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Systematic or Meta-analysis Studies

Retreatment with anti-EGFR monoclonal antibodies in metastatic colorectal cancer: Systematic review of different strategies

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ABSTRACT

Background: Despite advances in precision oncology and immunotherapy of tumors, little progress has been made in metastatic colorectal cancer (mCRC) in recent years. Therefore, making the most of available therapies is a necessity. Several studies, based on the pulsatile behavior of *RAS* clones under EGFR blockade, investigated whether readministration of EGFR-targeted agents is effective beyond second line.

Methods: A systematic review of studies of retreatment with anti-EGFR monoclonal antibodies has been performed from January 2005 to December 2018 according to PRISMA criteria from PubMed, ESMO and ASCO meetings libraries and Clinicaltrial.gov. Efficacy has been evaluated as objective response rate and survival in available publications. In addition, type and incidence of side effects occurring during on anti-EGFR retreatment have been considered.

Results: 26 publications have been retrieved, of which 20 full-text articles and 6 abstracts and categorized as for the retreatment strategy into five groups: rechallenge (n = 10), reintroduction (n = 4), sequence (n = 5), dose escalation (n = 1) and mixed (n = 6). Data of efficacy displayed high heterogeneity across different strategies (objective response rate, ORR = 0.0–53.8%; disease control rate, DCR = 24.0–89.7%), with best results in the setting of rechallenge (ORR = 2.9–53.8%; DCR = 40.0–89.7%).

Conclusions: Rechallenge with anti-EGFR provides clinical benefit in molecularly selected mCRC patients beyond second line. Further ctDNA-guided studies comparing this option of treatment with current approved advanced line treatments are warranted.

Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer worldwide, causing every year more than 1,500,000 deaths worldwide [1,2]. Overall survival (OS) after 5 years from diagnosis of CRC is 60% [3]. Median OS for patients with metastatic CRC (mCRC) is up to 30 months and more than double if compared to 20 years ago [3–7]. However, despite advances in precision oncology and immunotherapy of tumors, little progress has been made in mCRC in more recent years. Therefore, making the most of available therapies is a necessity.

Molecularly targeted agents offered more therapeutic options improving both progression-free survival (PFS) and OS of mCRC patients [6]. As reported by the most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines and by the National Comprehensive Cancer Network (NCCN) for treatment of mCRC, several biological targeted agents are recommended for first-line and second-line treatments in combination with FOLFOX, FOLFIRI or FOLFOXIRI

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[8,9]. The anti-Vascular Endothelial Growth Factor (VEGF) bevacizumab, or the anti-Epidermal Growth Factor Receptor (EGFR) cetuximab or panitumumab are approved in first as well as in second line treatment [8]. In further lines, treatment options are still limited [10]. The multi-tyrosine kinase inhibitor regorafenib and trifluridine/tipiracil are recommended after standard cytotoxic and targeted treatments, both leading to a modest incremental survival advantage that should be weighed against toxicity concerns [8,10–12]. In third-line/salvage therapy setting, in *RAS* wild-type patients not previously treated with anti-EGFR antibodies, cetuximab in combination with irinotecan or panitumumab monotherapy should be considered [8,13,14]. Beyond third line treatment, the best choice is represented by clinical trials enrollment.

There are well known molecular criteria to select patients more likely to benefits from anti-EGFR targeted treatment. *KRAS* mutations occurring in exon 2, both in codons 12 and 13, are reported in up to 35% − 45% of mCRC and they are negative predictive biomarkers for cetuximab or panitumumab efficacy [6,15,16]. An additional 14–20% of tumors are characterized by oncogenic mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2, 3 and 4 [17,18]. The full spectrum of *KRAS* and *NRAS* mutations ("all-*RAS*") must be analyzed to identify patients who will benefit from treatment based on anti-EGFR antibodies [6,8,9]. Several retrospective studies showed that also *BRAF* V600E and *PIK3CA* exon 20 mutations, together with PTEN loss, are negative predictive biomarkers for anti-EGFR monoclonal antibodies efficacy [19–21]. In particular, *BRAF* V600E mutation entails a limited benefit from anti-EGFR treatment [6,20,22]. In addition, gene alterations including mutations and amplifications in *ERBB2*, *EGFR, FGFR1, PDGFRA*, and *MAP2K1* have been described as additional potential mechanisms of primary or secondary resistance [23–27].

A major limitation to therapies with EGFR-targeted agents is the emergence of acquired (secondary) resistance [16,28]. This takes place through three main mechanisms: mutations in the antibody-binding site (such as the EGFR extracellular domain variants); activation of alternative pathways; or reactivation of downstream signalling (such as *KRAS* or *NRAS* mutations) [24,28–32]. While the latter confer resistance to both cetuximab and panitumumab and are often involved in primary as well as in secondary resistance, acquired point mutations occurring in the extracellular domain of *EGFR* such as S492R, G465R, G465E, V441D or V441G develop only under the selective pressure of anti-EGFR drugs and differentially impact on resistance to cetuximab or panitumumab [31–33]. Importantly, studies using liquid biopsy [34] for longitudinal monitoring have revealed that mutant *RAS* clones arise in blood during EGFR blockade and decline upon withdrawal of treatment [26], overall displaying a pulsatile behavior that can be clinically exploited by re-administering EGFR inhibitors after clearance of these biomarkers of resistance. In particular, *RAS* and *EGFR* mutant clones exponentially decay, with a cumulative half-life of 4.3 months [35].

Based on these data, with the aim of expanding therapeutic options in the context of the *continuum of care* of mCRC patients, several studies and case reports have reported data concerning retreatment with cetuximab or panitumumab in patients who previously displayed a partial response or durable stable disease to the same agents. Different strategies have been adopted in this setting (Fig. 1):

- *Rechallenge*: retreatment after an intervening treatment line or a time interval free of anti-EGFR (ideally > 6 months) in tumors that displayed initial sensitivity (partial response/durable stable disease) and then proved resistance while on treatment [36,37];
- *Reintroduction*: retreatment with an anti-EGFR agent or anti-EGFR-based regimen to which the tumor has not yet proved to be resistant: i.e. the progression of disease did not take place while on therapy and the drug or regimen was suspended due to avoid cumulative toxicities, side effects or patients request [38];
- *Sequence*: retreatment soon after a prior progression to a different anti-EGFR drugs (i.e. panitumumab following cetuximab progression);
- *Dose intensification:* retreatment with higher doses of the same anti-EGFR drug in order to overcome acquired resistance to standard dose (i.e. higher saturation of target sites) [39,40].

While multiple evidences indicate that some efficacy does take place with retreatment with anti-EGFR drugs in mCRC, this option is still under clinical scrutiny and, because of the lack of phase 3 data, it is not included in clinical guidelines for the management of mCRC. In this article we systematically review available studies, case reports, abstracts and ongoing clinical trials on anti-EGFR retreatment by rechallenge, reintroduction or other strategies.

