AZD0466, a nanomedicine of a potent dual Bcl-2/Bcl-xL inhibitor, exhibits anti-tumor activity in a range of haematological and solid tumor models

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Abstract

The induction of apoptosis in tumor cells represents a promising approach to the treatment of cancer. In tumor cells, the B cell lymphoma 2 (Bcl-2) protein family promotes cell survival through upregulation of anti-apoptotic Bcl-2 proteins, such as Bcl-2, Bcl-xL, Mcl-1 and Bfl-1. Clinical activity of the Bcl-2 inhibitor venetoclax has validated the approach of targeting this class of molecules, but additional value remains in jointly targeting Bcl-2 with other family members. AZD0466 is a novel drug-dendrimer conjugate, where the active moiety, AZD4320, is chemically conjugated to Starpharma’s clinically validated DEP® dendrimer platform, a 5-generation PEGylated poly-lysine dendrimer via a hydrolytically labile linker. AZD4320 is a dual Bcl-2/Bcl-xL inhibitor that is equipotent to venetoclax and 3-fold more potent than navitoclax. AZD0466 has been optimized to maintain efficacy whilst mitigating anticipated on-target toxicities of AZD43201.

Introduction

AZD0466 active moiety potently reduces viability of heme cancer cell lines, SCLC cell lines and primary leukemic cells

(A) Subset of cancer cell lines sensitive to single agent AZD4320 (active moiety of AZD0466) in Sanger panel. (B) Broader activity of AZD4320 in primary AML patient samples compared to venetoclax (red box).

AZD0466 has potential antitumor activity in preclinical hematological models

(A) Monotherapy activity of AZD0466 in a population-based PDX screen. (B) AZD0466 response is predominantly associated with SCLC-A and SCLC-P subtypes in cell lines and PDX models

AZD0466 combinations drive deep and durable response in preclinical DLBCL models

(A) Combination of AZD0466 with BTK inhibitor Acalabrutinib drives durable regression in ABC DLBCL. (B) AZD0466 combined with rituximab results in complete and durable regressions in GCB DLBCL

Results

AZD0466 active moiety potently reduces viability of heme cancer cell lines, SCLC cell lines and primary leukemic cells

AZD0466 has potential antitumor activity in preclinical hematological models

AZD0466 has potent antitumor activity in preclinical hematological models

AZD0466 combines drive deep and durable response in preclinical DLBCL models

Conclusions

• AZD0466 and its active moiety AZD4320 demonstrate differentiated activity from the Bcl-2 selective inhibitor venetoclax in preclinical models of SCLC and AML.

• AZD0466 has potential as a combinatorial agent to increase the depth and duration of response to novel and standard of care therapies, as demonstrated in models of DLBCL.

References

1. Design and optimization of a dendrimer-conjugated dual Bcl-2/Bcl-xL inhibitor, AZD0466, with improved therapeutic index, Ashford M et al, AACR (2020)