

REGORAFENIB IN METASTATIC COLORECTAL CANCER AND ADVANCED SOFT TISSUE SARCOMAS

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Speakers

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MEETING SUMMARY

Oncologists face multiple challenges when treating patients with cancer, especially if patients are elderly or if they experience adverse events (AEs). Several presentations at the American Society of Clinical Oncology (ASCO) 2016 meeting focussed on overcoming these challenges with regorafenib, an oral multikinase inhibitor approved for treating refractory metastatic colorectal cancer (mCRC), and gastrointestinal stromal tumours (GIST).

A retrospective analysis of the Phase IIIb CONSIGN study in patients with mCRC reported while most AEs were similar between age groups, when compared to the younger subgroup, the patients in the older subgroups had a higher incidence of Grade ≥ 3 fatigue and a lower incidence Grade ≥ 3 hand-foot syndrome (HFS), while other AEs were similar between age groups. Thus, patient age should not be considered a barrier to regorafenib use. This age analysis also highlighted the key role of dose modification in the management of regorafenib-related AEs.

Another tactic for AE management is to utilise specific treatments targeted to the AE of interest. Interim analysis of a Phase II study demonstrated that prophylactic dexamethasone had promising effects in reducing regorafenib-related fatigue and HFS in patients with mCRC. In an ongoing Phase II study, ReDOS, both regorafenib dose-escalation and use of clobetasol propionate to actively manage regorafenib-induced HFS are under investigation.

Finally, the success of regorafenib in treating GIST, the most common soft tissue sarcoma (STS), has been extended to patients with other STS. In REGOSARC, a Phase II study, regorafenib significantly prolonged progression-free survival (PFS) in patients with non-adipocytic STS, with an AE profile similar to that seen in mCRC and GIST. These presentations offer insights into the practical management of patients treated with regorafenib.

Introduction

Regorafenib is an oral multikinase inhibitor that targets several protein kinases involved in angiogenesis (vascular endothelial growth factors 1-3 and TIE2), regulation of the tumour microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptors), and oncogenesis (*KIT*, *RET*, *RAF-1*, and *B-RAF*).¹ Regorafenib significantly improved overall survival (OS) in patients with previously treated mCRC compared with placebo in the CORRECT Phase III trial.² A significant increase in PFS in patients with advanced GIST, a type of STS, was also reported for regorafenib versus placebo in the GRID Phase III trial.³ Based on these trials, regorafenib received approval for use in adult patients with mCRC (either previously treated with or who are not considered for available therapies), and those with unresectable or metastatic GIST (who have progressed on or are intolerant to prior treatment with imatinib and sunitinib). Regorafenib is also being evaluated in a wide range of solid tumours, including renal cell carcinoma, hepatobiliary, and upper gastrointestinal cancers.^{4,5}

Safety and Efficacy of Regorafenib in Metastatic Colorectal Cancer by Age in the Consign Trial

Professor Eric Van Cutsem

mCRC is a leading cause of cancer deaths, particularly in elderly patients. Moreover, 60% of patients diagnosed with mCRC are aged ≥ 65 years. This patient population may be undertreated in clinical practice and under-represented in clinical trials, as they are more susceptible to treatment-induced toxicities due to a range of comorbidities and reduced organ function. However, with appropriate management, certain elderly patients with mCRC can gain significant benefits from a range of cancer treatments, including biological therapies.^{6,7}

To gain further insight in to the management of elderly patients, a retrospective analysis of outcomes by patient age was carried out in CONSIGN (NCT01538680), a large, open-label, single-arm, Phase IIIb study conducted in 186 centres in 25 countries.^{8,9} Patients (N=2,872) recruited into CONSIGN had mCRC with disease progression following standard

therapies and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 . They received regorafenib at 160 mg/day for Weeks 1-3 of each 4-week cycle until unacceptable toxicity, disease progression, or death. The primary endpoint was safety, and the only efficacy measurement was investigator-assessed PFS.⁸

This latest analysis was presented at ASCO 2016 by Dr Eric Van Cutsem from the University Hospitals Leuven, Leuven, Belgium. Patients were categorised into two sets of different age groups: < 65 years (n=1,720) compared to ≥ 65 years (n=1,152), and < 70 years (n=2,245), compared to ≥ 70 years old (n=627).⁹ Baseline characteristics were generally well-balanced across the age subgroups. At least 50% of patients in each age subgroup had a mutated *KRAS* gene, which is slightly higher than typically seen in mCRC (35-45%).¹⁰ The results of this analysis indicate that patient age does not appear to impact treatment duration, impact treatment duration (2.2-2.5 months across age groups). No age effects were seen for the median number of median number of cycles (3.0 in all groups). Across the age groups, almost 90% of patients required treatment modification (defined as reductions, interruptions/delays or re-escalation of re-escalation of treatment). Treatment interruptions occurred in up to 84% of patients in each subgroup and almost half of the patients required dose reductions.

