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KRAS as a Predictive Biomarker for Vectibix® (panitumumab) Monotherapy

Oncologic Drugs Advisory Committee
December 16, 2008

Agenda

▪ Introduction and Overview	*Paul Eisenberg, MD, MPH* *Global Regulatory Affairs & Safety* *Amgen*
▪ *KRAS* Hypothesis ▪ Selection of *KRAS* Assay ▪ Panitumumab Monotherapy Data ▪ Combination Therapy Data	*David Reese, MD* *Global Clinical Development* *Amgen*

KRAS as a Predictive Biomarker in Patients with Colorectal Cancer

- **Biologic plausibility of the *KRAS* hypothesis**
  - Activating mutations well characterized
- **Strengths of monotherapy analysis**
  - High ascertainment of *KRAS* on archived samples (92%)
  - Pre-specified analysis plan
  - Use of reliable assay
  - Consistent high predictive value of mutated *KRAS* for non-response
- **Limitations of overall analysis**
  - Insight to *KRAS* predictive value arose during development program
  - FDA-approved *KRAS* assay currently not available
- **Use of *KRAS* as a predictive biomarker will improve the Benefit:Risk profile for panitumumab monotherapy in patients with colorectal cancer**

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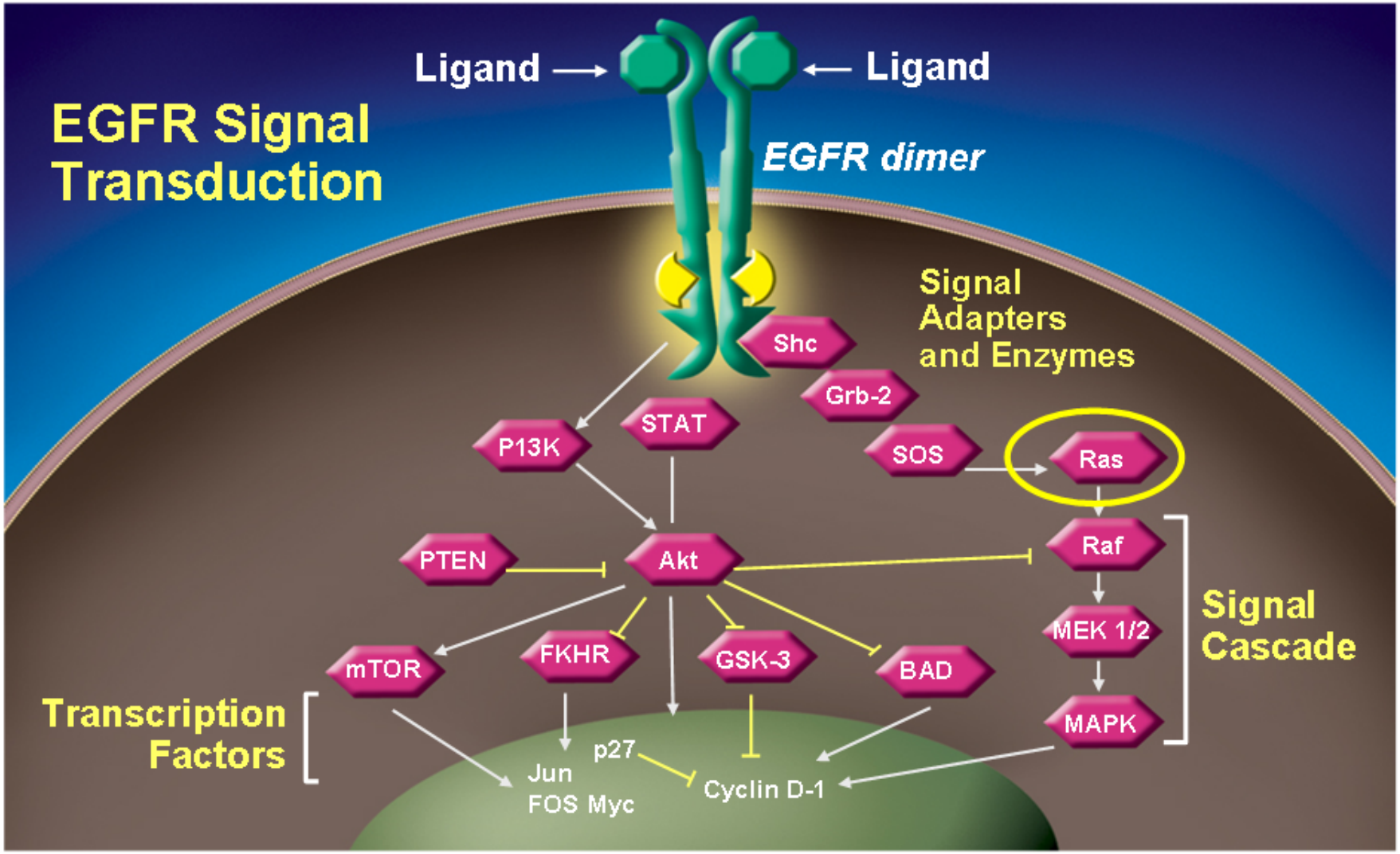
The *KRAS* Hypothesis: Biologic Plausibility

