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Navigating later lines of treatment for advanced colorectal cancer – Optimizing targeted biological therapies to improve outcomes

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ABSTRACT

Colorectal cancer (CRC) is the third most commonly diagnosed cancer among males and second among females worldwide. The treatment landscape for advanced CRC (aCRC) is rapidly evolving and there are now a number of randomized trials assessing treatment of aCRC beyond first-line, prompting important questions about how to optimize therapy and maximize benefit. The availability of targeted agents has increased the complexity of post-progression treatment of aCRC. Targeted biological agents with varying modes of action are now approved for use in second-line and beyond, including the VEGF-inhibitors bevacizumab and aflibercept, the VEGFR/multikinase-inhibitor regorafenib, and the EGFR-inhibitors cetuximab and panitumumab. This article provides a systematic overview of the available phase III trial data, discusses biomarkers predictive of response to treatment, addresses safety concerns associated with specific agents, and provides practical, evidence-based recommendations for the later lines of treatment for patients with unresectable aCRC.

Introduction

Colorectal cancer (CRC) represents a significant global health burden, as the third most commonly diagnosed cancer among males and second among females [1]. Worldwide, it is estimated that over 1.23 million new cases will be diagnosed per year, with over 600,000 related deaths [1]. Approximately 30% of patients are diagnosed with metastatic disease at presentation [2], and of the 60% initially treated with curative intent, 25–40% will experience disease recurrence and progression [3,4].

The primary backbone chemotherapy (CT) recommended for advanced CRC (aCRC) remains 5-fluorouracil (5-FU) [5–8]. Treatment with 5-FU plus leucovorin improves overall survival (OS) [9,10], with further benefits gained with the addition of irinotecan or oxaliplatin in first-line [11]. More recently, the addition of targeted biologic agents to combination CT has translated into improved survival [12]. The therapeutic benefits in unresectable aCRC are achieved vis-à-vis the strategic sequencing of all available treatment options, while managing toxicity and maintaining quality of life.

The currently accepted approach to first-line treatment of unresectable aCRC involves fluoropyrimidines (5-FU or capecitabine) used alone or in combination with irinotecan or oxaliplatin, with or without biologic agents [5–8]. Bevacizumab, the humanized monoclonal antibody (mAb) targeting vascular endothelial growth factor (VEGF), is now an established biologic companion for first-line CT. More recently, favorable phase III trial results have supported use of the epidermal growth factor receptor (EGFR)-inhibitors cetuximab and panitumumab as first-line biologic companions to standard CT for the treatment of RAS wild-type aCRC [13,14]. The choice of initial therapy for aCRC informs second-line strategy, as a switch of CT (irinotecan-based to oxaliplatin-based or *vice versa*) is most common [5–7]. With respect to targeted agents, the choice of biologic agent is influenced by biologic use in first-line as well as biomarker (i.e., *RAS*) status [5–7,15]. These considerations, along with the blurring of the standard "line of therapy" approach and the increased focus on individualization of therapy, have led to significant challenges in developing targeted treatment strategies for aCRC in second-line and beyond.

Given the number of randomized trials assessing treatment of aCRC beyond first-line, the purpose of this paper is to provide a

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systematic overview of the available phase III trial data and offer practical, evidence-based recommendations for the post-progression treatment of patients with unresectable aCRC.

Methods

PubMed (to September 18, 2014) and the proceedings of the Annual Meeting of the American Society of Clinical Oncology (2012–2014), the Annual Congress of the European Society for Medical Oncology (2012–2013), the European Cancer Congress (2013), the Gastrointestinal Cancers Symposium (2012–2014), and the World Congress on Gastrointestinal Cancer (2014) were searched for phase III clinical trials involving targeted therapies in previously treated, surgically unresectable aCRC using the key search terms, or aliases for, colorectal cancer, advanced, previously treated, targeted therapy (including names of targeted agents), and phase III clinical trials (Fig. 1). The literature search was supplemented with a bibliographic review of two recently published review articles to confirm inclusion of all relevant studies. A total of 14 eligible trials were identified (Fig. 1). Data were collected from the most up-to-date published or conference-presented source(s). Directed, trial-specific searches were conducted to identify all relevant associated reports of eligible trials.

Findings

VEGF-inhibitors for the treatment of unresectable advanced colorectal cancer in second-line and beyond

Five phase III trials have investigated the addition of VEGF-inhibitors, either bevacizumab or aflibercept, to standard fluoropyrimidine plus oxaliplatin or irinotecan-based CT for the second-line treatment of unresectable aCRC (Table 1) [16–20].

