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# Trial shows treatment-resistant advanced non-small cell lung cancer responds to rociletinib

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A new drug that targets not only common cancer-causing genetic mutations in patients with non-small cell lung cancer (NSCLC), but also a form of the mutation that causes resistance to treatment, has shown promising results in patients in a phase I/II clinical trial. The research will be presented today (Friday) at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain.

Approximately 10-15% of Caucasian and 30-35% of Asian patients with NSCLC have a mutation in the epidermal growth factor receptor (EGFR), which can be successfully targeted with EGFR inhibitors called tyrosine kinase inhibitors (TKI), such as erlotinib, gefitinib and afatinib. However, these patients will eventually develop resistance to EGFR TKI therapy and a further EGFR mutation called T790M accounts for 60% of this acquired resistance.

Professor Jean-Charles Soria, Chairman of the Drug Development Department at Gustave Roussy Cancer campus, France, will tell the Symposium: "Currently, there are no approved targeted therapies for mutant EGFR lung cancer patients who develop the T790M mutation, which means their disease inevitably will get worse. Rociletinib (CO-1686) is a new and potent oral EGFR inhibitor designed to selectively target both the initial activating EGFR mutations as well as the T790M resistance mutation. This compound spares normal (wild-type) EGFR and this means that it causes far fewer toxic side-effects than other EGFR inhibitors. Therefore, it may benefit patients both as a

first-line and second- or later-line treatment, by producing a durable clinical benefit and with a reduced toxicity profile compared to current EGFR inhibitor therapies. Current TKIs inhibit the normal EGFR as well as the mutant EGFR, causing acne-like skin rashes and paronychia - an inflammation of the folds of tissue around finger and toe nails - both of which can be very troublesome for patients."

Patients with advanced NSCLC with the EGFR mutation, with or without the T790M resistance mutation, were enrolled in the phase I/II clinical trial in centres in Europe, Australia and the USA; enrolment of patients for the phase I part of the study began in March 2012, and for the phase II part in August 2013. The phase I portion of the study examined two formulations and multiple doses and schedules of rociletinib; 625mg twice a day continuously of hydrobromide (HBr) salt tablet form of rociletinib was identified as the pivotal dose, schedule and formulation for the phase II part of the study.

By October 2014, 179 patients had been treated at therapeutic doses (either 900mg twice a day of freebase formulation, or 500mg or more twice a day of HBr salt tablet). Preliminary results for all of these patients (those with and without the T790M and T790M resistance mutation) include an overall response rate of 46% and a disease control rate of 84%.

Prof Soria will present detailed data to the Symposium on 56 patients who had the T790M resistance mutation and received the pivotal dose and formulation (625mg twice a day) or the reduced dose of 500mg twice a day. The median number of prior therapies for these patients was three; all the patients had been treated previously with at least one other EGFR TKI therapy, and most patients receiving chemotherapy as well. Approximately 80% of these patients were treated immediately after their cancer progressed during treatment with a TKI. The study is ongoing, accruing patients rapidly, and CT scan data are available on 27

of these patients, of whom 18 had a confirmed response to the treatment, giving an overall response rate of 67% and a median progression-free survival of 10.4 months.

Among an additional 11 evaluable patients who did not have the T790M mutation, four had a confirmed response to the treatment (overall response rate of 36%) and this group of patients had a median progression-free survival of 7.5 months. Prof Soria will say: "Re-sensitisation to TKI cannot account for the majority of these responses, since most patients had come off TKI as their immediate prior therapy."

Adverse side-effects of rociletinib were manageable and included asymptomatic hyperglycaemia (high blood sugar levels), nausea and diarrhoea, and these were mostly mild or moderate (grade 1 or 2). Only two patients had any form of rash, which was grade 1 and transient. The most common, more severe adverse event (grade 3) was hyperglycaemia, which was observed in 14% of patients. Hyperglycaemia can usually be managed with a commonly-prescribed oral drug.

Prof Soria will say: "Eventually, almost all lung cancer patients with EGFR mutations will develop resistance to currently available therapies, including TKI, leaving doctors and patients without effective options to treat this deadly disease. The data from the rociletinib clinical trials suggest that we may be able to successfully target and overcome resistance to EGFR inhibitors and bring new, targeted treatments to patients who need them the most."

The responses seen in the patients who had acquired resistance to earlier TKI treatment but without evidence of T790M mutation was unexpected. Possible explanations include:

- the presence of large regions of tumour that do have the T790M mutation, but were missed by the biopsy needle (tumour

heterogeneity);

- the test is not sensitive enough to detect low levels of the T790M mutation, resulting in a false negative;
- rociletinib inhibits an alternative pathway (a "bypass track"), other than EGFR, which drives acquired resistance to EGFR TKI. "Indeed, we now know a metabolite of rociletinib inhibits the IGF1-R pathway, which we believe may account for some of the activity observed in T790M-negative patients," Prof Soria will say.

**More information:** Abstract no: LBA 10, "Interim phase 2 results of study CO-1686-008: A phase 1/2 study of the irreversible, mutant selective, EGFR inhibitor rociletinib (CO-1686) in patients with advanced non small cell lung cancer". Proffered papers, plenary session 8, Auditorium, 11.00 hrs, Friday 21 November.

The abstract is online at: www.ecco-org.eu/Events/EORTC_N … Programme#anchorScpr

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