CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

DURVALUMAB AND TREMELIMUMAB (IMJUDO AND IMFINZI)

(AstraZeneca Canada Inc.)

Indication: Imjudo (tremelimumab for injection) in combination with durvalumab is indicated for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy.

October 20, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0308
Brand name (generic)	Imfinzi (durvalumab) and Injudo (Tremelimumab)
Indication(s)	Imjudo (tremelimumab for injection) in combination with durvalumab is indicated for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy.
Organization	Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (GI DAC)
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 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. OH-CCO provided a secretariat function to the group.		
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: • Dr. Erin Kennedy • Dr. Suneil Khanna		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Rachel Goodwin*
Position	*Member, OH-CCO GI DAC*
Date	*15-10-2023*
☒	**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**
AstraZeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0308-000
Brand name (generic)	IMFINZI (durvalumab) and Imjudo (tremelimumab)
Indication(s)	unresectable hepatocellular carcinoma
Organization	c
Contact information[a]	Name: Dr. Howard Lim, Medical Oncologist, BC Cancer Agency

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	☐
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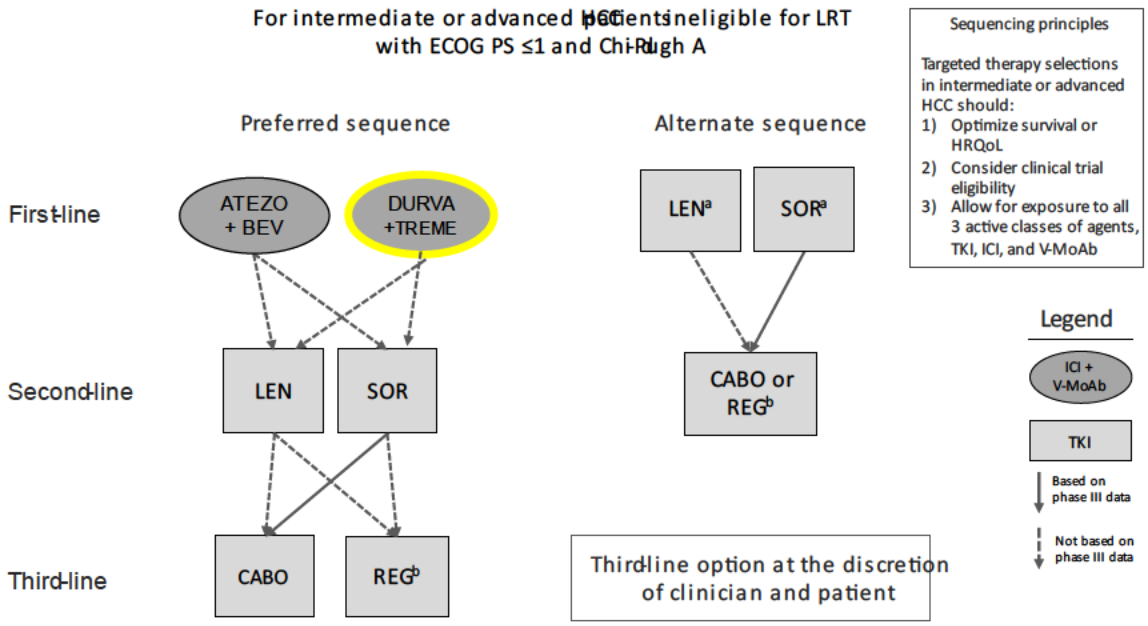
	No	☐
If not, please provide details regarding the information that requires clarification.		

In April 2021 CADTH conducted a provisional funding algorithm project that appears to have been triggered by the CADTH recommendation with respect to atezolizumab plus bevacizumab for first-line HCC.

We note that the draft recommendation addresses this issue (in Drug Program Implementation Questions p. 10): "*Tremelimumab in combination with durvalumab may change place in therapy of comparator drugs. PAG considered unresectable HCC to be a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.*"

CGOEN agrees that HCC is a complex therapeutic space. There has been evolving new data so the algorithm should be reviewed in totality to address the place of STRIDE as well as other options within the HCC landscape. For reference, here is the proposed evidence-based algorithm that should be adopted:



[a] Patients who are unsuitable for first-line ATEZO + BEV or those who started a TKI prior to ATEZO + BEV availability
[b] Patients with demonstrated ability to tolerate sorafenib
Abbreviations ATEZO, atezolizumab; BEV, bevacizumab; CABO, cabozantinib; PS, performance status; HBV, hepatitis B virus; ICI immune checkpoint inhibitor; LEN, lenvatinib; LRT, locoregional therapy; HRQoL, health-related quality of life; RAM, ramucirumab; REG, regorafenib; SOR, sorafenib; TKI, tyrosine kinase inhibitor; V-MoAb, VEGF(R) monoclonal antibody.

1

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.

There is evolving data about the use of immunotherapy in some patients with B7 disease and this should be a consideration. There are some borderline cases of A6/B7 that should be considered based on clinician discretion. In the case of immunotherapy since it is less toxic there is less risk of liver decompensation in these patients.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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Appendix 2. Conflict of Interest Declarations for Clinician Groups

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  - 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)*		

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0308
Name of the drug and Indication(s)	Tremelimumab with durvalumab for first-line unresectable HCC
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.

