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## **Budget Impact of Tyrosine Kinase Inhibitor Discontinuation in Chronic Myeloid Leukemia With Sustained Deep Molecular Response**

Cyril Astrugue, Antoine Benard, Pauline Bosco-Levy, Stephanie Dulucq, Magali Rouyer, Regis Lassalle, Nathalie Hayes, Francois-Xavier Mahon

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## **Title**

Budget impact of tyrosine kinase inhibitor discontinuation in chronic myeloid leukaemia with sustained deep molecular response.

## **Running Title**

Budget impact of TKI discontinuation in CML

## **Précis**

Systematically offering Tyrosin Kinase Inhibitors discontinuation to patients with CML in sustained Deep Molecular Response would save up to €25.5 million over 5 years.

## **Authors**

Cyril Astrugue <sup>1</sup>, Antoine Bénard <sup>1,2</sup>, Pauline Bosco-Levy<sup>3</sup>, Stéphanie Dulucq<sup>4</sup>, Magali Rouyer<sup>3</sup>, Régis Lassalle<sup>3</sup>, Nathalie Hayes <sup>5</sup>, François-Xavier Mahon <sup>4,6</sup>

1 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team EMOS, UMR 1219, F-33000 Bordeaux, France.

2 CHU de Bordeaux, Pôle de santé publique, Service d'information médicale, USMR & CIC-EC 14-01, F-33000 Bordeaux, France

3 Bordeaux PharmacoEpi, INSERM CIC 1401, University of Bordeaux, F-33000 Bordeaux, France

4 CHU de Bordeaux, Laboratoire d'hématologie, F-33000 Bordeaux, France

5 CHU de Bordeaux, Direction de la Recherche Clinique et de l'Innovation, F-33000 Bordeaux, France

6 Institut Bergonie, Cancer center Bordeaux, INSERM U1218, University of Bordeaux, F-33000 France

## **Corresponding author**

Professeur François-Xavier MAHON  
Directeur général de l'Institut Bergonié  
(f.mahon@bordeaux.unicancer.fr)  
Tél. 00.33.(0)5.56.33.33.00  
CRLCC Institut Bergonié  
229 cours de l'Argonne  
33076 Bordeaux Cedex  
FRANCE

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## **Abstract**

**Objective:** Tyrosine kinase inhibitors (TKI) account for the vast majority of health care expenditure on Chronic Myeloid Leukemia (CML) patients, and it has been demonstrated that TKI discontinuation in patients in long-term deep molecular remission (DMR) is safe and improves quality of life. Our objective was to estimate the budget impact of TKI discontinuation in CML patients in long-term DMR, from the perspective of the French healthcare system.

**Methods:** This Analysis was conducted over a 5-year time horizon using a Markov model with cycles of 6 months. Transition probabilities were estimated through systematic reviews and meta-analyses. Costs were estimated from the French National Claims Database. Monte-Carlo simulations were performed to take into account the uncertainty surrounding model parameters. Sensitivity analyses were carried out by varying the size of the target population and the cost of TKIs.

**Results:** Over a 5-year period and for a target population of 100 patients each year eligible and agreeing to stop TKI, the TKI discontinuation strategy would save € 25.5 million (95% confidence interval: -39.3; 70.0). In this model, the probability that TKI discontinuation would be more expensive than TKI continuation was 12.0%. In sensitivity analyses, mean savings ranged from €14.9 million to €62.9 million.

**Conclusions:** This study provides transparent, reproducible and interpretable results for healthcare professionals and policy makers. Our results clearly show that innovative healthcare strategies can benefit both the healthcare system and patients. Savings from generalizing TKI discontinuation in CML patients in sustained DMR should yield health gains for other patients.

## Highlights

- Systematically offering TKI discontinuation to patients with CML in sustained DMR would save up to €25.5 million over 5 years.
- It has already been shown that TKI discontinuation in patients with CML in sustained DMR is safe and generalizable. The savings we report here are another argument for generalizing TKI discontinuation for patients with CML in sustained DMR.

## Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder caused by a reciprocal translocation between chromosomes 9 and 22. The result is known as the Philadelphia Chromosome. The estimated prevalence of CML in France was 10 789 patients in 2014, corresponding to a crude prevalence rate of 16.3 per 100 000 inhabitants <sup>1</sup>, with current and predicted prevalence reaching levels around 18 and 24 per 100,000 in 2018 and 2030 respectively <sup>2</sup>. In the United States (US), this prevalence is expected to be approximately 144,000 in 2030 <sup>3</sup>. Tyrosine Kinase Inhibitors (TKI) are the gold standard treatment for CML and have completely revolutionized the outcome of CML patients. The life expectancy of CML patients under treatment with TKIs is nearly normal. This raises two important issues: quality of life and the economic impact of lifelong treatment <sup>4,5</sup>. As the mean age at CML diagnosis is around 60 in Europe and US <sup>6</sup>, lifelong TKI treatment represents a substantial burden on healthcare systems around the world. In France, the mean healthcare cost in the year following diagnosis of CML was estimated at a regional level to be 35,211€ (±15,573) between 2011 and 2015 <sup>7</sup>. TKIs are the most important budget item and represent 80% of this cost.

Multiple studies about TKI discontinuation for patients with sustained deep molecular response (DMR) have been reported <sup>8</sup>. Those studies estimate that 40 to 60% of patients in sustained DMR remain in treatment-free remission (TFR) after TKI discontinuation <sup>9-12</sup>. The majority of relapses, or more precisely molecular recurrences, occurred in the first 6 months following treatment discontinuation.

Attempting to discontinue treatment seems to be safe. Until now, the vast majority of the patients who experienced molecular recurrence after TKI discontinuation responded to TKI re-sumption <sup>13</sup>. Moreover, preliminary communications indicate that quality of life is not affected by TKI discontinuation <sup>14-16</sup>.

TKI discontinuation must be considered in appropriate patients after careful discussion employing the concept of shared decision making <sup>17</sup>. It should be considered only after at least 5 years of treatment and 2 years of DMR with no prior history of resistance or suboptimal/warning response and no hematopoietic stem cell transplantation with a typical transcript M BCR-ABL1, and  $\geq 18$  years old <sup>18</sup>.

As long as TKI discontinuation in CML patients in DMR is now part of the recommendations<sup>18</sup>, the question is not the cost-effectiveness of this strategy but its budget impact on a given health system.

Our objective was thus to estimate the budget impact of TKI discontinuation in patients with CML in sustained DMR, from the perspective of the French national healthcare insurance during the period 2017-2021.

## **Methods**

### ***Target population***

The target population in our model was patients with chronic phase CML, treated with TKI, in sustained DMR for at least 3 years and with 10 TKI deliveries by the city pharmacy in a year, that is patients eligible for a TKI discontinuation<sup>18</sup>. The annual number of incident cases of CML in France is 870 individuals<sup>1</sup>. Assuming that 20% of them will reach sustained DMR<sup>19</sup>, and taking into account that 40% will not accept TKI discontinuation, that gives around 100 patients who will initiate a TKI discontinuation for sustained DMR each year in France. We consequently built a multi-cohort model in which there is 100 additional patients each year over a 5-year time horizon (2017-2121).

### ***Comparators***

Two interventions were compared in this work:

- Life-long TKI treatment with quarterly PCR monitoring<sup>5</sup>.
- TKI discontinuation with closer PCR monitoring for the first 18 months following discontinuation, as recommended<sup>18</sup>.

The target population in our model is patients with chronic phase CML, treated with TKI, in sustained DMR for at least 3 years. It is thus a much selected population in which the recommendations cited above are followed. On another hand, a good compliance to TKI being a necessary condition to reach sustained deep molecular response<sup>20</sup>, we only considered in our model patients presenting a good compliance to TKI.

### ***Study design***

We developed a Markov multi-cohort model to simulate disease evolution as judged by a multidisciplinary team containing oncologists, a health economist, a molecular biologist, and clinical epidemiologists. Markov models are structured around mutually exclusive health states representing the possible consequences of the evaluated interventions. Prognosis is reflected by transitions between

health states over a series of discrete time periods (cycles). Costs are incorporated as a value per state per cycle <sup>21</sup>.

