Vemurafenib (Zelboraf®)

For the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma

Melanoma

- ~76,000 new cases diagnosed in the US in 2012
  - ~9000 deaths
  - Incidence is rising
- Up to 2011, there were very few treatment options for advanced disease
  - In 2011, 2 NMEs approved:
    - Ipilumumab for all advanced melanoma
    - Vemurafenib for BRAF V600E mutation positive melanoma

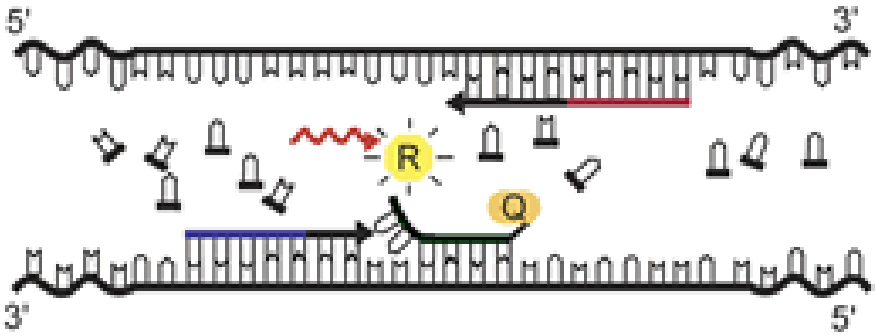
Mutations in Melanoma

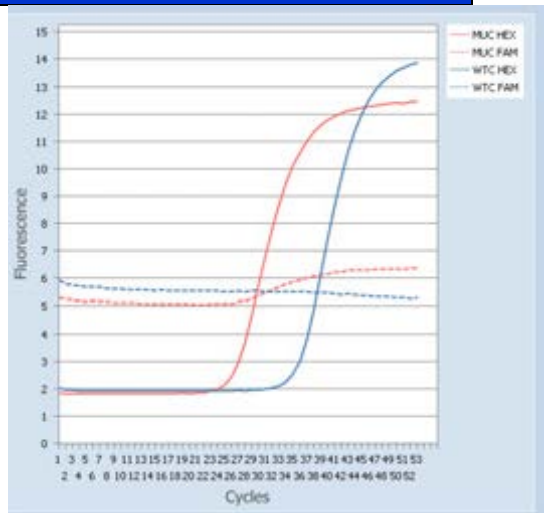
- BRAF
  - Frequency of 40-60%
  - 80-90% are V600E mutations with V600K next most common
  - Does not confer a more favorable prognosis compared to wild-type BRAF
- RAS
  - NRAS most frequent ~10-20%
  - Rarely KRAS and HRAS
- CD2KNA, CDK4, CMM1
  - Found in hereditary melanomas and syndrome of familial atypical mole and melanoma (FAMM).
- Reports of concomitant mutations in hereditary melanomas and in dysplastic nevi

BRAF Inhibition

- Landmark paper in 2002 identified BRAF as an oncogene
- IND-73620 submission in 2006
  - PLX4032 as a “selective” inhibitor of BRAF V600E kinase
    - We now know it inhibits a lot more than that
- Cutaneous SCC seen in phase 1 study (2007-2009)
- Literature in 2009, 2010 report proliferative effects of BRAF inhibitors on wtBRAF cell lines
- We now know of upstream RAS mutations, downstream MEK mutations, and intersplice variants of BRAF
  - Appear to mediate secondary resistance to BRAF inhibitors

Vemurafenib Companion Diagnostic: Roche cobas 4800 BRAF V600 Mutation Test





- Real-time PCR technology
- Detects and amplifies wild type and mutant BRAF gene
- Designed specifically to detect V600E
- Result output is either “Mutation Detected” Or “Mutation Not Detected”

