

2015 EUROPEAN CANCER CONGRESS

25-29 September 2015

Vienna, Austria

SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinary as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

Contents

SUMMARY.....	1
Contents.....	2
GASTROINTESTINAL CANCERS.....	3
TOPGEAR shows perioperative epirubicin, cisplatin, 5-FU (ECF) chemotherapy plus preoperative chemoradiation has comparable safety to sole ECF in patients with resectable gastric cancer.....	3
No benefit increase from adding bevacizumab to peri-operative chemotherapy in patients with resectable gastro-oesophageal adenocarcinoma.....	4
ICECREAM trial identifies subgroup of patients with metastatic colorectal cancer and rare KRAS mutation that responds to therapy with an EGFR agent plus irinotecan.....	5
Improved outcome in subgroup of patients with stage II rectal cancer and high-risk disease receiving adjuvant chemotherapy following pre-operative short course radiotherapy.....	8
Patient age and disease category may influence outcomes for patients with stage II-III resectable rectal cancer receiving preoperative chemoradiotherapy or radiotherapy prior to surgery.....	9
Related information.....	11
Affiliation and Disclosure.....	11
Affiliation.....	11
Disclosure.....	11
Acknowledgment.....	11

GASTROINTESTINAL CANCERS

TOPGEAR shows perioperative epirubicin, cisplatin, 5-FU (ECF) chemotherapy plus preoperative chemoradiation has comparable safety to sole ECF in patients with resectable gastric cancer

Trevor Leong, Peter MacCallum Cancer Centre, Victoria, Australia discussed phase II results from TOPGEAR, a randomised phase II/III trial comparing adding pre-operative chemoradiotherapy to standard peri-operative chemotherapy of epirubicin, cisplatin, 5-FU (ECF) with perioperative ECF alone for patients with resectable gastric cancer. The phase II part of the trial recruited 120 patients from 51 sites in Australia, New Zealand, Europe and Canada to assess feasibility, safety and preliminary efficacy of preoperative chemoradiotherapy (CRT); a phase III component is planned that will recruit an additional 632 patients with resectable adenocarcinoma of the stomach or gastro-esophageal junction. Patients were randomised to receive 3 pre-and 3 post-operative cycles of ECF (chemotherapy arm), or to CRT (45 Gy with concurrent 5-FU) plus 2 cycles of ECF prior to surgery and 3 further cycles of ECF following gastric resection (chemoradiotherapy arm).

Preliminary safety results from the 120 patients randomised from September, 2009 until June 2014 showed no significant differences between the 2 treatment groups. The proportion of patients receiving preoperative chemotherapy was 93.3% in the chemotherapy group and 98.3% in the chemoradiotherapy group, while 92% of patients received preoperative chemoradiotherapy; 90% of patients in the chemotherapy group compared to 85% in the chemoradiotherapy group proceeded to surgery. Of patients undergoing surgery, 64% and 50% received postoperative chemotherapy in the chemotherapy and chemoradiotherapy groups, respectively.

The rates of grade ≥ 3 adverse events (AEs) in the chemotherapy group included vomiting in 6.7% of patients, diarrhoea in 11.7%, neutropenia in 40%, and febrile neutropenia in 8.3% of patients compared with 8.3%, 16.7%, 45% and 10%, respectively, in the chemoradiotherapy group. Grade ≥ 3 anastomotic leak occurred in 3 (5.6%) and intra-abdominal sepsis following surgery in 4 (7.4%) patients in the chemotherapy group versus 4 (7.8%) and 3 (5.9%) patients, respectively, in the chemoradiotherapy group. The investigators have proceeded to part 2 (phase III) of the trial wherein 170 patients have been recruited by the time of presentation from 55 sites. The overall survival will be the primary end point. Leong et al. Abstract 2200.

