EUROPEAN HEMATOLOGY ASSOCIATION

EHA-MSH Hematology Tutorial

Self-assessment Case – Session 5
The roles of Novel Agents in the landscape of Hodgkin Lymphoma in 2024

Speaker: Prof. Dr. Peter Borchmann

Kuala Lumpur, Malaysia
April 17-18, 2024

Introduction

- A 25 year-old woman presented with weight loss, fatigue and drenching sweats at night
  - No travel history, weight loss was not intended
- Physical examination:
  - Lungs: Clear to auscultation; Heart: Regular rate and rhythm
  - Palpable cervical lymph nodes on both sides
- Lab:
  - Increased blood sedimentation rate

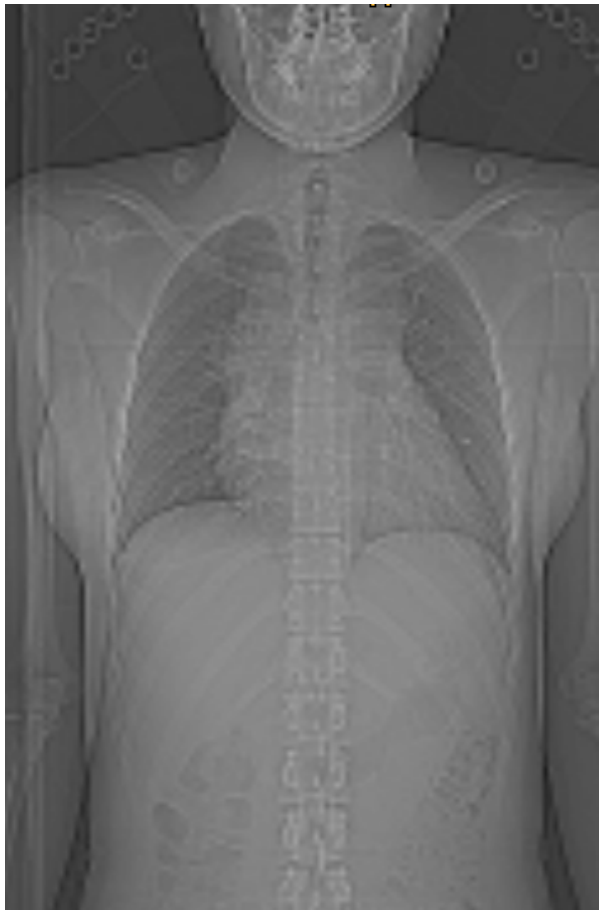
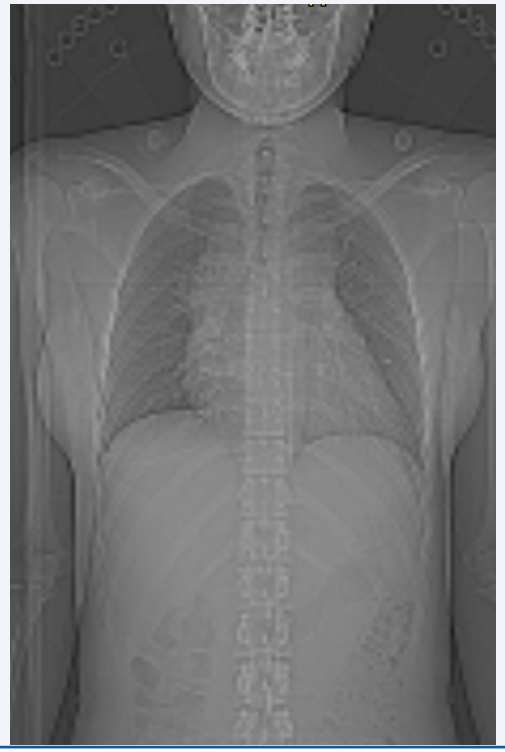
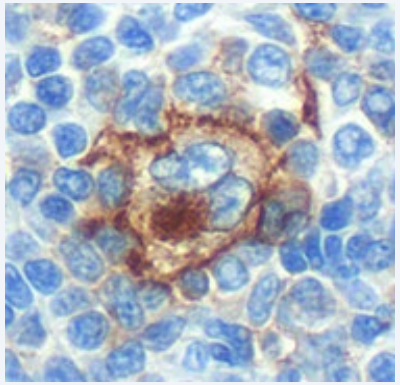


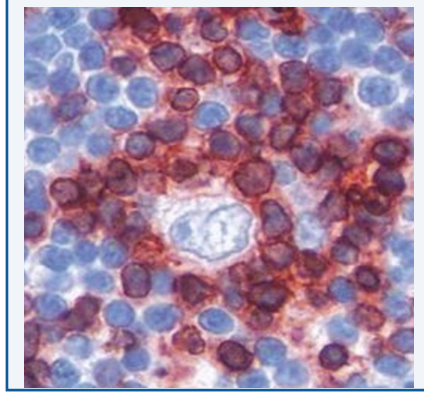
Fig. 1 Initial diagnosis

X-Ray



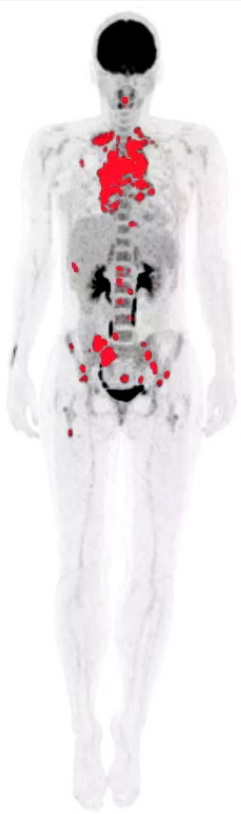
Histology





IHC positive for CD30, CD15, PAX5

PET



PET positive lymph nodes:

- Mediastinum
- Cervical
- Sternum/ Scalenus
- Disseminated in bone marrow

Confirmation of diagnosis in histology: Advanced-stage Hodgkin Lymphoma

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Questions can be answered by scanning the QR on your phone to access Slido.

For each question you have 15 seconds.

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5.1 Which stage is the patient in?

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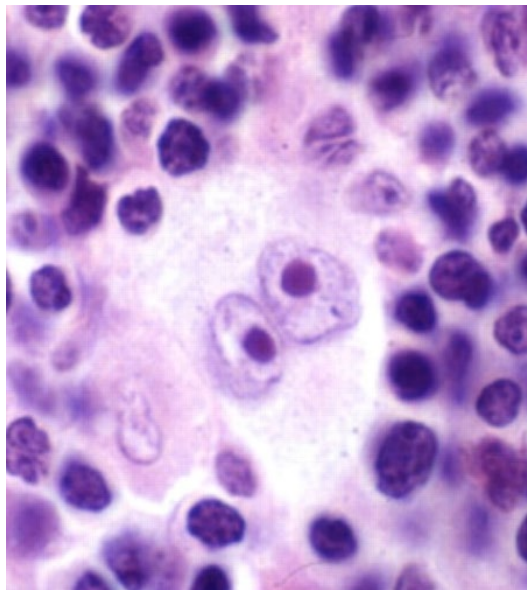
Hodgkin Lymphoma: GHSG clinical classification system



		Ann Arbor Stage			
		IA, IB, IIA	IIB	IIIA, IIIB	IVA, IVB
no RF		early stages			
Risk factors	≥ 3 LN-areas	early unfavourable stages			
	ESR > UNL				
	Large Mediastinal Mass (LMM)			advanced stages	
	Extranodal-Disease				

The definition of areas is based on x-rays using bones as landmarks, and the definition of the risk factors is based on clinical observations with very old protocols

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5.2 Which statement is true about treatment of this patient?

