CADTH

# pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

# Pembrolizumab (Keytruda) for Squamous Non-Small Cell Lung Cancer

January 3, 2020

# 3 Feedback on pERC Initial Recommendation

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|---|---|
| Name of the Drug and Indication(s): | pembrolizumab (KEYTRUDA®)<br><br>For the treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC |
| Role in Review (Submitter and/or Manufacturer): | Submitter and Manufacturer |
| Organization Providing Feedback | Merck Canada |

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

## 3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __X__ disagree

Merck Canada agrees with pERC that pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for metastatic squamous (SQ) NSCLC aligns with patient values in that this regimen has no detriment in quality of life and provides another treatment option. However, Merck disagrees with pERC's decision not to recommend pembrolizumab combination in this indication due to the duration of follow up in the submitted second interim analysis (IA2) data from KEYNOTE-407.

**Clinical Guidance**

pERC's main clinical rationale for the negative recommendation was that the follow up in the submitted KEYNOTE-407 interim analysis 2 (IA2) data was too short.

Results from KEYNOTE-407 IA2 were reported following review by the external monitoring committee on May 21, 2018. Since the committee reported that the efficacy boundaries for the primary hypotheses of overall survival (OS) and progression-free survival (PFS) had been met, the decision was made to report the results of IA2. The trial is continuing in order to evaluate outcomes with additional follow-up.

The time from first patient randomized (August 19, 2016) to database cut-off for IA2 (April 3, 2017) was 19.5 months. The time from last patient randomized (December 28, 2017) to database cut-off for IA2 (April 3, 2018) was 3.2 months. A 7.8 month (range 0.1, 19.1)

median follow-up duration across the two treatment arms was reported for IA2 (see table below), with follow-up duration conservatively defined as time from randomization to the date of death or database cutoff date if the subject is still alive.

| Follow-up duration (months)† | Pembro Combo (N=278) | Control (N=281) | Total (N=559) |
|---|---|---|---|
| Median (Range) | 8.3 (0.4, 18.9) | 7.4 (0.1, 19.1) | 7.8 (0.1, 19.1) |
| Mean (SD) | 8.6 (4.1) | 7.8 (4.2) | 8.2 (4.2) |

† Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 03APR2018

At IA2, pembrolizumab demonstrated OS and PFS were statistically significantly improved in the pembrolizumab combination group, resulting in a 36% reduction in the risk of death (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001) and a 44% reduction in the risk of disease progression or death (hazard ratio for disease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001) compared with the control group. The response rate was 57.9% (95% CI, 51.9 to 63.8) in the pembrolizumab combination group and 38.4% (95% CI, 32.7 to 44.4) in the placebo-combination group. The improvements in OS, PFS, and ORR were observed across all PD-L1 subgroups and all pre-specified demographic subgroups.

The protocol-specified final analysis (FA) for OS from KN-407 were subsequently presented at the ESMO 2019 Annual Meeting. The FA provided an additional 13.2 months follow-up (FA database cut-off May 9, 2019 vs. IA2 database cut-off April 3, 2018). The time from last patient randomized to database cut-off increased from 3.2 months (IA2) to 16.3 months (FA). The median follow-up across treatment arms increased from 7.8 months to 14.3 months (range 0.1, 31.3).

| Follow-up duration (months)† | Pembro Combo (N=278) | Control (N=281) | Total (N=559) |
|---|---|---|---|
| Median (Range) | 17.0 (0.4, 31.3) | 12.3 (0.1, 31.3) | 14.3 (0.1, 31.3) |
| Mean (SD) | 15.4 (8.0) | 13.3 (8.5) | 14.4 (8.3) |

† Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 09MAY2019

At the protocol pre-specified final analysis (FA) for OS, the pembrolizumab combination continued to provide clinically meaningful improvement in OS and PFS when compared to the chemotherapy regimen alone in the first-line treatment of participants with metastatic SQ NSCLC. The efficacy results at the protocol pre-specified FA were generally consistent with IA2. The pembrolizumab combination provided a clinically meaningful improvement in OS when compared with the control [HR=0.71 (0.58-0.88)], representing a 29% reduction in the risk of death. The HR for OS, adjusted for crossover, is 0.56 (95% CI: 0.39, 0.80) for the pembrolizumab combination arm vs. the control arm. The pembrolizumab combination provided a clinically meaningful improvement in PFS when compared with the control [HR=0.57 (0.47-0.69)], representing a 43% reduction in the risk of disease progression or death.

In the past, pERC has recognized net clinical benefit in other indications (Phase 3 trials) where the median follow up was less than 7.8 mths. In recent reviews, pERC recommended

reimbursement of nivolumab in patients with head and neck carcinoma[1] (median follow up: 5.1 mths), alectinib for the treatment of metastatic NSCLC[2] (median follow up: 6.5 mths) and regorafenib for patients with hepatocellular carcinoma[3] (median follow up: 7.0 mths).The recommendation for these files was based on statistically significant and clinically meaningful in OS and acceptable toxicity profile.

