ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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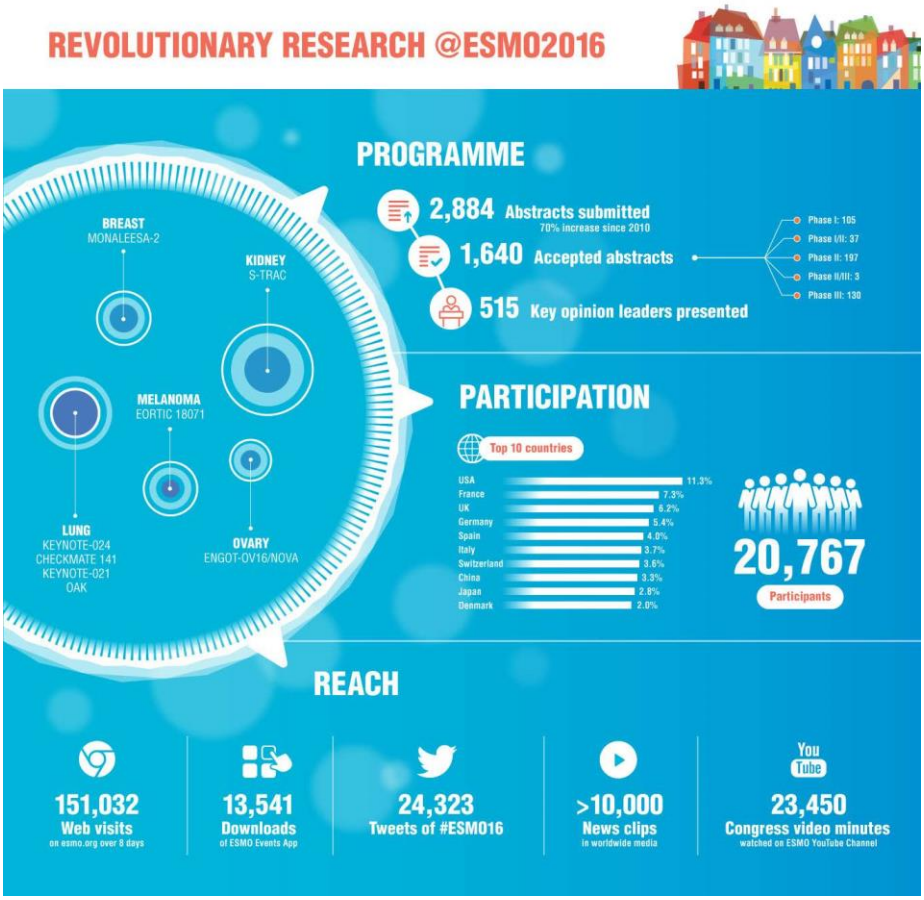
Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

GASTROINTESTINAL TUMOURS - Colorectal

Greater tumour downstaging with a 12 versus 6-week interval between interventions in rectal cancer

Jessica Evans, Colorectal Surgery, Royal Marsden Hospital NHS Foundation Trust, London, UK urged clinicians to employ a longer waiting interval from the end of preoperative chemoradiotherapy to surgery. A 12-week interval was found to increase the rate of pathological complete response (pCR) and to yield a higher proportion of patients achieving tumour downstaging, as compared to a 6-week interval in patients with locally advanced rectal cancer, according to findings from this prospective, randomised, multicentre trial.

The trial was designed to determine whether a 6- or 12-week interval between neoadjuvant chemoradiotherapy and surgery is optimal in patients with locally advanced rectal cancer to allow greater rectal cancer downstaging and tumour regression, which could improve the rates of sphincter preservation and achieve improved local control. This study enrolled 237 patients with locally advanced rectal cancer to receive chemoradiotherapy followed by surgery. Following chemoradiotherapy, 122 patients were randomised to a cohort with a planned 6-week interval and 115 patients were randomised to another cohort with a 12-week interval between chemoradiotherapy and surgery.

Differences were observed between the two cohorts in the proportion of patients achieving downstaging of their tumours and in the pCR rates. A greater proportion (58%) of patients in 12-week interval cohort had tumour downstaging compared with 43% of patients in the 6-week interval cohort ($p = 0.019$). An improved rate of pCR was also observed with a longer interval; the pCR rate was 20% in the 12-week versus 9% for the 6-week cohort ($p < 0.05$). Additionally, more patients in the 12-week interval cohort achieved magnetic resonance tumour regression grade of 1 or 2 (mrTRG 1-2 rate); the mrTRG 1-2 rate in the 12-week arm was 52% versus 34% in the 6-week arm ($p < 0.05$). Evans *et al.* Abstract 452O

Practice point and future research opportunities

Findings from this randomised study indicate that patients may benefit from a longer interval between chemoradiotherapy and subsequent surgery that ultimately could afford greater sphincter preservation and control of local disease recurrence. A longer interval of 12 rather than 6 weeks after chemoradiotherapy prior to surgery demonstrated significantly greater tumour downstaging, improved pCR rates, and greater mrTRG. Since obtaining a pCR after the neoadjuvant treatment is an accepted surrogate measure of disease-free survival, undertaking surgery before maximal regression may be disadvantageous in patients with locally advanced rectal cancer. The authors recommend adopting a change in the standard from undertaking surgery at 6 to 8 weeks to 12 to 14 weeks. These findings support this recommendation but this change can only be safely undertaken if MRI evaluation of response or progression is still made at 4 to 6 weeks.

