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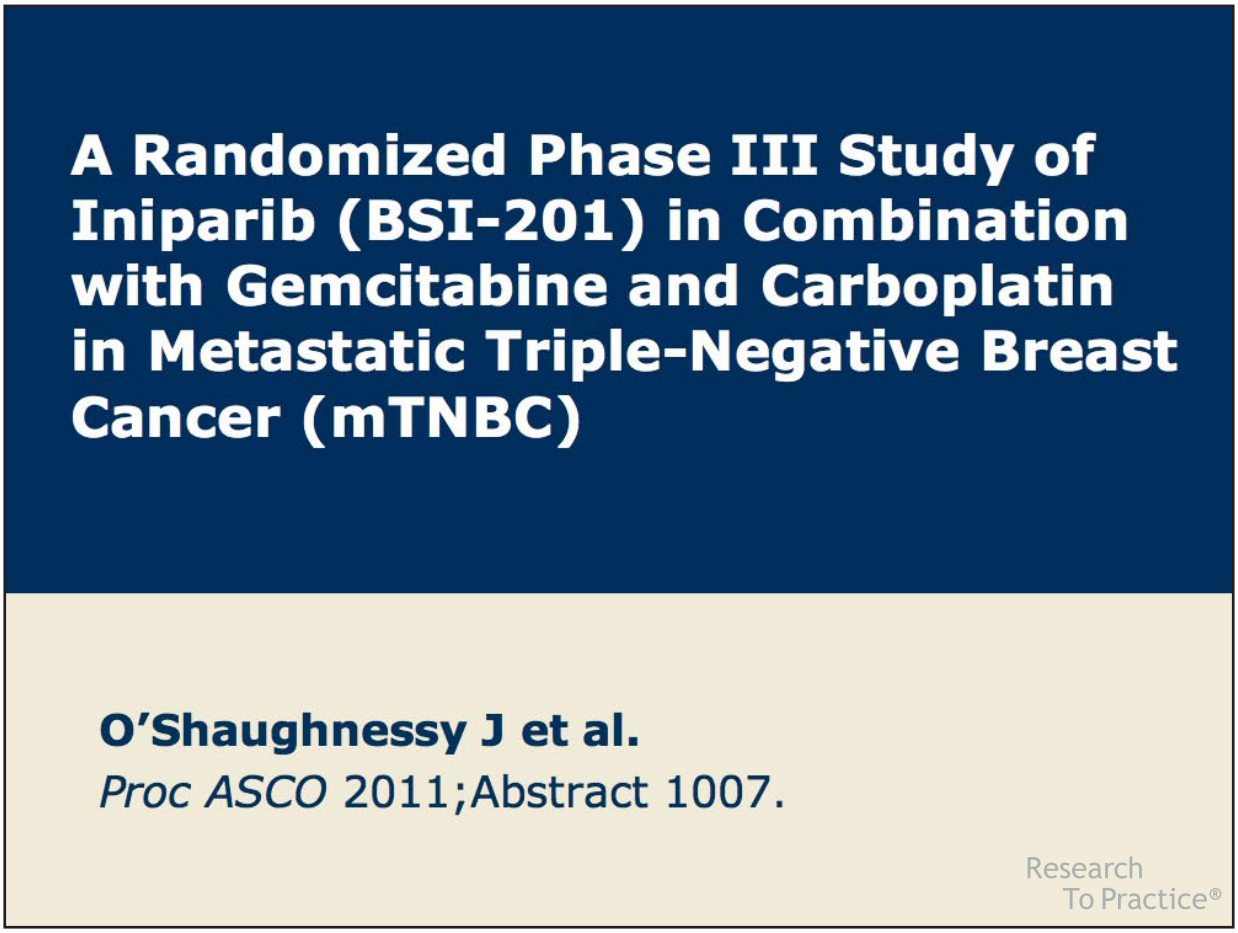
Effects of the Addition of Bevacizumab or Iniparib to Standard Chemotherapy for Breast Cancer, Including Triple-Negative Disease, in the Neoadjuvant and Metastatic Settings

Presentation discussed in this issue

O'Shaughnessy J et al. **A randomized Phase III study of iniparib (BSI-201) in combination with gemcitabine and carboplatin in metastatic triple-negative breast cancer (mTNBC).** *Proc ASCO* 2011;**Abstract 1007**.

