Curr Oncol Rep (2016) 18: 49
DOI 10.1007/s11912-016-0536-7

SARCOMAS (SR PATEL, SECTION EDITOR)

An Unusual Case of Central Retinal Vein Occlusion and Review of the Toxicity Profile of Regorafenib in GIST Patients

Gustavo Schvartsman[1] · Michael J. Wagner[1] · Chrystia M. Zobniw[2] · Van Anh Trinh[2] · Shreyaskumar Patel[3] · Neeta Somaiah[3]

Published online: 20 June 2016

Abstract Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract with around 5000 new cases per year. Outcomes for patients with GIST dramatically improved after the development of tyrosine kinase inhibitors targeted against the aberrant signaling pathways that drive GIST oncogenesis. Majority of patients derive benefit from first-line imatinib, and the type of driver mutation is predictive of response. However, almost half of the patients eventually develop resistance to initial targeted therapy and further lines of treatment do not have the same impact. Regorafenib is an oral multi-kinase inhibitor approved as a third-line therapy for advanced GIST and though its efficacy is limited in comparison to imatinib, it has activity across the various driver mutation categories in GIST even in the setting of imatinib resistance. Herein, we describe a case of central retinal vein occlusion (CRVO) secondary to regorafenib and review regorafenib's efficacy and toxicity profile.

This article is part of the Topical Collection on *Sarcomas*

Gustavo Schvartsman and Michael J. Wagner contributed equally to this work.

✉ Neeta Somaiah
nsomaiah@mdanderson.org

[1] Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, 1400 Holcombe Boulevard, unit 463, Houston, TX 77030, USA

[2] Department of Pharmacy Clinical Programs, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

[3] Department of Sarcoma Medical Oncology, University of Texas M.D. Anderson Cancer Center, 1400 Holcombe Boulevard, unit 450, Houston, TX 77030, USA

Keywords Gastrointestinal stromal tumor · GIST · Regorafenib · Tyrosine kinase inhibitors · KIT · Central retinal vein occlusion

Introduction

Gastrointestinal stromal tumors (GIST) arise from pluripotent mesenchymal cells. During physiologic development, these cells differentiate into interstitial cells of Cajal in the myenteric plexus of the GI tract to regulate gut motility. The majority of GIST tumors (60 %) arise in the stomach, 30 % arise in the small bowel and less frequently they are found in the appendix, colon, rectum, or esophagus [1]. GIST accounts for less than 1 % of GI cancers overall, however, it represents the most common mesenchymal neoplasm of the GI tract with an incidence of 5000 new cases per year in the USA.

The expression of KIT (CD117) is one of the hallmarks for diagnosis and present in approximately 95 % of GIST tumors assessed by immunohistochemistry [1]. Discovered-on-GIST-1 (DOG-1) is a more sensitive marker and can be helpful especially in the small percentage of KIT-negative GISTs. Gain-of-function mutations of *KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) genes are the key pathogenic drivers in 80 and 10 % of GISTs, respectively. These molecular lesions result in ligand-independent, constitutively active transmembrane receptor tyrosine kinases (RTKs), driving the development and progression of GIST via signaling through the MAPK and PI3K-AKT pathways [2, 3]. *KIT* and *PDGFRA* mutations activate similar pathways and are mutually exclusive in GIST [4, 5]. About 10–15 % of GISTs have no detectable *KIT* or *PDGFRA* mutations and are referred to as wild-type GIST. However, we now know that there are alternate aberrant pathways (succinate

dehydrogenase (SDH) deficiency, BRAF mutations, etc.) that are driving oncogenesis in these so-called wild-type tumors.

