ESMO Congress 2021: highlights from the EORTC gastrointestinal tract cancer group’s perspective

T. Koessler1,2*, M. Alsina3,4, D. Arnold5, I. Ben-Aharon6, M. Collienne5,7, M. P. Lutz8, C. Neuzillet9, R. Obermannova10,11, M. Peeters12, F. Scalfani13, E. Smyth14, J. W. Valle15,16, A. D. Wagner17, L. Wyrwicz18, E. Fontana19 & M. Moehler20

1Department of Oncology, Geneva University Hospital, Geneva; 2Swiss Cancer Center Leman (SCCL), University of Geneva, Lausanne, Switzerland; 3Hospital Universitario de Navarra (HUN), Medical Oncology Department, Pamplona; 4Val d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 5Department of Oncology, Haematology and Palliative Care, Asklepios Klinik Altona, Asklepios Tumorzentrum Hamburg, Hamburg, Germany; 6Division of Oncology, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion, Haifa, Israel; 7European Organisation for Research and Treatment of Cancer, Brussels, Belgium; 8Caritasklinikum, Saarbrucken, Germany; 9GI Oncology, Medical Oncology Department, Institut Curie Saint-Cloud, Versailles Saint Quentin University, Saint-Cloud, France; 10Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno; 11Department of Pharmacology, Faculty of Medicine, Masaryk University, Brno, Czech Republic; 12Department of Oncology, Universitätsklinikum Düsseldorf, Düsseldorf, Germany; 13European Organisation for Research and Treatment of Cancer, Brussels, Belgium; 14Cambridge University Hospitals NHS Foundation Trust, Addenbrooke’s Hospital, Cambridge; 15Division of Cancer Sciences, University of Manchester, Manchester; 16Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; 17Department of Oncology, Division of Medical Oncology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland; 18Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; 19Sarah Cannon Research Institute, London, UK; 20Department of Internal Medicine, Johannes-Gutenberg University, Mainz, Germany

There has been no major change of practice in gastrointestinal oncology at the European Society for Medical Oncology (ESMO) symposium 2021, but confirmation that immunotherapy in combination with chemotherapy has become standard of care in several indications. The European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Track Cancer Group has selected important phase II and III trials presented during the symposium across all gastrointestinal cancers as well as early reports on new drugs or new combinations that may change practice in the future.

Key words: oesophagus cancer, stomach cancer, pancreatic cancer, neuroendocrine tumours, colorectal cancer

UPPER GASTROINTESTINAL TRACT

EORTC Task force Oesophagus and Stomach, chairs: Elizabeth Smyth, Anna Dorothea Wagner

At this year’s European Society for Medical Oncology (ESMO) symposium, important further data supporting the benefit of immunotherapy in patients with upper gastrointestinal tumours were presented, along with encouraging activity of human epidermal growth factor receptor 2 (HER2) targeting drugs, both as monotherapy and in combination with immune checkpoint inhibitors. CheckMate 649 (LBA7), a global, open-label, randomized phase III trial including 2031 patients with resectable gastric/gastroesophageal junction (GEJ) or oesophageal adenocarcinoma already changed clinical practice and led to Food and Drug Administration approval of nivolumab with fluoropyrimidine-based and platinum-containing chemotherapy, for all randomised patients and those with a combined positive score (CPS) ≥5, and European Medicines Agency approval for patients with CPS ≥5, respectively. At ESMO 2021, long-term follow-up (minimum 24 months for the nivolumab plus chemotherapy arm and 35.7 months for the nivolumab plus ipilimumab arm) and microsatellite-instability-high (MSI-H) tumours had been reported. Improved benefits from the addition of nivolumab to chemotherapy in all randomized patients [hazard ratio (HR) for overall survival (OS) 0.79; 95% confidence interval (CI) 0.71-0.88] and patients with programmed death-ligand 1 (PD-L1) CPS ≥5 (HR for OS 0.70, 95% CI 0.61-0.81) were confirmed. Again in patients with MSI-H tumours, the HR was in favour of nivolumab-treated patients with 0.38 (0.17-0.84), defining this excellent combination for first-line treatment of advanced MSI-H gastric cancer. In addition, new results for patients treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg followed by nivolumab 240 mg every 2 weeks without chemotherapy were presented. Herein, the data monitoring committee had closed the treatment arm with this combination of nivolumab and ipilimumab prematurely after inclusion of 409 patients. In both, the group of patients with a CPS ≥5 and all randomized patients, median survival and HRs
demonstrated no significant benefit from this combination. Whereas, especially in patients with a CPS ≥5, an advantage in survival rates at 24 months (25 versus 17%) for patients treated with nivolumab and ipilimumab versus chemotherapy alone was demonstrated, patients living <1 year lived for a shorter time when treated without chemotherapy.

The importance of chemotherapy has also been confirmed for patients with HER2-positive advanced/metastatic gastric cancer in the randomized IIT phase II INTEGA (LBA54) AIO-trial, in which the combination of trastuzumab, nivolumab, and FOLFOX showed increased efficacy with 70% OS rate at 12 months. In the ToGA trial comparing trastuzumab plus chemotherapy with chemotherapy alone, the OS rate at 16 months was 55% and in the INTEGA chemotherapy-free arm, trastuzumab/nivolumab/ipilimumab did not improve the survival.

