

Sorafenib for Desmoid Tumors. A Cost Analysis: Too Much for Too Little?

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Abstract

Background: A recent randomized trial showed that sorafenib increased progression free survival (PFS) in patients with desmoid tumors despite many patients experiencing stable disease or spontaneous regression without treatment. Using these trial data, we completed a cost analysis of sorafenib efficacy through two years of treatment.

Methods: 2019 Medicare Part D rates for sorafenib were used (dose 400 mg/day, cost \$309/day). Yearly costs per progression and objective response were calculated. Radiologic progression and response were defined using Response Evaluation Criteria in Solid Tumors (RECIST). Patients with disease progression were separately analyzed in two groups: both clinical and radiologic (CAR), and radiologic alone.

Results: 84 previously randomized patients were analyzed (placebo: 35, sorafenib: 49). After 1 year, sorafenib was associated with 43% absolute risk reduction (ARR) of CAR progression and number-needed-to-treat (NNT) of 2.3 patients/year, costing \$259,406. After 2 years, ARR was 48% and NNT of 2.1 patients/year, costing \$473,697. When assessing only patients with RECIST defined radiologic progression, sorafenib patients had ARR of 13.9% with NNT 7.2 and estimated costs of \$812,052 at one year. Two-year ARR was 17.5% with NNT 5.7 and estimated costs \$1,285,052. Sorafenib patients experienced improved RECIST partial response rates at 1 and 2 years of 14.7% and 14.3%, with NNT 6.8 and 6.9, and costs of \$766,938 and \$1,556,433; respectively.

Conclusion: For the treatment of desmoid tumors, Sorafenib led to improved PFS, but at a substantial cost per patient. Beneficial RECIST outcomes were less likely and at higher cost. Patients should be informed of possible benefits of treatment versus potential financial burden.

Background

Desmoid tumors are rare, fibrous neoplasms arising from musculoaponeurotic structures with an incidence of approximately five per one million of population per year.¹ Despite no metastatic risk, these tumors can develop throughout the body and become symptomatic with extensive local invasion. Their natural history is unpredictable and highly variable where tumor recurrence can develop frequently in patients after complete resection and some tumors spontaneously regress without treatment.² A recent placebo-controlled, randomized trial demonstrated that sorafenib, a tyrosine kinase inhibitor, led to improved progression free survival (PFS) in patients with desmoid tumors and an overall response rate of 33%, however treatment costs were not evaluated.³ This review performs a cost analysis of the trial's data to understand the costs associated with sorafenib on tumor response and progression compared to placebo response.

Surgery has been the mainstay of treatment for desmoid tumors, but studies have shown a recurrence rate from 20–36%, and while effective, can involve extensive reconstruction and disfigurement depending on tumor location.⁴ Several medical therapies have been investigated for possible reduction in tumor

recurrence and efficacy for potentially unresectable disease, including anti-hormonals, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy, and tyrosine kinase inhibitors (TKIs); with varying levels of efficacy.^{4,5}

Kinase directed therapy has previously been investigated as treatment for desmoid tumors with imatinib showing only a partial response in 3 of 51 (6%) patients when observed \geq 18 months in a phase II multicenter trial.⁶ Sorafenib, an oral multi-kinase inhibitor, blocks tumor angiogenesis by inhibiting VEGF-R2, VEGF-R3, and RAF pathways.⁷ Sorafenib was previously evaluated as a treatment for desmoid tumors in 26 patients, 0% had complete response, 6/24 partial response, and 17/24 (70%) had stable disease.⁷ Based on these results, a prospective placebo-controlled randomized trial was performed.³

The noted randomized trial was effective at demonstrating survival and response measures in the sorafenib group. However, 20% of the placebo group showed RECIST partial response, and nearly the same percentage showed stable disease or response short of RECIST partial. This is a potentially high rate of spontaneous regression where medical intervention could be futile at best. Sorafenib, like many TKIs, is expensive, and it is important to understand if such costs might be considered justified for the clinical benefit in treating desmoid tumors. Therefore, we performed a cost analysis using Medicare reimbursement rates to determine the actual costs per the associated clinical benefit demonstrated in the trial.

