

Exclusive Coverage of the

2019 SAN ANTONIO BREAST CANCER SYMPOSIUM

December 10-14 | San Antonio, Texas

Node-Negative, Estrogen Receptor-Positive, Early-Stage Breast Cancer: 20-Year Distant Recurrence Risk After 5 Years of Endocrine Treatment is Likely One-Fourth Lower Than Previously Estimated

NICOLA M. PARRY, MSC, BVSC

The 20-year risk of distant recurrence (DR) after 5 years of endocrine therapy for women with node-negative (NO), estrogen receptor (ER)-positive, early-stage breast cancer is likely about one-fourth lower than previously reported, according to an analysis of data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the results of which were presented at the 2019 San Antonio Breast Cancer Symposium.¹

"In 2017, the EBCTCG published a paper in the *New England Journal of Medicine*² on the 20-year recurrence risks for women with ER-positive early breast cancer after adjuvant endocrine treatment for only 5 years," said Hongchao Pan, PhD, MSc, of the Nuffield

(Continued on page 2)

Real-World Use of Palbociclib Maintains Quality of Life in Patients With HR-Positive/HER2-Negative Advanced or Metastatic Breast Cancer

NICOLA M. PARRY, MSC, BVSC

Treatment with palbociclib may help to maintain or even improve quality of life (QOL) in patients with hormone receptor (HR)-positive/HER2-negative advanced or metastatic breast cancer (ABC/mBC), according to 6-month data from a prospective real-world study presented at the 2019 San Antonio Breast Cancer Symposium.¹

The interim results of this study¹ "would suggest that these patients maintain quality of life and experience some improvement in specific symptoms, including, notably, pain," explained lead study author Gabrielle Rocque, MD, assistant professor of medicine in the divisions of Hematology & Oncology and Gerontology, Geriatrics, & Palliative Care,

(Continued on page 3)

ALSO IN THIS ISSUE

Talazoparib is Associated With More Significant Improvements in Patient-Reported Outcomes Versus Chemotherapy in HER2-Negative, *BRCA1/2*-Mutated Advanced Breast Cancer: Post Hoc Analyses of Performance Status Subgroups From EMBRACA **4**

Bevacizumab Maintenance Benefits Patients With HR-Positive/HER2-Negative Advanced Breast Cancer Who Responded to a Fixed Dose of Chemotherapy **5**

Subcutaneous Pertuzumab-Trastuzumab Combination is Found to be Noninferior to Intravenous Pertuzumab and Trastuzumab **6**

plasmaMATCH Trial Results Suggest That ctDNA Can Identify Patients With *HER2* and *AKT1* Mutations **8**

Oral Paclitaxel Combined With Encequidar Significantly Increases Confirmed Response Rate Over Intravenous Paclitaxel in Phase 3 Trial in Metastatic Breast Cancer **9**

Genomic Study Provides Insight on Mechanisms of Resistance to CDK4/6 Inhibitors in HR-Positive/HER2-Negative Metastatic Breast Cancer **11**

Adjuvant Chemotherapy Shows Slight Benefit in Younger Women With Breast Cancer Who Have Mixed Clinical, Genomic Risk **12**

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Managed Care & Healthcare Communications, LLC, the editorial staff, or any member of the editorial advisory board. Managed Care & Healthcare Communications, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Managed Care & Healthcare Communications, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

EDITORIAL & PRODUCTION

Senior Vice President
Jeff Prescott, PharmD, RPh

**Assistant Director,
Content Services**
Angelia Szwed

Scientific Director
Darría Zangari,
PharmD, BCPS, BCGP

**Senior Clinical
Project Managers**
Ida Delmendo
Danielle Mroz, MA

**Clinical Project
Managers**
Lauren Burawski, MA
Ted Pigeon

Project Manager
Andrea Szeszko

Associate Editors
Hayley Fahey
Jill Pastor
Amanda Thomas

Medical Writers

Amber Schilling,
PharmD
Valerie Sjoberg

Copy Chief
Jennifer Potash

**Medical & Scientific
Quality Review Editor**
Stacey Abels, PhD

Copy Editors
Rachelle Laliberte
Amy Oravec
Paul Silverman

**Creative Director,
Publishing**
Ray Pelesko

Senior Art Director
Melissa Feinen

Art Director
Julianne Costello

SALES & MARKETING

Director, Sales
Gil Hernandez

**National Account
Managers**
Ben Baruch
Robert Foti
Megan Halsch
Ryan O'Leary

**National Account
Associate**
Kevin George

OPERATIONS & FINANCE

Circulation Director
Jon Severn
circulation@mjhassoc.com

**Vice President,
Finance**
Leah Babitz, CPA
Controller
Katherine Wyckoff

CORPORATE

Chairman & Founder
Mike Hennessy Sr

Vice Chairman
Jack Lepping

President & CEO
Mike Hennessy Jr

Chief Financial Officer
Neil Glasser, CPA/CFE

**Executive Vice
President, Operations**
Tom Tolvé

**Senior Vice President,
Content**
Silas Inman

**Senior Vice President,
I.T. & Enterprise
Systems**
John Moricone

**Senior Vice President,
Audience Generation &
Product Fulfillment**
Joy Puzzo

**Vice President,
Human Resources
and Administration**
Shari Lundenberg

**Vice President,
Business Intelligence**
Chris Hennessy

**Vice President,
Corporate Branding &
B2B Marketing**
Amy Erdman

**Executive
Creative Director**
Jeff Brown

Copyright © 2020 by Managed Care
& Healthcare Communications, LLC



AN **MJ** life sciences™ BRAND

Node-Negative (Continued from page 1)

Department of Population Health, University of Oxford, Oxford, United Kingdom, in an interview with an editor from *The American Journal of Managed Care*®. “We reported in the paper that, in women given 5 years of adjuvant endocrine therapy, appreciable risks continued during years 5 to 20, even for those with T1N0 [stage I disease with no nodal involvement].” For women with no nodal involvement, the risks of distant recurrence during years 5 to 20 were reported to be 13% for stage T1N0 disease and 19% for those with stage T2N0 disease, he added.

The late DRs reported in the study were largely contributed by women diagnosed before the year 2000, Pan explained. In women diagnosed after 2000, the 10- and 20-year DR risks remain unknown. To address this question and determine whether DR risk is lower for women diagnosed more recently, “we conducted this study by analyzing the updated data from the EBCTCG database,” he said. Their analysis included 86,000 women (median age at diagnosis, 55 years; 31% premenopausal) with T1 or T2 ER-positive breast cancer from 110 trials. These women were due to finish receiving adjuvant endocrine therapy at year 5.¹

The researchers examined the data to determine the risk for first DR according to the time period during which the women received their diagnoses: before 2000; 2000 through 2004; or 2005 or later. Overall, they noted that a patient’s original TN (tumor size and nodal status) was the main factor that predicted DR after stopping 5 years of endocrine therapy. However, women diagnosed with ER-positive breast cancer after 2000 had a better prognosis than those diagnosed before 2000, even after accounting for tumor size, nodal status, and use of chemotherapy or aromatase inhibitors.¹ Compared with women diagnosed before 2000, those “diagnosed after 2000 had 25% fewer DRs in years 5 through 9,” Pan told *The American Journal of Managed Care*®.

“For T1N0 disease with only 5 years of endocrine therapy, the absolute risk of DR

in years 5 through 20 was approximately 13% for women diagnosed before 2000 and projected to be about 10% for women diagnosed since 2000,” he said. “And for women with T2N0 disease, the 20-year risk was about 19% if diagnosed before 2000, and projected to be about 14% [if diagnosed] after 2000.”¹ Pan also explained that the 20-year risk in women diagnosed after 2000 was estimated by assuming that the proportional reduction in DR rate was also 25% in years 10 through 20 since diagnosis—the same as that observed in years 5 through 9.

