Results of a Phase II Trial of Brentuximab Vedotin As First Line Salvage Therapy in Relapsed/Refractory Hodgkin Lymphoma Prior to Autologous HCT

Abstract 501

Chen R, Palmer J, Martin P, Tsai N-C, Kim Y, Thomas S, Mott M, Sahebi F, Siddiqi T, Armenian S, Shan Y, Popplewell L, Forman S

Background

- **20%-30% of Hodgkin lymphoma (HL) patients are refractory/relapsed to induction regimen of ABVD**
- **Standard first-line salvage regimens such as ICE/DHAP/GDP have high response rates but are associated with significant toxicities.**

Salvage regimen	N	RR (%)	CR (%)	Grade III/IV AEs
ICE	65	88%	26%	Thrombocytopenia - 29% Febrile neutropenia - 13% Mobilization failures - 14% PRBC transfusions - 60% Platelet transfusions - 30%
DHAP	99	87%	21%	
GVD	91	70%	19%	
GDP	34	62%	9%	

Josting A, et al. *Ann Oncol.* 2005;16(1):116-123.
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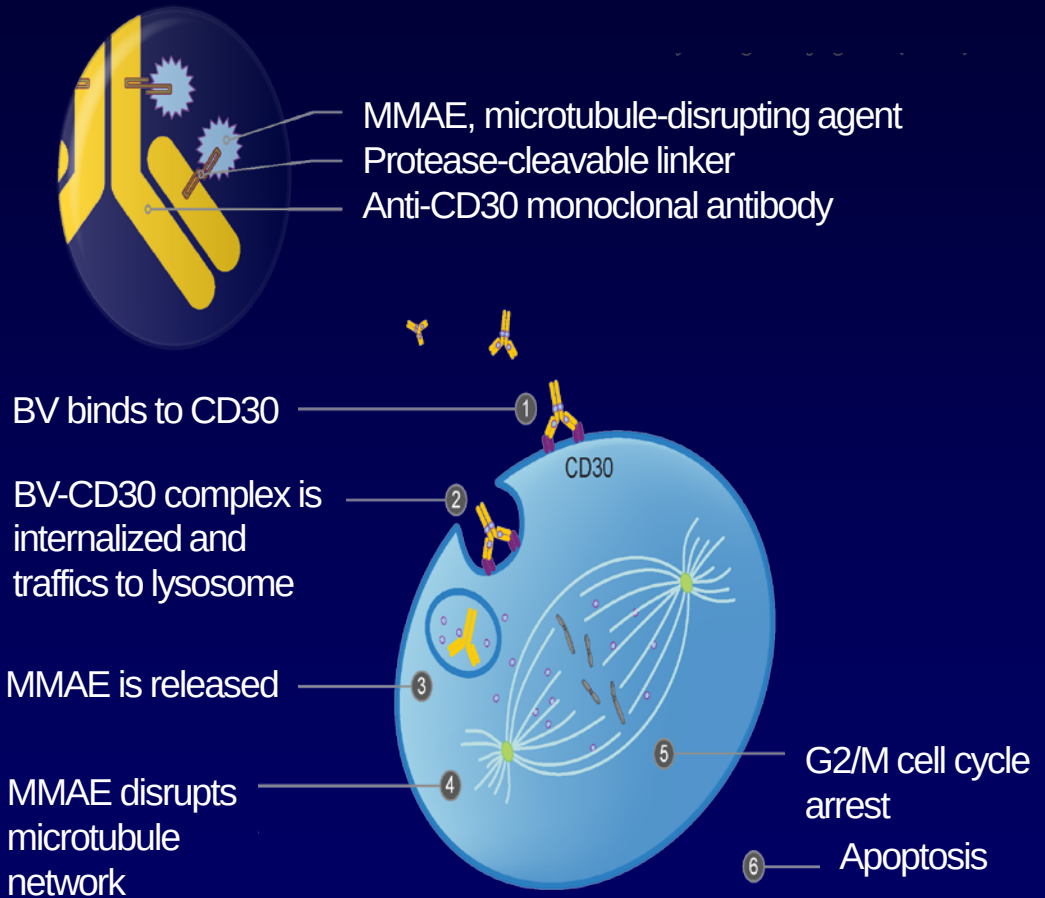
Brentuximab Vedotin

