Highlights in gastrointestinal oncology

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From October 7th till October 11th, Copenhagen formed the background for the 2016 annual meeting of the European Society for Medical Oncology (ESMO). This report will focus on some of the key studies presented during the meeting, referring to gastrointestinal cancer.

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Colorectal cancer

Molecular subtyping and sidedness: a story coming of age

Although the proposed classifications based on distinct molecular subtypes of colorectal cancer (CRC), or immunoscores of colorectal cancer are not superimposable with the idea of sidedness; all these biological theories offer new insights in the development of CRC and lead to new treatment possibilities for patients with colorectal cancer.[1-3]

At ESMO 2016, a special session was dedicated to sidedness. Retrospective analyses of previously reported phase III studies, such as the PRIME, PEAK, Crystal and FIRE-3, were re-evaluated with respect to sidedness. All presenters agreed on the fact that sidedness is a prognostic marker and that the prognosis is worse in mCRC arising from right-sided tumors as compared to left sided cancers; irrespective of *BRAF* status (5% left and +/- 22% right). Furthermore, data suggest that right-sided tumors fare worse under EGFR-targeted therapy and would perhaps benefit more from a VEGF-targeting therapy (although they also have some benefit from EGFR targeted therapy). *Table 1* demonstrates some of the key elements reported by the different authors.

Rare colon cancer subtypes: knowing more about less.

Several abstracts addressed the definition of specific tumor subgroups. These studies were usually based on retrospective translational analyses, using prospectively gained tissue in previous phase III trials.

Laurent-Puig et al. focused on *ERBB2* amplification, which was previously shown to be a valid targetable alteration in metastatic CRC.[4] From the 2,559 patients enrolled in the PETACC8 trial, 2,043 signed the translational research informed consent. Among them, tissues samples were available in 1,795 patients for next generation sequencing (NGS) screening, and 1,804 were available for immunochemistry and FISH analysis. The investigators found that *ERBB2* alterations are a rare event, occurring in approximately 4% of stage III CRC patients. Mutations were found in approximately 1% of cases, whereas a *ERBB2* gene amplification could be identified in 2.9% of patients. The *ERBB2* mutations were not related to *RAS* or *BRAF* mutations, nor were they mutually exclusive. Although it is established – in this patient population - to be a rarity, the investigators supported testing of anti-*ERBB2* therapy in the adjuvant setting, given its poor prognostic value and possible effective treatment (cfr. the Heracles trial).

Other investigators searched for patients with exceptionally mutated tumors, caused by mutations that impair DNA polymerase epsilon proofreading (POLE).[5] These mutations confer enhanced immunogenicity and were shown to be associated with an excellent prognosis in endometrial cancers. Their effect in CRC was examined using tissue from the VICTOR, QUASAR2 and PETACC3 clinical trials. Although *POLE* mutations were detected in only 1.0% of CRC cases, they presented with a specific immunogenicity and a good clinical prognosis. This finding could further improve the strat-

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Table 1. Sidedness of colorectal cancer: all patients *KRAS* wildtype

	Phase / N	Schedule	Right N (%)	OS Left	OS Right	PFS Left	PFS Right
PRIME	III 512	Folfox + panitumumab Folfox + placebo	39 (19) 49 (24)	30.3 23.6	11.1 15.4	12.9 9.2	7.5 7.0
PEAK	II 170	Folfox + panitumumab Folfox + bevacizumab	22 (19) 14 (21)	43.4 32.0	17.5 21.0	14.6 11.5	8.7 12.6
CRYSTAL	III 367	Folfiri + cetuximab Folfiri + placebo	33 (19) 51 (27)	28.7 21.7	18.5 15.0	12 8.9	8.1 7.1
FIRE-3	III 394	Folfiri + cetuximab Folfiri + bevacizumab	37 (14) 44 (22)	38.3 28.0	18.3 23.0	10.7 10.7	7.9 9.0
CALGB/SWAG 80405	III 474	Chemotherapy + cetuximab Chemotherapy + bevacizumab	71 78	39.3 32.6	13.6 29.2	12.7 11.2	7.5 10.2

ification of CRC patients.

