Medicom International Conference Series in Oncology

ESMO GI Congress 2024

European Society of Medical Oncology - Gastrointestinal Cancers

26–29 JUNE • MUNICH • GERMANY

PEER-REVIEWED

CONFERENCE REPORT

TAP and CPS both viable for PD-L1 expression measurement

In the trials RATIONALE-305 and RATIONALE-306, no significant differences were observed between PD-L1 subgroups defined by either tumour area positivity (TAP) score or combined positive score (CPS).

read more on PAGE 5

^{177}Lu-DOTATATE extends PFS in patients with GEP-NETs

A subgroup analysis of NETTER-2 showed a progression-free survival (PFS) benefit with ^{177}Lu-DOTATATE in treatment-naïve patients with GEP-NETs, regardless of the tumour grade or origin.

read more on PAGE 6

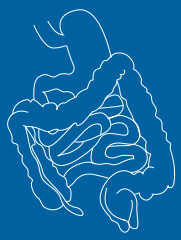
Post-operative MRD status more prognostic than TNM stage

In patients with colon adenocarcinoma, post-operative ctDNA-based molecular residual disease (MRD) status outperformed the prognostic value of TNM staging, a retrospective analysis demonstrated.

read more on PAGE 8

MEDICOM MEDICAL PUBLISHERS

Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrish, Luxembourg



COLOPHON

Editor	Dr Stefan Rauh Centre Hospitalier Emile Mayrish, Luxembourg
Reviewer	Dr Joëlle Collignon CHU Liège, Belgium
Publishing Director	Paul Willers
Editorial Operations Manager	Dr Rosalie Molenaar
Medical Science Officer	Dr Rachel Giles
Editorial Coordinators	Dr Joery Goossens Rune Bruls Sanne Lauriks
Medical Writers	Dr Rachel Giles Marten Dooper
Production Manager	Anouk Neijenhoff
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink
Printing	GVO drukkers & vormgevers B.V.
Cover Photo	Shutterstock
ISSN	2468-8762 24:12

MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
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 colleagues,

You are very welcome to our congress report of ESMO's Gastrointestinal Cancer Congress from Barcelona. Wait. No! It's Munich, this year! Some may feel sorrow trading vino tinto for beer and tapas for weisswurst – scientifically speaking, this was, however, a congress with remarkable news. Here is some of it:

You will see that ARMANI not only stands for highly elegant (albeit unaffordable) suits–but also for a rather intriguing study, exploring early systematic switch of chemotherapy in advanced gastric or gastroesophageal junction (G/GEJ) cancer: how much grade 3 toxicity would you consider a trade-off for 2 months survival? Or take the risk that your patient will never make it to second line?

An anti-claudin 18.2 conjugate may soon integrate the standard-of-care of advanced G/GEJ cancer, an even more important fact, since overexpression is frequent.

KEYNOTE-585 is an eagerly awaited study. At a first glance, adding a checkpoint inhibitor doesn't seem to bring a significant survival benefit as compared with standard FLOT in early G/GEJ cancers. Have a closer look, though, as some do seem to benefit, and not only MSI-high ones.

Wasn't Lu-DOTATATE reserved for low-grade GEP-NET's only? Maybe no longer so. Check out NETTER-2.

Maybe there's finally a monoclonal antibody with activity in ductal pancreatic cancer…

…and post-operative MRD status, detecting circulating tumour DNA is THE prognostic marker in early colorectal cancer.

As always, I just made some picks.
Enjoy your read.

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.

Gastric and Oesophageal Cancer

OS benefit in ARMANI, but is it worth it?

Modest improvements in progression-free survival (PFS) and overall survival (OS) were reported for patients with HER2-negative advanced gastric or gastroesophageal junction (G/GEJ) cancer and low/absent PD-L1 expression who switched their consolidation maintenance or early second-line therapy from CAPOX/FOLFOX to ramucirumab plus paclitaxel. However, toxicities were higher, and if patients would progress they would enter third-line therapy.

The past year has seen 5 new approvals for G/GEJ cancer treatments, all biomarker-driven, leaving patients without these markers in need of alternative strategies. About 40% of patients with locally advanced or metastatic G/GEJ cancer never reach second-line therapy, making the initial treatment phase critical. Dr Giovanni Randon (Fondazione IRCCS Istituto Nazionale dei Tumori, Italy) presented a potential strategy for patients with HER2-negative advanced G/GEJ cancer from the randomised, open-label, multicentre phase 3 ARMANI trial (NCT02934464) [1].

ARMANI randomised 280 patients who showed no disease progression after 3 months of initial oxaliplatin-based chemotherapy to receive either ramucirumab plus paclitaxel (8 mg/kg on days 1 and 15) plus paclitaxel (80 mg/m^2 on days 1, 8, 15, and every 28 days thereafter) (Arm A) or to continue with CAPOX/FOLFOX for another 3 months, followed by fluoropyrimidine monotherapy maintenance (Arm B). The primary endpoint was PFS difference between the 2 arms [2].

The median PFS was 6.6 months in Arm A compared with 3.5 months in Arm B (HR 0.63; 95% CI 0.49–0.81; P<0.001). Median OS was 12.6 months in Arm A versus 10.4 months in Arm B (HR 0.75; 95% CI 0.58–0.97; P=0.030). However, grade 3 or higher neuropathy and other toxicities were more common in Arm A.

An exploratory biomarker analysis showed no significant interaction between CLDN18 status, PD-L1 combined positive score (CPS) <5, and treatment outcomes. Positive CLDN18 expression was found in 35% of the participants, and 40% had PD-L1 CPS ≥5. In the subgroup with CLDN18-negative status and PD-L1 CPS <5 (34% of the participants), the median PFS was 7.5 versus 4.2 months in Arm A and B, respectively (HR 0.69; 95% CI 0.41–1.18; P=0.179).

These findings suggest that switching to ramucirumab and paclitaxel maintenance may prolong survival across various clinical and molecular subgroups. However, the increased toxicities, patients' quality-of-life, and the implication of already having used 2 lines of therapy if patients progress must be considered when deciding on this treatment approach.

1. Randon G, et al. Switch maintenance with ramucirumab plus paclitaxel versus continuation of oxaliplatin-based chemotherapy in advanced HER2-negative gastric or gastroesophageal junction (GEJ) cancer: Final results and key biomarkers of the ARMANI phase 3 trial. Abstract LBA4, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Di Bartolomeo M, et al. BMC Cancer. 2019;19(1):283.

SPOTLIGHT on new targets in immunotherapy: claudin 18.2

Chemotherapy in combination with zolbetuximab could be a potential first-line therapy for gastric or gastroesophageal junction (G/GEJ) adenocarcinomas. Along similar lines, antibody-drug conjugates targeting claudin 18.2 are being investigated, and while CAR-T cells have shown activity in a phase 1 study, there may be substantial obstacles for practical implementation in the clinic.

In an in-depth overview of new targets in immunotherapy beyond checkpoint inhibitors, Prof. Kohei Shitara (National Cancer Center Hospital East, Japan) focused on new data from clinical trials looking at tight-junction protein claudin 18.2 as a target in G/GEJ cancers [1]. The rationale is that most G/GEJ tumours overexpress claudin 18.2, and as a consequence of disrupted polarity in neoplastic growth, the tight junctions including claudin 18.2 are exposed to the lumen/cell surface. Zolbetuximab recognises an epitope on the first extracellular loop of claudin 18.2, which in healthy tissue would be inaccessible.

Notably, the randomised, double-blind, phase 3 GLOW trial (NCT03653507) showed that zolbetuximab combined with capecitabine and oxaliplatin improved outcomes compared with placebo and chemotherapy as first-line treatment in claudin 18.2-positive, HER2-negative G/GEJ

adenocarcinomas [2]. Updated data from the phase 3 SPOTLIGHT trial (NCT03504397) continued to demonstrate significant improvement in overall survival at 36 months of follow-up with the addition of zolbetuximab to the mFOLFOX6 regimen versus placebo (21% vs 9%; HR 0.75; 95% CI 0.60–0.94; P=0.0053) as well as median progression-free survival (PFS 10.61 months in the zolbetuximab group vs 8.67 months in the placebo group) for patients with claudin-positive, HER2-negative locally advanced unresectable or metastatic G/GEJ adenocarcinoma [3].

Prof. Shitara shared key practice considerations for this new potential standard-of-care first-line treatment for these patients, including toxicity concerns, since zolbetuximab is already approved in Japan [1]. He also shared data from a phase 1 trial (n=59) developing a claudin 18.2-targeted CAR T-cell therapy, which offered an objective response rate of 55% and a median PFS of 5.9 months in gastric cancer patients [4]. However, toxicity and production concerns are considerable barriers to clinical implementation, he concluded.

1. Shitara K. Cellular therapies in the treatment of GI cancer. Session: New targets in immunotherapy beyond CTL4 and PD(L)1, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Shah MA, et al. Nat Med. 2023;29(8):2133-2141.
3. Shitara K, et al. Lancet. 2023;401(10389):1655-1668.
4. Nakayama I, et al. Nat Rev Clin Oncol. 2024;21(5):354-369.

