ESMO World Congress on Gastrointestinal Cancer 2018

European Society for Medical Oncology

20-23 JUNE 2018 • BARCELONA • SPAIN

PEER-REVIEWED CONFERENCE REPORT

NEW! Includes E-Learning Module

Late-Breaking Abstracts
The TAGS-study demonstrated that oral combination of trifluridine/tipiracil is an effective treatment option for heavily pre-treated patients with metastatic gastric cancer, a patient group with poor prognosis.

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What is New in Metastatic Colorectal Cancer
Not all patients with mCRC benefit from triplet chemotherapy. However, a subgroup analysis of the CHARTA trial identified a group of patients that gain a significantly longer progression-free survival with this treatment.

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Liquid Biopsy: A Novel Tool to Monitor and Guide Therapy
Circulating DNA, the so-called liquid biopsy, opens many new possibilities with minimal invasiveness: it is useful to guide therapy and to identify patients at risk for recurrence, particularly when tumour tissue is not available.

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Esch, Luxembourg

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2468-8762 18:14

Letter from the Editor

Dr Stefan Rauh

Dear Reader,

I am delighted to introduce to you our coverage of this year's ESMO World Congress of Gastro-Intestinal Cancer (WCGIC), which took place from 20-23 June in Barcelona. It was the 20th edition of this annual event, which has established itself as a premier educational forum, providing its 3500 attendees from 120 countries a comprehensive overview of state-of-the-art diagnostics and features in the field of GI oncology.

Increasingly, the congress is also attracting investigators to present their study results and, thus, it should come as no surprise to you that Medicom launched its first WCGIC congress report this year. I am proud to count on an expert medical writer and contributions of a panel of expert reviewers for this edition.

Excitingly, there is truly practice-changing news, including for still highly challenging cancers with increasing incidence but limited treatment options: a third-line treatment in gastric cancer, several systemic treatments for advanced hepatocellular cancers, and also new treatment options for bile cancers on the horizon.

Detecting recurrence early enough to provide efficient treatment, including surgery, is of major importance in colorectal cancer. Read about the utility liquid biopsies in this setting; implementation should be watched closely.

Treatment outcomes in mCRC cancer have made a great leap in the beginning of this century. If oncologists still hope to see a new "blockbuster" soon, we will still have to wait. The WCGIC comes with modest – still important – new data: clarifying options in third-line treatment and better identification of patients benefitting from triplet chemotherapies combined with biologicals in metastatic colorectal cancer are two examples.

I hope you will enjoy going through our report in detail. To further enhance the educational experience, we have included some questions to check on what you retained from the provided information.

Yours sincerely,

Stefan Rauh

Biography

Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but is also involved in research and teaching activities, and is interested in public policy and international cooperation projects in oncology. He is Chair of the ESMO Practicing Oncologist's Working Group since 2015, member of the ESMO Quality Task Force, extended member of the ESMO Public Policy Committee, Assistant Editor of ESMO Cancer Horizons, and has been an ESMO Executive Board member in 2015-16. He is co-author of the 2017 ESMO ECPC Patient Survivorship Guide and an invited expert for the European Cancer Patient Coalition (ECPC).

Main reviewers of this report

Dr George Pentheroudakis

Biography

George Pentheroudakis holds an MD degree from the Aristotle University of Thessaloniki and a PhD degree from the University of Ioannina, Greece. He specialised in Internal Medicine in Thessaloniki, Greece (1993-1999), subsequently held a National Training Number in Medical Oncology at the Beatson Oncology Centre, Glasgow, United Kingdom (1999-2003). He currently serves as Professor of Oncology at the Medical School, University of Ioannina, Greece, where he is the Head of the Medical Oncology Department. He is actively involved in translational research and phase I-II studies evaluating novel agents targeting membrane receptors, cell signalling pathways, immune response and angiogenesis. He coordinates the GI Working Group of HeCOG, the Hellenic Cooperative Oncology Group active in the development of therapeutic approaches by running a large annotated tissue bank and a Greek clinical trial network of 15 centres. His main research interests are gastrointestinal cancer, cancer of unknown primary and new drug development.

Dr Pentheroudakis served as co-chair (2012-2014) and currently as Chair of the ESMO Guidelines Committee and is a member of the Executive Board of the European Society for Medical Oncology (ESMO, 2016-2017) and the ESMO CUP and Endocrine Tumour Faculty.

He is also member of the American Society of Clinical Oncology (ASCO) and is actively involved in different editorial boards including Cancers, Cancer Treatment Communications, EJSO - European Journal of Surgical Oncology, Rare Cancers and Therapy, ESMO Open. He has (co)authored 244 PubMed-indexed peer-reviewed papers and speaks English, French and Italian.

Dr Henk van Halteren

Biography

After finishing his clinical training at the University Medical Center Nijmegen (the Netherlands; Professor D.J.Th. Wagener) Henk van Halteren worked as consultant in Medical Oncology in a general teaching hospital (the Oosterschelde Hospital (2001-2008) and the Gelderse Vallei Hospital (2008-2012)). Since 2012, he is working in the Admiraal De Ruyter Hospital Medical Center, which is situated in the southwestern part of the Netherlands.

Dr van Halteren wrote his thesis in 2004, which encompassed preclinical research regarding the relation between tumour hypoxia and cancer cachexia. In the past two decades he has strived to combine everyday patient care with teaching of young doctors and multicentre trial participation.

Henk van Halteren has specialised in the treatment of urological, upper/lower GI and gynaecological malignancies, as well as breast cancer. Due to his broad spectrum of interest, he has published a broad range of topics in a variety of peer-reviewed journals. From 2008 until 2016 he worked as a member of the ESMO Publishing Working Group, which enabled him to be the (co-)editor of several relevant handbooks (Cancer Rehabilitation, Cancer and Nutrition, How to interpret reported clinical study results). Since 2016 he has been working as a member of Oncology Pro.

Late-Breaking Abstracts

Clearly, the most interesting studies were presented in the late-breaker session, which attracted a large audience. This chapter provides a selection of the most relevant and possibly practice-changing studies. New agents broaden treatment possibilities in advanced disease: inhibition of nucleoside metabolism with TAS-102 has shown to improve survival in patients with advanced gastric cancer. HCC patients with elevated AFP levels benefit from the VEGF receptor 2 antagonist ramucirumab. Last but not least, adjuvant treatment with modified FOLFIRINOX seems to be the new standard for fit patients with resected pancreatic cancer.

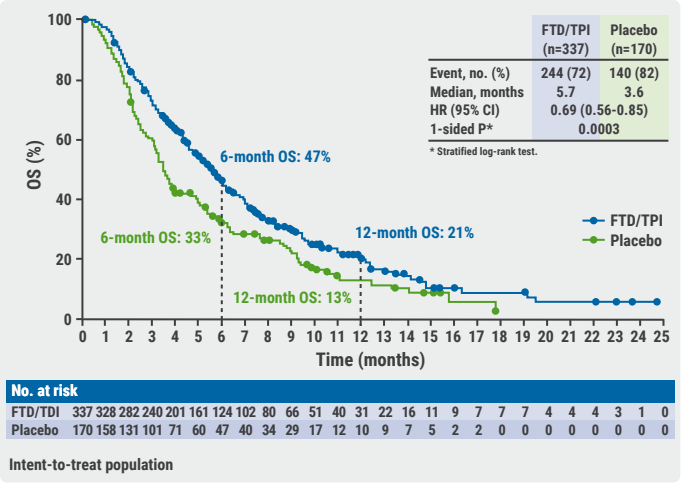
TAGS study shows: Trifluridine/tipiracil improves survival in patients with advanced gastric cancer

As Dr Josep Tabernero (Vall d' Hebron Institute of Oncology, Barcelona, Spain) pointed out, most patients with gastric cancer present with advanced or metastatic disease and have a poor prognosis. Their 5-year overall survival (OS) rate is just 4%. In this context, the presented results of the phase 3 TAGS study are encouraging: treatment with the orally administered combination agent TAS-102 (trifluridine/tipiracil) significantly improved OS in heavily pre-treated patients with metastatic or refractory gastric cancer [1].

Trifluridine/tipiracil is an oral combination therapy that inhibits nucleoside metabolism. Trifluridine is a nucleoside analogue that inhibits thymidylate synthase and is also integrated into DNA. Tipiracil hydrochloride inhibits thymidine phosphorylase, which degrades trifluridine, thus improving bioavailability of the coagent.

Included patients had previously received ≥2 prior treatments regimens for advanced disease. Patients were randomised to receive TAS-102 35 mg/m2 twice daily on days 1 to 5 and 8 to 12 of each 28-day cycle (n=337) or placebo plus best supportive care (n=170) until discontinuation, progression, unacceptable toxicity, or patient withdrawal. With TAS-102, the median OS (primary endpoint of the trial) was 5.7 months compared with 3.6 months for patients receiving best supportive care (HR 0.69; 95% CI 0.56-0.85; P=0.0003). This corresponds to a 31% reduction in risk of death by TAS-102 compared to best supportive care. Twelve-month OS rates were 21.2% in the trifluridine/tipiracil group and 13.0% in the placebo group (Figure 1). In addition, therapy with TAS-102 led to a statistically

Figure 1 Primary endpoint of the TAGS study: Kaplan-Meier analysis of OS [1]



significant increase in progression-free survival (PFS): median PFS was 2.0 months with TAS-102 vs 1.8 months with best supportive care (HR 0.57; 95% CI 0.47-0.70; P<0.0001).

Gastric was the primary cancer site in 71% of included patients, with the remaining having adenocarcinoma of the gastro-oesophageal junction (GEJ); 44% of patients in each treatment arm had received prior gastrectomy. Of the study participants, 63% had received 3 or more prior treatments that included different chemotherapy regimens (including fluoropyrimidine, platinum, irinotecan, taxanes, ramucirumab), and/or immunotherapy.

No new safety signals

Non-haematologic adverse events (AEs) were higher in the TAS-102 arm. Patients suffered most frequently from gastrointestinal symptoms (i.e. vomiting, diarrhoea, nausea, decreased appetite), and fatigue. Grade 3 or higher AEs occurred in 79.4% of treated patients who received TAS-102 and 57.7% of patients in the placebo group. The most common grade 3/4 haematologic laboratory abnormalities were neutropenia, leukopenia, lymphocytopenia, and anaemia. Observed AEs were consistent with those seen previously in patients with metastatic gastric cancer.

