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Survey: Most Oncologists Avoid the Word 'Cure' in Discussions with Patients

BY KURT SAMSON

In what is believed to be the first such study to give quantitative as well as qualitative data on this topic, oncologists said both that their patients are hesitant to ask whether they are cured, and that they as cancer care clinicians try not to use the word with patients. The implications are many, those interviewed for this article said, and open up multiple avenue of research. *Page 24*

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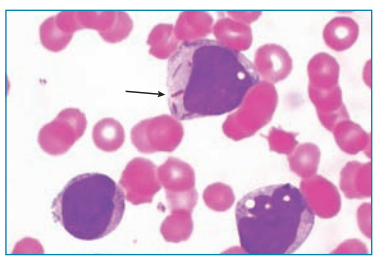

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HER2+ Advanced Breast Cancer: Combinations Beyond Trastuzumab Showing Promise

BY MARK FUERST

CHICAGO—New insights into the biology of human epidermal growth factor receptor-2 positive (HER2+) advanced breast cancer have begun to change clinical practice, with a combination of chemotherapy and anti-HER2 agents emerging as the most effective current therapy. That was the consensus here in discussions at the American Society of Clinical Oncology at an Educational Session titled "Beyond Trastuzumab and Lapatinib: New Options for HER2-Positive Breast Cancer" as well as in other presentations

Two agents, pertuzumab and trastuzumab emtansine (T-DM1), have been recently approved for advanced breast cancer, and new combinations, including trastuzumab, vinorelbine, and everolimus; pertuzumab, trastuzumab, and paclitaxel; and lapatinib plus vinorelbine are now being tested.

At the Educational Session, experts discussed potential therapeutic options in development for the treatment of patients with HER2+ breast cancer, particularly those resistant to HER2 blockade. Speakers outlined what is now understood about the efficacy of dual therapy, examined new clinical trial designs that may answer questions about the efficacy of anti-HER2 agents, and highlighted the questions that remain about how to best select patients who could benefit from chemotherapy or other options.

RUTH O'REGAN, MD, said she believes that the combination of everolimus, trastuzumab, and vinorelbine could be used as third-line therapy after trastuzumab and pertuzumab in the metastatic setting. "Ultimately, based on known mechanisms of resistance, and with more mature survival data, I hope it will become another treatment option for advanced breast cancer."

Combining anti-HER2 agents for the treatment of patients with HER2+ breast cancer is currently more effective than giving one agent on its own, said the chair of the session, David A. Cameron, MD, Professor of Oncology and Director of Cancer Services at the University of Edinburgh.

He noted that several studies have confirmed a higher number of pathologic complete responses with use of dual anti-HER2 therapy. In the EGF104900 trial, dual HER2 blockade with trastuzumab plus lapatinib resulted in significant prolongation of both median progression-free survival (PFS) and overall survival (OS), with an acceptable toxicity rate. Another monoclonal antibody, pertuzumab, has shown efficacy in combination with trastuzumab in the adjuvant and metastatic setting.

ASCO Annual '13 Meeting

In the randomized Phase III CLEOPATRA trial, patients were treated with either docetaxel plus trastuzumab or the same regimen plus pertuzumab, and the dual HER2 blockade significantly prolonged median PFS (18.5 months) compared with use of standard therapy (12.4 months).

DAVID A. CAMERON, MD, noted that several studies have confirmed a higher number of pathologic complete responses with use of dual anti-HER2 therapy.

BOLERO-3

In her report at an oral session, Ruth O'Regan, MD, Professor and Vice-Chair for Educational Affairs in the Department of Hematology and Medical Oncology at Emory University School of Medicine, explained that although trastuzumab has markedly improved outcomes for patients with all stages of HER2+ breast cancer, in the metastatic setting, the majority of patients do eventually develop resistance to the drug.

