REGORAFENIB IN ADVANCED AND REFRACTORY GASTROINTESTINAL CANCERS

Summary of Presentations from the European Society of Medical Oncology (ESMO) 18th World Congress on Gastrointestinal Cancer (WCGI) held in Barcelona, Spain from 28th June–2nd July 2016

Speakers

Eric Van Cutsem,[1] Michael Ducreux,[2] Diether Lambrechts[3]

1. University Hospitals Leuven, Leuven, Belgium
2. Gustave Roussy Cancer Campus Grand Paris, Villejuif, France
3. VIB Vesalius Research Center, Leuven, Belgium

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MEETING SUMMARY

The European Society for Medical Oncology's (ESMO) 18th World Congress on Gastrointestinal Cancer (WCGI) was held in Barcelona from 28th June–2nd July 2016. Presentations covered gastrointestinal (GI) cancers of every aetiology and site within the GI tract, as well as the major aspects of cancer management from screening to novel therapeutic options. Tyrosine kinase inhibitors (TKIs), with their ability to block key mechanisms required for tumour growth, featured heavily in this year's presentations at WCGI. Data on the oral TKI regorafenib featured prominently in both poster discussion tours and oral presentations, emphasising the continuing interest in the evolution of this therapy within the clinical arsenal of physicians tackling GI cancers.

Introduction

The multikinase inhibitor regorafenib acts on several protein kinases involved in important aspects of tumour growth including 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 receptors and fibroblast growth factor receptors).[1] Regorafenib has been approved for treatment of a number of cancers of the GI tract including metastatic colorectal cancer (mCRC) and GI stromal tumours based on the results of Phase III trials.[2,3] Presentations at the 2016 WCGI reflect the continuing efforts to refine and target current regorafenib treatment regimens.

The Effect of Single Nucleotide Polymorphisms on the Efficacy and Safety of Regorafenib in Metastatic Colorectal Cancer

Doctor Deither Lambrechts

Single nucleotide polymorphisms (SNPs) modify susceptibility to a wide range of diseases and also

contribute to the efficacy and side effect profile of therapeutic interventions. Genotyping already drives treatment decisions in the field of GI oncology, for example the TKI imatinib is indicated for use in KIT (CD117)-positive unresectable or metastatic GI stromal tumours.[4] Pharmacogenomics is also already well-established in other fields, with the US Food and Drug Administration (FDA) highlighting the utility of dose adjustment of warfarin based on genotyping of the drug-metabolising enzyme CYP2C9 in the avoidance of side effects.[4]

An analysis of SNPs in the CORRECT cohort (N=760), investigating putative relationships with both efficacy and safety was presented at WCGI. In the pivotal Phase III CORRECT trial,[5] regorafenib significantly improved overall survival (OS) (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.64–0.94; p=0.0052) and progression-free survival (PFS) (HR: 0.49; 95% CI: 0.42–0.58; p<0.0001) versus placebo in patients with mCRC refractory to available therapies.[3] The relationship between angiogenesis-related SNPs in the VEGF and TIE2 signalling pathways and efficacy was assessed, in addition to possible links between SNPs in absorption, distribution, metabolism, and excretion (ADME) genes, and selected Grade 3–4 adverse events (AEs) (diarrhoea, fatigue, mucositis, hypertension, and hand-foot skin reactions).

