TG-1701, a novel irreversible Bruton’s kinase (BTK) inhibitor, cooperates with ublituximab-driven ADCC and ADCP in vitro and in vivo models of ibrutinib-resistant mantle cell lymphoma

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BACKGROUND:

Mantle cell lymphoma is a rare but challenging subtype of B-cell non-Hodgkin lymphoma that generally responds to initial treatment but inevitably relapses, making it incurable with standard chemotherapy. The clinical presentation of MCL varies widely. Some patients have an indolent disease course with longer survival, and others can have a very aggressive course with shorter survival.

The first-in-class Bruton’s tyrosine kinase (BTK) inhibitor, ibrutinib, has proven to be an effective agent for patients with relapsed/refractory MCL. The development of a cytokine to secrete mutation at the BTK catalytic site (BTK
to G486V) or over-activation of the NF-KB pathway can impair MCL response to most BTK inhibitors (ibrutinib).

TG-1701 is a novel irreversible inhibitor highly specific to BTK, with improved selectivity when compared to ibrutinib, currently being evaluated in a phase 1 clinical trial in NHL and chronic lymphocytic leukemia (CLL) patients, alone or in combination with the anti-CD20 mAb ublituximab (U2 regimen).1

RESULTS #1: TG-1701 retains some activity in ibrutinib-resistant BTKC481S MCL cells

RESULTS #2: NF-kB-driven ibrutinib refractoriness impairs TG-1701 activity in vitro and in vivo in MCL

RESULTS #3: Ibrutinib, but not TG-1701, blocked ADCC and ADCP triggered by the anti-CD20 antibody ublituximab

RESULTS #4: In vivo TG-1701 demonstrates additive anti-tumor inhibition when combined with ublituximab and umbralisib (U2) regimen

RESULTS #5: TG-1701, currently tested in CLL and NHL patients, shows activity alone or in combination with umbralisib

CONCLUSIONS:

TG-1701 is a novel irreversible BTK inhibitor more selective and as active as ibrutinib in NHL models with BTK

When compared to ibrutinib, TG-1701 used at high doses retained notable antitumor activity in MCL cells with BTK to G486V mutation, while it did not show superior activity than the first-in-class BTKi in vivo and in vivo models of ibrutinib-resistant MCL with constitutive activation of the non-canonical NF-KB pathway.

Combinations have been shown to overcome resistances in various diseases. Here, we explored the combination of TG-1701 with the novel, glycogen synthase kinase 3 (GSK3) antibody ublituximab and the PI3Kδ inhibitor umbralisib. We first showed that TG-1701, in contrast to ibrutinib, does not block neither ibrutinib-driven ibrutinib nor ADCC in vitro. In vivo xenograft studies suggested that TG-1701 synergized with umbralisib and umbralisib. Part of the mechanism is related to the pro-immune interleukin signature and infiltration of NK cells in the tumor.

TG-1701 is currently tested in clinical trial alone or in combination with umbillicam and umbralisib. Preliminary data showed a strong activity of the bi-therapy.

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