Phase II Study of Everolimus (RAD001) in Previously Treated Small Cell Lung Cancer

Ahmad Tarhini1, Athanasios Kotsakis1, William Gooding1, Yongli Shuai1, Daniel Petro1, David Friedland1, Chandra P. Belani2, Sanja Dacic1, and Athanassios Argiris1

Abstract

Purpose: Mammalian target of rapamycin (mTOR) is a promising target in small cell lung cancer (SCLC). We designed a phase II study of everolimus, an mTOR inhibitor, in previously treated, relapsed SCLC.

Experimental Design: Patients were treated with everolimus 10 mg orally daily until disease progression. The primary endpoint was disease control rate (DCR) at 6 weeks. PI3K/Akt signaling pathway biomarkers were evaluated on baseline tumor tissue.

Results: A total of 40 patients were treated: 23 had 1 prior regimen/sensitive relapse, 4 had 1 prior regimen/refractory, and 13 had 2 prior regimens. Twenty-eight patients received 2 or more cycles of everolimus, 7 received 1 cycle, and 5 did not complete the first cycle. Best response in 35 evaluable patients: 1 (3%) partial response (in sensitive relapse), 8 (23%) stable disease, and 26 (74%) progression; DCR at 6 weeks was 26% (95% CI = 11–40). Median survival was 6.7 months and median time to progression was 1.3 months. Grade 3 toxicities included thrombocytopenia (n = 2), neutropenia (n = 2), infection (n = 2), pneumonitis (n = 1), fatigue (n = 1), elevated transaminases (n = 1), diarrhea (n = 2), and acute renal failure (n = 1). High phosphorylated AKT expression was modestly associated with overall survival (HR = 2.07; 95% CI = 0.97–4.43). Baseline S6 kinase protein expression was significantly higher in patients with disease control versus patients with progression (P = 0.0093).

Conclusions: Everolimus was well tolerated but had limited single-agent antitumor activity in unselected previously treated patients with relapsed SCLC. Further evaluation in combination regimens for patients with sensitive relapse may be considered. Clin Cancer Res; 16(23); 5900–7. ©2010 AACR.

Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer cases (1, 2). Although chemotherapy results in initially high response rates, disease recurrence is the most probable outcome and consequently, mortality rates are high. A combination of a platinum agent (cisplatin or carboplatin) and etoposide is considered standard for first-line treatment of SCLC. Survival of patients with extensive stage disease is dismal; median survival is about 10 months and 5-year survival is 1% to 2% (3). However, approximately 25% of patients with limited stage SCLC can achieve long-term survival when treated with combined radiation and chemotherapy (2). Recurrence after first-line chemotherapy has been categorized as chemo-sensitive or chemorefractory. Progression that occurs 60 to 90 days or more following completion of first-line chemotherapy is usually defined as sensitive relapse (4). In a phase II study, topotecan produced an objective response rate (RR) of 38% among patients with SCLC who recurred >90 days of primary chemotherapy (versus 6% in patients who relapsed within 90 days; ref. 4). In another phase II study, 11% of SCLC patients who progressed within 90 days of cisplatin-etoposide treatment responded to topotecan (5). In a phase III randomized trial conducted in patients with sensitive SCLC (defined as relapse >60 days), topotecan achieved a relatively modest response rate of 24% versus 18% with cyclophosphamide, Adriamycin, vincristine (CAV; ref. 6). The RR achieved with standard chemotherapeutics in patients with early (i.e., chemorefractory) relapses rarely exceed 10%. For example, gemcitabine has resulted in RRs of 0% to 13% in chemorefractory SCLC patients (7–9). Amrubicin is a synthetic anthracycline that inhibits topoisomerase II that has been extensively studied in Japan where it is approved for the treatment of SCLC. It appears to have significant activity in SCLC (10–12). Amrubicin is currently undergoing phase III testing versus topotecan in previously treated patients with SCLC in the United States. Patients with previously treated SCLC, and particularly the ones...
In vivo tumors and has an additive effect with platinum and other proliferation of numerous cell lines originating from solid studies have shown that everolimus can inhibit the pro-

12. The resulting FKBP-12/rapamycin complex then binds intracellular receptor protein, the immunophilin FKBP-

proliferation of cells through their high affinity for an

its activity on interleukin and growth-factor-dependent progression of cells from the G1 to S phase. Its own primary

is implicated in cell cycle control and specifically in the

ubiquitous protein kinase downstream of PI3K/AKT that

activated T-lymphocytes or neoplastic cells. mTOR is a kinase implicated in the control of cellular proliferation of

ferative drug with applications as an immunosuppressant with chemorefractory relapse, are in need for new effec-
tive treatment options.

