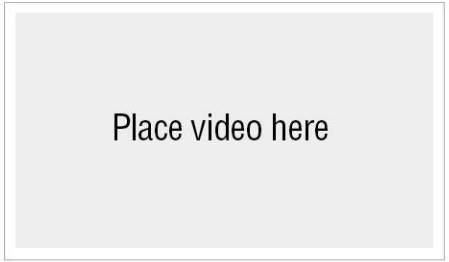
CMRG 004: A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma

Place video here

Michael Sebag[1], Nizar Bahlis[2], Christopher Venner[3], Arleigh McCurdy[4], Tom Kouroukis[5], Jesse Shustik[6], Darrell White[7], Rami Kotb[8], Julie Stakiw[9], Nicole Laferriere[10], Tony Reiman[11], Fernando Camacho[12], Julia Dobbin[12], Molei Fu[12], Engin Gul[12], Donna Reece[12,13]

[1]McGill University Health Center, Montreal, Quebec, Canada. [2]Tom Baker Cancer Centre, Calgary, Alberta, Canada. [3]Cross Cancer Institute, Edmonton, Alberta, Canada. [4]The Ottawa Hospital, Ottawa, Ontario, Canada. [5]Juravinski Cancer Centre, Hamilton, Ontario, Canada. [6]Fraser Valley Cancer Centre, BC Cancer, Surrey, British Columbia, Canada. [7]Nova Scotia Health Authority, Halifax, Nova Scotia, Canada. [8]Cancer Care Manitoba, Winnipeg, Manitoba, Canada. [9]University of Saskatchewan, Saskatoon, Saskatchewan, Canada. [10]Regional Cancer Centre, Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario, Canada. [11]Department of Oncology, Saint John Regional Hospital, Saint John, NB, Canada. [12]Canadian Myeloma Research Group, Ontario, Canada. [13]Princess Margaret Cancer Centre, Toronto, ON, Canada

Introduction and Objectives



- Lenalidomide is increasingly part of all first line regimens
- Poor options for patients that have progressed post PI and IMIDs
- Daratumumab + POM shows good responses on LEN exposed patients
- Low dose weekly Cyclophosphamide enhances POM activity, acts as immunomodulator
- This study: 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 regimen would give superior clinical results, we reasoned that a significant number of patients would not necessarily need all four drugs but could benefit from the addition of Pomalidomide at treatment failure
- We also reasoned that adding Cyclophosphamide to these regimens may improve overall responses

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

Trial Design

Primary Endpoint: PFS

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

Place video here

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

RANDOMIZATION

1:1
N=120

ARM A
N=61

DCdP

Cycle = 28 days

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

Daratumumab
16 mg/kg: Q4C1-2 QW; C3-6 Q2W; C7+ W
+
Dex + Cyclo$_{400mg}$ + POM$_{4mg/D1-21}$
(POM added at Disease Progression)

ARM B
N=59

DCd+P

Cycle = 28 days

DP – Disease Progression. Dex – Dexamethasone. Cyclo – Cyclophosphamide. POM – Pomalidomide

Patient and Disease Characteristics

Place video here

Prior Treatment	Arm A N=61	Arm B N=59
LOT, median (range)	2 (1-6)	2 (1-8)
1	16 (26.2%)	16 (27.1%)
2	24 (39.3%)	24 (40.7%)
3	12 (19.7%)	14 (23.7%)
4+	9 (14.4%)	5 (8.5%)
ASCT	42 (68.9%)	44 (74.6%)
BORT	55 (90.2%)	57 (96.6%)
LEN	59 (96.7%)	57 (96.6%)
LEN as last line of Rx	39 (63.9%)	39 (66.1%)

Patient and Disease Characteristics	Arm A N=61	Arm B N=59
Median age (range), years	65 (39-81)	64 (47-77)
Male, n (%)	37 (60.7%)	28 (47.5%)
Median time since diagnosis (range), years	4.3 (0.9-16.1)	3.6 (1.1-10.5)
ISS Stage, n(%)		
I	31 (50.8%)	28 (47.4%)
II	23 (37.7%)	25 (42.3%)
III	5 (8.2%)	6 (10.2%)

LOT – Lines of Therapy. ASCT – Autologous Stem Cell Transplant. BORT – Bortezomib. LEN - Lenalidomide

