EP498

THERAPEUTIC POTENTIAL OF TENALISIB, A PI3K DELTA/GAMMA PLUS SIK-3 INHIBITOR, IN HEMATOLOGICAL MALIGNANCIES

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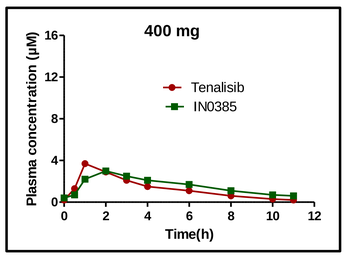
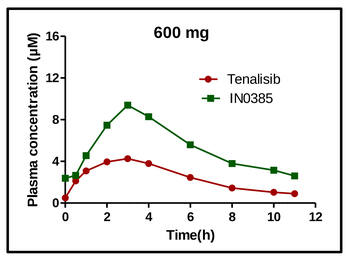
Background & Objectives

Tenalisib (RP6530) is a novel, potent, and selective small-molecule inhibitor with nanomolar potency against the δ and γ isoforms of PI3K. A phase-1 trial in Europe in patients with relapsed/refractory hematological malignancies indicated that Tenalisib was well tolerated with no dose limiting toxicities observed across the range tested (25-1200 mg BID and 600-800 mg TID). Single-agent Tenalisib at 800 mg BID in R/R PTCL and CTCL patients that failed multiple prior therapies (median 3 – 5.5) demonstrated impressive activity with an ORR of 47 and 45%, respectively, without any major AE. Efficacy continues to be encouraging in Phase-2 studies of Tenalisib 800 mg BID as a single agent in relapsed/refractory CLL as well as in combination with Romidepsin in relapsed/refractory T-cell lymphoma.

Pharmacokinetic evaluation of patient plasma from the ongoing combination trials indicated that Tenalisib underwent significant metabolism with levels of the major metabolite (IN0385) being approximately 2-fold higher than the parent thereby prompting further evaluation of IN0385 and its role in hematological malignancies.

Clinical Pharmacokinetics of Tenalisib





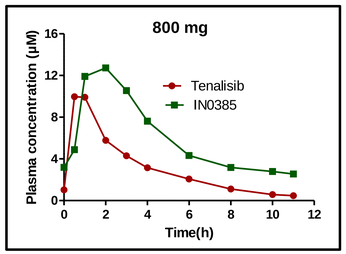


Figure 1. Mean plasma concentrations following administration of Tenalisib BID in Human. Plasma concentrations of Tenalisib and its metabolite (IN0385) were simultaneously determined using a high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Data indicated a ~2-fold higher concentrations of IN0385 compared to the parent in subjects treated with 800 mg Tenalisib dosed twice daily

Activity of IN0385

Compound	Enzyme IC_{50} (nM)						
	PI3K α	PI3K β	PI3K δ	PI3K γ	SIK-1	SIK-2	SIK-3
IN0385	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	237

Table 2. IN0385 was initially profiled in a Kinome*scan* @ 1 µM wherein it demonstrated significant inhibitory potency against Salt-inducible Kinase-3 (SIK-3) . IC_{50} of IN0385 against SIK-3 was determined using an enzymatic radiometric assay in the presence of [γ33P]ATP

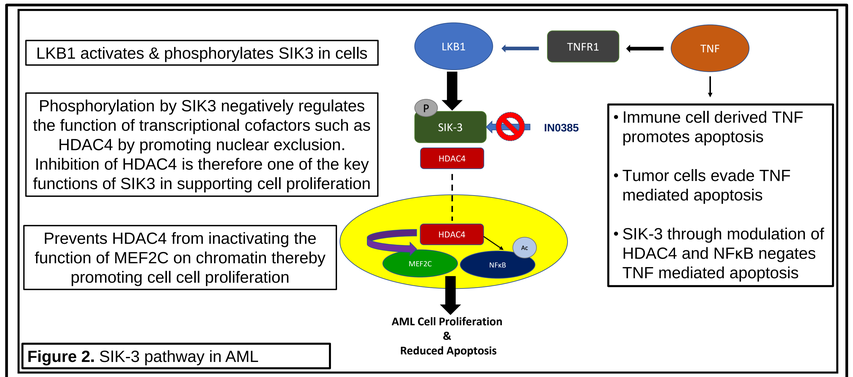
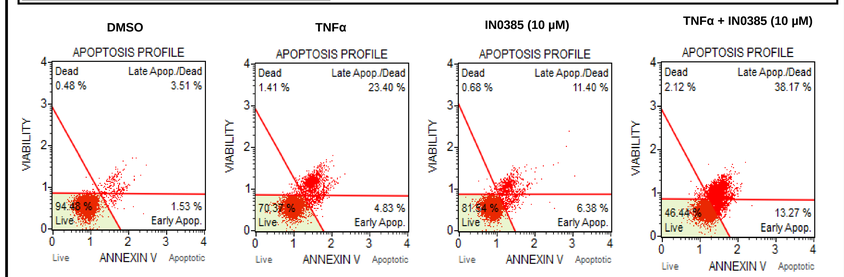
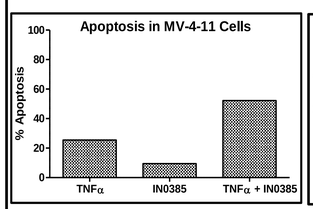


