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Original Research

Oligometastatic colorectal cancer: prognosis, role of locoregional treatments and impact of first-line chemotherapy—a pooled analysis of TRIBE and TRIBE2 studies by Gruppo Oncologico del Nord Ovest

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Abstract ***Background:*** Oligometastatic disease (OMD) identifies tumours with limited metastatic spread. OMD definition is not univocal and no data from clinical trials are available about the prognostic effect of OMD in metastatic colorectal cancer (mCRC), the impact of locoregional treatments (LRTs) and the effect of chemotherapy intensification in these patients. The role of tumour burden (TB) in driving therapeutic choices is also debated.
Patients and methods: We performed a pooled analysis of phase III TRIBE and TRIBE2 studies comparing FOLFOXIRI/bevacizumab (bev) to doublets (FOLFOX or FOLFIRI)/bev. Patients were grouped in OMD *versus* non-OMD based on the European Society for Medical Oncology definition. Among patients with OMD, those with OMD/low TB were compared with all the others.
Results: Of 1187 patients enrolled, 1096 were classified as OMD (N = 312 [28%]) or non-OMD (N = 784 [72%]). Among patients with OMD, 126 (40%) were OMD/low TB. OMD was associated with longer progression-free survival (14.0 *versus* 10.1 months; $p < 0.01$) and overall survival (38.2 *versus* 22.0 months; $p < 0.01$). These results were confirmed in multivariable models. The benefit provided by FOLFOXIRI/bev compared with doublets/bev did not differ in accordance with OMD and TB (p for interaction >0.05). Patients with OMD underwent LRTs more frequently ($p < 0.01$) and those with OMD/low TB had higher chance to undergo LRTs after the first progression ($p < 0.01$).
Conclusions: OMD is a positive prognostic factor in mCRC. The benefit from the upfront treatment intensification is independent of the metastatic spread extent and TB. LRTs should be highly considered in these patients, mainly during the first-line therapy but also at later stages of treatment history in selected cases.

1. Background

The concept of oligometastatic disease (OMD), initially proposed by Hellman and Weichselbaum [1], identifies solid tumours with limited metastatic spread. As a consequence, the aim of the treatment in these patients should be curative, and locoregional treatments (LRTs) should be considered in their therapeutic route with the intent of long-term survival or cure.

With regard to metastatic colorectal cancer (mCRC), the definition of OMD is not univocal. Recently, the European Society for Medical Oncology (ESMO) guidelines defined oligometastatic colorectal cancer as a disease characterised by metastases involving few sites and lesions (up to 2 or occasionally 3 sites with 5 or sometimes more metastases) [2], as well as recommended to consider LRTs in the treatment strategy of these patients. Nevertheless, the actual prognostic impact of OMD as defined by ESMO guidelines has never been investigated in clinical trials. The randomised phase II CLOCC trial showed a survival benefit from the multimodal treatment with LRTs (radiofrequency ablation with or without surgical resection) combined with the systemic therapy compared with the systemic treatment alone in a specific subgroup of patients with initially unresectable colorectal liver metastases [3].

Moreover, in the ESMO guidelines tumour burden (TB) and treatment's objective (cytoreduction *versus* disease control) are included among factors affecting the choice of the intensity of the upfront chemotherapy [2]. In particular, it is suggested that patients with low TB where cytoreduction is not a primary objective of the first-line treatment may not need an intensified upfront approach. However, the magnitude of the benefit provided by chemotherapy intensification in accordance with the extent of the metastatic spread at baseline remains unclear. Finally, the definition of OMD by ESMO guidelines does not take into account the maximum size or volume of individual metastases, thus not allowing to properly appraise the extent of TB, as suggested by a recent European consensus [4].

