Budgetary Impact of Treatment with Adjuvant Imatinib for 1 Year Following Surgical Resection of Kit-Positive Localized Gastrointestinal Stromal Tumors

Jaime L. Rubin, MA; Douglas C.A. Taylor, MBA; Myrlene Sanon, MPH;
John H. Coombs, PharmD, MBA; and Vamsi K. Bollu, PhD, MBA

ABSTRACT

BACKGROUND: Imatinib mesylate, an orally administered kinase inhibitor that targets the KIT (CD117) protein, currently has 10 approved indications including treatment of chronic myelogenous leukemia and metastatic gastrointestinal stromal tumors (GIST). Treatment with adjuvant imatinib following surgical resection of localized Kit-positive GIST, the most recent FDA-approved indication (December 2008), has been shown to significantly improve recurrence-free survival (RFS) compared with surgical resection alone. Although adjuvant imatinib has proven effective in clinical trials, it is important to consider the economic impact to health plans of introducing imatinib in accordance with its new labeled indication.

OBJECTIVE: To evaluate the budgetary impact over a 3-year time horizon of treating patients with localized Kit-positive GIST with 1 year of adjuvant imatinib following surgical resection.

METHODS: A Markov model was developed to predict patients' transitions across health states defined by initial treatment (surgical resection followed by adjuvant imatinib 400 milligrams [mg] daily versus surgical resection alone), recurrence, and progression. Treatments for a first recurrence were (a) imatinib 400 mg daily for recurrences following resection only or after completion of 1 year of treatment with imatinib 400 mg daily and (b) imatinib 800 mg daily for recurrence during active treatment with imatinib 400 mg daily. Treatments for further progression were imatinib 800 mg daily, sunitinib, or best supportive care (BSC) following imatinib 400 mg per day, and sunitinib or BSC following imatinib 800 mg daily. Recurrence rates were derived from the American College of Surgeons Oncology Group (ACOSOG) Z9001 clinical trial, which compared 1 year of adjuvant imatinib following surgical resection with surgical resection only. The total number of patients with localized and surgically resected GIST (incidence rate of 0.36 per 100,000) was estimated from epidemiologic studies of GIST. Uptake of treatment with imatinib was estimated from unpublished data from qualitative market research funded by the study sponsor. The uptake rate assumptions reflected both (a) the percentage of patients with Kit-positive disease and (b) the percentage of clinically eligible patients who would use imatinib. Costs were estimated by combining unit costs from published sources with expected resource utilization based on the clinical trial publication and National Comprehensive Cancer Network guidelines on the treatment of patients with GIST. To obtain estimates of the budgetary impact, we compared estimated health care costs with versus without adjuvant imatinib, where health care costs with imatinib reflected the costs of treatment minus cost offsets associated with delayed or avoided recurrence or progression. All "with" scenarios assumed no additional uses other than surgically resected localized Kit-positive GIST (i.e., no change in off-label use of imatinib). The budgetary impact was estimated for the first 3 years after the introduction of adjuvant imatinib in accordance with its new labeled indication in a hypothetical plan population of 10 million persons. Results were calculated both as total budgetary impact and as per member per month (PMPM) cost in 2009 dollars. Sensitivity analyses were performed to test the robustness of model results to changes in parameter estimates.

RESULTS: The model predicted 36 incident resected GIST cases per year in a health plan of 10 million members. The estimated counts of cases treated with adjuvant imatinib were 10.8, 16.2, and 21.6 in the first, second, and third years after introduction, respectively, with the annual increases attributable to changes in the proportion of patients with resected GIST assumed to use imatinib (30% in year 1, rising to 45% in year 2 and 60% in year 3). The model predicted that treatment of these cases with imatinib will increase pharmacy costs by an additional \$505,144 in the first year, \$757,717 in the second year, and \$1,010,289 in the third year. Increased resource use associated with monitoring patients during and after treatment with adjuvant imatinib would cost an additional \$21,564, \$38,145, and \$56,605 in the first, second, and third years, respectively. Recurrence would be avoided or delayed in 7 patients over the 3-year period. Avoided or delayed recurrences would result in cost offsets of \$61,583 in the first year, \$156,702 in the second year, and \$233,849 in the third year. The net budgetary impact was estimated to be \$465,126 in the first year (less than \$0.01 PMPM), \$639,159 in the second year (\$0.01 PMPM), and \$833,044 in the third year (\$0.01 PMPM). Results of sensitivity analyses indicated that the budgetary impact in the third year is most sensitive to changes in the price of adjuvant imatinib and recurrence rates.

CONCLUSIONS: The model predicted that the introduction of adjuvant imatinib for treatment of surgically resected, localized, Kit-positive GIST will lead to a net budgetary impact of \$0.01 PMPM in the third year after introduction assuming change in use only in accordance with the new labeled indication. Approximately 11.7%-21.9% of the cost of adjuvant imatinib is offset by the reduction in costs associated with GIST recurrence.

