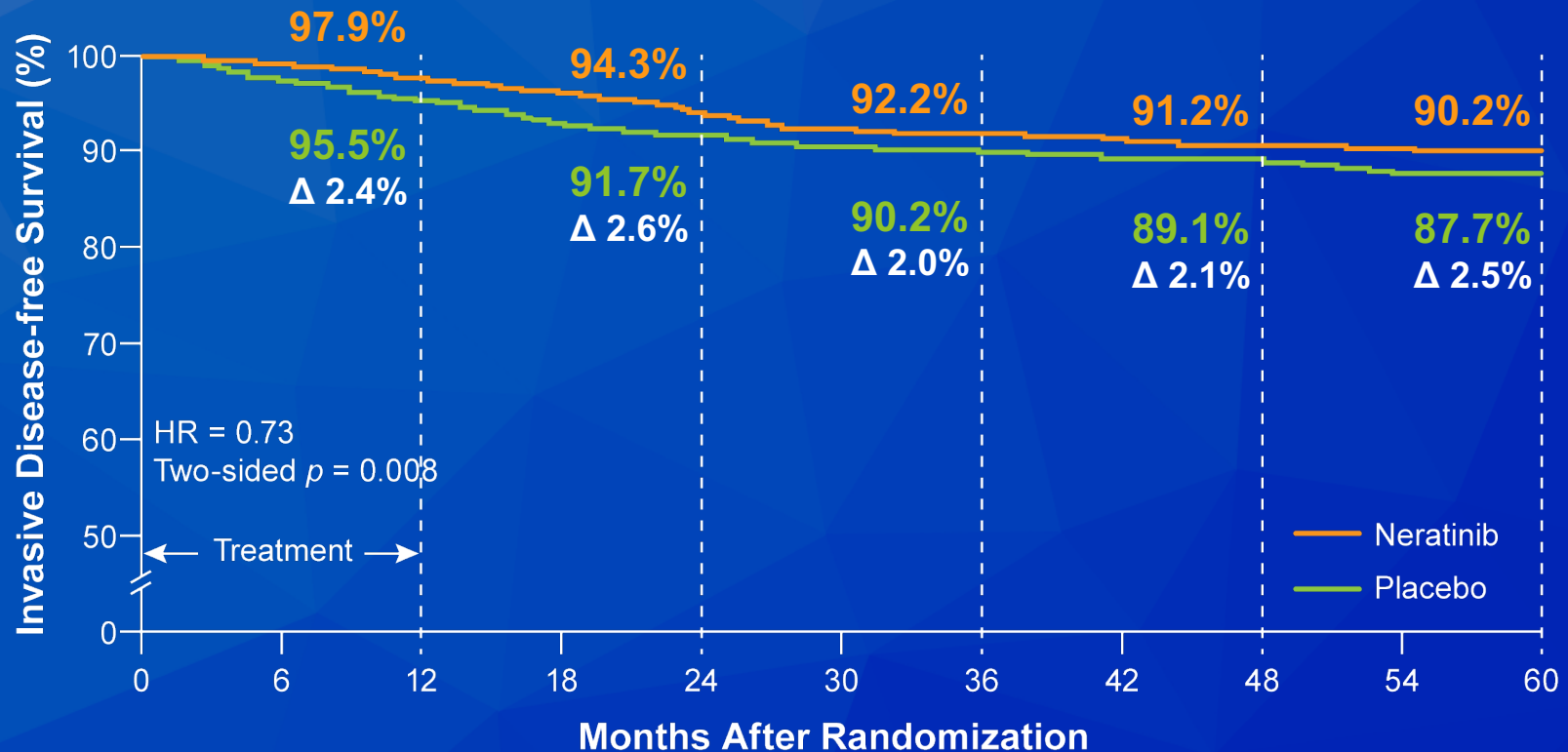
Accrual: 2,840



* Eligibility restricted to node-positive disease after 671 patients with node-negative breast cancer were enrolled

Primary endpoint: Invasive disease-free survival

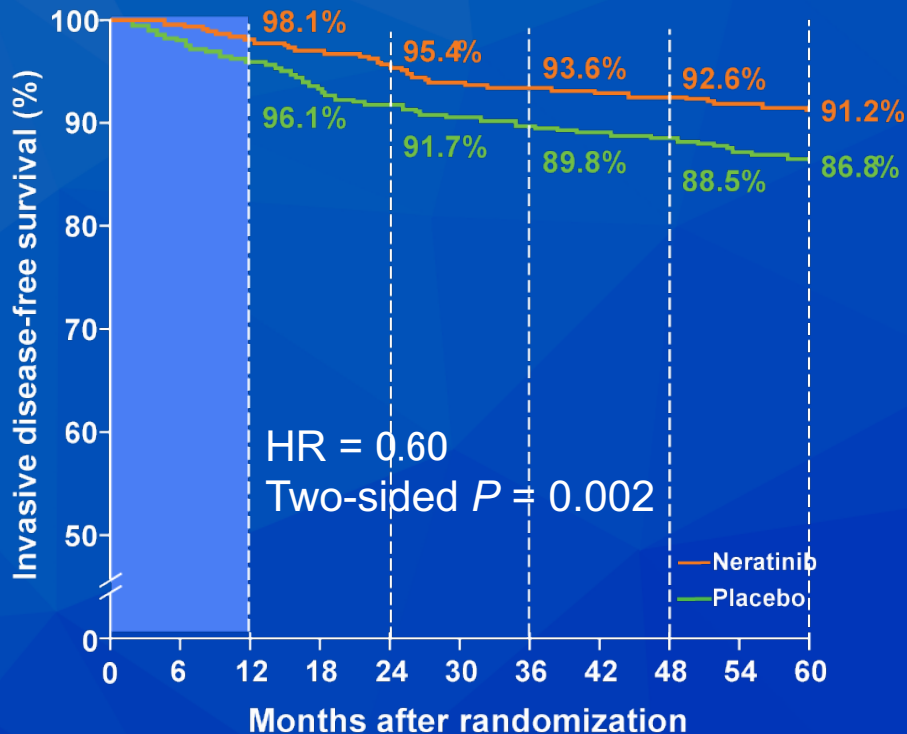
ExteNET: 5-Year Invasive Disease-Free Survival



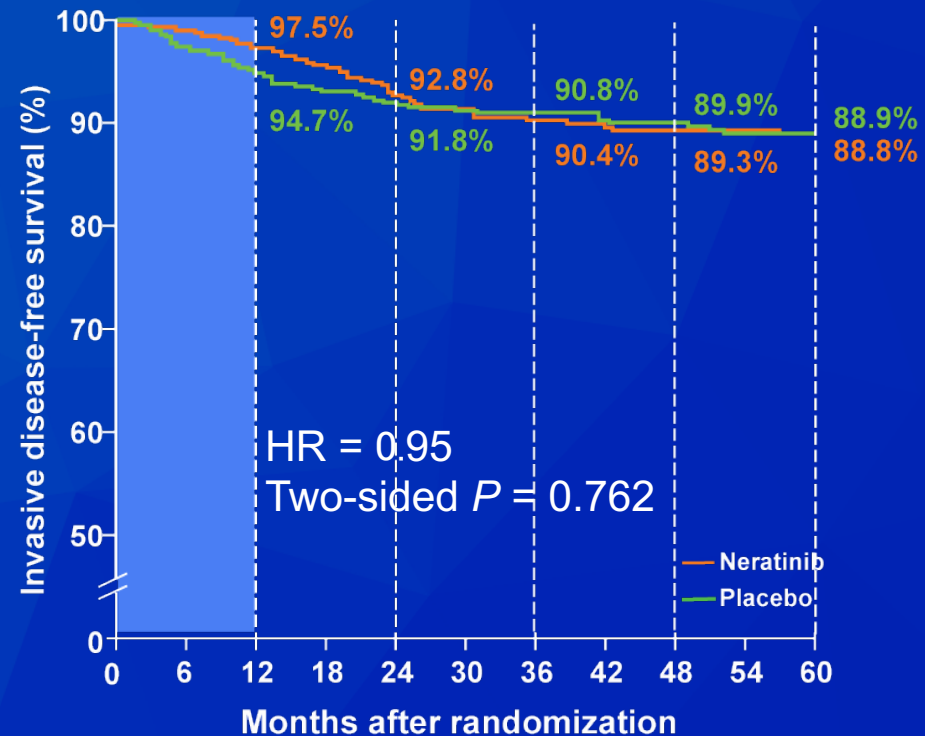
- HR-positive cohort: 4.4% absolute benefit (HR = 0.6, $p = 0.002$)
- No evidence of long-term toxicity with neratinib versus placebo or late-term consequences of neratinib-associated diarrhea

ExteNET: 5-Year Invasive Disease-Free Survival by Hormone Receptor Status

HR-positive subgroup



HR-negative subgroup



Editorial — Dr Rugo

Data from the ExteNET trial was recently updated with 5-year descriptive analysis of efficacy at the ESMO meetings, and based on the initial data from this phase III study, neratinib was approved by the US FDA in the summer of 2017 as extended adjuvant therapy for HER2+ early stage breast cancer. ExteNET randomized 2,840 women with HER2+ early stage breast cancer who had completed one year of adjuvant trastuzumab to receive neratinib or placebo for one additional year. Initially the trial planned for 2-year follow-up for IDFS, but based on the initial positive data, patients were reconsented for 5-year follow-up and overall survival; 76% consented but all were included as ITT.

Editorial — Dr Rugo (continued)

In the randomized population ~60% had hormone receptor positive disease, and ~24% had node negative disease. At 5 years, the absolute difference in IDFS was maintained at 2.5% (87.7% vs 90.2%, HR 0.73, $p = 0.008$), with a 1.5% absolute difference in distant DFS. Most strikingly, there was a greater benefit in the subset of patients with hormone receptor positive disease compared to those with hormone receptor negative disease (absolute difference in IDFS 4.4% [HR 0.60] versus 0.1%), and in those starting neratinib within one year of completing trastuzumab (absolute difference in IDFS 3.2%).

Editorial — Dr Rugo (continued)

What is the take home message from ExteNET? It is important to keep in mind the toxicity of neratinib, with a 40% rate of grade 3 and 32% rate of grade 2 diarrhea. Of note, the diarrhea occurs early, and prophylaxis with loperamide has been shown to markedly decrease severe symptoms. The CONTROL trial has shown that the addition of prophylactic budesonide and perhaps colestipol to loperamide can further reduce both incidence and grade. Neratinib appears to be a reasonable option for the treatment of high-risk hormone receptor positive HER2+ breast cancer, where it may play a role in improving response to hormone therapy. Interestingly, pre-clinical data suggested this effect from oral TKIs more than a decade ago.

