

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Min, ST;Roohullah, A;Tognela, A;Jalali, A;Lee, M;Wong, R;Shapiro, J;Burge, M;Yip, D;Nott, L;Zimet, A;Lee, B;Dean, A;Steel, S;Wong, HL;Gibbs, P;Lim, SHS

Title:

Patient demographics and management landscape of metastatic colorectal cancer in the third-line setting: Real-world data in an australian population

Date:

2022-04-01

Citation:

Min, S. T., Roohullah, A., Tognela, A., Jalali, A., Lee, M., Wong, R., Shapiro, J., Burge, M., Yip, D., Nott, L., Zimet, A., Lee, B., Dean, A., Steel, S., Wong, H. L., Gibbs, P. & Lim, S. H. S. (2022). Patient demographics and management landscape of metastatic colorectal cancer in the third-line setting: Real-world data in an australian population. *Asia Pacific Journal of Clinical Oncology*, 18 (2), pp.e56-e63. <https://doi.org/10.1111/ajco.13553>.

Persistent Link:

<https://hdl.handle.net/11343/298461>

Title Page

Title

Patient Demographics and Management Landscape of Metastatic Colorectal Cancer in the Third-line Setting: real-world data in an Australian Population

Tun Min S, Roohullah A, Tognela A, Jalali A, Lee M, Wong R, Shapiro J, Burge M, Yip D, Nott L, Zimet A, Lee B, Dean A, Steel S, Wong HL, Gibbs P, Lim SHS

Authors and Affiliations

Sandy Tun Min

- Macarthur Cancer Therapy Centre, Campbelltown, New South Wales 2560 Australia

Aflah Roohullah

- Macarthur Cancer Therapy Centre, Campbelltown, New South Wales 2560 Australia
- School of Medicine, Western Sydney University, Campbelltown, New South Wales 2560 Australia

Annette Tognela

- Macarthur Cancer Therapy Centre, Campbelltown, New South Wales 2560 Australia
- School of Medicine, Western Sydney University, Campbelltown, New South Wales 2560 Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajco.13553](https://doi.org/10.1111/ajco.13553).

This article is protected by copyright. All rights reserved.

Azim Jalali

- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Department of Medical Oncology, Western Health, St Albans, Victoria 3021 Australia

Margaret Lee

- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Department of Medical Oncology, Western Health, St Albans, Victoria 3021 Australia
- Department of Medical Oncology, Eastern Health, Box Hill, Victoria 3128 Australia

Rachel Wong

- Department of Medical Oncology, Eastern Health, Box Hill, Victoria 3128 Australia
- Department of Medicine, Monash University, Clayton, Victoria 3800 Australia
- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Epworth HealthCare, Box Hill, Victoria 3128 Australia

Jeremy Shapiro

- Cabrini Haematology and Oncology Centre, Malvern, Victoria 3144 Australia
- Department of Medicine, Monash University, Clayton, Victoria 3800 Australia

Matthew Burge

- Royal Brisbane and Women's Hospital, Herston, Queensland 4029 Australia
- Faculty of Medicine, University of Queensland, St Lucia, Queensland 4072 Australia

Desmond Yip

- Department of Medical Oncology, Canberra and Calvary Hospitals, Garran, Australia Capital Territory 2605 Australia

Louise Nott

- Royal Hobart Hospital, Hobart, Tasmania 7000 Australia

Allan Zimet

- Epworth HealthCare, Richmond, Victoria 3121 Australia

Belinda Lee

- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Peter MacCallum Cancer Centre, Melbourne, Victoria 3000 Australia
- The Northern Hospital, Epping, Victoria 3076 Australia

Andrew Dean

- Department of Medical Oncology, St John of God Hospital, Subiaco, Western Australia 6008 Australia

Simone Steel

- Peninsula Private Hospital, Frankston, Victoria 3199 Australia

Hui-Li Wong

- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Peter MacCallum Cancer Centre, Melbourne, Victoria 3000 Australia

Peter Gibbs

- Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria 3052 Australia
- Department of Medical Oncology, Western Health, St Albans, Victoria 3021 Australia
- Department of Medical Oncology, Royal Melbourne Hospital, Parkville, Victoria 3050 Australia

- Faculty of Medicine, University of Melbourne, Parkville, Victoria 3010 Australia

Stephanie Hui-Su Lim

- Macarthur Cancer Therapy Centre, Campbelltown, New South Wales 2560 Australia
- School of Medicine, Western Sydney University, Campbelltown, New South Wales 2560 Australia
- Ingham Institute for Applied Medical Research, Liverpool, New South Wales 2170 Australia

Short Running Title

Third-line treatment of Colorectal Cancer

Corresponding author contact details

Sandy Tun Min

Address: Macarthur Cancer Therapy Centre

Campbelltown Hospital

Therry Road Campbelltown NSW 2560

Ph: +61432415894

Email: sandy.tunmin@gmail.com

Funding and Acknowledgements

The TRACC database is supported by Roche Products Pty Limited (Australia); Roche has provided financial assistance for the development, installation and maintenance of this clinical database.

Sincere thanks to Michael Harold and Julie Johns, for assistance with data extractions.

Conflict of Interest

All authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available upon request from the corresponding author. This is subject to the approval and permission from Melbourne Health Research and Ethics Committee and data custodians of each participating sites.

Abstract and Keywords

Abstract

Background: Colorectal cancer is the third most common cancer and second leading cause of cancer mortality in Australia, thus carrying a significant disease burden.

Aims: This analysis aims to explore real-world treatment landscape of metastatic colorectal cancer in the third-line setting.

