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MedPAC Plan to Slash Fees  
for Oncologists 'Could Be  
Cataclysmic'

Last-Minute Reprieve Seen as Less Likely than Other  
Times, Announcement Due Nov 23

BY LOLA BUTCHER

A proposal to address one of America's big budget problems by cutting physician fees from the Medicare program is sending a whole new set of shivers through the medical community.

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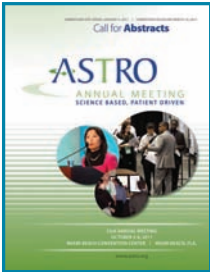
AACR Meeting Highlights Progress  
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CHARLES LOPRINZI: How I  
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# Drug Resistance to Trastuzumab: Dual MABs Inhibit HER2 Activity

BY ROBERT H. CARLSON

**H**OUSTON—Tandem use of two monoclonal antibodies that inhibit HER2 may help with drug resistance to trastuzumab, according to speakers here at the

“New Roles for the EGFR Family in Cancer” symposium on cancer research at the University of Texas MD Anderson Cancer Center.  
Carlos L. Arteaga, MD, Vice

Chancellor’s Chair in Breast Cancer Research and Director of the VICC Breast Cancer Research Program at Vanderbilt-Ingram Cancer Center, predicted that the standard treatment

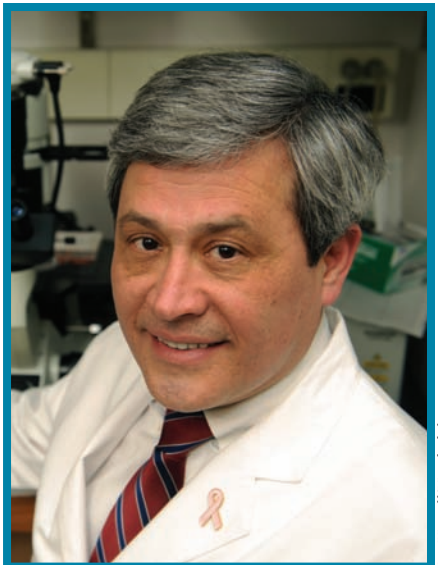
for HER2 resistance will be dual blockade with monoclonal antibodies using different mechanisms of action.

The data suggest synergy when two monoclonal antibodies are used, he said, describing his ongoing Phase III trial named Cleopatra (Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer) of approximately 800 patients with HER2-positive metastatic breast cancer or recurrent locally advanced disease.

Patients are being treated with either trastuzumab and docetaxel, the current gold standard, or with a dual HER2 blockade of trastuzumab, pertuzumab, and docetaxel.

The initial trial results are positive, he said. “How positive I don’t know, but my sense is that this study is going to change the landscape in the way we treat patients with metastatic disease with first-line therapy. The standard will become two antibodies plus chemo — that will be the way to go.”

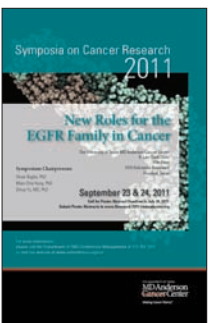
He cited a recent randomized Phase III trial by Kimberly Blackwell et al (*JCO* 2010;28:1124-1130) that tested whether total HER2 blockade with lapatinib plus trastuzumab increased overall survival compared with lapatinib alone in 296 patients with disease progression on or after trastuzumab treatment. Overall survival at six months was 80% for the combination arm versus 70% for the single-agent arm, and 56% and 41%, respectively, at one year.



Joe Howell/Vanderbilt

CARLOS ARTEAGA, MD: “My sense is that this study is going to change the landscape in the way we treat patients with metastatic disease with first-line therapy. The standard will become two antibodies plus chemo—that will be the way to go.”

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# Komen Undeterred by Pink October Criticism

BY ERIC T. ROSENTHAL

For the past several years critics have complained that the “pink” and awareness efforts that occur every October for National Breast Cancer Awareness Month have gone too far, becoming too commercial and exploitive, and have trivialized breast cancer, with some adding that it makes breast cancer seem safer than it really is, and that focusing on screening mammography detracts from research and prevention.

Much of this criticism has been focused on Susan G. Komen for the Cure, the world’s largest organization providing the greatest amount of nonprofit funds for the fight against breast cancer and the group most closely linked with pink symbolism and the overabundance of products of that hue.

When I asked for a specific response to the criticism, Komen officials told me that challenges about the prevalence of pink and pink fatigue have been a perennial issue at its Dallas headquarters, but that it hasn’t had an effect on the foundation’s mission or programs, and that Komen has been periodically placing op-ed articles in key publications to counter the criticism.