To fill some of the above reported gaps of knowledge about the management of oligometastatic CRC, we conducted an individual patient data-based pooled analysis of two phase III randomised trials by Gruppo Oncologico del Nord Ovest, TRIBE (NCT00719797) [5] and TRIBE2 (NCT02339116) [6], that compared FOLFOXIRI/bevacizumab (bev) with FOLFIRI (5-fluorouracil, leucovorin and irinotecan) or FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) plus bev, respectively, as upfront treatment of mCRC. Both trials met their primary and secondary end-points reporting significantly higher response rate and longer survival with the intensified first-line regimen.

In the present analysis, we investigated the prognostic impact of the extent of the metastatic spread at baseline defined in accordance with the ESMO definition of OMD, and the effect of the intensification of the upfront chemotherapy backbone and the role of LRTs in patients with OMD *versus* non-OMD. To investigate the impact of TB, we also took into account the maximum lesions' diameter and the number of metastases per organ to define patients with OMD and low TB (OMD/low TB).

2. Methods

2.1. Study design and procedures

TRIBE and TRIBE2 are two phase III randomised, open-label, multicentre trials involving 1187 initially unresectable untreated patients with mCRC (aged 18–70 years with Eastern Cooperative Oncology Group performance status [ECOG-PS] of 2 or less, and aged 71–75 years with an ECOG-PS of 0). In the TRIBE study, 508 patients were randomised in a 1:1 ratio to receive FOLFIRI/bev or FOLFOXIRI/bev, whereas in the TRIBE2 trial, 679 patients were randomised in a 1:1 ratio to receive FOLFOX/bev followed by FOLFIRI/bev after disease progression or FOLFOXIRI/bev followed by the reintroduction of the same agents after disease progression. All treatments were administered up to 12 cycles in TRIBE and up to 8 cycles in TRIBE2, followed by 5-fluorouracil plus bev until disease progression, unacceptable adverse events, or consent withdrawal in both trials.

2.2. Definitions and end-points

OMD was defined as a disease fulfilling all the following criteria: up to 5 metastases; no more than 3 organs involved; absence of ascites and peritoneal, bone and central nervous system metastases. All other cases were included in the non-OMD group. OMD/low TB was defined as a subgroup of OMD with no more than 3 metastases per organ, and of a maximum size of 3 cm.

The extent of the metastatic spread was assessed from data collected in the electronic case report forms (e-CRFs), where the diameter of the largest metastatic lesion and the number of metastases were reported. The definition of OMD versus non-OMD was based on the information provided by local investigators in e-CRFs. No central review of computed tomography scans was performed. Objective response rate (ORR), defined as the proportion of patients achieving partial or complete response in accordance with RECIST, version 1.0 and version 1.1 in TRIBE and TRIBE2 trials, respectively, progression-free survival (PFS) defined as the time from randomisation to the evidence of disease progression or death, whichever occurred first, and overall survival (OS), defined as the time from randomisation to the evidence of death due to any cause, were evaluated in the OMD *versus* non-OMD subgroup and in the patients with OMD/low TB *versus* all the others in the pooled study population and in accordance with the randomisation arm. LRTs were defined at curative intent when a surgical R0/R1 resection (resection of all lesions with or without evidence of microscopic residual tumour) and/or ablative treatments such as stereotactic body radiotherapy or radiofrequency/microwave ablation was performed.

2.3. Statistics

The chi-square test, Fisher's exact test and Mann-Whitney test were used, when appropriate, to compare clinical and biological features and ORR among different groups (OMD *versus* non-OMD and OMD/low TB *versus* all other patients). PFS and OS were determined in accordance with the Kaplan-Meier estimates method, and survival curves were compared using the log-rank test. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated with a logistic-regression model, and hazard ratios (HRs) and 95% CI were estimated with a Cox proportional hazards model. Subgroup analyses of FOLFOXIRI/bev *versus* doublets/bev for ORR, PFS and OS were carried out using interaction test. The impact of clinical and molecular prognostic variables on PFS and OS was firstly assessed in univariate analyses. Significantly prognostic covariates ($p < 0.10$) were included in a multivariable Cox proportional hazard model. All statistical tests were two-sided, and *p*-values of 0.05 or less were deemed significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). The data cut-off for the present analysis was July 31, 2014 and July 30, 2019 for TRIBE and TRIBE2, respectively.

