

# THE CLINICAL BENEFIT OF BEVACIZUMAB IN METASTATIC COLORECTAL CANCER IS INDEPENDENT OF K-RAS MUTATION STATUS: ANALYSIS OF A PHASE III STUDY OF BEVACIZUMAB WITH CHEMOTHERAPY IN PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER

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Metastatic CRC: O-035

## BACKGROUND

- Bevacizumab (BV) is a monoclonal antibody to vascular endothelial growth factor (VEGF)
- BV, combined with chemotherapy, prolongs both progression-free (PFS) and overall survival (OS) in the 1<sup>st</sup>- and 2<sup>nd</sup>-line treatment of mCRC<sup>1,2</sup>
- Mutations of the *K-ras* gene have been identified as prognostic markers in mCRC<sup>3</sup>
- Emerging data suggest that *K-ras* mutation is a negative predictor of benefit from anti-endothelial growth factor receptor (anti-EGFR) treatment in mCRC<sup>4,5</sup>
- VEGF expression measured by in situ hybridization and by immunohistochemistry did not correlate with *ras* mutation status (data on file)
- We previously reported that improvement in OS with BV is independent of alterations in the Ras/Raf/MEK/ERK pathway<sup>6</sup>

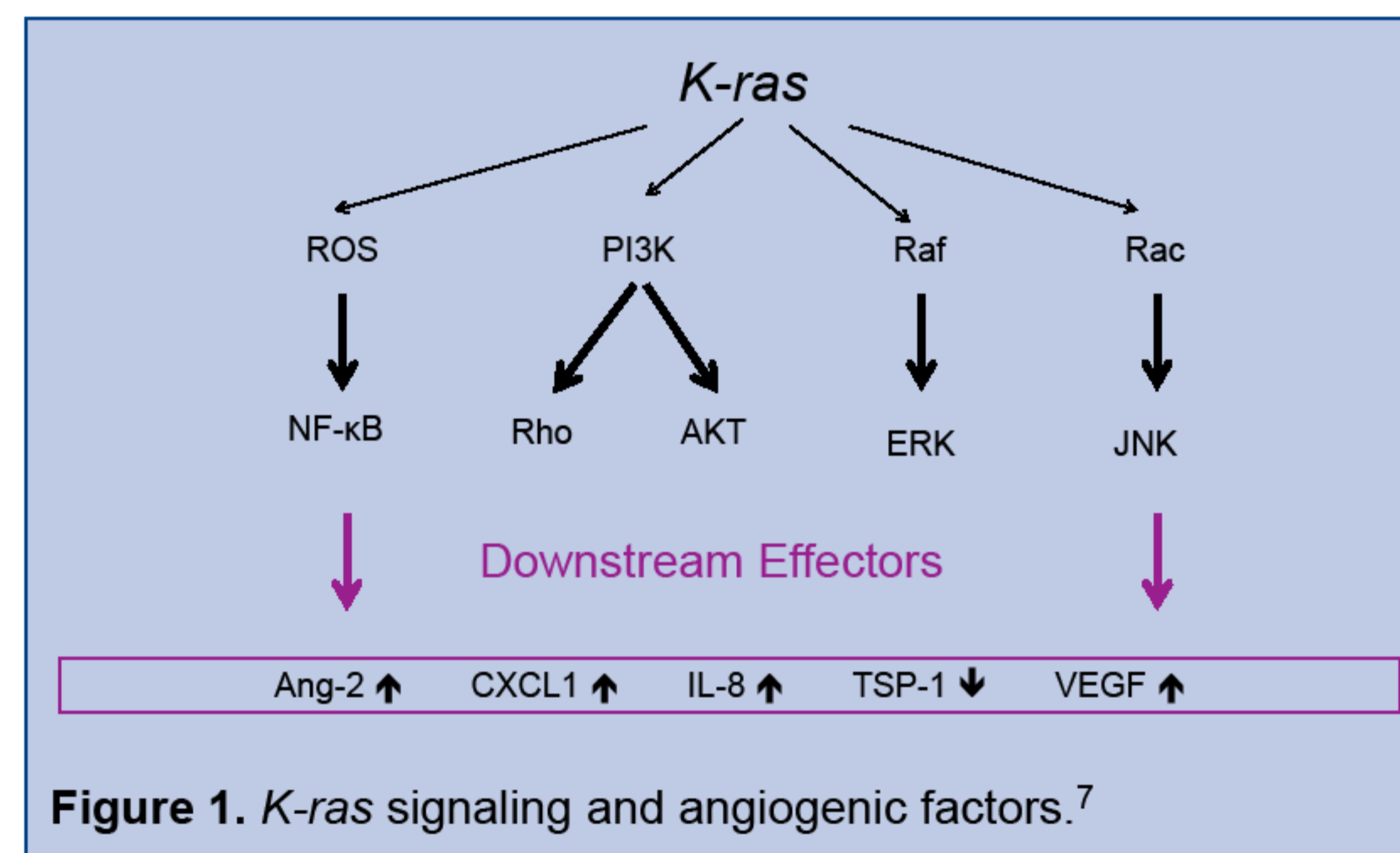


Figure 1. *K-ras* signaling and angiogenic factors.<sup>7</sup>

## OBJECTIVE

- To describe the clinical benefit of BV according to *K-ras* mutation status in patients with mCRC

## METHODS

- Study AVF2107 was a placebo-controlled randomized phase 3 trial of irinotecan, fluorouracil, and leucovorin (IFL) ± BV<sup>1</sup>
- Tumor samples were available from 230 of the 812 enrolled patients
