Medicom International Conference Series in Oncology

2023 Gastrointestinal Cancers Symposium

American Society of Clinical Oncology

19–21 JANUARY 2023 • SAN FRANCISCO • USA

PEER-REVIEWED CONFERENCE REPORT

Zolbetuximab plus mFOLFOX6 successful in claudin 18.2-positive gastric cancer

Zolbetuximab plus mFOLFOX6 improved PFS and OS in claudin-18.2 gastric cancer patients, according to the SPOTLIGHT trial.

read more on PAGE 3

Botensilimab plus balstilimab promising in colorectal cancer

Botensilimab plus balstilimab increased the anti-tumour activity and had a manageable safety profile in microsatellite-stable, colorectal cancer patients.

read more on PAGE 8

Surgery may be avoided with adequate rectal cancer therapy

Non-surgical treatment is feasible for patients with distal-middle, cT2-cT3a-b rectal cancer, according to the 38-month follow-up of the OPERA trial.

read more on PAGE 11

MEDICOM MEDICAL PUBLISHERS

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Luxembourg

COLOPHON

Editor	Dr Stefan Rauh Centre Hospitalier Emile Mayrisch, Luxembourg
Reviewer	Dr Joelle Collignon CHU Liège, Belgium
Publishing Director	Paul Willers
Editorial Operations Manager	Dr Rosalie Molenaar
Medical Science Officer	Dr Rachel Giles
Medical Project Manager	Anne van Ham
Editorial Coordinators	Rune Bruls Dr Joery Goossens
Medical Writers	Robert van den Heuvel
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink
Cover Photo	Shutterstock
ISSN	2468-8762 23:04

MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
De Ruijterlaan 1-A
3742 AE Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Contents

Letter from the Editor

Dear reader,

I'm delighted to introduce our congress report of this year's ASCO GI, which took place from January 19–21 in San Francisco.

Here's just some picks I'd like to highlight:

Claudin 18.2 is a new target in the fast-expanding range of treatments for advanced gastric cancer. In strong expressing tumours, adding the targeting monoclonal antibody to standard chemotherapy significantly improved progression free survival (and even overall survival, which was however not a primary endpoint) in a randomized, phase 3 study. More good news: strong CLDN 18.2 expression was observed in roughly a third of all screened patients.

Are we getting closer to "warming up" "cold" colorectal cancers? The combination of a Fc-enhanced CTLA-4 blocker and a PD-1 inhibitor showed a respectable response rate in heavily pretreated patients with metastatic, microsatellite stable, colorectal cancer. Sure, it's a phase 1 study. Still very intriguing – and confirmatory phase 1 and 3 studies are on their way.

And will surgeons soon get out of business? The OPERA study provides increasing evidence that some patients with localised/locally advanced rectum cancer may be spared surgery when in remission after chemo radiotherapy – truly potentially practice changing.

I won't reveal everything to you. Check out our congress report in detail for more. Enjoy our briefing!

Yours sincerely,

Stefan Rauh

Biography
Dr Stefan Rauh is currently working as oncologist/haematologist 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 a 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 interested in survivorship of cancer patients and has published a clinician's handbook on this topic: Survivorship Care for Cancer Patients.

Conflict of Interest Statement:
Nothing to declare.

Oesophageal and Gastric Cancer

Zolbetuximab plus mFOLFOX6 successful in CLDN18.2-positive subgroup of gastric cancer

Zolbetuximab added to 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) improved the progression-free survival (PFS) and overall survival (OS) of patients with claudin-18.2-positive (CLDN18.2-positive)/HER2–negative, locally advanced, unresectable or metastatic, gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma, primary results of the SPOTLIGHT study revealed.

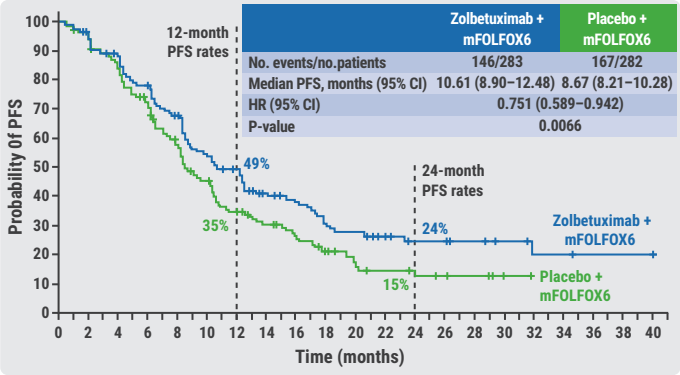
Zolbetuximab is a first-in-class chimeric, IgG1 monoclonal antibody targeting CLDN18.2 and inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [1,2]. In a phase 2b trial, this agent, in combination with epirubicin + oxaliplatin + capecitabine (EOX), improved the survival in patients with increased expression of CLDN18.2 in their tumour cells [3]. This result led to the development of the SPOTLIGHT study.

SPOTLIGHT (NCT03504397) is a global phase 3 trial randomising newly diagnosed patients with CLDN18.2-positive/HER2-negative, locally advanced, mG/GEJ adenocarcinoma (n=565) 1:1 to mFOLFOX6 plus zolbetuximab or to mFOLFOX6 plus placebo [4]. Over 38.5% of assessable patients were CLDN18.2 positive, defined as moderate to strong CLDN18.2 staining in ≥75% of tumour cells. PFS was the primary endpoint of the study and Dr Kohei Shitara (National Cancer Center Hospital East, Japan) presented the primary findings.

After a median follow-up of 12.9 months, the median PFS was significantly higher if patients were treated with zolbetuximab compared with mFOLFOX6 only (10.61 months vs 8.67 months; HR 0.75; 95% CI 0.59—0.94; P=0.0066; see Figure). The corresponding 24-month PFS rates were 24% and 15%, respectively. The OS results confirmed the benefit of the addition of zolbetuximab to mFOLFOX6 with a median OS of 18.2 months compared with 15.5 months for patients who received mFOLFOX6 only (HR 0.75; 95% CI 0.60—0.94; P=0.0053).

According to the authors, the safety profile of zolbetuximab and mFOLFOX6 was acceptable. The incidence of treatment-emergent adverse events was comparable for the 2 treatment arms, but grade 3 or higher nausea (16.1% vs 6.5%) and vomiting (16.1% vs 5.8%) were more common in the zolbetuximab arm. Dr Shitara commented that these events mostly occurred in the first cycle of zolbetuximab and that they were manageable with treatment adjustments. In total, 13.6% of the patients discontinued zolbetuximab due to treatment-related adverse events compared with 2.2% of the patients in the placebo arm.

Figure: Higher PFS for patients on zolbetuximab compared with mFOLFOX6 only [4]



PFS, progression-free survival; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

In conclusion, zolbetuximab plus mFOLFOX6 candidates as a new standard-of-care therapy for patients with CLDN18.2-positive/HER2-negative, locally advanced, mG/GEJ adenocarcinoma. It is the first moleculary targeted therapy to show a statistically significant survival benefit since trastuzumab.

1. Sahin U, et al. Eur J Cancer. 2018;100:17–26.
2. Rohde C, et al. Jpn J Clin Oncol. 2019;49:870–876.
3. Sahin U, et al. Ann Oncol. 2021;32:609–619.
4. Shitara K, et al. Zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients (pts) with claudin-18.2+ (CLDN18.2+) / HER2− locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary results from phase 3 SPOTLIGHT study. Late-breaking abstract 292, ASCO GI, 19–21 January, San Francisco, CA, USA.

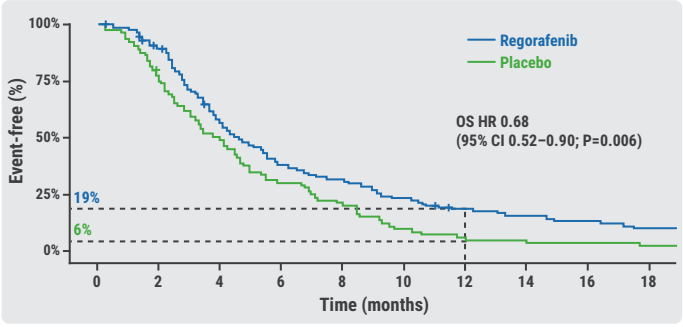
Regorafenib offers survival benefit for patients with pre-treated gastric cancer

Regorafenib outperformed placebo in terms of overall survival in patients with refractory, advanced gastric or oesophago-gastric junction cancer (AGOC) in the phase 3 INTEGRATE IIa trial, providing a new treatment option for this patient population. The phase 3 INTEGRATE IIb trial is currently ongoing to compare regorafenib plus nivolumab with chemotherapy in patients with refractory AGOC.

"The treatment options for patients with pre-treated AGOC are limite," said Prof. Nick Pavlakis (University of Sydney, Australia) at the start of his presentation [1]. "However, regorafenib showed promising anti-tumour activity in a phase 2 trial [2]." After these findings had been reported, a phase 3 study was designed to test regorafenib against placebo. The INTEGRATE IIa trial (NCT02773524) randomised 251 patients with AGOC who had received at least 2 prior lines of therapy 2:1 to regorafenib, 160 mg, once daily at days 1 to 21 of a 28-day cycle, or placebo [3]. The primary endpoint was the overall survival (OS).

