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Every year the American Society of Clinical Oncology Annual Meeting is one of the most awaited events for medical oncologists all around the world. This report briefly summarizes some of the most relevant news in the treatment of metastatic colorectal cancer patients with special regard to notable results from randomized trials in first-line treatment and the maintenance setting, and to new data regarding molecular determinants that will shortly enter the daily clinical practice.

'Building bridges to conquer cancer' was the slogan of the American Society of Clinical Oncology (ASCO) Annual Meeting 2013, which was held in Chicago from 31 May to 4 June, with more than 25,000 attendees. Sessions on colorectal cancer lived up to oncologists' expectations of gaining knowledge of long-awaited and potentially practice-changing results. This brief report will focus on three main questions about the metastatic setting that the presented results try to answer:

- Which is the best first-line biologic for metastatic colorectal cancer (mCRC) patients with *KRAS* wild-type disease? Is the molecular selection according to *KRAS* codon 12 and 13 enough?
- Is there any room for an intensive first-line chemotherapy in mCRC?
- What about maintenance treatment with bevacizumab (bev) ± chemotherapy? Is it mandatory?

Which is the best first-line biologic for mCRC patients with *KRAS* wild-type disease? Is the molecular selection according to *KRAS* codon 12 & 13 enough?

Up until recently, the choice of the targeted agent to be combined with first-line chemotherapy in *KRAS* wild-type patients (the anti-VEGF bev vs the anti-EGF receptor [EGFR] cetuximab [cet]) has been mainly based on cross-trial comparisons of results from Phase III studies and on meta-analyses aimed at estimating the magnitude of benefit provided by each targeted agent [1–4]. While anti-EGFR antibodies were regarded as powerful shrinking agents, bev was preferred as a cytostatic drug, able to delay tumor progression. Results from head-to-head trials were, therefore, highly invoked, in order to support clinical decisions with an evidence-based background.

Sebastian Stintzing (Klinikum Grosshadern and Comprehensive Cancer Center, Munich, Germany) presented in the oral

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abstract session results from the Phase III FIRE-3 trial [5], conducted by the German cooperative AIO group, which randomized 592 *KRAS* wild-type patients to receive 5-fluorouracil/leucovorin + irinotecan (FOLFIRI) plus cet or FOLFIRI plus bev as upfront treatment. The objective response rate (ORR) was the primary end point. In the intention-to-treat population, no differences were reported between treatment arms in terms of ORR (62% in FOLFIRI + cet vs 58% in FOLFIRI + bev; $p = 0.183$) or progression-free survival (PFS; hazard ratio [HR]: 1.06; 95% CI: 0.88–1.26; $p = 0.547$). Nevertheless, a significant advantage in terms of overall survival was evidenced in favor of the upfront anti-EGFR arm (HR: 0.77; 95% CI: 0.62–0.96; $p = 0.017$). These unexpected results need to be further explored and clarified with additional data in order to explain why no differences in ORR or PFS translated into a significant benefit in OS. A suggested hypothesis is that the increased tumor shrinkage induced by cet may lead patients in the anti-EGFR arm to undergo disease progression, as per RECIST, with a lower tumor load, so that the benefit in terms of deepness of response may influence the postprogression history of the disease [6]. Nevertheless, currently, the correlation of deeper response with longer survival in the present trial was not provided. Moreover, data regarding subsequent lines of treatment in both arms will deserve consideration in order to understand whether the sequence of administered agents matters in terms of survival. Further information regarding this head-to-head comparison will soon derive from a larger Phase III trial, by the CALGB and SWOG cooperative groups, C80405, which is randomizing 2900 patients to a first-line doublet plus bev or cet, with OS as the primary end point [7].

With regard to the use of anti-EGFR monoclonal antibodies, a clear message comes from the 2013 ASCO Annual Meeting: a better molecular selection, beyond *KRAS* codon 12 and 13 mutational status, allows identification of a wider population of patients that do not achieve benefit from anti-EGFR. Retrospective analyses of Phase III PRIME (first-line FOLFOX ± panitumumab [pan]) [8],

Phase II PEAK (first-line FOLFOX + bev vs FOLFOX + pan) [9], Phase III 20020408 (advanced lines, pan vs best supportive care) [10] trials consistently show that patients harboring rare *KRAS* mutations in exons 3 and 4, as well as *NRAS* exon 2, 3 and 4 mutations, do not benefit from the anti-EGFR. Even more relevant is the analysis of PRIME trial evidence that the addition of pan to first-line FOLFOX might be even detrimental in patients with *RAS* mutations, which represent approximately 15% of the *KRAS* codon 12 and 13 wild-type patients [8]. Similarly, a pooled analysis, including 35 chemorefractory *NRAS* mutated patients, treated with anti-EGFR monoclonal antibodies in advanced lines, clearly shows that only one (2.9%) of them achieved response, thus supporting the use of these agents only in *RAS* wild-type patients [11].

Is there any room for an intensive first-line chemotherapy in mCRC?

The choice of the upfront chemotherapy and the intensity of the chemobackbone is a crucial issue in the era of targeted agents. Two randomized trials, Phase II OLIVIA [12] and Phase III TRIBE [13], investigated the combination of the three-drug (triplet) regimen 5-fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFOXIRI) with the antiangiogenic bev providing impressive results in terms of both activity and efficacy, with a manageable safety profile. Previous results from a Phase III trial of FOLFOXIRI versus FOLFIRI, reporting a relevant advantage for the triplet in terms of activity (but also PFS and OS) and secondary resections, led to the consideration of such an intensive upfront regimen as a preferable choice when a remarkable tumor shrinkage is required [14].

