Antitumoral activity of the novel BTK inhibitor TG-1701 is associated with disruption of Ikaros signaling and improvement of anti-CD20 therapy in B-cell non-Hodgkin lymphoma

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Introduction

B-cell non-Hodgkin lymphomas (B-NHLs) account for up to 4% of globally diagnosed cancers. Targeting of the B-cell receptor (BCR) pathway through inhibition of Bruton’s tyrosine kinase (BTK) with the first-in-class irreversible inhibitor brutinib has demonstrated exceptional clinical activity as a monotherapy for various subtypes of B-NHL. However, its activity has been limited by its acquired resistance due to a development of a somatic mutation at the BTK catalytic site (G105V) or over-activation of the NFκB pathway, and off-target activity that introduces toxicity and also precludes its use in combination with anti-CD20 antibodies.

Materials and Methods

TGF-1701 is a novel irreversible and highly specific BTK currently under study in patients with relapsed/refractory (RR) B-NHL alone and in combination with rituximab. A novel, glycosylated anti-CD20 antibody, and umbilumab, a dual FcRIIb and casetux kinase-1 inhibitor (combinations also referred to as U2 regimen).

Results

TG-1701 is a novel clinical irreversible BTKi

TG-1701 treatment leads to BTK-dependent disruption of Ikaros transcriptional program

TG-1701 does not impair FcγR-driven ADCC and ADCP and cooperates with U2 in BTKi-sensitive and BTKi-resistant models of B-NHL

Impairment of Ikaros signaling is associated with clinical response to TG-1701

Conclusions

TG-1701 is a novel irreversible BTK inhibitor in Phase I clinical development, as monotherapy or in combination with umbilumab and umbralisib.

In patient samples from a Phase 1 clinical trial of TG-1701, phosphoproteome analysis differentiated early and late responders to TG-1701 therapy.

Disruption of an active Ikaros pathway is a signature of early responders, while absence of Ikaros modulation upon TG-1701 therapy is associated with non-/late responders.

TG-1701 did not impair FcγR-driven ADCC and ADCP and cooperated with U2 in in vivo models of B-NHL.

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