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Title: Place of anti-EGFR therapy in older patients with metastatic colorectal cancer in 2020.

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Abbreviations

mCRC: Metastatic Colorectal Cancer

SIOG: International Society of Geriatric Oncology

CGA: Comprehensive Geriatric Assessment

FPs: Fluoropyrimidines

EGFR: Epidermal Growth Factor Receptor

CRASH: Chemotherapy Risk Assessment Scale for High-Age Patients

MMSE: Mini Mental Status Examination

IADL: Instrumental Activities of Daily Living

GDS: Geriatric Depression Scale

ORR: Objective Response Rate

OS: Overall Survival

PFS: Progression-Free Survival

ABSTRACT

Almost half of the new cases of colorectal cancer concern patients aged ≥ 70 years. However, very few clinical trials have specifically included older patients. As a consequence, the treatment of these patients is controversial because the balance between clinical benefits and toxicities remains uncertain. In patients without comorbidities and with an ECOG performance score of 0–1, treatment indications are similar to those of younger patients. For frail patients, chemotherapy is possible, but a comprehensive geriatric assessment is recommended.

Anti-EGFR (epidermal growth factor receptor) therapy is indicated either in combination with chemotherapy in the first-line or second-line setting or as monotherapy in the third-line setting (i.e., after failure of chemotherapy). For fit older patients, clinical trials that compared chemotherapy alone with doublet chemotherapy plus anti-EGFR in either first-line or second-line setting suggested that age is not an absolute contraindication for the use of this regimen. In frail patients, anti-EGFR monotherapy in the first-line, second-line or third-line setting has shown feasibility and antitumor activity and had mainly cutaneous toxicities that were easily managed. In any case, administration of treatment must be very cautious in older patients and the treatment dose needs to be adapted according to comorbidities.

Key words: Anti-EGFR; older patients; metastatic colorectal cancer

1. Colorectal cancer and older patients

Over 1.8 million new cases of colorectal cancer (CRC) were estimated to occur in 2018 worldwide, accounting for approximately 1 in 10 cancer cases and deaths [1]. This disease has become a predominant cancer in Western countries in recent decades, ranking as the third most common cancer in women and men. Reasons explaining this increased incidence include the preponderance of poor dietary habits, smoking, low physical activity, obesity and population aging, which are considered markers of socioeconomic development. For example, in France, new cases of CRC have been recorded in 45% and 16% of patients aged ≥ 75 years and ≥ 85 years, respectively [2]. If the mortality declines in developed countries because of the adoption of better therapeutic practices, the survival will decrease with age, as the 5-year survival in patients aged ≥ 75 years is 49.3% and the 5-year survival in patients aged < 65 years is ≥ 60% [2, 3].

Despite the high incidence of cancer in older patients, patients aged > 70 years are underrepresented in clinical trials. Inclusion/exclusion criteria (performance status, organ dysfunction, and comorbidities), physician-related barriers (treatment tolerance and drug metabolism) and patient-related barriers (lack of autonomy and logistical difficulties) influence the lack of data in older patients with cancer and especially the lack of data in frail patients with cancer [4].

Older patients are defined by an age > 70 years by the International Society of Geriatric Oncology (SIOG) [5]. However, the population of older patients is very heterogeneous, and biological age should be differentiated from chronological age. Indeed, patients with few comorbidities, favorable psychosocial conditions and preserved functional capabilities are classified as “fit patients”. In contrast, patients with loss of autonomy and several comorbidities are considered as “frail patients” [6]. All therapeutic decisions will depend on the level of dependence and comorbidities: for fit patients, indications are close to those of

younger patients [7]; for frail patients, chemotherapy is possible, but a comprehensive geriatric assessment (CGA) performed by a geriatrician specialized in oncology is recommended. This CGA explores different domains (physical health, mental health, functional issues, social issues, and environmental issues) and is proposed if the G8 score is <14/17. G8 is an 8-item screening tool that predicts a poor CGA if the score is less than 14 [8, 9]. Patients with a G8 score >14/17 are considered to be fit, and they benefit from standard therapeutic management similarly to younger patients. Patients with G8 scores <14/17 are considered to be at risk of frailty and their treatment should be monitored with a geriatric oncologist. The G8 score alone is not sufficient for a therapeutic decision or a treatment dose adaptation, but it could be useful in the management of frail patients.

In this review, we will consider how to treat older patients with metastatic CRC (mCRC) and especially focus on the place of anti-epidermal growth factor receptor (anti-EGFR) therapies.

