Outcome of initial lenvatinib treatment in patients with unresectable anaplastic thyroid cancer

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Research Article

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Abstract

**Background:** Anaplastic thyroid cancer (ATC) is a very rare disease with a remarkably poor prognosis and with no established effective drug therapy. This study aimed to report the outcomes of lenvatinib single-agent therapy as an initial drug treatment in ATC and investigate its safety and efficacy.

**Methods:** This retrospective cohort study included 56 patients with ATC with unresectable primary tumors of whom 36 were treated with lenvatinib and 12 with weekly paclitaxel (PTX), and 8 patients who refused any drug treatment received palliative care.

**Results:** The average survival in the lenvatinib group is 5.8 months, which is significantly longer than 2.0 months in the PTX group ($P = 0.005$). The efficacy of lenvatinib in 36 patients with ATC, whose primary tumors were unresectable, was evaluated. The response rate was 33%, and the median overall survival was 5.0 months. A safety review indicated that lenvatinib should be used under the careful observation of local findings. Two patients, who showed a reduction with lenvatinib, underwent conversion surgery, which prolonged the prognosis in terms of avoiding events, such as asphyxia, fistula, and hemorrhage due to tumor growth; however, the surgical margins were positive, indicating that complete remission was impossible even if surgical resection was performed.

**Conclusions:** Therefore, starting with lenvatinib treatment and finding a therapeutic drug based on the genomic analysis is an acceptable treatment strategy for ATC while halting the disease progression.

**Background**

Anaplastic thyroid cancer (ATC) is a very rare disease with a remarkably poor prognosis. The Surveillance, Epidemiology, and End Results database reported a frequency of 0.92 per million patients. The median survival was 3.16 months [1]. As an orphan disease, and due to the exceptionally high grade of malignancy, effective drug therapy has not been established for ATC [2]. The American Thyroid Association guidelines recommend that genomic analysis should be performed first after diagnosis and a therapeutic drug should be the first choice of treatment if available. Additionally, antiangiogenic drugs have the risk of bleeding in this patient population where disease often invades the trachea, esophagus, and great vessels. Patients undergoing potent antiangiogenic drug treatment should be warned about these potential risks [3]. In Japan, lenvatinib is the only treatment approved by the health insurance system, and we have reported its efficacy [4, 5]. Previous reports revealed lenvatinib treatment results, including patients previously treated with other agents [6, 7]. Another report revealed results with lenvatinib in combination with other drugs [8]. Another report revealed the results of lenvatinib treatment with the primary tumor resected and the metastases targeted [9]. Genomic analysis is time-consuming, ATC disease progression is rapid, and death may occur while waiting for the genomic analysis report. Thus, this study aimed to report lenvatinib outcomes as an initial and single-agent treatment in unresectable ATC of the primary tumor and examine its safety and efficacy. Additionally, we reviewed the pathological findings in two cases in which conversion surgery was feasible after response to lenvatinib.
treatment and tumor shrinkage. Moreover, genomic analysis results indicated the extent to which a therapeutic drug for ATC might be found.

**Methods**

**Patients**

The study was approved by our Institutional Review Board (IRB), and each patient signed a comprehensive consent form and a treatment consent form. This single-institution, retrospective cohort study evaluated 81 patients who were diagnosed with ATC and treated in the Kanagawa Cancer Center, Japan from April 1, 2011 to July 31, 2022. Eligible patients were aged > 20 years, had at least one measurable target lesion, and had pathologically confirmed ATC. The pathological review was performed by three pathologists with experience in thyroid pathology. This study protocol was reviewed and approved by our IRB (#2019-34). Of the 81 cases of anaplastic carcinoma in our department, 4 with possible radical surgery upon initial diagnosis, 12 with metastases that turned into anaplastic carcinoma, and 9 with anaplastic transformation during lenvatinib treatment in differentiated thyroid cancer (DTC) were excluded from the study. Hence, this study included 56 patients with ATC with unresectable primary thyroid tumors, including 36 patients treated with lenvatinib and 12 with weekly paclitaxel (PTX), and 8 patients, who refused drug treatment, were treated with best supportive care (BSC). All patients were histopathologically diagnosed as ATC by biopsy or surgery. This study is a retrospective cohort study

**Drug treatment**

Lenvatinib was started at 24 mg and PTX at 80 mg/m\(^2\) weekly [10]. The starting dose of lenvatinib was reduced for patients with diabetes and/or hypertension, > 80 years, weighed < 40 kg, with chronic kidney disease, or were poorly controlled. Additionally, doses were reduced or withdrawn during treatment depending on the patient’s condition. The actual lenvatinib treatment was performed as reported according to DTC [11]. Renal function was evaluated by estimated glomerular filtration rate (eGFR), and the treatment was withdrawn when the eGFR was < 30 mL/min/1.73 m\(^2\).

