



January 10-11, 2013

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

*Walter Koch, Ph.D., VP Global Research  
Roche Molecular Diagnostics*

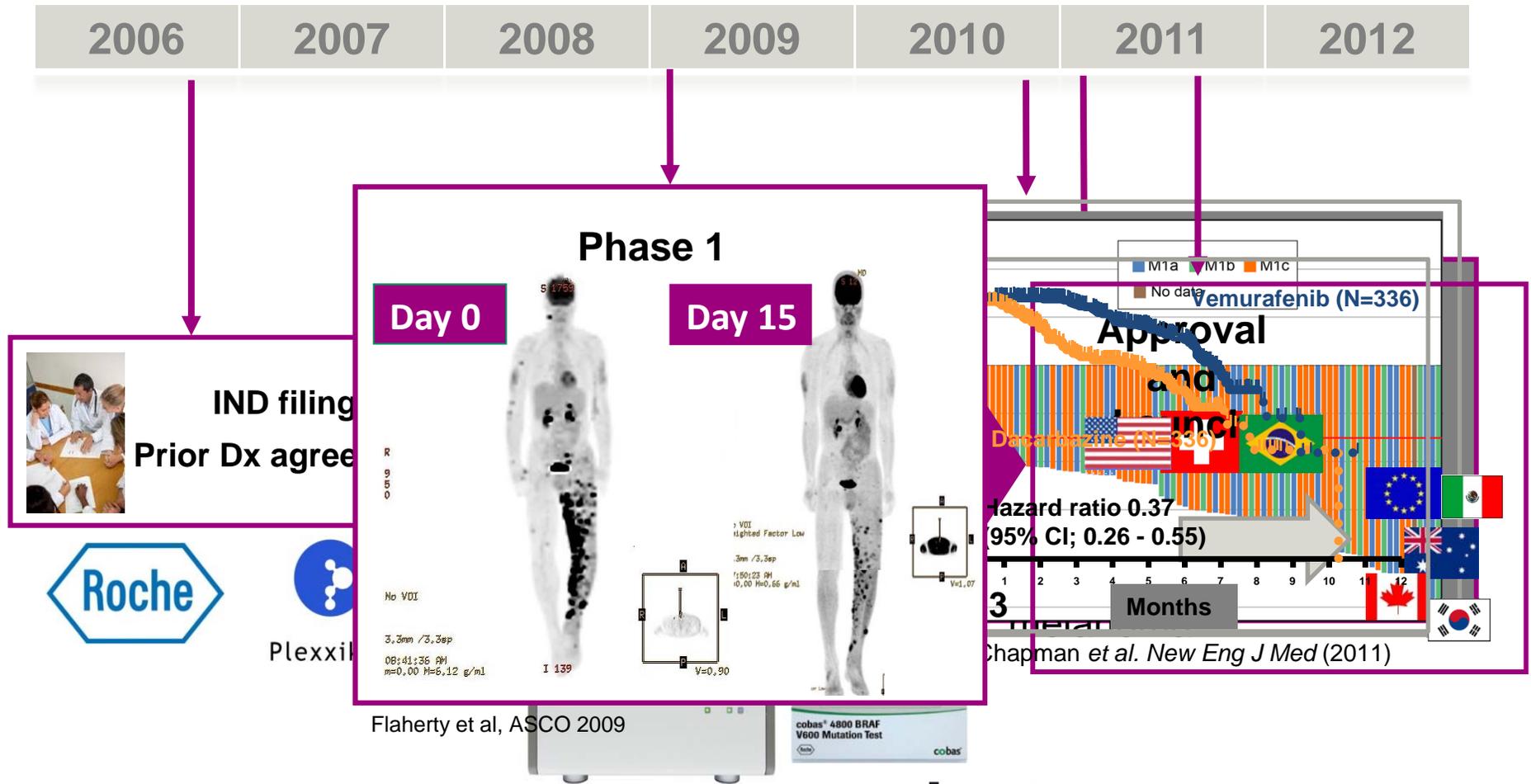


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# The Power of Prospective Patient Selection

*Clinical utility development for BRAF mutation<sup>+</sup> testing of melanoma patients for vemurafenib response*



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



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# **cobas<sup>®</sup> BRAF V600 test considered high risk class III device**

*Highest R&D investment hurdle to gain FDA premarket approval*

<b>PMA Requirement</b>	<b>Description of studies and requirements</b>
Analytically verified	25 assay performance verification studies using >600 specimens to support label claims.
Clinically validated	>2,300 metastatic melanoma patients in phase II and III clinical trials; patients that tested positive by cobas <sup>®</sup> BRAF test were shown to derive benefit from Zelboraf.
Highly reproducible	98.8% reproducibility achieved in 1440 samples in 3 external labs, 2 operators/lab, 3 reagent lots over 5 non-consecutive days.
Quality controlled system	System, reagents, software & hardware must meet GMP. Ongoing quality assessment through required annual reporting and FDA inspections of facilities.

cobas<sup>®</sup> 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*

*testino*



## 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

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## Intended Use

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

cobas® 4800 BRAF V600 Mutation Test. Package Insert. Roche Molecular Systems, Inc. 2011; Zelboraf™ (vemurafenib). US Package Insert. Genentech, Inc., 2011.