2. Treatment of older patients with metastatic colorectal cancer

2.1 Available treatments and precautions related to advanced age

The therapeutic armamentarium for older patients with mCRC is the same as that for younger patients, comprising fluoropyrimidines (FPs) as monotherapy (5FU and capecitabine) or combined with other drugs (FPs plus irinotecan and FPs plus oxaliplatin), targeted therapies (antiangiogenic agents: bevacizumab or aflibercept; anti-EGFR antibodies: cetuximab or panitumumab; and multikinase inhibitors: regorafenib) and others (antimetabolites: trifluridine-tipiracil).

Some precautions related to age must be taken in regard to cancer treatments. Indeed, the bone marrow reserve decreases with age, glomerular filtration decreases by 0.75 mL per year after 40 years, and polymedication is frequent, thus increasing the probability of interactions with the cytochrome P450 enzymes. Special attention should be paid to oral chemotherapy

due to the decrease in intestinal absorption and the modification of first-pass hepatic metabolism. Moreover, the distribution volumes of drugs and the ratio of fat mass to lean mass change according to age. All chemotherapies and biotherapies must be cautiously used in older patients with regimen adaptations [10]:

1) A bolus of 5FU increases toxicity compared to continuous infusion for patients > 70 years, leading to more mucositis and neutropenia. Therefore, age must be considered in the evaluation of febrile neutropenia risk and consequently in the decision to introduce a preventive treatment with G-CSF, which is recommended when the estimated risk is > 20%. Additionally, the oral form of 5FU, capecitabine, must be adjusted according to creatinine clearance.

2) The dose of irinotecan should be reduced for patients > 70 years because of changes in hepatic metabolism with age.

3) Thromboembolism risk is increased and arterial hypertension is more common in patients > 65 years treated with antiangiogenic agents such as bevacizumab.

4) Cutaneous and digestive toxicities of anti-EGFR are more frequent in patients > 70 years. A dose adaptation or discontinuation has to be considered in cases of severe (≥ Grade 3) reactions.

Extermann *et al* developed a chemotherapy toxicity risk prediction model, which produces a Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. The CRASH model includes several geriatric risk factors, such as impaired cognition, a Mini Mental Status Exam (MMSE) score < 30 and an autonomy score based on the Instrumental Activities of Daily Living (IADL) scale, which are predictive of chemotherapy toxicity [11].

2.2 Single-agent or doublet chemotherapy ± bevacizumab in older patients

In previously untreated older patients with mCRC, the clinical benefit of first-line doublet chemotherapy (oxaliplatin, irinotecan or 5FU plus bevacizumab or capecitabine) compared to monotherapy (5FU or capecitabine) is still debated.

The FOCUS 2 study, which included 459 older and frail patients (median age, 74 years) with advanced CRC, concluded that a combination including oxaliplatin was preferable to single-agent FPs by demonstrating a better objective response rate (ORR) without major toxicities. However, neither the primary endpoint, which was progression-free survival (PFS), nor the secondary end point, the overall survival (OS), was met [12]. The FFCD 2001-02 trial was a randomized phase III study that compared irinotecan plus 5FU doublet chemotherapy vs. 5FU monotherapy in 71 older patients (median age, 80 years) with mCRC. A higher tumor response rate was reported in the irinotecan arm than in the monotherapy arm (46.4% vs. 27.4%; $p = 0.002$), but PFS was not significantly improved (7.3 vs. 5.2 months; $p = 0.15$) [13]. In patients included in this aforementioned study, Aparicio *et al* used geriatric factors such as MMSE, IADL and Geriatric Depression Scale (GDS) scores. They first demonstrated that the geriatric parameters were predictive of severe toxicity (MMSE score ≤ 27/30 (OR, 3.84) and impaired IADL score (OR, 4.67)) and unexpected hospitalization (MMSE score ≤ 27/30 (OR, 4.56)) [14] and later showed a trend in favor of the IADL score being independently associated with better OS [15].

Two studies have demonstrated the benefit of adding the antiangiogenic agent bevacizumab to therapy in older patients. The first was the AVEX study, which randomized 280 patients over 70 years of age who were considered ineligible for doublet chemotherapy [16]. The treatment consisted of capecitabine twice a day in both arms combined with bevacizumab. The association arm showed significant improvement in PFS (9.1 versus 5.1 months). These patients were in good general condition (ECOG 0-1), with few comorbidities (mainly arterial

hypertension). Grade 3-4 adverse events were mainly arterial hypertension (2%) and thromboembolic events (2%). The randomized phase II study PRODIGE 20 studied bevacizumab in combination with chemotherapy (5FU monotherapy or combined with a drug of the investigator's choice) in patients 75 years of age and older [17]. The main objective was a composite criterion of tumor control and quality of life. PFS was 7.8 versus 10.7 months in favor of the bevacizumab arm. The main grade III-IV toxicity was hematological. A second publication showed that the IADL score was a predictor of efficacy and tolerance and that there was no impairment of quality of life in this study in treated patients [18].