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What is already known about this subject

- Gastrointestinal stromal tumor (GIST) is a sarcoma of the gastrointestinal tract that affects approximately 3,000-4,000 individuals per year in the United States, or about 1 to 2 patients per 100,000 health plan members.
- Localized disease accounts for approximately 30%-50% of all GIST cases, is associated with high risk of recurrence (more than 40% in first 2 years after surgical resection), and is treated with surgery and sometimes adjuvant imatinib. Imatinib was approved in the United States as adjuvant therapy in patients with surgically resected Kit-positive GIST in December 2008.
- In the American College of Surgeons Oncology Group (ACOSOG) Z9001 study, a randomized, double-blind, placebo-controlled trial, treatment with adjuvant imatinib following surgical resection of localized Kit-positive GIST significantly improved recurrence-free survival compared with surgical resection alone (98% vs. 83%, respectively, hazard ratio [HR]=0.35, 95% CI=0.22-0.53, at 1 year).

What this study adds

- We developed a decision analytic model to estimate the projected budgetary impact of treating localized GIST patients with 1 year of adjuvant imatinib following surgical resection in a health plan with 10 million members. Assuming annual incidence of 0.36 per 100,000 members (i.e., 36 patients with localized resected GIST each year) and increasing uptake over time, the predicted counts of incident cases would be 10.8 in the first year, 16.2 in the second year, and 21.6 in the third year.
- The model predicted that treatment with adjuvant imatinib will cost an additional \$526,709 in the first year, \$795,861 in the second year, and \$1,066,893 in the third year, inclusive of pharmacy costs and additional resource use associated with monitoring patients on adjuvant imatinib. Cost offsets associated with delayed and avoided GIST recurrences were predicted at \$61,583 in the first year, \$156,702 in the second year, and \$233,849 in the third year. After accounting for cost offsets, the predicted net costs of adjuvant imatinib in the first, second, and third years were \$465,126, \$639,159, and \$833,044, respectively. The predicted budgetary impact was less than \$0.01 PMPM in the first year and about \$0.01 in the second and third years.
- When disease incidence was increased to twice the estimated base-case incidence (0.72 per 100,000) in sensitivity analyses, the budgetary impact of adjuvant imatinib in a health plan with 10 million members ranged from \$929,204 in the first year to \$1.664 million in the third year, and the annual PMPM was approximately the same as in the base-case analysis. The budgetary impact was most sensitive to changes in drug costs and the risk of recurrence.

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the intestinal tract occurring most frequently in the stomach and small intestine and less frequently in the colon, rectum, and esophagus.¹ GISTs are rarely found outside the gastrointestinal tract.² It is estimated that GIST, the most common type of sarcoma in the intestinal tract, affects about 3,000-4,000 persons each year in the United States.³⁻⁵ Recent research has confirmed that GISTs are often the result of mutations of the c-KIT receptor.^{6,7} The identification of these mutations has led to advances in targeted therapies for the treatment of GIST.⁷⁻⁹ Imatinib (Gleevec/Glivec; Novartis), a tyrosine kinase inhibitor (TKI) that targets the KIT protein, is currently approved by the U.S. Food and Drug Administration (FDA) for 10 indications, including treatment of unresectable and/or metastatic GIST and as adjuvant treatment of adult patients following surgical resection.¹⁰

Resectable localized disease was historically treated with surgical resection and conventional chemotherapy,¹¹ however, prior to the availability of TKI therapy, chemotherapy did not appear to prolong survival in GIST patients.^{7,11} Until recently, resectable localized disease was often treated with complete surgical resection only⁵ without adjuvant pharmacotherapy because effective therapies were not available. Although surgical resection is the recommended treatment for localized

disease,¹² recurrence following resection is common, with greater than 40% of patients experiencing a recurrence within the first 2 years after surgery.⁷ Five-year survival among patients with localized disease treated with resection only is 54%.⁷

The American College of Surgeons Oncology Group (ACOSOG) Z9001 study, a randomized, double-blind, placebo-controlled trial, showed that treatment with adjuvant imatinib for 1 year significantly improved recurrence-free survival (RFS) in patients with surgically resected Kit-positive GIST compared with surgical resection alone (1-year RFS was 98% for adjuvant imatinib, 83% for placebo).¹ The clinical trial was terminated early (median follow-up of 14 months) due to significant RFS benefits associated with imatinib; the final published study results represented a median follow-up time of 19.7 months. The FDA approved the use of imatinib as adjuvant therapy in surgically resected Kit (CD117) positive GIST patients in December 2008, based on the 14-month results of the ACOSOG Z9001 study.¹³ At a median follow-up of 14 months, the 1-year hazard ratio (HR) for recurrence or death was 0.40 (95% confidence interval [CI]=0.26-0.61) for imatinib versus surgical resection only. At 19.7 months, the corresponding 1-year HR was 0.35 (95% CI=0.22-0.53).^{1,13}

Although adjuvant imatinib has the potential to improve RFS in patients with surgically resected GIST, it is important to assess the impact to payers of introducing newly approved therapies. We therefore used techniques of decision analysis to model the potential budgetary impact to a hypothetical U.S. managed care plan of the use of adjuvant imatinib in accordance with its most recent labeled indication, use in patients with Kit-positive surgically resected GIST.

Methods

Model Overview

Budgetary impact analysis assesses the impact of adopting a novel intervention on health plan costs by comparing a current scenario, which does not include the novel therapy, with a future scenario, which does include the novel therapy. We constructed a decision analytic model to assess the budgetary impact of treating surgically resected Kit-positive GIST patients with 1 year of adjuvant imatinib over a 3-year time horizon. Specifically, estimated health care costs were compared with versus without imatinib in the adjuvant GIST setting. Overall budgetary impact was calculated as net cost, reflecting the costs of treatment with adjuvant imatinib and any other associated costs (e.g., monitoring costs) minus cost offsets associated with delayed recurrence or slowed disease progression.

