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PEER-REVIEWED CONFERENCE REPORT

OS Benefit for T-DXd in HER2-positive Gastric Cancer

The final results of the phase 2 DESTINY-Gastric01 trial showed that trastuzumab deruxtecan was superior to a standard PC chemotherapy regimen in patients with HER2-positive advanced gastric or gastroesophageal cancer.

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Durvalumab ± Tremelimumab for Unresectable HCC

While durvalumab monotherapy was non-inferior, tremelimumab plus durvalumab improved the OS of patients with unresectable hepatocellular carcinoma compared with sorafenib in the HIMALAYA trial.

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Does Sintilimab Plus FOLFIRINOX Benefit Metastatic Pancreatic Cancer?

Although sintilimab improved ORR and maintained a tolerable safety profile, it did not improve OS or PFS in the phase 3 CISPD3 trial.

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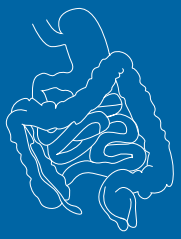

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Letter from the Editor

Dear colleagues,

It is my pleasure to introduce our report from ASCO's 2022 Gastrointestinal (GI) Cancers Symposium.

Preventive strategies have been refined for patients at risk for colorectal cancers (CRC): you will find a quite detailed proposal in this report, which has been adopted in the US – and should be so in Europe, soon. In the meanwhile, you might as well provide benefit for your patients as soon as tomorrow.

In advanced disease, be sure to check for HER2 – as there is firm benefit of targeted treatment (with a conjugate) in advanced gastric cancer – and beginning evidence in CRC, too.

Immunotherapy is still expanding its indications, with benefit in combination with chemotherapy in upper GI, but also biliary cancer.

The range of beneficial first-line treatment options in hepato-cellular cancer is also rapidly expanding, with both immune-monotherapies and combination of checkpoints.

And a Chinese study may have "reanimated" checkpoint inhibitors in advanced pancreatic cancer, combined with FolFirinox.

Interaction between checkpoint inhibitors and the gut microbioma, Artificial Intelligence in the management of GI cancers, new molecules; as always, there is a lot more for you to discover in this issue.

I wish you a pleasant and peaceful read in these troubled and violent times.

Yours, sincerely
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

EMR versus ESD in oesophageal cancer

A controversial topic in early-stage oesophageal cancer is the role of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The advantages and disadvantages of both methods were discussed with respect to the latest evidence on the subject [1].

"The treatment of oesophageal adenocarcinoma (OAC) and squamous cell carcinoma (SCC) require different approaches," said Dr Vani Konda (Baylor University Medical Center, TX, USA). "In both types of cancer, visible lesions need to be investigated by endoscopic resection to establish an accurate histopathologic diagnosis."

Endoscopic eradication therapy is the standard treatment option for high-grade dysplasia or intramucosal carcinoma in Barrett's oesophagus. "EMR can eradicate 96.6% or more of the neoplastic tissue," said Dr Konda. "However, complications (perforation in 2%; stricture in 37%) can occur during this procedure. If a hybrid therapy is used (i.e. EMR + radiofrequency ablation), the eradication rate is 93.4%, but complications are less common (perforation in 0.2%; stricture in 10.2%)."

"In OAC, the risk of lymph node metastasis is <2% if it concerns intramucosal carcinoma but may be 20% or higher when the tumour has infiltrated the submucosa. Nonetheless, patients with low-risk submucosal cancer fare well on EMR. Only when the patient has a medium-risk or high-risk submucosal cancer, or large or non-lifting lesions, ESD may deliver a better outcome than EMR. Although most patients can be treated with follow-up ablation, patients with high-risk features, such as lymph node metastasis, vascular or neural invasion, high-risk submucosal cancer, or positive vertical margins may require oesophagectomy."

The aggressiveness of SCC requires a different approach, said Dr Konda. "In SCC, the risk of lymph node metastasis or neural or vascular invasion is significantly larger than in OAC. Therefore, ESD is warranted for high-grade squamous dysplasia and superficial cancers of this type. Circumferential ESD may be used when extensive superficial lesions are present, but the risk for stricture is profound. In addition, small lesions (<15 mm) may be treated with EMR. Again, patients with high-risk features may need oesophagectomy." Finally, Dr Konda argued that patient and disease characteristics as well as the available expertise need to be considered in the decision-making process. We can conclude that the decision needs to be discussed in multidisciplinary team at an expertise centre.

1. Konda V, et al. Endoscopic Submucosal Dissection Versus Endoscopic Mucosal Resection for Early-Stage Esophageal Cancer. Controversial Issues in Localized Gastroesophageal Cancer, ASCO GI 2022, 20–22 January.

Pre-operative chemoradiation versus peri-operative chemotherapy for oesophageal cancer

Pre-operative chemoradiation and peri-operative chemotherapy are 2 treatment options for patients with lower oesophageal adenocarcinoma (OAC) and gastroesophageal junction adenocarcinoma (GEJAC). The latest evidence on this topic was discussed by Prof. Karyn Goodman (Icahn School of Medicine at Mount Sinai, NY, USA) [1].

"The R0 resection rate in patients with OAC or GEJAC is only 60%," said Prof. Goodman. "However, pre-operative chemoradiation has demonstrated to improve R0 resection rates." The CROSS trial showed that neoadjuvant chemoradiation delivered higher R0 resection rates (88%) compared with surgery alone (59%) in patients with OAC or GEJAC [2]. Notably, the overall risk of distant relapse was lower in the chemoradiation arm at 10 years follow-up, but the rate of isolated distant recurrences was similar between the 2 arms, suggesting that the low-dose chemotherapy of this regimen did not exert full control.

"The FLOT4 trial showed that peri-operative chemotherapy with FLOT delivered an R0 resection rate of 85% in patients with GEJAC or gastric cancers," continued Prof. Goodman [3]. The 5-year overall survival rates of the 2 regimens in FLOT4 (45%) and the CROSS trial (43%) appear similar. However, the populations of these trials were very different. FLOT4 included patients with gastric cancer (44%) and GEJ cancer (56%), whereas CROSS included patients with GEJ cancer (22%) and oesophageal cancer (74%) with mixed histologies (adenocarcinoma and squamous cell carcinoma). Interestingly, 95% of the patients completed the

CROSS regimen but only 46% completed the post-operative FLOT regimen, mostly due to grade 3 or 4 neutropaenia.

A direct comparison between chemoradiation and FLOT suggested similar efficacy of the 2 regimens in patients with oesophageal or GEJ cancer [4]. However, adjuvant immunotherapies may improve the outcomes of neoadjuvant chemoradiation [5]. "Given the current evidence, I would recommend neoadjuvant chemoradiation in patients with Siewert 1 or 2 OAC or GEJAC, patients with bulky tumours, or patients with contraindications to FLOT. For patients with gastric or Siewert 3 GEJ tumours, patients with contraindications to radiotherapy, or those with diffuse/signet ring cell histology, I would recommend peri-operative chemotherapy. To improve outcomes, we need to tailor neoadjuvant chemotherapy to the tumour biology. PET-directed therapy may be used for this purpose. All in all, I think that induction chemotherapy addresses micrometastatic disease, whereas radiotherapy exerts local control in patients OAC and GEJAC, offering the best of both worlds."

1. Goodman KA, et al. Preoperative Chemoradiation Versus Perioperative Chemotherapy for Lower Esophageal and Gastroesophageal Junction Adenocarcinoma. Controversial Issues in Localized Gastroesophageal Cancer. ASCO GI 2022, 20–22 January.
2. Van Hagen P, et al. N Engl J Med 2012;366:2074–2084.
3. Al-Batran SE, et al. Lancet. 2019;393(10184):1948–1957.
4. Reynolds JV, et al. Abstract 4004. ASCO 2021, 4–8 June.
5. Kelly RJ, et al. N Engl J Med 2021;384:1191–1203.

AK104 plus chemotherapy promising first-line option for gastric cancer

The combination therapy of the PD-1/CTLA-4 bispecific antibody AK104 plus chemotherapy showed promising activity and a manageable safety profile in patients with advanced gastric or gastroesophageal junction (GEJ) cancer [1]. The results of the current AK104-201 phase 1b/2 study drove the design of a phase 3 study investigating this combination therapy.

"Synergy between immune checkpoint inhibitors and chemotherapy in gastric or GEJ cancer has been demonstrated in 2 studies," Dr Jiafu Ji (Beijing Cancer Hospital, China) said [2,3]. "In addition, we have learned that anti-PD-1 plus anti-CTLA-4 co-therapy outperforms anti-PD-1 alone, but at the cost of higher toxicity."

The current phase 1b/2 AK104-201 study (NCT04380805) assessed the efficacy and safety of AK104, a PD-1/CTLA-4 bispecific antibody, in combination with XELOX or modified XELOX as first-line therapy for patients with gastric or GEJ cancer (n=96; mean age 62.7 years). Participants received doses of AK104 ranging between 4–15 mg/kg every 2 weeks. Objective response rate (ORR) based on RECIST v1.1 was the primary endpoint.

ORR was 65.9%, with 2.3% of the patients showing a complete response and 63.6% of the patients displaying a partial response. The ORR was numerically highest in the 10 mg/kg subgroup (83.3%) and lowest in the 6 mg/kg subgroup (56.4%). The median duration of response was 6.9 months. In the total cohort, the median progression-free survival was 7.1 months, and the median overall survival was 17.4 months.

The safety analysis did not reveal new safety issues of this combination. Moreover, no increase in treatment-related adverse events (TRAEs) was observed with dose escalation. Grade 3 or higher TRAEs were reported in 62.5% of the patients and the most common any-grade TRAEs were decreased platelet counts (28.1%), anaemia (26.0%), increased aspartate aminotransferase (26.0%), and decreased neutrophil count (22.9%).

Dr Ji concluded that the efficacy and safety data of this first-line treatment for patients with gastric or GEJ cancer are encouraging and need to be validated in the ongoing phase 3 study.

1. Ji J, et al. AK104-201: A phase 1b/2, multicenter, open-label study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with chemotherapy (chemo) as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer. Abstract 308, ASCO GI 2022, 20–22 January.
2. Yelena YJ, et al. Lancet. 2021;398:27–40.
3. Jianming X, et al. LBA53, ESMO 2021, 16–21 September.

DESTINY-Gastric01: OS benefit of T-DXd over chemotherapy for HER2-positive gastric cancer

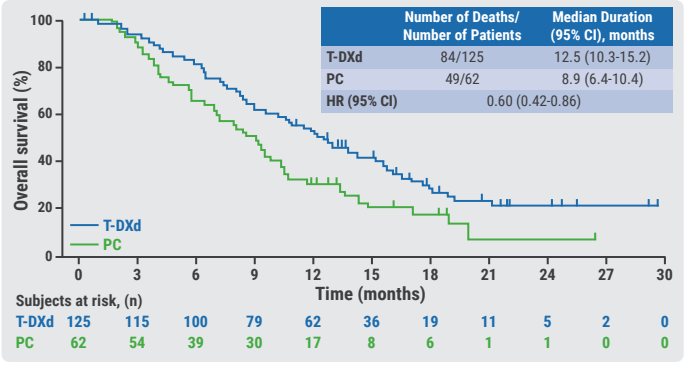
The final results of the phase 2 DESTINY-Gastric01 trial showed that trastuzumab deruxtecan (T-DXd) was superior to a standard PC chemotherapy regimen in patients with HER2-positive advanced gastric or gastroesophageal cancer. Also, the updated safety data were consistent with the primary analysis of this study [1].

The open-label, multicentre, phase 2 DESTINY-Gastric01 trial (NCT03329690) included 188 patients with HER2-positive advanced gastric or gastroesophageal cancer who had undergone 2 or more prior lines of therapy, including fluoropyrimidine and a platinum agent. Participants were randomised 2:1 to T-DXd, 6.4 mg/kg every 3 weeks, or a standard PC chemotherapy regimen (i.e. irinotecan and/or paclitaxel). In the primary analysis, T-DXd outperformed PC chemotherapy on the primary endpoint of objective

response rate (ORR) by independent central review. Dr Kensei Yamaguchi (Cancer Institute Hospital of JFCR, Japan) presented the final results of this trial.

