Ramucirumab beyond progression plus TAS 102 in patients with advanced or metastatic adenocarcinoma of the stomach or the gastroesophageal junction, after treatment failure on a ramucirumab based therapy – final results of the phase II RE-ExPEL study

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Background

- Ramucirumab is a proven and approved treatment option in patients with advanced gastric carcinoma, both as monotherapy and in combination with paclitaxel in 2nd line. According to the TAGS phase III study, TAS-102 showed an optimized median OS in the TAS-102 arm compared to the placebo arm in heavily pre-treated patients with gastric carcinoma or adenocarcinoma of the gastroesophageal junction.
- The RE-ExPEL trial investigated a safe and efficacious administration of a combination of TAS-102 and ramucirumab in patients with gastric carcinoma beyond progression, since VEGF/R blockade appears to be effective and very well tolerated in the posterior lines, in monotherapy as well in the combination therapies.
- Based on results of prior trials (TAGS, REGARD, RAINBOW), it seems promising to combine Ramucirumab (Ram) beyond progression (PD) with TAS-102 (trifluorlated/trifluritide). The purpose of RE-ExPEL is to investigate the tolerability, safety and benefit of Ram beyond PD in combination with TAS-102 in advanced esophagogastric adenocarcinoma (EGA).

Methods

- This is a multicenter, non-randomized, open-label investigator initiated pilot trial.
- 20 Ram-pretreated patients (pts) with advanced EGA were enrolled to a maximum of 4 cycles of ram 8mg/kg every 2 weeks (days 1, 15 q28) plus TAS-102 35 mg/m2/p.o. bid (d15 and d8-12 q28). Study treatment was continued until progression or intolerable toxicity for a max. of 4 cycles (Fig. 1. 2).
- During treatment, clinical visits (blood cell counts, detection of toxicity) were scheduled prior to every treatment at d1 and d15.
- Safety assessment included physical examinations, vital signs, performance status (ECOG), clinical laboratory profile, 12-lead ECG and continuous assessments of adverse events. Observed toxicities and side effects were graded according to NCI CTCAE v5.0. Treatment-related AEs and SAEs have been determined.
- Tumor assessments were scheduled according to clinical routine at screening and every 8 weeks (±7 days) during the treatment phase of the study and every 12 weeks (±14 days) during follow-up.
- A safety evaluation was planned when the last patient has received at least two cycles of study treatment or prematurely discontinued the study (EOT for any reason). Results of this evaluation were reviewed by the lead coordinating investigator, deputy lead coordinating investigator, members of the steering committee and by the safety monitoring board.
- The final analysis was planned when the last patient reached EOT + 30 days of follow-up and all patients were fully documented. The primary endpoint was statistically evaluated to determine if the increase of SAE rate is ≤ 30% compared to the TAS-102 group of the TAGS trial and thus whether the concept of combining TAS-102 and ramucirumab proofs to be valid and safe.

Endpoints

- Primary endpoint was tolerability and toxicity, defining a positive trial if SAE rate according to CTCAE v5.0 will increase less than 30% (up to 55%) compared with results from the TAGS trial (SAE-rate 43%).
- Secondary endpoints were further safety and efficacy data (PFS, OS, ORR).

Results

- The main conclusion of the trial was based on the predefined IIT population (20 pts).
- 20 pts were enrolled between Oct 2020 and Aug 2021 (Fig. 3).
- The median age of the patients was 56.5 years, and the majority of patients were male (80%). 20% gastric and 80% GEJ cancers, 55% of pts with ECOG 0. 90% of pts got study treatment in 3rd line whereas 10% were even further line pts.
- 25% of pts had at least one SAE and the total no. of SAEs was 9 (Tab. 2), one with fatal outcome, all without relation to systemic therapy. No SUSAR was reported.
- Median PFS was 2.04 months (Fig. 4).
- The overall median OS time was 9.07 months (95% CI [5.42,10.09]), based on 13 (65%) observed events (Fig. 4).
- The overall 3-months, 6-months and 9-months survival rate was 95%, 74% and 52%, respectively and the trial shows a DCR of 45%.

Conclusions

- The safety data showed a favorable safety profile with a low rate of severe toxicity for ram+TAS-102, maybe due to the long disease stabilization and therefore less tumor associated symptoms. Regarding the primary safety endpoint, the trial was positive with even a numerically lower SAE rate compared with TAGS.
- The combination seems to be more effective than TAS-102 alone according to TAGS-trial respecting the limitation of the one arm study design with only 20pts.
- The combination needs further evaluation in a randomized phase III trial.

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Table 1: Baseline Characteristics

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Table 2: Summary Serious Adverse Events (SAEs)

Fig. 1: Trial Design

Fig. 2: Recruitment

Fig. 3: Study Design

Fig. 4: Progression-Free (A) and Overall (B) survival in the IIT population

Fig. 5: Treatment Scheme

Fig. 6: Progression-Free and Overall survival in the IIT population