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Budget impact analysis of treatment-free remission in nilotinib-treated Japanese chronic myeloid leukemia patients

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Abstract

Treatment-free remission (TFR), in which patients discontinue pharmacotherapy and remain in molecular remission, is an emerging treatment goal for patients with chronic myeloid leukemia (CML). Attainment of TFR requires an increased frequency of molecular monitoring, to ensure that patients maintain a deep molecular response. The objective of this analysis was to assess the economic impact of stopping nilotinib among Japanese TFR-eligible patients. A Markov model evaluated the economic impact of TFR among the study population, TFR-eligible CML patients diagnosed since 2012. The model compared patients who had discontinued tyrosine kinase inhibitor (TKI) treatment (ie, attempted TFR) with patients that continued TKI treatment. A 3-y time horizon was modeled from a Japanese public payer perspective. Costs associated with drug treatment, hospital/physician visits, and molecular monitoring were considered. TFR-eligible patients were calculated from Japanese CML incidence rates and efficacy was derived from nilotinib trials. Japanese co-payment maximums were utilized to assess the patient perspective. An estimated 761 and 140 patients were eligible for first- and second-line nilotinib, respectively, in 2019. Assuming that 100% of eligible patients complied, TFR was associated with cost savings of ¥7 625 174 640 (US$66 567 775) over 3 y. In scenarios with reduced willingness to attempt TFR, cost savings persisted. Achievement of TFR was estimated to markedly reduce out-of-pocket expenses for CML patients, regardless of the timing of relapse. Stopping nilotinib for TFR-eligible patients in Japan may result in significant cost savings to both payers and patients. Monitoring costs contributed little to overall annual costs and decreased over time.

KEYWORDS

budget impact, chronic myeloid leukemia, molecular monitoring, nilotinib, treatment-free remission

1 | INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative blood cancer,[1,2] with an annual incidence in Japan of 0.5 cases per 100 000 population.[3] It is characterized by the Philadelphia chromosome (Ph), resulting from a translocation between chromosomes 9 and 22, and caused by the ensuing BCR-ABL fusion gene.[1,4] This oncogene encodes the BCR-ABL protein and has constitutive tyrosine kinase activity that facilitates a malignant phenotype through dysregulation of cellular pathways associated with proliferation, apoptosis, and adhesion,[5-7] making it an attractive target for inhibition.[1,2,4] CML is typically categorized into 3 phases: chronic phase (CP), accelerated phase (AP), and blastic phase/crisis (BP). Most patients are diagnosed in the CP phase, in which the primary goal of therapy is to prevent progression to advanced stages (AP and BP).[8]

Tyrosine kinase inhibitors (TKIs) radically improve the survival of CML patients by targeting the tyrosine kinase activity of BCR-ABL. Imatinib, the first approved TKI, increased 5-y overall survival from 47.3% to 80.8%.[9,10] After 2 y with imatinib, 10% of patients were found to achieve deep molecular response (DMR),[11] a widely used surrogate marker of treatment effectiveness, defined as either detectable disease with <0.01% (MR4) or <0.0032% (MR4.5) BCR-ABL levels on the International Scale.[8] Since imatinib, several BCR-ABL targeting TKIs have been approved.[8,12,13] Second-generation TKIs have shown superior rates of DMR. For example, 21% of newly diagnosed CML patients treated with nilotinib achieved DMR after 2-y.[11] In addition, the ENESTcmr study showed that nilotinib increased DMR rates from 20.8% to 42.9% after 2 y in patients previously treated with imatinib, compared with patients who remained on imatinib.[14]

With greater overall survival, drawbacks of long-term treatment of CML including mild and modest adverse events (AEs) can impair patient quality of life.[11] In addition, the high cost of long-term treatment is a growing burden on healthcare systems. An emerging treatment goal for many patients with CML is treatment-free remission (TFR).[15,16] A substantial percentage of CML-CP patients in TFR can maintain a molecular response after stopping treatment.[17-19] The ENESTfreedom trial demonstrated that 51.6% of first-line patients who received nilotinib and attempted TFR, following 1-y nilotinib consolidation and sustained DMR, remained in major molecular response (MMR) or better.[19] Similarly in the ENESTop trial, of second-line CML-CP patients who received nilotinib and achieved a sustained molecular response, 57.9% of patients maintained TFR after 1 y.[20] Patients in both trials (ENESTop and ENESTfreedom) experienced fewer musculoskeletal pain-related AEs over time, once in TFR.[20,21]

Historically, recommended management of CML patients includes indefinite TKI treatment of responders.[8] Recent updates to the National Comprehensive Cancer Network (NCCN), Japanese Society of Hematology (JSH), and European Society for Medical Oncology (ESMO) guidelines recommend that patients with DMR may be eligible for treatment discontinuation.[22-24] Routine monitoring of maintained molecular response is a requisite of TFR,[15] with both the European Leukemia Network (ELN) and ESMO having created molecular monitoring recommendations.[8,23] Achievement of TFR through regular molecular monitoring has been associated with cost savings in French,[25] Russian,[26] and Lebanese[27] national perspective analyses. The economic impact of treatment discontinuation in TFR-eligible patients is currently unknown in Japan, despite a growing interest in reducing healthcare costs. To address this need, a model was developed to estimate the expected budget impact of molecular monitoring and TFR in CML.

