GENOSCIENCE PHARMA

BARCELONA 2019 ESMO congress

Organised by: ESMO In partnership with: EACR

27 SEPT – 1 OCT 2019

Barcelona, Spain

Preliminary Safety and Pharmacokinetics of a New Lysosomotropic Oral Agent, GNS561, in a First-in-Human Study in Advanced Primary Liver Cancer Patients

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Lysosome has been described as target of interest for cancer therapy. GNS561 is a new lysosomotropic small molecule which displays meaningful activity against several tumor types, specifically in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). Herein, we report preliminary results of the Phase 1b/2a study of GNS561 in advanced primary liver cancer patients.

The Phase 1b portion is a non-randomized, one arm (3+3 design) clinical trial with a maximum enrolment of 36 patients. GNS561 was administered orally to histologically confirmed HCC or iCCA adult patients not eligible for curative therapy in 4 week cycles. The objectives are to assess the safety and pharmacokinetics (PK) of GNS561 and to determine the recommended phase 2 dose. Early safety, PD and PK data from patients of the 4 first dose levels are reported.

As of May 2019, 13 patients were enrolled with 10 patients having completed the study with at least one cycle of treatment. Median patient age was 66 years (range 31 - 80), 3 (23%) were female, 6 (46%) had HCC; median number of prior systemic therapies was 1 (range 1-5). Patients received a median number of 2 cycles of GNS561. Six (46%) patients interrupted treatment because of tumor progression, 31% (n=4) for investigator decision, and 7.7% (n=1) for serious adverse event. Thus far, no dose limiting toxicity (DLT), or DLT equivalent toxicity have been observed. Most of related-AEs are digestive toxicities (grade 1-2 nausea, vomiting and diarrhea), fatigue and blood parameters abnormalities. The 400 mg cohort is currently ongoing.

70% (n=7) patients were evaluable for tumor imaging assessment: 43% of them (n=3) were stable at the beginning of Cycle 3, among which 2 patients had stable disease at the beginning of Cycle 5.

Patients showed increasing exposure to GNS561 along with the dose in blood and liver, with dose-proportionality in plasma. Liver concentrations are at least 200 fold higher than in plasma.

Current data show patients that oral GNS561 displays a favorable safety profile, and exposure in blood and liver throughout the dosing interval. Enrollment in Phase 1b is continuing before extension to Phase 2a.

EudraCT 2017-003585-27