Real-world progression-free and overall survival of patients with metastatic colorectal cancer according to first and second-line treatment regimen: PROMETCO study

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INTRODUCTION

- Clinical emphasis for the treatment of unresectable metastatic colorectal cancer (mCRC) lies in avoidance of rapid disease evolution and prolonging survival.[1]
- Treatment advances have now improved median overall survival (OS) for mCRC patients to 30 months in clinical trials[1] and data on later line treatments such as trifluridine/tipiracil + bevacizumab and fruquintinib suggest OS can be prolonged further.[2,3]
- PROMETCO (NCT03935763) is the first international, prospective, real-world study to investigate the continuum of care in patients with mCRC after two disease progressions since diagnosis.
- PROMETCO provides an opportunity to assess treatment patterns and clinical outcomes according to first-line (1L) and second-line (2L) of treatment.

METHODS

- Enrolment in PROMETCO started in March 2019 and inclusion/exclusion criteria have been described previously.[4]
- At enrolment, patient data were collected retrospectively using electronic case report forms and the ClinInfo electronic data capture system[4] and were assessed prospectively for up to 18 months or until withdrawal or death.
- Data were analyzed by six different 1L/2L treatment groups: doublet/triplet chemotherapy (CT) + anti-vascular endothelial growth factor (VEGF) twice (CT+VEGF twice); doublet/triplet CT + anti-epidermal growth factor receptor (EGFR) and doublet/triplet CT+ anti-VEGF (any order; CT+EGFR/CT+VEGF); doublet/triplet CT alone twice (CT twice); doublet/triplet CT alone and doublet/triplet CT + anti-VEGF (any order; CT/CT+VEGF); doublet/triplet CT alone and doublet/triplet CT + anti-EGFR (any order; CT/CT+EGFR); any other treatment (other).
- Baseline data at diagnosis were collected, including patient and disease characteristics, treatment before PROMETCO inclusion, and the prognostic subgroups as defined by Tabernero et al.[5]
- Median progression-free survival (mPFS) and mOS are presented by treatment group and Kaplan-Meier calculations were used for analysis in the patient population that had completed the study as of 1st July 2023.
- OS was calculated from mCRC diagnosis or start of 3rd line treatment until death and PFS was assessed from 1L to fourth-line and was calculated from start date of treatment until outcome (progression or death due to any cause).

TAKE-HOME MESSAGES

- **Real-world data in PROMETCO show support for, and adherence to, ESMO guidelines.**
- **Patients who received CT alone had a shorter median OS than those treated with combo CT and targeted agents (including biologics).**
- **Most patients with *RAS* wild-type were treated with anti-EGFR, as recommended by guidelines, and this group had longer median OS.**
- **Third- and fourth-line median PFS was similar regardless of 1L and 2L treatment regimen.**

RESULTS

Baseline characteristics

- For this analysis, baseline characteristics from 655 mCRC patients (161 CT+VEGF twice, 117 CT+EGFR/CT+VEGF, 55 CT twice, 85 CT/CT+VEGF, 45 CT/CT+EGFR and 192 other) were collected (**Table 1**).
- Patients in the CT+VEGF twice and CT twice groups had a shorter time since diagnosis and a higher number of metastases at baseline, and patients with RAS wild-type were most frequent in treatment groups that received at least 1 line of treatment containing anti-EGFR (CT+EGFR/CT+VEGF and CT/CT+EGFR groups).
- The CT/CT+EGFR group had the lowest proportion of patients with Eastern Cooperative Oncology Group performance score (ECOG PS) 0 (20.0%) and the CT+EGFR/CT+VEGF group had the highest (50.0%).

