

2017 ASCO Highlights on Gastrointestinal Malignancies

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The 53rd annual meeting of American Society of Clinical Oncology (ASCO) is the premier educational scientific event in Oncology and was held in Chicago, Illinois, on June, 2017, gathering over 30,000 oncology professionals to discuss and view ground-breaking aspects in Oncology research. In this article the pivotal presentations at ASCO 2017 related to colorectal cancer (CRC) and other gastrointestinal malignancies have been discussed. This year the presentations on Colon cancer, Gastric/Gastroesophageal and Biliary cancers have practice changing potential. As expected, the immunotherapy and precision medicine continues to emerge in ASCO 2016. The selected presentations highlighting some early and mature trial updates in gastrointestinal malignancies have been reviewed here.

Colorectal Cancers

Although 6 months of oxaliplatin-based therapy (Fluoropyrimidine and Oxaliplatin (modified FOLFOX6), capecitabine and oxaliplatin [CAPOX]) is a standard of care for stage III colon cancer, it can cause substantial neurotoxicity^[1]. Grade 3 peripheral neuropathy affecting more than 12% of patients was noted in a study of patients with colon cancer who received 6 months of FOLFOX^[2]. It is of interest whether treatment duration could be reduced without loss of efficacy, so the IDEA^[3] [International Duration Evaluation of Adjuvant chemotherapy] collaboration was a prospective pooled analysis of 6 randomized phase 3 trials (>12,000 patients), that were done globally of 3 versus 6 months of oxaliplatin based chemotherapy. So the objective of the study was to evaluate the non-inferiority of 3 months compared to 6 months of adjuvant oxaliplatin based therapy in a global collaborative setting. So the primary endpoint is 3 year disease-free survival (DFS). There was a preplanned subset analysis or subgroup analysis by regimen and by T and N stage. There is varying degrees of CAPOX that were used anywhere from 0% in the North American trials to up to 75% in the Japanese trials. Historically a 24% relative risk reduction was seen with FOLFOX chemotherapy, so the idea consensus committee determined that a 12% relative risk increase for 3 months versus 6 months of therapy for disease free survival is acceptable and therefore the upper non-inferiority margin hazard ratio was determined to be 1.12. The primary endpoint, estimated 3-year DFS in the 3-month arm was lower than that in the 6-month arm by 0.9 percent (HR 1.07, 95% CI [1.00, 1.15]).

Three of the six randomized trials were independently presented at the oral colorectal session (the TOSCA^[4] from Italy, the SCOTT^[5] from UK and the IDEA France^[6]

from France). Neither TOSCA nor the IDEA France study were able to demonstrate the non-inferiority of 3 months compared to 6 months, and it seemed that the benefit in IDEA study was driven by the results from SCOT study which showed that 3 months adjuvant treatment is not inferior to 6 months treatment. Therefore, the 3 months of adjuvant treatment has a higher treatment compliance and a 3 fold lower risk of grade 2+ neurotoxicity however the intent to treat analysis the preplanned endpoint of 3 year DFS was not met. The 0.9% difference is minimal and appears to be dependent on risk group based on unplanned post-hoc analysis. The idea consensus group recommends that for a low risk stage III patients (T1-T3 N1) 3 months of oxaliplatin-based chemo is sufficient, for the high risk group (T4,N2-3) at least 3 months, up to 6 months is needed. The choice of chemotherapy is key here as 3 months of CAPOX is non inferior to 3 months of FOLFOX.

BRAF mutations constitute about 8% of colorectal cancer (CRC) patients and are notable for poor prognostic behavior. Kopetz *et al*^[7] presented a randomized phase 2 study (SWOG S1406) and showed the triplet combination of vemurafenib, cetuximab and Irinotecan showed an improvement in PFS with (HR 0.48 (0.31-0.75) $P=0.001$), improvement in OS and response rate 16% versus 4% ($P=0.08$) compared to irinotecan and cetuximab in heavily pretreated BRAF mutated metastatic CRC patients. The authors concluded the triplet treatment could be a potential new treatment option in this difficult to treat molecular subset.

