BMC Cancer

RESEARCH Open Access

ERBITAG: Non-interventional study on the efficacy of cetuximab in first-line therapy in patients with RAS wild-type metastatic colorectal cancer

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Abstract

Background Metastatic colorectal cancer (mCRC) is a difficult-to-treat disease with poor clinical outcomes. Systemic chemotherapy in combination with targeted anti-EGFR therapy has expanded the treatment options for mCRC. However, the therapeutic efficacy of anti-EGFR regimens and relevant prognostic factors vary according to age, performance status and tumor location. The non-interventional ERBITAG study was performed to evaluate the efficacy and safety of cetuximab in first-line therapy in *RAS* WT mCRC patients under routine clinical practice.

Methods ERBITAG is a non-interventional study of wild-type (WT) *RAS* mCRC patients initiating a first-line therapy with cetuximab from 2010 to 2018. Overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan-Maier methods. χ^2-test was used to compare selected categorial variables.

Results Of a total of 728 patients included, baseline characteristics were: median 67 years, male sex 69%, ECOG performance status ≤ 1 81.3%, left-sided tumors 64.5%, liver metastasis 73.4% and prior hepatic metastasis resection before cetuximab-based treatment 16.4%. Median PFS was 10.9 months, median OS was 23.6 months and ORR was 58.0%. Resection rate of liver and/or lung metastases under cetuximab-based therapy was 13.9% and 18.9% of liver metastases. The most common treatment-emergent event (TEAE) was acne-like rash (all grades: 46.8%; grade 3–4: 4.7%). Subgroup analysis showed better outcomes in younger patients (ORR, OS), patients with left-sided tumors (ORR, PFS, OS) and lower grade tumors (ORR, PFS, OS), patients with resected liver and/or lung metastases (PFS, OS) and patients with treatment breaks (OS). Skin prophylaxis with systemic antibiotics and/or topical steroids (ORR, OS, PFS) was associated with better outcomes.

Conclusions The ERBITAG study provides insights into the use of cetuximab in a large *RAS* WT mCRC cohort in real-life clinical practice in Germany. Cetuximab in combination with first-line chemotherapy demonstrates clinical outcomes and safety data similar to results from the other pivotal randomized controlled trials.

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Trial registration Study Number: EMR062202-515 (https://www.pei.de/SharedDocs/awb/nis-0101-0200/0114.html) Registered on 04-MAY-2010.

Keywords Cetuximab, Cetuximab-based combinational chemotherapy, Colorectal cancer, Metastatic colorectal cancer, Non-interventional study, First-line therapy, *RAS* WT, Skin prophylaxis

Background

Colorectal cancer (CRC) is the third most common cancer worldwide [1]. In 2020, CRC accounted for 9.4% of all cancer-related deaths, making it the second leading cause of death by cancer [1]. While 39% of patients are diagnosed with CRC at a localized stage, 25% of patients have metastatic disease (mCRC) at their initial diagnosis [2]. In the past, the 5-year overall survival rate for mCRC was less than 10%, compared to 91% for localized CRC [3]. Recent significant improvements in mCRC treatment, both in terms of surgery and systemic therapy for unresectable advanced or recurrent CRC, and the introduction of innovative multidisciplinary therapies, e.g., systemic cytotoxic chemotherapy with the addition of targeted therapy, such as monoclonal antibodies (mAbs) against epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGFR), and small molecule inhibitors, such as tyrosine kinase inhibitors (TKIs), have helped to prolong overall survival (OS) and progression-free survival (PFS) [4], and may delay, if not halt, tumor progression in mCRC patients [5]. First-line systemic chemotherapy for mCRC mainly consists of 5-fluorouracil (5-FU)/leucovorin (LV)/oxaliplatin (FOLFOX), 5-FU/LV/irinotecan (FOLFIRI) or 5-FU/LV/oxaliplatin/irinotecan (FOLFOXIRI) [6, 7], nowadays often combined with targeted mAbs, such as bevacizumab, cetuximab, or panitumumab [8].

Cetuximab is an immunoglobulin (IgG1) mAb directed against the EGFR. Binding of cetuximab to the extracellular domain of EGFR prevents endogenous ligand binding and promotes receptor internalization and degradation [9], thereby inducing apoptosis, while reducing cell proliferation angiogenesis as well as tumor invasiveness and metastasis [10]. However, the benefit of cetuximab either as monotherapy or in combination with chemotherapy (FOLFIRI, FOLFOX or FOLFOXIRI), is limited to *K-RAS/N-RAS* wildtype EGFR-expressing mCRC patients [11].

The RAS family of proto-oncogenes are important downstream signaling regulators of EGFR. Activating *RAS* mutations (*KRAS/NRAS*), which occur in 47% of all mCRC patients, induce constitutive activation of the mitogen-activated protein kinase (MAPK) pathway independent of EGFR, thereby weakening the response to anti-EGFR antibodies [12]. *K-RAS* is the most frequently mutated *RAS* gene in mCRC patients, accounting for approximately 85% of all *RAS* mutations [13]. Mutations in *N-RAS*, which is highly homologous to *K-RAS*, are less common in mCRC. The *BRAF* gene is an important key downstream effector of *RAS* in the MAPK pathway, which mainly affects cell proliferation, differentiation, and apoptosis [14]. Although *BRAF* mutations are less common than *RAS* mutations, 8–12% of mCRC patients are diagnosed with a *BRAF* mutation, > 90% of which are $BRAF^{V600E}$. $BRAF^{V600E}$ causes hyperactivity of its kinase activity and thereby stimulation of the MAPK signaling pathway in an *RAS*-independent manner [15]. $BRAF^{V600E}$-mutant mCRC forms an aggressive form of mCRC, associated with an unfavorable poor prognosis and a poor response to standard chemotherapy; the overall median survival ranges from 9.8 to 18.2 months and only 52.5% of patients receive second-line therapy [16]. Therefore, expanded testing for both *RAS* (*K-RAS/N-RAS*) and *BRAF* gene profiles is the standard to optimize anti-EGFR strategy for mCRC patients [17].

The location of the primary colorectal tumor also influences whether patients with mCRC will respond to anti-EGFR therapy. In the wild-type (WT) *RAS* population, patients with left-sided mCRC are more likely to respond well to anti-EGFR therapy and have a better prognosis compared to patients with right-sided mCRC [18–22]. Right-sided tumors are more likely to harbor mutations in *RAS* and *BRAF*, whereas left-sided tumors are more likely to harbor upregulated EGFR and/or ERBB2 (HER2) [23]. Therefore, tumor mutation status and tumor location are considered key decision drivers in guiding drug selection, according to the most recent ESMO guidelines [24, 25].

Overall, CRC incidence rates increase markedly with age and more than half of affected patients are diagnosed after the age of 70 years [10, 26, 27], when the disease has progressed, and health and functional capacity are impaired. Older patients > 65 years and especially > 75 years and patients with an ECOG performance score of 2 and worse are often underrepresented in clinical trials. Therefore, the non-interventional ERBITAG study was initiated to collect safety and efficacy data from a real-world mCRC patient population in Germany under everyday treatment conditions. The objective response rate was chosen as the primary endpoint because it correlates with secondary resectability and long-term survival. Of further interest was to evaluate whether the clinical study data can be transferred to the everyday clinical practice in terms of resectability of metastases.

