Value of Survival Gains in Chronic Myeloid Leukemia

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Abstract

Although clinical trial data have quantified patient survival gains associated with tyrosine kinase inhibitors in chronic myeloid leukemia, the overall value of these benefits is unknown.

Objective: To estimate the total value of survival gains associated with first- and second-line TKI therapy in chronic myeloid leukemia (CML) and the fraction of tyrosine kinase inhibitor (TKI)-related survival-gain value retained by patients and drug companies.

Study Design: This retrospective study identified CML patient data from the Surveillance, Epidemiology and End Results registry, dasatinib clinical trials, and insurance claims data sets.

Methods: Multivariate Cox proportional hazard models were used to estimate improvements in CML survival associated with the introduction of first-line imatinib therapy. Survival gains associated with second-line dasatinib treatment were identified via retrospective analyses and published clinical outcomes. An economic model was developed to calculate the social value of survival gains derived from first- and second-line TKI treatment. TKI costs were used to estimate the fraction of survival gain value retained by patients and drug companies.

Results: The introduction of TKIs in 2001 was associated with a hazard ratio of 0.833 (P <.01). Cost analyses indicate that the TKI drug class in CML therapy has created more than $143 billion in social value. Approximately 90% of this value is retained by patients and society, while approximately 10% is recouped by drug companies.

Conclusions: These estimates indicate that the introduction of TKI drugs to treat CML has generated significant social value as a result of survival gains, the vast majority of which has accrued to patients.

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For author information and disclosures, see end of text.

Cancer chemotherapy has long relied on generalized and nonspecific treatments that often involve substantial patient toxicity. One of the major chemotherapeutic advances over the past decade has been the discovery and deployment of targeted therapies directed at cancer-specific molecules and signaling pathways. In some cases this treatment specificity has proved very effective, appreciably improving survival rates for certain cancers.

Considered broadly, there have been substantial increases in cancer survival rates over the past several decades. The 5-year relative survival rate for all cancers diagnosed between 1996 and 2003 was 66%, up from 50% in the mid-1970s.[1] Improvements in survival have been particularly dramatic for breast cancer, colon cancer, and non-Hodgkin lymphoma—conditions for which there have been important advances in therapy, screening, or both.[2-4] It has, however, also been argued that some new cancer therapies only marginally extend life, and at a high cost.[5,6] Hence, the cost-effectiveness of expensive new cancer therapies has been called into question, with recommendations made for more comprehensive economic evaluations, as well as innovative approaches that consider the unique economic impact of cancer treatments.[7-11] The results of the recommended comprehensive economic analyses have important implications for the assessment of managed care, as they promote a better understanding of the total value of medical technologies.

The study described in this article examines the value of survival gains in chronic myeloid leukemia (CML) achieved by treatment with a new class of targeted therapy, tyrosine kinase inhibitors (TKIs), in first- and second-line therapy. In one multicenter, international, open-label, phase 3 randomized study, investigators compared the TKI imatinib with interferon as first-line treatment for CML, and demonstrated an 18-month survival rate of 97.2% for patients treated with imatinib.[12] These results were durable; at 60-month follow-up, the overall survival (OS) rate for imatinib-treated patients was 89% (95% confidence interval, 86-92),[13] and 7-year event-free survival and OS rates were 81% and 86%, respectively.[12] Two newer TKIs, dasatinib and nilotinib, have also been approved for first-line CML treatment.[14-16]

Studies of second-line TKI therapy in CML have also demonstrated efficacy. Patients receiving the newer TKIs (dasatinib and nilotinib) after imatinib failure experience significant cytoge-

netic response,[17-19] and can expect substantial survival benefits. Indeed, in a randomized, international, multicenter, open-label phase 3 trial of dasatinib as second-line treatment following imatinib failure or intolerance, the overall 60-month survival rate was 78%.[20]