2 | METHODS

2.1 | Model structure

A Markov model was developed to estimate the budget impact of discontinuing TKIs in TFR-eligible patients treated with nilotinib. The analysis was developed from a Japanese public payer perspective with a 3-y time horizon. The model was programmed in Microsoft Excel® 2013.

Analysis focused on Ph-positive (Ph+) CML-CP patients who were eligible for TFR after first- or second-line TKI treatment. In this analysis, patients were assumed to be treated with either first-line nilotinib or first-line imatinib followed by second-line nilotinib. Figure 1 shows a schematic diagram of the model structure and includes health states, as well as descriptions of the transitions between health states. Costs for first- and second-line patients were calculated separately, as drug acquisition costs differed between the lines (Table 1).

The reference case analysis compared 2 scenarios, one in which TFR-eligible patients discontinued TKI therapy ("TKI discontinuation scenario"), and the other in which TFR-eligible patients remained on TKIs ("TKI continuation scenario"). Patients enter the model eligible for TFR after at least 3 y of prior treatment, either on first- or second-line nilotinib, and achievement of DMR.[28,29] Patients willing to attempt TFR (assumed 100%) immediately discontinued TKI therapy. Patients not willing to attempt TFR remained on TKI therapy for the duration of the time horizon. Patients who did not maintain TFR (ie, patients who relapsed) re-initiated TKI therapy. In addition to Japanese yen (JPY), results were also presented in United States Dollars (US$). Costs were converted to November 2019 values using estimates from the Bank of America.[30]

2.2 | Target population

The target population for the model was Japanese patients who were eligible for TFR in 2019. Newly diagnosed CML patients were calculated from the incidence rate of CML in the Japanese population from 2012 to 2016, as all patients that started treatment during this time period would now be eligible for TFR (detailed calculations in Table S1). Based upon the TARGET trial, 30% of patients were

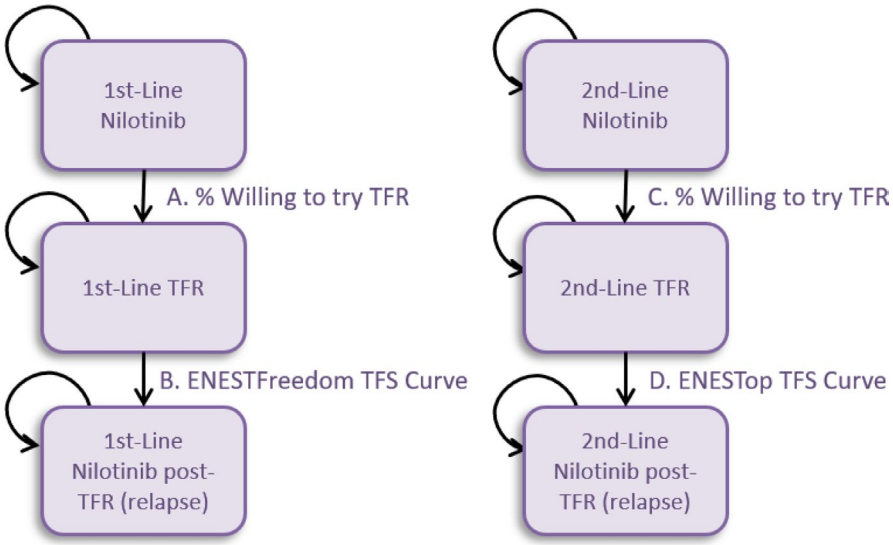

FIGURE 1 Diagram of the budget impact model structure. Patients enter the model eligible for treatment-free remission (TFR) either on first- or second-line nilotinib. The proportion of patients willing to attempt TFR who can immediately discontinue tyrosine kinase inhibitor therapy. Patient who are unable to maintain TFR were assumed to revert to nilotinib therapy.

TABLE 1 Model inputs

Parameter	Cost (JPY ¥)	Annual cost (JPY ¥)	Source
Daily drug costs (monthly)			
Nilotinib 1st line (600 mg)	14 468.00[a]	5 284 437.00[b]	Japanese National Health Insurance[34]
Nilotinib 2nd line (800 mg)	18 955.20[a]	6 923 386.80[b]	Japanese National Health Insurance[34]
Other costs (per visit/test)			
Hospital/physician visit cost	3160.00[c]	–	Japanese National Health Insurance[34]
Monitoring cost[d]	25 200.00[c]	–	Japanese National Health Insurance[34]
	Scenario		
Parameter	TKI discontinuation	TKI continuation	Source
Frequency of physician visits			
On TKI	12	12	ESMO Guidelines[23]
On TFR (year 1)	12	0	ESMO Guidelines[23]
On TFR (year 2+)	4	0	Expert opinion
Monitoring frequency			
On TKI	4	4	ESMO Guidelines[23]
On TFR (year 1)	12	0	ESMO Guidelines[23]
On TFR (year 2+)	4	0	Expert opinion

Abbreviations: ESMO, European Society for Medical Oncology; JPY, Japanese Yen; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

[a]Daily drug costs were provided by Novartis Oncology.

