CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

TRIFLURIDINE AND TIPIRACIL (Lonsurf)

(Taiho Pharma Canada, Inc.)

Indication: In combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.

February 15, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0330-000
Brand name (generic)	Lonsurf (Trifluridine and tipiracil) in combination with Avastin (bevacizumab)
Indication(s)	metastatic treatment-refractory colorectal cancer
Organization	The Canadian Gastrointestinal Oncology Evidence Network (CGOEN) with the Medical Advisory Board of Colorectal Cancer Canada (and other CCC-treating physicians)
Contact information[a]	Name: Dr. Howard Lim

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Eligible patients

The CADTH recommendation states in **Table 1: Reimbursement Conditions and Reasons** (Section 1.2, and 1.2.1):

> *1. Adult patients with all of the following:*
>
> *1.2. disease progression or documented intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.*
>
> *1.2.1. Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild type.*

While these criteria are generally aligned with the SUNLIGHT trial criteria, as written, this may preclude patients who **did not** receive prior anti-VEGF therapy.

72.4% of patients in the SUNLIGHT trial received anti-VEGF therapy and therefore Lonsurf with bevacizumab was used in patients who did not receive anti-VEGF therapy.

As the **Reimbursement Conditions and Reasons** can be interpreted that patients must have been exposed to anti-VEGF monoclonal antibody we advise that CADTH amend the Reimbursement Conditions be revised to allow patients who have NOT received prior anti-VEGR therapy to be eligible for this treatment.

1.2.1. Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, or an anti-EGFR monoclonal antibody for RAS wild type.

Below are other scenarios where the proposed **Reimbursement Conditions** do not align with the SUNLIGHT trial eligibility, current international treatment guidelines, and (likely) upcoming CADTH recommendations.

- Currently, patients with left sided tumors are eligible for EGFR therapy if they are not eligible for anti-VEGF therapy. The reality is that many clinicians prefer first line EGFR in this setting. These patients therefore would not have received anti-VEGF therapy, but should still be eligible for Trifluridine/tipiracil in combination with bevacizumab.
- Some provinces have provided second line funding for bevacizumab – many have not – and therefore there may be a set of patients who can not receive bevacizumab due to funding issues.
- Panitumumab for left-sided metastatic colorectal cancer (Project number: PX0333-000) is currently under review by CADTH. Recognizing the distinct likelihood that the first-line treatment (for mCRC patients with left-sided primary tumours that express wild-type RAS) will likely change, the **Reimbursement Conditions** as currently drafted will be out of date.

Patients with resolved previous contra-indication to anti-VEGF therapy

Patients who had a previous contra-indication to anti-VEGF therapy but has now resolved should be considered for this therapy despite not having receiving anti-VEGF therapy in the past. It currently states that you must have been exposed to Bev previously but with the first line EGFR – you had to be Bev ineligible but many of those issues were soft to allow first EGFR. And some provinces do not allow second line Bev – so according to table 1 they would not be eligible for this

Retreatment with bevacizumab:

The SUNLIGHT trial included patients with prior bevacizumab and bevacizumab naïve patients. In the Clinical Reviewer's report, the report notes: "There is not a subgroup that did not show a benefit and it should be noted that the majority of patients had previously received bevacizumab and a benefit is seen with retreatment with bevacizumab in combination with the drug under review". This was a pre-specified subgroup in the SUNLIGHT trial showing significant benefit in both groups.

The clinicians participating in this Feedback support treating patients with trifluridine/tipiracil + bevacizumab (based on the SUNLIGHT trial) who

i) are bevacizumab -naïve

AND

ii) those with prior bevacizumab treatment

Proposed algorithm for treatment:

Left sided RAS WT

5FU/Irinotecan or 5FU/Oxaliplatin +/- anti EGFR or +/- anti-VEGF

5FU/Irinotecan or 5FU/Oxaliplatin +/- anti-VEGF (if not given in first line)

Anti EGFR (if not given in first line)

Lonsurf/Anti-VEGF

Right sided RAS WT

5FU/Irinotecan or 5FU/Oxaliplatin +/- anti-VEGF

5FU/Irinotecan or 5FU/Oxaliplatin

Anti EGFR (if not given in first line)

Lonsurf/Anti-VEGF

RAS mutant

5FU/Irinotecan or 5FU/Oxaliplatin +/- anti-VEGF

5FU/Irinotecan or 5FU/Oxaliplatin

Lonsurf/Anti-VEGF

If tumor is dMMR – then treatment would start with immunotherapy (at present Pembrolizumab) and then move down the algorithm after failure or intolerance of immunotherapy

If BRAF mutant

Chemotherapy +/- anti-VEGF

Anti-EGFR + encorafenib

Lonsurf/Anti-VEGF

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. See above		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐

Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0330
Brand name (generic)	Lonsurf (trifluridine and tipiracil)
Indication(s)	In combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents
Organization	OH (CCO) Gastrointestinal Cancer Drug Advisory Committee
Contact information[a]	Name: Dr Erin Kennedy

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH-CCO provided a secretariat function to the group.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Erin Kennedy • Dr. Rachel Goodwin • Dr. Suneil Khanna • Dr. Bishal Gyawali		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Michael Raphael
Position	Member, OH (CCO) GI DAC
Date	09-02-2024
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dr. Tim Asmis
Position	Member, OH (CCO) GI DAC
Date	09-02-2024
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Taiho	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0330
Name of the drug and Indication(s)	Trifluridine and tipiracil for mCRC
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions
Complete this section if major or minor revisions are requested

Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation
Complete this section if editorial revisions are requested for the following elements

a) Recommendation rationale

Please provide details regarding the information that requires clarification.

b) Reimbursement conditions and related reasons

Please provide details regarding the information that requires clarification.