Disease-Free Survival in Neoadjuvant, Adjuvant and Postadjuvant Studies of HER2-Positive Breast Cancer by Hormone Receptor (HR) Status

	DFS (hazard ratio)	
	HR-negative	HR-positive
NEOSPHERE ¹	0.60*	0.86*
TEACH ²	0.68	0.98
N9831/B-31 ³	0.62	0.61
APHINITY ⁴	0.76	0.86
ExteNET ⁵	0.95	0.60

* Progression-free survival

1 Gianni L et al. *Lancet Oncol* 2016;17(6):791-800 (Appendix).

2 Goss PE et al. *Lancet Oncol* 2013;14(1):88-96.

3 Perez EA et al. *J Clin Oncol* 2014;32(33):3744-52.

4 von Minckwitz G et al. *N Engl J Med* 2017;377(2);122-31.

5 Jimenez MM et al. *Proc ESMO* 2017;Abstract 149O.

TBCRC 022: Phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM)

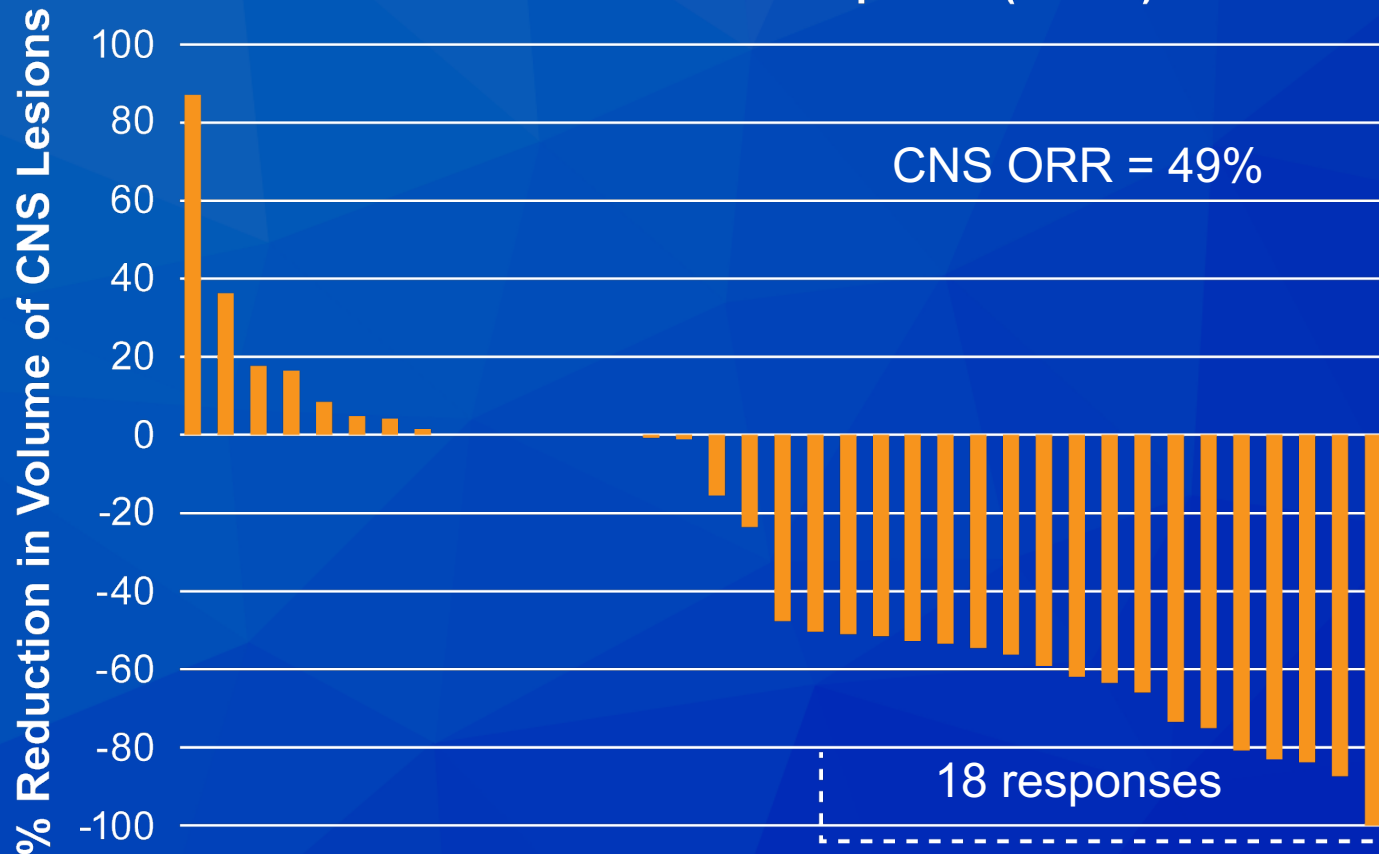
Freedman R et al.

Proc ASCO 2017;Abstract 1005.



Primary Endpoint: CNS Volumetric Response

Best CNS Volumetric Response (n = 31)



- Median overall survival: 13.5 mo
- Most frequent Grade 3 toxicity: Diarrhea (24% on prior pertuzumab, 44% without prior pertuzumab)

Editorial — Dr Rugo

Brain metastases continue to be a problem for patients with HER2+ breast cancer, serving as a site still poorly treated by standard therapeutic algorithms. This study combined two agents known to cross the blood-brain barrier and with single agent data supporting at least some degree of efficacy in the treatment of brain metastases. Neratinib is a highly potent oral pan-HER tyrosine kinase inhibitor. Clinical trial data already demonstrated efficacy of the combination of neratinib with capecitabine, and a phase III trial comparing lapatinib/capecitabine to neratinib/capecitabine in heavily pre-treated HER2+ MBC (NALA) has completed accrual and data is expected in the near future.

Editorial — Dr Rugo (continued)

Freedman and colleagues first studied neratinib alone in patients with progressive brain metastases, reporting a CNS ORR of 8% (JCO 2016). Cohort 3 treated 37 patients with progressive brain metastases and no prior lapatinib with neratinib 240 mg/day and capecitabine at 750 mg/m² BID 1-14 every 21 days. To evaluate response, the primary endpoint was volumetric change in CNS, and the secondary endpoint used the Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) criteria (Lin et al, *Lancet Oncol* 2015). The CNS overall response rate by volume in 31 evaluable patients was 49% (95% CI: 32%-66%), and by RANO-BM was 24% (95% CI: 12%-41%).

Editorial — Dr Rugo (continued)

Six-month PFS was 38%, and median TTP was 5.5 months with 51% of patients staying on therapy for at least 6 cycles. As we have seen with other neratinib trials, grade 3 diarrhea was frequent, although prophylactic anti-diarrheal therapy was not routinely used. Correlative studies are pending.

This data supports further evaluation of neratinib and capecitabine as treatment for HER2+ disease metastatic to the brain, and suggests that there may be some value for this combination or for neratinib as prevention of brain metastases. Subset analyses of the NALA trial will be quite helpful in further understanding this impact.

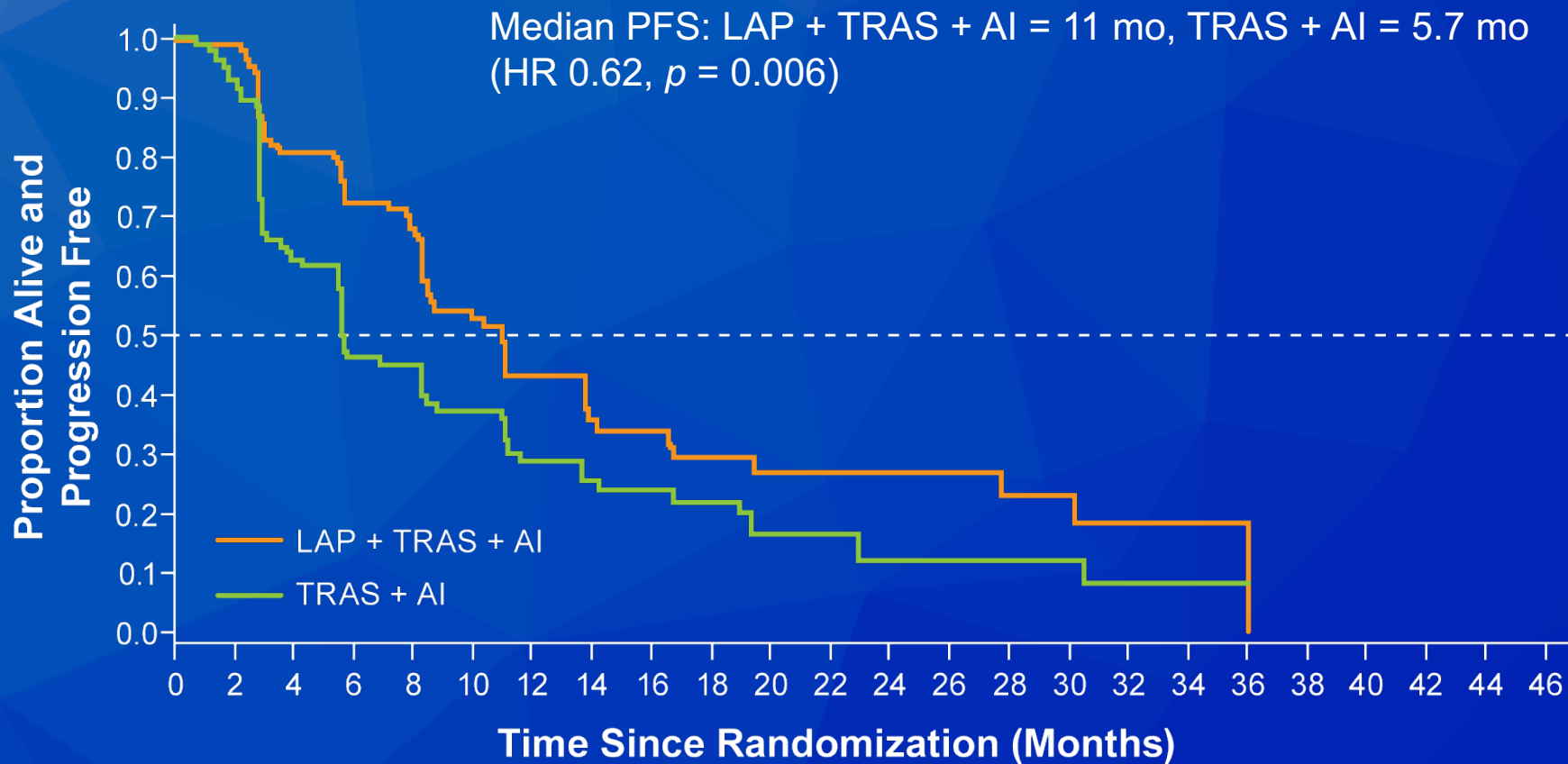
Phase III study of lapatinib plus trastuzumab and aromatase inhibitor vs TRAS+AI vs LAP+AI in postmenopausal women with HER2+, HR+ metastatic breast cancer: ALTERNATIVE

Gradishar W et al.

