Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema.

All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.

Please consider dosing formulation when calculating dose modifications for ORAL agents.

Dose modifications/treatment delays may be presented separately or together as appropriate.

The following table format is provided as an example and should be modified as appropriate for your protocol:

Dose Level	**Name of Agent (schedule)**	**Name of Agent (schedule)**	**Name of Agent (schedule)**	**Name of Agent (schedule)**
Level 1 (starting dose)	____ mg	____ mg	____ mg	____ mg
Level -1 (reduction)	____ mg	____ mg	____ mg	____ mg
Level -2 (reduction)	____ mg	____ mg ____ mg	____ mg	____ mg
Level -3 (reduction)	____ mg	____ mg	____ mg	____ mg

Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use as appropriate. In addition, for your convenience, a blank dose modification table has been provided. Note in the text that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Event Name	**Nausea**	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose	Hold until ≤ Grade 1. Resume at same dose

	level.	level.
Grade 3	Hold * until < Grade 2. Resume at one dose level lower, if indicated. **	Hold * until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Event Name	**Vomiting**	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Event Name	**Diarrhea**	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Event Name	**Neutropenia**	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Insert any recommended management guidelines, if appropriate.		

Event Name	**Thrombocytopenia**	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Insert any recommended management guidelines, if appropriate.		

Example of Dose Modification Table:

Event Name	***Name of Event***	
Grade of Event	**Management/Next Dose for Name of Agent**	**Management/Next Dose for Name of Agent**
≤ Grade 1	*Insert appropriate management guidelines in this column.*	*Insert appropriate management guidelines in this column.*
Grade 2		
Grade 3		
Grade 4		
**Footnote any relevant guidelines regarding how long a delay in therapy is allowed before patients should go off protocol therapy.* ***Footnote any relevant guidelines regarding how many dose reductions are allowed before patients should go off protocol therapy.*		
Insert any recommended management guidelines, if appropriate.		

Examples:

Hematologic Toxicity
On the day of starting each cycle, neutrophil and platelet hematologic parameters must have resolved to baseline or grade 1. If these criteria are not met, therapy will be held by 1 week increments for a maximum of 4 weeks. If treatment cannot be given during that time frame the patient will be removed from study.

Any grade IV hematologic (neutropenia, anemia, and thrombocytopenia) toxicity will result in a dose reduction. In the event of ANC nadir <500/mm3, hemoglobin <6.5g/dL, or platelets nadir <25,000/mm3, reduce the fludarabine to 25 mg/m2 administered only on days 1-3. Treatment can resume after allowing recovery to the pre-treatment criteria.

Should the patient develop a recurrent grade 4 hematologic toxicity, a 2nd dose reduction to fludarabine 15 mg/m2 administered only on days 1-3 will be required. Treatment can resume after allowing recovery to the pre-treatment criteria assuming that fludarabine and methoxyamine administration has not been delayed for more than 4 weeks. Otherwise, the study drugs must be discontinued (see Criteria for Discontinuation of Study Drug, section ___.)

Non-Hematologic Toxicity
Grade III/IV non-hematologic toxicity (except fatigue, or anorexia lasting < 7 days or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care) that is drug related must return to a grade 1 or better. If these criteria are not met, therapy will be held by 1 week increments for a maximum of 4 weeks. If

treatment cannot be given during that time frame the patient will be removed from study. Following resolution of the toxicity to grade 1 or better, toxicities deemed related to fludarabine will require dose reduction to 25 mg/m2 x3d. For toxicities felt to be related to methoxyamine, dose reduction to 1 dose level lower is required for further therapy. In the case of recurrence of the specific grade III/IV non-hematologic toxicity, the patient should be removed from study.
All scheduled visits will have a ±3-day window with the exception of cycle 1 week 1 given the need for exact timing of correlative studies.

Examples for Radiotherapy:

Radiotherapy Dose Modifications for In-field Non-Hematologic Toxicities

Radiation treatment will be interrupted for grade 4 in-field toxicity and/or grade 4 neutropenia with fever.

Aggressive supportive care is encouraged throughout the course of radiotherapy. If the patient is near completion of therapy, then every attempt should be made to complete treatment despite acute toxicity. Otherwise, treatment should be restarted when the accompanying toxicity declines to ≤ grade 2.

If treatment is interrupted for more than 3 weeks due to non-hematologic toxicity, remove the patient from protocol treatment.

Provide a treatment modification table for In-Field Non-Hematologic Toxicities