Prevalence of *RAS* Mutations Among Patients With Metastatic Colorectal Cancer: A Pooled Analysis of Randomized Controlled Trials

Abstract 520

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Background and Objectives

- Use of EGFR inhibitors to treat metastatic colorectal cancer (mCRC) requires prior confirmation of wild-type *RAS* mutation status (exons 2, 3, 4 for *KRAS* and *NRAS*)
  - There is a need to understand the epidemiology of wild-type vs mutant *RAS* status, in order to identify treatment options for patients

Objectives:

- To estimate the prevalence of *RAS* mutations overall and by demographic and clinical factors in mCRC patients
- To estimate *RAS* mutation prevalence by exon amongst mCRC patients
- To estimate prevalence of other *RAS* mutations (*KRAS* exons 3, 4, and *NRAS* exons 2, 3, 4) in mCRC patients of known wild-type *KRAS* exon 2 status
- To estimate prevalence of *BRAF* amongst mCRC patients

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Methods

- Retrospective pooled analysis of data from 5 RCTs
  - 3 phase III studies included mCRC patients irrespective of *RAS* mutation status[1-6]
  - 2 studies included mCRC patients with wild-type *KRAS* exon 2 tumor status[7-8]
- Patients had been treated with panitumumab, chemotherapy, and other targeted therapies or best supportive care
- *RAS* status testing:
  - Studies A, B, D, and E: Bidirectional Sanger sequencing at a single US laboratory, as previously described[2,4,7,8]
  - Study C: *RAS* status also tested by bidirectional sequencing; additional data were obtained with 5% sensitivity[6]

1. Douillard JY, et al. *J Clin Oncol.* 2010;28(31):4697-4705. 2. Douillard JY, et al. *N Engl J Med.* 2013;369(11):1023-1034. 3. Peeters M, et al. *J Clin Oncol.* 2010;28(31):4706-4713. 4. Peeters M, et al. *J Clin Oncol.* 2014;32(Suppl 3): Abstract LBA387. 5. Van Cutsem E, et al. *J Clin Oncol.* 2007;25(13):1658-1664. 6. Peeters M, et al. *Clin Cancer Res*. 2013;19(7):1902-1912. 7. Van Cutsem E, et al. *Clin Cancer Res.* 2014;20(16):4240-4250. 8. Schwartzberg LS, et al. *J Clin Oncol.* 2014;32(21):2240-2247.

NGS, next generation sequencing; RCT, randomized, controlled trial.

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Results

- **3,196 mCRC patient data were combined across 36 countries**

From a total of 2,832 mCRC subjects included in the three phase III studies:

- **The overall prevalence of *RAS* mutations was 55.9% (95% CI: [53.9%, 57.9%])**
- **The most frequent location of *RAS* mutations was *KRAS* exon 2 with an estimated prevalence of 42.6% (95% CI: 40.7%, 44.5%])**

From a total of 1,860 mCRC patients of wild-type KRAS exon 2 status (all five studies):

- **The prevalence of other *RAS* mutations (*KRAS* exons 3, 4 and *NRAS* exons 2, 3, 4) in patients with wild-type *KRAS* exon 2 status was 19.1% (95% CI: [17.2%, 21.1%])**

