ONCOLOGY TIMES

Publishing for 36 Years

Independent News on
HEMATOLOGY / ONCOLOGY

July 25, 2014 • Volume 36, Number 14 • oncology-times.com

Needle Biopsy Found to be Underused for Breast Cancer

BY HEATHER LINDSEY

Needle biopsy, the standard of care for diagnosing breast cancer, is underused in the United States, and patients are often influenced by surgeons to undergo unnecessary excisional biopsy, which may have a negative impact on diagnosis and treatment. That is the conclusion of a study now online ahead of print in the *Journal of Clinical Oncology* (***DOI.10.1200/JCO.2013.52.8257***).

Reflecting these findings, the senior author, Benjamin Smith, MD, Associate Professor in the Departments of Radiation Oncology and Health Services Research at MD Anderson Cancer Center, said that MD Anderson sees a number of patients who have undergone excisional biopsy when a needle biopsy would have been appropriate. And while patient characteristics such as geographic location tend to influence needle biopsy use, so do provider characteristics, he said.

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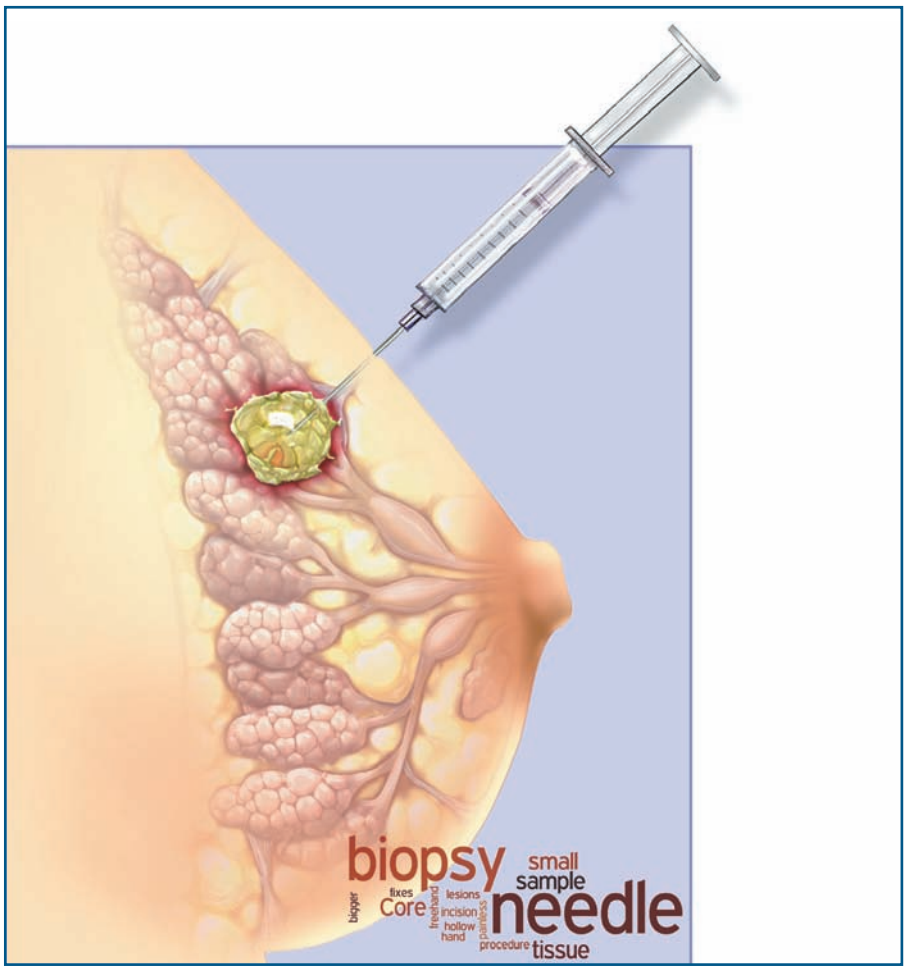
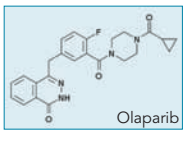


ODAC Votes No on Accelerated Approval of Olaparib for Ovarian Cancer Maintenance Therapy

BY PEGGY EASTMAN

SILVER SPRING, MD—The Oncologic Drugs Advisory Committee (ODAC) of the U.S. Food and Drug Administration voted 11 to 2 in a meeting here against recommending accelerated approval of olaparib as oral maintenance monotherapy for women with relapsed platinum-sensitive ovarian cancer—including fallopian tube or primary peritoneal—who have the germline BRCA (gBRCA) mutation.



