P-99 Pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract cancer: phase 3 KEYNOTE-966 trial in progress

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Background: Biliary tract cancer (BTC) is a rare and heterogeneous malignancy comprising intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancer. Surgery is potentially curative in patients with early disease, but recurrence is common. Combination chemotherapy with gemcitabine and cisplatin is the current standard of care for advanced BTC in most regions as well as S-1 therapy in Japan. Pembrolizumab has demonstrated modest but durable antitumor activity in patients with BTC as monotherapy and improved survival when used in combination with platinum-based chemotherapy in other oncologic indications. KEYNOTE-966 (NCT04003636) is a randomized, double-blind, phase 3 trial evaluating pembrolizumab or placebo plus gemcitabine and cisplatin in patients with advanced BTC.

Trial design: Eligible patients are ≥18 years old with histologically confirmed metastatic or unresectable BTC, measurable disease per RECIST v1.1, an ECOG performance status of 0 or 1, and adequate organ function. Patients who have received prior systemic therapy for advanced disease, or prior therapy with an anti-PD-1/PD-L1/PD-L2 or CTLA-4 agent, and those with a history of pneumonitis, HIV infection, or central nervous system metastases will be excluded. Patients with past or ongoing HCV or controlled HBV infection are eligible per protocol-defined criteria, provided they do not have dual active HBV and HCV infection at study entry. Approximately 788 patients will be randomly assigned 1:1 to pembrolizumab 200 mg or placebo IV every 3 weeks in combination with gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 IV on days 1 and 8 of every 3-week cycle. Cisplatin will be given for a maximum of 8 cycles; gemcitabine will be given until progression, unacceptable toxicity, or withdrawal. Treatment with pembrolizumab/placebo will be continued for up to 35 cycles (~2 years of treatment) or until progression, unacceptable toxicity, or withdrawal. Patients will be stratified by region (Asia, non-Asia), stage (locally advanced, metastatic), and tumor origin (gallbladder, intrahepatic, extrahepatic). Imaging will be performed every 6 weeks through week 54, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious adverse events). Co-primary endpoints are progression-free survival (PFS) per RECIST v1.1 by blinded independent central review (BICR) and OS. Secondary endpoints are objective response rate (ORR) and duration of response (DOR) per RECIST v1.1 by BICR, and safety. Exploratory endpoints are disease control rate (DCR) per RECIST v1.1 by BICR; PFS, ORR, DOR, and DCR per immune-modified RECIST; PFS and ORR per RECIST v1.1 by BICR; and health-related quality of life (by EORTC QLQ-C30, EORTC QLQ-BIL21, and EuroQol EQ-5D-5L). Recruitment began in September 2019 and is underway in 19 countries.

Acknowledgement: We thank the patients and their families and caregivers for participating in this trial, and all investigators and site personnel. Medical writing and editorial assistance were provided by Arman Nabatiyan and Jemimah Walker of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA.

Legal entity responsible for the study: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Funding: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosure: Arndt Vogel has an affiliation with Consultant: MSD; Speaker's Bureau: MSD.

https://doi.org/10.1016/j.annonc.2020.04.181

P-100 Quality of life assessment and reporting in gastric cancer treatment: A systematic review of phase 3 clinical trials published between 2010 and 2019

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Background: Quality of life (QoL) has emerged as a fundamental outcome in cancer clinical trials. The importance of integrating QoL with other traditional oncological outcome measures has been particularly emphasized in poor-prognosis malignancies such as gastric cancer. The present study aimed to evaluate the assessment and reporting of QoL in phase 3 clinical trials conducted in patients affected by gastric cancer.

Methods: We performed a literature search of primary phase 3 clinical trials testing anticancer drugs in gastric cancer published between 2010 and 2019 by 7 relevant scientific journals. Data concerning the presence of QoL among secondary and exploratory endpoints, the different assessment tools and the methods of analysis adopted were extracted from papers and study protocols. For every paper, secondary publications reporting QoL results were searched in PubMed.