Methods: We retrospectively analysed TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry database from 2009 onwards. Patients treated with palliative intent who progressed after two lines of therapies were included. One treatment line was defined as any combination of systemic therapy given until progression.

Results: Out of 1820 patients treated palliatively, 32% (590 patients) met study criteria. Of these, 43% (254 patients) proceeded to third-line therapy, equating to 14% of all metastatic patients. In *KRAS* mutant or unknown tumours (97 patients), fluoropyrimidine (FP)-oxaliplatin combination was the most common choice (51%), followed by FP-irinotecan (15%), trifluridine/tipiracil (11%), mono-chemotherapy (10%), regorafenib (5%) and others (7%).

Majority of FP-doublet (83%) was given as rechallenge. In 157 patients with *KRAS* wildtype disease, monotherapy with EGFR inhibitor was most commonly used (41%), followed by EGFR inhibitor with chemotherapy (20%), FP-doublet (18%), mono-chemotherapy (6%), trifluridine/tipiracil (6%), regorafenib (1%) and others (8%). Median overall survival was 7.1 months (range 0.4 – 41.2), and median time on third-line treatment was 3 months (range 0.1 – 40).

Conclusions: In real-world Australian population, treatment choices differed based on *KRAS* status and will likely change with the availability of newer drugs on the Pharmaceutical Benefits Scheme. Survival outcomes are comparable to newer agents in clinical trials for select patients.

Keywords

Metastatic colorectal cancer

Real-world practice

Rechallenge

Registry data

Third-line treatment

Main Text

1. INTRODUCTION

Colorectal cancer carries a significant burden of disease. It is the third most common cancer and second leading cause of cancer mortality in Australia and worldwide.^{1,2} In 2018, Australian Institute of Health and Welfare estimated over 17,000 new cases of colorectal cancer and 4100 associated deaths, resulting in 92,400 disability-adjusted life years (DALYs) lost.² Of all colorectal cancer diagnoses, 18% are identified at a late stage, which has a poor prognosis with a 5-year survival of around 13%.²

Active chemotherapeutic agents such as fluoropyrimidines (FP), oxaliplatin and irinotecan, used either in combination or as single agents, have been shown to improve survival.^{3–7} Typically, fluoropyrimidine doublet combinations with oxaliplatin or irinotecan are used as the first or second-line therapies for metastatic colorectal cancer with similar efficacy but differing toxicity profiles.^{8,9} Triplet combination chemotherapy leads to improved response rates and survival.^{10–13} However, clinicians remain wary of the associated toxicity. Molecular data, specifically *RAS* and *BRAF* mutational status, inform the use of biologic agents, along with primary tumour sidedness. Monotherapy with EGFR inhibitors cetuximab and panitumumab have shown efficacy in the chemorefractory disease setting, and the addition of anti-EGFR agents to a chemotherapy backbone improves survival in previously untreated patients with left-sided *RAS* wild-type tumours.^{14–18} Rationally targeted combination strategies against *BRAF* V600E mutant cancers have also shown a survival benefit.^{19,20} In a pooled analysis of seven randomised controlled trials, the angiogenesis inhibitor bevacizumab has been shown to reduce risk of death by 19% when used in combination with a chemotherapy backbone as first-line treatment of metastatic colorectal cancer.²¹

Beyond second-line therapy, there are a variety of treatment approaches but comparative trials evaluating one option against another are lacking. Clinicians hence determine suitable management strategies depending on molecular characteristics of the tumour, prior treatments or toxicities, and access to chemotherapeutics or clinical trials in their practising country. Trifluridine/tipiracil and regorafenib both improve survival by 1.4 to 2.5 months in pre-treated colorectal cancer irrespective of mutation status.^(22–24) In the 4–5% of metastatic colorectal cancers with microsatellite instability, immune checkpoint inhibitors such as ipilimumab, nivolumab and pembrolizumab have shown activity across lines of therapy, with objective response rates of 33–55% with combination immunotherapy in the chemorefractory population.^{25–27} Although rechallenging with previously used agents on which patients have developed progression is a recognised strategy, evidence for this treatment approach is limited to small or observational studies focused on either oxaliplatin or cetuximab-based treatment.^{28–31}

For patients who have progressed beyond two lines of chemotherapy, access to appropriate therapies can be challenging. In Australia, The Pharmaceutical Benefits Scheme (PBS) enables access to many expensive new therapies that many patients would otherwise struggle to afford.³² An independent committee of experts (Pharmaceutical Benefits Advisory Committee) assesses efficacy and cost-effectiveness of a drug before making recommendations to list a chemotherapeutic agent on the PBS schedule.³³ This process is not immediate and some drugs ultimately do not achieve a PBS listing. Current, self-funded non-reimbursed options include regorafenib (unselected patients), *BRAF* targeted therapy and immunotherapy (for mismatch repair deficient tumours).^{20,22,25–27} Here, we examine the real-world patient demographics and treatment landscape of metastatic colorectal cancer in the third-line setting over the last decade.

2. METHODS

Data was obtained from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry³⁴, which is a database maintained by BioGrid Australia. All participating sites across Australia, as shown in Table 1, prospectively collected and entered data on patients with metastatic colorectal cancer. Patients were eligible for inclusion in the current study if they had received treatment with palliative intent, and had progressed after two lines of therapy.