Olaparib is a PARP (poly ADP ribose polymerase) inhibitor, which preferentially induces cell death in BRCA-deficient cells. As usual, the FDA does not have to follow ODAC's recommendations, but frequently does.

The Society of Gynecologic Oncology, patients, and patient advocates expressed disappointment with ODAC's recommendation, as did olaparib's manufacturer, AstraZeneca.

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PERIODICALS

Hematological Malignancy Takeaways from ASCO 2014

BY RAVI VIJ, MD

Hematological malignancies were well represented this year at the ASCO Annual Meeting in the abstracts presented in the sessions on plasma cell disorders, lymphoma, and leukemia.

For multiple myeloma, Dr. Paul Richardson presented results of the PANORAMA-1 study: a randomized double-blind Phase III study of panobinostat or placebo plus bortezomib and dexamethasone and relapsed/refractory multiple myeloma (***Abstract 8510***).

Panobinostat is a pan-deacetylase inhibitor which in prior Phase I and II studies had demonstrated responses in relapsed and refractory multiple myeloma including bortezomib-resistant disease.

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ODAC VOTES NO ON ACCELERATED APPROVAL FOR OLAPARIB FOR OVARIAN CANCER MAINTENANCE

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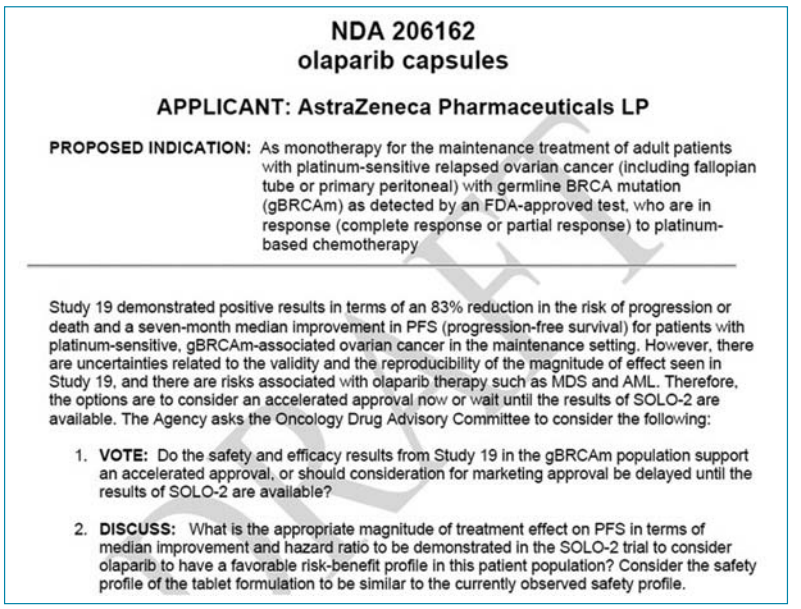
Briggs Morrison, MD, the company's Executive Vice President for Global Medicines Development and Chief Medical Officer, said in a statement, "Patients with germline BRCA-mutated serous ovarian cancer have few options available to treat this disease. We are disappointed with today's recommendation, and strongly believe that olaparib has the potential to provide patients with relapsed BRCA-mutated ovarian cancer and their doctors with a much needed treatment option." He said the company will continue its olaparib clinical trial development program, and pledged to work with the FDA to address its concerns.



NDA 206162
olaparib capsules

APPLICANT: AstraZeneca Pharmaceuticals LP

PROPOSED INDICATION: As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA mutation (gBRCAm) as detected by an FDA-approved test, who are in response (complete response or partial response) to platinum-based chemotherapy

Study 19 demonstrated positive results in terms of an 83% reduction in the risk of progression or death and a seven-month median improvement in PFS (progression-free survival) for patients with platinum-sensitive, gBRCAm-associated ovarian cancer in the maintenance setting. However, there are uncertainties related to the validity and the reproducibility of the magnitude of effect seen in Study 19, and there are risks associated with olaparib therapy such as MDS and AML. Therefore, the options are to consider an accelerated approval now or wait until the results of SOLO-2 are available. The Agency asks the Oncology Drug Advisory Committee to consider the following:

1. **VOTE:** Do the safety and efficacy results from Study 19 in the gBRCAm population support an accelerated approval, or should consideration for marketing approval be delayed until the results of SOLO-2 are available?

2. **DISCUSS:** What is the appropriate magnitude of treatment effect on PFS in terms of median improvement and hazard ratio to be demonstrated in the SOLO-2 trial to consider olaparib to have a favorable risk-benefit profile in this patient population? Consider the safety profile of the tablet formulation to be similar to the currently observed safety profile.

