Ipilimumab Versus Placebo After Complete Resection of Stage 3 Melanoma: Final Overall Survival Results From the EORTC 18071 Randomized, Double-Blind, Phase 3 Trial

- Alexander M. Eggermont, MD, PhD, Institut Gustave Roussy, Villejuif, France

Final overall survival results from the European Organization for Research and Treatment of Cancer (EORTC) 18071 trial of adjuvant ipilimumab versus placebo reveal a persisting benefit at 5.3 years of median follow-up—a significant 28% reduction in the relative risk of death. The trial included 951 patients with completely resected stage 3 melanoma who had been randomized double-blind to ipilimumab 10 mg/kg (induction and maintenance) or placebo. Patients were treated for up to three years or until disease progression, intolerable toxicity, or withdrawal.

In a 2015 report, the trial’s primary endpoint of recurrence-free survival (RFS) was 51.5% for ipilimumab compared with 43.8% for placebo after a median of 2.3 years of follow-up. Sixty more patients in the placebo arm relapsed than in the ipilimumab arm (294 versus 234). The three-year RFS rates were 46.5% for ipilimumab and 34.8% for placebo (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.64–0.9).

At an ESMO press briefing, Dr. Eggermont stated that five-year RFS was 41% in the ipilimumab arm and 30% in the placebo arm (HR, 0.76; 95% CI, 0.64–0.89; \( P = 0.0008 \)). Overall survival was 63% for ipilimumab and 54% for placebo (HR, 0.72; 95% CI, 0.58–0.88; \( P = 0.001 \)).

“Of course, this comes at a price in terms of side effects and toxicity,” Dr. Eggermont said. Immune-related events occurring with ipilimumab fell into five blocks: dermatological, gastrointestinal, endocrinological, hepatic, and neurological. The most significant grade 3–4 events that resulted when patients stopped treatment were gastrointestinal in nature (16%), and included colitis with fatal perforation in three patients and hypophysitis in 4.4%. The toxicity-related death rate was 1.1%. Overall, the immune-related grade 3–4 adverse event rates were 43% for ipilimumab and 2% for placebo.

Ipletimumab’s superiority was consistent across all survival endpoints at five years, and long-term safety results were also consistent with those in the primary report.

“Currently, adjuvant ipilimumab represents an important treatment option for patients with high-risk stage 3 melanoma,” Dr. Eggermont concluded.

The results were published simultaneously in the New England Journal of Medicine.1

Primary Analysis From OAK, a Randomized Phase 3 Study Comparing Atezolizumab With Docetaxel in 2L/3L NSCLC

- Fabrice Barlesi, MD, Aix-Marseille University, Marseille, France

Programmed death ligand 1 (PD-L1) inhibitors are a class of checkpoint inhibitors that impede the binding of PD-L1 to its receptors (PD-1 and B7.1), thereby restoring tumor-specific T-cell immunity. OAK was the first phase 3 study that compared atezolizumab, a PD-L1 inhibitor, with standard chemotherapy in patients with previously treated non–small-cell lung cancer (NSCLC).

In OAK, 1,225 patients with NSCLC were randomized 1:1 to intravenous atezolizumab (1,200 mg every three weeks) or docetaxel (75 mg/m² every three weeks). Patients were stratified according to PD-L1 status, number of prior chemotherapy regimens, and histology. The primary endpoint was overall survival. Dr. Barlesi presented preliminary results from the first 850 patients.

Overall survival after a minimum follow-up of 19 months was improved by 27% in patients receiving atezolizumab versus those receiving docetaxel (13.8 months versus 9.6 months, respectively; \( P = 0.0003 \)), regardless of PD-L1 expression levels. Dr. Barlesi noted that in the patients within the highest tertile of PD-L1 expression, overall survival was 59% greater than among the same group receiving docetaxel (\( P < 0.0001 \)). In patients with no PD-L1 expression, the gain in overall survival with atezolizumab was still a significant 25%. Squamous versus nonsquamous histology had no impact on overall survival (hazard ratio, 0.73 for each).

