Risk of infections in renal cell carcinoma (RCC) and non-RCC patients treated with mammalian target of rapamycin inhibitors

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation

Published Version
doi:10.1038/bjc.2013.278

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:12406778

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Risk of infections in renal cell carcinoma (RCC) and non-RCC patients treated with mammalian target of rapamycin inhibitors

M D Kaymakcalan1, Y Je2, G Sonpavde3, M Galsky4, P L Nguyen1,5, D Y C Heng6, C J Richards7 and T K Choueiri*,8

1Department of Pharmacy, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA; 2Department of Food and Nutrition, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 130-701, Korea; 3Department of Medical Oncology, University of Alabama at Birmingham (UAB) Comprehensive Cancer Center, 1824 4th St S, Birmingham, AL 35205, USA; 4Mount Sinai School of Medicine, Tisch Cancer Institute, 1190 5th Avenue, New York, NY 10029, USA; 5Department of Radiation Oncology, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA; 6Department of Medical Oncology, Tom Baker Cancer Center and University of Alberta, 1331 29 St NW, Calgary, AB T2N 4N2, Canada; 7Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA and 8Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, 450 Brookline Ave, Boston, MA 02215, USA

Background: Mammalian target of rapamycin (mTOR) inhibitors are used in a variety of malignancies. Infections have been reported with these drugs. We performed an up-to-date meta-analysis to further characterise the risk of infections in cancer patients treated with these agents.

Methods: Pubmed and oncology conferences’ proceedings were searched for studies from January 1966 to June 2012. Studies were limited to phase II and III randomised controlled trials (RCTs) of everolimus or temsirolimus reporting on cancer patients with adequate safety profiles. Summary incidences, relative risks (RRs), and 95% confidence intervals (CIs) were calculated.

Results: A total of 3180 patients were included. The incidence of all-grade and high-grade infections due to mTOR inhibitors was 33.1% (95% CI, 24.5–43.0%) and 5.6% (95% CI, 3.8–8.3%), respectively. Compared with controls, the RR of all-grade and high-grade infections due to mTOR inhibitors was 2.00 (95% CI, 1.76–2.28, \( P < 0.001 \)) and 2.60 (95% CI, 1.54–4.41, \( P < 0.001 \)), respectively. Subgroup analysis found no difference in incidences or risks between everolimus and temsirolimus or between different tumour types (renal cell carcinoma (RCC) vs non-RCC). Infections included respiratory tract (61.7%), genitourinary (29.4%), skin/soft tissue (4.2%), and others (4.9%).

Conclusion: Treatment with mTOR inhibitors is associated with a significant increase in risk of infections. Close monitoring for any signs of infections is warranted.

Mammalian target of rapamycin (mTOR) inhibitors are targeted agents that have developed into an important therapeutic drug class used in a variety of malignancies. Everolimus (Afinitor, Novartis Pharmaceuticals, East Hanover, NJ, USA) is currently approved by the Food and Drug Administration (FDA) for the treatment of several malignancies including advanced renal cell carcinoma (RCC; Motzer et al, 2008, 2010), progressive pancreatic neuroendocrine tumours (PNET; Yao et al, 2011), subependymal...
Mammalian target of rapamycin inhibitors do not usually produce the systemic toxicities that are traditionally seen with chemotherapy such as nausea, vomiting, alopecia, and bone marrow suppression. However, as more targeted agents are developed their different class-specific toxicities are emerging. Trials exploring the safety and efficacy of everolimus and temsirolimus reported some unique side effects including rash, mucositis, infection, pneumonitis, hyperlipidaemia, and hyperglycaemia (Hutson, 2002; Abraham and Gibbons, 2007). This process ultimately leads to the downregulation of hypoxia inducible factor genes, including vascular endothelial growth factor, necessary for cancer cell growth, survival, and angiogenesis (Thomas et al, 2006).

The association of infection with mTOR inhibitors and its possible clinical significance warrants further characterisation. We sought out to assess the magnitude of this problem by looking at the incidence and risk of infections in patients receiving mTOR inhibitors in a large, up-to-date meta-analysis of randomised control trials.

