Background: TH-302 is a hypoxia targeted prodrug with a hypoxia-triggered 2-nitroimidazole component designed to release the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM), when reduced in severe hypoxia. A randomized Phase IIb study (NCT01144455) was conducted to assess the benefit of G + T to standard dose G as first-line therapy of PAC.

Materials and methods: An open-label multi-center study of two dose levels of TH-302 (240 mg/m² or 340 mg/m²) in combination with G versus G alone (randomized 1:1:1). G (100 mg/m²) and T were administered IV over 30-60 minutes on Days 1, 8 and 15 of a 28-day cycle. Patients on the G could crossover after progression and be randomized to a G + T arm. The primary efficacy endpoint was a comparison of progression-free survival (PFS) between the combination arms and G alone (60% power to detect 50% improvement in PFS with one-sided alpha of 10%). Summary PFS outcome has previously been reported; more detailed PFS as well as the initial overall survival (OS) data are presented.

Results: 214 pts were treated; 164 (77%) Stage IV and 50 (23%) Stage IIIB. Median age 65 (range 29-88); 126 M/88 F; 40% ECOG 0/60% ECOG 1. Receiving 6 or more cycles: 32% G; 45% G + T240; 55% G + T340. Median PFS was 3.6 mo in G vs 2.9 mo in G + T240 (HR 0.81; 95% CI 0.61-1.07, p = 0.117). In the mEOC + P arm, OS was significantly improved compared to those without grade 3 rash (77%, n = 209) on treatment compared to those without grade 3 rash (23%, n = 63); median OS 10.2 vs 4.3 months (p < 0.001), with similar significant improvements seen in RR and PFS. Multivariate analysis demonstrated a negatively significant correlation between rash grade 3 and OS (HR 1.75; 95% CI 1.07-2.90, p = 0.024) and PFS (HR 1.57; 95% CI 1.02-2.40, p = 0.038).

Conclusions: The combination of G plus TH-302 improved the efficacy of G. A TH-302 dose of 340 mg/m² was identified for future studies. Skin and mucosal toxicity and myelosuppression were the most common TH-302 related AEs with no increase in treatment discontinuation.

Disclosure: All authors have declared no conflicts of interest.

References:

2. Oncology, Louisiana State University Health Sciences Center, Shreveport, LA, UNITED STATES OF AMERICA.
3. Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, UNITED STATES OF AMERICA.
4. Oncology, Duke University, Durham, NC, UNITED STATES OF AMERICA.
5. Oncology, Scripps Clinical Medical Group, La Jolla, CA, UNITED STATES OF AMERICA.
6. Oncology, Rocky Mountain Cancer Centers, Denver, CO, UNITED STATES OF AMERICA.
7. Oncology, University of Wisconsin, Madison, WI, UNITED STATES OF AMERICA.
8. Oncology, Institute for Translational Oncology Research, Greenville, SC, UNITED STATES OF AMERICA.
9. Clinical Operations, Threshold Pharmaceuticals, South San Francisco, CA, UNITED STATES OF AMERICA.
10. Oncology, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA.

**Gastrointestinal Tumors, Non-colorectal**

**TH-302 + GEMCITABINE (G + T) VS GEMCITABINE (G) IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED PANCREATIC CANCER (PAC)**


1. Oncology, Mayo Clinic Cancer Center - Arizona, Scottsdale, AZ, UNITED STATES OF AMERICA.
2. Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, UNITED STATES OF AMERICA.
3. Oncology, Duke University, Durham, NC, UNITED STATES OF AMERICA.
4. Oncology, Scripps Clinical Medical Group, La Jolla, CA, UNITED STATES OF AMERICA.
5. Oncology, Rocky Mountain Cancer Centers, Denver, CO, UNITED STATES OF AMERICA.
6. Oncology, University of Wisconsin, Madison, WI, UNITED STATES OF AMERICA.
7. Oncology, Institute for Translational Oncology Research, Greenville, SC, UNITED STATES OF AMERICA.
8. Oncology, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA.

Background: TH-302 is a hypoxia targeted prodrug with a hypoxia-triggered 2-nitroimidazole component designed to release the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM), when reduced in severe hypoxia. A randomized Phase IIb study (NCT01144455) was conducted to assess the benefit of G + T to standard dose G as first-line therapy of PAC.

Materials and methods: An open-label multi-center study of two dose levels of TH-302 (240 mg/m² or 340 mg/m²) in combination with G versus G alone (randomized 1:1:1). G (100 mg/m²) and T were administered IV over 30-60 minutes on Days 1, 8 and 15 of a 28-day cycle. Patients on the G could crossover after progression and be randomized to a G + T arm. The primary efficacy endpoint was a comparison of progression-free survival (PFS) between the combination arms and G alone (60% power to detect 50% improvement in PFS with one-sided alpha of 10%). Summary PFS outcome has previously been reported; more detailed PFS as well as the initial overall survival (OS) data are presented.

Results: 214 pts were treated; 164 (77%) Stage IV and 50 (23%) Stage IIIB. Median age 65 (range 29-88); 126 M/88 F; 40% ECOG 0/60% ECOG 1. Receiving 6 or more cycles: 32% G; 45% G + T240; 55% G + T340. Median PFS was 3.6 mo in G vs 2.9 mo in G + T240 (HR 0.81; 95% CI 0.61-1.07, p = 0.117). In the mEOC + P arm, OS was significantly improved compared to those without grade 3 rash (77%, n = 209) on treatment compared to those without grade 3 rash (23%, n = 63); median OS 10.2 vs 4.3 months (p < 0.001), with similar significant improvements seen in RR and PFS. Multivariate analysis demonstrated a negatively significant correlation between rash grade 3 and OS (HR 1.75; 95% CI 1.07-2.90, p = 0.024) and PFS (HR 1.57; 95% CI 1.02-2.40, p = 0.038).

Conclusions: The combination of G plus TH-302 improved the efficacy of G. A TH-302 dose of 340 mg/m² was identified for future studies. Skin and mucosal toxicity and myelosuppression were the most common TH-302 related AEs with no increase in treatment discontinuation.

Disclosure: All authors have declared no conflicts of interest.

References:

2. Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, UNITED STATES OF AMERICA.
3. Oncology, Duke University, Durham, NC, UNITED STATES OF AMERICA.
4. Oncology, Scripps Clinical Medical Group, La Jolla, CA, UNITED STATES OF AMERICA.
5. Oncology, Rocky Mountain Cancer Centers, Denver, CO, UNITED STATES OF AMERICA.
6. Oncology, University of Wisconsin, Madison, WI, UNITED STATES OF AMERICA.
7. Oncology, Institute for Translational Oncology Research, Greenville, SC, UNITED STATES OF AMERICA.
8. Oncology, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA.
d or 5-FU (1,000 mg/m²/day for 5 infusions)/cisplatin (100 mg/m² day) 1 q 28 d. OS analyses for non-inferiority, by pre-specified stratifications, were performed.

Results: OS for NI from CS (8.6 months) compared to CF (7.9 months) had a HR = 0.92 (two-sided 95% CI, 0.80-1.05). HR = 1.05 being lower than HR = 1.10 non-inferior margin, derived from a literature meta-analysis, CS remains statistically significantly non-inferior (p = 0.0068) to CF. The 74% preserved control effect by CS is well above the suggested 50% by Rothmann et al. (Statist-Med2003; 23:229-264), based on which the 1.10 non-inferiority margin was derived. Moreover, statistically significant safety advantages for the CS arm were observed for the rates of G3/4 neutropenia (18.6%, CS; 40.0%, CF), G3/4 febrile neutropenia (1.7%, CS; 6.9%, CF), G3/4 stomatitis (1.3%, CS; 13.6%, CF), renal adverse events (all grades: 18.8%, CS; 33.5%, CF), and severe hypokalemia (3.6%, CS; 10.8%, CF). On the other safety items, no significant differences were noted between CS and CF, especially regarding Head and Foot Syndrome which was anecdotal and limited to grade 1/2.

Treatment-related deaths were significantly reduced with CS compared to CF (respectively 2.5% and 4.9%).

Conclusion: CS is non-inferior to CF while providing safety advantages for the patients and is a treatment alternative in advanced gastric carcinoma.

Disclosure: All authors have declared no conflicts of interest.

609PD  MET AS PROGNOSTIC FACTOR AND THERAPEUTIC TARGET IN PRETREATED HEPATOCELLULAR CARCINOMA (HCC): FINAL RESULTS OF A RANDOMIZED CONTROLLED PHASE 2 TRIAL (RCT) WITH TIVANITINB (ARQ 197)

B. Daniele1, L. Rimensi2, C. Porta3, I. Borbath2, S. Salvagni2, J. van Laethem4, H. van Vlierberghe5, R. von Roemeling8, G. Abbadessa9, A. Santoro10

1Clinical Oncology, G. Rummo Hospital, Benevento, ITALY, 2Oncology, Hematology, Humanitas Cancer Center, Istituto Clinico Humanitas IRCCS, Rozzano, Italy, 3Oncologia Medica, Ospedali San Matteo, Pavia, Italy, 4Gastro-Enterology, Cliniques Universitaires St. Luc, Brussels, BELGIUM, 5Oncology, Azienda Ospedaliera Parma, Parma, Italy, 6Gastroenterology, Erasme University Hospital, Brussels, BELGIUM, 7Gastroenterology, Ghent University Hospital, Ghent, BELGIUM, 8Clinical Development Oncology, Daiichi Sankyo Pharma Development, Edison, NJ, UNITED STATES OF AMERICA, 9Oncology Hematology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, ITALY, 10Oncology, Hematology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, ITALY

Background: Tivantinib (T), a selective, oral inhibitor of MET, the hepatocyte growth factor (HGF) receptor, was tolerated in HCC as monotherapy and with sorafenib.

Methods: Multi center RCT; key selection criteria: unresectable HCC, prior systemic therapy, PS ≤ 2; no Child Pugh B-C. Randomization: 2:1 to T or placebo (P); dose: 360mg BID (TA), then 240 mg BID (TB) in all patients (pts) due to ≥ 3 neutropenia; stratification: PS, vascular invasion. Tumor evaluation: by CT / MRI every 6 weeks; central radiology review by RECIST 1.1. Crossover to open label T allowed after PD. Endpoints include: time to tumor progression (TTP) in the intent-to-treat (ITT) population; disease control rate (DCR), progression free survival (PFS), overall survival (OS), efficacy in MET+ pts ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥ ≥
Day 8. A second identical course was administered after a 2-week break. If patients could not swallow the oral S-1 capsule, it was administered in powder form. In patients who showed an objective response to CRT, at least 2 courses of chemotherapy with S-1 plus cisplatin were administered.

Results: Eighty-three patients participated, 12 with Stage II and 71 with Stage III LAEC. Seventy-seven patients (92.7%) completed CRT. The most frequent adverse events were Grades 3 and 4 neutropenia (36.6%); thrombocytopenia (13.3%), and anemia (9.6%). One patient died on Day 20 from febrile bone marrow aplasia. Non-hematological adverse events were mild. The most common were Grade 2 nausea (32.5%); esophageal pain and oral mucositis (16.9%); and renal dysfunction (10.8%). Adverse events from the first course of CRT resolved during the 2 weeks interval. Complete response rates in patients with Stage II and Stage III LAEC were 91.7% and 67.6%, respectively. No relapse occurred in patients with Stage II disease, and relapses occurred in 21 (43.8%) of 48 patients with Stage III disease who achieved CR. Median FFS for patients with Stage II and III patients was 6.6 and 1.6 years, respectively. Median survival time was 7 years for Stage II and 2.6 years for Stage III LAEC.

Conclusions: CRT combined with S-1 plus cisplatin showed promising safety and efficacy, as well as potential to become a standard treatment for LAEC.

Disclosure: All authors have declared no conflicts of interest.

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EFFECTS OF NEOADJUVANT CHEMORADIOThERAPY ON POSTOPERATIVE MORBIDITY AND MORTALITY ASSOCIATED WITH ESOPHAGEAL CANCER

Y. Hanai, J. Hihara, M. Erni, Y. Aoki, M. Okada
Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, JAPAN

Background: The results of clinical trials and meta-analyses suggest that neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy confers a survival benefit upon patients with locally advanced esophageal cancer compared with esophagectomy alone. However, whether neoadjuvant CRT increases the risk of postoperative morbidity remains controversial.

Methods: Data from 206 patients who underwent transthoracic esophagectomy with gastric tube reconstruction and cervical anastomosis between May 2003 and October 2011 were reviewed. Neoadjuvant CRT comprised 40 Gy of radiation and concurrent chemotherapy with 5FU plus one of docetaxel, cisplatin or combined docetaxel/cisplatin. We compared the surgical outcomes of 114 patients (55%) who underwent esophagectomy alone (group 1) and 92 (45%) who received neoadjuvant CRT followed by esophagectomy (group 2). We also assessed preoperative factors that influence postoperative major morbidity including esophageal leak, graft necrosis, multilobar pneumonia, empyema, chylothorax and recurrent nerve palsy with univariate analysis.

Results: The operative duration, blood loss and overall postoperative morbidity rates were 403 ± 79 and 421 ± 76 min (p = 0.10), 560 ± 407 and 589 ± 446 ml (p = 0.62) and 45% and 55% (p = 0.13) in groups 1 and 2, respectively. Rates of anastomotic leak (8.8 vs. 14.1%; p = 0.23), pneumonia (8.8 vs.13.0%; p = 0.32), recurrent nerve palsy (14.9 vs.9.8%; p = 0.27) and all other complications did not significantly differ between the groups. The 30-day mortality rate was 0% in each group and hospital mortality rates were 0.9 and 1.0% in groups 1 and 2, respectively (p = 0.88).

Univariate analysis of preoperative factors indicated that advanced age, a history of cardiovascular disease, a high serum creatinine and advanced tumor stage were significantly associated with postoperative major morbidity, whereas neoadjuvant CRT was unrelated to the incidence of major morbidity. Multivariable analysis revealed cardiovascular disease (Odds ratio, 2.46; 95%CI, 1.27 - 4.76; p = 0.008) and advanced tumor stage (Odds ratio, 2.24; 95%CI, 1.15 - 4.35; p = 0.017) as independent covariates for major morbidity.

Conclusion: Neoadjuvant CRT is safe and does not increase the incidence of postoperative morbidity and mortality compared with esophagectomy alone.

Disclosure: All authors have declared no conflicts of interest.

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INTERSTITIAL PULMONARY DISORDER IN PATIENTS WITH ESOPHAGEAL SQUAMOUS CELL CARCINOMA TREATED WITH DOXETAXEL AFTER CHEMORadioThERAPY

Y. Ezo1, M. Muto1, K. Ueda2, Y. Ozaki2, I. Aoyama2, T. Horimatsu2, S. Morita2, S. Miyamoto2, T. Chiba1

1Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, CHINA, 2Department of Surgery, Zhejiang Cancer Hospital, Hangzhou, CHINA

Background and aims: Docetaxel (DOC) is a key drug in second-line chemotherapy after the failure of chemoradiotherapy (CRT) for esophageal cancer. Interstitial pulmonary disorder (IPD) is one of the fatal adverse effects of DOC, but its frequency and risk factors have not been clarified. The aim of this study was to determine the frequency of and risk factors for IPD in patients with esophageal squamous cell carcinoma (ESCC), who were treated with DOC after the failure of CRT.

Patients and methods: We retrospectively reviewed the clinical data for 115 patients with ESCC who had been treated with CRT at Kyoto University Hospital from April 2007 to March 2011. Thirty-seven of these patients had been treated with DOC after CRT (D group) and 78 had not been treated with DOC (non-D group). We compared the incidence of IPD in the two groups and also identified the risk factors for IPD.

Results: The incidence of grade 3/4 IPD in the D and non-D groups was 10.8% (4/37) and 1.3% (1/78), respectively (p = 0.035). A median of 4 cycles of DOC was administered (range, 2–7). The median total radiation dose was 60 Gy. The mean value for V20 (% total lung volume receiving ≥20Gy) in patients with grade 3/4 IPD was greater than that in patients without IPD (20.0% vs 12.3%, respectively; p = 0.012). The V20 value was greater than 20% in 80% (4/5) of patients with grade 3/4 IPD. The mean lung dose (MLD) in patients with grade 3/4 IPD was also greater than that in patients without IPD (11.1 Gy vs 6.6 Gy, respectively; P = 0.01).

Conclusion: The incidence of grade 3/4 IPD was 10.8% in patients who received DOC after CRT. IPD must be considered to patients who have already received radiotherapy with high V20 and MLD in their first-line CRT.

Disclosure: All authors have declared no conflicts of interest.

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PROGNOSIS IMPACT OF POSTOPERATIVE RADIATION IN PATIENTS WITH RADICAL ESOPHAGECTOMY AND PATHOLOGICAL LYMPH NODES POSITIVE ESOPHAGEAL CANCER

Y. Xu1, W. Mao2, X.J. Sun1, Y.D. Zheng1, Y. Jiang2, J. Liu2

1Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, CHINA, 2Department of Surgery, Zhejiang Cancer Hospital, Hangzhou, CHINA

Purpose: Though postoperative radiation for esophageal cancer is offered in selected cases, there is conflicting evidence as to whether it improves overall survival (OS). We performed a retrospective investigation to analyze the prognosis impact of adjuvant radiation in a large cohort of patients.

Methods and materials: From 2002 to 2008, 545 patients underwent radical esophagectomy (RE) with or without postoperative radiation therapy were eligible for a retrospective analysis. Patients were grouped to surgery only (n = 346) and surgery plus postoperative radiation therapy (PORT) (n = 199). Radiation dose was 50 Gy in 25 fractions. Kaplan-Meier and Cox regression analysis were used to compare OS.

Results: The use of PORT was associated with significantly improved OS (p = 0.006). The median OS was 31 months in the group receiving PORT and 21 months in the group undergoing surgery alone. The addition of PORT improved OS at 3 years from 38.3 to 45.8% compared with surgery alone. For American Joint Committee on Cancer (AJCC) stage III esophageal cancer (T1-2N2M0, T3N1-2M0, T4N1-3M0), there was significant improvement in OS (p = 0.000) in PORT group, for not only metastatic lymph-node ratio <0.25 (p = 0.047), but also metastatic lymph-node ratio >0.25 (p = 0.031). However, for stages IIb disease (T1-2N1M0) there was no significant differences.

Conclusion: This large population-based analysis supports the use of PORT for pathological lymph nodes positive stage III esophageal cancer. Our results suggest that a subset of such patients may benefit from aggressive local therapy. As a retrospective study, our results do not have the same strength as a prospective study, however, it provides a basis for the design of future randomized, prospective clinical trials.

Disclosure: All authors have declared no conflicts of interest.

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A CLINICO-MOLECULAR RISK STRATIFICATION MODEL FOR RESECTED GASTRIC CANCER: PROGNOSTIC IMPACT OF HER2, FHT AND APEX EXPRESSION STATUS

E. Bria1, G. De Manzoni2, S. Beggelli1, A. Tommazzoli3, S. Barbi1, M. Frizziero1, L. Sperti1, S. Bersani1, G. Tortora1, A. Scarpa3

1Medical Oncology, Azienda Ospedaliera Universitaria Integrata Verona “Borgo Roma”, Verona, ITALY, 21st Division of General Surgery, University of Verona, Verona, ITALY, 3Pathology, ARC-NET Applied Research on Cancer Center, Verona, ITALY

Purpose: In order to complement the prognostic power of clinical parameters for resected gastric cancer, a stratification model to predict individual patient risk was developed taking into account 11 molecular factors.

Methods: Clinicopathological and molecular data (expression of Cdx2, Apc, β-Catenin, E-Cadherin, Fht, p53, Her2; HER2 and TOP2A gene copy number; PIK3CA mutations; microsatellite instability-MSI) were correlated to cancer-specific/ overall survival (CSS/OS) using a Cox model. A logistic equation including regression analysis coefficients was constructed to estimate individual patients’ probability (PP) of death. Internal cross-validation (100 simulations, 80% of the dataset) was accomplished. Ratios from the multivariate model served to derive a prognostic continuous score to identify risk classes.

Disclosure:

All authors have declared no conflicts of interest.

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Results: Two-hundred-eighty patients were studied (median follow-up 20 months). At multivariate analysis, sex (HR 1.53, p = 0.04), stage (HR 5.40, p < 0.0001), margins (HR 2.49, p < 0.0001), localization (HR 1.64, p = 0.008), resected nodes (HR 1.55, p = 0.02), APC (HR 1.91, p = 0.001), FHT (HR 1.54, p = 0.009) and HER 2 (HR 1.92, p = 0.08), were independent predictors for CSS; the same factors (plus age and except Fhit) predicted OS. Multivariate model predicted ITP with high prognostic accuracy (0.87 for CSS; 0.91 for OS). A 2-class risk stratification model, developed on the basis of the ROC, generated cut-off prognostic score (AUC 0.87; Sensitivity 85.3%; Specificity 78.9%), significantly separated low and high risk patients for CSS (16.4% and 82.5%, p < 0.0001) and OS (15.6% and 79.7%, p < 0.0001), with a prognostic performance of 0.82 for CSS and 0.81 for OS. A further 3-class model differentiated low, intermediate, and high-risk patients for CSS (7.5%, 37.3%, and 49.7%, p < 0.0001) and OS (0%, 23.3%, and 84.8%, p < 0.0001).

Conclusions: The concurrent evaluation of the expression of Apc, Fhit, Her2 proteins and clinicopathological parameters (Stage, Resected Nodes, Margins, Location, Sex) may powerfully discriminate the prognosis of resected gastric cancer patients.

Disclosure: All authors have declared no conflicts of interest.

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THE PROGNOSTIC VALUE OF TUMOR-INFILTRATING NEUTROPHILS IN GASTRIC ADENOCARCINOMA AFTER RESECTION

J. Xia1, J. Zhao2, S. Soi3, K. Pan1, W. Wang4, X. Li5, J. Chen1, D. Wang1
1Biotherapy, Cancer Center, Sun Yat-sen University, Guangzhou, CHINA, 2Medical Corporation Zushi, Tokyo, JAPAN, 3Gastro and Pancreatic Surgery, Cancer Center, Sun Yat-sen University, Guangzhou, CHINA, 4Thoracic Oncology, Cancer Center, Sun Yat-sen University, Guangzhou, CHINA

Background: Several pieces of evidence indicate that tumor-infiltrating neutrophils (TINs) are correlated to tumor progression. In the current study, we explore the relationship between TINs and clinicopathological features of gastric adenocarcinoma patients. Furthermore, we investigate the prognostic value of TINs.

Patients and methods: The study was comprised of two groups, training group (115 patients) and test group (97 patients). Biomarkers (intratumoral CD15+ neutrophils) were assessed by immunohistochemistry. The relationship between clinicopathological features and patient outcome were evaluated using Cox regression and Kaplan-Meier analysis.

Results: Immunohistochemical detection showed that the tumor-infiltrating neutrophils (TINs) are correlated to tumor progression. In the current study, we explore the relationship between TINs and clinicopathological features of gastric adenocarcinoma patients. Furthermore, we investigate the prognostic value of TINs.

Conclusions: The presence of CD15+ TINs was an independent and unfavorable factor for gastric adenocarcinoma surgical patients. The results verify that the number of CD15+ TINs can predict the survival of patients. Using another 97 patients as a test group and basing on the median (p = 0.028). Kaplan-Meier analysis showed that patients with a lower density of TINs had a better prognosis than patients with a higher density of TINs (p = 0.002). Multivariate Cox’s analysis showed that the density of CD15+ TINs was an independent prognostic factor for overall survival of gastric adenocarcinoma patients. Using another 97 patients as a test group and basing on the median number of TINs (21.60 cells/HFP) coming from the training group.

Kaplan Meier analysis also showed that patients with a lower density of TINs had a better prognosis than patients with a higher density of TINs (p = 0.032). The results verify that the number of CD15+ TINs can predict the survival of gastric adenocarcinoma surgical patients.

Conclusions: The presence of CD15+ TINs is an independent and unfavorable factor in the prognosis of gastric adenocarcinoma patients. Targeting CD15+ TINs may be a potential interventional therapy in the future.

Disclosure: All authors have declared no conflicts of interest.

677P
SURVIVAL IMPACT OF HER2 STATUS IN PATIENTS WITH GASTRIC CANCER: A MULTICENTER LARGE-SCALE STUDY IN JAPAN

1Gastroenterological Surgery, Osaka University, Osaka, JAPAN, 2Molecular Pathology, Osaka University, Osaka, JAPAN, 3Surgery, NTT West Osaka Hospital, Osaka, JAPAN, 4Surgery, St. Luke’s Hospital, Osaka, JAPAN, 5Surgery, Ikeda Municipal Hospital, Osaka, JAPAN, 6Surgery, Toyonaka Municipal Hospital, Osaka, JAPAN, 7Surgery, Osaka General Medical Center, Osaka, JAPAN

Background: Although it has been proven in the ToGA study that HER2 expression is a predictive factor of trastuzumab treatment, the relation between HER2 status and prognosis in gastric cancer patients was still unknown. A multicenter large-scale study was conducted to evaluate the prognostic value of HER2 status in gastric cancer.