Everolimus (RAD001) is a novel macrolide, antiprolif-
erative drug with applications as an immunosuppressant and anticancer agent. It acts by selectively inhibiting mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation of activated T-lymphocytes or neoplastic cells. mTOR is a ubiquitous protein kinase downstream of PI3K/AKT that is implicated in cell cycle control and specifically in the progression of cells from the G1 to S phase. Its own primary downstream substrates are the elf-4E-binding protein (4E-BP1) and p70 S6 kinase (S6K) which both play a role in the translational regulation of mRNAs encoding proteins involved in G1-phase progression (13). Everolimus exerts its activity on interleukin and growth-factor-dependent proliferation of cells through their high affinity for an intracellular receptor protein, the immunophilin FKBP-12. The resulting FKBP-12/rapamycin complex then binds with mTOR to inhibit downstream signaling events. In vitro studies have shown that everolimus can inhibit the pro-
liferation of numerous cell lines originating from solid tumors and has an additive effect with platinum and other chemotherapeutics (14). In vitro studies in rodent models have shown orally administered everolimus to be a potent inhibitor of tumor growth at well-tolerated doses. Preclini-
dical data suggest that ribosomal protein S6K1 activity in peripheral blood mononuclear cells (PBMC) may correlate with antitumor activity (13).

Phase I studies with everolimus monotherapy evaluated weekly (5–70 mg) and daily (5–10 mg) doses of admini-

stration in patients with advanced solid tumors (15, 16). Predominant toxicities were usually mild or moderate and included anorexia, fatigue, rash, mucositis, headache, hyperglycemia, hyperlipidemia, pneumonitis, and gastro-

intestinal disturbances. Myelosuppression occurs rarely but may be pronounced when everolimus is combined with chemotherapy agents, such as gemcitabine (17). Phama-
codynamic endpoints in PBMCs and tumor tissue sug-

suggested a dose–response effect with maximum S6K1 inhibition in PBMCs and p4E-BP1 inhibition and increasing pAKT levels in tumor tissue at 10 mg daily or at least 50 mg weekly, with indications that daily administration is more effective than weekly (15, 17, 18). A phase II trial in breast cancer that compared 2 everolimus schedules, 10 mg daily versus 70 mg weekly, suggested superior efficacy of the daily schedule (19). Everolimus is rapidly absorbed with peak levels after 1 hour and is metabolized primarily in the liver via CYP3A4. Terminal half-life is approximately 30 hours, and steady state levels with the daily regimen are achieved within 1 week (15, 16).

Everolimus (as Certican) is approved in Europe for prophylaxis of rejection after renal and cardiac transplanta-
tion in combination with cyclosporin A and glucocorticoids. In March 2009, everolimus at 10 mg once daily received US FDA approval for the treatment of advanced renal cell carcinoma after failure of treatment with suniti-
nib or sorafenib based on the results of a phase III trial demonstrating progression-free survival prolongation compared with placebo (20).

As mTOR plays a central role in signaling pathways downstream of the PI3K/AKT pathway, it may be important in proliferative and antiapoptotic signaling in SCLC (21). Moreover, mutations in PTEN, which regulates the PI3K/ 

Akt/PTEN signaling pathway for translation and protein synthesis via activation of 4E-BP1 and S6K, are seen in approximately 10% to 15% of SCLC (22). On the basis of the evidence above, we have conducted a phase II study of single agent everolimus in previously treated, recurrent SCLC.

Translational Significance

This phase II study tested everolimus, an mTOR inhibitor, in previously treated, relapsed small cell lung cancer (SCLC) and evaluated PI3K/Akt signaling path-

way biomarkers utilizing baseline tumor. One partial response was seen in a patient with sensitive relapse and the disease control rate at 6 weeks was 26%. High phosphorylated Akt (pAkt) expression was modestly associated with overall survival (HR = 2.07, 95% CI = 0.97–4.43), whereas baseline S6 kinase (S6K) protein expression was significantly higher in patients with disease control versus patients with progression (P = 0.0093). These results could support future combination studies utilizing everolimus in selected patients with SCLC. In addition, further exploration of pAkt and S6K as baseline tumor tissue biomarkers should be considered.