Patients in the regorafenib arm had an OS benefit compared with patients in the placebo arm (HR 0.68; 95% CI 0.52–0.90; P=0.00; see Figure) . The corresponding 12-month OS rates were 19% and 6%, respectively. Prof. Pavlakis mentioned that there were no significant differences among pre-defined subgroups. Furthermore, the progression-free survival results confirmed the OS results, demonstrating a benefit for patients on regorafenib over patients on placebo (HR 0.53; 95% CI 0.40–0.70; P<0.0001). Interestingly, patients receiving regorafenib displayed a significant delay in the deterioration of their global quality-of-life compared with patients receiving placebo (P=0.0043). According to Prof. Pavlakis, the safety profile of regorafenib was comparable with that of previously reported studies on this agent.

Figure: Overall survival of regorafenib versus placebo [3]



In conclusion, regorafenib improved the health outcomes in patients with pre-treated AGOC, presenting itself as a new treatment option for the population. The agent is further assessed in combination with nivolumab against chemotherapy in an estimated 450 patients with AGOC who failed on at least 2 prior lines of therapy in the INTEGRATE IIb trial (NCT04879368).

1. Smyth EC, et al. Lancet. 2020;396:635–648.
2. Pavlakis N, et al. JCO. 2016;34:2728–2735.
3. Pavlakis N, et al. INTEGRATE IIa: A randomised, double-blind, phase III study of regorafenib versus placebo in refractory advanced gastro-oesophageal cancer (AGOC)—A study led by the Australasian Gastro-intestinal Trials Group (AGITG). Late-breaking abstract 294, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Radiotherapy or not in locally advanced oesophageal or junctional cancer?

Peri-operative chemotherapy was not significantly inferior to neoadjuvant chemoradiation (CRT) plus surgery in patients with oesophageal or oesophago-gastric junction (OGJ) adenocarcinoma, the final overall survival (OS) analysis of the phase 3 Neo-AEGIS trial showed.

The Neo-AEGIS trial (NCT01726452) aimed to answer the question whether radiotherapy is needed in patients with locally advanced oesophageal or OGJ adenocarcinoma. To investigate this matter, 377 patients were randomised to peri-operative chemotherapy (arm A) or neoadjuvant CRT plus surgery (arm B) [1]. OS was the primary endpoint and Prof. Maeve Lowery (St James's Hospital, Ireland) presented the final analysis of this outcome.

Although arm B outperformed arm A in terms of the pathological complete response rate (17.3% vs 5.1%; P=0.001) and the major pathological response rate (42% vs 12.1%; P<0.001), the 3-year survival rates were nearly identical for the 2 study groups, with 55% in arm A and 57% in arm B (HR 1.03; 95% CI 0.77–1.38). As for safety, neutropaenia (14.1% vs 2.8%), diarrhoea (10.9% vs 0%), and vomiting (7.6% vs 2.8%) occurred more frequently in arm A than in arm B. Also, no negative effect of radiotherapy was seen with regard to operative complications.

All in all, peri-operative chemotherapy remains non-inferior to neoadjuvant chemoradiation and surgery in this population. "We need to further investigate how the improved response rates with chemoradiation did not extend to a survival advantage for patients who were exposed to this therapy," said Prof. Lowery. "Recurrence data may provide insights in the mechanism behind these results." Currently, the standard for patient with no pathologic complete response after CRT and surgery is adjuvant nivolumab.

1. Lowery M, et al. Neo-AEGIS (Neoadjuvant Trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Final primary outcome analysis. Abstract 295, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Neoadjuvant immunotherapy is safe and efficacious in a phase 2 gastric cancer trial

Neoadjuvant tremelimumab plus durvalumab displayed encouraging activity and a favourable safety profile in patients with microsatellite instability-high (MSI-H), resectable gastric or gastroesophageal junction adeno-carcinoma (GAC/GEJAC) in the phase 2 INFINITY trial.

In patients with GAC/GEJAC, MSI-H status has been linked to improved survival outcomes and a reduced benefit from chemotherapy [1]. On the other hand, immunotherapy is effective in MSI-H tumours [2]. Therefore, the combination of CTLA-4 inhibition and PD-L1 inhibition may result in the possibility of omitting chemotherapy or surgery in these patients.

The multicentre, single-arm, phase 2 INFINITY trial (NCT04817826) assessed the efficacy and safety of tremelimumab plus durvalumab as neoadjuvant therapy in a cohort of 18 patients with MSI-H, mismatch repair deficient (dMMR), and EBV-negative resectable GAC/GEJAC [3]. In a second cohort, this therapy will be assessed as a definitive treatment for patients with this indication. In the neoadjuvant cohort, patients received a single dose of 300 mg tremelimumab and 1,500 mg durvalumab, every 4 weeks. The primary endpoint was the pathological complete response (pCR) with negative ctDNA after 12 weeks of treatment. Dr Filippo Pietrantonio (Fondazione IRCCS Istituto Nazionale dei Tumori, Italy) presented the findings [3].

In total, 9 out of 15 evaluable patients achieved a pCR with negative ctDNA status (60%) prior to surgery. The major-complete pathological response rate (<10% viable cells) was 80%. According to Dr Pietrantonio, the global quality-of-life was preserved during the neoadjuvant treatment.

Pre-operative treatment with tremelimumab and durvalumab was generally safe. In 3 patients, grade ≥3 immune-related adverse events (AEs) occurred; hepatitis, colitis, and pneumonitis, one case each. The most common grade 1 or 2 AEs were pruritis (22%), thyroiditis (22%), hepatitis (17%), and skin rash (17%).

The combination of tremelimumab and durvalumab appeared to be safe and displayed encouraging activity in the current phase 2 trial. "Although larger studies are needed, chemotherapy-free, immune checkpoint inhibitor-based strategies will represent a standard-of-care in the molecular subgroup of MSI-H dMMR tumours in the foreseeable future," argued Dr Pietrantonio. "Of course, optimal combinations and therapy duration should be further investigated." This data is important for potential non-operative management as in locally advanced rectal cancer [4].

1. Pietrantonio F, et al. JCO. 2019;37(35):3392–3400.
2. Leone AG, et al. ESMO Open. 2022;7(1):100380.
3. Pietrantonio F, et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). Abstract 358, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

S-1 adjuvant chemotherapy: 4 or 8 courses in stage 2 gastric cancer?

The final follow-up data of the primary outcome of the phase 3 OPAS-1 trial suggested that 8 courses of S-1 adjuvant chemotherapy is the preferred option over 4 courses of this treatment regimen in patients with stage 2 gastric cancer who underwent resection.

The OPAS-1 trial (UMIN000007306) compared the standard-of-care treatment for patients with pathological stage 2 gastric cancer who underwent D2 gastrectomy, which is 8 courses of S-1 adjuvant chemotherapy, to a shortened version of this therapy, namely 4 courses [1]. In total, 590 patients were randomised to one of the 2 study groups. At the first interim analysis, the study was closed due to futility and it demonstrated that 4-courses of S-1 led to slightly inferior results in terms of relapse-free survival (RFS) compared with 8 courses [2]. Dr Souya Nunobe (Cancer Institute Hospital, Japan) presented the updated results of the trial.

The 5-year RFS rates displayed a slight numerical benefit for patients who had received 8 courses of S-1 compared with those who had received only 4 courses of this therapy (87.7% vs 85.6%; HR 1.27; 95% CI 0.85–1.89). The 5-year overall survival rates were 89.7% in the standard-of-care arm and 88.6% in the experimental arm (HR 1.12; 95% CI 0.72–1.75).

According to Dr Nunobe, 8 courses of S-1 adjuvant chemotherapy is highly recommended in Japanese guidelines in patients with pathological stage 2 gastric cancer.

1. Nunobe S, et al. Five-year follow-up results of a randomized phase III trial comparing 4 and 8 courses of S-1 adjuvant chemotherapy for pathological stage II gastric cancer: JCOG1104 (OPAS-1). Abstract 381, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. Yoshikawa T, et al. Annals of Oncology. 2017;28(5):V214.

LATG/LAPG demonstrates excellent long-term efficacy in stage 1 gastric cancer

Patients with stage 1 gastric cancer displayed excellent long-term survival outcomes after laparoscopy-assisted total or proximal gastrectomy (LATG/LAPG). According to the authors, the JCOG1401 study showed that LATG/LAPG can result in comparable results as open procedures.

The JCOG0912 study (UMIN000003319) demonstrated that laparoscopy-assisted distal gastrectomy (LADG) was non-inferior to open distal gastrectomy in patients with clinical stage 1 gastric cancer for safety and relapse-free survival [1,2],

indicating that LAPG may be the preferred standard treatment option if experienced surgeons are available. However, until now there have not been any prospective studies investigating LATG and LAPG in patients with early gastric cancer.

