



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Price, T;Burge, M;Chantrill, L;Gibbs, P;Pavlakis, N;Shapiro, J;Sjoquist, K

Title:

Trifluridine/tipiracil: A practical guide to its use in the management of refractory metastatic colorectal cancer in Australia

Date:

2020-04-01

Citation:

Price, T., Burge, M., Chantrill, L., Gibbs, P., Pavlakis, N., Shapiro, J. & Sjoquist, K. (2020). Trifluridine/tipiracil: A practical guide to its use in the management of refractory metastatic colorectal cancer in Australia. *Asia Pacific Journal of Clinical Oncology*, 16 (S1), pp.3-12. <https://doi.org/10.1111/ajco.13336>.

Persistent Link:

<https://hdl.handle.net/11343/275579>

# Trifluridine/tipiracil – a practical guide to its use in the management of refractory metastatic colorectal cancer in Australia

Timothy Price,<sup>1\*</sup> Matthew Burge,<sup>2\*</sup> Lorraine Chantrill,<sup>3,4,5\*</sup> Peter Gibbs,<sup>6,7,8\*</sup> Nick Pavlakis,<sup>9\*</sup> Jeremy Shapiro,<sup>10,11\*</sup> Katrin Sjoquist<sup>12,13\*</sup>

<sup>1</sup>The Queen Elizabeth Hospital, Woodville, SA.

<sup>2</sup>Royal Brisbane Hospital, University of Queensland, QLD.

<sup>3</sup>Illawarra Shoalhaven Local Health District, Illawarra Cancer Care Centre, Wollongong Hospital, NSW.

<sup>4</sup>University of New South Wales Sydney, NSW.

<sup>5</sup>The Garvan Institute of Medical Research, Sydney, NSW.

<sup>6</sup>Walter and Eliza Hall Institute, Parkville, VIC.

<sup>7</sup>University of Melbourne, Parkville, VIC.

<sup>8</sup>Western Hospital, Footscray, VIC.

<sup>9</sup>Royal North Shore Hospital, Sydney, NSW.

<sup>10</sup>Cabrini Hospital, Melbourne, VIC.

<sup>11</sup>Monash University, Melbourne, VIC.

<sup>12</sup>NHMRC Clinical Trials Centre, University of Sydney, NSW.

<sup>13</sup>Cancer Care Centre, St George Hospital, Sydney, NSW.

\* All authors contributed equally.

Journal: *Asia Pac J Clin Oncol*

Correspondence: Timothy Price, The Queen Elizabeth Hospital, Woodville, South Australia. Email: timothy.sa.gov.au. Phone: (08) 82228429.

## Potential conflicts of interest in relation to this paper

TP: none. MB: has received honoraria from Servier. LC: none. PG: has received honoraria and travel funding from Servier. NP: none. JS: has received travel funding from Servier. KS: has received honoraria from Servier.

## Full disclosures

TP – overall grants: Amgen; advisory board: MSD, Amgen, Takeda, Eisai. MB – honoraria: Servier, Merck, Ipsen; advisory board: Merck, Amgen; travel support: Amgen, Novartis. LC – advisory board:

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.13336](https://doi.org/10.1111/ajco.13336).

This article is protected by copyright. All rights reserved.

Amgen. PG – research funding: Roche, Ventana Medical Systems, Amgen, Merck Serono; honoraria: Roche, Amgen, Merck, Sirtex Medical, Servier, MSD Oncology; travel support: Servier. NP – research funding: Bayer, Pfizer; advisory boards/honoraria: Bristol-Myers Squibb, MSD, Merck KGaA, Boehringer Ingelheim, AstraZeneca, Roche, Bayer, Novartis, Merck Serono, Pfizer, Takeda, Ipsen; travel funding: Roche. JS – advisory board: Merck; travel support: AGITG and Servier. KS – honoraria: Merck, Servier, Amgen; advisory board: BMS.

## Acknowledgments

Administrative and medical writing support was provided by Donna Bartlett (Allori Pty Ltd, Australia) and Anja Becher, PhD, (Sydney, Australia) and was funded by Servier Australia.

## Abstract

Trifluridine/tipiracil is available on the Australian Pharmaceutical Benefits Scheme for the treatment of patients with metastatic colorectal cancer (mCRC) previously treated with, or not considered candidates for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents. This article reviews trifluridine/tipiracil clinical data and presents practical information on its use in the management of refractory mCRC in Australia. Whereas the primary mechanism of action of fluoropyrimidines such as fluorouracil (5-FU) and capecitabine is enzyme inhibition of nucleotide synthesis, trifluridine/tipiracil primarily acts by incorporation into DNA, resulting in DNA dysfunction. Trifluridine/tipiracil has activity in patients with 5-FU resistant tumors and can be considered in patients with prior intolerance or toxicity to 5-FU. In the pivotal phase 3 RECURSE trial evaluating trifluridine/tipiracil in chemotherapy-refractory mCRC, efficacy benefits were observed across all *a priori* prognostic subgroups including those defined by age ( $\geq 65$  years and  $\geq 75$  years), geographical origin, primary tumor site or *KRAS* status. Trifluridine/tipiracil therapy benefits appropriately selected patients who have an ECOG performance status of 0 or 1, with no more than mild hepatic impairment or mild-to-moderate renal impairment, and who are capable of adhering to oral therapy safely. Appropriate dosing, monitoring for adverse events and effective management of side effects are essential.

## KEYWORDS

Adverse effects; colorectal cancer; patient selection; treatment efficacy; trifluridine/tipiracil.

## 1. Introduction

Colorectal cancer is the second most commonly diagnosed cancer in Australia and among the three most common causes of death from cancer.<sup>1</sup> While treatment options for metastatic colorectal cancer (mCRC) have improved in the last two decades, there remains an unmet need for treatments where first- and second-line therapies are no longer successful or are not tolerated.<sup>2-4</sup> Patients often exhaust two lines of therapy whilst still fit, well and keen for further treatment. However, the

optimal treatment for mCRC beyond second line is not clear, and there are limited therapy choices for this patient population.<sup>2-4</sup> Realistic treatment goals in the third and subsequent lines of therapy differ from those in earlier lines. In the refractory mCRC setting, durable disease control and maintenance of quality of life/performance status are important. Guideline-recommended options beyond second line include trifluridine/tipiracil, regorafenib, anti-epidermal growth factor receptor (EGFR) antibody therapies (for *RAS* wild type if not used previously) and participation in clinical trials.<sup>3</sup> Knowledge of tumor *RAS* and *BRAF* mutation and DNA mismatch repair (MMR) deficiency status is now relevant to refine treatment strategies further with potential for anti-PD-1/PD-L1 and BRAF/MEK/anti-EGFR combinations for select subgroups.<sup>2-6</sup>

Trifluridine/tipiracil therapy has demonstrated improvements in overall survival (OS) and progression-free survival (PFS) in patients with refractory mCRC.<sup>7</sup> Based on positive pivotal trial results, trifluridine/tipiracil was approved for the treatment of patients with mCRC by the US Food and Drug Administration (FDA) in 2015 and the European Medicines Agency (EMA) in 2016, and is now registered in over 70 countries worldwide. In Australia trifluridine/tipiracil therapy for mCRC was approved by the Therapeutic Goods Administration (TGA) in May 2017 and has been available on the Pharmaceutical Benefits Scheme, since December 2018. It is indicated for the treatment of patients with mCRC with Eastern Cooperation Oncology Group (ECOG) status 0 or 1 who have been previously treated with, or are not considered candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-EGFR agents (for patients with *RAS* wild type) .

