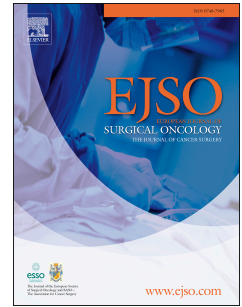# Accepted Manuscript

The role of cetuximab in converting initially unresectable colorectal cancer liver metastases for resection

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Abstract

In patients with metastatic colorectal cancer (mCRC) predominantly confined to the liver, whether a patient undergoes potentially curative resection of the liver lesions is a well-established principal determinant of long-term survival. There are a number of different agents, both chemotherapeutic and targeted biologic agents, which can aid in shrinking liver tumors, which would have otherwise been unresectable, allowing for potentially curative resection. The aim of this this review article is to summarize the available evidence regarding optimal therapeutic strategies for converting initially unresectable metastases for potentially curative resection; we do not discuss patients who present with initially resectable disease. We have taken the approach to review trials that included R0 resection rates as one of the principal study endpoints and specifically enrolled patients with liver limited disease. Primary tumor location has recently emerged as a putative prognostic and predictive factor in patients with mCRC; however, presently, there is a lack of resectability outcomes differentiating tumor location-defined subgroups and several ongoing trials and retrospective analyses are anticipated to guide insights in the future. In conclusion, in patients with *RAS* wild-type mCRC, the data support preferential use of the anti–epidermal growth factor receptor monoclonal antibody cetuximab when combined with standard-of-care infusional doublet chemotherapy regimens (FOLFOX or FOLFIRI) for the conversion of initially unresectable metastases for potentially curative resection. Furthermore, we discuss data involving intensified chemotherapy regimens (ie, 3-drug backbones such as FOLFOXIRI with or without a targeted biologic agent) to promote the conversion of initially unresectable metastases for potentially curative resection.

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Introduction

Despite significant progress over the past 20 years in terms of both the prevention and treatment of colorectal cancer (CRC), the disease remains a leading cause of cancer-associated mortality worldwide.[1] However, improvements in both targeted therapy and surgical intervention have significantly improved survival in patients with metastatic CRC (mCRC): Median survival now exceeds 30 months in randomized, phase 3 clinical trials involving patients with *RAS* wild-type (*RAS*-wt) mCRC.[2-5]

The prognosis for patients with mCRC depends on the extent of metastatic disease. Patients with liver-limited disease (LLD) have superior long-term survival outcomes relative to patients whose metastatic disease is more widely spread beyond the liver.[6] This is attributable, at least in part, to patients with LLD having an increased probability of undergoing potentially curative surgical resection of their metastatic lesions, which serves as a well-established principal determinant of long-term survival in patients with mCRC (resected patients with LLD can have a median survival of >60 months).[6]

It is critical to note that patients with mCRC can be deemed resectable either at initial diagnosis or following conversion therapy. Specifically, some patients present with initially unresectable disease due to tumor size, number of lesions, location of lesions, or other poor prognostic factors. However, by administering chemotherapy ± a biologic agent to suitable patients, it is possible to "convert" (via shrinkage and response of tumor lesions to therapy) initially unresectable metastatic lesions for potentially curative resection in a meaningful number of these initially unresectable cases.[7]

Nevertheless, it should be noted that, currently, no definition of "resectable" mCRC is universally accepted. Even among highly experienced hepatic surgeons, clinical opinions can differ due to a variety of factors. In fact, surgical experience or skill itself is a possible consideration when discussing resectability. Indeed, even patients with extrahepatic metastatic disease can present as potential candidates for resection in certain circumstances.[8]

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An evaluation by a multidisciplinary team (MDT) can also enhance the probability of ultimately undergoing potentially curative surgical resection. MDTs typically comprise oncologists, surgeons, pathologists, radiologists, and other healthcare providers, who all function collaboratively at multiple timepoints to ensure optimal treatment decisions for patient management. An MDT approach is therefore an emerging standard of care for effectively treating mCRC and is particularly important within the context of assessing resectability. More specifically, the absence of an MDT that includes an experienced hepatic surgeon, may result in patients with potentially resectable disease being precluded from receiving surgery with curative intent. This may lead to lower rates of resected patients, particularly in non–academic or community settings.[9-12] Empirical confirmation of this supposition has recently been provided by a central retrospective radiographic review of tumor lesions from the phase 3 FIRE-3 trial conducted by MDTs that included surgeons and medical oncologists. This study reported that multidisciplinary decision making would have afforded numerous additional opportunities for surgical resection.[12]

Although routine clinical practice in some countries may not conform fully to consensus guidelines, the ESMO guidelines advocate for the preferential use of an anti–epidermal growth factor receptor (anti-EGFR) antibody (cetuximab or panitumumab) for the conversion of initially unresectable metastases in patients with *RAS*-wt mCRC. The majority of the available supportive data derive from trials in which cetuximab is combined with standard-of-care infusional chemotherapy backbones: fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or fluorouracil, leucovorin, and irinotecan (FOLFIRI). Intensified regimens containing infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) chemotherapy in conjunction with a biologic are also described as a standard treatment option for the conversion of initially unresectable metastases.[20]

This article will summarize the available evidence for converting initially unresectable metastases for potentially curative resection, including data involving intensified FOLFOXIRI chemotherapy backbones.