Komen President Liz Thompson said that any changes made to granting, education, or outreach programs were a result of

moving Komen’s mission forward, not as a reaction to criticism.

“Our investments are dynamic for the needs of the people we serve. They are driven by our agenda of what’s needed, not by critics,” she said, noting that Komen has been reinvigorating its research efforts and taking a more prominent stance on dealing with health care disparities.

And she said that in her view there is still not enough awareness, citing a

This year, Komen officials said the organization asked *USA Today* if it would publish an op-ed in response to some of the newspaper’s past stories that questioned the pink issue.

In a piece titled “Ask survivors if there’s too much pink,” on Oct. 18, Brinker wrote: “In my view, there’s still not enough pink when every 74 seconds a woman in the world dies of breast cancer—almost a half a million women this year globally. There’s

not enough pink when women still tell me that they don’t get screened for breast cancer because they think they probably won’t get it. And there’s not enough pink when we still don’t understand why breast cancer starts in the first place, how it spreads and, the most important understanding of all, how to stop it before it starts, or stop it in its tracks when it does.”

She wrote that pink helps raise the funds to support research as well as outreach to underserved women, and that it “keeps breast cancer front-and-center before the public, with the knowledge that someone, somewhere, will get the message, get the facts, and get going to protect themselves from the leading cancer killer of women worldwide.”

As to whether there is too much awareness, she responded, “Trust me, there isn’t—not when women are asking me if underwire bras cause breast cancer.”



study of 1.5 million women presented at last year’s San Antonio Breast Cancer Symposium that found that half of those who were insured failed to have annual mammograms.

Komen has also been stating its case publically in a series of op-eds by founder and CEO Nancy G. Brinker that have appeared during the last few years in such media outlets as *Prevention*, the *Boston Globe*, and Huffington Post.

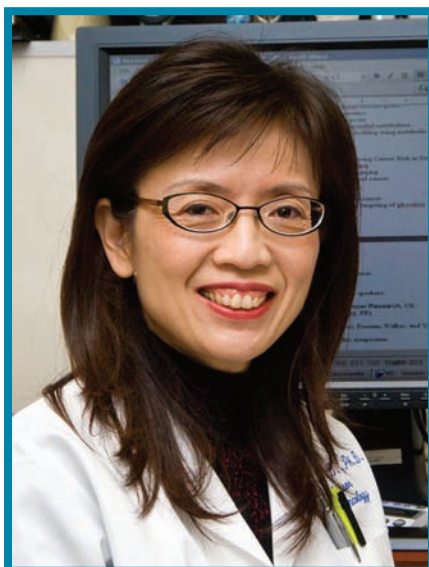
## →2 MABs

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The implications, Dr. Arteaga said, are that (1) Trastuzumab-resistant tumors respond to lapatinib, suggesting they remain dependent on HER2; (2) Lapatinib and trastuzumab each alone cannot inhibit the output of HER2 to HER3 and PI3K/Akt completely; and (3) Dual HER2 blockade with the two drugs trumps reactivation of HER3 and is superior to lapatinib alone.

He said this would be most effective in the adjuvant or neoadjuvant setting. “Whether they should be used together in combination with chemotherapy in the metastatic setting is more debatable,” Dr. Arteaga said, citing cost, toxicity, and the fact that the regimen is not curative.

He concluded by saying that in HER2-positive tumors, dual blockade of the HER2/HER3/PI3K pathway “at the least” is required for maximal therapeutic effect.



### Combine Trastuzumab with PI3K/Src Inhibitors

Another speaker at the meeting, Dihua Yu, MD, PhD, Professor and Deputy Chair of the Department of Molecular and Cellular Oncology at MD Anderson, said that trastuzumab resistance can be overcome by therapies combining trastuzumab with

Dihua Yu, MD, PhD, noted that trastuzumab dissociates Src from ErbB2, leading to PTEN activation and that it might be possible to overcome that by using novel combination therapies targeting PI3K/PTEN pathways.

PI3K/Src inhibitors. Trastuzumab dissociates Src from ErbB2 leading to PTEN activation, she said.

“Less than 35% of patients with metastatic breast cancer respond to Herceptin as a single agent,” she said, adding that two to five percent of patients suffer severe treatment-related side effects such as cardiac dysfunction.

Citing her own research and that of others, Dr. Yu hypothesized that trastuzumab resistance can result from PTEN-loss or PI3K activation. Overcoming this might be achieved by novel combination therapies targeting PI3K/PTEN pathways. As an example, she said, combined treatment with triciribine and trastuzumab significantly inhibits the growth of PTEN-treated BT474 xenografts.