The ORR was 51.3% in the T-DXd arm compared with 14.3% in the PC arm (P<0.0001). In the T-DXd arm, 9.2% of the patients displayed a complete response and 42.0% of the patients had a partial response. In addition, 35.5% of the patients in the T-DXd arm demonstrated stable disease. The median duration of response was 12.5 months in patients receiving T-DXd versus 3.9 months in patients receiving chemotherapy. The updated overall survival (OS) analysis, with a maturity of 71.1%, represented superior anti-tumour activity of T-DXd over chemotherapy (median OS 12.5 vs 8.9 months; see Figure). Dr Yamaguchi added that the 40% reduced risk of death in patients receiving T-DXd is a clinically meaningful OS benefit.

Figure: Overall survival in DESTINY-Gastric01 [1]



The updated safety analysis did not show unexpected safety issues. Grade 3 or higher adverse events (AEs) were more common among T-DXd receivers than among chemotherapy receivers (85.6% vs 56.5%). The most frequently reported grade 3 or higher AEs in the T-DXd arm were decreased neutrophil count (51.2%), anaemia (38.4%), and decreased white blood cell count (20.8%). Notably, 12.8% of the patients receiving T-DXd displayed interstitial lung disease (ILD)/pneumonitis after a median time to first onset of 102.5 days; 13 out of 16 cases of ILD/pneumonitis were grade 1 or 2 events, none were grade 5.

Dr Yamaguchi concluded that these updated results confirm that T-DXd has potential as a treatment option for patients with HER2-positive advanced gastric or gastroesophageal junction cancer after 2 or more previous lines of therapy.

1. Yamaguchi K, et al. Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results From a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01). Rapid Abstracts Session A, ASCO GI 2022, 20–22 January.

The emerging role of AI in gastroesophageal cancer

The role of artificial intelligence (AI) in the detection of upper gastrointestinal (GI) neoplasia has been emerging in recent years. Dr Wai Leung (University of Hong Kong, China) discussed the latest evidence on AI and the diagnosis, characterisation, risk prediction, and the examination of upper GI neoplasia [1].

A retrospective meta-analysis demonstrated that AI was accurate in detecting gastric neoplastic lesions, with an area under the receiver-operating characteristic curve (AUC) of 0.96, a sensitivity of 0.92, and a specificity of 0.88. For the detection of Barret's oesophagus neoplasia, the corresponding results were 0.96, 0.88, and 0.90. For squamous oesophagus neoplasia the data showed an AUC of 0.92, a sensitivity of 0.84, and a specificity of 0.90 [2]. In addition, a prospective study including 1,198 patients showed a similar accuracy of endoscopic detection of gastric lesions and neoplasms by AI (0.72) and by expert (0.68). However, the AI model displayed a higher sensitivity (100% vs 85.5%; P=0.003) and negative predictive value (100% vs 86.4%; P=0.002) [3].

Furthermore, AI has been investigated for the purpose of quality control during endoscopy. A randomised controlled trial including 1,050 patients demonstrated that the use of AI during endoscopy significantly reduced the number of blind spots (mean 5.38 vs 9.82; P<0.001) [4]. Also, a crossover study comparing AI-assisted examination and routine examination of upper GI lesions showed that the miss rate per lesion was lower in the AI-first group (6.1%) than in the routine-first group (27.3%; P=0.015), resulting in a lower biopsy rate among patients who underwent AI-assisted examination first [5].

Another focus of AI research is endoscopy training. A study showed that feedback from AI improved the endoscopic results of endoscopists in training compared with their endoscopic decisions before AI feedback: negative predictive value (74.7% vs 82.5%; P=0.049), accuracy (69.3% vs 74.7%; P=0.003), and AUC (0.69 vs 0.75; P=0.02) [6].

A study by Ali et al. showed that AI could also improve the 3D quantification of Barrett's oesophagus, which is helpful for further interventions and monitoring of these patients [7]. Also, the detection of oesophageal adenocarcinoma, a labour-intensive process, could be simplified using AI and thus reduce the manpower required [8]. Finally, AI was able to

predict the risk of Barrett's oesophagus (AUC 0.86) or gastric cancer development (AUC 0.90) in 2 recent studies [9,10].

Dr Leung concluded that these positive results need to be confirmed in future research, establishing the clinical applicability and cost-effectiveness of AI in the detection of upper GI neoplasia.

1. Leung WK, et al. Artificial Intelligence-Assisted Detection of Upper Gastrointestinal Neoplasia. Presentation 1, Breakout Session: Understanding Disparities and Expanding Access Through Diagnostic Technology and Treatment in Gastroesophageal Cancers, ASCO GI 2022, 20–22 January.
2. Lui TKL, et al. Gastrointest Endosc. 2020;92(4):821–830.
3. Wu L, et al. Gastrointest Endosc. 2022;95(2):269–280.e6.
4. Wu L, et al. Endoscopy. 2021;53:1199–1207.
5. Wu L, et al. Lancet Gastroenterol Hepatol. 2021;6(9):700–708.
6. Lui TKL, et al. Endosc Int Open. 2020;8(2):E139–E146.
7. Ali S, et al. Gastroenterology. 2021;161:865–878.e8.
8. Gehrung M, et al. Nat Med. 2021;27(5):833–841.
9. Rosenfeld A, et al. Lancet Digit Health. 2020;2(1):E37–48.
10. Leung WK, et al. Aliment Pharmacol Ther. 2021;53:864–872.

DCF outperforms standard-of-care for locally advanced oesophageal cancer

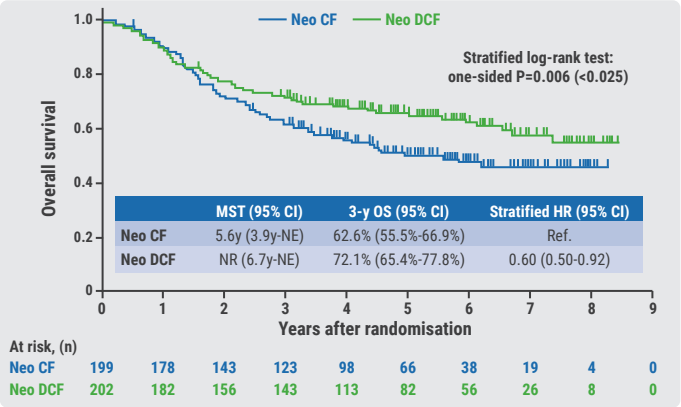
Docetaxel plus neoadjuvant cisplatin and 5-fluorouracil (DCF) chemotherapy was superior to CF chemotherapy alone in patients with locally advanced oesophageal cancer, according to the primary analysis of the phase 3 JCOG1109 NExT trial. Moreover, the toxicity profile of the DCF combination regimen was manageable. Therefore, neoadjuvant DCF represents a potential new standard therapy for this Japanese patient population [1].

"In Japan, neoadjuvant chemotherapy with CF is the standard-of-care in locally advanced oesophageal cancer," Dr Ken Kato (National Cancer Center Hospital, Japan) explained.

The current 3-arm, randomised-controlled, phase 3 JCOG1109 trial (UMIN000009482) compared neoadjuvant DCF with neoadjuvant CF and neoadjuvant CF with radiotherapy (CF-RT). In total, 601 patients were randomised 1:1:1 to one of the 3 treatment arms. Subsequently, all patients received transthoracic oesophagectomy with regional lymphadenectomy. The primary endpoint was overall survival (OS).

The 3-year OS rates were in favour of the DCF arm compared with the CF arm (72.1% vs 62.6%; HR 0.68; one-sided P=0.006; see Figure). There was no statistically significant OS benefit of CF-RT over CF (68.3% vs 62.6%; HR 0.84; P=0.12). These results were consistent across subgroups. Moreover, the median progression-free survival calculation displayed superior outcomes for the DCF arm compared with the CF arm (not reached vs 2.7 years; HR 0.67).

Figure: Overall survival with DCF vs CF in JCOG1109 [1]



The safety profile of DCF was manageable. In patients treated with DCF, certain grade 3–4 adverse events were more common than in the CF arm: neutropenia (85.2% vs 23.4%), hyponatraemia (26.0% vs 6.2%), febrile neutropenia (16.3% vs 1.0%), and appetite loss (21.4% vs 8.3%). Grade 3–4 oesophagitis was more frequently observed in the CF-RT arm (8.9%) than in the CF or DCF arms (both 1.0%). Furthermore, the intensified DCF regimen did not result in an increase in post-operative complications or post-operative mortality compared with the CF regimen.

Dr Kato concluded that the neoadjuvant DCF regimen represents a new standard treatment in patients with locally advanced oesophageal cancer, given the OS benefit of this treatment and its manageable toxicity profile. More data is needed in the Western population.

1. Kato K, et al. A randomized controlled phase 3 trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study. Oral Abstract Session A, ASCO GI 2022, 20–22 January.

Nivolumab in gastric cancer: Efficacy update and the role of gut microbiome

Nivolumab added to chemotherapy displayed ongoing increased efficacy over chemotherapy alone in treatment-naïve patients with advanced gastric cancer (GC), gastro-esophageal junction cancer (GEJC), or oesophageal adenocarcinoma (OAC). The long-term follow-up data of the CheckMate 649 trial also did not show new safety issues for this combination regimen [1]. In addition, the observational DELIVER study revealed that host-related biomarkers in the gut microbiome could predict toxic events related to nivolumab therapy in patients with advanced GC [2].

The phase 3 CheckMate 649 trial (NCT02872116) previously showed that, after 12 months of follow-up, treatment with

nivolumab plus chemotherapy was superior to chemotherapy alone in patients with advanced GC, GEJC, or OAC [3]. These results led to the approval of this regimen in the US and Europe. The CheckMate 649 trial randomised patients to nivolumab plus standard chemotherapy (n=789), chemotherapy alone (n=833), or nivolumab plus ipilimumab (n=409). The primary endpoints were overall survival (OS) and progression-free survival (PFS) in patients with PD-L1 combined positive score (CPS) ≥5. Dr Kohei Shitara (National Cancer Center Hospital East, Japan) presented the results after 24 months of follow-up of the nivolumab plus chemotherapy arm and the chemotherapy alone arm.

At 2 years, a clinically meaningful improvement in median OS was observed in the nivolumab plus chemotherapy arm (13.8 months) compared with the chemotherapy alone arm (11.6 months; HR 0.79). Similarly, long-term follow-up showed maintained PFS benefits for the combination arm (7.7 months vs 6.9 months; HR 0.79).

The safety analysis did not identify new safety issues. Grade 3 or 4 adverse events (AEs) were more common in the combination arm (60%) than in the monotherapy arm (45%). The most frequently reported grade 3 or 4 AEs in the combination arm were neutropenia (15%), decreased neutrophil count (11%), and anaemia (6%). Immune-related AEs of grade 3 or 4 occurred in ≤5% of patients in the combination group across organ categories. All in all, the safety profile of nivolumab plus chemotherapy was acceptable.

The OS benefit of nivolumab plus chemotherapy was consistent across key subgroups in patients with PD-L1 CPS ≥5. "Although patients with higher PD-L1 CPS cut-offs benefitted more from the combination regimen, a numerical benefit was also seen in patients with lower PD-L1 CPS," said Dr Shitara. In addition, the overall response rate and median duration of response in patients with PD-L1 CPS ≥5 were 60% and 9.7 months in the combination arm versus 45% and 7.0 months in the chemotherapy alone arm. The corresponding results for patients with PD-L1 CPS <5 were 55% and 7.7 months in the nivolumab plus chemotherapy group and 46% and 6.9 months for the chemotherapy group.

Prof. Stefano Cascinu (Università Vita-Salute San Raffaele, Italy) mentioned that next to PD-L1 CPS, the subgroup analysis revealed other factors that may influence patient selection for this novel combination therapy. "For example, patients with malnutrition or peritoneal involvement may benefit less from the nivolumab plus chemotherapy regimen. Furthermore, we need to establish the efficacy of this regimen in patients with ECOG PS scores of 2, a relevant subgroup in clinical practice."

Gut microbiome

Dr Yu Sunakawa (St. Marianna University School of Medicine, Japan) said that several studies indicated that the composition of the gut microbiome is associated with AEs of PD-1 inhibitor therapy. In GC, this association is not well investigated. Dr Sunakawa and colleagues designed the DELIVER trial (UMIN000030850) to assess whether host-related factors, including information in the gut microbiome, are associated with the efficacy of nivolumab and AEs evoked by nivolumab therapy in patients with advanced GC. The research team collected blood samples and faecal samples from 501 patients with GC who were treated with nivolumab. The secondary outcomes of this study, relationships between markers of the gut microbiome and clinical outcomes, were presented by Dr Sunakawa.