She presented data on BOLERO-3 (Breast cancer trials of OraL EveROlimus-3), a Phase III, randomized, double-blind study of trastuzumab and vinorelbine plus everolimus conducted at 159 clinical trial sites globally (***Abstract 505***). The addition of everolimus, an mTOR inhibitor, to trastuzumab and vinorelbine in heavily pretreated advanced breast cancer patients led to a 22 percent reduction in the risk of disease progression. This is the first Phase III study to show that inhibition of the HER2+ receptor and mTOR provides significant benefit in HER2+ advanced breast cancer, she said.

The trial included 569 women with HER2+ locally advanced or metastatic breast cancer who were previously treated with a taxane and were resistant to trastuzumab. Participants were randomized to receive either everolimus at 5 mg/day orally (284 patients) or placebo (285 patients), plus weekly vinorelbine at 25 mg/m^2 intravenously and weekly trastuzumab at 2 mg/kg intravenously following a loading dose of 4 mg/kg. All patients had prior taxane therapy, and 27 percent of patients in each group had received prior lapatinib.

The study met its primary endpoint of improved PFS, with a median time to progression of 7.0 months in the everolimus combination arm and 5.8 months in the placebo combination arm. Overall survival data are not yet mature, and will be available next year, she said.

She noted that in subgroup analyses everolimus seemed to have a greater effect on PFS among patients younger than 65, those with hormone receptor-negative cancers, and those who had received prior adjuvant or neoadjuvant trastuzumab. The overall response rate (ORR) was not significantly different between the two groups.

Adverse events were consistent with the known safety profile of everolimus, she said, and were "quite manageable." The most common all-grade adverse reactions were neutropenia, stomatitis, anemia, leukopenia, fatigue, pyrexia, diarrhea, nausea, decreased appetite, and constipation. The most common Grade 3-4 adverse reactions were neutropenia, leukopenia, anemia, stomatitis, fatigue, febrile neutropenia, diarrhea, pyrexia, nausea, hyperglycemia and thrombocytopenia.

The Global Health Status was not significantly different in the two arms: "The toxicity of everolimus did not affect quality of life," she said.

O'Regan said she believes that this everolimus combination could be used as third-line therapy after trastuzumab and pertuzumab in the metastatic setting.

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New insights into the biology of HER2+ advanced breast cancer have begun to change clinical practice, with a combination of chemotherapy and anti-HER2 agents emerging as the most effective current therapy.

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"Ultimately, based on known mechanisms of resistance, and with more mature survival data, I hope it will become another treatment option for advanced breast cancer," she said.

Joyce O'Shaughnessy, MD, Co-Director of Breast Cancer Research at the Baylor Charles A. Sammons Cancer Center, said the BOLERO-3 study could be practice changing: "It gives us another option in HER2+ metastatic breast cancer. Everolimus is already available, and we will see it used immediately."

In her remarks as Discussant for the study, Kimberly Blackwell, MD, Professor of Medicine at Duke University School of Medicine, said, "Everolimus should lessen the effect of upstream signaling and acquired resistance to trastuzumab. The unique aspect of the trial is that it allowed prior lapatinib, which suggests that patients were more treatment refractory."

The BOLERO-3 results have landed in a crowded space of trastuzumab-resistant trials, she added. "At the end of the day, there is a role for mTOR inhibition. This is an active combination and leads to significant improvement in PFS."

Overcoming Resistance

Resistance to therapeutic agents is a continuing problem in advanced breast cancer, but only a limited number of resistance mechanisms have been validated, said Ian Krop, MD, PhD, Instructor in Medicine, Adult Oncology, at Dana-Farber Cancer Institute. Speaking at the Education Session, he said that the goals of research in HER2+ breast cancer should be to reduce the relapses in the adjuvant setting, improve efficacy in metastatic breast cancer, reduce toxicity in both settings, and better tailor specific therapy to patients. Researchers need to identify ways to overcome mechanisms of resistance that could provide new therapeutic targets as well as predictive markers, he added.

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MARTINE PICCART-GEBHART, MD, PHD: "Much larger collaboration networks are needed to make progress in anti-HER2 agent 'tailoring,' and to discover and validate predictive biomarkers of response."