### MATERIALS AND METHODS

#### Study selection.
An independent review of the Pubmed databases from January 1966 to June 2012 was conducted. Searches were performed, limited to only human studies, with either the key terms ‘everolimus,’ ‘Afinitor,’ ‘RAD-001’ or ‘temsirolimus,’ ‘Torisel,’ ‘CCI-779.’ Citations investigating mTOR inhibitors in a non-oncological setting were excluded. Potentially relevant abstracts were collected and independently coded by four investigators (MDK, GS, CJR, and TKC). The full texts of the selected abstracts were obtained and analysed for appropriate trial design and safety reporting. Only randomised phase II or III studies with a placebo/control arm were used in order to properly calculate relative risk (RR). The Jadad scale was used to assess study quality based on study randomisation, double-blinding practice, and handling of withdrawals (Jadad et al, 1996). When more than one publication was drawn from the same clinical trial, the most recent or most complete report was used. The most recent package insert for each agent was assessed for the most current clinical information, and the manufacturer and/or the overall investigator was contacted to obtain clarification on infection information. The process was duplicated using the same search terms and limitations in the American Society of Clinical Oncology online databases of meeting abstracts from 2000 to 2012.

#### Data extraction.
Data extraction was conducted according to the Preferred Reporting Items for Systemic Reviews of Meta-Analyses statement (Moher et al, 2009). Any discrepancies between reviewers’ classifications of publications were resolved by consensus. The following information was extracted from each study: first author’s name, year of publication, trial phase, underlying malignancy, number of enrolled patients, treatment arms, median age and range, median treatment duration and range, median overall survival and 95% confidence interval (CI), number of patients available for analysis, number of all-grade infections attributed to study drug, and number of high-grade infections attributed to study drug. All-grade and high-grade infections were defined according to the National Cancer Institute Common Toxicity Criteria version 3.0 in all trials used for the analysis.

#### Statistical analysis.
We extracted the number of patients with all-grade and high-grade infections and the number of patients who were treated with mTOR inhibitors or control from the selected clinical trials to calculate incidence. The proportion of patients with all-grade infections and 95% CIs were derived from each trial. RRs and 95% CIs were also calculated by comparing the incidence of all-grade infection in patients assigned to mTOR inhibitors with the incidence among controls in the same trial. For studies reporting zero events in a treatment or control arm, we applied a classic half-integer continuity correction to calculate the RR and variance. We then repeated this for high-grade infections.

Statistical heterogeneity among trials included in the meta-analysis was evaluated using Cochrane’s Q statistic (Cochran, 1954), and inconsistency was quantified with the I² statistic that estimates the percentage of total variation across studies due to heterogeneity rather than chance (Higgins et al, 2003). The assumption of homogeneity was considered invalid for P-values <0.1. To calculate the summary incidence or RRs of all-grade or high-grade infections, we combined trial-specific estimates using random-effects or fixed-effects models depending on the heterogeneity of included trials. When no substantial heterogeneity among trials was found, the summary estimate calculated on the basis of the fixed-effects model was reported by using the inverse variance method. When substantial heterogeneity among trials was observed, the summary estimate calculated on the basis of the random-effects model was reported by using the DerSimonian and Laird (1986) method that considers both within-study and between-study variations. For trials with multiple treatment groups examining varying doses of mTOR inhibitors, we combined the treatment groups for the overall analysis.

To explore the possible reasons for the heterogeneity, we conducted meta-regression analyses to see whether there was a variation in risk estimates by type of drug, underlying malignancy, type of trial, and Jadad score. In addition, we conducted sensitivity analyses by omitting one study at a time to see the influence of each trial on the overall effect estimate. Finally, publication bias was evaluated through funnel plots (that is, plots of study results against precision) and with the Begg’s and Egger’s test (Begg and Mazumdar, 1994; Egger et al, 1997). A two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata SE version 12.0 software (Stata Corporation, College Station, TX, USA).
The most common were respiratory tract infections, representing studies that reported on the underlying type of infection (infection was not otherwise specified in the studies). Of the six, the rates of both all-grade and high-grade infections, with the overall RR of developing an all-grade infection for mTOR inhibitors vs control was 2.00 (95% CI, 1.76–2.28, P < 0.001). No significant heterogeneity was found among the trials (Q = 5.02, I² = 0.0%, P = 0.658; Figure 2). By drug type, everolimus-treated patients (5 trials, 1,312 patients) had an increased risk of all-grade infection, with a RR of 2.14 (95% CI, 1.81–2.53, P < 0.001), and temsirolimus-treated patients (3 trials, 612 patients) had an increased risk of all-grade infection, with a RR of 1.05 (95% CI, 0.87–1.28, P < 0.001). Comparing the RRs of everolimus with temsirolimus demonstrated no significant difference (P = 0.26; Table 2).