Methods

This review article will focus specifically on strategies for converting initially unresectable mCRC liver metastases for surgical resection. Accordingly, we will not discuss patients with widespread disease who would be treated with palliative intent nor studies conducted in patients who present with initially resectable mCRC. Thus, while we acknowledge the findings of the New-EPOC and Bendell et al trials, these studies will not be discussed in this review article, as these trials were conducted in a different patient population. Specifically, both studies included many patients with initially resectable disease). Such differences in approach also mirror the separation drawn in the updated European Society for Medical Oncology (ESMO) consensus guidelines.[13-19 20 21] Therefore, it has historically been challenging to draw meaningful cross-trial comparisons regarding rates of conversion of initially unresectable metastases for potentially curative surgical resection.

In an endeavor to circumvent these challenges, here we focus on clinical trials that included R0 resection rate as one of the principal study endpoints, as well as real-world studies designed to further address the topic of resectability. Our rationale stems from the notion that trials that were specifically designed to assess resectability are more likely to have remained vigilant of the above-described challenges. Thus, these trials may provide a more robust measure of surgical conversion rates in patients with initially unresectable mCRC. Indeed, we and others have previously noted that R0 resection rates are historically lower in clinical trials that were not designed to assess resectability (Figure 1).[22]

Most trials that included R0 resection rates as one of the principal study endpoints specifically enrolled patients with LLD, with the main aim of the study being resectability. Studies conducted in the

palliative patient population may also record resection rates, but these patients are not similarly strong candidates for conversion to resectability. Accordingly, in our discussion below, we have carefully specified whether the cited resection rates apply to the overall mixed patient population or to the (prognostically more favorable) LLD subgroup.

We also acknowledge the potential clinical benefits of R1 resections.[23,24] However, there is no uniform consensus on the definition of "R1" and R1 resection rates are not consistently reported in the literature and therefore cannot be discussed exhaustively here.

Finally, while resectability data for patients with initially unresectable mCRC treatment with nonintensified chemotherapy alone (ie, singlet/doublet chemotherapy that is not administered in combination with cetuximab, panitumumab, or bevacizumab) are available from a number of historical trials,[25-29] these findings will be reviewed only as appropriate to the available data and treatment landscape.

Resection rates in key mCRC clinical trials involving patients with initially unresectable metastases

Data evaluating a role for cetuximab in converting initially unresectable mCRC for resectability

Table 1 summarizes the available evidence evaluating the use of cetuximab in combination with conventional (ie, irinotecan- or oxaliplatin-based) chemotherapy backbones in clinical trials that evaluated patients with initially unresectable mCRC. All listed studies included R0 resection rate as one of the principal study endpoints. Assessed collectively, these data demonstrate that cetuximab in combination with conventional chemotherapy is consistently able to elicit impressive R0 resection rates in patients with initially unresectable disease who have *(K)RAS*-wt tumors.

Perhaps of paramount importance among these clinical trials is the Chinese BELIEF study (initially referred to as NCT01564810, with the BELIEF acronym only used for the *RAS* analysis). BELIEF was a phase 4 trial that assessed the impact of adding cetuximab to either FOLFOX or FOLFIRI in patients

with initially unresectable LLD compared to chemotherapy alone.[30,31] In the original *KRAS*-wt population, the addition of cetuximab to FOLFOX or FOLFIRI significantly increased the primary endpoint of R0 resection rate (25.7% vs 7.4%; $p < .01$). The key secondary endpoints of objective response rate (ORR; 57.1% vs 29.4%; $p < .01$), overall survival (median OS; 30.9 vs 21.0 months; $p = .013$), and progression-free survival (median PFS; 10.2 vs 5.8 months; $p = .004$) were also significantly improved.[30] Upon assessment of expanded *RAS* mutational status (exons 2-4 of both *KRAS* and *NRAS*), in general, the cetuximab-induced treatment effects were numerically even more pronounced. R0 resection rate (26.7% vs 6.3%; $p = .013$), ORR (62.2% vs 29.2%; $p = .002$), median OS (35.1 vs 21.7 months; $p = .009$), and median PFS (9.8 vs 5.3 months; $p = .002$) outcomes were all significantly greater in the cetuximab plus FOLFOX or FOLFIRI arm vs the chemotherapy-alone arm.[31]