Rates of treatment-related adverse events were lower in the atezolizumab group than in the docetaxel group (64% versus 86%). The rates of treatment-related grade 3–4 events were also lower in the atezolizumab group (15% versus 43%), even though the median treatment duration was longer with atezolizumab (3.4 months versus 2.1 months) and a higher percentage of atezolizumab patients were treated for 12 months or more (20.5% versus 2.4%). Treatment-related withdrawal rates were 8% and 19% in the atezolizumab and docetaxel groups, respectively.

Martin Reck, MD, of the Grosshansdorf Lung Clinic in Germany, who commented on the OAK study, pointed out...
that an improvement in overall survival, even in patients with no PD-L1 expression, shows that “we have a problem with using PD-L1 negativity as an exclusion factor for treatment.” He suggested that PD-L1 is perhaps an imperfect surrogate marker and that additional markers for the characterization of patients who might benefit from atezolizumab are needed.

Ceritinib Versus Chemotherapy in Patients With Advanced Anaplastic Lymphoma Kinase-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From the Confirmatory Phase 3 ASCEND-5 Study

• Giorgio Scagliotti, MD, University of Turin, Torino, Italy

Phase 2 findings from the ASCEND-2 trial showed durable responses in anaplastic lymphoma kinase-rearranged (ALK+) non–small-cell lung cancer (NSCLC) patients receiving ceritinib who had progressed on chemotherapy and crizotinib (including those with brain metastases). These findings were confirmed in the phase 3 ASCEND-5 study conducted with patients previously treated with crizotinib. Ceritinib is a next-generation ALK inhibitor with 20-fold greater potency than crizotinib.

Before the development of targeted therapies, chemotherapy was the standard of care for most patients with advanced NSCLC. While the ALK inhibitor crizotinib is effective in patients with ALK+ NSCLC, most patients develop resistance and progressive disease, Dr. Scagliotti said at an ESMO press conference.

Investigators enrolled 231 patients at 99 sites in 20 countries to the global, open-label ASCEND-5 study, randomizing them to ceritinib 750 mg once daily or chemotherapy (pemetrexed 500 mg/m² or docetaxel 75 mg/m² every 21 days). Patients were stratified according to baseline World Health Organization performance status and presence of brain metastases. The primary endpoint was progression-free survival (PFS), assessed by blinded independent review.

Compared with patients receiving chemotherapy, those receiving ceritinib had significantly better median PFS (5.4 versus 1.6 months) (hazard ratio [HR], 0.49; P < 0.001). Ceritinib also had a superior overall response rate compared with chemotherapy (39.1% versus 6.9%). Ceritinib benefits were consistent across subgroups. However, there was no improvement in overall survival with ceritinib compared with chemotherapy. Of the patients who discontinued chemotherapy due to disease progression, 75 crossed over to ceritinib. Dr. Scagliotti attributed the lack of overall survival benefit to the high crossover rate. “That probably diluted the potential benefit,” he said.

The most common grade 3–4 adverse events with chemotherapy were neutropenia (15.5%), fatigue (4.4%), and nausea (1.8%). The most common grade 3–4 adverse events with ceritinib were nausea (7.8%), vomiting (7.8%), and diarrhea (4.3%). Patient-reported outcomes, including lung-cancer–specific symptoms and overall health status, were better in the ceritinib group (P < 0.05). The safety profile of ceritinib was consistent with that reported in prior studies.

“Ceritinib demonstrated superior efficacy compared with standard second-line chemotherapy in crizotinib-resistant ALK+ patients, establishing ceritinib as a preferred treatment option in this patient population,” Dr. Scagliotti concluded.

KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy as First-Line Therapy For Advanced NSCLC With a PD-L1 Tumor Proportion Score of 50% or Higher

• Martin Reck, MD, Chief Oncology Physician, Grosshansdorf Lung Clinic, Grosshansdorf, Germany

In the KEYNOTE-024 trial, pembrolizumab was superior to platinum-based chemotherapy as first-line therapy for patients with advanced non–small-cell lung cancer (NSCLC) and a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of 50% or higher. High PD-L1 expression, Dr. Reck said in an ESMO press conference, is defined by PD-L1 expression in at least 50% of tumor cells.