Methods: A total of 1152 cases with gastric cancer which was surgically resected were evaluated according to the same criteria with the ToGA study. The relation between HER2 expression and clinicopathological factors was examined by Fisher’s exact test. The hazard ratio (HR) for death in HER2-positive cases was estimated, and overall survival (OS) were compared between HER2-positive and HER2-negative cases using log rank test.

Results: The number of cases with IHC 0/1+ 12+ 3+ was 662/288/120/162, and eighteen of IHC 2+ cases showed FISH-positive. In total, the proportion of HER2-positive was 15.6% (180/1152). HER2-positive cases were more frequent in differentiated type tumors (p < 0.001), in upper body tumors (p = 0.065), and in T3b-tumors (P = 0.074). OS in HER2-positive cases was clearly worse than in HER2-negative cases (HR 1.55 (95%CL 1.21-1.97); p < 0.001). According to the tumor stage classification, the HR (95%CI) in HER2-positive cases and P values were as follows; Stage I: 2.05 (1.34-3.88); P = 0.015; Stage II: 1.87 (1.003-3.47); P = 0.046; Stage III: 1.46 (0.95-2.27); P = 0.085; Stage IV: 2.93 (1.24-6.89); P = 0.010. There was no significant difference which showed interaction between HER2 status and any background factors. The Cox multivariate analysis with nine background factors revealed that HER2 expression was an independent prognostic factor (HR 1.55 (95%CI 1.19-20.32); P = 0.001).

Conclusions: HER2 expression is an independent factor of poor prognosis in resected gastric cancer, showing trends of higher HR in earlier stage.

Disclosure: All authors have declared no conflicts of interest.

678P
CLINICAL SIGNIFICANCE OF HER2 OVEREXPRESSION IN GASTRIC AND GASTROESOPHAGEAL JUNCTION CANCERS

1Medical Oncology, Gazi University Medical Faculty, Ankara, TURKEY, 2Medical Oncology, Gazi University Faculty of Medicine, Ankara, TURKEY, 3Internal Medicine, Gazi University Medical Faculty, Ankara, TURKEY, 4Department of Medical Oncology, Ataturk Education and Research Hospital, Ankara, TURKEY

Objectives: In this study, we investigated the rate of HER2 overexpression in gastric and gastroesophageal junction cancers (GC, GEJC), and the relationship with HER2 expression and clinical, pathological parameters and prognosis.

Materials and methods: Surgery or biopsy specimen of 285 (202 male, 83 female) patients with GC or GEJC, the presence of HER2 overexpression by immunohistochemistry (IHC) and silver insitu hybridization (SISH) were evaluated. The relationship between HER2 positivity and tumor size (TS), histopathology (H), lymph node metastasis (N), resected gastric cancer, showing trends of higher HR in earlier stage.

Results: The IHC scores were; 194 (68.1%) IHC 0, 34 (11.9%) IHC +1, 30 (10.5%) IHC +2, 27 (9.5%) IHC +3. Twelve of 30 (4.2%) patients with IHC +2, SISH positive, and 18 patients SISH negative. The number of patients evaluated with IHC +3 or IHC +2 and SISH positive, HER2 positivity was 13.7%. There was no relationship between HER2 positivity and tumor stage. HER2 positivity was 13.7%. There was no relationship between HER2 positivity and tumor stage. HER2 positivity was 13.7%. There was no relationship between HER2 positivity and tumor size (TS), histopathology (H), lymph node metastasis (N), resected gastric cancer, showing trends of higher HR in earlier stage.

1A Medical Oncology, Gazi University Medical Faculty, Ankara, TURKEY, 2Medical Oncology, Gazi University Faculty of Medicine, Ankara, TURKEY, 3Department of Medical Oncology, Ataturk Education and Research Hospital, Ankara, TURKEY

Disclosures:

Disclosure: All authors have declared no conflicts of interest.

679P
IDENTIFICATION OF RISK FACTORS OF RELAPSE AFTER CURATIVE SURGICAL RESECTION IN STAGE I GASTRIC CANCER

1Oncology, Internal Medicine, Asan Medical Center, Seoul, KOREA, 2Division of Oncology, Dept of Internat Med, Asan Medical Center, Seoul, KOREA, 3Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, KOREA, 4Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, KOREA, 5Department of Pathology, Asan Medical Center, Seoul, KOREA, 6Department of Surgery, Asan Medical Center, Seoul, KOREA

Background: The therapeutic benefit of adjuvant chemotherapy is well established in stage (by AJCC 6th edition) II or III gastric cancer (GC). However, it has not been
proven in stage I GC. The aim of this study was to identify risk factors of relapse in stage I GC, and to find out patients at high risk of relapse.

Methods: We retrospectively reviewed the medical records of 2783 patients with pathologically confirmed stage I GC who underwent curative surgical resection alone in Aomori Medical Center between 2003 and 2007. Clinicopathologic parameters of exclusion included: age, sex, histologic differentiation, WHO classification, Lauren classification, size, location, multiplicity, stage, lymphovascular or perineural invasion, preoperative serum levels of tumor markers (CEA, CA 19-9, CA 72-4), and type of surgery. Then, we performed univariate and multivariate analysis to correlate each parameter with relapse-free survival (RFS) and overall survival (OS).

Results: With a median follow-up of 54 months (range, 0–60), 213 (7.7 %) patients experienced recurrence or death, and 5-year RFS and OS was 90% and 94%, respectively. In univariate analysis, RFS was significantly related with age, sex, differentiation, WHO and Lauren classification, size, stage, lymphovascular invasion, perineural invasion, and serum levels of CEA and CA 19-9. The multiplicity of tumor instead of size was significantly related with OS. In multivariate analysis, 6 factors (age over 65 years, male stage II, lymphovascular invasion, perineural invasion, and elevated level of CEA) remained independent poor prognostic factors for RFS (p < 0.05). Four factors except the presence of lymphovascular or perineural invasion were also significantly related with inferior OS (p < 0.05). Patients with more than two out of 6 poor risk factors had 79% of 5-year RFS, whereas patients with less risk factors had 97% of 5-year RFS (p < 0.001).

Conclusion: In this study cohort, we identified 6 independent risk factors for relapse and death. The patients with more than two risk factors are expected to have significant risk of recurrence or death after curative resection, and should be considered as the future candidates of adjuvant treatment.

Disclosure: All authors have declared no conflicts of interest.

Background: Perioperative chemotherapy (CT) has demonstrated as survival benefit in locally advanced gastric cancer (GC) in randomized trials. However, the overall cure rate is 30-40% and a significant number of patients are not able to receive the postoperative part of their CT regimen. In Europe, the trifunctional antibody catumaxomab is approved for the treatment of malignant ascites based on a pivotal trial which also included GC patients. A new multimodal approach combining neoadjuvant CT, followed by gastrectomy and intraperitoneal (i.p.) immunotherapy with catumaxomab was assessed in a single-arm multicenter phase II study. We here report 2-year follow-up data.

Methods: GC pts (T2/T3/T4, N +, M0) received 3 cycles of neoadjuvant fluoropyrimidin/platinum-based CT followed by en-bloc R0-gastrectomy. Catumaxomab was administered i.p. as intraoperative bolus (10 µg) followed by 4 consecutive 3-hour infusions of 10-150 µg. Primary safety endpoint was the rate of predefined postoperative complications observed during 30 days after surgery. Key efficacy endpoints included disease-free (DFS) and overall survival (OS).

Results: The original study data presented at the WCCG in 2011 (Schuhmacher et al., Ann Oncol 2011 22(suppl 5)) showed that the primary endpoint was met and the described application regimen is safe. At time of surgery, 27.8% of patients were stage I, 27.3% were stage II, 22.3% of patients were stage III and 14.8% of patients were stage IV as assessed by pTNM analysis. At 24 months 39% (safety analysis set) patients were still alive, 14% were dead, (one patient lost to follow-up), 24/37 had no progression, only 13/37 patients relapsed (for 2 patients disease status was not recorded). At the 2 year cut off DFS was 56.4% (95% CI: 41–69%), OS was 75% (95% CI: 60–85%).

Conclusions: Catumaxomab as part of a multimodal therapy in primary resectable GC is a feasible option. The 2-year follow-up efficacy results show promising data for DFS and OS in a cohort of locally advanced gastric cancer pts.

Disclosure: All authors have declared no conflicts of interest.

Results: Postoperative ChT started 2.6–11.3 weeks after surgery (median 6 weeks). The treatment was completed according to the protocol in 59 patients. No death occurred due to the therapy. Stomatitis, dysphagia, nausea and vomiting, diarrhea, hand foot syndrome, stenocardia and aleopnia of grade three occurred in 1, 0, 5, 2, 9, and 4 patients, respectively. Some 56 patients lost weight as measured with respect to the weight they had at the beginning of treatment. The maximum body weight loss was 18.9% (mean 6.2%). The median follow-up time of 66 survivors was 4 years to the weight they had at the beginning of treatment. The maximum body weight loss was 18.9% (mean 6.2%). The median follow-up time of 66 survivors was 4 years. The maximum body weight loss was 18.9% (mean 6.2%). The median follow-up time of 66 survivors was 4 years (range 2.5-5.7 years). At 5 years, locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) rates were 95%, 69%, 63% and 63%, respectively.

Conclusion: Operable gastric carcinoma, postoperative radiochemotherapy with capecitabine is feasible and its toxicity is low.

Disclosure: All authors have declared no conflicts of interest.

RESULTS OF TREATMENT OF LOCALLY ADVANCED GASTRIC CANCER IN THE ELDERLY PATIENTS

D. Egamberdiev, M. Djuran, S. Khudayarov, O. Nematov, A. Babayev, H. Tuyev
Abdominal Oncology, National Cancer Center of Uzbekistan, Tashkent, UZBEKISTAN

Background: Although the incidence of gastric cancer has declined in the general population, it is the second most frequent cancer in Uzbekistan with its incidence in the elderly increasing as a result of increased life expectancy. This present study tried to determine the role of age on outcomes of surgical treatment for gastric cancer in Uzbek population.

Methods: The study reviewed 288 patients who underwent gastrectomy for locally advanced gastric cancer. The clinicopathological features of elderly patients (≥75 years) and younger patients (<70 years) were compared. The study inclusion. Clinico-pathological data, data on survival and Skeletal Related Events (SRE) have been collected in a master database and analyzed.

Results: The study inclusion. Clinico-pathological data, data on survival and Skeletal Related Events (SRE) have been collected in a master database and analyzed.

Conclusions: The present study is the result of the largest Israeli descriptive study concerning the natural history of bone disease in gastric cancer patients. Disclosure: All authors have declared no conflicts of interest.

OVERALL SURVIVAL (OS) TO FIRST- AND SECOND-LINE CHEMOTHERAPY ASSOCIATED WITH MRNA EXPRESSION OF MULTIPLE MYELOMA SET (MMSET) DOMAIN, PS3-BINDING PROTEIN 1 (3BP1) AND BREAST CANCER SUSCEPTIBILITY GENE 1 (BRCA1) IN ADVANCED GASTRIC CANCER PATIENTS (P)

J. Wei1, B. Liu1, L. Yu1, Z. Zou2, X. Glang3, J.J. Sánchez4, C. Costa3, A. Gimenez-Capitan1, N. Karachak1, R. Rossell5
1Oncology, Drum Tower Hospital, Nanjing, CHINA, 2Statistics, Autonomous University of Madrid, Madrid, SPAIN, 3Laboratory of Biologic Department, Panagia Biotech, USP Dexeus University Institute, Barcelona, SPAIN, 4Oncology, Instituto Oncologico Dr Rosell, USP Dexeus University Institute, Barcelona, SPAIN, 5Medical Oncology Service, Catalan Institute of Oncology Hospital Germans Trias i Pujol, Badalona, SPAIN

Background: Low BRCA1 expression enhances sensitivity to platinum, while high levels increase sensitivity to taxanes (Quinn et al. Cancer Res 2003). In response to clastatin-induced DNA double strand breaks (DSBs), MDC1 binds to γH2AX, promoting DSB repair by 53BP1 and BRCA1. MSSSET is required for the accretion of 3BP1, PIAS4 and Ubc9 to DSB sites. We hypothesized that the mRNA expression of these components of the MDC1-MSSSET-3BP1 pathway could impact the predictive model based on BRCA1 mRNA expression (Wei et al. INCT 2011).

Methods: Tumor samples were obtained from 132 advanced gastric cancer patients treated with first-line FOLFIRI, 58 of whom also received second-line docetaxel. mRNA expression of MDC1, MSSSET, 3BP1, PIAS4, Ubc9 and BRCA1 was analyzed by real-time PCR.

Results: A close correlation was found between MMSET and BRCA1 (r = 0.28; P = 0.002), 3BP1 (r = 0.54; p < 0.001), PIAS4 (r = 0.27; P < 0.001) and Ubc9 (r = 0.50; P < 0.001). Median OS for all 132 was 12.5 months (am). Among patients receiving only first-line treatment, OS was 12.3 m in p with low MSSSET and 8.8 m in p with high MSSSET (P = 0.004). In the subset of p with low levels of 3BP1 receiving only first-line treatment, OS was 19.9 m for p with low levels of MSSSET (2- and 5-year OS = 56.6% and 14.5%, respectively) vs. 5.9 m for p with high MSSSET (2-year OS = 16.7% (P = 0.02). Among p receiving second-line docetaxel, OS was 13.9 m in p with low MSSSET and 19.1 m in p with high MSSSET (P = 0.003). Among p receiving second-line docetaxel, OS was 28.6 m for p with high BRCA1 vs 9.8 m for p with low BRCA1 (P < 0.001). In the subset of p with high BRCA1 levels receiving second-line docetaxel, OS was 36.6 m in p with high MSSSET (2- and 5-year OS = 82.4% and 33%, respectively) and 13.9 m in p with low MSSSET (2-year OS = 25%) (P = 0.003).

Disclosure: All authors have declared no conflicts of interest.
Conclusions: Longer OS to FOLFOX was associated with low levels of both MMSET and 3BP1, while longer OS to second-line docetaxel was associated with high levels of both MMSET and BRCA1. MMSET, together with 3BP1 or BRCA1 can be useful for customizing chemotherapy in advanced gastric cancer patients.

Disclosure: All authors have declared no conflicts of interest.

Table: 687P

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<tr>
<th>Median OS (80% CI), mo</th>
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<th>Median PFS (80% CI), mo</th>
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<td>Arm C n = 39</td>
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<td>Arm A + B &lt; 27</td>
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<tr>
<td>Arm C n = 11</td>
<td>5.7 (4.5-10.4)</td>
<td>4.6 (3.7-5.2)</td>
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<tr>
<td>Arm A + B vs C</td>
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<td>Arm A + B &lt; 212</td>
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<td>Arm A + B vs C</td>
<td>0.18 (0.06-0.52)</td>
<td>0.19 (0.06-0.57)</td>
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</table>

**Notes:**
- **MET**+a, **R**++b, aPts with >50% tumor cells MET positive, bPts with R median Cminss ≥ 94 µg/mL.

**Disclosure:** All authors have declared no conflicts of interest.

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688P

**A RANDOMISED PHASE III CLINICAL TRIAL OF COMBINED THERAPY WITH CPT-11/CDDP VERSUS CPT-11 ALONE IN PATIENTS WITH ADVANCED OR RECURRENT GASTRIC CANCER RESISTANT TO S-TRICS STUDY:** SAFETY ANALYSIS


1Gastroenterology, National Hospital Organization Osaka National Hospital, Osaka, JAPAN, 2Surgery, Osaka General Medical Center, Osaka, JAPAN, 3Surgery, Gifu Central Hospital, Gifu, JAPAN, 4Surgery, Osaka Kose Inokuchi Hospital, Osaka, JAPAN, 5Clinical Oncology, Osaka City General Hospital, Osaka, JAPAN, 6Surgery, Shizuoka General Hospital, Shizuoka, JAPAN, 7Surgery, Kansai Rosai Hospital, Amagasaki, JAPAN, 8Biostatistics and Epidemiology, Yokohama City University Medical College, Yokohama, JAPAN, 9Social Life Science, Nagoya University, Nagoya, JAPAN, 10Surgery, National Hospital Organization Osaka National Hospital, Osaka, JAPAN

Background: There has been no established regimen as the second-line treatment for advanced gastric cancer (AGC), though CPT-11 showed survival benefit over BSC. Combination of CPT-11 with CDDP is one of the promising regimens as the second-line chemotherapy after S-1 mono-therapy.

Methods: This study was designed as a randomized, multicenter phase III study comparing CPT-11 + CDDP vs. CPT-11 alone in patients with advanced or recurrent gastric cancer resistant to S-1 mono-therapy or prior adjuvant chemotherapy using S-1. Eligibility criteria include: histologically confirmed gastric adenocarcinoma, showing PD after receiving S-1 mono-therapy or recurrence within 6 months after or during S-1 adjuvant chemotherapy, age over 20 years old, PS 0-2, adequate organ functions and written informed consent. Patients received either CPT-11 150 mg/m^2/day1 / q 2W (Arm A) or CPT-11 60mg/m^2/day1 + CDDP 30mg/m^2/day1 / q 2W (Arm B). Stratification was made according to PS, advanced or recurrence cases, institution and presence or absence of measurable target lesions. Primary endpoint is overall survival. Secondary endpoints are time to treatment failure (TTF), response rate, and safety (frequency and severity of adverse events). Calculated sample size was 160 assuming 74 events with alpha error 0.05 and beta error 0.02 to detect differences in survival. Planned number was 200 considering 40 for ineligibility or dropout.

Results: 168 patients were enrolled between 2007 and 2011. Arm A (n = 84) and Arm B (n = 84) were well balanced for baseline factors. Median age was 67 years old and median number of treatment courses was 5 (range: 1-39). Relative dose intensity (RDI) in Arm A was 97.5% and RDI in Arm B was 98.9%. The most common grade 3/4 toxicities in Arm A vs. Arm B were, neutropenia; 26.2 vs. 15.5%, anemia; 44.0 vs. 31.0%, thrombocytopenia; 7.5 vs. 1.2%, asthenia; 9.6 vs. 4.8%, and diarrhea; 12.0 vs. 2.4%. Grade 3/4 toxicities in Arm A vs. Arm B were, neutropenia; 26.2 vs. 15.5%, anemia; 44.0 vs. 31.0%, thrombocytopenia; 7.5 vs. 1.2%, asthenia; 9.6 vs. 4.8%, and diarrhea; 12.0 vs. 2.4%. Grade 3/4 toxicities in Arm A vs. Arm B were, neutropenia; 26.2 vs. 15.5%, anemia; 44.0 vs. 31.0%, thrombocytopenia; 7.5 vs. 1.2%, asthenia; 9.6 vs. 4.8%, and diarrhea; 12.0 vs. 2.4%.

Conclusions: In this initial safety analysis, the incidence and severity of adverse events in both Arms were acceptable as second-line treatment. Final efficacy results will be performed at the end of this year.

Disclosure: All authors have declared no conflicts of interest.

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BACKGROUND: In advanced gastric cancer (AGC), some type of progression such as peritoneal metastasis are hardly detected by imaging, and progression was sometimes judged clinically (C-PD) apart from imaging-determined progression (I-PD). Thus, C-PD is regarded as a PFS event as well as I-PD in most cooperative group trials. However, it has rarely been reported how often C-PD is observed in the clinical trials of AGC. Objectives of this study are to evaluate the proportion of C-PD and to compare the backgrounds and outcomes between C-PD and I-PD.

METHODS: JCOG9912 is a large-scale randomized phase III trial comparing 5-FU continuous infusion (5-FUci), irinotecan plus cisplatin and 5-in AGC. Among all randomized patients (n = 704), protocol terminations were treated in 697 patients at the final analysis, and the reasons for off-treatment were prospectively classified as PD (n = 545), toxicities (n = 59), patient’s refusal (n = 73), death (n = 3) and others (n = 17). We retrospectively categorized patients with PD to I-PD and C-PD by reviewing the case report forms.

RESULTS: The proportion of C-PD was only 4.4% (I-PD: n = 520, C-PD: n = 24, unknown: n = 11) among those who terminated treatment due to PD. There were some differences in patient backgrounds between I-PD and C-PD; age (median 63, 61.5 years old), diffuse type (51.0%, 70.8%), target lesion (+) (77.5%, 66.7%), sum of baseline in target lesion size and TN Cmin. Kaplan-Meier curves for select adverse events (AEs) by TN Cmin categories were prepared.

RESULTS: 656 pts were enrolled from Jul 2009 to Dec 2010 and received EVE (n = 439) or placebo (n = 217). Median age was 62 y, 74% were men, 55% were from Asia, and 18% had previous gastrectomy. Mean 75 mg/m² 1-3-hour IV on day 1, followed by fluorouracil 600 mg/m² 1’3-hour continuous IV for 5 days, every 3 weeks) or modified CF (mCF) (cisplatin 75 mg/m² 1’3-hour IV on day 1, followed by fluorouracil 600 mg/m² 1’3-hour continuous IV for 5 days, every 3 weeks). Treatment continued until disease progression, unacceptable toxicity, death, or consent withdrawal. The primary end point was progression-free survival (PFS).

RESULTS: Between Nov 2008 and Dec 2010, a total of 241 patients were randomized, 234 patients were treated and analyzed (mDCF = 119, mCF = 115) PFS was prolonged with mDCF vs mCF at 12.2 months, (HR = 0.83, 95% CI, 0.65-1.06). A 2.72-fold increase in TN Cmin corresponded to a significant 7.6% reduction from baseline in target lesion volume. No differences in noninfectious pneumonitis, stomatitis/oral mucositis, or infection/infestation risk in pts with TN Cmin <10 ng/mL vs >10 ng/mL were observed. More renal events occurred in the TN Cmin 10-25 ng/mL group (4 vs 1 in TN Cmin >25 ng/mL group).
Preliminary Safety Data from a Randomized Phase II Study Comparing Dose-Escalated Weekly Paclitaxel Versus Standard-Dose Weekly Paclitaxel for Patients with Previously Treated Advanced Gastric Cancer

S. Yuki1, K. Shitara2, D. Takahara2, M. Nakamura3, C. Kondo2, T. Tsuda4, T. Kif5, Y. Taji4, I. Oze1, K. Muro2

1Department of Gastroenterology, Hokkaido University Hospital, Sapporo, JAPAN, 2Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, JAPAN, 3Department of Gastroenterology, Sapporo City General Hospital, Sapporo, JAPAN, 4Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, JAPAN, 5Cancer Chemotherapy Center, Osaka Medical College, Osaka, JAPAN, 6Department of Medical Hospital, Sapporo, JAPAN, 7Department of Clinical Oncology, Saint Marianna University School of Medicine, Kawasaki, JAPAN, 8Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, JAPAN

Background: Recently, we studied the effects of neutropenia occurring during second-line chemotherapy with weekly paclitaxel in a retrospective analysis of 242 patients with advanced gastric cancer, and observed better survival among patients with neutropenia compared to patients without neutropenia (Shitara K, et al. Annals of Oncol. 2011). Therefore, we conducted a multi-institutional, open-label, randomized phase II trial comparing dose-escalated weekly paclitaxel with dose adjustments determined by degree of neutropenia versus standard-dose weekly paclitaxel for patients with previously treated advanced gastric cancer (protocol ID UMIN000004055).

Patients and methods: Patients with advanced or recurrent gastric cancer that progressed during or more previous chemotherapy regimens were included. Ninety patients were randomized to a standard dose of weekly paclitaxel (80 mg/m², Arm A) or an escalated dose of weekly paclitaxel (80 mg/m² on day 1, 100 mg/m² on day 8, and 120 mg/m² on day 15 unless severe toxicity is observed, Arm B). The primary endpoint was overall survival. Secondary endpoints included objective response rate, disease control rate, progression-free survival, and adverse events. We present the preliminary safety data from the first 8 weeks.

Results: From September 2010 to November 2011, a total of 90 patients were enrolled at 13 institutions. One patient in Arm B did not receive paclitaxel. The dose of paclitaxel was escalated to 100 mg/m² in 41 patients (91.3%) and then to 120 mg/m² in 29 patients (64.2%) in Arm B. In the first 8 weeks, 25 (55.5%) patients in Arm A patients and 20 (46.7%) patients in Arm B required dose reduction or treatment delay. Frequencies of grade 1 or more neutropenia were 66.4% in Arm A and 86.4% in Arm B. Grade 1 or more sensory neuropathy frequencies were 55.6% in Arm A and 68.1% in Arm B. Two patients in Arm A and one patient in Arm B experienced febrile neutropenia. No treatment-related deaths occurred.

Conclusions: Preliminary safety data during the first 8 weeks of treatment indicate comparable compliance between the two arms, despite the substantial number of patients who underwent dose escalation.

Disclosure: All authors have declared no conflicts of interest.

Efficacy and Safety of Dose-Dense Chemotherapy with Modified TCF Regimen (TCF-DD) in Elderly Patients with Metastatic Gastric Cancer (MGC)

G. Tomasso1, W. Ligugì2, S. Lazzarelli2, R. Poli3, F.M. Negri4, L. Toppo4, M. Ratti4, M. Briglenti1, F. Gerevini1, R. Passalacqua1

Oncology Division, Istituti Ospitalieri di Cremona, Cremona, ITALY

Background: GC is more common in elderly patients (pts). Most oncologists are reluctant to treat elderly pts with the most active polichemotherapy combinations because of safety concerns. Subgroup analysis of elderly pts enrolled in European studies show limited and conflicting data. We previously reported on the feasibility and high activity of a dose-dense TCF regimen (TCF-dd) (Tommaso 2010). This study aims to evaluate the efficacy and safety of this schema in the elderly pts subgroup (≥ 65 years).