Methods

Study design and study population

The ERBITAG study was a prospective, open-label, observational, non-interventional study to evaluate the efficacy and safety of cetuximab in first-line therapy of patients with *(K)RAS* WT mCRC. Eligible adult patients had EGFR-expressing *(K)RAS* WT mCRC. Patients with informed consent started therapy (chemotherapy or cetuximab) within 3 months after primary diagnosis of metastasis (in the case of prior hepatic metastasis resection before cetuximab-based treatment this might have differed from the initial mCRC diagnosis). Prior hepatic metastasis resection only included surgical resection; thermal ablation procedures were not included. Patients were not eligible for study participation if they had received prior chemotherapy – with or without targeted combination –in the metastatic stage. Patients were also ineligible if they had a *K-RAS* (exons 2, 3 and 4) or *N-RAS* (exons 2, 3 and 4) mutation or unclear *RAS* mutation status of the tumor, known grade 3 or 4 hypersensitivity to cetuximab, if they simultaneously participated in another Merck Healthcare Germany non-interventional study or an interventional clinical trial during the treatment phase or within the past 30 days, if they had no or limited contractual capacity, confinement to an institution by order of a court or authority, or in case of off-label treatment. If initiation of cetuximab treatment was delayed, patients could be included with a justification if the treating physician considered that therapy with cetuximab was indicated as first-line therapy in the metastatic setting.

The original approval for cetuximab changed from EGFR-expressing *K-RAS* WT mCRC to EGFR-expressing *RAS* WT mCRC during the study period, therefore, patients with unknown *RAS* mutation status or mutated *RAS* were no longer enrolled in the study after January 2, 2014. This was amended in the observational plan. Based on the regulatory changes regarding gene status, the study population was analyzed in total and stratified by gene status, resulting in two additional cohorts: the *K-RAS* WT cohort and the *RAS* WT cohort (Fig. 1). Statistical analyses revealed that *K-RAS* WT and *RAS* WT data were comparable. Since the *RAS* WT set includes patients who received cetuximab according to the current approval status, it represents the current real-world situation. Thus, only the results of the *RAS* WT cohort are presented in this manuscript.

Study objectives

The primary objective was to determine the objective response rate (ORR), defined as the proportion of patients with partial response (PR) or complete response (CR) assessed by RECIST (v1.1), WHO, or other criteria.

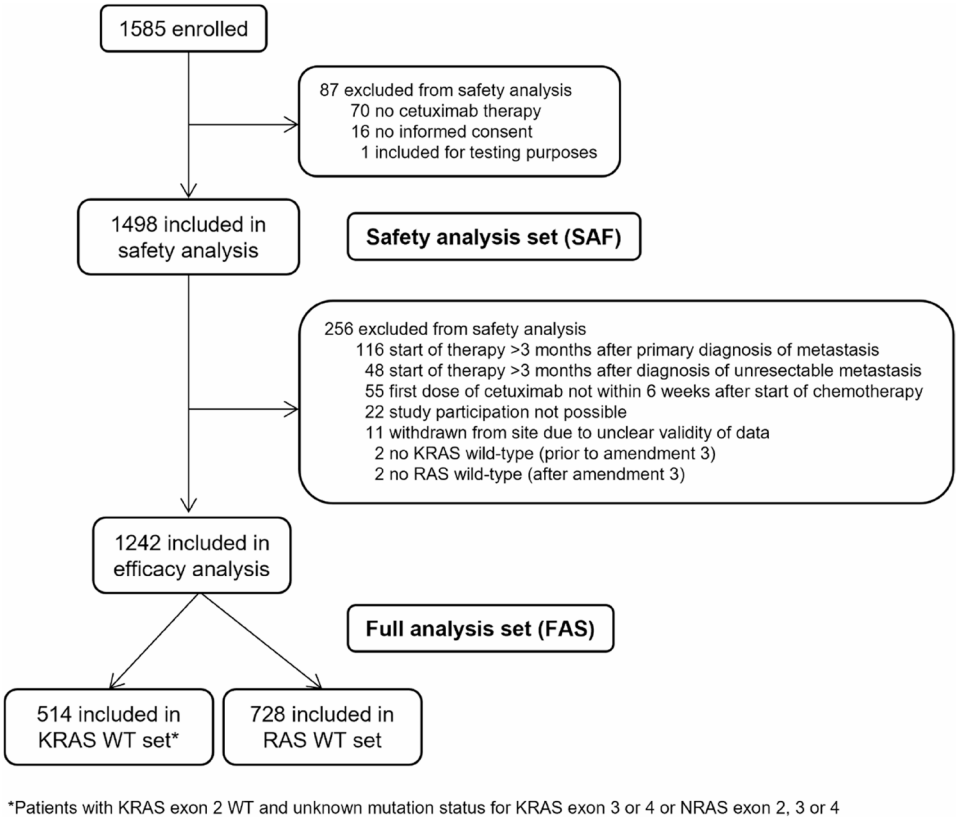

Fig. 1 Patient flow chart (all patients)

An additional analysis was performed for patients, whose response was solely assessed by RECIST criteria. Secondary objectives included the assessment of the median progression free survival (PFS), defined as the time from the first cetuximab infusion until the first progression of disease documented with imaging, and the median overall survival (OS) after start of cetuximab therapy. Further secondary endpoints included the PFS rate at 1 year, the OS rate at 1-, 2-, 3-, and 4-year, time to treatment failure (TTF), defined as the time from first cetuximab infusion until the end of cetuximab therapy due to any cause, resection rate and R_0 rate of liver and/or lung metastases, frequency of chemotherapy combinations (FOLFIRI, FOLFOX or FOLFOXIRI), details of cetuximab treatment, including duration, dose intensity and modifications, safety of cetuximab alone and in combination with different chemotherapy regimens, and whether a skin reaction prophylaxis was given, including evaluation of the success of the applied therapeutic agent(s). In addition, a subgroup analysis was performed to differentiate treatment of left-sided and right-sided mCRC.

Data collection

Due to the non-interventional character of the ERBITAG study, all decisions regarding diagnostic procedures, treatments and management of the disease depended entirely on mutual agreement between the patient and the treating physician and were performed as part of clinical routine. The observational period comprised a maximum of four years plus the treatment period after study inclusion per patient. After study inclusion, data on medical history and prior treatment were extracted from medical records and patients' baseline characteristics were collected using electronic case report forms. From the initiation of cetuximab therapy, treatment-related data, therapy outcomes and safety data were collected prospectively. Follow-up data were documented monthly during cetuximab therapy. In case of therapy discontinuation, follow-up data were collected annually until month 48 after the date of last cetuximab administration.

Statistical analysis

Statistical analyses were performed using SAS 9.4. Categorical variables are presented as numbers and percentages, continuous variables as medians with range. For primary and secondary endpoints, comparisons of selected categorical variables between subgroups were performed by χ^2-test or Fisher's exact test and comparisons of selected continuous variables with Wilcoxon Two-Sample test or Kruskal-Wallis test. Time-to-event endpoints (PFS, TTF, and OS) were analyzed using the Kaplan-Meier method and differences between selected subgroups (stratified by age categories, resection status, therapy breaks, type of skin prophylaxis administered, and *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) status were compared using the χ^2-test (for ORR) or log-rank test (PFS, OS). All reported *p*-values are two-sided. A correction for multiple testing was not done. The 95% confidence interval (CI) was calculated for selected parameters.

The full efficacy analysis set (FAS) included all enrolled patients with informed consent who received at least one infusion of cetuximab and who started therapy (chemotherapy or cetuximab) within three months after primary diagnosis of unresectable metastasis (in case of prior hepatic metastasis resection before cetuximab-based treatment this might be different from the initial mCRC diagnosis) and who additionally received the first dose of cetuximab within six weeks after the first administration of chemotherapy. Safety was assessed for all patients with informed consent who received at least one infusion of cetuximab (Safety analysis set, SAF). Primary and secondary endpoint analyses were performed for the FAS. For the primary endpoint analysis (ORR), patients without a post-baseline tumor assessment were counted as non-responders. Missing data were not imputed, except for death, progression, and treatment discontinuation. Patients who had completed the skin reactions and therapy management reaction form were included in the Skin FAS for analysis of skin reaction prophylaxis during cetuximab therapy.