[b]Daily drug costs were multiplied by 365.25 to obtain average annual treatment costs.

[c]Other costs were provided by Novartis Japan.

[d]Molecular monitoring tests were assumed to be reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) for quantifying BCR-ABL1 transcripts.

assumed to receive first-line imatinib and 70% first-line second-generation TKIs.[31] To estimate the total pool of TFR-eligible patients, those likely to have failed imatinib (40%)[32] were assumed to have received second-line therapy with the second-generation TKI nilotinib.

The proportion of first-line and second-line patients that achieved DMR, which was assumed to be patients eligible for TFR, was derived from the ENEST1st[28] and ENESTcmr[29] trials, respectively (Table 2). The annual proportion of patients that maintained TFR was assumed to be equal to estimates from the ENESTfreedom (for first-line patients)[33] and ENESTop (for second-line patients) trials[20] (Table 2). In the reference scenario, all patients were eligible and willing to try TFR. All patients were assumed to attempt TFR in the "TKI discontinuation" scenario, and no patients attempted TFR in the "TKI continuation" scenario. Patients who could not maintain TFR were assumed to revert to nilotinib therapy and to incur the same costs for drugs and monitoring as patients that remained on nilotinib (ie, those that did not attempt TFR). Patients that relapsed from TFR in any model year

TABLE 2 Population calculation inputs

	First-line nilotinib	Second-line nilotinib	Source
Newly diagnosed CML	0.5	0.5	Chihara et al 2014[3]
% of 1L nilotinib patients	70%	–	Kizaki et al 2019[31]
% of 1L imatinib patients	–	30%	Kizaki et al 2019[31]
% imatinib failure – all cause	–	40%	IRIS Trial[32]
% of patients remaining on treatment	95%	95%	ENESTnd 12-mo[33]
DMR rate	37.8%	42.9%	ENEST1st[a28] and ENESTcmr[b29]
Cumulative TFR eligible	761	140	*Calculated*
TFR maintenance			
0 mo	100%	100%	ENESTFreedom[a19] and ENESTop[b20]
12 mo	52.21%	59.29%	
24 mo	50.65%	55.80%	
36 mo	48.55%	51.04%	

Abbreviations: 1L, first-line; CML, chronic myeloid leukemia; DMR, deep molecular response; TFR, treatment-free remission.

[a]Rate used for patients on first-line nilotinib.

[b]Rate used for patients on second-line nilotinib.

were assumed to receive a full year of costs associated with the TKI health state for that year. Patients that remained on TFR at the end of any model year were assumed to receive a full year of costs associated with TFR for that year.

2.3 | Treatment costs

Drug acquisition costs, hospital/physician visits, and molecular monitoring costs were included (Table 1). These costs were acquired from the Japanese National Health Insurance fee schedule.[34] The per-patient costs of drug, visits, and monitoring were calculated according to whether patients were on TKI, in TFR (year 1), and in TFR (year 2+). Costs were multiplied by the number of patients in each health state at the end of each 1-y cycle to determine the total annual costs.

Drug acquisition costs were incurred in both scenarios by patients on TKI. For first-line (600 mg) and second-line (800 mg) nilotinib, monthly drug acquisition costs were JPN ¥14 468.00 and ¥18 955.20, respectively. Physician visit costs were incurred in both scenarios, and during both TKI treatment and TFR. Patients on TKI were assumed to have monthly physician visits, aligning with CML clinical management guidelines.[13,23] During TFR, patients were assumed to have monthly physician visits in the first year and quarterly visits thereafter[24] (Table 1). The cost per visit was to be ¥3160.[34]

Molecular monitoring, via reverse transcriptase quantitative polymerase chain reaction (RT-qPCR), for quantification of BCR-ABL1 transcripts cost an assumed ¥25 200. In the "TKI discontinuation" scenario, monitoring costs were incurred quarterly while on TKI, monthly while in the first year of TFR, according to ESMO guidelines,[23] and quarterly again thereafter, based on expert opinion. Monitoring costs were incurred quarterly by patients on TKI in the "TKI continuation" scenario.

2.4 | Model assumptions

The model included several assumptions. All incident patients were assumed to be treated with either first- or second-generation TKIs, while second-line therapy was exclusively second-generation TKIs. All second-generation TKI use was assumed to be nilotinib. Other costs, such as AE management costs, were omitted as they were assumed to have a small impact relative to the cost of monitoring and drug acquisition.