Long-term results show scheduled use of CEA and CT follow-up detects more recurrence of colorectal cancer than minimal follow-up

Lead author Sian Pugh, University Surgery, University of Southampton, Southampton, UK presented findings from the FACS trial, which evaluated the utility of adding computed tomography (CT) imaging, measurement of carcinoembryonic antigen (CEA), or both for follow-up of patients with undergoing curative R0 resection, stages I-III for colorectal cancer. An interim analysis showed that all intensive strategies identified more recurrences that could be surgically treated with curative intent compared to minimum follow-up; however, no advantage was seen in using both CT and CEA. At ESMO 2016, Dr. Pugh reported the results from the mature analysis, including overall survival (OS) up to 12 years post randomisation comparing the intensive modes of follow-up to minimum follow-up. The FACS study randomised 1202 participants to regular CEA measurement, regular CT imaging of the chest, abdomen, and pelvis, combined CEA plus CT, or to minimum follow-up comprising symptomatic follow-up with/without single CT. The primary endpoint was surgical treatment of recurrence with curative intent. The actual follow-up was for 5 years; thereafter OS monitoring continued using registry data for a median follow-up of 8.7 years.

Long-term surveillance revealed more recurrences treatable with curative intent were identified with intensive follow-up of 68 (7.5%) recurrences in the combined intensive cohort of 901 patients versus 8 (2.7%) recurrences in the minimal cohort of 301 patients ($p = 0.003$). Although no statistically significant difference in OS between groups was observed ($p = 0.45$), numerically more patients with recurrence were still alive in intensive groups; 43 (4.8%) patients in the intensive versus 7 (2.3%) in the minimal cohort ($p = 0.07$). An OS benefit in patients with recurrence was seen only in patients with a left colonic tumour, where median OS of 4.4 years with intensive versus 3.1 years with minimal follow-up ($p = 0.03$).

Analysis by site of primary tumour revealed a similar proportion of curatively treatable recurrences in patients with rectal tumours irrespective of follow-up; 27 (9.8%) versus 6 (6.9%) patients were detected in the intensive versus minimal cohorts, respectively ($p = 0.41$). However, patients with a colonic tumour benefited more from intensive follow-up wherein treatable recurrence was more commonly detected: 24 recurrences were detected in the left colon (7.3%) versus 1 (0.9%) in the minimal arm ($p = 0.01$); similarly, intensive follow-up detected 14 (5%) recurrences in the right colon versus none by minimal follow-up ($p = 0.02$). ISRCTN 41458548 Pugh *et al.* Abstract 453O

Practice point and future research opportunities

Intensive follow-up entailing CT, measurement of CEA, or both increased the detection of treatable recurrences over minimal follow-up, although further analysis suggested this was only the case for colonic tumours. Longer follow-up revealed a survival advantage with intensive versus minimal follow-up, but only patients with recurrence from a left colonic tumour, which underscores the heterogeneous biology of colorectal cancer.

Nintedanib in refractory mCRC

Lead author Eric Van Cutsem, head of Digestive Oncology at University Hospitals in Leuven, Belgium presented results on behalf of colleagues from the LUME-colon 1 study, which was the first phase III trial of nintedanib in colorectal cancer. The trial enrolled 768 patients with metastatic colorectal cancer (mCRC) in good general condition, defined as performance status 0 and 1, and with good organ function, who were refractory to standard therapies including oxaliplatin, irinotecan, fluoropyrimidines, anti-VEGF, and anti-EGFR (in patients with RAS wild-type tumours). The patients were randomised 1:1 to nintedanib or placebo, each plus best supportive care. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS).

Median PFS with nintedanib was 1.5 month compared to 1.4 month with placebo, hazard ratio 0.58; 95% confidence interval [CI] 0.49, 0.69 ($p<0.0001$). Significantly improved disease control was seen with nintedanib of 26% compared to 11% with placebo, odds ratio 2.96; 95% CI 2.00, 4.4 ($p < 0.0001$). However, no difference in OS was observed between the two groups; median OS was 6.4 months versus 6.1 months with nintedanib versus placebo, respectively. Nintedanib was well-tolerated. Serious adverse events occurred in 39% of patients on nintedanib and in 35% of patients on placebo. Treatment was discontinued in 14% of patients in the nintedanib due to adverse events, compared to 11% in the placebo group.

Professor Van Custom noted that patients on placebo survived longer than expected and speculated that treatments taken after the trial ended may have contributed to this finding, since the follow-up continued after the trial finished until the patient died. Additional analyses of molecular markers and the nintedanib response in subtypes of colorectal cancer are ongoing to identify patients that could benefit from nintedanib. NCT02149108. Van Cutsem *et al.* Abstract LBA20_PR

Practice point and future research opportunities

Colorectal cancer is a frequently occurring disease and a large proportion of patients develop metastases. There is a need to find new therapies for this large group of patients, many of whom initially respond to several different lines of treatment and then stop. Nintedanib is a multiple tyrosine kinase inhibitor that has shown to control angiogenic activity, which is necessary to support tumour growth**.**

This trial evaluated nintedanib in patients with metastatic colorectal cancer who were refractory to all available treatments including chemotherapy and biological therapies. Nintedanib gave a significant increase in PFS and disease control but patients receiving nintedanib did not live longer. Nintedanib delays disease progression and increases the rate of stable disease but these gains were lost when it came to OS, in contrast to regorafenib and trifluridine/tipiracil which improve both PFS and OS in these patients. The disparity may have arisen because patients who progressed in the LUME-colon 1 trial received more salvage treatments than in the earlier

trials, which is supported by the relatively long OS in patients receiving placebo. More data are needed to explain the findings and understand how strong the benefit of nintedanib really is.

