How Does the Selection of 1L Therapy Impact Subsequent Treatment Approaches

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Disclosures

- Advisory Board: Seattle Genetics

Objectives

- To discuss the role of traditional chemotherapy and novel therapy in relapsed Hodgkin lymphoma.
- To outline current treatment approaches in the setting of evolving frontline paradigms
- To describe the role of re-treatment with brentuximab or PD-1 based therapy in the relapsed setting.

Clinical Case

- 25-year-old is diagnosed with stage 4B classic Hodgkin lymphoma with lung and bone marrow involvement.
- He is treated initially with brentuximab and AVD chemotherapy for 6 cycles and achieves a complete response.
- He relapses within 6 months of completion of therapy.

What should he be treated with next?

Should he receive post-transplant maintenance?

Traditional Relapsed Paradigm

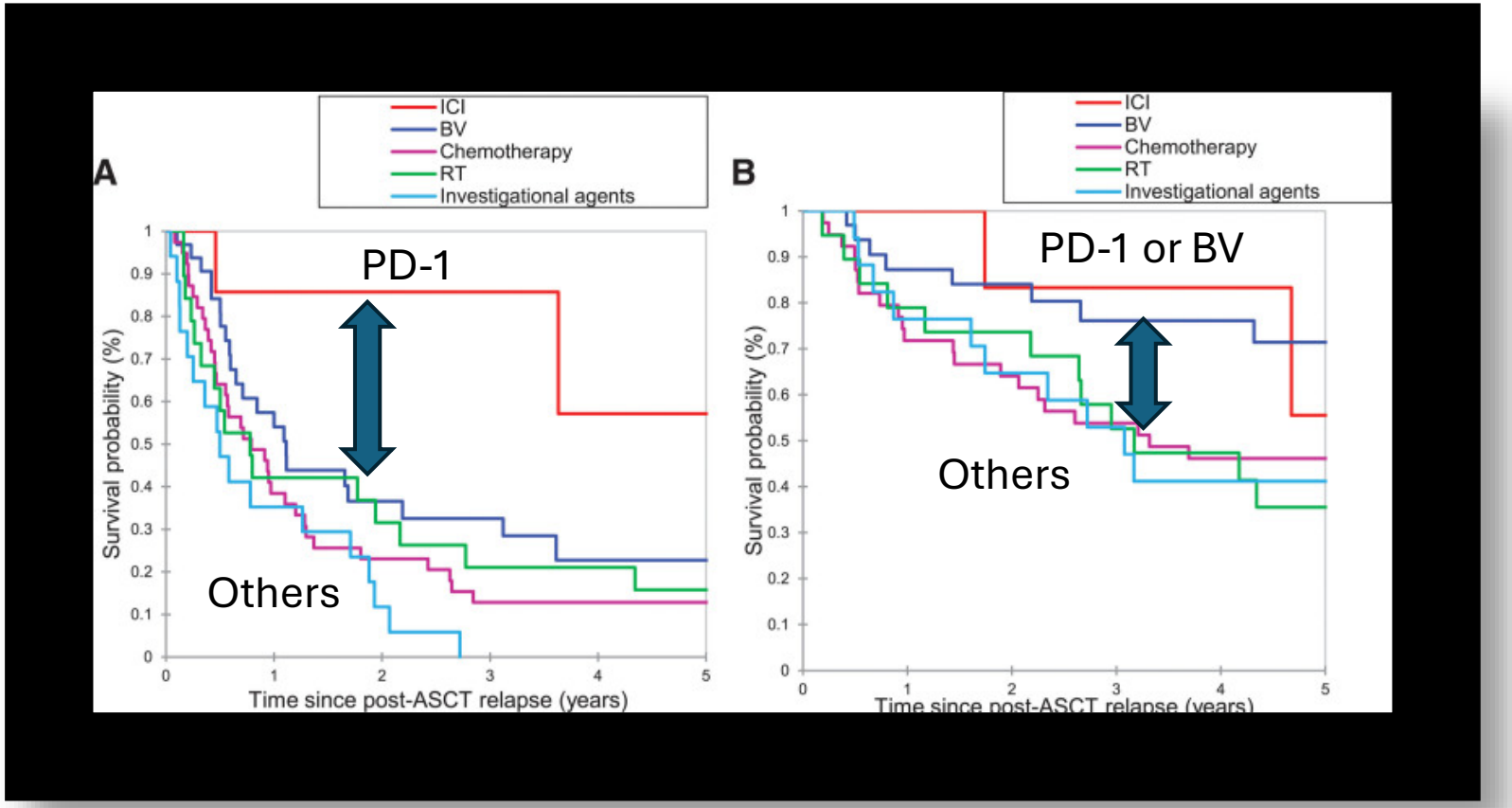
ABVD or BEACOPP

R

HSCT + ASCT

R

Brentuximab Vedotin
PD-1 antibodies

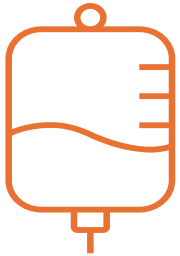


- The introduction of BV and anti–PD-1 antibodies significantly improved outcomes in the relapsed setting
- 2-year OS rates after ASCT reaching 75% vs ~50% following HDCT and ASCT alone.

Stuver R, et al. *Blood* 142:3069, 2023 (suppl 1)

Role of Brentuximab in Relapsed Therapy

Brentuximab Single Agent



BV single-agent

ORR of 75%, CR ~30%

Median PFS of 6-12 months regardless of whether treatment is pre- or post-transplant

Brentuximab Combination Therapy

BV + ICE (PET Directed)

27% CR (DV1-2) to BV alone, remainder received augmented ICE x2.

76% of patients achieved CR before ASCT; 2-year PFS of 80%.

No difference between patients achieving CR from BV alone versus after BV and augmented ICE.