KEYNOTE-024 included 305 treatment-naïve patients with PD-L1 TPS of 50% or higher randomized 1:1 to intravenous pembrolizumab 200 mg once every three weeks for two years or standard-of-care platinum-based doublet chemotherapy for four to six cycles. Patients with epidermal growth factor receptor-activating mutations and anaplastic lymphoma kinase translocations were excluded. Crossover to the pembrolizumab regimen was allowed in the chemotherapy arm after disease progression. The primary endpoint was progression-free survival (PFS).

Pembrolizumab significantly extended PFS by approximately four months compared with chemotherapy (10.3 months versus 6.0 months) (hazard ratio [HR], 0.50; P < 0.001). The PFS rates at six months and one year were 62% and 48% for pembrolizumab and 50% and 15% for chemotherapy, respectively. Overall survival rates, a secondary endpoint, were higher with pembrolizumab, with 80% of patients surviving at six months versus 72% in the chemotherapy arm (HR, 0.60; P = 0.005). Dr. Reck pointed out that the overall survival benefit with pembrolizumab was “remarkable” considering that more than 40% of patients in the control arm crossed over to pembrolizumab. At one year, the survival rates were 70% in pembrolizumab-treated patients and 54% in those who underwent chemotherapy.

Pembrolizumab was associated with a higher overall response rate compared with chemotherapy (45% versus 28%), a longer duration of response, and lower incidences of all and serious (grade 3–4) adverse events. Patients in the pembrolizumab arm tolerated treatment twice as long as those in the chemotherapy arm (7.0 months versus 3.5 months). Discontinuation rates for toxicity were 7% in the pembrolizumab arm and 11% in the chemotherapy arm.

“Pembrolizumab may be a new standard of care for first-line therapy for advanced NSCLC that expresses high levels of PD-L1,” Dr. Reck concluded.

The superior efficacy observed with pembrolizumab led the trial’s data monitoring committee to recommend stopping the trial.
Cabozantinib Versus Sunitinib as Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor- and Intermediate-Risk Groups: Results From the ALLIANCE A031203 Trial

- Toni Choueiri, MD, Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Cabozantinib is an oral inhibitor of tyrosine kinases, including MET and AXL, and of vascular endothelial growth factor (VEGF) receptors. “Both MET and AXL seem to be associated with tumor progression, but more importantly, animal models show that the development of resistance to VEGF inhibitors like sunitinib can be mediated through AXL and MET,” Dr. Choueiri said at an ESMO press conference. He noted that sunitinib has been the standard-of-care, first-line therapy for renal cell carcinoma (RCC) for years. Median progression-free survival (PFS) with first-line VEGF receptor tyrosine kinase inhibitors has been in the eight- to 11-month range.

In the ALLIANCE clinical trial, 157 treatment-naïve, poor- and intermediate-risk RCC patients received cabozantinib (60 mg once daily) or sunitinib (50 mg once daily) for four weeks on and two weeks off. Overall survival was the primary outcome, and objective response rate (investigator-assessed) and safety were secondary outcomes. Dr. Choueiri said that outcomes with VEGF-targeted therapy in the poor- and intermediate-risk groups are typically inferior (median, 5.6 months) to those in favorable-risk patients.

Cabozantinib improved PFS and the objective response rate compared with sunitinib in this poor- and intermediate-risk population. PFS was 8.2 months for cabozantinib and 5.6 months for sunitinib (hazard ratio, 0.69; P = 0.012). The objective response rate was 46% for cabozantinib and 18% for sunitinib. Safety profiles were similar, with grade 3 or higher adverse event rates of 70.5% in the cabozantinib arm and 72.2% in the sunitinib arm. Diarrhea, fatigue, hypertension, palmar-plantar erythrodysesthesia, and hematological events were most common. Toxicity led to treatment termination in 16 patients in each treatment group.

When asked in the press conference if evidence was sufficient to warrant a recommendation for first-line therapy, Dr. Choueiri replied, “If approved, I think the evidence is there. You have a drug based on a strong biological rationale that is approved in second-line with positive primary and secondary endpoint results. I would make the leap of faith.”

