Editorial

How to overcome resistance to therapy?

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In this issue of *Journal of Gastrointestinal Oncology*, Frank *et al.* present their experience with capecitabine and lapatinib in patients with chemo-resistent colorectal adenocarcinoma (1).

Expected median overall survival (mOS) for untreated patients with metastatic colorectal cancer (mCRC) is only around 6 months, however modern combination chemotherapy with irinotecan followed by oxaliplatin (or vice versa) with targeted therapy prolongs mOS to almost 24 months, but only in fit patients who are candidates for clinical trials (2).

At the time of further progression, many patients are still in an excellent performance status, but efficacy of further chemotherapy is disappointing with response rate less than 5%, median progression-free survival (mPFS) less than 2 months and mOS around 4 months, and therefore therapy is not recommended outside clinical trials.

A new treatment principle was introduced with the implementation of antibodies against EGFR, even though expression of EGFR does not correlate with outcome. Cetuximab and panitumumab are effective in chemoresistant mCRC in patients with KRAS wildtype (KRASwt) tumors, but even more successful in combination with irinotecan with tumor regression in 30-40% of patients and mOS around 12 months (3).

In patients with KRAS mutated (KRASmut) tumors and in patients with EGFR resistant KRASwt tumors, there is presently no valuable therapy. Still many patients are in an excellent performance status, and there is an unmet need of further efficient treatment options in these patients.

Lapatitinib (Tykerb©) is a tyrosine kinase inhibitor (TKI) of both EGFR (HER1) and HER2. These receptors share a common pathway leading to cell proliferation. Overexpression of EGFR and HER2 is associated with a worse prognosis in many malignancies, and recent data suggests that upregulation of HER2 may be seen after EGFR inhibition and may be involved in primary and acquired resistance to anti-EGFR therapy (4). It is thus an attractive hypothesis to block both HER1 and HER2 in colorectal cancer, both as an initial therapeutic strategy, as well as after acquired resistance to prior anti-EGFR therapy. It is therefore surprising that a previous study showed no efficacy of lapatinib in colon cancer (5), since responses could have been expected in the 4% HER2 amplified tumors or the 10% of unselected CRC shown to respond to monotherapy EGFR monoclonal antibodies. HER1-2 specific TKI potentially do not block HER1, HER3, HER4 interactions that could be inhibited by HER1 targeting antibodies. Pan-HER TKI inhibitors would potentially address this, but although final results are awaited, phase I data in mCRC with pan HER inhibitors as mono-therapy does not look promising. Other functions of HER1 targeting monoclonal antibodies, such as receptor internalisation and degradation may be key for the mode of action in colorectal cancer. In this study the authors decided to assign lapatinib another chance by relying on its potential synergy with capecitabine (6). However, the study was terminated early due to the pre-specified stopping criteria (Simons stage 2 design) as no responders were seen, and the authors concluded that "the combination of capecitabine and lapatinib failed to show any clinical activity in heavily pretreated patients with colorectal adenocarcinoma". We agree with their conclusion, however we think that objective response might not be an appropriate primary endpoint

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in late lines of therapy as the chance of objective response is very low in this setting leading to the risk of missing a potential clinical relevant benefit. This was recently noticed in the CORRECT trial, comparing regorafinib - an oral multikinase inhibitor of angiogenic, oncogenic, and stromal kinases - to best supportive care in mCRC patients, who had progressed after all approved standard therapies (7). Noteworthy response rate was only 1%, but despite lack of tumor regression, disease-control was seen in almost half of patients, and this translated into a significantly prolongation of median PFS (1.7 to 1.9 months; HR 0.49) and OS (5.0 to 6.4 months; HR 0.77). In the Franck *et al.* study, PFS was 2.1 months and OS 6.8 months, which are almost identical to the CORRECT study. It can therefore not be excluded that treatment with lapatinib may cause stabilisation of disease with prolongation of life without objective response according to RECIST in a selected group of patients.

There has been great progress in understanding of and treatment of mCRC in recent years. However our knowledge on the mechanisms contributing to disease progression and resistance to therapy are still sparse, and decisions on treatment strategy in later lines are most often based on the profile in the primary tumor. In breast cancer it has been demonstrated that there might be discordance in the molecular profile of the primary and metastases with potential implications for therapy (8). It is therefore very important that clinical studies - also in late lines of therapy - are combined with translational studies including re-biopsy of metastases resulting in new important knowledge which are the basis for further personalized treatment in patients with mCRC.

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