CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

Osimertinib (Tagrisso)

(AstraZeneca Canada Inc.)

Indication: Non-small cell lung cancer

April 16, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0246-000
Generic Drug Name (Brand Name)	Osimertinib (Tagrisso)
Indication	As adjuvant therapy after tumour resection in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (*EGFR*) exon 19 deletions or exon 21 (L858R) substitution mutations.
Name of the Clinician Group	Lung Cancer Canada
Author of the Submission	Dr Geoffrey Liu
Contact information	Name: Iwo Effiong Title: Program Coordinator, Lung Cancer Canada [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Lung Cancer Canada is a national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research and advocacy. Based in Toronto, Ontario, Lung Cancer Canada has a wide reach that includes both regional and pan-Canadian initiatives. Lung Cancer Canada is a member of the Global Lung Cancer Coalition and is the only organization in Canada focused exclusively on lung cancer.

Website Link: www.lungcancercanada.ca

2. Information Gathering

Please describe how you gathered the information included in the submission.

Information gathered for this submission was based on relevant published clinical data and expert evidence-based review amongst lung cancer medical oncologists across Canada.

Key References:

Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, Vu HV, Lu S, Lee KY, Akewanlop C, Yu CJ, de Marinis F, Bonanno L, Domine M, Shepherd FA, Zeng L, Hodge R, Atasoy A, Rukazenkov Y,

Herbst RS; ADAURA Investigators. Osimertinib in Resected *EGFR*-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Epub 2020 Sep 19. PMID: 32955177.

Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA *EGFR* mutation positive (*EGFR*m) NSCLC after complete tumor resection: ADAURA. J Clin Oncol. 2020;38(suppl 18):LBA5.

Wu YL, Herbst RS, Mann H, Rukazenkov Y, Marotti M, Tsuboi M. ADAURA: Phase III, Double-blind, Randomized Study of Osimertinib Versus Placebo in *EGFR* Mutation-positive Early-stage NSCLC After Complete Surgical Resection. Clin Lung Cancer. 2018 Jul;19(4):e533-e536. doi:

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

In Canada, the treatment for Stages IB-IIIA non-small cell lung cancer (NSCLC) is stage dependent. Current treatments do not differentiate between patients with *EGFR* mutations and those without *EGFR* mutations. Canadian practice is aligned with practices from around the world, as evidenced from data from both the IASLC Dataset and North American-based National Cancer Database[1]

For stage IB NSCLC, the primary goal is cure (i.e., to improve 5-year overall survival). To achieve this goal, the standard treatment is complete surgical resection (R0). Thereafter, a minority of fit patients are offered adjuvant platinum-doublet chemotherapy, particularly those with pathological findings consistent with high risk of relapse such as larger T-sizes, lymphovascular or perineural invasion, or spread through airspaces (STAS). In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context. In medically inoperable patients, sometimes localized radiation (external beam or stereotactic body radiation) is given in lieu of an operation.

For stage II NSCLC, the primary goal is cure (i.e., to improve 5-year overall survival). To achieve this goal the standard treatment is complete surgical resection (R0). Thereafter, fit patients are offered adjuvant platinum-doublet chemotherapy. In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context, which would be given sequentially to adjuvant chemotherapy.

For stage IIIA NSCLC, the primary goal is cure (i.e., to improve 5-year overall survival). To achieve this goal, the standard treatment depends on whether the primary tumour is considered resectable or not, balancing benefits and risks, including peri-operative risks, the ultimate chance of cure, the number of lobes that will be resected (e.g. lobectomy vs pneumonectomy), and the long-term residual effects of the operation (e.g. expected residual pulmonary reserve and function after a resection). If surgery is considered reasonable, neoadjuvant chemotherapy concurrent with radiation, followed by complete surgical resection is typically offered. If surgery is not considered reasonable, definitive chemotherapy concurrent with radiation is given, followed by consideration of a year of durvalumab. In a minority of cases, a patient is only found to be stage IIIA at the time of resection (where the initial work-up suggested an earlier stage of disease); patients who are found to have this form of “incidental” stage IIIA are then typically offered adjuvant platinum-doublet chemotherapy. In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context, but sequentially (and not concurrent) with any adjuvant chemotherapy.

Adjuvant platinum-doublet chemotherapy given after resection of stage IB-IIIA NSCLC patients typically consists of four cycles of treatment, with each cycle lasting 21 days, for a total of 12 weeks of therapy.

Specific platinum-doublet chemotherapy with the best evidence of efficacy has been with the combination of cisplatin and vinorelbine[2], but other platinum-doublet combinations have been increasingly used over the recent years.

References

[1] Chansky K, Detterbeck FC, N cho son AG, Rusch VW, Va ères E, Groome P, Kennedy C, Krasn k M, Peake M, Shemansk L, Bo ejack V, Crow ey JJ, Asamura H, Ram -Porta R; IASLC Stag ng and Prognost c Factors Comm ttee, Adv sory Boards, and Part c pat ng Inst tut ons. The IASLC Lung Cancer Stag ng Project: Externa Va dat on of the Rev s on of the TNM Stage Group ngs n the E ghth Ed t on of the TNM C ass f cat on of Lung Cancer. J Thorac Onco . 2017 Ju ;12(7):1109-1121. do : 10.1016/j.jtho.2017.04.011. Epub 2017 Apr 28. PMID: 28461257.

[2] P gnon JP, Tr bodet H, Scag ott GV, Dou ard JY, Shepherd FA, Stephens RJ, Dunant A, Torr V, Rose R, Seymour L, Sp ro SG, Ro and E, Fossat R, Aubert D, D ng K, Wa er D, Le Cheva er T; LACE Co aborat ve Group. Lung adjuvant c sp at n eva uat on: a poo ed ana ys s by the LACE Co aborat ve Group. J C n Onco . 2008 Ju 20;26(21):3552-9.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The most important goal that an ideal treatment would have for any adjuvant therapy in early-stage non-small cell lung cancer is ***to prolong cancer-free life and life itself*** (i.e., recurrence-free survival and overall survival). For adjuvant therapies that are given over a prolonged period of time, an additional goal is ***to minimize adverse effects and maintain health-related quality-of-life*** while receiving the adjuvant therapy.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Preface: Traditionally, the term disease-free survival has been used as a synonym for progression-free survival in the metastatic/incurable disease setting. In the context of this current submission, our clinician group will use the term "recurrence-free survival" for the same concept. As will be explained below, the clinical impact of developing a recurrence in early stage resected NSCLC is devastating, changing the vast majority of patients from the category of "potentially being curable" to "almost certainly incurable". We want to distinguish, in no uncertain terms, this outcome difference between early stage and advanced/metastatic NSCLC. This is especially important since all NSCLC submissions in the past decade dealt with locally-advanced or advanced/metastatic patients, while this is the first of a request for adjuvant drug funding for NSCLC in the early stage resected setting.

UNMET NEED 1: Current therapies are inadequate to achieve high rates of cure in early stage resected IB-IIIA NSCLC patients, based on 5-year overall survival rates.

The outcomes of such patients remain poor even with the best current treatments, falling far below the outcomes of other cancer disease sites. Unlike metastatic disease (where there has been significant progress), the clinical impact of improving outcomes in early-stage NSCLC is far greater, with patients having longer cancer-free intervals and being considered true cancer survivors (i.e. cured).

