A phase Ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer


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Background: This phase Ib study aimed to establish the feasible everolimus dose given with standard-dose etoposide plus cisplatin (EP) for extensive-stage small-cell lung cancer (SCLC).

Patients and methods: An adaptive Bayesian dose-escalation model and investigator opinion were used to identify feasible daily or weekly everolimus doses given with EP in adults with treatment-naive extensive-stage SCLC. A protocol amendment mandated prophylactic granulocyte colony-stimulating factor (G-CSF). Primary end point was cycle 1 dose-limiting toxicity (DLT) rate. Secondary end points included safety, relative EP dose intensity, pharmacokinetics, and tumor response.

Results: Patients received everolimus 2.5 or 5 mg/day without G-CSF (n = 10; cohort A), 20 or 30 mg/week without G-CSF (n = 18; cohort B), or 2.5 or 5 mg/day with G-CSF (n = 12; cohort C); all received EP. Cycle 1 DLT rates were 50.0%, 22.2%, and 16.7% in cohorts A, B, and C, respectively. Cycle 1 DLTs were neutropenia (cohorts A and B), febrile neutropenia (all cohorts), and thrombocytopenia (cohorts A and C). The most common grade 3/4 adverse events were hematologic. Best overall response was partial response (40.0%, 61.1%, and 58.3% in cohorts A, B, and C, respectively).

Conclusions: Everolimus 2.5 mg/day plus G-CSF was the only feasible dose given with standard-dose EP in untreated extensive-stage SCLC.

Key words: cisplatin, etoposide, everolimus, phase I, small-cell lung cancer

introduction

Etoposide and cisplatin (EP) chemotherapy is a current standard of care for treating small-cell lung cancer (SCLC) [1, 2]. For patients with extensive-stage SCLC, who account for the majority of cases, EP provides an 8.1–10.9-month median survival and a 2-year survival rate of <10% [3–7]. Despite extensive study, no regimen has consistently demonstrated significant benefit over EP without significantly increasing toxicity [1, 8].

Approximately 50%–55% of human SCLC tumors express mammalian target of rapamycin (mTOR) [9, 10], suggesting the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway is frequently upregulated in SCLC. mTOR signaling upregulation is also observed in SCLC cell lines [9, 11, 12], and SCLC culture growth is dependent on PI3K [12, 13]. In a murine SCLC xenograft model, the mTOR inhibitor everolimus completely suppressed tumor growth at 4 weeks [9]. Additional data suggest PI3K/Akt/mTOR pathway inhibition enhances etoposide-mediated cytotoxicity in SCLC cells and may overcome chemotherapy resistance [9, 13, 14].

We conducted a phase Ib study to establish the feasible dose levels and regimens of everolimus combined with EP in patients with extensive-stage, chemotherapy-naive SCLC (ClinicalTrials.gov identifier: NCT00466466).

methods

patients

Patients aged ≥18 years with histologically or cytologically confirmed extensive-stage SCLC, World Health Organization (WHO) performance status ≤1, and adequate organ function were eligible for enrollment. Exclusion...
criteria included previous systemic therapy for SCLC; chronic immunosuppressive therapy; symptomatic, leptomeningeal, or uncontrolled brain metastases; and grade 3 hypercholesterolemia or hypertriglyceridemia (grade ≥2 with history of coronary artery disease).

All patients provided written informed consent. The study protocol and all amendments were reviewed by the ethics body of each center. The study was conducted according to the protocol, good clinical practice guidelines, applicable local regulations, and the Declaration of Helsinki.

**study design**

This open-label, multicenter, phase Ib study was designed as a Bayesian sequential dose-escalation scheme based on a time-to-event model of the rate of dose-limiting toxicities (DLTs) estimating the probability that patients experience a DLT within their first treatment cycle (end-of-cycle 1 DLT rate). (See supplementary Information and Table S1, available at *Annals of Oncology* online, for DLT descriptions.) In the core phase, up to six 21-day cycles of EP plus daily or weekly everolimus were assessed. During each cycle, cisplatin (75 mg/m²) and etoposide (100 mg/m²) were given intravenously on days 1 and 1–3, respectively. Patients were alternately assigned to daily or weekly oral everolimus. Daily everolimus was given continuously starting on day 2 of cycle 1. Weekly everolimus was given on days 2, 8, and 15 of cycle 1 and days 1, 8, and 15 of every cycle thereafter. Everolimus doses and schedules were chosen based on earlier studies [15, 16]. Dosing adjustments were permitted for toxicities considered study drug related.