The current article provides an overview of trifluridine/tipiracil clinical trial data and presents practical recommendations on its use as a standard of care for patients with mCRC receiving treatment beyond the second line in Australia. The recommendations were developed based on review and discussion of available clinical evidence from published literature, and expert opinion.

## 2. Mechanism of action

Trifluridine is a thymidine-based nucleoside analogue.<sup>8</sup> After being taken up into cancer cells, trifluridine is rapidly phosphorylated to a DNA substrate and then readily incorporated into DNA; this activity interferes with DNA function to prevent cell proliferation and stop tumor growth.<sup>9</sup> Trifluridine is degraded by thymidine phosphorylase. Inclusion of tipiracil, a thymidine phosphorylase inhibitor, blocks the action of thymidine phosphorylase, thereby improving the bioavailability of trifluridine.<sup>8</sup>

The primary mechanism of action of trifluridine/tipiracil differs from that of fluoropyrimidines such as fluorouracil (5-FU) and capecitabine (which is metabolised to 5-FU). Whereas the central mechanism of trifluridine/tipiracil is DNA incorporation resulting in DNA dysfunction, 5-FU and its analogues act primarily as inhibitors of the nucleotide synthetic enzyme, thymidylate synthase.<sup>10</sup> Enzymatic metabolic conversion is needed for 5-FU anticancer activity, and decreased metabolic enzyme activity is a main mechanism of acquired resistance to 5-FU.<sup>11</sup> Trifluridine/tipiracil can therefore overcome acquired resistance to 5-FU.<sup>11</sup> Consequently

trifluridine/tipiracil also has activity in patients with 5-FU resistant tumors and may be a treatment option in patients with intolerance to fluoropyrimidine-based therapies.

### 3. Results from clinical trials and observation studies

#### 3.1. Efficacy

In the pivotal phase 3 RECURSE trial, trifluridine/tipiracil therapy demonstrated efficacy compared with placebo in patients with mCRC.<sup>7,12</sup> The trial, conducted in the USA, Europe, Asia and Australia, enrolled patients who had received two or more prior standard chemotherapy regimens and had experienced disease progression.<sup>7</sup> Patients had to have received regimens containing a fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab, and patients with *RAS* wild-type tumors also needed to have received cetuximab or panitumumab. All patients had an ECOG performance status of 0 or 1 at baseline. More than 90% of patients in the RECURSE trial had mCRC that was refractory to fluoropyrimidines during their last exposure and for more than 50%, their disease was refractory to fluoropyrimidines as part of their last treatment regimen before study entry. The median OS in the RECURSE trial was 7.1 months with trifluridine/tipiracil plus best supportive care, compared with 5.3 months in the placebo plus best supportive care group (hazard ratio [HR] for death: 0.68;  $p < 0.001$ ).<sup>7</sup> Extended OS analyses confirmed the survival benefits with trifluridine/tipiracil plus best supportive care versus placebo (7.2 vs 5.2 months; HR: 0.69;  $p < 0.0001$ ) (Figure 1).

Median PFS in the RECURSE trial was 2.0 months with trifluridine/tipiracil and 1.7 months with placebo, with a 52% reduction in risk of progression (HR for progression: 0.48;  $p < 0.001$ ).<sup>7</sup> Importantly, treatment with trifluridine/tipiracil also resulted in a significant delay in the deterioration of ECOG performance status compared with placebo (median time to ECOG performance status  $\geq 2$ : 5.7 vs 4.0 months; HR: 0.66;  $p < 0.001$ ).<sup>7</sup> The clinical disease control rate was 44%, with 1.6% achieving objective response. This is important when understanding the clinical impact of trifluridine/tipiracil in the later line setting. Of note, the OS and PFS benefits observed with trifluridine/tipiracil in the RECURSE trial were consistent across all subgroups examined.<sup>12</sup>

Improvements in OS with trifluridine/tipiracil compared with placebo were also observed in the phase 2 J003 trial, which was conducted in Japan and enrolled patients with pre-treated mCRC who were refractory to 5-FU, irinotecan and oxaliplatin (median OS: 9.0 vs 6.6 months; HR for death: 0.56;  $p = 0.0011$ ).<sup>13</sup> The efficacy of trifluridine/tipiracil was also supported by results from the phase 3 TERRA trial, which enrolled patients with mCRC in China, South Korea and Thailand (trifluridine/tipiracil vs placebo, median OS: 7.8 months vs 7.1 months; median follow-up: 13.8 vs 13.4 months; HR for death: 0.79;  $p = 0.035$ ).<sup>14</sup>

Preliminary results from the phase 3b PRECONNECT early-access study, which enrolled 462 patients from 10 countries, including 71 patients from Australia, support trifluridine/tipiracil as an efficacious treatment option in a real world setting.<sup>15</sup> Median PFS was 2.8 months in the whole

population and 3.2 months in patients who received at least one dose of trifluridine/tipiracil and had at least one baseline and one post-baseline tumor evaluation.<sup>15</sup>

### 3.2. Quality of life

Noting the lack of quality of life data from the prior randomized studies, there is evidence patients with pre-treated mCRC can maintain their health-related quality of life (HRQoL) while on trifluridine/tipiracil treatment, based on the PRECONNECT study.<sup>16</sup> Patients' HRQoL was assessed at baseline, day 1 of each cycle and end of treatment, using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and the EuroQol 5-dimensions (EQ-5D) questionnaires.<sup>16</sup> At data cut-off for the analysis, the median treatment duration was 3 months (range: 0.4–14.7 months), 59.7% of patients had three or more cycles of treatment, 83.6% of patients had withdrawn from the study because of disease progression and 1.9% had withdrawn due to treatment-related adverse events. There were no clinically relevant differences in mean change from baseline for EORTC QLQ-C30 global health status, functional and symptom scales, the EQ-5D utility score or the EQ-5D visual-analogue scale score (Figure 2).<sup>16</sup> Between 46.9% and 60.3% of patients experienced either an improvement or no deterioration in HRQoL or stable HRQoL, as assessed using the different HRQoL measures.<sup>16</sup>