Based on these clinical trial data, survival gains for CML patients treated with TKIs appear to be substantial. However, survival gains experienced in the community have not been studied, and the overall value of these survival gains—both in aggregate and relative to the cost of treatment—is unknown. In addition, the value of survival gains subsequently returned to patients and society has not been adequately evaluated. Prior research by Sun and colleagues[11] revealed that, between 1988 and 2000, a substantial majority (~80%) of US cancer-related survival gains were due to treatment improvements (as opposed to cancer detection strategies). Subsequently, Lakdawalla and colleagues[21] evaluated, from a societal perspective, the economic gains due to cancer treatment associated with these improved overall survival rates; the study used an economic model developed by Becker et al,[22] which was designed to assess patients' willingness to pay for improved survival rates achieved by cancer treatment. Predicated on this model, the estimated average increase in life expectancy of 4 years between 1988 and 2000 was associated with 23 million life-years and $1.9 trillion gained in social value. The model also demonstrated that drug companies acquired 5% to 19% of this total value as revenue.[21]

In this article we apply a similar approach to estimate the social value of TKIs in the treatment of CML. Observational data and clinical trial results were used to assess survival gains stemming from the introduction of both first- and second-line TKI therapies. Subsequently, an economic framework was employed to calculate the social value of improvements in survival gains due to TKI treatment. Lastly, to estimate the fraction of TKI treatment value retained by patients and society, as well as the proportion recouped by drug companies over time, the cost of TKI treatment was estimated from lifetime individual and population-level perspectives.

Methods

Survival Data

Multivariate Cox proportional hazard models were used to estimate survival improvements in CML associated with the 2001 introduction of first-line imatinib therapy. CML patient survival data were obtained from the Surveillance, Epidemiology, and End Results (SEER) registry. The SEER registry has tracked patients diagnosed with CML from 1973 to 2006 (the year of the most recent registry update). The key advantages of the SEER registry are that it is the only national cancer data base that: 1) follows patients over time in order to track survival, and 2) is large enough to contain sufficient sample sizes for survival analysis.

The sample for the survival analysis was restricted to CML patients diagnosed in 2000 or later. This ensured that the study captured the survival impact of the 2001 introduction of imatinib on the incident patient cohort, whose response to TKI therapy best represents the first-line survival effect of TKIs on present and future CML patients. Using multivariate hazard analysis, a rich set of demographic controls was applied, including age and squared age at diagnosis, gender, marital status, and separate indicator variables for white, black, Hispanic, Asian/Pacific Islander, and other races. To account for secular trends in CML survival unrelated to the introduction of imatinib, flexible controls for year and month of diagnosis were also included.

The key variable of interest in the proportional hazard model was the post-TKI indicator variable, which took the value of 1 in all years following 2000 and corresponded to the 2001 introduction of imatinib for first-line CML treatment. We report the estimated hazard ratio (HR) associated with the post-TKI variable, as well as the implied survival rate ratio.

The timing of second-line TKI approvals (2006 US Food and Drug Administration [FDA] approval for dasatinib; 2007 for nilotinib) precluded retrospective survival analysis of these drugs using the SEER registry. We estimated the community survival effect of new TKIs in second-line therapy by interpolation. First, we calculated the clinical survival effect of second-line relative to first-line treatment, which we obtained by dividing the 60-month OS rate in the second-line dasatinib clinical trial by the 60-month OS rate in the imatinib first-line clinical trial. We then applied this relative effectiveness rate of second-line therapy to the community-based survival effects estimated for imatinib in the retrospective SEER-based survival analysis. In performing this interpolation we assumed that the proportional difference in clinical and community survival rates for imatinib was the same as the proportional difference in clinical and community survival rates for dasatinib. Among newer TKIs we focused on dasatinib for this component of the analysis given the availability of recent 60-month survival results,[20] which are not yet available for nilotinib.

The survival effects of imatinib were calculated as the average across all CML patients, regardless of whether they received imatinib; this was interpreted as the "intent-to-treat" (ITT) effect. To estimate imatinib's "treatment-on-the-treated" (TOT) effect, the ITT effect was scaled based on the percentage of CML patients who received treatment.

