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Management of refractory metastatic colorectal cancer: consensus recommendations from Italian oncologists

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ABSTRACT

Introduction: Metastatic colorectal cancer (mCRC) constitutes approximately 10% of all cancers globally and ranks as the second leading cause of cancer-related deaths. Management of refractory mCRC remains challenging due to pharmacological resistance and limited effective therapeutic options.
Methods: This publication presents insights from a Delphi panel of Italian clinicians regarding mCRC therapeutic approaches, unmet medical needs, and fruquintinib's potential clinical utility within existing treatment algorithms. The project, guided by four leading Italian oncology experts, involved two survey rounds among 14 oncologists, achieving consensus on 15 statements with a 100% response rate.
Results: The expert panel identified critical epidemiological patterns in mCRC, with 20-25% of patients requiring further treatment after the failure of third-line therapy. The panel emphasized the clinical significance of fruquintinib's efficacy and tolerability profile demonstrated in the FRESCO-2 trial. The experts unanimously endorsed fruquintinib as a new standard of care for adult mCRC patients who have progressed through available standard therapies.
Conclusions: This recommendation is based on fruquintinib's observed survival benefit and manageable toxicity profile, which facilitate improved treatment management and potentially enhance patient quality of life. The structured consensus approach validates these recommendations, providing practical guidance for optimizing outcomes as therapeutic options for mCRC continue to expand in complexity.

Keywords: Colorectal cancer, Consensus, Delphi, Disease management, Fruquintinib

Introduction

Metastatic colorectal cancer (mCRC) represents a significant global health burden, accounting for approximately 10% of all cancers worldwide and ranking as the second leading cause of cancer-related mortality (1). Colorectal cancer is characterized by a multifactorial etiology comprising both modifiable and non-modifiable risk factors. Modifiable risk factors include alcohol consumption, cigarette smoking, diets rich in red and processed meats, obesity, and physical inactivity. Non-modifiable risk factors include hereditary syndromes (Lynch syndrome, familial adenomatous polyposis), inflammatory bowel diseases (ulcerative colitis and Crohn's disease), and type 2 diabetes mellitus. These factors contribute to the development of the disease through different pathogenetic mechanisms (2).

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The diagnosis of mCRC is often delayed due to the nonspecific nature of early symptoms, which include hematochezia, altered bowel habits, weight loss, abdominal or anal pain, and sensations of incomplete evacuation. This symptom ambiguity frequently leads to patient underestimation of disease severity and consequent postponement in seeking medical intervention (3). Clinically, CRC is categorized based on anatomical origin as either proximal/"right-sided" (cecum, ascending colon, and transverse colon) or distal/"left-sided" (descending colon and sigmoid colon), with disease staging and prognosis determined through the tumor-node-metastasis (TNM) classification system (4).

At the molecular level, CRC carcinogenesis primarily involves chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP), with each pathway conferring distinct tumor characteristics and therapeutic implications (5,6). The comprehensive understanding of these molecular mechanisms has facilitated the evolution of treatment strategies from conventional cytotoxic approaches to precision medicine paradigms incorporating targeted therapies and immunotherapeutic agents (7).

Current therapeutic management of mCRC follows a sequential approach, with first-line treatment typically consisting

of cytotoxic doublet or triplet regimens (FOLFOX, FOLFIRI, FOLFOXIRI) combined with targeted agents selected based on molecular profiling (anti-EGFR antibodies for RAS wild-type tumors, anti-VEGF agents regardless of RAS status) (4). Second-line therapy usually involves switching the chemotherapy backbone and maintaining or altering the targeted agent according to prior response and toxicity. Despite these advances, therapeutic options become increasingly limited in later treatment lines, creating a substantial unmet medical need for effective therapies in refractory settings (1).

The management of refractory mCRC presents several challenges, including acquired resistance mechanisms, cumulative toxicity, and declining patient performance status. Available third-line options include regorafenib and TAS-102, both associated with modest efficacy and considerable toxicity profiles (8), although the combination of TAS-102 with bevacizumab has further improved the efficacy of this agent (9), making it the preferred option in third line.

This therapeutic landscape underscores the urgent need for novel agents with improved efficacy-to-toxicity ratios and the capacity to overcome resistance mechanisms.

Fruquintinib has emerged as a promising option in this context, representing a potent and highly selective inhibitor of vascular endothelial growth factor receptors (VEGFR-1, −2, and −3) (10). The FRESCO-2 trial demonstrated significant improvements in overall survival (OS) and progression-free survival with fruquintinib compared to placebo in patients with refractory mCRC who had progressed through multiple lines of therapy, establishing its potential role in addressing current treatment gaps (11).

