SUPLEMMENTAL MATERIAL

Dosage Modification Based on Adverse Events

1- POMALIDOMIDE

Pomalidomide Dose Reduction Steps	
Starting Dose	**4 mg PO daily on days 1 through 21 every 28 days**
Dose Level -1	Decrease to 3 mg PO daily on days 1 through 21 every 28 days
Dose Level -2	Decrease to 2 mg PO daily on days 1 through 21 every 28 days
Dose Level -3	Decrease to 1.5 mg PO daily on days 1 through 21 every 28 days
Dose Level -4	Decrease to 1.0 mg PO daily on days 1 through 21 every 28 days
Dose Level -5	Decrease to 0.5 mg PO daily on days 1 through 21 every 28 days
Dose Level -6	Discontinue

Dose Modification for Pomalidomide (Based on Pomalidomide-Related Adverse Event Observed on Days 2-28)		
ADVERSE EVENT/SYMPTOMS	**Day 2-14 of Cycle**	**≥Day 14 of Cycle**
≥ Grade 3 Febrile neutropenia or Grade 4 Neutrophil Count Decreased	• Omit pomalidomide. Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose.
≥ Grade 4 Platelet Count Decreased	• Omit pomalidomide. Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle • Hold anticoagulation for platelet count < 50,000	• Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose. • Hold anticoagulation for platelet count < 50,000
Erythroderma Grade 3 Grade 4	• If Grade 3 Omit pomalidomide. Follow weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle • Discontinue all study drugs and go to event monitoring.	• Omit pomalidomide for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart next cycle at next lower dose. • Discontinue all study drugs and go to event monitoring.

Grade 1-3 Rash maculo-papular	• Omit pomalidomide and bortezomib for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart at next lower dose level on next cycle.	• Omit pomalidomide and bortezomib for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart at next lower dose level on next cycle.
Grade 3-4 Stevens-Johnson syndrome	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
≥ Grade 3 Erythema multiforme	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Peripheral motor neuropathy Or Peripheral sensory neuropathy Grade 3	• If Grade 3 Omit pomalidomide. Follow weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose.
Grade 4	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Sinus bradycardia/other cardiac arrhythmia Grade 2	• Omit pomalidomide. Follow at least weekly. • If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle	• Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose.
Grade 3	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Allergic reaction Grade 2-3	• Omit pomalidomide. Follow at least weekly. • If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle	• Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose.
Anaphylaxis Grade 4	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Constipation Grade 1-2	• Initiate bowel regimen and maintain dose level.	• Initiate bowel regimen and maintain dose level.
≥ Grade 3	• If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose.
Thromboembolic event ≥ Grade 3	• Omit pomalidomide and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit pomalidomide for remainder of cycle and start anticoagulation. Begin next cycle at physician discretion (maintain dose level).

Other Non-hematologic adverse events Assessed as POMALIDOMIDE-Related ≥ Grade 3	• Omit pomalidomide. Follow at least weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose.
≥ Grade 2 Hyperthyroidism or Hypothyroidism	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide next cycle (decrease dose by one dose level).	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide next cycle (decrease dose by one dose level).

2- BORTEZOMIB

Bortezomib Dose Reduction Steps			
Starting Dose	**1.3 mg/m^2**	**1.0 mg/m^2**	**0.7 mg/m^2**
Dose Level -1	Decrease to 1.0 mg/m^2 IV daily on days 1,8,15,22 every 28 days	Decrease to 0.7 mg/m^2 IV daily on days 1,8,15,22 every 28 days	Decrease to 0.3 mg/m^2 IV daily on days 1,8,15,22 every 28 days
Dose Level -2	Decrease to 0.7 mg/m^2 IV daily on days 1,8,15,22 every 28 days	Decrease to 0.3 mg/m^2 IV daily on days 1,8,15,22 every 28 days	Discontinue
Dose Level -3	Decrease to 0.3 mg/m^2 IV daily on days 1,8,15,22 every 28 days	Discontinue	
Dose Level -4	Discontinue		

Dose Modification for Bortezomib (Based on Bortezomib-Related Adverse Event Observed on Days 2-21)		
ADVERSE EVENT/SYMPTOMS	**Day 2-14 of Cycle**	**≥Day 14 of Cycle**
≥ Grade 3 Febrile neutropenia or Grade 4 Neutrophil Count Decreased	• Omit bortezomib. Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose.

