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Citation for final published version:

Cohen, Romain, Raeisi, Morteza, Chibaudel, Benoist, Shi, Qian, Yoshino, Takayuki, Zalcberg, John R., Adams, Richard, Cremolini, Chiara, Van Cutsem, Eric, Heinemann, Volker, Tabernero, Josep, Punt, Cornelis J.A., Arnold, Dirk, Hurwitz, Herbert I., Douillard, Jean-Yves, Venook, Alan P., Saltz, Leonard B., Maughan, Timothy S., Kabbinar, Fairouz, Bokemeyer, Carsten, Grothey, Axel, Mayer, Robert J., Kaplan, Richard, Tebbutt, Niall C, Randolph Hecht, J., Giantonio, Bruce J., Díaz-Rubio, Eduardo, Sobrero, Alberto F, Peeters, Marc, Koopman, Miriam, Goldberg, Richard M., Andre, Thierry and de Gramont, Aimery 2024. Prognostic value of liver metastases in colorectal cancer treated by systemic therapy: An ARCAD pooled analysis. *European Journal of Cancer* 207, 114160. 10.1016/j.ejca.2024.114160

Publishers page: <https://doi.org/10.1016/j.ejca.2024.114160>

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PII: S0959-8049(24)00816-5

DOI: <https://doi.org/10.1016/j.ejca.2024.114160>

Reference: EJC114160

To appear in: *European Journal of Cancer*

Received date: 20 April 2024

Revised date: 27 May 2024

Accepted date: 30 May 2024

Please cite this article as: Romain Cohen, Morteza Raeisi, Benoist Chibaudel, Qian Shi, Takayuki Yoshino, John R. Zalcborg, Richard Adams, Chiara Cremolini, Eric Van Cutsem, Volker Heinemann, Josep Tabernero, Cornelis J.A. Punt, Dirk Arnold, Herbert I. Hurwitz, Jean-Yves Douillard, Alan P. Venook, Leonard B. Saltz, Timothy S. Maughan, Fairouz Kabbinavar, Carsten Bokemeyer, Axel Grothey, Robert J. Mayer, Richard Kaplan, Niall C Tebbutt, J. Randolph Hecht, Bruce J. Giantonio, Eduardo Díaz-Rubio, Alberto F Sobrero, Marc Peeters, Miriam Koopman, Richard M. Goldberg, Thierry Andre and Aimery de Gramont, Prognostic value of liver metastases in colorectal cancer treated by systemic therapy: An ARCAD pooled analysis, *European Journal of*

Cancer, (2024) doi:<https://doi.org/10.1016/j.ejca.2024.114160>

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Prognostic value of liver metastases in colorectal cancer treated by systemic therapy: An ARCAD pooled analysis

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Funding: This work was supported by ARCAD Foundation (no grant number). Independently of this work, the ARCAD Foundation received donation in the 3 past years from Bristol Myers Squibb, Sanofi, AstraZeneca and dotation funds.

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Abstract**Background**

The liver is the most frequent site of metastases in colorectal cancer (CRC). This study aimed to assess the response rate and survival outcomes in metastatic CRC patients with non-liver metastases (NLM) compared to those with liver metastases (LM) across different lines of treatment.

Methods

A total of 17,924 mCRC patients included in 26 trials from the ARCAD CRC database were analyzed. The analysis was conducted based on the presence or absence of LM across different treatment groups: chemotherapy (CT) alone, CT + anti-VEGF, CT + anti-EGFR in KRAS wild-type tumors, within the first-line (1L) and second-line (2L), and patients enrolled in third-line (≥ 3 L) trials treated with trifluridine/tipiracil or regorafenib or placebo. The endpoints were overall survival (OS), progression-free survival (PFS), and overall response rate (ORR).

Results

Out of the 17,924 patients, 14,066 had LM (30.6% with only liver involvement and 69.4% with liver and other metastatic sites), while 3,858 patients had NLM. In the CT alone and CT + anti-VEGF subgroups, NLM patients showed better OS and PFS in the 1L and 2L settings. However, in the CT + anti-EGFR 1L and 2L subgroups, there was no significant difference in OS and PFS between NLM and LM patients. In the ≥ 3 L subgroups, better OS and PFS were observed in NLM patients. ORRs were higher in LM patients than in NLM patients across all cohorts treated in the 1L and only in the anti-EGFR cohort in the 2L.

Conclusion

LM is a poor prognostic factor for mCRC increasing from 1L to ≥ 3 L except for patients in 1L and 2L receiving CT+anti-EGFR. These data justify using LM as a stratification factor in future trials for patients with unresectable mCRC.

Keywords: Liver metastatic colorectal cancer, Prognostic value, Chemotherapy, Targeted therapy

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Introduction

The liver is the most frequent site of metastases in colorectal cancer (CRC). The treatment of patients with CRC liver metastasis (LM) has changed considerably over recent decades. Surgical resection of metastasis is potentially curative treatment for mCRC¹. The efficacy of chemotherapy with or without targeted therapies has improved over time, enabling complete resection and/or ablation of CRC LM in some cases following a significant and favorable response to chemotherapy and targeted therapies². This multimodality approach is commonly associated with enhanced overall survival (OS) even when complete metastasis resection/ablation is not possible. The sites of metastases are often not considered in multivariate analyses of prognostic factors in studies of patients with mCRC treated with chemotherapy, with or without targeted therapy for unresectable disease, even though these sites can be prognostic^{3,4}. A previous ARCAD (Aide et Recherche en CAncérologie Digestive) Foundation work showed the presence of peritoneal carcinomatosis to be a poor prognostic factor for mCRC patients⁵. Engstrand et al. reported demographic and clinic-pathological features of CRC patients with and without LM and found that cohorts of patients with LM had significantly lower 5-year OS compared to patients without LM (16.9% vs 70.4%, $P = 0.001$)⁶. The ARCAD database contains individual patient data collected from randomized trials that included CRC patients with initially unresectable metastases treated with systemic therapy⁷. The aim of this study was to assess the prognostic value of liver metastases in colorectal cancer patients treated with systemic therapy, using progression-free survival (PFS) and OS as endpoints. The study included patients with or without liver metastases (LM) who received the standard of care (SoC) across different lines of therapy. Additionally, subgroup analyses were conducted to compare outcomes between patients with LM as a single site versus those with non-liver single metastases, patients with LM plus other site(s) versus those with multiple sites without LM (NLM), and patients with NLM versus those with LM with or without peritoneal metastases, due to the poor prognostic significance associated with peritoneal metastases.

