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HIGHLIGHTS CONFERENCE REPORT

This Highlights report contains the following:

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Oesophageal and Gastric Cancer

Adding docetaxel to standard-of-care does not improve outcomes in gastric cancer

Docetaxel added to capecitabine plus oxaliplatin (CAPOX) or to 5-FU plus oxaliplatin (mFOLFOX7) did not improve overall survival (OS) in patients with advanced gastric cancers, but it did increase toxicity. Therefore, CAPOX and mFOLFOX7 remain the standard-of-care chemotherapies in this population.

The open-label, prospective, phase 3 DOC-GC study randomised 324 participants with advanced HER2 negative gastro-oesophageal junction or gastric adenocarcinoma to one of the standard regimens (i.e. CAPOX or mFOLFOX7) up to a maximum of 6 months, or to either CAPOX or mFOLFOX7 plus docetaxel for a maximum duration of 4 months followed by docetaxel monotherapy. Dr Anant Ramaswamy (Tata Memorial Centre, India) presented the OS primary endpoint results [1].

After a median follow-up of 19.2 months, no difference in OS was observed between the 2 arms. The median OS was 8.9 months in the experimental arm and 10.1 months in the control arm (P=0.30). Likewise, the median progression-free survival data did not reveal clinical benefits of one regimen over the other with 6.24 months and 7.05 months in the docetaxel arm and standard-of-care arm, respectively (P=0.88).

However, grade 3 or 4 treatment-related adverse events were more common in the experimental arm (53% vs 33%; P<0.001). More specifically, neutropaenia (21% vs 3%), hand-foot-syndrome (9% vs 4%), and peripheral neuropathy (17% vs 7%) occurred significantly more frequently in participants who received docetaxel.

"mFOLFOX7 or CAPOX, for a duration of 6 months, should continue to remain the standard chemotherapy in patients with HER2 negative gastric and gastro-oesophageal junction adenocarcinomas," concluded Dr Ramaswamy.

1. Ramaswamy A, et al. A two-arm randomized open-label prospective superiority design phase III clinical trial to compare the efficacy of docetaxel-oxaliplatin capecitabine/5 fluorouracil followed by docetaxel versus CAPOX/mFOLFOX-7 in advanced gastric cancers (DOC-GC study). LBA 248, ASCO Gastrointestinal Cancers Symposium 2024, 18– 20 January, San Francisco, CA, USA.

Thoracoscopic oesophagectomy non-inferior to open surgery in thoracic oesophageal cancer

Thoracoscopic oesophagectomy (TO) was non-inferior to open oesophagectomy (OO) with respect to overall survival (OS) in patients with thoracic oesophageal cancer. Moreover, patients undergoing TO showed an improved relapse-free survival (RFS) and fewer respiratory complaints at 3 months post-surgery compared with patients receiving open surgery.

The multicentre, phase 3 JCOG1409 trial (UMIN000017628) randomised 300 participants with stage 1–3 thoracic oesophageal cancer 1:1 to TO or to OO to confirm the non-inferiority of TO to OO regarding OS. Prof. Hiroya Takeuchi (Hamamatsu University, Japan) presented the primary findings of the trial [1].

TO was non-inferior to OO in terms of OS, with 3-year OS rates of 82.0% and 70.9% (HR 0.64; 95% CI 0.34–1.21; P=0.00073). Furthermore, the 3-year RFS rates appeared to favour the TE arm over the OO arm (72.9% vs 61.9%; HR 0.68; 95% CI 0.46–1.01).

The rate of grade 4 post-operative complications was somewhat higher in the OO arm than in the TO arm (5.4% vs 1.3%). Re-operation was needed in 4.1% of the participants in the OO arm and 2.0% of those in the TO arm. "We noted that respiratory function at 3 months post-surgery, measured by vital capacity, forced vital capacity, and forced expiratory volume, was significantly better in patients who underwent TO compared with those who underwent OO," added Prof. Takeuchi. "TO was shown to be a standard treatment for patients with stage 1–3 thoracic oesophageal cancer," he concluded.

1. Takeuchi H, et al. A randomized controlled phase III trial comparing thoracoscopic esophagectomy and open esophagectomy for thoracic esophageal cancer, JCOG1409 (MONET trial). Abstract 249, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

KEYNOTE-590: 5-Year outcomes confirm benefit of pembrolizumab in oesophageal cancer

The 5-year data of the KEYNOTE-590 study demonstrate that the addition of pembrolizumab to chemotherapy continues to improve overall survival (OS) in patients with advanced oesophageal cancer. No new safety issues were documented, confirming that chemotherapy plus pembrolizumab is the standard-of-care first-line therapy for this population.

The phase 3 KEYNOTE-590 study (NCT03189719) randomised 749 participants with advanced oesophageal cancer 1:1 to pembrolizumab plus chemotherapy or to placebo plus chemotherapy. The primary results displayed a clear efficacy benefit for participants in the pembrolizumab group [1]. Now, Prof. Manish Shah (Weill Cornell Medicine, NY, USA) presented the 5-year outcomes of the trial [2].