Proc ASCO 2017;Abstract 1004.



PFS (ITT population) in the ALTERNATIVE trial



- Median overall survival: LAP + TRAS + AI 46.0 mo, TRAS + AI 40.0 mo (HR 0.6, $p = 0.07$)

Editorial — Dr Rugo

ALTERNATIVE is a phase III trial that randomized 355 postmenopausal women with hormone receptor positive, HER2+ metastatic breast cancer with prior hormone, chemotherapy and trastuzumab treatment to receive lapatinib (1,000 mg/day), trastuzumab plus an aromatase inhibitor (arm 1), trastuzumab plus an aromatase inhibitor (arm 2), or lapatinib (1,500 mg/day) plus an aromatase inhibitor (arm 3) with a primary endpoint of PFS with arm 1 versus arm 2. PFS was superior in arm 1 compared to arm 2 (11 vs 5.7 months, HR 0.62, $p = 0.0064$), and arm 3 was superior to arm 2 as well (8.3 vs 5.7 months, HR 0.71, $p = 0.0361$). Overall survival was similar between the three arms with a trend towards improvement comparing arm 1 to arm 2.

Editorial — Dr Rugo (continued)

Response rates were markedly higher in arm 1, with subgroup analysis suggesting more benefit in patients with measurable disease. Although there were twice as many adverse events (AEs) in arm 1 compared to arm 2, there was no increase in AEs leading to treatment discontinuation.

What are the implications of ALTERNATIVE for the clinic? These data are consistent with previous results showing that the combination of trastuzumab and lapatinib was superior to lapatinib alone in patients with HER2+ advanced breast cancer progressing on prior trastuzumab.

Editorial — Dr Rugo (continued)

With the advent of pertuzumab, and the CLEOPATRA data showing a marked improvement in survival with double antibody treatment combined with paclitaxel as first-line therapy in the metastatic setting, this treatment would be used in the second or later line setting for most patients. However, there may be patients for whom chemotherapy is not feasible; in this case arm 1 (with double HER2 blockade) has been demonstrated to be effective and superior to single HER2 blockade with hormone therapy for hormone receptor positive disease. Without clear survival benefit (although the trial may have been underpowered to detect), toxicity needs to be taken into consideration.

Breast Cancer — Drs Rugo and O'Shaughnessy

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JOURNAL OF CLINICAL ONCOLOGY

A S C O S P E C I A L A R T I C L E

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update

Ian Krop, Nofisat Ismaila, Fabrice Andre, Robert C. Bast, William Barlow, Deborah E. Collyar, M. Elizabeth Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Catherine Van Poznak, Antonio C. Wolff, and Vered Stearns

J Clin Oncol 2017;35(24):2838-47.



ASCO Guideline on the Use of MammaPrint® for Adjuvant Systemic Therapy Decision-Making

Recommendations based on MINDACT and other published data on the use of MammaPrint to inform decisions on withholding adjuvant chemotherapy:

- MammaPrint may be used for patients with HR-positive, HER2-negative, node-negative BC with high clinical risk.
- The assay may be used for HR-positive, HER2-negative, node-positive BC (1-3 positive nodes) and a high clinical risk.
 - However, such patients should be informed that a benefit from chemotherapy cannot be excluded.
- Do not use MammaPrint for HR-positive, HER2-negative, node-positive BC at low clinical risk, nor for HER2-positive or triple-negative BC.

Editorial — Dr Rugo

Krop and colleagues have provided an update of the ASCO guidelines for use of gene expression panels to decide on the impact of adjuvant chemotherapy in patients with early stage hormone receptor positive breast cancer, based on the results of the MINDACT trial, published after the initial guidelines were created. The initial report set forth guidelines for use of the Recurrence Score (RS), EndoPredict, and the PAM50 Risk of Recurrence Score (RORS); these were not changed. The guidelines are divided by node status, with the panel noting that MINDACT provided evidence-based data for use of MammaPrint to decide which patients can safely avoid chemotherapy.

Editorial — Dr Rugo (continued)

For clinical high risk (based on a number of clinical variables), MammaPrint can be used in node negative and 1-3 node positive disease to adjudicate use of chemotherapy, with the caveat that a benefit from chemotherapy cannot be excluded for patients with 1-3 positive nodes, high risk clinical and low risk genomic scores.

The panel felt that there was not enough data to support the use of testing in clinically low risk disease, as these patients appear to have a good outcome regardless of the MammaPrint result. In addition, there is insufficient data about the impact of chemotherapy.

Editorial — Dr Rugo (continued)

In contrast, the panel maintained their prior statement that the RS should not be used to adjudicate chemotherapy use in node positive disease as yet, given the lack of data from a large prospective trial.

In clinical practice I think it is reasonable to use either test in patients with up to 3 positive nodes where there is a question about the potential benefit of adjuvant chemotherapy. However, it is important to keep in mind that the determination of 'clinical risk' in MINDACT was based on clinical criteria which may not align with current clinical thinking, and Ki67 was not included.



Editorial — Dr Rugo (continued)

The caution for patients with high clinical risk but low genomic risk regarding the unknown benefit of chemotherapy is important — balancing discordant risks is important particularly in patients with stage II (compared to stage I) disease, and clinical risk should be taken into account when deciding about the potential benefits of adjuvant chemotherapy. With all this in mind, hormone therapy remains critical, with adherence over time an ongoing challenge.

A 65-year-old woman presents with a 3.5-cm, strongly ER/PR-positive, HER2-negative IDC and wishes to undergo breast-conserving surgery but needs tumor shrinkage in order to achieve a good cosmetic result. How would you approach neoadjuvant therapy?

- a. Administer endocrine therapy
- b. Administer chemotherapy
- c. Order a 21-gene Recurrence Score and then decide
- d. Order another genomic assay and then decide
- e. Other

Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: A multicenter trial

Harry D. Bear MD, PhD¹  | Wen Wan PhD¹ | André Robidoux MD² |
Peter Rubin MD³ | Steven Limentani MD⁴ | Richard L. White Jr MD⁴  |
James Granfortuna MD³ | Judith O. Hopkins MD⁵ | Dwight Oldham MD⁶ |
Angel Rodriguez MD⁷ | Amy P. Sing MD⁸

J Surg Oncol 2017;115(8):917-23.



Use of the 21-Gene Recurrence Score[®] (RS) from Core Needle Biopsies to Select Neoadjuvant Therapy

- Patients (n = 64) with HR+, HER2-negative, invasive BC not suitable for breast-conserving surgery (BCS) enrolled
- Patients with
 - RS < 11, assigned to hormonal therapy (NHT)
 - RS > 25 received chemotherapy (NCT)
 - RS 11-25 randomized to NHT or NCT
- Of 33 patients with RS 11-25, 5 (15%) refused assignment to NCT, significantly lower than the 33% target ($p = 0.0292$)
- Clinical and pathologic responses were not negatively impacted with RS <25
 - Patients with an RS <11 had a high CR rate
 - Those with an RS 11-25 who received NHT had a similar rate of BCS success as the pts with RS <11.
 - Patients with RS >25 had the highest CR, pCR rates

Editorial — Dr Rugo

This relatively small study evaluated the feasibility of using the Recurrence Score (RS) from a core needle biopsy to determine the type of neoadjuvant therapy for early stage breast cancer. A total of 64 patients with early stage hormone receptor positive breast cancer were enrolled, with a primary endpoint of accepting the recommended treatment. Eligibility included tumors of at least 2 cm, defined as 'not suitable for breast conservation (BCS).' Using the TAILORx risk groupings, patients with a RS <11 received hormone therapy (4-6 months), patients with a RS >25 received chemotherapy (6-8 courses), and patients with a RS 11-25 were randomized to receive hormone or chemotherapy.

Editorial — Dr Rugo (continued)

The randomized group included 33 patients with a RS of 11-25, and 5 (15%) refused assignment to chemotherapy, meeting their endpoint of less than 33%. Fifty-five patients were treated, and the rate of BCS was relatively similar across the arms. The rate of pathologic complete response was low in all arms except those with a RS >25, as expected. Clearly it is reasonable to use tumor obtained from a core biopsy of a primary breast tumor to stratify patients into which tumors are more or less likely to benefit from neoadjuvant chemotherapy. The corollary of this is that post-menopausal women with lower scores could be reasonably treated with neoadjuvant hormone therapy.

Editorial — Dr Rugo (continued)

The study is significantly underpowered to assess the comparative clinical response between treatments in the randomized group, so it is impossible to make a conclusion about the type of therapy for the intermediate risk group. We will need to wait for data from TAILORx to hopefully answer that question.

The 21-Gene Recurrence Score Assay for Node-Positive, Early-Stage Breast Cancer and Impact of RxPONDER Trial on Chemotherapy Decision-Making: Have Clinicians Already Decided?

Jagar Jasem, MD, MPH^a; Christine M. Fisher, MD, MPH^b; Arya Amini, MD^b; Elena Shagisultanova, MD, PhD^c; Rachel Rabinovitch, MD^b; Virginia F. Borges, MD, MMSc^c; Anthony Elias, MD^c; and Peter Kabos, MD^c

JNCCN—Journal of the National Comprehensive Cancer Network | Volume 15 Number 4 | April 2017

The 21-Gene RS Assay for Node-Positive Early Breast Cancer

- Analysis of 80,405 node-positive early breast cancer cases diagnosed from 2010 through 2012 from the National Cancer Data Base with known RS assay status
- 13,288 (16.5%) of the 80,405 cases had an RS assay ordered.
- 10,434 (78.5%) of the 13,288 that had an RS assay ordered had pT1, pT2, pN1 (with 1-3 nodes involved), HR+/HER2- disease.