Methods

The original double-blind, phase III, placebo-controlled trial took place from March 2014 to January 2016, and enrolled patients to evaluate the efficacy of sorafenib for the treatment of advanced or refractory desmoid tumors and non-surgical candidates (ClinicalTrials.gov number, NCT02066181). The trial consisted of two treatment arms, of either sorafenib (400 mg once daily as initial dose) or placebo, to which patients were randomly assigned (2:1 ratio of sorafenib:placebo). Disease progression was assessed at baseline and every 8 weeks thereafter with MRI or CT scan. Patients continued to receive either medication until tumor progression, intolerable side effects, or voluntary withdrawal from the study. If progression occurred, patient's medication was unblinded and those receiving placebo had the option to cross over to the sorafenib arm.

The trial's primary endpoint was progression-free survival (PFS). This was defined as the time from randomization to a composite measure of progression (radiographic, defined by RECIST version 1.1, and/or clinical progression, determined by the treating physician's subjective clinical judgement) or death. Secondary end points were adverse events, radiologic response rate, and overall survival.

Kaplan-Meier curves and Cox proportional-hazards modeling were generated by the original investigators. Individual patient-specific changes in baseline tumor size and duration of response data were provided via waterfall and swimmer plots in the original manuscript, and were used to calculate the absolute risk reduction (ARR) and number needed to treat (NNT) for 1- and 2- year intervals.

For this cost analysis, patients that experienced progression were subdivided into two groups – both clinical and radiologic (CAR) and radiologic only (RAD) progression. Patients with RAD response were included in the response calculations. The sorafenib cost was based on Medicare Part D 2019 reimbursement rate of \$309 per 400 mg.⁸ Total cost of sorafenib was estimated for 1- and 2- year intervals based on ARR and NNT.

Results

Of the original 87 patients that underwent randomization, 84 patients were included for endpoint analysis. Errors in the original investigators' computer randomization were discovered and subsequently rectified mid-trial, which led to a ratio of 1.6 to 1.7:1 (sorafenib : placebo) instead of the prespecified 2:1. Based on this, 49 patients received sorafenib and 35 patients received placebo. Patient descriptive characteristics are listed in Table 1.

Table 1
Demographic and Clinical Characteristics of Patients at Randomization

| Characteristic | Placebo (n = 35) | Sorafenib (n = 49) |
|------------------------------------|------------------|--------------------|
| Median Age, years (range) | 37 (21–67) | 37 (18–72) |
| Female, n (%) | 26 (70) | 34 (68) |
| Intra-abdominal Disease, n (%) | 16 (43) | 16 (32) |
| Primary Tumor Site, n (%) | | |
| Abdominal | 16 (43) | 14 (28) |
| Extra-abdominal | 18 (49) | 32 (64) |
| Both Abdominal and Extra-abdominal | 3 (8) | 4 (8) |
| Previous radiation therapy, n (%) | 3 (8) | 6 (12) |
| Previous systemic therapy, n (%) | 15 (41) | 18 (36) |
| Previous surgical resection, n (%) | 18 (49) | 23 (46) |
| Disease Status, n/total (%) | | |
| Newly Diagnosed | 19/37 (51) | 26/48 (54) |
| Recurrent | 18/37 (49) | 22/48 (46) |

Median follow-up was 27.2 months (IQR: 22.0–31.7) among 83 surviving patients. Estimates of progression free survival rates at 1 year were 89% (95% CI, 80–90%) in the sorafenib group and 46% (95% CI, 32–67%) in the placebo group. Estimates at 2 years were 81% (95% CI, 69–96%) in the sorafenib group and 36% (95% CI 22–57%) in the placebo group.

Overall, 33% of patients (28/84) had CAR progression: 12% (6/49) in sorafenib group and 63% (22/35) in placebo group.

At one year of treatment, sorafenib was associated with a 43.2% ARR of CAR progression. This resulted in an NNT of 2.3 patients/year, which translates to a cost of \$259,406 to prevent one CAR. At two years, ARR for CAR progression was 47.8% and an NNT of 2.1 patients/year, costing \$473,697 (Table 2).