There are 3 main components of the budgetary impact model: the population component, the marketplace dynamics component, and the economic component. The population component defines the total number of patients eligible for treatment with adjuvant imatinib in accordance with the new labeled indication. The marketplace dynamics component

FIGURE 1 Markov Model Tree Structure Diagram

^aAll patients start in the “no recurrence and no active treatment” state or the “no recurrence and on imatinib adjuvant therapy” state depending on treatment choice.
BSC= best supportive care; GIST= gastrointestinal stromal tumors.

models the market share and uptake of adjuvant imatinib after its introduction to the market. The economic component predicts costs and cost offsets that result from the introduction of imatinib in the adjuvant setting.

Model Structure and Estimation

Techniques of decision analysis were used to construct and estimate a Markov model of treatment, outcomes, and costs for patients who undergo complete gross resection of primary localized GIST. The model focused on disease recurrence and progression as predictors of costs and outcomes following surgical resection.

The model structure was based on the ACOSOG Z90001 clinical trial protocol, National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines for the treatment of patients with GIST, and expert opinion.^{1,12,14} The model was structured in the form of a Markov process, with the primary health states grouping patients into the following 6 categories: (a) free of recurrent GIST and treated with adjuvant imatinib; (b) free of recurrent GIST and no active treatment; (c) recurrent GIST and on active treatment; (d) progression and on active second-line treatment; (e) best supportive care (BSC); or (f) death (Figure 1). All patients were

assumed to begin the model free of recurrent GIST and to be either treated with adjuvant imatinib or receive no additional treatment following surgical resection. In subsequent cycles of the Markov process, some patients remained in their originally assumed state, while others transitioned to the recurrent GIST or death states, based on probabilities associated with the treatment received (i.e., resection only vs. resection plus adjuvant treatment with imatinib). One year of treatment was used in the model in accordance with the ACOSOG Z9001 trial data used to obtain the FDA approval. The Markov model assumed that transitions between health states occur at 1-month intervals (1-month cycle length). This process continued until the time horizon of 3 years was reached (36 1-month cycles). All patients were assumed to begin the model at age 58 years to reflect the mean age of patients in the ACOSOG Z9001 trial.¹

Patients receiving adjuvant therapy were assumed to be subject to treatment-related adverse events (AEs) and subsequent discontinuation of treatment. Discontinuation due to AEs incurred costs.

It was assumed that during each model cycle (a) patients who do not have recurrent GIST are at risk of recurrence, (b) patients who experience a recurrence are subsequently subject to a disease progression based on treatment-specific rates, and

(c) patients who do not experience progression continue treatment. In accordance with the ACOSOG Z9001 study protocol, (a) treatments for a first recurrence were assumed to be imatinib 400 mg daily following resection only and imatinib 800 mg daily for patients who experience a first recurrence during active treatment with imatinib 400 mg daily, and (b) patients who experience a first recurrence after completion of 1 year of adjuvant treatment with imatinib 400 mg daily were assumed to be retreated with imatinib 400 mg daily.¹

Patients who progress while treated for first recurrence were assumed to receive either second-line therapy or BSC. Specifically, patients were assumed to be eligible for treatment with an increased dose of imatinib (800 mg per day second-line treatment), sunitinib (Sutent; Pfizer), or receive BSC if their first recurrence was treated with imatinib 400 mg per day. Patients whose first recurrence was treated with imatinib 800 mg per day were assumed to be eligible for treatment with sunitinib or receive BSC. Patients who discontinue therapy because imatinib for recurrence is not well tolerated were assumed either to be treated with sunitinib or to receive BSC. All patients who fail on second-line treatment (i.e., progress while taking either imatinib 800 mg per day or sunitinib second-line treatment) were assumed to transition to BSC; once in BSC, patients were assumed to remain there until death.

Data from published literature and the advice of 4 physicians with expertise in the treatment of GIST patients were used to estimate model input parameters (Tables 1 and 2).

Population Module

Because the budgetary impact is largely dependent on the number of patients receiving adjuvant imatinib, the determination of how many patients are candidates for adjuvant therapy constitutes an important focus of the budgetary impact analysis. The size of the eligible patient population for adjuvant imatinib was estimated from an analysis of the Surveillance, Epidemiology, and End Results (SEER) database using SEER*stat.^{15,16} Patients were identified using indications of (a) a GIST diagnosis in the SEER database in either 2001 or 2002; (b) localized disease as defined by the SEER histologic stage variable; and (c) surgical resection, identified by the SEER variable indicating surgical resection of the primary tumor. Assessment of whether the GIST was Kit-positive could not be made using the SEER database and was instead incorporated into market uptake assumptions. Diagnosis of GIST was based on either the *International Classification of Diseases for Oncology* (ICD-O)-3 for GIST (8936/3) or the algorithm validated by Tran et al. (2005).³ The Tran algorithm consists of ICD-O-2 codes for mesenchymal tumors (8680, 8711, 8800-8804, 8810-8811, 8890-8893, 8896-8897, 8930, 8990, 9120, 9150, 9490, 9491, 9500, 9503, 9505, 9540, 9560) combined with codes for the primary sites typical for GIST: esophagus (150-159); stomach (160-169); small intestine (170-179); colon and rectum (180-

189, 199, 260, 299); retroperitoneum (480); and peritoneum, omentum, mesentery (481-482).