In the first read-out from the MAHOGANY trial, however, encouraging response rates for the chemotherapy-free combination of margetuximab (anti-HER2) and retifanlimab [anti-programmed cell death protein 1 (anti-PD-1)] with a confirmed overall response rate (ORR) rate of 53% were reported. Additionally, in two randomized, first-line phase III trials conducted in China (Orient-15 and Orient-16), the combination of sintilimab (anti-PD-1) plus chemotherapy demonstrated significant survival benefits compared with chemotherapy alone in metastatic/advanced patients with oesophageal squamous cell carcinoma (Orient-15, PD-L1 CPS ≥10, 17.2 months versus 13.6 months; P = 0.0018 and all patients, 16.7 months versus 12.5 months; P < 0.0001) and adenocarcinoma (Orient-16, PD-L1 CPS ≥5, 18.4 months versus 12.9 months; P = 0.0023 and all patients, 15.2 months versus 12.3 months; P = 0.009).

So far, the promise of chimeric antigen receptor T-cell (CAR-T cell) therapy has not yet been realized in solid tumours, due to historically low response rates and concerns regarding off-target, off-tumour toxicities. Claudin 18.2, as a tight junction protein which is specifically expressed on tumours of the upper gastrointestinal tract, with very limited expression elsewhere in the body, renders it an attractive target for CAR-T cell therapy. In a single-centre Asian study, CAR-T cells targeting claudin 18.2 demonstrated encouraging efficacy signs with limited toxicity. In a cohort of chemorefractory gastrointestinal tumours the ORR was 48.6% (18/37), whereas in a subset of gastric and gastroesophageal adenocarcinoma patients the ORR was 61.1%. Toxicity was manageable, cytokine release syndrome was observed in 35 patients (94.5%), with all events only grade 1/2. Progression-free survival (PFS) was 5.6 months (95% CI 2.6-9.2 months) in patients treated at the recommended phase II dose in the gastric/GE cohort, with a relatively short follow up of 7.6 months (95% CI 5.6-8.6 months). The efficacy of claudin 18.2 CAR-T cells was not influenced by disease histology or previous immunotherapy use, but was affected by CAR-T cell peak levels. These data are quite encouraging but will require validation in further trials and in non-Asians.

In other ‘non-immunotherapy studies’, the DESTINY Gastric-02 study (LBA55) evaluated the antibody drug conjugate trastuzumab deruxtecan in retained HER2-positive advanced gastroesophageal cancer patients previously treated with chemotherapy plus trastuzumab. In the previously presented DESTINY Gastric-01 study, trastuzumab deruxtecan had demonstrated efficacy in Asian HER2-positive gastric cancer patients but had not yet been evaluated in non-Asian patients. The single-arm Gastric-02 second-line trial had a confirmed ORR of 38% to trastuzumab deruxtecan, also comparable to DESTINY Gastric-01, with an encouraging duration of response of 8.1 months (95% CI 4.1 months-NA). Importantly, significant numbers of drug-induced pneumonitis were not observed.

LOWER GASTROINTESTINAL TRACT

Task force Colon, Rectum, Anal canal, chairs: Mark Peeters, Thibaud Koessler, Francesco Scelfani, Dirk Arnold, Lucjan Wyrwicz

Localised rectal cancer. As yet, the role of neoadjuvant chemotherapy as a single modality in rectal cancer has not been precisely established. Only limited data from the randomized phase II study, FOWARC, suggested it may lead to similar outcomes as chemoradiation. In the CONVERT study, presented by Pei-Rong Ding et al., 663 patients with locally advanced rectal cancer with uninvolved mesorectal fascia-negative were randomized to four neoadjuvant cycles of CapeOx (nCT) or chemoradiation with concurrent capecitabine (nCRT). The early outcomes for both arms were similar, although nCRT was superior in the degree of tumour regression calculated as TRG 0-1 (38.6% for nCRT versus 24.0% for nCT; P < 0.001) with similar pathological complete responses rates (13.8% for nCRT and 11.0% for nCT; not significant). Sphincter preservation and R0 resection rates were also equal in both arms. The only parameters favouring nCRT were the numbers of perioperative distant metastases (0.7% in nCRT versus 3.1% in nCT; P = 0.034) and the fraction of patients with preventive diverting ileostomy (52.2% in nCT versus 63.6% in nCRT; P = 0.008). Thus, these early CONVERT data do not support changes for rectal cancer treatment but confirm neoadjuvant chemotherapy as an option for patients with contraindications to radiotherapy.