Throughout dose escalation, decision-making time points occurred after every critical DLT (i.e. any DLT occurring during cycle 1) and after the first six patients in a dose level completed cycle 1 or discontinued because of a critical DLT. If these events did not trigger assessment, escalation was considered at 2-month intervals. At each time point, recruitment options were to continue at the same dose, initiate at a higher or lower dose, stop based on identification of the feasible dose, or stop and end investigation because of failure to identify a feasible dose. Inpatient dose escalation was not permitted. In the original protocol, everolimus doses of 2.5, 5, and 10 mg/day and 20, 30, and 50 mg/week were planned. A protocol amendment introduced 7.5-mg/day and 40-mg/week doses and mandated prophylactic granulocyte colony-stimulating factor (G-CSF) use from cycle 1 onward per standard recommendations from the American Society of Clinical Oncology [17] and local clinical practice.

After completing the core phase or discontinuing chemotherapy early, patients could continue everolimus until disease progression or unacceptable toxicity.

**assessments**

Adverse events (AEs) were collected throughout the study and assessed per the Common Terminology Criteria for Adverse Events, version 3.0. Pharmacokinetic parameters were derived by standard noncompartmental techniques using WinNonlin® Version 5.2 (Pharsight, Mountain View, CA). (See supplementary Information, available at *Annals of Oncology* online, for full details.) Computed tomography was carried out at baseline, day 1 of core cycles 3 and 5, and every 6–8 weeks during the extension. Tumor response was assessed per RECIST 1.0. Complete (CR) and partial (PR) response required confirmation ≥4 weeks after initial response observation.

**end points and statistical analysis**

Primary end point was the end-of-cycle 1 DLT rate expressed as the probability of the end-of-cycle 1 DLT rate falling within prespecified intervals, estimated via a Bayesian time-to-event model [18, 19]. A dose was considered feasible if the probability of the end-of-cycle 1 DLT rate falling within the targeted toxicity interval was maximized and there was a <5% probability the end-of-cycle 1 DLT rate fell within the unacceptable toxicity interval and a <25% probability it fell within the excessive or unacceptable toxicity intervals combined. Secondary end points included safety, cisplatin and etoposide relative dose intensity (RDI), pharmacokinetics, and best overall response.

No formal sample size calculation was carried out. It was estimated that 30 patients across all doses investigated would suffice to complete dose escalation within a given everolimus schedule and ensure the desired confidence in the end-of-cycle 1 DLT rate and etoposide and cisplatin RDIs was reached.

**results**

**patients and treatment**

Between April 2007 and November 2009, 40 patients from eight centers in three countries enrolled. Twenty-eight patients enrolled before the amendment requiring mandatory G-CSF and received everolimus 2.5 or 5 mg/day or 20 or 30 mg/week with EP (non-G-CSF patients). The remaining 12 patients enrolled after the amendment and received everolimus 2.5 or 5 mg/day with EP (G-CSF patients). A majority of patients were male, aged <65 years, and had a WHO performance status of 1 (Table 1). Of all patients, 92% reported smoking >100 cigarettes in their lifetime, and 58% were current smokers at diagnosis.

Among non-G-CSF patients, 3 of 10 in the daily and 10 of 18 in the weekly schedule completed the targeted six chemotherapy cycles. Median duration of exposure to combined treatment ranged from 11.0 weeks with everolimus 5 mg/day to 18.9 weeks with everolimus 20 mg/week (supplementary Table S2, available at *Annals of Oncology* online). Proportions of patients with cisplatin and etoposide RDIs ≥80% were 100% and 67% in the 2.5 and 5 mg/day schedules, respectively, and 80% and 100% in the 20 and 30 mg/week schedules, respectively. Among G-CSF patients, 6 of 12 completed six cycles. Median duration of exposure to combined treatment was 12.0 and 18.0 weeks with everolimus 2.5 and 5 mg/day, respectively (supplementary Table S2, available at *Annals of Oncology* online). Proportions of patients with cisplatin RDI ≥80% were 71% and 80%, respectively. Etoposide RDI ≥80% was observed in 100% and 80% of patients, respectively.

Among the 20 patients (50%) who entered the extension phase, median (range) duration of everolimus exposure during the extension was 8.6 weeks (1.0–117.6 weeks) in the non-G-CSF (n = 13) population and 8.1 weeks (0.4–36.1 weeks) in the G-CSF (n = 7) population. Two non-G-CSF (15%) and three G-CSF (43%) patients experienced exposure ≥18 weeks.