We retrospectively extracted and analysed clinical information from the registry from July 2009 through to July 2019. One line of treatment was defined as any systemic therapy administered until disease progression. A change in treatment due to toxicity or a change in the components of the therapy, for example, switching to maintenance therapy, were considered as the same line of treatment. Individual patient data, particularly on each recorded line of treatment, were analysed to ensure the above definition of “line of treatment” was met. Descriptive statistics were used to examine patient demographics, tumour characteristics including mutational status, details of third-line treatment, time on each line of therapy, and survival. The Kaplan-Meier method was used to assess time to progression and overall survival. Statistical analyses were performed using Stata software, version 15.1. Ethics approval for this project was obtained from the Melbourne Health Research and

Ethics Committee (HREC/18/MH/28) and BioGrid Scientific Advisory Committee (Project ID 201902/4).

3. RESULTS

3.1 Patients proceeding to third-line treatment

3.1.1 Characteristics

Between July 2009 to July 2019, 2883 patients with metastatic colorectal cancer were enrolled in the TRACC registry. We excluded 1063 patients (37%) who had undergone a metastasectomy or were planned for a metastasectomy. Of the remaining 1820 patients who were initially treated with palliative intent, 590 patients (32%) had disease progression after receiving two lines of treatment, and were included in our analysis. Third-line therapy was administered to 254 patients (43%), equating to 14% of all patients with metastatic disease who were treated palliatively. Figure 1 shows the breakdown of patients.

The characteristics of patients who received third-line therapy are shown in Table 2. Median age was 62 years (range 24-85 years), and they were predominantly male (64%). Almost three-quarters (178 patients) had metastatic disease at the time of initial diagnosis of colorectal cancer. Of the 74 who had metachronous disease (a preceding history of early stage colorectal cancer, separate to time of diagnosis of metastatic disease), 49 patients (66%) had received adjuvant chemotherapy. The site of primary tumour was left-sided colon in 107 patients (42%), rectum in 72 patients (28%), right-sided colon in 66 patients (26%), and multi-sites or unspecified in 9 patients (4%). At the start of third-line treatment, majority of patients (82%) had a good performance status (ECOG 0-1), with 14% being ECOG 2 and 3% being ECOG 3.

Data on *KRAS* mutation status was available in 96% of patients. *KRAS* wild-type tumour was found in 157 patients (62%) and *KRAS* mutant colorectal cancer was diagnosed in 87 patients (34%). No data was entered for 10 patients. The use of next generation sequencing and targeted genomic panels has evolved over time, and so has the definition of *KRAS* mutant (exon 2 only versus extended *KRAS*). *NRAS* and *BRAF* mutations were not routinely

tested in the earlier years of the registry. Hence, *NRAS* and *BRAF* data was only available in 43% and 55% of the patients respectively.

3.1.2 Third-line treatment regimens

All three standard cytotoxic agents (FP, oxaliplatin and irinotecan) were given during the first two treatment lines in 197 patients (78%), with the majority (213 patients or 84%) also receiving bevacizumab. Of the 157 patients who had *KRAS* wild-type tumours, 117 patients (75%) did not receive EGFR inhibitors in the first or second-line setting.

As shown in Figure 2, out of the 97 patients with *KRAS* mutant or unknown colorectal cancer, FP-oxaliplatin combination was the most common third-line choice (51%), followed by FP-irinotecan doublet (16%), trifluridine/tipiracil (11%), mono-chemotherapy with either FP or irinotecan (10%), regorafenib (5%) and others (7%). Other treatment regimens included mitomycin C and capecitabine (n=4), aflibercept (n=1), and enrolment in clinical trials (n=2). In the majority of the 97 *KRAS* mutant or unknown patients, the FP-doublet combination (83%) was given as a rechallenge.

For the 157 patients with *KRAS* wild-type cancers, monotherapy with anti-EGFR therapy was the most favoured treatment option used in 41% as third-line treatment. EGFR inhibitors in combination with cytotoxic chemotherapy were the second most common choice (20%), followed by FP-doublet (18%), mono-chemotherapy with either FP or irinotecan (6%), trifluridine/tipiracil (6%), regorafenib (1%) and other less commonly utilised regimens (8%). The latter comprised mitomycin C and capecitabine (n=6), immunotherapy (n=2), and clinical trial enrolment (n=4).

3.1.3 Treatment durations and overall survival

In the cohort of patients who received third-line therapy, median overall survival was 7.1 months (range 0.4 – 41.2 months), as demonstrated in Figure 3. Median duration on third-line treatment was 3 months (range 0.1 – 40 months). Eight patients were receiving ongoing therapy at the time of data cut-off. Median duration on first line-therapy was 7.3 months (range 0.2 – 50 months), and median duration on second-line was 4.4 months (range 0.7 – 26 months).

In the subgroup of patients with *KRAS* mutant and unknown cancers, median overall survival was 5.9 months (range 1 – 18.5 months), and median duration on third-line therapy was 2.3 months (range 0.1 – 11.7 months), as illustrated in Figures 4 and 5. For patients who were rechallenged with FP-doublet, the median overall survival and median duration on treatment were 5.9 months (range 1 – 16.7 months) and 1.8 months (range 0.1 – 8.8 months) respectively.

As shown in Figures 4 and 5, median overall survival was 8.2 months (range 0.4 – 41.2 months), and median duration on third-line treatment was 3.2 months (range 0.1 – 40 months) for patients with *KRAS* wild-type tumours.

3.2 Patients not receiving third-line treatment

3.2.1 Characteristics

Of the 590 patients who progressed after two lines of palliative treatment, 336 patients did not receive third-line therapy. The median age of this cohort was 64 years (range 26-90 years), and 60% (200 patients) were male. De-novo metastatic disease was diagnosed in 70% (234 patients), and of the 101 patients who had metachronous disease, 72 patients (71%) received adjuvant chemotherapy. The site of primary tumour was left-sided colon in 119 patients (35%), right-sided colon in 111 patients (33%), rectum in 89 patients (27%), and unspecified in 17 patients (5%).