Therefore, the single-arm confirmatory JCOG1401 trial (UMIN000017155) included 245 patients with predominantly stage 1 proximal gastric cancer to assess the safety and long-term survival outcomes of LATG/LAPG [3]. The primary endpoint was the rate of grade ≥2 oesophageal anastomotic leak. A previous publication showed that this outcome remained below the expected value of 3.0% [4]. Dr Shinichi Sakuramoto (Saitama Medical University International Medical Center, Japan) presented the survival outcomes after 5 years of follow-up.

The 5-year overall survival rate was 91.2% (95% CI 86.9–94.2) and the 5-year relapse-free survival rate was 90.0% (95% CI 85.5–93.2). According to the authors, the long-term efficacy results for LATG/LAPG are excellent in this population and can match with the survival rates of open procedures.

1. Katai H, et al. Gastric Cancer. 2017;20(4):699–708.
2. Katai H, et al. Lancet Gastroent and Hepatol. 2020;5(2):142–151.
3. Sakuramoto S, et al. Long-term outcomes after laparoscopy-assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study (JCOG1401). Abstract 305, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
4. Katai H, et al. Gastric Cancer. 2019;22(5):999–1008.

3-year follow-up data confirms benefits of nivolumab plus + chemotherapy

The 3-year follow-up results of the CheckMate 649 study demonstrated long-term survival benefits for patients with newly diagnosed, advanced gastric cancer (GC), gastro-oesophageal junction cancer (GOJC), or oesophageal adenocarcinoma (OAC) if they followed a regimen of nivolumab plus chemotherapy.

In CheckMate 649 (NCT02872116), a global phase 3 study, 1,622 patients with previously untreated advanced GC, GOJC, or OAC were randomised 1:1 to chemotherapy or chemotherapy plus nivolumab [1]. "Following the 1-year results of this trial [2], nivolumab plus chemotherapy was approved as first-line therapy for patients with advanced GC/GOJC/OAC in more than 50 countries worldwide," added Dr Yelena Janjigian (Memorial Sloan Kettering Cancer, NY, USA). At ASCO GI 2023, she presented the 3-year follow-up results of CheckMate 649.

The median overall survival (OS) was 13.7 months in the experimental group compared with 11.6 months in the control group (HR 0.79; 95% CI 0.71–0.88). In addition, the 36-month OS rates were 17% and 10%, respectively. In patients with PD-L1 combined positive score ≥5, the median OS was 14.4 months in the nivolumab arm and 11.1 months in the chemotherapy arm (HR 0.70; 95% CI 0.61–0.81), with corresponding 3-year OS rates of 21% and 10%. The 3-year progression-free survival data showed similar results, favouring the nivolumab arm in all patients and in patients with PD-L1 combined positive score ≥5, specifically. Furthermore, patients with microsatellite instability-high (MSI-H) tumours appeared to have an increased benefit of the combination of chemotherapy and nivolumab compared with chemotherapy alone (median OS 38.7 vs 12.3 months; HR 0.34; 95% CI 0.16–0.74). According to Dr Janjigian, no new safety issues emerged with longer follow-up.

"These data further support the use of nivolumab plus chemotherapy in patients with advanced GC/GOJC/OAC," decided Dr Janjigian. Patients with higher PD-L1 expression levels or those with MSI-H tumours appeared to experience the largest benefits from the addition of nivolumab to chemotherapy.

1. Janjigian YY, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. Abstract 291, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. Janjigian YY, et al. Lancet. 2021;398:27–40.

Long-term results for nivolumab plus chemotherapy and nivolumab plus ipilimumab in oesophageal cancer

With long-term follow-up, both nivolumab plus chemotherapy and nivolumab plus ipilimumab continued to demonstrate clinically meaningful benefits over chemotherapy alone in the first-line treatment for patients with advanced oesophageal squamous cell carcinoma (OSCC). The updated results of the phase 3 CheckMate 648 trial further confirm these 2 treatment regimens as novel first-line options in patients with advanced OSCC.

The CheckMate 648 study (NCT03143153) showed that treatment with either nivolumab plus chemotherapy or nivolumab plus ipilimumab resulted in superior overall survival (OS) outcomes compared with chemotherapy alone in patients with advanced OSCC [1]. The study randomised 970 patients who were previously untreated for their advanced OSCC 1:1:1 to one of the 3 treatment arms. At the ASCO GI meeting, Dr Ken Kato (National Cancer Center Hospital, Japan) presented the results after a minimum follow-up of 29 months [2].

Nivolumab plus chemotherapy continued to outperform chemotherapy alone in terms of OS (median OS 12.8 vs 10.7 months; HR 0.78; 95% CI 0.65–0.93) and progression-free

survival (5.8 vs 5.6; HR 0.83; 95% CI 0.68–1.00). Corresponding results in patients with tumour cell PD-L1 expression levels ≥1% for OS (15.0 vs 9.1; HR 0.59; 95% CI 0.46–0.76) and PFS (6.8 vs 4.4; HR 0.67; 95% CI 0.51–0.89) demonstrated ongoing benefits in this subset of patients as well.

Likewise, nivolumab plus ipilimumab displayed a superior median OS compared with chemotherapy alone in all randomised patients (12.7 vs 10.7; HR 0.77; 95% CI 0.65–0.92) and in patients with PD-L1 levels ≥1% (13.1 vs 9.1; HR 0.62; 95% CI 0.48–0.80). For progression-free survival, the updated data did not show a benefit for the combination regimen over chemotherapy in all patients (2.9 vs 5.6; HR 1.26; 95% CI 1.04–1.51) or in the subset of patients with PD-L1 levels ≥1% (4.0 vs 4.4; HR 1.04; 95% CI 0.79–1.36).

According to Dr Kato, no new safety issues emerged with longer follow-up. The most common treatment related adverse events in the nivolumab plus chemotherapy arm were nausea (59%), decreased appetite (43%), and stomatitis (32%). For the nivolumab plus ipilimumab arm these were rash (17%), pruritis (13%), and hypothyroidism (13%), and for the chemotherapy alone arm, the most frequently reported safety issues were nausea (52%), decreased appetite (43%), and anaemia (22%).

The long-term follow-up results of CheckMate 648 continue to support the use of the assessed nivolumab-containing regimens in the first-line treatment of patients with advanced OSCC.

1. Doki Y, et al. N Engl J Med. 2022;386:449–462.
2. Kato K, et al. Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): 29-month (mo) follow-up from CheckMate 648. Abstract 290, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Promising phase 2 results for HER-Vaxx in gastric cancer

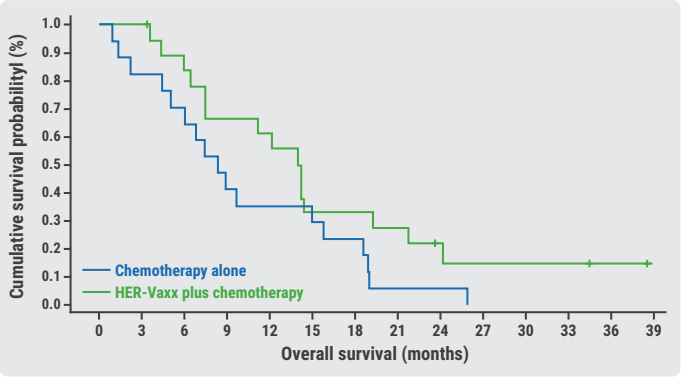
HER-Vaxx added to standard-of-care chemotherapy was associated with an improved overall survival compared with chemotherapy alone in patients with HER2-overexpressing advanced or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma. The current phase 2 HERIZON study did not reveal an increase in adverse events with the addition of HER-Vaxx to chemotherapy.

"HER-Vaxx is a B-cell immunotherapy, designed to target tumours that overexpress the HER2/neu receptor," outlined Dr Tanuj Chawla (Tata Medical Center, India). This novel agent showed promising efficacy data in a phase 1b study [1]. The phase 2, multicentre HERIZON study (NCT02795988) randomised 36 newly diagnosed patients with stage III or IV gastric or GEJ adenocarcinoma 1:1 to 6 cycles of standard-of-care chemotherapy or to chemotherapy plus 50 µg HER-vaxx, administered at days 1 and 15 of cycle 1, day 15 of cycle 2 and 4, and then every 9 weeks until disease progression occurred [2]. Dr Chawla added that the HERIZON study was performed in countries where trastuzumab was not available. The overall survival (OS) was the primary endpoint of this trial.

The safety outcomes showed comparable safety profiles for the 2 treatment regimens, with over grade 3 treatment-emergent adverse events (TEAEs) occurring in 42% of the patients in each arm. Moreover, the treatment discontinuation rate due to TEAEs appeared to be higher in the control arm than in the experimental arm (24% vs 11%).

The OS was significantly improved in patients who were randomised to the HER-Vaxx arm (median OS 14.0 vs 8.3 months; HR 0.56; 80% CI 0.35–0.90; one-sided P=0.054; see Figure). Also, the duration of response appeared to be longer in the HER-Vaxx arm, with 30 weeks, compared with 19 weeks in the control arm. Finally, persistent HER2-specific antibodies were associated with HER-Vaxx administration and correlated with clinical responses.

