RECENT DEVELOPMENTS IN REGORAFENIB TREATMENT FOR GASTROINTESTINAL CANCERS: PRESENTATIONS AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) CONGRESS 2016

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ABSTRACT

The European Society for Medical Oncology (ESMO) Congress was held in Copenhagen, Denmark from 7th–11th October 2016. The use of the promiscuous multikinase inhibitor regorafenib (Stivarga®, BAY 73-4506) in the treatment of cancers of the gastrointestinal (GI) tract was strongly featured at this meeting. Regorafenib targets multiple kinases involved in oncogenesis and angiogenesis, and is US Food and Drug Administration (FDA)-approved for the treatment of advanced metastatic colorectal cancer and GI stromal tumours, following progression on standard therapies. In this review, we summarise the results of completed clinical trials on the use of regorafenib alone or in combination with other therapies for the treatment of GI cancers. We highlight the results of the Phase III RESORCE study which demonstrated the efficacy of regorafenib as a second-line therapy in patients with advanced hepatocellular carcinoma who have progressed on sorafenib. We review some promising preliminary data on the use of regorafenib in other GI cancers, such as gastric cancer, oesophageal cancer, pancreatic cancer, and soft tissue carcinomas, and provide a brief overview of ongoing and planned trials. Finally, we discuss the incidence and management of regorafenib-related toxicities and summarise attempts to identify predictive biomarkers of regorafenib sensitivity.

Keywords: Colorectal cancer (CRC), gastric cancer (GC), gastrointestinal stromal tumours (GISTs), hepatocellular carcinoma (HCC), tyrosine kinase inhibitor.

INTRODUCTION

The term gastrointestinal (GI) cancer refers to all tumours affecting the digestive tract, including gastric cancer (GC), colorectal cancer (CRC), oesophageal cancer, pancreatic cancer, cholangiocarcinoma (CCC), hepatocellular carcinoma (HCC), and sarcomas such as GI stromal tumours (GISTs). CRC was one of the most frequently diagnosed GI malignancies within Europe in 2012, with a reported incidence of 446.8 per 100,000, followed by GC (139.6 per 100,000), and HCC (63.4 per 100,000).[1] The precise incidence of GISTs remains unknown, although it is estimated to comprise <1% of all GI cancers.[2] Recommended treatment varies depending on the type of GI tumour. Radical surgery is the mainstay treatment for all GI cancers; however, many patients will develop recurrent or metastatic disease: in most cases, the disease is deemed incurable. In this setting, targeted anti-angiogenic therapies, such as monoclonal antibodies targeting vascular

endothelial growth factor (VEGF) have attracted attention. Despite the success of these targeted therapies (summarised in Table 1),[3] primary and secondary resistance remains a clinical challenge, with clonal evolution of resistant cells leading to the need for additional lines of therapy. Following the development of resistance, tyrosine kinase inhibitors or multikinase inhibitors (MKIs) may present an effective option in the clinic, likely due to their broad substrate specificity.

Regorafenib (Stivarga®, BAY 73-4506) is a promiscuous MKI that is US Food and Drug Administration (FDA)-approved for the treatment of advanced metastatic CRC (mCRC) and GISTs following progression on standard therapies. However, despite its proven efficacy, regorafenib is associated with a number of treatment-related toxicities. Presentations at the European Society for Medical Oncology (ESMO) Congress 2016 reflected the continuing efforts to refine the regorafenib treatment regimens and manage treatment-related toxicities. In this review, we illustrate the recent advances in clinical trial data regarding regorafenib alone or in combination with other therapies for the treatment of GI cancers, provide an overview of some ongoing and planned trials, and discuss options for managing regorafenib-related toxicities.

