Colorectal Cancer Highlights – 2022 ESMO Annual Meeting

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The 2022 Annual Congress of the **European Society for Medical Oncology (ESMO)** was held in Paris, France, on **September 9-13, 2022**. The ESMO Congress 2022 had over 29,300 participants from over 150 countries attending onsite and virtually. Participants included clinicians, healthcare industry representatives, journalists, patient advocates, and researchers. A total of 1,912 abstracts offering the latest advances in cancer treatment were presented at the congress — there were 76 late-breaking abstracts, and 11 abstracts were selected for presidential symposia. Furthermore, of note were the practice-changing results presented from the NICHE-2 and FRESCO studies.

Early-stage Colorectal Cancer

Circulating tumour DNA (ctDNA) dynamics, CEA and sites of recurrence for the randomised DYNAMIC study: Adjuvant chemotherapy guided by ctDNA analysis in stage II colon cancer

The DYNAMIC study, a randomized phase 2 study in patients with stage II colon cancer, previously reported that a ctDNA-guided approach versus standard management reduced adjuvant chemotherapy use without compromising recurrence-free survival. The current study explored the relationship between post-op ctDNA and sites of recurrence, post-ACT ctDNA status and relapse, and post-op and post-ACT CEA from the same blood samples. Results suggested that ctDNA analysis is more sensitive for predicting distant than locoregional recurrences in stage II colon cancer patients. ctDNA clearance can be achieved with ACT in a high proportion of those with an initial positive post-op ctDNA and predicts for excellent outcome. Conversely, in ctDNA-negative patients, CEA lacks sensitivity and specificity as a marker of recurrence risk[1].

Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study

The results presented here were one of the highlights of the congress. This study was a phase 2 trial involving just under 100 patients with locally advanced MMR-deficient colon cancer treated with an initial cycle of nivolumab 3 mg/kg and ipilimumab 1 mg/kg, followed by a second cycle two weeks later of nivolumab 3 mg/kg before undergoing surgery at six weeks. The results of the study found a major pathologic response in 95% of patients, with 67% showing complete pathologic responses. While this study was only a phase 2 single-arm trial, this treatment could change clinical practice, particularly in tumors where there is a risk of one resection or in tumors with major peri- or postoperative morbidity due to large or difficult-to-operate tumours[2].

Prognostic effect of imaging and CEA follow-up in resected colorectal cancer (CRC): Final results and relapse free survival (RFS) - PRODIGE 13 a FFCD phase III trial

This study looked into optimal follow-up regimens in colorectal cancers that have been treated with surgery already. Patients were randomized to either standard follow-up with or without regular CEA surveillance or more or less intensive imaging surveillance involving CT scans every six months. The results suggested that adding CEA surveillance or increasing the intensity of imaging surveillance enabled more patients to undergo additional surgery; however, this made no difference to overall survival. The authors conclude that less intense follow-ups are enough and that CEA surveillance most likely doesn't provide additional benefits. Such surveillance depends on what the local practice recommends and keeping within the guidelines; however, increasing surveillance doesn't appear beneficial[3].

Metastatic Colorectal Cancer

FOLFOX/FOLFIRI plus either bevacizumab or panitumumab in patients with initially unresectable colorectal liver metastases (CRLM) and left-sided and AS/BRAFV600E wild-type tumor: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group

These were the first results presented from the CAIRO5 phase 3 trial focusing on left-sided RAS/RAFwt colorectal cancer, which is generally treated with chemotherapy and cetuximab or panitumumab. The study included patients with liver-only metastases that were initially unresectable that were randomized to first-line doublet chemotherapy plus bevacizumab versus doublet chemotherapy plus panitumumab. The results from the survival curve demonstrated no significant difference in overall progression-free survival between the two arms (HR 1.12 (95% CI 0.84-1.50); p=0.44). In addition, the resection rates between the two arms were similar. The overall survival data has yet to be finalized; however, based on these findings, the consensus is that the current practice should not change[4].

Phase III study with FOLFIRI/cetuximab versus FOLFIRI/cetuximab followed by cetuximab (Cet) alone in first-line therapy of RAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC) patients: The ERMES study

This phase 3 trial compared continuous FOLIR/cetuximab in a first-line setting for RAS/RAFwt colorectal cancer versus eight cycles of FOLIR/cetuximab followed by cetuximab maintenance. The study aimed

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to demonstrate non-inferiority for the cetuximab maintenance arm of the study; however, the results indicated the opposite for progression-free survival (HR 1.30 (CI 95% 1.03-1.64); p(non-inferiority)=0.43). The results for overall survival, however, showed no difference (HR 0.81 (CI 95% 0.60-1.09); p=0.157). Through discussion, some design flaws in the study were raised, suggesting that cetuximab maintenance should not be stopped in clinical practice[5].