- After microdissection, tumor samples underwent DNA sequence analysis for *K-ras* mutation<sup>6</sup>
  - Selected primers covered mutations in codons 12 and 13
- Retrospective correlation of OS, PFS, and overall response rate (ORR) was performed
- Hazard ratios for the BV group relative to the control group were estimated from an unstratified Cox regression model
  - Median PFS and OS durations were estimated using the Kaplan-Meier method
- Safety was summarized on the basis of reports of targeted adverse events previously shown to be associated with BV

## RESULTS OF THE ANALYSIS

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	<i>K-ras</i> subgroup		Overall	
	IFL + placebo (n = 101)	IFL + BV (n = 129)	IFL + placebo (n = 411)	IFL + BV (n = 402)
Median age, y (range)	58 (27–83)	62 (24–80)	60 (21–83)	60 (23–86)
Gender, no. (%)				
Male	54 (53.5)	75 (58.1)	248 (60.3)	237 (59.0)
Female	47 (46.5)	54 (41.9)	163 (39.7)	165 (41.0)
ECOG PS, no. (%)				
0	62 (61.4)	78 (60.5)	227 (55.2)	234 (58.4)
1	39 (38.6)	51 (39.5)	182 (44.3)	166 (41.4)
Mean duration of disease, mo (SD)	12.4 (16.3)	13.2 (22.8)	16.1 (22.0)	15.2 (23.2)
Location of primary tumor, no. (%)				
Colon	83 (82.2)	101 (78.3)	334 (81.3)	310 (77.1)
Rectum	18 (17.8)	28 (21.7)	77 (18.7)	92 (22.9)
Mean serum albumin, g/dL (SD)	3.7 (0.51)	3.7 (0.53)	3.7 (0.54)	3.7 (0.53)
Mean serum alkaline phosphatase, U/L (SD)	172.6 (139.6)	181.0 (163.2)	163.1 (148.9)	165.6 (146.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

