

# Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Colorectal Cancer

The Singapore Cancer Network (SCAN) Colorectal Cancer Systemic Therapy Workgroup

## Abstract

**Introduction:** The SCAN colorectal cancer systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for colorectal cancer in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network for colon (2014) and rectal (2014) cancer, the European Society of Medical Oncology for advanced (2012) and early (2013) cancer and the National Institute of Clinical Excellence (2011). Recommendations on systemic therapy in colorectal cancer were produced. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of colorectal cancer.

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**Key words:** Treatment recommendations, Multidisciplinary, Malignancy

## Introduction

Globally, colorectal cancer (CRC) is the third most common cancer with 1 million new cases per year. In Singapore, CRC is the most common cancer (8206 new cases, 2006 to 2010),<sup>1</sup> accounting for 18% and 14% of all cancers in males and females respectively. One in 25 male and 1 in 35 female Singaporeans will develop CRC in their lifetime.<sup>2</sup> Adjuvant postoperative systemic therapy is recommended for patients with stage III CRC and considered for patients with high risk stage II CRC. About half of CRC patients develop metastatic disease (either at diagnosis or as systemic recurrence after initial early stage CRC). Systemic therapy improves quality of life and overall survival (OS) in patients with stage IV CRC.

While several international guidelines for treatment of CRC exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists a need to develop a set of local Singapore guidelines to address this patient population and practice within our healthcare context.

## The SCAN Guidelines for the Systemic Therapy of CRC

The SCAN Guidelines are clinical practice guidelines for systemic treatment of CRC patients.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of CRC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

## Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with colorectal cancer.

## Guideline Recommendations/Development

The SCAN Colorectal Cancer Workgroup is made up of a panel of 11 medical oncologists with special interests in the management of CRC. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and

Address for Correspondence: Dr Iain Tan Bee Huat, Department of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.

Email: iain.tan@gmail.com

decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework<sup>3</sup> was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 6 main management issues which were selected for this topic:

1. Adjuvant systemic chemotherapy in colon cancer
2. Adjuvant systemic chemotherapy in rectal cancer
3. Systemic chemotherapy strategies in patients with metastatic CRC
4. First-line systemic chemotherapy in patients with metastatic CRC
5. Duration of therapy and maintenance/intermittent chemotherapy in patients with metastatic CRC
6. Second- and further-line treatment in patients with metastatic CRC

Five international guidelines were selected for review:

- “NCCN Guidelines for Colon Cancer Version 3.2014” by the National Cancer Comprehensive Network (NCCN), USA<sup>4</sup>

- “NCCN Guidelines for Rectal Cancer Version 3.2014” by NCCN, USA<sup>5</sup>
- “ESMO Consensus Guidelines for Management of Patients with Colon and Rectal Cancer. A Personalized Approach to Clinical Decision Making” by the European Society of Medical Oncology (ESMO), 2012<sup>6</sup>
- “Early Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by ESMO, 2013<sup>7</sup>
- “Colorectal Cancer: the Diagnosis and Management of Colorectal Cancer” by the National Institute of Health and Clinical excellence (NICE, UK), 2011<sup>8</sup>

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of CRC, it will be reviewed earlier.

### 1. Adjuvant Systemic Chemotherapy for Colon Cancer

Choices for adjuvant therapy for patients with resected, non-metastatic colon cancer depend on the stage of disease. Patients with stage I disease do not require any adjuvant therapy. Patients with low risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). The addition of oxaliplatin to 5-FU-based therapy is not considered appropriate adjuvant therapy in patients with stage II disease without high risk features.

Patients with high risk stage II disease, defined as those with poor prognostic features, including T4 tumours (stage IIB/IIC), poorly differentiated histology (exclusive of those cancers that are MSI-high [MSI-H]), lymphovascular invasion, perineural invasion (PNI), bowel obstruction, lesions with localised perforation or close, indeterminate, or positive margins, or inadequately sampled nodes (<12 lymph nodes) can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx), or bolus 5-FU/LV/oxaliplatin (FLOX). Observation without adjuvant therapy is also an option in this population. The benefit from adjuvant chemotherapy for stage II patients is a modest but significant survival benefit (83.6% vs 80% 5-year mortality, relative risk of death, 0.82; 95% CI, 0.70 to 0.95;  $P = 0.008$ ).