- Under Discussion Points, PAG suggests removing the bolded statement in the following paragraph: “pERC noted that in the SUNLIGHT trial, some patients (29% of patients in the combination and 20% in the trifluridine-tipiracil alone groups) received concomitant G-CSF as prophylaxis and to manage neutropenia. The committee discussed the existing variability in provincial funding of growth factors in the palliative setting **and suggested that public plans resolve this potential inequity to ensure that G-CSF is available to support all patients eligible for trifluridine-tipiracil in combination with bevacizumab.”**

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. • Under Relevant Comparators, PAG suggests removing the following statement: “pERC noted that for trifluridine-tipiracil, in combination with bevacizumab, to be successfully implemented, access to both the oral and IV components of the regimen should be aligned.” The term “access” may be misinterpreted as “funding” whereas the committee discussed drug administration and dispensing. Take-home cancer coverage is not universal among jurisdictions. • Under Care Provision Issues, PAG suggests removing the following statement: “The clinical experts consulted by CADTH indicated that trifluridine-tipiracil alone (as monotherapy) would only be considered to be administered without bevacizumab if a patient had a known contraindication or experienced an absolute contraindication (e.g., gastrointestinal perforation) to bevacizumab”. The second paragraph already answers the question. • Under System and Economic Issues, PAG suggests pERC issues a statement on the use of biosimilar bevacizumab. • In Table 2 under Generalizability, PAG suggests adding a time-limited question on the use of trifluridine-tipiracil with bevacizumab in patients who have received more than 2 prior chemotherapy regimens or prior treatment with trifluridine-tipiracil. PERC already stated: “Patients who were excluded from eligibility (with more than 2 prior chemotherapy regimens, had prior treatment with trifluridine-tipiracil, with ECOG PS greater than 1) were considered by the clinical experts consulted by CADTH to be eligible for treatment with trifluridine-tipiracil in combination with bevacizumab.” This would include patients who could not start trifluridine-tipiracil with bevacizumab when this regimen was not available yet.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. An update to the algorithm is needed (rapid)
2. Please specify other implementation questions or issues that should be addressed by CADTH

Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**LONSURF, in combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents**
Name of the Patient Group	**Colorectal Cancer Resource & Action Network (CCRAN)**
Author of the Submission	**Filomena Servidio-Italiano, President & CEO, CCRAN**
Name of the Primary Contact for This Submission	**Filomena Servidio-Italiano**
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

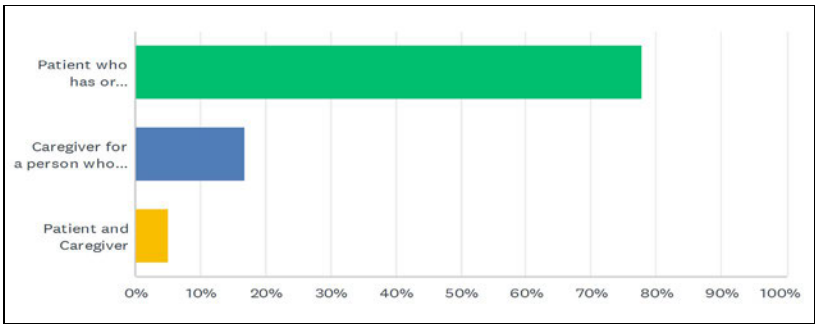
CCRAN is a national, not for profit patient advocacy group championing the health and wellbeing of Canadians touched by colorectal cancer and those at risk of developing the disease, by providing support, education and advocacy to help improve patient outcomes by way of longevity and quality of life. We have an expanded mandate to serve cancer patients outside of the colorectal cancer space through HTA patient evidence submissions, educational events and advocacy initiatives. Our mission is to reduce the burden of cancer in Canada.

2. Information Gathering

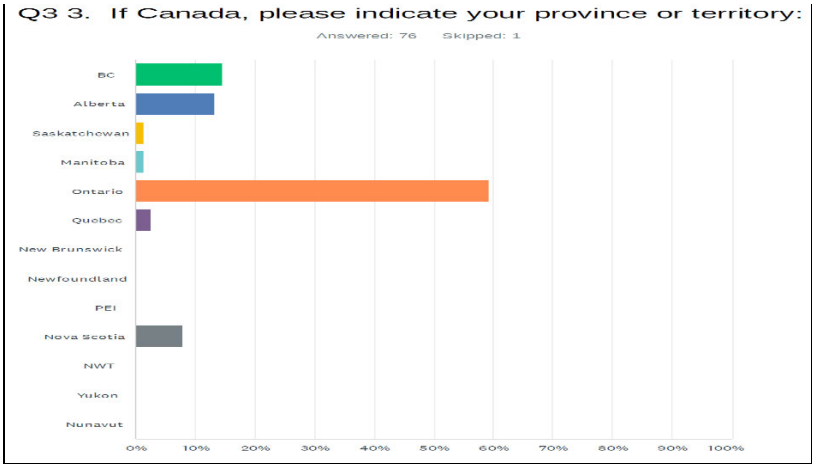
To ensure the metastatic colorectal cancer patient perspective was captured for this therapeutic under review, CCRAN employed a multi-faceted outreach approach. On **June 3rd, 2023**, we reached out to 27 Canadian Clinicians and 6 U.S.-based Clinicians (via email) who treat advanced colorectal cancer patients requesting their assistance in helping to identify patients (or caregivers) who had/have experience with Lonsurf in combination with Bevacizumab for the purposes of participating in a telephone interview. They would participate in the telephone interview to share that experience in an HTA patient input submission to help inform the deliberations of an expert drug review committee in Canada. In that email, we attached a patient flyer (**APPENDIX 3**) which we kindly requested be shared with patients who had experience with the therapy under review to encourage participation in the telephone interview process to help capture the patient perspective for this submission. That same email was then followed up 3 and 5 weeks later, resulting in 5 high quality patient interviews, whose data is captured and summarized in **APPENDIX 1**. Additionally, an online survey was developed to help capture the **metastatic colorectal cancer patient's**:

- Experience with respect to the diagnosis of their cancer, cancer journey and drug therapies administered prior to the therapy under review.

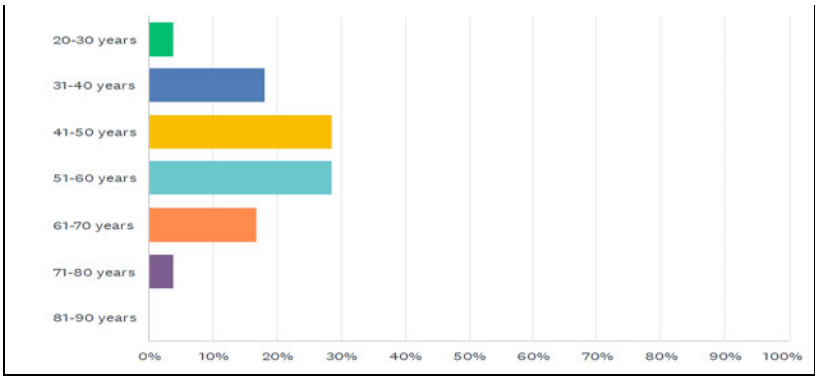
The online survey (targeting metastatic colorectal cancer patients only) was administered from **June 13 – August 5, 2023** and was promoted through CCRAN's email blasts, social media channels and support groups. **77 metastatic survey respondents** replied to the outreach by providing input, whose survey findings are herein attached and labelled as **APPENDIX 2**.



77 Survey respondents consisted of **60** patients, **13** caregivers and **4** patients who were also caregivers.



Survey respondents resided in **BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.**



Adults between the ages of 20 and 80 are well represented in the survey sample (**Q7**).
69% of the respondents were female (**Q6**).

