Highlights in gastrointestinal cancers

K. Papadimitriou, M. Rasschaert, J. Van Den Brande, M. Peeters
Department of Medical Oncology, Antwerp University Hospital

The 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO) took place once more in Chicago from June 2 to 6, bringing together more than 30,000 oncology professionals from around the world. This year's meeting theme is "Making a Difference in Cancer Care with You." Studies spanning the spectrum of GI cancer prevention and care, from new standards of care to immunotherapy and precision medicine, will be highlighted.

UPPER DIGESTIVE CANCER

IS FLOT THE NEW MAGIC TREATMENT IN OPERABLE ESOPHAGOGASTRIC CANCER?

The MAGIC trial established perioperative epirubicin, cisplatin, and 5-FU (ECF) as a standard treatment for patients with operable esophagogastric cancer, but survival remains poor.[1] The FLOT4, a multicenter, randomized, phase 3 trial presented this year, compares the docetaxel-based triplet FLOT with the MAGIC-regimen in the same setting.[2] In total, 716 patients were respectively randomized to 4 cycles of FLOT or 3 cycles of ECF/ECX pre- and post-surgery. For a median follow-up of 43 months, FLOT arm resulted in more R_0 surgery (84% *vs.* 77%) and deeper ypTNM responses. Furthermore, the progression-free (PFS) (30 *vs.* 18 months; HR[95%CI]: 0.75[0.62-0.91]; p= 0.004) (*Figure 1*) and overall survival (OS) (50 *vs.* 35 months, HR[95%CI]: 0.77[0.63-0.94]; p= 0.012) (*Figure 2*) were significantly improved. The 5-year projected survival rate was higher for FLOT arm at 45% *vs.* 36% in the control arm. Both regimens appeared tolerable and manageable. Diarrhea, neurosensory toxicity, infections and grade 3/4 neutropenia were more frequent with the FLOT regimen while less grade 3/4 nausea and vomiting were registered compared to ECF/ECX.
In conclusion, the FLOT-regimen seems to be the new standard of care replacing the ECF/ECX in resectable locally advanced gastric and GEJ tumors.

FINALLY ADJUVANT THERAPY FOR BILIARY TRACT CANCER? THE BILCAP TRIAL

BILCAP is a randomized phase III study which demonstrated OS benefit in patients receiving 8 cycles of adjuvant capecitabine compared to observation only in patients who underwent radical and complete resection for biliary tract cancer (BTC). 447 participants were randomized to capecitabine (N= 223) or observation (N= 224). Follow up was at least 36 months in more than 80% of the surviving patients. The OS in the intent-to-treat (ITT) population was better in the treated group, but did not reach the threshold for statistical significance (51.1 *vs.* 36.4 months; HR[95%CI]: 0.81[0.63-1.04]; p= 0.097). However, in the per protocol population the difference in OS was significant with a p-value of 0.028 (median OS 52.7 *vs.* 36.1 months; HR[95%CI]: 0.75[0.58-0.97]; p= 0.028).[3]
In conclusion adjuvant therapy with 8 cycles of standard dosage of capecitabine could become the new standard for resected patients with BTC and high risk for relapse, but more robust data are needed.

IS THE STROMA A PROMISING TARGET IN THE TREATMENT OF METASTATIC PANCREATIC CANCER

PEGPH20 is a PEGylated form of recombinant human hyaluronidase which degrades hyaluron and remodels the tumor stroma. HALO 202 is a randomized phase II trial in which gemcitabine/*nab*-paclitaxel (AG) is compared with AG and PEGPH20 (PAG). In total, 279 patients with metastatic pancreatic cancer (mPC) were randomized (2:1) between both treatment regimens. The PAG-regimen was associated with a statistically higher PFS than the AG regimen (median PFS 6.0 *vs.* 5.3 months; HR[95%CI]: 0.73[0.53-0.99]; p=0.045) (*Figure 3*). A subgroup analysis of the trial showed that especially patients with hyal-

Please send all correspondence to: M. Peeters, MD, PhD, Multidisciplinary oncological Centre Antwerp (MOCA), University Hospital Antwerp Wilrijkstraat 10, 2605 Edegem, Tel: +32 (0)3 821 33 23, E-mail: Marc.Peeters@uza.be