Lung cancer five-year survival, even amongst the early stages, has significantly worse outcomes than in other common cancers. **Figure 1** below illustrates how much of a gap there is between lung cancer and other common cancers, such as breast, colon and prostate cancers. In **Figure 1**, for the localized and extended (i.e. non-metastatic) stages of common cancers, such as breast, colorectal, and prostate cancer, the five-year survival times sit above 75%. In contrast, the results are significantly worse in lung cancer (30-55% five-year survival for Stages III-I lung cancer). Similar results are echoed in **Figure 2**, which demonstrate that regardless of whether one uses the 7th or 8th edition of the AJCC/UICC lung cancer staging system, the 5-year overall survival rates are between 36% (Stage IIIA) and 66-68% (Stage IB). All of these results presented are in the contemporary era where adjuvant chemotherapy has been widely adopted.

The last time there had been improvements in NSCLC adjuvant therapy was through the incorporation of adjuvant chemotherapy in Stages IB-III resected NSCLC. Following an earlier large meta-analysis[3], the publication of the LACE collaborative pooled analysis of multiple trials (IALT, NCIC CTG BR.10, BLT, ALPI, ANITA)[2], showed absolute survival improvements ranging from 8.8-15%. However, it has been almost two decades since the large-scale introduction of adjuvant chemotherapy into clinical practice across in Canada. There is a dire need to improve survival outcomes in our Stage IA-IIIB patients further, especially in the setting where long-term cancer-free survival and potential cure rates are involved.

UNMET NEED 2: Current therapies are inadequate to prevent recurrences in early stage resected IB-IIIA NSCLC patients, based on recurrence-free survival rates.

Improving lung cancer recurrence-free survival is an equally important unmet need, as it has biologic and clinical association with overall survival in early-stage NSCLC patients. Further, in Section 6.8, recurrences and recurrence-free survival are discussed in detail as to why these are legitimate and key clinical outcomes in their own right, with significant patient, healthcare and societal impacts.

Recurrences after resection of an initial early-stage NSCLC are primarily through distant spread or metastases. This metastatic disease is generally incurable (there are only rare instances of oligometastatic disease where recurrent disease may yield long term survival); looking at the survival curves of *de novo* stage IV cancers (see **Figure 2** below) is evidence of the poor outcomes that occur once metastatic disease has been diagnosed. Clinically, these findings demonstrate that, to impact on NSCLC overall survival, one needs to reduce disease recurrence substantially in early-stage NSCLCs.

Further, recurrence-free and overall survival mirrored each other the last time there was an effective adjuvant therapy for stage IB-IIIA resected NSCLC: in the LACE collaborative, the overall survival benefit of adjuvant chemotherapy was HR = 0.89 (95% CI, 0.82 to 0.96; P = .005) whilst for recurrence-free survival, the results were similar, HR = 0.84 (95% CI, 0.78 to 0.91; P < .001).

Please also see Section 6.8, which details the rationale for why recurrence-free survival should be its own clinically-relevant critical outcome measure.

UNMET NEED 3: Unmet needs 1 and 2 above also apply to patients carrying EGFR-mutations. In this setting, the potential implications of a recurrence are equally life-altering.

Stage IB-IIIA *EGFR*-mutated lung cancers have similar rates of recurrences as those patients who do not carry an *EGFR* mutation. In fact, patients with early-stage *EGFR*-mutated NSCLC have recurrence-free survival outcomes that are equally poor. Overall survival in these *EGFR*-mutated NSCLC also shows worse outcomes than in other disease sites. Further, recurrences in these *EGFR*-mutated patients are predominantly treated as advanced/metastatic (and therefore incurable) disease.

We present some upcoming Canadian (Princess Margaret Cancer Centre) data[4] in **Figure 3**, on the overall survival and recurrence-free survival of patients with completely resected Stage IB-IIIA NSCLCs diagnosed between 2014 and 2018, who have *EGFR* mutations (n=104); these patients matched the eligibility criteria of the ADAURA population. This data demonstrates that we have equally suboptimal recurrence-free survival of *EGFR*-mutated patients in our Canadian real-world data (**Figure 3**) as was observed in the ADAURA trial. Also demonstrated is poor OS in *EGFR*-mutated resected Stage IB-IIIA patients; here, in order to take into account, the improved OS due to the benefit of *EGFR*-TKI use when early-stage patients recur and become metastatic, we mark not only the 5-year OS, but also the 6.5-year OS, showing a shift in deaths due to the use of TKIs at the time of recurrent disease, but no true increase in cure rate.

In **Figure 4**, we show Canadian (Princess Margaret) data on the first sites of relapse – where lung and pleural disease (leading to shortness of breath), bone (leading to pain), and central nervous system (leading to a multitude of complications) are the most common first sites of recurrence[4]. In an upcoming World Conference of Lung Cancer submitted abstract[5], 83% of first recurrences in patients with early-stage *EGFR*-mutated resected tumours included distant sites, while only 17% of the first sites of recurrence were considered truly loco-regional (using same definition as ADAURA); however, only 8% were treated aggressively for cure (chemoradiation, surgery), while 92% of all relapses (regardless of whether they were loco-regional or advanced/metastatic) were treated as advanced/metastatic disease. Furthermore, the overall survival of patients with recurrences (counting from the date of discovery of recurrence) in this group of resected early-stage *EGFR* positive patients was similar to that of *de novo* advanced/metastatic *EGFR* positive patients (log-rank p-value 0.29; adjusted HR, 0.82 (95% 0.55-1.24)[5]. This data also provides evidence that recurrent disease has a devastating impact on *EGFR* positive early-stage patients that kicks the vast majority of patients into incurable disease with similar outcomes as other metastatic *EGFR* NSCLC patients.

Finally, in a newly submitted 2021 World Conference in Lung Cancer abstract, 104 Canadian Stage IB-IIIA resected *EGFR* mutated patients (diagnosed from 2012-2018) were tracked over time[5]. Hazard ratios for clinico-demographic-treatment variables (e.g. age, sex, smoking status, stage and adjuvant treatment) were compared between two outcomes: recurrence-free survival censored at 2 years and overall survival censored at 5 years. Hazard ratios were identical in direction of association, albeit somewhat attenuated in the outcome of overall survival at 5 years, when compared to recurrence-free survival at 2 years[5]. These results are consistent with the concept that recurrence-free survival can serve a reasonable surrogate for overall survival (after adjustment for magnitude of association), in an *EGFR* mutated cohort of resected Stage IB-IIIA patients.

