INHIBITION OF NFκB-INDUCING KINASE (NIK) SELECTIVELY ABROGATES NIK AND TRAF3 MUTANT MULTIPLE MYELOMA TUMOR GROWTH

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ABSTRACT

Enhanced NFkB signaling is a hallmark of aggressive lymphoid malignancies, including multiple myeloma (MM). Non-canonical NFkB signaling involves NIK-dependent activation of IkKα, which triggers nuclear accumulation of p52/RelB heterodimers. NIK is a highly unstable protein and degradation is mediated by a ubiquitin ligase complex consisting of TRAF2, TRAF3 and c-IAP1/2 (encoded by BIRC2/3). In a subset of MM, NIK is stabilized by mutations in NIK, TRAF2/3 or BIRC2/3. Here, we report on the first potent orally bioavailable NIK kinase inhibitor: TRC694 potently inhibits phospho-IkKα, prevents nuclear accumulation of p52/RelB (but not canonical NFkB) and represses the associated NFkB gene program selectively in MM cell lines with genetic activation of the non-canonical NFkB pathway. Proliferation of NIK translocated, TRAF3 or BIRC3 mutant MM cell lines is preferentially inhibited by TRC694 over MM cell lines which lack genetic activation of non-canonical NFkB. Consistently, elevated expression of a previously described 11-gene NFkB signature is predictive of sensitivity to TRC694 in MM. A single, oral dose of TRC694 to mice bearing a NIK-translocated MM tumor, inhibits phospho-IkKα, and represses p52-mediated transcription of NFkB regulated genes. Daily oral dosing of TRC694 completely inhibits expansion of NIK or TRAF3 mutant multiple myeloma tumors, with no signs of toxicities in these mouse models. In conclusion, TRC694 provides the first opportunity to test the clinical relevance of non-canonical NFKB inhibition in aggressive lymphoid malignancies.

RESULTS

A. In vitro selectivity

Pharmacology Summary TRC694

- NIK (efficacy and incidence) - Selectivity (Phospho-NIK)

B. In vivo results

Potent inhibition of nuclear p52/RelB, but not canonical NFkB subunit p65 (RelA) in NIK translocated MM

TRC694 Preferentially Represses NFkB Genes in IGL-NIK

TRC694 is Efficacious in the NIK-translocated JJN-3 Model

TRC694 is Efficacious in TRAF3 Mutant MM Models

CONCLUSIONS

- Genetic alterations (NIK, TRAF2/3, BIRC2/3), leading to NIK protein stabilization and activation of non-canonical NFkB, are found in aggressive B-cell malignancies.
- TRC694 is a potent and selective, first-in-class, orally bioavailable small molecule NIK inhibitor that inhibits the growth of B-cell malignancies with activation of the non-canonical NFkB pathway in vitro and in vivo.