A meta-analysis assessed the clinical benefit of first-line doublet chemotherapy (including oxaliplatin or irinotecan) compared to single-drug therapy (5FU) in older patients with mCRC [19]. A total of 1,225 patients were included and a cut-off of 70 years was chosen for oxaliplatin and 75 years for irinotecan. Doublet chemotherapy vs. 5FU alone did not improve OS (HR 1.00, CI 0.89–1.13) in older patients, but significantly improved PFS (HR 0.82, CI 0.72–0.93).

A recent meta-analysis included 10 studies and 1,652 older patients and had a cut-off of 70 or 75 years [20]. The addition of bevacizumab to FPs statistically improved both overall survival (OS) and PFS (HR 0.78, 95% CI 0.63–0.96 and HR 0.55, 95% CI 0.44–0.67, respectively). The addition of oxaliplatin did not statistically improve OS (HR 0.99, 95% CI 0.85–1.17) but improved PFS (HR 0.81, 95% CI 0.67–0.97), as did the addition of irinotecan (HR 1.01, 95% CI 0.84–1.22 and HR 0.82, 95% CI 0.68–1.00, respectively). The authors concluded that the addition of bevacizumab to FPs appeared more effective in terms of OS and PFS than the addition of oxaliplatin or irinotecan. In this meta-analysis, regardless of the added drug, either oxaliplatin added to 5FU (as in the FOCUS 2 study) or irinotecan added to 5FU (as in the

FFCD 2001-02 study), first-line doublet chemotherapy was associated with a modest benefit that must be balanced with the more frequent toxicities and impaired quality of life.

3. Place of anti-EGFR therapies

The anti-EGFR monoclonal antibodies cetuximab and panitumumab are approved for the treatment of adult patients with wild-type RAS mCRC, and both improve patient outcomes either as monotherapy or in combination with chemotherapy [21-23].

3.1 Doublet chemotherapy plus anti-EGFR therapy

International guidelines recommend not considering the age of the patient for treatment with anti-EGFR therapies [5, 7, 24]. However, data on the use of anti-EGFR drugs in older patients are limited. Only phase II studies, retrospective studies, cohort studies and post hoc subgroup analyses that compare clinical outcomes according to age classes are available.

For fit older patients who received doublet chemotherapy associated with anti-EGFR in clinical trials, some post hoc analyses suggested the potential of this combined regimen (**Table 1**).

First-line regimen. In the CRYSTAL and OPUS studies, older patients treated with cetuximab and chemotherapy in the first-line setting achieved comparable survival (approximately 23 months) to younger patients, and this survival was better than that associated with chemotherapy alone, regardless of the age:

- *CRYSTAL and OPUS studies.* A pooled analysis of these studies assessed the results of cetuximab as a first-line treatment combined with FOLFIRI for the CRYSTAL study and FOLFOX for the OPUS study [25]. Patient age ranged from 19 to 84 years in the CRYSTAL study and from 30 to 82 years in the OPUS study. The overall analysis of the two studies included 845 patients with wild-type KRAS mCRC. Among patients ≥ 70 years, 67 patients received chemotherapy alone, and 78 received chemotherapy plus

cetuximab. The median OS was comparable in patients ≥ 70 years (23.3 months) and patients < 70 years (23.6 months; p = 0.38). Although OS, PFS and the overall response rate were increased by the addition of cetuximab in both the older and younger patients, the differences were not statistically significant (likely because of the low power of the study) in the older group (p = 0.78 for PFS and p = 0.23 for response rate). The safety profiles of the two age groups were comparable, with an increased incidence of diarrhea in patients ≥ 70 years (at risk of dehydration) treated with chemotherapy plus cetuximab, but this difference in incidence did not achieve statistical significance (23.1% vs. 14.9%).

Similarly, an analysis of the FIRE3 study according to age (30% of patients > 70 years) showed a benefit of anti-EGFR plus chemotherapy in terms of survival regardless of age [26]:

- *FIRE3 study.* This study included 592 patients from 27 to 79 years with wild-type KRAS mCRC and compared first-line treatment with FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab. Approximately 45% of patients in each arm were more than 65 years of age. A nonsignificant benefit in terms of OS (secondary objective) was reported, regardless of the age class, in favor of the combination of cetuximab plus chemotherapy compared to bevacizumab plus chemotherapy: HR 0.75 (95% CI 0.56–1.01) for the 318 patients ≤ 65 years, and HR 0.80 (95% CI 0.58–1.09) for the 274 patients > 65 years.

