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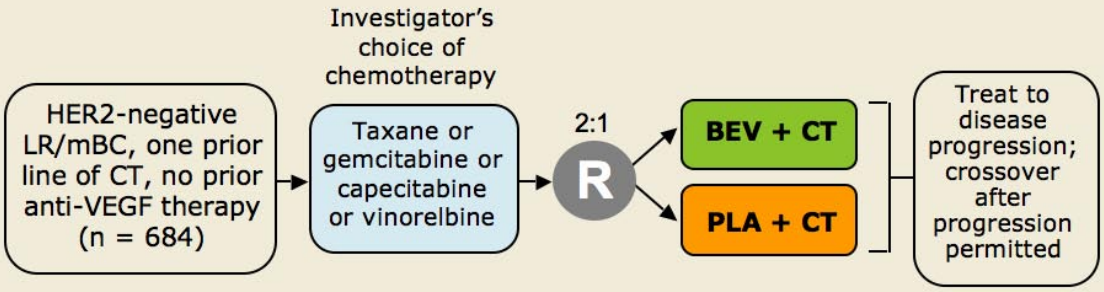
Effects of the Addition of Bevacizumab or Iniparib to Standard Chemotherapy for Breast Cancer, Including Triple-Negative Disease, in the Neoadjuvant and Metastatic Settings

Presentation discussed in this issue

Brufsky A et al. **Impact of bevacizumab (Bev) on efficacy of second-line chemotherapy (CT) for triple-negative breast cancer: Analysis of RIBBON-2.** *Proc ASCO* 2011;**Abstract 1010**.

Slides from a presentation at ASCO 2011 and comments from Julie R Gralow, MD

RIBBON 2: Trial Design



Taxane (paclitaxel, *nab* paclitaxel or docetaxel)

BEV, bevacizumab; CT, chemotherapy; PLA, placebo

Stratification Factors:
CT regimen, interval from LR/mBC diagnosis to first progression, ER and PR status

Brufsky A et al. *Proc ASCO* 2011;Abstract 1010.

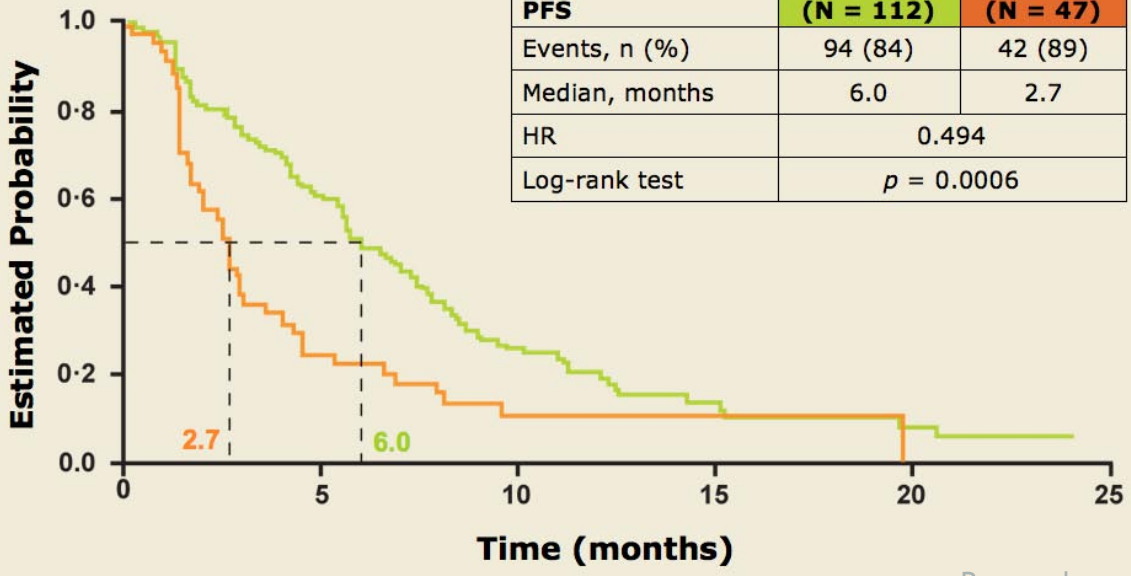
RIBBON 2: Efficacy Summary (All Patients)

