CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

## Olaratumab (Lartruvo) for Soft Tissue Sarcoma

**April 18, 2018**

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# FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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# TABLE OF CONTENTS

# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The main economic analysis **submitted to pCODR by Eli Lilly** compared olaratumab in combination with doxorubicin (Olara+DOX) to doxorubicin (DOX) monotherapy for patients with advanced soft tissue sarcoma (STS). Two other economic analyses were submitted comparing Olara+DOX to ifosfamide in combination with doxorubicin (IfoDOX) and gemcitabine in combination with docetaxel (GemDoc).

**Table 1. Submitted Economic Model**

| | |
|---|---|
| Funding Request/Patient Population Modelled | Adult doxorubicin-naïve or anthracycline-naïve patients with advanced or mSTS that is not amenable to curative treatment with surgery or radiotherapy. |
| Type of Analysis | *CUA & CEA* |
| Type of Model | *Partitioned-survival* |
| Comparator | *Doxorubicin (DOX) (standard for Canadian patients in the comparator setting)*<br>*NOTE: IfoDOX and GemDoc were not included in report because neither are considered a common relevant comparator in the Canadian setting.* |
| Year of costs | *2017* |
| Time Horizon | *25 years* |
| Perspective | *Public payer* |
| Olaratumab in combination with doxorubicin | |
| Cost of olaratumab | Olaratumab costs $788.12 and $2074.00 per 190mg and 500mg vials, respectively. This amounts to $4.15 per mg. The 500mg vial is currently available and it is anticipated that the 190mg vial will be available in Q4 2018. At the recommended dose of 15 mg/kg on days 1 and 8 of a 21-day cycle, olaratumab costs:<br><br>Using 190mg:<br>• $414.70 per day (no wastage)<br>• $11614.64 per 28-day course (no wastage)<br>• $450.35 per day (wastage)<br>• $12,609.92 per 28-day course (wastage)<br><br>Using 500mg:<br>• $414.80 per day (no wastage)<br>• $$11,614.40 per 28-day course (no wastage)<br>• $493.81 per day (wastage)<br>• $13,826.67 per 28-day course (wastage) |
| Cost of doxorubicin* | Doxorubicin costs $7.21 per mg. At the recommended dose of 75mg/$m^2$ IV on day 1 of 21 day cycle, doxorubicin costs:<br>• $43.75 per day<br>• $1225.33 per 28-day course |

| | |
|---|---|
| Model Structure | *Patients enter the model on either treatment therapy. They then remain progression-free, experience progression or die (as represented in a three-state model structure). Those with disease progression may have up to four lines of therapy or best supportive care. See Figure 1 for further details.* |
| Key Data Sources | *Phase 2 of Study JGDG* |

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on November 30, 2017 All calculations are based on = 70kg and BSA = 1.7m$^2$*

## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, the comparator DOX monotherapy is appropriate. The CGP agree that in the majority of instances in the Canadian setting, DOX is used; IfoDOX would have limited use in the Canadian setting.

Relevant issues identified included:

- The small size of the JGDG study (133 patients) across patients with heterogeneous tumour groups increases the risks of imbalance of prognostic factors (both known and unknown) across the treatment arms.
- The small size of the study also increases the risk of confounding by previous and subsequent chemotherapies.
- The early separation of the overall survival (OS) curves could suggest a biologic rather than a treatment effect, and this is consistent with the modest median PFS difference of 2.5 months. There is however no clear evidence of a specific targeted mechanism of action for Olaratumab, as PDGFα expression in the STS was not related to outcome.
- Treatment-related adverse events for the Olara+DOX combination were slightly higher than for those on DOX monotherapy. Quality of life (QoL), however, was not collected in the JGDG clinical study so it is unclear if the slight detriment in adverse events impacted patients' quality of life. The ongoing randomized phase 3 trial ANNOUNCE may provide data on the difference, if any, in QoL between treatment groups.
- Administration of olaratumab IV on days 1 and 8, every 3 weeks will be more inconvenient for patients and providers.
- In Canada, most patients qualifying for treatment with Olara+DOX would be chemotherapy-naive. A small number of patients, mainly with leiomyosarcomas often of uterine origin, may already have received chemotherapy before being considered for Olara+DOX.

