REGORAFENIB IN ADVANCED AND REFRACTORY GASTROINTESTINAL CANCERS

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Disclosure: Medical writing assistance was funded by Bayer.
Received: 08.02.16 **Accepted:** 09.03.16
Citation: EMJ. 2016;1[2]:18-25.

ABSTRACT

The American Society of Clinical Oncology's 2016 Gastrointestinal Cancer Symposium (ASCO-GI), held in San Francisco, California, USA, provided a forum for leading basic scientists and clinical cancer specialists to discuss cutting-edge research in the field of gastrointestinal (GI) oncology. The quest to improve outcomes and patient lives by targeting unmet clinical need, such as refractory illness, fuelled much of the research presented at the 2016 edition of ASCO-GI. The symposium saw the presentation of a number of studies on the current stage of clinical research on regorafenib, an oral tyrosine-kinase inhibitor approved for use in both refractory metastatic colorectal cancer and metastatic GI stromal tumours.

INTRODUCTION

Regorafenib is a promiscuous multikinase inhibitor which blocks the activity of several protein kinases involved with angiogenesis (vascular endothelial growth factor [VEGF] receptors 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 receptors [FGFR]).[1] Trials of regorafenib for metastatic colorectal cancer (mCRC) progressed rapidly from Phase I to completion of the Phase III CORRECT trial and subsequent worldwide approval as a third-line therapy within 2 years.[2] The rapid recruitment of these studies is an illustration of the previously unmet need in this patient population. In addition to mCRC, regorafenib is approved in gastrointestinal stromal tumours (GIST)[3] and Phase III trials for advanced oesophago-gastric cancer (AOGC) are underway.[4]

SAFETY AND EFFICACY OF REGORAFENIB IN METASTATIC COLORECTAL CANCER IN THE UNITED STATES

The open-label, single-arm, Phase IIIb CONSIGN study (NCT01538680) (N=2,872) was designed to provide patients with refractory mCRC access to regorafenib prior to market authorisation, and to further assess the drug's safety and efficacy. CONSIGN was conducted in 25 countries in patients ≥18 years of age, with good (≤1) Eastern Cooperative Oncology Group performance status (ECOG PS). Patients had experienced progression at or within 3 months of therapy with approved treatment options and received regorafenib 160 mg/day on a 3 week on, 1 week off cycle. The primary efficacy outcome was progression-free survival (PFS) assessed per investigator according to local standards.[5]

Dr Udit Verma, University of Texas Southwestern Medical Center, Dallas, Texas, USA, presented a retrospective analysis of the US patient cohort from the CONSIGN trial, conducted in order to assess the safety and efficacy of regorafenib in patients from the USA.[6]

All patients assigned to treatment from the USA (N=364) received treatment and were included in the safety analysis. Median patient age was 60 years, and the majority of patients were white (80%). Notably, 38% of patients had wild-type *KRAS* and 59% had a mutated *KRAS* gene, which is a higher proportion of mutation than typically seen in mCRC.[7] Dr Verma speculated that this reflected the rapid progression of patients with *KRAS* mutations to a refractory state due to reduced treatment options.[8] The population was

characterised by advanced disease, with 82% of patients having been diagnosed with metastases ≥18 months prior to enrolment.

In the CONSIGN trial, patients from the USA appeared to achieve a longer median treatment duration (2.3 months, range: 0.03–30) than in the CORRECT study.[2] The median number of cycles was three (range: 1–33). The range of both outcomes indicates that some patients stayed on treatment for >2.5 years. The majority of patients started ≥3 cycles (55%), 19% started ≥6, and 10% started ≥9 cycles of therapy. The mean dose (±SD), excluding interruptions, was 148 (±17) mg/day, and the mean percentage of the planned dose was 77% (±20).

Treatment modifications, including dose reductions and re-escalations, and treatment interruptions or delays, occurred in 86% of patients. Dose reductions were carried out in 45% of these patients and the median duration of reduced dosing was 12 days (range: 1–45). A treatment interruption or a delay, the majority of which were brief (median 4.5 days, range: 1–33), occurred in 82% of patients.

