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Updated treatment recommendations for third and further lines of treatment in advanced colorectal cancer: from the ESMO Metastatic Colorectal Cancer Living Guideline

The following European Society for Medical Oncology (ESMO) Living Guideline has been recently updated with new treatment recommendations: ESMO Metastatic Colorectal Cancer Living Guideline.[1,2]

LIVING GUIDELINE UPDATE

View the ESMO Metastatic Colorectal Cancer Living Guideline here: https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline.

Use of fruquintinib as third- and further-line treatment of metastatic colorectal cancer

In the FRESCO phase III trial, fruquintinib significantly prolonged progression-free survival (PFS) and overall survival (OS) versus placebo [hazard ratio (HR) for death 0.65, 95% confidence interval (CI) 0.51-0.83, $P < 0.001$] in a population with advanced colorectal cancer patients, who progressed after at least two lines of therapy and never received regorafenib.[3] A treatment-emergent adverse event (AE) of grade $\geq$3 severity was experienced in 61.2% of patients receiving fruquintinib versus only 19.7% receiving placebo. In the FRESCO-2 phase III trial, fruquintinib improved OS (HR 0.66, 95% CI 0.55-0.80, $P < 0.0001$) over placebo control in patients with chemorefractory metastatic colorectal cancer, who received a median number of four previous lines of treatment.[4] Eligible patients had received all current standard approved cytotoxic and targeted therapies and had progressed on, or were intolerant to, trifluridine—tipiracil, regorafenib or both. Grade $\geq$3 AEs occurred in 63% of patients treated with fruquintinib versus 50% in the placebo group. The most common grade $\geq$3 AEs in the fruquintinib group included hypertension (14%), asthenia (8%) and hand—foot syndrome (6%).

Fruquintinib was approved by the European Medicines Agency (EMA) and obtained an ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score of 3.[5] Figure 1 provides an updated treatment algorithm.

Recommendation

- Fruquintinib is recommended in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, after progressing either on regorafenib or trifluridine—tipiracil [I, A; ESMO-MCBS v1.1 score: 3].

Use of cetuximab—adagrasib as treatment of KRAS G12C-mutated advanced colorectal cancer after progression on fluoropyrimidines, oxaliplatin and irinotecan

In the KRYSTAL-1 single-arm trial, cetuximab—adagrasib achieved a 34% objective response rate with a median PFS of 6.9 months and a median OS of 15.9 months in a cohort of *KRAS* G12C-mutated advanced colorectal cancers previously exposed to fluoropyrimidine, oxaliplatin and irinotecan.[6,7] Grade 3-4 treatment-related AEs were observed in 28% of patients. The most common AEs were nausea (60%), vomiting (51%) and diarrhoea (49%). Cetuximab—adagrasib was approved by the Food and Drug Administration (FDA) and obtained an ESMO-MCBS v1.1 score of 3.[5]

Recommendation

- Cetuximab—adagrasib is recommended in patients with *KRAS* G12C-mutated advanced colorectal cancer pretreated with fluoropyrimidines, oxaliplatin and irinotecan [III, B; ESMO-MCBS v1.1 score: 3; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A; FDA approved, not EMA approved].

Use of panitumumab—sotorasib as treatment of KRAS G12C-mutated advanced colorectal cancer after progression on fluoropyrimidines, oxaliplatin and irinotecan

In the randomised CodeBreak 300 phase III trial, the combination of panitumumab and sotorasib (240 or 960 mg) showed an improvement in PFS (HR for 240 mg 0.58, 95% CI