Methods: From 11/04 to 05/12, 111 consecutive pts with MGC (median age 65, range 31-81) were enrolled in a single-centre phase II study. Pts received Docetaxel 70 mg/m² d1, CDDP 60 mg/m² d1, 1AF 100 mg/m² d1-2 followed by 5 FU 400 mg/m² bolus d1-2 and then 600 mg/m² as a 22 hr, 3.3 mg/kg q2w, plus G-CSF d1. Pts ≥ 65y (56) received the same schedule reduced by 30%.

Results: 86 pts evaluable for response and all for toxicity. In pts ≥ 65y we observed 4 CR (7%) 25 PR (45%) 10 SD (18%) 7 PD (13%); in younger pts: 2 CR (4%) 30 PR (55%) 9 SD (16%) 9 PD (17%); ORR by ITT 56% (95% IC 45-64). Median OS was 11.9 months (9.4-14.8); in elderly and younger pts 11.2 (8.4-11.1) and 127.9 (12.10-157) respectively. Out of 48 evaluable pts ≥ 65y, 26 (54%) were treated at full doses without any delay. In the elderly most frequent G3-4 toxicities were neutropenia (14%) thrombocytopenia (10%) febrile neutropenia (2%) and hypokalemia (17%); in the younger: neutropenia (56%) thrombocytopenia (21%) febrile neutropenia (16%) asthenia (43%) hypokalemia (21%).

Conclusions: This study shows that elderly pts can be treated with a TCF-dd regimen reduced by 30% achieving similar efficacy results of younger patients with lesser toxicity.

Disclosure: All authors have declared no conflicts of interest.

Quality of Life in Flags Trial A Randomized, Comparative, Open Label, Multicenter, Phase 3 of S-1 + Cisplatin (CS) Compared to S-5 + Cisplatin (CF) in Untreated Advanced Gastric Cancer (AGC) Patients

G. Bodoky1, A. Carrao2, A. Ravaïo3, J.A. Ajan1

1Dept of Medical Oncology, Szent Lazlo Kórház, Budapest, HUNGARY, 2Medical Oncology, Hospital Ramon y Cajal, Madrid, SPAIN, 3Primario Oncologia Médica, Ospedale "di Rimini", Rimini, ITALY, 4Gastrintestinal Medical Oncology, MD Anderson, Cancer center, Houston, TX, UNITED STATES OF AMERICA

Background: FLAGS’ primary objective was overall survival. We report below the Patient-Reported Outcomes (PRO) (i.e., Quality-of-Life (QoL)) which was one of the secondary objectives.

Methods: All patients who completed at least one PRO assessment were eligible for analysis. The primary PRO endpoint was the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Gastric (FACT-Ga). Patients completed the FACT-Ga at the beginning of Cycles 1, 2, 3, 4, 6 and then every 3 cycles prior to treatment administration. All individual subscales in the FACT-Ga were also evaluated as secondary endpoints. The Chemotherapy Convenience and Satisfaction Questionnaire (CCSQ) was administered at the beginning of the first 4 cycles.

Results: Of the 588 patients dosed at cycle 1 in the CF arm, and the 521 in the CS arm, 456 and 498 respectively at least one question on the FACT-Ga and 445 and 486 respectively completed at least 37 items. Compliance to questionnaire fulfillment was more than 80% through Cycle 9. Although there were no overall differences in FACT-Ga scores between the treatment arms and minimal changes over time, an advantage for CS relative to CF was observed for Physical Well-Being (PWB) (51.7% versus 45.1%, p = 0.044). CS treated patients experienced significantly longer time to worsening in PWB scores, with a median time of 4.5 months (95% CI: 3.0–5.1) compared to 3.0 months (2.8–4.6) with CF (p = 0.014). Patients receiving CS reported higher best and worst score of PWB, Chemotherapy Convenience and Chemotherapy Concerns scores.

Conclusions: Even if there is little evidence to indicate any difference in FACT-Ga scores, some advantage to CS relative to CF was observed for PWB, one of the
A MULTI-CENTER PHASE II STUDY AND PREDICTIVE BIOMARKER ANALYSIS OF COMBINED CETUXIMAB AND MODIFIED FOLFIRI AS SECOND-LINE TREATMENT IN PATIENTS WITH METASTATIC GASTRIC CANCER

L. Jin
Medical Oncology, Fudan University Cancer Center, Shanghai, CHINA

Background: This study was conducted to explore potential biomarkers for prediction of clinical outcome of cetuximab in combination with modified FOLFIRI (mFOLFIRI) and to analyze safety of this regimen as a second-line treatment in metastatic gastric cancer patients.

Methods: A total of 61 patients received an initial intravenous (IV) dose of cetuximab (400 mg/m²) and weekly doses (250 mg/m² thereafter. On day 2 of each 14-day period, patients received IV irinotecan (180 mg/m²), leucovorin (200 mg/m²), and an IV bolus dose of 5-FU (400 mg/m²) followed by a continuous infusion of 5-FU (2400 mg/m²) for 46 hours. The primary endpoint was time-to-progression (TTP).

Findings: The response rate (RR) was 33.3% among 54 evaluable patients. In the intention-to-treat (ITT) analysis, median TTP was 4.6 months (95% confidential interval [CI]: 3.6-5.6 months) and median overall survival (OS) was 8.6 months (95% CI: 7.3-9.9 months). It was demonstrated that plasma vascular endothelial growth factor (VEGF) level could be a predictive factor for the treatment efficacy. The patients with low (≤12.6 pg/ml) and high (>12.6 pg/ml) baseline plasma VEGF levels, RR values were 55.0% and 5.3%, respectively (P = 0.001); median TTP values were 6.9 months and 2.8 months, respectively (P = 0.0005); and median OS values were 12.6 months and 5 months, respectively (P < 0.0001). None of these patients experienced KRAS, BRAF, or PIK3CA mutations.

Interpretation: Low baseline plasma VEGF levels were identified as a potential predictive biomarker of prognosis. Combination therapy comprising cetuximab and mFOLFIRI was well tolerated, which would be potentially used as a second-line treatment for patients with advanced gastric cancer.

Funding: This study was supported by Fudan University Shanghai Cancer Center; Merck KGaA Darmstadt, Germany, and National "Eleventh Five-year plan" new drug discovery major projects of P. R. China.

Disclosure: All authors have declared no conflicts of interest.

PHASE II STUDY OF INTRAVENOUS AND INTRAPERITONEAL PACLITAXEL COMBINED WITH S-1 FOR GASTRIC CANCER WITH METASTASES TO THE DISTANT PERITONEUM

H. Ishigami1, J. Kitayama2, H. Yamaguchi2, S. Emoto2, T. Watanabe2
1Department of Outpatient Chemotherapy, The University of Tokyo, Tokyo, JAPAN, 2Department of Surgical Oncology, The University of Tokyo, Tokyo, JAPAN

Background: Intraperitoneal (i.p.) chemotherapy is a promising treatment option for gastric cancer with peritoneal metastasis. We previously carried out phase I and phase II studies of intravenous (i.v.) and i.p. paclitaxel (PTX) combined with S-1, and verified the safety and efficacy in gastric cancer with microscopic peritoneal metastasis and/or cancer cells on peritoneal cytology (Oncology 2009, Ann Oncol 2010). This regimen was approved as an advanced medical treatment by the Ministry of Health, Labour and Welfare of Japan, and further clinical studies were required for approval of coverage by the Japanese National Health Insurance System. Therefore, we carried out another phase II study in gastric cancer patients with microscopic peritoneal metastasis.

Patients and methods: Gastric cancer patients with microscopic peritoneal metastasis confirmed by staging laparoscopy were enrolled. PTX was administered i. v. at 50 mg/m² and i.p. at 20 mg/m² on days 1 and 8. S-1 was administered orally twice daily at 80 mg/m²/day for 14 consecutive days followed by 7 days rest. The primary endpoint was the 1-year overall survival rate. Secondary endpoints were the response rate, efficacy against malignant ascites and safety.

Results: Thirty-five patients were enrolled. All patients had several to numerous metastases to the distant peritoneum. The median number of courses was 11 (range 2-29). The 1-year overall survival rate was 77% (95% CI, 63-91%). The overall response rate was 71% in 7 patients with target lesions. Malignant ascites disappeared or decreased in 6 of 9 (67%) patients with massive ascites. Cancer cells ceased to be detected by peritoneal cytology in 28 of 29 patients. The incidences of grade 3/4 hematological and non-hematological toxicities were 34% and 9%, respectively, all of which were manageable and reversible. The frequent grade 3/4 toxicities included neutropenia (34%), leukopenia (23%) and anemia (9%). There were no treatment-related deaths.

Conclusion: Combination chemotherapy of weekly i.v. and i.p. PTX combined with S-1 is well tolerated and active in gastric cancer patients with microscopic peritoneal metastasis.

Disclosure: All authors have declared no conflicts of interest.

HER2 STATUS IN ADVANCED GASTRIC CARCINOMA PATIENTS TREATED WITH TRASTUZUMAB

G. Gomez-Martín1, J. C. Plaza2, E. Del Valle3, F. Pons Valladares4, P. Jimenez Forcada5, A. Salud6, A. Leon7, F. Rivera8, E. Garralda1, F. Lopez-Rios2
1Clinical Research Programme, Spanish National Cancer Research Center, Madrid, SPAIN, 2Laboratorio Dianas Terapeuticas, Hospital Universitario Madrid-Norte Sanchinarro, Madrid, SPAIN, 3Pathology Department, Hospital Universitario Miguel Servet, Zaragoza, SPAIN, 4Medical Oncology, Hospital de El Mar, Barcelona, SPAIN, 5Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, SPAIN, 6Medical Oncology, Hospital Universitario Arnau de Vilanova, Lerida, SPAIN, 7Medical Oncology, Fundacion Jimenez Diaz, Madrid, SPAIN, 8Medical Oncology, Hospital Universitario Marques de Valdecilla, Santander, SPAIN

Background: Trastuzumab (T) added to standard chemotherapy increases overall survival for HER2 positive advanced gastric carcinoma (AGC) patients. The approval of T by the EMA in AGC was linked to the determination of the HER2-status by immunohistochemistry (IHC), and hybridization was only permitted in the 2+
Background: The purpose of this trial is to determine the recommended dose (RD) of vorinostat (V), a histone deacetylase inhibitor, in combination with capcitabine (X) and cisplatin (P) and to explore feasibility of V-XP at the RD in advanced gastric cancer.

Patients and methods: The standard 3 + 3 method was used to determine the RD of 3-weekly V-XP during the first cycle. The doses of X (days 1-14, p.o.), P (day 1, i.v.), and V (days 1-14, p.o.) were escalated as following scheme: X 1,600 mg/m2/day, P 60 mg/m2, V 400 mg/day in level 2A; X 2,000 mg/m2/day, P 60 mg/m2, V 400 mg/day in level 2B; X 2,000 mg/m2/day, P 60 mg/m2, V 400 mg/day in level 3; X 2,000 mg/m2/day, P 60 mg/m2, V 400 mg/day in level 4.

Results: Total of 24 patients were enrolled. Median age was 50 years (range, 25-66), and 14 (60%) were male. Dose limiting toxicity (DLT) was noted in 1 of 6 in level 1 (Grade 4 thrombocytopenia), 0 of 3 in level 2A, 1 of 6 in level 2B (Grade 3 fatigue), 1 of 6 in level 3 (Grade 3 stomatitis) and 2 of 3 in level 4 (Grade 4 thrombocytopenia, and discontinuation of treatment due to neutropenia more than 3 weeks). Grade 3 toxicity included anemia (8.6%), nausea and vomiting (10.0%), stomatitis (5.7%), infection (8.6%), diarrhea (2.9%). In summary, our results show that a modified DCF regimen may have tolerable toxicities and be an effective and convenient palliative treatment of advanced gastric cancer.

Disclosure: All authors have declared no conflicts of interest.

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INTRAPERITONEAL INFUSION OF DOCETEXEL COMBINED WITH ORAL S-1 FOR METASTATIC OR RECURRENT GASTRIC CANCER PATIENTS WITH PERITONEAL METASTASIS

H. Yabuhashi, N. Atsushii, A. Matsuki, M. Aizawa
Surgery, Nigata Cancer Center Hospital, Nigata, JAPAN

Introduction: Though many modalities of chemotherapy have been tried for metastatic or recurrent gastric cancer (GC) patients (pts) with peritoneal dissemination, it remains uncontrollable yet. Docetaxel (D) and S-1 have different mechanisms of anti-tumor activity and they are effective against advanced GC. Recently, intraperitoneal administration (IP) of D has proved to be effective for peritoneal dissemination.

Material and methods: Eligibility included metastatic or recurrent GC with peritoneal dissemination, capability of oral intake, adequate organ function, and good PS (0-2). IP catheters were placed for all patients after histological confirmation of peritoneal dissemination by laparoscopy or laparotomy. The treatment of oral S-1 (80 mg/m2 daily dose day 1-14, q4w) and DO (55–45 mg/m2 ip day 1 and 15, q4w) was repeated every 4 weeks until disease progression or unacceptable toxicities.

Results: Between Aug. 2001 and Mar. 2012, 52 pts (P3; 25, P2; 4, PSCY1; 23) including 27 males and 25 females, with a median age of 59 (21-80) were enrolled. Total No. of cycle was 334, the median No. of cycle was 6 (2-15), reduced courses (>7 days) were 109, delayed courses (>7 days) were 46. Reductive gastrectomy was performed for 7 cases. The grade 3/4 toxicities were neutropenia (5.8%), anemia (7.7%), anorexia (13.5%), fatigue (9.6%), and diarrhea (9.6%), respectively. However febrile neutropenia, grade 4 non-hematological toxicities and TRD were not observed. The incidence of cancer cell positive cytology (CY1) changed to negative (CY0) was 61.0% (25/41), but no obvious peritoneal metastasis (P1-P3) disappeared. The MST was 11.1 months and l-, 2- and 3-year survival rate was 48.1%, 23.1 and 9.6%, respectively.

Conclusions: With respect to low toxicity and high feasibility, IP infusion of DOC with oral S-1 is an alternate treatment for metastatic or recurrent GC with peritoneal dissemination.

Disclosure: All authors have declared no conflicts of interest.

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A PHASE I DOSE-FINDING STUDY OF VORINOSTAT (V) COMBINED WITH CAPECITABINE (X) AND CISPATIN (P) AS FIRST-LINE THERAPY IN PATIENTS WITH ADVANCED GASTRIC CANCER

C. Yoo, M.H. Ryu, B. Ryoo, D.H. Koo, I. Park, Y. Kang
Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, KOREA

Background: In this study, we sought to evaluate the use of Dual Colour Silver-staining in situ hybridization (dc-SISH) for selecting patients with AGC as candidates to anti-HER2 therapies.

Material and methods: Sixty-nine AGC patients meeting a previously set specific inclusion criteria were included: previous treatment with Trastuzumab-based chemotherapy, adequate follow-up, available pathology data and suitable sample for molecular analyses. IHC results were determined by the Pathway anti HER2/neu (4B5) antibody in the fully automated platform Benmark ULTRA® (Ventana Medical Systems, Inc, Tucson, AZ). Automated dc-SISH was performed on Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ). INFORM HER2 DNA Probe and INFORM Chromosome 17 Probe was visualized on the same slide following the manufacturer’s protocols. Gene to CEN-17 ratio was calculated using the cut-off value of HER2/CEN-17 ratio ≥2 as amplified. IHC evaluation was performed according to published guidelines.

Results: All cases were amplified. Low polisomy was present in 4 cases. A statistical significant relationship was found between IHC and dc-SISH results (p < 0.0001), with 94% of IHC 3+ expressing dc-SISH ratio ≥4. Median OS was 19 months (95% CI: 13.4 – 23.9 months) for the entire population. Mean OS was significantly longer in the group of patients with amplification ratio ≥4 (21.4 vs. 8.0 months, HR 0.41, p = 0.0087, CI95% 0.236–0.818). No differences were observed in OS according to IHC results when stratified in two groups (3+ vs 0/1+2+) (21.0 vs 10.9 months, HR 0.5288, CI95% 0.2469 – 1.1325, p = 0.0955).

Conclusions: Dc-SISH amplification ratio ≥4 predicts OS benefit in AGC patients treated with trastuzumab in this study. Characterization in a larger cohort of patients is ongoing.

Disclosure: All authors have declared no conflicts of interest.
Results: Samples from 63 patients were obtained, ampullary tumours were excluded. The median age was 58 years. Tumour stages were I-II = n = 19 (30%), III = n = 22 (35%), IV = n = 20 (32%) and undefined = n = 2 (3%). A HER2 overexpression (3+) was observed in 5 (10%) cases in ileum. Overexpression of TP53 was observed in 23/53 (43%). Abnormal expression of β catenin was observed in 11/52 (21%) cases. A loss of MMR proteins occurred in 7/55 (13%) cases (3 MLH1, 2 MSH2, 2 MSH6), none was stage IV. A KRAS mutation was observed in 19/48 (40%) cases that involved codon 12 in 13/68 (cases) or G > A transition in 16/84 (cases). Tumours with KRAS mutation were stage IV in 31% of the cases. Survival analysis will be available at the meeting.

Conclusion: This large study suggests that molecular phenotype of SBA is close to colon phenotype with low level of HER2 overexpression and high level of KRAS mutation. Ileum tumours seem to have a different phenotype than proximal tumours.

Disclosure: All authors have declared no conflicts of interest.

704P COST-EFFECTIVENESS OF THREE-YEARS OF ADJUVANT IMATINIB IN GASTROINTESTINAL STROMAL TUMORS (GIST) IN CANADA

A. Parthan1, M. Sanon1, J. Coombs2, K. El Ouagari3
1Health Economics and Outcomes Research, OptumInsight, Medford, MA, UNITED STATES OF AMERICA, 2Health Economics, Novartis Pharmaceuticals, Florham Park, NJ, UNITED STATES OF AMERICA, 3Health Economics, Novartis Pharmaceuticals Canada Inc, Quebec, QC, CANADA

Background: Recent clinical trial data have demonstrated that 3 years (yrs) of adjuvant imatinib therapy for patients with surgically resected GIST leads to a significant improvement in recurrence free survival & overall survival vs. 1 yr of therapy. The objective of this study is to assess cost-effectiveness of treating with 3 yrs vs. 1yr of adjuvant imatinib in Canada from a payer’s perspective.

Methods: A Markov model was developed to predict GIST recurrence, treatment (txt) costs, & quality-adjusted survival over a lifetime horizon. Patients transitioned between 3 health states: free of GIST recurrence, GIST recurrence, & death. Monthly recurrence & mortality rates for 3 yr & 1yr imatinib were derived from SSGVIII/AIO clinical trial. The 5 yr recurrence rate observed in the trial was extrapolated for the remaining duration of the model horizon. First recurrence after active txt was treated with imatinib 400 mg daily and recurrence during active txt was treated with 800mg daily. For subsequent disease progression, patients were treated with imatinib 800mg, sunitinib or best supportive care. After 5 yrs, txt specific mortality rate was applied for patients with recurrence. Costs & utilities were derived from published literature. Expected costs & quality-adjusted life years (QALYs) were estimated for each txt strategy. Costs & QALYs were discounted at 5% per yr. Extensive sensitivity analyses were conducted.

Results: Patients on 3 yrs of imatinib had higher QALYs (7.70 vs 6.54) vs. 1yr of imatinib. Total lifetime cost per patient was $182,000, with 3 yrs vs. $134,500 for 1yr of imatinib therapy. Incremental cost effectiveness ratio of 3 yrs of imatinib vs 1yr of imatinib was $40,877/QALY. Model results were sensitive to rate of GIST recurrence beyond 5 yrs. At a threshold of $100,000 or $50,000/QALY, 3yr imatinib therapy was cost-effective in 100% of simulations vs 1 yr of imatinib.

Conclusions: Model results suggest that treating patients with 3 yrs of imatinib is cost-effective vs. 1yr of imatinib below the commonly used threshold in Canada. Both clinical & economic results suggest treating surgically resected GIST patients with 3 yrs of imatinib will result in improved quality-adjusted & overall survival.

Disclosure: A. Parthan: Study was sponsored by Novartis and I have consulting relationship with Novartis. M. Sanon: The study was sponsored by Novartis and I had consultancy relationship with Novartis at the time of the study. J. Coombs: Employed at Novartis and holds Stock for Novartis. K. El Ouagari: employed at Novartis and owns stocks for Novartis

705P PHASE I TRIAL OF SUNITINIB PLUS IMATINIB IN PATIENTS WITH METASTATIC OR UNRESECTABLE GASTROINTESTINAL STROMAL TUMORS (GIST)

A. Lopez Poussa1, L. Paz-Ares2, C. Pericay3, X. Garcia Del Muro4, M.J. Flor5
1Medical Oncology, Hospital de la Sta. Creu i St. Pau, Barcelona, SPAIN, 2Oncology Service, Hospital Virgen del Rocio, Sevilla, SPAIN, 3Medical Oncology, Corporatıon Santarıa Parı, Taulıt Instıtutı Parı, Sabadell, SPAIN, 4Medical Oncology, Institut Català d’oncología, L’Hosptal de Llobregat, SPAIN, 5Oncology Service, Hospital Virgen del Rocıo, Sevilla, SPAIN

Background: Patients (Pts) with GIST harboring mutations in KIT exon 9 or wild type tumors showed better responses to sunitinib along with longer median progression-free survival (PFS) rates compared with exon 11 mutant tumors Pts. We have hypothesized that the combination of s plus 1 in unresectable GIST would be synergistic and associated to a tolerable side effect profile.

Methods: This is a phase I, dose-escalation study to determine the maximum-tolerated dose (MTD), safety and antitumor activity measured by response rate of s plus 1 in naive patients with metastatic or unresectable GIST. Pts with adequate organ function, performance status (ECOG) 0–1, age >18 years, were eligible. Treatment consisted on oral s 25mg/day d1–28 combined with oral 1 300mg/ day d1–28 (level I) or oral 400mg/day d1–28 (level II).

Results: 3 pts were enrolled on level I. No DLTs were observed. At level II 7 pts were enrolled and 1 DLT was observed (posterior reversible encephalopathy syndrome on day19). Although 1DLT was observed in 7 pts, decision was not to increase the S dose to 37.5 mg due to toxicity. Other non-DLTS adverse events were G4 hyperbilirubinemia in cycle 2 and G4 intratumoral haemorrhage in cycle 3. The MTD was determined as 1400mg/day and S 25mg/day. Other toxicities were neutropenia, diarrhea, vomiting, asthenia, musculoskeletal pain, anaemia and bacteraemia. Median time on treatment with the combination was 16 weeks (range 12–152) on level I and 20 weeks (range 3–88) on level II. 66% of patients completed 20 weeks of treatment. Serious Adverse Events were reported in 4 pts; 3 deaths were reported, one due to disease progression, another due to reversible encephalopathy syndrome and the last one due to septic shock. A partial response was achieved in 6 (60%) pts; complete response in 2 (1 wild-type) and stable disease in 1 (10%).

Conclusions: Sunitinib 25mg/day plus Imatinib 400mg/day in the MTD and a safe and well tolerated combination in pts with metastatic or unresectable GIST. Response rates seems to be higher than those expected and previously observed with S or Imatinib monotherapy. This study was supported by an Independent Investigator Research grant from Pfizer, Inc

Disclosure: All authors have declared no conflicts of interest.
Results: Three years of adjuvant imatinib therapy for patients at high risk of recurrence was predicted to achieve an additional 1.58 QALYs compared with one year of treatment. These health benefits are gained at an estimated incremental cost per QALY of €14,108. These results were robust to changes in key model parameters.

Conclusions: The analysis suggests that, for patients at high risk of recurrence following surgical resection of localised GIST, three years of adjuvant imatinib treatment leads to improved long term quality-adjusted survival compared with one year’s therapy. Extended adjuvant treatment with imatinib represents good value for money according to currently accepted standards of cost-effectiveness in Scotland.

Disclosure: L. Gray: I am an employee of Novartis Pharmaceuticals UK Ltd, manufacturer of imatinib. All other authors have declared no conflicts of interest.
Background: CPT-11 showed modest activity and tolerability in metastatic pancreatic cancer (MPC). We developed a new strategy to improve efficacy and tolerability of CPT-11 based regimen in MPA patients (pts).

Methods: Chemotherapy-naive pts with histologically proven MPA, bilirubin levels < 1.5 ULN and performance status (PS) 0-1 were randomized in a phase II trial to receive either FOLFIRI.3 (CPT-11 90 mg/m2 as a 60-min infusion on day (D) 1, leucovorin 400 mg/m2 as a 2-hr infusion and CPT-11 90 mg/m2 as a 4-hr infusion and CPT-11 90 mg/m2, repeated on D3, at the end of the 5-FU infusion, every 2 weeks) for 2 months alternating with Gemcitabine (G) (1000 mg/m2 at a fixed dose rate of 10 mg/m2/min on D1, D8, D15, D29, D36 and D43) for 4 months (arm A) or G alone (arm B). Using Fleming design the primary end point was rate of progression free survival (PFS) at 6 months from (H0) 25% over (H1) 45% needing to include 98 pts/arm.

