PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Aldesleukin (Proleukin) for In-Transit Melanoma

June 22, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The economic analysis submitted by Cancer Care Ontario compared interleukin-2 (IL-2) therapy compared to usual care for treatment of patients with in-transit melanoma using a state-transition or Markov model. IL-2 is administered intralesionally and is a localized treatment option. IL-2 is a second line therapy for in-transit metastatic melanoma after failure of surgery. Treatment with IL-2 usually requires 6 treatments given in 2 week intervals. Patients undergoing 'usual care' could potentially undergo systemic therapy, isolated limb infusion, or radiation. The proportions of patients that underwent these possible therapeutic options were obtained via expert opinion. Patients undergoing IL-2 therapy were all assumed to eventually progress and undergo another line of therapy.

The Submitter conducted several model modifications to address some of these assumptions and also a probabilistic analysis to assess the probability of being cost-effective at various thresholds. Some of these modifications included lengthening the time horizon of the analysis, altering the estimates of survival for individual therapies, specifying different costs for treatments and also their associated costs. The motivation for these modifications was to ensure the robustness of the analysis with different or new information.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel reported that in the two trials identified for I-L2 (1,2) were single arm trials and therefore these do not provide any information on potential comparisons. The Clinical Guidance Panel opinion stated that there was no standard comparator for IL-2. As such, the comparators used by the submitter seem to be appropriate.

The Provincial Advisory Group (PAG) considered the following factors important in the review of IL-2 that had a bearing on the economic analysis. First, the PAG noted that IL-2 was less invasive than other therapies and was well tolerated. Second, the PAG acknowledged that a typical course of treatment would be approximately 4-8 administrations (every 2 weeks) but were concerned about the maximum number of administrations. Third, the PAG suggested that IL-2 would free up resources because it can primarily be accomplished as an outpatient procedure provided that the centre had the necessary equipment to provide the infusions. Currently, three provinces have the required resources/infrastructure/equipment to being IL-2 therapy.

IL-2 costs $508.47 per vial at a strength of 5 million IU/mL (22 million IU or 1.3 mg per vial). At the maximum of 22 million IU (5 syringes of 0.8 mL) given every 2 weeks, the average cost per day is $36.32 and the average cost per 28-day course is $1,016.94.

The Submitter assumed that the cost of IL-2 is $662 per treatment. This total cost included the cost of patient assessment, initial consult and follow-up costs, and biopsy costs. These additional costs were spread over 6 treatments with IL-2.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC/ΔE) is 'dominant' for eligible patients which represents a scenario where the proposed therapy has better effects and lower costs than the existing comparator therapies. The results of this model suggest that IL-2 is 'Dominant' to 'Usual Care' (isolated limb infusion [ILI], systemic therapy, and radiation) in patients with unresectable melanoma for in-transit metastases.

For this analysis, the IL-2 arm of the model resulted in incremental cost-savings of $5074 and improved outcomes, in terms of quality-adjusted life-years (0.304) and life years (0.589).

The incremental cost-effectiveness ratio was based on an estimate of the incrementally lower cost (-$5074) and the extra effect (an additional 0.589 life years or 0.304 quality-adjusted life-years). The EGP's best estimate of:

- The IL-2 strategy, from the submitter's calculations, has lower costs than 'usual care'. This incremental difference in costs is largely due to the delay associated with the avoidance of more expensive comparator therapies (ILI, radiation, and systemic therapy). The assumption regarding the proportion-use of these therapies, both in the IL-2 arm and the 'Usual Care' arm, were modified but IL-2 treatment remained 'dominant'.
- The incremental clinical effect of IL-2, in terms of QALYs is between 0.304 and 0.506. This difference is based on the source of utility values used in the analysis. This submission made assumptions regarding previously captured utility values and assigned these values to health states for patients at various stages of disease for in-transit metastases of melanoma. Using life-years as the analysis outcome, assumptions about the survival associated with systemic therapies (vemurafenib or ipilimumab) showed that a small survival improvement on these therapies changed the incremental effectiveness of IL-2.

The EGP based these estimates on the model submitted by Cancer Care Ontario and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- When the costs associated with Il-2 therapy were increased (3-fold), the extra cost is $5064), which increases the estimated incremental cost-effectiveness ratio to $18 441 per QALY, but remains under a threshold of $20 000 per quality-adjusted life-year.
- The costs of comparator therapies were all divided by two to see how reductions in these costs would affect the ICER. While the incremental cost difference between the two strategies narrowed (from -$5074 to -$738), the IL-2 strategy remained 'dominant'.
- The proportion of patients using ILI, radiation, and systemic therapy (10%, 10%, 80%, respectively) was varied to assess the impact of this mix of therapy on model results (to evenly split). In this modification of the model, IL-2 remained 'dominant'.

Several of the EGP's analyses using modifications of model parameter estimates still led to the IL-2 strategy being 'dominant'.

