2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Breast Cancer

Wendy H. Vogel, MSN, FNP, AOCNP®, of Wellmont Cancer Institute discusses results from a study in hormone receptor–positive metastatic breast cancer (MONALEESA-7), two studies in the metastatic HER2-positive setting (SOPHIA and NALA), as well as a new analysis of the TAILORx trial and a study on the effects of a low-fat diet on incidence and outcomes from the ASCO Annual Meeting, reported by *The ASCO Post*.

Abstract LBA1008

MONALEESA-7 Shows Overall Survival Benefit for Ribociclib/Endocrine Therapy

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/174827/abstract to read the full abstract and view disclosures.

The first statistically significant overall survival benefit has been shown for a cyclin-dependent kinase (CDK) 4/6 inhibitor plus endocrine therapy as first-line treatment of advanced breast cancer. The results are from the phase III MONALEESA-7 trial, which evaluated ribociclib plus endocrine therapy exclusively in peri- and premenopausal women with hormone receptor–positive, HER2-negative disease.

"Ribociclib plus endocrine therapy was associated with about a 29% relative reduction in risk of death," according to Sara A. Hurvitz, MD, Director of the Breast Cancer Clinical Research Program at the University of California Los Angeles Jonsson Comprehensive Cancer Center in Los Angeles, who presented the data at the 2019 ASCO Annual Meeting (Hurvitz et al., 2019). The study was concurrently published in *The New England Journal of Medicine* (Im et al., 2019).

"This is the first time that a statistically significant improvement in overall survival has been observed with a CDK4/6 inhibitor in combination with endocrine therapy in patients with hormone receptor–positive HER2-negative advanced disease," Dr. Hurvitz said. She emphasized that an overall survival benefit was shown for the combination despite the fact that patients with metastatic breast cancer typically receive multiple subsequent agents after coming off clinical trials. "It's very difficult to show a survival benefit in these studies," she noted.

The findings of MONALEESA-7 may influence the choice among the three approved CDK4/6 inhibitors in the clinic. "I think that as clinicians we have been quite comfortable using these agents interchangeably based on copay assistance, dosing, and side-effect profile. But now, we have survival benefits associated with one of them, and until we see that with other agents, this may influence the way physicians practice," Dr. Hurvitz said at a press briefing.

J Adv Pract Oncol 2019;10(6):565-575
https://doi.org/10.6004/jadpro.2019.10.6.6

Key Points

- The phase III MONALEESA-7 trial evaluated the CDK4/6 inhibitor ribociclib plus endocrine therapy in 672 peri- or premenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer.
- The combination led to a 29% reduction in risk of death vs endocrine therapy alone (P = .00973).
- Overall survival rates were 71.9% vs 64.9% at 36 months for the combination and control arms, respectively, and 70.2% vs 46.0% at 42 months.
- The study is the first to show a statistically significant improvement in survival for a CDK4/6 inhibitor in breast cancer and the first to evaluate this treatment exclusively in younger patients.

First to Evaluate Treatment in Premenopausal Subset

MONALEESA-7 randomly assigned 672 women to endocrine therapy alone (letrozole, anastrozole, or tamoxifen, by physician's choice) or the same plus ribociclib (600 mg/d for 3 weeks on, one week off). All women also received goserelin.

Importantly, the study was the first dedicated trial of endocrine therapy with and without a CDK4/6 inhibitor—ribociclib, in this case—in women younger than age 59 (ie, peri- or premenopausal).

In 2018, the investigators reported that MONALEESA-7 met its primary endpoint, with ribociclib plus endocrine therapy prolonging progression-free survival to 23.8 months, up from 13.0 months with endocrine therapy alone (hazard ratio [HR] = 0.55; P < .0001; Tripathy et al., 2018). At the ASCO Annual Meeting, Dr. Hurvitz reported the results for overall survival, which was the key secondary endpoint. Median follow-up was 34.6 months, which was an additional 15 months beyond the primary analysis.

Substantial Improvement in Overall Survival

Median overall survival was not reached with the combination and was 40.9 months in the control arm (HR = 0.712; P = .00973). The results crossed the prespecified stopping boundary for superior efficacy. In the landmark analysis, overall survival rates were, respectively, 71.9% vs 64.9% at 36 months and 70.2% vs 46.0% at 42 months, Dr. Hurvitz reported.

By endocrine partner subgroup, patients receiving a nonsteroidal aromatase inhibitor (n = 495) had a consistent improvement in overall survival with the combination vs placebo, mirroring the outcomes in the whole population. Median overall survival was not reached with the combination and was 40.7 months with placebo (HR = 0.699).