3. Results

Among 1187 patients enrolled in TRIBE and TRIBE2 studies, 1096 were classified as OMD (N = 312 [28%]) or non-OMD (N = 784 [72%]). One hundred twenty six (40%) of 312 patients in the OMD group were defined as OMD/low TB and were compared with all the others, including patients without low TB or OMD (N = 1032) (Fig. S1 and Table S1).

As shown in Table 1, patients with OMD had more frequently an ECOG-PS of 0 ($p < 0.001$), metachronous disease ($p < 0.001$), Rat sarcoma (*RAS*) and B-Rapidly Accelerated Fibrosarcoma ((*BRAF*) wild-type tumours ($p = 0.018$), left-sided ($p = 0.003$) and previously resected primary tumour ($p < 0.001$), liver only disease ($p < 0.001$) and had previously received adjuvant therapy ($p < 0.001$). As compared with others, more patients with OMD/low TB had ECOG-PS = 0 ($p < 0.001$),

Table 1
Patients' characteristics.

Study population N(%)	N = 1096			N = 1158		
	Non-OMD N = 784 (72)	OMD N = 312 (28)	p	Other patients N = 1032 (89)	OMD/low TB N = 126 (11)	p
Age (years)						
Median	61	62	0.217	61	61	0.533
Range	29–75	30–75		29–75	30–75	
Sex						
Male	462 (59)	182 (58)	0.857	607 (59)	70 (56)	0.483
Female	322 (41)	130 (42)		425 (41)	56 (44)	
Arm						
Doublet + bev	402 (51)	155 (50)	0.633	523 (51)	59 (47)	0.414
FOLFOXIRI + bev	382 (49)	157 (50)		509 (49)	67 (53)	
Site of primary tumour						
Right	289 (38)	87 (28)	**0.003**	362 (36)	35 (29)	0.103
Left and rectum	476 (62)	221 (72)		647 (64)	88 (71)	
NA	19	4		23	3	
Mutational status						
RAS mut	466 (69)	164 (62)	**0.018**	592 (68)	66 (61)	0.206
BRAF mut	67 (10)	21 (8)		83 (9)	9 (8)	
All wt	142 (21)	78 (30)		200 (23)	33 (31)	
NA	109	49		157	18	
Resected primary tumour						
Yes	418 (53)	212 (68)	**<0.001**	578 (56)	90 (71)	**0.001**
No	366 (47)	100 (32)		454 (44)	36 (29)	
Liver only disease						
Yes	169 (22)	122 (39)	**<0.001**	272 (26)	33 (26)	0.968
No	615 (78)	190 (61)		760 (74)	93 (74)	
Previous adjuvant therapy						
Yes	29 (4)	35 (11)	**<0.001**	60 (6)	11 (9)	0.198
No	755 (96)	277 (89)		972 (94)	115 (91)	
Time to metastases						
Synchronous	711 (91)	229 (73)	**<0.001**	893 (87)	96 (76)	**0.002**
Metachronous	73 (9)	83 (27)		139 (13)	30 (24)	
ECOG-PS						
0	653 (83)	289 (93)	**<0.001**	875 (85)	122 (97)	**<0.001**
1-2	131 (17)	23 (7)		157 (15)	4 (3)	

OMD = oligometastatic disease; TB = tumour burden; N = number; p = chi-square or Fisher's exact test when appropriate; bev = bevacizumab; NA = not available; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; *RAS* = Rat Sarcoma; *BRAF* = B-Rapidly Accelerated Fibrosarcoma.

metachronous disease (p = 0.002), and previously resected primary tumour (p = 0.001).