The data displayed a significant association of the genus of Arthrobacter and nivolumab-induced skin toxicities in both the training cohort (n=200; P=0.02) and the validation cohort (n=301; P=0.01). Moreover, the fatty acid metabolism pathway was related to skin toxicities in both cohorts (P=0.02 and P=0.01, respectively). Furthermore, certain genetic polymorphisms were related to toxicities. Single nucleotide polymorphisms (SNPs) of *SEMA4D* and *NOTCH1* were associated with diarrhoea, and SNPs of *IL6R* and *NLRC5* were related to skin toxicities. According to Dr Sunakawa, these SNPs may become biomarkers for nivolumab-induced diarrhoea and skin toxicities and could help in toxicity management.

1. Shitara K, et al. Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-months follow-up of CheckMate 649. Abstract 240, ASCO GI 2022, 20–22 January.
2. Sunakawa Y, et al. Host-related biomarkers including gut microbiome to predict toxicities of nivolumab in advanced gastric cancer: DELIVER trial (JACCRO GC-08). Abstract 308, ASCO-GI 2022, 20–22 January.
3. Janjigian YY, et al. Lancet. 2021;398(10294):27–40.

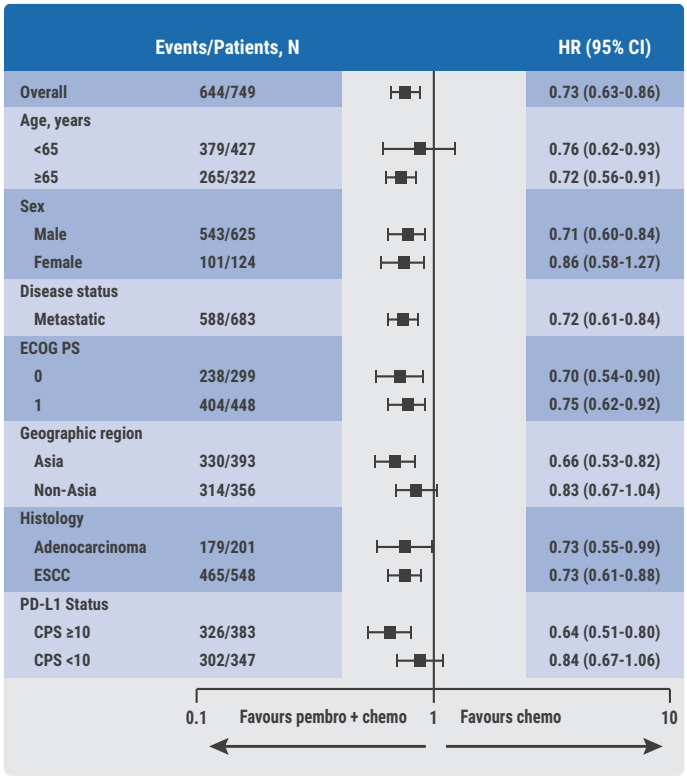
Updates on pembrolizumab for oesophageal and gastric cancer

Pembrolizumab plus chemotherapy showed clinically meaningful benefits compared with chemotherapy alone as first-line therapy in patients with locally advanced and metastatic oesophageal cancer. The longer-term follow-up data of the phase 3 KEYNOTE-590 study further displayed comparable safety profiles of the 2 treatment options [1].

An update from the phase 3 KEYNOTE-062 trial, investigating patients with PD-L1-positive (CPS ≥1) advanced gastric or gastroesophageal junction adenocarcinoma (GEJAC), did not show superiority of pembrolizumab plus chemotherapy over chemotherapy alone in these patients. However, pembrolizumab demonstrated non-inferiority to chemotherapy alone, with an improved safety profile [2].

The phase 3 KEYNOTE-590 trial (NCT03189719) was designed to assess whether pembrolizumab could offer additional benefits over chemotherapy alone to patients with oesophageal cancer and EGJ Siewert type 1. In total, 749 patients with locally advanced unresectable or metastatic oesophageal cancer (mixed histologies: adenocarcinoma and squamous cell carcinoma) were randomised 1:1 to chemotherapy plus pembrolizumab (200 mg, intravenous, every 3 weeks) or chemotherapy plus placebo. The primary analysis showed that additional pembrolizumab was associated with improved overall survival (OS; HR 0.73; P<0.001), progression-free survival (PFS; HR 0.65; P<0.001), and anti-tumour activity. Dr Jean-Philippe Metges (CHU Brest, France) presented the results after 12 months of additional follow-up.

Figure: Subgroup analyses of overall survival in KEYNOTE-590 [1]



After a median follow-up of 34.8 months, the data showed that the benefits of pembrolizumab were maintained, with a median OS of 12.4 versus 9.8 months (HR 0.73; P<0.001) and a median PFS of 6.3 versus 5.8 months (HR 0.64; P<0.001). The 2-year OS rates were 26% and 16% for patients receiving pembrolizumab or placebo, respectively. In addition, the 2-year PFS rates were 12% and 3%. The results were consistent across pre-defined subgroups, including patients with adenocarcinoma (see Figure). Moreover, the anti-tumour response data showed that 20.4% of the patients on pembrolizumab had a response duration of 24 months or longer. In the placebo group, 6.2% of the patients had a response duration of a minimum of 2 years. Also, the quality of life for patients in the pembrolizumab or placebo arm was comparable.

Importantly, the addition of pembrolizumab was not associated with increased toxicity, according to Dr Metges. The treatment arms had similar safety profiles, with 71.9% and 67.7% of the patients experiencing grade 3 or higher adverse events (AEs) in the pembrolizumab arm and placebo arm, respectively. The rate of grade 3 immune-mediated AEs was higher in the pembrolizumab arm (7.0% vs 2.2%).

Dr Metges concluded that the longer-term follow-up data of the KEYNOTE-590 trial confirm that pembrolizumab plus chemotherapy is a new first-line standard-of-care option for patients with locally advanced or metastatic oesophageal cancer, including patients with adenocarcinoma. It is important to note that the best results were shown in patients with PD-L1 CPS ≥10 (HR 0.64).

Updated KEYNOTE-062 results

The KEYNOTE-062 trial (NCT02494583) randomised 763 patients to pembrolizumab alone, chemotherapy alone, or pembrolizumab plus chemotherapy. The primary analysis showed that the combination regimen did not outperform chemotherapy alone with respect to OS and PFS [3]. However, pembrolizumab alone displayed non-inferiority to chemotherapy. Dr Zev Wainberg (University College Los Angeles, CA, USA) presented the updated results after 25 months of additional follow-up [2].

Pembrolizumab displayed non-inferiority to chemotherapy alone in patients with CPS ≥1, with 24-month OS rates of 26.6% for the pembrolizumab arm versus 18.8% for the chemotherapy arm (HR 0.90). This result was more pronounced in patients with CPS ≥10 (24-months OS rates: 39.1% vs 21.1%; HR 0.62).

The combination regimen did not significantly outperform chemotherapy alone in this population. The 24-month OS

rates for patients with CPS ≥1 were 24.5% in the combination arm and 18.8% in the chemotherapy arm. In patients with CPS ≥10, the corresponding results were 28.3% and 21.1%, respectively. According to Dr Wainberg, the updated safety profile was similar to that of the primary analysis. Grade 3-5 adverse events were less common in the pembrolizumab arm (50.4%) compared with the chemotherapy arm (82.4%) or the combination arm (84.8%).

The combination of pembrolizumab plus chemotherapy for patients with gastric adenocarcinoma or GEJAC is further assessed in the KEYNOTE-859 trial (NCT03675737).

1. Metges J-P, et al. First-line Pembrolizumab Plus Chemotherapy Versus Chemotherapy in Advanced Esophageal Cancer: Longer-term Efficacy, Safety, and Quality-of-life Results From the Phase 3 KEYNOTE-590 Study. Abstract 241, ASCO GI 2022, 20–22 January.
2. Wainberg ZA, et al. Pembrolizumab With or Without Chemotherapy Versus Chemotherapy Alone for Patients With PD-L1-Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: Update From the Phase 3 KEYNOTE-062 Trial. Abstract 243, ASCO GI 2022, 20–22 January.
3. Shitara K, et al. JAMA Oncol. 2020;6(10):1571–1580.

Anal and Colorectal Cancer

NIPICOL: New data on optimal ICI treatment duration in MSI/dMMR mCRC

Nivolumab maintenance therapy after nivolumab plus ipilimumab induction therapy, with a fixed treatment duration of 1 year, demonstrated to be efficacious in patients with microsatellite instability-high (MSI-h)/ mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC). The current phase 2 NIPICOL trial displayed that 2 years of therapy may thus not be needed for all patients in this population [1].

Dr Romain Cohen (Sorbonne University, France) explained that immune checkpoint inhibitors are the new standard-of-care for patients with MSI/dMMR mCRC. "Mostly, a fixed duration of 2 years of therapy is applied. However, maintained responses have been observed, despite treatment discontinuation in this population [2]. Therefore, the optimal treatment duration remains to be established." The multicentre, single-arm, phase 2 NIPICOL trial (NCT03350126) exposed patients with MSI/dMMR mCRC to nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) induction therapy, every 3 weeks, 4 cycles, followed by nivolumab maintenance therapy (3 mg/kg), every 2 weeks, maximum 20 cycles, constituting a treatment duration of 1 year. The primary analysis showed that the 12-week disease control rate, the primary endpoint of this study, was 86.0% (RECIST 1.1).

After an additional 16 months of follow-up, the 3-year progression-free survival rate was 70.0% and the 3-year overall survival rate was 73.1%. Moreover, after 34.5 months of follow-up, the median duration of response was still not estimable. A landmark analysis at 1 year, including 42 patients free of progression, displayed a 24-month median PFS rate of 92.9%. Furthermore, data in 4 patients who were re-treated with nivolumab after disease progression suggested that re-exposure to this agent may add additional anti-tumour activity in patients who experienced late resistance after immunotherapy treatment discontinuation. However, further studies with larger sample sizes are warranted to investigate this matter.

Dr Cohen concluded that the efficacy of the currently investigated 1-year fixed duration nivolumab and ipilimumab treatment regimen questions the need for 2 years of therapy in all patients with MSI/dMMR mCRC. "We need to develop tools to distinguish patients who require longer treatment duration from those who may be eligible for 1 year of therapy." This will also be important from an economic perspective.

1. Cohen R, et al. One-year duration of nivolumab plus ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Long-term follow-up of the GERCOR NIPICOL phase 2 study. Abstract 14, ASCO GI 2022, 20–22 January.
2. Overman MJ, et al. J Clin Oncol. 2018;36(8):773–779.

Dostarlimab may offer an alternative for dMMR rectal cancer

Treatment with dostarlimab resulted in a complete response in all patients with deficient mismatch repair (dMMR) locally advanced rectal cancer who completed therapy. This treatment may avoid chemoradiation and surgery in these patients, which are associated with

toxicity and morbidity. Although the durability of response needs to be assessed in long-term follow-up, PD-1 inhibition may become a new paradigm for the treatment of dMMR rectal cancer [1].

"The standard approach for locally advanced rectal cancer is total neoadjuvant therapy, including chemoradiation and total mesorectal excision," said Dr Melissa Lumish (Memorial Sloan Kettering Cancer Center, NY, USA). "Although patients who display a complete response may be offered non-operative management, targeted strategies for molecular subtypes of rectal cancer may further diminish toxicity and morbidity in these patients." Dr Lumish added that patients with dMMR rectal cancer have a 25% increased risk of progression on neoadjuvant chemotherapy. "In contrast, these patients are responsive to immune checkpoint inhibitors." The current, single-arm, phase 2 trial (NCT04165772) aimed to treat 30 patients with dMMR rectal cancer (stage 2 and 3) with the PD-1 inhibitor dostarlimab (500 mg intravenous, every 3 weeks, 9 cycles). If a complete response (CR) did not occur, patients were treated with chemoradiation therapy. Subsequently, they could receive surgery if a CR was still lacking. The primary objective was the overall response rate to dostarlimab.