Pre-Trial Planning: Companion Diagnostic

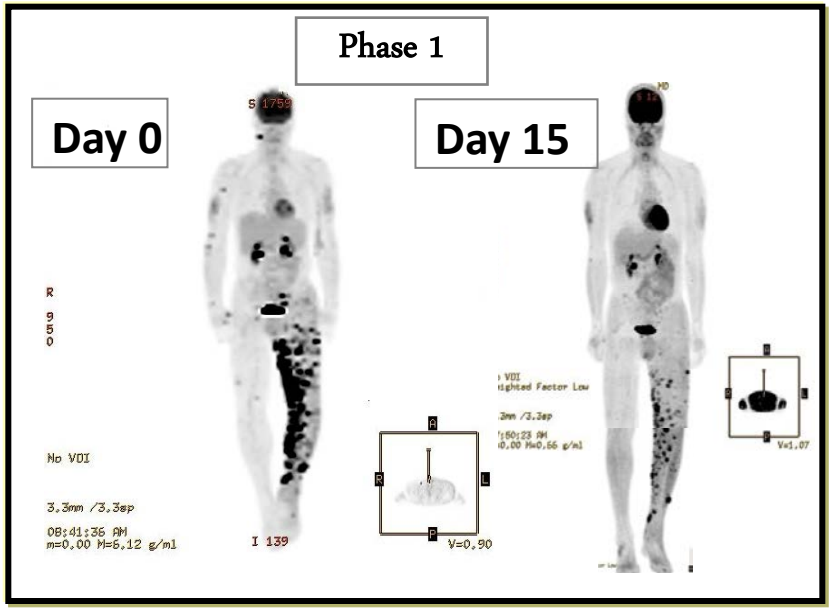
Is the population specified?

Can the population be identified in a reproducible manner?

- Fully specified test prior to use in trial
- Analytical studies are conducted prior to clinical validation
- Demonstrate the test measurements correct and reliable
  (if the test doesn't work, the drug could be improperly administered)
- Consider factors that impact test (e.g., interference, cross-reactivity)
- Consider impact of false negatives and false positives on trial population

Promising Efficacy Observed in Phase 1

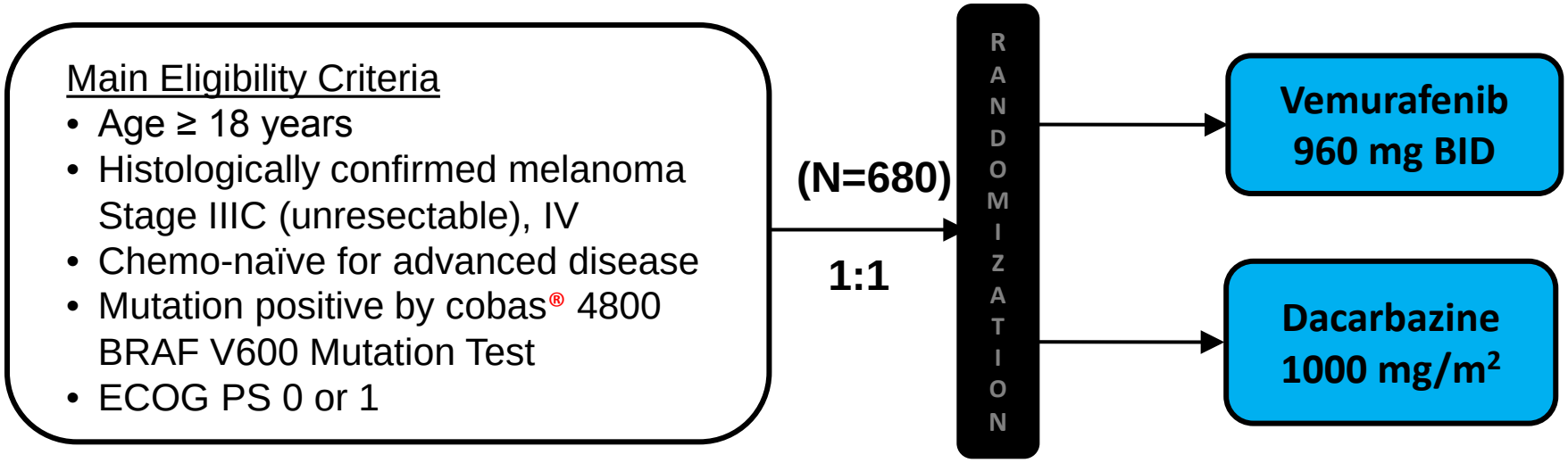
- Melanoma Extension Cohort (960 mg bid) in patients with $BRAF^{V600}$ mutation-positive tumors by prototype (TaqMan®) test
  - 81% (26/32 patients) unconfirmed response rate
  - 56% (18/32 patients) confirmed response rate



How to proceed?