For the smaller subgroup of tamoxifen-treated patients, median survival was not reached with the combination, nor was it reached with endocrine therapy alone in that comparison (HR = 0.791). Tamoxifen, however, was associated with an increase in QT-interval prolongation ≥ 10 milliseconds; therefore, the investigators concluded that tamoxifen should not be used with a CDK4/6 inhibitor.

The safety profile for ribociclib was consistent with its known tolerability profile. As of the data cutoff, 35% of patients in the ribociclib arm were continuing treatment.

References

Hurvitz, S. A., Im, S.-A., Lu, Y.-S., Colleoni, M., Franke, F. A., Bardia, A.,...Tripathy, D. (2019). Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2- advanced breast cancer treated with endocrine therapy with and without ribociclib: Overall survival results [Abstract LBA1008]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(18_suppl). https://doi.org/10.1200/JCO.2019.37.18_suppl.LBA1008

Im, S. A., Lu, Y. S., Bardia, A., Harbeck, N., Colleoni, M., Franke, F.,...Tripathy, D. (2019). Overall survival with ribociclib plus endocrine therapy in breast cancer. *New England Journal of Medicine, 381*, 307–316. https://doi.org/10.1056/NEJMoa1903765

Tripathy, D., Im, S. A., Colleoni, M., Franke, F., Bardia, A., Harbeck, N.,...Lu, Y. S. (2018). Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomized phase 3 trial. *Lancet Oncology, 19*(7), 904–915. https://doi.org/10.1016/S1470-2045(18)30292-4

The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®
Wellmont Cancer Institute

Overall survival benefit with ribociclib plus endocrine therapy (ET) is exciting news for women with hormone receptor–positive, HER2-negative disease, in both premenopausal and perimenopausal states. This is the first time that a CDK4/6 inhibitor or any targeted agent plus ET has demonstrated significantly longer overall survival vs. ET alone as initial endocrine-based therapy.

Overall survival benefit of a particular drug or regimen is always hard to prove, as there are multiple agents and regimens utilized in metastatic breast cancer, in varying sequences. The advanced practitioner in oncology should consider these data when choosing a first-line treatment with a CDK4/6 inhibitor.

Advanced practitioners should note that in the premenopausal women in MONALEESA, goserelin was also prescribed. Also of note was the investigators' finding that due to the potential increase in QT interval prolongation, tamoxifen should not be given with a CDK4/6 inhibitor. There were no new safety signals found in this trial, but advanced practitioners should note that dose interruptions and dose reductions may be required to keep patients on therapy.

Disclosure: Ms. Vogel is a network speaker for AMAG, Amgen, Celgene, Genentech, Ipsen, Janssen, Novartis, and Pfizer.

Abstract 503

Clinical Risk Enhances Utility of TAILORx Findings

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/172073/abstract to read the full abstract and view disclosures.

Clinical risk factors add prognostic information that complements the 21-gene recurrence score, according to a new analysis from the landmark TAILORx trial (Sparano et al., 2019a, 2019b).

The integration of clinical risk with the recurrence score provides greater precision in determining recurrence risk and guiding the use of adjuvant therapy than relying solely on the recurrence score. Moreover, using all this information together may help identify premenopausal patients who could derive benefit from more effective hormonal therapy as an alternative to chemotherapy, said Joseph A. Sparano, MD, Associate Director for Clinical Research at the Albert Einstein Cancer Center and Montefiore Health System, and Vice Chair of the ECOG-ACRIN Cancer Research Group, who was the lead author of TAILORx.

"The prognostic precision afforded by the integrated-risk model is superior to that by the use of clinical or genomic features alone," Dr. Sparano said at the 2019 ASCO Annual Meeting (Sparano et al., 2019a). The findings were simultaneously published in *The New England Journal of Medicine* (Sparano et al., 2019b).

Aim of Secondary Analysis

"It stands to reason," Dr. Sparano said, "that the integration of clinical and genomic risk offers the potential for greater precision in prognosis and ultimately guiding the use of adjuvant therapy." The objective of the prespecified secondary analysis, therefore, was to evaluate whether the addition of clinical risk (as determined by the binary clinical risk categorization employed in the MINDACT trial and Adjuvant! Online) provides more prognostic or predictive information than the recurrence score result alone.

Of 9,427 women in TAILORx with recurrence score and clinical risk information, 70% were determined to have low clinical risk (tumor ≤ 3 cm and low grade; ≤ 2 cm and intermediate grade; or ≤ 1 cm and high grade) and 30% were at high clinical risk (not meeting low clinical risk criteria). The new findings complement the study's original conclusion that 70% of women with hormone receptor–positive, HER2-negative, axillary lymph node–negative breast cancer can forgo chemotherapy when guided by their recurrence score.

