

# Updates from Gastrointestinal ASCO 2015

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## ABSTRACT

This year at ASCO GI we saw important data presented that has continued to shape the way we treat GI malignancies. Several important questions were addressed. Can we avoid surgery among patients with rectal tumors? Data from a provocative retrospective study indicated that certain subgroups of patients might not need surgery thereby preserving the rectum without compromising survival outcome. What is the role of ramucirumab among patients with advanced colorectal cancers? Data from the phase III RAISE trial revealed that the addition of ramucirumab to second line therapy significantly improved median overall survival. What is the role of immunotherapy in GI malignancies? Interesting results from the KEYNOTE-012 trial was presented that looked at the efficacy of pembrolizumab among patients with advanced gastric cancer with the investigators reporting interesting results of an objective response rate of 22.1% and a 6 months progression free survival of 24%. In this review we will briefly present these and other important highlights of the ASCO GI meeting.

**Key words:** *Colorectal cancer, pancreatic cancer, gastric cancer*

## INTRODUCTION

Over the last decade, we have seen some interesting data emerging that has essentially changed the treatment of patients with gastrointestinal (GI) malignancies. FOLFOX has become standard of care for adjuvant treatment of colorectal cancer. We now know that anti-epidermal growth factor receptor (EGFR) agents such as cetuximab and panitumumab work only among patients with colorectal cancer whose tumors are RAS wild type. The introduction of combination chemotherapy with Nab-Paclitaxel/Gemcitabine or FOLFOXIRI among patients with advanced pancreatic cancer has significantly impacted response rates and survival outcomes. The introduction of anti-human epidermal growth factor receptor 2 (HER2) agents into the treatment paradigm of patients with advanced gastric cancer whose tumors over express HER2 has also changed the natural course of this disease. This year at ASCO GI, we saw important data presented that have continued to shape the way we treat GI malignancies. Several important questions were addressed. Can we avoid surgery among patients with rectal tumors? What is the role of ramucirumab

among patients with advanced colorectal cancers? What is the role of immunotherapy in GI malignancies? Do Vitamin D levels impact outcome of patients with GI malignancies? In this review, we will briefly present the important highlights of the ASCO GI meeting.

## IMPORTANT HIGHLIGHTS OF COLORECTAL CANCER

Several epidemiological and preclinical studies have indicated that a potential link may exist between Vitamin D levels and the risk of and survival following a diagnosis of colorectal cancer. The biological basis of this includes the ability of Vitamin D to inhibit cell proliferation and angiogenesis, to induce cell differentiation and apoptosis. By prospectively collecting serum samples to test for baseline Vitamin D levels among treatment naïve patients enrolled in the CALB 80405 study (randomized Phase III study of chemotherapy plus either bevacizumab, cetuximab or both) Ng *et al.*<sup>[1]</sup> attempted to determine if a real association exists. Progression-free survival (PFS) was the primary endpoint. The investigators reported that among 1043 patients with newly diagnosed metastatic colorectal cancer where serum samples were available higher Vitamin D levels was associated with a better median overall survival (OS) with the difference between the highest and lowest quintile of Vitamin D levels being 8.1 months (32.6 months vs. 24.5 months,  $P = 0.002$ ). Furthermore median PFS was also significantly increased among patients in the highest quintile of Vitamin D compared to those in the lowest quintile (12.2 months vs. 10.1 months,  $P = 0.02$ ).

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DOI:  
10.4103/0971-5851.158852

Randomized trials of Vitamin D supplementation are currently planned and in the mean time maintaining recommended levels of Vitamin D levels is important to consider for overall health benefit.

