5 Minute JournalClub

Key ASCO Presentations
Issue 7, 2010

First-in-Human Study of the Oral ALK Inhibitor Crizotinib for Patients with ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

For more visit ResearchToPractice.com/5MJCMT2010

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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

- Recall the clinical activity and adverse event profile of the ALK inhibitor crizotinib in patients with ALK-positive NSCLC.

ACCREDITATION STATEMENT

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

Last Friday we hosted our annual daylong lung cancer Think Tank with seven renowned investigators, co-chaired by Tom Lynch (be on the lookout for the highlights audio program). One of the main objectives of this closed "recording session" was to review data sets from Chicago, and this dizzying scientific chat included discussion of the following work profiled in the enclosed slide sets:

1. **Crizotinib in patients with EML4-ALK mutations**
An update of the stunning Phase I-II data first presented at ASCO '09 included impressive waterfall plots in which almost all patients had reduced tumor sizes with this not-yet available agent. Approximately four to five percent of patients harbor this newly described translocation that fits the classic oncogene addiction model, and at the Think Tank Dr Lynch described one such individual from his practice who entered this study with substantial symptomatic tumor burden and is still in response two years later. All in attendance agreed on the urgency of making this agent available and of standardizing and disseminating the assay technology, but the faculty was unsure how long this will actually take.

2. **EGFR TKIs versus chemotherapy for patients with EGFR mutations**
A CALGB trial in first-line *metastatic* disease reinforced recent study results clearly demonstrating that a TKI without chemo is preferred for these patients. In contrast, the confusing and incomplete **BR19 trial** suggested the possibility that in the *adjuvant* setting, not only would EGFR TKIs not be beneficial, but for very much unknown reasons they could also be detrimental. Specifically because of this and one prior Stage III data set, there was a strong sentiment among the Think Tank investigators not to use these agents as adjuvant therapy outside a protocol setting.

By the end of this amazing day, it was apparent that a new tissue-based algorithm for systemic treatment of advanced non-small cell lung cancer was on the table. Specifically, the faculty endorsed the baseline evaluation for patients with adequate tumor specimens for EGFR and EML4-ALK mutations and maybe K-ras, which might be predictive of benefit with sorafenib. For patients with needle biopsies without the necessary tumor quantity to conduct these assays, the decision regarding rebiopsy must be individualized based on smoking history, site of disease and performance status. Ed Kim, who first reported his landmark "BATTLE" trial at AACR — followed by

more data from Roy Herbst at ASCO — cautioned that core biopsies by interventional radiology are much more likely to yield adequate tissue than those obtained by bronchoscopy. After hearing MD Anderson coinvestigator John Heymach comment on the unprecedented translational data in BATTLE, it was clear this was the future paradigm of lung cancer research.

3. **Palliative (supportive) care extends survival in the advanced disease setting**
In what some view as the biggest surprise of ASCO, a Harvard randomized trial demonstrated marked OS increases for patients who visited a palliative care specialist about once a month. Dr Lynch had a number of patients in this study and believes the benefits were primarily the result of better management of depression, anxiety and "existential angst." All agreed that "If this was a drug, we'd use it." How to get this advance to patients is unclear.

4. **Older patients may benefit from doublet chemotherapy in first-line advanced disease**
This **plenary presentation** confirmed an emerging theme within oncology: Older patients who can safely tolerate standard therapy derive the same benefits as younger patients.

Next up on our final ASCO issue of 5-Minute Journal Club: GI cancers and a provocative study in pancreatic cancer.

Neil Love, MD
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Miami, Florida