As noted, no HRQoL data were collected in the RECURSE trial;<sup>7</sup> however, patients treated with trifluridine/tipiracil maintained their performance status and remained in the study longer than those treated with placebo despite more frequently experiencing adverse events that are thought to affect HRQoL.<sup>17</sup> Quality-adjusted time without symptoms of disease or toxicity (QTwIST) was 5.5 months with trifluridine/tipiracil, compared with 4.0 months with placebo, representing a clinically meaningful improvement in quality-adjusted survival in patients treated with trifluridine/tipiracil.<sup>18</sup>

### 3.3. Adverse effects

Common adverse events and laboratory abnormalities in the RECURSE trial are listed in Table 1.<sup>7</sup> The most frequently observed events of grade 3 or higher in the trifluridine/tipiracil treatment arm were neutropenia (38% of patients, vs 0% with placebo) and anemia (18%, vs 3% with placebo).<sup>7</sup> Other common events of any grade were thrombocytopenia, nausea, vomiting, decreased appetite, diarrhea and fatigue (Table 1).<sup>7</sup> Any-grade events associated with treatment in the trifluridine/tipiracil arm were stomatitis (8%, vs 6% with placebo), febrile neutropenia (4%, vs 0% with placebo), hand-foot syndrome (2% in both treatment arms) and cardiac ischaemia (< 1% [trifluridine/tipiracil: 2/533; placebo: 1/265] in both treatment arms). Safety profiles in the J003 and TERRA trials, and the PRECONNECT early-access study were consistent with the pattern observed in the RECURSE trial.<sup>13-15</sup>

When the timing of trifluridine/tipiracil therapy-related adverse events of grade 3 or higher in the RECURSE trial was analyzed, most were found to occur in the first cycle (i.e. the first 28 days) of treatment.<sup>19</sup> Across all cycles, the median time to nadir (defined as the point at which the lowest

value was recorded) for grade 3 hematological abnormalities and non-hematological adverse events of grade 3 or higher was 63, 69 and 92 days for neutropenia, anemia and thrombocytopenia, respectively, and 35, 36 and 38 days for vomiting, nausea and diarrhea, respectively.<sup>19</sup>

In the RECURSE trial, treatment-related adverse events in the trifluridine/tipiracil arm led to dose delay of 4 days or more in 53% of patients, dose reduction in 14% of patients and treatment withdrawal in 4% of patients.<sup>7</sup> The incidence of hematological toxicities that resulted in dose reductions or delays was 43% in the trifluridine/tipiracil arm.<sup>20</sup> The high proportion of dose reduction or delays relating to hematological toxicity should be considered in the context of the study protocol requirement to delay treatment until a neutrophil count of at least  $1.5 \times 10^9/L$  was reached, a cut-off higher than the  $1.0 \times 10^9/L$  more commonly used in clinical practice.<sup>7</sup> Fifty patients (9.4%) in the trifluridine/tipiracil arm received granulocyte-colony stimulating factor (G-CSF) to manage hematological toxicities; however, the use of G-CSF in this setting should be balanced with the objectives of therapy in the third line and beyond.<sup>20</sup>

## 4. Practical guidance

### 4.1. Place in practice

A treatment algorithm for mCRC (Figure 3) should include management options beyond second line treatments. Cetuximab and panitumumab are third-line options for patients with *RAS*-wild type mCRC not previously treated with an anti-EGFR antibody.<sup>2,3</sup> However, data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) database and the South Australian mCRC registry show that anti-EGFR antibodies are increasingly being used in first- or second- line in Australia.<sup>21,22</sup> For patients with mCRC refractory to all standard therapies, the other subsequent systemic therapy options are trifluridine/tipiracil or regorafenib.<sup>2,3</sup> The phase 3 CORRECT study compared regorafenib with placebo. The study enrolled patients with previously treated mCRC, and the median OS was 6.4 months with regorafenib, compared with 5.0 months with placebo (HR: 0.77;  $p = 0.0052$ ).<sup>23</sup> The most frequent treatment-related adverse events of grade 3 or higher were hand-foot skin reaction (17% of patients in the regorafenib group), fatigue (10%), diarrhea (7%), hypertension (7%) and rash/desquamation (6%).<sup>23</sup> Regorafenib is currently approved in Australia but is not reimbursed on the Pharmaceutical Benefits Scheme, limiting its availability.

There are no randomized head-to-head data of trifluridine/tipiracil versus regorafenib. An indirect comparison of randomized controlled trials suggests that trifluridine/tipiracil and regorafenib have similar efficacy but, compared with trifluridine/tipiracil, regorafenib is associated with more toxicity at the published standard dose of 160 mg.<sup>24</sup> In a single-institution, retrospective study OS and time to treatment discontinuation were similar in patients treated with trifluridine/tipiracil and those treated with regorafenib, although in patients aged 65 years or above trifluridine/tipiracil resulted in higher OS and a longer time to treatment discontinuation compared with regorafenib.<sup>25</sup> The proportion of patients who required dose modifications or discontinued treatment due to toxicities was lower with trifluridine/tipiracil than regorafenib.<sup>25</sup> Observational studies conducted in Japan have shown similar efficacy but different toxicity profiles with

regorafenib versus trifluridine/tipiracil in patients with mCRC refractory to standard chemotherapy.<sup>26-28</sup>

Chemotherapies or monoclonal antibodies are sometimes re-used in patients who have previously been exposed to these agents, particularly if there is a prolonged drug-free interval or if treatment had previously been ceased for reasons other than progression, e.g. due to side-effects that have subsequently resolved. For example, patients may be re-challenged with an anti-EGFR antibody despite prior progression whilst on the drug, or oxaliplatin may be re-introduced after the drug was ceased for reasons other than progression. Evidence for the re-challenge or re-introduction of oxaliplatin or anti-EGFR antibody therapies is mostly limited to small, non-randomized phase 2 studies and retrospective observations.<sup>29, 30</sup> Given the absence of randomized data the overall benefit of these approaches is uncertain, as opposed to the proven benefits of trifluridine/tipiracil or regorafenib compared with placebo. Use of trifluridine/tipiracil in the third-line setting allows re-challenge with a first- or second-line therapy at a later therapy stage if required. A longer oxaliplatin-free interval may permit recovery from any persistent peripheral neuropathy. Decay of mutant *RAS* over time, as demonstrated in circulating tumor DNA analysis, also suggests that extending the time interval between an initial EGFR inhibitor and re-challenge may enhance patient benefit.<sup>31-33</sup>