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



Study Design: Multicenter, Randomized, Open-Label Phase III Trial (N = 519)

Study Population:

- Stage IV TNBC
- ECOG PS 0-1
- Stable CNS metastases allowed
- 0-2 prior chemotherapies for mTNBC
- Randomization stratified by prior chemotherapy in the metastatic setting:
  - 1st-line (no prior therapy)
  - 2nd/3rd-line (1-2 prior therapies)

R

Gem/carbo (GC)
(N = 258)
Gemcitabine 1,000 mg/m² IV d 1, 8
carboplatin AUC 2 IV d 1, 8

21-day cycles

→ Crossover allowed to GCI following disease progression (central review)

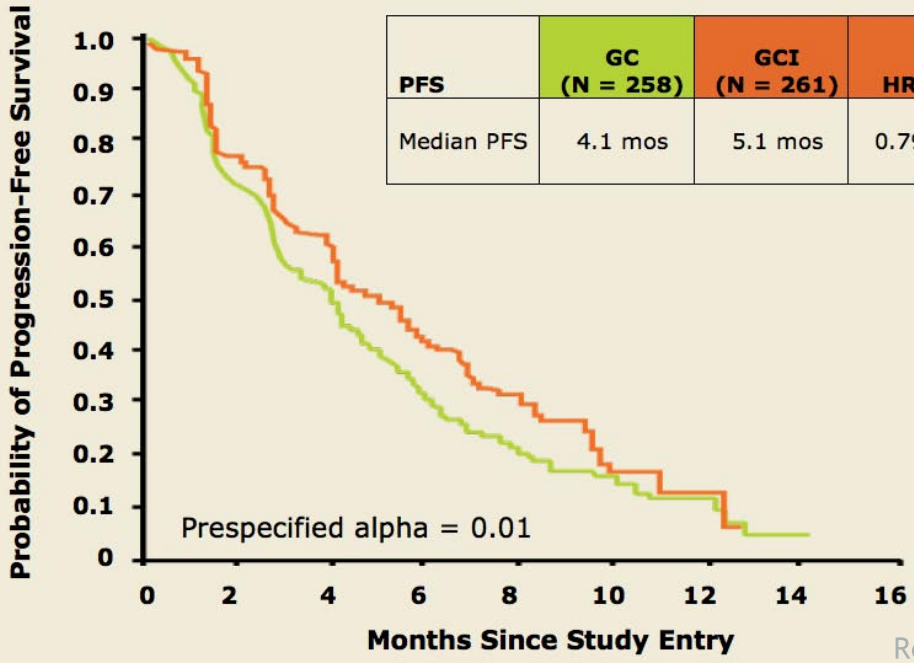
Gem/carbo + iniparib (GCI)
(N = 261)
Gemcitabine 1,000 mg/m² IV d 1, 8
carboplatin AUC 2 IV d 1, 8
iniparib 5.6 mg/kg IV d 1, 4, 8, 11

21-day cycles

95% (n = 152) of progressing patients crossed over to GCI at time of primary analysis.