Treatment-emergent adverse events (TEAEs) of Grade ≥3 occurred in 81% of patients, and were considered to be drug-related in 53% of patients. TEAEs leading to treatment modification occurred in 73% of patients, leading to a dose reduction in 43% of patients and discontinuation in 24%. Drug-related TEAEs leading to treatment modification occurred in 59% of patients.

The most common drug-related TEAEs of Grade ≥3 were hand-foot skin reactions (HFSRs; 16%), hypertension (15%), and fatigue (11%). Treatment-emergent hepatic and haematological laboratory values of Grade ≥3, which occurred regardless of relation to study drug, included increased bilirubin (9%), aspartate aminotransferase (6%), and alanine aminotransferase (3%); anaemia (5%); thrombocytopenia (2%); and neutropenia (2%). Median PFS was 2.3 months (Table 1), which was similar to data from the CORRECT trial (1.9 months). The effect of *KRAS* mutation on regorafenib efficacy in mCRC was investigated; however, PFS in the wild-type (2.1 months) and *KRAS*-mutant (2.3 months) sub-groups was similar in the CONSIGN USA cohort (Table 1).

To summarise, the safety profile of regorafenib in the US cohort was in line with the entirety of the international CONSIGN study, and the results were also similar to the CORRECT trial. PFS was similar irrespective of *KRAS* status and in line with results from CORRECT. The study demonstrated that a sub-group of patients respond very well to regorafenib (>2.5 years on the study drug). Characterising these individuals may offer an avenue to further investigate the presence of predictive biomarkers for regorafenib efficacy in this complex cancer, which has multiple potential contributory oncogenes.[9]

SAFETY AND EFFICACY OF REGORAFENIB IN JAPANESE PATIENTS WITH METASTATIC COLORECTAL CANCER IN CLINICAL PRACTICE

The Westernisation of diet and lifestyle in Japan is thought to be linked to an expected 10-fold increase in colorectal cancer incidence between 1975 and 2020.[10] Regorafenib was approved for unresectable mCRC in Japan based on the results of the CORRECT study, where *post hoc* analysis showed comparable efficacy in Japanese (CORRECT-J, n=100) and non-Japanese subpopulations (n=660), and a manageable adverse event (AE) profile.[2,11]

At ASCO-GI, Dr Yoshito Komatsu, Hokkaido University Hospital Cancer Center, Sapporo, Hokkaido, Japan, presented an interim analysis of a post-marketing surveillance (PMS) study on the efficacy and safety of regorafenib in Japanese patients with mCRC.[12] Patients with unresectable metastatic or recurrent CRC were treated with regorafenib 160 mg/day in a 3 week on, 1 week off cycle. Dose modifications, including reductions and interruptions, were applied at the discretion of the physician, depending on the severity of drug related AEs. Outcomes were prospectively monitored for 6 months post-initiation and 1-year survival data were also assessed.

Data from 796 of the 1,303 enrolled patients were included in the current analysis (March 2013–August 2015), with 787 patients included in the safety and efficacy data sets. The majority of the baseline characteristics in the PMS cohort were similar to the regorafenib-treated CORRECT-J cohort (N=67), except for baseline ECOG PS (≥2: 10% versus 0%, respectively) and prevalence of *KRAS* mutations (47% versus 58%, respectively). The majority of PMS patients (66%) started at the planned daily dose of regorafenib; starting dose was not affected by ECOG PS.

Table 1: Median progression-free survival (PFS) ±95% confidence interval (CI) in the USA CONSIGN cohort, and *KRAS*-wild-type and *KRAS*-mutant USA sub-groups.