When considering only high-grade infection events, the overall RR for mTOR inhibitors vs control was 2.60 (95% CI, 1.54–4.41, P < 0.001). No significant heterogeneity was found among the studies reporting high-grade infections (Q = 7.41, I² = 19.1%, P = 0.284) (Figure 2). By drug type, everolimus-treated patients (5 trials, 1,312 patients) had an increased risk of high-grade infection, with a RR of 3.63 (95% CI, 1.66–7.94, P = 0.001). Temsirolimus-treated patients (2 trials, 524 patients) tended to have an increased risk of a high-grade infection, but the RR for temsirolimus vs control (RR = 1.97; 95% CI, 0.97–4.03, P = 0.062) did not reach a level of statistical significance because of smaller numbers. No significant differences were observed when comparing the RRs of high-grade infection between everolimus and temsirolimus (P = 0.35; Table 2).

To determine whether the observed increases in RRs of all-grade and high-grade infections were influenced by tumour type, we performed a subgroup analysis of RCC, the most commonly occurring malignancy (3 studies and 1,197 total patients or 37.6% of all patients), vs all other malignancies. The RR of all-grade infection in patients treated with RCC was 1.84 (95% CI, 1.53–2.21; P < 0.001), whereas the RR of all-grade infection in patients with other malignancies (five trials) was 2.18 (95% CI, 1.82–2.60; P < 0.001). No significant difference was observed in RRs of all-grade infection between the patients with RCC or non-RCC (P = 0.25). Similarly, the RR of high-grade infection in patients with RCC treated with mTOR inhibitors (two trials) was 2.76 (95% CI, 1.31–5.81; P = 0.007). For non-RCC patients (five trials), the RR of all-grade infection was 2.46 (95% CI, 1.16–5.19; P = 0.018). No difference was found when comparing the RRs of high-grade infection in patients having RCC with other malignancies (P = 0.63; Table 2).