Treatment discontinuations due to AEs occurred in 10% of patients in the TAS-102 arm compared with 7% of patients in the best supportive care arm. Treatment-related death rates were low in both groups (0.3% and 0.6%). Taken together, TAS-102 showed a predictable and manageable safety profile.

According to Dr Tabernero, it represents an "effective treatment option for patients with heavily pre-treated metastatic gastric cancer". At present, TAS-102 is already approved for patients with refractory metastatic colorectal cancer (mCRC).

HCC patients with elevated serum alpha-fetoprotein benefit from second-line therapy with ramucirumab

A pooled analysis of the phase 3 trials REACH and REACH-2 showed that treatment with the vascular endothelial growth factor (VEGF) receptor 2 antagonist ramucirumab improves survival of patients with advanced hepatocellular carcinoma (HCC) and elevated serum alpha-fetoprotein (AFP) levels compared to placebo [2]. Both trials had a similar study design and included patients with HCC after prior sorafenib. REACH-2 was designed to confirm the ramucirumab treatment benefit for patients with serum baseline AFP ≥400 ng/ml first observed in the prespecified subgroup of patients in REACH, and therefore only included patients with elevated AFP levels. With the exception of AFP levels, eligibility for both REACH trials was similar. Baseline Barcelona clinic liver cancer staging system (BCLC) stage was C for 86.3% of patients and the majority discontinued prior sorafenib due to progressive disease (87.1%). A total of 41.7% had hepatitis B, 25.6% hepatitis C, and 21% consumed significant amounts of alcohol. Three-fourths of patients had extrahepatic spread (73.2%) and 35.1% had macrovascular invasion. Patients received ramucirumab at 8 mg/kg intravenously every 2 weeks or placebo together with best supportive care. The median serum baseline AFP across all patients in the pooled analysis was 408 ng/ml, and levels were similar between the placebo and ramucirumab arms.

The primary endpoint of the trials was OS. In addition, PFS, objective response rate (ORR), and patient-reported outcomes were assessed. The pooled analysis of patients with AFP ≥400 ng/ml (n=542) showed that therapy with ramucirumab significantly improved median OS (8.1 months vs 5.0 months with placebo), which represented a 30.6% reduction in the risk of death (HR 0.694; 95% CI 0.571-0.842; P=0.0002). In addition, there were distinct benefits in favour of ramucirumab in all secondary endpoints. The median PFS in the pooled analysis was 2.8 months with ramucirumab vs 1.5 months with placebo (HR 0.572; 95% CI 0.472-0.694; P<0.0001). The ORR was 5.4% and 0.9% for ramucirumab and placebo, respectively (P=0.0064). Therapy with ramucirumab led to a disease control rate (DCR; ORR + stable disease of 56.3% vs 37.2% in the placebo group; P<0.0001). As Dr Andrew Zhu (Liver Cancer Research, Massachusetts General Hospital, USA) pointed out, the OS benefit with ramucirumab was consistent and robust across all prespecified subgroups.

Favourable safety profile

Due to study treatment-related AEs, 9.5% of patients on the ramucirumab arm vs 3.6% on placebo discontinued treatment. Hypertension (12.0% ramucirumab vs 3.6% placebo) and hyponatremia (5.1% ramucirumab vs 2.2% placebo) were the only grade ≥3 treatment-emergent AEs occurring in ≥5% in ramucirumab-treated patients. According to Dr Zhu, ramucirumab represents an important new potential treatment option for patients with HCC and elevated AFP, a population associated with poor prognosis and aggressive disease. Ramucirumab was approved in Europe in 2015 across a variety of settings for patients with advanced gastric or GEJ adenocarcinoma, non-small cell lung cancer, and CRC.

Metastatic colorectal cancer: No superiority of atezolizumab combo compared to regorafenib

Patients with chemorefractory mCRC have no benefit from the combination of the PD-L1 inhibitor atezolizumab with the MEK inhibitor cobimetinib. This was the disappointing result of the IMblaze 370 study, a phase 3 trial including 363 patients with mCRC [3]. Atezolizumab inhibits the binding of PD-L1 to its receptors PD-1 and B7.1, leading to the re-invigoration of tumour-specific T-cell immunity. Cobimetinib inhibits MEK1/MEK2 in the mitogen-activated protein kinase (MAPK) pathway, and blocking the MAPK pathway has been shown to favourably alter the tumour microenvironment and T-cell response. The investigators hoped that combining these agents may allow for better immune recognition and generate greater anti-tumour effects than either agent alone in microsatellite stable/microsatellite instability (MSI)-low mCRC, a population with limited treatment options and relatively short survival. Therefore, in the multi-centre, open-label, randomised phase 3 trial IMblaze370, atezolizumab in combination with cobimetinib and atezolizumab monotherapy were compared to standard-of-care regorafenib in patients with previously treated, unresectable locally advanced or mCRC.

A total of 363 patients with mCRC were randomised in a 2:1:1 ratio to atezolizumab plus cobimetinib (n=183), atezolizumab alone (n=90), or single-agent regorafenib (n=90). Most patients were microsatellite stable (89% to 93%). Enrolment of patients with MSI-high status, which typically predicts response to immunotherapy, was limited to 5% of the study population, although the actual enrolment numbers were lower.

No difference in overall survival

The primary endpoint of the study was OS in intention-to-treat (ITT) patients. Median OS with the combination

of atezolizumab and cobimetinib was 8.9 months (95% CI 7.00-10.61) compared to 8.5 months with the multikinase inhibitor regorafenib (HR 1.00; 95% CI 0.73-1.38; P=0.9871). For atezolizumab monotherapy, the median OS was 7.1 months (95% CI 6.05-10.05), with a HR of 1.19 compared with regorafenib (95% CI 0.83-1.71; P=0.3360). In addition, PFS and ORR were similar across treatment arms.

The best ORR was 2.7% for the combination therapy compared to 2.2% in both monotherapy groups. No complete responses were observed. The median duration of response was 11.4, 4.8, and 9.2 months for the combination, atezolizumab monotherapy, and regorafenib, respectively. According to Dr Johanna Bendell (Sarah Cannon Research Institute at Tennessee Oncology, USA), dual inhibition of the PD-L1 immune checkpoint and the MAPK-mediated immune suppression may not be sufficient to generate the immune response that is needed for anti-tumour activity. The combination may be active, but not more active than therapy with regorafenib alone.

No new safety signals

Treatment-related grade 3-4 AEs were reported in 45% of patients who received the combination, 10% who received atezolizumab monotherapy, and 49% who received regorafenib. Treatment-related AEs of any grade with >30% occurrence were diarrhoea (56%), rash (42%), and nausea (32%) with atezolizumab+cobimetinib, none with atezolizumab monotherapy, and palmar-plantar erythrodysesthesia (51%), fatigue (43%), diarrhoea (35%), and decreased appetite (34%) with regorafenib.

Dr Bendell pointed out that the idea of combining immunotherapy and targeted therapies should not be given up, as there are various combinations with newer agents and different targeted agents that might show more promising results and better outcomes for these patients.

No survival benefit of pembrolizumab in gastric/GEJ cancers

In two previous trials, pembrolizumab showed promising anti-tumour activity and a manageable safety profile in patients with advanced or metastatic gastric or GEJ cancer. Therefore, the results of the KEYNOTE-061 study were disappointing: in this trial, patients with previously treated advanced gastric/GEJ cancer with a PD-L1 combined positive score (CPS) ≥ 1 did not benefit from therapy with pembrolizumab [4]. In the trial, 592 patients with metastatic or locally advanced and unresectable gastric or GEJ cancer who had received first-line systemic therapy were randomised 1:1 to receive pembrolizumab at 200 mg every 3 weeks or paclitaxel at 80 mg/m^2 on days 1, 8, and 15 of 4-week cycles.

At a median follow-up of 7.9 months, the median OS was 9.1 months (95% CI 6.2-10.7) in patients treated with pembrolizumab with positive PD-L1 expression and 8.3 months (95% CI 7.6-9.0) with paclitaxel. This translates into a statistically non-significant 18% reduction in the risk for death with pembrolizumab (HR 0.82; 95% CI 0.66-1.03).

Additionally, the median OS for patients with PD-L1 CPS <1 with pembrolizumab was 4.8 months (95% CI 3.9-6.1), compared with 8.2 months (95% CI 6.8-10.6) with paclitaxel. Patients with a PD-L1 CPS ≥10 treated with pembrolizumab experienced a median OS of 10.4 months (95% CI 5.9-17.3) compared with 8.0 months (95% CI 5.1-9.9) with paclitaxel.

The pembrolizumab treatment effect for OS was more evident in patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 (median OS 12.3 vs 9.3 months; HR 0.69; 95% CI 0.49-0.97), in patients with PD-L1 CPS ≥10 (median OS 10.4 vs 8.0 months; HR 0.64; 95% CI 0.41-1.02), and MSI-high tumours (median OS not reached vs 8.1 months; HR 0.42; 95% CI 0.13-1.31).

There was no improvement in PFS (median 1.5 months with pembrolizumab vs 4.1 months with paclitaxel; HR 1.27; 95% CI 1.03-1.57), in fact pembrolizumab was associated with inferior PFS, or ORR (15.8% vs 13.6%), but pembrolizumab responses were more durable (median 18.0 months vs 5.2 months; duration ≥12 months 59.5% vs 29.5%). Pembrolizumab had a better safety profile than paclitaxel. Incidence of grade 3-5 drug-related AEs was 14.3% with pembrolizumab vs 34.8% with paclitaxel.

As Dr Kohei Shitara (National Cancer Center Hospital East, Kashiwa, Japan) pointed out, a benefit of pembrolizumab emerged with long-term follow up. Therefore, current data supports further exploration to identify patients likely to benefit from pembrolizumab monotherapy and ongoing development of pembrolizumab-based combination therapy. Still, until further evidence, the present study results do not provide a role for pembrolizumab in gastric/GEJ tumours.

