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Potential new drug effective in breast cancer and melanoma resistant to targeted therapies

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LEE011, a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4/6 being developed by Novartis Oncology, showed promising results in drug-resistant melanoma and drug-resistant breast cancer when tested in combination with other targeted therapies, and based on these preclinical results, several phase I clinical trials were launched recently, according to results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 19-23.

In many cancers, a tumor suppressor protein called retinoblastoma is deactivated because of an increase in the activity of the proteins CDK 4 and 6. This results in unchecked cell proliferation. The activity of CDK4/6 is regulated by cyclin D, whose expression is increased by activation of BRAF and PIK3CA, which are implicated in some melanomas and breast cancers, respectively. Drugs targeting BRAF and PIK3CA have had success, but most treated cancers subsequently develop resistance to these drugs.

"Chemistry optimization has led to the discovery of LEE011, which, to our knowledge, is the most selective CDK4/6 inhibitor to date," said William Sellers, M.D., vice president and global head of oncology at the Novartis Institutes for Biomedical Research in Cambridge, Mass. "Utilizing the latest cancer genomics data and our knowledge of the role of CDK4/6 activity in the growth of tumor cells, we have identified unique indications and combinations of drugs with LEE011, in which LEE011 demonstrates a robust antitumor activity.

"One of the most notable findings is that, when paired with other targeted agents, LEE011 is often able to prevent the emergence of resistance to the partner compound that would otherwise arise when the partner compound is dosed alone."

Based on the results from preclinical experiments, Novartis has initiated multiple phase I trials in adult cancers, and a phase I trial in pediatric cancers is ongoing. "Preliminary data show LEE011 is well tolerated with excellent pharmacokinetic properties," said Sellers. Combination studies of LEE011 and other Novartis pipeline drugs are underway, according to him.

Sellers and colleagues conducted preliminary studies using cancer cells in culture and found that LEE011 inhibited the growth of tumor cells primarily by arresting the cells at a "checkpoint" called G1, which prevents the cell from multiplying. Further in vivo experiments showed that because cyclin D1 is a target of BRAF and PIK3CA, LEE011 was effective as a single agent in mice bearing melanomas with BRAF mutations, and those bearing breast cancers with PIK3CA mutations.

When tested in combination with an investigational BRAF inhibitor, LGX818, in melanoma, LEE011 showed robust antitumor activity in mice sensitive or resistant to LGX818. Similarly, when combined with an investigational PIK3CA inhibitor, BYL719, LEE011 showed significant antitumor activity in mice bearing breast cancers sensitive or resistant to BYL719.

In the phase I clinical trial in adult patients, the investigators are testing LEE011 as a single agent in cancers that are dependent on CDK4/6, including liposarcomas, mantle cell lymphomas, and head and neck cancers. In the ongoing phase I study on pediatric cancers, LEE011 is being tested as a single agent in neuroblastoma and malignant rhabdoid tumors.

"CDK4/6 inhibition offers a new strategy to directly attack the uncontrolled growth that defines cancer. LEE011 is a new and highly selective CDK4/6 inhibitor that Novartis hopes will be of clinical benefit, and we are progressing to patients as quickly as possible," said Sellers.

More information: Abstract Number: B264/PR02, Presenter: William Sellers, M.D.

Title: LEE011: An orally bioavailable, selective small molecule inhibitor of CDK4/6— Reactivating Rb in cancer

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The tumor suppressor Retinoblastoma protein (Rb) is often inactivated in cancer. In many tumors, the Rb protein itself is retained but functionally inactivated by increased CDK4/6 kinase activity. A number of key oncogenic aberrations can result in this increased activity, including inactivation of CDKN2A (p16), translocation or amplification of D-cyclins, amplification of CDK4/6 and mutations/deletions upstream of cyclin D, such as activating mutations of BRAF/PIK3CA and PTEN deletion. Abolishing CDK4/6 kinase activity and subsequent reactivation of Rb in these tumors has been demonstrated to inhibit tumor initiation and growth. Here we will describe LEE011- an orally bioavailable, selective small molecule inhibitor of CDK4/6 kinases. LEE011 inhibits CDK4/6 kinase activity with nM IC50 and is highly selective for these targets. In a number of preclinical tumor models, LEE011 demonstrates a dose dependent anti-tumor activity that tracks well with CDK4/6 inhibition. The primary mechanism for growth inhibitory effect appears to be G1 arrest in vitro, although, in some sensitive in vivo models, regressions are observed. Importantly, given the

role of CDK4/6 downstream of other oncogenic driver mutations, LEE011 shows single agent activity in melanomas with activating mutations of BRAF or NRAS, and in breast cancers with intact estrogen receptor and/or activating aberrations of PIK3CA/Her-2. Combining LEE011 with LGX818, a V600E BRAF specific inhibitor, leads to robust anti-tumor activity in melanoma models that are both sensitive and, importantly, those that are resistant to LGX818. Furthermore, combining LEE011 with BYL719, a PIK3CA specific inhibitor, also leads to significant anti-tumor activity in breast cancer models both sensitive and resistant to BYL719. Several clinical studies evaluating LEE011 as single agent and in combinations are underway.

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