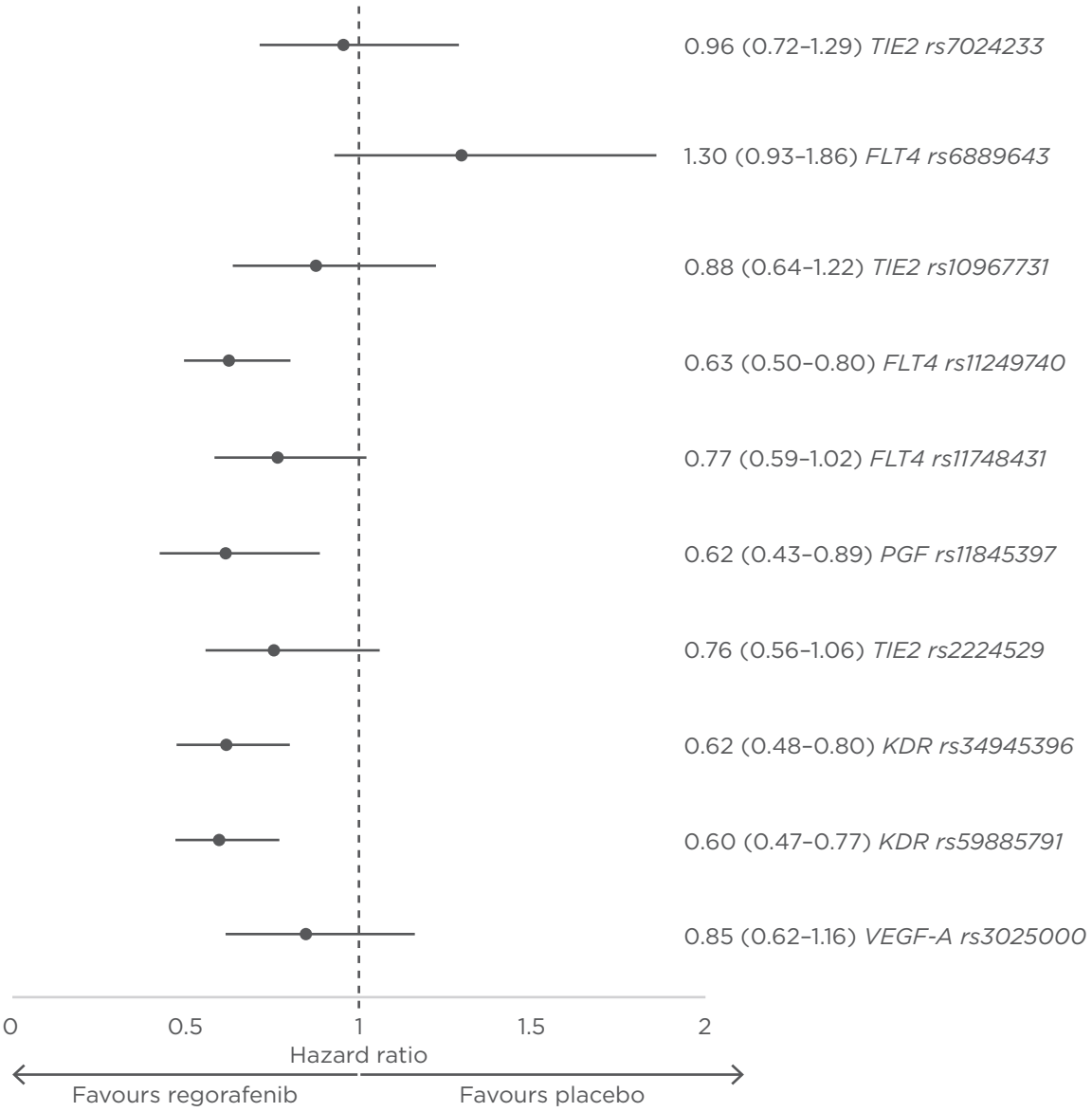

Figure 1: Cox regression analysis on overall survival for regorafenib 160 mg/day versus placebo for major homozygous genotype of all SNPs with an unadjusted p<0.05 and SNPs of special interest.
SNP: single nucleotide polymorphisms; VEGF-A: vascular endothelial growth factor A; FLT: F-fluorothymidine. PGF: placental growth factor; KDR: kinase insert domain-containing receptor.

