

APN311 (ch14.18/CHO)

Antibody-based treatment for children with high-risk neuroblastoma in the minimal residual disease setting

Mode of action:	Targeting GD2 on neuroblastoma cells thereby recruiting various effector mechanisms for tumor cell destruction
Target indication:	Minimal residual disease in high-risk neuroblastoma
Status:	Randomized Phase III ongoing in Europe
Current standard of care:	Isotretinoin
Potential line extensions:	Other settings in neuroblastoma, other GD2 positive tumors
Medical need / USP:	High medical need in high-risk neuroblastoma in the minimal residual disease setting to improve survival
Next milestone:	Agree on fast approval strategy with regulatory authorities; complete enrolment in ongoing Phase III
Licensing strategy:	Direct marketing considered

Background / Rationale

Neuroblastoma, after brain cancer, is the most frequent solid cancer in children under five years of age. In high-risk neuroblastoma, more than half of the patients receiving standard therapy have a relapse and ultimately die from the disease. 90% of cases occur between ages zero to six. The worldwide incidence in industrialized countries is around 2'000 cases p.a.

Monoclonal antibodies against specific antigens are increasingly being used in oncology. The entirely different mode of action compared to cytotoxic therapies have made them a valuable asset as is shown by forerunners like trastuzumab, cetuximab, bevacizumab, rituximab and others. The disialoganglioside GD2 is a glycosphingolipid expressed primarily on the cell surface. GD2 expression in normal tissues is rare and primarily restricted to the CNS, peripheral nerves and melanocytes. In cancerous cells, GD2 is uniformly expressed in neuroblastomas and most melanomas and to a variable degree in bone and soft-tissue sarcomas, small cell lung cancer, renal cell carcinoma and brain tumors (Navid et al., 2010). Because of the relatively tumor-selective expression combined with its presence on the cell surface, GD2 represents a promising target for antibody-based cancer immunotherapy.



In contrast to the anti-GD2 antibody-IL2 immunocytokine APN301 that is being developed in relapsed/refractory high-risk neuroblastoma, APN311 is an unconjugated anti-GD2 antibody and presently in late stage development for high-risk neuroblastoma patients with minimal residual disease. Hence, the two projects are complementing each other so that most patients suffering from high-risk neuroblastoma can be treated.

Development to date

In June 2011, Apeiron acquired the exclusive and worldwide rights to further develop and commercialize the chimeric monoclonal antibody ch14.18 (APN311) from the Children's Cancer Research Institute (CCRI) and the International Society of Paediatric Oncology European Neuroblastoma (SIOOPEN).

APN311 is produced in CHO cells, the standard mammalian cell line for production of commercially available antibodies. Clinical supplies are manufactured by Polymun Scientific (www.polymun.at), and Apeiron has now commissioned Polymun to continue production and to prepare for manufacture of material at market standard.

In a Phase I study in relapsed/refractory patients remarkable remission rates were achieved with this antibody as single agent. A Phase III trial was initiated in 2007 by SIOOPEN and is presently investigating the effects on event-free and overall survival of APN311 together with isotretinoin with or without s.c. IL-2. In a comparable US study using a treatment package of 4 drugs (a related antibody produced in SP2/0 murine hybridoma cells together with i.v. IL-2, GM-CSF and isotretinoin), interesting survival improvement was seen in children with neuroblastoma in complete remission following initial therapies and no evidence of disease.

Next steps

The ongoing phase III trial has already enrolled more than 100 patients. Full enrolment should be completed in about 24 months. Apeiron's partners CCRI and SIOOPEN are leading the study and have a long-standing experience in neuroblastoma treatment and a wide-spanning clinical network in more than 18 European countries plus countries like Australia and New Zealand.

Apeiron is in contact with the European regulatory agency EMA to evaluate options for fast approval for APN311 in an indication with high medical need and few treatment options. It is expected that this treatment regimen may improve survival rates of children with high-risk neuroblastoma by up to 30%, thereby rendering overall survival rates of 60-70% realistic.