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FOLFIRI with cetuximab or bevacizumab in RAS wild-type metastatic colorectal cancer: Refining first-line treatment selection by combining clinical parameters☆,☆☆

A post hoc analysis of the randomized open-label phase III trial FIRE-3/AIO KRK0306

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ABSTRACT

Background: Primary tumor sidedness (PTS) with discrimination of left-sided (LC) and right-sided tumors (RC) guides patient selection for targeted first-line therapy in *RAS* wild-type (*RAS*-WT) metastatic colorectal cancer (mCRC). This study assessed the hypothesis whether considering PTS with additional clinical parameters better predicts the treatment benefit of targeted first-line treatment.

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Biomarker combination
Comprehensive statistical modeling
FOLFIRI
Cetuximab
Bevacizumab

Methods: In FIRE-3, first-line treatment with folinic acid, fluorouracil and irinotecan (FOLFIRI) plus cetuximab (FOLFIRI/Cet) was compared to FOLFIRI plus bevacizumab (FOLFIRI/Bev) in patients with *RAS*-WT mCRC and unresectable metastasis. We evaluated whether combining PTS with number of metastatic sites (NOM), liver-limited disease status (LLD), age, sex, or carcinoembryonic antigen level (CEA) better predicts treatment benefit regarding overall survival (OS). Here, Cox regression models with second-order interactions were applied. Further, the results were validated by policy learning and Lasso regression analysis.
Findings: Among 400 *RAS*-WT mCRC patients, combining PTS with LLD status in a Cox regression model outperformed PTS alone for predicted treatment benefit (P = 0·005; c-index=0·603). Significant OS benefit from FOLFIRI/Cet over FOLFIRI/Bev was observed in LC/non-LLD patients (HR=0·62; 95 %-confidence interval [CI]= 0·46–0·82; P = 0·002), but mitigated in LC/LLD patients (HR=0·83; 95 %-CI=0·53–1·29; P = 0·400). In RC/non-LLD patients, FOLFIRI/Bev demonstrated a significant OS advantage over FOLFIRI/Cet (HR=2·09; 95 %-CI=1·20–3·63; P = 0·010). However, RC/LLD patients showed potential benefit from FOLFIRI/Cet, though not statistically significant (HR=0·59; 95 %-CI=0·25–1·39; P = 0·218).
Interpretation: Incorporating PTS and LLD status might improve selection of targeted first-line treatment in *RAS*-WT mCRC patients. FOLFIRI/Cet appears to be particularly beneficial for LC/non-LLD patients with mitigated benefit in patients with LC/LLD. In contrast, FOLFIRI/Bev is significantly favoured over FOLFIRI/Cet in patients with RC/non-LLD. Notably, RC/LLD patients may still benefit from anti-EGFR therapy despite right-sided primary tumor. These results are hypothesis-generating and warrant further validation.

1. Introduction

Colorectal cancer (CRC) ranks as the fourth leading cause of cancer-related mortality globally, with nearly half of all CRC patients developing distant metastasis (mCRC) [1]. The introduction of chemotherapy combined with monoclonal antibodies bevacizumab targeting vascular endothelial growth factor (VEGF) and cetuximab or panitumumab targeting epithelial growth factor receptor (EGFR) has significantly improved outcomes, extending median overall survival (OS) to 30–40 months in selected mCRC patient cohorts [2,3].

Patient stratification for first-line systemic treatment hinges on primary tumor sidedness (PTS) and the mutation status of *KRAS*, *NRAS* and *BRAF* genes as well as mismatch-repair–deficient or microsatellite-instability–high (dMMR/MSI-h) status, all of which are established predictive biomarkers for clinical decision making [4]. Upfront checkpoint inhibition is approved for patients with dMMR/MSI-h tumors [5, 6]. While first-line anti-EGFR agents plus standard chemotherapy offers survival benefit primarily in left-sided tumors (LC) with wild-type *KRAS*, *NRAS*, and *BRAF*, not all LC patients equally benefit, with over 20 % showing no objective tumor response [7]. The exploration of a broader panel of gene alterations using circulating tumor DNA (ctDNA) or gene expression analysis holds promises to enhance optimal treatment selection, however, challenges in costs and availability persist [8].