Ethical statement

The protocol, all protocol amendments as well as the patient information sheet/informed consent form and respective amendments and other relevant study documents were approved by the competent Ethics Committee of the coordinating investigator (Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster). The study was notified to the competent higher authority (Paul-Ehrlich-Institut (PEI), Langen, Germany; EMR062202-515).

Results

Study population

Between June 2010 and June 2018, 202 study sites throughout Germany enrolled 1585 patients (Fig. 1). Of these, 87 patients were excluded from analyses, mainly because no cetuximab therapy was administered or the informed consent was missing and 256 patients did not fulfill the inclusion criteria. Thus, 1242 patients were included in the FAS. In the current manuscript, we describe the *RAS* WT set comprising 728 patients (Fig. 1). It should be noted that the *K-RAS* WT and *RAS* WT sets were similar with respect to the outcome.

Baseline demographic and disease characteristics of the *RAS* WT FAS are shown in Table 1 and Additional

Table 1 Baseline patient characteristics, tumor characteristics, and resection data

Characteristic	RAS WT (*N* = 728)
Median age (range), years	67.0 (25.0–86.0)
Gender, N (%)	
Male	502 (69.0)
Female	226 (31.0)
ECOG performance status at start of cetuximab therapy, N (%)	
0	242 (33.2)
1	350 (48.1)
≥ 2	57 (7.8)
Missing	79 (10.9)
Previous therapy, N (%)	
Radiotherapy	92 (12.6)
Adjuvant chemotherapy	229 (31.5)
5-FU + FA	40 (17.5)
Capecitabine	27 (11.8)
5-FU + FA + Oxaliplatin (FOLFOX)	101 (44.1)
Capecitabine + Oxaliplatin	14 (6.1)
5-FU + FA + Irinotecan (FOLFIRI)	10 (4.4)
Other	33 (14.4)
Unknown	4 (1.8)
Location of primary tumor, N (%)	
Colon	408 (56.0)
Rectum	286 (39.3)
Other	46 (6.3)
Side of tumor and status of resection, N (%)	
Right-sided	146 (20.1)
Patients with primary surgery	119 (81.5)
R_0 resected	85 (71.4)
Left-sided	469 (64.4)
Patients with primary surgery	323 (68.9)
R_0 resected	255 (79.0)
Unspecific side	68 (9.3)
Patients with primary surgery	47 (69.1)
R_0 resected	36 (76.6)
Missing	45 (6.2)
Location of metastasis, N (%)	
Local recurrence	20 (2.8)
Liver	534 (73.4)
Lung	165 (22.7)
Lymph nodes	151 (20.7)
Peritoneum	134 (18.4)
Other*	98 (13.5)
Liver only	318 (43.7)
Number of metastatic locations, N (%)	
1	447 (61.4)
2	206 (28.3)
≥ 3	75 (10.3)

ECOG Eastern Cooperative Oncology Group, *FU* 5-Fluorouracil, *FA* Folinic acid

*including bones, cerebral locations, pleura, skin, kidney and other organs

Table 2 Cetuximab treatment

	RAS WT (*N* = 728)
Cetuximab dosing, *N* (%)	
Weekly cetuximab (q1w)	633 (87.0)
Cetuximab every 2 weeks (q2w)	95 (13.0)
Number of infusions, Median (Range)	
Total number of infusions q1w	18 (1-216)
Total number of infusions q2w	13 (1–62)
Cetuximab discontinued after first administration, N (%)	6 (0.8)
Cumulative dose [mg/m²]	
Median (Range)	4900 (250–54150)
Relative Dose Intensity [%]*	
Median (Range)	85.26 (17–271)
Treatment duration during observational period [weeks]	
Median (Range)	22 (1–286)

*The relative dose intensity was calculated assuming an initial dose of 400 mg/m² for the first week followed by weekly doses of 250 mg/m² in accordance with the SmPC of cetuximab. Calculation was done regardless of the applied cetuximab dosing schedule (q1w or q2w)

Table 1. Most patients had a left-sided tumor (64.4%, *N* = 469), mainly located to the colon (56.0%, *N* = 408). The liver was the primary site of metastasis (73.4%, *N* = 534) followed by the lung (22.7%, *N* = 165); 67.3% of patients were synchronously metastatic (Table 1). Prior hepatic metastasis resection before cetuximab-based treatment was performed in 16.4% of patients (*N* = 119), of which 59.7% were R_0-resected (*N* = 71) (Additional Table 1).

Previous treatment

The majority of patients underwent primary surgery (72.5%, *N* = 528) with a resection result of R_0 in 77.8% (*N* = 411) of them. 31.5% of the patients (*N* = 229) received adjuvant chemotherapy before the start of cetuximab therapy, mostly FOLFOX (44.1%, *N* = 101) (Table 1).

Cetuximab treatment and chemotherapy

In median, patients were treated 22 weeks with cetuximab with a wide range of individual treatment durations (range: 1–286 weeks). Most patients received cetuximab weekly (87.0%, *N* = 633); 13.0% (*N* = 95) received cetuximab biweekly. On average (median), 18 infusions were administered to patients who received weekly dosing of cetuximab and 13 infusions to those patients receiving cetuximab biweekly. Six patients (0.8%) discontinued cetuximab after first administration (Table 2).

The most frequently documented initial dose was 400 mg/m² for patients receiving cetuximab weekly

(81.2%, *N* = 591) and 500 mg/m² for patients receiving cetuximab biweekly (8.7%, *N* = 63) The main maintenance dose in week 2 was 250 mg/m² for the weekly schedule (83.0%, *N* = 604) and 500 mg/m² for the biweekly schedule (5.2%, *N* = 38). The median cumulative dose was 4.900 mg/m² (data not shown). Assuming an initial dose of 400 mg/m² for the first infusion followed by weekly doses of 250 mg/m², as specified in the summary of product characteristics of cetuximab [https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf], patients received in median 85.3% of this dose during their cetuximab treatment (Table 2). The most common chemotherapy regimens in combination with cetuximab treatment were FOLFIRI (54.0%, *N* = 393) and FOLFOX (36.2%, *N* = 264) (Additional Table 2).

Skin reaction prophylaxis

A skin prophylaxis/skin reaction form was created for 700 patients (96.2%, Skin *RAS* WT FAS, Table 3). Of these, 430 patients (61.4%) had documented skin reaction prophylaxis, mainly comprising systemic antibiotics (32.6%, *N* = 228) and/or Vitamin K cream (23.4%, *N* = 164) (Table 3, Additional Table 3). A detailed overview of the different types of skin reaction prophylaxis is provided in Additional Table 3. Effectiveness of skin management procedures showed that skin reactions were more frequently in male patients and in patients receiving prophylactic treatment with other skin care (data not shown).

No differences in the duration of cetuximab therapy or in the dose intensity of cetuximab over the course of the study were observed between patients receiving prophylactic systemic antibiotics and patients without prophylactic systemic antibiotics. Interruption of cetuximab therapy was about in about three-fourths of patients, regardless of prophylactic systemic antibiosis. Discontinuation rate was slightly higher among patients not receiving prophylactic systemic antibiosis (Additional Table 4).