Brentuximab vedotin antibody-drug conjugate (ADC)



MMAE, monomethyl auristatin E (MMAE)

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- **Brentuximab vedotin (BV), selectively induces apoptosis of CD30+ cells.**
- **A phase II pivotal trial demonstrated 75% ORR, with 34% CR, and a favorable toxicity profile in HL patients post autologous hematopoietic cell transplantation (AHCT).**
- **We report results of a phase II trial evaluating BV as first line salvage therapy in relapsed or refractory HL prior to AHCT**

Eligibility Criteria

- **Inclusion:**
  - Age ≥10 years old
  - Histologically documented CD30+ HL at relapse
  - Induction failure (ABVD, BEACOPP, ABVE-PC)
  - Radiographically measureable disease
  - Adequate organ functions
- **Exclusion:**
  - Received second-line salvage therapy
  - Prior autologous or allogeneic stem cell transplantation

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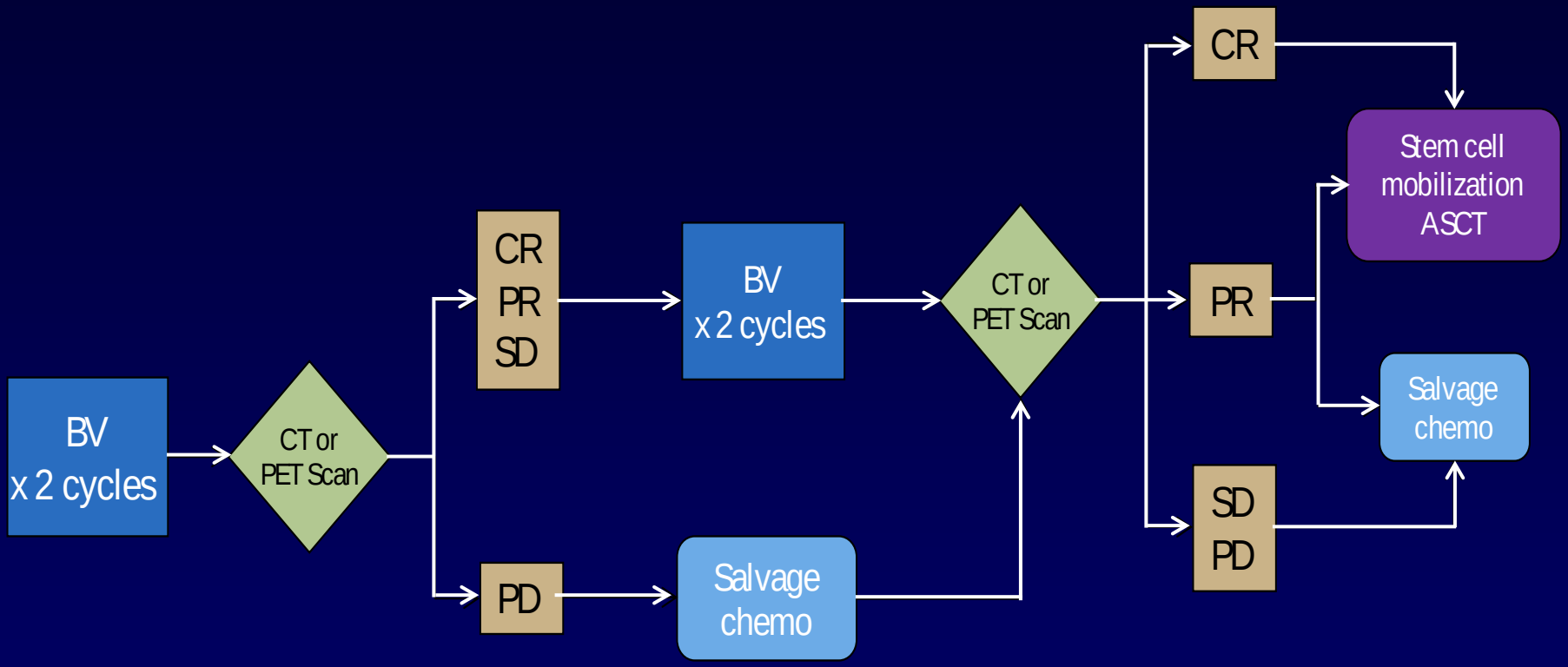
Study Schema



