A Phase I/II Study of Etanercept and Rituximab in Patients with Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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Abstract

Rituximab has modest activity in relapsed Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) but is associated with TNF-α release that can cause CLL proliferation and inhibit apoptosis. We examined whether disruption of TNF-α by etanercept improves response to rituximab in CLL. Eligible patients had previously treated CLL with performance status 0–3. Patients received etanercept 25 mg subcutaneously twice weekly (weeks 1–5) and rituximab 375 mg/m² intravenously thrice weekly (weeks 2–5) using a phase I/II design. Primary endpoints were response and toxicity. The 36 enrolled patients had a median of 2 prior treatments; 50% were fludarabine-refractory, and 22% had del(17p13.1). Of the 34 response-evaluable patients, ten (29%) responded, including 9 partial responses and 1 complete remission. Response was not affected by prior rituximab nor fludarabine-refractory status, but no patients with del(17p13.1) responded. Median PFS for responders was 9.0 months (range 1–43). Ten patients have had treatment-free intervals exceeding 12 months, including four who have remained untreated for 32, 43, 46 and 56 months. Adverse events were mild, including mild infusion reactions, transient cytopenias and grade 3 infections in 14%. The combination of etanercept and thrice weekly rituximab produces durable remissions in non-del(17p13.1) CLL patients and is well tolerated.

Keywords

Rituximab; Etanercept; chronic lymphocytic leukemia
Introduction

Chronic lymphocytic leukemia is the most common adult leukemia in the Western Hemisphere, accounting for 25% of all leukemia cases. Patients with CLL have a median age at diagnosis of 71 years with only 10% being under the age of 50. CLL patients have an increased frequency of infections, secondary malignancies, and autoimmune complications (1–3) that become more frequent as the disease progresses. Given the absence of a survival advantage with early treatment intervention, patients with low-risk early stage CLL are monitored closely without therapy until symptoms or cytopenias develop. The period before newly diagnosed asymptomatic CLL patients require therapy varies widely and is influenced to a great extent by genomic features including interphase cytogenetic abnormalities, IgV_H mutational status, ZAP-70, CD38 expression, and a variety of other biomarkers (reviewed in(4–6)). However, the presence or absence of these specific abnormalities do not influence when therapy is initiated for CLL(4).

The treatment of CLL has progressed significantly over the previous decade. While alkylator therapy was used in the past(7), randomized trials have demonstrated a higher response rate and longer progression free survival (PFS) with fludarabine(8–11) and subsequently with fludarabine and cyclophosphamide based combinations(11–13). At the same time, the chimeric anti-CD20 monoclonal antibody rituximab was introduced for the treatment of CLL. While initial studies with single agent rituximab utilizing a weekly schedule established in low grade NHL(14) demonstrated very modest activity in CLL(15–18), pharmacokinetically derived studies using a higher dose(19) or dose intensive treatment(20) improved efficacy with minimal toxicity. Nonetheless, despite dose escalation, single agent rituximab failed to achieve complete responses (CR), and PFS was less than a year. Rituximab’s efficacy has been improved by combining rituximab with traditional cytotoxic agents such as fludarabine(21, 22) or fludarabine and cyclophosphamide(23) which have produced high CR rates and extended PFS, compared to historical controls. These chemoimmunotherapeutic approaches are clearly promising but are complicated by myelosuppression and infection. Furthermore, patients eventually relapse, and some combinations such as fludarabine, cyclophosphamide and rituximab may not be applicable to the majority of CLL patients over the age of 70. Thus, alternative treatment approaches for CLL are needed.

