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PEER-REVIEWED CONFERENCE REPORT

Bemarituzumab Response for Gastric/GEJ Cancers

An update of the FIGHT trial demonstrated statistically significant and clinically meaningful improvements for bemarituzumab plus chemotherapy as frontline therapy in FGFR2b-overexpressing gastric/GEJ adenocarcinomas.

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Resistance to FOLFOX plus Bevacizumab in mCRC

In the PERMAD trial, using advanced bioinformatics, a biomarker was identified predicting treatment resistance to FOLFOX plus bevacizumab in patients with mCRC, 3 months prior to radiological progression.

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Ivosidenib in *IDH1*-Mutant Cholangiocarcinoma

The final overall survival analysis of the phase 3 ClarIDHy trial demonstrated that oral ivosidenib therapy achieved a 21% reduction in the risk of death compared with placebo.

read more on PAGE 14

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

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Letter from the Editor

Dr Stefan Rauh

Dear colleagues,

I am delighted to present you the 2021 ASCO GI Medicom Conference Report. I am sure you will find this report as interesting as I do.

Once disease entities difficult to treat, we are getting better in managing biliary and hepatocellular cancer as our arsenal gets broader – provided, the target is there. Targeted agents and immunotherapy also make some progress in gastrointestinal cancers.

Predictive markers get closer to clinical practice – maybe soon including the gut microbioma! Please also note the prognostic importance of tumor implant number in colorectal cancer, which may lead to changes in the next TNM classification..

… and after decades we will maybe finally get something to do with oxaliplatin-induced polyneuropathy (well, modest as it may be)?

As always, there's a lot more you should know by tomorrow morning.

Please enjoy the read.

Yours,
Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014-2018), member of the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015-2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

Conflict of Interest Statement:
Nothing to declare.

Oesophageal and Gastric Cancer

Bemarituzumab response for gastric/GEJ cancers correlates with FGFR2b levels

An update of the randomised placebo-controlled phase 2 FIGHT trial continued to underscore the potential of bemarituzumab plus chemotherapy as a frontline therapy in FGFR2b-overexpressing gastric and gastroesophageal junction (GEJ) adenocarcinomas. The primary and key secondary endpoints demonstrated statistically significant and clinically meaningful improvements, with a 56% reduction in disease progression.

Prof. Zev Wainberg (UCLA, USA) presented the updated results of the randomised phase 2 FIGHT trial (NCT03694522), which evaluated bemarituzumab plus mFOLFOX6 chemotherapy versus placebo plus mFOLFOX6 chemotherapy in patients with fibroblast growth factor receptor 2b (FGFR2b)-positive, HER2-negative frontline advanced and metastatic gastric or GEJ cancers [1]. Bemarituzumab (anti-FGFR2b) is a first-in-class targeted antibody for tumours overexpressing FGFR2b. The primary outcome of this study was progression-free survival (PFS). Key secondary endpoints were overall survival (OS) and overall response rate (ORR).

FGFR2b-positivity was determined by centrally performed prospective immunohistochemistry (IHC) for FGFR2b overexpression and/or a circulating tumour DNA blood assay demonstrating *FGFR2* gene amplification. Of the 910 evaluated patients, 275 (30%) were FGFR2b-positive. Eventually, 155 patients were randomised.

Prof. Wainberg reported a positive correlation between benefit and the percentage of FGFR2b-positive tumour cells. For patients with IHC results showing FGFR2b overexpression in at least 10% of the sample, the median PFS was 14.1 months for the bemarituzumab cohort, compared with 7.3 months for the placebo cohort (HR 0.44; 95% CI 0.25-0.77). The 1-year PFS rates were 57.0% and 26.4% in the bemarituzumab and placebo arms, respectively. In those with IHC FGFR2b overexpression in at least 5% of cells, the median PFS was 10.2 months in the bemarituzumab arm versus 7.3 months with the placebo arm (HR 0.54; 95% CI 0.33-0.87). The 1-year PFS rates were 56.3% and 28.6%, respectively. Overall, in the intent-to-treat population, the median PFS was 9.5 months and 7.4 months for the bemarituzumab and placebo arms, respectively (HR 0.68; 95% CI 0.44-1.04; P=0.0727). The 1-year PFS rates were 52.5% and 33.8%, respectively. The median OS was not reached in the bemarituzumab arm, versus 12.9 months in the placebo arm (HR 0.58; 95% CI 0.35-0.95; P=0.0268). Again, the percentage of FGFR2b-positive cells was indicative of OS; in the patients whose tumours were at least 5% FGFR2b-positive, the median OS was not reached with bemarituzumab versus 12.5 months with the placebo arm (HR 0.52; 95% CI 0.30-0.91), and for 10% or more FGFR2b-positivity the benefit was even more marked (HR 0.41; 95% CI 0.22-0.79).The ORR was 47% in the bemarituzumab arm, and 33% with placebo.

Corneal events, commonly associated with FGFR inhibition, were reported more frequently in the bemarituzumab arm (67.1% vs 10.4%), with the most common in the bemarituzumab arm being dry eye (26.3%), keratitis (15.8%), and punctate keratitis (14.5%). Stomatitis (31.6% vs 13.0%) and elevated transaminases (34.2% vs 19.5%) were also more common in the bemarituzumab arm. Grade 3 and higher adverse events (82.9% vs 74.0%), serious adverse events (31.6% vs 36.4%), and deaths (6.6% vs 5.2%) were comparable across arms.

Overall, these results justify a prospective, randomised phase 3 trial of bemarituzumab.

1. Wainberg ZA, et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 160.

Gut microbiome DELIVERs nivolumab forecast in gastric cancer

Can the gut microbiome serve as a biomarker for nivolumab efficacy in advanced gastric cancer? New data from the DELIVER trial indicates that immune checkpoint inhibitor response can be predicted by a microbiome assay.

Prof. Yu Sunakawa (St Marianna University School of Medicine, Kanagawa, Japan) presented the analysis of the DELIVER trial (UMIN000030850) [1]. DELIVER addressed

the need for predictive biomarkers to predict efficacy of nivolumab treatment in gastric cancer, by analysing the patients' gut microbiome. The primary endpoint was a significant relationship between the genomic signature in the gut microbiome and the efficacy of nivolumab.

Patients (n=501) with advanced gastric cancer received nivolumab between March 2018 and August 2019. Microbiomes were assessed in 2 cohorts. Firstly, 180 patients were included in a training cohort (median age 70 years; 76% men) for full microbiome analysis. Consequently, the top 30 microbial species were selected and, subsequently, an additional 257 patients forming the validation cohort (median age 71 years, 72% men) were tested for those 30 species.

The study found that disease progression occurred in 62.2% (95% CI 54.7-69.3) of patients in the training cohort and 53.2% (95% CI 47-59.4) of patients in the validation cohort. Patients without disease progression had a more diverse gut microbiome than those with progressive disease. Upregulation of the KEGG metabolic pathway was linked to progressive disease. An exploratory analysis indicated that *Odoribacter* and *Veillonella* species were associated with tumour response to nivolumab among patients in both cohorts (P=0.014).

Dr Sunakawa concluded that larger, prospective studies are needed to gain further confidence in these findings. In addition, longer follow-up of these patients will reveal whether the therapeutic response led to any survival gain.

1. Sunakawa Y, et al. Genomic pathway of gut microbiome to predict efficacy of nivolumab in advanced gastric cancer: DELIVER trial (JACCRO GC-08). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 161.

OS benefit for trifluridine/tipiracil in advanced gastric cancer from third-line onward

In third- and later-line, treatment with TAS-102 (trifluridine/tipiracil, FTD/TPI) provided a 33% reduction in the risk of death compared with placebo in patients with heavily pretreated metastatic or advanced gastric cancer. There was also a higher numerical difference between the arms for progression-free survival (PFS) and time to deterioration to ECOG ≥2. Quality of life was consistent in the third- and later-line when compared with earlier lines.

New exploratory subgroup findings from the TAGS study (NCT02500043) were presented by Prof. Josep Tabernero (Vall d'Hebron Institute of Oncology, Spain), specifically focused on results for third- and later-line treatment with trifluridine/tipiracil [1]. The TAGS study investigated the efficacy and safety of TAS-102 (trifluridine, an antineoplastic thymidine-based nucleoside analogue, and tipiracil, a thymidine phosphorylase inhibitor) plus best supportive care (BSC) compared with placebo plus BSC in patients with metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction) that was refractory to standard treatments.

Patients were randomised in a 2:1 ratio to receive TAS-102 at a 35 mg/m^2 twice daily on days 1 to 5 and 8 to 12 of each 28-day cycle (n=337) or placebo (n=170). CT scans were performed every 8 weeks and quality of life (QoL) assessments every 4 weeks. Crossover to open-label TAS-102 was allowed. The primary endpoint of the TAGS study was overall survival (OS), which was already met and published [2]. Key secondary endpoints were PFS and QoL. Patient characteristics were similar in the treatment arms; the primary cancer site was gastric in 71% of patients in both arms and 44% of patients per arm had received prior gastrectomy. Approximately 37% of patients in each group had received 2 prior treatments, and about 63% had received 3 or more prior treatments, including fluoropyrimidine, platinum, irinotecan, taxanes, ramucirumab, and immunotherapy.

Results showed a superior survival benefit with FTD/TPI in patients treated in the third- and later-line, with a median OS of 6.8 months in the FTD/TPI arm versus 2.8 months in the placebo arm (HR 0.67; 95% CI 0.47-0.97; P=0.032, see Figure on the next page). There was also a higher PFS benefit in the FTD/TPI arm for third-line (HR 0.54; P=0.004) and fourth- or later-line (HR 0.57; P<0.001). Time to deterioration to ECOG ≥2 was also superior in the FTD/TPI arm for third-line (HR 0.60; P=0.005) and fourth- or later-line (HR 0.75; P=0.03). QoL was consistent in the third- and later-line with the overall population.

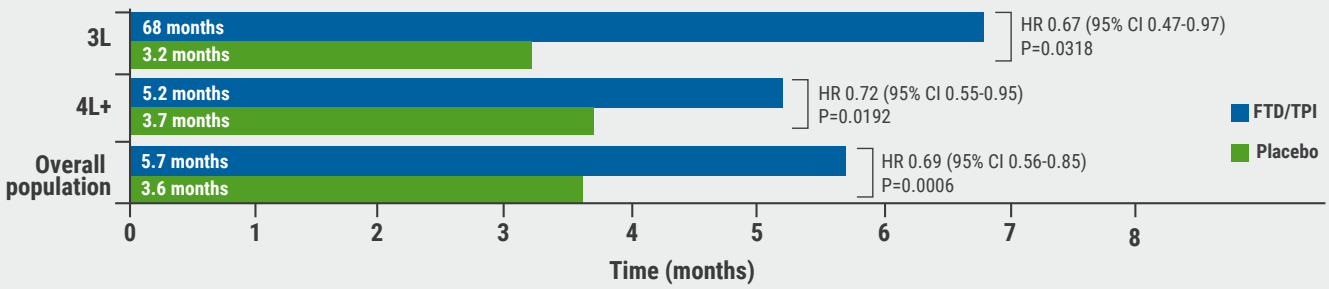
In short, this exploratory subgroup analysis of the TAGS study confirms the efficacy of FTD/TPI versus placebo for third- and later-line treatment of metastatic gastric cancer.