A Randomized, Double-Blind, Phase 3 Trial of Maintenance Therapy With Niraparib Versus Placebo in Patients With Platinum-Sensitive Recurrent Ovarian Cancer

- Mansoor Raza Mirza, MD, Chief Oncologist, Copenhagen University Hospital “Rigshospitalet,” Copenhagen, Denmark

Cumulative toxicities and lack of subsequent benefit with platinum-based chemotherapy are limitations of the current treatment landscape for ovarian cancer, Dr. Mirza noted in an ESMO press briefing. Maintenance therapy (approved only in the European Union) with bevacizumab can only be given once and confers just a few months’ progression-free survival (PFS). In addition, the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib is approved only for ovarian cancer patients with a germline BRCA mutation (10%–15% of patients).

Niraparib is an oral, highly selective inhibitor of PARP1/2. The ENGOT-OV16/NOVA study was the first randomized phase 3 trial of a PARP inhibitor as maintenance therapy for use after platinum chemotherapy in patients with platinum-sensitive recurrent ovarian cancer.

The hypothesis of ENGOT-OV16/NOVA was that niraparib would provide a clinical benefit to all patients with platinum-sensitive recurrent ovarian cancer regardless of BRCA mutation status. The study included 553 patients randomized 2:1 to niraparib 300 mg once daily or placebo and stratified according to germline BRCA mutation (gBRCAmut) (n = 203) or non-gBRCAmut status (n = 350). After four to six cycles of platinum-based chemotherapy, patients received the study regimen until disease progression.

Niraparib improved the primary endpoint of PFS significantly compared with placebo in both cohorts, as well as in all subgroups. Median PFS for niraparib compared with placebo was 21.0 months versus 5.5 months in the gBRCAmut group (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.173–0.410; P < 0.0001), 9.3 months versus 3.9 months in the non-gBRCAmut group (HR, 0.45; 95% CI, 0.338–0.607; P < 0.0001), and 12.9 months versus 3.8 months in a subgroup of the non-gBRCAmut cohort who had homologous recombination DNA repair deficiencies (HR, 0.38; 95% CI, 0.243–0.586; P < 0.0001).

While dose adjustments generally resolved toxicity issues and patient-reported quality of life was similar for both study arms, grade 3–4 adverse events were reported in more than 10% of patients receiving niraparib. The rates for thrombocytopenia, anemia, and neutropenia were 28%, 25%, and 11%, respectively.

“Pending approval, these landmark results could change the way we treat this disease and warrant niraparib maintenance treatment to the whole study population,” Dr. Mirza said. He commented further that the broad population benefiting from niraparib in this trial represents 70% of all ovarian cancer patients.

Cap cetebine Monotherapy in Patients 70 Years Of Age and Older With Metastatic Breast Cancer

- David O. Okonji, MD, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

“Chemotherapy with capecitabine has been around for about 25 years. Its registration dose of 1,250 mg/m² twice daily is very hefty for the elderly, however,” Dr. Okonji said at a poster session. Dose reductions and a modified schedule may work better for patients 70 years of age and older with metastatic breast cancer, according to his study results.

When all available endocrine therapies no longer offer benefit, capecitabine monotherapy is often prescribed. It also may be given as a last convenient oral agent before resorting to intravenous chemotherapy with its attendant potential side effects of alopecia, nausea, vomiting, and fatigue.
The clinical benefit rate of capecitabine as a monotherapy is 60%, and median time to progression in patients 65 years of age or older is four months. Dose reductions due to toxicity occur in 27% to 50% of patients. While the starting dose and schedule for capecitabine at Dr. Okonji’s institution is 2,000 mg/m² on days 1–14 every three weeks (two weeks on/one week off), older patients and those with poor performance status, comorbidities, and/or moderate-to-severe renal impairment may need dose reductions. A week on/week off (WOWO) schedule, first devised at Memorial Sloan Kettering Cancer Institute in New York, is being substituted to improve tolerance in the elderly.

Dr. Okonji’s single-center, retrospective, observational cohort study assessed safety and efficacy of low-dose capecitabine monotherapy in patients 70 years of age or older with relapsed de novo metastatic breast cancer. Toxicity was the primary outcome measure. Patients receiving the standard two weeks on/one week off regimen (2,000 mg/m²) were compared with those receiving a dose reduction or the WOWO schedule (2,000 mg/m²). Patients on the WOWO schedule were older (median age, 79 years versus 73 years [P < 0.001]), had impaired renal function (P = 0.016), and had lower performance status compared with the standard regimen group.