"Pembrolizumab added to chemotherapy continued to display a benefit in OS compared with chemotherapy plus placebo, with 5-year OS rates of 10.6% and 3.0%," said Prof. Shah. The median OS was 12.3 months in the experimental arm and 9.8 months in the control arm (HR 0.72; 95% CI 0.62–0.84). This result was consistent in the subpopulations of participants with a combined positive score (CPS) ≥10 (n=383) and those

with squamous cell carcinomas (n=549). Furthermore, the median progression-free survival was 6.3 months in the pembrolizumab arm and 5.8 months in the placebo arm (HR 0.64; 95% CI 0.54–0.75). "We also noticed numerical benefits in patients on pembrolizumab with respect to dysphagia, pain, and reflux," mentioned Prof. Shah.

There were no substantial differences in the safety profiles of the 2 treatment regimens, according to Prof. Shah. However, immune-mediated adverse events and infusion reactions appeared to occur somewhat more frequently in the pembrolizumab arm (27.3% vs 15.7%).

Overall, the 5-year results of KEYNOTE-590 continue to support the use of pembrolizumab plus chemotherapy as first-line therapy in patients with advanced oesophageal cancer.

1. Sun JM, et al. Lancet. 2021;398(10302):759-771.
2. Shah MA, et al. First-line pembrolizumab plus chemotherapy for advanced esophageal cancer: 5-year outcomes from the phase 3 KEYNOTE-590 study. Abstract 250, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

New standard-of-care for locally advanced oesophageal squamous cell carcinoma?

Neoadjuvant camrelizumab plus chemotherapy increased pathologic complete response (pCR) rates compared with chemotherapy alone in patients with locally advanced oesophageal squamous cell carcinoma (LA-OSCC) in the phase 3 ESCORT-NEO trial. This regimen could become a new standard-of-care neoadjuvant treatment in patients with LA-OSCC.

The randomised, open-label, phase 3 ESCORT-NEO trial compared the efficacy and safety of neoadjuvant camrelizumab plus chemotherapy with chemotherapy alone in patients with resectable LA-OSCC. The participants (n=391) were randomised 1:1:1 to group A: camrelizumab plus albumin-bound paclitaxel and cisplatin; group B: camrelizumab plus paclitaxel and cisplatin; or group C: paclitaxel and cisplatin alone. The co-primary endpoints were event-free survival (EFS) and pCR. Prof. Yin Li (National Cancer Center, China) presented the results of the pCR analysis [1].

The pCR rates were 28.0%, 15.4%, and 4.7% in groups A, B, and C, respectively. Both group A (OR 8.11; 95% CI 3.28–20.06; P<0.0001) and group B (OR 3.81; 95% CI 1.48-9.80; P=0.0034) outperformed group C. "The study continues to mature for the co-primary endpoint of EFS," added Prof. Li. Treatment-related adverse events of grade ≥3 occurred in 34.1%, 29.2%, and 28.8% of the participants in the respective arms of the study. Grade ≥3 immune-related toxicities were documented in 4.5% and 3.8% of the participants in groups A and B.

"Camrelizumab plus chemotherapy regimens displayed acceptable safety profiles and were more efficacious than chemotherapy alone," Prof. Li summarised the findings. "Therefore, neoadjuvant camrelizumab plus chemotherapy may hold promise as a potential standard-of-care of the neoadjuvant treatment of patients with LA-OSCC."

1. Li Y, et al. ESCORT-NEO/NCCES01: phase III study of camrelizumab plus chemotherapy versus chemotherapy as neoadjuvant treatment of resectable locally advanced esophageal squamous cell carcinoma. LBA244, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

MATTERHORN: FLOT plus durvalumab leads to high pCR rate in gastric cancer

Peri-operative durvalumab plus a regimen of 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) resulted in a significantly higher pathological complete response (pCR) rate than FLOT alone among patients with resectable gastric and gastro-oesophageal junction cancer.

The global, double-blind, placebo-controlled, phase 3 MATTERHORN trial (NCT04592913) randomised 948 participants with resectable gastric and gastro-oesophageal junction cancer to peri-operative FLOT or FLOT plus durvalumab. The primary endpoint of the study was event-free survival (EFS). Dr Yelena Janjigian (Memorial Sloan Kettering Cancer Center, NY, USA) shared findings of the key secondary endpoint of pCR [1].

pCR was significantly improved in participants receiving durvalumab compared with those who did not receive this additional agent (19% vs 7%; OR 3.08; 95% CI 2.03–4.67; P<0.00001). Combined complete and near-complete pathologic response rates showed a similar benefit of the durvalumab group (27% vs 14%; OR 2.19; 95% CI 1.58–3.04; P<0.00001). "The results were consistent in microsatellite instability (MSI)-high and non-MSI-high participants as well as in the subgroup of Asian patients," added Dr Janjigian.