Objective response rate

The objective response rate (ORR) according to RECIST (v.1.1), WHO, or other criteria FAS was 58.0% (CI 95%: 54.3–61.6) (Table 4). Forty-nine patients (6.7%) had complete responses, and 373 patients (51.2%) had partial responses to cetuximab-based therapy. Stable disease was observed in 108 patients (14.8%) (Table 4). Considering only responses assessed by means of RECIST (v1.1) criteria, the ORR was 49.7% (CI 95%: 44.30–55.12, *N* = 344) (Additional Table 5).

Progression free survival and overall survival

Median progression-free survival (PFS) was 10.9 months (CI 95%: 9.9 11.7 months), with a PFS rate at 1 year of 44.2% (CI 95%: 40.4–47.9, Fig. 2a). Median overall survival (OS) was 23.6 months (CI 95%: 21.2–25.6, Fig. 2b).

Table 3 Skin reaction prophylaxis / skin reaction form

	RAS WT (*N* = 728)
Patients with skin reaction prophylaxis/skin reaction form (Skin FAS), N (%)	700 (96.2)
Patients with documented skin reaction prophylaxis*, N (%)	430 (61.4)
Skin reaction prophylaxis categories, N (%)	
Systemic antibiotics	228 (32.6)
Topical antibiotics or topical corticosteroids*[1]	39 (5.6)
Other skin care	163 (23.3)

*Some patients were recorded as having skin reactions but did not receive prophylaxis

*[1]No systemic antibiotics

Table 4 Objective response rate and best response

	RAS WT (*N* = 728)
Response to treatment according to RECIST (v1.1), WHO or other criteria	
No. of patients evaluated	728
Confirmed objective response rate	
No. of patients with CR + PR as best response	422
Percent (95% CI)	58.0 (54.3–61.6)
Best response, N (%)	
Complete response (CR)	49 (6.7)
Partial response (PR)	373 (51.2)
Stable disease (SD)	108 (14.8)
Progressive disease (PD)	67 (9.2)
Not evaluable	131 (18.0)

CR Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease

Treatment failure and time-to-treatment failure

Treatment failure was observed in 705 patients, including 81 patients who discontinued treatment. The reason for discontinuation was a complete response to therapy in 28 patients and surgical resection of the metastases in 53 patients. Median time to treatment (TTF) was 5.3 months (CI 95%: 4.8–5.5 months) (Fig. 3).

Resection rates of metastases

116 resections of metastases during/after cetuximab treatment were documented in a total of 104 patients (14.3%). Most patients had one resection (91.4%, *N* = 95). 77.6% of performed resections comprised liver metastases (*N* = 90) and 11.2% lung metastases (*N* = 13). Most of these were R_0-resected (61.1% of the liver metastases [*N* = 55], 69.2% of the lung metastases [*N* = 9]). Complications occurred in 2.6% (*N* = 3) and 11.2% of the patients (*N* = 13) during and after surgery, respectively. A closer look at metastases of the liver and/or lung showed that 83.0% of the patients (*N* = 604) had metastases of the lung and/or liver and 43.7% had metastases confined to the liver only (*N* = 318). The resection rate based on the number of patients with liver and/or lung metastases

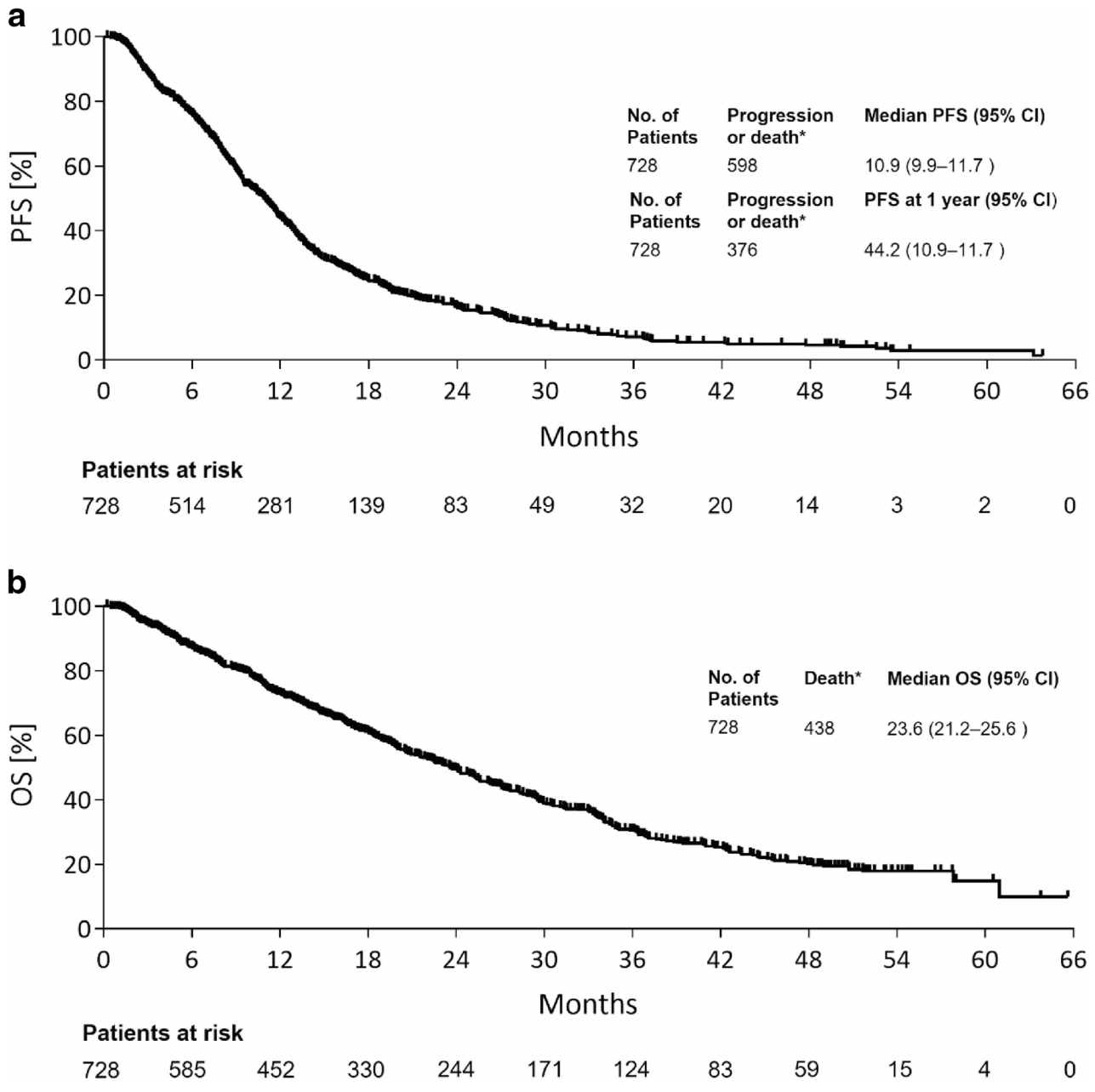

Fig. 2 Progression-free survival and overall survival after combination therapy with cetuximab. Kaplan-Meier curves depicting progression-free survival (PFS, a) and overall survival (OS, b) after combination therapy with cetuximab. The solid vertical lines represent censored data. A log-rank test was used to analyze differences in PFS and OS. *For patients with a documented death but a missing death date, death was imputed

was 13.9% (CI 95%: 11.3–16.9), of which 66.7% ($N = 56$; CI 95% 55.5–76.6) were R_0 resections. The resection rate in patients with liver metastases only was 18.9% (CI 95%: 14.7–23.6) (Table 5).