"Last year's TAILORx results gave clinicians high-quality data to inform personalized treatment recommendations for women," said Dr. Sparano. "With this new analysis, it is clear that women aged 50 or younger with a recurrence score between 16 and 20 and at low clinical risk do not need chemotherapy."

He added: "Furthermore, the integration of the recurrence score with clinical risk information could identify premenopausal women with high integrated risk who may benefit from more effective antiestrogen therapy including ovarian function suppression plus an aromatase inhibitor rath-

TAILORx Additional Analysis

- A secondary analysis of TAILORx found that clinical risk factors add prognostic information that complements the 21-gene recurrence score.
- Integration of clinical risk for those with a recurrence score 16 to 25 found benefit for chemotherapy in women aged 46 to 50 who are premenopausal, and a trend toward chemotherapy benefit in women aged 41 to 45.
- Integration of clinical risk for those with a recurrence score of 16 to 25 showed no benefit from chemotherapy in women ≤ 40 and those 46 to 50, who are less likely to develop premature menopause from chemotherapy.
- The chemotherapy benefit observed for the group with recurrence scores from 16 to 25 may be due to a castration effect associated with cytotoxic therapy, which is most notable in younger women.

er than tamoxifen, which most younger women in TAILORx received as their endocrine therapy."

Fine-Tuning Recommendations

For the group with a recurrence score of 11 to 25, there was a 2.5- to 3-fold higher relative risk and 5% higher absolute distant recurrence risk for the high vs low clinical risk group. For patients in the recurrence score ≥ 26 group, who were treated with chemotherapy plus endocrine therapy, there was a threefold higher relative risk and a 10% higher absolute difference for high vs low clinical risk.

Clinical risk did not provide predictive information for chemotherapy benefit for those with a recurrence score from 11 to 25. "Thus, the primary trial results remain unchanged and were not impacted by the integration of clinical risk," he added. "However, for women aged ≤ 50 years and a recurrence score of 16 to 25, integrated risk distinguished the 50% who derived no chemotherapy benefit from the 50% who derived an absolute benefit of 6% to 9%—a level that is higher than an unselected population."

For women ≤ 50, under the new framework, 68% of TAILORx subjects fell into the low–integrated-risk group (with < 5% distant recurrence risk), including all those with a recurrence score of 0 to 10, irrespective of clinical risk, and those with a recurrence score from 11 to 20 and low clinical risk. In contrast, 25% fell into the high–integrated-risk group (> 10% distant recurrence risk), including those with a recurrence score of 21 to 25 irrespective of clinical risk and recurrence score 16 to 20 and high clinical risk treated with endocrine therapy alone, and a recurrence score of 26 to 100 and a high clinical risk who received both chemotherapy and endocrine therapy. The remaining 7% had a distant recurrence risk of about 6% to 7% and thus were at intermediate integrated risk.

Among women who were ≤ 50 who had received endocrine therapy alone, the estimated rate of distant recurrence at 9 years was < 5% in the low integrated risk groups, including 1.8% with a recurrence score 0 to 10 irrespective of clinical risk, and 3.2% with an recurrence score 11 to 20 and low clinical risk. It exceeded 10% among women with a high integrated risk, including 14.7% for those with a recurrence score of 16 to 25 and high clinical risk and 11.4% for recurrence score of 21 to 25 and low clinical risk who received endocrine therapy alone, and 15.2% and among those with a high recurrence score of 26 to 100 and high clinical risk who received chemoendocrine therapy.

What Results Suggest for Younger Patients

Importantly, the study showed that the absolute chemotherapy benefit was greatest for premenopausal women aged 45 to 50 with a recurrence score of 16 to 25. "This suggests that the absolute chemotherapy benefit observed in younger women in TAILORx may be due to an endocrine effect," Dr. Sparano said.

Based on findings from TAILORx, for the low–integrated-risk group, tamoxifen alone should be adequate. For the high–integrated-risk group, ovarian function suppression plus an aromatase inhibitor could be considered as an alternative to chemotherapy in those with a recurrence score of 16 to 25, or in addition to chemotherapy in those with a recurrence score of 26 to 100 who have not developed chemotherapy-induced menopause, he said.