Table 2
Clinical and Radiologic (CAR) Progression and Associated Costs

| | Time | CAR Progression | Cost (\$USD) |
|------------------|--------|-----------------|--------------|
| Placebo | 1 year | 18/35 (51.4%) | - |
| Sorafenib | 1 year | 4/49 (8.2%) | 259,406 |
| Placebo | 2 year | 21/35 (60%) | - |
| Sorafenib | 2 year | 6/49 (12.2%) | 473,697 |

Patients who experienced an objective, RAD-only progression (no assessment of subjective clinical progression) were 17 of the 28 patients with CAR progression. In this subset, sorafenib patients experienced an ARR of 13.9% with NNT 7.2 and estimated costs of \$812,052 at one year. Two-year ARR was 17.5% with NNT 5.7 and estimated costs of \$1,285,052 (Table 3).

Table 3
RECIST Progression and Associated Costs

| | Time | RECIST Progression | Cost (\$USD) |
|------------------|--------|--------------------|--------------|
| Placebo | 1 year | 7/35 (20%) | - |
| Sorafenib | 1 year | 3/49 (6.1%) | 812,052 |
| Placebo | 2 year | 9/35 (25.7%) | - |
| Sorafenib | 2 year | 4/49 (8.2%) | 1,285,749 |

The objective response rate was 33% (95% CI 20–48%) in the sorafenib group (one complete response, 15 partial responses of 49 patients) and 20% (95% CI, 8–37%) in the placebo group (7 partial responses of 35 patients). The median time to a RECIST-defined response among those patients was 9.6 months (IQR 6.6 to 16.7 months) in the sorafenib group and 13.3 months (IQR 11.2 to 31.1 months) in the placebo group.

The RECIST response for sorafenib patients showed an absolute response increase at one year of 14.7% with an associated NNT of 6.8 and \$766,938 cost to add one responder. At two years, the absolute response increase was 14.3% with NNT of 6.9 and \$1,556,433 cost per treatment response (Table 4).

Table 4
RECIST Partial Response and Associated Costs

| | Time | RECIST Response | Cost (\$USD) |
|-----------|--------|-----------------|--------------|
| Placebo | 1 year | 2/35 (5.7%) | - |
| Sorafenib | 1 year | 10/49 (20.4%) | 766,938 |
| Placebo | 2 year | 5/35 (14.3%) | - |
| Sorafenib | 2 year | 14/49 (28.6%) | 1,556,433 |

The associated costs are compiled in Fig. 1.

Discussion

Given that desmoid tumors are rare, establishing standard treatment protocols has been challenging.¹ This has been further complicated by a natural disease history that is highly variable with unpredictable rates of regression, progression or stable disease, all developing over a protracted course of months or even years.^{9,10}

Despite their rarity, much has been learned about desmoid tumors, also called aggressive fibromatosis. They commonly form in the trunk (55%), extremities (35%), head and neck/intra-thoracic and/or intra-abdominal space (10%) and can be rather large in size at diagnosis.¹¹ They are associated with an increased incidence during pregnancy, which has led to the hypothesis of hormonal contribution in terms of development and difference in outcomes.¹² Molecularly, desmoid tumor development is related to the Wnt/beta-catenin signaling pathway, in both sporadic and FAP-associated disease, resulting in accumulation of beta-catenin in the cell due to dysregulation.¹³ It is documented that 10–20% of patients with FAP develop desmoid tumors, which represents an 850x increased risk over the general population.¹³

Historically, surgery has been the mainstay of treatment of desmoid tumors, based on the tumor's inability to metastasize.¹ Local growth, however, can contribute to significant morbidity, such as pain, functional limitation, decreased quality of life, obstruction and even death.¹⁴ Complete surgical resection has thus been the only potentially curative intervention and has achieved local control rates of around 80% at 5 years.¹

Unfortunately, this approach is fraught with many issues. Since desmoids are often large at presentation, surgery can be disfiguring, leading to large abdominal wall defects that require extensive reconstruction, can cause chronic pain, or require multi-visceral/vascular resections (for intra-abdominal tumors) with complex reconstructions that can cause significant short- and long-term morbidity.¹⁵ More importantly, up to 30% of patients develop a recurrence regardless of margin status, and the recurrent tumor tends to be more aggressive.¹⁶ As desmoid tumors are associated with pregnancy, surgery may pose unique problems for these patients. There is a risk of recurrence with subsequent pregnancies¹⁷, development of

recurrent abdominal hernias, and other pregnancy related complications (e.g. miscarriage).¹⁸ Through retrospective database analysis, a prognostic nomogram was developed to predict recurrence after surgical resection.¹⁹ Unfortunately, this (or other nomograms) is not likely to be prospectively validated, does not address how to treat asymptomatic patients, is not predictive of the natural history of any particular lesion and does not address patients that are not candidates for surgery based on tumor anatomy or patient physiology.