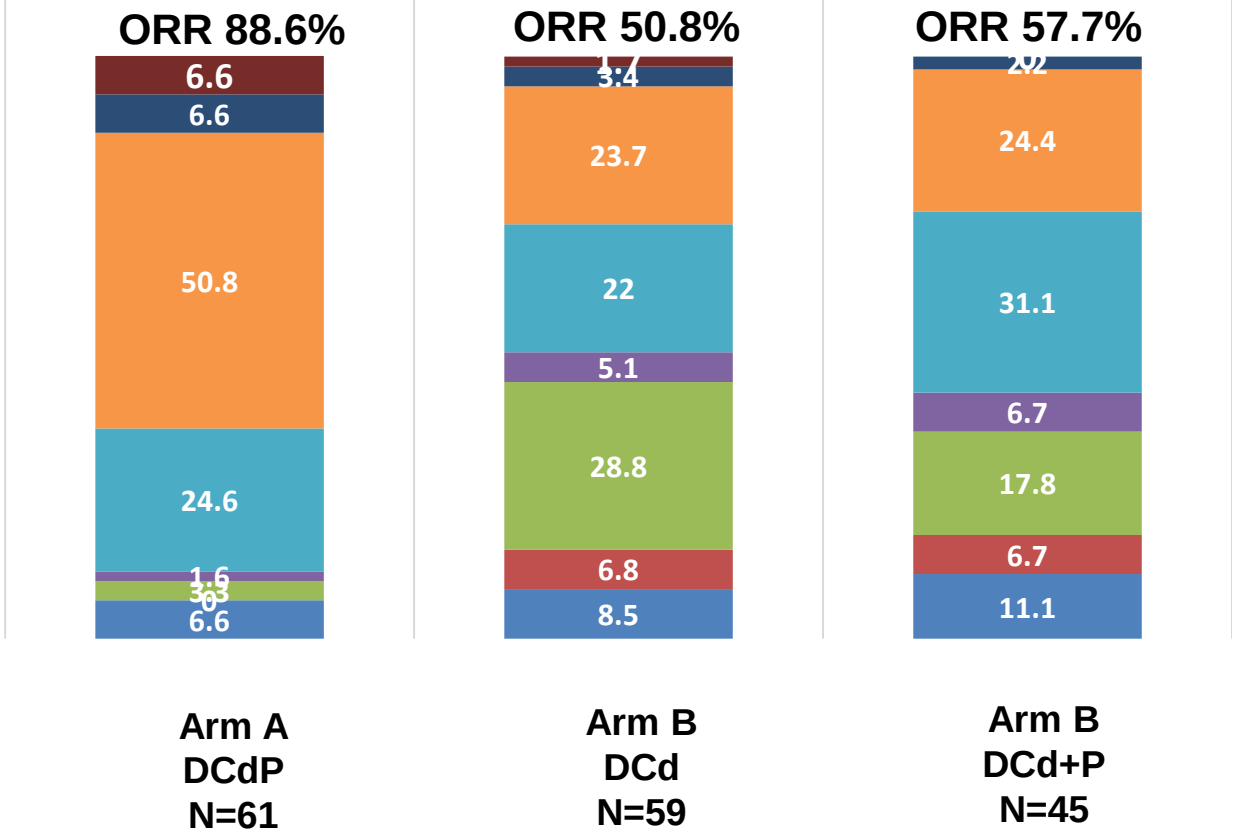
Patient Outcomes

Place video here

- 120 patients enrolled
- Data cut-off: Nov 1, 2020. Median Follow-up: 25.3 months.
- 45 patients in Arm B progressed on DCd and 100% received at least 1 cycle of Pom
- Median follow-up time for Arm B after the addition of Pomalidomide = 8.9 months

Reasons for Treatment Discontinuation	Arm A N=61	Arm B Overall N=59
Progressive disease	24 (39.3%)	26 (44.1%)
Patient withdrawal	3 (4.9%)	3 (5.1%)
Intercurrent illness	0	2 (3.4%)
Death	0	2 (3.4%)
Other	3 (4.9%)	3 (5.1%)
Unknown	4 (6.6%)	5 (8.5%)

Responses



Place video here

sCR
CR
VGPR
PR
MR
SD
PD

ORR

ORR by Previous Lines of Therapy

Place video here

ORR by Previous LOT	Arm A N=61	Arm B (pre-POM) N=59	Arm B (post-POM) N=45
LEN exposed (n)	59	57	43
ORR	89.8%	54.4%	65.1%
LEN as last line of Rx (n)	39	39	27
ORR	84.6%	61.5%	51.9%
1 previous line of Rx (n)	16	16	18
ORR	87.5%	50%	81.8%
2 previous lines of Rx (n)	24	24	18
ORR	83.3%	58.3%	33.3%
3+ previous lines of Rx (n)	21	19	11
ORR	100%	42.1%	68.8%