REGORAFENIB AS AN ANTI-TUMOUR AGENT

Regorafenib demonstrates anti-tumour activity in a variety of *in vitro* and *in vivo* models.[4,5] It acts on several protein kinases involved in important aspects of tumour growth, including angiogenesis (VEGF receptors [VEGFRs] 1–3 and TIE2), oncogenesis (KIT, RET, RAF1, B-RAF, and B-RAF-V600E), and the tumour microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptor [FGFR]).[4] Regorafenib also targets apoptosis-related pathways (e.g. SHP-1 and PUMA).[6,7] It was recently shown to display anti-angiogenic, anti-proliferative, and pro-apoptotic activity in patient-derived murine models of GC.[5] Regorafenib first demonstrated clinical activity in a Phase I trial in heavily pretreated mCRC patients,[8] and has since shown promising efficacy and tolerability for the treatment of various GI cancers in a number of Phase II and Phase III clinical trials (Table 2).

REGORAFENIB AND METASTATIC COLORECTAL CANCER

Regorafenib therapy demonstrated significant improvements in terms of overall survival (OS, primary endpoint), progression-free survival (PFS), and disease control (DCR) in heavily pretreated mCRC patients in two placebo-controlled, randomised, Phase III trials: CORRECT (NCT01103323, N=753) and CONCUR (NCT01584830, N=204) (Table 2).[9,10] In CONCUR, median OS was 8.8 versus 6.3 months for placebo (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.40–0.77; p=0.0002), whereas median OS was 6.4 versus 5 months for placebo in CORRECT (HR: 0.77; 95% CI: 0.64–0.94; p=0.0052).[9,10] The longer OS observed in the CONCUR trial may reflect the fact that patients were not as heavily pretreated: 38% of patients in the regorafenib arm in CONCUR were treated with ≥4 lines of prior therapy versus 49% in CORRECT.[9,10] In CORRECT, all patients were pretreated with anti-VEGF therapies and ~50% (all *KRAS* wild-type cancers) were pretreated with an anti-epidermal growth factor receptor (EGFR), whereas in CONCUR, only ~60% were pretreated with either of these therapies (40% were not pretreated with any targeted therapy).[9,10] The sample size was also smaller in the CONCUR trial. Another difference is that all patients in CONCUR were of Asian descent compared to only 15% of patients in CORRECT. The most frequent regorafenib-related adverse events (AEs) (Grade ≥3) in the CORRECT trial were hand-foot-skin reaction (HFSR; 17%), fatigue (10%), diarrhoea (7%), and hypertension (7%);[9] in CONCUR, they were HFSR (16%), hypertension (11%), hyperbilirubinaemia (7%), hypophosphatemia (7%), and alanine aminotransferase increase (7%).[11]

Similar efficacy and safety results were observed in two open-label, single-arm studies performed in real-world settings: REBECCA (NCT02310477) and CONSIGN (NCT01538680) (Table 2).[12-14] REBECCA, a French compassionate programme, was a cohort study designed to evaluate the efficacy and safety of regorafenib in pretreated mCRC patients in real-life clinical practice. All patients (N=654) included in REBECCA received regorafenib, resulting in a median OS of 5.6 months and a 12-month survival rate of 22%.[12,13] Fatigue and HFSR were the most common AEs (Grade ≥3).[12,13] The open-label, single-arm, Phase IIIb CONSIGN study (N=2,872) conducted across 25 countries was designed to further characterise the safety of regorafenib

in mCRC patients who had failed standard therapy.[14,15] In CONSIGN, regorafenib-related AEs (all grades) were observed in 91% of patients.[14,15] It was proposed that elderly patients may be at increased risk of these toxicities; however, subgroup analysis of the CONSIGN study population based on age showed that regorafenib-related AEs were generally comparable in patients aged <65 and ≥65 years, with both subgroups showing similar PFS (~2.5 months).[16]

Regorafenib has been examined as a first-line therapy in mCRC patients who were frail or unfit for polychemotherapy (due to various comorbidities) in the Phase II REFRAME trial (NCT01875380), an ongoing open-label single-arm study with a primary outcome measure of PFS.[17] Preliminary safety data from REFRAME on 44 patients revealed that 9 patients discontinued treatment due to regorafenib-related toxicity or death;[18] however, there remains insufficient data regarding the efficacy of regorafenib in this setting.

