

Upcoming market catalysts in Q1 2011

Several orphan drugs have exciting catalysts in the first quarter of 2011. These include Prescription Drug User Fee Act (PDUFA) action dates for ipilimumab for pretreated metastatic melanoma and vandetanib for medullary thyroid cancer (MTC) as well as results from the second Phase III trial of teduglutide for short bowel syndrome (SBS).

A decision by the US Food and Drug Administration (FDA) on the approval of ipilimumab — a fully human monoclonal antibody developed by Medarex (now part of Bristol-Myers Squibb) that targets the immune-cell receptor CTLA4 (cytotoxic T lymphocyte-associated antigen 4) to block the T-cell inhibitory pathway — is expected by 26 March. Ipilimumab was developed as a monotherapy for advanced melanoma in patients who have received prior therapy,

for whom the median overall survival is 6 to 9 months. The drug failed to meet the end point of an objective response rate of more than 10% in a pivotal study. Medarex subsequently met with the FDA and the agency requested additional overall survival data to further determine the benefit of ipilimumab.

Recent results from a Phase III trial of ipilimumab as a monotherapy or in combination with a gp100 peptide vaccine demonstrated a median overall survival of 10.1 months and 10.0 months, respectively (*N. Engl. J. Med.* **363**, 711–723; 2010). Although some significant toxicities were noted with treatment, given the impressive efficacy in increasing survival, ipilimumab is poised to become the first approved agent for metastatic melanoma.

An FDA decision is also anticipated soon on vandetanib, developed by AstraZeneca, for the treatment of patients with unresectable locally advanced or metastatic MTC, which accounts for 5% of all thyroid cancers and is incurable. Vandetanib is a multitargeted kinase inhibitor exhibiting potent activity against vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and rearranged during transfection (RET) pathways.

Phase III results showed that treatment with vandetanib significantly extended progression-free survival, demonstrating a 54% reduction in the rate of progression compared to placebo. Significant differences for vandetanib compared to placebo were also observed in objective response rate and disease control rate. Given these results, the drug's acceptable safety profile, and a positive outcome at an FDA advisory committee meeting on 2 December, vandetanib seems to be in a good position to win approval in January 2011.

Finally, data are expected from a confirmatory trial of teduglutide (developed by NPS Pharmaceuticals), in patients with SBS, which is primarily caused by surgical removal of half or more of the small intestine. Parenteral nutrition (intravenous feeding) can help compensate for the reduced nutrient absorption; however, it is associated with serious complications, such as infections or liver damage.

Teduglutide is an analogue of glucagon-like peptide 2 (GLP2), a naturally occurring hormone that regulates the growth, proliferation and maintenance of the cells lining the small intestine. Results from a Phase III study showed a trend for the high dose in improvement of total parenteral nutrition (TPN) requirement, but this was not statistically significant. Although the statistical criteria were such that if the high dose failed, the low dose would not be analysed, the company went forward with the low-dose analysis, which demonstrated a significant improvement in TPN. Consequently, a second Phase III study was initiated to evaluate the low dose and to confirm the previously reported data. Positive results may enable NPS to file a regulatory application for teduglutide for adult patients with SBS who are dependent on parenteral nutrition.

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