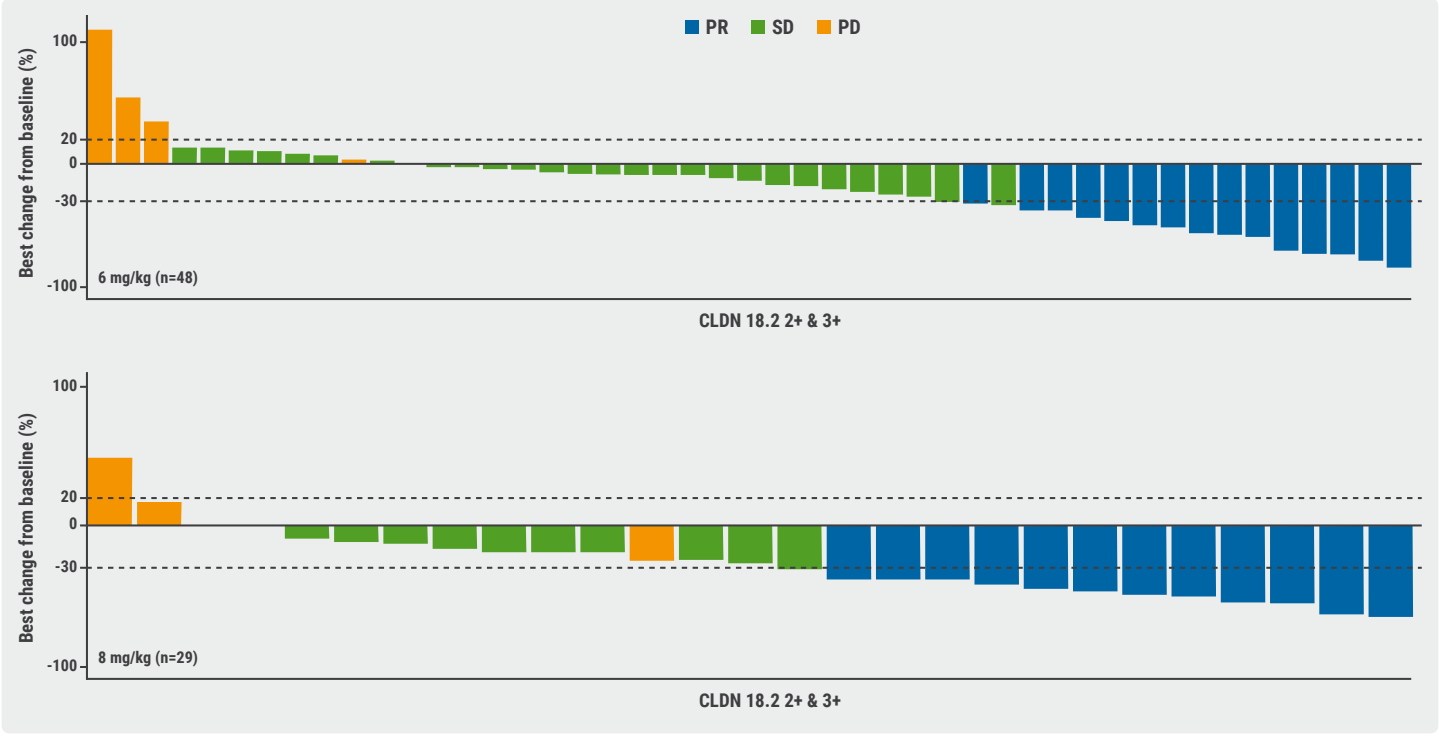
Encouraging efficacy of anti-claudin 18.2 ADC in G/GEJ cancer

In a phase 1 trial, IBI343, a monoclonal antibody-drug conjugate (ADC) targeting claudin 18.2, was well-tolerated and demonstrated encouraging efficacy in heavily pretreated patients with advanced unresectable or metastatic gastric or gastro-oesophageal junction (G/GEJ) cancer.

Claudin 18.2 is a tight-junction molecule predominantly found in the non-malignant gastric epithelium that becomes accessible on the tumour cell surface during malignant transformation, providing an appealing target for cancer therapy [1]. IBI343 is an ADC targeting claudin 18.2-expressing tumour cells. After claudin 18.2-dependent internalisation, the payload (exatecan, a topoisomerase inhibitor) induces apoptosis of the tumour cells. The released drug can also diffuse across the plasma membrane to reach and kill the neighbouring cells, resulting in a "bystander killing effect".

A phase 1 trial (NCT05458219) evaluated the safety and efficacy of IBI343 in 159 patients with heavily pretreated advanced G/GEJ cancer with confirmed claudin 18.2 expression. Dr Jia Liu (St Vincent's Hospital Sydney, Australia) presented the results [2].

Figure: Efficacy with IBI343 in G/GEJ cancer patients with moderate-to-high claudin 18.2 expression [2]



PD, progressive disease; PR, partial response; SD, stable disease.

Safety findings showed that grade ≥3 treatment-related adverse events (AEs) occurred in 37.7% of the participants treated with 6 or 8 mg/kg IBI343. Gastrointestinal AEs of grade ≥3 occurred at low rates: vomiting 1.9%; nausea 1.3%; decreased appetite 1.3%. Hypoalbuminemia occurred in 24.5% of the participants and was of grade 1–2; no cases of interstitial lung disease (ILD) were reported.

In participants with moderate-to-high (≥40%) claudin 18.2 expression, the overall response rate was 31.2% and 41.4% in the 6 and 8 mg/kg IBI343 groups, respectively, with an associated disease control rate of 89.6% and 82.8% (see Figure). No response was observed in participants with low (<40%) claudin 18.2 expression.

Based on these results, Dr Liu concluded that "IBI343 is well-tolerated and has an encouraging efficacy in patients with G/GEJ cancer with moderate or high claudin 18.2 expression." A registrational phase 3 clinical trial (NCT06238843) is being initiated.

1. Nakayama I, et al. Nat Rev Clin Oncol. 2024;21:354-369.
2. Liu JJ, et al. Anti-claudin 18.2 (CLDN18.2) antibody-drug conjugate (ADC) IBI343 in patients (pts) with solid tumors and gastric/gastro-esophageal junction adenocarcinoma (G/GEJ AC): A phase 1 study. Abstract 396MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

KEYNOTE-585: negative trial, but long-term benefit in PD-L1-high/MSI subgroups?

Data from the KEYNOTE-585 trial demonstrated a clear increase in pathological complete responses (pCRs) with peri-operative pembrolizumab plus FLOT versus FLOT alone, but only modest improvements in overall survival (OS).

Dr Kohei Shitara (National Cancer Center Hospital East, Japan) presented the third scheduled interim analysis of the phase 3 KEYNOTE-585 trial (NCT03221426), which assessed the efficacy of peri-operative pembrolizumab combined with chemotherapy versus placebo with chemotherapy in patients with untreated, locally advanced, resectable gastric or gastro-oesophageal junction (G/GEJ) cancer [1]. The initial results did not show a significant improvement in event-free survival (EFS), though the pCR rate did improve [2].

Participants (n=804) were randomised 1:1 to receive neoadjuvant pembrolizumab (200 mg IV every 3 weeks) or a placebo, combined with chemotherapy (cisplatin plus capecitabine or cisplatin plus 5-FU) for 3 cycles [1]. Post-surgery, participants received adjuvant pembrolizumab or placebo plus chemotherapy every 3 weeks for 3 cycles, followed by adjuvant pembrolizumab or placebo every 3 weeks for 11 cycles. In a separate FLOT cohort, participants were randomised to receive either pembrolizumab or placebo with docetaxel, oxaliplatin, leucovorin, and 5-FU every 2 weeks. The primary endpoints were pCR, EFS, OS, and safety in the FLOT cohort.

With a median follow-up of 59.9 months, the pCR rate was 13.4% with pembrolizumab plus chemotherapy versus 2.0% with placebo plus chemotherapy, showing a difference of 11.4%. The median EFS was 44.4 months with pembrolizumab plus chemotherapy versus 25.5 months with placebo plus chemotherapy (HR 0.81; 95% CI 0.67–0.99); median OS was 71.8 versus 55.7 months, respectively (HR 0.86; 95% CI 0.71–1.06). Grade ≥3 drug-related adverse event rates were 65% in the pembrolizumab group versus 63% in the placebo group.

The efficacy and safety outcomes were thus consistent with previous analyses, although the pCR in the control arm is low compared with that in the original FLOT4 trial [3]. Improvement in EFS was not statistically significant, raising questions about the overall benefit of adding pembrolizumab to the treatment regimen [1]. The discussant, Dr Lizzy Smyth (Oxford University Hospitals NHS Foundation Trust, UK) pointed out that immunologically "hot" tumours, namely those that have high microsatellite instability or have PD-L1 expression >10%, showed the greatest pCR improvement (38% increase; see Figure) as well as marked improvements in EFS and OS (both with HR 0.60). This subgroup of patients would likely benefit in the short- and long-term from peri-operative pembrolizumab.

Figure: Efficacy outcomes of KEYNOTE-585 in key biomarker groups [1]

PD-L1 CPS <1	PD-L1 CPS ≥1	PD-L1 CPS ≥10	MSI-H
ΔpCR 4.2%	ΔpCR 12.1%	ΔpCR unknown	ΔpCR 38.1%
EFS HR 0.87	EFS HR 0.77	EFS HR 0.68	EFS HR 0.60
OS HR 0.90	OS HR 0.84	OS HR 0.70	OS HR 0.60
No improved EFS or OS in immunologically cold tumours	**Short-term benefit** (improved pCR and EFS) in modestly immunosensitive tumours	**Short- and long-term benefit** (improved pCR, EFS, and OS) in immunologically hot tumours	

CPS, combined positive score; EFS, event-free survival; MSI-H, microsatellite instability-high; OS, overall survival; pCR, pathological complete response.