In total, 16 patients with dMMR rectal cancer had been enrolled at the time of the presentation, 11 of whom had completed anti-PD-1 therapy. Endoscopic CR was observed in 100% of the patients who had completed anti-PD-1 treatment, without chemoradiation and surgery (see Figure). The other 5 patients that had been included had not yet completed treatment. Similarly, radiographic CR was achieved in all 11 patients that had completed therapy. Dr Lumish argued that the observed 100% clinical CR rate demonstrates that PD-1 inhibition may offer a new paradigm for patients with locally advanced dMMR rectal cancer. However, long-term follow-up needs to objectify the durability of response to dostarlimab. These data are in concordance with the NICHE trial in early stage MSI-H colon cancer where neoadjuvant therapy with one course of ipilumumab 1 plus nivolumab 3 before surgery showed 100% major pathologic response [2].

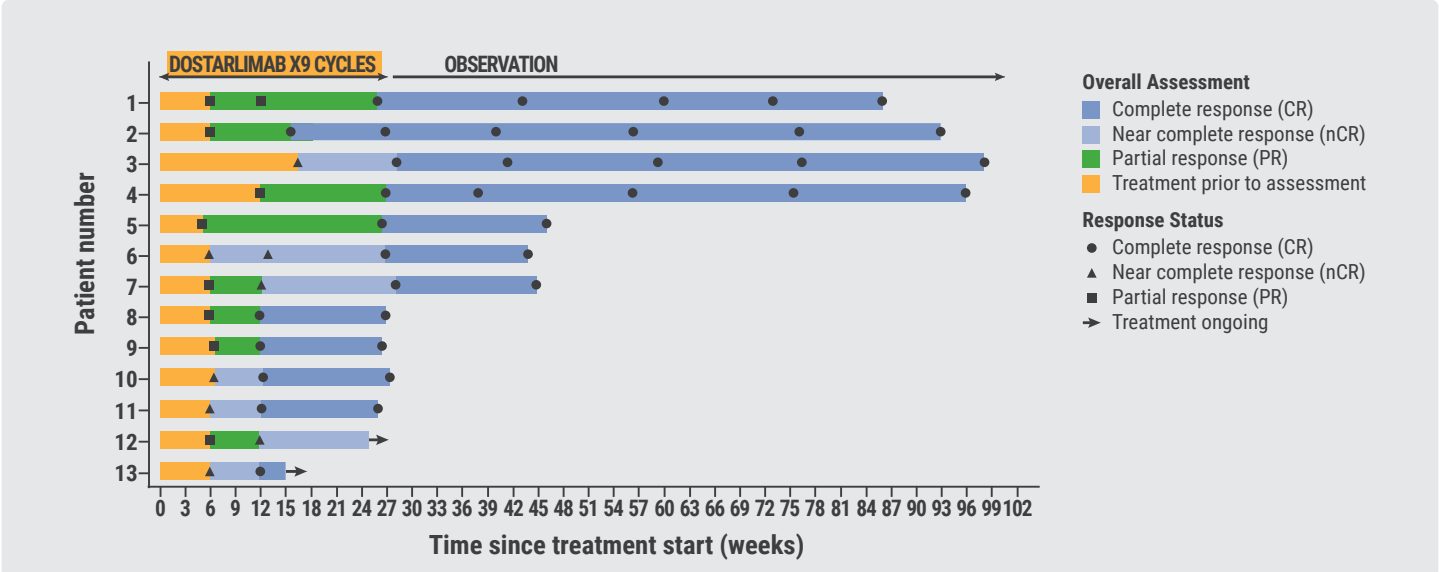
1. Lumish MA, et al. PD-1 Blockade Alone for Mismatch Repair Deficient Locally Advanced Rectal Cancer: Phase 2 Clinical Trial. Abstract 16, ASCO GI 2022, 20–22 January.
2. Chalabi M, et al. Nat Med. 2020 Apr;26(4):566-576.

DESTINY-CRC01: Maintained efficacy of T-DXd in mCRC

Trastuzumab deruxtecan (T-DXd) demonstrated encouraging activity and durable responses in patients with HER2-positive metastatic colorectal cancer (mCRC) in the phase 2 DESTINY-CRC01 study. Moreover, the final results of this study showed that the safety profile of T-DXd is acceptable. These results support further exploration of this agent in patients with HER2-positive mCRC [1].

The open-label, multicentre, phase 2 DESTINY-CRC01 study (NCT03384940) investigated the safety and efficacy of T-DXd in patients with mCRC across 3 cohorts. Cohort A included

Figure: Endoscopic response from time since dostarlimab treatment initiation [1]



patients with true HER2-positive status (IHC 3+ or IHC 2+/ISH+; n=53). Cohort B (IHC 2+/IHC-; n=15) and cohort C (IHC 1+; n=18) included patients with less HER2 expression. The patients received doses of 6.4 mg/kg T-DXd, administered every 3 weeks. The primary analysis of this trial showed promising anti-tumour activity in cohort A and an acceptable safety profile of T-DXd in this population. After an additional 35 weeks of follow-up, Dr Takayuki Yoshino (National Cancer Center Hospital East, Japan) presented the final results of this trial.

After a median follow-up of 62.4 weeks in cohort A, the confirmed overall response rate was 45.3%. All of these responses were partial responses. There were no confirmed responses observed in cohorts B and C. The median duration of response was 7.0 months. Furthermore, the median progression-free survival was 6.9 months in cohort A, compared with 2.1 and 1.4 months in cohorts B and C, respectively. The median overall survival was 15.5 months in cohort A, demonstrating a clinically meaningful improvement over cohorts B and C (7.3 and 7.7 months). Notably, within cohort A, patients with IHC3+ status were significantly more likely to show a response than patients with IHC2+/ISH+ status.

The safety profile was consistent with the known safety profile of T-DXd. Approximately 65% of the patients experienced a grade 3 or higher treatment-emergent adverse event (TEAE). In 15.1% of the patients, a TEAE led to drug discontinuation. In addition, in 17.4% of the patients, dose reductions were incited by TEAEs. Interstitial lung disease (ILD)/pneumonitis occurred in 9.3% of the patients, with 4 grade 2 events, 1 grade 3 event, and 3 grade 5 events. The median time to adjudicated onset of ILD/pneumonitis was 61 days. Dr Yoshino argued that the safety profile of T-DXd is acceptable in this population but that ILD/pneumonitis remains an important risk that requires careful monitoring.

1. Yoshino T, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). Abstract 119, ASCO GI 2022, 20–22 January.

Key updates in colorectal cancer screening

Dr Robin Mendelsohn (Memorial Sloan Kettering Cancer Center, NY, USA) discussed the latest updates on screening for colorectal cancer (CRC), including the age to start screening, which tests to use, the timing of follow-up, and when to stop screening [1].

The US Preventive Services Task Force (USPSTF) and the American Cancer Society have both recently adjusted the recommended age to start screening individuals with average risk for CRC to 45 years [2,3]. The starting age of 45 years in the general population is based on research by Peterse et al., showing that earlier screening increased the number of life-years gained (6.2%) [4]. The US Multi-Society Task Force (USMSTF) of Colorectal Cancer did not yet change the recommended screening age from 50 to 45 years, except for African-American individuals [5]. Dr Mendelsohn explained that the lower recommended age for African-Americans is based on a higher incidence of CRC in this subgroup.

The recommendations for individuals at a higher risk for CRC are different (see Table).

Table: Screening recommendations for individuals at higher risk for CRC [1]

History	Recommendation
Lynch syndrome	Age 20–25 (or 2–5 years younger than age when youngest relative diagnosed if <25, whichever earlier)
FDR* CRC or **advanced** adenoma <60 2 FDRs with CRC or advanced adenoma	Age 40 (or 10 years younger than age when youngest relative diagnosed, whichever earlier)
FDR* CRC or **advanced** adenoma ≥60	Age 40
Inflammatory bowel disease	Start at 8 years after diagnosis
History of abdomen/pelvic radiation	Start 5 years after radiation or at age 30, whichever occurs last

CRC, colorectal cancer; FDR, first-degree relative.

The USMSTF recommends colonoscopy or faecal immunochemical test (FIT) for the first-tier test. CT colonography, MTsDNA, or Flex Sig are the recommended second-tier tests [4]. In contrast, the USPSTF advocates a 'just screen' policy [2]. "The best test is the test that gets done, gets done well, and with appropriate follow-up," added Dr Mendelsohn.

The USMSTF recommends a follow-up colonoscopy at 10 years for a normal profile, 7–10 years for 1–2 small tubular adenomas, 3–5 years for 3–4 small tubular adenomas, 3 years for 5–10 small tubular adenomas or when a large or high-grade dysplasia or villous pathology is observed [6]. If there are >10 tubular adenomas, the recommended follow-up time is 1 year.

The USPSTF recommends to stop screening at age 85, but the age range from 76–85 years is up for debate [2]. The USMSTF recommends to stop screening at age 75 if the life expectancy is <10 years and the individual had a negative screening [4]. Dr Mendelsohn added that microsimulation models have not demonstrated one model that is most

efficient in deciding when to stop screening. "This decision should be individualised, based on previous screening (if any), comorbidities, age, and risk profiles." We must adapt those recommendations to European guidelines.

1. Mendelsohn RB, et al. Key Updates and Important Changes in Colorectal Screening Guidelines. Breakout Session: Endoscopic Screening and Surveillance in Colorectal Cancer—What's New? ASCO GI 2022, 20–22 January.
2. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(19):1965–1977.
3. Wolf AMD, et al. CA Cancer J Clin. 2018;68(4):250–281.
4. Peterse EFP, et al. Cancer. 2018;124(14):2964–2973.
5. Rex DK, et al. Am J Gastroenterology. 2017;112(7):1016–1030.
6. Gupta S, et al. Am J Gastroenterology. 2020;115(3):415–434.

Impact of COVID-19 on screening for colorectal cancer

The impact of the COVID-19 pandemic on the screening and surveillance of colorectal cancer (CRC) was discussed during a breakout session called "Endoscopic Screening and Surveillance in Colorectal Cancer—What's New?" [1].

Dr John Carethers (University of Michigan, MI, USA) said that there are 9 or more options for CRC screening but that colonoscopy is the only available option for surveillance. "Colonoscopy is the dominant strategy for CRC screening in the USA and patients need to visit their healthcare facility to get this procedure done."

The COVID-19 pandemic is associated with a significant reduction in cancer care, especially when it comes to performed breast cancer screenings and CRC screenings, which dropped with 89.2% and 84.5% in April 2020, respectively. "The estimated increase of cancer deaths due to the screening shutdown is approximately 1,000 individuals per year if the screening trajectory recovers within 6–12 months. However, this number may be up to 10,000 if cancer screening remains deficient." Dr Carethers said that the consequences are likely to be worse in underserved populations, such as African-Americans, since these populations are disproportionally affected by COVID-19.

Efforts have been made to overcome the reduced screening capacity by developing non-invasive home screening tests. These screening options include direct visualisation and measurements of protein, DNA, RNA, low molecular weight metabolites, or shifts in gut microbiome. "mSEPT9 is the first blood-based test that has been approved by the FDA, displaying a sensitivity of 70% for CRC and 27% for advanced adenomatous polyps," said Dr Carethers. "However, most tests are still under investigation." Although at-home CRC screening is cheap, some patients have difficulty correctly completing these tests. Moreover, the accuracy needs to be improved, especially for adenoma detection. "Also, patients still require a colonoscopy if they have a positive at-home test."

Dr Carethers concluded by arguing that preventive healthcare should not be delayed just because of COVID-19, since excessive delay will cost lives.

1. Carethers JM, et al. Impact of COVID-19 on Screening and Diagnosis. Breakout Session: Endoscopic Screening and Surveillance in Colorectal Cancer—What's New? ASCO GI 2022, 20–22 January.

Nivolumab plus standard-of-care does not meet primary endpoint for mCRC

In the phase 2/3 CheckMate 9X8 trial, nivolumab plus standard-of-care did not significantly improve progression-free survival (PFS) compared with standard-of-care alone in the first-line treatment of patients with metastatic colorectal cancer (mCRC). However, the results numerically favoured patients receiving additional nivolumab. Moreover, exploratory analyses revealed that patients with CMS1 and CMS3 molecular subtypes, or CD8 levels ≥2% displayed benefits from nivolumab [1].

