Memorial Sloan Kettering Cancer Center

Bendamustine for Hodgkin lymphoma

Alison Moskowitz, MD
Assistant Attending
Memorial Sloan Kettering, Lymphoma Service

Bendamustine in Hodgkin lymphoma

- Bifunctional molecule
  - Nitrogen mustard component (meclorethamine)
  - Purine analog component (benzimidazole ring)

- Partial cross-resistance to other alkylating agents[1]

- Potential mechanisms of action include:[1]
  - DNA damage
  - Cell cycle inhibition
  - Mitochondrial catastrophe

[1]Gandhi W. Semin Oncol 2002, 29: 4-11.

Memorial Sloan Kettering Cancer Center

Bendamustine in Hodgkin lymphoma

- Efficacy in the relapsed/refractory setting

- First salvage combinations with bendamustine
  - BV plus bendamustine
  - BeGEV

- Role in the front-line setting for older HL patients?

Bendamustine - phase II study in rel/ref HL

Bendamustine
120 mg/m2
days 1,2 every 28 days
Pegfilgrastim support

↓

PET scan every 2 cycles
Up to 6 cycles given

Patient characteristics	N=36
Median age	34 (21-75)
Male	13 (36%)
Female	23(64%)
Median No. of prior therapies	4 (1-17)
Response to last chemotherapy	
Sensitive	18
Resistant	18
History of auto transplant	27 (75%)
History of allo transplant	6 (17%)

Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60.

Bendamustine in HL - Dose reductions and delays

Delay/Reduction	No.	%
Total No. cycles administered	120	
Total No. cycles delayed	13	11
Reason for delay		
Thrombocytopenia	9	
Pneumonia	2	
Upper respiratory infection	1	
HSV infection	1	
Total No. cycles reduced	10	8
Reason for reduction		
Thrombocytopenia	7	
Neutropenia	1	
Grade 3 nausea/vomiting	1	
Pneumonia with neutropenic fever	1	

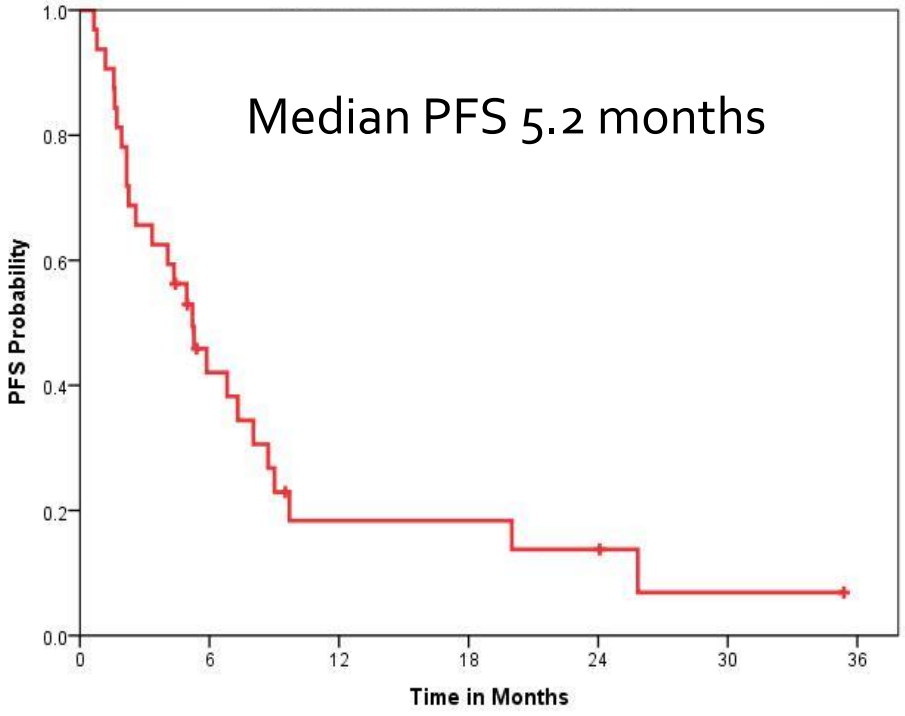
Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60.

