Author's response to reviews

Title: Cost-effectiveness of adding rituximab to the existing treatments of splenectomy and romiplostim for steroid-resistant idiopathic thrombocytopenic purpura in adult.

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Author's response to reviews: see over
October 10, 2014

MS: 1971295331219730
Title: Cost effectiveness of adding rituximab to the existing treatments of splenectomy and romiplostim for steroid-resistant idiopathic thrombocytopenic purpura in adult.

Dear Prof Howard,

Thank you for your email and the valuable comments of the three reviewers.

Please find attached a revised version of our manuscript “Cost effectiveness of adding rituximab to the existing treatments of splenectomy and romiplostim for steroid-resistant idiopathic thrombocytopenic purpura in adult” and cropping figures, which we would like to resubmit for publication in BMC Health Services Research.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Health Services Research.

Thank you in advance for your kind consideration of this paper.

Sincerely yours,

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Our responses to the reviewers’ comments are as follows:

<Response to reviewer: Philippe Boierling>
We wish to express our appreciation to you for your insightful comments on our paper. The comments have helped us significantly improve the paper.

Comment 1: The reviewer don't propose major revisions but suggest that the discussion could be greatly shortened

Response: In accordance with the reviewer's request, we have shortened the manuscript in discussion.

Comment 2: It should be asserted in the title and along the text that the study/conclusions concern adults with ITP.

Response: In accordance with the reviewer’s comment, we have added “in adult” to the title and text. (Title, p4, line 50, p8, line 131, p9 line 138 and p22, line 388)

Comment 3: -p4: the description of the natural history of ITP concerns japanese. It could be of interest to describe the difference between natural history in american/European people (for exemple the place ohf helicobacter pylori infection is very different in this population). In the same way the percentage of patients that are able to discontinue steroids is, in european/american, more important than 10/20%

Response: H. pylori infection is found frequently in Asians, and H. pylori eradication leads to a remission in more than 50% of Japanese ITP patients, while the remission is reportedly achieved in a few percent of the patients in Europe and the United States [1]. In addition, steroids are terminated early in Europe and the United States, as the reviewer pointed out. In Japan, guidelines recommend to use a maintenance steroid dose of 10 mg or less to prevent recurrence, since adverse effects occur less commonly in Japanese patients than in patients in Europe and the United States [2].
I would like to note that the description in page 4 has been modified as follows to clarify that it concerns the situation in Japan. (p6, line 79)
“and most patients are required to continue taking corticosteroid.”

To

“and most patients are required to continue taking corticosteroid in Japan.”

References

Comment 4: the mortality rates of splenectomy seems higher than the reality. Splenectomy by laparoscopy necessitate 3/5 days of hospitalization.

Response: The mortality rates of splenectomy used in this study was calculated based on the report that the mortality in ITP patients with a platelet count of ≤30 × 10⁹/L was 4.2-times higher than that in the general healthy subjects [1] and an additional 0.02% mortality reported for laparoscopic splenectomy [2]. On the advice of ITP specialists and the current situation in Japan, the splenectomy is performed during a 7-day hospitalization.

References

Comment 5: The reviewer don't understand how the adverse events are included in
the model. Questions concerning the hematological long term effect (i.e. myelofibrosis) of TPO RA exist.

**Response:** In addition, we consider that bone marrow fibrosis is a serious event and its occurrence in humans is undeniable. However, it was not taken into account in this study, because the incidence rate is unknown due to the limited number of patients in clinical trials and no incidence was reported in a long-term study on romiplostim [1].

**References**

**Comment 6:** Half of the patients relapse after ritux at one/two years. I don't know if this notion is taken into account by the authors. Even if I'm not a specialist of the Markov model, it seems to me that this notion is important for the results. I don't understand the relapse rates of table1

**Response:** The relapse rate for rituximab was taken into account. The relapse rate for rituximab shown in Table1 is a rate of relapse occurring in 28 days. Since one cycle of the Markov model was assumed to be 28 days, the relapse rate in Table 1 was used as a rate of transition from a state of PL ≥30 × 10^9/L to a state of PL <30 × 10^9/L.

