Crizotinib in Patients with ROS1+ Non-Small Cell Lung Cancer: Rationale and Results

Mace L. Rothenberg, MD
Chief Development Officer - Oncology

EMA-ESMO Workshop on Single Arm Trials in Oncology
30 June 2016
Identification of ROS1 and Relationship to NSCLC

- The ROS1 receptor tyrosine kinase (RTK) was first identified in 1986 as a cellular homologue of the \( v\text{-}ros \) sequence in an avian sarcoma virus.
- No ligand for wild-type ROS1 identified and mice lacking wild-type ROS1 appeared healthy.
- Cancer-related rearrangements in ROS1 first identified in a human glioblastoma cell line in 1987.
- First oncogenic rearrangements of ROS1 in NSCLC identified in 2011.
- Large scale screening of human NSCLC found ROS1 gene translocations in ~1.5% of tumors.

How can a medicine be rigorously tested in such a rare circumstance?

## IC<sub>50</sub> Concentrations for Crizotinib

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM) mean</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-MET</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>ALK</td>
<td>40–60</td>
<td>5–8X</td>
</tr>
<tr>
<td>ROS1</td>
<td>60</td>
<td>7X</td>
</tr>
<tr>
<td>RON</td>
<td>80</td>
<td>10X</td>
</tr>
<tr>
<td>Axl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>294</td>
<td>34X</td>
</tr>
<tr>
<td></td>
<td>322</td>
<td>37X</td>
</tr>
<tr>
<td>Tie-2</td>
<td>448</td>
<td>52X</td>
</tr>
<tr>
<td>Trk A</td>
<td>580</td>
<td>67X</td>
</tr>
<tr>
<td>Trk B</td>
<td>399</td>
<td>46X</td>
</tr>
<tr>
<td>Abl</td>
<td>1,159</td>
<td>166X</td>
</tr>
<tr>
<td>IRK</td>
<td>2,887</td>
<td>334X</td>
</tr>
<tr>
<td>Lck</td>
<td>2,741</td>
<td>283X</td>
</tr>
<tr>
<td>Sky</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>&gt;10,000</td>
<td>&gt;1,000X</td>
</tr>
</tbody>
</table>

*Cui et al. J Med Chem 2011;54: 6342-6363*
Preclinical Activity of Crizotinib

Crizotinib (BaF3 cells)

IC50 (nM)
- CD74-ROS1: 4.2
- EML4-ALK v1: 20.8
- Ba/F3 parental (IL-3+): 839.3

Relative cell number (% of control)
Concentration (nM)

Ryohei Katayama, unpublished
Phase I Study of Crizotinib (PROFILE 1001)

Part 1: Dose escalation

- Cohort 1 (n=3)
  - 50 mg QD

- Cohort 2 (n=4)
  - 100 mg QD

- Cohort 3 (n=8)
  - 200 mg QD

- Cohort 4 (n=7)
  - 200 mg BID

Part 2: Dose expansion

- Cohort 5 (n=6)
  - 300 mg BID

- Cohort 6 (n=9)
  - 250 mg BID

MTD/RP2D

ClinicalTrials.gov Identifier NCT00585195

ALK-positive tumors including NSCLC

c-MET-positive tumors

ROS1-positive tumors including NSCLC

QD, once daily; BID, twice daily

MTD, maximum tolerated dose; RP2D, randomized phase 2 dose

9 November 2009 Amendment
(Data as of June, 2012)

<table>
<thead>
<tr>
<th>Best response†</th>
<th>ROS1-Positive (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>57.1%</td>
</tr>
<tr>
<td><strong>Median duration of treatment (weeks)</strong></td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Disease control rate at 8 weeks</strong></td>
<td>79%</td>
</tr>
</tbody>
</table>

† RECIST 1.0; *Kwak et al., ASCO 2009

Shaw et al., ASCO 2012
PROFILE 1001: Waterfall Plot of ROS1+ Patients

(Data as of June, 2012)

*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression ‡Crizotinib held for >6 wks prior to first scans which showed PD. +Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

