A prospective, randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC in patients with advanced or metastatic gastric cancer: the ANGEL study

Background

Apatinib and Gastric Cancer

- Vascular endothelial growth factor receptor-2 (VEGFR-2) signaling plays a pivotal role in solid tumor angiogenesis. Many clinical studies have demonstrated that selective inhibition of VEGFR-2 can limit tumor growth and disease progression, resulting in improved overall survival in gastric cancer (GC).
- Apatinib is an orally administered, highly selective tyrosine kinase inhibitor of VEGFR-2 that has been studied in many clinical trials, primarily in China, treating various solid tumors.
- Phase 1 and 2 studies of apatinib outside of China reported the first experience of apatinib in Caucasian patients and supported further investigation in GC and other solid tumors. Apatinib was well tolerated with manageable toxicities.
- Apatinib was approved in China in 2014 for the treatment of advanced GC (apatinib vs. placebo HR=0.709; P=0.0156).
- This multinational, placebo-controlled, phase 3 study investigates the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC (2:1) in previously treated advanced GC patients in North America, Europe, and Asia Pacific. This is the first randomized, placebo-controlled study of apatinib outside of China.

Study Design

Figure 1. ANGEL Trial—Design

Patients with previously treated advanced or metastatic GC

Randomization (2:1)

Apatinib 700 mg daily 28-day cycles

Placebo daily 28-day cycles

BSC

Geographic region

Disease measurability

Prior ramucirumab

Line of treatment (3rd or 4th)

Stratification Factors

Dose reduction permitted each cycle to reduce/resolve AEs

Dose adjustments during entire study

Apatinib 700 mg daily

Apatinib 600 mg daily

Apatinib 400 mg daily

Dose reductions permitted

Apatinib 700 mg to 600 mg

Apatinib 600 mg to 400 mg

Dose re-escalation allowed if AEs resolve

Patients may continue study treatment blinded beyond disease progression if the investigator believes they are receiving clinical benefit from treatment

Total study duration: approximately 18 months.

Study start date: February 2017.

Eligible patients are randomly assigned to apatinib or matched placebo at a 2:1 ratio. All patients will receive best supportive care (BSC). BSC is defined as palliative non-cancer therapy given at the investigator’s discretion.

Patients will be treated until disease progression, intolerable toxicity, or withdrawal of consent. However, when the investigator assesses that further treatment would be tolerable and beneficial, the patient can continue blinded treatment.

All patients will be followed after randomization until data analysis is performed and then monitored for survival status thereafter.

Figure 2. ANGEL Trial—Dose Adjustment Scheme

Statistical Assumptions and Analysis

Sample Size

459

Randomization

2:1 (apatinib:placebo)

Primary Endpoint

Overall survival

Power

80%

alpha

two-sided 0.05

Hazard Ratio Assumption

HR = 0.72

6.53 vs. 4.70 months

Assumed Drop-Out Rate

10%

Events Needed

325

Duration

18 months

- The primary analysis of OS will be conducted in the intention-to-treat population using a stratified log-rank test.
- If the primary analysis of OS is statistically significant, then PFS and ORR will be analyzed using a fixed-sequence testing procedure.
- All other secondary efficacy endpoints will be analyzed using two-sided tests at alpha = 0.05 level of significance.
- An interim analysis for futility will be conducted with collected clinical data when approximately 162 events (approximately 50% of the required 325 events) are observed.

References


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Contact Information

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