Last year at ASCO 2016, it was reported from CALGB/SWOG 80405 (Alliance), that the sidedness has prognostic and predictive role in KRAS wild type metastatic colorectal cancer. This year the research reported that the primary colon cancer tumor location has emerged as an independent prognostic factor when adjusted for age, gender, synchronous/metachronous, CMS, MSI, and BRAF status. The Authors^[8] also concluded that BRAF is a strong negative prognostic factor in metastatic CRC, even when sidedness is taken into consideration. BRAF mutated patients appear to have longer overall survival (OS) when treated with bevacizumab compared to cetuximab arm ($P 0.041$).

The FOXFIRE, SIFLOX, and FOXFIRE-Global randomized trials^[9] (1,103 patients in 14 countries) evaluated the efficacy of combining first-line chemotherapy (FOLFOX based) for metastatic colorectal cancer with selective internal radiotherapy (SIRT) using yttrium-90 resin microspheres in patients with liver metastases or Liver dominant disease. There was no significant difference

in OS between Y90+chemo vs chemo alone, 22.6 mo vs 23.3mo (HR 1.04 (0.90, 1.19); $P=0.609$).

The SUNSHINE^[10] study was a randomized, double-blind phase II trial of vitamin D supplementation in patients with previously untreated mCRC where 139 patients randomized to daily high dose vitamin D (4000IU) experienced longer PFS benefit compared to those randomized to daily Low dose group (400IU) (12.4 movs. 10.7 mo; log rank $P=0.03$). there was no difference in grade 3 adverse events and in fact the grade 3 for diarrhea was significantly reduced with those taking high-dose vitamin D. These findings need to be confirmed in a phase III setting.

Gastric And Gastroesophageal Cancers (G/Ge)

The FLOT4-AIO^[11] is the phase III trial of 716 patients with resectable G/GE cancers randomized to perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) or with epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX). FLOT significantly improved PFS and overall survival OS among patients with resectable G/GE cancers compared with ECF/ECX. Median OS was 50 months with FLOT versus 35 months with ECX/ECF (HR 0.77, $P=0.012$). Median PFS was 30 months with FLOT versus 18 months with ECX/ECF (HR 0.75; $P=0.004$). Fiver year survival was significant in FLOT arm as well (45% vs 36%) Perioperative morbidity between both groups was comparable and the investigators concluded that FLOT is considered to be a new standard of care.

Janjigian^[12] and colleagues presented updated results of immunotherapy in advanced G/GEJ, CheckMate-032 study of nivolumab (N) +/- ipilimumab (I) in 160 patients were randomized to three arms to receive - N 3 mg/kg Q2W (N3) or N 1 mg/kg + I 3 mg/kg Q3W (N1+I3) or N 3 mg/kg + I 1 mg/kg Q3W (N3+I1). The primary endpoint overall response rate (ORR) was 12 percent in N3, 24 percent in N1+I3, and 8 percent in N3+I1. However, based on potential biomarker assessment, in patients with PD-L1 $\geq 1\%$, ORR was found to be 19% in N3, 40% N1+I3, and 23%) N3+I1 compared to patients with PD-L1 $<1\%$ where ORR was found to be 12%, 22% and 0%, respectively. Median OS was 6.2 months in N3, 6.9 months in N1+I3, and 4.8 months in N3+I1. The investigators concluded that N \pm I led to durable responses and long-term OS advanced G/GEJ cancer. Fuchs^[13] *et al* presented data on cohort 1 of Keynote-059, reporting ORR and safety of pembrolizumab (Keytruda) in 259 patients with treated advanced gastric cancer who had progressed on ≥ 2 prior regimens were enrolled. Overall response rate was 11.2% and in PD-L1 $^{+}$ patients ORR was 15.5%. The authors also reported Eighteen gene T-cell inflamed gene expression profile score that showed significant association with response to Pembrolizumab ($P=0.014$).The cohort2 of Keynote-059^[14], assessed the efficacy of pembrolizumab plus 5-FU (fluorouracil) and cisplatin in 25 patients for

first-line treatment of HER2 negative G/GEJ cancers. ORR was 60 percent (95% CI, 38.7-78.9) in all patients, 69 percent (95% CI, 41.3-89.0) in PD-L1 $^{+}$ patients, and 37.5 percent (95% CI, 8.5-75.5) in PD-L1 $^{-}$ patients median OS was noted as 13.8 months.