BV+ Nivolumab

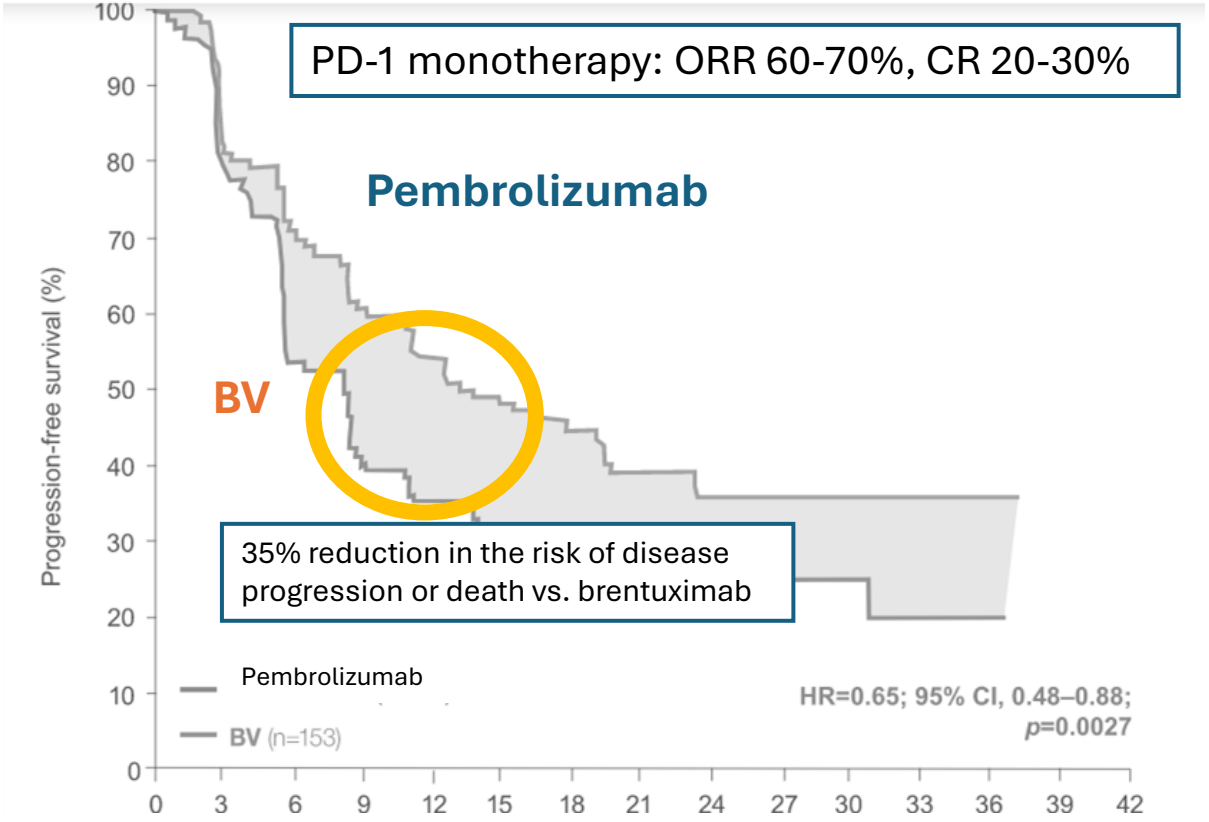
61% CR, 82% ORR

2-year PFS if taken directly to transplant= 97% (82% whole cohort)

Younes A, et al. *J Clin Oncol* 30:2183-2189, 2012; Moskowitz AJ, et al. *Lancet Oncol* 16:284-292, 2015

Anti-PD-1-Based Relapsed Therapy

PD-1 Monotherapy



PD-1 Combination Therapy

Pembrolizumab + GVD x 2-4 cycles

- **95% with CR** proceeded to transplant after 2 or 4 cycles.
- **100% PFS** following transplant.