Metastatic colorectal cancer (phase II and III). In 218 first-line, mismatch repair (MMR)-unselected, metastatic colorectal cancer (mCRC) patients, immunotherapy (atezolizumab, anti-PD-L1) with triplet chemotherapy plus a biologic agent was studied in the randomized, phase II AtezoTRIBE trial, comparing folinic acid, fluorouracil, irinotecan and oxaliplatin (FOLFOXIRI)-bevacizumab (eight or more cycles) followed by maintenance [5-fluorouracil (5-FU)/leucovorin-bevacizumab] with FOLFOXIRI-bevacizumab-atezolizumab followed by maintenance (5-FU/leucovorin-bevacizumab-atezolizumab). At progression, FOLFOXIRI-bevacizumab or without atezolizumab was reintroduced. The primary endpoint was PFS. Adding atezolizumab increased median PFS from 11.5 to 13.1 months (HR 0.69, 80% CI 0.56-0.85; P = 0.012) in the entire population, with this marginal benefit likely to be driven by MSI tumours. In fact, in the
mCRC (early phase). O6-Methylguanine DNA methyltransferase (MGMT) repairs DNA damage induced by alkylating agents such as temozolomide (TMZ). Secondary resistance to TMZ within MGMT-silenced tumours may be associated with a hypermutated status, frequently coupled with acquired mutations in MMR genes. MAYA was a proof-of-concept phase II trial in chemorefractory microsatellite stable (MSS), MGMT-silenced, mCRC. After two cycles of TMZ (150 mg/m² daily for 5 days every 4 weeks), patients who had not progressed were treated with TMZ plus nivolumab and ipilimumab. The primary endpoint was 8-month PFS rate. Out of 703 screened patients, 142 (29%) were molecularly eligible and enrolled. Of these, 24% did not experience early progression and entered the second immunotherapy part. At 8 months, the median PFS rate was 36%. Median OS was 18.4 (14-NA) months, while ORR was 42%, showing promising results in a highly selected subgroup.

KRAS mutations occur in 3%-4% of all mCRC tumours. After the first results on KRAS inhibition in mCRC during last year’s ASCO with the multicohort CodeBREAK 100 study for sotorasib, the phase Ib/II trial KRYS--TAL-1 investigated presented adagrasib, a selective and irreversible inhibitor of KRAS, combined with the epidermal growth factor receptor inhibitor cetuximab (n = 32, phase Ib) or as monotherapy (n = 46; mostly phase II) in unresectable mCRC. Primary endpoints for phase I were safety, maximum tolerated dose, pharmacokinetics, recommended phase II dose and ORR in phase II. Median follow-up was 7 and 8.9 months in the combination and monotherapy group, respectively. Patients were heavily pretreated in both groups, with more than three prior lines in 55%-65%. Response rates were 22% (monotherapy) and 43% (combination); disease control rate (DCR) 87% and 100%, respectively. These results compare favourably with the 15.4% confirmed ORR with sotorasib and panitumumab in CodeBreaK 101. In KRYS--TAL-1, treatment was generally well tolerated, with grade 3/4 treatment-related adverse events <5%, 12.9% in CodeBreaK 101. Adagrasib plus cetuximab is now being evaluated in the 2L phase III KRYS--TAL-10 study (NCT04793958). Further combinations of interest are those with a downstream MEK inhibitor, as well as with an inhibitor of the RAS activation factor, SOS.

Agents targeting the DNA damage repair (DDR) pathway have been successful in tumours with DDR pathway alterations. WEE1 plays a central role in cell cycle regulation and genomic stability, whereas WEE1 inhibition induces DNA damage and DNA replication stress. Preclinical models harbouring RAS-positive TP53-mutant mCRC tumours generally produce G1/S checkpoint failure. Thus, a WEE1 inhibitor may lead to impaired checkpoint control and DNA replication stress. In the multicohort FOCUS4-C maintenance study, RAS-positive TP53-mutant patients without disease progression after 16 weeks of standard chemotherapy induction were randomized to either active monitoring (n = 25) or the WEE1 inhibitor adavosertib (n = 44). The primary endpoint, PFS, was significantly improved (HR 0.35, 95% CI 0.18-0.68; P = 0.0022), although median PFS was rather short in both arms (1.87 versus 3.61 months, respectively). According to an exploratory analysis, this effect was more pronounced in left-sided tumour primaries (HR left/right sidedness: 0.24/1.02).

The antibody/drug conjugate trastuzumab deruxtecan had remarkable activity in patients with unresectable or mCRC, showing HER2 expression and RAS/BRAF/VEGFDW wild-type status, even after at least two prior regimens, in the multicentre phase II DESTINY-CRC01 trial: Siena et al. recently reported an ORR of 45.3% and a DCR of 83% in HER2+ immunohistochemistry 3+ (IHC3+) or IHC2+/ISH+ patients (n = 53) with trastuzumab deruxtecan. The corresponding median PFS and OS were 6.9 and 15.5 months, respectively. The biomarker analysis at ESMO 2021 suggests an association between baseline HER2 expression levels, as the median PFS of IHC3+ patients (n = 40; 8.3 months) was markedly longer than those with IHC2+/ISH+ status (n = 13; 4.1 months). This was the strongest prognostic denominator, amongst many exploratory factors, including plasma cERBB2 amplification status, plasma RAS- and BRAF-mutation and plasma PIK3CA gain-of-function mutation.
status. The ctDNA analysis suggested relevant antitumour activity in patients with HER2⁺ mCRC who have RAS- or PIK3CA-activating mutations or higher baseline TMB levels. All these cautious conclusions, given the limited sample size, will be undergoing confirmation in the upcoming DESTINY-CRC02 trial (NCT04744831).^{20}