Subgroup analyses

A better ORR (64.9% vs. 45.5%; p-value 0.0045) and a longer OS (27.1 months vs. 16.9 months; p-value 0.0003) was observed in patients ≤ 65 years compared to patients > 75 years. PFS was similar between the different age categories (median ranges from 10.6 to 11.2 months; p-value 0.6984). A markedly better ORR rate was observed in patients with resected metastases compared to those without resection (86.9% vs. 56.7%; p-value < 0.0001). Similarly, PFS (18.4 months vs. 10.0 months; p-value < 0.0001) and OS (61.0 months vs. 22.0 months; p-value < 0.0001) were obviously longer in resected than in unresected patients (Fig. 4).

In addition, clearly better outcomes were observed in patients with left-sided primary tumors compared to

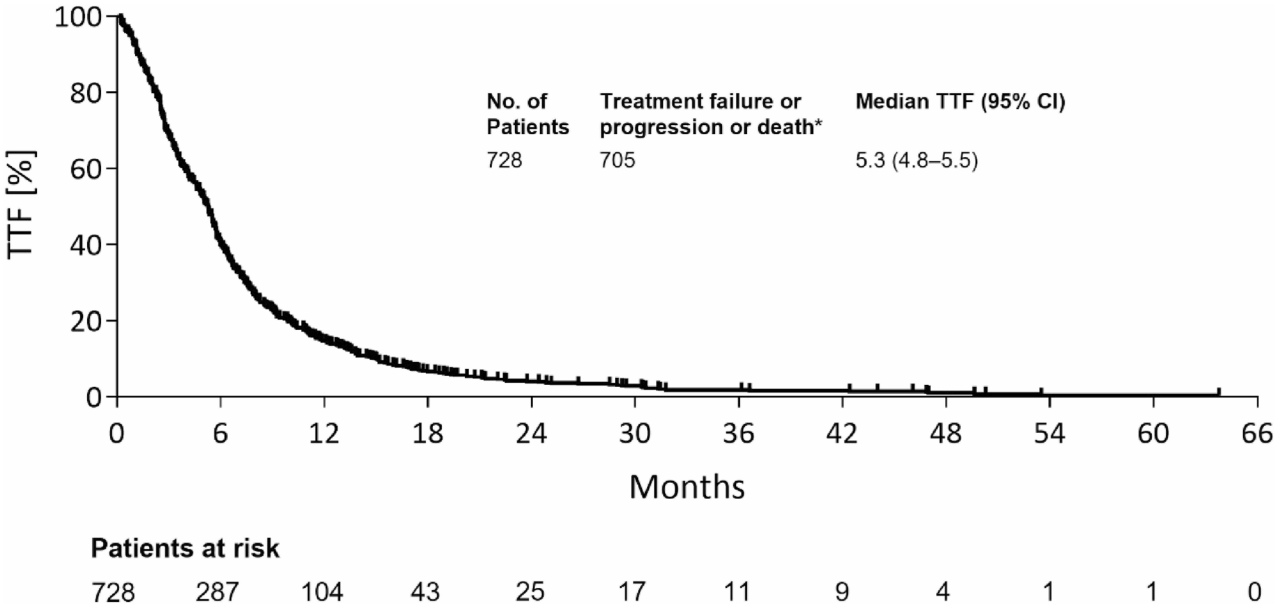

Fig. 3 Time-to-treatment failure after combination therapy with cetuximab. Kaplan-Meier curves depicting time-to-treatment failure (TFF) after combination therapy with cetuximab. The solid vertical lines represent censored data. A log-rank test was used to analyze differences in TTF. *For patients with obvious discontinuation of therapy but missing discontinuation date, treatment failure was imputed

patients with right-sided primary tumors, including ORR (64.4% vs. 46.6%; *p*-value 0.0003), PFS (12.1 months vs. 7.6 months; *p*-value 0.0001) and OS (26.8 months vs. 12.2 months; *p*-value < 0.0001). Resection of liver metastases appears to have a relevant positive impact on OS and PFS, regardless of primary tumor location (Fig. 5; Additional Table 6) or age. Better outcomes (ORR, PFS and OS) were also observed in patients who received prophylactic SA treatment in comparison to patients without prophylactic SA administration (Additional Table 6).

Safety

A total of 4,039 TEAEs (including skin reactions) were reported in 794 patients (93.9%) during the observational period (Additional Table 7). The most frequently documented TEAEs (> 10.0%) were rash (acne/acneiform, 46.8%, *N* = 396), diarrhea (32.9%, *N* = 278), other dermatologic/skin events (21.6%, *N* = 183), nausea (14.4%, *N* = 122), fatigue (13.4%, *N* = 113), and sensory neuropathy (13.2%, *N* = 112). Grade 3/4 TEAEs occurred in 473 (55.9%) of patients; incidence of grade 3/4 toxicities was similar among young and elderly patients and comparable to the total population (Additional Table 8). Grade 4 TEAEs with a frequency of > 0.5% included thrombosis/thrombus/embolism (1.2%, *N* = 10) and hypocalcemia (0.6%, *N* = 5). TEAEs associated with death (grade 5) were documented in ten patients (1.2%) and included other constitutional symptoms (0.5%, *N* = 4), thrombosis/thrombus/embolism (0.2%, *N* = 2), or other infection, ileus/neuro-constipation, other metabolic/laboratory events, and other pulmonary/respiratory events (each 0.1%, *N* = 1) (Additional Table 7). In total, 522 serious TEAEs in 273 patients (32.3%) were documented. Diarrhea (4.73%, *N* = 40), ileus (2.4%, *N* = 20), and general physical health deterioration (2.0%, *N* = 17) were the most frequently reported serious TEAEs (Additional Table 9).

Discussion

The ERBITAG study was designed to evaluate the efficacy and safety of cetuximab in a representative *RAS* WT mCRC patient population in routine clinical practice. Our study showed that combination therapy with cetuximab demonstrated response rates similar to the results of e.g., the pivotal randomized controlled OPUS and CRYSTAL trials [27]. In addition, the confirmed ORR of 58.0% and the median PFS of 10.92 months achieved in this study in the *RAS* WT population compared favorably with the ORR of 66% or 61% and the median PFS of 10 months or 9.2 months reported in the FIRE-3 and TAILOR trials, respectively, combining FOLFIRI (FIRE-3) or FOLFOX-4 (TAILOR) with cetuximab [28, 29]. The observed median OS of 23.62 months fits in the range of randomized clinical trials (31 months in FIRE-3, 20.7 months in TAILOR). Cetuximab in combination with FOLFOX or FOLFIRI significantly improves OS, PFS, ORR in patients with RAS WT mCRC [29, 30]. Therefore, it is considered an effective standard-of-care first-line treatment regimen for *RAS* WT mCRC patients. The median cetuximab treatment duration of 22 weeks in ERBITAG is similar to other first-line cetuximab clinical treatment trials [27, 30–33].