Trifluridine/tipiracil is a preferred evidence-based and reimbursed treatment choice as third-line therapy in refractory mCRC. Exceptions are patients with mismatch repair-deficient/microsatellite-instability (MSI)-high tumors if anti-PD-1 therapy is available,<sup>6, 34</sup> or patients with *BRAF*-mutated mCRC if clinical trial enrolment is an option. Data from the BEACON and SWOG studies related to targeting *BRAF* mutations support doublet or triplet therapy as a standard of care for patients with *BRAF*-mutated mCRC.<sup>5, 35, 36</sup> Data from the HERACLES and MyPathway studies related to targeting HER2 overexpression reveal that these approaches also have activity.<sup>37, 38</sup> The phase 3 BEACON study assessed triplet therapy with encorafenib, binimetinib and cetuximab, compared with standard care consisting of investigator's choice of either irinotecan or folinic acid/fluorouracil/irinotecan (FOLFIRI) plus cetuximab in patients with *BRAF*-mutated mCRC.<sup>5, 36</sup> Results from BEACON showed that, compared with standard care, triple therapy to target *BRAF* mutations in mCRC significantly improved OS (median: 9.0 months with triple therapy vs 5.4 months with standard therapy; HR: 0.52;  $p < 0.0001$ ) and objective response (26% with triple therapy vs 2% with standard therapy;  $p < 0.0001$ ).<sup>5</sup> Patients receiving doublet therapy with encorafenib and cetuximab achieved a median OS of 8.4 months (HR vs standard therapy: 0.60;  $p = 0.0003$ ).<sup>5</sup> Combination EGFR and BRAF inhibition should therefore now be standard for patients with *BRAF*-mutated mCRC.

Patients with mCRC with mismatch repair deficiency/MSI-high tumors have been shown to obtain substantial benefit from immune checkpoint inhibition, with benefits seen with pembrolizumab and nivolumab combined with low dose ipilimumab for this indication.<sup>6, 34</sup> Anti-PD-1 is standard therapy in this setting in Australia and pembrolizumab is TGA-listed. Clinicians should discuss this option and the associated cost with their patients. Ongoing studies evaluating other immunotherapy agents are ongoing to determine the overall place of immunotherapy in mCRC.

## 4.2. Appropriate patient selection

The RECURSE trial was conducted in patients with ECOG performance status of 0 or 1, and efficacy benefits were observed across all *a priori* prognostic subgroups including those defined by age ( $\geq 65$  years and  $\geq 75$  years), geographical origin, primary tumor site or *KRAS* status.<sup>12</sup> Hematological toxicity is associated with trifluridine/tipiracil efficacy.<sup>39-41</sup> Interestingly, subsequent analysis of the RECURSE trial found the onset of neutropenia was associated with treatment response.<sup>42, 43</sup>

A key practical advantage of trifluridine/tipiracil therapy is oral delivery, which patients often prefer over intravenous regimens. When selecting patients for trifluridine/tipiracil therapy compliance with oral therapy needs to be considered, along with each patient's ability to understand the importance of stopping treatment and seeking medical advice when adverse events are experienced. Tablet strength, dosing and dose modification information can be complex. Patient education prior to commencement of trifluridine/tipiracil therapy is considered vital to ensure patient safety, drug tolerability and compliance. Patient resources including a dosing calendar are available.<sup>44</sup> Trifluridine/tipiracil should be dispensed by a pharmacist familiar with counseling on oral chemotherapies wherever possible. Ideally, education by a pharmacist or nurse practitioner who can provide additional education and ongoing support to patients on trifluridine/tipiracil therapy would also be included.

Trifluridine/tipiracil has not been studied in patients with severe hepatic impairment, or in patients with severe renal impairment or end-stage renal disease and is thus not recommended in these patient groups.<sup>8, 45</sup> Trifluridine/tipiracil is also not recommended in patients with moderate hepatic impairment,<sup>8</sup> results from a small study showed grade 3 or 4 increases in bilirubin levels following administration of trifluridine/tipiracil in this cohort.<sup>46</sup> For patients with mild hepatic impairment or mild-to-moderate renal impairment, starting dose reductions are not necessary. Treatment administration guidelines such as eviQ note limited data availability in patients with mild-to-moderate renal impairment and recommend use with caution in this population.<sup>45</sup>

Trifluridine/tipiracil can be considered in patients who experienced prior intolerance or toxicity to 5-FU, with careful monitoring and management of expected toxicities and relevant dose adjustment as required. Patients who had previously experienced unresolved 5-FU-related cardiotoxicity ( $\geq$  CTCAE Grade 2) were excluded from the RECURSE study.<sup>7</sup> However, based on mechanism of action, cross-reactivity with 5-FU cardiotoxicity is considered unlikely. In the RECURSE study, the reported incidence of cardiac disorders was 0.9% (5/533) in the trifluridine/tipiracil group and 0.8% (2/265) in the placebo group.<sup>7</sup> Preliminary results from the phase 3b PRECONNECT early-access study showed an incidence of cardiac ischemic events less than 1% (1/462), with no events of grade 3 or higher.<sup>15</sup> Post-marketing surveillance, which includes an estimated 64,664 patients worldwide who have been exposed to trifluridine/tipiracil since the first marketing authorization to February 2018, reports 48 cases of cardiac disorders of any type, which represents an incidence of 0.074% in the treated population.<sup>47</sup> As with raltitrexed,<sup>48</sup> there may be the potential to consider trifluridine/tipiracil in patients who have had 5-FU-related coronary spasm, but data are limited and careful monitoring would still be recommended if switching to trifluridine/tipiracil.

### 4.3. Initiating therapy

The recommended starting dose of trifluridine/tipiracil is 35 mg/m<sup>2</sup> of body surface area (BSA) up to a maximum of 80 mg per dose, based on the trifluridine component, taken orally twice daily.<sup>8</sup> Doses are taken on days 1–5 and 8–12 of each 28-day cycle.<sup>8</sup> Prescribing physicians may want to advise patients to schedule their doses from Monday to Friday of two consecutive weeks to make it easier for patients to remember when to start and stop taking their tablets.

Trifluridine/tipiracil comes in boxes of 20 tablets and is available in two tablet strengths: 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil. Dosing calendars are available to help patients with scheduling treatment days and breaks.<sup>44</sup> Ideally, patients should only be dispensed the number of boxes of each strength that is required to complete one cycle, to reduce the risk of medication error. In addition, prescribing and dispensing trifluridine/tipiracil treatment one cycle at a time simplifies any dose adjustments that may be required for subsequent cycle(s).