The survey findings will be referenced throughout this submission for they reflect the perspectives of the advanced colorectal cancer patients who completed the survey.

Telephone interviews were conducted by CCRAN between **June 12th and July 26th, 2023 inclusive**, with each patient or caregiver providing first hand, compelling, relevant and high quality input regarding their:

- Experience with respect to the diagnosis of their cancer
- Disease experience
- Experience with respect to previously administered therapies prior to the therapy under review and
- Experience with respect to Lonsurf + bevacizumab

The mean age of the interviewed patients is **47.4** years and median age of the patients at the time of their diagnosis is **51** years. The qualitative data from the interviews is summarized and represented entirely in **APPENDIX 1,** which is attached, and will serve for the most part, as the basis for this qualitative submission, in addition to the objective survey findings.
Finally, a focus group was conducted via zoom on **Friday, August 4th , 2023** between 7:30 and 9:00 p.m. ET with nine metastatic colorectal cancer patients (**Patient F-N**) across Canada to ensure CCRAN captured their perspectives on the disease journey, specifically, relating to metastatic disease-induced symptoms. The patients who participated were tasked with answering the question: "***What symptoms, if any, did you experience from your metastatic colorectal cancer?***" Their thoughtful replies were captured and entered into **TABLE 1** appearing within the second part of the document entitled **APPENDIX 1** and will be referenced herein in **Section 3** of this submission.

3. Disease Experience

Colorectal cancer is the third most common cancer and the second leading cause of cancer related death in Canada. Despite optimized surgical procedures and adjuvant combination chemotherapy, many of our patients will experience a disease recurrence,

often with a fatal course. And when relapsed, the prognosis is poor, with a median overall survival of approximately 30 months from initiation of first line systemic therapy and a relative 5 year survival of 15% (NCI SEER Program 2022). While systemic treatments such as combination chemotherapies, targeted therapy, immunotherapy, and their combinations have improved overall survival in the metastatic colorectal cancer patient population over the past ten years, there is an urgent, unmet clinical need to identify new and more effective treatment options to improve the survival and **quality of life** for patients diagnosed with metastatic disease – a need that is repeatedly reported by our patients. More effective therapeutic approaches are required for this patient population because a subset of our patients are currently not benefiting from standard of care therapies while being exposed to and experiencing substantial toxic side effects nevertheless.

The online survey results identified **fatigue, bloody stools and diarrhea** as the most prevalent colorectal cancer-induced symptoms as per **Question 9** (**Q9**). Fatigue resulting from the cancer was reported to be the most important symptom to control according to patients and caregivers (**Q10**). In **Q11**, patients relayed that their colorectal cancer-induced symptoms most certainly interfere with their quality of life (**QoL**) and their daily activities. They are unable to function "normally" in their family or work setting: **87%** are unable to work and **60%** are unable to exercise, while **27%** are unable to concentrate and **25%** are no longer able to drive. These are daily functions or tasks that prevent our patients from leading a semi-normal life. There are limitations that are imposed upon them resulting directly from their cancer. Limitations such as:

- "***Mental well-being: depression, anxiety, frustration and scared of what is to come***."
- "***Not knowing when I can leave my house due to bowel irregularity***"

The top three limitations that had a psychological impact from patients' colorectal cancer (**Q12**) were:

- An inability to experience joy (72%)
- Chemo brain making me feel forgetful (46%)
- Constant fatigue makes it difficult to function normally – can't think straight (43%)

And some of the open-ended replies to this question included:

- "***Anxiety, flashbacks***"
- "***Tired having cancer on my mind all the time and worry about it…"***
- ***"Want more children but can't"***

It is important to note that not all metastatic patients experience cancer-induced symptoms. 13% of the survey respondents did not experience any symptoms at all prior to their diagnosis: their diagnosis was a result of an incidental finding.

Hence, to that end, three of the five interviewed patients had not experienced cancer-induced symptoms prior to their diagnosis (**Patients A, B, and C**). For the patients who did experience symptoms prior to their diagnosis, interviewed patients reported the following:

"***In most of 2020, I was not feeling well…… I had been complaining of breathing issues, because I had picked up a cold the previous winter and I still could not shake it, nor could I shake the cough, it just would not resolve."*** **Patient D**

"…..had pain on my right hand side which led me to go to the ER and they performed a CT scan. I had that pain for about a few weeks but was getting worse which led me to go to the ER." **Patient E**

Patient A was a longstanding Crohn's patient, diagnosed with the pathology at a young age, who underwent annual colonoscopies starting at the age of 14. At the age of 28, his colonoscopy identified a primary tumor and a subsequent colectomy revealed metastatic disease to the peritoneum.

A trip to the Emergency Room (ER) for what was believed to be food poisoning revealed an obstructed bowel and liver metastases for **Patient B**. And a positive Fecal Occult Blood Test (FOBT) is what led to **Patient C's** diagnosis whose workup revealed an obstructed sigmoid colon, metastatic disease to both lobes of the liver and mesentery tissue. **Patient C** relayed:

"***I was really surprised. Because when the colonoscopy was done, I was actually awake, I couldn't believe it, how could this be happening to me? The survival for stage 4 is about 30% after 5 years. I was so healthy and not symptomatic and secondly, what can I do to fight and get rid of this…..(became tearful). Once I was diagnosed, it got easier to cope with it than not knowing what was happening to me. I was so lucky to have tests done in an expedited manner and have found it so fast."*** **Patient C**

All five interviewed patients were diagnosed with stage 4 disease at time of diagnosis. Metastatic colorectal cancer patients who participated in the focus group, **Patients F through N** (**TABLE 1**) identified the following metastatic colorectal cancer-induced symptoms:

- Anemia, bloody stools, abdominal and low back pain
- Difficulty breathing, poor appetite, fatigue
- Abdominal cramping, migraines, dizziness, vomiting, all of which were due to a brain metastasis
- Gas, bloating, occasional diarrhea, daily multiple bowel movements, and the feeling as though bowels had not been completely emptied.