PFS and OS were clearly improved in patients from the PRIME study who received panitumumab plus chemotherapy compared to chemotherapy alone in the first-line setting. This difference remained interesting in patients > 65 years but not for patients > 75 years [23, 27]:

- *PRIME study* [23, 27, 28]. FOLFOX4 plus panitumumab was compared to FOLFOX4 alone as a first-line treatment in 1,183 wild-type KRAS mCRC patients less than 85 years old (40% of patients were more than 65 years old) [23, 27]. FOLFOX4 plus panitumumab was compared to FOLFOX4 alone as a first-line treatment in 1,183 wild-type KRAS

mCRC patients less than 85 years old (40% of patients were more than 65 years old). A post hoc analysis expanded the RAS analyses beyond KRAS exon 2 and studied the impact of age [28]. For PFS, the HR was 0.66 (95% CI 0.52–0.83) in patients < 65 years (n=316) and 0.88 (95% CI 0.65–1.19) in patients ≥ 65 years (n=89). For OS, the HR was 0.75 (95% CI 0.58–0.96) in patients < 65 years and 0.80 (95% CI 0.58–1.09) in patients ≥ 65 years. Nevertheless, patients > 75 years did not benefit from the association of FOLFOX + panitumumab in terms of survival. Grade 3-4 toxicities related to panitumumab were mainly cutaneous toxicities (37%), diarrhea (18%) and hypomagnesemia (7%) in the overall population. The rate of serious adverse events was increased in patients ≥ 65 years who received chemotherapy plus panitumumab compared to those who received chemotherapy alone (41% vs. 16%).

Second-line regimen. Some studies of mCRC patients in the second-line setting suggested some improvement in survival with the addition of anti-EGFR to chemotherapy:

- A *German cohort* compared patients aged 65 years and over receiving a cetuximab chemotherapy combination [29]. A total of 657 patients were recruited (305 patients ≥65 years old). A reduced ECOG score of 1–2 was found in 80% of patients, and 95% had received at least one palliative treatment. Progression-free survival and response rates were identical regardless of the age group studied, and the same pattern was seen for the overall tolerance of the treatment. There was an increase in grade 3-4 cutaneous toxicities in the older patients, and this difference just reached significance (p = 0.05).
- *Peeters et al study* [30, 31]. Panitumumab was given along with FOLFIRI in this study of second-line treatments in wild-type KRAS mCRC with prespecified analyses according to age. The median PFS was increased in the groups with panitumumab plus chemotherapy (n = 208) compared to the groups with chemotherapy alone (n = 213), both in patients < 65 years (6.4 vs. 4.6 months, p = 0.0089) and in patients ≥ 65 years (6.4 vs. 3.9 months,

p = 0.077). The median OS was mainly improved in older patients, although statistical significance was not achieved: 15.7 vs. 15.0 months (p = 0.27) in patients < 65 years and 18.7 vs. 12.2 months in patients ≥ 65 years (p = 0.12). Grade 3-4 adverse events were more frequent in the groups with panitumumab than in the groups with chemotherapy alone, but there was no difference according to age: 77% vs. 50% for patients < 65 years and 70% vs. 54% for patients ≥ 65 years.

Conclusion for treatment with doublet chemotherapy plus anti-EGFR. These clinical trials with doublet chemotherapy plus anti-EGFR (cetuximab or panitumumab) suggest that age is not an absolute contraindication for this regimen compared to chemotherapy alone, either in the first-line or second-line setting. However, the benefit is still unclear because there is a substantial bias coming from the age cutoff (< or > 65 years), which does not definitively represent the older patient subgroup. The safety profile with anti-EGFR was acceptable, but there were increased digestive and cutaneous toxicities, which could be more difficult to manage in the older adult.

3.2 Anti-EGFR combined with single-drug chemotherapy or as monotherapy

For patients not sufficiently fit to benefit from doublet chemotherapy, some rare studies have assessed the efficacy of anti-EGFR combined with single-drug chemotherapy **(Table 1)** or as a single agent **(Table 2)** in chemotherapy-refractory patients. Of interest, some of these studies specifically explored anti-EGFR monotherapy in frail patients.