As appreciation of the natural history of desmoid tumors grew, it became apparent that many patients who did not undergo surgery developed stable disease and a subset of patients (around 20–30%) developed spontaneous regression.¹⁰ Based upon these observations, several investigators attempted a watchful waiting or “wait and see” approach.^{14,20–22} These studies confirmed that many patients do have prolonged periods of stable disease and some regress (even after periods of growth) without intervention.^{14,20–22} Not only did “watchful waiting” demonstrate high rates of stability and/or regression, but it neither hindered surgery at a later date nor negatively affected surgical outcomes if surgery was ultimately pursued. These findings have led to a paradigm shift in the surgery first approach such that more patients are being managed non-operatively.¹

Although “watchful waiting” is an effective strategy, it is precluded in many symptomatic patients. Furthermore, patients that develop regression are still the minority and the time scale for improvement can be somewhat long. Additionally, there are patients that present with unresectable disease or, at minimum, very locally advanced disease that would require extensive resection, such that watchful waiting or a surgery first approach might not be an acceptable option and thus alternative local or systemic therapies would be preferable.

The Gounder et al trial was the first phase III randomized-controlled trial (RCT) to investigate sorafenib for treating desmoid tumors, and it represents the strongest published data with potentially practice changing results. The survival gains are clear and could place sorafenib as a first line option. However, given a high rate of spontaneous regression, there remains a question as to whether these benefits outweigh the costs to treat.

Utilizing these trial data, we performed our cost analysis assuming patients received the specified dose of 400 mg/day at 2019 Medicare-D rates. The approximate annual cost of uninterrupted daily sorafenib was high at approximately \$113,000 and the cost has been rising yearly by over 10% from 2014 to 2018 (Fig. 2), which was not factored into our calculation.⁸ Had we done this, the cost would likely be substantially higher for patients that remained on the drug long-term.

The annual costs for an individual patient are very high, but pale in comparison to the cost to treat enough patients to either achieve *one objective response* at 1 and 2-years (\$766,938, \$1,556,433; respectively) or prevent *one objective progression* at 1 and 2-years (\$812,052, \$1,285,749; respectively). These costs come down substantially when patients who experienced improved clinical response (CAR) are included but remain substantial at \$259,406 and \$473,697 to prevent a single progression at 1 and 2

years, respectively. The trial did not specify how physicians determined clinical progression. Presumably, most oncologists could make similar decisions based on patients' performance status decline or worsening symptoms. Additionally, the RECIST system is a helpful tool to standardize progression measures but has been shown to underestimate changes in other sarcomas.²³ The trial did not report on MRI comparisons to augment radiologic response where CT scan was equivocal. Ultimately, relying on this undefined subjective clinical assessment to quantify efficacy of a drug or its cost-effectiveness creates a challenge to broad application of the results. Therefore, the RAD results could be more reproducible.

Our findings were calculated out to two years (based on the trial period), but actual duration of treatment would significantly affect final costs. In the trial, median time until response was 9.6 months for sorafenib and 13.3 months for placebo patients, demonstrating delayed effects and, for the responders at least, significant costs to increase median response time 2.7 months. Currently, there is no consensus on the length of treatment, dose, durability of response, or how to approach stable disease. Interestingly, several patients in the trial achieved RECIST measures short of the 20% threshold for partial response (e.g. not included in results) where perhaps treatment duration might have converted them. Treatment goals could include achieving resectability, reducing an operation's morbidity, or symptom palliation, and might greatly affect duration. TKIs have become effective long-term maintenance therapy in some malignancies and might be used similarly for desmoid tumors. The varying costs of these approaches could be arguably prohibitive and questionably justifiable.

