

eAPPENDIX

**Data Collection Process**

Table 1<sup>1-3</sup> provides a list of therapies for chronic myeloid leukemia (CML) and the dates of approval by the US Food and Drug Administration.

**Conceptual Framework**

The traditional calculation of a given health innovation’s survival benefits assumes no background progress in medical technology during the period in which the user’s life is being extended by the innovation. As a consequence, the survival gains that the innovation offers are measured against the prevailing life expectancy and under the assumption that no further improvements will occur.

However, this assumption may be unrealistic given substantial advances in life expectancy in general and in particular fields of medicine (such as oncology). For example, a patient with cancer who achieves a lower risk of death from cancer will typically face a decreased risk of death from hypertension, diabetes, heart disease, and other conditions over his newly extended life expectancy. These additional benefits multiply the traditionally measured effect and are not considered when valuing the cancer treatment that extended life initially.

In reality, the true value of an innovation includes an individual’s newly gained opportunity to see future medical breakthroughs in other areas, as illustrated by the calculation in Figure 1. We refer to the difference between the true value and the traditional calculation as the option value. In finance, an option holder has the right to buy or sell a security at a contracted price in the future. Part of the value of the option is the expected benefit of having the right to buy or sell the security in the future, should its market price evolve in a favorable direction.

■ **Figure 1.** Traditional Value, Option Value, and True Value

$$\text{(Traditional value)} = \text{(Survival benefits of the innovation)}$$

$$\text{(Option value)} = \text{(Survival benefits of the innovation)} \times \text{(Expected future survival improvements)}$$

$$\text{(True value)} = \text{(Survival benefits of the innovation)} \times (1 + \text{Expected future survival improvements})$$

The traditional value is the increased chance of remaining alive, due to the technology. Intuitively, option value is the increased chance of remaining alive, multiplied by the life expectancy gains enjoyed by those who remain alive. This is, therefore, the benefit of gaining the opportunity to live longer. The sum of the traditional value and the option value provide the true value of a technology. Next, we develop the economic framework to value a health innovation and incorporate its option value.

**Technical Framework for Calculating the Option Value of an Existing Innovation**

The economic framework for incorporating option value into health technology assessment using historical and forecasted changes in survival due to new technologies is based on a competing risk model in which overall mortality is driven by CML and all alternative causes. In this framework, option value derives from 2 sources: (1) treatment may enable patients with CML to live to see new innovations for CML; and (2) treatment may enable patients with CML to live to see new innovations for other causes of morbidity and mortality (eg, heart disease).

■ **Table 1.** Timeline of Approval of Therapies for CML

Targeted Therapies for CML <sup>1,2</sup>			
Brand Name	Active Ingredient	Date of FDA Approval for CML	
Gleevec	imatinib mesylate	5/10/2001	
Sprycel	dasatinib	6/28/2006	
Tasigna	nilotinib	10/29/2007	
Other Therapies Used for CML <sup>2,3</sup>			
Brand Name	Active Ingredient	Formulation/Strength(s)	Original FDA Approval Date
Cytosan	cyclophosphamide	Tablet (oral); 25 mg, 50 mg	11/16/1959
Cytarabine	cytarabine	Injectable; multiple strengths	6/17/1969
Neosar	cyclophosphamide	Injectable; multiple strengths	2/16/1982
Cyclophosphamide	cyclophosphamide	Injectable; 500 mg/vial	7/3/1986
Cytosar-U	cytarabine	Injectable; multiple strengths	12/30/1998

CML indicates chronic myeloid leukemia; FDA, US Food and Drug Administration.

Let  $s(a, u)$  denote the probability that person  $i$ , alive after having the disease  $a$  years, will survive 1 more year. This survival probability explicitly depends on person  $i$  having access to the medical technology available at time  $u$ , and implicitly depends on person  $i$ 's age, other demographics, and health status.

Let  $s'(a, u)$  denote the same probability in the presence of a new medical innovation (eg, a new drug for person  $i$ 's disease).

Let  $A$  denote a person's maximum remaining lifetime at the time of diagnosis (that is, 120 minus his current age).