Overall, patients with OMD reported longer PFS (14.0 *versus* 10.1 months; HR: 0.56, 95% CI: 0.49–0.65; p < 0.001) and OS (38.2 *versus* 22.0 months; HR: 0.47, 95% CI: 0.39–0.55; p < 0.001) compared with those with non-OMD (Table 2 and Fig. 1, panel A and C). This was confirmed in the multivariable models (PFS and OS: p < 0.001) (Table S2). No difference was observed in terms of ORR (61% *versus* 56%; OR: 0.90, [95% CI: 0.58–1.40], p = 0.633) (Table 2).

Similarly, patients with OMD/low TB reported longer PFS (14.3 *versus* 10.5 months; HR: 0.64, 95% CI: 0.52–0.79; p < 0.001) and OS (44.3 *versus* 24.0 months; HR: 0.46, 95% CI: 0.35–0.60; p < 0.001) compared with others (Table 2 and Fig. 1, panel B and D). This was confirmed in the multivariable models (PFS: p = 0.003; OS: p < 0.001) (Table S3). No difference was observed in terms of ORR (63% *versus* 57%; OR: 0.76, 95% CI: 0.51–1.11; p = 0.151) (Table 2). Among patients with OMD, no difference was shown between those with low TB and those with non-low TB in terms of PFS (14.3 *versus* 13.5 months; HR: 1.00, 95% CI: 0.78–1.28; p = 0.993), whereas a trend for better OS was reported in favour of the OMD/low TB group (44.3 *versus* 35.1 months; HR: 0.75, 95% CI: 0.55–1.03; p = 0.079) (Fig. S2, panel A and B).

The benefit provided by FOLFOXIRI/bev compared with doublets/bev did not differ in accordance with OMD or TB, without interaction effects in terms of PFS (*p* for interaction: 0.755 and 0.575, respectively), OS (*p* for interaction: 0.935 and 0.233, respectively) and ORR (*p* for interaction: 0.284 and 0.099, respectively) (Table 2).

Patients with OMD underwent LRTs with radical intent during first-line chemotherapy more frequently than patients in the non-OMD group (p < 0.001). Moreover, patients with OMD/low TB received other

Table 2
Efficacy in accordance with treatment group and oligometastatic state/tumour burden.

Study population	N = 1096				N = 1158			
	Non-OMD N = 784	OMD N = 312		p	Other patients N = 1032	OMD/low TB N = 126		p
PFS (months)	10.1	14.0		**< 0.001**	10.5	14.3		**< 0.001**
HR (95% CI)	0.56 (0.49–0.65)				0.64 (0.52–0.79)			
OS (months)	22.0	38.2		**< 0.001**	24.0	44.3		**< 0.001**
HR (95% CI)	0.47 (0.39–0.55)				0.46 (0.35–0.60)			
ORR (%)	56	61		0.633	57	63		0.151
OR (95% CI)	0.90 (0.58–1.40)				0.76 (0.51–1.11)			
	Doublet/bev N = 402	FOLFOXIRI/bev N = 382	Doublet/bev N = 155	FOLFOXIRI/bev N = 157	p for interaction	Doublet/bev N = 523	FOLFOXIRI/bev N = 509	Doublet/bev N = 59	FOLFOXIRI/bev N = 67	p for interaction
PFS (months)	9.5	11.1	12.0	18.1	0.755	9.6	11.7	13.9	15.9	0.575
HR (95% CI)	0.76 (0.66–0.88)		0.80 (0.62–1.02)			0.76 (0.67–0.87)		0.84 (0.57–1.25)		
OS (months)	21.2	23.2	36.4	39.0	0.935	22.5	26.3	48.4	43.7	0.233
HR (95% CI)	0.84 (0.72–0.99)		0.83 (0.61–1.13)			0.82 (0.71–0.95)		1.20 (0.71–2.01)		
ORR (%)	52	61	53	69	0.284	52	61	51	75	0.099
OR (95% CI)	1.46 (1.10–1.94)		1.96 (1.24–3.11)			1.46 (1.14–1.87)		2.84 (1.34–6.02)		

OMD = oligometastatic disease; TB = tumour burden; N = number; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival; ORR = objective response rate; OR = odds ratio; bev = bevacizumab.