Microsatellite instability (MSI) is a marker of a more favourable outcome. The panel recommends that mismatch repair (MMR) testing be considered to assist decision-making in patients with stage II disease.

For patients with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical treatment. The treatment options are FOLFOX (preferred) or CapeOx (preferred) FLOX or single-agent capecitabine or 5-FU/LV in patients for whom oxaliplatin therapy is

believed to be inappropriate. The addition of oxaliplatin to 5-FU/LV conferred an OS benefit compared to 5-FU/LV alone at the 6-year follow-up update (72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97;  $P = 0.023$ ). CapeOx showed an improved 3-year disease-free survival (DFS) rate compared with 5-FU/LV (70.9% vs 66.5%, HR = 0.80; 95% CI, 0.69 to 0.93;  $P = 0.0045$ ).<sup>9</sup>

Overall, the benefit and toxicities of 5-FU-based adjuvant therapy seem to be similar in older and younger patients. In contrast, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer. Individualised assessment will assist in decision-making for older patients with CRC.

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for non-metastatic disease.

### Recommendations for Adjuvant Systemic Chemotherapy in Colon Cancer

The workgroup members unanimously support the general adoption of the NCCN guidelines.

The workgroup members unanimously support the following statements as modifications to the NCCN guidelines:

The lack of convincing benefit of adjuvant therapy in stage II colon cancer without any poor prognostic features supports observation alone as the preferred option for the majority of low risk stage II colon cancer patients. The QUASAR trial showed a modest but significant survival benefit for patients treated with 5-FU/LV compared to observation (83.6% vs 80% 5-year mortality, relative risk of death, 0.82; 95% CI, 0.70 to 0.95;  $P = 0.008$ ). However, the trial also included more than 60% of patients who had <12 lymph nodes sampled, and may reflect patients with higher risk features.<sup>9</sup> Pooled analysis from SEER databases and meta-analysis showed that OS benefit from chemotherapy was statistically significant for stage III patients but not for (unselected) stage II.<sup>10,11</sup> However, it can be considered if at least 1 high risk clinical feature is present.

The MOSAIC trial did not show a benefit of the addition of oxaliplatin to 5-FU/LV (FOLFOX) for patients with stage II disease, both for DFS and OS, despite accounting for such patients with high risk features as described above (HR = 0.72; 95% CI, 0.50 to 1.02;  $P = 0.063$  and HR = 0.91; 95% CI, 0.61 to 1.36;  $P = 0.648$ , respectively).<sup>12</sup> The 5-year DFS rate was 82.3% for FOLFOX vs 74.6% for 5-FU/LV, while the 6-year OS rate was 85% versus 83.3%. Similar results were seen in the C-07 study comparing FLOX to 5-FU/LV<sup>13</sup> (absolute benefit of 2% for 5-year DFS and 0.1% for OS, both statistically not significant). Given the potential risk of

long-term peripheral neuropathy among other side effects and the lack of evidence, the routine addition of oxaliplatin to 5-FU/LV is not advised in the adjuvant treatment of most patients with stage II colon cancers.

The efficacy and safety data of randomised trials comparing either FOLFOX or CapeOx to 5-FU-based regimens are more convincing compared to randomised trials comparing FLOX to 5-FU-based regimens. In general, FLOX should not be considered a regimen of choice.

## 2. Adjuvant Systemic Chemotherapy in Rectal Cancer

Neoadjuvant/adjuvant therapy of clinical stage II (T3-4, node-negative disease with tumour penetration through the muscle wall) or stage III (node positive disease without distant metastasis) rectal cancer often includes locoregional treatment due to the relatively high risk of locoregional recurrence. A total of approximately 6 months of 5-FU-based perioperative treatment is preferred. Preoperative chemoradiotherapy showed fewer local recurrences (relative risk, 0.46; 95% CI 0.26 to 0.82; from 6% to 13%) and less acute and late toxicities.

Patients, with resected stage II or III rectal cancer, who have not received preoperative radiotherapy should be offered postoperative therapy with concurrent chemoradiotherapy in addition to fluoropyrimidine-based chemotherapy. It is recommended that the total duration for perioperative therapy be approximately 6 months.