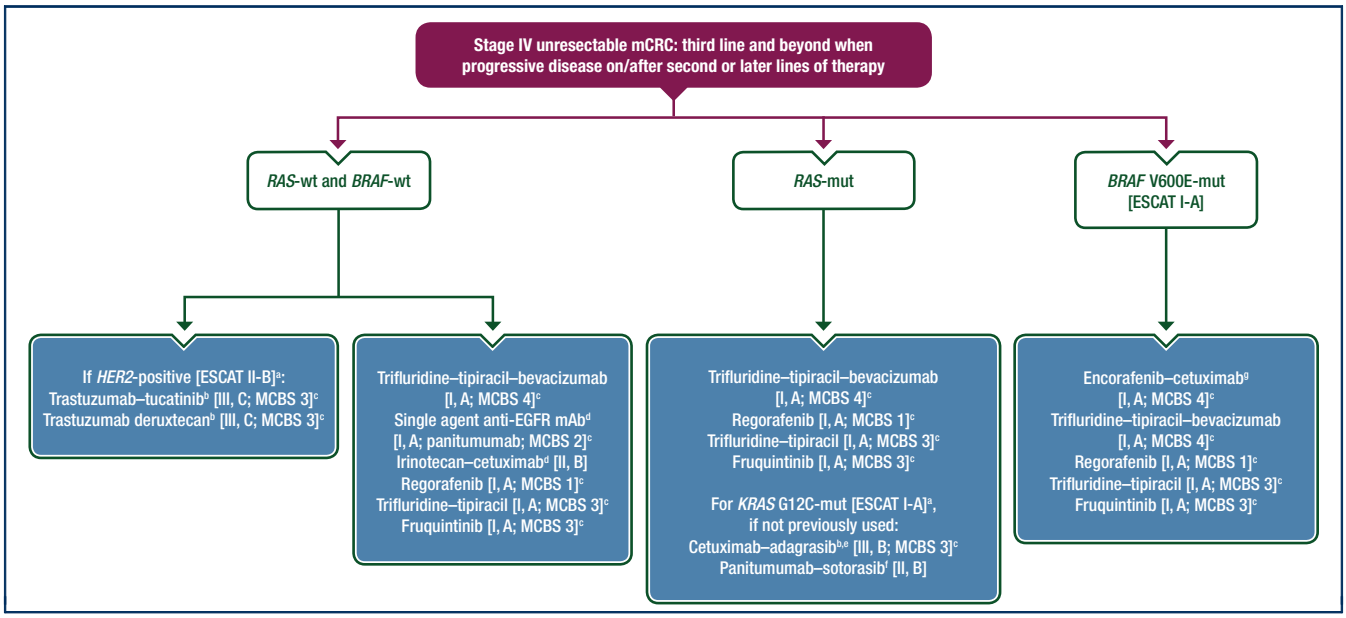

Figure 1. Management of patients with stage IV unresectable mCRC who have progressed on or after second or later lines of therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutation; wt, wild type.
[a]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[9]
[b]FDA approved, not EMA approved.
[c]ESMO-MCBS v1.1[5] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[d]In *RAS*-wt patients not previously treated with anti-EGFR monoclonal antibodies.
[e]Cetuximab—adagrasib can be optionally given in the second line if patients have been previously exposed to fluoropyrimidines, oxaliplatin and irinotecan.
[f]Not FDA or EMA approved.
[g]Treatment of *BRAF*-mut patients if not used in the second line.

0.36-0.93, $P = 0.03$ and HR for 960 mg 0.49, 95% CI 0.30-0.80, $P = 0.006$) over standard of care in patients with *KRAS* G12C-mutated advanced colorectal cancers previously exposed to fluoropyrimidine, oxaliplatin and irinotecan.[8] In the panitumumab—sotorasib arm, treatment-related AEs were observed in 36% of patients. The most common AEs were hypomagnesaemia (30%), rash (28%) and acneiform dermatitis (22%). Panitumumab—sotorasib has not yet been approved by the FDA or the EMA and, therefore, cannot yet be recommended. The ESMO-MBCS has not been calculated.

METHODOLOGY

The new ESCAT score has been defined and validated by the ESMO Translational Research and Precision Medicine Working Group (TRPM WG).[9,10] ESMO-MCBS v1.1[5] was used to calculate scores for new therapies/indications approved by the EMA or the FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing. Levels of evidence and grades of recommendation have been applied using the ESMO-adapted system based on that of Dykewicz et al.[11]

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Letter to the Editor regarding 'Clinical validation of a tissue-agnostic genome-wide methylome enrichment molecular residual disease assay for head and neck malignancies' by G Liu et al.

We read with great interest the article by Liu et al. titled 'Clinical validation of a tissue-agnostic genome-wide methylome enrichment molecular residual disease assay for head and neck malignancies'.[1] This study substantiates the potential utility of a tissue-independent genome-wide methylation molecular residual disease (MRD) assay in patients with head and neck cancer, demonstrating high sensitivity in both human papillomavirus (HPV)-positive and HPV-negative cohorts. In comparison to circulating tumor HPV DNA used exclusively for HPV-positive oropharyngeal cancer, the assay presented in this research offers a broader scope of application. It is imperative, however, that the results are interpreted with caution.

First, data derived from a solitary research center may not possess universal applicability. Within the Americas, the prevalence trends of HPV virus subtypes exhibit significant variability across countries such as the USA, Mexico, and Brazil. While HPV16 is widely recognized as the most prevalent subtype associated with head and neck tumors, HPV39 is notably prevalent in Mexico.[2] These divergent prevalence trends of HPV subtypes across these nations may impact the robustness and generalizability of the classifier.

Second, the schedule for blood specimen collection in this study included baseline, ∼3 months after treatment (ranging from 0.7 to 8.5 months), 12 months after treatment, and 24 months after treatment. The limited number of time points for blood collection could potentially lead to an increased rate of false positives and diminished sensitivity in detecting disease recurrence. The researchers found that longitudinal surveillance at 3-month intervals is worth