Year in Review

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

Saturday, February 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Research To Practice®

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Disclosures

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Disclosures

Contracted Research	Amgen Inc, Bayer HealthCare Pharmaceuticals, BioMarin, Boehringer Ingelheim Pharmaceuticals Inc, Cascadian Therapeutics, Dignitana, Genentech BioOncology, GlaxoSmithKline, Lilly, Medivation Inc, a Pfizer Company, Merrimack Pharmaceuticals Inc, Novartis, OBI Pharma Inc, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc, Seattle Genetics
Paid Travel	Bayer HealthCare Pharmaceuticals, Lilly, Novartis, OBI Pharma Inc

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 Burstein and Hurvitz

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

Novel Investigational Agents

FDA grants regular approval to pertuzumab for adjuvant treatment of HER2-positive breast cancer

Press Release — December 20, 2017

"On December 20, 2017, the Food and Drug Administration granted regular approval to pertuzumab for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Approval was based on data from APHINITY (NCT01358877), a multicenter, randomized, double-blind, placebo-controlled trial in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm590005.htm

The NEW ENGLAND JOURNAL of MEDICINE

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

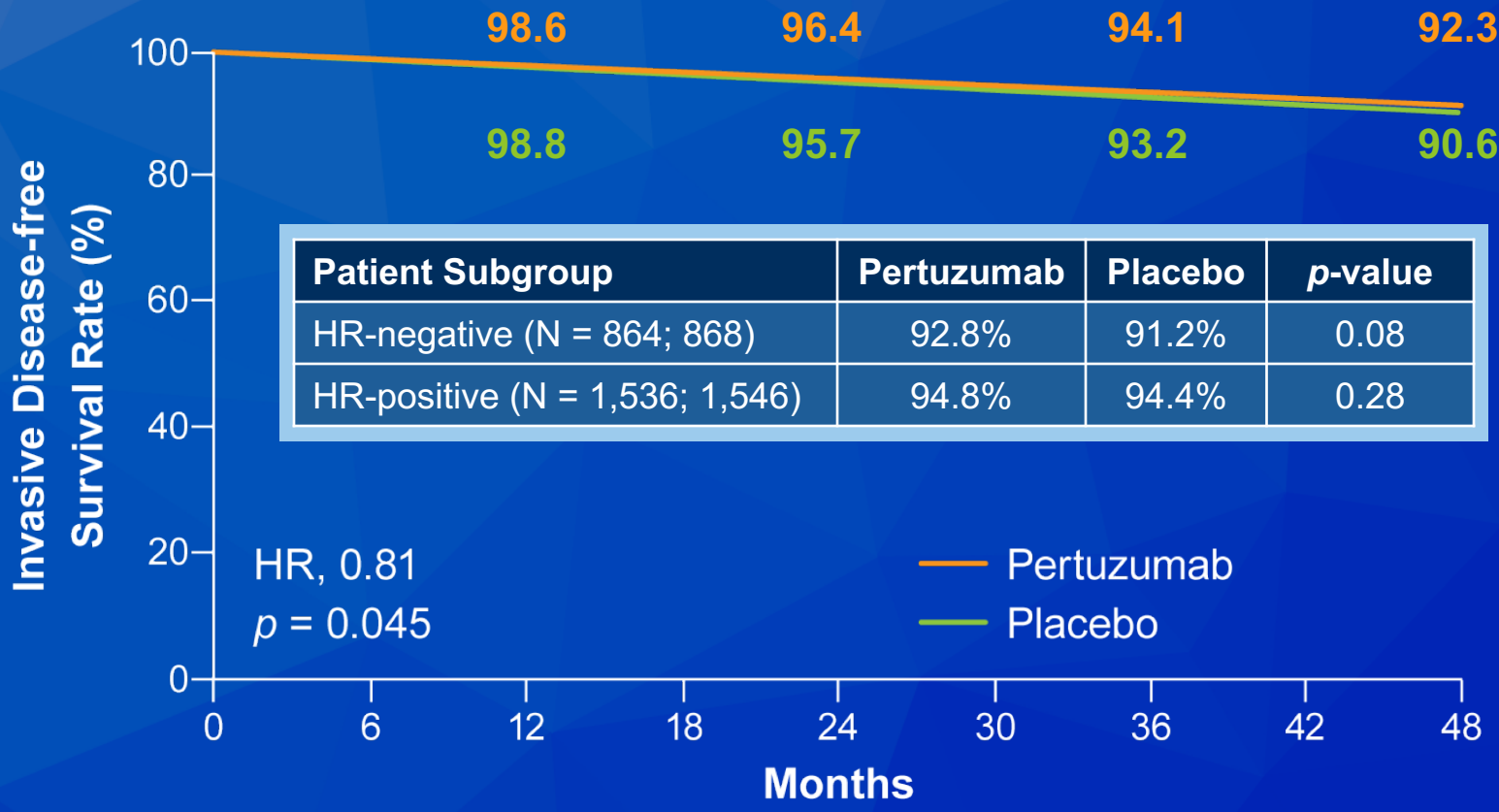
Gunter von Minckwitz, M.D., Marion Procter, Ph.D., Evandro de Azambuja, M.D., Dimitrios Zardavas, M.D., Mark Benyunes, M.D., Giuseppe Viale, M.D., Thomas Suter, M.D., Amal Arahmani, Ph.D., Nathalie Rouchet, M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D., Istvan Lang, M.D., Christelle Levy, M.D., Denise 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).

Von Minckwitz G et al. *Proc ASCO* 2017;Abstract LBA500.

APHINITY: Invasive Disease-Free Survival

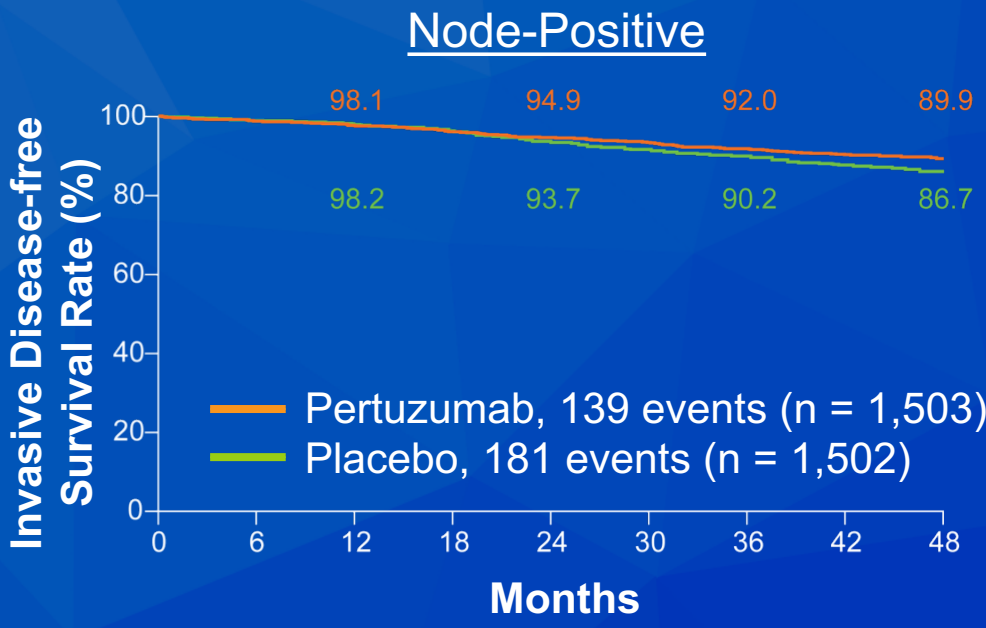


Patient Subgroup	Pertuzumab	Placebo	*p*-value
HR-negative (N = 864; 868)	92.8%	91.2%	0.08
HR-positive (N = 1,536; 1,546)	94.8%	94.4%	0.28

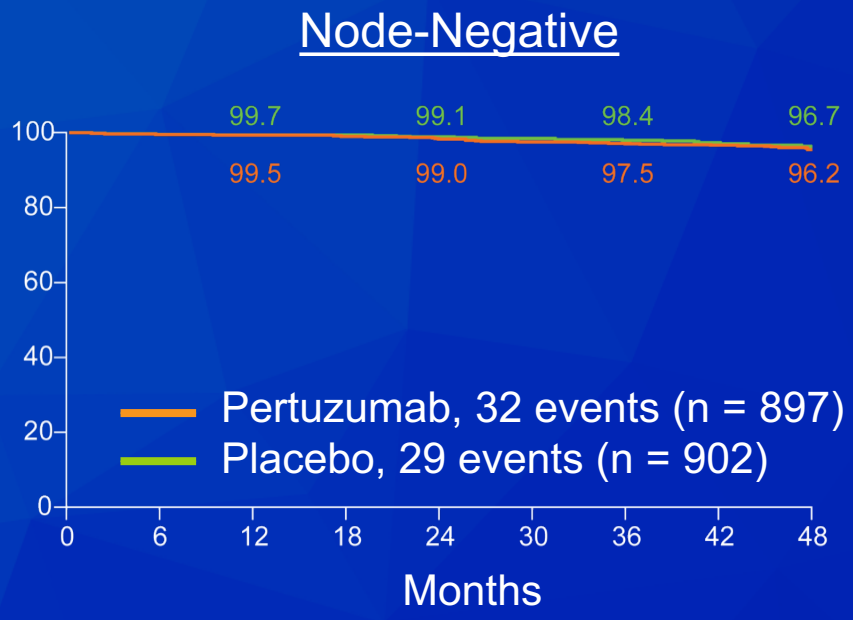
- Patients with node-positive or hormone receptor-negative disease derived the most benefit from pertuzumab
- Overall survival: no significant difference between arms (HR 0.89, $p = 0.47$)

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



Unstratified hazard ratio, 0.77
P = 0.02



Unstratified hazard ratio, 1.13
P = 0.64

Von Minckwitz G et al. *N Engl J Med* 2017;372(2):122-31.

APHINITY: Safety Summary

	Pertuzumab n = 2,364	Placebo n = 2,405
Grade ≥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%

Von Minckwitz G et al. *N Engl J Med* 2017;372(2):122-31.

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-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 Ejlertsen, 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**

Martin M et al. *Lancet Oncol* 2017;18(12):1688-1700.