Given the pivotal role of PTS in patient stratification and the need for practical and accessible predictive tools, we hypothesized that integrating PTS with additional clinical parameters may offer a feasible approach to optimize first-line treatment selection.

For our analysis, we chose clinical parameters based on potentially predictive relevance. Specifically, recent reports highlighted the relevance of the metastatic patterns in the management of mCRC. For instance, presence of liver metastasis has been identified as a negative predictive factor for immunotherapy in non-dMMR mCRC [9]. Further, different metastatic patterns, e.g. peritoneal carcinomatosis and lung metastasis, influence the ability to measure circulating tumor DNA (ctDNA) [10]. Finally, the presence of liver-limited disease (LLD) was subject to the randomized phase III trial CAIRO5 which evaluated the best systemic conversion regimen for secondary resection of initially unresectable liver metastases, questioning the relevance for anti-EGFR treatment in patients with LC and LLD [11,12]. Hence, in our current analyses, we evaluated the LLD status and number of metastatic sites (NOM) alongside potentially predictive baseline demographics age, sex as well as carcinoembryonic antigen serum level (CEA) based on previous results of the FIRE study group [13–17].

The current study utilized data of the open-label randomized phase III trial FIRE-3 (AIO KRK0306), which assigned *RAS*-WT patients with irresectable mCRC to receive fluorouracil, folinic acid and irinotecan (FOLFIRI) plus either cetuximab (FOLFIRI/Cet) or bevacizumab (FOLFIRI/Bev) [2, 18, 19]. At comparable progression-free survival (PFS) between both treatment arms, FOLFIRI/Cet compared to FOLFIRI/Bev resulted in a significantly higher objective response rate (ORR) in the per protocol population as primary endpoint and longer overall survival (OS) further reflecting the relevance of PTS [2].

2. Methods

2.1. Trial design and patient population

FIRE-3/AIO KRK0306 was a prospective, multicenter, open-label phase III study (NCT00433927) recruiting patients both in Germany and Austria between Jan 23, 2007, and Sept 19, 2012. The study design, conduct of the trial, the full study population, treatment schedules, concordance with the Declaration of Helsinki and approval of ethics committees were reported previously [2]. Written informed consent was obtained from all patients before any study-related procedures took place. Sex was documented by the treating physician according to registration in the patient chart; options were male or female.

Briefly, FIRE-3 compared FOLFIRI combined with either cetuximab or bevacizumab as first-line treatment in patients with unresectable mCRC and *KRAS*-WT tumors. In light of the adoption of *RAS* analyses as an improved biomarker of response to cetuximab therapy and its evaluation in FIRE-3, we focused our current analyses on the the *RAS*-WT population, as previously described [19]. With comparable PFS between treatment arms despite OS advantage for FOLFIRI/Cet over FOLFIRI/Bev in the intention-to-treat as well as per-protocol population of FIRE-3 [2,19], we selected OS as the primary endpoint for this subgroup analysis focusing on patient survival.

2.2. Statistical analysis

For stratifying patients, a range of baseline clinical parameters and their combinations were investigated in terms of OS comparing FOLFIRI/Cet and FOLFIRI/Bev to test for potential treatment benefits.

Specifically, the investigated binary parameters included age (>65 years), liver-limited disease status (LLD), number of metastatic sites (<1; NOM), primary tumor sidedness (left- or right-sided according to splenic flexure; PTS), sex (male or female) and carcinoembryonic antigen level (>10 ng/ml; CEA). Missing CEA values were imputed using the mice R package to ensure completeness of the dataset.

