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

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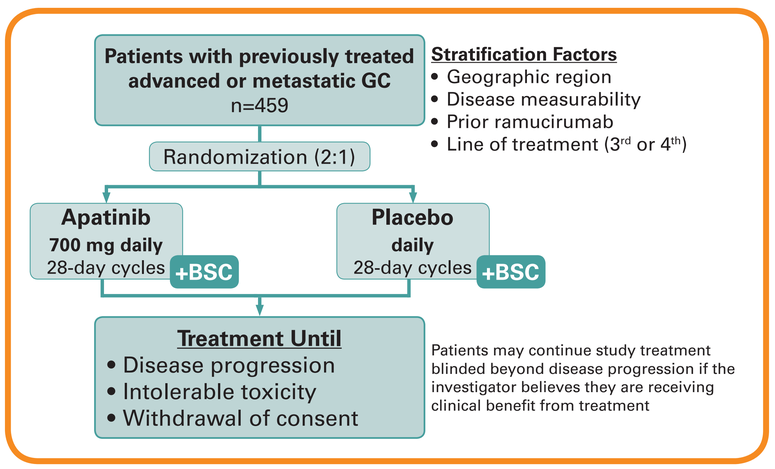
Background

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).[1]
- 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.[2,3]
- Apatinib was approved in China in 2014 for the treatment of advanced GC (apatinib vs. placebo HR=0.709; P=0.0156).[4]
- 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



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.

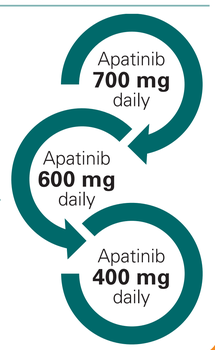
Figure 2. ANGEL Trial—Dose Adjustment Scheme

Dose reduction permitted each cycle to reduce/resolve AEs

- Dose reductions permitted
  - Apatinib 700 mg to 600 mg
  - Apatinib 600 mg to 400 mg
- Dose re-escalation allowed if AEs resolve

Dose adjustment during entire study

- Up to two dose reductions permitted
- Dose reduction <400 mg not allowed



Study Objectives

Primary Objectives

To compare the overal survival (OS) of patients assigned to apatinib versus placebo.

Secondary Objectives

- Progression free survival (PFS).
- Objective response rate (ORR).
- Disease control rate (DCR).
- Quality of life (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D-5L).
- Pharmacodynamic markers (VEGF, sVEGFR-1, sVEGFR-2, sVEGFR-3).
- Pharmacokinetics (AUC, C_{trough}).
- Safety:
  - Adverse events
  - Laboratory tests
  - Vital signs
  - Physical examination
  - 12-lead ECG
  - ECOG performance status.

Major Inclusion Criteria

- Locally advanced, unresectable, or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.
- Disease progression within 6 months after last treatment.
- Failure or intolerance to 2 prior lines of standard chemotherapies for unresectable or metastatic GC with each containing at least one of the following agents: fluoropyrimidine, platinum, taxanes or epirubicin, irinotecan, trastuzumab in case of HER2-positive disease, ramucirumab.
- ≥1 measurable or non-measurable but evaluable lesions per RECIST 1.1.
- Adequate bone-marrow, renal, and liver function.
- ECOG performance status of 0 or 1.
- Expected survival of ≥12 weeks.

Major Exclusion Criteria

- Malignancies other than gastric or GEJ adenocarcinoma (including hematologic malignancies) within 2 years. Subjects with following malignancies, as long as they do not post a significant risk to life expectancy, are eligible:
  - Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma *in situ* (Tis)
  - Curatively treated cervical carcinoma *in situ*
  - Thyroid papillary cancer with prior treatment
  - Carcinoma of the skin without melanomatous features
  - Prostate cancer which has been surgically or medically treated and not likely to recur within 2 years.
- CNS metastases as shown by radiology records or clinical evidence of symptomatic CNS involvement within 3 months.
- Other targeted, cytotoxic, or immunotherapy within 3 weeks (4 weeks for ramucirumab, mitomycin C, or lomustine), surgery within 3 weeks, adjuvant radiotherapy within 2 weeks, or biopsy within 1 week.
- History of severe adverse events that were related to ramucirumab requiring discontinuation and indicating higher risk with further anti-angiogenesis treatment.
- History of uncontrolled hypertension.
- Prior major surgery or presence of any non-healing wound ≤3 weeks.
- Ascites with history of therapeutic paracentesis ≤3 months.
- History of significant gastrointestinal ulcerations and/or bleeding ≤3 months.
- Gastrointestinal malabsorption that might affect the absorption of the study drug.
- Known clinically significant thrombosis within 3 months.
- Known clinically significant cardiac, cardiovascular, and renal history.
- Known history of HIV infection or active or uncontrolled chronic hepatitis B or C infection.
- Active bacterial infection.
- Previous treatment with apatinib.

Figure 3. ANGEL Trial—Participating Countries

Enrollment Opened
February, 2017

Current Enrollment
44 patients

Total Study Countries
12 countries

Total Study Sites
95 sites

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 163 events (approximately 50% of the required 325 events) are observed.

References

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Contact Information

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