Number of nodes	RS assay ordered	No RS assay ordered
1 node (n = 21,009)	38.4% (8,070)	61.6% (12,939)
2 nodes (n = 7,782)	23.8% (1,851)	76.2% (5,931)
3 nodes (n = 3,634)	14.1% (513)	85.9% (3,121)

Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Armando E. Giuliano, MD¹; James L. Connolly, MD²; Stephen B. Edge, MD³; Elizabeth A. Mittendorf, MD, PhD⁴; Hope S. Rugo, MD⁵; Lawrence J. Solin, MD⁶; Donald L. Weaver, MD⁷; David J. Winchester, MD⁸; Gabriel N. Hortobagyi, MD⁹

Breast Cancer — Drs Rugo and O'Shaughnessy

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Anti-PD-1/PD-L1 Checkpoint Inhibitors

FDA-Approved CDK4/6 Inhibitors

Drug	Key studies	Indication in ER-positive, HER2-negative mBC	Dosing
Palbociclib (accelerated approval February 2015; regular approval 3-31-17)	PALOMA-1 (Finn <i>Lancet Oncol</i> 2015; Finn ASCO 2017)	<ul style="list-style-type: none"> • With letrozole, no prior endocrine-based therapy • With an AI, postmenopausal women, as initial endocrine-based therapy • With fulvestrant, disease progression after ET 	125 mg once daily with food for 21 out of 28 days
	PALOMA-2 (Finn <i>NEJM</i> 2016)		
	PALOMA-3 (Cristofanilli <i>Lancet Oncol</i> 2016)		
Ribociclib (3-13-17)	MONALEESA-2 (Hortobagyi <i>NEJM</i> 2016)	<ul style="list-style-type: none"> • With an AI, postmenopausal women, as initial endocrine-based therapy 	600 mg orally (3 x 200-mg tablets) taken once daily with or without food for 21 out of 28 days
Abemaciclib (9-28-17)	MONARCH 1 (Dickler <i>Clin Cancer Res</i> 2017)	<ul style="list-style-type: none"> • As monotherapy, previous ET and chemotherapy • With fulvestrant, disease progression after ET 	200 mg BID continuous until disease progression as monotherapy; 150 mg BID in combination with fulvestrant
	MONARCH 2 (Sledge <i>JCO</i> 2017)		

mBC = metastatic breast cancer; AI = aromatase inhibitor; ET = endocrine therapy

ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

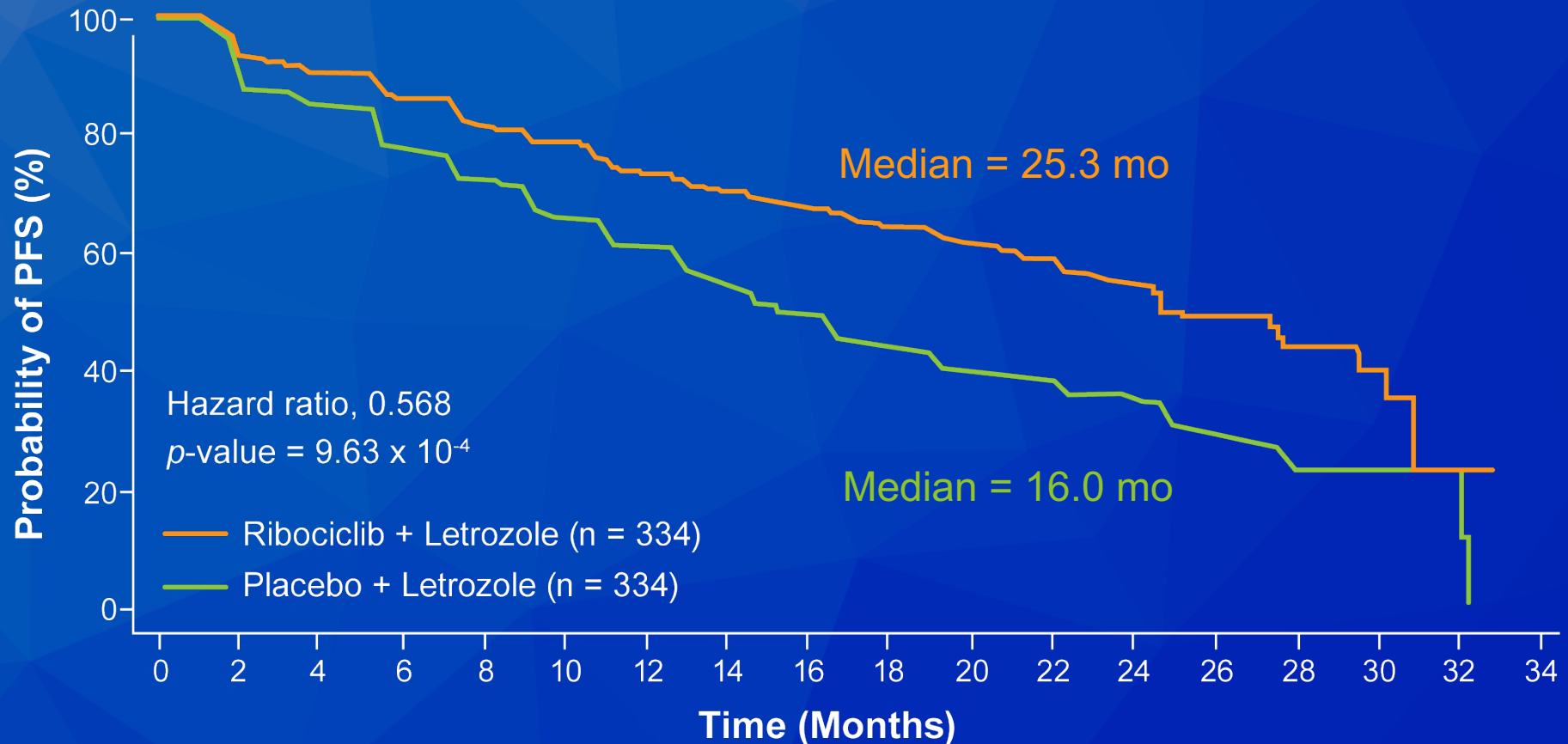
G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy

N Engl J Med 2016;375(18):1738-48.

Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2-), advanced breast cancer (ABC).



MONALEESA-2: PFS with First-Line Ribociclib/Letrozole



- Median follow-up: 26 mo
- Median overall survival (data are immature): Ribociclib arm: not reached; placebo arm: 33 mo

MONALEESA-2: Select Adverse Events

	Ribociclib + letrozole (n = 334)		Placebo + letrozole (n = 330)	
	All grades	Grade 3-4	All grades	Grade 3-4
Neutropenia	74%	60%	5%	<1%
Nausea	52%	2%	29%	<1%
Infections	50%	4%	42%	2%
Diarrhea	35%	1%	22%	<1%
Leukopenia	33%	20%	4%	<1%
Increased alanine aminotransferase	16%	9%	4%	1%
Increased aspartate aminotransferase	15%	6%	4%	1%

- Increased QTcF interval >60 msec from baseline:
 - Ribociclib: 2.7%
 - Placebo: 0%

Editorial — Dr O'Shaughnessy

The MONALEESA-2 phase III trial randomized 668 first-line HR+ HER2- MBC patients to receive letrozole + the CDK4/6 inhibitor ribociclib vs letrozole + placebo. At the first planned interim analysis the DSMB recommended that the trial be unblinded because the primary endpoint of PFS had been met with a significant improvement seen with the addition of ribociclib, HR 0.56, $p = 3.29 \times 10^{-6}$. The median PFS had not been reached for the ribociclib arm and was 14.7 months with letrozole alone (a later analysis of this trial showed the median PFS on the ribociclib arm to be 25.3 mos vs 16 mos with letrozole alone). Benefit from ribociclib was seen across all of the prespecified subsets.

Editorial — Dr O'Shaughnessy (continued)

The ribociclib therapy was well tolerated with 7.5% of patients discontinuing therapy for adverse events. Grade 3/4 neutropenia rate was 59% (with 1% febrile neutropenia rate), and 9% of patients had grade 3/4 elevation of hepatic transaminases. 3.3% of patients had prolongation of QTc to more than 480 msec, which was reversible with holding ribociclib.

An analysis of the 37% of patients (n = 227) who had de novo MBC who enrolled on MONALEESA-2 showed that those treated with ribociclib had a substantial improvement in PFS, HR 0.448 (95% CI 0.267-0.75). 12-month PFS rates were 82% with ribociclib + letrozole vs 66% with letrozole alone.

Editorial — Dr O'Shaughnessy (continued)

The results from the MONALEESA-2 trial demonstrate that the addition of ribociclib to first-line aromatase inhibitor therapy dramatically improves PFS with excellent tolerability, and corroborates the 10-month improvement in PFS that had been previously demonstrated in the PALOMA-2 trial with combined letrozole and palbociclib. Importantly, even de novo MBC patients in MONALEESA-2, whose disease would be expected to generally be highly sensitive to endocrine therapy alone, had an even greater benefit from the addition of ribociclib than the overall population, suggesting that ribociclib is highly effective in ER-driven breast cancer. The addition of ribociclib or palbociclib to first-line letrozole therapy has become the standard of care in the US. Overall survival data are awaited.

MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2– Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy

George W. Sledge, Jr., Masakazu Toi, Patrick Neven, Joohyuk Sohn, Kenichi Inoue, Xavier Pivot, Olga Burdaeva, Meena Okera, Norikazu Masuda, Peter A. Kaufman, Han Koh, Eva-Maria Grischke, Martin Frenzel, Yong Lin, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Antonio Llombart-Cussac

J Clin Oncol 2017;35(25):2875-84.

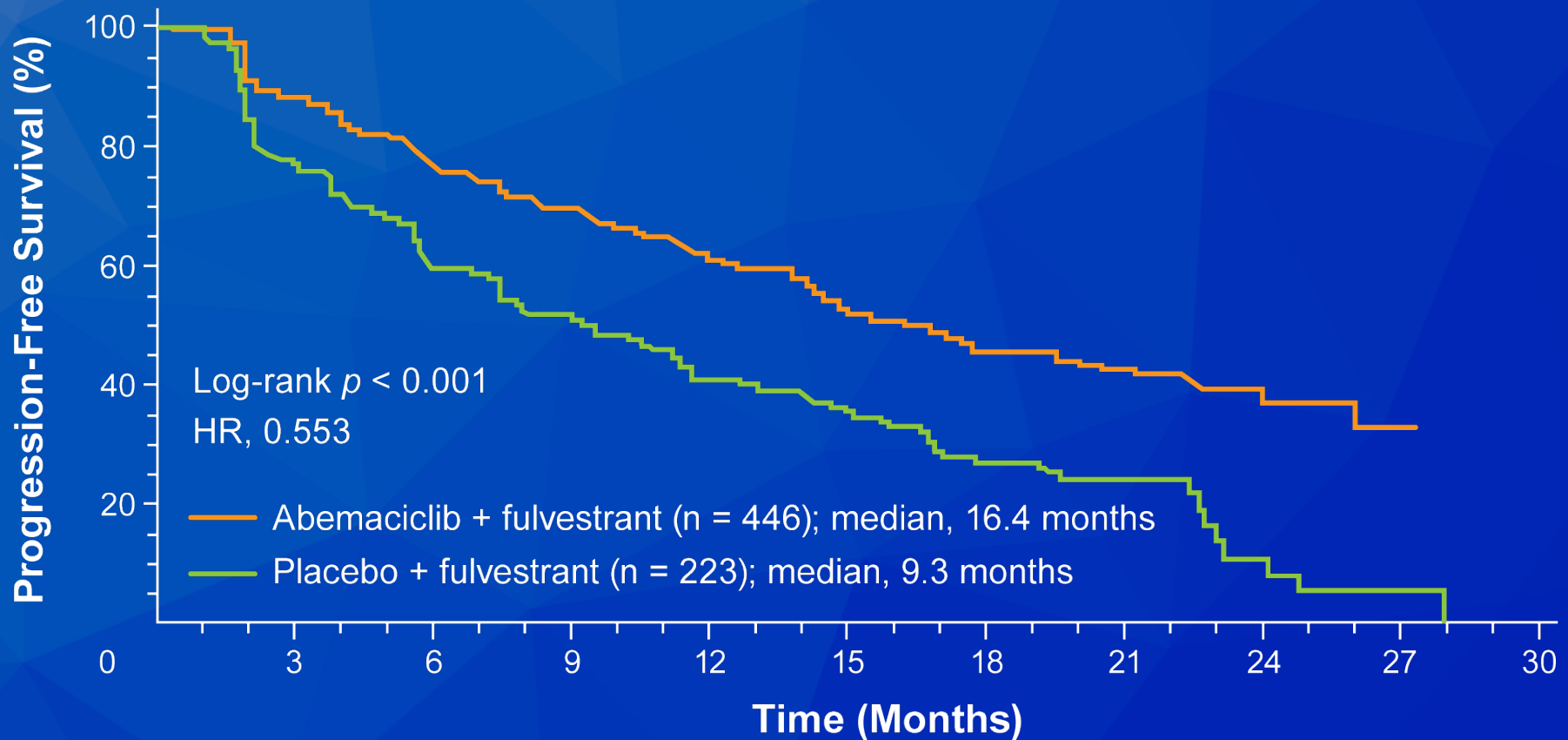
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