In the absence of the innovation, we calculate person  $i$ 's life expectancy  $LE(a, t)$  at  $a$  years from diagnosis and time  $t$ , using the standard techniques, as follows:

$$LE(a, t) = s(a, t) + \sum_{\alpha = a+1}^A s(a, t) \prod_{\gamma = 1}^{\alpha - a} s(a + \gamma, t)$$

(Note that we are abstracting away from any discounting for simplicity.)

In contrast, person  $i$ 's expected lifetime  $EL(a, t)$  is calculated as:

$$EL(a, t) = s(a, t) + \sum_{\alpha = a+1}^A s(a, t) \prod_{\gamma = 1}^{\alpha - a} s(a + \gamma, t + \gamma)$$

This gives the following difference:

$$EL(a, t) - LE(a, t) = \sum_{\alpha = a+1}^A s(a, t) \left\{ \prod_{\gamma = 1}^{\alpha - a} s(a + \gamma, t + \gamma) - \prod_{\gamma = 1}^{\alpha - a} s(a + \gamma, t) \right\}$$

This difference represents the benefits of future medical progress (in curly brackets) multiplied by the probability of surviving to see those benefits,  $s(a, t)$ . In other words, the expected lifetime calculation takes into account that survival technologies will improve over time, whereas the standard life expectancy does not.

Now let  $S(a, u)$  denote the (unconditional) survival probability after having the disease  $a$  years, and consider a more general innovation which raises each year's survival probability by some amount,  $\Delta S(a)$ . This implies:

$$S'(a, u) = S(a, u) + \Delta S(a)$$

We evaluate the option value of this innovation in terms of its survival benefit (ie, the expected years of life it provides). Let  $P\{S_a | LE\}$  denote the probability of surviving  $a$  years after diagnosis, using the life expectancy method (ie, ignoring medical advances). Similarly, let  $P\{S_a | EL\}$  denote the probability of surviving  $a$  years after diagnosis, using the expected lifetime method (ie, incorporating medical advances). The option value of the innovation is the difference between the expected lifetime benefits and the life expectancy benefits owing to the innovation. It can be approximated as follows:

$$\begin{aligned} \Delta EL - \Delta LE &\cong \sum_{a=0}^A (P\{S_a | EL\} - P\{S_a | LE\}) (\Delta S(a)) \\ &= \sum_{a=0}^A (\text{medical\_progress\_survival\_gain}) \times \\ &\quad (\text{innovation\_survival\_gain}) \end{aligned}$$

Although the specifics of this calculation can be complex, some general points are worth noting. First, the option value will be positive as long as medical technology is advancing. Second, the option value can be expressed as the product of the increased chance of surviving to enjoy the benefits of medical advances multiplied by the survival value of those advances.

The reasoning behind this analytic framework is the following. Suppose the innovation is introduced at time  $t$ . The traditional or direct value of the innovation is the change in survival probability due to the innovation itself. The option value is the increased probability of being alive, multiplied by the value of staying alive in terms of future improvements in medical technology. However, in each time period from time  $t$  onward, the option value can be calculated as the product of the change in survival probability due to the innovation multiplied by the change in survival benefits from other medical advances between time  $t$  and the time period being considered. The total option value of the innovation is simply the sum of these combined survival benefits over the time periods its user may live to see. The total value of the therapy should hence add this option value to the conventionally calculated value.

### Estimating Past and Future Improvements in CML Survival and All-Cause Mortality

We quantified past improvements in survival from CML and all-cause mortality by fitting 2 separate Cox proportional hazard models to the Surveillance, Epidemiology, and End Results (SEER) cancer registry data.<sup>4</sup> The first model focused exclusively on CML mortality and the second model analyzed mortality from all other causes.