References

Sparano, J. A., Gray, R. J., Makower, D. F., Lively, T. G., Saphner, T. J., Keane, M. M.,...Sledge, G. W. (2019a). Impact of clinical risk category on prognosis and prediction of chemotherapy benefit in early breast cancer by age and the 21-gene recurrence score in TAILORx [Abstract 503]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.503

Sparano, J. A., Gray, R. J., Ravdin, P. M. Makower, D. F., Pritchard, K. I., Albain, K. S.,...Sledge, G. W., Jr. (2019b). Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. *New England Journal of Medicine, 380*, 2395–2405. https://doi.org/10.1056/NEJMoa1904819

The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®
Wellmont Cancer Institute

The results from this study indicating that less chemotherapy can be administered to younger (< 50) breast cancer patients are exciting. The data noted that integrating clinical risk factor prognostication to the TAILORx recurrence scoring may identify women under the age of 50 with a recurrence score between 16 and 20 and at low clinical risk who will get little benefit from chemotherapy. This study also showed that the absolute chemotherapy benefit was greatest for premenopausal women aged 45 to 50 with a recurrence score of 16 to 25, likely due to endocrine effects.

Risk assessment is based on clinical features such as tumor size and histologic grade. Low risk was defined as tumors 1 cm or smaller and high grade; 2 cm or smaller and intermediate grade; or 3 cm or smaller and low grade. Tumors outside of this categorization were considered high-risk tumors.

The oncology advanced practitioner should be familiar with these data in order to have in-depth discussions regarding an individual woman's risk. The 2019 ASCO Guidelines for Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy recommend the use of the Oncotype DX Breast Recurrence Score test and the TAILORx results to guide chemotherapy treatment use in patients with node-negative early-stage breast cancer.

Disclosure: Ms. Vogel is a network speaker for AMAG, Amgen, Celgene, Genentech, Ipsen, Janssen, Novartis, and Pfizer.

Abstract 1002

NALA Trial: Neratinib Plus Capecitabine Shows Benefit in Metastatic Breast Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/170932/abstract to read the full abstract and view disclosures.

In the global phase III NALA trial, treatment of metastatic HER2-positive breast cancer with neratinib plus capecitabine significantly improved progression-free survival, delayed the time to intervention for central nervous system disease, and showed a trend toward improved overall survival vs lapatinib plus capecitabine (Saura et al., 2019). The study was reported at the 2019 ASCO Annual Meeting.

"The landmark analysis showed the curves began to separate after 6 months, almost doubling the progression-free survival from 15% to 29% at 12 months. Even out to 18 months, the curves remained separated," reported senior investigator Adam Brufsky, MD, PhD, of Magee-Womens Hospital of the University of Pittsburgh Medical Center. The study's first author was Cristina Saura, MD, of Vall d'Hebron University Hospital, Barcelona.

NALA is a multinational, randomized, open-label, phase III trial of neratinib plus capecitabine in patients with heavily pretreated stage IV HER2-positive metastatic breast cancer. The novel regimen was compared with lapatinib plus capecitabine in 662 women who had received at least two prior HER2-directed regimens for metastatic disease. Approximately 80% had visceral metastases, and about 30% had received at least three anti-HER2 therapies.

As Dr. Brufsky explained, neratinib is a pan-HER inhibitor, targeting and irreversibly binding to HER1, HER2, and HER4; lapatinib targets and binds reversibly to HER1 and HER2. Neratinib is approved by the FDA and the European Medicines Agency based on a reduced risk of recurrence of invasive disease in the ExteNET trial (Martin et al., 2017). In the I-SPY2 neoadjuvant trial, neratinib plus chemotherapy led to higher pathologic complete response rates than chemotherapy plus trastuzumab (Park et al., 2016). In metastatic HER2-positive disease, activity has been shown for neratinib plus various agents, including capecitabine, trastuzumab emtansine (T-DM1), and paclitaxel.

NALA Details

In the NALA trial, patients were randomly assigned to neratinib (240 mg daily) plus capecitabine (750 mg/m^2 twice daily) or lapatinib (1,250 mg daily) plus capecitabine (1,000 mg/m^2 twice daily) until disease progression. The co-primary endpoints were centrally assessed progression-free survival and overall survival by central review. The study

was to be considered positive if either co-primary endpoint was met, with $P < .01$ for progression-free survival and $P < .04$ for overall survival. The design called for performing a prespecified restricted means analysis if the assumption of constant proportional hazards was not shown.

Benefits of Neratinib/Capecitabine

Neratinib/capecitabine reduced the risk of disease progression or death by 24% (hazard ratio [HR] = 0.76; $P = .0059$). The rates of progression-free survival were 47% vs 38%, respectively, at 6 months; 29% vs 15% at 12 months; and 16% and 7% at 18 months.

