5 Minute JournalClub

Key ASCO Presentations
Issue 5, 2010

Activity of Bevacizumab in Combination with First- and Second-Line Chemotherapy for Metastatic Breast Cancer (mBC)

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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 serial 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Counsel patients with mBC about the incremental benefit of bevacizumab when it is combined with diverse chemotherapeutic regimens in the first- and second-line settings.

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To go directly to the slides and commentary, **click here**.

The oral sessions on breast cancer in Chicago this year reflected a huge volume of ongoing research, and as usual there were lots of important messages for oncologists in practice, including the following:

1. **Axillary node dissection is on the way out, while intraoperative breast irradiation may be on the way in**
   Several related trial reports were the highlight of one major oral session. The NSABP confirmed what most have believed for years: There is no value in axillary dissection for a patient with a clinically negative axilla and a well-performed negative sentinel node biopsy. Two American College of Surgeons trials demonstrated no prognostic value in IHC staining of H&E-negative sentinel nodes and showed that axillary dissection may not be necessary in all patients with positive sentinel nodes. Finally, the legendary trial champion Mike Baum **proved that** 30 minutes of intraoperative radiation therapy with a $300,000 device may yield comparable results to six weeks of conventional radiation therapy in patients after lumpectomy.

2. **Anti-HER2 therapy continues to gallop along**
   Kathy Miller's early data evaluating the fascinating combination of the chemo/trastuzumab conjugate T-DM1 plus the novel anti-HER2 dimerization inhibitor pertuzumab demonstrated safety, and a related study revealed some possible tissue correlates with efficacy. It's challenging to think of a more creative systemic strategy presented at ASCO.

3. **More of the same and something new for advanced disease**
   Two presentations on bevacizumab/chemotherapy reinforced much of what we already knew. The first, Joyce O'Shaughnessy's presentation of a mini-meta-analysis of first-line bev/chemo trials confirmed the benefit of this agent on progression-free but not overall survival. This seems to be an emerging theme in cancers with long natural histories, as first-line trials often fail to show a survival benefit, whereas studies with patients who have received multiple prior treatments may show a survival advantage, perhaps because of the complexities of post-first-line therapy, including the potential for crossover. Chris Twelves' ASCO data set

demonstrating a survival advantage with the **new antitubulin agent eribulin** is a clear example of this increasingly discussed phenomenon.

In a second presentation addressing anti-angiogenic therapy for advanced breast cancer, Adam Brufsky's reanalysis of the second-line RIBBON 2 trial demonstrated what most believed already: The impact of bev seems relatively independent of its chemo partner.

Next up on 5-Minute Journal Club: The once-mighty imatinib gets another shove out the door with new data on dasatinib, nilotinib and bosutinib in CML.

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Activity of Bevacizumab in Combination with First- and Second-Line Chemotherapy for Metastatic Breast Cancer (mBC)

Presentations discussed in this issue

O'Shaughnessy J et al. **A meta-analysis of overall survival data from three randomized trials of bevacizumab and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC).** *Proc ASCO* 2010;**Abstract 1005**.

Brufsky A et al. **Progression-free survival in patient subgroups in RIBBON-2, a phase III trial of chemotherapy plus or minus bevacizumab for second-line treatment of HER2-negative, locally recurrent or metastatic breast cancer.** *Proc ASCO* 2010;**Abstract 1021**.

Slides from presentations at ASCO 2010 and transcribed comments from recent interviews with Adam M Brufsky, MD, PhD (6/18/10), Kathy D Miller, MD (6/11/10) and Eric P Winer, MD (7/6/10)

A Meta-Analysis of Overall Survival Data from Three Randomized Trials of Bevacizumab (BV) and First-Line Chemotherapy as Treatment for Patients with Metastatic Breast Cancer (MBC)[1]

Progression-Free Survival in Patient Subgroups in RIBBON-2, a Phase III Trial of Chemotherapy Plus or Minus Bevacizumab for Second-Line Treatment of HER2-Negative, Locally Recurrent or Metastatic Breast Cancer[2]

[1] O'Shaughnessy J et al.
Proc ASCO 2010;Abstract 1005.
[2] Brufsky A et al.
Proc ASCO 2010;Abstract 1021.