The annual incidence of surgically resected localized GIST was estimated as an average over the 2-year period (2001-2002) to be 0.36 per 100,000 population in the SEER analysis. This incidence rate was used to estimate the size of the patient cohort entering the model each year. The budgetary impact was assessed for a hypothetical plan population of 10 million persons.

Marketplace Dynamics Module

The expected proportion of eligible patients treated with adjuvant imatinib and the annual uptake of adjuvant imatinib after its introduction were estimated based on proprietary, unpublished data from qualitative market research funded by the study sponsor. The uptake rate assumptions reflected both (a) the percentage of patients with Kit-positive disease, estimated at 75% of patients with surgically resected localized GIST; and (b) the percentage of clinically eligible patients who would use imatinib. It was estimated that in the first year after introduction, 30% of patients with localized GIST would receive adjuvant imatinib following surgical resection; market uptake was assumed to increase to 45% in the second year and 60% in the third year. All localized resected GIST patients not receiving adjuvant imatinib were assumed to receive no pharmacotherapy initially after surgical resection. The analysis considers only patients with Kit-positive localized GIST being treated with adjuvant imatinib after surgical resection; the numbers of patients treated with adjuvant imatinib based on market shares assumed no new off-label use of the product.

Economic Module

Probabilities of Recurrence. Monthly probabilities of first recurrence were derived from the clinical trial publication of the ACOSOG Z9001 study.¹ Data were presented for up to 48 months of follow-up in the clinical trial publication. We therefore used trial data directly to estimate recurrence probabilities for each of the 3 years of the model for both the imatinib and surgical resection only arms. RFS probabilities from the trial report were converted to probabilities of recurrence by first subtracting reported overall survival from RFS and then subtracting the proportion recurrence-free (RF) from 1. Annual probabilities were converted to monthly probabilities as $1 - \text{RF}^{(1/12)}$.

Discontinuation. Persons treated with adjuvant imatinib in the model were assumed to discontinue treatment at rates reported in the publication of the clinical trial. Because the trial data were reported from an intent-to-treat perspective, discontinuation observed in the trial is already reflected in the recurrence rates reported. We assumed that patients discontinued only due to adverse events (i.e., 16% discontinued during a

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TABLE 1 Probabilities of Recurrence, Discontinuation, and Death, and Treatment Pathways

Parameter	Value	Source
Monthly probability of recurrence for patients with recurrence-free GIST		
Adjuvant imatinib 400 mg daily		DeMatteo et al., 2009 ^{1,a}
First year (on treatment)	0.0019	
Second year (off treatment)	0.0075	
Third year (off treatment)	0.0102	
Surgical resection only		
First year after surgical resection	0.0151	
Second year after surgical resection	0.0093	
Third year after surgical resection	0.0016	
Treatment for recurrence/progression during or after adjuvant imatinib (%)		
First recurrence while on active treatment with imatinib 400 mg per day: imatinib 800 mg per day	100	DeMatteo et al., 2009 ¹
First recurrence after completing 1 year of adjuvant imatinib 400 mg per day: retreatment with imatinib 400 mg per day	100	DeMatteo et al., 2009 ¹
Progression		
Sunitinib second-line treatment	85	Expert assessment ^b
Best supportive care	15	Expert assessment ^b
Treatment for recurrence/progression following surgical resection only (%)		
First recurrence: imatinib 400 mg per day	100	DeMatteo et al., 2009 ¹
Progression		
Imatinib 800 mg per day second-line treatment	83.8	Expert assessment ^b
Sunitinib second-line treatment	13.8	Expert assessment ^b
Best supportive care	2.4	Expert assessment ^b
Monthly probability of progression while treated with:		
Imatinib 400 mg per day for first recurrence	0.0336	Verweij et al. 2004 ^{8,c}
Imatinib 800 mg per day for first recurrence	0.0285	Verweij et al. 2004 ^{8,d}
Imatinib 800 mg per day second-line therapy	0.1259	Verweij et al. 2004, Contreras-Hernández et al. 2008 ^{8,18,e}
Sunitinib second-line therapy	0.1541	Demetri et al. 2006 ^{17,f}
Monthly probability of discontinuation		
Adjuvant imatinib (due to adverse events)	0.0143	DeMatteo et al., 2009 ^{1,g}
Imatinib 400 mg per day first-line treatment for recurrence	0.0029	Verweij et al. 2004 ^{8,h}
Imatinib 800 mg per day first-line treatment for recurrence	0.0029	Verweij et al. 2004 ^{8,h}
Monthly probability of death from GIST following GIST recurrence		
Imatinib 400 mg per day first-line treatment	0.0135	Verweij et al. 2004 ^{8,i}
Imatinib 800 mg per day first-line treatment	0.0125	Verweij et al. 2004 ^{8,i}
Imatinib 800 mg per day second-line treatment	0.0373	Demetri et al. 2006 ^{17,j}
Sunitinib second-line treatment	0.0373	Demetri et al. 2006 ^{17,j}
Best supportive care	0.0432	Tran et al. 2005, Demetri et al. 2006, Huse et al. 2007 ^{3,17,20,k}
Monthly probability of death from other causes		
Age 58 years	0.0079	U.S. life tables, 2004 ^{19,l}
Age 59 years	0.0086	
Age 60 years	0.0095	