Bevacizumab plus metronomic chemotherapy yields no added benefit over sole bevacizumab as maintenance following FOLFOXIRI/bevacizumab in mCRC

Alfredo Falcone, U.O. Oncologia Medica 2 Universitaria, Azienda Ospedaliera Universitaria S. Chiara, Pisa, Italy headed a team of investigators from Italian institutions in conducting the phase II MOMA multicentric study. MOMA compared two maintenance therapies in patients with unresectable metastatic colorectal cancer (mCRC). After receiving up to 8 cycles of FOLFOXIRI plus bevacizumab, randomised patients received either bevacizumab (arm A; n=117), or bevacizumab plus metronomic chemotherapy consisting of capecitabine 500 mg/tid and cyclophosphamide 50 mg/die per os (arm B; n=115) until disease progression. The primary endpoint was progression-free survival (PFS) which required 173 events.

Patients in arms A and B had a median age of 61 versus 62 years, presence of synchronous metastases in 81% versus 83%, liver-only disease in 27% versus 35%, and right-sided primary tumour in 32% versus 42% patients, respectively. RAS mutations were present in 66% versus 63%, BRAF mutation in 7% versus 10%, and RAS/BRAF was wild-type in 18% versus 14% patients in arms A and B, respectively. RAS or BRAF was not evaluable 9% of arm A versus 13% of arm B patients and 85% of patients in each arm were ECOG performance status 0.

At a median follow up of 25.7 months, 188 patients overall had progressive disease. No significant difference in PFS was demonstrated between arms; median PFS was 9.5 months in arm A compared to 10.6 months in arm B, hazard ratio 0.99 (p = 0.926). The response rate with induction FOLFOXIRI plus bevacizumab was 63% overall, and 68% versus 58% in arm A versus arm B, respectively.

The subgroup of 72 patients with metastasis limited to the liver demonstrated a secondary resection rate of 49% overall, and 53% versus 45% in arm A versus arm B, respectively.

Grade 3/4 adverse events of neutropenia were reported in 51% of patients overall, febrile neutropenia in 11%, and diarrhoea in 13% of patients during induction, whereas during maintenance, hypertension was reported in 4.6% versus 2.6%, and venous thrombosis in 2% versus 3% of patients in arms A and B, respectively. Hand-foot syndrome was reported by 8% of patients in arm B only. NCT02271464. Falcone *et al.* Abstract LBA21

Practice point and future research opportunities

Although a common treatment strategy in mCRC is to alternate induction and maintenance phases, the optimal duration of induction and the optimal maintenance remain unresolved. In the MOMA study, metronomic chemotherapy added to bevacizumab showed no additional benefit over bevacizumab as maintenance. These findings show a response rate that confirms the activity of induction FOLFOXIRI plus bevacizumab in a patient population with a high prevalence of RAS and BRAF mutant tumours.

Napabucasin (BBI608) trial in advanced colorectal cancer halted early after futility analysis

Dereck J. Jonker, Department of Medicine, Division of Medical Oncology, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada Presented results from the phase III study that enrolled 282 patients with advanced colorectal cancer (aCRC) who had failed all available standard therapies. The patients' median age was 64 (range: 32 to 85) years, and 65% of patients were male, and ECOG perfomance status was 0 or 1 in 28% and 72% of patients, respectively. The majority, 98%, of patients had received >4 prior regimens, including 89% of patients receiving prior anti-VEGF. Fifty-two percent of patients had KRAS wild-type tumours. The trial randomised 138 patients to napabucasin at 480 mg orally and 144 patients to placebo. Patients were treated from April, 2013 to May 2014 when the trial was unblinded, accrual closed, and the protocol treatment was halted after the futility analysis of the disease control rate in the first 96 patients. The pre-defined Minimum Effective Treatment in patients who received ≥50% of the total daily dose for 6.4 weeks or more was 6.6 months with napabucasin versus 5.8 months with placebo, hazard ratio [HR] 0.88 (p = 0.5). The primary endpoint, overall survival (OS), was not met; median OS was 4.4 months with napabucasin versus 4.8 months with placebo hazard ratio [HR] 1.13 (p = 0.34).

Napabucasin did demonstrate activity in a subgroup of 55 patients that were positive for STAT3 expression, as identified in a pre-specified biomarker analyses that included pSTAT3 positivity by immunohistochemistry in archival tissue based on nuclear staining of cancer cells >5% and stroma ≥2+. Median OS in this group was significantly prolonged with napabucasin to 5.1 months versus 3.0 months with placebo, HR 0.24; 95% confidence interval [CI] 0.12, 0.51 (p = 0.0002).

Adverse events (AEs) were more common with napabucasin than placebo. The most common grade 3 AEs with napabucasin were diarrhoea, occurring in 88% of patients, nausea in 63%, and fatigue in 65% of patients. Anorexia occurred in 56% of patients, and grade 3 diarrhoea occurred in 57% of patients. NCT01830621. Jonker *et al.* Abstract 454O

Practice point and future research opportunities

Despite early-phase research showing antitumour activity for napabucasin, a cancer stemness inhibiting agent that targets STAT3, no significant difference in OS, was seen between napabucasin and placebo in the intention to treat analysis in unselected patients. While pSTAT3 positivity was a poor prognostic factor in untreated patients, napabucasin treatment in patients with positive pSTAT3 significantly improved OS.