1. Shitara K, et al. Final analysis of the phase 3 KEYNOTE-585 study of pembrolizumab plus chemotherapy vs chemotherapy as perioperative therapy in locally-advanced gastric and gastroesophageal junction cancer. Abstract LBA3, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Shitara K, et al. Lancet Oncol. 2024;25(2):212-224.
3. Al-Batran SE, et al. Lancet. 2019 May 11;393(10184):1948-1957.

New analyses validate TAP and CPS scores for PD-L1 expression

Exploratory post-hoc analyses of the RATIONALE-305 and the RATIONALE-306 studies showed no significant difference in the results of PD-L1 subgroups when they were defined by either PD-L1 tumour area positivity (TAP) score or combined positive score (CPS). Because generating a TAP score can be automated, this could substantially improve workflows and be easy to implement.

PD-L1 scoring based on the combined positive score (CPS) has shown predictive value for checkpoint inhibitors [1,2]. Although CPS is well-established, it remains a labour-intensive process with heterogeneous results between centres.

The TAP scoring system [3], which evaluates both immune and tumour cells to generate a score for PD-L1 tumour area, was validated for advanced gastric or gastro-oesophageal junction (G/GEJ) cancer in the RATIONALE-305 study (NCT03777657) and for advanced or metastatic oesophageal squamous cell carcinoma (ESCC) in RATIONALE-306 (NCT03783442) [4,5].

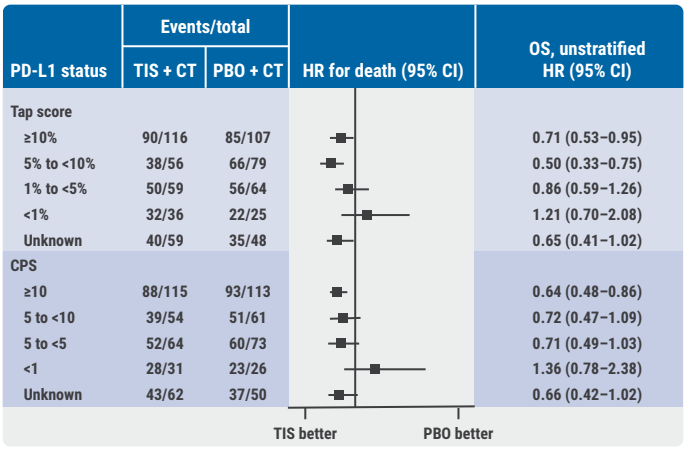
In the phase 3 RATIONALE-305 trial (n=1,657), tislelizumab plus chemotherapy demonstrated a significant overall survival (OS) benefit versus placebo plus chemotherapy as first-line therapy, in all randomised participants (HR 0.80; 95% CI 0.70–0.92; P=0.001) and participants with PD-L1 TAP scores ≥5% (HR 0.71; 95% CI 0.58–0.86) [6].

The phase 3 RATIONALE-306 trial recently demonstrated a superior OS with first-line tislelizumab plus chemotherapy compared with placebo plus chemotherapy, in all participants (HR 0.66; 95% CI 0.54–0.80) and in participants with PD-L1 TAP scores ≥10% (HR 0.62; 95% CI 0.44–0.86) [7].

In both trial cohorts, researchers directly compared the prognostic value of CPS versus TAP score [4,5]. The results showed that PD-L1 status was comparable across arms by TAP score or CPS under different thresholds. Both TAP and CPS scores similarly predicted OS and PFS in patients with PD-L1 1%, 5%, and 10% cut-off thresholds (see Figure).

In addition, a good correlation was observed between TAP score and CPS based on the interclass correlation coefficient (ICC 0.81 and 0.85 in respective trials). TAP and CPS scores also showed substantial concordance in terms of Cohen's Kappa and overall percent agreement (OPA) at matched thresholds for each score.

Figure: OS improvement for tislelizumab plus chemotherapy versus placebo plus chemotherapy across PD-L1 subgroups by TAP score and CPS in RATIONALE-306 [5]



CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; OS, overall survival; PBO, placebo; TAP, tumour area positivity; TIS, tislelizumab.

The conclusions from these analyses are that both TAP and CPS scores are viable for PD-L1 expression measurement in patients with G/GEJ cancer and ESCC. TAP score and CPS at matched thresholds exhibited substantial concordance among patients. Tislelizumab plus chemotherapy improved OS and PFS of patients within prespecified PD-L1 subgroups by TAP score, and demonstrated comparable OS and PFS results in PD-L1 subgroups by matched CPS.

1. Shitara K, et al. Nature. 2022;603(7903):942-948.
2. Rha SY, et al. Lancet Oncol. 2023;24(11):1181-1195.
3. Liu C, et al. Diagn Pathol. 2023;18:48.
4. Moehler M, et al. Tislelizumab (TIS) plus chemotherapy (CT) vs placebo (PBO) plus CT in HER2-negative advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (GC/GEJC): PD-L1 biomarker analysis from RATIONALE-305. Abstract 397MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
5. Raymond E, et al. Tislelizumab (TIS) + chemotherapy (CT) vs placebo (PBO) + CT in advanced or metastatic esophageal squamous cell carcinoma (ESCC): PD-L1 biomarker analysis from RATIONALE-306. Abstract 395MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
6. Qiu MZ, et al. BMJ. 2024;385:e078876.
7. Xu J, et al. Lancet Oncol. 2023;24(5):483-495.

Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract

AI facilitates early detection of hepatocellular carcinoma

An AI-driven algorithm based on routine blood tests outperformed ultrasonographic screening combined with alpha-fetoprotein (AFP) testing for the early detection of hepatocellular carcinoma (HCC) in high-risk individuals.

Most patients with HCC are diagnosed with advanced-stage disease, when palliative treatment is the only option, because early detection of HCC is challenging. The sensitivity of ultrasonographic screening combined with AFP testing, the most commonly used biomarker for HCC, is limited, especially in the lower stages of HCC. In addition, individuals often avoid screening appointments because of anxiety around an ultrasound test. To improve early detection of HCC, Dr Kin Nam Kwok (Hong Kong University, Hong Kong) and colleagues aimed to develop an AI-driven algorithm based on routine blood tests [1].

The algorithm was trained using data from 3,415 patients with HCC, including complete blood counts, liver and renal function tests, and clotting profiles. This led to a sensitivity of 79.4% in the detection of HCC in blood samples at 1–30 days before clinical diagnosis (compared with a sensitivity of 43.7% for AFP testing). In time, sensitivity decreased to 61.3% for the detection of HCC at 1–3 months before clinical diagnosis, 50.1% for 3–6 months before diagnosis, 44.2% for 6–9 months before diagnosis, and 41.3% for 9–12 months before diagnosis. In comparison, the sensitivity of the AFP test to reach those time goals in the same cohort was 41.9%, 37.9%, 29.8%, and 21.3%, respectively. In addition, the specificity of the algorithm was over 75% in all time intervals.

"This AI algorithm based on routine blood tests might bring forward the diagnosis of HCC in 40% of patients by 1 year, and thus creates a meaningful window for timely intervention. Potentially, this can lead to cancer mortality reduction," Dr Kwok concluded.

Further prospective studies to validate the potential of the algorithm are needed. Moreover, validation in a non-Asian cohort is essential.

1. Kwok KN, et al. Early detection of HCC by routine blood based-AI. Abstract 165MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

^{177}Lu-DOTATATE significantly extends PFS in patients with GEP-NETs, regardless of grade or origin

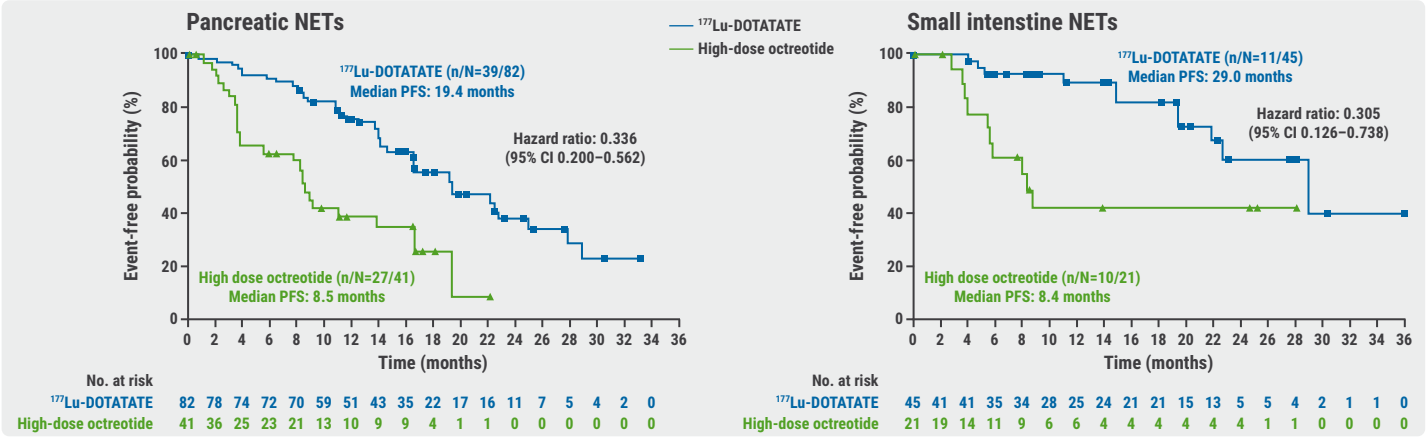
Results from a subgroup analysis of the NETTER-2 trial support the use of ^{177}Lu-DOTATATE, a peptide receptor radionuclide therapy, in treatment-naïve patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs), regardless of the tumour grade or origin.

