INTRODUCTION

AT13387 inhibits growth of imatinib-sensitive and -resistant GIST xenografts

Tolerability of AT13387 and imatinib

GIST430 tumor growth study

Liver H&E

Histology of GIST430 xenograft

SUMMARY AND CONCLUSIONS

The HSP90 inhibitor, AT13387, demonstrates potent anti-tumor activity in both imatinib-sensitive and -resistant gastrointestinal stromal tumor models

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INTRODUCTION

Activating mutations in the receptor tyrosine kinase, KIT, are found in the majority of gastrointestinal stromal tumors (GIST) and further secondary resistance mutations in KIT frequently arise upon treatment with tyrosine kinase inhibitors such as imatinib. KIT and its mutant forms are clients of HSP90 and it has been suggested that HSP90 inhibition might be a valuable treatment option for GIST, which would be equally effective on imatinib-sensitive and -resistant clones that may coexist within a patient.

AT13387 is a fragment-derived, potent HSP90 inhibitor, which is currently being tested in clinical trials. To evaluate its anti-tumor activity against GIST, AT13387 was tested in both imatinib-sensitive (GIST882, GIST-PSW) and -resistant (GIST430, GIST48) in vitro and in vivo GIST models.

AT13387 inhibits growth of imatinib-sensitive and -resistant GIST xenografts in vivo

Anti-tumor activity of AT13387 and imatinib as single-agents and in combination against imatinib-sensitive and -resistant GIST xenografts.

Effects of AT13387 and imatinib combination therapy on KIT signaling in imatinib-sensitive (GIST882) and -resistant (GIST430) xenografts.

Histological analysis from animals treated with AT13387, imatinib and combination therapy (top). No signs of necrosis were observed in H&E-stained livers of the animals at the end of tumor growth study (bottom).

T tolerability of AT13387 and imatinib combination

AT13387 has significant anti-tumor activity against imatinib-sensitive and -resistant GIST xenografts.

The combination of imatinib and AT13387 was well tolerated and no histological signs of hepatotoxicity were observed in these mouse preclinical models.

These data strongly support the clinical testing of AT13387 as monotherapy and in combination with tyrosine kinase inhibitors in GIST.

AT13387 is currently being evaluated in combination with imatinib in a Phase II trial in GIST (NCT01254202).