Tumor necrosis factor-α (TNF-α) inhibits CLL cell death by upregulating bcl-2 and other anti-apoptotic proteins and increases proliferation of CLL cells (24–28). In addition, TNF-α upregulates CD55 and CD59. Furthermore, TNF-α is one of the cytokines released as part of the infusion toxicity associated with thrice weekly rituximab. For these reasons, we hypothesized that a TNF-α blocking agent such as etanercept may be an ideal candidate to combine with rituximab in the treatment of CLL. Etanercept is a dimer of two molecules of the extracellular portion of the p75 TNF receptor that is fused to the Fc portion of type 1 human IgG1. While etanercept is mainly used in the treatment of rheumatoid arthritis, clinical trials have been performed in a variety of human diseases. In healthy volunteers exposed to endotoxin, etanercept blocked the expected cytokine release and decreased levels of TNF-α, IL-6, IL-8, G-CSF, norepinephrine, cortisol, plasminogen activator inhibitor, and tissue plasminogen activator (29). Additionally, etanercept was safely administered to
patients with hematologic malignancies, and a subset of patients, including those with CLL, experienced improvement in disease related symptoms (30).

Therefore, we initiated a phase I/II clinical study to add etanercept to thrice weekly rituximab, to test the hypothesis that blocking TNF-α with etanercept would diminish initial infusion toxicity and improve response rate and response duration.

**Patients and Methods**

**Patient Selection**

Eligible patients had CLL/SLL by NCI 1996 criteria, (31) had relapsed after prior therapy, had active disease requiring treatment by NCI 1996 criteria, and expressed CD20 on their CLL cells. Patients had to be greater than 18 years of age and have an ECOG performance status of 0–3. Exclusion criteria included pregnancy, breast-feeding, renal or hepatic dysfunction, prior alemtuzumab treatment, active infection, concurrent immunosupression, history of demyelinating disease, active viral hepatitis, or uncontrolled diabetes. Patients had to be capable of providing informed consent. After the first 19 patients were accrued, an interim analysis of our previous thrice weekly rituximab study (20, 32) and this trial demonstrated that there were no responses among 14 patients with del(17p13.1). Since the likelihood of response in del(17p13.1) patients was estimated to be <5%, further accrual was limited to patients without del(17p13.1).

**Study Design**

Prior to study initiation, patients underwent screening for eligibility, assessment of measurable disease by computed tomography (CT) scans, and bone marrow biopsy. All patients received etanercept at a dose of 25 mg subcutaneously twice weekly (weeks 1–5). The third dose was administered 1 hour prior to the first dose of rituximab. Patients received rituximab 375 mg/m² intravenously (IV) three times weekly during weeks 2–5. The first rituximab dose was given as a 100 mg IV bolus over 4 hours. Aggressive monitoring for infusion toxicity was performed, and infusion was held temporarily for tachycardia, hypotension, hypoxia, or bronchospasm.

**Interphase Cytogenetics**

Pretreatment samples were obtained, and 1 × 10⁶ cells/mL were isolated using methods previously described. (33) Slides for fluorescent in situ hybridization (FISH) were made by hybridizing probes for del(17)(p13.1), del(13)(q14.3), del(11)(q22.3), del(6)(q21), and centromere 12. Interphase cytogenetics were prioritized utilizing the Döhner criteria (34) utilizing methods previously published by our group (33).

**FcγR Polymorphism expression analysis**

In patients who consented, Fcγ receptor polymorphism were analyzed to determine whether specific Fcγ receptor polymorphisms correlated with response to therapy. DNA was extracted using QIAamp kits according to the manufacturer’s instructions (Qiagen, Valencia, CA). A nested PCR strategy was performed to assess FcγRIIIa and FcγRIIa polymorphisms as previously described (35).
Response Assessment

Criteria for response utilized the 1996 Revised NCI-sponsored Working Group Guidelines. Adverse events were recorded using the NCI CTC version 2.0. Following completion of therapy, patients were followed every 3 months until relapse as defined by the NCI 1996 criteria. (31)