David Reese, MD
Global Clinical Development
Amgen

RAS is a Crucial Intermediate in EGFR Signaling



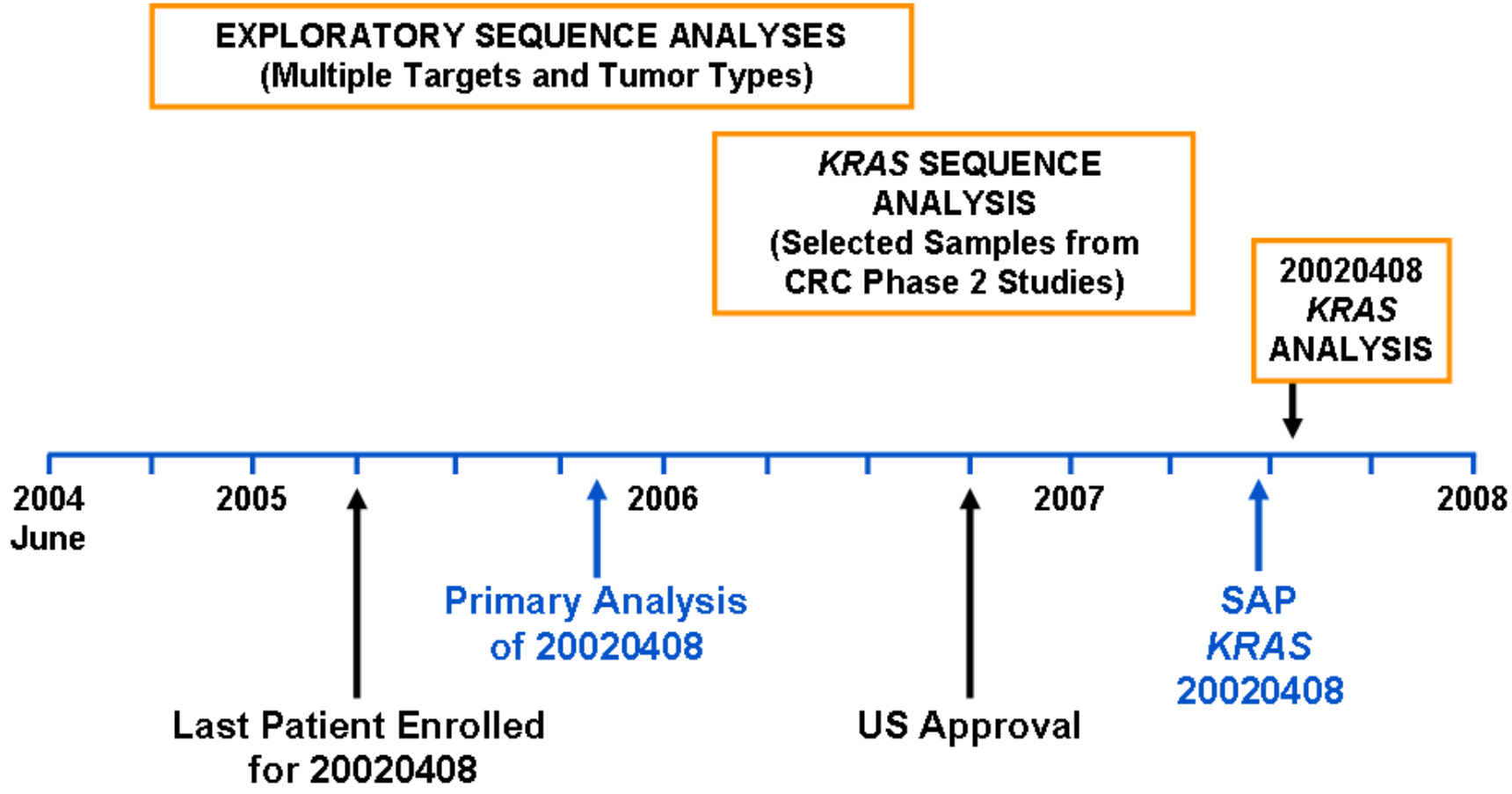
Adapted from: Mendelsohn J. *J Clin Onc.* 2002;20(suppl 1):1s-13s.