Regorafenib as a first or second-line treatment for mCRC in combination with chemotherapy (FOLFIRI or irinotecan, 5-fluorouracil, and leucovorin) was examined in a Phase Ib multicentre, randomised, placebo-controlled study.[19] Of the 45 patients undergoing the combined therapy, 33 achieved DCR (partial response or stable disease) for a median of 126 (range: 42–281) days.[19] Treatment was stopped in 17 patients due to regorafenib-related AEs or death.[19] Regorafenib-related AEs (Grade ≥3) occurred in 32 patients, mostly neutropenia (53%), leukopenia (12.5%), HFSR (12.5%), and hypophosphatemia (12.5%).[19] Subsequently, a Phase II study confirmed that the addition of regorafenib on an intermittent schedule to FOLFIRI was tolerable and resulted in a statistically significant prolongation of PFS compared to FOLFIRI alone (Table 2).[20] While regorafenib plus FOLFIRI treatment also improved OS in this study, the difference was not statistically significant.[20] However, whether subsequent therapies or crossover influences the OS in this population remains under investigation.

Ongoing trials include the prospective cohort CORRELATE trial (N≥1,000, NCT02042144) on the safety of regorafenib for mCRC therapy in routine clinical practice[21] and the open-label Phase II REGARD trial (NCT01853319) enrolling 100 Turkish mCRC patients with progression after standard therapy with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR inhibitor (if the patient is *KRAS* wild-type).[22,23]

Table 1: Examples of currently available targeted therapies for gastrointestinal cancers approved by the European Medicines Agency (EMA) or US Food and Drug Administration (FDA).

Name	Target(s)	Indication
Bevacizumab	mAb (targets VEGF-A)	Metastatic colorectal cancer
Aflibercept	VEGFR decoy receptor	Metastatic colorectal cancer
Ramucirumab	mAb (targets VEGF-binding domain of VEGFR-2)	Metastatic gastric cancer, metastatic colorectal cancer, metastatic gastro-oesophageal junction adenocarcinoma, oesophageal cancer
Cetuximab	mAb (targets EGFR)	Metastatic colorectal cancer
Panitumumab	mAb (targets EGFR)	Metastatic colorectal cancer
Trastuzumab	mAb (targets HER2)	HER2-overexpressing metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma
Sorafenib	Multitarget TKI	Advanced hepatocellular carcinoma
Imatinib	Multitarget TKI	Gastrointestinal stromal tumours
Sunitinib	Multitarget TKI	Imatinib-resistant gastrointestinal stromal tumours
Regorafenib	Multitarget TKI (targets VEGFR1–3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, RAF-1, B-RAF, and p38 MAP kinase)	Metastatic colorectal cancer, advanced gastrointestinal stromal tumours

EGFR: epidermal growth factor receptor; FGRF: fibroblast growth factor receptor; HER2: human epithelial growth factor receptor 2; mAb: monoclonal antibody; PDGFR: platelet-derived growth factor receptor; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

Table 2: Summary of the results of completed Phase II/III trials on the use of regorafenib in gastrointestinal cancers.