1. Tabernero J, et al. Trifluridine/tipiracil outcomes in third- or later lines versus placebo in metastatic gastric cancer treatment: An exploratory subgroup analyses from the TAGS study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 229.
2. Shitara K, et al. Lancet Oncol. 2018 Nov;19(11):1437-1448.

Neoadjuvant chemotherapy does not increase perioperative complications in thoracic oesophageal cancer

In the phase 3 JCOG 1109 trial, perioperative complication risk in patients with potentially resectable advanced thoracic oesophageal cancer did not appear to be adversely affected

Figure: Median overall survival in the ITT population and 3L and 4L + subgroups [1]



by neoadjuvant chemotherapy, including regimens of docetaxel, cisplatin, and 5-fluorouracil (DCF) and radiation with cisplatin and 5-fluorouracil (CF-RT).

Prof. Kazuo Koyanagi (National Cancer Center, Japan) presented the initial results [1]. The 3-arm JCOG 1109 trial (UMIN000009482) is evaluating the overall survival benefit of DCF and CF-RT compared with standard CF as preoperative therapy in patients with thoracic oesophageal cancer. The primary analysis for the trial is planned for 2023; the current analysis focused on the impact on perioperative complications with the 3 neoadjuvant regimens as the impact of preoperative therapy for oesophageal cancer has not been fully investigated yet.

Patients with stage IB/II/III thoracic oesophageal cancer (n=601) were randomised equally to 1 of 3 arms to receive neoadjuvant chemotherapy prior to transthoracic oesophagectomy with regional lymphadenectomy:

- In the control arm (arm A), patients received cisplatin 80 mg/m^2 on day 1 plus 5-FU at 800 mg/m^2 on days 1 to 5 of the 3-week cycle for 2 cycles.
- Patients in arm B received cisplatin 70 mg/m^2 on day 1, 5-FU 700 mg/m^2 on days 1 to 5, and docetaxel 70 mg/m^2 on day 1 every 3 weeks for 3 cycles.
- Arm C received cisplatin 75 mg/m^2 on day 1 with 5-FU 1,000 mg/m^2 days 1 through 4 every 4 weeks for 2 cycles in addition to radiation therapy at a total of 41.4 Gy.

The incidence of postoperative complications did not significantly increase with DCF or CF-RT. The rate of grade 3/4 pneumonia was 7.6% in arm A, 5.5% in arm B, and 6.2% in arm C. Grade 3/4 leakage was observed in 3.2% in arm A, 6.6% in arm B, and 7.3% in arm C. The rate of recurrent laryngeal nerve paralysis was 3.2%, 1.6%, and 1.7% in arms A, B, and C, respectively. Postoperative complications of any kind and of grade 2 or higher in severity were observed more in the CF arm (56.2%) compared with the DCF arm (43.7%; P=0.02) and compared with the CF-RT arm (47.8%; P=0.11). "From these results we could at least say preoperative DCF or CF-RT did not increase the risk of postoperative complications," Prof. Koyanagi concluded.

1. Koyanagi K, et al. Impact of preoperative therapy for locally advanced thoracic esophageal cancer on the risk of perioperative complications: Results from multicenter phase III trial JCOG 1109. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 162.

Adjuvant nivolumab: good quality-of-life

New results from the phase 3 CheckMate 577 trial showed favourable oesophageal-specific and health-related quality-of-life (QoL) data with adjuvant nivolumab versus placebo in patients with oesophageal/gastroesophageal (GEJ) cancer.

Prof. Eric Van Cutsem (University of Leuven, Belgium) presented the results [1]: "It was previously reported that nivolumab is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in disease-free survival versus a placebo in resected oesophageal/GEJ cancer following neoadjuvant chemoradiotherapy."

The primary endpoint of the phase 3 CheckMate 577 trial (NCT02743494) was disease-free survival (DFS), with secondary endpoints of overall survival (OS) and OS rates at 1, 2, and 3 years. Of the 794 patients enrolled, 532 were randomised to receive nivolumab, and 262 patients were randomised to the placebo arm. The current presentation focused on health-related QoL data. The investigators used the FACT-E and EQ-5D-3L patient-reported outcome questionnaires to determine health-related QoL, general- and disease-related symptoms, and functioning disease burden. The questionnaires were administered at baseline, every 4 weeks during the 12-month treatment, and at post-treatment follow-up visits. Completion rates for patient reports at baseline were 95%, and approximately 90% at 12 months.

At baseline, mean health-related QoL scores were similar in both groups. After 1 year, both groups reported significant improvements. Scores were similar in the nivolumab and placebo groups for the following: FACT-E total score (133.4 vs 134.03, respectively), EQ-5D Visual Analogue Scale (70.4 vs 69.1, respectively), and EQ-5D Utility Index (0.82 vs 0.831, respectively). Scores for the oesophageal cancer subscale were also comparable in both groups (50.2 vs 50.1, respectively).

Prof. van Cutsem concluded that patients treated with adjuvant nivolumab did not experience a reduction in health-related QoL, further supporting clinical data to demonstrate benefit and tolerability for adjuvant nivolumab in patients with resected oesophageal /GEJ cancer.

1. Van Cutsem E, et al. Checkmate 577:Health-related quality of life (HRQoL) in a randomized, double-blind phase III study of nivolumab (NIVO) versus placebo (PBO) as adjuvant treatment in patients (pts) with resected esophageal or gastroesophageal junction cancer (EC/GEJC). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 167.

Adding docetaxel to adjuvant S-1 reduces gastric cancer relapse

Results from a phase 2 trial indicate that combination treatment with adjuvant S-1 and docetaxel led to an estimated 29% reduction in the risk of relapse compared with S-1 alone in Asian patients with stage 3 gastric cancer.

Prof. Kazuhiro Yoshida (Gifu University, Japan) presented the phase 2 JACCRO GC-07 trial (UMIN000031675) [1]. This randomised, controlled trial evaluated adjuvant docetaxel added to standard of care (in Asia) S-1 treatment compared with S-1 alone after gastrectomy for stage 3 gastric cancer. Patients (median age 66 years; 70% male) received either S-1 alone (n=459) at 80 mg/m^2 on days 1 to 28 in every-6-week cycles, or S-1 with added docetaxel (n=453) at 40 mg/m^2 on day 1. Both arms continued therapy for up to 1 year following surgery. The primary endpoint was 3-year relapse-free survival (RFS) rate; key secondary endpoints included 3- and 5-year overall survival (OS), 5-year RFS, time to treatment failure, and safety.

With a median follow-up of 42.5 months (range 0.3-85.16), the primary endpoint was met. The 3-year relapse-free survival (RFS) rate was 67.7% in the combination arm versus 57.4% in the S-1-alone arm in the intent-to-treat (ITT) population (HR 0.71; 95% CI 0.59-0.89; P=0.0008). An interim published analysis had already shown that the combination led to reduction in the risk of relapse or death (HR 0.632; 99.99% CI 0.400-0.998; P=0.0007) [2]. The data presented at the ASCO Gastrointestinal Cancers Symposium had longer follow-up, and continued to support this finding.

Prof. Yoshida concluded: "The 3-year RFS and OS in the S-1 plus docetaxel group were significantly superior to those in the S-1 group. Adjuvant S-1 plus docetaxel is recommended for Asian patients with stage 3 gastric cancer who underwent D2 gastrectomy without neoadjuvant chemotherapy."

1. Yoshida K, et al. Confirmed three-year RFS and OS of the randomized trial of adjuvant S-1 versus S-1 plus docetaxel after curative resection of pStage III gastric cancer (JACCRO GC-07). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 159.
2. Yoshida K, et al. J Clin Oncol.2019;37(15):1296-1304.

Anal and Colorectal Cancer

First-line pembrolizumab shows superior PFS in MSI-H/dMMR mCRC

When compared with chemotherapy, patients with microsatellite-instability high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) showed superior progression-free survival (PFS) with frontline pembrolizumab monotherapy, which also improved health-related quality of life (QoL) in an updated analysis of the phase 3 KEYNOTE-177 trial.

Dr Kai-Keen Shiu (University College London Hospitals NHS Foundation Trust, UK) reported findings of the phase 3 KEYNOTE-177 trial (NCT02563002), in which patients either received 200 mg pembrolizumab every 3 weeks for up to 2 years (n=153) or investigator's choice of mFOLFOX6 or FOLFIRI every 2 weeks, with or without bevacizumab or cetuximab [1].

Patients were treated until progression, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35

cycles in the pembrolizumab arm. Patients in the chemotherapy arm could crossover to pembrolizumab treatment for up to 35 cycles after confirmed progressive disease (total 56 patients in the chemotherapy arm, 36%). Primary endpoints included PFS per RECIST v1.1 by blinded independent central review (BICR), and overall survival (OS). Secondary endpoints were overall response rate (ORR) per RECIST v1.1 by BICR and safety. Duration of response (DOR) per RECIST v1.1 by BICR, PFS2, and health-related QoL served as exploratory endpoints. Tumour response per RECIST v1.1 by BICR was assessed at week 9 and every 9 weeks thereafter.

After a median follow-up of 32.4 months, pembrolizumab demonstrated superior PFS, compared with chemotherapy (median 16.5 months vs 8.2 months; HR 0.60; 95% CI 0.45-0.80; P=0.0002). The 12- and 24-month PFS rates were 55.3% and 48.3%, respectively, in the pembrolizumab monotherapy arm, compared with 37.3% and 18.6% in the chemotherapy arm. PFS benefit with pembrolizumab was seen across all subgroups, including age, gender, ECOG performance score, geographic region, stage, and tumour site. Pembrolizumab also induced superior ORR compared with chemotherapy (43.8% vs 33.1%, respectively). In the pembrolizumab arm, 11.1% of patients experienced a complete response, 32.7% a partial response, 20.9% stable disease, and 29.4% had progressive disease, compared with 1.9%, 29.2%, 42.2%, and 12.3%, respectively, in the chemotherapy arm. OS analysis of the study is ongoing.

Patients treated with pembrolizumab monotherapy also experienced better health-related QoL, including improvements in global health status/QoL, physical functioning, role functioning, emotional functioning, and social functioning, as well as improvements in symptoms like fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhoea, and financial burden.

Safety was favourable. Fewer patients treated with pembrolizumab, compared with chemotherapy, experienced a grade 3 adverse events (22% vs 66%). Grade 3 or higher immune-mediated adverse events occurred in 9% of the pembrolizumab arm, compared with 2% in the chemotherapy arm, and were consistent with known profiles for these agents.

Dr Shiu concluded: "[Data from this trial] support pembrolizumab as a new standard of care for first-line therapy in patients with MSI-H/dMMR mCRC. We also look forward to upcoming studies both in the neoadjuvant and adjuvant setting."

1. Shiu KK, et al. KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 6.

Short-course radiotherapy with delayed surgery better for elderly rectal cancer patients

Preliminary results show that short-course radiotherapy with delayed surgery is associated with better compliance than radiochemotherapy in elderly patients and could give an advantage in overall survival. This regimen may be preferred in elderly patients and, when confirmed in the final analyses, could become practice-changing.

Presented by Dr Eric Francois (Centre Antoine-Lacassagne, France), the multicentre randomised clinical trial PRODIGE 42-GERICO 12 NACRE (NCT02551237) prospectively compared preoperative radiochemotherapy (RCT) (50 Gy, 2Gy/fraction [fr]; 25 fr + capecitabine) and delayed surgery (Arm A) with short-course radiotherapy (25 Gy, 5Gy/fr, 5fr) and delayed surgery (Arm B) [1].