Localized GISTs are best managed with surgical resection. Prognosis is primarily based on tumor characteristics: mitotic rate, size, and site of origin. Tumors less than 5 cm with less than 5 mitoses per 50 high-power field (HPF) have a metastasis rate and mortality less than 4 %, while tumors with a mitotic rate greater than 5/50 HPF and greater than 10 cm in size can have a metastasis rate and mortality of up to 90 %. Prior to imatinib, outcomes for GIST patients were very poor since response rate to chemotherapy was less than 5 % [6]. Targeted therapy with tyrosine kinase inhibitors revolutionized care for these patients. Imatinib was approved for first-line treatment for advanced GIST in 2002 and for adjuvant treatment after surgical resection in high-risk patients in 2012 [7–9]. Although more than 80 % of patients treated with imatinib will show clinical improvement, half of them eventually progress after 2 years on therapy due to acquired imatinib resistance. Resistance can develop through various mechanisms, the most common being secondary *KIT* mutations in clonally expanded cancer cells, hindering drugs from binding or inactivating the aberrant kinases [10, 11, 12••]. Although both sunitinib and imatinib bind within the ATP-binding domain of both KIT and PDGFRs, they belong to different chemical classes and presumably have different binding characteristics and affinities. Furthermore, sunitinib inhibits the vascular endothelial growth factor (VEGF) receptors, which are important in tumor-related angiogenesis, a characteristic that imatinib does not share [13–15]. Sunitinib was approved as second-line therapy in 2006 after showing improved time to progression compared with placebo in GIST patients previously treated with imatinib [16]. Several other agents were studied in an attempt to overcome imatinib resistance, such as nilotinib, dasatinib, sorafenib, and pazopanib [17–28]. Phase I and II studies showed some activity in heavily treated GIST patients, but overall, the efficacy of these agents is limited. Regorafenib (Stivarga, Bayer HealthCare), a multikinase inhibitor structurally related to sorafenib, was approved for the treatment of unresectable GIST after failure of imatinib and sunitinib in 2013 based on improved progression free survival (PFS) demonstrated in the GRID trial [29••]. Regorafenib targets VEGFR1-3, c-KIT, TIE-2, PDGFR-b, FGFR-1, RET, RAF-1 (CRAF), BRAF, and p38 MAP kinase.

Compared to imatinib, the toxicity profile for second- and third-line therapies for GIST is less favorable [7]. Specifically, the tolerance to regorafenib tends to be poor in GIST patients and affects therapeutic adherence. Here, we report an unusual case of central retinal vein occlusion (CRVO) that occurred in a patient undergoing treatment with regorafenib followed by a review of the toxicity profile of regorafenib in GIST.

Case Report

A 74-year-old Caucasian male presented to the clinic for treatment recommendations for metastatic GIST of the omentum. His medical history was significant for hypertension, type 2 diabetes mellitus, benign prostate hyperplasia, hyperlipidemia, and glaucoma. The patient achieved a significant tumor response on imatinib 400 mg daily and subsequently underwent surgical resection. Approximately 2.5 years after his diagnosis, routine surveillance imaging showed pelvic recurrence that was biopsy proven to be GIST with a *KIT* exon 11 mutation. Therapy was switched to sunitinib 37.5 mg daily, which was discontinued 4 weeks later due to mucositis, intermittent fever, and decreased appetite. He then received nilotinib 400 mg twice a day, which he tolerated with minimal side effects. However, nilotinib was discontinued after disease progression at 3 months. Thereafter he was initiated on regorafenib 120 mg daily. After 8 weeks of treatment, he developed painful blisters with peeling and hyperkeratosis in his palms and soles (grade 3 hand-foot syndrome CTCAE v 4.0), which required dose reduction to 80 mg daily. He continued regorafenib 80 mg daily for 11 months, when he noted significant deterioration in vision manifesting as blurry vision and floaters in his right eye. After being evaluated by his ophthalmologist and a retina specialist, he was diagnosed with CRVO in the right eye. Given his other risk factors for CRVO were under good control, the event was attributed to the regorafenib therapy. Regorafenib was discontinued with stabilization of his eye symptoms and he resumed imatinib 800 mg daily. This was felt to be the best since some of his metastases were beginning to progress on regorafenib. Soon he began intravitreal injections of bevacizumab with significant improvement in his vision. He remained on imatinib for approximately 2 months while awaiting enrolment on a clinical trial. Although there was no recurrence of his visual symptoms, his GIST continued to progress and he ultimately succumbed to the disease.