"The separation of the curves occurred after roughly 6 months; therefore, statistical testing showed that the proportional hazards assumption of constant proportional hazard was not met," Dr. Brufsky reported. "For that reason, we performed a prespecified restricted means analysis for progression-free survival, restricting follow-up to 24 months—since few events occurred after 24 months—and compared the area under the survival curve for the regimens," he said.

In the restricted means analysis, the difference between the arms was 2.2 months, based on a mean progression-free survival of 8.8 months in the neratinib arm vs 6.6 months in the lapatinib arm ($P = .0003$).

According to subgroup analysis, statistically significant reductions in risk, favoring neratinib, were observed in patients with nonvisceral metastases (HR = 0.44) and hormone receptor–negative tumors (HR = 0.42). For most other subgroups, trends favored the neratinib arm as well.

In the restricted means analysis of overall survival, with time to disease progression or death set at 48 months, a difference of 1.7 months nonsignificantly favored neratinib. The mean overall survival was 24.0 months in the neratinib arm and 22.2 months in the lapatinib arm (HR = 0.88; $P = .2086$).

Response rates were also numerically higher with neratinib/capecitabine in patients with measurable disease (33% vs 27%; $P = .1201$), and statistically significant improvements were shown in the clinical benefit rate (45% vs 36%; $P = .0328$). In addition, the median duration of response (8.5 vs 5.6 months; HR = 0.50; $P = .0004$) favored the novel combination.

The time to intervention for symptomatic disease of the central nervous system was significantly delayed, with an overall cumulative incidence of 23% with neratinib/lapatinib vs 29% with lapatinib/capecitabine ($P = .043$). "Intervention was predominantly with radiation therapy, which was needed less in the neratinib arm (11% vs 15%)," said Dr. Brufsky. "It is important to note, there was a significant difference in the absolute percentage of patients who required intervention."

Tolerability of Regimens

Dose reductions and dose holds were comparable between the treatment groups. There were slightly more dose reductions with capecitabine/lapatinib due to the higher dose of capecitabine used in that arm.

Treatment-emergent adverse events were similar between the arms. There was a higher rate of grade 3 diarrhea with neratinib (24% vs 13%), but treatment discontinuation due to diarrhea was similar, about 2.5% in each arm, and the median number of cumulative days with grade 3 diarrhea was four in each arm. Loperamide prophylaxis was mandated during the first month of neratinib treatment and could be continued at the physician's discretion.

More patients discontinued lapatinib/capecitabine because of a treatment-emergent adverse event (15% vs 11%), "most likely because of more hand-foot syndrome due, again, to the higher dose of capecitabine," Dr. Brufsky noted. Quality of life was similar between the arms and was maintained throughout the study, he added.

References

Martin, M., Holmes, F. A., Ejlertsen, B., Delaloge, S., Moy, B., Iwata, H.,...Chan, A. (2017). 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. *Lancet Oncology, 18*(12), 1688–1700. https://doi.org/10.1016/S1470-2045(17)30717-9

Park, J. W., Liu, M. C., Yee, D., Yau, C., van 't Veer, L. J., Symmans, W. F.,...Berry, D. A. (2016). Adaptive randomization of neratinib in early breast cancer. *New England Journal of Medicine, 375*(1), 11–22. https://doi.org/10.1056/NEJMoa1513750.

Saura, C., Oliveira, M., Feng, Y. H., Dai, M.-S., Hurvitz, S. A., Kim, S.-B.,...Brufsky, A. (2019). Neratinib + capecitabine vs lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial [Abstract 1002]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.1002

The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®
Wellmont Cancer Institute

In this study, progression-free survival benefits were seen in heavily pretreated patients with HER2-positive, metastatic breast cancer. This trial compared neratinib plus capecitabine with lapatinib plus capecitabine in heavily pretreated patients with stage IV HER2-positive metastatic breast cancer. Patients had to have received at least two prior HER2-directed regimens for metastatic disease. The differences between the two arms occurred after about 6 months of treatment. The rates of progression-free survival were 47% vs. 38%, respectively, at 6 months; 29% vs. 15% at 12 months; and 16% and 7% at 18 months.

One of the most interesting findings was the delay in time to intervention for symptomatic disease of the central nervous system with an overall cumulative incidence of 23% with neratinib/lapatinib vs. 29% with lapatinib/capecitabine (p = .043).

Oncology advanced practitioners should note there was a higher incidence of grade 3 diarrhea in the neratinib arm and be prepared to expertly manage this adverse event. Prophylactic loperamide was mandated for the first month of neratinib therapy. Dose interruptions and dose reductions may be required. At this time, neratinib is only indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

Disclosure: Ms. Vogel is a network speaker for AMAG, Amgen, Celgene, Genentech, Ipsen, Janssen, Novartis, and Pfizer.

