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Custirsen shows no survival benefits in metastatic prostate cancer

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A phase III randomized controlled trial of custirsen in combination with cabazitaxel/prednisone in patients with previously-treated metastatic, castration-resistant prostate cancer has shown no significant survival gains compared to cabazitaxel/prednisone alone, according to data presented at the ESMO 2016 Congress in Copenhagen.

"Despite the negative outcome of the trial, the evaluation of custirsen in prostate cancer was conducted on the basis of solid preclinical and clinical evidence supporting anti-tumour activity," said principal investigator Professor Karim Fizazi, head of the Department of Cancer Medicine at the Institut Gustave Roussy, Villejuif, France.

Custirsen blocks production of the protein clusterin, which is known to be involved in carcinogenesis and tumour growth, as well as contributing to treatment resistance.

A previous phase II trial of custirsen combined with chemotherapy in men with metastatic castration-resistant prostate cancer suggested inhibition of clusterin may lead to improved clinical outcome, and an earlier phase III trial of custirsen in combination with docetaxel suggested patients with more aggressive cancers may benefit from the combination.

In the AFFINITY trial, 635 patients with metastatic, castration-resistant prostate cancer – who had previously been treated with docetaxel - were randomized to 21-day cycles of custirsen plus cabazitaxel/prednisone or

cabazitaxel/prednisone plus placebo, until disease progression, unacceptable toxicity, or ten cycles.

Researchers saw no significant difference in overall survival between the custirsen and placebo arms of the study, with a median overall survival of 14.2 months in the custirsen arm and 13.4 months in the placebo arm ($p = 0.529$).

The same was observed in the 62% of patients who met the criteria for poor prognosis, where median overall survival was 11.1 months among those taking custirsen and 10.9 months in those in the placebo group.

Similar numbers of patients in each arm discontinued due to progressive disease – 28.9% in the custirsen arm and 25% in the placebo arm – while 21.9% of patients treated with custirsen and 18.9% of patients in the placebo arm discontinued due to adverse events.

The most frequently reported serious adverse events were neutropenia, anemia, fatigue, asthenia, bone pain, and febrile neutropenia.

"I am obviously disappointed with the results but am proud to have been involved in this program, and we will take the learnings of this trial to advance our knowledge of the disease in the hope to further advance care," Fizazi said.

"Custirsen remains a viable candidate currently being evaluated for the treatment of non-small cell lung cancer, as failure in one tumour type does not predict the outcome of trials in other indications," said Fizazi.

Commenting on the study, Dr Cora Sternberg, Chief of the Department of Medical Oncology at

San Camillo Forlanini Hospital in Rome, Italy, said "A number of

approaches have been investigated to overcome resistance in prostate cancer, including the use of novel taxanes and tubulin inhibitors, and the inhibition of cell survival pathways."

"Given the results observed using a taxane as either first-line or second-line chemotherapy in castration resistant prostate cancer, the hypothesis was that combination with custirsen may decrease taxane resistance and enhance the survival benefit of taxane therapy," Sternberg said.

"There was a strong rationale for adding custirsen to chemotherapy to overcome resistance but unfortunately the final results were negative. We likely need even more robust biological molecular stratification before launching phase III trials," concluded Sternberg.

More information: "Final overall survival (OS) from the AFFINITY phase 3 trial of custirsen and cabazitaxel/prednisone in men with previously treated metastatic castration-resistant prostate cancer (mCRPC)" presented by Professor Karim Fizazi during the Presidential Symposium 3, on Monday 10 October 2016, 16:30 to 18:10 (CEST) in Room Copenhagen.

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