“The possible reasons for the observed improvement in prognosis over time are likely multifactorial,” said Pan. One factor may relate to emergence of better treatments, he explained, including improvements in surgery, radiotherapy, chemotherapy, endocrine therapy, and human epidermal growth factor receptor 2–directed therapy. Advances in screening also facilitate better and earlier disease detection, which increases the likelihood of identifying patients with treatable disease. In addition, the availability of treatment guidelines helps to ensure that more patients receive optimal treatment tailored to their disease.¹

Although the risk of DR after 5 years of endocrine therapy is lower for women with ER-positive disease diagnosed after 2000 than it is for those diagnosed before 2000, the risk is still substantial, stressed Pan. Long-term follow-up studies involving patients in this population who were diagnosed more recently are needed to accurately determine patients’ long-term DR risks.¹

Pan concluded by describing the decline in breast cancer mortality among women aged 30 to 69 years over recent decades in the United States and United Kingdom. Sharing data from World Health Organization mortality and United Nations population estimates, he noted that the risk of breast cancer death before age 70 years was cut by approximately half between 1980 and 2015, dropping from

about 2.0% to about 1.1% in the United States, and from about 2.5% to about 1.2% in the United Kingdom. Several moderate effects combined to produce this large effect on breast cancer mortality, he said. Because additional moderate effects are yet to be achieved in this area, Pan predicts that this beneficial trend will continue, further improving the long-term prognosis for patients who will receive a diagnosis of breast cancer in the future.●

REFERENCES

1. Pan H, Braybrooke J, Gray R, et al. Improvements in long-term outcome for women with estrogen receptor positive (ER+) early stage breast cancer treated with 5 years of endocrine therapy: analyses of 82,598 women in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) database. Presented at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS2-04. abstractsonline.com/pp8/#/17946/presentation/2232. Accessed December 12, 2019.
2. Pan H, Gray R, Braybrooke J, et al; Early Breast Cancer Trialists' Collaborative Group. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846. doi: 10.1056/NEJMoa1701830.

Real-World (Continued from page 1)

at the University of Alabama in Birmingham, in an interview with *The American Journal of Managed Care*®.

The emergence of novel agents such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, including palbociclib, has considerably changed the landscape of ABC/mBC treatment.² Indeed, based on results of the recent PALOMA clinical trials showing that palbociclib combined with endocrine therapy (an aromatase inhibitor or fulvestrant) helped patients with HR-positive/HER2-negative ABC/mBC to maintain QOL, treatment with a CDK4/6 inhibitor in combination with endocrine therapy has now become the standard of care in this patient population.³⁻⁵ Nevertheless, real-world evidence to demonstrate how palbociclib affects QOL in these patients remains lacking.¹

Rocque emphasized that this real-world study was thus particularly important because it considered patients who were receiving palbociclib as standard of care. "It is critical that we evaluate novel medications in real-world populations [because] clinical trial populations may not reflect the patients who are typically seen in clinic," she said. "As such, we wanted to understand what the patient experience—particularly QOL—would be for a more diverse patient population receiving treatment outside of a clinical trial."

With this in mind, Rocque and colleagues designed the Palbociclib in Hormone Receptor-Positive Advanced Breast Cancer: a Multicenter Prospective Noninterventional Study (POLARIS), which aims to investigate real-world use and outcomes associated with palbociclib treatment in HR-positive/HER2-negative ABC/mBC.^{1,6} POLARIS is a 1500-patient observational study that remains ongoing in female and male patients across 110 sites in North America.¹

To assess patients' health-related QOL, the investigators used the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30),⁷ administered via an interactive web response system or in paper form. Patients completed a baseline questionnaire when they initially enrolled in the study and before starting treatment with palbociclib.¹ Patients who were enrolled in the study received palbociclib treatment combined with letrozole or anastrozole

(n = 285), fulvestrant (n = 218), or exemestane (n = 19).¹ After starting treatment, they completed the EORTC QLQ-C30 once per month for the first 3 months, and then every 3 months until treatment ended or they withdrew from the study or died.¹

This interim analysis included the first 522 patients (98% female; 83% white; median age, 64 years) in POLARIS who had undergone at least 6 months of palbociclib treatment, with 390 patients receiving it as first-line treatment and 132 as second- or later-line treatment.¹

“ [T]he study's preliminary findings highlight that palbociclib treatment can help patients with HR-positive/HER2-negative ABC/mBC to maintain their QOL. ”

Overall, "we observed that patients receiving palbociclib had stable to modestly improved QOL," Rocque said. During the first 6 months of treatment, patients' mean (SD) global health/QOL scores on the EORTC QLQ-C30 were relatively similar, rising slightly from 66.2 (22.6) at baseline to 68.3 (19.7) at 3 months and 70.2 (21.3) at 6 months. Although the mean scores for most individual symptom scales and functional scales changed by fewer than 5 points during this time period, the investigators found that pain scores decreased by 7 points, falling from 33.5 (30.0) at baseline to 27.3 (27.2) at 3 months and 26.5 (26.9) at 6 months.¹

In general, Rocque and colleagues stressed that because none of the individual parameters had a mean score change from baseline to 6 months that reached the predefined 10-point threshold, the differences were not considered to be clinically

significant. Nevertheless, they stressed that the study's preliminary findings highlight that palbociclib treatment can help patients with HR-positive/HER2-negative ABC/mBC to maintain their QOL.¹

"This is an important study because it is a large prospective registry study that evaluated patient-reported outcomes, which are often not prioritized in the same way as survival and [adverse] effects," Rocque said. "However, these outcomes are very important to patients and should be evaluated and prioritized." ●

REFERENCES

1. Rocque G, Blum JL, Montero A, et al. Quality of life in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer treated with palbociclib in real-world practice settings. Abstract PD10-03. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.
2. Preusser M, De Mattos-Arruda L, Thill M, et al. CDK4/6 inhibitors in the treatment of patients with breast cancer: summary of a multidisciplinary round-table discussion. *ESMO Open*. 2018;3(5):e000368. doi: 10.1136/esmoopen-2018-000368.
3. Mahtani RL, Vogel CL. Addressing physician barriers to administering cyclin-dependent kinases 4 and 6 inhibitors in first-line treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. *Cancer Manag Res*. 2019;11:513-524. doi: 10.2147/CMAR.S186658.
4. Harbeck N, Iyer S, Turner N, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. *Ann Oncol*. 2016;27(6):1047-1054. doi: 10.1093/annonc/mdw139.
5. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer, version 3.2019. National Comprehensive Cancer Network website. nccn.org/professionals/physician_gls/default.aspx. Published September 6, 2019. Accessed December 11, 2019.
6. Palbociclib in Real World Practice. clinicaltrials.gov/ct2/show/NCT03280303. Updated August 30, 2019. Accessed December 11, 2019.
7. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376. doi: 10.1093/jnci/85.5.365.

Talazoparib is Associated With More Significant Improvements in Patient-Reported Outcomes Versus Chemotherapy in HER2-Negative, *BRCA1/2*-Mutated Advanced Breast Cancer: Post Hoc Analyses of Performance Status Subgroups From EMBRACA

KARA L. GUARINI, MS

Talazoparib is potent, selective inhibitor of poly(adenosine diphosphate-ribose) polymerase (PARP); it blocks PARP catalytic activity and sequesters PARP-DNA complexes, resulting in the death of *BRCA1/2*-mutated tumor cells.^{1,2} EMBRACA was a phase 3, randomized, open-label study of talazoparib versus physician's choice of chemotherapy (ie, capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with human epidermal growth factor receptor 2-negative (HER2-negative), *BRCA1/2*-mutated locally advanced/metastatic breast cancer.³ Results from the trial demonstrate that talazoparib was associated with significant improvements in progression-free survival (hazard ratio [HR], 0.54; 95% CI, 0.41-0.71; $P < .001$)³ and improvements in patient-reported outcomes (PROs) compared with physician's choice of chemotherapy.⁴

Hope S. Rugo, MD, FASCO, professor in the department of medicine and the director of Breast Oncology and Clinical Trials Education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, and coinvestigators conducted post hoc subgroup analyses of data from EMBRACA in patients with an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or higher. The results were recently presented at the 2019 San Antonio Breast Cancer Symposium.¹

In patients with ECOG status 0, talazoparib was associated with a significant improvement in overall change from baseline in patient-reported global health status (GHS) and quality of life (QOL), in the physical, role, social, and body image functioning scales, and in the fatigue, pain, appetite loss, and breast symptom scales compared with physician's choice of chemotherapy.