Folfirinox also successful in adjuvant setting in patients with resected pancreatic ductal adenocarcinomas

The results of the phase 3 Unicancer GI PRODIGE 24/CCTG PA.6 trial were first presented at the 2018 ASCO Annual Meeting, but due to its practice-changing results intensively discussed in a session during the ESMO GI meeting [5,6]. In this trial, adjuvant treatment with modified FOLFIRINOX,

resulted in the longest OS ever reported for patients with resected pancreatic cancer.

PRODIGE 24/CCTG PA.6 was a phase 3, multicentre, French-based study involving 493 fit patients with potentially resectable pancreatic cancers. The study aimed to evaluate modified FOLFIRINOX (oxaliplatin at 85 mg/m^2, leucovorin at 400 mg/m^2, irinotecan at 150 mg/m^2 on day 1, plus 5-FU at 2.4 g/m^2 over 46 hours) vs gemcitabine.

After a median follow-up of 30.5 months, multiple outcomes were significantly improved with modified FOLFIRINOX vs gemcitabine. Median disease-free survival was 12.8 months in the gemcitabine arm vs 21.6 months in the modified FOLFIRINOX arm (primary endpoint), and median OS was 35.0 months vs 54.4 months, respectively. The use of modified FOLFIRINOX resulted in an additional 15% of patients being alive without pancreatic cancer after 3 years. As expected, this tremendous treatment benefit comes at a high price regarding tolerability: grade 3/4 adverse events were reported for 51.5% of the gemcitabine arm vs 75.5% of the modified FOLFIRINOX arm, including grade 4 events in 12% of each arm, with 1 toxic death in the gemcitabine arm. The three most common grade 3/4 toxicities included diarrhoea (18.6% vs 3.7%; P<0.001), fatigue (11.0% vs 4.6%; P=0.014), and sensory peripheral neuropathy (9.3% vs 0%; P<0.001).

References

1 Tabernero J et al. Abstract No. LBA-002, ESMO GI, 20-23 June, 2018.
2 Zhu A et al. Abstract No. LBA-001, ESMO GI, 20-23 June, 2018.
3 Bendell JC et al. Abstract No. LBA-004, ESMO GI, 20-23 June, 2018.
4 Shitara K et al. Abstract No. LBA-005, ESMO GI, 20-23 June, 2018.
5 Conroy T et al. Abstract No. LBA4001, ASCO, 1-5 June, 2018.
6 Conroy T, ESMO GI, 20 June, 2018.

What is New in Metastatic Colorectal Cancer?

Colorectal cancer is a leading cause of death both in Europe and worldwide [1,2]. During the previous decade, the clinical outcome for patients with mCRC has improved significantly. Today, the median OS for patients with mCRC being treated both in phase 3 trials and in large observational series or registries is ~30 months, which is more than double that of 20 years ago [3]. During the ESMO GI meeting, promising new regimens for first-line treatment as well as for intensively pre-treated patients were presented.

First-line treatment is a crucial starting point in the therapeutic route of every mCRC patient [4]. The strategic value of this choice lies in the importance of obtaining disease control, preventing disease progression and achieving symptoms' relief. Prof. David Cunningham (The Royal Marsden Hospital & Institute of Cancer Research London and Surrey, UK), discussed three abstracts presented during the meeting that might be practice changing in this patient population [5].

TASCO1 trial: Patients benefit from TAS-102 bevacizumab combination

Trifluridine/tipiracil, as compared with placebo, has been associated with a significant improvement in OS in patients with refractory colorectal cancer [6]. For patients with previously untreated mCRC who are not eligible for treatment with standard chemotherapy or surgical resection, treatment with trifluridine/tipiracil (TAS-102) combined with bevacizumab could be an interesting novel treatment option. However, this combination did not significantly improve PFS compared to capecitabine plus bevacizumab in the TASCO1 trial [7].

In this randomised, global, non-comparative phase 2 study patients with unresectable mCRC who were not considered fit enough for intensive oxaliplatin-based or irinotecan-based chemotherapy or a curative resection were included. They were randomised 1:1 to the novel combination (trifluridine/tipiracil 35 mg/m^2 given orally twice-daily on days 1–5 and 8–12 in a 28-day cycle) plus bevacizumab (5 mg/kg on

days 1 and 15 of a 28-day treatment cycle) or capecitabine (1250 or 1000 mg/m²/dose twice-daily on days 1-14 in a 21-day cycle) plus bevacizumab (7.5 mg/kg on day 1 in a 21-day treatment cycle). According to Prof. Cunningham, the latter combination was chosen, because it proved to be an effective and well tolerated regimen in elderly mCRC patients in the AVEX study [8].

In the TASCO1 trial, median PFS (primary endpoint) was 9.23 months (95% CI 7.59-11.56) with trifluridine/tipiracil plus bevacizumab compared to 7.82 months (95% CI 5.55-10.15) in patients receiving capecitabine plus bevacizumab (HR 0.71; 95% CI 0.48-1.06). The effect of the novel combination on PFS was consistent across most predefined subgroups (subgroups under analysis included RAS or BRAF mutation status, ECOG performance status, gender, and neutrophil vs lymphocyte count). OS data are not yet mature. The incidence of any treatment-emergent AEs or any serious event was similar with both treatments. However, the incidence of grade ≥3 AEs was higher with trifluridine/tipiracil at 77.9% vs 43.4% in the capecitabine arm. The opportunity to conduct a global confirmatory phase 3 trial comparing the trifluridine/tipiracil and bevacizumab combination to capecitabine and bevacizumab is currently being evaluated.

Triplet chemotherapy for mCRC patients with synchronous metastases: An option for cytoreduction

The FOLFOXIRI/bevacizumab combination has shown superiority in first-line compared to FOLFIRI/bevacizumab (TRIBE trial) [9]. Now, the CHARTA trial (n=250) compared induction therapy with FOLFOX and bevacizumab vs FOLFOXIRI and bevacizumab followed by maintenance with capecitabine and bevacizumab, in patients with previously untreated mCRC [10]. Prof. Cunningham pointed out that there was no significant difference in PFS between the 2 treatment groups (median 9.8 vs 12 months; HR 0.7), similar to the TRIBE trial (9.7 vs 12.1 months). In the subgroup analysis, patients with synchronous metastases (n=211, 91%), however, showed a PFS benefit from triple chemotherapy (PFS 27.96 vs 22.51; HR 0.74; 95% CI 0.55-1.01; P=0.054). The strongest improvement with the triplet combination was seen in patients with synchronous metastases, who had not undergone resection of the primary tumour (52% of patients; 17.0 vs 26.5 months; HR 0.64; 95% CI 0.42-0.96; P=0.028).

In addition, the study might have been underpowered to show a statistical effect. The evaluated combination therapy showed tolerable toxicity without major differences except for grade 3 and 4 diarrhoea (12%/16%) and neutrophils (14%/20%). This study hints at efficacy of triplet/bevacizumab therapy for patients with adverse biology mCRC and for cytoreduction.

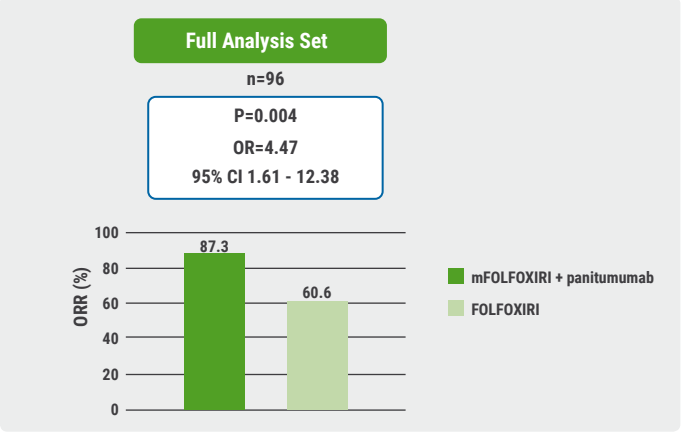
VOLFI trial: Addition of an EGFR-inhibitor significantly improves objective response rate

Another way to improve treatment results in previously untreated mCRC patients is the addition of a blocking epidermal growth factor (EGFR) receptor antibody. In the VOLFI trial, addition of panitumumab led to a significantly improved ORR 11].

Triple chemotherapy with panitumumab has demonstrated promising activity with some safety concerns (i.e. skin rash, fatigue, nausea, diarrhoea, fever, and decreased magnesium levels) in single arm phase 2 trials. Therefore, the VOLFI trial evaluated activity and safety of mFOLFOXIRI + panitumumab vs FOLFOXIRI in ECOG performance status 0-1, primarily non-resectable mCRC patients with RAS wild-type tumours. Cohort 1 included patients with definitely inoperable or unresectable mCRC, whereas cohort 2 included patients with a chance of secondary resection with curative intent. All patients were randomised 2:1 to receive a modified FOLFOXIRI regimen and the EGFR inhibitor panitumumab or the FOLOFOXIRI regimen alone. Treatment was performed until disease progression, resectability, or to a maximum of 12 cycles. Primary endpoint was ORR, secondary endpoints were PFS, OS, disease control rate (DCR), duration of response, quality of life (QoL), secondary resection rate of metastases, pathological response, and liver toxicity (cohort 2).

In this study the primary endpoint was met and the response rate to FOLFOXIRI was increased by the addition of panitumumab from 60.6 to 87.3% (P=0.004; Figure 2). Surprisingly, in BRAF mutant tumours, which are typically regarded as being resistant to EGFR inhibitors, the ORR was

Figure 2 VOLFI trial: Primary endpoint objective response rate (ORR) [11]



increased from 22.2 to 85.7%, but the total number of patients was small (n=16). Unfortunately, no improvement in PFS was seen in patients treated with FOLFOXIRI and panitumumab. OS data are immature.

Treatment-related serious AEs grade 3-5 occurred in 32.8% of the panitumumab group and 12.1% of the control arm, respectively (P=0.0297). The addition of the EGFR inhibitor led to an increase of grade 3 and 4 diarrhoea from 12 to 25%. There was also increased skin toxicity. Nevertheless, no differences in global health status, functional scales, and symptom scales were reported.

The impact on secondary resection from 36.4 to 75% in patients of cohort 2 was notable but failed to reach statistical significance (P=0.056).

