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CANCER RESEARCH UK

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Brentuximab Vedotin pre and post allogeneic transplant

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Overview

1. BV pre allogeneic transplant :

- What are the long term outcomes using allogeneic transplant after BV ?
- Is allogeneic transplant required in suitable patients who achieve CR after BV ?

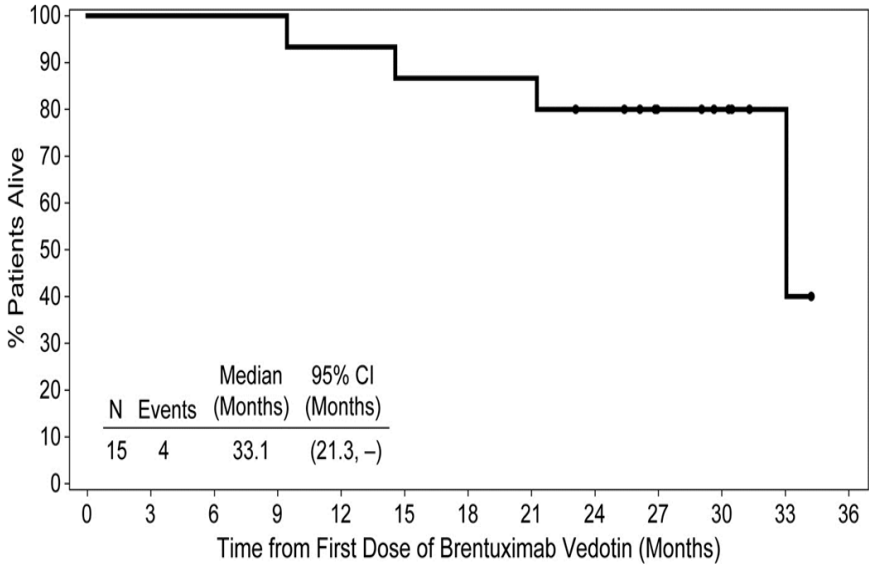
2. BV post allogeneic transplant

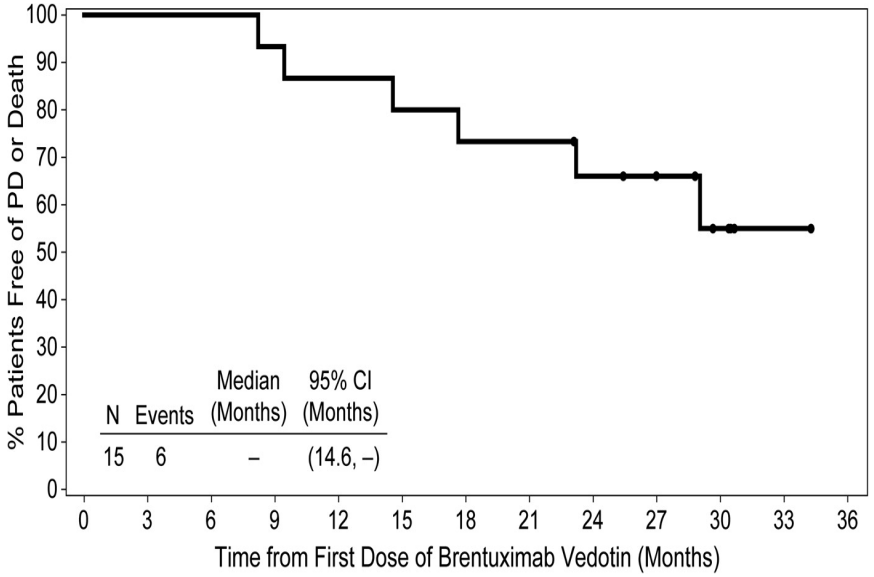
- What are the efficacy and safety data?
- Is there a role for BV and DLI ?

Allogeneic transplant following brentuximab vedotin in patients with relapsed or refractory HL and sALCL

Illidge T, Bouabdallah R, Chen R, Gopal AK, Moskowitz CH, Ramchandren R, Shustov AR, Tilly H, Trippett TM, Gibb A, Grove LE Advani R *Leukemia & Lymphoma* **2015,** 56, 703-710.

- Two pivotal phase 2 studies relapsed or refractory HL and sALCL.
- 15 of 160 patients in studies received a consolidative allo-SCT following BV (1.8 mg/kg q3 up to 16 cycles).
- Estimated 2-year PFS rate 66%, median PFS not reached.
- 11 of 15 patients alive 2-OS 80%.
- BV appears safe and able to reduce tumor burden to facilitate a consolidative allo-SCT.





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Brentuximab vedotin is associated with improved progression-free survival after allogeneic transplantation for Hodgkin lymphoma.
Chen R et al Biol Blood Marrow Transplant. 2014 Nov;20(11):1864-8

- BV enabled successful RIC-alloHCT in relapsed Hodgkin lymphoma, after a median follow-up of 14.4 months.
- 21 patients treated from 2009–2012 with BV prior to RIC-alloHCT with a uniform fludarabine/melphalan conditioning regimen and donor source - median follow-up of 29.9 months.
- Retrospective comparison of patient characteristics and outcomes of BV pre-treated patients to 23 patients who received fludarabine/melphalan RIC-alloHCT without prior BV, (2003–2009, pre-BV era).