Figure: Overall survival benefit when HER-vaxx is added to chemotherapy [2]



"With no added toxicity of HER-Vaxx to standard-of-care chemotherapy and promising efficacy data, the current phase 2 study supports further exploration of HER-Vaxx in patients with gastric or GEJ adenocarcinoma," decided Dr Chawla. The results have initiated the nextHERIZON study (NCT05311176), which further investigates the potential of HER-Vaxx in the gastric cancer population.

1. Wiedermann U, et al. Clin Cancer Res. 2021;27(13):3649–3660.
2. Maglakelidze M, et al. HERIZON: A phase 2 study of HER-Vaxx (IMU-131), a HER2-targeting peptide vaccine, plus standard of care chemotherapy in patients with HER2-overexpressing metastatic or advanced gastric/GEJ adenocarcinoma—Overall survival analysis. Abstract 289, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Anal and Colorectal Cancer

Combination botensilimab plus balstilimab demonstrates promising activity in heavily pre-treated MSS CRC

The combination therapy of botensilimab plus balstilimab resulted in encouraging anti-tumour activity in heavily pre-treated patients with microsatellite stable colorectal cancer (MSS CRC) in a phase 1a/1b trial. According to the authors, the safety profile of this treatment regimen was manageable.

"Botensilimab is an Fc-enhanced CTLA-4 inhibitor, which displayed activity in 'cold' and immunotherapy-refractory tumours," said Prof. Anthony El-Khoueiry (Norris Comprehensive Cancer Center, CA, USA) [1]. The phase 1a/1b C-800 study (NCT03860272) is the first in-human trial to combine botensilimab plus balstilimab (a PD-1 antagonist) in patients with advanced cancer [2]. In total, 70 patients with refractory metastatic MSS CRC received 1 or 2 mg/kg of botensilimab, every 6 weeks, and 3 mg/kg of the PD-1 inhibitor, every 2 weeks. Patients had received a median of 4 prior lines of therapy.

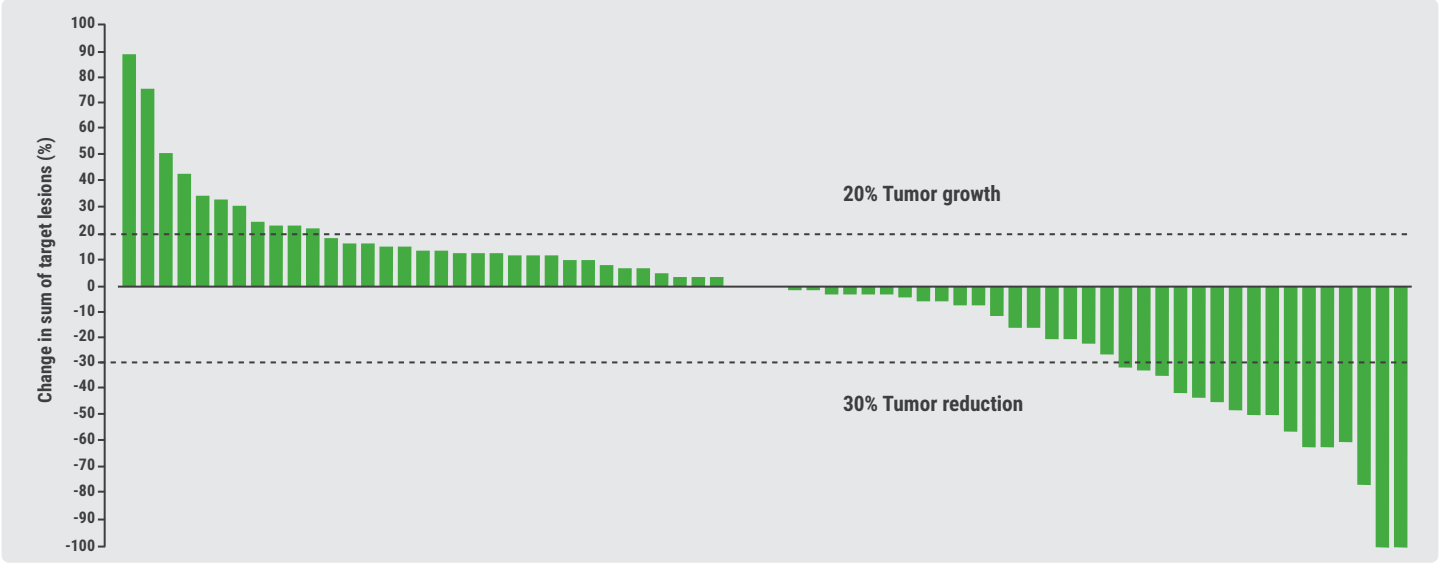
The overall response rate was 23%, mostly comprised by partial responses (21%; see Figure). In addition, the stable disease rate was 53%, resulting in a disease control rate of 76%. The median progression-free survival was 4.1 months and the median overall survival (OS) had not been reached at the time of the presentation. In patients with active liver metastases the 12-month OS-rate was 40%, whereas the corresponding rate in patients without active liver metastases was 81%.

According to Prof. El-Khoueiry, the safety profile of the combination therapy was manageable. Any grade treatment-related adverse events were seen in 91% of the patients and grade 3 or 4 events were observed in 40% and 3% of the patients, respectively. Immune-mediated diarrhoea and colitis was the most common grade 3 adverse event, occurring in 20% of the participants.

The promising anti-tumour activity and manageable safety profile of the combination therapy of botensilimab and balstilimab in this phase 1a/1b trial has instigated further investigation of this regimen. A randomised, phase 2 trial in MSS CRC patients is enrolling (NCT05608044) and a global, phase 3 trial is planned.

1. Waight JD, et al. Cancer Cell. 2018;33(6):1033–1047.
2. El-Khoueiry AB, et al. Results from a phase 1a/1b study of botensilimab (BOT), a novel innate/adaptive immune activator, plus balstilimab (BAL; anti-PD-1 antibody) in metastatic heavily pretreated microsatellite stable colorectal cancer (MSS CRC). Late-breaking abstract 8, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Figure: Deep objective responses with botensilimab plus balstilimab [2]



Mutation-based selection to identify patients suitable for panitumumab treatment

Patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC) without gene alterations had superior health outcomes with mFOLFOX6 plus panitumumab compared with mFOLFOX6 and bevacizumab, regardless of primary tumour side location, a biomarker analysis of the phase 3 PARADIGM trial showed. Therefore, negative hyperselection using ctDNA may identify patients who will benefit from panitumumab more effectively than selection based on primary tumour side.

The PARADIGM trial (NCT02394795) randomised 733 patients with *RAS* WT mCRC 1:1 to mFOLFOX6 and panitumumab or to mFOLFOX6 plus bevacizumab [1]. Previous results displayed an overall survival benefit for patients in the panitumumab arm with left-sided primary tumours [2]. Before treatment, plasma samples were sequenced with a custom ctDNA panel to identify mutations. Dr Kohei Shitara (National Cancer Center Hospital East, Japan) presented the findings from an analysis on the effects of the assessed therapies in respect to patients' mutations. Preplanned gene alterations for hyperselection included *KRAS*, *NRAS*, *PTEN*, and extracellular domain *EGFR* mutations, *HER2* and *MET* amplifications, and ALK, *RET*, or *NTRK1* fusions.

In total, 27.8% of the patients had gene alterations, whereas 72.2% of the patients did not. The panitumumab arm performed better than the bevacizumab arm in terms of overall survival (OS) in patients without gene alterations (median OS 41.3 months vs 34.4 months; HR 0.75; 95% CI 0.62–0.92). The corresponding data for patients with gene alterations showed no difference between the 2 treatment groups (median OS 19.0 months vs 22.2 months; HR 1.14; 95% CI 0.84–1.54). In addition, a significant P-value for interaction was reported (P=0.029). Interestingly, this trend was also visible in patients with right-sided tumours and no gene alterations (median OS 38.9 months vs 30.9 months; HR 0.82; 95% CI 0.50–1.35). The hazard ratio for patients with gene-altered right-sided tumours was 1.33, numerically favouring the bevacizumab arm over the panitumumab arm (median OS 14.1 months vs 18.5 months; 95% CI 0.84–2.11; P-value for interaction 0.145).

Dr Shitara argued that these results indicate that negative hyperselection of patients with RAS WT mCRC using ctDNA analysis rather than primary tumour side may select the right patients for treatment with panitumumab in the first line.

1. Shitara K, et al. Negative hyperselection of patients with RAS wild-type metastatic colorectal cancer for panitumumab: A biomarker study of the phase III PARADIGM trial. Abstract 11, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. Yoshino T, et al. JCO. 2022;40:17suppl LBA1.

Fucoidan associated with quality-of-life benefits in patients with rectal cancer receiving CCRT

A randomised trial investigating oral supplement fucoidan in patients with locally advanced rectal cancer (LARC) receiving concurrent chemoradiotherapy (CCRT) before surgery demonstrated quality-of-life benefits in terms of physical well-being and improved colorectal cancer subscale score in patients taking the long-chain sulphated polysaccharide.

