

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Brentuximab for systemic anaplastic large cell lymphoma

Product: brentuximab (Adcetris®)

Class of Drugs: anti-CD30 monoclonal antibody-drug conjugate

Reason for Use: systemic anaplastic large cell lymphoma (sALCL)

Manufacturer: Seattle Genetics

Date of Review: December 11, 2013

CED Recommendation

The CED noted that systemic anaplastic large cell lymphoma (sALCL) is a rare malignancy with an aggressive clinical course and few other effective treatments. Although the clinical benefits observed were deemed substantive, the magnitude of improvement and the safety profile of brentuximab were uncertain, and the treatment was not cost-effective. The CED recommended brentuximab (Adcetris®) not be funded for the treatment of sALCL. This recommendation is aligned with the pan-Canadian Oncology Review recommendation.

Executive Officer Decision*

Taking into consideration the CED's recommendation and based on an agreement with the manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund brentuximab (Adcetris®) for the treatment of systemic anaplastic large cell lymphoma (sALCL) according to specific criteria.

Funding Status*

Funded through Cancer Care Ontario's New Drug Funding Program according to specific criteria.

* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.

Highlights of Recommendation:

- The SG035-0004 study demonstrated that a substantial proportion of patients treated with brentuximab experienced a sustained and complete response. SG035-0004 was a phase II, non-randomized and non-comparative study; as such, there was considerable uncertainty regarding the magnitude of the observed clinical benefit.
- It is unknown whether brentuximab improves or maintains a patient's quality of life because this was not measured in the clinical study.
- The lack of a randomized comparative trial made it challenging to assess the safety of brentuximab.
- At the recommended dose of 1.8mg/kg every 3 weeks, the average cost per 28-day course is \$16,262 and the total cost for treating a patient with 16 cycles could be as much as \$232,230. Based on economic analyses conducted by the manufacturer and pCODR, brentuximab was not considered to be cost-effective.
- Overall, systemic anaplastic large cell lymphoma (sALCL) is an uncommon malignancy with few effective treatment options. The results of the SG035-0004 study suggested treatment benefit. The non-randomized, non-comparative nature of the study made it difficult to assess the magnitude of the trial results and the safety profile of this drug. Furthermore, brentuximab was not considered to be cost-effective. There are several ongoing trials of brentuximab and these may help to confirm the drug's effectiveness and safety.

Background:

Anaplastic large cell lymphoma (ALCL) is a subset of T-cell non-Hodgkin lymphomas (NHL). Systemic ALCL (sALCL) is an aggressive malignancy. For transplant-eligible patients with relapsed, chemotherapy-sensitive sALCL, high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) is generally recommended. For sALCL patients who have relapsed after HDT-ASCT or who are not eligible for intensive treatment, a variety of non-curative approaches could be tried.

Detailed Discussions:

- For this evaluation, the CED considered:
 - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee;
 - Information in the manufacturer's submission;
 - One patient group submission received by pCODR.
 - Feedback from Cancer Care Ontario's Hematology Disease Site Group.
- The CED evaluated one single-arm, phase II clinical trial, the SG035-0004 study.
- The primary endpoint of SG035-0004 was objective response rate (ORR). Secondary outcomes included complete response rate (CRR) and duration of response.

- The ORR was 86% (95% CI: 74.6%-93.9%) and the CRR was 57% (95% CI: 43.2%-69.8%). The proportion of patients who experienced a complete response was considered substantial in comparison to rates historically observed with sALCL therapies.
- The median duration of objective response was 12.6 months and the median duration of complete response was 13.2 months.
- The estimated median progression-free survival (PFS) was 13.3 months (95% CI: 6.9 months to not estimable). The observed length of PFS was noted to be longer than the length of PFS for the patients on their most recent prior treatment (HR=0.48, p=0.001). This improvement in PFS was considered to be significant for a patient population that has been previously treated. It is uncommon for PFS to be longer than that observed for previous lines of chemotherapy.
- The non-randomized, non-comparative nature of the SG035-0004 study made it difficult to assess the magnitude of the observed treatment benefits. Other limitations with the study include the small sample size and eligibility for/receipt of stem cell transplant.
- Quality of life (QOL) data were not measured in SG035-0004. It is unknown whether treatment with brentuximab improves or maintains QOL.
- The most common Grade 3 or 4 adverse events observed with brentuximab included peripheral sensory neuropathy (12%), neutropenia (21%), and thrombocytopenia (14%). The lack of a randomized comparative trial made it challenging to assess the safety of brentuximab. The risk of progressive multifocal leukoencephalopathy (PML) in sALCL patients treated with brentuximab is unknown. PML have been observed in three patients treated with brentuximab for Hodgkin lymphoma.
- The cost of brentuximab is high relative to other cancer drug treatments. At the list price, it costs \$4,840.00 per 50 mg vial. At the recommended dose of 1.8mg/kg every 3 weeks, the average cost per 28-day course is \$16,262 and the total cost for treating a patient with 16 cycles could be as much as \$232,230. Based on economic analyses conducted by the manufacturer and pCODR, brentuximab was not considered to be cost-effective.
- The CED reviewed a patient group submission received by pCODR. The patient submission highlighted the impact of the disease and patients' wishes for treatments that increase survival and reduce relapses.
- Overall, systemic anaplastic large cell lymphoma (sALCL) is an uncommon malignancy with few effective treatment options. The results of the SG035-0004 study suggested treatment benefit. The non-randomized, non-comparative nature of the study made it difficult to assess the magnitude of the trial results and the safety profile of this drug. Furthermore, brentuximab was not considered to be cost-effective. There are several ongoing trials of brentuximab and these may help to confirm the drug's effectiveness and safety.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

For more information, please contact:

Ministry of Health and Long-Term Care

Ontario Public Drug Programs

Hepburn Block, 9th Floor

80 Grosvenor Street, Queen's Park

Toronto, Ontario M7A 1R3

www.health.gov.on.ca/en/pro/programs/drugs/