Methods

Trials and patients' selection

A total of 26 randomized controlled trials of patients with mCRC from the ARCAD CRC database were included in this analysis⁸⁻³³. Patients from trials with contemporary treatments and all relevant data available were eligible. Detailed information on trials and treatment arms included in this analysis is provided as supplementary material (Table A.1). All trials used in this analysis were approved by appropriate research ethics committees and regulatory authorities and conducted in accordance with the Declaration of Helsinki.

Outcomes

The primary outcome was OS defined as time from randomization to death due to any cause. We also analyzed PFS, defined as time from randomization to first documented progression or death due to any cause, whichever occurred first, and the overall response rate (ORR) as per RECIST version 1.1, defined the percentage of patients who achieved a complete response or a partial response as the best response..

Statistical analysis

Baseline patient and tumor characteristics were described using frequency and percentage and were compared according to LM status (presence or absence of LM), using the Chi-squared test, as all variables were categorized. The association between liver metastases status and OS and PFS was investigated within each line of therapy in sub-populations defined below:

- Patients enrolled on first-line (1L) trials and treated with combination chemotherapy (CT) alone, FOLFOX/CAPOX or FOLFIRI, (Group A) or treated with combination therapy either with anti-VEGF or anti-EGFR targeted monoclonal antibodies (Group B);
- Patients enrolled on second-line (2L) trials and treated with combination CT alone, FOLFOX/CAPOX or FOLFIRI, (Group C) or treated with combination therapy either with anti-VEGF or anti-EGFR targeted monoclonal antibodies (Group D);

- Patients enrolled on over third-line ($\geq 3L$) trials having received either trifluridine/tipiracil or regorafenib (TT or R) (Group E) as well as patients treated with placebo in the same trials (Group F).

Regarding patients treated with anti-EGFR combination therapy in groups B and D, only those with wild-type (WT) KRAS tumor were included in the analysis. Treatment arms containing both anti-VEGF and anti-EGFR targeted monoclonal antibodies were excluded.

Prognostic value of LM was investigated also in either single site (SS) or multi-sites (MS) in each treatment group. The primary and secondary endpoints, OS and PFS, were assessed and compared using Kaplan-Meier estimates and Cox model between patients with and without LM, within each line of therapy. Log-rank tests were used for univariate analyses. To assess the prognostic associations of LM status with OS and PFS, Cox models were further adjusted for sex, age, and eastern cooperative oncology group performance score (ECOG PS). Results were summarized using adjusted hazard ratios (HR_{adj}) and 95% confidence intervals (95%CI). ORR was compared between LM and NLM in groups from pooled data and tested using the Chi-squared test. The association between LM status and ORR were evaluated using logistic regression models. Results were reported using odds ratios (OR) and 95% CIs. Analyses were done with R (version 3.6.3). All statistical tests were two-sided and P -values of less than .05 were considered to be significant.

Results

This analysis included 17,924 patients (Figure 1). Of these, 14,066 patients had LM, while 3,858 patients had NLM. The NLM population represented 20%, 22% and 27% of the overall populations that were accrued in 1L, 2L and 3L or later, respectively. More patients with LM had primary tumors that originated in the colon (as opposed to rectum) vs those with NLM (72% vs 62%, $P < .001$) and less often manifested a single metastatic site (31% vs 47%, $P < .001$) than those with NLM. Table 1 displays patient and tumor characteristics according to LM

status. Patient characteristics according to LM status in all subgroups are also reported in the supplementary A (Table A.2 to Table A.9). OS, PFS, and ORR differences in subgroups are reported below.

Group A (CT alone in 1L)

In the 1L CT alone sub-population, 85.8% (1,832) had LM, and 14.2% (409) had NLM. Of those, 56.8% (1,040) with LM and 47.4% (194) with NLM achieved a treatment response (Chi-squared P -value = .001). There was a significant difference in the likelihood of experiencing a response in the NLM vs LM cohorts (OR (95%CI): 0.67 (0.54-0.83), $P < .001$). Significant differences in OS (HR 0.76, 95%CI=0.68-0.84; $P<.001$) and PFS were found between the NLM vs LM cohorts (Figure 2 A). While there was a significant difference in OS in patients with a single metastatic site, the difference in PFS was not significant. Significant differences in OS and PFS were also observed in patients with multiple metastatic sites (Table 2 and Figure B.1). Combination of peritoneal and LM (LM-P) with or without involvement of other sites was associated with poorer survival compared to LM and lymph node and/or lung metastases (LM-LL) (OS HR 1.20, 95%CI=1.03-1.39; $P=0.016$; PFS HR 1.17, 95%CI=1.02-1.34; $P=0.028$). Moreover, the difference between patients with LM-P compared to NLM was more pronounced (Table A.10). A similar detrimental effect of LM vs NLM was observed in patients receiving oxaliplatin-based chemotherapy, whereas it was not evident among those undergoing irinotecan-based chemotherapy (Table A.11).

Group B (CT + targeted therapy in 1L)

In 1L trials, among the CT + anti-EGFR treated KRAS WT sub-population of 1,265 patients, 88.1% (1026) had LM, and 11.9% (239) had NLM. A response was achieved in 73.1% (750) of patients with LM and 54.4% (130) with NLM (Chi-squared P -value $< .001$). There was a difference in the odds of experiencing response (NLM vs LM OR (95%CI): 0.43 (0.33-0.60), $P < .001$). No significant difference in OS and PFS was found for the NLM vs LM cohorts

(Figure 2 B). However, a significant difference in OS favoring the LM cohort was observed only in patients with a single metastatic site. In patients with multiple metastatic sites, there was a non-significant difference in OS favoring NLM. There was no significant difference in PFS (Table 2 and Figure B.1). Furthermore, OS and PFS differences between NLM vs LM-LL or vs LM-P were non-significant (Table A.10). These results were influenced by primary tumor sidedness only in patients with multiple metastatic sites. We found a significant difference on OS in the cohort of patients with a left-sided primary tumor (HR 0.77, 95%CI=0.62-0.96, $P=.018$) and a non-significant OS difference but a significant PFS difference in the cohort of patients with a right-sided primary tumor (HR 1.49, 95%CI=1.07-2.08, $P=.019$).