Table 5 Resection of metastases and resection rate in patients with liver or lung metastases

	RAS WT (*N* = 728)
Resection of metastases	
Number of patients with documented resection(s), N (%)	104 (100.0)
1 resection	95 (91.4)
2 resections	7 (6.7)
> 2 resections	2 (1.9)
Total number of documented resections, N (%)	116 (100.0)
Locations of documented resections*, N (%)	
Liver	90 (77.6)
Lung	13 (11.2)
Results of documented resections, N (%)	
Liver: R_0	55 (61.1)
R_1 or R_2	13 (14.4)
R_X	22 (24.4)
Lung: R_0	9 (69.2)
R_X	4 (30.8)
Complications during surgery, N (%)	3 (2.6)
Complications after surgery, N (%)	13 (11.2)
Resection rate	
Patients with liver and/or lung metastases	
No. of patients	604
No. of patients with resection*[1]	84
Percent (95% CI)	13.9 (11.25–16.93)
Patients with R_0 resection	
No. of patients	84
No. of patients with resection*[1]	56
Percent (95% CI)	66.7 (55.54–76.58)
Patients with liver metastases only	
No. of patients	318
No. of patients with resection*[1]	60
Percent (95% CI)	18.9 (14.72–23.61)

*In the eCRF only lung and liver could be documented (some patients received surgery for other sites)

*[1]Patients with progression prior to resection are counted as unresected (8 patients)

The liver is the most common site of metastatic disease in CRC, with at least 25–50% of patients developing liver metastases during the course of their disease, and more than half of patients resected for liver metastases will develop a recurrence [34]. In ERBITAG, approximately half of the *RAS* WT patients (43.7%) had metastases confined to the liver and 18.9% of these patients underwent secondary resection after systemic therapy. These data are consistent with those seen in other randomized clinical trials, such as FIRE-3 or PARADIGM [28, 35]. Notably, *RAS* WT patients with resected liver and/or lung metastases, which were predominantly R_0-resected (61.1% of liver metastases, 69.2% of lung metastases) similar to the *K-RAS* WT cohort, had an obviously better ORR than those without resection (86.9% vs. 56.73%). These data suggest that ORR correlates with secondary resectability and long-term survival, supporting data from randomized clinical trials.

There is increasing evidence that mCRC is a genetically heterogeneous disease and that the location of the primary tumor in mCRC is a strong predictor of disease progression, and treatment response, which may be reflected by differences in the embryonic origin of the tumor [36]. Right-sided tumors, which are more likely to harbor *RAS* and *BRAF* mutations, have poor prognosis and limited treatment benefit from targeted therapy [19, 23]. Anti-EGFR therapy is more effective in left-sided tumors, while right-sided tumors often show resistance or diminished responses [37]. In a meta-analysis comparing cetuximab, bevacizumab and panitumumab, cetuximab was shown to be the most effective treatment regimen in left-sided *RAS* WT mCRC with better PFS and OS compared to bevacizumab, as this has also been shown in pivotal trials, such as FIRE-3 or CALGB/SWOG 80,403 [2, 28, 38]. In the FIRE-3 trial, in which 79% of patients had left-sided tumors (64% in ERBITAG), FOLFIRI plus cetuximab significantly prolonged OS in *RAS* WT patients with left-sided tumors compared to FOLFIRI plus bevacizumab (38.2 months vs. 28.2 months). In contrast, FOLFIRI plus cetuximab showed limited benefit in patients with right-sided tumors [28]. In the CALGB/SWOG 80,403 trial, cetuximab improved OS and PFS compared to bevacizumab in patients with *RAS* WT. Although bevacizumab (in combination with chemotherapy) is the preferred regimen for right-sided *RAS* WT tumors, anti-EGFR therapy regimen showed an effective tumor shrinkage benefit in patients with right-sided tumors [39]. In the phase III clinical trial PARADIGM, adding panitumumab compared to bevacizumab to standard first-line chemotherapy conferred an OS benefit only in *RAS* WT mCRC patients with left-sided tumors [35]. In a prespecified exploratory biomarker analysis of the PARADIGM clinical trial, an OS benefit was also shown with panitumumab plus modified FOLFOX6 in comparison to bevacizumab plus modified FOLFOX6 in patients with circulating tumor DNA (ctDNA) with no gene alterations in a broad panel usually associated with resistance to EGFR inhibition, referred to as negative hyperselected. However, OS was similar or inferior with panitumumab in patients with ctDNA that contained any gene alteration in the panel, regardless of tumor sidedness (left vs. right). These data suggest that the observed differences in efficacy are likely related to greater molecular alterations contributing to resistances

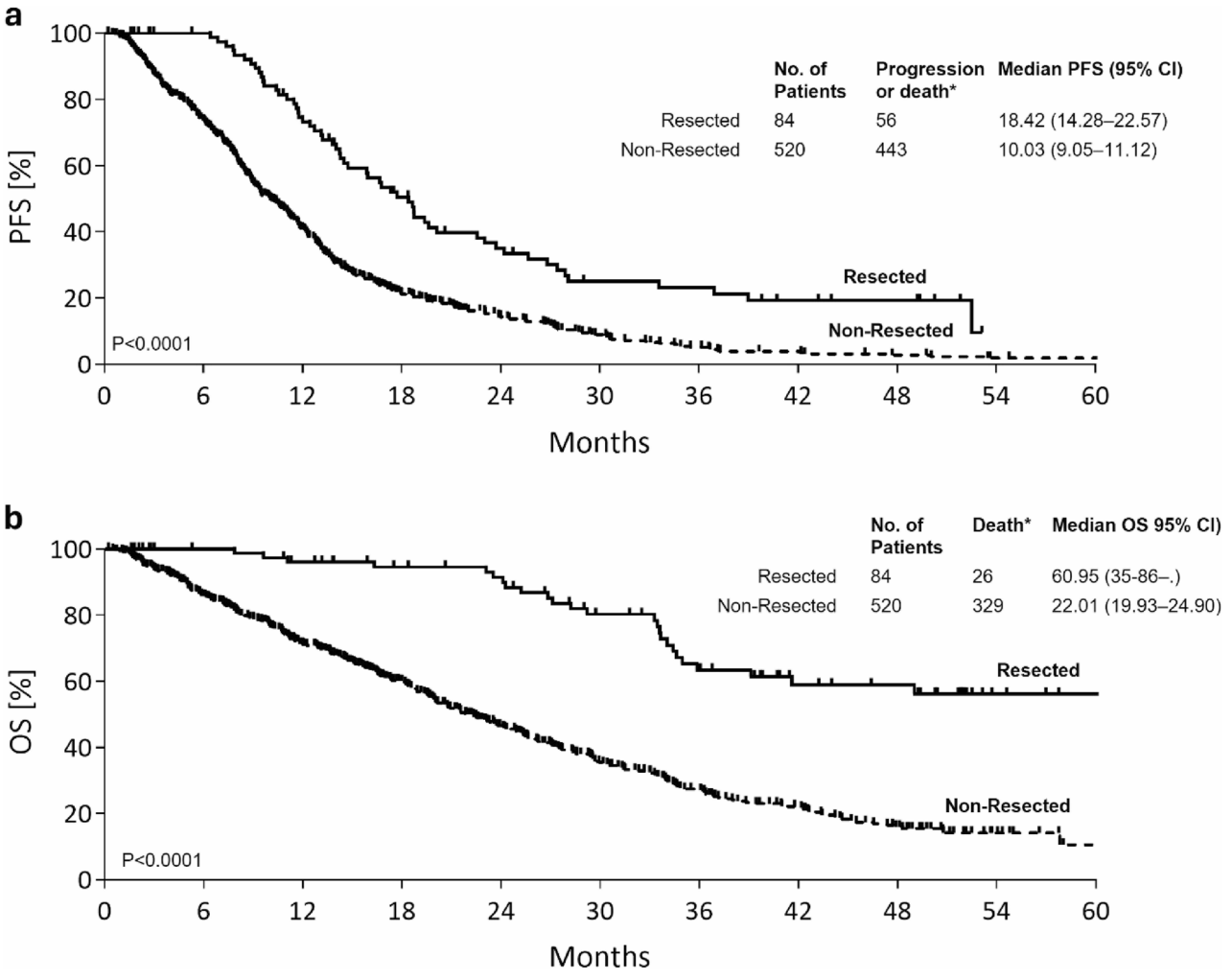

Fig. 4 Progression-free and overall survival in resected patients with liver or lung metastases. Kaplan-Meier curves depicting progression-free survival (PFS, a) and overall survival (OS, b) after combination therapy with cetuximab in resected patients with liver or lung metastases. The solid vertical lines represent censored data. A log-rank test was used to analyze differences in PFS and OS. *For patients with a documented death but a missing death date, death was imputed

(beyond *RAS* mutations) in right-sided tumors [40]. Conversely, chemotherapy plus bevacizumab may provide a greater clinical benefit than anti-EGFR therapy in *RAS* WT mCRC patients with right-sided tumors [41]. In addition, chemotherapy plus cetuximab is recommended for right-sided tumors in cases where a higher response to conversion therapy is required, according to the latest ESMO guidelines. The ESMO guidelines also show that chemotherapy plus cetuximab is an effective treatment option for patients with right-sided tumors where early tumor shrinkage is the goal [25]. To date, there are no clear recommendations on the relevance of tumor sidedness in heavily pretreated mCRC, i.e., second line and beyond treatment [22].