**Comment 7:** The first dose of ritux could be done in an outpatient

**Response:** In Japan, the first administration of rituximab is recommended to be performed for all the ITP patients hospitalized for safety. In addition, inpatient treatment is also covered by public health insurances. Therefore, we assumed that the initial dose of rituximab requires the patient to stay in hospital overnight.

**Comment 8:** The authors choose Romiplastin as TPO RA when Elthrombopag is cheaper (in Europe) and as effective
Response: We appreciate the reviewer’s comment on this point. We choose romiplostim, based on that eltrombopag was not recommended by NICE in the UK [1]. However, as you pointed out, eltrombopag is cheaper in Japan. Therefore, we changed from TPO-RA to romiplostim in the text, including the title. In addition, we have changed the following text from (p 21, line 369):

“Therefore, we conducted the sensitivity analyses for efficacy of TPO-RA. However, the results of the base case analysis were robust.”

To

“Therefore, we conducted the sensitivity analyses for efficacy and cost of romiplostim. However, the results of the base case analysis were robust.”

References
1. NICE technology appraisal guidance 205: Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura; 2010

Thank you again for your comments on our paper. I trust that the revised manuscript is suitable for publication.
<Response to reviewer: Helmut Ostermann>
We wish to express our appreciation to you for your insightful comments on our paper. The comments have helped us significantly improve the paper.

Minor essential Revisions

Comment 1: Abstract Conclusions: The addition of rituximab is innumbers more efficient however the difference is so small that I would suggest to change to "marginally more effective"

Response: In accordance with the Reviewer's comment, we have changed the following text from (p4, line 50)

“Adding the treatment option of rituximab (sequence 2, 3) is less costly and more effective than sequence1 for the treatment of ITP.”

to

“Adding the treatment option of rituximab (sequence 2, 3) is less costly and marginally more effective than sequence1 for the treatment of ITP.”

Comment 2: page 4 line 68: The authors should change their wording regarding long term steroids. Most patients are required to take steroids long term is not true, because most patients are switched to alternative treatments (splenectomy, TPO-RA)

Response: As the reviewer pointed out, steroids are terminated early in Europe and the United States. In Japan, guidelines recommend to use a maintenance steroid dose of 10 mg or less to prevent recurrence, since adverse effects occur less commonly in Japanese patients than in patients in Europe and the United States [1]. I would like to note that the description in page 4 has been modified as follows to clarify that it concerns the situation in Japan. (p6, line 79)

“and most patients are required to continue taking corticosteroid.”

To
“and most patients are required to continue taking corticosteroid in Japan.”

References

Comment 3: page 5 line 93: Authors should mention that there are relapses following rituximab treatment as well

Response: In accordance with the reviewer’s comment, we have changed the following text from (p7, line104):

“it was reported that the platelet count exceeded 50×10⁹/L in 62.5% of patients [7].”

to

“it was reported that the platelet count exceeded 50×10⁹/L in 62.5% of patients, while relapses are also reported [7].”

Comment 4: page 8 line 148: Authors should a that the dose will be titrated individually and that in some patients it is possible to use a much lower dose than the licensed dose.

Response: In accordance with the reviewer’s comment, we have changed the following text from (p10, line 157)

The dose is 4μg/kg, based on the results of long-term continuation tests in Japanese therefore, 240μg/ dose calculated for a 60kg patient.

To

The dose will be titrated individually and that in some patients it is possible to use a much lower dose than the licensed dose. The dose in this study is 4μg/kg, based on the
results of long-term continuation tests in Japanese therefore, 240μg/dose calculated for a 60kg patient.

Comment 5: page 9 line 155: What is the data source for pulmonary embolism?

Response: The data source is the examination report of romiplostim in Japan and the opinions of ITP specialists. The cost of pulmonary embolism was summed based on the DPC/PDPS (Diagnosis Procedure Combination / Per-Diem Payment System). Accordingly, we have added reference No.15 to line 169.