ExteNET Phase III Schema

Accrual: 2,840

Eligibility

- HER2-positive breast cancer
- Prior adjuvant trastuzumab and chemotherapy
- Lymph node-positive disease* or invasive disease after neoadjuvant therapy
- ER/PR-positive or negative

R

(1:1)

Neratinib x 1 year 240 mg/day

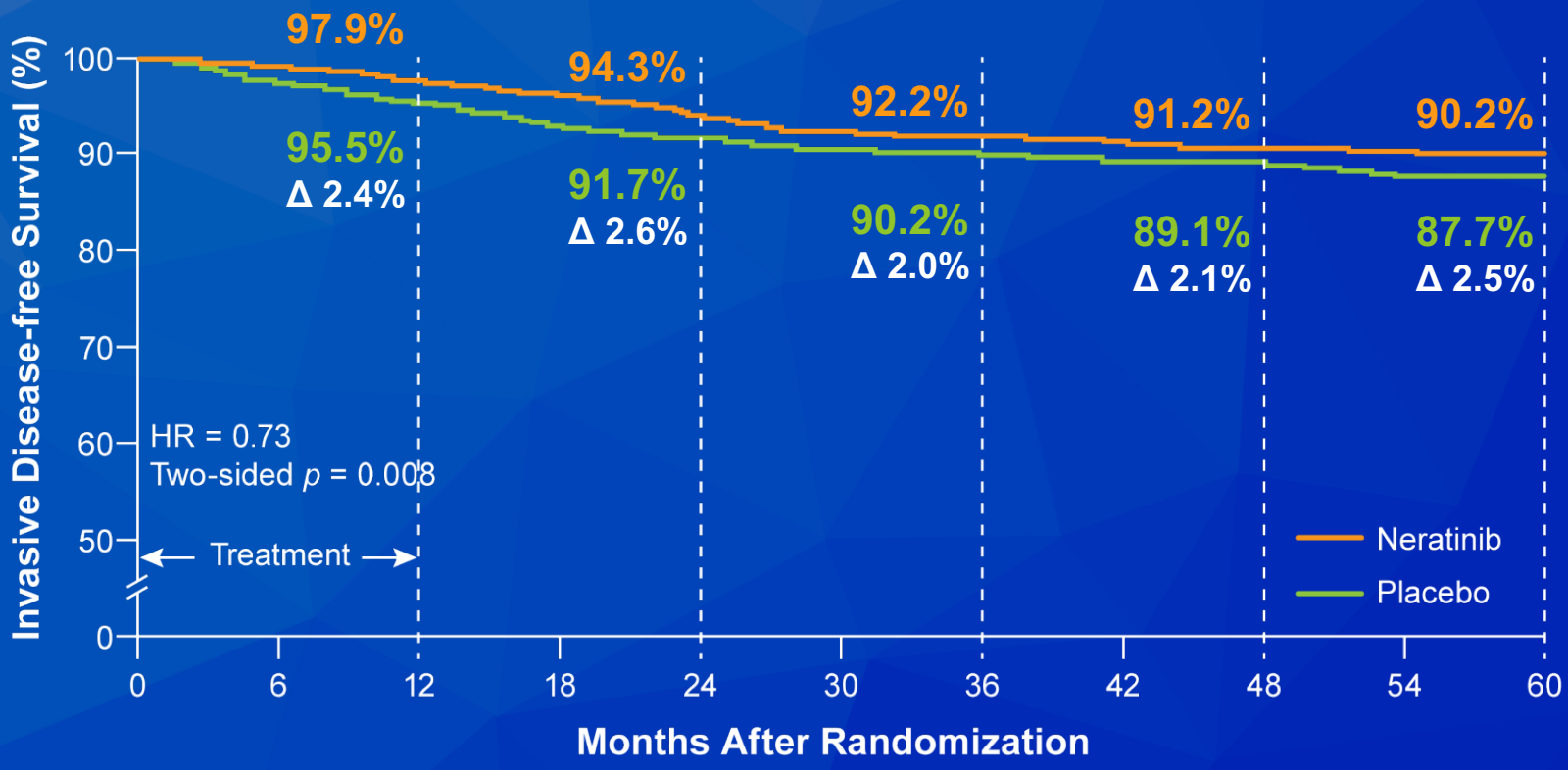
Placebo x 1 year

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

Primary endpoint: Invasive disease-free survival

Martin M et al. *Lancet* 2017;18(12):1688-1700; *Proc ESMO* 2017;Abstract 149O.

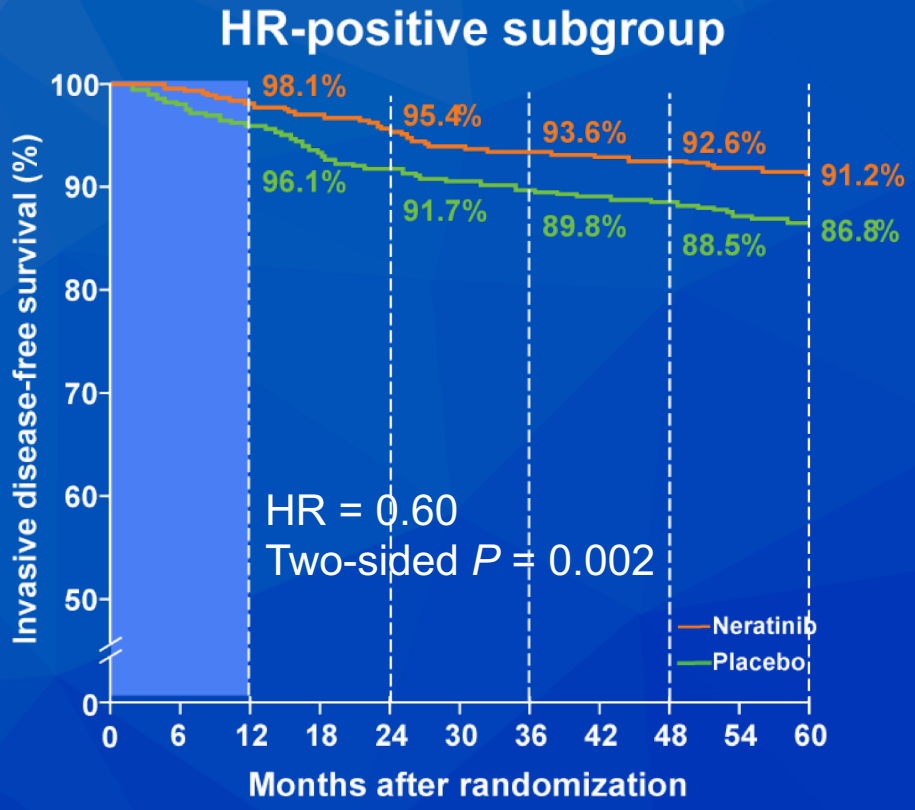
ExteNET: 5-Year Invasive Disease-Free Survival

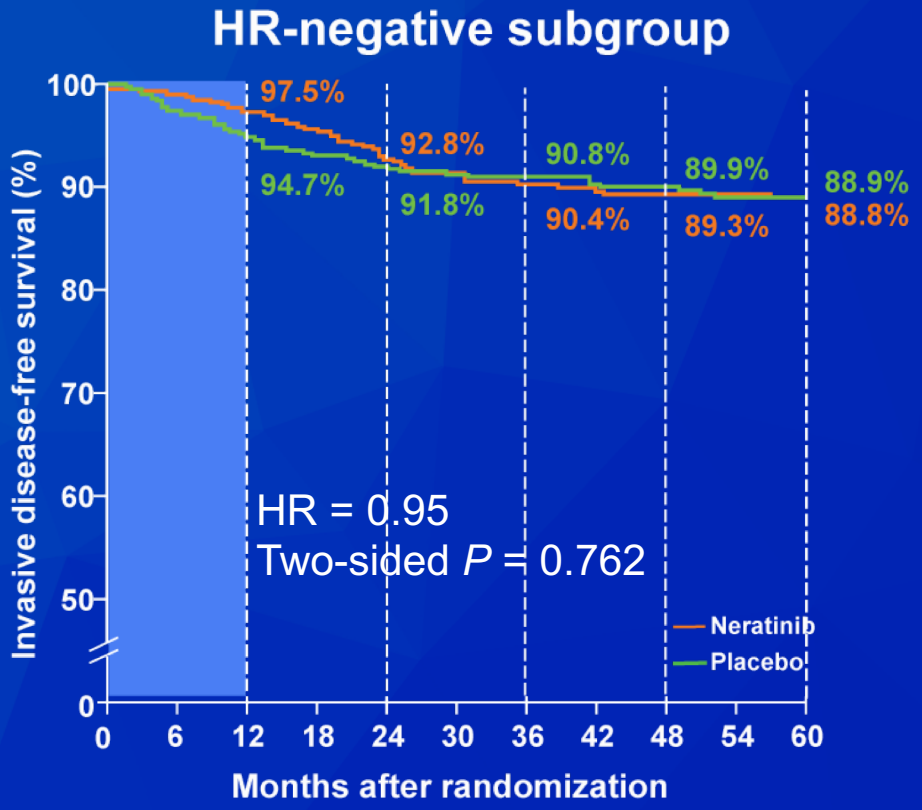


- HR-positive cohort: 4.4% absolute benefit (HR = 0.6, $p = 0.002$)
- No evidence of long-term toxicity with neratinib versus placebo or late-term consequences of neratinib-associated diarrhea

Martin M et al. *Lancet* 2017;18(12):1688-1700; *Proc ESMO* 2017;Abstract 149O.

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





Martin M et al. *Lancet* 2017;18(12):1688-1700; *Proc ESMO* 2017;Abstract 149O.

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

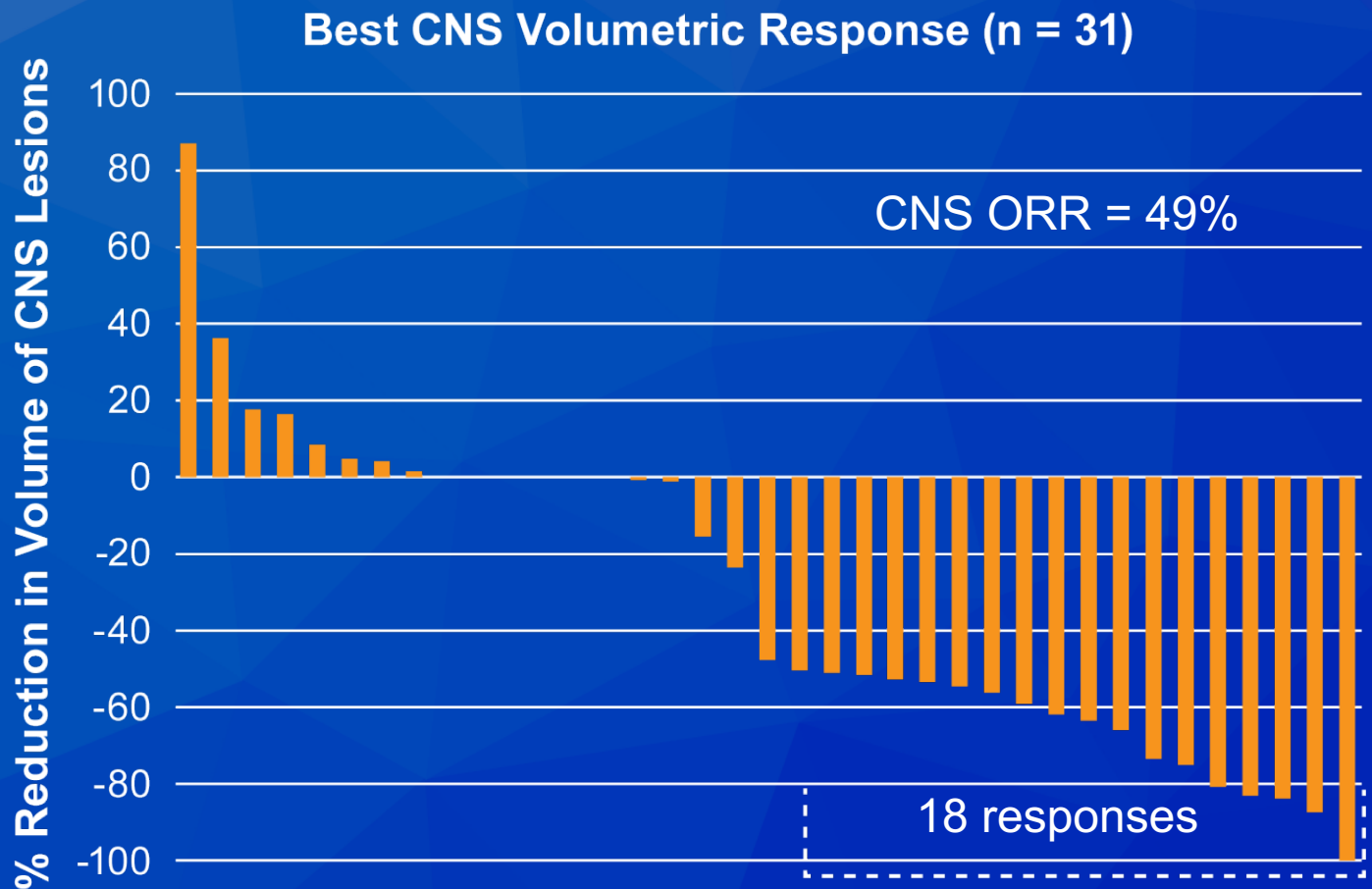
* Progression-free survival

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 Martin M et al. *Lancet* 2017;18(12):1688-1700; *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



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

Freedman R et al. *Proc ASCO* 2017;Abstract 1005.