Biliary Cancers

Biliary cancers are relatively uncommon and generally have poor clinical outcomes, with a 1-year survival rate $<25\%$ and a 5-year survival rate $<10\%$ ^[15]. Surgical resection increases the 5-year survival rate to 15-20%), however 15-20% of patients are resectable at presentation. The BILCAP^[16] is the randomized trial assessing the role of adjuvant capecitabine for BTC (intrahepatic, hilar, extrahepatic CCA, and muscle-invasive gallbladder cancers) in 447 patients who were randomized, 1:1 to capecitabine ($n=223$) or observation ($n=224$). By ITT analysis ($n=447$), median OS was 51 months for capecitabine compared to 36 months for observation group, (0.63, 1.04) $P=0.097$; HR 0.80). Capecitabine had modest toxicity and patient quality of life was not reduced. Thus, confirming the benefit of adjuvant capecitabine and considered to be a standard of care for BTC.

Pancreatic Cancers

Hingorani SR *et al*^[17], presented the results of the randomized, phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) versus AG in patients with untreated, metastatic PDAC. Breifly PEGPH20 degrades hyaruloran (HA), is a naturally occurring polysaccharide secreted in excessive amounts in many pancreatic cancers into the interstitium causing elevated interstitial pressure. The pegylated form of recombinant human hyaluronidase PH20, has been shown in preclinical studies to degrade intratumoral HA and the subsequent decrease in fluid pressures can improve blood flow, allowing better drug delivery to the tumor bed increasing the access and therapeutic index of anticancer agents. It was shown that the primary progression free survival endpoint was statistically significant for PAG versus AG (mPFS 6.0 vs. 5.3; HR 0.73,). In patients with HA-High, PFS was also statistically significant in the PAG versus AG (9.2 mo vs 5.2 mo; HR 0.51). OS in HA-High patients was 11.5 months (PAG) and 8.5 months (AG) (HR 0.96). The data support HA as a potential predictive biomarker for use of PEGPH20 and the results suggests statistically significant and clinically important progress in this tough to treat cancers.

The randomized phase II portion of NRG Oncology/RTOG 0848^[18] evaluating the addition of Erlotinib to adjuvant gemcitabine for patients with resected pancreatic head adenocarcinoma showed no benefit for Erlotinib added to Gemcitabine in adjuvant setting. The median & 3-yr OS are 29.9 mo (95% CI 21.7-33.4) & 39% (95% CI 30, 45) for Gemcitabine and 28.1 mo (20.7-30.9) & 39% (31, 47)

for Gemcitabine + Erlotinib (log-rank $P=0.62$). There is a modest increase in grade ≥ 3 GI toxicity was seen with the addition of Erlotinib.

Hepatocellular Cancers

Sorafenib has been the sole systemic agent for advanced disease for a decade, and now, after several failed phase III trials of other agents and combinations, Regorafenib has been approved in the second-line setting. METIV-HCC^[19] was a second-line, 2:1 randomized, phase III study evaluating the efficacy and safety of second line Tivantinib in 589 patients with MET-high HCC who had progressed or were intolerant to sorafenib compared to placebo. The primary endpoint median OS was 8.4 months in Tivantinib arm and 9.1 months in placebo (HR=0.9, $P=0.81$). No significant response was noted in either arm. Neutropenia was the common adverse effect leading to dose reductions. Therefore overall this is a negative study.