Table 1. Summary Statistics

Variable	All CML Patients in SEER Registry	CML Patients Diagnosed in 2000 or Later
Age at diagnosis	58.929	57.990
Standard deviation	(19.28)	(19.08)
Fraction female	0.435	0.435
Standard deviation	(0.50)	(0.50)
Married at diagnosis	0.550	0.526
Standard deviation	(0.50)	(0.50)
Fraction Hispanic	0.098	0.141
Standard deviation	(0.30)	(0.35)
Fraction white	0.829	0.807
Standard deviation	(0.38)	(0.39)
Fraction black	0.096	0.098
Standard deviation	(0.29)	(0.30)
Fraction Asian/Pacific Islander	0.063	0.074
Standard deviation	(0.24)	(0.26)
Observations	14,698	5,523

CML indicates chronic myeloid leukemia; SEER, Surveillance, Epidemiology, and End Results.

The fraction of CML patients who received TKI treatment following its introduction was estimated using Ingenix Touchstone data,[23] a database of private-sector healthcare claims, including prescription drug claims and inpatient emergency ambulatory medical claims from approximately 35 Fortune 500 firms. Individuals with CML were identified based on the presence of 2 or more *International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM)* diagnoses (primary, secondary, or tertiary) with medical claims codes of 205.1x, or 1 *ICD-9-CM* code and TKI therapy use after diagnosis. Based on this data set, between 2001 and 2002, 40% of CML patients received treatment with imatinib; therefore, the TOT effect was calculated as the ITT survival effect divided by 0.4.

Value of Survival Gains

The economic model developed by Becker et al[24] was employed to calculate the social value of survival gains due to first- and second-line TKI therapy. Clinical evidence suggests that, relative to TKI therapy, prevailing treatments are associated with relatively rapid mortality in CML, not slight increments in mortality risk. This economic model calculates patients' willingness to pay (ie, value to patients) for longevity gains, accounting for discrete (rather than marginal) increases in survival probabilities. The technical details regarding the application of this methodological approach are presented in Appendix A.

In keeping with this methodology, the benefit derived by CML patients was calculated based upon survival gains pertaining to TKI treatment and the average income level among CML patients. In particular, patients' lifetime value was estimated using income data from the 2005 and 2006 Medical Expenditure Panels Study (MEPS). Due to the small number of CML patients in the MEPS, all MEPS cancer patients were used to estimate CML patient income. The estimated value was then aggregated across all CML cohorts to obtain the total social value of survival gains due to TKI treatment.

Costs

The Ingenix Touchstone Data database provided estimates of annual imatinib treatment costs, as well as information on drugs utilized, total drug costs, and patient cost-sharing information. Because claims-based costs for dasatinib were not available, these costs were estimated via imputation by applying the proportional difference between the manufacturers' prices of imatinib and dasatinib to the claims-based cost estimates.

As with the lifetime value of TKI treatment, lifetime treatment cost was determined by calculating the present value of annual imatinib treatment costs given the life expectancy implied by the post-TKI survival curve. The total value of TKI therapy was estimated by summing lifetime costs for a CML patient across all CML patients in a cohort, and then summing present discounted lifetime costs across all present and future cohorts. This took into account the decreased costs associated with the patent expiration of imatinib (2015) and dasatinib (2020). It was assumed that current lifetime and total cohort costs prevailed until patent expiration, after which costs were assumed to be zero. In addition, MEPS and SEER data were used to estimate the size of each CML cohort (4,500), of which 30% were expected to be resistant or intolerant to imatinib based on prior evidence in the literature.[25]

Results

Descriptive Data

Table 1 shows the patient characteristics of all CML patients in the SEER registry and the SEER CML sample. Incident cohorts of CML patients diagnosed in 2000 or later were included in survival-gain estimations associated with the introduction of first-line imatinib treatment. Restricting

Table 2. Impact of Introduction of TKIs for First-Line CML Treatment

HR associated with *post-TKI* = 1	0.833[a]
	(0.059)
Implied survival rate ratio (ITT)	1.123
Implied survival rate ratio (TOT)	1.307
Observations	5,523

CML indicates chronic myeloid leukemia; HR, hazard ratio; ITT, intent to treat; TKI, tyrosine kinase inhibitor; TOT, treatment on treated.
[a]Significant at the 99% level.
The table reports the HR associated with the post-TKI variable. HR is the ratio of the post-TKI hazard rate over the counterfactual hazard rate in the absence of TKI effect. The survival ratio is the ratio of the post-TKI survival probability at the pre-TKI median of 90 months over the counterfactual survival probability in the absence of the TKI effect. Demographic controls include age at diagnosis, age-at-diagnosis squared, sex, marital status, indicators for white, black, Asian/Pacific Islander, and other race, and a Hispanic indicator. Year-of-diagnosis indicators and a quadratic trend in month-of-diagnosis are also included as controls for secular time trends in survival.