According to the presenter, the positive response in BRAF mutant tumours might be considered as an approach in these cases where downsizing for surgery is a clinical objective. Prof. Cunningham indicated that a meta-analysis of triplets vs doublets may provide more insight, as both VOLFI and CHARTA study were underpowered.

Heavily pre-treated mCRC: More possibilities on the horizon

In a lecture on late treatments in mCRC, Prof. Roberto Labianca (Cancer Center Ospedale Giovanni XXIII, Bergamo, Italy) gave an overview of the perspectives of intensively pre-treated mCRC patients [12]. At present, data from a US population show that only 53% of patients undergo second-line therapy and 28% undergo third-line therapy [13]. In the FIRE-3 cohort, 69.9% of mCRC patients received a second-line and only 43% a third-line therapy [14].

Treatment sequences depend primarily on the type of the tumour (Table 1). Two options for late treatment appear (indirectly) equally effective: trifluridine/tipiracil (TAS-102) and regorafenib. However, TAS-102 seems to have a more acceptable and manageable safety profile. Both agents have recently demonstrated statistically significant survival gains in patients with refractory mCRC [15,16]. The optimal sequence of those two therapies is likely to emerge as an important topic. It should be noted that life expectancy ≥12 weeks was an inclusion criterion in some registrative trials. Therefore, identification of proper clinical selection tools for the use of these drugs is needed. Last year, a trial was published with the aim to build a nomogram for predicting the probability of death within 12 weeks from the date of assessment of refractory mCRC [17]. Four "easy to collect" variables (ECOG status [P<0.0001], LDH value [P=0.0001], primary tumour resection [P=0.027], and peritoneal involvement [P=0.081]) were included in the model. According to the authors, this nomogram is a useful tool to predict the probability of death within 12 weeks and may improve mCRC patients' selection for later-line therapies

A direct comparison between the two drugs could be matter of a clinical trial or, alternatively, by making a choice according to patient characteristics and/or preference, said Prof. Labianca.

A couple of trials during the meeting dealt with how to treat this patient population in daily practice. According to Prof. Labianca, for regorafenib, dose is an issue and an escalating approach appears feasible and useful, as could be shown in the dose escalation arm of the ReDOS study [18].

Table 1 A look at the global strategy of mCRC patients. Adapted from Labianca 2018 [12] according to comments from G Pent.

	RAS/BRAF wild-type tumours	RAS mutated	BRAF mutated
First-line	• FOLFOXIRI/ bevacizumab • FOLFIRI-FOLFOX/ bevacizumab • FOLFIRI/cetuximab • FOLFOX-FOLFIRI/ panitumumab	• FOLFOXIRI/ bevacizumab • FOLFIRI-FOLFOX/ bevacizumab	• FOLFOXIRI/ bevacizumab
Second-line	• FOLFIRI-FOLFOX/ bevacizumab • FOLFIRI/aflibercept • FOLFIRI-FOLFOX/ cetuximab-panitumumab • FOLFIRI/ramucirumab (after bevacizumab exposure)	• FOLFIRI/bevacizumab • FOLFIRI/aflibercept • FOLFIRI/ramucirumab (after bevacizumab exposure)	• FOLFIRI/aflibercept • FOLFIRI/ramucirumab (after bevacizumab exposure) • FOLFOXIRI/ bevacizumab
Third-line	• Trifluridine-tipiracil • Regorafenib	• Trifluridine-tipiracil • Regorafenib	• Trifluridine-tipiracil • Regorafenib

Regorafenib titration regime improves tolerability in pre-treated mCRC

A higher percentage of patients with mCRC were able to continue receiving the most effective dose of regorafenib with a dose escalation regimen. This was the most important result of the dose escalation arm of the ReDOS study [18]. Regorafenib confers a survival benefit in refractory mCRC patients. However, toxicities such as palmar-plantar erythrodysesthesia syndrome (PPES) and fatigue have limited its use. These treatment-emergent AEs are usually observed within the first 2 to 3 weeks of treatment.

Patients in the dose escalation arm (n=54) received regorafenib 80 mg during week 1, followed by regorafenib 120 mg during week 2, and 160 mg in week 3. Patients in the control arm (n=62) received regorafenib 160 mg for all 3 weeks. The study met its primary endpoint as 43% of patients were able to proceed to the third cycle of therapy with the escalation regimen, compared with only 24% of patients in the control arm (P=0.0281). Most common reason for not initiating cycle 3 was progressive disease (35% in the dose

escalation arm vs 47% in the control arm). Median OS was improved in the dose escalation arm (9.0 months vs 5.9 months in the control; P=0.094). Median PFS in the escalation arm was 2.5 months compared with 2.0 months in the control arm (HR 0.89; P=0.5534). Median OS was longest among patients who were able to initiate the third cycle treatments (11.0 months in the escalation group and 12.4 months in the control group). Patients in the escalation arm had lower rates of fatigue and hypertension than controls during cycle 1, and also had less grade 2/3 PPES during cycles 1 and 2. (28% vs 35% in cycle 1 and 13% vs 34% in cycle 2, respectively). In addition, multiple QoL parameters were favourable in the dose-escalation arm compared to the controls. According to first author Dr Tanios Bekaii-Saab (Mayo Clinic, Phoenix, USA) these results conceivably establish a new standard for optimising regorafenib dosing through dose escalation.

TAS-102 also effective in a real-world study

The 3b open-label PRECONNECT study evaluated the safety and efficacy of trifluridine/tipiracil in a real-world treatment setting for patients with mCRC [19]. All included patients had histologically confirmed mCRC, an ECOG performance status of 0 or 1, and were previously treated with or not considered candidates for available therapies. A study cohort of 462 patients from 10 countries had received at least one dose of treatment at cut-off. Emergent AEs were reported in 92.4%. Drug-related AEs were reported in 74.5%; most common were neutropenia, nausea, and diarrhoea, which occurred in 49.5%, 27.7%, and 20.6% of patients, respectively. Drug-related grade ≥3 AEs were reported in 48.6%; most common haematological were neutropenia (38%), anaemia (7.1%), febrile neutropenia (1.7%), and thrombocytopenia (1.3%), while most common non-haematological were diarrhoea (3.5%) and fatigue (2.2%). Trifluridine/tipiracil was associated with a median PFS of 3.2 months (95% CI 2.8–3.4) and DCR of 41.1% (95% CI 36.3–46.0) in the 414 patients who received treatment and had at least 1 post-baseline tumour evaluation. Median time to ECOG status ≥2 was 8.7 months. At cut-off time, 91.3% were still alive and, thus, median OS was not yet reached. These preliminary data on the widespread clinical use are encouraging regarding safety and efficacy and show that TAS-102 is a favourable treatment option for mCRC patients.

Better one-year survival with triple combination in BRAF-mutated CRC

An update of the safety lead-in of the phase 2-study BEACON CRC showed that patients with BRAFV600E mutated mCRC benefit from the triplet combination of encorafenib (a BRAF inhibitor), binimetinib (a MEK inhibitor), and cetuximab (an anti-EGFR antibody) [20]. Patients with this mutation, which occurs in 10%-15% of all patients with mCRC, are in urgent need of more effective therapies, as they have a poor prognosis. After failure of first-line approaches, standard therapies in such patients provide limited benefits, with ORRs <10%, PFS of about 2 months, and OS of 4–6 months [21,22]. The risk of mortality in CRC patients with the BRAFV600E mutation is more than two times higher than for those with wild-type BRAF [23]. BEACON CRC (NCT02928224) is an ongoing phase 2 trial with a primary endpoint of OS for the triple combination, and during ESMO GI the results of the safety lead-in were presented. Current data reflect patient study drug exposure of up to 11.9 months (median: 7.8). At this time, the OS data were fully mature through 12.6 months and the median OS had not yet been reached. The one-year OS rate for this cohort was 62%. The confirmed ORR was 48%, including complete response in 3 of 29 patients. The median PFS for patients treated with the triplet was 8 months (95% CI 5.6-9.3) and was similar between patients receiving one prior line of therapy and patients receiving two prior lines of therapy.

No unexpected toxicities

The treatment was generally well-tolerated with no unexpected toxicities. The most common grade 3 or 4 AEs seen in at least 10% of patients were fatigue (13%), urinary tract infection (10%), anaemia (10%), increased blood creatine phosphokinase (10%), and increased aspartate aminotransferase (10%). Dr Axel Grothey (Division of Hematology/Oncology, Mayo Clinic, Rochester, USA) stated that the results of the BEACON CRC safety lead-in demonstrate substantial improvements in efficacy outcomes when compared to current approved standard of care benchmarks in patients with BRAF-mutant mCRC. The median PFS of 8 months is a meaningful improvement compared to the benchmark of about 2 months, and the OS of 62% at 12 months is very promising given that with current approved standards of care, half of patients will succumb to their disease within 4 to 6 months. The phase 3 portion of the BEACON CRC trial has now been initiated with enrolment ongoing. The presentation also referenced updated, mature phase 2 results for the doublet of encorafenib and cetuximab that showed a median OS of 9.3 months, median PFS of 4.2 months, and an ORR of 24%.

CORRELATE trial shows: Regorafenib also effective in a real-world scenario

In the phase 3 trials CORRECT and CONCUR, regorafenib significantly improved OS vs placebo in patients with mCRC

who progressed on standard therapies [24,25]. However, the safety and efficacy of regorafenib might be different in a real-world scenario. The aim of the CORRELATE trial was to assess these parameters in daily practice conditions [26]. This prospective, observational study was conducted in 13 countries across Europe, Latin America, and Asia and recruited patients with mCRC who had previously been treated with approved therapies, and for whom the decision to treat with regorafenib was made by the treating physician prior to enrolment. Primary study endpoint was the incidence of treatment-emergent AEs. Secondary endpoints included OS, PFS, and DCR. Dose interruptions and reductions were permitted in case of AEs.

A total of 1037 patients could be included in this study. Of those patients, 56% had KRAS mutations. The most common metastatic sites were the liver (72%) and the lungs (57%). Overall, 40% of patients had dose reductions, 48% an interruption/delay and in 35% of patients no dose modifications were necessary.