Table 1. Baseline characteristics at diagnosis

Baseline characteristic	CT+VEGF twice (n=161)	CT+EGFR/CT+ VEGF (n=117)	CT twice (n=55)	CT/CT+VEGF (n=85)	CT/CT+EGFR (n=45)	Other (n=192)
Age, years, n (%)						
<70	91 (56.5)	76 (65.0)	37 (67.3)	52 (61.2)	28 (62.2)	110 (57.3)
≥70	70 (43.5)	41 (35.0)	18 (32.7)	33 (38.8)	17 (37.8)	82 (42.7)
Sex, n (%)						
Female	73 (45.3)	49 (41.9)	29 (52.7)	31 (36.5)	12 (26.7)	80 (41.7)
Male	88 (54.7)	68 (58.1)	26 (47.3)	54 (63.5)	33 (73.3)	112 (58.3)
ECOG PS, n (%)						
0	59 (37.8)	57 (50.0)	19 (35.8)	38 (46.3)	9 (20.0)	60 (31.7)
1	87 (55.8)	48 (42.1)	29 (54.7)	37 (45.1)	31 (68.9)	112 (59.3)
2/3	10 (6.2)	9 (7.7)	5 (9.4)	7 (8.5)	5 (11.1)	17 (8.6)
Prognosis subgroup, %*						
Poor prognosis characteristics	45.3	31.2	58.3	36.0	28.0	39.1
Good prognosis characteristics	40.9	57.8	25.0	40.5	46.0	40.0
Best prognosis characteristics	13.8	10.9	16.7	23.6	26.0	20.9
Metastatic site location, n (%)						
Liver	134 (83.2)	101 (86.3)	36 (65.5)	61 (71.8)	33 (73.3)	132 (68.8)
Lung	72 (44.7)	31 (26.5)	24 (43.6)	37 (43.5)	18 (40.0)	72 (37.5)
Other	25 (15.5)	20 (17.1)	11 (20.0)	11 (12.9)	11 (24.4)	57 (29.7)
Disease sidedness, n (%)						
Left	102 (63.4)	102 (87.2)	40 (72.7)	58 (68.2)	36 (80.0)	133 (69.3)
Right	64 (39.8)	16 (13.7)	15 (27.3)	27 (31.8)	10 (22.2)	60 (31.2)
Type of metastasis, n %						
Metachronous	33 (20.5)	27 (23.1)	19 (34.5)	35 (41.2)	15 (33.3)	92 (47.9)
Synchronous	128 (79.5)	90 (76.9)	36 (65.5)	50 (58.8)	30 (66.7)	100 (52.1)
***RAS/BRAF* status, n (%)**						
RAS mut	137 (85.1)	1 (0.9)	39 (70.9)	64 (75.3)	2 (4.4)	94 (49.0)
RAS wild-type	12 (7.5)	114 (97.4)	10 (18.2)	10 (11.8)	36 (80.0)	76 (39.6)
BRAF mut	6 (3.7)	2 (1.7)	2 (3.6)	6 (7.1)	1 (2.2)	22 (11.5)
BRAF wild-type	91 (56.5)	97 (82.9)	33 (60.0)	44 (51.8)	35 (77.8)	113 (58.9)
MSI/MSS status, n (%)						
MSI high	1 (0.6)	3 (2.6)	1 (1.8)	3 (3.5)	0 (0.0)	1 (0.5)
MSI low	6 (3.7)	5 (4.3)	5 (9.1)	0 (0.0)	2 (4.4)	6 (3.1)
MSS	103 (64.0)	51 (43.6)	27 (49.1)	46 (54.1)	15 (33.3)	113 (58.9)
Unknown	51 (31.7)	58 (49.6)	22 (40.0)	36 (42.4)	28 (62.2)	72 (37.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; max, maximum; mCRC, metastatic colorectal cancer; min, minimum; MSI, microsatellite instability; MSS, microsatellite stable; mut, mutant; WT, wild-type.
*Good prognosis characteristics [GPC], defined as having <3 metastatic sites at study entry and ≥18 months from diagnosis of metastatic disease to study entry, best prognosis characteristics [BPC; subgroup of GPC who also had no liver metastasis], and the remaining patients had poor prognosis characteristics [PPC].[5]

Prior treatment

- Most patients received colorectal surgery before inclusion in PROMETCO, most frequently in patients in the CT/CT+VEGF group (**Table 2**).
- Previous radiotherapy was most frequent in patients in the CT twice group (**Table 2**).

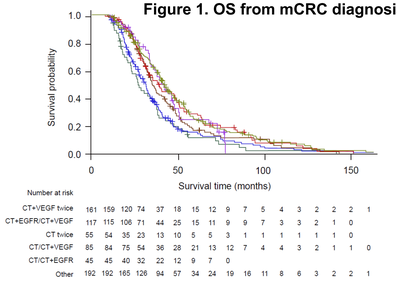
Table 2. Treatment before PROMETCO inclusion

	CT+VEGF twice (n=161)	CT+EGFR/CT+ VEGF (n=117)	CT twice (n=55)	CT/CT+VEGF (n=85)	CT/CT+EGFR (n=45)	Other (n=192)
Surgery before PROMETCO inclusion, n (%)						
Colorectal	88 (54.7)	76 (65.0)	25 (45.5)	62 (72.9)	28 (62.2)	140 (72.9)
Liver	18 (11.2)	26 (22.2)	7 (12.7)	27 (31.8)	9 (20.0)	45 (23.4)
Lung	3 (1.9)	1 (0.9)	4 (7.3)	7 (8.2)	2 (4.4)	9 (4.7)
Radiotherapy before PROMETCO inclusion, n (%)	23 (14.3)	19 (6.2)	18 (32.7)	23 (27.1)	12 (26.7)	155 (23.7)

Efficacy outcomes

- Patients in the CT twice group have a trend towards shorter OS from mCRC diagnosis than patients who received doublet/triplet therapy with targeted agents (including biologics) (**Figure 1**).
- Patients may gain additional benefit from having an anti-EGFR and an anti-VEGF rather than an anti-VEGF twice (**Figure 1**).
- Patient groups that had a higher percentage of patients with poor prognosis characteristics (CT+VEGF twice and CT twice groups; **Table 1**) had a trend towards shorter mOS from mCRC diagnosis (**Figure 1**) and from third-line treatment (**Figure 2**) than other groups.