"The efficacy of standard therapies in patients with mCRC may be enhanced by the addition of an immunotherapeutic agent," Dr Heinz-Josef Lenz (USC Norris Comprehensive Cancer Center, CA, USA) explained. The phase 2/3 CheckMate 9X8 trial (NCT03414983) investigated whether nivolumab, a PD-1 inhibitor, may deliver patient benefits when added to first-line standard-of-care. Patients with mCRC were randomised to nivolumab 240 mg every 2 weeks plus mFOLFOX6/bevacizumab (n=127) or mFOLFOX6/bevacizumab alone (n=68). The primary endpoint was PFS.

The primary endpoint was not met, with the median PFS reaching 11.9 months in both treatment arms. However, PFS rates after 12 months were numerically higher in patients receiving nivolumab than in patients receiving standard-of-care only, with 15-month PFS rates of 45% and 21.5%, and 18-months PFS rates of 28% and 9%, respectively. Subgroup analyses numerically favoured the nivolumab arm over the standard-of-care arm across all pre-defined subgroups. Furthermore, the objective response rate was numerically higher in the nivolumab arm (60% vs 46%) and the median duration of response was longer for patients on nivolumab (12.9 months vs 9.3 months). Also, exploratory analyses showed that CMS1 and CMS3 subsets of patients were likely to benefit more from nivolumab, as well as patients

who displayed CD8 levels ≥2%. Further studies are warranted to select patients that may benefit from this novel regimen.

No new safety issues were identified and the safety profile of nivolumab plus standard-of-care was acceptable, according to Dr Lenz. The rate of grade 3 or 4 adverse events (AEs) was higher in the nivolumab arm than in the standard-of-care arm (75% vs 48%). The most common grade 3 or 4 AEs among nivolumab receivers were neutropenia (26%), decreased neutrophil count (20%), and diarrhoea (7%). Any grade immune-related AEs in the nivolumab arm were predominantly of gastrointestinal (42%), endocrine (22%), or dermatologic (27%) origin.

1. Lenz H-J, et al. Nivolumab + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab versus mFOLFOX6/bevacizumab for first-line treatment of metastatic colorectal cancer: phase 2 results from CheckMate 9X8. Abstract 8, ASCO GI 2022, 20–22 January.

No benefit of additional oxaliplatin in elderly patients with mCRC

Elderly patients with metastatic colorectal cancer (mCRC) did not benefit from the addition of oxaliplatin to the first-line standard-of-care fluoropyrimidine plus bevacizumab treatment regimen. In addition, patients treated with additional oxaliplatin experienced a higher grade of toxicity. Therefore, the authors recommend the omission of oxaliplatin during the initial treatment of elderly patients with mCRC [1].

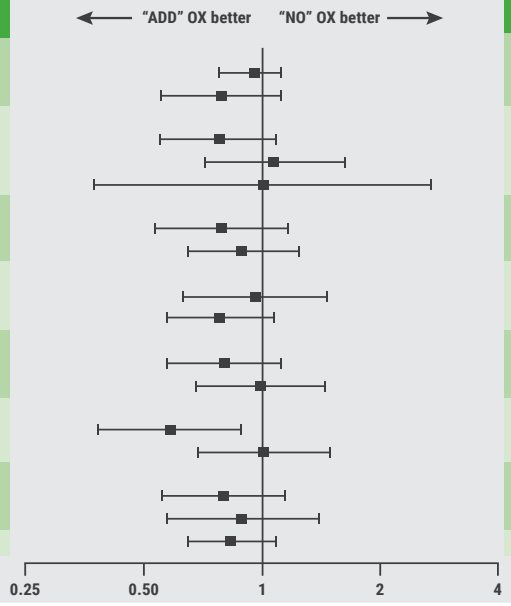
"Fluoropyrimidine plus oxaliplatin with bevacizumab is a first-line standard-of-care option for patients with mCRC," said Dr Tetsuya Hamaguchi (National Cancer Center, Japan). "However, elderly patients are under-represented in clinical trials investigating potential therapies for mCRC. The JCOG1018 RESPECT study (UMIN000008866) assessed the effect of added oxaliplatin to standard-of-care regimens in elderly patients (≥70 years) with unresectable mCRC. Patients in the 'no oxaliplatin' arm (n=125) received a 5-fluorouracil and low-dose leucovorin plus bevacizumab regimen or a capecitabine plus bevacizumab regimen. Patients in the 'added oxaliplatin' arm (n=126) received one of the same regimens plus oxaliplatin: 85 mg/m^2 (mFOLFOX) or 130 mg/m^2 (CapeOX), every 2 weeks. The primary endpoint was progression-free survival (PFS).

The addition of oxaliplatin did not lead to a significantly prolonged median PFS compared with the regimens that omitted oxaliplatin (10.0 vs 9.4 months; HR 0.837; one-sided P=0.086). However, subgroup analyses suggested that patients with wildtype *RAS* status may benefit from added oxaliplatin (median PFS 11.0 months) compared with no oxaliplatin (9.6 months; HR 0.578) (see Figure). Furthermore, the overall survival analysis displayed no survival benefit of added oxaliplatin over no oxaliplatin (median 19.7 vs 21.3 months) in the study population.

The safety analysis discouraged the addition of oxaliplatin to standard treatment regimens in this population. The addition of oxaliplatin resulted in a higher rate of grade 3–4 neutropenia (24% vs 15%) and higher rates of grade 2–4 nausea (22% vs 10%), diarrhoea (16% vs 7%), fatigue (32% vs 21%), and sensory neuropathy (57% vs 15%).

Figure: Subgroup analyses of PFS in JCOG1018 [1]

	"NO" OX (events/N)	"ADD" OX (events/N)	"NO" OX mPFS (m)	"ADD" OX mPFS (m)	HR (95% CI)
Age					
70-79 years	58/62	63/64	10.0	9.9	0.965 (0.674-1.381)
≥80	61/63	59/62	8.7	10.1	0.787 (0.549-1.127)
ECOG PS					
0	59/62	71/72	9.5	11.3	0.777 (0.548-1.103)
1	49/52	44/47	9.4	8.9	1.086 (0.723-1.633)
2	11/11	7/7	6.2	9.8	1.012 (0.374-2.735)
No. of mets site					
1	55/57	46/49	10.3	10.7	0.793 (0.534-1.176)
≥2	64/68	76/77	8.7	9.8	0.894 (0.640-1.247)
Location					
Right	44/47	40/42	8.1	8.8	0.960 (0.625-1.475)
Left	75/78	82/84	9.7	10.3	0.781 (0.569-1.073)
Fluoropyrimidine					
5FU-based	70/71	67/67	8.5	10.0	0.803 (0.573-1.126)
Cape-based	49/54	55/59	10.0	10.3	0.990 (0.673-1.457)
***RAS*-status**					
Wildtype	47/47	49/53	9.6	11.0	0.578 (0.380-0.879)
Mutant	48/52	49/53	7.8	9.7	1.016 (0.687-1.502)
VES-13					
1-2	56/58	60/61	10.0	11.1	0.799 (0.553-1.156)
≥3	59/42	35/38	8.2	8.6	0.890 (0.563-1.407)
Overall	119/125	122/126	9.4	10.0	0.873 (0.648-1.083)



CI, confidence interval; ECOG PS, ECOG performance status; HR, hazard ratio; mPFS, median progression-free survival; OX, oxaliplatin.

These data are in concordance with the PANDA trial favouring first line 5-fluoroacil + panitumumab versus FOLFOX + panitumumab in elderly *RAS* wildtype mCRC and the AVEX trial in favour of capecitabine + bevacizumab [2,3].

1. Hamaguchi T, et al. A randomized phase 3 trial of mFOLFOX7 or CapeOX plus bevacizumab versus 5-FU/l-LV or capecitabine plus bevacizumab as initial therapy in elderly patients with metastatic colorectal cancer: JCOG1018 study (RESPECT). Abstract 10, ASCO GI 2022, 20–22 January.
2. Lonardi S, et al. Abstract 4002, ASCO Annual Meeting 2020, 29–31 May.
3. Cunningham D, et al. Lancet Oncol. 2013 Oct;14(11):1077-1085.

Prognostic impact of early oxaliplatin discontinuation in colon cancer unravelled

A pooled analysis of 11 adjuvant trials showed that early treatment discontinuation (ETD) in patients with stage 3 colon cancer receiving 6 months of chemotherapy led to a reduced disease-free survival (DFS) and overall survival (OS). In contrast, early oxaliplatin discontinuation (EOD) was not associated with decreased DFS or OS if the patients had received at least 50% of the oxaliplatin cycles [1].

Dr Claire Gallois (Université de Paris, France) explained that approximately 30% of the patients with localised colon cancer discontinue their 6-month prescribed adjuvant chemotherapy early. "However, robust data on the prognostic impact of ETD or EOD is lacking." Therefore, the current study assessed the factors associated with ETD and EOD. Moreover, the study evaluated the prognostic impact of ETD and EOD on DFS and OS. Patients were classified as ETD or EOD if they received less than 75% of the prescribed cycles of chemotherapy (i.e. FOLFOX or CAPOX) or oxaliplatin, respectively. Assessed were 10,444 patients with stage 3 colon cancer undergoing a 6-month, oxaliplatin-based chemotherapy.

ETD was experienced by 20.9% of the patients and EOD was experienced by 18.8% of the patients. Women, older patients (≥65 years), patients with an ECOG PS ≥1, and patients following a CAPOX regimen had a significantly higher risk of ETD or EOD (P<0.001). Also, patients with a BMI of <18.5 had an increased risk of ETD (P<0.001).

ETD resulted in a significant reduction in DFS: 3-year DFS rates were 69.0% vs 78.8% for ETD and non-ETD (HR 1.61; P<0.001). The 3-year OS rates show a similar result (74.7% vs 84.7%; HR 1.73; P<0.001). The result was consistent across subgroups, except for the low-risk cancer group treated with CAPOX. In contrast, EOD did not result in decreased 3-year DFS rates (EOD 77.2% vs no-EOD 78.3%; HR 1.07; P=0.28) or 3-year OS rates. This result was consistent across pre-defined strata. Notably, patients who received <50% of their oxaliplatin cycles had a decreased 3-year DFS rate compared with patients who did not discontinue oxaliplatin (74.1% vs 78.3%; HR 1.35; P=0.018). This association was not observed for patients who received ≥50% of their oxaliplatin cycles (3-year DFS rate 78.1%).

Dr Gallois concluded that it seems important to maintain the planned number of treatment cycles in this population. However, patients with grade 1–2 neurotoxicity may discontinue oxaliplatin after 3 months, without impairing clinical outcomes.

1. Gallois C, et al. Prognostic impact of early discontinuation of treatment and oxaliplatin in patients treated with 6 months of oxaliplatin-based chemotherapy for stage 3 colon cancer: an ACCENT/IDEA pooled analysis of 11 adjuvant trials. Abstract 11, ASCO GI 2022, 20–22 January.

Long-course chemoradiation versus short-course radiotherapy in rectal cancer

In a discussion of the key considerations for short-course radiotherapy (SCR) or long-course chemoradiation (LC-CRT) in the context of total neoadjuvant therapy (TNT) for patients with locally advanced rectal cancer (LARC), both options seem reasonable and evidence-based, although SCR is the preferred option in most patients [1].

"TNT is the clear standard-of-care in patients with LARC," explained Dr Emma Holliday (MD Anderson Cancer Center, University of Texas, TX, USA). "The RAPIDO trial (NCT01558921) compared TNT with standard-of-care in patients with LARC who displayed at least one high-risk feature. TNT was favoured over the standard-of-care with regard to the primary endpoint, 3-year disease-related treatment failure (HR 0.75; P=0.019). This effect was mainly driven by distant metastases (HR 0.69; P=0.0048) [2]. In addition, the phase 3 PRODIGE 23 trial (NCT01804790) also demonstrated improved short-term and long-term outcomes of TNT compared with standard-of-care. "However, it has not yet been established whether SCR or LC-CRT is the best option for these patients."

SCR is defined as delivering 25 Gy in 5 days, whereas LC-CRT consist of 45–50 Gy given in 25 days. Several phase 3 trials have demonstrated comparable efficacy and toxicity profiles of these options [3–5]. "However, with SCR, chemotherapy can be administrated earlier, which is especially important for patients with high-risk features. Moreover, in the light of the current COVID-19 pandemic, SCR provides a reduced exposure of our patients to the healthcare system, decreasing the risk of infection. Finally, SCR is less costly than LC-CRT.