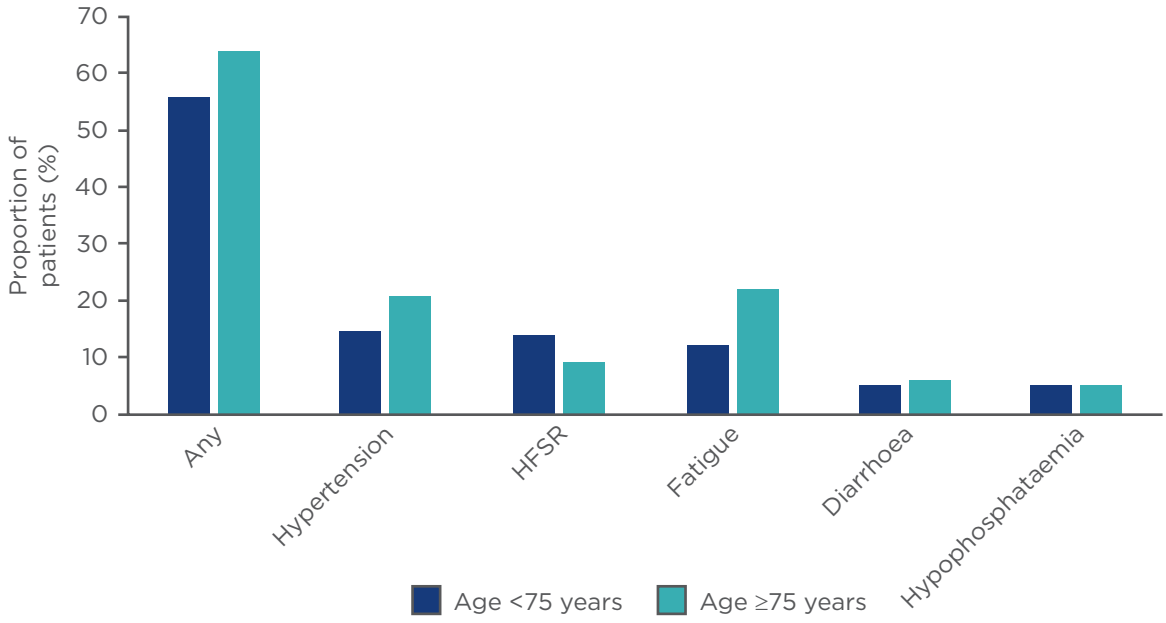

Figure 2: Treatment-emergent adverse events of Grade ≥3.
Adverse events were graded using the NCI-CTCAE v4.0.
HFSR: hand-foot skin reaction; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.

Whole-blood genotyping was performed on close to two-thirds of the CORRECT study population. Baseline characteristics and outcomes were similar in the genotyped proportion of the CORRECT population compared with the full population. Notably, none of the eight identified efficacy-related SNPs represented VEGF-A SNPs, which are known to be related to other antiangiogenic therapies such as bevacizumab or aflibercept.[6-8] Furthermore, the results were in line with the diverse nature of regorafenib's TKI blockade resulting in a wider range of efficacy-related SNPs in comparison with bevacizumab, which solely targets VEGF and angiogenesis. SNPs with significant relationships to efficacy were associated with either the *TIE2* gene or the *FLT4* tyrosine kinase receptor gene (Figure 1).

Following statistical analysis for multiple testing only a single SNP in the *TIE2* gene, *rs7024233*, remained significant (Figure 1). However, the level of stringency involved in correcting the large number of angiogenesis-related SNPs (n=258) in this study set an extremely high bar for statistical significance, and further studies may add to the weight of evidence in those SNPs where significance did not survive correction.

A total of 211 VEGF SNPs and 54 ADME SNPs remained following quality control and were included in the analysis. The particular rarity of the ADME SNPs necessitated a combined gene-wise analysis. Following this revised analysis, four genes were found to be significantly associated with specific safety-related events. The combined prevalence of these SNPs was estimated at 10–20%, which is similar to the proportion of patients suffering these Grade 3–4 AEs during regorafenib therapy.[3]

In summary, preliminary exploratory analysis of SNPs in the CORRECT population found that only a single SNP in the *TIE2* gene showed a statistically significant interaction with treatment and OS, following stringent statistical correction methods. Four significant variants in metabolism genes were found, which may have the potential to predict tolerability in patients with mCRC treated with regorafenib. Gene sequencing may allow clinicians to anticipate those patients who will suffer more AEs, enabling early dose adjustment.

Safety and Efficacy of Regorafenib in Elderly Metastatic Colorectal Cancer Patients

Professor Eric van Cutsem

Over the past 15 years, oncologists have seen a large upward shift in the numbers of elderly

patients with mCRC in their clinics. The very definition of elderly appears to have changed over the past 10–15 years, with patients >65 years no longer deemed elderly by some in the clinical community. However, elderly patients may still present treatment challenges due to an increased risk of drug-related toxicity.[9] Specific data are needed in order to aid treatment decisions in elderly patients where expectations from therapy and risk-benefit ratios may be weighted differently. To this end, a study on the efficacy and safety of regorafenib in a subgroup of the CONSIGN-study population aged ≥75 years of age was conducted, following and in complement to a previous analysis presented at ASCO 2016.[10]

The open-label, single-arm, Phase IIIb CONSIGN study[11] (N=2,872) was designed to provide patients with refractory mCRC access to regorafenib prior to market authorisation, following FDA, and European Medicines Agency (EMA) approval based on data from CORRECT. In addition, the CONSIGN study allowed continued assessment of regorafenib 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 within 3 months of therapy with approved treatment options and received regorafenib, 160 mg/day on a 3 weeks on, 1 week off cycle. The primary endpoint was safety, and the efficacy outcome was PFS assessed per investigator according to local standards.[12]

Dose interruptions and delays were indicative of similar tolerability in the two age groups. Although the majority of patients underwent some form of treatment interruption or delay, the median duration of these interruptions was low for both groups. Similarly, differences between the two groups in Grade 3 AEs were slight (Figure 2). Some regorafenib-related AEs tended to be somewhat more common in the elderly patient group compared with the younger age group. Treatment-emergent National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 tended to be more common in the younger age group; however, the differences were slight and unlikely to be indicative of a difference in toxicity between the two groups. The sole efficacy outcome assessed in the CONSIGN trial was PFS. Both age groups had a similar median PFS of approximately 2.5 months.