Results: Between 2007 and 2011, 98 pts were enrolled (males: 59, median age: 62 years, PS 0: 32%). Median follow-up was 23 months. Grade 3-4 toxicities per pts (% in arm A/B were diarrhea 13/0, nausea-vomiting 11/4, neutropenia 51/25 and febrile neutropenia 4/0. No toxic death occurred. Response rate were 40 and 11% as disease control rate (CR + PR + SD) were 73 and 52% in arm A and B, respectively. The primary endpoint of the trial was met with rate of PFS at 6 months of 48% (95% CI: 33-63) in arm A while in arm B PFS was 30% (95% CI: 17 - 44). One year PFS was 23% (95%CI: 11.5-36) and 11% (95%CI: 4.21), respectively.

Conclusions: FIBGEM strategy is feasible and efficient with a manageable toxicity profile in good condition pts with MPA. A phase III trial comparing this strategy with the FOLFIRINOX triplet therapy focusing on quality of life should now be performed.

Disclosure: All authors have declared no conflicts of interest.

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DOES FDG-PET-CT BASED RE-STAGING INFLUENCE INITIAL MANAGEMENT DECISION AND CLINICAL OUTCOME IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CARCINOMA PLANNED TO UNDERGO CHEMORADIOThERAPY?

C. Parlak,1 O.C. Ouler,1 U. Selcuk,1 O. Ozyilkan,1 E. Topkan1

1Department of Radiation Oncology, Baskent University Adana Medical Faculty, Adana, TURKEY, 2Department of Radiation Oncology, American Hospital-University of Texas M.D. Anderson Radiation Oncology Center, Istanbul, TURKEY, 3Medical Oncology, Baskent University Faculty of Medicine/Adana Uygulama Ve Arastirma Mer., Adana, TURKEY

Background: Impact of re-staging with 18F-fluoro-deoxy-glucose positron emission tomography (PET-CT) on management decision and clinical outcomes in patients with locally-advanced pancreatic carcinoma (LAPC) initially planned to undergo concurrent chemoradiotherapy (CRT) was assessed.

Materials and methods: Seventy-one consecutive patients with conventionally staged LAPC were re-staged with PET-CT before CRT. Patients were categorized into non-metastatic (M0) and metastatic (M1) groups according to PET-CT findings. M1 patients underwent 50.4 Gy (1.8 Gy/2) of radiotherapy and concurrent 5-FU followed by maintenance gemcitabine.

Results: Re-staging PET-CT revealed conventional imaging occult distant metastases in 19 cases (26.8%). OS of 52 patients with LAPC confirmed by PET-CT, additional regional lymph nodes were identified to be involved in 7 (13.4%), mandating enlargement of radiation field. Taken together, PET-CT results changed or revised initial management decision in 37.2% patients. Median follow-up times for the whole, M0 and M1 cohorts were 11.3, 14.5, and 6.2 months, respectively. Median overall, locoregional progression-free, and progression-free survival for the same cohorts were 11.8, 16.1, and 5.1 months, 16.1, 9.9, and 7.4 months, and 6.2, 3.4, and 2.5 months, respectively. Survival differences between M0 and M1 cohorts were statistically significant (p < 0.05, for each).

Conclusions: Current results demonstrated the importance of PET-CT based re-staging of LAPC in selection of suitable patients for CRT, prevention of useless aggressive treatment in metastatic cases, and precise estimation of survival outcomes of LAPC patients following radical CRT.

Disclosure: All authors have declared no conflicts of interest.

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MISTLETOE EXTRACT THERAPY VERSUS NO ANTI NEOPLASTIC THERAPY IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC PANCREATIC CANCER: A RANDOMIZED CLINICAL PHASE III TRIAL ON OVERALL SURVIVAL

D. Galun1, W. Tröger2, M. Reif3, A. Schumann4, N. Stankovic5, M. Milčević1

1HPB Surgical Department, First Surgical Clinic of the Clinical Centre of Serbia, Belgrade, SERBIA, 2Directorship, CRDT, Freiburg, GERMANY, 3Directorship, Institute for Clinical Research, Berlin, GERMANY, 4Biometry, Institute for Clinical Research, Berlin, GERMANY, 5Data Management, Clinica Boss, Niš, SERBIA

Purpose: To compare the overall survival (OS) and quality of life (QoL) of advanced pancreatic cancer patients receiving mistletoe extract (ME) therapy or no antineoplastic therapy.

Patients and methods: In this prospective, parallel, open label, monocenter, group-sequence, randomized phase III study patients with locally advanced or metastatic adenocarcinoma of the pancreas were stratified according to their prognosis index, a binary composite of age, tumor stage and performance status, and were evenly randomized to s.c. injections of ME (Iscaradin® Qa special) in a dose-escalating manner from 0.01 mg up to 10 mg three times per week, or no antineoplastic therapy. All patients received best supportive care. The primary endpoint was 12-month OS to be repeatedly assessed in three subsequent group-sequential analyses. Secondary efficacy parameters were the QoL dimensions of the core questionnaire of the European Organisation for Research and Treatment of Cancer.

Results: This first interim analysis includes data from 220 patients. Baseline characteristics were well balanced between the ME and control groups. Median OS for ME versus control patients was 4.8 vs 2.7 months (progression-group adjusted hazard ratio, HR = 0.49; p < 0.0001); within the ‘good’ prognosis subgroup 6.6 vs 3.2 months (HR = 0.43; p < 0.0001); within the ‘poor’ prognosis subgroup 3.4 vs 2.0 months (HR = 0.55; p = 0.0031). Thirteen of the 15 QoL dimensions significantly favored ME. The ‘Global Health Status/QoL’ was significantly higher for ME versus control patients by 23.5 points (average patients’ post-baseline median: 54.2 ± 8.17 vs. 30.7 ± 8.46 p < 0.0001). No ME-related serious or non-serious adverse events were observed.

Conclusion: In this analysis ME therapy showed a significant and clinically relevant increase of OS and quality of life. The independent data monitoring committee recommended the termination of the trial due to proven efficacy. ME may provide an effective second-line therapy for patients with locally advanced or metastatic pancreatic cancer after failure of, or ineligibility for, first-line therapies.

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713P

NEOADJUVANT GEMOX FOLLOWED BY GEM-BASED CHEMORADIATION FOR LOCALLY ADVANCED UNRESECTABLE UNRESSECTABLE PANCREATIC CANCER

V. Vacarcj,1 I. Sperduti2, E. Bria,3 B. Saracino4, M.S. Pino,5 G. Grazi?, A. Grippi2, M.L. Vallà,5 F. Cossuet1, M. Milla1

1Medical Oncology, Regina Elena National Cancer Institute, Roma, ITALY, 2Biostatistics, Regina Elena Institute, Roma, ITALY, 3Medical Oncology, Azienda Ospedaliera Universitaria Integrata Verona-"Borgo Roma", Verona, ITALY, 4Medical Oncology, USL 10 Firenze, Firenze, ITALY, 5Surgical Oncology, Regina Elena National Cancer Institute, Roma, ITALY, 6Radiology, Regina Elena National Cancer Institute, Roma, ITALY

Purpose: To assess activity, safety and secondary resectability in unresectable locally advanced pancreatic cancer (LAPC) patients (pts).

Methods: Unresectable LAPC pts were eligible for this phase II study. Primary endpoint was clinical benefit (CB = CR + PR + SD). A sample size of 37 pts was
considered sufficient to give an 80% probability of rejecting a baseline clinical benefit rate of 55%, with an exact 5% one-sided significance test when the true disease control rate was 75%. The drug regimen would have been considered inferior at least 26 patients in each arm. Non-inferiority of chemotherapy. Neoadjuvant chemotherapy (CET) encompassed gemcitabine (GEM) 1000 mg/m² (100 min infusion on d1) and oxaliplatin 100 mg/m² (2-hr infusion on d2) every 2 wks, for 6 cycles. After CET pts were rested for surgery and/or chemoradiation (CRT) consolidation (EBRT up to a total dose of 50.4 Gy plus concomitant GEM 300 mg/m²/week). After CRT completion, pts were rested to evaluate secondary surgery.

**Results:** From January 2005 to January 2012, 35 pts (M/F: 17/18; median age: 68 yrs, range: 46-78; ECOG PS 0-1/2: 28/7) entered the study. A median of 5 (range 1-7) CET induction cycles were delivered. Toxicity was mild, with G4 neutropenia in 2 pts (6%), G3 thrombocytopenia in 1 pt (3%), G3 anemia in 5 pts (14%), and G3 diarrhea in 2 pts (6%). CET dose was reduced or delayed in 8 and 7 pts, respectively. Nine confirmed PR and 17 SD were observed for a CB of 74% (95% confidence interval [CI]: 62.7-87.5%). A decompression CT 19.9±0.5% of the baseline was observed in 14 of 23 evaluable pts. Nine-teen pts completed CRT, including 5 pts who subsequently underwent surgery; 1 pt underwent surgery without CRT. Toxicity for the CRT phase was mild, with G3 thrombocytopenia in 1 pt (3%) and G3 neutropenia in 3 pts (8%). Median overall survival (OS) and progression free survival (PFS) for all 35 patients were 10 (95% CI, 8-12) and 9 mos (95% CI, 56.7-87.5%). A decrease in serum CA 19.9 was observed in 14 of 23 evaluable pts. Nine-teen pts completed CRT, including 5 pts who subsequently underwent surgery; 1 pt underwent surgery without CRT. Toxicity for the CRT phase was mild, with G3 thrombocytopenia in 1 pt (3%) and G3 neutropenia in 3 pts (8%). Median overall survival (OS) and progression free survival (PFS) for all 35 patients were 10 (95% CI, 8-12) and 9 mos (95% CI, 56.7-87.5%).

**Conclusions:** The regimen under study is active and well tolerated. Although an encouraging response rate was reported, OS remains poor, calling for a better selection strategy for LAPC pts who are candidates to neoadjuvant treatment.

**Disclosure:** All authors have declared no conflicts of interest.

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**714P MODIFIED FOLFOXIRI IN ADVANCED PANCREATIC CANCER**


Oncologia, Triapianti e Nuove Tecnologie in Medicina, Polo Oncologico - Azienda Ospedaliero-Universitaria Pisana - Istituto Toscano Tumori, Pisa, ITALY

**Background:** The combination regimen of 5-fluorouracil/folinic acid, oxaliplatin and irinotecan named FOLFOXIRI has been proposed as a new standard of care for metastatic pancreatic cancer patients. However, FOLFOXIRI was associated with high incidence of grade 3 and 4 toxicities (neutropenia in 45.7% of patients with G-CSF use in 42.5% of patients; febrile neutropenia in 5.4%; diarrhea in 12.7%). Our group had developed a very similar schedule in colorectal cancer named FOLFOXIRI which contains no bolus 5-fluorouracil and a slight lower dose of irinotecan.

**Methods:** The objective of this study was to prospectively evaluate the tolerability and activity of a modified (m) FOLFOXIRI regimen in metastatic or locally advanced pancreatic cancer patients. The regimen included a lower dose of irinotecan (administered at 150 mg/m² on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/m² administered as a 48-hour continuous infusion on days 1 to 3 every 14 days). Folinic acid and oxaliplatin remained unchanged.

**Results:** Thirty-nine patients with cytological or histological diagnosis of pancreatic adenocarcinoma have been treated with mFOLFOXIRI from August 2010 onwards; 17 had metastatic disease while 22 had locally advanced disease. A total of 260 cycles have been administered so far. The grade 3-4 toxicities reported were: neutropenia in 35.9% of patients; thrombocytopenia 2.6%; diarrhea 5.1%; stomatitis 7.7%; nausea/vomiting 5.1%; fatigue 2.6%; liver toxicity 5.1%; sensory neuropathy 5.1%. No toxic deaths and no febrile neutropenia have been occurred. G-CSF has been used in seven patients (18%). A delay in the administration of chemotherapy was required in 12 patients (31%) and a reduction of doses in 7 cases (18%). Among 30 evaluable patients 11 partial responses (36.7%) and 14 stable disease (46.7%) have been observed. Median progression-free survival (PFS) was 11.5 months and median overall survival (OS) 25.5 months. For metastatic patients only, response rate resulted 33% with a PFS and OS of 8.4 and 14.8 months, respectively.

**Conclusions:** The mFOLFOXIRI regimen as we used resulted feasible and quite well tolerated and it maintained its good activity in metastatic pancreatic cancer. **Disclosure:** All authors have declared no conflicts of interest.

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**716P FOLFIRINOX FOR LOCALLY ADVANCED PANCREATIC ADENOCARCINOMA. RESULTS OF AN AGE MULTICENTRIC PROSPECTIVE STUDY**

L. Marthey1, A. Sa-Cunha2, J. F. Blanc2, A. Cuet3, E. Francois4, I. Trouilloud5, D. Malka6, J. Bachelet7, R. Coriat7, J. Taieb10

1Gastroenterology, Bicêtre Hospital, Kremlin Bicêtre, FRANCE, 2Digestive Surgery, Haut Levêque Hospital, Pessac, FRANCE, 3Digestive Oncology, Saint André Hospital, Bordeaux, FRANCE, 4Biostatistics and Epidemiology, Georges Leclerc Cancer Institute, Dijon, FRANCE, 5Medical Oncology, Antoine Lacassagne Cancer Institute, Nice, FRANCE, 6Digestive Oncology, European Georges Pompidou Hospital, Paris, FRANCE, 7Medical Oncology, Gustave Roussy Cancer Institute, Villejuif, FRANCE, 8Gastroenterology, Pitié-Salpêtrière Hospital, Paris, FRANCE, 9Digestive Oncology, Cochin Hospital, Paris, FRANCE, 10Oncologie Digestive, Hospital Européen Georges Pompidou, Paris, FRANCE

**Background:** The FOLFIRINOX regimen improves survival when compared to gemcitabine as first line treatment for patients (pts) with metastatic pancreatic cancer (1). There is no such data in non resecable, non metastatic, locally advanced adenocarcinoma (LAPA). The aim of this study was to evaluate the safety and efficacy of FOLFIRINOX in this setting.

**Methods:** From February 2010 to February 2012, all pts from eleven French hospitals, who started FOLFIRINOX for a pathologically proven LAPA were included in a prospective database. Non resectability was determined by each local multidisciplinary staff. The absence of metastases was assessed by TAP CT-scans. FOLFIRINOX was administered every 2 weeks (oxaliplatin 85 mg/m²; irinotecan 180 mg/m²; leucovorin 400 mg/m²; fluorouracil 400 mg/m² as bolus and 2400 mg/m² as 46-hour continuous infusion).

**Results:** Seventy seven pts were enrolled. We report the preliminary analysis of the first 53 pts as data collection is still ongoing. Patients characteristics were M/F: 30/23; median age 63 (46-79); PS 0/1/2: 24/28/1. Twenty one pts had a bilary stent before starting treatment. The median number of cycles administered was 5 (1-30). There were no treatment-related deaths and 8% of pts stopped treatment because of toxicity. Grade 3-4 toxicities were neutropenia (15%), nausea (13%), diarrhea (8%), anemia (2%), and thrombocytopenia (2%). Grade 2-3 sensitive neuropathy occurred in 19% of pts. Dose reduction was necessary in 28% and prophylactic G-CSF was used in 18% of pts. Partial response rate was 30% (95% CI 17%-43%), and 53% of pts showed stable disease (95% CI 39%-67%), resulting in a disease control rate of 83% (95% CI 73%-93%). Closure external radiotherapy was performed in 62% of pts and 32% underwent surgical resection of their tumour. With a median follow up of 8.5 months (95% CI 7-11), median overall and progression free survivals have not been reached. One year overall and progression free survival rates were 80% (95% CI 75%-92%) and 54% (95% CI 29%-74%), respectively.

**Conclusion:** FOLFIRINOX in LAPA seems efficient with a manageable toxicity profile and led to secondary potentially curative surgery in approximately one third of the pts. These promising results are encouraging to test this regimen in a phase 3 trial. (1) Connolly et al. NEJM 2013; 368: 1841.

**Disclosure:** All authors have declared no conflicts of interest.
A THREE-STEP STRATEGY OF INDUCTION CHEMOTHERAPY, CHEMO-RADIOThERAPY AND SURGERY IN LOCALLy ADVANCED PANCREATIC CANCER (LAPC), A SINGLE INSTITUTIONAL EXPERIENCE

O.E. Carranza Rua1, E. Arevalo1, J.P. Fusco1, E. Castanon Alvarez1, L. Zubiri1, J. A. Gonzalez2, L. Areia1, F. Pardo1, S. Martin Algarra1, J. Rodriguez3
1Medical Oncology, Clinica Universitaria de Navarra, Pamplona, SPAIN, 2Radiation Oncologist, Clinica Universidad de Navarra, Pamplona, SPAIN, 3Surgical Oncology, Clinica Universidad De Navarra, Pamplona, SPAIN

Background: Pancreatic cancer is one of the most highly fatal cancers. A growing evidence suggests that even potentially resectable patients (pts) benefit from a multidisciplinary approach aimed to improve resectability and reduce recurrence. We report our experience after a long-term follow-up.

Methods: From December 2005 to July 2011, 69 histologically confirmed LAPC, endoscopic ultrasound (EUS) staged T3/T4, N0/N1 were scheduled to receive induction gemcitabine-oxaliplatin-based chemotherapy followed by chemo-radiotherapy with weekly oxaliplatin and capecitabine (mean radiotherapy dose of 50.4 Gy) and salvage surgery when feasible. Adjuvant chemotherapy was considered depending on results of the pathologic report.

Results: The median age was 63 years (range 35-83 years). Male to female ratio was 37/37. Forty-one pts (59%) completed the whole program (group A), whereas 26 (37%) received chemo and chemo-radiotherapy but were not eligible for surgery (group B). Two patients (3%) progressed after induction chemotherapy (group C). Endoscopic stent placement was performed in thirty-four pts (49%). Toxicity profile was mild, with no grade 4 toxicity being documented. Grade 3 toxicity included leukopenia (7%), neutropenia (11%), anemia (13%) and nausea, diarrhea and anorexia (1%).

Conclusions: Our data suggest that this three-step strategy is feasible and active in LAPC patients. Correlative molecular analysis seem warranted to rule out the subset of pts most likely to benefit from this approach.

Disclosure: All authors have declared no conflicts of interest.

720P PANCREATIC DUCTAL ADENOCARCINOMA: A HOMOGENEOUS MORPHOLOGICALLY BUT MOLECULARLY HETEROGENEOUS TUMOR. IMPLICATIONS FOR ITS MANAGEMENT

L. Faiodzi1, A. Mandolese2, M. Scartozi1, C. Loretti1, M. Bianconi1, A. Bittoni1, R. Giampieri1, M. Del Prete1, I. Bearzi2
1Clinica di Oncologia Medica, AOU Ospedali Riuniti Ancona Università Politecnica delle Marche, Ancona, ANCONA, ITALY, 2Medicina Interna, Sapporo Hokuyu Hospital, Sapporo, JAPAN

Pancreatic cancer has not achieved significant improvements in therapeutic results, probably due to a poor comprehension of the underlying molecular mechanisms. The aim of our study was to classify pancreatic tumors in categories from a molecular point of view, in order to better identify the main pathogenetic molecular alterations potentially useful as targets for new drugs. In 110 histological samples of pancreatic ductal adenocarcinoma were performed immunohistochemical evaluations of K-ras, stromal IL-6 (IL-6s), tumoral IL-6 (IL-6s), Cox-2, EGFR, Her2, Her3, MLH1, MSH2, MSH3 and molecular biology assessment of CD24, MUC6, HGF, MET, SMAD4, CDK4, CDK6, CDKN2A, P53, VEGF-A, VEGF-C, PDGF-B, WNT1, BMP4,

Genes expression was evaluated for the main genes involved in the progression of pancreatic cancer and the presence of mesenchymal or epithelial traits.

Results: We identified two main clusters, each characterized by specific and unique alterations potentially associated to a different behavior.

Conclusions: Our study suggests that pancreatic ductal adenocarcinoma is a heterogeneous tumor, with distinct molecular and clinical traits. This knowledge will allow a better classification of pancreatic tumors and will provide new opportunities for specific treatments.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: and stable disease occurred in 25% and 43% of 28 evaluable pts, with a disease G-CSF administration did not significantly change G3/4 neutropenia (5/155 [3.2%], presence/absence of biliary stent were found, in terms of G3/4 toxicities. Prophylactic cycle for G3 GI toxicity in 1 pt and early PD in 2 pts. No differences according to cycles, with the exception of G3/4 neutropenia (16.6% of pts, 3.7% of cycles); hematologic toxicity and increased risk of AE in pts carrying biliary stents, may prophylaxis is not currently recommended, it can be considered for older/less fit/ comorbid pts with aPDAC.

Methods: The clinical protocols of 36 aPDAC pts undergone 1st-line FOLFIRINOX in 2 different institutions were reviewed. Toxicities, activity and efficacy were determined according to 1) primary G-CSF prophylaxis (dd 7-9; yes/no 21/15 pts), and 2) presence/absence biliary stent.

Results: Pts characteristics: N: 36; cycles: 241; M/F: 22/14; median age: 57 yrs [range 37-70]; ECOG PS 0/1: 33/3; stage III/IV: 10/26. G3/4 toxicity occurred in ≤1 of cycles, with the exception of G3/4 neutropenia (16.6% of pts, 3.7% of cycles); 25%-dose reduction occurred in 49/205 cycles (23%), with 3 pts stopping after 1 cycle for G3 GI toxicity in 2 pts and early PD in 2 pts. No difference in terms of presence/absence of biliary stent were found, in terms of G3/4 toxicities. Prophylactic G-CSF administration did not significantly change G3/4 neutropenia (5/155 [3.2%], versus 4/66 [6.4%]). Pts receiving G-CSF significantly experienced more anaemia (p < 0.001) and the thrombocytopenia (p = 0.088). Given the administration of PALO/ aprepitant/dexamethasone, complete control of nausea/vomiting was achieved at cycle 1 in 72% (95% CI: 58-87%) and 86% (95% CI: 75-97%) of pts. Partial response and stable disease occurred in 25% and 43% of evaluable pts, with a disease control rate of 68% (95% CI: 51-85%). Median PFS was 8 mos (95% CI: 6-9 mos), 61% of pts experienced ≥50% reduction in CA19.9.

Conclusions: These data indicate that FOLFIRINOX seems to be well tolerated and easily manageable in young (<70 yrs) and fit (PS 0-1) aPDAC pts on an outpatient basis, and may be employed in pts with biliary stents. Although the routine G-CSF prophylaxis is not currently recommended, it can be considered for older/less fit/ comorbid pts with aPDAC.

Disclosure: All authors have declared no conflicts of interest.

A PILOT TRIAL OF GEMCITABINE IN COMBINATION WITH CAPECITABINE OR ERLOTINIB COMPARED TO GEMCITABINE ALONE IN PATIENTS WITH ADVANCED PANCREATIC CANCER

J.Y. Cho1, J.Y. Lim1, S.J. Lee2, D.K. Lee3, J.S. Park4, D.S. Yoon5, Y.H. Min6
1Medical Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, KOREA, 2Gastroenterology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, KOREA, 3Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, KOREA, 4Hematology, Severance Hospital, Seoul, KOREA

Aims: This pilot study was designed to compare the survival benefit of gemcitabine plus capecitabine (GEM-X) or gemcitabine plus erlotinib (GEM-T) over gemcitabine alone (GEM) in pts with locally advanced or metastatic pancreatic carcinoma of the pancreas were recruited. Patients were assigned to GEM, GEM-T, or GEM-X. The primary end points were the overall survival (OS) and response rate.

Results: A total of 127 patients were assigned to receive GEM (n = 47), GEM-T (n = 44), and GEM-X (n = 36). GEM-X significantly improved the objective response rate (21.2% vs. 12.7% and 15.9%) and the overall disease control rate (partial response plus stable disease; 72.7% vs. 63.8% and 59.1%) compared to GEM and GEM-T, respectively.

Conclusion: GEM-X is plausible first-line treatment for locally advanced and metastatic pancreatic cancers. GEM-X was superior to GEM and GEM-T. The incidence of adverse events was not significantly different among groups.

Disclosure: All authors have declared no conflicts of interest.

