Targeting Resistance to Current CDK4/6 Therapies by RGT-419B, an Inhibitor with an Optimized Kinase Activity Spectrum

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ABSTRACT

Cyclin-dependent Kinases (CDKs) 4/6 inhibitors are a powerful class of therapeutic drugs for the treatment of advanced metastatic breast cancer. However, the currently approved CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib have dose-limiting toxicities that require treatment holidays or reductions to sub-optimal doses, thus limiting sustained full target inhibition. The residual CDK4/6 activity, together with persisting signaling through CDK/cyclin E are among key resistant mechanisms that can compromise full clinical benefit. RGT-419B is a new generation CDK inhibitor with an optimized kinase activity spectrum that has been discovered by deploying Computer Accelerated Neutral Design (Carbon) technology platform. RGT-419B has potent sub-nM CDK4 activity with desired degrees of selectivity against kinases such as CDK9, CDK4 and GSK3β, aiming to enable full target engagement with an improved safety profile. Furthermore, single digit nM CDK2 kinase activity has been incorporated into the design of RGT-419B to combat Cyclin E/CDK2-driven resistance. In vitro, RGT-419B showed more robust activity against palbociclib-resistant and abemaciclib-resistant breast cancer cells than abemaciclib. In ER+/T47D breast cancer cells with overexpression of Cyclin E1, RGT-419B exhibited better anti-proliferation activity than either abemaciclib or palbociclib. RGT-419B also demonstrated more durable in vivo tumor growth inhibition when compared with abemaciclib in the Abema-resistant T47D xenograft model. The optimized kinase activity spectrum of RGT-419B offers an opportunity to treat ER+ breast cancer patient refractory to the existing CDK4/6 inhibitors as either a single agent or in combination with other therapies.

RESULTS

CONCLUSIONS

RGT-419B is a new generation CDK4/6/8 inhibitor with an optimized kinase selectivity spectrum, aiming to improve safety and control resistance of the currently approved CDK4/6 inhibitors.

RGT-419B caused G1 cell cycle arrest and suppressed the proliferation of ER+ T47D cells in vivo.

It demonstrated sustained tumor growth inhibition in the ER+ breast cancer MCF7 xenograft as single agent in vivo.

Furthermore, RGT-419B demonstrated full suppression of the proliferation of the ER+ breast cancer cells with acquired resistance to the currently approved CDK4/6 inhibitors as single agent, and the activity can be further augmented in combination with SERDs and inhibitors of PI3K signaling pathway in vivo.

In ER+ T47D cells overexpressing Cyclin E1, RGT-419B exhibited more potent anti-proliferation activity when compared with abemaciclib and palbociclib.

In summary, RGT-419B, with an optimized kinase activity spectrum, provides an opportunity to treat ER+ breast cancer patients with primary or acquired resistance to the currently approved CDK4/6 inhibitors as either a single agent in combination with other therapies such as next-Gen SERDs.

REFERENCES


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