2.5 | Deterministic sensitivity analyses

A series of one-way sensitivity analyses was performed to gain insight into the factors influencing the results. All key model parameters were tested individually at ±20% of the reference case value; parameters included in the sensitivity analyses were: (a) drug costs, (b) monitoring/visit frequency, (c) proportion of patients willing to attempt TFR, and (d) first-line and second-line TFR rates. Although the parameters used to calculate the target population were not direct inputs in the model, they were also analyzed to determine the influence of total eligible patient number. Key population parameters included: (a) proportion of patients receiving first-line nilotinib, (b) proportion of patients receiving first-line imatinib, (c) DMR rate, and (d) proportion of patients receiving treatment.

2.6 | Scenario analyses

Plausible alternative model inputs for physician visit/monitoring frequency and willingness to try TFR were evaluated through

scenario analyses. Scenario analysis 1 (SA 1) evaluated the impact of increased physician visit/monitoring frequency, based upon ESMO guideline recommended monitoring (every 6 wk or 8.7 times per year in years 2+ of TFR).[23] Scenario analysis 2 (SA 2) assessed the impact of decreased physician visit/monitoring frequency, based upon NCCN guideline recommended monitoring (8 times per year in year 1 of TFR).[22] Scenario analysis 3 (SA 3) tested a range (90%, 80%, 70%, 60%, and 50%) of patient willingness to try TFR.

2.7 | Patient perspective

Continuous drug acquisition costs for treatment of CML causes a financial burden to patients. The budget impact of TFR was calculated from the perspective of a Japanese patient that either: achieves TFR and does not relapse, fails to achieve TFR, or achieves TFR and relapses at 6 mo, or 1, 2, or 3 y. Cumulative costs were calculated over a 3-y time horizon based on monthly co-payment maximums within the Japanese Health Insurance System. Assumptions required for this analysis included: (a) patients were assumed to be <70 y old with an income of ¥3.3 to 7.7 million, (b) patients were assumed to have monthly hospital visits, and (c) that patients enter the analysis at a co-payment of ¥44 400. Upon discontinuation of TKI, the co-payment decreased to ¥7914. Co-payment at the time of relapse was dependent upon whether the patient incurred maximum co-payment limits 3 times within the previous 12 mo (cap of ¥44 400) or not (cap of ¥82 050). Once the co-payment cap was met 3 times in 12 mo, the monthly cost decreased to ¥44 400.

3 | RESULTS

3.1 | Population results – reference case

The number of TFR-eligible patients in Japan in 2019 was estimated from the number of incident CML patients in Japan between 2012 and 2016, as these patients would all be TFR eligible in 2019. From 2012 to 2016, there was an estimated 635-638 incident patients per year (Table S1), yielding approximately 3179 total cases. Here, 2225 patients were estimated to start first-line nilotinib, and 761 of these patients were estimated to be TFR eligible as of 2019. Of the 953 patients calculated to start first-line imatinib, 140 were estimated to now be eligible for TFR on second-line nilotinib, after first-line failure (Table S1).

The reference case assessed the impact of TFR in the estimated Japanese TFR-eligible population (761 first-line nilotinib and 140 second-line nilotinib patients). Discontinuation of TKI treatment via TFR, was estimated to yield incremental cost savings of ¥7 625 174 640 (US$66 567 775[30]) (Figure 2). Cost savings were mostly due to reduced drug costs during TFR (Table 3). With monitoring and TFR, total costs were nearly halved from *c.* ¥5 billion to *c.* ¥2.5 billion each year, despite an increased frequency of monitoring in the "TKI discontinuation" scenario compared with the "TKI continuation" scenario. Monitoring costs decreased in each subsequent year but, overall, contributed little to costs.

3.2 | Deterministic sensitivity analyses

As expected, the model results were most sensitive to eligible patient population size calculations and drug costs. Varying population calculations produced the largest budget impact range from ¥5 021 193 297 (US$45 140 528[30]) to ¥9 148 625 370 (US$82 246 142[30]). Model results were also sensitive to the proportion of patients willing to attempt TFR, and first-line and second-line TFR rates. As expected, a lower proportion of patients willing to attempt TFR produced lower cost savings because fewer patients discontinued TKI and continued to incur costs. Higher rates of sustained TFR produced more cost savings, as expected, due to fewer relapses. In addition, varying first-line TFR rates produced a larger budget impact compared with second-line TFR rates because the calculated eligible patient population in the analysis consisted of more first-line patients than second-line patients. Other parameters, such as monitoring costs, visit costs, and monitoring/visit frequency, remained stable. Finally, all tested scenarios resulted in cost savings. Results of the deterministic analysis are shown in Figure 3.

