



SPECIAL EDITION

Issue 1, 2011

**Phase II Trial Results with
Cabozantinib (XL184) in
Metastatic Castration-Resistant
Prostate Cancer**

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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 OBJECTIVE

- Recall the results of new research on the efficacy and safety of the novel tyrosine kinase inhibitor cabozantinib (XL184) for patients with metastatic castration-resistant prostate cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Last review date: September 2011
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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.

Neil Love, MD

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Phase II Trial Results with Cabozantinib (XL184) in Metastatic Castration-Resistant Prostate Cancer

Presentation discussed in this issue

Hussain M et al. **Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial.** *Proc ASCO 2011*; **Abstract 4516**.

Slides from a presentation at ASCO 2011 and comments from William K Oh, MD and Christopher J Logothetis, MD

Cabozantinib (XL184) in Metastatic Castration-Resistant Prostate Cancer (mCRPC): Results from a Phase II Randomized Discontinuation Trial

Hussain M et al.

Proc ASCO 2011; Abstract 4516.

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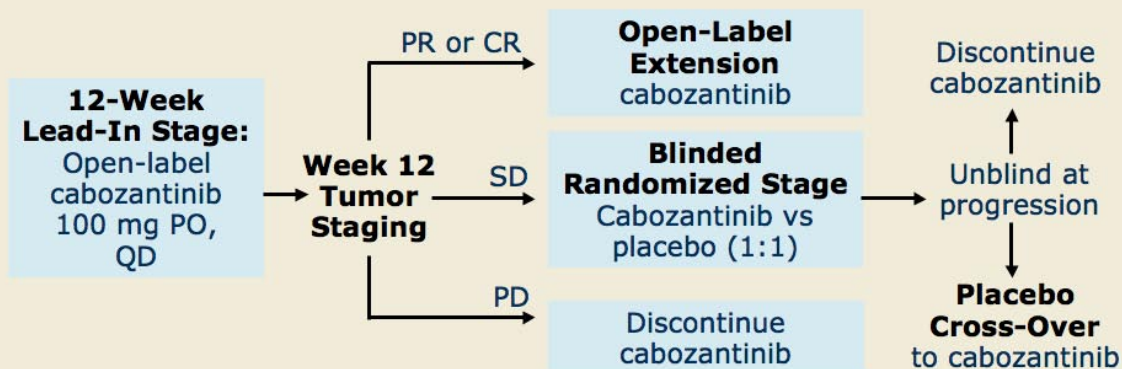
Introduction: Cabozantinib

- Cabozantinib is a tyrosine kinase inhibitor (TKI) that blocks MET and VEGFR2 in vivo.
- MET and its ligand, HGF, drive tumor cell invasion and metastasis.
- MET and VEGFR2 synergize to promote angiogenesis.
- Bone metastases are associated with high levels of MET expression.
 - HGF and VEGF direct cross talk between tumor cells, osteoblasts and osteoclasts.
- In prostate cancer:
 - Preclinically androgen deprivation increases MET expression.
 - MET increases with progression and metastasis in bone and lymph nodes.

Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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XL184-203: Phase II Trial Design



CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

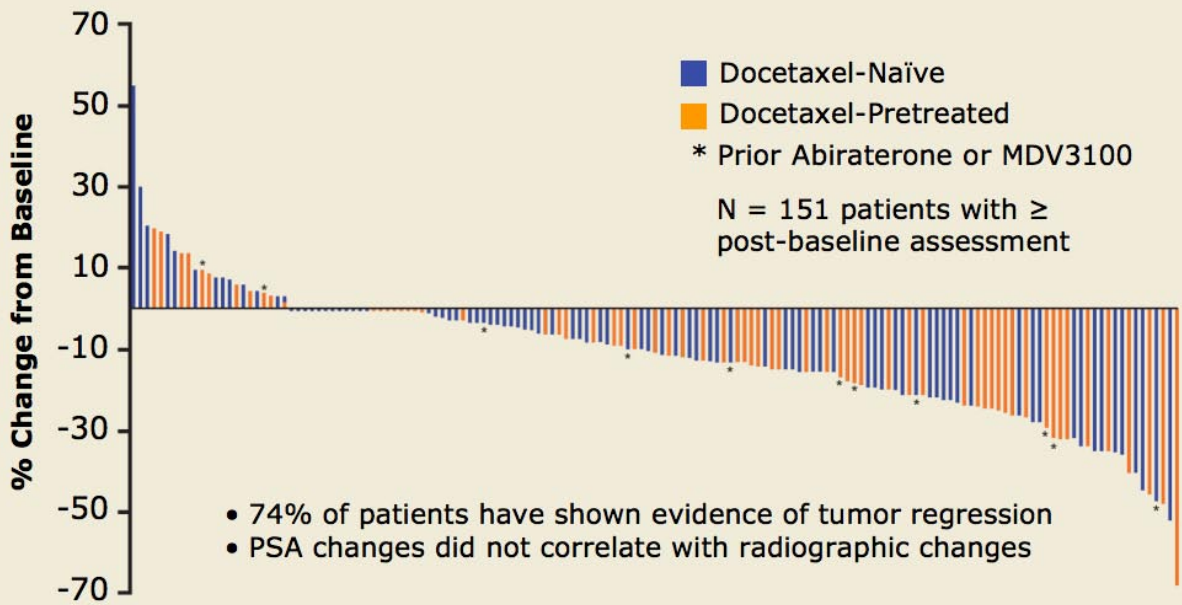
Primary objective: Evaluate the efficacy of cabozantinib in multiple solid tumors (Lead-in stage: Objective response rate (mRESIST 1.0), Randomized stage: Progression-free survival (PFS))

Secondary objectives: Safety and tolerability; assess potential pharmacodynamic effects of cabozantinib

Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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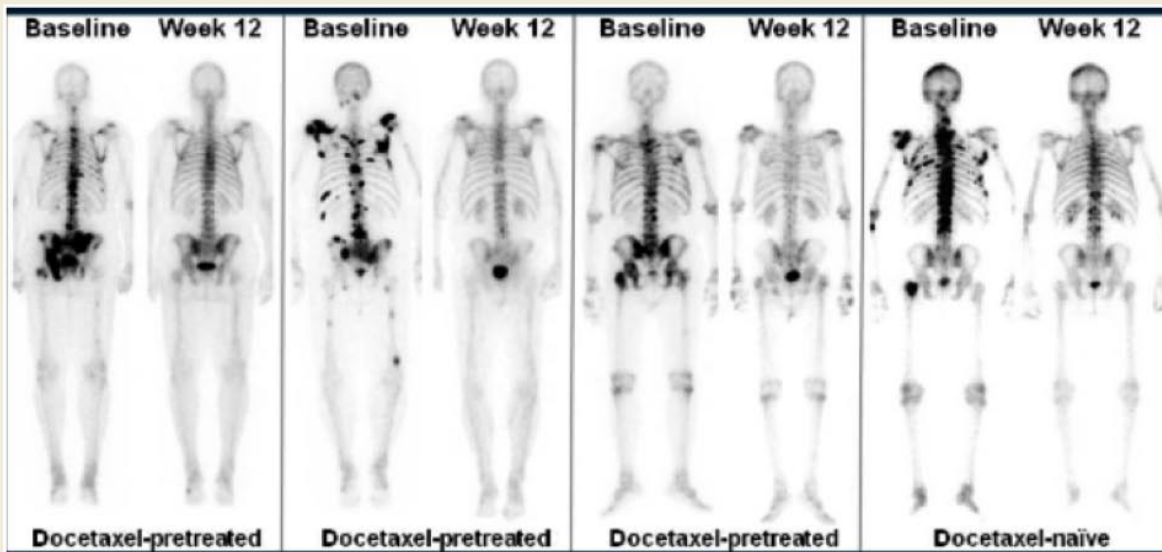
XL184-203: Tumor Regression in Soft Tissue Lesions



With permission from Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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XL184-203: Bone Scan Effects — Representative Images