Methods

Definition of the outcome

The purpose of this systematic review is to analyze the efficacy of an anti-EGFR targeted retreatment in mCRC patients. We considered the percentage of objective response rate (RR), stable disease (SD) and disease control rate (DCR) for each of the currently available publications. Studies reporting outcome in terms of survival have been included as well. In addition, we further analyzed type and incidence of side effects occurring during anti-EGFR retreatment.

Data sources and search strategy

A systematic literature review was performed on 4 December 2018 according to PRISMA Criteria of 2009 (Fig. 2) [41,42]. We reviewed MEDLINE/PubMed, ASCO Meeting Library, ESMO library and ClinicalTrials.gov for citation or ongoing trials from January 2005 to December 2018. The search criteria were limited to human studies published in English language. The Medical Subject Headings terms used for the search in PubMed were ("((((((rechallenge) OR (reintroduction) OR (retreatment) OR (readministration)) AND ((cetuximab) OR (panitumumab) OR (anti-egfr)))) OR intermittent panitumumab) OR panitumumab after cetuximab) OR intermittent cetuximab"). The Medical Subject Headings used for the search both in ASCO and ESMO Libraries were (panitumumab/cetuximab rechallenge), (panitumumab/cetuximab reintroduction), (panitumumab/cetuximab intermittent), (panitumumab/cetuximab retreatment) and (panitumumab/cetuximab readministration). The Medical Subject Headings terms used for the search in ClinicalTrials.gov were ("colorectal cancer" as *condition/disease*) and ("panitumumab OR cetuximab" as *other terms*).

Selection criteria

To be included in this review, a publication had to fulfill the following inclusion criteria: study performed in mCRC patients treated with anti-EGFR monoclonal antibodies after a previous anti-EGFR based therapy. We included studies, abstracts and case reports published starting from 2005. The exclusion criterium was: publications written in language other than English.

Article analysis

Among the articles included in the systematic review according to selection criteria, we performed a comparison on the endpoints of different studies taking into consideration treatment strategies, primary tumor sidedness, RAS molecular status, outcome according to Response Rate (RR), Stable Disease (SD) and Disease Control Rate (DCR) and treatment related toxicities.

Results

According to the PRISMA Statement Criteria 2009 [42], we

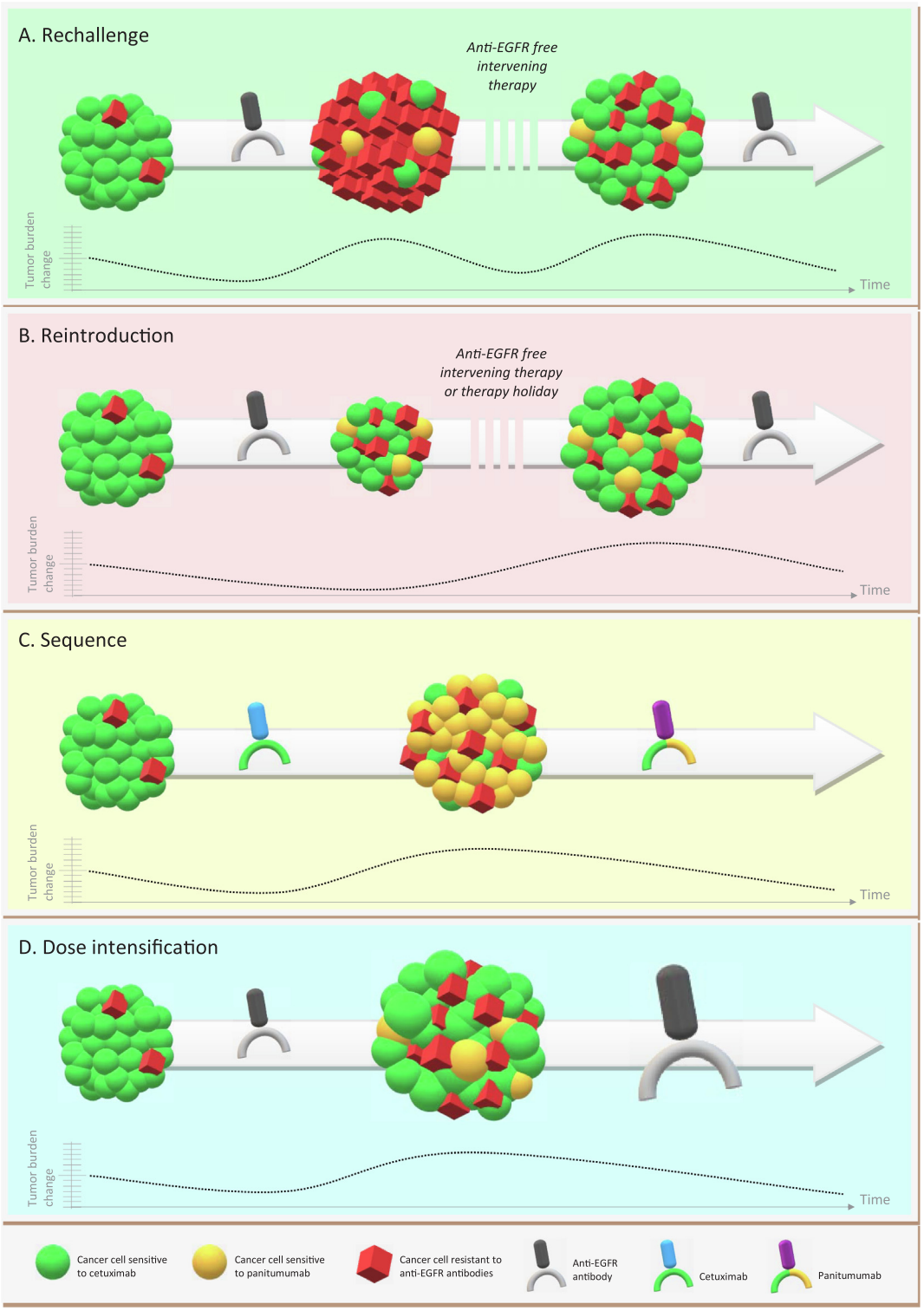

Fig. 1. Different strategies of retreatment with anti-EGFR antibodies. The lines under the figures represent hypothetical changes in tumor burden during different therapies. (A) Rechallenge: retreatment after an intervening treatment line without anti-EGFR or after a therapy vacation in tumors that displayed initial sensitivity. (B) Reintroduction: retreatment with an anti-EGFR agent to which the tumor has not yet proved to be resistant. (C) Sequence: retreatment soon after a prior progression to a different anti-EGFR drug (i.e. panitumumab following cetuximab). (D) Dose intensification: retreatment with higher doses of the same anti-EGFR drug in order to overcome acquired or primary resistance to standard dose.