Napabucasin has demonstrated benefit when used in combination with weekly paclitaxel, resulting in the FDA granting orphan drug designation to napabucasin as a treatment for patients with gastric or gastroesophageal junction cancer. In addition to gastric cancer, napabucasin is also being explored as a potential treatment for patients with pancreatic cancer, ovarian cancer, triple-negative breast cancer, and colorectal cancer.

Integrated biomarker analysis done for combination dabrafenib / trametinib / panitumumab therapy in BRAF V600E mutation positive mCRC

Lead author Ryan B Corcoran, Translational Research Director for the Gastrointestinal Cancer Center at Massachusetts General Hospital, Boston, USA and a Damon Runyon Clinical Investigator, presented findings on behalf of colleagues from a study testing whether combined inhibition of the EGFR pathway with panitumumab, and dual inhibition of the MAPK pathway could improve clinical benefit in BRAF mutated metastatic colorectal cancer (mCRC). This study evaluated the efficacy and safety of panitumumab plus MAPK pathway inhibitors dabrafenib or trametinib, and in triple combination with both. The trial enrolled 134 patients with BRAF mutated mCRC who were randomised to receive panitumumab plus dabrafenib (n=20), panitumumab plus trametinib (n=31), or a triple combination of panitumumab, dabrafenib and trametinib (n=83). Each agent in the combination could be administered at a dose of up to the full monotherapy dose. The majority of study participants, 120 patients, had received prior chemotherapy for mCRC and 14 patients were treatment-naive. The trial included integrated biomarker analyses. Tumour biopsies that were taken prior to and during treatment were evaluated by immunohistochemistry for phosphorylated ERK (pERK). Serial circulating tumour DNA (ctDNA) samples were obtained and profiled for mutations in the BRAF, KRAS, NRAS, and PIK3CA genes.

The highest response was observed with the triple combination treatment. Patients in the dabrafenib/panitumumab arm showed a confirmed complete response and partial response (CR/PR) rate of 10%, and 80% of patients achieved stable disease (SD). With trametinib/panitumumab no patients attained CR/PR but 53% showed SD. However, the two agents combined with panitumumab yielded an 18% CR/PR rate and 67% of patients showed SD. Median PFS for combined dabrafenib/trametinib/panitumumab was not yet been reached compared with median PFS of 3.4 and 2.8 months demonstrated with dabrafenib/panitumumab and trametinib/panitumumab, respectively. The triple combination showed acceptable toxicity, and the most common adverse events were dermatitis acneiform, diarrhoea, fatigue, nausea and rash.

The integrated biomarker analysis detected changes in different genes with response and upon disease progression. Immunohistochemistry done in biopsies revealed a reduction in pERK in on-treatment versus pre-treatment biopsies. The median pERK reductions were 23% for dabrafenib/panitumumab, 50% for trametinib/panitumumab, and 54% for the triple combination. Serial ctDNA analysis also showed reductions in the BRAF V600E mutant fraction of more than 70% as early as week 4 of treatment in 12 of 14 (86%) patients receiving dabrafenib/trametinib/panitumumab. This finding corresponds with the PR achieved by 6 of these 12 patients by week 6. Conversely, ctDNA analysis also demonstrated increased BRAF V600E mutant fraction in 10 patients upon progression.

Other mutations that were not present at baseline were detected in ctDNA upon progression. Of the 12 patients showing a best response of CR/PR or SD, 7 (58%) patients had RAS mutations in ctDNA upon progression that were not detectable at baseline; 3 of these patients developed multiple RAS mutations. In addition, BRAF V600E and RAS mutations were co-expressed in 2

patients at baseline. NCT01750918. Corcoran *et al.* Abstract 455O

Practice point and future research opportunities

Dabrafenib and trametinib have demonstrated activity and have been approved for BRAF-V600E-mutated melanoma, for use either as single agents or in combination; both drugs block the MAPK pathway, dabrafenib by inhibiting BRAF and trametinib by inhibiting MEK1 and MEK2. BRAF-V600E mutations have been reported in 5% to 10% of mCRC cases; however, BRAF and MEK inhibiting monotherapies have been shown to have little activity in mCRC, where the presence of a BRAF V600E mutation often signals a poorer prognosis.

This study demonstrated that the response in BRAF V600 mutated mCRC could be improved by blocking the EGFR pathway and dual blocking of the MAPK pathway. Patients with mCRC whose tumours harboured BRAF V600E mutation that received triple therapy comprising dabrafenib, trametinib, and panitumumab showed an improved best overall response and prolonged PFS compared to a double blocking combination of panitumumab plus either dabrafenib or trametinib. The demonstrated efficacy taken together with acceptable toxicity demonstrate that this triple combination may be a possible treatment option in mCRC.

The integrated biomarker analysis by immunohistochemistry provided evidence of downstream target inhibition. The ctDNA data suggested that changes in BRAF V600E mutation frequency may serve as a biomarker of response, and could be used to monitor treatment response by decreased pERK and disease progression, which was reflected in an increase of BRAF V600 mutation fraction. The presence of emergent RAS mutations may represent potential mechanisms of resistance to combination treatment.