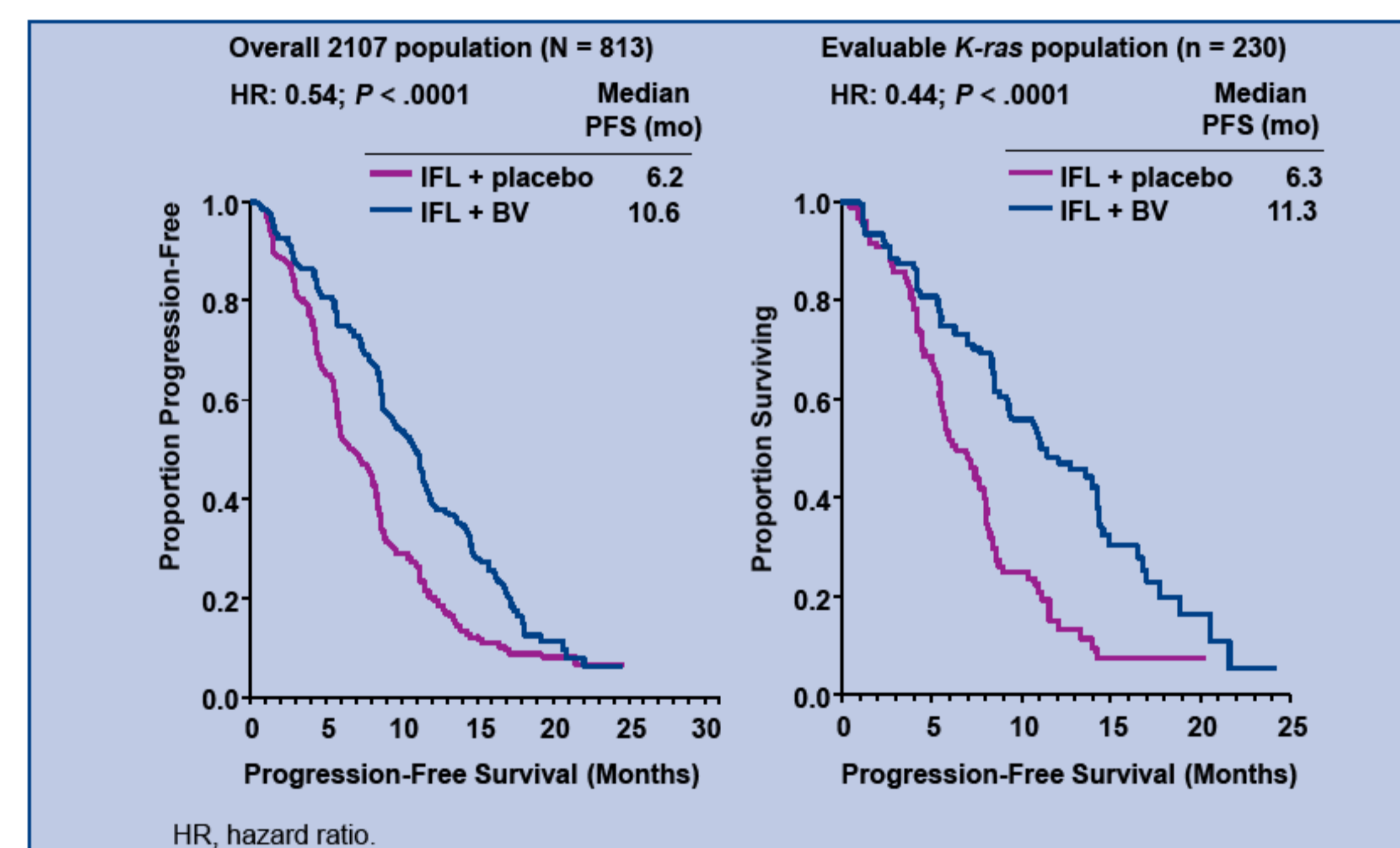


Figure 2. PFS—comparability of results in the overall and *K-ras* evaluable populations.