"Preliminary results from the OPRA trial (NCT02008656) showed that LC-CRT may be the preferred option if a watch and wait strategy is indicated [6]. This approach has been associated with improved organ preservation in this population. However, SCR may be used in this population as well, but we need to wait for more evidence. Currently, randomised trials are running to investigate this matter." In anticipation of more results, we need to discuss in multidisciplinary team and perhaps reserve PRODIGE 23 for fit young people with high locally advanced disease.

1. Holliday EB, et al. Short-course radiotherapy vs Long course chemoradiation: As a component of TNT for LARC. Total Neoadjuvant Therapy for Rectal Cancer: The Key Considerations. ASCO GI 2022, 20–22 January.
2. Bahadoer RR, et al. Lancet Oncol. 2021;22(1):29–42.
3. Bujko K, et al. Br J Surg. 2006;93(10):1215–1223.
4. Erlandsson J, et al. Lancet Oncol. 2017;18(3):336–346.
5. Ngan SY, et al. J Clin Oncol. 2012;30(31):3827–3833.
6. Garcia-Aguilar J, et al. Abstract 4008, ASCO 2020, 29–31 May.

Analysis of metastasectomy in CRC reveals benefits and disparities

Metastasectomy is associated with improved overall survival in patients with colorectal cancer (CRC) and concurrent lung and liver metastasis. However, this approach is not often utilised, as a study of the National Cancer Database showed. The authors concluded that future studies are needed to improve the identification of patients who may benefit from metastasectomy [1].

Dr Jude Khatib (University of Texas, TX, USA) explained that CRC is associated with concurrent lung and liver metastasis. The current study aimed to assess the trends in the utilisation of metastasectomy in patients with CRC and concurrent lung and liver metastasis, and the effect of this treatment option on survival.

Patients with stage 4 CRC who displayed concurrent liver and lung metastasis between 2010 and 2016 were selected from the National Cancer Database (n=10,106). Only 6.2% of this population underwent metastasectomy, whereas 93.8% did not. The patients that underwent metastasectomy were more likely to be younger than 50 years (P=0.009), women (P<0.001), and White (P=0.01). In addition, right-sided CRC was more common among these patients (P=0.001), and they were more likely to have received resection of the primary site (P<0.001). Furthermore, patients who received metastasectomy were significantly more likely to have private health insurance (P<0.001) and to receive treatment at an academic centre (P=0.03).

A matched analysis was performed to compare overall survival between patients who underwent metastasectomy and those who did not. This analysis demonstrated a significant survival benefit for patients who had received metastasectomy (23.2 vs 11.6 months; P<0.001). After multivariable analysis, this result remained significant (HR 0.74; P<0.001). It thus seems very important to discuss surgery of oligometastatic cancer to increase overall survival.

1. Khatib J, et al. Metastasectomy in colorectal cancer patients with concurrent lung and liver metastasis: Trends in utilization and impact on survival. Abstract 53, ASCO GI 2022, 20–22 January.

EPOCH trial: Subgroup analyses and additional endpoints for TARE plus chemo

Patients with liver-dominant metastatic colorectal cancer (mCRC) benefit from the addition of trans-arterial radio-embolisation (TARE) to chemotherapy, according to subgroup analyses of the phase 3 EPOCH trial. Compared with chemotherapy alone, the combination regimen improved depth of response, objective response rate, and duration of disease control in these patients [1].

The phase 3 EPOCH trial (NCT01483027) randomised 428 patients with liver-dominant mCRC 1:1 to Y-90 glass TARE plus chemotherapy or chemotherapy alone to compare the efficacy of these therapies in the second-line [2]. The primary analysis showed improved progression-free survival (PFS), and hepatic PFS in the combination arm compared with the chemotherapy arm. Dr William Harris (Seattle Cancer Care Alliance, WA, USA) presented the results from subgroup analyses and additional endpoints of this trial.

Subgroup analyses showed that males (HR 0.65), patients with *KRAS* mutations (HR 0.57), patients with a hepatic tumour burden between 10 and 25% (HR 0.43), patients with a biological agent added to their treatment regimen (HR 0.58), and patients with baseline carcinoembryonic antigen (CEA) levels ≥35 ng/mL benefitted significantly from the combination regimen compared with chemotherapy alone, with regard to PFS. In addition, all other subgroups displayed numerical trends towards a PFS benefit for the combination regimen over the standard of care arm.

Furthermore, objective response rates were higher in the combination arm (34.0%) than in the chemotherapy arm (21.1%; P=0.0019). In addition, the disease control rates numerically favoured the TARE plus chemotherapy arm

over the standard of care arm (79.5% vs 72.8%; P=0.063). Also, the median duration of disease control was higher in patients treated with TARE and chemotherapy (7.2 vs 5.8 months; P=0.0009). Finally, the mean depth of response was significantly improved in the combination arm compared with the chemotherapy arm, as displayed by the mean change from baseline to nadir (-25.6% vs -13.0%; P=0.0001).

1. Harris WP, et al. Radioembolization with chemotherapy for liver-dominant colorectal cancer: Analysis of Patient Subgroups in the EPOCH Trial. Abstract 115, ASCO GI 2022, 20–22 January.
2. Mulcahy MF, et al. J Clin Oncol. 2021;39(35):3897¬–3907.

Hepatobiliary Cancer

Adjuvant S-1 therapy superior to observation in resected biliary tract cancer

Adjuvant S-1 therapy improved the overall survival (OS) of patients with biliary tract cancer (BTC) who underwent resection via surgery. Also, S-1 therapy was well tolerated in this patient population. Therefore, adjuvant S-1 therapy may be considered as standard-of-care in patients with resected BTC in Japan [1].

"In Japan, capecitabine is currently accepted as the standard adjuvant therapy for patients with curatively resected BTC, despite the fact that no significant OS benefit has been demonstrated of this agent in this population," Dr Masafumi Ikeda (Japan Clinical Oncology Group, Japan) explained. "In addition, a phase 2 trial demonstrated that S-1, an oral fluoropyrimidine derivative, may provide benefits for patients with advanced BTC [2]."

The current phase 3 JCOG1202 ASCOT trial (UMIN000011688) investigated the safety and efficacy of adjuvant S-1 therapy in 440 adult patients with curatively resected BTC. The patients were randomised 1:1 to surgery alone or surgery plus adjuvant S-1 therapy, 40 mg/m^2 twice daily, 4 weeks on, 2 weeks off, for 4 cycles. The primary endpoint was OS.

Adjuvant S-1 therapy outperformed observation regarding the 3-year OS rates (77.1% vs 67.6%; HR 0.69; P=0.008). Moreover, subgroup analyses revealed that this effect was consistent across most subgroups. Although the 3-year relapse-free survival rate was higher in patients receiving adjuvant S-1 therapy compared with patients receiving surgery alone (62.4% vs 50.9%), this effect was not significant at the time of the analysis. Dr Ikeda argued that a longer follow-up is needed to see whether a significant result can be reached for this secondary outcome measure.

Adjuvant S-1 therapy was well tolerated. The most common adverse events were related to myelosuppression, gastrointestinal toxicity, or skin toxicity. All grade 3 events occurred in less than 5% of the participants, except for decreased neutrophils, which occurred in 14% of the patients receiving adjuvant S-1 therapy.

"This trial showed that adjuvant S-1 therapy is well tolerated and leads to significantly longer OS times in patients with resected BTC. Therefore, this therapy should be considered as standard therapy in the investigated patient population," concluded Dr Ikeda.

1. Ikeda M, et al. Adjuvant S-1 vs. observation in curatively resected biliary tract cancer: a phase 3 trial (JCOG1202:ASCOT). Rapid Abstract Session B, ASCO GI 2022, 20–22 January.
2. Furuse J, et al. Cancer Chemother Pharmacol. 2008;62:849–855.

Pembrolizumab safe and efficacious in advanced hepatocellular carcinoma

Pembrolizumab plus best supportive care outperformed placebo plus best supportive care in overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) in the second-line treatment of patients with advanced hepatocellular carcinoma (HCC). Moreover, a meta-analysis of the phase 3 KEYNOTE-394 and KEYNOTE-240 trials provided support for global generalisability of the results [1].

Pembrolizumab, a PD-1 inhibitor, added to best supportive care demonstrated superiority over placebo plus best supportive care in a phase 2 (KEYNOTE-224; NCT02702414)

and a phase 3 (KEYNOTE-240; NCT02702401) trial [2,3]. The current, multicentre, phase 3 KEYNOTE-394 study (NCT03062358) compared pembrolizumab with placebo in the second-line treatment for Asian patients with advanced HCC after sorafenib (90.7%) or chemotherapy. Patients received pembrolizumab (200 mg, every 3 weeks) plus best supportive care (n=300) or placebo plus best supportive care (n=153). OS was the primary endpoint of this trial. Prof. Shukui Qin (Nanjing University of Chinese Medicine, China) presented the results.

The median OS was significantly higher among patients who received pembrolizumab (14.6 vs 13.0 months; HR 0.79; P=0.0180). In addition, the 24-month OS rates were 34.3% in the pembrolizumab arm and 24.9% in the placebo arm. Similarly, the median PFS was higher in the pembrolizumab arm than in the placebo arm (2.6 vs 2.3 months; HR 0.74; P=0.0032). The 24-month PFS rates were 11.0% and 0%, favouring the pembrolizumab arm. The ORR was 12.7% for pembrolizumab receivers and 1.3% for placebo receivers. Furthermore, the median duration of response was 23.9 months in the pembrolizumab arm and 5.6 months in the placebo arm. A meta-analysis of the results of the KEYNOTE-394 and the KEYNOTE-240 trials showed an OS benefit for pembrolizumab receivers (median OS 14.2 vs 12.5 months; HR 0.79).

The safety analysis did not display unexpected issues. Any grade treatment-related adverse events (TRAEs) were reported in 66.9% and 49.7% of the patients in the pembrolizumab arm and the placebo arm, respectively. Grade 3 or higher TRAEs were observed in 14.4% of the pembrolizumab receivers and 5.9% of the placebo receivers. In addition, 3.0% of the patients in the pembrolizumab arm experienced grade 3 or higher immune-mediated AEs. In 5 cases, these events led to treatment discontinuation and in 1 case it resulted in death. "All in all, the safety profile of pembrolizumab was manageable and consistent with prior publications on this agent in this population," concluded Dr Qin.

1. Qin S, et al. Pembrolizumab Plus Best Supportive Care Versus Placebo Plus Best Supportive Care as Second-line Therapy in Patients in Asia With Advanced Hepatocellular Carcinoma: Phase 3 KEYNOTE-394 Study. Abstract 383, ASCO GI 2022, 20–22 January.
2. Zhu AX, et al. Lancet. 2018;7:940–952.
3. Finn RS, et al. J Clin Oncol. 2020;38(3):193–202.

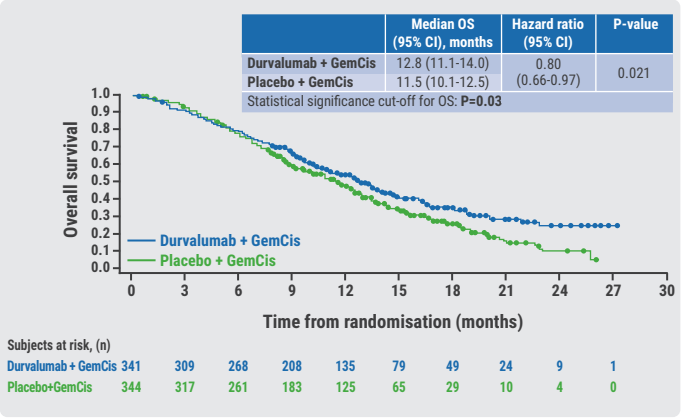
TOPAZ-1: Adding durvalumab to chemotherapy effective in advanced biliary tract cancer

Durvalumab plus chemotherapy was superior to chemotherapy alone as a frontline therapy for patients with advanced biliary tract cancer in the phase 3 TOPAZ-1 trial. Moreover, the addition of durvalumab did not lead to increased toxicity. Therefore, durvalumab plus chemotherapy could be a new standard-of-care for this population [1].

