A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma

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INTRODUCTION

As lenalidomide (Len) has become an integral part of therapy for newly diagnosed MM patients, most will have been either exposed or refractory to Len at the time of first or second relapse. The monoclonal antibody, Daratumumab, in combination with the more potent IMID pomalidomide (Pom) demonstrates good responses in patients previously exposed to lenalidomide. Low dose weekly cyclophosphamide has been shown to enhance the potency of pomalidomide in association with dexamethasone. In this clinical trial, we set out to compare the combination of daratumumab, weekly low dose cyclophosphamide, dexamethasone and pomalidomide (DCdP) to daratumumab, cyclophosphamide and dexamethasone (DCd) with pomalidomide added only at disease progression. Although we expected that a four-drug regiment would give superior clinical results, we hypothesized that a significant number of patients would not necessarily need all four drugs but could benefit from the addition of pomalidomide at treatment failure.

OBJECTIVES

To evaluate and compare the efficacy of either the combination of daratumumab, weekly low dose cyclophosphamide, dexamethasone and pomalidomide (DCdP) to daratumumab, cyclophosphamide and dexamethasone (DCd) with pomalidomide added only at disease progression.

METHODS

120 patients from 11 centres across Canada were randomized to receive the following:

Relapsed/Refractory Multiple Myeloma Patients

- ≥ 1 line of prior therapy
- relapsed or relapsed/refractory disease defined as DP during or after completing their last treatment line that contained either bortezomib and/or lenalidomide
- prior exposure to daratumumab or pomalidomide excluded

N=120

RANDOMIZATION 1:1

ARM A
DCdP **Daratumumab**
16 mg/kg : C1-2 QW; C3-6 Q2W; C7+ Q4W
+
Dex + Cyclo$_{400mg}$ + POM$_{4mg/D1-21}$

ARM B
DCd+P **Daratumumab**
16 mg/kg: C1-2 QW; C3-6 Q2W; C7+ Q4W
+
Dex + Cyclo$_{400mg}$ + POM$_{4mg/D1-21}$
(POM added at Disease Progression)

Cycle = 28 days

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Primary Endpoint: PFS

Secondary Endpoints: 1 year OS, DOR, ORR (DCP *vs* DC), ORR (DCP *vs* DC+P)

Data cut-off: October 2019. Median Follow-up: 12.5 months. Follow up for ARM B after addition of POM: 5.3 months

RESULTS

Table 1. Patient and Disease Characteristics

Characteristic	Arm A N-61	Arm B N=59
Median age (range), years	64.7 (39.0-82.0)	64.7 (47.0-77.0)
Male, n (%)	37 (60.7%)	28 (47.5%)
Median Follow-up time (months)	13.4 (0.2-21.7)	12.7 (1.5-20.9) 5.3 months post POM addition
ISS stage , n (%)		
I	31 (50.8%)	28 (47.4%)
II	23 (37.7%)	25 (42.3%)
III	5 (8.2%)	6 (10.2%)
Previous Lines of Therapy		
1	16 (26.2%)	16 (27.1%)
2	24 (39.3%)	24 (40.7%
3	12 (19.7%)	13 (22.0%)
4+	9 (14.4%)	6 (10.2%)
No. of prior therapies, median (range)	2 (1-6)	2 (1-8)
Prior therapies, n (%)		
ASCT	42 (68.9%)	44 (74.6%)
BORT	55 (90.2%)	57 (96.6%)
LEN	60 (98.4%)	57 (96.6%)
LEN as last line of Rx	39 (63.9%)	39 (66.1%)
Refractory to LEN, n (%)	52 (85.2%)	50 (84.7%)
Number of cycles of Pomalidomide	13 (1-22)	5 (1-12)

Patients Enrolled

-120 patients enrolled
Males or females, age 18 years or older, ECOG performance status score ≤2

Measurable disease according to the IMWG criteria defined as: Serum monoclonal paraprotein (M-protein) ≥ 10 g/L (if IgG) or ≥5g/L (if IgA), Urine M-protein ≥ 200 mg/24 h. Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/L and an abnormal serum free light chain ratio (< 0.26 or > 1.65) if disease otherwise unmeasurable by a and b.