The MATTERHORN study showed that durvalumab, added to peri-operative FLOT, delivers a pCR benefit for patients with resectable gastric and gastro-oesophageal junction cancer. The study is ongoing for the primary endpoint of EFS.

1. Janjigian YY, et al. Pathological complete response to 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) with or without durvalumab in resectable gastric and gastroesophageal junction cancer: subgroup analysis by region from the phase 3, randomized, double-blind MATTERHORN study. LBA246, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

SKYSCRAPER-08: Adding tiragolumab to oesophageal cancer regimen improves outcomes

Chemotherapy plus tiragolumab and atezolizumab was superior to chemotherapy alone in patients with locally advanced unresectable or metastatic oesophageal squamous cell carcinoma (OSCC), according to the results of the phase 3 SKYSCRAPER-08 trial. This combination therapy may become an alternative first-line treatment option in this population.

"Tiragolumab is a human anti-TIGIT monoclonal antibody that may elevate anti-tumour activity of other immunotherapies, such as atezolizumab, in patients with OSCC," explained Prof. Chih-Hung Hsu (National Taiwan University Hospital, Taiwan) [1]. The phase 3, multicentre, double-blind SKYSCRAPER-08 study randomised 461 previously untreated participants with locally advanced unresectable or metastatic OSCC 1:1 to the combination of tiragolumab,

atezolizumab, and chemotherapy, or to chemotherapy alone. The primary endpoints were overall survival (OS) and progression-free survival (PFS). At ASCO-GI, Prof. Hsu shared the results of the final OS analysis.

The median OS was 15.7 months in the experimental arm and 11.1 months in the placebo arm, reflecting a significant OS benefit for participants on tiragolumab (stratified HR 0.70; 95% CI 0.55–0.88; P=0.0024). The PFS data revealed a benefit for participants on tiragolumab as well, with a median PFS of 6.2 months and 5.4 months in the respective arms of the study (stratified HR 0.56; 95% CI 0.45–0.70; P<0.0001).

The rate of adverse events (AEs) leading to treatment discontinuation was higher in the experimental arm than in the control arm (19.7% vs 10.6%) as was the rate of grade 3 or 4 AEs of special interest (12.7% vs 4.8%). Immune-mediated rash (3.1%), immune-mediated hepatitis (3.5%), infusion-related reactions (3.1%), and immune-mediated pneumonitis (1.8%) were the most common grade 3 or 4 AEs of special interest in the experimental arm.

"Combining tiragolumab, atezolizumab, and chemotherapy led to clinically meaningful improvements in OS, PFS, and other efficacy endpoints in patients with untreated OSCC," Prof. Hsu summarised the findings. "The safety profile was consistent with the known safety profiles of combined tiragolumab and atezolizumab, and individual chemotherapies."

1. Hsu C-H, et al. SKYSCRAPER-08: a phase III, randomized, double-blind, placebo-controlled study of first-line tiragolumab plus atezolizumab and chemotherapy in patients with esophageal squamous cell carcinoma. Abstract 245, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

CheckMate 648: More quality time for patients with oesophageal cancer on nivolumab

Participants with advanced oesophageal squamous cell carcinoma (OSCC) who were treated with nivolumab plus chemotherapy or with nivolumab plus ipilimumab had clinically meaningful prolonged overall survival times without symptoms or toxicity compared with participants who were treated with chemotherapy alone, revealed an analysis into the data of the CheckMate 648 trial.

Nivolumab plus chemotherapy and nivolumab plus ipilimumab have been approved as first-line therapies for patients with advanced OSCC based on the results of the phase 3 CheckMate 648 trial (n=970) [1]. At ASCO-GI, Prof. Ian Chau (Royal Marsden Hospital, UK) presented the results of a quality-adjusted time without symptoms and toxicity (Q-TWiST) analysis to compare the quality and quantity of survival of participants who received either one of the two nivolumab-containing regimens with patients who received chemotherapy alone [2].

Participants in the nivolumab plus chemotherapy arm spent the most time in survival without symptoms or toxicity (8.0 months). In the nivolumab plus ipilimumab arm and chemotherapy alone arm the corresponding durations were 6.6 months and 5.8 months, respectively. Participants in the nivolumab-containing arms also spent more survival time in toxicity or with symptoms.

Prof. Chau shared that the difference in Q-TWiST duration between the nivolumab plus chemotherapy arm and chemotherapy alone arm was 1.7 months, exceeding the threshold for clinical importance of 1.1 months. Similarly, the Q-TWiST difference between nivolumab plus ipilimumab and chemotherapy alone was 1.3 months, in favour of the first regimen.

"The Q-TWiST analysis favoured nivolumab plus chemotherapy and nivolumab plus ipilimumab over chemotherapy alone, further supporting these regimens as first-line treatment options for patients with advanced OSCC," concluded Prof. Chau.

