January 10-11, 2013

NCI Workshop: Defining Clinical Utility of Molecular Diagnostics for Cancer Treatment

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Roche Molecular Diagnostics
The Power of Prospective Patient Selection

Clinical utility development for BRAF mutation+ testing of melanoma patients for vemurafenib response

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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IND filing
Prior Dx agreement

Basel, 19 January 2011

Roche personalized investigational medicine shows survival benefit in advanced skin cancer

Phase III (BRIM3) study shows promising results for RG7204 in BRAF V600 mutation-positive metastatic melanoma

Adapted from F. Borellini, PMWC Jan2012; S. Horning AACR Apr2012

Sosman et al, SMR 2010

Flaherty et al, ASCO 2009


Approval and Launch

< 5 years from IND to Launch

Overall survival (%)

Vemurafenib (N=336)

Hazard ratio 0.37 (95% CI: 0.26 - 0.55)

Phases:
- Phase 1
- Phase 2
- Phase 3
### PMA Requirement

<table>
<thead>
<tr>
<th>Description of studies and requirements</th>
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<tr>
<td><strong>Analytically verified</strong> 25 assay performance verification studies using &gt;600 specimens to support label claims.</td>
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<td><strong>Clinically validated</strong> &gt;2,300 metastatic melanoma patients in phase II and III clinical trials; patients that tested positive by cobas® BRAF test were shown to derive benefit from Zelboraf.</td>
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<td><strong>Highly reproducible</strong> 98.8% reproducibility achieved in 1440 samples in 3 external labs, 2 operators/lab, 3 reagent lots over 5 non-consecutive days.</td>
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<td><strong>Quality controlled system</strong> System, reagents, software &amp; hardware must meet GMP. Ongoing quality assessment through required annual reporting and FDA inspections of facilities.</td>
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cobas® 4800 BRAF V600 Mutation Test Package Insert; Halait et al. Diagn Mol Pathol 2012 Mar;21(1):1; Anderson et al Arch Pathol Lab Med. 2012;136:1
Drug (Zelboraf™) and Diagnostic (cobas® BRAF test)

US package inserts are cross-labeled regarding BRAF mutation testing

**Indications and usage**

ZELBORAF™ is a kinase inhibitor for the treatment of patients with unresectable or metastatic melanoma with BRAF<sup>V600E</sup> mutation as detected by an FDA-approved test

ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma

**BRAF<sup>V600E</sup> testing**

Confirmation of BRAF<sup>V600E</sup> mutation-positive melanoma as detected by an FDA-approved test is required for selection of patients for ZELBORAF because these are the only patients studied and for whom benefit has been shown

**Intended Use**

Intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with ZELBORAF
Competition from Laboratory Developed Tests

Lack of oversight allows unsubstantiated claims on clinical validation

“Molecular Response, LLC announced today through press release the expansion of their clinical offerings with the launch of a clinically validated BRAF test.”

“Molecular Response's BRAF V600E mutation test is a PCR-based test that has been validated as a CLIA Laboratory Developed Test and demonstrated superiority in terms of sensitivity and sample acceptance criteria to other clinical laboratories offering BRAF V600E mutation testing. “

- Within August 2011, Propath, Genzyme Genetics, MPL, UNC Labs started offering their own BRAF test for Melanoma

- NCCN Guidelines v2.2013 Melanoma: “[BRAF] Mutational status should be determined by an FDA approved test or a facility approved by CLIA”

Need for regulatory oversight and standardization

Should your therapy depend upon the lab your physician uses?

- 30% of European laboratories in an external quality assessment scheme unable to accurately report KRAS mutation status in quality control specimens

“If this EQA scheme reflects KRAS testing on a routine basis, at least one in 10 samples is wrongly genotyped in >30% of laboratories.” (Bellon et al 2011)

The Future: Putting the “PERSONALIZED” into Cancer Care
Evolution of NSCLC Molecular Pathology Knowledge & Drugs

Adenocarcinoma Driver Gene Mutations

- KRAS 25%
- EGFR 23%
- ALK 6%
- BRF 3%
- PI3KCA 3%
- MET 2%
- HER2 2%
- MEK1 0.4%
- NRAS 0.2%
- No Driver Mutation 35.4%

Targeted Therapeutics
(Approved/In Development)

- Crizotinib (ALK TKI)
- Erlotinib (EGFR TKI)
- Afatinib (EGFR/HER2 Inh)
- Onartuzumab (MetMAb)
- Tivantinib (cMET TKI)
- Selumetinib (MEK1/2 Inh)
- Trametenib (MEK1/2 Inh)
- Dafrafenib (BRAF Inh)

Highly multiplexed differential diagnosis or many single gene CoDx?
We Innovate Healthcare

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