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Acceleron/Celgene's sotatercept garners enthusiasm in MDS-related anemia due to novel mechanism

Acceleron Pharma (NASDAQ:XLRN) and **Celgene**'s (NASDAQ:CELG) sotatercept offers an exciting novel mechanism to treat anemia related to myelodysplastic syndromes (MDS), six physicians said. They pointed to the agent's clean toxicity profile in hematology indications and promising approach to stimulating red blood cell production.

Celgene is running sotatercept's ongoing Phase II trial in low or intermediate-1 risk MDS patients (NCT01736683), which is evaluating the appropriate dose via a primary endpoint of erythroid hematologic improvement. Dose-escalation data from the 100-patient study is expected at the June European Hematology Association meeting with final Phase II results by YE14, according to analyst reports.

Acceleron declined to comment.

Sotatercept clearly has dramatic effects on bone and in hemoglobin, Mark Alles, executive vice president and global head, hematology and oncology, Celgene, told this news service at the December 2013 American Society of Hematology (ASH) meeting. Due to sotatercept's pan activity, Celgene is interested in pursuing renal anemia and lytic bone disease, which is often seen in multiple myeloma patients, as well, Alles said. The firm may pursue sotatercept in both these indications, but the decision has not yet been made.

MOA holds promise

MDS patients often receive erythropoietin-stimulating agents (ESAs) to treat anemia, but the biologic rationale for using these agents in MDS is not entirely clear, said investigator Dr Johnson Liu, associate professor, Pediatric Hematology & Oncology, Hofstra North Shore-LIJ School of Medicine, New York. Sotatercept, initially developed to treat bone lesions, showed a principle side effect of increasing hemoglobin levels in the initial Phase I trial, noted investigator Dr Robert Rifkin, hematologist/oncologist, Rocky Mountain Cancer Centers, Denver, Colorado. Normal volunteers who received sotatercept developed significant polycythemia, which was the catalyst to the finding that sotatercept affects erythropoiesis, added Liu.

Sotatercept, formerly ACE-011, is an antibody conjugate that targets the activin receptor type 2a. Activin 2a inhibits bone growth, which is why sotatercept was initially developed for osteoporosis and still may have a future there, he added.

Sotatercept operates outside of erythropoietin's regulatory functions, Liu said. Erythropoietin is made in the kidney and is the primary regulator for red blood cell function, he explained. Erythropoietin stimulates erythropoiesis, whereas sotatercept modulates the interaction between the stem cells and the bone marrow microenvironment, said Dr Uwe Platzbecker, professor of hematology, University Hospital, Dresden, Germany.

Lower-risk MDS a reasonable indication

Evaluating sotatercept in lower-risk MDS patients makes sense, since higher-risk MDS patients have more serious blast progression problems that require intensive treatments to manage the risk of developing acute myeloid leukemia (AML), explained Dr David Steensma, attending physician, hematologic oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. Higher-risk MDS patients have higher blasts and are very close to progressing to AML, which would introduce confounding variables and added safety concerns, added Liu.

Sotatercept will likely have the greatest effect on anemia, as it is unlikely to kill blasts or have much effect on white blood cells or platelets, said Steensma. The TGF-beta pathway inhibits red blood cell production quite

strikingly, he noted, whereas inflammation increases platelets. Sotatercept selectively binds to the TGF-beta proteins that suppress erythropoiesis, thus stimulating red blood cell production. Patients treated with sotatercept may show low platelet counts, but they are unlikely to fall outside normal ranges, he noted.

The drug is unlikely to improve symptoms of MDS beyond anemia, Platzbecker said, noting that preclinical data showed that the agent modulates erythropoiesis and hemoglobin but did not have an effect on blasts.

It is too early to say if sotatercept will represent a major change in the treatment landscape, but the MDS community is desperate for new developments, Steensma said. Sotatercept's initial Phase IIa data in beta-thalassemia was presented at ASH 2013 (#3448).

Sotatercept also has potential in diamond-blackfan anemia, where it is being tested in a Phase II investigator-sponsored trial, noted Liu, an investigator on this trial. Diamond-blackfan anemia originates from a germline mutation in the ribosome protein, he explained.

In preclinical models, zebrafish were genetically engineered to have the same genetic abnormalities as humans with diamond-blackfan anemia, Liu noted. When sotatercept was injected into these fish models, their anemia markedly improved, he explained. These patients frequently progress to develop MDS and often also exhibit osteoporosis, so sotatercept can potentially aid in both these areas, he pointed out. Diamond-blackfan anemia patients generally receive transfusions every three weeks and require chronic steroids, Liu explained.

Clean side-effect profile in hematology indications

It is possible that sotatercept's bone density changes may be a negative side effect, Steensma noted, but expects the agent will be fairly safe since it is highly targeted. Liu, however, said he had not considered that changes in bone density could be a negative side effect but has not heard of any bone density concerns so far. In animal models, hemoglobin response was the only side effect, Platzbecker said.

Sotatercept's Phase II trial in solid tumors was closed early due to safety concerns, noted Dr Mahesh Seetharam, hematologist/oncologist, Arizona Oncology, who worked on this trial. Renal failure and thrombosis were the primary toxicities, he noted. Sotatercept was efficacious in solid tumors, but it was too toxic, he explained, adding it may work well in MDS if the protocol was changed or the dose reduced.

According to the Phase I solid tumor study's ClinicalTrials.gov listing (NCT01190644), the trial's status was changed to "terminated" from "recruiting" on 8 April 2013, with the following explanation, "Isotope needed to conduct [red blood cell/polycythemia vera] analysis (primary endpoint) no longer available from manufacturer. No alternatives available for use."

The MDS trial is evaluating three doses of sotatercept each given via subcutaneous injection every three weeks for five cycles: 1 milligram per kilogram (mg/kg), 2mg/kg and 0.5mg/kg, according to ClinicalTrials.gov.

Acceleron completed its IPO in September 2013. As per a 2008 partnership agreement, Celgene became responsible for all clinical, manufacturing and commercialization costs associated with sotatercept on 1 January 2013. Acceleron financed sotatercept's Phase I and IIa trials, which were completed in 2011. Celgene is running all trials going forward, including the Phase II trials in beta-thalassemia, MDS and chronic kidney disease.

Sotatercept is also being evaluated in Phase II investigator-sponsored trials in multiple myeloma, diamond-blackfan anemia and myelofibrosis. Acceleron has copromotion rights to sotatercept in North America, for which it will receive tiered royalties based on net sales from Celgene.

by Juliana Wexler in New York