- No responses seen in patients with confirmed wtBRAF (n=5, doses above 240 mg)
- Dramatic responses seen in patients with V600E BRAF
  - Sponsor chose to initiate simultaneous Phase 2 and 3 trials

A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine



Primary Endpoint: OS

- 468 events provides 80% power for HR=0.75, alpha=0.025 (2-sided)
- Two planned Interim analyses: 234 events (50%) and 351 events (75%)

Secondary Endpoints: PFS, BORR, DoR, Time to Response, Safety, PK

[1] estimates of median unreliable; few patients in follow-up after month 7

Interactions with FDA

- Eight teleconferences and meetings from August to October 2010
  - All in conjunction with CDER and CDRH
- All parties involved had to be flexible and quickly adapt to the amount of data coming in and the speed at which it was coming.
  - Response rates
    - Changed the statistical assumptions of the phase 3 trial and included PFS as co-primary endpoint
  - Cutaneous SCC
    - Comprehensive safety monitoring plan
    - Commend the sponsor on the molecular characterization of the new lesions (ASCO 2011 abstract)
  - Device development

BRIM-3: Revised Statistical Assumptions Prior to IA

OS, PFS Co-primary endpoints

	Overall survival	
	Original	**Revised**
Hazard ratio	**0.75**	**0.65**
Power	**80%**	**80%**
α	**0.025 (two-sided)**	**0.045 (two-sided)**
Target median (months)	**8.0 to 10.7**	**8.0 to 12.3**
Events	**468**	**196**
Interim analysis	**50%, 75%**	**50%**
	Progression-free survival	
	Original	**Revised**
Hazard ratio	**-**	**0.55**
Power	**-**	**90%**
α	**-**	**0.005 (two-sided)**
Target median (months)	**-**	**2.5 to 4.5**
Events	**-**	**Projected 187**
Final analysis	**-**	**At interim analysis for OS**

At 1st Planned Interim Analysis (50% of OS events, n=100)

