P-15 Histology classification highlights the difference in the effectiveness of S-1 over capecitabine when combined with cisplatin in patients with HER2-negative unresectable advanced or recurrent gastric cancer with measurable disease

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Background: As there is no clear preference between S-1 plus cisplatin (SP) and capecitabine plus cisplatin (XP) as first-line therapy for patients with HER2-negative unresectable advanced or recurrent gastric cancer with measurable disease, we performed an integrated analysis of three phase II randomized trials (HERBIS-2, HERBIS-4A, and XParTS II) with the use of individual participant data (IPD) from each trial. The aim of this trial was to investigate any differences in therapeutic efficacy between SP and XP for this subset, by focusing on the differences in histology.

Methods: IPD from three randomized phase II trials were collected where patients received either SP [S-1 (40—60 mg twice daily for 21 days) plus cisplatin (60 mg/m2 on day 8), every 5 weeks] or XP [capecitabine (1000 mg/m2 twice daily for 14 days) plus cisplatin (80 mg/m2 on day 1), every 3 weeks].

Results: Overall, SP (n=79) vs. XP (n=83) showed significantly better overall survival (median OS, 14.2 vs. 11.0 months; hazard ratio [HR], 0.704; P = 0.048) and time to treatment failure (median TTF, 4.7 vs. 3.8 months; HR, 0.664; P= 0.011) and a trend toward better progression-free survival (median PFS, 5.9 vs. 5.1 months; HR, 0.717; P = 0.052), whereas no difference in overall response rate (ORR, 47.5% vs. 50.6%). Despite no difference of ORR by histological classification, the differentiated tumors showed significantly better OS but not PFS or TTF of SP against XP, due to a deeper tumor shrinkage of SP over XPas demonstrated by the fact that cases achieved >60% reduction were significantly more common in SP than in XP (28.2% [11/39] vs. 6.7% [2/30]; P = 0.029, Fisher's exact test). The undifferentiated tumors showed a consistent better trend of OS, PFS and TTF of SP vs. XP, likely as cases without tumor shrinkage tended to be less in SP than XP (2.6% [1/38] vs. 13.0% [6/46]; P=0.121, Fisher's exact test). Our subgroup analysis further identified that a significant benefit of SP vs. XP was found in OS for differentiated tumors with a tumor reduction of 30% or more [SP, 23.7 months (95%CI, 13.2-NA) vs. XP, 11.7 months (95%CI, 7.8-19.6); HR of 0.339 (95 % CI 0.163—0.705), interaction P = 0.003], strongly suggesting that deeper tumor shrinkage by SP vs. XP contributed most to OS in the differentiated tumors.

Conclusions: Our data showed that SP is superior to XP in this setting, but there is a qualitative difference between the effects of SP and XP, which depends on the histological type of the tumor. For the undifferentiated tumors, SP has fewer treatment failures than XP, reflecting better PFS, OS, and TTF in SP than XP. For the differentiated tumors, SP achieves deeper tumor shrinkage than XP, which contributes to longer OS, but not PFS or TTF. Further study is needed to determine whether these differences of S-1 vs.capecitabine are reproduced by the combination of oxaliplatin and immune-checkpoint inhibitors, the new standard of care for HER2-negative unresectable advanced or recurrent gastric cancer.

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P-16 PROOF 301: A multicenter, open-label, randomized, phase 3 trial of infigratinib vs gemcitabine + cisplatin in patients with advanced cholangiocarcinoma with an FGFR2 gene fusion/rearrangement

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Background: First-line treatment options are limited for patients with advanced cholangiocarcinoma (CCA). Genetic alterations in the fibroblast growth factor receptor (FGFR) gene play an important role in CCA. FGFR gene fusions/rearrangements are present in 10—16% of intrahepatic CCA and may predict tumor sensitivity to FGFR inhibitors. Infigratinib (BGJ398) is a potent, orally bioavailable, selective, ATP-competitive, small-molecule tyrosine kinase inhibitor of FGFRs that showed promising clinical activity and a manageable adverse event profile in a phase 2 study in patients with previously treated, unresectable locally advanced/metastatic CCA with an FGFR2 gene fusion/rearrangement. The multicenter, open-label, randomized, controlled phase 3 PROOF 301 trial is evaluating infigratinib vs standard-of-care gemcitabine + cisplatin as first-line treatment for patients with advanced/metastatic or inoperable CCA with an FGFR2 gene fusion/rearrangement.

Trial design: Approximately 300 patients ≥18 years of age with histologically or cytologically confirmed, advanced/metastatic or inoperable CCA with an FGFR2 gene fusion/rearrangement (confirmed by central laboratory) are randomized 2:1 to oral infigratinib 125 mg once daily for the first 21 days of a 28-day treatment cycle vs intravenous standard gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle. Randomization will be stratified by unresectable locally advanced vs metastatic disease, geographic region, prior neo-adjuvant/adjuvant treatment vs none, and receipt of up to 1 cycle of gemcitabine-based chemotherapy for unresectable locally advanced/metastatic disease prior to randomization vs none. Treatment will continue until confirmed progressive disease by blinded independent central review (BICR), intolerance, withdrawal of informed consent, or death. Patients on the gemcitabine + cisplatin arm who develop disease progression (confirmed by BICR) can cross-over to receive infigratinib. The primary endpoint is progression-free survival (PFS; RECIST v1.1; confirmed by BICR). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, best overall response, disease control rate, duration of response (BICR and investigator determined), and the type, frequency, and severity of adverse events (AEs) and serious AEs. PFS after subsequent therapy (PFS2), quality of life, pharmacokinetics and other exploratory genetic alterations/biomarkers will also be evaluated. Trial enrollment is ongoing in the US, EU, and APAC (including Australia). The data monitoring committee last reviewed the trial in December 2021. Clinicaltrials.gov identifier: NCT03773302. The PROOF 301 trial is funded by QED Therapeutics and Helsinn Healthcare SA.

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