Study quality. Randomised treatment allocation sequences were generated in all trials used in the analysis. All five everolimus trials were double-blinded, placebo-controlled, and of highest quality achieving the highest Jadad score of 5. All three temsirolimus trials were not double-blinded nor placebo-controlled, but they did all have active treatment controls. All studies were of good methodological quality according to the 5-point Jadad score (all trials ≥3). To further assess study quality, we also compared the RRs of all-grade and high-grade infection among phase II vs phase III trials. There were no statistically significant differences between the RRs of all-grade and high-grade infection among phase II vs phase III trials. There were no statistically significant differences between the RRs of all-grade and high-grade infection among phase II vs phase III trials. There were no statistically significant differences between the...
Table 1. Baseline characteristics of the included trials in the meta-analysis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Phase</th>
<th>Histology</th>
<th>Patients enrolled</th>
<th>Treatment arms/ dose</th>
<th>Median age (years) (range)</th>
<th>Median treatment duration (months) (Range)</th>
<th>Median OS (months) (range)</th>
<th>Median PFS (months) (range)</th>
<th>Patients for safety analysis</th>
<th>All grade</th>
<th>High grade</th>
<th>Reported all-grade infections</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselga et al, 2012</td>
<td>3</td>
<td>HR (+) BC</td>
<td>724</td>
<td>Everolimus 10 mg QD</td>
<td>62 (34-93)</td>
<td>6.0</td>
<td>Not reached</td>
<td>Not reached</td>
<td>11</td>
<td>482</td>
<td>241</td>
<td>24</td>
<td>Resp, GU, sepsis, candida, hepatitis C</td>
</tr>
<tr>
<td>Baselga et al, 2009</td>
<td>2</td>
<td>HR (+) BC</td>
<td>270</td>
<td>Everolimus 10 mg QD</td>
<td>69 (46-88)</td>
<td>Not Reported</td>
<td>N/A</td>
<td>N/A</td>
<td>137</td>
<td>3</td>
<td>1</td>
<td>Resp, skin/soft tissue</td>
<td>5</td>
</tr>
<tr>
<td>Motzer et al, 2010</td>
<td>3</td>
<td>RCC</td>
<td>416</td>
<td>Everolimus 10 mg QD</td>
<td>61 (27-85)</td>
<td>4.7 (0.63-15)</td>
<td>14.8</td>
<td>4.9 (4.0-5.5)</td>
<td>274</td>
<td>101</td>
<td>27</td>
<td>Resp, GU, sepsis, candida aspergillosis</td>
<td>5</td>
</tr>
<tr>
<td>Pavel et al, 2011</td>
<td>3</td>
<td>NET</td>
<td>429</td>
<td>Everolimus 10 mg QD</td>
<td>60 (29-79)</td>
<td>2 (0.7-6.5)</td>
<td>14.4</td>
<td>1.9 (1.8-1.9)</td>
<td>137</td>
<td>24</td>
<td>11</td>
<td>NOS</td>
<td>5</td>
</tr>
<tr>
<td>Yao et al, 2011</td>
<td>3</td>
<td>PNET</td>
<td>410</td>
<td>Everolimus 10 mg QD</td>
<td>58 (23-87)</td>
<td>9.2</td>
<td>Not reached</td>
<td>Not reached</td>
<td>13.7 (11.2-18.8)</td>
<td>204</td>
<td>83</td>
<td>0</td>
<td>Resp, GU</td>
</tr>
<tr>
<td>Hess et al, 2009</td>
<td>3</td>
<td>MCL</td>
<td>162</td>
<td>Temsirolimus 175 mg QW followed by 75 mg QW</td>
<td>68 (44-87)</td>
<td>3 (0.25-24.4)</td>
<td>12.8 (8.6-19.3)</td>
<td>4.8 (3.1-8.1)</td>
<td>54</td>
<td>15</td>
<td>4</td>
<td>NOS</td>
<td>3</td>
</tr>
<tr>
<td>Hudes et al, 2007</td>
<td>3</td>
<td>RCC</td>
<td>626</td>
<td>Temsirolimus 25 mg QW INF-α 3 million IU TIW</td>
<td>58 (32-81)</td>
<td>3.8 (3.5-3.9)</td>
<td>10.9 (8.6-12.7)</td>
<td>5.5 (3.9-7.0)</td>
<td>208</td>
<td>118</td>
<td>9</td>
<td>Resp, GU</td>
<td>3</td>
</tr>
<tr>
<td>Negrier et al, 2011</td>
<td>2</td>
<td>RCC</td>
<td>171</td>
<td>Temsirolimus 25 mg QW Sunitinib 50 mg Q6W days 1–28 INF-α 9 million IU TIW</td>
<td>62 (33-83)</td>
<td>5.1 (0.5-12)</td>
<td>Not reached</td>
<td>8.2 (7.0-9.6)</td>
<td>88</td>
<td>51</td>
<td>N/A</td>
<td>Resp, GU, skin/soft tissue, GI, sepsis, fungal, Candida, herpes, parastic</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: GI = gastrointestinal; GU = genitourinary; HR (+) BC = hormone receptor-positive breast cancer; INF-α = interferon alpha; MCL = mantle cell lymphoma; mIU = million international units; NET = neuroendocrine tumour; No. = number; NOS = not otherwise specified; OS = overall survival; PFS = progression-free survival; PNET = pancreatic neuroendocrine tumour; QD = once a day; QW = once a week; Q28D = once a month; Q2W = twice weekly; Q6W = every 6 weeks; RCC = renal cell carcinoma; Resp = respiratory; TIW = three times a week.
the phase subgroups for either grade (all-grade \( P = 0.33 \); high-grade \( P = 0.57 \)). To assess the influence of each study on the overall RRs of all-grade and high-grade infection, we performed a sensitivity analysis by omitting one study at a time and found that there were no studies that had a significant impact on the overall RR.