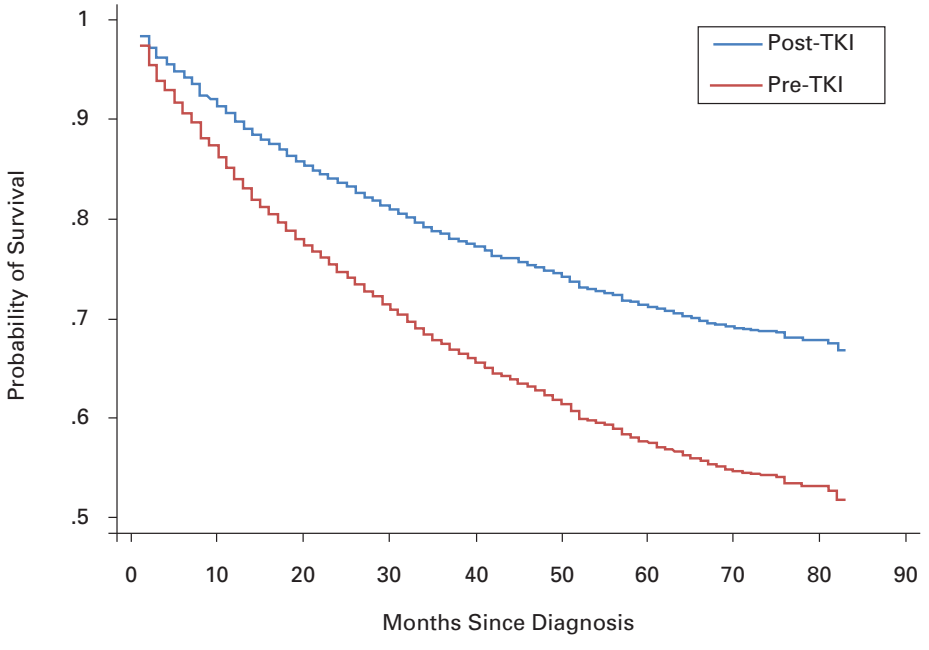
the data to SEER CML registrants for whom key demographic controls were reported generated a final analytical sample of 5,523 patients. Those in the CML subsample were demographically similar to patients from the full SEER CML sample, with the exception of 2 variables; namely, survival time (which was expected given the greater probability of survival among CML patients diagnosed at later dates) and Hispanic race (which likely resulted from a broader definition of "Hispanic" in more recently diagnosed patients).

Survival Gains: First-Line Therapy

Table 2 shows the results from the multivariate Cox proportional hazard analysis of survival impact following the 2001 introduction of first-line TKI therapy. The independent variable of interest is the post-TKI variable, which takes the value of 1 in 2001 and thereafter. The coefficient of this variable can be interpreted as the HR corresponding to the introduction of imatinib. Table 2 also depicts the most flexible form of the secular effects of time trend and time since diagnosis; year-of-diagnosis indicators and quadratic trend for month-of-diagnosis were included as controls for the secular trend in survival. As shown, the post-TKI variable was associated with an HR of 0.833 (P <.01). The implied TOT survival ratio of 1.307 can be interpreted as imatinib causing an immediate ~30% increase in the probability of CML survival at 90 months. This effect can be seen in the Figure, which shows the estimated pre-TKI and post-TKI survival curves for the treated patients. The survival ratio is equivalent to the vertical distance between curves at 90 months. Alternatively, the HR can be characterized by the median survival length (the life expectancy of a 50th percentile CML patient; ie, the horizontal distance between the curves). The HR of 0.833 corresponds to an estimated increase in median survival from 90 to 210 months.