In 1L trials, among the CT + anti-VEGF treated sub-population of 4,412 patients, 79.8% (3,521) had LM, and 20.2% (891) did not have LM, of whom 61.8% (2,177) with LM and 52.2% (492) without LM achieved a response (Chi-squared P -value < .001). There was a difference in the odds of experiencing response (NLM vs LM OR (95%CI): 0.76 (0.65-0.88), $P < .001$). A significant difference in OS and PFS was found between the NLM and LM cohorts (Figure 2 C). The same findings were observed in patients with single metastatic site or multiple metastatic sites for OS and PFS, although the observed difference of PFS did not reach statistical significance in the cohort of patients with a single metastatic site (Table 2 and Figure B.1). OS and PFS differences were significant in the cohort of patients with multiple metastatic sites with NLM vs LM-LL or LM-P (Table A.10).

Group C (CT alone in 2L)

In 2L trials, among 2,145 patients treated with CT alone, 79.2% (1,698) had LM, and 20.8% (447) did not. Of those, 14.0% (238) with LM and 15.9% (71) without LM achieved a response to treatment (Chi-squared P -value = .317). There was no difference in the odds of experiencing response (NLM vs LM OR (95%CI): 1.15 (0.85-1.52), $P = .353$). A significant difference in OS and PFS was found between the NLM and LM patient cohorts in favor of NLM (Figure 3

A). Similar findings were observed in patients with single and multiple metastatic sites for OS and PFS (Table 3 and Figure B.2). Significant differences were also found in patients with multiple metastatic sites without LM vs LM-LL or LM-P (Table A.10). A similar trend of difference according to LM status was observed among patients receiving irinotecan-based chemotherapy but not among those treated with oxaliplatin-based chemotherapy (Table A.12).

Group D (CT + targeted therapy in 2L)

In 2L trials, among the CT + anti-EGFR treated KRAS WT sub-population of 364 patients, 82.1% (299) had LM, and 17.9% (65) did not. Of those, 44.1% (132) with LM and 29.2% (19) without LM achieved a response (Chi-squared P -value = .027). There was a difference in the odds of experiencing response (NLM vs LM, OR (95%CI): 0.51 (0.28-0.91), P = .025). No significant difference in OS and PFS was found between the NLM and LM patient cohorts (Figure 3 B). The same findings were observed in the patient cohorts with single and multiple metastatic sites for OS and PFS (Table 3 and Figure B.2). With small sample size for survival comparison of patients with multiple metastatic sites in this subgroup, we found non-significantly poorer survival outcomes in NLM and in LM-P versus LM-LL (Table A.10).

In 2L trials, among the CT + anti-VEGF treated sub-population of 1,096 patients, 76.3% (836) had LM, and 13.7% (260) did not. Of those, 15.5% (121) with LM and 23.1% (60) without LM achieved a response (Chi-squared P -value = .001). There was a difference in the odds of experiencing response (NLM vs LM OR (95%CI): 1.77 (1.24-2.51), P = .001). A significant difference in OS and PFS was found in NLM vs LM patient cohorts (Figure 3 C). The same findings were observed in patients with single and multiple metastatic sites for OS and PFS (Table 3 and Figure B.2) and significant differences were found in comparison of the cohort of patients with multiple metastatic sites NLM vs LM-LL or LM-P (Table A.10).

Group E (Trifluridine/tipiracil or regorafenib in 3L)

In 3L trials, among the TT or R treated arms of the 968 patients, 73.8% (714) had LM, and 16.2% (254) did not. Of those, 1.0% (7) with LM and 2.8% (7) without LM achieved a response (Chi-squared P -value = .042). There was a difference in the odds of experiencing response (NLM vs LM OR (95%CI): 2.97 (1.00-8.77), P = .045). A significant difference in OS and PFS was found in NLM vs LM (Figure 4 A). The same findings were observed in patients with single and multiple metastatic sites for OS and PFS (Table 4 and Figure B.3), and significant differences were found in comparison of the cohort of patients with multiple metastatic sites with NLM vs LM-LL or LM-P (Table A.13).

Group F (Placebo in 3L)

In 3L trials, the placebo arms of the sub-population of 484 patients contained 68.4% (331) patients with LM and 31.6% (153) with NLM, of whom 0% (0) with LM and 1.3% (2) with NLM achieved a response (Chi-squared P -value = .037). A significant difference in OS and PFS was found in the NLM vs LM patient cohorts (Figure 4 B). The same findings were observed in patients with single and multiple metastatic sites for OS and PFS (Table 4 and Figure B.3) and significant differences were found in comparison of the cohort of patients with multiple metastatic sites with NLM vs LM-LL or vs LM-P (Table A.13).

Discussion

Liver involvement has not definitively been shown to affect the efficacy of cytotoxic chemotherapy or targeted therapy in mCRC^{23,34}. However, the efficacy of individual agents or combinations in liver metastatic colorectal cancer has not been comprehensively studied. Engstrand et al. found the patients with liver metastases had a significantly lower 5-year OS compared to those without liver metastases (16.9% vs. 70.4%, P = 0.001)⁶. To our knowledge, our study is the largest analysis focusing on the prognostic importance of LM in patients with mCRC treated with systemic therapy across different lines of therapy. We assessed the prognostic implication of liver metastases as the only metastatic disease manifestation and of

liver involvement in combination with other metastatic sites. We found that the presence of LM is a poor prognostic factor for patients with mCRC with increasing negative impact on prognosis from 1L to ≥ 3 L, except for patients treated with anti-EGFR + CT. The impact of LM on OS is substantial for patients with unresectable mCRC in third line, with a median OS twice as high in patients without LM compared to patients with LM. The results observed for PFS trended in a similar manner although for some settings in 1L and 2L the differences did not reach statistical significance.

LM remains a poor prognostic factor in patients with left-sided primary tumor and multiple metastatic sites treated with anti-EGFR + CT in 1L. As response rate is higher with anti-EGFR combinations, we would have expected that patients with liver dominant disease could have benefited from liver directed therapies but data are lacking. Interestingly, ORRs were higher in LM than NLM in all patient cohorts treated in 1L. In 2L only the anti-EGFR treated population had higher ORR in LM than in NLM. There was no difference in ORR in 2L CT cohort and higher ORR in NLM than LM in the anti-VEGF cohort. In 3L ORRs were less than 3% in all cohorts.

