5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Effects of the Addition of Bevacizumab or Iniparib to Standard Chemotherapy for Breast Cancer, Including Triple-Negative Disease, in the Neoadjuvant and Metastatic Settings

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Apply the results of new research when recommending neoadjuvant chemotherapy with anti-angiogenic treatment to patients with untreated HER2-negative primary breast cancer.
- Recognize the discordant benefits with bevacizumab-based neoadjuvant therapy in hormone receptor-positive and triple-negative subsets across clinical data sets.
- Consider the results of new research when recommending second-line therapy options to patients with triple-negative breast cancer.
- Recognize the progression-free survival and overall response rate benefits with the addition of bevacizumab to second-line chemotherapy in triple-negative breast cancer.

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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Breast/CME.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

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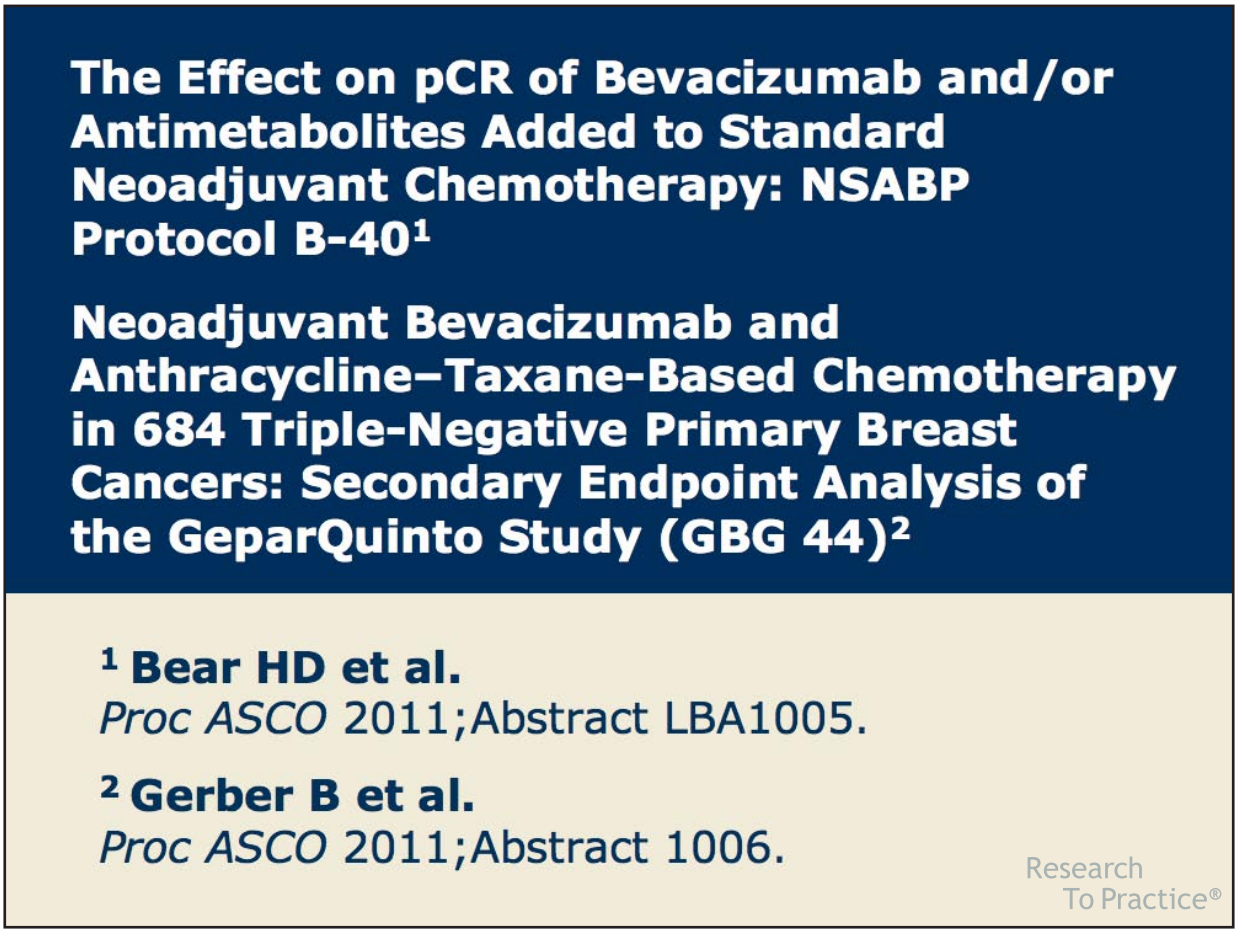
Effects of the Addition of Bevacizumab or Iniparib to Standard Chemotherapy for Breast Cancer, Including Triple-Negative Disease, in the Neoadjuvant and Metastatic Settings