Although acknowledging that few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and that its role is not well defined, NCCN recommends adjuvant chemotherapy for all patients with stage II/III rectal cancer following neoadjuvant chemo-RT/surgery regardless of the surgical pathology results (e.g. NCCN recommends that most patients should receive postoperative chemotherapy even following an apparent complete response (CR)).

The role and optimal duration of treatment with adjuvant oxaliplatin in addition to 5-FU in rectal cancer is still unclear. Oxaliplatin may be added to 5-FU as adjuvant therapy. Most of the support for addition of oxaliplatin to 5-FU as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer. The use of a shorter course of adjuvant oxaliplatin in addition to 5-FU in rectal cancer (i.e. ~ 4 months) is justified when preoperative chemo-RT is administered.

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for non-metastatic disease.

### Recommendations for Adjuvant Systemic Chemotherapy in Rectal Cancer

The workgroup members unanimously support the general adoption of the NCCN guidelines.

The workgroup members unanimously support the following statements as modifications to the NCCN guidelines:

Evidence for the role of adjuvant 5-FU and oxaliplatin in rectal cancer is limited and at times conflicting, nevertheless till more definitive data emerges, adoption of the NCCN guidelines is prudent.

The role of adjuvant therapy in patients with pT3N0 rectal cancer following upfront surgery remains contentious.

### 3. Systemic Chemotherapy Strategies in Patients with Metastatic CRC

Our panel proposes to adopt the ESMO guidelines as a pragmatic guideline for systemic therapy in metastatic colorectal cancer. The key recommendations are listed below. Patients can be divided into treatment groups. Systemic treatment recommendations are listed based on these groups:

Group 0: Upfront R0 resectable liver ± lung metastases.

Group 1: Potentially resectable metastatic disease after systemic treatment.

Group 2: Non-resectable, intermediate intensive treatment (e.g. extensive disease, tumour-related symptoms).

Group 3: Non-intensive/sequential treatment.

#### *Upfront R0 Resectable Liver ± Lung Metastases (Group 0)*

When patients undergo upfront resection of metastases (including primary resection in cases of synchronous presentation), postoperative adjuvant FOLFOX for 6 months could be considered. Postoperative chemotherapy with FOLFOX for 6 months is generally recommended. However, adjuvant 5-FU has not shown significant benefit in 2 small randomised trials and no data is available for FOLFOX. The use of FOLFOX in this situation is supported only by the indirect evidence with regard to the potential value of FOLFOX in the perioperative situation.

Upfront resection of metastases followed by adjuvant systemic chemotherapy may be a preferred option in good prognosis patients with a single small (<2 cm) liver metastasis since this lesion may not remain visible during surgery if responding well to chemotherapy.

For initially R0 resectable metastatic disease, perioperative chemotherapy is another option. In this situation 3 months pre and postoperative FOLFOX should be applied analogous to the EORTC 40983 trial.<sup>14</sup>

Achieving CR to chemotherapy is of major prognostic importance for liver metastases but should be avoided in

order to enable resection (before complete disappearance). Therefore, close follow-up with imaging and multi-disciplinary discussion is mandatory. If an anatomical resection can be performed, CR is not a major problem, because resection will be based on initial sites of liver metastases. In case of CR on CT and no option for anatomical resection, different imaging methods might be used (MRI, PET scan, contrast-enhanced ultrasound) or resection might be delayed until relapse occurs.

#### *Potentially Resectable Metastatic Disease after Chemotherapy (Group 1)*

Although never prospectively proven, it seems evident, that the achievement of a disease-free status after downsizing by induction chemotherapy or enabling secondary surgery is the only means of giving the potential of long-term survival or cure in an otherwise incurable/palliative situation. For this aim, the most active induction chemotherapy which is able to induce downsizing as much as possible in as many patients as possible should be selected upfront.

If metastases become resectable, surgery for the metastases (and the primary) should be performed, followed by postoperative continuation of the same regimen for a total of 6 months of systemic therapy (including preoperative). If metastases remain unresectable, treatment should be continued or switched, depending on quality of response.

#### *Never (Unlikely) Resectable Metastatic Disease (Group 2/3) and Group 1 Patients Not Becoming Resectable*

Multiple factors should be considered in determining appropriate frontline chemotherapy in patients with metastatic CRC.