Conceptually, the Cox proportional hazard model assumes that the hazard function takes the form

$$h(t) = h_0(t) \exp(X\beta)$$

where  $h_0(t)$  is the baseline hazard (for  $X = 0$ ) and  $X$  is the vector of covariates. In this way, the effect of the covariates on the hazard can be estimated without specifying an exact functional form of the baseline hazard  $h_0(t)$ . In the Cox model, for a covariate  $X_k$ , the risk of death at any point in time, relative to  $X_k = 0$ , is  $\exp(X_k \beta_k)$ , where  $\beta_k$  parameterizes the mortality risk associated with  $X_k$ . The coefficient vector  $\beta$  is estimated by maximum likelihood. This estimation al-

lowed us to identify the key effect of innovative CML treatments on CML survival probabilities.

Covariates in each model include year of diagnosis (year 2000 is the reference category), age of diagnosis, age of diagnosis squared, number of other cancers at diagnosis, race (white is the reference category), ethnicity (non-Hispanic is the reference category), sex (female is the reference category), marital status (married is the reference category), calendar month of diagnosis, and county of residence. These patient characteristics affect mortality risk and the use of innovative CML treatments. Hence, failure to control for these observables would confound their effect on CML and all-cause mortality with the survival benefits from first- and second-line treatments. **Table 2** presents the regression estimates of the Cox model applied to CML mortality. As a sensitivity analysis, Table 2 includes different cohorts of patients diagnosed with CML as early as 1995. Patients diagnosed before 1995 were excluded from this sensitivity analysis given their limited comparability to the post-2001 treatment groups in terms of unobservable characteristics (such as frailty, wealth, education, and environmental factors). Overall, these different specifications show quantitatively similar results. The most notable difference is that year coefficients decreased in magnitude as cohorts diagnosed earlier than 2000 are included since these patients received treatment at a more advanced disease stage. Regression model 6 considered patients diagnosed between 2000 and 2008 to measure the benefit/cost of accelerating/delaying treatment by a year. This is our preferred specification to quantify the option value of innovative CML therapies. While CML mortality is significantly decreasing over time, the decline in background (ie, other-cause) mortality is less prominent.

Future improvements in CML and all-cause mortality were forecasted using the Lee-Carter method.<sup>5</sup> This method has been widely used as a benchmark for long-term mortality projections, including by the US Census Bureau in creating population forecasts and by the Social Security Administration in forecasting the number of future beneficiaries.<sup>6</sup> The Lee-Carter method assumes that the age-specific death rate pertaining to age  $x$  at time  $t$  can be modeled as

$$\ln m_{x,t} = a_x + b_x k_t + \varepsilon_{x,t}$$

where  $a_x$  describes the time-invariant shape of the age-specific death rates,  $k_t$  describes the improvement in all-cause mortality over time,  $b_x$  describes the tendency of mortality at age  $x$  to respond to overall improvements in mortality at time  $t$ , and  $\varepsilon_{x,t}$  is an error term. The Lee-Carter method assumes that the time trend in mortality improvements takes the form of a random walk plus drift:

$$k_t = k_{t-1} + c + e_t$$

Here  $c$  is the drift and  $e_t$  is the error.

We estimated coefficients  $a_x$ ,  $b_x$ , and  $k_t$  and to fit the historical data on the age-specific death rates in the SEER registry over the 2000 to 2008 period. We gauged the sensitivity of the results to our forecast of improvements in all-cause mortality by re-estimating option value at the upper and lower bounds of the 95% confidence intervals from the survival forecasts.

### Identifying Survival From First- and Second-Line Treatment

We identified survival from first- and second-line treatment algebraically from year-specific survival curves observed between 2000 and 2008. We set up and solved a system of equations linking observed survival in year  $t$ ,  $S_t$  with survival under first- ( $S_t^{1st}$ ) or second-line treatment ( $S_t^{2nd}$ ) in that year, and the probability of developing resistance to first-line treatment ( $\theta$ ). We set survival in 2000 as the control group's survival and assumed that patients diagnosed with CML between 2001 and 2005 (ie, before the introduction of second-generation tyrosine kinase inhibitors [TKIs]) faced this survival profile if they developed resistance to first-line treatment. Hence, the observed survival curves between 2001 and 2005 satisfy:

$$S_t = \theta S_{2000} + (1 - \theta) S_t^{1st}, t = 2001, \dots, 2005$$

By solving this system of equations for  $S_t^{1st}$ , we obtained the survival under first-line treatment for patients who have not developed resistance to it.