Complete response rates were 7% and 0% for the standard therapy (n = 43) and WOWO (n = 34) groups, respectively, with corresponding partial response rates of 37% and 16%. Progressive disease was reported in 30% of those receiving the higher dose of capecitabine and in 50% of those receiving the WOWO course of therapy.

While clinical benefit rates were higher in those receiving the higher dose, the higher rates of time to progression (11.7 months versus 6.2 months; P = 0.111) and overall survival (18.6 months versus 13.3 months; P = 0.288) were not significant. Patients in the WOWO cohort experienced less grade 3–4 toxicity with fewer subsequent dose reductions. “Patients on the WOWO schedule tolerated capecitabine better because of less diarrhea, less hand inflammation, and little or no reduced white cell counts with their infection risk. This enabled them to stay on their dose for a longer time, despite their poor performance status and impaired kidney function, which is usually a contraindication for this drug,” Dr. Okonji said.

“Capecitabine toxicity can be managed by dose reduction and/or a switch to a WOWO schedule. Both strategies enabled continued treatment in those deriving clinical benefit,” Dr. Okonji said. “With this modification of the capecitabine regimen, we’ve given this old drug a new lease on life and allowed it to be used in patients who would not otherwise be able to tolerate it. And, it’s off-patent and cheap.”

First-Line Ribociclib Plus Letrozole For Postmenopausal Women With Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

- Gabriel Hortobagyi, University of Texas MD Anderson Cancer Center, Houston, Texas

Among postmenopausal women with metastatic hormone receptor-positive breast cancer, treatment with ribociclib and letrozole significantly improved progression-free survival (PFS) compared with placebo in interim results from the MONALEESA-2 trial.

Increased cyclin-dependent kinase (CDK) 4/6 activity is associated with endocrine therapy resistance, Dr. Hortobagyi said in an ESMO press briefing. While endocrine therapy is an established first-line treatment for advanced breast cancer, endocrine therapy resistance and disease progression eventually occur in most patients. CDK 4/6 inhibition is a valid treatment strategy for hormone receptor-positive advanced breast cancer and may help overcome or delay endocrine therapy resistance. Ribociclib (LEE011) is an orally bioavailable selective CDK 4/6 inhibitor.

In MONALEESA-2, a phase 3, double-blind, placebo-controlled trial of ribociclib plus letrozole, 668 postmenopausal women with hormone receptor-positive/HER2-negative metastatic or locally advanced breast cancer with no prior therapy for advanced disease were randomized to two treatment groups: ribociclib (600 mg/day, three weeks on/one week off) plus letrozole (2.5 mg/day, continuous) (n = 334) or letrozole plus placebo (n = 334).

At interim analysis, median PFS was not met in the ribociclib plus letrozole arm (95% confidence interval, 19.3–NR). Median PFS was 14.7 months (range, 13.0–16.5 months) in the placebo plus letrozole arm (P = 0.00000329). Differences between the treatment arms emerged early and were sustained.

Dr. Hortobagyi said that patients with measurable disease at baseline had a significantly higher objective response rate to ribociclib plus letrozole compared with letrozole plus placebo (53% versus 37%, respectively; P = 0.00028). Ribociclib plus letrozole also improved the clinical benefit rate compared with letrozole plus placebo (80% versus 72%, respectively; P = 0.02).

Most adverse events were grades 1–2 and were managed with dose interruptions and reductions. Very few patients discontinued treatment. Although serious adverse events were uncommon (less than 5%) in both arms, adverse events occurred more often in the ribociclib-treated patients. The most common adverse events were related to uncomplicated myelosuppression: neutropenia (59% for ribociclib/letrozole versus 1% for letrozole/placebo), leukopenia (21% versus 1%), and lymphopenia (7% versus 1%). Nausea, vomiting, diarrhea, alopecia, rash, and transaminase elevations were also reported more frequently in ribociclib-treated patients.

As a result of the interim analysis showing that the primary endpoint had already been met, the data monitoring and safety board recommended termination of the trial.