1. Doki Y, et al. N Engl J Med 2022;386:449-462.
2. Chau I, et al. A quality-adjusted time without symptoms and toxicity analysis comparing nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy in patients with advanced esophageal squamous cell carcinoma: CheckMate 648. Abstract 251, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

CheckMate 649: Nivolumab plus chemotherapy continues to deliver efficacy benefit in gastric cancer

The 4-year follow-up data of CheckMate 649 continued to demonstrate an efficacy benefit of nivolumab plus chemotherapy over chemotherapy alone in newly diagnosed patients with advanced gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma. With no newly identified safety issues, the regimen of nivolumab plus chemotherapy is further supported as the first-line standard-of-care in this population.

The open-label, global, phase 3 CheckMate 649 study (NCT02872116) randomised 2,031 participants with previously untreated advanced gastric cancer, gastro-oesophageal junction cancer, or oesophageal adenocarcinoma to nivolumab plus chemotherapy, to chemotherapy alone, or to nivolumab plus ipilimumab. Nivolumab plus chemotherapy outperformed chemotherapy alone in terms of efficacy [1]. Dr Kohei Shitara (National Cancer Center Hospital East, Japan) presented the updated results after 4 years of follow-up [2].

The median overall survival was 13.7 months in the nivolumab arm and 11.6 months in the chemotherapy arm, resulting in a significant difference between the 2 groups (HR 0.79; 95% CI 0.71–0.88. This finding was consistent in the subgroup of participants with PD-L1 CPS ≥1 (HR 0.77; 95% 0.68–0.88) and appeared to be more pronounced among patients with PD-L1 CPS ≥5 (HR 0.71; 95% CI 0.62–0.82). Also, progression-free survival (PFS) was prolonged among participants receiving nivolumab and chemotherapy compared with those receiving chemotherapy alone, with median PFS durations of 7.7 months and 6.9 months (HR 0.80; 95% CI 0.71–0.89).

The efficacy benefit of nivolumab plus chemotherapy over chemotherapy alone was sustained across various endpoints, further supporting the use of nivolumab plus chemotherapy as standard first-line treatment in patients with advanced gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma.

1. Janjigian YY, et al. Lancet. 2021;398(10294):27-40.
2. Shitara K, et al. Nivolumab (NIVO) + chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 4 year (yr) follow-up of CheckMate 649. Abstract 306, ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA, 18-20 January 2024.

Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract

Promising efficacy data for next-gen FGFR inhibitor tinengotinib in CCA

The next-generation fibroblast growth factor receptor (FGFR) inhibitor tinengotinib delivered encouraging efficacy results in patients with advanced, metastatic cholangiocarcinoma (CCA) in a phase 2 study. The agent was well tolerated, and a phase 3 trial has been initiated to further investigate the potential of tinengotinib in the CCA population.

Dr Milind Javle (MD Anderson Cancer Center, TX, USA) presented the findings of an interim analysis of a phase 2 study (NCT04919642) investigating tinengotinib, a novel, multi-kinase inhibitor of FGFR [1]. The trial enrolled 55 patients with advanced, metastatic CCA, who were divided into 4 cohorts:

- A1: patients with *FGFR2* fusions who had progressed on prior FGFR inhibitor therapy (n=18);
- A2: patients with *FGFR2* fusions who had a response on prior treatment with FGFR inhibitor but acquired resistance, and thus subsequently discontinued due to progressive disease (n=11);
- B: patients with other, non-fusion *FGFR* alterations (n=13); and
- C: patients with *FGFR* wildtype (n=13).

All participants received 10 mg tinengotinib once daily, until disease progression, unacceptable toxicity, or another discontinuation criterion was met. The primary endpoint was overall response rate (ORR).

In the combined cohorts A1, A2, and B, the ORR was 26.3% and the disease control rate was 94.7%. In participants with acquired resistance to prior FGFR inhibitors the ORR appeared to be highest, at 40%. Next, in participants with other *FGFR* alterations, the ORR was 30.8%. "The median progression-free survival was 5.4 months in cohort A, 8.1 months in cohort B, and 3.8 months in cohort C," added Dr Javle.

The safety profile of tinengotinib was favourable, with no reported grade 4 or 5 treatment-emergent adverse events (TEAEs). Dose interruptions, dose reductions, and treatment discontinuations due to TEAEs occurred in 62%, 31%, and 13% of the participants, respectively. Hypertension (62%), stomatitis (40%), and diarrhoea (40%) were the most common TEAEs.

"Tinengotinib is a next-generation FGFR inhibitor with promising efficacy in patients with CCA and *FGFR* alterations who are refractory to current FGFR-targeted therapies," decided Dr Javle. "A phase 3 trial (FIRST-308; NCT05948475) has been launched to further evaluate this agent."