CONSIGN sub-group	Number of patients (N)	Median PFS (months)	95% CI
USA cohort	364	2.3	2.0–2.6
USA *KRAS*-wild-type patients	138	2.1	1.8–2.7
USA *KRAS*-mutant patients	215	2.3	2.1–2.7

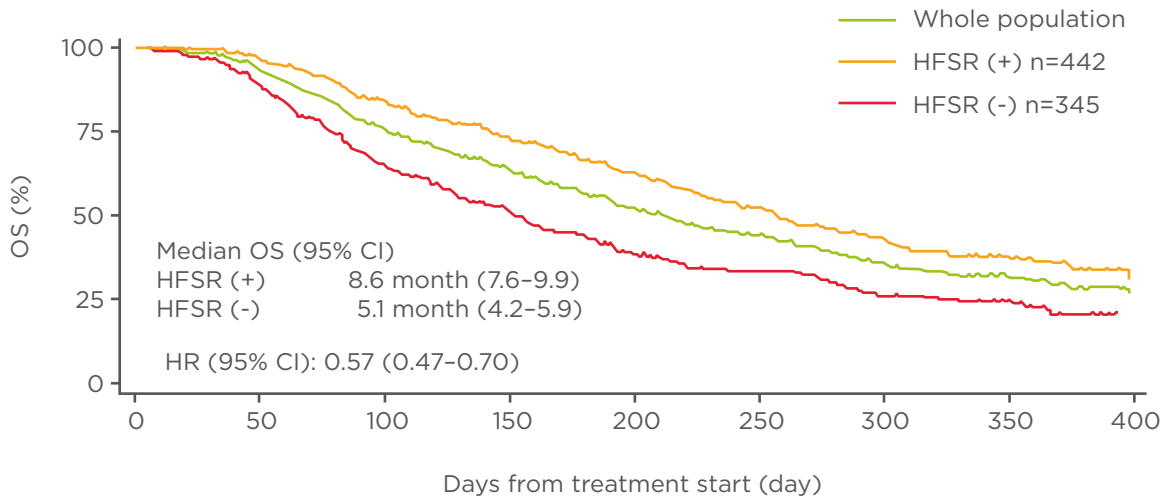

Figure 1: Interim analysis of survival stratified by the presence of any grade of HFSR.
HFSR: hand-foot skin reaction; OS: overall survival; HR: hazard ratio.

The majority of the 671 patients who had discontinued treatment at the time of analysis did so due to disease progression (58%). However, discontinuation due to drug-related AEs occurred more often in the PMS (37%) than in the CORRECT-J cohort (14%). Drug-related AEs of Grade ≥3 occurred in 51% of patients. The most common AEs were HFSR (18%), liver dysfunction (11%), hypertension (14%), thrombocytopenia (6%), fatigue (2%), and fever (1%). Although HFSR was the most common AE causing discontinuation, HFSR prophylaxis was not performed in all cases.

Common regorafenib-related AEs were most frequent in the first 3 weeks. The incidence of HFSR was highest in the second week (≈20%) and dropped to <5% from Week 5 onwards. The incidence of HFSR and liver dysfunction was lower in patients with a ≤120 mg/day initial dose than in patients starting on 160 mg/day.

Efficacy data were in line with the CORRECT-J population. Median (95% confidence interval [CI]) overall survival (OS) was 7.0 months (6.3–7.8; CORRECT-J, 6.6 months), and time-to-treatment failure was 2.1 months (1.9–2.2). Patients who had worse ECOG PS (≥2) had a shorter median OS (2.9 months [2.3–5.0]) than patients who had ECOG PS of 1 (5.9 months [5.2–6.8]) or 0 (9.9 months [8.4–11.6]).

Dr Komatsu indicated that the data from an exploratory analysis showing that median OS was longer in patients with HFSR than in those without HFSR was novel and in need of further investigation (Figure 1). Possible explanatory factors such as a higher dose of regorafenib have yet to be investigated. In addition, patients who developed HFSR during the first 4 weeks of treatment and who survived beyond Week 4 showed better median OS (8.3 months [7.0–9.5]) than those surviving at Week 4 who had not experienced HFSR (6.0 months [5.2–7.0]).

In conclusion, the interim results of the PMS suggest that the safety and efficacy profiles of regorafenib in Japanese patients in clinical practice is consistent with those from the CORRECT study. However, discontinuation due to regorafenib-related AEs occurred more often in the PMS than in the CORRECT-J cohort. The early onset of TEAEs suggest that frequent monitoring, particularly

in the early stages of treatment, may help physicians and patients manage drug-related AEs. In addition, dose modification and appropriate AE management including prophylaxis may help reduce discontinuation. The findings of the exploratory analysis suggesting a possible relationship between occurrence of HFSR and better OS warrants further investigation in the full analysis set and beyond.