Importantly, the outcomes of the studies cited in Table 1 collectively support the importance of successful implementation of an MDT approach when using cetuximab-based regimens, as high R0 resection rates were consistently observed in cetuximab trials that incorporated an MDT requirement in their study design.[32-34]

Notably, the randomized, phase 2 CELIM trial has suggested that the resection-promoting activities of cetuximab in patients with initially unresectable mCRC are similar when combined with either FOLFOX or FOLFIRI chemotherapy backbones.[32,33] CELIM also informed us that "convertability" is not a static concept. Specifically, liver surgery timing is not predetermined for best outcomes, in contrast to for example, New-EPOC, where surgery was mandated after 3 months of chemotherapy. Other clinical studies have also demonstrated that cetuximab is safe and effective when combined with either oxaliplatin- or irinotecan-based conventional chemotherapy backbones involving infusional fluorouracil.[5,35-38]

Despite these trials not being specifically designed to assess resectability, observations from the randomized, phase 3 CRYSTAL and phase 2 OPUS studies support the notion that adding cetuximab to

conventional chemotherapy improves R0 resection rates in patients with initially unresectable LLD who have *(K)RAS*-wt tumors. Indeed, in the *RAS*-wt population of CRYSTAL, the R0 resection rate was increased from 6.5% to 16.3% with the addition of cetuximab to FOLFIRI in patients with LLD. Similar findings were reported in the *KRAS*-wt population of OPUS, although the *RAS*-wt population was too small to permit meaningful interpretation).[39,40] Notably, these data from CRYSTAL and OPUS further show that the addition of cetuximab to FOLFIRI and FOLFOX, respectively, also numerically increases R0 resection rates in patients with non-LLD who have *(K)RAS*-wt mCRC, indicating that even patients who have more widespread metastatic disease beyond the liver may also have enough tumor shrinkage to enable R0 resection to take place.[39,40] Also of interest, Adam et al showed that even in patients who had failed to become resectable with chemotherapy alone, rescue treatment with cetuximab was able to ensure meaningful rates of hepatic resection.[42]

While the above-described findings reinforce the importance of the MDT approach, the lack of widespread implementation of MDTs at the time of the CRYSTAL and OPUS studies may have reduced the absolute number of R0 resections in both treatment arms of the LLD as well as the non-LLD subgroups.[9-12] In contrast to these data from CRYSTAL and OPUS, the randomized, phase 3 COIN study did not report an increase in potentially curative liver resections—despite an increase in ORR—with the addition of cetuximab to oxaliplatin-based chemotherapy in the LLD subgroup of patients with initially unresectable disease.[43] However, interpretation of the COIN data is limited by the use of a noninfusional fluorouracil-containing chemotherapy regimen (CAPOX) in combination with cetuximab in many patients, which was previously postulated to account for the unexpectedly negative findings of this trial.[44]

In further support of the observation that cetuximab promotes the conversion of initially unresectable metastases, real-world evidence from the *KRAS*-wt populations of the EREBUS and ERBITAG observational studies suggests that cetuximab in combination with conventional chemotherapy

elicits impressive resection rates. In EREBUS, the resection rate was 20.8% in the overall population and 36.7% in the LLD subgroup.[45] An interim analysis of ERBITAG reported an R0 resection rate of 16.9% in the overall population and 30.6% in the LLD subgroup.[46] These findings reinforce real-world observations from the *KRAS* wt population of patients with initially unresectable LLD included in the RESECT study, in which a 28% R0 resection rate was reported.[34]

Data evaluating a role for panitumumab in converting initially unresectable mCRC for resectability

In contrast to the wealth of evidence described above supporting a pivotal role for cetuximab in conversion therapy for patients with *RAS*-wt mCRC, to date only limited data have evaluated whether panitumumab in combination with conventional chemotherapy also promotes conversion to resectability in patients with initially unresectable mCRC. Indeed, there has been only a single panitumumab trial specifically designed to assess resectability in a pure population of patients with initially unresectable mCRC: the phase 2 PLANET study, which randomized patients with LLD who had *KRAS*-wt tumors to receive panitumumab in combination with either FOLFOX or FOLFIRI and reported that 51.9% of patients underwent surgical resection of liver metastases after perioperative treatment (77.5% of these resections were either R0 or R1).[47]

When also considering trials that were not specifically designed to assess resectability, the complete resection rate was only modestly numerically higher with the addition of panitumumab to FOLFOX in patients with initially unresectable *KRAS*-wt mCRC in the randomized, phase 3 PRIME trial (10% vs 8%, although the complete resection rate was numerically higher in the panitumumab arm in the LLD subgroup [28% vs 18%]). In this analysis, resections were categorized as either "complete" or "partial," and the status of the surgical margins was not recorded.[48] Furthermore, in the *KRAS*-wt population of the randomized, phase 2 PEAK trial of patients with initially unresectable mCRC, the R0

resection rate was comparable between the panitumumab plus FOLFOX and bevacizumab plus FOLFOX arms (10% vs 8%, respectively).[4]

Hence, despite the fact that panitumumab is frequently grouped together with cetuximab under the heading "anti-EGFR antibody," currently only limited data have evaluated safety and the resection-promoting role for panitumumab in patients with initially unresectable mCRC.

