Diagnostic Testing for Targeted Agents: Perspectives from the Crizotinib Post Approval Space

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Refining Processes for the Co-Development of Genome Based Therapeutics and Companion Diagnostic Tests: A Workshop

To Solve a Problem – Define It Well!

- ASCO- Better understanding of tumor biology/drug of target. How and what oversight should be provided for CoDX and LDT's?
- CAP – What's relevant analyte for Drug efficacy?
- ACLA – Assure clinical validity. Establish test registries

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At the Finish Line It's Two Labels Not One

- Xalkori

----------INDICATIONS AND USAGE----------

XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as **detected by an FDA -approved test** (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

- AMD FISH

INTENDED USE

The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded **(FFPE)** non-small cell lung cancer **(NSCLC)** tissue specimens to aid in identifying those patients eligible for treatment with **XALKORI®(crizotinib)**

The test is for prescription use only.

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Should Clinical Outcome be the Gold Test Standard?

TEST Result	Clinical Benefit: Yes	Clinical Benefit: No
Positive	Right patient	Why no patient benefit? (False Positive?)
Negative	How to identify? (False Negative?)	Don't treat

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“False” Positive Tests

- May be revealed clinically as “non responders” or suggested in method comparison studies when there is no clinical outcome available as a ultimate measure of test validity
- Assay or sample technical issues
- Opportunity to understand disease biology
  - Drug resistant disease
    - ALK L1196Q, I1171N mutation, Kit or EGFR signal activation
- Importance of the reference “standard”

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"False" Negative Tests

- Not revealed if clinical studies only include marker positive patients
- Assay or sample technical issues
- Magnitude of the problem increases as prevalence of disease decreases
- Opportunity to understand disease biology
  - FISH and PCR positive but IHC ***negative***
    - Mir-96 transcriptional regulation of ALK
- Other targets
  - ROS1 and cMet for crizotinib

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Central Lab ALK FISH Testing

Expected positive test rate ~3.5-5%

Reference Lab	Total ALK FISH Tests performed	ALK Positive Rate(%)
Registration Lab #1	1007	27-10
Registration Lab #2	733	17-13
Registration Lab #3	1243	27-28
Registration Lab #4	2395	13-15
Registration Lab #5	414	15-16
Post Approval Lab #1	~15,000	~2.1
Post Approval Lab #2	~13,500	~3.1
Post Approval Lab #3	~2,000	~5.5
Post Approval Lab #4	~11,000	~3.2

"Uninformative" samples in most labs in range of ~9-10%

A 1% change in test positives in the post approval sample impacts >500 patients

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Hypothesis Generating Observations From Crizotinib Registration Studies

- Clinical benefit observed in ALK+ patients regardless of test used for diagnosis (IUO or LDT)
- Higher rates of response, longer median duration of therapy for patients diagnosed with IUO
  - Retrospective observations, not subjected to multivariate analysis, or large enough numbers to characterize specific nonIUO platforms individually

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Pfizer Engagement to Understand Testing Differences

- Broad clinical trial program
- Post-marketing commitment to evaluate "true" FISH negatives and confirm also negative for cMet and ROS1
- Support for test comparison studies of sequential cases at multiple academic medical centers globally
- Currently working with Ventana to submit a second ALK test based upon IHC to the PMA approval process
- Working with central laboratories to understand testing outcomes in the market place
- IIR studies and prospective studies across platforms to better understand "discordant" cases
- Would enthusiastically support testing/outcome registries

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Focus on the patient to ensure treatments provide a maximum benefit /risk ratio