Initially, we employed Cox regression modeling to assess clinical parameters individually, examining their first-order interactions with the treatment arm. For this analysis, we compared the baseline model, which included a single clinical parameter and the treatment arm as

main effects, with the more complex model adding a first-order interaction term between the clinical parameter and the treatment arm. The significance of each clinical parameter's contribution was evaluated using a Chi-squared test to compare both models. P-Values obtained from testing all clinical parameters were corrected for multiple hypothesis testing using the Holm-Bonferroni method.

To investigate second-order interactions, patients were stratified based on pairs of clinical parameters. The baseline Cox regression model included the clinical parameter pair, their interaction terms, and the first-order interactions with the treatment arm. The more complex model was constructed by incorporating a second-order interaction term between the two clinical parameters and the treatment arm. Significance of models was evaluated using a Chi-squared test, and P-Values resulting from all tested parameter pairs were adjusted for multiple hypothesis testing with the Holm-Bonferroni method.

The Cox regression model with the highest test statistic and lowest P-value was visualized by using Kaplan-Meier and forest plots for survival endpoints.

To validate these results and account for the reduced statistical power due to the limited number of patients in certain subgroups (particularly RC), an alternative approach was applied to identify the optimal treatment strategy using policy learning. Here, a causal survival forest was fitted for OS using the 'causal_forest' function with default parameters from the *grf* R package [20]. Next, the 'policy_tree' function from the *policytree* R package [21] with a depth of 2 was employed to construct a decision tree.

Finally, a third approach was used for internal validation using Lasso regression. Here, we applied the 'glmnet' function from the *glmnet* R package to fit Lasso regression models for OS, incorporating all clinical parameters and the treatment arm, including all associated first- and second-order interaction terms. These models were trained using 10-fold cross-validation repeated 10 times, and the concordance index (c-index) was recorded for each test set as a measure of predictive performance. The reported c-index and model coefficients for each term were calculated as the mean between all fitted models.

2.3. Role of funding sources

The FIRE-3 study was supported by grants from Pfizer GmbH, Germany, and Merck KGaA, Darmstadt, Germany. Alexander Ohnmacht and Michael P. Menden were supported by the European Union's Horizon 2020 Research and Innovation Programme (Grant agreement No. 950293 - COMBAT-RES). The funding sources had no role in the design and conduct of the study, and in the collection, management, analysis, and interpretation of the data as well as decision to submit the paper.

3. Results

3.1. Patients and treatment

The baseline characteristics, disposition of *RAS*-WT, per-protocol population and treatment details within the FIRE-3 trial have been reported previously [2].

3.2. Identification of predictive biomarkers and biomarker combinations

We systematically evaluated the predictive value of each proposed clinical parameter for treatment benefit within the FIRE-3 trial. First, we assessed the statistical interactions between treatment arms and individual or combined clinical parameters (Table 1). Treatment efficacy was assessed by comparing OS between the two treatment arms (FOLFIRI/Cet and FOLFIRI/Bev), as indicated by hazard ratio (HR) and corresponding 95 % confidence interval (CI). Among the single biomarkers, only PTS demonstrated a significant interaction with the treatment arm (P = 0·016).

The assessment of parameter combinations demonstrated notable differences in their predictive value for treatment benefit. The PTS and LLD model (P = 0.005) exhibited the strongest statistical interaction and highest concordance index (c-index = 0.603; Table 1). While the model incorporating NOM and sex (P = 0.015) showed a stronger association than the combination of LLD and sex (P = 0.039), only the PTS and LLD model remained significant after applying multiple hypothesis correction with a 10 % family-wise error rate. In summary, the PTS and LLD combination emerged as the most robust predictor of treatment benefit.

To validate the predictive superiority of the biomarker combination of LLD and PTS over PTS alone, policy learning causal survival forests was applied to evaluate all clinical biomarkers. The resulting decision tree suggests considering PTS and LLD in a hierarchical order (Fig. 1). Additionally, to further validate our findings, Lasso regression was performed. Here, incorporating interaction terms for OS achieved a high concordance index (c=0·593) and revealed the largest coefficients for second-order interactions between LLD, PTS and the treatment arm, further supporting an increased benefit of FOLFIRI/Bev in patients with RC/non-LLD (Figure S1).