Prof. Jaw-Yuan Wang (Pingtung Hospital, Taiwan) and colleagues randomised 87 patients with LARC receiving CCRT prior to surgery 1:1 to low molecular-weight fucoidan (LMF), 4 gr, oral administration, twice daily, or placebo [1]. Fucoidan algae extract is widely used as a food supplement. Quality-of-life was the primary outcome of the trial, which was assessed by comparing the FACT-C health-related quality-of-life mean scores of the 2 study groups.

Patients in the fucoidan group displayed a significantly higher score on the 'physical well-being' item of the questionnaire than patients in the placebo group (mean 23.27 vs 21.12; P=0.006). Furthermore, those who were exposed to fucoidan had an improved score on the 'colorectal cancer subscale' (mean 18.70 vs 16.53; P=0.034). Interestingly, rash or itching of the skin was less common in the fucoidan arm than in the placebo arm (0% vs 9.3%; P=0.038). Likewise, fatigue was less frequently reported in the experimental arm (75.0% vs 95.3%; P=0.008). Finally, Prof. Wang added that fucoidan was associated with an increase of the parabacteroides genus.

1. Wang J-Y, et al. A double-blind, randomized, placebo-controlled, parallel study to investigate the auxiliary effects of fucoidan in patients with locally advanced rectal cancer who receive neoadjuvant concurrent chemoradiotherapy before surgery. Abstract 12, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

ctDNA appears useful in monitoring patients with anal cancer undergoing CRT

With a high detectability rate and a low technical failure rate, measuring circulating tumour (ct)DNA was a useful response assessment in patients with anal cancer who were treated with chemoradiation (CRT). Further studies need to clarify whether patients can be stratified according to risk, and whether treatment de-escalation can be aligned with ctDNA measurements.

"The response evaluation in patients with anal cancer who underwent CRT is often delayed by 3–6 months," stated Dr Janet Alvarez (Memorial Sloan Kettering Cancer Center, NY, USA) [1]. "Therefore, there is a strong need for an early

response biomarker and ctDNA has demonstrated to be a promising candidate for this matter." The retrospective study that was performed by Dr Alvarez and colleagues included 31 patients with non-metastatic anal squamous cell carcinoma who were treated with definitive-intent CRT.

In 23 of the 27 assessable patients, ctDNA was detected at baseline, corresponding to a detectability rate of 85%. In addition, 2 out of 4 patients in whom ctDNA was not detectable at baseline had excisional biopsies prior to baseline ctDNA measurement. According to Dr Alvarez, the technical failure rate was 3%. Furthermore, ctDNA was cleared within 21 days of treatment in 57% of the patients. In further detail, 73% of the patients with stage I or II disease cleared mid-treatment in a median of 30 days and 50% of the patients with stage III disease cleared mid-treatment in a median of 31 days. Next, in 96% of the patients, ctDNA was cleared by the end of treatment. Finally, ctDNA clearance appeared to precede a clinical complete response, which was observed in this group of patients in a median of 136 days.

In summary, ctDNA showed to be a useful biomarker to track responses in patients with anal cancer undergoing CRT, with ctDNA clearance preceding clinical complete response by approximately 100 days. Longer follow-up data and larger trials are needed to assess the clinical utility.

1. Alvarez J, et al. Circulating tumor DNA (ctDNA) for response assessment in patients with anal cancer treated with definitive chemoradiation. Abstract 1, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

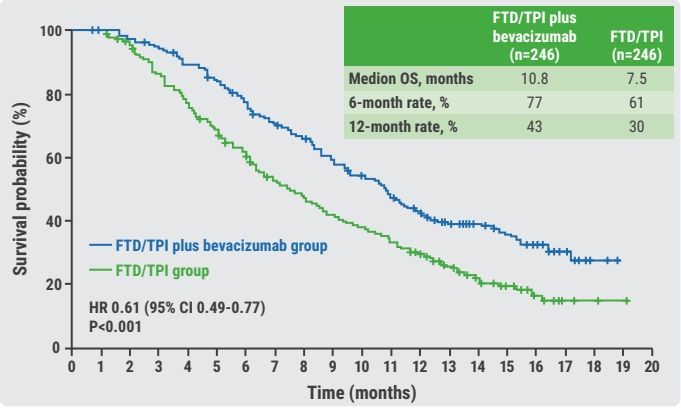
SUNLIGHT trial meets primary endpoint in refractory metastatic CRC

The phase 3 SUNLIGHT trial demonstrated that bevacizumab plus trifluridine/tipiracil (FTD/TPI) significantly improved overall survival (OS) and progression-free survival (PFS) compared with FTD/TPI as a single agent in patients with refractory metastatic colorectal cancer (mCRC), representing a novel standard-of-care for patients who had received 2 prior lines of therapy.

The SUNLIGHT study (NCT04737187) was designed to evaluate the efficacy and safety of the addition of bevacizumab to FTD/TPI compared with FTD/TPI alone in patients with refractory mCRC [1]. For this purpose, 492 patients who had received 2 prior lines of therapy were randomised 1:1 to the bevacizumab arm or to the FTD/TPI only arm. In both arms, 72% of the patients had prior treatment with bevacizumab. The primary outcome was OS and the results were presented by Prof. Josep Tabernero (Val d'Hebron University Hospital and Institute of Oncology, Spain).

The primary endpoint was met, favouring the bevacizumab arm over the FTD/TPI-only arm (median OS 10.8 months vs 7.5 months; HR 0.61; 95% CI 0.49–0.77; P<0.001; see Figure). The PFS was also significantly improved in the bevacizumab group compared with the control group (median PFS 5.6 months vs 2.4 months; HR 0.44; 95% CI 0.36–0.54; P<0.001). Furthermore, the time to deterioration in global health status was prolonged in the experimental arm (median time 8.5 months vs 4.7 months; HR 0.50; 95% CI 0.38–0.65; P<0.001). The safety profiles of the 2 treatment regimens were comparable. Severe adverse events (AEs) were reported in 72% and 70% of the patients in the respective study groups. Also, 13% in each group discontinued the study due to AEs.

Figure: Overall survival higher in the bevacizumab arm versus the FTD/TPI-only arm [1]



FTD/TPI, bevacizumab plus trifluridine/tipiracil.

"FTD/TPI plus bevacizumab improved the OS and PFS of patients with refractory mCRC compared with an active control, with a manageable safety profile," said Prof. Tabernero. "Therefore, this regimen represents a new standard of care for patients who have received 2 prior lines of therapy."

1. Tabernero J, et al. Trifluridine/tipiracil plus bevacizumab for third-line treatment of refractory metastatic colorectal cancer: The phase 3 randomized SUNLIGHT study. Abstract 4, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Does cell-free DNA influence MRD testing in post-operative colon cancer?

Although cell-free (cf)DNA is significantly increased in the first 14 days after surgery in patients with colon cancer, this did not influence circulating tumour (ct)DNA detection. Furthermore, minimal residual disease (MRD) testing delivered similar results between weeks 2 to 4

after surgery as did testing between weeks 4 to 8 after surgery, implying that standard MRD testing could be initiated as early as 2 weeks post-surgery.

"A sudden increase in cfDNA, which may occur after surgery in patients with colorectal cancer (CRC), could potentially reduce assay sensitivity in the context of measuring ctDNA," said Dr Stacey Cohen (University of Washington, WA, USA) [1]. "Also, the ideal timing to test for ctDNA after surgery or other events increasing cfDNA, such as systemic therapy, is yet to be determined." The current study analysed cfDNA kinetics and its impact on MRD detection via ctDNA measurement in patients with colon cancer [2]. The study included 14,425 patients with stage 1–3 colon cancer and at least 1 ctDNA result. In addition, a fully annotated cohort included 450 patients.

ctDNA was significantly increased in the first 2 weeks after surgery, decreased in weeks 2 to 4, and further decreased in weeks 4 to 8 (P<0.0001). In the fully annotated cohort, it was shown that patients on treatment had higher cfDNA levels than patients who were 'on surveillance' only. In the first 2 weeks after surgery, variability in ctDNA-positivity was reported. Although cfDNA levels were still high in weeks 2 to 4, ctDNA was consistently detected, with similar results as in weeks 4 to 12, indicating that ctDNA testing may be executed as soon as 15 days after surgery. It was further established that cfDNA concentration did not influence ctDNA-positivity, but that the results beyond 8 weeks after surgery are likely confounded by adjuvant chemotherapy.

In short, post-operative surges in cfDNA concentration did not impact ctDNA detection in a population of patients with colon cancer. Furthermore, according to the results of this study, standard MRD testing could be initiated 2 weeks after surgery.

1. Henriksen T, et al. Mol Oncol. 2020;14(8):1670–1679.
2. Cohen SA, et al. Circulating tumor DNA (ctDNA) for response assessment in patients with anal cancer treated with definitive chemoradiation. Abstract 5, ASCO-GI 2023, San Francisco, CA, USA, 19-21 January.