In making their decision, ODAC committee members reviewed clinical data from a pivotal trial known as Study 19. That study of several hundred women demonstrated an 83 percent reduction in the risk of disease progression or death and a median improvement of 7.1 months in progression-free survival (PFS) for patients with gBRCA-mutated ovarian cancer taking olaparib as maintenance therapy. But data from Study 19 also raised questions about an increased risk of myelodysplastic syndromes (MDS) and acute myelogenous leukemia (AML), as well as questions about side effects, and statistical-design concerns about the validity and reproducibility of the magnitude of the benefit observed.

An important factor for voting ODAC members was that a larger global confirmatory trial of olaparib as maintenance monotherapy, SOLO-2, is now enrolling patients; results from SOLO-2, which will enroll only women with the gBRCA mutation and use a different oral formulation, are expected by the end of 2016.

Pazdur: 'This Trial Has Problems…'

"This trial has problems… that's why we're having this discussion," said Richard Pazdur, MD, Director of FDA's Office of Hematology & Oncology Products in the Office of New Drugs. "If we were dealing with a pristine clinical trial… we wouldn't be here," he added, noting that the sponsor's New Drug Application for olaparib (which was filed in February), was "a very difficult application to discuss."

He emphasized that the FDA is not against progression-free survival (rather than overall survival) as a primary endpoint in ovarian cancer trials—which was clearly a problem for some of the ODAC members. Pazdur said the FDA will work with AstraZeneca on the trial design of SOLO-2. He also asked AstraZeneca speakers about the drug company's philosophy on providing expanded access to olaparib. The company has such a program, but it is somewhat limited, said Hesham A. Abdullah, MD, MSc, RAC, AstraZeneca's Vice

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IBRUTINIB

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prospect of using ibrutinib is fantastic," she said.

Another patient population to benefit may be younger patients with 17p deletion who would otherwise be considered for allogeneic stem cell transplant. "The presence of ibrutinib is going to change the landscape now and force us to reevaluate in a meaningful way how to approach these patients," Odenike said.

"I have had many of my own CLL patients who were almost to the point of having hospice discussions, and with ibrutinib therapy I've seen them come back in so many ways, in performance and quality of life."

ANTHONY MATO, MD, predicted that the success of the RESONATE trial for ibrutinib will lead to an acceleration of research in B-cell receptor signaling, which will translate into the development of more targeted drugs for CLL.

'Transformative'

Also asked for his opinion for this article Anthony Mato, MD, Director of the Center for Chronic Lymphocytic Leukemia at the University of Pennsylvania, said: "By far this is a transformative drug; it is transforming the way we treat patients with CLL."

Mato said he was impressed that ibrutinib appears to overcome the traditional poor-risk factors for patients with CLL. "Patients generally respond well whether or not they have unmutated CLL or a chromosome-17 abnormality—patients who would have traditionally done poorly, especially in the relapsed/refractory setting. And when those response rates are translated to duration of response, the duration is very impressive with a median progression-free survival that has not been reached."

Mato said this trial is one of the few examples in CLL where a novel approach was compared with a standard approach and survival is actually improved. The most recent example he could recall of a successful new approach was from the CLL-8 trial which added rituximab to fludarabine-cyclophosphamide (FCR), and at three years achieved 65 percent progression-free survival versus 45 percent for FC (***Hallek et al: Lancet 2010; 376:1164-1174***).

He predicted that the success of RESONATE will lead to an acceleration of research in B-cell receptor signaling, which will translate into the development of more targeted drugs for CLL. "Ibrutinib is probably the tip of the iceberg [for that direction of research], as we are recognizing more and more how important B-cell receptor signaling is."

A question to answer now is how to combine ibrutinib with current standards, particularly rituximab, he said. "Rituximab is not approved for use as a single agent—it's usually combined with fludarabine and cyclophosphamide, but studies presented at previous meetings looking at the combination of ibrutinib and rituximab had response rates exceeding 80 percent."

He cited a Phase II study of the ibrutinib-rituximab combination presented at the most recent American Society of Hematology Annual Meeting, which showed responses exceeding 90 percent (***ASH Abstract 675***).

"I have had many of my own CLL patients who were almost to the point of having hospice discussions, and with ibrutinib therapy I've seen them come back in so many ways, in performance and quality of life."

ODAC

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President for Global Regulatory Affairs in Oncology. "The best expanded access is regulatory approval," he said.