Exploratory Analyses Suggested *KRAS* Mutations Correlate with a Lack of Response in CRC

Publication	Treatment (panitumumab or cetuximab)	No. of Subjects	Mutant %	Objective Response N (%)	
				Wild-type	Mutant
M Moroni (*Lancet Oncology. 2005*)	Pmab or Cmab or Cmab + CT	31	32	8 (38)	2 (20)
S Benvenuti (*Cancer Res.* 2007)	Pmab or Cmab or Cmab + CT	48	33	10 (31)	1 (6)
W De Roock (*ASCO Proceedings.* 2007)	Cmab ± CT	37	46[a]	8 (40)	0
D Finocchiaro (*ASCO Proceedings. 2007*)	Cmab ± CT	81	40	13 (26)	2 (6)
F Di Fiore (*Br J Cancer.* 2007)	Cmab + CT	59	27[b], 37[c]	12 (28)	0
S Khambata-Ford (*J Clin Oncol.* 2007)	Cmab	80	38[a]	5 (10)	0
A Liévre (*AACR Proceedings.* 2007)	Cmab ± CT	76	36	24 (49)	0

[a]PCR sequencing; [b]*KRAS* status by sequencing; [c]*KRAS* status by SNaPShot® analysis or PCR-LCR
CRC, colorectal cancer; Pmab, panitumumab; Cmab, cetuximab; CT, chemotherapy

KRAS Hypothesis in CRC Emerged in Parallel with Clinical Trial Data



CRC, colorectal cancer; SAP, statistical analysis plan

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Selection of an Assay for *KRAS* Testing

Selection of a *KRAS* Assay

- Greater than 95% of activating *KRAS* mutations affect codons 12 and 13[1]
- A comparison study identified an assay that could be used in routinely available clinical specimens (DxS Mutation Test Kit)

Assay Comparability

		Bidirectional DNA Sequencing		
		Wild-type	Mutant	Total
DxS	Wild-type	20	1	21
	Mutant	0	19	19
	Total	20	20	40

[1]Cosmic Database accessed at: http://www.sanger.ac.uk/genetics/CGP/cosmic/
Data on file, Amgen

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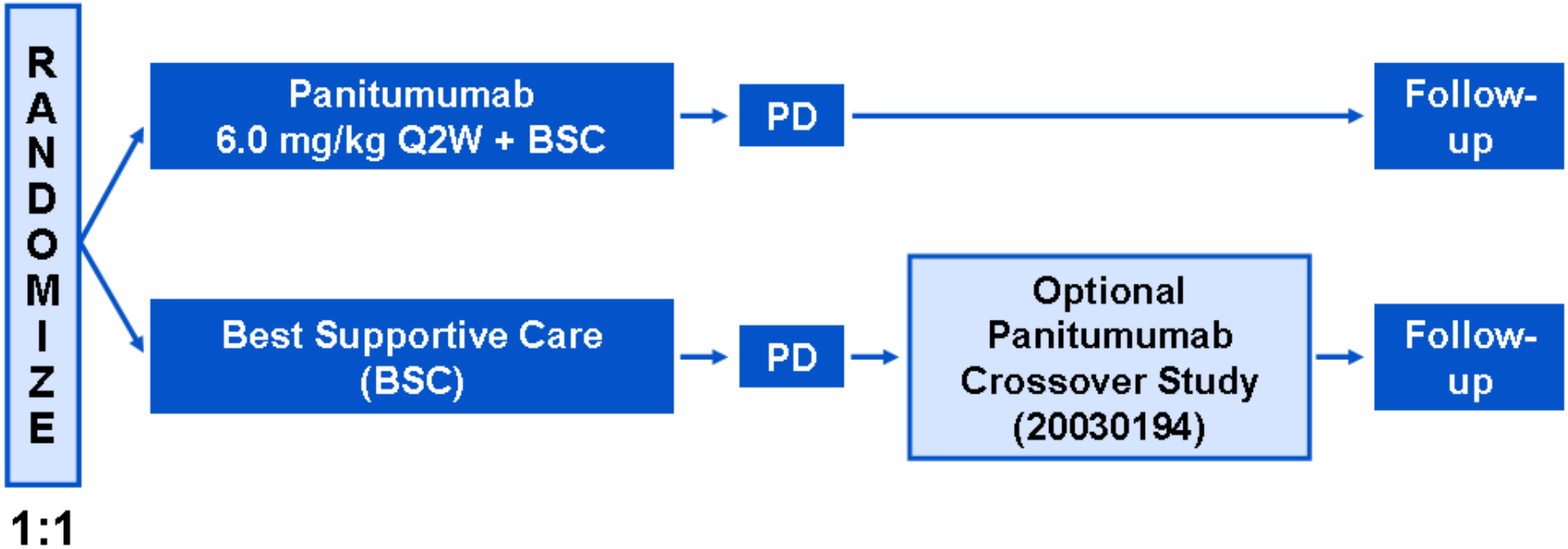
Predictive Value of *KRAS* in Vectibix® (panitumumab) Monotherapy