**HEPATOBILIARY AND PANCREATIC CANCER, NEUROENDOCRINE TUMOURS**

**Task force Hepatobiliary, NETs, chairs: Juan W Valle, Jens Ricke**

Recent years in biliary tract cancer (BTC) have been marked by the advent of routine molecular screening and personalized therapy for specific patients with IDH1 mutation, FGFR2 fusions, BRAF mutations, HER2 alterations, or MSI.\(^{21}\) This ESMO congress provided new data regarding chemotherapy in non-molecularly selected BTC as Perkhofer et al.\(^{22}\) presented the randomized, non-comparative phase II NIFE AIO trial, which evaluated first-line 5-FU/leucovorin plus nanoliposomal irinotecan (nal-iri). Of note, nal-iri with 5-FU/leucovorin was approved for metastatic pancreatic cancer based on positive survival of the NAPOLI-1 phase III trial.\(^{23}\) The randomized, phase II NIFTY trial, presented at ASCO 2021, reported first results of this combination chemotherapy in second-line Asian cholangiocarcinoma carcinoma (CCA) patients, with improved PFS, OS, and ORR versus 5-FU/leucovorin alone.\(^{24}\)

In the NIFE AIO trial, chemotherapy-naïve, intra- or extrahepatic CCA patients with Eastern Cooperative Oncology Group performance status 0-1 received standard cisplatin plus gemcitabine (CISGEM) or the 5-FU/leucovorin plus nal-iri combination. The primary endpoint was PFS at 4 months, with a fixed PFS rate of interest of ≥50% in the intention to treat (ITT) population. The primary endpoint was met for 93 patients with a 4-month PFS rate of 51% with 5-FU/leucovorin plus nal-iri (59.5% with CISGEM). Median PFS was 6.0 months (95% CI 2.4-9.6 months) with 5-FU/leucovorin plus nal-iri and 6.9 months (95% CI 2.5-7.8 months) with CISGEM. Median OS (data not mature) was 15.9 months (95% CI 10.6-21.8 months) and 13.6 months (95% CI 6.5-17.7 months), and ORR was 24.5% and 11.9%, respectively. Interestingly, a differential effect was observed according to primary tumour location, with median PFS in intrahepatic CCA of 3.5 months (95% CI 2.1-6.0 months) with 5-FU/leucovorin plus nal-iri versus 7.7 months (95% CI 6.0-9.5 months) with CISGEM (median OS 14.2 versus 16.4 months, \(n = 66\)), and 9.6 months versus 1.8 months in extrahepatic CCA (median OS 18.2 versus 6.3 months, \(n = 25\)). Overall, this trial met its prespecified threshold of activity, providing new data for the use of nal-iri in BTC, particularly in extrahepatic CCA. With the limited sample size, however, this differential effect between intra- and extrahepatic CCA remains to be confirmed and the underlying biological mechanisms to be explored. Thus, these results are not practice changing and more data are needed. Further results of the randomized phase II AIO NALIRICC trial (NCT03043547), which evaluates 5-FU/leucovorin plus nal-iri combination versus 5-FU/leucovorin alone after gemcitabine-based first-line chemotherapy (i.e. the same design as the NIFTY trial but in a non-Asian population), are awaited.

The academic First International Randomized phase II Study in Malignant Progressive Pheochromocytoma and Paragangliomas (FIRSTMAPP) study\(^{25}\) randomized 78 patients with these very rare tumours with strong expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and VEGF receptor (VEGFR)-1,2 and PDGF receptor (PDGFR), to sunitinib [37.5 mg once daily shown to be effective in pancreatic neuroendocrine tumours (NET)\(^{26}\)] or placebo. The study met its primary endpoint with a 12-month PFS (centrally reviewed) of 35.9% on sunitinib (18.9% in the control arm, which included 20% in the 95% CI, confirming the statistical assumption). The median PFS was 8.9 months (95% CI 5.5-12.7 months) with sunitinib versus 3.6 months (95% CI 3.1-6.1 months) with placebo. No new toxicity concerns emerged, despite hypertension being an issue in patients with pheochromocytoma and paragangliomas. This is a first practice-changing study in this patient group, previously thought to be too rare, also as treatment options are limited for these rare cancers.

The phase III SPINET study\(^{27}\) evaluated the activity of somatostatin analogue lanreotide in patients with advanced well-differentiated bronchopulmonary NETs. Seventy-seven patients were randomized (2 : 1) to lanreotide or placebo, stratified by tumour grade: typical versus atypical carcinoid. As the study closed early due to slow accrual, the primary endpoint, median PFS, was 16.6 months (95% CI 11.3-21.9 months) although patients with typical carcinoids derived greater benefit from lanreotide (21.9 months versus 13.9 months with placebo) than those with atypical carcinoids (13.8 months versus 11.0 months with placebo), in keeping with findings of lanreotide\(^{28}\) or octreotide\(^{29}\) in well-differentiated gastrointestinal NETs.