ARM A DCdP

ARM B DCd

ARM B+ Pom DCdP

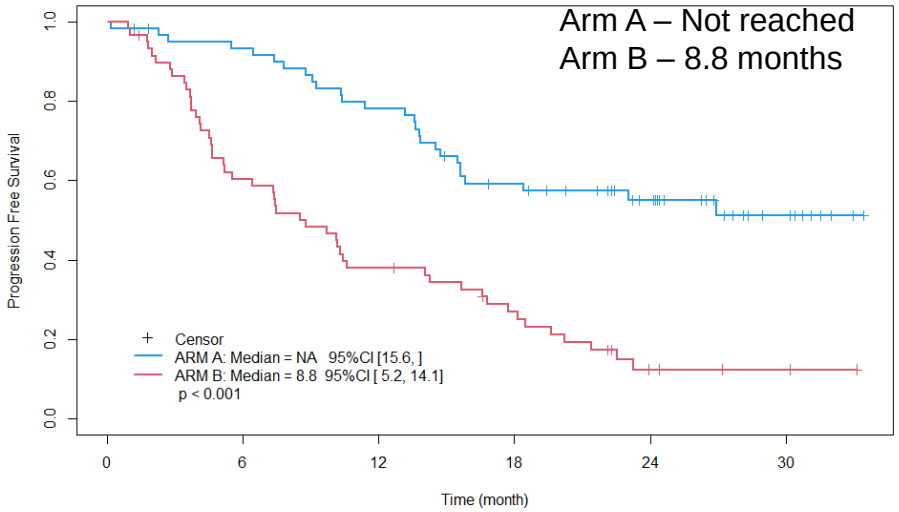
ORR= PR or greater by IMWG criteria

Progression Free Survival

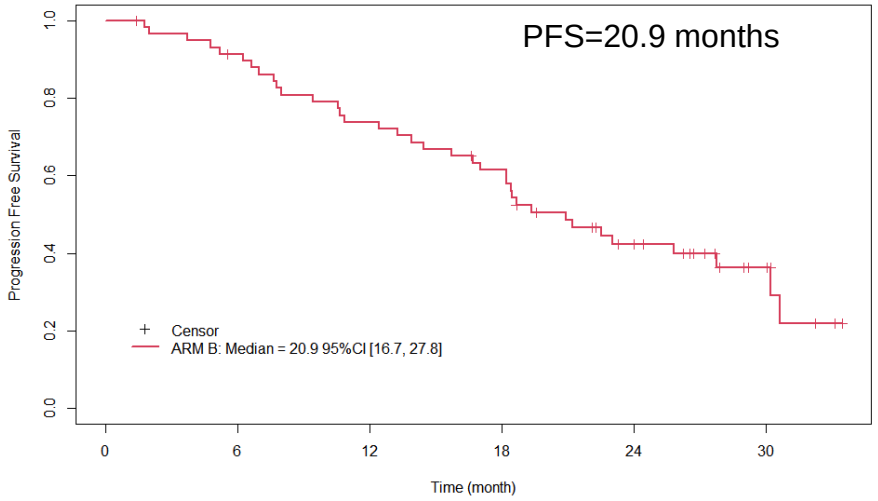
Place video here

Median follow up time 25.3 months
Median follow up Arm B after POM 8.9 months

PFS Arm A vs Arm B prior to POM



PFS of Arm B after addition of POM

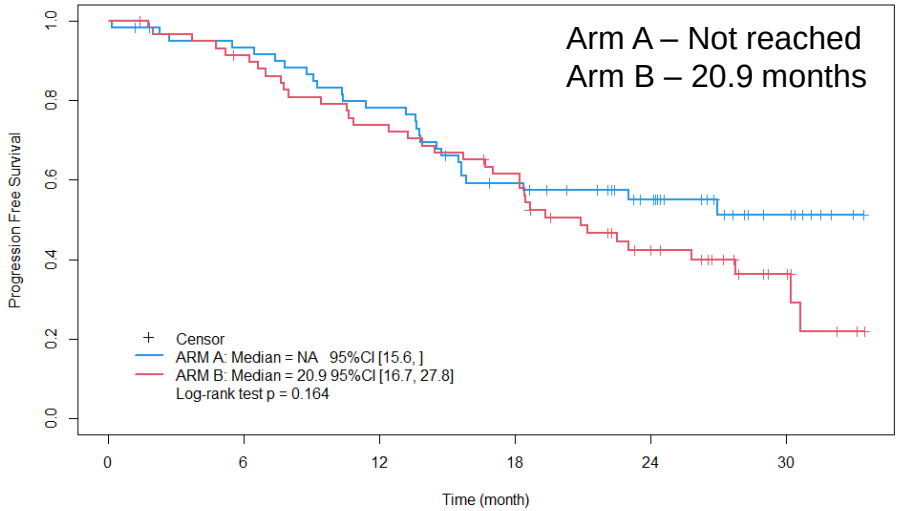


Progression Free Survival

Median follow up time 25.3 months
Median follow up Arm B after POM 8.9 months
PFS ARM A (DCdP) vs PFS ARM B (DCd+P)