#### Tumour Biology-related Factors

- Localisation and extent: Liver- or lung-only metastases versus multiple sites; potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension; imminent relevant tumour symptoms should be considered.
- Growth dynamics: Aggressive versus indolent growth.
- Asymptomatic versus symptomatic disease: Possibility that patient may not be fit/able to receive second-line therapy following ineffective first-line therapy.
- Prognostic molecular or biochemical markers (e.g. BRAF mutation).

#### Patient-related Factors

- Biological age.
- Comorbidity.

- Physical capacity to tolerate more intensive treatment.
- Eligibility for potential secondary resection of liver/lung.
- Psychological capacity/willingness to undergo more intensive treatment.

#### Treatment Factors

- Potential to induce maximal regression of metastases size/number.
- Drug efficacy/toxicity profile of chemotherapy.
- Potential to prolong progression-free survival (PFS) or OS.
- Toxicity profile.
- Drug sensitivity/predictive biomarkers.
- Drug availability and cost.

For Group 2 patients, where there is significant disease bulk or treatment-related symptoms, reliable and rapid regression of metastases is important. In this situation, an escalation strategy (single agent followed by combination) might have the risk that the first-line treatment is not effective, and switching to more effective second-line treatment may not be possible. Therefore, very active first-line treatment that has a high likelihood to induce metastases regression in a short time seems to be appropriate for most of Group 2 patients. It should be noted that there may be individual cases whereby surgery becomes feasible following exceptional response despite initial assessment of unresectability. For the majority of patients, the treatment aim is palliative rather than curative. The duration of any response, time to progression and OS are also relevant in choosing the most optimal regimen.

For Group 3 patients, maximal shrinkage of metastases is not the primary treatment aim. Rather, without present or imminent symptoms and limited risk for rapid deterioration, prevention of tumour progression with symptom disappearance and prolongation of life with minimal treatment burden is the aim. Therefore, an escalation strategy seems to be appropriate, starting with single agent or well tolerated 2-drug combination.

Local ICER analyses were not available for all drugs. While ICER analyses have been performed by NICE,<sup>15,16</sup> these cannot be extrapolated due to different costs of molecular testing, surgery and infusional therapy. NICE did not provide precise estimates for anti vascular endothelial growth factor (VEGF) first-line or second-line therapy.

#### **Recommendations for Systemic Chemotherapy Strategies in Patients with Metastatic CRC**

The workgroup members unanimously support the general adoption of the ESMO guidelines.

The workgroup members unanimously support the following statements as modifications to the ESMO guidelines:

A recent UK study found that addition of cetuximab to chemotherapy and surgery for operable colorectal liver metastases in KRAS exon 2 wild-type colorectal cancer patients results in shorter PFS.<sup>17</sup> (PFS at 12 months 60% in group receiving chemotherapy plus cetuximab vs 72% in group on chemotherapy alone; median PFS 14.1 months (95% CI, 11.8 to 15.9) in the group receiving chemotherapy with cetuximab compared with 20.5 months (95% CI, 16.8 to 26.7) in the chemotherapy alone group (HR = 1.48; 95% CI, 1.04 to 2.12;  $P = 0.030$ ). Cetuximab should be used with caution in patients with upfront resectable CRC.

#### **4. First-line Systemic Chemotherapy in Patients with Metastatic CRC**

The selection of the first-line regimen depends on the chosen treatment strategy (Table 1). In the absence of conclusive comparative data, options in Table 1 should be regarded as proposals rather than as strong recommendations, reflecting the available options and the likelihood of efficacy with respect to the specific treatment aim in the different disease groups. They can be modified according to individual patients' situations and experience. The majority of the proposals are not supported by sufficient randomised data but rather by small trials and retrospective subgroup analyses.

For Group 1 patients (Table 1), downsizing by induction chemotherapy (conversion therapy) enabling secondary surgery is the only means of giving the potential of long-term survival or cure in an otherwise incurable/palliative situation. Data emerging from randomised and single-arm trials suggest that the addition of a targeted agent (bevacizumab or epidermal growth factor receptor (EGFR)-antibody) to a doublet or even to a triplet might lead to a higher R0 resection rate in liver limited disease. The combination of a chemodoublet with EGFR-antibodies has led to high overall response rate (ORR) of 75% to 80% of liver metastasis and higher resection rates accordingly (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wild-type CRC. In contrast, the combination of a FU with oxaliplatin and bevacizumab has led to a non-significant trend of an increased resection rate compared with the chemo-backbone alone, although no increase in response rate was shown. FOLFOXIRI could be an alternative to FOLFIRI/FOLFOX combined with EGFR-antibodies, and is the preferred option if targeted drugs, in particular EGFR-antibodies, are not available, and in particular for KRAS mutant tumours.