The phase II/III AXINET study provided an updated blinded central review of PFS in advanced well-differentiated (grade 1-2) extra-pancreatic NET patients treated with a somatostatin analogue (octreotide LAR) with either axitinib or placebo. The results of the investigator-assessed primary endpoint PFS were previously presented at ASCO-GI 2021,\(^{30}\) median PFS 17.2 months versus 12.3 months (HR 0.816; \(P = 0.169\)). The robust method of blinded central radiological assessment (secondary endpoint) determined the PFS as 16.6 months versus 9.9 months for axitinib and placebo, respectively (HR 0.687, \(P = 0.01\)).\(^{31}\) This clinically relevant difference is in keeping with the effects of VEGF inhibition in pancreatic NET\(^{32}\) and the FIRSTMAPP study detailed above.\(^{25}\)

**PANCREATIC CANCER**

**Task force Pancreas, chair: Cindy Neuzillet**

Data on perioperative chemotherapy in resectable pancreatic ductal adenocarcinoma (PDAC) are limited. The PRE-OPANC phase III study compared immediate surgery
followed by adjuvant gemcitabine and chemoradiotherapy with gemcitabine followed by surgery and adjuvant gemcitabine, versus upfront surgery followed by adjuvant gemcitabine, in a mixed population of borderline and resectable tumours. The trial initially negative, now showed an OS improvement, but only on its updated long-term follow-up OS data in the overall population (ASCO 2021), with no benefit in the resectable PDAC subgroup.

Seufferlein et al. presented the non-comparative, randomized, phase II NEONAX trial with perioperative versus adjuvant chemotherapy of gemcitabine/nab-paclitaxel in patients with resectable PDAC. Of note, this chemotherapy regimen failed to show its superiority over surveillance in the previous phase III APACT study. In NEONAX, 127 patients with resectable PDAC were randomized 1:1 between perioperative gemcitabine plus nab-paclitaxel (two preoperative and four post-operative cycles, arm A) or adjuvant treatment (six cycles, arm B). Two populations were defined: ITT corresponding to patients fulfilling the inclusion criteria (n = 59 in both arms), and modified ITT (mITT) comprising patients from the ITT population who either completed neoadjuvant therapy and underwent surgery (RO/1 resection) in arm A, or patients after surgery (RO/R1 resection) having started adjuvant therapy (at least one cycle) in arm B. The primary objective was improved DFS at 18 months from 38% to 55% in the mITT population. The ORR in arm A was 28.9%, with a low rate of progression during neoadjuvant chemotherapy of 6.7%. The resection rate was 69.5% in arm A and 78.0% in arm B, with more R0 resections in arm A (87.8% versus 67.4%). In the ITT population, the 18-month PFS rate was 28.7% in arm A versus 19.3% in arm B, and the median PFS was 11.4 months versus 5.9 months. The 18-month PFS rate in mITT was 32.2% in arm A (n = 39, 66.1% of ITT patients) and 41.4% in arm B (n = 25, 42.4%), however, not reaching the prespecified target in both arms, and the median DFS was 14.1 months and 17.0 months, respectively. Thus, perioperative chemotherapy was safe, but did not achieve the expected 18-month PFS rate of 55% in the mITT population. The definition of this population was questionable, however, and the analysis in the ITT population (considered as more clinically relevant) favoured perioperative chemotherapy. Even if negative, this study reinforces the rationale for neoadjuvant chemotherapy in resectable pancreatic cancers, pending the results of the PANACHE-01 (NCT02959879) and ALLIANCE 021806 (NCT04340141) randomized studies evaluating perioperative versus adjuvant chemotherapy with FOLFIRINOX.

The phase III PRODIGE 24 study demonstrated superiority of modified FOLFIRINOX (mFOLFIRINOX) compared with gemcitabine as adjuvant chemotherapy for resected PDAC on DFS (primary endpoint). At the initial publication, OS data were not mature and prognostic factors for OS could not be analysed. At ESMO 2021, updated 5-year OS results with median follow-up of 69.7 months and the analysis of prognostic factors were presented by Conroy et al. The median OS was 53.5 months (95% CI 43.5-58.4 months) with mFOLFIRINOX versus 35.5 months (95% CI 30.1-40.3 months) with gemcitabine, with a stratified HR of 0.68 (95% CI 0.54-0.85; P = 0.0009). The 5-year OS rates were 43.2% (95% CI 36.5% to 49.7%) and 31.4% (95% CI 25.5% to 37.5%), respectively. Specific survival (HR 0.65, 95% CI 0.51-0.82, P = 0.0003) and metastasis-free survival (HR 0.64, 95% CI 0.52-0.80, P = 0.0001) also improved with mFOLFIRINOX. Treatment arm, tumour grade and stage, and patient age were independent prognostic factors for OS; volume of the centres was not retained. In addition, completion of all 12 treatment cycles (regardless of duration and dose intensity) was also associated with a more prolonged OS (HR 0.64, 95% CI 0.49-0.84, P = 0.002). Thus, these updated results of PRODIGE 24/CCTG PA6 confirm adjuvant mFOLFIRINOX as standard of care in PDAC. Completion of adjuvant therapy is also an important prognostic factor, already shown in the ESPAC-3 study.

**EARLY TRANSLATIONAL PHASE TRIALS**

**Task Force for individualized cancer therapy, chairs: Radka Obermannová, Maria Alsina**

Metastatic MSI-H/dMMR gastrointestinal tract cancers (GITC) should be addressed for first-line immunotherapy, according to different presentations at ESMO 2021, clearly further supporting this clinical unmet need. A phase II study evaluating the efficacy of neoadjuvant pembrolizumab in localized MSI-H/dMMR solid tumours enrolled mostly colorectal (n = 27), pancreatic (n = 2), and duodenal (n = 2) cancers. High response rates were observed with ORR of 75% and pCR of 69% in patients undergoing surgical resection. The already reported frequency of MSI-H nonmetastatic esophagogastric adenocarcinoma had been verified in the phase II DANTE trial and at the EURECCA database at Vall d’Hebron University Hospital. The DANTE trial added atezolizumab to perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT). High frequency of pCR (38.5%) was described in 5 of 23 MSI-H tumours treated with atezolizumab. The EURECCA database identified 12 of 92 (13%) MSI-H patients with local and locally advanced oesophagogastric cancers.