Instead of searching for specific targets, screening with a NGS panel, could allow for a broader yield and identify specific subgroups of therapeutic interest. The EORTC has developed such a screening platform for efficient clinical trial access in advanced colorectal cancer (SPECTAcolor).[6] It concerns a prospective, pan-European screening program aiming at the molecular characterization of tumors using an exceptionally large NGS panel (consisting of 328 genes). *Folprecht et al*. presented the results of the first cohort of 389 patients that were screened. This gene panel did identify new potential therapeutic targets in approximately 10% of patients. The most frequent mutations are summarized in *Table 2*.

Non-metastatic CRC

Rectal Cancer: How long is the optimal interval between radiotherapy and TME?

At the Royal Marsden academy in London, a prospective randomized trial was set up to determine the optimal duration of the interval between radiotherapy and surgery.[7] Prior evaluations in this respect demonstrated that down staging and regression of the primary tumor (and lymph nodes) is a good prognostic marker for improved OS. Therefore, 237 patients were randomized between a 6-week (N=122, 51%) interval and a 12-week (N=115, 49%) interval between radiotherapy and surgery. The primary endpoint of the study was the difference in the proportion of patients in each arm with down staging (via MRI T-stage; defined as any reduction in T-stage /sub stage).

A significantly greater proportion of patients was down staged with the 12-week (58%) interval *vs.* 43% in the 6-week arm (p= 0.019). The pCR rate was 9% in the 6-week *vs.* 20% for the 12-week arm ($p < 0.05$). The investigators concluded that waiting 12-weeks after CRT results in significantly more tumor down staging and a higher pCR rate. Therefore, they would suggest not to embark on surgical intervention before maximal regression.

However, these results are challenged by *Lefevre et al*. who previously published somewhat contradictory data.[8] The GRECCAR6 trial, a phase III, multicenter, randomized, open-label, parallel-group controlled study, included 265 patients with cT3/T4 or Tx N+ rectal tumors. Patients were randomized to a 7- or 11-week waiting period between radiotherapy and surgery. In their experience, waiting 11 weeks did not increase the rate of pCR and waiting longer may be associated with higher morbidity and a more difficult surgical resection. In conclusion it is still unclear what the perfect interval might be. However, 7 to 9 weeks seems to be enough to ensure efficacy (pCR) without compromising surgical outcome.

Intensive monitoring seems imperative in the follow up of curative treatment in CRC

The FACS trial was revisited after 12 years, to offer more mature data on surgical treatment of recurrence with curative intent (primary endpoint) and OS results.[9] This trial examined the use of CT imaging and carcinoembryonic antigen (CEA) measurements in the follow-up of patients with curatively treated colorectal cancer (R0 resection, stages I-III). In total, 1,202 patients were randomized to 1 of 4 groups: regular CEA, regular CT imaging (chest abdomen pelvis), CEA + CT or minimum

Table 2. Most frequent mutations according to location and MSI-status (%)

	MSS (N= 370)			MSI-H (N= 19)
	total	left	right	total
APC	77.8	80.8	73.6	21.1
TP53	72.2	76.5	62.3	52.6
KRAS	47.8	45.5	53.8	42.1
PIK3CA	17.6	14.1	25.5	47.4
FBXW7	11.1	12.2	8.5	36.8
BRAF	10.5	5.1$	22.6	36.8
SOX9	8.1	6.2	13.2	21.1
SMAD4	7.6	7.1	9.4	0
ARD1A	5.1	5.5	3.8	0
NRAS	5.1	4.3	7.5	0

$ L vs. R: p< 0.0001

follow-up (symptomatic follow-up +/- single CT).
The interim analysis, after 5 years of follow-up, showed that all intensive strategies (CEA, CT and CEA + CT) identified more recurrences treatable surgically with curative intent compared to minimum follow-up. There was no advantage in using both CT and CEA.
At 12 years, intensive follow-up identified more recurrences treatable with curative intent (INT 68/901 7.5% *vs.* MIN 8/301 2.7%, p= 0.003). There was no difference in OS between groups (p= 0.45), but numerically more patients with recurrence were still alive in the intensive groups (INT 43/901 4.8% *vs.* MIN 7/301 2.3%, p= 0.07). Analyses by site of primary tumor revealed that a similar proportion of curatively treatable recurrences in those with rectal tumors were identified, irrespective of follow-up. However, among colon cancer cases, recurrences were more commonly detected in patients with left sided colon cancer by intensive follow-up. Furthermore, in patients with a recurrence, an OS benefit was only seen in those with a left colonic tumor (median OS: INT 4.4 years *vs.* MIN 3.1 years; p= 0.03).

