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Patients with rare, incurable digestive tract cancers respond to new drug combination

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Dublin, Ireland: Patients with rare, but incurable cancers of the digestive tract have responded well to a combination of two drugs that block the MEK and BRAF pathways, which drive the disease in some cases. They have survived for longer without the disease progressing than the usual average time of less than five months, even though their cancer was advanced and had not responded to previous therapies.

In a late-breaking presentation to the 30th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today (Friday), Dr. Zev Wainberg reported on results from a phase II international clinical trial of dabrafenib plus trametinib in 36 patients with biliary tract cancer (BTC) and adenocarcinoma of the small intestine (ASI). These patients had one of the most common mutations in the BRAF gene -BRAF V600E—which is implicated in a number of cancers and in about 15% of BTC and ASI cancers.

He reported that cancers in 13 out of 32 patients (41%) with BTC and two out of the three patients (67%) with ASI shrank when treated with dabrafenib (a BRAF inhibitor) plus trametinib (a MEK inhibitor).

Dr. Wainberg, who is Associate Professor of Medicine at the University of California Los Angeles, USA, said: "As of the end of October, six of the biliary tract cancers were still responding to the treatment and responses had lasted for at least six months in seven patients. The median time before the cancer started to grow again was 7.2 months, with some patients surviving without their disease progressing for more

than a year. The median overall survival time was 11.3 months, with some surviving up to two years.

"These are patients with rare, aggressive cancers that have very poor prognoses and for which there are currently limited therapeutic options. Their cancer has failed to respond to previous treatments—at least two prior chemotherapies had failed in 78% of them—so these are significant and promising results that provide proof that BRAF is a validated target in patients with biliary tract cancer."

Research in other cancers, such as melanoma, thyroid cancer and lung cancer, has shown that combinations of drugs that inhibit both the BRAF and MEK cancer pathways can be effective.

Dr. Wainberg continued: "This is one of very few trials of targeted therapies for biliary tract cancers and adenocarcinoma of the small intestine, and the first time that we have obtained data about drugs that target the BRAF mutation in these patients. The results support the idea that all biliary tract cancer patients should be tested to see if they have the mutation."

Both dabrafenib and trametinib were given in pill form: 150 mg of dabrafenib twice a day and 2 mg of trametinib once a day. The patients all had cancer that was advanced or had started to spread (metastasised) to other parts of the body. Most of the side effects from the treatment were manageable, with fatigue and fever being the most troublesome.

BTC and ASI are very rare cancers, occurring in approximately one to two people per 100,000 of the population. They are hard to detect at an early stage and so most cases have grown and spread by the time they are diagnosed. It is usually not possible to cure patients, with most treatments aimed at slowing the growth of the cancer; only about 5% are still alive five years after diagnosis. Due to the fact that it is so hard to

treat and that patients die so quickly, there are very limited data on the effectiveness of second or third lines of therapy. Large international trials, such as this one, are the best way of testing new treatments.

Dr. Wainberg concluded: "There is an urgent unmet need for these patients and we believe these exciting data represent a potential new treatment option for patients with this BRAF mutation."

Co-chair of the EORTC-NCI-AACR Symposium, Dr. James L. Gulley, who is Director of the Medical Oncology Service at the NIH / NCI Center for Cancer Research in the USA, and was not involved in the research, commented: "Conducting trials of new therapies in rare cancers such as biliary tract cancer is difficult because of problems in recruiting enough patients to obtain meaningful results. Professor Wainberg and his international colleagues are to be congratulated on their collaboration in this trial. These early results from 36 patients demonstrate the potential of the combination of dabrafenib and trametinib to lead to meaningful responses in appropriately selected patients."

More information: Abstract no: 2 LBA, "Efficacy and safety of dabrafenib plus trametinib in patients with BRAF V600E-mutated biliary tract cancer and adenocarcinoma of the small intestine". Proffered papers, plenary session 10, Auditorium, 14.00 hrs, Friday 16 November.

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