

JKCCN E-Newsletter Supplement, 8/4/10: Attention Investigators Participating in Study E5103

Dear Investigator:

Since 2008, the drug bevacizumab (Avastin) has been approved by the Food & Drug Administration (FDA) under its “accelerated approval” mechanism for use in combination with paclitaxel (Taxol), to treat HER2-negative metastatic breast cancer patients who have not yet received chemotherapy for advanced disease. This approval was based upon the results of ECOG E2100 (N Engl J Med 2007; 357:2666-2676) and a dossier based upon these results submitted to the FDA by (then) Genentech BioOncology. ECOG E2100 was an open label study testing weekly paclitaxel +/- bevacizumab in first line metastatic breast cancer, which yielded both the longest progression free survival (PFS) (12 months) and absolute difference (5.5 months) seen to date in randomized trials in this setting. As part of the FDA submission, an independent radiologic review verified the PFS and response endpoints found in E2100. No significant survival advantage was found. Since the report of E2100, studies employing the exact regimen have shown similar results:

- Mackey J et al, CIRG/TORI 010: 10-Month Analysis of a Randomized Phase II Trial of Motesanib Plus Weekly Paclitaxel as First Line Therapy in HER2-Negative Metastatic Breast Cancer (MBC), Cancer Research 69 (Meeting Abstract Supplement), 47, December 15, 2009. doi: 10.1158/0008-5472.SABCS-09-47.
- Rugo, HS et al, Randomized phase II study of weekly versus every-3-week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC). J Clin Onc 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May 20 Supplement), 2009: 1029.
- Masuda N et al, Phase II study of bevacizumab (Bev) combined with weekly paclitaxel (wPac) as first-line therapy for Japanese patients (pts) with HER2-negative metastatic breast cancer (MBC). J Clin Onc 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 28, No 15S (May 20 Supplement), 2010: 1121.

On Tuesday, July 20th, 2010, the FDA received a recommendation from its Oncologic Drugs Advisory Committee (ODAC) to withdraw this approval, after the review of two placebo-controlled randomized studies, AVADO and RIBBON1, comparing different chemotherapy regimens +/- bevacizumab in first line metastatic breast cancer. Both studies met their predefined endpoints for PFS but the magnitude of the difference was less than reported with the E2100 paclitaxel/bevacizumab regimen. Neither study showed a survival advantage for the bevacizumab-containing regimens. The toxicity profile observed in these studies was similar to previous reports.

The purpose of this correspondence is to confirm and clarify the status of the E5103 trial. As you know, E5103 is a randomized Phase III trial to evaluate the potential benefit of adding bevacizumab to standard chemotherapy for breast cancer patients with high risk of relapse. It is not known at this time whether there is any benefit that would result from adding bevacizumab to the standard therapy or from continuing bevacizumab treatment after chemotherapy . These are the questions that we hope will be answered by this trial. In short, E5103 is proceeding as planned. The scientific rationale for E5103 has not changed and the data that supported its design remain. Additionally, the safety profile for bevacizumab remains identical to that seen in prior studies -- no new safety signals have emerged.

Information for Patients

The recent ODAC recommendation, along with its coverage by numerous media organizations, may cause questions to arise among your patients and/or their family members regarding the use of Avastin in the E5103 study design. With this likelihood in mind, we have prepared written responses to several questions, which you will see below.

Q: Does E5103 employ paclitaxel and bevacizumab as used in E2100?

A: Yes. E5103 is based upon the positive results of E2100 which employed the weekly paclitaxel backbone. This regimen may have been an important factor in the success of E2100, so it was chosen as the taxane portion of the treatment regimen in E5103.

Q: Did the AVADO and RIBBON1 studies show no benefit or unexpected toxicities?

A: AVADO and RIBBON1 confirmed statistically significant improvements in PFS and overall response rate (ORR) similar to E2100, although the absolute differences in PFS were smaller than seen in E2100. No unexpected toxicities were reported in AVADO or RIBBON1.

Q: Were there any differences in the design of E2100 compared with AVADO and RIBBON1?

A: Although all three trials evaluated chemotherapy alone or used in combination with bevacizumab, they are not identical in design. In E2100, bevacizumab was combined with weekly paclitaxel, and both drugs were continued until disease progression. In AVADO, bevacizumab was combined with docetaxel (Taxotere) every 3 weeks; all patients discontinued docetaxel after 9 docetaxel doses (after about 6 months), and treatment with bevacizumab alone continued until disease progression. In RIBBON1, several different agents were combined with bevacizumab, including capecitabine (Xeloda), doxorubicin, and docetaxel or nab-paclitaxel (Abraxane) given every 3 weeks.

Q: Do any studies employing chemotherapy and bevacizumab in the first line metastatic setting show a survival advantage?

A: No. None of the trials, either individually or taken together, show an improvement in overall survival.

Q: Is E5103 still enrolling new patients?

A: Yes. At its current pace, the trial will continue enrolling patients December 2010/January 2011, at which time it will complete its accrual.

We hope that this information is helpful to your participation in E5103. If you have any questions please don't hesitate to let us know.

Sincerely,

Kathy D. Miller, MD and Joseph Sparano, MD

Co-chairs, ECOG Breast Committee

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