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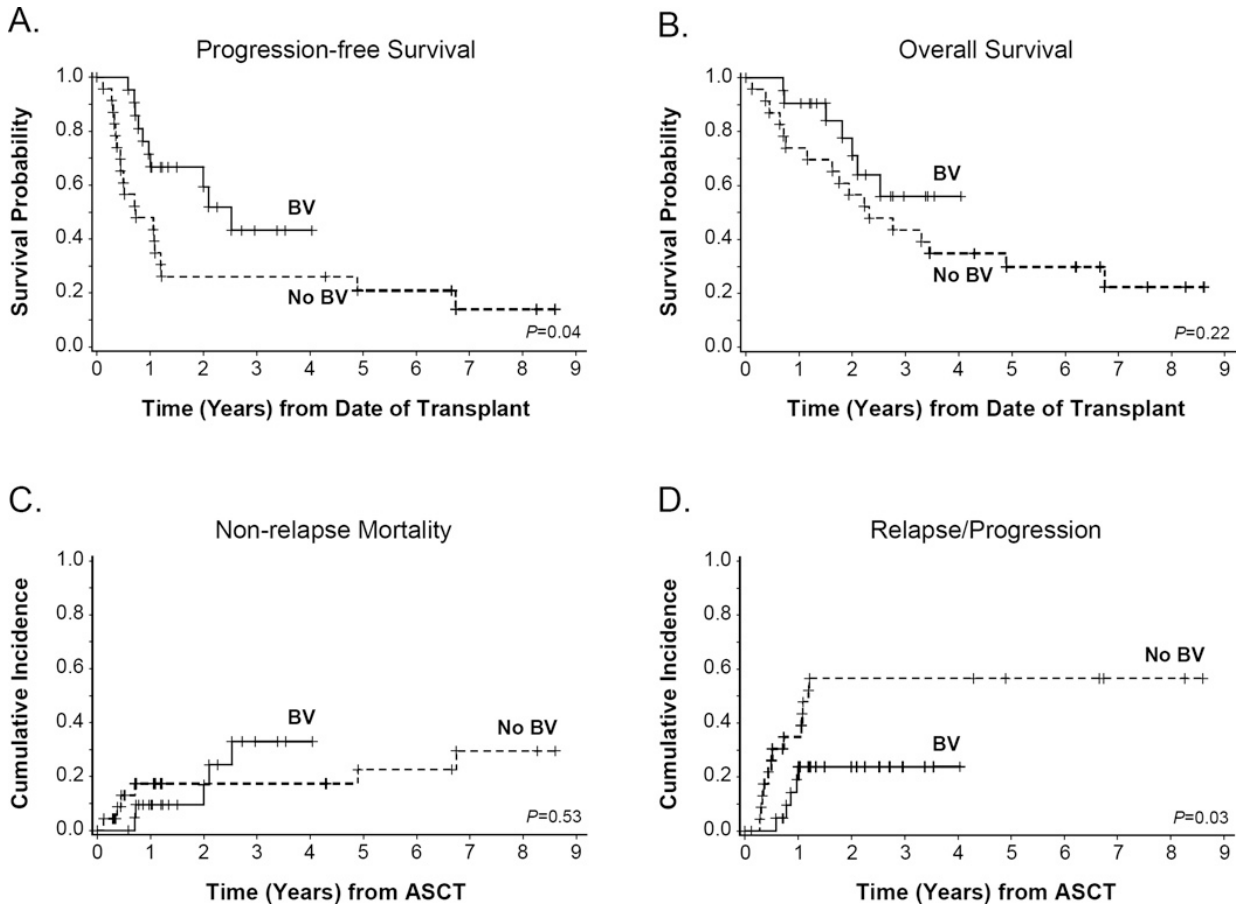

Improvements in 2-year PFS (59.3% versus 26.1%) (A) and cumulative incidence of relapse/progression (23.8% versus 56.5%). (D). No significant difference in OS (B) or TRM (C)

Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma.

Gopal AK, Chen R Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Connors JM, Engert A, Larsen EK, Chi X, Sievers EL, Younes A. Blood. 2015 Feb 19;125(8):1236-43

- Pivotal phase 2 trial of BV in relapsed/refractory HL following ASCT (N = 102)
- Median OS estimated at 40.5 months and PFS at 9.3 months.
- Improved outcomes were observed in patients who achieved a CR on BV, with estimated 3-year OS and PFS rates of 73% and 58%
- Of 34 CR patients, 16 (47%) remain progression-free after a median of 53.3 months (29.0 - 56.2 months)
- 12 patients remain progression-free without a consolidative allogeneic stem cell transplant.

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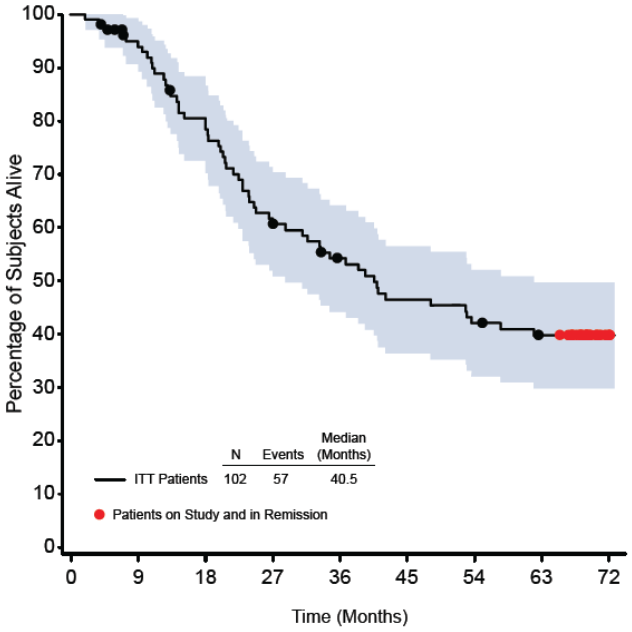
ORR: 72%; CR rate: 33% (per investigator)

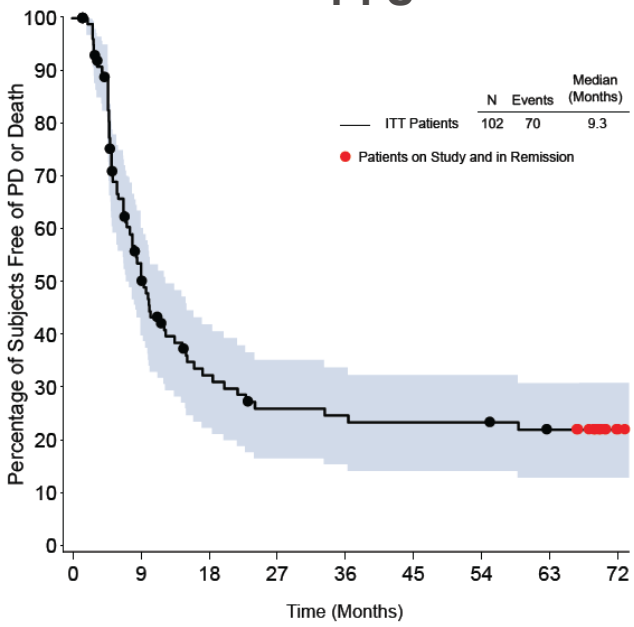
OS



Median OS: 40.5 mos
(95% CI: 28.7, 61.9 [1.8–72.9+])