In summary, regorafenib was well-tolerated in the elderly and younger subpopulations of the CONSIGN trial. Treatment modifications and discontinuations were similar between the two groups; the high rates were likely indicative of active management of AEs by physicians, which is key to the management of treatment-emergent AEs during therapy with regorafenib. Given the similar efficacy between the two groups and adequate tolerability profiles, regorafenib appears to be a suitable treatment for elderly patients with previously treated mCRC.

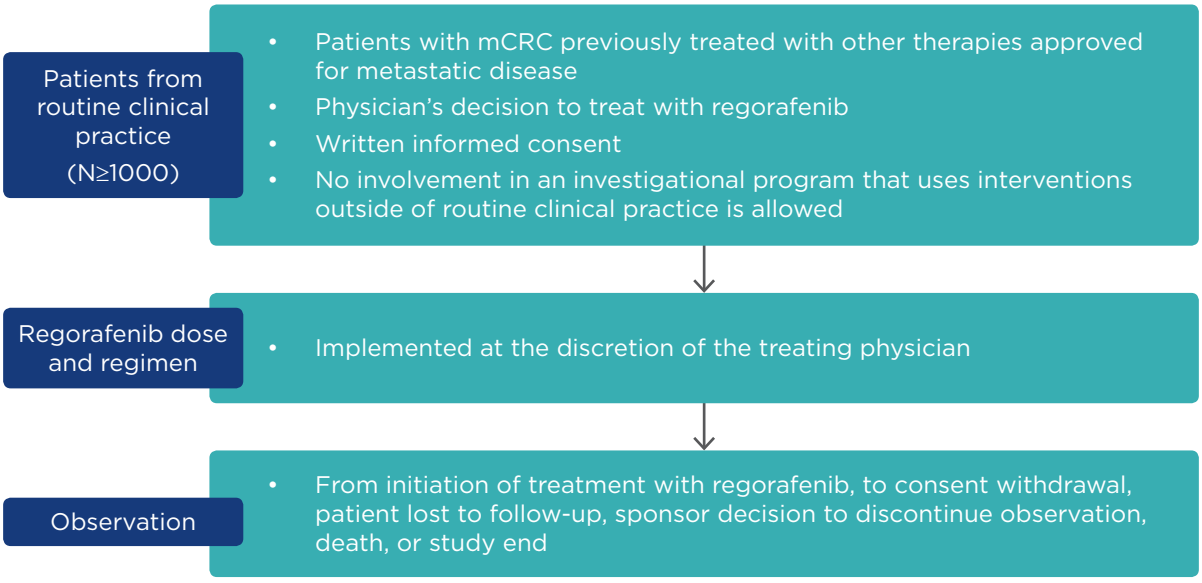

Figure 3: CORRELATE[13] study design.
mCRC: metastatic colorectal cancer.

Regorafenib in Metastatic Colorectal Cancer in Routine Clinical Practice

Professor Michael Ducreux

The CORRELATE trial[13] aims to characterise the safety and efficacy of regorafenib for mCRC in a real-world population in routine clinical practice. CORRELATE is a prospective, observational, multicentre trial conducted in >25 countries in Europe, Latin America, and the Asia-Pacific region. Approximately 1,000 patients with mCRC, selected for regorafenib therapy according to local health authority guidelines, will be recruited. Dose interruptions and reductions will be permitted for the management of AEs (Figure 3).

The primary endpoint is the incidence of treatment-emergent AEs with OS, PFS, disease control rate, health-related quality of life, and healthcare resource use as secondary endpoints. Data will be sourced from medical records, routine measurements, and patient-reported outcomes. Patients receiving at least one dose of regorafenib will be included in the analysis. The final analysis will be performed when all patients have been followed for 6 months from the time they discontinue regorafenib (excluding those withdrawing early due to death, consent withdrawal, or patient/investigator decisions). An interim analysis will occur after 500 patients have been observed for at least 3 months.

As of February 2016, 404 patients have been enrolled with recruitment ongoing. The primary completion date is estimated as September 2017.[14]

Conclusion

Positive data in mCRC continues to accrue with the prospect of genetic screening guiding treatment decisions to promote both safety and efficacy. Regorafenib appears to be an effective treatment option in the sometimes difficult-to-treat elderly population, and data from the ongoing CORRELATE study will add further to the understanding of safety and patient-related outcomes, as well as real-world efficacy, in the near future.

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