identified 27 records through database searching and 16 additional records through other sources (i.e. online meeting library, ClinicalTrial.gov) (Fig. 2). A total of 43 records were therefore screened to be included in the systematic review. Seven records were excluded for the following reasons: 5 were review articles [36,43–46] and 2 studies evaluated a combination of anti-EGFR with other targeted therapies [44,47]. As a result, 36 records were eligible and included in the systematic review: 26 publications, of which 20 full-text articles studies on anti-EGFR retreatment and 6 abstracts presented at international congresses, and 10 ongoing clinical trials (Table 1). Seven articles were

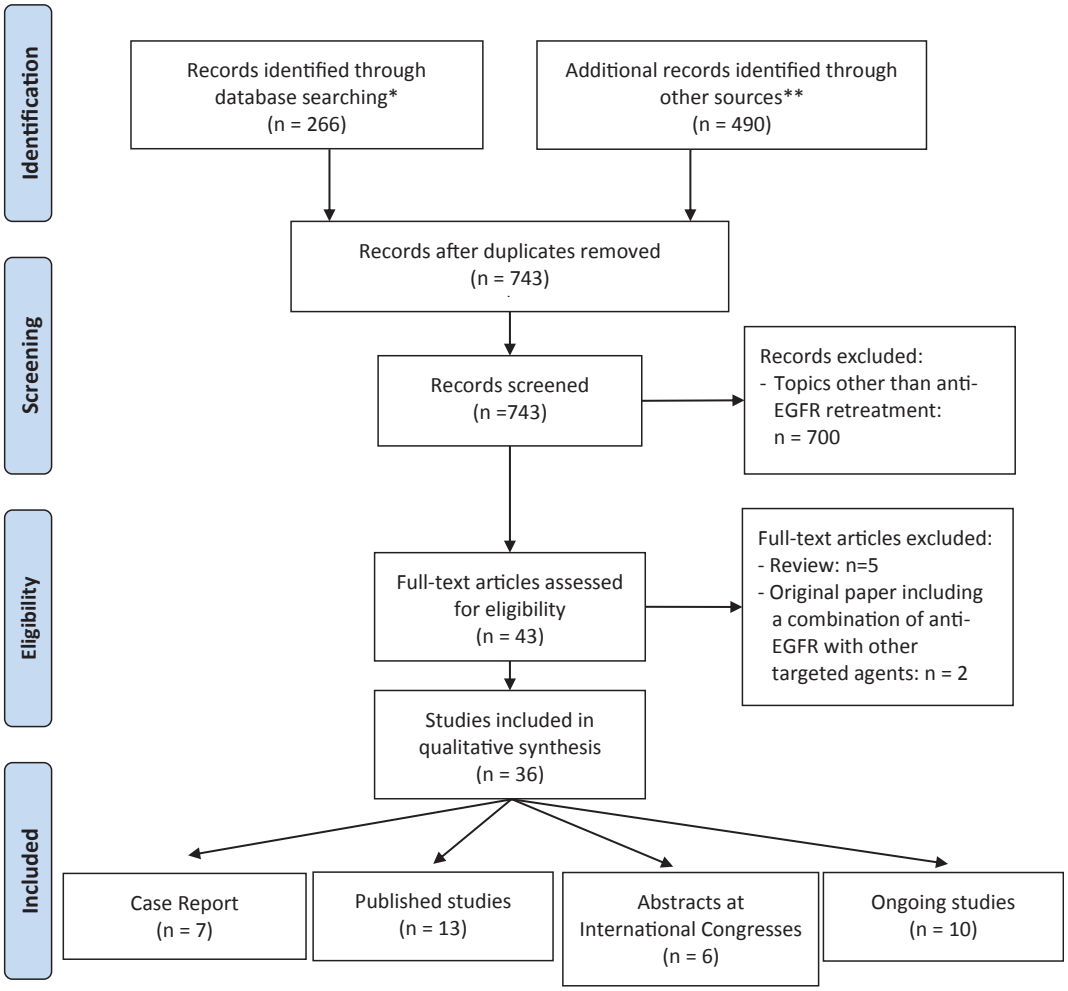

Fig. 2. Flow diagram representing the systematic review process performed according to PRISMA Statement [44].

reports describing 5 or less patients but due to small sample size we did not analyzed percentages of RR, DCR and SD which may have altered overall interpretation of data. The remaining studies had a minimum of 13 up to 78 patients enrolled.

Table 1 displays studies included in the systematic review according to the retreatment strategies defined in Fig. 1 reporting the type of study, the drug sequence adopted, the number of patients, sidedness of colorectal tumor, *RAS* status and the specimen analyzed, the anti-EGFR free interval, and the outcome. 10 publications has been classified as "rechallenge" [26,48–56], 4 as "reintroduction" [57–60], 5 as "sequence" [61–65] and 1 as "dose intensification" [66]. Six more articles were included as "mixed strategy" [67–71], as in these studies different modalities were used in the same study (i.e. rechallenge and sequence) or the retreatment strategy was not clearly stated by the authors.

As a whole, the studies displayed high heterogeneity in terms of efficacy across different strategies (RR = 0.0–53.8%; DCR = 24.0–89.7%), with best results in the setting of rechallenge (RR = 2.9–53.8%; DCR = 40.0–89.7%).

Rechallenge

Among articles *in extenso* two prospective peer-reviewed studies could be defined rechallenge studies, since *(K)RAS* wild-type patients had to progress to a previous cetuximab-based regimen before cetuximab and irinotecan and following an intervening treatment, with a median anti-EGFR-free interval of 6 months [48,54]. RR was 53.8%, SD 35.9% and DCR 89.7% in the article by Santini and coworkers [48] and RR was 21.4%, SD 32.1% and DCR 53.5% in the article by Cremolini et al. [48]. A statistically significant correlation between benefit from the first cetuximab administration and the rechallenge was noticed [48]. In the recent CRICKET study, *RAS* and *BRAF* wild-type status was required to be included in the study [54]. In addition to these trials, other two case reports have been published adopting a rechallenge strategy [26,51]. More recently, several abstracts on anti-EGFR rechallenge strategy have been presented at ASCO and ESMO International Congresses. Three of them used cetuximab combined with chemotherapy in the retreatment setting, after a prior cetuximab benefit, with a RR ranging between 8.3 and 13.3%, and DCR between 40 and 50% [49,50,56]. Siena and colleagues described survival data of panitumumab rechallenge combined or not with a cytotoxic agent after a prior response to panitumumab: in this study OS was available (14.2 months) but no data on RR were provided [53]. Tsuji and collaborators reported data from panitumumab rechallenge in combination with irinotecan after prior response to panitumumab with chemotherapy, showing a 50% of DCR with 8% of RR [52]. Interestingly, studies in this category provide clinical confirmation of the seminal finding that *RAS* clones, as determined by circulating tumor DNA (ctDNA), display a pulsatile behavior and decline after interruption of EGFR pharmacological blockade leading to renewed susceptibility at retreatment [26,54]. The CRICKET study retrospectively evaluated ctDNA at the moment of rechallenge and reported that all patients achieving a PR were *RAS* wild-type in the ctDNA [54]. Finally, ctDNA *RAS* wild-type patients experienced a significantly longer PFS if compared to ctDNA *RAS* mutated ctDNA (4.0 vs 1.9 months), while no

Table 1
Main characteristics of the published studies available in the literature and abstracts presented at international congresses with anti-EGFR retreatment in metastatic colorectal cancer (mCRC).