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/m^2 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)

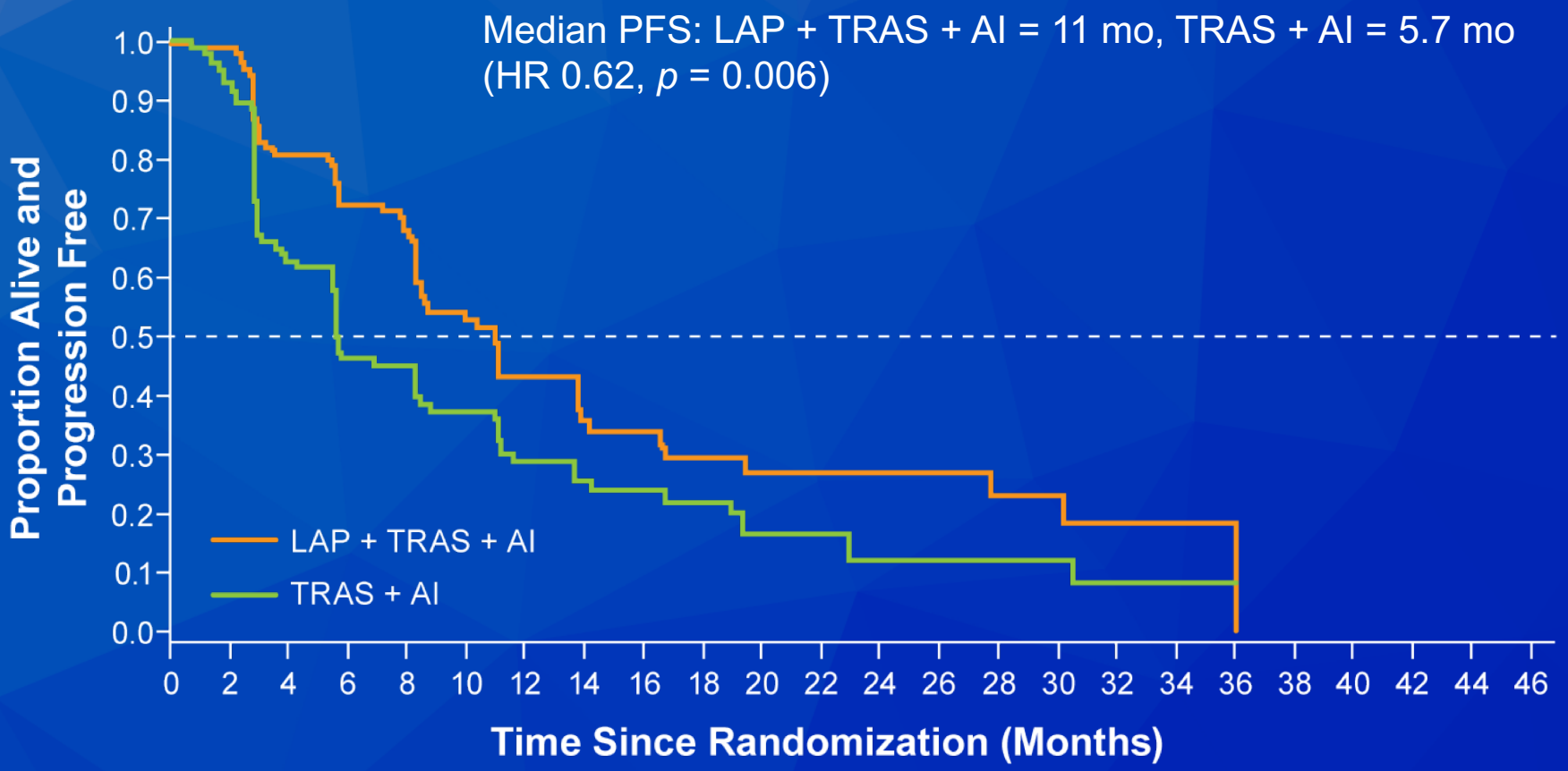
Six-month PFS was 38%, and median TTP was 5.5 months with 51% of patients staying on therapy for at least 6 cycles. As we have seen with other neratinib trials, grade 3 diarrhea was frequent, although prophylactic anti-diarrheal therapy was not routinely used. Correlative studies are pending.

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)

Gradishar W et al. *Proc ASCO* 2017;Abstract 1004.

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 Burstein and Hurvitz

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

Novel Investigational Agents

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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.

Krop I et al. *J Clin Oncol* 2017;35(24):2838-47.

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.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of 70-Gene Signature Use on Adjuvant Chemotherapy Decisions in Patients With Estrogen Receptor–Positive Early Breast Cancer: Results of a Prospective Cohort Study

Anne Kuijer, Marieke Straver, Bianca den Dekker, Annelotte C.M. van Bommel, Sjoerd G. Elias, Carolien H. Smorenburg, Jelle Wesseling, Sabine C. Linn, Emiel J.Th. Rutgers, Sabine Siesling, and Thijs van Dalen

J Clin Oncol 2017;35(24):2814-9.

Impact of the 70-Gene Signature (GS) in Adjuvant Chemotherapy (CT) Decision Making

Preliminary Rec	Post test Rec		Adherence to results*	Actual Admin of CT		Adherence to results*
	No CT	CT		No	Yes	
No CT (n = 107)	65%	35%	94%	68%	32%	91%
CT (n = 270)	58%	42%	97%	60%	40%	90%
Unsure (n = 283)	61%	39%	95%	65%	35%	91%

Rec = Recommendation; Admin = administration

* % of pts in whom the posttest rec/actually administered CT was in line with the 70-GS test result (ie, no CT in pts with a low-risk profile and CT in pts with a high-risk profile).

- Out of 377 patients, there was a change in CT rec in 51% (p = 0.001) of pts who had a clear pretest CT rec (i.e. yes or no CT).
- Actually administered CT differed from the preliminary CT rec in 52% (p = 0.001) of pts who had a clear pretest CT rec.

Kuijer A et al. *J Clin Oncol* 2017;35(24):2714-9.

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

Harry D. Bear MD, PhD[1] | Wen Wan PhD[1] | André Robidoux MD[2] | Peter Rubin MD[3] | Steven Limentani MD[4] | Richard L. White Jr MD[4] | James Granfortuna MD[3] | Judith O. Hopkins MD[5] | Dwight Oldham MD[6] | Angel Rodriguez MD[7] | Amy P. Sing MD[8]

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

Bear H et al. *J Surg Oncol* 2017;115(8):917-23.

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.

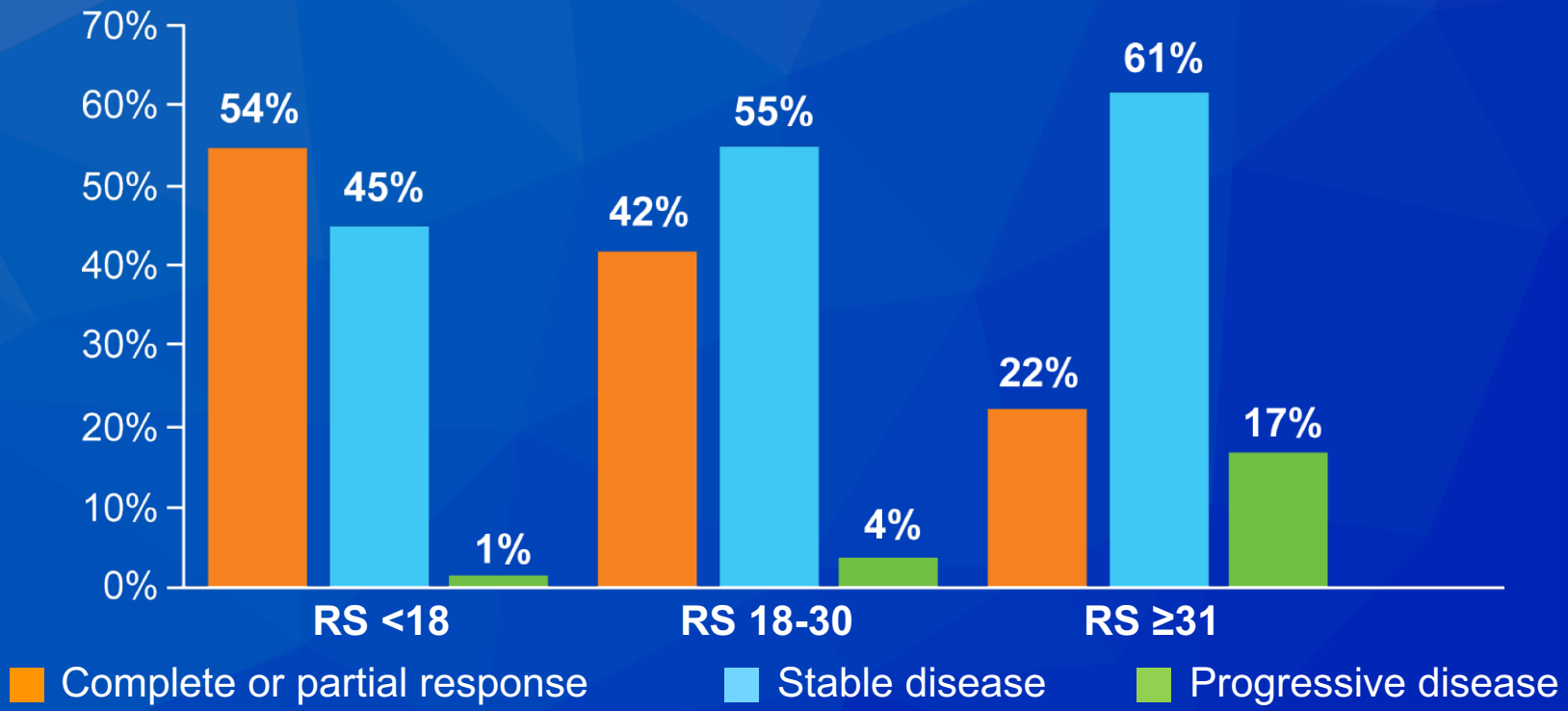
Editorial — Dr Rugo (continued)

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.

TransNEOS: Validation of the Oncotype DX Recurrence Score Testing Core Needle Biopsy Samples from NEOS as Predictor of Clinical Response to Neoadjuvant Endocrine Therapy for Postmenopausal ER+, HER2-Negative Breast Cancer Patients

Yamamoto Y et al.
San Antonio Breast Cancer Symposium 2017;Abstract PD5-03.