Cholangiocarcinoma is a rare but heterogeneous disease with a frequency of ~3% of gastrointestinal tumours. Several molecular pathways including mutations in IDH1, IDH2, BRAF, PI3K, MET, or translocations in FGFR2 are targetable. In the upcoming PAMICC study, EORTC addresses the role of IDH1 and HRD mutations inducing a homologous recombination repair defect which increases tumour sensitivity to poly(ADP-ribose) polymerase (PARP) inhibition (NCT04796454). At ESMO 2021, the 334TiP trial is a phase I trial of dual-targeted drugs niraparib (PARP inhibitor) plus anlotinib (VEGFR, FGFR, PDGFR, and c-kit inhibitor) in homologous recombination repair (HRR) gene-mutated advanced solid tumours including BTC. FGFR2 fusions/rearrangements (FGFR2 fusion in ~15% of intrahepatic cholangiocarcinoma) were addressed in FIDES-01. Derazinib (FGFR1-3 inhibitor), in the FGFR2 fusion cohort (n = 103), showed encouraging efficacy and met its primary endpoint with a centrally confirmed ORR of 21.4%. (95% CI
Meanwhile, a new improved example is the German ‘Generation-multinational-cancer-clinical-trial-infrastructure/.

www.eortc.org/blog/2015/01/14/spectacolor-viable-next-SPECTACOLOR platform for CRC already in 2015:https://

FOLFOX in patients with HER2-positive gastric, oesophageal, and GEJ adenocarcinoma, cholangiocarcinoma, gallbladder carcinoma, and CRC.49

DISCUSSION

During the ESMO 2021 Congress, we and other academic groups did not present any practice-changing trials in advanced gastrointestinal cancers. Important proof-of-concept studies, however, suggest new possible future treatment avenues, including cellular therapies in upper gastrointestinal malignancies and chemotherapy-immunotherapy combinations in historically immune-refractory MSS colorectal cancers. Whereas anti-PD1 inhibitors continue to improve outcomes in several subgroups of gastrointestinal tumours and in different indications, some drawback signals for immune checkpoint combination strategies, with anti-CTLA4 as an example, are now coming to light such as in the CheckMate 649 trial or in the INTEGA trial for instance.

Chemotherapy dependency as a one-size-fits-all approach maintains its validity in several gastrointestinal cancers and continues to be successfully explored, especially in academic trials and in difficult to treat indications, like the practice-changing PRODIGIE-24 study in pancreatic cancers or the newly reported NIFE AIO trial in BTCs. Conversely, precision medicine approaches with targeted agents continue to evolve and explore molecularly selected subgroups of patients with tumours carrying very rare molecular events, with frequency below 5%, but potentially very effective. Such personalized approaches based on genomic testing are changing daily oncology practice. Initially, Gunnar Folprecht and our GITCG group started the EORTC SPECTACOLOR platform for CRC already in 2015: https://www.eortc.org/blog/2015/01/14/spectacolor-viable-next-generation-multinational-cancer-clinical-trial-infrastructure/.

Meanwhile, a new improved example is the German’s Platform for Analyzing Targetable Tumour Mutations (PLATON): a permanently open, multicenter, prospective, cohort study including bio-banking and sharing the platform infrastructure for associated substudies.50 The platform PLATON focuses on GITC tumour molecular profiling and offers clinical investigators to select optimal clinical trials based on their molecular profile. An interactive web application in a virtual Molecula Tumour Board is also available and has already analysed 75 patients.

This is why continuous efforts in maintaining fruitful interactions between academia, Pharma, and new cutting-edge technologies of diagnostic providers are essential for the successful development of new drugs and strategies to ultimately improve clinical outcomes for our cancer patients. We as the EORTC Gastrointestinal Tract Cancer Group welcome further interactions between academic key opinion leaders, national groups, active clinicians and scientists across Europe, pharma-companies, and biotech partners, to foster the development of innovative, multidisciplinary, and patient-centred ideas for future practice-changing trials.

FUNDING

This work was supported by a donation from the Swiss Cancer Research Foundation from Switzerland. MC was supported by a grant by EORTC Cancer Research Fund (ECRF) and the Gastrointestinal Tract Cancer Group.

DISCLOSURE

TK discloses consulting or advisory role for Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Lilly, Roche, Boehringer Ingelheim, and Servier. MA discloses consulting or advisory role for MSD, BMS, Lilly, and Servier. RO discloses consulting or advisory role for BMS, Eli Lilly, Merck, Roche, and Servier, and received Travel Grants from BMS, Merck and Servier. JWV discloses consulting or advisory role for Agios, AstraZeneca, Delcath Systems, Keocyt, Genoscience Pharma, Incyte, Ipsen, Merck, Mundipharma EDO, Novartis, PCI Biotech, Pfizer, Pieris Pharmaceuticals, QED, and Wren Laboratories; Speakers Bureau for Imaging Equipment Limited, Ipsen, Novartis, Nucana; and received Travel Grants from Celgene and Nucana. All other authors have declared no conflicts of interest.

