



ASCO 2021 – an update on metastatic colorectal cancer

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Summary The 2021 ASCO Annual Meeting provided updates on novel therapies in rare subgroups of metastatic colorectal cancer, such as immunotherapy in microsatellite instable colorectal cancer and antibody–drug conjugate therapy in HER2-positive disease. Furthermore, the concept of anti-EGFR rechallenge therapy has received additional momentum with data from the CHRONOS trial in regard to treating patients in later lines as well as how to integrate analysis of circulating tumor DNA in clinical decision-making.

Keywords Treatment · Update · Immunotherapy · Circulating tumor DNA · CtDNA

Pembrolizumab as first-line standard in MSI-H mCRC

Microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) can be identified in 5–10% of patients with metastatic colorectal cancer (mCRC) and is associated with a dramatically increased sensitivity towards immune checkpoint inhibitor therapy [1]. Following last year’s presentation of data on progression-free survival (PFS), overall survival (OS) data have been eagerly awaited at this year’s update of the KEYNOTE-177 trial [2]. In this randomized phase 3 trial, a total of 307 patients have been treated with either immunotherapy with pembrolizumab or with doublet-chemotherapy combined with a biological (mFOLFOX6 or FOLFIRI combined with bevacizumab or cetuximab) for previously untreated MSI-H or dMMR mCRC.

The updated PFS data could confirm the superiority of pembrolizumab with a median of 16.5 months compared to 8.2 months in the standard chemotherapy arm (HR 0.59, 95% CI 0.45–0.79). Overall response rate (ORR; 45.1% vs. 33.1%) and complete remission rate (13.1% vs. 3.9%) also clearly favored immunotherapy with pembrolizumab, which at the same time has a beneficial toxicity profile when compared to standard chemotherapy (grade 3/4 adverse events 21.6% vs. 66.4%).

Despite not meeting the predefined criteria for statistical significance, OS analysis revealed a clinically meaningful benefit for immunotherapy: median OS in the chemotherapy arm was 36.7 months, whereas it has not been reached yet in the pembrolizumab arm (HR 0.74 [0.5–1.03]); at 3 years 61% of patients were still alive in the pembrolizumab arm compared to 50% of patients in the chemotherapy arm. For correct interpretation of the data, it has to be emphasized that 60% of patients in the chemotherapy arm have subsequently received immunotherapy—including cross-over within the trial or afterwards outside the trial.

In the light of these PFS and OS data, immunotherapy with pembrolizumab has been confirmed as the new first-line standard in this indication and has also been approved by the European Medicines Agency (EMA).

Open questions still exist with respect to the higher rate of primary disease progression during pembrolizumab when compared to chemotherapy (29.4% vs. 12.3%) and the initial “crossing of the curves” in PFS analysis. Some argue that the lack of central assessment of MSI-H/dMMR status may have led to misclassification of some patients and the phenomenon of pseudo-progression may have biased PFS analysis. Furthermore, superiority of pembrolizumab was not as clear in the *KRAS/NRAS*-mutated subgroup

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as for other subgroups—however, there were also no signs of inferiority.

Further in-depth analyses of the KEYNOTE-177 trial, as well as upcoming results of still ongoing phase 3 trials with nivolumab ± ipilimumab (NCT04008030) [3] or atezolizumab (NCT02997228) [4] will help to elucidate the true potential of immunotherapy in MSI-H or dMMR mCRC.

Maintenance therapy with panitumumab and FU/LV

The German PANAMA trial investigated a combination maintenance therapy with the anti-EGFR antibody panitumumab and fluorouracil/leucovorin (FU/LV) compared to maintenance therapy with FU/LV alone [5]. In this phase 3 trial, 148 patients with RAS wildtype mCRC were randomized following induction therapy with FOLFOX and panitumumab, and evidence of at least stable disease. The study met its primary endpoint showing a significantly longer median PFS with panitumumab and FU/LV when compared to chemotherapy with FU/LV alone (8.8 months vs 5.7 months; HR 0.72 [0.60–0.85]).

Given the toxicity profile of anti-EGFR antibodies, mainly patients with proven good tolerability during induction therapy would qualify for such a maintenance strategy in clinical practice.