References

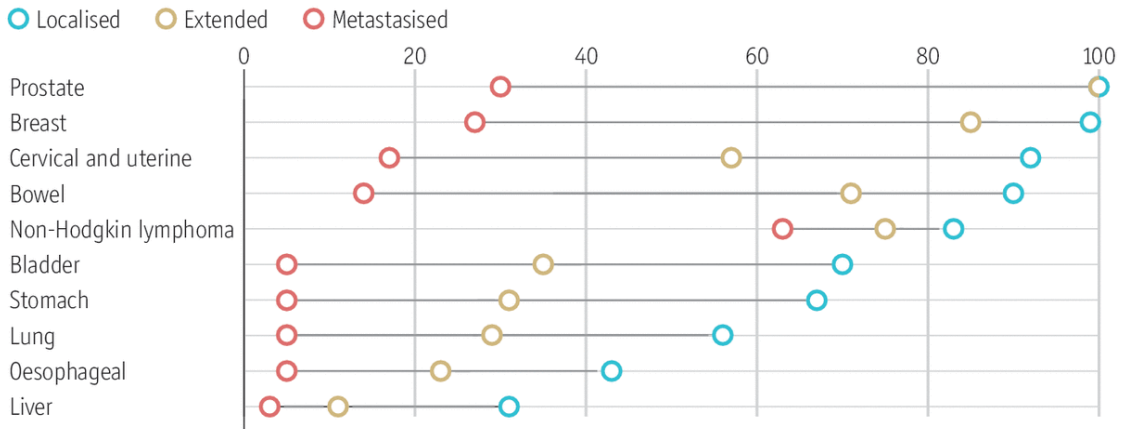
[3] Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311::899,1995-909

[4] Schm d S, Garc a M, Huen ken K, Ba aratnam K, Pate D, Zhan L, Brown MC, Sacher AG, Bradbury PA, Le gh NB, Shepherd FA, L u, G. Preva ence, treatment patterns and ong-term c n ca outcomes of pat ents w th EGFR pos t ve resected stage IB-IIIA NSCLC (subm tted, 2021 Wor d Conf Lung Cancer)

[5] Garc a M, Schm d S, Huen ken K, Zhan L, Ba aratnam K, Khan K, Fares AF, Chan SWS, Sm th EC, Aggarwa R, Brown MC, Pate D, Sacher AG, Bradbury PA, Shepherd FA, Le gh NB, L u G. Is Re apse-Free Surv va at 2-Yrs an appropr ate surrogate for Overa Surv va at 5-Yrs n EGFR-mutated resected NSCLC? (subm tted, 2021 Wor d Conf Lung Cancer)

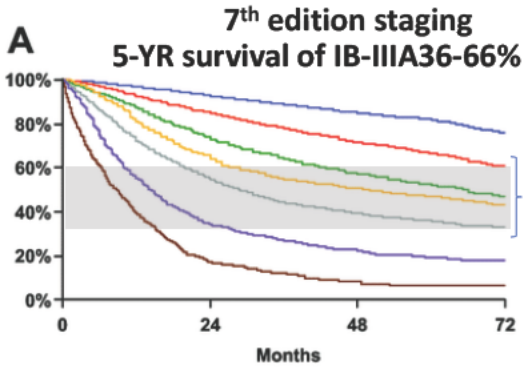
FIGURES FOR THIS SECTION

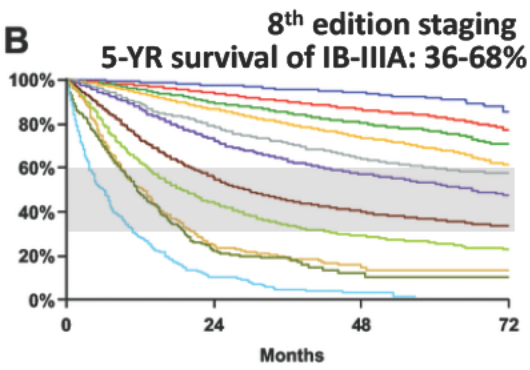
United States SEER data (2016) on five-year survival rates of various cancers, by disease stage at diagnosis. Stage I = localized; Stage II-III = Extended



Adapted from the Technology Quarterly section of The Economist on September 16th 2017

Figure 1. The relatively poor outcomes, shown as 5-year overall survival rates, as demonstrated in Stage IB-IIIA lung cancer patients (represented by localized [blue, Stage I] and extended [yellow, stage II-III] open circles), when compared to other common cancers, such as prostate, breast, and colorectal cancer.





7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other.

Nicholson, Andrew & Chansky, Kari & Crowley, John & Beyruti, Ricardo & Kubota, Kaoru & Turrisi, Andrew & Eberhardt, Wilfried & Meerbeeck, Jan & Rami-Porta, Ramon. (2015). The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology. 11. 10.1016/j.jtho.2015.10.008.

Figure 2. Overall survival is poor in Stage IB (red), IIA (green), IIB (yellow), and IIIA (grey) NSCLC patients, regardless of whether one is using the seventh or eighth edition of non-small cell lung cancer staging, ranging from 36% through 68%.

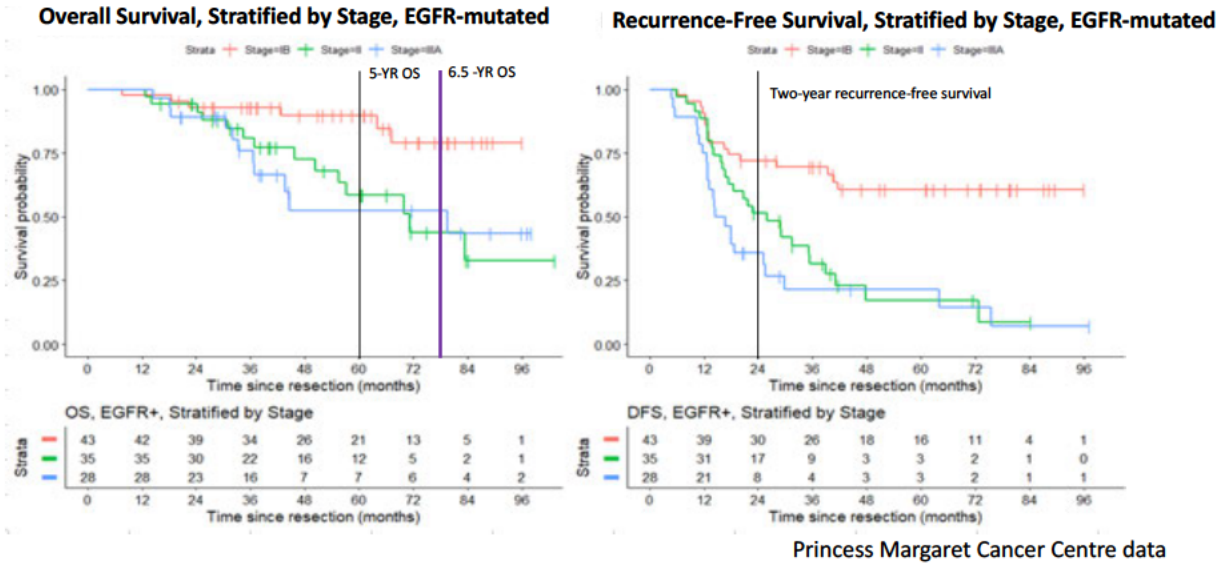


Figure 3. In 106 *EGFR*-mutated Stage IB-IIIA NSCLCs, Kaplan-Meier curves (**Left**) overall survival and (**Right**) recurrence-free (aka disease-free) survival, stratified by stage (red, Stage IB; green, Stage II; blue, Stage IIIA). Vertical lines are shown at 5-years and 6.5-years for OS, and at 2-years for RFS/DFS. The line at 6.5 years is there to show a shift in OS due to improved survival due to benefit of *EGFR*-TKIs in this population – in essence, the cure rate does not improve but patients live longer with advanced/metastatic/recurrent disease. AJCC 8th edition staging was used. (Reference 4; Schm d et a)