### *Structure and main assumptions of our model*

Figures 1 and 2 show the model created for each intervention. These models respect the guidelines for good practice issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)<sup>22-24</sup>. They track the evolution of patients between different health states. Once per cycle, patients can either stay in the same health state or move to another. The duration of cycles was set at 6 months in order to take into account that the risk molecular relapse is higher during the first 6 months after TKI discontinuation.

In the TKI continuation model, we assumed that patients developing long-term TKI toxicity would stop their TKI treatment. PCR monitoring was planned once every four months but was the same as in the discontinuation strategy if TKIs were stopped for toxicity.

In the TKI discontinuation model, the maximum number of TKI discontinuation attempts was two. In case of relapse, patients could not try TKI discontinuation again before completing 5 cycles in DMR with TKI treatment. All patients do not attempt a second TKI discontinuation. The probability of attempting a second TKI discontinuation is one of our model's parameters. PCR monitoring was scheduled five times in the first cycle, three times in cycle 2 and 3, then twice in the remaining cycles. For both models, after three cycles (18 months) without relapse, patients could not relapse <sup>13</sup>. The probability to go back to DMR with TKI treatment after relapse was the same at each cycle. The probability of death was the same as the general population for both models, as CML patients have a life expectancy near to the general population, and was the same for all health states. At the beginning of the model, the age of patients was set at 60 years.

### *Estimating costs*

Costs were estimated from the perspective of the French healthcare system. TKIs and all CML related healthcare costs are reimbursed at 100% by the French healthcare system.

Estimated costs were based on the French National Claims Database (SNDS). The SNDS covers around 99% of the French population from birth to death, even if a subject changes occupation or retires<sup>25</sup>. It contains pseudonymized information on all reimbursed healthcare consumptions including medical and paramedical encounters, drugs claims, hospital admissions and procedures, and their corresponding costs. It also provides information on registration for Long Term Disease, ensuring full coverage for all medical expenses related to some chronic diseases (LTD) and cause and date of death. Drugs are coded according to the Anatomic Therapeutic Chemical (ATC) classification and hospital or LTD diagnoses according to the ICD-10 (C92.1).

We developed a claim-based algorithm using healthcare consumption data from the SNDS including outpatient dispensing, LTD registration or hospitalisation diagnosis or medical procedures. TKIs included imatinib, dasatinib, nilotinib, bosutinib and ponatinib. Using this algorithm, the included patients were all adults ( $\geq 18$  years, as recommended for TKI discontinuation) presenting with CML and a first discontinuation of TKI treatment (i.e. no TKI dispensing for  $\geq 61$  days) in 2010-2014 after a 3 year-period of TKI regular treatment (i.e.  $\geq 10$  TKI dispensing per year over 3 years). The excluded patients were all patients who died  $< 1$  year after TKI discontinuation, or had an allogeneic or autogenic hematopoietic stem-cell transplant, a diagnosis of HIV/AIDS or a chronic Hepatitis C or B during the 3-year period before TKI discontinuation, or had a recent or ongoing pregnancy, a concomitant cancer, a TKI related adverse effect leading to hospitalization or psychiatric disorders ongoing at the time of TKI discontinuation.

In addition, causes of TKI discontinuation were investigated by reviewing all discharge diagnoses related to the hospitalizations surrounding the TKI discontinuation date in order to exclude patients who discontinued TKIs for reasons other than complete molecular response. This was done by a multidisciplinary team containing oncologists, a health economist, a molecular biologist, clinical epidemiologists and pharmacoepidemiologists.

Costs were then calculated within 2009 (one year before the first included TKI discontinuation) and 2015 (one year after the last included TKI discontinuation), for three different periods: the year before the discontinuation (*TKI-treated remission*), the treatment-free period (*TKI-free remission*) and,

potentially the period after TKI re-introduction in case of relapse (*relapse after TKI discontinuation*). Costs were detailed for the following items: TKIs, all drugs (TKI included), outpatient medical visits, procedures, nursing act, physiotherapy act, lab test, products and services, transports, hospitalizations and outpatient hospital visits, other medical healthcare resources, and other non-medical resources.