Given the evolving therapeutic landscape and persistent unmet needs in mCRC management, this publication aims to synthesize insights from a Delphi panel of experienced Italian clinicians regarding: (i) current therapeutic approaches for mCRC management; (ii) unmet medical needs in the mCRC treatment continuum; and (iii) the potential clinical utility and positioning of fruquintinib within existing treatment algorithms. This expert consensus is intended to provide practical guidance for optimizing patient outcomes in the context of expanding but increasingly complex therapeutic options for mCRC.

Methods

The consensus procedure followed a Delphi approach, comprising two sequential assessment and rating phases conducted among expert oncologists. This methodology is well established for developing consensus-based clinical practice guidelines and recommendations (12,13).

A Steering Committee (SC) of four nationally recognized experts in mCRC was convened from across Italy (Table 1). SC members were selected based on their extensive clinical experience in mCRC management, record of scientific publications, and involvement in clinical trials. The SC convened in April 2024 to discuss and select, based on the most recent evidence from the literature and their personal clinical experience, the main topics to be addressed by the consensus statements, which were: (i) epidemiology of treatment lines in mCRC, (ii) management of mCRC, (iii) the role of fruquintinib in the treatment of mCRC.

TABLE 1 - Steering Committee members

Expert	Hospital	City
Fortunato Ciardiello	University Hospital Luigi Vanvitelli	Naples, IT
Carmine Pinto	Arcispedale Santa Maria Nuova	Reggio Emilia, IT
Salvatore Siena	Grande Ospedale Metropolitano Niguarda	Milan, IT
Alberto Sobrero	IRCCS Ospedale Policlinico San Martino	Genoa, IT

Through detailed discussion of these topics, the SC developed 15 consensus statements. These statements formed the basis of an online questionnaire employing a 5-point Likert scale ("strongly disagree," "disagree," "somewhat agree," "agree," and "strongly agree") to quantify agreement levels. Consensus threshold was prospectively defined as ≥70% agreement.

The questionnaire was distributed to a panel of 14 oncology experts (Table 2) from throughout Italy, all with substantial experience in mCRC treatment. The consensus process employed a two-round survey approach, which is methodologically optimal for achieving robust consensus while allowing participants sufficient opportunity for reflection and reconsideration.

First-round responses were collected, analyzed, and shared anonymously with the SC. Statements failing to reach consensus due to syntactic or communicative issues were reformulated through discussion and unanimous agreement of the SC before redistribution in the second and final survey round. Throughout the process, respondent anonymity was maintained for all ratings and comments. Following completion of both survey rounds, final results were presented and discussed during an online meeting attended by both the SC and expert panel members.

Results

All panel members responded to both the first and second rounds of the Delphi process. Of the 15 statements submitted and evaluated by the expert panel during the first round, consensus (defined as agreement) was achieved on 12 statements, while no consensus was reached on the remaining 3 statements. Following reassessment by the SC (with reformulation of statements 4, 11, and 14), all 15 statements were resubmitted to the expert panel for the second round of responses. At the conclusion of this second phase, consensus (defined as agreement) was achieved on all 15 statements. The detailed results are available in Table 3.

Epidemiology of Treatment Lines in mCRC

The expert panel reached consensus on several key epidemiological aspects of mCRC. The panel agreed that approximately 25% of patients with colorectal cancer (CRC) present with metastases at diagnosis. Regarding treatment patterns, approximately 70% of patients with mCRC will receive second-line therapy following failure of first-line treatment. Furthermore, about 40% of patients who receive first-line

TABLE 2 - Panel of experts

Expert	Hospital	City
Antonuzzo Lorenzo	University Hospital Careggi	Florence, IT
Avallone Antonio	Istituto Nazionale Tumori IRCCS Fondazione Pascale	Naples, IT
Berardi Rossana	University Hospital of Marche	Torrette (Ancona), IT
Bordonaro Roberto	ARNAS Garibaldi	Catania, IT
Cremolini Chiara	University Hospital Pisana	Pisa, IT
Fenocchio Elisabetta	Istituto di Candiolo – Fondazione del Piemonte per l'Oncologia – IRCCS	Candiolo (Turin), IT
Latiano Tiziana	Fondazione Casa Sollievo della sofferenza	San Giovanni Rotondo (Foggia), IT
Martinelli Erika	University Hospital Luigi Vanvitelli	Naples, IT
Prete Alessandra Anna	Istituto Oncologico Veneto IRCCS	Padova, IT
Ricardi Umberto	Ospedale Città della Salute e della Scienza	Turin, IT
Santini Daniele	Policlinico Umberto I	Rome, IT
Sartore Bianchi Andrea	Grande Ospedale Metropolitano Niguarda and Università degli Studi di Milano	Milan, IT
Scartozzi Mario	University Hospital of Cagliari	Cagliari, IT
Silvestris Nicola	University Hospital Gaetano Martino	Messina, IT