3.3 | Scenario analyses

Increasing the visit and monitoring frequency in the years 2+ of TFR in SA 1 reduced cost savings slightly, to ¥7 504 613 625 (US$65 515 277[30]) (Table 4), due to the additional costs of hospital/physician visits and monitoring tests. In contrast, decreasing the visit and monitoring frequency in the first year of TFR in SA 2 increased the cost savings slightly to ¥7 679 662 606 (US$67 043 455[30]). Decreasing the proportion of patients willing to try TFR in the third scenario analysis reduced incremental cost savings to a minimum of ¥3 816 547 814 (US$33 318 462[30]) with 50% of patients unwilling to attempt TFR. In all the tested cases, the "TKI discontinuation" scenario was associated with cost savings compared with the "TKI continuation" scenario.

3.4 | Patient perspective

Japanese patients with CML can incur notable out-of-pocket expenses. Patients that do not achieve (or attempt) TFR were estimated to incur nearly ¥1 598 400 (US$13 954[30]) in out-of-pocket expenses (Figure 4 and Table 5). Patients who remain in TFR longer before relapse obtain greater savings, with patients achieving TFR and not relapsing estimated to incur nearly ¥1 277 010 (US$11 148[30]) less in healthcare costs.

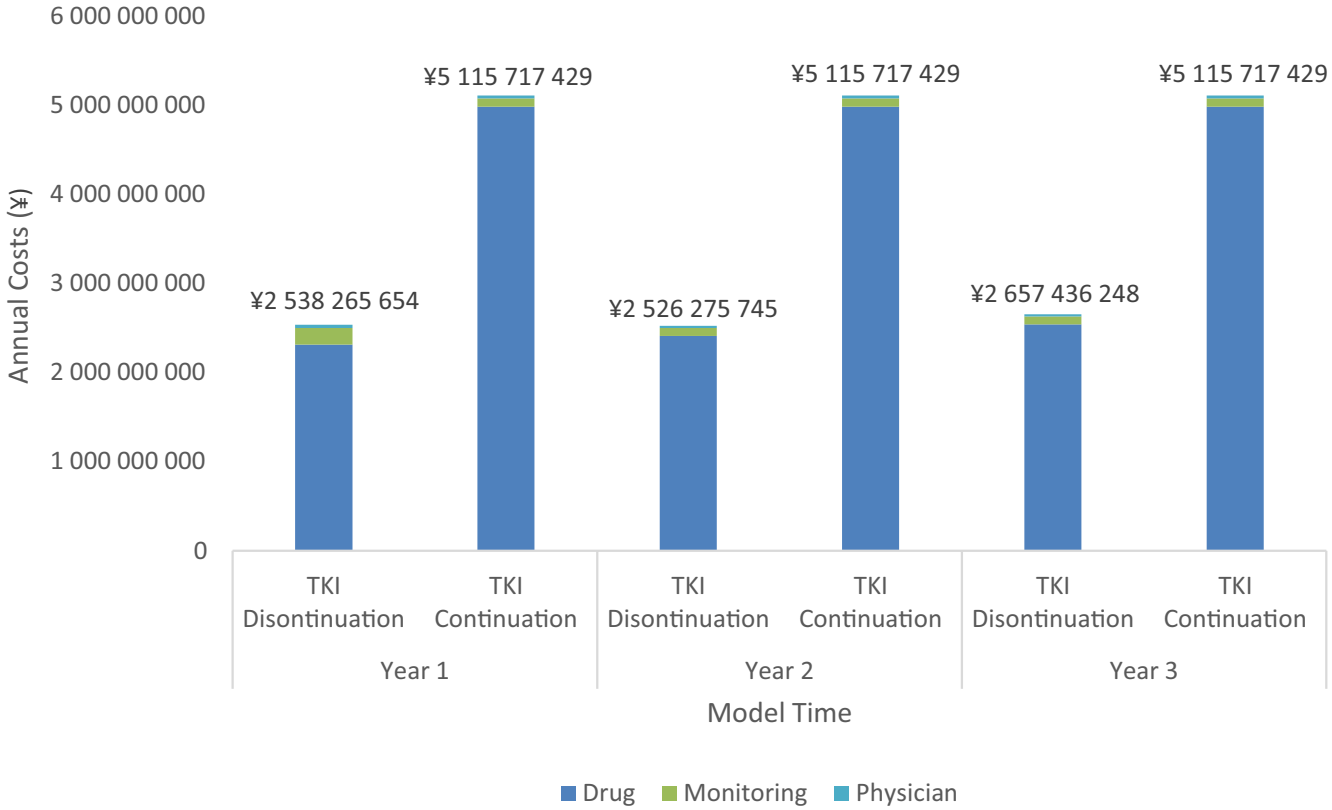

FIGURE 2 Annual healthcare costs comparing the "tyrosine kinase inhibitor (TKI) discontinuation" scenario and the "TKI continuation" scenario. Abbreviation: TFR, treatment-free remission