Statistical Considerations

The primary endpoints of this study were to determine the toxicity and efficacy of the combination of etanercept and rituximab in patients with CLL/SLL and to determine the frequency and severity of adverse events. The overall study design was an abbreviated 6-patient phase I evaluation to ensure that the maximum tolerated dose had not been exceeded. If fewer than two of the initial six patients experienced dose limiting toxicity, the study would proceed to a two-stage phase II evaluation. For the phase II study, a Mini-max two-stage design of Simon (36) was used with an alpha of 0.10 and beta of 0.10, resulting in a trial with two stages and decisions to continue after 19 and 36 response-evaluable patients. The regimen would be considered ineffective or uninteresting if the PR + CR rate was <20%. The regimen would be considered worthy of further study if the PR + CR rate was >40%. Responses intermediate between this would be judged in the context of toxicity and other endpoints such as remission duration associated with therapy. If fewer than 4 PR + CR were seen during the first 19 patients, the study would be terminated; otherwise, the study would accrue to 36 patients.

In the final data analysis, time to next treatment (TTNT) was determined from the date of treatment completion to the date of the next CLL treatment. Progression free survival (PFS) was calculated from the date of treatment completion to disease progression. Overall survival (OS) was determined from the date of treatment completion to death from any cause or censored at the date of last contact. Actuarial TTNT, PFS and OS were estimated using the method of Kaplan-Meier. Other correlations with response to therapy were performed using Fisher’s two-sided exact test.

Results

Patient Demographics

After providing informed consent, 36 patients with CLL/SLL were enrolled in this Institutional Review Board-approved phase I/II study between November 2002 and June 2006. Patient demographics are outlined in table 1. All had received prior therapy, with a median of 2 prior treatment regimens. Twenty-six patients (72%) had received rituximab previously. They had intermediate-risk Rai stage I–II (47%) or high-risk Rai stage III–IV (53%) disease, and 50% were refractory to fludarabine therapy as defined previously. All patients had baseline cytogenetics performed, and 50% had high-risk cytogenetic abnormalities, including del(17p13.1) (22%), del(11q22.3) (14%), or complex karyotype (14%).
Treatment Administered

Thirty-three of 36 patients received the full 5-week treatment course. Three patients did not complete the entire treatment course due to toxicity or disease progression. These withdrawals occurred during week 1, 2, and 5.

Response and Progression Free Survival

Thirty-four of 36 patients were evaluable for response. Response data are outlined in Table 2. Ten patients responded (29%) including nine partial responses (PR) and 1 CR. In addition, 19 patients (56%) had stable disease, and 5 patients (15%) had progressive disease. Forty-one percent of Rai stage I–II patients responded to therapy, whereas only 18% of Rai stage III–IV patients responded. Twenty-eight percent of fludarabine-refractory patients responded to treatment. Two of 10 rituximab-naïve patients (20%) responded, and 33% of patients who had received rituximab previously responded. Two of four patients with trisomy 12 achieved a PR, and a third patient had stable disease. None of eight patients with del(17p13.1) and only 1 of five patients with del(11q22.3) responded to treatment. The response rate for patients without del(11q22.3) or del(17p13.1) was 43%.

Median PFS for the 10 responding patients was 9.0 months (95% CI, 5–18) as outlined in Figure 1. TTNT for responders and non-responders is outlined in Figure 2. Median TTNT for the 10 responding patients was 14.5 months (range 4–56 months, 95% CI, 10 to not estimable), compared to 3 months (95% CI, 2–6) for non-responders. Eight of 10 responders relapsed and received further therapy, but two responders have not required additional treatment, with follow-up of 43 and 56 months respectively. Two additional patients who had stable disease have not required additional treatment, with follow-up of 32 and 46 months since treatment. In all, ten patients who responded or had stable disease did not require therapy for more than 12 months after study completion. Overall survival is shown in Figure 3; median OS for responders was 53 months (95% CI, 24 to not estimable), compared to 42 months (95% CI, 15 to 64) for non-responders.

Adverse Events

Adverse events were generally mild and did not require cessation of therapy except in three patients described below. A full listing of adverse events is outlined in Table 3. As previously described, the most common adverse effects associated with rituximab therapy were infusion reactions and hematologic toxicity.