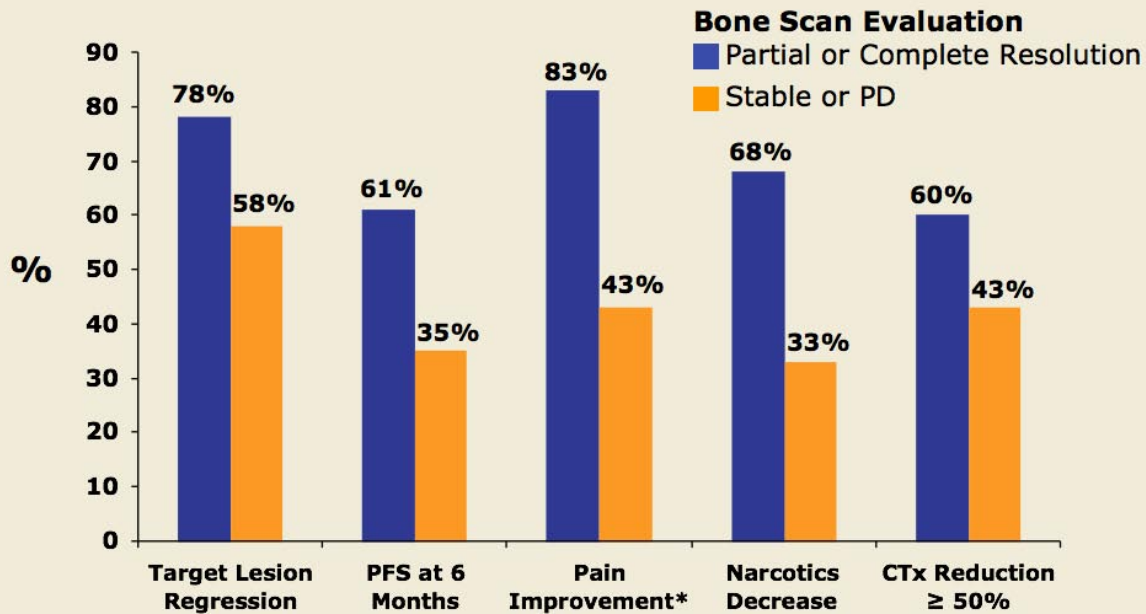


Each patient achieved partial response and pain improvement.

With permission from Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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XL184-203: Correlation of Bone Scan Resolution with Clinical Effects