TABLE 3 Detailed annual healthcare costs

	Drug costs (¥)	Monitoring costs (¥)	Physician visit costs (¥)	Total (¥)	Cost savings (incremental difference; ¥)[a]
Scenario with "TKI discontinuation"					
Year 1	2 316 445 596	187 654 139	34 165 920	2 538 265 654	
Year 2	2 413 007 986	90 820 800	22 446 959	2 526 275 745	
Year 3	2 543 596 023	90 820 800	23 019 424	2 657 436 248	
			Total	7 721 977 647	
Scenario with "TKI continuation"					
Year 1	4 990 730 709	90 820 800	34 165 920	5 115 717 429	2 577 451 775
Year 2	4 990 730 709	90 820 800	34 165 920	5 115 717 429	2 589 441 684
Year 3	4 990 730 709	90 820 800	34 165 920	5 115 717 429	2 458 281 181
			Total	15 347 152 287	7 625 174 640

Abbreviation: TKI, tyrosine kinase inhibitor.

[a]Annual and total incremental difference calculated between scenario with "TKI discontinuation" and scenario with "TKI continuation."

4 | DISCUSSION

The introduction of TKIs has markedly improved the survival of patients with CML,[9,10] which has increased the number of CML patients who remain on therapy. The long-term, potentially indefinite, TKI treatment of CML can burden patients physically and financially and stress drug budgets. The high cost of treatment has been associated with decreased treatment adherence, which may lead to decreased 5-y event-free survival.[35-37] Given the high economic burden of CML, healthcare payers and decision makers are interested in quantifying the budget impact of TFR, a new treatment goal for CML in which patients can suspend TKI therapy. This analysis was designed to compare the cost impact of nilotinib discontinuation, and the associated increase in molecular monitoring while in TFR, with the cost of standard TKI management of CML (ie, continued TKI treatment and reduced monitoring requirements). It was estimated

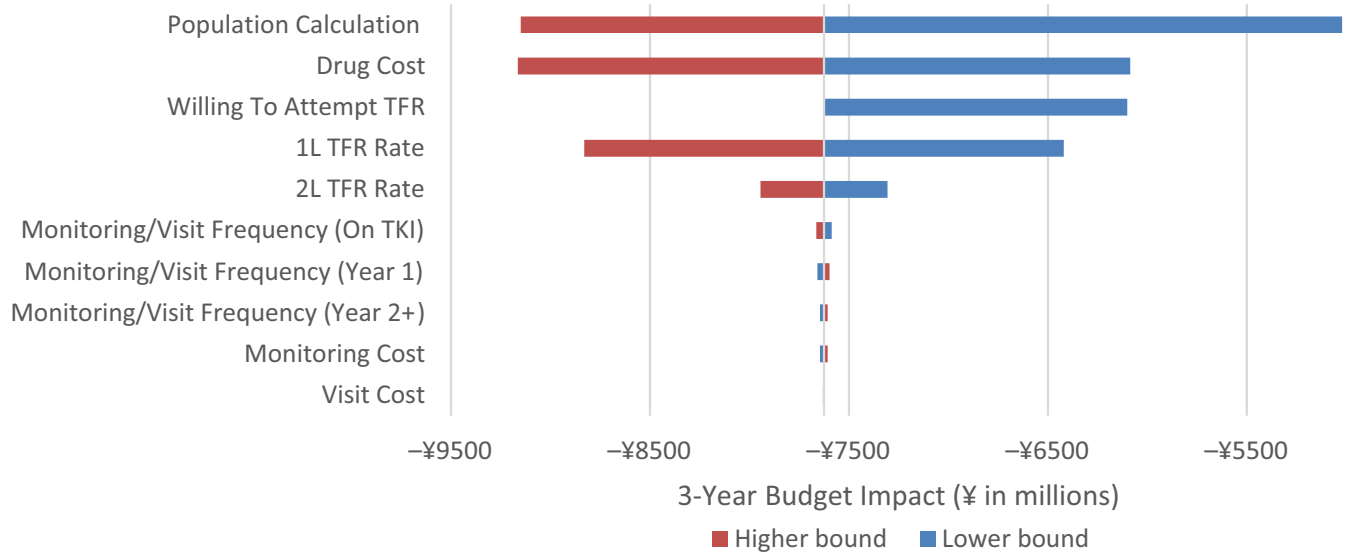

FIGURE 3 Results of the deterministic sensitivity analysis. Key model parameters were tested individually to gain insight into the factors influencing the results. Abbreviations: TFR, treatment-free remission; TKI, tyrosine kinase inhibitor

TABLE 4 Scenario analyses results

Case analyses	Monitoring frequency		Incremental costs
	On TFR (year 1)	On TFR (year 2+)	
Physician and monitoring frequency			
SA 1—Increased frequency[a]	12	8.7	¥7 504 613 625
SA 2—Decreased frequency[b]	8	4	¥7 679 662 606
Case analyses	**Model population**		**Incremental costs**
	1L nilotinib	**2L nilotinib**	
SA 3—Reduced willingness to try TFR			
90% of patients	685	126	¥6 863 449 275
80% of patients	609	112	¥6 101 723 909
70% of patients	533	98	¥5 339 998 544
60% of patients	457	84	¥4 578 273 179
50% of patients	381	70	¥3 816 547 814

Abbreviations: 1L, first-line; 2L, second-line; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; SA, scenario analysis; TFR, treatment-free remission.

