Commentary

Can we effective use sym004 in tumours harboring EGFR extracellular domain mutations?

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Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of death (1). The therapeutic options available for the treatment of metastatic CRC have significantly increased over the past years. Together with the advances in surgical techniques, the introduction of irinotecan and oxaliplatin first and drugs targeting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) later, have led to a median overall survival (OS) now approaching 30 months (2).

Cetuximab is a chimeric murine/human mAb, whereas panitumumab is a fully humanized monoclonal antibody (mAb); both of them bind to the extracellular ligand-binding sites of EGFR leading to the inhibition of EGFR phosphorylation and activation of downstream intracellular signaling pathways. These two mAbs have been granted approval for the upfront treatment of metastatic CRC. Even among patients who initially respond to EGFR mAb, the duration of this response is usually transient and does not last >12 months when secondary resistance occurs (3).

Some recent studies have addressed the molecular mechanisms underlying acquired resistance. Accumulating evidence suggests that *RAS* wt tested tumors may harbor small *RAS* mutated subclones at diagnosis that emerge and thus mediate secondary resistance under the selective pressure of treatment with EGFR antibodies (4-6).

Other mechanisms of acquired resistance include development of the S492R mutation in the ectodomain of the EGFR, as well as amplification of tyrosine kinase receptor genes HER2 or MET (7-11). Moreover, three additional EGFR alleles have been recently observed: S464L, G465R and I491M: structurally these mutations are located in the cetuximab-binding region, except for the R451C mutant, whereas functionally they all prevent binding to cetuximab (8).

In this issue of clinical cancer research, Sánchez-Martin *et al.* published efficacy of Sym004 to circumvent cetuximab resistance driven by *EGFR* ECD mutations. Sánchez-Martin *et al.* detected that Sym004 effectively inhibits proliferation and EGFR downstream signaling in cetuximab-resistant derivatives harboring the S492R (12). Arena *et al.* was detected *EGFR* S492R mutation in 3 out of 37 postcetuximab tissue samples (8%) (8), while Newhall *et al.* reported 16% of S492R EGFR mutation detection in 239 post-cetuximab plasma samples (9). When S492R EGFR mutation devolops both panitumumab and Sym004 were effectively inhibiting the proliferation of the parental DiFi as well as DCR7 cells. Sym004 doesn't increase the population eligible for anti-EGFR treatment compared with panitumumab.

Preclinical data demonstrate a superior antitumor effect of Sym004 in comparison with cetuximab. However side effects restricting the use of anti-EGFR treatment, such as acneiform exanthema Common Toxicity Criteria Adverse Events (CTCAE) grade 3, occurred in both of the tested dosages in more than 60% of the patients. Clearly we know additive effect of Anti-EGFR therapies when added to chemotherapy. For offering Sym004 an treatment option in anti-EGFR naïve patients, despite its increased side effects, it needs to be defined optimally by head-to-head comparisons with the established antibodies.

The G465R mutation has been shown to emerge in cetuximab-resistant cell lines as well as in patients with disease progressing to panitumumab. This mutation is effectively targeted by Sym004. Friederike Braig *et al.* found an acquired *EGFR G465R* ectodomain mutation after treatment with panitumumab and FOLFOX in post-treatment tumor material in 1 out of 37 patients (13). But we don't know the actual frequency of this mutation. Sym004 can take a role again tumors harboring G465R mutation after cetuximab therapy So the patient population eligible for anti-

EGFR treatment be increased by Sym004 when compared with panitumumab or cetuximab. Pannitumumab and Sym004 both are active drugs binding to other ektodomain receptor mutations such as S492R and K467T. But increased drug toxicity due to Sym004 should be considered.

The aim for the near future for mCRC treatmant is the development of personalized anti-cancer drugs through definition of the mutation profile of key signaling genes in individual tumors. To understand the mechanisms of treatment resistance and develop new treatments via these reasons seem to be a rational approach.

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Footnote

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