Highlights in digestive oncology

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At ASCO 2019, several clinical trials regarding upper and lower gastro-intestinal tumors were presented.

UPPER GASTRO-INTESTINAL TUMORS

After a press release in February 2019, claiming that the POLO pancreatic cancer study was positive, clinicians were eagerly waiting for the presentation of the full data at the plenary session of the ASCO 2019 conference. The randomized phase III POLO trial revealed that maintenance therapy with the poly ADP-ribose polymerase (PARP) inhibitor olaparib significantly delayed the progression of metastatic pancreatic cancer patients with germline BRCA gene mutations compared with placebo (progression-free survival (PFS) 7.4 *versus* 3.8 months respectively) (*Figure 1*).[1] It is even though important to keep in mind that only four to seven percent of metastatic pancreatic cancer patients harbor a germline BRCA1 and/or BRCA2 mutation. Moreover, in the POLO trial, olaparib or placebo were administered only in patients not progressing after a minimum of 16 weeks of platinum-based chemotherapy. After 2 years, 22% of patients receiving olaparib had no disease progression, *versus* 9.6% of patients treated with placebo. The overall survival data of the study are not mature yet. In view of the results of the POLO study, we would advise to discuss testing for cancer susceptibility (including BRCA) with individuals diagnosed with pancreatic cancer, even if family history does not suggest an inheritable cancer related syndrome.

Another important study is the phase III open label, randomized APACT trial evaluating the use of adjuvant nab-paclitaxel plus gemcitabine *vs.* gemcitabine for surgically resected pancreatic adenocarcinoma.[2] In contrast with the metastatic setting where the phase III MPACT trial demonstrated a longer overall survival (OS) with nab-paclitaxel plus gemcitabine versus gemcitabine alone (median OS 8.7 *vs.* 6.6 months), in the adjuvant setting the primary endpoint of independently assessed disease free survival (DFS) was not met. However, the investigators stated that the median DFS with gemcitabine monotherapy was longer than historical data and that additional OS follow-up may better support nab-paclitaxel plus gemcitabine as an option in the adjuvant setting.

More and more treatment options are available for hepatocellular carcinoma (HCC) such as sorafenib and lenvatinib in first line and regorafenib, cabozantinib and ramucirumab in second-line. Small studies already showed promising results with checkpoint inhibitors in sorafenib pretreated advanced HCC patients and therefore the FDA already granted accelerated approval to nivolumab and pembrolizumab in this setting. At ASCO 2019, the results of the phase III KEYNOTE-240 study with pembrolizumab versus placebo in sorafenib progressing HCC patients were presented (*Figure 2*). Although pembrolizumab reduced the risk of death by 22% and improved PFS in patients with advanced HCC, significance was not reached per pre-specified statistical criteria.[3] Subsequent anticancer therapy in the placebo arm likely impacted the OS results. Overall, these results are consistent with those of KEYNOTE-224, further supporting second line therapy with pembrolizumab in HCC patients. Better predictive biomarkers are even though still needed.

Results with pembrolizumab were also presented from the KEYNOTE-062 study in HER2-negative, PDL1 positive (CPS ≥1) metastatic gastric or gastroesophageal junction patients in a first-line setting.[4] Patients were randomized between pembrolizumab monotherapy, pembrolizumab in

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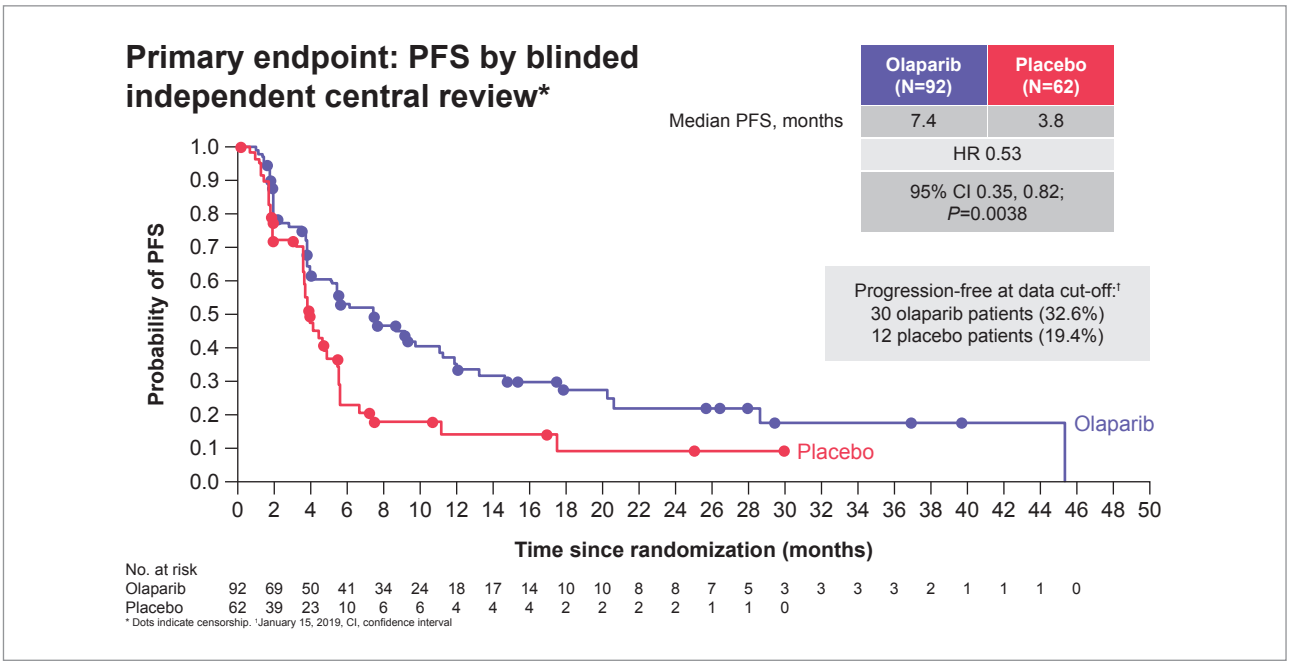

