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# Panitumumab: The KRAS Story

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# Clinical Background: panitumumab in mCRC

- Panitumumab is a fully human IgG2 monoclonal antibody directed against EGFR
- Colorectal Cancer
  - ~ 20% present with metastatic disease, ~ 50% will develop it
- Panitumumab development program covers 3 lines of mCRC therapy each with a phase 3 study
  - 1st Line in combination with chemotherapy: FOLFOX ± panitumumab
  - 2nd Line in combination with chemotherapy : FOLFIRI ± panitumumab
  - 3rd Line monotherapy: BSC ± panitumumab
- KRAS story started in the monotherapy setting with the phase 3 study
  - Positive study (HR=0.54, p<0.0001) but CHMP concluded benefits did not outweigh the risks

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# Phase 3 Study Provided an Experimental Setting to Assess *KRAS* in 3rd line mCRC

- *KRAS* Hypothesis was generated independently of the phase 3 data
  - Biologic plausibility of the *KRAS* hypothesis (20 years of research)
  - Available external and internal data (from Amgen's phase 2 monotherapy studies) suggested restricted benefit only for patients with wild-type tumors
- *KRAS* was the only biomarker evaluated for correlation with clinical outcome
- Expected *KRAS* evaluable sample size was sufficiently large to ensure random allocation between treatment arms
- A reliable *KRAS* testing kit was available
  - A comparison study identified an assay that could be used in routinely available clinical specimens (DxS Mutation Test Kit)
- Testing performed in an independent laboratory without patient-level knowledge of randomization or outcome

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# Prospective *KRAS* Statistical Analysis Plan for Phase 3 Study

- The *KRAS* Statistical Analysis Plan (SAP) was finalized prior to unblinding of *KRAS* status
- Objectives were to formally address the *KRAS* hypothesis:
  - To test that the treatment by KRAS interaction on PFS
  - To test the treatment effect on PFS, objective response and overall survival in *KRAS* wild-type stratum
  - Analysis designed to control overall type 1 error for the set of comparisons in the *KRAS* analysis
- This Prospective/Retrospective analysis (July 2007) provided robust evidence for treatment by *KRAS* interaction
  - High ascertainment of *KRAS* on archived samples (92%)
  - Large separation of treatment effect on PFS by KRAS Status with quantitative interaction test P-value < 0.0001
- EMA conditional approval in Dec 2007
  - Specific obligation: a phase 3 study head-to-head with cetuximab