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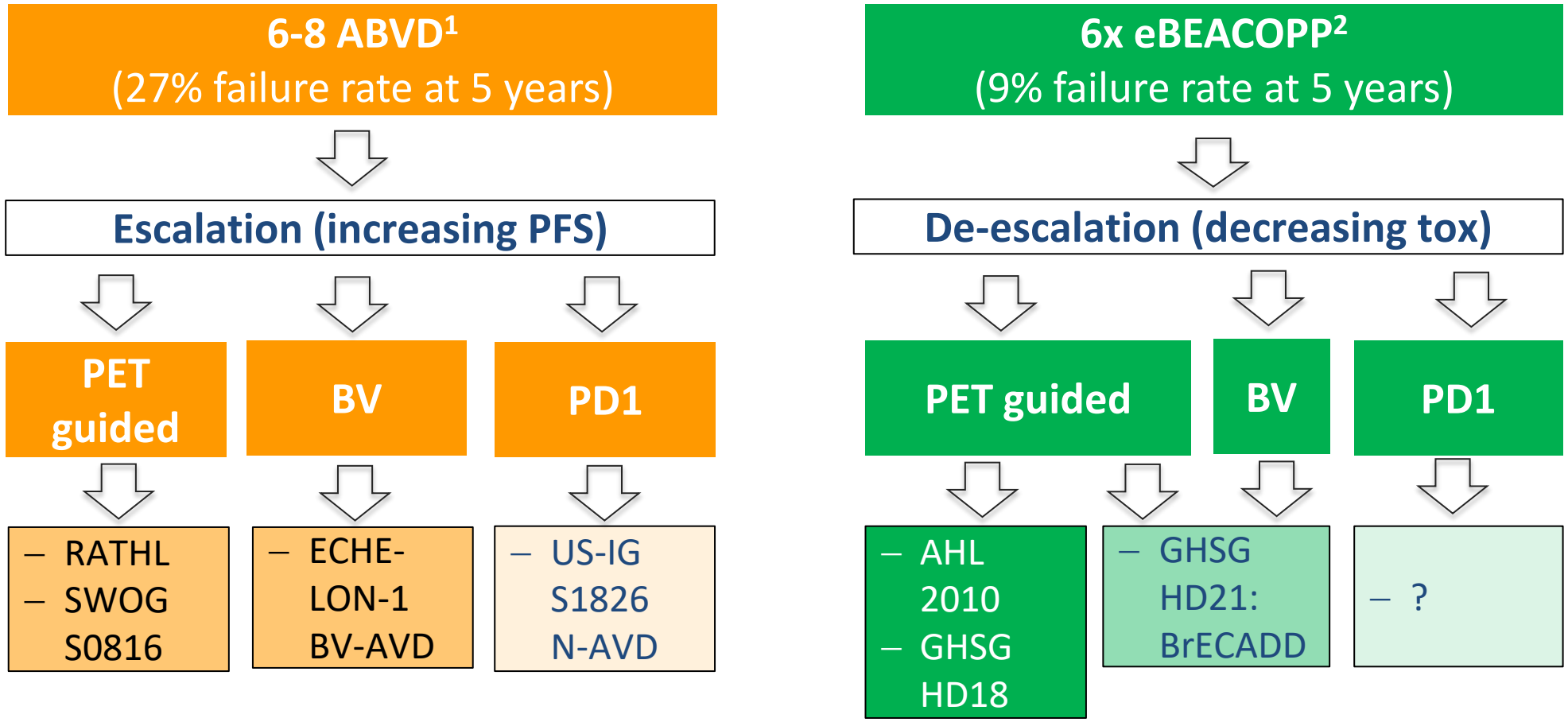
Treatment strategies for advanced stage HL

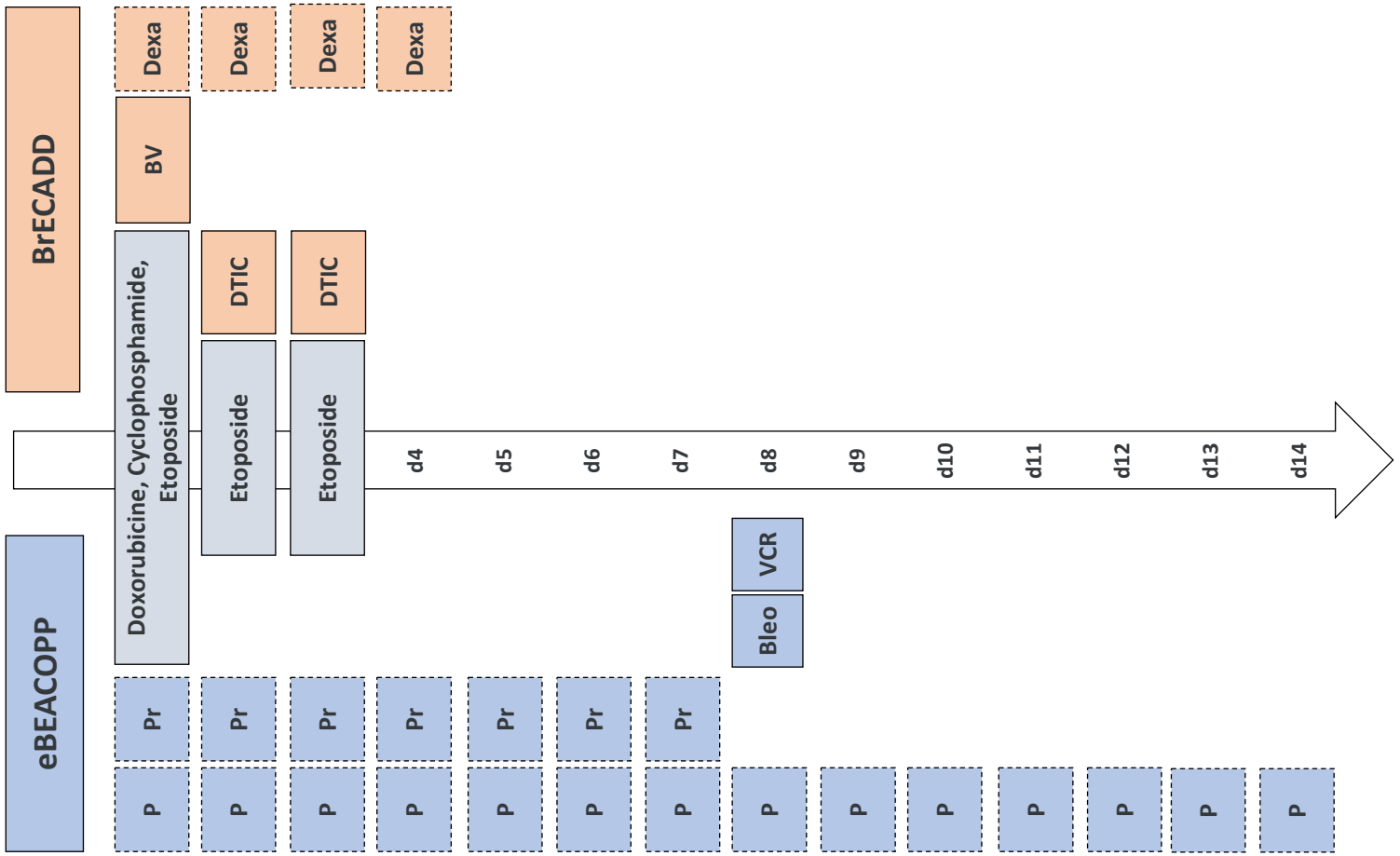


[1]Gordon et al, JCO, 2012,[2]Engert et al., Lancet, 2012

Outcomes in the first-line setting for HL patients within GHSG trials

Risk Group	SOC trial	Published	Treatment modality		PFS [%] at 5 years	OS [%] at 5 years
			Chemotherapy	Radiotherapy		
Early stages	**HD10**	**2010**	**2x ABVD**	**IS-RTx 20 Gy (100%)**	**91,6**	**96,6**
Intermediate stages	**HD17**	**2021**	**2x BEACOPP + 2x ABVD**	**PET4 guided IS-RTx 30 Gy (16%)**	**95,1**	**98,6**
Advanced stages	**HD18**	**2018**	**PET2 guided 4-6x eBEACOPP**	**EOT PET guided RT to RD (~10%)**	**93**	**98,1**