Patients with ECOG status higher than 0 experienced significant improvements with talazoparib in patient-reported GHS/QOL, in the physical, role, emotional, cognitive, and social functioning scales, and in the fatigue, pain, dyspnea, insomnia, appetite loss, and systemic therapy adverse effects symptom scales. Moreover, talazoparib was associated with significant delays in time to definitive clinically meaningful deterioration (TTD) compared with physician's choice of chemotherapy based on GHS and QOL scores in both subgroups: ECOG status of 0 (median, 24.3 vs 10.3 months; HR, 0.40; 95% CI, 0.24-0.67; $P = .0003$) and ECOG status higher than 0 (median, 21.1 vs 6.0 months; HR, 0.34; 95% CI, 0.19-0.61; $P = .0001$).¹

EMBRACA enrolled 431 patients from 145 sites in 16 countries. Patients were randomized 2:1 to receive talazoparib 1 mg per day or physician's choice of chemotherapy. Treatment occurred in 21-day cycles and continued until disease progression or unacceptable toxicity.^{1,3} PROs were recorded at baseline (day 1), the start of each treatment cycle (every 3 weeks), and at the end of treatment using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) and the breast cancer-specific module, QLQ-BR23.¹ Higher scores in GHS and QOL and functional scales represent improved GHS/QOL and functioning, respectively; higher scores in symptom scales suggest greater symptom severity.

The PRO-evaluable population was defined as those patients who completed at least 1 question at baseline and at least 1 time point post baseline. Repeated measures mixed-effects analyses were performed to ascertain on-treatment overall change from baseline

scores among the 2 treatment groups for GHS/QOL, functioning, and symptoms, using a model with the variables of treatment, times, treatment by time, and baseline as a covariate with no adjustment for multiple comparisons.¹ TTD was estimated using Kaplan-Meier curves. A stratified log-rank test and Cox proportional hazards model were used for between-arm comparisons of TTD. TTD for GSH/QOL and functioning scales was defined as the time from randomization to the first observation with at least a 10-point decrease and no subsequent observations with less than a 10-point decrease from baseline. TTD for symptom scales was defined as the time from randomization to the first observation with at least a 10-point increase and no subsequent observations with less than a 10-point increase from baseline.¹

Baseline scores were similar among the 2 subgroups.¹ The PRO-evaluable population with ECOG status 0 consisted of 142 and 64 patients given talazoparib and physician's choice of chemotherapy, respectively; 119 and 50 patients in these respective arms had an ECOG status greater than 0.¹ Talazoparib therapy resulted in a significant delay in TTD compared with physician's choice of chemotherapy, as measured by patient-reported pain symptoms in those with ECOG status 0 (median, 21.5 vs 5.9 months; HR, 0.29; 95% CI, 0.17-0.49; $P < .0001$) and those with ECOG status greater than 0 (median, not reached vs 7.5 months; HR, 0.36; 95% CI, 0.19-0.68; $P = .0011$).¹ Similar results favoring talazoparib were observed in patient-reported fatigue for both subgroups: those with ECOG status 0 (median, 17.1 vs 6.1 months; HR, 0.40; 95% CI, 0.25-0.65; $P = .0001$) and those with ECOG status greater than 0 (median, 16.9 vs 7.1 months; HR, 0.41; 95% CI, 0.24-0.69; $P = .0006$).¹

In patients with ECOG status 0, talazoparib was also associated with a significant delay in TTD in the physical, role, emotional, cognitive, social, and body image functioning scales, and in diarrhea, nausea/vomiting, dyspnea, insomnia, appetite loss, systemic therapy side effects, and arm symptom scales.¹ In those with ECOG status greater than 0, talazoparib therapy resulted in significant improvements in the physical, role, emotional, cognitive, social, and body image functioning scales, and in the dyspnea, insomnia, nausea/vomiting, constipation, appetite loss, breast symptoms, arm symptoms, and systemic therapy side effects symptom scales. None of the analyses resulted in significant changes in PROs that favored physician's choice of chemotherapy over talazoparib.¹

In patients with HER2-negative germline *BRCA1/2* advanced breast cancer, these results reinforce that talazoparib has a favorable risk-benefit profile compared with physician's choice of chemotherapy in patients with ECOG status 0 and higher. ●

REFERENCES

1. Rugo HS, Quek RGW, Bhattacharyya H, Gonçalves A, Ettl J, Hurvitz SA. Patient-reported outcomes in patients with HER2-advanced breast cancer and a germline *BRCA1/2* mutation receiving talazoparib vs physician's choice of chemotherapy: a focus on EMBRACA ECOG performance status subgroups. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Poster PD10-01.
2. de Bono J, Ramanathan RK, Mina L, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline *BRCA1/2* mutations and selected sporadic cancers. *Cancer Discov*. 2017;7(6):620-629. doi: 10.1158/2159-8290.CD-16-1250.
3. Litton JK, Rugo HS, Ettl J. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N Engl J Med*. 2018;379(8):753-763. doi: 10.1056/NEJMoa1802905.
4. Ettl J, Quek RGW, Lee KH. Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline *BRCA1/2* mutation: patient-reported outcomes from the EMBRACA phase III trial. *Ann Oncol*. 2018;29(9):1939-1947. doi: 10.1093/annonc/mdy257.

Bevacizumab Maintenance Benefits Patients With HR-Positive/HER2-Negative Advanced Breast Cancer Who Responded to a Fixed Dose of Chemotherapy

Maintenance endocrine therapy with bevacizumab improves outcomes for patients with hormone receptor-positive (HR+), HER2-negative advanced or metastatic breast cancer (ABC/MBC) who respond to a fixed dose of chemotherapy, according to results from the randomized phase 2 JBCRG-M04 BOOSTER trial (NCT01989780).

In an interview with *The American Journal of Managed Care*[®], Shigehira Saji, MD, PhD, of Fukushima Medical University Hospital, Fukushima, Japan, emphasized that this is the first study to show the benefit of maintenance endocrine therapy in this patient population. In particular, bevacizumab therapy extended time to failure of strategy (TFS), she said.

When managing ABC/MBC, the typical approach involves maintaining active therapy until either disease progression (PD)

occurs or intolerable toxicities arise that require the patient to discontinue treatment. For example, although first-line therapy with bevacizumab plus weekly paclitaxel has shown efficacy in these patients, it is associated with neurotoxicity, predominantly in the form of peripheral sensory neuropathy, which leads some patients to discontinue treatment.

With this in mind, Saji and colleagues designed a multicenter study including women with HR+, HER2-negative breast cancer to assess the efficacy of interventional maintenance endocrine therapy with bevacizumab after they received fixed doses of induction chemotherapy with weekly paclitaxel and bevacizumab. The study enrolled 160 patients who underwent induction therapy with 4 to 6 cycles of weekly paclitaxel and bevacizumab as first-line treatment.

