Poster number: **55C**

A Phase 1/2 Study (NCT01541332) of Pomalidomide (POM), Dexamethasone (DEX) and Pegylated Liposomal Doxorubicin (PLD) for Patients with Relapsed/Refractory (R/R) Multiple Myeloma (MM)

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Background

- Thalidomide and its immunomodulatory derivatives (IMiDs) such as lenalidomide have shown great promise as a treatment option for multiple myeloma (MM) patients[1]
- Pomalidomide is an IMiD immunomodulatory agent with high *in vitro* potency that has shown promise as an effective treatment option for relapsed/refractory (RR) MM patients
  - Pomalidomide shows similar anti-angiogenic effects as thalidomide but exhibits greater anti-proliferative and immunomodulatory activity
- Recent data has shown pomalidomide to be effective in combination with dexamethasone, even for patients refractory to bortezomib and lenalidomide[1,2]
- Other data has shown that pegylated liposomal doxorubicin (PLD) is effective in combination with thalidomide or lenalidomide[3-6]
- Finally, our recent trial has shown that the efficacy and tolerability of regimens combining bortezomib with the combination of PLD, dexamethasone, and IMiDs such as lenalidomide can be improved by adjusting the traditional dosing and schedule of these drugs[6]
- These data holistically point to the combination of pomalidomide with dexamethasone and PLD using a modified dosing schedule as a potentially effective treatment option for R/R MM patients

Purpose

- We investigated the safety and efficacy of the combination of pomalidomide with dexamethasone and PLD using a modified dosing schedule for patients with progressive myeloma

Design

- Phase 1/2 multi-center, open-label, single-arm study
- Planned enrollment: 60 patients

Eligible Patients

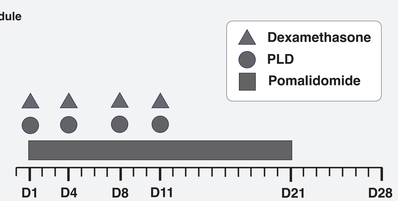
- Diagnosed with MM based on Durie criteria
- Currently have MM with measurable disease
- Currently have progressive MM that has relapsed or is refractory as follows:
  - Phase 1: relapsed following stabilization or response to at least one anti-myeloma regimen or refractory defined as progressed while receiving an anti-myeloma treatment
  - Phase 2: refractory to lenalidomide as demonstrated by progressive disease while on lenalidomide or that relapsed within 8 weeks of the last dose of lenalidomide either as a single agent or in combination.
- Age ≥ 18 years, life-expectancy ≥ 3 months, ECOG performance status 0-2

Assessments

- All subjects were evaluated for disease response according to a modified version of the IMWG Uniform Response Criteria for Multiple Myeloma[7,8]
  - Disease assessment occurred between D22-D25 during the rest period of each cycle
- Safety assessments graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0

Drug Administration Schedule

- Modified 28-day cycle
  - Dexamethasone administered IV on D1, D4, D8, & D11
  - PLD administered IV on D1, D4, D8, & D11
  - Pomalidomide administered daily PO on D1-D21



Dosage and Cohorts

- Phase 1: patients enrolled in up to three cohorts
  - Pomalidomide dosed at 2, 3, or 4 mg depending on cohort
- Phase 2: all patients dosed at m aximum-tolerated dose (MTD) determined in Phase 1 (later amended to 3 mg dosing for all new pts: see Results)

Table 1. Dosing Regimens By Phase & Cohort

Dosing Regimens			
Phase 1	**Pomalidomide**	**Dexamethasone**	**PLD**
Cohort 1	2 mg	40 mg	5 mg/m²
Cohort 2	3 mg	40 mg	5 mg/m²
Cohort 3	4 mg	40 mg	5 mg/m²
Phase 2			
Phase 2 (initial)	MTD (4 mg)	40 mg	5 mg/m²
Phase 2 (amended)	3 mg	40 mg	5 mg/m²

MTD & MAD

- MTD was determined as the maximum-administered dose (MAD) with no more than 1 dose-limiting toxicity (DLT) amongst 6 patients per cohort (only 3 patients required if no DLT).
  - DLT defined as any of the following occurring during Cycle 1: G4 neutropenia or thrombocytopenia lasting more than 7 days; febrile neutropenia (any grade); G3 or G4 diarrhea or constipation refractory to anti-diarrheal or constipation therapy; any study treatment-related grade 3 or 4 non-hematological toxicity (except alopecia); any drug-related death