Abstract 1000

SOPHIA Trial Tests Margetuximab in Heavily Pretreated Patients With HER2-Positive Metastatic Breast Cancer

by Caroline Helwick

Visit https://meetinglibrary.asco.org/record/170929/abstract to read the full abstract and view disclosures.

In the phase III SOPHIA trial of 536 heavily pretreated patients with HER2-positive metastatic breast cancer, the novel anti-HER2 antibody margetuximab plus chemotherapy led to significant improvements in progression-free survival, response, and clinical benefit compared with trastuzumab/chemotherapy (Rugo et al., 2019). The benefits were enhanced in patients with low-affinity CD16A-158F genotypes.

"This is the first prospective analysis of the CD16A genotype as a predictor of efficacy from anti-HER2 therapy," according to Hope S. Rugo, MD, of the University of California San Francisco Helen Diller Family Comprehensive Cancer Center, who presented the primary progression-free survival analysis of SOPHIA at the 2019 ASCO Annual Meeting. "Although the 1-month absolute benefit in progression-free survival has slight clinical relevance, the benefit was enhanced in patients who carry at least one F allele," she added.

Controversy exists about the role of CD16A polymorphisms on the efficacy of trastuzumab, Dr. Rugo noted. Two retrospective studies of patients with HER2-positive early and metastatic breast cancers suggested that those who carry the low-affinity F allele have shorter progression-free survival and lower overall response rates with trastuzumab than those who are homozygous for the higher-affinity V allele.

The current standard of care for HER2-positive metastatic breast cancer is trastuzumab plus pertuzumab and chemotherapy in the first-line setting and trastuzumab emtansine (T-DM1) in the second line. After patients experience disease progression on these treatments, there is no recognized standard of care, although continued anti-HER2 therapy is generally preferred in combination with chemotherapy, Dr. Rugo commented.

Unique Characteristic of Margetuximab

Margetuximab is an Fcγ-engineered antibody designed to activate an immune response. Previous preclinical and phase I studies showed that margetuximab does, indeed, enhance innate immunity and HER2-specific adaptive immunity.

Margetuximab has similar HER2-binding and antiproliferative effects as trastuzumab. By contrast,

however, its Fcγ region is engineered to increase affinity for both alleles of the activating Fc receptor (FcgR)—CD16A—and to decrease affinity for the inhibitory FcgR, CD32B. The low-affinity CD16A-158F allele (which is seen in about 85% of the population) has been associated with diminished clinical response to trastuzumab, explained Dr. Rugo.

"The hypothesis of SOPHIA was that margetuximab would have greater benefit than trastuzumab in the lower-binding CD16A-158F carriers, as it has increased affinity for CD16A-158F over trastuzumab," she said.

SOPHIA Details

The open-label phase III SOPHIA trial enrolled 536 patients with HER2-positive metastatic breast cancer who had been treated with at least two prior lines of anti-HER2 therapy, including pertuzumab, and one to three prior lines in the metastatic setting. Patients were randomly assigned 1:1 to margetuximab (15 mg/kg intravenously every 3 weeks) or trastuzumab (6 mg/kg [8-mg/kg loading dose]). In both arms, anti-HER2 therapy was given with physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). The primary endpoints were progression-free and overall survival, by central blinded assessment.

All patients had received trastuzumab and pertuzumab, and more than 90% had also received T-DM1. Almost all had received a taxane, more than 40% had received an anthracycline, and almost half had received an endocrine agent.

Risk of Disease Progression Reduced

In the progression-free analysis of the intent-to-treat population, the risk of disease progression was reduced by 24% in the central blinded review (primary endpoint), based on a median progression-free survival of 5.8 months with margetuximab/chemotherapy vs 4.9 months with trastuzumab chemotherapy (hazard ratio [HR] = 0.76; P = .033). Risk reduction was 30% according to investigator assessment (secondary endpoint).

In the planned exploratory analysis by CD16A genotype, the benefit was enhanced in patients with low-affinity CD16A genotypes containing a 158F allele, whose disease progression was reduced by 32% (Table 1).

The objective response rate was higher with margetuximab/chemotherapy than with trastuzumab/chemotherapy, 22.1% vs 16.0% (P = .060), as was the clinical benefit rate, 36.6% vs 24.8% (P = .003).