As previously discussed, the effect of imatinib was estimated from the sustained shift in the survival curve that occurred in 2001, the year of the drug's introduction. As a sensitivity analysis, we evaluated whether shifts were observ-

Figure. Estimated Pre-TKI and TOT Post-TKI Survival Curves



TKI indicates tyrosine kinase inhibitor; TOT, treatment on treated.
The pre-TKI curve reports the estimated survival function for the incident cohort of chronic myeloid leukemia (CML) patients diagnosed immediately prior to TKI introduction in 2001. The post-TKI curve is the estimated survival function immediately following TKI introduction for the incident cohort of CML patients treated with TKIs. Estimates were based on a Cox proportional hazards model with 1-year indicators and cubic trend in time since diagnosis using Surveillance, Epidemiology, and End Results (SEER) cancer registry data.

Table 3. Overall Survival in First- and Second-Line TKI Treatment of CML at 60 Months

Imatinib for First-Line Treatment of Chronic Phase CML		
Study	**Sample Size**	**60-Month OS Rate**
de Lavallade et al (2008)[26]	204	83%
Druker et al (2006)[13]	553	87%
Average at 60 months		85%
Dasatinib for the Treatment of Imatinib-Resistant or Imatinib-Intolerant Chronic Phase CML		
Study	**Sample Size**	**60-Month OS Rate**
Shah et al (2011)[20]	167	78%
Ratio of dasatinib OS (second-line treatment) to imatinib OS (first-line treatment) at 60 months		91%

CML indicates chronic myeloid leukemia; OS, overall survival; TKI, tyrosine kinase inhibitor.
The table reports OS rates at 60 months for imatinib for the first-line treatment of CML and for dasatinib for the second- or third-line treatment of imatinib-resistant or imatinib-intolerant chronic phase (CP)-CML. The last row of the table reports the OS rate of dasatinib as second- or third-line therapy relative to the OS rates of imatinib as first-line therapy in CP-CML.

able in the survival curve at other years, as a large, sustained shift in survival occurring in any other year might imply that the estimated survival effect at 2001 was driven by factors unrelated to imatinib. To evaluate this, the survival analysis was repeated using a post-year variable for each year between 1998 and 2005. Reported *P* values for each estimated HR of the post-year variable are available in **Appendix B**. The only statistically significant coefficient corresponded to the post-2001 (ie, post-TKI) variable.

Survival Gains: Second-Line Therapy

OS rates reported in first-line imatinib studies[13,26] were averaged, with response rates weighted by study sample size. This was then compared with OS rates in second-line dasatinib therapy.[20] As shown in **Table 3**, the relative effectiveness of dasatinib in second-line therapy, as compared with imatinib in first-line therapy, was 91%. Under the assumption that the differences in clinical versus community survival rates would be the same for dasatinib and imatinib, we applied this 91% to the survival rate ratio of imatinib estimated in the SEER-based proportional hazard analysis.

Value and Costs

Table 4a shows the cost of treatment, the value of survival gained through treatment, and the value of gains for patients treated with imatinib as a first-line response to CML. Estimated annual and lifetime costs are reported in the first line of Table 4a. The annual value of TKI-related survival gains (column 1) is equivalent to the increase in annual income necessary to make a CML patient indifferent to the pre- and post-treatment survival curves, which is also equivalent to the patient's willingness to pay for treatment. Column 2 shows the present lifetime value of survival gains per individual treated with imatinib, column 3 illustrates the lifetime value of TKI treatment across all newly diagnosed US CML patients over a 1-year period, and column 4 shows the lifetime value of TKI treatment for all present and future US CML patient cohorts. Note that the fraction of total value recouped by drug manufacturers is lower in column 4 than in columns 1 through 3. This reflects the assumption that the cost to future CML cohorts of treatment after patent expiration is negligible relative to prices under patent. Columns 1 to 4 in **Table 4b** show corresponding values for dasatinib in second-line therapy.

