#39P EFFECT OF DOSE LEVEL OF THE SELECTIVE FGFR2 INHIBITOR ALOFANIB ON TOXICITY, PHARMACOKINETICS AND PRELIMINARY EFFICACY: A PHASE 1B STUDY IN PATIENTS WITH ADVANCED GASTRIC CANCER (RPT835GC1B)

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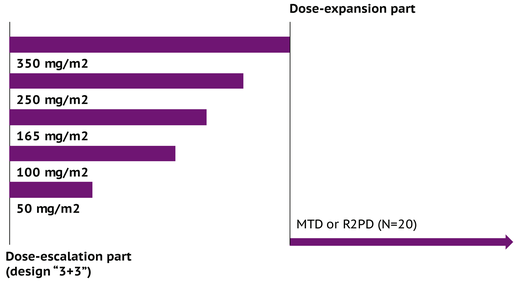
BACKGROUND

- Fibroblast growth factor receptor 2 (FGFR2) molecular changes was observed in gastric cancer at a frequency of 4-15% and associated with shorter progression-free survival and overall survival.
- Acquired mutations in FGFR2 develop resistance to multikinase inhibitors
- Besides, resistance to monoclonal antibodies depends on the type of FGFR2 isoforms IIIc or IIIb expressed by cancer cells.
- Alofanib (RPT835) is a novel selective inhibitor that binds allosterically to the extracellular domain of FGFR2.

TRIAL DESIGN

- RPT835GC1B is a Phase 1b study, evaluating the safety and preliminary efficacy of alofanib in patients with advanced and metastatic gastric adenocarcinoma pretreated with ≥ 1 previous lines of therapy



This trial consists of two parts:

- The **standard dose-escalation part** (design 3+3) aims to establish the maximum tolerated dose (MTD) or recommended phase 2 dose (R2PD).
- The first part of the study includes a 28-day period when alofanib is administered daily intravenously for 5-days followed by a 2-day interval (rest).
- There are five dose levels: 50, 100, 165, 250, and 350 mg/m2.
- The **dose-expansion phase** accrues additional 20 patients, where comprehensive information to be collected.

ENDPOINTS

- **Primary endpoint:**

- maximum tolerated dose (MTD)
or recommended phase 2 dose (R2PD)

- **Secondary endpoints:**

- rate of adverse events
- pharmacokinetic parameters
- overall survival
- progression-free survival
- objective response rate
- FGFR2 amplification and overexpression

KEY INCLUSION CRITERIA

- Histologically confirmed gastric cancer (adenocarcinoma)
- Progression of the disease (clinical and/or radiological) on previous standard systemic therapy
- Measurable lesions according to the RECIST 1.1 criteria
- Possibility to assess the FGFR2 amplification or overexpression
- ECOG PS 0-2
- Age >= 18 years old
- Adequate function of organs
- Signed Informed Consent

PATIENT CHARACTERISTICS

- Predominantly male (85%)
- 54% patients had 2 and more metastatic sites, including liver metastases (54%)
- Patients were heavily pretreated (60% received previous 3-6 lines of therapy)
- The median time from diagnosis of gastric cancer to study treatment was 28.5 months

Number of previous lines:

1 line – 3 (30%)
2 lines – 1 (10%)
3 lines – 2 (30%)
4 lines – 1 (10%)
5 lines – 1 (10%)
6 lines – 1 (10%)

MTD AND TOXICITY

- The MTD was not reached (to date, 13 patients were evaluated).
- Grade 3–4 adverse events (related to alofanib) occurred in 3 (23%) patients
- 93% of patients had any grade adverse events
- One patient discontinued treatment due to grade 3 uncontrolled diarrhea.

HEMATOLOGICAL TOXICITY

ADVERSE EVENT	GRADE	N (%)
Hyperphosphatemia	1	3 (25)
Anaemia	1	3 (23)
Thrombocytopenia	1	3 (23)
Hypophosphatemia	1	2 (17)
Increased alkaline phosphatase levels	1 and 2	2 (15)
Leukopenia	2	1 (8)
Neutropenia	2	1 (8)
Increased aspartate aminotransferase concentration	3	1 (8)
Increased alanine aminotransferase concentration	3	1 (8)
Increased bilirubin levels	1	1 (8)
Hypoproteinemia	1	1 (8)
Increased potassium levels	1	1 (8)
Increased sodium levels	1	1 (8)
Decreased sodium levels	3	1 (8)

OTHER NON-TREATMENT-RELATED ADVERSE EFFECTS

ADVERSE EVENT	GRADE (N)
Catheter-associated infection	3 (1) 2 (1)
Secondary generalized seizures	3 (1)
Pain at the site of the intravenous injection	1 (1)
Weight loss	1 (1)
Bacterial pneumonia	5 (1)
Hypertension	2 (1)

GENERAL DISORDERS AND ADMINISTRATION CONDITIONS

ADVERSE EVENT	GRADE (N)	N (%)
Fatigue	1 (2) 2 (2)	3 (23)
Infusion related reaction (facial flushing, dizziness, weakness, sweating, and sinus tachycardia)	3 (1)	3 (23)
Diarrhea	3 (1) 2 (1)	2 (15)
Nausea	2 (1) 1 (1)	2 (15)
Numbness of fingers	1 (1)	1 (8)
Rash	1 (1)	1 (8)
Hoarse voice	1 (1)	1 (8)

OBJECTIVE RESPONSE RATE

- Disease control rate was 75%

	N (%)
Patients with baseline assessment	12 (100)
Patients with measurable disease at baseline	12 (100)
Partial response	1 (8.3)
Stable disease	8 (66.7)
Progressive disease	3 (25)
Disease control rate	9 (75)

- After a median follow-up of 4.5 months, the median progression-free survival and overall survival was not reached.

PHARMAKOKINETICS

- PK parameters have increased with dose.
- PK values (Cmax, AUC, and t1/2) did not correlate with response, progression-free survival and overall survival (all P > 0.1).

CONCLUSIONS

- In conclusion, dosing up to 350 mg/m2 of alofanib was well tolerated, DLT and MTD were not reached.
- The early biologic activity of alofanib in the late-line treatment of metastatic gastric cancer is encouraging.
- This activity will allow to terminate study early after inclusion of additional 3 patients in the expanded cohort.