There are currently no standard first-line treatment options for patients with higher grade 2–3, well-differentiated, advanced GEP-NETs. Recently, results from the phase 3 NETTER-2 trial (NCT03972488) showed that ^{177}Lu-DOTATATE plus octreotide (30 mg) significantly improved progression-free survival (PFS) compared with high dose octreotide (60 mg) in patients with somatostatin receptor-positive, higher grade GEP-NETs [1]. Now, Dr Simron Singh (University of Toronto, Canada) presented results from a pre-planned subgroup analysis of the trial [2].

NETTER-2 randomised 226 participants to first-line treatment with ^{177}Lu-DOTATATE plus octreotide (^{177}Lu-DOTATATE arm, n=151) or high dose octreotide alone (control arm, n=75). In the total study population, the median PFS was 22.8 months in the ^{177}Lu-DOTATATE arm versus 8.5 months in the control arm (HR 0.276; 95% CI 0.182–0.418; P<0.0001) [1].

The subgroup analysis demonstrated a benefit of ^{177}Lu-DOTATATE both in participants with grade 2 (n=142) or grade 3 (n=79) GEP-NETs: median PFS of 29.0 versus 13.8 months (HR 0.306) and of 22.0 versus 5.6 months (HR 0.266), respectively [2]. In addition, a benefit of ^{177}Lu-DOTATATE was observed regardless of the primary tumour origin (see Figure on the next page). The median PFS in participants

Figure: PFS benefit with ^{177}Lu-DOTATATE for patients with GEP-NETs [2]



GEP-NETs, gastroenteropancreatic neuroendocrine tumours; PFS, progression-free survival.

with pancreatic NETs (n=123) was 19.4 versus 8.5 months (HR 0.336); in participants with small intestine NETs (n=66) it was 29.0 versus 8.4 months (HR 0.305). Median PFS in participants with other GEP-NETs (n=37) was not shown.

Objective response rates for ^{177}Lu-DOTATATE were 40.4%, 48.1%, 51.2%, and 26.7% in participants with grade 2, grade 3, pancreatic, and small intestine NETs, respectively. The median duration of response was 24.9 months, 19.3 months, 18.4 months, and not yet reached in the respective subgroups. Based on these results, Dr Singh concluded that "first-line ^{177}Lu-DOTATATE plus octreotide should be considered a standard-of-care for patients with advanced, well-differentiated, grade 2 or 3, somatostatin receptor-positive GEP-NETs."

1. Singh S, et al. Lancet. 2024;403(10446):2807-2817.
2. Singh S, et al. First-line efficacy of [177Lu]Lu-DOTA-TATE in patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors by tumor grade and primary origin: subgroup analysis of the phase 3 NETTER-2 study. Abstract 211MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

Durvalumab plus chemotherapy enhances 3-year survival in advanced biliary tract cancer

Updated findings from the phase 3 TOPAZ-1 trial revealed that durvalumab combined with standard-of-care chemotherapy significantly improved 3-year overall survival (OS) compared with chemotherapy alone in patients with advanced biliary tract cancer.

TOPAZ-1 (NCT03875235) randomised participants to receive 1,500 mg of durvalumab (n=341) or placebo (n=344) on day 1 of each 21-day cycle, alongside gemcitabine and cisplatin for up to 8 cycles. This was followed by durvalumab or placebo monotherapy every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was OS, with secondary endpoints including progression-free survival, objective response rate, safety, and patient-reported outcomes [1,2].

With a median follow-up of 41.3 months, the combination of durvalumab and chemotherapy reduced the risk of death by 26% compared with chemotherapy alone (HR 0.74; 95% CI 0.63–0.87), and this was an improvement over the primary analysis (HR 0.80, 95% CI 0.66–0.97). Participants receiving the combination treatment had a median OS of 12.9 months versus 11.3 months for those on chemotherapy plus placebo. The 3-year OS rate was 14.6% in the combination arm and 6.9% in the placebo arm.

The combination regimen was generally well-tolerated, with no new safety concerns. Serious treatment-related adverse events occurred in 15.4% of the participants in the combination arm and 17.3% of those in the placebo arm.

This analysis represents the longest survival follow-up in a global phase 3 immunotherapy trial for advanced biliary tract cancer. The long-term survival benefit was not driven by any particular subgroup of participants.

"The latest data from TOPAZ-1 shows that twice as many patients with advanced biliary tract cancer were still alive at 3 years with durvalumab and chemotherapy, which is a significant advance given the historically poor prognosis in this setting," concluded Prof. Do-Youn Oh (Seoul National University, Korea).

1. Oh DY, et al. Three-year survival, safety and extended long-term survivor (eLTS) analysis from the Phase 3 TOPAZ-1 study of durvalumab (D) plus chemotherapy in biliary tract cancer (BTC). Abstract 279MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Burris HA 3rd, et al. Lancet Oncol. 2024;25(5):626-635.

Promising first results of mitazalimab in metastatic pancreatic ductal adenocarcinoma

The anti-CD40 antibody mitazalimab in combination with mFOLFIRINOX demonstrated a manageable safety profile and promising clinical efficacy in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the phase 1/2 OPTIMIZE-1 trial.

With a 5-year overall survival (OS) rate below 5%, current systemic therapies for mPDAC are associated with poor outcomes. Previously, CD40 agonists were shown to alter macrophage phenotype polarisation to favour the M1 phenotype and suppress pancreatic cancer [1].

The phase 1/2 OPTIMIZE-1 trial (NCT04888312) explored the safety and efficacy of mitazalimab, a second-generation CD40 agonist, combined with modified FOLFIRINOX in mPDAC patients. The primary endpoint was overall response rate (ORR); secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. Dr Teresa Macarulla (Vall d'Hebron University Hospital, Spain) presented the first results [2].

In phase 1b of OPTIMIZE-1, 900 µg/kg mitazalimab was determined to be the recommended phase 2 dose. A total of 70 patients were enrolled in phase 2 (efficacy set: n=57; safety set: n=70). After a median follow-up of 18 months, confirmed ORR was 42.1%. Median DoR was 12.6 months, median PFS was 7.7 months, and median OS was 14.9 months. A high CD4 effector T-cell expansion after the first cycle of mitazalimab correlated with a better median OS.

Treatment-emergent adverse events (TEAEs) of grade ≥3 were observed in 55 (79%) participants, with neutropenia (25.7%), hypokalemia (15.7%), and thrombocytopenia (11.4%) being the most common. Safety was overall consistent with the known mFOLFIRINOX safety profile.

Based on these results, Dr Macarulla concluded that "mitazalimab in combination with mFOLFIRINOX demonstrated a well-manageable safety profile and a promising clinical efficacy. These encouraging results warrant continued development in a randomised phase 3 trial."

1. Lim CY, et al. Gut Liver. 2022;16:645-659.
2. Macarulla T, et al. CD40 agonist mitazalimab combined with mFOLFIRINOX (mFFX) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): Primary analysis of the OPTIMIZE-1 phase 1b/2 study. Abstract 280MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

Cancers of the Colon, Rectum, and Anus

Post-operative MRD status more prognostic than TNM stage

Post-operative, circulating tumour (ct)DNA-based molecular residual disease (MRD) status is highly prognostic and outperforms the prognostic value of TNM staging in patients with colon adenocarcinoma, results from a retrospective analysis of clinical data of more than 3,000 patients demonstrated.

Currently, the prognosis and treatment plan for patients with colon adenocarcinoma is primarily dictated by AJCCs TNM staging, which includes tumour extent (T), lymph node involvement (N), and distant metastases (M). However, TNM status does not accurately predict disease-free survival (DFS) and/or the benefit of treatment.

Recent studies have highlighted the prognostic and predictive value of ctDNA-based detection of MRD after surgery [1]. Therefore, a study was performed to incorporate post-operative ctDNA results into the staging of colon adenocarcinoma. Dr Arvind Dasari (MD Anderson Cancer Center, TX, USA) presented the results [2].

The study retrospectively analysed clinical data of 3,148 patients with TNM stage I–III colon adenocarcinoma from 3 cohorts with available post-operative MRD results: GALAXY trial (UMIN000039205; n=2,170), BESPOKE CRC trial (NCT04264702; n=635), and real-world testing (n=343). Overall, 48% of the evaluated participants had stage III, 38% had stage II, and 14% had stage I colon adenocarcinoma. Adjuvant treatment and subsequent surveillance were per standard guidelines. DFS was determined as time from

surgery to tumour recurrence, second primary tumour, or death. The median follow-up ranged from 22 to 32 months.

ctDNA-based MRD status was assessed at 2–10 weeks post-resection. MRD-positivity was observed in 13% of the participants and correlated with pathological stage (stage I: 1%, stage II: 7%, and stage III: 20%). In participants with TNM stage II and stage III, MRD-positivity was significantly correlated with poor prognosis, with 24-month DFS having a hazard ratio of up to 28 for the comparison of MRD-negative versus MRD-positive participants.

MRD status was more prognostic for DFS than pathological TNM stage. For example, 24-month DFS rate in MRD-positive participants with stage IIA disease was 35.1%, while it was 80.1% in MRD-negative participants with stage IIIC disease (see Table). Regardless of the TNM stage, most participants with MRD-positivity are expected to have disease recurrence within 2 years.