Results

**Data cutoff: 04/01/13*

Demographics

- 27 patients have been enrolled as of data cutoff with 24 completing at least one full cycle of treatment
- Patients received a median of 5 prior regimens, with a median of 1 prior PLD-containing regimen
- The trial is still actively enrolling with less than half the planned enrollment currently completed

Table 2. Patient demographics

Patient Demographics	
No. enrolled	27
No. that received study drug	27
No. that received ≥ 1 MM assessment	26
No. that completed at least 1 full cycle	23
Median age in years (range)	69 (49-87)
Sex: M,F	17, 10
Prior Regimens	
Median no. of prior regimens (range)	5 (1-18)
Median no. of prior PLD-containing regimens (range)	1 (0-2)

MTD & DLTs

Table 3. Trial enrollment & dose details

Enrollment & Dose Data	
Median no. cycles completed (range)	3 (0-8)
Median follow-up in months (range)	3.2 (0.2-8.2)
Number of DLTs	0
Number of dose reductions	3
Phase 1 Cohort Enrollment*	
2 mg POM	3
3 mg POM	4
4 mg POM	4
Phase 2 Cohort Enrollment**	
3 mg POM	0
4 mg POM	16

**2 patients replaced after AE during C1*

***Protocol later amended so that all future phase 2 enrollment occurs at 3 mg, despite established MAD. Amendment not instated before data cutoff*

Table 4. Trial MTD determination

Pomalidomide MAD/MTD	
Established MAD	4 mg
Amended MAD	3 mg

- To date, patients have completed a median of 3 cycles (range: 0-8) with a median follow-up of 3.2 months (range: 0.2-8.2)
- MAD was declared at the highest dose of 4 mg: no DLTs through 11 evaluable patients
  - Starting with patient 12, all patients were enrolled as part of phase 2
  - Toxicity issues at the MAD resulted in a protocol amendment such that dosing will be reduced to 3 mg for all subsequent pts (see Results: Safety)

Efficacy

- Efficacy data stems from both phase 1 and 2 patents
- Response was seen in 10 patients so far, predominantly PR
  - Response seen at all 3 doses of POM
  - A majority of responding patients had prior exposure to a PLD-containing regimen
- Twelve patients progressed on study, three of which progressed after initial response
- Phase 2 ORR (lenalidomide failures) was 25.0% (CBR: 31.3%) out of 16 phase 2 pts

Table 5. Trial regimen details

Best Response	n	%
CR	0	0.0%
VGPR	0	0.0%
PR	9	33.3%
MR	1	3.7%
SD	7	25.9%
PD	8	29.6%
Not evaluable	2	7.4%
Overall Response Rate (PR+VGPR+CR)	9	33.3%
Clinical Benefit Rate (MR +PR+VGPR+CR)	10	37.0%

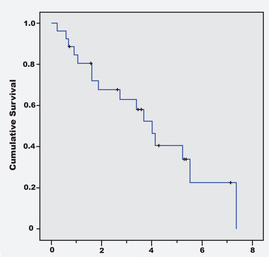
PD: progressive disease; SD: stable disease; MR: minimal response; PR: partial response; VGPR: very good partial response; CR: complete response

Table 6. Time-to-event data

Time to event	Time (mo)
Time to progression (TTP)	
Median (Kaplan-Meier)	4.0
95% confidence interval	3.2-4.8
Progression-free survival (PFS)	
Median (Kaplan-Meier)	4.0
95% confidence interval	3.1-5.0
Duration of response (DOR)	
Median (Kaplan-Meier)	not reached
95% confidence interval	not reached
Overall survival (OS)	
Median (Kaplan-Meier)	not reached
95% confidence interval	not reached

- Time-to-event data is early, but suggests at least a median of 4 months before progression on this combination regimen
- Estimates will improve with increased follow-up as the trial progresss

Figure 1: Progression-Free Survival/Time to Progression (Kaplan-Meier)