Pembrolizumab + ICE

- 2-year PFS **87.2%**
- 2-year OS **87.2%**

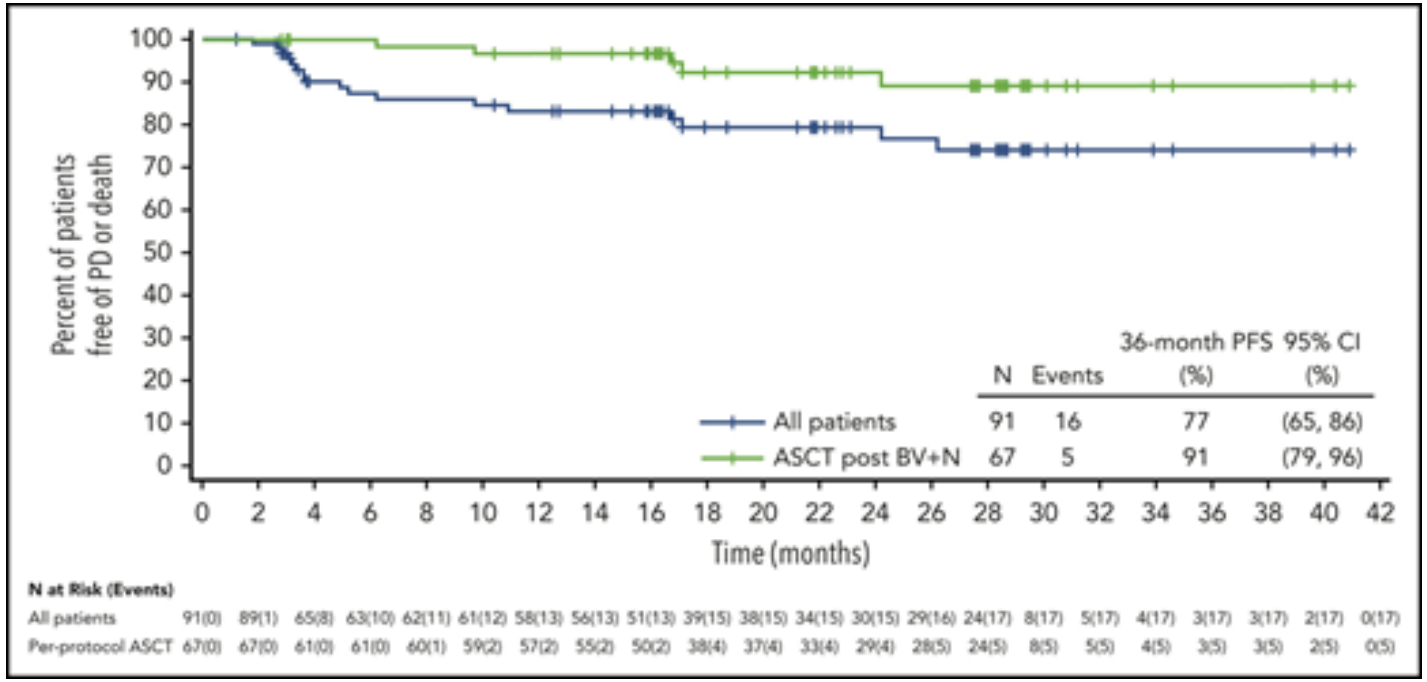
Nivolumab + ICE

- **2-year PFS of 94%** in patients who went on to transplant

Kuruvilla Jet al. Lancet Oncol. 2021 Apr;22(4):512-524; Mei, et al. *Blood* 139:3605-3616, 2022, 2012; Moskowitz AJ, et al. *Lancet Oncol* 16:284-292, 2015; Bryan LJ et al. JAMA Oncol 9:683-691, 2023

Combination Novel Therapy:

Brentuximab + Nivolumab in Relapsed HL