Metastatic Colorectal Carcinoma (mCRC)

New treatment options?

Two trials with novel therapeutic options were presented, one exploiting the known role of anti-angiogenesis and one with a new mechanism of action, targeting stemness and STAT3.
Nintedanib is a multiple angiokinase signaling pathway inhibitor (including VEGFR, PDGFR and FGFR). Van *Cutsem et al* reported on a global, randomized Phase III study (NCT02149108) evaluating the efficacy and safety of nintedanib in patients with mCRC after failure of standard therapies.[10] In total, 768 patients with mCRC, refractory to standard treatment, were randomized 1:1 to receive either nintedanib (200 mg bid) + best supportive care (BSC) or placebo (bid) + BSC. The co-primary endpoints were PFS by central review and OS. A statistically significant improvement in PFS was observed (HR[95%CI]: 0.58 [0.49, 0.69]; p< 0.0001; median PFS 1.5 months with nintedanib *vs.* 1.4 months with placebo). However, no difference in OS could be demonstrated (HR[95%CI]: 1.01[0.86,1.19]; p= 0.8659; median OS 6.4 months with nintedanib *vs.* 6.1 months with placebo). Disease control by central review was 26% with nintedanib as compared to 11% with placebo (OR[95%CI]: 2.96[2.00,4.4]; p< 0.0001). The most frequent ≥Grade 3 AEs occurring nintedanib *vs.* placebo patients were liver related investigations (16% *vs.* 8%) and fatigue (9% *vs.* 6%).
Napabucasin (NAPA) is a first-in-class cancer stemness inhibitor that targets STAT3. In the presented study, 282 patients who failed all standard treatment were randomized 1:1 to NAPA 480mg p.o. q12h, or placebo. The primary endpoint of the trial was OS.[11] No significant difference was observed in OS or progression free survival (PFS) between NAPA and placebo in the ITT analysis. Of the 251 (89%) patients with available pSTAT3 data, 55 (22%) were positive. In patients on placebo, pSTAT3 positivity was a poor prognostic factor (median OS 3.0 *vs.* 4.9 months, HR[95%CI]: 2.3[1.5-3.6], p= 0.0002). In the study, NAPA did improve the OS in pSTAT3 positive patients (HR 0.24).

Gastric and esophageal carcinoma

We have witnessed the groundbreaking work of the cancer genome atlas (TGCA), which allowed for a taxonomy for gastric and esophageal cancer.[12] In Copenhagen the group of MSSK has expanded and added to this knowledge.[13] Results of an NGS assay (MSK-IMPACT) were presented, capable of detecting somatic mutations (MUT), deletions and amplifications (AMP) in 429 tumors in 319 patients. These results were correlated with clinical outcomes. Of these 319 patients, 80 had HER+ disease and in 28 patients, paired pre/post HER2 treatment samples were analyzed. In the paired samples, investigators observed post-therapeutic loss of HER2 amplification (16%); gain of new AMP of MET (7%), EGFR (4%), and IGF1R (4%); MUT in ERBB4 (14%), *KRAS* (11%), PIK3CA (7%), MTOR (7%). Furthermore, 20 of 319 patients (6%) had deleterious somatic (N= 15) or germline (N= 5) *BRCA1/2* mutations. Four of five *BRCA1/2* germline mutation positive patients displayed loss of the wild type allele and exhibited dramatic tumor regression on 5FU/platinum. Twelve of 319 patients (4%) had MSI tumors; and these patients had encouraging results after PD1(/CTLA4) blockade.

These findings demonstrate the dynamic gain or loss of genetic mutations throughout treatment and that detection of these genetic alterations can create personalized treatment possibilities.