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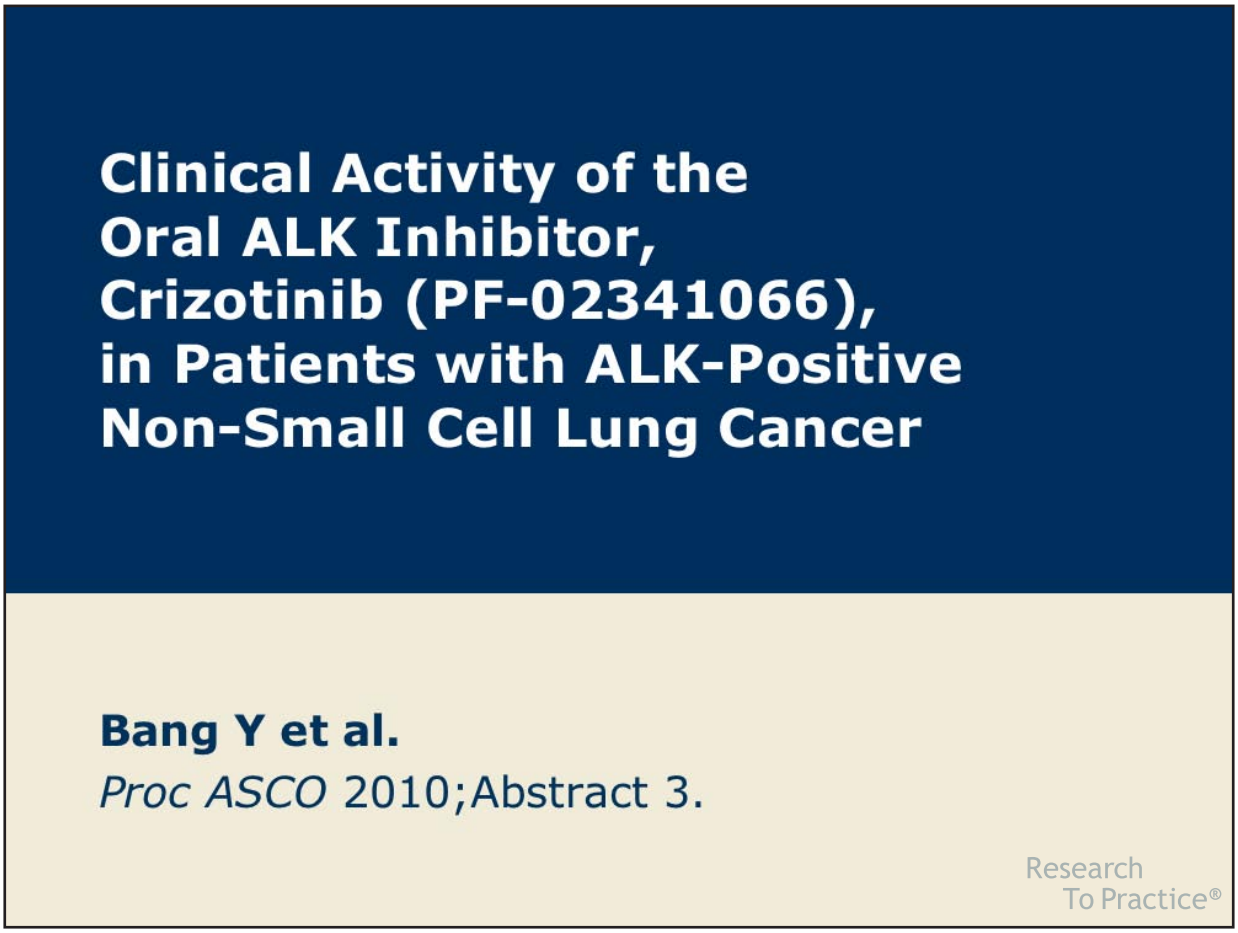
First-in-Human Study of the Oral ALK Inhibitor Crizotinib for Patients with ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Presentation discussed in this issue

Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Roy S Herbst, MD, PhD (6/23/10), Corey J Langer, MD (7/2/10) and Lecia V Sequist, MD, MPH (6/18/10)



Introduction

- Crizotinib is an orally bioavailable inhibitor of anaplastic lymphoma kinase (ALK) and select tyrosine kinase receptors.
- In non-small cell lung carcinoma (NSCLC), EML4-ALK has been identified as a unique tumor specific fusion gene present in approximately 4% of patients (*Nature* 2007;148:561).
- **Current study objective:**
  - Investigate the safety and clinical activity of crizotinib in patients with ALK-positive non-small cell lung carcinoma.