Of the 160 patients, 125 achieved complete response, partial response, or stable disease and were randomized 1:1 either to continue weekly paclitaxel and bevacizumab therapy (n = 63; arm A) or to instead receive maintenance endocrine therapy (the aromatase inhibitor [AI] fulvestrant, or AI with a luteinizing hormone-releasing hormone analogue) with bevacizumab until disease progression (n = 62; arm B). Patients in arm B would undergo weekly paclitaxel maintenance endocrine therapy and bevacizumab reinduction therapy if clinical PD should occur. This type of “switch maintenance strategy with endocrine therapy after induction chemotherapy has been thought to be a reasonable choice,” and is included in many practice guidelines, Saji told *The American Journal of Managed Care*®. “However, there [had been] no study showing this is really safe and effective,” she added.

The study’s observation period lasted 2.5 years. Its primary end point was TFS, which the investigators defined as the time from when patients were randomized to occurrence of an event such as introduction of a nonstudy agent into the treatment regimen, PD, or death. Secondary end points included patient-reported health-related quality of life (HRQoL), safety assessment, efficacy according to biomarkers, and overall survival.

After analyzing the data, the researchers found that TFS was longer in patients who switched to maintenance endocrine therapy with bevacizumab (arm B; 16.82 months) than in those who continued with weekly paclitaxel and bevacizumab (arm A; 8.87 months) (hazard ratio, 0.51; 95% CI, 0.34-0.75; $P < .001$). Because of PD, 52% of patients in arm B underwent reinduction therapy with maintenance therapy.

Patients who switched to maintenance endocrine therapy with bevacizumab also experienced a greater deterioration rate of HRQoL, as shown by results of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire—specifically, the

FACT-B Trial Outcome Index (TOI). According to the researchers, a change in score of 5 points or more on the TOI reflects clinically meaningful change. Although the clinically meaningful deterioration rates were similar between the 2 arms at 2 months ($P = 1.000$), 4 months ($P = .497$), and 1 year ($P = .477$), the deterioration rate in the arm receiving maintenance endocrine therapy with bevacizumab at 2 years was more than twice the rate in the arm that continued with weekly paclitaxel and bevacizumab (42.9% vs 19.4%; $P = .088$). However, the difference remained statistically nonsignificant.

The researchers analyzed Patient Neurotoxicity Questionnaire (PNQ) data and found a significantly greater rate of severe (PNQ grades D and E) motor neurotoxicity at all times in the arm that continued with weekly paclitaxel and bevacizumab (arm A) than in the arm receiving maintenance endocrine therapy with bevacizumab. This difference was most pronounced at 1 year (26.1% vs 5.1%; $P = .017$). Although the rate of severe sensory neurotoxicity was also greater in arm A at all times during the study, the differences were statistically nonsignificant.

According to Saji, these data suggest that after undergoing induction chemotherapy, patients with HR+, HER2-negative ABC/MBC could safely undergo a chemotherapy-free interval with endocrine-based therapy. Overall, the results of this study suggest that this treatment strategy should be further investigated for other targeted agents in this therapeutic area, she concluded. ●

REFERENCE

Saji S, Kitada M, Takano T, et al. A randomized, multicenter, phase II study evaluating the efficacy of interventional maintenance endocrine therapy with bevacizumab following fixed cycles of bevacizumab plus paclitaxel in advanced/metastatic ER-positive HER2-negative breast cancer: JBCRG-M04 BOOSTER trial. Poster presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Poster P2-15-01. abstractsonline.com/pp8/#1/7946/presentation/797. Accessed December 11, 2019.

Subcutaneous Pertuzumab–Trastuzumab Combination is Found to be Noninferior to Intravenous Pertuzumab and Trastuzumab

GINA BATTAGLIA

A subcutaneous fixed-dose combination of pertuzumab and trastuzumab plus intravenous chemotherapy yielded noninferior serum concentrations of pertuzumab and trastuzumab compared with standard regimens of intravenous pertuzumab, trastuzumab, and chemotherapy in patients with HER2-positive early breast cancer, according to a primary analysis of the FeDeriCa trial presented by Antoinette R. Tan, MD, MHSc, chief of breast medical oncology and co-director of the Phase 1 Program at the Levine Cancer Institute, Atrium Health, in Charlotte, North Carolina.¹

Trastuzumab was the first targeted monoclonal antibody approved for HER2-positive early-stage breast cancer. The addition of pertuzumab, another HER2-targeted therapy, is thought to complement the activity of trastuzumab by binding to a different site on the HER2 receptor, leading to more comprehensive blockade of HER2 signaling pathways than with either agent alone. The NeoSphere trial showed that the addition of pertuzumab to docetaxel and trastuzumab led to a more significant pathologic complete response (PCR) rate compared with the PCR rate with trastuzumab and chemotherapy in the

neoadjuvant setting.² In the adjuvant setting, adding pertuzumab to trastuzumab and chemotherapy reduced risk for recurrence of invasive disease or mortality in patients with HER2-positive early-stage breast cancer.³

The intravenous infusions of pertuzumab and trastuzumab used for HER2-positive breast cancer take approximately 150 minutes for a loading dose and 60 to 150 minutes for a maintenance dose.⁴ The fixed-dose combination, which is based on a proprietary recombinant human hyaluronidase PH20 that temporarily degrades hyaluronan to improve dispersion and absorption, is administered subcutaneously in 8 minutes for a loading dose and 5 minutes for a maintenance dose.⁴ According to Tan, an effective subcutaneous formulation would reduce the amount of time in the treatment chair, which not only would shorten treatment time for the patient but would increase the availability of chairs at infusion centers for other patients. “Shorter administration time provides greater flexibility in a center for scheduling appointments,” said Tan. She added that subcutaneous therapy could reduce pain and discomfort for patients, not to mention costs related to drug delivery and the use of pharmacy and nursing resources.

In the FeDeriCa trial, Tan and colleagues aimed to investigate whether the subcutaneous formulation of pertuzumab and trastuzumab—thought to be the first to combine 2 monoclonal antibodies with recombinant human hyaluronidase in 1 vial—plus chemotherapy could provide noninferior pharmacokinetics, efficacy, and safety compared with standard intravenous pertuzumab, trastuzumab, and chemotherapy in women with HER2-positive early-stage breast cancer.¹ Patients with centrally confirmed HER2-positive invasive breast cancer (tumor size ≥ 2 cm, node-positive disease, stage II-IIIc) were randomized 1:1 to receive 8 cycles of chemotherapy plus intravenous trastuzumab (loading and maintenance doses of 8 mg/kg and 6 mg/kg, respectively) and pertuzumab (loading and maintenance doses of 840 mg and 420 mg, respectively) every 3 weeks during cycles 5 to 8 or the fixed-dose combination of trastuzumab and pertuzumab administered subcutaneously (loading dose 600 mg trastuzumab/1200 mg pertuzumab and maintenance doses 600 mg each of trastuzumab and pertuzumab) every 3 weeks during treatment cycles 5 to 8. The chemotherapy regimen was chosen by the investigator and was either 4 cycles of dose-dense doxorubicin and cyclophosphamide administered once every 2 weeks plus 4 cycles of weekly paclitaxel or 4 cycles of doxorubicin and cyclophosphamide every 3 weeks plus 4 cycles of docetaxel every 3 weeks. After patients underwent surgery, patients continued HER2-targeted therapy as per randomization, completing a total of 18 cycles.¹

The primary objective of the study was noninferiority of the serum trough concentration of pertuzumab prior to dosing at cycle 8 within the fixed-dose subcutaneous formulation versus the intravenous pertuzumab. Secondary objectives

included noninferiority of the serum trough concentration of trastuzumab between the fixed-dose subcutaneous formulation and intravenous trastuzumab; total PCR in the breast and axilla; and safety, including primary and secondary cardiac events. The noninferiority margin for the lower bound of the 90% confidence interval of the geometric mean ratio (GMR) was greater than or equal to 0.8.¹

A total of 242 patients in the intravenous arm and 234 patients in the subcutaneous arm completed the neoadjuvant treatment period. Baseline demographics and disease characteristics were similar between the 2 arms, with approximately 80% in each arm presenting initially with stage II to IIIa disease and 61% presenting with hormone (estrogen or progesterone) receptor-positive disease. GMRs for the pre-dose serum trough concentration at cycle 8 was 1.22 (90% CI, 1.14-1.31) for pertuzumab and 1.33 (90% CI, 1.24-1.43) for trastuzumab. Additionally, rates of total PCR were “nearly identical in each arm” and comparable with rates seen in other trials of chemotherapy plus HER2-targeted therapy with pertuzumab and trastuzumab, according to Tan.