“This is an important advance,” Dr. Hortobagyi said. He commented also that available data suggest that the three leading approved CDK 4/6 inhibitors seem to have very similar therapeutic value and toxicity profiles. He called the results “paradigm changing” and said, “We have not had studies in metastatic breast cancer before with this magnitude of benefit.”
Efficacy and Safety of Nab-Paclitaxel in Patients With Metastatic Breast Cancer: Final Results Of the Noninterventional NABUCCO Study

• Karin Potthoff, MD, iOMEDICO, Freiburg, Germany

While several clinical trials of nab-paclitaxel have been conducted, prospective data on real-world practice consistent with increased use of prior taxane-containing regimens in the neoadjuvant setting have been lacking. “We wondered if patients, in fact, were able to receive the recommended 260 mg/m² dose or if it was too toxic,” Dr. Potthoff said in an interview at her poster.

In a pivotal phase 3 trial conducted by Gradishar et al., nab-paclitaxel demonstrated high efficacy (overall response rate, 33%; time to tumor progression, 23.0 weeks; overall survival, 60 weeks) with an acceptable toxicity profile. Peripheral sensory polyneuropathy (grade 3) in 10% of patients was the most critical safety issue.²

In order to test that idea, NABUCCO study investigators collected data from approximately 100 oncology outpatient centers across Germany on the routine treatment of 697 patients with metastatic breast cancer in whom anthracycline therapy was contraindicated. Data on treatment for a maximum of six months were captured with follow-up data for a median of 17.7 months, including details on disease progression, overall survival, and safety with a focus on neurotoxicity.

Neurotoxic adverse events at grades 3 and 4 were observed in a low number of patients (5.2% overall: peripheral sensory neuropathy in 4.3%; peripheral motor neuropathy in 1.1%; and paresthesia in 0.1%). Among grade 1 and 2 events, which were reported in 47.3% of patients, peripheral sensory neuropathy was most common (35%).

Median age in the overall trial was 62.3 years; 58.2% of the patients were younger than 65 years of age. Median time from primary diagnosis was 65.2 months. Among the entire cohort, 419 patients (60.1%) had received prior taxane therapy with treatment schemes ranging from 78–260 mg/m² every three or four weeks. Nab-paclitaxel was received as first-, second-, third-, and fourth-or-greater-line therapy in 40%, 24%, 20%, and 15% of patients, respectively.

Over half of the patient population had hormone receptor-positive/HER2-negative (HR+/HER2–) disease (58.4%). The rest of the patients had HR+/HER2+ (9.9%), HR–/HER2+ (3.9%), and triple-negative (13.8%) breast cancer, and receptor status was unknown in 14.1%.

Overall response rates ranged from 29.0% in fourth-or-greater-line therapy to 46.1% in first-line therapy. Those with stable disease ranged from 30.5% patients in third-line therapy to 37.3% in second-line therapy. Response rates were highest among patients who were HR–/HER2+ (55.6%) and lowest in triple-negative breast cancer (32.7%). “That rate for triple-negative disease is still quite good,” Dr. Potthoff noted. The progressive disease rate was highest in patients with triple-negative breast cancer (27.1%) and lowest in those with HR–/HER2+ disease (11.1%).

While overall response rates were lower in patients older than 65 years compared with patients younger than 65 years (31.6% versus 41.1%, respectively), the progressive disease rate was not higher in older patients compared with younger patients (17.2% versus 20.0%). Patients receiving nab-paclitaxel doses lower than 260 mg/m² did not have lower overall response rates. Median time to tumor progression was 5.9 months for the overall population and similar for those younger than age 65 years (5.7 months) and those age 65 years or older (6.5 months). It was shortest for those with triple-negative disease (4.9 months) and longest for those who were HR+/HER2+ (8.6 months).

“Our real-world data from NABUCCO confirm the earlier clinical trial findings. They confirm also that nab-paclitaxel is an effective and safe treatment option with a favorable benefit-risk profile in metastatic breast cancer patients not eligible for anthracycline therapy,” Dr. Potthoff concluded. She underscored that response rates were high in populations typically difficult to treat—patients who had received multiple lines of prior therapy, older patients, and patients with triple-negative disease.

REFERENCES