TransNEOS: Response to Neoadjuvant Hormonal Therapy by RS Group



Clinical response, n	RS <18	RS 18-30	RS ≥31	Total
CR + PR	85	35	12	132
SD	70	46	33	149
PD	1	3	9	13
Total	156	84	54	294

Yamamoto Y et al. San Antonio Breast Cancer Symposium 2017;Abstract PD5-03.

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)

Jasem J et al. *JNCCN* 2017;15(4):494-503.

Breast Cancer — Drs Burstein and Hurvitz

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

Novel Investigational Agents

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 *Lancet Oncol* 2015; Finn ASCO 2017) PALOMA-2 (Finn *NEJM* 2016) PALOMA-3 (Cristofanilli *Lancet Oncol* 2016)	• 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
Ribociclib (3-13-17)	MONALEESA-2 (Hortobagyi *NEJM* 2016)	• 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 *Clin Cancer Res* 2017) MONARCH 2 (Sledge *JCO* 2017)	• 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

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

ORIGINAL ARTICLE

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

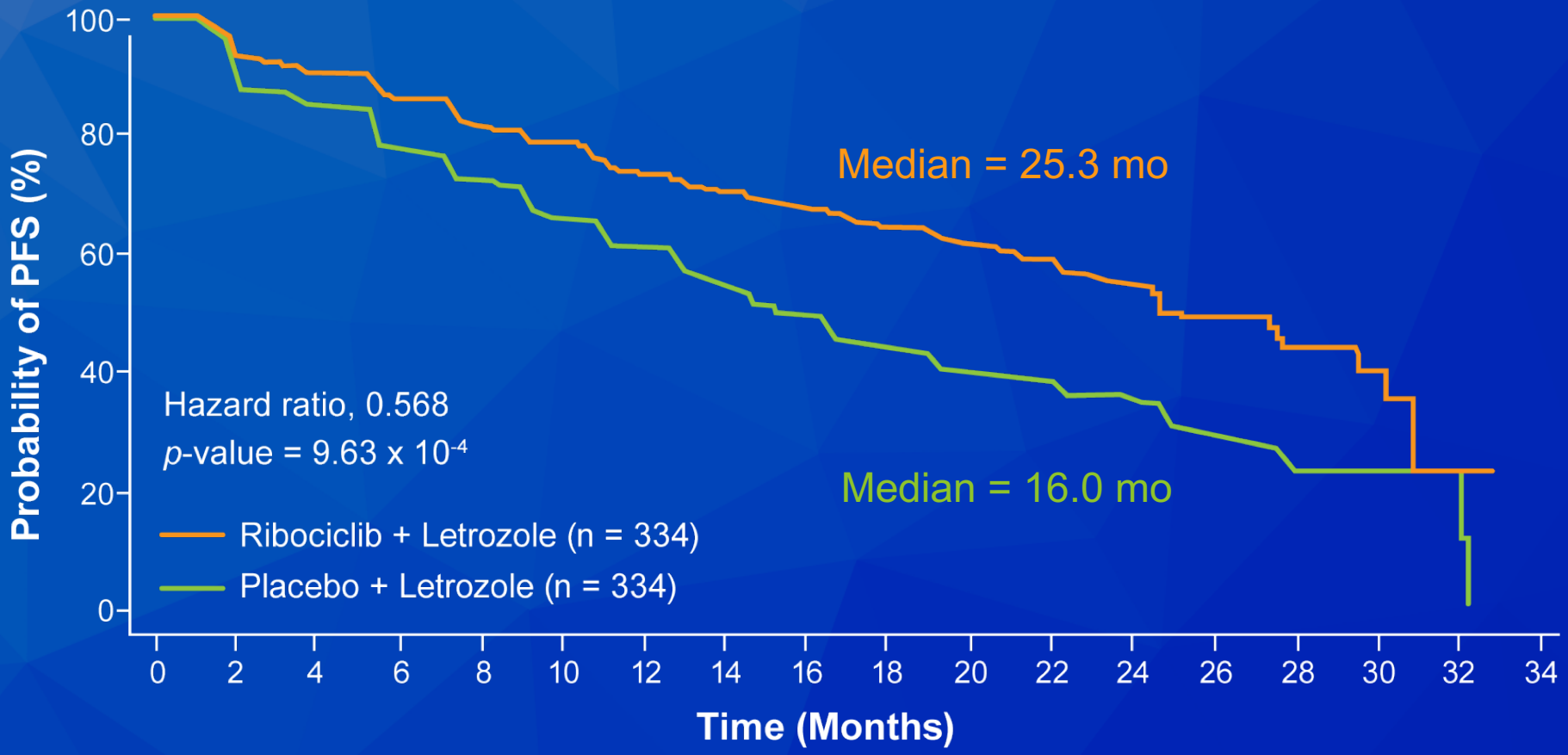
G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, 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).

Proc ASCO 2017;Abstract 1038.

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

Hortobagyi GN et al. *Proc ASCO* 2017;Abstract 1038.

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%

Hortobagyi GN et al. *N Engl J Med* 2016;375:1738-48.

Editorial — Dr Burstein

These are the updated results from the MONALEESA-2 trial, a study of first-line endocrine therapy for ER positive metastatic breast cancer comparing letrozole alone against letrozole in combination with the CDK4/6 inhibitor ribociclib. As with the original report from this trial (see Table 1), adding ribociclib to letrozole improved progression free survival. This finding has been very consistent for each of the 3 FDA-approved CDK4/6 inhibitors in ER+ breast cancer (see Table 1).

Editorial — Dr Burstein (continued)

Table 1. Randomized trials of endocrine therapy +/- CDK4/6 inhibition

Line	Trial	Schema	HR compared with endocrine alone
1st	PALOMA-1	Letrozole +/- palbociclib	0.49
	PALOMA-2	Letrozole +/- palbociclib	0.58
	MONALEESA-2	Letrozole +/- ribociclib	0.56
	MONARCH 3	Letrozole or anastrozole, +/- abemaciclib	0.54
2nd	PALOMA-3	Fulvestrant +/- palbociclib	0.46
	MONARCH 2	Fulvestrant +/- abemaciclib	0.55

Editorial — Dr Burstein (continued)

An important critique of the CDK4/6 inhibitor trials is that, to date, while the drugs have each shown a benefit with respect to disease-free survival, there has been no reported improvement in overall survival. The update for MONALEESA-2 is important because it shows the most mature survival results so far, and there is an intriguing numerical reduction in deaths in the combination arm, which is nearing statistical significance (15% vs 20% deaths; HR 0.746, $p = 0.059$). These results are encouraging for two reasons. First, given the 12+ month improvement in PFS with CDK4/6 inhibitors, it would be nice to see an emerging survival benefit. Secondly, in the climate of greater emphasis on value-based care, a survival advantage argues that the drugs are more valuable, which may affect regulatory approval in many parts of the world.

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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.

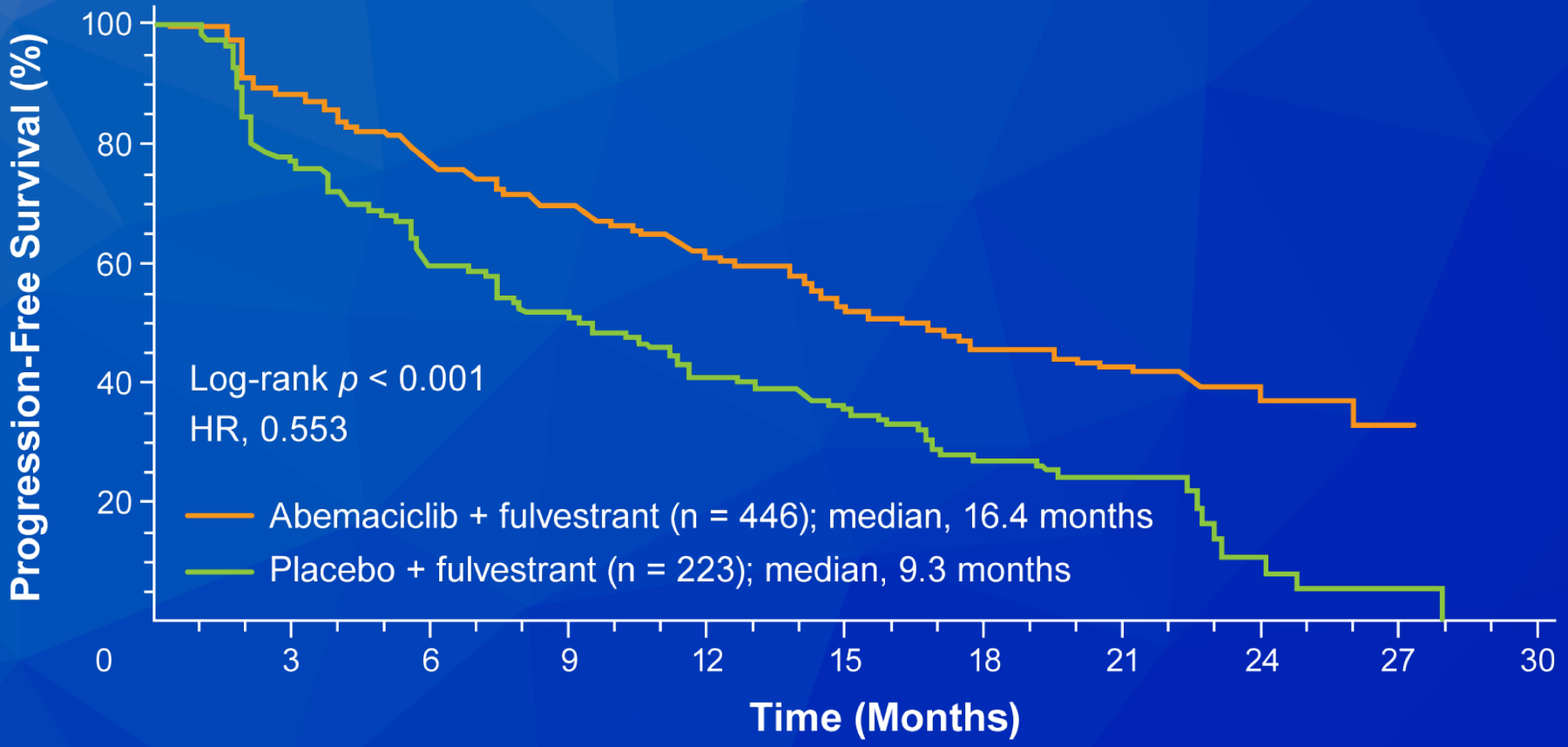
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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].