“ [F]urther analysis of the trial results will be important for confirming efficacy and safety of subcutaneous HER2-targeted therapy.”

Safety outcomes were comparable between treatment groups, with low rates of cardiac events. The most common adverse events were alopecia, nausea, diarrhea, anemia, and asthenia. Although infusion/administration-related reactions within 24 hours of treatment were not different between groups (13.5% in the intravenous arm vs 17.3% in the subcutaneous arm), Tan noted that injection- or administration-related reactions with subcutaneously delivered drugs could be a “small challenge” with future use of the fixed-dose combination.¹

The authors concluded that the subcutaneous fixed-dose combination of trastuzumab and pertuzumab could provide a faster and simpler delivery method for HER2-targeted treatment of breast cancer. Tan added that further analysis of the trial results will be important for confirming efficacy and safety of subcutaneous HER2-targeted therapy. If these data hold up, developing protocols for subcutaneous administration outside of the infusion center could further improve convenience for

patients and infusion centers, according to Tan. “Developing a home administration protocol for a subcutaneous formulation is an area of future research and can be advantageous for patients and infusion centers,” she said, adding that specific methods would be necessary to ensure patient safety with home-based treatment administration. ●

REFERENCES

1. Tan AR, Im SA, Mattar A, et al. Subcutaneous administration of the fixed-dose combination of trastuzumab and pertuzumab in combination with chemotherapy in HER2-positive early

breast cancer: primary analysis of the phase III, multicenter, randomized, open-label, two-arm FeDeriCa study. Presented at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract PD4-07.

2. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9.

3. von Minckwitz G, Procter M, de Azambuja E, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med.* 2017;377(2):122-131. doi: 10.1056/NEJMoa1703643.

4. Roche’s fixed-dose subcutaneous combination of Perjeta and Herceptin showed non-inferiority when compared to intravenous formulations for people with HER2-positive breast cancer [news release]. Basel, Switzerland: Roche; September 13, 2019. roche.com/media/releases/med-cor-2019-09-13.htm. Accessed December 14, 2019.

plasmaMATCH Trial Results Suggest That ctDNA Can Identify Patients With *HER2* and *AKT1* Mutations

LAURIE ANNE WALDEN, DVM

Testing the blood for circulating tumor DNA (ctDNA) is a viable alternative to obtaining tissue biopsies to identify gene mutations in breast tumors, according to plasmaMATCH trial results presented at the 2019 San Antonio Breast Cancer Symposium. Patients in the plasmaMATCH trial also received targeted therapies matched to their tumors’ specific mutations. Results presented at the symposium indicated that patients with *HER2* and *AKT1* mutations had clinically relevant response rates to these targeted treatments.¹

“The choice of targeted treatment we give to patients is usually based on the mutations found in the original breast tumor. But the cancer can have different mutations after it has moved to other parts of the body,” said Nicholas Turner, MA, MRCP, PhD, consultant medical oncologist at the Royal Marsden NHS Foundation Trust and team leader in molecular oncology at the Institute of Cancer Research, London, United Kingdom. “We have now confirmed that liquid biopsies [blood tests for DNA] can quickly give us a bigger picture of the mutations within multiple tumours throughout the body, getting the results back to patients accurately and faster than we could before. This matters a lot in terms of making decisions, particularly for those with advanced breast cancer who need to be put on new treatments quickly.”²

Gene mutations in breast tumors can change over time as the cancer progresses or is altered by treatment. However, patients with advanced breast cancer do not commonly undergo repeated biopsy procedures that can detect new mutations. Tests for tumor DNA released into the bloodstream, known as ctDNA, may be a less invasive alternative to biopsy to identify a tumor’s current genotype.^{1,3}

The plasmaMATCH trial was conducted to (1) determine whether tests for ctDNA could be used to identify patients who might benefit from therapies targeted to their tumor mutations

and (2) evaluate the efficacy and safety of these targeted therapies.⁴ The study was an open-label, multicenter, multicohort platform trial that included patients with advanced breast cancer.¹

“We aim to assess whether liquid biopsies can replace standard, invasive biopsies and help improve treatment for women with advanced breast cancer,” explained Turner. The trial “will help us to determine whether a liquid biopsy is a reliable test that may spare future breast cancer patients from having invasive biopsies,” he added.⁵

Methods

Patients enrolled in the trial were sorted into 4 parallel treatment cohorts according to mutations identified on tests for ctDNA. In the part of the trial intended to provide proof of principle efficacy for selected targeted therapies,⁴ patients received treatments matched to their mutations. A fifth treatment cohort consisted of patients with triple-negative breast cancer (negative for estrogen receptors, progesterone receptors, and HER2 protein⁶) and no applicable mutations. Data from this fifth cohort will be presented in a separate report. The investigators used a specific phase 2 single-arm design for each cohort. The treatment cohorts and corresponding therapies were as follows¹:

- Cohort A: *ESR1* mutation; extended-dose fulvestrant 500 mg every 2 weeks
- Cohort B: *HER2* mutation; neratinib with or without fulvestrant (standard dosing)
- Cohort C: *AKT1* mutation in patients with estrogen receptor-positive cancer; capivasertib plus fulvestrant (standard dosing)
- Cohort D: *AKT1* mutation in patients with estrogen receptor-negative cancer or a *PTEN* inactivating mutation; capivasertib

- Cohort E: Triple-negative breast cancer; olaparib plus AZD6738 (an inhibitor of ATR, a serine/threonine protein kinase)

The investigators compared the results of ctDNA testing with DNA sequencing performed on biopsy specimens of advanced disease. The researchers used 2 technologies to assess ctDNA: digital droplet polymerase chain reaction (PCR) testing, conducted prospectively in all patients, and error-corrected sequencing (Guardant360, Guardant Health, Inc), conducted prospectively beginning partway into the recruitment period and retrospectively in patients recruited earlier. Biopsy specimen sequencing was performed retrospectively and did not affect cohort assignment.¹

For patients in cohorts A through D, the primary end point was confirmed objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points were clinical benefit rate, progression-free survival (PFS) rate, safety, and frequency of mutations detected on tests for ctDNA.¹

Results

Registration for ctDNA screening for cohorts A through D ended on April 26, 2019. A total of 1044 patients were registered in these 4 cohorts. Screening results were available for 1033 patients (99%). A total of 142 patients were ultimately included in cohorts A through D: 84 patients in cohort A, 21 in cohort B, 18 in cohort C, and 19 in cohort D.¹

In the analysis of targeted therapies, efficacy criteria were met in cohorts B and C. Cohort B, patients with *HER2* mutations receiving neratinib, had a confirmed response rate of 25.0% (95% CI, 8.7%-49.1%) and a median PFS of 5.4 months (interquartile range [IQR], 3.4-9.1 months). Cohort C, patients with *AKT1* mutations receiving capivasertib, had a confirmed response rate of 22.2% (95% CI, 6.4%-47.6%) and a median PFS of 10.2 months (IQR, 3.2-18.2 months).¹