GHSG HD21 remodeling eBEACOPP with Brentuximab vedotin

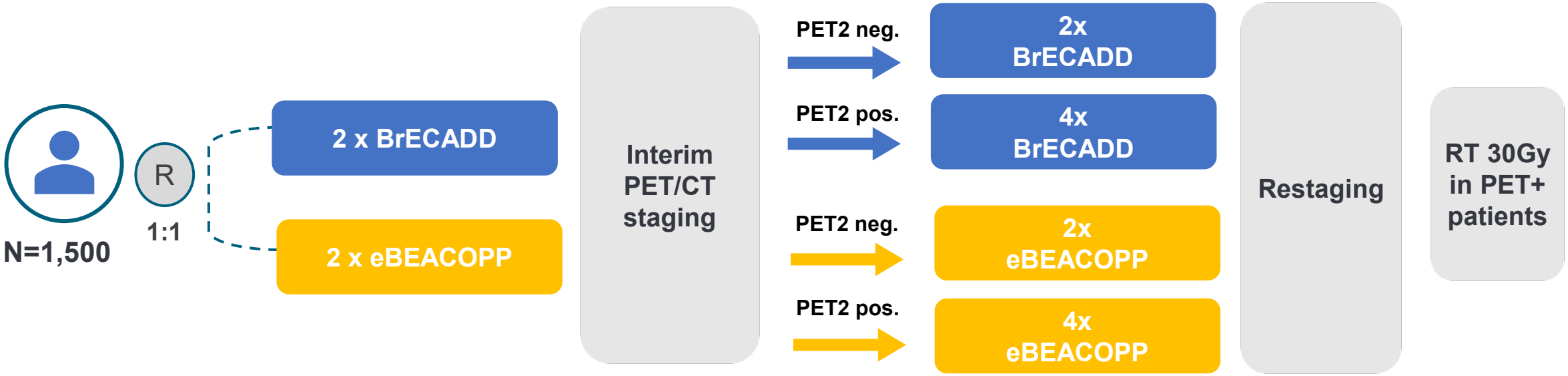


Modifications:

- Keeping the **backbone** of intensified chemotherapy
- Introducing highly active and well tolerated **Brentuximab Vedotin**
- Omitting Bleomycin (pulmonary toxicity) and Vincristine (neuropathy): **removal of d8 infusions overall**
- Switching from Procarbazine to **less geno- and gonadotoxic DTIC**
- Switching from 14 days of Prednisone to 4 days of **Dexamethasone**

GHSG HD21 study design and primary endpoints

HD21 is an ongoing, randomized, open-label, Phase 3 study of BrECADD versus eBEACOPP in patients with previously untreated, advanced cHL



Co-primary objectives:

1. Demonstrate reduced treatment-related morbidity (TRMB) with BrECADD.
2. Demonstrate non-inferiority of 4-6 x BrECADD compared with 4-6 x BEACOPP in terms of PFS

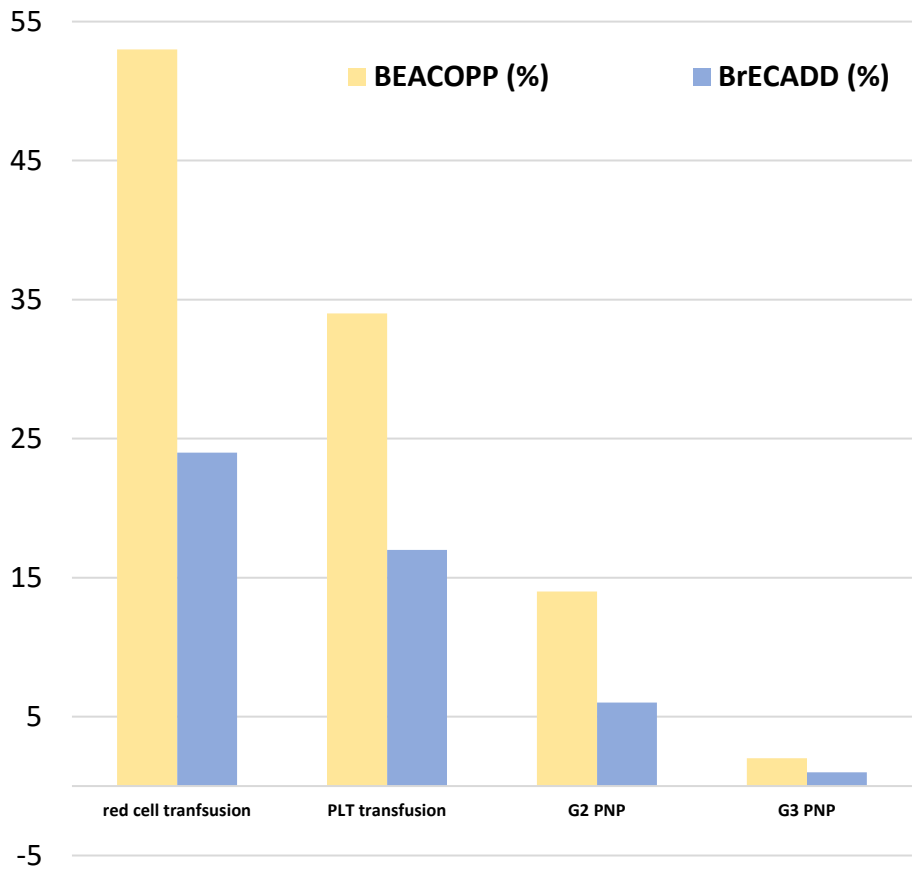
GHSG HD21 clinical implications of observed differences