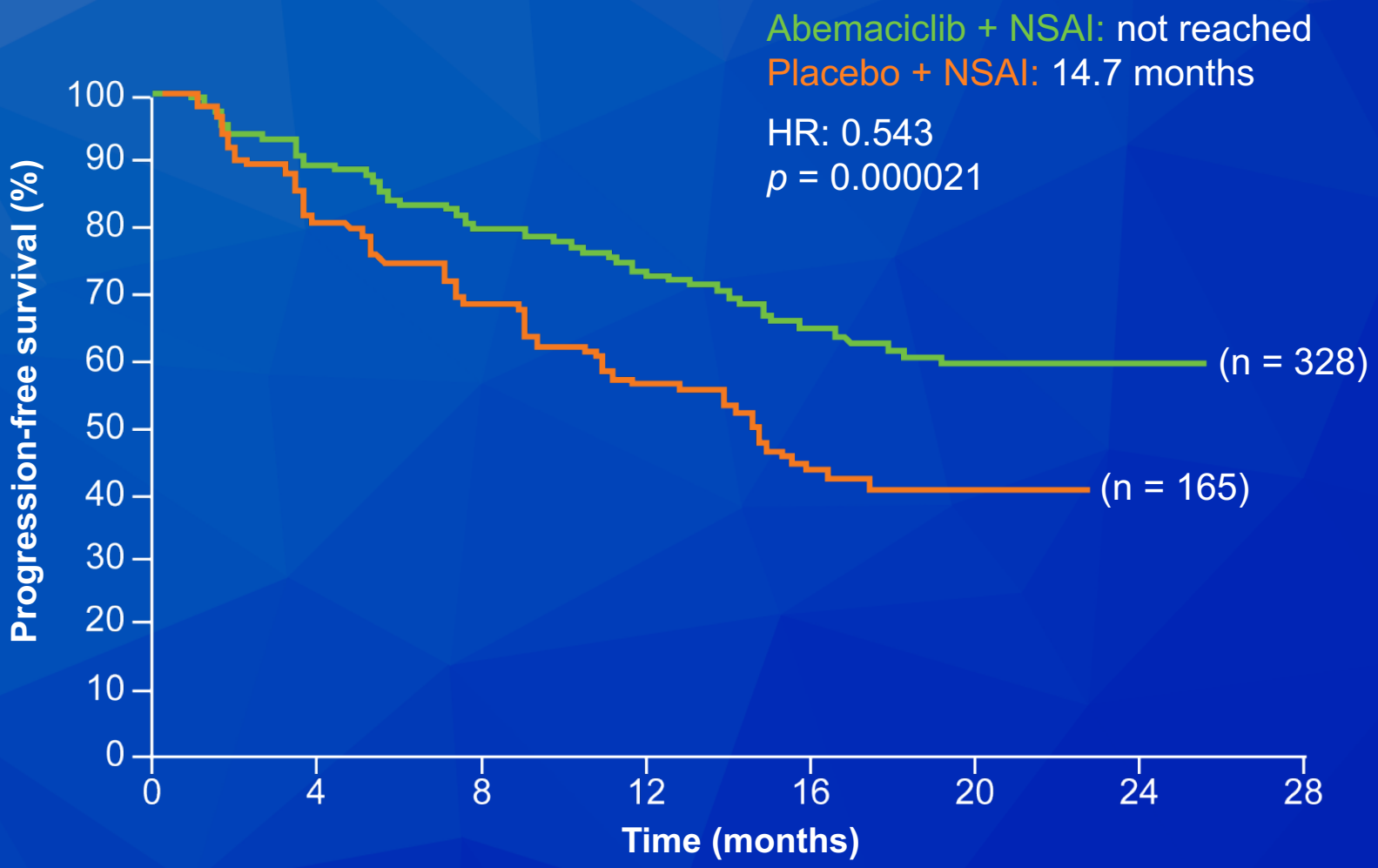
MONARCH 2: PFS with Abemaciclib/Fulvestrant After Disease Progression on Prior ET



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

Sledge G et al. *J Clin Oncol* 2017;35(25):2875-84.

MONARCH 3: PFS with Abemaciclib as First-Line Therapy



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

Goetz MP et al. *J Clin Oncol* 2017;[Epub ahead of print].

Editorial — Dr Burstein

CDK4/6 inhibitors have transformed treatment of ER-positive metastatic breast cancer in recent years. Based on preclinical studies showing synergy with anti-estrogen treatments and activity in ER+ breast cancer cell lines, pharmaceutical companies have developed these agents alongside existing endocrine treatments for ER+ MBC. There are now data from randomized trials in 1st or 2nd line endocrine therapy for each of the three commercially available CDK4/6 inhibitors (see Wander, et al. JCO 2017;35:2866 for discussion).

The three agents differ slightly in dosing and side effects. Palbociclib and ribociclib are dosed discontinuously, 3 weeks on and 1 week off.

Editorial — Dr Burstein (continued)

Abemaciclib is dosed continuously. Abemaciclib is more likely to cause symptomatic diarrhea and less likely to cause significant neutropenia; palbociclib and ribociclib are more likely to cause neutropenia requiring dose modification but cause less in the way of lower-GI toxicity.

The data from the MONARCH 2 and MONARCH 3 trials demonstrate that abemaciclib has activity in 1st or 2nd line therapy for ER+ MBC. While cross-study comparisons are frequently problematic owing to different patient populations, the efficacy results in 1st or 2nd line hormonal therapy using palbociclib, ribociclib, and abemaciclib look nearly identical (see Table 1). Clinically the CDK4/6 inhibitors are interchangeable at this point.

Editorial — Dr Burstein (continued)

Table 1. Randomized trials of endocrine therapy +/- CDK4/6 inhibition

Line	Trial	Schema	HR compared with endocrine alone
1st	PALOMA-1	Letrozole +/- palbociclib	0.49
	PALOMA-2	Letrozole +/- palbociclib	0.58
	MONALEESA-2	Letrozole +/- ribociclib	0.56
	MONARCH 3	Letrozole or anastrozole, +/- abemaciclib	0.54
2nd	PALOMA-3	Fulvestrant +/- palbociclib	0.46
	MONARCH 2	Fulvestrant +/- abemaciclib	0.55

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

Malorni L et al. *Proc ASCO* 2017;Abstract 1002.

Editorial — Dr Burstein

Palbociclib has been FDA approved in combination with endocrine therapy as either first-line (letrozole) or second-line treatment (fulvestrant) of ER positive metastatic breast cancer. The pharma-led randomized studies for each of the CDK4/6 inhibitors all shared the design of endocrine therapy +/- CDK4/6 inhibitor. The TREnd trial asked a different, related question — namely, what is the value of single-agent palbociclib, and does endocrine therapy make palbociclib more effective?

In this patient population of moderately pre-treated ER+ MBC, single-agent palbociclib had some activity with response rate on the order of 7%.

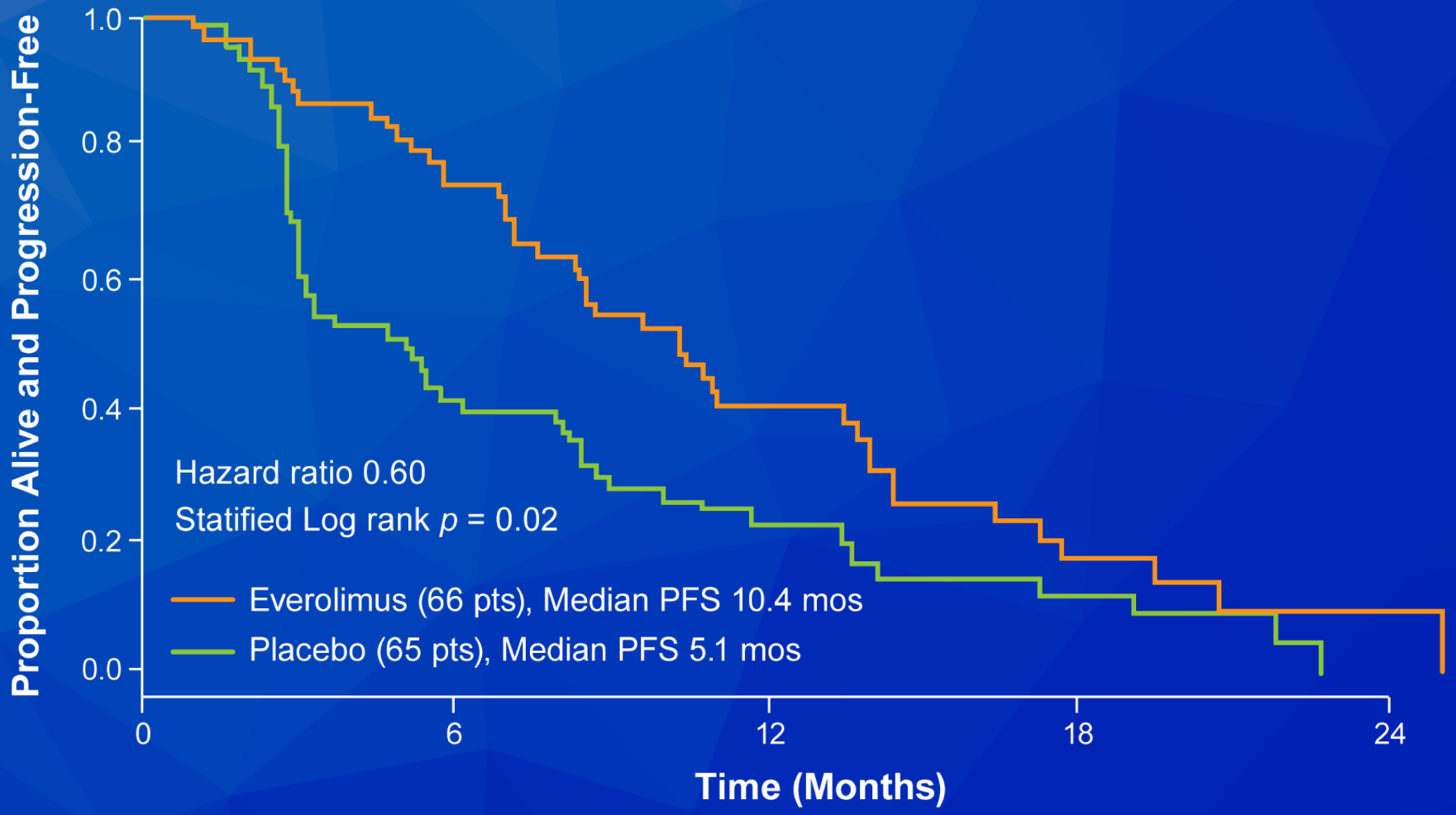
Editorial — Dr Burstein (continued)

Combining endocrine treatment with palbociclib improved the response rate to 11%, and improved the duration of clinical benefit. These results argue modestly that the optimal use of CDK4/6 inhibitor treatment is in combination with endocrine treatment, as opposed to single agent therapy, and bear on the related results from the MONARCH 1 study, which was a trial of single agent abemaciclib showing response rate of approximately 20%.

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



Kornblum NS et al. San Antonio Breast Cancer Symposium 2016;Abstract S1-02.

Editorial — Dr Burstein

Everolimus, the mTOR inhibitor, is an orally available targeted therapy that is FDA approved for use in combination with aromatase inhibitors in previously treated, ER positive metastatic breast cancer. PrECOG 0102 was a randomized phase II study to evaluate the activity of everolimus in combination with fulvestrant. The primary endpoint of the study was progression free survival, which went from 5.1 months with fulvestrant to 10.4 m with fulvestrant and everolimus. As in previous studies of everolimus, there was a risk of grade 3 side effects, including mucositis, pneumonitis, fatigue and hyperglycemia.

Editorial — Dr Burstein (continued)

These data are of interest given the widespread use of aromatase inhibitors as adjuvant therapy such that many women receive fulvestrant as 1st line treatment of metastatic disease. None of the patients on this trial had previously had CDK4/6 therapy, leaving open the question as to whether treatment with everolimus or CDK4/6 inhibition would be the preferred approach with fulvestrant, and whether the activity of everolimus would be different after CDK4/6 inhibitor therapy.