First-line regimen

- *Sastre et al study* [32]. This study assessed the efficacy of cetuximab plus capecitabine as a first-line treatment in 66 older patients (median age, 77 years; range, 70–87 years) with a performance status of 0–1. The trial results were weakened because KRAS status was determined in 58/66 patients (88%), and the dose of capecitabine was reduced during the course of the trial for safety reasons. The overall response rate was 31.8% but was higher

(48.3%) in the wild-type KRAS tumor subgroup than in the subgroup with KRAS mutations. The median PFS and OS for the entire population were 7.1 months and 16.1 months, respectively. The overall response rates, PFS and OS were low and in the range of those obtained with classical chemotherapy. The safety profile was poor, with a high incidence of severe paronychia (29.6%) that declined after dose adjustment of capecitabine (7.7%). Of note, the three-arm MRC COIN study also showed a possible negative interaction between capecitabine and cetuximab [33].

- *PANEL GITuD-2011-01* [34]. This ongoing phase II trial includes 26 older patients (age ≥ 70 years) with wild-type RAS and BRAF mCRC who received panitumumab plus capecitabine until disease progression or unacceptable toxicity. The first analyses showed an overall objective response of 38% (69% of patients achieved at least stable disease), a median PFS of 9.6 months and a median OS of 23.7 months. Grade 3 cutaneous toxicities (rash) were reported in 27% of patients.

Some studies specifically included older frail patients treated with anti-EGFR monotherapy or anti-EGFR in combination with chemotherapy as a first-line treatment:

- *SAKK 41/10 study* [35]. This study evaluated the benefit of cetuximab, either alone or in combination with capecitabine, in vulnerable older patients with mCRC. The median age was 80 years (range 71-89), and patients harbored a RAS/BRAF-wild-type status. The trial was stopped prematurely due to slow accrual (requiring both geriatric and molecular eligibility criteria) after the inclusion of 24 patients: 11 in the monotherapy arm and 13 in the combination arm. The response rates were 9% and 38% in the monotherapy and combination arms, respectively, with a higher incidence of toxicities and need to stop treatment in the combination arm than in the monotherapy arm. Due to the small sample size, the authors could only conclude that cetuximab monotherapy appeared tolerable and showed evidence of antitumoral activity.

- *FRAIL study* [36]. This phase II study evaluated panitumumab as a first-line monotherapy in frail older mCRC patients with wild-type KRAS (exon 2) tumors. A total of 33 patients were included (median age 81 years; range (73–89 years)); 57.6% of patients had an ECOG performance status of 2, and 69.7% of patients had at least 3 comorbid conditions and were not able to function independently. The objective response rate was 9.1% (all partial responses), and there were 18 patients (54.5%) with stable disease. The median PFS and OS were 4.3 months (95% CI 2.8–6.4) and 7.1 months (95% CI 5.0–12.3), respectively. There was a significant association between clinical response and RAS status ($p = 0.037$). Thus, in the expanded wild-type RAS subgroup (wild-type exons 2, 3, and 4 of KRAS and NRAS, n = 15), the 6-month PFS rate was 53.3% (95% CI 30.1–75.2), the median PFS was 7.9 months, and the median OS was 12.3 months. No grade 4 or grade 5 adverse events were reported, and the most common grade 3-related adverse event was acneiform rash (15.2%). No adverse event led to permanent discontinuation of panitumumab.
- *OGSG 1602 study* [37]. In this multicenter phase II study, older patients with wild-type RAS unresectable CRC, chemotherapy-naïve and considered unsuitable for intensive chemotherapy, received panitumumab 6 mg/kg every 2 weeks. A total of 34 patients were analyzed (median age, 81 years and 85% being aged over 76 years). The response rate was 50.0% including three cases (8.8%) of complete response and stable disease rate was 26.5% The authors of the study concluded that panitumumab monotherapy showed a favorable efficacy and feasibility in frail or older patients with unresectable CRC. Note however that frailty was based mainly on performance status and not on a questionnaire for comprehensive assessment of older patients with cancer.

Second-line regimen

Most of the studies using anti-EGFR as a single agent in the second-line setting are retrospective. The main prospective study using anti-EGFR monotherapy (in the first-line or second-line setting) is the study by Pietrantonio *et al.*, in which the endpoint was the objective response rate:

- *Pietrantonio et al study* [38]. This study evaluated panitumumab monotherapy in 40 older patients (median age, 80 years; range, 76–90) diagnosed with wild-type RAS and wild-type BRAF mCRC. Patients were considered frail, but 82% had an ECOG performance status of 0–1. Panitumumab was used as a first-line treatment in patients with contraindications for chemotherapy (25% of patients) and as a second-line treatment for 75% of patients (previous treatments were oxaliplatin-based doublet chemotherapy in 43% of patients, capecitabine monotherapy in 37% of patients and capecitabine plus bevacizumab in 20% of patients). The overall response rate was 32.5%, and the disease control rate was 72.5% (no complete response). The median PFS and OS values were 6.4 months (95% CI 4.9–8 months) and 14.3 months (95% CI 10.9–17.7 months), respectively. The most frequent grade 3 adverse event was skin rash (20%), but no permanent treatment discontinuation was reported.