SIGNIFICANT ASSOCIATION BETWEEN VEGF-A AND ABCB1 POLYMORPHISMS AND SURVIVAL IN METASTATIC PANCREATIC ADENOCARCINOMA (MPA) PATIENTS (PTS) TREATED WITH MAINTENANCE SUNITINIB (MS)

M. Reni1, E. Giovannetti2, S. Cereda1, C. Belli1, A. Passardi3, G. Di Lucca4, E. Ferrari1, F. Bergamo6, A. Novarino7, H.M. Verheul2
1Oncologia, IRCCS San Raffaele, Milano, ITALY, 2Department of Medical Oncology, VU University Medical Center, Amsterdam, NETHERLANDS, 3Biostatistics, Regina Elena Institute, Rome, ITALY, 4Medical Oncology, USL 10 Firenze, Firenze, ITALY, 5Division Medical Oncology A, Istituto Regina Elena, Roma, ITALY

A randomised multi-centre phase II trial explored the role of MS in pts with MPA without progressive disease (PD) after induction chemotherapy (CT), using an observation only group (O) as calibration arm (Reni et al. Proc ASCO 2012). The aim of this present study was to identify genetic polymorphisms related to pharmacokinetcis and pharmacodynamics of sunitinib that are associated with outcome. Adult pts with pathologic diagnosis of MPA, performance status (PS) ≥0, no PD within 6 months of CT were randomized to O (pts A) or MS at 37.5 mg daily until PD or a maximum of 6 months (arm B). Functional polymorphisms of 6 genes involved in sunitinib activity, metabolism and transport (VEGFA, VEGFR-2, CYP3A5, CYP1A1, ABCB1, ABCG2) were studied in genomic DNA from baseline blood samples, using PCR Taqman®-probes-based assays. Associations of genotypes with overall survival (OS) and progression-free survival (PFS) were evaluated by Log-rank test. Genotyping was successfully performed in all the DNA samples of 43 consenting pts of 55 enrolled in the trial (78%; arm A/B: 83%/73%; p = 0.39). Significantly, 7nger OS was observed in (P < 0.05) group-1 arm A (median OS 20 months) as compared to 36 pts with 3435CC/CT genotype (group-2; median OS 7 months; p < 0.005). Median OS was 24 months in group-1 arm A pts, 7 months in group-2 arm B pts (p = 0.12); 16 months in group-1 arm A pts and 9 months in group-2 arm A pts (p = 0.67). No OS difference was observed in 28 pts harbouring the VEGFA-634G-C genotype.
(group-3; median OS 10 months) as compared to 15 pts with -634G/G genotype (group-4; median OS 8 months; p = 0.15). However, median OS was 13 months in 13 group-3 arm B pts, 6 months in 6 group-4 arm B pts (p = 0.016); 9 months in 15 group-3 arm A pts and 11 months in 9 group 4 arm A pts (p = 0.67). These results suggest that polymorphisms of genes involved in expression of the main ligand for VEGFR2 (VEGFA 634G>C) and of efflux transporters (ABCB1 3435C>T) are promising candidates as predictive marker for selecting pts with MPA who may benefit of M. Given the small sample size of these analyses, a larger confirmatory trial is necessary and appears worthwhile.

Disclosure: All authors have declared no conflicts of interest.

725P PATHOLOGICAL PROOF AND SURVIVAL FOR PATIENTS WITH BILIARY-TRACT OR PANCREATIC TUMOR

C. Desaures1, F. El Hajbi1, K. Ligier1, A. Duhamel1, F. Richard2, C. Rosell2
1Medical Oncology, C.H.U. Claude Huriez, Lille, FRANCE, 2Hospital St Vincent de Paul, Service D’Onco-Hématologie, Université Catholique de Lille, Lille, FRANCE.

As recommended by ESMO, a final pathological diagnosis (PD) has to be obtained before any chemotherapy, radiotherapy or other non-surgical oncological therapy for pancreatic or biliary tract cancer. PD is also required for inclusion in a clinical trial. In practice, it is sometimes difficult to obtain this pathological proof because of difficult access or poor performance status. Treatment decision is then collegial, based on a clinical, radiological and biological suspicion. We studied patient survival based on availability of PD from the cancer registry of Lille and its region (800 000 inh. - Nord France). We reviewed patients records over 15 years old diagnosed in 2005 or 2008 for a pancreatic or biliary tract cancer (neuroendocrine excluded). The point was made on 01/12/2011. Patients were divided into 5 groups: PD and surgery (PD-Surg), PD and radiotherapy or chemotherapy (PD-RC), PD and untreat (PD-Un), no PD and radiotherapy or chemotherapy (noPD-RC), no PD or untreated (noPD-Un). Observed survival analysis was obtained from Kaplan-Meier method and statistical significance from log-rank test. Males accounted for 45.8% of 260 patients. The average age was 71.8 years (+/- 12.1). 59.6% were diagnosed as pancreas cancer. PD was not obtained in 54.2% (60% in pancreas and 45.7% in biliary tract respectively). Seven patients were lost of follow-up.

n (%) PD-Surg PD-RC noPD-RC PD-Un noPD-Un

Median survival (days)

709 198 203 76 60

2 years survival

46.7% 6.8% 2.9% 0% 2.1%

27 patients were alive beyond 24 month: 21 in PD-Surg group, 3 in PD-RC, 1 in noPD-RC and 2 in noPD-Un. In conclusion, the absence of PD is common in clinical practice, without apparent impact on survival. 14.2% of patient were treated with no PD. These patients not to be taken account in current recommendations because of Centralized monitoring of this condition would be required. In the absence of treatment plan, PD is not essential.

Disclosure: All authors have declared no conflicts of interest.

726P NEOADJUVANT MODIFIED FOLFOXIRI IN LOCALLY ADVANCED Pancreatic CANCER

E. Vasile1, N. De Lio2, C. Cappelli2, L. Gincocc2, S. Caporini3, A. Sainato1, C. Greco1, F. Mosca1, A. Falconi1, U. Boggii2
1Oncologia, Trapianti e Nuove Tecniche in Medicina, Polo Oncologico - Azienda Ospedaliero-Universitaria Pisana - Istituto Toscano Tumori, Pisa, ITALY, 2Dipartimento di Oncologia, dei Trapianti e delle Nuove Tecniche in Medicina, U.O. Chirurgia Generale e Trapianti - Azienda Ospedaliero-Universitaria Pisana, Pisa, ITALY, 3Department of Radiodiagnostic and Radiology intervention, Azienda Ospedaliero-University Pisana, Pisa, ITALY.

Among the 15 patients so far evaluated, 6 partial responses (40%) and 9 stable disease (60%) have been observed. A local treatment after chemotherapy was received by 9 patients until now: 5 (55.5%) underwent to radical surgery; 1 underwent an explorative laparotomy with evidence of liver metastases; 3 received concomitant chemo-radiotherapy with gemcitabine. Median progression-free survival was 24.5 months and median overall survival was 30.1 months.

Conclusions: Chemotherapy with mFOLFOXIRI seems active in locally advanced pancreatic cancer patients and may allow to obtain a downstaging of disease leading some patient to achieve a curative surgical resection. Longer follow up is needed to better evaluate long-term outcome of this strategy.

Disclosure: All authors have declared no conflicts of interest.

728P RANDOMIZED PHASE II TRIAL OF S-1 VERSUS S-1 PLUS OXAL PLATIN IN PATIENTS WITH GEMCITABINE REFRACTORY PancreATIC CANCER

T. Okusaka1, S. Ohkawa1, H. Isayama2, A. Fukutomi1, K. Yamaguchi3, M. Ikeda1, A. Furukoshi1, M. Nagase1, S. Nakamori4, Y. Hamamoto5
1Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, JAPAN, 2Department of Gastroenterology, Kanagawa Cancer Center Hospital, Kanagawa, JAPAN, 3Department of Gastroenterology, Graduate School of Medicine The University of Tokyo, Tokyo, JAPAN, 4Division of Gastrointestinal, Shizuoka Cancer Center, Shizuoka, JAPAN, 5Division of Gastroenterology, Saitama Cancer Center, Saitama, JAPAN, 6Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Chiba, JAPAN, 7Department of Gastroenterology, National Kyushu Cancer Center, Fukuoka, JAPAN, 8Department of Medical Oncology, Jichi Medical University Hospital, Tochigi, JAPAN, 9Department of Surgery, Osaka National Hospital, Osaka, JAPAN, 10Tochigi, Department of Clinical Oncology, Tochigi Cancer Center, Tochigi, JAPAN

Background: Gemcitabine (Gem) monotherapy or Gem-based combination therapy is used as standard first-line therapy for advanced pancreatic cancer (PC). There is no consensus on second-line therapy in patients (pts) with disease progression (PD)

mFOLFOXIRI consisted of: oxaliplatin 85 mg/sqm, irinotecan 150 mg/sqm and 5-fluorouracil 200 mg/sqm on day 1, plus infusional 5-fluorouracil 2800 mg administered in 48 hours on days 1 to 3, with cycle repeated every 14 days. The study enrolled patients with cytological or histological diagnosis of pancreatic adenocarcinoma, stage III locally advanced disease without evidence of metastatic disease, ECOG performance status (PS) 0 or 1, age 18-75. The primary end-point of the study was the percent of patients who can achieve radical surgical resection after chemotherapy; the trial was designed with a percentage of low activity of 30% and a percentage of interest of 50% with an α and β error of 0.05 and 0.20.

Results: Twenty-two patients have been so far enrolled; 8 men and 14 women; PS was 0 in 10 patients. Median age was 60 years (range 44-75); Celiac axis was involved in 7 patients, superior mesenteric artery in 10 cases, both arteries in 5 patients. Among the 15 patients so far evaluated, 6 partial responses (40%) and 9 stable disease (60%) have been observed. A local treatment after chemotherapy was received by 9 patients until now: 5 (55.5%) underwent to radical surgery; 1 underwent an explorative laparotomy with evidence of liver metastases; 3 received concomitant chemo-radiotherapy with gemcitabine. Median progression-free survival was 24.5 months and median overall survival was 30.1 months.

Conclusions: Chemotherapy with mFOLFOXIRI seems active in locally advanced pancreatic cancer patients and may allow to obtain a downstaging of disease leading some patient to achieve a curative surgical resection. Longer follow up is needed to better evaluate long-term outcome of this strategy.

Disclosure: All authors have declared no conflicts of interest.
after Gem-based therapy. The addition of oxaliplatin (L-OHP) to 5-FU/LV, however, yielded a significant improvement in overall survival (OS) and progression-free survival (PFS) in a second-line setting in the CONKO 003 trial. As 5-FU, an oral fluoropyrimidine, is commonly used in the advanced PC rather than 5-FU/LV in Japan, we conducted a randomized phase II trial to evaluate the efficacy and safety of 1 plus L-OHP (SOX) compared with 1 alone in a second-line setting.

**Material and methods:** The inclusion criteria were as follows: 1) histologically or cytologically proven pancreatic adenocarcinoma or adenosquamous carcinoma; 2) confirmed PD after Gem treatment; 3) ECOG PS, 0-1; 4) measurable metastatic lesion based on RECIST criteria; 5) age ≥20 years. Patients were randomized to receive 1 plus 80/100/120 mg/day based on BSA, po, d1-28, q6w, Arm A) or SOX (L-OHP 100 mg/m², iv, d1 plus 1-80/100/120 mg/day based on BSA, po, d1-14, q3w; Arm B). The primary endpoint was PFS to detect the superiority of Arm B over Arm A.

**Results:** Of a total of 271 pts enrolled between January 2009 and July 2010, 264 were eligible (130 randomized to Arm A and 134 to Arm B). Median PFS in Arm A and B was 2.8 and 3.0 months, respectively (HR = 0.838; 95% CI, 0.649-1.082; P = 0.1795) with a median follow-up time of 12.6 months. Median OS in Arm A and B was 7.0 and 7.5 months, respectively (HR = 1.031; 95% CI, 0.791-1.344; P = 0.8235) with a median follow-up time of 13.8 months. Response rate (RR) was 11.5% in Arm A (15/130; 95% CI, 6.6-18.3%) and 20.9% in Arm B (28/134; 95% CI, 14.4-28.8%) (P = 0.0395). The incidences of grade 3/4 toxicities were as follows: neutropenia (11.4% and 12.5%), thrombocytopenia (3.8% and 9.8%), anorexia (11.4% and 12.5%), diarrhea (4.5% and 5.1%), nausea (3.0% and 9.8%) in Arm A and B, respectively. Both regimens were tolerable.

**Conclusions:** Although SOX showed an advantage in RR, it provided no significant improvement in PFS or OS compared with 1 alone.

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K. Yamakado7, M. Kudo8, K. Imanaka9, Y. Arai10
All authors have declared no conflicts of interest.

A phase III global study was initiated in 2010 to evaluate the survival benefit of TSU-68 sequential and repeated TACE sessions may provide additional clinical benefits to than was observed for controls. This result suggests that TSU-68 combined with

Conclusion:

median values.

Pugh A liver function and those with hepatitis C. Among patients with baseline

in the TSU-68 group and 12% of controls) and alanine aminotransferase elevation

The most frequent grade 3/4 adverse events were AST elevation (46% of patients

technique using anticancer drugs, lipiodol, and gelatin sponge. TACE was completed
twice daily or no medication. TACE was performed according to the standard

carcinoma (HCC).

In this multicenter, open-label phase II study, we randomly assigned

Cisplatin and Gemcitabine (CisGem) as first-line treatment.

Sixty-three eligible patients (median age: 61.6 years (range: 39.8 – 78.3 years)) were identified between Feb 2007 and Feb 2011, from 9 centres. Patients were treated mostly with a platinum based regimen (n = 42), either a re-challenge of CisGem (n = 17), an oxaliplatin/ infused 5 FU regimen (mFOLFOX, n = 17) or oxaliplatin with capetibane (n = 4). Most patients had a performance status of 0 or 1. A median PFS of 4.0 months (95% CI: 3.3 – 5.6 months) and an OS of 8.1 months (95% CI: 5.3 – 11.4 months) following second line therapy were demonstrated. Patients had an overall OS of 19.5 months (95% CI: 17.0 – 25.2 months) from the start of first-line therapy; this compares with a median OS of 11.7 months from the ABC-02 study.

Conclusions: Use of second-line chemotherapy in advanced BTC is of potential benefit. These data, although retrospective, suggest there is a population suitable for second-line, prospectively randomised studies with chemotherapy or targeted agents and provide baseline outcome data with which to statistically design such studies. Updated data will be shown.

Disclosure: All authors have declared no conflicts of interest.

Purpose: TSU-68 is an antitumor drug that acts by inhibiting angiogenesis. We evaluated the efficacy and safety of TSU-68 in combination with transcatheter arterial chemoembolization (TACE) in patients with intermediate-stage hepatocellular carcinoma (HCC).

Methods: In this multicenter, open-label phase II study, we randomly assigned patients with HCC who had been treated by TACE to either receive either 290 mg TSU-68 twice daily or no medication. TACE was performed according to the standard technique using anticancer drugs, lipiodol, and gelatin sponge. TACE was completed for all patients within the 2 weeks prior to randomization. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were safety and biomarker assessments.

Results: In total, 103 patients were enrolled. Median PFS was 5.2 months in the TSU-68 group and 4.0 months in the control group (HR in the TSU-68 group, 0.59; p = 0.054, log rank test with a 2.5%-sided significance level). Fatigue, elevated aspartate aminotransferase (AST), elevated alkaline phosphatase, edema, and anorexia were more frequent in the TSU-68 group than in the control group. The most frequent grade 3/4 adverse events were AST elevation (46% of patients in the TSU-68 group and 12% of controls) and alanine aminotransferase elevation (26% of patients in the TSU-68 group and 8% of controls). Subgroup analyses suggested that treatment with TSU-68 may extend PFS for patients with Child–Pugh A liver function and those with hepatitis C. Among patients with baseline t-PA concentrations below the median value, the PFS of the TSU-68 group was longer than that of the control group. TSU-68 treatment may also improve PFS among patients with VCAM-1, ELAM-1, IL-8, or PDGF-BB levels above the median values.

Conclusion: TSU-68 was well tolerated, and may provide longer PFS after TACE than was observed for controls. This result suggests that TSU-68 combined with sequential and repeated TACE sessions may provide additional clinical benefits to patients, including prolongation of overall survival. A randomized placebo-controlled phase III global study was initiated in 2010 to evaluate the survival benefit of TSU-68 in combination with repeated TACE.

Disclosure: All authors have declared no conflicts of interest.
Background: The predictive role of radiographic parameters in HCC pts undergoing transarterial hepatic selective internal radiotherapy (SIRT) is not fully characterized. The objective of this retrospective study was to determine whether radiographic parameters at baseline and/or radiographic changes following SIRT predict outcome in HCC pts treated with Yttrium-90 glass microsphere radioembolization.

Methods: Base-line and post-SIRT CT images (median of 6 weeks) were analyzed. Various features such as tumor size; attenuation; margins; enhancement; and amount of tumor necrosis were examined. Selected radiographic parameters were evaluated & correlated with PFS & OS. Objective response was assessed by RECIST 1.1 and Morphylography, Attenuation, Size, and Structure (Mass) criteria (favorable (FR) vs. non-favorable). Differences were analyzed using Wilcoxon Signed Rank Test and Fisher’s Exact Test. Kaplan-Meier methods were used to estimate survival curves.

Cox regression was used in uni- & multi- variable survival analyses

Results: Twenty-four pts (79% M; median age 63 y) received a median radiation dose of 1.965 GBq. On post-SIRT CT, 65% of tumors had decreased longest diameter (median decrease 8%, p = 0.27); 64% had decreased attenuation (median decrease 18 HU, p = 0.067), and 45% demonstrated increased tumor necrosis (p < 0.001). RECIST-defined partial response was observed in 10% of pts, stable disease in 40% and 10% had disease progression. Median PFS and OS were 4.4 and 11.6 months, respectively. Of the 9 pts who were response evaluable by MASS criteria, FR was a predictor of PFS (p = 0.03) with median time to progression not being reached vs. 5.5 months for the non-FR group. In univariable analysis, the well-defined tumor margins, lower hepato-pulmonary shunt fraction and peripheral hypervascularization were associated with prolonged PFS. On multivariable analysis, tumor margins and shunt fraction were correlated with PFS whereas extrapathic disease and liver cirrhosis were independent predictors of OS.

Conclusions: In pts with HCC, pre-treatment tumor margins and shunt fraction may be developed as biomarkers to identify pts who are unlikely to benefit from SIRT. In addition, response evaluation by MASS criteria may provide better and earlier determination of lack of benefit from SIRT and the need for further therapy.

Disclosure: All authors have declared no conflicts of interest.

THE USE OF SECOX (SORAFENIB, OXALIPLATIN, CAPITABINE) AS THE TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA (HCC) – A SINGLE CENTER RETROSPECTIVE STUDY

J. Chu1, V. Tang1, P. Chan2, R. Leung1, H. Wong1, R. Poon1, S.T. Fan1, T. Yau1
1Medicine, Queen Mary Hospital, The University of Hong Kong, HONG KONG, 2Medicine, Ruttonjee Hospital, HONG KONG, 3Surgery, Queen Mary Hospital, The University of Hong Kong, HONG KONG

Background: Combining sorafenib with chemotherapy can potentially provide a new regime with enhanced benefit. Phase II study has demonstrated promising activity in combining sorafenib, oxalaplatin and capicabine (SECOX) in treating advanced HCC. We reported our experience in using this regime in our centre.

Methods: This retrospective study included all consecutive advanced HCC patients treated in our centre with SECOX regimen: daily oral sorafenib 400 mg B.D., oxalaplatin 85 mg/m² infusion on D1, and oral capicabine 850 mg/m² B.D. from D1-7 every 2 weeks. Univariate and multivariate analyses were employed to explore the potential predictive factors for overall survival benefits treated with this combination.

Results: 89 patients were included in the analysis with 28 patients previously enrolled in the phase II trial and another 61 pts treated outside the clinical trial in our centre. Of 89 patients received SECOX (male, 85%; median age, 53 year; hepatitis B carrier, 91%), 72 (81%) patients had CP A and 17 (29%) patients had CP B. Moreover, 42.7% patients had ECOG performance status (PS) 0, 53.9% patients had PS 1 and 3.4% patients had PS 2. The most common grade 3 or 4 drug-related toxicities were fatigue 54% (Gr3: 0%), and thrombocytopenia 52% (Gr3: 33%). A higher level of toxicity was observed in pts weighing ≥60 kg compared to pts <60 kg correlating with differences in drug exposure. ORR based on IRR was (PR = 32.6%, SD = 45.7%). Median Time to progression (TTP) is 7.9 mo (95% CI: 5.4 - 9.4)(based on minimum 6 mo. f/u). Median overall survival (OS) is 13.9 mo (95% CI: 11.8 -) (based on minimum 8 mo. f/u, with 46% death events). OS data has not yet matured and will be reported in the future.

Conclusions: In this Phase II/III study, lenvatinib administrated to patients with advanced HCC was not associated with any new toxicities associated with TKI class and was managed by dose adjustments. A weight-based starting dose (<60 Kg: 8 mg qd, vs ≥60kg: 12 mg qd) may be appropriate to minimize toxicity due to higher drug exposure in pts <60 kg. The observed OS and TTP indicate lenvatinib has activity in patients with advanced HCC and may be a new therapeutic option.

Disclosure: K. Ikeeda: K. Ikeeda has served as an advisor for Eisai and has received honoraria from Eisai. H. Kumada: M. Kudo has served as an advisor for Eisai and has received honoraria and research funding from Eisai. M. Kudo: M. Kudo has received honoraria from Eisai. Y. Osaki: Y. Osaki has received honoraria from Eisai. T. Okusaka: T. Okusaka has received honoraria from Eisai. T. Suzuki: T. Suzuki is an employee of Eisai. J.P. O’Brien: J. P. O’Brien is an employee of Eisai. K. Okita: K. Okita has served as an advisor for Eisai and has received honoraria from Eisai. All authors have declared no conflicts of interest.

EXPOSURE-RESPONSE RELATIONSHIP TO ASSESS THE RISK OF NEUTROPHILIA IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH TIVANTINIB

H. Zhai1, H. Kastrissios2, T. Carotherns3, M. Jarsen3, R. Savage2, G. Abbadessa6, F. Chai7, B. Schwartz6, R. Miller8, T. Tokui9
1Clinical Pharmacology, Daichi Sankyo, Inc., Edison, NJ, UNITED STATES OF AMERICA, 2Pharsight, a Certara Company, Sunnyvale, CA, UNITED STATES OF AMERICA, 3Clinical Pharmacology, Pharsight, a Certara Company, Sunnyvale, CA, UNITED STATES OF AMERICA, 4Clinical Pharmacology, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 5Division of Hematology & Oncology, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 6Medical Administration, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 7Medical Administration, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 8Translational Medicine & Clinical Pharmacology, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 9Clinical Development & Clinical Pharmacology, ArQuile, Inc., Woburn, MA, UNITED STATES OF AMERICA

Background: Tivantinib is a selective MET inhibitor that is extensively metabolized in the liver. In a randomized, placebo-controlled, phase 2 study in patients (pts) with...
advanced HCC, tivantinib monotherapy improved time to progression by 56%. However, in that study at the standard phase 2 dose of 360 mg twice daily (BID), tivantinib exposure was increased, and the absolute incidence of severe neutropenia increased approximately 2.5 times compared to pts with BTC from previous studies. An exposure-response analysis was conducted to explore the relationship between neutropenia and tivantinib pharmacokinetics (PK).

Methods: Tivantinib plasma concentration and incidence of grade ≥ 2 neutropenia were calculated from phase 1/II and 2 studies. A population PK model (NONMEM v7.1.0) was used to predict tivantinib exposure in HCC. The relationship between tivantinib exposure and neutropenia was evaluated by logistic regression analysis (S plus v8.0).

Results: Data were available from 289 cancer pts, including 73 pts with HCC and mild-to-moderate hepatic impairment. Cases of grade ≥ 3 (n = 28) and grade ≥ 4 (n = 40) neutropenia were included in the analysis. Based on the population PK analysis, tivantinib clearance was reduced approximately 67% in HCC pts, resulting in approximately 3 times higher exposure compared with other cancer pts. There was a significant (P < 0.01) relationship between tivantinib exposure and incidence of grade ≥ 2 neutropenia. By reducing the tivantinib starting dose from 360 to 240 mg BID, the incidence of grade ≥ 3 neutropenia is modeled to decrease from 28% to 16% in HCC pts. Further reduction in the risk of neutropenia (~6%) was achieved with intensive clinical monitoring and an aggressive dose-reduction schema.

Conclusions: Based on the current analysis, the increased incidence of neutropenia in HCC pts compared to pts with other solid tumors resulted from increased tivantinib exposure due to hepatic impairment. Consistent with the model, the risk of neutropenia was successfully managed in HCC pts by implementing dose reduction and tighter clinical monitoring without compromising efficacy.

Disclosure: H. Zahir: H Zahir is an employee of Daiichi Sankyo, Inc. H. Kastrissos: H Kastrissos is an employee of Phrasight Corporation and was retained by Daiichi Sankyo to provide scientific consulting services on tivantinib. M. Jansen: M Jansen is an employee of Daiichi Sankyo, Inc. R. Savage: R Savage is currently an employee of ArQule. F. Chai: F Chai is an employee of ArQule Inc., the sponsor of the studies. F. Chai holds ArQule stock. B. Schwartz: B Schwartz is currently an employee (Chief Medical officer) of ArQule and own stock in the company. R. Miller: R Miller is a medical officer (Medical director) of ArQule and own stock in the company. F. Chai is an employee of Daiichi Sankyo Co, Ltd. All other authors have declared no conflicts of interest.