One potential explanation of the worse prognosis for patients with CRC LM may be the immune suppressive microenvironment in the liver. The immunosuppressive characteristics of the liver microenvironment has been proposed as an explanation for the low efficacy of immune checkpoint inhibitors (ICIs) in patient cohorts with LM³⁵. Studies have shown that LM were associated with reduced response to ICIs in various solid tumors³⁶. Bullock AJ et al. recently reported a 24% response rate in patients with relapsed/refractory MSS mCRC in an early study of the Fc-enhanced anti-CTLA-4 monoclonal antibody, botensilimab, in combination with the anti-PD-1 monoclonal antibody, balstilimab. Responses were higher in patients without LM (ORR = 42% (10/24) in NLM vs 0% (0/17) in LM)³⁷. The worse outcome of mCRC patients with LM might also be explained by the risk of disease-induced organ failure, that is higher

when patients have LM than in those with NLM (i.e., lung metastases, distant lymph node metastases). However, separating LM and NLM may be too simplistic as important prognostic genomic alterations may not be balanced between arms/trials. Molecular profiling beyond like BRAF mut, RAS mut or MMR status is unfortunately lacking in our dataset.

Intriguingly, a lower frequency of NLM was observed in the patients enrolled in 1L trials than in trials evaluating later lines of therapy (20% of NLM in 1L, compared to 27% in 3L or more). One might have expected a decrease of NLM frequency over the course of the metastatic disease. This observation might be explained by a lower probability for mCRC patients with LM at diagnosis to reach the 3L setting. Alternatively, patients with persistent disease that do not to develop LM may be more likely to be eligible for trials of 3L therapy.

The strength of the present study lies in its large sample size and high data quality. Individual patient data were collected from prospective randomized trials that specifically included patients with liver involvement. However, the study has also limitations. Firstly, it did not assess volume-related disease burden. It is well-recognized that higher metastatic volume burden is a negative predictive factor, both for liver-only sites³⁸ and peritoneum-only disease sites³⁹⁻⁴¹. Additionally, important prognostic factors were missing, especially in the oldest studies, like KRAS status (41%), BRAF status (68%), and primary tumor side (47%), as well as microsatellite status and the number of metastases per organ. These limitations resulted in a difficulty to conduct head-to-head comparisons to investigate the prognostic value of liver metastases based on these prognostic factors. Therefore, future studies should include these prognostic factors to provide a more comprehensive analysis of the prognostic value of liver metastases in metastatic colorectal cancer.

Conclusion

All in all, our data justify using LM as a stratification factor in trial design, especially in 3L trials. Moreover, our data may help defining OS, PFS and/or ORR hypotheses of future trials

selecting patients based on the metastatic spread pattern, such as clinical trials dedicated to LM-only mCRC patients or to NLM-only mCRC patients.

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Table 1. Characteristics of patients according to liver metastases involvement

Characteristic	Overall population (N = 17924)	Patients without liver metastases (N = 3858)	Patients with liver metastases (N = 14066)	
	No. (%)	No. (%)	No. (%)	P-value
Sex				< .001
Female	6978 (38.93)	1614 (41.84)	5364 (38.13)	
Male	10946 (61.07)	2244 (58.16)	8702 (61.87)	
Age				.850
< 75	16502 (92.08)	3549 (91.99)	12953 (92.10)	
≥ 75	1420 (7.92)	309 (8.01)	1111 (7.90)	
Missing	2	-	2	
ECOG PS				.003
0	10017 (55.98)	2248 (58.40)	7769 (55.31)	
1	7426 (41.50)	1505 (39.10)	5921 (42.15)	
≥ 2	452 (2.53)	96 (2.49)	356 (2.53)	
Missing	29	9	20	
Primary tumor				< .001
Colon	10578 (69.79)	1954 (61.74)	8624 (71.91)	
Rectum	4048 (26.71)	1124 (35.51)	2924 (24.38)	
Both	531 (3.50)	87 (2.75)	444 (3.70)	
Missing	2767	693	2074	
No. of mets sites				< .001
1	6095 (34.00)	1797 (46.58)	4298 (30.56)	
≥ 2	11829 (66.00)	2061 (53.42)	9768 (69.44)	
Metastatic site				
Lung	8308 (59.28)	2328 (70.25)	5980 (55.88)	< .001
Lymph Nodes	6350 (55.07)	1791 (67.28)	4559 (51.41)	< .001
Peritoneal	1608 (24.78)	499 (32.38)	1109 (22.41)	< .001
Trial line				< .001
1	10922 (60.94)	2198 (56.97)	8724 (62.02)	
2	5457 (30.45)	1242 (32.19)	4215 (29.97)	
≥ 3	1545 (8.62)	418 (10.83)	1127 (8.01)	

Table 2. Median (95% CI) overall survival (OS) and progression free survival (PFS) in months for patients receiving CT alone and CT + targeted therapy in 1L according to the groups with or without liver metastases as either single (SS) or multiple (MS) sites

Group		OS					PFS				
		Liver		No liver		NLM vs LM	Liver		No liver		NLM vs LM
		Event/N	Median (95% CI)	Event/N	Median (95% CI)	HR _{adj} (95% CI) P-value	Event/N	Median (95% CI)	Event/N	Median (95% CI)	HR _{adj} (95% CI) P-value
CT	All pts	2187/3006	16.8 (16.2-17.4)	468/740	20.7 (19.3-22.5)	0.76 (0.68-0.84) <.001	2507/3006	7.33 (7.13-7.49)	609/740	7.39 (6.77-8.02)	0.84 (0.77-0.92) <.001
	SS	637/946	19.5 (18.7-20.7)	189/326	25.1 (21.0-27.5)	0.79 (0.67-0.94) .008	717/946	7.69 (7.36-8.05)	257/326	7.36 (6.28-8.15)	0.93 (0.80-1.08) .339
	MS	1550/2060	15.7 (15.0-16.3)	279/414	19.0 (16.9-21.0)	0.76 (0.67-0.86) <.001	1790/2060	7.16 (6.74-7.36)	352/414	7.43 (6.57-8.41)	0.81 (0.72-0.91) <.001
CT+ anti-EGFR	All pts	1352/1710	23.7 (22.5-25.2)	347/430	24.6 (22.4-27.6)	0.97 (0.86-1.10) .670	1433/1710	9.49 (9.17-10.1)	365/430	9.13 (8.31-9.95)	1.03 (0.91-1.16) .640
	SS	485/672	31.0 (28.-34.8)	191/236	25.6 (23.7-30.4)	1.24 (1.04-1.47) .017	517/672	11.3 (10.5-12.7)	201/236	9.53 (8.71-11.1)	1.13 (0.95-1.34) .154
	MS	867/1038	19.7 (18.5-21.2)	156/194	22.4 (18.8-27.5)	0.85 (0.72-1.01) .073	916/1038	8.74 (8.31-9.33)	164/194	8.44 (7.33-9.56)	1.07 (0.90-1.27) .424
CT+anti-VEGF	All pts	2460/4008	23.1 (22.3-23.8)	563/1028	26.6 (25.4-28.9)	0.81 (0.74-0.89) <.001	3368/4008	10.2 (9.99-10.5)	841/1028	10.2 (9.63-10.8)	0.91 (0.84-0.98) .013
	SS	921/1568	27.0 (25.5-29.0)	316/566	29.3 (26.7-32.2)	0.88 (0.77-1.00) .050	1286/1568	11.2 (10.8-11.7)	463/566	10.6 (9.92-11.6)	0.99 (0.89-1.10) .841
	MS	1539/2440	21.0 (20.0-21.8)	247/462	23.9 (22.5-26.5)	0.84 (0.73-0.96) .011	2082/2440	9.53 (9.30-9.89)	378/462	9.59 (8.97-10.6)	0.88 (0.79-0.99) .028

