CORRESPONDENCE

Reply to Comment on ‘Clinical significance of BRAF non-V600E mutations on the therapeutic effects of anti-EGFR monoclonal antibody treatment in patients with pretreated metastatic colorectal cancer: the Biomarker Research for anti-EGFR monoclonal Antibodies by Comprehensive Cancer genomics (BREAC) study’

In a recent comment on our manuscript “Clinical significance of BRAF non-V600E mutations on the therapeutic effects of anti-EGFR monoclonal antibody treatment in patients with pretreated metastatic colorectal cancer: the Biomarker Research for anti-EGFR monoclonal Antibodies by Comprehensive Cancer genomics (BREAC) study”,1 Dankner and Rose (2018)2 suggested insightful and important limitations of our study. Dankner and Rose discussed that it remains to be seen whether all BRAF non-V600E mutations in mCRC tumours are equally predictive of non-response to EGFR inhibitors, based on the recent classification of BRAF mutation as well as their original data. They reported that some class 3 BRAF mutants (i.e., G446V) were sensitive to anti-EGFR antibodies in both clinical and preclinical models. We agree with the speculation that it is not the same of BRAF non-V600E mutations, and we concluded that ‘certain’ BRAF non-V600E mutations might contribute to a lesser benefit of anti-EGFR monoclonal antibody treatment. We also consider the hypothesis of the difference in RAS dependencies of class 3 BRAF mutations as intriguing.

We would like to address the points raised by Dankner and Rose in their comment regarding our data. They pointed out the differences in overall survival (OS) between the two studies and our cohort. Firstly, we would like to highlight that the definition of OS was different; survival was calculated from the time of first diagnosis of metastatic disease in Jones et al. and from the start of later line treatment in our study. Furthermore, our cohort only consisted of patients that survived until later line treatment. Truly aggressive disease cases might not complete later line treatment. One of the explanations for our cohort might be the inclusion of very selective patients in our later line treatment cohort; patients with highly aggressive disease and those harbouring BRAF V600E were inevitably excluded.

We re-summarised the individual PFS data of BRAF non-V600E in Table 1. One case with D495G, class 3, showed long stable disease (SD) as efficacy. However, 4 of 7 were not reported in BRAF categories by Yao et al., regardless of their statement that the majority of BRAF non-V600E mutations in CRC are class 3 mutations. Furthermore, we do not have enough data in Asian populations and the racial differences in BRAF/KRAS mutation rates are well known; this was discussed in our discussion. In our cohort, only 2 cases were categorised as class 3, and the kinase activity of the other unclassified cases was classified high or intermediate. Regarding the response rate, other than the sample size, the proportion of BRAF class category might be affected for efficacy in this cohort.

We recognise the limitations of this study: a retrospective study with a small number of subgroups of BRAF non-V600E mutations. Further investigation in much larger scale data set from clinical trials such as randomised control trials is necessary to conclude the significance of anti-EGFR antibody treatment for each subtype of BRAF non-V600E mutational variants.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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Table 1. Individual data of patients harbouring the BRAF non-V600E mutation

| ID         | Amino acid variation | Kinase activity | PFS (mo) | Class* |
|------------|----------------------|-----------------|----------|--------|
| GQ0XS      | G469A                | High            | 2.8      | NR     |
| GLCh7      | L485F                | Intermediate    | 2.1      | NR     |
| SC12PCQ3IA02 | Q524L             | Intermediateb   | 2.3      | NR     |
| G90JR      | L525R                | Highb           | 4.0      | NR     |
| GQ4U5      | D594G                | Impaired        | 6.6      | III    |
| GUGZG7     | D594G                | Impaired        | 2.4      | III    |
| GS3A5      | V600R                | High            | 2.1      | I      |

mo month, NR not reported, PFS progression-free survival *Class (by Yao et al, 2017) bOur reported data

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