5-yr OS: 41%
(95% CI: 31%, 51%)

PFS



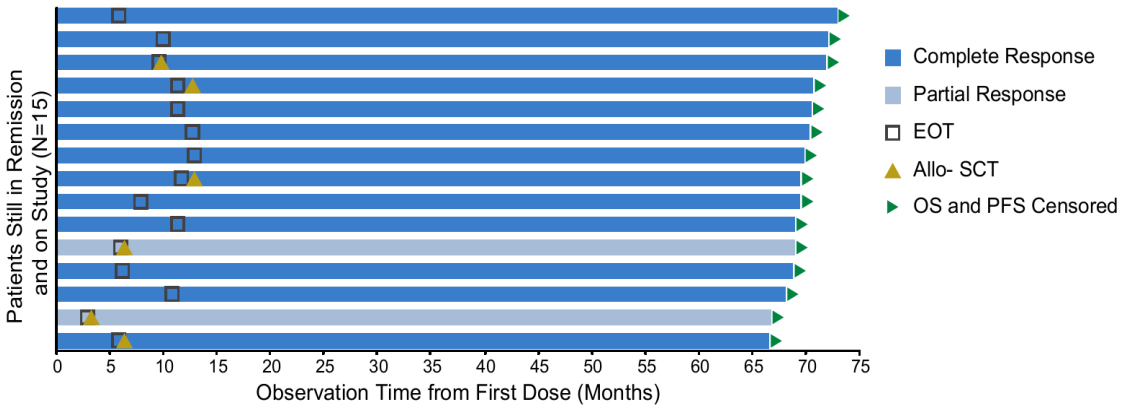
Median PFS: 9.3 mos
(95% CI: 7.1, 12.2)

Chen R, et al. ASH 2015, Poster presentation from Abstract #2736
1. Previous publications: Younes A, et al. J Clin Oncol 2012;30:2183–9; Gopal AK, et al. Blood 2015;125:1236–43

SGN35-003: 5-year follow-up from phase II study of brentuximab vedotin in R/R HL post-ASCT[1] – Update ASH 2015 (NCT00848926)

- Median DOR not reached for CR pts (n=34). DOR range 2–71.6+ months
- Of 34 CR patients, 16 (47%) remain progression-free after a median of 53.3 months (29.0 - 56.2 months)
- 12 patients remain progression-free without a consolidative allogeneic stem cell transplant.
- Younger age, good performance status, lower disease burden at baseline characteristic of CR patients (majority by cycle 7) : favorable prognostic factors for overall survival.

Pts in follow-up and in remission at end of study



Time to best response for pts in long term remission	CR (n=13)	PR (n=2)	Total (n=15)
Visit of earliest best response[a] (day 15–21), n (%)			
Cycle 2	2 (15)	2 (100)[b]	4 (27)
Cycle 4	5 (38)	0	5 (33)
Cycle 7	3 (23)	0	3 (20)
Cycle 10	2 (15)	0	2 (13)
Cycle 16	1 (8)	0	1 (7)

Chen R, et al. ASH 2015, Poster presentation from Abstract #2736
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Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation.
Gopal AK et al Blood.2012;120(3):560-8

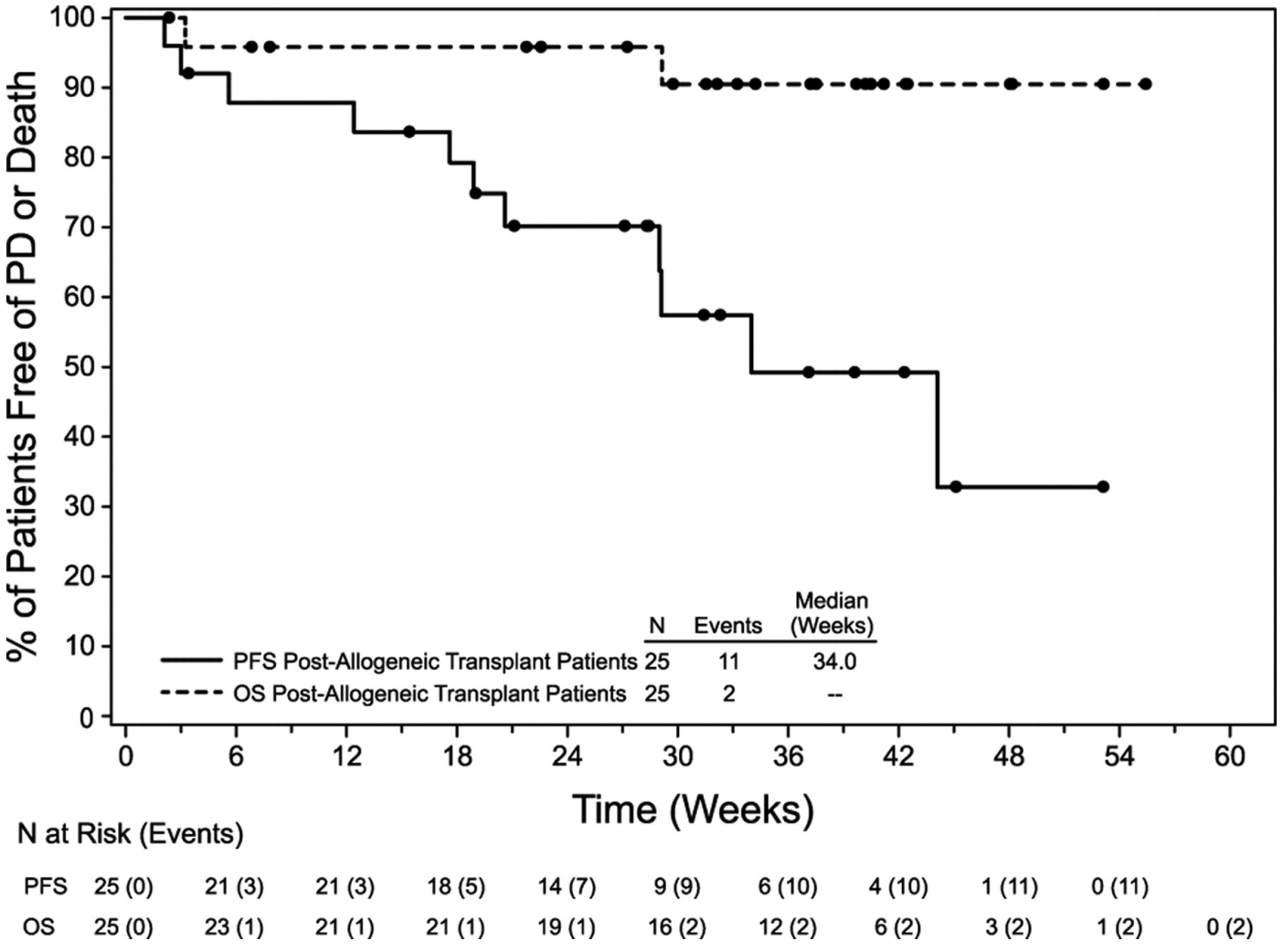
- 25 HL patients (median age, 32 years; range, 20-56) with recurrent disease after alloSCT (11 unrelated donors).
- Patients were > 100 days after alloSCT, had no active GVHD, and received a median of 9 (range, 5-19) prior regimens.
- Nineteen (76%) had refractory disease.
- Patients received 1.2 or 1.8 mg/kg of brentuximab vedotin IV every 3 weeks (median, 8 cycles; range, 1-16).
- ORR 50% and CR rates 38%

Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation.
Gopal AK et al Blood.2012;120(3):560-8

- Median time to response was 8.1 weeks, median PFS 7.8 months, and median OS not reached.
- Cough, fatigue, and pyrexia (52% each), nausea and peripheral sensory neuropathy (48% each), and dyspnea (40%) were the most frequent adverse events.
- The most common adverse events ≥ grade 3 were neutropenia (24%), anemia (20%), thrombocytopenia (16%), and hyperglycemia (12%).
- Cytomegalovirus was detected in 5 patients (potentially clinically significant in 1).

OS and PFS after brentuximab vedotin therapy.

Gopal AK et al Blood.2012;120(3):560-8



Ajay K. Gopal et al. Blood 2012;120:560-568

- median progression-free survival was 7.8 months, median overall survival was not reached.

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Brentuximab Vedotin Combined With Donor Lymphocyte Infusions for Early Relapse of Hodgkin Lymphoma After Allogeneic Stem-Cell Transplantation Induces Tumor-Specific Immunity and Sustained Clinical Remission

Sebastian Theurich et al. JCO 2013;31 (5):

Hypothesis : treatment with BV for relapsed HL after alloSCT will enhance GvL response by the induction of immunogenic cell death and further increase the GvL effect.

- Focused on T cells that expressed the natural-killer–cell c-type lectin receptor (CD161), characterizes a heterogeneous population comprised of activated T cells, natural killer T-cell–like cells and T helper 17 (TH17) cells with immunomodulatory properties depending on the surrounding microenvironment.

- **T helper 17 cells** (**T_h17**) are a subset of pro-inflammatory T helper cells defined by their production of interleukin 17 (IL-17). They are related to T regulatory cells and the signals that cause T_h17s to differentiate actually inhibit Treg differentiation

- Emerging data underline their effect on tumor and transplant immunology.

- TH17 cells, which derive from $CD4^+$ T-cell precursors and strongly express CD161, involved in the HL microenvironment

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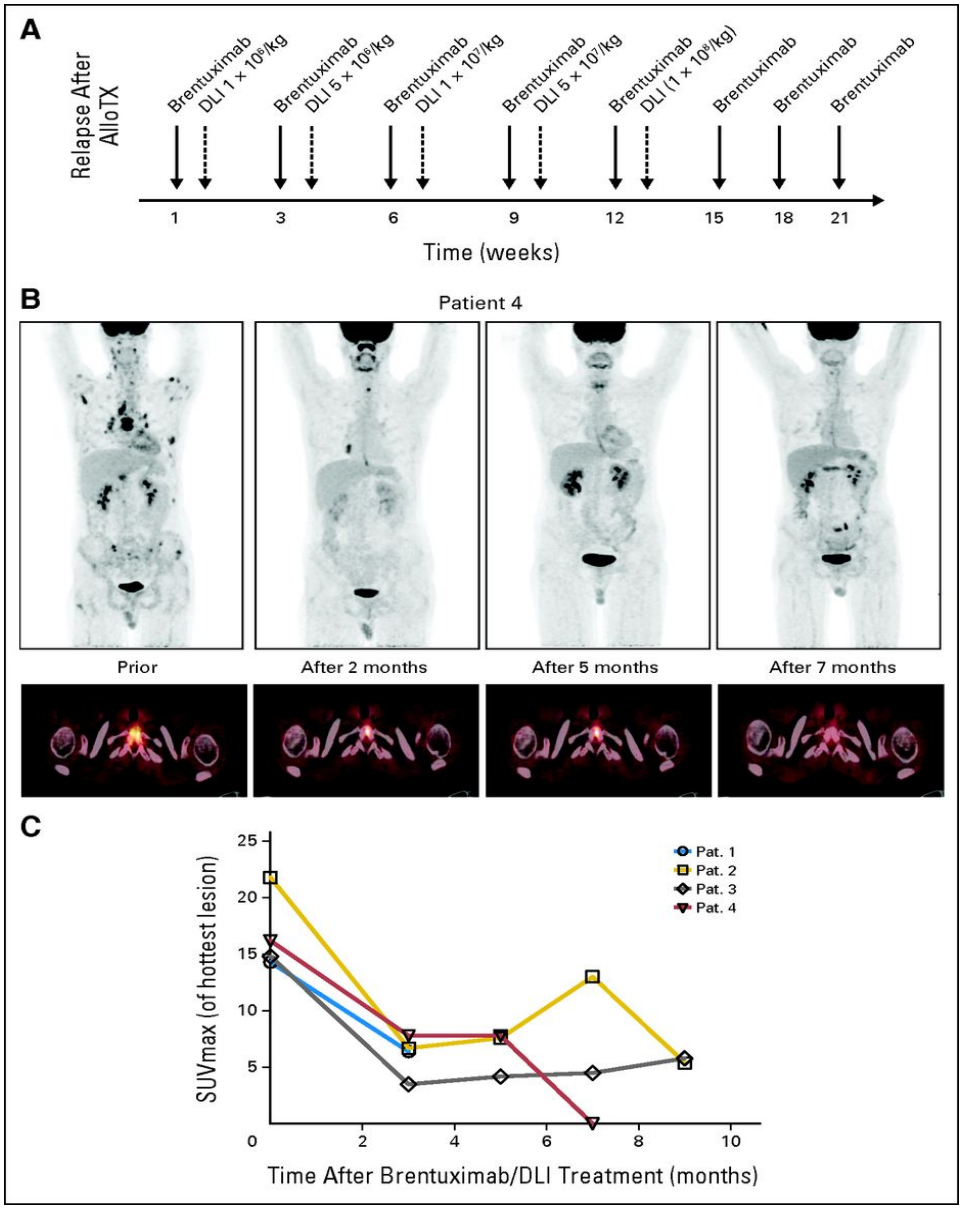
- Treatment algorithm combining brentuximab infusions (1.8 mg/kg per day every 21 days) with DLI administration in an alternating regimen
- Three patients were free of GvHD initially (patients 1, 2, and 3) and, thus, received DLI in increasing doses that were continued as long as no signs of GvHD occurred but to a maximum of five doses.
- An evaluation of treatment response Using PET CT every 2 to 3 months.
- All four patients showed marked clinical and metabolic responses with a median duration of disease control of at least 349 days (range, 259 -366 days) after treatment initiation. Still ongoing in 3 patients