Doses are taken within one hour of morning and evening meals, respectively, with a glass of water. Patients should not 'make up' for any missed doses. Trifluridine/tipiracil should only be prescribed by physicians experienced in the administration of anti-cancer therapy. Complete blood counts need to be obtained before initiating each new 28-day cycle.

### 4.4. Managing adverse events

Awareness of the temporal nature of potential adverse events can help physicians manage them effectively in the outpatient setting. Most events were found to occur in the first cycle of treatment in the RECURSE trial.<sup>19</sup> Nausea of any grade was reported in 48% of patients receiving trifluridine/tipiracil therapy in the RECURSE trial, but only 28% reported any vomiting and only 2% reported severe (grade 3) nausea or severe vomiting.<sup>7</sup> Precautionary prescription of an anti-emetic, to be taken if required, is advisable at commencement of therapy with trifluridine/tipiracil; recommended anti-emetics include metoclopramide, or alternatives prochlorperazine or cyclizine.<sup>45</sup> Additional anti-emetics, such as a 5HT<sub>3</sub> receptor antagonist, or a dose reduction should be considered if regular metoclopramide is ineffective.<sup>45</sup> Education about the use of antidiarrheals, such as loperamide for management of diarrhea, is also recommended.<sup>45</sup> For chemotherapy- and targeted therapy-induced diarrhea unresponsive to high dose loperamide, eviQ guidelines recommend octreotide and thus could also be considered for trifluridine/tipiracil.<sup>45</sup>

Dose delays and/or dose reductions may be necessary in the case of moderate to severe adverse events, and guidance or recommendations for dose modifications are available both from eviQ and from the trifluridine/tipiracil product information.<sup>8, 45, 49</sup> General principles of toxicity management, such as relevant supportive care, dose delay until resolution of adverse event to grade 1 or less and consideration for subsequent dose reduction, should be applied.

If neutropenia occurs, the authors suggest dose delay until the neutrophil count improves to at least 1.0 x 10<sup>9</sup>/L; this differs from the more conservative threshold of at least 1.5 x 10<sup>9</sup>/L that is recommended by eviQ and the product information.<sup>8, 45</sup> If a dose reduction is needed, trifluridine/tipiracil should be reduced by 5 mg/m<sup>2</sup> for subsequent cycles. In accordance with the

product information, a dose reduction is required only if the neutrophil count is below  $0.5 \times 10^9/L$  and the corresponding dose delay is more than one week. If febrile neutropenia occurs, the product information recommends that treatment should be delayed until the neutrophil count is greater than or equal to  $1.5 \times 10^9/L$  and that the trifluridine/tipiracil dose should be reduced by  $5 \text{ mg}/\text{m}^2$  for subsequent cycles.<sup>8, 49</sup> Some clinicians would consider re-initiating treatment at a lower threshold depending on the patient's clinical circumstances; we recommend a neutrophil count of at least  $1.0 \times 10^9/L$ .

For thrombocytopenia, if the pre-treatment blood test shows a platelet count below  $75 \times 10^9/L$ , both eviQ and the product information recommend that doses should be delayed until the platelet count is greater than or equal to  $75 \times 10^9/L$ ,<sup>8, 45, 49</sup> but physicians should apply discretion to individual cases. In accordance with the product information, treatment should be interrupted if the platelet count is below  $50 \times 10^9/L$ .<sup>8, 49</sup> If the platelet count is below  $25 \times 10^9/L$  and the corresponding dose delay is more than one week, then trifluridine/tipiracil dose should be reduced by  $5 \text{ mg}/\text{m}^2$  for subsequent cycles should re-introduction be considered clinically desirable.<sup>8, 49</sup> Again physicians should apply their clinical judgment depending on the patient's clinical circumstances.

Dose interruption criteria for non-hematological adverse events are grade 3 nausea, vomiting or diarrhea not responsive to medication, and any other grade 3 or grade 4 adverse events.<sup>8, 49</sup> Once these are resolved to grade 1 or baseline, trifluridine/tipiracil treatment should be resumed, but with the dose level decreased by  $5 \text{ mg}/\text{m}^2$ .<sup>8, 49</sup> Grade 3 nausea, vomiting or diarrhea that are responsive to medication must be resolved to grade 1 or baseline prior to resuming the next cycle of trifluridine/tipiracil treatment at the same dose level.<sup>8</sup>

#### 4.5. Monitoring

Patient follow-up should include regular monitoring of adverse events, clinical symptoms, and laboratory values (including full blood count, kidney and liver function) and computed tomography (CT) scans. Blood tests are recommended immediately prior to the start of the next cycle. Close supervision is recommended in the first treatment cycle in particular, and a phone or clinic review mid first cycle should be considered.

### 5. Future developments

Ongoing trials are assessing the combination of trifluridine/tipiracil with other standard mCRC therapies such as irinotecan, oxaliplatin, anti-VEGF and anti-EGFR, in the first-line, second-line, maintenance and refractory settings (Table 2). A phase 3 study of trifluridine/tipiracil in combination with bevacizumab, compared with capecitabine plus bevacizumab, in patients not suitable for intensive therapy in first-line is ongoing, with phase 2 results showing promising activity.<sup>50</sup> The activity of trifluridine/tipiracil has also been explored in other tumor types. Most notably, positive phase 3 data versus best supportive care in refractory metastatic gastric and gastroesophageal junction cancer have been published.<sup>51</sup>

## 6. Conclusions

In conclusion, trifluridine/tipiracil therapy has demonstrated efficacy in patients with mCRC beyond the second-line setting, and is a proven and convenient treatment option for patients with refractory disease. It has activity in patients with 5-FU resistant tumors, and may also be a treatment option in patients with intolerance to previous fluoropyrimidine-based therapies. Trifluridine/tipiracil therapy demonstrates benefit in appropriately selected patients who are capable of taking oral tablets and adhering to therapy safely. Patients should have an ECOG performance status of 0 or 1, with no more than mild hepatic impairment or mild-to-moderate renal impairment. In the refractory mCRC setting, where trifluridine/tipiracil is currently indicated, treatment goals differ from those in earlier lines of therapy; durable disease control and maintenance of quality of life/performance status are important targets in this setting. Appropriate dosing, monitoring for adverse events and effective management of side effects are all essential. Evidence for the benefits of trifluridine/tipiracil therapy in other settings is evolving.

