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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P-17 Real-life use and long-term effectiveness results from CIREL – the multi-centre, observational study on irinotecan-eluting transarterial chemoembolization in CRLM

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Background: Transarterial chemoembolization (TACE) using irinotecan-eluting beads as a treatment approach for patients with unresectable colorectal cancer liver metastases (CRLM) is finding use beyond treatment guidelines but real-life data from multi-centre studies are lacking. The CIrse REgistry for LifePearl microspheres (CIREL, NCT03086096) is a prospective, Europe-wide, multi-centre, observational study on the real-life clinical outcomes of LifePearlTM microspheres TACE (LP-irinotecan TACE). The study was conducted by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE).

Methods: Eligible patients were adults with CRLM treated with LP-irinotecan TACE and were enrolled between February 2018 and August 2020. Baseline characteristics and treatment-related data were collected. The median follow-up inclusion according to reverse Kaplan-Meier was 19 months (95% CI: 17-23) during which data on overall survival (OS), progression-free survival (PFS), hepatic progression free survival (hPFS) and adverse events (AEs) graded according to CTCAE 4.03 were collected.

Results: 152 patients were enrolled in the study. Median age was 66 years and 39% were female. Eastern Cooperative Oncology Group was 0 in 59%; 1 in 34%; and $\geq$2 7%; liver involvement was 50% in 7% of patients. 84% had progressive disease at baseline. 42% received 1 line, 40% 2 or more lines and 18% no line of previous systemic therapy. 91 (60%) patients experienced 266 adverse events within 24 hours after a TACE session, of which 19 (7%) were grade 3 or higher in 12 (8%) patients. The complete treatment plan was administered in 80% of patients and no treatment-related deaths were reported. The median OS for the whole cohort was 13.0 months (95% CI 10.5-15.0), median hPFS was 6.2 months (95% CI 5.1-6.9) (hPFS rate at 9 months: 29%) and median PFS was 4.7 months (95% CI 3.8-5.3) (PFS rate at 9 months: 13%). We could observe statistically significant differences (p=0.005) in OS for different treatment strategies. When LP-irinotecan TACE was used as a first-line treatment or as consolidation after response to first-line treatment (41, 27%), the median OS was 17 months (95% CI 12.7-23.1). When it was used in combination with ablation (with curative intent) (19, 13%), the median OS was 17.1 (95% CI 10.5-NA). When chemo-refractory patients still eligible for further systemic treatment were treated with LP-irinotecan TACE (41, 27%), the median OS was 10.3 months (95% CI 7.5-14.0). Salvage treatment of chemo-refractory patients not eligible for further systemic treatment (46, 30%) resulted in the smallest median OS of 9.0 months (95% CI 6.8-13.0). For 5 (3%) patients LP-irinotecan TACE was used after response to second-line treatment.

Conclusions: The results from this large prospective multi-centre observational study show that in a real-world context, LP-irinotecan TACE is well tolerated with low occurrences of severe adverse events and patients with CRLM receiving LP-irinotecan have a median overall survival comparable to gold-standard systemic treatment for later lines.

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Legal entity responsible for the study: The authors.

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P-18 Prognostic association between (so over-expression of vascular) of vascular endothelial growth factor receptor and micro-vascular invasion in patients with hepatocellular carcinoma

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Background: Overexpression of vascular endothelial growth factor (VEGF) receptor promotes angiogenesis and vascular invasion in hepatocellular carcinoma (HCC). More strict patient selection for VEGF receptor targeted therapy based on evidence of micro vascular invasion may have prognostic benefit. In the present study, we aimed to investigate prognostic association between over expression of VEGF receptor and micro vascular invasion in patients with HCC.

Methods: We used a web-based gene survival analyzer Kaplan Meier Plotter (KMplotter) to demonstrate association between VEGF receptor expression and long-term outcomes in patients with HCC with and without micro vascular invasion. Overall survival rate was calculated in study cohorts which stratified by median expression level of VEGF (gene probe set 7422).

Results: A total of 293 patients with HCC were selected from an online KM plotter database and number of patients with and without micro vascular invasion were 90 and 209, respectively. The VEGF receptor over expression was significantly associated with increased risk of mortality in patients with micro vascular invasion (HR=2.84, 95% CI 1.30-6.23, p=0.006) (optimal threshold value of 6500) but not in patients without micro vascular invasion (HR=1.55, 95% CI 0.83-2.87, p=0.160) (no optimal threshold value). Furthermore, patients with micro vascular invasion who revealed VEGF receptor overexpression had significantly lower overall survival rate (26 months vs. 83 months, log-rank p=0.006) compared to patients without micro vascular invasion (71 months vs. 85 months, log-rank p=0.160).

Conclusions: VEGF receptor overexpression is associated with significantly lower overall survival rate in patients with HCC who have micro vascular invasion. Non-invasive detection of micro vascular invasion in patients with HCC may allow more strict patient selection for VEGF receptor targeted therapy.

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