LRTs after the first disease progression more frequently than the others (52% *versus* 19%; $p < 0.001$) (Table 3).

As expected, in the OMD group, patients who received LRTs with curative intent during first-line (N = 121, 39%) reported longer PFS (23.9 *versus* 10.6 months; HR: 0.41, 95% CI: 0.31–0.53, $p < 0.001$) and OS (52.6 *versus* 28.0 months; HR: 0.34, 95% CI: 0.24–0.48; $p < 0.001$) compared with those who did not (N = 191, 61%) (Fig. S3, panel A and C). In addition, in the OMD/low TB group, patients who underwent LRTs with curative intent during first-line (N = 35, 28%) reported longer PFS (23.7 *versus* 12.6 months; HR: 0.46, 95% CI: 0.29–0.73, $p < 0.001$) and OS (59.6 *versus* 33.5 months; HR: 0.24, 95% CI: 0.11–0.51; $p < 0.001$) compared with those who did not (N = 91, 72%) (Fig. S3, panel B and D). Similar results were achieved, in the non-OMD group (Fig. S4).

Among patients who underwent radical LRTs during upfront chemotherapy, those with OMD/low TB at baseline (N = 35, 17%) reported longer OS than others (N = 167, 83%) (59.6 *versus* 50.6 months; HR: 0.47, 95% CI: 0.23–0.99; $p = 0.041$). Conversely, no difference was reported in terms of OS between patients with OMD and non-OMD (52.6 months for OMD *versus* 48.4 months for non-OMD; HR: 0.76, 95% CI: 0.48–1.20; $p = 0.233$) (Fig. 2).

4. Discussion and conclusions

In the last years, significant improvements in the treatment of mCRC progressively increased the survival expectancy of the overall patients' population to more than 2 years. Major contributions to these achievements were given by an optimal integration of more active systemic regimens, innovative surgical techniques and LRTs [2,5–7]. As recommended by international guidelines, the multimodal approach should be highly considered especially when the metastatic spread is limited to improve long-term survival and to offer a chance of cure to some of these patients [2,7]. Even if intriguing translational data suggest that specific biologic features of OMD may be associated with long-term survival [8], the clinical definition of OMD is not univocal, and evidence from clinical trials about the optimal management of patients with OMD is currently lacking.

First of all, the clinical relevance of proposed definitions has never been assessed. In particular, the prognostic impact of the OMD has never been demonstrated. Here we showed that patients with OMD defined in accordance with ESMO guidelines show better outcome than those without OMD, and this association is independent of other established clinical and molecular prognostic factors.

Secondly, we attempted to further refine the ESMO definition of OMD and to identify those patients with