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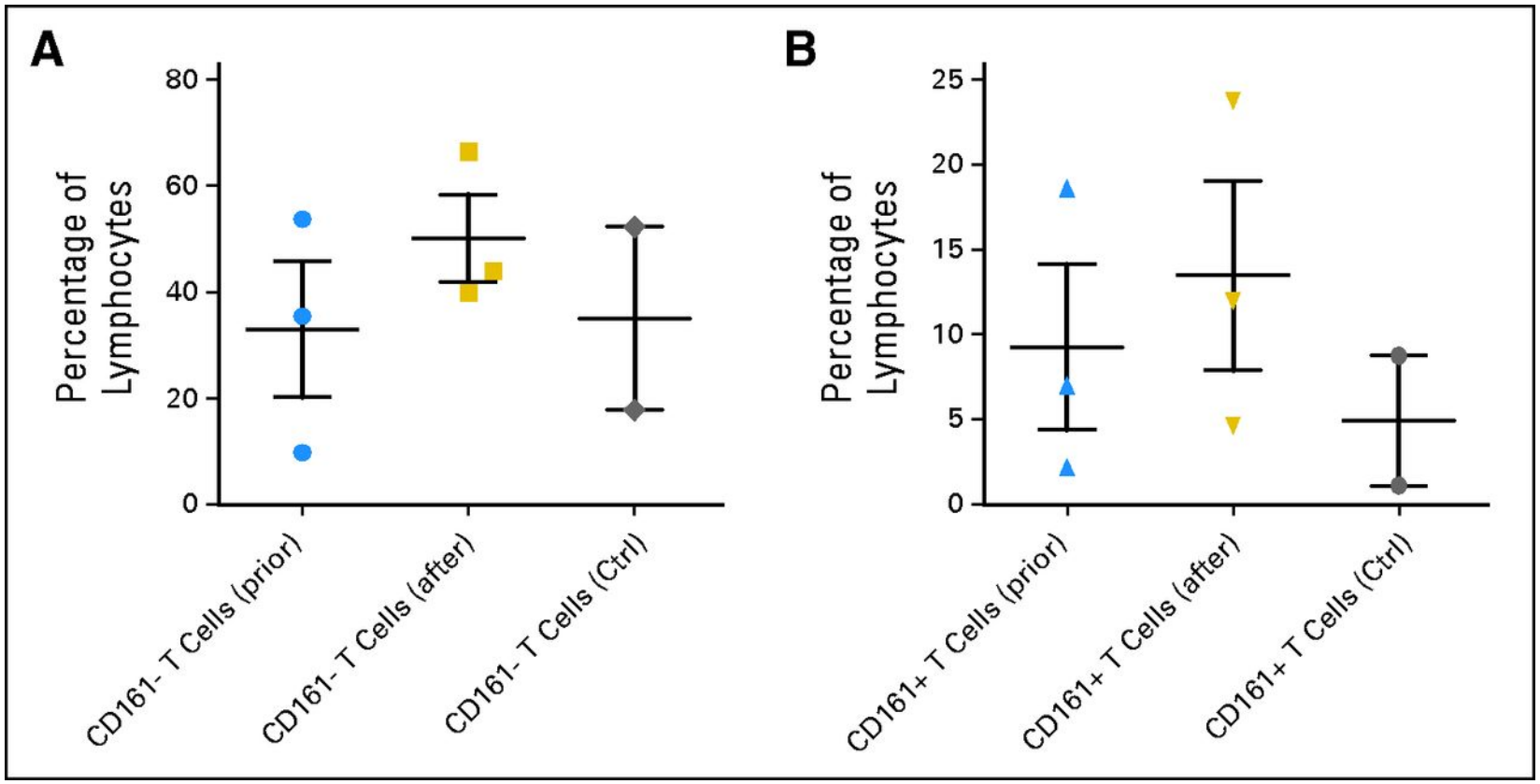
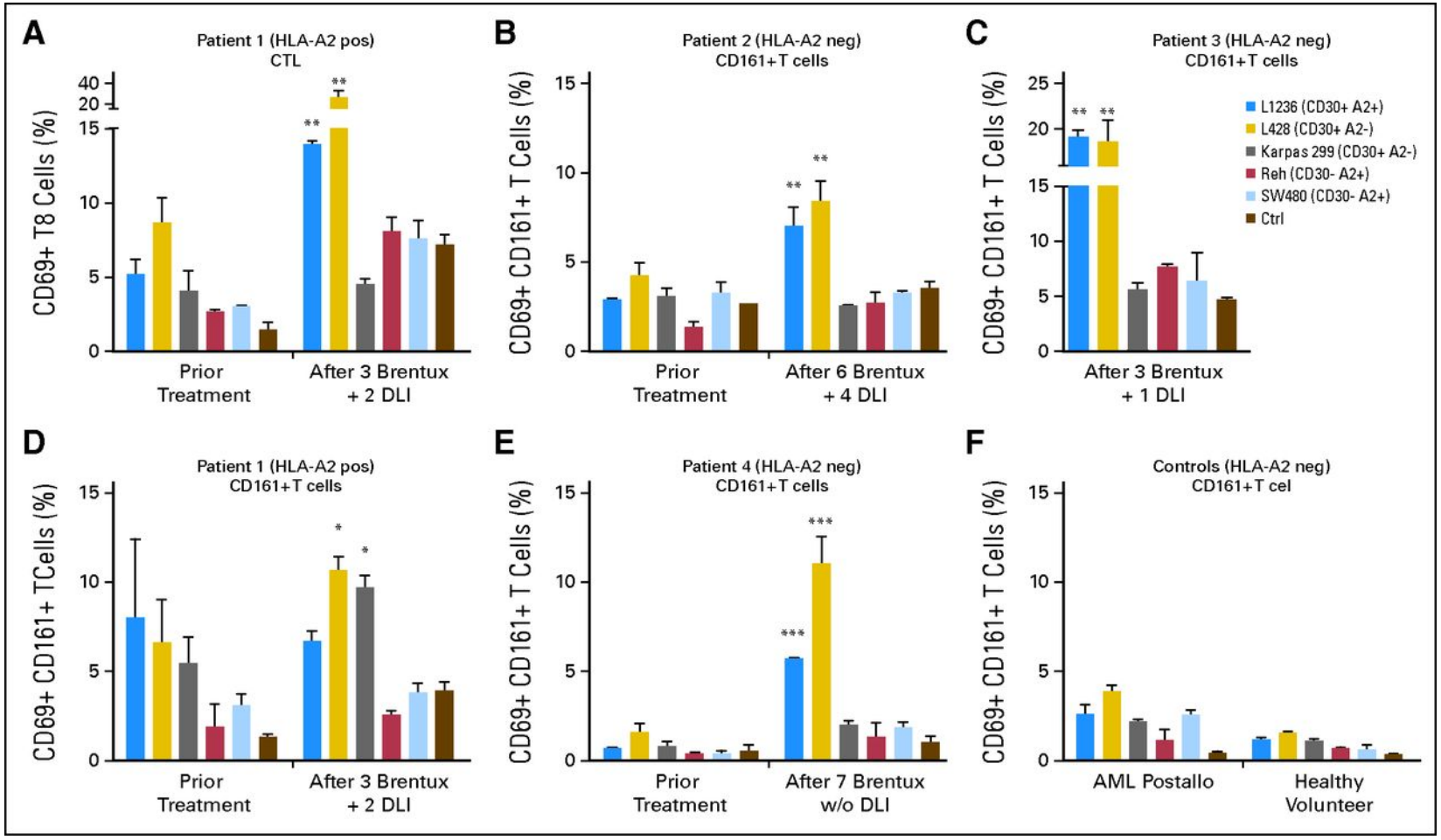