Phase 3 Study Design Leading to Accelerated Approval for Panitumumab (Study 20020408)

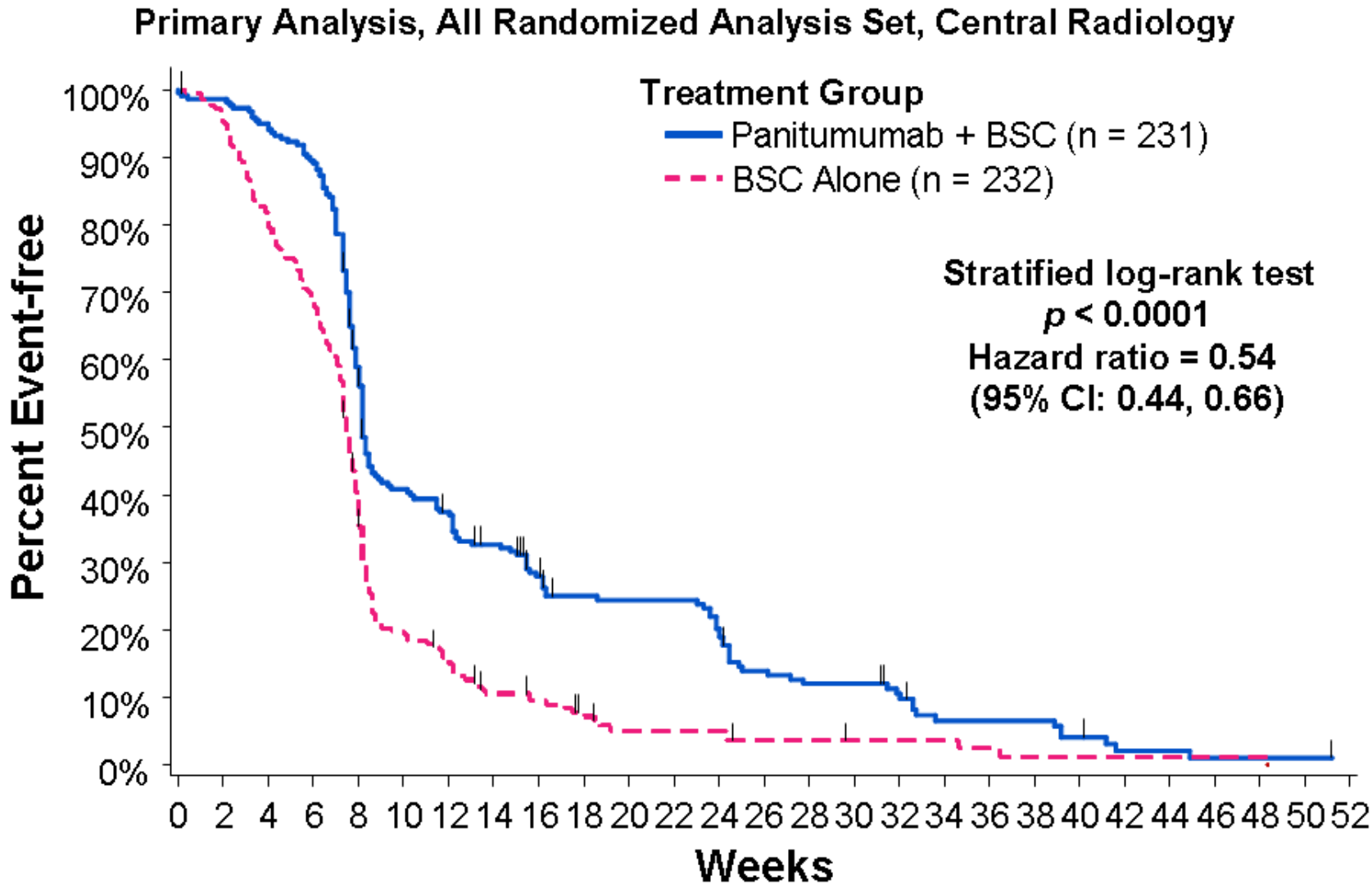


Primary Endpoint: Progression-free Survival (PFS)

PD, progressive disease

Van Cutsem P, et al. *J Clin Onc.* 2007;25:1658-1664.

Panitumumab Improves Progression-free Survival in Advanced Colorectal Cancer



Van Cutsem P, et al. *J Clin Onc.* 2007;25:1658-1664.

Phase 3 Trial (Study 20020408) Provided an Opportunity to Assess *KRAS*

- Protocol required tumor samples which were archived for potential biomarker correlative analyses
- Expected *KRAS* evaluable sample size was sufficient to provide balance between treatment arms
- *KRAS* was the only biomarker evaluated for correlation with clinical outcome
- High power (> 90%) to test whether *KRAS* was a predictive biomarker for progression-free survival (PFS)

Prospective Statistical Analysis Plan for Phase 3 Trial (Study 20020408)