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

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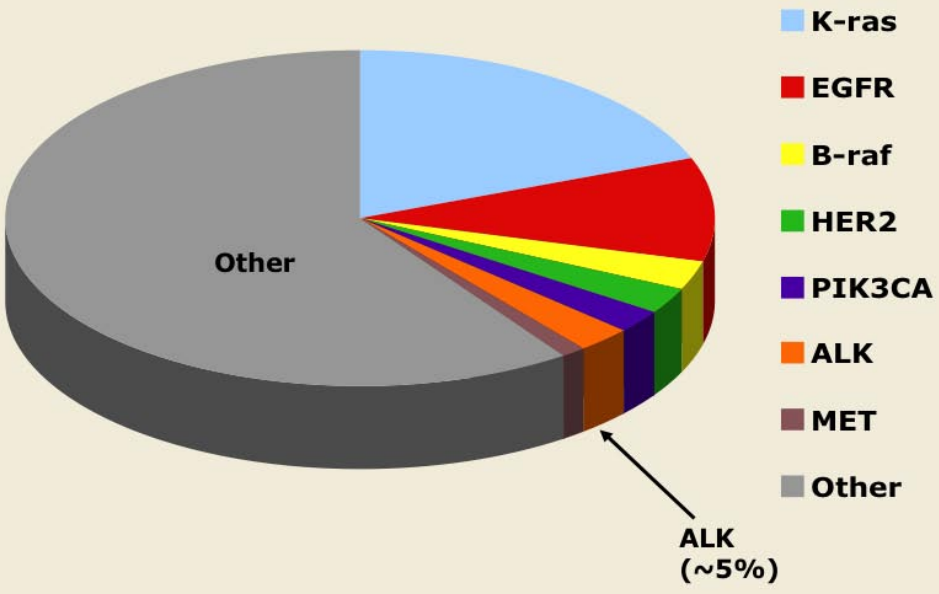
Potential Oncogenic Drivers in NSCLC Adenocarcinoma



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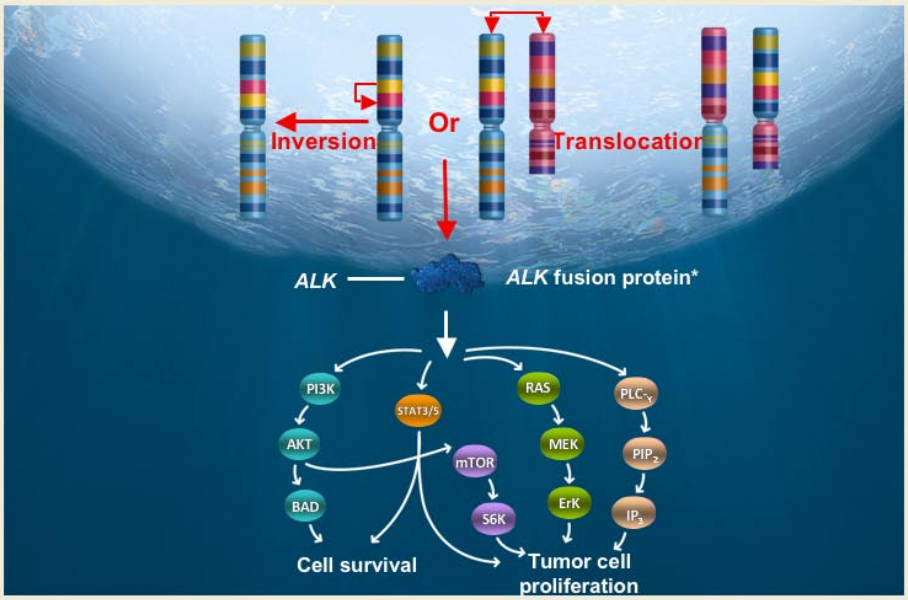
ALK Pathway



*Subcellular localization of the ALK fusion protein is thought to occur in the cytoplasm, but it is not confirmed.