^aTo estimate the monthly probability of recurrence, annual probability of recurrence was derived from RFS in Figure 2 in DeMatteo et al. 2009.¹ We removed mortality from RFS (based on OS in Figure 4 in DeMatteo et al.) to arrive at the probability of no recurrence (p) and estimated the monthly probability of recurrence as $1 - p^{(1/12)}$. Estimated RFS (OS) for imatinib was 0.975 (0.997) in year 1, 0.884 (0.990) in year 2, and 0.755 (0.965) in year 3. Estimated RFS (OS) for surgical resection only was 0.830 (0.997) in year 1, 0.723 (0.979) in year 2, and 0.730 (0.956) in year 3. Because patients in the trial were treated for only 1 year, trial data from years 2 and 3 represent RFS for patients after they stopped active treatment with adjuvant imatinib.

^bExpert assessment: 4 U.S. GIST opinion leaders were surveyed and asked to describe treatment patterns for their patients with GIST. Best supportive care indicates no active treatment. ^cEstimated using 2-year PFS reported in Verweij et al. 2004⁸ for the imatinib 400 mg per day arm; 2-year PFS was estimated as 0.44 and converted to a monthly probability of recurrence as $1 - \text{PFS}^{(1/24)}$.

^dEstimated using 2-year PFS reported in Verweij et al. 2004⁸ for the imatinib 400 mg BID arm (0.50); 2-year PFS was converted to a monthly rate of recurrence as $1 - \text{PFS}^{(1/24)}$.

^eEstimates include both recurrence and discontinuation due to AEs. Risk of recurrence was estimated from the median PFS in Contreras-Hernández et al. 2008¹⁸ (5.28 months) and the risk of discontinuation due to an AE reported in Verweij et al. 2004⁸ (7% over 25 months). Annual probabilities were converted to monthly probabilities as $1 - \text{PFS}^{(1/24)}$.

^fEstimates include both recurrence and discontinuation due to AEs. Adapted from the median time to progression reported for the ITT sunitinib arm (27.3 weeks) in Demetri et al. 2006,¹⁷ converted to monthly probability of recurrence as $1 - 0.5^{(1/6.3)}$ and the risk of discontinuation due to an AE (9%) reported in Demetri et al. 2006.¹⁷

^gEstimated based on Figure 1 in DeMatteo et al. 2009.¹ 16% discontinued due to AEs. Monthly probability of discontinuation estimated as $1 - (1 - \text{discontinuation})^{(1/12)}$.

^hBased on 7% discontinuation in approximately 25 months reported in Verweij et al. 2004;⁸ estimated as $1 - (1 - 0.07)^{(1/25)}$.

ⁱAdapted from Verweij et al. 2004;⁸ estimated from reported 1-year OS of 85% for imatinib 400 mg per day and 86% for imatinib 400 mg BID (e.g., $1 - 0.85^{(1/12)}$).

^jAdapted from Demetri et al. 2006;¹⁷ estimated from reported median OS of 73 weeks. It was assumed that persons on second-line treatment with 800 mg per day imatinib had the same OS as those on sunitinib second-line treatment. Estimated as $1 - 0.5^{(1/16.8)}$.

^kEstimated as the average OS reported by Huse et al. 2007²⁰ (median OS of 20 months), Tran et al. 2005³ (1-year OS of 77%), and Demetri et al. 2006¹⁷ (median OS of 36 weeks).

^lEstimated directly from U.S. life tables 2004,¹⁹ where annual probabilities were converted to monthly probabilities.

AE=adverse event; BID=twice daily; GIST=gastrointestinal stromal tumors; ITT=intention-to-treat; mg=milligrams; OS=overall survival; PFS=progression-free survival; RFS=recurrence-free survival.

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TABLE 2 Monthly Costs Associated with GIST and GIST Recurrence