Several important strides have been made in the management of metastatic colorectal cancer including the introduction of biological agents and the recognition that anti-EGFR should only be given to patients whose tumors are RAS wild type. As such median survival of patients with metastatic colorectal cancer is now above 30 months. This year at ASCO GI two important abstracts looking at improving management of patients with metastatic colorectal cancer were presented. Cremolini *et al.*<sup>[2]</sup> presented an update of the TRIBE III trial that randomized patients with untreated metastatic colorectal cancer to either FOLFIRI plus bevacizumab or FOLFOXIRI plus bevacizumab. The initial data presented revealed that the study had met its primary endpoint with the authors demonstrating that FOLFOXIRI plus bevacizumab significantly prolonged PFS. Updated OS results were presented at the meeting. The investigators demonstrated that at a median follow-up of 48.1 months OS was significantly improved among patients who received FOLFOXIRI and bevacizumab compared to those who were treated with FOLFIRI and bevacizumab (29.8 months vs. 25.8 months  $P = 0.030$ ); an effect that was observed across all analyzed subgroups. The absolute difference in 5-year survival rate between the two groups was 12.5% favoring the group receiving FOLFOXIRI and bevacizumab. Tabernero *et al.*<sup>[3]</sup> presented the important results of the RAISE study that was a Phase III trial that randomized patients with metastatic colorectal cancer who had progressed on an oxaliplatin-based regimen plus bevacizumab to either FOLFIRI and ramucirumab or FOLFIRI and placebo. The investigators reported that addition of ramucirumab to second line therapy significantly improved median OS compared to placebo (13.3 months vs. 11.7 months, hazard ratio [HR]: 0.79, 95% confidence interval [CI]: 0.70-0.90,  $P = 0.0005$ ). Based on these results, the Food and Drug Administration has recently approved ramucirumab for second line treatment of patients with metastatic colorectal cancer.

An important emerging question is whether we can avoid surgery in the management of patients with rectal cancer. Smith *et al.*<sup>[4]</sup> presented the results of a retrospective study where the investigators compared 145 patients (treated between 2006 and 2014) who had Stage I to III rectal cancers and had completed neoadjuvant therapy who then either underwent nonoperative management (if they had achieved a complete clinical response) or underwent total mesorectal excision and were found to have achieved a pathological complete response. The investigators observed a 4-year survival rate of 91% and 95% among patients who

did not and did undergo surgery, respectively. Furthermore, no difference in the rate of distant recurrences was observed between the two groups studied. These data are provocative in that it indicates that certain subgroups of patients may essentially not need surgery thereby preserving the rectum without compromising survival outcome. However, this study is retrospective in nature, and the results would need to be confirmed in a prospective study.

### IMPORTANT HIGHLIGHTS IN PANCREATIC, GASTRIC AND HEPATOCELLULAR CARCINOMA

Major advances in the realm of metastatic pancreatic cancer have been observed over the last decade with the introduction of combination chemotherapy regimens such as gemcitabine/Nab-Paclitaxel and FOLFOXIRI which have improved both response rates and survival outcomes. Chen *et al.*<sup>[5]</sup> presented the results of the expanded analysis of the NAPOLI-1 Phase III trial. NAPOLI-1 study was a Phase III trial that randomized patients with metastatic pancreatic cancer who had progressed on gemcitabine-based chemotherapy to receive either 5-FU/LV alone or in combination with MM-398, nanoliposomal encapsulation of irinotecan with significant improvement in survival observed in the combination arm. In the present prespecified expanded analysis, the investigators continue to observe an OS advantage in the combination of arm of the study compared to 5-FU/LV alone (6.1 months vs. 4.2 months, HR: 0.57,  $P = 0.0009$ ). Patients who receive MM-398 as monotherapy did not have a significant survival advantage compared to the patients who received 5-FU/LV.

The CLARINET trial was a randomized study that reported a significantly prolonged PFS among patients with metastatic Grade 1 or 2 nonfunctioning enteropancreatic neuroendocrine tumors who received somatostatin analog lanreotide 120 mg compared to those who received placebo (HR for progressive disease [PD]/death: 0.47 [95% CI: 0.30, 0.73].) Phan *et al.*<sup>[6]</sup> presented the results of a subgroup of patients who had metastatic pancreatic neuroendocrine tumors ( $n = 91$  patients) (PNETs). The authors that in this subgroup that median PFS was not reached among patients who had received lanreotide compared to those who had received placebo (12.1 months, HR for PD/death: 0.58 [0.32, 1.04]). The authors concluded that the combination of the demonstrated antitumor effects of lanreotide together with its long-term safety profile supports its use as first line treatment for metastatic PNETs.