**Summary of registered clinician input relevant to the economic analysis**

Registered clinicians considered:

- This drug has demonstrated survival benefit in adults with advanced STS and represents a necessity for Canadian patients. The economic model incorporates overall survival.
- Olara+DOX was associated with increased myelosuppression, mucositis, vomiting, abdominal and musculoskeletal pain compared with doxorubicin alone. These were accounted for in the model.
- Olara+DOX would be considered first-line for patients with advanced/metastatic STS. The combination would replace single agent doxorubicin as first-line therapy for adults with advanced/metastatic STS. The submitted model was based on the JGDG trial which included both previously treated and untreated patients, as reflected in the clinical trial where 59% and 54% of patients were previously treated in the Olara+DOX vs DOX groups,

respectively. The submitter also provided the option to looking at the economic analysis by line of therapy.

**Summary of patient input relevant to the economic analysis**
**Patients** considered:

- Available treatments for STS, such as chemotherapy, can be harsh and provide low quality of life. Patients expressed living in considerable pain, along with experiencing sleeplessness, exhaustion and various difficulties depending on the location of the tumour.
- Patients are seeking new treatments that will improve their quality of life, "halt disease progression", increase length of life and have manageable side effects. The submitted economic model incorporates these important outcomes to patients via survival, quality of life and adverse events.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for olaratumab which are relevant to the economic analysis:

- Concern for drug wastage given the low patient numbers. Wastage was included in the submitted base case analysis.
- Available vial sizes available (500 mg and 190 mg vials). The submitted economic model includes two vial sizes: 190 mg and 500 mg vials. However, the 190 mg vial size is anticipated to be available at the end of 2018. Use of the 190 mg vial would minimize drug wastage. To address the concern around wastage if only the 500 mg vial size was available, the EGP conducted a scenario analysis. If only the 500 mg vial were available, the ICER would increase from $175,001 to $198,682.The EGP noted that there is no information on whether or not additional smaller vial sizes may be available in the future, which have the potential to further reduce wastage.
- Olaratumab administration will require additional chemotherapy chair time and nursing resources, since two doses are administered in a 21 day cycle compared to treatment with single agent doxorubicin. The increased cost of administration of olaratumab was considered in the economic model with the additional administration costed for day 8.

## 1.3 Submitted and EGP Reanalysis Estimates (Deterministic results)

**Table 2. Submitted and EGP Estimates**

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 1.37 | 1.07 | 0.88 |
| Progression-free | N/A | N/A | N/A |
| Post-progression | N/A | N/A | N/A |
| ΔE (QALY) | 0.73 | 0.57 | 0.47 |
| Progression-free | 0.09 | 0.09 | 0.09 |
| Progressed | 0.63 | 0.48 | 0.38 |
| Adverse events | -0.01 | -0.01 | -0.01 |
| ΔC ($) | $127,075 | $128,682 | $124,109 |
| ICER estimate ($/QALY) | $175,001 | $224,817 | $263,340 |

**The main assumptions and limitations with the submitted economic evaluation were:**

- **Time horizon**: The submitted time horizon in the economic model was 25 years. The CGP stated that 25 years is not representative of the clinical disease course of STS and therefor much too long to use in this patient population. Though 5 years aligns with previous reviews in this patient population, the CGP indicated that a relevant time horizon for these patients is between 5 - 10 years. The EGP acknowledges the limitations in the availability of long term data in this patient population, however the van Glabbeke paper supported a time horizon of 10 years. In order to examine the potential range of time horizons, the EGP used 10 years in the lower bound and 5 years in the upper bound.
- **Patient characteristics to determine drug acquisition costs**: In the submitted base case, the patient characteristics used to determine the drug acquisition costs were taken from published UK data. The submitter provided no justification for not using the data based on the JGDG trial. The EGP used patient characteristics from the JGDG trial to determine drug costs.
- **Utilities**: Utilities were not collected in the JGDG trial. The submitter identified utilities for the economic model through a systematic literature review, and then averaged the first and second line utilities to apply to the all-line analyses in the economic model. The CGP found the utilities imputed into the model to be relatively high for this patient population. Lower utilities were explored in scenario analyses.
- **Adjustment for cross-over**: In the JGDG trial, patients on doxorubicin monotherapy were allowed to cross-over to receive olaratumab upon progression. The submitter examined adjustment for cross-over, however, neither of the methods assessed were deemed appropriate due to the assumption of the "common treatment effect". The manufacturer concluded that the control-arm patients (ie. those randomized to doxorubicin monotherapy) who received olaratumab upon progression had similar overall survival compared to patients who did not receive olaratumab after discontinuation of doxorubicin. Given the limited data to support this statement, this assumption may introduce uncertainty in survival, and cost-effectiveness.