As second-line treatments became available in 2006, survival in years 2006 to 2008 can be expressed as:

$$S_t = \theta S_t^{2nd} + (1 - \theta) S_{2005}^{1st}, t = 2006, \dots, 2008$$

Unlike the previous scenario, patients who developed resistance to first-line treatment could benefit from second-line treatments and achieve survival profile  $S_t^{2nd}$ . Patients who do not fail first-line treatment do not obtain survival benefits (and hence, option value) from second-line treatment. We assigned these patients a survival of  $S_{2005}^{1st}$ , the most recent survival profile under first-line treatment that we can identify with our data, and solved the system of equations for  $S_t^{2nd}$ .

We computed the survival gains from first-line TKI therapy by taking the difference of the 5 survival curves under first-line treatment in years 2001 to 2005 relative to the control group's survival and aggregating the differences over this 5-year period. Similarly, we estimated the survival gains from second-line TKI therapy by aggregating the difference between the 3 survival curves under second-line treatment in years 2006 to 2008 and the control group's survival.

■ **Table 2.** Cox Proportional Hazard Regression Estimates

	CML Mortality						Other-Cause Mortality					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	1995-2008	1996-2008	1997-2008	1998-2008	1999-2008	2000-2008	1995-2008	1996-2008	1997-2008	1998-2008	1999-2008	2000-2008
<b>Year 1995</b>	0.255 <sup>a</sup>						0.497 <sup>a</sup>					
	(0.076)						(0.119)					
<b>Year 1996</b>	0.329 <sup>a</sup>	0.327 <sup>a</sup>					0.274 <sup>b</sup>	0.266 <sup>b</sup>				
	(0.077)	(0.077)					(0.129)	(0.129)				
<b>Year 1997</b>	0.147 <sup>c</sup>	0.140 <sup>c</sup>	0.146 <sup>c</sup>				0.396 <sup>a</sup>	0.385 <sup>a</sup>	0.390 <sup>a</sup>			
	(0.079)	(0.079)	(0.079)				(0.122)	(0.122)	(0.123)			
<b>Year 1998</b>	0.128	0.126	0.131	0.136 <sup>c</sup>			0.249 <sup>c</sup>	0.244 <sup>c</sup>	0.242 <sup>c</sup>	0.221 <sup>c</sup>		
	(0.081)	(0.081)	(0.081)	(0.081)			(0.128)	(0.128)	(0.129)	(0.130)		
<b>Year 1999</b>	0.158 <sup>b</sup>	0.157 <sup>b</sup>	0.158 <sup>b</sup>	0.163 <sup>b</sup>	0.158 <sup>b</sup>		0.147	0.149	0.15	0.146	0.158	
	(0.080)	(0.080)	(0.080)	(0.080)	(0.080)		(0.133)	(0.133)	(0.133)	(0.133)	(0.133)	
<b>Year 2001</b>	-0.185 <sup>a</sup>	-0.184 <sup>a</sup>	-0.185 <sup>a</sup>	-0.184 <sup>a</sup>	-0.186 <sup>a</sup>	-0.186 <sup>a</sup>	0.134	0.138	0.143	0.149	0.153	0.161