- **BV given at 1.8 mg/kg IV outpatient every 3 weeks for 4 cycles max**
- **No premedication with first cycle**

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Study Design

- Prospective multicenter phase II study
- Primary endpoint – overall response rate (ORR – CR + PR)
- Secondary endpoints: toxicity, stem cell mobilization rate, engraftment, biomarker assessment
- Simon optimal two-stage design used to assess ORR
- First stage, 12/23 patients must achieve CR or PR to continue
- Second stage, accrue up to 37 patients, with 23 or more responses regarded as sufficient to warrant further investigation.
- Target response rate is 60%
- Two-sided test at the *P* = .05 significance provides 80% power
- Toxicity was assessed and graded using the NCI CTCAE v4.03

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Baseline Patient Characteristics

Characteristics	N (%) or Median (Range)
Age	34 (11-67)
Institution	
City of Hope	31 (84%)
Weill Cornell	6 (16%)
Stage at Diagnosis	
I-II	19 (51%)
III-IV	18 (49%)
B symptoms	23 (62%)
Bulky Disease (> 5 cm)	32 (86%)
Induction Chemotherapy	
ABVD	34
ABVD/BEACOPP	2
ABVE-PC	1
Prior XRT	9 (24%)
Best Response to Induction	
Primary Refractory	24 (65%)
Relapsed (within 7 months)	13 (35%)

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Response Rate

37 accrued, 37 eligible for toxicity evaluation, 36 eligible for response evaluation

	Best Response	Best Response at Cycle 2	Response at Cycle 4 or EOT
ORR	25/36 (69%)	24/36 (67%)	22/36 (61%)
CR	13/36 (36%)	13/36 (36%)	13/36 (36%)
PR	12/36 (33%)	11/36 (31%)	9/36 (25%)
SD	10/36 (28%)	11/36 (31%)	10/36 (27%)
PD	1/36 (3%)	1/36 (3%)	4/36 (11%)

Univariate analysis: no differences in terms of age, sex, disease stage, response to induction, bulky disease, or B symptoms.

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Heme AE, Non Hem AE Occurred ≥15%, All Grade III-IV

Adverse Event	Grade 1	Grade 2
Anemia	**16%**	**3%**
Neutropenia	**11%**	
Thrombocytopenia	**8%**	
Lymphopenia		**3%**
Peripheral neuropathy	49%	3%
AST elevation	32%	5%
ALT elevation	27%	11%
Rash (new)	**24%**	**11%**
Muscle weakness	24%	5%
Hypoglycemia	22%	
Fatigue	19%	11%
Pruritis	19%	3%
Nausea	16%	3%
Abdominal Pain	11%	5%

Adverse Event	Grade 3	Grade 4
Anemia	**0%**	
Neutropenia	**5%**	
Thrombocytopenia		
Lymphopenia	**3%**	**3%**
AST elevation	3%	
Hyperuricemia		3%
Tumor lysis syndrome	3%	
Rash (new)	**5%**	
Pruritis	3%	
Creatinine elevated	3%	

No Growth Factor, PRBC, or PLT transfusions

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AHCT

- 33/37 successfully proceeded to AHCT (89%): 1 went to allo-HCT; 3 could not be salvaged
- 17/33 (52%) received BV only
- 16/37 (48%) received additional salvage chemotherapy (ICE/DICE/IGEV/GVD)
- 13 CR and 4/12 PR went to AHCT directly
- 24/33 (73%) were in CR at time of AHCT
- 8/33 (26%) were in PR at time of AHCT
- 1/33 SD at time of AHCT

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Stem Cell Mobilization

Patients were primed with G-CSF/cyclophosphamide/plerixafor

Characteristics	N (%) or Median (Range)
Cell count	5.97 x 10^6 CD 34 (2.64-34.45)
Days required for collection	2 (1-6)
Plerixafor usage	9 (27%)
ANC engraftment	11 (10-12)
Platelet engraftment	13 (9-23)