CT: chemotherapy; Anti-EGFR: anti-Epidermal Growth Factor antibodies; Anti-VEGF: anti Vascular Endothelial Growth Factor antibodies; SS: Single Site; MS: Multi-Site

Table 3. Median (95% CI) overall survival (OS) and progression free survival (PFS) in months for patients receiving CT alone and CT + targeted therapy in 2L according to the groups with or without liver metastases as either single (SS) or multiple (MS) sites

Group		OS					PFS				
		Liver		No liver		NLM vs LM HR _{adj} (95% CI) P-value	Liver		No liver		NLM vs LM HR _{adj} (95% CI) P-value
		Event/N	Median (95% CI)	Event/N	Median (95% CI)		Event/N	Median (95% CI)	Event/N	Median (95% CI)	
CT	All pts	1995/2436	10.4 (10.1-10.8)	492/708	15.3 (14.0-16.9)	0.64 (0.58-0.71) <.001	2326/2436	3.91 (3.75-4.07)	655/708	5.52 (5.16-5.72)	0.72 (0.66-0.79) <.001
	SS	423/539	11.9 (10.8-13.0)	167/270	18.3 (16.4-20.6)	0.58 (0.48-0.69) <.001	513/539	4.14 (3.94-4.37)	250/270	6.05 (5.55-6.90)	0.67 (0.57-0.78) <.001
	MS	1572/1897	10.2 (9.63-10.5)	325/438	13.6 (12.7-15.2)	0.71 (0.63-0.81) <.001	1813/1897	3.81 (3.68-4.01)	405/438	4.90 (4.34-5.52)	0.77 (0.69-0.87) <.001
CT+ EGFR	All pts	271/323	14.3 (12.6-15.6)	62/77	11.3 (9.40-16.0)	1.12 (0.84-1.49) .445	296/323	5.72 (5.39-7.33)	76/77	5.54 (4.99-7.16)	1.22 (0.93-1.59) .147
	SS	48/58	16.2 (13.2-24.0)	7/13	18.8 (7.26-NA)	1.11 (0.44-2.88) .824	51/58	7.36 (4.45-10.7)	13/13	4.07 (1.35-NA)	1.85 (0.88-3.87) .104
	MS	223/265	13.6 (12.0-15.1)	55/64	11.1 (9.26-15.7)	1.09 (0.80-1.48) .589	245/265	5.55 (5.36-6.90)	63/64	6.01 (5.36-7.46)	1.09 (0.82-1.46) .560
CT+VEGF	All pts	1167/1456	12.0 (11.5-12.5)	292/457	18.1 (16.5-19.9)	0.62(0.55-0.71) <.001	1385/1456	5.91 (5.68-6.21)	412/457	7.36 (6.87-8.31)	0.75 (0.67-0.84) <.001
	SS	293/389	13.3 (12.5-14.4)	122/226	22.6 (19.8-30.5)	0.55 (0.44-0.64) <.001	363/389	6.18 (5.72-6.67)	196/226	7.49 (6.97-8.57)	0.76 (0.63-0.91) .003
	MS	874/1067	11.5 (10.9-12.1)	170/231	15.2 (12.7-17.7)	0.81 (0.68-0.95) .013	1021/1067	5.85 (5.59-6.18)	216/231	7.10 (6.11-8.34)	0.79 (0.68-0.91) .002

CT: chemotherapy; Anti-EGFR: anti-Epidermal Growth Factor antibodies; Anti-VEGF: anti Vascular Endothelial Growth Factor antibodies; SS: Single Site; MS: Multi-Site

Table 4. Median (95% CI) overall survival (OS) and progression free survival (PFS) in months for patients received trifluridine/tipiracil or regorafenib (TT or R) and placebo in 3L according to the groups with or without liver metastases as either single (SS) or multiple (MS) sites

Group		OS					PFS				
		Liver		No liver		NLM vs LM HR _{adj} (95% CI) P-value	Liver		No liver		NLM vs LM HR _{adj} (95% CI) P-value
		Event/ N	Median (95% CI)	Event/N	Median (95% CI)		Event/ N	Median (95% CI)	Event/ N	Median (95% CI)	
Trifluridine _Tipiracil or regorafenib	All pts	533/764	5.85 (5.39- 6.24)	102/264	12.9 (11.9- 17.3)	0.36 (0.29-0.44) <.001	711/764	1.87 (1.84- 1.91)	206/264	3.71 (3.52- 4.80)	0.52 (0.44- 0.60) <.001
	SS	63/96	7.46 (6.14- 9.26)	36/110	14.7 (12.3- NA)	0.33 (0.21-0.51) <.001	88/96	1.84 (1.81- 2.04)	83/110	4.63 (3.68- 5.72)	0.43 (0.31- 0.59) <.001
	MS	470/668	5.55 (5.13- 3.08)	66/154	12.2 (8.87- NA)	0.39 (0.30-0.51) <.001	623/668	1.87 (1.84- 1.94)	123/154	3.52 (2.66- 3.91)	0.58 (0.48- 0.71) <.001
Placebo	All pts	284/363	4.14 (3.58- 4.53)	82/154	7.85 (7.16- 9.86)	0.40 (0.32-0.52) <.001	356/363	1.68 (1.64- 1.71)	145/154	1.84 (1.81- 1.87)	0.60 (0.49- 0.73) <.001
	SS	24/30	3.91 (3.25- 5.42)	21/50	11.0 (7.85- NA)	0.14 (0.07-0.28) <.001	30/30	1.61 (1.38- 1.84)	47/50	1.84 (1.74- 1.94)	0.43 (0.25- 0.73) .002
	MS	260/333	4.14 (3.58- 4.57)	61/104	7.26 (5.95- 8.57)	0.51 (0.39-0.68) <.001	326/333	1.68 (1.64- 1.74)	98/104	1.84 (1.77- 1.87)	0.62 (0.50- 0.79) <.001