Practice point and future research opportunities

The Intergroup 0116 and MRC MAGIC trials, respectively, established postoperative chemoradiation and perioperative chemotherapy with epirubicin, cisplatin, 5-FU as standards of care for adjuvant therapy in resectable gastric cancer in Western countries. Phase II of TOPGEAR demonstrated that adding preoperative chemoradiotherapy to this regimen is safe and feasible; phase III efficacy findings are awaited.

No benefit increase from adding bevacizumab to peri-operative chemotherapy in patients with resectable gastro-oesophageal adenocarcinoma

David Cunningham, Royal Marsden NHS Trust, London, UK presented findings from the UK Medical Research Council, multicentre, open-label, phase II/III randomised ST03 trial, which assessed the safety and efficacy of adding bevacizumab to standard chemotherapy in patients with histologically proven, resectable, gastric/gastro-oesophageal junction or lower oesophageal adenocarcinoma. From 2007 to 2014, 1063 patients were recruited from 87 UK centres and randomised 1:1 to receive either the standard treatment comprising 3 pre- and 3 post-operative cycles of epirubicin at 50 mg/m² i.v., cisplatin 60 mg/m² i.v., and capecitabine at 1250 mg/m² (ECX) and surgery, or to the investigational arm, wherein bevacizumab at 7.5 mg/kg on day 1 was added to ECX/surgery and followed by 6 maintenance cycles of bevacizumab (ECX/B) every 3 weeks. Surgical techniques were pre-specified and laparoscopic procedures were allowed after quality assurance review. The primary outcome measure was overall survival (OS) and secondary outcomes included disease-free survival (DFS), progression-free survival (PFS), chemotherapy response rate and curative resection rate.

After a median follow-up of 33 months, 233 ECX and 239 ECX/B patients had died. No significant difference in OS between the treatments was observed, HR 1.067 (p = 0.478). The 3-year survival rates were 48.9% with ECX versus 47.6% with ECX/B. Similar rates in the treatment groups were also seen for DFS, HR 1.006 (p = 0.943) and for PFS, HR 1.026; (p = 0.768). Response rates to pre-operative chemotherapy were also similar between the groups; response rates overall were 32% with ECX versus 30% with ECX/B, and 39% versus 38% in the respective groups in patients undergoing surgery. No significant difference was observed between the groups regarding curative resection rates, which were 59% with ECX versus 55% with ECX/B in all patients, and 66% with ECX versus 64% with ECX/B in patients undergoing surgery.

Similar toxicity during chemotherapy was observed in both groups. Accrual of patients requiring oesophago-gastrectomy was closed early for the ECX/B group after an elevated post-operative

anastomotic leak rate was seen in this group in patients following oesophago-gastrectomy; 9% of ECX versus 23% of ECX/B patients underwent oesophago-gastrectomy. The rates of any post-operative complication were 48% with ECX versus 56% with ECX/B. Rates of post-surgical life-threatening complications were 7% and 8% in the ECX and ECX/B groups, respectively.

NCT00450203. Cunningham *et al.* Abstract 2201.

Practice point and future research opportunities

The standard of care for resectable gastro-oesophageal adenocarcinoma is peri-operative epirubicin, cisplatin, and capecitabine plus surgery. Although bevacizumab plus chemotherapy improved response rates and progression-free survival but not overall survival in advanced gastric cancer (Ohtsu JCO 2011), this trial does not support adding bevacizumab to the standard of care in resectable gastro-oesophageal adenocarcinoma.

ICECREAM trial identifies subgroup of patients with metastatic colorectal cancer and rare KRAS mutation that responds to therapy with an EGFR agent plus irinotecan

Patients with metastatic colorectal cancer (mCRC) and KRAS exon 2 c.38G>A: pGly13Asp (G13D mutation) receiving cetuximab together with irinotecan demonstrated both objective responses and some delay of disease progression, according to results from the phase II ICECREAM trial presented by Eva Segelov, University of New South Wales, Sydney, Australia. She reported results on behalf of the Australian Gastrointestinal Trials Group (AGITG) that also confirmed the lack of activity of cetuximab monotherapy in patients with G13D mutated mCRC, which has previously been reported in smaller series.