REFERENCES

1. Janjigian YY, Ajani JA, Moehler M, et al. LBA7 Nivolumab (NIVO) plus chemotherapy (Chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 study. Ann Oncol. 2021;32:S1329-S1330.
2. Stein A, Paschold L, Tintelnot J, et al. LBAS4 Ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive locally advanced or metastatic esophaogastrophic adenocarcinoma (EGA): results of the randomized phase II INTEGA trial (AIO STO 0217). Ann Oncol. 2021;32:S1331.
3. Bang YJ, van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-697.
4. Catenauci DV, Park H, Shim BY, et al. 1379P Margetuximab (M) with retifanlimab (R) in HER2-+, PD-L1+ 1st-line unresectable/metastatic gastroesophageal adenocarcinoma (GEA): MAHOGANY cohort A. Ann Oncol. 2021;32:S1043-S1044.
5. Shen L, Lu Z-H, Wang J-Y, et al. LBAS2 Sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: first results of the phase III OREINT-15 study. Ann Oncol. 2021;32:S1330.
6. Xu J, Jiang H, Pan Y, et al. LBAS3 Sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastro-esophageal junction (G/GEJ) adenocarcinoma (OREINT-16): first results of a randomized, double-blind, phase III study. Ann Oncol. 2021;32:S1331.
7. Qi C, Qin Y, Liu D, et al. 13720 CLDN 18.2-targeted CAR-T cell therapy in patients with cancers of the digestive system. Ann Oncol. 2021;32:S1040.
van Cutsem E, Di Bartolomeo M, Smyth E, et al. LBAS Primary analysis of a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients (Pts) with HER2-positive (HER2+) unresectable or metastatic gastric or gastroesophageal junction (GEJ) cancer who progressed on or after a trastuzumab-containing regimen. Ann Oncol. 2021;32:S1332.

Shilata K, Bang Y-J, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419-2430.

Deng Y, Chi P, Lan P, et al. Modified FOLF ox6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial. J Clin Oncol. 2018;36:3502-3502.

Ding P-R, Wang X-Z, Li Y-F, et al. LBA22 Neoadjuvant chemotherapy with oxaliplatin and capecitabine versus chemoradiation with capecitabine for locally advanced rectal cancer with uninvolved mesorectal fascia (CONFORT): Initial results of a multicenter randomised, open-label, phase III trial. Ann Oncol. 2021;32:S1296.

Cremolini C, Rossini D, Antoniotti C, et al. LBA20 FOLFIRXIRI plus bevacizumab (bev) plus atezolizumab (atezo) versus FOLFIRXIRI plus bev as first-line treatment of unresectable metastatic colorectal cancer (mCRC): patients: results of the phase II randomised AtezoTRIBE study by GONO. Ann Oncol. 2021;32:S1294-S1295.

Mulcahy MF, Salem R, Mahvash A, et al. LBA21 Radioembolization with chemotherapy for colorectal liver metastases: a randomized, open-label, international, multicenter, phase III trial (EPOCH study). Ann Oncol. 2021;32:S1295.

Pietrantonio F, Morano F, Lonardi S, et al. 3830 MAYA trial: Temozolomide (TMZ) priming followed by combination with low-dose ipilimumab and nivolumab in patients with microsatellite stable (MSS), MGMT silenced metastatic colorectal cancer (mCRC). Ann Oncol. 2021;32:S530-S531.

Hong DS, Fakhil MG, Strickler JH, et al. KRAS G12C inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383:1207-1217.

Weiss J, Yaeger RD, Johnson ML, et al. LBA24 Adagrasib (MRTX849) as monotherapy or combined with cisatuzumab (Cetux) in patients (Pts) with colorectal cancer (CRC) harboring a KRAS G12C mutation. Ann Oncol. 2021;32:S1294.

Fakhil M, Falchook GS, Hong DS, et al. 434P CodeBreak 101 subprotocol H: Phase Ib study evaluation combining of sotorasib (Soto), a KRAS G12C inhibitor, and panitumumab (PMAb), an EGFR inhibitor, in advanced KRAS p.G12C-mutated colorectal cancer (CRC). Ann Oncol. 2021;32:S551.

Seligmann J, Fisher DJ, Brown LC, et al. 3820 Inhibition of WEE1 is effective in TP53 and RAS mutant metastatic colorectal cancer (mCRC): a randomised phase II trial (FOCUS4-C) comparing adavosertib (AZD1775) with active monitoring. Ann Oncol. 2021;32:S530.

Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2021;22:779-789.

Siena S, Raghav K, Masushi T, et al. 3860 Exploratory biomarker analysis of DESTINY-CRC01, a phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd, DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC). Ann Oncol. 2021;32:S532.

Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet. 2021;397:428-444.

Perkhofer L, Striefler JK, Sinn M, et al. LBA10 NaI-NIR with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer: Final results of the NIFE-trial (AIO-YMO HEP-0315), a randomized phase II study of the AIO biliary tract cancer group. Ann Oncol. 2021;32:S1282.

Wang-Gillam A, Li HP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387:545-557.