Materials and Methods

Patients

Patients were eligible if they had cytologically or histo-

logically confirmed SCLC that had progressed after prior chemotherapy and had measurable disease by RECIST (23). Mixed small and nonsmall cell tumors were excluded. Up to 2 prior chemotherapy regimens for SCLC were allowed but no prior therapy with an mTOR inhibitor (e.g., temsirolimus or CCI-779). Eligible patients were also required to have met the following criteria: age ≥ 18 years; Eastern Cooperative Oncology Group performance status (ECOG) 0–1; and adequate hematologic values (absolute neutrophil count ≥ 1,500 cells/µL, hemoglobin ≥ 10 g/dL, platelet count ≥ 100,000/µL), hepatic function [serum bilirubin ≤ 1.5 × the upper limit of normal (ULN) and serum ALT and serum AST ≤ 3 × ULN; ≤ 5 × ULN in patients with liver metastases]. Patients with treated brain and no evidence of progression in the brain were eligible.

Patients were ineligible if they had any of the following: (a) a significant other medical or psychological condition that could interfere with protocol treatment, (b) concomi-
tant second malignancy except for basal cell carcinoma and squamous cell carcinoma in situ of the skin or cervix
(previous malignancies of other sites are eligible provided patients have been disease free continuously for at least 3 years). (c) impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). (d) requirement for chronic systemic glucocorticoids or other immunosuppressant, and (e) pregnancy or lactation. Patients were advised to discontinue drugs that interact with CYP3A4, if determined to be medically safe. All acute toxicities from previous therapies must have resolved. The study protocol was approved by the University of Pittsburgh Institutional Review Board and all patients provided written informed consent.

Treatment, toxicity, and response assessments

Everolimus was administered at a dose of 10 mg daily orally and continued until disease progression. A cycle was defined as 3 weeks of therapy. Everolimus was provided by Novartis formulated as tablets for oral administration of 2.5 mg or 5 mg strength. This study utilized the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 for grading toxicities (http://ctep.cancer.gov/form). Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematologic and blood chemistry, regular measurement of vital signs, and the performance of physical examinations. Treatment interruption and dose reductions to lower doses of everolimus (5 and 2.5 mg) were required for grades 3 and 4 toxicities per a study protocol algorithm. No concurrent anticancer agents or radiation therapy was allowed. Imaging studies (computed tomography or magnetic resonance scans, including imaging of the brain, chest, and abdomen) were performed at baseline. Tumor assessments were performed after every 2 cycles (6 weeks) with repeat imaging studies and RECIST were applied to determine response (23). Sensitive relapse was defined as relapse occurring more than 60 days from completion of first-line chemotherapy and refractory relapse as relapse occurring within 60 days after completion of first-line chemotherapy for SCLC.

Immunohistochemistry

Tumor specimens obtained prior to treatment initiation were used to evaluate PI3K/AKT signaling pathway molecular markers. Immunohistochemistry (IHC) was performed on 4-μm thick formalin-fixed, paraffin-embedded tissue sections according to the manufacturer’s instructions. Primary antibodies used were a rabbit monoclonal antibody for AKT (1:50; Cell Signaling Technology, Inc.), pAKT (1:10; Cell Signaling Technology, Inc.), S6K (1:100; Cell Signaling Technology, Inc.), and 4E-BP1 (1:100; Cell Signaling Technology, Inc.); and a rabbit polyclonal antibody for pS6K (1:25; Cell Signaling Technology, Inc.) and p-4E-BP1 (1:25; Cell Signaling Technology, Inc.). Sections of lung adenocarcinoma previously identified as positive for the above proteins served as positive control samples. Negative controls included omitting the primary antibody and replacing it with normal serum. Tumor staining was scored by a pathologist (S.D.) who had no knowledge of patient clinical data. Each tumor was scored as 0, 1, 2, or 3, which corresponded to negative, weak, moderate, and strong staining intensities. Percentages of stained tumor cells were determined (0%–100%). A final histochemical score (H-score) was calculated by multiplying the products of staining intensities (0–3) and distributions (0%–100%); H-scores ranged from 0 to 3.

Statistical methods

The study proceeded as an optimal 2-stage design (24). The null hypothesis was a disease control rate (DCR) of 30% where disease control was defined as a complete response (CR), partial response (PR), or stable disease (SD) using RECIST. Patients had to complete 1 cycle to be evaluable for response and to be included in the computation of DCR. A target DCR of 50% was selected as sufficiently high to warrant interest in further study of everolimus. After 21 patients were treated a decision to continue to the second stage required 7 or more patients to exhibit disease control. If 17 or more cases of disease control were observed after completion of the second stage, everolimus would be considered to have sufficient activity to warrant further study. This design limited both type I and type II error to 10%. Kaplan–Meier estimates of progression-free survival and overall survival were calculated. A landmark analysis was conducted to assess the influence of disease control on survival (25). The landmark of 2 months was selected as patients were initially evaluated for response at 6 weeks. For patients with available tumor tissue a panel of selected tumor proteins was assessed by IHC. Immunoreactive protein levels were scored by the pathologist by intensity (0, 1, 2, 3) and percent of cells stained. These 2 parameters were multiplied and normalized to a scale from zero to 3.0. The resulting IHC score, defined as the H-score, was then tested for association with overall survival. The association between tumor IHC scores and overall survival was analyzed by Cox proportional hazards regression and recursive partitioning. Recursive partitioning, also known as classification and regression trees, searches the data for variables and values that split data into classes (26).