Endpoint	BEV + CT (n = 459)	PLA + CT (n = 225)
Median progression-free survival (PFS)	7.2 mo	5.1 mo
	HR 0.78; p = 0.0072	
Median overall survival (OS)	18.0 mo	16.4 mo
	HR 0.90; p = 0.3741	
1-year OS rate, %	69.5%	66.2%
Overall response rate (ORR)	40%	30%
	p = 0.0193	

Brufsky A et al. San Antonio Breast Cancer Symposium 2009;Abstract 42.

RIBBON 2: PFS in TNBC Subgroup

PFS	BEV + CT (N = 112)	PLA + CT (N = 47)
Events, n (%)	94 (84)	42 (89)
Median, months	6.0	2.7
HR	0.494	
Log-rank test	p = 0.0006	



With permission from Brufsky A et al. *Proc ASCO* 2011;Abstract 1010.

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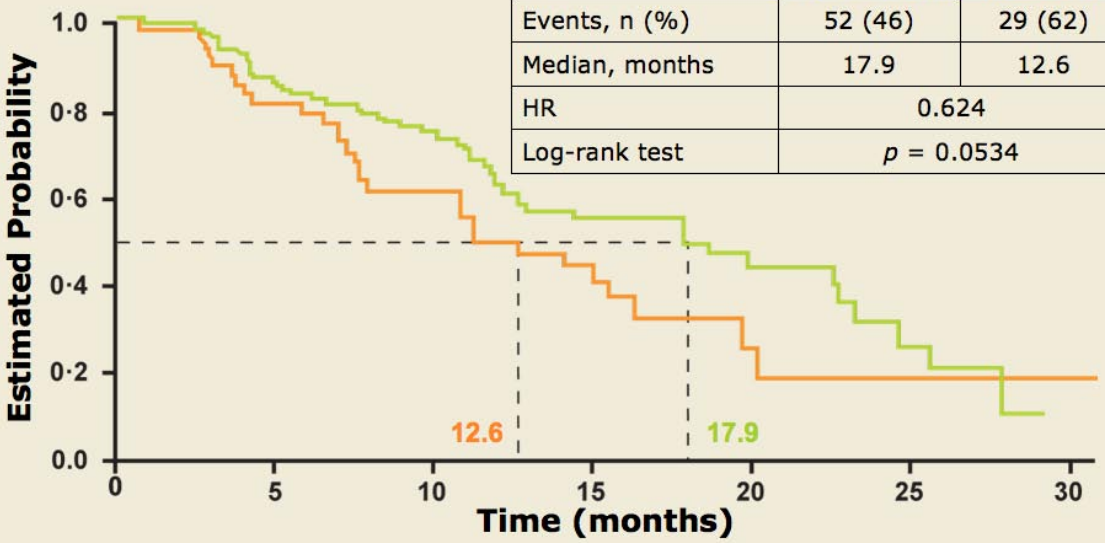
RIBBON 2: Interim OS in TNBC Subgroup

OS	BEV + CT (N = 112)	PLA + CT (N = 47)
Events, n (%)	52 (46)	29 (62)
Median, months	17.9	12.6
HR	0.624	
Log-rank test	p = 0.0534	