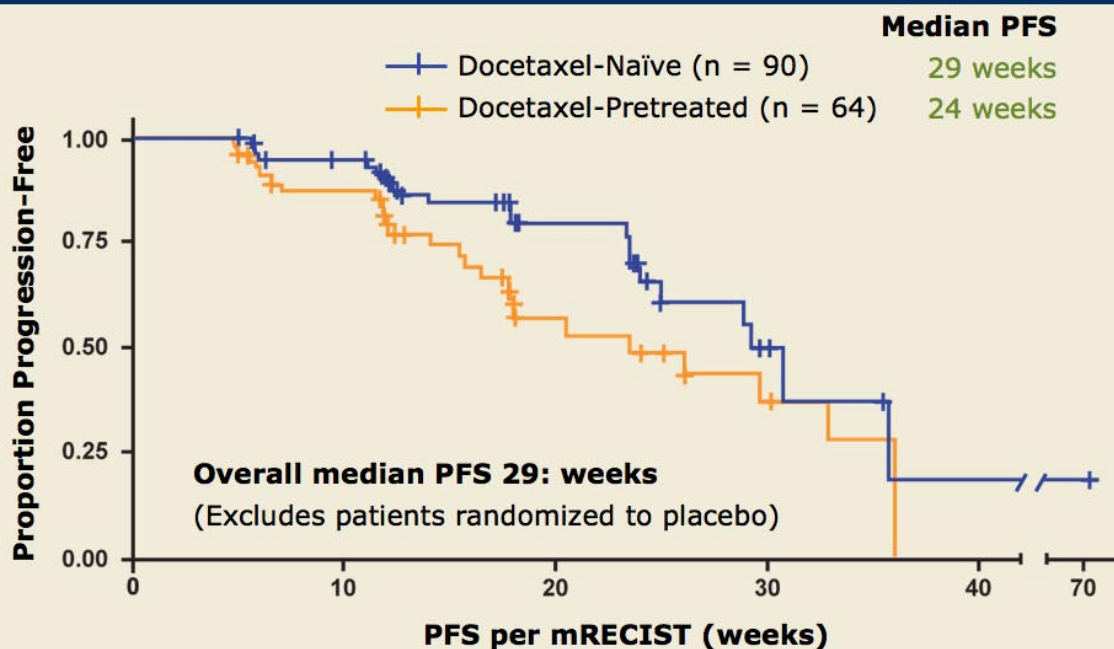


* Limited to patients treated with narcotics at baseline

With permission from Hussain M et al. *Proc ASCO 2011*;Abstract 4516.

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XL184-203: PFS — Overall and by Docetaxel Pretreatment Status



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XL184-203: Select Adverse Events (n = 171)*

Adverse event	All grades	Grade 3	Grade 4
Fatigue	63%	16%	—
Decreased appetite	49%	5%	—
Diarrhea	46%	2%	—
Nausea	44%	4%	—
PPE syndrome	27%	6%	—
Vomiting	26%	4%	—
Mucosal inflammation	20%	1%	—
Hypertension	19%	6%	—
Thrombosis venous	8%	2%	5%
Gastrointestinal perforation	1%	1%	1%

* Most frequently reported AEs during lead-in stage regardless of causality

Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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Author Conclusions

- Cabozantinib has substantial antitumor activity in patients with mCRPC and progressive disease.
 - Overall objective disease control at week 12: 68%
 - Measurable disease regression: 74%
 - Complete or partial resolution of bone scans: 76%
 - Pain improvement in patients with pain at baseline: 67%
 - Overall median progression-free survival: 29 weeks
 - Significant PFS improvement post-randomization
- Cabozantinib has a moderate but manageable adverse event profile similar to other TKIs.
- Cabozantinib is being evaluated in docetaxel-pretreated patients with mCRPC (NCT00940225).

Hussain M et al. *Proc ASCO* 2011;Abstract 4516.

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Investigator Commentary: The Phase II Trial Results with Cabozantinib in mCRPC

This randomized discontinuation trial received much attention because of the high response rates and substantial proportion of patients whose bone scans normalized. The data showed correlation between normalization of bone scans and improvement in pain and PSA response. However, we know that bone scans are not the best indicators of disease response to treatment in prostate cancer, so we are concerned that this may not be a real effect.

Cabozantinib is an exciting drug that appears to target MET in addition to VEGF. It is theorized that the MET pathway may be an escape mechanism for VEGF, so blocking both pathways may lead to the enhanced response we are seeing with this agent. Only a third to half of patients with prostate cancer would have met the trial eligibility criterion of having a measurable soft tissue lesion, but the response rate to measurable disease was high. The rate of partial response by RECIST was only 4%, although the waterfall plot showed that most patients experienced shrinkage of their tumors, which was better than the stable disease expected. This suggests that we are using imperfect tools to measure prostate cancer lesions and response to therapy.

William K Oh, MD
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Additional Investigator Commentary on Bone Scan Effects Reported with Cabozantinib in mCRPC

Another interesting aspect of this study of the c-MET and VEGFR2 inhibitor cabozantinib was the striking changes in bone scans. This effect happened rapidly and was linked to a reduction in bone pain. Those patients who had an improvement in bone scan and reduction in bone pain seem to be the ones whose disease is controlled longest and best with cabozantinib.

Some patients also experienced regression of soft tissue metastases. So it's clear that cabozantinib does much more than just alter images of bone scans. It causes favorable events in the cancer as well.

Precisely how this agent is working remains unclear. c-MET expression is increased in the osteoblasts adjacent to the tumor, and it may be that the antitumor activity results from blocking c-MET function in osteoblasts. I don't believe all the changes can be attributed to just changes in the bone scan. These patients benefit too much for too long, and we see soft tissue regression.

Christopher J Logothetis, MD

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