O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

Efficacy Endpoints Progression-Free Survival (PFS) – ITT Population

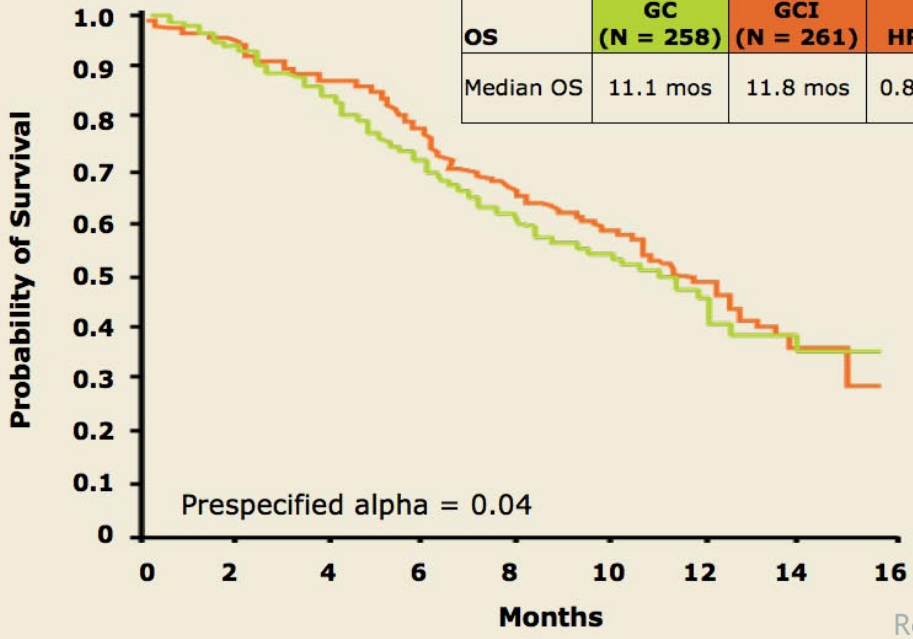


PFS	GC (N = 258)	GCI (N = 261)	HR	*p*-value
Median PFS	4.1 mos	5.1 mos	0.79	0.027

With permission from O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

Efficacy Endpoints
Overall Survival (OS) – ITT Population

OS	GC (N = 258)	GCI (N = 261)	HR	*p*-value
Median OS	11.1 mos	11.8 mos	0.88	0.28



With permission from O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

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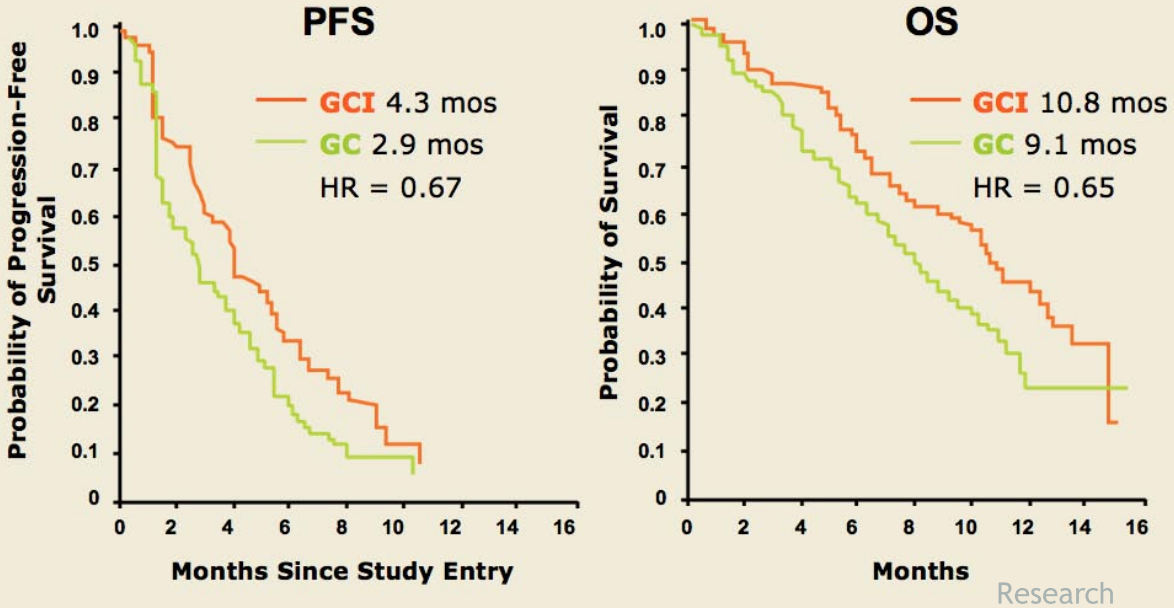
Exploratory Analysis: Second- or Third-Line ITT Population

Second- or third-line – 43% patients (222/519)



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Treatment-Emergent Adverse Events Safety Population*

AE	GC N = 244		GCI N = 255	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Neutropenia	65	53	71	61
Febrile neutropenia	2	2	2	2
Anemia	62	22	64	18
Thrombocytopenia	54	24	54	28
Fatigue	64	6	71	8
Alanine aminotransferase increased	19	6	28	6
Dyspnea	27	4	29	6