Matthew P. Goetz, Masakazu Toi, Mario Campone, Joohyuk Sohn, Shani Paluch-Shimon, Jens Huober, In Hae Park, Olivier Trédan, Shin-Cheh Chen, Luis Manso, Orit C. Freedman, Georgina Garnica Jaliffe, Tammy Forrester, Martin Frenzel, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Angelo Di Leo

J Clin Oncol 2017;[Epub ahead of print].

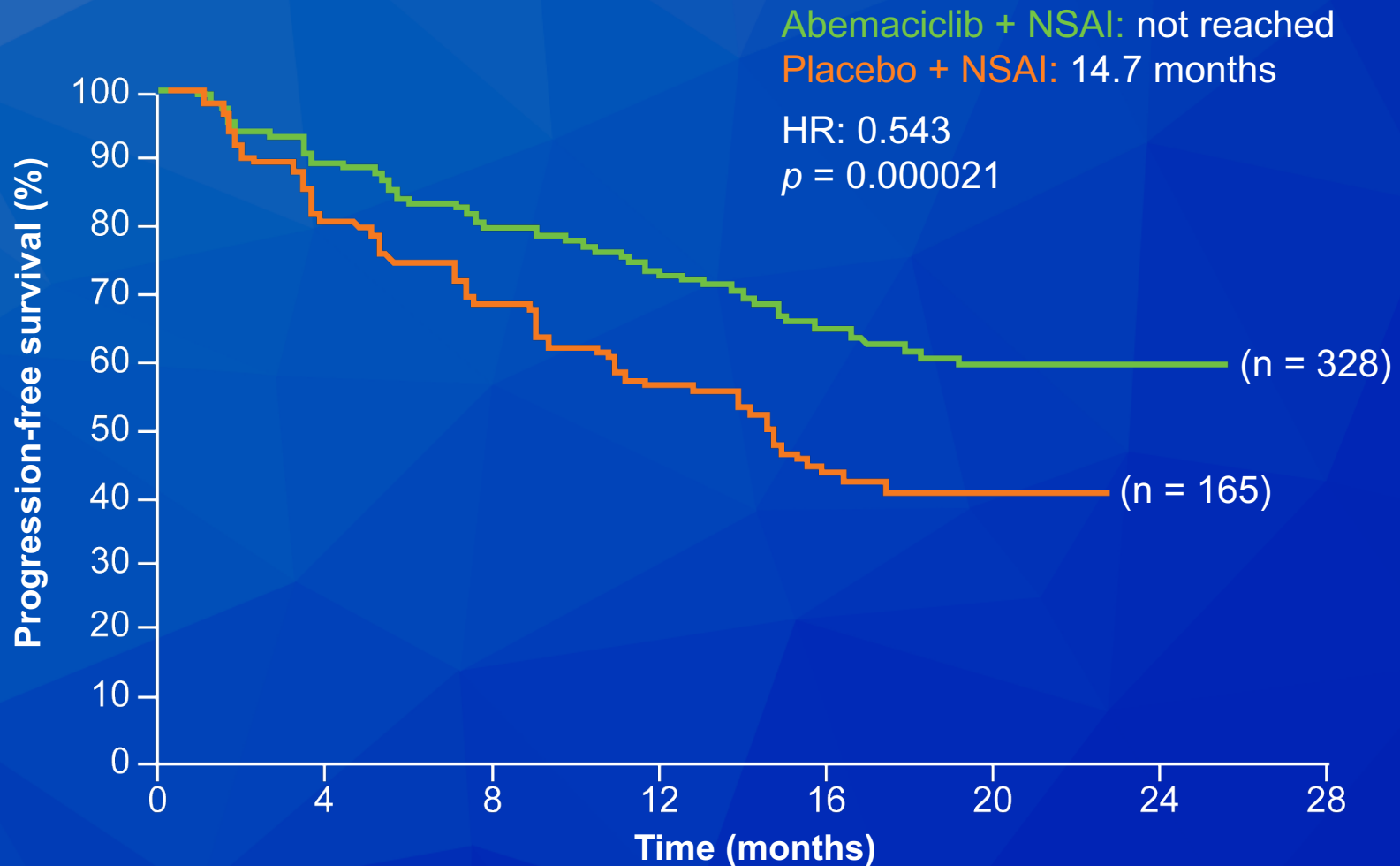


MONARCH 2: PFS with Abemaciclib/Fulvestrant After Disease Progression on Prior ET



- Objective response rate: Abemaciclib arm: 48.1%; placebo arm: 21.3%

MONARCH 3: PFS with Abemaciclib as First-Line Therapy



- Overall response rate: Abemaciclib + NSAID: 59.2%, NSAID: 43.8%

Editorial — Dr O'Shaughnessy

In the MONARCH 2 trial, 669 HR+ MBC patients whose disease had progressed on or within 1 year of adjuvant endocrine therapy were randomized to receive fulvestrant plus the CDK4/6 inhibitor abemaciclib vs fulvestrant plus placebo. 59% of the patients received study therapy as their first-line treatment for MBC. The trial met its primary endpoint, showing a significant improvement in PFS, with median PFS of 16.4 mos vs 9.3 mos in the abemaciclib vs placebo arms, respectively (HR 0.553, 95% CI 0.448-0.681). All the prespecified patient subsets benefited from abemaciclib. The ORR was 48% vs 21% with fulvestrant/abemaciclib vs fulvestrant/placebo. The all-grade diarrhea rate was 86% with 13% grade 3/4 diarrhea.

Editorial — Dr O'Shaughnessy (continued)

Grade 3/4 neutropenia rate was 27%, and the most commonly reported serious adverse event was thromboembolism, which occurred in 2% of the patients. The MONARCH 3 phase III trial was presented at ESMO 2017 and showed that first-line abemaciclib combined with an aromatase inhibitor (AI) greatly improved PFS compared to AI plus placebo in the 493 randomized (2:1) patients. The median PFS with abemaciclib had not been met and was 14.7 mos with AI/placebo, HR 0.543 (95% CI 0.409-0.723). All preplanned patient subgroups benefited from the addition of abemaciclib. Patients who had a treatment-free interval (TFI) of less than 3 years after stopping adjuvant endocrine therapy derived greater benefit from abemaciclib than did those with a longer TFI.

Editorial — Dr O'Shaughnessy (continued)

In addition, patients with liver metastases had greater benefit with the addition of abemaciclib than did patients who did not have liver disease. 19.7% of patients discontinued abemaciclib due to toxicity. The all-grade diarrhea and grade 3/4 rates were 81% and 9.5%, respectively, and the grade 3/4 neutropenia rate was 21%. 4.9% of patients developed a thromboembolic event on the abemaciclib arm.

The MONARCH 2 and MONARCH 3 trials demonstrate that abemaciclib substantially improves PFS in both the first- and second-line HR+ MBC settings, to a comparable degree as has been seen with palbociclib and ribociclib with letrozole first-line and with palbociclib plus fulvestrant second-line.

Editorial — Dr O'Shaughnessy (continued)

Dose reduction of abemaciclib has been demonstrated to reduce the severity of diarrhea, and abemaciclib has less bone marrow toxicity than do palbociclib and ribociclib. The differential benefit of abemaciclib in patients with a short TFI and those with liver metastases suggest that this agent may have greatest clinical utility in patients with more virulent, less endocrine therapy-sensitive metastatic disease.

A phase II trial of the CDK4/6 inhibitor palbociclib (P) as single agent or in combination with the same endocrine therapy (ET) received prior to disease progression, in patients (pts) with hormone receptor positive (HR+) HER2 negative (HER2-) metastatic breast cancer (mBC) (TREnd trial)

Malorni L et al.

Proc ASCO 2017;Abstract 1002.



TREnd: Efficacy of Palbociclib Alone or with Endocrine Therapy (ET)

Outcome	Palbo + ET (n = 57)	Palbo (n = 58)	HR, p
Clinical benefit rate	54%	60%	—
Partial response	10%	7%	
Stable disease	44%	53%	
Median PFS	10.8 mo	6.5 mo	0.69, 0.12

- No complete responses observed
- Median duration of clinical benefit
 - Palbo + ET: 11.5 mo
 - Palbo: 6 mo

Editorial — Dr O'Shaughnessy

At ASCO 2017 Malorni et al presented results of the TREnd randomized phase II trial, which showed that continuing the first- or second-line endocrine therapy on which HR+ MBC patients' disease was progressing and adding palbociclib was more effective than switching to palbociclib alone. 115 patients whose disease was progressing on an AI or fulvestrant were randomized to receive palbociclib alone or palbociclib plus continuation of the same endocrine agent they had been receiving. The primary endpoint, clinical benefit rate, was the same at 54% vs 60% with ET + palbociclib vs palbociclib alone, respectively; however, the duration of response in those who had clinical benefit was 11.5 mos vs 6 mos with ET + palbociclib vs palbociclib alone ($p = 0.021$).