The rationale for the trial was that although neoadjuvant therapy followed by total mesorectal surgery is the standard of care for locally advanced rectal carcinoma (RC), for elderly patients this may not be based on high levels of evidence as elderly patients are underrepresented in clinical trials. The NACRE study investigated the role of short course radiotherapy with delayed surgery specifically for elderly patients.

The median age of the 101 randomised patients was 80 years. Randomisation was stratified by centre (n=29), disease stage (T2/T3-T4), and age (≤ 80 or >80 years). Co-primary endpoints were R0 resection rate (non-inferiority test with an 8% non-inferiority margin), and preservation of autonomy using IADL score (superiority test with 15% absolute difference margin). Key secondary endpoints were survival and toxicity.

The R0 resection rate in arm B (86.0%; 95% CI 73-94%) was non-inferior to the R0 resection rate in arm A (89.8%; 95% CI 77-97%; P=0.04 (non-inferiority test). With a median follow-up of 15.8 months (95% CI 14.8-26.0), the 6-month mortality rate was 10.0% (95% CI 3.0-22.0) in arm A and 3.92% (95% CI 0 -13.0) in arm B, with overall survival significantly favouring Arm B (P=0.04). Disease-free survival, however, was not statistically different (P=0.9). Of note, 14% of patients in arm A did not receive all of the planned neoadjuvant treatment compared with 0% in arm B.

In conclusion, these preliminary results show that short-course radiotherapy with delayed surgery in elderly patients

with rectal cancer is associated with a better compliance and could give an advantage in overall survival when compared with standard radiochemotherapy followed by surgery.

1. Francois E, et al. NACRE: A randomized study comparing short course radiotherapy with radiochemotherapy for locally advanced rectal cancers in the elderly—Preliminary results. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 4.

Circulating tumour DNA predicts recurrence in colorectal cancer

Circulating tumour DNA (ctDNA) was analysed in plasma samples of colorectal cancer patients after surgery and adjuvant chemotherapy. Patients positive for ctDNA were shown to be at higher risk of recurrence, with ctDNA analysis being more predictive than standard CEA measurements. Furthermore, ctDNA analysis identified relapse 8 months earlier than radiologic examination.

PhD candidate Tenna Henriksen (Aarhus University, Denmark) presented the analysis of a promising novel biomarker in colorectal cancer patients [1]. There is a high relapse rate in colorectal cancer (CRC) despite curative intent treatment. To enhance recurrence risk assessment, ctDNA was assessed as a potential biomarker for minimal residual disease (MRD), which could help to detect recurrence early and thus increase patient survival. The aim of the presented study was to detect MRD, stratify patients into high and low risk of recurrence, assess post-therapy relapse risk in ctDNA-positive patients, and determine the lead time of ctDNA detection compared to radiological recurrence.

Serial postsurgical ctDNA assessment was performed in a prospective, multicentre study including 260 stage 1-3 CRC patients, who underwent tumour resection, of whom 166 were treated with adjuvant chemotherapy (ACT). Plasma samples were taken prior to surgery for baseline levels, and thereafter at 30 days and 3 months after surgery, and then every 3 months for 3 years, with a median follow-up time of 29.9 months in non-relapsed patients. Tumour recurrence was clinically assessed by computer tomography at 12 and 36 months after surgery. Individual tumours and matched germline DNA were whole-exome sequenced and somatic single nucleotide variants (SNVs) were identified. Personalised multiplex PCR assays were designed to track tumour-specific SNVs in each patient's plasma sample.

Postoperative ctDNA status before ACT was assessed in 218 patients: 20/218 (9.17%) were MRD-positive, of whom 75% relapsed. The remaining 25% (5/20) of MRD-positive patients that did not relapse, received ACT. Of the MRD-negative patients, only 27/198 (13.6%) relapsed (HR 11; 95% CI 5.7-20; P<0.001). Post ACT-treatment, a ctDNA-positive status was associated with even higher relapse rates (HR 36; 95% CI 16-81; P<0.001).

To compare ctDNA assessment with standard of care carcinoembryonic antigen (CEA) measurements these were analysed in parallel. While single-time point CEA assessment post-surgery and post-ACT did not have a predictive power for recurrence-free survival, longitudinal CEA assessment was shown to have predictive power (HR 4.9; 95% CI 3.2-15; P<0.0001). Longitudinal ctDNA assessment, however, was significantly more predictive (HR 95.7; 95% CI 28-322; P<0.0001). In comparison with clinical CT evaluation, serial ctDNA analysis detected MRD markedly earlier in relapsing patients, with a median of 8 months (0.56-21.6 months).

In summary, postoperative ctDNA-positive status was associated with markedly reduced relapse-free survival. In a longitudinal setting, ctDNA analysis predicted the risk of recurrence and is a more reliable biomarker for treatment response monitoring.

1. Henriksen T, et al. Circulating tumor DNA analysis for assessment of recurrence risk, benefit of adjuvant therapy, and early relapse detection after treatment in colorectal cancer patients. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 11.

Neoadjuvant pembrolizumab in locally-advanced rectal cancer: primary results

Patients with locally-advanced rectal cancer (LARC) received total neoadjuvant treatment of FOLFOX and chemoradiation therapy with or without pembrolizumab prior to surgery. Results of the primary endpoint analysis as well as first results of secondary endpoints indicate that pembrolizumab treatment did not result in statistically significantly improved outcomes.

Dr Osama Rahma (Dana-Farber Cancer Institute, USA) presented the first results of the pembrolizumab experimental arm of a phase 2 clinical trial (NCT02921256) using total neoadjuvant therapy in LARC [1]. Total neoadjuvant therapy is an emerging treatment option of LARC in which systemic chemotherapy is added to chemoradiotherapy in order to improve clinical outcome as currently loco-regional relapse rates are still 5-6%, and long-time survival is only 65%. Radiation therapy can lead to immunogenic cell death and tumour antigen release, associated with upregulation of immunogenic surface markers and cytokines, eventually

causing expression of PD-L1 in both tumour cells and immune cells. The researchers hypothesised that this immunotherapy resistance could be overcome by combining chemoradiation and anti-PD-1 therapy, and tested novel agents in combination with neoadjuvant FOLFOX, followed by chemoradiation.

Stage 2 or stage 3 LARC patients with one or more of the following conditions were included: distal location [cT3-4 #5cm from anal verge, any N]; bulky [any cT4 or tumour within 3mm of mesorectal fascia]; high risk for metastatic disease [cN2]; or not a sphincter-sparing surgery candidate. The patients were randomised to neoadjuvant FOLFOX + chemoradiation + capecitabine ± pembrolizumab (200 mg IV every 3 weeks x 6 doses; control arm n=95; pembrolizumab arm n=90), followed by surgery 8–12 weeks after the last dose of radiotherapy. The primary endpoint was improvement in the Neoadjuvant Rectal Cancer score (NAR). Key secondary endpoints included complete response, local recurrence, disease-free and overall survival, and toxicity.

The primary endpoint was not met; mean NAR score was 14.08 in the control arm versus 11.53 for the pembrolizumab arm (P=0.26). None of the secondary endpoints reached significance either. The side effects observed with additional pembrolizumab therapy were consistent with both chemoradiotherapy and pembrolizumab safety profile. Grade 3/4 adverse events were slightly increased on the pembrolizumab arm during and after chemoradiotherapy (48.2 vs 37.3%). There were 2 deaths during FOLFOX, one on the control arm due to sepsis, the other on the treatment arm due to pneumonia.

In summary, the additional treatment with pembrolizumab did not lead to statistically significantly increased efficacy in primary as well as available secondary endpoints. Analysis of disease-free and overall survival will be presented in the future. Ongoing analysis of genomic and immune correlatives will further explore the immune resistance mechanisms.

1. Rahma OE, et al. NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 8.

Prognostic value of tumour deposits in stage 3 colon cancer patients

In a post-hoc analysis of CALGB/SWOG 80702 phase 3 study, the presence and number of tumour deposits (TDs) in patients with stage 3 colon cancer was correlated to disease-free and overall survival, indicating prognostic value.

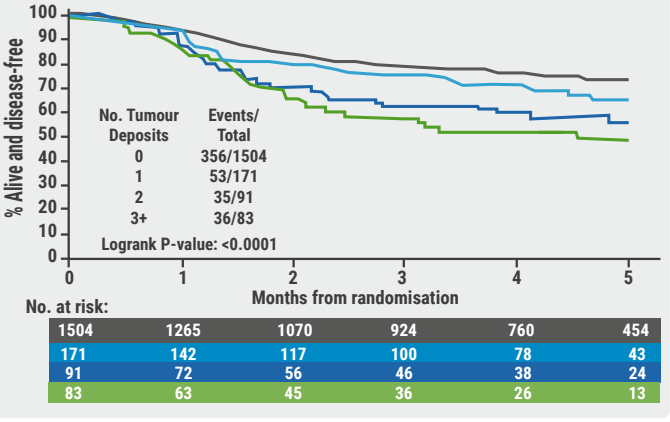
In colon cancer, TDs have been associated with worse prognosis. However, this marker is included in the TNM staging system only in the absence of lymph node metastasis (i.e., stage 3 pN1c tumours). Dr Romain Cohen (Mayo Clinic, USA) presented the prognostic value of TDs and addition of TDs in the count of lymph node metastases in patients with stage 3 colon cancer from the CALGB/SWOG 80702 phase 3 trial (NCT01150045) [1].

Pathology reports of evaluable patients (n=2,028) were reviewed for presence and count of TDs, primary tumour sidedness, lymphovascular invasion, and perineural invasion. Disease-free survival (DFS) and overall survival (OS) were evaluated by multi-variable Cox models adjusting for treatment arm, T-stage, N-stage, lymphovascular invasion, perineural invasion, and lymph node ratio.

Of the included patients, 524 (26%) were TD-positive and 1,504 (74%) were TD-negative. Of the TD-positive patients, 80 (15.4%) were node negative (i.e., pN1c), 239 (46.1%) were pN1a/b, and 200 (38.55%) were pN2; 17.2% and 37.0% of all pN1a/b and pN2 tumours had TDs. Overall median follow-up was 69.3 months. The presence of TDs was associated with poorer DFS (HR 1.59; 95% CI 1.28-1.91) and OS (HR 1.52; 95% CI 1.18-1.95). The negative effect of TD on these endpoints was observed for both pN1a/b and pN2 groups.

Among TD-positive patients, the number of TDs had a linear negative effect (see Figure). Adding TD to the count of lymph node metastases, 104/1,570 (6.6%) patients initially considered as pN1 were re-staged as pN2. Re-staged pN2 patients experienced worse DFS (3-year DFS rate: 65.5% vs 80.3%, P=0.0003) and OS (5-year OS rate 69.1% vs 87.8%; P=0.0005) than patients confirmed as pN1. Re-staged pN2 patients had similar DFS than patients initially staged as pN2

Figure: Linear effect of the number of TDs on disease-free survival [1]



(3-year DFS rate: 65.5% vs 63.1%, P=0.1992). OS curves of these 2 groups crossed, with better outcomes during the first 3 years of follow-up, but poorer 5-year estimates for re-staged pN2 patients (5-year OS rate: 69.1% vs 74.8%, P=0.0436).

Dr Cohen summarised: "Tumour deposits are found in more than a quarter of stage 3 colon cancers. Tumour deposits should be considered as a quantitative barometer, since their number has an impact on patients' prognosis. By adding the number of tumour deposits to the count of lymph node metastases, we improve the prognostication accuracy of the TNM staging system."