Data evaluating a role for bevacizumab in converting initially unresectable mCRC for resectability

Similarly, limited studies have evaluated whether bevacizumab in combination with conventional chemotherapy promotes conversion to. The only dedicated study in which R0 resection rate was a principal endpoint in a pure population of patients with initially unresectable mCRC was a relatively small, single-arm, phase 2 study evaluating bevacizumab in combination with FOLFOX in patients with LLD. Although the data appeared positive (R0 resection rate = 44.4%),[49] a clear need exists for additional empirical evidence to support a resection-promoting role for bevacizumab in combination with conventional chemotherapy.

When studies that were not specifically designed to assess resectability are also considered, a large meta-analysis of 29 bevacizumab trials that included 3502 patients treated with bevacizumab plus FOLFIRI reported a 9.3% pooled rate of surgical resection of metastases without stipulation of outcome (with an 18% rate of liver resections).[50] In the randomized, phase 3 NO16966 study, adding bevacizumab to oxaliplatin-based chemotherapy increased neither the R0 resection rate nor the ORR.[51] Furthermore, real-world data from the ETNA cohort of patients treated with bevacizumab plus irinotecan-based chemotherapy reported an R0 resection rate in the overall patient population of 12.2% (only 14.7% in the LLD subgroup),[52] which is very similar to that observed for irinotecan alone.[53] Thus, only limited evidence is available supporting a resection-promoting role for bevacizumab. Furthermore, given bevacizumab's angiogenesis-based mechanism of action and established impact on wound healing, it

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has been noted that, following neoadjuvant bevacizumab, a longer therapy-free interval prior to surgery is needed to circumvent potential bleeding-related issues.[22]

Head-to-head trials of cetuximab vs bevacizumab in conjunction with conventional chemotherapy

Importantly, studies in both the conversion and palliative setting have now begun to evaluate cetuximab vs bevacizumab head-to-head in terms of their capacity to convert initially unresectable metastases for potentially curative resection in combination with conventional chemotherapy in patients with *RAS*-wt mCRC. Currently, no head-to-head data compare first-line cetuximab vs panitumumab – nor first-line panitumumab vs bevacizumab – in this setting.

In a single-institution, 3-arm study (n = 104) that used resection rate as the primary study endpoint, a trend was observed that favored cetuximab plus conventional chemotherapy (FOLFOX or FOLFIRI) vs FOLFOX or FOLFIRI alone vs bevacizumab plus FOLFOX or FOLFIRI (resection rate = 51.4% vs 43.3% vs 30.7%, respectively; cetuximab vs bevacizumab comparison: hazard ratio [HR] = 0.42; 95% CI, 0.14-1.20; p = .07) in patients with initially unresectable *KRAS*-wt mCRC.[54]

Two head-to-head studies that did not specifically emphasize resectability as a principal study endpoint were FIRE-3 and CAGB/SWOG 80405. Data from the *RAS*-wt population of the randomized, phase 3 FIRE-3 trial showed that the percentage of patients who discontinued treatment owing to their eligibility for secondary resection of metastases was comparable between patients who were treated with cetuximab plus FOLFIRI vs those receiving bevacizumab plus FOLFIRI (11.6% vs 11.0%, respectively).[55] However, in the *KRAS*-wt population of the randomized, phase 3 CALGB/SWOG 80405 trial, although the long-term outcomes for successfully resected patients were similar between treatment arms, more patients treated with cetuximab plus conventional chemotherapy (either FOLFOX or FOLFIRI) underwent surgical resection than those in the bevacizumab plus FOLFOX or FOLFIRI arm (n = 105 [18.2%] vs n = 75 [13.4%], respectively).[56]