KRAS was mutated in 142 patients (42%) and wild-type in 154 patients (46%); no data was available for 40 patients (12%). Similar to the cohort that received third-line treatment, data were limited for *NRAS* and *BRAF* mutation status in this group of patients who did not proceed to third-line treatment.

3.2.2 Treatment durations and overall survival

For 336 patients who did not receive third-line treatment, median overall survival after progression on second-line was 2.3 months (range 0.03 – 28.2 months). Median duration on

first-line treatment was 6.8 months (range 0.1 – 43.7 months), and median duration on second-line was 2.5 months (range 0.1 – 22.3 months).

4. DISCUSSION

Beyond second-line therapy for metastatic colorectal cancer, treatment options differ depending on molecular characteristics, prior therapies and toxicities, and drug availability.

In a real-world Australian population, 14% of all metastatic patients treated with palliative intent proceeded to receive third-line treatment based on real-time registry data. This proportion excludes patients currently receiving second-line treatment as they were not part of this analysis and may be an underestimation of the true numbers. Patient demographics in our analysis are similar to those reported in clinical trials in the third-line setting. Median age was 62 years and patients were predominantly male. Majority of the patients had good performance status (ECOG 0-1), but it is interesting to note that 14% consisted of less robust patients with ECOG 2 who would be excluded from most clinical trials. Baseline characteristics of the patients who received third-line treatment and those who did not were similar with regard to age and gender. However, we noted that a numerically higher proportion of patients had *KRAS* wild-type tumours (61%) in the group that proceeded to third-line therapy compared to the group that did not (46%). Additionally, there were also numerically more patients with right-sided cancers who did not receive third-line treatment (33% compared to 26% of those who received third-line treatment). These observations may reflect the poor prognosis generally associated with these tumours.^{35–37}

We found that rechallenging with FP-doublet cytotoxic chemotherapy was the most commonly chosen treatment option for *KRAS* mutant colorectal cancer in the third-line setting, whilst EGFR inhibitors were most commonly used for *KRAS* wild-type tumours. This treatment landscape is likely influenced by several factors that have evolved over time, in particular, access to newer drugs such as regorafenib and trifluridine/tipiracil, which was only introduced on the PBS in December 2018. It is anticipated that the rechallenge strategy may be replaced by increasing uptake of trifluridine/tipiracil in the third-line setting as clinicians become more familiar with this option. For *RAS* wild-type cancers, the use of EGFR inhibitors in second or third-line was approved on PBS in September 2011, and its use in the

first-line setting only in June 2015.³⁸ Higher EGFR inhibitor use in the third-line setting likely reflects temporal drug reimbursement status. In addition, this would also account for the high percentage of patients with *KRAS* wild-type tumours proceeding to third-line therapy without having received an EGFR inhibitor. The change in the pattern of EGFR inhibitor use over time is of interest, but initial analysis of the TRACC data showed limited uptake in the first-line setting.³⁹

The median overall survival for all patients treated with third-line therapy was 7.1 months and is comparable to survival times in clinical trials of third-line agents. Our analysis also demonstrated that in the *KRAS* wild-type subgroup, longer median overall survival was achieved. In most clinical trials, this population of patients would be treated with EGFR inhibitors in the first or second-line settings whereas most patients in our analysis were not anti-EGFR therapy refractory. Rechallenging with FP-doublet chemotherapy in our cohort of patients shows comparable survival times to trials in newer efficacious agents, therefore the continued use of this strategy may still be appropriate in select patients. However, this approach may be mitigated by drug toxicity, especially in the case for oxaliplatin which is associated with cumulative dose-related neurotoxicity.⁴⁰ Other novel strategies currently being investigated include combining immunotherapy with targeted agents such as TRK-protein inhibitors, depending on mismatch repair status and presence of TRK proteins.^{25,26,41}

This study gives us insight into the real-world practice of Australian clinicians in the management of metastatic colorectal cancer in the third-line setting over the last decade, and survival outcomes. Limitations of this analysis includes errors and nuanced differences in data entry, data availability based on changes in molecular sequencing, drug access over time, and unintentional selection bias. Terms such as 'lines' of therapy are subject to interpretation in cases which are less clear-cut, however we did look through individual patient data hence this should have been avoided.

Future work proposed includes exploring the use and efficacy of EGFR inhibitor rechallenge, once EGFR inhibitor use becomes more common place in the first-line setting. Translational and early clinical studies show that rechallenging with anti-EGFR therapy may be effective once the resistant clones have declined and sensitive clones repopulate with a break from treatment.^{42,43}

5. CONCLUSION

In conclusion, our study provides valuable insight into real-world data over the last 10 years in the Australian practice of treatment of metastatic colorectal cancer in the third-line setting, with good outcomes observed and identified a select cohort of patients in which a rechallenging strategy may be efficacious. This treatment landscape will likely change with the availability of newer drugs on the Pharmaceutical Benefits Scheme.

References

1. International Agency for Research on Cancer [homepage on internet]. Cancer Fact Sheets. 2018 [cited 2019 Dec 25]. Available from: <http://gco.iarc.fr/today/fact-sheets-cancers>
2. Australian Institute of Health and Welfare [homepage on internet]. Colorectal and other digestive-tract cancers. Canberra: AIHW; 2018 [cited 2019 Apr 20]. Available from: <https://www.aihw.gov.au/reports/cancer/colorectal-other-digestive-tract-cancers/contents/table-of-contents>
3. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**: 2938–2947.
4. Douillard JY, V-303 Study Group. Irinotecan and high-dose fluorouracil/leucovorin for metastatic colorectal cancer. *Oncology (Williston Park)* 2000; **14**: 51–55.
5. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; **19**: 2282–2292.