Editorial — Dr O'Shaughnessy (continued)

Continuing the endocrine therapy was particularly effective in prolonging PFS in patients who had been on the prior single-agent endocrine therapy for at least 6 months prior to disease progression, ie, in patients who had had endocrine therapy-sensitive disease.

The authors concluded that the addition of palbociclib to a hormonal therapy could reverse the acquired resistance that the HR+ MBC had developed while on that hormonal agent. Conversely, continuing the endocrine therapy agent did not add to palbociclib's effectiveness in patients whose disease had progressed within 6 months of beginning the endocrine therapy as a single agent.

Editorial — Dr O'Shaughnessy (continued)

Another interpretation could be that continuing the endocrine therapy prolonged the benefit from palbociclib by inhibiting the emergence of resistance due to ER signaling. While provocative, the small overall sample size of the trial and the exploratory subset analysis of PFS in patients with endocrine therapy-sensitive vs resistant disease allows generation of hypotheses that are worthy of further evaluation in a phase III trial. In the meantime, fulvestrant + a CDK4/6 inhibitor remains the standard of care in HR+ MBC patients whose disease is progressing on first-line AI therapy.

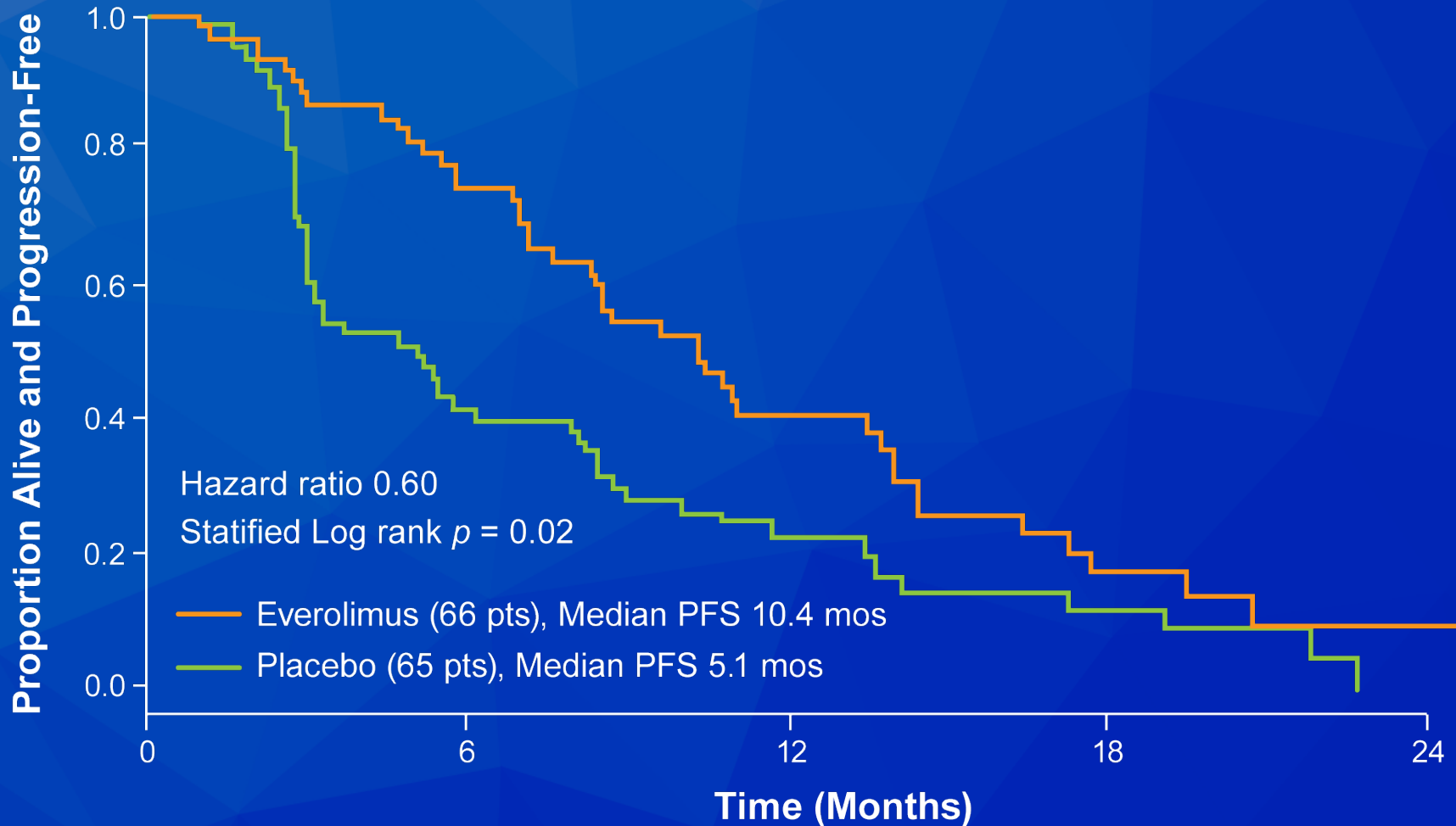
PrECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in post-menopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy

Kornblum N et al.

San Antonio Breast Cancer Symposium
2016;Abstract S1-02.



PrECOG 0102: Progression-Free Survival



Editorial — Dr O'Shaughnessy

In the PrECOG 0102 trial, Kornblum et al showed that inhibiting the PI3K pathway, a common mechanism of resistance to endocrine therapy, with the mTOR inhibitor everolimus substantially improved PFS in combination with fulvestrant compared with fulvestrant plus placebo. 130 pts in the randomized phase II trial had disease that was resistant to prior adjuvant or metastatic AI therapy. The median PFS was 10.4 vs 5.1 mos with fulvestrant/everolimus vs fulvestrant/placebo, HR 0.6, $p = 0.02$.

Editorial — Dr O'Shaughnessy (continued)

Stomatitis was the main toxicity associated with everolimus (which can be greatly ameliorated with the prophylactic use of a steroid mouth rinse for the first 6-8 weeks), and 6% of patients developed grade 3 everolimus-associated pneumonitis and 6% developed grade 3 hyperglycemia.

This is the third randomized trial to show that adding everolimus to an endocrine therapy agent following progression of disease on an AI substantially improves PFS, supporting the hypothesis that the PI3K pathway commonly drives AI resistance. Combining everolimus with either exemestane, fulvestrant or tamoxifen are all now supported by phase III or randomized phase II data.

Editorial — Dr O'Shaughnessy (continued)

The magnitude of benefit obtained with the addition of everolimus to fulvestrant is similar to that observed in the second-line fulvestrant plus CDK4/6 inhibitor (palbociclib or abemaciclib) phase III trials. However, the superior tolerability of the CDK4/6 inhibitors has led to their preferential use in patients whose disease has become resistant to an AI.

Breast Cancer — Drs Rugo and O'Shaughnessy

HER2-Positive Disease

Genomic Assays to Guide Decisions in Early-Stage Breast Cancer

CDK4/6 Inhibitors in Breast Cancer

PARP Inhibitors in Patients with Germline BRCA Mutations and HER2-Negative Disease

Anti-PD-1/PD-L1 Checkpoint Inhibitors

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

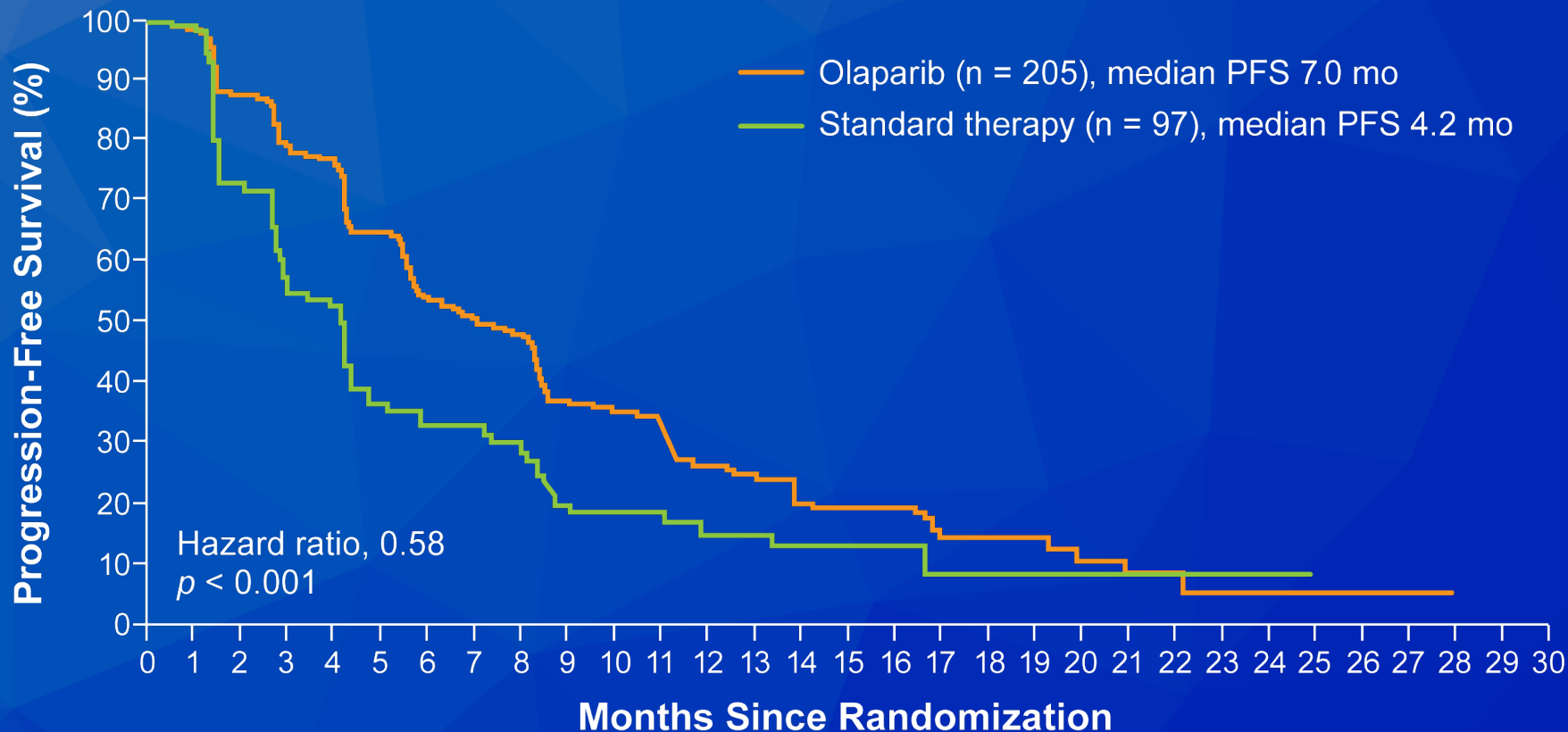
Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delalogue, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D.,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

New Engl J Med 2017;377(6):523-533.

