Background:

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) is currently supplying the ch14.18 monoclonal antibody only for patients enrolled on ANBL0032 and ANBL0931. All patients enrolled on these studies receive ch14.18 plus cytokines based on the positive results from ANBL0032 in which patients in the minimal disease setting following autologous stem cell transplantation showed improved EFS with this regimen (66% versus 46% two year EFS) [1].

Prior to the ANBL0032 study, the ch14.18 monoclonal antibody had undergone phase I and II testing in the pediatric setting. This included single agent phase I testing [2], a second phase I study (CCG-0935) that examined increased doses of ch14.18 in combination with GM-CSF among neuroblastoma patients who had recently undergone stem cell transplant [3], and a study (CCG-0935a) in which ch14.18 was delivered with IL-2 and GM-CSF in the same manner as it was used for the ANBL0032 randomized evaluation of ch14.18 [4]. A phase 2 study (POG-9347) among children with recurrent neuroblastoma used ch14.18 at 50 mg/m^2/day for 4 days given with 14 days of GM-CSF (10 mcg/kg/day) [5]. These studies noted limited antitumor activity in patients with neuroblastoma who had measurable disease, but some responses were observed for patients with only bone marrow or MIBG-positive disease.

The toxicity associated with the administration of ch14.18 has been significant, and toxicity appears to be enhanced with the use of IL-2. Neuropathic pain occurs in the majority of recipients secondary to antibody interaction with the peripheral nervous system. This pain is significant enough that patients routinely receive a continuous morphine infusion during the antibody administration and for a period afterward. Significant allergic reactions are common and require medical intervention. Additionally, due to antibody interactions with the cardiovascular system and the need for morphine to control pain, many patients experience hypotension during the antibody treatment necessitating fluid support. Fluid management has been complicated by capillary leak syndrome associated with the IL-2 and antibody treatment. Moderate electrolyte imbalances including hypokalemia and hyponatremia also occur.

Special Exception Access Guidelines:

Institutional criteria for participation in the special exception program for ch14.18 include:

- The Investigator must have IRB approval for ANBL0032.
- The Investigator/Institution must have successfully completed the ANBL0032 COG-training module.
- The following documents must be sent to CTEP prior to drug shipment
    - IRB approval communication for ANBL0032 (most current version)
    - Copy of the Investigator's ANBL0032 Training Certification
    - IRB approval communication for chimeric MOAB 14.18 Special Exception protocol for each patient
    - Copy of signed written informed consent obtained from patient (if applicable), parent or legal guardian.

The following groups of patients are eligible for access to ch14.18:

- Newly diagnosed patients: ch14.18 plus cytokines and cis retinoic acid has proven efficacy for children with high-risk neuroblastoma when administered in the minimal disease setting soon after recovery from autologous stem cell transplantation (i.e., patients eligible for the ch14.18 randomization in ANBL0032). NCI supplies ch14.18 for newly diagnosed patients meeting the ANBL0032 eligibility criteria though the

COG protocol ANBL0032.

Newly diagnosed patients who are in their first line of therapy but do not meet eligibility criteria for ANBL0032 may receive ch14.18 by special exception if they meet relevant criteria provided below for relapsed patients not previously treated with ch14.18.

- Relapsed patients not previously treated with ch14.18: For patients with relapsed neuroblastoma having measurable disease, ch14,18 efficacy has been limited. Therefore, therapies other than ch14.18 received through Special Exception Access should be sought. The activity of ch14.18 in patients who relapse and have never received ch14.18 and who have achieved a CR or near CR is not known. Based on the potential similarity of these patients to newly diagnosed patients with minimal disease, these patients are eligible to receive ch14.18 through the special exception process as long as they meet the following eligibility criteria as listed below.
    - Patients must be diagnosed with neuroblastoma and have recurrent or refractory disease.
    - Patients should have received standard therapy appropriate for their stage of disease at the time of diagnosis.
    - Patients who have responded to second line therapy with PR, VGPR or CR are eligible and who do not have RECIST measurable disease are eligible.
    - Patients must not have received prior anti-GD2 antibody therapy; and
    - Patients must meet performance scale criteria and organ function as outlined in ANBL0032 Sections 4.8 and 4.9.

Patients with recurrent disease should strongly consider entry onto research protocols including those aimed at identifying novel therapies, more effective ways to use ch14.18 or identifying alternative immunotherapy treatments. For further information as to how to obtain ch14.18, please contact

Matt Boron (boronm@ctep.nci.nih.gov) or Nita Seibel (seibelnl@mail.nih.gov).

References:

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5. Yu AL, Batova A, Alvarado C, et al. Usefulness of a chimeric anti-GD2 (ch14.18) and GM-CSF for refractory neuroblastoma: a POG phase II study. Proc Annu Meet Am Soc Clin Oncol 1997:16:513a.