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Reply to FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer–subgroup analysis of patients with *KRAS*-mutated tumours in the randomised German AIO study KRK-0306

We read with great interest the article of Stintzing et al. published in *Annals of Oncology* on July 2012 [1] and would make a few remarks.

The results of this unplanned retrospective analysis, carried out on 96 *KRAS*-mutated colorectal cancer patients, did not show any substantial difference in terms of response rate, progression-free and overall survival between anti-epidermal growth factor receptor- and anti-vascular endothelial growth factor-based treatments. These results may be just related to operative bias: for example, the similar response rate observed in the cetuximab and bevacizumab arms is explainable by the lack of independent radiological review and the limitation of standard radiological assessment for anti-angiogenic treatments, which may delay disease progression mainly through disease stabilization: in fact, biological response is often characterized by a reduction of lesions' density, without a substantial RECIST response [2].

Overall survival seemed to favour cetuximab over bevacizumab (22.7 versus 18.7 months), although this difference was not statistically significant (HR = 0.86, 95% CI, 0.55–1.35; $P = 0.55$). Since cetuximab arm was affected by a higher and earlier dropout rate, it is possible that lower median treatment duration in the cetuximab arm may have led to earlier initiation of effective bevacizumab-based second-line treatment. In fact, half of the patients treated with FOLFIRI plus cetuximab received subsequent bevacizumab-based regimens. Not surprisingly, a combination of bevacizumab and oxaliplatin-based regimens was shown to prolong overall survival in the second-line setting [3].

Even though the addition of cetuximab to FOLFIRI regimen seems to be at least not detrimental for progression-free survival in KRAS-mutated patients, [4] the apparent lack of benefit from the addition of bevacizumab could also derive from confounding factors and imbalance between prognostic factors rather than *KRAS* mutation itself. For example, the rate of patients undergoing surgery was twice as high in the cetuximab arm: although this is clearly not attributable to treatment (given the identical response rate in both the arms), a multimodality strategy may have improved progression-free and overall survival in patients treated with the cetuximab-based combination.

The authors stated that *KRAS* G13D mutations, found in 20% of cases, may be associated with poorer prognosis independently of the treatment arm. However, in the recently published pooled analysis of CRYSTAL and OPUS trials, *KRAS* G13D-mutated patients receiving first-line chemotherapy alone failed to show a statistically significant difference in terms of progression-free survival and overall survival, when compared with other *KRAS*-mutated subtypes [5].

We believe that the study of Stintzing et al. is particularly valuable because it stimulates the investigation on the predictive role of *KRAS* mutation in bevacizumab-based treatment. However, given the small sample and evidence of great benefit of bevacizumab independently of KRAS status, [6] the preliminary nature of these results add a few more to what was previously known and any conclusions about the present analysis should be drawn very carefully.

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Association of telomerase expression with recurrence of sacral chordoma

Originated from the remnants of the notochord in the process of fetal development, chordoma is a rare, slow growing and locally invasive low-grade malignant tumor with an annual incidence rate of 1/8 000 000 [1]. There are no standard prognostic markers in this disease. This retrospective study assessed telomerase in 20 patients of sacral chordoma (10 males and 10 females, aged 18–77 years). The samples of tumor tissues were obtained intraoperatively from all the patients, and samples of normal tissues 3 cm adjacent to the tumors were from seven patients. Follow-ups were scheduled every 3 to 6 months. Recurrence was evaluated from clinical examinations and imaging. Surgical resection samples were fixed in formalin and embedded in paraffin block before sliced into 4 μm in thickness for telomerase staining. Samples of colorectal cancer were used as the positive control and phosphate-buffered saline (PBS) was as the negative control. The scale of percentage of the positive cell number was defined as 0, 0%; 1, 1–25%; 2, 26–50% and 3, >50%. The scale of the color intensity was 0, none; 1, light brown; 2, brown and 3, dark brown. The overall score was summarized from both scales as 0, negative; 1–4, weakly positive and 5–6, strongly positive.

Among the 20 patients, eleven of them had relapse. Recurrence rates of 1, 3, 5 and 10 years were 5, 25, 55 and 90%, respectively. Telomerase expression was positive in all 20 cases (11 strongly positive and 9 weakly positive) (Fig. 1). The peritumoral normal tissues had telomerase expression negative. Positive expression of telomerase with chordoma recurrence was significantly higher than those without recurrence

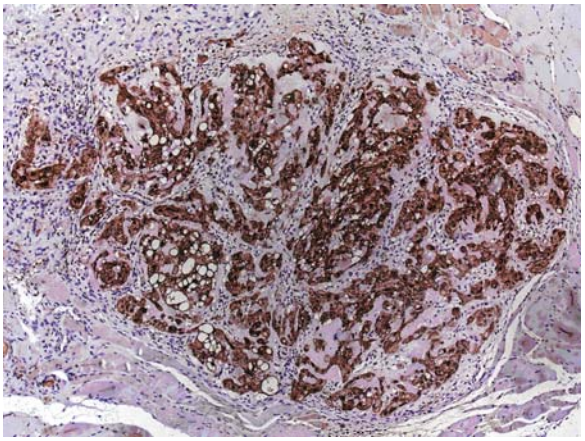

Figure 1. A typical telomerase expression of strongly positive chordoma (streptavidin biotin peroxidase complex × 100).

($P = 0.003$). Telomerase expression in relapse was significantly different from that without recurrence ($P < 0.001$).

To our knowledge, 20 patients are the largest clinical series in sacral chordoma. Recurrence after surgical resection is a common occurrence. Our study demonstrated the association of telomerase expression with recurrence, suggesting that the telomerase expression could be another predictor of recurrence and survival.

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disclosure

The authors have declared no conflicts of interest.

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