1. Cohen R, et al. Prognostic value of tumor deposits in stage III colon cancer patients, a post-hoc analysis of CALGB/SWOG 80702 phase III study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 10.

Ipilimumab/nivolumab plus panitumumab in patients with microsatellite-stable mCRC

Based on preclinical studies, it was hypothesised that the combination of anti-epidermal growth factor receptor (anti-EGFR) treatment with dual checkpoint inhibition could be beneficial for patients with *KRAS/NRAS/BRAF* wildtype microsatellite-stable metastatic colorectal cancer (mCRC). The phase 2 clinical trial met its primary endpoint with at least 35% response rate at 12 weeks.

Anti-EGFR treatment with panitumumab is a standard therapy in patients with *KRAS/NRAS/BRAF* wildtype mCRC. However, anti-EGFR antibody therapy resistance and increased expression of CTLA-4 and PD-L1 commonly develop. The aim of the study presented by Dr Michael Lee (University of Texas MD Anderson Cancer Center, USA) was to assess the efficacy of a combined treatment with anti-PD-1 (nivolumab) and anti-CTLA-4 antibodies (ipilimumab) with anti-EGFR therapy (panitumumab) in a multicentre, single-arm, phase 2 clinical trial (NCT03442569) in these patients [1].

Eligible patients received 1-2 prior lines of therapy and no prior anti-EGFR or immune checkpoint inhibitor therapy. Subjects received ipilimumab 1 mg/kg IV every 6 weeks, nivolumab 240 mg IV every 2 weeks, and panitumumab 6 mg/kg IV every 2 weeks until progression, toxicity, or patient withdrawal. Response rate at 12 weeks (per RECIST 1.1) served as the primary endpoint, key secondary endpoints included progression-free survival (PFS) and duration of response.

First, 6 patients were enrolled in a pre-specified safety run-in cohort. No dose-limiting toxicities were observed within the first 12 weeks. The first stage of the clinical trial (n=32) had sufficient response rate to merit full enrolment and a total of 56 subjects were included in this study. Among the 49 evaluable subjects, 17 patients (35%) showed a 12-week response rate and 20 patients (41%) showed at least an unconfirmed response at any time. Median PFS was 5.7 months (95% CI 5.5-7.9 months), median overall survival was 27 months (95% CI 14.5-not evaluable). Given that the pre-specified number of 12-week responders was 17 patients, the study met its primary endpoint.

There were 2 grade 5 adverse events: myocarditis, which was possibly related to treatment and colonic perforation, which was unlikely related. Grade 3-4 adverse events included increase of lipase, amylase, ALT and AST, and diarrhoea. Toxicities were thus consistent with the expected adverse event profiles of the drugs used.

Dr Lee concluded that the combination of panitumumab, ipilimumab, and nivolumab met its primary endpoint with a 35% 12-week response rate and demonstrated promising activity in second- or third-line *KRAS/NRAS/BRAF* wildtype microsatellite-stable mCRC.

1. Lee MS, et al. Phase II study of ipilimumab, nivolumab, and panitumumab in patients with KRAS/NRAS/BRAF wild-type (WT) microsatellite stable (MSS) metastatic colorectal cancer (mCRC). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 7.

Preliminary surgery salvage data after watch & wait policy from OPERA trial

Non-surgical treatment of rectal cancer is becoming more popular as it avoids the morbidity of extirpative TME surgery and a stoma. Preliminary data from the OPERA phase 3 trial shows that organ preservation is feasible in patients who received chemoradiotherapy with capecitabine and two different types of radiotherapy boosts.

As non-operative modality treatment of rectal adenocarcinoma is gaining popularity, a phase 3 randomised trial (OPERA, NCT02505750) was set up to assess a dose escalation contact x-ray brachytherapy (CXB) which could potentially improve organ preservation rates compared to the standard of care.

Inclusion criteria were MRI-stage cT2, cT3a, or b, up to 3 affected lymph nodes (<8 mm), and a maximum tumour diameter of 5 cm. A total of 148 patients were enrolled and randomised between Arm A (standard arm), treated with external beam chemoradiotherapy (EBCRT) 45 Gy/25/5 weeks with oral capecitabine 825 mg/m^2 and external beam

boost of 9 Gy/5/5 days, and Arm B (experimental arm) treated with EBCRT followed by CXB boost (90 Gy/3/4 weeks). Patients were assessed at 14, 20, and 24 weeks. Watch and wait policy was adopted for patients with complete clinical response at 24 weeks after randomisation. Surgery (TME or local excision) was offered for residual disease and also for local recurrence at a later date. The primary endpoint was organ preservation at 3 years.

Preliminary surgical salvage data from OPERA was presented. Median follow-up was 19 months (range 2-36 months). Overall complete clinical response was observed in 103 patients (81%) at 24 weeks, both arms combined (blinded). At 19 months, surgery was performed in 49/144 patients (34%): in 36 because of suspected residual tumour and in 13 as salvage surgery at a later date for local regrowth. Surgery included local excision in 24/49 patients (49%; of which 3 patients proceeded to TME surgery due to R1 or ypT2 adverse histology) and TME surgery in 28/49 (57%). In total, organ preservation was achieved in 116/144 patients (80.5%), again both arms combined (blinded). Overall TME-free survival was 76% at 19 months.

In summary, nonsurgical treatment of cT2, cT3 rectal cancer seems feasible in those who are fit but wish to avoid surgery. Those who failed with residual tumour or those who have a local recur after achieving a complete response, can be offered surgical salvage. Organ preservation of over 80% can be achieved without compromising the chance of cure.

1. Myint AS, et al. Does non-TME surgery of rectal cancer compromise the chance of cure? Preliminary surgical salvage data from OPERA phase III randomized trial. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 12.

Predicting resistance to first-line FOLFOX plus bevacizumab in mCRC using circulating markers

In the multicentre, international PERMAD trial, using advanced bioinformatics, a cytokines and angiogenic factors (CAF) marker combination was identified predicting treatment resistance to FOLFOX plus bevacizumab in patients with metastatic colorectal cancer (mCRC), 3 months prior to radiological progress.

Antiangiogenic agents, in particular monoclonal antibodies (mAbs) against vascular endothelial growth factor (VEGF), a major driver of tumour angiogenesis, are widely used in cancer therapy including mCRC. However, some patients do not profit from antiangiogenic treatments or develop resistance. So far, no biomarkers are available to predict resistance to antiangiogenic treatments. Prof. Thomas Seufferlein (University of Ulm, Germany) and co-workers hypothesised that repeated analysis of multiple cytokines related to angiogenesis together with machine learning approaches may enable an accurate prediction of anti-VEGF resistance during first-line treatment of mCRC patients with FOLFOX plus bevacizumab [1].

The PERMAD trial, a phase 1/2 biomarker trial (NCT02331927), aimed at establishing a cytokines and angiogenic factor (CAF) profile that enables the prediction of treatment resistance of patients with mCRC receiving bevacizumab plus mFOLFOX6 in a palliative first-line setting about 3 months prior to radiological progress, using an omics approach and bioinformatics. In total, 50 treatment-naïve mCRC patients were enrolled. Conventional switch of antiangiogenic agent and chemotherapy was carried out according to progressive disease (RECIST 1.1).

At baseline, 102 different, preselected CAFs were prospectively collected and centrally analysed in plasma samples (n=647) obtained prior to treatment and biweekly until radiological progress determined by CT scan every 2 months. The values of CAFs affected in a similar fashion by both chemotherapy and disease progress were excluded.

Change in CAF values/pattern correlated with subsequent progress 3 months prior to radiological progress according to RECIST 1.1. Using a random forest predictor, a CAF marker combination comprising 5 CAFs was established, whose specific change in value/pattern over time indicated treatment resistance 3 months prior to radiological progress. The model allowed to differentiate timepoints without progress from timepoints predicting progress 100 days before radiological progress with an accuracy of 83%, a sensitivity of 76%, and specificity of 88%.

In summary, using advanced bioinformatics, a CAF marker combination was identified that points out treatment resistance to FOLFOX plus bevacizumab in patients with mCRC, 3 months prior to radiological progress. Having an accurate assessment of resistance to antiangiogenic treatment may enable time to respond, by treating the patient with a more broadly acting antiangiogenic agent, thereby delaying resistance and avoiding the use of an inefficacious treatment.

1. Seufferlein T, et. al. Predicting resistance to first-line FOLFOX plus bevacizumab in metastatic colorectal cancer: Final results of the multicenter, international PERMAD trial. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 115.

Final OS analyses comparing trifluridine/tipiracil + bevacizumab versus capecitabine + bevacizumab in first-line unresectable mCRC patients noneligible for intensive therapy

Patients with unresectable metastatic colorectal cancer (mCRC) not eligible for standard intensive chemotherapy randomly received treatment with trifluridine/tipiracil and bevacizumab or capecitabine and bevacizumab. Patients treated with the first combination showed a 4.64 months longer median overall survival (OS).

Prof. Eric Van Cutsem (KU Leuven, Belgium) presented the final end-of-study OS analysis of the phase 2 randomised study TASCO1 (NCT02743221) in patients with unresectable mCRC [1]. The results of the primary study analysis were reported earlier and demonstrated a promising efficacy in terms of progression-free survival (PFS) and an acceptable safety profile for the combination of trifluridine/tipiracil + bevacizumab [2].

Previously untreated patients not eligible to receive standard oxaliplatin- or irinotecan-based chemotherapy regimens were enrolled into 2 study arms to receive either trifluridine/tipiracil administered orally at 35 mg/m²/dose twice daily from days 1-5 and days 8-12, and bevacizumab at 5 mg/kg on days 1 and 15 of a 28-day treatment cycle (TT-B; n=77), or capecitabine administered orally at 1,250 or 1,000 mg/m²/dose twice daily (according to the patient's status) from days 1-14 and bevacizumab at 7.5 mg/kg on day 1 of a 21-day treatment cycle (C-B; n=76). Cycles were repeated until documented disease progression, unacceptable toxicity, or investigator's/patient's decision. Following treatment discontinuation, all patients were followed for OS until the end-of-study, i.e. the date of the withdrawal visit for the last patient.

Of the 153 patients randomised and followed until end-of-study, 21 were alive (11 in TT-B, 10 in C-B arm) and censored for the analysis. Median OS was 22.31 months in TT-B and 17.67 months in C-B (HR 0.78; 95% CI 0.55-1.10; see Figure). Survival probability at 18 months in TT-B was 0.62 versus 0.47 in C-B.

The safety profiles of both study arms remained unchanged from the initial analysis [2], with a generally good tolerance in patients treated with TT-B.