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Background for Meta-Analysis

- Three randomized Phase III trials have demonstrated that BV improves progression-free survival (PFS) when added to chemotherapy in front-line MBC.
  - E2100 (*J Clin Oncol* 2009;27:4966)
  - AVADO (*Proc ASCO* 2008;Abstract LBA1011)
  - RIBBON-1 (*Proc ASCO* 2009;Abstract 1005)
- BV combined with chemotherapy improved PFS in the above studies irrespective of HR status, sites of metastases, disease-free interval and prior adjuvant taxane use.
- **Current study objective:**
  - To quantify the treatment benefit of BV combined with chemotherapy by performing a meta-analysis of patient data from the E2100, AVADO and RIBBON-1 trials.

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

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Comparison of the 1st-Line MBC Studies

	E2100	AVADO[1]	RIBBON-1[1]
Number of Patients	722	488[2]	1,237
Chemotherapy	Paclitaxel	Docetaxel	Capecitabine, Taxanes, Anthracyclines
Primary Endpoint	PFS[3]	PFS[4]	PFS[4]
Key Secondary Endpoints	OS, ORR	OS, ORR, 1-Year Survival	OS, ORR, 1-Year Survival

PFS = progression-free survival; OS = overall survival; ORR = objective response rate

[1] Permitted continuing on bevacizumab or crossing over to bevacizumab; [2] Includes patients from the chemotherapy alone and chemotherapy with BV 15 mg/kg cohorts; [3] Primary endpoint analysis based on independent radiologist's assessment; [4] Primary endpoint analysis based on investigator's assessment

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

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Overview of Efficacy Results from Individual Studies

	E2100		AVADO		RIBBON-1 (Capecitabine)		RIBBON-1 (Taxane, Anthra)	
	Non-BV	BV	Non-BV	BV[1]	Non-BV	BV	Non-BV	BV
Median PFS (months)	5.8	11.3	8.0	8.8	5.7	8.6	8.0	9.2
Hazard Ratio	0.48		0.62		0.69		0.64	
p-value	<0.0001		0.0003		0.0002		<0.0001	

Anthra = Anthracycline
[1] Bevacizumab 15 mg/kg data

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

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Results of Meta-Analysis of Phase III Studies

	Non-BV (n = 1,008)	BV (n = 1,439)	Hazard Ratio	*p*-value
PFS (in months)	6.7	9.2	0.64	<0.0001
OS (in months)	26.4	26.7	0.97	0.56
1-Year Survival	77%	82%	—	0.003

PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

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Conclusions

- Bevacizumab, when combined with first-line chemotherapy, results in clinically and statistically meaningful improvement in PFS.
- No statistically or clinically significant difference in overall survival (OS) is seen in this meta-analysis.
  - In MBC, the duration of survival post-progression (SPP) affects the ability of Phase III trials to report an effect on OS (*J Natl Cancer Inst* 2009;101:1642).
  - The probability of affecting OS is lower in patient populations with longer SPP (SPP was 20 mo in the three trials used in the meta-analysis).
- Pooled analysis suggests an early survival benefit at one year.

O'Shaughnessy J et al. *Proc ASCO* 2010;Abstract 1005.

Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

The take-home message of this meta-analysis of ECOG-2100, AVADO and RIBBON-1 is there was an improvement in progression-free survival (PFS) of about 26 percent, a 17 percent improvement in response rate and no overall survival benefit from the addition of bevacizumab to first-line chemotherapy.

Interestingly, when they examined the number of subsequent agents these patients received after progression, approximately one quarter of the patients had four or more regimens in the metastatic setting. At least 90 percent of patients had three regimens of therapy. So this raises the issue of post-progression survival.

A nice article was published in the *JNCI* last year, in which statisticians modeled a trial that had a significant PFS benefit of three months. Patients had a post-progression survival of approximately 24 months. They demonstrated that in order to show a statistically significant survival benefit, 2,400 to 2,500 patients would be required. So this tells us that if patients have a long survival post progression, a huge trial will be needed to demonstrate that the up-front intervention was effective in impacting overall survival.

Interview with Adam M Brufsky, MD, PhD, June 18, 2010

Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

Unfortunately, in this meta-analysis there was no improvement in overall survival. Sometimes it's argued that the reason we don't see survival benefits in the first-line setting in patients with mBC is due to the length of survival and the fact that subsequent therapies may dampen the effect of an earlier treatment. However, this was a more-than-adequately powered analysis that should have been able to demonstrate a small improvement in overall survival, and yet it did not.