Table 1
P-values for first-order interactions (grey cells) and second-order interactions (white cells) between displayed parameters and parameters combinations with treatment benefit regarding OS comparing FOLFIRI/Cet to FOLFIRI/Bev. Significance (printed in bold) is assumed at level P = 0·05 and 10 % false discovery rate (Table S1).

	CEA	Age	Sex	PTS	LLD	NOM
CEA	0·371	0·784	0·909	0·108	0·923	0·854
Age		0·196	0·47	0·204	0·660	0·708
Sex			0·444	0·207	0·039	0·015
PTS				**0·016**	**0·005**	0·134
LLD					0·857	1·000
NOM						0·391

Abbreviations: Bev, bevacizumab; CEA, carcinoembryonic antigen; Cet, cetuximab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; LLD, liver-limited disease; NOM, number of metastatic sites; OS, overall survival; PTS, primary tumor sidedness.

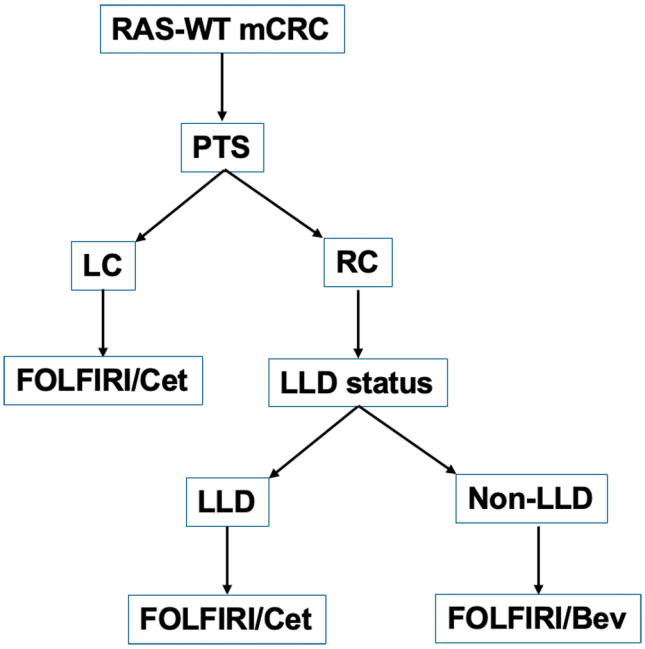

Fig. 1. Resulting decision tree from policy learning using the policytree method with causal survival forests. Abbreviations: Bev, bevacizumab; Cet, cetuximab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; LC, left-sided colorectal cancer; LLD, liver-limited disease; RC, right-sided colorectal cancer; WT, wildtype·.

3.3. Baseline characteristics and subgroup prevalence

The FIRE-3 trial included 400 patients with *RAS*-WT mCRC, with baseline data on LLD and PTS available for 398 patients. Three patients were excluded due to synchronous colorectal cancer (Figure S2), resulting in a full analysis set (FAS) of 395 *RAS*-WT patients. Baseline characteristics were well balanced across both treatment arms (Table S2). Further analysis using a Chi-squared test revealed significant differences in baseline characteristics between PTS and LLD subgroups, with associations observed for NOM ($P < 0{\cdot}001$), *BRAF* mutation status ($P < 0{\cdot}001$), timing of metastasis ($P < 0{\cdot}001$), resection of primary tumor ($P = 0{\cdot}029$) and adjuvant treatment ($P < 0{\cdot}001$). These differences highlight important factors that may influence treatment outcomes.