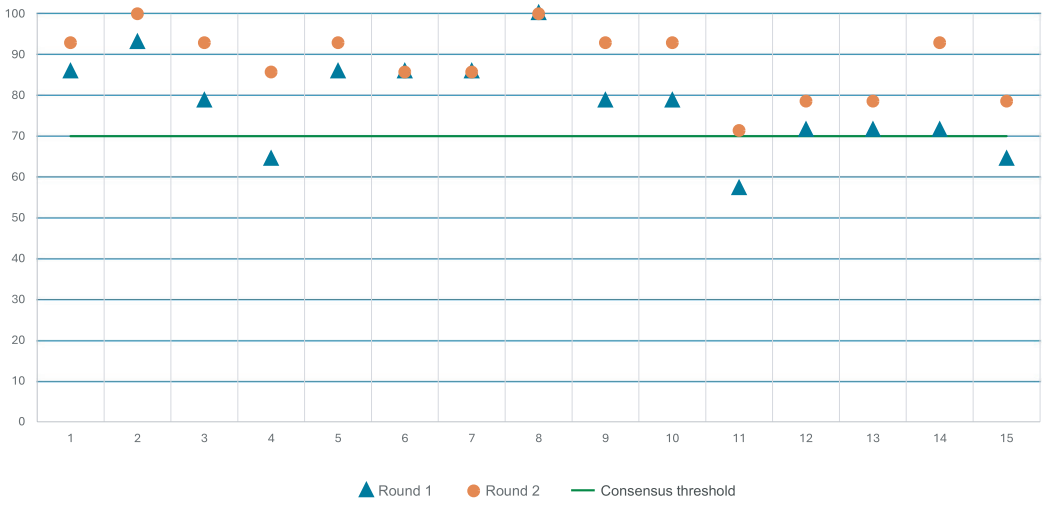

FIGURA 1 - Scatter plot showing the average level of agreement for each statement across the two rounds.

treatment will proceed to third-line therapy after failure of second-line treatment, while approximately 20% will receive at least one additional treatment following failure of second and third-line therapies.

Management of mCRC

The panel unanimously agreed that the emergence of drug resistance represents a significant limitation in the effectiveness of mCRC treatment. The primary unmet need in mCRC management, after exhaustion of currently available standard therapies, was identified as the lack of efficacy among available therapeutic options.

Consensus was reached on the definition of Best Supportive Care as encompassing all interventions (e.g., nutritional support, symptomatic pharmacological therapies, etc.) aimed at controlling the symptomatic aspects of the disease. The panel also agreed that the clinical objective of new therapeutic options specifically designed for treatment following current standard therapies should be to prolong patient survival while preserving or improving quality of life.

The Role of Fruquintinib

The expert panel evaluated the clinical evidence and potential therapeutic role of fruquintinib in the treatment of mCRC, with particular focus on the results from the pivotal FRESCO-2 study. Consensus was reached on the clinical relevance of the median OS of 7.4 months observed in the FRESCO-2 trial, which was considered a meaningful outcome at this advanced stage of the disease.

The panel unanimously recognized the favorable efficacy profile of fruquintinib compared to the control arm. Specifically, the 2.6-month increase in median survival

observed with fruquintinib compared to the control arm (7.6 vs. 4.8 months; HR = 0.66) was deemed clinically significant for patients with mCRC who have exhausted all currently available treatment alternatives. This survival benefit was considered particularly valuable given the limited therapeutic options in the refractory setting.