Results

Patient characteristics

A total of 40 patients met protocol eligibility requirements and were enrolled between February 2007 and November 2008. Seventeen patients had an ECOG PS of 0 and 23 had a PS of 1. Twenty-three patients had received 1 prior regimen with sensitive relapse (i.e., relapse >60 days from completion of first-line chemotherapy) and 4 patients had 1 prior regimen with refractory relapse. Thirteen patients had 2 prior regimens. Baseline patient and disease characteristics are shown in Table 1.
Treatment delivery

Twenty-eight patients (70%) received 2 or more cycles of everolimus and 7 patients (18%) received only 1 cycle. Five patients (12%) did not complete the first cycle of everolimus (received 9 days or less of everolimus) due to early progressive disease (PD). Median number of days on treatment was 42 (3–175). The reasons for treatment discontinuation were disease progression in 35 patients (87.5%), toxicity in 3 patients (7.5%; these patients withdrew their consents due to adverse events: 2 patients with neutropenia and infection after 5 and 8 cycles, respectively, and 1 patient due to fatigue and dyspnea after 1 cycle), and study protocol violation in 1 case (2.5%). 1 patient was lost to follow-up (2.5%; Table 2).

Response and survival analysis

At interim analysis (stage 1), among 21 evaluable patients for response (completed at least 1 cycle of everolimus), 7 patients had no disease progression: 6 SD and 1 PR. Because 7 patients showed disease control the criterion for continuing to the second phase was satisfied with the study continuing to the second stage of accrual. At study completion, 40 patients met protocol eligibility requirements and were considered evaluable for response. One patient (3%) had a partial response, 8 (23%) had stable disease, and 26 (74%) had disease progression. Disease control rate at 6 weeks was 26% (95% CI = 13–43). The duration of disease control ranged from 82 to 175 days with a median of 110 days. Table 3 summarizes disease control results by prior treatment history. DCR and 95% confidence intervals in patients with sensitive relapse, refractory relapse, and 2 prior regimens were 30% (10–50), 25 (0%–67), and 22% (0–41), respectively. Because this 2-stage trial successfully continued to the second stage, an internal radiological review of randomly selected patients was conducted by the University of Pittsburgh Cancer Institute and the Department of Radiology to verify response staging. The review confirmed that tumor response staging was valid and complied with RECIST.

Among 35 evaluable patients, all 35 progressed. Median time to progression was 1.3 months (95% CI = 1.4–1.4). The probability of 3 month progression-free survival was 0.14 (95% CI = 0.05–0.27). Of the 40 patients beginning the trial 36 have died. Four patients were alive at 11, 12, 16 and 21 months. Median survival was 6.7 months (95% CI = 4.0–8.6 months). The probability of 1-year survival was 0.20 (95% CI = 0.09–0.33; Fig. 1). A landmark analysis was conducted at 2 months, the approximate time of the first response evaluation, to compare survival for the patients with disease control to those without. Patients with disease control did not have significantly improved survival ($P = 0.205$).

Safety

Table 4 summarizes the most frequently reported adverse events by severity. There were no grade 4/5 toxicities that were considered drug related. Grade 3 toxicities included thrombocytopenia (2 patients), neutropenia (2), infection (2), pneumonitis (1), fatigue (1), elevated transaminases (1), hyperglycemia (2), hypercalcemia (1), diarrhea (2), and acute renal failure due to dehydration from diarrhea and...
poor oral intake (1). Of the 36 deaths reported to date, none was considered treatment-related.

Correlation with tumor biomarkers

Of the 40 patients completing the trial, 22 had sufficient quantity and quality of archival tissue for immunohistochemical staining for the expression of 6 proteins: 4E-BP1, p4E-BP1, S6K, pS6K, AKT and pAKT. A composite score was constructed for each protein (see Materials and methods). The association with overall survival was analyzed by proportional hazards regression. The first 5 proteins above were independent of overall survival (all P > 0.20). High levels of pAKT were modestly associated with overall survival with the approximately doubling of the risk of death for an increase of 1 unit in the IHC score (HR = 2.07, 95% CI = 0.97–4.43). A recursive partitioning model applied to pAKT suggested that an IHC score equal to or higher than 0.75, on the scale of 0 to 3.0 may be associated with an elevated risk of mortality. Figure 2 provides the Kaplan–Meier plot of overall survival by baseline pAKT.