Additional analyses have been performed in patients who have been reinduced with FOLFOX and panitumumab upon progression during maintenance therapy. Although an uncommon choice of therapy, these results give interesting insights: response to reinduction therapy could only be observed in 8.9% of patients in the FU/LV and panitumumab arm compared to 34.7% of patients in FU/LV alone arm as well as a shorter median PFS for patients in the combination maintenance arm (3.3 months vs. 5.8 months). Therefore, it seems that an anti-EGFR-free interval is prerequisite for response to anti-EGFR-based reinduction.

ctDNA-guided anti-EGFR rechallenge

RAS-mutated clones may develop under the selection pressure of anti-EGFR based therapies and thereby confer secondary anti-EGFR resistance. A growing body of evidence shows that an ensuing anti-EGFR-free interval may lead to a decrease in RAS-mutated clones with re-establishment of a RAS wildtype situation [6]. This is the basis of the therapeutic concept of anti-EGFR rechallenge, where anti-EGFR treatment is re-employed despite disease having progressed during previous anti-EGFR treatment. Although contradicting general principles of systemic cancer therapy, anti-EGFR rechallenge may demonstrate impressive clinical efficacy.

The CHRONOS trial represents the next evolutionary step of the concept of anti-EGFR rechallenge [7]:

using the analysis of circulating tumor-DNA (ctDNA) patients are preselected for presumably anti-EGFR sensitive disease. Patients with RAS/BRAF wildtype mCRC, who have previously been treated with and have responded to anti-EGFR treatment and in the following have progressed during anti-EGFR treatment have been subjected to ctDNA analysis. Only patients with no evidence of a potentially resistance-mediating mutation—e.g., in *KRAS*, *NRAS*, *BRAF* or the extracellular domain of *EGFR*—could be included in this trial. Thereby, 31% of 52 screened patients were excluded from trial participation and a presumably ineffective rechallenge therapy was avoided. The remaining 27 patients were treated with panitumumab monotherapy resulting in an ORR of 30% and a disease control rate of at least 4 months in 63% of patients. Of note, response was independent from the number of previous lines of therapy.

In summary, the presented CHRONOS trial corroborates the concept of anti-EGFR rechallenge similarly to the already published CRICKET trial (NCT02296203) [8]. Despite the impressive response rates observed in these small trials, it is currently unclear how to best integrate anti-EGFR rechallenge in clinical practice, especially in relation to approved third-line therapies such as regorafenib and tipiracil/trifluridine with rather modest clinical activity, which have been tested in large randomized phase 3 trials [9, 10]. Until availability of further data, the use of anti-EGFR rechallenge will depend on local availability of ctDNA analysis and could be guided by the need for response in individual patients. Results from trials such as the FIRE 4 trial (NCT02934529) are eagerly awaited but also retrospective real world data from “early adopters”.

Trastuzumab deruxtecan in HER2+ mCRC

Final results of the DESTINY-CRC01 trial have been presented at this year's ASCO [11]: this single arm phase 2 trial investigated the antibody–drug conjugate trastuzumab deruxtecan in HER2-positive mCRC. An ORR of 45.3% could be achieved in heavily pretreated patients with a median of 4 previous lines of therapy—but only in clearly HER-positive disease defined as IHC3+ or IHC2+/ISH+. The 53 patients belonging to this HER+ cohort have shown a median PFS of 6.9 months and a median OS of 15.5 months. With all due caution this compares rather favorably with response rates achieved by approved third-line options [9, 10]. Three out of 86 patients died from therapy-related pneumonitis or interstitial lung disease—which is in line with other trials with trastuzumab deruxtecan [12]. Therefore, it is of utmost importance to monitor patients for the development of potential lung toxicity to allow early intervention.

Depending on the local availability of anti-HER-directed therapies, HER2 analysis of tumor tissue should be encouraged although only 2–3% of mCRC cases are

reported to be HER2 positive [13]. HER2 overexpression is also an important mechanism of secondary resistance to anti-EGFR therapy in *RAS* wildtype mCRC [14], which might increase the number of patients eligible for anti-HER directed therapies.

However, the EMA has not approved trastuzumab deruxtecan for the treatment of HER2+ mCRC yet, in contrast to other indications such as HER2+ metastatic breast cancer [12].

FOLFOXIRI with cetuximab or bevacizumab in first-line treatment

The Japanese DEEPER (JACCRO CC-13) trial evaluated the combination of FOLFOXIRI with either cetuximab or bevacizumab in previously untreated patients with *RAS* wild-type mCRC [15]. In this phase 2 trial, 359 patients were randomized 1:1 with the primary endpoint of depth of response (DpR). In this regard, FOLFOXIRI and cetuximab was superior to FOLFOXIRI and bevacizumab with a median DpR of 57.4% vs. 46.0% ($p=0.001$). However, this did not translate into an increased R0 resection rate and there was no significant difference in overall response. As expected, more cutaneous adverse events were observed in the cetuximab arm.

The FIRE 4.5 trial included 107 previously untreated patients with *BRAF*-mutated mCRC [16]. In this randomized phase 2 trial, ORR was not significantly different between the treatment arms, but with a numerically higher ORR for FOLFOXIRI and bevacizumab when compared to FOLFOXIRI and cetuximab (66.7% versus 52.0%; $p=0.23$). Median PFS was significantly longer with FOLFOXIRI and bevacizumab (8.3 months) than FOLFOXIRI and cetuximab (5.9 months; $p=0.03$; HR 1.8). In conclusion, FOLFOX(IRI) and bevacizumab remains the standard first-line treatment for *BRAF*-mutant mCRC.