Three patients did not complete therapy. One patient withdrew after the first dose of etanercept, without any adverse event or early disease progression, and did not receive any rituximab. A second patient began the study with pancytopenia and ANC <500, experienced infectious complications, elected to enroll in hospice, and did not complete treatment. A third patient was removed from the study for grade 4 thrombocytopenia, which was felt to be ITP, resolved with steroid therapy, and has not recurred.

Infusion reactions were noted in 39% of patients. These reactions were all grade 1 or grade 2, and none limited therapy. Hematologic toxicity was similar to that previously observed with thrice weekly rituximab therapy. Grade 3/4 anemia was seen in 3% of patients,
thrombocytopenia in 19%, and neutropenia in 33%. Two of three patients having a pre-treatment platelet count of 50 × 10^9/L or less developed grade 4 thrombocytopenia. In contrast, only two of 32 patients with platelet counts > 50 × 10^9/L developed grade 4 thrombocytopenia. Thrombocytopenia was not associated with bleeding but four patients required platelet transfusion. Recovery of platelets was seen in those patients who did not have disease progression. As with thrombocytopenia, neutropenia was generally transient unless related to disease progression. For the most part, the neutropenia was not associated with increased risk of infections, with 11% of patients experiencing grade 3 neutropenic infections (one-third of patients with grade 3 or 4 neutropenia), and 6% experiencing grade 3 non-neutropenic infections. No grade 4 or grade 5 infections were reported. No opportunistic infections were observed.

**FcγR IIIa and IIa Genotype and Response to Therapy**

Previous reports suggested that Fcγ receptor IIIa and IIa polymorphisms are important for the *in vivo* efficacy of rituximab in lymphoma(35, 39) and that response to rituximab is modulated by Fcγ receptor polymorphisms and the resulting variations in IgG1 binding affinity. Therefore, we attempted to correlate anti-tumor responses with FcγR IIIa and IIa polymorphisms, and the results are outlined in Table 2. While the proportion of patients with each genotype was similar to that previously reported(35, 39, 40), we noted no correlation of FcγR polymorphism with response or PFS.

**Discussion**

This trial demonstrates that the combination of etanercept and thrice weekly rituximab is clinically effective and produces a durable response in relapsed CLL patients who do not have del(11q22.3) or del(17p13.1). This regimen is effective even in patients who have failed rituximab and/or refractory to fludarabine. The most dramatic responses were observed in patients with intermediate risk disease, who were less refractory to therapy, and who had not acquired del(11q22.3) or del(17p13.1). The addition of etanercept to rituximab did not appear to confer significant response benefit over what we previously observed in our trial of single agent thrice weekly rituximab. (20) However, the duration of response and TTNT appeared to be improved by the addition of etanercept. The durability of responses seen in this trial is encouraging, as two of ten patients with partial responses as well as 2 patients with stable disease have not required further treatment for 32, 43, 46, and 56 months, respectively. Furthermore, median OS was 53 months for responders and 42 months for non-responders, suggesting improved outcome compared to historical controls examining cytotoxic based therapies. However, this OS benefit may also reflect improved salvage therapies for patients who received additional treatment after they failed etanercept and rituximab. The only true way to determine the benefit of adding entanercept to rituximab monotherapy is to perform a randomized phase II trial. While the addition of etanercept did not improve the response rate, the number of extended remissions and treatment-free intervals in this study suggests that such a randomized study of entanercept with rituximab may be reasonable in elderly patients who may not be appropriate candidates for aggressive chemoimmunotherapy. Alternatively, such a trial could be conducted using...
one of the newer, alternative anti-CD20 antibodies with potentially improved features such as increased IgG1 binding for low affinity FeR polymorphisms.