	(0.071)	(0.071)	(0.071)	(0.071)	(0.071)	(0.071)	(0.109)	(0.109)	(0.110)	(0.110)	(0.110)	(0.111)
<b>Year 2002</b>	-0.176 <sup>b</sup>	-0.177 <sup>b</sup>	-0.180 <sup>b</sup>	-0.181 <sup>b</sup>	-0.184 <sup>b</sup>	-0.185 <sup>b</sup>	-0.062	-0.059	-0.056	-0.052	-0.044	-0.040
	(0.073)	(0.073)	(0.073)	(0.073)	(0.073)	(0.074)	(0.119)	(0.119)	(0.119)	(0.120)	(0.120)	(0.121)
<b>Year 2003</b>	-0.433 <sup>a</sup>	-0.436 <sup>a</sup>	-0.442 <sup>a</sup>	-0.445 <sup>a</sup>	-0.450 <sup>a</sup>	-0.450 <sup>a</sup>	-0.052	-0.046	-0.043	-0.043	-0.035	-0.029
	(0.077)	(0.077)	(0.077)	(0.077)	(0.077)	(0.077)	(0.115)	(0.116)	(0.116)	(0.116)	(0.117)	(0.118)
<b>Year 2004</b>	-0.415 <sup>a</sup>	-0.419 <sup>a</sup>	-0.425 <sup>a</sup>	-0.431 <sup>a</sup>	-0.432 <sup>a</sup>	-0.430 <sup>a</sup>	-0.216 <sup>c</sup>	-0.210 <sup>c</sup>	-0.200	-0.197	-0.185	-0.174
	(0.077)	(0.077)	(0.077)	(0.077)	(0.077)	(0.078)	(0.125)	(0.125)	(0.126)	(0.126)	(0.127)	(0.128)
<b>Year 2005</b>	-0.393 <sup>a</sup>	-0.404 <sup>a</sup>	-0.415 <sup>a</sup>	-0.423 <sup>a</sup>	-0.432 <sup>a</sup>	-0.430 <sup>a</sup>	-0.184	-0.182	-0.175	-0.179	-0.165	-0.162
	(0.081)	(0.081)	(0.081)	(0.082)	(0.082)	(0.082)	(0.131)	(0.131)	(0.132)	(0.132)	(0.133)	(0.134)
<b>Year 2006</b>	-0.328 <sup>a</sup>	-0.343 <sup>a</sup>	-0.355 <sup>a</sup>	-0.367 <sup>a</sup>	-0.381 <sup>a</sup>	-0.379 <sup>a</sup>	-0.258 <sup>c</sup>	-0.262 <sup>c</sup>	-0.251 <sup>c</sup>	-0.251 <sup>c</sup>	-0.236	-0.235
	(0.083)	(0.083)	(0.083)	(0.083)	(0.084)	(0.084)	(0.142)	(0.143)	(0.143)	(0.143)	(0.144)	(0.145)
<b>Year 2007</b>	-0.412 <sup>a</sup>	-0.429 <sup>a</sup>	-0.446 <sup>a</sup>	-0.463 <sup>a</sup>	-0.488 <sup>a</sup>	-0.488 <sup>a</sup>	-0.139	-0.151	-0.144	-0.144	-0.127	-0.126
	(0.093)	(0.093)	(0.093)	(0.094)	(0.094)	(0.094)	(0.152)	(0.152)	(0.152)	(0.153)	(0.154)	(0.155)
<b>Year 2008</b>	-0.506 <sup>a</sup>	-0.527 <sup>a</sup>	-0.555 <sup>a</sup>	-0.572 <sup>a</sup>	-0.609 <sup>a</sup>	-0.621 <sup>a</sup>	0.153	0.145	0.163	0.145	0.150	0.136
	(0.138)	(0.138)	(0.138)	(0.139)	(0.139)	(0.139)	(0.190)	(0.191)	(0.191)	(0.192)	(0.193)	(0.194)
<b>Age at diagnosis</b>	-0.0141 <sup>a</sup>	-0.0144 <sup>a</sup>	-0.0141 <sup>a</sup>	-0.0145 <sup>b</sup>	-0.0139 <sup>b</sup>	-0.0138 <sup>b</sup>	-0.007	-0.004	-0.009	-0.003	-0.002	-0.004
	(0.005)	(0.005)	(0.005)	(0.006)	(0.006)	(0.006)	(0.010)	(0.010)	(0.011)	(0.012)	(0.012)	(0.013)