The cost of Reverse Transcription quantitative Polymerase Chain Reaction of *BCR-ABL1 RNA* (RT-q PCR-*BCR-ABL1*) was extracted from the Ministry of Health frame of reference because it is not reimbursed by the healthcare system, so it was not available in the SNDS. According to FiLMC recommendations, we assume follow-up was monthly during the first 6 months, then every 2 months until month 12, then every 3 to 6 months in patients remaining in MR4.5 and every 3 months thereafter <sup>18</sup>.

All costs were based on 2017 prices and converted into half-yearly costs before entry into the model. The currency used was the euro (€).

The time horizon for this BIA was 5 years (2017 – 2021). The results were also given annually and no discounting was applied, as recommended by French National Authority for Health (HAS) <sup>26</sup>. To convert costs from the SNDS in 2017 prices, the health consumer prices index averaged between 2009 and 2016 was applied using the data produced by the French national institute for statistical and economic studies <sup>27</sup>. An annual inflation rate of -0.81% was applied.

### ***Estimating transition probabilities***

All of the transition probabilities in the Markov models were estimated through systematic reviews and meta-analyses. This part of the work has been published elsewhere <sup>13</sup>. As there was no data available, the probability of TKI withdrawal due to toxicity was estimated from a local cohort of CML patients (unpublished data). As the overall survival of CP-CML patients has reached that of the normal

population <sup>28</sup>, the probability of death was derived from French National Institute of Demographic Studies (INED) data for the general population aged from 60 to 64 in 2014 <sup>29</sup>.

### *Analytical methods and statistical analysis*

We performed a deterministic analysis, using central estimation of costs and transition probabilities in the model. As cycles were 6 months long, a half-cycle correction was used <sup>30</sup>. Costs were calculated for each strategy and a difference of costs between interventions was also calculated. To take into account the uncertainty of model parameter estimates, a probabilistic analysis was conducted with 1,000 Monte Carlo iterations. Beta distributions were used for transition probabilities, and Gamma distributions for costs. The method of moments was used to derive the parameters of the Beta and Gamma distributions from the standard deviation of the transition probabilities and costs (appendix)<sup>31</sup>. The resulting distribution was used to derive 95% confidence interval (CI) and to estimate the probability that the TKI discontinuation strategy is more expensive than the TKI continuation strategy. Sensitivity analyses were carried out by increasing the number of eligible patients up to 200 per year (assuming that 40% of incident cases of CML patients would reach sustained deep molecular response each year), and by taking into account the reduction in the price of TKI due to generics (€987.21 per box of TKI) <sup>32</sup>.

The Markov model was analysed using Microsoft Excel (2016) software (Microsoft Corp., Redmond, WA, USA). Statistical analysis of SNDS data was performed with SAS<sup>®</sup> software (SAS Institute, Version 9.4, North Carolina, USA).

This study was authorized by the French national data protection committee (CNIL) on 20 July 2017, and registered under number 18568 in the European Union electronic Register of Post-Authorisation Studies (EU PAS).

## Results

### *Transition probabilities*

Table I summarizes all half-yearly transition probabilities with their point estimates, standard deviation, and probability distributions' parameters. Some probabilities were time-dependent, such as the probability of relapse from DMR without TKI (35% during the first 6 months after TKI discontinuation then 8% and 3% respectively during cycles 2 and 3). Over a 6-month period, relapsing patients had a 90% probability of recovering DMR after TKI reintroduction. The probability of relapsing after the second TKI discontinuation attempt was much higher than after the first attempt.

### *Costs*

All half-yearly costs for each intervention, detailed by budget item, are presented in table II. Those costs were estimated for 355 CML patients identified in the SNDS as stopping TKIs while in sustained DMR. During the 1-year follow-up period, TKIs were not reintroduced in 188 patients (53%), while 167 (47%) resumed TKIs. "All drugs" including TKIs were the most expensive item in the TKI continuation strategy, with TKIs accounting for 96.5% of the cost. Far behind, hospitalizations were the second most expensive item, and were the most expensive item in TKI-free remission. The cost of RT-q PCR-*BCR-ABL1* was 110.7€.

### Cost of compared interventions and differential cost between interventions

The cost of the TKI continuation strategy was estimated at € 55.496 million (95% CI: 26.691; 100.833) and that of the TKI discontinuation strategy at € 29.946 million (95% CI: 11.459; 91.306). Thus, up to € 25.550 million could be saved in France over 5 years by the healthcare system by adopting the TKI discontinuation strategy (table III). With a 95% CI of -66.984 million to +39.306 million €, there is a 12.0% probability that the TKI discontinuation strategy is actually more expensive than the TKI continuation strategy. Each year, the savings would be between 2.381 and 6.965 million €.