Dermatological toxicities are common adverse events associated with cetuximab due to the role of EGFR signaling in normal epidermal development and physiology, and its high expression in basal keratinocytes and hair follicles While the rapid onset of moderate-to-severe skin rash may serve as a surrogate marker for tumor response [42], skin reactions may also negatively impact treatment duration and may cause patients to discontinue therapy if skin toxicities become severe. Although TEAEs, including skin reactions, were reported in 93.9% of the safety population in ERBITAG, acne-like rash (46.8%) was less common compared to the pooled analysis by Hofheinz et al. The benefit in reducing the severity of skin reactions may be due to skin prophylaxis, which was received by 61.4% of patients in ERBITAG. However, a positive correlation between prophylactic administration of antibiotics and a reduction in skin irritation was not observed, contrary to previous analyses [43]. Nevertheless, prophylactic antibiotics do not seem to interfere with cetuximab treatment.

Managing skin reactions in clinical practice includes antibiotics or glucocorticosteroids. As CRC is a disease

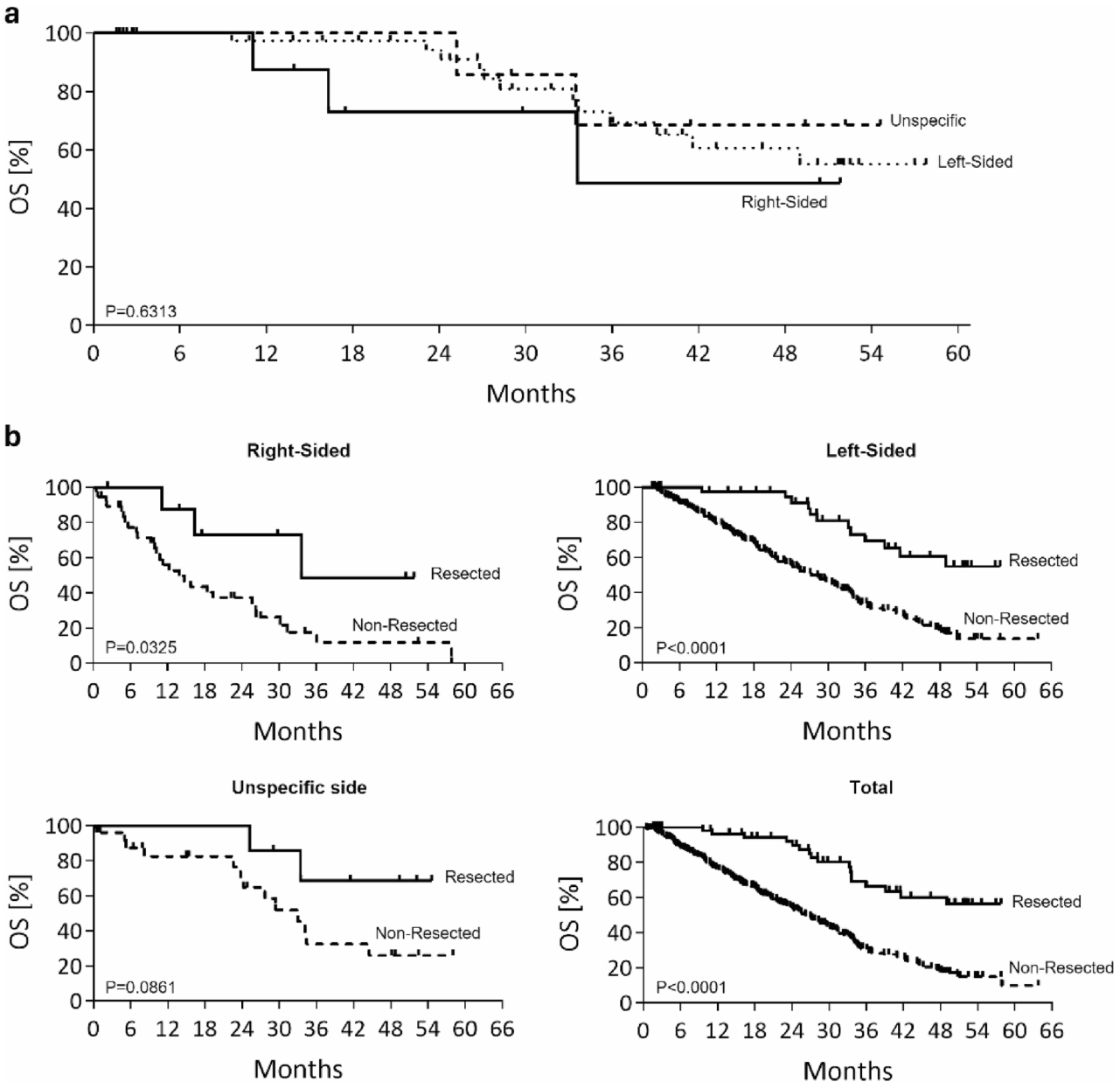

Fig. 5 Overall survival after combination therapy with cetuximab in patients with liver metastases only. Kaplan Meier curves depicting overall survival (OS) after combination therapy with cetuximab in patients with liver metastases only, **a** stratified by localization of primary tumor, **b** in relation to the location of the primary tumor and stratified by resected vs. non-resected. The solid vertical lines represent censored data. A log-rank test was used to analyze differences in OS

associated with alterations in the bacterial composition of the gut microbiota, the use of antibiotics can lead to changes in the diversity and composition of the commensal gut microbiota, which may negatively impact the therapeutic response beyond tumor genomics [44, 45]. However, it is not well understood whether disrupting the gut microbiota is causal for adverse effects and poor clinical outcomes. In ERBITAG, patients receiving systemic antibiotics showed better outcomes. Consistent with this finding, administration of certain antibiotics to patients with acneiform rash has been shown to be associated with a better response to treatment with cetuximab. Since anti-EGFR-induced dermatologic toxicities can occur as early as two days after the first treatment, preventive approaches, including antibiotics and vitamin K1 cream, should be used to reduce the severity of rash [46, 47]. However, the results for the prophylaxis of skin reactions must be interpreted with caution, as treatments could be used therapeutically. This is particularly true for the efficacy endpoint of skin management

procedures, where fewer skin reactions were observed in patients without prophylactic treatment. Nevertheless, prophylactic management should be recommended for all patients treated with cetuximab to reduce the severity of skin reactions.