1. Javle M, et al. Efficacy and safety results of FGFR1-3 inhibitor, tinengotinib, as monotherapy in patients with advanced, metastatic cholangiocarcinoma: interim results from phase II clinical trial. Abstract 434, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

NETTER-2: Practice-changing results for ^{177}Lu-DOTATATE in GEP-NETs

A regimen of lutetium oxodotreotide (^{177}Lu-DOTATATE) and octreotide was superior to high-dose octreotide as first-line therapy in patients with high grade 2 and grade 3 gastroenteropancreatic neuroendocrine tumours (GEP-NETs). According to the authors, this is a practice-changing result.

The phase 3 NETTER-2 trial (NCT03972488) randomised 226 newly diagnosed patients with high grade 2 or grade 3 GEP-NETs 2:1 to ^{177}Lu-DOTATATE, 4 x 7.4 GBq, plus octreotide long-acting release (LAR), 30 mg every 8 weeks, or to high-dose octreotide LAR, 60 mg every 4 weeks. Progression-free survival (PFS) was the primary endpoint. Dr Simron Singh (University of Toronto, Canada) shared the first results [1].

First-line treatment with ^{177}Lu-DOTATATE plus octreotide resulted in a prolonged median PFS compared with treatment with high-dose octreotide (22.8 vs 8.5 months; stratified HR 0.28; 95% CI 0.18–0.42; P<0.0001). "There was a 72% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high-dose octreotide arm," added Dr Singh. Moreover, the overall response rate was 43.0% in the experimental arm and 9.3% in the control arm (stratified OR 7.81; 95% CI 3.32–18.40; P<0.0001). "This is an unprecedented response rate in patients with NETs," emphasised Dr Singh.

Nausea, diarrhoea, and abdominal pain were the most common any-grade side effects in both arms. The most common grade ≥3 adverse events in the experimental arm were decreased lymphocyte count (5.4% vs 0%), increased GGT (4.8% vs 2.7%), small intestinal obstruction (3.4% vs 0%), and abdominal pain (2.7% vs 4.1%).

Dr Singh concluded: "This data has clinically practice-changing implications and supports the use of ^{177}Lu-DOTATATE earlier within the disease course of high grade 2 and grade 3 GEP-NETs."

1. Singh S, et al. Efficacy and safety of [177Lu]Lu-DOTATATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: Primary analysis of the phase 3 randomized NETTER-2 study. LBA 588, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

EMERALD-1: TACE plus immunotherapy meets primary endpoint in unresectable HCC

Transarterial chemoembolisation (TACE) plus durvalumab and bevacizumab achieved a significantly improved progression-free survival (PFS) compared with TACE and placebo in patients with unresectable hepatocellular carcinoma (HCC) who were eligible for embolisation. This combination therapy has the potential to set a new standard-of-care for this population.

The phase 3 EMERALD-1 trial (NCT03778957) randomised 616 patients with unresectable HCC who were eligible for embolisation 1:1:1 to TACE plus placebo, TACE plus durvalumab, or TACE plus durvalumab and bevacizumab. The primary outcome was the PFS comparison between the placebo arm and the bevacizumab arm. Dr Riccardo Lencioni (University of Pisa, Italy) presented the findings [1].

The median PFS was significantly longer in the bevacizumab arm than in the placebo arm (15.0 vs 8.2 months; HR 0.77; 95% CI 0.61–0.98; log-rank P=0.032). The corresponding 18-month PFS rates were 43.1% and 28.3%. No significant difference regarding median PFS was observed between the durvalumab and placebo arms (10.0 vs 8.2 months; HR 0.94; 95% CI 0.75–1.19; log-rank P=0.64). According to Dr Lencioni, the safety profile of the experimental therapy was manageable and consistent with the known safety profiles of TACE, durvalumab, and bevacizumab in unresectable HCC.

"This is the first global, phase 3 trial to demonstrate a clinically meaningful improvement in PFS with an immunotherapy- and TACE-based regimen in patients with unresectable HCC who were eligible for embolisation," decided Dr Lencioni.

1. Lencioni R, et al. EMERALD-1: A phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. LBA 432, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Can adjuvant radiotherapy improve outcomes in resected HCC with narrow margin?

In a phase 2 study, post-operative radiotherapy improved recurrence-free survival (RFS) in patients with hepatocellular carcinoma (HCC) who had received curative resection with a narrow surgical margin (<1 cm). Combining adjuvant radiotherapy and systemic immunotherapy may lead to even more promising outcomes, argued the authors of the study.

Prof. Ming Kuang (Sun Yat-sen University, China) and colleagues designed the multicentre, randomised-controlled, phase 2 RAISE trial (NCT03732105) to evaluate the efficacy of post-operative radiotherapy in patients with HCC who had a narrow margin after resection [1]. The 148 participants were randomised 1:1 to intensity-modulated radiotherapy, 50 Gy in 25 fractions, or to the control arm (active monitoring). RFS was the primary endpoint.