≥ Grade 4 Platelet Count Decreased	• Omit bortezomib. Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 11 • Hold anticoagulation for platelet count < 50,000	• Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. • Hold anticoagulation for platelet count < 50,000
Erythroderma Grade 3 Grade 4	• If Grade 3 Omit bortezomib. Follow weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle • Discontinue all study drugs and go to event monitoring.	• Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. • Discontinue all study drugs and go to event monitoring.
Grade 1-3 Rash maculo-papular Grade 3-4 Stevens-Johnson syndrome	• Omit pomalidomide and bortezomib for remainder of cycle. Restart at next lower dose level on next cycle. • Discontinue all study drugs and go to event monitoring.	• Omit pomalidomide and bortezomib for remainder of cycle. Restart at next lower dose level on next cycle. • Discontinue all study drugs and go to event monitoring.
≥ Grade 3 Erythema multiforme	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Peripheral motor neuropathy Or Peripheral sensory neuropathy Grade 3 Grade 4	• If Grade 3 Omit bortezomib. Follow weekly. • If the adverse event resolves to ≤ grade 1 or baseline grade and restart at next lower dose level and continue the cycle • Discontinue all study drugs and go to event monitoring.	• Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. • Discontinue all study drugs and go to event monitoring.
Sinus bradycardia/ other cardiac arrhythmia Grade 2 Grade 3	• Omit bortezomib. Follow at least weekly. • If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle • Discontinue all study drugs and go to event monitoring.	• Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose. • Discontinue all study drugs and go to event monitoring.

Allergic reaction Grade 2-3	• Omit bortezomib. Follow at least weekly. • If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle	• Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose.
Anaphylaxis Grade 4	• Discontinue all study drugs and go to event monitoring.	• Discontinue all study drugs and go to event monitoring.
Constipation Grade 1-2	• Initiate bowel regimen and maintain dose level.	• Initiate bowel regimen and maintain dose level.
≥ Grade 3	• If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose.
Thromboembolic event ≥ Grade 3	• Omit bortezomib and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit bortezomib for remainder of cycle and start anticoagulation. Begin next cycle at next lower dose.
Other Non-hematologic adverse events Assessed as bortezomib - Related ≥ Grade 3	• Omit bortezomib. Follow at least weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle	• Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose.

3- DEXAMETHASONE

Dexamethasone Dose Reduction Steps	
Starting Dose	**40 mg/day PO on days 1, 8, 15, 22. Cycles repeat very 28 days**
Dose Level -1	Decrease to 20 mg/day PO on Days 1, 8, 15, 22
Dose Level -2	Decrease to 12 mg/day PO on Days 1, 8, 15, 22
Dose Level -3	Decrease to 8 mg/day PO on Days 1, 8, 15, 22
Dose Level -4	Decrease to 4 mg/day PO on Days 1, 8, 15, 22
Dose Level -5	Discontinue

SYSTEM ORGAN CLASS (SOC)	**ADVERSE EVENT/SYMPTOMS**	**DOSAGE CHANGE**
Gastrointestinal Disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	≥Grade 3 (requiring hospitalization or surgery)	Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level along with concurrent therapy with H2 blockers, sucralfate, or omeprazole.
Investigations	Grade 3 or 4 Serum amylase increased	Discontinue dexamethasone and do not resume. Hold pomalidomide and bortezomib at physician discretion and restart once resolved to ≤grade 2.
General disorders and administration site conditions	Edema limbs or Edema trunk ≥Grade 3 (limiting function and unresponsive to therapy or anasarca).	Diuretics as needed, and decrease dexamethasone dose by 1 dose level.
Psychiatric disorders	Confusion or Anxiety or Depression ≥ Grade 2 (interfering with function +/- interfering with activities of daily living).	Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level.

Musculoskeletal and connective tissue disorders	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living).	Decrease dexamethasone dose by 1 dose level. If weakness persists decrease dose by 1 dose level as needed.
Metabolism and nutrition disorders	Hyperglycemia □ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level.
Any Other non- hematologic	□ Grade 3 or higher	Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level.

4- A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ 50,000/μL;
- Any pomalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ Grade 1 severity;
- Any other pomalidomide-related adverse event that may have occurred has resolved to ≤ Grade 1

CONSORT Flow Diagram for Phase II part of the trial