Design and optimisation of a dendrimer-conjugated dual Bcl-2/Bcl-x_L inhibitor, AZD0466, with improved therapeutic index

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Introduction

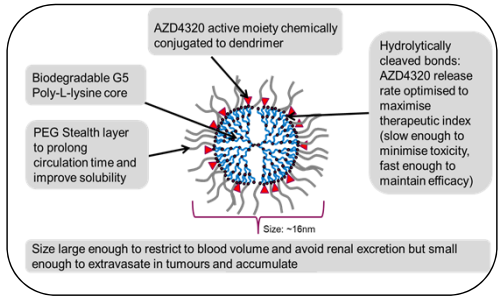
Dual Bcl-2/Bcl-xL inhibitors are expected to deliver therapeutic benefit in many hematological and solid tumors, but their clinical application has been limited by tolerability issues, including thrombocytopenia. AZD4320, a potent dual Bcl-2/Bcl-xL inhibitor, showed good efficacy but encountered dose limiting cardiovascular toxicity in preclinical species, and had challenging physicochemical properties which prevented its clinical development. Nanocarriers can provide prolonged circulation time, controlled release, tumor accumulation and retention. Consequently, they have been explored to improve the therapeutic index of small molecules in oncology.

This work describes the design and development of AZD0466, a novel drug-dendrimer conjugate, where AZD4320 is chemically conjugated to Starpharma's DEP® dendrimer platform, a 5-generation PEGylated poly-lysine dendrimer via a hydrolytically labile linker (Figure 1). Release of AZD4320 is through hydrolytic cleavage of the linker , which is characterized by a "release half-life", defined as the time to release 50% of the active moiety. This release half-life can be modified through linker design. This work describes the optimisation of the release half life

Methods

- Initially three drug-dendrimer conjugates with a range of AZD4320 release half-lives were synthesised and their release half-lives measured
- Efficacy was investigated in C.B-17 SCID mice bearing RS4;11 tumors
- Cardiovascular parameters and tolerance were assessed in a telemetered rat model
- A mathematical model was developed and used to optimize the desired release rate of the active moiety, AZD4320, from the dendrimer conjugate for maximal therapeutic index in terms of preclinical anti-tumor efficacy and cardiovascular profile.
- AZD0466, with a modelled optimum release half-life of 25.5 h, was synthesised
- Efficacy studies were carried out in RS4;11 xenograft model and cardiovascular studies carried out in rat and dog telemetered models

Figure 1 Structure of AZD4320-dendrimer conjugates

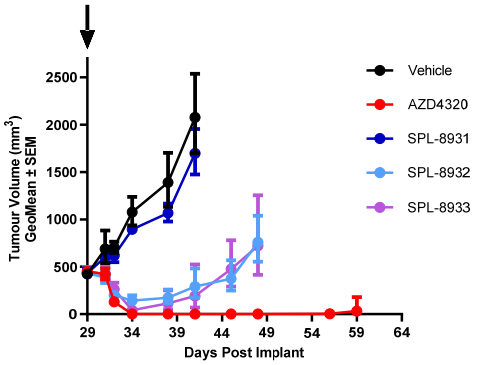


Results

Efficacy & Tolerability of Initial Conjugates

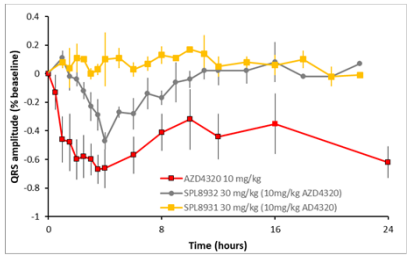
Three drug-dendrimer conjugates had measured release half-lives of 1.7 h (SPL-8933), 5.4 h (SPL-8932), 217 h (SPL-8931). The results of the efficacy study are shown in Figure 2. SPL-8933 and SPL-8932 with the faster release half-life initially produced tumor regression with similar kinetics to AZD4320 however the conjugate with the slowest release rate, SPL-8931, showed no efficacy.

Figure 2 Efficacy of AZD4320 and initial drug dendrimer conjugates



In the rat tolerability study only SPL-8931, the conjugate with the slowest release half-life and no efficacy, showed no effect on QRS amplitude (Figure 3)

Figure 3 Cardiovascular Effects of AZD4320 and initial drug dendrimer conjugates



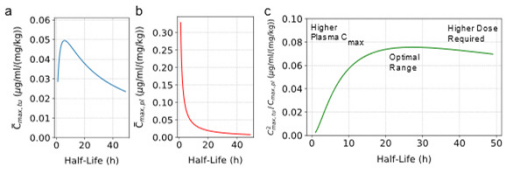
Mathematical Modelling Guided Optimization

A mathematical model was developed to describe aspects of the in-vivo disposition of AZD4320 dosed as drug dendrimer conjugates.

Output from the modelling allows the prediction of the maximum released concentration of AZD4320 in both tumor and plasma as a function of the release rate. The highest tumor C_{max} is predicted for a drug dendrimer conjugate with a 5 h release half-life but this is at the expense of high systemic levels. A release half-life in the range 20 – 30 h results in the best compromise between tumor and systemic C_{max} ; maximising potential efficacy whilst minimising cardiovascular risk (Figure 4).

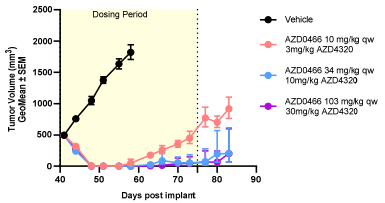
AZD0466 with a release half-life of 25.5 h falls within the optimum range identified from the mathematical modelling.

Figure 4 (a and b) Simulated dependence of released AZD4320 tumour and plasma C_{max} on release half-life (per unit dose)
(c) Optimisation Index (Therapeutic Index per unit dose) as a function of release half-life.



AZD0466 was shown to be efficacious in the RS4; 11 xenograft model (Figure 5).

Figure 5 Efficacy of AZD0466 in RS4;11 tumour xenograft model at various doses



AZD0466 had no effect on QRS amplitude in a rat telemetry study (Figure 6). In the dog telemetry study 60 mg/kg AZD0466 (equivalent to 18 mg/kg AZD4320) was not associated with any adverse clinical signs and gave significantly less decrease in QRS amplitude than 1 mg/kg AZD4320 (Figure 7).

Figure 6 Effects of AZD0466 on QRS amplitude in rat

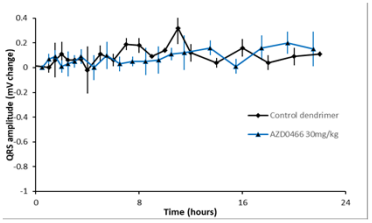
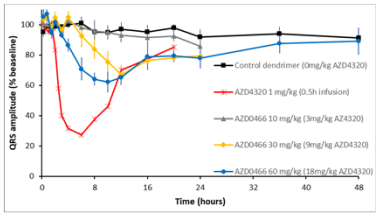


Figure 7 Effects of AZD0466 on QRS amplitude in dog versus AZD4320



Conclusions

The AZD4320-dendrimer conjugate, AZD0466, identified in this study has delivered an improved therapeutic index enabling this promising Bcl-2/Bcl-xL inhibitor to progress into clinical development.

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