"I think we need to take a deeper dive into cytopenias on this study," said ODAC Chair Mikkael Sekeres, MD, MS, Director of the Leukemia Program and Chair of the Hematology/Oncology Pharmacy & Therapeutics Committee at the Cleveland Clinic's Taussig Cancer Institute, and *OT*'s Clinical Advisory Editor for Hematology/Oncology.

Presiding at his final meeting as ODAC Chair, Sekeres said he was particularly concerned about the increased risk of MDS on Study 19, since MDS is underdiagnosed and some ovarian cancer patients put on olaparib as maintenance therapy could have undiagnosed MDS. He said he was also concerned about subjecting women on olaparib maintenance monotherapy to potential side effects such as nausea and vomiting, even though most nausea and vomiting in Study 19 was reported as mild.

He noted that the current standard of care is for platinum-sensitive ovarian cancer patients not to be treated until they relapse, at which time they would have another platinum-based chemotherapy treatment. For the majority of patients in Study 19, while their quality of life was no worse on olaparib than on placebo, it also did not change for the better.

Speaking in favor of the Accelerated Approval application for olaparib, Ursula A. Matulonis, MD, Medical Director and Program Leader of the Medical Gynecologic Oncology Program at Dana-Farber Cancer Institute, stressed that women with advanced ovarian cancer on olaparib maintenance therapy are "absolutely overjoyed" not to have to come into the clinic as frequently to have IV chemotherapy. "This is an overwhelmingly well-tolerated drug… patients want this drug now, and not to have to wait for it," she said.

Ozols: 'Meaningful PFS Increase'

Also speaking on behalf of approving olaparib, consultant Robert F. Ozols, MD, PhD, a pioneer in ovarian cancer research who formerly held positions at the National Cancer Institute and at Fox Chase Cancer Center, stressed that olaparib "capitalizes on ovarian cancer tumor biology," thus leading to an acceptable toxicity profile in which "normal cells are less affected." Ozols added, "Extending PFS by 7.1 months is meaningful, prolonging the chemotherapy-free interval." He noted that "BRCA status allows patient selection sensitive to PARP inhibition."

Voting for the accelerated approval application, temporary ODAC voting member Edward L. Trimble, MD, MPH, Director of NCI's Center for Global Health, said he was persuaded by the data on the prolonged disease-free interval.

The pivotal Study 19 found an 83% reduction in disease progression or death and a median improvement of 7.1 months in PFS for patients with gBRCA-mutated ovarian cancer taking olaparib as maintenance therapy.

He added, "I support PFS as a primary endpoint, and so does the ovarian cancer advocacy community."

The other person who voted for the New Drug Application was ODAC member Tito Fojo, MD, PhD, Program Director for Medical Oncology at NCI.

Disappointing to Many

Speaking on behalf of the Society of Gynecologic Oncology (SGO) during the public session of the ODAC meeting, G. Larry Maxwell, MD, FACOG, Col. (ret), Chair of the Department of Obstetrics and Gynecology at Inova Fairfax Hospital in Virginia, said, "SGO highly endorses this application."

The data from Study 19 are "impressive" and olaparib maintenance therapy for gBRCA-mutated ovarian cancer

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ASCO14 HEMATOLOGIC MALIGNANCY HIGHLIGHTS

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By RAVI VIJ, MD
Associate Professor of Medicine, Section of Stem Cell Transplant and Leukemia, Division of Medical Oncology, Washington University School of Medicine, St. Louis, Missouri.

In the trial presented at ASCO, 768 patients with relapsed or relapsed and refractory multiple myeloma not refractory to bortezomib who had one to three prior lines of therapy were randomized to treatment with panobinostat, bortezomib, and dexamethasone and compared with a group receiving placebo with bortezomib and dexamethasone. Nearly half the patients enrolled had received at least two prior regimens at time of randomization.

After a median follow-up of approximately 125 weeks, the primary endpoint of progression-free survival was met, with the panobinostat arm having a median progression-free survival of 12 months versus 8.1 months in the comparator arm ($p < 0.0001$). The overall response rate was 60.7 percent in the panobinostat arm versus 54.6 percent in the comparator arm ($p = 0.087$). The CR/near-CR rates were 27.6 versus 15.7 percent ($p = 0.00006$), respectively.

The benefit did come at the cost of greater toxicity, with grade III/IV diarrhea observed in 25.5 percent of patients in the panobinostat arm versus eight percent in the comparator arm. Grade III/IV fatigue was seen in 23.9 percent of patients in the panobinostat arm versus 11.9 percent in the comparator arm.

This trial is likely to lead to the approval of panobinostat for the therapy of patients with multiple myeloma, allowing for a new option with a novel mechanism of action. In the future, selective HDAC6 inhibitors like ACY-1215 may be able to demonstrate a better efficacy-to-toxicity profile.