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.

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. A rapid algorithm is needed.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. Under Considerations for initiation of therapy (p. 9), PAG is asking for clarification: is there a need to specify a disease-free interval if this is for metastatic disease? Does the retreatment apply to the combination (tremelimumab-durvalumab) or the single agents? CADTH to clarify if the 6-month break is for re-treatment or continuation of treatment after a treatment break ("If patients have treatment stoppage for greater than 6 months (other than toxicity) it is the opinion of the clinical experts that retreatment would be reasonable?")
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

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**PC0308-000**
Brand name (generic)	Tremelimumab (Imjudo) in combination with durvalumab (Imfinzi)
Indication(s)	First-line treatment of adult patients with unresectable hepatocellular carcinoma who require systemic therapy.
Organization	Colorectal Cancer Resource & Action Network (CCRAN)
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.

There are unmet needs in the management of unresectable hepatocellular carcinoma (HCC) patients, who require systemic therapy, that were identified throughout the patient evidence submission. The expert review committee kindly acknowledged these unmet needs: effective, durable, and less-toxic therapies are required for the advanced HCC patient population who currently have limited treatment options available to them and suffer a poor prognosis. The current standard of care options are limited. The need for effective treatments that prolong life, improve quality of life and have manageable side effects speak to the patients' needs to have an additional effective treatment option.

THANK YOU!

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, both the quantitative and qualitative data was nicely considered in pERC's deliberations as reflected in the conditional recommendation. This was much appreciated.

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.

	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	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

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Filomena Servidio-Italiano*
Position	*President & CEO, Colorectal Cancer Resource & Action Network (CCRAN)*
Date	*(14-10-2023)*
☒	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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0308
Brand name (generic)	IMFINZI (durvalumab) and IMJUDO (tremelimumab)
Indication(s)	Imjudo (tremelimumab for injection) in combination with durvalumab is indicated for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy.
Organization	AstraZeneca Canada Inc.
Contact information[a]	Name: Bianca Li, Market Access & Health Economics, Sr. Mgr [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.

AstraZeneca (AZ) agrees with pERC's Draft Recommendation to reimburse IMJUDO (tremelimumab) in combination with IMFINZI (durvalumab) for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who require systemic therapy based on statistically significant and clinically meaningful improvement in overall survival and a sustained survival benefit at 3 years as demonstrated in the HIMALAYA trial.

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?

- AZ wishes to provide further clarification regarding the publications and associated data used to inform the MAICs as described in the Critical Appraisal section of the Draft Recommendation (pg 17). The updated data on PFS, ORR and DoR from the IMbrave150 trial (Cheng et al. 2022 publication)[1] were not selected for the MAIC analysis because the endpoints were assessed by independent review only. The same endpoints were assessed by both independent, and investigator review for the IMbrave150 primary analysis. To ensure consistency with the HIMALAYA trial where the same endpoints were assessed by investigator review only, the data used from the IMbrave150 trial reflected the investigator reviewed outputs. Of note, the exclusion of the longer follow-up data from the IMbrave150 trial would have only influenced results in favour of atezolizumab/bevacizumab. Regarding PRO data from the REFLECT trial, the analyses were not selected for the MAIC given the lack of validity of the proportional hazards assumption and therefore was excluded from the MAIC analysis.

- AZ acknowledges CADTH's re-analyses to the CEM, specifically the scenario analyses that were conducted (Table 4. Summary of Economic Evaluation, CADTH reanalysis results, pg

20). In the last bullet of the CADTH reanalysis results section, the results of "a scenario analysis" is presented in the absence of CADTH's base case scenario analysis. In line with CADTH's Guidelines for the Economic Evaluation of Health Technologies, results of the base case scenario should always be presented first with any accompanying sub-scenarios to provide full context of the analysis and conclusions. For greater clarity, AZ suggests the inclusion of the following bolded text:

> *A scenario analysis assuming that the clinical efficacy of STRIDE and atezolizumab plus bevacizumab was equivalent found that STRIDE was more costly and equally effective.* ***This scenario analysis was derived from CADTH's base case Scenario A re-analysis.*** *A comparison of costs found that the total treatment costs for both comparators are equal at approximately 60 weeks of continuous treatment.*

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.

- The current Implementation guidance in Table 1. Reimbursement Conditions and Reasons (pg 3) specifies Child-Pugh score class A as a criteria to be eligible for tremelimumab in combination with durvalumab. The Draft Recommendation also notes that "clinical experts noted that, while only including patients with a Child-Pugh score of A is reasonable in clinical trials, it may also be reasonable to include other patients (e.g., Child-Pugh score of B7) in clinical practice." (pg 10, 16). It is also stated in Table 2 (pg 10) that pERC acknowledged the input from clinical experts regarding patients with Child-Pugh score of B7. To ensure clarity in the Implementation guidance of Table 1. Reimbursement Conditions and Reasons, AstraZeneca proposes to add the following:

  pERC acknowledged that clinical experts noted that while only including patients with a Child-Pugh score of A is reasonable in clinical trials, it may also be reasonable to include patients with Child-Pugh score of B7 in clinical practice.

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

Sponsor's References

1. Cheng AL, Qin S, Ikeda M et al. (2022) Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *Journal of Hepatology*. 2022;76 862-73.