pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Trabectedin for Metastatic Liposarcoma or Leiomyosarcoma

August 5, 2016

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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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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Janssen Inc.** compared trabectedin to dacarbazine for patients with metastatic liposarcoma or leiomyosarcoma who were previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus additional chemotherapy regimen.

Table 1. Summary of submitted economic model

Funding Request/Patient Population Modelled	*Funding request and economic model match*
Type of Analysis	*CEA & CUA*
Type of Model	*Markov state transition model*
Comparator	*Dacarbazine*
Year of costs	*2014*
Time Horizon	*5 years (cycle length of one month)*
Perspective	*Government payer*
Cost of Trabectedin *(current market price)*	• $3,061.33 per mg • At the recommended dose of 1.5 mg/m^2 intravenous infusion over 24-hours every 21 days, trabectedin costs o $371.73 per day o $10,408.52 per 28-day course
Cost of Dacarbazine*	• $0.3852 per mg • At the recommended dose of 1 g/m^2 intravenous infusion over 20- to 120- minutes every 21 days, dacarbazine costs o $80.59 per day o $2,266.67 per 28-day course
Model Structure	The model was a Markov state transition model and was comprised of 3 health states: pre-progression, post-progression and death. In these models the transition probabilities of patients in the pre- and post-progression state to death are calculated independently. The submitter did not have access to patient-level data. All results are based on digitized curves. Upon request by the EGP, the submitter provided a partitioned-survival model in order for the EGP to compare and contrast the results produced in the pre- and post-progression states. The partitioned-survival model was considered as a scenario analysis to the submitted base case analysis.
Key model assumptions	• All patients will have died by cycle 60 (to align with the time horizon used by the pCODR Economic Guidance Panel in their review of pazopanib for advanced STS); • All grade 3 or 4 adverse events result in hospitalization.
Key Data Sources	*SAR-3007* *Expert opinion*
**Drug costs for the comparator in this table are based on costing information obtained 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.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, though the appropriateness of dacarbazine is not universally accepted. Though it should be noted that the CGP did not identify a more appropriate comparator.

Relevant issues identified included:

- *Trabectedin did not improve the primary endpoint of overall survival in the clinical trial. However, the CGP recognized there is a net clinical benefit of trabectedin compared to dacarbazine.*
- *The patient population enrolled in the clinical trial was limited to those with an ECOG of 0 - 1, whereas in the clinical setting in Canada, the patient population eligible for treatment would have an ECOG of 0 - 2.*
- *The 24-hour continuous infusion schedule has been readily adopted in Canadian practice.*

Summary of patient input relevant to the economic analysis
Patients considered slowing or stopping of disease progression as the most important factor in treating metastatic liposarcoma or leiomyosarcoma. Progression-free survival was considered in the economic model. Patients also wanted a tolerable safety profile; adverse events were considered in the economic analysis. Patients primarily want access to an additional treatment for this cancer.

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 reimbursement recommendation for trabectedin, which are relevant to the economic analysis.

Enablers to implementation:

- Provides another treatment option for patients with liposarcoma and leiomyosarcoma.

Barriers to implementation:

- Incremental costs due to wastage. Wastage was included in the base case analysis.
- Administration of trabectedin as a 24-hour infusion via central line. Costs associated with implantable venous access and administration were included in the base case analysis. Though PAG has noted the need to be admitted to hospital, the CGP confirmed that an infusion could be used instead. The infusion pump has been included in the base case analysis.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ICER estimate ($/QALY)	$167,863	$318,519	$583,041
ΔE (QALY)	0.15	0.09	0.09
Progression-free	0.14	0.14	0.14
Post-progression	0.00	-0.06	-0.06
ΔE (LY)	0.20	0.10	0.10
Progression-free	0.20	0.20	0.20
Post-progression	0.00	-0.10	-0.10
ΔC ($)	$25,019	$28,626	$52,458

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

- *The primary end point of the clinical trial – overall survival – was not significant, though progression-free survival was significant. This is a limitation as the benefits from progression-free survival did not translate to overall survival, implying the influence of another factor, other than the drug intervention, on outcomes.*
- *Subsequent treatments are a major cost driver in the economic model. Subsequent treatment costs were higher for the dacarbazine group, due to different proportions of subsequent treatments from the clinical trial, and this incremental difference drives the cost in the model. Treatments post-progression may vary across jurisdictions in Canada, therefore there is uncertainty around the true ICER due to the impact of subsequent treatments on the economic model.*

