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PROSTATE CANCER

Dasatinib fails to improve on docetaxel for metastatic CRPC

Promising early results with the tyrosine kinase inhibitor dasatinib have not translated into clinical benefit in combination therapy with docetaxel for metastatic castration-resistant prostate cancer (mCRPC). In a phase III, double-blind, randomized controlled trial of 1,522 men with chemotherapy-naive mCRPC who received docetaxel plus prednisone along with either dasatinib or placebo, no difference was seen between median overall survival times of 21.5 months with dasatinib and 21.2 months with placebo (HR 0.99, 95.5% CI 0.87–1.13).

Furthermore, dasatinib treatment did not confer benefits in the secondary end points of time to PSA progression (HR 0.89), progression-free survival (HR 0.92), time to first skeletal-related event (HR 0.81), reduction in urinary N-telopeptide (OR 1.28), reduction in pain intensity (OR 0.79), and objective response (OR 0.94). These data mean that dasatinib can be added to the list of targeted therapies, including bevacizumab and atrasentan, which do not improve the survival of men with mCRPC when given in combination with docetaxel.

> “Promising early results ... have not translated into clinical benefit...”

The decision to proceed to a large-scale phase III trial on the basis of limited preclinical and clinical data, without a convincing biochemical mechanism to justify combining dasatinib and docetaxel, was criticized in a commentary by Lara and Evans. They argue that it is a “logical, albeit simplistic, notion that simultaneous targeting of the tumour cell (with docetaxel) and its microenvironment (with dasatinib) will lead to synergistic efficacy effects.”

To explain the failure of dasatinib in their trial, Araujo *et al.* point to the heterogeneity of mCRPC in the study population. To identify patients within this population who might have a positive response, they are currently analysing serial serum and plasma samples from 75 study participants for appropriate biomarkers.

Lara and Evans question whether Src family kinase inhibition by dasatinib is relevant to mCRPC therapy, but Araujo *et al.* think that further understanding of the drug’s mode of action could identify a therapeutic role. An ongoing study is investigating whether resistance to dasatinib is mediated by persistent androgens in men with mCRPC. It might not be the end of the line for dasatinib just yet.

Robert Phillips

Original article Araujo, J. C. *et al.* Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol.* doi:10.1016/S1470-2045(13)70479-0

Further reading Lara, P. N. & Evans, C. P. Dasatinib and docetaxel in advanced prostate cancer. *Lancet Oncol.* doi:10.1016/S1470-2045(13)70500-X