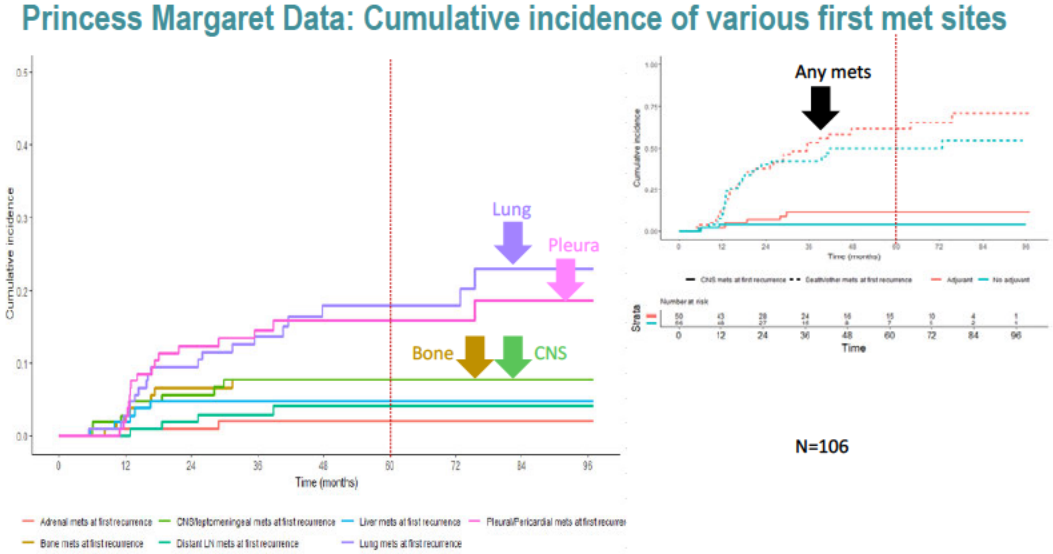


Figure 4. Left: cumulative incidence of individual metastatic disease sites using competing risk model in 106 *EGFR*-mutated Stage IB-IIIA NSCLCs, from date of surgery. **Right:** cumulative incidence of any metastatic disease and of brain metastases as first site of metastases, by whether patients received adjuvant or no adjuvant therapy in 106 *EGFR*-mutated Stage IB-IIIA NSCLCs, from date of surgery. (Reference 4, Schm d et a)

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

***Section 5.2a**. Would these patients be considered a subpopulation or niche population?*

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response: Patients with *EGFR*-mutated Stage IB-IIIA resected tumours are considered a niche population. The proportion of *EGFR*-mutated patients amongst all patients with early-stage NSCLC varies depending on the ethnic/race distribution and the smoking-rates. In Canada, taking into account differences in demographic characteristics geographically, a reasonable estimate would be approximately 15% of all NSCLC patients carry *EGFR* mutations.

Lifetime never-smokers and individuals originating from East Asian, South-east Asian, and South-Asian countries have a higher chance of carrying an *EGFR* mutation[6 7]. Regardless, *EGFR*-mutations are observed in all races, clinico-demographic subgroups, and with all smoking histories. The clinical trial ADAURA, reported results across each of these subgroups, demonstrating benefit (highly significant HRs ranging from 0.12-0.39) in subgroups by age, sex, smoking status, race, stage, subtype of *EGFR* mutation, and concurrent use or non-use of adjuvant chemotherapy.

As such, osimertinib addresses the unmet need of all Stage IB-IIIA resected NSCLC patients carrying sensitizing *EGFR* mutations.

***Section 5.2b**. Are there any subgroups within this niche population that have the greatest unmet need?*

Response: Similar to the role of adjuvant chemotherapy, patients with resected *EGFR*-mutations tumours of Stages II and IIIA have the greatest unmet need, because their baseline DFS and OS are poorer than that of Stage IB. However, even with adjuvant chemotherapy, higher risk individuals within the Stage IB cohort (for example, larger tumour sizes, perineural or lymphovascular invasion, or spread through air space) may be identified who also have a strong unmet need; ADAURA trial data may not be able tease out whether such higher risk groups may benefit more from osimertinib within the Stage IB cohort, but there is precedent and guidelines that can be extrapolated from adjuvant chemotherapy data to suggest that at least a subset of Stage IB patients with high-risk pathological characteristics could benefit more.

References:

[6] M dha A, Dearden S, McCormack R. *EGFR* mutat on nc dence n non-sma -ce ung cancer of adenocarc noma h sto ogy: a systemat c rev ew and g oba map by ethn c ty (mutMapII). Am J Cancer Res. 2015;5(9):2892-2911. Pub shed 2015 Aug 15.

[7] Schabath MB, Cress D, Munoz-Anton a T. Rac a and Ethn c D fferences n the Ep dem o ogy and Genom cs of Lung Cancer. Cancer Contro . 2016 Oct;23(4):338-346.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

***Section 6.1a**: Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?*

Response: Based on the ADAURA results, osimertinib should be ***added*** to the current post-operative management of resected Stage IB-IIIA NSCLC patients carrying a sensitizing *EGFR* mutation. Osimertinib should ***not*** be considered a replacement for any other therapy.

ADAURA included both patients who did and did not receive adjuvant chemotherapy. Osimertinib showed no significant difference in efficacy or toxicity when comparing adjuvant and non-adjuvant treated patients. Thus, patients who were previously appropriate for adjuvant chemotherapy should continue to be offered adjuvant chemotherapy. The mechanisms of action between cytotoxic chemotherapy and osimertinib do not overlap, and should not interfere with each other theoretically.

Osimertinib showed no significant differences in quality-of-life measures longitudinally when compared to placebo[8].

Section 6.1b: *Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?*

Response: Osimertinib is the first drug to demonstrate benefit of a targeted agent in the adjuvant resected NSCLC setting where the tumour carries the corresponding target. ADAURA is the first study to demonstrate the underlying benefit of using *EGFR*-targeting agents to decrease or delay recurrences in the subset of early stage, resected NSCLC patients whose tumours carry sensitizing *EGFR*-mutations.

There is ample evidence from clinical trials in the advanced/metastatic setting, in addition to extensive pre-clinical and experimental data, that demonstrate the mechanism of *EGFR*-TKIs (and osimertinib in particular) on tumours and cancer cells driven by sensitizing *EGFR* mutations[9].

Section 6.1c: *Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?*

Response: It must be made clear that “lines of therapy”, as discussed in the question above, refers mostly to the metastatic setting. Osimertinib used for adjuvant purposes is designed to improve recurrence-free survival in order to improve cure rates, and thus, this submission should not be confused with the more modest goals of improving outcomes of advanced/metastatic NSCLC. Osimertinib has been shown to reduce NSCLC recurrence rates (i.e. improve recurrence-free survival) when administered alone for three years as an adjuvant therapy. The independent roles of adjuvant chemotherapy and osimertinib have already been discussed in *Section 6.1a*.

Section 6.1d: *Is the drug under review expected to cause a shift in the current treatment paradigm?*

Response: Three years of administration of an oral agent will change the paradigm of how patients are managed currently. The only current adjuvant treatment available in this population is adjuvant chemotherapy, which is completed over 3-4 months. Nonetheless, the impact to the healthcare utilization system may be modest because osimertinib is a home-based oral, low-toxicity agent.