Presentations discussed in this issue

Bear HD et al. **The effect on pCR of bevacizumab and/or antimetabolites added to standard neoadjuvant chemotherapy: NSABP protocol B-40.** *Proc ASCO* 2011;**Abstract LBA1005**.

Gerber B et al. **Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 684 triple-negative primary breast cancers: Secondary endpoint analysis of the GeparQuinto Study (GBG 44).** *Proc ASCO* 2011;**Abstract 1006**.

Slides from presentations at ASCO 2011 and comments from Charles E Geyer Jr, MD and Harold J Burstein, MD, PhD



The Effect on pCR of Bevacizumab and/or Antimetabolites Added to Standard Neoadjuvant Chemotherapy: NSABP Protocol B-40

Bear HD et al.

Proc ASCO 2011;Abstract LBA1005.

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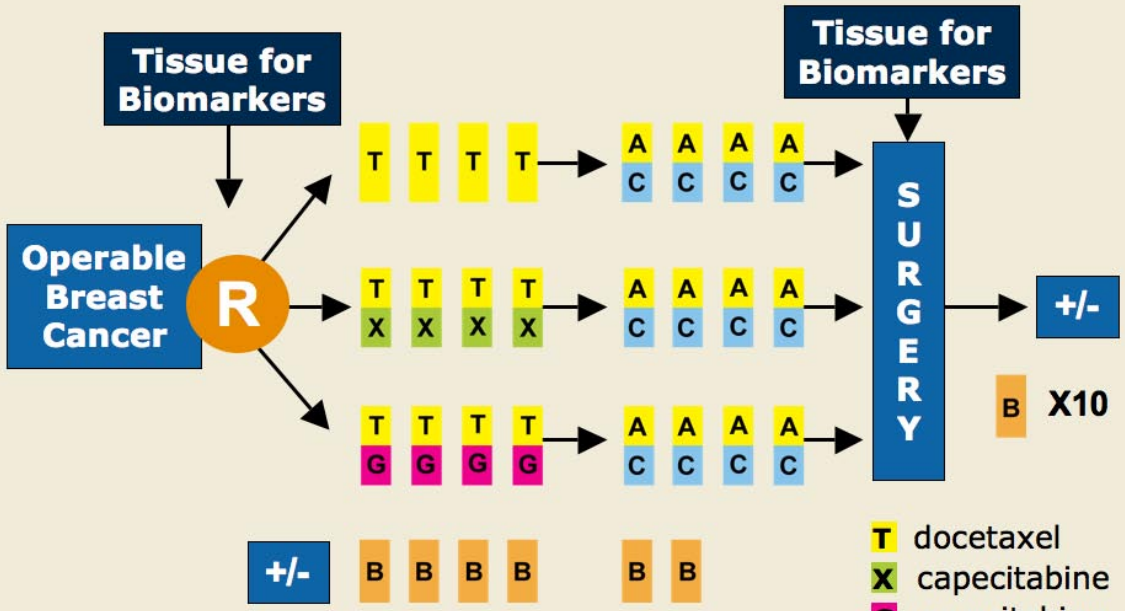
NSABP B-40: Chemotherapy ± Bevacizumab in Patients with Operable HER2-Negative Breast Cancer



Endpoints: pCR, cCR, DFS, gene expression patterns

Bear HD et al. *Proc ASCO* 2011;Abstract LBA1005.