Most importantly, patients with metastatic NSCLC of SQ histology have historically had no first-line treatment options beyond cytotoxic chemotherapy, which imparts limited survival benefit for these patients. The pERC's negative recommendation for KEYNOTE-407 would mean that these patients would continue to have chemotherapy as the only first-line treatment option despite the fact that the trial demonstrated a significant OS benefit with the pembrolizumab combination versus SOC chemotherapy-alone in the first-line setting even at a mFU of 14.3 months.

For the above reasons, Merck believes that pERC should reconsider its clinical negative recommendation for KEYNOTE-407.

**Economic Guidance**

Merck Canada does not agree with the EGP Reanalysis estimates in the Economic Guidance Report, (page 9 Table 4).

Chemotherapy arm OS log-logistic extrapolation: Merck is perplexed by the inclusion of this modification in the reanalysis' upper bound. It is mentioned in the economic guidance document that this "reanalysis projects that chemotherapy OS would overtake pembrolizumab+chemotherapy around week 182", which does not seem scientifically plausible given the within-trial trend in efficacy observed based on KM data for each arm. Additionally, it is not mentioned that this modification results in an unrealistic OS for chemotherapy treated SQ NSCLC patients. In fact, the log-logistic function generates OS with chemotherapy of 11% at 5 years, and 5.3% at 10 years. It is generally accepted in clinical practice that SQ NSCLC is harder to treat and more aggressive than non-squamous (NSQ) NSCLC[4]. In its review of the KN189 study, pCODR's reanalysis accepted the submitted base case exponential extrapolation for chemotherapy OS, which generated OS of 3.9% at 5 years and 0% at 10 years. In light of this, it doesn't seem rational that first-line chemotherapy treated SQ patients would have longer OS than their NSQ counterparts. Furthermore, long term data from pooled analysis of Checkmate017/057 demonstrate that only 13% of patients are alive at 5-year. Considering that only half of the patients treated in the 1L setting are eligible to receive a 2L treatment, it seems highly implausible that 1L OS with chemotherapy would be similar to 2L OS with immunotherapy.

Although the EGP mentioned two examples of possible clinical scenarios that could contribute to combined immunotherapy/chemotherapy being less effective and more costly than chemotherapy alone as 1L treatment (p.6), Merck considers those 2 examples to be inadequate:

Example 1: The Clinical Guidance Panel (CGP) itself noted that it is uncertain how likely this example could be. Merck would also like to reiterate that there was no difference in adverse events leading to death between the pembrolizumab combination arm and the chemotherapy-alone arm. In addition, the adverse event rates observed in KN407 at a median follow-up of 7.8 months are similar to those seen in an updated analysis of the data at a median follow-up of 14.3 months. Furthermore, the incidence of immune-mediated adverse events in Merck's phase I study examining pembrolizumab in metastatic NSCLC (KN001) are similar at both 3-year and 5-year follow-ups.

Example 2: In this example, it is mentioned that sequential chemotherapy and immunotherapy could be as effective as first-line therapy with the pembrolizumab combination. However, data from an array of first line pembrolizumab trials show that front-

line treatment with immunotherapy is more efficacious for patients with metastatic NSCLC. PFS2 data from KN024[5], KN189[6] and KN407[7] show that front-line use of pembrolizumab as a monotherapy or in combination with chemotherapy delays disease progression when compared with first-line treatment with chemotherapy alone followed by second-line treatment with immunotherapy. These trials also demonstrated that OS with front-line use of pembrolizumab as a monotherapy or in combination with chemotherapy was superior to the OS with front-line chemotherapy alone, even when a significant portion of patients in the front-line chemotherapy-alone arm received immunotherapy as a second-line treatment. Specifically, in KN407, front-line pembrolizumab in combination with chemotherapy gave rise to a significant OS benefit versus front-line chemotherapy alone despite the fact that approximately 50% of patients who were treated with front-line chemotherapy alone received immunotherapy as a second-line treatment. It is also important to note that only about 30% of metastatic NSCLC Canadian patients who receive front-line chemotherapy alone move on to receive second-line treatment[8]. Considering these points, it is not reasonable to consider that sequential chemotherapy and immunotherapy could be as effective or a better option than front-line therapy with pembrolizumab in combination with chemotherapy.

The CGP mentions in the Economic Guidance Report that it "agreed that the chemotherapy alone OS is unlikely to be greater than pembrolizumab + chemotherapy OS", hence "the EGP believe that the ICER will be likely closer to the lower bound of the reanalysis." With this in mind, it seems odd that the pERC retained the conclusions of an analysis that both the CGP and the EGP don't believe in.