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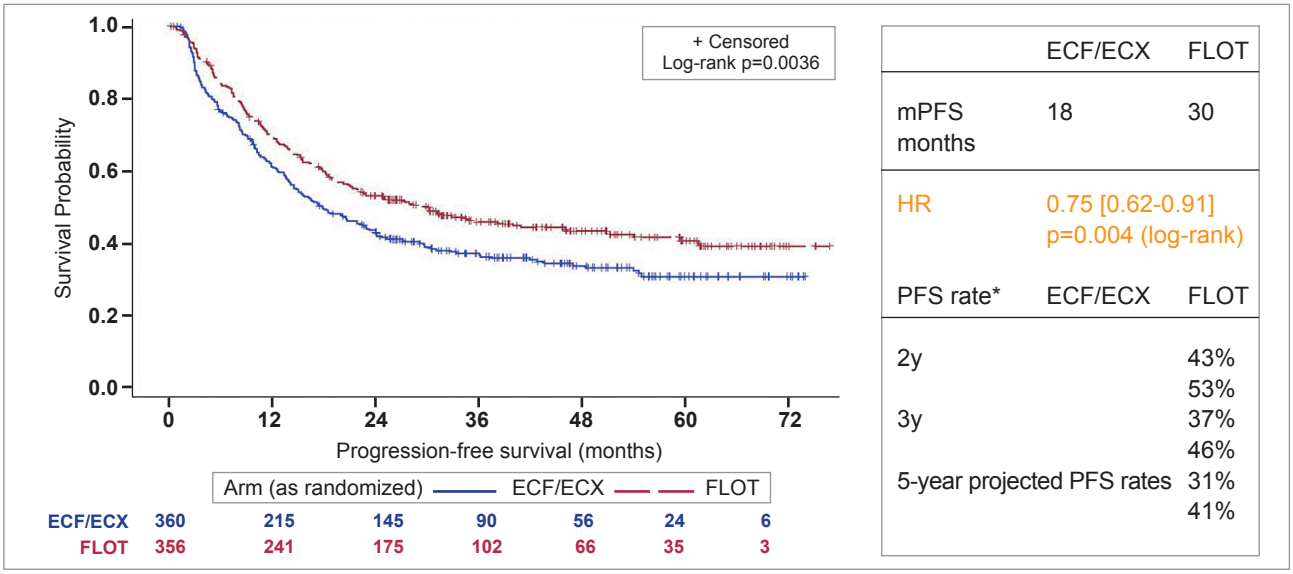

FIGURE 1. PFS in the phase III FLOT4 study.[2]

uron-high tumors derived a strong PFS benefit from the PAG regimen (9.2 *vs.* 5.2 months HR[95%CI]: 0.51[0.26-1.00]; p= 0.048).

In summary, targeting the stroma might be a new strategy in the treatment of patients with mPC. The interesting biomarker driven results of this phase II study form the background for the ongoing phase III HALO 301 study.[4]

CAN WE DO MORE FOR UNRESECTABLE HEPATOCELLULAR CARCINOMAS (HCC)?

Two interesting trials focusing on treatment of unresectable hepatocellular carcinomas were presetend.

In the non-inferiority, phase III REFLECT trial the novel TKI lenvatinib was studied in HCC. Lenvatinib is an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet derived growth factor receptor α, RET, and KIT. Patients in REFLECT were randomized to lenvatinib or sorafenib as first-line therapy for patients with unresectable HCC. The study met its primary endpoint demonstrating a non-inferior OS with lenvatinib (median OS 13.6 *vs.* 12.3 months; HR[95%CI]: 0.92[0.79-1.06]). Additionally, both PFS (7.4 *vs.* 3.7 months; HR[95%CI]: 0.66[0.57-0.77]; p< 0.00001) and ORR (24.1% *vs.* 9.8%; OR[95%CI]: 3.13[2.15-4.56]; p< 0.00001) were significantly increased in the lenvatinib arm. Overall, the side effects with the experimental drug were manageable.[5]

In the SIRveNIB phase III trial, 360 patients with non-resectable, Child-Pugh A HCC were randomized (1:1) to selective

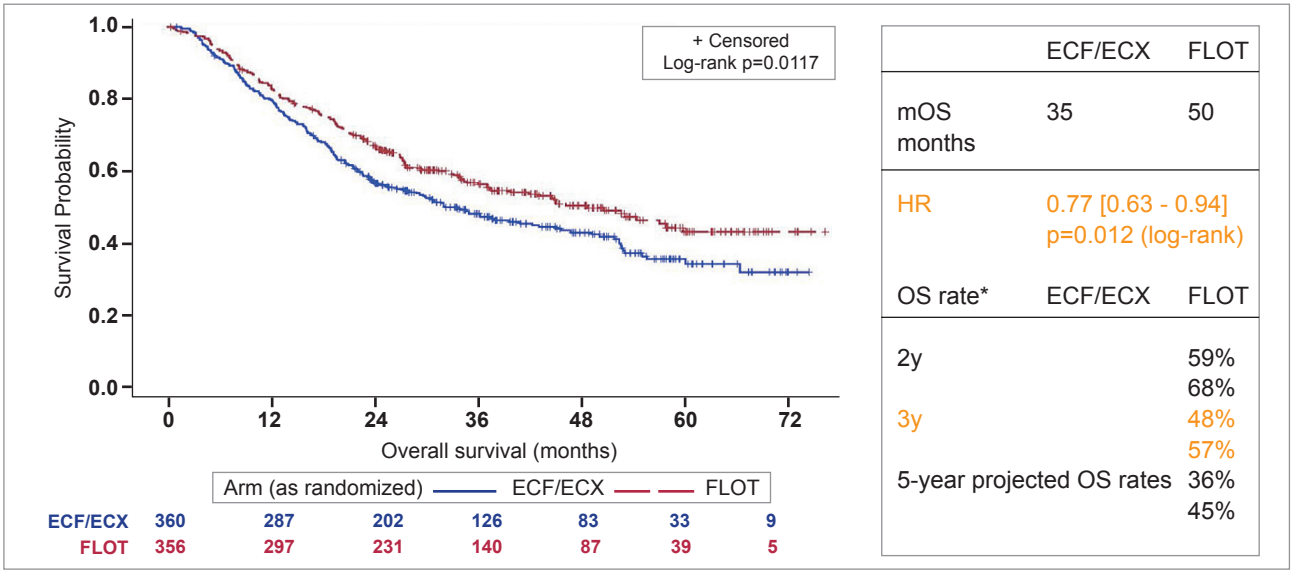

FIGURE 2. OS in the phase III FLOT4 study.[2]

