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# Antibody-drug conjugate may provide new treatment option for pancreatic cancer patients

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Patients with pancreatic cancer may benefit from an investigational member of an emerging class of anticancer drugs called antibody-drug conjugates, according to preclinical results presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19-23.

Antibody-drug conjugates are a new type of targeted anticancer therapy, which use an antibody to deliver an attached drug directly to those cells that display the antibody's target on their surfaces. This precision reduces the side effects of the attached drug compared with conventional systemic administration. Currently, there are two U.S. Food and Drug Administration-approved antibody-drug conjugates used for the treatment of certain cancers.

"Our investigational antibody-drug conjugate, MLN0264, is designed to selectively bring a highly potent cytotoxic payload to tumors that express guanyl cyclase C (GCC)," said Petter Veiby, global head of BioTherapeutics, Oncology DDU at Takeda Pharmaceuticals International Co. in Boston, Mass. "Our findings in preclinical pancreatic tumor models support the testing of MLN0264 in combination with gemcitabine in patients with advanced pancreatic cancer."

MLN0264 consists of the highly toxic agent monomethyl auristatin E (MMAE) attached to an antibody that recognizes GCC via a cleavable

linker. When the antibody portion of the drug recognizes the protein GCC on tumor cells, the entire drug is taken up by the cells. Once inside the tumor cells, the linker that attaches MMAE to the antibody is severed, allowing the tumor cells to be exposed to the cytotoxic activity of MMAE.

According to Veiby, at least 50 percent of the pancreatic tumors he and his colleagues have examined express some level of GCC. They, therefore, investigated the activity of MLN0264 in preclinical models of pancreatic cancer that mimicked the various patterns of GCC expression observed in patient biopsies.

They found that MLN0264 markedly inhibited the growth of five of seven different human pancreatic tumors transplanted into mice.

Further analysis in two of the preclinical models, one in which MLN0264 had significantly inhibited tumor growth and one in which it had little effect, showed that a combination of MLN0264 and the traditional chemotherapy agent gemcitabine caused greater tumor shrinkage than either drug alone.

Based on their preclinical data, the researchers plan to investigate the activity of the combination of MLN0264 and gemcitabine in patients with GCC-expressing pancreatic cancer in a phase II study, which they hope will begin sometime in 2014. They are also evaluating the activity of MLN0264 in preclinical models of two other cancers known to frequently express GCC, metastatic colorectal cancer and gastric cancer.

**More information: Abstract Number: PR12/B194**
Presenter: Petter Veiby

Title: MLN0264, an investigational, first-in-class antibody-drug conjugate (ADC) targeting guanylyl cyclase C (GCC), demonstrates

antitumor activity alone and in combination with gemcitabine in human pancreatic cancer xenograft models expressing GCC

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Background: MLN0264 consists of a fully human anti-GCC monoclonal antibody linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker (MMAE and linker technology licensed from Seattle Genetics). The transmembrane cell surface receptor GCC is expressed by ~95% of primary and metastatic colorectal cancer (mCRC) tumors. MLN0264 has shown selective binding and antitumor activity in mouse xenograft models of mCRC expressing GCC, and is currently being investigated in a phase 1 study in patients with advanced gastrointestinal malignancies. GCC is also expressed in subsets of pancreatic cancers. Further to the findings in mCRC, we investigated GCC expression in human pancreatic tumors and evaluated MLN0264 activity in mouse xenograft models of GCC-expressing human pancreatic cancer.

Methods: GCC expression in multiple human pancreatic cancer samples including tissue microarrays (TMAs) was evaluated by immunohistochemistry (IHC). For in vivo studies, 7 mouse xenograft primary human tumor explant (PHTX) models of pancreatic cancer were developed, including tumor tissue from patients with wild-type and mutant KRAS. Animals were treated when the tumor reached ~230 mm3. In single-agent studies, animals were administered vehicle, MMAE 0.135 mg/kg once weekly (QW), or MLN0264 3.75 or 7.5 mg/kg QW. In combination studies, animals received vehicle, or MLN0264 7.5 mg/kg QW alone or in combination with gemcitabine 15 or 20 mg/kg twice weekly (BIW), or gemcitabine 15 mg/kg on days 1, 3 each week. Average tumor volume was determined at multiple time

points following the start of treatment using vernier calipers.

Results: In the GCC-expressing PHTX-249 mouse xenograft model (KRAS mutant G12), single-agent MLN0264 showed significant tumor growth inhibition (TGI) versus vehicle or free MMAE by day 21, with the 7.5 mg/kg dose significantly better than 3.75 mg/kg by day 20-22. Similarly, in the GCC-expressing PHTX-215 model (KRAS wild-type), MLN0264 7.5 mg/kg resulted in significantly greater TGI (79%) versus free MMAE or MLN0264 3.75 mg/kg by day 22, including some tumor regression. Across the 7 models (variable apical GCC expression; KRAS wild-type and mutant), TGI ranged from 24% (p=0.17) to 79% (p

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