Notably, these observations are largely consistent with a previously proposed model that improved ORR leads to improved conversion to resectability (Figure 1),[22,57] likely via the induction of superior tumor shrinkage. Because cetuximab consistently elicited a higher ORR than bevacizumab in head-to-head, phase 3, randomized clinical trials involving patients with initially unresectable *RAS*-wt mCRC,[5,58] it is therefore logical that cetuximab would also better facilitate conversion to resectability. Finally, it should be stated that more sophisticated metrics for assessing response and tumor shrinkage (eg, quantitative assessments of depth of response [DpR], which is commonly defined as the maximal extent of tumor shrinkage) may reflect the activity of therapeutic agents even better than conventional ORR in patients with mCRC.[59] Logically, then, cetuximab plus FOLFIRI showed significantly greater DpR compared to bevacizumab plus FOLFIRI in the head-to-head FIRE-3 trial (−48.9% vs −32.3%; $p < .0001$) and DpR correlated significantly with PFS and OS.[60]

Taken together, the evidence cited above suggests that it would be beneficial to favor the use of cetuximab (vs bevacizumab) when combined with standard-of-care FOLFOX or FOLFIRI chemotherapy backbones for the conversion of initially unresectable metastases in patients with *RAS*-wt mCRC.

Emerging data involving intensified chemotherapy regimens (FOLFOXIRI)

The preceding discussions have been confined to trials employing conventional doublet chemotherapy backbones (eg, FOLFOX or FOLFIRI) combined with biologic agents. However, resectability data involving intensified (triplet) FOLFOXIRI chemotherapy backbones in patients with initially unresectable mCRC are also now emerging. Table 2 summarizes the available evidence evaluating the utility of FOLFOXIRI chemotherapy backbones (in combination with bevacizumab or cetuximab) in clinical trials that evaluated patients with initially unresectable mCRC and included R0 resection rate as one of the principal study endpoints.

The randomized, phase 2 OLIVIA trial compared bevacizumab plus FOLFOXIRI vs bevacizumab plus FOLFOX (ie, evaluated the effect of adding irinotecan to bevacizumab plus FOLFOX) in patients with initially unresectable LLD. Overall resection rate (R0/R1 and /R2) was the primary study endpoint, with R1 and R2 rates serving as a quality-assurance comparison. The authors reported that R0 resection rates were higher in the bevacizumab plus FOLFOXIRI arm (49% vs 23%).[61]

In contrast, in the randomized, phase 3 TRIBE study, although not a dedicated resectability study, the R0 resection rate was not improved upon intensifying the chemotherapy backbone in conjunction with bevacizumab (R0 resection rates = 15% vs 12% [32% vs 28% within the LLD subgroup] in the bevacizumab plus FOLFOXIRI and bevacizumab plus FOLFIRI arms, respectively). This study evaluated the impact of adding oxaliplatin to bevacizumab plus FOLFIRI.[62] This finding differs from prior observations from the randomized, phase 3 GONO trial, in which the R0 resection rate was increased from 6% in the FOLFIIRI arm to 15% in the FOLFOXIRI (12% vs 36%, respectively, within the LLD subgroup).[63] Thus, whereas adding oxaliplatin to FOLFIRI appeared to increase the R0 resection rate in the absence of bevacizumab, no notable increase in the R0 resection rate was reported when bevacizumab was also included in the intensified therapeutic regimen. In the phase 2 STEAM trial, adding irinotecan to bevacizumab plus FOLFOX numerically improved R0 resection rates (15% vs 6%) in the first-line treatment of patients with initially unresectable mCRC.[64] Importantly, whether the addition of bevacizumab to FOLFOXIRI improves R0 resection rates has not yet been evaluated (the above studies only assessed intensifying the chemotherapy backbone itself and don't allow evaluation of whether any benefit is derived from adding bevacizumab to an intensified regimen). In this respect, the results of a recently published pooled analysis of 3 GONO trials, as well as a second pooled analysis of 11 trials, investigating resection rates in patients treated with bevacizumab plus FOLFOXIRI (not dedicated to resectability)—which reported, respectively, a 36.1% R0/R1 resection rate in patients with LLD and a 39.1% surgical conversion rate (28.1% R0 resection) in an unselected population —fail to provide

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definitive evidence supporting a resection-promoting role for bevacizumab in combination with FOLFOXIRI.[65,83]

Importantly, presently available data suggest that intensifying the chemotherapy regimen administered in conjunction with cetuximab may be an alternative (or, in certain contexts, even an improvement) over cetuximab plus doublet chemotherapy in terms of converting initially unresectable metastases for potentially curative resection in patients with *RAS*-wt mCRC, albeit using a modified FOLFOXIRI schedule due to toxicity concerns with the cetuximab plus FOLFOXIRI combination.

In a single-arm, phase 2 study that included both initially unresectable patients with LLD and those with extrahepatic disease, Saridaki et al reported an R0 resection rate of 37% in patients treated with cetuximab plus FOLFOXIRI who had *KRAS*-wt mCRC.[66]

Similarly, a 60% R0 resection rate was observed in the single-arm, phase 2 POCHER trial, in which *RAS*-unselected patients with initially unresectable LLD were treated with cetuximab plus triplet chemotherapy (chrono-IFLO [irinotecan, fluorouracil, leucovorin, and oxaliplatin]).[67] Notably, the POCHER study design incorporated an MDT requirement, which may have optimally facilitated the likelihood of detection of conversion to potential resectability.