One **focus group member** (**Patient M**) provided the following input:

"***Yes, I sure was symptomatic. I just wasn't feeling well. I experienced bloody stools, abdominal pain, gas and bloating, occasional diarrhea, daily multiple bowel movements and a feeling as though I wasn't done emptying my bowels. This went on for a couple of years till I finally was sent for colonoscopy which revealed a massive tumour in my sigmoid colon that had almost completely blocked my colon. And then they discovered 23 tumours in both lobes of my liver. I was pretty devastated but I suffered for many, many months – 2 years actually - with those symptoms and it's symptoms that were due to an advanced case of colorectal cancer – Stage 4. My family doctor really should have listened to me but failed to do so, I think because of my young age."*** **Patient M**

And interviewed **Patient F** thoughtfully relayed:

"***Oh, there was so much going on with me. I had been experiencing anemia and bloody stools for about 10 years before I was actually diagnosed with metastatic colon cancer. I was so young and this was part of the problem. I had low back pain that I kept complaining about to my GP for well over 2 years, but nothing was done about it, I think because of my young age. My upper right abdomen hurt, and this was due to the 20 metastatic tumours in my liver. It felt like pressure, deep pressure that just kept gnawing constantly in my right side. And with every passing day, it hurt more and more."***

As for the toll the disease has taken on caregivers, caregivers who responded to the online survey identified the following as the top three difficulties when caring for colorectal cancer patients (**Q34**):

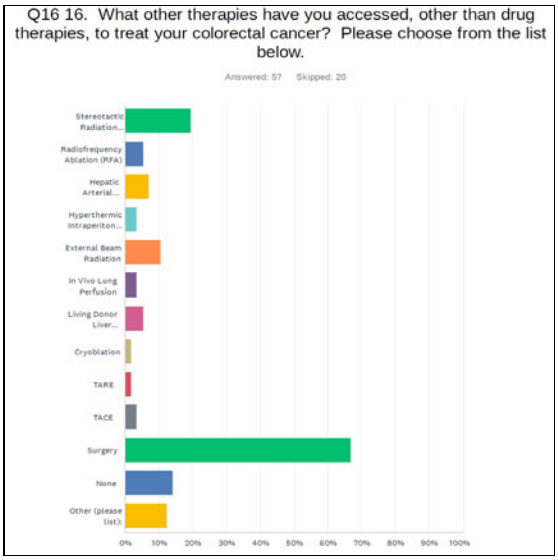
- Loss of lifestyle (70.6%)
- Difficulty managing treatment-induced side effects (54.9%)
- Loss of income (45.1%)

These challenges merely underscore the impact of the disease on the caregiver as they struggle with the emotional turmoil of the diagnosis, but as one survey respondent states, "***try to run the household on their own while also working, and being a full time caregiver***" is a considerable ongoing challenge imposed upon the caregiver from which there is little to no reprieve. (**Q34**)

4. Experiences With Currently Available Treatments

Patients with metastatic disease who completed the online survey generally received treatment with fluorouracil-based chemotherapy (with oxaliplatin and irinotecan – **65%**), vascular endothelial growth factor (VEGF)-based therapy (mainly bevacizumab – **50%**), and epidermal growth factor receptor (EGFR)-targeted therapies in confirmed RAS wild type disease (either Cetuximab or Panitumumab – **8%** and **17%** respectively). For patients whose disease was identified to be Microsatellite Instability-High (MSI-High), Pembrolizumab was accessed by **3.4%** of the survey respondents and in patients identified to have a BRAF V600E mutation, Encorafenib in combination with an anti-EGFR therapy was accessed by **5.1%** of respondents. One patient accessed Regorafenib. Open ended replies revealed additional systemic therapies were also accessed: Opdivo in combination with Yervoy for the treatment of a patient's metastatic disease; and Raltitrexed in combination with Oxaliplatin was also identified as a prescribed treatment for a patient (**Q15**).

Q16 highlighted the additional non-systemic therapies utilized in the management of the patients' metastatic disease:



Additional non-systemic therapies included Surgery, SBRT, External Beam Radiation, HAIP, Living Donor Liver Transplant, and In Vivo Lung Perfusion, to mention a few. Complimentary Therapies were included in the open ended replies.

Patients cited fatigue, peripheral neuropathy, hair loss, diarrhea and nausea as the most commonly induced side effects from their colorectal cancer treatments (**Q17**). The three treatment induced side effects that were most difficult to tolerate as identified in the survey findings were ***fatigue*** (52%), ***neuropathy*** (48%), and ***nausea*** (40%) (**Q19**).

In **Question 20**, patients were asked to rate those three side effects across a scale of "***No impact***" to "***Significantly impacting***" their daily life, the results of which appear below:

	NO IMPACT	SMALL IMPACT	MODERATE IMPACT	SIGNIFICANT IMPACT	TOTAL	WEIGHTED AVERAGE
Side Effect #1:	3.77% 2	5.66% 3	33.96% 18	56.60% 30	53	3.43
Side Effect #2:	4.00% 2	8.00% 4	42.00% 21	46.00% 23	50	3.30
Side Effect #3:	4.35% 2	4.35% 2	43.48% 20	47.83% 22	46	3.35

The three weighted averages of ***3.43, 3.30 and 3.35*** each reflect the profound impact the treatment-induced side effects had/have on the patients' daily lives, regardless of the side effects selected: the majority of the respondents selected "***significant impact***" for **Side Effect #1** and the majority then proceeded to select either "***significant impact***" and/or "***moderate impact***" for **Side Effect #2** and **Side Effect #3**.

Medications were prescribed to help address the treatment-induced side effects which included (**Q21**):

"***Emend and Zofran for vomiting, iron for anemia, ondansetron for nausea/fatigue, and CBD, acupuncture and physiotherapy for neuropathy***".

Survey respondents relayed they were required to pay out of pocket for some of the medications prescribed to help address the treatment-induced side effects (**Q22**):

"***Mouthwash was $50, not covered, required 4x."***
"I paid a lot prior to trillium kicking in."
***"Hundreds, in* the deductibles**."
"$500 per year."

Four patients and one caregiver participated in the telephone interviews that allowed CCRAN to capture a significant amount of qualitative data with respect to their treatment journeys. Interviewees provided thoughtful and at times heart wrenching input regarding their treatment journeys, describing the treatments accessed, the impact on their quality of life and the amount of time to disease progression. By way of summary, all five patients received a minimum of two previous fluorouracil-based chemotherapy treatment regimens for metastatic disease (FOLFOX/FOLFIRI); one of whom received the anti-VEGF therapy - Bevacizumab (**Patient E**) as part of their second line therapy in combination with FOLFIRI and thee patients received anti-EGFR therapy as part of third line (**Patient B**), fourth line (**Patient C**) and first line (**Patient D**) therapy. **Patient A** accessed Stivarga in fourth line.