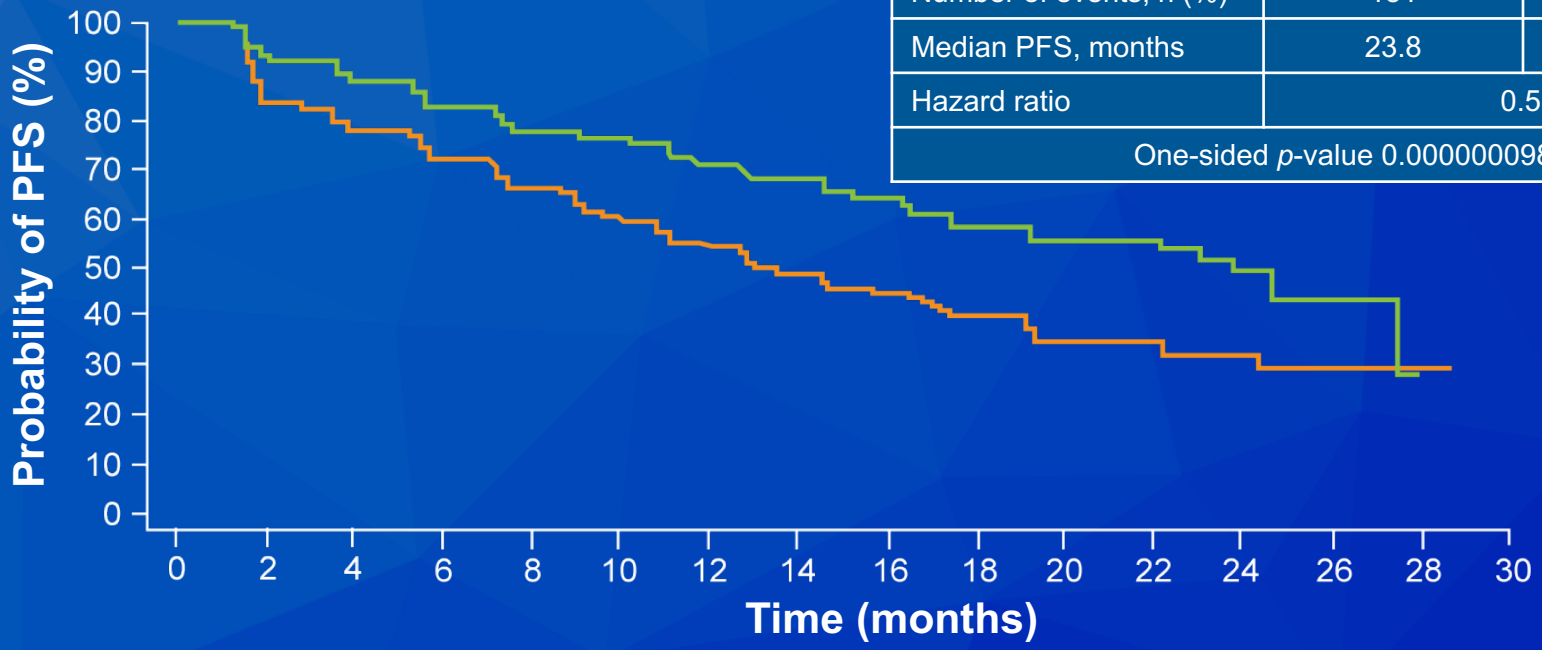
In my own practice, I typically use a CDK4/6 inhibitor earlier in the course of therapy than everolimus, as I believe the patients tolerate these agents more easily.

First-Line Ribociclib vs Placebo with Goserelin and Tamoxifen or a Non-Steroidal Aromatase Inhibitor in Premenopausal Women with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer: Results from the Randomized Phase III MONALEESA-7 trial

Tripathy D et al.
San Antonio Breast Cancer Symposium 2017;Abstract GS2-05.

MONALEESA-7: PFS by INV Assessment

PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n = 335	Placebo + tamoxifen/NSAI n = 337
Number of events, n (%)	131	187
Median PFS, months	23.8	13.0
Hazard ratio	0.553	
One-sided *p*-value 0.0000000983		



PFS by ET partner	Tamoxifen		NSAI	
	Ribociclib	Placebo	Ribociclib	Placebo
Median PFS	22.1 mo	11.0 mo	27.5 mo	13.8 mo
HR	0.585		0.569	

ET = endocrine therapy, NASI = nonsteroidal aromatase inhibitor

Tripathy D et al. San Antonio Breast Cancer Symposium 2017;Abstract GS2-05.

MONALEESA-7: Select Adverse Events

Adverse Event	Ribo + Tam/NSAI (n = 335)		Placebo + TAM/NSAI (n = 337)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Neutropenia	75.8%	60.6%	7.7%	3.6%
Leukopenia	31.3%	14.3%	5.6%	1.2%
Anemia	20.9%	3.0%	10.1%	2.1%
Nausea	31.6%	0.6%	19.6%	0.3%
Arthralgia	29.9%	0.9%	27.3%	0.9%
Diarrhea	20.3%	1.5%	18.7%	0.3%
Thrombocytopenia	8.7%	0.9%	2.1%	0.6%

TAM = Tamoxifen; Ribo = ribociclib; NR = not reported

- QTc prolongation: Ribo (n = 1) vs Placebo (n = 2)

Tripathy D et al. San Antonio Breast Cancer Symposium 2017;Abstract GS2-05.

Breast Cancer — Drs Burstein and Hurvitz

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

Novel Investigational Agents

FDA approves olaparib for germline BRCA-mutated metastatic breast cancer

Press Release — January 12, 2018

"On January 12, 2018, the Food and Drug Administration granted regular approval to olaparib tablets, a poly (ADP-ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer (mBC) who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.

This is the first FDA-approved treatment for patients with gBRCAm HER2-negative mBC. Patients with hormone receptor (HR)-positive BC should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm592357.htm

ORIGINAL ARTICLE

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

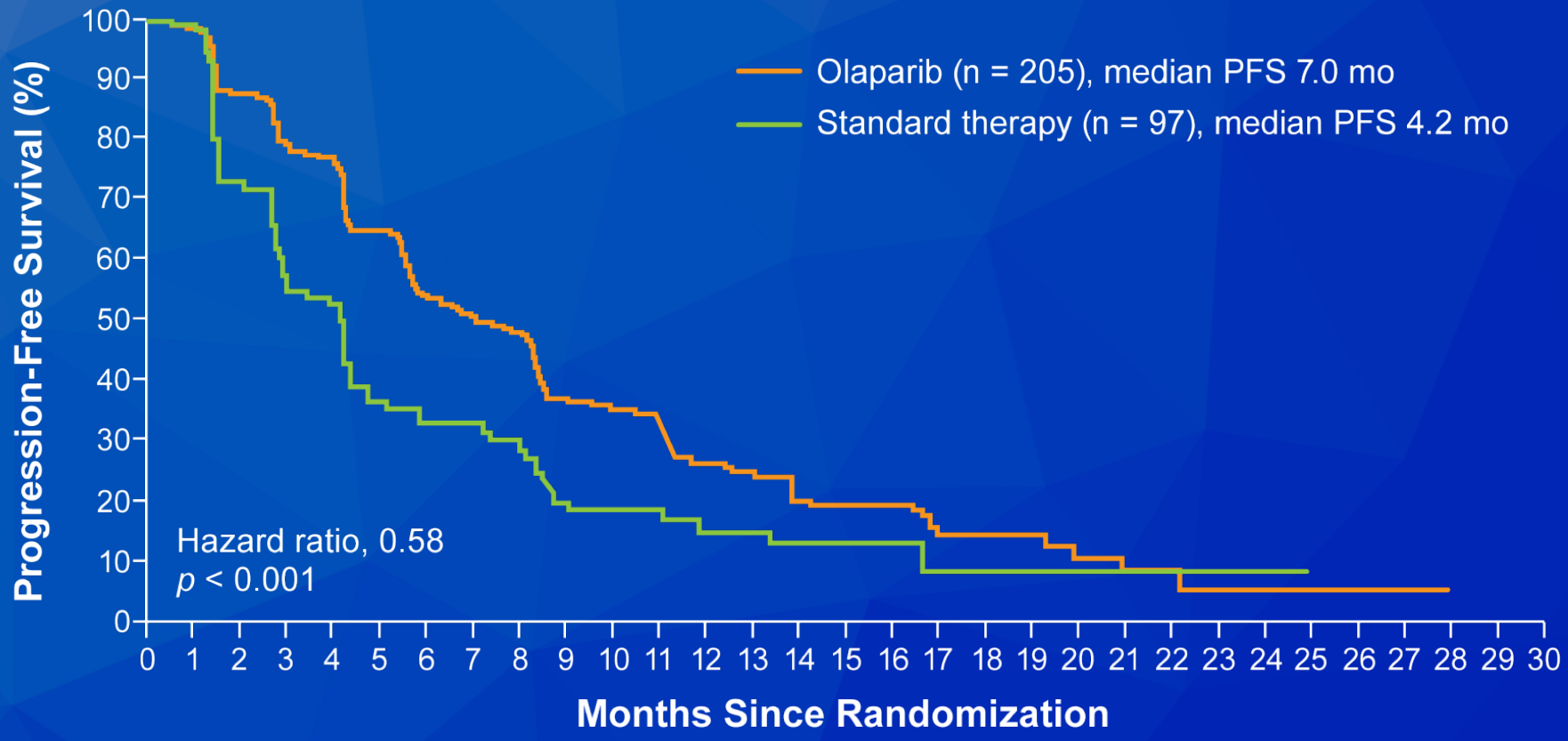
Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D.,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

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.

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

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).

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	• Olaparib • Placebo
PARTNER (Neoadjuvant)	527	TNBC or gBRCAm	• Olaparib + paclitaxel/carbo • Paclitaxel/carbo
BROCADE (LABC or metastatic)	500	HER2-, gBRCAm	• Veliparib + paclitaxel/carbo • Placebo + paclitaxel/carbo
TNBC 3000-03-004 (Advanced)	306	TNBC	• Niraparib + anti-PD-1 Ab • Standard of care

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

www.clinicaltrials.gov. Accessed October 2017.

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

Turner NC et al. *Proc ASCO* 2017;Abstract 1007.

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.