PHASE 1 EXPERIENCE OF Tivantinib in Patients with Hepatocellular Carcinoma (HCC) or Biliary Tract Cancer (BTC)

F. Chai1, G. Abbadesa,2, R. Savage3, H. Zahir,4 Y. Chen5, M. Lamar6, J. Kaziak7, D. Ferrari8, R. von Roemeling9, B. Schwartz10
1Medical Administration, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 2Clinical Development, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 3Preclinical Development and Clinical Pharmacology, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 4Clinical Operations, Daiichi Sankyo, Inc., Edison, NJ, UNITED STATES OF AMERICA, 5Clinical Operations, ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 6ArQule, Inc., ArQule, Inc., Woburn, MA, UNITED STATES OF AMERICA, 7Clinical Development, Daiichi Sankyo Pharma Development, Edison, MA, UNITED STATES OF AMERICA

Background: Tivantinib is a selective MET inhibitor that is extensively metabolized by the liver. Since 2006, > 700 cancer patients (pts) have been treated with tivantinib. Herein we summarize safety, pharmacokinetic (PK), and efficacy data for pts with HCC or BTC treated with tivantinib in phase 1 clinical trials.

Methods: Adverse events (AEs) were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Tumor responses were assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PK parameters were calculated using blood samples collected on day 1 and on day 2 or day 15 of treatment.

Results: A total of 28 pts (73% Caucasian) have been treated: 13 in group I (Median [range] days: 345 [7–275]; 100/150/200 mg bid, n = 6/3/4) and 15 in group II (median [range] days: 74 [17–428]; 50/100/150/200mg bid, n = 3/4/4/4). No dose-limiting toxicities (DLTs) were seen in group I or II during Course 1 at doses up to 200mg bid, which was the MTD of nintedanib. After the dose-escalation phase and determination of MTD, seven pts reported DLTs at various dose levels (CTCAE grade ≥ 3; 50/100/150mg bid, n = 6/3/1; CP 3-5 or ALT ≥ 2 x ULN, or CP 4-7. Utilising a 3 + 3 design, cohorts received oral nintedanib continuously in 28-day courses, starting at 50mg bid (group II) or 100mg bid (group I) and escalating up to 200mg bid in 50mg bid intervals. Therapy was continued until no clinical benefit or undue toxicity. The phase 1 primary endpoint was the maximum tolerated dose (MTD) of nintedanib in Course 1.

Results: A total of 28 pts (71% Caucasian) have been treated: 13 in group I (median [range] days: 345 [7–275]; 100/150/200mg bid, n = 6/3/4) and 15 in group II (median [range] days: 757 [17–428]; 50/100/150/200mg bid, n = 3/4/4/4). No dose-limiting toxicities (DLTs) were seen in group I or II during Course 1 at doses up to 200mg bid, which was the MTD of nintedanib. After the dose-escalation phase and determination of MTD, seven pts reported DLTs at various dose levels (CTCAE grade ≥ 3; 50/100/150mg bid, n = 6/3/1; CP 3-5 or ALT ≥ 2 x ULN, or CP 4-7. Utilising a 3 + 3 design, cohorts received oral nintedanib continuously in 28-day courses, starting at 50mg bid (group II) or 100mg bid (group I) and escalating up to 200mg bid in 50mg bid intervals. Therapy was continued until no clinical benefit or undue toxicity. The phase 1 primary endpoint was the maximum tolerated dose (MTD) of nintedanib in Course 1.

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validate the revised AJCC 7th staging system based on outcomes of patients undergoing liver resection for HCC from a single institution.

Methods: Records for all patients undergoing potentially curative surgery for localized HCC between 1992 – 2007 were retrospectively reviewed. Pathological staging were determined post-operatively. Survival curves were plotted with the Kaplan-Meier method and were compared by using a log-rank test for various disease stages based on AJCC 7th staging system.

Results: 543 patients were included (439 male) and 80% were Chinese ethnicity. 303 patients were chronic hepatitis B carriers. The median follow up was 1.78 years with 282 relapsed patients (51.9%) and 189 deaths (34.8%). Median survival (MS) and time-to-relapse (TTR) were 4.83 years and 2.00 years respectively. MS for AJCC 7 stage I, II, III and IV were 6.35, 4.44, 2.41 and 0.49 years respectively (p <0.0001). MS and TTR for AJCC 7th Stage IIIA (n = 56) and IIIB (n = 33) however were not significantly different (MS 2.74 vs 2.41 years, HR 1.11 (95% CI 0.56, 2.18); TTR 0.83 vs 0.48 years, HR 1.36 (95% CI 0.80, 2.32)).

Conclusions: The revised AJCC 7th TNM staging system has prognostic significance and predicts OS and TTP in resected HCC patients. However subdividing HCC into Stage IIIA and IIIB showed no significant difference in prognosis.

Disclosure: All authors have declared no conflicts of interest.

Table: 743P

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743P PERCUTANEOUS HEPATIC PERFUSION (CHEMOSAT® OR CS-PHP) OF MELPHALAN IN PATIENTS (PTS) WITH HEPATIC METASTASES FROM MELANOMA: PHASE III PHARMACOKINETIC ANALYSIS

E. Gardneron behalf of Phase 3 Principle Investigators,1 W. Figgii, D.S. Johnstonii, H.R. Alexander, Jr.iii
1Analytical Pharmacology Consultant, Vienna, VA, UNITED STATES OF AMERICA, 2Medical Oncology Branch, National Cancer Institute, Bethesda, MD, UNITED STATES OF AMERICA, 3Pharmaceutical Research and Development, Delcath Systems Inc., New York, NY, UNITED STATES OF AMERICA, 4Surgery, University of Maryland Medical Center, Baltimore, MD, UNITED STATES OF AMERICA

Background: CS-PHP (CHEMOSAT®, Delcath Systems Inc, New York, NY) is a regional therapy which: i) isolates the liver using a system of percutaneously positioned catheters; ii) delivers high-dose chemotherapy directly into the hepatic artery; and iii) minimizes systemic toxicity by hemofiltration of hepatic venous blood.

Methods: A randomized phase III study compared CS-PHP delivery melphalan with best alternative care in pts with liver metastases from melanoma. A pharmacokinetic analysis was performed in a subset of pts from this study. Pts received melphalan 3.0 mg/kg ideal body weight via CS-PHP over 30 min with 60 min of hemofiltration starting at the time of perfusion. Blood samples (7 mL) were collected during cycle 1. Sample collection sites: arterial line; prefilter (extracorporeal circuit); postfilter (extracorporeal circuit). Sampling times: baseline; mid-infusion; immediate post-infusion; 5, 10, 15, 30 min post-infusion. Melphalan plasma concentrations were determined by HPLC with UV detection. Data were analyzed using a non-compartmental approach. Pharmacokinetic parameters: maximum plasma concentration (Cmax), area under concentration-time curve from t0 to final sample (AUClast) minus (pre-filter AUClast) divided by (pre-filter AUClast). Results: Plasma samples were available from 48 pts, of which 40 were evaluable. Mean absolute melphalan dose was 19 mg (range 137-220mg) and duration of perfusion was 30 min (range 16-52 min). Mean filter extraction efficiency was 71.2% ± 10.4%. Filter efficiency did not change significantly with absolute melphalan dose (p = 0.86, Spearman) or rate of perfusion (p = 0.064, Spearman).

Conclusions: CS-PHP exposes the liver to high concentrations of melphalan. Filter extraction efficiency is consistent among pts and does not appear to be influenced by melphalan dose or rate of perfusion.

Disclosure: D.S. Johnston: Employee of Delcath Systems Inc. Stock ownership in Delcath. All other authors have declared no conflicts of interest.

744P EARLY DATA FROM A PHASE I STUDY OF NINTEDANIB (BIBF 1120) IN ASIAN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

C. Yen1, Y. Shen2, H. Shiah3, J. Chen2, C. Hsu2, C. Hsu2, D.C. Huang2, J. Flocke1, W. Su1, A. Cheng2
1Oncology, National Cheng Kung University College of Medicine and Hospital, Tainan, TAIWAN, 2Oncology, National Taiwan University Hospital, Taipei, TAIWAN, 3Oncology, National Health Research Institute, Tainan, TAIWAN

Background: Nintedanib is an oral, triple angiokinase inhibitor targeting VEGFRs, PDGFRs and FGFRs. This multicentre, open-label, phase I/randomised phase II study (NCT010987935; phase II ongoing) evaluated the efficacy, safety and pharmacokinetics of nintedanib versus sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC) from Asia, where HCC is endemic and has unique clinical features. Phase 1 data are presented.
Methods: Phase I pts had histologically, cytologically or clinically confirmed HCC. ECOG performance status ≤2, Child–Pugh (CP) score ≤7, and ≤1 line of prior systemic therapy. Using a 3 + 3 design, pts were stratified into two groups by liver function and CP score: (I) AST ≤ALT ≤2 x upper limit of normal (ULN), and TP 5–6; (II) AST or ALT >2 x ≤5 x ULN, or CP 7. Nintedanib (given continuously in 28-day courses) was started at 50mg bid (group II) or 100mg bid (group I) and increased in 50mg bid increments up to 200mg bid. Therapy was continued until no clinical benefit or undue toxicity. The phase I primary endpoint was the maximum-tolerated dose (MTD) of nintedanib.

Results: Overall, 35 pts have received nintedanib: 11 in group I (100/150/200mg bid, n = 4/3/4; median [range] duration: 140 [10–357] days) and 24 in group II (50/100/150/200mg bid, n = 3/7/3/11; median [range] duration: 81 [2–587] days). In group I, no dose-limiting toxicities (DLTs) were seen at any dose during the first course. In group II, one pt experienced a DLT (CTCAE Grade [G] 3 AST increase) at 100 mg bid in Course 1 (dose-escalation phase). The MTD of nintedanib was thus 200 mg bid in both groups. DLTs seen after MTD assessment were G4 gastrointestinal (GI) haemorrhage/anaemia (50 mg bid), G3 ALT increase (150 mg bid), G3 GI haemorrhage (150 mg bid), G3 hypertension (200 mg bid; n = 2) and G4 gastric ulcer (200 mg bid). The most common adverse events, by system organ class, were GI (83%) and general/administration site disorders (51%), and investigations (51%). Hypertension and rash (any grade) occurred in 6 and 8 pts, respectively.

Conclusions: Nintedanib has an acceptable safety profile in this Asian HCC population. As in other cancer types and European HCC pts, the MTD of nintedanib was 200 mg bid.


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**PACLITAXEL AND CISPLATIN COMBINED WITH INTENSITY-MODULATED RADIOTHERAPY FOR UPPER ESOPHAGEAL CARCINOMA**

L. Tu1,2, L. Sun1,2, Y. Gorg1,2, Y. Liu1, L. Zhou1,2, X. Zhou1, Y. Xu1, J. Wang1, M. Hou1, Y. Liu1

1Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, CHINA, 2State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, CHINA

Purpose: Concurrent radio-chemotherapy has been recommended as a standard therapy in patients with upper esophageal carcinoma which is not suitable for surgery. Although INT 0123 trial indicated that the 5-fluorouracil (5-FU) plus cisplatin (DDP) combined with radiotherapy was the initial strategy, the optimal management of upper esophageal carcinoma remains undetermined. This study was conducted to evaluate the effectiveness and safety of intensity-modulated radiotherapy (IMRT) and concurrent paclitaxel plus cisplatin (TP regimen) for upper esophageal carcinoma.

Materials and methods: 36 patients of upper esophageal carcinoma were retrospectively analyzed. Patients were treated with IMRT (median 60 Gy) combined with concurrent TP regimen chemotherapy. The Kaplan Meier analysis was performed in statistical analysis. Toxicities were recorded according to the NCI CTC version 3.0.

Results: 36 patients aged 43-73 years (median 57 years). The median follow-up period was 14.0 months. The 1-year and 2-year survival rates were 83.3% and 42.8%, respectively. The median progression-free survival (PFS) time and overall survival (OS) time were 12.0 (95% CI 8.6–15.4 months) and 18.0 months (95% CI 14.2–21.8 months), respectively. Grade 3 neutropenia, radiation-induced esophagitis and radiodermatitis were observed in 5 (13.9%), 3 (8.3%) and 8 (22.2%) patients, respectively. There were two treatment-related deaths due to esophageal perforation and hemorrhoea.

Conclusions: For those patients with upper esophageal carcinoma, IMRT combined with concurrent TP regimen chemotherapy was an effective treatment. However, special attention should be paid to the occurrence of perforation and hemorrhoea.

Disclosure: All authors have declared no conflicts of interest.

**747P**

**PREVALENCE, CLINICAL FEATURES AND PROGNOSIS OF DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA (DMPM): DO PATIENTS IN CLINICAL TRIALS REFLECT THE REAL WORLD?**

F. Grosso1, D. Degiovanni2, A. Roveta1, S. Barbero2, R. Libener1, F. Musante3, C. Testoni1, D. Mirabello1, P. G. Betta4, M. Botta4

1Oncology, SS Antonio e Biagio General Hospital, Alessandria, ITALY, 2Palliative Care, S Spirito General Hospital, Casale Monferrato, ITALY, 3Radiology, S Spirito General Hospital, Casale Monferrato, ITALY, 4Radiology, SS Antonio e Biagio General Hospital, Alessandria, ITALY, 5Nuclear Medicine, SS Antonio e Biagio General Hospital, Alessandria, ITALY, 6Epidemiology Cancer Unit, University of Turin, Turin, ITALY, 7LILT, SS Antonio e Biagio General Hospital, Alessandria, ITALY, 8Oncology, S Spirito General Hospital, Casale Monferrato, ITALY

Background: Peritoneum is the second most frequent site of origin of malignant mesothelioma (MM). DMPM is the most frequent primary peritoneal malignancy in developed countries. Highly specialised centres have reported improved outcomes following an aggressive loco-regional approach, including cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC), with median overall survival (OS) approaching 50 months and almost 50% relapse-free patients at 5 years. Conversely, in population based studies prognosis still remains very poor with OS in the range of 5.7-10. To describe clinical features and prognosis in unselected consecutive patients, we report on the clinical outcome of a series of DMPM treated at a single Oncological Department, in a highly asbestos polluted area in Piedmont.

Patients and methods: By using our database (MesoDB), we retrieved DMPM patients diagnosed between November 1993 and September 2011 at Alessandria and CasaleMonferratoHospitals. All cases were confirmed by the same expert pathologists.
Results: Among 862 MM we identified 35 patients, 9 F and 26 M. Median age at diagnosis was 67 years, IQR 61-73, range 30-83. Occupational asbestos exposure was definite in 23 and probable in 2 patients, whereas environmental in 10. The histological diagnosis followed local and national guidelines, and among these 3 received a subcutaneous IFNalpha, 21 received a subcutaneous IFNbeta, and 2 intraperitoneal IFNbeta. PFS of the 12 patients receiving systemic therapy was 3.9 months (range 1-7.7). Median OS was 6.1 months (95% CI 2.4-7.7).

Conclusions: DMPM accounts for 5% of MMs in our mesoDB, a percentage lower than reported in the literature. Outcomes in our patients were more disappointing compared to those reported by referral centres, but similar to population-based studies. These differences emphasize the strict selection of patients enrolled into aggressive loco-regional treatment programs and the need for new therapeutic approaches suitable for the real clinical practice setting.

Disclosure: All authors have declared no conflicts of interest.

749 EXPRESSION AND CLINICAL SIGNIFICANCE OF NPRA IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

J. Wang1, Z. Zhao1, H. Fang1, E. Tangsakar1, J. Zhang1
1Department of Surgery, The First Affiliated Hospital of Zhejiang University, Hangzhou, CHINA, 2Department of Thoracic Surgery, Second Affiliated Hospital of Yulin University, Yulin, CHINA

Background and objective: Esophageal cancer is a main reason of cancer related mortality, and the tumor targeted therapy is a new and effective treatment. NPRA (natriuretic peptide receptor A), as a new oncogene, that promotes tumorigenesis in several cancer types might represent a novel therapeutic target in esophageal cancer. In this study we suggested that the expression and clinical significance of NPRA in esophageal squamous cell carcinoma (ESCC).

Methods: The expression of NPRA in 45 cases of ESCC tissues, 40 cases of adjacent tissues, and 22 positive lymph node tissues were assessed by SP immunohistochemical method. No patients received preoperative chemotherapy, radiation therapy, and immune therapy and all of patients were assessed by SP immunohistochemical method. No patients received preoperative chemotherapy, radiation therapy, and immune therapy. Informed consent was obtained from each patient. No patients received preoperative chemotherapy, radiation therapy, and immune therapy. The patients enrolled in this study were assessed by SP immunohistochemical method.

Results: In esophageal squamous cell carcinoma, the expression of NPRA was strongly detected in cytoplasm, while undetectable or very weak in nuclei. The positive rates of NPRA in the cancer tissues was 71.1%, while that in the adjacent tissues group was 17.5%, and showed 63.2% and 24.3% in the positive lymph node tissues and non-lymph node tissues respectively, there was a significant difference among the association of age, gender, and lymph node tissues respectively, there was a significant difference between 17.5% and showed 63.32% and 24.3% in the positive Lymph node tissues and non-lymph node tissues respectively, there was a significant difference between 17.5% and showed 63.32% and 24.3% in the positive Lymph node tissues and non-lymph node tissues respectively. And patients with ESCC showed significant differences in clinicopathological variables between HER2(-) and HER2(+) disease.

Conclusion: Our findings demonstrate that the NPRA has high expression in ESCC tissues, and the positive rate is closely correlated with the differentiation and TNM stage, and suggest that NPRA represents a potential therapeutic target.

Disclosure: All authors have declared no conflicts of interest.

748 A PHASE II TRIAL OF NEOADJUVANT CONCURRENT CHEMO-RADIOThERAPY CONTAINING CISPLATIN AND 5-FU FOLLOWED BY RESECTION FOR ESOPHAGEAL CARCINOMA

K. Anvari, S.A. Aledavood, M. Stelianian Toussi, F. Nosrati
Cancer Research Center, Omid Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, IRAN

Introduction: Combined modality treatments have been adopted to improve survival in patients with esophageal carcinoma. In this trial, we evaluated the efficacy and toxicity of a preoperative concurrent chemoradiotherapy protocol in patients with locally advanced esophageal carcinoma.

Method and material: Between 2006 and 2011, eligible patients with locally advanced esophageal carcinoma underwent concurrent radiotherapy (40 Gy/20 fractions) and chemotherapy (cisplatin 20 mg/m² for 4 days plus 5-FU 700 mg/m²/24-hour infusion for 4 days on the first and the last week of radiation therapy). In patients with unsuitable hematological or general condition only one cycle of chemotherapy was prescribed. The patients underwent esophagectomy 3 to 4 weeks following radiation therapy. Pathologic response, overall survival rate, toxicity and feasibility were evaluated.

Results: 197 patients with a median age of 59 (range: 27-70) with a female to male ratio of 100/97 entered the protocol. 194 cases (98.9%) had esophageal SCC. Grades 3-4 of toxicity were as follows: neutropenia in 41 (21%) and esophagitis in 5 (2.5%) cases. There were 11 (5.6%) early death probably due to treatment related toxicities. The other reasons for not completing the protocol were as follows: toxicity in 6 (3%), refusing surgery in 35 (17.8%), improper general condition for surgery in 18 cases (9.1%). 127 cases (64.5%) completed the protocol among which 60 cases received 2 courses of chemotherapy. For patients who underwent surgery, the complete pathological response was shown in 38 cases (29.9%) with a 5-year overall survival rate of 47.2% and median overall survival of 33 months. There were no significant difference in overall survival rates in patients receiving one or two cycles of chemotherapy (log-rank p = 0.64).

Conclusion: The pathological response rate and the overall survival rate are promising in patients who completed the protocol as receiving at least one cycle of chemotherapy. However, the toxicity rates were relatively high. Prescribing two cycles of chemotherapy resulted in no significant improvement in survival rate as compared with those receiving one cycle.

Disclosure: All authors have declared no conflicts of interest.

750 HER2 STATUS IN OESOPHAGO GaSTRIC JUNCTION AND GASTRIC CANCER – THE IRISH LANDSCAPE

A. Jayaram1, J.E. Battley2, M.Y. Teo3, R. Abdul Rahman4, R. Bambury5, M.W. Bennet6, M. Margaret Sheehan6, R. McDermott7, D.G. Power7, G. Lenon8
1MA, Galway University Hospital, Galway, IRELAND, 2Medical Oncology, Cork University Hospital, Cork, IRELAND, 3Dept. of Medical Oncology, AMNCH Adelaide and Meath Hospital, Dublin, IRELAND, 4Medical Oncology, AMNCH Adelaide and Meath Hospital, Dublin, IRELAND, 5Pathology, Cork University Hospital, Cork, IRELAND, 6Pathology, Galway University Hospital, Galway, IRELAND, 7Medical Oncology, Mercy University Hospital, Cork, IRELAND, 8Medical Oncology, University College Hospital Galway, Galway, IRELAND

HER2 is overexpressed in ~73% of gastroesophageal (GE) adenocarcinomas. The ToGA study, established the benefit of trastuzumab in combination with chemotherapy in HER2(+) metastatic GE tumours. In this study, 22% of patients were HER2(+) (immunohistochemistry (IHC)3+ or fluorescence in situ hybridization (FISH)+). We report a multi-center Irish experience by examining HER2 status by IHC and FISH in GE tumours.

Methods: Database from three regional cancer centres were examined to identify pts with junctional or gastric adenocarcinoma. HER2 testing was performed on biopsy or resection specimens of patients with early stage and metastatic GE tumours between 2008-2011. We defined HER2(+) as FISH(+) [HER2:17c ≥ 2]. In addition, age, gender, histology, stage of disease, were recorded. Clinicopathologic characteristics were extracted and compared with t-test or Fisher’s exact as appropriate.

Results: Between 2008 and 2011, 177 pts were identified. Median age was 68 years (range: 25 – 96), 36% were male. Gastric tumours were identified in 51%, while 53% were metastatic at diagnosis. Median number of metastatic sites was 1 (0 – 4). IHC and FISH were performed on 170 pts (96%) and 131 (74%) of patients. Distribution of IHC score of 0, 1, 2 and 3 were 38%, 32%, 19% and 11%, respectively. With respect to tumour heterogeneity of HER2 amplification, in IHC3+, 50% were FISH(+), IHC2+ +, 21.1% were FISH(+) and IHC1+ +, 3.7% were FISH(-). Overall HER2(+) ratio for the cohort was 16.4% (n = 29). Comparing patients with HER2(+) and HER2(-) disease, gender (males, 38 vs 38%, p = .84), age (69 vs 68, p = .79) and site distribution gastric, (45 vs 52%, p = .54) were identical. The rate of metastasis at diagnosis were similar, at 54 vs 53%. Presence of metastases in the liver (69 vs 48%, p = .22), peritoneum (38 vs 49%, p = .55), brain (8 vs 3%, p = .44) were comparable in both patient cohorts.

Conclusions: HER2(+) GE adenocarcinomas in the analyzed cohort displays similar pattern of heterogeneity in IHC staining and FISH positivity but with lower incidence (16.4%) of HER2 amplification than was reported in the ToGA study. Further analysis did not identify differences in clinicopathologic characteristics in HER2(+) vs patients.

Disclosure: All authors have declared no conflicts of interest.

751 CLINICOPATHOLOGICAL SIGNIFICANCE OF HYPOXIA-INDUCIBLE FACTOR-1 ALPHA (HIF-1α) EXPRESSION IN GASTRIC CANCER

Department of Surgery, Kurume University School of Medicine, Kurume, Fukuoka, JAPAN

Background: Hypoxia is a common feature of rapidly growing solid tumors. Therefore, cellular adaptation to hypoxia and altered glucose metabolism are fundamental to the biology of cancer cells. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor for over 60 genes recognized to control the delivery of oxygen and nutrients through the induction of angiogenesis and glycolysis under hypoxic condition. Therefore, Inhibition of expression of HIF-1α will be expected to the tumor specific molecular target-based therapy. In this study, we evaluated the significance of HIF-1α expression in relation to the clinicopathological factors, the
prognosis, VEGF expression, and microvesSEL density (MVd) expressed as the mean count of CD34 immunostained vessels in gastric cancer.

Methods: Paraffin-embedded tumor specimens from 128 patients who underwent gastrectomy at the Kurume University from 2004 to 2005 were used to assess the clinical significance of HIF-1α expression. We used ARC method to perform an immunohistochemical analysis of HIF-1α, VEGF expression, and MVd.

Results: 84(65.6%) of gastric cancer specimens were positive for HIF-1α expression. The multivariate analysis showed that the histology, depth of invasion, VEGF expression, and MVd were significantly associated with the HIF-1α expression. On relapse-free and overall survival curves, the HIF-1α negative group was significantly higher than the HIF-1α positive group. The HIF-1α expression was identified as a significant predictor of relapse-free survival and overall survival by Multivariate Cox’s proportional hazard analyses.

Conclusion: Overexpression of HIF-1α was found to be a poor prognostic factor for patients with gastric cancer and correlated with histology, depth of invasion, and VEGF.

Disclosure: All authors have declared no conflicts of interest.

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CLINICOPATHOLOGIC SIGNIFICANCE OF EXPRESSION OF NUCLEAR FACTOR KAPPA B AND VASCULAR ENDOTHELIAL GROWTH FACTOR IN GASTRIC CANCER PATIENTS

H. Kwon1, K.W. Park2, S. Kim1
1Internal Medicine, Dong-A University Medical Center, Busan, KOREA, 2Internal Medicine, Dankook University, Cheonan, KOREA

AIM: Nuclear factor-kB (NF-kB) and vascular endothelial growth factor (VEGF) are involved in cell proliferation, invasion, angiogenesis and metastases. The principal objective of this study was to assess the prognostic significance of NF-kB and VEGF expression in gastric cancer.