Table: MRD status is associated with 24-month DFS [2]

Stage	MRD-negative, n	MRD-negative 24-month DFS, % (95% CI)	MRD-positive, n	MRD-positive 24-month DFS, % (95% CI)
I	294	95.9 (92.3–99.9)	2	50.0 (12.5–100)
IIA	629	96.1 (94.2–97.9)	39	35.1 (21.3–58.0)
IIB	103	86.9 (79.6–95.0)	13	28.9 (11.8–70.3)
IIC	31	88.8 (77.5–100)	5	40.0 (13.7–100)
IIIA	80	88.4 (78.9–99.0)	9	22.2 (6.6–75.4)
IIIB	606	88.8 (85.8–91.9)	115	32.7 (24.1–44.4)
IIIC	171	80.1 (72.4–88.5)	72	17.0 (9.0–32.2)
IVA	34	56.1 (39.5–79.5)	24	12.1 (3.7–39.8)
IVB/C	14	83.6 (10.8–64.9)	73	0.0 (N/A)

N/A, not available

"This data strongly suggests that the addition of post-operative, ctDNA-based MRD status to TNM staging can better risk-stratify patients with colon adenocarcinoma," Dr Dasari concluded. Longer follow-up is needed to further validate these results.

1. Dasari A, et al. Nat Rev Clin Oncol. 2020;17:757-770.
2. Dasari A, et al. Is it time for a new staging system for colon adenocarcinoma? Abstract 4MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

CAPRI 2 GOIM trial navigates biomarker-driven therapy

The CAPRI 2 GOIM trial demonstrated that liquid biopsy-based comprehensive genomic profiling was feasible and might improve the selection of *RAS/BRAF* wildtype metastatic colorectal cancer (mCRC) patients for the most appropriate treatments across 3 sequential lines of therapy. The collection of efficacy data is ongoing.

Previous clinical trials have explored the use of cetuximab or panitumumab monoclonal antibodies to target EGFR in the treatment of *RAS* wildtype mCRC across various treatment lines. Despite significant improvements in patient responses, resistance to anti-EGFR therapy due to innate or acquired mechanisms impairs its effectiveness. Several molecular biomarkers have been identified retrospectively in preclinical and clinical analyses to predict resistance to cetuximab and panitumumab. Among these, *RAS* mutational status is currently the principal biomarker of poor response to anti-EGFR drugs, and patients with *RAS*-mutated mCRC are excluded from such treatments.

CAPRI 2 GOIM (NCT05312398) is investigating the efficacy and safety of a biomarker-driven cetuximab-based treatment regimen over 3 treatment lines in mCRC patients with *RAS/BRAF* wildtype tumours at the start of first-line therapy. The primary endpoint is the response rate for each line of treatment according to the RECIST v1.1 guidelines.

Dr Giulia Martini (University of Campania Luigi Vanvitelli, Italy) presented the initial feasibility analysis of CAPRI 2 GOIM, based on 205 participants in the first-line treatment [1]. Tumour tissue and plasma circulating tumour DNA (ctDNA) next-generation sequencing (NGS) was performed both at the local trial site laboratory as well as centrally through a commercial service, showing a concordance rate of 90.7% (186/205). Baseline ctDNA plasma analysis identified additional molecular alterations compared with PCR-based tumour tissue analyses, which could be involved in resistance to anti-EGFR drugs in mCRC. There was a high concordance between tumour tissue and ctDNA NGS analysis (95.1%; 156/165) at both local and centralised laboratories.

Dr Martini concluded that using local laboratories for liquid biopsy-based comprehensive genomic profiling was feasible. Furthermore, efforts to improve sensitivity are ongoing and include: tracking more mutations (whole-exome sequencing versus panel), reducing background noise (sequencing peripheral blood mononuclear cells, technical improvements), and increasing circulating free DNA input.

1. Martini G, et al. Evaluation of plasma assessed comprehensive genomic profiling before first-line treatment with FOLFIRI plus cetuximab in RAS/BRAFV600E wild type metastatic colorectal cancer patients in the CAPRI 2-GOIM trial. Abstract 6MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

Meta-analysis of triplet therapy in *BRAF*^{V600E}-mutated mCRC

A systematic review and meta-analysis examined the safety and efficacy data from 8 trials using encorafenib, binimetinib, and cetuximab triplet therapies as first-line treatment options for patients with metastatic colorectal cancer (mCRC), and observed high heterogeneity in the results.

The *BRAF*^{V600E} mutation in mCRC, present in 5–21% of patients depending on the study population, is associated with a poor prognosis. On the other hand, this mutation can also predict a positive response to targeted therapy. Recent evaluations of a triplet therapy strategy including encorafenib, binimetinib, and cetuximab, have shown promising efficacy results, particularly in the BEACON CRC trial (NCT02928224) [1].

After conducting a systematic review, Dr Davi Said G. Celso (Federal University of Viçosa, Brazil) and colleagues performed a single-arm meta-analysis to pool the proportions of binary outcomes and their respective 95% confidence intervals [2]. The analysis included 8 studies with a total of 489 participants. Among these participants, 45.7% were men, 52.4% had an ECOG status of 0, 10.1% had high microsatellite instability, 72.1% received at least 1 line of previous therapy, and 61.5% presented with liver metastases.

The pooled proportions for 12-month and 24-month overall survival were 0.35 (95% CI 0.14–0.64) and 0.07 (95% CI 0.01–0.27), respectively. The 12-month progression-free survival rate was 0.08 (95% CI 0.03–0.20). The pooled overall response rate was 0.34 (95% CI 0.25–0.42). Adverse events leading to drug discontinuation and death occurred in 16% (95% CI 0.09–0.27) and 3% (95% CI 0.02–0.06) of the participants, respectively, while serious adverse events were reported in 53% (95% CI 0.48–0.59) of cases. The most common adverse events included diarrhoea (62.1%), dermatitis acneiform (49.6%), and nausea (47.3%).

The results of this analysis suggest that triplet therapy with encorafenib, binimetinib, and cetuximab can be a safe and effective strategy for patients with *BRAF*^{V600E}-mutated mCRC, across a diverse population from 8 trials. However, the high heterogeneity observed indicates a lack of uniformity in study designs across those trials, highlighting the need for further research to standardise treatment protocols.

1. Kopetz S, et al. N Engl J Med 2019;381(17):1632-1643.
2. Celso DSG, et al. Safety and Efficacy of Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer: A Systematic Review and Single-Arm Meta-Analysis. Abstract 61P, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

CheckMate 8HW: Nivolumab/ipilimumab in MSI-H/dMMR mCRC

Findings from the phase 3 CheckMate 8HW trial demonstrated that the frontline combination of nivolumab and ipilimumab reduced the deterioration of health-related quality-of-life (HRQoL) with symptom relief, compared with chemotherapy in patients with MSI-H/dMMR metastatic colorectal cancer (mCRC).

Dr Sara Lonardi (Veneto Institute of Oncology, Italy) presented the results from the multicentre, open-label CheckMate 8HW trial (NCT04008030) [1]. Patients with histologically confirmed unresectable or metastatic microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) CRC and an ECOG performance status of 0 or 1 were enrolled and randomly assigned to 3 arms: nivolumab monotherapy (n=202), nivolumab plus ipilimumab (n=202), or chemotherapy (n=101).

The dual primary endpoints were progression-free survival (PFS) in the nivolumab/ipilimumab arm versus chemotherapy arm across the frontline setting, and PFS in the nivolumab/ipilimumab arm versus nivolumab monotherapy arm across all treatment lines. Secondary endpoints included safety, overall survival, overall response rate, and HRQoL.

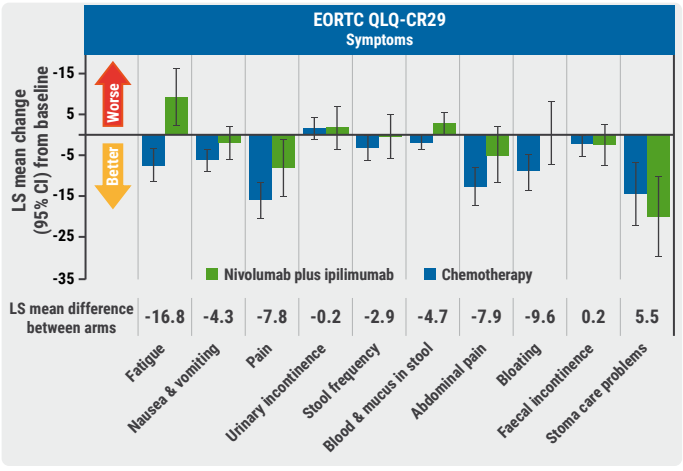
Findings from the interim analysis revealed that the median PFS was not reached with the nivolumab/ipilimumab combination versus 5.9 months with chemotherapy (HR 0.21; 97.91% CI 0.13-0.35; P<0.0001). The 12-month PFS rates were 79% for nivolumab/ipilimumab versus 21% for chemotherapy, and 24-month rates were 72% versus 14% [2].

HRQoL assessments indicated that the nivolumab combination improved global health status starting at week 13 and surpassed the trial's prespecified minimally important difference (MID) threshold at week 13, with a least squares mean difference of 9.7 (95% CI 3.6–15.9)) [1]. By week 21, significant improvements in global health status with nivolumab/ipilimumab were observed.

The nivolumab/ipilimumab combination also demonstrated improvements in physical, role, and social functioning based on the EORTC QLQ-C30 assessment. The least squares mean differences between the nivolumab/ipilimumab and chemotherapy arms were 10.6 for global health status, 7.3 for physical functioning, 12.0 for role functioning, and 9.6 for social functioning. Symptoms severity, measured by

the EORTC QLQ-CR29, showed reductions in fatigue (-16.8), nausea and vomiting (-4.3), and pain (-7.8) with nivolumab/ipilimumab compared with chemotherapy (see Figure).