Study	Phase, prospective/ retrospective	Treatment strategy *Drug time 1 - > drug time 2 (Combination / Monotherapy)*	Pts. (N)	Anatomic site (N)	*RAS/BRAF*	Tissue specimen *Primary/Mets*	Anti-EGFR free interval *(months)*	Outcome	RR%	SD%	DCR%
Rechallenge											
Santini, 2012	II, Prosp	Cmab - > Cmab (C)	39	Colon ns (19) Rectum or rectosigmoid (20)	*KRAS* cod 12–13 wt	nr	Median 6.0 (2.0–12.0)		53.8	35.9	89.7
Siravegna, 2015	Retrosp	Cmab - > Cmab (M)	3	nr	*KRAS wt*	Mets/ctDNA	10.4	PR			
		Cmab - > Pmab (M)			*KRAS wt*	Mets/ctDNA	6.3	SD			
		Pmab - > Pmab (M)			*KRAS wt* (°)	Mets/ctDNA	29.5	PR			
Marks, 2015		Cmab - > Pmab (C)	1	Rectum	*KRAS, BRAF wt*	Primary	6.5	SD			
Tsuji, 2016 (Abs.)	II, Prosp	Cmab - > Cmab (C)	34	nr	*KRAS wt*	nr	nr		2.9	53.0	55.9
Nogueira, 2016 (Abs.)	Retrosp	Cmab - > Cmab (C)	15	Colon ns (10) Rectum (5)	*KRAS wt*	nr	Median 7.7 (1.6–30.0)		13.3	26.7	40.0
Cremolini, 2018	II, Prosp	Cmab - > Cmab (C)	28	Right colon (9) Left colon or rectum (19)	*RAS/ BRAF wt*	nr/ctDNA (°°°)			21.4	32.1	53.5
Siena, 2017 (Abs.)	Retrosp	Pmab - > Pmab (C/M)	69	Right sided (8) Left sided (49) nr (12)	*RAS wt, 2 BRAF mut*	nr	nr	Median OS 14.2 months			
Tanioka, 2018	Retrosp	Cmab - > Cmab (C)	14	nr	*KRAS ex 2 wt (12 allRAS wt, 2 RAS mut)*	nr	Median 13.1 (6.0–37.1)		21.4	50.0	71.4
Tsuji, 2018 (Abs.)	II, Prosp	Pmab - > Pmab (C)	24	nr	*KRAS wt*	nr	nr		8.3	41.7	50.0
Osawa, 2018 (Abs.)	II, Prosp	Cmab - > Cmab (C)	33	Right colon (4) Left colon (29)	*RAS wt*	nr	> 4.0	Median PFS 2.9 / Median OS 8.7	15.6	40.6	56.2
Reintroduction											
Kaechele, 2008		Cmab - > Cmab (C)	5	Rectum or sigmoid colon (5)	nr	nr	13.0	PR			
		Cmab - > Cmab (C)			nr	nr	14.1	SD			
		Cmab - > Cmab (C)			nr	nr	28.0	SD			
		Cmab - > Cmab (C)			nr	nr	32.0	PD			
		Cmab - > Cmab (C)			nr	nr	13.3	PD			
Pietrantonio, 2013	Retrosp	Cmab - > Pmab (M)	30	nr	*KRAS* wt (**)	Prim/Mets (***)	Median 13.0 (8.0–39.0)		30.0	37.0	67.0
Wasan, 2014 (°)	II, Prosp	Cmab - > Cmab (C)	78	Right or transvers colon (23) Left colon or rectum (55)	*KRAS* codons 12, 13, and 61 wt (°°)	nr	Median 3.7 (3.5 – 4.6)	Median Median OS 16 months			
Ma, 2017		Cmab - > Cmab (C)	1	Ascending colon	*KRAS* wt	nr	> 36.0	PR			
Sequence											
Metges, 2010 (Abs.)	Prosp	Cmab - > Pmab (M)	32	Rectum (12) Colon ns or double sites (20)	*KRAS* wt	nr			22.0	9.0	31.0
Wadlow, 2012	II, Prosp	Cmab - > Pmab (M)	20	nr	*KRAS* wt	nr			0.0	45.0	45.0
Kasagi, 2013		Cmab - > Pmab (M)	1	Rectum	*KRAS*, BRAF wt	Primary		PR			
Marino, 2015	Retrosp	Cmab - > Pmab (M)	25 (^)	Rectum (9) Colon ns (16)	*KRAS* wt(ex 2 in 12 pts, ex 2–3 in 13 pts)	nr	nr		4.0	20.0	24.0
Kiss, 2016	Retrosp	Cmab - > Pmab (M)	26 (^^)	nr	*KRAS* wt	nr			11.5	26.9	38.4
Dose intensification											
Fora, 2013	II, Prosp	Cmab - > Cmab (C)	20	nr	*KRAS* wt (BRAF wt in 2/2 pts tested)	nr	nr		5.0	55.0	60.0
Mixed (readministration)											
Power, 2010	Retrosp	Cmab - > Pmab (C)	22	nr	*KRAS* cod 12–13 wt in 15 pts, mut in 3 pts, nr in 4 pts	nr	nr		41.0	14.0	55.0

(*continued on next page*)

Table 1 (*continued*)

Study	Phase, prospective/ retrospective	Treatment strategy *Drug time 1 - > drug time 2 (Combination / Monotherapy)*	Pts. (N)	Anatomic site (N)	*RAS/BRAF*	Tissue specimen *Primary/Mets*	Anti-EGFR free interval *(months)*	Outcome	RR%	SD%	DCR%
Saif, 2010	Retrosp	Cmab - > Pmab (M)	15 (§)	nr	*KRAS* status evaluable in 3/15 pts: 1 wt, 2 mut	nr	nr		0.0	40.0	40.0
Naing, 2010		Cmab - > Cmab (C)	4	nr	nr	nr	11.0	SD			
		Cmab - > Cmab (C)		nr	nr	nr	/	SD			
		Pmab-Cmab - > Cmab (C)		nr	nr	nr	/	SD			
		Cmab - > Cmab (C)		Rectum	nr	nr	4.0	SD			
Sonoda, 2013	Retrosp	Cmab - > Pmab (M/C)	16	Rectum (11) Colon (5)	*KRAS* wt in 13/16 pts, mut in 3/16 pts	nr	nr		12.5	31.3	43.8
Hata, 2013		Pmab - > Pmab (C)	2	nr	*KRAS* wt	Primary	> 4.0	PR			
		Pmab - > Pmab (C)		nr	*KRAS* wt	Primary	> 8.0	SD			
Kajitani, 2017	Prosp	Cmab / Pmab - > Cmab (C) / Pmab (C/M)	13	Rectum (5) Colon ns (8)	*KRAS* wt	nr	0.8 (0.2–10)		0.0	54.0	54.0

Keys: M = monotherapy. C = combination therapy. Abs. = abstract. L = left. R = right. Nr = not reported. Ns = not specified.