Circulating T cells, both CD161$^-$ and CD161$^+$, were increased after brentuximab and DLI and the fraction of CD161$^+$ T cells that coexpressed CD4 increased from 20% to 30% before treatment to greater than 50% after treatment, which suggested an induction of a predominant TH17-like phenotype.

Sebastian Theurich et al. JCO 2013;31:e59-e63

BV and DLI induces Tumor specific immunity



Sebastian Theurich et al. JCO 2013;31:e59-e63

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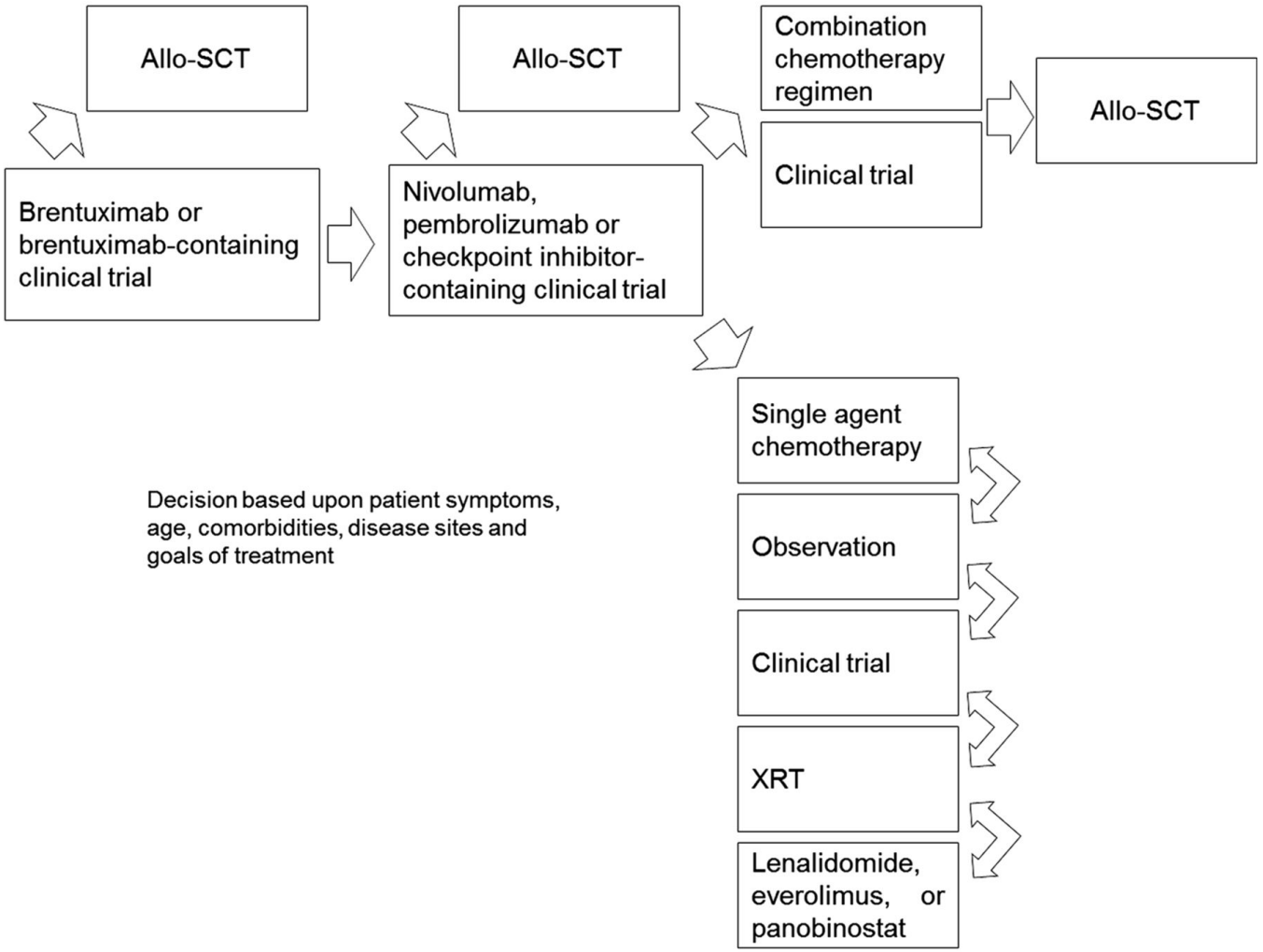
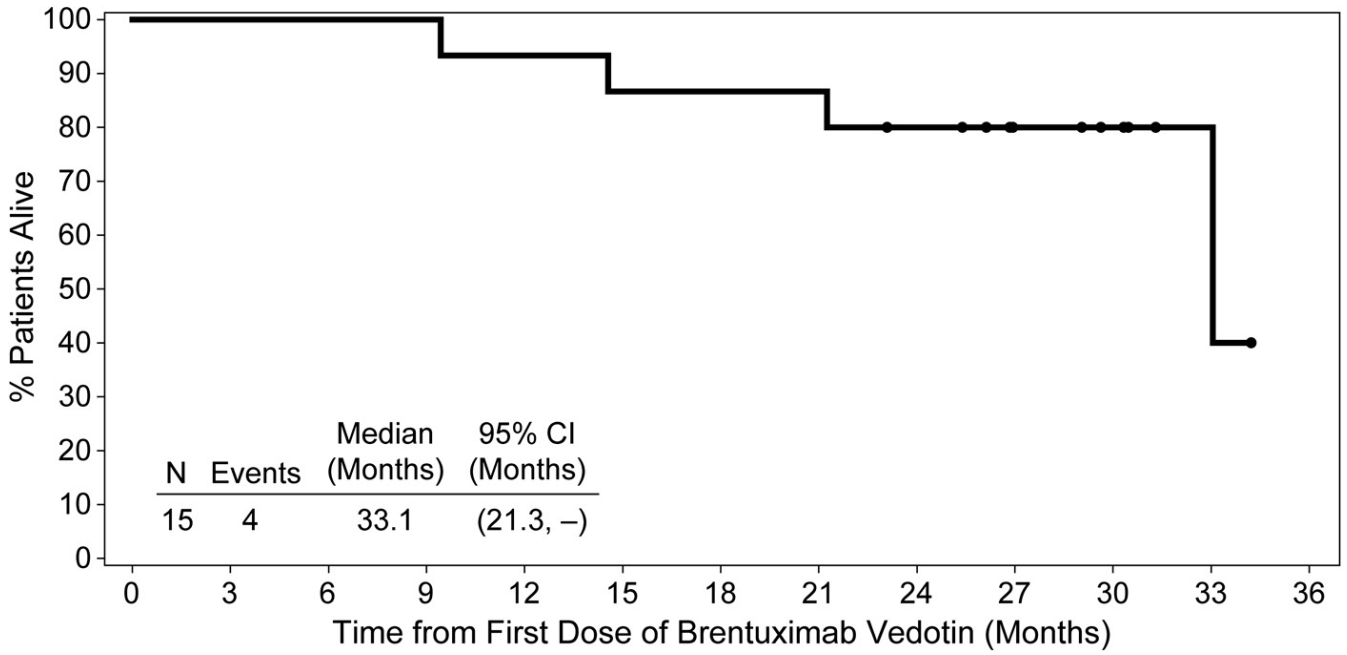
Summary

- Brentuximab vedotin (BV) appears safe and is able to substantially reduce tumour burden to facilitate a consolidative allogeneic-SCT.
- BV may be associated with improved progression-free survival after allogeneic-SCT for Hodgkin lymphoma
- BV post allogeneic transplant led to high ORR 50% and CR rates 38%. median PFS 7.8 months, median OS not reached.
- BV combined with DLI after Allogeneic Transplantation may induces tumor-specific immunity and sustained clinical Remission and requires further investigation

Suggested algorithm for the treatment of cHL patients who relapse after ASCT. Allo-SCT, allogeneic stem cell transplant; XRT, radiation therapy.