Comment 6: Page 11 and table 1: How were the emergency treatment rates calculated? Were they based on relapse rates?

Response: The 4-week relapse rate was calculated based on a report that the 1-week emergency treatment rate was 3.6% when PL was <30 × 10^9/L, and was 0.1% when PL was ≥30 × 10^9/L [1]. When a patient has relapsed, PL is <30 × 10^9/L, and the emergency treatment rate is thus higher than that before the relapse. Therefore, the relapse was also taken into account in calculations of emergency treatment rate.

References

Comment 7: Page 13 see comment No 4.

Response: We thank the reviewer for this comment. The remainder of the drug in the vial would be discarded, the expected dose was one vial per dose. As you pointed out, the dose will be titrated individually and that in some patients it is possible to use a much lower dose than the licensed dose. However, one vial per dose is the minimum dosage. Therefore, a sensitivity analysis was only conducted assuming that the romiplostim dose was two vials per dose.
Comment 8: page 17, line 308: Response rates of TPO-RA differed in the pivotal trials between patients before and after splenectomy

Response: The pivotal trials reported that the efficacy of romiplostim differs before and after splenectomy. However, the mechanism of a difference in the efficacy of TPO-RA before and after splenectomy is not clear and this difference may derive from the different duration of disease up to starting TPO-RA treatment, thus, in this study, the analysis was conducted assuming that the efficacy of TPO-RA before and after splenectomy is the same. It should be noted that TPO-RA was used after splenectomy in all the options in this study. In a future study involving an additional option where TPO-RA is used before splenectomy, we will pay attention to what the reviewer pointed out and conduct a sensitivity analysis assuming that the efficacy of romiplostim differs between patients receiving it before and after splenectomy.

Comment 9: page 17, line 318: The authors have to discuss that there are relapses following rituximab treatment as well

Response: In accordance with the reviewer’s comment, we have changed the following from (p19, line 329):

“The reduction in cost is largely related to the fact that patients are completely cured with rituximab and require no further treatment.”

To

“The reduction in cost is largely related to the fact that, although some patients relapsed, patients who achieved the complete cure and required no further treatment were by no means rare.”

Comment 10: The discussion section is rather long and lengthy explanations are used at times. It should be shortened and made more concise.
Response: In accordance with the reviewer’s request, we have shortened the manuscript in discussion.

Comment 11: The authors should include in the discussion section a notion to possible side effects of rituximab in this patient population like sepsis in this patient cohort, a part of which has experienced long term steroid immunosuppression

Response: Reported side effects of rituximab include fever and chills at the time of administration. Given its immunosuppressive effect, care should be taken to the possibility that patients on rituximab may develop various infectious diseases. In this study, we chose to include only sepsis in the model, as it is an infectious disease that is severe and seriously impacts the cost.

Discretionary Revisions
Comment 12: page 3 line 55 spleen and liver

Response: In accordance with the reviewer’s comment, we have changed the following text from (p5, line 61):

The pathology of the disorder involves destruction of autoantibody-presenting platelets by the spleen,

to

The pathology of the disorder involves destruction of autoantibody-presenting platelets by the spleen and liver,

Comment 13: page 3 line 57: exchange prolonged with persistent

Response: In accordance with the reviewer’s comment, we have changed the following text from (p5, line 64)

TP is classified on the basis of the length of time from the diagnosis, newly diagnosed
cases of within 3 months, **prolonged** cases of between 3 and 12 months, and chronic cases of longer than 12 months.

to

ITP is classified on the basis of the length of time from the diagnosis, newly diagnosed cases of within 3 months, **persistent** cases of between 3 and 12 months, and chronic cases of longer than 12 months.

