DOSE LIMITING TOXICITIES (DLT)

Example:
Dose escalation will proceed within each cohort according to the following scheme.

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter at least 3 more subjects at this dose level. If 0 of these 3 subjects experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the maximum tolerated dose (MTD). At least 6 subjects must be entered at the maximum tolerated dose.

Example:
Dose limiting toxicity will be defined as any of the following AEs considered possibly related to [Agent X] that occur any time from the initial dose of study treatment of [Agent X] in combination with [Agent Y] and [Agent X], with severity graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

Hematologic Toxicity:
Example:
- Grade 4 ANC, hemoglobin, or platelets.

Note: Grade 4 lymphocytes should be recorded, but is not dose limiting.

Example:
A hematologic toxicity is defined as neutropenia, anemia, leukopenia, lymphopenia, and/or thrombocytopenia. Number 3 and 4 above are classified as a DLT since this toxicity would be abnormal for this subject population.

Non-Hematologic Toxicity:
Example:

- Any treatment related Grade 3 or higher non-hematologic toxicity except elevations in gamma-glutamyltransferase (GGT)

GENERAL DLT SECTION EXAMPLES;

Example:
DLT is any treatment related:

1. Any ≥ Grade 4 non-hematologic toxicity with the exception of nausea and vomiting (if manageable with supportive care measures), alopecia, drug-related fever, and toxicities secondary to neutropenia and sepsis
2. Any ≥ Grade 3 neurologic toxicity (sensory or autonomic)
3. Grade 4 platelet count (less than 25,000/mm^3) 50 days beyond the start of the most recent chemotherapy (not related to recurrent leukemia)
4. Grade 4 neutropenia 50 days beyond the start of the most recent chemotherapy (not related to recurrent leukemia)
5. Any grade 3 non-hematologic toxicity (excluding toxicities such as alopecia or toxicities secondary to neutropenia and sepsis) that did not resolve to grade 2 by 45 days beyond the start of the most recent chemotherapy.

A subject who dies from leukemia or a recognized complication of the illness and its treatment (such as sepsis) will not be considered a DLT. This subject will need to be replaced.

Infections due to neutropenia (including pneumonia with respiratory failure, hypotension with renal failure, and death) when clearly secondary to sepsis up to 45 days after the start of treatment will not be considered DLTs. Because hyperbilirubinemia, anorexia, and fatigue are common toxicities associated with standard induction chemotherapy for AML, the following are redefined as not being DLT events: (1) anorexia requiring total parenteral nutrition (TPN); (2) fatigue requiring bed rest; (3) grade 2, 3, and 4 hyperbilirubinemia will be redefined as 1.5-<10 x ULN, 10.0-20.0 x ULN, and > 20 x ULN respectively.

Example:
A dose limiting toxicity (DLT) is defined as any of the following [Agent X]-related adverse event (AE) that occurs during the DLT period, graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

• Grade 4 neutropenia lasting ≥ 7 days;
• Grade 3 or 4 neutropenia complicated by fever ≥ 38.0°C or infection;

Dose Limiting Toxicities (DLT)

- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia;
- Grade ≥ 3 AST/ALT elevation [exceptions may be made for transient (e.g. lasting < 7 Days) Grade 3 elevations of ALT/AST in the presence of known liver metastases and without evidence of other hepatic injury, if agreed by the Principal Investigator]
- Grade ≥ 2 AST/ALT elevation and Grade ≥ 2 bilirubin elevation [exceptions may be made for transient (e.g. lasting < 7 days) elevations of ALT/AST and bilirubin in the presence of known liver metastases without evidence of other hepatic injury, if agreed upon by the treating physician and the Principal Investigator]; and/or
- Grade 3 or 4 non-hematologic toxicity (excluding fatigue or anorexia lasting < 7 days, or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care).

Dose Limiting Toxicities (DLT)