Parameter	Value	Source/Comment
Resource costs²⁴		
Gastroenterologist visit	\$99	CPT codes 99213, 99215
CT scan	\$331	CPT codes 74150, 74160, 74170
General practitioner visit	\$39	CPT code 99212
Monthly pharmacy costs²³		
Imatinib 400 mg	\$4,340	Based on 30-day supply of imatinib 400 mg per day.
Imatinib 800 mg	\$8,681	Assumes that imatinib 800 mg per day is twice the price of 400 mg per day.
Sunitinib	\$6,177	Assumes 4 weeks on treatment with sunitinib 50 mg per day and 2 weeks off treatment, averaged over a 1-year period and divided by 12.
Monthly monitoring and medical costs by health state		
Recurrence-free GIST		
No treatment	\$120	Because high-risk (defined as tumors large in size, with high mitotic count, and c-KIT exon 11 mutation) and low-risk patients will have different resource use, we estimated resource use and costs for high- and low-risk patients separately and calculated a weighted average cost for high- and low-risk patients using the proportion in each stratum in the Z9001 study ¹ and ESMO treatment guidelines ¹² to determine service use. Low-risk: 1 GE per 6 months, 1 CT per 6 months, 2 GP per year. High-risk: 1 GE per 3 months, 1 CT per 3 months, 2 GP per year. ^a
Imatinib		
First 3 months	\$522	Frequency of visits/tests based on trial protocol from the Z9001 study. ¹ In the first 3 months, 5 GE, 3 CT; 2 GP per year.
4 months to 2 years	\$150	Frequency of visits/tests based on trial protocol from the Z9001 study. ¹ 1 GE every 3 months, 1 CT every 3 months, 2 GP per year. Costs were applied to all patients in the adjuvant imatinib arm who have not experienced a recurrence.
Year 3	\$78	Frequency of visits/tests based on trial protocol from the Z9001 study. ¹ 1 GE every 6 months, 1 CT every 6 months, 2 GP per year. Costs are applied to all patients in the adjuvant imatinib arm who have not experienced a recurrence.
Adverse events (cost per event)	\$311	Based on frequency of top 15 adverse events from the Z9001 clinical study report and unit costs from the Medicare Physician's Fee and Coding guide. ^{1,24}
Recurrent GIST	\$133	Based on 1 GE every 3 months, 1 CT every 3 months, and 2 GP per year (NCCN). ¹⁴
BSC	\$4,099	Estimates for the cost of BSC were derived from reported costs per month in the last year of life (\$7,030) and the cost of a continuing phase of cancer (\$2,062) with no active treatment. ²⁵ Based on the proportion of individuals in the model in the last year of life (41%) and those in a continuing phase of cancer (59%) in the first year, we calculated a weighted average cost for BSC. ^b
One-time cost of recurrence	\$13,214	Assumed that first recurrence is associated with a 1-time cost that includes: 1 GP, 1 specialist visit, 1 CT, and surgical resection; the surgical resection cost was estimated as \$12,753. ²²

^aCalculated as $(0.59 \times [4 \times \$99 + 4 \times \$331 + 2 \times \$39] + 0.41 \times [2 \times \$99 + 2 \times \$331 + 2 \times \$39]) / 12$.

^bCalculated as $(0.41 \times \$7,030) + (0.59 \times \$2,062)$.

BSC=best supportive care; CPT=Current Procedural Terminology; CT=computed tomography scan; ESMO=European Society of Medical Oncology; GE=gastroenterologist visit; GP=general practitioner visit; GIST=gastrointestinal stromal tumors; mg=milligrams; NCCN=National Comprehensive Cancer Network; Z9001=American College of Surgeons Oncology Group clinical trial (DeMatteo et al. 2009¹).

1-year period, monthly probability of 0.014).¹ This assumption was conservative because assuming discontinuation for other reasons would reduce the predicted costs associated with adjuvant imatinib treatment.

Post-Recurrence Transition Probabilities and Treatment Pathways. Estimates of discontinuation and progression during treatment for recurrence were obtained from a published study of imatinib in the treatment of advanced or metastatic GIST.⁸ Data for discontinuation and progression, survival on second-line treatment with sunitinib, and the rate of progression on second-line treatment with imatinib 800 mg per day were estimated from published literature.^{8,17,18}

Data on specific treatment pathways for patients who

experience GIST recurrence following surgical resection were limited. We therefore invited 37 global GIST medical experts to participate in a survey to establish estimates of these parameters. Fourteen of these medical experts from 7 different countries agreed to participate in the survey. We administered the survey as a structured telephone interview and asked physicians about treatment patterns for GIST patients at varying stages of disease and treatment. In this model, the proportions of patients treated with TKI therapy (imatinib or sunitinib) or BSC after failure on imatinib 400 mg per day or imatinib 800 mg per day were chosen to reflect the responses from the 4 participating U.S. GIST medical experts.

Mortality. Patients in the recurrence-free GIST health state

were assumed to be free of GIST after surgery and therefore not at increased risk of death from GIST. All patients in the model were at risk of age-specific background mortality estimated from U.S. life tables.¹⁹ Patients with recurrent GIST were assumed to be at increased risk of death, with probabilities estimated from published studies of imatinib and sunitinib, as well as epidemiological studies of GIST.^{3,8,17,20}

Costs. Costs can be categorized as drug, medical care associated with a health state, or a one-time cost associated with recurrence or adverse events. Costs associated with health states comprise visits, tests, and procedures typical for that health state. All costs in the model reflected 2009 dollars; that is, for unit cost estimates derived from years other than 2009, costs were adjusted to 2009 dollars using the medical care component of the Consumer Price Index.²¹ All visits/procedures were assigned costs from the published literature.²²⁻²⁴ The frequencies of visits and tests were estimated from the clinical trial study protocol and other published literature.^{12,14,25,26} For patients in the imatinib arm, costs for monitoring were assumed to continue after completion of the 12 months of active treatment; this assumption was made to be consistent with the clinical trial protocol.

Analyses. Results were calculated as the overall budgetary impact and as per member per month (PMPM) costs in each of the first 3 years after the introduction of adjuvant imatinib. Budgetary impact was calculated by subtracting total expected costs in the current scenario (without adjuvant imatinib) from total expected costs in the future scenario (with adjuvant imatinib). PMPM costs were calculated as the total budgetary impact divided by the plan population, divided by 12. Results represent the budgetary impact of imatinib as adjuvant therapy only in patients with surgically resected localized Kit-positive GIST, the tenth approved indication for imatinib, and do not consider off-label use of the product.