## 1.4 Detailed Highlights of the EGP Reanalysis

**The EGP made the following changes to the submitted economic model:**

- Time horizon 5 years: The CGP confirmed that 25 years is too optimistic for these patients. A previous review for pazopanib in advanced STS conducted by pCODR used a time horizon of 5 years. As the CGP felt that a time horizon of 5 years was potentially too conservative for these patients, the EGP explored a range of time horizons for the re-analysis with 10 years in the lower bound and 5 years in the upper bound.
- Parametric curve selection for OS function: In the submitted economic model, at 5 years, approximately 20% of the population is still alive. The CGP stated that this was overly optimistic for this population. The log-normal had similar AIC scores to the submitted base case of generalized gamma in the ITT population; further the log-normal had the lowest BIC. The EGP felt the visual fit of the log-normal was also acceptable. At 5 years with a log-normal curve, 16% of the population was alive, as opposed to 20% with the generalized gamma. The EGP felt this was a more conservative parametric approach that better aligns with what is observed in clinical practice.
- Patient characteristics for drug acquisition costs taken from JGDG clinical trial: In the submitted base case, patient characteristics to determine drug acquisition was taken from published UK data and not the JGDG clinical trial. The EGP felt that using the characteristics from the clinical trial, as the clinical trial informed the effectiveness estimates and other assumptions in the model, was reasonable.

**Table 3. Detailed Description of EGP Reanalysis (deterministic results)**

| | ΔC | ΔE QALYs | ICUR (QALY) | |
|---|---|---|---|---|
| **Baseline** | $127,075 | 0.73 | **$175,001** | ----- |
| **EGP's Reanalysis for the Best Case Estimate - Lower Bound** | | | | |
| Description of Reanalysis | ΔC | ΔE QALYs | ICUR (QALY) | Δ from baseline submitted ICER |
| *Time horizon - 10 years* | $121,677 | 0.60 | **$203,992** | $28,991 |
| *OS parametric curve - log-normal* | $122,609 | 0.61 | **$200,093** | $25,092 |
| *Patient characteristics drug acquisition - JGDG trial* | $131,201 | 0.73 | **$180,684** | $5,683 |
| Best case estimate - lower bound | $128,682 | 0.57 | **$224,817** | $49,816 |
| **EGP's Reanalysis for the Best Case Estimate - Upper Bound** | | | | |
| *Time horizon - 5 years* | $115,302 | 0.44 | **$259,880** | $84,879 |
| *OS parametric curve - log-normal* | $122,609 | 0.61 | **$200,093** | $25,092 |
| *Patient characteristics drug acquisition - JGDG trial* | $131,201 | 0.73 | **$180,684** | $5,683 |
| Best case estimate - upper bound | $124,109 | 0.47 | **$263,340** | $88,339 |

## 1.5 Evaluation of Submitted Budget Impact Analysis

Notably, the BIA presented is based on Ontario. The factors that most influence the budget impact analysis include the market share and availability of the 190mg vial size. The EGP also explored the impact of including dexrazoxane and removing IfoDOX and Pac from the market share. These did not have a large impact on the BIA.

The key limitation of the BIA model includes that the 3-year budget impact is limited to the population of Ontario. Although the EGP was unable to consider the BIA for the Canadian population as a whole, the model allowed separate scenarios for each province.

## 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for Olara+DOX when compared to DOX is:**

- Between $224,817/QALY and $263,340/QALY
- The extra cost of Olara+DOX is between $124,109 and $128,682 (ΔC). *The factors that most influence ΔC include the time horizon, the line of therapy (any line versus first or second) and the mean number of administrations of Olara.*
- The extra clinical effect of Olara+DOX is between 0.47 and 0.57 (ΔE). *The factors that most influence ΔE include the time horizon, the line of therapy (any line versus first or second) and the utilities for the progressed state.*

**Overall conclusions of the submitted model:**

- *The submitted model was well designed, and easy to manipulate. Though there were some limitations with the assumptions, nearly all parameters were modifiable and explored in scenario analyses by the EGP.*

# 2 DETAILED TECHNICAL REPORT

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.

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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 information redacted from this publicly available Guidance Report.

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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.

# REFERENCES

CADTH-pan-Canadian Oncology Drug Review Manufacturer Submission: olaratumab (Lartruvo) 190mg and 500mg vials; Company: Eli Lilly Canada. Toronto (ON): Eli Lilly Canada; 2017 Oct.

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