Commonly, treatment durations and dosing are also affected by drug toxicity. In the trial, 29% patients taking sorafenib experienced grade 3 or 4 adverse events, and 20% had to discontinue the regimen due to adverse events. Common drug toxicities also include diarrhea, fatigue, hand-foot skin reaction and hypertension.²⁴ The authors' noted the trial dose was chosen to be lower than sorafenib use in other cancers, to minimize side effects without efficacy change. The long-term use of TKIs in oncology has replaced the severe, near-term side effects of chemotherapy (e.g. myelosuppression) with milder but persistent side effects (e.g. nausea, vomiting) of long-term TKIs.^{25,26} It is not known how long sorafenib side effects would persist or if patients would tolerate long term treatment.

The high-quality results of the well-designed RCT underscore this cost analysis and provide a reasonable insight into sorafenib treatment costs for desmoid tumors. Medicare rates were chosen because the publicly available national rates serve as a benchmark to apply our results broadly. Despite the small sample size, we believe our results are generalizable to larger populations, but others may disagree.

The cost analysis was based on the trial's initial treatment groups and did not consider patients who crossed treatment arms (12 placebo subjects eventually received sorafenib). Additionally, the cost calculation was performed utilizing a Medicare-D cost estimate, which would not account for private insurance, Medicaid, or varying out-of-pocket costs (which could be significant for some patients). Recent research has indicated that overall health care spending from employer and private insurance was 247% of Medicare payments for the same services in 2018.²⁷ While this is not delineated for specific

medications, it suggests a potential benchmark for elevated cost expectations beyond that calculated in our analysis. Use of the trial limited our analysis to a single medication, so there is no comparison to the costs and clinical or radiologic benefit of alternative systemic agents. Furthermore, the potential costs of up-front surgery, post-operative recovery, and changes in quality-of-life, were not assessed and could represent a clinical and financial benefit to some patients.

Treating desmoid tumors with sorafenib can result in meaningful clinical improvement while at a high cost for payers and patients. Ultimate, real-world costs, outside the parameters of the clinical trial, could be greatly affected by variables such as drug dose, duration, and tolerability. Patients' individual disease course and treatment preferences should be considered before determining if sorafenib is too much for too little.

Conclusion

For the treatment of desmoid tumors, Sorafenib leads to improved PFS, but at a significant cost. Favorable RECIST outcomes were less likely and costlier. Patients should be informed of possible benefits of treatment versus potential financial burden. This is critical in an era of continued increased medical costs to our patients.

Abbreviations

| | |
|--------|--|
| ARR | absolute risk reduction |
| CAR | clinical and radiologic progression |
| CI | confidence interval |
| IQR | inter-quartile range |
| NNT | number needed to treat |
| PFS | progression-free survival |
| RAD | radiologic only progression |
| RCT | randomized controlled trial |
| RECIST | response evaluation criteria in solid tumors |
| TKI | tyrosine kinase inhibitor |

Declarations

Ethics approval and consent to participate: The original clinical trial, on which our analysis is based, was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and federal and local policy on bioethics and human biologic specimens. Trial institutions received approval from their institutional review boards, and all trial patients signed informed consent forms in line with federal and institutional guidelines. This cost analysis used the published anonymized aggregate data from the manuscript by Gounder et al. and no additional approval was needed or requested.

Consent for publication: not applicable

Availability of data and materials: All data gathered or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have not competing interests.

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Authors' contributions: All authors contributed to the study conception and design. MJ, WM, MT, and GT, contributed to the acquisition, analysis, and interpretation of data. The first draft was written by MJ. All authors provided critical revision for intellectual content and approved the manuscript for publication.