Hepatocellular carcinoma

Several abstracts addressed new treatment options for hepatocellular carcinoma (HCC). However, HCC is a very diverse disease and often patients present with multiple comorbidities. The following options will add to the armamentarium, but need to be correlated with the specific origin of the disease and the general condition (and age) of the patient.[14]

Ramucirumab (RAM)

RAM is a fully human monoclonal antibody (IgG1) directed against the vascular endothelial growth factor receptor 2 (VEGFR2). By binding to VEGFR2 it works as a receptor antagonist, blocking the binding of vascular endothelial growth factor (VEGF) to VEGFR2. It was evaluated in "REACH" a global, randomized, phase 3 study in patients with advanced HCC after prior sorafenib.[15] REACH demonstrated no OS benefit in the ITT population but some survival benefit was seen in patients with baseline alpha-fetoprotein (AFP) ≥400 ng/mL (N= 250) (median OS 7.8 months with RAM *vs.* 4.2 months with placebo; HR: 0.67; p= 0.006).

At ESMO 2016, data of a subgroup analysis by liver disease etiology was presented. Overall, this analyses did not differ much with the previous report. However, patients with HepB related HCC had a shorter survival, compared to patients with a HepC or another tumor etiology. Finally, a potential improvement in survival with RAM remained in all etiology subgroups with a baseline AFP ≥400 ng/mL.

Regorafenib

In this randomized phase III study, a population of "good" / selected adults with BCLC stage B or C HCC who had radiological progression on sorafenib; and had Child-Pugh A liver function, and ECOG PS 0–1 were randomized 2:1 to regorafenib 160 mg/day or placebo on weeks 1–3 of each 4-week cycle until progression, death, or unacceptable toxicity.[16]

A total of 573 patients was randomized. Regorafenib was associated with a 37% reduction in the risk of death (HR[95%CI]: 0.63[0.50–0.79]; p< 0.001). The median OS with regorafenib was 10.6 months as compared to 7.8 months with placebo. Regorafenib also improved the PFS (HR[95%CI]: 0.46[0.37–0.56]; p< 0.001), prolonged the time to progression (HR[95%CI]: 0.44[0.36–0.55]; p < 0.001), and increased the disease control rate (65.2% *vs.* 36.1%; p< 0.001). However, regorafenib is associated with high rates of grade ≥3 adverse events: 79.7%. Nevertheless, the health-related quality of life (HRQoL) was apparently not influenced.

Checkmate-040

In Checkmate-040, a total of 262 HCC-patients were treated with nivolumab; irrespective of etiology. In total, 48 patients were included in the dose escalation (ESC) stage and 214 patients were enrolled in the dose expansion phase of the study.[17]

The overall response rate remains about 15-16% and the median OS was prolonged to 14.3 months. The safety profile of nivolumab remains similar across the 4 cohorts: uninfected sorafenib naïve/intolerant, uninfected progressed on sorafenib, HBV-, and HCV-infected. Responses occurred regardless of underlying HCC etiology or PD-L1 expression.

Small bowel adenocarcinoma

Small bowel adenocarcinoma (SBA) was previously demonstrated to be a distinctly different molecular disease than CRC. Comprehensive genomic profiling (CGP) challenges the current dogmatic way of treating these diseases.

In a prospective analysis of clinical samples from 358 patients with SBA, 6.353 patients with CRC, and 889 patients with gastric carcinoma, specific mutational patterns were presented. *APC* alterations were less frequent in SBA (27%) than in CRC (76%) ($p< 0.001$).[18] *BRAF* alterations were found in 8% of cases in both CRC and SBA series. However, V600E mutations were much less common in SBA, representing only 10% of all *BRAF*-mutated cases. Amplification of *ERBB2* and *EGFR* was most common in GC and least common in SBA. Both *ERBB2* and *EGFR* point mutations were more common in SBA (7% and 1.4% of cases) than in the other tumor types that were examined. An MSI-high status was more frequently seen in SBA (6.9%) than in CRC (3.9%) and in GC (4%). Overall, the molecular profile of unspecified SBA was similar to that of duodenal adenocarcinoma (DA). Targetable alterations in several additional genes including *PIK3CA* and *MEK1* mutations and *RTK* fusions were identified in all three series.

This presentation, along with many others, makes a clear case for CGA screening during the course of disease to identify targetable genomic alterations and possibly treat them.

