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MEETING SUMMARY
ASCO 2018 and WCGIC 2018

Prof. Armin Gerger
Medical University Graz
Austria

CANCERS OF THE LIVER, SMALL INTESTINE AND PANCREAS TRACT

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Unicancer GI PRODIGE 24/CCTG PA.6 TRIAL: A MULTICENTER INTERNATIONAL RANDOMIZED PHASE III TRIAL OF ADJUVANT mFOLFIRINOX VERSUS GEMCITABINE IN PATIENTS WITH RESECTED PANCREATIC DUCTAL ADENOCARCINOMAS

Conroy et al. ASCO 2018, LBA4001

BACKGROUND

- 6 months of adjuvant gemcitabine (plus capecitabine) is standard of care for metastatic PC
- >70% of patients relapse within 2 years despite adjuvant treatment
- FOLFIRINOX is more effective than gemcitabine as first-line treatment for metastatic PC in patients with good performance status

Conroy et al. ASCO 2018, LBA4001
Neoptolemos JP et al. Lancet 2017; Mar 11;389(10073):1011-1024
FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; PC, pancreatic cancer

STUDY DESIGN

- Phase III multicentre, randomised clinical trial
- Pts aged 18-79 years with histologically proven pancreatic ductal adenocarcinomas, 21-84 days after R0 or R1 resection, WHO PS ⩽1, adequate hematologic and renal function and no cardiac ischemia
- Randomisation stratified by centre, pN, R margin status, and post-operative CA 19-9 level (⩽ 90 U/mL vs 91-180)
  - Arm A pts received 28-day cycles of gem on days 1, 8, and 15 for 6 cycles
  - Arm B pts received mFOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 D1, and 5-FU 2.4 g/m^2 over 46 h) every 14 days for 12 cycles
- Primary endpoint DFS
- Secondary endpoints OS, MFS and adverse events

Conroy et al. ASCO 2018, LBA4001

CA, cancer antigen; DFS, disease-free survival; gem, gemcitabine; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX ; OS, overall survival; MFS, metastasis-free survival; PS, performance status; pts, patients; WHO, World Health Organisation

KEY RESULTS

- **Median DFS: 21.6 months (mFOLFIRINOX)** vs 12.8 months (gemcitabine)
  - HR 0.59 (95% CI, 0.47-0.74), p>0.0001

- **Median OS: 54.4 months (mFOLFIRINOX)** vs 34.8 months (gemcitabine)
  - HR 0.66 (95% CI, 0.49-0.89)

- Grade 3-4 AEs (GEM vs mFOLFIRINOX) were reported in 51.1% vs 75.5% of the patients.

Conroy et al. ASCO 2018, LBA4001

CI, confidence interval; DFS, disease-free survival; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; HR, hazard ratio; mFOLFIRINOX, modified FOLFIRINOX; OS, overall survival

CLINICAL TRANSLATION

- mFOLFIRINOX should be considered a new standard of care after pancreatic cancer resection in patients with good performance status

Conroy et al. ASCO 2018, LBA4001
FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX;

KEY MESSAGES

- Adjuvant mFOLFIRINOX significantly improves DFS, MFS and OS compared to gemcitabine
- mFOLFIRINOX is a generally safe regimen, however it is more toxic than gemcitabine regimen
- mFOLFIRINOX should be considered a new standard of care after pancreatic cancer resection in patients with good performance status
- In this study the patient population was highly selected (CA19-9 < 180 U/mL)

CA, cancer antigen; DFS, disease-free survival; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX; MFS, metastases-free survival; OS, overall survival

REACH-2: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF RAMUCIRUMAB VERSUS PLACEBO AS 2ND-LINE TREATMENT IN PATIENTS WITH ADVANCED HCC AND ELEVATED BASELINE AFP FOLLOWING 1ST-LINE SORAFENIB

Zhu et al. ASCO 2018, Abst #4003

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma

BACKGROUND

- Sorafenib (1L) and regorafenib (2L) are the only globally approved drugs for treatment of advanced HCC. Nivolumab is also available for advanced HCC but in the US only
- In the REACH study, ramucirumab (2L) was not associated with a significant OS benefit in patients with advanced HCC
  - the survival benefit of ramucirumab was confirmed patients with AFP ⩾400ng/ml (HR 0.67, p=0.006) and was well tolerated
- Patients with advanced HCC and elevated AFP have a poorer prognosis
- The REACH-2 study aimed to confirm the survival benefit of ramucirumab treatment (2L) observed in the REACH study, for advanced HCC patients with high baseline AFP (⩾400ng/ml)

Zhu et al. ASCO 2018, Abstract #4003; Zhu AX et al. JAMA Oncol 2016; Sep 22. doi: 10.1001/jamaoncol.2016.4115. [Epub ahead of print]
1L, first-line; 2L, second-line; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; OS, overall survival

STUDY DESIGN

- Pts ⩾18 yrs with HCC with BCLC stage C or B disease refractory or not amenable to locoregional therapy
  - Baseline AFP ⩾400 ng/mL
  - Child-Pugh A
  - ECOG PS 0 or 1
  - Adequate hematologic and biochemical parameters
  - Progressed on or following, or intolerant to sorafenib
- Pts randomized (2:1) to receive RAM 8 mg/kg iv or placebo Q2W plus best supportive care, until disease progression or unacceptable toxicity
- Primary endpoint OS
- Secondary objectives included PFS, ORR per RECIST v1.1 and safety

Zhu et al. ASCO 2018, Abst #4003

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pts, patients; Q2W, dosed every 2 weeks; RAM, ramucirumab; RECIST, response evaluated criteria in solid tumors

KEY RESULTS

- Median OS: 8.5 months (ramucirumab) vs 7.3 months (PBO + BSC); HR 0.71, p=0.0199

- Significant survival benefit of ramucirumab (2L) in patients with HCC and AFP ⩾400 ng/mL following progression / intolerance to sorafenib

- Grade ⩾3 AES in >5% of patients in the ramucirumab arm were hypertension (12.2% ramucirumab, 5.3% PBO) and hyponatremia (5.6%, 0%)

Zhu et al. ASCO 2018, Abst #4003

2L, second-line; AFP, alpha-fetoprotein; AEs, adverse events; BSC, best supportive care; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PBO, placebo

CLINICAL TRANSLATION

- Potential role of ramucirumab should be considered in context of future overall landscape
  - (lenvatinib [1L] and cabozantinib [2L] have demonstrated benefits in phase III trials)
- Based on results of single-arm phase 2 study, Nivolumab has been approved by the FDA for 2nd-line treatment of HCC

Zhu et al ASCO 2018; Kudo M et al. Lancet 2018;391:1163-73; Abou-Alfa GKM et al. J Clin Oncol 2018;36(suppl 4S;abstr 207); El-Khoueiry AB et al. Lancet 2017;389:2492-502
1L, first-line; 2L, second-line; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma

KEY MESSAGES

- Significant survival benefit of ramucirumab treatment (2L) in patients with HCC and AFP ⩾400 ng/mL who progressed on or were intolerant to sorafenib
- Ramucirumab was well tolerated. REACH-2 confirms the efficacy and safety observed in the pre-specified group of patients from REACH with an AFP ⩾400 ng/ml
- First positive study in a biomarker-selected patient population

2L, second-line; AFP, alpha fetoprotein; HCC, hepatocellular carcinoma

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GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com