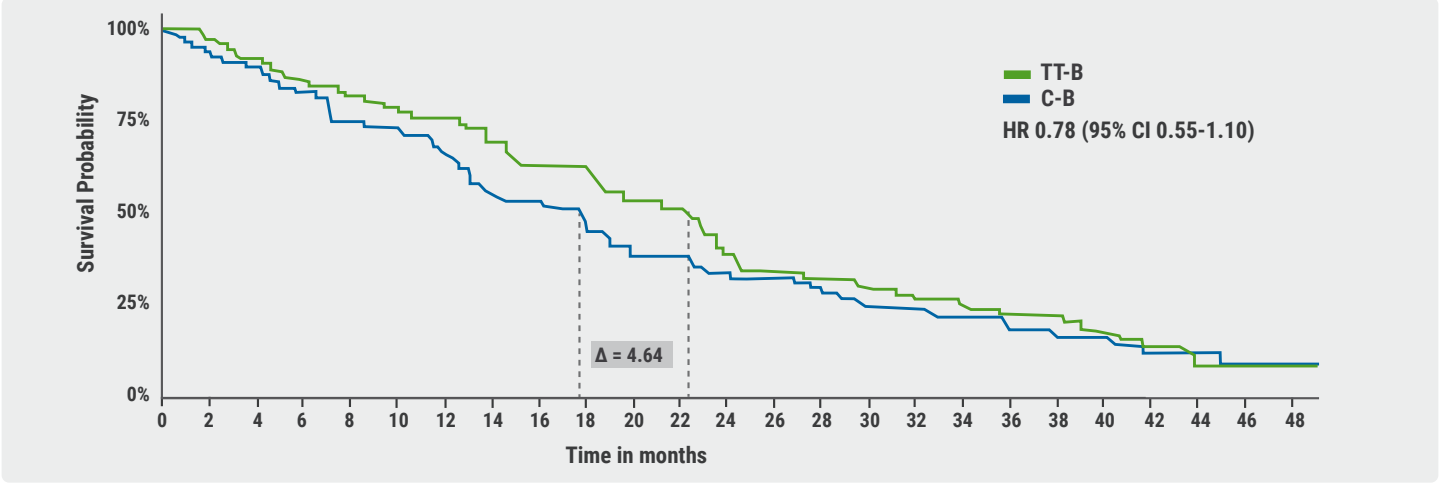
In summary, in line with the earlier published PFS, the OS analyses shows promise for TT-B in patients with previously untreated unresectable mCRC ineligible for standard combination chemotherapy. The final study analysis provided further evidence for TT-B as a noteworthy valuable regimen in this population settings. There is an ongoing randomised phase 3 study (SOLSTICE, NCT03869892) to confirm these results.

1. Van Cutsem E, et al. Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are noneligible for intensive therapy (TASCO1): Results of the final analysis on the overall survival. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 14.
2. Van Cutsem E, et al. Ann Oncol. 2020 Sep;31(9):1160-1168.

Maintenance treatment with cetuximab versus observation in RAS wildtype mCRC

Cetuximab was studied as a maintenance therapy in metastatic colorectal cancer (mCRC) patients during chemotherapy-free intervals in the randomised phase 2 PRODIGE 28-time UNICANCER study. Compared with observation only, treatment with cetuximab did not lead to a significantly higher 6-month progression-free survival (PFS) rate. However, PFS time was clinically meaningful improved.

Figure: Overall survival in TASCO1 trial [1]

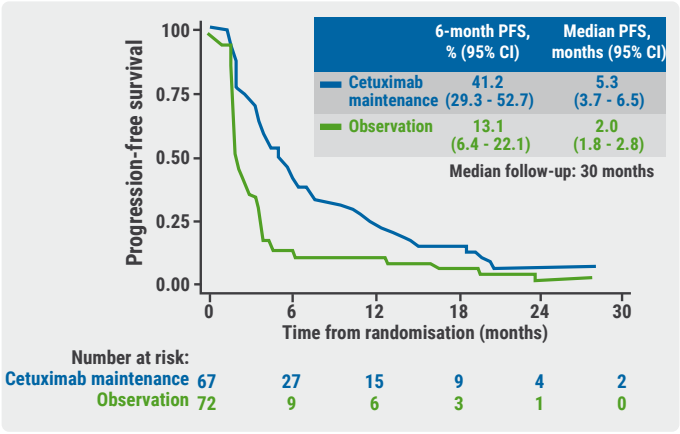


Although anti-EGFR agents are active as single-therapy in *RAS* wildtype mCRC, only few studies are available on their role in maintenance therapy during chemotherapy-free intervals. Compared to observation, maintenance therapy with fluoropyrimidine ± bevacizumab showed significant improvement in PFS but not in overall survival (OS) in patients with unresectable mCRC and disease control after first-line doublet chemotherapy ± bevacizumab [1]. The aim of the presented multicentre, non-comparative phase 2 trial study (NCT02404935) was to compare maintenance treatment with bi-weekly cetuximab alone (arm A) or observation only (arm B) until disease progression, unacceptable toxicity, or death [2].

A total of 214 *RAS* wildtype unresectable mCRC patients with controlled disease after FOLFIRI + cetuximab (8 cycles) were enrolled, of which 139 were randomised (n=67 arm A, n=72 arm B). Randomisation was stratified according to tumour response, centre, baseline Köhne Score, CEA, and platelet count. In case of tumour progression during the chemotherapy-free interval, FOLFIRI + cetuximab was reintroduced for 8 cycles, followed by a new chemotherapy-free interval. Tumour response was assessed per RECIST 1.1 every 8 weeks. The primary endpoint was 6-month PFS after initiation of maintenance therapy. Secondary endpoints were overall response rate (ORR), time to strategy failure, PFS, OS, safety, quality of life, circulating tumour cells and circulating tumour DNA detection, and dynamic changes during treatment. Of the secondary endpoints, only PFS was presented.

The median follow-up was 30 months. The 6-month PFS rate was 34.3% (95% CI 23.2-46.9) in arm A and 6.9% (95% CI 2.3-15.5) in arm B. Although showing a large difference in PFS, the study did not meet its primary endpoint according to the power calculation. Evaluation of PFS as a secondary endpoint showed a median PFS during the first chemotherapy-free interval of 5.3 months in arm A and 2 months in arm B without overlap of 95% CI (see Figure).

Figure: PFS after randomisation [2]



Dr Valérie Boige (Institut Gustave Roussy, France) concluded: "Based on the study hypothesis, the cetuximab maintenance arm did not meet the primary objective. However, the clinically meaningful difference in PFS without any overlap in the confidence intervals between both arms warrants further investigation."

1. Sonbol M.B. et al. JAMA Oncol. 2020 Mar 1;6(3):e194489.
2. Boige V. et al. Maintenance treatment with cetuximab versus observation in RAS wild-type metastatic colorectal cancer: Results of the randomized phase II PRODIGE 28-time UNICANCER study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 15.

Duloxetine ameliorates oxaliplatin-induced peripheral neuropathy

Duloxetine resulted in a clinically significant improvement in peripheral neuropathy (PN) induced by oxaliplatin, with a manageable toxicity profile in this retrospective study. Additionally, duloxetine also improved depression and pain score. However, a prospective study should be conducted to conclude on efficacy and caution must be taken about duloxetine and other drugs interaction.

Dr Jeffrey Chi (Northwell Health Cancer Institute, NY, USA) presented the study, which included patients with gastrointestinal cancers [colorectal (CRC), pancreatic (PC), and gastric (GC)] receiving oxaliplatin-based chemotherapy regimens from November 2016 to November 2019 [1].

Duloxetine is a second-generation selective serotonin and norepinephrine reuptake inhibitor (SNRI) used for the treatment of depression, anxiety, PN associated with diabetes, or ongoing pain due to medical conditions such as fibromyalgia. In this retrospective study, the researchers evaluated the role of duloxetine in reduction of oxaliplatin-induced neuropathy. Neurological evaluations were performed at baseline and every 4 weeks thereafter according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Oral duloxetine was given at 30 mg once daily and if tolerated after 3 days, was escalated to 60 mg once daily. Data was classified by PN grade (G0 being absence of PN, to G3 being severe PN).

A total of 53 patients with gastrointestinal cancer (CRC: 40%, PC: 30%, GC: 10%, others: 10%; median age 53 years) received duloxetine for oxaliplatin-induced PN. At 4 weeks into the study, 3/53 (6%) patients improved from G3 PN to G2, 6/53 (11%) from G3 to G1, and 28/53 (52.8%) from G2 to G1, 14/53 (26%) and 2/53 (4%) had stable G3 and G2 PN, respectively. At 8 weeks of duloxetine, 10/53 (19%) of patients improved from G3 to G2, 3/53 (6%) from G2 to G1, 23/53 (43%) from G1 to G0, while 11/53 (21%), 2/53 (4%), and 4/53 (8%) remained stable

at G1, G2, and G3, respectively. Overall, duloxetine resulted in a response rate of 89% and stable PN in 11%. In addition to PN, duloxetine helped in improving depression in 50% of these patients and decreased the pain score in an additional 23%.

Overall, duloxetine was well-tolerated with majority of toxicities in G1-2 grade: dizziness (15%), drowsiness (11%), sexual side effects (11%), dry mouth (11%), insomnia (8%), headache (8%). Only 5 patients had to stop duloxetine due to G3 drowsiness, insomnia, dry mouth, and headache.

Dr Chi concluded by pointing to the need for a prospective randomised trial to study the effectiveness of duloxetine in treating oxaliplatin-induced PN. Moreover, cost effectiveness of duloxetine in concurrently improving PN, depression, and pain needs to be studied as well.

1. Chi J, et al. Duloxetine (DL) in treatment of oxaliplatin-induced peripheral neuropathy (PN). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 195.

Hepatobiliary Cancer

Ivosidenib in second-line improves OS in IDH1-mutant cholangiocarcinoma

The final overall survival (OS) analysis of the phase 3 ClarIDHy trial demonstrated that oral ivosidenib therapy achieved a 21% reduction in second-line in the risk of death in patients with *IDH1*-mutant cholangiocarcinoma compared with placebo.

Approximately 13% of patients with intrahepatic cholangiocarcinoma have somatic mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*), which confers a poor clinical outcome. Dr Andrew Zhu (Harvard Medical School, USA) presented the final OS analysis of the international phase 3 ClarIDHy study (NCT02989857), which tested the efficacy and safety of ivosidenib, oral, first-in class, oral small molecule IDH1 inhibitor, in patients with previously treated *IDH1*-mutant cholangiocarcinoma [1].

Patients were randomised 2:1 to receive 500 mg ivosidenib daily (n=126) or placebo (n=61). Crossover from the placebo arm to ivosidenib was allowed upon radiographic progression; with the longer follow-up, 70.5% of patients had crossed over to receive ivosidenib. The primary endpoint of the trial was progression-free survival (PFS) by blinded independent review; key secondary end points were OS, objective response rate, PFS by local review, safety and tolerability, pharmacokinetics and pharmacodynamics, as well as health-related quality-of-life. The primary endpoint was previously met; median PFS 2.7 months in the ivosidenib arm versus 1.4 months in the placebo arm (HR 0.37; 95% CI 0.25–0.54, P<0.0001) [2].

The presentation at ASCO GI focused on the updated OS results, which showed that the median OS was 10.3 months in patients who received ivosidenib compared with 7.5 months for those who received placebo (HR 0.79; 95% CI 0.56-1.12; 1-sided P=0.093). The 6-month OS rates were 69% and 57% for ivosidenib and placebo, respectively, and 43% and 36% at 1 year. Adjusting for crossover to ivosidenib showed that the median OS for patients in the placebo arm was 5.1 months (HR 0.49; 95% CI 0.34-0.70; P <0.0001).

Regarding safety, updated results showed that the most common treatment-emergent adverse effects (AEs) in the total ivosidenib and placebo groups comprised of nausea (38.0% vs 28.8%), diarrhoea (33.1% vs 16.9%), fatigue (28.9% vs 16.9%), abdominal pain (22.3% vs 15.3%), cough (21.7% vs 8.5%), decreased appetite (21.7% vs 18.6%), ascites (19.9% vs 15.3%), vomiting (19.9% vs 18.6%), and anaemia (18.1% vs 5.1%). Grade 3 or higher treatment-emergent AEs were seen in 53% of ivosidenib-treated patients, which includes those who also crossed over from placebo, compared with 37.3% for placebo-treated patients. The most common grade 3 or higher treatment-emergent AEs reported in the ivosidenib and placebo groups, respectively, were ascites (9.0% vs 6.8%, respectively), blood bilirubin increase (5.4% vs 1.7%), and anaemia (7.2% vs 0%).