**Efficacy**

Time to treatment failure, progression-free survival (PFS), and overall survival (OS) in the lenvatinib and PTX groups were performed by the log-rank test. We evaluated the response rate according to Response Evaluation Criteria in Solid Tumors [12] version 1.1 [13]. A spider plot of the change in maximum tumor diameter from the start of treatment to the time of clinical progressive disease was shown in the lenvatinib treatment group. The time of best response was determined based on these results. Comprehensive genomic profiling (CGP) was performed on cases after 2019 when insurance reimbursement became available. The results of 13 and 14 patients with ATC and DTC, respectively, who had completed standard treatment in the same period were combined and compared.

**Safety and tolerability**
Safety parameters, including adverse events (AE), hematology and clinical chemistry, urinalysis, vital signs, and electrocardiograms, were assessed at the baseline and every visit during the follow-up. AEs were graded from 1 to 5 according to the Common Terminology Criteria for Adverse Events version 5.0 (http://www.jcog.jp/doctor/tool/ctcaev5.html), and the maximum value was totaled for each patient.

Statistics

Statistical analyses were performed using the EZR version 1.37 (https://www.jichi.ac.jp/saitama-sct/SaitamaHPFiles/download.html). Continuous variables are presented as medians with their 95% confidence intervals (CI), and categorical variables are presented as numbers with percentages. The Kaplan-Meier method was used to plot the OS curve. Univariate regression analysis, with calculated hazard ratios and their 95% CI, was used to identify the clinical features associated with PFS and OS. All p-values were two-sided, and p-values of < 0.05 were considered statistically significant.

Results

Two cases are currently alive, while 54 have died. The mean survival was 4.34 months. Table 1 compares patient backgrounds in the lenvatinib, PTX, and BSC treatment groups. No significant differences were found in age, gender, weight, or TNM staging (AJCC Cancer Staging Manual 8th Edition, 2017). Additionally, no significant differences were found in the percentage of radiotherapy intervention, lung metastases, and maximum tumor size. Survival was significantly longer in the lenvatinib group, averaging 5.8 months (\( P = 0.004 \)). The PTX and BSC groups survived 1.98 and 1.20 months, respectively.
### Table 1

List of patient background in lenvatinib, PTX, and BSC treatment groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Group</th>
<th>BSC</th>
<th>Lenvatinib</th>
<th>PTX</th>
<th>p-value</th>
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<tbody>
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<td>N</td>
<td></td>
<td>8</td>
<td>36</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>74.75 [62, 87]</td>
<td>72.33 [47, 85]</td>
<td>72.75 [61, 86]</td>
<td>0.809</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Female</td>
<td>5 (62.5)</td>
<td>19 (54.3)</td>
<td>7 (58.3)</td>
<td>0.904</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3 (37.5)</td>
<td>16 (45.7)</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td>PS (%)</td>
<td>0</td>
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<td>27 (75.0)</td>
<td>9 (75.0)</td>
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<tr>
<td></td>
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<td>9 (25.0)</td>
<td>2 (16.7)</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (12.5)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td></td>
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<tr>
<td>Stage (%)</td>
<td>B</td>
<td>1 (12.5)</td>
<td>7 (19.4)</td>
<td>1 (8.3)</td>
<td>0.634</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>7 (87.5)</td>
<td>29 (80.6)</td>
<td>11 (91.7)</td>
<td></td>
</tr>
<tr>
<td>Lung metastasis (%)</td>
<td></td>
<td>7 (87.5)</td>
<td>29 (80.6)</td>
<td>11 (91.7)</td>
<td>0.634</td>
</tr>
<tr>
<td>Radiation therapy (%)</td>
<td></td>
<td>0 (0.0)</td>
<td>9 (25.0)</td>
<td>1 (8.3)</td>
<td>0.155</td>
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<tr>
<td>Body weight (kg)</td>
<td></td>
<td>47.00 [40,58]</td>
<td>56.27 [41,88]</td>
<td>51.29 [37,70]</td>
<td>0.15</td>
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<tr>
<td>Maximum diameter(mm)</td>
<td></td>
<td>56.79 [37,85]</td>
<td>48.78 [24,92]</td>
<td>57.29 [30,92]</td>
<td>0.213</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td></td>
<td>1.20 [0.3,2.2]</td>
<td>5.83 [0.5,28.9]</td>
<td>1.98 [0.2,4.9]</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

*P* < 0.05. Continuous variables are indicated using median and range [minimum and maximum].