Figure: Quality-of-life improved with nivolumab/ipilimumab in CheckMate 8HW [2]



The rate of global health status deterioration was lower in the nivolumab/ipilimumab arm compared with chemotherapy (HR 0.32; 95% CI 0.18–0.57). Deterioration in physical functioning (HR 0.49; 95% CI 0.26–0.94), role functioning (HR 0.50; 95% CI 0.29–0.87), social functioning (HR 0.54; 95% CI 0.28–1.04), and fatigue (HR 0.50; 95% CI 0.31–0.80) was also less frequent.

Dr Lonardi concluded: "These HRQoL results provide further support for the use of first-line nivolumab and ipilimumab in MSI-H/dMMR mCRC."

1. Lonardi S, et al. Health-related quality of life (HRQoL) with first-line (1L) nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) in patients (pts) with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): CheckMate 8HW. Abstract 20, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Lenz H-J, et al. J Clin Oncol 2024;42:16S_3503.

Sequence effect for third-line treatment of mCRC

For patients with metastatic colorectal cancer (mCRC) whose cancer progressed despite 2 lines of chemotherapy treatment with trifluridine/tipiracil followed by regorafenib is a better option than treatment with regorafenib followed by trifluridine/tipiracil, results from the phase 2 SOREGATT trial showed.

Until recently, only 2 treatment options were available for patients with mCRC whose cancer progressed despite 2 lines of chemotherapy: regorafenib or trifluridine/tipiracil. Both treatment options showed comparable efficacy in phase 3 studies against placebo.

The phase 2 SOREGATT trial (NCT04450836) was designed to investigate the optimal sequence of regorafinib and trifluridine/tipiracil. The primary endpoint was the feasibility of the treatment sequences, i.e. the percentage of participants treated with at least 2 cycles of both regorafenib and trifluridine/tipiracil. Prof. Michel Ducreux (Gustave Roussy, France) presented the results [1].

The study meant to randomise 340 participants who failed on 2 lines of chemotherapy 1:1 to regorafenib followed by trifluridine/tipiracil (Arm A) or trifluridine/tipiracil followed by regorafenib (Arm B). However, enrolment was prematurely stopped after presentation of the results of the SUNLIGHT trial demonstrating superior efficacy of trifluridine/tipiracil plus bevacizumab over trifluridine/tipiracil alone [2]. Eventually, 231 participants were randomised and treated in the SOREGATT trial.

In Arm A of SOREGATT, 40% of the participants were treated with at least 2 cycles of both treatment regimens, in Arm B this was 55.5% (P=0.018). The main reasons to end the first treatment were disease progression (80.4% in Arm A; 90.8% in Arm B) and toxicity (14.3% in Arm A; 7.6% in Arm B). No significant difference was observed between both study arms in median overall survival (6.0 vs 6.9 months; P=0.3) nor median progression-free survival (1.87 vs 1.97 months; P=0.10). A trend of a better outcome in Arm B was observed for PFS2 (the time interval from randomisation until death or disease progression observed in the second sequence of treatment): 26.9% at 6 months in Arm B versus 16.1% in Arm A. In addition, time to failure was longer in Arm B: 22.7% non-failure in Arm B after 6 months versus 12.2% non-failure in Arm A.

Despite the premature termination of the study due to the publication of data from the SUNLIGHT study, this study provides important information, Prof. Ducreux concluded. "There is indeed a sequence effect, and starting with trifluridine/tipiracil clearly appears to be a better strategy. However, the median overall survival of these patients remains short: around 6 to 7 months."

1. Ducreux MP, et al. PRODIGE 68 - UCGI 38 - SOREGATT: A randomized phase 2 study comparing the sequences of regorafenib (reg) and trifluridine/tipiracil (t/t) after failure of standard therapies in patients (pts) with metastatic colorectal cancer (mCRC). Abstract 30, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Prager GW, et al. N Engl J Med 2023;388:1657-1667.

High efficacy of pembrolizumab combined with standard therapy in patients with MSS/pMMR mCRC and high immune infiltrate

Preliminary results of the phase 2 POCHI trial showed high efficacy of pembrolizumab, combined with standard therapy, in patients with MSS/pMMR metastatic colorectal cancer (mCRC).

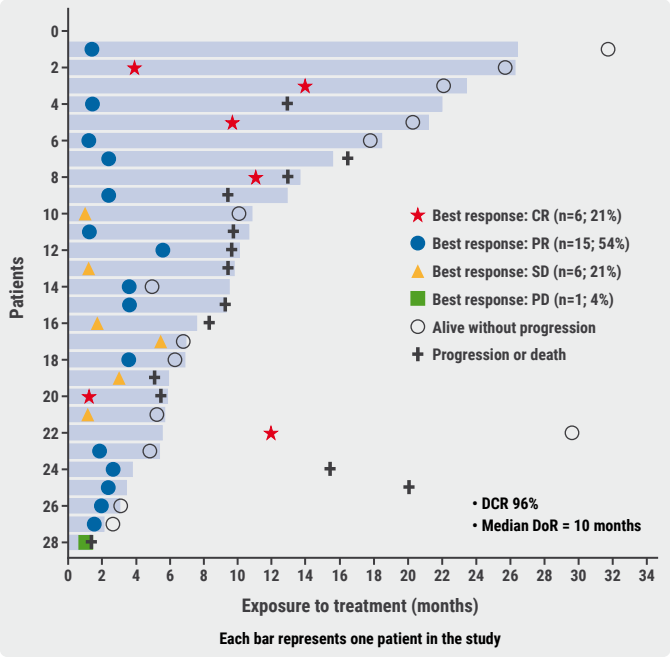
In contrast to microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) mCRC, microsatellite stable/proficient mismatch repair (MSS/pMMR) mCRC is currently considered non-responsive to immune checkpoint inhibitors. However, about 15% of MSS/pMMR CRCs are highly infiltrated by tumour-infiltrating lymphocytes and may therefore be sensitive to immune checkpoint inhibitors.

The multicentre, single-arm, phase 2 POCHI trial (NCT04262687) evaluates the efficacy of the immune checkpoint inhibitor pembrolizumab in combination with CAPOX and bevacizumab as first-line treatment of unresectable MSS/pMMR mCRC in patients with a high immune infiltrate (defined by at least 1 positive immune score [Immunoscore® and/or TuLIS] on primary tumour resection specimens). The primary objective is to increase progression-free survival (PFS) at 10 months from 50% to 70%. The main secondary endpoints are overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety. Prof. David Tougeron (Poitiers University Hospital, France) presented the results of a preliminary analysis [1].

A total of 28 participants with unresectable MSS/pMMR mCRC and at least 1 positive immune score were treated every 3 weeks with a combination of pembrolizumab, CAPOX, and bevacizumab. After a median follow-up of 19 months, 13 participants were still on treatment. A complete response was achieved in 6 participants and a partial response in 15, leading to an ORR of 75%; 6 participants showed stable disease and 1 had disease progression. Median DoR at data cut-off was 10 months (see Figure). Preliminary efficacy data shows a PFS rate at 12 months of 68% and a 24-month OS rate of 67%. Regarding safety, 64% of the participants experienced at least 1 grade 3–4 treatment-related adverse event, but no toxic deaths were observed.

"These preliminary results suggest a high efficacy of pembrolizumab combined with standard therapy in patients with MSS/pMMR mCRC and a high immune infiltrate. The observed complete response and disease control rates justify further evaluation of this treatment in a randomised phase 3 trial," Prof. Tougeron concluded. The trial is still enrolling and biomarker analyses are ongoing.

Figure: High overall response with pembrolizumab added to standard therapy in POCHI [1]



CR, complete response, DCR, disease control rate; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

1. Tougeron D, et al. Pembrolizumab in combination with xelox and bevacizumab in patients with microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) and a high immune infiltrate: a proof of concept study. Preliminary results of FFCD 1703 POCHI trial. Abstract LBA1, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

REGINA meets stage 1 endpoint in rectal cancer and moves to stage 2 with reduced dose regorafenib

The phase 2 REGINA trial yielded encouraging results for the use of neoadjuvant regorafenib together with nivolumab and short-course radiotherapy (SCRT) as a treatment for patients with stage II–III rectal cancer, although toxicities were more common than anticipated.

Regorafenib, an oral multi-kinase inhibitor, targets angiogenic, stromal, and oncogenic receptor tyrosine kinases. Dr Francesco Sclafani (Institut Jules Bordet, Belgium) presented the interim analysis of the REGINA trial (NCT04503694), which investigated the triplet combination of neoadjuvant regorafenib, nivolumab, and SCRT in 36 patients with stage II–III rectal cancer [1]. Participants received 160 mg of regorafenib daily for 3 weeks, followed by a 1-week break, in

repeated 28-day cycles, in addition to nivolumab and SCRT treatments. The primary endpoint is the pathological and clinical complete response (pCR and cCR) at 1 year.

The predefined statistical criteria for this interim analysis were met, supporting further investigation of the combination of regorafenib, nivolumab, and SCRT as neoadjuvant therapy for locally advanced rectal cancer. Promising pCR rates and "watch & wait" adoption were observed regardless of mismatch repair or microsatellite stability (MMR/MSS; n=30) status. Of the 36 participants, 8 achieved cCR prior to surgery and moved to "watch & wait", while 27 underwent surgery. Eight of those participants (30%) achieved pCR, concluding that over one-third (16/36, 44%) of the study population achieved pCR or cCR with this approach.