Dr Zhu concluded: “The ClarIDHy study represents the first phase 3 study of a targeted, oral therapeutic with a noncytotoxic mechanism of action in advanced *IDH1*-mutant cholangiocarcinoma. Along with a tolerable safety profile

and supportive quality of life, these final efficacy results demonstrate the clinical benefit of ivosidenib in this patient population, for which there is an urgent need for new therapies."

1. Zhu A, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 266.
2. Abou-Alfa GK, et al. Lancet Oncol. 2020 Jun;21(6):796-807.

Final phase 2 results of second-line infigratinib for advanced cholangiocarcinoma

FGFR inhibitor infigratinib showed overall response rate (ORR) of 23% and median duration of response (DOR) of 5 months against chemotherapy-refractory cholangiocarcinoma with *FGFR* fusions, while being generally well tolerated. Including unconfirmed responses increased the response rate to 34.2%, and >80% of patients obtained disease control.

Final results from this open-label phase 2 study of infigratinib (BGJ398; NCT02150967), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harbouring an *FGFR2* gene rearrangement (which occurs in 13-17% of intrahepatic cholangiocarcinoma) were presented by Prof. Milind Javle (The University of Texas MD Anderson Cancer Center, USA) [1]. All patients (n=122, median age 53 years, median of 2 prior lines of therapy) had either progressed on or were intolerant to gemcitabine-based chemotherapy; they received infigratinib at a daily dose of 125 mg for 21 days in 28-day treatment cycles. The co-primary endpoints of the trial were ORR and DOR, while key secondary endpoints included progression-free survival (PFS), disease control rate (DCR), best overall response (BOR), overall survival (OS), safety, and pharmacokinetics.

The final results showed that 1 patient achieved a confirmed complete response, 24 had partial responses, and 66 patients had stable disease during treatment, resulting in a DCR of 84.3%. Because an additional 12 patients had unconfirmed responses, the BOR was 34.3%. Median time to response was 3.6 months and median DOR was 5.0 months. Median PFS was 7.3 months and median OS was 12.2 months. In a subgroup analysis, patients who had received just 1 prior line of therapy had better response when compared with patients with 2 or more prior lines of therapy, with an ORR of 34.0% (vs 27.6%), DOR of 5.6 months (vs 4.9 months), DCR of 88% (vs 81%), and BOR of 42.0% (vs 27.6).

Infigratinib was well tolerated; the most frequently reported adverse events included calcium phosphate homeostasis (85.2%), tissue calcification (2.8%), pathological fracture (0.9%), vascular calcification/mineralisation (0.9%), and eye disorders (70.4%). Retinopathy events occurred in 16.7% of patients.

Prof. Javle concluded, "Infigratinib, administered as second- and later-line treatment, represents a new therapeutic option for [these] patients."

1. Javle MM, et al. Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 265.

Landmark OS for HCC, updated IMbrave150 data

Updated overall survival (OS) data showed continued benefit for atezolizumab in combination with bevacizumab versus sorafenib in people with unresectable and metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Prof. Richard Finn (UCLA, USA) presented the extended phase 3 IMbrave150 study findings [1].

The recently published IMbrave150 (NCT03434379) initial analysis, demonstrated superior OS and progression-free survival (PFS) data [2]. In the global, open-label, phase 3 trial, patients with unresectable HCC who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either 1,200 mg of intravenous atezolizumab every 3 weeks plus 15 mg/kg of intravenous bevacizumab every 3 weeks (n=336) or 400 mg of sorafenib twice daily (n=165) until unacceptable toxic effects occurred or there was a loss of clinical benefit. The co-primary endpoints were OS and progression-free survival (PFS) in the intention-to-treat population, as assessed at an independent review facility according to RECIST 1.1 criteria.

After a median follow-up of 15.6 months, the updated analysis showed that atezolizumab in combination with bevacizumab increased OS by 34%, with a median OS of 19.2 months, compared with 13.4 months for sorafenib (HR 0.66; 95% CI 0.52–0.85; P=0.0009, see Figure on the next page). The updated median progression-free survival (PFS) was 6.9 months versus 4.3 months, respectively (HR 0.65; 95% CI 0.53-0.81; P=0.0001). The updated OS, along with PFS and objective response rate (ORR) results, were consistent with the primary analysis (even more complete responses; 7.7%)

and support the use of the combination in HCC. Safety data for atezolizumab in combination with bevacizumab were consistent with the known safety profiles of each individual drug, with no new safety signals identified.

1. Finn RS, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 267.
2. Finn RS, et al. N Engl J Med 2020; 382:1894-1905.

Second-line pembrolizumab after progression on sorafenib benefits OS/PFS in advanced HCC

Updated 3-year follow up data from the KEYNOTE-240 trial have finally met its co-primary endpoints of overall survival (OS) and progression-free survival (PFS), confirming benefit for pembrolizumab in a second-line setting in advanced hepatocellular carcinoma (HCC) patients who have already received sorafenib.

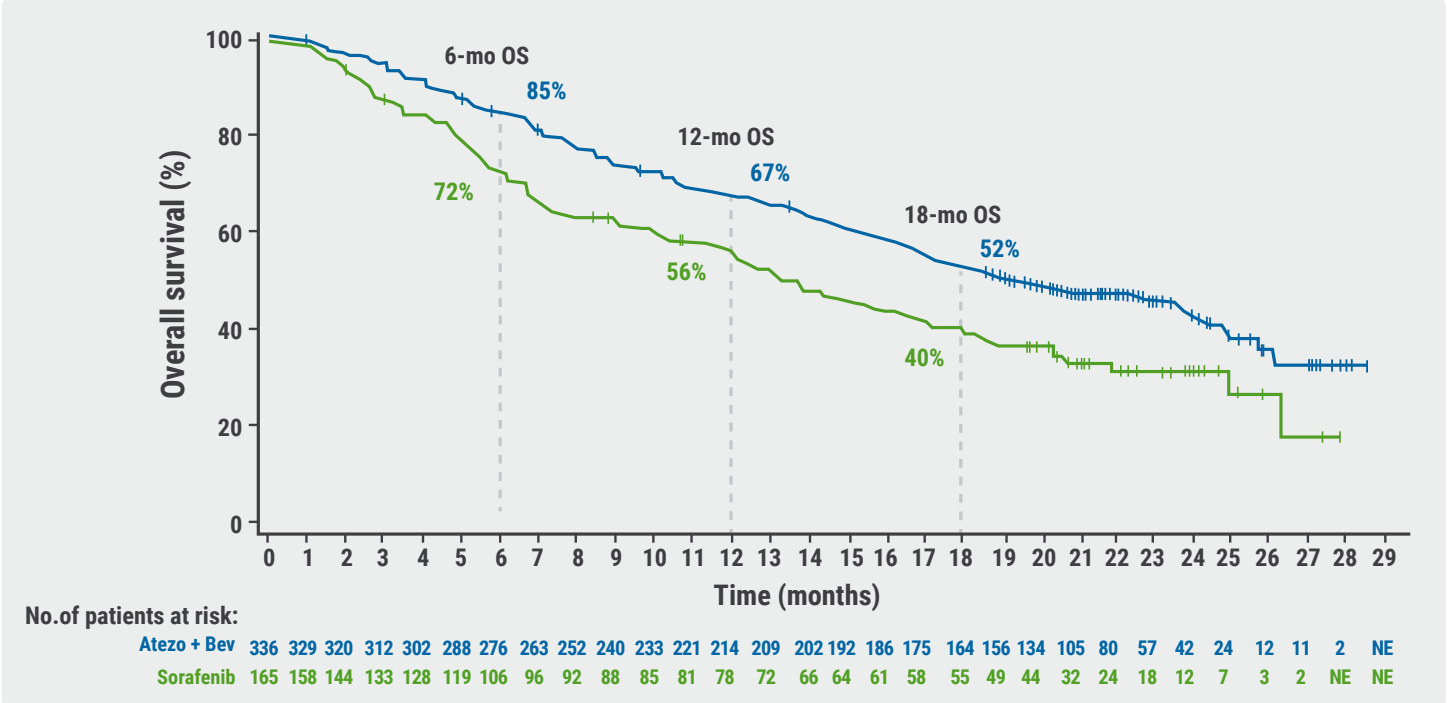
Presented by Prof. Philippe Merle (University Hospital Lyon, France), KEYNOTE-240 (NCT02702401) was a randomised, double-blind, phase 3 study which included patients with advanced HCC, who had progressed or become refractory to sorafenib [1]. Patients were randomly assigned 2:1 to receive pembrolizumab (200 mg intravenously every 3 weeks) plus best supportive care (BSC; n=278) or placebo plus BSC (n=135). Primary endpoints were OS and PFS. Initial 1-year follow-up data showed numerical benefit for pembrolizumab in OS and PFS, but the predetermined statistical significance criteria were not reached [2].

Now, with a median follow up of nearly 40 months, the median OS was 13.9 months with pembrolizumab versus 10.6 months with placebo (HR 0.77; 95% CI 0.62-0.96; P=0.011). At 36 months, the estimated OS rates were 17.7% and 11.7%, respectively. The median PFS with pembrolizumab was 3.3 months versus 2.8 months with placebo (HR 0.70; 95% CI 0.56-0.89; P=0.0011). The estimated 36-month PFS rates were 9% and 0%, respectively. Best overall responses among patients who received pembrolizumab included 10 complete responses (CRs), 41 partial responses (PRs), and 121 instances of stable disease (SD). No patients achieved a CR with placebo, 6 had PRs, and 66 had SD.

There were no new safety signals reported for pembrolizumab. Prof. Merle concluded: "The safety profile of pembrolizumab remained consistent over time with no new or unexpected adverse events.

1. Merle P, et al. Pembrolizumab (pembro) vs placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase III KEYNOTE-240 study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 268.
2. Finn RS, et al. J Clin Oncol. 2020 Jan 20;38(3):193-202.

Figure: Kaplan-Meier curve for overall survival (OS) with a median follow-up of 15.6 months [1]



Phase 2 study supports first-line pembrolizumab in advanced HCC

Patients receiving pembrolizumab monotherapy for previously untreated advanced hepatocellular carcinoma (HCC) in a phase 2 trial delivered durable responses. Results supported a favourable risk-to-benefit ratio for pembrolizumab in this population.

Dr Jean-Luc van Laethem (Hôpital Erasme–Université Libre de Bruxelles, Belgium) presented the data from cohort 2 of the single-arm, multicentre phase 2 KEYNOTE-224 trial (NCT02702414), in which patients with treatment-naïve HCC (n=51; mean age 68 years; 86% male) received pembrolizumab every 3 weeks intravenously for 35 cycles, followed by a potential re-treatment phase of 1 year [1]. The primary endpoint of the trial was objective response rate (ORR) with key secondary endpoints being duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and safety.