Bendamustine in HL - Efficacy

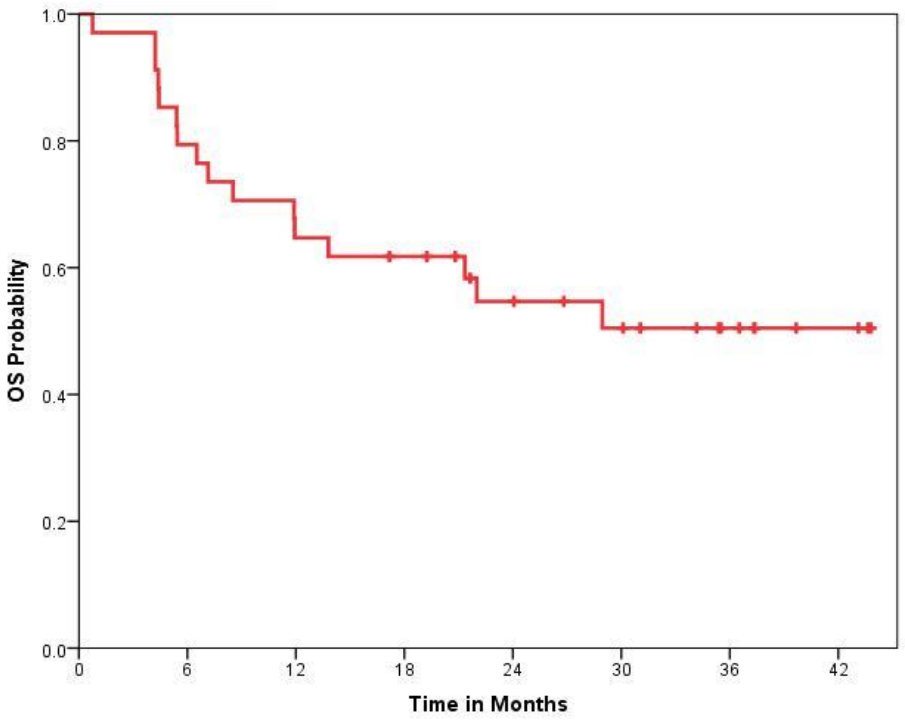
Parameter	No.	CR (%)	PR (%)	ORR (%)	p
Response (all pts)	36	12(33)	7 (19)	19 (53)	
Response (evaluable pts)	34	12 (35)	7 (21)	19 (56)	
Median No. prior therapies					p=1.0
< 4	16	6 (38)	3 (19)	9 (56)	
≥ 4	18	6 (33)	4 (22)	10 (55)	
Response to last Rx					p=0.2
Sensitive	16	9 (56)	2 (13)	11 (69)	
Resistant	18	3 (17)	5 (28)	8 (45)	
Previous ASCT	26	10 (38)	5 (19)	15 (57)	p=1.0
Relapsed within 3 months of ASCT	5	0	0	0	p=0.01
Previous alloSCT	6	2 (33)	2 (33)	4 (66)	p=0.7

Bendamustine in HL - Outcomes

Progression free survival



Overall Survival



5 of 25 (20%) eligible patients proceeded to allogeneic stem cell transplant

Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60.

Memorial Sloan Kettering Cancer Center

Efficacy confirmed in additional retrospective series

Reference	n	Dose	ORR	CR	Prior Rx
Corazzelli	41	90-120 mg/m2, days 1 &2, every 3-4 wks	58%	31%	
Ghesquieres	28	90-120 mg/m2, days 1 &2, every 4 wks	50%	29%	
Anastasia	67	90-120 mg/m2, days 1 &2, every 4 wks	57%	25%	67% failed auto SCT 33% failed allo SCT
Zinzani	27	90 mg/m2, days 1 &2, every 4 wks	56%	37%	All received prior BV 56% refractory to BV

