Highlights in digestive oncology

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This report will focus on some of the key studies in the field of digestive oncology, presented during the 2019 annual ESMO meeting. During the congress, many studies were presented from early phase I to large phase III trials. Different approaches to activate the immune system against tumours as well as PARP and CDK4/6 inhibitors were once more at the centre of interest for different types of cancer and settings.

COLON CANCER

The findings of the IDEA trial (adjuvant three *versus* six months of chemotherapy) in stage III colon cancer were initially presented at the 2017 ASCO annual meeting followed by a subsequent analysis in the high-risk stage II subset presented at ASCO 2019, earlier this year. Although the study did not confirm non-inferiority of three *versus* six months of adjuvant FOLFOX or CAPOX in the overall population, it showed that three months of CAPOX can be sufficient, especially in lower-risk patients. Therefore, there is an urgent need for better biomarkers to determine the ideal duration of adjuvant chemotherapy in colon cancer. In this respect, an interesting analysis was presented by *Prof. Julien Taieb*, focusing on the role of circulating tumour DNA (ctDNA) as a potential prognostic and predictive marker for treatment duration (three or six months) for patients with resected stage II and III colon cancer. The analysis was based on the data of the IDEA-FRANCE trial in which ctDNA was collected. ctDNA was tested by using the detection of 2 methylated markers (WIF1 and NPY) by digital droplet PCR. Of the 1,345 (out of 2,010) patients that consented to the IDEA translational research program, 696 patients were ctDNA negative and 109 ctDNA positive (13.5%). ctDNA positive patients more frequently had T4 disease, were more likely to have poorly differentiated tumours and more frequently had tumour perforation. The 2-year disease free survival (DFS) was 64% *vs.* 82% in ctDNA positive and negative patients, respectively (HR: 1.75, p=0.001). ctDNA proved to be an independent prognostic marker in multivariate analysis including parameters like age, gender, MSI, perforation, T stage, N stage and treatment arm (adjusted HR[95%CI]: 1.85[1.31-2.61], p<0.001). Adjuvant treatment for six months was superior to three months in both ctDNA negative (HR[95%-CI]: 0.69[0.52-0.93], p=0.015) and ctDNA positive patients (HR[95%CI]: 0.50[0.27-0.95], p=0.033). Interestingly, ctDNA positive patients treated for six months had a similar prognosis to ctDNA negative patients treated for three months (*Figure 1*). Patients with advanced colon cancer and ctDNA positivity who received oxaliplatin-based adjuvant therapy were less likely to be disease free at two years than patients with ctDNA negative samples. This represents the first ctDNA analysis done on a large series of patients in a phase III adjuvant clinical trial to find 13.5% of patients with ctDNA post-surgery and also the first report of the predictive value of ctDNA in this setting.[1]

In the HERACLES-A trial, *Sartore-Bianchi et al.* were the first to show that a dual blockade of HER2 (trastuzumab and lapatinib) is effective in metastatic colorectal cancer (mCRC) patients harbouring *HER2* amplification. At ESMO 2019, the same group presented results of the open-label phase II HERACLES-B study, which is a follow-up study of HERACLES-A. The study evaluated the combination of pertuzumab with T-DM1 as a potential treatment approach for *HER2* amplified mCRC. The HERACLES-B trial enrolled 30 patients with *RAS/BRAF* wild-type *HER2* amplified mCRC with progression following treatment with 5-FU, oxaliplatin, irinotecan and anti-EGFR containing regimens. Overall response rate (ORR) and progression-free survival (PFS) were the primary

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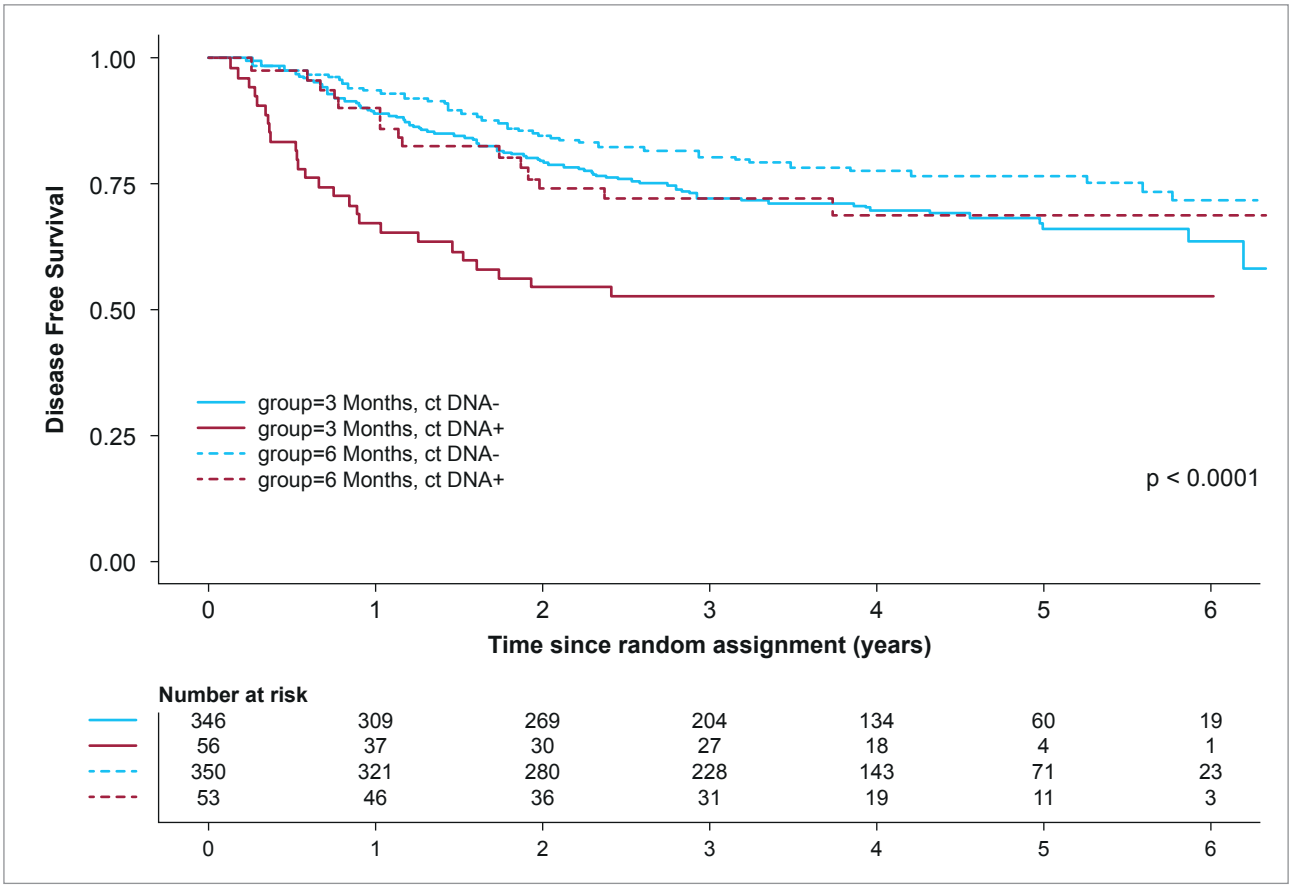


FIGURE 1. Disease free survival in the IDEA-FRANCE phase III trial.[1]

and secondary endpoint of the trial. The ORR was 10% (while 30% in HERACLES-A) with an additional 70% of patients achieving stable disease (SD). The median PFS was reported at 4.8 months (95%CI: 3.6-5.8). A higher HER2 IHC score (3+ *vs.* 2+) turned out to be associated with a higher chance of having an objective response or SD ≥4 months (p=0.03). Although HERACLES-B did not reach its primary endpoint, disease control was achieved in 80% of patients with a median PFS of 4.8 months. As such, this result is better than the 4.2 months median PFS reported in the positive HERACLES-A trial. However, further research is warranted to determine why response rates are lower than in the HERACLES-A trial.[2] One of the ground-breaking studies in colon cancer presented in 2019 consists of the BEACON trial. This study showed for the first time that a combination of three targeted agents (encorafenib, binimetinib and cetuximab) improves the outcome of *BRAF*^{V600E} mutated metastatic colon cancer patients who have failed first-line treatment. Updated results based on 444 randomised patients were presented and showed that the triplet combination was associated with an increased median overall survival (OS) (9.0 *vs.* 8.4 months; HR[95%CI]: 0.79[0.59–1.06]) and a higher ORR (26 *vs.* 20%) compared with the doublet encorafenib and cetuximab. However, the study was not powered to formally compare the results of the triplet *versus* the doublet combination. Future studies should explore the need of either triplets or doublets depending on the biology of the *BRAF* mutated tumour as we know that *BRAF* mutated CRC is a very heterogeneous group.[3]

OESOPHAGEAL CANCER

Therapeutic options in the treatment of metastatic oesophageal squamous cell carcinoma (ESCC) are limited. Previous studies, such as Keynote-181, evaluated the use of the PD-1 inhibitor pembrolizumab as a second-line treatment for patients with oesophageal cancer (both squamous and adenocarcinoma). Notwithstanding the fact that these trials were negative, they did show promising findings in the subgroup of squamous patients. Results of the phase III ATTRACTION-3 study, comparing nivolumab (NIVO) with standard chemotherapy (CT) in patients with unresectable advanced or recurrent ESCC refractory or intolerant to 1 prior fluoropyrimidine/platinum-based chemotherapy, were therefore eagerly awaited. In this trial, 419 patients were randomised (1:1) to nivolumab or CT regardless of PD-L1 expression. The primary endpoint of this trial was OS. Nivolumab significantly improved the OS *vs.* CT (HR[95%CI]: 0.77[0.62–0.96], p=0.02]; median

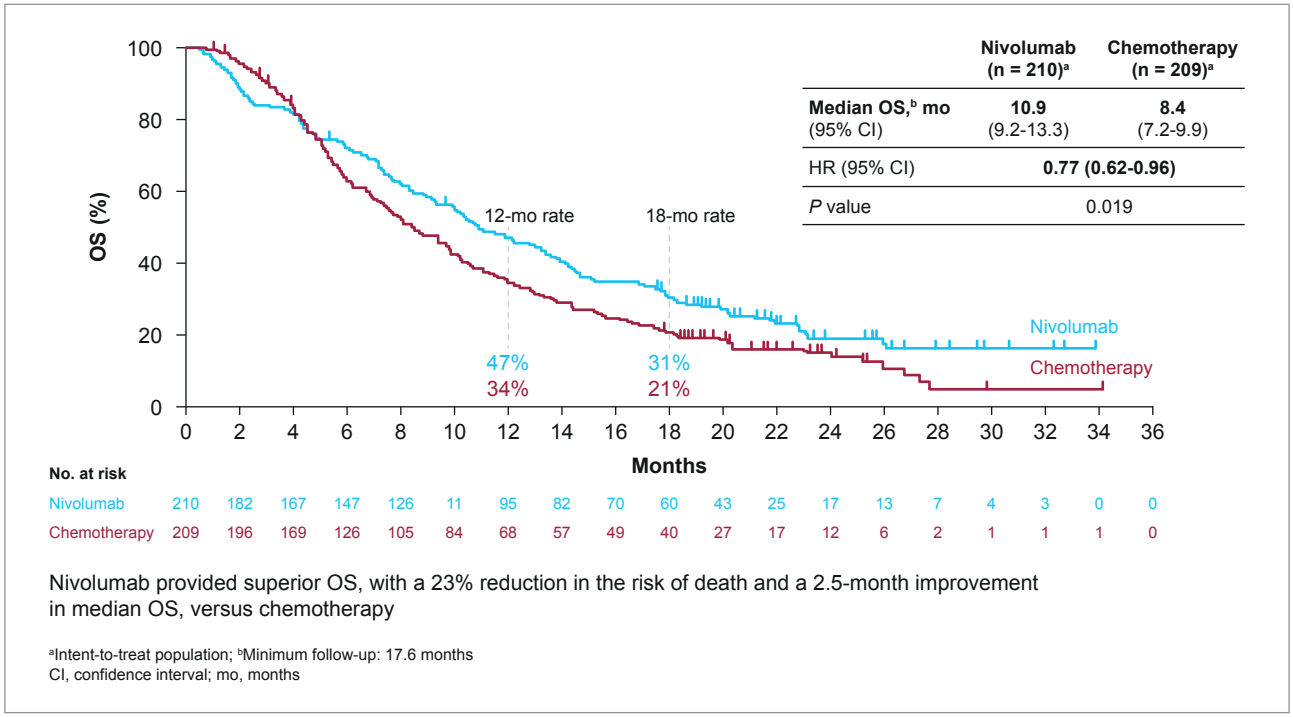


FIGURE 2. Overall survival in the ATTRACTION-3 trial.[4]

OS, 10.9 *vs.* 8.4 months) (*Figure 2*) and this benefit was consisted across pre-specified subgroups, including tumour PD-L1 expression. HRs for the risk of death favoured nivolumab over CT across all tumour PD-L1 expression levels (PD-L1 ≥1%, HR [95% CI]: 0.69 [0.51-0.94]; PD-L1 <1%, HR[95%CI]: 0.84 [0.62-1.14]). Nivolumab and chemotherapy had comparable ORRs, but the responses proved to be more durable with nivolumab. In addition, nivolumab induced a significant overall improvement in quality of life (QoL) of patients compared to CT through on-treatment week 42 in both the EQ-5D visual analogue scale and EQ-5D utility index. It can therefore be concluded that nivolumab represents a potential new standard second-line treatment option for patients with advanced ESCC.[4]

LIVER AND BILE DUCT CANCER

Currently available treatment options for hepatocellular carcinoma (HCC) consist of sorafenib and lenvatinib in first-line

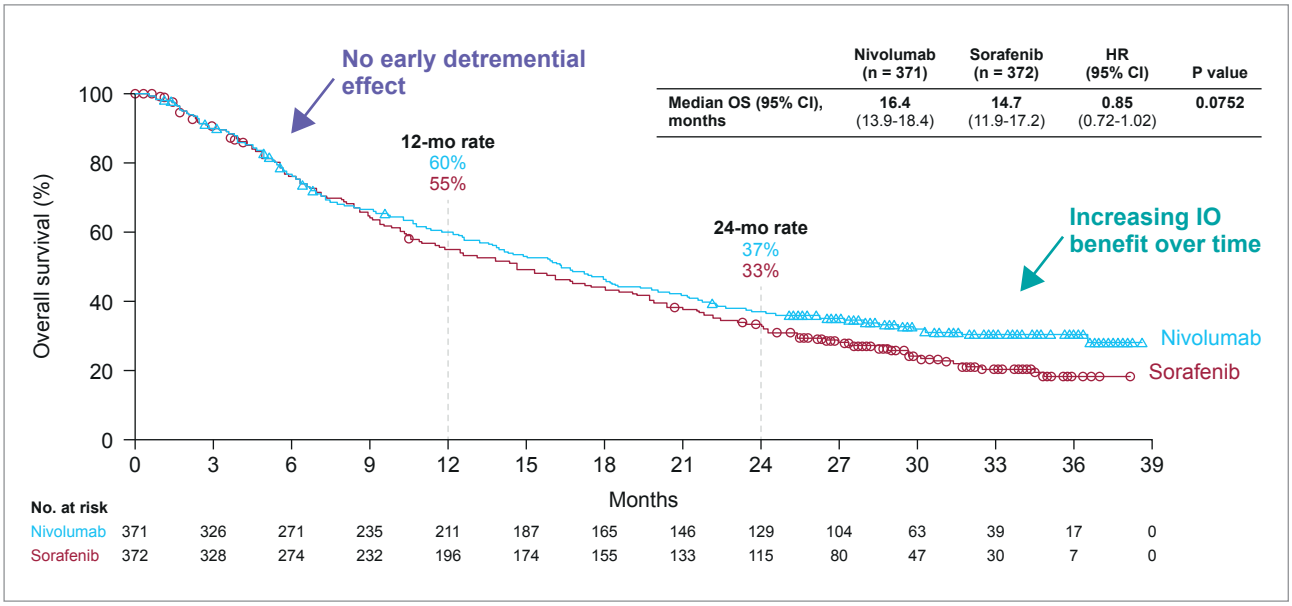
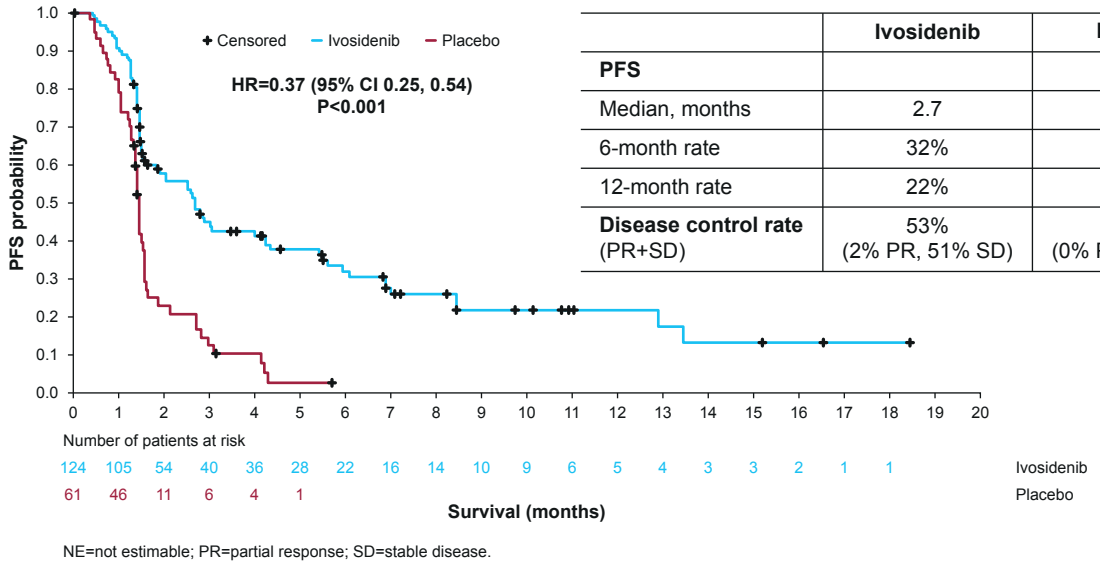


FIGURE 3. Overall survival in the CheckMate-459 trial.[5]



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

NE=not estimable; PR=partial response; SD=stable disease.

FIGURE 4. Progression-free survival by ICR in the ClarIDHy trial.[8]

and regorafenib, cabozantinib and ramucirumab in second-line. Emerging data also suggest a place for immunotherapy in the treatment of HCC. Both the Keynote-224 (pembrolizumab in second-line after sorafenib) and CheckMate-040 (nivolumab both in sorafenib naïve and in treated patients) trials showed promising response rates with checkpoint inhibitors in this disease. Recently, the phase III Keynote-240, evaluating pembrolizumab *versus* best supportive care in the second-line treatment for advanced HCC, was presented at ASCO 2019 and showed a higher ORR but no statistically significant difference in OS. At ESMO 2019, the results from the CheckMate-459, a randomised phase III study of nivolumab *versus* sorafenib as first-line treatment in patients with advanced HCC, were presented. Although OS did not meet the predefined threshold of statistical significance (HR: 0.84, p= 0.0419), the reported median OS (16.4 months) was the longest ever seen in a first-line phase III trial in HCC *(Figure 3)*. PD-L1 expression did not seem to be a good predictive marker in this study.[5]

Promising phase Ib data were also presented with a combination of atezolizumab (anti-PD-L1) and bevacizumab in HCC with impressive response rates (12% CR, 24% PR, 35% SD). A phase III trial is ongoing and was recently announced to be positive, but no further details are currently available.[6]

Finally, targeted treatment is finding its way in the treatment of advanced cholangiocarcinoma. Data from FIGHT-202, a phase II study of the FGFR inhibitor pemigatinib in patients with previously treated advanced cholangiocarcinoma, were presented. *FGFR2* fusions or rearrangements are almost exclusively found in intrahepatic cholangiocarcinoma (iCCA) and present in 10-16% of patients with iCCA in the United states and Europe. The trial demonstrated durable objective responses to pemigatinib in more than one-third of patients with an *FGFR2* rearrangement or fusion. The ORR was 35.5% with a median duration of response of 7.5 months. A phase III study is ongoing in the first-line setting to evaluate pemigatinib *versus* gemcitabine plus cisplatin in patients with cholangiocarcinoma and *FGFR2* fusions or rearrangements (NCT03656536).[7]

In one of the presidential sessions of ESMO 2019, *Prof. Juan Valle* presented the results of the phase III ClarIDHy trial, evaluating the efficacy of targeted therapy with ivosidenib, a first-in-class oral small-molecule inhibitor of the mutant IDH1 protein in 185 patients with unresectable or metastatic *IDH1*-mutant cholangiocarcinoma. Patients in the trial were randomised (2:1) to ivosidenib (IVO) or matched placebo and stratified by the number of prior systemic therapies. Crossover from placebo to IVO was permitted at radiographic disease progression and PFS was the primary endpoint of the study. The primary endpoint was met with a median PFS of 2.7 *vs.* 1.4 months for IVO and placebo, respectively (HR[95%CI]: 0.37[0.25-0.54]; p<0.001) *(Figure 4)*. PFS rates with IVO at 6 and 12 months were 32.0% and 21.9%, respectively. The ORR for IVO was 2.4% (3 PRs), with 50.8% SD (N=63) *vs.* 0% ORR in placebo with 27.9% SD (N=17). In the intent-to-treat analysis, the median OS was 10.8 months for IVO as compared to 9.7 months for placebo (HR: 0.69; one-sided p=0.06). Of note, 57% of placebo-treated patients crossed over to IVO. The toxicity profile was acceptable. In conclusion, IVO resulted in a significant improvement in PFS

KEY MESSAGES FOR CLINICAL PRACTICE

1. ctDNA post-surgery has potential as a predictive marker for oxaliplatin-based adjuvant therapy in patients with stage III colon cancer.
2. In a phase II trial, pertuzumab plus T-DM1 associated with DCR of 80% and a median PFS of 4.8 months in patients with *HER2* amplified mCRC.
3. Encorafenib, binimetinib plus cetuximab is associated with an increased median OS and a higher ORR compared with encorafenib and cetuximab in *BRAF*^{V600E} mutated metastatic colon cancer.
4. Nivolumab significantly improves the OS compared to chemotherapy in patients with unresectable advanced or recurrent ESCC refractory or intolerant to 1 prior fluoropyrimidine/platinum-based chemotherapy.
5. CheckMate-459 did not show a significantly longer OS with nivolumab than with sorafenib in the first-line treatment of patients with advanced HCC. However, the reported median OS of 16.4 months was the longest ever seen in a first-line phase III trial in HCC.
6. Promising phase I data were reported with a combination of atezolizumab and bevacizumab in patients with advanced HCC.
7. Pemigatinib is associated with an ORR of 35.5% and a median duration of response of 7.5 months in patients with *FGFR2*-fusion positive advanced cholangiocarcinoma.
8. Ivosidenib resulted in a significant improvement in PFS with a favourable trend in the OS compared to placebo in unresectable or metastatic *IDH1*-mutant cholangiocarcinoma.

with a favourable trend in the OS *vs.* placebo. These pivotal data demonstrate the clinical relevance and benefit of ivosidenib in *IDH1*-mutant cholangiocarcinoma and establish the role of genomic testing in this rare cancer type with a high unmet need. Given the limited effective therapeutic options for cholangiocarcinoma, the incidence of up to 20% of *IDH1* mutations in this disease and the poor prognosis of patients with this mutation, molecular profiling and ivosidenib as a standard later line treatment option for this population must be considered.[8]

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