The item that account for most of the savings was TKI medication (€29.756 million). Conversely, outpatient consultations and RT-qPCR*BCR-ABL1* were more expensive in the TKI discontinuation strategy (€ 1.94 million and € 0.83 million, respectively) than in the TKI continuation strategy (€ 0.63 million and € 0.48 million, respectively) (supplemental table).

To note, 213 CML patients experienced a relapse and only 17 tried a second TKI discontinuation during the 5-year time horizon of our model.

Not surprisingly, sensitivity analyses show that savings would be lower (€ 14.868 million) if all TKIs were generics, and savings would be higher (€ 62.889 million) with an annual target population of 200 CML patients eligible for stopping and willing to discontinue TKIs (table III). The probability that the TKI discontinuation strategy is more expensive than the TKI continuation strategy ranged from 4.1 to 20.7% depending on the scenario.

## **Discussion**

From the perspective of the French national healthcare system, our model accurately estimates that the TKI discontinuation strategy in CML patients with a sustained DMR would induce a saving up to € 25.5 million over a 5-year period. This is an important result for health policy makers as CML is now a chronic disease with patients having a life expectancy near to that of the general population. Given their high cost, TKIs for CML impose an important and growing economic burden on healthcare systems.

Our study confirmed that TKI discontinuation for patients with CML in sustained DMR is an effective strategy to reduce cost. Such savings could be adequately reallocated within the healthcare system. In a context of constrained budgets, these savings could usefully be spent elsewhere or devoted to newly diagnosed CML patients.

These results are in agreement with studies already published on the cost of TKI discontinuation. In a long term follow-up of the STIM trial, the authors estimated that the savings related to TKI discontinuation was around €5.5 million in 100 patients during a median follow-up of 51 months<sup>33</sup>. In the Euroski trial, the savings related to TKI discontinuation were €22 million over a median follow-up of 27 months in 755 patients<sup>34</sup>. In a cohort study conducted in Lebanon where 162 patients with CML receiving imatinib, nilotinib, or dasatinib were followed-up over 4 years, the savings related to TKI discontinuation were estimated at about 7 million US dollars<sup>35</sup>. A single center evaluation of cost savings related to treatment-free remission reported savings of about €3.5 million in 54 patients without precision on the follow-up duration<sup>36</sup>.

But the economic results presented in those three studies were secondary objectives based on estimation of the costs of care in potentially unrepresentative samples, not population-wide budget impact analyses as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)<sup>23</sup>. To our knowledge, only one budget impact analysis of TKI discontinuation in CML with DMR has been published so far. In this study from Japan, the mean savings from the TKI discontinuation strategy was 7,625,174,640 yen (approximately 63,288,850€) in a target population of 901 CML patients within a 3-year time horizon<sup>37</sup>. We strictly followed the ISPOR recommendations

and our results are therefore interpretable by policy makers, transparent and reproducible. Another strength of our study is that we used real-life healthcare costs retrieved from the French national claims database (SNDS), which covers 98% of the French population. Among the 355 CML patients who stopped TKI identified in this database, 188 (53%) did not resume TKIs. This is consistent with results from the literature about the probability of molecular relapse after TKI discontinuation. As the SNDS strictly captures all the diversity in healthcare management and reimbursement, the use of these data reinforces the relevance and the reliability of our results and their usefulness for health authorities.

We have also taken into account the uncertainty regarding the model parameters estimates. Our probabilistic analysis enables us to produce 95% confidence intervals and to estimate the probability that TKI discontinuation might be more expensive than TKI continuation.

We have considered the emergence of generic drugs in sensitivity analyses. As expected, savings were lower with generics but still significant in a context of constrained budget, and more than offset the extra cost due to more frequent PCR monitoring after TKI discontinuation.