Brentuximab and Nivolumab x 4 cycles

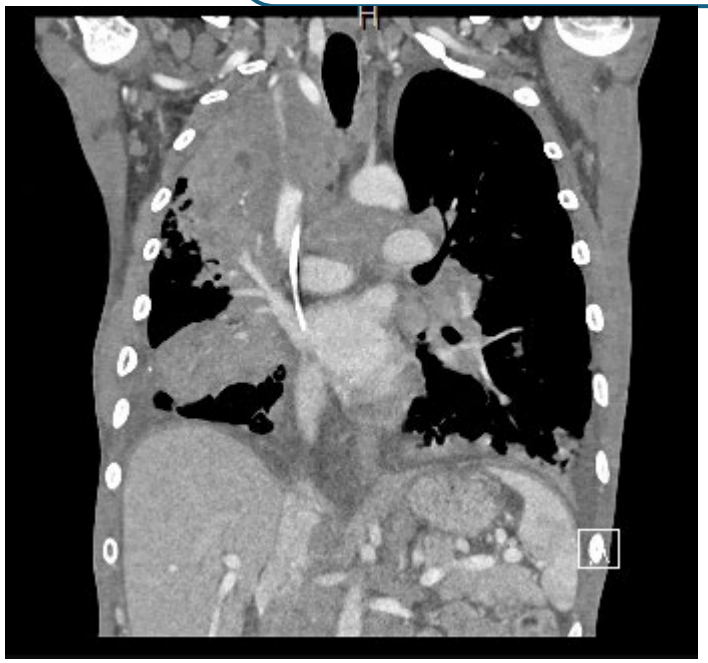
- Efficacy:
  - ORR 85%, CR 67%
  - 3-year PFS of 77% (whole cohort) and 91% for those who underwent ASCT.
- Safety:
  - No impact on mobilization or collection
  - 5 patients (8%) were treated with systemic steroids for immune-related side effects

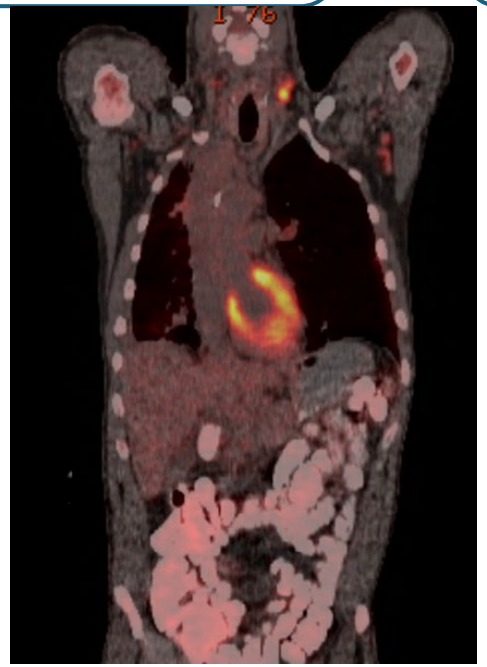
Advani et al. *Blood* (2021) 138 (6): 427–438.