EVALUATION OF CIRCULATING VASCULAR ENDOTHELIAL GROWTH FACTOR BASED BIOMARKERS IN THE INTEGRATE TRIAL

INTEGRATE (ANZCTR12612000239864) was a Phase II trial of regorafenib versus placebo (2:1; N=152) in refractory AOGC with crossover to active treatment allowed for patients in the placebo arm after progression. This multicentre, international trial recruited patients from countries including Australia, New Zealand, Canada, and Korea. Regorafenib was highly effective in prolonging PFS (11 weeks) compared with placebo (4 weeks). Although regorafenib was effective across geographical regions, the effect on PFS was significantly greater in Korea.[13]

Dr Sonia Yip, Senior Translational Research Fellow, NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia, presented a translational biomarker study on data from the INTEGRATE trial which aimed to predict which patients would benefit most from regorafenib.[4] Patients' blood samples were collected (N=145) at three time points: baseline, and Day 1 of cycles two and four. Dr Yip presented analyses VEGF isoforms (VEGF-A, B, C, and D) and serum vascular endothelial growth factor receptors (sVEGFR-1, 2, and 3), as well as interleukin (IL)-8, at baseline. As in the majority of cancers, high VEGF and circulating sVEGFR expression, which indicate upregulation of angiogenesis pathways, are associated with poor prognosis in gastric cancer.[14-16]