OlympiAD: Further efficacy outcomes in patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician's choice.



OlympiAD: PFS with Olaparib versus Standard Therapy



- Median overall survival: No significant difference between arms (HR 0.9, $p = 0.57$)
- ORR: olaparib (n = 167): 59.9%, standard therapy (n = 66): 28.8%

Robson M et al. *N Engl J Med* 2017;377(6):523-33.

Delaloge S et al. *Proc ESMO* 2017;Abstract 243PD.

OlympiAD: Grade ≥ 3 Adverse Events

Adverse event (AE)	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

Robson M et al. *N Engl J Med* 2017;377(6):523-33.

Robson M et al. *Proc ASCO* 2017;Abstract LBA4 (Plenary).

Editorial — Dr Rugo

The long story of PARP inhibitors for patients with breast cancer associated with a germline mutation in BRCA genes has finally reached the beginning with the results of the OlympiAD trial. After disappointing data in sporadic TNBC and significant bone marrow suppression when olaparib was combined with chemotherapy, this phase III trial in ~300 patients with germline mutations in BRCA1 or 2 and up to 2 prior lines of chemotherapy for metastatic disease demonstrated a doubling of response rate (29% to 60%) and a 42% relative improvement in PFS from 4.2 months with treatment of physicians choice (TPC) to 7 months with olaparib. The impact of olaparib was greater in patients with TNBC compared to those with ER+ disease; prior exposure to platinum without progression did not impact improvement in PFS.

Editorial — Dr Rugo (continued)

Further analysis of subgroups was provided in a poster discussion at ESMO, demonstrating similar efficacy of olaparib compared to TPC across visceral and non-visceral disease and regardless of the number of metastatic sites. Treatment was well tolerated, with nausea as the primary toxicity, and health related quality of life improved with olaparib but deteriorated with TPC. There is no survival difference at 46% data maturity, but even without differences in survival, these data are practice changing. Having a less toxic option for patients with advanced BRCA-associated breast cancer is clearly a step forward. Results from a similar phase III trial with the PARP inhibitor talazoparib are expected in the near future.

Editorial — Dr Rugo (continued)

Future and ongoing studies are evaluating the effect of olaparib as first-line therapy, in combination with immunotherapy, and in the early stage setting (OlympiA trial). One concern with PARP inhibitors is the relatively rapid development of resistance. It may be that combination therapy, or starting treatment earlier in the course of disease, can help to delay or avoid development of resistance. Of note, the dosing used in OlympiAD of 300 mg BID requires 150- or 100-mg tablets (as opposed to 50-mg tablets, which are dosed at 400 mg BID).

Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO)

Turner NC et al.

Proc ASCO 2017;Abstract 1007.



ABRAZO: Efficacy Analysis with Talazoparib

Outcome	Cohort 1* (n = 48)	Cohort 2† (n = 35)	Total (n = 83)
Objective response rate	21%	37%	28%
Median PFS	4.0 mo	5.6 mo	Not reported
Median OS	12.7 mo	14.7 mo	Not reported

* Cohort 1: PR or CR to platinum-based therapy

† Cohort 2: ≥3 platinum-free cytotoxic regimens

- Manageable safety profile: primarily myelosuppression
- 4% discontinued due to drug-related adverse events

Editorial — Dr Rugo

Talazoparib is a highly potent inhibitor of PARP that demonstrated a 50% response rate in 18 patients with BRCA1 or 2 germline mutations in a phase I trial. The ABRAZO trial enrolled patients into two cohorts; cohort 1 with prior response without progression on platinum therapy (48 patients) and cohort 2 with ≥ 3 lines of therapy not including a platinum, with a primary endpoint of ORR (35 patients). ORR was 21% for cohort 1 and 37% in cohort 2 with a median duration of response of 5.8 and 3.8 months respectively. The primary toxicity was modest bone marrow suppression.

Editorial — Dr Rugo (continued)

This exciting data suggests continuing and at least relatively durable responses even in patients with prior exposure to platinum, and we await the results of the phase III EMBRACA trial that also randomized patients with BRCA germline mutations to receive talazoparib or TPC, without prior exposure to platinum.

Select Ongoing Phase III Studies of PARP Inhibitors in Breast Cancer

Study (Setting)	No. of patients	Population	Randomization
OlympiA (Adjuvant)	1,500	gBRCAm, high-risk, HER2- after (neo)adj chemo	<ul style="list-style-type: none"> • Olaparib • Placebo
PARTNER (Neoadjuvant)	527	TNBC or gBRCAm	<ul style="list-style-type: none"> • Olaparib + paclitaxel/carbo • Paclitaxel/carbo
BROCADE (LABC or metastatic)	500	HER2-, gBRCAm	<ul style="list-style-type: none"> • Veliparib + paclitaxel/carbo • Placebo + paclitaxel/carbo
TNBC 3000-03-004 (Advanced)	306	TNBC	<ul style="list-style-type: none"> • Niraparib + anti-PD-1 Ab • Standard of care
EMBRACA (LABC or metastatic)	442	gBRCAm	<ul style="list-style-type: none"> • Talazoparib • Physician's choice of chemo

Carbo = carboplatin; LABC = locally advanced breast cancer; Ab = antibody

Breast Cancer — Drs Rugo and O'Shaughnessy

HER2-Positive Disease

Genomic Assays to Guide Decisions in Early-Stage Breast Cancer

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PARP Inhibitors in Patients with Germline BRCA Mutations and HER2-Negative Disease

Anti-PD-1/PD-L1 Checkpoint Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im,
B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, K. Aogi, H. Iwata, J. Jeong,
A. Kim, K.-H. Park, H. Sasano, Y. Ohashi, and M. Toi

N Engl J Med 2017;376:2147-59.



CREATE-X: Efficacy of Adjuvant Capecitabine

Outcome	Capecitabine	Control	HR <i>p</i> -value
Five-year DFS (ITT)	74.1%	67.6%	HR = 0.70 <i>p</i> = 0.01
TNBC	69.8%	56.1%	HR = 0.58
HR-positive	76.4%	73.4%	HR = 0.81
Five-year OS (ITT)	89.2%	83.6%	HR = 0.59 <i>p</i> = 0.01
TNBC	78.8%	70.3%	HR = 0.52
HR-positive	93.4%	90.0%	HR = 0.73

DFS = disease-free survival; TNBC = triple-negative breast cancer

Editorial — Dr O'Shaughnessy

The CREATE-X trial results have changed the standard of care in that patients with HER2-negative breast cancer who have residual disease in their breast and/or axillary lymph nodes following anthracycline- and/or taxane-based neoadjuvant chemotherapy are being considered for 6 months of post-operative capecitabine therapy. In this phase III trial, Masuda et al randomized 910 patients with residual disease to capecitabine 1,250 mg/m² BID 14 days on then 7 days off for 8 cycles vs no further chemotherapy (endocrine therapy and radiation therapy (given before the capecitabine was initiated) were given per standard of care.

Editorial — Dr O'Shaughnessy (continued)

The primary endpoint of DFS in the ITT population was met with 74% vs 68% of patients remaining disease-free at 3.6 years median follow-up (HR 0.7, 95% CI 0.53 to 0.92, $p = 0.01$) and OS also significantly favoring the addition of capecitabine at 89% vs 84% (HR 0.59, 95% CI 0.39 to 0.90, $p = 0.01$) with capecitabine vs no therapy, respectively. Patients with triple-negative breast cancer (TNBC) had the greatest benefit from capecitabine with DFS rates of 70% vs 59% (HR 0.58, 95% CI 0.39 to 0.87) and OS rates of 79% vs 70% (HR 0.52, 95% CI 0.3 to 0.9) with capecitabine vs no therapy, respectively. Capecitabine-related toxicity was predictable and manageable, and 11.7% of patients had grade 3 hand foot syndrome.

Editorial — Dr O'Shaughnessy (continued)

The CREATE-X trial showed a statistically significant improvement in DFS and OS while several other adjuvant trials of capecitabine had failed to meet their overall DFS primary endpoint, potentially because CREATE-X enrolled a higher-risk population who were at very elevated risk for rapid recurrence, especially the TNBC patients. The addition of adjuvant capecitabine following preoperative chemotherapy and surgery in patients who have not obtained a pCR has become the standard of care in TNBC and high-risk HR+ patients. A meta-analysis of all the adjuvant capecitabine trials that have been performed is planned.

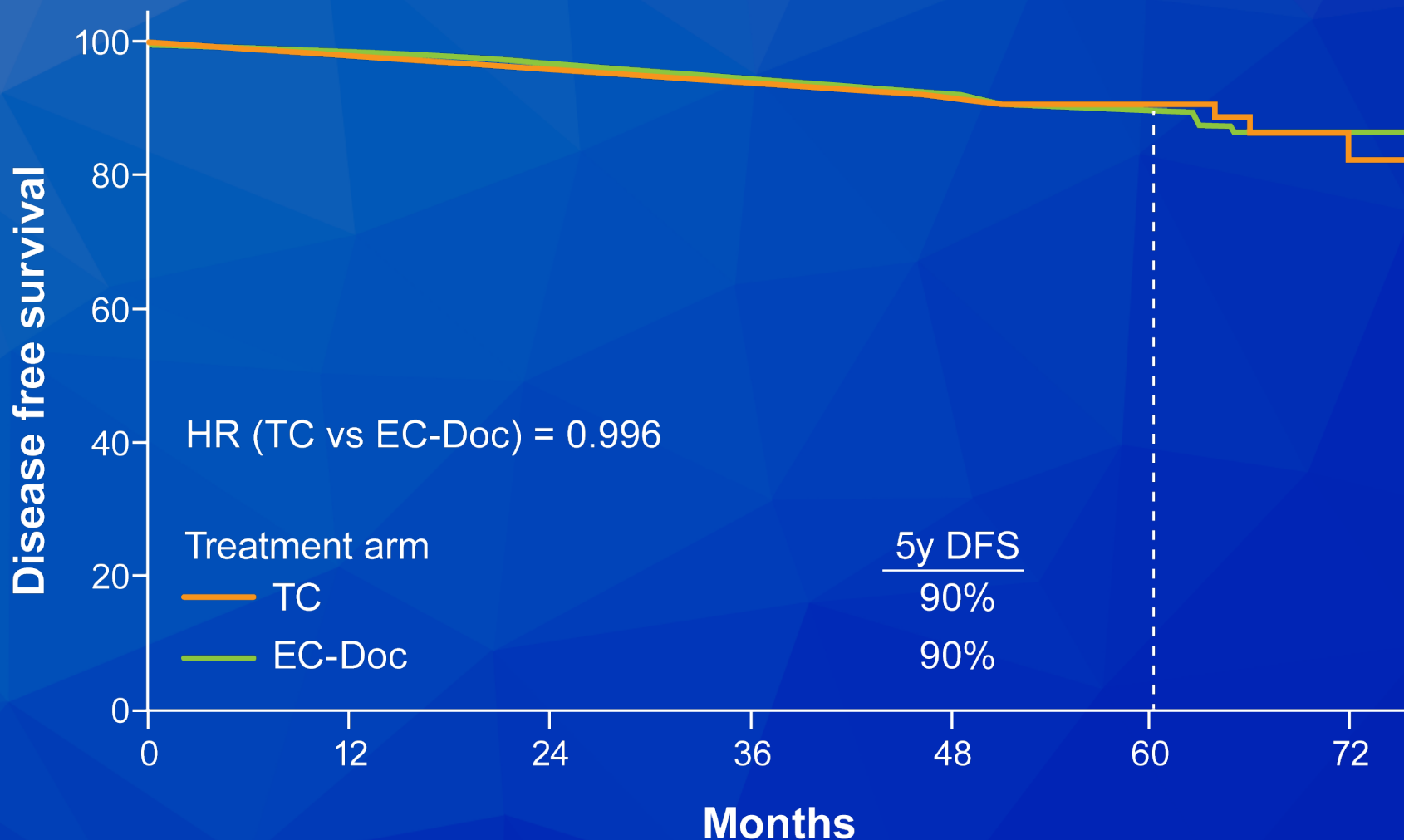
Prospective WSG phase III PlanB trial: Final analysis of adjuvant 4xEC → 4x doc vs 6x docetaxel/cyclophosphamide in patients with high clinical risk and intermediate-to-high genomic risk HER2-negative, early breast cancer