Reference:

[8] Majem M, Go dman JW, John T, et a . Pat ent-reported outcomes from ADAURA: os mert n b as adjuvant therapy n pat ents w th resected *EGFR* mutated (*EGFR*m) NSCLC. Abstract presented at: 2020 Wor d Conference on Lung Cancer; January 28-31, 2021

[9] https://go.drugbank.com/drugs/DB09330

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

This question is not designed for the current submission. Adjuvant chemotherapy should be administered independently of consideration of osimertinib, where appropriate, as explained in *Section 6.1a*. If the question is whether there is an alternative *EGFR*-TKI to osimertinib that could be used in place of osimertinib, then the following provides the rationale for why an alternative *EGFR*-TKI is inappropriate:

First, there is no other *EGFR*-TKI with positive Phase III data. There is only the ADAURA trial of osimertinib for patients with *EGFR*-mutated tumours.

Second, osimertinib is the best in class among all of the currently approved *EGFR* TKIs in the metastatic setting, and thus would be expected to be the best to use in the early-stage curative patient setting, as demonstrated by the ADAURA trial.

Third, the magnitude of benefit of Osimertinib primary endpoint in all patients and across subgroups is massive. Osimertinib's ability to reduce recurrence rates (i.e. improve recurrence-free survival) is associated with a striking hazard ratio of HR 0.17 (99% CI, 0.11-0.26); p<0.001 for resected Stages II-IIIA, and HR 0.20 resected for Stages IB-IIIA. In the ADAURA trial, this benefit cuts across all subgroups.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Re-using a drug in the metastatic setting after use in the adjuvant setting is a consideration.

Data is not available as to when and if to reuse osimertinib in the recurrent/advanced/metastatic setting, when osimertinib was used in the adjuvant setting. ADAURA does not mandate how patients should be treated at disease recurrence and had no specific protocol to track patients longitudinally post-recurrence for treatment and treatment outcomes; thus, osimertinib reuse data may not be readily available from the trial, even in the future. Real world evidence from outside Canada will take a long time to generate.

With the lack of available data on osimertinib, one reasonable consideration is to allow clinicians to reuse osimertinib at their discretion in the metastatic setting, after use in the adjuvant setting, if the clinician feels that there could be benefit. A precedence example would be the use of adjuvant imatinib for gastrointestinal stromal tumours (GIST), in which there is benefit to retreating with imatinib whenever recurrence occurs, regardless of the imatinib-free period.

However, if guidelines are absolutely required, based on the example of immunotherapies in the advanced lung cancer setting and pragmatic examples from other cancer disease sites, we can extrapolate the following:

(1) There is generally no role for osimertinib in the recurrent disease setting when disease recurrence occurred during the administration of adjuvant osimertinib.

(2) There is likely no role for osimertinib in the recurrent disease setting when disease recurrence occurred **WITHIN** the first number of months after completion of adjuvant osimertinib. Pragmatically, six months has been used as this period of time in other settings, and would be a reasonable interval of time between the end of adjuvant osimertinib and the discovery of recurrence.
(3) There may be a role for osimertinib in the recurrent disease setting when disease recurrence occurred **AFTER** the first number of months after completion of adjuvant osimertinib; pragmatically, six months has been used as this period of time in other settings, and would be a reasonable interval of time between the end of adjuvant osimertinib and the discovery of recurrence. Should osimertinib be re-initiated, short-term (2-3 months) assessment of treatment response will be important.
(4) After the development of recurrent disease, data for the use of osimertinib in the second or subsequent-line of therapy for metastatic disease is lacking and there are no comparable precedents. This strategy is best pursued in the context of a clinical trial.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

The sub questions in this section are worded for the advanced/metastatic setting. Response to treatment has little clinical meaning in the context of the adjuvant setting. ADAURA Kaplan-Meier sub-analyses, however, do indicate that the higher the stage, the worse the Kaplan-Meier RFS survival curve appears in the control arm, while the Kaplan Meier RFS curves for each of the osimertinib arms of Stages IB, II, and IIIA are, in fact, very similar. This suggests that the patients with higher disease stage who have the greatest need for an intervention are also the ones who will benefit the most from osimertinib.

In addition to the visual impact of survival curves, the data are shown through hazard ratios. Although Stage II-IIIA patients had the greatest magnitude of relative benefit (HR of 0.17 (0.08-0.31) for Stage II and HR of 0.12 (0.07-0.20) for Stage IIIA) and would also have the greatest absolute benefit, even Stage IB patients had statistically and clinically significant relative benefit, with HR of 0.39 (0.18-0.76), albeit with a likely smaller absolute benefit.

As discussed in detail in *Section 5.1a* and *Section 5.1b*, all subsets of patients by clinico-demographic data benefited from osimertinib.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

Typically, patients fit for surgery should be able to tolerate osimertinib, so we anticipate minimal drop off of patients who meet eligibility requirements and who undergo complete resection.

EGFR testing infrastructure for advanced/metastatic disease has been fully set up across Canada, and routine testing is the norm in practice and by consensus[10]. There will be no major infrastructure gaps when expanding to include testing in the adjuvant setting.

In contrast, the current infrastructure was designed for routine testing of advanced/metastatic NSCLC, and not necessarily in early-stage NSCLCs. Currently, only a proportion of centres (estimated 50-60% in Canada) are testing for *EGFR* routinely for early-stage NSCLC patients.

However, similar to *EGFR*, *ALK*, *ROS1* and PDL1 testing in the advanced/metastatic NSCLC setting, we anticipate that the proportion of centres will increase over a period of time, with recent Health Canada approval. Until then, there will continue to be a degree of underdiagnosis of *EGFR* mutations in our Canadian population.

Across places in Canada where *EGFR* mutation testing already occurs routinely (or reflexively) for early stage resected tumours, there will no increase in cost of testing to the healthcare system to accommodate adjuvant use of osimertinib.

Across places in Canada where routine (or reflexive) testing *EGFR* mutations in the adjuvant setting has not yet been instituted, there may be increased costs associated with testing early stage resected patients with NSCLC. However, these costs are significantly mitigated by the knowledge that more than half of these resected Stage IB-IIIA patients would otherwise have developed recurrences, and such an event would lead to *EGFR* mutation testing at relapse, in any case. Thus, there may be a shift of *EGFR* mutation testing from advanced/metastatic to early stage, but not an actual increase in the number of total *EGFR* mutation tests. The actual increase in the number of tests would be modest, occurring only in the subset of patients whose tumours would never have relapsed in the era prior to adjuvant osimertinib. Further, more and more centres are multiplexing their mutation tests, such that the incremental cost of an individual test such as *EGFR* mutation testing is small when upwards of dozens to over a hundred mutation tests are performed through next-generation sequencing platforms (for example, Oncomine Comprehensive Assay v3.0 assesses *EGFR* mutations as one of 161 genes that also include ALK and ROS1). Amortizing these costs across all of the potential targetable molecular alterations, the incremental cost of *EGFR* mutation testing becomes even smaller.

In summary, we do not anticipate the need for increases in infrastructure costs, and only minimal to modest increases in costs in order to accommodate *EGFR* mutation testing in the adjuvant resected NSCLC setting.

Reference:

[10] Me osky B, B a s N, Cheema P, et a . Standard z ng b omarker test ng for Canad an pat ents w th advanced ung cancer. Curr Onco . 2018;25(1):73-82. do :10.3747/co.25.3867

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients who do not carry *EGFR* mutations or who do not have surgically resected non-small cell lung cancer.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

We anticipate that this question was designed for submissions related to the advanced/metastatic setting, and not relevant for this submission involving adjuvant therapy.