Shaw et al ASCO 2012
PROFILE 1001: Dramatic Response in ROS+ Patients

Pre-Treatment

8 Weeks of Crizotinib

Patient 10021119
(Data as of April, 2013)

<table>
<thead>
<tr>
<th>Response (RECIST v1.0)</th>
<th>Number &amp; Per Cent of evaluable patients (n=36*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response to therapy</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>20 (56%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Indeterminate response</td>
<td>0</td>
</tr>
<tr>
<td>Early death</td>
<td>2(6%)</td>
</tr>
<tr>
<td>ORR (%) (95% CI)</td>
<td>61% (44–77%)</td>
</tr>
</tbody>
</table>

* Two patients were subsequently confirmed negative for the ROS1 rearrangement. One patient was ALK+ and had a Partial Response.
+Treatment ongoing; duration of response/SD is from first documentation of tumor response/first dose to the time of PD or death. For ongoing patients, duration of response/SD is from first documentation of tumor response/first dose to last available on-treatment scan.

Duration is in weeks.

Excludes patients with early death (n=2)

*This patient ALK+

Data as of April 24, 2013.

36 evaluable patients; 2 CRs and 20 PRs

Overall response rate: 61% (95% CI: 44–77)

Best overall response

- PD
- PR
- SD
- CR

PROFILE 1001: Waterfall Plot of ROS1+ Patients

(Data as of April, 2013)
PROFILE 1001: PFS in ROS1+ NSCLC Patients

Patients

Median PFS not reached
26 patients (62%) still in follow-up for progression
Event-free probability: 76% (95%CI: 55–88) at 6 months

(Data as of April, 2013)
PROFILE 1001: Efficacy in ROS1+ Patients (n=50)

(Data as of May, 2014)

Best Response

- ORR = 72% (95% CI: 58%, 84%)
  - 3 patients (6%) achieved a CR
  - 33 patients (66%) achieved a PR
- Median duration of response: 17.6 months (95% CI: 15, NR)

Progression-Free Survival

- Median PFS: 19.2 months (95% CI: 14, not reached)
- 50% remain in follow-up for PFS

ROS1+ NSCLC: Predictive or Prognostic?

Did ROS1+ simply identify a subset of NSCLC patients with a good prognosis or did it predict for sensitivity to a ROS1-targeted therapy?

**Fig 3.** Progression-free survival on pemetrexed-based chemotherapy in patients with lung cancer and an ROS1 rearrangement.

**Fig 5.** Progression-free survival on crizotinib in patients with lung cancer and an ROS1 rearrangement.

- PFS with pemetrexed-based therapy: \( \text{mPFS} = 7.2 \text{ months} \)
- PFS with crizotinib: \( \text{mPFS} = 9.1 \text{ months} \)

EUROS: Efficacy in ROS1+ Patients (n=30)

**ORR = 80%**

**mPFS = 9.1 months**

AcSé: Efficacy in ROS1+ Patients (n=37)

ORR = 71%

mPFS = 10 months
mOS = Not achieved

D Moro-Sibilot et al: ASCO 2015
OxOnc: Efficacy in ROS1+ Patients (n=127)


IRR-assessed Best Percent Change from Baseline in Target Lesion Size*

- Complete Response (n=14)
- Partial Response (n=74)
- Stable Disease (n=19)
- Progressive Disease (n=7)

ORR = 88%
mPFS = 13.4 months
OS probability at 12 months: 84.4%

* N is based on the response-evaluable population, excluding patients with early death, indeterminate response, and without measurable disease.

IRR, independent radiology review.
## OxOnc ROS1 Companion Diagnostic Testing

### OO12-10 Patient Selection

<table>
<thead>
<tr>
<th>ROS1 Test</th>
<th>Laboratory</th>
<th>Number (%) of patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR AmoyDx ROS1 Gene Fusion Detection Kit</td>
<td>Central</td>
<td>110 (100)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>110 (100)</td>
</tr>
</tbody>
</table>

Commercially available as CE-IVD test
PROFILE 1001 ROS1 Companion Diagnostic Testing