Results of the first cohort of patients screened within the new EORTC SPECTAcolor platform for patients with colorectal cancer

Gunnar Folprecht, Medical Department I, University Hospital Carl Gustav Carus in Dresden, Germany, presented findings on behalf of colleagues from the first cohort screened in conjunction with SPECTAcolor (Screening Platform for Efficient Clinical Trial Access in advanced colorectal cancer), which was initiated by the European Organisation for Research and Treatment of Cancer (EORTC) as the first prospective, fully annotated tumour sample biobank and biomarker analysis platform for genetic profiling of patients with advanced colorectal cancer. The aim is to facilitate patient-access to a clinical trial for treatment with a targeted agent. Since the inception in 2013, this biobank has enrolled more than 900 patients from 32 clinical centres in 11 European countries and anticipates enrolling at least this many patients yearly in the upcoming years.

Dr. Folprecht reported findings from a cohort of 389 patients with CRC who underwent screening

using a large next generation sequencing (NGS) panel comprising 328 cancer genes. All analyses were performed according to Good Clinical Laboratory Practice (GCLP) Standards. Limited gene fusions were assessed in a subset of samples and genetic events were detected by an ISO 13485-accredited analysis pipeline.

Using immunohistochemistry or fragment length analysis, the investigators determined that 370 of the 389 (95.2%) patients overall were microsatellite stable (MSS) and 19 (4.8%) patients were highly microsatellite instable (MSI-H). Both MSS and MSI-H tumours were found to contain a median of 3 (range: 0 to 16) driver mutations and a median of 8 (range: 3 to 16) potential driver mutations. Among patients with MSS colorectal cancer, 77.8% had mutations in APC, 72.2% in TP53, and 47.8% of patients showed KRAS mutation. Mutated PIK3CA, FBXW7, and BRAF were present in 17.6%, 11.1% and 10.5% of patients. Mutations in the SOX9, SMAD4, ARD1A, and NRAS were present in less than 10% of patients.

More patients with MSI-H tumours that showed TP53 mutations (52.6%), PIK3CA (47.4%), and 42.1% had KRAS mutation. FBXW7 and BRAF mutations were each present in 36.8% of patients and APC and SOX9 were each mutated in 21.1% of patients. No mutations in SMAD4, ARD1A, and NRAS were detected in MSI-H patients.

Tumour localisation of APC and TP53 was more often on the left versus right side, 80.8% versus 73.6%, and 76.5% versus 62.3%, respectively, whereas KRAS and PIK3CA occurred more often on the right; KRAS location was 45.5% versus 53.8%, and PIK3CA was 14.1% versus 25.5%, left versus right, respectively. The prevalence of BRAF mutated tumours was predominately right side: 5.1% left versus 22.6% right ($p < 0.0001$).

Additionally, the investigators detected BRCA2 mutation in 1.6% of patients, located left at 0.8% versus 3.8% right, and in 5.3% of MSI-H tumours. A total of 1.9% of patients showed ERBB2 mutation, which was found twice as often in left sided tumours; left 2.0% versus 1.0% right. Other potentially actionable targets included ERBB2 amplification in 2.5% of patients, FGFR1/2/3 amplification in 3.5%, and TSC1 mutation in 16% of patients with MSI-H tumours. Single ALK and ROS fusions were also observed. NCT01723969. Forprecht *et al.* Abstract 458O

Practice point and future research opportunities

Results of gene panel sequencing from the first cohort of patients with advanced colorectal cancer participating in SPECTAcolor, a large European screening platform revealed new, potentially actionable genetic alterations in these patients, many of whom were now eligible to enter a clinical trial of targeted therapies. New therapeutic targets were detected by gene panel sequencing in approximately 10% of patients with colorectal cancer participating in SPECTAcolor. These first results show that SPECTAcolor is an effective platform for screening patients with colorectal cancer to identify rare but potentially actionable genomic targets; Patients participating in SPECTAcolor will have better access to targeted therapy.

ERBB2 alterations emerged from a FOLFOX based adjuvant trial as a potential new prognostic biomarker in stage III colon cancer