6. Thirion P, Michiels S, Pignon JP, Buyse M, Braud AC, Carlson RW, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: an updated meta-analysis. *J Clin Oncol* 2004; **22**: 3766–3775.
7. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2006–2012.
8. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**: 229–237.
9. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; **23**: 4866–4875.
10. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670–1676.
11. Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, Baldi G, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. *J Natl Cancer Inst* 2011; **103**: 21–30.
12. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer. *N Engl J Med* 2014; **371**: 1609–1618.
13. Cremolini C, Antoniotti C, Lonardi S, Bergamo F, Cortesi E, Tomasello G, et al. Primary Tumor Sidedness and Benefit from FOLFOXIRI plus Bevacizumab as Initial Therapy for Metastatic Colorectal Cancer. Retrospective analysis of the TRIBE trial by GONO. *Ann Oncol* 2018; **29**: 1528-1534.
14. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337–345.

15. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007; **25**: 1658–1664.
16. Douillard J-Y, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; **28**: 4697–4705.
17. Van Cutsem E, Köhne C-H, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; **29**: 2011–2019.
18. Qin S, Li J, Wang L, Xu J, Cheng Y, Bai Y, et al. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. *J Clin Oncol* 2018; **36**: 3031–3039.
19. Kopetz S, McDonough SL, Morris VK, Lenz H-J, Magliocco AM, Atreya CE, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). *J Clin Oncol* 2017; **35**: 520–520.
20. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. *N Engl J Med* 2019; **381**: 1632–1643.
21. Hurwitz HI, Tebbutt NC, Kabbinavar F, Giantonio BJ, Guan Z-Z, Mitchell L, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. *Oncologist* 2013; **18**: 1004–1012.
22. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303–312.
23. Li J, Qin S, Xu R, Yau TCC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated

metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015; **16**: 619–629.

24. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *N Engl J Med* 2015; **372**: 1909–1919.
25. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509–2520.
26. Overman MJ, Lonardi S, Wong KYM, Lenz H-J, Gelsomino F, Aglietta M, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol* 2018; **36**: 773–779.
27. Le DT, Kim TW, Van Cutsem E, Geva R, Jäger D, Hara H, et al. Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol* 2020; **38**: 11–19.
28. Gebbia V, Del Prete S, Borsellino N, Ferraù F, Tralongo P, Verderame F, et al. Efficacy and safety of cetuximab/irinotecan in chemotherapy-refractory metastatic colorectal adenocarcinomas: a clinical practice setting, multicenter experience. *Clin Colorectal Cancer* 2006; **5**: 422–428.
29. Lièvre A, Samalin E, Mitry E, Assenat E, Boyer-Gestin C, Lepère C, et al. Bevacizumab plus FOLFIRI or FOLFOX in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study. *BMC Cancer* 2009; **9**: 347.
30. Suenaga M, Mizunuma N, Matsusaka S, Shinozaki E, Ozaka M, Ogura M, et al. Phase II study of reintroduction of oxaliplatin for advanced colorectal cancer in patients previously treated with oxaliplatin and irinotecan: RE-OPEN study. *Drug Des Devel Ther* 2015; **9**: 3099–3108.
31. Matsuda C, Honda M, Tanaka C, Fukunaga M, Ishibashi K, Munemoto Y, et al. Multicenter randomized phase II clinical trial of oxaliplatin reintroduction as a third- or later-line therapy for metastatic colorectal cancer-biweekly versus standard triweekly XELOX (The ORION Study). *Int J Clin Oncol* 2016; **21**: 566–572.
32. Australian Government Department of Health [homepage on internet]. About the PBS. Australian Government Department of Health [updated 2020 Jan 1; cited 2020 Jan 4]. Available from: <http://www.pbs.gov.au/info/about-the-pbs>

33. Australian Government Department of Health [homepage on internet]. Pharmaceutical Benefits Advisory Committee (PBAC) Membership. Australian Government Department of Health [updated 2019 June 21; cited 2020 Jan 4]. Available from: <http://www.pbs.gov.au/info/industry/listing/participants/pbac>
34. Field K, Wong H-L, Shapiro J, Kosmider S, Tie J, Bae S, et al. Developing a national database for metastatic colorectal cancer management: perspectives and challenges. *Intern Med J* 2013; **43**: 1224–1231.
35. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference Between Left-Sided and Right-Sided Colorectal Cancer: A Focused Review of Literature. *Gastroenterology Res* 2018; **11**: 264–273.
36. Nakagawa-Senda H, Hori M, Matsuda T, Ito H. Prognostic impact of tumor location in colon cancer: the Monitoring of Cancer Incidence in Japan (MCIJ) project. *BMC Cancer* 2019; **19**: 431.
37. Lee JM, Han YD, Cho MS, Hur H, Min BS, Lee KY, et al. Impact of tumor sidedness on survival and recurrence patterns in colon cancer patients. *Ann Surg Treat Res* 2019; **96**: 296–304.
38. Australian Government Department of Health [homepage on internet]. Cetuximab, panitumumab and bevacizumab for metastatic colorectal cancer. Australian Government Department of Health; 2018 [updated 2018 Aug 22; cited 2020 Mar 3]. Available from: <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2018-02/metastatic-colorectal-cancer-february-2018>
39. Semira C, Wong H-L, Field K, Lee M, Lee B, Nott L, et al. Chemotherapy and biologic use in the routine management of metastatic colorectal cancer in Australia: is clinical practice following the evidence? *Intern Med J* 2019; **49**: 446–454.
40. Park SB, Lin CSY, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC. Long-Term Neuropathy After Oxaliplatin Treatment: Challenging the Dictum of Reversibility. *Oncologist* 2011; **16**: 708–716.
41. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018; **378**: 731–739.
42. Parseghian CM, Loree JM, Morris VK, Liu X, Clifton KK, Napolitano S, et al. Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge. *Ann Oncol* 2019; **30**: 243–249.

43. Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, et al. Rechallenge for Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan: A Phase 2 Single-Arm Clinical Trial. *JAMA Oncol* 2019; **5**: 343–350.

Tables

Table 1: Participating sites for the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry.

Participating sites for TRACC registry
South West Sydney Local Health District, Sydney, New South Wales, Australia
Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
Eastern Health, Box Hill, Victoria, Australia
Western Health, Footscray, Victoria, Australia
Cabrini Health, Malvern, Victoria, Australia
Royal Brisbane Hospital, Herston, Queensland, Australia
Canberra and Calvary Hospitals, Garran, Australian Capital Territory, Australia
Royal Hobart Hospital, Hobart, Tasmania, Australia

Epworth HealthCare, Box Hill and Richmond, Victoria, Australia

Melbourne Private Hospital, Melbourne, Victoria, Australia

Western Private Hospital, Footscray, Victoria, Australia

The Northern Hospital, Epping, Victoria, Australia

St John of God Hospital, Subiaco, Perth, Australia

Peninsula Private Hospital, Frankston, Victoria, Australia

Table 2: Demographic and characteristics of patients who progressed after two lines of palliative therapies, categorised by whether they proceeded to receive third-line therapy.

ECOG = eastern cooperative oncology group.

	Patients who proceeded to third-line treatment n = 254	Patients who did not have third-line treatment n = 336
Age	62 years (24-85)	64 years (26-90)
Gender		

- Male	162 (64%)	200 (60%)
- Female	92 (36%)	136 (40%)
Metastatic at diagnosis		
- Yes	178 (70%)	234 (70%)
- No	74 (29%)	101 (30%)
- Unknown	2 (< 1%)	1 (<1%)
Site of tumour		
- Left colon	107 (42%)	119 (35%)
- Right colon	66 (26%)	111 (33%)
- Rectum	72 (28%)	89 (27%)
- Unspecified	9 (4%)	17 (5%)
ECOG at start of 3rd line therapy		
- 0-1	208 (82%)	Not applicable
- 2	35 (14%)	
- 3	8 (3%)	
- Unknown	3 (1%)	

KRAS mutation		
- Mutant	87 (34%)	142 (42%)
- Wild-type	157 (62%)	154 (46%)
- Unknown	10 (4%)	40 (12%)
NRAS mutation		
- Mutant	3 (1%)	6 (2%)
- Wild-type	107 (42%)	99 (29%)
- Unknown	144 (57%)	231 (69%)
BRAF mutation		
- Mutant	13 (5%)	21 (6%)
- Wild-type	127 (50%)	127 (38%)
- Unknown	114 (45%)	188 (56%)

Figure Legends

Figure 1: Total number of patients in the TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry and patients eligible for inclusion in analysis. *This number includes active patients who are still on earlier lines and may go on to receive third-line treatment later.

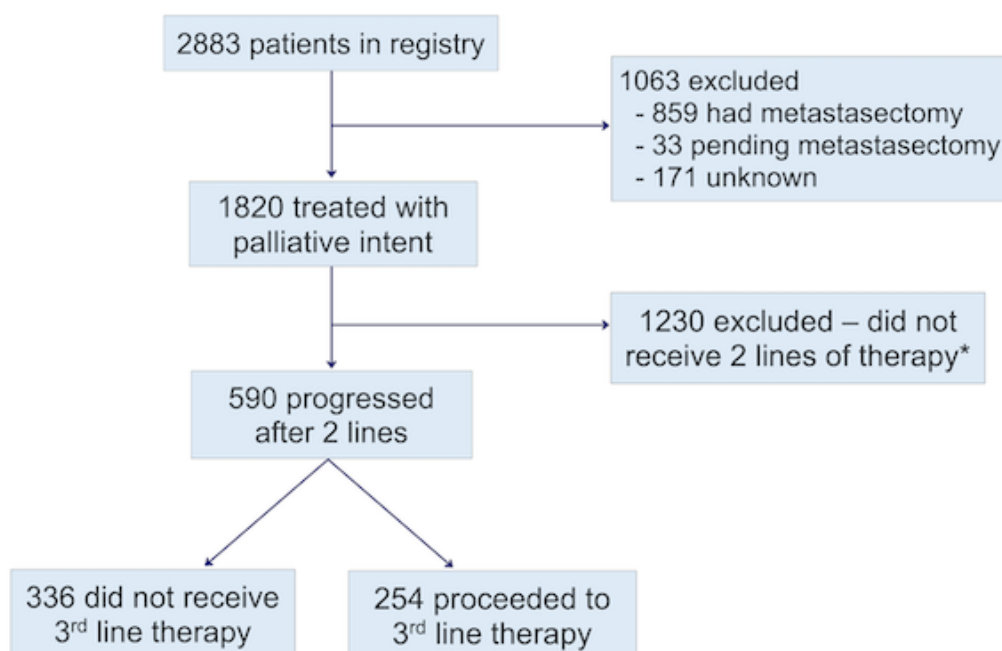


Figure 2: Third-line treatment choices, categorised by *KRAS* mutation status.

FP = fluoropyrimidine; EGFRi = Epidermal growth factor receptor inhibitor; TAS102 = trifluridine/tipiracil.