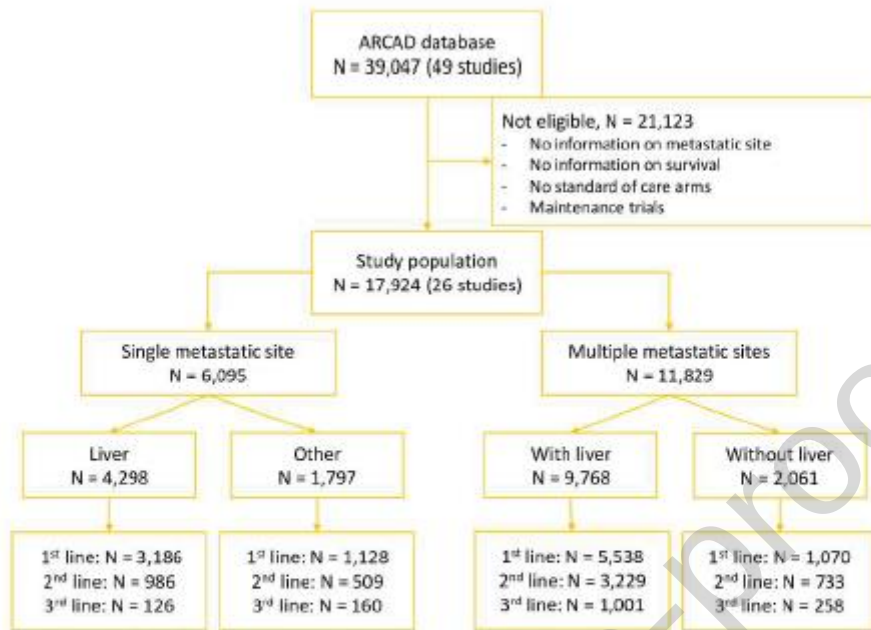


Figure 1. Consort Diagram.

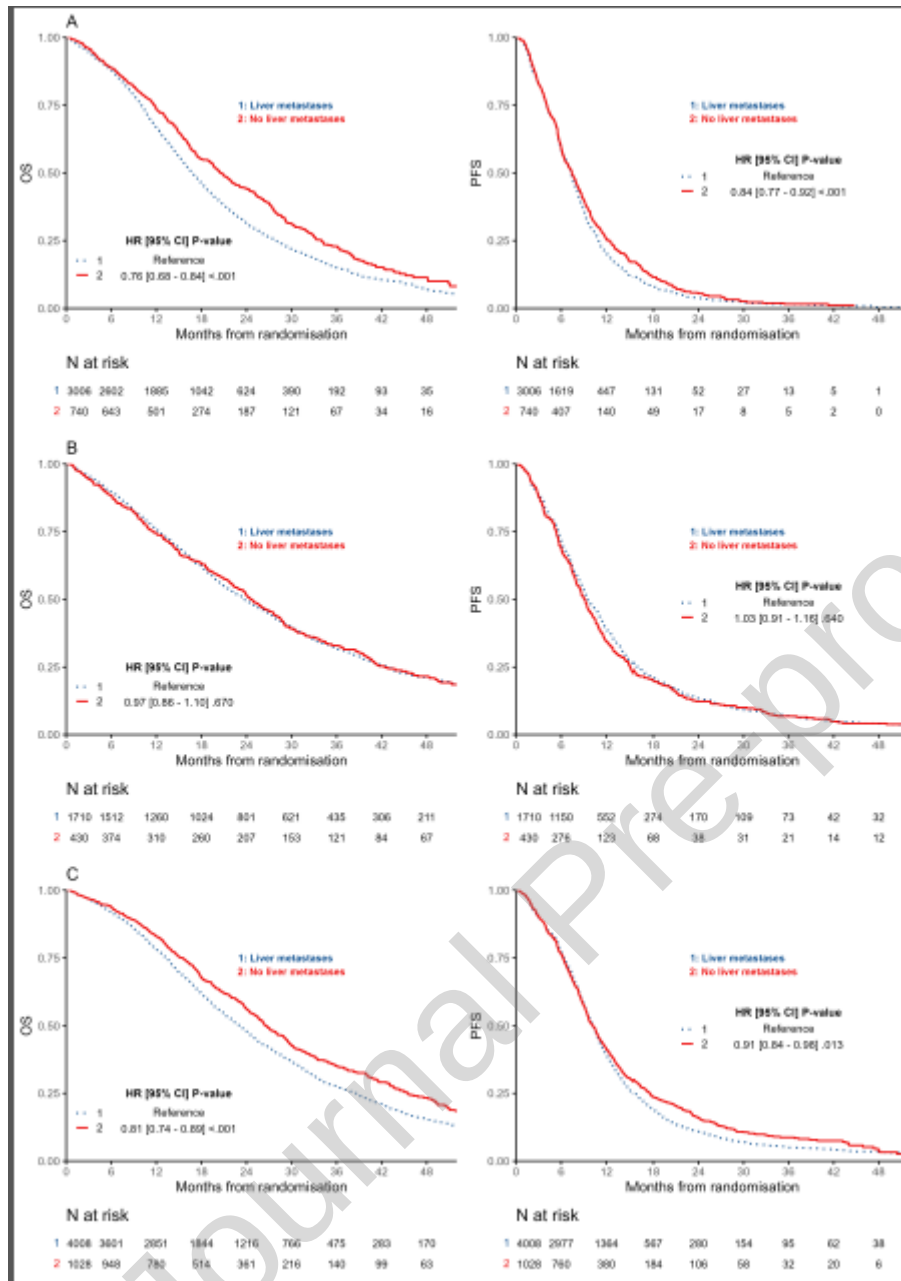


Figure 2. OS and PFS benefit of chemotherapy alone (A), chemotherapy + anti-EGFR (B), and chemotherapy + anti-VEGF (C) in first line according to the groups defined with or without liver metastases