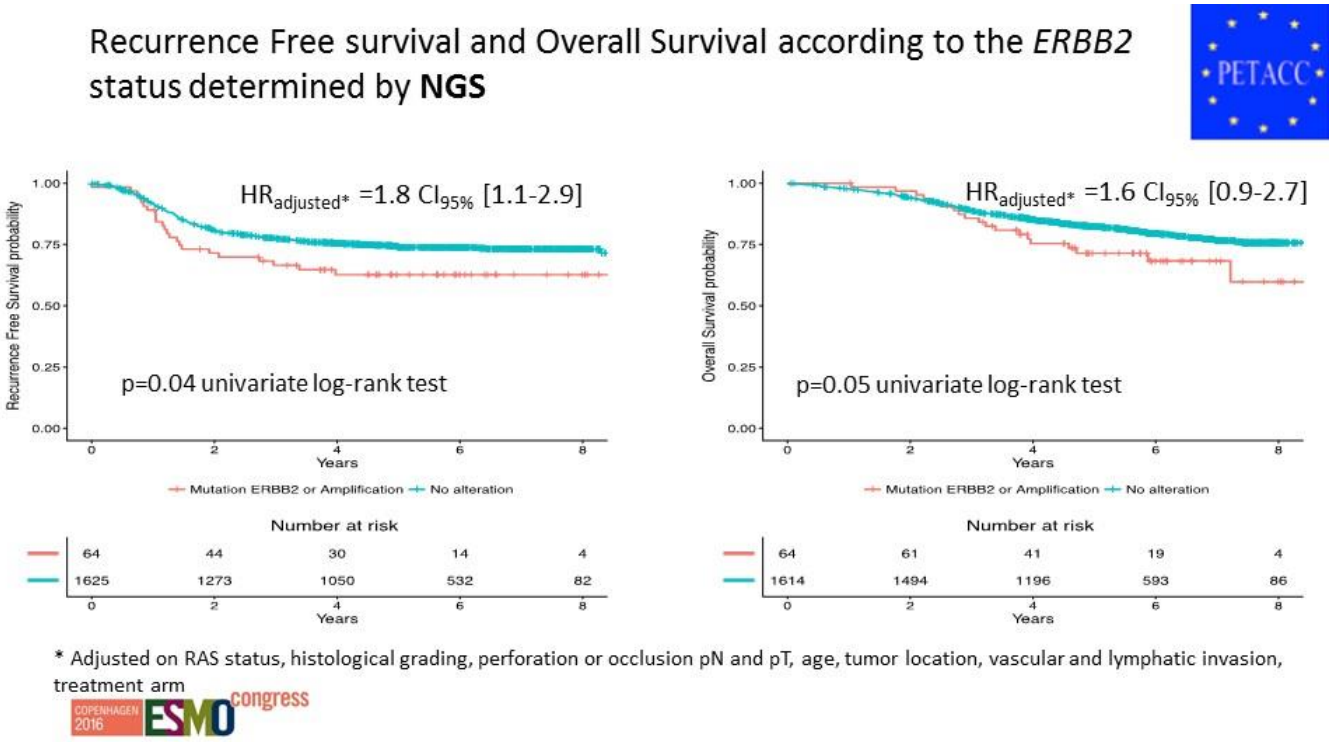
Pierre Laurent-Puig, Department of Biology, Hôpital Européen Georges Pompidou, INSERM UMR-S1147, Paris Descartes University in Paris, France, explained that ERBB2 amplifications have recently been shown to be a targetable alteration in metastatic colorectal cancer (mCRC). Lending further impetus to this study was the response seen in the HERACLES trial with dual-targeted therapy comprising trastuzumab and lapatinib in patients with HER2-positive mCRC. Prof. Laurent-Puig emphasised that defining the occurrence and prognostic role of ERBB2 alterations in stage III colon cancer could lead to additional adjuvant strategies, which are sorely needed in colon cancer.

The PETACC8 trial enrolled 2559 patients with resected, histologically proven stage III colon adenocarcinoma and 2043 patients signed the informed consent for the translational research programme. Of these,1795 patients had tissue samples for screening by next generation sequencing (NGS), and 1804 patients had samples for immunochemistry and FISH analyses.

The investigators searched for amplification of the ERBB2 gene and for mutation in exons 19 to 21 using the colon/lung cancer panel V2 and an algorithm that had been previously validated. All samples were screened for ERBB2 staining with polyclonal antibody HER2 clone 4B5 from Ventana Roche and by FISH using kit zytolight SPEC ERBB2/CEN17 dual colour.

By these methods, ERBB2 alterations were detected in 64 (3.8%) patients; of these, 17 (1%) samples contained ERBB2 mutations. The most frequently detected mutations were p.V842I in 5 patients, and 3 samples each harboured p.V777L and p.L755S mutations. Neither a significant association with RAS or BRAF mutations nor mutual exclusivity was determined. ERBB2 amplification was detected in 49 (2.9%) patient samples by NGS that were confirmed in 28 cases by FISH.

On univariate analysis, ERBB2 alterations signalled a poorer prognosis and were associated with both shorter time to recurrence (TTR), hazard ratio [HR] 1.55; 95% confidence interval [CI] 1.02, 2.36 (p = 0.04), and shorter overall survival, HR 1.57; 95% CI 0.99, 2.5 (p = 0.05). The prognostic value in TTR remained following adjustments for confounders, including treatment, the presence of RAS mutation, histological grade, tumour location, pT and pN status, and the presence of bowel obstruction or perforation, and venous or lymphatic embolism. EudraCT number 2005-003463-23. Laurent-Puig *et al.* Abstract 459O



Recurrence-free survival and overall survival according to the ERBB2 status determined by next-generation sequencing.

© Pierre Laurent-Puig.

Practice point and future research opportunities

Findings from the adjuvant PETACC8 trial and results of a large-scale molecular analysis suggest that ERBB2 gene alterations may be prognostic of poorer outcome in stage III colon cancer. Although ERBB2 alterations, including mutations and amplification, occur at a low frequency in colon cancer, their presence associated with a markedly poorer prognosis, making both screening for ERBB2 alterations and the testing of anti-ERBB2 therapies a consideration in the adjuvant colon cancer setting. ERBB2 alteration occurs in approximately 4% of patients with stage III colon cancer, and associated with decreased time to recurrence and shorter overall survival. Since ERBB2 alteration signals a poor prognosis, the use of anti-ERBB2 therapies in the adjuvant setting is supported for testing in a clinical trial context. ERBB2 has emerged as a new prognostic, albeit rare, biomarker in stage III colon cancer.