3.4. Predictive relevance of the selected biomarker combination

The analysis of treatment outcomes in *RAS*-WT mCRC patients revealed that the predictive value of FOLFIRI/Cet vs. FOLFIRI/Bev depends on biomarker status. A significant treatment benefit for FOLFIRI/Cet over FOLFIRI/Bev was observed in patients with LC and non-LLD (26·5 vs. 33·7 months, HR 0·62, 95 %-CI=0·46–0·82; $P = 0{\cdot}002$; Fig. 2; Fig. 3; Table 2). No significant benefit was found in patients with LC and LLD (36·5 vs. 41·5 months, HR=0·83; 95 %-CI=0·53–1·29; $P = 0{\cdot}400$). In RC and non-LLD patients, FOLFIRI/Cet was associated with worse OS compared to FOLFIRI/Bev (23·4 vs. 15·6 months; HR=2·09; 95 %-CI=1·20–3·63; $P = 0{\cdot}010$). Contrary, in patients with RC and LLD, OS tended to be longer for FOLFIRI/Cet over FOLFIRI/Bev (24·0 vs. 25·5 months, HR=0·59, 95 %-CI=0·25–1·39, $P = 0{\cdot}218$).

3.5. Sensitivity analyses

Sensitivity analyses were performed to evaluate the robustness of the identified statistical model. LLD status, compared to non-LLD, was predictive of secondary resection with curative intent (21·8 % vs. 6·7 %, $P < 0{\cdot}0001$). Excluding patients who underwent secondary resection yielded similar results, confirming the model's predictive relevance (Figure S3). Furthermore, an analysis excluding patients with activating BRAF V600E mutations, intended to address baseline imbalances (Table S2), showed consistent results with the FAS population (Figure S4). These analyses reinforce the stability and robustness of the model.

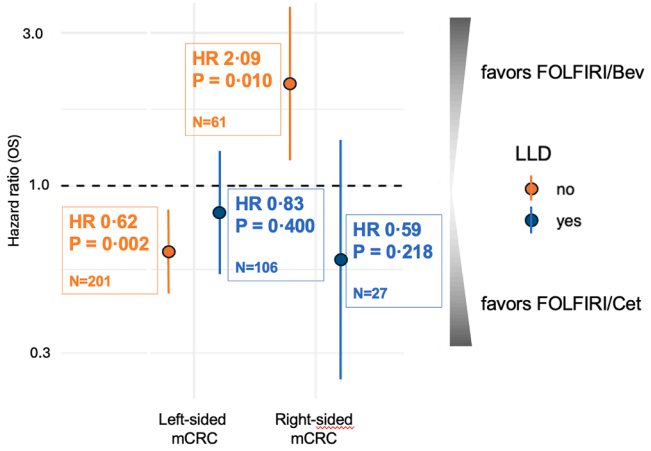

Fig. 3. Forest plot indicating the efficacy regarding OS according to treatment arm stratified by PTS and LLD status. Abbreviations: Bev, bevacizumab; Cet, cetuximab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; HR, hazard ratio; LLD, liver-limited disease; N, numbers; PTS, primary tumor sidedness·3.

3.6. Further clinical endpoints

Further clinical endpoints, including progression free survival (PFS) and objective response rate (ORR), we evaluated in subgroups stratified by LLD status and PTS. No statistically significant interaction between the subgroups according to PTS and LLD status was identified for PFS ($P = 0{\cdot}29$; Table S3, Figure S5) or ORR ($P = 0{\cdot}92$; Table S4). Similar to OS, patients with LC and non-LLD status showed a significant increased ORR when treated with FOLFIRI/Cet over FOLFIRI/Bev (77 % vs. 65 %; odds ratio [OR]=0·51; 95 %-CI=0·26–0·99; $P = 0{\cdot}045$). In contrast, this effect was diminished in patients with LC and LLC (82 % vs 77 %, OR=0·75; 95 %-CI=0·28–2·07; $P = 0{\cdot}567$).