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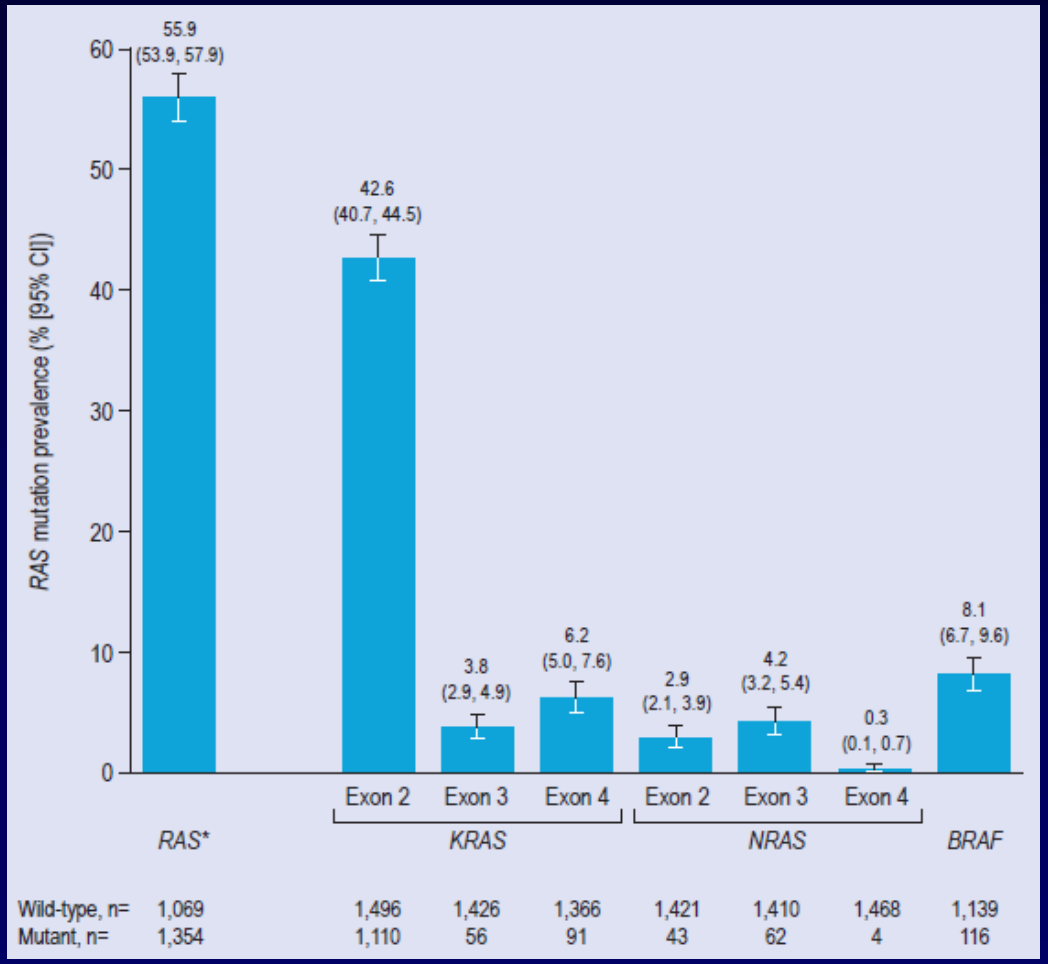
Results: Overall *RAS* Mutation Prevalence in All Patients With mCRC in the Three Phase III Studies



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Results

- *RAS* mutation prevalence was higher in females (*P* = .030)
- *RAS* mutation prevalence was statistically significant between countries with over 50 patients included (*P* = .007)
  - The *RAS* mutation prevalence ranged from 45.1% (95% CI: [39.7%, 50.5%]) for Belgium to 65.6% (95% CI: [53.3%, 76.2%]) for France
- The *RAS* mutation estimate varied by study with a significantly lower estimate observed in the phase III study reported by Douillard et al, 2010[1] and 2013[2] (*P* = .001)
- *BRAF* mutation prevalence was 8.1% (95% CI: [6.7%, 9.6%])

1. Douillard JY, et al. *J Clin Oncol.* 2010;28(31):4697-4705. 2. Douillard JY, et al. *N Engl J Med.* 2013;369(11):1023-1034.

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Conclusions

- This large retrospective pooled analysis of randomized clinical trials provides the most robust prevalence estimates of *RAS* mutations to date
- The overall prevalence of *RAS* mutations in mCRC patients was estimated as 55.9% (95% CI: [53.9%, 57.9%])
- There seems to be little variation on *RAS* mutation prevalence across trial population demographics and clinical characteristics
  - The only variables showing differences in *RAS* prevalence were gender and country where the patient was enrolled

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