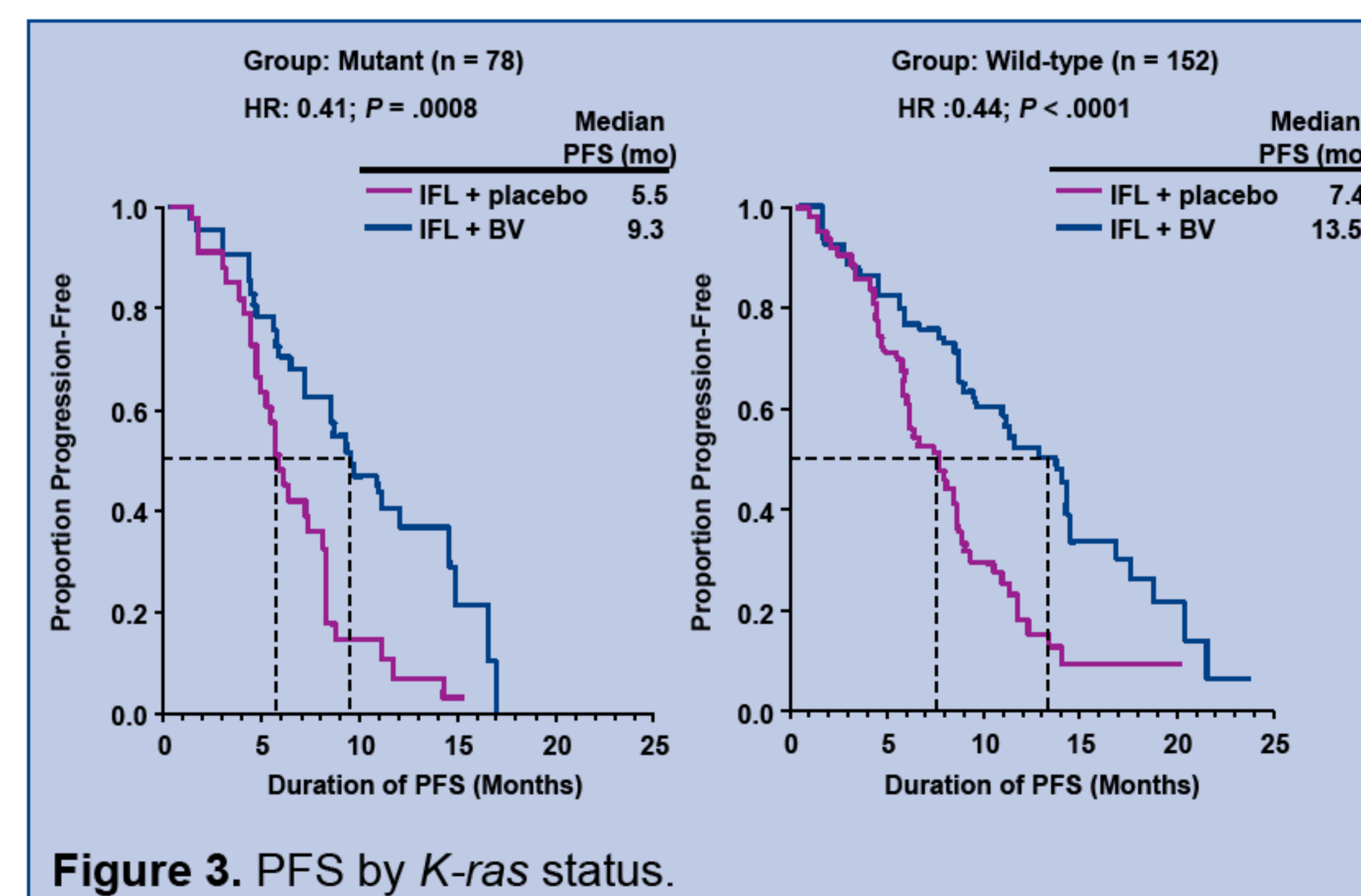


Figure 3. PFS by *K-ras* status.