For Group 2 and 3 patients (Table 1), a retrospective

Table 1. Systemic Therapy Recommendations in Colorectal Cancer (CRC)

Group	KRAS Wild-type	Recommendation*	KRAS Mutant	Recommendation*
1	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan/Cet	+++	FOLFOXIRI	++(+) <sup>†</sup>
	FOLFOX/XELOX + Bev	++(+)	FOLFIRI/XELIRI + Bev	++(+) <sup>‡</sup>
	FOLFOXIRI	++(+) <sup>†</sup>	FOLFOX/XELOX	+
	FOLFIRI/XELIRI + Bev	++(+) <sup>‡</sup>	FOLFIRI/XELIRI	+
	FOLFOX/XELOX	+	IRIS	+
	FOLFIRI/XELIRI	+	-	-
	IRIS	+	-	-
2	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan	+++	FOLFIRI/XELIRI + Bev	++(+) <sup>‡</sup>
	FOLFOX/XELOX + Bev	+++	FOLFOX/XELOX	++
	FOLFIRI/XELIRI + Bev	++(+) <sup>‡</sup>	FOLFIRI/XELIRI	++
	FOLFOXIRI	+(+) <sup>†</sup>	FOLFOXIRI	++ <sup>†</sup>
	FOLFOX + Cet	+(+)	IRIS	+
	FOLFOX/XELOX	+	-	-
	FOLFIRI/XELIRI	+	-	-
3	FUFOL/Cape (mono)	+++	FUFOL/Cape (mono)	+++
	FUFOL/Cape + Bev	+++	FUFOL/Cape + Bev	+++
	XELOX/FOLFOX	++	XELOX/FOLFOX	++
	FOLFIRI/XELIRI	++	FOLFIRI/XELIRI	++
	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	Watchful waiting	+ Selected pts. <sup>§</sup>
	Watchful waiting	+ Selected pts. <sup>§</sup>	Triplets (±Bev)	+ Option for spec.
	Triplets (+/-Bev or Cet/ Pan)	+ Option for spec.	-	Situations <sup>  </sup>
-	Situations <sup>  </sup>	-	-	

XELIRI: capecitabine + irinotecan; IRIS: irinotecan + S1

\*Consented recommendation; however decision might be modified based on individual objective and subjective parameters.

<sup>†</sup>FOLFOXIRI: Only 2 (small) phase III trials with contradictory results.

<sup>‡</sup>No randomised data for FOL (XEL) IRI + Bev.

<sup>§</sup>Option in case of low tumour burden, asymptomatic, indolent disease: close control until definitive progression (not until symptoms).

<sup>||</sup>Patients who are Group 3 but deserve (and tolerate) more intensive treatment due to specific reasons.

pooled analysis revealed a correlation between improved survival and the availability of 5-FU/LV, oxaliplatin and irinotecan at some point during the course of the disease.

In Group 3 patients (Table 1), large trials evaluated different sequential approaches. Although ORR and PFS were improved with upfront combination treatment, OS

was similar for both approaches with a non-significant median difference of 1 month. Comparable results could be shown in an elderly and/or frail population in the FOCUS 2 trial.<sup>18</sup> Upfront single-agent fluoropyrimidine does not have a significant negative impact on final outcome, although these studies reported a lower OS (<20 months), as would

nowadays be expected (>20 months) at least in a patient population mainly from Groups 2 and 3. Patient selection may well explain these differences.

Watchful waiting can be recommended in patients with the following criteria: low tumour burden, but not eligible for secondary resection, indolent disease, asymptomatic, patient is fully informed and agrees to this approach, and the patient is monitored frequently. It should be noted that the 3 pivotal trials from the 5-FU-only era have conflicting outcomes.

### **Recommendations for First-line Systemic Chemotherapy in Patients with Metastatic CRC**

The workgroup members unanimously support the general adoption of the ESMO guidelines.