Yoo C, Kim K-P, Kim I, et al. LBA19 Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic biliary tract cancer (BTC) after progression on gemcitabine plus cisplatin (GemCis): multicenter comparative randomized phase 2b study. J Clin Oncol. 2021;39:4006-4006.

Baudin E, Goichot B, Berruti A, et al. 567O First international randomised study in malignant progressive pheochromocytoma and paragangliomas (FIRSTMAPPP): an academic double-blind trial investigating sunitinib. Ann Oncol. 2021;32:S621.

Raymond E, Dahan L, Roaul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501-513.

Baudin E, Horsch D, Singh S, et al. 1096O Nanoliposomal irinotecan with docetaxel (NANO) in patients with advanced bronchopulmonary (BP) neuroendocrine tumors (NETs): results from the phase III SPINET study. Ann Oncol. 2021;32:S5906.

Caplin ME, Patel M, Cwikla JB, et al. LNAtez in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224-233.

Rinke A, Müller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomised study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009;27:4656-4663.

Garcia-Carbonero R, Benavent M, Jiménez Fonseca P, et al. A phase II/III randomized double-blind study of octreotide acetate LAR with axitinib versus octreotide acetate LAR with placebo in patients with advanced G1-G2 NETs of non-pancreatic origin (AXINET trial-GETNET-1107). J Clin Oncol. 2021;39:360-360.

Garcia-Carbonero R, Benavent M, Fonseca PJ, et al. 1097O the AXINET trial (GETNET1107): axitinib plus octreotide LAR improves PFS by blinded central radiological assessment vs placebo plus octreotide LAR in G1-2 extrapancreatic NETs. Ann Oncol. 2021;32:S907-S908.

Versteijne E, Soker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020;38:1763-1773.

Van Eijck CHJ, Versteijne E, Soker M, et al. Preoperative chemoradiotherapy to improve overall survival in pancreatic cancer: long-term results of the multicenter randomized phase III PREOPANC trial. J Clin Oncol. 2021;39:4016-4016.

Seufferlein T, Uhl W, Algü H, et al. LBA56 Perioperative or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer: results of the NEONAX trial, a randomized phase II AIO study. Ann Oncol. 2021;32:S1283-S1346.

Tempero M, O’Reilly E, van Cutsem E, et al. LBA-1 Phase 3 APACT trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P+ Gem) vs gemcitabine (Gem) alone in patients with resected pancreatic cancer (PC): updated 5-year overall survival. Ann Oncol. 2021;32:S522.

Conroy T, Hammel P, Hebbel M, et al. LBA10 FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395-2406.

Conroy T, Hammel P, Turpin A, et al. LBA7 Unicancer PRODIGE 24/CCTG PA6 trial: updated results of a multicenter international randomized phase III trial of adjuvant mFOLFIROX (mFFX) versus gemcitabine (Gem) in patients (pts) with resected pancreatic ductal adenocarcinomas (PDAC). Ann Oncol. 2021;32:S1334.

Valle JW, Palmer D, Jackson R, et al. Optional duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32:504-512.

Ludford K, Raghav K, Murphy MAB, et al. 1758O Neoadjuvant pemigatinib alone in patients with resected pancreatic cancer (PC): results of the multicenter randomized phase II NEIMOS study. J Clin Oncol. 2021;39:4016-4016.
esophagogastric adenocarcinoma. A randomized, open-label phase IIb trial of the German gastric group at the AIO and SAKK. Ann Oncol. 2021;32:S1069-S1070.

43. Al-Batran SE, Lorenzen S, Homann N, et al. 1429P Pathological regression in patients with microsatellite instability (MSI) receiving perioperative atezolizumab in combination with FLOT vs. FLOT alone for resectable esophagogastric adenocarcinoma: results from the DANTE trial of the German gastric group at the AIO and SAKK. Ann Oncol. 2021;32:S1069.

44. Mirallas O, López-Valbuena D, García-Illescas D, et al. 1431P Descriptive analysis and prognostic factors of microsatellite instability (MSI) gastric cancer patients (pts) compared to microsatellite stable (MSS) pts in a tertiary hospital. Ann Oncol. 2021;32:S1070.

45. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016;13:261-280.

46. Pamiparib and low dose temozolomide in patients with platinum sensitive biliary tract cancer (PAMICC). Available at https://clinicaltrials.gov/ct2/show/NCT04796454. Accessed October 21, 2021.

47. Zhang J, Wang A, Li Z, et al. 334TiP A phase I trial of niraparib plus anlotinib in advanced solid tumors with homologous recombination repair (HRR) gene mutations. Ann Oncol. 2021;32:S512.

48. Busset MDD, Shaib WL, Mody K, et al. 47P Derazantinib for patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusions/rearrangements: primary results from the phase II study FIDES-01. Ann Oncol. 2021;32:S376-S381.

49. Park H, Bekaii-Saab T, Kim S, et al. 1437TiP Phase Ib/II, open label, dose escalation and expansion trial of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy in patients with unresectable or metastatic HER2+ gastrointestinal cancers (trial in Progress). Ann Oncol. 2021;32:S1073-S1074.

50. Vogel A, Behringer DM, Bröckling S, et al. 1871TiP PLATON — "Platform for analyzing targetable tumor mutations": a pilot study. Ann Oncol. 2021;32:S1255.