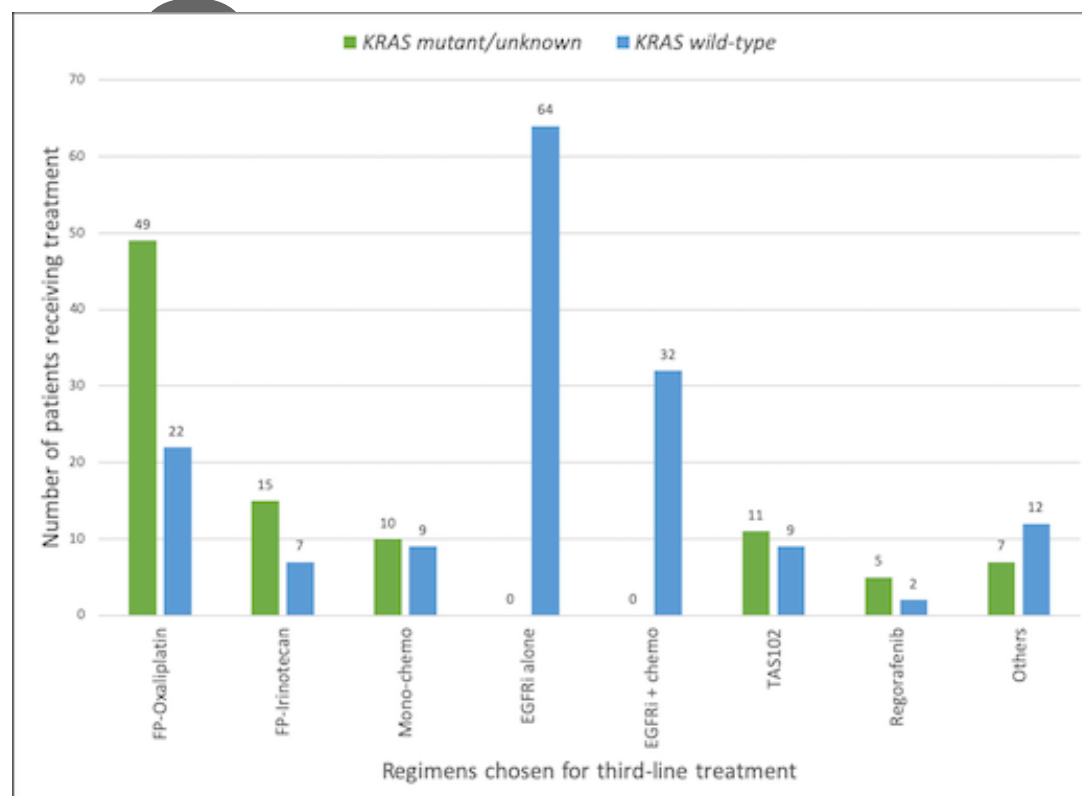


Figure 3: Kaplan-Meier curve for overall survival for all patients who received third-line treatment.