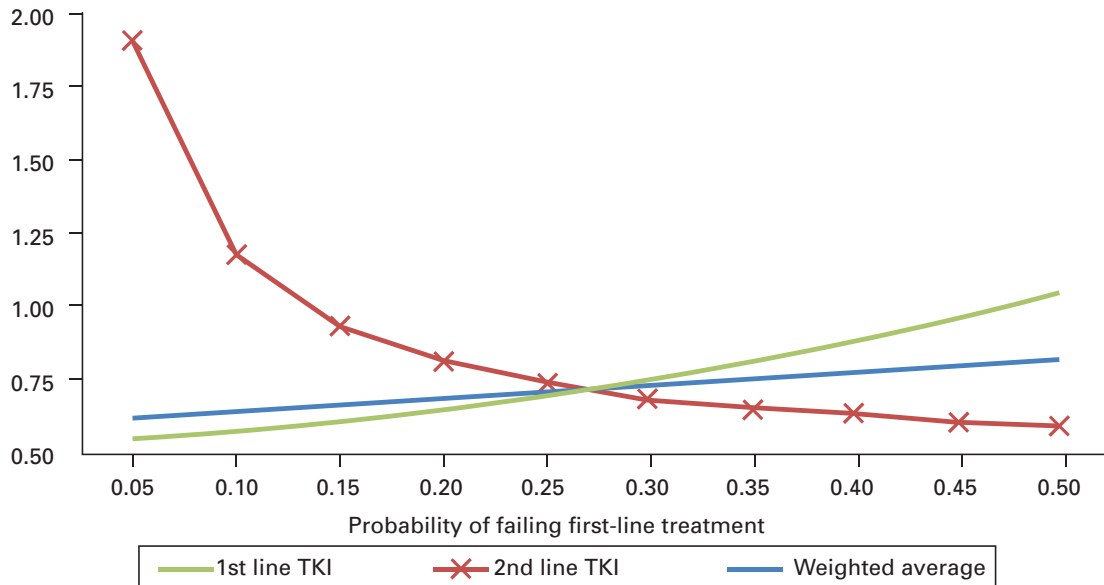
(continued)

■ **Table 2.** Cox Proportional Hazard Regression Estimates (*Continued*)