Toxicity	eBEACOPP (%)	BrECADD (%)
red cell transfusion*	53	24
platelet transfusion*	34	17

	eBEACOPP (%)	BrECADD (%)
Sensory PNP		
All grades	49	38
Grade 2	14	6
Grade 3	2	1

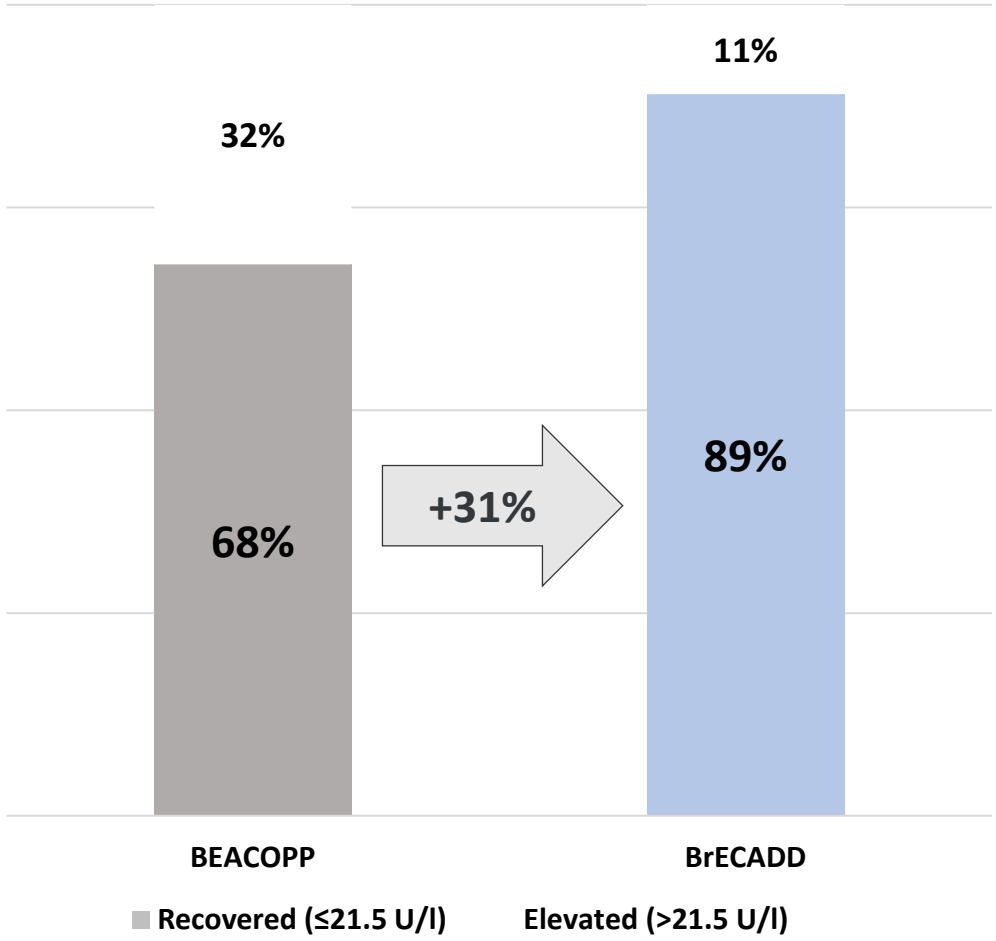
	eBEACOPP (%)	BrECADD (%)
Treatment related mortality	< 1%	0%