With a mean follow-up of 21 months (range 17-23 months) at this presentation, the ORR was 16%, all of which represented partial responses. In addition, 21 patients (41%) had stable disease. The median DOR was not reached (range 3 to >20 months), with 70% of patients estimated as having a response duration of ≥12 months, across all patient subgroups analysed. Furthermore, median TTP was 4 months with a rate at 12 months of 31%. The 12-month PFS rate was 24% (median of 4 months). OS was a median of 17 months, with a 12-month rate of 58%.

Overall, pembrolizumab was well tolerated in this patient population, with safety signals entirely consistent with the known profile. The phase 3 study results have to be awaited to conform the efficacy.

1. Van Laethem JL, et al. Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): Phase II KEYNOTE-224 study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 297.

Yttrium-90 (Y-90) glass microspheres for HCC

Findings from the retrospective LEGACY trial showed that application of yttrium-90 (Y-90) glass microspheres in the neoadjuvant stetting induced an overall response rate (ORR) of 72.2% per blinded independent central review (BICR), in 143 evaluable patients with unresectable hepatocellular carcinoma (HCC).

Prof. Robert Lewandowski (Northwestern University, Chicago, USA) presented the data from the single-arm LEGACY study (NCT01556490), in which 162 patients (mean age 66 years) with unresectable solitary HCC ≤8 cm were enrolled [1]. Of those, 143 patients were evaluable.

Patients received selective, lobar, or mixed administration of Y-90 glass microspheres at a median dose of 410 Gy, adjusted to liver volume. Most patients received the microspheres as stand-alone treatment, but they were also given as neoadjuvant therapy with the intent to bridge patients to transplant or resection as treatment. In total, 80.2% received 1 microsphere infusion, while the remainder of patients received at least 2 treatments. The primary efficacy endpoints included ORR and duration of response (DoR).

With a median follow-up of 29.9 months, ORR was 72.2% in all evaluable patients. Furthermore, of those patients who did respond, most had a good DoR ≥6 months (76.1%). Overall 3-year OS was 86.6%.

Y-90 microspheres were administered as neoadjuvant therapy for 45/162 (28%) of patients. Of those, 34 received a transplantation (21%) and 11 (7%) had resection. For neoadjuvant treatment, ORR was 80% (36/45), DoR ≥ 6 months was 31% (11/45), and 3-year OS was 93%. In total, 35 of the 45 patients (78%) receiving neoadjuvant microspheres achieved complete response (CR), while 1 achieved partial response (PR), and 9/45 (20%) were deemed not evaluable as they underwent surgery prior to the 6-month mark and did not have imaging assessments post-day 46. Histological assessment of those 9 censored participants, however, revealed that 7/9 (78%) achieved complete pathologic necrosis, 1/9 (11%) had extensive pathologic necrosis, and 1 (11%) had partial pathologic necrosis. The investigators concluded that the neoadjuvant application was effective in virtually all cases.

For the 117/162 (72%) patients who did not go on to surgical treatment, ORR was 92% (107/117), DoR ≥6 months was 73% (78/117), and 3-year OS was 84%.

Prof. Lewandowski concluded that treating solitary unresectable HCC with Y-90 glass microspheres provided robust response rates, good duration of response, and had a survival benefit, both as stand-alone treatment as well as in the neoadjuvant setting.

1. Lewandowski R, et al. Use of yttrium-90 (Y90) glass microspheres (TheraSphere) as neoadjuvant to transplantation/resection in hepatocellular carcinoma: Analyses from the LEGACY study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 300.

Sorafenib extends PFS, but not OS, for HCC transcatheter arterial chemoembolisation

The phase 2 TACTICS trial examined the combined use of transcatheter arterial chemoembolisation (TACE) and sorafenib in hepatocellular carcinoma (HCC) patients who were ineligible for resection or ablation treatment. The combination therapy prolongs progression-free survival (PFS) compared to TACE alone. However, adding sorafenib did not extend overall survival (OS).

Prof. Masatoshi Kudo (Kindai University, Osaka, Japan) presented the final OS data from TACTICS (NCT01217034), a randomised, open label, multicentre, phase 2 trial of TACE therapy in combination with sorafenib as compared with TACE alone in HCC patients [1]. Previous reports had already established that the median PFS was significantly longer in the TACE plus sorafenib arm than in the TACE alone group (25.2 vs 13.5 months; P=0.006). At that point, OS was immature with insufficient number of events [2].

Patients with unresectable HCC were randomised to TACE plus sorafenib (n=80) or TACE alone (n=76). Patients in the combination group received sorafenib 400 mg once daily for 2-3 weeks before TACE, followed by 800 mg once daily during on-demand conventional TACE sessions until time to untreatable (unTACEable) progression (TTUP). Co-primary endpoints were TTUP/PFS, and OS.

Unfortunately, the OS endpoint was not met. Median OS at this final analysis was 36.2 months in the TACE plus sorafenib arm, compared with 30.8 months in the TACE-alone arm (HR 0.86; 95% CI 0.61-1.22; P=0.40), representing a numerical benefit of 5.4 months. Updated PFS with this longer follow-up sustained significance was 22.8 month in the TACE plus sorafenib arm, compared with 13.5 months in the TACE-alone group (HR 0.66; 95%CI 0.47-0.94; P=0.02). There were no unexpected toxicities.

Prof. Kudo placed the data into perspective, stressing that the TACTICS trial clearly showed that TACE in combination with sorafenib should not be terminated at the point of intrahepatic tumour progression, when TACE is still deemed effective. Although there was a numerical OS benefit of a median 5.4 months, he speculated that the major reason that the OS did not reach significance was that many post-trial active treatments were performed in the control arm (76%), which implies that OS endpoint in TACE combination trial may not be feasible anymore in the current era of sequential therapy, with many active locoregional and systemic treatments. The results also suggest that pre-treatment of sorafenib before TACE and continued use of sorafenib after TACE will prolong the PFS and prolong the interval between each TACE session, providing the prevention of liver function deterioration often caused by TACE repetition. However, further large-scaled validation in a randomised controlled trial is warranted to establish the real benefits of the combined use of targeted agents with TACE.

1. Kudo M, et al. TACTICS: Final overall survival (OS) data from a randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients (pts) with hepatocellular carcinoma (HCC). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 270.
2. Kudo M, et al. Gut. 2020 Aug;69(8):1492-1501.

Zanidatamab provides ORR in HER2+ biliary tract cancer

In a small number of patients in a phase 1 expansion cohort, the bispecific investigational HER2-targeted antibody zanidatamab was found to safely induce durable antitumour activity in patients with HER2-overexpressing biliary tract cancer (BTC).

Findings from the phase 1 study's (NCT02892123) expansion cohort (n=21), testing the safety and initial efficacy of zanidatamab in patients with HER2-overexpressing BTC (representing 5-19% of BTC), were presented by Prof. Funda Meric-Bernstam (University of Texas MD Anderson Cancer Center, USA) [1]. In the dose-escalation part of the phase 1 study, the investigators reported that 20 mg/kg of zanidatamab administered every 2 weeks was the recommended dose. Tumours were imaged every 8 weeks.

Patients had a median age of 63 years, and 67% of patients were female. The most common diagnosis was gall bladder cancer (57%), followed by intrahepatic cholangiocarcinoma (24%), and extrahepatic cholangiocarcinoma (19%). In total, 24% of patients had received prior HER2-targeted therapy.

Reduction in tumour volume was observed in nearly all patients (16/20 evaluable patients), with a confirmed objective response rate of 40%, and an additional 40% achieving a partial response. The disease control rate was 65%, and the median duration of response was 7.4 months. Zanidatamab was found to be well-tolerated. All patients experienced treatment-emergent adverse events, the most common of which were diarrhoea (43%) and infusion-related reactions (33%). No patient experienced a grade 3 or higher

drug-related adverse event. Although 2 deaths were reported during the study, 1 was due to progressive disease and the other was attributed to an adverse event not related to zanidatamab.

"Based on these results, zanidatamab has the potential to address unmet needs in patients with HER2-positive biliary tract cancer," Prof. Meric-Bernstam concluded. A phase 2b trial in second-line is in progress (NCT04466891).

1. Meric-Bernstam F, et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 299.

Pancreatic Cancer

Borderline resectable pancreatic cancer: phase 2 results

Neoadjuvant therapy is known to improve radical resection, but overall survival (OS) benefit has not yet been proven. mFOLFIRINOX is a preoperative regimen that may change this notion.

Prof. Matthew H. Katz (University of Texas MD Anderson Cancer Center, USA) presented the results from the Alliance A021501 study (NCT02839343) [1]. This phase 2 study included 126 patients who were randomly assigned to receive either an mFOLFIRINOX regimen (8 cycles of neoadjuvant mFOLFIRINOX; arm A) or a combination regiment of mFOLFIRINOX plus radiotherapy (7 cycles of neoadjuvant mFOLFIRINOX followed by 5 days of hypofractionated radiotherapy with either stereotactic body radiotherapy or hypofractionated image-guided radiotherapy; arm B). Post-pancreatectomy, all patients received 4 cycles of adjuvant mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 2400 mg/m^2). The primary endpoint was a prespecified 13% improvement of 18-month OS in comparison to a historical control of 50%, however, treatment arms could only be compared if both met the 63% OS rate. As a consequence, arm B was considered futile and closed subject accrual following the interim analysis of the first 30 patients.

At 18 months, evaluable study participants in arm A (n=62) had an OS rate of 66.4%, which was significantly higher than the 47.3% rate in arm B (n=62). The median OS in arm A was 29.8 months, with a median event-free survival of 15 months; in arm B, OS was 17.1 months and event-free survival was 10.2 months. Nearly half (49%) of the participants in arm A proceeded to pancreatectomy following neoadjuvant therapy, as opposed to 35% in arm B. For those who had undergone resection and adjuvant therapy, the 18-month OS for arm A was 93.1%, while for arm B it was 78.9%.

Prof. Katz concluded: "Preoperative mFOLFIRINOX was associated with favourable OS relative to historical criteria in patients with borderline resectable PDAC, and mFOLFIRINOX with radiation therapy met the predefined futility boundary for R0 resection at interim analysis. Therefore, mFOLFIRINOX represents a reference preoperative regimen for patient with borderline resectable PDAC."

1. Katz MH, et al. Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 377.

No survival benefit for olaparib in *BRCA*-mutated metastatic pancreatic cancer

Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer demonstrated improved outcomes for key primary endpoints, but failed to provide improved overall survival (OS) benefit.

Prof. Talia Golan (Sheba Medical Center, Israel) presented the OS data from the phase 3 POLO trial (NCT02184195) [1]. In this trial, patients with germline *BRCA*-mutated metastatic pancreatic cancer who had had not progressed on frontline platinum-based chemotherapy for at least 16 weeks were randomised to poly(ADP-ribose) polymerase (PARP) inhibitor olaparib or placebo as maintenance therapy. Previously published results demonstrated significantly improved median progression-free survival (PFS) favouring the olaparib arm of this trial [2]. In POLO, patients were randomised 3:2 olaparib (300 mg tablet twice daily; n=92) or placebo (n=62). OS was a key secondary endpoint. Dr Golan presented the

updated findings of the primary analysis of OS after 108 deaths. Though patients were not permitted to cross over, patients in the placebo arm were eventually treated with olaparib.

With a median follow-up of 31.3 and 23.9 months for the olaparib and placebo arms, respectively, median OS was 19.0 months with olaparib and 19.2 months with placebo (HR 0.83; 95% CI 0.56-1.22; P=0.3487). OS at 36 months was 33.9% for olaparib and 17.8% for placebo. The time from randomisation to second disease progression or death (PFS2) was 16.9 months for olaparib compared with 9.3 months for the placebo group (HR 0.66; 95% CI 0.43–1.02; P=0.0613). The time to discontinuation of treatment was significantly different between the 2 arms (7.5 months for olaparib vs 3.8 months for placebo; HR 0.43; 95% CI 0.29-0.63; P<0.0001).

