JAGUAR: A Randomized Phase II Study of the Akt inhibitor Ipatasertib (GDC-0068) versus Placebo in Combination with mFOLFOX6 Chemotherapy in Patients with Locally Advanced or Metastatic HER2-Negative Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

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BACKGROUND

Activation of PI3K/Akt Signaling in Gastric and GEJ Cancers
- Gastric and GEJ cancers are the second leading cause of cancer death worldwide, and about 80% of patients with HER2-negative gastric cancers have no effective targeted agent
- Activation of PI3K/Akt signaling may occur in > 60% of gastric/GEJ cancers by decreased PTEN expression (Figure 1) and/or PI3KCA mutation/amplification (Ingalla et al. 2013), which may lead to enhanced gastric cancer survival and chemoresistance

PTEN loss may be prognostic; patients with resected gastric cancers with PTEN loss may have decreased overall survival (OS) (Lee et al. 2003)

Inhibition of PI3K/Akt Signaling in Gastric Cancer with Ipatasertib Combined with Chemotherapy
- Ipatasertib (GDC-0068) is a potent and selective ATP-competitive small molecule inhibitor of all three isoforms of Akt
- Single-agent ipatasertib is well-tolerated at the maximum tolerated dose (MTD) of 600 mg oral (PO) daily (QD) for 21 days on/7 days off, with down-regulation of Akt signaling at doses ≥ 100 mg
- In gastric cancer xenografts, the combination of ipatasertib with fluorouracil (5-FU) and platinum chemotherapy leads to synergistic responses (Ingalla et al. 2013)
- In a Phase Ib study, ipatasertib at the recommended Phase II dose of 600 mg PO QD for 7 days on with 7 days off was well-tolerated with mFOLFOX6 chemotherapy (Meng et al. 2012)

STUDY DESIGN

- JAGUAR is a randomized, placebo-controlled, double-blind, global Phase II study for patients with untreated, locally advanced or metastatic HER2-negative gastric/GEJ adenocarcinoma (Figure 2)
- JAGUAR will evaluate the safety, tolerability, and clinical efficacy of ipatasertib combined with mFOLFOX6 versus placebo with mFOLFOX6

Study Endpoints
- Primary Endpoint: Progression-free survival (PFS) in all patients and in patients with PTEN low tumors
- Secondary Endpoints: OS, objective response rate (ORR), and duration of response

Key Inclusion Criteria
- Age ≥ 18 years
- Histologically documented, inoperable or metastatic or recurrent gastric/GEJ adenocarcinoma
- Adequate archival or newly obtained fresh tissue samples
- Measurable disease by RECIST version 1.1

Key Exclusion Criteria
- Previous chemotherapy for gastric/GEJ adenocarcinoma, although prior neoadjuvant or adjuvant chemotherapy is allowed, if completed ≥ 6 months prior to randomization
- Known HER2-positive gastric/GEJ adenocarcinoma, defined as IHC 3+ or IHC 2+ in combination with in-situ hybridization (ISH) positivity
- Previous therapy with Akt, PI3K, and/or mTOR inhibitors
- Major surgery within 28 days of randomization

Stratification Factors
- Adjuvant treatment (yes vs. no)
- Geographic location (Asia vs. United States vs. Europe)
- PTEN status of tumor (low/null vs. moderate vs. normal)

Study Treatment
- Patients will be randomized (1:1) to receive mFOLFOX6 plus ipatasertib (600 mg) or mFOLFOX6 plus placebo (Figure 3)
- All patients will receive mFOLFOX6 on Day 1 and blinded ipatasertib or placebo (600 mg PO QD on Days 1-7), of each 14-day cycle (Figure 3)
- Following 8 cycles, patients will discontinue oxaliplatin but will continue chemotherapy with ipatasertib/placebo, until disease progression or discontinuation due to toxicity
- Tumor evaluation by RECIST v1.1 with CT scans every 4 cycles

Study Statistical Methods
- Primary and secondary efficacy analyses will include all randomized patients, grouped by treatment at randomization
- Kaplan–Meier curves will be produced for analyses of PFS, OS, and duration of objective tumor response, and Log-rank tests will compare treatments. Hazard ratio estimates and 90% CI will be produced for each treatment comparison from Cox proportional hazards model.
- Confirmed tumor response rate, with 90% CI, will be evaluated and compared by categorical analyses

PREDICTIVE BIOMARKERS
- This study will try to define a biomarker of sensitivity to the combination of ipatasertib and mFOLFOX6
- The lead biomarker for ipatasertib is evaluation of PTEN by IHC

SUMMARY
- There is robust scientific rationale to inhibit PI3K/Akt signaling with ipatasertib combined with mFOLFOX6 in metastatic gastric/GEJ cancer
- This global Phase II study will evaluate safety and efficacy of ipatasertib with mFOLFOX6
- The study is currently enrolling up to about 120 patients worldwide

REFERENCES

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