There are always some limitations in decision model-based analyses that are inherently a simplification of reality. However, we voluntarily chose to create models with multiple health states in order to represent all the possible trajectories of CML patients in DMR after TKI discontinuation or not. We have particularly taken into account the possibility of a second TKI discontinuation attempt. The duration of cycles was set to 6 months in order to take into account that the risk of molecular relapse decreases with time after TKI discontinuation.

The target population was estimated on the basis of the incidence of the disease in France and as the proportion of patients reaching DMR<sup>1,19</sup>. The savings of TKI discontinuation applies to France but the model could be used for other healthcare systems; potential savings increase linearly with target population size.

The large confidence intervals of our estimates result from uncertainty regarding the cost of drugs (including TKI), and the cost of hospitalizations which 95% confidence intervals are wide as reported in the supplemental table. As reported in table 1, the standard deviation of the probabilities of

molecular relapse after a second TKI discontinuation attempt are rather high relatively to the central estimates. Indeed, TKI discontinuation trials are recent, so it was expected that few patients would have made a second attempt, but the number of these studies is expected to increase over time, and consequently the transition probabilities after a second attempt of TKI discontinuation will gain in precision. However, this lack of precision in the estimates probabilities of molecular relapse after a second TKI discontinuation attempt is not responsible for the large confidence intervals of our estimates as very few patients attempted a second TKI discontinuation attempt within the 5-year time horizon of our model.

Another possible limitation relates to the data used to populate our model. The available TKI discontinuation studies in CML are non-comparative clinical trials or cohort studies. We did not formally evaluate the quality of the studies included in our meta-analyses. That said, we only selected studies where results were sufficiently informative that we could extract the data required to calculate the transition probabilities (follow-up in person-years, number of events, number of individuals at risk), the key determinants of methodological quality. There is also undesirable heterogeneity in these studies regarding the thresholds for defining molecular remission or relapse. We used the French National Claims Database (SNDS) to estimate the costs of our model. This may yield two potential limitations to our work. First, the diagnostics of remission or relapse are not available in the SNDS. Hence, even if the number of CML patients in remission or relapsing we identified in the SNDS is consistent with results from the literature (as stated above), we cannot exclude limited false positive or false negative diagnostic of remission or relapse generated by the algorithm we used. Second, one could argue that our model does not predict savings outside of the French setting. Our Microsoft Excel file, containing all the parameters of our model, is freely available from the corresponding author. Replacing the costs in our model by costs from another healthcare system will yield tailored results. Proposing our Microsoft Excel file to any researcher aiming at reproducing our results or using our model to produce results specific to another healthcare system is part of our willingness to provide transparent, reproducible and interpretable results for healthcare professionals and policy makers. Based on data from clinical trials, recommendations on TKI discontinuation have been recently published<sup>18,38</sup>, and patients are now likely to stop TKI outside clinical trials. The concept of lifelong

treatment for all patients is no longer valid, this is a shift in the care of CML patients. Our study is an important tool that will allow health policy makers to incorporate this new paradigm into health care planning. Our results clearly show that innovative healthcare strategies can benefit both patients and the healthcare system. We predict that reducing the burden of TKIs in CML will help to maintain the sustainability of healthcare systems through better allocation of resources.

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## **Figure legend**

Figure 1. Markov model for the current recommendation of life-long TKI (Tyrosine Kinase Inhibitors) treatment (DMR: Deep Molecular Response)

Figure 2. Markov model for the TKI (Tyrosine Kinase Inhibitor) discontinuation intervention (DMR: Deep Molecular Response)

Table I. Half-yearly transition probabilities. Point estimate and probability distributions parameters.

	<b>Point estimate</b>	<b>Standard deviation</b>	<b><math>\alpha</math></b>	<b><math>\beta</math></b>	<b>Source of data</b>
DMR 1 without TKI=> Relapse 1 (0-6 months)	0.3500	0.020	190.830	354.398	13
DMR 1 without TKI=> Relapse 1 (7-12 months)	0.0800	0.013	36.111	415.276	13
DMR 1 without TKI=> Relapse 1 (13-18 months)	0.0300	0.005	33.507	1,083.398	13
Relapse 1 => DMR with TKI	0.9000	0.018	253.116	28.124	13
DMR 2 with TKI => DMR 2 without TKI	0.2300	0.054	13.963	46.746	10,39-41
DMR 2 without TKI=> Relapse 2 (0-6 months)	0.4800	0.079	18.677	20.234	13
DMR 2 without TKI=> Relapse 2 (7-12 months)	0.2700	0.054	18.273	49.405	13
DMR 2 without TKI=> Relapse 2 (13-18 months)	0.1200	0.051	4.748	34.819	13
DMR 1 => TKI withdrawal for toxicity	0.0059	0.004	2.368	395.632	Clinical cohort (unpublished data)
All health states => Death	0.0039	-	-	-	29

$\alpha$  and  $\beta$  are the parameters of the Beta distributions.