Second-line bevacizumab in bevacizumab-naïve patients

E3200 compared bevacizumab (10 mg/kg every two weeks) plus FOLFOX4 with FOLFOX4 alone in a bevacizumab-naïve patient population [17]. Bevacizumab plus FOLFOX4 led to improved median progression-free survival (PFS) (7.3 months vs. 4.7 months; hazard ratio [HR] = 0.61; $p < .0001$; Table 1) and OS (12.9 months vs. 10.8 months; HR = 0.75; $p = .0011$; Table 1) vs. control, with increased rates of manageable related adverse events (AEs).

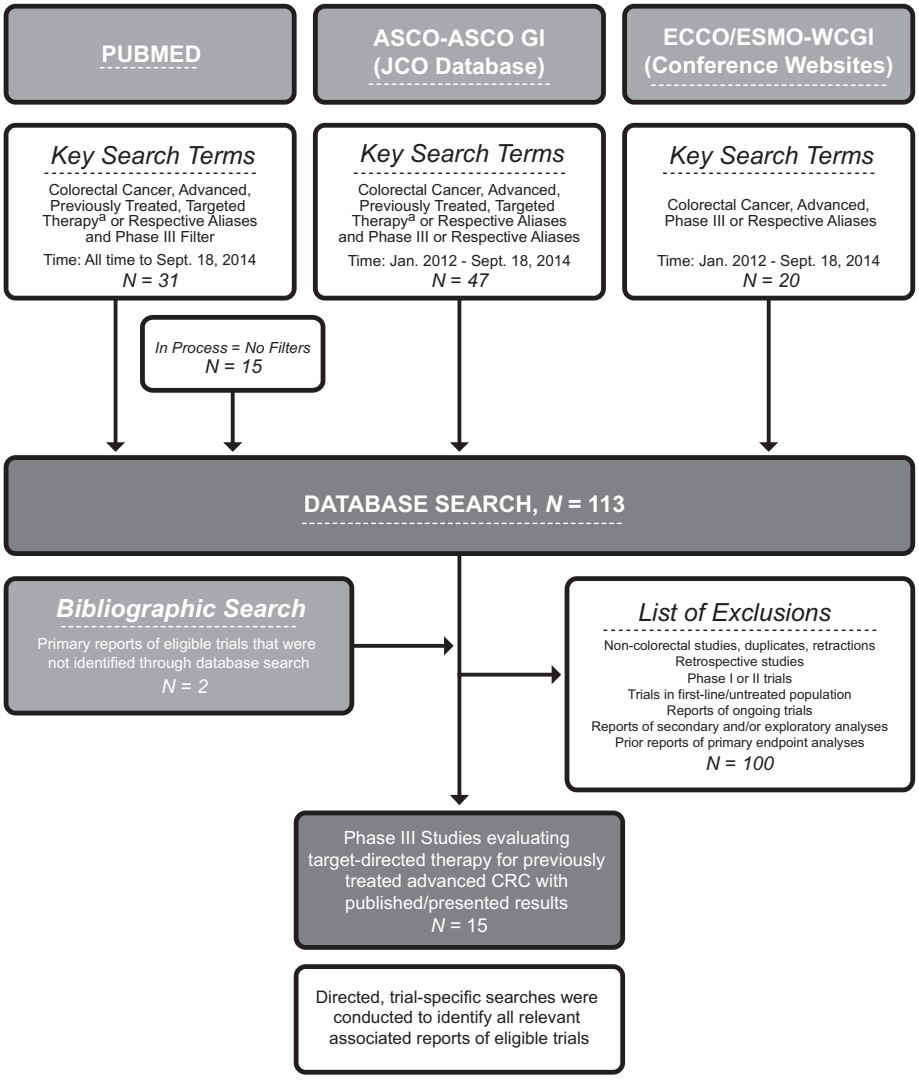

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses diagram of eligible phase III target-directed trials in previously-treated, advanced colorectal cancer. [a]Names of target-directed agents. *Abbreviations:* CRC, colorectal cancer; ASCO, American Society of Clinical Oncology; ASCO GI, American Society of Clinical Oncology Gastrointestinal Cancers Symposium; ECCO, European Cancer Congress; ESMO, European Society for Medical Oncology; WCGI, World Congress on Gastrointestinal Cancer. PubMed "Phase III" filter used for MEDLINE-indexed records.