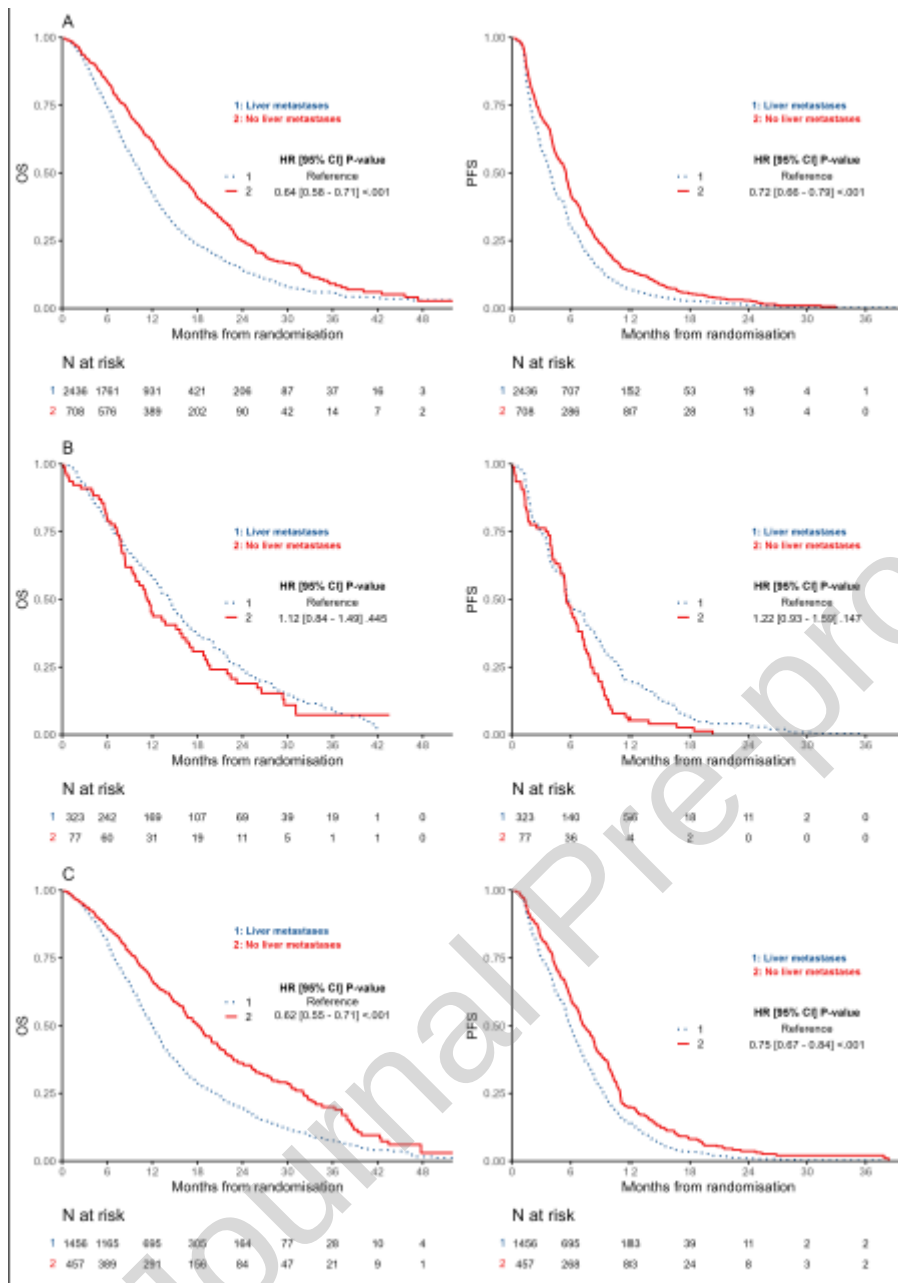


Figure 3. OS and PFS benefit of chemotherapy alone (A), chemotherapy + anti-EGFR (B), and chemotherapy + anti-VEGF (C) in second line according to the groups defined with or without liver metastases

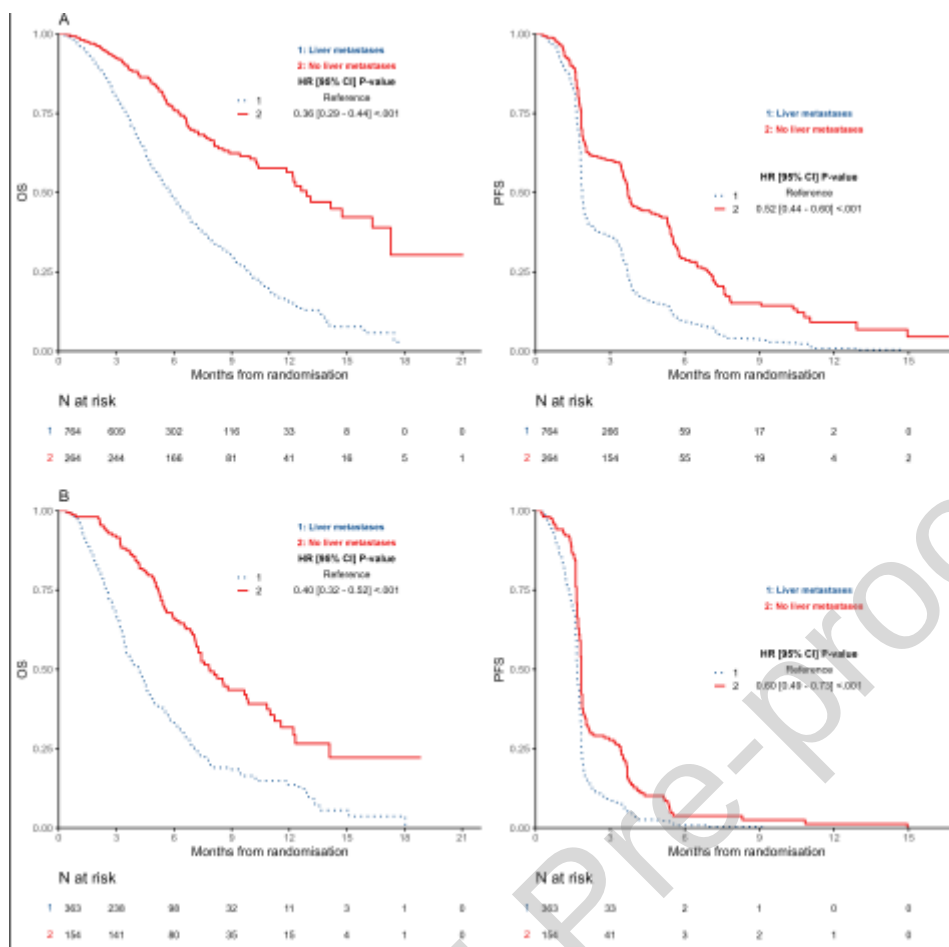


Figure 4. OS and PFS benefit of trifluridine/tipiracil or regorafenib (A) and placebo (B) in third line according to the groups defined with or without liver metastases

Declaration of Interest statement

Benoist Chibaudel reports consulting and advisory role from Amgen, Bayer, Beigine, Biocartis, Lilly, Merck, MSD, Pfizer, Pierre Fabre, Revolution Medicines, Roche, SeqOne, Sanofi, Servier, Takeda.