Safety signals were consistent with previous reports of olaparib, with the most common being anaemia, hyperglycaemia, or upper abdominal pain. Treatment discontinuation attributable to adverse events occurred in 8.9% patients taking olaparib compared with 1.6% taking placebo.

In conclusion, there was no statistically significant difference concerning OS for olaparib maintenance treatment for patients with germline *BRCA*-mutated metastatic pancreatic cancer whose disease had not progressed during platinum-based chemotherapy.

1. Golan T, et al. Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 378.
2. Golan T, et al. N Engl J Med. 2019;381(4):317-327.

Metastatic pancreatic adenocarcinoma: second-line nal-IRI plus 5FU/LV

Patients with metastatic pancreatic adenocarcinoma who progressed after conventional irinotecan-based therapies were treated with liposomal irinotecan (nal-IRI) plus fluorouracil/leucovorin (5-FU/LV), with manageable toxicities. Furthermore, the cumulative dose of prior conventional irinotecan-based therapy may be inversely correlated with response to nal-IRI plus 5FU/LV.

Prof. Kyunghye Bang (Asan Medical Center, Korea) presented this multicentre retrospective analysis [1]. The rationale was that although nal-IRI plus 5-FU/LV has demonstrated clinical benefit in patients with metastatic pancreatic adenocarcinoma who progressed after gemcitabine-based chemotherapy, this therapy on patients previously treated with conventional irinotecan has not been investigated.

All patients (n=35; median age 58 years) received prior irinotecan as the component of FOLFIRINOX. The median duration of prior irinotecan was 4.6 months and median cumulative dose of prior irinotecan was 1,230 mg (range 150-4,650 mg). The objective response rate to nal-IRI plus 5-FU/LV was 2.9% and stable disease was achieved in 31.4%. With median follow-up duration of 9.2 months, the median PFS and OS were 2.0 months and 4.4 months, respectively; 6-month PFS rate was 16.3% and OS rate was 37.5% (see Table).

Table: Outcomes of nal-IRI plus 5-FU/LV [1]

Variables	nal-IRI+5-FU/LV (n=35)
Best response	
CR	0 (0.0%)
PR	1 (2.9%)
SD	11 (31.4%)
PD	21 (60.0%)
Not evaluable	1 (2.9%)
Median PFS, months (95% CI)	2.0 (1.4–2.6)
6-month PFS rate (95% CI)	16.5% (7.5-36.0%)
Median OS, months (95% CI)	4.4 (3.0-5.7)
6-month OS rate (95% CI)	37.5% (24.2-58.2%)

The investigators measured the ratio of time-to-progression with nal-IRI plus 5-FU/LV versus time-to-progression with conventional irinotecan (0.41; range 0.07-2.07), and observed a negative correlation with the cumulative dose of prior irinotecan (R=-0.37; P=0.041). Similarly, the duration of prior irinotecan exposure was also negatively correlated to the time-to-progression with nal-IRI plus 5-FU/LV, although this did not reach statistical significance (R=-0.35; P=0.062).

1. Bang K, et al. Efficacy and safety of liposomal irinotecan plus fluorouracil/leucovorin after progression on conventional irinotecan-containing chemotherapy for metastatic pancreatic adenocarcinoma. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 382.

Neuroendocrine Cancer

No benefit of adding axitinib to ocreotide acetate in non-pancreatic neuroendocrine tumours

Adding axitinib to ocreotide acetate long-acting release to treat non-pancreatic neuroendocrine tumours (NETs) resulted in demonstrated activity with numerical clinical benefit, but did not reach significance, according to the results of a phase 2/3 study. Axitinib in this setting had a tolerable safety profile.

Dr Rocio Garcia-Carbonero (Hospital Universitario 12 de Octubre, Spain) presented the results of the randomised, double-blind phase 2 (n=106) and phase 3 (n=150) AXINET trial-GETNE-1107 (NCT01744249), which aimed to assess the efficacy of angiogenesis inhibitor axitinib in patients with advanced extra-pancreatic G1-G2 NETs.

Eligible patients (n=256; median age 61 years) were randomised to receive octreotide acetate long-acting release (30 mg every 4 weeks) with either axitinib (5 mg, twice daily; n=126) or placebo twice daily (n=130) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), time to progression, overall response rate (ORR), duration of response, biochemical response, and safety.

The primary endpoint was not met at this analysis; although median PFS favoured the axitinib arms, the difference did not reach statistical significance (17.2 vs 12.3 months; HR 0.816; P=0.169). However, ORR was significantly improved in axitinib- as opposed to placebo-treated patients (17.5% vs 3.8%; P=0.0004).

Adverse events occurred more frequently in the subjects receiving axitinib compared with placebo; grade 3-4 events occurred in 52% versus 13.8%, respectively. There were 3 treatment-related deaths, 1 in the axitinib arm (cardiac failure) and 2 in the placebo arm (myocardial infarction and hepatorenal syndrome).

1. Garcia-Carbonero R, 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-GETNE-1107). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 360.

Phase 2 abemaciclib trial in patients with advanced NETs

Prof. Kaylyn Kit Man Wong (University of Washington, USA) presented a trial-in-progress, the phase 2 trial investigating the CDK4/6 inhibitor abemaciclib in patients with advanced and refractory well-differentiated gastroenteropancreatic neuroendocrine tumours (GEP NETs).

The rationale behind this study is that long-term disease control of NETs remains a challenge, and although a number of preclinical studies have indicated proof-of-concept for CDK 4/6 inhibition in NETs *in vitro* and *in vivo*, there have been no prospective trials demonstrating efficacy. Specifically, the clinical use of selective small molecule CDK 4/6 inhibitor abemaciclib in some metastatic breast cancer subtypes has supported clinical efficacy, demonstrated good tolerability, and has demonstrated central nervous system penetration.

This phase 2 trial is accruing patients with metastatic or locally advanced unresectable well-differentiated grade 1-2 GEP NETs to receive abemaciclib (200 mg orally every 12 hours continuously in 28-day cycles). Patients must have progressed on ≥1 prior systemic therapy; somatostatin analogues can be concurrent or used previously. The primary endpoint is objective response rate (ORR) by RECIST v1.1. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and toxicity. A 2-stage design with 88% power to detect an increase in ORR to 20% with abemaciclib at the 1-sided 0.05 level would require a total of 37 patients.

Stage 1 will include 20 patients. Of those, if at least 1 response is observed, the study will continue to enrol another 17 patients. To date, 3 patients have been enrolled in stage 1, and data collection is ongoing.

1. Wong KM, et al. Phase II trial of the CDK4/6 inhibitor abemaciclib in patients (pts) with advanced and refractory well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP NETs). ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract TPS376.

COVID-19

COVID-19 impact on gastrointestinal cancer care

A new study identified that patients with colorectal cancer experienced the most disruption from the COVID-19 pandemic, resulting in delays in screening, diagnosis, and treatment that will likely increase morbidity and mortality. A second study found that continuing systemic therapy during the pandemic is relatively safe.

The first study evaluated the healthcare utilisation of patients with gastrointestinal cancers. A retrospective cohort was compared during and prior to the COVID-19 pandemic at the University of Pennsylvania Health System in the first 20 weeks of both 2019 and 2020. Results were presented by Dr Nicholas Perkons (University of Pennsylvania, Philadelphia, USA) [1].

COVID-19 was attributable for a 45% decline in new patient visits for screening across all gastrointestinal malignancies. Notably, colorectal cancers were most affected, with a 53% decrease in new patient visits compared with 2019, and a 91% decrease in colonoscopies (P<0.0001). Hospital admissions for patients with diagnosed gastrointestinal malignancies decreased by 37% over the same period in 2019 (P<0.0001). Radiology services decreased by 38% (P<0.0001), radiation oncology encounters fell 12% (P<0.01), and surgeries decreased by 16% (P<0.01).

A second prospective study analysed the effects of the pandemic on systemic therapies for gastrointestinal cancer patients in a large UK comprehensive Cancer Centre, as presented by Dr Eirini Tsotra (Guy's and St Thomas' NHS Foundation Trust, London, UK) [2]. Of 417 gastrointestinal cancer patients receiving systemic therapies during the study period, 14 (3.4%) were diagnosed with COVID-19, of whom 57.1% had severe infection and 21.4% died from COVID-19 (vs 3.7% mortality in the non-infected group). All the patients who died from COVID-19 were male and were receiving palliative chemotherapy. Only 1 patient was neutropenic (grade 1) when diagnosed with COVID-19. Although limited, this single-centre study indicates that continuing systemic therapy throughout the pandemic is relatively safe.

The findings of both these studies highlight the importance of proactively reinstating regular gastrointestinal cancer screening and cancer therapies. Future studies will assess the impact of these disruptions on long-term morbidity and mortality.

1. Perkons N, et al. Quantifying the impact of the COVID-19 pandemic on gastrointestinal cancer care delivery. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 30.
2. Tsotra E, et al. COVID-19 infection in gastrointestinal (GI) cancer patients receiving systemic anticancer treatment (SACT) during the outbreak of the pandemic: The Guy's Cancer Centre experience. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 455.

Treatment delay for cholangiocarcinoma adjuvant therapy does not affect OS

A retrospective analysis of patients with biliary cancers identified relevant patient characteristics for the timing of adjuvant treatment initiation. Importantly, especially concerning the COVID-19 pandemic, there was no survival difference between groups when comparing initiation of adjuvant therapy before or after 2-, 3-, or 4-month timepoints.

The analysis was presented by Dr Matthew Parsons (University of Utah, USA) [1]. With the current pandemic, there was a need to understand the factors associated with timing of adjuvant therapy in the management of intrahepatic and extrahepatic cholangiocarcinoma and the impact of delays on overall survival (OS).

To this end, patients who had undergone surgery and adjuvant chemotherapy and/or radiotherapy were analysed with regard to the timing of the initiation of adjuvant therapy (n=7,422). Patients who underwent neoadjuvant therapy or received chemotherapy or radiotherapy with palliative intent were excluded. Just over half (53%) initiated adjuvant therapy within 2 months of surgery, 84% by 3 months, and 94% by 4 months.

The analysis indicated that high-grade disease, macroscopically positive margins, and tumours >5 cm were associated with earlier initiation of adjuvant treatment, i.e. at 2 months or earlier. Patients who received early adjuvant therapy were also more likely to be treated with a combination of chemotherapy and radiotherapy. Factors associated with

delay of adjuvant therapy beyond 3 months post-surgery included Charlson scores ≥1, and Hispanic race. There was no survival difference between groups when comparing initiation of adjuvant therapy before or after 2-, 3-, or 4-month time points.

In conclusion, these findings are relevant in the era of COVID-19 when minimising patient exposure to healthcare settings may need to be considered when deciding on the timing of adjuvant therapy. If a delay is necessary, these results suggest that there is no survival detriment to initiating adjuvant therapy beyond 3 or 4 months after surgery for biliary cancers. Of note, adjuvant chemotherapy is not standard practice in all European countries.

1. Parsons M et al. The implications of treatment delays in adjuvant therapy for cholangiocarcinoma patients. ASCO Gastrointestinal Cancers Symposium 2021, 15-17 January. Abstract 291.