Efficacy criteria were not met in cohort A, patients with *ESR1* mutations receiving extended-dose fulvestrant (confirmed

response rate, 8.1%; 95% CI, 3.0%-16.8%). The median PFS in cohort A was 2.2 months (IQR, 1.7-5.3 months). In cohort D, capivasertib was found to be active in the subset of patients with *AKT1* mutations (confirmed response rate, 33.3%; 95% CI, 4.3%-77.7%). The overall confirmed response rate for all patients in cohort D was 10.5% (95% CI, 1.3%-33.1%) and the median PFS was 3.4 months (IQR, 1.8-5.5 months).¹

The results of the safety analysis showed that adverse events were similar to those previously reported. The investigators reported that patients tolerated extended-dose fulvestrant well.¹

Genotype results according to blood tests for ctDNA via digital PCR were similar to results of gene sequencing of biopsy specimens. Individual gene level agreement was 95.5% to 99.4% (κ , 0.89-0.93).¹

The investigators concluded that testing ctDNA to determine tumor genotype is accurate and adequate for clinical practice. They suggested that ctDNA tests can be used to identify patients with *HER2* and *AKT1* mutations, who may respond to therapies targeted to their tumor mutations.¹ ●

REFERENCES

1. Turner N, Kingston B, Kilburn L, et al; plasmaMATCH Trial Management Group. Results from the plasmaMATCH trial: a multiple parallel cohort, multi-centre clinical trial of circulating tumour DNA testing to direct targeted therapies in patients with advanced breast cancer (CRUK/15/010). Abstract GS3-06. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.
2. The big picture. Royal Marsden NHS Foundation Trust website. royalmarsden.nhs.uk/big-picture. Published December 12, 2019. Accessed December 17, 2019.
3. A trial using a blood test to find certain gene changes and decide treatment for advanced breast cancer (plasmaMATCH). Cancer Research UK website. www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-using-a-blood-test-to-find-certain-gene-changes-and-decide-treatment-for-advanced-breast. Accessed December 17, 2019.
4. The UK Plasma Based Molecular Profiling of Advanced Breast Cancer to Inform Therapeutic Choices trial (plasmaMATCH). clinicaltrials.gov/ct2/show/study/NCT03182634. Published June 9, 2017. Updated January 21, 2019. Accessed December 17, 2019.
5. Q&A: plasmaMATCH trial. Royal Marsden NHS Foundation Trust website. royalmarsden.nhs.uk/rm-magazine/qa-plasmamatch-trial. Accessed December 17, 2019.
6. Triple negative breast cancer. Cancer Research UK website. www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/types/triple-negative-breast-cancer. Accessed December 17, 2019.

Oral Paclitaxel Combined With Encequidar Significantly Increases Confirmed Response Rate Over Intravenous Paclitaxel in Phase 3 Trial in Metastatic Breast Cancer

KARA L. GUARINI, MS

Taxane-based chemotherapy regimens are among the most common and effective systemic therapies in breast cancer.^{1,2} Currently, the taxane paclitaxel is available only as an intravenous (IV) formulation.³ In a press briefing at the 2019 San Antonio Breast Cancer Symposium, Gerardo Antonio Umanzor Funez, MD, a medical oncologist at Liga Contra El Cáncer, Honduras, acknowledged that “it has been very frustrating to

have an effective chemotherapy like [IV] paclitaxel, which a lot of patients cannot tolerate.” The results of an ongoing phase 3 trial in which patients were administered oral paclitaxel along with encequidar—a potent, highly specific inhibitor of P-gp that increases absorption of paclitaxel—have revealed that the frustrations of not having an oral option for paclitaxel may soon be alleviated.^{1,4}

Encequidar, in combination with oral paclitaxel (OPE), “was designed to overcome [the tolerability] issue,” according to Umanzor Funez. Oral treatment also provides the advantages of patient convenience and at-home treatment, while removing the risks associated with infusion and the need for IV access.^{5,6}

Umanzor Funez and his coinvestigators assessed the efficacy and safety of OPE compared with IV paclitaxel in a phase 3, open-label study of patients with metastatic breast cancer. The study enrolled 402 patients (OPE, n = 265; IV paclitaxel, n = 137) from 45 sites in Central and South America with histologically or cytologically confirmed metastatic breast cancer and an Eastern Cooperative Oncology Group performance status grade of 0 or 1. Patients were required to have measurable metastatic target lesion disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).¹

Patients were randomized 2:1 to receive OPE (administered as 205 mg/m² oral paclitaxel [each capsule contained 30 mg solubilized paclitaxel] and encequidar 15 mg) once daily for 3 consecutive days per week (1 cycle) or IV paclitaxel (at the current labeling dose of 175 mg/m²) via a 3-hour infusion once a week for 3 weeks (1 cycle).^{1,3} Patients assigned to OPE received their first dose at the clinic and took the rest of their medication at home. Patients were instructed to adhere to a 4-hour fasting period before taking the encequidar tablet, wait 1 hour, then take the oral paclitaxel capsules, followed by another 4-hour fasting period. Imaging was completed at weeks 10, 16, and 19 (primary end point analysis), and optionally at week 22 for a confirmatory scan of partial response (PR)/complete response (CR).¹ Patients with responding or stable disease could continue in the extension period of the trial.

The prespecified modified intention-to-treat (mITT) population included all patients (OPE, n = 240; IV paclitaxel, n = 120) who had a baseline evaluable scan showing metastatic lesion by RECIST v1.1 on central review and who received at least 7 doses of OPE or 1 dose of IV paclitaxel. The primary efficacy end point was based on 2 consecutive scans of PR/CR using RECIST v1.1 criteria, as assessed by blinded and adjudicated central independent review. Assessment of safety and tolerability also was a primary objective. Secondary end points were progression-free survival (PFS) and overall survival (OS).¹

OPE was found to significantly increase the confirmed response rate (RR) compared with IV paclitaxel. The primary end point was confirmed tumor RR by week 19. In the protocol-defined mITT population, the RR was 40.4% for OPE and 25.6% for IV paclitaxel ($P = .005$), representing an absolute improvement of 14.8% with OPE. Final analysis of the primary end point in the ITT population demonstrated that OPE was associated with a significantly higher confirmed tumor RR (35.8%) compared with IV paclitaxel (23.4%) ($P = .011$). Ongoing analyses of the mITT population suggest that OPE significantly increases median OS (27.9 vs 16.9 months; $P = .035$) and median PFS (9.3 vs 8.3 months; $P = .077$) compared with IV paclitaxel.¹

Patient baseline characteristics, including prior taxane therapy, were similar among the 2 treatment groups. Treatment responses were durable. In an ongoing analysis of duration of confirmed response, the median duration of response was 39.0 weeks with OPE compared with 30.1 weeks for IV paclitaxel.¹

In patients with evaluable postbaseline scans, the confirmed response rates were significantly higher with OPE (50.3%) than with IV paclitaxel (29.6%) ($P = .0005$). In all clinically essential subgroups, tumor response was similar to the overall confirmed response profiles.¹

The toxicity profile of OPE was similar to that of IV paclitaxel, according to Umanzor Funez. OPE was associated with higher rates of neutropenia, infection, and gastrointestinal adverse events¹ (AEs) “but they were low grade and manageable,” he said.