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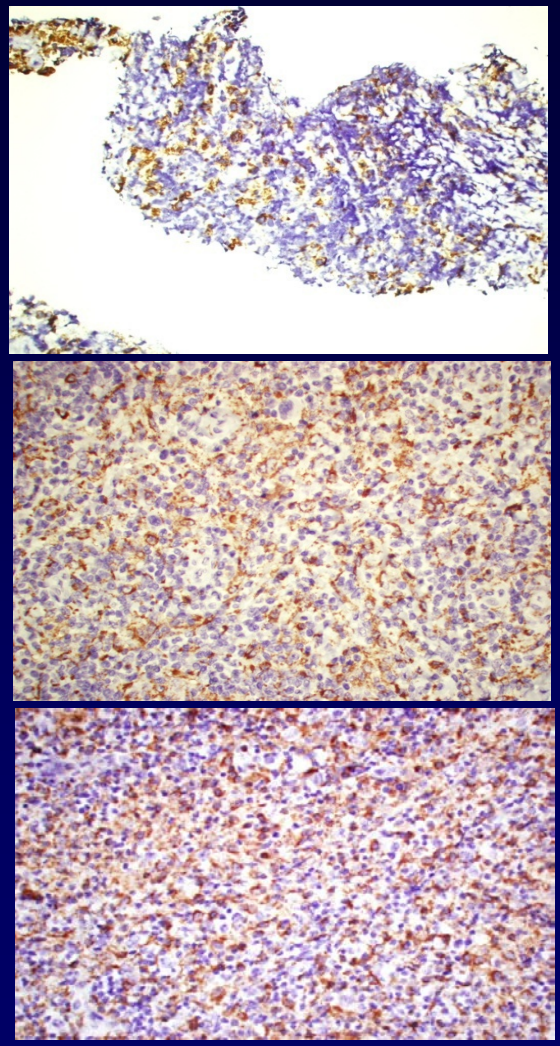
Biological Correlatives

- **CD 68 macrophages associated with failure to induction ABVD**
- **Performed IHC staining on COH samples prior to BV treatment**
  - **All COH samples were CD 68+**
  - **2+ (31%)**
  - **3+ (62%)**
  - **4+ (6%)**
- **CD 68 does not appear to be associated with outcome for BV**



2 +

3 +

4 +

Steidl C, et al. *N Engl J Med.* 2010;362(10):875-885.

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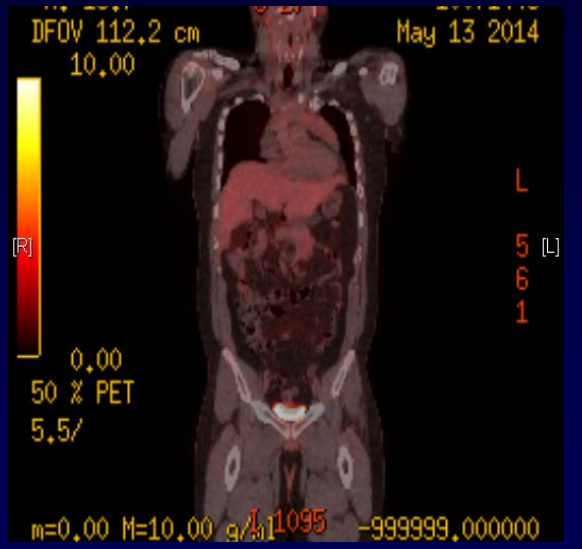
Patient Case, CR

- 30-year-old male
- Stage IVB
- Bulky disease
- ABVD x 6
- No XRT
- Relapse 4 month

Baseline



Cycle 2

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Summary/Conclusion

- ORR 69%, CR 36%
- Toxicity profile well tolerated
- Patients required no growth factor support, PRBC, or platelet transfusions
- 89% went to AHCT successfully, 52% went to AHCT without additional salvage chemotherapy
- Stem cell mobilization and engraftment not affected
- For patients with relapsed/refractory HL after induction chemotherapy, BV can be considered as first-line salvage therapy
- Risk of progression for patients not achieving CR after 2 cycles