Trial name/ID	Indication	Study design	Study size (N)	Line of therapy	Efficacy outcomes	Safety
CONCUR **Clinical Trial: NCT01103323**[10]	mCRC	Randomised (2:1) Phase III	204	Third or fourth	Improved OS (8.8 versus 6.3 months for placebo; HR: 0.55; 95% CI: 0.40–0.77; p=0.00016).	Treatment-related AEs (all grades) were reported in 97% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (16%) and hypertension (11%).
CORRECT **Clinical Trial: NCT01103323**[9]	mCRC	Randomised (2:1) Phase III	753	Third or fourth	Improved OS (6.4 versus 5.0 months for placebo; HR: 0.77; 95% CI: 0.64–0.94; p=0.0052).	Treatment-related AEs (all grades) were reported in 93% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (17%) and fatigue (10%).
CONSIGN **Clinical Trial: NCT01538680**[14,15]	mCRC	Expanded access Phase IIIb	2,872	Third or fourth	Median PFS (95% CI) was 2.7 months (2.6–2.7).	Treatment-related AEs (all grade) were reported in 91% of patients. Most common treatment-related AEs (Grade ≥3) were HFSR (57%), fatigue (15%), diarrhoea (14%), and hypophosphatemia (13%).
REBECCA **Clinical Trial: NCT02310477**[12,13]	mCRC	Open-label single arm, real-life, observational	654	Second or third	Median OS of 5.6 months and 12-month survival rate of 22%.	Treatment-related AEs (all grades) were reported in 80% of patients. Most common treatment-related AEs (Grade ≥3) were fatigue (15%), HFSR (9%), and diarrhoea (4%).
REG+FOLFIRI **Clinical Trial: NCT01289821/ NCT01298570**[19]	mCRC	Randomised (2:1) Phase II efficacy	45	First or second (after FOLFOX regimen)	DCR achieved in 73% of patients for a median of 126 days (range, 42–281 days).	Treatment-related AEs were reported in 98% of patients. Most common treatment-related AEs (Grade ≥3) were neutropenia (38%), HFSR (8%), and hypophosphatemia (8%).
REG IN HCC **Clinical Trial: NCT01003015**[24]	HCC	Phase II (safety)	36	Second (after sorafenib)	DCR achieved in 72% of patients. Median OS of 13.8 months.	Most common treatment-related AEs (Grade ≥3) were fatigue (17%), HFSR (14%), diarrhoea (6%), hyperbilirubinemia (6%), and hypophosphatemia (6%).
RESORCE **Clinical Trial: NCT01774344**[25-27]	HCC	Randomised (2:1) Phase III	573	Second (after sorafenib)	Improved OS (10.6 versus 7.8 months in placebo) and PFS (3.1 versus 1.5 months for placebo).	Most common treatment-related AEs (Grade ≥3) were hypertension (15.2%), HFSR (12.6%), fatigue (9.1%), and diarrhoea (3.2%).

Table 2 continued.

Trial name/ID	Indication	Study design	Study size (N)	Line of therapy	Efficacy outcomes	Safety
INTEGRATE **Clinical Trial: ANZCTR 12612000239864**[29]	AOGC	Randomised (2:1) Phase II	152	Second or third	Improved PFS (2.6 versus 0.9 months for placebo; HR: 0.40; 95% CI: 0.28–0.59; p<0.001).	Toxicity generally consistent with the known profile of REG.
REG IN GIST **Clinical Trial: NCT01068769**[34]	GIST	Phase II	33	Second (after imatinib and sunitinib)	Median PFS was 10 months (95% CI: 8.3–14.9).	Most common treatment-related AEs (Grade ≥3) were hypertension (36%) and HFSR (24%).
GRID **Clinical Trial: NCT01271712**[35,48]	GIST	Randomised (2:1) Phase III	199	Second (after imatinib and sunitinib)	Improved PFS (4.8 versus 0.9 months for placebo; HR: 0.27; 95% CI: 0.19–0.39; p<0.0001).	Treatment-related AEs (all grades) were reported in 98% of patients.

AEs: adverse events; AOGC: advanced oesophago-gastric cancer; CI: confidence interval; DCR: disease control; GIST: gastrointestinal stromal tumours; HCC: hepatocellular carcinoma; HFSR: hand-foot-skin reaction; HR: hazard ratio; mCRC: metastatic colorectal cancer; OS: overall survival; PFS: progression-free survival; REG: regorafenib.