Given an unexpectedly high toxicity rate, in the second stage of the study the regorafenib dose will be reduced to 60 mg/day in hopes of improving the treatment safety profile. The nature of adverse events was consistent with known profiles, including hand-foot skin reaction, hypertension, and fatigue. Importantly, the trial reported no new safety concerns.

Dr Sclafani concluded: "The phase 2 REGINA trial brings both challenges and hope. The 60% incidence of grade ≥3 serious adverse events underscores the need for meticulous patient management, while a 25% pCR in MRR/MSS patients is promising. Balancing efficacy and toxicity remains crucial."

1. Sclafani F, et al. Efficacy interim analysis of REGINA, a phase II trial of neoadjuvant regorafenib (Rego), nivolumab (Nivo), and short-course radiotherapy (SCRT) in stage II-III rectal cancer (RC). Abstract LBA2, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

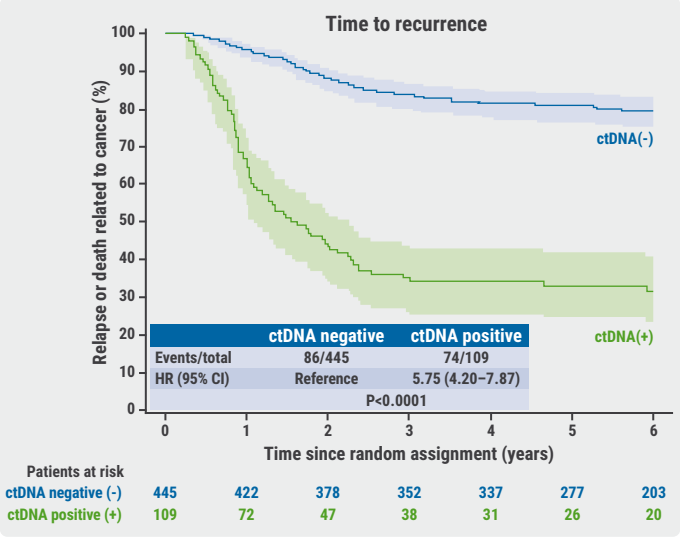
Prognostic value of ctDNA in stage III colon cancer

Circulating tumour (ct)DNA was found to be the most significant prognostic factor for disease recurrence and death in stage III colon cancer patients eligible for adjuvant therapy in multivariable analyses across 2 trials. ctDNA's prognostic value was independent of disease stage and treatment duration. Immunoscore® was not prognostic in ctDNA-positive patients but remains discriminant in ctDNA-negative patients.

Prof. Julien Taieb (Paris Descartes University, France) presented a combined analysis of 2 trials, IDEA-France (GERCOR; NCT00958737) and IDEA-Greece (HORG; NCT01308086), to investigate ctDNA and assess its prognostic value in terms of time to recurrence (TTR) and overall survival (OS) in patients with stage III colon cancer [1–3]. The rationale is to enhance personalised treatment approaches by leveraging ctDNA to track minimal residual disease, which could significantly improve prognostication. Both Immunoscore® (image analysis of CD3+ and CD8+ positive cells in the tumour centre and invasion margin) and ctDNA detection (using a clinically validated 16-plex PCR next-generation sequencing assay) were assessed.

Out of 554 participants with available ctDNA results, 445 were ctDNA-negative (80.3%) and 109 were ctDNA-positive (19.7%). Baseline characteristics revealed more T4/N2 cases among ctDNA-positive participants (58% vs 38%; P<0.01). With a median follow-up of over 80 months, ctDNA emerged as an independent prognostic marker for both TTR (adjusted HR 5.75; 95% CI 4.2–7.9; P<0.0001; see Figure) and OS (adjusted HR 5.31; 95% CI 3.8–7.5; P<0.0001). ctDNA's prognostic significance remained robust across various disease stages, treatment durations, and Immunoscore® categories. Immunoscore® showed prognostic value in ctDNA-negative participants but not in ctDNA-positive ones. For ctDNA-negative participants, those with a high Immunoscore® had a 5-year TTR of 92%, compared with 78–82% for those with low/intermediate Immunoscores.

Figure: ctDNA status predicts time to recurrence of stage III colon cancer [1]



In conclusion, this combined analysis of 2 adjuvant trials confirms that post-surgery ctDNA, present in 19.7% of the participants, is a major independent prognostic marker in stage III colon cancer. Immunoscore® also served as an independent prognostic tool in ctDNA-negative participants, comprising 80.3% of the cohort. Key findings include that

ctDNA, assessed with a tumour-informed commercial test, significantly correlates with TTR and OS, outperforming previous methylation tests.

1. Taieb J, et al. Combined analyses of ctDNA and Immunoscore in stage III colon cancer patients: a post hoc analysis of the IDEA-France and -Greece trials. Abstract 7MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Souglakos J, et al. Ann Oncol. 2019;30(8):1304-1310.
3. Gallois C, et al. J Clin Oncol. 2023;41(4):803-815.

Neoadjuvant combined immunotherapy also effective in MSS/pMRR CRC

Neoadjuvant treatment with a combination immunotherapy of botensilimab/balstilimab is safe and active in both MSS/pMMR and MSI-H/dMRR resectable colorectal cancer (CRC), first results from the phase 2 NEST-1 trial demonstrated.

Previously, the phase 2 NICHE-2 trial (NCT03026140) demonstrated that neoadjuvant nivolumab/ipilimumab induced a high rate of major pathological complete response (pCR) in patients with locally advanced microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) CRC [1]. In contrast, microsatellite stable/proficient mismatch repair (MSS/pMMR) resectable CRC is currently considered non-responsive to immune checkpoint inhibitors. However, good responses were observed recently with neoadjuvant botensilimab (an anti-CTLA-4 antibody) and balstilimab (an anti-PD-1 antibody) in 2 patients with resectable MSS/pMMR CRC [2].

To further evaluate the efficacy of neoadjuvant botensilimab/balstilimab in MSS/pMMR resectable CRC, Dr Mehraneh Jafari (Weill Cornell Medical Center, NY, USA) and colleagues performed the phase 2 NEST-1 trial (NCT05571293) [3]. NEST-1 enrolled 20 participants with resectable, non-metastatic CRC; 10 participants received neoadjuvant treatment with 1 dose of botensilimab and 2 doses of balstilimab followed by surgery, 10 participants received neoadjuvant treatment with 1 dose of botensilimab and up to 4 doses of balstilimab followed by surgery. Median time to surgery was 29.5 days in cohort 1 and 57 days in cohort 2.

Only 3 participants had MSI-H/dMMR CRC. They all achieved a major pathological response (≥50% regression), as did 71% of the MSS/pMMR participants. A pCR was achieved by 2 MSI-H/dMMR participants and by 6 MSS/pMMR participants.

Based on these results, Dr Jafari concluded that "neoadjuvant botensilimab/balstilimab is a safe and active regimen in both MSS/pMMR and MSI-H/dMRR resectable CRC. Responses increased with more doses of balstilimab, in conjunction with a longer interval to surgery."

1. Chalabi M, et al. N Engl J Med 2024;390:1949-1958.
2. Kasi PM, et al. Oncogene. 2023;42:3252-3259.
3. Kasi PM, et al. Neoadjuvant botensilimab (BOT) plus balstilimab (BAL) in resectable mismatch repair proficient and deficient colorectal cancer: NEST-1 clinical trial. Abstract 8MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

Neoadjuvant immunotherapy plus radiation effective in advanced MSI-H rectal cancer

The phase 2 ECOG-ACRIN EA2201 trial showed that combination immunotherapy of nivolumab/ipilimumab followed by short-course radiotherapy (SCRT) may prevent more aggressive trimodality interventions in patients with MSI-H/dMMR locally advanced rectal cancer.

The current standard treatment for locally advanced rectal cancer is neoadjuvant chemoradiotherapy and radiation followed by radical surgery. However, this approach can lead to multiple complications. Single institution studies have demonstrated variable efficacy of anti-PD-1 monotherapy with high clinical and/or pathological complete response (cCR and pCR) rates in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) locally advanced rectal cancer of 38–100% [1,2]. In localised MSI-H/dMMR colon cancer, the combination of anti-PD-1 and anti-CTLA4 therapy in the neoadjuvant setting led to a pCR rate of 68% [3].

The phase 2, multicentre ECOG-ACRIN EA2201 trial (NCT04751370) aimed to evaluate the potential of combination immunotherapy (i.e. nivolumab/ipilimumab) followed by SCRT to increase pCR and decrease the need for surgery in patients with MSI-H/dMMR locally advanced rectal cancer. Dr Kristen Ciombor (Vanderbilt University Medical Center, TN, USA) presented the results of the first stage of the trial (n=14) [4].

Patients with MSI-H/dMMR cT3-4Nx or cTxN+ rectal cancer received 2 cycles of nivolumab/ipilimumab followed by SCRT, an additional 2 cycles of nivolumab/ipilimumab, disease reassessment, and total mesorectal excision (TME). The primary endpoint was pCR rate or, in case of a low TME rate, pCR + cCR rate.