"Response to therapy" is not an appropriate outcome in this population. If the purpose of this question is to address which patients are most likely to benefit, this has already been covered in *Section 5.2a* and *Section 5.2b*.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

It should be noted that this question is framed in the context of advanced/metastatic setting, as responses to treatment are not a primary focus of early stage resected cancer.

We have re-framed this question to read "What outcomes are used to determine whether a patient is benefiting from this treatment in clinical practice".

The primary outcome in this trial to determine whether osimertinib has worked is whether disease recurrence has occurred, (recurrence-free survival) and ultimately, cure rates, as measured by 5-year OS and Kaplan Meier curves for OS. Typically, most recurrences of Stage IB-IIIA NSCLC patients occur within 2-3 years, as shown in the Canadian *EGFR*-mutated resected Stage IB-IIIA data (**Figure 3**, right panel), while OS typically requires a greater number of years of follow-up (**Figure 3**, left panel).

In the setting of early-stage NSCLC, there has been growing clinician recognition of the enormous negative impact of recurrent disease on patients (in all patients and in those with *EGFR* mutations), independent of overall survival. Recurrent disease can occur across a multitude of organ systems (**Figure 4**). For example, bone metastases and CNS metastases are often symptomatic, requiring local therapies such as radiation to manage symptoms. Lung metastases and pleural disease, common sites of initial failure of stage IB-IIIA NSCLC patients carrying *EGFR* mutations (**Figure 4**) can lead to shortness of breath and requiring such procedures as thoracenteses. The actual impact of the development of these metastases is far greater than is shown in **Figure 4**, which only shows sites of first metastases, and not cumulative rates of metastases per person over time, after diagnosis of recurrent disease. Thus, reducing the rate of recurrence or delaying recurrences will impact patients greatly, independent on their ultimate impact on overall survival.

The impact of disease recurrence is also shown by the fact the vast majority of patients are treated as having incurable disease at the time of recurrence (92% in Canadian data). Thus, therapies beyond *EGFR* TKIs, such as chemotherapy and immunotherapy, and symptom management (radiation, palliative care, etc.) now need to be considered in the management of these patients. The costs to patient health,

quality of life, utilization of health care resources, economic loss of productivity, and overall costs to the society are substantial. Delaying or reducing disease recurrence thus has enormous benefit from each of these perspectives.

Taking the devil's advocate position, in the worst-case scenario, one can theorize that osimertinib only delays the development of recurrent disease, but does not actually "cure" patients (a theory that runs counterintuitive to the ADAURA data and its extremely strong recurrence-free survival hazard ratios). Nonetheless, delaying NSCLC recurrence still means substantially better health related quality of life, especially since on-trial patients (i.e. patients with no recurrences) in both arms of ADAURA had very similar quality-of-life parameters. Our own Canadian data has demonstrated high longitudinal health utility scores in patients with metastatic/recurrent disease on osimertinib[7]; this mirrors ADAURA data showing that osimertinib use in patients whose disease is under control is associated with a good quality-of-life[11]. However, in Canadian data, our multivariable analysis also demonstrates that subsequent chemotherapy treatment (even when disease is stable), increasing numbers of metastatic sites, and presence of disease recurrence or progression is associated significantly with worse/lower health utility scores[11].

Thus, in summary, outcomes used in current practice (recurrences or recurrence-free survival, and overall survival) are aligned with the ADAURA primary and secondary clinical outcomes. In an older era, recurrence-free survival may only have been seen as a surrogate for overall survival; however, in our contemporary era, our clinician group sees recurrent disease as its own critical outcome, with substantial patient-level, health-care level, and societal-level ramifications. Recurrence-free survival (or its synonym, disease-free survival) is already an acceptable outcome in other disease sites (e.g. breast, melanoma), partly because of such impact. The same standard should be applied to adjuvant NSCLC therapy.

Reference:

[11]J ang SX, Wa ton RN, Huen ken K, Baek J, McCartney A, Labbé C, Sm th E, Chan SWS, Chen R, Brown C, Pate D, L ang M, Eng L, Sacher A, Bradbury P, Le gh NB, Shepherd FA, Xu W, L u G, Hurry M, O'Kane GM. Rea -wor d hea th ut ty scores and tox c t es to tyros ne k nase nh b tors n ep derma growth factor receptor mutated advanced non-sma ce ung cancer. Cancer Med. 2019 Dec;8(18):7542-7555. do : 10.1002/cam4.2603. Epub 2019 Oct 24. PMID: 31650705; PMCID: PMC6912023.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

Again, this question is worded for the metastatic setting.

We will re-frame this question as "What would be considered a clinical meaningful improvement in outcome?"

The only comparison for adjuvant therapy in NSCLC is adjuvant chemotherapy, which has been accepted and funded in Canada and globally. Based on this standard, novel therapeutic strategies with a

recurrence-free survival benefit of a hazard ratio of 0.84 or lower[2] would be considered a clinical meaningful improvement in outcome. ADAURA's recurrence-free-survival benefit has a HR of 0.17, a rate that is multi-fold better.

Note that the absence of statistical significance in the current data-cut of the secondary outcome of OS is neither surprising, nor of concern. In our Canadian *EGFR*-mutated early-stage data, two-year OS was 92% (**Figure 3**), identical to the ADAURA placebo-controlled arm (also 92%). Our Canadian cohort had much longer OS follow-up than the ADAURA: in the Canadian cohort, the four-year OS values were 90% for Stage IB, 73% for Stage II, and 52% for Stage III, showing that deaths have been occurring with longer follow-up, as recurrences translate eventually into deaths in this Canadian cohort (**Figure 3**).

6.10. How often should treatment response be assessed?

Response:

Again, this question is phrased for the advanced/metastatic NSCLC setting.

We will re-frame this question to "How often should follow-up of patients with early-stage lung cancer take place when osimertinib is administered adjuvantly?"

Given that adjuvant osimertinib is administered over a three-year period, there will need to be periodic follow-up for toxicity of the drug and periodic follow-up for recurrent disease.

Follow-up intervals for assessment of osimertinib toxicity will vary. Patients are likely to have shorter follow-ups (monthly to every two-months) near the initiation of treatment, and then longer periods between follow-ups (in some cases up to 6 months for compliant, well-informed, longer-term patients who have not had any prior osimertinib toxicity).

Time intervals between imaging will also vary for the same reasons, with longer time intervals occurring the longer the time interval from surgical resection. Initially, imaging scans at 3-4 month intervals would be common-place, and towards the end of adjuvant therapy and beyond, imaging as sparse as 6+ months intervals may occur.

These follow-up and imaging time intervals, in part, reflect the wide range of follow-up practices across Canada and globally, where there has been no consensus. However, resected Stage IB-IIIA NSCLC patients generally are followed-up for at least 5-years post-operatively by at least one oncologist (typically surgical or medical oncologist) in most settings.

These follow-up periods also reflect a changing paradigm. Whereas adjuvant chemotherapy takes place over 3-4 months, adjuvant osimertinib is administered over 3 years. In clinical practice, follow-up in the real-world setting need not be as frequent as the clinical trial it was based on, when the novel therapeutic strategy is well-tolerated (i.e. low toxicity rates). Nonetheless, any suggested follow-up shown plans above may need to be further refined with the accumulation of additional long term real-world data.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

The primary reason for drug discontinuation is the presence of disease recurrence.