*pts with at least one transfusion

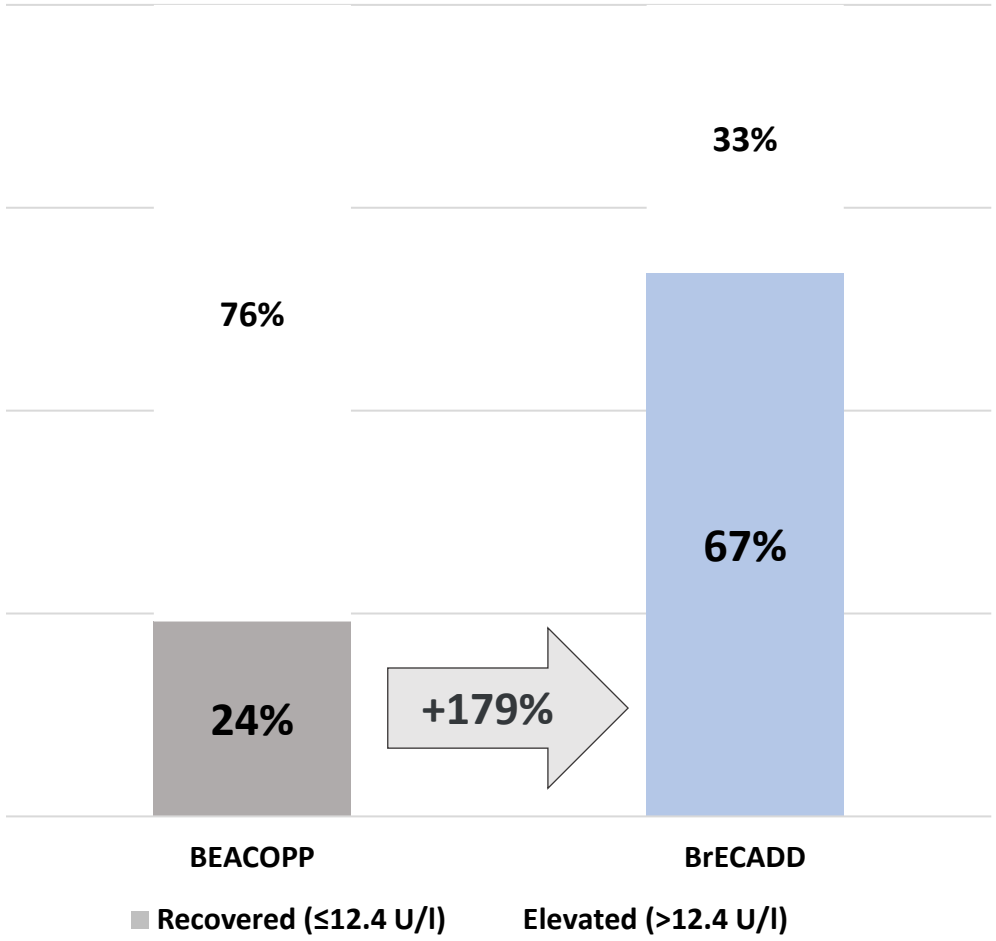


GHSG HD21 Gonadal function recovery after one year

FSH (U/l) recovery in **female** (18-39) patients

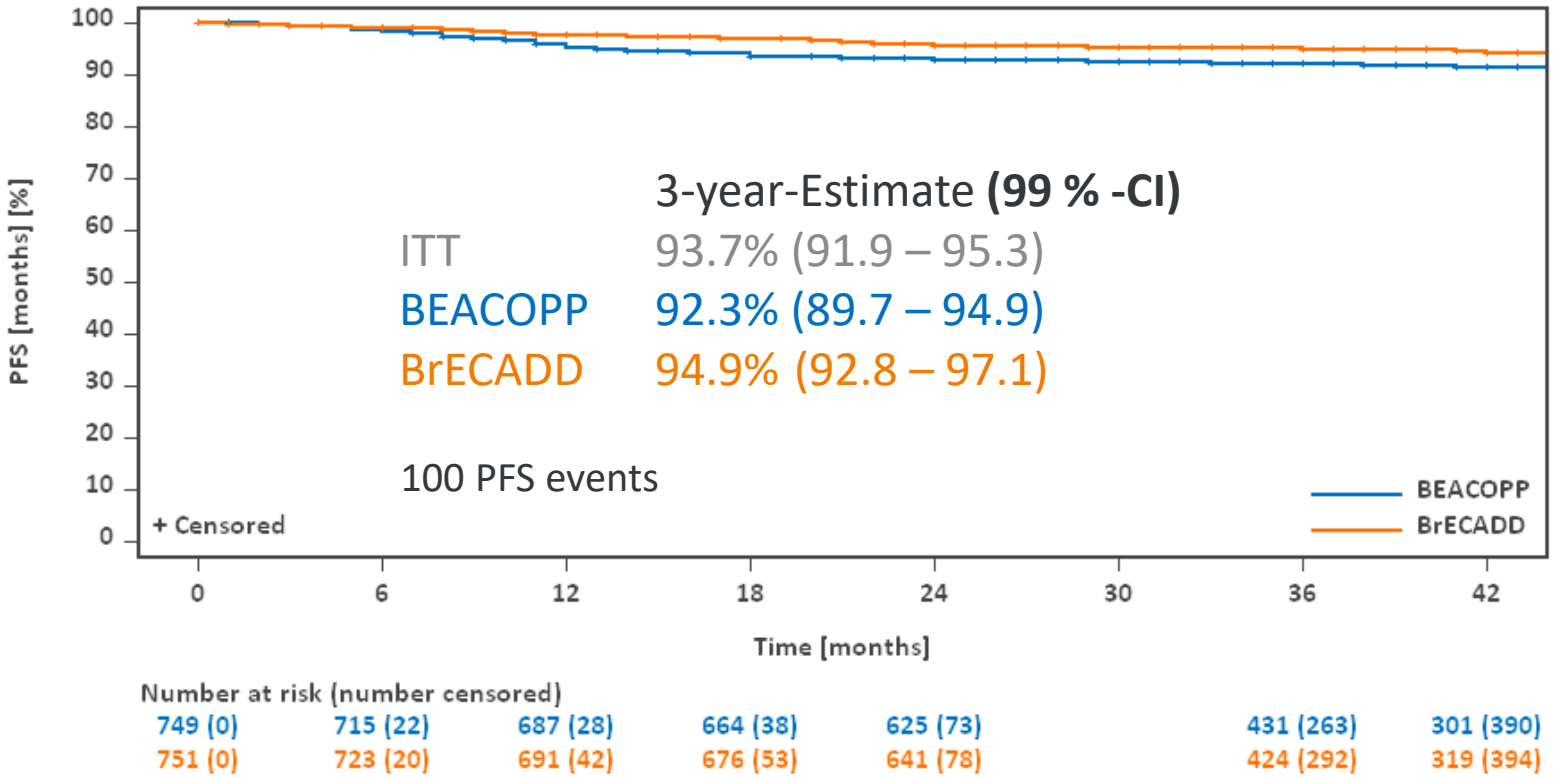


FSH (U/l) recovery in **male (18-49)** patients



*(mean Fu12-Fu24)

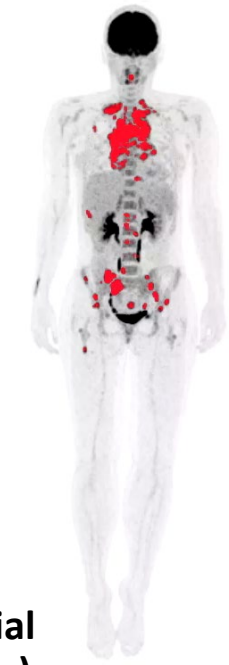
HD21 PFS – ITT interim analysis with 40 months mFU



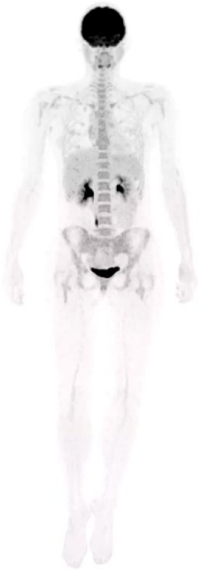
- HR is 0.63 and bound of 1,02 is safely excluded
- ***non-inferiority of BrECADD thus fully established at IA***

Fig. 2 Disease progressed under treatment with eBEACOPP

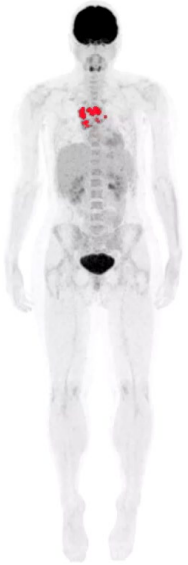
PET 0



PET 2



PET 6



cHL (initial diagnosis)

6x eBEACOPP

- PET-2: CR (DS2)
- PET-6: PD (DS5)

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5.3 Which treatment is adequate for this patient?

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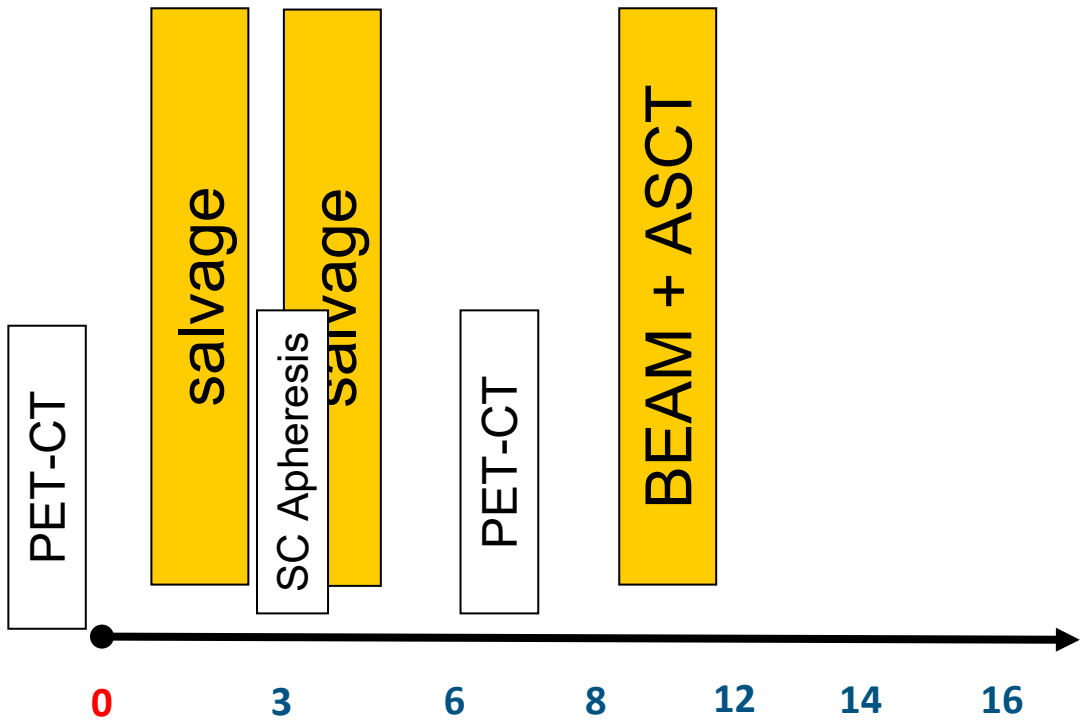
General treatment schedule for r/r transplant eligible patients



This standard has been established by the HD-R1 trial (Schmitz et al.) in the treatment of relapsed, transplant eligible HL patients.

FFTF at 3 years:
34% (conventional chemotherapy) vs
55% (BEAM high dose chemotherapy)

- How can we improve on this rather poor outcome?

Schmitz et al., Lancet. 2002 Jun 15;359(9323):2065-71.

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5.4 Which statement is true for second line therapy of r/r HL?