Case continued

He is treated with pembrolizumab ICE on a clinical trial and collects stem cells but due to COVID he loses his job and healthcare insurance and is lost to follow up for 1 year.

He calls into the office noting he is having new night sweats, itch without a rash, and dyspnea on exertion. He is seen in clinic and is hypoxic with minimal activity and has palpable bulky adenopathy in the cervical and supraclavicular regions.

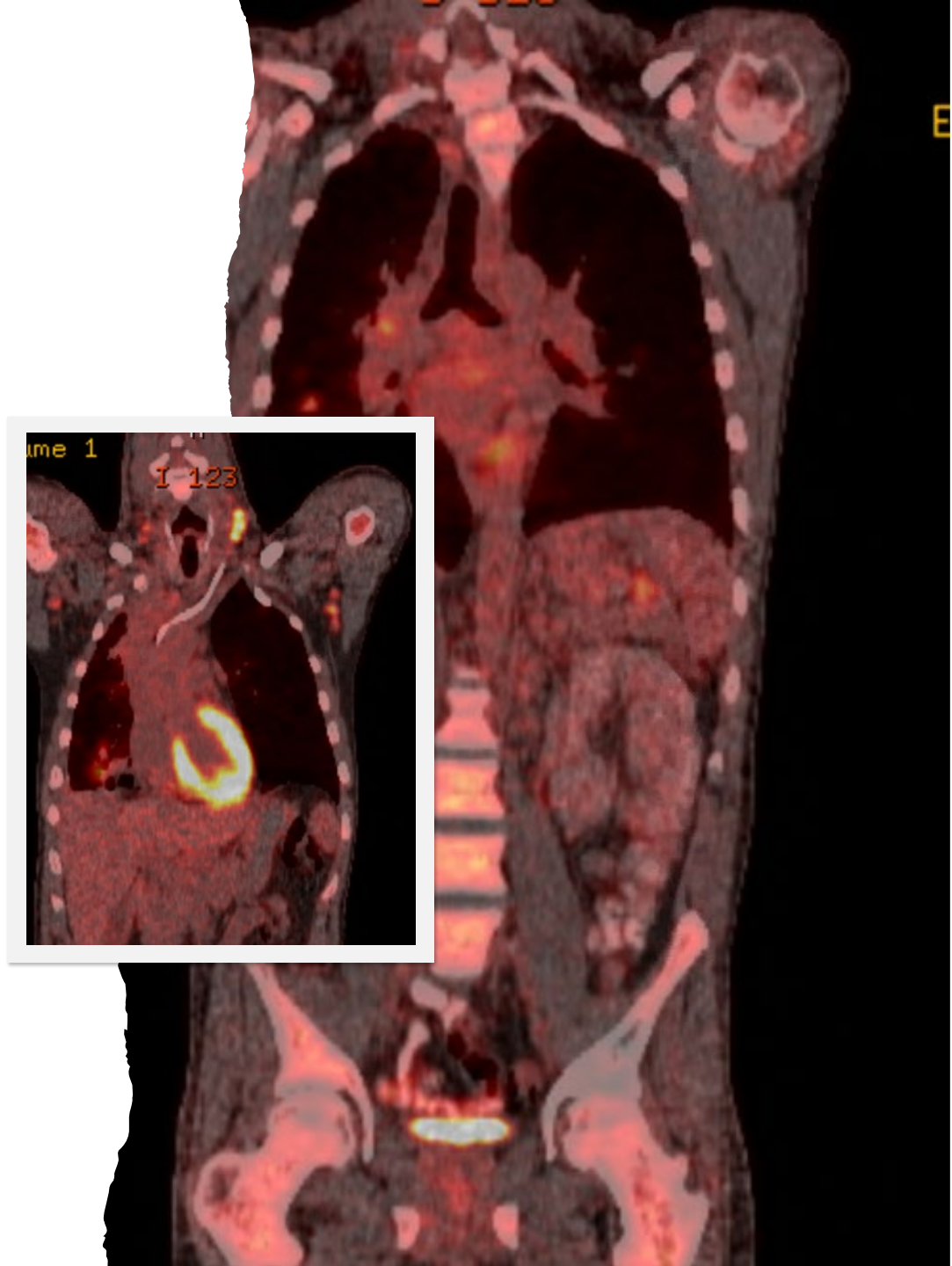




What should I treat with next?