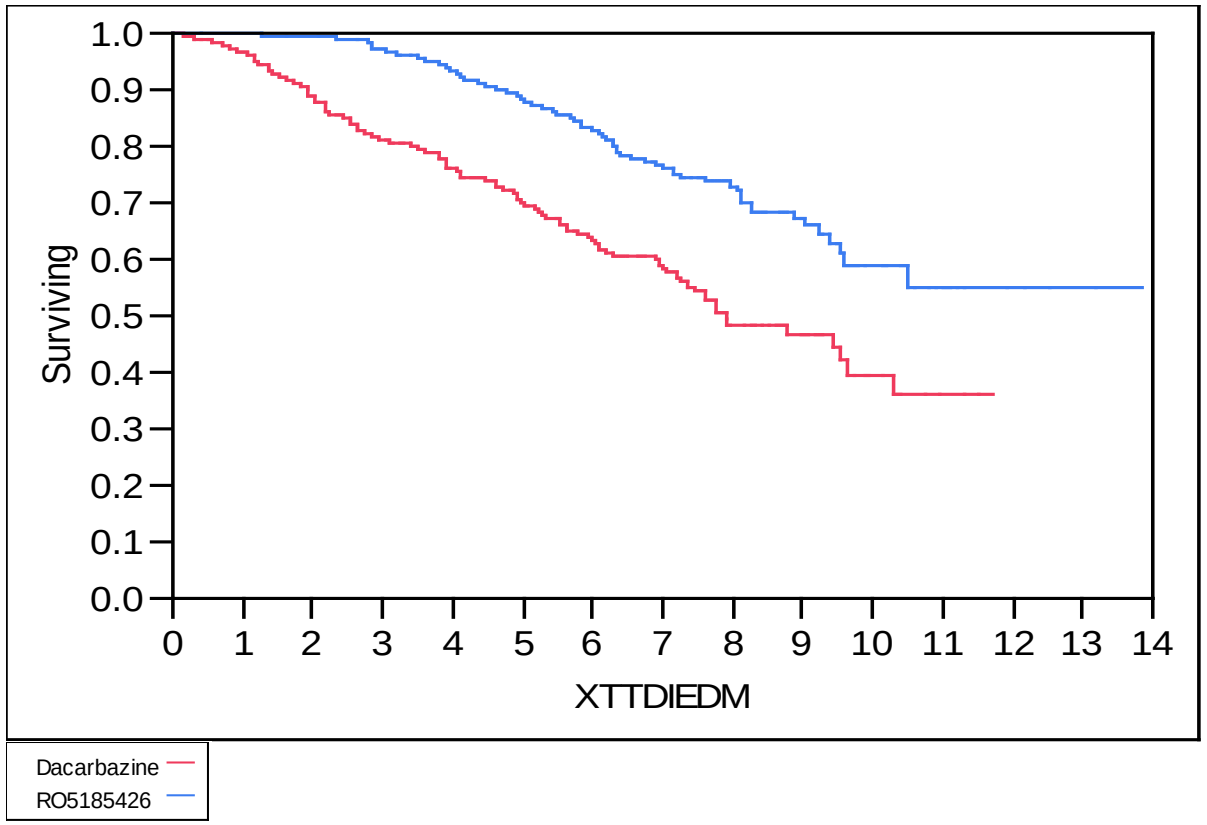
Full ITT Population*

Study NO25026-FDA (Data Cutoff 12-30-10)

Overall Survival	Vemurafenib N = 337	Dacarbazine N = 338
Number of Events	43 (12.8)	75 (22.2)
Censored	294 (87.2)	63 (18.6)
Median OS**	**9.2 months (8.03, NE[2])**	**7.7 Months (6.2, NE[2])**
Hazard Ratio[1] (95% CI)		**0.37 (0.26-0.54)**
p-value (logrank test)		**<0.0001**

Phase 3 Results-Efficacy; Final OS

Kaplan Meier OS Estimates



HR 0.44 (0.33-0.59) p<0.0001 (199 total events)
median OS Vemurafenib= NE (9.6 – NE)
Dacarbazine= 7.9 (7.2 – 9.6)

Phase 3 Results – Other Endpoints

- Improvement in PFS:
  - HR=0.26 (95% CI: 0.2,0.33)
- Confirmed ORR = 48.4% vs. 5.5%

Warnings and Precautions in The Label

- Cutaneous squamous cell carcinomas
- Serious hypersensitivity reactions, including anaphylaxis
- Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- QT prolongation
- Liver laboratory abnormalities
- Photosensitivity
- Serious ophthalmologic reactions
- New primary malignant melanomas
- Pregnancy: May cause fetal harm
- BRAFV600E testing

Vemurafenib Companion Diagnostic

Test Intended Use: The cobas® 4800 BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue.

RMS provided analytical data to support the reliability of the test prior to use in trial

- **Validation with specific specimen type**
- **Accuracy for V600E vs. Wild type V600**
- **Sensitivity for V600E in a background of Wild type**
- **Cross-Reactivity**

Indication

- *ZELBORAF™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.*
- *Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.*
  - Why the limitations of use statement?
  - Why V600E?

To Answer Both Questions

- Limited to no experience in patients who do not test positive for the V600E mutation
- Positive risk-benefit assessment has not been established for patients with wtBRAF or mutV600 that test negative.
  - Other mutations to be addressed in a PMC
  - Patients with wtBRAF should only be treated with Zelboraf in the context of a clinical trial

Enrichment Strategy

- Example of a predictive enrichment strategy
- Allowed for recalculation of statistical assumptions for the pivotal trial
  - Lower number of events needed
- Led to rapid approval (4 months)

Challenge Question

What Were the Key Factors That Led to the Rapid Approval of Vemurafenib and the Cobas V600 Mutation Test?

- A) The statistically significant and clinical meaningful improvement in an endpoint that directly measures clinical benefit
- B) An analytically valid and reliable companion diagnostic test that enriched the trial population with patients that have a higher likelihood to respond to treatment
- C) The development of a comprehensive monitoring plan for an unexpected adverse reaction
- D) Early, frequent, and interdisciplinary interactions with the FDA to address issues that arose during development
- E) All of the above