PROOF 302: A randomized, double-blind, placebo-controlled, phase III trial of infigratinib as adjuvant therapy in patients with invasive urothelial carcinoma harboring susceptible FGFR3 alterations


Objectives

- Determine if treatment with infigratinib in a phase III trial reduces disease-free survival (DFS) compared with placebo in patients with invasive urothelial carcinoma with suscep-tible FGFR3 alterations after nephroureterectomy, distal ureterectomy, or cystectomy.
- Explore whether infigratinib or placebo treatment reduces overall survival (OS).
- Characterize safety and tolerability of infigratinib or placebo treatment in patients with invasive urothelial carcinoma with susceptible FGFR3 alterations.
- Characterize for safety and tolerability of infigratinib administered as prophylactic adjuvant monotherapy.
- Explore the safety and tolerability of infigratinib in patients treated with infigratinib or placebo.

Endpoints

- Primary endpoint: DFS (assessed centrally; blinded to treatment arm).
- Secondary endpoints:
  - OS
  - MFS
  - Safety / tolerability
  - Exploratory endpoints

Study population

- Inclusion criteria:
  1. Presence of positive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy.
  2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for non-Muscle Invasive Bladder Cancer (NMIBC) within the previous 30 days.

- Exclusion criteria:
  1. Have current evidence of diabetes mellitus (e.g., active diabetes, uncontrolled ketosis, microvascular complications).
  2. Have current evidence of any concomitant disease that may significantly affect the absorption of oral infigratinib.

Pharmacokinetic (PK) and pharmacodynamic (PD) analyses

- Infigratinib is metabolized by CYP3A4 and is an inducer of CYP3A4. Inhibition of CYP3A4 by infigratinib is dose dependent.
- Infigratinib is a substrate for P-glycoprotein (P-gp) and bcl-2.

Planned sample size statistics

- Initial, 218 patients are planned to be enrolled at ≥120 sites in 9 countries.
- The sample size will provide approximately 80% power to detect a difference in disease recurrence rate at the 3-year mark between the two treatment groups.
- The required initial sample size is designed to assess 70 centrally reviewed DFS events, assuming a 5-year uniform enrollment, 1 year follow-up, 10% yearly drop-out rate, and a hazard ratio (HR) of 0.5.

Current status

- The study was initiated in late 2019.
- The first patient will be enrolled in early 2020 and the last patient is expected to complete treatment in late 2024.

PROOF 302 study design

- Multicenter, double-blind, randomized, placebo-controlled Phase 3 study to evaluate efficacy of infigratinib as adjuvant therapy for patients with invasive urothelial carcinoma with susceptible FGFR3 genetic alterations.
- Eligible patients: adults with high-risk invasive UBC with or without metastatic disease at diagnosis. Patients with metastatic disease at diagnosis are eligible if they have had disease recurrence and are ineligible for additional chemotherapy.

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