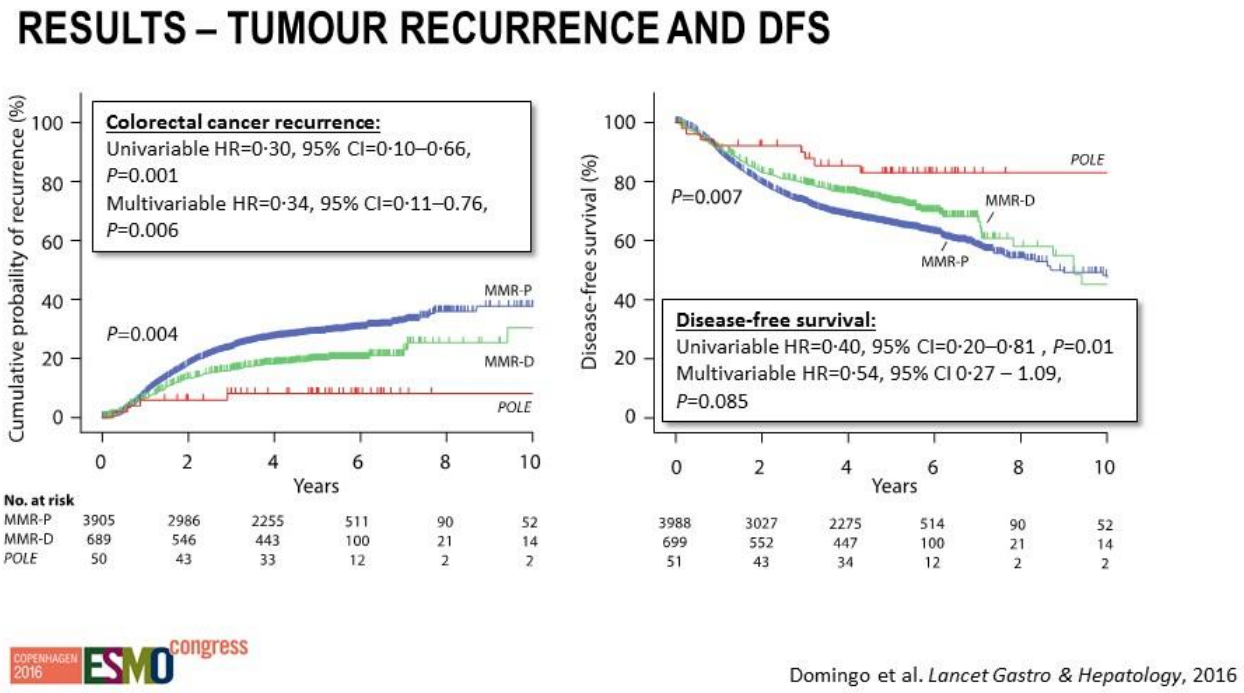
Mutations in the *POLE* proofreading domain identify a subset of colorectal cancers that have enhanced immunogenicity and an excellent prognosis

Mark Andrew Glaire, of the Oxford Centre for Cancer Gene Research, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK underscored the importance of using biomarkers, even those occurring at low frequencies, in defining distinct tumour subgroups. He explained that exceptionally mutated (ultramutated) tumours resulting from mutations that impair

DNA polymerase epsilon (*POLE)* proofreading function confer enhanced immunogenicity and excellent prognosis in the approximately 10% of endometrial cancers in which they are found; however, their effect in colorectal cancer had not yet been defined.

In order to determine the clinical relevance of *POLE* mutations in colorectal cancer, Dr. Glaire and colleagues performed Cox regression analysis on pooled data from more than 4500 patients participating in 3 clinical trials (VICTOR, QUASAR2 and PETACC-3) and multiple patient cohorts (LUMC, Oslo, Bern, AMC-AJCC-II, EPICOLON, and TCGA), and investigated the association between *POLE* mutations and prognosis in stage II/III disease. They detected *POLE* mutations in just 66 of 6,448 (1.0%) colorectal cancer samples. Although uncommon, *POLE* mutations were significantly associated with several patient and tumour factors, including young age, male sex, right-sided location, early disease stage, and absence of mismatch repair deficiency (MMR-D; p ≤ 0.003 for all associations).

Importantly, multivariable analysis revealed a statistically significant association between *POLE* mutation and a greatly reduced risk of disease recurrence: hazard ratio [HR] 0.34; 95% confidence interval [CI] 0.11, 0.76 (p = 0.006). This reduced risk was particularly strong in stage II disease, HR 0.22; 95%CI 0.02, 0.78 (p = 0.014). This reduction in relative risk was greater than that associated with MMR-D (HR 0.72; 95%CI 0.60, 0.87), an accepted biomarker of favourable prognosis in this setting.



Results – Tumour recurrence and disease-free survival.

These results may be explained by increased immune activity in *POLE*-mutant tumours including increased $CD8^+$ lymphocyte infiltration, expression of cytotoxic T cell markers, and effector cytokines, which was similar to that observed MMR-D cancers, well-recognised to be immunogenic. Glaire *et al.* Abstract 460O

Practice point and future research opportunities

POLE proofreading domain mutations, which indicate enhanced immunogenicity and improved prognosis in endometrial cancer, also serve as a biomarker of better prognosis in colorectal cancer. In this large analysis, the presence of *POLE* mutations associated with a reduced risk of disease recurrence. *POLE* proofreading domain mutations define a subset of colorectal cancers that are more immunogenic resulting in greater immune activity and, therefore have a favourable prognosis. This novel biomarker shows promise to improve stratification of patients with colorectal cancer.