## References

1. Australian Institute of Health and Welfare. Cancer in Australia: in brief 2019. Cancer series no. 122. Cat no. CAN 126. Canberra: AIHW. 2019.
2. Van Cutsem E, Cervantes A, Adam R *et al*. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386–422.
3. Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. 2018 Sydney: Cancer Council Australia. Available from: [https://wiki.cancer.org.au/australia/Guidelines:Colorectal\\_cancer](https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer). Accessed 4 June 2019.
4. Messersmith WA. NCCN Guidelines updates: management of metastatic colorectal cancer. *J Natl Compr Canc Netw* 2019;17:599–601.
5. Kopetz S, Grothey A, Yaeger R *et al*. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N Engl J Med* 2019;381:1632–43.
6. Overman MJ, Lonardi S, Wong KYM *et al*. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773–9.
7. Mayer RJ, Van Cutsem E, Falcone A *et al*. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372:1909–19.
8. Servier Laboratories (Australia) Pty Ltd. LONSURF (trifluridine/tipiracil) Product Information.

9. Matsuoka K, Iimori M, Niimi S *et al.* Trifluridine induces p53-dependent sustained G2 phase arrest with its massive misincorporation into DNA and few DNA strand breaks. *Mol Cancer Ther* 2015;14:1004–13.
10. Lyseng-Williamson KA, Burness CB, Duggan ST. Trifluridine/tipiracil in metastatic colorectal cancer: a guide to its use. *Drugs Ther Perspect* 2017;33:110–8.
11. Lenz HJ, Stintzing S, Loupakis F. TAS-102, a novel antitumor agent: a review of the mechanism of action. *Cancer Treat Rev* 2015;41:777–83.
12. Van Cutsem E, Mayer RJ, Laurent S *et al.* The subgroups of the phase III RECURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. *Eur J Cancer* 2018;90:63–72.
13. Yoshino T, Mizunuma N, Yamazaki K *et al.* TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2012;13:993–1001.
14. Xu J, Kim TW, Shen L *et al.* Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA Study. *J Clin Oncol* 2018;36:350–8.
15. Falcone A, André T, Edeline J *et al.* O-013 Safety and efficacy of trifluridine/tipiracil in previously treated metastatic colorectal cancer (mCRC): preliminary results from the phase IIIb, international, open-label, early-access PRECONNECT study. *Ann Oncol* 2018;29:O-013 (abstract and poster).
16. Taieb J, Price TJ, Ciardiello F *et al.* Health-related quality of life in the early-access phase IIIb study of trifluridine/tipiracil in pretreated metastatic colorectal cancer (mCRC): results from PRECONNECT study. *J Clin Oncol* 2019;37:638 (abstract and poster).
17. Van Cutsem E, Falcone A, Garcia-Carbonero R *et al.* Proxies of quality of life in metastatic colorectal cancer: analyses in the RECURSE trial. *ESMO Open* 2017;2:e000261.
18. Tabernero J, Van Cutsem E, Ohtsu A *et al.* QTWiST analysis of the RECURSE trial of trifluridine/tipiracil in metastatic colorectal cancer. *ESMO Open* 2017;2:e000284.
19. Van Cutsem E, Ohtsu A, Lopez Busto N *et al.* Time to grade  $\geq 3$  adverse events in pts receiving trifluridine/tipiracil (TAS-102). *J Clin Oncol* 2017;35:788 (abstract and poster).
20. Mayer RJ, Van Cutsem E, Yoshino T *et al.* Supportive treatment for hematologic toxicities in the phase 3 RECURSE trial of TAS-102 vs placebo with best supportive care in patients with metastatic colorectal cancer. *J Clin Oncol* 2016;34 (suppl):e15021 (abstract).
21. Tomita Y, Karapetis CS, Ullah S *et al.* Survival improvements associated with access to biological agents: results from the South Australian (SA) metastatic colorectal cancer (mCRC) registry. *Acta Oncol* 2016;55:480–5.

22. Semira C, Wong HL, Field K *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;49:446–54.
23. Grothey A, Van Cutsem E, Sobrero A *et al.* Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:303–12.
24. Abrahao ABK, Ko YJ, Berry S *et al.* A comparison of regorafenib and TAS-102 for metastatic colorectal cancer: a systematic review and network meta-analysis. *Clin Colorectal Cancer* 2018;17:113–20.
25. Patel AK, Ng K, Duh MS *et al.* Trifluridine/tipiracil (FTD/TPI) and regorafenib (REG) in patients with metastatic colorectal cancer (mCRC): a single institution retrospective study. *J Clin Oncol* 2019;37:592 (abstract and poster).
26. Masuishi T, Taniguchi H, Hamauchi S *et al.* Regorafenib versus trifluridine/tipiracil for refractory metastatic colorectal cancer: a retrospective comparison. *Clin Colorectal Cancer* 2017;16:e15-e22.
27. Moriwaki T, Fukuoka S, Taniguchi H *et al.* Propensity score analysis of regorafenib versus trifluridine/tipiracil in patients with metastatic colorectal cancer refractory to standard chemotherapy (REGOTAS): a Japanese society for cancer of the colon and rectum multicenter observational study. *Oncologist* 2018;23:7–15.
28. Sueda T, Sakai D, Kudo T *et al.* Efficacy and safety of regorafenib or TAS-102 in patients with metastatic colorectal cancer refractory to standard therapies. *Anticancer Res* 2016;36:4299–306.
29. Chibaudel B, Tournigand C, Bonnetain F *et al.* Platinum-sensitivity in metastatic colorectal cancer: towards a definition. *Eur J Cancer* 2013;49:3813–20.
30. Suenaga M, Mizunuma N, Matsusaka S *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;9:3099–108.
31. Cremolini C, Rossini D, Dell'Aquila E *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;5:343–50.
32. Arnold D, Prager GW, Quintela A *et al.* Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review. *Ann Oncol* 2018;29:835–56.
33. Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. *Eur J Cancer* 2019;109:70–83.
34. Le DT, Uram JN, Wang H *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509–20.