Relapsed or relapsed and refractory disease defined as documented disease progression during or after completing their last treatment line and it must have contained either bortezomib and/or lenalidomide.

Have undergone at least 1 prior line of therapy. Induction therapy followed by ASCT and consolidation/maintenance will be considered as one line.

Have achieved at least a Minimal Response (MR) or better to at least one previous line of therapy.

Have received at least 2 consecutive cycles of prior treatment that have included lenalidomide or bortezomib, either alone or in combination regimens, unless intolerant to these agents.

Patient Characteristics

120 patients enrolled
-61 patients in ARM A; 59 in ARM B
Median follow up time as of October 2019: 13 months
-Median number of lines of previous therapies was 2
-35 patients in ARM B (of 59) have progressed at data cutoff and have received POM with a median follow up time of 5.3 months
-Median number of cycles of POM in ARM A – 13 (1-22)
-Median Number of cycles of POM in ARM B – 5 (1-12)

Fig 1. Best Responses

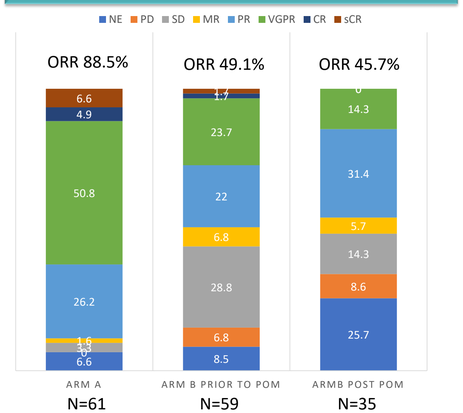


Table 2 ORR by Previous Lines of Therapy

	Arm A	Arm B (pre POM)	Arm B (post POM)	ARM B Total
LEN exposed (n)	57	57	30	57
ORR	92.8%	52.63%	60.0%	75.4%
LEN as last line of Rx (n)	36	36	16	37
ORR	91.7%	66.7%	56.3%	81.1%
1 previous line of Rx (n)	16	14	5	14
ORR	87.5%	50.0%	100%	85.7%
2 previous lines of Rx (n)	21	25	12	24
ORR	95.2%	60.87%	41.7%	70.8%
3 previous lines of Rx (n)	12	17	9	17
ORR	100%	52.9%	66.7%	70.6%

Responses
At a median of 60 weeks follow up, overall response in ARM A was 88.5%, ARM B 49% and 47% for patients in ARM B after progression and addition of POM/
In patients in whom LEN was the last line of therapy, the ORR was 91% and 81% for ARMs A and B respectively. In patients who had received 1 line of previous therapy the ORR was 87.5% for ARM A and 86% for ARM B overall, but lower for ARM B prior to the addition of POM at 50%. For those having received 2 lines of previous therapy, the ORR was much higher in ARM A (95%) as compared to overall ARM B 70% or ARM B prior to addition of POM (61%).