These results indicate that patients place an annual value of $110,600 on first-line TKI treatment relative to annual costs (under patent) of $30,500. This implies that, for all patients in present and future CML cohorts, the present social value of first-line TKI therapy is $88 billion. The present value of these costs, accounting for future patent expirations, was estimated to be $8.24 billion. Hence, approximately 91% of the social value of TKIs in first-line therapy is retained by patients, while 9% is recouped by drug companies. Likewise, dasatinib used as second-line CML therapy creates $55 billion in social value, of which patients retain roughly 90%, while 10% is recouped by drug companies.

Discussion

This study evaluated the social value of CML survival gains achieved by treatment with TKIs. This analysis attributes the discrete 2001 HR drop in CML deaths observable in SEER data to the effect of imatinib treatment; this finding was robust to flexible controls for secular time trends in the survival analysis.

The study applied a novel model to assess the social benefit associated with improved CML patient longevity following the introduction of the TKI drug class. Based on this analysis, the TKI drug class in first- and second-line CML therapy has created over $143 billion in present discounted social value. Approximately 90% of this value will be derived from survival gains to be retained by patients and society, while ~10% will be recouped by drug companies.

Table 4a. Values for CML Patients Treated With Imatinib

	Figures at Annual per-Patient Level	Figures at Lifetime per-Patient Level	Lifetime Figures for a Single Cohort of CML Patients	PDV of Lifetime Figures for All Cohorts
(Column)	(1)	(2)	(3)	(4)
Cost	$30,500	$360,200	$729.28 m	$8.24 bn
Value of survival gains	$110,600	$1,305,600	$2.63 bn	$88.13 bn
Consumer benefit	$80,100	$945,400	$1.91 bn	$79.89 bn

Table 4b. Values for CML Patients Treated With Second- or Third-Line Dasatinib

	Figures at Annual per-Patient Level	Figures at Lifetime per-Patient Level	Lifetime Figures for a Single Cohort of CML Patients	PDV of Lifetime Figures for All Cohorts
(Column)	(1)	(2)	(3)	(4)
Cost	$32,700	$386,100	$538.56 m	$5.73 bn
Value of survival gains	$100,500	$1,185,900	$1.65 bn	$55.15 bn
Consumer benefit	$67,800	$799,800	$1.11 bn	$49.42 bn

CML indicates chronic myeloid leukemia; PDV, present discounted value; TKI, tyrosine kinase inhibitor.
A model from Becker et al[22] was used to calculate the utility to CML patients given their income and the improved survival curve they face as a result of treatment. The increase in income necessary for patients to achieve the same level of utility given the pre-treatment survival curve was then found. This increase in income was interpreted as the annual value to a CML patient of an increase in the survival profile attributed to TKI treatment. Column (1) reports annual values at the individual patient level. Column (2) reports present value over the lifetime of an individual patient. Column (3) reports present value over the lifetime for annual cohort of new imatinib-resistant or -intolerant CML patients. Costs are estimated from annual costs in 2006 and 2007 reported in the private medical and pharmaceutical claims data. All figures are reported in 2010 dollars. The size of each CML cohort is 4,500, of which 30% are expected to be resistant or intolerant to imatinib.

This proportional allocation corresponds with prior research using a similar model, which found that, between 1988 and 2006, 3% to 12% of the value of overall survival gains from cancer treatments was appropriated by drug companies.[21] These estimates also suggest that, at current price levels, the vast majority of value created by TKI therapy in CML is appropriated as aggregate benefit to consumers; in other words, patients, not drug companies, are the primary beneficiaries of TKI therapy in CML.

An understanding of the social value of TKI treatment in CML has implications for therapeutic reimbursement and pricing, as well as for healthcare professionals' awareness of how CML treatment costs contextualize to overall social benefit. Payers succeed in a competitive marketplace when they provide value to patients. From this perspective, the sizable lifetime value of TKI therapy to CML patients (relative to the cost of therapy) provides ample justification for facilitating patients' access to TKI therapy. While the extant literature calls into question the cost-effectiveness of some seemingly expensive new cancer therapies, the results of this study (based upon comprehensive economic-impact evaluation) underscore the importance of taking into account the social value of such therapies and the attendant lifetime benefits accruable to patients (and not just the contemporaneous cost) in making payer and policy decisions. For instance, it is important to weigh the social value of therapies against costs in making assessments about the impact of managed care on the quality of healthcare delivery.