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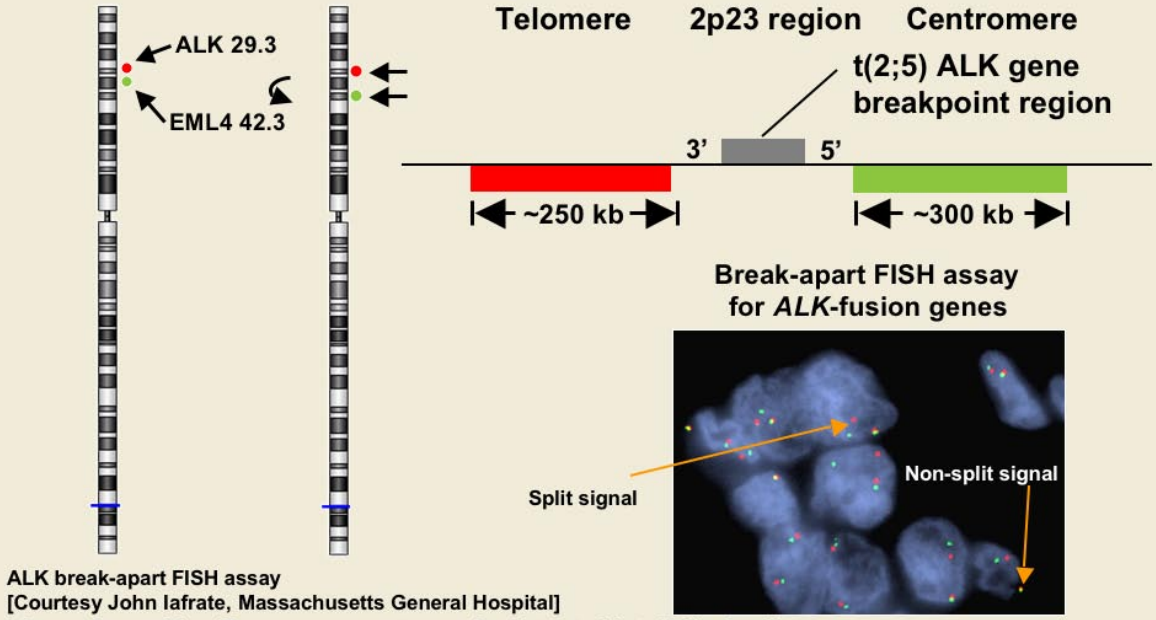
FISH Assay for ALK Rearrangement*



ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]

*Assay is positive if rearrangements can be detected in ≥15% of cells

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

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Crizotinib First-in-Human Study Design

Accrual: 82 (Open)

Eligibility

Advanced NSCLC harboring ALK fusion (determined by FISH assay)

Prior therapy allowed

Treated brain metastases allowed

→ **Crizotinib 250 mg/d PO BID***

***Maximum tolerated dose of 250 mg/d BID was established in the dose escalation phase of the study.**

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

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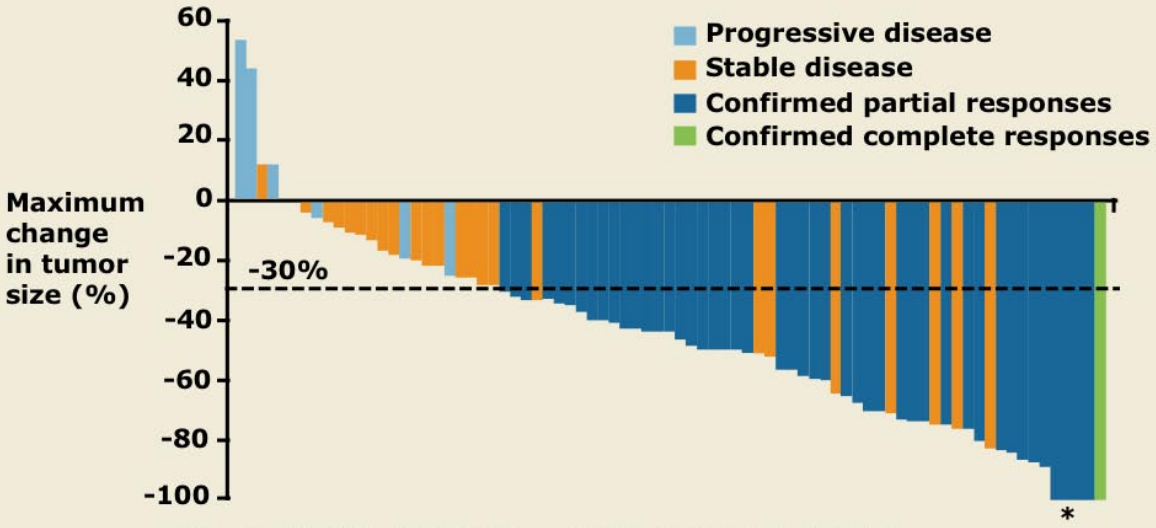
Tumor Responses to Crizotinib for Patients with ALK-Positive NSCLC



A change of ≥30% is defined as a partial response by RECIST.