TNM staging was performed using the 8th edition of the AJCC staging system for thyroid cancer (AJCC-8).

Table 2 shows the results of the 36 lenvatinib-treated patients with the best response. The mean starting dose and treatment duration was 20.2 mg and 4.89 months, respectively. Median PFS was 3.5 months (95% CI: 2.3–5.37). In contrast, the PTX group revealed no cases of PR, and the mean duration of treatment was 1.65 months.
### Table 2
Comparison of lenvatinib and paclitaxel outcomes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lenvatinib</th>
<th>PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>ORR Partial Response (%)</td>
<td>12 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease (%)</td>
<td>19 (52.8)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>4 (11.1)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Not evaluated (%)</td>
<td>1 (2.8)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Starting dose (mg)</td>
<td>20.2 (4.7)</td>
<td>a, 80 mg/m² weekly</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td>4.89 (5.0)</td>
<td>1.65 (1.3)</td>
</tr>
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</table>

Figure 1 shows the comparison of OS between the lenvatinib and PTX groups. The median OS was 4.77 and 2.07 months in the lenvatinib and PTX groups, respectively, indicating a significant survival benefit ($P = 0.0000163$).

The average lenvatinib treatment duration was 4.89 months, and Fig. 2 graphically depicts the AEs that appeared during that time. The most common AE was hypertension, which occurred in 29 (80.6%) patients, but there were no Grade 3 or higher AEs that would interfere with continued treatment. The next most common AEs were loss of appetite in 18 (50.0%), cavitation in 17 (47.2%), proteinuria and fatigue in 15 (41.7%), necrosis in 14 (38.9%), cutaneous fistula in 12 (33.3%), and tracheal fistula (including pharyngoesophageal fistula) in 9 (25.0%), and hand-foot syndrome in 8 (22.2%) patients. Necrosis was observed in 2 patients, who died of hemorrhage. Two patients had Grade 3 loss of appetite and one had a gastrointestinal hemorrhage, of whom treatment was discontinued and the patient was treated with BSC.

Surgical treatment was performed for tracheotomy upon initial presentation to avoid asphyxia or for local control in five cases in the lenvatinib group and in three cases in the other treatment groups, all of which were resectable and positive for margins. Conversion surgery was possible in two cases, and their histopathological images are shown in Fig. 3. No residual tumor was observed on gross examination in both cases; however, pathology was positive for margins. Fibrosis without necrosis was found in the tumor in case A and localized tumor necrosis was found in case B; however, both specimens showed residual viable cells. Local tumor necrosis was observed in case B; however, both specimens showed residual viable cells. Radical surgery was impossible although lenvatinib treatment reduced the tumor size.

Figure 4 shows the evolution of the maximum tumor diameter after lenvatinib treatment. The plots are shown until the final image evaluation at the end of treatment. Tumor shrinkage is observed within 1–2 months of treatment in most cases. Thereafter, treatment is maintained at the current level and discontinued at 4 months. The longest period of imaging evaluation is 9 months.
CGP results were listed in Table 3. The CGP results of 13 patients with ATC showed that 6 (46.2%) had \textit{BRAF} mutation, 4 (30.8%) had \textit{RAS} mutation, 7 (53.8%) had \textit{TERT} mutation, 9 (69.2%) had \textit{TP53} mutation, and 1 (7.7%) had \textit{RET} fusion, \textit{TMB} high, \textit{PTEN} and \textit{FGF} mutation, respectively. \textit{RET} fusion, \textit{TMB} high, \textit{PTEN}, and \textit{FGF} mutations were detected in one case (7.7%), respectively. Among the 10 patients with papillary thyroid cancer (PTC), 10 (100.0%) had \textit{BRAF} mutation, 7 (70.0%) had \textit{TERT} mutation, and 1 (70.0%) had high \textit{TMB}. Among the four patients with follicular thyroid cancer (FTC), one had a \textit{RAS} mutation, but none had a \textit{TP53} mutation. Therefore, ATC cases 1–7 are of PTC origin, while cases 8–12 are of FTC origin; cases 1–3 are consistent with the coexistence of PTC in the surgical specimens, and case 7 is consistent with PTC as the tissue before the anaplastic transformation.