Cheng AL *et al*^[20] reported the randomized phase III trial of Lenvatinib (LEN) versus sorafenib (SOR) in first-line for unresectable HCC. A total of 954 patients were randomized 1:1 and the primary endpoint median OS was 13.6 months for LEN versus 12.3 for SOR (HR, 0.92) concluding that LEN is noninferior to SOR. However, the discontinuation rate is slightly higher in LEN arm. Overall in unresectable HCC patients, Lenvatinib compared with sorafenib provided significant and clinically meaningful improvement in PFS, TTP, and ORR.

Most patients with HCC have locally advanced disease which often is not amenable to a surgery. These patients are currently being treated with liver directed interventions such as ablation or transarterial chemoembolization (TACE) or selective internal radiation therapy (SIRT). SIRT is a form of brachytherapy that delivers radiation to the tumor via yttrium-90 resin microspheres. The randomized phase III SIRveNIB study^[21] of SIRT vs sorafenib evaluated the role of selective internal radiation therapy using SIR-Spheres yttrium-90 microspheres in 360 patients from Asia-Pacific countries with locally advanced unresectable HCC who were not amenable to surgical resection or transplantation. The primary endpoint OS was in the Y90 and sorafenib arms was 8.54 vs 10.58 mo, respectively (HR 1.17, $P=0.203$). Tumor response rate was 16.5 percent and 1.7 percent ($P<0.001$), respectively. SIRT was associated with fewer AEs and SAEs compared with sorafenib. Overall this study was negative in terms of clinical outcomes-OS and PFS and therefore the role of Y90 remain unclear.

Data on immunotherapy for HCC was reported on Nivolumab in sorafenib-naïve and treated patients with advanced HCC (CheckMate 040 study^[22]) in GI ASCO 2017. Overall, in 262 patients with a median follow-up of 12.9 months, and 98 percent with Child-Pugh scores 5 to 6, In sor-naïve patients ($n=80$), the ORR was 23% percent, with 44 percent of responses (8/18) still ongoing. The

disease control rate was 63%. In sorafenib treated patients ($n=182$) the ORRs were 18%. Response is not associated with PD-L1 expression. Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced hepatocellular carcinoma. Durable objective responses show the potential of nivolumab for treatment of advanced hepatocellular carcinoma.

Conclusion

- The IDEA consensus recommended 3 months of adjuvant chemotherapy for patients with low-risk disease. The use of short course for high-risk patients should be individualized and balanced with the potential adverse effects.
- There was improved OS and PFS with the triplet (vemurafenib, cetuximab, and irinotecan) in patients with treatment-refractory BRAF^{V600} mutated mCRC, and can serve as a potential new treatment option in this molecular subset.
- The addition of Y90 (SIRT) to first-line FOLFOX for patients with liver-only and liver-dominant mCRC did not improve OS or PFS.
- The high-dose vitamin D seem prospectively showed objective benefit in metastatic colorectal cancer patients
- The primary tumor location has emerged as an independent prognostic factor when adjusted in multivariate analysis of age, gender, CMS, MSI, and BRAF status.
- The FLOT regimen and can be considered as the new standard of care in perioperative management of G/GEJ cancers.
- The data on anti-PD1/PDL1 therapy in untreated and treated cohorts of G/GEJ cancers is encouraging..
- BILCAP study confirmed the benefit of adjuvant chemotherapy in resected biliary cancer and should be the new standard of care.
- Higher PFS and OS in the HA-high metastatic pancreatic cancers supports HA as a potential predictive biomarker for patient treated with PEGPH20 in metastatic pancreatic cancer. The phase III HALO 301 study is ongoing.
- Ongoing studies with encouraging results with checkpoint blockade therapies in HCC suggest The emerging role for the first and subsequent line anti-PD1 therapy for HCC is encouraging and promising in near future
- Tivantinib failed to improve OS compared with placebo as a second-line therapy for patients with MET-high inoperable HCC.
- Lenvatinib was found no better than sorafenib in first-line treatment of patients with unresectable HCC,
- The Y90 (SIRT) did not show improved outcomes compared to sorafenib in locally advanced HCC based on SIRveNIB study. The role of Y90 in HCC remains uncertain

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