Case continued

- He is treated emergently with DHAP in the hospital with improvements in his respiratory status and then received nivolumab and brentuximab for 4 cycles of therapy. His symptoms have completely resolved. At the end of his 4 cycles his PET shows:
  - ***" FDG avid LAD involving bilateral cervical, supraclavicular, bilateral axillary, multistation mediastinal, aortocaval and perisplenic lymph nodes. Majority of these lymph nodes appear increased in size and FDG avidity with some newly apparent FDG avid lymph nodes."***
  - ***"Interval progression of pulmonary metastatic disease with grossly stable size of right anterior mediastinal conglomerate mass but increased size and number of FDG avid pulmonary nodules."***
- He is referred for a biopsy, but surgical oncology could not find a site to biopsy.
- A repeat CT of the chest shows resolution of disease.
- He is admitted for autologous stem cell transplant and BEAM conditioning.



What is the Role of Retreatment with Novel Agents?

Brentuximab Retreatment

- Hodgkin Patients retreated with BV following A + AVD
  - 10 patients initially responding to A + AVD were retreated with BV
    - Monotherapy= 8; Combination = 2,
    - Neither treatment duration nor ORR were reported.
- Responses occur, but are not durable
  - ORR the BV retreatment in cHL is ~ 50-60% (CR =20-30%).
  - Responses rarely last > 1 year
  - In PTCL 29 BV retreatment ORR 59% (CR 38%), median treatment duration of 2.1 months.