- **The Statistical Analysis Plan (SAP) was finalized prior to unblinding of *KRAS* status**
- **Objectives were to formally address the *KRAS* hypothesis:**
  - To test that the relative improvement in progression-free survival (PFS) is larger in the wild-type vs. mutant *KRAS* stratum
  - 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

KRAS Results Obtained in > 90% of Patients from Phase 3 Trial (Study 20020408)

	Panitumumab + BSC	BSC alone	Total
Patients randomized, n	231	232	463
Tumor sample available, n (%)	220 (95)	225 (97)	445 (96)
KRAS tests failed, n (%)*	12 (5)	6 (3)	18 (4)
Patients included in *KRAS* analysis, n (%)	208 (90)	219 (94)	427 (92)
Wild-type *KRAS*, n (%)	124 (60)	119 (54)	243 (57)
Mutant *KRAS*, n (%)	84 (40)	100 (46)	184 (43)

**KRAS* tests failed due to insufficient DNA quality or quantity
BSC, Best Supportive Care

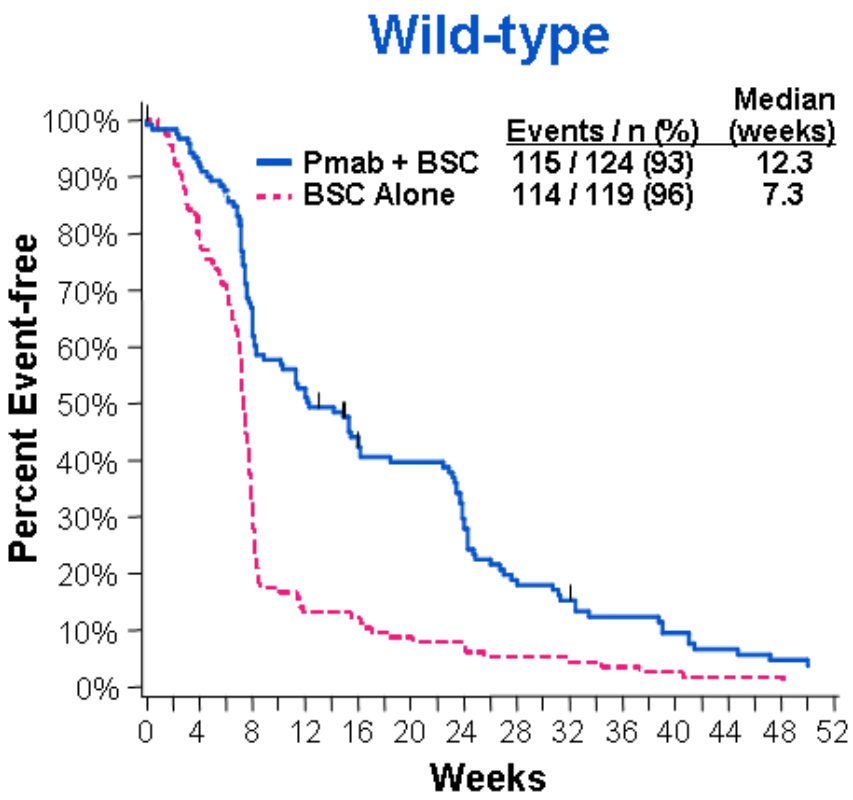
Amado, et al. *J Clin Onc.* 2008;26:1626-1634.

