Editorial

TAILORing targeted therapies to the right patient at the right time: how close are we?

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The therapeutic landscape of metastatic colorectal cancer has dramatically evolved over the last decade leading to improved survival outcomes. Patients can now achieve median survival times in excess of 2 years with the use of targeted therapies that have become an integral part of colon cancer therapeutics (1). The administration of multiple lines of therapy ultimately leads to patient exposure to a series of therapeutic agents with accumulation of incremental survival benefits, even in the third- or fourth-line setting (2). However, controversy still remains regarding the optimum first line therapy selection, a therapy that bears the most influential positive impact on prolongation of progression-free and overall survival (OS). This inevitably leads to the unanswered question of optimal therapy sequencing when treating colon cancer patients (1,3).

Monoclonal anti-EGFR antibodies (cetuximab, panitumumab) are a valid option for the treatment of patients with KRAS and NRAS exons 2, 3, 4 wild type metastatic colorectal cancer where clinical benefit has been established through large scale clinical trials. The results of the phase III CRYSTAL study demonstrated that adding cetuximab to first-line irinotecan-based chemotherapy for treatment of patients with extended RAS wild type metastatic colorectal cancer significantly improves OS, progression free survival (PFS) and objective response rates (ORR) when compared to FOLFIRI alone (4). However the combination of cetuximab with oxaliplatin-based chemotherapy in the first-line setting had not been extensively validated. Until now, only the randomized phase II OPUS trial demonstrated that the combination of oxaliplatin with cetuximab improves first-line PFS and ORR whereas the MRC phase III COIN trial did not confirm those results, possibly as a result of the bolus FU or oral fluoropyrimidine regimens used alongside oxaliplatin and anti-EGFR (5,6). The phase III TAILOR trial is the first to investigate the use of FOLFOX4 combined with cetuximab in the first line setting of metastatic colorectal cancer patients. Despite lack of high-level evidence, the regimen is widely used by oncologists in chemonaïve patients with advanced colorectal cancer, consequently the TAILOR trial results of improved PFS, its primary endpoint, but also ORR and OS, should be accepted with relief. Patients in TAILOR harbored tumors that were KRAS/NRAS exon 2, 3, 4 wild type (7).

Primary tumor location has also emerged as a prognostic marker as well as a surrogate marker for therapy selection in the first line setting (3). Retrospective analyses from large scale studies but also more recent meta-analyses have confirmed higher response rates and an OS advantage when anti-EGFR monoclonal antibodies are used with doublets of chemotherapy in RAS wild type left-sided tumors, as compared to chemotherapy-only or chemotherapy + bevacizumab regimens (8). Moreover, even in cases of right-sided tumors anti-EGFRs can be a promising option by their high tumor regression rates, when cytoreduction is the aim of first line therapy either for proceeding to later

metastasectomy or for relief of symptoms/impending life threating conditions due to extensive tumor load. The TAILOR phase III study confirms the effectiveness of anti-EGFRs in left and right sided tumors by citing ORR, median PFS and OS of 66.4% *vs.* 44.4%, 9.2 *vs.* 7.6 months and 22 *vs.* 11.3 months in left and right-sided colonic tumor patients, respectively.

BRAF mutation is considered by many oncologists as a negative predictive marker to anti-EGFR therapy in metastatic colon cancer, and a dismal prognostic characteristic. To date, patients with BRAF mutant tumors are considered candidates for intensive triplet chemotherapy upfront in combination with anti-angiogenesis targeted therapy, in an effort to favorably modulate the aggressive, adverse prognosis of such patients, who often do not make it to second line therapy due to fulminant disease course. The rather poor results reported with the use of anti-EGFR targeted therapy in the BRAF-mutant subset of patients are confirmed by data from TAILOR. BRAF wild type tumors derived greater benefit from the use of cetuximab contrary to BRAF mutated ones where a possible negative treatment effect might be suggested. Effective management of patients with BRAF mutant tumors remains elusive despite emergence of some preliminary promising results. The combination of triplet chemotherapy with anti-EGFR as used in the randomized phase II VOLFI trial resulted in ORR of 76% for the combination versus 22% for triplet chemotherapy alone, however these responses were short-lived and PFS, OS were not improved (9,10). Encouraging results recently announced from phase II and the ongoing BEACON phase III trial suggest that inhibiting BRAF, MEK and abrogating the reactivation of EGFR by administering cetuximab may prove effective in BRAF-mutant tumors and change the current treatment algorithm if ultimately verified (11,12).

In a more pessimistic note, what is noteworthy regarding the TAILOR phase III study is the rather low median OS of 20.7 months in the combination therapy arm, in sharp contrast to median OS of 33 months reported in FIRE 3 and 32 months reported in GALGB/SWOG 80405 (the latter mostly using FOLFOX regimens) (9,13). The same results were also reported from phase II PEAK trial in which a 34.2-month median OS was reported in the subset of patients receiving mFOLFOX6 plus panitumumab (14). As already outlined by the investigators of TAILOR, a relatively small proportion of patients underwent second line treatment and a limited access to targeted therapy in further lines of treatment was also the case in the population studied, whereas data on metastasectomy after conversion therapy are not provided. This reflects differences in the availability, access or choice of therapy administered across the globe and may have contributed to the disappointing, by modern standards, median OS of patients on chemotherapy + anti-EGFR in TAILOR. It also serves as a reminder on the importance of later lines of therapy for optimizing treatment outcomes for patients with advanced colorectal cancer.

Currently, data support the use of anti-EGFR monoclonal antibodies in extended RAS wild type tumors while no specific biomarker has been validated for the use of antiangiogenesis which is also an integral part of colon cancer therapeutics. The multiplicity of available targeted agents for the treatment of metastatic colorectal cancer patients inevitably raises the question of optimal therapy sequencing (15,16). The CALGB/SWOG 80405 phase III trial announced no differences when cetuximab or bevacizumab are used for the first line treatment of RAS wild type colorectal cancer patients in combination with either oxaliplatin or irinotecan regimens. On the other hand, FIRE-3 results support the use of FOLFIRI plus cetuximab over bevacizumab in wild type RAS population due to documented OS advantage. Although the discrepant results of those two studies could be attributed to several confounding factors, discussed in detail in many reviews, the results of TAILOR suggest that oxaliplatin regimens plus cetuximab are a valid and effective option in the first line setting.

Colorectal cancer therapeutics is a field of ongoing research where the ultimate goal is maximum clinical benefit through personalized medicine. Current data are continuously enriched with insights in molecular driver mechanisms shifting the frame of cancer therapeutics from cytotoxic chemotherapy to targeted therapy. The advent of liquid biopsies may further enhance our understanding of those specific molecular drivers and enhance our ability to monitor them in real time and finally, overcome them. The results of the phase III TAILOR study on the combination of FOLFOX plus cetuximab documented superior activity in the first line therapy of RAS wild type metastatic colorectal cancer patients in all relevant metrics (PFS, OS and ORR) over chemotherapy alone. Validation of positive predictive markers that will allow us to identify tumors with activated EGFR pathway signaling suitable for inhibition by cetuximab or panitumumab will further enrich the group of patients benefiting from anti-EGFR approaches.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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