The 24-month RFS rates were 78.7% and 58.4%, significantly favouring the radiotherapy arm over the control arm (HR 0.55; 95% CI 0.30–0.99; P=0.043). Prof. Kuang noted that the rate of marginal intra-hepatic recurrence was higher in the control arm than in the experimental arm (17.6% vs 6.8%).

"Various any-grade adverse events were more frequently seen among patients on radiotherapy, including neutropenia, ALT and AST elevations, hypoalbuminaemia, nausea, and diarrhoea," said Prof. Kuang. "However, there were no clear differences with respect to the occurrence of grade 3 or 4 adverse events between study arms."

In conclusion, the current phase 2 study revealed that post-operative radiotherapy may improve RFS in patients with HCC with narrow surgical margins after curative resection.

1. Kuang M, et al. Adjuvant radiotherapy after curative resection of hepatocellular carcinoma with narrow margin (<1 cm): a phase 2 multicenter, randomized controlled trial (RAISE). Abstract 722, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Encouraging preliminary data for glecirasib in pancreatic ductal adenocarcinoma

Glecirasib displayed promising anti-tumour activity in patients with KRAS G12C-mutated pancreatic ductal adenocarcinoma (PDAC) or other solid tumours previously treated with other therapies. Based on these preliminary data, a pivotal clinical study has been initiated to further assess glecirasib in patients with PDAC in China.

Dr Jian Li (Peking University Cancer Hospital and Institute, China) evaluated the efficacy and safety of the highly selective covalent KRAS inhibitor glecirasib in patients with PDAC and other solid tumours who were enrolled in either JAB-21822-1001 (NCT05002270) or JAB-21822-1002 (NCT05009329). These phase 1/2 trials enrolled Chinese, American, European, and Israeli participants with locally advanced or metastatic solid tumours who had progressed on a first-line therapy. The current analysis looked at 52 participants with PDAC (n=31) or other solid tumours (n=21) which were not colorectal cancer or non-small cell lung cancer [1].

The overall response rate was 56.0%, with all of these responses being partial responses. An additional 34.0% of the participants had stable disease. The response rate was consistent across tumour types, albeit the 3 included participants with small bowel cancer had a response rate of 100%. Furthermore, in participants with PDAC, the median progression-free survival (PFS) was 5.6 months and the median overall survival (OS) was 10.7 months. In participants with

other solid tumours, the corresponding median PFS and median OS were 7.0 months and 'not reached', respectively.

Grade ≥3 adverse events were reported in 25.0% of the participants, most commonly being anaemia (5.8%) or hypertriglyceridaemia (3.8%). Other common any-grade side effects were increased blood bilirubin (50.0%), increased conjugated bilirubin (36.5%), and asthenia (23.1%). No treatment-emergent adverse events led to drug discontinuation or death.

"The impressive clinical activity of glecirasib in patients with PDAC and other solid tumours, together with a favourable safety profile, warrant further development of this agent," concluded Dr Li.

1. Li J, et al. Preliminary activity and safety results of KRAS G12C inhibitor glecirasib (JAB-21822) in patients with pancreatic cancer and other solid tumors. Abstract 604, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

ALPACA: Promising results for dose de-escalated regimen of gemcitabine/nab-paclitaxel in metastatic PDAC

The results of the phase 2 ALPACA trial showed that alternating gemcitabine monotherapy with gemcitabine/nab-paclitaxel yields similar efficacy but with improved tolerability, compared with continuous gemcitabine/nab-paclitaxel, in patients with metastatic pancreatic ductal adenocarcinoma (PDAC).

Prof. Frank Kullmann (Hospital Weiden, Germany) and colleagues randomised 325 participants with metastatic PDAC 1:1 to continuous therapy with gemcitabine/nab-paclitaxel or to alternating cycles of gemcitabine/nab-paclitaxel and single agent gemcitabine [1]. The primary endpoint of ALPACA (NCT02564146) was overall survival (OS).

The median OS was 10.4 months in the continuous application arm and 10.5 months in the alternating application arm (HR 0.90; 95% CI 0.72–1.13; P=0.56). Similarly, no difference was seen in median progression-free survival between the 2 arms of the study (5.4 vs 5.5 months; P=0.18). However, there was a difference in tolerability: Grade ≥3 peripheral neuropathy (21.3% vs 14.1%) and grade ≥3 infections (20.0% vs 10.6%) occurred more frequently in the continuous application arm than in the alternating application arm.

"After 3 cycles of induction therapy with gemcitabine/nab-paclitaxel, treatment with alternating cycles of gemcitabine/nab-paclitaxel and single agent gemcitabine was associated with comparable survival times as therapy with continuous application of gemcitabine/nab-paclitaxel but with a clinically meaningful improvement in tolerability," concluded Prof. Kullman.