**Comment 14:** page 5 line 86: There are reports of patients stopping TPO-RA and remaining in remission, please add

**Response:** In accordance with the reviewer’s comment, we have added the following to the Background (p6, line 97):

New text

"It has been recently reported that some patients do not relapse after discontinuation of TPO-RA. However, further investigation over a larger-scale, longer-term observational study is required, because this data is from a short-term observational study involving a small number of subjects."

**Comment 15:** page 5 line 94: The reference to the textbook should be replaced by citing a guideline.

**Response:** In accordance with the reviewer’s comment, we have changed the following text from (p7, line 105)

"Rituximab is described as a treatment for intractable ITP cases in Harrison's Principles of Internal Medicine, an internal medicine textbook referenced worldwide and it is acknowledged as a highly evidenced therapy."

to

"Rituximab is described as second-line treatment option for intractable ITP cases in the American guidelines [5]."
Comment 16: Page 15 line 276: what is "sates"?

Response: In accordance with the reviewer's comment, we have changed from “sates” to “states” (p17 line 288)

Comment 17: Page 20 line 375: eltrombopag

Response: In accordance with the reviewer's comment, we have changed from “eltronbopag” to “eltrombopag” (p21 line366)

Thank you again for your comments on our paper. I trust that the revised manuscript is suitable for publication
<Response to reviewer: Anneke Brand>
We wish to express our appreciation to you for your insightful comments on our paper. The comments have helped us significantly improve the paper.

Comment:
Mortality/morbidity from SP (despite platelet cts > 30), as shown in table 1 add to total 2 year costs of variants 1,2 and 3. If the authors include the variant of SP only this would make it easier to follow the costs in options 1-3.

Response: We strongly appreciate the reviewer’s comment on this point. It is extremely interesting. However, we did not consider treatment by splenectomy only in this study, since it is not performed in Japan.

Discretionary revisions:
Background
Comment 1: Q1 Page 5, line 89/90: 2 courses RI may be sufficient for a proportion of patients, however (line 93) although 60% of patients show a sufficient platelet increment, the median response duration is limited and after 5 years 20-25% have sufficient platelet cts.(ref 7)

Response: In accordance with the reviewer’s comment, we have changed the following text from (p7, line 104):

“it was reported that the platelet count exceeded 50×10⁹/L in 62.5% of patients [7].”

to

“it was reported that the platelet count exceeded 50×10⁹/L in 62.5% of patients, while relapses are also reported [7].”

Comment 2: Q2 Page 5. line 94: referral to Harrison: highly evidenced does not include dose or number of treatments of RI.
Response: In accordance with the reviewer’s comment, we have changed the following text from (p 7, line 105)

“Rituximab is described as a treatment for intractable ITP cases in Harrison's Principles of Internal Medicine, an internal medicine textbook referenced worldwide and it is acknowledged as a highly evidenced therapy.”

to

“Rituximab is described as second-line treatment option for intractable ITP cases in the American guidelines [5].”

Treatment option

Comment 3: Q3 Page 7, line 133: TOP-RA=TPO-RA

Response: In accordance with the other reviewer's comment, we have changed from “TOP-RA” to “romiplostim” (p9 line 145)

Comment 4: Q4 Page 8, line 140: before SP (and before RI if RI is applied before SP) vaccinations must be administered.

Response: We appreciate the reviewer's comment on this point. Pneumococcal vaccination before splenectomy is recommended also in Japan. For rituximab, the vaccination is not specifically recommended in Japan by academic societies, manufacturers or the government. In the present study, we did not include the vaccination in the cost, because it is a preventive medical care. We intend to deal with the vaccination cost in the next analysis. We would like to note that the costs for splenectomy and vaccination are $19,124 and about $80, respectively, and are unlikely to affect the results from this study.

Comment 5: Q5 Page 10, line 182: 4 weeks of treatment for PE is unclear, anticoagulant treatment is 3 – 6 months and has its own complications and need regular blood control.
Response While treatment with low-molecular-weight heparin or an anti-Xa inhibitor is the mainstream in Europe and the United States, hospital treatment with unfractionated heparin over about 2-4 weeks is the standard practice in Japan. Therefore, we assumed that a patient was hospitalized for 16 days for treatment according to Japanese DPC/PDPS (Diagnosis Procedure Combination / Per-Diem Payment System) and tested thereafter on an outpatient basis.