The addition of etanercept appeared to mitigate infusion toxicity to rituximab, as we had hypothesized might be the result of blocking TNF-α. In our previous study with thrice weekly rituximab,(20) infusion toxicity was common with 61% of patients experiencing a reaction during the first infusion of rituximab and 7% experiencing grade 3–4 adverse events. In comparison, only 39% of patients in this study experienced an infusion reaction, and there were no grade 3 or grade 4 infusion reactions. This absence of significant infusion toxicity may allow a small subset of patients to avoid significant early morbidity that can be observed with rituximab.(41–43) Again, elderly patients, who constitute the majority of CLL patients in the community, may benefit the most from this reduction in infusion toxicity by the addition of etanercept to rituximab monotherapy.

The observed non-infusion toxicity with rituximab and etanercept was acceptable. Grade 3–4 adverse events were rare and, as expected, were mainly limited to hematologic toxicity. Hematologic toxicity was not significantly different from that previously described with thrice weekly rituximab(20). Infectious adverse events were also rare and generally mild, with most infections not associated with neutropenia and no grade 4–5 infections. None of the adverse events were treatment limiting. In addition, we did not observe any opportunistic infections with this regimen. An acceptable toxicity profile may make this an ideal regimen for patients who would not tolerate standard fludarabine-based therapy, especially the elderly or those with poor performance status.

As part of this study, we sought to examine clinical and biologic features associated with response to therapy. Previous clinical trials with chlorambucil (44), fludarabine/rituximab(33), and fludarabine/cyclophosphamide(45) demonstrated that select interphase cytogenetic abnormalities predict response to therapy or PFS. In this study we noted low response rates and a corresponding short TTNT in patients with del(17p13.1) and del(11q22.3). In contrast, patients with fewer prior treatments and more favorable interphase cytogenetic abnormalities such as del(13q14) and trisomy 12 responded favorably. These results suggest that future studies of this regimen or its permutations should occur in patients who are not heavily pretreated and those without high risk genomic features. However, this regimen appeared to be effective in fludarabine-refractory patients, whose expected survival is less than 12 months. Thus, etanercept and rituximab may be a potential treatment for patients who are refractory to fludarabine and may not be candidates for alemtuzumab therapy.

Previous studies in follicular lymphoma have demonstrated that response and PFS correlate with specific FcγR receptor IIIa and IIa polymorphisms that enhance IgG1 antibody engagement. Our previous study with thrice weekly rituximab did not suggest that response correlates with Fcγ receptor polymorphisms, in contrast to what has been reported in follicular NHL.(46) The results of this study similarly demonstrate that FcγR status does not predict response to rituximab in CLL. These data collectively suggest that alternative mechanisms of tumor clearance other than ADCC contribute to CLL tumor clearance by rituximab.

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In conclusion, the combination of etanercept and thrice weekly rituximab is effective and produces durable responses in a subset of patients. This combination is well tolerated, with generally mild hematologic and infectious toxicities. The addition of etanercept may lessen the infusion toxicity associated with rituximab, but a larger randomized study is required to answer this question definitively. Although clinical responses were not seen in del(17p13.1) patients and only one del(11q22.3) patient, this regimen was clinically active in fludarabine-refractory patients and attained longer response durations and treatment-free intervals than were observed with rituximab monotherapy historically. Thus, this regimen may be worthy of further investigation, perhaps in those populations who are not candidates for more aggressive therapies, such as alemtuzumab or chemoimmunotherapy regimens, or who may be particularly susceptible to infusion toxicity from rituximab monotherapy.

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Figure 1.
Progression free survival among responding patients attaining a complete (CR) or partial (PR) response to therapy.
Figure 2.
Time to next treatment, among all patients receiving therapy as part of this trial. Median time to next treatment for responders was 14.5 months compared to 3 months for non-responders.
Figure 3.
Overall Survival among patients receiving therapy as part of this trial. The median overall survival for responders was 53 months compared to 42 months for non-responders.
Table 1