Case Discussion

Central retinal vein occlusion (CRVO) is a major vascular cause of visual deterioration in patients older than fifty. CRVO occurs due to thrombus formation in the area of the lamina cribrosa within the central retinal vein. It is characterized by a "blood and thunder" appearance with extensive, widespread intraretinal hemorrhages radiating from the optic nerve head, and dilated and tortuous retinal veins [30]. The incidence of CRVO is estimated to be about 0.1 % [31]. Predisposing factors include hypertension, diabetes mellitus, hypercoagulable states, or glaucoma [30, 32]. Standard treatment for CRVO includes intravitreal injections of bevacizumab or ranibizumab, both of which are antibodies directed against VEGF [33]. To our knowledge, there have been no published case reports

documenting the development of CRVO in patients treated with regorafenib and the patient described above represents the first case of CRVO associated with regorafenib.

Bilateral CRVO has previously been reported in a patient on sorafenib [34]. Both sorafenib and regorafenib inhibit RAF-1 and BRAF. Compared with sorafenib, regorafenib is a more potent inhibitor of KIT, PDGFR, and VEGFR-2. The spectrum of activity of regorafenib is also broader than that of sorafenib, encompassing additional kinases involved in oncogenesis and angiogenesis, such as p38 mitogen-activated protein kinase and TIE-2 [35].

The eye and its adnexa can be susceptible to targeted anticancer therapy because many of the critical signaling molecules that drive cancer growth are also expressed in ocular tissues. The optic nerve in particular is susceptible to the effects of c-KIT or MEK inhibitors. VEGF targeting agents have rarely been reported to cause direct ocular toxicity, but they are commonly associated with toxicities that can lead to visual symptoms such as hypertension and increased risk of arterial and venous thromboembolic events [36]. Although the exact mechanism of thromboembolic events is not well understood, it is postulated to involve the role of VEGF and nitric oxide in maintaining the integrity of endothelial cells and platelet aggregation and degranulation [33]. Anti-VEGF therapy can cause disruption of this mechanism, triggering the thrombotic cascade.

Although this patient had a CRVO while on regorafenib, it was treated with additional VEGF inhibition using direct intravitreal administration of bevacizumab. Intravitreal injections of VEGF pathway inhibitors have been shown effective in the treatment of several ocular disorders including diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, and retinal vein occlusion complications [36]. It is proposed that the ischemia caused by these conditions including CRVO leads to an upregulation of VEGF and inflammatory mediators. VEGF causes increased vascular permeability by loosening tight junctions between endothelial cells, break down of the inner and outer blood-retinal barrier, and promotes endothelial cell migration and proliferation leading to neovascularization. The neovascularization and increased vascular permeability lead to the vision loss. Hence, intraocular injection of various VEGF inhibitors has been studied and shown to improve visual symptoms associated with retinal vein occlusion [37]. For this patient who developed visual impairment secondary to CRVO while on regorafenib, intravitreous bevacizumab injection and regorafenib discontinuation led to improvement in his vision.

Review of Regorafenib Toxicity in GIST Patients

Regorafenib is currently approved for the treatment of patients with unresectable or metastatic GIST previously treated with imatinib and sunitinib and for metastatic colorectal cancer after failure of oxaliplatin and irinotecan-based chemotherapy. A phase I dose escalation trial that included several solid tumors recommended the dose of 160 mg daily in a 21 days on, 7 days off schedule for further studies [38••]. In this trial, regorafenib showed an acceptable safety profile, with 83 % patients experiencing at least one treatment-related adverse event (AE). The most frequent AEs were voice changes (55 %), hand-foot skin reaction (40 %), mucositis (36 %), diarrhea (32 %), and hypertension (30 %). Grade 3 or 4 treatment-related AEs occurred in 49 % of patients; the most common were hand-foot skin reaction (19 %) and hypertension (11 %). No fatal events related to the drug occurred. Disease control rate (DCR) was achieved in 66 % of patients, with a 6 % response rate by RECIST criteria. There were no significant differences in activity for dose levels between 120 and 220 mg. However, at the 120 mg dose, no dose-limiting toxicities were observed, compared with 2 out of 12 patients at 160 mg and 5 out of 12 at 220 mg.