Figure 2. SIK-3 pathway in AML





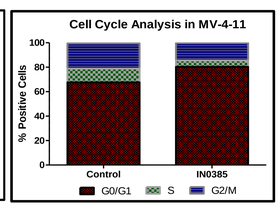
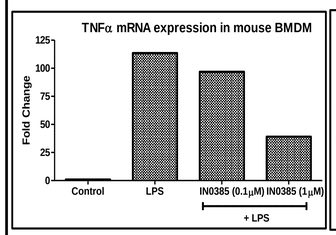


Figure 3. Apoptosis in MV-4-11 cells. Cell lines were plated in media at a pre-determined cell density in 6-well plates and cells were treated with TNFα and IN0385 for 48 h. ***Data demonstrated combination of IN0385 (10 µM) potentiated the activity of TNFα by increasing the apoptosis by 25%.*** **Cell cycle in MV-4-11 cells**. Cell lines were plated in media at a pre-determined cell density in 6-well plates and cells were treated with IN0385 for 48 h ***IN0385 (10 µM) caused an increase in G0/G1 population***



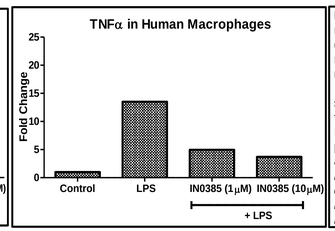


Figure 4. TNFα in mouse bone-marrow derived macrophages (BMDM) and human macrophages. BMDM/human macrophages were treated with IN0385 for 1h and were stimulated with LPS (1000 ng/ml) for 2 h (mRNA or 4 h (cytokine). Real-time PCR and ELISA was performed to determine mRNA and cytokine levels respectively. ***IN0385 inhibited the gene expression and cytokine levels in mouse BMDM and human Macrophages respectively.***

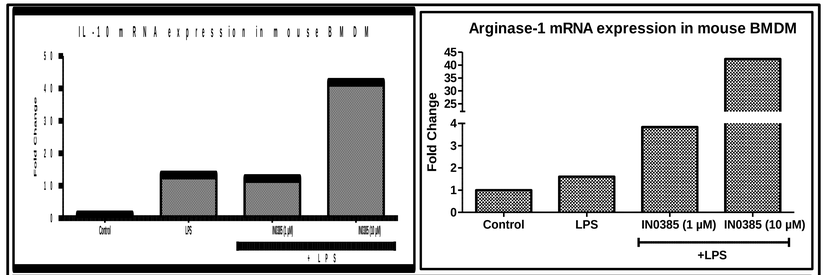


Figure 5. LPS induced gene expression in mouse bone-marrow derived macrophages (BMDM). BMDM cells were treated with IN0385 for 1 h followed by LPS (1000 ng/ml) stimulation for 2 h. mRNA was collected and Real-time PCR was performed. ***IN0385 caused a multi-fold stimulation of IL-10 and arginase-1 mRNA expression in mouse BMDM.***

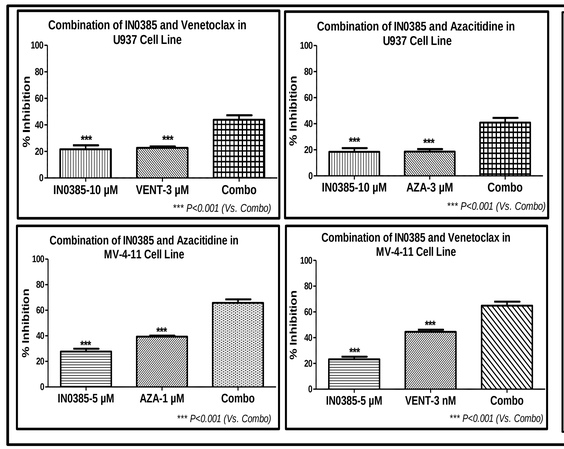


Figure 6. Combination of IN0385 and Azacitidine or Venetoclax in THP-1,U937,MV-4-11 cells. AML cell lines were plated in complete media at pre-determined density in 96-well plates and cells were simultaneously treated with IN0385 and Azacitidine (AZA) or Venetolcax (VENT) for 72 hours. Tukey's multiple comparison was performed using GraphPad prism (5.0) to determine the effect of combination. ***Addition of IN0385 potentiated Azacitidine and Venetoclax activity manifested by a significant (P<0.05) growth inhibition when compared to the activity of the individual agents***

Summary & Conclusions

- Phase-2 trials of Tenalisib continue to demonstrate impressive efficacy in TCL and CLL by virtue of its activity against the PI3K δ and γ isoform.
- Tenalisib is significantly metabolized to IN0385, a potent inhibitor of SIK-3, with immune-modulatory activity that include effects on IL-10, arginase-1 and TNFα in BMDM
- Addition of IN0385 led to significant potentiation in activity of approved/standard of care drugs in AML cell lines *in vitro*
- The added influence of IN0385 on SIK-3 could potentially augment the activity of Tenalisib in aggressive cancers such as leukemias and solid tumors.

25th Congress of the European Hematology Association (EHA25 Virtual)

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