Model design
Comment 6: Q6 Page 10, line 188: always return to corticosteroids after failure of SP/RI/TPO-RA is not correct. Generally from the wide list of third line options (page 5, lines 81), drugs are tried. Also the assumption that in case of option 1,2,or 3 failure the platelet ct will be < 30 is not black and white, but acceptable in this model. Another minor weakness?.

Response: We appreciate the reviewer’s comment on this point.
In Japan, the third-line treatment options of the immunosuppressants azathioprine and cyclosporine, the anticancer agent vincristine and cyclophosphamide etc. have not been reimbursed for ITP. Therefore, we assumed that the patient would then be put on maintenance therapy with corticosteroids, if no effect is seen after the entire treatment consisting of splenectomy, romiplostim and rituximab, or if the patient relapses.

Discussion
Comment 7: Q7 Page 15, line 276: sates? I cannot find this in a dictionary.

Response: In accordance with the reviewer’s comment, we have changed from “sates” to “states” (p17 line 288)

Comment 8: Q8 Page 17, line 318: can be instead of are completely cured with rituximab.

Response: In accordance with the reviewer’s comment, we have changed the following from (p19, line 327):
“The reduction in cost is largely related to the fact that patients are completely cured with rituximab and require no further treatment.”

To

“The reduction in cost is largely related to the fact that, although some patients relapsed, patients who achieved the complete cure and required no further treatment were by no means rare.”

Minor essential remarks

Background

Comment 9: Q9 Page 4, line 62: it should be noted that although mortality in patients with platelet cts < 30 while on third line treatment is 4.2 fold higher than in healthy individuals (ref 2), in this reference 50% was the result of immunosuppressive treatment and not because of thrombocytopenia (bleeding). Moreover these data were obtained prior to availability of RI and TPO-RA, using third line drugs not widely used anymore.

Response: We appreciate the reviewer’s comment on this point. In accordance with the reviewer’s comment, we have added the following to the Background (p5, line 68):

New text
However, opportunities to choose immunosuppressive agents has been reduced currently as rituximab and TPO-RA have become available, and it is possible that the risk of death, even if the PL is <30 × 10⁹/L, is no longer 4.2 times as high as that of a healthy individual.

Methods

Comment 10: Q10 Page 7, line 120: Give a motivation why the cost-effectiveness analysis was set at 2 years and not at for instance 1 and 5 years? Although in the discussion it is mentioned that TPO-RA is licensed in Japan since 2011, most other input is from North-West European origin.

Response: Similarly to this study, the cost-effectiveness by the treatment order was analyzed in the application data to NICE of eltrombopag and the analysis period therein
was two years. In this study, we set the two-year period in reference to this previous study. This previous study showed that the treatment in the order of rituximab→eltrombopag→romiplostim→IVIG was cost-effective [1]. It should be noted that, while the analysis period in previous cost-effectiveness analysis of romiplostim was a lifetime, we did not use this, because safety concerns, such as development of bone marrow fibrosis, remains about long-term use of TPO-RA. In accordance with the reviewer's comment, we have changed the following text from (p21, line 357)

“In this study, long-term use was not investigated due to a short time since TPO-RA was approved and its insufficient evidence. However, many groups are collecting data on long-term use of TPO-RA and it is possible to use these data to conduct a simulation in the future.”

to

“Similarly to this study, the cost-effectiveness by the treatment order was analyzed in the application data to NICE of TPO-RA agents eltrombopag and the analysis period therein was two years. In this study, we set the two-year period in reference to this previous study. It should be noted that, while the analysis period in previous cost-effectiveness analysis of romiplostim was a lifetime, we did not use this, because safety concerns, such as development of bone marrow fibrosis, remains about long-term use of TPO-RA.”