Safety

Hematological

- The most common hematological adverse events (all grades; any cause) were leukopenia (88.9%), neutropenia (74.1%), lymphopenia (70.4%), anemia (51.9%), thrombocytopenia (48.2%), and low toal protein (44.4%),
- ≥ G3 hematological adverse events included leukopenia (40.7% ≥ G3), neutropenia (37.0% ≥ G3), lymphopenia (29.6% ≥ G3), anemia (11.1% ≥ G3), and thrombocytopenia (3.7% ≥ G3),
- There were 2 instances of G4 adverse events, both G4 neutropenia

Non-hematological

- The most common non-hematological adverse events were hypocalcemia (55.6%), high blood urea nitrogen (48.2%), hyponatremia (48.2%), hypokalemia (48.2%), hypoalbuminemia (40.7%), upper respiratory infection (37.0%), fatigue (37.0%), diarrhea (33.3%), nausea (29.6%), constipation (29.6%), rash (22.2%), and edema (22.2%)
- ≥ G3 non-hematological adverse events included hyponatremia (11.1% ≥ G3), hypokalemia (3.7% ≥ G3), upper respiratory infection (3.7% ≥ G3), hyperglycemia (3.7% ≥ G3), high ALP (3.7% ≥ G3), and hypoglycemia (3.7% ≥ G3), fatigue (3.7% ≥ G3), mouth sores (3.7% ≥ G3), sepsis (3.7% ≥ G3), abdominal pain (3.7% ≥ G3), pneumonia (3.7%), and vasovagal response (3.7% ≥ G3)
- There were 6 patients (18.5%) who experienced non-hematologic SAEs after receiving study drug: 1 G3 abdominal pain, 1 G3 pulmonary infiltrate, 1 G3 hyponatremia, 1 G3 vasovagal response, 1 G4 hyperglycemia, and 1 G5 sepsis

Dose Modifications

- Only two dose reductions due to pomalidomide so far, with 4 pts discontinuing due to an adverse event

Neutropenia and Protocol Amendment

- So far, ≥ G3 neutropenia was seen in 10/20 (50%) patients receiving 4 mg dosing of pomalidomide. Due to this toxicity, the study has been amended so that all future phase 2 enrollment (pt 28 and beyond) will occur at 3 mg pomalidomide dosing (identical to Cohort 2 of phase 1)

Table 7. Number of patients experiencing selected adverse events (highest grade; any cause). Listed are all adverse events occurring in ≥ 15% of evaluable patients, as well as all ≥ G3 or serious adverse events.