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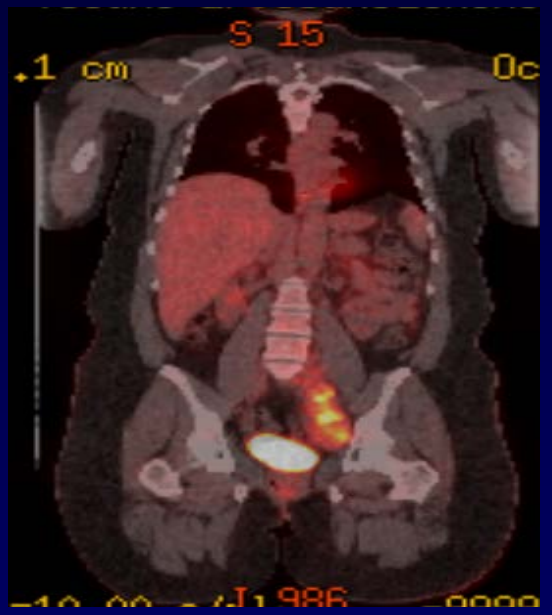
Patient Case, Progression

Baseline **Cycle 2** **Cycle 4**



- 45 female
- Stage IIB, Bulky disease
- ABVD x 6 cycle, no XRT
- Primary refractory

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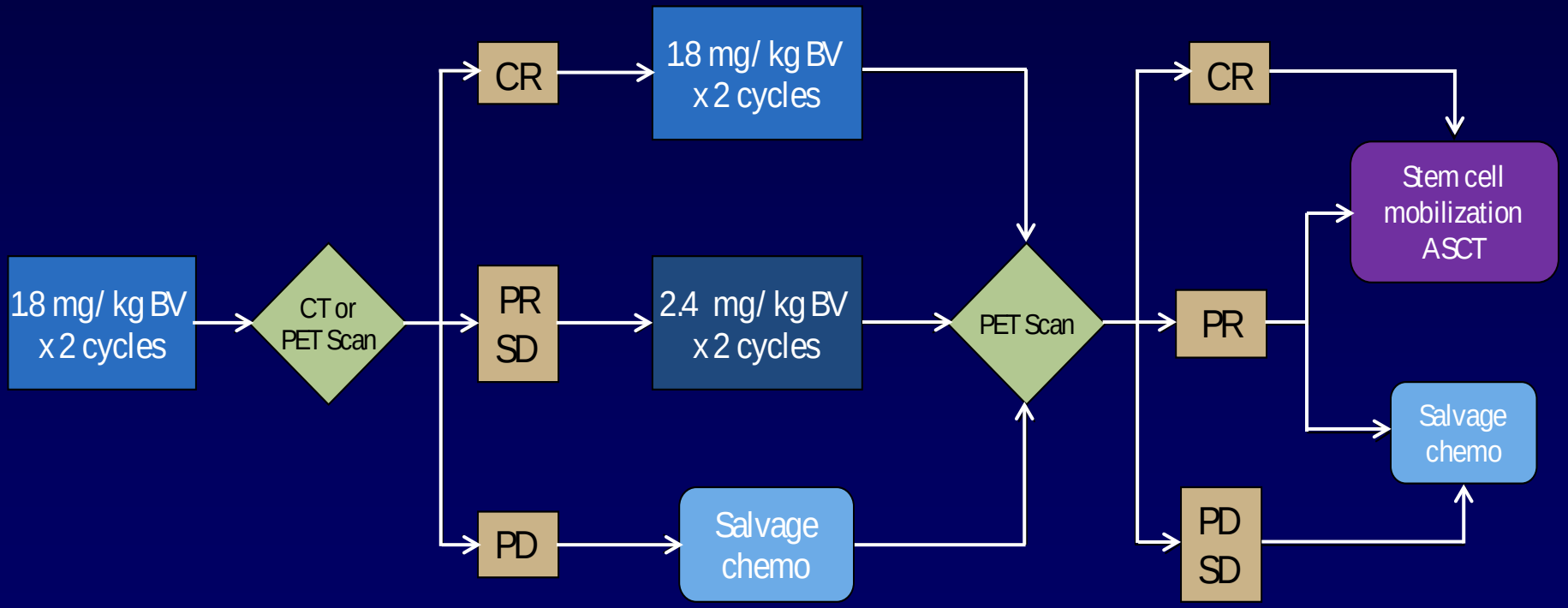
Amendment

BV dose increased from 1.8 mg/kg to 2.4 mg/kg after 2nd cycle for patients not achieving CR.



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