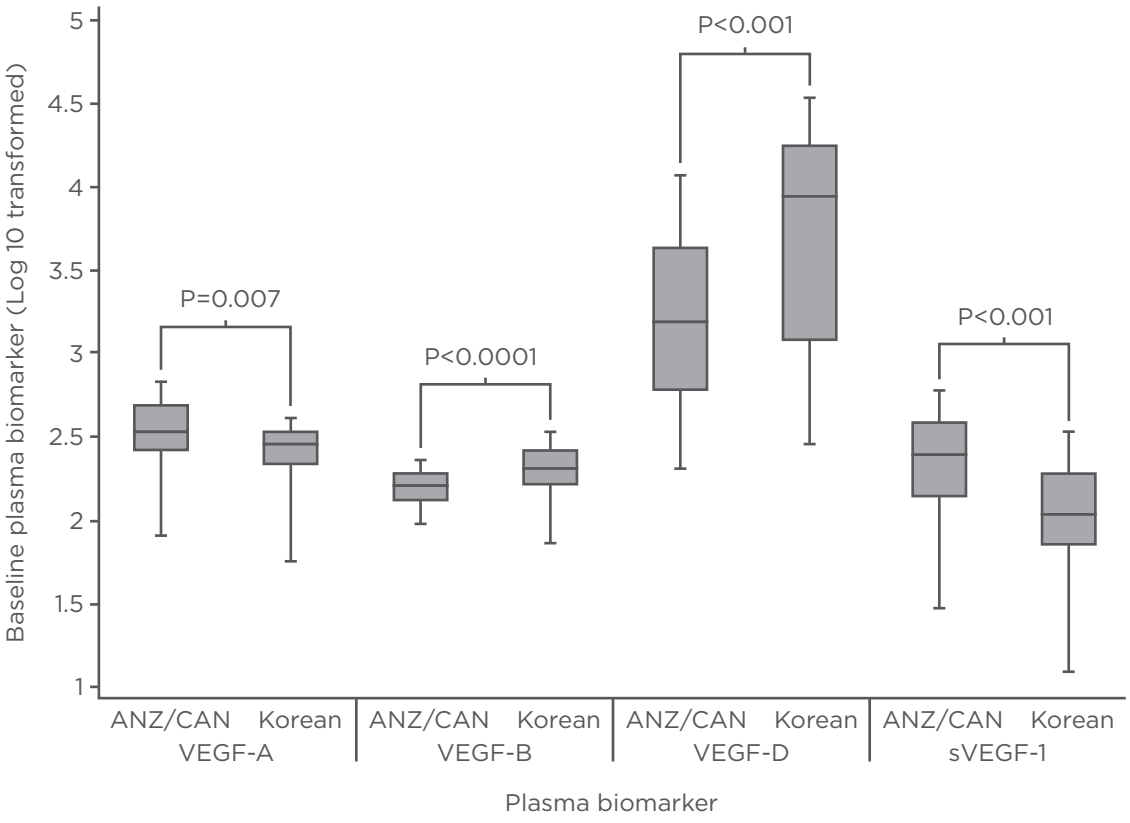

Figure 2: Median levels of circulating biomarkers in patients from Australia, New Zealand, and Canada versus those from Korea.

ANZ: Australia and New Zealand; CAN: Canada; VEGF: vascular endothelial growth factor; sVEGFR: serum vascular endothelial growth factor receptor.

All P values based on Wilcoxon test on median values. Boxes, median (±interquartile range). Whiskers, maximum and minimum.

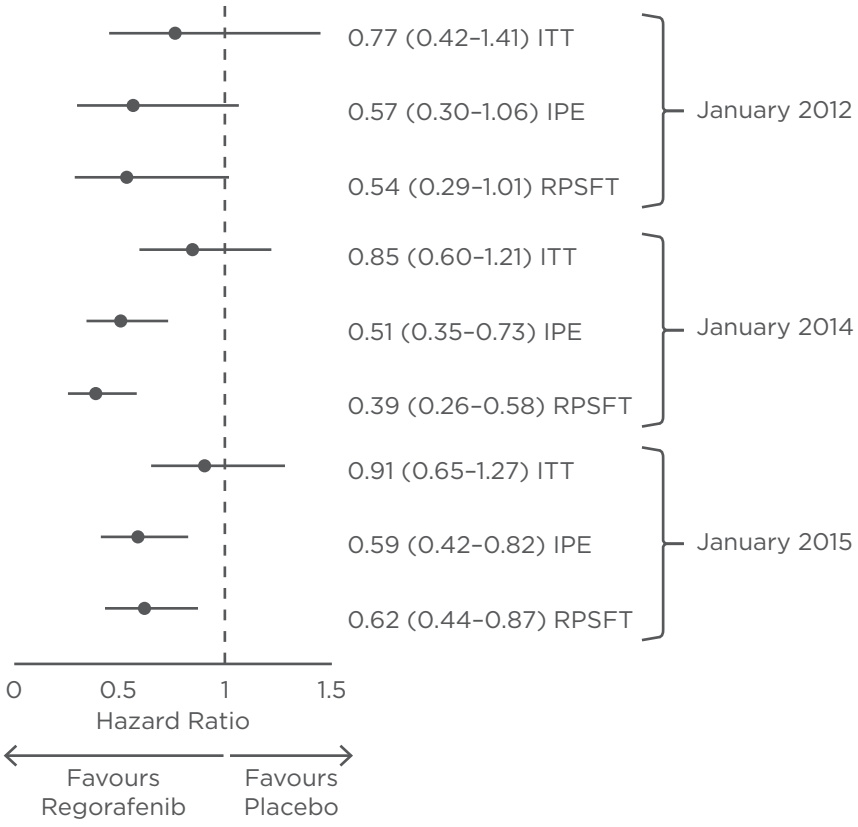

Figure 3: Forest plot of hazard ratio for overall survival in unadjusted (intent-to-treat) and model populations at three time points.

ITT: intent-to-treat, IPE: iterative parameter estimation; RPSFT: rank-preserving structural failure time.

Analysis of baseline markers revealed regional differences, with higher VEGF-A and sVEGFR-1 levels in patients from Australia, New Zealand, and Canada, compared with Korean patients (Figure 2). In contrast, VEGF-B and D isoforms were higher in Korean patients (Figure 2). The effect of region on the efficacy of regorafenib that was observed in the initial analysis of INTEGRATE was also maintained when evaluated in a multivariate analysis alongside baseline biomarkers. The physiological or treatment-related basis of regional differences in efficacy and VEGF-isoform levels remains to be elucidated.