Sano et al. Curr Oncol. 2024 May 2;31(5):2598–2609

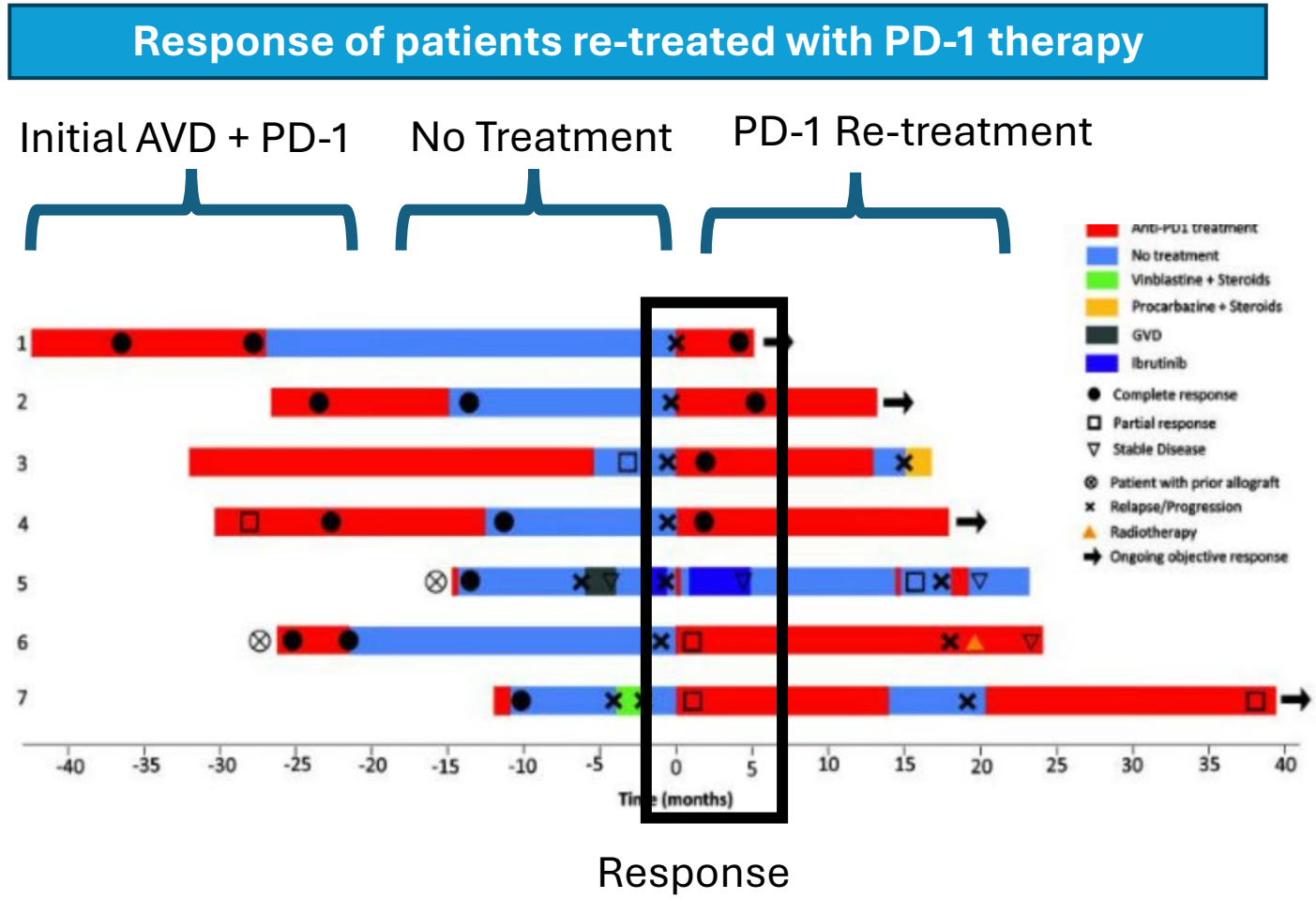
PD-1 Retreatment is Effective with No or Minimal Reduction in Efficacy

Retrospective analysis of cHL Re-Treatment

- Median # prior therapy=6;
  - 7 BV, 5 ASCT, 2 AlloSCT
- ORR 100%; CR for 4/7 and PR 3/7.
- 4 /7 patients have ongoing responses to anti-PD1 monotherapy, 3 beyond 12 months.
- Anti-PD1 discontinued after a median of 11.4 months

Retreatment after Avelumab:

- ORR 86% with PD-1 post avelumab
- Median duration of response of 26.4 months and
- Median time to progression of 22.2 months.



Manson et al. Haematologica. 2020 Feb 13;105(11):2664–2666; Thiruvengadam et al. Clin Lymphoma Myeloma Leuk. 2022 Oct;22(10):e893-e897.

Post-Transplant Maintenance Approaches

Maintenance with Brentuximab

Phase III AETHERA trial demonstrated superior 5-year PFS of 59% versus 41% compared with placebo.
BV-naïve high-risk patients with ≥ 1 of the following: primary refractory disease, relapse <1 year, or extranodal disease