Josep Tabernero reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiff Oncology, Chugai,

Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Tessa Therapeutics, TheraMyc and Tolremo Therapeutics. Stocks: Oniria Therapeutics and also educational collaboration with Imedex/HMP, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resource (PER).

Qian Shi reports consulting/advisory role from Yiviva Inc, Boehringer Ingelheim Pharmaceuticals, Inc, Regeneron Pharmaceuticals, Inc., Hoosier Cancer Research Network, Kronos Bio, and Mirati Therapeutics Inc; Honorarium/speaker role from Chugai Pharmaceutical Co., Ltd (to myself), research funds from Celgene/BMS, Roche/Genentech, Janssen, Novartis (to institution).

Thierry Andre reports attending advisory board meetings and receiving consulting fees from Abbvie, Astellas, Aptitude Health, Bristol Myers Squibb, Gritstone Oncology, Gilead, GlaxoSmithKline, Merck & Co. Inc., Nordic Oncology, Seagen, Servier, Takeda and Transgène and honoraria from Bristol Myers Squibb, GlaxoSmithKline, Merck & Co. Inc., Merck Serono, Pierre Fabre, Roche, Sanofi, Seagen and Servier; and support for meetings from Merck & Co. Inc. and Servier.

John Zalcborg reports leadership from ICON Group, Lipotek, PRAXIS; Stock from Biomarin, Ophthea, Amarin, Concert Pharmaceuticals, Frequency Therapeutics, Gilead, Madrigal Pharmaceuticals, UniQure, Zogenix, Orphazyme, Moderna Therapeutics, TWST, Novavax, Teladoc; Honoraria from Gilead Sciences, MSD Oncology, Viartis; Consulting & Advisory Role from Merck Sharp & Dohme, Specialized Therapeutics, CEND, Deciphera, REVOLUTION MEDICINE, FivePHusion, Genorbio, 1Global, Novatech, Alloplex

Biotherapeutics Inc, Oncology Republic; Research Funding from BMS, AstraZeneca, Pfizer, IQvia, Mylan, Ipsen, Eisai, Medtronic, MSD Oncology, Servier; Travel from MSD Oncology, ICON Group, PRAXIS.

Eric Van Cutsem reports participation to advisory boards for Abbvie, ALX, Amgen, Array, Astellas, Astrazeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Takeda, Terumo, Taiho, Zymeworks; research grants from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to his institution.

Takayuki Yoshino reports honoraria from Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Bayer Yakuhin, Ltd., Ono Pharmaceutical Co., Ltd., MSD K.K.; consulting fee from Sumitomo Corp.; research grant from Amgen K.K., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd, FALCO biosystems Ltd., Genomedia Inc., MEDICAL & BIOLOGICAL LABORATORIES CO., LTD., Merus N.V., Molecular Health GmbH, MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Roche Diagnostics K.K., Sanofi K.K., Sysmex Corp., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd.

Richard Adams reports receiving consulting fees from Takeda, Bayer, GSK; honoraria from Amgen, Bayer, Seagen; Support for attending meetings and/or travel from Servier, Takeda; Participation on Advisory Board from Takeda, Seagen.

Carsten Bokemeyer reports receiving consulting fees as advisory boards from Astra Zeneca, Bayer Healthcare, BioNTech, Heaxal, Lindis Biotech, and Sanofi Aventis; as Invited Speaker from AOK Germany, med update, and Roche Pharma; reports honoraria from DGHO, Hamburg

Cancer Society, National Network of German Cancer Centers (DKH), Northern German Society of Internal Medicine, DGHO, German Cancer Society.

Cornelis J. A. Punt reports receiving consulting fees as advisory boards from Nordic Pharma.

Richard M Goldberg receiving consulting fees as advisory boards from Fight for Colorectal Cancer, US NCI.

Volker Heinemann reports receiving consulting fees from Merck, Amgen, Roche, AstraZeneca, Celgene, Servier, Novartis, Pierre-Fabre, Halozyme, MSD, BMS, GSK, Janssen, Terumo, Sirtex, Oncosil, Nordic, Boehringer-Ingelheim; honoraria from Merck, Amgen, Roche, Sanofi, Servier, Pfizer, Pierre-Fabre, AstraZeneca, BMS, MSD, Novartis, Boehringer-Ingelheim, Celgene, Sirtex, Seagen, GSK; support for attending from Merck, Amgen, MSD, Nordic, AstraZeneca, Servier; reports stock from BionTech.

Chiara Cremolini reports receiving consulting fees from Nordic Pharma, Merck, Pierre Fabre, Servier, Takeda; reports honoraria from Takeda, MSD, Amgen, Merck, Pierre Fabre, Servier, Bayer; participation to advisory board from Mirat.

Miriam Koopman reports receiving consulting fees from Bayer, Bristol Myers Squibb, Merck, Personal Genome Diagnostics (PGDx), Pierre Fabre, Roche, Sirtex, Servier and PI participation from the international cohort study PROMETCO with Servier as sponsor; participation to advisory board from Eisai, Nordic Farma, Merck-Serono, Pierre Fabre, Servier; as leadership or fiduciary role in Chair ESMO RWDD working group, co-chair DCCG, PI PLCRC (national observational cohort study), involved in several clinical trials as PI or co-investigator in CRC.

Alan Venook reports receiving consulting fees from Amgen, Genentech/Roche, Deciphera; participation on Advisory Board in Amgen, Agenus.

Timothy Maughan reports receiving consulting fees from Merck KGaA, Cancer Research UK, Astrazeneca, Ground Truth Laboratories, Perspectum, Nordin Pharma; participation on

Advisory Board and leadership in Cancer Research UK, National Cancer Research Institute-University of Liverpool.

All remaining authors have declared no conflicts of interest.

Highlights

- LM in CRC are associated with poorer OS and PFS versus NLM across treatment lines.
- Prognostic impact of LM increases from first-line to third-line therapy settings.
- The presence of LM is a poor prognostic factor particularly in third-line therapy.
- Using LM as a stratification factor in future trials for mCRC is recommended.