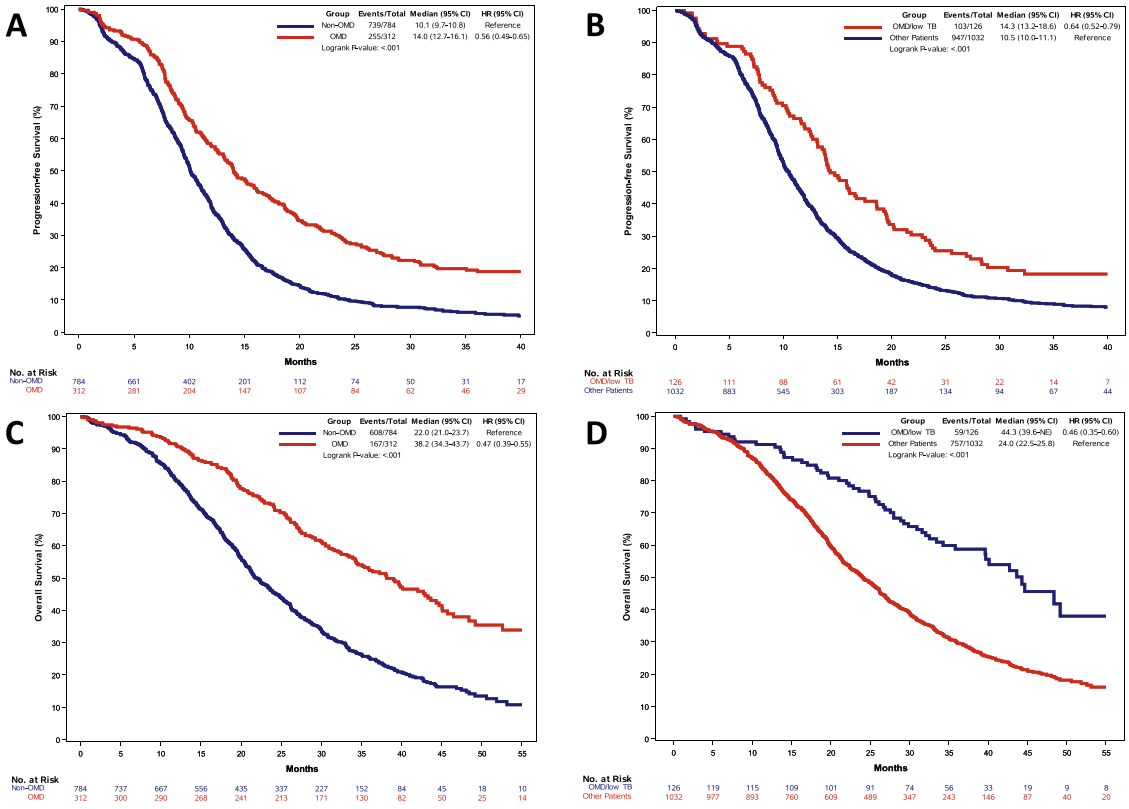

Fig. 1. Kaplan-Meier estimates of PFS in the OMD and non-OMD subgroups (panel A) and in the OMD/low TB and other patients subgroups (panel B); Kaplan-Meier estimates of OS in the OMD and non-OMD subgroups (panel C) and in the OMD/low TB and other patient subgroups (panel D). TB, tumour burden; PFS, progression-free survival; OMD, oligometastatic disease; OS, overall survival.

low TB, independently of their chance to undergo secondary resection. Patients with ascites and peritoneal [9], bone [10] and central nervous system [11] metastases were not included in the OMD subgroup due to the association of these metastatic sites with significantly poor prognosis. Based on the recommendations of a recent European consensus [4], we introduced two additional criteria: the highest diameter of metastases (up to 3 cm) and the maximum number of lesions per organ (up to 3). Although recognising that these choices were somehow arbitrary, a maximum diameter of 3 cm and a maximum number of three lesions per organ [12,13] are widely considered as conditions for the optimal efficacy of LRTs such as stereotactic body radiotherapy [14,15] and radiofrequency/microwave ablation [16,17].

Thirdly, TB and treatment's objective are included in the ESMO guidelines among other drivers of choice to modulate the intensity of the first-line therapy of patients with mCRC [2]. Particularly for right-sided and/or *RAS*-mutated tumours, it is suggested that intensified regimens should be adopted when cytoreduction is the primary objective of the first-line treatment (i.e. in the case of potentially resectable metastases or high TB), whereas less-intensive regimens could be preferred in the case when disease stabilisation is pursued and/or if the TB is low. Therefore, we investigated the impact of the intensification of the upfront chemotherapy in accordance with the extent of the metastatic spread and showed that the benefit provided by FOLFOXIRI/bev compared with doublets/bev did not significantly differ in the OMD *versus* non-OMD subgroups, or in the patients with OMD/low TB *versus* others. As a consequence, it appears that also patients with OMD and among these also those with limited TB do achieve benefit from an intensified upfront approach. Similarly, in a previous subgroup analysis of a phase III randomised trial of chemotherapy with or without cetuximab, the benefit of the addition of the antiepidermal growth factor receptor to chemotherapy did not differ in patients with liver-limited *versus* non–liver-limited disease [18], thus challenging the actual role of TB and treatment objective as determinants of the choice of the first-line therapy [18].