(*) 1 case with *KRAS* amplification, 1 case *KRAS* wt at baseline, mut at first-line PD, wt at rechallenge.

(**) 3 *KRAS* mutations identified with mutant enriched PCR and not by standard Sanger sequencing (1 G13D, 1 G13S, 1 G12D): all three patients showed a partial response to previous cetuximab-based regimen but failed to respond to panitumumab at rechallenge (2 SD/1 PD).

(***)Tissue blocks were available before reintroduction for 21 patients treated with single agent Pmab and consenting for biomolecular analyses. Pretreatment samples were obtained from 14 (67%) primary tumors and 7 (33%) resected metastases.

(°) We reported data of the intermittent cetuximab arm,.

(°°) PAN-*RAS* and *BRAF* wt: 53 (68%), *NRAS* mutation 7 (9%), *BRAF* mutation 8 (10%).

(°°°) At treatment baseline patients were included in the study based on tissue RAS and BRAF wild-type assessment; ctDNA at rechallenge baseline enable the detection of RAS mutations in 12 out of 25 (48%).

(^) 20 out of 25 patients were evaluable for ORR.

(^^) In 3 cases (11.5%) response was not evaluable.

(§) response to treatment evaluable only in 11 patients out of 15 due to deterioration of clinical conditions.

significant differences were observed in OS [54].

Reintroduction

Reintroduction strategy has been adopted in four studies in which the Authors stated that the reasons for first anti-EGFR including regimen interruption were other than PD [57–60]. The study by Pietrantonio and coworkers consisted in a reintroduction study with panitumumab monotherapy after a previous benefit from cetuximab based regimen in *KRAS* wild-type patients (n = 30) [58]. After a median of 13 months of anti-EGFR-free interval, the RR was 30%, SD 37% and DCR 67% [58]. No statistically significant correlation was found between the previous benefit from cetuximab and response to panitumumab [58]. Side effects or adverse events related to panitumumab reintroduction were not presented [58].

The COIN-B was a randomized phase 2 trial in which patients were assigned to intermittent FOLFOX plus intermittent cetuximab or to intermittent FOLFOX plus continuous cetuximab [60]. In both arms, the respective therapy was reintroduced after evidence of RECIST progression. Continuous cetuximab was associated with a greater failure-free survival (defined as stopping maximum tolerated treatment because of progression or death from any cause), greater PFS, and OS than was intermittent cetuximab, and with improved disease control at 24 weeks (32% vs 22%). However, the trial was not powered for statistical comparison between the treatment groups [60]. Kaechele and colleagues treated 5 patients with cetuximab-based regimen until disease stabilization. Then it was discontinued and reintroduced upon tumor progression with a clinical benefit in 3 patients [57]. A partial response to cetuximab reintroduction, after surgery and 3 years of therapy holiday, was reported by Ma and colleagues [59].

Sequence

In five publications, anti-EGFR retreatment with panitumumab monotherapy was started soon after a prior progression to cetuximab. Objective response rate adopting this strategy ranged between 0 and 22.0% and DCR 24% − 45% [61–65]. All patients treated with this schedule had *RAS* wild-type tumors, but none of them were tested for EGFR external domain mutations, known to confer resistance to cetuximab but not to panitumumab [31,32]. Metges et al. firstly, in 2010, presented results of treatment of 32 patients with panitumumab monotherapy after progression to cetuximab associated with irinotecan. The RR and DCR were 20% and 31%, respectively. In the subgroup of patients that received clinical benefit from cetuximab and irinotecan, the RR to panitumumab was increased up to 54.5% with DCR of 72.7% (in case of cetuximab resistance, RR was 7.7% and DCR 15.4%) [61]. In contrast, Wadlow et al. found 0% of RR, a DCR of 45% with a median duration of 1.7 months in 20 patients treated with the same strategy [62].

More recently, Marino et al. and Kiss et al. retrospectively analyzed patients with *KRAS* wild-type mCRC who received panitumumab monotherapy after progression on cetuximab [64,65]. In the former study, 21 out of the 25 patients enrolled actually progressed on cetuximab (in 4 patients cetuximab was interrupted because of infusion reactions) and 20 patients were evaluable for -RR (5 died after 1–2 cycles of panitumumab). Among all patients included in the former, the RR was 4% and the DCR was 24% [64]. In the latter study, 26 patients were treated, RR was achieved in 11.5% with DCR of 38.4% (in 3 cases response was not available) [65].

Dose intensification

The phase II study by Fora and coworkers is the only one exploring this option of treatment. They tested the hypothesis of overcoming resistance to cetuximab in *KRAS* wild-type patients increasing its dosage up to 500 mg/m^2/week together with irinotecan at standard dosage [66]. Interestingly, the authors reported that patients enrolled in study later than 2 month from PD on standard doses of cetuximab experienced a significantly better PFS [66]. The study reported a good toxicity profile, obtaining a DCR up to 60% with a RR of 5% [66]. No significant difference in PFS with high doses of cetuximab was noted according to prior objective response to standard doses [66].

Mixed

In several studies, clinical criteria underlying anti-EGFR retreatment were not clearly established. In these reports, RR and DCR were comparable to studies in which anti-EGFR retreatment strategy had been clearly stated in the manuscript (RR: 4–41%; DCR: 24–55%). Power and colleagues showed the highest RR (41%) and DCR (55%), using panitumumab retreatment [67]. The majority of patients who responded to cetuximab continued to respond to panitumumab (8/9, 89%). Anti-EGFR free-interval was not reported but reasons for stopping cetuximab included hypersensitivity reactions (32%), disease progression (14%), convenience of bi-weekly schedule (23%), preceding surgery (18%), and no evidence of disease after resection of metastases (9%) [67]. Notably, this study was focused on the rates of cross hypersensitivity and infusion reactions between cetuximab and panitumumab, thereby only 14% of patients experienced PD during prior anti-EGFR therapy with cetuximab [67]. Saif et al. and Kajitani et al. reported a 0% of RR with DCR of 40% and 54%, respectively [68,70]. In the first study, all but one patient progressed on prior cetuximab therapy before to receive panitumumab monotherapy, *KRAS* status was mostly unknown and the interval between the two anti-EGFR therapy lines was not clearly reported [68]. In the second study, the prior chemotherapy with anti-EGFR antibody led to a partial response in four patients (31%), with 54% of stable disease. Patients who did not show clinical benefit from prior anti-EGFR antibody did not show evidence of clinical benefit from its readministration, with a median interval of 26 days [70]. Sonoda et al. reported a RR of 12.5% and a DCR of 43.8% from panitumumab retreatment (with or without chemotherapy) in patients that stopped prior cetuximab therapy principally for disease progression (81%). In the cohort of patients affected by *KRAS* wt mCRC (13/16), DCR was 53.8%. Anti-EGFR free interval was not reported [69].

Molecular assessment

Details of tissue specimen on which molecular assessment was performed have been reported in the minority of publications [26,51,58,63,71]. Three publications reported molecular assessment performed on primary tumor tissue [51,63,71], one clearly stated the percentage of assessment carried out on primary or metastatic tissue [58] and in one article assessment was performed on metastatic tissue and ctDNA [26]. Most of publications included patients with reported *KRAS* wild-type CRC, while only a few screened tumor specimen also for *BRAF* mutations [51,54]. Occasionally also patients harboring *KRAS* mutated CRC were included [58,67–69]. In only one study a dynamic evolution of *KRAS* alterations between first administration and re-challenge with anti-EGFR drugs was demonstrated by ctDNA [26]. Furthermore, in the CRICKET study *RAS* status in the ctDNA was retrospectively reported as predictive to identify patients more likely to obtain a PR to cetuximab rechallenge [54].

Toxicity

Data of grade 3 and 4 toxicity upon retreatment with anti-EGFR are reported in Table 2. The most frequent G3-4 toxicities were skin rashes and nail changes (5–38.5%) in studies using both anti-EGFR monotherapy or combination [48,50,54,60,64,66–68]. Neutropenia was reported in 8.3–40% of patients treated with combination of anti-EGFR and cytotoxic agents (mainly irinotecan) [48,49,52,54,57,60,66]. Other G3-4 toxicities reported were hypomagnesaemia (4–25%) and diarrhea

Table 2
Toxicities in patients undergoing anti-EGFR retreatment according to available peer-reviewed articles, abstracts and case reports included in the systematic review.

Study	Type of study *Prosp/retrosp (Phase)*	Treatment strategy *Drug time 1 - > drug time 2 (Combination / Monotherapy)*	Pts. N	Toxicities G3-4%	Type of toxicities
Rechallenge					
Santini, 2012	Prosp (II)	Cmab - > Cmab (C)	39	38.5	Skin rash
				7.7	Diarrhea
				18	Neutropenia
Siravegna, 2015	Retrosp	Cmab - > Cmab (M) Cmab - > Pmab (M) Pmab - > Pmab (M)	3	nr	nr
Marks, 2015		Cmab - > Pmab (C)	1	nr	nr
Tsuji, 2016 (Abs.)	Prosp (II)	Cmab - > Cmab (C)	34	28.6	Neutropenia
Nogueira, 2016 (Abs.)	Retrosp	Cmab - > Cmab (C)	15	13	Skin rash
Cremolini, 2018	Prosp (II)	Cmab - > Cmab (C)	28	18	Diarrhea
				14	Skin Toxicity
				14	Neutropenia
				7	Hand and foot syndrome
				4	Febrile neutropenia
				4	Stomatitis
				4	Nausea
				4	Conjunctivitis
				4	Hypomegnesiemia
Siena, 2017 (Abs.)	Retrosp	Pmab - > Pmab (C/M)	69	nr	nr
Tanioka, 2018	Retrosp	Cmab - > Cmab (C)	13	7	Rash
				7	Diarrhea
Tsuji, 2018 (Abs.)	Prosp (II)	Pmab - > Pmab (C)	24	8.3	Neutropenia
Osawa, 2018 (Abs.)	II, Prosp	Cmab - > Cmab (C)	33	nr	nr
Reintroduction					
Pietrantonio, 2013	Retrosp	Cmab - > Pmab (M)	30	nr	nr
Kaechele, 2008		Cmab - > Cmab (C)	5	40	Neutropenia
		Cmab - > Cmab (C)		20	Skin rash and paronychia
		Cmab - > Cmab (C)		20	Diarrhea
		Cmab - > Cmab (C)			
		Cmab - > Cmab (C)			
Wasan, 2014	Prosp (II)	Cmab - > Cmab (C)	78	29	Neutropenia
				27	Skin rash
				26	Lethargy
				18	Diarrhea
				19	Pain
				12	Stomatitis
				11	Vomiting
				8	Nausea
				8	Anorexia
				8	Hand-Foot Syndrome
				5	Peripheral neurotoxicity
				4	Hypomagnesaemia
				4	Cetuximab-hypersensitivity
				3	Thrombocytopenia
Ma, 2017		Cmab - > Cmab (C)	1	0	–
Sequence					
Metges, 2010 (Abs.)	Prosp	Cmab - > Pmab (M)	32	nr	nr
Wadlow, 2012	Prosp (II)	Cmab - > Pmab (M)	20	5	Hyperglicemia
				5	Hyperbilirubinemia
				5	Hypokeliemia
Kasagi, 2013		Cmab - > Pmab (M)	1	nr	nr
Kiss, 2016	Retrosp	Cmab - > Pmab (M)	26	7.6	Skin rash
				3.8	Thrombosis
Dose intensification					
Fora, 2013	Prosp (II)	Cmab - > Cmab (C)	20	25	Hypomagnesiemia
				10	Neutropenia
				5	Skin rash
				5	Diarrhea
				5	Hypokaliemia
				5	Nausea
				5	Fatigue
Mixed (readministration)					
Power, 2010	Retrosp	Cmab - > Pmab (C)	22	22	Skin rash
				14	Nail changes
				14	Diarrhea
				9	Hypomegnesiemia
Saif, 2010	Retrosp	Cmab - > Pmab (M)	15	33.3	Skin rash
				6.6	Asthenia
Sonoda, 2013	Retrosp	Cmab - > Pmab (M/C)	16	6.3	Hypomagnesiemia
				6.3	Hypocalcemia
Hata, 2013		Pmab - > Pmab (C) Pmab - > Pmab (C)	2	0	–

(*continued on next page*)

Table 2 (*continued*)

Study	Type of study *Prosp/retrosp (Phase)*	Treatment strategy *Drug time 1 - > drug time 2 (Combination / Monotherapy)*	Pts. N	Toxicities G3-4%	Type of toxicities
Marino, 2015	Retrosp	Cmab - > Pmab (M)	25	32	Skin rash
Naing, 2010		Cmab - > Cmab (C)	4	nr	nr
		Cmab - > Cmab (C)			
		Pmab-Cmab - > Cmab (C)			
		Cmab - > Cmab (C)			
Kajitani 2017	Prosp	Cmab/Pmab - > Cmab (C)/Pmab (C/M)	13	8	Thrombocytopenia
				8	Paronychia
				8	Peripheral sensory neuropathy
				8	Ileitis

Keys: nr = not reported. N = number. G = grade. C = combination. M = monotherapy. Cmab = cetuximab. Pmab = Panitumumab. Prosp = prospective. Retrosp = retrospective. Abs = abstract.