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References

1. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509–20. <https://doi.org/10.1056/NEJMoa1500596>.
2. Andre T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, Punt CJA, et al. Final overall survival for the phase III KN177 study: pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). *J Clin Oncol*. 2021;39(15_suppl):3500. https://doi.org/10.1200/JCO.2021.39.15_suppl.3500.
3. Lenz H-J, Lonardi S, Zagonel V, van Cutsem E, Limon ML, Wong M, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): two-year clinical update. *J Clin Oncol*. 2020;38(15_suppl):4040. https://doi.org/10.1200/JCO.2020.38.15_suppl.4040.
4. Overman MJ, Yothers G, Jacobs SA, Sanoff HK, Cohen DJ, Guthrie KA, et al. Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: a randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC)—NRG-GI004/SWOG-S1610. *J Clin Oncol*. 2021;39(15_suppl):TPS3618. https://doi.org/10.1200/jco.2021.39.15_suppl.tps3618.
5. Modest DP, Karthaus M, Frühauf S, Graeven U, Müller L, Koenig A, et al. Maintenance therapy with 5-fluorouracil/leucovorin (5FU/LV) plus panitumumab (pmab) or 5FU/LV alone in *RAS* wildtype (WT) metastatic colorectal cancer (mCRC)—the PANAMA trial (AIO KRK 0212). *J Clin Oncol*. 2021;39(15_suppl):3503. https://doi.org/10.1200/JCO.2021.39.15_suppl.3503.
6. Siravegna G, Mussolin B, Buscarino M, Corti G, Cassingena A, Crisafulli G, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. *Nat Med*. 2015;21(7):795–801. <https://doi.org/10.1038/nm.3870>.
7. Sartore-Bianchi A, Pietrantonio F, Lonardi S, Mussolin B, Rua F, Fenocchio E, et al. Phase II study of anti-EGFR rechallenge therapy with panitumumab driven by circulating tumor DNA molecular selection in metastatic colorectal cancer: the CHRONOS trial. *J Clin Oncol*. 2021;39(15_suppl):3506. https://doi.org/10.1200/JCO.2021.39.15_suppl.3506.
8. Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, et al. Rechallenge for patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer with acquired resistance to first-line cetuximab and irinotecan: a phase 2 single-arm clinical trial. *JAMA Oncol*. 2019;5(3):343–50. <https://doi.org/10.1001/jamaoncol.2018.5080>.
9. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303–12. [https://doi.org/10.1016/S0140-6736\(12\)61900-X](https://doi.org/10.1016/S0140-6736(12)61900-X).
10. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909–19. <https://doi.org/10.1056/NEJMoa1414325>.

11. Yoshino T, di Bartolomeo M, Raghav KPS, Masuishi T, Loupakis F, Kawakami H, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). *J Clin Oncol.* 2021;39(15_suppl):3505. https://doi.org/10.1200/JCO.2021.39.15_suppl.3505.
12. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2020;82(7):610–21. <https://doi.org/10.1056/NEJMoa1914510>.
13. Ross JS, Fakih M, Ali SM, Elvin JA, Schrock AB, Suh J, et al. Targeting HER2 in colorectal cancer: the landscape of amplification and short variant mutations in ERBB2 and ERBB3. *Cancer.* 2018;124(7):1358–73. <https://doi.org/10.1002/cncr.31125>.
14. Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, et al. A molecularly annotated platform of patient-derived xenografts (“xenopatients”) identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. *Cancer Discov.* 2011;1(6):508–23. <https://doi.org/10.1158/2159-8290.CD-11-0109>.
15. Tsuji A, Ohori H, Yamaguchi T, Matsuura M, Nishioka A, Makiyama A, et al. The randomized phase II study of FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab as the first-line treatment in metastatic colorectal cancer with RAS wild-type tumors: The DEEPER trial (JACCRO CC-13). *J Clin Oncol.* 2021;39(15_suppl):3501. https://doi.org/10.1200/JCO.2021.39.15_suppl.3501.
16. Stintzing S, Heinrich K, Tougeron D, Modest DP, Schwane I, Eker J, et al. Randomized study to investigate FOLFOXIRI plus either bevacizumab or cetuximab as first-line treatment of BRAF V600E-mutant mCRC: the phase-II FIRE-4.5 study (AIO KRK-0116). *J Clin Oncol.* 2021;39(15_suppl):3502. https://doi.org/10.1200/JCO.2021.39.15_suppl.3502.

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