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**LEUVEN**

**Abstract# 4692**

# Efficacy of IPI-504 “a novel inhibitor of heat shock protein 90” in a preclinical mouse model of gastro intestinal stromal tumor (GIST)



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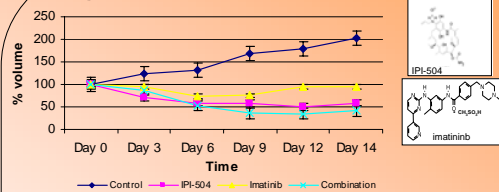
### Background:

The inhibition of the chaperone heat shock protein 90 (Hsp90) by the Hsp90 inhibitor IPI-504 has emerged as an appealing strategy in the treatment of advanced GISTs. IPI-504 is an IV-administered water soluble Hsp90-inhibitor that has recently entered a phase III registration trial in GIST. In this study, we assessed the therapeutic potential of IPI-504 in imatinib-sensitive GIST xenografts, alone or in combination with imatinib.

### Material and Methods:

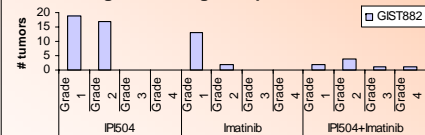
Human GIST882 cells with a *KIT* exon 13 mutation were grafted bilaterally in 43 nude mice. Animals were randomized to four groups: A (n=13; control), B (n=18; IPI-504 100 mg/kg 3x/week p.o.), C (n=8; imatinib 50 mg/kg 2x/day p.o) and D (n=4; combination IPI-504/imatinib, same dose/schedule as above). Treatment lasted for 15 days. Histopathological assessment was done by H&E and KIT immunostaining. Histologic response (HR) was graded based on the magnitude of necrosis, myxoid degeneration, or fibrosis as: grade 1 (0-10%), 2 (10-50%), 3 (50-90%), and 4 (>90%) respectively. The expression and activation of KIT and its signaling cascade was assessed by Western blot.

**Fig.:1 tumor volume assessment**



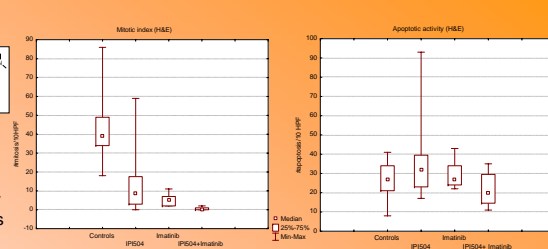
IPI-504 given as a single agent significantly reduced tumor volume (41%) at day 14. This reduction was further enhanced by the combination of IPI-504 and imatinib (58% reduction), whereas imatinib alone led to only a 5% reduction in tumor volume.

**Fig.:2 Histologic response**



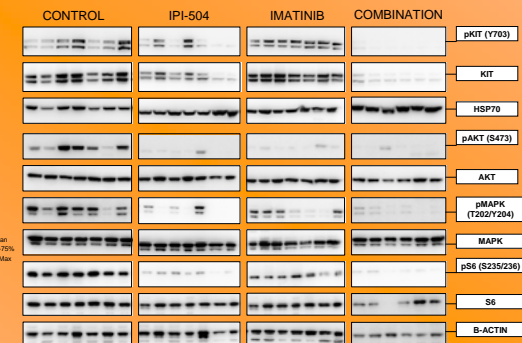
IPI-504 induced grade 2-HR in nearly half (17 out of 36) of the tumors, whereas under imatinib treatment the majority of tumors (n=13) showed 1-HR, with only two 2HR. Grade 3/4-HRs were only seen in the combination arm.

**Fig.:3 Mitotic and apoptotic activity**



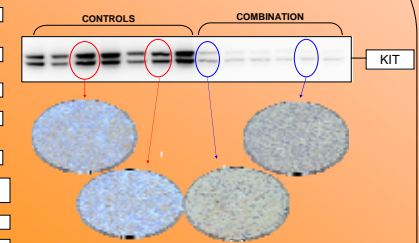
Mitotic activity (as measured by H&E) decreased 3.3 fold in the IPI-504 arm, and apoptosis (as measured by H&E) increased 1.3 fold. Despite the substantial reduction in mitotic activity for groups C (imatinib) and D (combination) (8.2- and 82-fold, respectively), apoptotic activity was virtually unaffected in both groups.

**Fig.:4 Western blot analyses**



In the IPI-504 arm, KIT levels were partially downregulated. Imatinib treatment alone had no effect on KIT protein levels; however, the combination IPI-504 and imatinib produced a marked suppression of total KIT protein, which was accompanied by complete downregulation of the KIT signaling pathway. Although KIT was not completely degraded with IPI-504 treatment, measurable effects on the phosphorylation levels of AKT, S6 and MAPK were observed.

**Fig.:5 Total KIT expression**



Loss of KIT protein expression in the combination arm (as shown by the Western immunoblot) was confirmed by immunostaining.

### Conclusions:

**IPI-504 treatment has considerable effects on GIST xenografts resulting in tumor shrinkage, necrosis and myxoid degeneration. The combination of IPI-504 with a low dose of imatinib results in enhanced/additive anti-tumor activity in imatinib-sensitive GIST xenografts. These results provide a strong rationale for exploring IPI-504 in the clinical setting of GIST as single agent and in combination with tyrosine kinase inhibitors.**