CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

osimertinib (Tagrisso)

(AstraZeneca Canada Inc.)

Indication: In combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

September 19, 2024

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0336-000
Brand name (generic)	Osimertinib (Tagrisso)
Indication(s)	In combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
Organization	OH (CCO) Lung Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Donna Maziak

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 Lung DAC agrees with the decision to recommend funding for osimertinib in combination with pemetrexed and platinum chemotherapy. However, we disagree with the comments about price. The $50,000 per QALY figure is at least 40 years old and never adjusted for inflation. Additionally, this is not an incremental therapy. The treatment algorithm would either be sequential osimertinib then pemetrexed/platinum, or combination therapy. So, the more pertinent economic comparison in terms of cost should be sequential therapy vs concurrent therapy.		
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		
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. Donna Maziak • Dr. Peter Ellis • Dr. Andrew Robinson • Dr. Mihaela Mates		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Natasha Leighl
Position	Member, OH (CCO) Lung DAC
Date	06-09-2024
☒	**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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dr. Stephanie Brule
Position	Member, OH (CCO) Lung DAC
Date	10-09-2024
☒	**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**
AstraZeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0336-000
Brand name (generic)	Osimertinib (Tagrisso)
Indication(s)	In combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies), or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
Organization	• Lung Cancer Canada – Patient Group • Lung Cancer Canada – Medical Advisory Committee
Contact information[a]	Name: Shem Singh, Executive Director [redacted]

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

This feedback on the draft recommendation for osimertinib is on behalf of both Lung Cancer Canada's Medical Advisory Committee (Clinician Group) and Patient Group.

Lung Cancer Canada's Medical Advisory Committee and Patient Group thanks pERC for the positive recommendation to reimburse osimertinib (Tagrisso) in combination with permetrexed and platinum-based chemotherapy for the treatment of NSCLC patients with EGFR exon 19 or 21 mutations. The approval of osimertinib within this indication as per the successful results of the FLAURA2 clinical trial brings a very welcome expansion of indications where osimertinib is already funded as a monotherapy, and will ensure that all patients who harbour these specific mutations are able to access an important therapy that has become standard of care for this biomarker.

Overall, Lung Cancer Canada finds this draft recommendation as very positive and excellent news, and hopes that CDA is able to bring this to a positive final recommendation.

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	*Shem Singh*
Position	*Executive Director*
Date	*September 17, 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	☐	☐	☐	☐

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.
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- 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.		
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. Barbara Melosky (lead) • Dr. Alison Wallace • Dr. Biniam Kidane • Dr. Nathalie Daaboul • Dr. Nicole Bouchard • Dr. Michela Febbraro • Dr. Randeep Sangha • Dr. Sunil Yadav • Dr. Catherine Labbe • Dr. Shaqil Kassam • Dr. Stephanie Snow • Dr. Susanna Cheng • Dr. Rosalyn Juergens • Dr. Geoffrey Liu • Dr. Kevin Jao • Dr. Normand Blais		

- Dr. Ron Burkes
- Dr. Mark Vincent
- Dr. David Stewart
- Dr. Mahmoud Abdelsalam
- Dr. Zhaolin Xu
- Dr. David Dawe
- Dr. Silvana Spadafora

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	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0336
Name of the drug and Indication(s)	Osimertinib
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	☐
	No requested revisions	X

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.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0336
Brand name (generic)	Tagrisso (osimertinib)
Indication(s)	TAGRISSO in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to curative therapies) or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
Organization	AstraZeneca Canada Inc.
Contact information[a]	[redacted]

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

AstraZeneca (AZ) acknowledges a fair review and agrees with the committee's recommendation to reimburse with conditions. AZ generally agrees with the conditions listed, though we firmly disagree with the methodological approach used to determine the recommended price reduction in the first two of three scenarios presented on various pages and highlighted below:

Page 4, Table 1, Pricing, Implementation Guidance

- *In addition to **CADTH's standard approach**, alternative approaches to calculating price reduction were considered: **a price reduction for all drugs including chemotherapy**;…*

Page 5, Discussion Point #4:

- *"Using CADTH's typical approach to price reduction, there was **no price at which osimertinib plus chemotherapy achieved an ICER at or below $50,000 per QALY gained** …A scenario analysis was performed in which a price reduction was applied to all drugs including chemotherapy. This scenario analysis suggested that a **91% reduction in the price of osimertinib and chemotherapy would be necessary to reach an ICER of $50,000 per QALY gained…**."*

Page 20, CADTH reanalysis results

- *"Due to the cost of chemotherapy and the presence of osimertinib in both modeled treatment cohorts, **no price reduction could be calculated that resulted in osimertinib plus chemotherapy being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained**."*