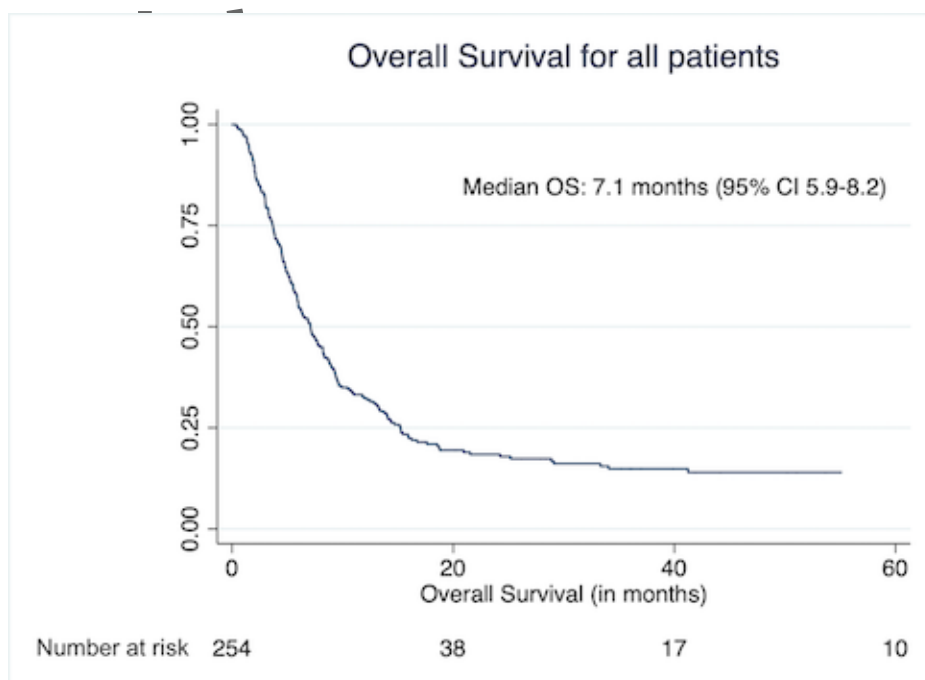
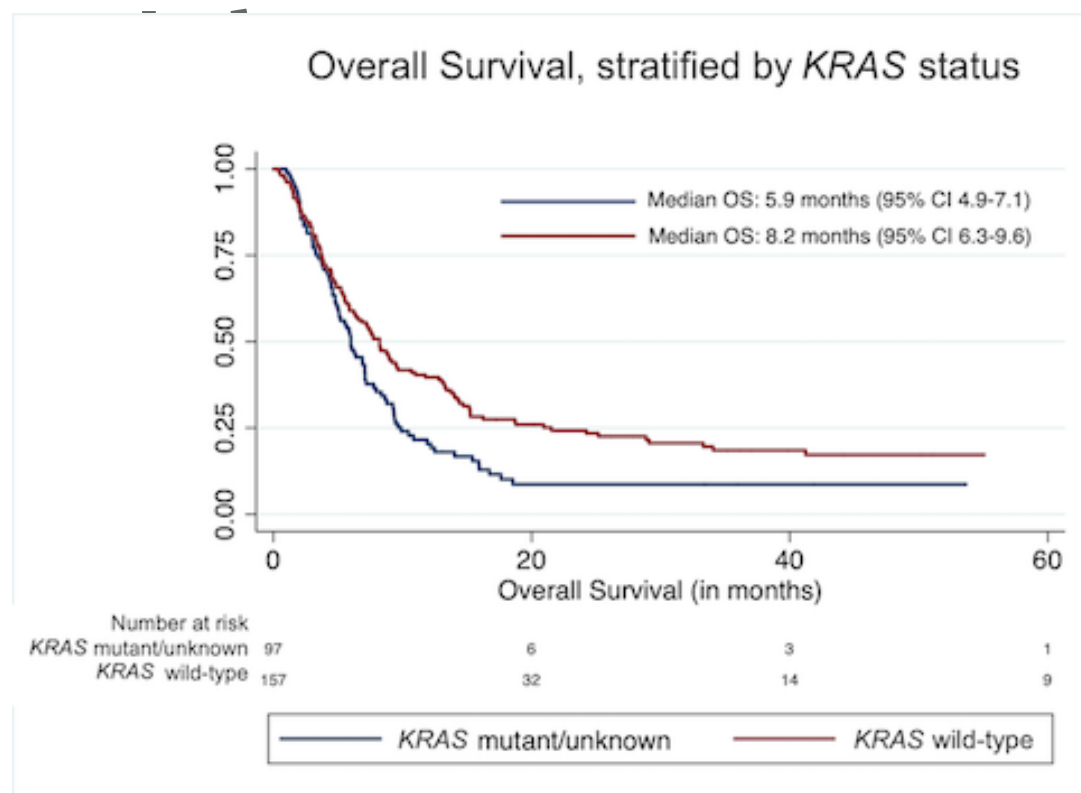
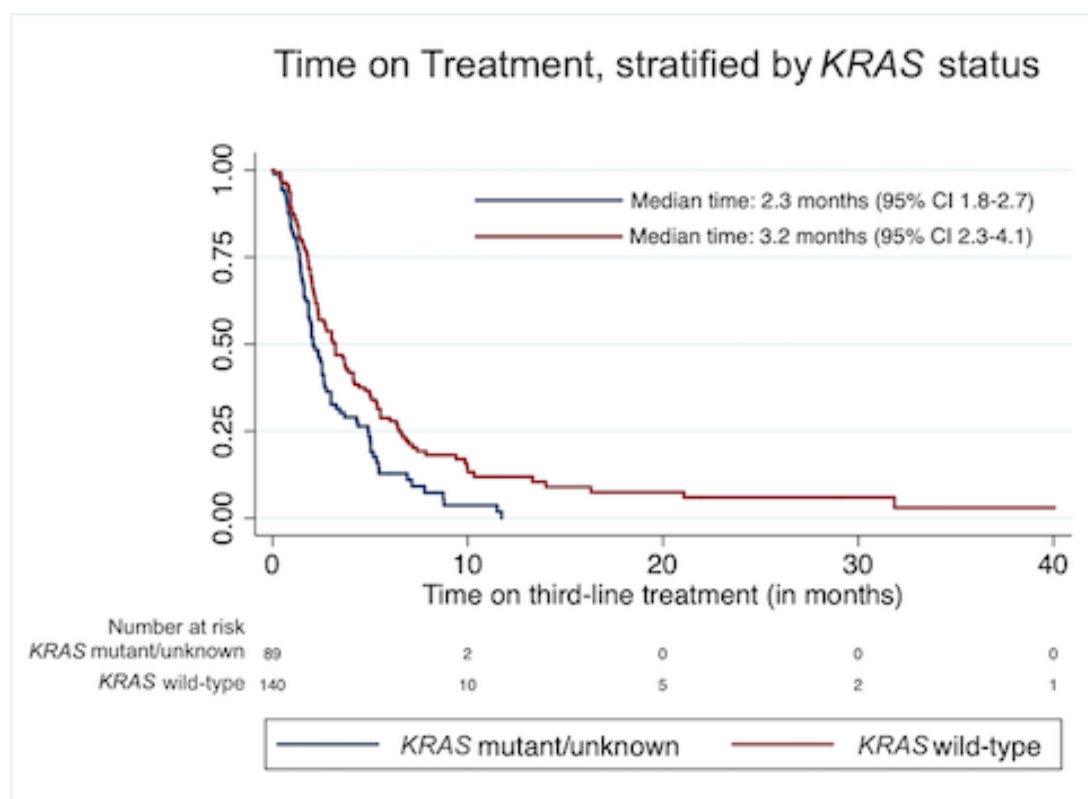


Figure 4: Kaplan-Meier curve for overall survival for all patients who received third-line treatment, stratified by *KRAS* status.



Author M

Figure 5: Kaplan-Meier curve for time on third-line treatment, stratified by *KRAS* status.



This study explored the registry data to understand real-world management landscape in the setting of third-line treatment for metastatic colorectal cancer. Less than half (43%) received third-line therapy and the treatment choices vary depending on the molecular profiles of the tumours.