Finally, patients with OMD underwent LRTs with curative intent during first-line chemotherapy more frequently than those in the non-OMD group. LRTs with curative intent had a major positive effect on survival in all subgroups. In particular, median OS was >50 months in patients with OMD and, among patients undergoing radical LRTs, those who had limited TB at baseline achieved longer survival, probably also as the

Table 3
Locoregional treatments.

Study population N(%)	N = 1096			N = 1158		
	Non-OMD N = 784 (72)	OMD N = 312 (28)	p	Other patients N = 1032 (89)	OMD/low TB N = 126 (11)	p
First-line LRTs with curative intent						
Yes	78 (10)	121 (39)	<0.001	167 (16)	35 (28)	0.001
No	706 (90)	191 (61)		865 (84)	91 (72)	
LRTs population	N = 199			N = 202		
	Non-OMD N = 78 (39)	OMD N = 121 (61)	p	Other Patients N = 167 (83)	OMD/low TB N = 35 (17)	p
First-line LRTs with curative intent						
Surgery	52 (67)	92 (76)	0.353	122 (73)	24 (69)	0.045
RT/RFA	7 (9)	8 (7)		9 (5)	6 (17)	
Surgery and RT/RFA	19 (24)	21 (17)		36 (22)	5 (14)	
Patients progressed after first LRT	N = 67	N = 85	p	N = 128	N = 25	p
Further LRTs with curative intent						
Yes	13 (19)	22 (26)	0.348	24 (19)	13 (52)	<0.001
No	54 (81)	63 (74)		104 (81)	12 (48)	
Further LRTs with curative intent						
Surgery	4 (6)	12 (14)	0.442	12 (9)	6 (24)	0.005
RT/RFA	5 (7)	6 (7)		7 (6)	4 (16)	
Surgery and RT/RFA	4 (6)	4 (5)		5 (4)	3 (12)	
No further LRTs	54 (81)	63 (74)		104 (81)	12 (48)	

LRTs = locoregional treatments; N = number; OMD = oligometastatic disease; TB = tumour burden; p = chi-square or Fisher's exact test when appropriate; RT = radiotherapy; RFA = radiofrequency ablation.

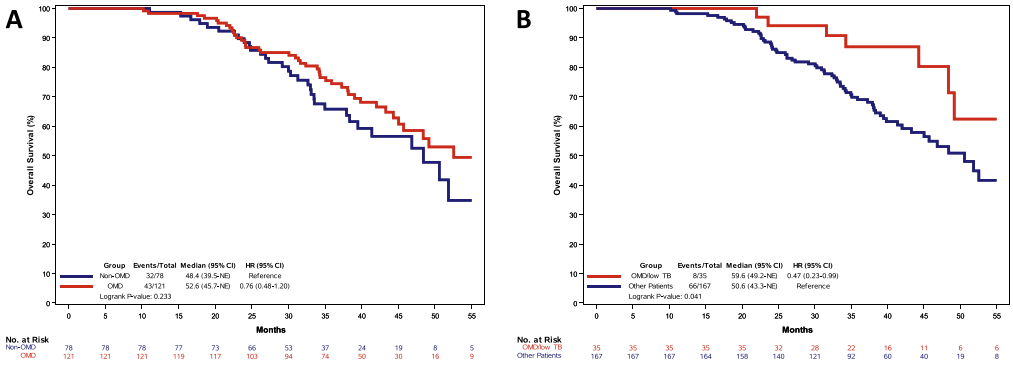

Fig. 2. Kaplan-Meier estimates of OS in the OMD and non-OMD subgroups (panel A) and in the OMD/low TB and other patient subgroups (panel B) among those undergoing first-line locoregional treatments. TB, tumour burden; OMD, oligometastatic disease; OS, overall survival.