CDA mentions a 'typical' approach to price reduction, however AZ has not been able to identify any examples where CDA conducted a price reduction analysis by changing the price of the comparator regimen. Such an approach goes against core principles of health economic evaluation. Fundamental to health economic evaluation methods, the comparator arm must represent the alternative choice to the proposed intervention, which is to use the current standard of care, osimertinib monotherapy, at its current price. The fact that osimertinib appears in both the comparator and intervention arm should not change the decision problem which is to assess the cost effectiveness of a new intervention compared to the current standard of care. Thus, the only correct approach to estimating the price reduction needed to achieve cost-effectiveness is in CDA's scenario analysis in which the price reduction is only

applied to the intervention arm. This results in a 14% recommended price reduction based on the CDA base case reanalysis.

Consider a hypothetical scenario where osimertinib is combined with chemotherapy into a single oral pill and branded as new product X. Product X delivers the same QALYs and same incremental costs as osimertinib + chemotherapy. In this scenario, a price reduction is calculated for product X to reach an ICER below $50,000/QALY gained compared to osimertinib monotherapy. The same principle should apply when calculating a price reduction for the proposed intervention of osimertinib + chemotherapy regardless of the form of administration or product branding of the comparator and interventions.

Employing methods that incorrectly reduce the price of the comparator arm introduces perverse outcomes. Consider a similar hypothetical scenario for the entry of a new product Y, that provides fewer QALYs than osimertinib + chemotherapy but the same costs. In this world, the price reduction required for product Y to achieve cost effectiveness is calculated by reducing the price of product Y only (the price of osimertinib monotherapy remains unchanged). This results in a 15% discount in the price of product Y to achieve cost-effectiveness. How then is it acceptable that the recommendation to the health care system is to pay significantly more for product Y, an intervention that provides *fewer* health benefits compared to osimertinib + chemotherapy as is the case with CDA's 'typical' approach? This concept is further illustrated in the figure below.

In summary, AstraZeneca acknowledges that a price reduction may be required to achieve cost-effectiveness but estimation of such a price reduction must follow proper health economic evaluation methods, which was only done in CDA's scenario analysis where a price reduction was applied only to the intervention arm, resulting in a 14% recommended price reduction.

AZ proposed changes: AZ requests CDA remove references to price reduction analyses that involve reducing the price of the comparator regimen as these are inappropriate methods that result in misleading conclusions. Given the uniqueness of this decision problem, AZ suggests including a statement to note that the recommended price reduction represents the savings required to achieve cost-effectiveness when using osimertinib plus chemotherapy instead of osimertinib monotherapy rather than for all indications and uses of osimertinib.

Expert committee consideration of the stakeholder input		
	Yes	☒

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

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

In general, AZ is aligned with the implementation considerations discussed and believes them to be adequately addressed and articulated clearly. During consultations with clinical experts in preparation for this submission, physicians highlighted an additional implementation consideration that does not appear in the report regarding initiation of therapy, specifically flexibility when initiating the IV and oral components of this regimen.

While reflex testing of EGFR is well established in Canada, it is AZ's understanding that there is significant variability with respect to turnaround times across centres and jurisdictions. Clinicians have reported instances of initiating chemotherapy while awaiting an EGFR test result and later switching to osimertinib upon confirmation of an EGFR mutation. In the case of FLAURA2, it is at this same junction that clinicians would appreciate the option to either switch to osimertinib or add it in to the treatment regimen while continuing chemotherapy.

AZ also understands there to be variability with respect to chair time across institutions and jurisdictions. Clinicians have highlighted to AZ the desire to be able to initiate oral osimertinib therapy right away in situations where chair time/scheduling of chemotherapy infusions pose a challenge. This situation more accurately reflects the reality of clinical practice at some centres in Canada, and given the aggressive nature of EGFR mutated disease, allows for immediate action.

AZ proposed changes to provide clarity: AZ recommends adding a statement to Table 1, page 4, Prescribing Condition #5 under Implementation Guidance as follows:

- "***A staggered initiation approach may be appropriate when parallel initiation of osimertinib and chemotherapy is not possible, at the discretion of the treating clinician.*** *Osimertinib may be continued as monotherapy once the disease is responding even if chemotherapy is discontinued due to side effects or toxicity."*

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

In general, AZ agrees that the reimbursement conditions with rationale are clearly articulated in the draft recommendation apart from the pricing condition. AZ acknowledges that a price reduction may be required to achieve cost-effectiveness, however, the rationales provided for a recommended price reduction are predicated on a methodologically incorrect approach (see response to Question 1).

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