* Prior to crossover

O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

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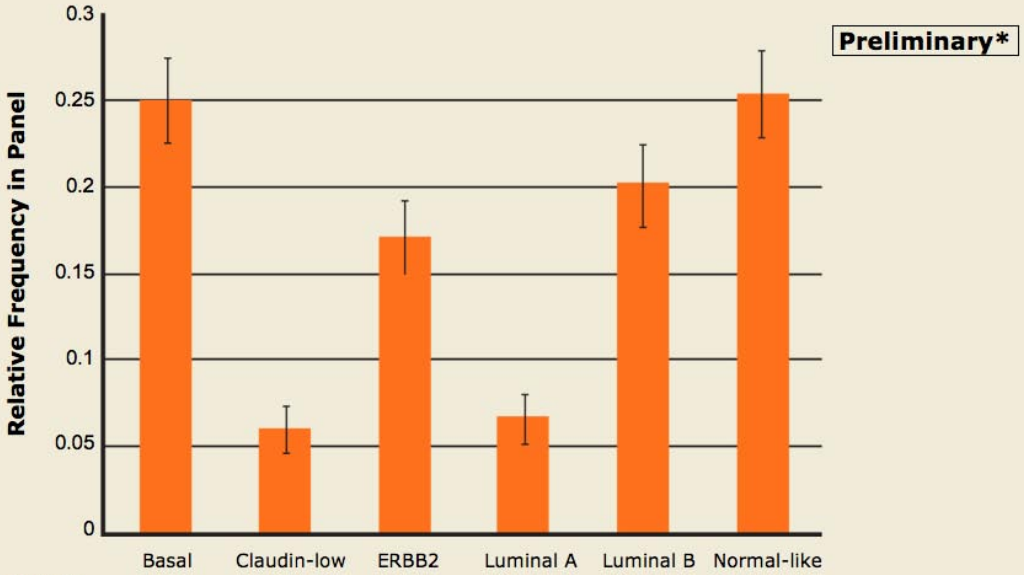
TNBC Comprised of Diverse Molecular Subtypes



* Validation ongoing
Affymetrix gene expression profiling of FFPE samples
Intrinsic subtypes assigned using Sorlie et al, PNAS, 2003 data set and claudin-low classifier (Prat et al, BCR, 2010) [courtesy of J Theilhaber and D Bergstrom, Sanofi]

With permission from O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

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Author Conclusions

- The addition of iniparib to GC did not improve PFS or OS according to the pre-specified criteria for these co-primary endpoints.
  - 96% of patients receiving GC who were eligible for crossover at time of analysis crossed over to GCI and received a median of two cycles of therapy.
- Exploratory analyses of PFS and OS by prior therapy suggests:
  - Potential efficacy benefit among 2nd/3rd line patients.
  - Confirmatory study needed.
- GCI safety profile confirmed; toxicity comparable to GC arm.
- mTNBC population is highly heterogeneous on intrinsic subtyping.
- Biomarker analyses underway to evaluate patient populations that may benefit from iniparib.

O'Shaughnessy J et al. *Proc ASCO* 2011;Abstract 1007.

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Investigator Commentary: Results from a Phase III Trial of Gemcitabine/Carboplatin (GC) ± Iniparib

Joyce O'Shaughnessy began her presentation at ASCO 2011 by saying iniparib is not a PARP inhibitor. It does inhibit cell cycle arrest and repair DNA damage, but inhibiting PARP is probably not the majority of what it's doing.

The trial had coprimary endpoints of both PFS and OS and had to achieve much stronger *p*-value significance than with a single primary endpoint. That might have hurt them a little bit. But when you evaluate the data for the trial as a whole, PFS was only improved by 1 month with the addition of iniparib. There was not even a month difference between the groups for OS. With respect to OS, crossing over was allowed, and 96% of eligible patients did so. So that could have influenced OS but not the PFS or the response rate.

An exploratory analysis was performed of patients with first-line metastatic recurrence versus second or third line, who seemed to gain more benefit from iniparib than the first-line group. We must critically examine what iniparib does and who might benefit most. I don't believe we can translate anything from this result to the true PARP inhibitors, such as veliparib or olaparib. Those agents need to be carefully studied, and we shouldn't shut down any analysis of those due to this result.

Julie R Gralow, MD