Adverse Event	Patients per grade [n (%)]: 27 total										No. of Events	
	G1		G2		G3		G4		G5		Total		SAE
Hematologic													
Anemia	7	25.9%	4	14.8%	3	11.1%	0	0%	0	0%	14	51.9%	0
Bilirubin (low)	6	22.2%	0	0%	0	0%	0	0%	0	0%	6	22.2%	0
Eosinophils (high)	9	33.3%	0	0%	0	0%	0	0%	0	0%	9	33.3%	0
Hematocrit (low)	8	29.6%	1	3.7%	0	0%	0	0%	0	0%	9	33.3%	0
Hypotension	0	0.0%	0	0%	1	3.7%	0	0%	0	0%	1	3.7%	0
Leukopenia	8	29.6%	5	18.5%	11	40.7%	0	0%	0	0%	24	88.9%	0
Lymphopenia	2	7.4%	9	33.3%	8	29.6%	0	0%	0	0%	19	70.4%	0
Monocytes (high)	9	33.3%	0	0%	0	0%	0	0%	0	0%	9	33.3%	0
Neutropenia	3	11.1%	7	25.9%	8	29.6%	2	7%	0	0%	20	74.1%	0
Total protein (low)	12	44.4%	0	0%	0	0%	0	0%	0	0%	12	44.4%	0
Thrombocytopenia	10	37.0%	2	7.4%	1	3.7%	0	0%	0	0%	13	48.1%	0
Thrombocytosis	5	18.5%	0	0%	0	0%	0	0%	0	0%	5	18.5%	0
Non-Hematologic													
Abdominal pain	1	3.7%	0	0%	1	3.7%	0	0%	0	0%	2	7.4%	1
Alkaline phosphate (high)	2	7.4%	0	0%	1	3.7%	0	0%	0	0%	3	11.1%	0
ALT (low)	9	33.3%	0	0%	0	0%	0	0%	0	0%	9	33.3%	0
ALT (high)	8	29.6%	1	3.7%	0	0%	0	0%	0	0%	9	33.3%	0
AST (low)	7	25.9%	0	0%	0	0%	0	0%	0	0%	7	25.9%	0
Blood urea nitrogen (high)	11	40.7%	2	7.4%	0	0%	0	0%	0	0%	13	48.1%	0
Creatinine (low)	5	18.5%	0	0%	0	0%	0	0%	0	0%	5	18.5%	0
Constipation	6	22.2%	2	7.4%	0	0%	0	0%	0	0%	8	29.6%	0
Diarrhea	7	25.9%	2	7.4%	0	0%	0	0%	0	0%	9	33.3%	0
Edema	6	22.2%	0	0%	0	0%	0	0%	0	0%	6	22.2%	0
Fever	4	14.8%	1	3.7%	0	0%	0	0%	0	0%	5	18.5%	0
Fatigue	7	25.9%	2	7.4%	1	3.7%	0	0%	0	0%	10	37.0%	0
Gastrointestinal bleeding	1	3.7%	1	3.7%	1	3.7%		0%	0	0%	3	11.1%	0
Hyperglycemia	5	18.5%	2	7.4%	1	3.7%	0	0%	0	0%	8	29.6%	0
Hypoalbuminemia	7	25.9%	4	14.8%	0	0%	0	0%	0	0%	11	40.7%	0
Hypocalcemia	14	51.9%	1	3.7%	0	0%	0	0%	0	0%	15	55.6%	0
Hypoglycemia	0	0.0%	0	0%	0	0%	1	3.7%	0	0%	1	3.7%	0
Hypokalemia	11	40.7%	1	3.7%	1	3.7%	0	0%	0	0%	13	48.1%	0
Hyponatremia	10	37.0%	0	0%	3	11.1%	0	0%	0	0%	13	48.1%	1
Mental status change	0	0%	0	0%	0	0%	1	4%	0	0%	1	3.7%	0
Mouth sores	1	3.7%	1	3.7%	1	3.7%	0	0%	0	0%	3	11.1%	0
Nausea	7	25.9%	1	3.7%	0	0%	0	0%	0	0%	8	29.6%	0
Pneumonia	1	3.7%	0	0%	1	3.7%	0	0%	0	0%	2	7.4%	0
Pruritus	4	14.8%	1	3.7%	0	0%	0	0%	0	0%	5	18.5%	0
Pulmonary infiltrate	0	0%	0	0%	1	3.7%	0	0%	0	0%	1	3.7%	1
Rash	6	22.2%	0	0%	0	0%	0	0%	0	0%	6	22.2%	0
Sepsis	0	0%	0	0%	0	0%	0	0%	1	4%	1	3.7%	1
Ulcer	0	0%	0	0%	1	3.7%	0	0%	0	0%	1	3.7%	0
Upper respiratory infection	4	14.8%	5	18.5%	1	3.7%	0	0%	0	0%	10	37.0%	0
Vasovagal response	0	0%	0	0%	1	3.7%	0	0%	0	0%	1	3.7%	1

Conclusions

- Using a 28-day cycle, the combination of pomalidomide at 4 mg daily for 21 days with IV dexamethasone (40 mg) and PLD (5 mg/m²) both administered on D1, D4, D8, & D11 produced no DLTs during Phase 1 evaluation
  - While MAD was established at 4 mg during phase 1, there was a significant incidence of ≥ G3 neutropenia at this dose during phase 2: thus, the protocol has been amended so that future patients will be treated at 3 mg
  - Otherwise, treatment has been relatively well tolerated with this combination regimen, with a low incidence of other ≥ G3 adverse events
- Early efficacy data from all enrolled patients (phase 1 & 2) has shown an overall response rate of 33.3% (CBR: 37.0%) across all doses
  - Further enrollment will determined the safety and efficacy of the 3 mg dosing

Early data from this Phase 1/2 trial suggests that the combination of pomalidomide, IV dexamethasone, and PLD on a modified 28-day cycle is an effective and tolerable treatment strategy at appropriate dosing for MM patients who progressed on their most recent MM regimen

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Conflict of Interest disclosures

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