Older patients are hardly studied and are therefore often underrepresented in clinical trials. When elderly patients are included, the efficacy of anticancer therapy is often limited, with elderly patients showing less favorable outcomes when compared to younger patients, with age being considered a robust prognostic factor for survival [48]. As demonstrated in randomized clinical trials, poor clinical outcomes are multifactorial. In FIRE-3, the significantly shorter OS (25.9 months in patients ≥ 65 years vs. 29.3 months in patients < 65 years) was correlated with an overrepresentation of right-sided tumors and a lower secondary resection rate in older patients [49]. Overall, right-sided tumors are associated with significantly shorter OS in both older and younger patient cohorts, and the incidence of resection rates strongly correlates with OS [50]. The shorter median OS in the ObservEr clinical trial in older patients (≥ 70 years) of 19 months vs. 27 months in younger patients was likely due to a lower proportion of metastatic resections and less frequent second-line therapy in the older population. Cetuximab caused a similar incidence of adverse events in younger patients (< 60 years), suggesting that fit older mCRC patients can benefit from a cetuximab-based regimen [51]. In general, older patients (≥ 70 years) are more likely to have prognostically more unfavorable characteristics, such as ECOG performance status ≥ 1 and higher rates of comorbidities and frailty [52]. The molecular biology underlying CRC, such as tumor mutational burden or epigenetic modifications, may also explain the differences [53]. The subgroup analysis in ERBITAG showed similar results. Elderly patients, especially those aged 75 years and older, showed reduced ORR, and OS compared to younger (≤ 65 years) *RAS* WT patients, but PFS was similar.

Intratumoral heterogeneity is a central feature of mCRC and resistance to anti-EGFR therapy remains a major obstacle in the treatment of mCRC. Intrinsic tumor heterogeneity and genomic instability promote emergence of pre-existing or newly emerged resistant subpopulations, leading to a progressive decline in response and disease progression. In patients initially responsive to anti-eGFR therapy, continuous EGFR inhibition can foster resistant subclones, leading to a progressive decline in response and disease progression. The OPTIPRIME trial recently demonstrated that, in patients with RAS/BRAF wild-type mCRC, a "stop-and-go" approach to EGFR-targeted therapy aids in recovery from cumulative toxicity while preserving future responsiveness to anti-EGFR agents [54]. Consistent, the subgroup analysis of the *RAS* WT cohort showed a longer OS in patients with therapy breaks (29.2 months with vs. 22.0 months without therapy breaks). Circulating tumor DNA (ctDNA) has emerged as a valuable, non-invasive tool for capturing tumor heterogeneity by sampling DNA from multiple sites, for detecting acquired resistance mutations emerging under anti-EGFR therapy in real time, and for guiding anti-EGFR rechallenge [55]. The recently published, prospective Fire-4 study evaluated this re-challenge with chemotherapy plus cetuximab compared to physician's choice. Although the study did not show a significant difference in OS between both treatment groups, the longest OS in 3rd line treatment at this point was shown for the rechallenge group (17.6 months) [56]. Selecting patients most likely to benefit from EGFR blockade, while directing others to alternative targeted options, and aiming for improved outcomes while minimizing unnecessary toxicity is the fundamental goal in the management of mCRC nowadays.

The strengths of the ERBITAG cohort reside first in the large number of participating centers, which included all eligible patients consulting during the study period. This allowed the recruitment of a large number of patients and an accurate assessment of the effects of *RAS* WT and the performance of a subgroup analysis. The real-world context of the ERBITAG study allows to investigate the occurrence of RAS WT in mCRC patients treated with cetuximab under various aspects of routine clinical practice in contrast to randomized clinical trials in which a small, highly selected patient population is included. As this was a real-world study, all visits took place in routine clinical practice without specific visit and examination schedules, and the data are unlikely to be as complete as in interventional clinical studies. A limitation of the ERBITAG study is the lack of identifying patients who received antibiotics as primary prophylaxis starting from the first cetuximab infusion. Health care professionals only stated whether a (skin) prophylaxis was used without giving a reason. Therefore, it cannot be ruled out that the administration was pro-reactively given only or potentially for secondary prophylaxis. Taken together, the results of the ERBITAG study appear to confirm the observations on the efficacy of chemotherapy combined with cetuximab regimens, in general, in terms of response rates, progression free and overall survival previously observed in randomized controlled trials. The safety analysis in this study revealed no new findings in the safety profile of cetuximab.

Conclusions

The results of ERBITAG confirm the efficacy of chemotherapy in combination with cetuximab regimens in general in terms of ORR, PFS, and OS in the real-world patient population, as previously observed in randomized

controlled trials. The safety analysis did not provide any new information on the safety profile of cetuximab. No negative impact was observed for prophylactic systemic antibiotics with cetuximab, efficacy parameters were even increased (OS, ORR, PFS). Secondary resection of liver metastases seems to have a relevant positive impact on OS and PFS regardless of primary tumor location or age. Nevertheless, since ORR and OS are negatively correlated with increasing age, elderly patients need to be closely monitored and properly selected regarding comorbidities.

Abbreviations

FOLFIRI	5-Fluorouracil (5-FU) / leucovorin (LV)/irinotecan
FOLFOX	5-Fluorouracil (5-FU)/leucovorin (LV)/oxaliplatin
FOLFOXIRI	5-Fluorouracil (5-FU)/leucovorin (LV)/oxaliplatin/irinotecan
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CCI	Charlson Comorbidity Index
CRC	Colorectal cancer
CI	Confidence interval
CR	Complete response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2
FAS	Full analysis set
HER2	Human epidermal growth factor receptor 2
K-RAS	Kirsten Rat Sarkoma Oncogene
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
mCRC	Metastatic colorectal cancer
N-RAS	Neuroblastoma Rat Sarkoma Oncogene
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SAF	Safety analysis set
TEAE	Treatment-emergent event
TKI	Tyrosine kinase inhibitors
TTF	Time-to-treatment failure
VEGFR	Vascular endothelial growth factor
WHO	World Health Organization
WT	Wild type

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-026-15753-5.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

Supplementary Material 9.

Acknowledgements

We thank the participating patients and families. Medical writing was supported by Dr. Katharina Bakhaus and Dr. Mareike Pötsch (Alcedis GmbH, Gießen, Germany) and funded by Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA.

Authors' contributions

SWS, UPN, MOZ, MS, CM, TG, OR, CHS, JJ and FO contributed to the generation, collection, and assembly of the data. All authors were involved in the analysis and interpretation of the data, drafting of the manuscript, and revising it critically for intellectual content. All authors approved of the final version of this manuscript and agreed to be accountable for all aspects of the work.

Funding

This study was financially supported by Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945).

Data availability

The datasets supporting the conclusions of this article are included within the article and its additional files.

Declarations

Ethics approval and consent to participate

The methods were carried out following the relevant guidelines and regulations. The ERBITAG study was conducted in accordance with the Declaration of Helsinki. Approval was granted by the ethics committee of the coordinating investigator (ethics committee of the Medical Association of Westphalia-Lippe and the Medical Faculty of the Westphalia Wilhelms University Münster). All study-relevant data were documented in a pseudonymous manner. Patients provided written informed consent prior to inclusion in the study.

Consent for publication

Not applicable.

Competing interests

SWS holds shares and stock options from Merck and received honoraria from MSD and research grant/funding from Merck. UPN received honoraria from Merck, Astellas, Dr. Falk Pharma international, Astra Zeneca, Roche AG, Amgen, and Bristol Myers Squibb. MOZ holds shares and stock options from Gilead and Bayer and received honoraria from Bristol Myers Squibb, Astra Zeneca, NCO, Novartis, and IOMEDICO. CHS received honoraria from Novartis, and Sanofi and act as a consultant for Amgen, JJ receives sponsorship for advisory boards and study participation from the following companies: BMS, Novartis, Astra Zeneca, Roche, Pfizer, Johnson and Johnson and Ipsen. KS is a fulltime employee at Merck Germany Healthcare GmbH. JR is a fulltime employee at Merck Germany Healthcare GmbH. All other authors have no conflicts of interest.

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Received: 6 August 2024 / Accepted: 12 February 2026
Published online: 25 February 2026

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