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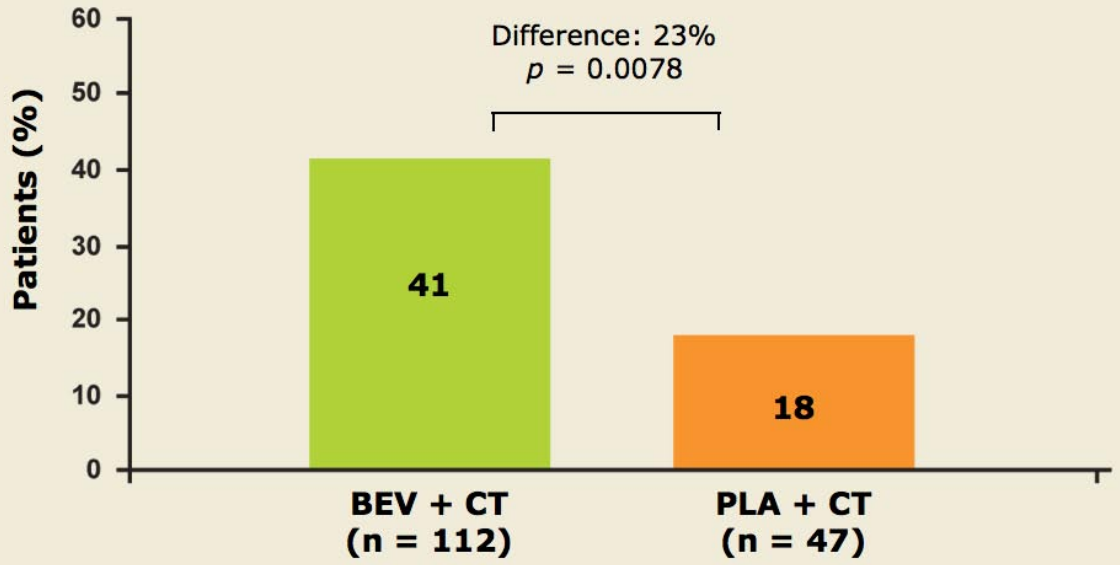
RIBBON 2: ORR in TNBC Subgroup



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RIBBON 2: Select Grade ≥3 Adverse Events in TNBC Subgroup

Adverse event	BEV + CT (n = 112)	PLA + CT (n = 47)
Neutropenia	18.8%	10.6%
Febrile neutropenia	0.9%	0
Hypertension	10.7%	0
Proteinuria	5.4%	0
Wound healing complications	1.8%	0
Thromboembolic event	2.7%	4.3%
Cardiac disorders*	0.9%	4.3%
Congestive heart failure (CHF)	0.9%	0
Treatment related death	1.8%	4.3%

* Excluding arterial thromboembolic event and CHF

Brufsky A et al. *Proc ASCO* 2011;Abstract 1010.

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Author Conclusions

- In this analysis, bevacizumab combined with second-line chemotherapy demonstrated a PFS and ORR benefit in patients with TNBC versus chemotherapy alone.
  - PFS: HR 0.49 (median 6.0 vs 2.7 months)
  - ORR: 41% vs 18%
- Despite immature data and small sample size, there was a trend towards improved OS.
  - HR 0.624 (p = 0.0534; median 17.9 vs 12.6 months)
  - Mature OS analysis of RIBBON 2 anticipated in Spring 2012
- In patients with metastatic TNBC who have not received first-line bevacizumab, second-line anti-VEGF therapy may be a potential option.

Brufsky A et al. *Proc ASCO* 2011;Abstract 1010.

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Investigator Commentary: Results from the TNBC Subset Analysis of Patients on the RIBBON 2 Trial

RIBBON 2 was an interesting trial that evaluated second-line chemotherapy with or without bevacizumab. The overall Phase III trial results were presented at San Antonio in 2009. Investigators were allowed their choice of second-line chemotherapy — taxane, gemcitabine, capecitabine or vinorelbine — with or without bevacizumab. The trial as a whole was positive — progression-free survival (PFS) went from 5.1 to 7.2 months and overall survival (OS) went from 16 to 18 months.

This current presentation at ASCO 2011 focused on the patients in the triple-negative breast cancer (TNBC) subset. That's the group of patients for whom our only treatment option is chemotherapy. So evaluating a biologic is of great interest here. About a quarter of patients on the trial had TNBC. In that patient population, we saw more benefit for the addition of bevacizumab. PFS went from 2.7 months to 6 months and OS from 12.6 to 18 months, with a strong trend toward significance. The p-value was a little over 0.05, though you have to be careful evaluating p-values when you're analyzing subsets. Response rate went from 18% to 41%. I believe this does suggest that the triple-negative population should be explored more fully in terms of the benefit of bevacizumab.

Julie R Gralow, MD