FRESCO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer

The study was suggested to be practice changing and was a randomized phase 3 trial with patients on LONSURF or regorafenib that had progressed who received either fruquintinib (VEGFR 1/2/3 TKI) or a placebo in a fourth or fifth line setting. The results of this study were positive, with fruquintinib having a median survival advantage of 2.6 months which is practice changing and provides clinicians with a new line of therapy regardless of the molecular subtype[6].

New targeted therapies for molecular subgroups

Additional analyses of MOUNTAINEER: A phase II study of tucatinib and trastuzumab for HER2-positive mCRC

An update from the MOUNTAINEER phase 2 trial focusing on HER2+ mCRC which affects 2-5% of patients. This small trial has been expanded to include a single agent tucatinib arm and a doublet arm treated with tucatinib and trastuzumab. Results revealed that in the doublet arm, the overall response rate was 38.1% (27.7-49.3%) compared to the single agent, which was 3.3% (0.1-17.2%), indicating that the double will proceed forward. In addition, the double post-crossover had an overall response rate of 17.9% (6.1-36.9%) indicating that patients should receive the doublet upon treatment. The study now needs to move into phase 3 testing[7].

BREAKWATER safety lead-in (SLI): Encorafenib (E) + cetuximab (C) + chemotherapy (chemo) for BRAFV600E metastatic colorectal cancer (mCRC)

This study presented early efficacy and safety data, which combined encorafenib/cetuximab with chemotherapy in the first- and second-line settings to treat BRAF V600E mutant mCRC. Two cohorts are being assessed, incorporating FOLFIRI and mFOLFOX8. The pharmacokinetic results indicate that there are no interactions of oxaliplatin-containing chemotherapy with encorafenib; however, there was lower exposure with irinotecan/SN38 when combined with encorafenib. Overall the efficacy data is encouraging, with both regiments demonstrating an almost 70% response rate in the first-line settings. This data has supported the progression of the trial to phase 3[8].

Therapy Resistance

Genomic mechanisms of acquired resistance of patients (pts) with BRAF V600E-mutant (mt) metastatic colorectal cancer (mCRC) treated in the BEACON study

This study looked at the genomic mechanisms of acquired resistance in patients with BRAF V600E mutant mCRC as part of the BEACON study in which patients received EC chemotherapy in the second-line setting. Results indicate that KRAS, NRAS and MAP2K1 mutations and MET and KRAS amplifications generally emerged at progression. Resistance occurs through the reactivation of the MAPK pathway. The problem is that the reactivation occurs in several genes, which are often non-targetable. In addition, more than one gene is frequently mutated in patients, conferring polyclonal resistance[9].

References

1. Tie J, Cohen J, Lahouel K, et al. 318MO Circulating tumour DNA (ctDNA) dynamics, CEA and sites of recurrence for the randomised DYNAMIC study: Adjuvant chemotherapy (ACT) guided by ctDNA analysis in stage II colon cancer (CC). *Annals of Oncology*. 2022;33:S683.
2. Chalabi M, Verschoor Y, van den Berg J, et al. LBA7 Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. *Annals of Oncology*. 2022;33:S1389.
3. Lepage C, Phelip J, Cany L, et al. LBA28 Prognostic effect of imaging and CEA follow-up in resected colorectal cancer (CRC): Final results and relapse free survival (RFS)-PRODIGE 13 a FFCD phase III trial. Annals of Oncology. 2022;33:S1395.
4. Bond M, Bolhuis K, Loosveld O, et al. LBA21 FOLFOX/FOLFIRI plus either bevacizumab or panitumumab in patients with initially unresectable colorectal liver metastases (CRLM) and left-sided and RAS/BRAFV600E wild-type tumour: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. *Annals of Oncology*. 2022;33:S1389.
5. Pinto C, Orlandi A, Normanno N, et al. LBA22 Phase III study with FOLFIRI/cetuximab versus FOLFIRI/cetuximab followed by cetuximab (Cet) alone in first-line therapy of RAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC) patients: The ERMES study. *Annals of Oncology*. 2022;33:S1390.
6. Dasari N, Lonardi S, Garcia-Carbonero R, et al. LBA25 FRESCO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. *Annals of Oncology*. 2022;33:S1391-S1392.
7. Strickler J, Cercek A, Siena S, et al. LBA27 Additional analyses of MOUNTAINEER: A phase II study of tucatinib and trastuzumab for HER2-positive mCRC. *Annals of Oncology*. 2022;33:S1394.
8. Tabernero J, Yoshino T, Kim T, et al. LBA26 BREAKWATER safety lead-in (SLI): Encorafenib (E)+ cetuximab (C)+ chemotherapy (chemo) for BRAFV600E metastatic colorectal cancer (mCRC). *Annals of Oncology*. 2022;33:S1392-S1393.
9. Kopetz S, Murphy D, Pu J, et al. 316O Genomic mechanisms of acquired resistance of patients (pts) with BRAF V600E-mutant (mt) metastatic colorectal cancer (mCRC) treated in the BEACON study. *Annals of Oncology*. 2022;33:S681-S682.

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