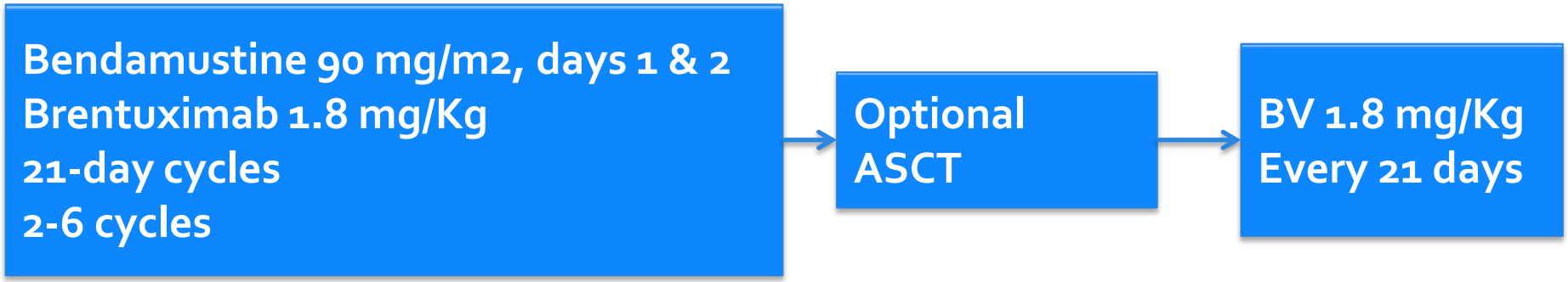
Corazzelli, et al. British Journal of Haematology, 2013;160:207-215
Ghesquieres, et al. Leukemia & Lymphoma, 2013;54(11):2399-2404
Anastasia, et al. British Journal of Haematology, 2014;166:140-153
Zinzani, et al. Clinical Lymphoma, Myeloma & Leukemia, 2015;15(7):404-408

Bendamustine combinations in HL

- First salvage combinations
  - Brentuximab vedotin plus bendamustine
  - BeGEV

Bendamustine plus brentuximab as first salvage

- **Main eligibility:**
  - **Classical HL**
  - **18 years and older**
  - **R/R disease after frontline chemotherapy**



- **Up to 16 cycles of BV total**
- **PET/CT after cycles 2, 4 and pre-transplant**
- **CT every 3 months during monotherapy**
- **Response assessment: Cheson 2007**

LaCasce, et al. ASH 2015, abstract 3982

Memorial Sloan Kettering Cancer Center

Bendamustine plus BV – patient population

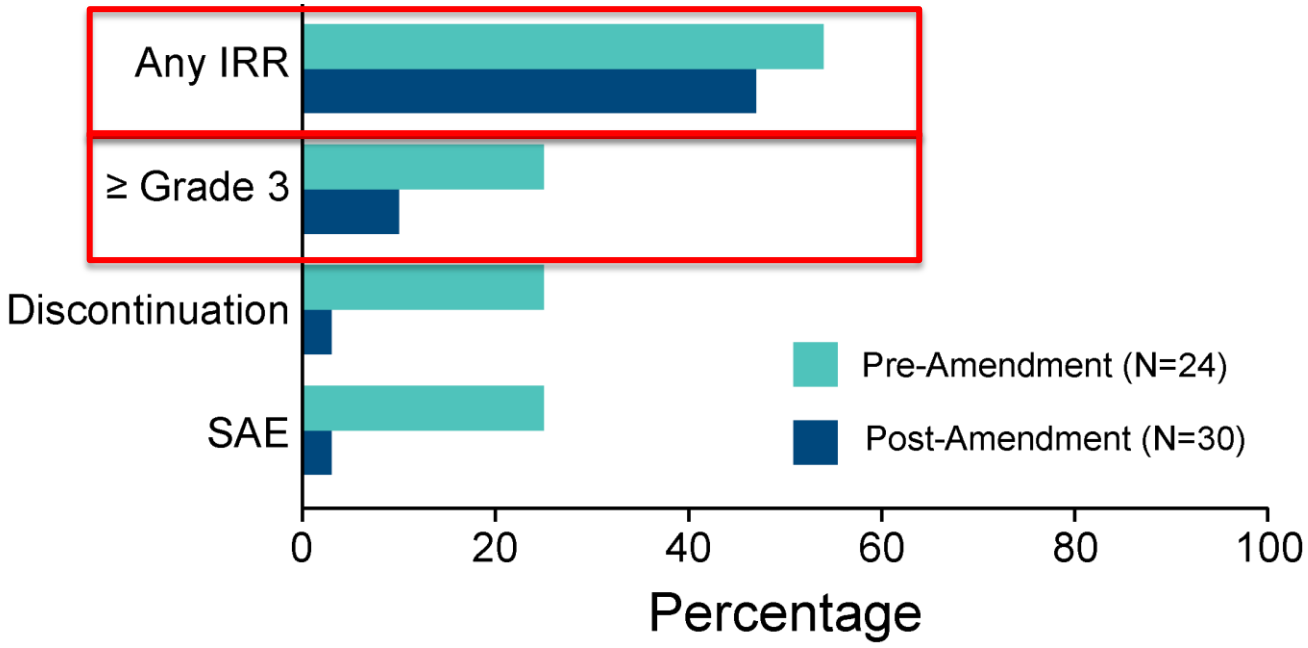
Characteristic	
Total enrolled	55
Age, median (range)	36 (19-79)
Females	31 (56%)
Relapsed	28 (51%)
Refractory	27 (49%)