[a]Based on ESMO guidelines.

[b]Based on NCCN guidelines.

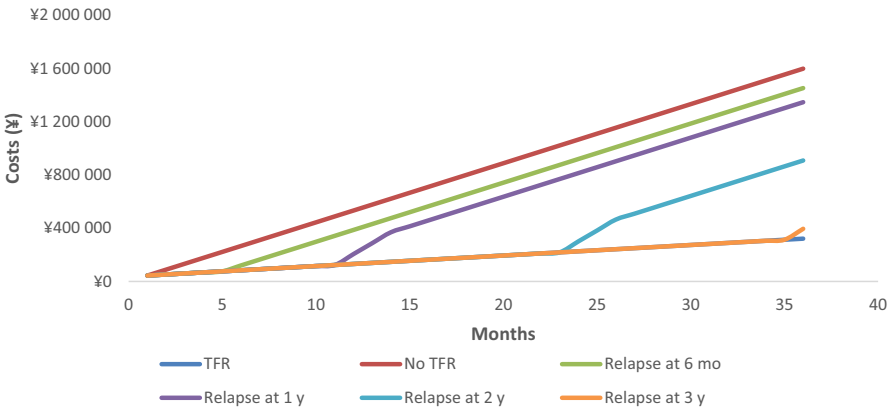

FIGURE 4 Cumulative healthcare costs from a patient perspective. Results are shown for patients who achieved treatment-free remission (TFR) and did not relapse, failed to achieve TFR, or achieved TFR and relapsed at 6 mo, or 1, 2, or 3 y.

TABLE 5 Cumulative healthcare costs – patient perspective

Case analysis	Cumulative costs (¥) at			Likelihood of sustained TFR
	Year 1	Year 2	Year 3	
Achieved TFR with no relapse	131 454	226 422	321 390	–
Did not achieve TFR	532 800	1 065 600	1 598 400	–
Achieved TFR, relapsed 6 mo	386 856	919 656	1 452 456	61.30%
Achieved TFR, relapsed 12 mo	205 590	813 690	1 346 490	59.30%
Achieved TFR, relapsed at 24 mo	131 454	300 558	908 658	55.80%
Achieved TFR, relapsed at 36 mo	131 454	226 422	395 526	51.00%

Abbreviation: TFR, treatment-free remission.

that nilotinib discontinuation in all TFR-eligible Japanese CML patients would yield incremental cost savings of ¥7 625 174 640 (US$66 567 775[30]) over 3 y, compared with continued TKI treatment. Importantly, cost savings highlight the fact that nilotinib discontinuation offsets the cost of increased molecular monitoring in patients that are in TFR. These results remained stable after varying key parameters in a deterministic sensitivity analysis. As expected, the results were most sensitive to population size and drug costs. In all tested scenarios, TKI discontinuation remained cost saving. To our knowledge, this is the first analysis to estimate the budget impact of TFR in TFR-eligible patients in Japan and identify marked cost savings.

Molecular monitoring (qPCR testing) of patients with CML is necessary for the optimization of treatment,[38] and for appropriate and timely assessment of treatment response.[39,40] Regular monitoring during TFR is required to identify patients who have relapsed and who require re-initiation of TKI therapy to regain molecular response. As a result, many guidelines recommend an increased frequency of molecular monitoring in patients in TFR compared with patients on TKI therapy.[22,23] The reference case demonstrated the discontinuation of nilotinib therapy to be cost saving, despite a 3-fold increase in monitoring in year 1 of TFR. Scenario analysis 1 demonstrated that nilotinib discontinuation remained cost saving even when an elevated rate (based upon ESMO guidelines[23]) of monitoring was considered in subsequent years of TFR. In contrast, if NCCN recommended monitoring (less frequent than the base case and ESMO) is adhered to, cost savings were expected to increase by over ¥50 million.

As patient willingness to try TFR is not likely to be 100% in the real world, a range of possibilities was tested to evaluate the impact of more plausible estimates. At all tested willingness to try probabilities (from 50%-90%), nilotinib discontinuation remained cost saving. Based on expert opinion, *c*. 80% of TFR-eligible patients may be willing to attempt TFR. A willingness to try TFR of 80% yielded an estimated cost saving of ¥5 882 169 792 (US$51 351 342[30]). In a scenario that assumed a more conservative (50%) willingness to try, nilotinib discontinuation still yielded cost savings of ¥3 676 356 120 (US$32 094 589[30]). Results from these scenario analyses confirmed the cost-saving potential of TFR in Japan.