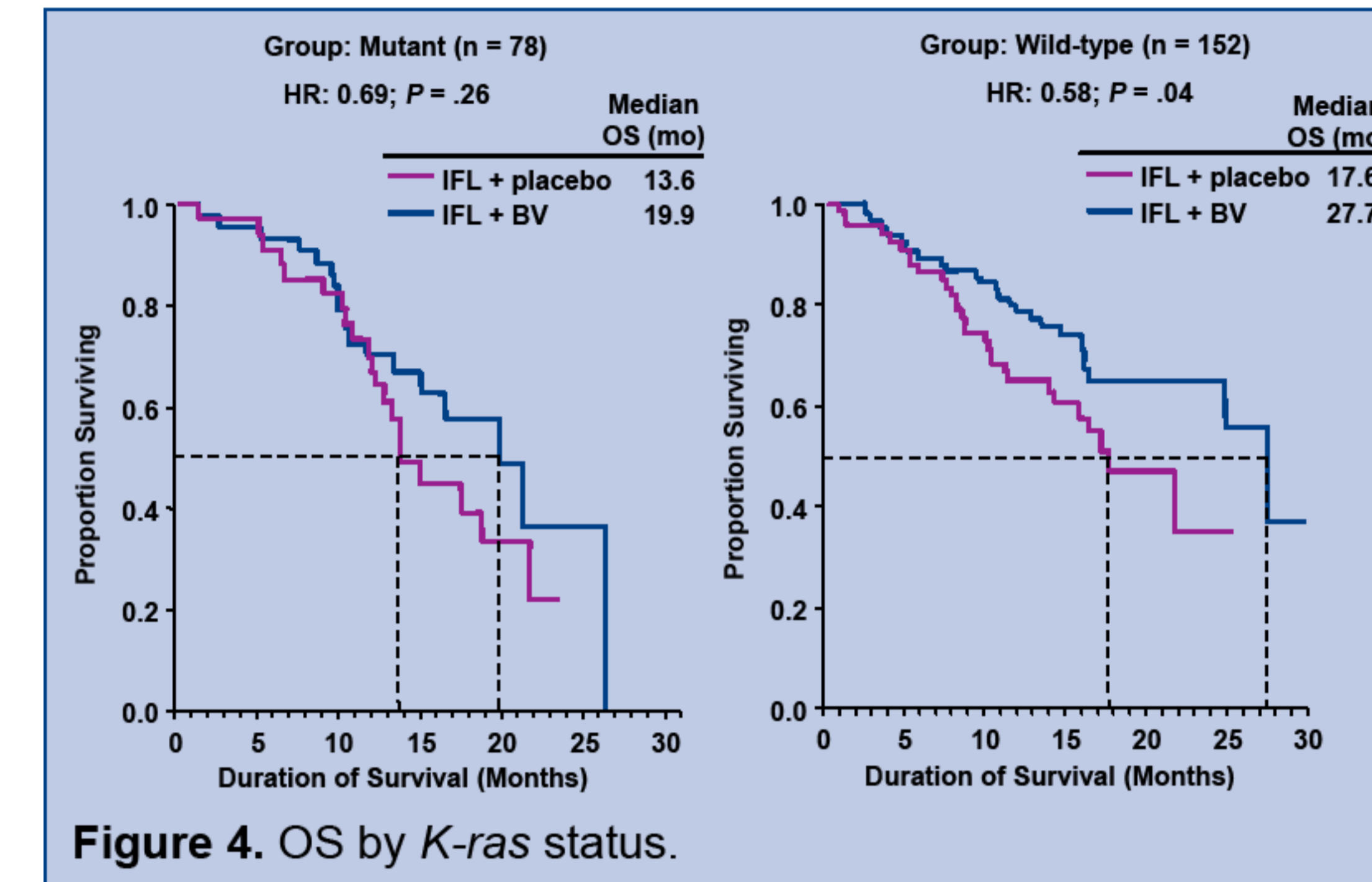


Figure 4. OS by *K-ras* status.

Table 2. Objective Response Rate According to *K-ras* Mutation Status

	Wild-type <i>K-ras</i>		Mutant <i>K-ras</i>		Overall 2107 population	
	IFL + placebo	IFL + BV	IFL + placebo	IFL + BV	IFL + placebo	IFL + BV
ORR, %	37.3	60.0	41.2	43.2	38.6	54.3
CR	3.0	3.5	0.0	6.8	2.0	4.7
PR	34.3	56.5	41.2	36.4	36.6	49.6
P value	.006		.86		.02	

CR, complete response; PR, partial response.

Table 3. Incidence of Adverse Events of General Interest for Treated Patients, by *K-ras* Status

Adverse event, <sup>a</sup> no. (%)	Wild-type <i>K-ras</i>		Mutant <i>K-ras</i>	
	IFL + placebo (n = 67)	IFL + BV (n = 85)	IFL + placebo (n = 34)	IFL + BV (n = 44)
On-study death from any cause	5 (7.5)	2 (2.4)	0 (0)	1 (2.3)
Arterial thrombotic event, any grade	1 (1.5)	1 (1.2)	0 (0)	1 (2.3)
GI perforation, <sup>b</sup> any grade	0 (0)	1 (1.2)	0 (0)	3 (7.0)
Bleeding, <sup>c</sup> grade 3/4	3 (4.5)	2 (2.4)	1 (2.9)	3 (7.0)
Hypertension, grade 3/4	2 (3.0)	8 (9.4)	2 (5.9)	8 (18.6)
Diarrhea, grade 3/4	14 (20.9)	21 (24.7)	4 (11.8)	15 (34.9)

<sup>a</sup> Selected from adverse events reflective of toxicity related to BV or chemotherapy.  
<sup>b</sup> GI perforation was defined as gastrointestinal abscess, perforation, or fistula.  
<sup>c</sup> Reported adverse events included gastrointestinal hemorrhage, hematuria, hemorrhage, hemothorax, melena, rectal hemorrhage.

## STRENGTH AND LIMITATIONS OF THE ANALYSIS

- Patient and tumor characteristics in the *K-ras* subgroup are comparable to those in the overall study population
- The incidence of *K-ras* mutation is within the expected range based on previous reports
- Analyses are of a retrospective nature
- A substantial proportion of the study population was not available for *K-ras* testing
  - Risk of an unintentional selection bias
- A relatively small sample size precludes a definitive assessment of the presence or absence of an interaction

## CONCLUSIONS

- In this analysis, *K-ras* mutation did not predict for lack of benefit from BV treatment
  - BV provides significant clinical benefit in patients with mCRC expressing either mutant or wild-type *K-ras*
  - These findings suggest the independence of the VEGF and RAS signaling pathways regarding the therapeutic effect of BV
- ORR was increased with BV treatment in the wild-type *K-ras* group; no difference was observed in the mutant *K-ras* group
- *K-ras* testing is not warranted in the selection of patients for BV-based therapy in mCRC

## REFERENCES

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