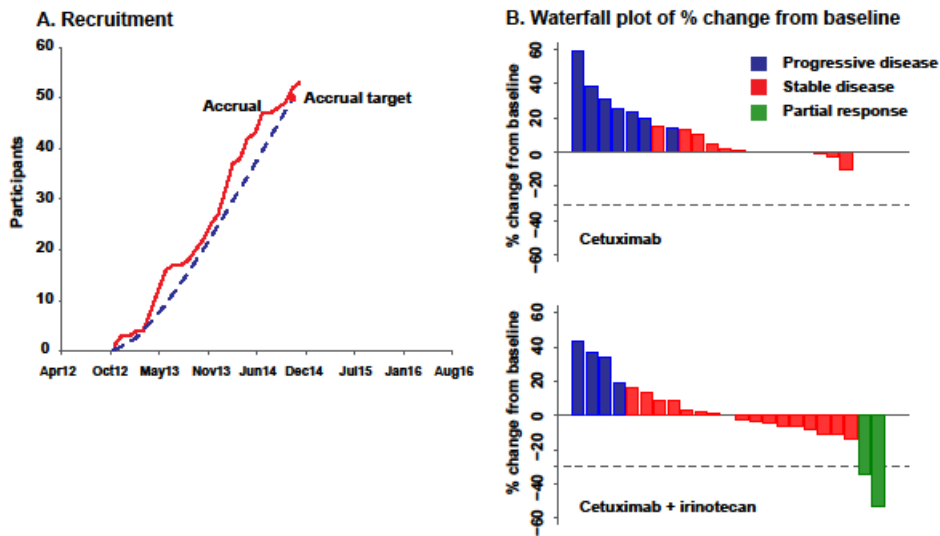
The importance of these findings is underscored by the fact that patients with mCRC and KRAS or NRAS mutations are generally not offered EGFR inhibitors due to lack of response to these agents. However, there is a 40% incidence of KRAS mutations in CRC, with approximately 19% of these mutations consisting of KRAS G13D mutation; the absolute incidence of the G13D mutation is 8% in mCRC and represents a subgroup of patients likely to respond to EGFR therapy.

Additionally, several retrospective clinical reports suggested treatment benefit with cetuximab in patients with mCRC and G13D mutation that may be similar to that seen in patients with KRAS wild-type tumours. However, these reports have been confounded by small sample sizes and by co-administered chemotherapy, making it difficult to isolate the actual effect of the EGFR inhibitors. Furthermore, adding irinotecan to agents targeting EGFR has been shown to increase the response rate and to delay progression in patients with KRAS unselected mCRC, leading

investigators to anticipate that irinotecan could potentiate the response in patients with G13D mutated tumours.

ICECREAM enrolled patients with mCRC, ECOG PS 0-2 that were refractory to irinotecan, which was defined as having progressed within 6 months of irinotecan treatment and being intolerant of or refractory to fluoropyrimidine and oxaliplatin, to directly compare the efficacy of cetuximab versus combined cetuximab/irinotecan. Patients were stratified by G13D mutation or by wild-type KRAS, NRAS, BRAF and PI3KCA genes (this arm still accruing) and randomised 1:1 to receive either cetuximab at 400 mg/m² i.v. loading then 250 mg/m² weekly or the same cetuximab regimen plus irinotecan at 180 mg/m² every two weeks. Patient characteristics were well balanced between treatment groups, except age (61 versus 66 years), time since first metastatic diagnosis (19.1 versus 28.1 months), and time since last irinotecan dose (2.8 versus 4.8 months) in the cetuximab and cetuximab/irinotecan arms, respectively.