OPERA: surgery may be avoided with adequate therapy in rectal cancer

The 38-month follow-up data of the phase 3 OPERA trial showed that non-surgical treatment is feasible for patients with distal-middle, cT2-cT3a-b rectal cancer (RC). In patients who need surgery, this treatment can be administered without comprising the chance of a cure.

The OPERA trial (NCT02505750) randomised 142 patients with cT2-cT3a-b RC 1:1 to external beam chemoradiotherapy (EBCRT) with capecitabine and external beam radiotherapy (EBRT) boosts of 9Gy, 5 fractions, every 5 days (arm A) or to EBCRT followed by targeted radiotherapy using contact X-ray brachytherapy 50 kV (CXB), 90 Gy, 3 fractions, every 4 weeks (arm B) [1]. Prof. Arthur Sun Myint (Clatterbridge Cancer Centre, UK) presented the results.

After 24 weeks, the investigators observed a clinical complete response in 92% of the patients in arm B and in 64% of the patients in arm A. After a median follow-up time of 38.2 months, 46 patients had received surgery in arm A, either total mesorectal excision (TME), or local excision, compared with 20 patients in arm B. In addition, the TME rate was 39% in arm A and 19% in arm B (HR 0.36; P=0.004). Importantly, the organ preservation rates in patients with tumours <3 cm was 63% in arm A and 97% in arm B (HR 0.072; P=0.01) and the 3-year overall survival rates with organ preservation were 57% in arm A and 79% in arm B (P=0.0026).

"In short, non-surgical treatment was feasible for well selected patients (T2-T3a-b) and those who needed surgery could be saved without a decreased chance of cure," concluded Prof. Sun Myint. Contact X-ray is, however, not feasible everywhere.

1. Sun Myint A, et al. Do nonoperative modality (NOM) treatments of rectal cancer compromise the chance of cure? Final surgical salvage results from OPERA phase 3 randomised trial (NCT02505750). Abstract 6, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Can we improve total neoadjuvant therapy for rectal cancer?

Veliparib or pembrolizumab, added to total neoadjuvant therapy (TNT), did not improve short-term outcomes in patients with locally advanced rectal cancer (LARC), the NRG-GI002 trial demonstrated. However, the updated data indicate that pembrolizumab may improve the overall survival of these patients.

"The NRG-GI002 trial (NCT02921256) is designed to seek novel therapeutic options to improve the current TNT in patients with LARC," said Dr Thomas George (University of Florida, FL, USA). All included patients with very high-risk stage 2 or 3 LARC received 8 cycles of mFOLFOX6 chemotherapy, chemoradiotherapy, and surgery. In the 2 experimental arms, patients were administered to additional veliparib (n=90), during radiotherapy, or pembrolizumab (n=90), starting from the first day of radiotherapy [1]. The primary endpoint was the reduction in the neoadjuvant rectal (NAR) score. Previous results did not reveal a benefit

for either one of the experimental arms over the control arm regarding the primary outcome [2,3]. Dr George presented the updated findings.

There was no significant difference between the control arm (mean 12.5) or the veliparib (mean 13.3) arm in terms of the Neoadjuvant Rectal (NAR) score (Log-rank P=0.81) [4] or any of the other short-term or long-term outcomes. Dr George added that there was a trend towards a worse overall survival (OS) in the veliparib group compared with the control group: 3-year OS (85% vs 92%; HR 2.13; 95% CI 0.86–5.29; P=0.10). Patients in the pembrolizumab arm (mean 11.5) did not demonstrate a significant advantage over the control arm (mean 14.4) in terms of NAR score either (Log-rank P=0.21). The 3-year OS rates, however, suggest that pembrolizumab may deliver a benefit for these patients in the long run (95% vs 87%; HR 0.35; 95% CI 0.12–1.00; Log-rank P=0.04).

"Molecular interrogation of tumour and circulating biomarkers is ongoing to identify subgroups that may benefit from these targeted treatments," mentioned Dr George at the end of his talk.

1. George TJ, et al. Long-term results from NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC). Abstract 7, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. George TJ, et al. JCO. 2019;37(15suppl):abstr 3505.
3. Rahma OE, et al. JAMA Oncol. 2021;7(8):1225–1230.
4. George Jr TJ, et al. Curr Colorectal Cancer Rep. 2015;11(5):275–280.

Hepatobiliary Cancer

Palliative radiation therapy improves hepatic pain in HCC and liver metastasis

Single fraction radiation therapy (RT) added to best supportive care (BSC) outperformed BSC only in reducing hepatic pain in patients with either end-stage hepatocellular carcinoma (HCC) or liver metastasis. A trend was reported towards improved survival for patients receiving RT.

"An important minority of patients with end-stage HCC and liver metastases experience hepatic pain," said Prof. Laura Dawson (Princess Margaret Cancer Centre, Canada) [1]. She explained that systemic therapy is not swiftly effective in reducing pain and that opioids have a small therapeutic window due to a reduced clearance and underlying liver disease. A study by Soliman et al. showed that single fraction 8 Gy RT to the whole liver was safe, providing the rationale for the current study [2].

A randomised, multi-centre, phase 3 trial (NCT02511522) included 66 patients with either painful end-stage HCC (n=23) or liver metastasis (n=43) to compare palliative RT, single fraction, 8 Gy, plus BSC with BSC only [1]. The primary endpoint was the reduction of hepatic pain, defined as an improvement of at least 2 points on the 'intensity at worst' item of the Brief Pain Inventory (BPI) after 1 month.

The primary endpoint was met by 67% of the patients in the RT arm and by 22% of the patients in the BSC arm (P=0.004). A sensitivity analysis, treating patients without assessment at 1 month as having 'no improvement' still favoured the RT arm over the BSC arm (49% vs 12%; P=0.002). In addition, 21% of the patients in the RT arm achieved the primary endpoint without an increase in opioid use compared with 0% in the BSC arm, a result that trended towards significance (P=0.07). Interestingly, the authors observed a trend towards improved survival in the experimental arm, with 3-month overall survival rates of 51% and 33%, respectively (P=0.07).

"Single fraction RT improved hepatic pain in the majority of patients with painful end-stage HCC or liver metastases," concluded Prof. Dawson. Further studies need to clarify whether there is in fact a prolonged survival for patients on RT compared with those receiving BSC only.

1. Dawson LA, et al. Canadian Cancer Trials Group HE.1: A phase III study of palliative radiotherapy for symptomatic hepatocellular carcinoma and liver metastases. LBA492, Rapid Abstract Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. Soliman H, et al. JCO. 2013;31(31):3980–3986.

Improved survival following postoperative sorafenib plus TACE in HCC

The postoperative adjuvant combination therapy of sorafenib plus transarterial chemoembolisation (TACE) proved to be superior to sorafenib alone in patients with hepatocellular carcinoma (HCC) and portal vein tumour thrombus (PVTT) after surgery in a phase 3 study.

Prof. Ming Kuang (The First Affiliated Hospital, China) and colleagues designed a phase 3 trial to assess the efficacy and safety of sorafenib plus TACE as a post-operative adjuvant treatment in patients with HCC and PVTT after surgery (n=158) [1]. The included patients were randomised 1:1 to sorafenib only or to sorafenib plus TACE. Recurrence-free survival (RFS) was the primary endpoint of the trial.

The RFS was significantly improved in patients receiving the combination therapy compared with those receiving sorafenib only (median RFS 16.8 months vs 12.6 months; HR 0.57; 95% CI 0.39–0.83; Log-rank P=0.0024). The median overall survival (OS) was longer in patients in the sorafenib plus TACE arm than in patients in the sorafenib-only arm (30.4 months vs 22.5 months; HR 0.57; 95% CI 0.36–0.91; Log-rank P=0.0174). Prof. Kuang added that sorafenib plus TACE was well tolerated and that the safety profiles of the 2 treatment regimens were similar.

The improved RFS and OS in patients receiving sorafenib and TACE indicate that this combination therapy may provide an effective strategy to control advanced HCC after surgery. Of note, this data concerns a niche of patients with PVTT and currently adjuvant treatment even with sorafenib is not recommended by NCCN guidelines (NCCN version 5.2002).

1. Peng Z, et al. Adjuvant Transarterial Chemoembolization with Sorafenib for Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus after Surgery: A Phase III, Multicenter, Randomized, Controlled Trial. Abstract 493, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Quality-of-life benefits for tislelizumab in uHCC

Tislelizumab delivers improved health-related quality-of-life (HRQoL) outcomes compared with sorafenib in patients with unresectable hepatocellular carcinoma (uHCC), the latest results from the phase 3 RATIONALE 301 study show. These findings, together with the efficacy results, support the use of tislelizumab in the first-line treatment of patients with uHCC.