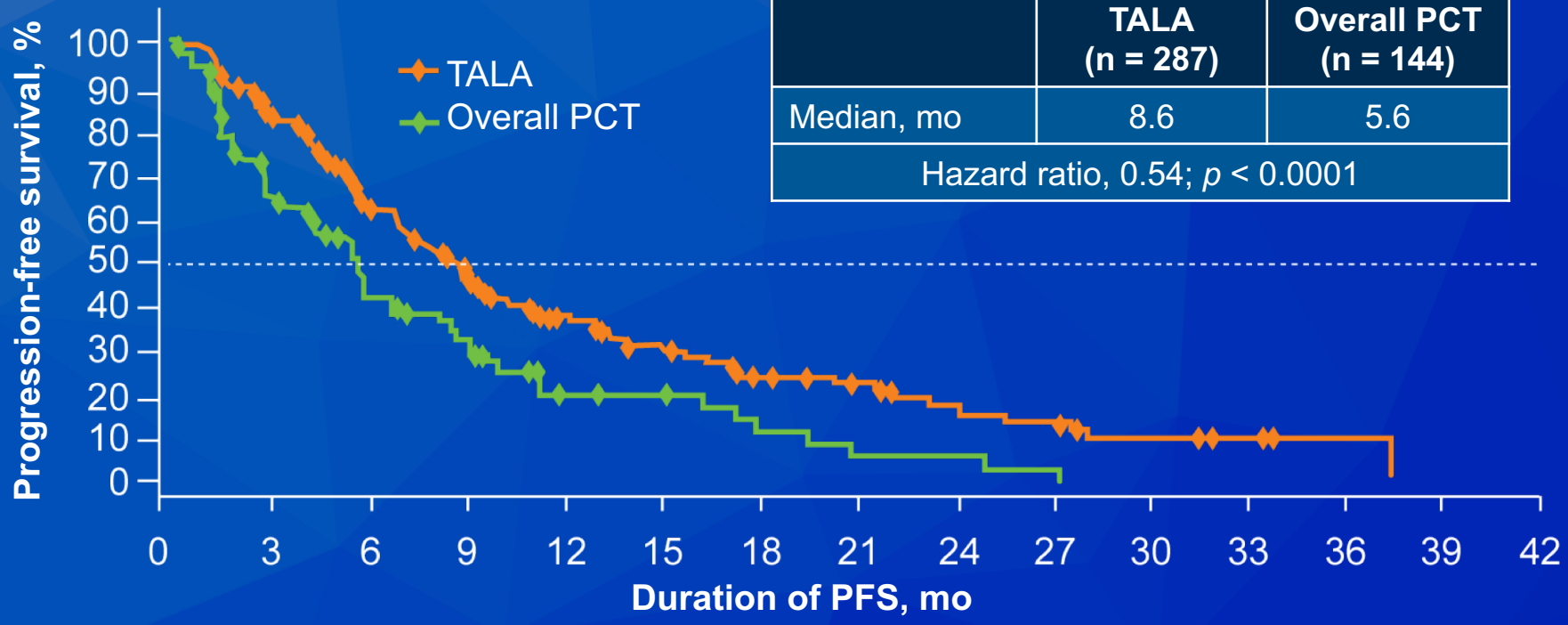
Editorial — Dr Rugo (continued)

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.

EMBRACA: A Phase 3 Trial Comparing Talazoparib, an Oral PARP Inhibitor, to Physician's Choice of Therapy in Patients with Advanced Breast Cancer and a Germline BRCA-Mutation

Litton JK et al.
San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

EMBRACA: PFS by Blinded Central Review



	TALA (n = 287)	Overall PCT (n = 144)
Median, mo	8.6	5.6
Hazard ratio, 0.54; $p < 0.0001$		

TALA = Talazoparib; PCT = physician's choice of therapy (capecitabine, eribulin, gemcitabine or vinorelbine)

- All key secondary endpoints demonstrated benefit with talazoparib

Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

EMBRACA: Select Adverse Events

Adverse Event	TALA n = 286		Overall PCT n = 126	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Anemia	52.8%	39.2%	18.3%	4.8%
Neutropenia	34.6%	21.0%	42.9%	34.9%
Thrombocytopenia	26.9%	14.7%	7.1%	1.6%
Febrile neutropenia	0.3%	0.3%	0.8%	0.8%
Vomiting	24.8%	2.4%	23.0%	1.6%
Dyspnea	17.5%	2.4%	15.1%	2.4%
Palmar-plantar erythrodysesthesia syndrome	1.4%	0.3%	22.2%	2.4%
Pleural effusion	2.1%	1.7%	8.7%	4.0%

Litton JK et al. San Antonio Breast Cancer Symposium 2017;Abstract GS6-07.

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	• Olaparib • Placebo
PARTNER (Neoadjuvant)	527	TNBC or gBRCAm	• Olaparib + paclitaxel/carbo • Paclitaxel/carbo
BROCADE (LABC or metastatic)	500	HER2-, gBRCAm	• Veliparib + paclitaxel/carbo • Placebo + paclitaxel/carbo
TNBC 3000-03-004 (Advanced)	306	TNBC	• Niraparib + anti-PD-1 Ab • Standard of care
EMBRACA (LABC or metastatic)	442	gBRCAm	• Talazoparib • Physician's choice of chemo

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

www.clinicaltrials.gov. Accessed October 2017.

Breast Cancer — Drs Burstein and Hurvitz

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

Novel Investigational Agents

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 Trial: PFS Results

ITT population	Cohort 1 (No prior ET)		Cohort 2 (Prior ET)	
	ENZ/EXE (n = 63)	PBO/EXE (n = 64)	ENZ/EXE (n = 60)	PBO/EXE (n = 60)
Median PFS	11.8 mo	5.8 mo	3.6 mo	3.9 mo
HR	0.82		1.02	
p-value	0.3631		0.9212	
Biomarker positive	**n = 24**	**n = 26**	**n = 15**	**n = 20**
Median PFS	16.5 mo	4.3 mo	6.0 mo	5.3 mo
HR	0.44		0.55	
p-value	0.0335		0.1936	

ET = endocrine therapy; ENZ = enzalutamide; EXE = exemestane; PBO = placebo

Krop I et al. San Antonio Breast Cancer Symposium 2017;Abstract GS4-07.

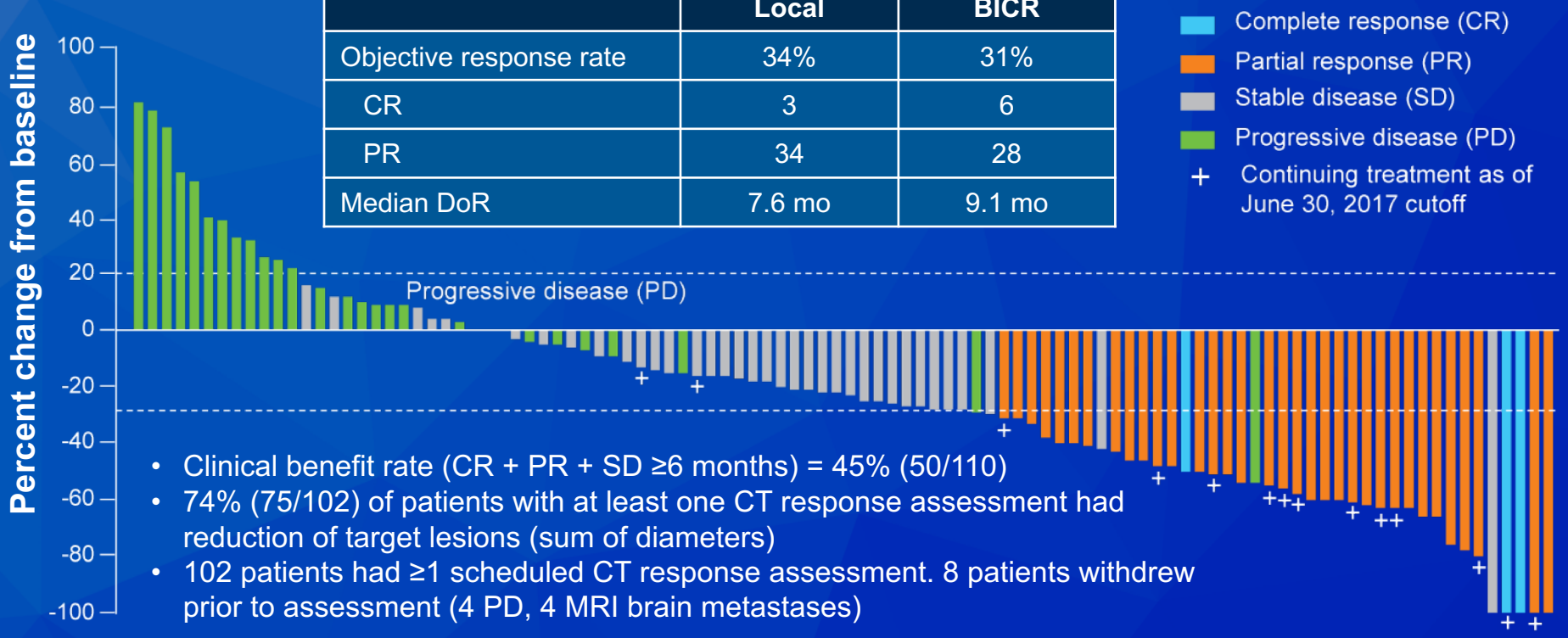
Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-Line Therapeutic Option for Patients with Relapsed/ Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Bardia A et al.
San Antonio Breast Cancer Symposium 2017;Abstract GS1-07.

Sacituzumab Govitecan (IMMU-132): Efficacy Results

Tumor Response to Treatment

	Local	BICR
Objective response rate	34%	31%
CR	3	6
PR	34	28
Median DoR	7.6 mo	9.1 mo



- Clinical benefit rate (CR + PR + SD ≥6 months) = 45% (50/110)
- 74% (75/102) of patients with at least one CT response assessment had reduction of target lesions (sum of diameters)
- 102 patients had ≥1 scheduled CT response assessment. 8 patients withdrew prior to assessment (4 PD, 4 MRI brain metastases)

Survival	n = 110
Median OS	12.7 mo
Median PFS	5.5 mo

Bardia A et al. San Antonio Breast Cancer Symposium 2017;Abstract GS1-07.

Sacituzumab Govitecan (IMMU-132): Select Adverse Events

AEs (n = 110)	All Grades	Grade 3/4
Neutropenia	63%	41%
Febrile neutropenia	8%	7%
Anemia	52%	10%
Leukopenia	24%	14%
Nausea	63%	5%
Diarrhea	56%	8%
Vomiting	46%	5%
Constipation	32%	1%
Hyperglycemia	23%	4%
Hypomagnesemia	21%	1%
Hypophosphatemia	15%	8%

No treatment related deaths; 2 discontinuations; Treatment was well tolerated.

Bardia A et al. San Antonio Breast Cancer Symposium 2017;Abstract GS1-07.

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 *p*-value
Five-year DFS (ITT)	74.1%	67.6%	HR = 0.70 *p* = 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 *p* = 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

Masuda N et al. *N Engl J Med* 2017;376:2147-59.

Editorial — Dr Burstein

Women with residual tumor after neoadjuvant chemotherapy are at greater risk for tumor recurrence than women who experience a complete pathological response. Clinical trials are now focusing on the population of women with residual disease to see whether additional therapy would be valuable to them. The CREATE-X trial was a randomized study of capecitabine or no further treatment for women who had residual breast cancer after standard neoadjuvant therapy. The major finding in CREATE-X was that adjuvant capecitabine in this population led to an improvement in overall survival, especially in the cohort of women with triple-negative breast cancer.

Editorial — Dr Burstein (continued)

This finding has been somewhat surprising because previous studies of adjuvant capecitabine had not shown a major reduction in risk of tumor recurrence compared to standard chemotherapy. Perhaps in retrospect there is a small signal among women with TNBC. It is not known what would account for the positive result here, though there is no doubt that women with residual TNBC were at higher-than-average recurrence risk.

Capecitabine was given at 2,500 mg/m^2 per day, 14 days on, 7 days off for 6 or 8 cycles. This is a substantial dose of capecitabine. For unclear reasons, the capecitabine proved well tolerated in this cohort of Korean and Japanese women, with fewer side effects than typically seen at that dose in North American women.