Novel results were revealed in a correlation analysis of biomarkers with a very strong positive correlation existing between the plasma levels of VEGF-C and VEGF-A (r=0.88) and a strong correlation between IL-8 and VEGF-A, C, and D (r=0.57, 0.68, 0.66; respectively). A modest negative correlation was found between VEGF-D and sVEGFR-1 (r=-0.33).

Hazard ratios (HR [95% CI]) initially suggested a prognostic relationship between PFS and IL-8 (1.89 [1.01–3.56], p=0.047), VEGF-A (1.14 [1.01–1.30], p=0.037), and sVEGFR-1 (1.64 [1.01–2.66], p=0.045). However, the significance of these putative prognostic markers was lost when adjusting for age and neutrophil-to-lymphocyte ratio (NLR). A high NLR is a strong negative prognostic marker in gastric cancer and was found to be a strong prognostic marker for both poorer PFS (HR 1.56, p=0.01) and poorer OS (HR 1.83, p=0.001) in the INTEGRATE study.[17] Once again regional differences emerged, with lower NLRs observed in Korean patients (mean, 3.1 [2.3]) compared with patients from Australia, New Zealand, and Canada (mean, 5.4 [4.6], p<0.001). However, despite this indicator for better prognosis existing in Korean patients, who responded better to regorafenib, NLR was not found to be predictive of regorafenib efficacy.

In summary, despite novel study findings in terms of regional differences and correlations between VEGF and VEGFR isoforms, a predictive biomarker for the indication of regorafenib benefit remains elusive. Dr Yip and colleagues are continuing to analyse a broad base of biomarkers beyond the VEGF axis (IL-6, TIE-1, TIE-2, FGFR, PDFR, PDGFR, PAI-1, and PAI-2), other time points from within the

regorafenib treatment cycle will be investigated in addition to tissue biomarkers. Putative results will be used to inform the biomarker analysis of the Phase III INTEGRATE II study.[4]

OVERALL SURVIVAL ANALYSIS: MODELLING CROSSOVER IMPACT IN ADVANCED GASTROINTESTINAL STROMAL TUMOURS

The management of GIST has radically improved over the last 16 years, driven by an understanding of the root cause of most cases of the disease, mutated tyrosine-kinase signalling.[18] A series of highly potent tyrosine kinase inhibitors (TKIs; imatinib, sunitinib, and regorafenib), are now approved by regulatory authorities worldwide for the treatment of unresectable and metastatic GIST.[19]

ASCO-GI saw data presented from an exploratory analysis on the Phase III GRID trial of regorafenib in advanced GIST, conducted by a team led by Prof George D. Demetri, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA.[20] GRID (NCT01271712) was a randomised, multinational trial of regorafenib (160 mg/day, 3 weeks on, 1 week off) versus placebo (2:1; N=199). The primary endpoint was PFS with OS as a secondary endpoint, allowing the trial to be designed with a crossover to open-label regorafenib for patients initially randomised to placebo whose GIST progressed objectively. Regorafenib significantly prolonged PFS compared with placebo (median PFS, 4.8 months versus 0.9 months, HR 0.27 [0.19, 0.39], p<0.0001). However, there was no significant difference in OS at the time of primary-endpoint assessment due to low numbers of death in the initial analysis and, likely also to the confounding effect of placebo patients crossing to open-label regorafenib.[3]

The advantages of the PFS endpoint in allowing crossover to active therapy is recognised by the Food and Drug Administration (FDA).[21] Dr Demetri noted that this type of trial design was particularly advantageous to patients with advanced TKI-resistant GIST where progression commonly occurs in <1 month and a fatal outcome from uncontrolled disease is rapid.[3] In addition, crossover design may also address patient concerns that placebo-controlled trials withhold treatment from those in need. However, the use of a crossover design, particularly in the case of a highly-active study drug and rapidly-progressing disease, has the disadvantage of confounding OS as an endpoint due to swift mixing of the placebo group with patients who cross over to receive the active study drug.