Most patients ($\geq 91\%$) in each age subgroup had a regorafenib-related, treatment-emergent AE (TEAE) of any grade. A low number of patients ($\leq 13\%$) in each age category discontinued regorafenib as a result of regorafenib-related TEAEs. The proportion of patients with some Grade ≥ 3 regorafenib-related TEAEs (i.e hypophosphataemia and diarrhoea) was also generally similar across the age subgroups.⁹ However, the incidence of ≥ 3 regorafenib-related HFS tended to be lower and hypertension and fatigue appeared to be higher in the older subgroups compared with the younger subgroups. The incidence of Grade ≥ 3 TEAEs seen in CONSIGN were typical of those reported in other regorafenib studies.² Treatment-emergent Grade ≥ 3 hepatic laboratory toxicities were also similar across age groups.

The estimated median PFS was comparable between the age subgroups. The median (PFS 95% confidence interval [CI]) was 2.7 (2.6-2.8) and 2.6 (2.5-2.7) months for patients aged < 65 years and ≥ 65 years, respectively. Similarly, for patients aged

<70 years and ≥70 years, median (95% CI) PFS was 2.7 (2.6–2.8) and 2.5 (2.3–2.7) months, respectively.

In conclusion, this subgroup analysis of CONSIGN demonstrated that the safety and dosing profiles, as well as efficacy (based on PFS), were generally similar in older versus younger mCRC patients. The overall high rate of dose interruptions and reductions in all age subgroups highlights the importance of this tactic in managing TEAEs.

Impact of Dexamethasone on Regorafenib-Related Fatigue and Malaise in Metastatic Colorectal Cancer

Doctor Yuji Miyamoto

Fatigue is a well-recognised symptom of many cancers,¹¹ and can also be caused by cancer treatments, including multikinase inhibitors.¹² With regorafenib, fatigue is a common drug-related AE that has been observed across a range of clinical trials.⁵ In common with other regorafenib-related AEs, fatigue occurred mainly in the first few cycles of treatment in the Phase III CORRECT study, with a lower incidence in later cycles.¹³ Oral corticosteroids have been used to treat cancer-related fatigue, although the evidence for their effectiveness is limited.^{14,15}

A Phase II, multicentre, randomised, double-blind, placebo-controlled study (KSCC1402/HGCSG1402) prospectively evaluated the prophylactic effects of oral dexamethasone on regorafenib-related fatigue and malaise in patients with unresectable mCRC. Interim results¹⁶ were presented for 74 patients aged ≥20 years with histologically confirmed mCRC that failed to respond to standard therapy, had adequate organ function, and had an ECOG PS ≤1. They were randomised 1:1 to receive either regorafenib 160 mg/day for Weeks 1–3 of a 4-week cycle and dexamethasone 2 mg/day for 4 weeks, or regorafenib and placebo. Patients with Grade ≤1 fatigue or malaise were allowed to enrol in this study.

The primary endpoint was the incidence of all-grade fatigue or malaise as assessed by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 during the first 4 weeks. Secondary endpoints included patient-reported outcome (PRO; assessed by the Brief Fatigue Inventory), AEs, and the relative dose intensity of regorafenib.

Baseline characteristics were generally well-balanced between the arms. There were more patients with an ECOG PS of 0 in the dexamethasone arm (61% versus 47% in the placebo arm), and correspondingly more patients with an ECOG PS of 1 in the placebo arm (53% versus 39% in the dexamethasone arm). More patients in the placebo arm had hypertension (64%) as a comorbidity versus the dexamethasone group (33%).

The study highlighted that the incidence of all-grade fatigue and/or malaise by both the NCI-CTCAE v4.0 (regorafenib plus dexamethasone arm: 55.6% versus regorafenib plus placebo arm: 58.3%, $p=0.8119$) and PRO (regorafenib plus dexamethasone arm: 47.2% versus regorafenib plus placebo arm: 58.3%, $p=0.3450$) were numerically lower with the co-administration of dexamethasone with regorafenib compared with placebo, although these results were not statistically significant.¹⁶ The incidence of fatigue and/or malaise Grade ≥2 by PRO was significantly lower in the regorafenib plus dexamethasone arm versus the regorafenib plus placebo arm (27.8% versus 52.8%, $p=0.0306$). Using the PROs, reduction in the incidence of Grade ≥2 fatigue and/or malaise with dexamethasone versus placebo was seen from Week 1.