Analysis by CD16A Genotype

Within the CD16A-158F genotype, important differences were also observed according to alleles. The median progression-free survival with margetuximab/chemotherapy vs trastuzumab/chemotherapy in the various allele subsets follows:

- FF or FV genotype: 6.9 vs 5.1 months (HR = 0.68; P = .005)
- VV genotype: 4.8 vs 5.6 months (HR = 1.78; P = .110)
- FF genotype (n = 192): 8.2 vs 5.6 months (HR = 0.69; P = .080)
- FV genotype: 6.3 vs 4.3 months (HR = 0.71; P = .055).

"In this preplanned exploratory analysis, we saw that the alleles for CD16A made a difference in the efficacy of margetuximab/chemotherapy," Dr. Rugo said. "In patients who were homozygous for the high-affinity VV allele, the effect of margetuximab and trastuzumab was relatively similar, but in the 85% who carry at least one F allele, the progression-free benefit was enhanced, and it was further enhanced in patients who were homozygous for the F allele, who had a greater difference in progression-free survival."

Table 1. Progression-Free Survival With Margetuximab/Chemotherapy vs Trastuzumab/Chemotherapy in the SOPHIA Trial

	Intent-to-treat population (n = 536)			Low-affinity CD16A-158F allele carriers (n = 437)		
Treatment arm	M/C	T/C	HR	M/C	T/C	HR
Median progression-free survival	5.8 mo	4.9 mo	0.76 (P = .033)	6.9 mo	5.1 mo	0.68 (P = .005)

Note. HR = hazard ratio; M/C = margetuximab/chemotherapy; T/C = trastuzumab/chemotherapy.

The interim overall survival analysis similarly showed that most benefit occurred in CD16A-158F carriers. In the whole population, the median overall survival was 18.9 months with margetuximab and 17.2 months with trastuzumab (HR = 0.95); however, in the carriers, it was 23.6 months and 16.9 months, respectively (HR = 0.82), although this was not yet statistically significant. "Of course," she commented, "this isn't ready for statistical significance, but it's an intriguing finding."

"The most interesting finding was in the interim analysis, where only 40% of the overall survival events needed for assessment had occurred. Despite this, there was a marked and clinically significant difference in overall survival in the F allele carriers receiving margetuximab. This needs to be confirmed in the second interim analysis, which is expected later this year," Dr. Rugo told *The ASCO Post*.

Safety profiles were comparable, with grade ≥ 3 adverse events and serious adverse events occurring in 52% and 15% of the margetuximab arm, respectively, vs 48% and 17% receiving trastuzumab; treatment discontinuation rates were about 3% in each arm. Infusion-related reactions were more common with margetuximab, but just 1.5% were grade ≥ 2 and were managed with premedication.

The next milestone will be the second interim overall survival analysis, expected in late 2019, Dr. Rugo indicated.

Reference

Rugo, H. S., Im, S. A., Wright, G. L. S., Escriva-de-Romani, S., DeLaurentils, M., Cortes, J.,...Gradishar, J. (2019). SOPHIA primary analysis: A phase 3 study of margetuximab + chemotherapy versus trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies [Abstract 1000]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.1000

The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®
Wellmont Cancer Institute

Margetuximab plus chemotherapy significantly improved progression-free survival (by 24%) in HER2-positive, heavily pretreated, metastatic breast cancer compared to trastuzumab. Patients had to have been treated with at least two prior lines of anti-HER2 therapy, including pertuzumab, and one to three prior lines in the metastatic setting.

Margetuximab is an Fcγ-engineered antibody shown to enhance innate immunity and HER2-specific adaptive immunity. While it is similar to trastuzumab in HER2-binding and antiproliferative effects, it has increased affinity for both alleles of the activating Fc receptor (FcgR), CD16A, and decreased affinity for the inhibitory FcgR, CD32B. The CD16A-158F allele (found in about 85% of the population) has been associated with diminished clinical response to trastuzumab. In the planned exploratory analysis by CD16A genotype, the benefit was enhanced in patients with low-affinity CD16A genotypes containing a 158F allele, whose disease progression was reduced by 32%. This study is the first prospective analysis of the CD16A genotype as a predictor of efficacy from anti-HER2 therapy. Overall survival analysis should be available in late 2019. Margetuximab is also being studied in gastroesophageal cancer.

Advanced practitioners should be aware that the most common side effects of margetuximab reported in this trial were fever, nausea, anemia, diarrhea, and fatigue. There were more infusion reactions with margetuximab, with most being low grade and with the first infusion, managed with premedications.

Disclosure: Ms. Vogel is a network speaker for AMAG, Amgen, Celgene, Genentech, Ipsen, Janssen, Novartis, and Pfizer.