Beyond efficacy considerations, the expert panel acknowledged the favorable manageability and tolerability profile of fruquintinib demonstrated in the FRESCO-2 trial compared to the control arm. The panel agreed that the use of fruquintinib in adult patients with mCRC previously treated with available standard therapies who have progressed or are intolerant to

TABLE 3 - Consensus statements—detailed results

ID	Statement	Consensus cut-off: >70%
EPIDEMIOLOGY OF TREATMENT LINES IN mCRC		
1	At diagnosis, approximately 25% of patients with CRC present with metastases.	**92.90%**
2	Approximately 70% of patients diagnosed with mCRC will receive second-line treatment after the failure of first-line therapy.	**100.00%**
3	Approximately 40% of patients with mCRC who receive first-line treatment will go on to receive third-line treatment after the failure of second-line therapy.	**92.90%**
4	Considering the national context in current clinical practice, on average, 20-25% of patients with mCRC will receive at least one additional treatment after the failure of first-, second-, and third-line therapies.	**85.70%**
MANAGEMENT OF mCRC		
5	The limitation in the effectiveness of mCRC treatment is the inevitable development of pharmacological resistance.	**92.90%**
6	In the management of mCRC, the primary unmet need after exhausting currently available standard therapies* is the lack of effectiveness of the available therapeutic options. **fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs.*	**85.70%**
7	Best Supportive Care (BSC) refers to all interventions (e.g., nutritional support, symptomatic pharmacological therapies, etc.) aimed at symptom control of the disease.	**85.70%**
8	The clinical goal of new therapeutic options, specifically designed for treatment after current standard therapies*, is to prolong patient survival while preserving or improving quality of life. **fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs.*	**100.00%**
THE ROLE OF FRUQUINTINIB		
9	The median OS of 7.4 months observed in the FRESCO-2 registration clinical study represents a clinically significant result at this stage of the disease. **Adult patients with mCRC previously treated with available standard therapies, including fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs, who have experienced progression or shown intolerance to treatment with trifluridine-tipiracil or regorafenib*	**92.90%**
10	In the FRESCO-2 registration clinical study, fruquintinib demonstrated a favorable efficacy profile compared to the control arm.	**92.90%**
11	In the FRESCO-2 registration clinical study, fruquintinib demonstrated a favorable manageability and tolerability profile compared to currently available drugs in this setting.	**71.40%**
12	The use of fruquintinib in adult patients with mCRC previously treated with available standard therapies* who have experienced progression or shown intolerance to treatment with trifluridine-tipiracil or regorafenib results in an improvement in quality of life compared to the control arm. **fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs.*	**78.60%**
13	The tolerability and oral administration of fruquintinib facilitate better treatment management, contributing to increased therapeutic adherence and improved patient quality of life.	**92.90%**
14	The increase of 2.6 months in median OS with fruquintinib compared to the control arm (7.6 vs 4.8 months; HR = 0.66) observed in the FRESCO-2 study represents a clinically significant result in current clinical practice for patients with mCRC who have exhausted all currently available alternatives.	**78.60%**
15	In line with the positive opinion expressed on the indication of fruquintinib by the CHMP of the EMA, fruquintinib will become the standard of care for adult patients with mCRC previously treated with available standard therapies, including fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs, who have experienced progression or shown intolerance to treatment with trifluridine-tipiracil or regorafenib.	**85.70%**

treatment with trifluridine-tipiracil or regorafenib results in improved quality of life compared to the control arm.

The panel further emphasized that practical aspects of fruquintinib administration contribute to its overall clinical utility. The oral administration route and favorable tolerability profile were recognized as features that facilitate better treatment management in clinical practice, potentially contributing to increased therapeutic adherence and improved patient quality of life in this challenging treatment setting.

Based on the comprehensive evaluation of available evidence and in accordance with the indication authorized by the European Medicines Agency (EMA)—which had received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) at the time this consensus process was conducted—the expert panel unanimously agreed that fruquintinib should be established as the standard of care for adult patients with mCRC who have previously received all available standard therapies. This recommendation specifically applies to patients who have undergone prior treatment with fluoropyrimidine-based chemotherapies regimens, oxaliplatin and irinotecan, anti-VEGF drugs and anti-EGFR drugs, and who have either experienced disease progression, or demonstrated intolerance to treatment with trifluridine-tipiracil or regorafenib.

Discussion

The consensus achieved regarding epidemiological aspects of mCRC aligns with current literature, confirming that approximately one-quarter of CRC patients present with metastatic disease at diagnosis (1).

The panel's identification of pharmacological resistance as the primary limitation in mCRC treatment effectiveness echoes established understanding of disease biology. Multiple resistance mechanisms, including alterations in drug targets, activation of bypass signaling pathways, and changes in tumor microenvironment dynamics, contribute to therapeutic failure and disease progression (5-7). This biological reality underscores the urgent need for novel agents with distinct mechanisms of action capable of overcoming established resistance patterns.