Dexamethasone was well-tolerated in this study. Compared to placebo, dexamethasone reduced the incidence of certain AEs (all grades), including alopecia (11.1% versus 27.8%), anorexia (30.6% versus 47.2%), and neutropenia (2.8% versus 19.4%). Dexamethasone compared with placebo also reduced the incidence of Grade ≥3 HFS (8.3% versus 13.9%) and Grade ≥3 sensory neuropathy (0% versus 5.6%). It was suggested that these effects of dexamethasone warrant further investigation to clarify if this oral steroid could help to limit the side effects of regorafenib in patients with mCRC.

In summary, although this study did not meet its primary endpoint, the PRO results indicated that dexamethasone might have a role to play in reducing the incidence of regorafenib-induced Grade ≥2 fatigue and/or malaise. Furthermore, certain other treatment-related AEs, such as HFS, were apparently reduced by dexamethasone co-administration. Patient follow-up is continuing and the longer-term outcomes in this study will be analysed in due course.

Regorafenib Dose Optimisation Study in Refractory Metastatic Colorectal Cancer

Doctor Tanios S. Bekaii-Saab

The most common AEs with regorafenib include palmar-plantar erythrodysesthesia syndrome (PPES, also known as hand-foot syndrome [HFS]),^{2,17,18} and fatigue.² HFS is a common side effect of multikinase drugs, and can have a profound effect on quality of life. Generally, HFS is seen in the first few weeks of regorafenib treatment.¹³ Thus, there is a need for effective management of regorafenib-associated toxicities.

In clinical practice, the approaches used to minimise regorafenib toxicities include dose reduction and/or revision of the interval schedule.^{19,20} However, there is a lack of high-quality evidence to support these strategies. A Phase II regorafenib dose optimisation study (ReDOS; NCT02368886)²¹ is being led by the Academic and Community Cancer Research Unit (ACCRU) network in the USA and aims to compare the effects of the standard regorafenib dose with a lower dose strategy.

ReDOS is a four-arm study during which approximately 120 patients will be randomised to either the escalating regorafenib dosing group (during which patients receive 80 mg/day in Week 1, 120 mg/day in Week 2, and 160 mg/day in Week 3, followed by 1 week off then cycle 2 will commence) or the stable regorafenib dosing group (patients receive daily regorafenib 160 mg for 21 days, then 1 week off followed by cycle 2). Within the two treatment arms, patients will then be assigned to either a pre-emptive strategy for palmar-plantar erythrodysesthesia syndrome (PPES) where clobetasol cream is prophylactically applied to hands and soles for the first 12 weeks or a reactive PPES treatment strategy where treatment is initiated at investigator discretion.²¹

Key inclusion criteria include: men and women (non-pregnant and using adequate contraception, surgically sterilised, or post-menopausal) aged >18 years; histologically confirmed mCRC; ECOG PS ≤1; acceptable bone marrow and organ function; and no prior regorafenib use. Patients are required to have failed all standard treatments for mCRC, including biological agents.

The primary endpoint of ReDOS is the 8-week planned continuation rate. This endpoint is defined as the proportion of patients that have completed two treatment cycles, and, if there is no disease

progression, intend to initiate a third cycle. Secondary endpoints include PFS, OS, and time-to-progression. Other assessments will be, the cumulative regorafenib dose, and the proportion of patients with Grade 3 or 4 HFS and/or fatigue. Patients will also self-report outcomes using the HFS-14 questionnaire, and these results will be compared between arms and between pre-emptive and reactive HFS strategies.

In order to calculate the required sample size, the assumed 8-week planned continuation rate is 75% in the control arm and the target continuation rate is 90% in the dose-escalation group. Thus, a one-side test with $\alpha=0.20$ and 80% power will require a total of 110 patients in this study. The aim is to enrol a total of 120 patients to allow for patient withdrawals. The accrual and follow-up of patients in ReDOS is expected to take approximately 2 years.