- **No dose-limiting toxicity was observed in safety cohort**
- **Median 2 cycles (range 1-6) of combination adminstered**
- **Median 9 cycles (range 1-14) of single-agent BV administered**

LaCasce, et al. ASH 2015, abstract 3982

Memorial Sloan Kettering Cancer Center

Key adverse event: Infusion related reactions



- Fever (26%), chills (20%), dyspnea (15%), nausea (15%), flushing (13%), and hypotension (11%) were most common symptoms
- Decreased incidence following amendment requiring premeds (steroids/antihistamines)
- 24% (pre-amendment) and 7% (post-amendment) off study for IRR

LaCasce, et al. ASH 2015, abstract 3982

Memorial Sloan Kettering Cancer Center

Best Response to BV + Bendamustine

Best clinical response	N=53
Complete remission (CR)	39 (74%)
CR rate among relapsed pts	84%
CR rate among refractory pts	64%
Partial remission (PR)	10 (19%)
Objective response rate (ORR [CR + PR])	49 (93%)

- Successful mobilization in 37/40 (93%) with first attempt
- 40 patients underwent autoSCT
  - Median post-transplant f/u: 10 months
  - 7 post-transplant progressions
- 13 patients did not undergo autoSCT
  - 5 progressions

LaCasce, et al. ASH 2015, abstract 3982

Memorial Sloan Kettering Cancer Center

BeGEV as second-line therapy in HL

Patient population:

- HL patients refractory to or relapsed after 1 line of chemotherapy

Primary endpoint:

- CR rate after 4 cycles

Secondary endpoints:

- ORR, stem cell mobilization, toxicity

Bendamustine 90mg/m2, days 2 and 3
Gemcitabine 800mg/m2, days 1 and 4
Vinorelbine 25mg/m2, day 1

→ **Every 21 days**
Total of 4 cycles

59 patients enrolled:
54% refractory; 46% relapsed

Santoro, et al. ASH 2015, abstract 581

Memorial Sloan Kettering Cancer Center

BeGEV Results

Response	n=59
ORR	49 (83%)
CR	43 (73%)
PR	6 (10%)
SD	1 (2%)
PD	8 (14%)

Parameter	n=59
Mobilization	57 (97%)
ASCT	43 (88%)
2-yr PFS	51%
2-yr OS	69%

Grade 3-4 toxicity:
Febrile neutropenia (7); infection (4)
Thrombocytopenia/neutropenia (8)

Santoro, et al. ASH 2015, abstract 581

Memorial Sloan Kettering Cancer Center

Bendamustine in Hodgkin lymphoma

- Efficacy in the relapsed/refractory setting

- First salvage combinations with bendamustine
  - BV plus bendamustine
  - BeGEV

- Role in the front-line setting for older HL patients?

Brentuximab Vedotin plus Dacarbazine or Bendamustine for Frontline Treatment of Hodgkin Lymphoma in Patients ≥60 Years

Interim Analysis[1]

Brentuximab vedotin monotherapy[2]	Brentuximab vedotin Dacarbazine 375 mg/m2	Brentuximab vedotin Bendamustine 70-90 mg/m2
27 pts ORR: 92% CR: 73% 12 month PFS: 38% Median PFS: 10.5 months	22 pts ORR: 100% (of 21 pts) CR: 62% 12 month PFS: 66%	20 pts ORR: 100% (of 9 pts) CR: 78% PFS: Too early ***Significant number of serious adverse events (60%) observed leading to closure of this arm

[1]Yasenchak, et al. ASH 2015, abstract 587

[2]Forrero-Torres, et al. Blood. 2015;126(26):2798-2804

Bendamustine in Hodgkin lymphoma

- Single-agent bendamustine in relapsed/refractory setting
  - Response rate around 50% in heavily treated pts
  - Durability of response limited

- First salvage combinations with bendamustine
  - BV plus bendamustine
  - BeGEV
  - Both show high CR rates, therefore promising as 1st salvage

- BV plus bendamustine is not a viable option as first-line therapy for older HL patients due to toxicity