	CML Mortality						Other-Cause Mortality					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	1995-2008	1996-2008	1997-2008	1998-2008	1999-2008	2000-2008	1995-2008	1996-2008	1997-2008	1998-2008	1999-2008	2000-2008
<b>Age at diagnosis sq.</b>	0.0004 <sup>a</sup>	0.0004 <sup>a</sup>	0.0004 <sup>a</sup>	0.0004 <sup>a</sup>	0.0005 <sup>a</sup>	0.0005 <sup>a</sup>	0.0005 <sup>a</sup>	0.0005 <sup>a</sup>	0.0006 <sup>a</sup>	0.0006 <sup>a</sup>	0.0005 <sup>a</sup>	0.0006 <sup>a</sup>
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
<b>Male</b>	0.219 <sup>a</sup>	0.227 <sup>a</sup>	0.222 <sup>a</sup>	0.239 <sup>a</sup>	0.270 <sup>a</sup>	0.267 <sup>a</sup>	0.282 <sup>a</sup>	0.263 <sup>a</sup>	0.274 <sup>a</sup>	0.297 <sup>a</sup>	0.325 <sup>a</sup>	0.307 <sup>a</sup>
	(0.035)	(0.036)	(0.038)	(0.039)	(0.041)	(0.043)	(0.054)	(0.057)	(0.059)	(0.062)	(0.065)	(0.067)
<b>Black</b>	0.228 <sup>a</sup>	0.217 <sup>a</sup>	0.212 <sup>a</sup>	0.198 <sup>a</sup>	0.157 <sup>b</sup>	0.169 <sup>b</sup>	0.145	0.151	0.114	0.184	0.174	0.167
	(0.058)	(0.061)	(0.064)	(0.067)	(0.070)	(0.073)	(0.097)	(0.102)	(0.109)	(0.112)	(0.116)	(0.121)
<b>Asian/Pacific islander</b>	-0.104	-0.0871	-0.104	-0.174 <sup>b</sup>	-0.173 <sup>b</sup>	-0.191 <sup>b</sup>	-0.110	-0.102	-0.127	-0.078	-0.101	-0.066
	(0.071)	(0.074)	(0.078)	(0.084)	(0.088)	(0.095)	(0.117)	(0.122)	(0.129)	(0.133)	(0.141)	(0.149)
<b>Other race</b>	-0.924 <sup>a</sup>	-0.983 <sup>a</sup>	-1.069 <sup>a</sup>	-1.144 <sup>a</sup>	-1.237 <sup>a</sup>	-1.382 <sup>a</sup>	-0.011	0.053	-0.095	-0.157	-0.144	-0.112
	(0.181)	(0.194)	(0.206)	(0.215)	(0.231)	(0.260)	(0.190)	(0.193)	(0.209)	(0.218)	(0.223)	(0.229)
<b>Hispanic</b>	0.030	0.035	0.031	-0.011	-0.052	-0.079	0.018	0.042	0.032	0.043	0.075	0.027
	(0.058)	(0.060)	(0.063)	(0.067)	(0.072)	(0.075)	(0.097)	(0.101)	(0.105)	(0.110)	(0.113)	(0.120)
<b>Married</b>	-0.0995 <sup>a</sup>	-0.107 <sup>a</sup>	-0.117 <sup>a</sup>	-0.120 <sup>a</sup>	-0.140 <sup>a</sup>	-0.120 <sup>a</sup>	-0.241 <sup>a</sup>	-0.236 <sup>a</sup>	-0.234 <sup>a</sup>	-0.225 <sup>a</sup>	-0.212 <sup>a</sup>	-0.200 <sup>a</sup>
	(0.035)	(0.037)	(0.038)	(0.040)	(0.042)	(0.044)	(0.055)	(0.058)	(0.060)	(0.063)	(0.065)	(0.068)
<b>Number of tumors</b>	-2.019 <sup>a</sup>	-1.969 <sup>a</sup>	-1.920 <sup>a</sup>	-1.960 <sup>a</sup>	-1.952 <sup>a</sup>	-1.932 <sup>a</sup>	-0.967 <sup>a</sup>	-1.004 <sup>a</sup>	-1.038 <sup>a</sup>	-1.042 <sup>a</sup>	-0.983 <sup>a</sup>	-0.936 <sup>a</sup>
	(0.084)	(0.085)	(0.087)	(0.092)	(0.096)	(0.101)	(0.074)	(0.079)	(0.083)	(0.087)	(0.089)	(0.092)
<b>Calendar month</b>	0.004	0.005	0.005	0.007	0.006	0.003	0.003	0.000	-0.001	-0.007	-0.011	-0.012
	(0.005)	(0.005)	(0.005)	(0.006)	(0.006)	(0.006)	(0.008)	(0.008)	(0.008)	(0.009)	(0.009)	(0.009)
<b>County of residence</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Observations</b>	12,647	12,040	11,481	10,896	10,344	9,760	12,647	12,040	11,481	10,896	10,344	9,760
<b>χ<sup>2</sup></b>	2,578	2,403	2,222	2,103	2,006	1,819	2,578	2,403	2,222	2,103	2,006	1,819
<b>P value of χ<sup>2</sup></b>	0	0	0	0	0	0	0	0	0	0	0	0

Standard errors are shown in parentheses.  
 CML indicates chronic myeloid leukemia.  
<sup>a</sup>P < .01, <sup>b</sup>P < .05, <sup>c</sup>P < .10.

**Figure 2.** Option Value From Future Innovations in CML Treatment by Probability of Failing First-Line Treatment



CML indicates chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

**Monetizing Option Value**

We measured the option value of innovative CML treatments in monetary terms following Becker et al<sup>7</sup> and Philipson et al.<sup>8</sup> We had an individual's lifetime indirect utility function  $V(S,y)$  depend on annual full income of  $y$  and survival profile  $S$ . We supposed that a medical innovation improved survival from  $S$  to  $S'$ . We defined the individual's willingness to pay (WTP)  $w$  as the monetary value that satisfies  $V(S,y) = V(S',y-w)$ .