**dose-limiting toxicities**

Among the 10 non-G-CSF patients in the daily schedule, 70% experienced a DLT, 50% during cycle 1 (Table 2). In the non-G-CSF weekly schedule (n = 18), 39% experienced a DLT, 22% during cycle 1. All cycle 1 DLTs occurred in the 30-mg group (Table 2). Among the 12 patients enrolled after introduction of mandatory G-CSF use, 25% experienced a DLT, 17% during cycle 1 (Table 2).

**dose escalation**

There was divergence between the model-based dose-escalation recommendations and what the investigators and sponsor considered feasible based on the observed toxicities. At all times, the most conservative decision was made to ensure patient safety. In the daily schedule, three of six patients initially
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-G-CSF population</th>
<th>Weekly everolimus(^a)</th>
<th>G-CSF population</th>
<th>Total (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily everolimus(^a)</td>
<td>20 mg (N = 5)</td>
<td>30 mg (N = 13)</td>
<td>Total (N = 18)</td>
</tr>
<tr>
<td></td>
<td>2.5 mg (N = 4)</td>
<td>5.0 mg (N = 6)</td>
<td>Total (N = 10)</td>
<td>2.5 mg (N = 7)</td>
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<td>Age, median (range), years</td>
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<td>62.5 (36–70)</td>
<td>60.0 (36–70)</td>
<td>58.0 (53–63)</td>
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<td>Age, n (%), years</td>
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<td>62.5 (36–70)</td>
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<td>58.0 (53–63)</td>
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<td>&lt;65</td>
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<td>62.5 (36–70)</td>
<td>60.0 (36–70)</td>
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<td>2 (50)</td>
<td>3 (50)</td>
<td>5 (50)</td>
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<tr>
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<td>3 (50)</td>
<td>5 (50)</td>
<td>1 (20)</td>
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<td>WHO PS, n (%)</td>
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<td>2 (50)</td>
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<td>1</td>
<td>2 (50)</td>
<td>4 (67)</td>
<td>6 (60)</td>
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<td>2</td>
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<td>Smoking history, n (%)</td>
<td>51.0 (40–60)</td>
<td>62.5 (36–70)</td>
<td>60.0 (36–70)</td>
<td>58.0 (53–63)</td>
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<tr>
<td>Ever(^b)</td>
<td>3 (75)</td>
<td>5 (83)</td>
<td>8 (80)</td>
<td>5 (100)</td>
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<tr>
<td>Current</td>
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<td>4 (67)</td>
<td>5 (50)</td>
<td>3 (60)</td>
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<tr>
<td>Never</td>
<td>1 (25)</td>
<td>1 (17)</td>
<td>2 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)All patients received etoposide and cisplatin in addition to everolimus.

\(^b\)Defined as having smoked >100 cigarettes over a lifetime.

G-CSF, granulocyte colony-stimulating factor; WHO PS, World Health Organization performance status.
enrolled at everolimus 5 mg/day experienced a critical DLT; therefore, the next four patients enrolled at 2.5 mg/day. After the amendment mandating G-CSF use, seven patients enrolled at everolimus 2.5 mg/day. Based on clinical opinion alone (because of lack of priority data entry from investigational sites), everolimus was re-escalated to 5 mg/day. Five patients received 5 mg/day before enrollment was permanently discontinued due to poor recruitment.

In the weekly schedule, the first patient enrolled at everolimus 30 mg/week experienced a critical DLT; consequently, the next five patients were enrolled at 20 mg/week. None of these patients experienced a DLT, and everolimus was re-escalated to 30 mg/week. After 13 patients received 30 mg/week, no dose escalation was recommended because >60% of patients experienced grade 3/4 neutropenia. After the amendment, recruitment focused on the daily schedule only because of low enrollment.

Based on investigator and medical monitor opinion, everolimus 2.5 mg/day + G-CSF was deemed the only feasible dose given with standard-dose EP, with no other doses considered feasible because of myelosuppression.

**Safety**

All but one patient in each non-G-CSF schedule experienced ≥1 grade 3/4 AE, most commonly neutropenia (Table 3). Six grade 3/4 infections were reported in five non-G-CSF patients; only one led to discontinuation. In the G-CSF population, 58% of patients experienced ≥1 grade 3/4 neutropenia and thrombocytopenia (Table 3). No patients reported grade 3/4 infections. AEs leading to discontinuation occurred in five patients in the non-G-CSF daily population and one patient each in the non-G-CSF weekly and G-CSF populations. One patient treated with everolimus 2.5 mg/day + G-CSF died on day 7. No autopsy was carried out, but the investigator considered death likely due to disease progression.

