Galeterone shows activity in a variant form of castration-resistant prostate cancer

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Results from a trial of the anti-cancer drug galeterone show that it is successful in lowering prostate-specific antigen (PSA) levels in men with a form of prostate cancer that is resistant to treatment with hormone therapy (castration-resistant prostate cancer or CRPC).

Associate professor Mary-Ellen Taplin, of the Dana-Farber Cancer Institute, Boston, USA, will tell the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, today (Wednesday) that galeterone was well tolerated by patients in the ARMOR2 trial, and also lowered PSA levels in a subset of men with CRPC that was resistant to other drugs that target the cancer, such as enzalutamide and abiraterone.

"Recent data have shown that a variant of the androgen receptor called AR-V7, found in tumour cells circulating in the blood of patients with metastatic CRPC, predicted resistance to treatment with enzalutamide and abiraterone," she will say. "Indeed, we believe AR-V7 and other, related variants are a mechanism of resistance in this disease and patients who have them may have a poorer prognosis."

Researchers believed that galeterone could be effective against CRPC because it disrupts the androgen receptor signalling pathways that are involved in the cancer, and preclinical work has shown it is active against the AR-V7 variant.

Several clinical centres in the USA and Canada recruited four groups of

men with CRPC to a phase II study to receive 2550mg of galeterone orally once a day: 22 men had CRPC that had not metastasised (spread) and had received no previous treatment; 39 men had metastatic CRPC and no previous treatment with abiraterone or enzalutamide; 37 and nine men had metastatic CRPC and had failed treatment with abiraterone and enzalutamide respectively.

As well as evaluating PSA responses to the drug, the researchers also analysed levels of circulating tumour cells, including identifying whether or not they contained the AR-V7 variant. The AR-V7 variant is formed when an androgen receptor loses the end part of the receptor, called the C-terminal end; this is deleted due to an error in RNA processing in tumour cells, leaving only the beginning part of the receptor, the N-terminal end. The researchers concluded that patients with circulating tumour cells with more N-terminals than C-terminals had the androgen receptor variants.

"We found that galeterone resulted in meaningful PSA declines in patients with metastatic CRPC, and imaging showed that the disease was stable or had responded to the drug," Prof Taplin will say. "Galeterone was safe, without any unexpected toxicity. We also detected circulating tumour cells, which were found in higher numbers in patients who had received more prior therapies.

"In a subset of seven patients who had circulating tumour cells with a higher ratio of N-terminal compared to C-terminal androgen receptors and so were likely to have the AR-V7 variant, six had favourable PSA responses to galeterone. This suggests that the presence of AR-V7 in circulating tumour cells does not preclude response to galeterone as has been shown to be the case for abiraterone and enzalutamide."

Among the group of men who had non-metastatic and metastatic disease who had not received prior treatment with abiraterone and enzalutamide,

data for 60 were available for analysis. PSA levels declined by 30% or more (PSA30) in 50 out of 60 (83%) patients, of whom 42 (70%) went on to have declines of 50% or more (PSA50). Among patients who were resistant to abiraterone, 37 were available for evaluation; 13 out of 37 (35%) had any PSA decline. Among patients who were resistant to enzalutamide, nine were evaluable; five out of nine (56%) had any PSA decline.

The presence of circulating tumour cells were evaluated in 71 patients and were found to be higher in 64 (90%) of the patients who had more advanced cancer that had failed more previous treatments.

Galeterone will now be tested in a phase III trial in which patients with metastatic CRPC with the AR-V7 variant will be randomised to receive either galeterone or enzalutamide. The researchers will be looking to correlate AR-V7 with response to galeterone and to see what effect the drug has on the length of time patients survive without their disease progressing.

"This phase III trial will be noteworthy for being the first prostate cancer trial to assess a biomarker, namely AR-V7 in circulating tumour cells, as a predictor of response at the same time as testing the efficacy of the drug," Prof Taplin will conclude.

Professor Josep Tabernero, a member of the scientific committee for the EORTC-NCI-AACR Symposium and head of the medical oncology department at Vall d'Hebron University Hospital and director of the Vall d'Hebron Institute of Oncology, Barcelona, Spain, commented: "These are encouraging results, which show that galeterone has significant clinical activity in men with castration-resistant prostate cancer that fails to respond to other drugs. Understanding the biological and genetic basis to drug resistance and cancer progression has enabled researchers to identify and develop a targeted drug that may prove to be beneficial in

this type of cancer, without causing unmanageable side-effects. We look forward to the results from the phase III trial with interest."

More information: Abstract no: 4, "Activity of galeterone in castrate-resistant prostate cancer (CRPC) with C-terminal AR loss: Results from ARMOR2". Proffered papers, plenary session 2, Auditorium, 13.15 hrs, Wednesday 19 November.

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