Third-line regimen

- *Cetuximab monotherapy* [39]. This study enrolled 572 previously treated patients who had colorectal cancer expressing immunohistochemically detectable EGFR. Patients received cetuximab plus best supportive care (BSC) (287 patients) or BSC alone (285 patients). In comparison with BSC alone, cetuximab treatment was associated with a significant improvement in overall survival (primary endpoint) (6.1 months versus 4.6 months, HR 0.77; 95% CI, 0.64 to 0.92; P=0.005), as well as progression-free survival (HR 0.68; 95% CI, 0.57 to 0.80; p <0.001). Partial responses occurred in 23 patients (8.0%) in the cetuximab group. Quality of life was better preserved in the cetuximab group than in the

BSC alone group, with less deterioration in physical function and global health status scores (both p<0.05), although the incidence of any adverse event of grade 3 or more was higher in the cetuximab group than in the BSC group (78.5% versus 59.1%, p <0.001). Notably, no specific data are available regarding age groups.

- *Panitumumab monotherapy* [40]. In this study, 463 patients were enrolled and randomly assigned to panitumumab or BSC arms. The study was not conducted specifically in older patients; however, 187 of the 463 patients were ≥ 65 years (median age 62 years (27-83)). All but one patient had received at least two prior lines of chemotherapy. PFS (8.0 vs 7.3 weeks; p < 0.0001) and ORR (10% vs 0%; p < 0.0001) were significantly higher in the panitumumab arm than in the BSC arm. No difference was observed in OS (crossover was permitted). Skin toxicities, hypomagnesemia, and diarrhea were the most common toxicities observed with panitumumab. No patients had grade 3/4 infusion reactions.

The ASPECCT study assessed the non-inferiority of panitumumab compared to cetuximab in chemotherapy-refractory patients [41]. The subgroup analysis suggested higher PFS and OS in older patients treated with panitumumab than in older patients treated with cetuximab:

- *ASPECCT study* [41]. This multicenter randomized phase III head-to-head study included 999 evaluable patients (345 with an age ≥ 65 years) with chemotherapy-refractory mCRC, an ECOG performance status of 0–2 and wild-type KRAS exon 2 in tumor cells who received panitumumab or cetuximab as monotherapy. The noninferiority of panitumumab was demonstrated, with a median OS of 10.4 months (95% CI, 9.4–11.6) for panitumumab and 10.0 months (9.3–11.0) for cetuximab (HR 0.97; 0.84–1.11). Although statistical significance was not achieved, the HR for OS was 0.85 (0.67–1.08) in patients ≥ 65 years and 1.04 (0.87–1.23) in patients < 65 years in favor of panitumumab and the same pattern

was seen for PFS: HR 0.86 (0.69–1.07) in patients ≥ 65 years and HR 1.10 (0.94–1.28) in patients < 65 years.

Conclusion for anti-EGFR combined with single-drug chemotherapy or as monotherapy. To date, no scientifically robust clinical trials have been performed to assess the benefit of anti-EGFR as monotherapy or combined with single-drug chemotherapy in older patients. In frail patients, all studies using anti-EGFR as a single agent include a limited number of patients and are not comparative. The objective response rate and survival rates were quite similar in those studies compared to the rates in studies with standard chemotherapies but had a superior toxicity profile. The safety of anti-EGFR monotherapy in this frail older population was acceptable, with mainly cutaneous toxicities that were easily managed.

3.3 Real-life data and ongoing studies

Several observational and clinical studies have aimed to define the place of anti-EGFR therapy in older patients with mCRC.

EREBUS. Few real-life data are available on cetuximab benefit. The primary objective of this observational study performed in France was to determine the rate of metastatic resection in 389 wild-type KRAS mCRC patients (aged 27 to 88 years) with initially unresectable metastases treated with cetuximab combined with chemotherapy as a first-line treatment [42]. The subgroup of older patients (> 70 years) comprised 116 patients (72.4% with an ECOG performance status of 0–1). Chemotherapy was combined with anti-EGFR: irinotecan for 56.8% of patients and oxaliplatin for 38.5% of patients. The clinical results were comparable in older and younger patients: the median PFS was 9.5 months (95% CI 7.1–10.5) vs. 9.2 months (95% CI, 8.1–9.8), respectively, and the overall response rate was 46.5% (95% CI 37.4–55.6) vs. 56.7% (95% CI 50.8–62.6), respectively.