According to the economic analysis that was submitted by Cancer Care Ontario, when IL-2 is compared with isolated limb infusion, radiation, and systemic therapy ('usual care'):

- the extra cost of IL-2 is -$5074 (ΔC). Costs considered in the analysis included the cost of IL-2, the costs of systemic therapies (ipilimumab and vemurafenib), isolated limb infusion, and radiation.
- the extra clinical effect of IL-2 is 0.304 quality-adjusted life years or 0.589 life years gained (ΔE). The clinical effect considered in the analysis was based utilities that were

assumed to correspond with disease states for in-transit melanoma but were not specific to the disease.

The Submitter estimated that the incremental cost-effectiveness ratio -$5074 / 0.304 per QALY and -$5074 / 0.589 life years gained.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The EGP estimates were similar to those reported by the Submitter.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

The two main concerns that emanated from the Patient Advocacy Group submissions was the therapy impact on length of life and quality of life. The side effects of the treatment were generally minor, short-term, and well-tolerated. The associated side-effects were all said to be favourable compared to other courses of treatment. The submitted economic model conducted separate analyses for both length of life (life-years gained/lost) and quality of life (quality-adjusted life-years) to address the concerns of patients.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes. The design and structure of the submitted economic model were adequate to answer this question. The model transitions, in particular, reflected a conservative estimate of the effects of IL-2 by requiring that patients who received IL-2 would eventually transition into another line of therapy. Naming of the particular model states within the Markov model could be improved. Markov states are described with respect to treatments as opposed to actual health states (i.e. specific stage of disease).

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

Model assumptions appear to be valid. The issues surrounding model assumptions are largely with availability of data. Model costs are specific to the submitters' province/institution which could be improved or validated by including cost data from other provinces/institutions. Utilities used in this model were not specific to the disease states of the particular patients and could be improved be obtaining utility values specific to patients with this condition. Survival for several health states was considered to be constant or fixed over time. While Markov models typically assume that transition probabilities are indeed constant over time, it is possible to relax this assumption to more accurately reflect reality (3). The limitation of using constant transition probabilities for survival is that this may be an oversimplification of reality, particularly in the case of survival, and may influence (bias) model results. It is possible to allow for transition probabilities to be time-dependent, and vary with time 'in' the model provided the data exists to do so and the correct techniques are employed (3). Finally, the base-case time

horizon was specified as being 10 years, and could be improved by specifying a life-time horizon.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Yes. The largest limitation of this analysis is the availability of data for effectiveness to populate the model. The submitter provided estimates from the literature that are based on single arm trials **(1,2)** for IL-2. The systematic review noted that no other evidence was available to populate the economic model. Cost data seems to be accurate for the submitters' institution but could be improved by using cost estimates from other provinces/institutions.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Three important considerations for IL-2 therapy are important for the budget impact analysis. First, the size of the population that developed in-transit metastasis from melanoma is very small. Second, the cost of IL-2 is not substantial (one vial = $661). Therefore, the estimated budget impact is not anticipated to be substantial. Third, the submitted budget impact analysis calculates that if 5% of patients are able to avoid systemic therapies, the IL-2 treatment becomes cost-saving.

What are the key limitations in the submitted budget impact analysis?

The epidemiological evidence used in the submitted budget impact analysis was largely dependent on expert clinical opinion. The manufacturer declined to provide input into the analysis, therefore the submitter had no data on market share. Knowledge on the extent to which IL-2 can delay the use would add substantial benefit robustness of the budget impact analysis. However, the analysis also used a conservative approach in that *all* patients eventually underwent systemic therapy which improves the robustness of the analysis. The budget impact analysis could also be improved with cost data from other participating provinces/institutions.

1.5 Future Research

Is there economic research that could be conducted in the future that would provide valuable information related to?

The current analyses were limited in the availability of trials evaluating IL-2. It is hoped that future analyses will have better trial data to populate an economic model. The time horizon chosen for the base-case analysis was 10 years. While this assumption is not incorrect, to align better with published guidelines of economic evaluation (4), the base-case analysis would be improved if a 'lifetime' model time horizon was adopted. Quality-adjusted life-year estimates were based on utility values from Beurenstein et al (5). This paper used general public responses to a standard gamble exercise to value health states associated with response to treatment and decrements for treatment associated toxicities (and symptoms). In the future, analyses could also obtain patients' or societal preferences for states specific to melanoma and the treatments under consideration.

Is there economic research that could be conducted in the future that would provide valuable information related to Intra-lesional interleukin-2 for melanoma in-transit metastases?

There were no other identified economic evaluations for intra-lesional interleukin-2 for melanoma in-transit metastases. The submitter used costs specific to their jurisdiction so validation of these costs across provinces could be an important consideration. As mentioned above, obtaining health state utility values for this specific patient group (and the associated treatments) could be valuable information to inform future economic analyses.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of aldesleukin for in-transit melanoma. A full assessment of the clinical evidence of aldesleukin for in-transit melanoma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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