(5–20%) [48,54,55,57,66,67,69]. In particular, hypomagnesemia was the most common G3-4 side effect in intensification dose strategy [66]. No toxic deaths have been reported. No correlation between response to anti-EGFR and toxicity has been statistically investigated in these studies likely due to the small number of patients in these studies.

Ongoing clinical trials

10 currently ongoing studies investigating efficacy and feasibility of anti-EGFR retreatment (Table 3) were found through ClinicalTrial.gov. These are all phase II trials except for FIRE-4 which is a phase III trial currently recruiting in Germany. Anti-EGFR monotherapy is used in 5 out of 10 studies (CHRONOS, RASINTRO, PACER, NCT03524820, and NCT03087071). Two studies are based on dynamic of changes of *RAS* mutated clones assessed by ctDNA by liquid biopsy (CHRONOS and RASINTRO) (Fig. 3).

Discussion

Anti-EGFR retreatment in mCRC has been empirically investigated in a limited number of mainly retrospective studies soon after the introduction of cetuximab and panitumumab in clinical practice. However, the underlying molecular bases of this therapeutic option have been recently demonstrated and clinicians are increasingly focused towards its optimization in the context of the *continuum of care*. To this aim, we adopted a categorization of the clinical use of retreatment into four classes (rechallenge, reintroduction, sequence and dose intensification) to overcome heterogeneity of available studies and compare different strategies. However, in most articles criteria driving anti-EGFR retreatment strategy were ambiguous, hampering a clear generalizable categorization for clinical use and making difficult to derive definite conclusions to translate in the clinical practice.

In most of the studies, information about intervening treatments and length of intervals between first anti-EGFR treatment and retreatment were missing. However, the role of an intervening treatment is paramount in this setting, especially since its length can impact the re-establishing of anti-EGFR drugs sensitivity [26,35]. Experimental and clinical data suggest that *RAS* and *EGFR* mutant clones exponentially decay [26], with a cumulative half-life of 4.3 months in patients [35]. Therefore, the time interval between first exposure and retreatment with an anti-EGFR should be taken into account for evaluating potential (in)success at rechallenge. This has not been demonstrated when adopting retreatment strategies different from rechallenge, providing the latter with the strongest potential for selection of patients before readministration of anti-EGFR drugs. Ongoing trials such as CHRONOS (Fig. 3) and RASINTRO (Table 3) are evaluating patients with longitudinal liquid biopsy and could provide prospective data concerning optimal biologically driven timing for rechallenge. In addition to rechallenge, also sequence with anti-EGFR drugs has an underlying molecular rationale, as there are acquired mutations occurring in the extracellular domain of EGFR under selective pressure of cetuximab (i.e. S492R) leading to resistance to cetuximab but not to panitumumab [31,32]. However, sequence-strategic studies considered in this review did not screen patients for these alterations [61–65]. Finally, dose intensification strategies have also been demonstrated to have a preclinical biological rationale [39,40]. Overall, it is fundamental to consider timing between first use and retreatment and type of drug sequencing (cetuximab and then panitumumab or viceversa, or the same drugs given as retreatment) to reconcile clinical use of retreatment with the underlying biological mechanisms and make results more generalizable and successful.

A major limitations in the majority of studies reviewed is that the molecular status of *KRAS* was assessed retrospectively on archival tissue [50,53,58,64–66]. In addition, another limitation is that in some studies also *KRAS* mutant CRC patients were included [67–69]. It is well known that tumor heterogeneity can increase along different lines of metastatic treatments [26,72–74], making molecular information retrieved from archival tissue analysis potentially outdated. Furthermore, selection exerted by therapy continuously reshape individual lesions. Molecular characterization of mCRC can also take place by liquid biopsy for ctDNA detection at the actual moment of retreatment [26,54,75,76], and application of this technique for driving anti-EGFR retreatment is warranted and will likely impact on this therapeutic strategy. Moreover, it should be noted that tumor sidedness was reported only in some of the studies evaluated in present review [48,50,51,53,54,57,59,63,64,69,70]. As expected based on data showing that a different underlying genetic make-up ultimately lead to better results of anti-EGFR drugs in left-sided tumors [77,78], most of study considered in this review were enriched of tumors arising in this side of the colon [48,53,54,57,60]. However, efficacy of anti-EGFR retreatment has been reported also in right sided CRC [59] and conclusive comparisons are not available even if it would be reasonable to expect a greater benefit of anti-EGFR retreatment in left sided rather than in right sided CRC, similarly to first line treatment [77,78]. Finally, another limitation of performing a systemic review on these trials is that data of efficacy have mostly reported as objective response rate rather than survival data. OS was stated in only one retrospective publication and one prospective phase II study [53,60].

We found that toxicities given by readministration of anti-EGFR drugs were generally reported as mild, and the most common severe G3-4 adverse events were skin rashes, paronychia and hypomagnesaemia when given as monotherapy and in addition neutropenia and diarrhea when associated with other cytotoxic agents, usually irinotecan [48,49,54,57,60,66]. These effects probably favorably compare with those experienced by patients after rechallenge with cytotoxic agents such as oxaliplatin that might be worse and even lethal [79,80]. Nevertheless, these assumptions should be confirmed by clinical trials comparing efficacy as well as safety of the different third-line treatment options such as the FIRE-4 AIO-KRK-0114 (NCT02934529) clinical trial testing anti-EGFR rechallenge as third line option of

Table 3
Ongoing studies investigating activity of anti-EGFR antibodies retreatment in metastatic colorectal cancer.