“Chemotherapy-induced peripheral neuropathy is a highly debilitating [AE] of IV paclitaxel,” Umanzor Funez explained. The incidence of neuropathy up to week 23 was markedly less in patients given OPE (17%) compared with those given IV paclitaxel (57%). Grade 3 neuropathy was observed in 1% and 8% of patients, respectively, and according to Umanzor Funez, there was “about 50% less alopecia [in patients taking] oral paclitaxel than those taking IV [paclitaxel].”¹

Based on the dosing scheme, the average patient given OPE received 11 capsules on each day of treatment. When asked if the number of capsules or fasting requirements caused an issue with treatment adherence during the trial, Umanzor Funez acknowledged that they had “doubt at the beginning, but [received] no complaints at all. Patients were so excited that they were getting an oral treatment and we had very good compliance.” OPE represents the first orally administered paclitaxel associated with a significant increase in confirmed response rate compared with IV paclitaxel. It may provide a meaningful improvement in the clinical efficacy and safety of paclitaxel in metastatic breast cancer.¹ ●

REFERENCES

1. Umanzor Funez G, Cutler DL, Barrios FJ, et al. Oral paclitaxel with encequidar: the first orally administered paclitaxel shown to be superior to IV paclitaxel on confirmed response and survival with less neuropathy: a phase III clinical study in metastatic breast cancer. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS6-01. abstractsonline.com/pp8/#/7946/presentation/2050.
2. Gradishar WJ. Taxanes for the treatment of metastatic breast cancer. *Breast Cancer (Auckl)*. 2012;6:159-171. doi: 10.4137/BCBCR.S8205.
3. Taxol [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; 2011. accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf. Accessed December 10, 2020.
4. Jackson CGCA, Deva S, Bayston K, et al. An international randomized cross-over bio-equivalence study of oral paclitaxel + HM30181 compared with weekly intravenous (IV) paclitaxel in patients with advanced solid tumours. *Ann Oncol*. 2019;30(suppl_5):v159-v193. doi: 10.1093/annonc/mdz244.
5. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol*. 1997;15(1):110-115. doi: 10.1200/JCO.1997.15.1.110.
6. Eek D, Krohe M, Mazar I, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. *Patient Prefer Adherence*. 2016;10:1609-1621. doi: 10.2147/PPA.S106629.

Genomic Study Provides Insight on Mechanisms of Resistance to CDK4/6 Inhibitors in HR-Positive/HER2-Negative Metastatic Breast Cancer

GINA BATTAGLIA

Molecular mechanisms involved in resistance to cyclin-dependent kinase (CDK) 4/6 inhibitors are highly heterogeneous in hormone receptor (HR)-positive, HER2-negative metastatic breast cancer, according to a recent genomic analysis presented by Seth Wander, MD, PhD, at the San Antonio Breast Cancer Symposium (SABCS).¹

Three CDK4/6 inhibitors have been approved by the FDA and are a standard component of first- or second-line regimens, along with estrogen therapy, in patients with HR-positive, HER2-negative metastatic breast cancer. Phase 3 trials showed that first-line therapy with palbociclib (PALOMA-2),² ribociclib (MONALEESA-2),³ and abemaciclib (MONARCH 3)⁴ improved progression-free survival (PFS) in postmenopausal women with HR-positive metastatic breast cancer. Similarly, phase 3 trials in the second-line setting showed that addition of palbociclib (PALOMA-3),⁵ ribociclib (MONALEESA-2),⁶ or abemaciclib (MONARCH 2)⁷ to fulvestrant improved PFS.

Although most patients demonstrate benefit with CDK4/6 inhibition initially, intrinsic resistance occurs in a small proportion of patients and acquired resistance eventually occurs in virtually all patients, according to Wander, a medical oncologist at Massachusetts General Hospital and instructor of medicine at Harvard Medical School, both in Boston. “We’re always trying to understand that process [of resistance], because the more we can understand that process, the better we can intervene early or at the time of progression with intelligent strategies to overcome these mechanisms of resistance,” he said.

Wander added that insight into the molecular mechanisms responsible for response and resistance to CDK4/6 inhibitors is limited due to the relative newness of the drugs. A recent review categorized mechanisms of intrinsic or acquired resistance to CDK4/6 inhibitors identified in preclinical models as specific to or independent of cell cycle regulation.⁸ The cell cycle-specific mechanisms discussed were loss of RB; amplification of p16, CDK6, CCNE1/2/CDK2, E2F, or CDK4; overexpression of WEE1, CDK7, or MDM2; activation of histone deacetylase; and loss of FZR1. The mechanisms independent of cell cycle regulation included activation of the FGFR or PI3K/AKT/mTOR pathways; loss of estrogen receptor or progesterone receptor expression; increased transcriptional activity of AP-1; activation of the epithelial-mesenchymal transition pathway; suppression of Smad3; activation of autophagy; and enrichment of immune-related pathways.⁸

However, most clinical studies have been unable to corroborate these preclinical findings, an issue that is not unique to CDK4/6 inhibitors, said Wander. He stated that the “very detailed

clinical annotation of the biopsies” in the study presented at SABCS was a key advantage for increasing the clinical applicability of the study’s findings. “In many cases on a clinical trial or as part of a research program, there may be lots of tissue that gets collected, but if you don’t have a really detailed understanding of what happened to the patient, the tissue is very difficult to interpret,” he said. “There may be a mutation that is present or absent, but you have to have the clinical insight to understand that [the patient] did or didn’t respond.”

In the study, Wander and colleagues performed whole-exome sequencing on metastatic tumor biopsies from 58 patients with HR-positive, HER2-negative metastatic breast cancer who received a CDK4/6 inhibitor (with or without anti-estrogen therapy) at the Dana-Farber Cancer Institute in Boston. Seven patients had biopsy pairs before and after exposure to CDK4/6 inhibitors. Overall, 69.5% of the biopsies had intrinsic or acquired resistance to CDK4/6 inhibition, whereas the remaining 30.5% were considered to be sensitive.

To validate potential mediators of resistance found in tumor samples, HR-positive, HER2-negative breast cancer cells were modified via clustered regularly interspaced short palindromic repeats knockout or lentiviral overexpression. Researchers tested sensitivity of the cells to antiestrogen drugs and CDK4/6 inhibitors using CellTiter-Glo assays. The investigators also cultured HR-positive, HER2-negative breast cancer cells for resistance in the presence of escalating doses of a CDK4/6 inhibitor. Western blotting was performed on derivative cell lines to investigate potential mediators of resistance identified in patient tumor samples, and novel dependencies were recognized through treatment with targeted agents *in vitro*.¹

The whole-exome sequencing of tumors exposed to CDK4/6 inhibitors showed that candidate mechanisms of resistance included biallelic disruption of RB1 (n = 4; 10%) and activating events in AKT1 (n = 5; 12.5%), AURKA (n = 11; 27.5%), RAS (n = 4; 10%), and CCNE2 (n = 6; 15%). In 1 patient with 1 pre- and 2 postexposure biopsies, convergent evolution toward biallelic RB1 disruption was demonstrated, and pre- and postexposure biopsies in 2 other patients demonstrated acquisition of a mutation and amplification of AKT.

In vitro experiments showed that RB1 knockout and overexpression of AKT1, KRAS G12D, AURKA, and CCNE2 led to resistance to CDK4/6 inhibitors and antiestrogen therapies. Concordant acquisition of RB1 downregulation, RAS/ERK activation, AURKA overexpression, and CCNE2 overexpression was demonstrated in breast cancer cells cultured for resistance to CDK4/6 inhibitors. Sensitivity to the novel AURKA inhibitor

LY3295668 was enhanced in the derivative resistant cell lines with loss of RB1 or gain of AURKA, and cells with activation of RAS were sensitive to ERK inhibition with LY3214996. In addition, cells that overexpressed CCNE2 were highly sensitive to the CHEK1 inhibitor prexasertib.¹

“What we’ve learned, both from our work and a couple of other projects that have been coming out over the last year or so, is that there is not a single dominant mechanism of resistance to these drugs,” said Wander. “We’ve identified upward of 7 or 8 different molecular changes that can provoke resistance, both in patient samples and in the laboratory. Taking a one-size-fits-all approach [to treatment] in the resistant population probably isn’t the best strategy. What we need to do is think about how to leverage our understanding from next-generation sequencing to design strategies for individual patients.”