References

Treatment option
Comment 11: Q11 Page 9, line 153-155: the life-long risk of sepsis after SP is estimated up to 10% and up to 5% of patients on TPO-RA suffer a thrombotic event and 15% need control because of liver function test disturbances. Activation of HBV can be expected with RI. How these percentages are used in the 2 year observation period should be clarified.
Response: In this study, pulmonary embolism and sepsis were used for analysis as representative thrombotic and infection events, respectively. These were chosen since we thought that they would have impacts on the cost-effectiveness analysis because of their high incidence rates and high treatment costs. The incidence rates are shown in Table 1. The incidence rates of these adverse events were used as the rate of transition from one state (PL $< 30 \times 10^9/L$) to another state (PL $\geq 30 \times 10^9/L$) of the Markov model.

"Liver function test disturbances" and "activation of HBV", which the Reviewer pointed out, were not taken into account in this study. Although reactivation of hepatitis B by rituximab was an issue initially, relevant guidelines have been already developed internationally, and prior tests and, if necessary, prophylactic use of therapeutic drugs for hepatitis has been practiced in Japan. As a result, virtually no incidence of hepatitis reactivation is found in Japan, and therefore, it was not included as an adverse event in this study.

In accordance with the reviewer’s comment, we have added references numbers to the following text. (p10, line168)

Assuming sepsis as the adverse event that would occur during the splenectomy and rituximab treatment period as well as post-treatment, the patient would be hospitalized for treatment [7][19]. As for the romiplostim treatment period, pulmonary embolism was assumed as the adverse event and the patient would be hospitalized for treatment [15].

Model design

Comment 12: Q12 Page 10, lines 172-188. See also remark for page 9 above. The estimated incidence of the distinct AEs in the various treatment arms during the 2 year study period (that determine costs of arms 1-3) cannot be found in text or table 1.

Response: We strongly appreciate the reviewer’s comment on this point. We assumed that the adverse event during the perioperative period of splenectomy and the rituximab administration or after these treatments was sepsis (p11, line188). We assumed that pulmonary embolism was the adverse event during TPO-RA treatment (p12, line193). The adverse event incidence during the 1 cycle (28 days) obtained from literature are shown in Table 1. Using these AE incidence rates as rates of transition from each state of the Markov model to a state of "treatment for AE", we calculated how many people developed adverse events in 2 years in a 10,000 population. The derived numbers of
people are "manifesting AE" in Table 3.

In accordance with the reviewer’s comment, we have added the following text to legend of Table 3:
New text:
§ Using these AE incidence rates as rates of transition from each state of the Markov model to a state of "treatment for AE", we calculated how many people developed adverse events in 2 years in a 10,000 population.

Model inputs
Comment 13: Q13 Page 11, line 209: physicians honoraria and out of hospital costs (missing working days of the patient, home care) are not included, please mention this explicitly.

Response: We did not consider indirect costs, since we focused on the public medical costs and analysis was conducted from the healthcare payer’s perspective in this study. Moreover, we consider that ITP involves no major work loss other than physical activity restrictions and time restrictions due to hospital visits, except for some types of work.

Discussion
Comment 14: Q14 Page 17, line 320: I cannot find the reference of Boland [9]

Response: In accordance with the reviewer's comment, we have changed from Boland to G Mowatt. (p19, line 331)

Comment 15: Q15 Page 18, line 324-9: difference in option 2 and 3 are largely due to AE and emergencies, which are based on the “weaker” assumptions in the model. Can more clearly be explained why emergency incidences/treatment costs are estimated higher in option 3 as compared to option 2.

Response: We agree that this sentence is not clear. We have not determined which of sequence2 and sequence3 is cost-effective. Therefore, for clarity, we have changed the following from (p19, line 335):
“However, the numbers of deaths and adverse events of sequence 2 were less than the numbers of sequence 3. It is clear in this study that splenectomy-TPO-RA-rituximab (sequence 2) and splenectomy-rituximab-TPO-RA (sequence 3) are cost-effective compared to splenectomy-TPO-RA (sequence 1). However, further investigation over the long term and using quality-adjusted life year (QALY) is needed to determine which of sequence 2 and sequence 3 is cost-effective.”