Standard deviations (SD) were calculated as follows:  $\frac{(\text{upper 95\% CI end} - \text{lower 95\% CI end}) \div 2}{1,96}$ .

Table II. Half-yearly per-patient costs. Point estimates and parameter estimates for the probability distributions.

	TKI treated remission				TKI free remission				Relapse after TKI discontinuation			
	Point estimate (€)	Standard deviation	$\alpha$	$\beta$	Point estimate (€)	Standard deviation	$\alpha$	$\beta$	Point estimate (€)	Standard deviation	$\alpha$	$\beta$
All drugs (TKI included)	17,186.65	5,424.8	10.04	1,712.32	1,167.60	3,739.2	0.10	11,974.66	23,708.40	68,585.4	0.12	198,408.88
TKI	16,590.40	5,244.2	10.01	1,657.68	-	-	-	-	22,002.60	56,005.2	0.15	142,555.08
Hospitalizations	1,212.80	5,070.9	0.06	21,202.62	1,461.00	4,880.4	0.09	16,302.74	2,528.40	8,695.2	0.08	29,902.90
Outpatient hospital visits	210.80	255.4	0.68	309.56	853.80	4,879.8	0.05	17,630.41	713.40	5,450.4	0.04	16,688.06
Transport services	169.75	352.9	0.23	733.86	251.40	470.4	0.29	880.18	210.60	395.4	0.28	742.36
Outpatient medical visits	138.35	124.0	1.24	111.14	150.0	145.2	1.07	140.55	150.60	150.0	1.01	149.40
Lab tests	110.40	108.1	1.04	105.95	133.80	191.4	0.49	273.80	140.40	148.2	0.90	156.40
Nursing acts	105.40	506.1	0.04	2,430.14	105.60	514.2	0.04	2,503.80	181.20	876.0	0.04	4,235.00
Products and services	103.15	356.2	0.08	1,230.04	124.80	444.0	0.08	1,579.62	168.60	537.6	0.10	1714.20
Procedures	100.10	170.8	0.34	291.43	165.00	629.4	0.07	2400.87	177.60	562.2	0.10	1,779.67
Physiotherapy acts	65.20	214.2	0.09	703.71	87.60	250.2	0.12	714.61	81.60	220.8	0.14	597.46
Other medical healthcare resources	49.45	112.7	0.19	256.85	45.00	113.4	0.16	285.77	75.60	219.60	0.12	637.89
Other non-medical healthcare resources	0.45	2.2	0.04	10.76	0.20	4.2	0.04	5.00	0.60	9.00	0.36	1.67

$\alpha$  and  $\beta$  are the parameters of the Gamma distributions.

Table III. Results of the budget impact analyses.

	<b>Total costs (€)</b>		<b>Difference (€)</b>	<b>95% confidence interval of the difference (€)</b>	<b>Probability that the TKI discontinuation strategy is more expensive than the TKI continuation strategy (%)</b>
<b>Base case analysis</b>	Continuation strategy	Discontinuation strategy			
100 patients/year No generics	55,495,722.09	29,946,055.73	-25,549,666.36 €	[-66,984,265.30 ; 39,306,186.48 ]	12.0
<b>Sensitivity analyses</b>					
100 patients/year Generics	39,469,177.98	24,601,139.78	-14,868,038.20	[-72,515,577.74;46,228,696.80 ]	20.7
200 patients/year No generics	110,736,891.44	47,848,381.93	-62,888,509.51	[-145,769,247.04 ; 12,740,649.59 ]	04.1
200 patients/year Generics	78,735,928.56	39,565,736.71	-39,170,191.84	[-134,263,453.45; 40,911,034.74 ]	16.4