Lower incidence of some AEs

Treatment-emergent AEs of any grade occurred in 95% of patients and were considered regorafenib-related in 80% of patients. Grade ≥3 AEs occurred in 62% of patients, and in 36% of patients they were attributed to regorafenib. The most common grade ≥3 AEs were fatigue (10%), hypertension (8%), and hand–foot skin reaction (7%). As the authors pointed out, in this real-world study AEs were generally consistent with the known safety profile of regorafenib, although reported incidence rates of some AEs were lower compared to clinical trials. Median OS was 7.6 months (95% CI 7.1–8.2) and median PFS was 2.8 months (95% CI 2.6–2.8). Again, these efficacy endpoints are in line with those observed in the phase 3 trials. Of note, only 57% of patients were treated with the initial daily regorafenib dose of 160 mg/day, which means that almost half of patients cannot tolerate the usual starting dose.

PD-L1-inhibition – also an option for mCRC patients?

The advent of immunotherapies—in particular, checkpoint inhibitors—has opened a potential new avenue of treatment. As with other targeted approaches, previous trials have shown that patients with defective DNA mismatch repair system/MSI-high are more responsive to immunotherapy [27]. During the meeting, data from cohort B of the KEYNOTE-164 trial was presented, demonstrating durable anti-tumour activity and a manageable safety profile. This trial was conducted to evaluate the checkpoint inhibitor pembrolizumab in an MSI-high patient population. All enrolled patients had MSI-high CRC and were previously treated with ≥1 line of therapy. Patients received pembrolizumab 200 mg every 3 weeks for 2 years or until progression, unacceptable toxicity, or withdrawal of consent. Endpoints included ORR (primary endpoint), PFS, OS, and safety (secondary). After a median follow-up of 12.6 months (range 0.1-15.4) ORR was 32% (95% CI 21-45), with 2 complete responses and 18 partial responses. Median PFS was 4.1 months (95% CI 2.1-not reached) and median OS was not reached. The 12-month PFS rate was 41% and the 12-month OS rate was 76%. 64% of patients experienced treatment-emergent AEs of any grade, most commonly fatigue (18%), hypothyroidism (16%), and hyperthyroidism (11%). 32% of patients had immune-mediated AEs of any grade. Grade ≥3 immune-mediated AEs of pneumonitis and colitis were observed in 1 patient each.

References:

1 Ferlay J et al. Eur J Cancer 2013;39:1374-1303.
2 Ferlay J et al. Int J Cancer 2015;136: E359-86.
3 Van Cutsem E et al. Annals of Oncol 2016;27:1386-1422.
4 Cremolini C et al. Nat Rev Clin Oncol 2015;12: 607-19.
5 Cunningham D. Lecture during ESMO GI, 20-23 June, 2018.
6 Mayer RJ et al. New Engl J Med 2015;372:1909-19.
7 Lesniewski-Kmak K et al. Abstract No. O-022, ESMO GI, 20-23 June, 2018.
8 Cunningham D et al. Lancet Oncol 2013;14:1077-1085.
9 Loupakis F et al New Engl J Med. 2014;371:1609–18.
10 Schmoll HJ et al. Abstract No. O-023, ESMO GI, 20-23 June, 2018.
11 Geissler M et al. Abstract No. O-024, ESMO GI, 20-23 June, 2018.
12 Labianca R. Lecture during ESMO GI, 20-23 June, 2018.
13 Abrams TA et al. J Natl Cancer Inst 2014;106:djt371.
14 Modest DP et al. J Clin Oncol 2015;33:3718-26.
15 Mayer RJ et al. New Engl J Med 2015;372:1909-19.
16 Grothey A et al. Lancet 2013;381:303-12.
17 Pietrantonio F et al. Ann Oncol 2017;28:555-61.
18 Bekaii-Saab T et al. Abstract No. O-014, ESMO GI, 20-23 June, 2018.
19 Falcone A et al. Abstract No. O-013, ESMO GI, 20-23 June, 2018.
20 Van Cutsem E et al. Abstract No. O-027, ESMO GI, 20-23 June, 2018.
21 Ulivi P et al. J Transl Med 2012;10:87. doi: 10.1186/1479-5876-10-87.
22 Saridaki Z et al. PLoS One 2013;8:e84604.
23 Safaee Ardekani G et al. PLoS One 2012;7:e47054.
24 Grothey A et al. Lancet 2013;381:303-12.
25 Li J et al. Lancet Oncol 2015;16:619-29.
26 Ducreux M et al. Abstract No. O-012, ESMO GI, 20-23 June, 2018.
27 Birendra KC et al. AJHO 2017;13:4-8.

Liquid Biopsy: A Novel Tool to Monitor and Guide Therapy

The broad clinical potential of circulating DNA has attracted increasing focus over the past decade. In mCRC, a tumour entity that is characterised by many clinically relevant genetic alterations, liquid biopsy has emerged as an excellent molecular diagnostic tool for assessing predominant spatial and temporal intratumoural heterogeneity with minimal invasiveness. Liquid biopsies have shown to be useful to guide therapy, to identify patients at risk for recurrence, and to monitor patients for acquired resistance in mCRC patients. They are most useful when tumour tissue is unavailable or insufficient for testing.

Tumour tissue sampling is currently the gold standard for diagnosing gastrointestinal cancers, but also for genomic/immune component analyses that can help in the selection of therapy [1]. However, this approach of studying a 'representative' sample of the tumour does not address inherent heterogeneity. This disadvantage could be overcome by so-called liquid biopsies. As Prof. Fortunato Ciardiello (Universitá degli Studi della Campania Luigi Vanvitelli, Naples, Italy) pointed out in his lecture, the term liquid biopsy refers to the possibility to perform tumour molecular profiling by using tumour-derived biomarkers that can be isolated from the peripheral blood or any other body fluid of cancer patients [2]. For example, tumour-specific genomic alterations can be identified in the circulating cell-free DNA (cfDNA). However, there are a couple of challenges in cfDNA analysis. The absolute levels are low, in the range of few nanograms per ml of plasma, and highly sensitive methods are therefore required for the detection of biomarkers in the cfDNA. Also, the cfDNA contains both tumour-derived DNA (ctDNA) and normal DNA originating from dividing cells (e.g. blood cells, gastrointestinal tract, and skin cells) making ctDNA only a fraction (<0.1-50%) of the total cfDNA. Levels are usually correlated with tumour burden and are higher in advanced cancer.

Furthermore, cfDNA has a short half-life of about 2 hours. These limitations offer challenges for routine implementation of liquid biopsy tests, which necessitates specialised personnel, instrumentation, and software, as well as further development of quality management. However, there is a potential for cost savings when this method allows avoiding or halting the ineffective use of expensive new anticancer drugs; serial genomic profiling can detect resistance mutations up to 16 weeks before radiographic progression.

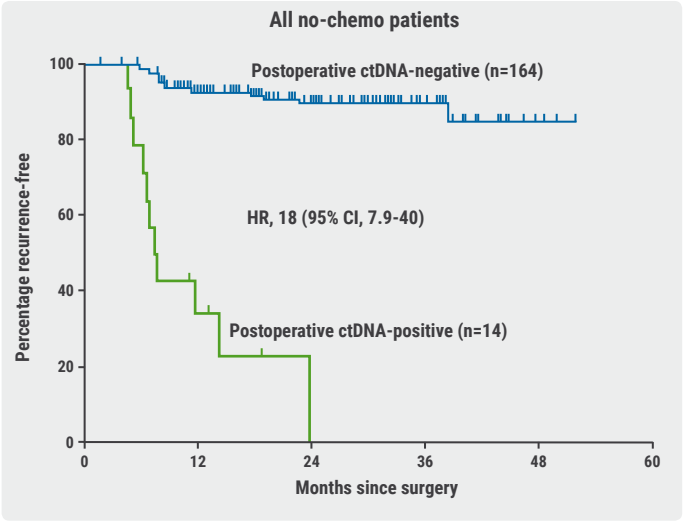
Important role in early and advanced CRC

Colorectal tumours are characterised by a high frequency of well known, clinically relevant genetic alterations, which can be readily detected in the cfDNA. This approach holds potential for tailoring palliative therapy and for monitoring during treatment [3]. Prof. Cardiello pointed out that liquid biopsy might therefore have a relevant role in the management of CRC patients.

Possible applications of cfDNA analysis are early diagnosis of cancer, detection of minimal residual disease, molecular profiling (identification of prognostic and predictive markers), and monitoring response to therapy. Genomic/immune profiling is also useful for selection of appropriate therapy and to track resistance. For example, it is known that early detection of recurrence during follow-up may be associated with improved survival in patients with early-stage colorectal cancer, provided curative salvage therapy is administered [4]. A prospective biomarker trial showed that cfDNA analysis is indeed a valuable tool to detect minimal residual disease and predict recurrence in patients with stage 2 colon cancer [5].

In this trial, ctDNA was analysed in 1046 plasma samples from a prospective cohort of 230 patients. Blood was collected at 4-10 weeks postoperatively in a subset of patients (n=167) 3-monthly serial blood collection up to 2 years were performed. ctDNA was detected postoperatively in 14 of 178 (7.9%) patients not treated with adjuvant chemotherapy. Detection of ctDNA increased the risk of recurrence 18-fold and 11 patients (79%) recurred at a median follow-up of 27 months. In contrast, recurrence occurred in only 16 (9.8 %) of remaining 164 patients with negative ctDNA (HR 18; 95% CI 7.9 to 40; P<0.001; Figure 3). In patients treated with adjuvant chemotherapy, the detection of ctDNA after completion of

Figure 3 Risk of recurrence after resection in patients according to postoperative ctDNA status [5]



chemotherapy was associated with an 11–fold increased risk of recurrence (HR 11; 95% CI 1.8 to 68; P=0.001).