Results for the G13D cohort of 51 patients were reported at the ECC showing a 6-month progression-free survival (PFS) rate of 10% (95% CI 2%, 26%) in the cetuximab arm compared to 23% (95% CI 9%, 40%) in the cetuximab/irinotecan arm, HR 0.75 (95% CI 0.42, 1.33). The median time to progression was similar in the respective arms at 2.5 versus 2.6 months. Complete response (CR) was not demonstrated in either treatment arm and no partial response (PR) was seen in the cetuximab monotherapy arm; however, 9% of patients receiving combination therapy achieved a PR. Stable disease was achieved by 58% of patients receiving cetuximab compared with 70% of patients in the cetuximab/irinotecan arm.



Caption: AGITG ICECREAM study.

Panel A: Recruitment to the study exceeded projection despite this being a rare molecular subtype of colorectal cancer.

Panel B: Best response for target lesions by patient for the Cetuximab arm (above) and Cetuximab plus Irinotecan arm (below), based on maximum tumour reduction with no new lesions, coloured by RECIST best response.

Credit: Eva Segelov

Consistent with previous studies, one or more grade 3/4 event occurred in 11 (44%) patients receiving monotherapy and in 16 (64%) patients receiving combination therapy. Segelov et al. Abstract 32LBA.

Practice point and future research opportunities

ICECREAM is the first trial to date providing prospective data on treatment in patients with a rare molecular subtype of colorectal cancer, KRAS G13D mutation. These findings contribute to the management of these patients. While no evidence for treating G13D mutant colorectal cancer with cetuximab or panitumumab monotherapy is provided, the results may support using combined cetuximab/irinotecan in this cohort. Combination therapy, but not cetuximab monotherapy, may warrant further evaluation to confirm whether irinotecan acts synergistically with EGFR inhibitors in

patients with mCRC and G13D mutation. Data from the cohort of KRAS wild-type patients participating in the ICECREAM study is eagerly awaited, which may identify markers beyond RAS for determination of resistance to anti-EGFR antibodies.

Improved outcome in subgroup of patients with stage II rectal cancer and high-risk disease receiving adjuvant chemotherapy following pre-operative short course radiotherapy

After noting that adjuvant chemotherapy is most often offered to renal cancer patients with high-risk disease who received a long course of chemoradiotherapy, Jonathan Loree, British Columbia Cancer Centre, British Columbia, Canada presented findings from a study that evaluated the benefit in patients with pathologic stage II rectal cancer receiving adjuvant chemotherapy following pre-operative short course radiotherapy (SCRT).

The retrospective study analysed data from the 5 regional cancer centres in British Columbia between 1998 and 2009 of patients diagnosed with stage II (pT3/4 pN0) tumours following SCRT, focusing on the 123 (37.3%) patients who also received adjuvant chemotherapy. Patients receiving adjuvant chemotherapy were younger, with a median age of 61 years compared with 73 years in the overall cohort of patients experiencing recurrence following SCRT who did not receive adjuvant chemotherapy ($p < 0.0001$). Patients receiving adjuvant chemotherapy also had a better ECOG PS ($p < 0.001$), and more high-risk features ($p < 0.0001$) than patients not receiving adjuvant chemotherapy. Median follow-up was 8.57 years in the adjuvant chemotherapy arm and 7.92 years in the non-adjuvant chemotherapy arm.

Univariate analysis showed a significant association between adjuvant chemotherapy and improved overall survival (OS), HR 0.42; 95%CI 0.30, 0.59 ($p < 0.0001$); adjuvant chemotherapy was also associated with prolonged disease specific survival (DSS), HR 0.58; 95%CI 0.36, 0.94 ($p = 0.028$), and recurrence-free survival (RFS), HR 0.62; 95%CI 0.39, 0.98 ($p = 0.043$). These associations did not remain significant in multivariate analysis; the association between adjuvant chemotherapy and OS was HR 0.62, 95%CI 0.37, 1.03 ($p = 0.064$); DSS HR 0.83; 95%CI 0.43, 1.61 ($p = 0.58$), and the association between adjuvant chemotherapy and RFS was HR 0.82; 95%CI 0.44, 1.50 ($p = 0.51$). Further analysis revealed that only the subgroups of patients with ≥ 2 high-risk features showed benefit following adjuvant chemotherapy: OS, HR 0.22; 95%CI 0.069, 0.70, ($p = 0.011$), DSS, HR 0.25; 95%CI 0.07, 0.89, ($p = 0.033$), and RFS was HR 0.24; 95%CI 0.07, 0.85 ($P = 0.027$). Loree *et al.* Abstract 2002.

