Development of a Novel Autophagy Inducing Multi-Kinase Inhibitor for the Treatment of Castration Resistant Prostate Cancer

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Background

Prostate cancer remains the second leading cause of cancer-related death in men in the United States. Inhibition of the androgen axis has revolutionized the treatment of metastatic castration resistant prostate cancer (mCRPC). However, these treatments are generally not curative and thus novel approaches to treat advanced prostate cancer are urgently needed. There is also a prevailing hypothesis that combination treatments will be needed to achieve durable responses in advanced cancers. Multi-tyrosine inhibitors (MTKIs), inherently hit multiple targets, and thus may have utility as combination regimens. Cabozantinib is an FDA approved multi-tyrosine kinase inhibitor (MTKI) which has been explored pre-clinically and is in Phase III clinical studies for the treatment of mCRPC. Despite promising early phase clinical trial results, a recently presented phase III trial evaluating cabozantinib in CRPC did not meet its primary survival endpoint. Thus, other MTKIs are very much needed for the treatment of prostate cancer.

Methods

In our search to re-position Phase I cleared MTKIs for the treatment of specific cancers and cancer subsets, we synthesized and evaluated a Phase I-cleared multi-kinase inhibitor, ESK981, in prostate cancer pre-clinical models in comparison to other kinase inhibitors that have been evaluated clinically in prostate cancer including cabozantinib and crizotinib.

Results

ESK981, unlike other MTKIs tested induced robust vacuolization and activated the autophagy pathway in prostate cancer pre-clinical models, a phenotype conserved and recapitulated in yeast model systems. ESK981-induced autophagy can be blocked by either the depletion of the autophagy vesicle formation gene, atg5, or autophagy inhibitors such as bafilomycin. ESK981 was further shown to induce autophagy in yeast which is an evolutionarily conserved core cellular pathway. Notably, ESK981 markedly inhibited growth in vivo and induced autophagic cell death of multiple prostate cancer xenografts in animal models.

Conclusions

ESK981 is a novel and potent autophagy inducing multi-kinase inhibitor that effectively inhibits CRPC growth through activation of the autophagic cascade.

Conflict of Interest

No potential conflict of interest is disclosed.

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