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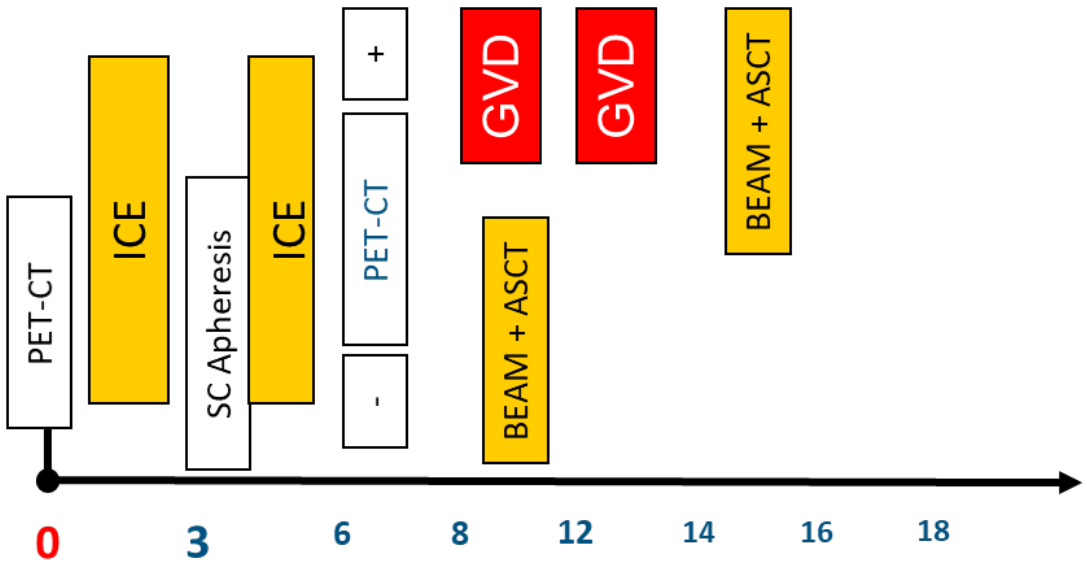
Switching salvage chemotherapy for non-responder ("MSKCC" approach)



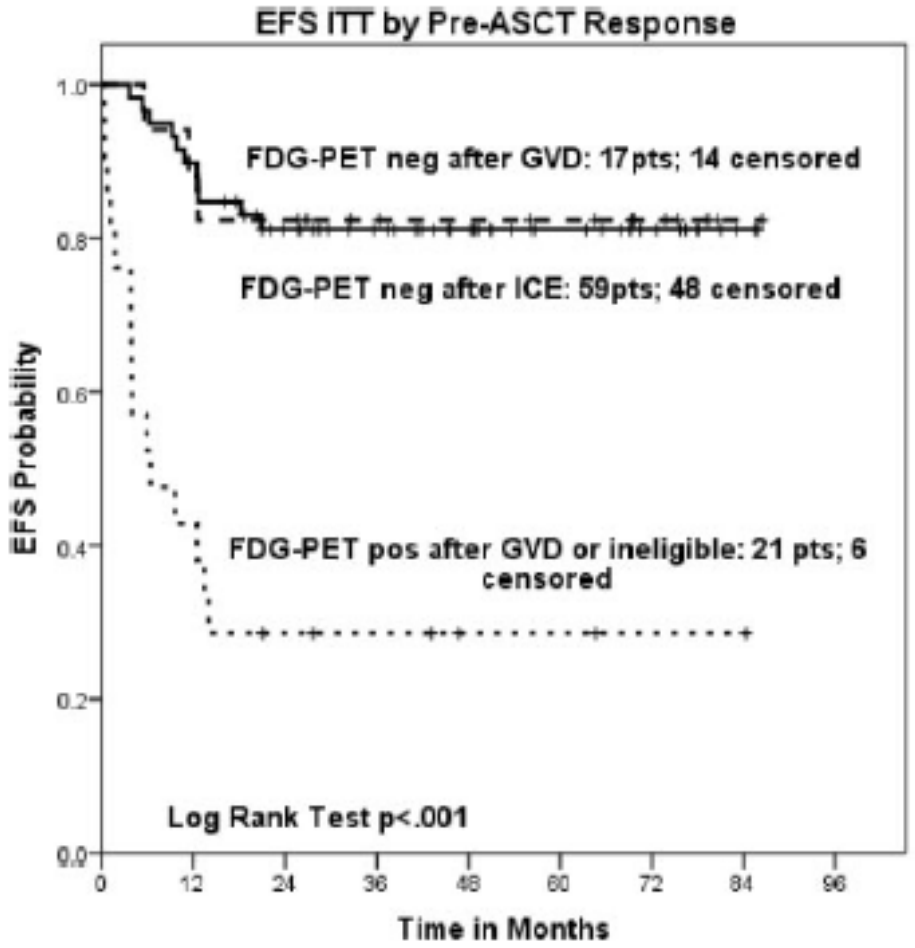
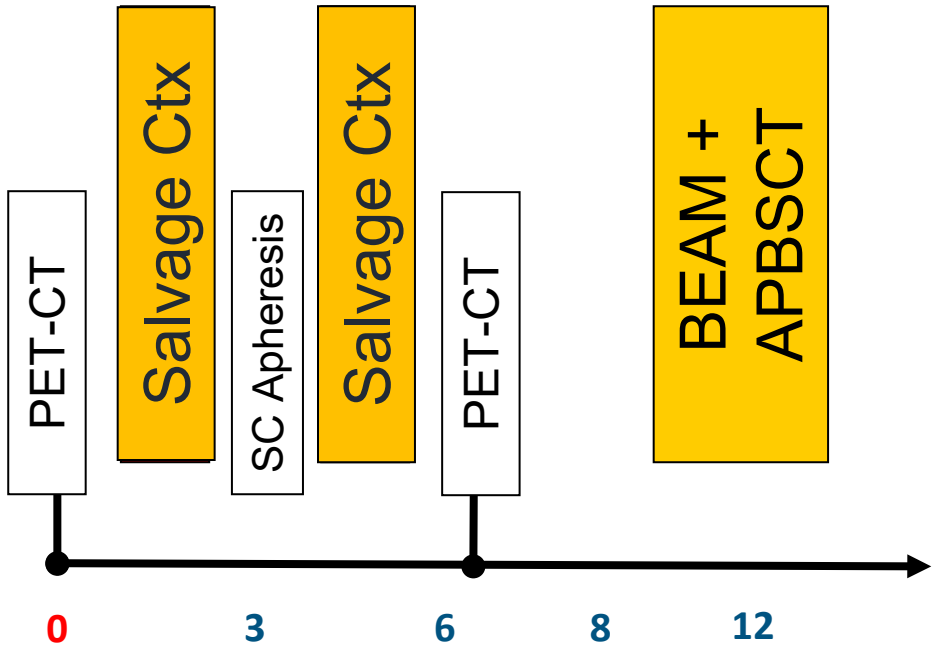


Figure 3. EFS Intent to treat by pre-ASCT response.