Table 3A. Results of genetic analysis at anaplastic thyroid cancer

<table>
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<th>7</th>
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<td>A</td>
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<td>\textit{BRAF}</td>
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<td>1</td>
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</table>

1 = Detect mutations or fusion genes; 0 = no abnormality

A. anaplastic thyroid cancer; ND, not detectable

Table 3B. Genetic analysis results of patients with differentiated thyroid cancer who have completed lenvatinib treatment
### Discussion

The antitumor effect of lenvatinib in ATC has been reported as a phase II study, which included patients who are previously treated by other agents \([6, 7]\). The median PFS and OS were 2.6 months (95% CI: 1.4–2.8) and 3.2 months (95% CI: 2.8–8.2), respectively, which may not be an effective ATC treatment. Lenvatinib treatment resulted in disappointing survival for patients with unresectable ATC. None of the results were satisfactory. A report describing the treatment results of distant metastases in ATC in which the primary lesion was resected \([14]\) was shown in relatively good results. The median PFS and OS were 7.4 months (95% CI: 1.7–12.9) and 10.6 months (95% CI: 3.8–19.8), respectively, and the objective response rate was 24%. This report revealed that not all of the distant metastases have been pathologically proven to be ATC. ATCs, in which at least the primary tumor can be resected, have a better prognosis than unresectable cases. Another real-world report \([9]\) included patients with previously treated cases or target lesions that include distant metastases. The number of patients is small, but this is the

\[\text{P, papillary thyroid cancer; F, follicular thyroid cancer}\]
only study that investigated the effect of initial lenvatinib treatment, pathologically proven, unresectable ATC only. Median PFS and OS were 3.5 and 4.7 months, respectively. The result was slightly better than [6]. This may be because patients were initially treated. However, CR with lenvatinib alone is not possible considering the pathology of the two cases of conversion surgery, and external irradiation or other drug therapy must be sequentially added postoperatively. ATC requires additional treatment, unlike the previously reported conversion surgery for DTC, because residual lesions can quickly enlarge and affect surrounding organs. This is not surprising given the much lower frequency of CR in studies of lenvatinib for RAI-refractory DTC [15].

The frequency of AEs themselves is less than reported for DTC because of the short administration duration in terms of safety [11]. Grade 3 or higher fistulas (cutaneous and tracheal fistulas) were observed in three patients, and necrosis was observed in two patients, who died of hemorrhage. Additionally, two cases had Grade 3 loss of appetite and one case had gastrointestinal bleeding. Eight of these patients (21.1%) could not continue lenvatinib treatment due to serious AEs. In contrast, 30 (78.9%) patients were able to continue treatment until they recognized progressive disease. The most clinically serious AEs of lenvatinib are fistula formation, rapid necrosis, and hemorrhage, as previously reported [4, 5]. Two deaths due to hemorrhage were caused by fistula formation and aseptic abscess from necrosis, and local washing and continuous lenvatinib treatment in the hope that the tumor would shrink. Cutaneous fistulas are often fistulized at the site of needle biopsy. Lenvatinib treatment can be continued if the fistula is localized to the superficial skin, but lenvatinib should be immediately discontinued if there is a risk of tracheal or esophageal fistula and bleeding. Thus, we believe that safety can be assured by carefully monitoring local findings once lenvatinib therapy is initiated and preventing serious fistulas or bleeding events.

There are more numerous reports of CGP results [16], but our results revealed a high number of $BRAF$ mutations, which are PTC-derived ATCs, indicating many PTC-derived ATCs, and FTC-derived ATCs inheriting RAS mutations and de novo ATC, all of which are consistent with previous reports. Additionally, the high prevalence of TP53 and TERT abnormalities as comorbid genetic abnormalities is consistent with previous reports [17]. Results of drugs targeting the driver gene have been reported [18, 19]. Another study reported the combination with immune checkpoint inhibitors [8]. These drugs could not be used in Japan because it was not reimbursed by health insurance. Therefore, this was a single-agent study of lenvatinib, but it is significant as real-world data. The median PFS was 3.7 months, indicating an effective treatment to halt disease progression for a little more than a month before the CGP results are known. Patients with $BRAF$ mutations should be treated with $BRAF$ inhibitors. Some reports are in combination with an immune checkpoint inhibitor. A study of 36 ATCs, including distant metastases, reported good results with median PFS and OS of 6.7 and 14.5 months, respectively [20]. Drugs for RAS mutations may be applied or drugs targeting other driver genes may be developed in the future.