Maintenance with Pembro

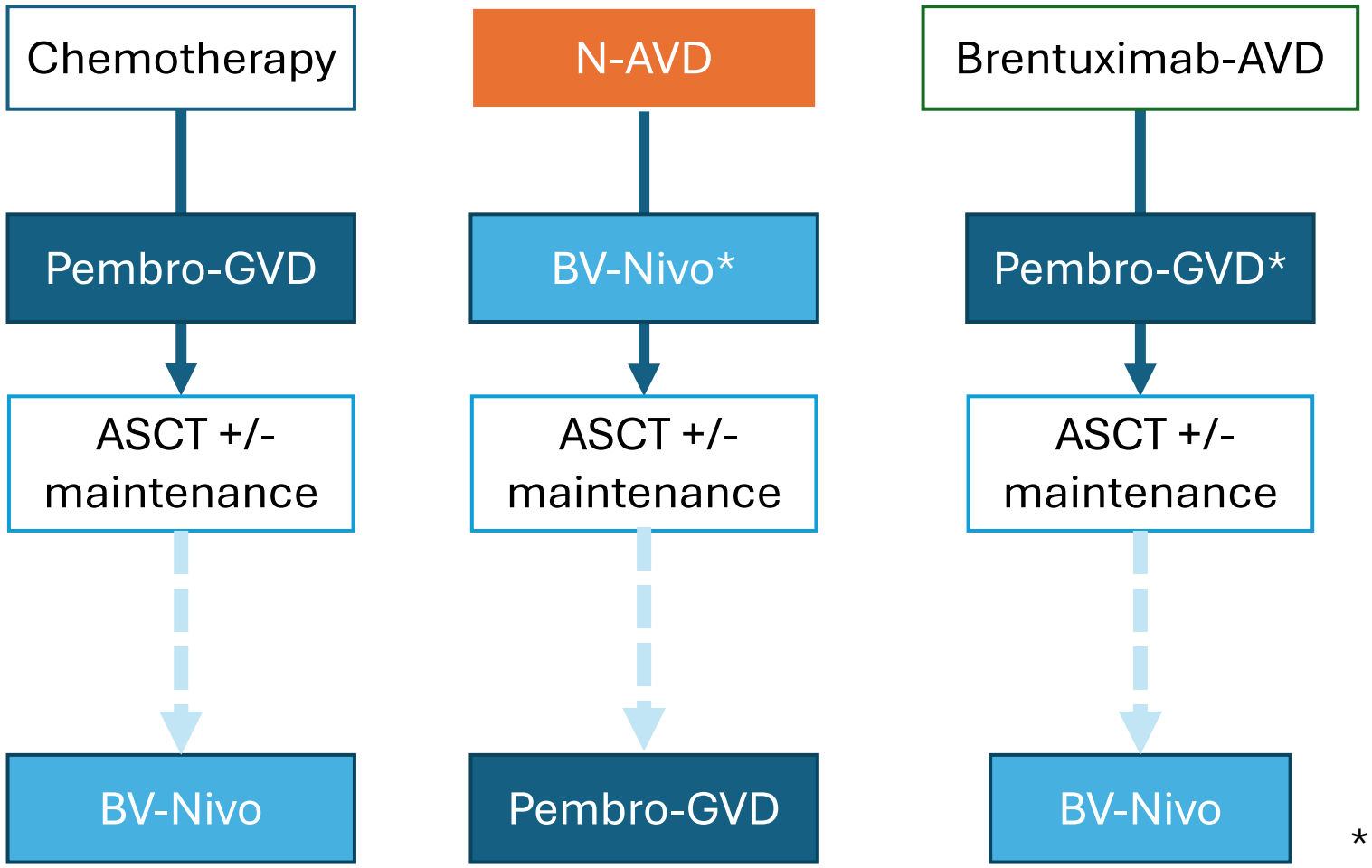
Phase II study of 8 cycles of pembro 60 days post ASCT in patients with RR cHL (90% with high-risk factors per AETHERA).
20% Prior BV; 20% Prior PD-1
18-month PFS 82% and OS of 100%.

Maintenance with BV + Nivo

Phase II Study of 8 cycles.
51% prior BV; 42% Prior PD-1. Prior novel agent had no effect on efficacy
18-month PFS of 94%
Increased toxicity: 53% PN, 29% CS for irAE

Moskowitz et al. *Lancet.* 2015 May 9;385(9980):1853-62. Armand et al. *Blood* (2023) 142 (10): 878–886; Herrera et al. Lancet Haematology 142:3062, 2023

My Approach



* Clinical Trial of Brentuximab + Nivolumab in patients with Prior novel agent exposure

Summary

- Brentuximab and PD-1 therapies have improved outcomes for frontline and relapsed Hodgkin lymphoma
- Frontline therapy options may impact initial therapy for relapsed Hodgkin lymphoma
- Re-treatment can be considered with novel agents, however anti-PD-1 based-therapy may have improved efficacy in the re-treatment setting.
- Post-transplant maintenance strategies unclear in the current era and require additional data.

Thank You!

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