Liquid biopsy: An alternative to tissue-based RAS testing

Other trials have determined the level of concordance between plasma and tissue RAS mutation status in patients with mCRC [6,7]. These trials showed high agreement between plasma RAS determination and tumour-based detection of RAS, which indicates that blood-based RAS testing could be used to guide anti-EGFR therapy. cfDNA analysis can also be a valuable tool in monitoring response to therapy in mCRC patients. This was shown by a prospective study involving 53 mCRC patients who received standard first-line chemotherapy [8].

ctDNA was assessed in plasma by massively parallel sequencing-based assay that permits the detection of low-frequency mutations. Samples were collected before treatment, 3 days after treatment, and before cycle 2. Tumours were sequenced using a panel of 15 genes frequently mutated in mCRC to identify candidate mutations for ctDNA analysis. For each patient, one tumour mutation was selected to assess the presence and the level of ctDNA in plasma samples using a digital genomic assay. CT scans were carried out at baseline and at 8–10 weeks and were centrally assessed using RECIST v1.1 criteria. Significant reductions in ctDNA levels (median 5.7-fold; P<0.001) were observed before cycle 2, which correlated with positive CT responses at 8–10 weeks (OR 5.25 with a 10-fold ctDNA reduction; P=0.016). Major reductions (≥10-fold) vs lesser reductions in ctDNA precycle 2 were associated with a trend for increased PFS (median 14.7 vs 8.1 months; HR 1.87; P=0.266). Therefore, the authors concluded that early changes in ctDNA during first-line chemotherapy predicted the later radiologic response.

Liquid biopsy: A method to track EGFR resistance

A potential future application of liquid biopsies is the monitoring for resistance [9]. Cetuximab, a monoclonal antibody that binds to EGFR, is effective in a subset of KRAS wild-type mCRC. After an initial response, secondary resistance invariably ensues, thereby limiting the clinical benefit of this drug. Analysis of metastases from patients who developed resistance to cetuximab or panitumumab showed the emergence of KRAS amplification in one sample and acquisition of secondary KRAS mutations in 60% (6 out of 10) of the cases. KRAS mutant alleles were detectable in the blood of patients as early as 10 months before radiographic progression of disease. Early detection of EGFR resistance could enable early addition of alternate targeted therapeutics such as addition of a MEK inhibitor with the goal to delay or reverse drug resistance.

Prof. Ciardiello concluded that the analysis of cfDNA reveals high levels of tumour heterogeneity and prospective clinical trials are needed to translate this information in more effective therapeutic strategies.

Liquid biopsy to identify patients that benefit from rechallenge therapy

The prospective CRICKET trial presented during the ESMO GI meeting showed that liquid biopsies are a valuable tool to identify patients more likely to benefit from a rechallenge with cetuximab and irinotecan as third-line treatment in RAS/BRAF wild-type mCRC patients with acquired resistance to first-line cetuximab and irinotecan-based therapy [10]. Included patients had received prior first-line irinotecan-based, cetuximab-containing regimen with at least RECIST partial response, first-line PFS ≥6 months, and progression within 4 weeks after the last cetuximab dose was given. As a second-line therapy, they received oxaliplatin-based and bevacizumab-based treatment. Liquid biopsies were collected at the rechallenge baseline. ctDNA was analysed for specific RAS/BRAF mutations with digital PCR, and then by ultra-deep, next-generation sequencing. Patients were treated with third-line cetuximab and irinotecan-based therapy until progression of disease.

A total of 28 patients received the rechallenge therapy. 6 patients gained a partial response, and 9 disease stabilisations.

RAS mutations were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable patients. No RAS mutations were detected in samples from patients who achieved a confirmed partial response. Patients with RAS wild-type ctDNA had significantly longer PFS than those with RAS mutant ctDNA (median 3.9 vs 1.9 months; HR 0.48; 95%CI 0.20-0.98; P=0.048).

The CRICKET trial is the first prospective demonstration of the activity of rechallenge with cetuximab and irinotecan in mCRC patients initially sensitive and then resistant to first-line cetuximab and irinotecan-based therapy, with no RAS/BRAF mutations in pre-treatment liquid biopsies.

References

1 Lopez A et al. Expert Rev Anticancer Ther 2018;18:19-38.
2 Ciardiello F, Lecture during ESMO GI, 20-23 June, 2018.
3 Spindler KL G. Acta Oncologica 2017;56:7-16.
4 Pita-Fernàndez S et al. Ann Oncol 2015;26:644–56.
5 Tie J et al. Sci Transl Med 2016;8:346ra92.
6 Schmiegel W et al. Mol oncol 2017;11:208-19.
7 Grasselli J et al. Ann Oncol 2017;28:1294-1301.
8 Tie J et al. Ann Oncol 2015;26:1715-22.
9 Misale S et al. Nature 2012;486: 532-6.
10 Rossini D et al. Abstract No. O-007, ESMO GI, 20-23 June, 2018.

Advanced Hepatocellular Carcinoma: What is New?

Despite improvement in screening and diagnosis of hepatocellular carcinoma (HCC), advanced stage remains the most common presentation at diagnosis, with limited management options [1]. However, in contrast to the previous decade, there have been several advances in the past 1.5 years [2]. Two studies presented during the ESMO GI meeting gave another glimpse of hope – at least for certain subgroups of HCC patients. For some patients, selective internal radiation seems to be a valuable method to enhance efficacy of sorafenib. In addition, the tyrosine kinase inhibitor cabozantinib leads to a distinct reduction of large lesion size in intensively pre-treated patients with HCC.

Regorafenib emerges as a valuable second-line treatment

A breakthrough were the results from the RESORCE study that showed that therapy with regorafenib provided a survival benefit in HCC patients progressing on sorafenib treatment [3]. In this phase 3 trial, 573 HCC patients who tolerated sorafenib, progressed on sorafenib, and had Child-Pugh A liver function were enrolled. They were randomised to receive either best supportive care and regorafenib or best supportive care and placebo. The primary endpoint of this trial was OS.

Regorafenib improved OS (primary endpoint; HR 0.63; 95% CI 0.50-0.79; one-sided P<0.0001). Treatment with regorafenib was associated with a median OS of 10.6 months compared with a 7.8-month median OS for placebo. All patients in the regorafenib group and 93% of patients in the placebo group suffered from side effects. The most common clinically relevant grade 3 or 4 AEs during treatment with regorafenib were hypertension, hand-foot skin reaction, fatigue, and diarrhoea.

The results of the RESORCE trial has led to FDA approval of regorafenib as second-line treatment for patients with HCC who have previously received sorafenib. Regorafenib is the only systemic treatment shown to provide survival benefit in HCC patients progressing on sorafenib treatment. Future trials will also explore combinations of regorafenib with other systemic agents in this clinical setting.

Lenvatinib: A novel first-line treatment option for HCC

This year, in the REFLECT study, first-line treatment with lenvatinib, an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, and RET (Figure 4), proved non-inferior to therapy with sorafenib [4]. In this open-label phase 3 trial of first-line therapy, patients with unresectable HCC were recruited. 954 eligible patients were randomly assigned to receive oral lenvatinib or sorafenib in 28-day cycles. Median survival for

lenvatinib was 13.6 months (95% CI 12.1-14.9), which was non-inferior to sorafenib (12.3 months, 10.4-13.9; HR 0.92; 95% CI 0.79-1.06).

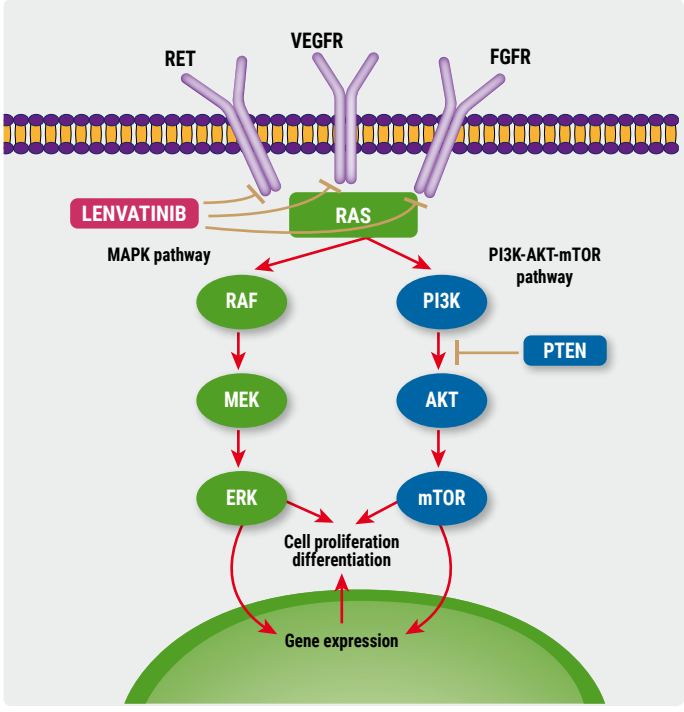
The most common any-grade AEs were hypertension, diarrhoea, decreased appetite, and decreased weight for lenvatinib, and PPES, diarrhoea, hypertension, and decreased appetite for sorafenib. Lenvatinib is currently awaiting approval by the FDA.

Immunotherapy: Also an option for HCC patients?

Programmed cell death protein-1 (PD-1) immune checkpoint inhibitor nivolumab was granted an accelerated approval by the FDA for the treatment of patients with HCC following prior sorafenib in September 2017. The approval was based on findings in a 154-patient subgroup of the CheckMate 040 trial consisting of patients with hepatocellular carcinoma and Child-Pugh A cirrhosis, whose disease progressed or who were intolerant of sorafenib [6]. Treatment consisted of nivolumab at 3 mg/kg via intravenous infusion every 2 weeks.

The confirmed ORR was 14.3% (95% CI 9.2%–20.8%), with 3 complete responses and 19 partial responses observed. Of note, some patients gained a remarkably long response duration ranging from 3.2 to 38.2+ months; 91% of responders had responses lasting at least 6 months and

Figure 4 Mode of action of lenvatinib. Adapted from Stjepanovic & Capdevila 2014 [5]



55% had responses lasting at least 12 months. Nivolumab showed a manageable side-effect profile. The toxicity profile of nivolumab observed in patients with advanced HCC was generally similar to that observed in patients with other cancers; except for a higher incidence of elevations in transaminases and bilirubin levels. New data presented during the ESMO GI meeting demonstrated that the effect of sorafenib therapy can be intensified, and there are even more novel promising agents for intensively pre-treated HCC patients.

Sorafenib plus selective internal radiation: Better survival in a subgroup of HCC patients

Although the addition of selective internal radiation therapy (SIRT) to sorafenib compared to sorafenib alone failed to reach the primary endpoint of the complete palliative cohort of patients with advanced HCC, a significant survival benefit was seen in a subgroup of patients [7]. SORAMIC is a prospective randomised, controlled, phase 2 trial comprising diagnostic, local ablation, and palliative studies. During the ESMO meeting, results of the palliative cohort were presented.