REGORAFENIB AND HEPATOCELLULAR CARCINOMA

Sorafenib is the recommended first-line treatment for advanced HCC patients; however, there are no proven or approved second-line treatment options for sorafenib-treated patients who experience disease progression. Therefore, following promising Phase II data,[24] the international, randomised, Phase III, double-blind, placebo-controlled trial RESORCE study (NCT01774344) was initiated to investigate single-agent therapy with regorafenib in patients with intermediate/advanced HCC after progression on sorafenib (Table 2).[25] In RESORCE, patients with HCC Barcelona Clinic Liver Cancer (BCLC) Stage B or C, who had documented radiological progression on sorafenib, Child–Pugh A liver function, and Eastern Cooperative Oncology Group (ECOG) performance status 0–1, were randomised (2:1) to regorafenib (n=379) or placebo (n=194).[26,27] Compared to placebo, regorafenib improved median OS (primary endpoint, 10.6 versus 7.8 months for placebo; HR: 0.62; 95% CI: 0.50–0.78; p<0.001) and PFS (3.1 versus 1.5 for placebo; HR: 0.46; 95% CI: 0.37–0.56; p<0.001).[27] Regorafenib also significantly improved DCR (65.2% versus 36.1% for placebo; p<0.001).[27] The most common regorafenib-related AEs (Grade ≥3) were hypertension (15.2%), HFSR (12.6%), and fatigue (9.1%).[27] Therefore, single-agent regorafenib may fulfil the need to provide effective second-line treatment in advanced HCC patients who have progressed on sorafenib.

REGORAFENIB IN GASTRIC AND OESOPHAGEAL CANCER

Regorafenib has shown anti-tumour activity in patient-derived murine models of GC.[5] While further research is required to confirm its efficacy in GC patients, single-agent regorafenib has shown promising results in the randomised, double-blind, placebo-controlled Phase II INTEGRATE study (ACTRN12612000239864) on refractory advanced oesophago-gastric cancer patients (Table 2).[28] In INTEGRATE, median PFS (primary endpoint) was significantly longer in the regorafenib arm (n=97) than the placebo arm (n=50; 2.6 versus 0.9 months, respectively; HR: 0.40; 95% CI: 0.28–0.59; p<0.001).[29] The effect on PFS was greater in South Korea than in Australia, New Zealand, and Canada combined (HR: 0.12 versus 0.61; interaction p<0.001) but was consistent across age, neutrophil-to-lymphocyte ratio, primary site, lines of chemotherapy, peritoneal metastasis presence, number of metastatic sites, and plasma VEGF-A.[29] Regorafenib treatment

also showed a longer survival trend compared to placebo (although this difference was not statistically significant) and AEs were similar to those previously reported.[29] Following the success of INTEGRATE, a randomised Phase III trial (INTEGRATE II) is currently recruiting participants (ACTRN12616000420448).[30] In addition, regorafenib is currently being investigated in combination with FOLFOX in a randomised Phase II study of patients with unresectable or metastatic, advanced oesophago-gastric cancer (NCT01913639).[31]

REGORAFENIB AND PANCREATIC CANCER

Promising data concerning the use of regorafenib in pancreatic cancer arose from the Phase I, multicentre, single-arm trial that enrolled 15 patients with treatment-refractory solid tumours, in which the most common tumour site was the pancreas.[32] More than half of these patients achieved DCR with regorafenib therapy (partial response, n=1; stable disease, n=7).[32] Regorafenib-related toxicities were mostly mild or moderate, and included HFSR, diarrhoea, hypophosphatemia, and liver transaminase elevation.[32] A Phase II trial comparing regorafenib with gemcitabine in the treatment of metastatic pancreatic cancer is also ongoing (NCT02383433).[33] However, until its safety and efficacy is confirmed, regorafenib must not be used in the treatment of pancreatic cancer outside clinical trial settings.