Harbeck N et al.

Proc ASCO 2017;Abstract 504.



PlanB: Disease-Free Survival by Chemotherapy Arm



- OS (5-y): TC: 95%; EC-Doc: 95% (HR = 0.94)

Editorial — Dr O'Shaughnessy

The West German Study Group PlanB trial evaluated the role of adjuvant anthracyclines when added to a taxane and cyclophosphamide (TC) in node-positive and node-negative, *Oncotype* DX Recurrence Score[®] (RS) >11 early stage breast cancer patients. 2,449 patients were randomized to 6 cycles of docetaxel/cyclophosphamide (Arm A) vs 4 cycles of epirubicin/cyclophosphamide followed by 4 cycles of docetaxel (Arm B). At a median follow-up of 5 years, there was no difference in DFS or OS between the 2 trial arms, including in TNBC, higher RS and 4+ node patient subgroups. Treatment-related deaths occurred in 0.4% vs 0.1% of patients in Arms A and B, respectively.

Editorial — Dr O'Shaughnessy (continued)

The results of this trial suggest that anthracyclines do not improve outcome when added to TC in high-risk node-negative or positive HER2-negative patients and contradict those of the recently reported ABC trials, which showed that TNBC patients and HR+ patients with 4+ nodes had a significantly improved DFS with the addition of doxorubicin to a taxane/cyclophosphamide regimen. The discordant results are believed to have occurred because the ABC trials enrolled a greater proportion of TNBC and node-positive patients than did the PlanB trial, and because these higher risk patients benefited disproportionately from the addition of the anthracycline. Based on the results of the ABC trials, anthracyclines remain the standard of care as neo/adjuvant therapy for higher-risk TNBC and node-positive patients.

Have you or would you use an anti-PD-1/anti-PD-L1 antibody in a patient with breast cancer outside of a clinical trial setting?

- a. I have
- b. I have not, but I would for the right patient
- c. I have not and would not

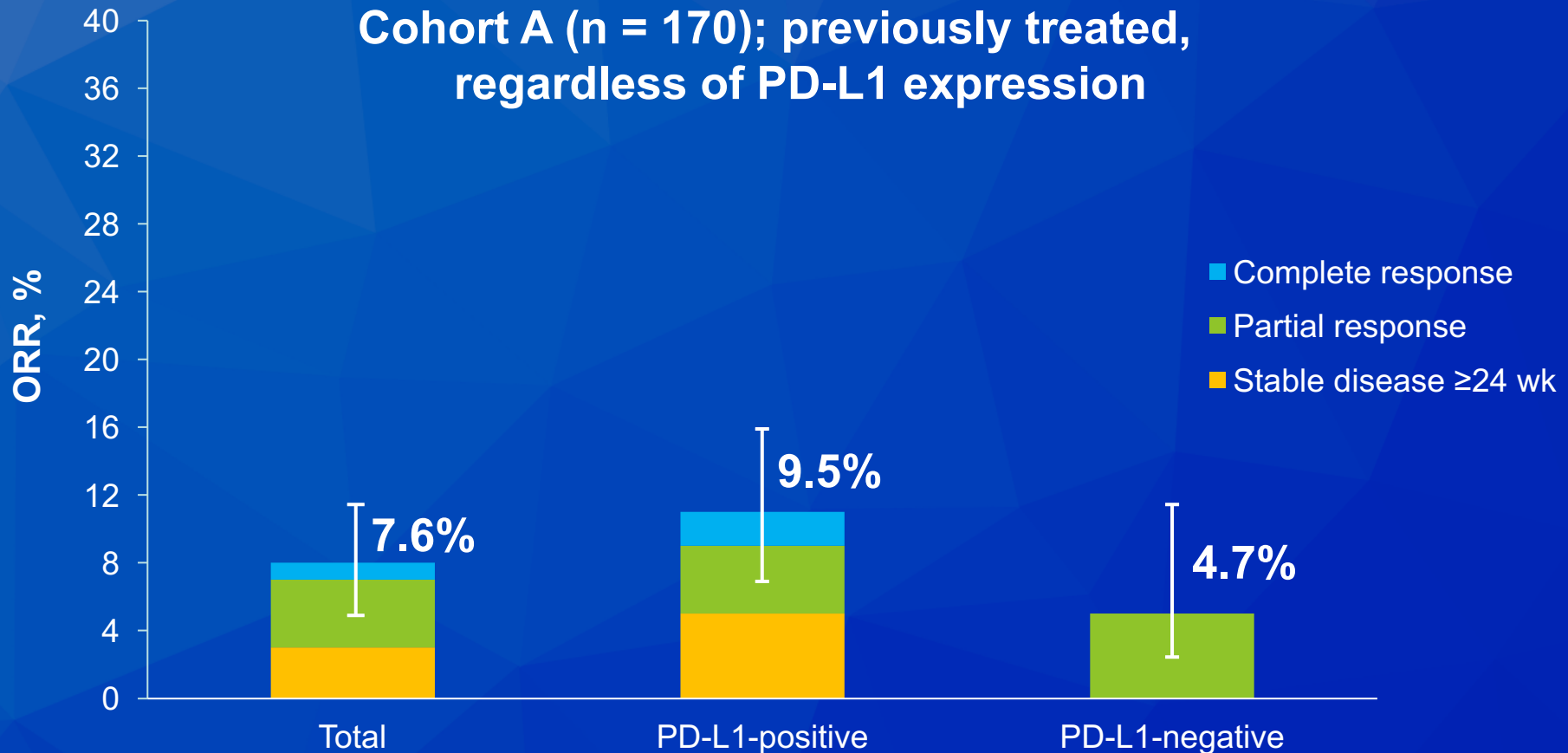
**Phase 2 study of pembrolizumab
monotherapy for previously treated
metastatic triple-negative breast cancer:
KEYNOTE-086 cohort A**

Adams S et al.

Proc ASCO 2017;Abstract 1008.



KEYNOTE-086: Response Rates



- Median overall survival
 - All patients: 8.9 mo
 - Patients with CR/PR or SD: not reached

Atezolizumab in metastatic TNBC (mTNBC): Long-term clinical outcomes and biomarker analyses

Schmid P et al.

Proc AACR 2017;Abstract 2986.



Atezolizumab for Metastatic TNBC

Outcome	All patients	Atezo as first line	Atezo after ≥ 2 lines of therapy
ORR (n = 112, 19, 93)	10%	26%	7%
Median duration of response	21 mo	21 mo	Not evaluable
OS rate (n = 113, 19, 94)			
1-year	41%	63%	37%
3-year	22%	Not evaluable	18%

Editorial — Dr O'Shaughnessy

In the KEYNOTE-086 trial, in Cohort A (n=170), metastatic TNBC patients who had been previously treated with chemotherapy in the metastatic setting were treated with single agent pembrolizumab (pembro) 200 mg IV every 3 weeks. The objective response rate (ORR) in this phase II trial was low at 5%, regardless of PD-L1 expression; 5% of patients were still on pembro 10+ mos after beginning therapy. Patients who had lower LDH levels and non-visceral disease had a higher ORR than the overall population. Patients who responded to or had stable disease with pembro had a substantially greater OS than those whose disease rapidly progressed on pembro.

Editorial — Dr O'Shaughnessy (continued)

In the Cohort B patients (n = 52), who had not received chemotherapy in the metastatic setting and whose disease was PD-L1-positive, the ORR with pembro was 23%. There were very few grade 3/4 immune-related toxicities (1.2%) observed in this study, and pembro was well tolerated.

The Phase Ia TNBC expansion cohort of single agent atezolizumab (atezo) enrolled 112 response-evaluable metastatic TNBC patients receiving first, second or third+ line therapy regardless of PD-L1 status. The ORR was 26% in first, 4% in second and 8% in third+ line patients, and obtaining a response or stable disease was associated with improved OS compared with patients whose disease rapidly progressed.

Editorial — Dr O'Shaughnessy (continued)

Median duration of response was impressive at 21 mos. Predictive factors for benefit from atezo included no prior chemotherapy for metastatic disease, having more than 10% of the tumor bed containing tumor-infiltrating T cells (TILs) and CD8+ cells, and to a lesser extent, PD-L1 expression. Atezo was well tolerated overall. 11% of patients developed a grade 3/4 immune-related adverse event, and 2 patients had treatment-related death.

The single-agent, single-arm trials of pembro and atezo in metastatic TNBC patients showed similar findings: that a proportion of patients will obtain highly durable responses with the checkpoint inhibitors (CPIs), that obtaining an objective response or stable disease is associated with improved OS, and that first-line metastatic TNBC patients are more likely to benefit from these agents.

Editorial — Dr O'Shaughnessy (continued)

Prior chemotherapy for metastatic disease, high LDH or liver metastases predicted for lack of benefit from pembro and atezo. The extent of TIL infiltration is emerging as a better predictor of benefit from CPIs than PD-L1 expression. Both pembro and atezo are being evaluated in phase III trials comparing chemotherapy alone vs chemotherapy plus a CPI in first-line metastatic TNBC patients, as well as in combination with chemotherapy in the neoadjuvant and adjuvant TNBC settings.