Lenvatinib treatment became available in 2015 and CGP testing became available in 2019, so there is a bias in which possible treatments and tests are selected depending on the timing of availability, and the limitation of this study is that it is not a random trial.
Conclusions

We evaluated the efficacy of lenvatinib in 36 patients with ATC with primary target organs. The response rate was 33%, and the median OS was 4.77 months. A safety review indicated that lenvatinib should be used under the careful observation of local findings. Two patients, who showed a reduction with lenvatinib, underwent conversion surgery, which prolonged the prognosis in terms of avoiding AEs, such as asphyxia, fistula, and hemorrhage due to tumor growth. However, the resection specimens were positive for margins, and CR was not possible even if the reduction was observed. At present, a treatment strategy of obtaining CGP results while the initial drug lenvatinib remained effective and lead to effective drug therapy is appropriate.

Abbreviations

AE    Adverse events
ATC   Anaplastic thyroid cancer
BSC   Best supportive care
CGP   Comprehensive genomic profiling
CI    Confidence intervals
DTC   Differentiated thyroid cancer
FTC   Follicular thyroid cancer
OS    Overall survival
PFS   Progression-free survival
PTC   Papillary thyroid cancer

Declarations

Ethics approval and consent to participate

The chemotherapy committee of Kanagawa Cancer Center approved this regimen of lenvatinib for use in patients with ATC. The cancer board of the hospital also approved lenvatinib treatment, including surgery, for patients with ATC. Informed consent was obtained from all subjects. All experimental protocols were approved by the Institutional Review Board of Kanagawa Cancer Center. And we confirmed that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not Applicable.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

No funding was received.

**Authors’ contributions**

HI and ST designed the study. AT analyzed the data. HI, ST, AT, and KM contributed by performing the surgery and caring for the patients. All authors read and approved the final manuscript.

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**Authors’ information**

HI is an endocrine surgeon working at the Kanagawa Cancer Center and has extensive experience in several surgeries for ATC, as well as ATC treatment.

**References**


Figures

Survival curves of 36 patients treated with lenvatinib and 12 patients treated with PTX were compared. The black line represents the lenvatinib group and the red line represents the PTX group. The 2-month survival rate in the lenvatinib-treated group is 83%, and 50% in the PTX-treated group. The median OS

<table>
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<th>OS (95% CI)</th>
<th>P-value</th>
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<td>0.83 (0.67–0.92)</td>
<td>4.77 (3.07–6.50)</td>
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<tr>
<td>PTX</td>
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<td>0.50 (0.21–0.74)</td>
<td>2.07 (0.33–2.83)</td>
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</tr>
</tbody>
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Figure 1

OS comparison between lenvatinib and PTX treatment

Survival curves of 36 patients treated with lenvatinib and 12 patients treated with PTX were compared. The black line represents the lenvatinib group and the red line represents the PTX group. The 2-month survival rate in the lenvatinib-treated group is 83%, and 50% in the PTX-treated group. The median OS
was 4.77 months in the lenvatinib group and 2.07 months in the PTX group, indicating a significant survival benefit ($P = 0.0000163$).

**Figure 2**

AEs recognized lenvatinib treatment for ATC

Among the AEs that appeared, the blue bar indicates grades 1 and 2, and the orange bar indicates grades 3 or higher, in decreasing order of frequency as a stacked bar graph. All grade AE frequencies were displayed in % next to the bar.
Figure 3

Histopathology of two cases in which surgical intervention was possible

HE staining 100× images were shown. A, there was fibrosis without necrosis in the tumor and viable tumor cells are also present. B, there was localized tumor necrosis and there are viable tumor cells around it.
Figure 4

Changes in the maximum tumor diameter after lenvatinib treatment

Colors were separated from baseline and final values. Blue lines indicate PR, yellow indicates SD, and red indicates PD. In most cases, tumor shrinkage is observed within 1–2 months of treatment; thereafter, treatment is maintained at the current level and discontinued at 4 months. The longest period of imaging evaluation is 9 months.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistv4combined.doc