REGORAFENIB AND SARCOMAS

Regorafenib was FDA-approved as a third-line therapy for patients with metastatic and/or unresectable GIST following results of the Phase II[34] and Phase III (NCT01271712) GRID trials[35] (Table 2). Regorafenib is also under investigation for the treatment of patients with advanced soft tissue sarcomas (STS) in the REGOSARC trial (NCT01900743), which comprises four parallel, double-blind placebo-controlled, randomised Phase II trials defined by four histological subgroups: liposarcoma, leiomyosarcoma, synovial sarcoma, and other sarcomas.[36] In REGOSARC, 182 patients with anthracycline pretreated metastatic STS were randomly assigned to one of the above four cohorts.[37] While liposarcoma patients treated with regorafenib showed no significant difference in median PFS (primary outcome) compared to placebo (1.1 versus 1.7 months, respectively; HR: 0.89; 95% CI: 0.48–1.64; p=0.7), leiomyosarcoma patients treated with regorafenib had significantly longer PFS (3.7 versus 1.8 months for placebo; HR: 0.46; 95% CI: 0.46–0.80; p=0.0045).[37] Similarly, in the synovial sarcoma cohort, the median PFS of patients treated with regorafenib was significantly longer compared to placebo (5.6 versus 1.0 months, respectively; HR: 0.10; 95% CI: 0.03–0.35; p<0.0001).[38] In patients with other types of sarcomas, PFS was also significantly longer in the regorafenib arm compared to placebo (2.9 versus 1.0 months, respectively; HR: 0.46; 95% CI: 0.25–0.81; p=0.0061).[38] Therefore, further clinical evaluation of regorafenib in patients with sarcomas is warranted.

REGORAFENIB IN OTHER CANCERS

Regorafenib is currently undergoing numerous Phase II clinical trials for cancers beyond the GI tract, including the randomised REGOBONE trial (NCT02389244) on the efficacy and safety of regorafenib in the treatment of metastatic bone sarcomas.[39] Recruitment is also ongoing for a Phase II trial on single-agent regorafenib in patients with advanced and metastatic biliary tract carcinoma/CCC who have failed first-line chemotherapy (NCT02053376),[40] as well as the Phase II randomised REACHIN trial for CCC (NCT02162914).[41] Although the final analysis is yet to be completed, a Phase II study for the treatment of progressive, recurrent/metastatic adenoid cystic carcinoma was recently reported to have failed to meet its primary endpoints.[42] Finally, a Phase I study (NCT02466802) on the combined use of regorafenib and sildenafil citrate (an inhibitor of phosphodiesterase Type 5 that potentiates anti-cancer activity)[43] in the treatment of advanced solid tumours is currently recruiting participants.[44]

PREDICTIVE BIOMARKERS OF THE REGORAFENIB RESPONSE

While biomarkers have been extensively investigated in randomised trials, we are yet to identify a single factor predictive of regorafenib sensivitiy.[45] Indeed, preliminary analysis of genetic prognostic and predictive factors in the REGOSARC study showed that none of the individual genes encoding regorafenib-targeted proteins (i.e. *VEGFR1–3*, *FGFR1*, *KIT*, *PDGFRB*, *RAF1*, *RET1*, *TIE2*, *TP53*, and *CHP2*) were predictive of response or PFS in STS patients, although further combinatorial analyses are ongoing.[46] In GIST patients, regorafenib treatment suppressed plasma

nitric oxide levels and increased endothelin-1 levels,[47] indicating they are potential biomarkers. Regorafenib also showed a particular benefit among GIST patients with primary *KIT* exon 11 mutations and those with succinate dehydrogenase-deficient GIST.[48] In pancreatic cancer, PD-L1^{+}/PD-1^{+} patients may have improved benefit from regorafenib.[49]

For mCRC patients, post hoc subgroup analyses of the CORRECT and CONSIGN study populations according to PFS revealed that patients with long PFS (>4 months) tended to have better performance status, fewer metastatic tumour sites, and a longer time since diagnosis of metastatic disease compared to those with short PFS (≤4 months).[50,51] However, a prospective validation of this data is needed to draw further conclusions. Similarly, subgroup analysis of the REBECCA trial data revealed that survival was independently and unfavourably affected by poor performance status, short time from initial diagnosis of metastases to the start of regorafenib, low initial regorafenib dose, >3 metastatic sites, presence of liver metastases, and *KRAS* mutations.[12,13] These data suggest that mCRC patients could be classified into prognostic groups by collecting simple baseline characteristics and or mutational status. Indeed, retrospective analysis of the CORRECT trial data indicated that *KRAS* and *PIK3CA* mutational status and circulating DNA concentration are potentially associated with clinical benefit from regorafenib.[52]