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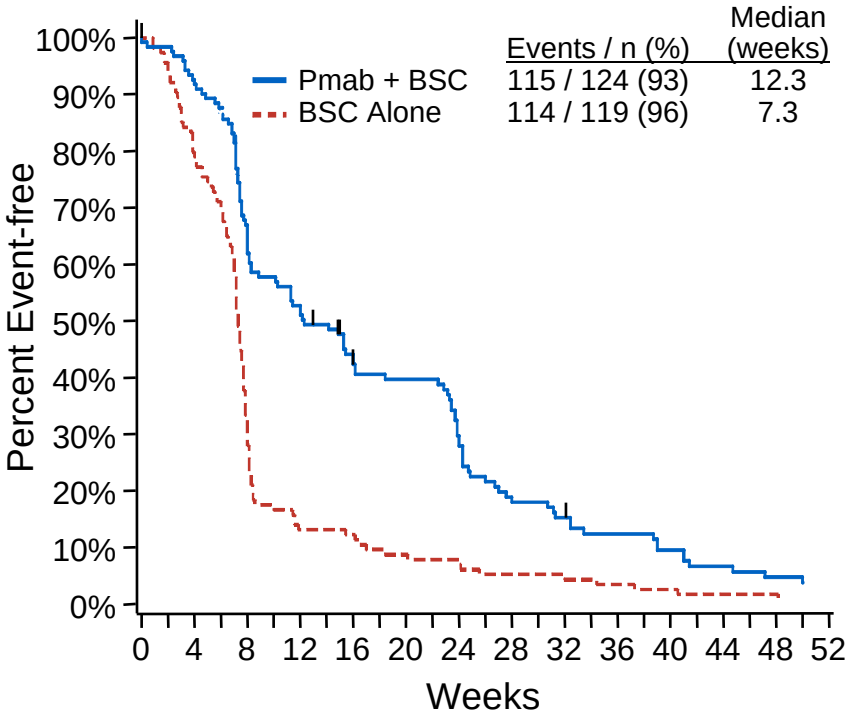
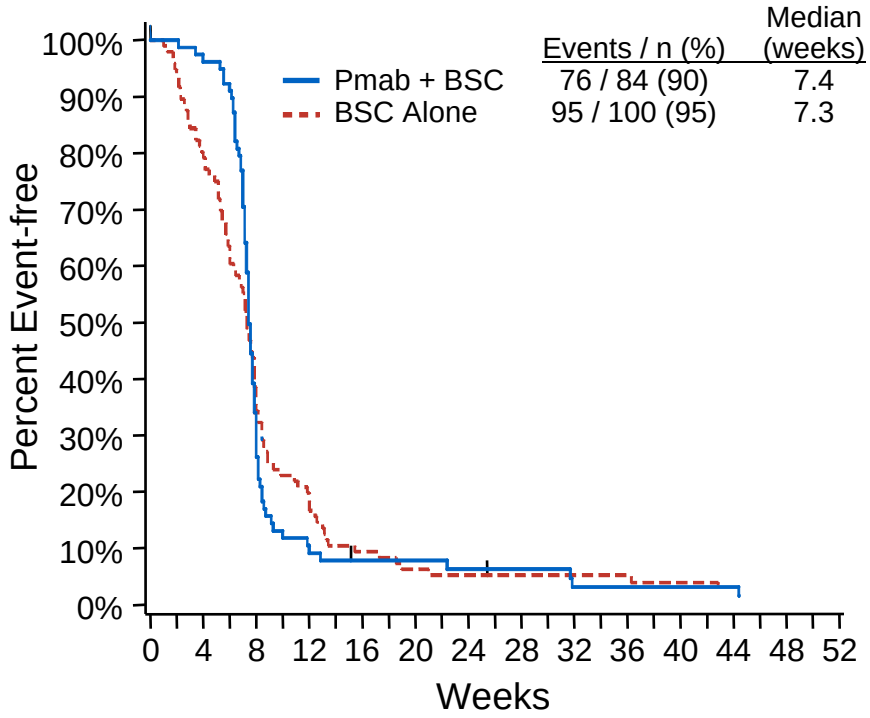
# Increased PFS Observed in Patients with *KRAS* Wild-type Tumors

## Wild-type




Hazard Ratio = 0.45 (95% CI: 0.34–0.59)
Stratified Log Rank Test $p < 0.0001$

## Mutant




Hazard Ratio = 0.99 (95% CI: 0.73–1.36)

Quantitative interaction test $p < 0.0001$

Adapted from: Amado, et al. *J Clin Onc.* 2008;26:1626-1634.

# Discovery of *KRAS* as a Predictive Biomarker Changed the Clinical Landscape of mCRC

- Enrolment (unselected population) for the two phase 3 trials of panitumumab in first-line and second-line mCRC was close to completion at the *KRAS* analysis
- Subsequently, the protocols were amended to prospectively analyze clinical outcomes by *KRAS* status
- Protocols and SAPs were reviewed by CHMP before the *KRAS* unblinding prior to the primary analyses
  - Primary endpoint:
    - PFS for first-line
    - Co-primary of PFS and OS for second-line (with split of alpha for testing)
  - Enrolment (unselected population) in both studies was increased to assure adequate testing power in the wild-type KRAS stratum
  - Sequential testing schema was used to control overall type 1 error rate: testing mutant after positive wild-type results

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# Results by *KRAS* Status in 1st/2nd line mCRC

- Both studies reported results in Q4 2009
  - High ascertainment of *KRAS* (>90%) for both studies
- Both studies confirm clinical benefit of panitumumab restricted to patients with KRAS WT tumours
- Patients with KRAS MT tumours had no benefit (in combination with FOLFIRI) or worse outcomes (combination with FOLFOX) with panitumumab
- Results were similar to those from cetuximab trials
- EC approval in Nov 2011

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