Study (study ID) STATUS Phase Main location	Anti-EGFR agent or combination in rechallenge setting	Main inclusion criteria
A-REPEAT (NCT03311750) **RECRUITING** Phase II Trial Greek	Panitumumab + CT	• *RAS* wt on tumor tissue • Clinical benefit from 1st line regimen including anti-EGFR drugs • Second line intervening treatments without anti-EGFR
REGAIN (NCT02316496) **TERMINATED** Phase II Trial France	Cetuximab + irinotecan	• *RAS* and *BRAF* wt on tumor tissue • First line chemotherapy regimen with FOLFIRI + cetuximab with initial PR/CR and PD with PD > 6 weeks after the last administration of cetuximab.
FIRE-4 (NCT02934529) **AIO-KRK-0114** **RECRUITING** Phase III Trial Germany	Cetuximab + CT vs CT in third line	• *RAS* wt on tumor tissue • First-line FOLFIRI + cetuximab therapy producing at least PR or SD lasting ≥ 6 months.
CHRONOS (NCT03227926) **RECRUITING** Phase II Trial Italy	Panitumumab monotherapy	• *RAS* and *BRAF* wt on tumor tissue at baseline • First line anti-EGFR therapy producing at least PR • Defined criteria of *RAS* mutational load measurement by liquid biopsy during first line treatment and before rechallenge • > 50% drop in *RAS*-extended mutational load between BML and RML (Fig. 3)
(NCT01832467) **ACTIVE NOT RECRUITING** Phase II Trial Hong Kong	Cetuximab + CT	• Retreatment with cetuximab-based chemotherapy in patients upon PD while under observation, defined as radiological or clinical PD more than 60 days from the last day of administration • Previously responded to first-line or second-line treatment with cetuximab-based chemotherapy.
RASINTRO (NCT03259009) **NOT RECRUITING YET** Phase II Trial France	Cetuximab/Panitumumab monotherapy	• Previous anti-EGFR based chemotherapy having provided an OR • No longer mutated *RAS* clone in plasma that appeared during PD with the first anti-EGFR treatment.
PACER (NCT01801904) **ACTIVE NOT RECRUITING** Phase II Trial Italy	Panitumumab monotherapy in patients cetuximab-refractory	• Documented PD following a treatment with cetuximab in patients who showed an OR after 8 weeks or SD after 16 weeks
(NCT03087071) **RECRUITING** Phase II Trial USA	Panitumumab monotherapy	• Previous treatment with cetuximab with evidence of clinical benefit • Ultimate PD through previous treatment with cetuximab with documented PD • Must not have EGFR ectodomain mutation or any mutations in *KRAS*, *NRAS*, or *BRAF* in cfDNA
(NCT03524820) **RECRUITING** Phase II Trial Israel	Cetuximab monotherapy	• *RAS* WT on tumor tissue • At least three months progression free time in first line cetuximab treatment. • Monitoring liquid biopsy during rechallenge but it is not a liquid biopsy driven study
OPTIPRIME (NCT03584711) **RECRUITING** Phase II Trial France	Panitumumab + FOLFOX	• *RAS* WT on tumor tissue • Reintroduction “Stop and go” strategy • No prior chemotherapy as first line treatment for metastatic disease and adjuvant chemotherapy discontinued for more than 12 months

treatment in *RAS* wild-type patients.

Overall, the emerging message of this review is that the benefit from anti-EGFR retreatment seems maximized when anti-EGFR drug are used in the rechallenge setting rather than other strategies [48,54]. However, all the studies, because of their retrospective nature or, if prospective phase II trials, for the low number of patients included, are not robust enough to drive clinical decision making and therefore conclusions obtained from our systematic review should be taken with caution. Further perspective trials, especially if based on monitoring of actual genetic make-up of resistance derived by ctDNA, comparing anti-EGFR retreatment with standard treatments in the third- or later line settings are warranted to affirm the role of this strategy in the *continuum of care* of mCRC.

Author agreement/declaration

All authors have approved the final article. The article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Contributors

- Gianluca Mauri: conception and design of the review, acquisition, analysis and interpretation of data, drafting of the article.
- Elio Gregory Pizzutilo: conception and design of the review, acquisition, analysis and interpretation of data, drafting of the article.
- Alessio Amatu: acquisition and interpretation of data, critical revision of the draft.
- Katia Bencardino: analysis and interpretation of data, critical revision of the draft.
- Laura Palmeri: acquisition and interpretation of data, critical revision of the draft.
- Erica Francesca Bonazzina: acquisition and interpretation of data, critical revision of the draft.

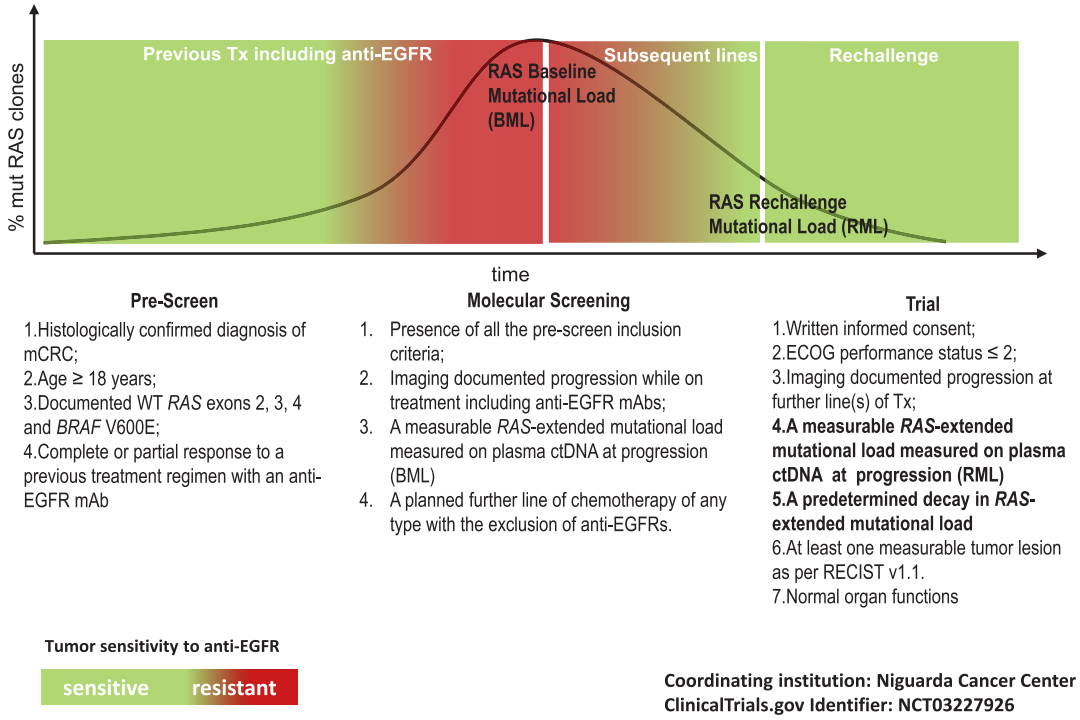

Fig. 3. The 3-steps selection strategy of the CHRONOS Trial (see also Table 3).

- Federica Tosi: acquisition and interpretation of data, critical revision of the draft.
- Giulia Carlo-Stella: analysis and interpretation of data, critical revision of the draft.
- Giovanni Burrafato: analysis and interpretation of data, critical revision of the draft.
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- Salvatore Siena: conception and design of the review, analysis and interpretation of data, critical revision of the draft, final approval of the version to be submitted.
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Declaration of interests

A.S-B. has acted as a consultant/advisory member for Amgen, Bayer, Lilly and Merck-Serono. S.S is advisory board member for Amgen, Bayer, BMS, Celgene, Incyte, Merck, Novartis, Roche, Seatlle Genetics. A.B. has acted as a consultant/advisory member for Horizon Discovery, Biocartis and Trovagene. A.A. is advisory board member for Amgen and Bayer.

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