Imaging techniques may also prove useful in this area, with contrast-enhanced computed tomography (CT) texture reported as a potential biomarker for response to tyrosine kinase inhibitor therapy in metastatic renal cell carcinoma.[53] In addition, cavitation of lung metastases on contrast-enhanced CT observed during treatment with regorafenib was associated with the absence of progression at Week 8 in a retrospective study of 75 mCRC patients.[54] Similarly, a prospective study examined tumour attenuation (in Hounsfield units) in contrast-enhanced CT and the cavitary changes of lung metastases in 80 regorafenib-treated mCRC patients.[55] While this study was largely inconclusive (no differences in DCR, PFS, or OS were observed based on radiological changes),[55] the role of CT density changes as biomarkers for regorafenib is undergoing further investigation.

Other potential biomarkers are emerging in the literature; for example, a study showed that resistance of mCRC to regorafenib is associated with mutations of the FBW7 tumour suppressor and that FBW7 mutational status is a key genetic determinant of mCRC response to targeted therapies such as regorafenib.[56] PUMA expression may be useful as an indicator of regorafenib sensitivity in mCRC,[7] whereas p-STAT3 expression was identified as a potential biomarker in HCC.[6] To identify new biomarkers, the RELAIS multicentre translational biomarker Phase II trial (EudraCT: 2014-004927-27) of regorafenib in non-resectable pretreated mCRC patients is currently investigating circulating tumour DNA as an indicator of regorafenib efficacy in terms of OS.[57] There is also an ongoing Phase II study (NCT01949194) that aims to identify biomarkers in mCRC patients treated with single-agent regorafenib who have failed one prior treatment.[58]

PREVENTION AND MANAGEMENT OF REGORAFENIB-RELATED TOXICITIES

Despite the reported benefits of regorafenib in various cancers, treatment-related AEs may limit its clinical use. As these AEs typically occur early, close monitoring of patients immediately following commencement of regorafenib therapy is strongly recommended. Some AEs may be managed by incorporating simple prophylactic measures, as outlined by Sastre et al.[59] For example mild soaps, intense hydration, and comfortable clothes, as well as non-urea-based skin creams should be recommended to patients to prevent skin toxicities, and keratolytic creams should be recommended for hyperkeratotic lesions. Other regorafenib-related AEs may be managed in the clinical setting with dose modifications. Indeed, dose modifications were frequently required to manage regorafenib-related toxicities in GIST patients in long-term follow-up (median follow-up of 41 months) from the multicentre Phase II GRID trial.[48] Therefore, the Phase II randomised ReDOS Study (NCT02368886) is currently exploring novel strategies to improve the tolerability of regorafenib.[60] These include the use of a steroid (clobetasol propionate) cream to alleviate HFSR, as well as using incremental regorafenib dose escalations (starting at 80 mg/day, with weekly dose escalations until the goal of 160 mg is reached).[60]

CONCLUSIONS AND FUTURE DIRECTIONS

The collective clinical trial data indicate that regorafenib has good efficacy in patients with different types of advanced or refractory GI

cancers who have progressed on prior standard therapy. In addition to the FDA-approved use of regorafenib in advanced mCRC and GIST following progression on standard therapies, data from the RESORCE study suggest that regorafenib can also be used as a second-line therapy in advanced HCC patients who have progressed on sorafenib. Further clinical evaluation of the use of regorafenib as either a first, second, or third-line therapy, alone, or in combination with chemotherapy, in gastric/oesophageal cancer, pancreatic cancer, soft tissue carcinomas, and metastatic bone sarcomas, is required. Investigating the utility of this drug in cancers beyond the GI tract is also warranted.

Future studies relating to regorafenib in GI cancers should aim to decipher whether ethnicity, pretreatment approaches, or other prognostic factors can affect patient outcomes. The identification of biomarkers would also help us to accurately select the appropriate population(s) to treat with regorafenib in clinical practice. Currently, the main downside of regorafenib therapy is its toxicity profile; a high incidence of HFSRs and fatigue has been observed in the real-world setting. While these toxicities can generally be managed in the clinic with appropriate dose modifications, novel strategies such as steroid creams should be explored to improve the tolerability of regorafenib.

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