4. Discussion

The present analysis assessed the hypothesis whether combining readily available clinical parameters beyond PTS improves the ability to predict benefit of targeted first-line chemotherapy in *RAS*-WT mCRC. This study was based on the open-label randomized phase III study FIRE-3 (AIO KRK0306), which previously demonstrated the superiority of FOLFIRI/Cet over FOLFIRI/Bev, particularly in patients with LC [2,19].

In a systematic approach, clinical parameters reflecting metastatic pattern (NOM, LLD) and additional potentially predictive baseline characteristics (age, sex, CEA) were selected based on prior findings

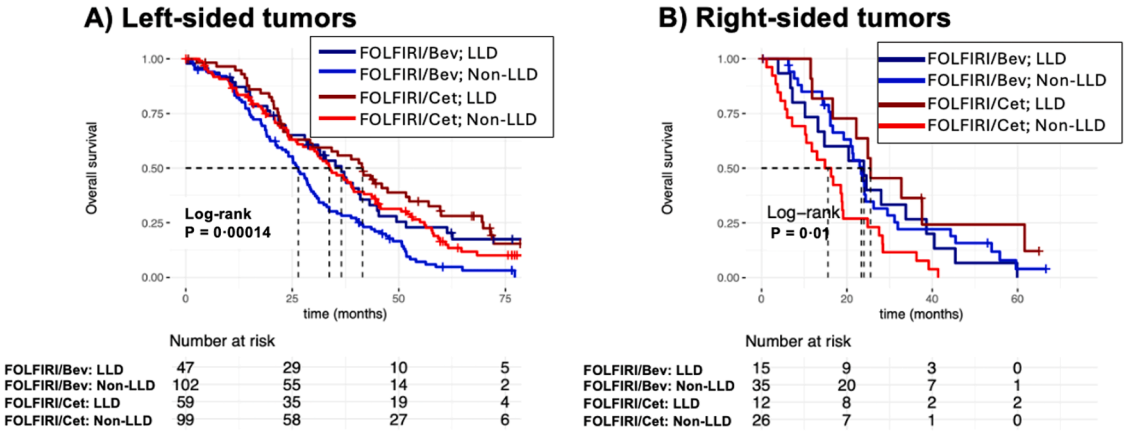

Fig. 2. (A) OS according to LLD status and treatment arm in patients with left-sided primary tumor· (B) OS according to LLD status and treatment arm in patients with right-sided primary tumor. Bev, bevacizumab; Cet, cetuximab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; OS, overall survival; LLD, liver-limited disease·.

Table 2
Impact of PTS and LLD status on treatment efficacy comparing FOLFIRI/Cet and FOLFIRI/Bev regarding OS. Significance (printed in bold) is assumed at level P = 0·05.

PTS	**LC**				**RC**			
LLD status	**LLD**		**non-LLD**		**LLD**		**non-LLD**	
Treatment arm	**FOLFIRI/Bev**	**FOLFIRI/Cet**	**FOLFIRI/Bev**	**FOLFIRI/Cet**	**FOLFIRI/Bev**	**FOLFIRI/Cet**	**FOLFIRI/Bev**	**FOLFIRI/Cet**
Number of patients (%)	47 (11·9)	59 (14·9)	102 (25·8)	99 (25·1)	15 (3·8)	12 (3·0)	35 (8·9)	26 (6·6)
Median OS, months [95 % CI]	36·5 [28·4–44·9]	41·5 [29·2–57·0]	26·5 [22·6–30·0]	33·7 [29·1–41·8]	24·0 [13·2–40·5]	25·5 [22·2-NA]	23·4 [19·3–29·5]	15·6 [10·2–24·9]
HR [95 % CI]	0·83 [0·53–1·29]		0·62 [0·46–0·82]		0·59 [0·25–1·39]		2·09 [1·20–3·63]	
logrank test (P-value)	0·400		**0·002**		0·218		**0·010**	
interaction test (P-value)	**0·005**							

