Role of KRAS let-7 LCS6 SNP in metastatic colorectal cancer patients

We read with interest the study by Zhang et al. [1] on the association between the LCS6 T/G variant (rs61764370) and
response in wild-type codons 12 and 13 KRAS (wt KRAS) metastatic colorectal cancer (mCRC) patients treated with cetuximab monotherapy. The authors reported that patients with wt KRAS and with LCS6 T/T genotype (55 cases) had worse objective response rate (ORR) compared with patients (12 cases) with T/G or G/G genotype (G-allele), 9% versus 42% ORR, respectively ($P = 0.02$). Moreover, it was shown that patients with G-allele had also a longer progression-free survival (PFS) and overall survival (OS). At the same time, the authors warn against the fact that analysis does not reach statistical significance because of the small sample size ($P > 0.05$).

Di Nicolantonio et al. [2] and Loupakis et al. [3] found that wt BRAF is required for response to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (moAbs), panitumumab or cetuximab, in mCRC and that the V600E mutation (mt BRAF) represents approximately 10% of all mutations responsible for resistance to anti-EGFR moAbs. Notably, Loupakis et al. [3] also included the analysis of KRAS mutations in codon 61 (about 8% of cases). Both studies also showed that mt BRAF patients have an ORR of 0% versus 32% in wt BRAF patients. Recently, Tol et al. [4] in a retrospective analysis in 516 mCRC patients found that the mt BRAF status is associated with significantly adverse PFS and OS, in patients treated with chemotherapy plus bevacizumab/cetuximab ($P = 0.01$ and $P = 0.001$, respectively), and chemotherapy plus bevacizumab alone ($P = 0.003$ and $P = 0.002$, respectively). They concluded that mt BRAF is a negative prognostic marker in patients with mCRC and this effect, in contrast to KRAS mutation, is not restricted to anti-EGFR therapy.

We recently published a study similar [5] to that performed by Zhang et al. on the association between the LCS6 single nucleotide polymorphism (SNP) and survival outcomes in patients with mCRC treated with cetuximab/irinotecan, but we included a comprehensive analysis of codons 12, 13, and 61 in KRAS and mt BRAF. We found that patients with wt KRAS and wt BRAF and with LCS6 G-allele showed worse OS ($P = 0.001$) and PFS ($P = 0.004$) than T/T genotype carriers (confirmed in the multivariate model including the KRAS status). Apparently, these two papers report conflicting results, but to reach a firm conclusion, it would be of interest to know the percentage of mutated 61 KRAS and the BRAF status in the 55 patients with LCS6 T/T genotype analyzed by Zhang et al. In fact, if we consider that about 18% of wt 12–13 KRAS patients could carry a mutated codon 61 KRAS or BRAF (8% of 61 KRAS plus 10% of BRAF, therefore approximately 9–10/55 cases), the nonresponders to cetuximab among the LCS6 T/T patients could be attributed at least in part to the presence of KRAS or BRAF mutations. The same considerations could apply to OS and PFS analyses.

Finally, the authors should comment on the fact that in the abstract presentation of their work at the 2009 American Society of Clinical Oncology meeting [6], they reported an analysis of the LCS6 variant in patients from the IMCL-0144 trial and the EPIC trial. In this report, T/T carriers with mt KRAS who were treated with irinotecan/cetuximab in the EPIC trial had significantly better PFS of 12 weeks (95% confidence interval (CI) 6.4–18) compared with those harboring a G-allele with median PFS of 6.4 weeks (95% CI 5.7–7) ($P = 0.037$ log-rank test). Also, in the multivariate analysis, the polymorphism remained independently associated with PFS in the EPIC [6]. Notably, this finding parallels our results [5].

In summary, we appreciate the study of Zhang et al., but additional data could help the readers to evaluate the results and in defining the true role of LCS6 SNP in response to biologics.

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**disclosure**

The authors declare no conflict of interest.

**references**


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