35. Innocenti F, Ou FS, Qu X *et al.* Mutational analysis of patients with colorectal cancer in CALGB/SWOG 80405 identifies new roles of microsatellite instability and tumor mutational burden for patient outcome. *J Clin Oncol* 2019;37:1217–27.
36. Van Cutsem E, Huijberts S, Grothey A *et al.* Binimetinib, encorafenib, and cetuximab triplet therapy for patients with *BRAF* V600E-mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON colorectal cancer study. *J Clin Oncol* 2019;37:1460–9.
37. Sartore-Bianchi A, Trusolino L, Martino C *et al.* Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:738–46.
38. Meric-Bernstam F, Hurwitz H, Raghav KPS *et al.* Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2019;20:518–30.
39. Yamashita F, Komoto I, Oka H *et al.* Exposure-dependent incorporation of trifluridine into DNA of tumors and white blood cells in tumor-bearing mouse. *Cancer Chemother Pharmacol* 2015;76:325–33.
40. Kimura M, Usami E, Iwai M *et al.* Severe neutropenia: a prognosticator in patients with advanced/recurrent colorectal cancer under oral trifluridine-tipiracil (TAS-102) chemotherapy. *Pharmazie* 2017;72:49–52.
41. Nishina T, Yoshino T, Shinozaki E *et al.* Onset of neutropenia as an indicator of treatment response in the randomized phase II of TAS-102 vs placebo in Japanese patients with metastatic colorectal cancer (Study J003-10040030). *J Clin Oncol* 2016;34 (suppl):abstr 3557 (abstract).
42. Kasi PM, Kotani D, Cecchini M *et al.* Chemotherapy induced neutropenia at 1-month mark is a predictor of overall survival in patients receiving TAS-102 for refractory metastatic colorectal cancer: a cohort study. *BMC Cancer* 2016;16:467.
43. Pavlakis N, Tran B, Ohtsu A *et al.* Onset of neutropenia as an indicator of treatment response in the Phase 3 RECURSE trial of trifluridine/tipiracil (TAS-102) vs. placebo in patients with metastatic colorectal cancer. Poster presented at the Australasian Gastro-Intestinal Trials Group Annual Scientific Meeting; October 4–6, 2017; Cairns, Australia.
44. Dosing calendar. Available at: [mydosingcalendar.com.au](http://mydosingcalendar.com.au).
45. Cancer Institute NSW. eviQ Education. Colorectal metastatic trifluridine/tipiracil. Available at: <https://www.eviq.org.au/medical-oncology/colorectal/metastatic/1940-colorectal-metastatic-trifluridine-tipiracil>. Accessed 19 June 2019.
46. Saif MW, Rosen L, Rudek MA *et al.* Open-label study to evaluate trifluridine/tipiracil safety, tolerability and pharmacokinetics in patients with advanced solid tumours and hepatic impairment. *Br J Clin Pharmacol* 2019;85:1239–46.

47. Data on file – Periodic Benefit Risk Evaluation Report (March 2018).
48. Kelly C, Bhuva N, Harrison M *et al.* Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. *Eur J Cancer* 2013;49:2303–10.
49. Servier Laboratories (Australia) Pty Ltd. LONSURF Dosing Ruler.
50. Lesniewski-Kmak K, Moiseenko V, Saunders M *et al.* Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): results of the primary analysis. *Ann Oncol* 2018;29 (suppl 5):mdy149.021 (abstract O-022).
51. Shitara K, Doi T, Dvorkin M *et al.* Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018;19:1437–48.

## Tables and Figures

Table 1. Common adverse events and laboratory abnormalities in the RECOURSE trial.<sup>7</sup>

| Event   | Trifluridine/tipiracil (N = 533)<br>n (%) |           | Placebo (N = 265)<br>n (%) |           |
|---|---|-----------|----------------------------|-----------|
|   | Any grade                                 | Grade ≥ 3 | Any grade                  | Grade ≥ 3 |
| Common adverse events                             |   |           |                            |           |
| Diarrhea  | 170 (32)                                  | 16 (3)    | 33 (12)                    | 1 (<1)    |
| Nausea  | 258 (48)                                  | 10 (2)    | 63 (24)                    | 3 (1)     |
| Vomiting  | 148 (28)                                  | 11 (2)    | 38 (14)                    | 1 (<1)    |
| Decreased appetite                                | 208 (39)                                  | 19 (4)    | 78 (29)                    | 13 (5)    |
| Fatigue   | 188 (35)                                  | 21 (4)    | 62 (23)                    | 15 (6)    |
| Events associated with fluoropyrimidine treatment |   |           |                            |           |
| Febrile neutropenia                               | 20 (4)                                    | 20 (4)    | 0 (0)                      | 0 (0)     |
| Stomatitis  | 43 (8)                                    | 2 (< 1)   | 17 (6)                     | 0 (0)     |
| Hand–foot syndrome                                | 12 (2)                                    | 0 (0)     | 6 (2)                      | 0 (0)     |
| Cardiac ischaemia                                 | 2 (< 1)                                   | 1 (< 1)   | 1 (< 1)                    | 1 (< 1)   |
| Common laboratory abnormalities <sup>†</sup>      |   |           |                            |           |

|                             |          |          |          |         |
|-----------------------------|----------|----------|----------|---------|
| Neutropenia                 | 353 (67) | 200 (38) | 2 (< 1)  | 0 (0)   |
| Leukopenia                  | 407 (77) | 113 (21) | 12 (5)   | 0 (0)   |
| Anemia                      | 404 (77) | 96 (18)  | 87 (33)  | 8 (3)   |
| Thrombocytopenia            | 223 (42) | 27 (5)   | 21 (8)   | 1 (< 1) |
| Increase in ALT             | 126 (24) | 10 (2)   | 70 (27)  | 10 (4)  |
| Increase in AST             | 155 (30) | 23 (4)   | 91 (35)  | 16 (6)  |
| Increase in total bilirubin | 189 (36) | 45 (9)   | 69 (26)  | 31 (12) |
| Increase in ALP             | 205 (39) | 42 (8)   | 118 (45) | 28 (11) |
| Increase in creatinine      | 71 (13)  | 5 (< 1)  | 32 (12)  | 2 (< 1) |

<sup>†</sup>The denominator for the proportion of patients with laboratory abnormalities is the number of patients with at least one post-baseline measurement during treatment.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2. Planned and ongoing trials of trifluridine/tipiracil therapy in patients with metastatic colorectal cancer.

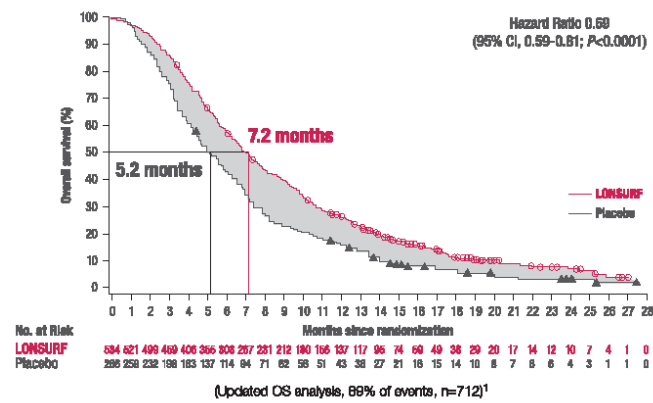
| NCT #       | Agents  | Phase |
|-------------|---|-------|
| NCT03869892 | Trifluridine/tipiracil plus bevacizumab                                     | 3     |
| NCT03520946 | Trifluridine/tipiracil plus ramucirumab                                     | 2     |
| NCT03305913 | Trifluridine/tipiracil plus regorafenib                                     | 1     |
| NCT02848079 | Trifluridine/tipiracil plus oxaliplatin                                     | 1/2   |
| NCT02848443 | Trifluridine/tipiracil plus oxaliplatin and either bevacizumab or nivolumab | 1     |
| NCT03317119 | Trifluridine/tipiracil plus trametinib                                      | 1     |
| NCT03368963 | Trifluridine/tipiracil plus nanoliposomal irinotecan                        | 1/2   |

Information from ClinicalTrials.gov, searched 12 August 2019.