Of 14 participants, all received immunotherapy, 12 received SCRT, and 3 received TME. Because of the low TME rate, the primary endpoint assessed was pCR + cCR rate, with a result

of 57% (8/14). All participants who underwent TME (3/3) achieved pCR. In 5 participants, TME was deferred due to the achievement of cCR, 2 participants withdrew consent, and 4 did not complete all protocol-specified treatments due to adverse events (AEs). All participants experienced grade 1–2 treatment-related AEs (most commonly fatigue, diarrhoea, and hyperthyroidism); 5 participants had treatment-related AEs of grade 3–4, including 1 grade 4 event of hypokalemia.

"This data shows a promising impact of combination immunotherapy for patients with MSI-H/dMMR locally advanced rectal cancer, that may prevent more aggressive trimodality interventions," concluded Dr Ciombor. The EA2201 trial is now being redesigned to give all 4 cycles of immunotherapy upfront, followed by 2 cycles of nivolumab monotherapy, SCRT, and TME (with disease reassessment at every step).

1. Chen G, et al. Lancet Gastroenterol Hepatol. 2023;8:422-431.
2. Cercek A, et al. N Engl J Med 2022;386:2363-2376.
3. Chalabi M, et al. N Engl J Med 2024;390:1949-1958.
4. Ciombor KK, et al. Neoadjuvant nivolumab plus ipilimumab in microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) rectal tumors: ECOG-ACRIN EA2201. Abstract 242MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

General GI Cancer

Peri- or post-operative chemotherapy benefits patients with resectable CRCLM

Administering chemotherapy to patients with resectable colorectal cancer liver metastases (CRCLM) significantly reduced the risk of recurrence and was associated with better overall survival in an analysis of individual patient data from 4 phase 3 trials.

The liver is the most frequent site of metastatic spread of CRC. The optimal management of resectable CRCLM remains a matter of debate, and practice in this setting is highly heterogeneous. In particular, the value of post-operative or peri-operative systemic chemotherapy is uncertain. The relatively small available sample size of randomised phase 3 studies precludes meaningful survival analyses in the entire population and specific subgroups.

To get more insight into the value of post-operative or peri-operative systemic chemotherapy in patients with CRCLM, individual patient data (IPD) was collected from 3 randomised phase 3 trials investigating post-operative chemotherapy (i.e. FFCD-ACHBTH-AURC 9002, ENG [EORTC/NCIC CTG/GIVIO], and UMINC000000013) and 1 randomised phase 3 trial investigating peri-operative chemotherapy (EORTC 40983), with a total of 821 participants [1–4]. The primary endpoint of the IPD analysis was disease-free survival (DFS). Secondary endpoints included overall survival (OS) and survival outcomes in pre-specified subgroups. Dr Giacomo Bregni (Brussels University Hospital, Belgium) presented the results [5].

Of all patients included in the analysis, 411 had undergone surgery alone and 410 had undergone surgery and chemotherapy. A statistically significant difference in median DFS was observed between cohorts: 1.2 versus 1.9 years in the surgery alone and chemotherapy cohort, respectively (HR 0.79; 95% CI 0.67–0.93; P=0.004). DFS benefit for chemotherapy was maintained after leaving out IPD from the peri-operative trial. A trend was observed for a better median OS in the chemotherapy cohort (HR 0.82; 95% CI 0.68–1.00; P=0.048 in all trials; HR 0.77; 95% CI 0.58–1.02; P=0.063 in post-operative trials).

Analysis of pre-planned subgroups showed a significant improvement of DFS both in patients with normal alkaline phosphatase levels (P=0.026 vs raised levels) and patients with synchronous metastases (P=0.036 vs metachronous metastases). However, no significant improvement in OS was observed in any subgroup.

"This largest IPD meta-analysis to date shows that administering chemotherapy to patients with resectable CRCLM significantly reduces the risk of recurrence and is associated with better OS," Dr Bregni concluded. Patients with synchronous liver metastases or normal alkaline phosphatase levels may benefit most from chemotherapy.

1. Portier G, et al. J Clin Oncol. 2006;24:4976-4982.
2. Langer B, et al. Proc Am Soc Clin Oncol 2002;21:149a.
3. Hasegawa K, et al. PLoS One 2016;1(9):e0162400.
4. Nordlinger B, et al. Lancet Oncol. 2013;14:1208-1215.
5. Bregni G, et al. Individual patient data (IPD) meta-analysis of randomised phase III trials (RP3) of chemotherapy for resectable colorectal cancer liver metastases (CRCLM): EORTC RP-2145. Abstract 5MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

MINOTAUR: Promising phase 1 data for lunresertib plus FOLFIRI

Initial data from the ongoing phase 1 MINOTAUR clinical trial, evaluating lunresertib (RP-6306) in combination with FOLFIRI for patients with advanced solid gastrointestinal tumours, indicated an 18.2% overall response rate (ORR) in heavily pretreated patients with target alterations, regardless of prior irinotecan exposure.

Lunresertib, a first-in-class PKMYT1 inhibitor, targets *CCNE1* amplification, *FBXW7* alterations, and *PPP2R1A* alterations in solid tumours. The combination of lunresertib and FOLFIRI is under evaluation in several phase 1 and phase 2 trials. Dr Elisa Fontana (Sarah Cannon Research Institute, UK) presented the efficacy and tolerability data from the phase 1 MINOTAUR trial (NCT05147350) on the combination therapy, particularly for tumours with *CCNE1* amplification and deleterious *FBXW7* mutations, which are associated with poor prognosis and lack approved treatments [1].

The trial results demonstrated an ORR of 18.2% in heavily pretreated patients (n=33), including 4 confirmed and 2 unconfirmed partial responses (PR), regardless of prior irinotecan exposure. The prolonged clinical benefit rate among all tumour types was 51.5%, including 46.7% of the participants with recurrent colorectal cancer (CRC; n=15), suggesting prolonged duration of therapy for this particular group. Indeed, 40% of irinotecan-naïve CRC (2/5) patients remained on treatment for over 9 months, supporting this hypothesis. The recommended phase 2 dose of lunresertib was established at 60 mg twice daily plus standard FOLFIRI.

The combination therap y was well tolerated, with a safety profile consistent with FOLFIRI alone, and no excess toxicity. Neutropenia and leukopenia were the most common grade 3/4 treatment-related AEs, reversible with FOLFIRI interruption.

In conclusion, this data is encouraging for early efficacy and tolerability, and suggests the need for further development in a randomised phase 2 study. The combination of lunresertib with FOLFIRI could potentially provide a new treatment option for gastrointestinal tumours with target alterations.

1. Fontana E, et al. Phase 1 Study of the PKMYT1 Inhibitor Lunresertib (Lunre) in Combination with FOLFIRI in Advanced Gastrointestinal (GI) Cancers (MINOTAUR Study). Abstract 504MO, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.

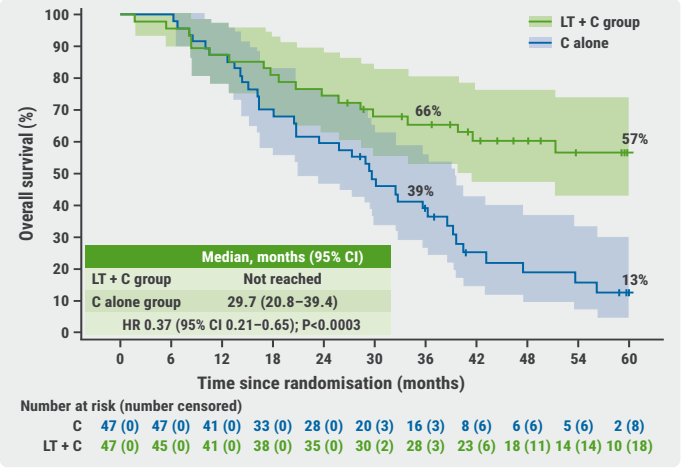
TRANSMET meets OS endpoint

Updated results from the TRANSMET trial revealed that combining chemotherapy with liver transplantation significantly extended survival for patients with colorectal cancer whose liver metastases cannot be surgically removed. The trial demonstrated a 4-fold increase in the 5-year overall survival (OS) rate for patients receiving the combined treatment compared with chemotherapy alone.

Dr Maximiliano Gelli (Gustave Roussy, France) presented the 5-year survival outcomes of the TRANSMET trial (NCT02597348) [1]. TRANSMET investigated the curative potential of chemotherapy followed by liver transplantation versus chemotherapy alone in patients with unresectable colorectal cancer liver metastases (CRCLM) [2].

After a median follow-up of 59 months, 57% of the participants in the combined treatment group survived 5 years versus just 13% in the chemotherapy-only group (HR 0.37; 95% CI 0.21–0.65; P=0.003; see Figure). Despite a high recurrence rate in the combined treatment group, these participants still showed significantly better survival outcomes, pointing to the critical role of liver health in OS.

Figure: Rate of overall survival in the intention-to-treat population of TRANSMET [1]



C, chemotherapy; CI, confidence interval; HR, hazard ratio; LT, liver transplant.

The study's findings suggest a potential shift in the treatment of patients with unresectable CRCLM, though the approach is suitable only for a very select group due to strict eligibility criteria and the limitations of donor organ availability. Dr Gelli also noted the logistical and ethical challenges in expanding liver transplantation criteria for cancer patients, pointing to the need for careful patient selection and resource allocation.

1. Adam R, et al. Chemotherapy and liver transplantation versus chemotherapy alone in patients with definitively unresectable colorectal liver metastases: Updated results from the randomized TRANSMET trial. Abstract 1O, ESMO Gastrointestinal Cancers Congress 2024, 26–29 June, Munich, Germany.
2. Adam R, et al. eClinicalMedicine. 2024:72:102608.