Addition of cetuximab to FOLFOX does not improve DFS in patients with type stage III colon cancer and specific RAS or BRAF types

Lead investigator Julian Taieb, Department of Gastroenterology and GI oncology, Université Paris Descartes, Hopital European George Pompidou in Paris, France and colleagues evaluated data from the PETACC8 trial of cetuximab plus FOLFOX versus FOLFOX in patients with full wild type RAS and BRAF stage III colon cancer to determine the prognostic value of mutated forms of these genes, which are known to confer resistance to anti-EGFR treatment. The investigators sequenced exons 2, 3 and 4 of KRAS and NRAS as well as BRAF exon 11 and 15 using the ampliseq colon lung cancer panel V2 in patients participating in PETACC8 who also signed informed consent for translational research. The relationship between cetuximab and time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS) was assessed in patients with RAS wildtype, RAS and BRAF double wildtype tumours, and in patients with rare RAS mutations.

The analysis comprised 2559 patients; of these 745 (29%) patients were known to have tumours with KRAS exon 2 mutation and 163 (6.4%) had tumours harbouring BRAF V600E mutation. Of the remaining 1654 patients, 1054 had given informed consent for additional analyses and were assessed by next generation sequencing (NGS). NGS identified 227 (21%) patients that were newly diagnosed as KRAS exon 3,4 or NRAS exon 2,3,4 mutated, and 46 (4.4%) patients as having non-V600E BRAF mutated tumours.

The TTR, DFS, and OS were not improved with cetuximab in patients with RAS wild-type or RAS/BRAF double wild-type tumours (hazard ratio [HR] ranging from 0.77 to 1.05; all $p > 0.05$). FOLFOX plus cetuximab did not have a significant deleterious effect in patients with RAS mutation patients (HR ranging from 1.13 to 1.29, all $p > 0.05$). No significantly different outcome was observed with and without cetuximab in patients with RAS or BRAF rare mutations (HR ranging from 1.42 to 1.61, all $p > 0.05$).

Pooled data from both treatment arms demonstrated that, in comparison to patients with double wild-type, patients with KRAS and NRAS codon 61 rare mutations were associated with poorer TTR; KRAS, HR 2.42; 95% confidence interval [CI] 1.40, 4.20 (p = 0.001), and NRAS, HR 2.18; 95% CI1.21, 3.93 (p = 0.008). DFS was similarly poorer in patients with these mutations; KRAS, HR 1.98; 95% CI 1.15, 3.42 (p = 0.01), and NRAS, HR1.99; 95% CI 1.13, 3.50 (p = 0.015). Other RAS or BRAF rare mutations did not associate with poorer TTR or DFS. EudraCT number 2005-003463-23. Taieb *et al.* Abstract 461O

Practice point and future research opportunities

Adding cetuximab to standard FOLFOX adjuvant therapy did not significantly improve outcome in patients with RAS wild-type and RAS/BRAF double wild-type of in patients with RAS mutant tumours. Rare mutations in NRAS or KRAS codon 61 were the only mutations detected in this trial that have the pejorative prognostic value similar to KRAS codon 12 and 13 or BRAF V600E mutations.

Phase III trial demonstrates 48 weeks of capecitabine adjuvant chemotherapy is not superior to conventional 24-week treatment in patients with stage III colon cancer: Final results of JFMC37-0801

Shigeki Yamaguchi, Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka, Japan presented findings on behalf of colleagues from the JFMC37-0801 phase III study, which was designed to demonstrate the superiority of 48 weeks of capacitance adjuvant chemotherapy over the conventional duration of 24 weeks of capecitabine treatment. The primary endpoint was disease-free survival (DFS) in patients with stage III colon and rectosigmoid cancer. The trial enrolled patients with curatively resected stage III colon and rectosigmoid cancer, with performance status 0 to 1, aged 20 to 79 years that had not received prior therapy. The patients were randomly assigned to receive daily capecitabine at 1,250 mg/m^2 for 14 of 21 days for 24 weeks (n=654), or capecitabine at the same dose for 48 weeks (n=650). The primary endpoint was DFS, and the secondary endpoints were overall survival (OS) and relapse-free survival (RFS).

At data cut-off of March, 2016, median follow-up was 60 months and 434 DFS events were observed. The 3-year and 5-year DFS rates were 75.3% and 68.7% in the 24 week cohort versus 70.0% and 65.3% in the 48 week cohort, respectively, hazard ratio [HR] 0.866; 95% confidence interval [CI] 0.717, 1.046 (p = 0.068). Five-year OS rates were 87.6% in the 24 week and 83.2% in the 48 week arms, HR 0.737; 95%CI 0.557, 0.975 (p = 0.0259). The 5-year RFS was 74.1% versus 69.3% in the respective arms, HR 0.808; 95%CI 0.658, 0.992 (p = 0.0207). An increased incidence of hand-foot syndrome was observed in the 24-week cohort; however overall grade 3/4 adverse events were comparable in both arms. Yamaguchi *et al.* Abstract 469PD

Practice point and future research opportunities

Findings from this trial did not support the superiority of 48-weeks of treatment with capecitabine adjuvant chemotherapy over 24 weeks of capecitabine in patients with stage III colon cancer, in terms of DFS, the primary endpoint. However, regarding OS and PFS, the p-values for the comparison of 48 weeks treatment with 24 weeks treatment were less than 0.025, perhaps leaving the optimal duration of adjuvant chemotherapy for stage III colon cancer unresolved.

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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