Methods: The tumor tissues of 154 patients with gastric cancer, all of whom underwent potentially curative resection, were immunohistochemically evaluated using monoclonal antibodies against NF-kB and VEGF.

Results: Positivity rates of NF-kB and VEGF were 44.2% and 39.6%, respectively. NF-kB expression in tumor tissues was correlated significantly with VEGF expression (p < 0.001). VEGF expression was related to Lauren’s classification (p = 0.012), differentiation (p = 0.043), depth of invasion (p = 0.005), carcinomembryonic antigen (p = 0.032), and stage (p = 0.026). However, NF-kB expression was not related to any of these parameters. Univariate analysis demonstrated that NF-kB expression was significantly related with both 5-year disease free survival (65.2% vs. 46.4%, p = 0.007), and 5-year overall survival (60.0% vs. 42.5%, p = 0.014). Multivariate analysis verified that NF-kB was independently associated with disease free survival (hazard ratio: 2.082, p = 0.005), and overall survival (hazard ratio: 1.841, p = 0.008). However, VEGF did not appear to be related to adverse clinical outcome.

Conclusion: NF-kB expression in tumor tissue is associated with poor survival in gastric cancer patients.

Disclosure: All authors have declared no conflicts of interest.

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DOCETAXEL, CISPLATIN AND FLUOROURACIL AS PERIOPERATIVE CHEMOTHERAPY IN RESECTABLE GASTROESOPHAGEAL CARCINOMA: A RETROSPECTIVE ANALYSIS

F. Fiten1, Z. Lakies2, T. Nguyen1, C. Borg1, B. Benzidine1, V. Nerich1, B. Heyd1, X. Piot1, C.H.S. Kim1
1Medical Oncology, Hopital Minjoz, Besançon, FRANCE, 2Digestive Surgery, Hopital Minjoz, Besançon, FRANCE, 3Pharmacy, Hopital Minjoz, Besançon, FRANCE

Introduction: Perioperative chemotherapy has demonstrated a survival benefit versus surgery alone in resectable gastroesophageal adenocarcinoma (RGC). The association Docetaxel, cisplatin, and fluorouracil (DCF) is superior to cisplatin and fluorouracil for locally advanced or metastatic gastro-oesophageal adenocarcinoma has not been previously investigated and is well tolerated. Response rates are comparable with standard chemotherapy and updated data will be presented.

Patients and methods: All patients with RGC were retrospectively analyzed.

Results: Forty-nine patients with gastric cancer were analysed (38 adenocarcinoma subtype and 11 Signet Ring Cell (SRC)). A total of 37 patients (76%) completed the 3 perioperative cycles of DCF (day 1) and cisplatin 75 mg/m² (day 1) plus fluorouracil 750 mg/m² (days 1 to 5) every 3 weeks followed by 3 postoperative cycles of this regimen.

Results: Forty-nine patients with gastric cancer were analysed (38 adenocarcinoma subtype and 11 Signet Ring Cell (SRC)). A total of 37 patients (76%) completed the 3 perioperative cycles of DCF (day 1) and cisplatin 75 mg/m² (day 1) plus fluorouracil 750 mg/m² (days 1 to 5) every 3 weeks followed by 3 postoperative cycles of this regimen.

Conclusion: 89% among patients with adenocarcinoma and 55% among patients with SRC. Median overall survival and progression-free survival were 58 months (95% CI, 58-non achieved) and 43 months (95% CI, 16-non achieved) respectively.

Disclosure: All authors have declared no conflicts of interest.

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A PHASE I TRIAL OF BORTEZOIMI IN COMBINATION WITH EPIRUBICIN, CARBOPLATIN AND CAPECITABINE (ECAFOX) IN ADVANCED GASTRIC AND GASTRO-oesophageal Junction (GOJ) ADENOCARCINOMA

R.C. Turkington, C. Purcell, R.H. Wilson, M.M. Eatock
Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, UNITED KINGDOM

Background: Combination chemotherapy is the treatment of choice for patients with advanced oesophago-gastric cancer and efforts to incorporate novel agents into chemotherapy regimens have been problematic. Bortezomib (Velcade®) attenuates the action of the transcription factor NF-kB, and has shown preclinical activity alone and in combination with chemotherapy in oesophago-gastric cell lines.

Design: A Phase I dose-escalation study using a 3 + 3 design was performed with Bortezomib (Velcade®) in combination with Epirubicin 50 mg/m² day 1, Carboplatin AUC 5 day 1 and Capecitabine 625 mg/m² BD days 1-21 every 3 weeks, in advanced or metastatic gastro-oesophageal adenocarcinoma. Bortezomib was administered at four dose levels of 0.7, 1.0, 1.3 and 1.6 mg/m² on days 1 + 8. Due to myelotoxicity the dose of capecitabine was reduced to 500 mg/m² after the first patient cohort. The primary end point was to define the maximum tolerated dose (MTD) of Bortezomib when combined with ECAbox with secondary end points of radiological response rate (RR) and toxicity.

Results: 20 patients, 18 evaluable for response, were enrolled (6 gastric, 9 GOJ and 3 oesophageal), 2 were Stage III and 16 Stage IV. The overall RR was 33.3% with 6 patients achieving a partial response. An additional 7 patients had stable disease for an overall Disease Control Rate (DCR) of 61.1%. Common grade 3/4 adverse events included nausea, fatigue, anaemia, neutropenia and thrombocytopenia. The first 3 patients developed grade 4 neutropenia and pyrexia resulting in a protocol amendment reducing the Capecitabine dose to 500 mg/m² BD. Bortezomib-induced pulmonary infiltrates occurred in one patient treated at dose level 2, requiring discontinuation of Bortezomib and withdrawal from the study. Recruitment is ongoing at dose level 4 and the MTD is yet to be defined.

Conclusions: The addition of Bortezomib to amended combination chemotherapy for locally advanced or metastatic gastro-oesophageal adenocarcinoma has not been previously investigated and is well tolerated. Response rates are comparable with standard chemotherapy and updated data will be presented.

Disclosure: All authors have declared no conflicts of interest.

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OXALIPLATIN, IRINOTECAN, BEVACIZUMAB FOLLOWED BY DOCETAXEL, BEVACIZUMAB IN INOPERABLE GASTRIC CANCER: A MULTICENTER PHASE II TRIAL (GASTRIC-3) OF THE ARBEITSGEMEINSCHAFT MEDIKAMENTÖSE TUMORTHERAPIE (AGMT)

E. Wölfl, F. Keil1, J. Thaler3, B. Grauenberger4, M. Hejna5, W. Eister6, MA. Pickl2, F. Romeder4, R. Greil1
1Internal Medicine, St. Vinzenz Krankenhaus Zams, Zams, AUSTRIA, 2Internal Medicine, Hanusch Krankenhaus, Vienna, AUSTRIA, 3Internal Medicine, Klinikum Wels Grieskirchen, Wels, AUSTRIA, 4Medical Oncology, Krankenhaus der Barmherzigen Br, Vienna, AUSTRIA, 5Internal Medicine, Medical University Vienna, Vienna, AUSTRIA, 6Department of Internal Medicine, University Hospital Innsbruck, Innsbruck, AUSTRIA, 7Internal Medicine 3, Allgemeines Krankenhaus Linz, Linz, AUSTRIA, 8Internal Medicine III, University Hospital Salzburg, Salzburg, AUSTRIA

Background: In previous phase II trials (AGMT-Gastric-1 and AGMT-Gastric-2) we could show efficacy of oxaliplatin and irinotecan as well as oxaliplatin, irinotecan and cetuximab in advanced gastric cancer. Time to progression however was short suggesting acquired chemotherapy resistance. To address this problem sequential chemotherapy combined with bevacizumab is investigated in the presented Gastric-3 trial.

Methods: Oxaliplatin 85 mg/m² biweekly (q2w) and irinotecan 125 mg/m² q2w are administered for the first three months followed by docetaxel 50mg/m² q2w for subsequent three months. Chemotherapy is combined with bevacizumab 5 mg/kg q2w which is administered until progression. For this abstract 36 pt. with histologically proven unresectable and/or metastatic gastric adenocarcinoma treated in a first line setting have been evaluated. Median age: 62.5 years (range 26-80 years), PS 0-2 patients: 10 patients, missing: 1 patients, single metastatic site: 24 patients, multiple metastases: 10 patients, missing: 2.
A randomized, single center phase II trial of capecitabine plus cisplatin versus ts-1 plus cisplatin as first line treatment in patients with advanced or metastatic gastric cancer

J. Lee1, S.Y. Ro2, E. Jeon1, S.H. Hong1, Y.H. Ko1, H.S. Won1, H.J. An1, K.W. Park1, J.H. Kim1, Y.S. Hong1
1Division of Oncology, Department of Internal Medicine, Seoul St. Mary’s Hospital, Seoul, KOREA, 2Medical Oncology, Catholic Medical Center, Seoul, KOREA, 4Medical Oncology, Fatima Hospital, Daegu, KOREA

Background: Platinum agents and oral fluoropyrimidines are widely used in the treatment of advanced gastric cancer. This study was aimed to evaluate the efficacy and safety of two combination regimens (capecitabine plus cisplatin [XP] vs S-1 plus cisplatin [SP]) in patients with untreated recurrent or metastatic gastric cancer.

Methods: Patients diagnosed as untreated recurrent or metastatic gastric cancer were randomly assigned to either capecitabine (2500 mg/BSA/day; day 1-14) plus cisplatin (60 mg/BSA/day; day 1) every 3 weeks or to TS-1 (900 mg/day; day 1-14) plus cisplatin (60 mg/BSA/day; day 1, every 3 weeks. Primary endpoint was overall response rate (ORR), accessed by RECIST criteria (ver. 1.0). The secondary end point was progression free survival (PFS), overall survival (OS), and toxicities.

Results: 86 patients were anticipated to be enrolled, but 51 patients were randomized to XP (25 patients) arm or SP (26 patients) arm because enrollment was slower than expected. ORR of XP and SP was 52% (13 of 25 assessable patients) vs. 44% (15 of 25 assessable patients), and no significant differences were found (P = 0.778). OS of XP vs. SP was 10.3 months (95% CI: 4.8-15.8) vs. 12 months (95% CI: 9.5-14.3), with no differences (P = 0.785). PFS was 4.6 months (95% CI: 4.6-5.2) for 4.4 months (95% CI: 2.2-6.6) each (P = 0.68). The incidence of grade 3-4 neutropenia of XP vs. SP was 40% vs. 43.2%. There were no febrile neutropenia in XP arm, but 7.7% in SP arm. Grade 3-4 thrombocytopenia was 12%, 3.8% each. Other grade 3-4 toxicities were: neutropenia (4% vs. 4%), stomatitis (2% vs. 3.8%), Hand-foot syndrome (16% vs. 0%), Diarrhea (0% vs. 3.8%). Median relative dose intensity of capecitabine vs. TS-1 was 78.7% (range 51.9-116.7%), 87.5% (range 57.1-166.7%).

Conclusion: There were no significant differences in ORR, OS, and PFS between XP vs. SP arms. The incidence of grade 3-4 neutropenia was similar in both arms, but thrombocytopenia was relatively more common in XP arm. SP was more tolerable than XP in non-hematologic toxicities. Considering the usual dosage of capecitabine in monotherapy is 2500 mg/BSA/day, capecitabine 2500 mg/BSA/day combined with cisplatin 60 mg/BSA/day may be overdosed, and higher rate of non-hematologic toxicity can be explained. Dosage of capecitabine when combined with cisplatin, needs to be further adjusted for routine use.

Disclosure: All authors have declared no conflicts of interest.
efficacy benefit of adding docetaxel to CF (cisplatin + 5-fluorouracil) (DCF). DCF is associated with significant toxicity, making it less tolerable to pts. We modified the original DCF regimen to reduce its toxicity without decreasing efficacy.

### Results

- **Objective:** The use of systemic chemotherapy increased median survival of advanced gastric cancer patients. Besides fluoropyrimidines and platinum compounds, different active agents such as docetaxel and irinotecan became available giving physicians the opportunity to administer to patients further lines of treatment. Second-line chemotherapy with docetaxel or irinotecan showed improved overall survival over best supportive care. There are many patients progressed after two lines of therapy who maintain a good performance status that could be evaluated for further treatment.

### Methods

The aim of this retrospective analysis was to evaluate the activity of the combination of AGC pts received docetaxel 75 mg/m² and cisplatin 75 mg/m² in day 1 and fluorouracil 750 mg/m² in day 1-3 every 3w (TPF) instead of original DCF (docetaxel 75 mg/m², cisplatin 75 mg/m² in day 1 and fluorouracil 750 mg/m² in day 1-3 continuous infusion).

## Results

- **Results:** 89 CT-naïve pts with AGC were included in our study from Feb2008 to Dec2010 (20 female, 19 male). ECOG 0/1/2 were 80/10/10% pts. ORR was 40% (16/39), SD – 40% (16/39), PD – 20% (7/39). Median PFS and median OS were evaluated in 38pts and were 5.4m and 9.5m, respectively. Toxicity was moderate. Grade 3 and 4 toxicities included: anemia 3 pts, neutropenia 6 pts, diarrhea 1 patient, fatigue, stomatitis 12 pts, neutropenia 6 pts, febrile neutropenia 1 pt (2.5%), thrombocytopenia 3 pts, febrile neutropenia 1 pt, 25% and 40% respectively.

- **Conclusions:** A total of 151 cycles of third-line FOLFIRI were administered (median number 7; range 2-18). Treatment was well tolerated; grade 3 or 4 toxicities included neutropenia in 3 patients, diarrhea in 3 patients, asthenia and vomiting in 1 patient each; delay of treatment was required in 9 patients and a reduction of doses only in 3 cases. Among the twenty evaluable patients, two (10%) partial responses and 8 (40%) stable disease were observed, thus obtaining a disease control in half of patients. Median duration of response was 7 months. Median progression-free survival was 3.8 months. Median overall survival from the start of third-line treatment was 9.1 months.

### Disclosure

All authors have declared no conflicts of interest.
gastric cancer patients with CNS metastasis and to clarify treatment outcomes in metastatic gastric cancer to the CNS.

Methods: This retrospective study reviewed data from gastric cancer patients with CNS metastasis treated at our institution from 2000 to 2011.

Results: 2195 patients with metastatic gastric cancer were included in this study. 41 of these patients (1.87%) were found to have CNS metastasis (32 men, 9 women; median age, 62.0 years). Leptomeningeal metastases and brain metastases were identified in 11 and 30 patients; Stage IV disease and recurrence were identified in 25 and 16 cases; and main metastatic sites were lymph nodes, peritoneum, liver, and bone in 22, 12, 7 and 6 cases, respectively. Histopathologically, 29 patients (70.7%) had diffuse-type adenocarcinoma. Most frequent symptoms were headache, nausea/emesis, cataplexy, and convulsion. Thirty-six patients received systemic chemotherapy. The median interval from the initiation of systemic chemotherapy to the diagnosis of CNS metastasis was 7.4 months. Among leptomeningeal patients, 9 patients received symptomatic therapy such as steroid and 2 patients received intrathecal chemotherapy. Median survival time from the diagnosis of leptomeningeal metastases was 27 days. Among brain metastasis patients, 47% had a solitary lesion, while 53% had multiple lesions. Five patients received symptomatic therapy (group 1), 18 patients received radiotherapy (group 2) such as whole-brain radiation therapy or gamma knife radiosurgery, and 7 patients received resection + radiotherapy (group 3). Median survival time from the diagnosis of brain metastases was approximately 1.8 months for patients in group 1 and 2. Group 3 patients survived longer than group 1 and 2 patients at median 8.4 months.

Conclusions: The treatment outcome in metastatic gastric cancer to the CNS was poor. Among brain metastases patients, patients who received resection + radiotherapy showed a more favorable outcome compared to other treatment groups.

Disclosure: All authors have declared no conflicts of interest.

RESULTS OF SURGERY OF GASTRIC LYMPHOMAS COMPROMISED WITH BLEEDING, STENOSIS AND PERFORATION

V. Shaikenov, S. Niered, I. Stilidi
Abdominal Surgery, N.N. Blokhin Russian Cancer Research Center of Russian Academy of Medical Sciences, RUSSIAN FEDERATION

Background: Our purpose is to study results of surgery of patients with primary non-Hodgkin’s lymphomas complicated with bleeding, stenosis and perforation.

Materials and methods: 66 patients with primary non-Hodgkin’s lymphomas were treated in our centre between 1984 and 2009 because of bleeding, stenosis – 11, gastric perforation – 6. Group under study included 28 females and 38 males, mean age was 49. Bleedings from benign gastric ulcers and gastric perforations outside of tumor lesions’ zones were excluded from the study. The histological types: diffuse large B cell lymphoma – 50 patients (76%), MALT-lymphoma – 12 (18.5%), Burkitt’s lymphoma – 4 (6%). Localization of the lesions: overall – 29 patients (44%), antrum – 22 (33%), stomach’s body – 9 (15%), proximal part – 6 (9%). 26 patients (39%) had stage I, 19 (29%) – II, 21 (31.5%) – III, 45 patients (68%) had complications before chemotherapy, 8 (12%) – during the course, 13 (20%) – after. Patients after chemotherapy had gastric perforation more frequent (in 20% of cases) than chemo-naive patients (4.3%, p = 0.006). Gastrectomy was performed for 47 patients (71%), subtotal gastrectomy – 12 (19%).

Results: 43 (65.1%) patients had radical operations, 14 (21.2%) had palliative gastrectomy or gastric resection, 4 (6%) had bypass operations and 5 (7.5%) had only explorative laparotomy. Overall postoperative mortality was 11%. 35 patients had postoperative complications. The most frequent complications were subdiaphragmatic abscess (5.2%), postoperative wound infection (5.2%) and pneumonia (5.2%). Overall 3-, 10- and 10-year survival rate in the group under study was 75%, 65% and 40%, respectively; median survival was 100 months. Patients after radical operations had higher three- and five-year survival rates than patients after palliative gastrectomies and resections (82% and 73% vs. 51% and 44%), however ten-year survival rates in both groups were practically the same.

Summary: Complications of gastric lymphomas can occur at any stage of the disease. Aggressive surgical approach allows to ablate affected organ and remove the source of fatal complications for 86% of patients. Due to postoperative chemotherapy, more than half of patients survive 5 years after surgery.

Disclosure: All authors have declared no conflicts of interest.

THE DIAGNOSIS OF MALIGNANT PANCREATIC TUMOURS BY CIRCULATING TUMOUR CELL DETECTION

P. Basel1, I. Iwanicki-Canon2, E. Toure1, M. Antonietti1, S. Leclere1, F. Di Fiore1, J.C. Sabourin3, P. Michel1
1Gastroenterology and Digestive Oncology, University Hospital of Rouen, Rouen, FRANCE, 2Gastroenterology and Digestive Oncology, CHU de Rouen, Rouen, FRANCE, 3Department of Pathology, Inserm U614, Rouen University Hospital, Rouen, FRANCE, 4Digestive Oncology Unit, C.H.U. Charles Nicolle, Rouen, FRANCE

Introduction: The fine needle aspiration by endoscopic ultrasound guide (EUS FNA) is a diagnostic examination of choice in solid tumour of the pancreas. This invasive technique has a sensitivity of about 70%. The search for circulating tumour cells (CTC) is a non invasive procedure, which could represent an alternative or complement to EUS FNA diagnostic. The objective of this prospective pilot study was to evaluate the diagnostic value of research CTC versus EUS FNA for the diagnosis of a solid tumour of the pancreas (STP).

Patients and methods: From 01/01 to 30/09/2011, all patients undergoing an EUS FNA for a STP were included. EUS FNA was performed with a 22 gauge needle and analyzed by two experienced pathologists. For detection of CTC, 10 ml of blood collected in the periphery before FNA was filtered by technology ScreencellCyto à, stained with Giemsa and analyzed by a cytologist. Peripheral cells were considered tumour if they had the following morphology: kernell > 7 m, anisocytosis, membrane irregularities, presence of a large nucleus.

Results: Twenty six patients with TSP were included (14 men and 12 women), mean age was 64.2 years. The tumor was potentially resectable in 11 cases, 8 cases had a locoregional recurrence and 7 a metastatic extension. In total, 23/26 cases were analyzed due to technical failure of the CTC research (insufficient material) and two technical failures of EUS FNA. 20 patients had cancer objectified (including 15 adenocarcinomas or 57%) by EUS FNA pancreatic histological analysis of the specimen and/or clinical course. In this population of 26 patients the sensitivity of the search CTC was 60%, specificity 100%, positive predictive value 100% and negative predictive value of 27%. On the results of FNA sensitivity for the diagnosis of cancer was 75%, specificity 100%, PPV of 100% and NPV of 37.5%. In patients whose FNA was contributory to the sensitivity of CTC research was 83%, specificity 54%, PPV of 66% and NPV of 75%.
Conclusion: The detection of CTC for the diagnosis of adenocarcinoma in case of tumours of the pancreas is a technique feasible, non-invasive, with a satisfactory diagnostic yield. The results of this pilot study, the continued progress in the analysis of CTC and a confirmation of this results in a higher independent population could allow us to propose this procedure in a first diagnostic step.

Disclosure: All authors have declared no conflicts of interest.

GEMOX PLUS ERLOTINIB FOR THE TREATMENT OF METASTATIC PANCREATIC ADENOCARCINOMA

T. Füredy1, C. V. Konkoly1, K. Ühry1, C. Zielinski1, J. Koch1, W. Schieithauer1
1Internal Medicine I, Medical University of Vienna, Vienna, AUSTRIA, 2Surgery, Medical University of Vienna, Vienna, AUSTRIA, 3Department of Medicine I and Clinical Division of Oncology, Medical University of Vienna and Central European Cooperative Oncology Group (CECOG), Vienna, AUSTRIA

Introduction: Based on demonstration of a significant improvement in overall survival in a placebo-controlled phase III trial, gemcitabine in combination with erlotinib has been approved for the treatment of metastatic pancreatic cancer. In patients with good performance status, gemcitabine combination chemotherapy, i.e. with oxaliplatin (GEMOX) is commonly being used. Although there is some evidence that GEMOX plus erlotinib is beneficial in a subgroup of patients compared to GEMOX alone in cholangiocellular carcinoma no such data exist for pancreatic cancer. Thus, we performed this retrospective analysis in unselected patients to investigate the efficacy and safety of this chemotherapy regimen.

Patients and methods: Forty-four patients with metastatic adenocarcinoma of the pancreas receiving off-protocol GEMOX in combination with erlotinib at a single institution between January 2006 and September 2011 were included in this analysis. Data collection included baseline demographic, clinical and toxicity data as well as objective response according to RECIST criteria, progression-free survival (PFS) and overall survival (OS).

Results: A total of 44 patients were included in this study. The mean age was 60.5 years, and the median ECOG performance score was 1 (range, 0–1). GEMOX in combination with erlotinib was first line regimen in 84% of the patients. Clinical response and disease stabilization was achieved in 45% of the patients. The median PFS was 4 months (range 0.5–43) and median overall survival was 9.6 months (range 0.7–54.7). However, the subgroup of 20 patients, who benefited from this regimen in terms of abrogation of progression, had a PFS of 11.2 and an OS of 15.4 months. Myelosuppression was the most frequent side effect. The most common severe nonhematological toxicity was diarrhea (5/44).

Conclusions: These data suggest that the combination of GEMOX plus erlotinib is safe and active in about half of the patients treated with this regimen. Identification of (bio)markers would be desirable in order to be able to select patients, who are most likely to benefit from this therapeutic strategy.

Disclosure: All authors have declared no conflicts of interest.

CYCLIN E1 SUPPRESSION CONTRIBUTES TO SORAFENIB-INDUCED APOPTOSIS IN HEPATOCELLULAR CARCINOMA (HCC)

C. Hsu1, D. Ou2, Y. Cheng3, Y. Lin1, Y. Chang3, K. Yeh2, A. Cheng2
1Department of Oncology, National Taiwan University Hospital, Taipei, TAIWAN, 2Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, TAIWAN, 3Graduate Institute of Medical Technology, National Taiwan University College of Medicine, Taipei, TAIWAN

Background: We have found that sorafenib can inhibit cyclin E1 expression in HCC cells, which is independent of the inhibitory effects of sorafenib on mitogen-activated protein kinase-extracellular signal-regulated kinase/extracellular signal-regulated kinase signaling. The present study sought to clarify the role of cyclin E1 in sorafenib-induced apoptosis in HCC cells.

Methods: A panel of HCC cell lines, including sorafenib-sensitive (Huh-7, HepG2) and sorafenib-resistant (HepG2R, Huh-7R and HepG2R) HCC cells, was tested. Apoptosis was measured by flow cytometry. Knockdown of cyclin E1 expression were used by RNA interference. Over-expression of cyclin E1 was done by transient transfection of pcMV6-AC-GFP-CCNE1 vector (RG204286; Oregene Technologies). The activity of pertinent signaling pathways, cell-cycle-related proteins and expression of apoptosis-related proteins were measured by Western blotting.