It is also important to consider that the submitted model allowed for multiple other ways to assess the uncertainty around the pembrolizumab combination OS, such as: selecting a different OS extrapolation curve for pembrolizumab combination, shortening the time horizon of the model, using a treatment effect waning option, changing the modelled population to patients whose tumours express PD-L1 TPS < 50%, and others. All of which were available in the model to allow the end-user to modulate the uncertainty on the OS benefit.

When conducting an economic analysis, common belief is that the external validity of the comparator's efficacy should be assessed first. As such, the NICE Methods Guidance[9] mentions that "*The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources*." A similar statement is made in CADTH's guidelines for the economic evaluation of health technologies[10]. By modifying the OS estimate of the comparator in its upper bound reanalysis, the EGP doesn't address any of the mentioned uncertainty surrounding the efficacy of the pembrolizumab combination. On the opposite, it creates implausible findings that adversely impact the external validity of the model results.

Statistical fit is not enough to determine the best fitting OS curve. A NICE DSU technical support document[11] states that "*Assessing the suitability of alternative survival models is concerned with demonstrating whether or not models are appropriate, which is defined by whether the model provides a good fit to the observed data and whether the extrapolated portion is **clinically** and **biologically plausible**. Models that meet only one of these criteria are likely to be **inappropriate***." It also mentions that AIC and BIC criteria "*address the internal validity of fitted models, but not their external validity*". The previous paragraphs demonstrate that the log-logistic curve used in the upper bound reanalysis lacks external validity. Therefore, it could be said that pCODR's upper bound ICER is clinically implausible and inappropriate.

Based on all the above, Merck kindly asks pERC to reconsider their initial position and recognize that scenarios in which pembrolizumab combination is dominated by chemotherapy are unfit for decision making.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

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| Support conversion to final recommendation. | | _X___ | Do not support conversion to final recommendation. |
| Recommendation does not require reconsideration by pERC. | | | Recommendation should be reconsidered by pERC. |

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

| Page Number | Section Title | Paragraph, Line Number | Comments and Suggested Changes to Improve Clarity |
|---|---|---|---|
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### 3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

| Page Number | Section Title | Paragraph, Line Number | Comments related to Submitter or Manufacturer-Provided Information |
|---|---|---|---|
| p.7 | Economic Guidance Report | PSA Uncertainty | The Manufacturer would like to remove the following statement:" The submitter's PSA assumed that most standard errors were 20% of the corresponding parameter's base value, hence not reflecting the true parameter uncertainty. This is not in compliance with CADTH HTA guidelines." |

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| | | | The previous statement is erroneous. Most standard errors (SE) are **taken from parameters distribution information**. The 20% SE is applied only on costs parameters, for which distribution information is not available or doesn't exist. This methodology is compliant with CADTH HTA Guidelines which states that "If data on the degree of uncertainty are unavailable, a conservative approach should be adopted whereby an estimate of the standard error is assumed that allows for plausible parameter values" |
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### 3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

| Page Number | Section Title | Paragraph, Line Number | Additional Comments |
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1 RL Ferris, G Blumenschein Jr, J Fayette, et al., Nivolumab for recurrent squamous-cell carcinoma of the head and neck, N Engl J Med, 375 (2016), pp. 1856-1867
2 https://www.cadth.ca/sites/default/files/pcodr/pcodr_alectinib_alecensaro_nsclc_2ln_fn_rec.pdf
3 https://www.cadth.ca/sites/default/files/pcodr/pcodr_regorafenib_stivarga_hcc_fn_rec.pdf
4 Socinski MA, Obasaju C, Gandara D, et al. Current and Emergent Therapy Options for Advanced Squamous Cell Lung Cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(2):165-183.
5 Julie R. Brahmer, Delvys Rodriguez-Abreu, Andrew George Robinson, et al. Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumor proportion score (TPS) ≥50% enrolled in KEYNOTE-024. Journal of Clinical Oncology 2017 35:15_suppl, 9000-9000
6 Shirish M. Gadgeel, Marina Chiara Garassino, Delvys Rodriguez-Abreu, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. Journal of Clinical Oncology 2019 37:15_suppl, 9013-9013
7 L Paz-Ares, D Vicente, A Tafreshi, et al. Pembrolizumab (pembro) + chemotherapy (chemo) in metastatic squamous NSCLC: Final analysis and progression after the next line of therapy (PFS2) in KEYNOTE-407, Annals of Oncology, Volume 30, Issue Supplement_5, October 2019, mdz394.080, https://doi.org/10.1093/annonc/mdz394.080
8 Adrian G. Sacher, Lisa W. Le, Anthea Lau1, et al. Real-World Chemotherapy Treatment Patterns in Metastatic Non–Small Cell Lung Cancer: Are Patients Undertreated? Cancer (2015) 2562-2569
9 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Last updated April 2013. https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781
10 Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf
11 National Institute for Health and Care Excellence. Decision Support Unit technical support document 14: Suvival analysis for economic evaluations alongside clinical trials: extrapolation with patient-level data. Last updated

March 2013. http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf