

World Journal of *Gastroenterology*

World J Gastroenterol 2021 July 28; 27(28): 4484-4745



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The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; Production Department Director: *Yu-Jie Ma*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

July 28, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Recent advances in gastrointestinal cancers

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Author contributions: Bordry N, Astaras C and Koessler T designed the study and wrote the manuscript; Ongaro M, Goossens N and Frossard JL reviewed and corrected the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: No conflict of interest.

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Manuscript source: Unsolicited manuscript

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Abstract

Gastrointestinal cancers occur in a total of eight different locations, each of them with a different standard of care. This article is not an exhaustive review of what has been published in 2020. We have concentrated on the thirteen phase III randomized studies that are practice-changing. All these studies are oral presentations which have been given in one of the four major oncology congresses, namely American Society of Clinical Oncology (ASCO), ASCO gastrointestinal (GI), European Society of Medical Oncology (ESMO) and ESMO-GI. We provide a concise view of these major trials and their main outcomes, and put these results into context.

Key Words: Practice changing trials; Immunotherapy; Gastrointestinal cancers; Gastrointestinal; Gastric cancer

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Core Tip: Gastrointestinal cancers are one of the most frequent cancers and a leading cause of cancer deaths worldwide. Gastroenterologists, hepatologists and visceral surgeons interact daily with these patients. Bringing the community up to speed with new treatment paradigms in gastrointestinal oncology could improve patient care. Here we provide a clear, comprehensive and short overview of the most important practice changing trials from 2020.

Citation: Bordry N, Astaras C, Ongaro M, Goossens N, Frossard JL, Koessler T. Recent advances in gastrointestinal cancers. *World J Gastroenterol* 2021; 27(28): 4493-4503

URL: <https://www.wjgnet.com/1007-9327/full/v27/i28/4493.htm>

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Switzerland

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 28, 2021

Peer-review started: January 28, 2021

First decision: March 29, 2021

Revised: April 11, 2021

Accepted: July 5, 2021

Article in press: July 5, 2021

Published online: July 28, 2021

P-Reviewer: Lang SA

S-Editor: Gao CC

L-Editor: Webster JR

P-Editor: Wang LL



DOI: <https://dx.doi.org/10.3748/wjg.v27.i28.4493>

INTRODUCTION

Gastrointestinal cancers are the most common form of cancer, affecting both men and women. A multidisciplinary approach is critical to ensure the most effective treatment and best care for each individual patient. 2020 has been a significant year with regard to gastrointestinal cancers, with many practice-changing trials taking place. Here, we aim to provide a clear, comprehensive and brief overview of highlights in the care of gastrointestinal cancer in 2020.

GASTROEOSOPHAGEAL CANCER

Neoadjuvant

Human epidermal growth factor receptor 2 (HER2) inhibition by trastuzumab and chemotherapy has shown clinically and statistically significant improvements in disease-free survival (DFS) and overall survival (OS) in HER2-positive advanced gastroesophageal cancer compared to chemotherapy alone and is now the standard of care for these patients[1].

NRG-RTOG 1010, presented at American Society of Clinical Oncology (ASCO) 2020, was an open-label randomized phase III trial including 203 patients with newly diagnosed HER2-positive (immunohistochemistry 3+ or FISH positive) esophageal cancer (EC) or gastroesophageal junction (GEJ) cancer[2]. Patients were randomized to receive trimodal standard of care (chemotherapy, radiotherapy and surgery) with or without trastuzumab. Participants in the standard of care arm received chemoradiation therapy (CXRT) for 6 wk followed by surgery. Participants on the experimental treatment arm received weekly neoadjuvant trastuzumab during CXRT followed by adjuvant trastuzumab for 13 treatments after surgery. The primary endpoint of the trial was DFS. The median DFS was 14.2 mo in the standard of care arm and 19.6 mo in the experimental arm with a hazard ratio (HR) 0.97 (0.69, 1.36) and $P = 0.85$. OS was similar in both arms, 38.9 mo *vs* 38.5 mo in the experimental arm. Pathological complete response was equivalent in both arms: 29% *vs* 27% in the experimental arm.

Impact: HER2 inhibition is currently not recommended in the neoadjuvant setting for localised HER-2 amplified EC or GEJ cancer.

CXRT improves local control and survival in EC; however, local recurrence will occur in 50% of patients.

The ARTDECO trial presented at ASCO-GI 2020 was a randomised phase III multicentre study which randomised 260 patients with locally advanced unresectable EC (93%) and GEJ cancer (7%)[3]. Patients were treated with a standard dose of 50.4 Gy/1.8 Gy/5.5 wk to the tumor and regional lymph nodes *vs* the same dose combined with an integrated boost of 0.4 Gy per fraction (total 61.6 Gy) to the primary tumor. Chemotherapy consisted of 6 weekly concurrent carboplatin and paclitaxel in both arms. The primary endpoint was local progression-free survival (LPFS). There was no statistical difference in 3-year LPFS with 71% in the standard arm *vs* 73% in the experimental arm, nor was there a statistically significant difference in OS, with 41% *vs* 40% for the standard arm and experimental arm, respectively. LPFS was similar per histology. Overall grade 4 and 5 toxicity was 12% and 4% in the standard arm *vs* 14% and 10% in the experimental arm.

Impact: Radiation dose escalation in definitive CXRT treatment for locally advanced EC does not improve local control or OS.

Adjuvant

The risk of recurrence after neoadjuvant CXRT followed by surgery remains high, > 50% during the first 2 years in EC and GEJ cancer[4]. Currently there is no established adjuvant treatment in this setting. Nivolumab – an anti-PD1 checkpoint inhibitor – demonstrated superior survival in previously treated unresectable advanced or recurrent esophageal squamous cell carcinoma (ESCC) *vs* chemotherapy (ATTRACTION-3 trial)[5] and in gastric cancer (GC)/EGJ cancer *vs* placebo (ATTRACTION-2 trial)[6].

The CheckMate 577 study presented at European Society of Medical Oncology (ESMO) 2020 and recently published in the New England Journal of Medicine was a randomised, double-blind phase III study, evaluating nivolumab *vs* placebo in the adjuvant setting after trimodal therapy for EC and GEJ cancer[7]. Following R0 resection, 794 patients with stage II (approximately 35%) or III (approximately 65%), EC (approximately 60%) and EGJ cancer (approximately 40%) and residual pathologic disease were randomised to receive nivolumab for one year or placebo. Most patients (approximately 70%) had adenocarcinomas. The primary endpoint was DFS. At a pre-specified interim analysis, adjuvant nivolumab showed an improved DFS of 22.4 mo compared to 11 mo in the placebo arm with HR = 0.69 (0.56-0.86) and $P = 0.0003$. Treatment-related adverse events (TRAEs) occurred in 13% of the nivolumab arm *vs* 6% in the placebo arm (Figure 1), patient-reported outcomes were similar in both arms.

Impact: Nivolumab is the first adjuvant therapy to provide a reduction in the risk of recurrence or death in resected EC/GEJ cancer with residual disease after trimodal treatment. These results establish nivolumab as a new standard of care in these patients.

Advanced/metastatic

Patients with inoperable or metastatic GC have a median OS of less than 1 year[8,9]. Currently, these patients are treated with doublet chemotherapy which has improved OS and quality of life (QoL) compared to single-agent chemotherapy or best supportive care alone[10,11].

The CheckMate 649 trial, presented at ESMO 2020, evaluated in an open label, randomised phase III trial the efficacy of nivolumab in the treatment of previously untreated, unresectable advanced or metastatic GC/EGJ cancer and esophageal adenocarcinoma[12]. A total of 1581 patients were treated with nivolumab plus chemotherapy (FOLFOX or XELOX) or chemotherapy alone. Programmed cell death ligand 1 (PD-L1) protein expression in gastric or GEJ adenocarcinoma is determined by using the combined positive score (CPS), which is the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if $CPS \geq 1$. Primary outcomes were OS and PFS in patients with $CPS > 5\%$. OS in $CPS > 5\%$ was 14.4 mo in the nivolumab and chemotherapy arm *vs* 11.1 mo in the chemotherapy arm alone with HR: 0.71 (0.59-0.86, $P < 0.0001$) (Figure 2A). PFS in $CPS > 5\%$ was 7.7 mo in the experimental arm *vs* 6 mo ($P < 0.0001$) in the control arm (Figure 2B). A statistically significant benefit was also seen with nivolumab when assessing OS and PFS in patients with PD-L1 $CPS \geq 1\%$ and the overall randomised population. Serious TRAEs occurred in 22% of the experimental arm *vs* 12% in the control arm.

The ATTRACTION-4 trial, presented at ESMO 2020, was a double-blind, phase III randomised trial evaluating the combination of nivolumab with chemotherapy (SOX or CAPOX) *vs* chemotherapy alone in GC/EGJ cancer[13]. Primary outcomes were PFS and OS. At an interim-analysis, median PFS was improved in the experimental arm at 10.45 mo *vs* 8.34 mo, HR: 0.68 (0.51-0.90) and $P = 0.0007$. However, OS was comparable in both arms 17.45 mo *vs* 17.15 mo in the experimental arm ($P = 0.257$).

The Keynote 590 study, presented at ESMO 2020, was a double-blind, placebo-controlled study evaluating pembrolizumab (anti-PD-1) plus chemotherapy (cisplatin and 5FU) *vs* placebo plus chemotherapy as first-line treatment for locally advanced unresectable or metastatic AEC or ESCC or advanced/metastatic EGJ Siewert I adenocarcinoma[14]. Primary outcomes were OS in ESCC with $CPS > 10\%$ and whole population and PFS in the whole population. The majority of subjects (approximately 70%) had ESCC, AEC represented approximately 15% and EGJ approximately 12% of the study population. OS was significantly increased in the experimental arm in ESCC with $CPS > 10\%$ with a median OS of 13.9 mo *vs* 8.8 mo in the control arm ($P < 0.0001$) as well as in the ESCC overall population with OS of 12.4 mo *vs* 9.8 mo ($P = 0.0006$). PFS in ESCC was significantly increased in the experimental arm with 6.3 mo *vs* 5.8 mo ($P < 0.0001$).

Impact: The combination of PD-1 blockage (nivolumab or pembrolizumab) with chemotherapy could be considered a new standard first-line option for advanced or metastatic ESCC $CPS > 10\%$, GC and EGJ $CPS > 5\%$.

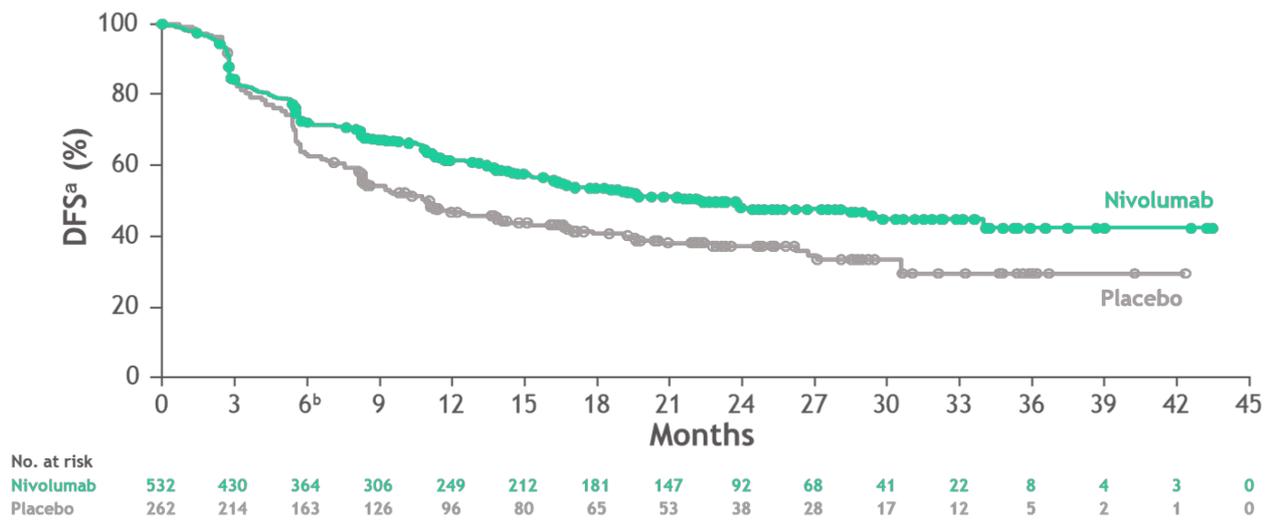


Figure 1 Disease-free survival in the study population (CheckMate 577). Citation: Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, Uronis H, Elimova E, Grootsholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM, Moehler M; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med* 2021; 384(13): 1191-1203. Copyright ©The Authors 2021. Published by Massachusetts Medical Society[7]. DFS: Disease-free survival.

HEPATOCELLULAR CARCINOMA

Advanced/metastatic

For the last 10 years the first-line treatment of unresectable hepatocellular carcinoma (HCC) was sorafenib. In 2018, lenvatinib showed its non-inferiority compared to sorafenib, offering a second option in first-line treatment[15].

The IMbrave150 trial was an open-label, phase III trial. Patients with unresectable HCC and without previously systemic treatment were randomly assigned to receive either atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) or sorafenib[16]. All patients were Child-Pugh A and the aetiology of underlying liver disease was viral hepatitis in approximately 70% of the study population. The co-primary endpoints were OS and PFS. At the first interim analysis, OS at 12 mo was 67.2% in the experimental arm and 54.6% in the standard arm with HR 0.58 (0.42-0.79, $P < 0.001$). Median PFS was 6.8 mo in the experimental arm *vs* 4.3 mo ($P < 0.001$). Grade 3 or 4 adverse events occurred in 56.5% in the experimental arm and in 55.1% in the control arm. Moreover, this combination delayed the deterioration of patient-reported functioning and QoL *vs* sorafenib in this patient population to a meaningful degree.

Impact: Atezolizumab + bevacizumab is now considered first-line standard of care therapy in patients with unresectable HCC.

COLON CANCER

Adjuvant

For stage III colon cancer, the addition of oxaliplatin to a fluoropyrimidine improved DFS and OS in the adjuvant setting. Since 2004, a 6-mo regimen of FOLFOX or CAPOX is the standard adjuvant therapy in stage III disease[17-19]. However, oxaliplatin is associated with cumulative neurotoxicity that can be severe, which potentially affects patients' activities of daily living, and can persist long beyond the actual treatment. If efficacy were maintained, shorter adjuvant therapy duration would be beneficial for patients as it could spare them toxic effects and health expenditures.

An international duration evaluation of adjuvant therapy trial investigated the non-inferiority of 3 mo of adjuvant therapy (either FOLFOX or CAPOX) compared to 6 mo of treatment[20]. The primary endpoint was the rate of DFS at 3 years. Non-inferiority of 3 mo of therapy, as compared to 6 mo, was not confirmed in the overall population. However, in patients treated with CAPOX, 3 mo of therapy was as effective as 6 mo, particularly in the lower-risk subgroup.

At this year's ASCO, Sobrero *et al*[21] presented the OS (secondary outcome) and an update of the DFS (median follow-up of 6 years). Again non-inferiority of OS for 3 mo

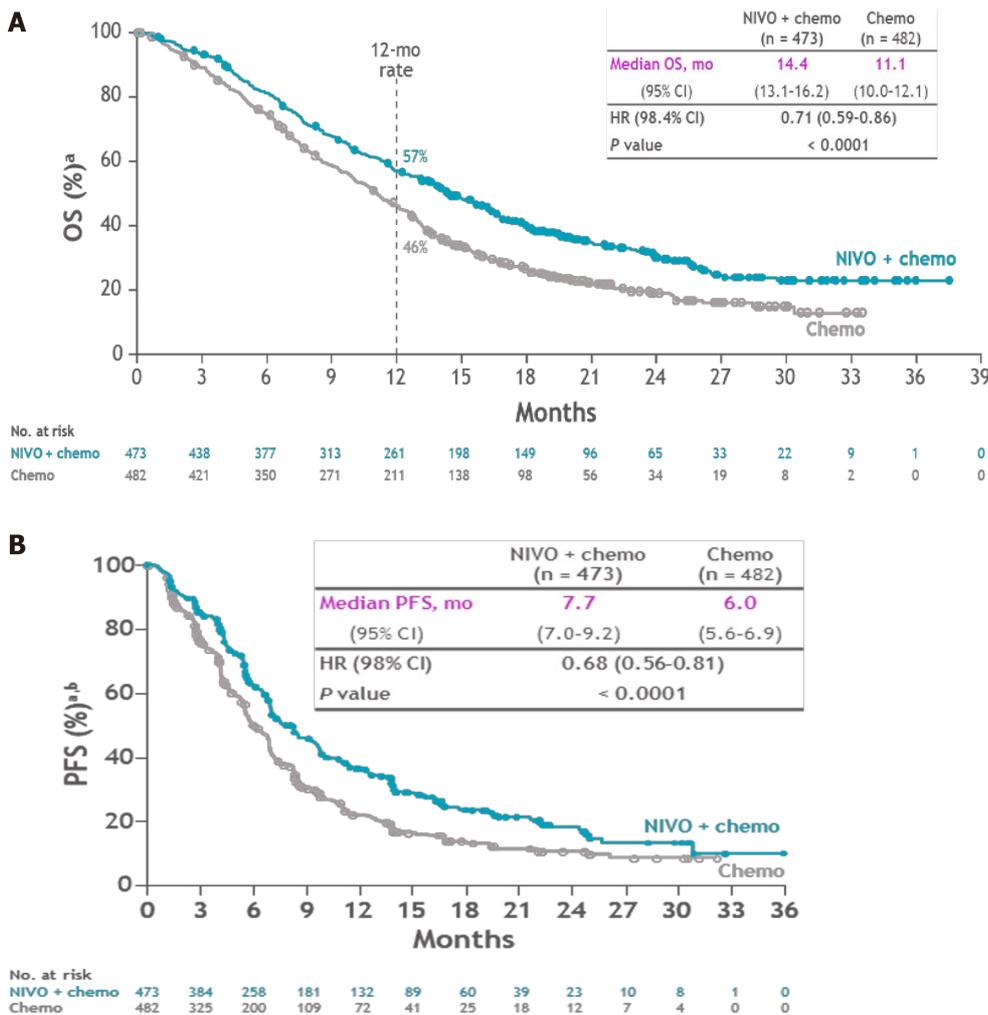


Figure 2 Overall survival and progression-free survival in patients with programmed cell death ligand 1 combined positive score of more than 5% (CheckMate 649). A: Overall survival; B: Disease-free survival. Citation: Moehler M, Shitara K, Garrido M, Salman P, Shen L, Wyrniewicz L, Yamaguchi K, Skoczylas T, Bragagnoli AC, Liu T, Schenker M, Yanez P, Tehfe M, Poulart V, Cullen D, Lei M, Kondo K, Li M, Ajani JA, Janjigian YY. Nivolumab (nivo) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. *Ann Oncol* 2020; 31(4): S1191. Copyright ©The Author(s). Published by European Society of Medical Oncology[12]. PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival.

(82.4%) vs 6 mo (82.8%) treatment was not demonstrated ($P = 0.0583$). OS was 82.1% for patients treated with 3 mo of CAPOX compared to 81.2% in those receiving it for 6 mo. In patients treated with FOLFOX, 3 mo survival was 82.6% compared to 83.8% for 6 mo survival (Figure 3A). Five-year DFS was 70% for 3 mo CAPOX compared to 69.3% for 6 mo and 68.4% for 3 mo FOLFOX compared to 71.7 for 6 mo (Figure 3B). Finally, for low risk (T1-3, N1) cancers, OS with 3 mo treatment was 89.6% compared to 88.9% for 6 mo. In high risk (T4 / N2) cancers, OS was 72% for 3 mo and 74.1% for 6 mo.

Impact: Stage III low risk colon cancer can be treated with either 6 mo FOLFOX or 3 mo CAPOX. High-risk stage III colon cancer can be treated with 6 mo FOLFOX or 6 mo CAPOX, although the difference in clinical benefit between 3 and 6 mo CAPOX is small.

Follow-up

In colon cancer, 30%-50% of all patients will relapse and die of the disease. Intensive follow-up of patients after curative surgery to detect recurrence and/or metachronous cancers is recommended[22]. However, these recommendations are based on expert opinions, and clinical trials have shown contrasting results[23]. A Cochrane meta-analysis showed no survival benefit of intensive follow-up[24]. Which tests should be performed and what the optimal frequency for surveillance of cancer recurrence might be are still unknown.

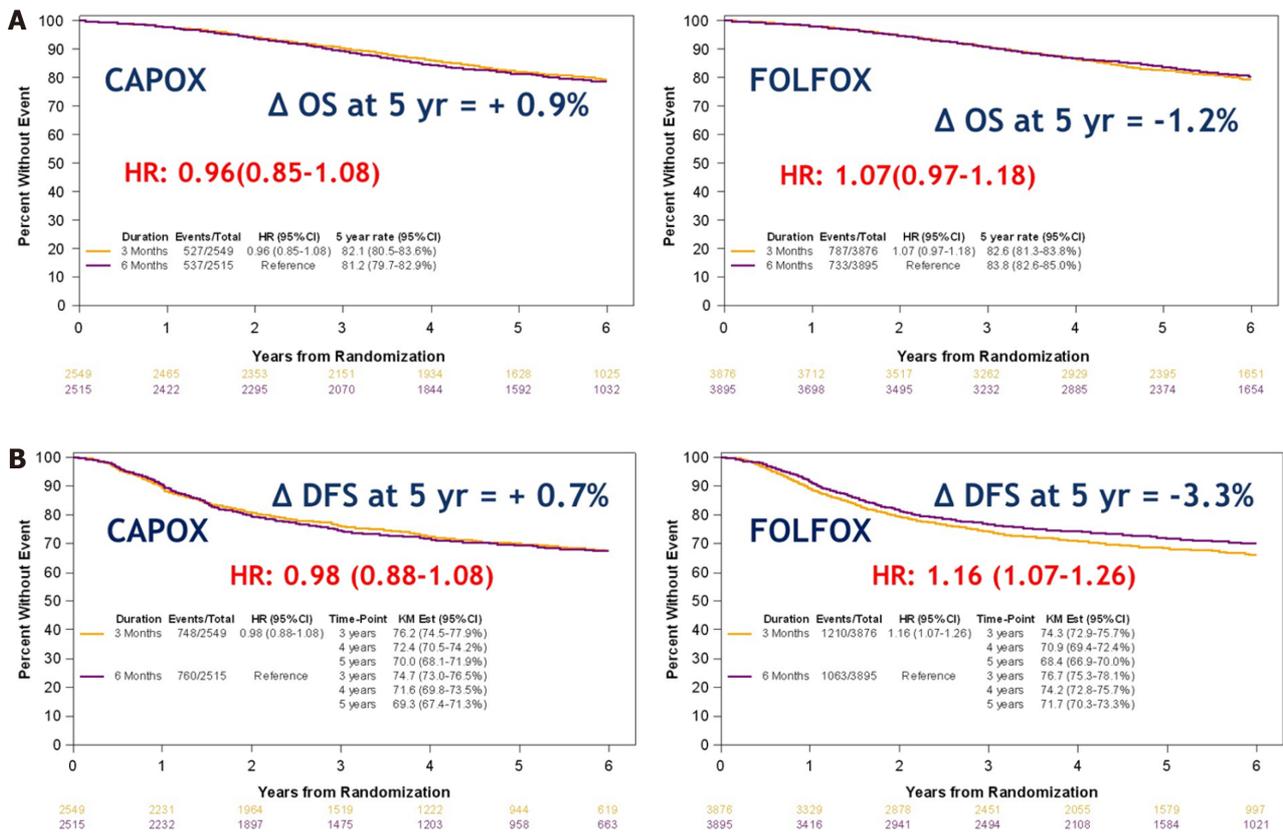


Figure 3 Overall survival and disease-free survival with 3 mo vs 6 mo of adjuvant therapy (international duration evaluation of adjuvant therapy). A: Overall survival; B: Disease-free survival. Citation: Sobrero AF, Andre T, Meyerhardt JA, Grothey A, Iveson T, Yoshino T, Souglakos I, Meyers JP, Labianca R, Saunders MP, Vernerey D, Yamanaka T, Boukovinas I, Oki E, Georgoulas V, Torri V, Harkin A, Taieb J, Shields AF, Shi Q. Overall survival (OS) and long-term disease-free survival (DFS) of three vs six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): Final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration. *J Clin Oncol* 2020; 38(15): 4004-4004. Copyright ©The Author(s). Published by the American Society of Clinical Oncology[21]. DFS: Disease-free survival; HR: Hazard ratio; OS: Overall survival.

The PRODIGE 13 study, presented at ESMO 2020, was a prospective multicentre phase III-controlled trial evaluating the impact of intensive follow-up on OS in 1995 resected stage II or III colorectal cancer (CRC) patients[25]. Patients were double randomised, first in the CEA assessment arm *vs* no assessment and then in the intensive radiological follow-up arm [computed tomography (CT)-scan every 6 mo] *vs* low intensity follow-up (abdominal ultrasound every 3 mo and thoracic radiography every 6 mo). The primary endpoint was 5-year OS.

The majority (77%) of patients were less than 75 years old and had CRC (16% rectal, 84% colon cancer). Half of them had stage II disease, 50% being high risk stage II. This study showed no difference in terms of OS and recurrence-free survival for any of the surveillance arms. In the sub-group of patients with recurrence, curative surgery was achieved in 40.9% of the “minimum follow-up” group, 66.3% in the “CEA” group and standard imaging, 50.7% in the “no CEA and CT scan” group, and 59.5% in the maximum follow-up group. Although the differences were significant ($P = 0.0035$), OS was identical in all arms ($P = 0.887$).

Impact: A low intensity surveillance (no CEA, abdominal ultrasound and chest X-ray) could soon be the new standard for CRC surveillance after curative resection for patients not amenable to a second curative resection.

Metastatic

Patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC represent 5% of all patients with metastatic CRC. The presence of MSI-H is associated with decreased survival rates and less response to conventional chemotherapy[26]. However, MSI-H or dMMR tumours respond better than microsatellite stable tumours to anti-PD1 or anti-PD-L1, immunotherapy. In May 2017, the FDA approved the use of pembrolizumab (anti-PD-1), for the treatment of metastatic MSI-H/dMMR CRC patients who have progressed on chemotherapy.

The KEYNOTE-177 trial presented at the plenary session at ASCO 2020 and recently published in the *New England Journal of Medicine* was a randomised, phase III clinical trial that evaluated the efficacy of pembrolizumab in the first-line treatment of newly diagnosed MSI-H/dMMR metastatic CRC compared to chemotherapy (doublet +/- biologic)[27]. The co-primary outcomes were PFS and OS. At a median follow-up of 32.4 mo, the median PFS with pembrolizumab was 16.5 mo compared to 8.2 mo with chemotherapy HR: 0.60 (0.45-0.80, $P = 0.0002$). Adverse events grade ≥ 3 were less common (22%) in the experimental arm compared to the standard arm (66%). QOL assessed with QLQ-C30 and EQ-5D was improved with pembrolizumab compared to chemotherapy ($P = 0.002$).