It is worth noting that the current study's survival improvement estimates are somewhat smaller than those reported in clinical trials of TKIs. This study estimated a 90-month TOT survival rate of 65% after the introduction of imatinib, which is substantially lower than the 90-month survival rate reported in clinical trials.[12,17,27] This may be due to inadequate dosing or poorer monitoring/adherence in community settings relative to clinical trial settings, particularly in the years immediately following the introduction of imatinib. These survival estimates suggest the potential value of addressing real-world obstacles to TKI efficacy, such as poor adherence.

In terms of study limitations, the value of survival gains and costs in second-line therapy identified by this study were confined to clinical trial and cost data for dasatinib, which was the first molecule to receive approval for a second-line CML indication. The additional benefit of a subsequently approved second-line TKI molecule (nilotinib) was not evaluated in this study. As a result, the current figures are conservative to the extent that they omit possible benefits that could accrue from having another second-line agent available. Moreover, the estimated value due to the availability of these second-generation TKI agents is conservative, because

the empirical analysis did not capture the incremental benefits that these agents would provide in first-line use. Both dasatinib and nilotinib have demonstrated superiority to imatinib in first-line clinical trials, and received FDA approval for this use in 2010.[14-16,28]

In addition, the current study's estimate of value is derived solely from survival gains. To the extent that treatment leads to other benefits, such as reduced caregiver burden or reductions in medical expenditures due to improved health, the fraction of total value retained by patients and society is likely to be underestimated.

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APPENDIX A

Methodological Framework: Value of Survival Gains

An economic model developed by Becker et al[1] was employed to calculate the social value of survival gains derived from first- and second-line tyrosine kinase inhibitor (TKI) therapy. This economic model calculates patients' willingness to pay for longevity gains, accounting for discrete (rather than marginal) increases in survival probabilities. Adapting this methodology to the present study, the utility of chronic myeloid leukemia (CML) patients was calculated given the survival curve resulting from TKI treatment and the average income level among CML patients.

Patient income was estimated using the 2005 and 2006 Medical Expenditure Panels Study. Next, the amount of additional annual income necessary for patients to achieve the same level of utility given the counterfactual survival curve in the absence of the estimated TKI effect was calculated. This annual payment was interpreted to be the annual value to a CML patient of an increase in the survival curve associated with TKI treatment.

The present value of annual survival gains was calculated to produce an estimate of the per-patient lifetime value of survival gains derived from TKI treatment. The lifetime value for individual CML patients was summed across all individuals in a CML cohort, and then summed with discounted lifetime values across all present and future cohorts to determine the total social value of survival gains associated with TKI treatment. The estimated social value of TKIs to future cohorts was discounted at 3% per annum, via a method with precedents in the literature.[2]

APPENDIX A REFERENCES

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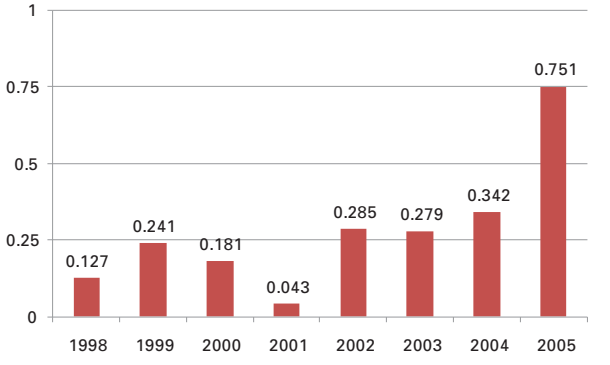
APPENDIX B

Figure. Statistical Significance of Hazard Models Testing for Sustained Shift in CML Survival Curve by Year



CML indicates chronic myeloid leukemia. Figure reports *P* values associated with separate hazard models that test for a sustained shift in the survival curve in the labeled year. For example, a model with a trend break in 2002 has an estimated trend break in the hazard rate that is insignificantly different from zero (the coefficient on the break in trend is associated with a *P* value of .285).