<table>
<thead>
<tr>
<th>ROS1 LDT</th>
<th>Laboratory</th>
<th>Number (%) of patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>All labs</td>
<td>51 (96.2)</td>
</tr>
<tr>
<td></td>
<td>MGH</td>
<td>26 (49.1)</td>
</tr>
<tr>
<td></td>
<td>Non-MGH</td>
<td>25 (47.2)</td>
</tr>
</tbody>
</table>

| PCR       | All labs   | 2 (3.8)                          |
|           | MGH        | 0 (0)                            |
|           | Non-MGH    | 2 (3.8)                          |

Total 53 (100)

- Biopsy
  - Single Marker Test
    - ROS1

- Next Gen Sequencing (NGS)
  - Oncomine Universal Dx Test (ThermoFisher Ion PGM platform)
  - Multi-Marker (multiplex) Test
    - EGFR
    - ALK
    - BRAF
    - KRAS
    - ROS1
    - Others (analytical)

- Oncomine Solid Tumor DNA panel and Solid Tumor Fusion Transcript kit available as CE-IVD tests

- Laboratory Developed Tests
- Limited commercial accessibility for CDx use in US (MGH FISH test available via MGH reference lab)
Similarities between ALK+ and ROS1+ NSCLC

<table>
<thead>
<tr>
<th>Experience</th>
<th>Similar?</th>
<th>Different?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease: NSCLC</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Activating Genomic Translocation</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Predictive, not Prognostic</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Defined by Companion Diagnostic</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>High ORR and Prolonged PFS</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

**PROFILE 1005: Phase II (2011) ALK+ NSCLC**

- Median PFS (All Lines) = 9.9 months (95% CI: 7.7, 13.4)
- 83 events (56%; 67 PD events)
- 66 patients (44%) censored, 60 (91%) in follow-up for PFS

**PROFILE 1007: Phase III (2013) ALK+ NSCLC**

- Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI 0.37–0.64) P<0.001
- Median PFS: 7.7 (6.0-8.8 mo) vs 3.0 (2.6-4.3 mo)

**Crizotinib in ROS1+ NSCLC: US Regulatory Summary**

<table>
<thead>
<tr>
<th>HA Consultations</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Registration strategy and data package agreed to by the FDA for regular approval</td>
<td></td>
</tr>
<tr>
<td>• Two informational teleconferences held at the request of FDA + pre-sNDA meeting</td>
<td></td>
</tr>
<tr>
<td>• Breakthrough Designation Granted: April 2015</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Package</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efficacy and safety data for 53 patients with ROS1 positive advanced NSCLC from single arm cohort in Study 1001 (pivotal study)</td>
<td></td>
</tr>
<tr>
<td>• Locally developed test (Massachusetts General Hospital) as CDx initially with next generation sequencing post-marketing requirement</td>
<td></td>
</tr>
</tbody>
</table>

| Submission | sNDA Submitted: 8 October 2015 |

| Approval | sNDA Granted: 11 March 2016 |
Summary and Conclusion

- Single arm clinical trial data suggest that crizotinib has promising activity against ROS1+ NSCLC
- The clinical activity of crizotinib in patients with ROS1+ NSCLC appears to be similar – as reflected by ORR, durability of response, and mPFS – to what is achieved in patients with ALK+ NSCLC
- Both the FDA and EMA granted accelerated/conditional marketing approval to crizotinib in ALK+ NSCLC based on the results of Phase II trials
  - Date of US approval: August, 2011 (Phase III results not available)
  - Date of EU approval: October, 2012 (Phase III results available)
- FDA granted regular approval (sNDA) to crizotinib in March, 2016 for patients with ROS1+ NSCLC based on Phase II data

Where certain criteria are met, are data from single-arm trials sufficient to support marketing authorization in the EU?
Acknowledgements

• Keith Wilner
  – Crizotinib Global Clinical Lead

• Silvia Chioato
  – Global Regulatory Portfolio Lead for Thoracic Malignancies

• Ramzi Dagher
  – Head, Worldwide Regulatory Strategy – Oncology

• Robin Wiltshire
  – Crizotinib Global Medical Affairs Lead

• Chuck Mebus
  – Crizotinib Asset Team Lead

• Leena Das-Young
  – Late Phase Strategy and Development Lead - Oncology