A second reason for drug discontinuation is due to adverse events, which occurred in 11% of patients on the ADAURA trial.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

This oral medication is suitable in all oncology settings. Specifically, this medication is appropriate for treatment in the community setting, including medical oncology outpatient clinics, and even in the inpatient setting.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

This question does not apply to the current submission.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

There are additional important factors that are pertinent to this review:

(1) The overall number of patients impacted by this indication in Canada is relatively small. Despite, over 29,000 new cases of lung cancer in Canada, NSCLC occurs in ~85%, and Stage IB-IIIA occur in ~30%. When we factor in the proportion of such patients who are actually resected (with R0 resections), the proportion of patients in early stage who are tested for *EGFR*, and the ~15% of patients whose tumours carry *EGFR* mutations, our clinician group estimates that the total number of patients who will qualify for adjuvant osimertinib will range between 300-400 patients/year in the first few years after approval. The impact of any uncertainty of the degree of benefit would be mitigated by the small number of patients receiving this adjuvant therapy.

(2) When treating an actual patient, not being able to offer this low-toxicity, efficacious treatment to reduce cancer relapse is highly problematic. To many of us, it is unconscionable to have to forego such a therapy due to lack of funding or an inability of patient to self-pay. It is equally unconscionable when the HR for recurrence-free survival is 0.17. This clinician group strongly discourages waiting for more data on OS outcome, which we consider an outdated concept. As shown in our Canadian data (**Figure 3**), the OS benefit will take years to document in ADAURA, resulting in hundreds (up to over a thousand) of needless patient recurrences and deaths that could have been prevented or delayed significantly.

(3) Recurrence-free survival in adjuvant trials has already been accepted as an acceptable outcome alone in the absence of mature OS data in other disease sites, including breast cancer (KATHERINE study)[12] and melanoma (COMBI-AD, CHECKMATE-238, KEYNOTE-054)[13-15]. None of these other trials had close to the magnitude of benefit in preventing recurrences (HR of 0.17) as reported in ADAURA.

(4) We posit that the impact of improvement in ***recurrence*** of NSCLC alone of the magnitude of HR of 0.17 is significantly greater than the impact of each of the recently-funded therapeutic strategies in the advanced/metastatic setting, given that the downstream implications of having recurrent disease are far worse than disease progression in the advanced/metastatic setting.

(5) Although ADAURA restricted patients to having either *EGFR* exon 19 deletions or L858R mutations, knowledge is evolving. These two mutations represent approximately 85-90% of all *EGFR* mutations. As more information arrives from the real-world on the benefit of osimertinib in rare *EGFR* mutations, some of the rarer *EGFR* mutations may also be found to benefit from osimertinib. This clinician group encourages using the term "sensitizing *EGFR* mutations" rather than restrict the definition to the two main mutations, to allow for these rare mutations (likely <5% of all *EGFR* mutations) to be considered for funding on a case-by-case basis.

[12] https://www.cadth.ca/trastuzumab-emtansine-kadcyla-early-breast-cancer-ebc-details

[13] https://cadth.ca/tafinlar-mekinist-combo-melanoma-adjuvant-therapy-details

[14] https://cadth.ca/opdivo-melanoma-adjuvant-therapy-details

[15] https://cadth.ca/keytruda-melanoma-adjuvant-treatment-details

8. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

None.

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

None.

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. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	Geoffrey Liu
Position	*Professor of Medicine, University of Toronto* *Medical Oncologist, University Health Network*
Date	*15-04-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Takeda	☐	☐	☐	☒
Roche	☐	☐	☒	☐
Pfizer	☐	☐	☒	☐
Astra Zeneca	☐	☐	☐	☒
Bristol Myers Squibb	☒	☐	☐	☐
Boehringer Ingelheim	☐	☐	☒	☐

AbbVie	☐	☒	☐	☐
Merck	☐	☒	☐	☐
EMD Serono	☒	☐	☐	☐
Novartis	☐	☐	☒	☐
Glaxo Smith Kline	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Rosalyn Juergens*
Position	*Medical Oncologist and Head of Department of Clinical Trials at the Juravinski Cancer Centre*
Date	*15-04-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☐	☒	☐	☐
Bristol-Myers Squibb	☒	☐	☐	☐
Merck Sharp and Dohme	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Paul Wheatley-Price*
Position	*Medical Oncologist, The Ottawa Hospital Cancer Centre* *Professor, University of Ottawa*
Date	*15-04-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☐	☒	☐	☐
Bayer	☒	☐	☐	☐
Boehringer Ingelheim	☒	☐	☐	☐
Bristol-Myers Squibb	☒	☐	☐	☐
Merck	☐	☒	☐	☐

Novartis	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	Dr. Quincy Chu
Position	*Medical Oncologist, Cross Cancer Institute, Alberta*
Date	*15-04-2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Astra Zeneca	☐	☐	☐	☒
Boehringer Ingelheim	☐	☒	☐	☐
Bristol-Myers Squibb	☐	☒	☐	☐
Eisai	☒	☐	☐	☐
Merck	☐	☐	☒	☐
Novartis	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Roche	☐	☒	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Ronald Burkes*
Position	*Medical Oncologist, Mount Sinai Hospital* *Professor, University of Toronto*
Date	*15-04-2021*
☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Randeep Sangha*
Position	*Medical Oncologist, Cross Cancer Institute* *Associate Professor, University of Alberta*
Date	*15-04-2021*
☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Donna Maziak*
Position	*Professor and Thoracic Surgeon, University of Ottawa*
Date	*15-04-2021*
☒	**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				
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	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Jeffrey Rothenstein*
Position	*Medical Oncologist, Lakeridge Health, Oshawa*
Date	*15-04-2021*

☒	**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

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

Declaration for Clinician 9

Clinician Information	
Name	*Callista Phillip*
Position	*Medical Oncologist and Clinical Lead* *Oncology Clinic, Joseph Brant Hospital*
Date	*15-04-2021*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*David Dawe*
Position	*Medical Oncologist, CancerCare Manitoba*
Date	*15-04-2021*
☒	**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

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

Astra Zeneca	☐	☐	☒	☐
Merck	☒	☐	☐	☐
Boehringer-Ingelheim	☒	☐	☐	☐

Declaration for Clinician 11

Clinician Information	
Name	*Stephanie Snow*
Position	*Medical Oncologist, QEII hospital* *Associate Professor, Dalhousie University*
Date	*15-04-2021*
☒	**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

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Amgen	☒	☐	☐	☐
Astra Zeneca	☐	☐	☒	☐
Bayer	☐	☒	☐	☐
Boehringer Ingelheim	☒	☐	☐	☐
Bristol-Myers Squibb	☐	☐	☒	☐
Eisai	☒	☐	☐	☐
Merck	☐	☐	☒	☐
Novartis	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Purdue	☒	☐	☐	☐
Roche	☐	☐	☒	☐
Taiho	☒	☐	☐	☐
Takeda	☐	☒	☐	☐

Declaration for Clinician 12

Clinician Information	
Name	*Parneet Cheema*
Position	*Medical Oncologist, William Osler Health Centre*
Date	*15-04-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Bristol-Myers Squibb	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 13

Clinician Information	
Name	*Mahmoud Abdelsalam*
Position	*Medical Oncologist, The Moncton Hospital*
Date	*15-04-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bristol-Myers Squibb	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 14