In 2012, the initial phase II trial of regorafenib in GIST reported that 82 % of patients on 160 mg daily for 3 weeks on and 1 week off required a dose reduction for drug toxicity [39]. Of the 27 patients that required dose reduction, 12 were dose reduced to 120 mg, 11 patients to 80 mg, and 4 patients to 40 mg per day. Eleven of the 15 patients with initial dose reduction to less than 120 mg per day were able to be re-escalated to a dose between 120 and 160 mg. Overall, only 33 % tolerated a final dose of 160 mg per day. The most common toxicities of any grade were hand-foot syndrome (85 %), fatigue (79 %), hypertension (67 %), and diarrhea (61 %). The most common grade 3 events were hypertension (36 %), hand-foot syndrome (24 %), and hypophosphatemia (15 %). The toxicity rate in GIST patients appeared higher compared to the phase I study where patients had a variety of solid tumors. DCR was documented at 75 %, with 4 partial responses and 22 instances of stable disease. Median PFS was 10 months.

The GRID trial that led to regorafenib approval for GIST in 2013 was a large phase III, randomized, placebo-controlled trial [29••]. In this study, 98 and 72 % of regorafenib-treated patients experienced drug-related AE and required dose modifications, respectively. Grade 3 or 4 AEs occurred in 60 % of cases. The most common grade 3 events were hypertension (23 %), hand-foot syndrome (20 %), and diarrhea (5 %). Other side effects included fatigue, oral mucositis, alopecia, hoarseness/voice alteration, maculopapular rash, anorexia, nausea, constipation, and myalgia. Seven deaths were reported in the regorafenib group, three of which were deemed to be drug-related. Median PFS was 4.8 months in the regorafenib group versus (vs) 0.9 months in the placebo group (hazard ratio (HR) 0.27, $p < 0.0001$). No significant difference was seen in overall survival (22 % events in the regorafenib group vs 26 % in the placebo group). However, patients were allowed to cross over to regorafenib upon progression, and

derived a 5-month PFS benefit after switching arms. Six of the 133 patients in the regorafenib group had a partial response (4.5 %) vs one of 66 patients in the placebo group (1.5 %). Stable disease was noted in 71.4 % of patients in the regorafenib group vs 33.3 % in the placebo group. The benefit with regorafenib, though small compared with imatinib, was seen across the various mutation subtypes of GIST.

In the phase III study (CORRECT) in patients receiving regorafenib as third-line therapy for metastatic colorectal cancer, 93 % of patients experienced any-grade treatment-related AEs [40]. Fatigue and hand-foot skin reaction were the most common events, each occurring in 47 % of cases. The most frequent regorafenib-related AEs of grade 3 or higher were hand-foot skin reaction (17 %), fatigue (10 %), diarrhea (8 %), hypertension (7 %), and rash (6 %). Dose reduction and treatment interruptions due to AEs occurred in 38 and 61 % of patients, respectively. Though the toxicity profile is similar to what was reported in GIST patients, it appears that more dose reductions were required in the GIST population, with higher rates of grade 3 hand-foot skin reactions and hypertension. This difference may be attributable to prior exposure to tyrosine kinase inhibitors with anti-VEGF activity in GIST patients.