Furthermore, the single-arm, phase 2 OPTILIV study, which investigated the activity of cetuximab in combination with hepatic artery infusion of intensified chemotherapy in previously treated patients with initially unresectable LLD who had *KRAS*-wt tumors, met its primary endpoint (R0/R1 resection rate = 29.7%).[68] This observation is consistent with prior reports suggesting the utility of hepatic artery infusion for converting initially unresectable metastases for resection.[69]

Also of interest, data from the single-arm, phase 2 ERBIFORT trial suggest that patient selection on the basis of *UGT1A1* status may effectively identify individuals who can tolerate regimen intensification (here, high-dose irinotecan delivered within the context of a FOLFIRI chemotherapy

backbone vs a triple combination). This resulted in an 80.7% rate of metastatic resection in these biomarker-selected patients who received high-dose irinotecan.[70]

Critically, the preliminary head-to-head data favor cetuximab vs bevacizumab within the context of the FOLFOXIRI backbone in patients with initially unresectable mCRC. Data from the *(K)RAS*-wt population of the phase 2 METHEP-2 trial, which randomized patients to receive either FOLFOX, FOLFIRI, or FOLFOXIRI in combination with a targeted agent (either bevacizumab or cetuximab, with the assignment dependent on *[K]RAS* biomarker status), suggest that not only was the rate of R0/R1 resection numerically higher in patients treated with FOLFOXIRI (vs FOLFOX or FOLFIRI), but also in patients receiving cetuximab vs bevacizumab (55.6% vs 44.7%; unstratified for chemotherapy backbone and also subject to the caveat that comparison between cetuximab vs bevacizumab was not supported by randomization and may be confounded by differences in *[K]RAS* status).[71] These observations build on previous data from the randomized, phase 2 METHEP trial, in which patients with initially unresectable mCRC receiving FOLFOXIRI had a numerically higher rate of conversion to resectability vs those patients receiving FOLFOX or FOLFIRI (67% vs 40%).[72]

Analogously, in the randomized, phase 2 MACBETH study, R0 resection rates were numerically higher in patients with *RAS*-wt/*BRAF*-wt tumors receiving maintenance cetuximab vs bevacizumab following 8 cycles of induction with cetuximab plus FOLFOXIRI in the first line (32.2% vs 22.8% in the overall population and 53.6% vs 45.8% within the LLD subgroup, respectively).[73]

Taken together, these exciting initial observations provide a clear impetus for further evaluation of the capacity of cetuximab in combination with FOLFOXIRI to promote the conversion of initially unresectable metastases in patients with *RAS*-wt mCRC. Thus, we eagerly anticipate the completion of the ongoing CELIM2, DEEPER, and FOCULM trials. Notably, they raise the possibility that cetuximab plus FOLFOXIRI may prove to be a viable alternative to bevacizumab plus FOLFOXIRI in these patients. In this respect, the ongoing CELIM2 trial is particularly pivotal, as this large (n = 232) study is anticipated to

afford not only insights regarding the optimal chemotherapy backbone for promoting conversion to resectability (FOLFIRI vs FOLFOXIRI) but perhaps also the optimal antibody to combine with chemotherapy in this setting (cetuximab vs bevacizumab). Although, at present, the data are more limited, further study of panitumumab in combination with FOLFOXIRI is also merited (eg, the VOLFI study).

Conclusions

In this review article, we have synthesized and contextualized data pertaining to optimal therapeutic strategies for converting initially unresectable metastases for potentially curative resection in patients with mCRC, a treatment outcome that is inextricably associated with improved long-term survival. Importantly, this guidance strongly recommends that patients with initially unresectable mCRC should be evaluated within the context of an MDT at multiple timepoints, an emerging standard of care that has proven essential for ensuring that no eligible patients are precluded from undergoing potentially curative surgical resection of their metastatic lesions.

Of course, even when optimally assessed within the context of an MDT, not all patients with mCRC will have an opportunity to benefit from liver surgery. It is therefore essential to bear in mind the important improvements in nonsurgical treatments (both targeted therapy and chemotherapy), which have significantly contributed to improved survival (median OS now exceeds 30 months in randomized, phase 3 clinical trials involving patients with *RAS*-wt mCRC).[2-5] However, an important open topic involves how best to manage patients with never-resectable disease, particularly in light of the fact that median OS is only one metric that may not fully account for various quality-of-life considerations, including control – and not just cure – of liver metastases.