Results: 46 publications of phase 3 clinical trials were included in our analysis (9 in neoadjuvant/adjuvant/perioperative setting, 37 in metastatic setting). Only 14/46 (30.4%) trials strictly enrolled patients affected by gastric cancer, while 26/46 studies (56.5%) included gastroesophageal junction and 6/46 (13.0%) esophageal cancer. In 21 publications (45.7%), QoL was not listed among the endpoints in 7/9 (77.8%) trials in the neoadjuvant/adjuvant/perioperative setting, in 7/18 (38.9%) first-line trials and in 7/19 (36.8%) second- and further lines trials, including 15/20 (75.0%) trials conducted exclusively in an Eastern population vs 3/9 (33.3%) trials conducted only in a Western population. A decreasing trend was recognized over time: QoL was not reported in 13/26 (50.0%) publications between 2010-2015 and in 8/20 publications (40.0%) between 2016-2019; surprisingly, this tendency was not confirmed in the metastatic setting, where the lack of QoL concerned 7/20 (35.0%) of publications between 2010-2015 and 7/14 (41,2%) of publications between 2016-2019). Out of 25 (54.3%) primary publications of trials reporting QoL as a secondary or exploratory endpoint, QoL results were published in 11/25 (44.0%). Additionally, QoL results were published in 5/11 (45.5%) primary publications of trials with positive results and in 5/21 (23.8%) no profit trials. However, we found 4 secondary publications reporting QoL results. For trials including QoL among endpoints but no QoL results in the primary publication, the probability of secondary publication was 0%, 25.0%, and 50.0% after 1, 3 and 5 years, respectively. Most common tools used for QoL assessment in patients were EORTC QLQ-C30 (22, 88.0%) and EORTC QLQ-STO22 (14, 56.0%); most common methods of analysis were mean change/mean score (10, 40.0%) and time to deterioration (9, 36.0%).

Conclusion: Despite a general decreasing tendency to exclude QoL from oncologic outcome measures in the last five years, QoL is not assessed or published in many phase III trials in gastric cancer, including trials conducted in the metastatic setting and no profit trials. The methodology of QoL analysis is heterogeneous for type of instruments, method of analysis and presentation of results. In conclusion, there is a strong need for QoL definition for supporting therapeutic decision-making and helping clinicians in the optimal management of gastric cancer patients.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: The first author and the presenting author have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.04.182

P-101 Oncologic outcomes of mitomycin-C induced severe neutropenia after hyperthermic intraperitoneal chemotherapy with cytoreductive surgery in colorectal cancer patients

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Background: Mitomycin-C (MMC) is the most commonly used anticancer drug for hyperthermic intraperitoneal chemotherapy (HIPEC) to treat colorectal cancer patients with peritoneal metastasis. Because MMC has hydrophilic properties with pharmacologic stability to use in the intraperitoneal cavity, it was widely used for HIPEC. However, one of its famous side effects is myelosuppression. There were concerns that severe neutropenia after cytoreductive surgery with HIPEC is related to postoperative recovery. However, there is no report as to whether MMC-induced neutropenia influences oncologic outcomes so far. The aim of this study was to evaluate whether MMC-induced severe neutropenia affects oncologic outcomes after cytoreductive surgery with HIPEC in colorectal cancer patients with peritoneal metastasis.

Methods: From March 2015 to June 2019, colorectal cancer patients who underwent CRS and HIPEC to treat peritoneal carcinomatosis at Gangnam Severance Hospital, Seoul, South Korea were evaluated. We excluded the patients with extraperitoneal metastasis (e.g. liver, lung), Krukenberg tumor, re-do HIPEC, incompleteness of cytoreduction, and peritoneal cancer index (PCI) ≥ 10. HIPEC-induced severe neutropenia was defined as absolute neutrophil count (ANC) less than 1000 /m^3 during postoperative 30 days according to the Common Terminology Criteria for Adverse Events. We divided the patients into two groups: Group1, patients with severe neutropenia ANC< 1000) vs. Group2, patients without severe neutropenia (ANC≥1000). Finally, 57 patients (Group1: n=20, Group2: n=37) were evaluated in this study. After cytoreduction, HIPEC was performed with 35mg/m^2 of MMC mixed in 3 liters of peritoneal dialysis solution for 90 minutes at 42℃. Overall survival and progression-free survival were analyzed using the Kaplan–Meier method and the log-rank test.

Results: There were no statistical differences for baseline patient characteristics such as age, sex, body mass index, body surface area, and primary cancer location. The mean PCI of Group 1 and Group 2 were 4.9±2.8 (mean±standard deviation), and 4.6±2.6, respectively (p=0.731). There was no statistical difference between the two groups regarding total operation times (8.1±3.9 vs 7.1±2.0 hours, p=0.200), and