RATIONALE-301 (NCT03412773) randomised 674 patients with untreated uHCC 1:1 to sorafenib or tislelizumab [1]. Previous results from this trial showed that tislelizumab was non-inferior to sorafenib for overall survival [2]. Here, Prof. Richard Finn (University of California Los Angeles, CA, USA) outlined the data of HRQoL measures for the assessed agents. The EORTC QLQ-C30 scale showed that patients in the sorafenib arm had a reduction from baseline in global health status/quality-of-life at cycles 4 (-5.1 vs -0.7; P=0.0037) and 6 (-5.9 vs -0.9; P=0.0022) of therapy, but that those in the tislelizumab arm did not show this deterioration. The corresponding results for physical functioning at cycle 4 (-7.7 versus -1.3; P<0.0001) and 6 (-7.2 vs -1.0; P<0.0001) displayed a benefit for tislelizumab as well. Moreover, patients in the sorafenib arm showed an increase in fatigue whereas those in the tislelizumab arm did not: cycle 4 (+9.1 vs +1.5; P<0.0001); cycle 6 (+9.8 vs +2.2; P<0.0001). The pain scores of the EORTC QLQ – HCC18 scale were comparable for the 2 arms, with an increase around +2.5 for both treatment arms at cycles 4 and 6.

After meeting its primary endpoint, data from RATIONALE-301 now demonstrated quality-of-life benefits for patients with newly diagnosed uHCC receiving tislelizumab compared with those receiving sorafenib.

1. Finn RS, et al. Tislelizumab versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: Impact on health-related quality of life in RATIONALE-301 population. Abstract 495, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.
2. Qin S, et al. Annals of Oncology. 2022;33(7):S1402–S1403.

Stereotactic body radiation therapy beneficial for patients with locally advanced HCC

Stereotactic body radiation therapy (SBRT) followed by sorafenib outperformed sorafenib alone in patients with advanced hepatocellular carcinoma (HCC) in a phase 3 trial, adding this technique to the armamentarium of treatment options for patients with HCC, particularly those with locally advanced disease and microvascular invasion.

The phase 3 NRG/RTOG1112 trial (NCT01730937) aimed to evaluate the role of SBRT plus systemic therapy in patients with HCC [1]. In total, 193 patients with locally advanced HCC who were ineligible to receive surgery, radiofrequency ablation, or transarterial chemoembolisation were randomised 1:1 to the former standard-of-care, sorafenib, or to SBRT, 27.5-50 Gy in 5 fractions, followed by sorafenib. Prof. Laura Dawson (Princess Margaret Cancer Centre, Canada) emphasised that approximately 75% of the included patients had microvascular invasion.

The overall survival (OS) appeared to be improved in patients in the SBRT arm compared with those in the control arm (median OS 15.3 months vs 12.3 months; HR 0.77; 90% CI 0.59–1.01; 1-sided P=0.055). Next, progression-free survival (PFS) results favoured the experimental arm over the control arm (median PFS 9.2 months vs 5.5 months; HR 0.55; 95% CI 0.40–0.75; P=0.0001). The rates of grade 3 or higher adverse events were comparable for the study groups (74% and 75%). Finally, the FACT-Hep questionnaire suggested a quality-of-life benefit for patients in the SBRT arm compared with the

control arm, with 35% and 10% reporting an improvement by at least 5 points in the respective arms.

"SBRT is a standard treatment option for patients with locally advanced HCC, especially in patients with microvascular invasion," concluded Prof. Dawson. Dr Laura Williams Goff (Vanderbilt University Medical Center, TN, USA), discussant of this abstract, concluded: "SBRT plus sorafenib is particularly attractive for patients who cannot receive immunotherapy as post-transplant recurrence."

1. Dawson LA, et al. NRG/RTOG 1112: Randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). Abstract 489, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

SWOG 1815, first-ever phase 3 trial in BTC, fails

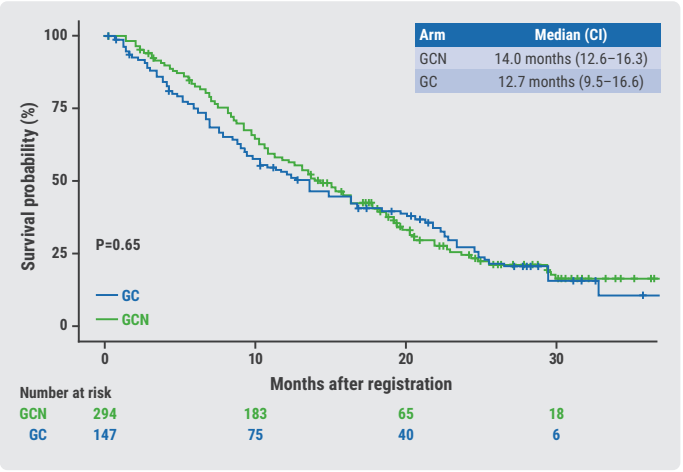
The triplet regimen of nab-paclitaxel plus gemcitabine plus cisplatin (GCN) did not improve the health outcomes in untreated patients with advanced biliary tract cancer (BTC), the first-ever phase 3 trial in this population demonstrated.

A phase 2 study displayed encouraging anti-tumour activity of GCN in patients with advanced BTC, with a reported median overall survival (OS) of 19.2 months [1]. Following these results, Prof. Rachna Shroff (University of Arizona Cancer Center, AZ, USA) and co-investigators designed the first phase 3 trial in patients with untreated, advanced cholangiocarcinoma or gallbladder cancer (n=441) [2]. Patients were randomised 2:1 to gemcitabine, 800 mg/m^2, plus cisplatin, 25 mg/m^2, and nab-paclitaxel, 100 mg/m^2, intravenous administration at days 1 and 8 of a 21-day cycle, or to standard-of-care gemcitabine plus cisplatin. The OS was the primary endpoint of the study.

Patients receiving the triplet regimen did not show a significantly improved OS compared with patients receiving the standard-of-care (median OS 14.0 months vs 12.7 months; P=0.65; see Figure). Progression-free survival data of the 2 study groups confirmed this result (8.2 months vs 6.4 months; P=0.43). Prof. Shroff added that grade 3 or 4 haematologic toxicities were more common in the GCN arm than in the control arm: anaemia (33% vs 22%); neutropaenia (37% vs 28%); thrombocytopenia (20% vs 15%); leukopenia (25% vs 10%). Discontinuation due to toxicity was 24% versus 19% (P=0.26) with GCN versus the standard-of-care.

The first randomised phase 3 trial in patients with these rare types of cancer did not deliver evidence that supports

Figure: No overall survival benefit for triplet regimen versus doublet regimen [2]



the addition of nab-paclitaxel to gemcitabine and cisplatin. The experimental arm showed higher haematologic toxicity with no improved OS. Currently, the standard arm should be gemcitabine/cisplatin plus immunotherapy.

1. Shroff RT, et al. JAMA Oncology. 2019;5(6):824–830.
2. Shroff RT, et al. SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. Late-breaking abstract 490, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

IMbrave 151 missed primary endpoint in advanced BTC

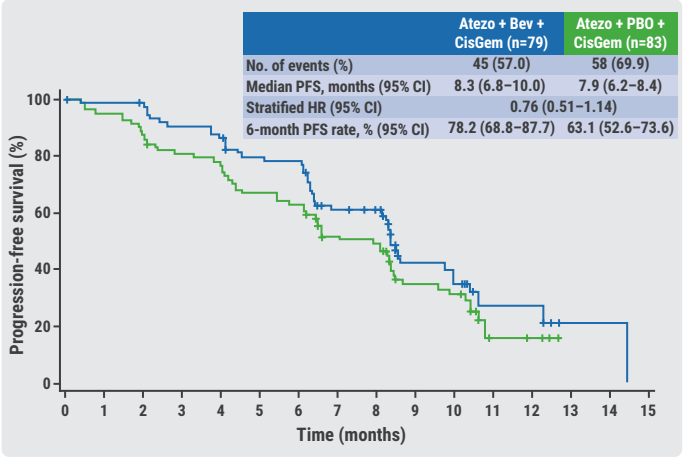
Adding bevacizumab to atezolizumab plus cisplatin and gemcitabine did not significantly improve the progression-free survival (PFS) of patients with newly diagnosed, advanced biliary tract cancer (BTC), the phase 2 IMbrave 151 trial showed.

"The combination of the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab is the main standard-of-care for patients with unresectable hepatocellular carcinoma (HCC) [1]," explained Prof. Anthony El-Khoueiry (USC Norris Comprehensive Cancer Center, CA, USA). The phase 2 IMbrave151 study (NCT04677504) evaluated atezolizumab and bevacizumab in combination with chemotherapy in newly diagnosed patients with advanced BTC (n=162) [2].

Patients who were randomised to the experimental arm received 8 cycles of gemcitabine plus cisplatin chemotherapy and bevacizumab and atezolizumab until disease progression, unacceptable toxicity, or until there was no longer a clinical benefit. In the placebo arm, bevacizumab was replaced with placebo. PFS was the primary endpoint.

PFS was not significantly improved in the bevacizumab arm compared with the control arm, although the investigators noticed a numerical benefit of the experimental arm over the control arm (median PFS 8.3 months vs 7.9 months; HR 0.76; 95% CI 0.51–1.14; see Figure). The overall survival (OS) data displayed a similar trend (median OS 'not reached' vs 11.4 months; HR 0.74; 95% CI 0.43–1.27). Prof. El-Khoueiry mentioned that bevacizumab did not add substantial toxicity to the safety profile of the treatment regimen. The rates of grade 3 or 4 adverse events (AEs) during the chemotherapy phase were similar for the 2 treatment arms, with 69.2% and 70.4%. After the chemotherapy phase, these rates dropped to 31.5% in the bevacizumab arm and to 24.5% in the control arm. Finally, it was highlighted that any grade hypertension was more common in the bevacizumab arm than in the placebo arm (34.6% vs 16.0%).