Wander noted that one limitation of such a detailed analysis of patient biopsies is the relatively small number of samples (n = 58) that they were able to include in the study. “Obviously, it would be better if there were several hundred, and I think the trade-off to having the degree of detail and insight that we have is that it’s hard to scale to very large numbers,” he said. “There has to be some middle ground where we’re doing this in a large enough cohort to have meaningful statistics and results but we’re also not compromising the quality of the information that we’re able to obtain.”

Nevertheless, Wander concluded that the results from this study provide a platform to pursue future studies to further investigate the clinical relevance of these resistance mechanisms. “Some important next steps are to try to translate these findings into clinically meaningful conclusions. We’re in the process of designing these clinical trials and thinking about how we

might leverage this information to help patients who are becoming resistant [to CDK4/6 inhibitors]. We’re also starting to think about how we can use additional technology to identify similar or new mechanisms of resistance,” he explained. “A lot of emerging technology can give us deeper insight into these and other mechanisms of resistance, and we’re in the process of pursuing those experiments with the biopsy samples and in the laboratory.” ●

REFERENCES

1. Wander SA, Cohen O, Gong X, et al. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in patients with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). Presented at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract PD2-09.
2. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. doi: 10.1056/NEJMoa1607303.
3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer [published correction appears in *N Engl J Med*. 2018;379(26):2582. doi: 10.1056/NEJMx180043]. *N Engl J Med*. 2016;375(18):1738-1748. doi: 10.1056/NEJMoa1609709.
4. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646. doi: 10.1200/JCO.2017.75.6155.
5. Cristofaniilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial [published corrections appear in *Lancet Oncol*. 2016;17(4):e136. doi: 10.1016/S1470-2045(16)00155-8; and *Lancet Oncol*. 2016;17(7):e270. doi: 10.1016/S1470-2045(16)30222-4]. *Lancet Oncol*. 2016;17(4):425-439. doi: 10.1016/S1470-2045(15)00613-0.
6. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24):2465-2472. doi: 10.1200/JCO.2018.78.9909.
7. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. doi: 10.1200/JCO.2017.73.7585.
8. Pandey K, An HJ, Kim SK, Lee SA, et al. Molecular mechanisms of resistance to CDK4/6 inhibitors in breast cancer: a review. *Int J Cancer*. 2019;145(5):1179-1188. doi: 10.1002/ijc.32020.

Adjuvant Chemotherapy Shows Slight Benefit in Younger Women With Breast Cancer Who Have Mixed Clinical, Genomic Risk

Patients with premenopausal breast cancer and discordant clinical and genomic risk had a small increase in distant metastasis if they did not receive adjuvant chemotherapy, according to a post hoc analysis of the MINDACT trial (NCT00433589).¹ The difference was about 3% in absolute terms and was based on data for patients younger than 50 years who were deemed to be at high clinical risk of recurrence but at low genomic risk by the 70-gene MammaPrint assay. In contrast, women older than 50 years had nearly identical 5-year distant metastasis-free survival (DMFS) rates with or without adjuvant chemotherapy.

The implications of the findings from the MINDACT trial² remain unclear but are consistent with a trend seen in a subgroup analysis of the phase 3 TAILORx trial³ that also employed a

genomic test to evaluate the need for adjuvant chemotherapy in patients with early breast cancer.

“This was an unplanned and underpowered subgroup analysis,” study investigator Fatima Cardoso, MD, of the Champalimaud Cancer Center in Lisbon, Portugal, said in a presentation. “Cautious interpretation is needed because of the large confidence intervals associated with the hazard ratios. Nonetheless, the analysis suggests that [treating with tamoxifen alone in] women younger than 50 years who were in the clinical high-risk/genomic low-risk group, [ie, the discordant group]...might not be the optimal treatment, although the difference seen between the chemotherapy and nonchemotherapy groups is small,” she noted. “It is possible that this age-dependent effect

is due to chemotherapy-induced ovarian function suppression,” Cardoso added. “Neither the MINDACT nor TAILORx trial is able to answer this question.”

MINDACT involved 6693 women with newly diagnosed early-stage breast cancer. Their risk of postoperative recurrence was evaluated by a clinical risk assessment tool and by the MammaPrint 70-gene assay. Patients who were deemed at high risk by both assessments received adjuvant chemotherapy, while those judged to be at low risk by both methods received no chemotherapy. Patients who had discordant clinical and genomic risk assessments were randomized to adjuvant chemotherapy or no chemotherapy. All patients with hormone receptor (HR)-positive disease received adjuvant endocrine therapy.

“ [S]mall differences in the younger patients could reflect the use of endocrine therapy, primarily with tamoxifen, without ovarian function suppression.”

The primary end point was 5-year DMFS in patients with discordant findings who were randomized to no chemotherapy; the trial was statistically powered to demonstrate a significant outcome if DMFS exceeded 92%. Additionally, the 5-year DMFS rate was significant if the 95% 2-sided CI exceeded 92%. The results showed a 5-year DMFS of 94.7%, and the 95% CI exceeded 92%.

The TAILORx trial involved more than 10,000 patients with HR-positive, HER2-negative early breast cancer. The primary results showed that adjuvant endocrine therapy was noninferior to chemotherapy plus endocrine therapy for patients judged to have an intermediate risk of recurrence by the OncotypeDx genomic assay.

Subsequently, TAILORx investigators reported findings from a subgroup analysis, which suggested a differential benefit of chemotherapy for DMFS by age. Patients younger than 50 years with an intermediate risk of recurrence were shown to have

about a 3% higher risk of recurrence without chemotherapy versus less than 1% among older women.⁴

Within the range of values for intermediate risk, the analysis showed that younger women with a high clinical risk benefited substantially more from chemotherapy than did patients who had a low clinical risk. At the upper end of the range for intermediate-risk values, younger patients derived greater benefit from chemotherapy, irrespective of clinical risk.

Cardoso and colleagues sought to determine whether a similar age-related divergence in chemotherapy benefit might exist in the MINDACT population. The analysis included 1317 patients with clinical high-risk/genomic low-risk profiles, 452 younger than 50 years and 865 at least 50 years.

The data showed that the younger patients had a 5-year DMFS of 93.1% without adjuvant chemotherapy; DMFS increased to 96.1% if they were randomized to receive chemotherapy. The findings suggested that chemotherapy reduced relative risk of distant recurrence by 46% in younger women, albeit with overlapping CIs (hazard ratio, 0.54; 95% CI, 0.24-1.22). In the group of women 50 years or older, 5-year DMFS was virtually identical with or without chemotherapy (95.4% vs 95.2%).

Calculated as distant metastasis-free interval, the results were similar: a 2.5% absolute difference that favored chemotherapy in younger patients (96.1% vs 93.6%) and demonstrated no difference in the older subgroup (96.3% vs 96.7%).

Cardoso said the small differences in the younger patients could reflect the use of endocrine therapy, primarily with tamoxifen, without ovarian function suppression. ●

REFERENCES

1. Piccart MJ, Poncet C, Cardoso F, et al. Should age be integrated together with clinical and genomic risk for adjuvant chemotherapy in early luminal breast cancer? MINDACT results compared to those of TAILOR-X. Presented at: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. Abstract GS4-05.
2. Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. doi: 10.1056/NEJMoa1602253.
3. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121. doi: 10.1056/NEJMoa1804710.
4. Sparano JA, Gray RJ, Makower DF, et al. Clinical outcomes in early breast cancer with a high 21-gene recurrence score of 26 to 100 assigned to adjuvant chemotherapy plus endocrine therapy: a secondary analysis of the TAILORx randomized clinical trial [published online September 30, 2019]. *JAMA Oncol*. doi: 10.1001/jamaoncol.2019.4794.

NOTES