Patient Demographics

| Characteristic                        | Number (%) |
|---------------------------------------|------------|
| Total patients                        | 36         |
| Age                                   |            |
| Median                                | 59.5       |
| Range                                 | 30–79      |
| Gender                                |            |
| Female                                | 11 (31%)   |
| Male                                  | 25 (69%)   |
| Risk Category                         |            |
| Intermediate (Rai stage I–II)         | 17 (47%)   |
| High (Rai stage III–IV)               | 19 (53%)   |
| Number of Prior Treatments            |            |
| Median                                | 2          |
| Range                                 | 1–8        |
| Previous Rituximab                    | 26 (72%)   |
| Fludarabine Refractory                | 18 (50%)   |
| Favorable Cytogenetics                |            |
| del13q only                           | 9 (25%)    |
| Hgh-Risk Cytogenetics                 |            |
| del 17p                               | 8 (22%)    |
| del 11q                               | 5 (14%)    |
| Complex karyotype                     | 5 (14%)    |
Table 2

Response and Duration by Pre-treatment Demographics

| Characteristic                  | CR + PR | SD  | PD  | Median Time to Next Treatment in Months (range) |
|--------------------------------|---------|-----|-----|-----------------------------------------------|
| All Patients                   | 29%     | 56% | 15% | 6.5 (1–56)                                    |
| **Risk Category**              |         |     |     |                                               |
| Intermediate Risk Disease      | 41%     | 47% | 12% | 9.25 (1–56)                                   |
| High Risk Disease              | 18%     | 65% | 18% | 3.7 (1–35)                                    |
| **Previous Therapy**           |         |     |     |                                               |
| Prior Rituximab                | 33%     | 46% | 21% | 4.1 (1–35)                                    |
| Fludarabine Refractory         | 28%     | 50% | 22% | 4 (1–15)                                      |
| ≤2 prior regimens              | 27%     | 55% | 18% | 8.6 (1–56)                                    |
| >2 prior regimens              | 33%     | 58% | 8%  | 4 (1–20)                                      |
| **Baseline Cytogenetics**      |         |     |     |                                               |
| del (17p13.1)                  | 0%      | 100%| 0%  | 4 (1–52)                                      |
| del(11q22.3)                   | 20%     | 60% | 20% | 3.8 (1–7)                                     |
| trisomy 12                     | 50%     | 25% | 0%  | 11 (9–13)                                     |
| **FcγR status**                |         |     |     |                                               |
| FcγIIla V/V (n=3)              | 33%     | 33% | 33% | 2 (1–15)                                      |
| FcγIIla V/F (n=12)             | 42%     | 50% | 8%  | 9.6 (3.5–56)                                  |
| FcγIIla F/F (n=13)             | 31%     | 54% | 33% | 4.8 (1–52)                                    |
| FcγIIla His/His (n=8)          | 38%     | 63% | 33% | 4 (1–56)                                      |
| FcγIIla His/Arg (n=13)         | 46%     | 31% | 23% | 7.6 (1–52)                                    |
| FcγIIla Arg/Arg (n=7)          | 14%     | 71% | 14% | 4 (1–17)                                      |
| **Response**                   |         |     |     |                                               |
| Responders (CR+PR)             |         |     |     | 12.3 (4–56) \(^1\)                           |
| Stable Disease                 |         |     |     | 5.1 (1–46) \(^2\)                            |
| Progressive Disease            |         |     |     | 2 (1–3)                                       |

\(^1\) Includes 2 patients who have not required treatment for 43+ and 56+ months respectively

\(^2\) Includes 2 patient who have not required treatment for 32+ and 46+ months respectively

