Professor Hope S. Rugo: Reversing resistance and hormone therapy for metastatic breast cancer

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Hope S. Rugo (Figure 1), MD, is a Professor of Medicine in the Division of Hematology and Oncology at the Helen Diller Family Comprehensive Cancer Center of the University of California, San Francisco (UCSF), where she directs Breast Cancer and Clinical Trial Education Breast Oncology and Clinical Trails Education. Her research interests include novel therapies for advanced breast cancer, immune modulation to restore chemotherapy sensitivity evaluation of circulating cells as novel markers of response and resistance to therapy, neoadjuvant therapy, and supportive care.

Prof. Rugo is an investigator in the Bay Area Spore at the UCSF Breast Cancer Center, the national multi-center ISPY2 trial, and is the principal investigator of a number of clinical trials. She serves on steering committees for national and international studies. Prof. Rugo is a member of the ALLIANCE Breast Core Committee and the Translational Breast Cancer Research Consortium, and serves on several committees for the American Society of Clinical Oncology. She has published many peer-reviewed papers and has given presentations on a variety of cancer related topics.

With a summa cum laude undergraduate degree from Tufts University, Prof. Rugo received her medical degree from the University of Pennsylvania School of Medicine and completed both a residency in internal medicine and fellowship in hematology and oncology at the UCSF. Additionally, she completed a two-year post-doctoral fellowship in immunology at Stanford University. She received the Cancer Care Physician of the year award in 2010.

Figure 1 Professor Hope S. Rugo.

CCO: What are the advantages of the hormone therapy for metastatic breast cancer?

Prof. Rugo: Hormone therapy is a very active treatment for patients with hormone receptor-positive disease, even those who have received prior hormone therapy for advanced cancer can benefit from sequential hormone therapy. It's generally well-tolerated and patients have less side effects using hormone therapy compared to chemotherapy. Some patients enjoy a very long progression free survival with this approach.

CCO: We all know drug resistance is a serious problem for the hormone therapy treatment of metastatic breast cancer. What strategies do you think we can take to reverse the drug resistance?

Prof. Rugo: Resistance has been an ongoing problem in the treatment of hormone receptor-positive disease and although most hormone receptor positive tumors will initially respond to hormone therapy, followed by progression, others are primarily resistant to anti-hormone treatment. Regardless of initial response, all cancers will eventually progress. In addition, there is the frustrating situation with late recurrences after appropriate adjuvant hormone therapy. We've been interested for decades in trying to find effective approaches to reverse resistance and improve response to hormone therapy. Now, we have both an approved agent, the mTOR inhibitor everolimus, and other drugs that block activation of the PI3K/AKT/mTOR pathway that seem to be highly active in hormone receptor-positive disease and have demonstrated efficacy in the treatment of hormone receptor positive advanced breast cancer. In addition, there

are agents that block activation of important enzymes for cell cycle progression, cyclin dependent kinases 4 and 6 (CDK 4 and 6), that seem quite promising and are in all phases of clinical trials with two phase III registration trial currently in active enrollment. The combination of inhibitors of the PI3K pathway and CDK 4/6 appears to be quite effective in preclinical models, and is just starting testing in patients.

CCO: Many researchers are paying close attention to mTOR inhibition for its effect on breast cancer treatment. Could you briefly introduce the main mechanism?

Prof. Rugo: The way mTOR inhibition works is as follows: mTOR is a downstream target of PI3K; everolimus blocks the activation of a complex that involves mTOR called mTORC1. By blocking that complex, signaling induced by activation of PI3K pathway is suppressed. It appears that estrogen can actually prevent cell death caused by blockade of the PI3K pathway in vitro, so the hypothesis is that the combination of an aromatase inhibitor or other hormone active agent with the mTOR inhibitor is important for efficacy.

CCO: Doctors usually choose to use an alternative (other drugs) when encountering drug resistance rather than considering solving the resistance itself. What do you think is the main reason?

Prof. Rugo: It's an interesting question. I think some of this is because they are familiar with some treatments more than others. Often physicians are more comfortable starting with chemotherapy, as they feel that this is a quicker and more insured way to guarantee tumor response. However, it is clear that this approach does not improve survival; chemotherapy as an initial approach is only indicated in the situation of 'visceral crisis'. However, our goal in the treatment of metastatic breast cancer is to help patients live as long as possible with the best quality of life. Therefore I believe that there are significant benefits from continuing hormone therapy for as long as possible, and this also allows more independence from the clinic for our patients. Sequential hormone therapy, now with the combination of everolimus and exemestane, can be effective for a number of years.

CCO: What are the main difficulties and challenges for revising resistance for metastatic breast cancer treatment?

Prof. Rugo: This is also very good question, and of course there are still significant challenges. We're excited to now have approval of an effective agent that can improve response to hormone therapy for patients with advanced breast cancer. One important challenge is to identify the patients who are most likely to benefit from this treatment approach. We don't yet have a predictive marker other than the estrogen receptor and clinical drug resistance. The second challenge is managing toxicity. As we become more confident and experienced using mTOR inhibitors, we are better able to both prevent and manage toxicity. Patient education as well as physician education is very important. A third challenge is finding new agents that are complementary to our current approved agents, such as those that block PI3K or CDK 4/6. Even more exciting is the study of combinations of these targeted agents. Then the last big challenge is allowing this new combination therapy of everolimus and hormone therapy to be available to patients worldwide.

CCO: why is it important to consider everolimus in combination with hormone therapy in patients whose cancers have progressed on nonsteroidal aromatase inhibitors?

Prof. Rugo: The Bolero 2 trial demonstrated a marked, more than doubling of progression free survival with maintained quality of life. This is a clinically important benefit, and was seen along with appropriate management of toxicity including dose reductions and delays when necessary. It is important to treat patients early in their disease, similar to patients in Bolero 2, when they are more likely to respond and have less toxicity. If therapy is only given late, after multiple lines of chemotherapy, then you may have a situation with low clinical benefit and more side effects. I would recommend instituting therapy earlier in the course of the disease, following the eligibility from Bolero 2.

CCO: Thank you very much!

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