Conclusions

At ESMO 2016 no new practice changing results in the field of digestive oncology were presented. However, "sidedness" has confirmed its prognostic status and right sided CRC is definitely a different disease from left sided tumors. Much information addressed the molecular and genetic diversification within tumor types, leading to a more precise taxonomy in CRC, gastric cancer and HCC. As such, genetic profiling provides enrichment strategies for clinical research and further hope for personalized treatments.

References

1. Guinney J, Dienstmann R, Wang X et al. The Consensus Molecular Subtypes of Colorectal Cancer. Nat Med. 2015; 21(11): 1350–1356.

2. Galon J, Mlecnik B, Marlot F et al. Validation of the Immunoscore (IM) as a prognostic markerin stage I/II/III colon cancer: Results of a worldwide consortium based analysis of 1336 patients. J Clin Oncol 2016;34 (suppl): abstr 3500.

3. Venook A, Niedzwiecki D, Innocentiet F et al. Impact of primary tumour location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer(mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34(Suppl):Abstr 3504.

4. Laurent-Puig P, Balogoun R, Cayre A et al. ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8). Annals of Oncology 2016; 27(suppl 6): Abstr 4590

5. Glaire M, Domingo E, Vermeulen L et al. POLE proofreading domain mutation defines a subset of immunogenic colorectal cancers with excellent prognosis. Annals of Oncology 2016; 27(suppl 6): Abstr 4600

6. Folprecht g, Beer P, Salazar R et al. Frequency of potentially actionable genetic alterations in EORTC SPECTAcolor. Annals of Oncologly 2016; 27(suppl 6):Abstr 4580

7. Evans J, Bhoday J, Sizer Be et al. Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? Annals of Oncology 2016; 27(suppl 6): Abstr 4520

8. Lefevre JH, Mineur L, Kotti S et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). J Clin Oncol 2016; 34(31): 3773-3780.

9. Mant D, Shinking B, Mellor J et al. Scheduled use of CEA and CT follow-up to detect recurrence of colorectal cancer: 6-12 year results from the FACS randomised controlled trial. Annals of Oncology 2016; 27(suppl 6): Abstr 4530

10. Van Cutsem E, Yoshino T, Lenz H et al. Nintedanib plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients (pts) with colorectal cancer (CRC) refractory to standard therapies: Results of the phase III LUME-colon 1 study. Annals of Oncology 2016; 27(suppl 6): LBA20_PR.

11. Jonker D.J, Nott L, Yohino T et al. A randomized phase III study of napabucasin [BBI608] (NAPA) vs placebo (PBO) in patients (pts) with pretreated advanced colorectal cancer (ACRC): the CCTG/AGITG CO.23 trial. Annals of Oncology 2016; 27(suppl 6): Abstr 4540.

12. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202-209.

13. Janjigian Y, Sanchez-Vega F, Jonsson P et al. Clinical next generation sequencing (NGS) of esophagogastric (EG) adenocarcinomas identifies distinct molecular signatures of response to HER2 inhibition, first-line 5FU/platinum and PD1/CTLA4 blockade. Annals of Oncology 2016; 27(suppl 6): Abstr 6120

14. Ang C, Shields A, Xiu J et al. Molecular characteristics of hepatocellular carcinomas (HCC) from different age groups. Annals of Oncology 2016; 27(suppl 6): Abstr 618PD

15. Okusaka T, Blanc J, Chau I et al. Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Prognosis, efficacy, and safety by liver disease etiology. Annals of Oncology 2016; 27(suppl 6):Abstract 617PD.

16. Bruix J, Merle P, Granito A et al. Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial Annals of Oncology 2016; 27(suppl 6):. Abstr LBA28.

17. Melero I, Sangro B, Yau T et al. 615O - Safety and preliminary efficacy of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (aHCC): Interim analysis of the phase ½ CheckMate-040 study. Annals of Oncology 2016; 27(suppl 6): Abstr 6150

18. Overman M, Schrock A, Devoe C et al. Genomic profiling of small bowel adenocarcinoma: Insights from a comparative analysis with gastric and colorectal cancer and opportunities for targeted therapy. Annals of Oncology 2016; 27(suppl 6): Abst 6130