Sensitivity analyses were performed to test the robustness of model results to changes in key parameters. Sensitivity analyses were performed around the population incidence, where we estimated the budgetary impact at twice the base-case incidence (0.72 per 100,000) and one-half the base-case incidence (0.18 per 100,000). We also varied cost and efficacy (recurrence probabilities) parameters, discontinuation probabilities, and the proportion treated with each therapy for recurrence by +/- 25% (high, low), to test the robustness of model results to changes in these parameters.

Results

Budgetary Impact Analysis

Table 3 presents the number of patients with localized resected GIST, the number of recurrences avoided, and the costs and cost-offsets associated with adjuvant imatinib in the first 3 years after its introduction. The model predicted an estimated

net budgetary impact of \$465,126 in the first year, \$639,159 in the second year, and \$833,044 in the third year after introduction. The PMPM predicted budgetary impact was less than \$0.01 in the first year after introduction and approximately \$0.01 in the second and third years.

The additional cost of treatment with adjuvant imatinib (\$526,709 in the first year, \$795,861 in the second year, and \$1,066,893 in the third year, inclusive of pharmacy treatment and increased monitoring costs) was partially offset by avoiding and delaying recurrences. The model predicted that in a plan population of 10 million members, with 36 incident cases of localized GIST per year, adjuvant imatinib will avoid or delay 2 recurrences in the first and second years and 3 recurrences in the third year (7 total over the 3-year period). Predicted cost offsets attributable to avoided treatment and medical care costs associated with recurrence were \$61,583 in the first year, \$156,702 in the second year, and \$233,849 in the third year, where the average cost of recurrent GIST is approximately \$39,000 per year.

Sensitivity Analyses

Disease incidence is a major driver of budgetary impact. As expected, when the incidence was assumed to be twice the rate of the base-case (0.72 per 100,000), the overall budgetary impact approximately doubled (\$929,204 in the first year, \$1.277 million in the second year, and \$1.664 million in the third year). Similarly, when the incidence was assumed to be one-half the rate of the base-case (0.18 per 100,000), the overall budgetary impact was reduced by about one-half.

The impact of +/- 25% changes in cost and recurrence parameters on the budgetary impact of adjuvant imatinib 3 years after its introduction are presented in a tornado diagram in Figure 2. The tornado diagram displays the budgetary impact relative to the base-case budgetary impact in the third year after the introduction of adjuvant imatinib (\$833,044); the length of the bars indicates the magnitude difference between the expected budgetary impact when the parameter is varied by 25% of the base-case value. The 10 parameters with the greatest impact on model results are displayed.

The budgetary impact of adjuvant imatinib in the third year after its introduction is most sensitive to changes in the price of imatinib. If the price of imatinib were reduced by 25%, the projected budgetary impact would be \$579,684 (30% lower); if the price increased by 25%, the projected impact would be \$1.084 million (30% higher). The budgetary impact is also sensitive to rates of recurrence, with the budgetary impact most sensitive to rates of recurrence in the first year for patients treated with surgical resection only (+/- 11% change). Changes of +/- 25% in other rates of recurrence (e.g., the rate of recurrence for adjuvant imatinib) had less impact (approximately 2%). All other parameters, including the proportions of patients treated with each of the treatment options for

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TABLE 3 Budgetary Impact Results in the First 3 Years After the Introduction of Imatinib as Adjuvant Therapy for Localized Resected GIST^a

	Current Scenario			Future Scenario			Difference [PMPM]		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Number of GIST patients									
Incident cases treated with surgical resection + adjuvant imatinib	0	0	0	10.8	16.2	21.6	—	—	—
Incident cases treated with surgical resection only	36	36	36	25.2	19.8	14.4	—	—	—
Prevalent cases and deaths	0	36	72	0	36	72	—	—	—
Total patients being followed in model ^b	36	72	108	36	72	108	—	—	—
Total number of recurrences	7	9	10	5	7	7	-2	-2	-3
Costs									
Nonrecurrent GIST									
Adjuvant imatinib	\$0	\$0	\$0	\$505,144	\$757,717	\$1,010,289	\$505,144	\$757,717	\$1,010,289
Medical care/monitoring costs	\$46,824	\$86,966	\$124,330	\$68,388	\$125,111	\$180,935	\$21,564	\$38,145	\$56,605
Total	\$46,824	\$86,966	\$124,330	\$573,533	\$882,827	\$1,191,224	\$526,709	\$795,861	\$1,066,893
Recurrent GIST									
Pharmacy	\$168,830	\$494,002	\$772,556	\$130,149	\$382,845	\$606,311	-\$38,681	-\$111,157	-\$166,245
Medical care costs	\$83,937	\$134,435	\$148,345	\$62,153	\$99,951	\$112,308	-\$21,784	-\$34,484	-\$36,037
BSC	\$4,367	\$42,847	\$122,594	\$3,249	\$31,785	\$91,027	-\$1,118	-\$11,062	-\$31,567
Total	\$257,134	\$671,284	\$1,043,495	\$195,551	\$514,582	\$809,646	-\$61,583	-\$156,702	-\$233,849
Total Costs	\$303,958	\$758,251	\$1,167,825	\$769,084	\$1,397,410	\$2,000,869	\$465,126	\$639,159	\$833,044
							[<\$0.01]	[\$0.01]	[\$0.01]

^aDifference in total costs between the future and current scenarios is equal to the budgetary impact. Budgetary impact results represent only those related to imatinib as adjuvant therapy for localized resected GIST.