Figure 1. OS from mCRC diagnosis according to first and second treatment line

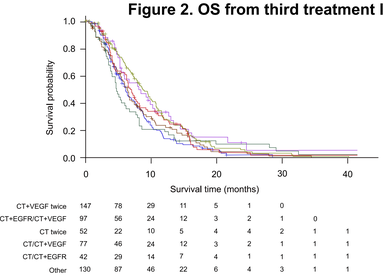


	Event, n	Median OS, months (95% CI)
CT+VEGF twice (n=161)	135	31.2 (27.3-33.5)
CT+EGFR/CT+VEGF (n=117)	100	35.0 (32.0-41.7)
CT twice (n=55)	50	26.7 (22.7-36.5)
CT/CT+VEGF (n=85)	74	38.3 (32.4-48.6)
CT/CT+EGFR (n=45)	36	41.9 (34.4-47.9)
Other (n=192)	155	41.6 (39.1-46.4)

CI, confidence interval; max, maximum; min, minimum; OS, overall survival.

- Patients in the CT twice group have a trend towards shorter OS from third-line treatment than patients who received doublet/triplet therapy with targeted agents (including biologics) (**Figure 2**).
- A trend towards longer mOS was seen in patients in the CT/CT+EGFR group (**Figure 2**).

Figure 2. OS from third treatment line according to first and second treatment line

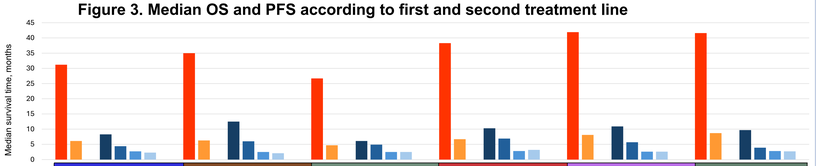


	Event, n	Median OS, months (95% CI)
CT+VEGF twice (n=161)	125	6.1 (5.3-7.3)
CT+EGFR/CT+VEGF (n=117)	84	6.3 (5.3-7.4)
CT twice (n=55)	47	4.7 (3.9-6.1)
CT/CT+VEGF (n=85)	67	6.7 (6.0-8.1)
CT/CT+EGFR (n=45)	35	8.1 (5.4-10.5)
Other (n=192)	108	8.7 (7.3-10.6)

CI, confidence interval; max, maximum; min, minimum; OS, overall survival.

- Patients in the CT+EGFR/CT+VEGF group had a trend towards longer PFS in the first treatment line, and patients in the CT twice group had the shortest (**Figure 3**).
- PFS in third- and fourth-line treatment is similar regardless of first and second treatment lines (**Figure 3**).

Figure 3. Median OS and PFS according to first and second treatment line



	CT+VEGF twice (n=161)	CT+EGFR/CT+VEGF (n=117)	CT twice (n=55)	CT/CT+VEGF (n=85)	CT/CT+EGFR (n=45)	Other (n=192)
OS from mCRC diagnosis	31.2 (27.3-33.5)	35.0 (32.0-41.7)	26.7 (22.7-36.5)	38.3 (32.4-48.6)	41.9 (34.4-47.9)	41.6 (39.1-46.4)
OS from 3L	6.1 (5.3-7.3)	6.3 (5.3-7.4)	4.7 (3.9-6.1)	6.7 (6.0-8.1)	8.1 (5.4-10.5)	8.7 (7.3-10.6)
PFS from 1L	8.3 (1.4-87.4)	12.5 (0.6-87.8)	6.1 (0.1-22.7)	10.3 (0.0-81.6)	10.9 (0.8-34.6)	9.7 (0.2-43.3)
PFS from 2L	4.4 (0.0-29.5)	6.0 (0.3-51.5)	4.9 (0.5-28.2)	6.9 (0.5-53.2)	5.7 (0.6-24.2)	3.9 (0.1-68.7)
PFS from 3L	2.7 (0.1-11.5)	2.5 (0.1-17.4)	2.5 (0.2-44.7)	2.8 (0.2-44.7)	2.6 (0.3-11.1)	2.8 (0.0-13.4)
PFS from 4L	2.3 (0.5-12.1)	2.1 (0.5-12.1)	2.5 (1.6-6.2)	3.2 (0.1-14.9)	2.6 (0.2-12.3)	2.7 (0.3-28.4)

OS, overall survival; mCRC, metastatic colorectal cancer; PFS, progression-free survival; 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line.
OS presented as months (95% CI), PFS presented as months (range)

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