**Pharmacokinetics**

In the non-G-CSF population, everolimus exposure and clearance were comparable when everolimus was administered alone and with EP (supplementary Table S3, available at *Annals of Oncology* online). Etoposide exposure and clearance were comparable across daily and weekly everolimus doses and were unaffected by everolimus co-administration. Cisplatin maximum plasma concentrations were not affected by increasing daily or weekly everolimus doses (supplementary Table S3, available at *Annals of Oncology* online). Pharmacokinetic findings were similar in the G-CSF population (data not shown).

**Efficacy**

Best overall response during core treatment was PR (Table 4). The disease control rate (CR + PR + stable disease) was 60%, 78%, and 58% in the non-G-CSF daily, non-G-CSF weekly, and daily G-CSF schedules, respectively. Based on an exploratory analysis combining data from the core (n = 40) and extension (n = 20) phases, median progression-free survival (PFS) ranged from 22.0 weeks in the G-CSF 5-mg/day group to 35.1 weeks in the G-CSF 2.5-mg/day group. Seven patients had PFS >200 days, including two patients who experienced PFS of 408 and 470 days.

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**Table 2. Dose-limiting toxicities (dose-determining population)**

<table>
<thead>
<tr>
<th></th>
<th>Non-G-CSF population</th>
<th>G-CSF population</th>
<th>Total (N = 40)</th>
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<tbody>
<tr>
<td></td>
<td>Daily everolimus a</td>
<td>Weekly everolimus b</td>
<td>Total (N = 12)</td>
</tr>
<tr>
<td></td>
<td>2.5 mg (N = 4)</td>
<td>5.0 mg (N = 6)</td>
<td>7 (50)</td>
</tr>
<tr>
<td></td>
<td>Grade 3 neutropenia, n (%)</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Grade 4 neutropenia, n (%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Grade 4 febrile neutropenia, n (%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Grade 4 thrombocytopenia, n (%)</td>
<td>0</td>
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<tr>
<td></td>
<td>All patients received etoposide and cisplatin in addition to everolimus.</td>
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</tbody>
</table>

aAll patients received etoposide and cisplatin in addition to everolimus. bNumber of patients. cNumber of events. dDLT at any cycle, n (%) eCritical DLTs, cycle 1, n (%) fGrade 3 neutropenia, n (%) gGrade 4 neutropenia, n (%) hGrade 4 febrile neutropenia, n (%) iGrade 4 thrombocytopenia, n
This was the first study to investigate everolimus plus standard-dose EP as first-line therapy for extensive-stage SCLC. Without G-CSF, a high incidence of myelosuppression was observed. Grade 3/4 febrile neutropenia occurred in 40% of patients receiving daily everolimus, exceeding the negligible incidence observed with everolimus monotherapy and the >10% incidence previously observed with EP [3, 5–7]. With prophylactic G-CSF, the only feasible everolimus dose given with standard-dose EP was 2.5 mg/day. After the protocol amendment and considering the previously observed toxicity, the daily schedule was favored for further enrollment. Therefore, no feasible weekly everolimus dose given with EP was identified.

The everolimus doses chosen for this study were based on previous data showing everolimus monotherapy to be pharmacodynamically active and tolerable at doses of 5 and 10 mg/day and 20–70 mg/week [15, 16]. Based on partially overlapping everolimus and EP toxicity profiles and lack of historical data on the proposed combination, both daily and weekly everolimus dosing was evaluated, with starting doses of 5 mg/day and 20 mg/week. In the present study, an adaptive Bayesian model instead of the traditional ‘3 + 3’ design typically used in dose-finding studies was used [18, 19]. Advantages of this design include a flexible dose-escalation scheme using DLT data from all doses at each decision point, the ability to evaluate the DLT rate at any time, and flexibility in the number of patients enrolled at each dose. The adaptive Bayesian model permitted rapid response to the observed myelosuppression and subsequent protocol modification to mandate prophylactic G-CSF.