Abbreviations: Bev, bevacizumab; Cet, cetuximab; 95 % CI, 95 % confidence interval; FOLFIRI, folinic acid, fluorouracil, and irinotecan; HR, hazard ratio; LC, left-sided colorectal cancer; LLD, liver-limited disease; N, numbers; OS, overall survival; RC, right-sided colorectal cancer; PTS, primary tumor sidedness·

from the FIRE study group [11, 13–17]. These parameters were evaluated individually and in pairs to assess their predict value for treatment efficacy (OS) in each treatment arm using Cox regression analyses. Further, to validate these results and account for reduced statistical power due to limited number of patients in certain subgroups (particularly RC), policy learning and Lasso regression were applied. Altogether, our results demonstrate that considering LLD status alongside PTS might improve patient selection compared to the current standard of PTS alone in patients with *RAS*-WT mCRC.

Consistent with previous findings and current guideline recommendations, our analysis demonstrate a survival benefit associated with anti-EGFR-based treatment with FOLFIRI/Cet in patients with LC. Importantly, this benefit was observed predominantly in patients with non-LLD status (HR=0·62, P = 0·02), whereas the advantage over FOLFIRI/Bev was mitigated in patients with LC/LLD (HR=0·83, P = 0·40). These results align closely with the most recent update of the CAIRO5 trial [12]. CAIRO5 was the first prospective clinical study to systematically evaluate PTS in conjunction with LLD in mCRC [11]. This randomized phase III trial investigated the optimal systemic conversion strategy for RC and LC in patients with initially unresectable LLD, while also accounting for *RAS* and *BRAF* mutation status. Direct comparison with FIRE-3 is challenging due to CAIRO5's clear definition and centralized assessment of unresectability. Additionally, CAIRO5 evaluated FOLFOXIRI plus bevacizumab in RC and FOLFOX or FOLFIRI plus bevacizumab or panitumumab in LC. Here, comparable OS and PFS, as well as local treatment rates in LC and LLD patients across treatment arms, align with our results in FIRE-3.

The phase II DEEPER trial (JACCRO CC-13) also evaluated anti-EGFR versus anti-VEGF based treatment in conjunction with FOLFOXIRI. Most recently, the authors reported on subgroup results also based on PTS and metastatic pattern [22]. Of note, the survival benefit of FOLFOXIRI plus Cetuximab observed in LC patients was confined to patients with non-LLD, further mirroring our results of FIRE-3, although chemotherapy backbone differs.

Together with CAIRO5 and DEEPER, our results support using first-line chemotherapy in conjunction with bevacizumab for initially unresectable LLD and LC challenging current guideline recommendations [11, 12, 23].

Of note, patients with initially resectable LLD were evaluated in the phase III New EPOC trial regarding a potential benefit from adding cetuximab to doublet chemotherapy [24]. Here, even a detrimental effect of adding cetuximab to chemotherapy was observed in patients with LLD. However, due to limited patient number with RC, no definitive conclusions regarding PTS can be drawn in New EPOC. Current guidelines recommend against the usage of anti-EGFR based treatment in patients with resectable LLD [4,23].

In patients with RC, guidelines suggest combining chemotherapy with bevacizumab in first-line setting [23]. In our data, we found a significant OS benefit from FOLFIRI/Bev over FOLFIRI/Cet in patients with RC and non-LLD (HR=2·09, P = 0·010). Interestingly, patients with LLD may benefit from FOLFIRI/Cet despite right-sided primary tumor (HR=0·59, P = 0·218). According to current guidelines, doublet chemotherapy plus anti-EGFR antibody in RC is an option if tumor shrinkage is the primary goal [23]. Our findings suggest this could be particularly relevant for patients with LLD, who are more likely to be candidates for secondary resection following a response to systemic treatment [14].

Given that LLD status is a predictive factor for secondary resection in initially unresectable mCRC [14], we assessed its relevance in our dataset. A sensitivity analysis excluding patients who underwent secondary resection of metastatic sites revealed that the combined evaluation of LLD and PTS retained its predictive accuracy for treatment benefits. This aligns with prior analysis of LLD in FIRE-3, indicating it defines a subgroup with distinct tumor biology akin to PTS [14]. Notably, this is reflected in the differential distribution of prognostic baseline characteristics, including a higher incidence of activating *BRAF* mutation and variations in the timing of metastasis (Table S1).

