Canada's Drug Agency
L'Agence des médicaments du Canada

Blinatumomab

FMEC Responses to Questions From the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response	FMEC response
Relevant comparators		
Issues have been identified with the choice of comparator in the submitted trials. For patients with low-risk first-relapse ALL, the COG AALL1331 study compared block 2 chemotherapy with 4 weeks of blinatumomab replacing block 3 followed by continuation chemotherapy intercalated with two 4-week blinatumomab blocks before maintenance vs. standard therapy including 2 intensive chemotherapy blocks (block 2 and block 3 chemotherapy) followed by 2 continuation cycles and maintenance chemotherapy.	The clinical experts agreed that this remains an appropriate comparator for patients in the low-risk population, and that the blinatumomab regimen mentioned is currently used in most institutions in Canada. The experts also noted that the current standard chemotherapy regimen is highly intensive and associated with a higher risk of treatment-related mortality. They suggested that it may be advisable to deintensify the chemotherapy for adolescents and young adults, as these patients tend to experience greater toxicity and poorer outcomes. This is especially relevant for those transitioning to immunotherapy with blinatumomab.	FMEC agrees with the experts.
Considerations for initiation of therapy		
Would patients with CNS disease be eligible for treatment?	The experts indicated that patients with CNS disease would be eligible for treatment with blinatumomab if they have evidence of combined systemic and bone marrow disease. However, 1 expert noted that, per the COG AALL1331 trial, in a subgroup analysis for patients with low-risk first-relapse ALL with isolated CNS relapse, blinatumomab was demonstrated to have inferior outcomes compared to the standard treatment arm.	FMEC agrees with the experts. Refer to the initiation condition as outlined in Table 2 of the recommendation report.

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Considerations for prescribing of therapy		
Blinatumomab is administered as a 28-day infusion requiring specialized pumps and training of staff. Jurisdictions have implemented blinatumomab for other indications and/or criteria and have experience with the drug. Patients may need to travel to facilities that are equipped to prepare and support patients who use these pumps. Is it anticipated that patients will receive additional cycles and/or doses of blinatumomab in this setting vs. the second-line or later relapse settings?	The experts noted that in the first-relapse setting, blinatumomab can be administered with curative intent, without necessarily proceeding to HSCT. However, for patients in second relapse or beyond, the standard of care for curative therapy remains HSCT or CAR T-cell therapy. As the standard of care differs between these settings, direct comparisons are challenging due to the distinct nature of each situation.	FMEC agrees with the experts. FMEC also notes that different blinatumomab dosage regimens have been evaluated in the included studies. In the Locatelli study, patients who were considered high risk received 1 cycle of blinatumomab administered as a continuous infusion of 15 mcg/m^2 once daily over 28 days. In the COG ALL1331 study, patients received up to 3 cycles of blinatumomab.
Generalizability		
Patients with Down syndrome, Ph-positive ALL, prior HSCT, or prior blinatumomab treatment were excluded from the trial. Patients with Burkitt leukemia and/or lymphoma, T-ALL, or B-ALL were not eligible. In the second line or later, patients whose disease failed following HSCT were eligible. Would this be applicable for patients with first or later relapse as well? Would patients with Ph-positive disease be considered eligible recognizing that in practice, all patients with relapsed or refractory disease are treated the same?	The experts indicated that these patients should be considered eligible for blinatumomab, despite their exclusion from clinical trials for various reasons. For example, patients with Down syndrome experience higher toxicity from intensive chemotherapy, which can potentially skew trial results. However, these factors should not preclude them from receiving blinatumomab. Only patients who have lost CD19 expression are unlikely to benefit from the therapy. The experts also indicated that patients whose disease has previously failed following HSCT and are in first relapse should be eligible for blinatumomab. Additionally, they emphasized that patients with Ph-positive disease should be eligible for the treatment, noting that in the adult population, where Ph-positive cases are more common, blinatumomab is considered a standard of care	FMEC cannot comment on the use of blinatumomab in these subpopulations as they are out of scope for this review. There is also a lack of evidence for blinatumomab in these subpopulations.

Drug program implementation questions	Clinical expert response	FMEC response
	treatment. Biologically, there is no reason to believe patients who have Ph-positive disease would respond differently.	
Funding algorithm		
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	NA	This is a comment from the drug plans to inform FMEC deliberations.
Blinatumomab may change the place in therapy of drugs reimbursed in subsequent lines.	NA	This is a comment from the drug plans to inform FMEC deliberations.
Care provision issues		
This drug is initiated in the inpatient setting.	NA	This is a comment from the drug plans to inform FMEC deliberations.
Tumour lysis syndrome, cytokine release syndrome, and neurological toxicities may occur upon initiation and will be monitored and managed in the hospital.	NA	This is a comment from the drug plans to inform FMEC deliberations.
System and economic issues		
There is concern about the budget impact and sustainability of blinatumomab. Will additional doses of blinatumomab be required in this setting compared to the current funded blinatumomab for patients in second relapse or later? A cost-effectiveness utility analysis may be useful to assess the ICER as patients who are in first relapse or later would be fitter than those in second relapse.	NA	This is a comment from the drug plans to inform FMEC deliberations.
Blinatumomab has gone through confidential pricing negotiations for multiple indications.	NA	This is a comment from the drug plans to inform FMEC deliberations.

ALL = acute lymphoblastic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; CAR = chimeric antigen receptor; CNS = central nervous system; FMEC = Formulary Management Expert Committee; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; NA = not applicable; Ph = Philadelphia chromosome; T-ALL = T-cell acute lymphoblastic leukemia; vs. = versus.