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NSABP B-40: Effect of Capecitabine or Gemcitabine Added to Docetaxel on pCR Rates

	T - AC	TX - AC*	TG - AC*
pCR_{breast} (n = 395; 394; 391)	32.7%	29.7%	32.0%
$pCR_{breast + nodes}$ (n = 393; 390; 388)	26.0%	23.3%	27.3%

* *p*-value not significant versus T - AC
T = docetaxel; X = capecitabine; G = gemcitabine

Bear HD et al. *Proc ASCO* 2011;Abstract LBA1005.

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NSABP B-40: Benefit of Adding Bevacizumab to Standard Chemotherapy

- Benefit of bevacizumab predominant in HR+ rather than TNBC patient subgroup, although *p*-values for interaction were not significant
- pCR_{breast} (without bev vs with bev):
  - Patients with HR+ disease:15.2 vs 23.3% ($p = 0.008$)
  - Patients with TNBC: 47.3 vs 51.3% ($p = 0.44$)

Bear HD et al. *Proc ASCO* 2011;Abstract LBA1005.

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Author Conclusions

- Neither capecitabine nor gemcitabine added to docetaxel increased clinical or pathologic response rates.
  - Addition of capecitabine or gemcitabine increased toxicity (data not shown).
- Bevacizumab added to regimens based on T followed by AC significantly increased clinical and pathologic complete response rates.
  - Most apparent in HR+ subset, though p values for interaction were not significant.
- Bevacizumab did not change surgical options (data not shown).

Bear HD et al. *Proc ASCO* 2011;Abstract LBA1005.

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Neoadjuvant Bevacizumab and Anthracycline–Taxane-Based Chemotherapy in 684 Triple-Negative Primary Breast Cancers: Secondary Endpoint Analysis of the GeparQuinto Study (GBG 44)

Gerber B et al.

Proc ASCO 2011;Abstract 1006.

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GEPARQUINTO: Benefit of Bevacizumab Added to Neoadjuvant Chemotherapy in TNBC Subgroup

- Primary endpoint: pCR (no inv/non-inv in breast and nodes)
  - 27.8% with chemotherapy alone versus 36.4% with chemotherapy/bevacizumab (p = 0.021)
- Secondary endpoint: pCR (no inv in breast [**NSABP**])
  - 36.5% with chemotherapy alone versus 44.6% with chemotherapy/bevacizumab (p = 0.04)
- Benefit of bev limited to TNBC subgroup as no difference observed in overall pCR analysis (15.0% vs 17.5%, p = NS)

Gerber B et al. *Proc ASCO* 2011;Abstract 1006.

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Author Conclusions

- Addition of bevacizumab to neoadjuvant chemotherapy significantly increases pCR rate in patients with triple-negative breast cancer.
  - 27.8 vs 36.4% (p = 0.021)
- Effect of bevacizumab is limited to the TNBC subgroup in GeparQuinto, as pCR rates with or without bevacizumab were not different in the overall analysis (15% vs 17.5%)
- Addition of bevacizumab, young age, Grade 3, and small tumor size independently predicted pCR in multivariate analysis in TNBC (data not shown).
- A large biomarker program is ongoing to identify further predictive benefit.

Gerber B et al. *Proc ASCO* 2011;Abstract 1006.

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Investigator Commentary: Results from the NSABP-B-40 and GeparQuinto Trials

NSABP-B-40 accrued 1,200 patients with HER2-negative breast cancer (BC) and evaluated whether the addition of an antimetabolite — capecitabine or gemcitabine — and/or bevacizumab to docetaxel followed by AC would improve outcomes in terms of pCR. The additional antimetabolites didn't improve what we reported with docetaxel followed by AC. Not surprisingly, capecitabine increased toxicity as did gemcitabine. The addition of bevacizumab did provide a statistically significant benefit overall. The most striking numerical differences clearly were in patients with hormone receptor-positive disease. There was not a statistically significant difference in patients with triple-negative BC.

Charles E Geyer Jr, MD

These results are difficult to put together as we also have the GeparQuinto study, which reported a negative aggregate result, but perhaps with a signal in patients with triple-negative disease. I hope that other studies emerge or some better correlative science comes forward that will provide a unifying hypothesis here. But, for the moment, I believe these results have led a number of people to throw their hands up in the air and say, "It's not clear what bevacizumab means in the neoadjuvant setting."

Harold J Burstein, MD, PhD