1. Dorman K, et al. Alternating gemcitabine/nab-paclitaxel and gemcitabine versus continuous gemcitabine/nab-paclitaxel after induction treatment of metastatic pancreatic cancer: the randomized ALPACA trial (AIO-PAK-0114). Abstract 605, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Cancers of the Colon, Rectum, and Anus

CheckMate 8HW: Excellent results for nivolumab plus ipilimumab in MSI-H/dMMR mCRC

First-line nivolumab plus ipilimumab outperformed standard-of-care chemotherapy in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer (MSI-H/dMMR mCRC). With consistent results across subgroups and a manageable safety profile, nivolumab plus ipilimumab presents a potential novel standard-of-care first-line therapy for this population.

The phase 3 CheckMate 8HW study (NCT04008030) randomised participants with MSI-H/dMMR mCRC 2:2:1 to nivolumab alone, nivolumab plus ipilimumab, or to investigator's choice chemotherapy to compare these treatment regimens in the first line. The dual primary endpoints were progression-free survival (PFS) of nivolumab plus ipilimumab versus nivolumab monotherapy and PFS of nivolumab plus ipilimumab versus chemotherapy. Prof. Thierry André (Sorbonne University, France) shared the primary results of the comparison between participants who received the combination therapy (n=202) and those who received chemotherapy (n=101) [1].

After a median follow-up of 24.3 months, nivolumab plus ipilimumab was superior to chemotherapy with regard to median PFS (not reached vs 5.9 months; HR 0.21; 95% CI 0.13–0.35; P<0.0001). The 24-month PFS rates were 72% and 14%, respectively.

Grade 3 or 4 treatment-emergent adverse events (TEAEs) were less common in the experimental arm (23% vs 48%). "The safety profile of nivolumab plus ipilimumab was different from that of chemotherapy but consistent with the established profiles of the individual agents," added Prof. André.

In conclusion, the findings of the CheckMate 8HW trial support nivolumab plus ipilimumab as first-line standard-of-care for patients with MSI-H/dMMR mCRC.

1. André T, et al. Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for micro satellite instability-high/mismatch repair-deficient metastatic colorectal cancer: first results of the CheckMate 8HW study. LBA 768, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Can ctDNA-directed therapy improve outcomes in low-risk colon cancer?

In a low-risk population of patients with stage II colon cancer, treating ctDNA-positive patients with adjuvant chemotherapy for 6 months did not lead to an improvement in ctDNA clearance, results of a phase 2 study showed.

In the phase 2 NRG-GI005/COBRA study (NCT04068103), 635 patients with resected stage IIA colon cancer were randomised 1:1 to standard-of-care active surveillance (arm 1) or to assay-directed therapy (arm 2). In the latter arm, participants with detected ctDNA were treated with mFOLFOX6 or CAPOX chemotherapy for 6 months. Dr Van Morris (MD Anderson Cancer Center, TX, USA) presented the findings [1].

In total, ctDNA positivity was detected in 33 patients. The current analysis included 16 of them: 7 had been randomised to arm 1 and 9 had been randomised to arm 2. The ctDNA clearance rate was 43% in arm 1 and 11% in arm 2 (one-sided P=0.98). "Since the one-sided P-value exceeded 0.35, the null hypothesis could not be rejected and we had to stop the trial due to futility," said Dr Morris.

Despite the neutral trial results, Dr Morris pleaded for more ctDNA trials: "Prospective trials assessing ctDNA as a surrogate for minimal residual disease are feasible and necessary in order to confirm clinically relevant hypotheses in oncology," he reasoned. "Future clinical trial design should account for the evolution of ctDNA methodologies and assay performance, in order to answer relevant questions in the field."

1. Morris VK, et al. Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study. Abstract 6, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Clinical biomarkers may guide therapy selection in RAS wildtype mCRC

Combining certain clinical biomarkers may improve patient selection for targeted first-line therapy in patients with RAS wildtype metastatic colorectal cancer (mCRC), a substudy of the phase 3 FIRE-3 trial showed. Primary tumour side and liver-limited disease status were identified as relevant for this purpose.

Dr Julian Holch (Ludwig-Maximilians-University of Munich, Germany) and co-investigators performed a study that evaluated the predictive value of various clinical biomarkers on overall survival (OS) in the 2 treatment arms of the phase 3 FIRE-3/AIO KRK0306 trial (NCT00433927). In this study, patients with RAS wildtype mCRC were allocated to FOLFIRI plus cetuximab or to FOLFIRI plus bevacizumab. The primary analysis demonstrated that participants receiving cetuximab outperformed those receiving bevacizumab with regard to OS [1].

The combination of primary tumour side and liver-limited disease (LLD) status had the highest predictive value of therapy selection on OS [2]. In patients with left-sided tumours and no LLD (n=201), FOLFIRI plus cetuximab was the most effective therapy option (HR 0.62; P=0.02). In contrast, there was no significant difference between the effect of the 2 therapies on OS in the population of participants with left-sided tumours and LLD (n=106; HR 0.83; P=0.40). In patients with right-sided tumours and no LLD (n=61), FOLFIRI plus bevacizumab was the favoured therapy (HR 2.09; P=0.01), whereas FOLFIRI plus cetuximab had a numerical, but non-significant advantage over FOLFIRI plus bevacizumab in patients with right-sided tumours and LLD (n=27; HR 0.59; P=0.22).