The initial dose of 160 mg accounts for most of the toxicity and led to dose reductions in 82 % of the patients in the phase II trial and 72 % of the patients in the phase III study in GIST. Pharmacokinetic study showed that doses above 120 mg led to a 40 % drop in tumor perfusion, thus, in theory, limiting the exposure of cancer cells to drug [38••]. With intermittent dosing, plasma levels of VEGF remained high during the 21-day period and dropped to baseline during the 7-day off period. Considering similar activity of doses between 120 and 220 mg and the improved toxicity profile with lower doses, most experts use alternate dosing strategies to improve the tolerance and compliance to regorafenib. Some of the alternate dosing strategies used at tertiary centers include starting regorafenib at the 80 mg dose and based on tolerance escalating up to 160 mg 3 weeks on, 1 week off, or utilizing a continuous daily dosing with 120 mg. In addition, pro-active monitoring and support for the common toxicities of hand-foot syndrome and hypertension has helped limit grade 3 or higher toxicities in GIST patients on regorafenib [41].

In postmarketing experience, rare and unusual cases of life-threatening toxicity attributable to regorafenib have been reported in GIST patients. One patient with GIST developed hypertensive crisis and seizures after a single dose of 160 mg of regorafenib. Another patient with GIST presented with acute confusion after 13 months of the approved intermittent dosing schedule of 160 mg per day and was later diagnosed with hyperammonemic encephalopathy [42, 43]. Both conditions resolved after appropriate management and cessation of the drug. Similarly, our report of CRVO while on regorafenib is a rare event that has not previously been reported with regorafenib.

Conclusions

Oral tyrosine kinase inhibitors are generally well tolerated in comparison to standard chemotherapy. In the treatment of GIST, imatinib was a significant breakthrough not only in terms of dramatic response but also favorable toxicity profile. Second-line and third-line therapy with sunitinib and regorafenib offer additional therapeutic options, although with less impressive clinical benefit in comparison with imatinib. They target multiple RTKs, including VEGFR, which likely contributes to their efficacy in the setting of imatinib resistance. However, this also leads to the less favorable toxicity profile. In postmarketing experience, some unusual and serious toxicities have been reported and linked to the vascular effects of these agents. Central retinal vein occlusion can rarely occur in agents that target VEGF/VEGFR, including regorafenib. Currently, there are no recommendations regarding routine ophthalmologic monitoring in patients taking regorafenib, but it is important for physicians to be aware of these risks to promptly manage toxicities and interrupt regorafenib after consideration of the risks and benefits.

Acknowledgments MJW is supported by NIH grant T32CA009666.

Compliance with Ethical Standards

Conflict of Interest Gustavo Schvartsman declares that he has no conflict of interest.

Michael J. Wagner declares that he has no conflict of interest.

Chrystia M. Zobniw declares that she has no conflict of interest.

Van Anh Trinh declares that she has no conflict of interest.

Shreyaskumar Patel has received research support through grants from Janssen, Eisai, and Morphotek, and has received compensation for service as a consultant from Janssen, EMD Serono, CytRx, Bayer, and Eli Lilly and Company.

Neeta Somaiah declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130(10):1466–78.
2. Hirota S et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577–80.
3. Kindblom L-G et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol. 1998;152(5):1259.