*Partial response patients with 100% change have non-target disease present

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

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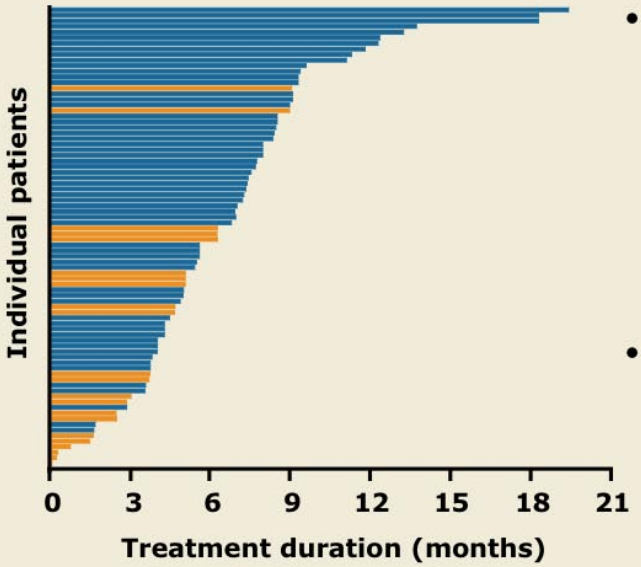
77% of Patients with ALK-Positive NSCLC Remain on Treatment



- **Duration of treatment**
  (median: 5.7 months)

0-3 mo	13 pts
>3-6 mo	29 pts
>6-9 mo	24 pts
>9-12 mo	9 pts
>12-18 mo	4 pts
>18 mo	3 pts

- **Reasons for discontinuation**

- Related AEs	1
- Non-related AEs	1
- Unrelated death	2
- Other	2
- Progression	13

N = 82; orange bars represent discontinued patients

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

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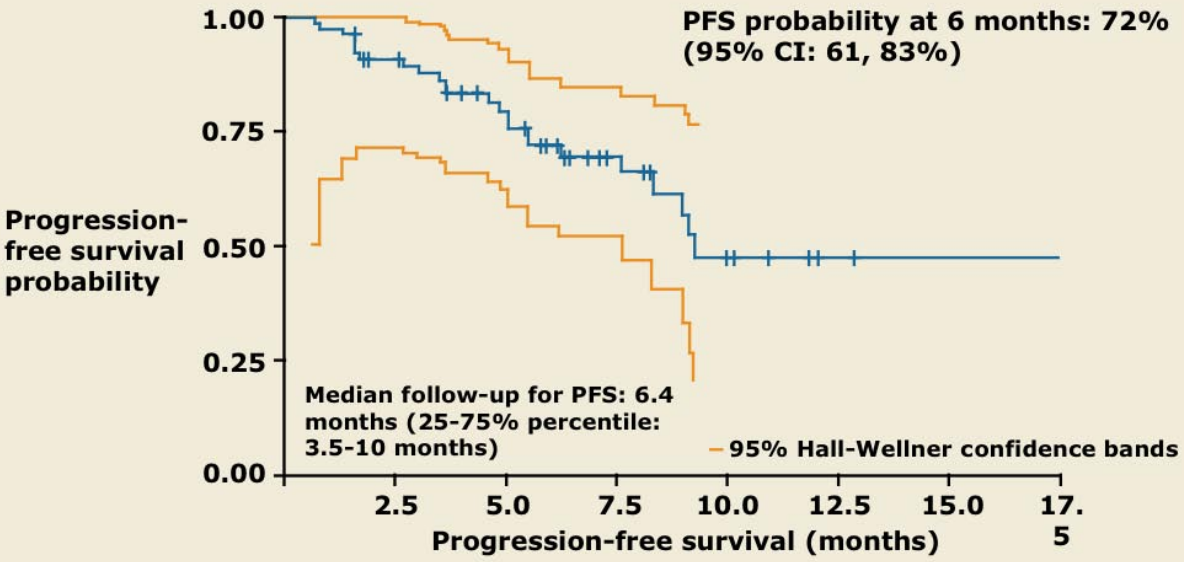
Progression-Free Survival