Finally, we attempted to assess the possible association between risk of infection and increased exposure to mTOR inhibitors. In convention with other studies, we calculated the mean of the median durations of therapy as a cut-off, which was found to be 5.8 months. When comparing the RRs of all-grade and high-grade infections due to mTOR inhibitors amongst long-coursed trials

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of events/total no. of patients</th>
<th>mTOR inhibitor</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselga et al, 2012</td>
<td>241/482</td>
<td>59/238</td>
<td>2.02 (1.59–2.56)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Baselga et al, 2009</td>
<td>3/137</td>
<td>1/132</td>
<td>1.45 (0.25–8.51)</td>
<td>0.684</td>
<td></td>
</tr>
<tr>
<td>Yao et al, 2011</td>
<td>83/204</td>
<td>38/203</td>
<td>2.17 (1.56–3.03)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Pavel et al, 2011</td>
<td>42/215</td>
<td>13/211</td>
<td>3.17 (1.75–5.73)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Motzer et al, 2010</td>
<td>101/274</td>
<td>24/137</td>
<td>2.10 (1.42–3.12)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Hudes et al, 2007</td>
<td>188/416</td>
<td>50/200</td>
<td>1.81 (1.39–2.35)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Hess et al, 2009</td>
<td>26/108</td>
<td>4/53</td>
<td>3.19 (1.17–8.67)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Negrier et al, 2011</td>
<td>51/88</td>
<td>28/82</td>
<td>1.70 (1.20–2.41)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Overall (Fixed-effects model) | 735/1924 | 218/1256 | 2.00 (1.76–2.28) | \(<0.001\) |

Test for heterogeneity: \(Q=5.02, P=0.658, I^2=0.0\%\)

Relative risks of high-grade infections:

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of events/total no. of patients</th>
<th>mTOR inhibitor</th>
<th>Control</th>
<th>Relative risk (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselga et al, 2012</td>
<td>4/238</td>
<td>1/132</td>
<td>0.97 (0.06–15.25)</td>
<td>0.979</td>
<td></td>
</tr>
<tr>
<td>Baselga et al, 2009</td>
<td>1/137</td>
<td>1/132</td>
<td>0.33 (0.01–8.09)</td>
<td>0.498</td>
<td></td>
</tr>
<tr>
<td>Yao et al, 2011</td>
<td>1/203</td>
<td>0/204</td>
<td>10.80 (1.41–82.88)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Pavel et al, 2011</td>
<td>1/211</td>
<td>11/215</td>
<td>1.35 (1.85–98.30)</td>
<td>0.628</td>
<td></td>
</tr>
<tr>
<td>Hudes et al, 2007</td>
<td>31/416</td>
<td>7/200</td>
<td>2.13 (0.95–4.75)</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>Hess et al, 2009</td>
<td>6/108</td>
<td>2/53</td>
<td>1.47 (0.31–7.05)</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

Overall (Fixed-effects model) | 100/1836 | 17/1174 | 2.60 (1.54–4.41) | \(<0.001\) |

Test for heterogeneity: \(Q=7.41, P=0.284, I^2=19.1\%\)
and short-coursed trials, we did not observe a statistically significant difference (all-grade $P = 0.33$; high-grade $P = 0.80$).

**Publication bias.** The Begg’s test and the Egger’s test were conducted on the incidence and RR of all-grade infection, and both showed no evidence of publication bias (for RR of all-grade infection, Begg’s $P = 0.54$ and Egger’s $P = 0.31$). Similarly, the Begg’s and Egger’s tests were performed on the incidence and RR of high-grade infection, and no evidence of publication bias was found (for RR of high-grade infection, Begg’s $P = 0.55$ and Egger’s $P = 0.97$).

**DISCUSSION**

Our meta-analysis combined eight RCTs investigating mTOR inhibitors for the treatment of cancers. To our knowledge, this is the first large study of RCTs demonstrating a significant increase in the risk of infection with the use of mTOR inhibitors in cancer patients. Our analysis found that the risk of developing an infection of any grade was two-fold higher in patients treated with mTOR inhibitors. And, more importantly, there is a 2.6-fold increase in the risk of high-grade infection associated with the use of mTOR inhibitors. The observed infection risk can possibly be explained by the potential immunosuppressant effects of mTOR inhibitors. Everolimus and sirolimus, the principal active metabolite of temsirolimus, are known to inhibit interleukin (IL)-2-, IL-7-, and IL-15-driven proliferation of activated T cells and B cells (Lai and Tan, 1994; Schuler et al, 1997; Shegal, 2003; Chapman and Perry, 2004).

Although there were no statistically significant differences between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there was a heavier contribution from everolimus to the RR between temsirolimus and everolimus when comparing their RRs, there...
progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. Oncologist 16: 632–640.


This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License.