Baseline Characteristics were Balanced Between Treatment Arms

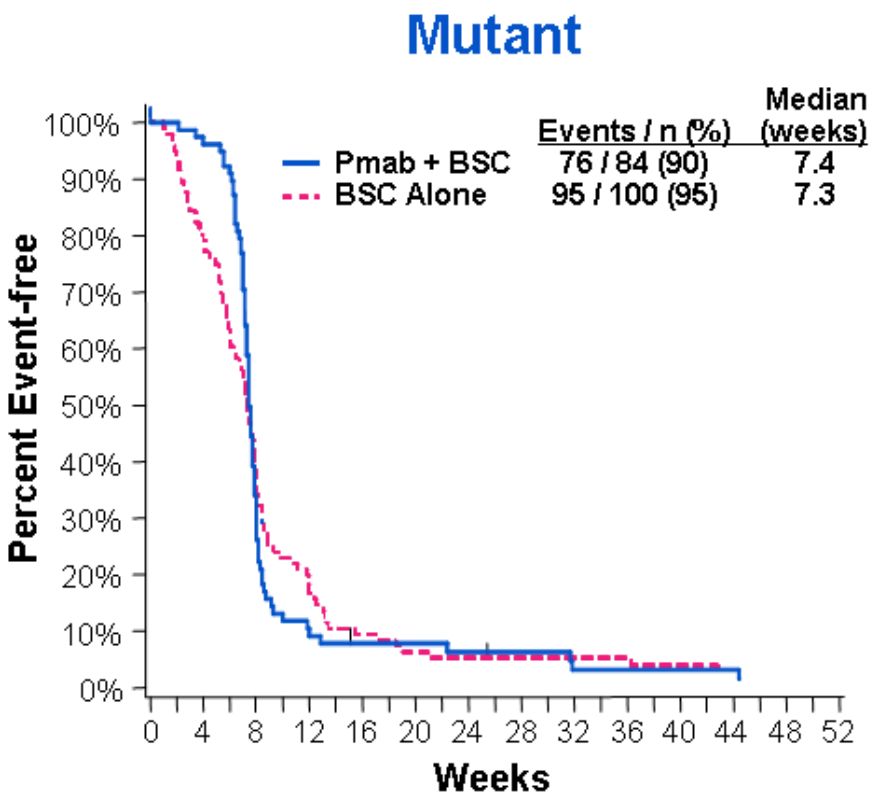
	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab plus BSC (n = 124)	BSC alone (n = 119)	Panitumumab plus BSC (n = 84)	BSC alone (n = 100)
Sex, %				
Men	67	64	56	64
Baseline age, years				
Median (min, max)	62.5 (29, 82)	63.0 (32, 81)	62.0 (27, 79)	62.0 (27, 83)
Primary diagnosis, %				
Colon cancer	69	69	63	65
Months since primary diagnosis				
Median	25.2	25.0	23.5	25.5
ECOG performance status, %				
0–1	88	86	85	84
≥ 2	12	14	15	16
Prior adjuvant chemotherapy, %				
Yes	40	27	32	40
Cells with EGFR membrane staining, %				
1– < 10	25	24	24	23
10–100	75	75	75	77