The relevance of this analysis is constrained by its retrospective design. Furthermore, the use of multiple parameters to predict treatment benefit reduces subgroup sample size diminishing statistical power. This limitation is especially pronounced in patients with RC and LLD, a subgroup comprised of 27 patients. Internal validation of our results by using different statistical approaches (Cox and Lasso regression besides policy learning method) support our findings. Still, they are hypothesis-generating and necessitate external validation through further trials that compare anti-EGFR with anti-VEGF strategies.

This study dissected the predictive relevance of readily available clinical parameters while also acknowledging the critical need to expand predictive molecular biomarkers in mCRC, such as genetic hyper-selection or consensus molecular subgroups (CMS) [8, 25–27]. The patient subgroup identified based on PTS and LLD may aid in refining molecular biomarkers in the context of clinically relevant subtypes, as previously discussed for the FIRE-3 trial [28,29]. Further investigation into the molecular characteristics of these subgroups remains essential and is currently ongoing.

In conclusion, this analysis underscores the value of integrating multiple biomarkers to refine first-line treatment selection in *RAS*-WT mCRC. Incorporating metastatic pattern with LLD and PTS might improve the predictive accuracy for anti-EGFR versus anti-VEGF strategies. Benefit from FOLFIRI/Cet over FOLFIRI/Bev is pronounced in patients with LC and non-LLD as compared to LC and LLD. Patients with RC and non-LLD exhibited a significant survival advantage for treatment with FOLFIRI/Bev. Notably, RC and LLD patients may still benefit from anti-EGFR therapy, but further validation is needed. These findings support a biomarker-driven approach to optimizing personalized treatment and improving patient outcomes. Future research integrating molecular and clinical parameters holds promise for further refining therapeutic strategies.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Julian W. Holch** served on advisory board for Merck, Roche and Servier, has received travel support from Novartis, Merck and Servier.

Sebastian Stintzing reports receiving fees for talks and advisory board roles from AMGEN, AstraZeneca, Bayer, BMS, CV6, Daiichi-Sanyko, ESAI, Isofol, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda

Kathrin Heinrich reports honoraria from Amgen, BMS, Merck, Roche, Taiho, Servier, streamedup!, consulting or advisory role for Amgen, Servier, MSD (Institutional), Merck, Janssen and travel support/Expenses: Amgen, Merck, Servier.

Lena Weiss received honoraria for scientific presentations and advisory board role from Roche and Servier and travel accommodation expenses from Amgen and Merck.

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Michael P. Menden is a former employee of AstraZeneca, academically collaborates with AstraZeneca, GSK and Roche, and receives funding from GSK and Roche.

Volker Heinemann reports receiving fees for talks and advisory board roles from Merck, Amgen, Roche, Sanofi, Servier, Pfizer, Pierre-Fabre, AstraZeneca, BMS, MSD, Novartis, Terumo, Oncosil, NORDIC, Seagen, GSK and for receiving research funding from Merck, Amgen, Roche, Sanofi, Boehringer-Ingelheim, SIRTEX, Servier.

All remaining authors declare no conflict of interest.

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Data sharing statement

Information that will be considered for disclosure includes individual participant data that underlie the results reported in this article (text, tables, figures, and appendices). Additionally, study Protocol and statistical analysis plan can be made available. All data shared must be anonymized to protect the privacy of the patients who participated in the trial, in accordance with applicable laws and regulations and in compliance with the International Council for Harmonisation and Good Clinical Practice (ICH/GCP). Researchers should provide a scientifically sound proposal directed to the corresponding author for approval to gain access to the requested data. Shared data are only to be used to achieve aims of the approved proposal.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115388.

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