Clinician Information	
Name	*Andrew Maksymiuk*
Position	*Medical Oncologist, CancerCare Manitoba* *Professor, University of Manitoba*
Date	*15-04-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
GlaxoSmithKline	☐	☒	☐	☐

Merck	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 15

Clinician Information	
Name	*Diana Ionescu*
Position	*Consultant Pathologist, BC Cancer Agency*
Date	*15/04/2021*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Roche	☐	☒	☐	☐
BMS	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Eli Lilly	☒	☐	☐	☐

Declaration for Clinician 16

Clinician Information	
Name	*Zhaolin Xu*
Position	*Pathologist, QEII Health Sciences Centre*
Date	*15-04-2021*
☒	**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

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

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0246-000
Generic Drug Name (Brand Name)	osimertinib (Tagrisso); AstraZeneca Canada Inc.
Indication	Tagrisso (osimertinib) is indicated as adjuvant therapy after tumour resection in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
Name of the Clinician Group	Ontario Health (Cancer Care Ontario) – Lung Cancer Drug Advisory Committee
Author of the Submission	Dr. Gail Darling, Dr. Peter Ellis, Dr. Natasha Leighl, Dr. Andrew Robinson, Pamela Ng (pharmacist)
Contact information	Name: Dr. Gail Darling Title: Cadriothoracic surgeon/Ontario Cancer Lead [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Discussed jointly via emails.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Adjuvant chemotherapy is standardly offered to patients with completely resected primary tumours over 4cm or other high risk features such as positive nodes, invasion of chest wall, satellite nodules in the same lobe or ipsilateral lung etc. In the 7th edition staging system, these included most patients with stage IB to stage IIIA tumours, while in the 8th edition staging system this includes mostly stage IIA to IIIB tumours. The ADAURA study examined adjuvant osimertinib in patients with stage IIA - IIIB disease (8th edition)

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The ultimate goal of any adjuvant therapy is to improve overall survival or quality of life. In most circumstances, reducing the risk of recurrence (recurrence or disease free survival), translates into improved overall survival. In situations where recurrence is often symptomatic and unpredictable, improving "disease-free time" may also translate in to DFS. Improving OS and QOL while minimizing side effects is the ultimate goal.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Despite adjuvant chemotherapy for resected NSCLC, the risk of recurrence for stage IIA-IIIB remains high. 5 year overall survival ranges from 70% for stage IIA to as little as 40% for stage IIIB. In addition, adjuvant chemotherapy is not used or accepted by a sizable portion of lung cancer patients, with over 30% of patients not receiving adjuvant chemotherapy. Better therapy is needed to improve these survival figures. In more advanced EGFR mutated NSCLC, targeted therapies are routinely used.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients with stage II and III NSCLC have high rates of recurrence and death. EGFR mutated patients are often non smokers and therefore would not be eligible for screening programs for lung cancer.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Adjuvant chemotherapy is routinely offered to patients with resected stage IIA-IIIB (8th edition) NSCLC. Uptake in stage IIA is lower than stage IIB and III disease. Patients with EGFR mutated resected NSCLC are also offered adjuvant chemotherapy. Osimertinib would represent an incremental therapy post adjuvant chemotherapy in patients who choose or are unable to receive chemotherapy, and an incremental step in patients who do not receive chemotherapy. Most patients with stage IIB and III NSCLC in the ADAURA trial received adjuvant chemotherapy prior to randomization. Osimertinib is an EGFR TKI that is specific therapy for patients with exon 19 delation or exon 21 L858R mutated NSCLC. Therapy with osimertinib would be expected to result in substantial reduction in the risk of recurrent lung cancer or delay in recurrence.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Patients with resected stage IB-IIIA NSCLC would still be recommended to receive adjuvant chemotherapy. Osimertinib would be recommended post adjuvant chemotherapy. Ie those patients with exon 19 deletion, or L858R point mutation EGFR NSCLC would now be offered adjuvant chemotherapy followed by osimertinib. In patients who are unable to or choose not to receive adjuvant chemotherapy osimertinib would still be indicated.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Osimertinib is currently used as first-line therapy for advanced/metastatic NSCLC. If patients receive adjuvant osimertinib and relapse with widespread disease on therapy, they would not receive osimrtinib for advanced/metasatic disease. However, patients who complete three years of adjuvant osimertinib and relapse at least 6 months following completion of therapy, would still be considered for osimertinib therapy for advanced/metastatic disease. In addition, for patients who exhibit oligoprogression or in some cases 'flare' (such as bone metastases revealing themselves after therapy) while on osimertinib, osimertinib would be expected to be continued in some patients.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with resected stage IIA-IIIB NSCLC with exon 19 deletion, or exon 21 L858R EGFR mutations would be candidates for adjuvant osimertinib.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

As stated above, osimertinib would be offered upon completion of adjuvant chemotherapy. EGFR mutation testing should be reflexively performed on all newly diagnosed non squamous NSCLC. Therefore patients with exon 19 deletion, or exon 21 L858R point mutation, EGFR mutations should be readily identified.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Adjuvant therapy with osimertinib is limited to patients with specific EGFR mutations – exon 19 deletion and L858R point mutation. It is not indicated in patients with other types of EGFR mutations, or those with EGFR wild type tumors

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Therapy is limited to patients with specific EGFR mutations described above. Subgroup analyses of the ADAURA trial did not identify any subgroups that would not benefit from osimertinib

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Osimertinib would be administered in the adjuvant setting. There would be no outcomes that specifically identified patients as benefitting from therapy. Evidence of recurrence would be an indicator of treatment failure though

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

The absence of recurrent lung cancer is the most meaningful indicator of benefit from therapy

6.10. How often should treatment response be assessed?

Response:

It would be appropriate to monitor patients every three months on therapy. Scans to rule out recurrence should be conducted at least every 6 months during the three years of osimertinib therapy

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Reasons to discontinue therapy would be evidence of recurrent lung cancer, intolerable side effects of therapy, or completion of three years of adjuvant therapy

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

This therapy would be administered in the outpatient setting, under the supervision of an oncologist

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

N/A

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

The ADAURA trial demonstrated a very large reduction in the risk of recurrent NSCLC in patients with EGFR mutated resected NSCLC. In patients with resected stage II and III disease, the magnitude of benefit is very large. While OS data are immature, it is hard to believe that the improvements in DFS will not translate into improvements in OS. Osimertinib is generally well tolerated therapy, with a large benefit and should be incorporated into standard treatment algorithms, pending OS data.

8. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   OH-CCO provided secretariat support to the DAC in completing this input.

2. Did you receive help from outside your clinician group to collect or analyze any information 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. **Please note that this is required for <u>each clinician</u> that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Gail Darling*
Position	Cardiothoracic Surgeon/Ontario Cancer Lead
Date	*16-April-2021*

☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Andrew Robinson*
Position	*Medical Oncologist/Lung DAC member*
Date	*9-March-2021*
☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Peter Ellis*
Position	*Medical Oncologist/Lung DAC member*
Date	*5-April-2021*
☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Natasha Leighl*
Position	*Medical Oncologist/Lung DAC member*
Date	*5-April-2021*
☒	**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

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	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Pamela Ng*
Position	*Pharmacist*
Date	*06-April-2021*
☒	**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

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	☐	☐	☐	☐