In this treatment arm, 424 HCC patients who were ineligible for transarterial chemoembolisation were included and randomised to receive sorafenib 400 mg twice-daily with or without SIRT using SIR-Spheres yttrium-90 (Y-90) resin microspheres. The trial enrolled patients with extrahepatic disease, but not pulmonary metastases, and patients receiving prior resection or local/locoregional procedures, but patients receiving prior external beam radiation to the liver or prior treatment with monoclonal antibodies were excluded from the study. In the intent-to-treat population, the median OS (primary endpoint) with the combination was 12.1 months compared with 11.5 months with sorafenib alone (HR 1.067; P=0.951). In the per-protocol population, an insignificant trend towards improved OS was observed (median OS 14.1 months vs 11.1 months; HR 0.86; P=0.25).

Benefit for younger, non-cirrotic and no alcohol aetiology

As Dr Jens Ricke (University Hospital Munich, Germany) pointed out, "Subgroup analyses of the per-protocol population suggest a clinical benefit for non-cirrhotic patients, patients presenting with non-alcohol aetiology, and younger patients". The subgroup analysis showed that OS was 22.16 months with SIRT plus sorafenib among patients with non-cirrhotic HCC compared with 9.53 months in patients receiving sorafenib alone (HR 0.46; P=0.02).

A second group with a significant survival benefit were patients having no alcohol tiology (15.32 months vs 11 months; HR 0.63; P=.012).

Adding SIRT to sorafenib also provided improved OS in patients aged younger than 65 years (18.57 months vs 11.34 months; HR 0.68; P=0.043).

The combination showed to be safe, and the toxicity profile with SIRT plus sorafenib was similar to that of sorafenib alone: Grade ≥3 adverse events were observed in 72.3% of patients receiving the combination treatment and in 68.5% of patients receiving sorafenib.

Cabozantinib leads to target lesion regression in pre-treated advanced HCC patients

Intensively pre-treated patients with HCC experienced an improved time to progression, higher rates of tumour reduction, and improved serum AFP levels from baseline when they were treated with the tyrosine kinase inhibitor cabozantinib [8]. Cabozantinib inhibits tyrosine kinases including MET, VEGF receptors, and AXL. These findings resulted from a secondary analysis of tumour response in 707 patients, who participated in the CELESTIAL study. The CELESTIAL study included patients with unresectable HCC who experienced disease progression after at least 1 prior systemic sorafenib-containing therapy. All patients were randomised 2:1 to receive cabozantinib 60 mg once daily, or placebo.

In the ITT population, nearly half of the patients (47%) treated with cabozantinib demonstrated any post-baseline reduction in the sum of target lesion diameters (SOD) as a best response compared with 11% of patients on placebo. Of 470 patients, 39 (8%) in the cabozantinib arm and 3 out of 237 patients (1%) in the placebo arm had at least 1 post-baseline tumour assessment with a ≥ 30% reduction in SOD. Among patients receiving cabozantinib with a baseline AFP level <400 ng/mL, 9% showed a 30% reduction in SOD and this reduction was also achieved by 7% of patients with baseline AFP levels ≥400 ng/ml. Cabozantinib showed a remarkably improved time to progression (5.4 months vs 1.9 months) compared to placebo (HR 0.41; 95% CI 0.34-0.49).

References:

1 Gomaa A & Waked I. Hepatoma Res 2017;3:112-22.
2 Finn RS. Lecture during ESMO GI, 20-23 June, 2018.
3 Bruix J et al. Lancet 2017;389:56-66.
4 Kudo M et al. Lancet 2018;391:1163–73.
5 Stjepanovic N & Capdevila J. Biologics 2014;8:129-39.
6 El-Khoueiry AB et al. Lancet 2017;389:2492-2502.
7 Ricke J et al. Abstract No. O-029, ESMO GI, 20-23 June, 2018.
8 Merle P et al. Abstract No. O-011, ESMO GI, 20-23 June, 2018.

New Agents on the Horizon in Bile Duct Cancer

Biliary tract cancer remains an aggressive tumour. Therefore, there is an urgent need for therapeutic options, in particular for advanced disease. As shown in a trial presented during the meeting, very early data on anti-FGFR (Fibroblast Growth Factor Receptor) agents is promising. In addition, immunotherapy might be a novel treatment option for these patients. Second-line therapy with the PD-1 blocker nivolumab was able to gain durable responses in patients with advanced disease.

Biliary tract cancers (BTCs) are rare but deadly diseases, subdivided into intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma. As Prof. Juan Valle (University of Manchester, UK) pointed out in his lecture, the incidence of the most frequent types of BTC, cholangiocarcinoma (CCA), and gall bladder cancer is increasing worldwide with high mortality rates due to their aggressiveness [1]. CCA is the second most common primary liver tumour and consists of a heterogeneous group of malignancies with features of biliary tract differentiation [2].

Table 2 Objective response rates in ABC-08 and ABC-02 studies [1]

	ABC-08	ABC-02
	NUC-1031 + cisplatin 625 mg/m² + 25 mg/m²	gemcitabine + cisplatin 1000 mg/m² + 25 mg/m²
Complete Response	13% (1/8)	0.6% (1/161)
Partial Response	38% (3/8)	25.5% (41/161)
Objective Response Rate	50% (4/8)	26.1% (42/161)

Gallbladder cancer, though generally considered rare, is the most common malignancy of the biliary tract, accounting for 80%-95% of BTCs. An early diagnosis is essential, as this malignancy progresses silently with a late diagnosis, often proving fatal. Its carcinogenesis follows a progression through a metaplasia-dysplasia-carcinoma sequence [3]. The only curative treatment option for BTCs at this time is surgical resection, but a majority of patients will have disease recurrence.

Capecitabine in the adjuvant setting

Until recently, no recommended standard for adjuvant therapy existed in bile duct cancer. The efficacy of adjuvant systemic therapy was assessed in three phase 3 trials. The BCAT trial tested the hypothesis whether gemcitabine would improve survival probability in resected bile duct cancer [4]. Unfortunately, the survival probability was not significantly different between the gemcitabine adjuvant chemotherapy group and the observation group. In addition, no subgroup had a benefit of the treatment. In the PRODIGE 12-ACCORD 18, patients with BTC were randomised to gemcitabine/oxaliplatin 85 mg/m^2 (GEMOX 85) for 12 cycles vs observation only after complete resection (R0, R1) for nonmetastatic disease [5]. The results were again disappointing. There was no difference in relapse-free survival between the two groups (HR 0.83; 95% CI 0.58-1.19; P=0.31). Grade 3 AEs were reported in 57.5% of participants in the treatment group vs 22.2% in the observation-only group. Most recently, the BILCAP study estimated the effect of adjuvant capecitabine in biliary cancer. Eligible patients had undergone an R0 or R1 resection for BTC. They were randomised to receive oral capecitabine (1250 mg/m2) twice daily for 14 days every 3 weeks for 8 cycles in the absence of disease progression or serious toxicity vs observation alone. The primary outcome was 2-year OS. There were 223 participants randomised to the treatment arm and 224 on observation. OS was improved in the per-protocol analysis, but not in the ITT population. A treatment benefit was also seen following sensitivity analysis (lymph node status, disease grade, gender) with a HR of 0.70 (95% CI 0.55-0.91; P=0.007). Based on the results of BILCAP, capecitabine was established as a new standard of care for the adjuvant treatment of biliary cancers.

Cisplatine-gemcitabine in metastatic disease

Standard of care in first-line therapy of locally advanced or metastatic disease is the combination of gemcitabine and cisplatin. This combination was associated with a significant survival advantage without the addition of substantial toxicity compared to monotherapy with gemcitabine in patients with locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer [6]. This combination is therefore recommended in the ESMO clinical practice guidelines for biliary cancer [7].

According to Prof. Valle, new developments in chemotherapy convey a glimpse of hope for patients with advanced BTC. NUC-1031 is a first-in-class nucleotide analogue, which achieves higher intracellular levels of the activated, key anti-cancer triphosphate metabolite of gemcitabine (dFdCMT). This agent was tested in the phase 1B study ABC-08. If combined with cisplatin remarkable complete and partial response rates could be demonstrated (Table 2).

Irreversible fibroblast growth factor receptor inhibition: A new treatment possibility for CCA?

Very early data showed that the irreversible fibroblast growth factor receptor (FGFR) inhibitor TAS-120 demonstrated a clinically meaningful benefit with a manageable toxicity profile in patients with CCA harbouring FGFR2 gene fusions, including patients who had progressed on an FGFR inhibitor [8].

In this phase 1 trial, 45 patients with CCA (41 patients with intrahepatic cancer) harbouring FGF/FGFR aberrations were treated.

A total of 28 patients (62%) had FGFR2 gene fusions and 17 (38%) had other FGF/FGFR aberrations, e.g. mutations, amplifications, and rearrangements. All patients had received prior systemic therapies and 13 had received at least one prior reversible FGFR inhibitor. Of 28 patients with FGFR2 gene fusions, 20 (71%) experienced tumour shrinkage. TAS-120 induced a confirmed partial response in 7 of these patients. The ORR was 25%. Of the 7 responders, 6 remain on treatment, including one patient with an ongoing cPR of > 1 year. Of 28 patients, 15 patients (54%) experienced stable disease as their best response, with 7 still on treatment. In 17 CCA patients with other FGF/FGFR aberrations, 3 reached a confirmed partial response and 10 had stable disease. Eleven patients had tumour shrinkage. Median time on treatment was 7.4 months and ongoing. Of the 13 patients who had received

prior FGFR inhibitors, 4 (3 with FGFR2 gene fusions and 1 with FGFR2 amplification) gained a confirmed partial response on TAS-120. The most frequent all-grade AEs were expected and manageable, including hyperphosphatemia (78%), and cutaneous and gastrointestinal toxicity. Treatment-related grade 3 AEs occurred in 51.1% of patients, with the most common including hyperphosphatemia (22.2%), ALT increase (6.7%), PPES (4.4%), constipation (2.2%), AST increase (2.2%), and diarrhoea (2.2%). There were no grade ≥4 AEs observed in this study.