When faced with a new patient who has metastatic breast cancer and who will be receiving chemotherapy, the decision to add bevacizumab should not be based on hoping that she will live longer. It's a decision that needs to focus on the improvement in progression-free survival only. In my mind, the time when we want to focus on using bevacizumab is in that first-line setting for a patient who has either a high disease burden or a great deal of symptoms, for whom controlling the cancer longer or getting a response will lead to an improvement in quality of life. At the moment, we don't have reason to believe we will extend a woman's life.

Interview with Eric P Winer, MD, July 6, 2010

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Investigator comment on the results of a meta-analysis of overall survival data from three randomized trials of bevacizumab with first-line chemotherapy

One of the big questions has been whether bevacizumab impacts survival in patients with mBC. No survival advantage has been observed in any of the individual first-line studies, but each was woefully underpowered to address survival. With three randomized trials now, the meta-analysis was conducted and none of the messages regarding efficacy and safety have changed from the individual studies. The improvements in progression-free survival and response rate absolutely held up, and no rare toxicity issues emerged. Importantly, no overall survival advantage was evident with the addition of bevacizumab to first-line chemotherapy.

Overall survival is clearly an important endpoint, but it is a composite that is driven by the patient's age and comorbidities and the inherent biology of her disease, some of which may not be changed by the therapy that we administer. It's partly driven by toxicity and the ability to receive therapy. To a small extent, it may be altered by initial therapy. It may also be altered by second-, third-, fourth- or fifth-line therapy. So, in essence, first-line therapy must have a large impact in order to demonstrate an overall survival benefit. That's not true for progression-free survival.

Interview with Kathy D Miller, MD, June 11, 2010

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Progression-Free Survival in Patient Subgroups in RIBBON-2, a Phase III Trial of Chemotherapy Plus or Minus Bevacizumab for Second-Line Treatment of HER2-Negative, Locally Recurrent or Metastatic Breast Cancer

Brufsky A et al.

Proc ASCO 2010;Abstract 1021.

Background

- Three Phase III trials (E2100[1], AVADO[2] and RIBBON-1[3]) have established that bevacizumab (BV) improves progression-free survival (PFS) when added to first-line chemotherapy ([1] *J Clin Oncol* 2009;27:4966, [2] *Proc ASCO* 2008;Abstract LBA1011, [3] *Proc ASCO* 2009;Abstract 1005).
- RIBBON-2 has shown improved PFS when BV is combined with various chemotherapies as second-line therapy for metastatic breast cancer (*Proc SABCS* 2009;Abstract 42).
- **Current study objective:**
  - To analyze PFS in prespecified and exploratory subgroups of RIBBON-2 patients.

RIBBON-2 Study Design

Previously treated MBC (n = 684)

Stratification Factors
Chemotherapy choice
Interval from MBC to 1st PD
ER/PR Status

Investigator choice of chemotherapy
Taxane
Gemcitabine
Capecitabine
Vinorelbine

2:1 R

Chemotherapy + BV[1] (n = 459)	Chemotherapy + Placebo (n = 225)

