

Final results from a Phase III study of IPI-504 (retaspimycin hydrochloride) versus placebo in patients (pts) with gastrointestinal stromal tumors (GIST) following failure of tyrosine kinase inhibitor (TKI) therapies

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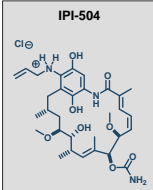


Abstract

IPI-504, a novel Hsp90 chaperone inhibitor, demonstrated activity in a phase I trial of pts with advanced GIST who had progressed after treatment with imatinib and/or sunitinib, with a progression-free survival (PFS) of 12 weeks and an overall response rate of 3%. Based upon these data, a phase III study of IPI-504 in this pt population was conducted. **Methods:** The primary aim of this randomized, placebo-controlled, international trial was to evaluate the efficacy of IPI-504 in pts with metastatic and/or unresectable GIST following failure of at least imatinib and sunitinib. Any number of prior regimens was allowed. The primary efficacy assessment was PFS. Pts were randomized to receive IPI-504 (400 mg/m²) or placebo in 21-day cycles as a 30-minute intravenous infusion twice weekly for 2 weeks followed by a 1-week rest, then resume the cycle. Cross-over to the IPI-504 arm was allowed after central determination of progression. **Results:** 47 of the projected 195 patients were enrolled. Median age was 59 yrs (± 12.4 yrs) and median number of yrs since diagnosis was 5.3 yrs (± 2.5 yrs) with 68% male. 62% had ≥ 3 prior treatments, 98% had prior surgeries, and 19% had prior liver resections. The trial was terminated early due to the occurrence of a on-treatment deaths in the IPI-504 arm. These deaths were considered drug-related and included renal failure, liver failure, metabolic acidosis, and cardiopulmonary arrest. Grade 3 or 4 AST or ALT abnormalities were present in 3 of the 4 deaths. Full unblinded analysis of all data is in progress. **Conclusions:** This study represents the first placebo-controlled randomized trial in patients with GIST who had progressed while receiving at least two prior TKI therapies. In this heavily pretreated pt population, IPI-504 was not well tolerated at this dose and schedule, and the study was terminated early. Complete unblinded safety and efficacy analyses will be available in January. IPI-504 continues to be evaluated at lower doses and alternative schedules in other clinical trials for patients with other forms of cancer.

Background

Hsp90 is a protein chaperone responsible for the proper folding, function, and stability of various oncoproteins. In GIST, activation mutations of PDGF and c-KIT play a role in progression. >90% of tumors have activating mutations in the c-KIT or PDGFRα receptor tyrosine kinases.



IPI-504 is a potent, water soluble Hsp90 chaperone inhibitor.

A trial of IPI-504 at 400 mg/m² BW 2 weeks on/1 week off in 37 patients with advanced GIST who had failed prior imatinib and/or sunitinib resulted in a disease control rate of 70% at 6 weeks (3% PR, 67% SD) and progression-free survival (PFS) of 12 weeks (Wagner et al., ASCO Annual Meeting, 2008).

Based on these data, a Phase III study of IPI-504 in this patient population was conducted.

IPI-504-06 Study Design

Study stopped early after 47 patients were enrolled due to a higher mortality rate among patients in the treatment arm compared to the placebo arm