☞ *Continued on the following page*

Abstract 520

Low-Fat Diet May Reduce the Risk of Death From Breast Cancer in Postmenopausal Women

By Jo Cavallo

Visit https://meetinglibrary.asco.org/record/173478/abstract to read the full abstract and view disclosures.

Excluding skin cancer, breast cancer is the most common cancer diagnosed in women in the United States. In 2019, the American Cancer Society estimates that about 268,600 new cases of breast cancer will be diagnosed in women, and about 41,760 women will die from their disease.

Although observational studies of dietary fat intake and its effect on breast cancer have had inconsistent results, nearly 20-year data from the Women's Health Initiative Dietary Modification Trial, a randomized clinical trial assessing how a low-fat diet may influence breast cancer incidence and outcome, show that the adoption of a low-fat diet containing increased portions of vegetables, fruits, and grains significantly reduces the risk of death from breast cancer in postmenopausal women. The study by Chlebowski et al was presented during the 2019 ASCO Annual Meeting (Abstract 520).

Study Methodology and Results

From 1993 to 1998, researchers randomly assigned 48,835 postmenopausal women aged 50 to 79 years with no previous history of breast cancer and a dietary fat intake ≥ 32% of total energy to a usual-diet comparison group (60%) or a dietary-intervention group (40%). The goal was to reduce fat intake to 20% of energy and increase vegetable, fruit, and grain intake.

The dietary-intervention group significantly reduced their fat intake and increased their fruit, vegetable, and grain intake with modest weight loss (3%, all $P < .001$). The researchers found that during 8.5 years of dietary intervention, there were 8% fewer breast cancers, and deaths from breast cancer were somewhat fewer in the intervention group, but the rates were not significantly different.

However, researchers found that deaths after breast cancer (ie, breast cancer followed by death from any cause) were significantly reduced in the intervention group, both during intervention (hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.45–0.95) and through 16.1 years of cumulative follow-up. After a long-term, cumulative follow-up of 19.6 years, with 3,374 incidences of breast cancer, the significant reduction in deaths after breast cancer continued, with 1,011 deaths (HR = 0.85, 95% CI = 0.74–0.96) and a significant reduction in deaths from breast cancer (ie, breast cancer followed by death attributed to the disease) emerged, with 383 deaths (HR = 0.79, 95% CI = 0.64–0.97).

"[The] adoption of a low-fat dietary pattern associated with increased vegetable, fruit, and grain intake, demonstrably achievable by many, significantly reduced the risk of death from breast cancer in postmenopausal women. To our review, these findings provide the first randomized clinical trial evidence that a dietary change can reduce a postmenopausal woman's risk of dying from breast cancer," concluded the study authors.

First author Rowan Chlebowski, MD, PhD, also noted that greater uptake of the balanced, low-fat diet could lead to a major reduction in deaths from breast cancer in the United States, as well as savings in health-care costs.

Key Points

- The adoption of a diet low in fat and high in vegetables, fruits, and grains significantly reduces the rate of mortality after breast cancer in postmenopausal women.
- The researchers found that during 8.5 years of dietary intervention, there were 8% fewer breast cancers, and deaths from breast cancer were somewhat fewer in the intervention group, but the rates were not significantly different.

Reference

Chlebowski, R. T., Aragaki, A. K., Anderson, G. L., Pan, K., Neuhouser, M. L., Manson, J. E.,...Prentice, R. L. (2019). Low-fat dietary pattern and long-term breast cancer incidence and mortality: The Women's Health Initiative randomized clinical trial [Abstract 520]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 37*(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.520

The Advanced Practitioner Perspective

Wendy H. Vogel, MSN, FNP, AOCNP®
Wellmont Cancer Institute

Data from the Women's Health Initiative Dietary Modification Trial, a randomized clinical trial examining the effects of a low-fat diet on breast cancer incidence and outcome, show that the adoption of a low-fat diet (increased portions of vegetables, fruits, and grains) significantly reduces the risk of death from breast cancer in postmenopausal women.

The study group of 48,835 postmenopausal women aged 50 to 79 years with no previous history of breast cancer and a dietary fat intake ≥ 32% of total energy was assigned to a usual-diet comparison group (60%) or a dietary-intervention group (40%). The latter group had 8% fewer breast cancers and fewer deaths from breast cancer (although rates were not statistically significant).

The oncology advanced practitioner can utilize this data in both women at high risk for breast cancer as well as those diagnosed with breast cancer. Education of patients and caregivers using practical dietary models could decrease both the incidence and the mortality of breast cancer.

Disclosure: Ms. Vogel is a network speaker for AMAG, Amgen, Celgene, Genentech, Ipsen, Janssen, Novartis, and Pfizer.