CD38 antibodies

Additional data with two monoclonal antibodies to CD38, daratumumab and SAR650984, both as single agents and in combination with lenalidomide and dexamethasone, were reported.

Dr. Henk Lokhorst presented data on daratumumab as monotherapy in patients with relapsed or refractory multiple myeloma (***Abstract 8513***). The results reported earlier from the Phase I dose-escalation study had shown impressive responses in patients with refractory disease. The authors here presented preliminary data from the first 50 patients in an ongoing cohort expansion phase of the monotherapy trial. The drug achieved a response rate of 35 percent at a dose level of 16 mg/kg with a median progression-free survival of 23 weeks.

> "The PANORMA trial is likely to lead to the approval of panobinostat for the therapy of patients with multiple myeloma, allowing for a new option with a novel mechanism of action for patients with the disease."

Dr. Thomas Martin reported on a Phase IB dose-escalation trial *of* SAR650984 in combination with lenalidomide and dexamethasone in relapse-refractory myeloma (***Abstract 8512***). A total of 31 patients were treated, of whom 74 percent were refractory to their last lenalidomide-containing regimen. Twenty nine percent of patients were deemed pomalidomide refractory, 52 percent refractory to bortezomib, and 48 percent refractory to carfilzomib. An overall response rate of 58 percent with a very good partial response rate of 23 percent was observed. A total of 48 percent of patients refractory to lenalidomide responded to the regimen.

Monoclonal antibodies are expected to provide the next big leap in improving the outcomes of patients with multiple myeloma, and both of these abstracts provided rationale for the continued enthusiasm about these drugs.

MPT vs. MPR

Dr. A. Keith Stewart reported results of E1A06: an intergroup Phase III randomized controlled trial comparing melphalan, prednisone, and thalidomide versus melphalan, prednisone, and lenalidomide in newly diagnosed multiple myeloma patients who were not candidates for high-dose therapy (***Abstract 8511***). The patients received the three-drug induction regimens for a planned 12 cycles and were then continued on thalidomide and lenalidomide respectively until disease progression.

A total of 64 percent of patients in the thalidomide arm and 60 percent of patients in the lenalidomide arm had a partial response ($p = 0.557$) with very good partial response rates of 19 and 23 percent ($p = 0.401$), respectively. The progression-free survival was 21 months for the thalidomide arm and 18.7 months for the lenalidomide arm ($p = 0.19$). After a median follow-up of 41 months, the median overall survival was reported to be 52.6 months in the thalidomide arm and 47.7 months in the lenalidomide arm (hazard ratio 0.88). The overall rates of grade III and non-hematological toxicity were lower in the lenalidomide arm.

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patients represents "truly individualized therapy," ushering in "personalized medicine for this patient population," added Maxwell, who is also Professor in the Department of Obstetrics and Gynecology at Virginia Commonwealth University School of Medicine.

"We've waited 10 years just for this," Lisa Schlager, Vice President for Community Affairs & Public Policy of FORCE (an advocacy group for people fighting hereditary breast and ovarian cancer), told *OT*.

In her formal presentation during the public session, Schlager said, "Women with BRCA-associated ovarian cancer cannot and should not have to wait another decade to have access to a PARP inhibitor. We ask that the FDA consider our community carefully when reviewing this drug application and grant approval to olaparib for maintenance therapy in ovarian cancer patients who are BRCA positive… How many more women will die or suffer the effects of advanced disease and chemotherapy while we are waiting for larger trials to be completed? Women fighting hereditary ovarian cancer do not have time to wait."

> Study 19 also raised questions about an increased risk of MDS and AML, as well as concerns about side effects and statistical design.

Ovarian cancer survivor Nancy Long, a nurse practitioner who is Co-Chair of the Leadership Council for the Central Maryland Chapter of the National Ovarian Cancer Coalition (NOCC), stated during the public session, "Olaparib is one of the promising targeted drugs. I urge you to approve this drug. We cancer survivors are desperate for new drugs and treatments."

And, in a letter sent to ODAC on behalf of the Ovarian Cancer National Alliance (OCNA), ovarian cancer survivor Kathleen S. Fallon said, "It is striking and disheartening to see that despite progress made in recent years, ovarian cancer continues to claim the lives of so many women.

"Furthermore, there are few FDA-approved medications for the treatment of ovarian cancer. … To ensure that women have access to therapeutics necessary for their care, the Alliance advocates for the approval of every treatment and therapy that shows a benefit in fighting ovarian cancer, provided that benefit has been clearly documented through appropriate trials and review process."