Caregiver A summarized her 28 year old husband's treatment journey as quite "*hellish*" having been diagnosed with metastatic disease at such an early age. Having been a Crohn's patient most of his life, **Patient A** was diagnosed with colon cancer in December 2015 through an annual colonoscopy and his peritoneal metastases were discovered through his colectomy. He subsequently underwent 12 rounds of FOLFOX, cytoreductive surgery (CRS) plus HIPEC in the U.S., followed by 12 months of FOLFIRI in combination with Avastin, a rechallenge of FOLFOX, SBRT, short course of STIVARGA, and then finally Lonsurf in combination with bevacizumab for almost two years. The only time he was declared No Evidence of Disease (NED) was immediately after the CRS + HIPEC which lasted nine months. The balance of the therapies he accessed never allowed him to achieve complete remission and according to the patient's caregiver, the therapies were quite toxic:

*"**While he was on the FOLFOX, he had a difficult time. It was one of the worst therapies he endured. Probably the worst. He had trouble eating and sleeping, he had bad neuropathy, was brutal, not working, weak, lost weight, and generally unhappy. When he accessed FOLFIRI, that wasn't too bad; he was pretty functional and able to work on that treatment on his off week only, about 15-20 hours per week. The STIVARGA gave him a bad acne/rash and fatigue which he did not appreciate so the med onc lowered the dose and meds were prescribed to help with that. None of the therapies really worked for him. They just tried to buy him time."*** **Caregiver A**

Patient B is a 53 year old female diagnosed at 51 years of age and had no symptoms consistent with colorectal cancer. Were it not for an episode she believed to be food poisoning which led to an ER visit, her metastatic sigmoid cancer (liver) would not have been discovered in May 2021. Surgical resection ensued to address the partially obstructed bowel, followed by 6 months of FOLFIRI, 7 months of FOLFOX (February 2022-August 2022), followed by the introduction of Panitumumab in September 2022 to February 2023. She was happy to have a treatment holiday for 2.5 months which then resulted in surgical resection in April 2023. She then commenced Lonsurf plus bevacizumab in May 2023. She relayed that each therapy would elicit a response of approximately 6-7 months and then she would be required to switch to another therapeutic because of disease progression. Two of the treatments were problematic for her:

"I would say that for the FOLFIRI and FOLFOX, the nausea was the worst for me on those two treatments. I found it difficult to eat and nothing would work in terms of anti-nausea meds. So I lost a lot of weight. I would lie down all the time on the couch and close my eyes and do nothing. I would barely do anything every day that I was on those two therapies. I did try my best to work on my off days when I was not on treatment, but I could barely keep up because of lingering effects. With respect to Panitumumab, …. it caused a rash and I ended up with an infection on my face for which I required additional meds to treat it. It lasted so long. Right up until I came off of the treatment. Nothing worked even though I saw a dermatologist. The med he wanted to put me on wreaked havoc on my liver so I couldn't take it." **Patient B**

Patients C, D and E have similar accounts of their treatment journeys:

"***The FOLFIRI: That was the most problematic, I was weak and lethargic, I couldn't recover so fast, so tired and feeling low, constipated, I suffered abdominal pain, sensitivity to smells so I couldn't cook, and I love to cook but I couldn't be in the kitchen when my husband was cooking."*** **Patient C**

"***So the FOLFIRI plus the PANI gave me acne from the top of my head to my waist because of the PANI. That was really the worst. I was on the Pani plus FOLFIRI for 16 months and I was actually NED but then once I was off it for 4 months, my cancer came back. And when I went on the FOLFOX, it didn't take very long to progress on that treatment, only 4 months. So that's when I went on the Lonsurf + BEV ."*** **Patient D**

"***I found the folfiri to be worse than the folfox and it wasn't even close. The folfiri was way worse than the folfox….. but the second year was hard for me. I had extreme nausea, vomiting, it's like having the flu for 4 days every two weeks.*** " **Patient E**

Of note**: Patient E** experienced a one year disease free interval after his adjuvant therapy, 28 months on FOLFIRI plus Avastin and 1.5 months on a rechallenge of FOLFOX.

Generally, all interviewed patients and one caregiver reported debilitating side effects while undergoing treatments for their metastatic colorectal cancer, which compromised their quality of life. While patients may have derived a clinical benefit in terms of response, that response was accompanied by incapacitating side effects such as fatigue, nausea, lack of energy, diarrhea, neuropathy, skin rash, lethargy and flu like symptoms that prevented them from engaging in life on any meaningful level. Patients were quite emphatic about their experience with combination chemotherapies which compromised their well being some or most of the time which necessitated time off work, inability to care for children, lack of self-care, and time spent enjoying life in general. Normal daily activities could not be resumed nor could quality time with friends and family be spent, permitting them the freedom to "live life again".

5. Improved Outcomes

Patients treated for their advanced stage colorectal cancer, along with their families, are faced with an ongoing challenge: the prognosis for these patients continues to be poor and as such the goal is to provide these patients with additional therapeutics to manage their disease to ensure improved longevity and quality of life is achieved. Hence, when asked "***What improvements would you like to see in new treatments that are not available in current treatments***?", online survey respondents clearly highlighted their desire to access therapies that will effectively control their disease with respect to improvements in their physical condition (for example, tumour shrinkage, tumour stability, reduction of pain and improved breathing – **Q38**). Patients found these improvements to be of utmost importance, as reflected in the weighted average score of **9.78** out of a possible 10. However, the survey results revealed therapies that provide improvements in a patient's quality of life (i.e. improvement in mobility, sense of wellness, relief from side effects) **are also important to patients and caregivers** and scored equally as high, with a weighted score of **9.50** (**Q39**). 87.1% of patients would take a therapy that could provide better quality of life during their lifetime even if it does not extend survival (**Q41**). And after being told there is no other available treatment for their cancer, patients would be prepared to access a toxic therapy provided an appropriate survival benefit is realized for them: the greater the survival benefit (**2 months, 6 months, 1 year**), the more likely the patient was willing to access a toxic therapy and endure the treatment's toxic side effects (**Qs 42, 43 and 44**), generating the following weighted scores: **5.02 (2 months), 6.59 (6 months) and 7.53 (1 year)** respectively. Patients provided the following open-ended replies;

- "***Oral drugs… and we need access to as many drugs as possible and we need to know the ones that will work for our cancer before hand (i.e. biomarker testing)***
- ***Meaningful improvement in survival time***
- ***Develop a drug that does not involve hair loss. Give me something to treat metal mouth other than sucking on lemon drops or rinsing with salt water – avoid these…***
- ***The chemos available will not cure me. There needs to be more options."***

The interviewed patients provided their perspective on the improvements they would like to see in a drug therapy, which they believe is currently not available in other previously accessed therapies. They maintain a therapy should regress disease with minimal to no side effects. They prefer a therapy that is designed to cure a patient's cancer. And while the therapy is destroying the cancer, it should not be destroying the balance of the body's healthy tissues, rendering the patient debilitated and unwell. The patient's quality of life should be maintained at all times to ensure they are living their best life **and not a former glimpse of what used to be their life**. If a therapy cannot provide a cure, it should indeed provide a significant extension in survival. A drug therapy should also be conveniently administered: it should be an **orally administered therapy** in the comfort of a patient's home. This would eliminate considerable travel and stress for the patient, their caregiver and the entire family, such that travel costs are avoided and precious time spent away from home is spared. And if the therapy must be infused at a cancer centre, then it should be infused in the shortest amount of time possible with minimal chair time for the patient. Additionally, they emphasized the need for treatments that could provide a durable, longstanding response. When these patients were asked if their life would be any different if the drug therapies had these desired improvements, an emphatic and overwhelming "***yes***" was their reply. **Caregiver A** summarized these points quite articulately:

"***I think we want good quality of life, want to be able to extend longevity while we are able to have a good quality of life, and of course, let's try to avoid infusions as best we can, but if we can't avoid infusions at the cancer centre, then let's make them short infusions. We don't want any side effects from treatments because that will impact our quality of life: it doesn't help if you're living longer but you have no quality of life, right?" Caregiver A***

All five interviewees maintained that Lonsurf plus bevacizumab possessed the desired improvements. According to the patients and caregiver, it is capable of regressing disease, prolonging life while providing improved quality of life, with minimal to no side effects. This is a protocol that can allow patients to resume daily activities, some of whom were able to become gainfully employed again, engage in life by spending time with family and friends, good quality time, raise their young children, and permit them the freedom to appreciate life despite the horrors they have endured through toxic treatments. In **Patient's B** words:

"***Absolutely. It has the oral part covered, and it is convenient for me. And it's a better treatment for sure. I am not debilitated like I used to be. Pharma companies need to take into consideration what they are doing to patients' lives when developing drug therapies, especially elder patients. This drug company, Taiho, did that with Lonsurf. It's a great pill. And the Bev is good too***."

6. Experience With Drug Under Review

As evidenced by the input provided by our 5 interviewees, patients with mCRC who have progressed following fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and anti-EGFR antibodies (in confirmed RAS Wild type disease) have limited treatment options but do have a good performance status and should be considered for further treatment. **APPENDIX 1** (**Q10-26**) captured the treatment-related experiences for 5 interviewed Canadian patients, (one of whom is represented by their caregiver – **Caregiver A**) who have or are currently undergoing the therapy under review. **Patients A, B and E** had their treatments covered through private insurance ± compassionate care as part of **5th, 4th and 3rd** line treatment respectively and **Patient E** also received some assistance from the manufacturer's Patient Support Program; **Patient C** accessed Lonsurf through the manufacturer's Patient Support Program as part of **5th line** treatment and **Patient D** had their treatments covered through RAMQ as part of **3rd line** treatment.

Caregiver A described her late husband's journey with great care and pain. Her husband accessed Lonsurf + bevacizumab as part of 5th line therapy at the young age of 32 years in March 2020 – August 2021 as an mCRC patient, whose metastatic disease was confined to his peritoneum and pelvic lymph nodes. After having received, FOLFOX, CRS + HIPEC, FOLFIRI + Avastin, FOLFOX, SBRT, Stivarga, he received 18 months of the therapy under review which not only regressed his disease but allowed him to

achieve an excellent quality of life, capable of engaging him in his life once again. In **Caregiver A's** words: "***He was able to work on a modified schedule, able to drive longer distances and went to work longer distances, did housekeeping chores, performed tasks such as vacuuming, cleaned the bathrooms and kitchen, walked the dog every day, he had a great appetite, so he ate well, and was able to put on weight. I used to make fun of him, because he was bigger than he ever was. He would cook one or two times per month something requiring time and effort. He was able to do family activities, day trips during the pandemic. He had a really good life with this therapy. Yes. His CEA was a good indicator and it just kept going down. His CT scans were showing regression as well. Apparently, right off the bat, there was a 50% response rate and then the disease had disappeared altogether. It was so wonderful."*** It is worth noting that **Patient A** experienced no side effects, according to **Caregiver A,** which accounts for the excellent quality of life and **Caregiver A** rated her husband's experience with the therapy as a **10 out of a possible 10**, which she maintains her husband would most certainly concur were he alive today.

Patient B received her diagnosis of mCRC (liver and ovarian) in May 2021 through an ER visit. She underwent surgical resection of her primary sigmoid tumour followed by FOLFIRI (June-December 2021), FOLFOX (February-August 2022) and Panitumumab (September 2022-February 2023), in confirmed RAS WT disease. Surgical resection of Krukenberg tumours ensued in April 2023. Lonsurf + bevacizumab therapy was initiated in May 2023. **Patient B** is delighted to be on the therapy. She claims to be experiencing only one side effect: "itchiness" throughout her body, predominantly at night, which she attributes to the Lonsurf, and some "***mild abdominal cramping two days post avastin infusion, but then it subsides***." She claims, "***this is a great therapy in comparison to what I have been on previously"*** and rates her quality of life while on the therapy a **10**.
Patient B shared what she is able to do now that she is on this therapy which she could not otherwise do on previous therapies (**Q23**):
"***Shopping which I love! Freedom to live my life like I used to! That is huge for me. I get to go to lunch all the time now, and I couldn't do that before. I join my friend Elizabeth all the time socially. I am working towards going back to school because of this therapy. Isn't that great? I get to go to church on Sundays now. I couldn't do that before. Just being able to go for walks, do gardening and household chores, take day trips, all this because of the therapy. It's fantastic. And I am so happy***"

Patient C was diagnosed with metastatic disease to liver, lungs, mesentery, spinal and 9th rib and initiated Lonsurf + bevacizumab on December 26, 2022 as part of **5th line** therapy. The patient reports no side effects while undergoing the therapy and, therefore, rates her quality of life while undergoing treatment as a **9-10** out of a possible 10. The patient had cancer induced symptoms before starting Lonsurf + bevacizumab that included: vague pain, constipation, nausea, lack of appetite, etc and according to **Patient C**: "***…..all of the previous symptoms have resolved because of the therapy***." And her most recent CT scan has confirmed response to the therapy and her CEA is trending downwards. In her words:
"***I had a CT scan one month ago which confirmed response. My lung and liver mets have continued to regress! And my CEA is trending downwards. Since December 2022, it has dropped 400 points! And clinically, I feel wonderful. It is incomparable to what I used to feel like back in December of 2022. So all around, I am really happy with where I am at today because of this terrific therapy***."

Patients D and E were diagnosed in August 2020 (liver and lungs) and February 2018 (liver, lungs, chest wall and peritoneum) respectively. They initiated Lonsurf + bevacizumab therapy in February 2023 (bevacizumab only, then added Lonsurf in June 2023) and April 2023 respectively, as part of 3rd line treatment. Neither experienced any side effects and both rated their quality of life while on the protocol as a **9** and **9 or 10**, respectively. **Patient D** reports:
"..this is the best I have felt all year! Before the Lonsurf plus Bev, I was feeling a pressure in my lungs and on my side, which was due to cancer progression. But now, that pressure has literally decreased overnight. Everything feels like it is moving in the right direction at the moment. I am so happy and grateful." And **Patient E relayed**: "…***cuz you would never know, I feel completely normal. I don't know if it's the nature of stopping the other treatments or my cancer shrinking***."