Place video here

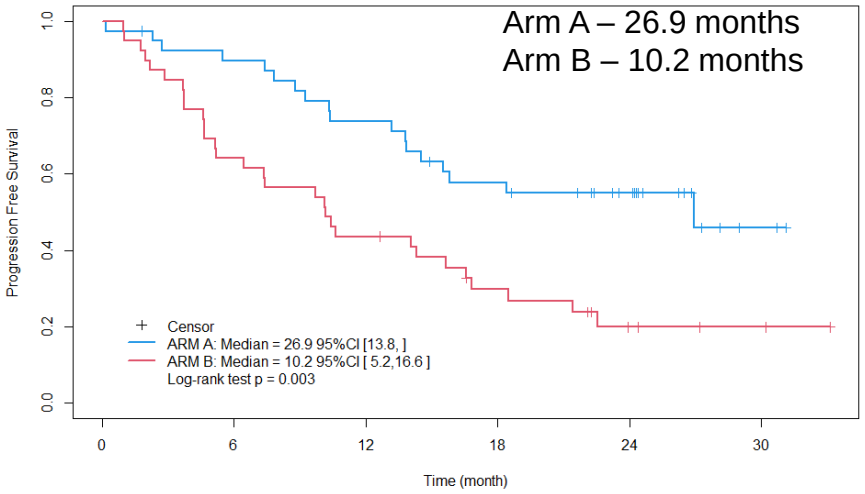
PFS ARM A vs PFS of ARM B post POM



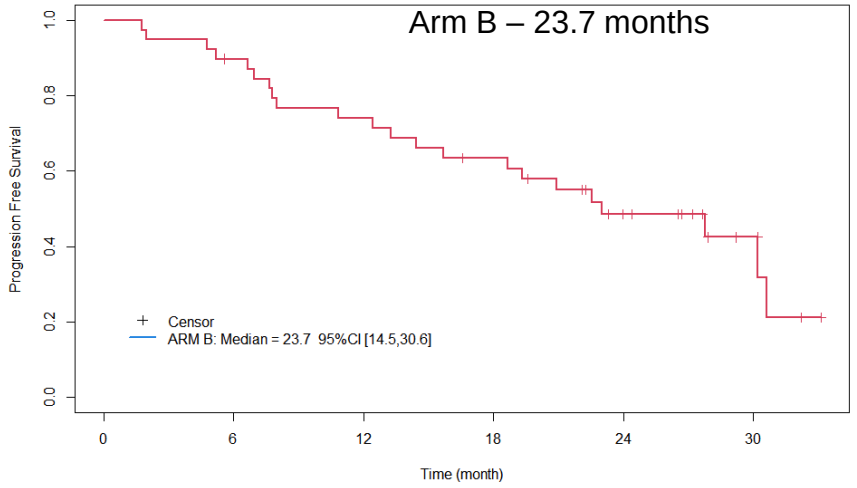
PFS for LEN as Last Line of Rx

Place video here

PFS Arm A vs Arm B prior to POM



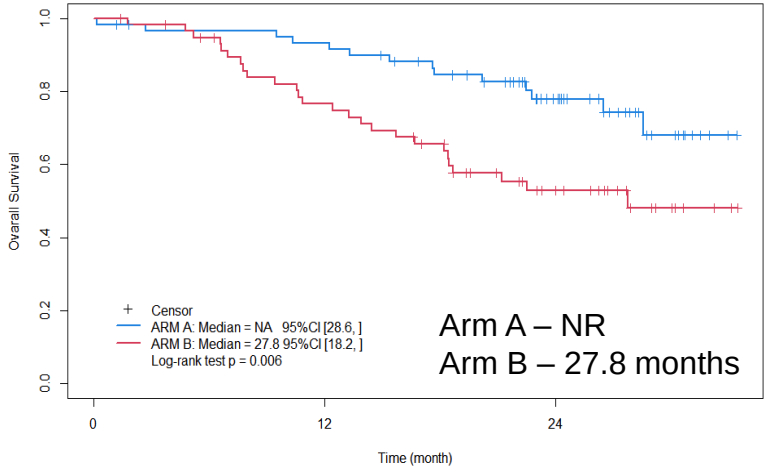
PFS of ARM B After addition of POM (DCd+P)



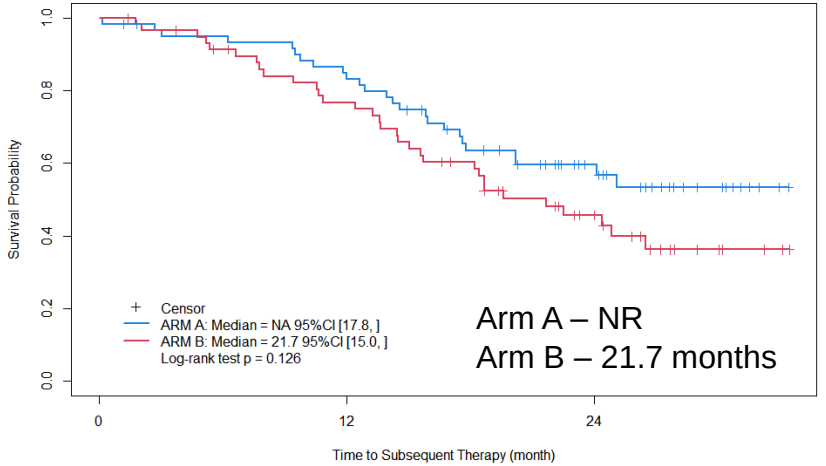
TTN and OS

Place video here

Overall Survival Arm A vs Arm B



Time to Subsequent Therapies



Adverse Events

Place video here

Grade 3-4 Adverse Events	Arm A N=61	Arm B (pre-POM) N=59	Arm B (post-POM) N=45
Hematologic			
Neutropenia	52 (85.2%)	17 (28.8%)	23 (50.0%)
Febrile neutropenia	8 (13.1%)	2 (3.4%)	9 (19.6%)
Thrombocytopenia	5 (8.2%)	7 (11.9%)	6 (13.0%)
Anemia	8 (13.1%)	13 (22.0%)	10 (21.7%)
Infectious			
Pneumonia	13 (21.3%)	4 (6.8%)	12 (26.1%)
Other Infections	18 (29.5%)	9 (15.3%)	16 (34.8%)
Fatigue	4 (6.6%)	4 (6.8%)	6 (13.0%)
Dyspnea	5 (8.2%)	0	2 (4.3%)
Venous Thromboembolism	1 (1.6%)	0	2 (4.3%)

Summary and Conclusions

Place video here

- In a significantly pretreated MM population (median 2, range 1-8):
  - DCdP gives an ORR of 88.6% which compares favourably with Dara-Pom-Dex given after a median of 1 line of therapy that included Len (MM-014, ORR 77.7%)[1]
  - Despite 25.3 months of median follow-up PFS has not been reached for Arm A (DCdP) but looks headed to be similar to that of the MM-014 update[2] despite a more heavily pre-treated population, suggesting that addition of cyclophosphamide may improve responses and outcomes with an acceptable toxicity profile
  - Although DCd (Arm B) gave a disappointing ORR of 50.8% and PFS of only 8.8 mos., addition of POM salvages over half of patients that progress. In addition there are a considerable number of patients in which an IMID free Dara combination could be successful if we could identify them beforehand
  - Although addition of POM upon failure of a 3 drug regimen appears to salvage over half of patients, there is a trend to improved overall PFS for those who got all 4 drugs at once
- Phamacoeconomic and immunomonitoring analyses are currently being performed

[1] Seigel et al, Leukemia May 6, 2020 [2] Bahlis et al, ASH poster #2314

Acknowledgements

Place video here

- This study is supported by Janssen Inc.
- This study was run by the Canadian Myeloma Research Group
- All authors contributed to this presentation
- Wish to thank the clinical research teams at participating sites across Canada.
- Wish to thank patients and their families who made this study possible