The workgroup members unanimously support the following statements as modifications to the ESMO guidelines:

Recent data has demonstrated that anti-EGFR therapy should be reserved for patients wildtype for KRAS and NRAS (exons 2, 3 and 4). Testing of KRAS and NRAS mutational status should be performed for patients for whom anti-EGFR therapy is considered. Anti-EGFR therapy should not be used in patients whose tumours are found to have mutation in KRAS or NRAS. In addition, the aggregate data from randomised trials suggests that anti-EGFR therapy added to either FOLFIRI or FOLFOX is efficacious and can confer a DFS and/or OS advantage in RAS wild-type metastatic CRC.

Whilst FOLFOXIRI may be considered in selected Group 1 patients, it should be balanced against the elevated risk of substantial toxicity.

### **5. Duration of Therapy and Maintenance/Intermittent Chemotherapy in Patients with Metastatic CRC**

The treatment duration is dependent on the treatment aim. If the intention of treatment is potential conversion to resectability, induction chemotherapy should be continued until potential resectability might be achieved, ideally at least for 3 to 4 months, with first evaluation after 6 to 8 weeks, to evaluate whether the chosen regimen is active at all, and if resectability is still not achieved, for up to 6 and 8 months. Further treatment (>8 months) with the same regimen is not recommended, since it is unlikely that by continuation of the same treatment, resectability will be achieved. At this point and, in case of insufficient response within 3 to 4 months (again judged by the multidisciplinary team (MDT)), a switch to alternative chemotherapy could be considered. Cumulative liver toxicity with the risk of perioperative morbidity/mortality and delayed recovery

after liver resection will be increased by prolonged treatment duration. However, the potential toxicity of the treatment should be balanced with the potential benefits of achieving a resectable status.

For Group 2 and 3 patients, in clinical trials, the median treatment duration is only 6 months indicating that in many patients (~60% to 70%) treatment is stopped not because of progression but because of other reasons. Re-induction with the same treatment regimen is recommended in cases whereby treatment was discontinued in the absence of cancer progression. Drug-specific toxicity must be taken into account when deciding to re-induce treatment. For example, in case of oxaliplatin limiting toxicity second-line treatment must be started since oxaliplatin might not be applicable any more.

Treatment break is appropriate in a subset of patients. This requires careful patient selection and close monitoring for disease progression. In patients with aggressive disease and poor prognostic features, survival may be impaired if first-line combination treatment with all drugs is not given continuously until progression. In all other patients, induction chemotherapy (without oxaliplatin) might be stopped after 3 to 4 months until progression; in case of progression, the same treatment should be reinstated if feasible ("stop go"). However, if complete discontinuation of induction chemotherapy is chosen, accurate selection of patients and close monitoring for progression (rather than waiting until progression is clinically evident through symptoms) is strongly recommended.

An alternative to "stop and go" is the preplanned treatment intervals and break duration ("intermittent treatment") of 1 or all drugs resulting in comparable overall outcome in comparison to treatment until progression. However, the 2 approaches, intermittent and "stop and go", have not been prospectively compared yet.

The role of maintenance therapy in bevacizumab and anti-EGFR inhibitors was not established as of 2012, when the ESMO guidelines were developed.

### **Recommendations for Duration of Therapy and Maintenance/Intermittent Chemotherapy in Patients with Metastatic CRC**

The workgroup members unanimously support the general adoption of the ESMO guidelines. The workgroup members support the following statements as modifications to the ESMO guidelines:

Maintenance bevacizumab/capecitabine may lead to a modest PFS benefit in metastatic CRC.<sup>19</sup> Two workgroup members felt that maintenance bevacizumab/capecitabine's benefit came after bevacizumab/capecitabine and oxaliplatin, a regimen which in itself is not convincingly

better than capecitabine/oxaliplatin although widely practised.

There is limited data (COIN-B)<sup>20</sup> on the role of intermittent or maintenance scheduling of anti-EGFR inhibitors.

## 6. Second- and Further-line Treatment in Patients with Metastatic CRC

Second-line is defined as when the first-line chemotherapy backbone has to be changed. The general sequence is either FU/oxaliplatin followed by FU/irinotecan or the reverse sequence, which yields similar results in terms of OS.

