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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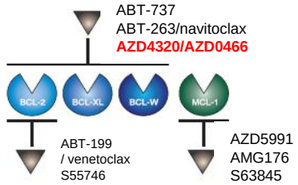
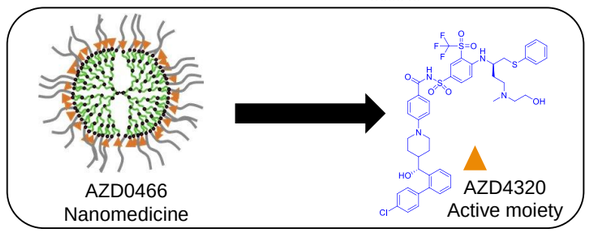
Abstract

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 AZD4320[1].

Introduction



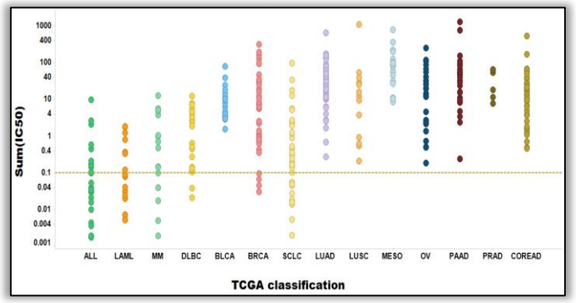


- AZD0466: a dendrimer-conjugate of AZD4320, small molecule inhibitor of Bcl-2 and Bcl-xL
- Enhanced solubility compared to AZD4320
- Once weekly dosing schedule with PK properties optimized to maximize therapeutic index

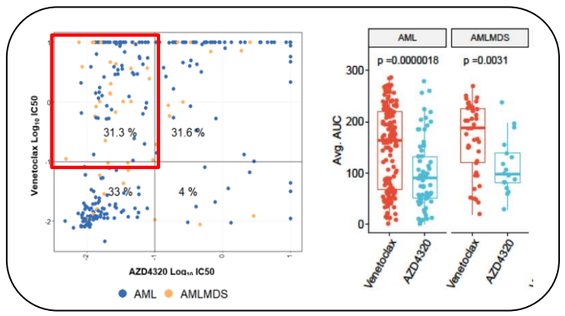
Results

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

A: Sanger Panel



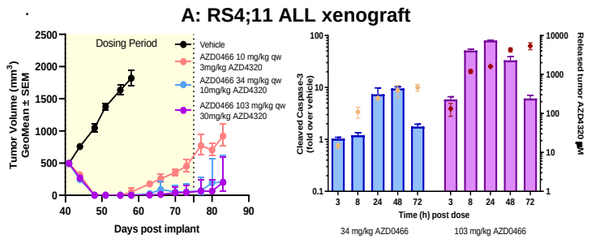
B: Beat AML Screen



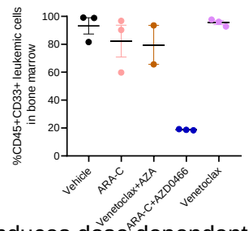
(A) Subset of cancer cell lines sensitive to single agent AZD4320 (active moiety of AZD0466) in Sanger panel. (B) Broader activity of AZD4320 in primary AML patient samples compared to venetoclax (red box).

AZD0466 has potent antitumor activity in preclinical hematological models

A: RS4;11 ALL xenograft



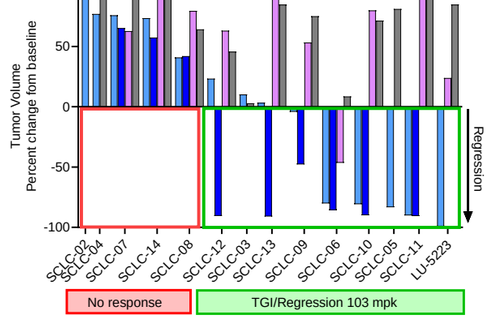
B: AML PDX xenograft



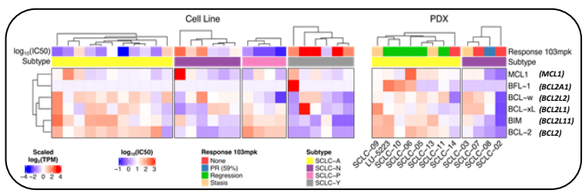
(A) AZD0466 induces dose dependent tumor regression and cleaved caspase 3 induction. (B) AZD0466 in combination with AraC decreases tumor burden in bone marrow of mice implanted with primary AML cells.

AZD0466 is more efficacious in SCLC PDX models compared to standard-of-care

A: SCLC PDX screen



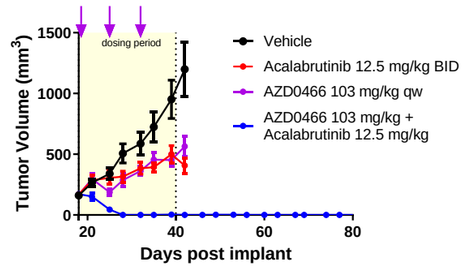
B: SCLC molecular analysis



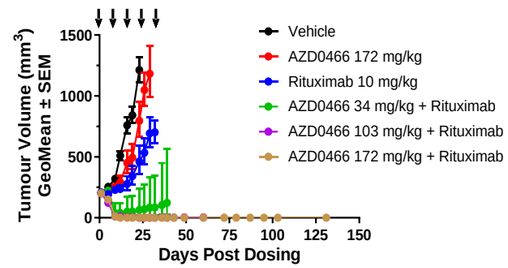
(A) Monotherapy activity of AZD0466 in a population-based PDX screen. (B) AZD0466 response is predominantly associated with SCLC-A and SCLC-P subtypes in cell lines and PDX models

AZD0466 combinations drive deep and durable response in preclinical DLBCL models

A: OCI-LY10 ABC DLBCL xenograft



B: SUDHL-4 GCB DLBCL xenograft



(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

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)

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