result of the more frequent use of LRTs after the evidence of disease progression. At the same time, potentially curative LRTs may have been offered to patients with more favourable disease course independently of the initial extent of the metastatic spread. The high percentage of patients with metastases not confined to one organ [5,6] could have contributed to the rather low rate of patients undergoing radical LRTs also in the OMD (39%) and OMD/low TB (28%) subgroups. Moreover, around 60 oncology units took part to TRIBE and/or TRIBE2, thus reflecting the current landscape of treatment of these patients in a scenario close to the Italian real-life clinical practice.

Our study has some clear limitations including the retrospective nature of this unplanned subgroup analysis of two phase III trials and the inevitable arbitrariness of the definitions that were adopted. In particular, an objective definition of TB has never been proposed, and in our analysis, we were able to identify those patients with low TB within the subgroup of patients with OMD, that are reasonably the vast majority of patients defined at low TB in the common practice, but we acknowledge that a few patients deemed at low TB may not meet the criteria of OMD definition.

Our results may provide useful information for the daily practice: the clinical reliability of the ESMO definition of OMD, the positive impact of FOLFOXIRI/bev *versus* doublets/bev also in the OMD and low TB subgroups, the importance of LRTs in extending the survival of patients with mCRC and the special relevance of these approaches in patients with OMD where they can be usefully integrated in different steps of the therapeutic route.

Author contribution statement

Roberto Moretto: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Supervision. **Daniele Rossini:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization. **Gemma Zucchelli:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization. **Sara Lonardi:** Investigation, Resources, Writing - Review & Editing. **Francesca Bergamo:** Investigation, Resources, Writing - Review & Editing. **Daniele Santini:** Investigation, Resources, Writing - Review & Editing. **Samanta Cupini:** Investigation, Resources, Writing - Review & Editing. **Gianluca Tomasello:** Investigation, Resources, Writing - Review & Editing. **Salvatore Caponnetto:** Investigation, Resources, Writing - Review & Editing. **Alberto Zaniboni:** Investigation, Resources, Writing - Review & Editing. **Carlotta Antoniotti:** Investigation, Resources, Data Curation. **Filippo Pietrantonio:** Investigation, Resources, Writing - Review & Editing. **Angela Buonadonna:** Investigation, Resources, Writing - Review & Editing. **Federica Marmorino:** Investigation, Resources, Data Curation. **Roberto Bordonaro:** Investigation, Resources, Writing - Review & Editing. **Elena Fea:** Investigation, Resources, Writing - Review & Editing. **Emiliano Tamburini:** Investigation, Resources, Writing - Review & Editing. **Alessandra Boccaccino:** Investigation, Resources, Data Curation. **Roberta Grande:** Investigation, Resources, Writing - Review & Editing. **Giuseppe Aprile:** Investigation, Resources, Writing - Review & Editing. **Alfredo Falcone:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. **Chiara Cremolini:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Conflict of interest statement

S.L. reported receiving advisory board fees from Amgen, Eli Lilly, and Merck.

F.P. reports having declared Honoraria/speaker's bureau from Roche, Amgen, Merck Serono, Lilly, Sanofi, Bayer, Servier; has received research grants from BMS.

R.B. reports receiving fee payments by Bayer, Astra Zeneca, Sanofi, Novartis, Amgen, Roche, Pfizer, Janssen, Cilag, Bristol Meyers Squibb.

G.A. reports receiving personal fees and has been a consultant or played an advisory role with Merck Serono, Amgen, Roche, and Servier.

A.F. reports being a consultant/advisory board member for Bayer, Roche, Amgen, Eli Lilly, Merck Serono, Sanofi, Servier.

C.C. is a consultant/advisory board member for Roche, Amgen, Bayer, Merck Serono, Servier.

All the other authors have declared no conflicts of interest.

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Appendix A. Supplementary data

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