“Add on” designs with new compounds, e.g. PD1 Ab



Potential advantage:

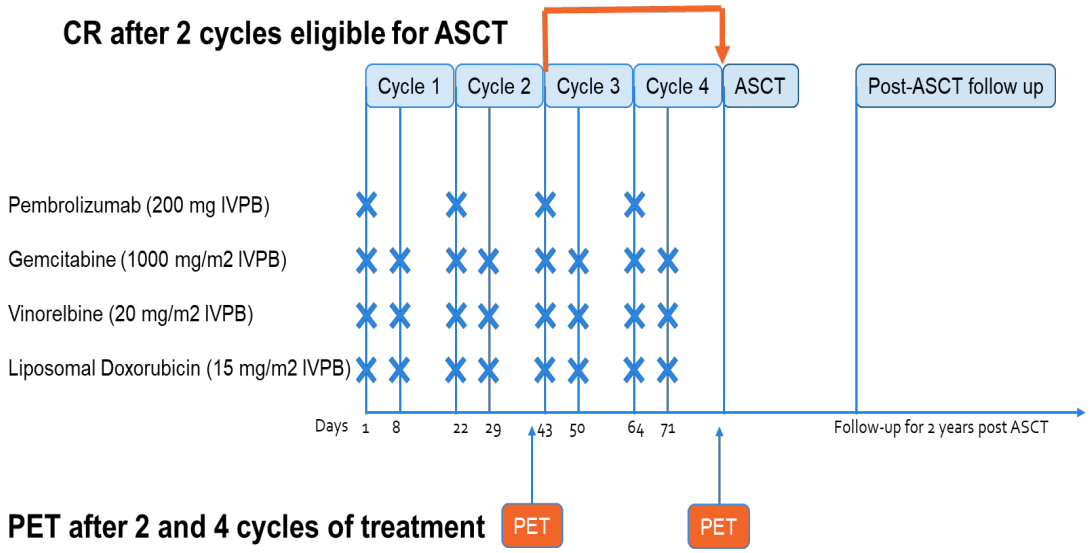
- Higher CR rate pre consolidation might improve PFS and OS
- Very high response rates (?) may allow omission of consolidation HDCT (!)

Potential disadvantage

- Option for high risk-patients? Selection?

Improving response by addition of PD-1 antibodies to CTx: Phase II study of pembro-GVD as second-line therapy for cHL

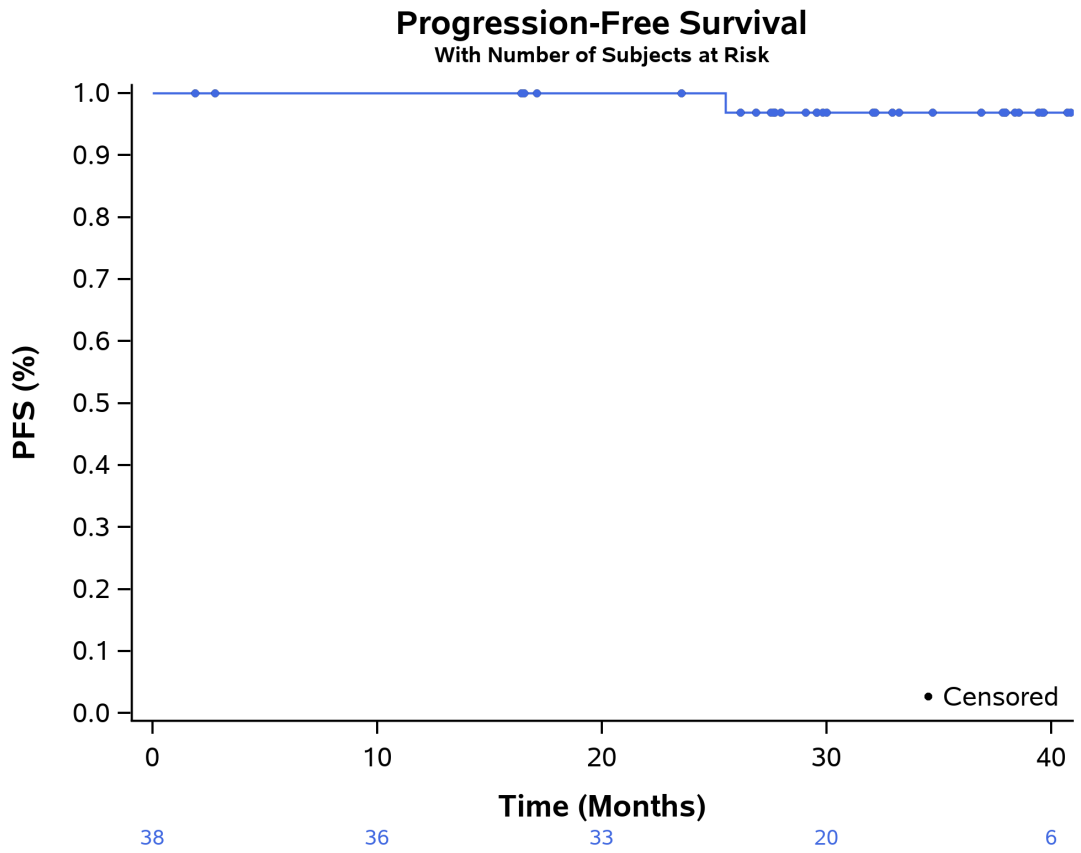
- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles



Characteristic	Pembro-GVD Overall (n = 38)
ORR, % (95% CI)	100 (91 to 100)
CR, % (95% CI)	95 (82 to 99)
PR, % (95% CI)	5 (1 to 18)
Best response, No. (%)	
CR	36 (95)
PR	2 (5.3)

Moskowitz et al., J Clin Oncol. 2021; 39(28): 3109-3117.