Jehn et al study. This non-interventional study was performed in 497 mCRC patients treated with cetuximab and irinotecan and pretreated with irinotecan [43]. The objective response rates were similar for age <65 or > 65 years: 38.1% vs. 36.4%, respectively (p = 0.57). PFS did not differ between patients < 65 years (6.0 months) and patients >65 years (6.2 months; p = 0.99).

ObserEr study. In this retrospective study, the influence of age (< and ≥ 70 years) was studied in patients with wild-type KRAS mCRC and treated with chemotherapy plus cetuximab [44]. No difference was reported on PFS and on disease control rates between according to age. Median OS was higher in patients <70 years (27 months, 95% CI 22.7–31.3) than in patients ≥70 years (19 months, 95% CI 14.7–23.4; p = 0.002); This difference was most probably due to higher proportions of metastatic resection and use of second-line therapy in the younger group.

PANDA. This is a randomized phase II study of first-line FOLFOX plus panitumumab vs. 5FU/leucovorin plus panitumumab in older patients (≥ 70 years) with wild-type RAS and wild-type BRAF mCRC [45]. Older patients will benefit from geriatric assessment with the G8 scale and baseline CRASH scores. The primary endpoint is PFS, and secondary endpoints include prospective evaluation of the prognostic role of the G8 score and the correlation of CRASH risk categories with toxicity.

OPALO. The objective of this phase II single-arm trial is to assess the efficacy and safety of first-line therapy with panitumumab plus FOLFIRI in older patients (≥ 70 years) with wild-type RAS and wild-type BRAF mCRC [46]. Only patients with a performance status of 0-1 and no more than one comorbidity will be included. Tumor response will be evaluated every 8 weeks until disease progression. Approximately 80 patients will be included.

MONARCC [47]. This on-going study is a prospective non-comparative randomized phase II study in untreated patients aged 70 years or older with wild-type RAS and BRAF mCRC.

Patients receive as first-line treatment panitumumab monotherapy or panitumumab plus 5FU. The primary end-point is PFS at 6 months for a sample size of 80 patients.

4. DISCUSSION

The population of older patients is underrepresented in clinical studies for various reasons. This situation is particularly striking in CRC where a large proportion of patients are aged 75 years and over. In the recent study of Canouï-Poitrine et al, three-quarters of older patients with CRC were ineligible for a clinical trial (one-third of the eligible patients were not invited to participate and 17% of invited patients were not included) [48]. In addition, patients aged ≥ 80 years were significantly less likely to be eligible for a trial and invited to participate.

In the absence of solid data for this population, many frail patients are not treated due to insufficient evidence on the appropriate management of this population. In clinical practice, decisions for treatment are based on data obtained in younger patients with mCRC. Guidelines for the management of patients with mCRC recommend that fit older patients should be treated with a combination of chemotherapy plus targeted agents. The use of bevacizumab in combination with chemotherapy has demonstrated its benefit in terms of survival and is still the standard of care. However, for unfit older patients incapable of receiving standard combination chemotherapy (with or without targeted agents), less intensive therapies are appropriate in first- or second-line settings [5, 7]. For these older patients, reduced-dose oxaliplatin plus 5-FU or lower dose capecitabine plus bevacizumab may be used [5].

In fit older patients, clinical trial subgroup analyses with doublet chemotherapy plus anti-EGFR suggested that age is not an absolute contraindication for this regimen, as seen in results that compared chemotherapy alone with cetuximab (the CRYSTAL, OPUS and FIRE3 studies) or panitumumab (the PRIME study) in the first-line setting or cetuximab (the Jehn *et al* study) or panitumumab (the Peeters *et al* study) in the second-line setting.

In frail patients, anti-EGFR (cetuximab in the Sastre *et al* study [32] or panitumumab in the PANEL study [34]) combined with single-agent chemotherapy and more specifically with capecitabine failed to show a significant benefit in terms of survival and had more toxicity than chemotherapy alone. However, anti-EGFR as a single agent (the SAKK 41/10 study (cetuximab) [35], FRAIL study [36] or Pietrantonio *et al* study (panitumumab) [38]) demonstrated interesting results and was well tolerated. Of note, in the FRAIL study, there was a significant association between clinical response and RAS status, thus suggesting that some patients could experience improved clinical outcomes. Nevertheless, robust clinical trials using anti-EGFR in combination with single-drug monotherapy or as monotherapy in frail patients are lacking, though this treatment remains the standard first-line or second-line off-label regimen.

In older patients treated with anti-EGFR, the occurrence of cutaneous and digestive toxicities and hypomagnesemia was increased, and these toxicities should be regularly monitored. Managing older patients with cancer is a matter of predicting the toxicity of treatment and mortality. A recent publication has established an easy way to assess toxicity and mortality prediction scores [49]. In the future, these scores will need to be validated in further metastatic and adjuvant colorectal studies.