At the time this consensus process was conducted, the lack of effective therapeutic options following exhaustion of standard treatments was unanimously recognized as the predominant unmet need in the management of refractory mCRC. This perspective aligns with recent reviews of the therapeutic landscape, which have consistently emphasized the limited efficacy and considerable toxicity profiles associated with current late-line treatment options (4,8). In this context, the expert panel's consensus regarding the primary clinical goal of new therapeutic agents—to prolong survival while preserving or improving quality of life—establishes a clear benchmark against which emerging therapies should be evaluated.

The panel's assessment of fruquintinib, particularly in relation to the FRESCO-2 trial results, provides important clinical context for the integration of this agent into treatment algorithms. The consensus that the observed median OS of 7.4 months represents a clinically significant outcome reflects the challenging nature of treating heavily pretreated mCRC patients, where even modest absolute gains may translate to meaningful relative improvements. The 2.6-month increase in median survival compared to placebo (HR = 0.66) was deemed particularly relevant in a setting where therapeutic options are limited, and prognosis is poor (10,11).

Beyond efficacy considerations, the panel's recognition of fruquintinib's favorable tolerability profile and oral administration route highlights the multidimensional nature of clinical benefit assessment. In patients with advanced disease who have experienced cumulative toxicities from previous treatments, tolerability becomes increasingly important as a determinant of both treatment adherence and quality of life. The consensus that fruquintinib facilitates better treatment management and potentially improves therapeutic adherence acknowledges the practical aspects of patient care that extend beyond traditional efficacy endpoints (11).

The unanimous endorsement of fruquintinib as a new standard of care for adult patients with mCRC who have progressed through available standard therapies is significant. This recommendation positions fruquintinib as an important addition to the therapeutic armamentarium for managing refractory mCRC. The consensus reflects recognition of both the efficacy and tolerability advantages demonstrated in the FRESCO-2 trial and the pressing need for effective options in this challenging clinical scenario (11).

Limitations of the study

It is important to note several limitations of this consensus process. The panel was composed exclusively of Italian oncologists, potentially limiting generalizability to different healthcare contexts. Although panelists were recruited from different Italian regions, not all regions were represented. The selection of panelists was neither systematic nor randomized; rather, the limited number of experts included reflects the choice to involve professionals with recognized national expertise and extensive experience in the management of mCRC. Panelists were selected based on their clinical reputation and contributions to the field. While this approach strengthens the credibility of the recommendations, it may further limit generalizability. Nevertheless, the structured approach, high response rate, and achievement of consensus across all statements support the validity of the recommendations.

Conclusions

This Delphi consensus highlights the substantial unmet needs that persist in the management of refractory mCRC despite advances in early-line treatment strategies. The development of resistance to standard therapies and subsequent exhaustion of effective treatment options remain significant challenges in optimizing patient outcomes. In this context, fruquintinib emerges as a valuable addition to the therapeutic landscape, offering meaningful improvements in survival with a manageable toxicity profile.

The expert panel's consensus supports the incorporation of fruquintinib into treatment algorithms for adult patients with mCRC who have progressed through available standard

therapies, including fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF drugs, and anti-EGFR drugs, and who have either experienced progression or demonstrated intolerance to trifluridine-tipiracil or regorafenib. This recommendation is based on the clinically significant survival benefit demonstrated in the FRESCO-2 trial and the favorable tolerability profile that facilitates treatment management in this heavily pretreated population.

As the therapeutic landscape continues to evolve, further research is warranted to optimize sequencing strategies and explore potential combination approaches. Nevertheless, the current evidence and expert consensus support fruquintinib as an important standard of care option that addresses a critical gap in the treatment continuum for patients with refractory mCRC.

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Disclosures

Conflict of interest: FC received personal fees for advisory roles from Merck-Serono, AstraZeneca, Eli Lilly, Roche, and Bayer. CP received personal fees for advisory roles, speaker engagements and travel and accommodation expenses from Amgen, Astellas, AstraZeneca, Bayer, Bristol Meyer Squibb, Celgene, Clovis Oncology, Eisai, Ipsen, Janssen, Incyte, Merck-Serono, Merck Sharp and Dohme, Novartis, Roche, Sandoz, Sanofi, and Servier. SS received personal fees for consulting and advisory roles with Bayer, Bristol Myers Squibb, Daiichi Sankyo, Merck, Novartis, CheckmAb, Agenus, AstraZeneca, GSK, MSD Oncology, Pierre Fabre, Seagen, and T-One Therapeutics. AS received personal fees for advisory roles and speaker engagements from Servier, Amgen, Bayer, Hutchmed, BMS, MSD Oncology, and GlaxoSmithKline. MM is a consultant of PharmaLex Italy S.p.A. and has no conflicts of interest in this research.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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