FIGURE 1. Progression free survival in metastatic pancreatic cancer patients with germline BRCA gene mutations.[1]

combination with chemotherapy or placebo plus chemotherapy. Pembrolizumab was non-inferior to chemotherapy for overall survival in CPS≥1, with clinically meaningful improvement for overall survival in CPS≥10. The safety profile was more favorable for pembrolizumab *vs.* chemotherapy and the combination pembrolizumab and chemotherapy could not show superiority to chemotherapy.

LOWER GASTRO-INTESTINAL TUMORS

In the adjuvant setting of stage III colon cancer, practice changing results have already been presented and published of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaborative studies, evaluating three versus six months of chemotherapy. Four out of six studies however also included patients with high risk stage

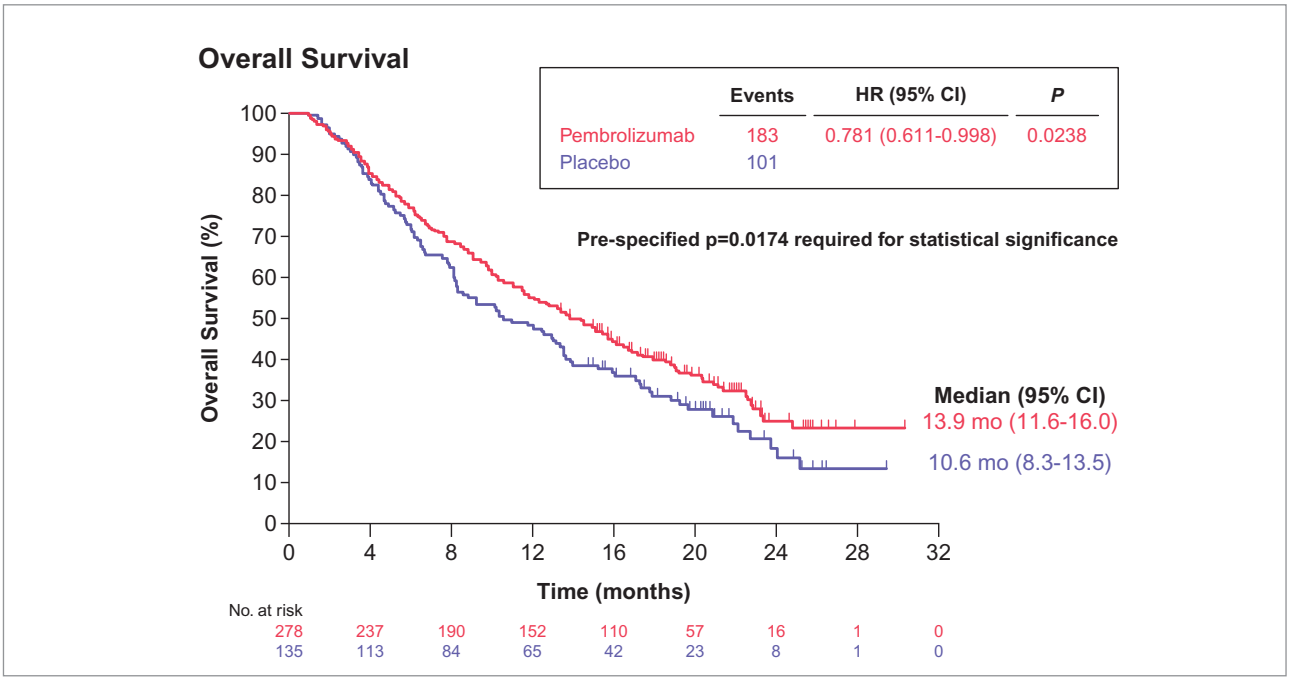

FIGURE 2. Overall survival in the phase III KEYNOTE-240 study with Pembrolizumab vs. placebo in Sorafenib progressing HCC patients.[3]