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

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



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

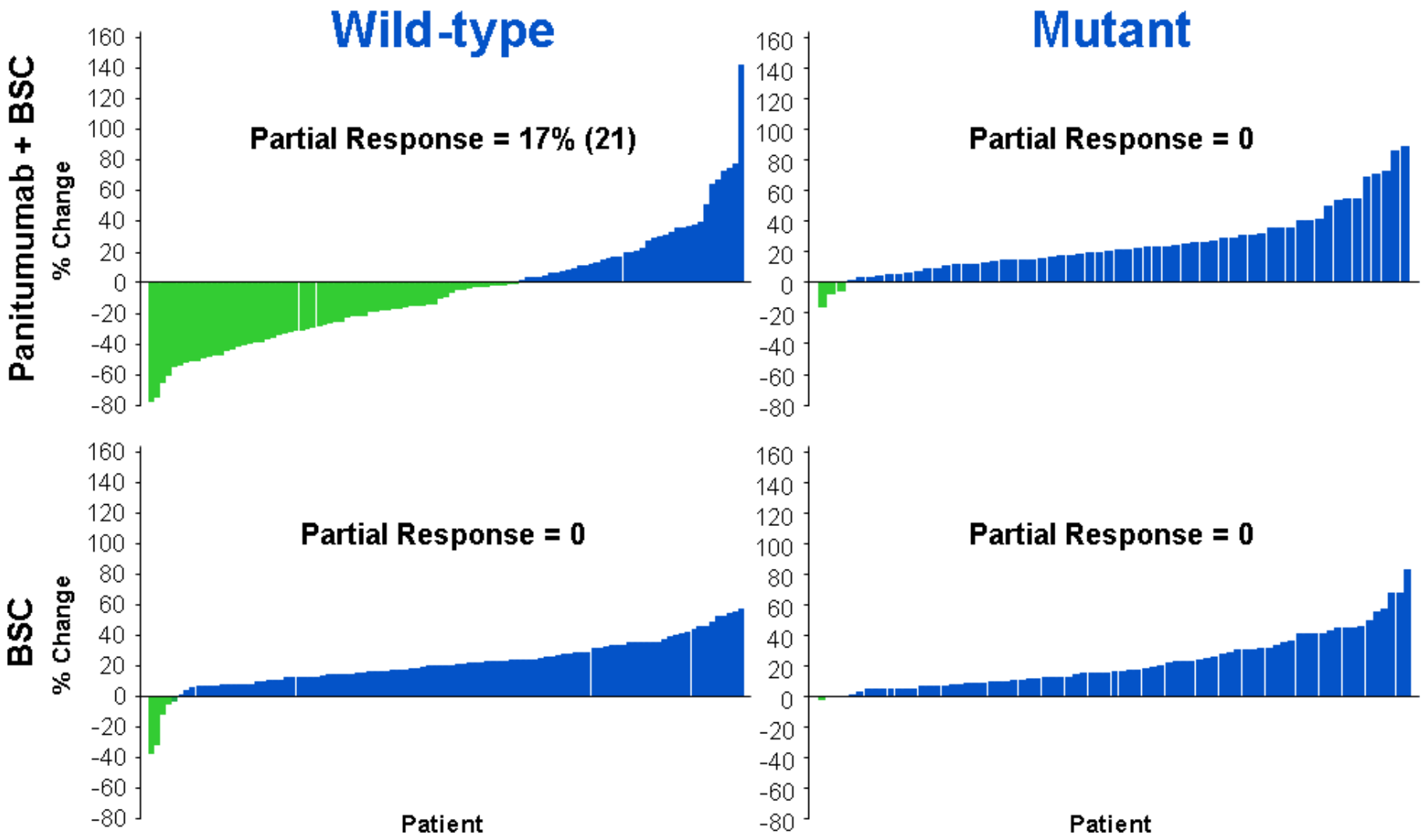


Hazard Ratio = 0.99 (95% CI: 0.73–1.36)

Quantitative interaction test $p < 0.0001$

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

Decreases in Target Lesions Observed in Patients with Wild-type *KRAS* Tumors Treated with Panitumumab



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

Safety Profiles by *KRAS* Status

	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab + BSC (n = 123)	BSC alone (n = 120)	Panitumumab + BSC (n = 84)	BSC alone (n = 100)
Mean number of infusions per patient	10.0 infusions	NA	4.9 infusions	NA
Worse grade 3 or 4 AEs, %				
Treatment-related	25	NA	12	NA
Integument-related	25	1	13	3
Diarrhea	2	0	1	0
Infections	9	5	5	0
Hypomagnesemia as an AE (all grades), %	3	0	0	0
Infusion reactions (all grades), %	2	NA	7	NA

AE, Adverse Event; NA, Not Applicable

Amado, et al. *J Clin Onc*. 2008;26:1626-1634.
Amado, et al. *Annal Onc*. 2008:19(8);359P (viii126).