A study by Spanish researchers called Long-HER, reported by Enrique Espinosa, MD, a medical oncologist at Hospital de la Pas in Madrid, used whole genome analysis to find predictors of early progression to trastuzumab, particularly in the phosphatidylinositol-3-kinase (PI3K) pathway (***Abstract 608***). The researchers used clinical and molecular analysis of advanced HER2+ breast cancer patients treated with trastuzumab.

This observational, multicenter study compared 103 long-term survivors of breast cancer who had an objective response or stable disease for at least three years after trastuzumab therapy, with a control group of 18 patients who had disease progression in the first year of similar first-line therapy.

A microarray platform was used to assess whole genome expression in 53 samples, including 35 from the long-term survivors and all of the controls. The PI3K pathway was most strongly associated with response to trastuzumab, and to elucidate the mechanisms responsible for trastuzumab resistance, 97 genes related to the PI3K-mTOR pathway were evaluated. Five of these genes act upstream of mTOR complexes, and could modulate mTOR signaling, he said. Most patients in the control group had low expression of three of the genes and high expression of the other two.

"It appears that you need several hits of the mTOR pathway for the tumor to become resistant to trastuzumab," he said. "A patient who has one or two alterations in the pathway is more likely to do well. For a patient with four or five alterations at the same time, the tumor is more likely to be resistant."

He said he believes that combining new drugs, such as pertuzumab plus everolimus, makes sense after it is possible to define which patients are more likely to benefit from therapy, because they are more likely to be resistant to trastuzumab.

"In the near future, we will have a way to select patients for new anti-HER2 therapies," he said. "When a patient needs an anti-HER2 drug, we will be able to test the tumor to see if it responds to trastuzumab. If the tumor is resistant, then we should combine trastuzumab with something else, such as an mTOR inhibitor."

Anthony Goncalves, MD, of Marseille University commented: "The PI3K-mTOR pathway is frequently activated in HER2+ breast cancer and may play a major role in resistance to trastuzumab. Trastuzumab has transformed the natural history of HER2+ metastatic breast cancer, but primary or secondary resistances are ineluctable.

"Thirty to 50 percent of patients with HER2+ metastatic breast cancer do not respond to trastuzumab-based treatments, and virtually all will relapse ultimately."

O'Shaughnessy added that it is necessary to have a good reason to order genomic tests, and that includes clinical utility to justify the costs.

Speaking at the Education Session, Martine J. Piccart-Gebhart, MD, PhD, Director of the Medicine Department at Institut Jules Bordet in Belgium, said, "Optimization of treatment in this setting is our obligation."

IAN KROP, MD, PHD: "It appears that you need several hits of the mTOR pathway for the tumor to become resistant to trastuzumab. A patient who has one or two alterations in the pathway is more likely to do well, but the tumor is more likely to be resistant in patients who have four or five alterations at the same time.

Methods must be devised that can identify patients who do not need intensified regimens and those with disease-resistant HER2 blockade. "Much larger collaboration networks are needed to make progress in anti-HER2 agent 'tailoring,' and to discover and validate predictive biomarkers of response."

Several other studies presented at the meeting examined various combinations of agents in advanced breast cancer. For example, researchers at Memorial Sloan-Kettering Cancer Center combined pertuzumab, trastuzumab, and weekly paclitaxel in a Phase II study of 53 patients with HER2-overexpressing metastatic breast cancer. The preliminary six-month progression-free survival rate was 81 percent in the 36 evaluable patients, with few grade 3/4 toxicities and no sign of increased cardiac toxicity to date.

In addition, a multicenter Phase II study examined a combination of lapatinib with vinorelbine as first- or second-line therapy in 44 women with HER2-overexpressing metastatic breast cancer. The combination of lapatinib and vinorelbine resulted in a 44 percent overall response rate, where half of the patients were receiving second-line therapy, and it was well tolerated.

"Optimization of treatment in this setting is our obligation."