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### Table 3

| Adverse Event     | Grade 1 | %  | Grade 2 | %  | Grade 3 | %  | Grade 4 | %  |
|-------------------|---------|----|---------|----|---------|----|---------|----|
| Infusion rxn      | 5       | 14 | 9       | 26 |         |    |         |    |
| Heme              |         |    |         |    |         |    |         |    |
| Anemia            | 17      | 48 | 3       | 9  | 1       | 3  |         |    |
| Thrombocytopenia  | 6       | 17 | 9       | 25 | 3       | 9  | 4       | 11 |
| Neutropenia       | 7       | 20 | 7       | 20 | 7       | 20 | 5       | 14 |
| Coagulopathy      |         |    |         |    | 1       | 3  |         |    |
| Infectious        |         |    |         |    |         |    |         |    |
| With neutropenia  |         |    |         |    | 4       | 11 |         |    |
| Without neutropenia|       | 10 | 28      | 2  | 6       |    |         |    |
| General           |         |    |         |    |         |    |         |    |
| Fatigue           | 6       | 17 | 1       | 3  | 1       | 3  |         |    |
| Myalgias          | 3       | 9  |         |    |         |    |         |    |
| Fever             | 3       | 9  | 1       | 3  |         |    |         |    |
| Chills            | 1       | 3  |         |    |         |    |         |    |
| Pruritis          | 1       | 3  |         |    |         |    |         |    |
| Edema             | 2       | 6  |         |    |         |    |         |    |
| Pain (various locations) | 1 | 3  | 2   | 6 |         |    |         |    |
| Rash              | 1       | 3  |         |    |         |    |         |    |
| Rhinitis/rhinorrhea|     | 1  | 3    |    |         |    |         |    |
| CV                |         |    |         |    |         |    |         |    |
| HTN               | 1       | 3  |         |    |         |    |         |    |
| Chest pain        | 1       | 3  |         |    |         |    |         |    |
| Autoimmune        |         |    |         |    |         |    |         |    |
| ITP               |         |    |         |    | 1       | 3  |         |    |
| Pulm              |         |    |         |    |         |    |         |    |
| Cough             | 2       | 6  | 2       | 6  |         |    |         |    |
| Dyspnea           |         |    |         |    | 1       | 3  |         |    |
| Adverse Event          | Grade 1 | %   | Grade 2 | %   | Grade 3 | %   | Grade 4 | %   |
|------------------------|---------|-----|---------|-----|---------|-----|---------|-----|
| pulm hemorrhage        |         |     |         |     |         |     |         |     |
| GI                     |         |     |         |     |         |     |         |     |
| Nausea                 | 5       | 14  | 2       | 6   | 1       | 3   |         |     |
| Diarrhea               | 1       | 3   |         |     |         |     |         |     |
| Constipation           | 4       | 11  | 5       | 14  |         |     |         |     |
| abd pain               | 2       | 6   | 1       | 3   |         |     |         |     |
| abnormal LFTs          | 6       | 17  | 1       | 3   | 1       | 3   |         |     |
| inc amylase            | 1       | 3   |         |     |         |     |         |     |
| Dysphagia              | 1       | 3   |         |     |         |     |         |     |
| Anorexia               |         |     |         |     |         |     |         |     |
| dec albumin            | 3       | 9   | 1       | 3   |         |     |         |     |
| Neuro                  |         |     |         |     |         |     |         |     |
| HA                     | 5       | 14  |         |     |         |     |         |     |
| Dizziness              | 1       | 3   |         |     |         |     |         |     |
| Confusion              |         |     |         |     | 1       | 3   |         |     |
| Palsy                  |         |     |         |     | 1       | 3   |         |     |
| Renal                  |         |     |         |     |         |     |         |     |
| increased Cr           | 2       | 6   |         |     |         |     |         |     |
| Hyponatremia           | 1       | 3   |         |     |         |     |         |     |
| Endo                   |         |     |         |     |         |     |         |     |
| Hyperglycemia          | 10      | 28  | 9       | 25  |         |     |         |     |
| Chemistry Abnormality  |         |     |         |     |         |     |         |     |
| inc uric acid          | 1       | 3   |         |     |         |     |         |     |
| hypomagnesuemia        | 1       | 3   |         |     |         |     |         |     |
| Hypocalcemia           | 4       | 11  | 1       | 3   |         |     |         |     |
| hypophosphatemia       | 2       | 6   |         |     |         |     |         |     |
| Hypokalemia            | 1       | 3   |         |     |         |     |         |     |