Impact: Pembrolizumab (anti-PD1) is a new standard of care in the first-line treatment of MSI-H/dMMR metastatic CRC.

Approximately 20% of patients with CRC are diagnosed with stage IV disease. For those with an asymptomatic primary tumour, the question remains whether the primary tumour should be removed first.

The iPACS study presented at ASCO-GI 2020 was a randomised phase III trial comparing primary tumour resection (PTR) plus chemotherapy compared to chemotherapy alone in asymptomatic stage IV CRC patients[28]. The primary endpoint was OS. Investigators aimed to recruit 770 patients but due to slow accrual the sample size was decreased to 280. The Data and Safety Monitoring Committee (DSMC) recommended early termination of the trial due to futility at the first interim analysis in September 2019. With a median follow-up period of almost 2 years, there was no OS difference ($P = 0.69$) between PTR plus chemotherapy (OS: 25.9 mo) and the chemotherapy alone arm (26.7 mo). Median PFS was 10.4 mo for PTR plus chemotherapy *vs* 12.1 mo for chemotherapy alone. There were three treatment-related deaths following PTR due to postoperative complications.

Impact: Currently, PTR in asymptomatic stage IV CRC patients cannot be recommended.

RECTAL CANCER

Neoadjuvant

Locally advanced rectal cancer is treated with neoadjuvant CXRT followed by surgery 8 to 12 wk later. Neoadjuvant CXRT provides a significant reduction in local recurrence but not in distant metastasis rate[29]. Furthermore, adjuvant chemotherapy in rectal cancer is difficult to administer due to poor compliance[30-32]. Indeed, rectal cancer surgery is frequently associated with a high complication rate and patients are not always able to receive chemotherapy postoperatively.

To ensure efficient treatment of both the local tumour and possible micro-metastases, an alternative approach would be to administer the systemic therapy preoperatively after short-course radiotherapy (5 d). During this waiting period the patient is in a good condition to receive an optimal dose of chemotherapy. Two phase III trials (RAPIDO and PRODIGE 23) hypothesized that neoadjuvant chemotherapy will result in increased survival in locally advanced rectal cancer patients.

The RAPIDO trial, presented at ASCO 2020 and recently published in *The Lancet Oncology*, is a phase III randomised trial comparing standard CXRT before surgery +/- adjuvant chemotherapy (standard arm) to total neoadjuvant treatment (TNT) with short-course radiotherapy (5 \times 5 Gy) followed by chemotherapy (XELOX 6 cycles or FOLFOX 9 cycles) before surgery (experimental arm)[33]. The trial accrued only patients with locally advanced rectal cancers defined as cT4a/b, extramural vascular invasion, cN2, involved mesorectal fascia, or enlarged lateral lymph nodes. The primary outcome was disease-related treatment failure (DrTF) defined as distant metastasis, locoregional failure, new primary CRC or treatment-related death. The 3-year DrTF was improved in the experimental arm at 23.7% *vs* 30.4% for the control arm ($P = 0.019$). The experimental arm showed an improved pathological complete response (28% *vs* 14%; $P < 0.001$) and reduced distant metastases (20.0% *vs* 26.8%, $P = 0.005$), but no improvement in locoregional failure rates (8.7% *vs* 6.0%, $P = 0.09$), 3-year OS (89.1% *vs* 88.8%, $P = 0.59$) or QoL.

The PRODIGE 23 trial presented at ASCO was a phase III randomised trial investigating TNT with modified (m)FOLFIRINOX (leucovorin, infusional 5-FU, irinotecan, oxaliplatin) before standard CXRT, followed by surgery and adjuvant treatment in locally advanced rectal cancer patients compared to standard CXRT followed by surgery and compulsory adjuvant treatment[34]. This trial also accrued only patients