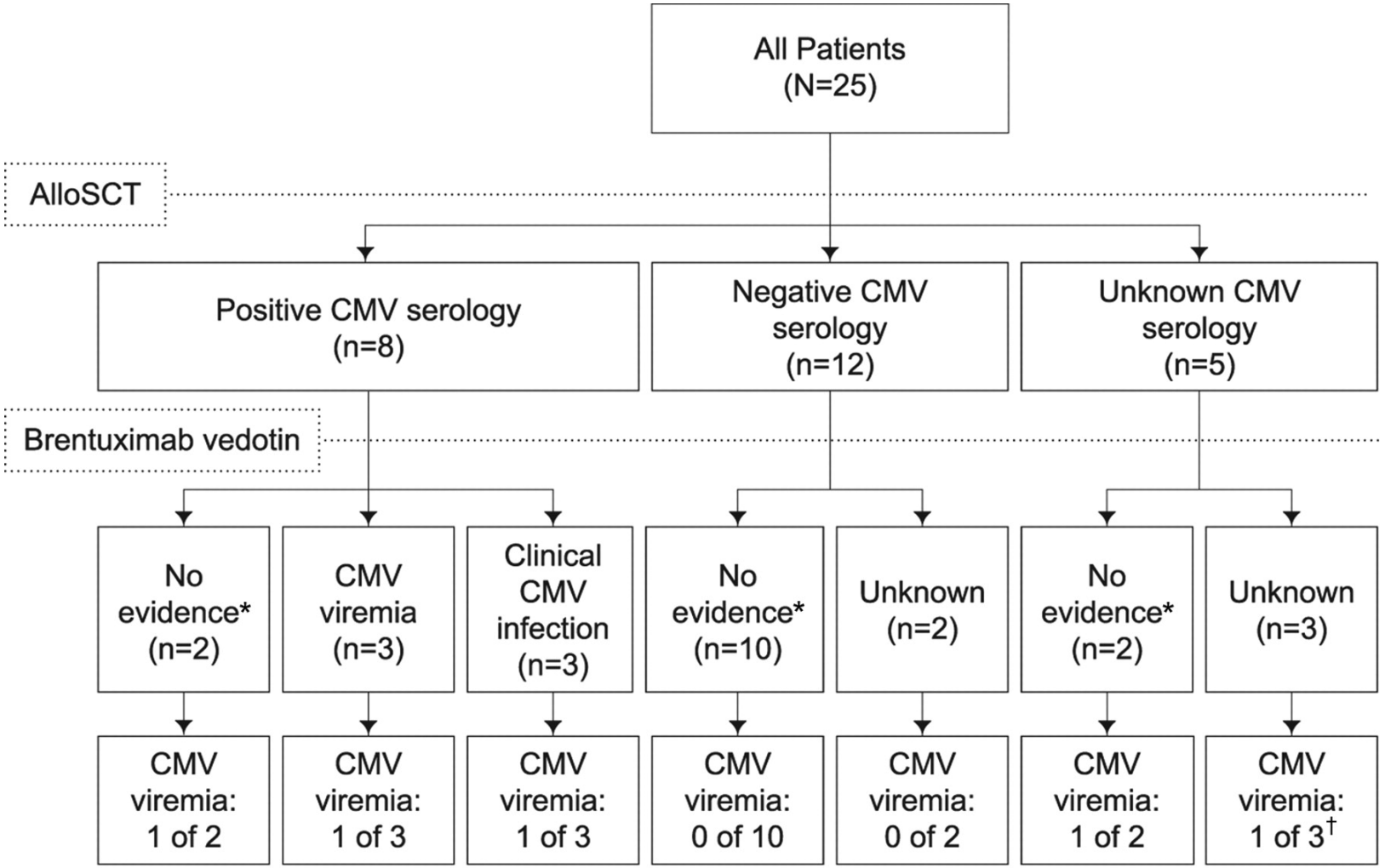


Lapo Alinari, and Kristie A. Blum Blood 2016;127:287-295



Published in: Tim Illidge; Reda Bouabdallah; Robert Chen; Ajay K. Gopal; Craig H. Moskowitz; Radhakrishnan Ramchandren; Andrei R. Shustov; Herve Tilly; Tanya M. Trippett; Adam Gibb; Laurie E. Grove; Ranjana Advani; *Leukemia & Lymphoma* **2015,** 56, 703-710.