"Gemcitabine/cisplatin chemotherapy has been the first-line standard-of-care for patients with advanced biliary tract cancer (BTC) for over a decade," Dr Do-Youn Oh (Seoul National University College of Medicine, South Korea) explained. "However, the prognosis for these patients is poor. Durvalumab is a PD-L1 inhibitor that has demonstrated encouraging anti-tumour activity in patients with advanced BTC in a phase 2 study" [2]. The double-blind, placebo-controlled, phase 3 TOPAZ-1 trial (NCT03875235) randomised 685 patients 1:1 to 8 cycles of gemcitabine/cisplatin chemotherapy plus durvalumab 1,500 mg every 3 weeks followed by durvalumab 1,500 mg every 4 weeks, or gemcitabine/cisplatin plus placebo. Overall survival (OS) was the primary endpoint.

Patients receiving durvalumab had a higher median OS than patients receiving placebo (12.8 vs 11.5 months; HR 0.80; P=0.021; see Figure). Notably, the absolute OS differences showed that the effect increased with time from randomisation: 12-month OS was 6.1%, 18-month OS 9.5%, and 24-month OS 14.5%. OS subgroup analysis displayed consistency across pre-defined strata. Furthermore, the progression-free survival data favoured the durvalumab arm over the placebo arm (median 7.2 vs 5.7 months; P=0.0001).

Figure: Overall survival analysis of TOPAZ-1 [1]



The safety analysis revealed similar toxicity profiles for the 2 treatment arms. The observed adverse events (AEs) were in line with the known safety profile of gemcitabine/cisplatin chemotherapy. Immune-related AEs occurred more

frequently in patients on durvalumab than in patients on placebo (12.7% vs 4.7%). Hypothyroid events and dermatitis/rash were the most commonly observed immune-related AEs. Fortunately, grade 3 or higher immune-related AEs were rare (durvalumab 2.4% vs placebo 1.5%).

1. Oh D, et al. A phase 3 randomized, double-bind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin in patients with advanced biliary tract cancer: TOPAZ-1. Abstract 378, ASCO GI 2022, 20–22 January.
2. Oh D, et al. Abstract 4520, ASCO Annual Meeting 2020, 29–31 May.

HIMALAYA: Durvalumab ± tremelimumab new first-line option for unresectable HCC

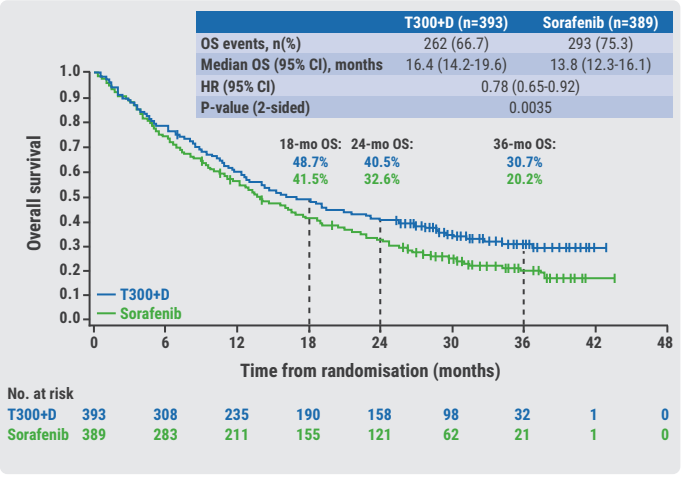
Tremelimumab plus durvalumab improved the overall survival (OS) of patients with unresectable hepatocellular carcinoma (uHCC) compared with sorafenib. Also, durvalumab monotherapy was non-inferior to sorafenib. Durvalumab monotherapy and the combination with tremelimumab had manageable safety profiles and may represent new first-line treatment options for this population [1].

"First-line options for patients with uHCC have been limited, with sorafenib and lenvatinib being the main options," Prof. Ghassan Abou-Alfa (Memorial Sloan Kettering Center, NY, USA) said. "These agents have been associated with a median OS of approximately 1 year and quality-of-life reducing toxicity." Recently, atezolizumab and bevacizumab outperformed sorafenib [2]. Also, tremelimumab, a CTLA-4 inhibitor, plus durvalumab, a PD-L1 inhibitor, showed promising activity in this population in a phase 2 trial [3].

The current open-label, multicentre, phase 3 HIMALAYA trial (NCT03298451) randomised patients with uHCC 1:1:1 to tremelimumab 300 mg single dose plus durvalumab 1,500 mg every 4 weeks (T300+D regimen; n=393), durvalumab monotherapy (n=389), or sorafenib 400 mg twice daily (n=389). The primary objective was to compare the T300+D regimen with sorafenib regarding OS.

T300+D was superior to sorafenib in terms of median OS (16.4 vs 13.8 months; HR 0.78; P=0.0035). The OS difference between the 2 treatment regimens increased over time: 18-month OS rates were 48.7% and 41.5%; 36-month OS rates were 30.7% and 20.2% (see Figure). The superiority of T300+D over sorafenib was consistent across subgroups. Furthermore, the median OS for patients on durvalumab monotherapy was non-inferior to that of patients in the sorafenib arm (16.6 vs 13.8 months; HR 0.86).

Figure: Overall survival of T300+D versus sorafenib [1]



CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg x 1 dose + durvalumab 1500 mg Q4W.

The safety profiles of the novel treatment regimens were manageable. Grade 3 or 4 adverse events (AEs) occurred in 25.8%, 12.9%, and 36.9% of the patients on T300+D, durvalumab monotherapy, and sorafenib, respectively. Hepatic or haemorrhagic SMQ events were limited in the T300+D arm, with 7.0% and 0.5% grade 3 or higher events in this treatment arm. The prevalence of immune-mediated AEs met the expectations of the authors. The most common grade 3 or 4 AEs in the T300+D and durvalumab arms were hepatic events (4.1%, 4.4%), diarrhoea (3.6%, 0.3%), and dermatitis/rash (1.8%, 0.3%).

In conclusion, the authors suggested that durvalumab ± tremelimumab is a possible new standard for patients unable to receive bevacizumab.

1. Abou-Alfa GK, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA. Abstract 379, ASCO GI 2022, 20–22 January.
2. Finn RS, et al. N Engl J Med. 2020;382:1894–1905.
3. Kelley RK, et al. J Clin Oncol. 2021;39(27):2991–3001.

Modest activity of atezolizumab plus bevacizumab in Child-Pugh B HCC

The combination of atezolizumab plus bevacizumab demonstrated modest clinical activity in patients with Child-Pugh B advanced hepatocellular carcinoma (HCC) in the phase 3 IMbrave150 trial. However, the frequency of serious adverse events (AEs) was relatively high. Further studies are needed to carefully select the patients who may benefit from this combination regimen [1].

"The phase 3 IMbrave150 trial (NCT03434379) showed encouraging efficacy and safety of atezolizumab plus bevacizumab as first-line therapy in patients with advanced HCC,"

said Dr Hyeyeong Kim (Ulsan University Hospital, South Korea). "However, this trial did not include patients with Child-Pugh B HCC. Therefore, a retrospective study was performed to assess 37 Child-Pugh B classified patients with advanced HCC who underwent atezolizumab plus bevacizumab therapy in the first-line." The data was compared with a cohort of Child-Pugh A patients from the same registry (n=139).

After atezolizumab plus bevacizumab therapy, the objective response rate (ORR) was 10.8% in Child-Pugh B classified patients, with all responses being partial. In addition, 45.9% of the patients demonstrated stable disease. In the Child-Pugh A cohort the ORR was 33.8%, with 1 complete response. Also, 42.4% of the patients in this cohort had stable disease. The median progression-free survival was 2.9 months in the Child-Pugh B group and 9.6 months in the Child-Pugh A group (P<0.001). The median overall survival (OS) was longer in the Child-Pugh A cohort (not-reached vs 6.0 months; P<0.001). Notably, patients with Child-Pugh B7 classification had a longer median OS time than Child-Pugh B8–9 classified patients (6.4 vs 3.6 months; P=0.016).

The safety analysis showed that grade 3 or 4 AEs were more common in the Child-Pugh B cohort than in the Child-Pugh A cohort (43.2% vs 18.0%). In addition, grade 3 or 4 gastrointestinal haemorrhage (10.8% vs 0.7%; P=0.001), neutropenia (10.8% vs 0%; P<0.001), and thrombocytopenia (10.8% vs 0.7%; P=0.001) occurred significantly more frequently in the Child-Pugh B cohort. Also, the rate of treatment discontinuations due to AEs was higher in the Child-Pugh B group (16.2% vs 5.8%; P=0.047).

1. Kim H, et al. Atezolizumab plus bevacizumab in Child-Pugh B advanced hepatocellular carcinoma patients. Abstract 397, ASCO GI 2022, 20–22 January.

LAUNCH: TACE plus lenvatinib efficacious in advanced HCC

Lenvatinib plus transarterial chemoembolisation (TACE) may represent a novel frontline therapy for patients with advanced hepatocellular carcinoma (HCC). The phase 3 LAUNCH trial demonstrated the superiority of this combination regimen over lenvatinib monotherapy, with an acceptable safety profile [1].

Prof. Ming Kuang (Sun Yat-sen University, China) explained that TACE reduces tumour burden swiftly in patients with advanced HCC but with potential post-treatment neovascularisation and subsequent tumour recurrence and metastasis. Lenvatinib inhibits angiogenesis and tumour cell proliferation. Therefore, Prof. Kuang argued that the assessment of a TACE plus lenvatinib combination in advanced HCC is reasonable. The multicentre, phase 3 LAUNCH trial (NCT03905967) randomised patients with advanced HCC (n=338) 1:1 to lenvatinib monotherapy 8 mg (bodyweight <60 kg) or 12 mg (bodyweight ≥60 kg) once daily, or lenvatinib plus TACE. The primary endpoint was overall survival (OS), and the secondary endpoint was time to progression.

The objective response rate was significantly higher in the lenvatinib plus TACE arm compared with the lenvatinib monotherapy arm (45.9% vs 20.8%; P<0.001). Also, the median OS favoured the TACE arm over the lenvatinib arm (17.8 vs 11.5 months; HR 0.45). Similarly, the median progression-free survival demonstrated superiority of the combination regimen over monotherapy (10.6 vs 6.4 months; HR 0.43). These results were consistent across the majority of pre-defined subgroups. In addition, patients in the TACE arm had a significantly longer median duration of lenvatinib exposure (8.2 vs 5.1 months; P=0.025). Notably, after treatment discontinuation, 26 patients in the combination arm versus 3 patients in the monotherapy arm underwent curative surgical resection (P<0.001).

Certain adverse events (AEs) were significantly more common in the combination arm, namely abdominal pain, nausea, fever, ascites, vomiting, and hypoalbuminaemia. Also, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and hyperbilirubinaemia were more frequently reported as grade 3 or 4 events in the TACE arm. However, Prof. Kuang added that the AEs disappeared after 2 weeks of treatment.

In conclusion, lenvatinib plus TACE demonstrated superior efficacy over lenvatinib alone with an acceptable safety profile. Thus, representing a new potential first-line therapy for patients with advanced HCC.

1. Peng Z, et al. Lenvatinib plus Transarterial Chemoembolization versus Lenvatinib alone as first-line treatment for Primary Advanced Hepatocellular Carcinoma: A Phase 3, Multicenter, Randomized Controlled Trial (LAUNCH). Abstract 380, ASCO GI 2022, 20–22 January.

Pancreatic Cancer

Sintilimab plus FOLFIRINOX may provide benefits in metastatic pancreatic cancer

The health outcomes of patients with metastatic and recurrent pancreatic cancer may improve when sintilimab is added to the standard treatment regimen of modified FOLFIRINOX chemotherapy. Moreover, the phase 3 CISPD3 trial displayed a manageable safety profile of the combination therapy [1].

"(Modified) FOLFIRINOX is the standard first-line therapy for patients with metastatic pancreatic adenocarcinoma," said Dr Qihan Fu (Zhejiang University School of Medicine, China). "The anti-PD1 monoclonal antibody sintilimab may provide additional benefits for this difficult-to-treat patient population." The phase 3 CISPD3 trial (NCT03977272) randomised 110 patients with metastatic pancreatic cancer 1:1 to sintilimab plus modified FOLFIRINOX chemotherapy or chemotherapy alone. Patients in the sintilimab arm received 200 mg sintilimab every 3 weeks. The treatment was continued until disease progression or unacceptable toxicity occurred. The primary endpoint was overall survival (OS).