To

“However, the numbers of deaths and adverse events of sequence 2 were less than the numbers of sequence 3. It is clear in this study that splenectomy-TPO-RA-rituximab (sequence 2) and splenectomy-rituximab-TPO-RA (sequence 3) are cost-effective compared to splenectomy-TPO-RA (sequence 1). Therefore, further investigation over the long term and using quality-adjusted life year (QALY) is needed to determine which of sequence 2 and sequence 3 is cost-effective.”

Comment 16: Q16 Table 1: mention in the legends what is indicated between [], apparently these are the references

Response: In accordance with the reviewer’s comment, we have changed the following from (Table 1)
Table 1 Probability parameters

<table>
<thead>
<tr>
<th>Events</th>
<th>Splenectomy</th>
<th>TPO-RA</th>
<th>Rituximab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy rates</td>
<td>76.1% [14]</td>
<td>84.1% [15]</td>
<td>71.6% [16][17]</td>
<td>—</td>
</tr>
<tr>
<td>Relapse rates</td>
<td>0.45% [3]</td>
<td>0%*</td>
<td>0.88% [18]</td>
<td>—</td>
</tr>
<tr>
<td>Adverse event rates</td>
<td>0.44% [19]</td>
<td>0.58% [15]</td>
<td>0.24% [7]</td>
<td>11% [20]</td>
</tr>
<tr>
<td>Emergency treatment rate (PL≥ 30 x 10^9/L)</td>
<td>0.4% [21]</td>
<td>0.4% [21]</td>
<td>0.4% [21]</td>
<td>—</td>
</tr>
</tbody>
</table>

*If TPO-RA treatment is effective, the patient wouldn’t relapse.
**The mortality rate of 0.02% was added when splenectomy was conducted.

to
Comment 17: Q17 Table 2: give for sepsis, PE and IVIG in table legend that these are the costs of the event, (not corrected for the number of events expected in 28 days).

Response: We thank the reviewer for this comment. Because one event was assumed to complete in 28 days in this study, the costs in Table 2 denote the treatment costs for a 28-day period. This is shown in Model design session (p11-12, line 177-198).

Comment 18: Q18 Table 3: how is the period of platelet cts > 30 calculated? Or mention this in method section and refer.

Response: In accordance with the reviewer’s comment, we have added the following to the Table3 legend:

New text
* The period was calculated as $N_S \cdot P/N_T$, wherein $N_S$, $P$, and $N_T$ denote, respectively, the
average number of people in the PL ≥30 × 10⁹/L states in the simulated population, the
time period of simulation (2 years), and the total number of people simulated (10,000).

Comment 19: Q19 Fig 1 Splenectomy is included as cost factor in all three scenario's,
why not show the costs of SP alone (not needing third line treatment, but leading to
death and costs from AEs; this would enhance the message for non-Japanese countries
who tend to replace SP as second line treatment for RI and TPO-RA prior to SP.

Response: We strongly appreciate the reviewer's comment on this point. We have
started examining additional options in which RI and TPO-RA are used prior to SP (e.g.
TPO-RI-SP, RI-TPO-SP), and are going to report the results next time.

Comment 20: Q20 Fig 2 is not very helpful and can be better explained in text.

Response: In accordance with the reviewer's comment, we have added the following to
Fig.2 legend.

New text:
The model is composed of six states. A cycle is a 28-day period. The cycle starts from
the ITP treatment state (PL <30 × 10⁹/L) and moves on to the next states after 28 days.
However, if PL is still <30 × 10⁹/L after the treatment, the cycle remains at the ITP
treatment state. The broken line shows the flow of patients treated with splenectomy
and rituximab, i.e., those other than romiplostim.

Thank you again for your comments on our paper. I trust that the revised manuscript is
suitable for publication