5-FU can and should be used again in second- and further-lines, despite proven resistance to first-line combination. Continuation of bevacizumab with changed chemotherapy backbone in second-line increases OS after progression with first-line bevacizumab and chemotherapy [ML18147 study: OS at 12 months 48% vs 42% in bevacizumab plus chemotherapy group vs chemotherapy alone] (ML18147 study: median OS in the bevacizumab plus chemotherapy group was 11.2 months (95% CI, 10.4 to 12.2) vs 9.8 months (8.9 to 10.7) for chemotherapy (HR = 0.81; 95% CI, 0.69 to 0.94;  $P = 0.0062$ )). 5-FU and bevacizumab could be continued throughout first- and second-line treatment, and solely irinotecan and oxaliplatin will be exchanged by each other.

For EGFR antibodies, there is no clear data on the efficacy of continuing EGFR antibodies beyond progression. After FOLFOX combination chemotherapy (with or without bevacizumab), aflibercept and bevacizumab in combination with FOLFIRI are active with increase in PFS and OS.

Second-line FOLFOX and bevacizumab is superior in terms of ORR, PFS and OS compared with FOLFOX after failure of FU/irinotecan. (E3200: OS at 12 months 58% vs 45% in group receiving bevacizumab in combination with FOLFOX4 vs those treated with FOLFOX4 alone; bevacizumab in combination with FOLFOX4 had a median survival of 12.9 months compared with 10.8 months for those treated with FOLFOX4 alone; HR = 0.75;  $P = 0.0011$ .)

Second-line treatment with aflibercept plus FOLFIRI is superior in terms of response rate (RR), PFS and OS compared with FOLFIRI after failure of FOLFOX. (Velour study: OS at 12 months 50% vs 44% in aflibercept plus FOLFIRI vs placebo plus FOLFIRI.)

(Velour study: median OS with aflibercept + FOLFIRI vs placebo + FOLFIRI 13.50 vs 12.06 months, HR = 0.817;  $P = 0.0032$ . Two-year survival rate, 28% vs 18.7%.)

For KRAS wild-type patients not previously treated with anti-EGFR antibodies, cetuximab with or without irinotecan and panitumumab with or without FOLFIRI are possible options.

In patients refractory to FU, oxaliplatin, irinotecan, anti-EGFR antibodies (only KRAS wild-type), bevacizumab, and regorafenib, treatment with fluoropyrimidines and mitomycin or reintroduction of oxaliplatin (and irinotecan) results in very limited improvement in some patients treated last-line. However, despite poor data, these treatment strategies may be appropriate in selected patients.

Last-line salvage treatment with regorafenib is superior to placebo in terms of OS. (CORRECT: OS at 12 months: ~25% in both arms, OS at 6 months 52% vs 48% in regorafenib group vs placebo group.)

(CORRECT: HR for OS was 0.77 for regorafenib vs placebo); 95% CI, 0.64 to 0.94;  $P = 0.0052$ ; median OS was 6.4 months in the regorafenib group and 5.0 in the placebo group. The OS rate was 80.3% in the regorafenib group and 72.7% in the placebo group at 3 months, 52.5% and 43.5%, respectively, at 6 months, 38.2% and 30.8%, respectively, at 9 months, and 24.3% and 24.0%, respectively, at 12 months.

## Recommendations for Second- and Further-line Treatment in Patients with Metastatic CRC

The workgroup members unanimously support the general adoption of the ESMO guidelines. The workgroup members unanimously support the following statement as modification to the ESMO guidelines:

Recent data has demonstrated that anti-EGFR therapy should be reserved for patients wild-type for KRAS and NRAS (exons 2, 3 and 4). Testing of KRAS and NRAS mutational status should be performed for patients for whom anti-EGFR therapy is considered. Anti-EGFR therapy should not be used in patients whose tumour is found to have a mutation in KRAS or NRAS.

