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EMBARGO LIFTED - Everolimus slows disease progression in advanced papillary kidney cancer patients

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The first Phase II study to investigate the use of the anti-cancer drug, everolimus, for the initial treatment of advanced papillary kidney cancer has shown that it is successful in slowing or preventing the spread of the disease, according to research to be presented today (Sunday) at the 2013 European Cancer Congress (ECC2013) [1].

Dr Bernard Escudier, Head of the French Group of Immunotherapy and chairman of the Genitourinary tumour board at the Institut Gustave Roussy in Villejuif, France will say: “Our results showed that for 59% of patients who received everolimus as their first-line treatment, their disease did not get worse and remained stable. These findings are important and indicate that more than half of these cancer patients are getting some kind of benefit from everolimus treatment.

“Advanced papillary kidney cancer is a very difficult cancer to treat, and because there is no standard of care, there is disagreement amongst experts regarding the best treatment option for these patients. Our clinical findings are encouraging and suggest that everolimus may represent a new treatment option.”

Papillary kidney cancer is the second most frequent type of kidney cancer and accounts for approximately 15% of all kidney cancer cases; it is five times more common in men than in women. When the cancer is confined to one location, surgical removal is usually associated with an excellent prognosis. However, when it spreads to other parts of the body, therapies are ineffective. There are two types of papillary cancer, based on cell appearance (histology), known as type I and type II. Type I are more common and grow slowly, whereas type II papillary kidney cancers are much more aggressive and have a poor prognosis.

Everolimus is an anti-cancer drug known as an mTOR inhibitor; mTOR stands for “mammalian target of rapamycin” and it is a protein that regulates vital cell growth processes, including cell metabolism, growth and proliferation. Its failure to function correctly is involved in the development of several cancers. [2]

Dr Escudier and his colleagues in France, Germany, Italy, Spain, Poland and the UK recruited 92 patients into the RAPTOR (RAD001 in Advanced Papillary Tumor Program in Europe) study, which started in July 2009. The patients, who had never received systemic treatment, were instructed to take the drug orally, once a day, at a dose of 10 mg for as long as they could tolerate it.

Of the 92 enrolled patients, 83 were included in the intention-to-treat (ITT) analysis and 63 were included in the per-protocol (PP) analysis. An ITT analysis examines the study results based on the treatment to which a group of patients is assigned, rather than the treatment received, and reflects real clinical practice. The PP analysis determines the real biological effect of the new drug as it only includes patients who were compliant with the treatment to which they were assigned, and who also adhered to the clinical study instructions. All of the 92 enrolled patients were included in the safety analysis of the data. Tissue samples were analysed by pathologists in the local hospitals to check whether or not the cancer had spread, and the samples were also checked centrally by an independent, expert group of pathologists.

According to the PP analysis carried out by the local investigators, disease was stable and had not progressed after six months in 59% of patients, while the central review confirmed this in 35% of patients. The local investigators found that the time that elapsed before the cancer spread or worsened (progression-free survival) was 7.8 months, while the central pathology review found it was 3.9 months. At least half of the patients were alive at 20 months.

Dr Escudier will say: “Similar results were seen in the ITT analysis and strongly confirm the overall study findings. According to assessments by the local investigators, progression-free survival was 7.6 months, according to the central review it was 3.7 months, and more than half of the patients were alive at 21 months.

“These results underline the differences that are often observed between local investigator assessment and central review according to the established set of rules used to evaluate anti-cancer drugs.

“As far as we know, this study is unique as it was the first study of an mTOR inhibitor to only include patients with advanced papillary kidney cancer and diagnosis was also confirmed by an independent group of pathologists experienced in the classification of kidney cancer to prevent any tumours being classified incorrectly.

“Everolimus represents another interesting treatment option for advanced papillary kidney cancer patients as it seems to extend their survival and time without the disease progressing.”

Adverse side-effects were generally well tolerated. They included weakness, tiredness and anaemia; 27% of patients discontinued everolimus due to these side-effects. “The typical patient being treated for advanced papillary kidney cancer is middle-aged, active and still working, and the impact of side-effects may be more important to them,” he will say.

“While the results from this Phase II study are encouraging, a Phase III trial would need to be done to fully characterise the efficacy and safety profile of everolimus in this patient population,” he will conclude.

President of ECCO, Professor Cornelis van de Velde, commented: “Papillary tumours have been excluded from many of the targeted therapy trials. This study on targeting the mTOR pathway in patients with advanced papillary kidney cancer provides a basis for a Phase III trial and is potentially practice changing. It also emphasises the need for expert pathology, since central review gave markedly different results than local review.”

ESMO spokesperson, Professor Manuela Schmidinger, Professor of Medicine in the Department of Oncology at the University of Vienna, Austria, commented: “Treatment strategies for metastatic renal cell cancer (RCC) have dramatically improved within the last few years. However, these achievements have been mostly restricted to patients with clear-cell (cc)-RCC. Patients with non-cc-RCC are usually underrepresented in clinical trials, thus the benefits of novel targeted agents remains unclear in this population. So far, attempts to investigate the impact of new drugs in the non-cc-RCC-population have resulted in inconsistent but mostly modest results. This is also due to the fact that studies included different types of non-cc-RCCs; however, these are tumours of different epithelial origin, with different genetic background and different clinical behaviour. RAPTOR is the first prospective study that investigated the impact of a targeted agent, everolimus, in patients with papillary RCC. In this study, Escudier et al demonstrated that everolimus provides a promising median average overall survival in this patient setting. A strength of this trial in contrast to other non-cc-RCC -studies is that only patients with papillary subtypes I and II were included, rather than all different types of non-cc-RCC.”

[1] The 2013 European Cancer Congress is the 17th congress of the European CanCer Organisation (ECCO), the 38th congress of the European Society for Medical Oncology (ESMO) and the 32nd congress of European Society for Therapeutic Radiology and Oncology (ESTRO).

[2] Everolimus is also called RAD-001, and by its brand names Afinitor, and Afinitor Disperz.

[3] The work was funded by Novartis Pharmaceuticals.