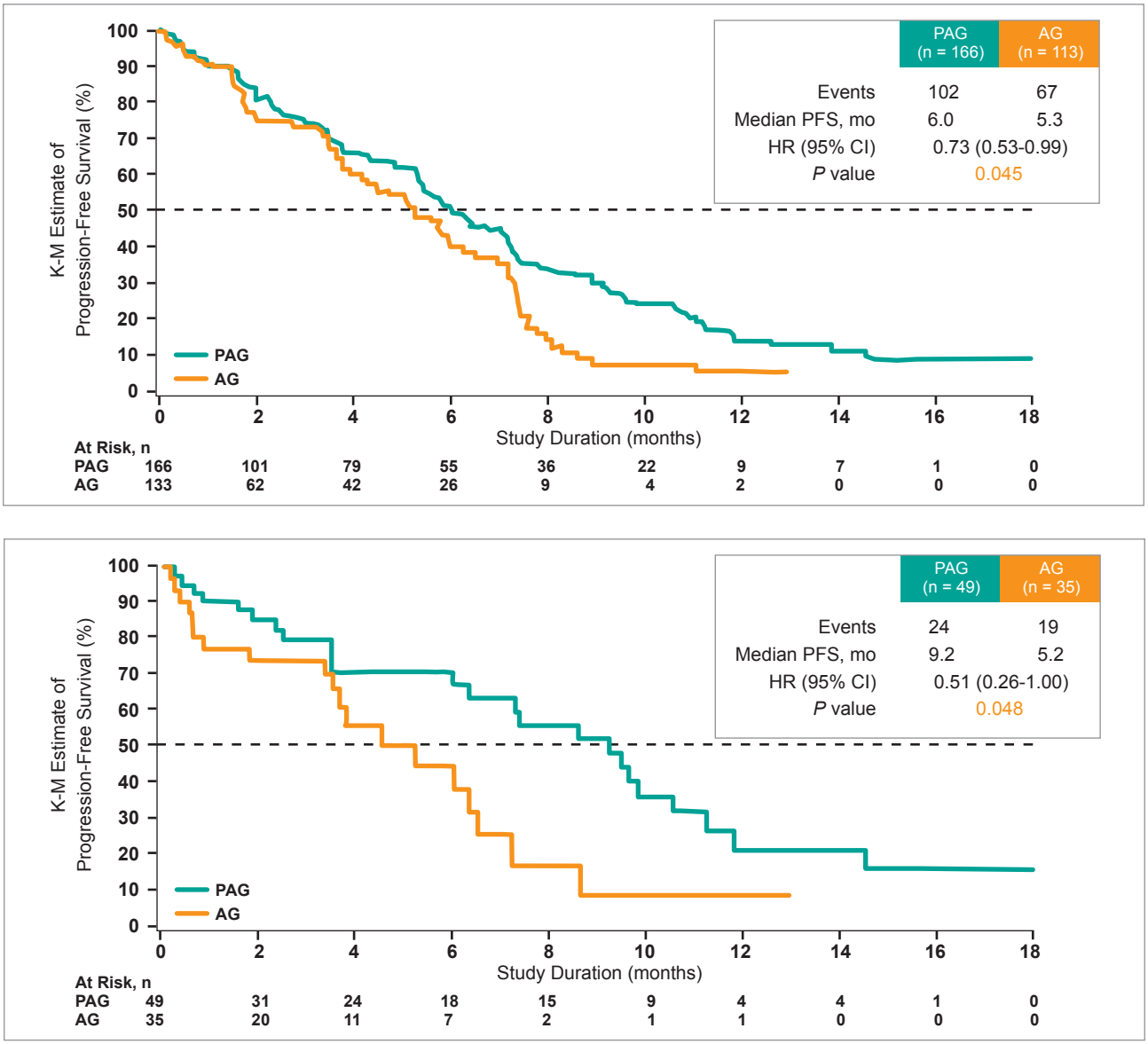

FIGURE 3. PAG- was associated with a statistically higher PFS than the AG regimen in patients with mPC (top). This effect was even more pronounced among patients with HA-high tumors (bottom).[4]

internal radiation therapy (SIRT) with Y90 resin microspheres or sorafenib in the first line setting. The ITT analysis demonstrated a comparable OS in the Y90 and sorafenib arms at 8.84 and 10.02 months respectively (HR[95%CI]: 1.12[0.88-1.42]; p= 0.360). However, a clinically meaningful ORR benefit was reported for SIRT (16.5% *vs.* 1.7% respectively; p<0.001). The median PFS reached 5.85 months with SIRT and 5.06 months with sorafenib (HR[95%CI]: 0.89[0.71-1.12]; p= 0.306). The liver specific median PFS was 6.01 months with SIRT and 5.06 months with sorafenib (HR[95%CI]: 0.88[0.70-1.10]; p= 0.259). At least one severe (grade 3 or more) adverse event was observed in 27.7% of the SIRT patients and in 50.6% of the sorafenib treated subjects.[6]

In conclusion SIRT and lenvatinib could represent potential alternatives for sorafenib in the treatment of unresectable HCC.

IMMUNOTHERAPY IN GASTRIC CANCER: DOSING AND COMBINATION MAY IMPACT RESULTS

In the phase II ONO-12 study, nivolumab monotherapy in 3rd- or later-line prolonged the OS compared to placebo in Asian patients with advanced gastric, gastroesophageal junction (G/GEJ) cancer (median OS: 5.3 *vs.* 4.1 months; HR: 0.63; P< 0.0001).[7]

In the phase I/II CheckMate 032 study of nivolumab with or without ipilimumab showed favorable clinical activity in Western patients with advanced chemotherapy refractory G/E/GEJ cancer. Patients received combinations of nivolum-

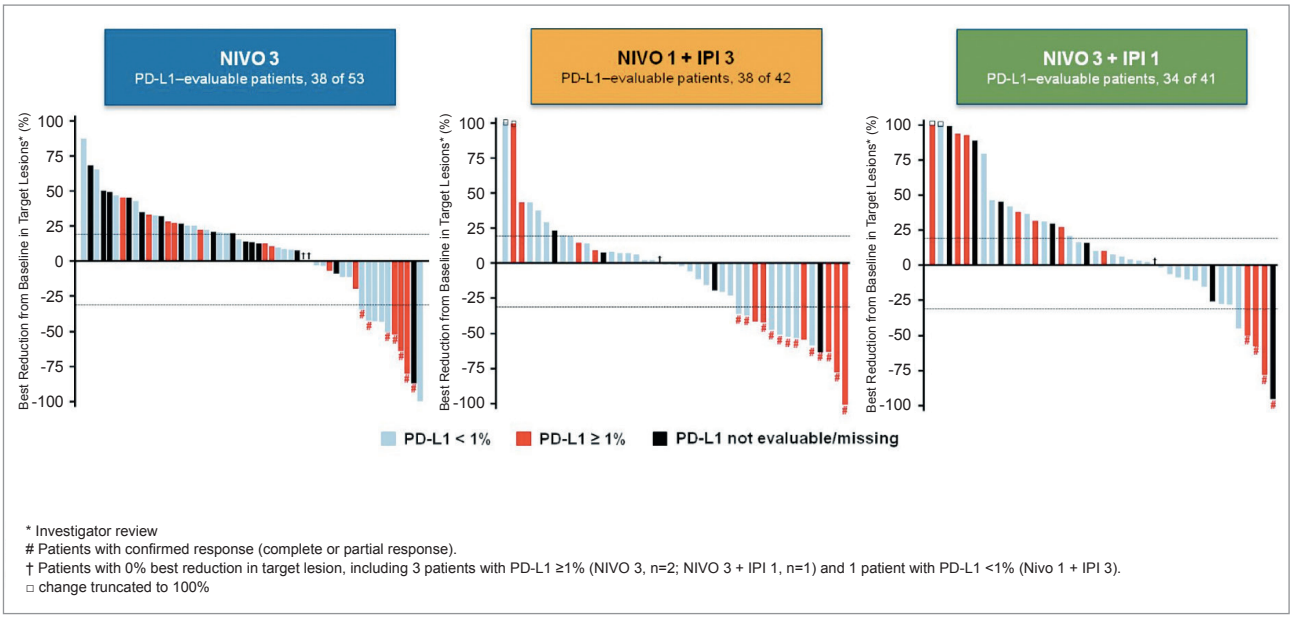

FIGURE 4. Best reduction in target lesion in the CheckMate 032 EG cohort.[8]

ab +/- ipilimumab in 3 different dose regimens: a) nivolumab monotherapy at 3 mg/kg Q2W (N3) (N=59), b) nivolumab at 1 mg/kg + ipilimumab at 3 mg/kg Q3W (N1+I3) (N=49), or c) nivolumab at 3 mg/kg + ipilimumab at 1 mg/kg Q3W (N3+I1) (N=52). The primary endpoint was ORR, with duration of response (DoR), OS, PFS, and safety as secondary objectives.[8]

In total, 160 heavily pretreated patients (79% had ≥ 2 prior Tx) were enrolled in the study. The ORR was 12% in N3, 24% in N1+I3, and 8% in N3+I1. In patients with PD-L1 expression in at least 1% of cells, the ORR was 19% (3/16) in N3, 40% (4/10) in N1+I3, and 23% (3/13) in N3+I1. Patients with PD-L1 expression in less than 1% of cells had an ORR of 12% (3/26) in the N3 arm, 22% (7/32) in the N1+I3 arm and 0% (0/30) with N3+ I1 (*Figure 4*). The median DoR was 7.1 months in N3, 7.9 months in N1+I3, and was not yet reached in the N3+I1 arm. In general, overall responses were better with combination regimens; however, this usually came at the cost of an increased toxicity.[8]

In summary, nivolumab with or without ipilimumab led to durable responses and long-term OS results in heavily pretreated western patients with advanced G/E/GEJ cancer. This is consistent with the clinical activity observed in Asian patients in the ONO-12 study. Safety was also consistent with prior reports.

COLORECTAL CANCER

COMBINATION SIRT AND SYSTEMIC THERAPY: LIVER-PROVEN, BUT NO IMPACT ON OVERALL SURVIVAL

Van *Hazel et al.* recently published the results of the SIRFLOX study.[9] In this study, patients with metastatic colorectal cancer (mCRC) were in randomized between first-line treatment with FOLFOX with or without bevacizumab and the same combination plus SIRT. No difference in global PFS was detected. Nevertheless, a clear impact of SIRT on the liver was reported.[9]

A meta-analysis of three randomized clinical trials (SIRFLOX, FOXFIRE and FOXFIRE) presented at ASCO 2017 failed to support the use of SIRT in combination with first-line oxaliplatin and fluorouracil chemotherapy in patients with liver-only and liver-dominant metastatic colorectal cancer. The impact on the liver was confirmed with an increase in response and time to progression (TTP) in the liver for the combination with SIRT. Unfortunately, no difference in OS could be detected (23.3 *vs.* 22.6 months, HR[95%CI]: 1.04[0.90-1.19], p= 0.609).[10]

Despite increasing the likelihood of radiologic response and prolonging liver-specific PFS, SIRT added to first-line chemotherapy yielded no improvement in OR or PFS. Nevertheless, for patients in whom liver control is important, this strategy could be still be a valid option.

Is three months of adjuvant chemotherapy for colon cancer a good idea?

The results of the MOSAIC-trial set the standard for adjuvant therapy in stage III colon cancer, consisting of six months of oxaliplatin-based chemotherapy. A major drawback of this treatment is the oxaliplatin-related persisting neuropathy in 12.5% of patients treated with 6 months of FOLFOX. Therefore, the collaborative effort was started some years ago to answer the question whether 3 months of adjuvant therapy is sufficient.[11]

More than 12,800 patients were randomized in 6 concurrent-

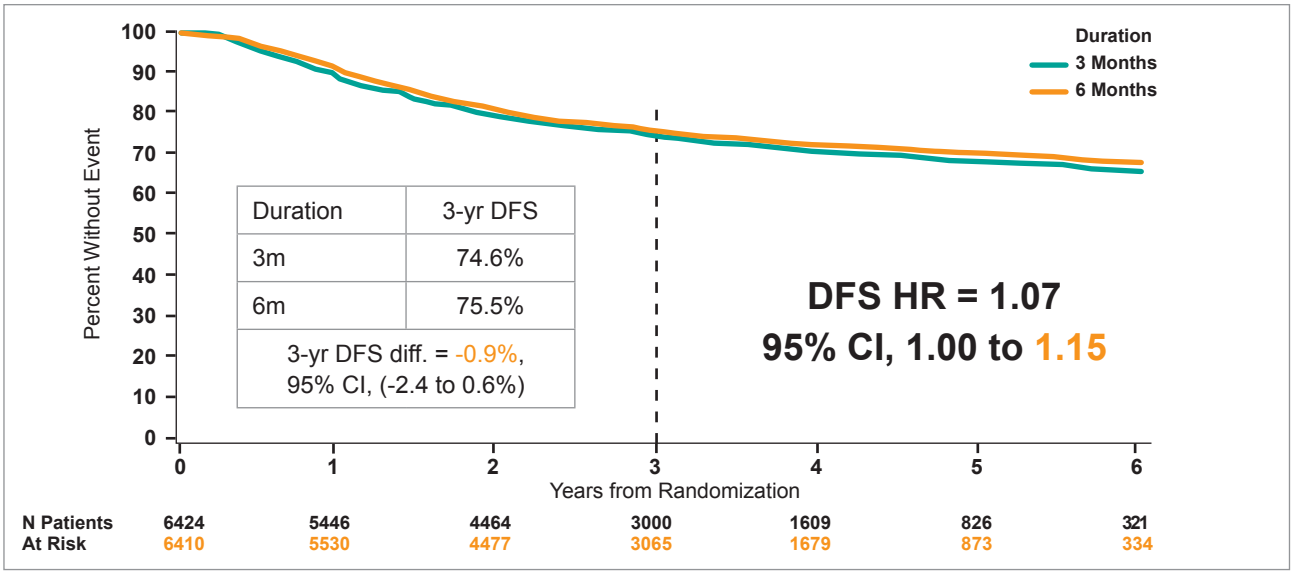

FIGURE 5. Primary DFS analysis in the IDEA study.[12]

ly conducted phase III randomized trials. The IDEA study was designed to prove non-inferiority of the 3-month adjuvant regimen as compared to the standard 6-month regimen. The primary endpoint was DFS. Although the curves were close to each other, the study failed to confirm non-inferiority for stage III patients (*Figure 5*). Patient and treatment heterogeneity might have an influence on the overall result. In fact, stage II & III patients were included in some of the trials in the meta-analysis, as well as colon and rectum primaries, while treatments included CAPOX, FOLFOX4 and mFOLFOX6.[11]

However, in a subgroup analysis comparable efficacy was shown for the 3- and 6-month regimens in the low-risk group ($pT_{1-3}N_1$) (*Figure 6*). Especially CAPOX showed comparable results. Still IDEA was not desiged to compare DFS between regimens and patients were not randomized between regimens. Hence there is a selection bias affecting DFS comparison between FOLFOX and CAPOX. As could be expected, the incidence of neurotoxicity was substantially lower with 3 months of adjuvant therapy, compared to 6 months. (17% *vs.* 48% for FOLFOX regimen and 15% *vs.* 45% for CAPOX).[11]

In conclusion, the trade-off between potential loss of DFS and reduced neurotoxicity should be considered in the decision on treatment duration. In daily clinical practice, it could be an option to start for 6 months and stop oxaliplatin after 3-4 months especially if patients prove to be intolerant. If we consider 3 months instead of 6 months, maybe we should select CAPOX and not FOLFOX given the fact that the cumulative oxaliplatin dose is higher per treatment period with CAPOX. Still, three *vs.* six months remains a statistically unanswered question; probably practice changing, but validating data are needed.

PRIMARY TUMOR LOCATION IS AN IN DEPENDED PROGNOSTIC MARKER FOR OS

SWOG 80405 found no OS or PFS) difference when bevacizumab or cetuximab was added to 1st-line FOLFOX or FOLFIRI in all RAS wild type mCRC patients. There was however, a significant biologic interaction (p interaction: OS= 0.008, PFS= 0.001) favoring patients with left-sided tumors

An interesting meta-analysis of the SWOG 80405 was presented at ASCO 2017. This analysis focused on the prognostic impact of primary tumor location (left vs right) when adjusted for age, gender, synchronous/metachronous, CMS, MSI and *BRAF* status. Data were available from 782 patients. Sidedness (R vs L) remained an independent prognostic marker even after adjusting for all these molecular features: HR[95%CI]: = 1.392[1.032-1.878], p= 0.031).[12]

These data again highlight the prognostic role of primary tumor location as an independent factor, giving a strong background for further analysis in this field.

INTEGRATING CONSENSUS MOLECULAR ANALYSIS IN TREATMENT DECISION IN MCRC?

At this ASCO the two well-known studies (CALGB80405 and FIRE3) comparing bevacizumab and cetuximab in the first-line treatment of mCRC, were once more the subject of an interesting ad hoc analysis focusing on the CMS-classification.[13,14]

In accordance with the data published by Guinney J *et al.* (Nat Med 2015;21:1350-6), the different prognostic CMS groups in both studies were confirmed.[13-15]

In the CALGB 80405 study CMS classification for 392 of 431

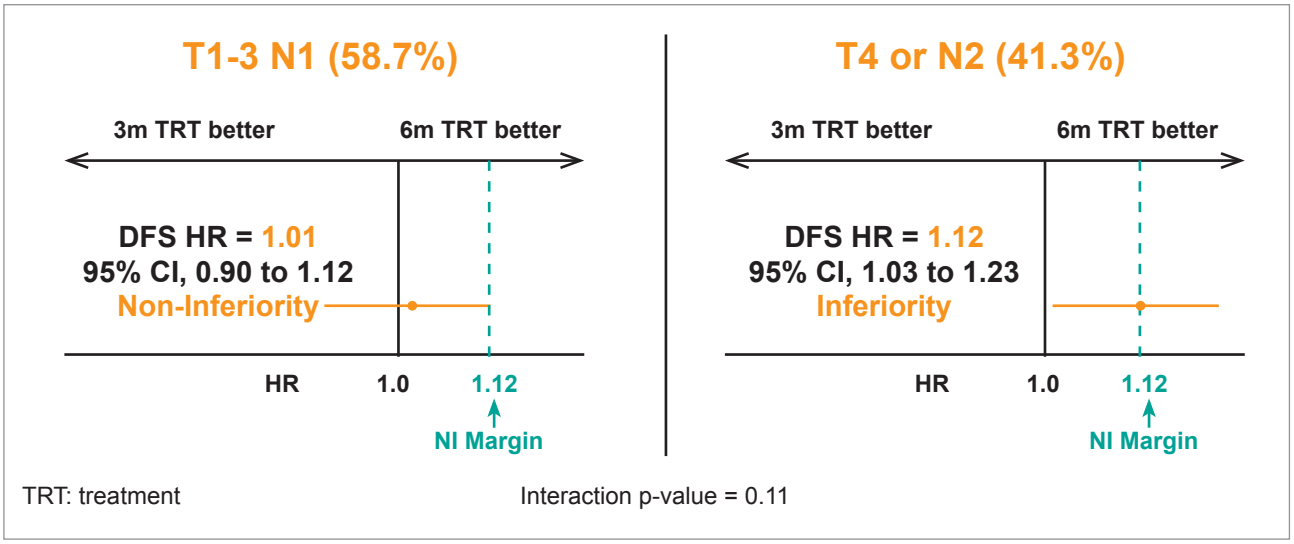

FIGURE 6. DFS comparison by risk group in the IDEA study.[12]

tumors was defined using a custom CRC Nanostring panel. Distribution of CMS subgroups was as follows: CMS1: 14%, CMS2: 47%, CMS3: 2%, CMS4: 29% and 8% of non-consensus cases. In right-sided tumors a higher incidence of CMS1 (37% *vs.* 9% in left-sided tumors) was reported, while CMS2 was more prevalent in left-sided tumors (48% *vs.* 23% in right-sided). The cohort with the CMS2 subtype had the best OS (median 40 months) and CMS1 had the worst median OS (15 months). Patients with CMS1 who received a combination including bevacizumab had significantly longer OS and DFS than those who received cetuximab, while patients with CMS2 who received bevacizumab tended to have shorter OS than those who received cetuximab (*Figure 8*). Primary tumor location remained an independent prognostic factor when adjusted for age, gender, synchronous/metachronous, CMS, MSI and *BRAF* status.[13]

The CMS data analysis from 313 RAS-wildtype patients included in the FIRE3 study, was based on ALMAC's Xcel tissue array. In this population, CMS frequencies were: CMS1: 10.4%, CMS2: 36.6%, CMS3: 11.7%, CMS4: 29.1% and non-consensus: 12.2%. These findings were in striking accordance with the frequencies reported in CALGB 80405 data. Similarly, CMS1 was again the prevalent subtype in right-sided tumors (59%). CMS2 tumors had the best response rates (RR: 76%) while CMS1 had the worst RR (54%). Survival data in terms of OS across the different subtypes were in agreement with

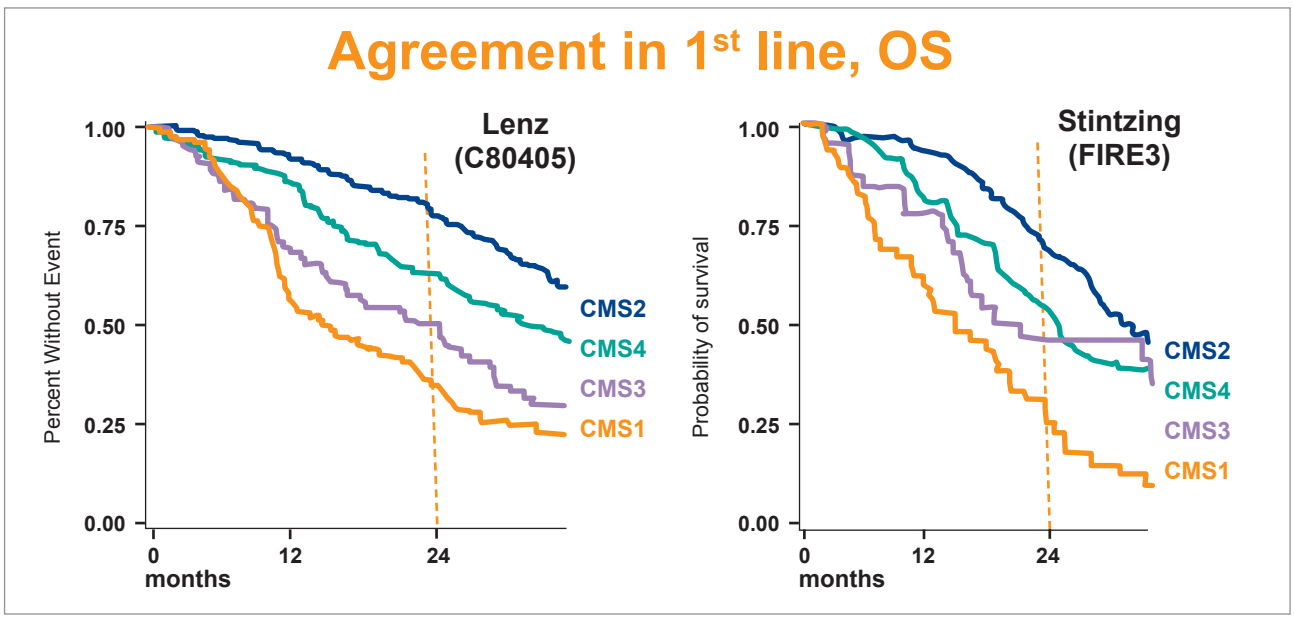

FIGURE 7. Striking agreement between CALGB 80405 and FIRE3 CMS analysis.[13,14]

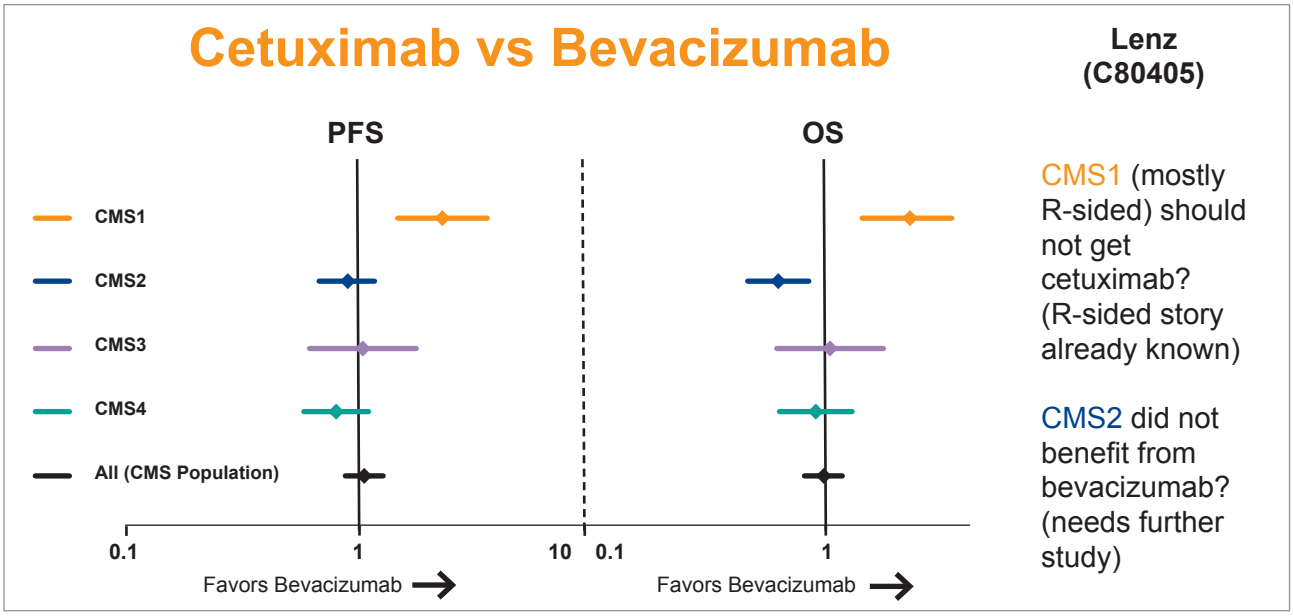

FIGURE 8. PFS and OS in function of the CMS subtype in FIRE3.[13]

what was reported in CALGB 80405: CMS2 had the best OS followed by CMS4, CMS3 and CMS1 in both trials (*Figure 7*).[14] The OS survival benefit induced by the cetuximab *vs.* the bevacizumab combination appears to be driven by CMS4 and to a lesser extent by the CMS2 subtype. No CMS subtype was favored by the bevacizumab combination, in contrast to the analysis of CALGB 80405. The authors concluded that there was no significant difference in survival benefit across CMS groups, in RAS wildtype patients treated with FOLFIRI cetuximab *vs.* FOLFIRI bevacizumab, although there were trends for different OS HRs between categories (with CMS4 showing the best HR) (*Figure 9*).

Summarizing the CMS reports from CALGB 80405 and FIRE-3, we conclude that there was high consistency between both analyses (*Figure 7*). We should still notice that the analysis was performed by the same bioinformatics group (SWISS institute). Furthermore, we cannot separate prognosis from prediction as every patient received 5FU and other agents. The analyses did yield some signals for differences between FOLFOX and FOLFIRI, or cetuximab *vs.* bevacizumab

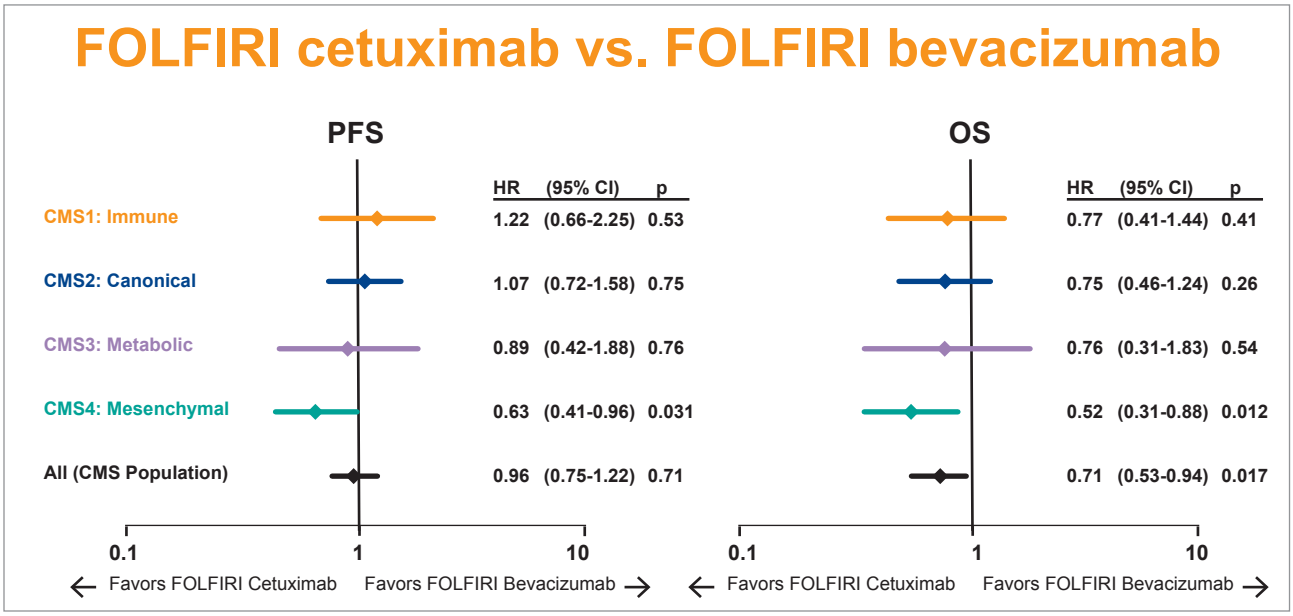

FIGURE 9. FOLFIRI cetuximab vs. FOLFIRI bevacizumab per CMS category in FIRE3.[14]

KEY MESSAGES FOR CLINICAL PRACTICE

1. Upper gastrointestinal cancers:

- Sandwich with FLOT in upper GI? YES
- Adjuvant capecitabine in biliary tract cancer? Probably YES
- Levantinib in HCC: possible OPTION
- SIRS in HCC: useful LOCALLY

2. Lower gastrointestinal cancers:

- SIRS in mCRC: LOCALLY
- Three months adjuvant therapy in mCRC: Yes for some
- Classification in mCRC: prognostic relevance

in the different subtypes. However, these data are immature and currently we do not see clinical applicability of these results. However, future trials should consider incorporating CMS subtypes in their design and these data confirm the prognostic role of CMS classification in mCRC.

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