Although primary tumor location has recently emerged as a putative prognostic and predictive factor in patients with mCRC,[74] at present, there is a lack of resectability data within tumor location–

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defined subgroups (save several recent reports that the prognostic difference in left- vs right-sided tumors persists even following surgical resection of LLD[75-77]). We eagerly anticipate dedicated resectability data on this important topic (eg, from the ongoing CELIM2 trial). Until such additional data are available, we will refrain from espousing firm treatment recommendations, although we note that a trend toward improved response rates in patients with right-sided tumors receiving anti-EGFR antibodies may hold implications when conversion to resectability is the therapeutic goal.

Taken together, the available evidence supports the preferential use of an anti-EGFR antibody (with the majority of the available supportive data deriving from cetuximab trials) in combination with standard-of-care FOLFOX or FOLFIRI chemotherapy backbones for the conversion of initially unresectable metastases in patients with *RAS*-wt mCRC.

Furthermore, we acknowledge the recent publication of even more positive resectability data from therapeutic strategies involving an intensified FOLFOXIRI chemotherapy backbone in patients with initially unresectable mCRC. In fact, higher rates of conversion to resectability have been observed in multiple studies comparing FOLFOXIRI vs either FOLFOX or FOLFIRI. Notably, evidence supporting the utility of cetuximab plus FOLFOXIRI vs bevacizumab plus FOLFOXIRI for the conversion of initially unresectable metastases in patients with *RAS*-wt mCRC is now emerging. It should be noted that not all patients are suitable for an intensified – and potentially more efficacious – FOLFOXIRI regimen, which has significant tolerability concerns (including the potential for liver damage) in comparison to well-established conventional chemotherapy backbones such as FOLFOX and FOLFIRI. Accordingly, the current evidence supports that cetuximab plus either FOLFOX or FOLFIRI remains the standard-of-care regimen for effectively converting initially unresectable metastatic lesions for potentially curative resection in patients with *RAS*-wt mCRC.

Conflict of Interest Statement

GP has attended advisory boards for Merck KGaA, BTG, and Sirtex, and is on the speaker panels of those organizations. RA has received honoraries (ad-hoc advisory boards and lectures) from Merck, Amgen, and Sanofi. BB is an employee of Merck KGaA. RE is an employee of Merck KGaA and reports stock ownership. HW has attended advisory boards and given lectures for Merck KGaA, Roche, and Sirtex. The rest of the authors have nothing to disclose.

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Tables

Table 1. Available clinical evidence evaluating the utility of cetuximab in combination with conventional chemotherapy backbones in studies that included R0 resection rate as one of the principal study endpoints.

Study	Patient Population	Treatment Groups (relevant arms only)	n	Primary Endpoint	R0 Resection Rate	Reference
BELIEF	*KRAS*-wt initially unresectable LLD	Cetuximab + FOLFOX/FOLFIRI vs FOLFOX/FOLFIRI	138	R0 resection rate	25.7% vs 7.4%	30
	RAS-wt initially unresectable LLD	Cetuximab + FOLFIRI/FOLFOX vs FOLFIRI/FOLFOX	93	R0 resection rate	26.7% vs 6.3%	31
CELIM	*RAS*-unselected initially unresectable LLD	Cetuximab + FOLFOX vs cetuximab + FOLFIRI	106	ORR	38% vs 30%	32
	KRAS-wt initially unresectable LLD	Cetuximab + FOLFOX/FOLFIRI	67	ORR	32.4%	33
RESECT	*KRAS*-wt initially unresectable LLD	Cetuximab + CT*	60	R0 resection rate	28%	34
CLIME	*KRAS*-wt initially unresectable LLD	Cetuximab + FOLFOX	100	R0 resection rate	27%	78
Ashwin et al	*KRAS*-wt initially unresectable LLD	Cetuximab + FOLFIRI/FOLFOX vs FOLFIRI/FOLFOX	152	ORR	42.1% vs 28.9%	79
Somashekhar et al	*KRAS*-wt initially unresectable LLD	Cetuximab + FOLFOX/FOLFIRI	46	R0 resection rate	60.9%	80
Ji et al	*KRAS*-wt initially unresectable LLD	Cetuximab + FOLFOX	73	R0 resection rate	27%	81
Min et al	*RAS*-unselected initially unresectable LLD and non-LLD	Cetuximab + FOLFIRI	23	R0 resection rate	30.4%	82

CT, chemotherapy; FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; LLD, liver-limited disease; ORR, objective response rate; wt, wild-type.

*The chemotherapy backbone was FOLFOX- or FOLFIRI-based in ≈75% of patients; other chemotherapy backbones included irinotecan, oxaliplatin, capecitabine + oxaliplatin, and oxaliplatin + fluorouracil.