When asked what has the therapy allowed you to do, **Patient D** thoughtfully replied:

"***There are hydrangea bushes that have to be torn out on my property so I am finally going to do that cuz I can finally feel well enough to do it. I haven't been able to do it in the past cuz I haven't felt well enough to do due to silly chemo but I do now because of this therapy that gives me really good quality of life. It's stuff like this that I am able to do, everyday stuff like this that is meaningful and relevant in the average every day Canadian."***

All five patients have shown excellent tolerance to Lonsurf + bevacizumab despite having suffered so terribly with standard of care therapies. None of the 5 patients experienced interruptions in their Lonsurf + bevacizumab treatments and all five interviewees maintained it was well worth accessing the therapy under review (**Q22**) because compared to previously accessed regimens, Lonsurf plus bevacizumab reduced the incidence of adverse events with subjective symptoms and clearly maintained their quality of life:

Caregiver A: "***Yes, his quality of life was the best on this therapy."***
Patient B: ***"Oh, ya, for sure. It gives me, like, I am not stuck at the hospital having to receive long infusions of toxic therapy. When I was on the other treatments, I could never go out. Now with this therapy, I am on treatment, you would never know it! I am good. It offers me hope to continue my life."***
Patient C: ***"Of course it was worth it. For sure. It is giving me length of life and quality of life. That's a lot."***
Patient D: ***"The fact that within the first week taking it, it reduced the pain in my side and the pressure in my chest, this is wonderful. The results so far seem to be so positive, so definitely worth it for me!"***
Patient E: "***Of course it was! Of course, of course, it's gonna keep me going. I am out of options. Something that is relatively easy to take and endure. Some people can keep going on this for quite some time, I hope it's me."***

Caregiver A shared what she and her family were able to experience in life because of Lonsurf + bevacizumab therapy:

"***We got to take one last vacation to a cottage as a family up north. It was so precious for us. We did again with friends too. We would not have been able to do that if he was on toxic chemo. He would have been too sick. He also got to stay at home taking care of his daughter while I worked and he continued to work from home. He was a structural engineer able to contribute in such a meaningful way to society and his family. He was such a good guy. A good human, a good husband and father. Wonderful friend and son. The therapy allowed him to do what he wanted to do which is raise his daughter, work from home and live his life to the fullest. Isn't that what we want from a therapy?"***

Patients clearly expressed what they perceived to be a survival benefit and enhanced quality of life in respect of Lonsurf + bevacizumab; and while our sample size is small, the clinical response and improved quality of life being observed is quite remarkable and is irrespective of age, gender, location of primary tumour, treatment line, number of metastatic sites, prior therapy received with bevacizumab and RAS mutational status. This clearly indicates, according to the data provided herein, that Lonsurf + bevacizumab is a viable treatment option for all clinically relevant subgroups of metastatic colorectal cancer.

7. Anything Else?

Interviewed patients provided thoughtful and compelling examples of why Lonsurf + bevacizumab was worth accessing. Their values, preferences and priorities were captured in **APPENDIX 1**, the majority of which have already been highlighted throughout this submission. We would, however, like to summarize the astounding benefits experienced by all interviewed patients by providing one last quote from **Caregiver A** which speaks to the therapy's benefits in terms of: ease of use, oral administration, extension in life, amelioration of symptoms and preferred toxicity profile:

"***You know, since the Lonsurf was an oral medicine, it was significantly easier to use than the previous infusions which were long and tedious. This oral medicine was administered in the comfort of his home and didn't require any effort, travel, cost, nothing. As for the BEV, it was a short infusion and not too time consuming. Chair time was minimal. It was good. His life was not impacted in the same way his life was impacted by the other therapies he had in the past. It really did make a difference. It was time he got to spend with me and his daughter – 18 months. Therein lies the difference. Time with family, vs time at the cancer centre***." **Caregiver A**

Our interviewed patients accessed the therapy under review in third (2), fourth (1) and fifth (2) line therapy and were happy to report what they believed to be a therapeutic benefit, which suggests this protocol could be applicable not only in third line but later line therapy as well, in patients with refractory disease. It is important to note that therapeutic benefits were observed irrespective of gender, location of primary tumour, age, number of metastatic sites, number of tumours and RAS mutational status. Patients who had previously accessed bevacizumab in an earlier line of therapy, also experienced a clinical benefit, which merely supports a role for continued anti-vegf therapy with bevacizumab beyond progression in this patient population. This is certainly encouraging because it allows patients who were heavily pretreated, such as **Patient A** with bevacizumab, to access a therapy with minimal to no side effects while experiencing a durable response, not only to Lonsurf but to previously administered bevacizumab as well. And as previously noted, responses were experienced by all clinically relevant subgroups: RAS Wild type and RAS Mutated colorectal cancer alike. As it relates to the **RAS mutated colorectal cancer** patient population, the administration of Lonsurf + bevacizumab in third line and beyond is helping to address **an unmet need** in our refractory colorectal cancer patients for there are currently no approved therapies targeting this relevant subgroup. It will provide a new treatment option for these patients with superior quality of life due to fewer and less severe side effects.

It was made abundantly clear by our interviewed patients that the treatment protocol under review allowed them to maintain their physical function – a highly sought-after benefit by cancer patients and caregivers alike. In **Patient C's** words: "***I get to live more in a good way. This is a big accomplishment to live in a better way, a good life***". The therapy under review certainly managed to preserve interviewed patients' performance status as they recalled their compromised selves on combination chemotherapies previously received, living a grueling and "*less than*" life. When compared to another drug therapy administered in third line (Stivarga), **Patient A** experienced no response and his caregiver described the experience as "*hellish*" with respect to adverse events, which necessitated not only a dose reduction, but eventually a treatment termination.

All interviewed patients had failed previous treatment for their colorectal cancer, including surgery, chemotherapy, biologic therapy and radiation therapy and were desperately in need of another therapeutic to help manage their metastatic disease. Each patient was beyond delighted to have accessed what they described as a non-toxic therapy, demonstrating a level of benefit unlike any other previously accessed therapy with respect to quality of life maintenance. Additionally, to have observed, in some, the magnitude of response in our interviewed patients who had progressed so quickly following prior treatments confirms that Lonsurf + bevacizumab is effective and amenable for long term administration.