Shah *et al.*<sup>[7]</sup> presented the results of a Phase II double-blind placebo-controlled study of 123 patients with untreated

metastatic gastroesophageal cancer randomized to receive to either modified FOLFOX 6 plus onartuzumab (a humanized, monovalent anti-MET antibody that inhibits hepatocyte growth factor binding and receptor activation) or placebo. The investigators observed similar median PFS among patients who received onartuzumab and those who received placebo (6.77 months vs. 6.97 months). In the subgroup of patients whose tumors were MET positive PFS was 5.95 months among those receiving onartuzumab and 6.8 months among those who received placebo. The authors subsequently concluded that addition of onartuzumab did not improve PFS in the overall population and among those with MET positive tumors. Kwak *et al.*<sup>[8]</sup> presented the results of the Phase I study of the use of AMG 337 (an oral MET kinase inhibitor) among patients with MET-amplified gastroesophageal, gastric or esophageal cancers. The investigators observed 8 partial or near-complete responses among 13 patients with MET amplified tumors treated once daily with AMG-337 with one responded experiencing shrinkage of more than 90% of the tumor. Muro *et al.*<sup>[9]</sup> presented the results of the KEYNOTE-012 trial that looked at the efficacy of pembrolizumab among patients with advanced gastric cancer whose tumors had a  $\geq 1\%$  expression of programmed cell death ligand 1. The authors reported that the 39 patients enrolled 22.1% objective response rate was observed. Median time to response was 8 weeks and median duration of response was 24 weeks. Six months PFS and OS rates was 24% and 69%, respectively.

Two interesting abstracts were presented looking specifically at esophageal cancer. Mariette *et al.*<sup>[10]</sup> presented the results of the Phase III MIRO trial of 207 patients with esophageal cancer randomized to either hybrid minimally invasive esophagectomy or open esophagectomy. The authors reported lower rate of postoperative mortality (35.9% vs. 64.4%,  $P = 0.0001$ ), lower rate of pulmonary complications (17.7% vs. 30.1,  $P = 0.037$ ) and similar 30 day mortality (49.7% in both arms of the trial) among patients who underwent minimally invasive procedure compared to the open procedure. Penniment<sup>[11]</sup> reported on the results of the TROG 03.01, NCIC CTG ES2 Phase III trial that compared radiation therapy alone or in combination with chemotherapy for palliation of dysphagia among patients with advanced esophageal cancer. The authors reported that the rate of improvement in swallowing was 41% among patients who received radiation therapy alone and 47% among those who received chemoradiotherapy ( $P = 0.4163$ ). Bowel toxicity was reported to be worse among patients who received chemoradiotherapy. Median survival was reported to be 203 days among patients who received radiation therapy alone and 210 days among those who received chemoradiotherapy.

At the ESMO, 2014 symposium results of the Phase III REACH study was presented that the randomized patients with advanced hepatocellular carcinoma, who had progressed on sorafenib to either single agent ramucirumab or placebo. Median OS was reported to 9.2 months among patients receiving ramucirumab compared to 7.6 months among those receiving placebo (0.866 [95% CI: 0.717, 1.046;  $P = 0.1391$ ]). At ASCO GI Zhu *et al.*<sup>[12]</sup> presented the results of the prespecified subgroup analysis stratified by alpha-fetoprotein (AFP) levels. The authors reported that among patients with AFP levels of 400 ng/ml or greater treatment with ramucirumab was associated with significant survival advantage compared to those who received placebo (7.8 months vs. 4.2 months; HR: 0.674,  $P = .0059$ ) with no significant survival advantage observed among those with lower baseline AFP levels (10.1 months vs. 11.8 months).

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**How to cite this article:** Dawood S. Updates from Gastrointestinal ASCO 2015. Indian J Med Paediatr Oncol 2015;36:133-6.  
**Source of Support:** Nil, **Conflict of Interest:** None declared.

### Important Meeting dates in 2015

Meeting	Venue	Contact
33 <sup>rd</sup> ICON, 4 <sup>th</sup> -6 <sup>th</sup> Sept	Coimbatore	33rdicon@gmail.com
7 <sup>th</sup> UAE Cancer congress, 29 <sup>th</sup> -31 <sup>st</sup> Oct	Dubai	uaecancercongress@mci-group.com
APNETS, 30-31 <sup>st</sup> Oct	Penang, Malaysia	admin@apnets.org
Haematocon , 5 <sup>th</sup> -8 <sup>th</sup> Nov	Bangalore	info@haematocon2015.com
Biennial Joint Conference of ISMPO & ISO, 6 <sup>th</sup> -8 <sup>th</sup> Nov	Mumbai	ismpoiso2015@gmail.com
2 <sup>nd</sup> Brinker Awardee /Breast Cancer Symposium, 14 <sup>th</sup> Nov	Bangalore	Bhawna.sirohi13@gmail.com