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Figures

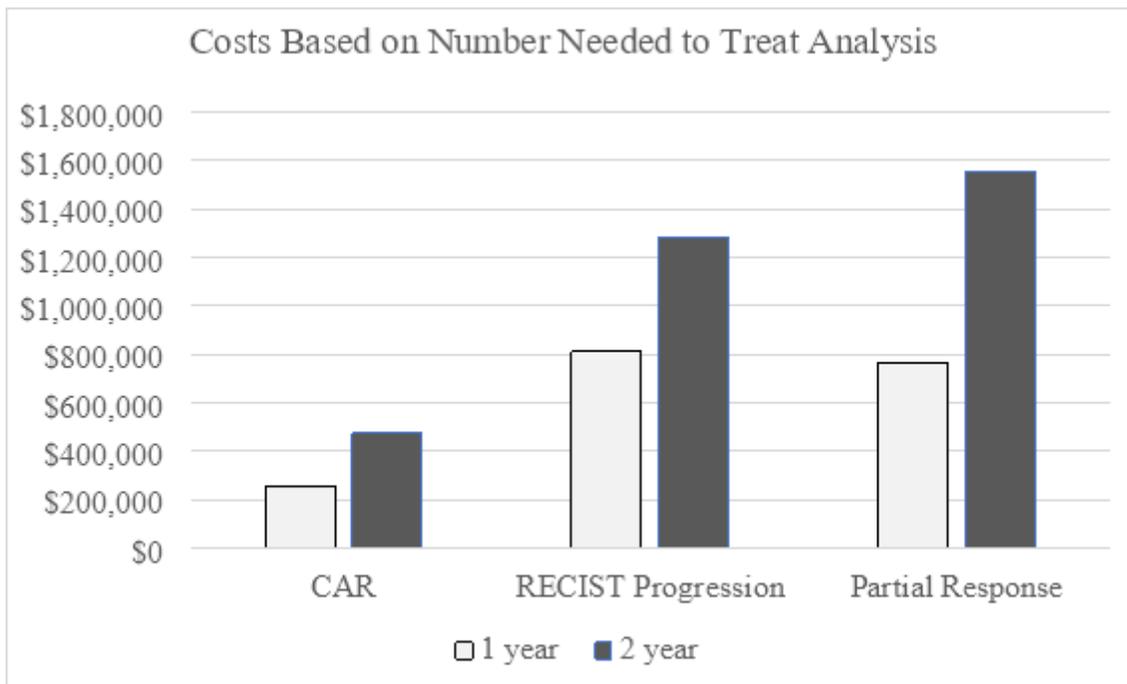


Figure 1

COSTS BASED ON NNT ANALYSIS

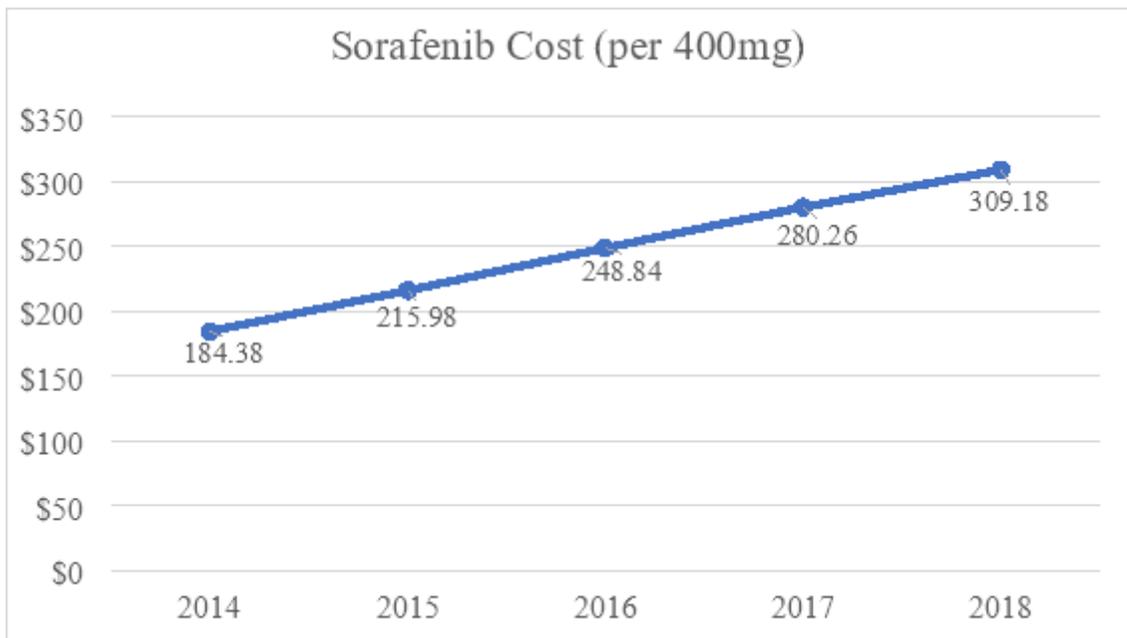


Figure 2

Medicare Part D Cost of Sorafenib from 2014-2018