4. Heinrich MC et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299(5607):708–10.
5. Hirota S et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125(3):660–7.
6. Edmonson JH et al. Contrast of response to dacarbazine, mitomycin, doxorubicin, and cisplatin (DMAP) plus GM-CSF between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. Cancer Investig. 2002;20(5-6):605–12.
7. Demetri GD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472–80.
8. DeMatteo RP et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097–104.
9. Joensuu H et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. Jama. 2012;307(12):1265–72.
10. Antonescu CR et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res. 2005;11(11):4182–90.
11. Chen LL et al. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. Cancer Res. 2004;64(17):5913–9.
12.•• Debiec-Rychter M et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology. 2005;128(2):270–9. **This study points out the mechanisms of resistance to imatinib, which are of utmost importance for different therapeutic approaches in this resistant population**.
13. Abrams TJ et al. SU11248 inhibits KIT and platelet-derived growth factor receptor β in preclinical models of human small cell lung cancer. Mol Cancer Ther. 2003;2(5):471–8.
14. Mendel DB et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003;9(1):327–37.
15. Osusky KL et al. The receptor tyrosine kinase inhibitor SU11248 impedes endothelial cell migration, tubule formation, and blood vessel formation in vivo, but has little effect on existing tumor vessels. Angiogenesis. 2004;7(3):225–33.
16. Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329–38.
17. Cauchi, C., et al. Evaluation of nilotinib (N) in advanced GIST previously treated with imatinib mesylate (IM) and sunitinib (S). in ASCO Annual Meeting Proceedings. 2010.
18. Demetri GD et al. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2009;15(18):5910–6.
19. Dewaele B et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor–associated PDGFRAD842V mutation. Clin Cancer Res. 2008;14(18):5749–58.
20. Ganjoo KN et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol. 2014;25(1):236–40.
21. Kefeli U et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third-or fourth-line treatment: a retrospective multicenter experience. Oncol Lett. 2013;6(2):605–11.
22. Kindler, H., et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): final results of a University of Chicago Phase II Consortium trial. in ASCO Annual Meeting Proceedings. 2011.
23. Montemurro M et al. Sorafenib as third-or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: a retrospective analysis. Eur J Cancer. 2013;49(5):1027–31.
24. Montemurro M et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer. 2009;45(13):2293–7.
25. Park S et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Investig New Drugs. 2012;30(6):2377–83.
26. Reichardt P et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol. 2012;23(7):1680–7.
27. Sawaki A et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer. 2011;117(20):4633–41.
28. Trent, J., et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). in ASCO Annual Meeting Proceedings. 2011.
29.•• Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295–302. **This phase 3 trial demonstrated increase progression-free survival for GIST patients treated with regorafenib vs placebo that progressed on previous imatinib and sunitinib, leading to FDA approval of the drug**.
30. London NJ, Brown G. Update and review of central retinal vein occlusion. Curr Opin Ophthalmol. 2011;22(3):159–65.
31. Klein R et al. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2000;98:133–41. discussion 141-3.
32. Risk factors for central retinal vein occlusion. The Eye Disease Case-Control Study Group. Arch Ophthalmol, 1996. 114(5): p. 545-54.
33. Braithwaite T et al. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2014;5, CD007325.
34. Szczepanik S, Kecik D. Bilateral central retinal vein occlusion in a patient with disseminated metastatic renal cell carcinoma treated with sorafenib. Retin Cases Brief Rep. 2012;6(2):148–50.
35. Strumberg D. Sorafenib for the treatment of renal cancer. Expert Opin Pharmacother. 2012;13(3):407–19.
36. Renouf DJ et al. Ocular toxicity of targeted therapies. J Clin Oncol. 2012;30(26):3277–86.
37. MacDonald D. The ABCs of RVO: a review of retinal venous occlusion. Clin Exp Optom. 2014;97(4):311–23.
38.•• Mross K et al. A phase I dose–escalation study of regorafenib (BAY 73–4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012;18(9):2658–67. **This phase 1 study determined the recommended dose of 160 mg, 3 weeks on, 1 week off for subsequent phases of regorafenib both in GIST and colorectal cancer patients**.
39. George, S., et al., Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. Journal of Clinical Oncology, 2012: p. JCO. 2011.39. 9394.
40. Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303–12.

41. McLellan B et al. Regorafenib-associated hand-foot skin reaction: practical advice on diagnosis, prevention, and management. Ann Oncol. 2015;26(10):2017–26.
42. Kuo JC, Parakh S, Yip D. Regorafenib-induced hyperammonemic encephalopathy. J Clin Pharm Ther. 2014;39(4):446–8.
43. Yilmaz B et al. Single dose regorafenib-induced hypertensive crisis. Exp Oncol. 2014;36(2):134–5.