We assumed that the individual's utility function in a given time period takes the form

$$u(c) = \frac{c^{1-(1/\gamma)}}{1-(1/\gamma)} + \alpha$$

where  $c$  is consumption in the period,  $\alpha$  is a parameter that normalizes the consumption value of death to zero, and  $\gamma$  is the inter-temporal elasticity of substitution. Given these assumptions, we computed the annual WTP for the medical innovation as

$$w = y - \left[ \left( \frac{1}{1-\gamma} \right) \left( \frac{A(S)}{A(S')} u(\gamma) - \alpha \right) \right]^{\frac{\gamma}{\gamma-1}}$$

where  $A(S)$  is the value of an annuity that pays 1 dollar in perpetuity under survival curve  $S$ . The lifetime WTP is the present value of the annual WTP over the lifetime:  $A(S)w$ . We assumed that  $y = \$100,000$ ,  $\alpha = -14.97$ , and  $\gamma = 1.25$  following Philipson et al.<sup>8</sup>

**Sensitivity Analysis: Option Value Under Different Probabilities of Failing First-Line Treatment**

Figure 2 shows the option value from future innovations in CML treatment under a probability range for failing first-line treatment. We focused on the option value from future innovations in CML treatment given the almost negligible option value from future improvements in background mortality. The option value of first-line TKI therapy increased with the probability of failing treatment because the survival improvements observed between 2001 and 2005 are attributable to a lower fraction of patients that did not develop resistance to treatment. An analogous argument explains why the option value from second-line TKIs decreased with the probability of failing first-line treatment. Importantly, the average option value for the patient recently diagnosed with CML is not greatly sensitive to this parameter. Varying the probability of failing first-line treatment over a wide spectrum, the average option value for a patient recently diagnosed with CML ranges from 0.62 life-years (under a failure probability of 0.05) to 0.82 life-years (under a failure probability of 0.50). In our final analysis, we used a probability of 0.30 based on a clinical study by Quintas-Cardama et al.<sup>9</sup>

**Sensitivity Analysis: Option Value Under Different Survival Forecasts**

Table 3 shows the option value estimates evaluated at the lower and upper bounds of the 95% confidence intervals

■ **Table 3.** Option Value Evaluated at the Lower and Upper Bounds of the 95% Confidence Intervals for the Survival Forecasts

	1st-line TKI		2nd-line TKI		Average <sup>a</sup>	
	LB <sup>b</sup>	UB	LB	UB	LB	UB
<b>Gains from innovations against CML mortality</b>						
Survival gains (life-years)	7.55		6.01		7.09	
Option value						
Life-years	0.46	1.02	0.36	1.00	0.43	1.01
Fraction of survival gains	6.1%	13.5%	5.9%	16.7%	6.1%	14.3%
Dollars <sup>c</sup>	\$39,692	\$88,035	\$29,178	\$81,848	\$36,524	\$86,359
<b>Gains from innovations against non-CML (background) mortality</b>						
Survival gains (life-years)	1.99		0.82		1.64	
Option value						
Life-years	-0.09	0.18	-0.02	0.08	-0.07	0.15
Fraction of survival gains	-4.6%	9.0%	-2.2%	9.3%	-4.3%	9.1%
Dollars <sup>c</sup>	(\$4,158)	\$8,118	(\$411)	\$1,753	(\$2,763)	\$5,883
<b>Total gains from innovations against all-cause mortality</b>						
Survival gains (life-years)	9.54		6.82		8.73	
Option value						
Life-years	0.37	1.20	0.34	1.08	0.36	1.16
Fraction of survival gains	3.9%	12.6%	5.0%	15.8%	4.1%	13.3%
Dollars <sup>c</sup>	\$35,534	\$96,153	\$28,767	\$83,601	\$33,761	\$92,242

CML indicates chronic myeloid leukemia; LB, lower bound of survival forecast's 95% confidence interval; TKI, tyrosine kinase inhibitor; UB, upper bound of survival forecast's 95% confidence interval.

<sup>a</sup>Weighted average based on a probability of failing first-line treatment of 0.30.

<sup>b</sup>Gains valued according to Becker et al<sup>7</sup> and Philipson et al.<sup>8</sup>

<sup>c</sup>Dollar amounts in parentheses represent negative values.

for the survival forecasts. As we move from least to most optimistic forecast scenarios, the average option value for a newly diagnosed patient increased from 0.36 life-years (with a net worth of \$34,000) to 1.16 life-years (with a net worth of \$92,000).

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