^bTotal patients followed in the model each year include incident cases (treated with either surgical resection only or surgical resection plus adjuvant imatinib), prevalent cases (i.e., still living and incident in a previous year), and patients who have died.

BSC = best supportive care; GIST = gastrointestinal stromal tumors; PMPM = per member per month.

recurrence and progression, had minimal impact on model results (less than 2% change). In addition, increasing the proportion of patients treated with adjuvant imatinib each year increases the budgetary impact directly. The proportion of patients treated with adjuvant imatinib was assumed not to exceed 75% of patients with localized resected GIST in sensitivity analyses because 75% was the assumed proportion of patients who are Kit-positive and therefore eligible for adjuvant imatinib.²⁷

Discussion

In a hypothetical health plan of 10 million members, the net budgetary impact of adjuvant imatinib was estimated to be \$465,126 in the first year, \$639,159 in the second year, and \$833,044 in the third year after its introduction. The total impact to health plans was calculated as a function of the number of persons treated, the increased costs associated with the treatment itself, and cost offsets associated with avoiding GIST recurrences. The model predicted that adjuvant imatinib will avoid or delay a total of 7 recurrences over a 3-year period in a hypothetical plan population of 10 million persons, partially offsetting the costs of imatinib treatment. The increase in

budgetary impact over the 3 years is due to an increase in utilization of adjuvant imatinib each year. Although the estimated impact increased over the 3 years, the estimated PMPM impact was \$0.01 in the third year.

Limitations

First, results of the ACOSOG Z9001 study were used to estimate the probability of recurrence over a 3-year period for patients in both treatment arms. The median follow-up time in the ACOSOG study was 19.7 months, and estimates of recurrence in the third year are based on small sample sizes (n = 105 for the imatinib arm and n = 89 for the surgical resection only arm). Because rates from the ACOSOG trial were used to estimate recurrence for both the adjuvant imatinib arm and the surgical resection only arm, the direction of any potential bias from using these rates is unknown.

Second, we accounted for discontinuation only due to adverse events. This approach is conservative; a greater rate of discontinuation would reduce costs of imatinib but would not affect recurrence probabilities because discontinuation is implicit in the RFS analysis. Additionally, because discontinuation probabilities are based on clinical trial results and we do

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FIGURE 2 Tornado Diagram Presenting Sensitivity Analyses of Budgetary Impact of Adjuvant Imatinib in the Third Year After Introduction to 25% Changes in Costs and Transition Probabilities

^aIndicates that when the value of a parameter is increased (e.g., high) the model produces a result that is lower than the base-case budgetary impact.

not have estimates of discontinuation for other reasons, we did not estimate the effects of other reasons for discontinuation (e.g., out-of-pocket costs).

Third, the model is subject to limitations inherent in the study design. The decision analytic model is a simplified representation of disease natural history and associated outcomes and may not account for all possible health states and complications associated with disease. In addition, the data used to estimate transition probabilities and costs were derived and synthesized from a variety of sources, and this process is subject to bias. We also used the ACOSOG trial clinical study protocol to determine the resource utilization associated with monitoring patients treated with adjuvant imatinib after surgical resection of GIST. Protocol-driven care generally includes more visit and test use than would be observed in a real-world setting, thus making our estimates of the cost of monitoring imatinib patients conservative, that is, potentially higher than they would be in clinical practice. We performed sensitivity analyses to quantify how different parameter assumptions would change results, and we identified that the model was most sensitive to recurrence rates and drug costs.

Conclusion

A decision analytic model was used to estimate the potential budgetary impact of the introduction of imatinib as adjuvant treatment in accordance with its labeled indication for patients

with surgically resected, Kit-positive GIST to health plans in the United States. The model predicted that use of adjuvant imatinib would lead to fewer patients experiencing a cancer recurrence, which is beneficial from a clinical perspective, and to cost offsets associated with avoiding treatment for recurrence. The introduction of adjuvant imatinib would increase a health plan budget by an estimated \$833,000 in a plan of 10 million members, or approximately \$0.01 PMPM, in the third year after introduction.

Authors

JAIME L. RUBIN, MA, is Project Manager, Health Economics & Outcomes; DOUGLAS C.A. TAYLOR, MBA, is Director, Health Economics & Strategic Consulting, Ingenix Fellow; and MYRLENE SANON, MPH, is Health Economics Research Analyst, i3 Innovus, Medford, Massachusetts. JOHN H. COOMBS, PharmD, MBA, is Associate Director, Novartis Pharmaceuticals Corporation, Florham Park, New Jersey; and VAMSI K. BOLLU, PhD, MBA, is Associate Director, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

AUTHOR CORRESPONDENCE: Jaime L. Rubin, MA, Health Outcomes, i3 Innovus, 10 Cabot Rd., Ste. 304, Medford, MA 02155. Tel.: 781.518.4032; Fax: 781.338.9522; E-mail: Jaime.Rubin@i3innovus.com.

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DISCLOSURES

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Concept and design were performed by Rubin, Taylor, and Coombs. Rubin, Coombs, and Sanon collected the data. Data interpretation was performed by Sanon and Rubin, with assistance from the other authors. Rubin was primarily responsible for writing the manuscript with input from the other authors. Manuscript revisions were performed primarily by Rubin and Bollu, assisted by Sanon.

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