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Select Grade 3/4 Adverse Events

Adverse Event (AE)	Grade 3 n (%)	Grade 4 n (%)
Any adverse event	10 (12)	1 (1)
ALT elevation	4 (5)	1 (1)
AST elevation	5 (6)	0
Lymphopenia	2 (2)	0
Dyspnea	1 (1)	0
Pulmonary embolism	1 (1)	0
Hypoxia	1 (1)	0

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Conclusion

- Crizotinib resulted in impressive clinical activity in patients with ALK-positive advanced NSCLC, with:
  - Objective response rate: 57%
  - Disease control rate at eight weeks: 87%
  - Progression-free survival probability at six months: 72%
- The most frequent AEs were mild and moderate gastrointestinal events and mild visual disturbances.
- The data also support molecular profiling of patients as a personalized approach to NSCLC treatment.
- Overall, crizotinib was well tolerated and may offer a potentially new standard of care in the treatment of NSCLC.

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

This was clearly the "big bang" of ASCO, and it speaks to the fact that targeted therapy works in patients who have the target. This is a newly identified target — an EML4-ALK translocation, which occurs in approximately four to five percent of patients, but that's four to five percent of 200,000 patients in the United States and several million around the world.

Crizotinib is an oral agent that targets the ALK tyrosine kinase. The bottom line of this report is that in a group of 82 patients treated, nearly 75 had some tumor shrinkage. Approximately 60 percent had a response as defined by RECIST and about 90 percent had at least stable disease. Most of these patients had received prior therapy. The objective response rate was 80 percent for patients who had no prior regimens, but even for patients with three or more prior regimens the response rate was 56 percent. This is an extraordinary result for a drug that is so well tolerated. The adverse events were quite mild — some nausea, diarrhea and vomiting — and consistent with what's been observed with oral tyrosine kinase inhibitors (TKIs).

Interview with Roy S Herbst, MD, PhD, June 23, 2010

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

This is a paradigm-shifting study for a smaller population of patients. The four to five percent of patients with advanced NSCLC who have the EML4-ALK translocation derive tremendous benefit from crizotinib.

The responses are impressive, with an objective response rate close to 60 percent, and several of the patients who were clearly starting to respond weren't included in that group because they hadn't received their second or third assessments. The results are as good, if not better, than we observed with erlotinib in patients with the EGFR mutation. The median overall survival endpoint has not yet been reached. These results are particularly impressive because the majority of patients had received two or more prior regimens and were essentially refractory or only marginally responsive to standard treatment. In general, these patients don't respond to EGFR inhibitors.

We are now routinely screening for EGFR, K-ras and EML4-ALK in all patients with adenocarcinoma of the lung. Phase II and III clinical trials are ongoing, and I don't believe we can deny crizotinib to any patient who harbors this translocation.

Interview with Corey J Langer, MD, July 2, 2010

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

One of the most important take-home messages from ASCO this year was for personalized targeted therapy in lung cancer. For several years we have been hearing the EGFR story, and now a parallel story is emerging with the EML4-ALK translocation.

An exciting Phase I study was presented at the ASCO plenary session this year that evaluated an oral TKI — crizotinib — that specifically blocks the ALK receptor. The side effects were very mild, especially when compared to those of chemotherapy, and were distinct from the side effects of EGFR TKIs. Crizotinib does not cause a lot of diarrhea or rash. The main side effects are lower extremity edema, reversible vision changes and some liver function test abnormalities. The response rate was approximately 60 percent by RECIST, and other patients had very durable stable disease. The overall clinical benefit rate was approximately 90 percent.

Currently, EGFR and K-ras genotyping are widely available nationally. ALK testing is not yet as accessible but it will be soon. This study is exciting and provides a paradigm that will be repeated again and again in lung cancer.

Interview with Lecia V Sequist, MD, MPH, June 18, 2010

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