The Phase II OLIVIA trial randomized 80 mCRC patients with liver-only metastases, defined as initially unresectable by a multidisciplinary team, to receive FOLFOX + bev or FOLFOXIRI + bev [12]. Overall (R0/R1/R2) resection rate, the primary end point, was numerically higher in the FOLFOXIRI + bev arm (61.0 vs 48.7%; $p = 0.271$). The triplet + bev achieved a higher R0 resection rate (48.8 vs 23.1%; $p = 0.017$) and an impressively

higher ORR (80.5 vs 61.5%; $p = 0.061$), with a substantial benefit also in terms of PFS (18.8 vs 12.0 months; $p = 0.0002$), thus confirming the effectiveness of the triplet, combined with bev, in this setting.

Alfredo Falcone presented, on behalf of the Italian GONO group, results from the TRIBE trial, which randomized 508 unresectable mCRC patients to receive upfront FOLFIRI + bev or FOLFOXIRI + bev [13]. The primary end point was met: patients in the experimental arm achieved a significant increase in PFS (12.1 vs 9.7 months; HR: 0.77; 95% CI: 0.64–0.93; $p = 0.006$). The triplet also provided a significant increase in ORR (65 vs 53%; $p = 0.006$), but not in radical resection rate (15 vs 12%; $p = 0.327$). Nevertheless, the study population was unselected for conversion to surgical resectability, since only 20% of the randomized patients had liver-limited disease. Preliminary OS data showed a trend toward improved survival in the FOLF- OXIRI + bev arm (31.0 vs 25.8 months; HR: 0.83 [95% CI: 0.66–1.05]; $p = 0.125$). In conclusion, the trial confirms the high activity of the regimen, but also its impact on PFS and, perhaps, on OS outcomes.

Based on these results, the triplet + bev should be regarded as a new standard option for the first-line treatment of mCRC patients, selected according to the trial's inclusion criteria (i.e., age 18–75 years; Eastern Cooperative Oncology Group performance status ≤ 2 if age ≤ 70 and Eastern Cooperative Oncology Group performance status = 0 if age = 71–75 years), and also in a palliative setting, independently from a conversion objective. Furthermore, a significant correlation of the early response with PFS and, more relevantly, with OS, was demonstrated by an individual patient data meta-analysis from the Aide et Recherche en Cancérologie Digestive (ARCAD) database, including 15 randomized trials. Overall, these results support the hypothesis that the advantage in terms of activity of an intensive upfront regimen may translate into a prolongation of survival independently of the opportunity to achieve secondary resections [15].

What about maintenance treatment with bev $\pm$ chemotherapy? Is it mandatory?

The choice to prosecute the antiangiogenic until disease progression, also in the case of a partial or total interruption of the associated chemotherapy, is not uncommon in clinical practice, though in the absence of an evidence-based demonstration. For this reason, results from the Phase III SAKK 41/06 and CAIRO-3 trials, comparing an observation with a maintenance strategy following an induction phase of chemotherapy plus bev, were awaited with great interest. Dieter Koeberle (Kantons- spital St Gallen, Switzerland) presented the Swiss SAKK 41/06 study [16], a non-inferiority trial that randomized 262 patients, not experiencing disease progression after 4–6 months of first-line chemotherapy plus bev, to receive bev until disease progression or to be only observed. The noninferiority of the observation strategy was not demonstrated in terms of time to progression or OS. Patients treated with bev reported a 1.2 month absolute advantage in time to progression (4.1 vs 2.9 months from randomization; HR: 0.74; 95% CI: 0.57–0.95; p -value for noninferiority = 0.470) and a 3.3-month advantage in OS (26.1 vs 22.8 months; HR: 0.83; 95% CI: 0.61–1.12; p -value for difference = 0.218).

In the CAIRO-3 trial, presented in the oral session by Miriam Koopman (University Medical Center Utrecht, The Netherlands), patients achieving a disease stabilization or response after six cycles of capecitabine plus oxaliplatin (CAPOX) + bev were randomized between observation or maintenance treatment with capecitabine + bev [17]. Upon the first disease progression, CAPOX + bev were reintroduced and continued until the second evidence of disease progression. The primary end point was the 'PFS2', defined as the time from randomization to progression upon reintroduction of CAPOX + bev. Patients in the maintenance arm achieved a significant benefit in terms of PFS2 (11.8 vs 10.5 months; HR: 0.81; 95% CI: 0.67–0.98; $p = 0.028$), PFS (8.5 vs 4.1 months; HR: 0.44; 95% CI: 0.36–0.53; $p < 0.00001$) and a nonsignificant advantage in OS (21.7 vs 18.2 months;

HR: 0.87; 95% CI:0.71–1.06; $p = 0.156$), which becomes significant in the adjusted analysis (HR: 0.80; $p = 0.035$).

On the basis of this evidence, the opportunity to alternate induction and maintenance phases in the disease history of mCRC patients seems a valuable option. New trials will define which is the ‘best’ maintenance treatment (i.e., the German AIO KRK0207 trial, randomizing to observation vs maintenance with bev alone vs maintenance with bev + capecitabine [101]) and whether the maintenance period, instead of a period of observation (when no systemic treatment

is administered), is actually required for all patients.

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Website

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