The observed myelosuppression was not unexpected, as it is common in EP-treated patients. Although the grade 3/4 neutropenia rate among non-G-CSF patients in the present study was within the range observed in randomized studies of EP (28%–68%), grade 3/4 thrombocytopenia, anemia, and febrile neutropenia rates were higher than in previous EP studies [3–7]. This suggests an additive myelosuppressive effect when everolimus is combined with EP. Theoretically, adding everolimus to EP could increase infection risk because of the immunosuppressive activity of both everolimus and chemotherapy. However, no evidence of increased infection unrelated to neutropenia was observed, and all severe infections were reported in the non-G-CSF population. Interestingly, pneumonitis, an AE associated with mTOR inhibitors, was not observed in this study. Although almost 50% of patients experienced stomatitis, another AE associated with mTOR inhibitors, no patient experienced stomatitis as a DLT, and grade 3/4 stomatitis was reported in only one patient.

Everolimus pharmacokinetics were comparable when administered alone and with EP and consistent with those previously observed with everolimus monotherapy [15, 16]. PR occurred in ~50% of patients across all everolimus dose levels and schedules. However, the present study included only 40 patients, and 9 (23%) did not have their best overall response assessed because they discontinued treatment before postbaseline tumor assessment (n = 4), or because they did not meet criteria for CR, PR, or stable or progressive disease (n = 5). It appears that everolimus plus EP did not substantially improve tumor response compared with EP alone, which, in randomized trials, is 46%–63%
[3–7], suggesting the identified feasible dose level of everolimus in combination with EP may be suboptimal. In an exploratory analysis, median PFS of the seven patients who received the feasible everolimus dose level was 8.1 months, or 3–4 months longer than the median survival typically observed with EP in extensive-stage SCLC [20]. This prolongation of PFS may reflect the highly selected patient population, which may have better prognostic factors, or may be due to the maintenance phase of everolimus. The latter hypothesis appears to be refuted by results of a phase II study in which everolimus monotherapy displayed only modest clinical activity in relapsed/refractory SCLC [21]. To date, no molecular predictors of response or to mTOR inhibitors have been identified, precluding selection of patients who might benefit from everolimus.

In conclusion, everolimus 2.5 mg/day plus G-CSF was identified as the feasible everolimus dose given with standard-dose EP in patients with treatment-naive extensive-stage SCLC. Based on the modest clinical activity observed with everolimus monotherapy in relapsed/refractory SCLC and the hematologic and infectious complications observed with everolimus plus EP, everolimus is unlikely to be further investigated in an unselected SCLC population.

**disclosure**

VAP has had a consultant/advisory role with Genentech. DRC has had a consultant/advisory role with Novartis. SU is employed by and has stock ownership in Novartis Pharmaceuticals Corporation. IP and KP are employed by and have stock ownership in Novartis Pharma AG. NM is a former employee of Novartis Pharma AG and has stock ownership in Novartis Pharmaceuticals Corporation. VAP has a consultant/advisory role with Genentech. SD is a former legal representative for Novartis Pharma AG. BEJ has served as a consultant to AstraZeneca, Genentech, Sanofi, Millennium, and Transgenomics. BB has received research grants from Novartis Pharmaceuticals. VAP has received research funding from Novartis, Merck, AstraZeneca, Bristol-Myers-Squibb, and Astellas. All of the other authors declare no conflict of interest.

**references**


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Cancer risk in amyloidosis patients in Sweden with novel findings on non-Hodgkin lymphoma and skin cancer

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Background: Systemic amyloidoses include immunoglobulin light chain (AL) amyloidosis, serum amyloid (AA)-related amyloidosis and senile systemic amyloidosis (SSA). AL amyloidosis is associated with myeloma, and we showed recently that transthyretin-related hereditary amyloidosis was related to non-Hodgkin lymphoma (NHL). In SSA, amyloids constitute wild-type transthyretin. We wanted to analyze cancer risks in amyloidosis, particularly in SSA.

Patients and methods: Nonhereditary amyloidosis patients were identified from the Swedish Hospital Discharge and Outpatients Registers from years 1997 through 2010. Their cancer risk was assessed based on the Swedish Cancer Registry using standardized incidence ratio (SIR) between amyloidosis patients and the remaining population. To gain information about amyloidosis subtypes, we used the Swedish Prescribed Drug Register from years 2005 through 2010 to determine whether patients were prescribed medications that affected cancer risk.

Results: Among 1400 identified amyloidosis patients, cancer risk was increased for myeloma, NHL and squamous cell skin cancer. Myeloma and skin cancers were diagnosed 7–8 years earlier than in the population, whereas NHL was diagnosed in elderly patients. The SIR was 204 for myeloma in patients who received AL amyloidosis medication, and it was 17.22 in patients receiving rheumatoid arthritis medication, suggesting AA amyloidosis. In remaining patients, including SSA patients, cancer risk was increased for myeloma, NHL and squamous cell skin cancer.