Table 2. Available clinical evidence evaluating the utility of FOLFOXIRI chemotherapy backbones in combination with bevacizumab or cetuximab in studies that included R0 resection rate as one of the principal study endpoints.

Study	Patient Population	Treatment Groups (relevant arms only)	n	Primary Endpoint	R0 Resection Rate	Reference
OLIVIA	*RAS*-unselected initially unresectable LLD	Bevacizumab + FOLFOXIRI vs bevacizumab + FOLFOX	80	Overall resection rate (R0/R1/R2)	49% vs 23%	61
Saridaki et al	*KRAS*-wt initially unresectable LLD and non-LLD	Cetuximab + FOLFOXIRI	30	ORR	37%	66
METHEP-2	*(K)RAS*-wt initially unresectable LLD*	Cetuximab + FOLFOX/FOLFIRI/ FOLFOXIRI vs bevacizumab + FOLFOX/FOLFIRI/ FOLFOXIRI	256	R0/R1 resection rate	55.6% vs 44.7%**	71***
MACBETH	*RAS*/*BRAF*-wt initially unresectable LLD and non-LLD	Cetuximab + FOLFOXIRI + maintenance	116	10-month progression-free rate	32.2% vs 22.8%	73***
	RAS/*BRAF*-wt initially unresectable LLD	cetuximab vs cetuximab + FOLFOXIRI + maintenance bevacizumab	52		53.6% vs 45.8%	

FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan; LLD, liver-limited disease; ORR, objective response rate; wt, wild-type.

* *(K)RAS*-wt requirement pertains only to the cetuximab-containing arm

** Combined R0/R1 resection rate (the R0 resection rate was not reported in the poster).

*** Data derive from congress presentations and therefore remain preliminary.

Figures

Figure 1. Association between objective response rate (ORR) and resection rate in clinical trials involving patients with metastatic colorectal cancer, stratified on the basis of whether resection was included as a secondary study endpoint.
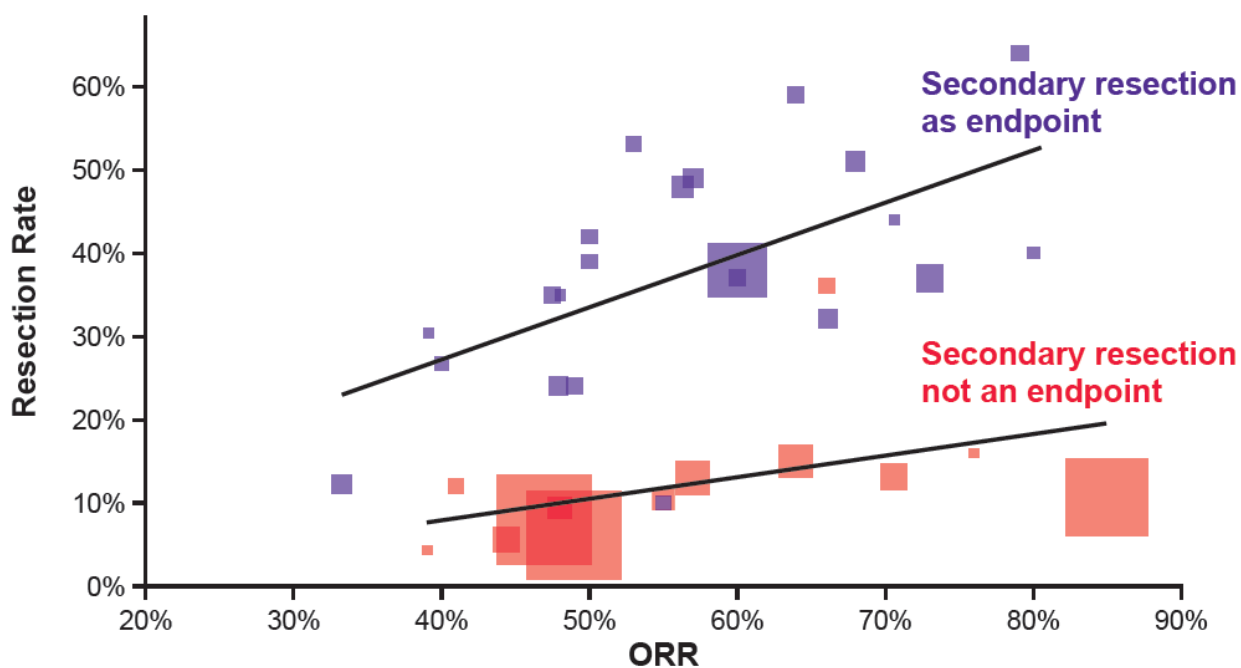
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The size of each square denotes the relative number of patients included in the study.