Table 1 Overview of latest phase III trials in gastrointestinal cancers

Studies	Population	Intervention	Control	Primary endpoints	Results
Gastroesophageal cancers					
Neoadjuvant					
NRG-RT0G 1010	HER2-positive EC or GEJ	Trastuzumab + CXRT + surgery	CXRT + surgery	DFS	19.6 mo <i>vs</i> 14.2 mo (HR = 0.97)
ARTDECO	Locally advanced unresectable EC and GEJ	Standard CXRT + RT boost	Standard CXRT	3-yr LPFS	73% <i>vs</i> 71% (NS)
Adjuvant					
Checkmate-577	EC and EGJ and residual pathologic disease	Nivolumab	Placebo	DFS	22.4 mo <i>vs</i> 11 mo (HR = 0.69)
Advanced/metastatic					
Checkmate-649	Untreated, unresectable advanced or metastatic GC/EGJ	Nivolumab + CT	CT	OS; PFS	14.4 mo <i>vs</i> 11.1 mo (HR = 0.71); 7.7 mo <i>vs</i> 6 mo (HR = 0.68)
ATTRACTION-4	Untreated, unresectable advanced or metastatic GC/EGJ	Nivolumab + CT	CT + placebo	OS; PFS	17.45 mo <i>vs</i> 17.15 mo (HR = 0.90); 10.45 mo <i>vs</i> 8.34 mo (HR = 0.68)
Keynote-590	Untreated, unresectable advanced or metastatic EC/EGJ	Pembrolizumab + CT	CT + placebo	OS; PFS	12.4 mo <i>vs</i> 9.8 mo (HR = 0.73); 6.3 mo <i>vs</i> 5.8 mo (HR = 0.65)
Hepatocellular carcinoma					
Advanced/metastatic					
Imbrave 150	Untreated, unresectable HCC	Atezolizumab + bevacizumab	Sorafenib	12-mo OS; PFS	67.2% <i>vs</i> 54.6% (HR = 0.58); 6.8 mo <i>vs</i> 4.3 mo (HR = 0.59)
Colon cancer					
Adjuvant					
IDEA	Resected stage III CRC	3 mo adj. CAPOX 3 mo adj. FOLFOX	6 mo adj. CAPOX ; 6 mo adj. FOLFOX	5-yr DFS	70% <i>vs</i> 69.3% (HR = 0.95); 68.4% <i>vs</i> 71.7% (HR = 1.16)
Follow-up					
PRODIGE 13	Resected stage II or III CRC	Low intensity follow-up	High intensity follow-up	5-yr OS	NS
Metastatic					
Keynote-177	Untreated, unresectable metastatic MSI-H/dMMR CRC	Pembrolizumab	CT	PFS	16.5 mo <i>vs</i> 8.2 mo (HR = 0.6)
iPACS	Asymptomatic stage IV CRC	Tumor resection + CT	CT	OS	25.9 mo <i>vs</i> 26.7 mo (HR = 1.10)
Rectal cancer					
Neoadjuvant					
RAPIDO	Locally advanced rectal cancer	RT + Neoadj. CT + surgery	CXRT + surgery +/-adj. CT	3-yr DrTF	23.7% <i>vs</i> 30.4% (HR = 0.76)
PRODIGE 23	Locally advanced rectal cancer	Neoadj. CT + CXRT + surgery + adj. CT	CXRT + surgery +/-adj. CT	3-yr DFS	75.7% <i>vs</i> 68.5% (HR = 0.69)

CRC: Colorectal cancer; CT: Computed tomography; CXRT: Chemo-radiation therapy; DFS: Disease-free survival; dMMR: Mismatch repair deficient; DrTF: Disease-related treatment failure; EC: Esophageal cancer; GC: Gastric cancer; GEJ: Gastroesophageal junction cancer; HCC: Hepatocellular carcinoma; HR: Hazard ratio; LPFS: Local progression-free survival; MSI-H: Microsatellite instability high; NS: Not significant; OS: Overall survival; PFS: Progression-free survival; RT: Radiotherapy.

with locally advanced rectal cancers defined as cT3 or cT4 M0. The primary endpoint

was DFS. Surgical morbidity did not differ between the two arms. TNT significantly improved pathological complete response rate at 27.5% compared to 11.7% in the CXRT alone arm ($P = 0.001$). TNT significantly improved 3-year DFS (75.7% *vs* 68.5%, HR 0.69, $P = 0.034$) and 3-year metastasis-free survival (78.8% *vs* 71% in CXRT alone, HR 0.64, $P = 0.02$). Global quality-of-life scores were similar.

Impact: TNT could be an option in locally advanced rectal cancer patients.

CONCLUSION

This year has been particularly significant in gastrointestinal oncology (Table 1). Immunotherapy has finally entered the scene with numerous indications - first-line MSI-H/dMMR metastatic CRC, first-line metastatic ESCC CPS > 10%, as adjuvant treatment in GC with CPS > 5%, as adjuvant treatment in resected EC/GEJ cancer with residual disease after trimodal treatment and first-line advanced HCC. The field has reached maturity with treatment de-escalation in the adjuvant setting for CRC and in the follow-up after curative surgery for CRC. On the other hand, in locally advanced rectal cancer intensification with TNT has found its place in the treatment landscape.

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