The current exploratory analysis was conducted on long-term follow-up data from patients enrolled in GRID and tested two statistical methods designed to model the effect of patients continuing on placebo without crossover. Beyond assessing the effect of regorafenib on OS in advanced GIST, the study aimed to compare exploratory analyses that adjusted for the effect of crossover on OS using high-quality study data. Dr Demetri and colleagues compared two established randomisation-based statistical methods, rank-preserving structural failure time (RPSFT) and iterative parameter estimation (IPE).[22,23] Analyses were conducted at three different points of data collection (January 2012, January 2014, and June 2015), each of which included the full randomised patient population.

Characteristically for patients with advanced disease, participants had been heavily pre-treated. Close to half (43%) of patients had received >2 lines of therapy previously, indicating that they had been treated with experimental/investigational or off-label TKIs in addition to the standard imatinib and sunitinib, which all participants had received.

At analysis of the primary endpoint in the GRID study in 2012, 46 deaths (23% of total study population) had occurred. Mean (SD) time on regorafenib was 5.5 months (2.8) for the regorafenib arm and 3.5 months (2.1) for the placebo arm. The majority of placebo-treated patients (n=56, 85%) had crossed over to regorafenib immediately after progression. By the 2014 data analysis, 139 (70%) deaths had occurred, and mean time on regorafenib was 12.6 months (10.4) and 9.7 months (8.7) for the regorafenib and placebo arms, respectively. At this time point, all surviving patients were receiving regorafenib and 58 (88%) of the placebo arm had crossed over. At the final analysis time point, 162 (81%) deaths had occurred and mean time on regorafenib was 14.0 months (13.2) and 10.8 months (11.3) for the regorafenib and placebo arms, respectively.

Kaplan–Meier curves showed that survival probability in the unadjusted placebo arm was statistically similar to that of the regorafenib arm at all time points analysed, indicative of the effect of crossover to open-label regorafenib. However, in both models statistically adjusted for the impact of

crossover, survival probability diverged, showing a marked advantage for patients in the regorafenib arm over the modelled results of placebo treatment alone. Dr Demetri noted that the survival curves for the IPE and RPSFT were strikingly similar, a reassuring sign in terms of the statistical validity of the models.

HRs for the unadjusted intent-to-treat (ITT) population and the two models are illustrated in Figure 3. In 2012, the HR for the unadjusted ITT population indicated a 23% decrease in the risk of death in the regorafenib arm. The decreased risk fell to 15% and 9% for the 2014 and 2015 time points, respectively, further illustrating the effect of post-progression crossover treatment in the placebo arm. In contrast, the decreased risk of death in the IPE model was 43%, 49%, and 41%, at the 2012, 2014, and 2015 time points, respectively. Data from the RPSFT model showed a 46%, 61%, and 38% decrease in the risk of death at the three respective time points. The data from the IPE model appeared more stable, suggesting this may be the preferred model for future studies. Dr Demetri emphasised the benefit shown in the two models which was of a magnitude rarely reached within clinical trials in oncology. This was backed up by Kaplan–Meier analysis of the ITT population showing that approximately 12% of patients with advanced TKI-resistant GIST were still alive after 4 years on regorafenib.

In his conclusion, Dr Demetri discussed two potentially exciting implications from the current study, beyond the positive treatment effect. Firstly, the use of these statistical models on data from a high-quality clinical trial increases the understanding of the effect of the increasingly utilised and ethically sound crossover clinical-trial design on the OS endpoint. Secondly, the relative preponderance of long responders to regorafenib treatment combined with the comparatively simple tumour biology found in GIST may provide a small but powerful pool of participants for future predictive-biomarker studies on regorafenib.

CONCLUSION

Regorafenib has shown efficacy in different types of advanced and metastatic gastrointestinal (GI) cancers in randomised trials. Prospective studies have now replicated both efficacy and safety data from these trials in the clinical setting. Identifying the patient population who will benefit most from regorafenib treatment remains challenging and research continues to identify predictive biomarkers, towards a rational placement of regorafenib in the optimal care of patients with GI cancers. Studies on the growing population of patients who show long-term benefit from regorafenib treatment may offer an avenue of research. Finally, the use of the modelling in crossover studies will be of use across the field of oncology and regulatory science to estimate efficacy in terms of OS in refractory disease states where a lack of crossover may not be ethically tenable.

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