ADDITIONAL FILE 2

Supplemental Table 1 Definition of a DLT

Non-hematologic toxicity
• Grade 4 (life-threatening) vomiting or diarrhea
• Grade 4 electrolyte abnormality
• Grade 4 systemic reaction
• Any grade ≥3 non-hematologic toxicity, except for the following:
  ○ Transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms.
  ○ Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours.
  ○ Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids and that resolves to grade 1 within 14 days.
  ○ An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity.
  ○ Asymptomatic changes in lipid profiles.
  ○ Singular or non-fasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on two separate occasions).
  ○ Immune-related adverse events of grade 3 or higher that improve to grade ≤1 in <5 days by appropriate care or with corticosteroid therapy.

Hematologic toxicity • Grade ≥3 thrombocytopenia, with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia of any duration. • Grade 4 neutropenia lasting >3 days. • Grade ≥3 febrile neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L and fever >101°F/38.5°C).

• Grade 4 neutropenia that does not recover to grade ≤2 in ≤3 days after interrupting study drug. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
General • Patients being unable to receive ≥75% of study drug doses during the DLT observation period because of toxicity, even if the toxicity does not meet the DLT criteria defined above. Note: Exceptions include the DLT exclusions mentioned above.
Maximum tolerated dose • One dose level below that at which at least one-third of patients in a particular cohort have DLTs. DLT will be defined as the occurrence of any of the toxicities in ***this table*** occurring up to and including study day 21.

3 DLT, dose-limiting toxicity.

4