### Conflicts of Interest

*Dr Kong reports receiving personal fees from Merck Serono, Roche, Pfizer and Bayer; Dr Soh, receiving conference support and travel and accommodation grants from Merck and Roche; Dr Tan, receiving honoraria from Roche, Bayer, GSK, Amgen and Merck; Dr Yeo, receiving advisory board fees from Bayer and Roche; Dr Yong, receiving fees from Roche as a trial data safety monitoring committee member; Dr Zee, receiving advisory board fees from Bayer and conference support from Roche, Bayer and Merck; Dr Chong, Dr Chua, Dr Chuah, Dr Poon and Dr Toh have nothing to disclose.*

### Workgroup Members

*The Members of the SCAN Colorectal Cancer Systemic Therapy Workgroup are Section Lead (Adjuvant): Thomas Soh, MBBS (Singapore), MRCP (UK), Department of Haematology-Oncology, National University Cancer Institute, Singapore,*

Singapore; Section Lead (Metastatic): Clarinda WL Chua, MBBS, MRCP, MMed, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Chairperson: Iain BH Tan, MBBS, MRCP (UK), PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Dawn Chong, MBBS, MRCP (UK), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Benjamin Chuah, MBBS, BAO (Ireland), MRCP (UK), Oncocare Cancer Centre, Singapore; Hwai Loong Kong, MBBS, MRCP (UK), FAMS (Med Onc), HL Kong Medical Oncology Centre, Singapore; Donald Poon, MBBS (S'pore), MRCP (UK), MMed (Int Med), Medical Oncology, Raffles Cancer Centre, Singapore; Han Chong Toh, MB ChB (Cambridge), MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Wee Lee Yeo, MBBS, MRCP, FAMS, Department of Medical Oncology, Tan Tock Seng Hospital, Singapore; Wei Peng Yong, MB ChB (University of Aberdeen), MRCP (UK), Clinical Pharmacology Fellowship (University of Chicago), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Ying Kiat Zee, MBBS (London), MRCP (UK), FAMS (Med Onc), Medical Oncology, Parkway Cancer Centre, Singapore.

### Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Young Suk Park, MD, PhD, Division of Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea.

### REFERENCES

- Teo MC, Soo KC. Cancer trends and incidences in Singapore. *Jpn J Clin Oncol* 2013;43:219-24.
- National Registry of Diseases Office, Singapore. Trends of Colorectal Cancer in Singapore 2007-2011. Available at: [https://www.nrdo.gov.sg/docs/librariesprovider3/Publications-Cancer/health\\_factsheet\\_colorectal\\_2013feb.pdf?sfvrsn=0](https://www.nrdo.gov.sg/docs/librariesprovider3/Publications-Cancer/health_factsheet_colorectal_2013feb.pdf?sfvrsn=0). Accessed on 1 June 2014.
- Fervers B, Burgers JS, Haugh MC, Latreille J, Mlika-Cabanne N, Paquet L, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. *Int J Qual Health Care* 2006;18:167-76.
- National Comprehensive Cancer Network. NCCN guidelines for colon cancer version 3.2014. Available at: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed on 1 June 2014.
- National Comprehensive Cancer Network. NCCN guidelines for rectal cancer version 3.2014. Available at: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed on 1 June 2014.
- Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol* 23:2479-516, 2012
- Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24:vi64-72.
- National Institute of Health and Clinical excellence (NICE). Colorectal cancer: the diagnosis and management of colorectal cancer. Available at: <http://www.nice.org.uk/guidance/cg131/chapter/guidance>. Accessed on 1 July 2014.
- Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;370:2020-9.
- Gill S, Loprinzi CL, Sargent DJ, Thomé SD, Alberts SR, Haller DG, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol* 2004;22:1797-806.
- Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. *J Clin Oncol* 1999;17:1356-63.
- Tournigand C, Andre T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol* 2012;30:3353-60.
- Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011;29:3768-74.
- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;371:1007-16.
- National Institute for Health and Care Excellence. Cetuximab for the first-line treatment of metastatic colorectal cancer. Available at: <http://www.nice.org.uk/guidance/TA176/chapter/1-Guidance>. Accessed on 1 June 2014.
- National Institute for Health and Care Excellence. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118). Available at: <http://www.nice.org.uk/guidance/TA242/chapter/4-Evidence-and-interpretation%29>. Accessed on 1 June 2014.
- Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014;15:601-11.
- Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd S, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet* 2011;377:1749-59.
- Koopman M, Simkens L, May AM, Mol L, van Tinteren H, Punt CJA. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC). *J Clin Oncol* 2014;32:5s (suppl;abstr 3504). Available at: <http://meetinglibrary.asco.org/content/131325-144>. Accessed on 1 June 2014.
- Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol* 2014;15:631-9.