Patients in the sintilimab plus chemotherapy arm displayed a higher objective response rate compared with patients who received chemotherapy alone (50.0% vs 23.9%; P<0.05). In addition, the response duration was numerically higher in the sintilimab plus chemotherapy arm than in the chemotherapy alone arm (7.85 vs 4.63 months; see Figure). However, the median OS in the intention-to-treat population was comparable between the 2 treatment arms (10.9 vs 10.8 months). Similarly, there was no notable difference in median progression-free survival (5.9 vs 5.7 months).

Figure: Tumour response results in CISPD3 trial [1]

	Sintilimab + mFFX (n=55)	mFFX (n=55)	P-value
Best overall response			
Complete response	1	0	
Partial response	21	11	
Stable disease	15	22	
Progressive disease	7	13	
Not evaluable	11	9	
Objective response rate	50.0%	23.9%	**P<0.05**
Disease control rate	84.0%	71.7%	P>0.05
Response duration	7.85 months	4.63 months	P>0.05

According to Dr Fu, the safety profile of sintilimab plus chemotherapy was acceptable and manageable. Nonetheless, more grade 3 or higher adverse events (AEs) were reported in patients who received sintilimab plus chemotherapy compared with patients who received chemotherapy alone (84.9% vs 74.1%). In particular, neutropenia (58.5% vs 44.4%), thrombocytopenia (17.0% vs 11.1%), increased aminotransferase (11.3% vs 5.6%), and immune-related AEs (5.7% vs 0.0%) were more frequently observed in patients receiving sintilimab.

Dr Fu concluded that this data suggests that the benefits of (modified) FOLFIRINOX may be expanded with the addition of an antibody that is blocking PD-1, but it is not yet practice-changing; we need more data.

1. Fu Q, et al. Randomized Phase 3 study of Sintilimab in combination with modified FOLFRINOX versus modified FOLFRINOX alone in patients with metastatic and recurrent pancreatic cancer in China: the CISPD3 trial. Rapid abstract session B, ASCO GI 2022, 20–22 January.

TRYbreCA-1: Eryaspase + chemotherapy does not meet primary endpoint in pancreatic cancer

Eryaspase plus chemotherapy did not significantly outperform chemotherapy alone in the second-line treatment for patients with advanced pancreatic adenocarcinoma. However, the phase 3 TRYbeCA-1 study did suggest an advantage of additional eryaspase for resectable patients and patients with low or normal CA19-9 levels at baseline [1].

A phase 2 trial showed promising activity of eryaspase, an L-asparaginase within red blood cells, when added to FOLFOX or gemcitabine chemotherapy as a second-line therapy for patients with advanced pancreatic cancer [2]. Prof. Pascal Hammel (Université Paris VII, France) presented the results of the phase 3 TRYbeCA-1 trial (NCT03665441), in which 512 patients with stage III or IV pancreatic cancer, who underwent 1 previous line of chemotherapy, were randomised 1:1 to chemotherapy alone (gemcitabine + nab-paclitaxel, or FOLFIRI), or chemotherapy plus eryaspase. The primary endpoint was overall survival (OS).

The median OS for patients receiving the eryaspase plus chemotherapy regimen was not significantly longer than

the median OS for patients receiving chemotherapy alone (7.5 vs 6.7 months; P=0.469). The median progression-free survival was 3.7 months and 3.4 months for patients in the eryaspase arm and patients in the chemotherapy alone arm, respectively. The disease control rate was higher in the eryaspase arm compared with the chemotherapy alone arm (57.6% vs 49.0%; P=0.047). Notably, a trend in the OS analysis suggested that patients on FOLFIRI chemotherapy may benefit from additional eryaspase (median OS of 8.0 vs 5.7 months). In addition, subgroup analyses revealed that resectable patients (HR 0.53; 95% CI 0.32–0.87) or patients with low or normal CA19-9 levels (HR 0.49; 95% CI 0.27–0.90) may benefit more from the addition of eryaspase to chemotherapy. Future studies should investigate whether these biologically favourable subgroups indeed benefit from eryaspase.

Eryaspase did not significantly increase adverse events. However, haematologic events, such as neutropenia (25.4% vs 20.3%) and anaemia (17.3% vs 12.2%) were more common in the eryaspase arm. Dr Hammel concluded that the addition of eryaspase did not elevate the toxicity of chemotherapy.

1. Hammel P, et al. A Randomized Phase 3 Study of Eryaspase in Combination with Chemotherapy versus Chemotherapy Alone as Second-line Treatment in Patients with Pancreatic Adenocarcinoma – TRYbeCA-1 Study. Abstract 518, ASCO GI 2022, 20–22 January.
2. Hammel P, et al. Eur J Cancer. 2020;124:91–101.

Persisting disparities in pancreatic cancer care

Disparities in pancreatic cancer care are persistent and have an impact on the health outcomes of underserved patients. Physician/surgeon bias, underrepresentation of certain subgroups in clinical trials, and lack of access to high-volume hospitals may be factors that drive these disparities. In addition, precision medicine may exacerbate the observed health inequalities [1].

Prof. Susan Tsai (Medical College of Wisconsin, WI, USA) explained that health disparities in pancreatic cancer surgery are persistent. "Patients who are White, insured, and have a high socioeconomic status (SES) are more likely to receive pancreatic surgery than their counterparts. Moreover, patients who live in an urban environment are more likely to receive surgery than those who live in a rural setting."

It has been demonstrated that the mortality rate following pancreatic surgery performed in high-volume hospitals (approximately 20 per year) is significantly lower than surgeries performed in low-volume hospitals [2]. The benefits of experienced surgeons and superior post-operative care in high-volume hospitals come at the expense of an increased travel distance and travel cost, which predominantly affects vulnerable minorities.

"The physician's bias towards minority groups may add to these disparities," said Prof. Tsai. A study by Lopez-Verdugo et al. demonstrated that non-Black minorities were less likely to receive neoadjuvant therapy than White patients and that a longer travel distance was associated with a reduced likelihood of being offered neoadjuvant therapy [3]. In addition, another study showed that patients from deprived areas were less likely to receive adjuvant therapies [4]. "Furthermore, Black and Hispanic patients are underrepresented in trials leading to cancer drug approval," said Prof. Tsai. "In addition, disparities are perpetuated in the development of precision medicine. Since genomic data is mostly retrieved from European individuals, the artificial intelligence models based on these data are biased.

Centralisation and standardisation of high-risk surgery, optimising the delivery of locoregional care, leveraging emerging technologies, and developing community partnerships to engage underserved minorities are some of the measures we need to take to reduce the persisting disparities in pancreatic cancer care."

1. Tsai S, et al. Access and Disparities in Pancreatic Cancer. Breakout Session: New Approaches and Equalizing Access in Pancreatic Cancer. ASCO GI 2022, 20–22 January.
2. Birkmeyer JD, et al. N Engl J Med. 2002;346:1128–1137.
3. Lopez-Verdugo F, et al. Ann Surg. 2021;Dec 23.
4. Mora J, et al. Am J Surg. 2021;222(1):10–17.

ctDNA promising biomarker for recurrence of pancreatic cancer

In patients with pancreatic duct adenocarcinoma (PDAC), ctDNA positivity after surgery was associated with decreased recurrence-free survival (RFS) rates. In contrast, the standard-of-care biomarker CA19-9 did not display this association. Furthermore, ctDNA may be able to predict recurrence long before it can be detected on radiographic imaging. This may allow clinicians to switch therapies in time and offer better health outcomes for their patients with PDAC [1].

"Carbohydrate antigen (CA19-9) is widely used as a biomarker in patients with pancreatic cancer," said Dr Gregory Botta (UCSD Moores Cancer Center, CA, USA). "However, CA19-9 lacks sensitivity and specificity. Since ctDNA has shown to be

a promising biomarker in other types of cancer, the current study aimed to investigate whether ctDNA is predictive of recurrence in patients with PDAC. With early detection of recurrence, interventions can be initiated swiftly." In total, 116 patients with PDAC (stage I to III) were followed up for a median of 13.6 months to assess ctDNA levels with a personalised, tumour-informed ctDNA assay.

After adjusting for clinical risk factors, ctDNA detection after surgery (any time) was a strong predictor for RFS (HR 5.64; 95% CI 2.4–12.88; P<0.001). In addition, a longitudinal analysis showed that ctDNA was significantly prognostic for RFS (HR 8.2; 95% 3.4–19.9; P<0.001), whereas CA19-9 was not (HR 2.4; P=0.17). Dr Botta added that case analyses showed that ctDNA can predict recurrence of PDAC with significant lead time, providing an opportunity to change treatment regimens before recurrence can be detected on radiographic imaging.

1. Botta GP, et al. Association of personalized and tumor-informed ctDNA with patient survival outcomes in pancreatic adenocarcinoma. Abstract 517, ASCO GI 2022, 20–22 January.

Head-to-head: Etoposide and irinotecan equally effective in neuroendocrine carcinoma

Etoposide and irinotecan showed equal efficacy in a head-to-head study among patients with advanced neuroendocrine carcinoma (NEC) of the digestive system [1]. Therefore, these agents both remain first-line therapeutic options for this population.

"Platinum-based chemotherapy regimens are recommended for advanced NEC," said Dr Chigusa Morizane (National Cancer Center Hospital, Japan). "Etoposide plus cisplatin (EP) and irinotecan plus cisplatin (IP) are standard-of-care options for patients with this condition. However, it is currently unknown which combination is more effective." Therefore, the phase 3 TOPIC-NEC study (UMIN000014795) was designed to compare EP and IP head-to-head in patients with advanced NEC (n=170). The patients were randomised 1:1 to either EP: etoposide (100 mg/mg^2, day 1, 2, 3) and cisplatin (80 mg/m^2, day 1, every 3 weeks); or IP: irinotecan (60 mg/m^2, day 1, 8, 15) and cisplatin (60 mg/m^2, day 1, every 4 weeks).

The median overall survival (OS), primary endpoint of this study, did not differ significantly between EP and IP (12.5 vs 10.9 months; P=0.80). Similarly, the median progression-free survival (PFS) times were comparable (5.6 vs 5.1 months, respectively; P=0.72). The objective response rates were also similar for patients in the EP and IP arm (54.5% vs 52.5%, repectively). Interestingly, a post-hoc subgroup analysis showed that patients with pancreatic poorly differentiated NEC may benefit more from EP therapy (HR 4.10; 95% CI 1.26–13.31).

The safety analysis showed that grade 3 or 4 reductions in neutrophil count were more common in the EP group than in the IP group (91.5% vs 53.7%). Also, grade 3 or 4 febrile neutropenia occurred more often in the EP arm (26.8% vs 12.2%; see Figure). Notably, prophylactic administration of granulocyte colony-stimulating factor (G-CSF) reduced the prevalence of grade 3 or 4 neutropenia from 27.9% to 9.5% in the first treatment cycle. Finally, patients in the IP arm experienced more any-grade diarrhoea than those in the EP arm (47.6% vs 23.2%).

Figure: Safety profiles of etoposide plus cisplatin versus irinotecan plus cisplatin [1]

	EP (n=82)		IP (n=82)	
	All grade (%)	Grade 3–4 (%)	All grade (%)	Grade 3–4 (%)
White blood cell ↓	82.9	61.0	74.4	30.5
Neutrophil count ↓	93.9	91.5	73.2	53.7
Anaemia	90.2	25.6	85.4	17.1
Platelet count ↓	89.0	12.2	54.9	3.7
Febrile neutropenia	26.8	26.	12.2	12.2
Biliary tract infection	2.4	2.4	6.1	6.1
Anorexia	85.4	13.4	73.2	15.9
Nausea	69.5	4.9	50.0	7.3
Diarrhoea	23.2	1.2	47.6	6.1
Fatigue	70.7	11.0	63.4	8.5
AST (GOT) ↑	59.8	6.1	65.9	3.7
ALT (GPT) ↑	59.8	13.4	58.5	9.8
Hyponatremia	67.1	13.4	68.3	8.5
Hypokalemia	23.2	6.1	29.3	4.9

Dr Morizane concluded that both regimens remain first-line standard-of-care options for patients with NEC of the digestive system. "Future studies should investigate whether additional immune checkpoint inhibitors may provide benefits for our patients."

1. Morizane C, et al. Randomized phase 3 study of etoposide plus cisplatin versus irinotecan plus cisplatin in advanced neuroendocrine carcinoma of the digestive system: A Japan Clinical Oncology Group study (JCOG1213, TOPIC-NEC). Abstract 501, ASCO GI 2022, 20–22 January.