In conclusion, doublet chemotherapy combined with anti-EGFR showed a benefit in fit patients under the age of 75 years, but might be cautiously considered for patients over 75 years. According to international guidelines, there is no age limit in frail patients for anti-EGFR monotherapy either as an off-label, second-line or first-line therapy. In any case, treatment must be cautious in older patients and the dose needs to be managed according to comorbidities.

Disclosures and conflicts of interest statement

Dr. GILABERT reports other from AMGEN during the conduct of the study; other from AAA, personal fees and other from AMGEN, personal fees, non-financial support and other from BAYER, other from BMS, other from CELGENE, other from HalioDx, personal fees, non-financial support and other from IPSEN, other from LILLY, personal fees, non-financial support and other from MERCK, grants, personal fees, non-financial support and other from NOVARTIS, other from PIERRE FABRE, personal fees, non-financial support and other from ROCHE, personal fees and other from SANDOZ, personal fees, non-financial support and other from SERVIER, personal fees from INCYTE, non-financial support from PFIZER, grants from INTRAGEN, outside the submitted work.

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Authors' contributions

MG, ST, EF, AL and FR collaborated on the paper's conception and wrote the paper. MG, PR, BC, ST, EF, AL and FR reviewed the paper and approved the final version of the article to be published.

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Table 1. Studies using chemotherapy plus anti-EGFR in older patients with mCRC.

Regimen	Studies (year)	Type of study	Type of mCRC	Age of older patients analyzed	Number of older patients analyzed	Anticancer therapy	Treatment setting
Doublet chemotherapy plus anti-EGFR	CRYSTAL and OPUS (2010) [25]	Pooled analysis of two comparative prospective studies	Wild-type KRAS	≥ 70 years	67 CT alone 78 CT plus cetuximab	Cetuximab + FOLFIRI (CRYSTAL) and cetuximab + FOLFOX (OPUS)	First line
	FIRE3 (2014) [26]	Subgroup exploratory analysis of comparative study	Wild-type KRAS	> 65 years	274	FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab	First line
	PRIME (2014) [28]	Post hoc analysis of comparative study	Wild-type KRAS	≥ 65 years	189	FOLFOX plus panitumumab vs. FOLFOX alone	First line
	Jehn (2012) [29]	Prespecified analyses of noninterventional studies	Wild-type KRAS	≥ 65 years	305	CT + cetuximab	Second line
	Peeters (2014) [31]	Prespecified post hoc analyses of phase III study	Wild-type KRAS	≥ 65 years	236	Panitumumab plus FOLFIRI vs. FOLFIRI alone	Second line
Single-drug chemotherapy plus anti-EGFR	Sastre (2012) [32]	Prospective single-arm study	N=29 with wild-type KRAS	≥ 70 years	66	Cetuximab plus capecitabine	First line
	PANEL (2017) [34]	Phase II study	Wild-type KRAS and BRAF	≥ 70 years	26	Panitumumab plus capecitabine	First line

mCRC: metastatic colorectal cancer; CT: chemotherapy; FOLFIRI: irinotecan and 5FU/leucovorin; FOLFOX: oxaliplatin and 5FU/leucovorin.

Table 2. Studies using anti-EGFR as a single agent in older patients with mCRC.

Regimen	Studies (year)	Type of study	Type of mCRC	Age of older patients analyzed	Number of older patients analyzed	Anticancer therapy	Treatment setting
Anti-EGFR monotherapy	SAKK 41/10 (2019) [35]	Phase II study	Wild-type RAS and BRAF	≥ 70 years (frail patients)	24	Cetuximab	First line
	FRAIL (2015) [36]	Phase II study	Wild-type KRAS	≥ 73 years (frail patients)	33	Panitumumab	First line
	OGSG 1602 [37]	Phase II study	Wild-type RAS	≥ 76 years	34	Panitumumab	First line
	Pietrantonio (2015) [38]	Prospective single-arm study	Wild-type RAS and BRAF	≥ 76 years (frail patients)	40	Panitumumab	First and second line
	Jonker (2007) [38]	Phase III study	IHC-detectable EGFR expression	≥ 70 years	?	Cetuximab	Third line
	Van Cutsem (2007) [39]	Phase III study	Wild-type KRAS exon 2	≥ 65 years	187	Panitumumab	Third line
	ASPECCT (2014) [41]	Non-inferiority phase III study	Wild-type KRAS	≥ 65 years	345	Panitumumab or cetuximab	Undefined (refractory to chemotherapy)

EGFR: epidermal growth factor receptor; IHC: immunochemistry