Other studies have used cost-effectiveness analyses to evaluate another aspect of economic values of TFR and stop TKI strategy in Japan. For example, Yamamoto et al[41] conducted a cost-effectiveness analysis using a Markov model to compare treatment initiation strategies with imatinib, dasatinib, nilotinib, or any TKI at the physician's discretion with incorporation of treatment discontinuation. In addition, Shih et al[42] compared the cost-effectiveness of generic imatinib and second-generation TKIs as front-line therapy including treatment discontinuation using a decision analytic model. Both studies concluded that an imatinib-first CML treatment is the most cost-effective approach available even with the incorporation of TKI treatment discontinuation. These results proposed that, although second-generation TKIs provide fast and profound responses, the clinical benefit does not outweigh the low cost of imatinib. Conversely, our budget impact analysis solely focused on the financial consequences of TFR and stop TKI strategy from various perspectives. Interestingly, Japan has a unique benefit system that addresses high healthcare costs, and that enables patients to access second-generation TKIs that have higher rates of DMR and treatment discontinuation with shorter duration compared with imatinib.[19,43,44] Under this benefit system, patients thought to incur high medical costs are exempt from paying more than a fixed amount, which is calculated from their income level. Regardless of the treatment they receive, almost all patients with CML treated with TKIs are covered by the benefit program. Because of this program, there is a minimal cost-benefit from the patient's perspective for starting treatment with imatinib. Therefore, the scenarios explored through the current budget impact analysis will reflect the treatment pathways in Japan and the associated impacts on overall medical costs that provide relevant findings from a payer's perspective.

Beyond cost savings to the Japanese health system, the analysis also evaluated the budget impact of TKI discontinuation to an average Japanese CML patient, which has not been demonstrated previously. The cost to Japanese patients (ie, total co-payment amounts) who discontinued TKI was compared with the cost to patients who choose not to discontinue TKI. The analysis showed substantial reduction in CML-related treatment costs for patients. With the median duration of TFR extending beyond 3 y in trials of nilotinib, median cost savings for Japanese patients that discontinued nilotinib treatment are likely to exceed ¥1 202 874 (US$10 501[30]).

Importantly, it was estimated that even patients who relapsed within 6 mo of nilotinib cessation would save ¥145 944 (US$1274[30]). As such, in addition to being cost saving to Japan's National Health Insurance, stopping treatment with nilotinib and possibly with other TKIs in TFR-eligible patients is expected to reduce out-of-pocket expenses for Japanese patients.

Currently, only patients who achieve DMR (suppression of BCR-ABL fusion protein to <0.01% [MR4] or <0.0032% [MR4.5]) can attempt TFR.[8] Recent studies have shown that up to *c*. 43% of patients can achieve this level of response.[28,29] The remaining patients are considered ineligible for TFR and must remain on TKI treatment. As shown in the model, these patients incurred much higher treatment costs compared with TFR-eligible patients who attempt TFR. At the national level, cost savings obtained through discontinuation of TKI therapy in eligible patients may be reallocated to assist patients who are ineligible for TFR or in post–remission (consolidation) therapy.

Chronic myeloid leukemia is pioneering the concept of TFR as a treatment goal due to the ability of efficacious therapies to deeply suppress BCR-ABL expression in a manner that allows maintenance of response post–treatment cessation. Treatment-free remission is currently a unique goal for all forms of cancer, but hopefully the concept will be tested in other malignant diseases, as it represents an attractive mechanism to alleviate the burden on health systems and patients. Future studies to evaluate the impact of TFR as a treatment option are warranted, and economic evaluations of the impact of TFR could guide the understanding of where TFR may be the most impactful.

4.1 | Limitations

Although the model confirmed the cost-saving potential of TFR, there are limitations of the study to be considered. The model was developed using data from nilotinib trials such as ENEST1st,[28] ENESTcmr,[29] ENESTfreedom,[21] and ENESTop,[20] and a TKI monthly cost representative of the cost of nilotinib. As such, model results may not be generalizable to other TKI treatments. Patients who are ineligible for TFR (ie, patients who did not achieve a deep and sustained molecular response) were not considered in the model. Costs incurred by these patients were assumed to remain the same in both scenarios, therefore they were not added into the calculations. In addition, the model does not consider patients in the consolidation phase, nor costs associated with this phase of treatment. The cost of adverse event management resulting from treatment with TKIs was also not considered. Finally, the patient perspective analysis only considered a certain age and income category, however the co-payment cap may differ by age and income status.

Discontinuation of nilotinib therapy in TFR-eligible patients may provide significant cost savings to both payers and patients. Additional monitoring costs incurred upon discontinuation of nilotinib therapy contributed little to overall annual costs and declined over time, while notable cost savings were derived from drug costs during TFR. Total annual costs to the Japanese National Health Insurance were reduced by approximately 50% when all TFR-eligible patients discontinued nilotinib therapy. Cost savings persisted despite increased visits/monitoring frequency and the patients' reduced willingness to attempt TFR, demonstrating that these findings are likely to be robust and translatable to the real world.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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