Percentage of Patients with Adverse Events Observed in the First 8 Weeks from 20020408

	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab + BSC (n = 123)	BSC alone (n = 120)	Panitumumab + BSC (n = 84)	BSC alone (n = 100)
Mean number of infusions per patient	3.7 infusions	NA	3.6 infusions	NA
Worse grade 3 or 4 AEs, %				
Treatment-related	16	NA	11	NA
Integument-related	16	1	12	2
Diarrhea	2	0	0	0
Infections	3	4	5	0
Hypomagnesemia as an AE (all grades), %	0	0	0	0
Infusion reactions (all grades), %	2	NA	7	NA

AE, Adverse Event; NA, Not Applicable

Data on file, Amgen

A Pooled Analysis of Panitumumab Monotherapy Studies Demonstrates Consistent Results

- Similar study designs in 4 monotherapy trials
- *KRAS* was tested with the same methodology independent of study outcomes (and treatment in the phase 3 study)
- A high rate of *KRAS* ascertainment was achieved in each study (84–96%)
- Each study had consistent outcomes by *KRAS* status

The Utility of *KRAS* as a Predictive Biomarker Consistently Seen in Panitumumab Monotherapy Studies

Study	*KRAS* Ascertainment	Objective Response	
		Wild-type	Mutant
20020408[1] (n = 208)	90%	17%	0%
20030194 (n = 168)	96%	22%	0%
20030167 (n = 168)	91%	6%	0%
20030250 (n = 171)	84%	9%	0%
Total (n = 715)	90%	14%	0%

[1]Panitumumab arm
Amado, et al. *Annal Onc.* 2008:19(8);359P (viii126)

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Future Analysis: Panitumumab and Chemotherapy

Randomized Controlled Trials of Panitumumab in Combination Regimens

Study	Regimens	N	Study Status
Chemotherapy + Panitumumab			
20050181	FOLFIRI ± panitumumab 2nd line	1150 (1187 enrolled)	Fully enrolled
20050203 (PRIME)	FOLFOX ± panitumumab 1st line	1150 (1183 enrolled)	Fully enrolled
20060141 (SPIRITT)	FOLFIRI + panitumumab vs. FOLFIRI + bevacizumab 2nd line	210	Ongoing
Chemotherapy + Bevacizumab ± Panitumumab			
20040249 (PACCE)	Oxaliplatin or irinotecan regimen + bevacizumab ± panitumumab 1st line	823 oxaliplatin 230 irinotecan	Complete

Ongoing Phase 3 Trials Will Evaluate *KRAS* as a Predictive Biomarker for Panitumumab in Combination with Chemotherapy

20050181: Second-line mCRC

- 1:1 randomization
- Co-1º Endpoints: PFS and OS
- N = 1,187

Stratification Factors:

- Prior oxaliplatin exposure for mCRC
- Prior bevacizumab exposure for mCRC
- ECOG performance status (0 or 1 vs. 2)

20050203: First-line mCRC

- 1:1 randomization
- 1º Endpoint: PFS
- N = 1,183

Stratification Factors:

- Geographic region (Western Europe, Canada and Australia vs. rest of world)
- ECOG performance status (0 or 1 vs. 2)

KRAS and Monotherapy: Key Goals

- Avoid toxicity in patients with *KRAS* mutant tumors, who are highly unlikely to benefit
- Enhance benefit from therapy
- Ensure that reliable *KRAS* testing is available
- Provide reliable information to healthcare providers and patients

Use of *KRAS* as a predictive biomarker will improve the Benefit:Risk profile for panitumumab monotherapy in patients with colorectal cancer

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The DxS Assay Is a Diagnostic Kit With High Sensitivity and Specificity

- '*KRAS* Mutation Test Kit' is intended for the detection of 7 somatic mutations in the *KRAS* oncogene using separate assays
- Each assay can detect approximately 1% of mutant *KRAS* sequence in a background of wild type genomic DNA
- The assays have limits of detection of between 5 and 10 copies (need about 500 copies of the gene (cells) in the total reaction)