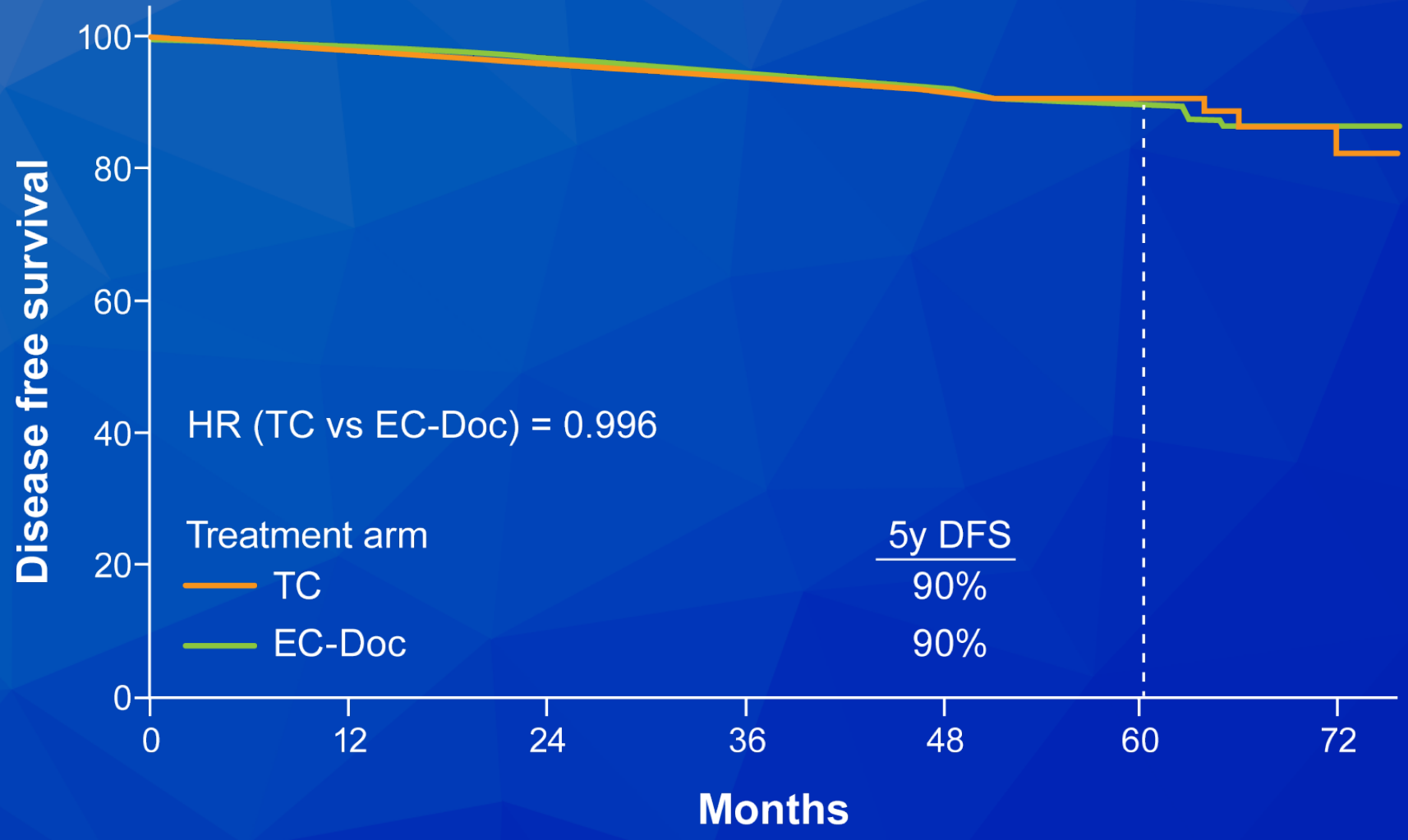
Editorial — Dr Burstein (continued)

The trial suggests that women with residual TNBC after standard anthracycline- and taxane-based neoadjuvant chemotherapy should strongly consider additional chemotherapy with capecitabine to improve overall survival. Ongoing studies are also looking at platinum chemotherapy and immunotherapy options in similar patients.

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)

Harbeck N et al. *Proc ASCO* 2017;Abstract 504.

Editorial — Dr Burstein

Anthracyclines are an integral component of most conventional chemotherapy regimens. A question is whether, given the improvements in taxane-based chemotherapy and selection of HER2 negative breast cancers, anthracyclines could be omitted. That is an appealing prospect given their well-known side effects, including rare risks of heart damage and secondary leukemia.

The West German PlanB study compared EC/T vs the non-anthracycline TC regimen for HER2 negative breast cancer. Interestingly, the TC arm performed as well as the EC/T arm, suggesting that patients could safely avoid the anthracycline exposure. This was true for ER positive as well as triple negative breast cancer, and regardless of Onco*type* DX Recurrence Score.

Editorial — Dr Burstein (continued)

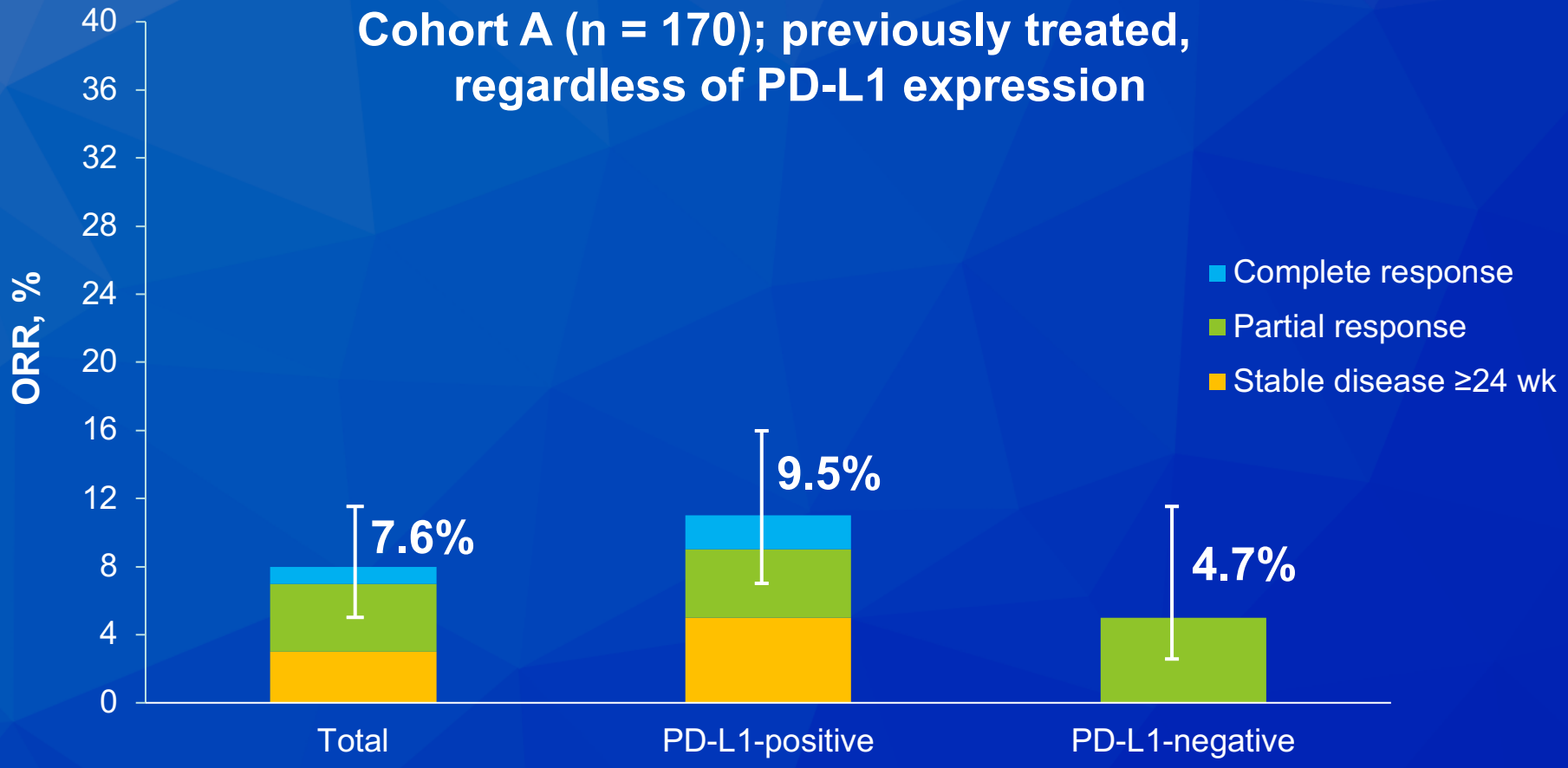
These results are at odds with the NSABP-B-55 / US Oncology study that also compared anthracycline- and taxane-based chemotherapy vs TC (Blum et al. JCO 2017;35:2647). In that study, anthracycline-based treatments were “better” than non-anthracycline regimens in triple-negative breast cancer and in high risk ER positive breast cancer.

In my practice, I still favor anthracycline-based regimens in triple-negative cancers and stage 3 ER positive breast cancers. For other cases, these data support the omission of anthracyclines.

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

Adams S et al. *Proc ASCO* 2017;Abstract 1008.

Editorial — Dr Burstein

Immunotherapy approaches are being vigorously studied in many tumor types, including breast cancer. Keynote 086 was one in the large series of studies to evaluate the anti-PD-1 receptor antibody pembrolizumab in a number of different malignancies. This was an open label phase 2 study of pembrolizumab in women with metastatic triple-negative breast cancer, regardless of PD-L1 expression by the tumor. Patients were heavily pre-treated, averaging 3 or more lines of prior chemotherapy.

The study endpoint was response rate, and the response rate was disappointingly low at 5%. PD-L1 expression did not predict response rate, though patients with visceral tumors had even lower response rates.

Editorial — Dr Burstein (continued)

These negative results suggest that single-agent pembrolizumab has little activity in heavily refractory TNBC. Studies looking at combination treatment with chemotherapy or targeted therapy in concert with immunotherapy approaches, and with more biomarker selection, are ongoing.

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%

Schmid P et al. *Proc AACR* 2017;Abstract 2986.

Editorial — Dr Burstein

Atezolizumab is an anti-PD-L1 antibody, an approved immunotherapy agent for treatment of a variety of tumor types. This study was an updated report of an open-label trial of single-agent atezolizumab as treatment for metastatic triple-negative breast cancer. A total of 113 patients were treated on study. As first line therapy for 19 patients, atezolizumab had a response rate of 26%. As 2nd or later line therapy in 93 patients, the response rate was 7%. Response rates were somewhat higher in patients whose tumors had PD-L1 expression (n = 71; RR 13%) than in tumors lacking PD-L1 expression (n = 37, RR 5%).

Editorial — Dr Burstein (continued)

These data pair with the single-agent study of pembrolizumab (above) and suggest that single-agent PD-L1/PD-1 targeted therapy in refractory TNBC has limited activity. Higher response rates are seen in first-line treatment.

In a related trial (Adams et al. *Proc ASCO* 2016;Abstract 1009), atezolizumab was studied in combination with *nab* paclitaxel chemotherapy. In first line the RR was 67% to combination therapy, and 25%-30% in second or third line treatment. This was a very small study of only 32 patients, but the results suggest that response rates are higher with the combination treatment. These sets of findings have led to phase III trials of taxane-based chemotherapy +/- immunotherapy agents for TNBC. Data from those trials are still awaited.