Results: Cyclin E1 mRNA and protein expression were suppressed after sorafenib treatment in sorafenib-sensitive but not in sorafenib-resistant HCC cells. The changes in cyclin E2 or cyclin D1 expression after sorafenib treatment were not correlated with sorafenib sensitivity of HCC cells. Knockdown of cyclin E1 expression reversed the resistance of HCC cells to sorafenib in terms of cell growth and apoptosis induction, whereas over-expression of cyclin E1 increased the resistance of HCC cells to sorafenib. Combination of sorafenib and the cyclin-dependent kinase (CDK) inhibitor flavopiridol synergistically inhibited cell growth and induced apoptosis in HCC cells. The synergistic efficacy was associated with suppression of Bcl-XL expression in HCC cells.

Conclusion: Cyclin E1 expression in HCC cells may serve a predictive biomarker for treatment efficacy. Combination of sorafenib and CDK inhibitors may improve the therapeutic efficacy of sorafenib in HCC. (Supported by grants: NSC100-2314-B-002-058-MY3, NSC101-2325-B-002-039, and NHRF-EX-101-9911BC)

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SORAFENIB VERSUS CAPECITABINE IN THE MANAGEMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

M. Abdelwahab1, M. Shaker1, S. Abdelwahab1, M. Elbasouliy4, M. Eltitly5, O. AbdelHamam1
1Clinical Oncology, Ain Shams University, Cairo, EGYPT, 2Tropical Medicine, Ain Shams University, Cairo, EGYPT

Background: The only approved systemic therapy for patients with advanced hepatocellular carcinoma (HCC) till now is sorafenib. A preliminary study suggested that capcitabine, an oral fluoropyrimidine may be effective in advanced HCC. We have tested this hypothesis in this phase 2 study.

Methods: In this single centre, phase 2, open label trial, we randomly assigned 52 patients with advanced HCC who had not received previous systemic treatment to receive either sorafenib (at a dose of 400 mg twice daily) or capcitabine 1000 mg/m^2 twice daily (day 1–day 14). Primary outcomes were progression free survival. Secondary outcomes included overall survival and safety.

Results: Median overall survival was 7.05 months in the sorafenib group and 5.07 months in the placebo group (hazard ratio in the capcitabine group: 2.36; 95% confidence interval, 1.174–4.74; P = 0.016). The median progression free survival was 6 months in the sorafenib group and 4 months in the capcitabine group (P = 0.005). Three patients in the sorafenib group (11.5%) and 1 patient in the capcitabine group (3%) had a partial response; one patient (3%) had a complete response in the sorafenib group. hand–foot skin reaction was more frequent in the sorafenib group.

Conclusion: In patients with advanced HCC, capcitabine monotherapy is inferior to sorafenib in terms of median progression free survival and overall survival and it should not be used alone for the treatment of advanced HCC but rather combination therapy of capcitabine plus sorafenib should be considered for further randomized clinical trials.

Disclosure: All authors have declared no conflicts of interest.

LIVER SPECIFIC GRADED PROGNOSTIC ASSESSMENT CAN PREDICT THE OUTCOME FOR PATIENTS WITH BRAIN METASTASES FROM HEPATOCELLULAR CARCINOMA

S. Lim1, S. Lee1, K. Han2, H. Choi3
1Medical Oncology, Severance Hospital, Seoul, KOREA, 2Gastroenterology, Severance Hospital, Seoul, KOREA

Background: After the introduction of sorafenib which showed prolongation of survival in patients with advanced HCC, the incidence of brain metastasis seemed to increase. Assessment of prognostic factors might useful to decide treatment in patients with brain metastases. Although diagnosis-specific Graded Prognostic Assessment (GPA) has been identified for several cancer types, optimal treatment strategy for brain metastasis from HCC has not been well established.

Methods: A total of 128 HCC patients were newly diagnosed with brain metastasis at Yonsei University Health Center between 1995 and 2011. Using SPSS program, univariate and multivariate analyses of the prognostic factors were performed. With the P value less than 0.10 as cutoff value, the significant prognostic factors were used to develop the HCC-specific GPA (HCC-GPA).

Result: The median overall survival after brain metastasis in all patients was only 6.1 weeks (95% confidence interval, 4.8–7.4 week). Significant prognostic factors were the presence of extracranial lesion, and Child-Pugh–Class score. Using those variables, we developed the HCC-specific GPA (HCC-GPA).

Conclusion: Although the overall prognosis of patients with brain metastasis from HCC is dismal, the present data showed that newly developed HCC-GPA score can
discriminate the prognosis of HCC patients with brain metastasis. It can be used as a valuable tool to select patients who can be good candidates for active local treatment.

Disclosure: All authors have declared no conflicts of interest.

### T72 TRANSCATHETER ARTERIAL CHEMOEMBOLISATION FOR HEPATOCELLULAR CARCINOMA IN CIRRHOSIS: FEASIBILITY OF HEPATIC RESECTION

O. Nematov1, S. Narzuov1, M. Djuraev1, S. Khudayrov1, D. Egamberdiev1, R. Tuyin1

1Abdominal Oncology, National Cancer Center of Uzbekistan, Tashkent, UZBEKISTAN, 2Administration, National Cancer Center of Uzbekistan, Tashkent, UZBEKISTAN

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. It mostly occurs in patients with cirrhosis. The aim of investigation is to evaluate the efficiency of transcatheter arterial chemorromobilization (TACE) for unresectable HCC in cirrhosis and use of it in preoperative stage.

Materials and methods: We evaluated data from 49 patients who had a confirmed diagnosis of HCC on cirrhosis. Median age of the patients was 56 years. Male - 35 (71.4%), female - 14 (28.6%). In 33 (67.3%) cases tumor located in right lobe and in 16 (32.7%) cases located in left lobe. In 7 (14.3%) cases tumor size consisted 8-12 cm, in 32 (65.3%) 12-15 cm and in 10 (20.4%) cases more than 15 cm. The underlying cirrhosis was staged as Child-Pugh A in 14(28.6%) cases and Child-Pugh B in 35 (71.4%). We selectively catheterized the tumour via arteria femoralis and used Embolization with Lipiodol as embolic material.

Results: In follow up, we carried out laboratory studies and CT. Three weeks after TACE there are dominated tumours with the sizes 8-12 cm (in 16 (32.7 patients)) due to reduction of tumour sizes. Reduction of tumour sizes averaged 26.7 ± 0.4 mm. There were noted physical increase of opposite part of live from 1 up to 3 cm. Averagely 23 ± 0.32 mm in 46 (93.9%) patients. Alpha-fetoprotein normalized in 37 patients, which was high before manipulation. After TACE patients were restaged and Child-Pugh class A noted in 25 (51%), class B noted in 24 (49%) patients. There is noted full clinical effect, partial effect noted in 21 (42.9%) patients, stable process in 13 (26.5%) patients. Twenty one of the 49 patients (49%) selected for surgical treatment according operative conditions, reduction of tumour sizes and improvement of opposite part of live after TACE.

Conclusions: TACE is safe method, it provides reduction of tumour sizes, intensifies effect of arterial blood to the opposite part of liver which improves liver function and conducts to hypertrophy of remaining part of liver. In 49% of unresectable HCC patients TACE conducts to curative hepatic resection.

Disclosure: All authors have declared no conflicts of interest.

### T75 IMPACT OF LYMPH NODE LEVEL ASSESSMENT FOR SURVIVAL ON TIME TO RELAPSE IN BILIARY TRACT CANCERS

J. Martinez-Galan1, P. Ballesteros2, A. Gonzalez-Astorga1, J.A. Ortega1, A. Gonzalez-Vicente1, J. Soberino Garcia1, C. Gonzalez-Rivas1, J. Ruiz Vozmediano1, T. Villegas5, J.R. Delgado1

1Medical Oncology Department, Hospital Universitario Virgen de las Nieves, Granada, SPAIN, 2Medical Oncology Department, Hospital Universitario de Ceuta, Ceuta, SPAIN, 3Surgical Department, Hospital Universitario Virgen de las Nieves, Granada, SPAIN

Background: Biliary tract cancers (BTCs) are relatively rare neoplasms encompass both cholangiocarcinoma (CC). The role of routine lymphadenectomy at the time of surgical resection remains poorly defined. We sought to identify factors associated with outcome following and examine the impact of lymph node (LN) assessment on survival.

Methods: 43 patients who underwent curative intent surgery between 2000-2010 were identified from a database. We calculated prognostic factors and impact lymph node (LN) assessment for survival.

Results: A total of 43 patients were identified with no metastatic BTCs. The median age was 65 years (29–82 years); performance status of 0 in 33/34 (76%); PS1 in 8/43 (19%) and PS2 in 2/43 (5%) pts. A histological diagnosis of adenosquamous carcinoma was confirmed in 100%. Surgical resection was performed in all patients. After resection 42/18(43) had positive nodes. Adjuvant chemotherapy had 31/43 (72%), preferred (19%) and PS2 in 2/43 (5%) pts. A histological diagnosis of adenocarcinoma was obtained in 32 (65.3%) cases and ovarian origin in 28% of cases. All patients have been operated, one patient had neoadjuvant chemotherapy. Only two patients had HIPEC. 52% (13 cases) has post-operative systemic chemotherapy with complete response in 8 cases. Disease recurrence was noted in 48% of patients (12 cases). Second-level surgery has been performed in 8 cases. 8 patients had chemotherapy after recurrence. The median patient follow-up was 36 months (range, 1 to 120 months). 1 and 3-year progression free survival was 40% and 12% respectively. Overall survival at 1, 3, 5 year was 80%, 30%, 20% respectively. One patient developed bone metastases at 13 months of follow up.

Conclusion: Pseudomyxoma peritonei is a rare disease that must be treated in specialized centers with complete surgical removal, per or immediate post operative intraperitoneal chemotherapy and accurate histological classification.

Disclosure: All authors have declared no conflicts of interest.

### T74 PSEUDOMYXOMA PERITONEI: PATHOLOGICAL AND THERAPEUTIC ASPECTS OF 26 CASES

M. Nsirine1, A. Aloui1, R. Helia1, M. Ayadi1, N. Chaie1, B. Allani1, H. Raies1, A. Medini1

1Medical Oncology, Salah Azaeiz Institute, Tunis, TUNISIA, 2Medical Oncology, Institut Salah Azaiz, Tunis, TUNISIA

Introduction: Pseudomyxoma peritonei is defined by mucus collection in the peritoneal cavity with or without presence of neoplastic cells. Recent immunohistochemical and cytogenetic applications have confirmed the appendiceal origin. Surgical removal combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the main treatment. The aim of this study is to evaluate pathological and therapeutic aspects of a Tunisian series of 25 cases.

Methods: We retrospectively studied 25 patients, in a 17-year period from 1994 to 2011. Data were collected from surgical records and included: Patient presentation, radiological-pitological findings; surgical procedure, adjuvant therapy and follow up. Initial and subsequent surgical treatment were conducted at the Salah Azaie institute.

Results: The mean age was 38 years (range 32-83 years) and 92% (23/25) were females. The most frequent symptom was abdominal distension (68%). Pathologic specimen showed peritoneal mucinosis carcinomatosis in 40% of patients and desmominimized peritoneal adenomucinosis in 20% of patients. The appendiceal origin was found in 60% of cases and ovarian origin in 28% of cases. All patients have been operated, one patient had neoadjuvant chemotherapy. Only two patients had HIPEC. 52% (13 cases) has post-operative systemic chemotherapy with complete response in 8 cases. Disease recurrence was noted in 48% of patients (12 cases). Second-level surgery has been performed in 8 cases. 8 patients had chemotherapy after recurrence. The median patient follow-up was 36 months (range, 1 to 120 months). 1 and 3-year progression free survival was 40% and 12% respectively. Overall survival at 1, 3, 5 year was 80%, 40%, 20% respectively. One patient developed bone metastases at 13 months of follow up.

Conclusion: Pseudomyxoma peritonei is a rare disease that must be treated in specialized centers with complete surgical removal, per or immediate post operative intraperitoneal chemotherapy and accurate histological classification.

Disclosure: All authors have declared no conflicts of interest.

### T77 RELATIONS OF QOL TO TUMOR RESPONSE AND ADVERSE EVENTS IN UNRESECTABLE ADVANCED PANCREATIC CANCER PATIENTS IN THE GEST STUDY

Y. Ohashi1, T. Ioka2, T. Okusaka3

1Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, JAPAN, 2Division of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, JAPAN, 3Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, JAPAN

Background: The GEST study demonstrated the non-inferiority of S-1, but not the superiority of gemcitabine plus S-1 (GS) to gemcitabine alone (G) with respect to overall survival in unresectable advanced pancreatic cancer patients (Ioka et al. ASCO 2011, Abstract 4007). The results of QOL evaluation based on EQ-5D demonstrated that S-1 and G were equivalent and GS was superior to G (Ohashi et al. ASCO 2011, Abstract 9070). We report the relations of QOL to adverse events and tumor response.

Methods: Chemotherapy was administered until PD, consent withdrawal, or unacceptable adverse events. EQ-5D questionnaires were filled in at baseline and 6, 12, 24, 48, and 72 weeks and converted to 0-1 utility scores by the Japanese value set. We estimated the effects of adverse events (nausea, vomiting, diarrhea, fatigue, anorexia) and level nosal affections are the strongest predictors of relapse and survival.

Conclusions: This presentation evaluates the clinically important aspects of a binary cancer cohort with survival benchmarks obtained in the modern era of multidisciplinary care. Surgical resectability and adjuvant chemotherapy offers the optimal treatment outcome in patients with ICC. From our results depth of tumor invasion (T), the presence the lymph node metastases (N) and level nodal affections are the strongest predictors of relapse and survival.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: QOL in the studied patient population was negatively affected by fatigue and anorexia, and was improved by good response probably through decreased pain.


Abstract withdrawn in exceptional circumstances.

Background: GIDEON (NCT00812175) is an ongoing, global, prospective, non-interventional study of patients with unresectable hepatocellular carcinoma (HCC) receiving sorafenib (Nexavar®) in real-life practice. The aim is to evaluate sorafenib safety and efficacy in diverse settings and patient groups. The second interim analysis was triggered when ~1500 patients had been treated for ≥4 months. We describe sorafenib use in Europe according to disease stage.

Methods: Patient/disease characteristics (including Barcelona Clinic Liver Cancer [BCLC], tumour node metastases [TNM], Cancer for the Liver Italian Programme [CLIP]) and treatment history were recorded at enrolment; sorafenib dose, concomitant medications, performance status, liver function, adverse events (AEs) and efficacy are recorded at follow-up visits.

Results: Of 1571 patients in the safety population, 588 are in Europe (see table). The majority of patients were BCLC-C (52.9%), TNM III (40.3%) or CLIP 1/2 (26.0%/26.5%), although sorafenib was also used in patients with early, intermediate and end-stage disease. Generally, AEs and serious AEs (SAEs) increased with advancing disease (AEs: 66.0%, 87.4%, 85.5%, 89.7%; SAEs: 22.6%, 37.8%, 38.3%, 58.6%; for BCLC-A, B, C and D, respectively), whereas sorafenib-related AEs and SAEs were comparable across BCLC groups (AEs: 60.4%, 74.1%, 68.5%, 41.4%; SAEs: 7.5%, 15.4%, 10.3%, 10.3%; for BCLC-A, B, C and D, respectively). Evaluation will continue with more mature data.

Conclusions: These data reflect real-world sorafenib given to a broad range of patients, indicating a similar safety profile across the different disease stages. Evaluation is ongoing, with more mature data expected from the final analysis.

Disclosure: B. Daniele: Dr B. Daniele has participated in advisory boards and received lecture fees from Bayer. J. Turnes: Dr J. Turnes has participated in advisory boards for Roche Pharma. C. Papandreou: Prof. C. Papandreou has participated in advisory boards for Bayer, Sanofi Aventis, Novartis, Bristol Meyers Squibb and Janssen. P. Stål: Prof. Stål has advised and received a grant from Bayer. A. Croitoru: Dr A. Croitoru has consulted for and received an investigator fee from Bayer. P. Mathurin: Dr P. Mathurin was paid speaking at symposia for Roche, Schering-Plough, Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag and Bayer Healthcare pharmaceutical companies. He is an investigator for Roche, Schering-Plough, Bristol-Myers Squibb, Gilead Sciences, Vertex pharmaceuticals Janssen-Cilag, Boehringer, Novartis and Bayer Healthcare companies. He is a member of the French boards of experts in Hepatology for Roche Schering-Plough, Gilead Sciences, Bayer Healthcare and Bristol-Myers Squibb pharmaceutical companies. He is consulting for the Gilead Sciences, Bristol-Myers Squibb, Bayer Healthcare and Vertex pharmaceutical companies. All other authors have declared no conflicts of interest.

Background: The efficacy of Sorafenib in patients (pts) with hepatocellular carcinoma (HCC) has been proven in randomized, controlled trials. INSIGHT is a non-interventional study in patients with hepatocellular carcinoma treated with sorafenib.

Methods: We describe sorafenib use in Europe according to disease stage.

Results: Of 1571 patients in the safety population, 588 are in Europe (see table). The majority of patients were BCLC-C (52.9%), TNM III (40.3%) or CLIP 1/2 (26.0%/25.9%), although sorafenib was also used in patients with early, intermediate and end-stage disease. Generally, AEs and serious AEs (SAEs) increased with advancing disease (AEs: 66.0%, 87.4%, 85.5%, 89.7%; SAEs: 22.6%, 37.8%, 38.3%, 58.6%; for BCLC-A, B, C and D, respectively), whereas sorafenib-related AEs and SAEs were comparable across BCLC groups (AEs: 60.4%, 74.1%, 68.5%, 41.4%; SAEs: 7.5%, 15.4%, 10.3%, 10.3%; for BCLC-A, B, C and D, respectively). Evaluation will continue with more mature data.

Conclusions: These data reflect real-world sorafenib given to a broad range of patients, indicating a similar safety profile across the different disease stages. Evaluation is ongoing, with more mature data expected from the final analysis.

Disclosure: B. Daniele: Dr B. Daniele has participated in advisory boards and received lecture fees from Bayer. J. Turnes: Dr J. Turnes has participated in advisory boards for Roche Pharma. C. Papandreou: Prof. C. Papandreou has participated in advisory boards for Bayer, Sanofi Aventis, Novartis, Bristol Meyers Squibb and Janssen. P. Stål: Prof. Stål has advised and received a grant from Bayer. A. Croitoru: Dr A. Croitoru has consulted for and received an investigator fee from Bayer. P. Mathurin: Dr P. Mathurin was paid speaking at symposia for Roche, Schering-Plough, Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag and Bayer Healthcare pharmaceutical companies. He is an investigator for Roche, Schering-Plough, Bristol-Myers Squibb, Gilead Sciences, Vertex pharmaceuticals Janssen-Cilag, Boehringer, Novartis and Bayer Healthcare companies. He is a member of the French boards of experts in Hepatology for Roche Schering-Plough, Gilead Sciences, Bayer Healthcare and Bristol-Myers Squibb pharmaceutical companies. He is consulting for the Gilead Sciences, Bristol-Myers Squibb, Bayer Healthcare and Vertex pharmaceutical companies. All other authors have declared no conflicts of interest.
prospective, non-interventional study, conducted in Germany and Austria in pts with HCC. The objectives of this study are the evaluation of safety and efficacy under practice conditions in both hospitals and private practices. Enrollment into INSIGHT is not restricted to a particular tumor stage. Recruitment into the study is ongoing.

Methods: The second interim analysis (data cut-off 23 FEB 2012) evaluated overall survival and safety data in relevant subgroups. All patients with HCC were observed for the duration of their sorafenib therapy. In addition to baseline data the performance status, liver cirrhosis status (clinical and/or radiological), time to progression and overall survival time are documented. Documentation of adverse events comprises relationship with drug, seriousness, grade (CTCAE version 3.0), and outcome.

Results: Until the data cut-off 623 pts have been enrolled; 618 of which are evaluable for safety and efficacy analyses. The table summaries major baseline characteristics together with median overall survival (mOS) data for relevant subpopulations.

| Patients recruited n, Male n (%) | 618, 528 (85) |
| ECOG PS n, (%), 0, 1, 2 | 203 (33); 310 (50); 98 (16) |
| BCLC-Stage n, (%), A, B, C, D | 80 (13); 149 (24); 319 (52); 12 (2) |
| Child Pugh Stage, n, (%), A(7), B7-9(7), C (>9), Missing | 264 (43); 99 (16); 12 (2); 243 (39) |
| mOS total population (Events n = 164) | Months | 17.1 |
| mFPS total population (Events n = 408) | 4.1 |
| mOS according to BCLC A, B, C, D | 29.2; 19.6; 14.5; 4.0 |
| mOS according to Child Pugh A, B, C | n.r.; 7.2; 4.0 |
| mOS Child Pugh A & B | 11.9; 9.5; 2.5 |
| mOS Duration of therapy > 24 weeks | 19.8; 26.7 |
| n.r.- not reached |

Conclusions: Results of mOS in pts with HCC treated under daily practice conditions in hospitals and private practices confirm the general efficacy of Sorafenib known from registration trials and gives further insight into pts with Child B/C cirrhosis and BCLC stage A/B. Further demographic data and efficacy and safety results will be presented.


A RANDOMIZED PHASE II TRIAL OF BIWEEKLY S-1 WITH PACLITAXEL (SPA) OR OXALIPLATIN (SOX) AS FIRST-LINE CHEMOTHERAPY IN ADVANCED GASTRIC CANCER PATIENTS: PRELIMINARY RESULTS

M. Haba, W. Fang, Y. Zheng, P. Zhao, C. Miao, X. Zhang, J. Qian, H. Jiang, Y. Zheng, N. Xu
Department of Medical Oncology, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, CHINA

Background: Gastric cancer patients are commonly treated with S-1-based chemotherapy for three weeks or more to ensure two weeks of exposure to therapeutic doses. Severe side effects of S-1 such as mucositis, diarrhea and neutropenia often occur in the second week of treatment. We evaluated the activity and safety of every other week S-1 regimens with paclitaxel or oxaplatin in patients with advanced gastric cancer. Patients and methods: Eligible patients with pathologically confirmed advanced gastric cancer were randomized into two arms. S-1 was administered orally (80 mg/m2/day) on day 1 every 2 weeks and capecitabine (1000 mg/m2/day) was added on day 3 and 5. Patients were subsequently treated with a combination of S-1 and oxaplatin as first-line treatment for patients with advanced gastric cancer.

Results: Eighty-one gastric cancer patients were enrolled from June 2010 to March 2012. Patients were randomized to receive SPA (43) or SOX (38). Results are presented for 76 patients. The ORR for arm A was 43.6%, and that for arm B was 33.3% with no significant difference between the two arms (p = 0.35). The median PFS was 6.2 months for arm A vs. 5.1 months for arm B (p = 0.60); the median OS was 10.8 months for arm A and 10.0 months for arm B (p = 0.17). No treatment-related deaths occurred during the study. The most frequent toxicity was neutropenia (30.8% and 17.4% of grade 3/4 in arms A and B, respectively). The most common non-hematological toxicities were mucositis, diarrhea, and peripheral neuropathy, in all less than 5% of patients.

Conclusions: These preliminary findings suggest that biweekly S-1-based regimens have an acceptable ORR with tolerable side effects in advanced gastric cancer patients. The study will continue until 100 patients have been enrolled.

Disclosure: All authors have declared no conflicts of interest.
Conclusion: The combination of everolimus and capecitabine has a reasonable toxicity profile and may show significant activity in patients with advanced HCC pretreated with sorafenib. This combination therapy warrants further investigation as a possible second line treatment for selected patients with HCC.

Disclosure: All authors have declared no conflicts of interest.

REVIEW OF THE MANAGEMENT OF ADVANCED GASTRIC CANCER; AN EXPERIENCE FROM A LOW RESOURCE SETTING

K. Beecham¹, V.D.N.K. Vanderpuye¹, N.A. Adu-Aryee²
¹Radiotherapy, Korlebu Teaching Hospital, Accra, GHANA, ²Surgery, Korlebu Teaching Hospital, Accra, GHANA

Purpose: Adjuvant treatment combines Epirubicin, Cisplatin and 5-FU (ECF). Replacement of 5FU and Cisplatin with Capecitabine (X) and Oxaliplatin (O) has shown an efficacy similar to ECF, with improved tolerability and safety. The outcome of management of advanced gastric cancer at the Oncology Unit was assessed, with emphasis on the use of Capecitabine alone or in combination.

Patients & methods: 27 patients adenocarcinoma of the stomach between 2004 and 2008 were eligible. Time to disease progression (TTP) as well as tolerability of treatment was assessed retrospectively.

Results: Median follow up was 12 months (1 to 60 months). No adjuvant treatment was given in 36%. 26% received concurrent chemoradiation with Capecitabine. 11.1% received palliative radiotherapy only. One patient did not complete radiotherapy due to side effects. 26.6% received Capecitabine alone and combined with Oxaliplatin in 11.1%. Grade 3/4 diarrhoea was reported in 7.4%; neuropathy and neutropenia were seen in 3.7%. Median time to progression in patients who had adjuvant treatment was 6.4 months (2 to 13 months).

Conclusion: There is a favorable tolerability of Capecitabine used alone or in combination with radiotherapy or other chemotherapy drugs.

Disclosure: All authors have declared no conflicts of interest.