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# Competition from Laboratory Developed Tests

*Lack of oversight allows unsubstantiated claims on clinical validation*

August 18, 2011, press releases from Molecular Response and Response Genetics

*“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**”

<http://www.businesswire.com/news/home/20110817006533/en/Molecular-Response-Expands-Clinical-Offerings-BRAF-Mutation>

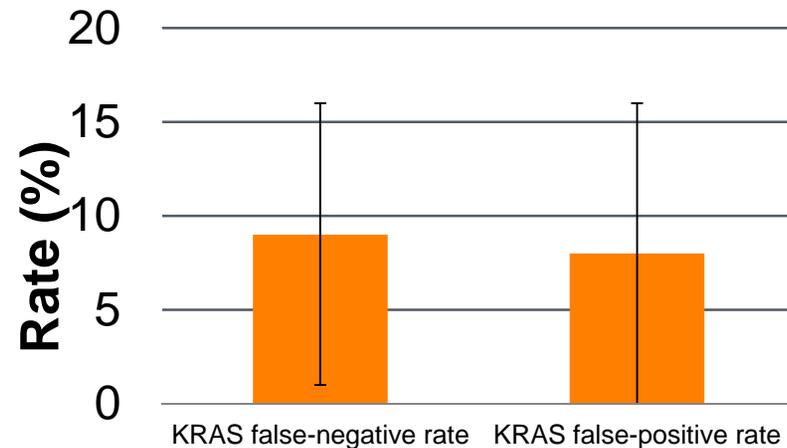
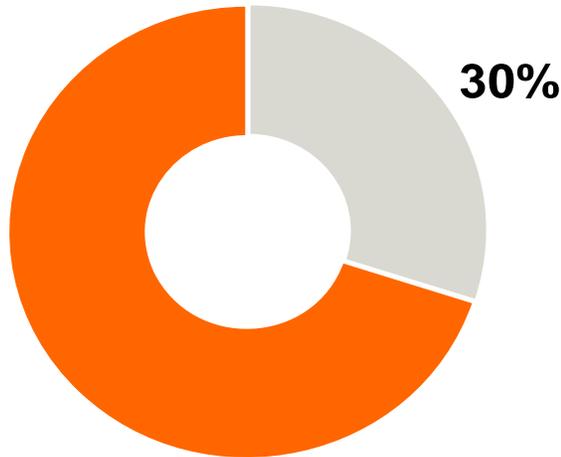


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# Need for regulatory oversight and standardization

*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)**

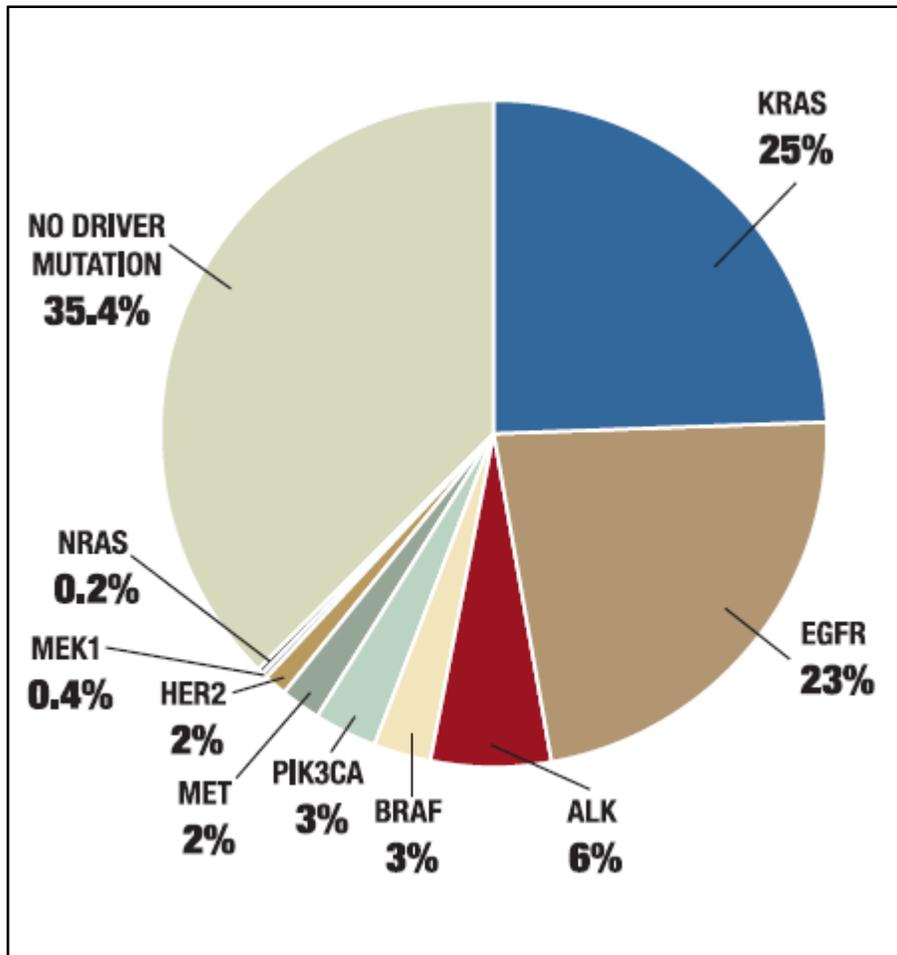
Bellon et al. *The Oncologist* 2011;16, 467; Beau-Faller et al. *J Thorac Oncol* 2011; 6, 1006



# The Future: Putting the “PERSONALIZED” into Cancer Care

## *Evolution of NSCLC Molecular Pathology Knowledge & Drugs*

### Adenocarcinoma Driver Gene Mutations



Clin Cancer Res 18 (Suppl 1) S67. Nov 1, 2012

### 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)
- Dabrafenib (BRAF Inh)



Highly multiplexed differential diagnosis or many single gene CoDx?





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