Efficacy and Safety of Regorafenib in Advanced Soft Tissue Sarcomas

Doctor Nicolas Penel

STS are a very heterogeneous group of rare solid tumours, with more than 100 types accounting for <1% of all adult tumours.^{22,23} Treatment of metastatic STS is challenging, and the median OS is only 12–18 months.^{24,25} The current mainstay of treatment for metastatic STS is chemotherapy, the choice of which depends upon the type of STS.²³ As angiogenesis plays a key role in STS biology,²⁶ targeted therapies are under investigation for STS management,^{23,27} including regorafenib.^{26,27} First-line treatment is generally doxorubicin, but there is no consensus on second-line treatment of STS, and the different options include: ifosfamide, trabectedin, pazopanib, dacarbazine, and eribulin.

The stratified, double-blind, placebo-controlled, randomised, Phase II trial REGOSARC (NCT01900743)²⁷ had four parallel cohorts of patients with advanced, refractory STS, mainly doxorubicin pre-treated.²⁸ Patients with liposarcomas (n=43), leiomyosarcomas (n=56), synovial sarcomas (n=27), or other sarcomas (n=56) were randomised 1:1 to receive either regorafenib at 160 mg/day for 3 weeks of each 4-week cycle or placebo, both with best supportive care. This study had a 95% statistical power to detect a 3-month longer PFS with regorafenib versus placebo.

In the final analysis, baseline characteristics were generally balanced between both arms within each STS cohort regarding proportion of women, age, metastases, and prior treatments. However, 50% of patients with leiomyosarcomas in the regorafenib group had ECOG PS Grade 3 versus 25% in the placebo group. Other sarcomas included in the trial were undifferentiated pleomorphic sarcoma (n=24), solitary fibrous tumours (n=7), angiosarcoma (n=6), and fibrosarcoma (n=4). Only a small number of patients had received prior pazopanib.

The primary endpoint was PFS assessed by the Response Evaluation Criteria in Solid Tumours in a blinded central radiological review. Regorafenib significantly prolonged PFS versus placebo in all sarcoma groups with the exception of liposarcomas, which may not be surprising due to the heterogeneity of angiogenesis in liposarcomas.²⁹ A pooled analysis of non-adipocytic sarcomas also showed significantly prolonged PFS with regorafenib versus placebo.²⁷ OS was not statistically significantly different between the regorafenib and placebo groups for any STS type,²⁷ which is most likely because 82% of patients in the placebo group crossed-over to the regorafenib group after disease progression.

No patients in REGOSARC had a complete tumour response. Five patients had a partial tumour response: one in the placebo arm (leiomyosarcoma, lasting 6 months), and four in the regorafenib arm (synovial sarcoma, 2.8 months; other sarcomas: 2, 7, and 13 months). Overall, the most frequent drug-related AEs (all grades) in the regorafenib group were asthenia (63%), diarrhoea (44%), mucositis (44%), HFS (44%), anorexia (38%), and arterial hypertension (36%). These AEs were all Grade 1-3 in severity. There was one toxic death due to hepatitis in the regorafenib group, which was considered to be drug-related.

Regorafenib met the primary objective of prolonging PFS in patients with pre-treated, non-adipocytic sarcoma versus placebo, and

showed superiority to placebo with regards to PFS. However, REGOSARC was not powered to demonstrate a statistically significant improvement in OS, due to the cross-over option for patients in the placebo group, and the small sample sizes. The AE profile was as expected for regorafenib.

The challenges in sarcoma treatment should be emphasised, particularly as there are numerous receptor tyrosine kinases, which are all potential targets for inhibition.³⁰ Of note, the PFS results with regorafenib²⁷ were similar to those with pazopanib, which is approved for refractory non-adipocytic STS with a significant 3-month PFS benefit,³¹ but is not active in liposarcomas.³²

Conclusions

Continued interest in regorafenib is clearly evident from these studies reported at ASCO 2016. As with other treatments for cancer, the use of regorafenib in elderly patients as well as management of TEAEs are key aspects of using the drug in clinical practice. These studies demonstrated that regorafenib not only has a similar efficacy and safety profile in elderly patients with mCRC compared with their younger counterparts, but that dose modifications are important in managing TEAEs regardless of age. Dexamethasone may also be an option to reduce regorafenib-related fatigue and other regorafenib related AEs, including HFS, although further investigation is warranted. Moreover, results from an ongoing study on dose-escalation and active use of clobetasol propionate will help to further refine the management of regorafenib-related HFS. The significant effects of regorafenib in extending PFS in non-adipocytic STS (leiomyosarcomas, synovial sarcomas, or other sarcomas) follows on from the success of regorafenib in the treatment of GIST, the most common type of STS, and may provide a much needed additional option in treating these challenging range of cancers.

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