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Post-progression mortality:** In the clinical trial, progression-free survival was significantly different (in favour of trabectedin). However, overall survival was not significantly different between the two treatments. The survival for post-progression mortality for dacarbazine in the submitted base case was actually *lower* than trabectedin, which is opposite the results from the clinical trial. As a conservative estimate, we made post-progression mortality equal between the two treatments to reflect the results of the clinical trial, as well as feedback from the CGP.
- **Time horizon:** The submitted base case chose a time horizon of 5 years where 100% of patients are dead at 5 years. However, the CGP has suggested that it is highly unlikely that patients live to 5 years. In the submitted base case, 95% of patients are dead at 4 years and the CGP felt that this reflected what they see in clinical practice.
- **Determination of progression:** Progression was determined either by investigator assessed PFS (progression and death) or time to progression (TTP) (progression only). Given that the model accounts for deaths in the pre-progression state as a separate input, the use of TTP to determine progression is appropriate.
- **Subsequent treatment costs:** The SAR-3007 trial did not enrol any Canadian patients. Based on input from our CGP, there is no clinical reason why costs following progression should be different between the two treatments, though the distribution of some treatments may not be identical. As a conservative estimate for the upper bound, the EGP elected to make the subsequent treatment costs for both treatment arms the same as what the submitter determined to be for the dacarbazine arm (the cheaper of the two at $6,687).

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$25,019**	**0.15**	**0.20**	**$167,863**	**----**
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Post-progression mortality equal	$14,902	0.09	0.10	$162,958	-$4,905
Time horizon - 4 years	$24,951	0.15	0.20	$170,484	$2,621
Determination of progression - by TTP	$38,604	0.15	0.20	$259,010	$91,147
Best case estimate of above three parameters	*$28,626*	*0.09*	*0.10*	*$318,159*	*$150,296*
UPPER BOUND					
Subsequent treatment costs per cycle - equal ($6,687 both arms)	$47,456	0.15	0.20	$318,402	$150,539
Best case estimate of above four parameters	*$52,458*	*0.09*	*0.10*	*$583,041*	*$415,178*

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include population growth and the cost of trabectedin.

Key limitations of the BIA model include the lack of consideration of wastage and best supportive care as a comparator, which does not align with the economic model or clinical reality (though this provides a conservative estimate as it increases incremental costs). These parameters were not able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for trabectedin when compared to dacarbazine is:

- Between $318,519/QALY and $583,041/QALY
- It is difficult to estimate where the best estimate would likely be within this range, as it depends on the proportion and type of subsequent treatments.
- The extra cost of trabectedin is between $28,626 and $52,458. The biggest impact on costs are the cost per cycle of subsequent treatments, the type of subsequent treatments, and the determination of progression.
- The extra clinical effect of trabectedin is estimated at 0.09 (ΔE). The biggest impact on the effectiveness is post-progression mortality rates.

Overall conclusions of the submitted model:

- *Though the data inputs are taken directly from a clinical trial, this is but one source of information and some of the inputs are not supported by our CGP. Notably, the higher post-progression mortality for dacarbazine and the difference in subsequent treatment costs as provided in the submitted base case. Further, with input from the CGP, the EGP felt that a time*

horizon of 4 years and using the time to progression curve to determine progression should be part of the base case.

- *If you believe that subsequent treatment costs would be different for the two treatment arms and higher for dacarbazine, then the ICER is most likely closer to the lower bound of $318,159. If you believe that subsequent treatment costs are most likely to be the same for both treatment arms, then the ICER is most likely closer to the upper bound of $583,041.*

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 Sarcoma 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 Trabectedin (Yondelis) for Metastatic Liposarcoma or Leiomyosarcoma. A full assessment of the clinical evidence of Trabectedin (Yondelis) for Metastatic Liposarcoma or Leiomyosarcoma 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.

REFERENCES

1. Reichardt P, Leahy M, Garcia Del Muro X, et al. Quality of Life and Utility in Patients with Metastatic Soft Tissue and Bone Sarcoma: The Sarcoma Treatment and Burden of Illness in North America and Europe (SABINE) Study. *Sarcoma.* 2012;2012:740279.

2. Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. *Current oncology (Toronto, Ont.).* Apr 2013;20(2):e90-e106.

3. Guerriere DN, Zagorski B, Fassbender K, Masucci L, Librach L, Coyte PC. Cost variations in ambulatory and home-based palliative care. *Palliative medicine.* Jul 2010;24(5):523-532.

4. Cheung MC, Earle CC, Rangrej J, et al. Impact of aggressive management and palliative care on cancer costs in the final month of life. *Cancer.* Sep 15 2015;121(18):3307-3315.

5. Horgan AM, Knox JJ, Liu G, Sahi C, Bradbury PA, Leighl NB. Capecitabine or infusional 5-fluorouracil for gastroesophageal cancer: a cost-consequence analysis. *Current oncology (Toronto, Ont.).* Apr 2011;18(2):e64-70.

6. Janssen Inc. Clinical Study Report - SAR-3007 Final Analysis. 2015.