"These findings indicate that interactions and combinations of biomarkers should be considered to increase their predictive accuracy regarding the treatment of mCRC," argued Dr Holch.

1. Heinemann V, et al. Br J Cancer. 2021;124(3):587-594.
2. Holch JW, et al. Refining first-line treatment decision in RAS wildtype (RAS-WT) metastatic colorectal cancer (mCRC) by combining clinical biomarkers: results of the randomized phase 3 trial FIRE-3 (AIO KRK0306). Abstract 13, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January, San Francisco, CA, USA.

Laparoscopic or open surgery in low rectal cancer?

Laparoscopic-assisted rectal resection was non-inferior to open surgery regarding disease-free survival (DFS) in patients with low rectal cancer, results of the randomised-controlled LASRE trial showed. Other outcomes, such as sphincter preservation and duration of hospital stay, favoured the laparoscopic-assisted surgery arm.

The multicentre, non-inferiority, randomised-controlled LASRE trial (NCT01899547) compared laparoscopic-assisted rectal resection with conventional open surgery in 1,070 patients with low rectal cancer who did not have evidence of pelvic lateral lymph nodes or distant metastasis. Randomisation occurred in a 2:1 fashion, with the majority of participants being randomised to the laparoscopic-assisted surgery arm. The primary endpoint was 3-year DFS. Prof. Pan Chi (Fujian Medical University, China) presented the findings [1].

There was no difference between the 2 study arms regarding 3-year DFS (81% vs 79%; HR 0.92; 95% CI 0.69–1.23; log-rank P=0.56). This result was consistent across clinical stage I and clinical stage II/III subgroups of patients. Similarly, there was no difference in 3-year overall survival between the study arms (HR 1.34; 95% CI 0.82–2.19; log-rank P=0.24). "However, laparoscopic-assisted surgery was favoured over open surgery regarding sphincter preservation (71.7% vs 65.0%; P=0.03) and duration of hospitalisation (median 8.0 days vs 9.0 days; P=0.008)," noted Prof. Chi.

In conclusion, the results of the LASRE trial support the use of laparoscopic-assisted surgery in patients with low rectal cancer.

1. Chi P, et al. Effect of laparoscopic-assisted vs open surgery on 3-year disease-free survival in low rectal cancer: the LASRE randomized clinical trial. Abstract 8, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January 2024, San Francisco, CA, USA.

Investigational agent DKN-01 promising for advanced MSS CRC

Encouraging anti-tumour activity was reported for a combination of chemotherapy, bevacizumab, and the investigational agent DKN-01 in the second-line treatment for patients with advanced microsatellite-stable (MSS) colorectal cancer (CRC). In the current study, the largest benefit was observed for patients with rectal/ rectosigmoid junction cancer.

DKN-01 is an investigational IgG4 monoclonal antibody targeting DKK1, which is a regulator of the Wnt signalling pathway; a pathway that drives CRC [1]. The current part A of the phase 2 DeFianCe study (NCT05480306) tested a regimen of standard-of-care chemotherapy (FOLFIRI/FOLFOX) plus bevacizumab and DKN-01 as second-line treatment for 33 patients with advanced MSS CRC [2].

The best overall response rate (ORR) was 30%, partial responses only, and the disease control rate (DCR) was 93%. In patients with left-sided tumours (n=25) the ORR was 33% and the DCR was 100%. Furthermore, in patients with rectal or rectosigmoid tumours (n=15) the ORR was 46% and the DCR was 100%. The corresponding median progression-free survival in the overall population, left-sided tumour subgroup, and the rectal or rectosigmoid tumour subgroup was 6.3 months, 8.6 months, and 9.4 months, respectively.

Serious adverse events were documented in 21.2% of the participants, but only 1 of these events was deemed related to the investigational agent. Diarrhoea, fatigue, and neutropenia were the most common side-effects.

Dr Meredith Pelster (Sarah Cannon Research Institute, TN, USA) and co-researchers concluded that the second-line treatment regimen of standard-of-care chemotherapy plus bevacizumab and DKN-01 was well tolerated and displayed encouraging anti-tumour activity in a heterogeneous population of patients with advanced MSS CRC. Part B of the DeFianCe trial is currently enrolling.

1. Giannakis M, et al. Nat Genet. 2014;46(12):1264-1266
2. Pelster M, et al. DKN-01 plus bevacizumab and chemotherapy as second-line (2L) investigational therapy in advanced micro satellite (MSS) colorectal adenocarcinomas (CRC): DeFianCe trial. Poster 104, ASCO Gastrointestinal Cancers Symposium 2024, 18–20 January 2024, San Francisco, CA, USA.