Figure legends

Figure 1. Kaplan–Meier curves for extended overall survival in the RECURSE trial. Adapted from Van Cutsem et al.<sup>12</sup> Reproduced with permission from Elsevier Ltd.

Lonsurf, trifluridine/tipiracil.



Author

Figure 2. Quality of life scores in the PRECONNECT study, based on the European Organisation for Research and Treatment of Cancer QLQ-C30 Global Health Status, EQ-5D Utility and EQ-5D VAS scales.<sup>16</sup>

QLQ-C30, core quality of life questionnaire; EQ-5D, EuroQol 5-dimensions questionnaire; VAS, visual-analogue scale.

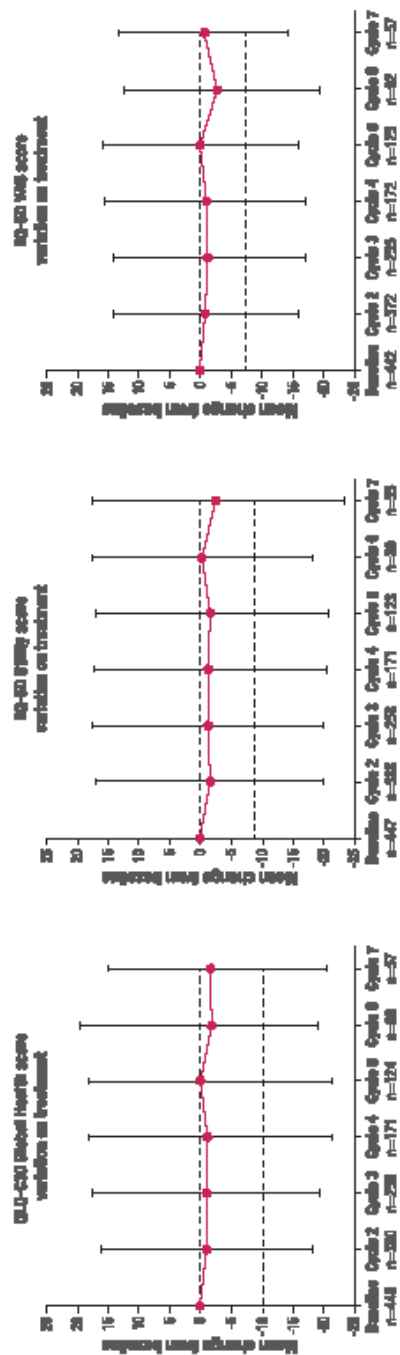
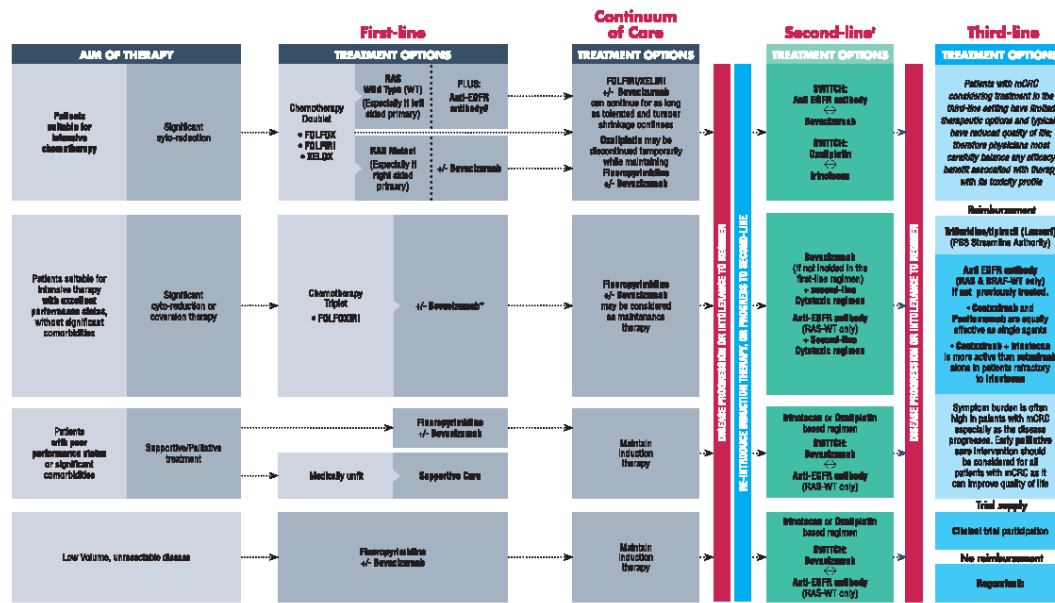


Figure 3. Treatment algorithm for metastatic colorectal cancer. Based on the Cancer Council Australia colorectal cancer guidelines.<sup>3</sup> Graphic reproduced with permission from Servier Australia (Pty. Ltd.)



FOLFIRI: 5-FU/Leucovorin + Oxaliplatin. FOLFIRI: 5-FU/Leucovorin + Irinotecan. BEZLEC: Bevacizumab + Oxaliplatin. BEZLEC: Bevacizumab + Irinotecan. FOLFIRI/CELEBRIL: 5-FU/Leucovorin + Irinotecan + Celecoxib. SWITCH: Oxaliplatin ↔ Irinotecan. EGFR: Epidermal Growth Factor Receptor.

\*Anti-EGFR antibody should not be combined with Capecitabine based and both 5FU-based regimens. Anti-EGFR antibodies may be less effective in BRAF mutation. <sup>1</sup>Not PBS. Combination of Bevacizumab, Irinotecan or Afatinip or Ramucicab. Adaptation from: [http://www.cancer.org.au/health/clinical/mc/mc\\_colorectal\\_mccc](http://www.cancer.org.au/health/clinical/mc/mc_colorectal_mccc)

Author