Immune checkpoint inhibition promising in advanced biliary tract cancers

The PD1-inhibitor nivolumab showed promise as second-line treatment for advanced BTCs [9]. First author Dr Richard Kim (Moffitt Cancer Center, Tampa, USA) stated that there is no established second-line option for patients with advanced BTC who have failed one prior systemic therapy. The rationale to perform his study was evidence from pre-clinical studies and small series of clinical data that supports the use of immunomodulatory agents.

Nivolumab was evaluated in 34 patients with histologically proven advanced BTC who progressed on at least one line of systemic therapy. Nivolumab in a fixed dose of 240 mg was administered intravenously every 2 weeks for 16 weeks and then at 480 mg every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was ORR by RECIST 1.1. In addition, PFS, OS, and safety data were assessed as secondary endpoints. All 34 patients in the study received at least 1 dose of nivolumab; however, 4 patients discontinued the study due to disease progression and 1 other patient withdrew consent.

Of the 29 patients who underwent response assessment, 5 (17%) achieved a partial response and 11 (38%) demonstrated stable disease. The DCR was 55%. The 4 patients who responded were all microsatellite stable and still remain on treatment (of note, 2 patients have durations of response >12 months). For all 34 patients with a median follow-up of 8 months, median PFS was 3.5 months and the median OS has not been reached. Six-month OS was 76.3%. The primary tumour sites were intrahepatic CCA in 64.7% of patients, extrahepatic in 2.9%, and gallbladder in 32.4% of patients.

Manageable safety profile

In general, nivolumab was well tolerated. The most common treatment-related AEs were fatigue and elevated AST/ALT levels. Seven patients experienced grade 3 AEs, the most common being elevated bilirubin levels and elevated alkaline phosphatase levels. In light of the promising efficacy in refractory BTC, including durable responses lasting over 1 year, in this study, future trials evaluating nivolumab for advanced BTCs in randomised settings are warranted, concluded Dr Kim.

References

1 Valle JW. Lecture during ESMO GI, 20-23 June, 2018.
2 Banales JM et al. Nat Rev Gastroenterol Hepatol 2016;13:261-80.
3 Hundal R, Shaffer EA. Clin Epidemiol 2014;6:99-109.
4 Ebata T et al. Br J Surg 2018:105:192-202.
5 Edeline J et al. J Clin Oncol 2017;35 (suppl 4; abstr 225):225-225.
6 Valle JW et al. N Engl J Med 2010;362:1273-81.
7 Valle JW et al. Ann Oncol 2016;27 (suppl 5):v28-37.
8 Meric-Bernstam F et al. Abstract No. O-001, ESMO GI, 20-23 June, 2018.
9 Kim R et al. Abstract No. O-009, ESMO GI, 20-23 June, 2018.

Selected Posters

Dr Takayuki Yoshino (National Cancer Center Hospital East, Japan) presented highlights of posters on colorectal cancer (CRC) [1]. A quality-of-life analysis of the REVERCE trial demonstrates that quality of life is not different whether patients are treated first by regorafenib followed by cetuximab ± irinotecan or vice versa. In any case, quality of life is more impaired by regorafenib compared to cetuximab. Furthermore, data on advanced oesophageal and pancreatic cancer demonstrated that it may not be justified to exclude elderly patients from effective treatment due to safety concerns.

Earlier this year, the results of the REVERCE trial demonstrated longer OS with the therapeutic sequence of regorafenib followed by cetuximab ± irinotecan (R-C arm) compared with that of cetuximab ± irinotecan followed by regorafenib (C-R arm) for patients with mCRC [2]. All study participants had mCRC and treatment failure with fluoropyrimidine, oxaliplatin, and irinotecan. During the ESMO GI meeting, the quality-of-life (QoL) analysis of this trial was presented [3].

QoL was assessed with the EQ-5D questionnaire that consists of 5 dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The average EQ-5D

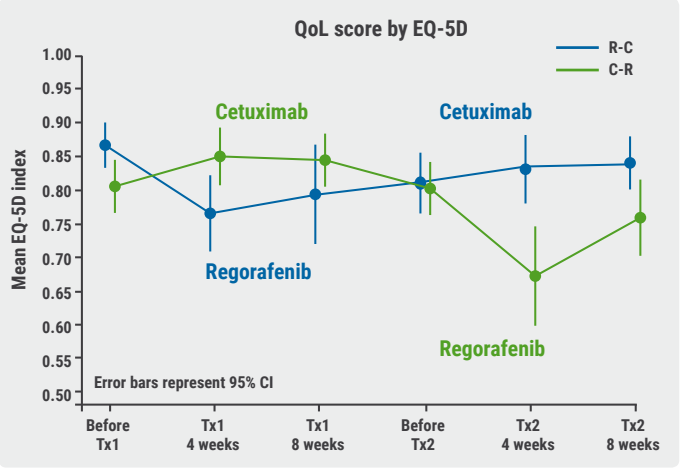
index during sequential treatment was not significantly different between the two arms (P=0.65), although regorafenib treatment was associated with a lower score than cetuximab in both treatments R-C and C-R (Figure 5). The two agents have a different safety profile. Hypertension, hand-foot syndrome, and elevated lipase occurred more frequently with regorafenib treatment than with cetuximab treatment (>10%), whereas the treatment with cetuximab was more frequently accompanied by acneiform rash and hypomagnesemia. Among the 4 AEs, anorexia, hand-foot syndrome, rash, and fatigue, fatigue had by far the largest negative impact on QoL in patients.

Early tumour shrinkage leads to better symptom control

Systemic therapy with EGFR inhibitors ± chemotherapy can result in tumour shrinkage in patients with wild type RAS mCRC, potentially facilitating curative surgery. A data analysis of 3 trials with the anti-EGFR monoclonal antibody panitumumab: 1) PRIME (phase 3; FOLFOX4 ± panitumumab); 2) PEAK (phase 2; mFOLFOX6 ± either panitumumab or bevacizumab); and 3) '314 (phase 2; panitumumab + FOLFIRI). All three trails aimed to investigate whether early tumour shrinkage (ETS) is related to the time to occurrence of new tumour-related symptoms (e.g. new opiate use, first weight-loss event, new anaemia-type event, and new asthenia-type event, all greater than grade 1), and time to ECOG decline during first-line treatment of mCRC [4]. ETS was defined as a reduction of ≥30% in the sum-of-the-longest-diameters of measurable target lesions at 8 weeks after initiation of study treatment.

In the pooled analysis, median time to ECOG decline was numerically longer for patients with ETS (13.9 vs 7.9 months; P=0.204). ETS was significantly associated with delayed time-to-onset of all new tumour-related symptoms described above. For the composite endpoint, ETS was associated with delayed median time to onset of any of the assessed symptoms (5 vs 3.4 months for ETS<30%; P=0.021). More patients with ETS than without ETS had not experienced any new symptom at both 6 and 12 months. This analysis shows that tumour shrinkage leads to better symptomatic control and improved QoL. However, as Prof. Julien Taieb (Paris Descartes University, Paris, France) pointed out during presentation of the data, the analysis is retrospective and the symptom endpoints were not pre-defined. Therefore, prospective trials are needed to confirm these results.

Figure 5 Although there was no difference in the QoL between the R-C and C-R group, treatment periods with regorafenib were associated with an impaired QoL [3]



Metastatic pancreatic cancer: Elderly patients derive same clinical benefit from chemotherapy

Real-world data from an Austrian study demonstrated that patients aged older than 70 years derive the same clinical benefit as younger patients from chemotherapy with gemcitabine plus nabpaclitaxel. In addition, this combination proved generally effective and tolerable in patients with metastatic pancreatic cancer under conditions of daily practice [5].

"Nabpaclitaxel plus gemcitabine has demonstrated tolerability and superior efficacy as first-line treatment of metastatic pancreatic cancer in the phase 3 MPACT clinical trial; however, real-life clinical practice is comprised of diverse treatment conditions and heterogeneous patient populations," said Prof. Wolfgang Eisterer (KABEG Klinikum Klagenfurt, Austria). Therefore, he performed a non-interventional study of nabpaclitaxel in combination with gemcitabine with 239 adult patients with confirmed metastatic pancreatic cancer. They were treated with the combination at a dose regimen of nab paclitaxel 125 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of every 28-day cycle in its labelled indication until progression and prospectively observed until disease progression or unacceptable toxicity.

Median treatment duration was 4 cycles. Primary objectives were safety and tolerability and secondary objectives included ORR and the assessment of real-life dosing in daily clinical routine.

The ORR of the current interim analysis was conducted in 145 patients and consisted of 43% partial responses. A total of 41% had stable disease, and the DCR was 83%. Progression of disease was seen in 16.55% of patients.

Benefit independent of age

A comparison of 130 patients aged ≤70 years with 109 patients >70 years revealed an ORR of 40.96% and 45.16% (all partial

response) in the respective age groups. Stable disease was achieved by 39.76% and 41.94%, respectively, for a DCR of 81% and 87%. Progressive disease was reported in 19.28% and 12.9% of patients, respectively. Median PFS was 5.1 months in the overall cohort and in both age-based subgroups.

The treatment was well tolerated overall with comparable rates of adverse drug reactions in the younger and older aged patients. Overall, AEs were not serious in 86% of patients. AEs requiring hospitalisation occurred in 13% of younger vs 11% of older patients. Treatment was discontinued by 171 patients. The primary cause of discontinuation was tumour progression in 45% of patients, followed by death in 19% of patients, and 5% of patients discontinued treatment due to toxicity.

"These findings from our preliminary analysis confirm the efficacy of nabpaclitaxel/gemcitabine for the treatment of metastatic pancreatic cancer in a clinical setting," concluded Prof. Eisterer.

References:

1 Yoshino T. Lecture during ESMO GI, 20-23 June, 2018.
2 Shitara K et al. J Clin Oncol 2018;36:557.
3 Yoshino T et al. Poster PD-010, ESMO GI, 20-23 June, 2018.
4 Taieb J et al. Poster PD-012, ESMO GI, 20-23 June, 2018.
5 Eisterer W et al. Poster P-034, ESMO GI, 20-23 June, 2018.