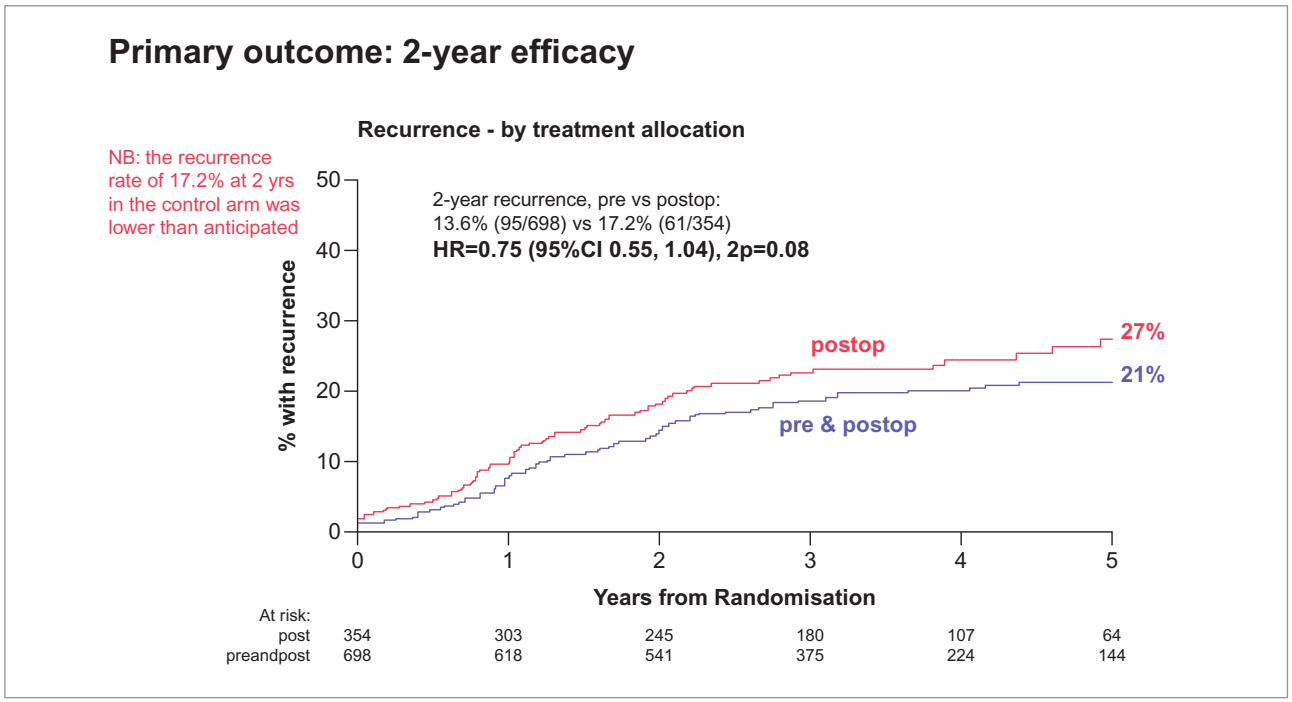

FIGURE 3. Improved two-year efficacy of neo-adjuvant chemotherapy in colon cancer.[6]

II disease of which the pooled results were now presented at ASCO 2019.[5] In the overall population, non-inferiority for 3 months adjuvant treatment in patients with high-risk stage II colon cancer could not be shown. In line with the stage III population, the results suggest non-inferiority for 3 months CAPOX (*vs.* 6 months CAPOX), although this was not statistically significant. Data strongly suggest inferiority of 3 months FOLFOX therapy *vs.* 6 months FOLFOX. However, as 3 months treatment resulted in significantly less toxicity, we can therefore state that three months of CAPOX is certainly a valuable option in high risk stage II colon cancer.

As there were no ground-braking results presented in the metastatic setting of colon cancer at this year's ASCO meeting, we would like to focus on a study in the neo-adjuvant setting of colon cancer, the FOxTROT study.[6] This is an international randomized controlled trial in 1,052 patients evaluating neo-adjuvant chemotherapy (NAC) with FOLFOX/XELOX for 6 weeks followed by surgery and adjuvant 18 weeks the same regimen versus upfront surgery and postoperative 24 weeks of FOLFOX/XELOX. In conclusion, NAC was well tolerated and safe, with no increase in perioperative morbidity and a trend towards fewer serious postoperative complications. Evidence of histological regression was seen in 59% of patients after NAC, including some pCRs. This resulted in marked histological down staging and a 50% reduction of the rate of incomplete resections. Seymour *et al.* observed an improvement in two-year failure rate (HR=0.75), but this fell short of statistical significance (p=0.08) (*Figure 3*). In conclusion, NAC for colon cancer improves surgical outcome but longer follow-up and further trials are required to confirm the long-term benefits, refine its use and optimize case selection.

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