Figure: Progression-free survival of bevacizumab-containing regimen versus placebo [2]



Atezo, atezolizumab; Bev, bevacizumab; CisGem, cisplatin and gemcitabine; PBO, placebo.

Although the results of the IMbrave 151 study showed a modest improvement in PFS with the addition of bevacizumab to atezolizumab and chemotherapy in patients with newly diagnosed advanced BTC, this finding did not reach statistical significance. The 2 arms were experimental with a small sample size.

1. Finn RS, et al. NN Engl J Med. 2020;382:1894–1905.
2. El-Khoueiry AB, et al. IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. Abstract 491, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Acceptable safety profile and encouraging efficacy of nanvuranlat in BTC

Patients with pre-treated, advanced biliary tract cancer (BTC) may benefit from treatment with nanvuranlat, efficacy data from a phase 2 study indicated. According to the authors, the safety profile was clean. Further, larger studies are needed to establish the efficacy and safety of nanvuranlat in this population.

High expression of LAT1 in tumor specimens has been identified as a predictor of poor prognosis in patients with various cancer types, including BTC [1], explained Dr Junji Furuse (Kanagawa Cancer Center, Japan). Nanvuranlat, a selective LAT1 inhibitor, may therefore improve the situation of patients with BTC. A previous phase 1 trial showed encouraging efficacy data in 5 patients with BTC [2]. The current phase 2 study randomised 104 patients with advanced, refractory BTC with a NAT-2 non-rapid phenotype 2:1 to nanvuranlat, 25 mg/m^2, 5 days administration followed by 9 days wash-out, intravenous, or placebo [1]. Most patients had received at least 2 previous lines of therapy. The primary endpoint was the progression-free survival (PFS) by blinded independent central review.

Patients treated with nanvuranlat had a significantly improved PFS compared with patients treated with placebo (HR 0.557; 95% CI 0.34–0.90; P=0.016) and this result was consistent across pre-defined subgroups. Furthermore, the disease-control rate appeared to be higher in the experimental arm than in the control arm (24.6% vs 11.4%). In addition, all patients who achieved disease control showed stable disease, except for 1 patient in the nanvuranlat arm who had a partial response.

As for safety, grade 3 or higher adverse event rates were generally low in both arms, not surpassing the 3.0% for a specific event in either study group. However, it seemed that grade 3 or higher cholangitis occurred more frequently in the nanvuranlat arm than in the placebo arm (12.9% vs 0%).

In conclusion, data from the current phase 2 study support further investigation of nanvuranlat in patients with heavily pre-treated advanced BTC.

1. Kaira K, et al. BMC Cancer. 2013;13:482.
2. Okano N, et al. Invest New Drugs. 2020;38(5):1495–1506.
3. Furuse J, et al. Nanvuranlat, an L-type amino acid transporter (LAT1) inhibitor for patients with pretreated advanced refractory biliary tract cancer (BTC): Primary endpoint results of a randomized, double-blind, placebo-controlled phase 2 study. Abstract 494, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Pancreatic Cancer

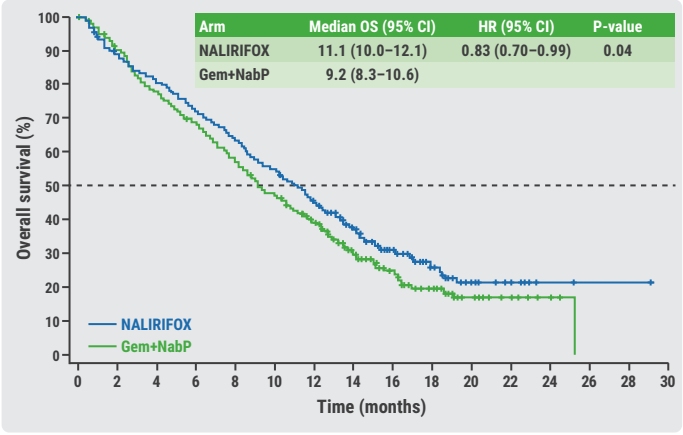
First-line NALIRIFOX superior to standard treatment in mPDAC

The phase 3 NAPOLI-3 trial showed that liposomal irinotecan plus 5-fluorouracil/leucovorin and oxaliplatin (NALIRIFOX) outperformed nab-paclitaxel plus gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma (mPDAC).

The phase 3 NAPOLI-3 trial (NCT04083235) compared nab-paclitaxel plus gemcitabine with NALIRIFOX for the first-line treatment of 770 patients with mPDAC [1]. Eligible patients were randomised 1:1 to evaluate the primary endpoint of overall survival (OS). Prof. Zev Wainberg (University of California Los Angeles, CA, USA) presented the late-breaking results.

After a median follow-up of 16.1 months, the OS was significantly improved in the NALIRIFOX arm compared with the control arm (median OS 11.1 months vs 9.2 months; HR 0.83; 95% CI 10.0–12.1; P=0.04; see Figure). Prof. Wainberg added that the OS curves started to separate from 3 months and remained separated through the further course of the study. Similarly, progression-free survival (PFS) was improved in patients receiving NALIRIFOX arm compared with those receiving nab-paclitaxel plus gemcitabine (median PFS 7.4 months vs 5.6 months; HR 0.69; 95% CI 0.58–0.83; P<0.0001). Additionally, all subgroups showed to have a benefit.

Figure: Overall survival of NALIRIFOX versus nab-paclitaxel plus gemcitabine [1]



NALIRIFOX, liposomal irinotecan plus 5-fluorouracil/leucovorin and oxaliplatin; Gem, gemcitabine; NabP, nab-paclitaxel.

Prof. Wainberg mentioned that NALIRIFOX had a manageable safety profile, consistent with the toxicity profiles of the individual treatment components. Comparable rates of grade 3 or higher adverse events (AEs) were reported for the 2 study groups (87.0% and 86.0%). However, grade 3 or 4 haematologic AEs were more common among patients receiving nab-paclitaxel plus gemcitabine, whereas those who were exposed to NALIRIFOX showed higher rates of grade 3 or 4 diarrhoea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), and vomiting (7.0% vs 2.1%).

Prof. Wainberg concluded that these results support the administration of NALIRIFOX as first-line therapy for patients with mPDAC. Of note, NALIRIFOX is a new standard-of-care for fit patient if liposomal irinotecan is available in the first line.

1. Wainberg ZA, et al. NAPOLI-3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Late-breaking abstract 661, ASCO GI 2023, 19–21 January, San Francisco, CA, USA.

Novel approach delivers quality-of-life benefits for patients with pancreatic cancer

Celiac plexus radiosurgery reduced pain and the use of opioids in patients with pancreatic cancer or other tumours that involved the celiac axis. Furthermore, the health-related quality-of-life (HR-QoL) of patients appeared to be improved following this therapy. These were the main results of an international phase 2 study investigating a novel therapy that aimed to target pancreatic pain.

"At Sheba Medical Center, we developed a novel technique to target pain from pancreatic cancer, involving the administration of a very high dose of radiation, not to the tumour but to the celiac plexus (25 Gy * 1)," explained Dr Yaacov Lawrence (Sheba Medical Center, Israel). A pilot trial delivered encouraging response rates for this approach [1], instigating the current, international, phase 2 study. Dr Lawrence and co-investigators included 149 patients with retroperitoneal pain from pancreatic cancer or any other cancer involving the celiac blood vessels [2]. A previous publication reported that the primary endpoint, change in

Brief Pain Inventory 'average pain', was met [3]. Dr Lawrence presented the HR-QoL results of the study.

The Functional Assessment of Cancer Therapy – General (FACT-G) was significantly improved from baseline to 3 and 6 weeks after therapy (mean score 57 vs 63 vs 67; P<0.05). A similar result was observed for the FACT-Hep questionnaire (mean score 96 vs 107 vs 113; P<0.05), the hepatobiliary cancer subscale (P<0.05), and the FACT-Hep trial outcome index (P<0.05). Data from FACT-G subscales demonstrated that improvements were made on the physical well-being subscale (P<0.05) and the emotional well-being subscale (P<0.05) but not on the social/family and functional well-being subscales.

These results warrant further investigation of this promising approach for the pancreatic cancer population, with a treatment showing improve HR-QoL.

1. Hammer L, et al. Int J Radiat Oncol Biol Phys. 2022;113(3):588–593.
2. Lawrence YR, et al. Celiac plexus radiosurgery for pain management in advanced cancer: An international phase II trial, health-related quality of life (HRQOL) outcomes. Abstract 662, ASCO-GI 2023, San Francisco, CA, USA, 19-21 January.
3. Lawrence YR, et al. Int J Radiat Oncol Biol Phys. 2022;114(5):1060–1061.