ESMO 2021—highlights in colorectal cancer

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Summary
This short review reflects on a personal selection of three abstracts on colorectal cancer (CRC) presented at the 2021 ESMO Congress: (1) KRASG12C as a new therapeutic target in metastatic CRC, supported by data from the KRYSRAL-1 and CodeBreaK101 trials, (2) positive phase 3 data on the possible role of selective internal radiotherapy (SIRT) in the second-line treatment of liver-limited metastatic CRC, and (3) the impact of the coronavirus disease 2019 (COVID-19) pandemic on CRC screening, management and mortality, now and in the upcoming years.

Keywords Treatment · Update · KRASG12C · SIRT · COVID-19

Targeted therapy in KRAS G12C-mutated metastatic CRC

Although KRAS is one of the most frequently mutated genes in colorectal cancer (CRC), only 3–4% of all patients with metastatic CRC exhibit a KRAS G12C mutation [1]. KRAS G12C is a point mutation in the KRAS gene resulting in a glycine-to-cysteine amino acid substitution at codon 12, thereby, leading to constitutive activation and oncogenesis. These patients show a worse prognosis when compared to patients with non-KRAS G12C mutated disease.

Adagrasib is a covalent inhibitor of KRAS G12C which irreversibly and selectively binds to KRAS G12C [2]. In the KRYSRAL-1 phase 1/2 trial, adagrasib was investigated as monotherapy \( (n=46) \) or in combination with the anti-EGFR antibody cetuximab \( (n=32) \) in heavily pretreated KRAS G12C-mutated metastatic CRC [3]. This combination is based on the rationale that EGFR signaling has been identified as the dominant mechanism of CRC resistance to KRAS G12C inhibitors [4].

Adagrasib alone resulted in an overall response rate (ORR) of 22% and disease control rate (DCR) of 87% among 45 evaluable patients. Median progression-free survival (PFS) for monotherapy was 5.6 months (95% confidence interval [CI] 4.1–8.3). The addition of cetuximab could increase clinical efficacy to an ORR of 43% and DCR of 100% among 28 evaluable patients. Here, median time to response was 1.3 months and 71% of patients remained on treatment at the time of analysis. Grade 3/4 adverse events for combination therapy could be observed in 16% of patients, with diarrhea, acneiform rash, stomatitis and QTc prolongation being the most frequent (each 3%).

Based on these results, adagrasib and cetuximab is compared to standard chemotherapy plus/minus antiangiogenic agent in the KRYSRAL-10 trial, a phase 3 randomized trial in patients with KRAS G12C mutated metastatic CRC who have progressed after first-line treatment (NCT04793958).

These data are supported by another trial: in the phase Ib CodeBreaK101 trial, sotorasib, another KRAS G12C inhibitor, was investigated in combination with the anti-EGFR antibody panitumumab in 31 chemorefractory patients [5]. The investigators reported a confirmed plus unconfirmed ORR of 27% and a DCR of 81%.

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Sotorasib is already approved by the European Medicines Agency for the treatment of patients with advanced non-small cell lung cancer whose tumors harbor a KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy [6].
The combination of sotorasib and panitumumab will be investigated in the CodeBreak300 trial, a phase 3 randomized trial in patients with KRAS G12C mutated metastatic CRC in the third-line setting (NCT04793958).

**First positive phase 3 trial for selective internal radiotherapy in CRC**

Selective internal radiotherapy (SIRT) or radioembolization describes the transarterial delivery of microscopic glass beads containing radioactive yttrium (Y-90) to liver metastases through hepatic tumor-feeding arteries.

The EPOCH trial investigated the role of SIRT when added to standard second-line chemotherapy in patients with metastatic CRC limited to the liver [7].

In this phase 3 study, 428 patients were randomized to either chemotherapy alone or the combination with SIRT applied in a single setting, before or after the first cycle of chemotherapy. Both primary endpoints were met, with a slight increase in median PFS (8.0 vs 7.2 months, hazard ratio [HR] 0.69; 95% CI, 0.54–0.88; \( p = 0.0013 \)) as well as in median hepatic PFS (9.1 vs 7.2 months, HR 0.59, \( p = 0.0019 \)) when adding SIRT. Moreover, ORR was also higher in the combination arm with 34.0% compared to 21.1% with chemotherapy alone. However, this did not translate into an increased median overall survival (14.0 vs 14.4 months, HR 1.07, \( p = 0.7229 \)).

Grade 3 adverse events—especially neutropenia—were reported more frequently with SIRT (68.4% vs 49.3%) but not leading to dose reductions in chemotherapy.

So after failing to show an improvement in PFS or OS in the first-line setting [8], adding SIRT to standard chemotherapy to liver-limited metastatic CRC may be beneficial in the second-line setting.

**Impact of the COVID-19 pandemic on CRC screening and diagnosis**

Due to the immense challenges posed by the coronavirus disease 2019 (COVID-19) pandemic to health care systems worldwide, cancer screening programs had to be scaled back or were not sought by patients out of fear of COVID-19 infection.

At ESMO 2021, Tehfe M et al. presented their analysis of data of the Canadian province of Quebec regarding fecal occult blood test and colonoscopy for CRC screening, as well as CRC surgery [9]. When comparing the 4-month period during the first wave of the pandemic (April–July 2020) to the same time period in the preceding year (April–July 2019), the researchers could observe a dramatic drop in CRC screening but also CRC surgeries (Table 1).

Although prior to the second wave (August–October 2020) many health care services could be resumed, CRC screening was still less than in the previous year (fecal occult blood test: –5%, colonoscopy: –11.4%) as were CRC surgeries (–28%).

These data are in line with other reports [10] and exemplify how the COVID-19 pandemic is impacting CRC management. Since CRC survival is closely linked to stage of disease [11], the delays in diagnosis of CRC are expected to lead to a stage-shift at first diagnosis as well as in an increase in emergency admissions, both known to negatively affect prognosis in CRC [12].

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