If publicly funded, Lonsurf + bevacizumab would be an extremely important third line and beyond therapy for patients whose disease has been deemed to be refractory or ineligible for standard of care therapies. Funding this therapy aligns well with the patient perspectives captured within this submission. We, therefore, strongly support and urge that a positive funding recommendation be issued for Lonsurf + bevacizumab for the treatment of metastatic colorectal cancer in adult patients who have been been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents . We believe it aligns well with the identified patient need for a new, effective, quickly administered, oral, less toxic treatment option that is capable of maintaining a high quality of life for the patient. This should become the new standard of care for this subset of the patient population.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Taiho			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Filomena Servidio-Italiano
Position: President & CEO
Patient Group: Colorectal Cancer Resource & Action Network (CCRAN)
Date: Friday, August 18, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	Colorectal Cancer Resource & Action Network (CCRAN)
CADTH project number	PC0330-000
Brand name (generic)	Lonsurf (Trifluridine-tipiracil)
Indication(s)	In combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.
Organization	**Colorectal Cancer Resource & Action Network (CCRAN)**
Contact information[a]	Name: **Filomena Servidio-Italiano, President & CEO, CCRAN**

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

CCRAN happily agrees with the committee's recommendation, with one exception: In Table 1.2, it states that adult mCRC patients meet the reimbursement condition with *disease progression or demonstrated intolerance to a **maximum** of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.*

CCRAN significantly grappled with the above-noted portion of the recommendation in respect of patients who are eligible for Lonsurf in third line ***and beyond***. Patients who undergo third line treatment for their RAS wild-type disease or those who may have accessed a clinical trial as an earlier-line therapy, should be permitted to access the therapy under review in third line and beyond to ensure equitable access and to promote consistency within the mCRC patient population. As evidenced in CCRAN's patient input submission, this therapeutic protocol clearly provides patients with a survival benefit and improved quality of life, helping to serve an unmet need in all later lines of therapy (third line **and beyond**).

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

If not, what aspects are missing from the draft recommendation?

Yes, the committee respectfully considered CCRAN's input in respect of how Lonsurf + bevacizumab in third line and beyond is helping to address an unmet need in our refractory colorectal cancer patients, particularly for those within the RAS mutated mCRC patient population where there are currently no approved therapies targeting this relevant subgroup. Once publicly funded, Lonsurf + bevacizumab will be an extremely important third line and beyond therapy for patients whose disease has been deemed to be inoperable or metastatic.

A positive funding recommendation for this therapy aligns well with the patient perspectives captured within CCRAN's submission.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

From the perspective of access to Lonsurf, the implementation issues have been clearly articulated and adequately addressed, with the exception of clarity related to access in third line ***and beyond***, as described above.

What is less clear, however, is the reimbursement recommendation for bevacizumab given in combination with Lonsurf. Many patients access bevacizumab in earlier lines of treatment (i.e. patients whose disease is RAS MT), and CCRAN respectfully requests that reimbursement for bevacizumab be clearly supported and articulated, so that patients who have accessed bevacizumab in prior lines of therapy may continue to avail themselves of this life-extending therapeutic which enhances the benefits derived from Lonsurf.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

Yes, the reimbursement conditions and the rationale are clearly stated in the recommendation. However, CCRAN implores this kind committee to be mindful of the reimbursement of bevacizumab administered in combination with Lonsurf for patients who have already accessed bevacizumab in earlier lines of therapy. Patients should not be deprived of access to bevacizumab in combination with Lonsurf as a result of prior access and administration. Therefore, CCRAN respectfully requests that the recommendation is clear that bevacizumab be reimbursed in third line and beyond, when taken in combination with Lonsurf.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Filomena Servidio-Italiano*
Position	*President & CEO*
Date	*14-02-2024*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**PC0330-000**
Brand name (generic)	Lonsurf (Trifluridine and tipiracil) in combination with Avastin (bevacizumab)
Indication(s)	metastatic treatment-refractory colorectal cancer
Organization	Colorectal Cancer Canada
Contact information[a]	Name: Iris Karry

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The CADTH recommendation states in **Table 1: Reimbursement Conditions and Reasons** (Section 1.2, and 1.2.1):

> *1. Adult patients with all of the following:*
>
> *1.2. disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.*
>
> *1.2.1. Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild type.*

72.4% of patients enrolled in the SUNLIGHT trial had received previous anti-VEGF therapy while the remaining patients had not. In the final paragraph of the discussion of the SUNLIGHT trial, the authors state that "The data from this trial confirm that FTD–TPI plus bevacizumab is an effective treatment option for patients with refractory metastatic colorectal cancer, irrespective of mutational status, which side the tumor is on, and **whether patients have previously been treated with bevacizumab**." We believe that CADTH's recommendations should therefore not preclude <u>any</u> patients who may experience potential benefit from this combination therapy.

Our suggestion is to amend statement 1.2.1 such that patients who have never received previous anti-VEGF monoclonal antibody are also included:

1.2.1. Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, ~~an anti-VEGF monoclonal antibody and/~~or an anti-EGFR monoclonal antibody for RAS wild type.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. Please see above note in Section 1		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Iris Karry*
Position	*Manager, Patient Education & Research*
Date	*14-02-2024*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0330
Brand name (generic)	Trifluridine-tipiracil
Indication(s)	In combination with bevacizumab, for the treatment of adult patients with metastatic colorectal cancer who have previously been treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF biological agents, and, if RAS wild-type, anti-EGFR agents.
Organization	Taiho Pharma Canada
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
See #5 below		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Section 1.2.1 of the reimbursement conditions states the following:

- Prior treatment must include fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild type.

In the SUNLIGHT trial, 72.4% of patients had received prior treatment with an anti-VEGF monoclonal antibody while 27.6% had not. Taiho is requesting that this section be revised to make it clear that patients would be eligible for trifluridine-tipiracil in combination with bevacizumab regardless of prior bevacizumab exposure.

Section 1.2 of the reimbursement conditions states the following:

- disease progression or demonstrated intolerance to a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.

There are a number of different treatment approach scenarios (based on various treatment guidelines), many of which are related to timing of the use of an anti-EGFR agent for RAS wildtype patients or dMMR status.

Examples of this include patients who do not receive an anti-EGFR first line because they have right-sided disease and patients who have left-sided disease but cannot access an anti-EGFR first line due to funding constraints. In these situations, the patient would typically start treatment with a chemo doublet +/- bevacizumab, proceed to an alternative chemo doublet, and then move to an anti-EGFR therapy. Taiho would like to clarify if these types of patients would be eligible for the combination of Lonsurf plus bevacizumab as a next line of therapy.

Taiho also notes that in Table 2 (Funding algorithm), 'pERC acknowledged that clinicians and patients may want access to trifluridine-tipiracil in combination with bevacizumab for use in the third line setting **and beyond**.**'** [*emphasis adde*d by Taiho]

[a] CADTH may contact this person if comments require clarification.