CMV history and CMV viremia after brentuximab vedotin therapy. *No evidence of CMV viremia or clinical infection was reported.



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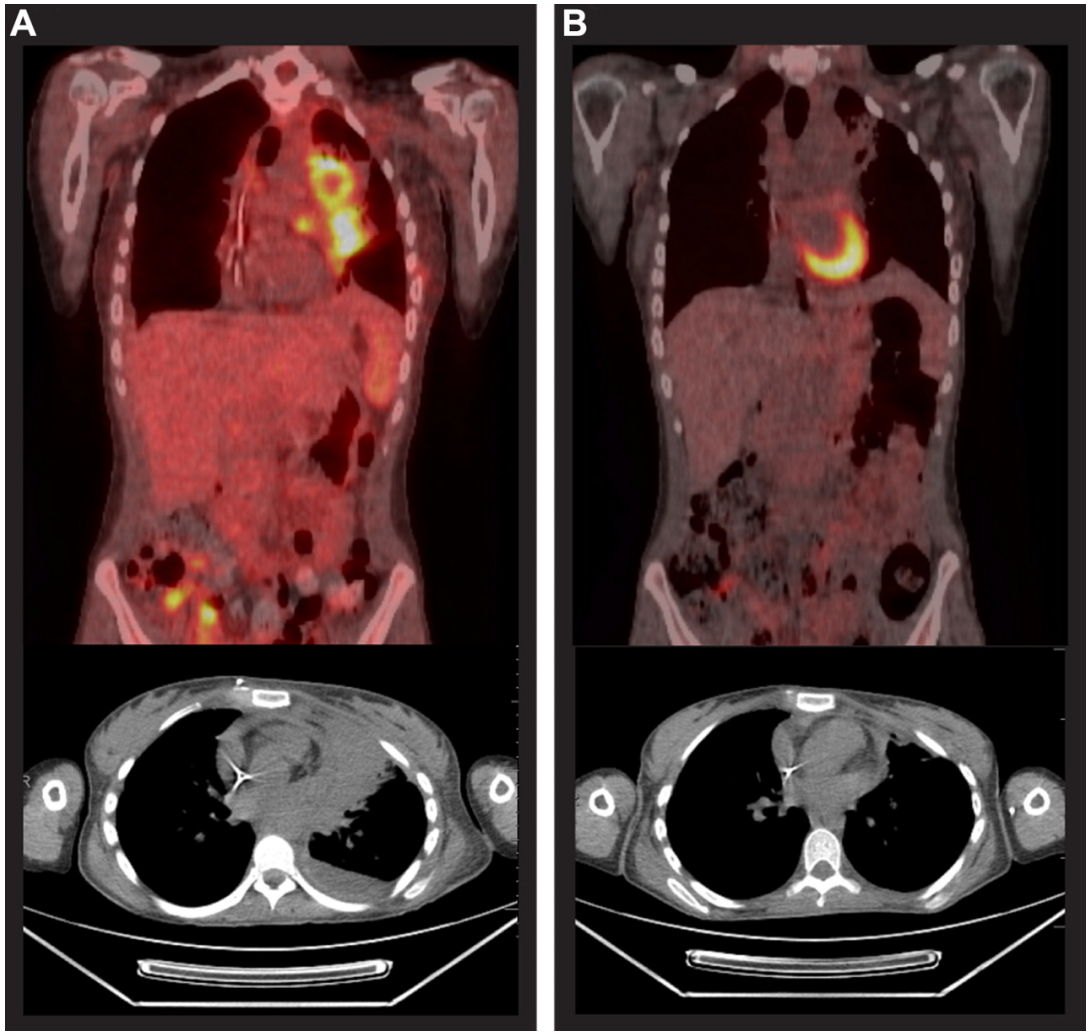
Case study before and after brentuximab vedotin therapy.



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