616. ACUTE MYELOID LEUKEMIA: NOVEL THERAPY, EXCLUDING TRANSPLANTATION: POSTER II | DECEMBER 7, 2017

CT7001, a Novel Orally Bio-Available CDK7 Inhibitor, Is Highly Active in in-Vitro and in-Vivo Models of AML

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Abstract

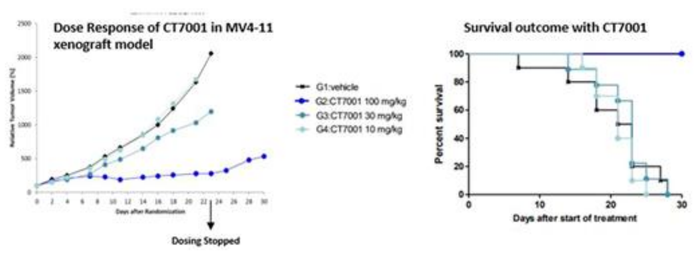
CDK7 is considered an important new target for the treatment of human cancer as it controls the activity of key enzymes involved in cell cycle progression, including other cyclin dependent kinases such as CDK1, CDK2, CDK4 and CDK6. As a master regulator of transcription CDK7 also promotes the expression of key oncogenes such as c-Myc through the phosphorylation of RNA polymerase II. Both transcription and cell cycle regulation are dysregulated in Acute Myeloid Leukaemia (AML).

Here, we investigated the therapeutic potential of CT7001 (ICEC0942), a novel orally bio-available ATP competitive CDK7 inhibitor (Hazel et al 2017) in pre-clinical AML models. CT7001 potently inhibited the proliferation of several AML cell lines and patient derived AML cells in vitro, with IC50 values ranging from 0.15-2.6 µM. Consistent with the inhibition of CDK7 in cells, treatment of the FLT3 internal tandem duplication (ITD) positive MV-4-11 cells with CT7001 led to a concentration dependent decrease in the phosphorylation of RNA polymerase II at Ser2, Ser5 and Ser7 as well as the phosphorylation of cell cycle signalling intermediates including CDK1, CDK2 and Rb1. Moreover, CT7001 treatment decreased the expression levels of c-Myc and the pro-survival factor Mcl-1 and induced the accumulation of cleaved PARP as a consequence of apoptosis. Finally, once daily oral administration of CT7001 to mice led to a sustained total growth suppression in a MV-4-11 xenograft model.

CT7001 is a potent, selective and orally bioavailable inhibitor of CDK7 that shows promise as a potential new treatment for AML.

Reference: Hazel et al. ChemMedChem. 2017 12(5):372-380 Inhibitor Selectivity for Cyclin-Dependent Kinase 7: A Structural, Thermodynamic, and Modelling Study

Figure



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Disclosures

Clark: *Carrick Therapeutics:* Research Funding. **Ainscow:** *Carrick Therapeutics:* Employment, Equity Ownership. **Peall:** *Carrick Therapeutics:* Research Funding. **Thomson:** *Carrick Therapeutics:* Research Funding. **Leishman:** *Carrick Therapeutics:* Employment. **Elaine:** *Carrick Therapeutics:* Employment, Equity Ownership. **Ali:** *Carrick Therapeutics:* Consultancy, Equity Ownership, Patents & Royalties: Patent Inventor for CT7001. **Coombes:** *Carrick Therapeutics:* Consultancy, Equity Ownership, Patents & Royalties: Inventor on CT7001 patent. **Barrett:** *Carrick Therapeutics:* Consultancy, Equity Ownership, Patents & Royalties: Inventor on CT7001 patent. **Bahl:** *Carrick Therapeutics:* Employment, Equity Ownership.

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Author notes

* Asterisk with author names denotes non-ASH members.

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