Practice point and future research opportunities

In this study, univariate analysis showed an association with improved overall survival in patients receiving adjuvant chemotherapy following pre-operative short course radiotherapy in stage II rectal cancer that was not confirmed by multivariate analysis. In this population-based cohort of patients with stage II rectal cancer, adjuvant chemotherapy after short course radiotherapy did not improve outcomes in unselected patients, however the presence of two or more clinicopathological risk factors may identify patients who benefit from adjuvant chemotherapy following short course radiotherapy.

Patient age and disease category may influence outcomes for patients with stage II-III resectable rectal cancer receiving preoperative chemoradiotherapy or radiotherapy prior to surgery

Laura Kairevice, Lithuanian University of Health Sciences Academy of Medicine, Kaunas, Lithuania presented findings on behalf of colleagues from a randomised controlled trial that sought to determine which neoadjuvant treatment is superior in the stage II-III resectable rectal cancer setting. The investigators conducted a head to head comparison of treatment with standard chemoradiotherapy (CRT; preoperative conventional CRT, 50 Gy/25 fr, 2Gy/fr with 5-FU 400mg/m²/d i/v 1–4d and LV 20mg/m²/d i/v 1–4d on the 1st and the 5th week of radiotherapy (RT) followed by surgery after 6 to 8 weeks and then by 4 adjuvant cycles of 5-FU 425mg/m²/d i/v and LV 20mg/m²/d i/v 1–5d every 4 weeks) versus RT (preoperative short-term RT, 25Gy/5fr, 5Gy/fr followed by surgery in 6 to 8 weeks). Data from 72 patients in the CRT arm and 68 in the RT arm were included in the statistical analysis. The baseline characteristics of age, sex, tumour localisation in the rectum, cT, cN, and clinical stage were similar in both arms ($p > 0.05$).

The analysis was done after a median follow-up of 43 (range: 6 to 80) months and revealed disease-free survival (DFS) and overall survival (OS) were superior with CRT over RT; the 5-year DFS rate was 69% with CRT versus 44% with RT ($p = 0.011$) and 5-year OS was 76% with CRT versus 64% with RT ($p = 0.055$).

By univariate analysis, the risk for disease progression was 1.9-fold higher after RT versus CRT ($p = 0.0187$), and 2-fold higher for patients aged 65 years or more ($p = 0.0107$); it was also determined that risk of progression increased by 2.2-fold for cN2 ($p = 0.039$), and by 2.9-fold higher for ypN2 ($p = 0.0056$), as compared to cN0 and ypN0 category patients, respectively. The risk for death was 3.7-fold higher for patients aged 65 years or more ($p = 0.0009$), 2.5-fold higher for cN2 patients ($p = 0.042$) and 3-fold higher for ypN2 patients ($p = 0.023$). CRT showed an

influence on reducing the risk for death of 1.8-fold, as compared to RT that did not reach statistical significance ($p = 0.0585$). NCT0059731. Klarevics *et al.* Abstract 2004.

Practice point and future research opportunities

Findings from this study favour adjuvant chemoradiotherapy over radiotherapy alone and identified older patients and disease categories cN2 and ypN2 as factors that may indicate poorer disease-free survival in patients with stage II-III resectable rectal cancer undergoing adjuvant treatment plus surgery.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

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