Figure 2 PFS Arm A vs Arm B prior to POM

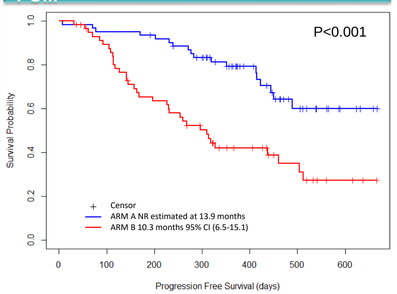


Figure 3 PFS ARM A vs PFS of ARM B post POM

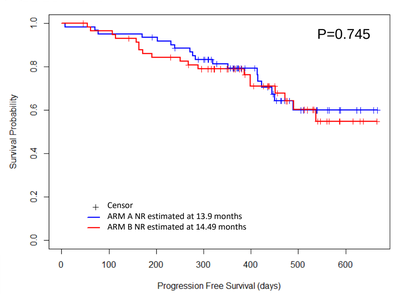
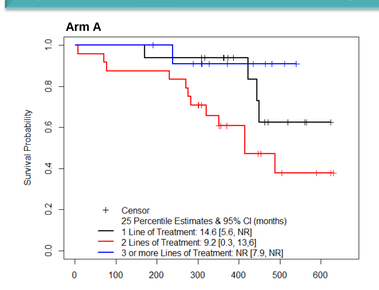


Figure 4 PFS in Prior Number of Therapies



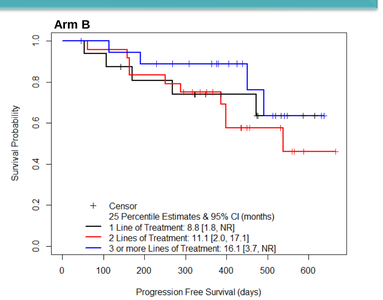


Figure 5 Time to Subsequent Therapy

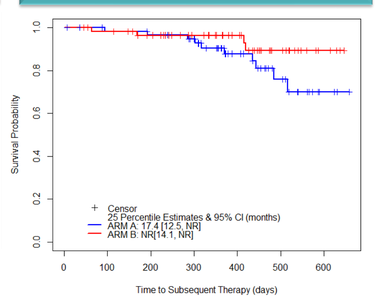


Figure 4 OS

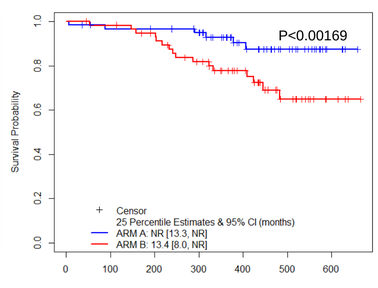


Table 3. Grade 3-4 Adverse Events

	Arm A N-61	Arm B (prior to POM) N=59	ARM B post POM N=35
Hematologic			
Neutropenia	50 (82.0%)	12 (20.3%)	25 (42.4%)
Febrile Neutropenia	7 (11.5%)	2 (3.4%)	7 (11.9%)
Thrombocytopenia	4 (6.6%)	5 (8.5%)	9 (15.3%)
Anemia	7 (11.5%)	9 (15.3%)	14 (23.7%)
Infectious			
Pneumonia	13(21.3%)	4 (6.8%)	7 (22.6%)
Other Infections	7 (11.5%)	9 (15.3%)	14 (23.7%)
fatigue	3 (4.9%)	5 (8.5%)	13 (37%)
dyspnea	5 (8.2%)	1 (5.7%)	2 (3.4%)
Venous Thrombo-embolism	0	0	0

CONCLUSIONS

-In patients who have been previously treated with both proteasome inhibitors and Lenalidomide, the combination of Daratumumab, Cyclophosphamide, Dexamethasone and Pomalidomide (DCdP) produces impressive response rates.
-Patients with who received Daratumumab, Cyclophosphamide and Dexamethasone (DCd) without POM had appreciably lower response rates and initial PFSs but most were salvageable after the addition of POM. Furthermore, this sequential addition of POM did not appear to compromise their overall PFS or time to subsequent therapies. OS so far appears to be superior for ARM A. As the follow up time is relatively short, these data are subject to evolve with time.
-Number of cycles of POM given were predictably lower in ARM B as compared to ARM B
-Cost effectiveness analyses are scheduled to be performed with the current data
-Immune profiling of subjects at pre-determined timed intervals is pending
-Adverse events in both arms were predictable, with predominant hematologic toxicities and an increased rate of pulmonary infections principally in patients receiving Dara and POM simultaneously.
In conclusion, addition of POM upon failure of a Dara based regimen appears to be an overall effective strategy, though at the cost of lower initial ORR and PFSs.