[1] BV 10 mg/kg q2 weeks or 15 mg/kg q3 weeks

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

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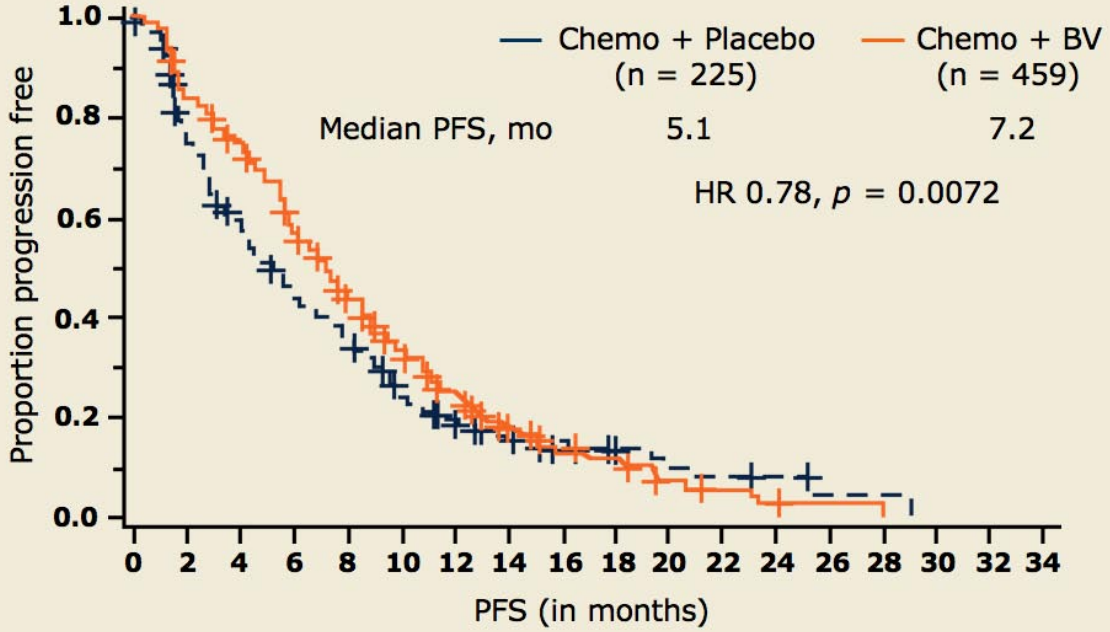
Primary Endpoint (PFS)



With permission from Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

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Median PFS by Chemotherapy Cohorts

Group	PFS in months (Chemo + BV)	PFS in months (Chemo + Placebo)	Hazard Ratio
All Patients (n = 684)	7.2	5.1	0.78
Taxanes (n = 304)	8.0	5.8	0.64
Gemcitabine (n = 160)	6.0	5.5	0.90
Capecitabine (n = 144)	6.9	4.1	0.73
Vinorelbine (n = 76)	5.7	7.0	1.42

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

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Median PFS by Other Cohorts

Group	PFS in months (Chemo + BV)	PFS in months (Chemo + Placebo)	Hazard Ratio
All Patients (n = 684)	7.2	5.1	0.78
Age <65 (n = 539) Age ≥65 (n = 145)	7.0 7.4	5.2 4.5	0.82 0.58
HR Positive (n = 494) HR Negative (n = 190)	7.4 6.5	6.0 2.8	0.89 0.53
Time from metastatic dx to PD <6 mo (n = 192) Time from metastatic dx to PD ≥6 mo (n = 492)	7.2 7.2	4.2 5.6	0.67 0.81
Triple Negative (n = 159) Non-Triple Negative (n = 498)	6.0 7.4	2.7 6.0	0.49 0.89

dx = diagnosis; PD = progressive disease

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

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Conclusion

- RIBBON-2 subgroup analysis is consistent with the primary results of RIBBON-2.
- RIBBON-2 subgroup analysis suggests that BV provides a PFS benefit when combined with various chemotherapies.
- RIBBON-2 subgroup analysis suggests that the PFS benefit is observed in patients with differing clinical characteristics and disease histories.

Brufsky A et al. *Proc ASCO* 2010;Abstract 1021.

Investigator comment on the results of RIBBON-2: Second-line chemotherapy ± bevacizumab

In RIBBON-2 we treated 684 patients with second-line chemotherapy of the investigator's choice, which typically included taxanes, gemcitabine, capecitabine or vinorelbine. Patients were randomly assigned two-to-one to chemotherapy with or without bevacizumab and treated until disease progression. In the initial overall study results, progression-free survival improved from 5.1 to 7.2 months with the addition of bevacizumab.

In the analysis presented at ASCO, we evaluated progression-free survival by the individual chemotherapy cohorts. The bottom line is that the taxanes work quite well, regardless of whether it's paclitaxel, docetaxel or *nab* paclitaxel. Capecitabine was effective when combined with bevacizumab. Gemcitabine did not work well, and for reasons that are puzzling, there may have been a detriment in combining vinorelbine with bevacizumab. However, there were few patients on the vinorelbine control arm, which could account for these findings.

Intriguingly, in a subgroup analysis of patients with triple-negative mBC, the progression-free survival improved from 2.7 months to 6 months, which is similar to what would happen with PARP inhibitors.

Interview with Adam M Brufsky, MD, PhD, June 18, 2010