Another observation is the apparent differential expression of S6K among patients with DCR versus PD as tested by IHC. S6K protein levels (alone) were significantly higher in the 6 patients with disease control versus 15 patients with PD (P = 0.0093; 2-tailed Wilcoxon test).

Discussion

This is the first phase II trial evaluating single-agent everolimus in previously treated, relapsed SCLC. One partial response was observed (in a patient with sensitive relapse), with an objective response rate of 3% (95% CI = 0–8) and an additional 8 patients had SD as best response for a DCR of 26% (95% CI = 13–43) which did not meet the prespecified criteria for sufficient activity to warrant further study of the drug in this setting. Our patients were heavily pretreated: 43% had received 1 prior regimen and were refractory or had received 2 prior regimens. In 20 sensitive relapse patients, 6 (30%; 95% CI = 10–50) exhibited disease control, including a partial response. It is possible that the benefit of everolimus may be limited to patients with sensitive relapsed SCLC.

Although 8 patients had stable disease, the duration until disease progression was relatively short. Stable disease of short duration may not be clinically meaningful. In a recent article, Vidaurre et al. (27) reviewed 143 phase II trials of cytotoxic and targeted therapies, reported in 5 journals between October 2006 and March 2008, showing that the percentage of stable disease was not positively correlated with either progression-free or overall survival. Conversely, the overall response rate (complete plus partial responses) was strongly correlated with both survival endpoints.

Table 3. Objective response results

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Response duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (23)</td>
</tr>
<tr>
<td>PD</td>
<td>26 (74)</td>
</tr>
</tbody>
</table>

**Table 3. Objective response results**

<table>
<thead>
<tr>
<th>Response according to prior treatment</th>
<th>1 prior regimen/sensitive (n = 20)</th>
<th>1 prior regimen/refractory (n = 4)</th>
<th>2 prior regimens (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>1 (5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>5 (25%)</td>
<td>1 (25%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>PD</td>
<td>14 (70%)</td>
<td>3 (75%)</td>
<td>9 (82%)</td>
</tr>
</tbody>
</table>

NOTE: There were 35 evaluable patients. Evaluable for response means the patient had completed at least one cycle of therapy with everolimus.
P < 0.0001). On the other hand, Lara et al. (28) reviewed data from 984 NSCLC patients entered onto 3 randomized Southwest Oncology Group trials of platinum-based chemotherapy and reported that the DCR at week 8 is a more powerful predictor of subsequent survival than is the traditional tumor response rate in advanced NSCLC. Moreover, based on a meta-analysis of previously collected data from 42 cooperative group melanoma phase 2 trials, Korn et al. (29) proposed the use of 1-year OS or 6-month PFS rates as benchmarks for future phase II trials. Clearly, these analyses may or not apply to phase II studies in SCLC. Although an optimal endpoint for phase II trials in relapsed SCLC is yet to be defined, both objective response rates and durable stable disease should be considered when evaluating antitumor efficacy.

Another mTOR inhibitor, temsirolimus (CCI-779) has been studied in SCLC. A randomized phase II trial in patients with extensive stage SCLC tested maintenance therapy with another temsirolimus at 25 or 250 mg weekly following responsive or stable disease after induction chemotherapy (30). The median PFS for the 25 mg arm was 1.9 months (95% CI = 1.6–2.3) and for the 250 mg arm, it

### Table 4. Summary of adverse events by severity (N = 40)

<table>
<thead>
<tr>
<th>Hematologic type</th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9 (22.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (32.5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (15)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonhematologic type</th>
<th>All grades, n (%)</th>
<th>Grade 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional Fatigue</td>
<td>10 (25)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>6 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (15)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (7.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>3 (7.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Infection (without neutropenia)</td>
<td>5 (12.5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6 (15)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargy, confusion</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, pneumonitis</td>
<td>3 (7.5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine (dehydration)</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>6 (15)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Fig. 2. Overall survival by baseline pAKT. A recursive partitioning model suggests that survival may be split into 2 classes depending upon baseline pAKT with higher levels (≥0.75) portending worse outcome (P = 0.063, log rank). Numbers along the X axis are the number of patients at risk at the start of each 6-month interval.
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