Pembro-GVD: Long-term follow up in the ITT cohort



Next cohort: Pembro-GVD -> maintenance

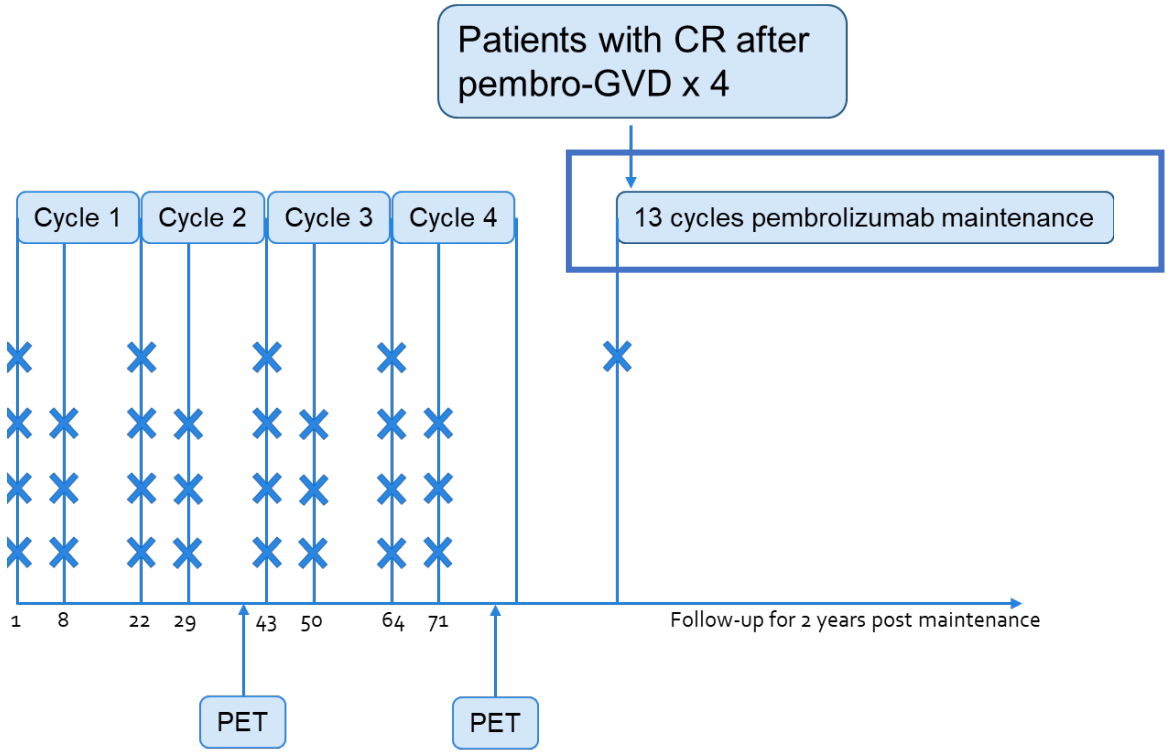
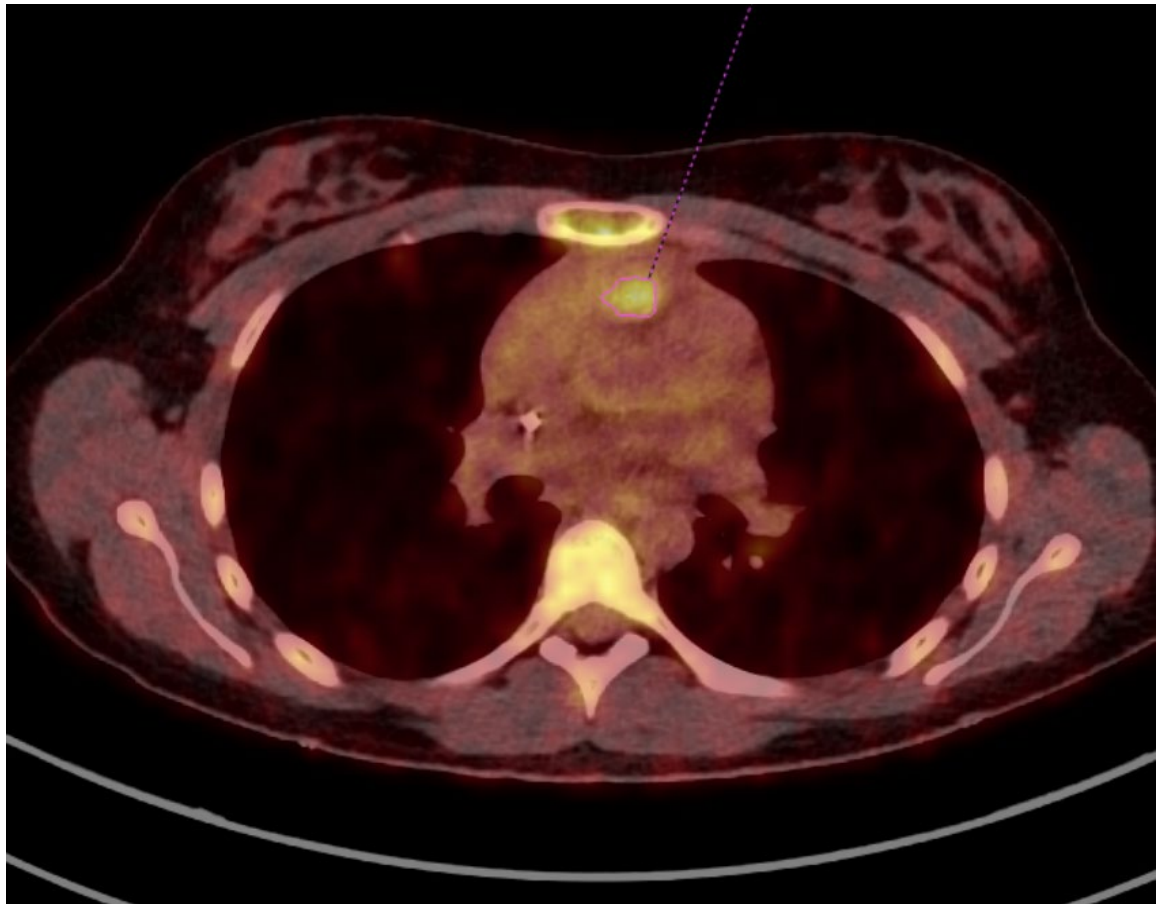
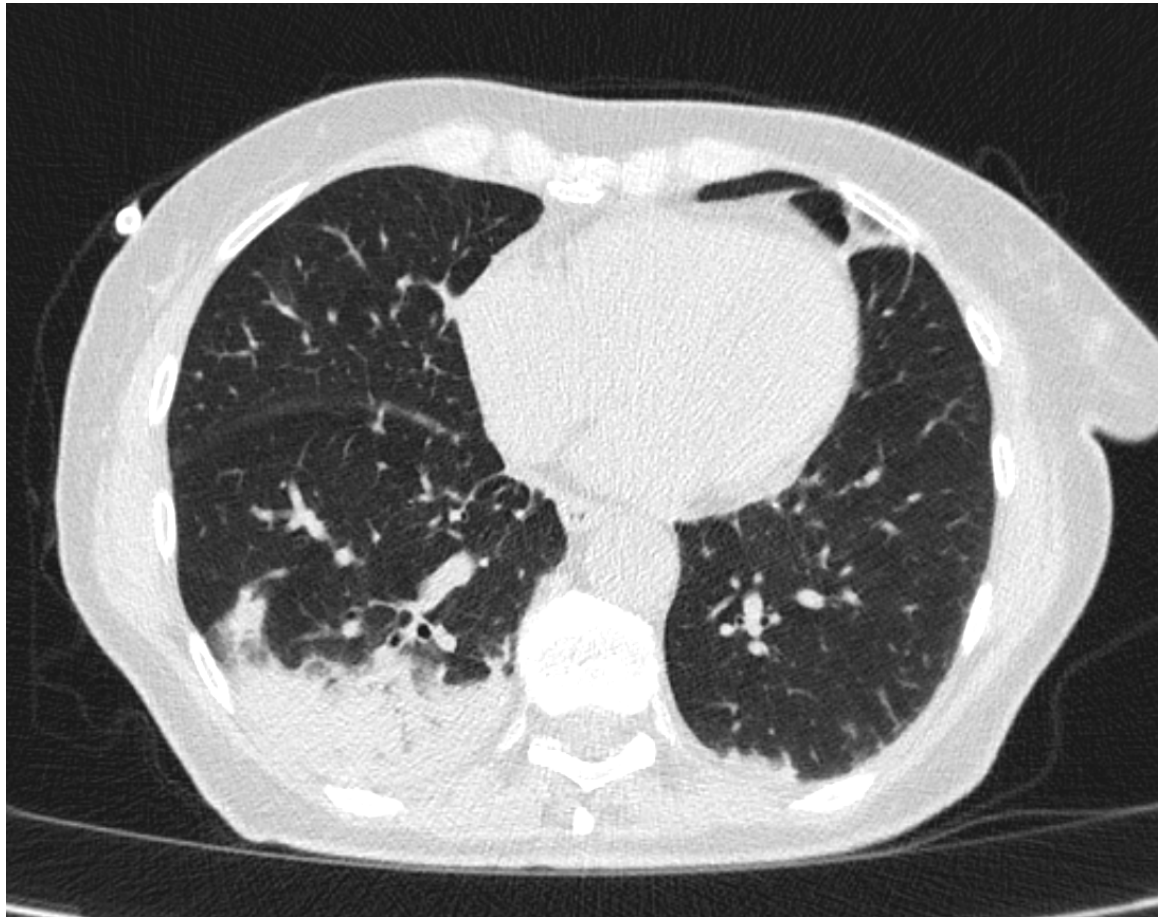


Fig. 3 Patient received P-GVD + HDCT



Reinduction

Fig. 4 While receiving therapy, patient experience shortness of breath



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5.5 What is the most likely cause of her symptoms?

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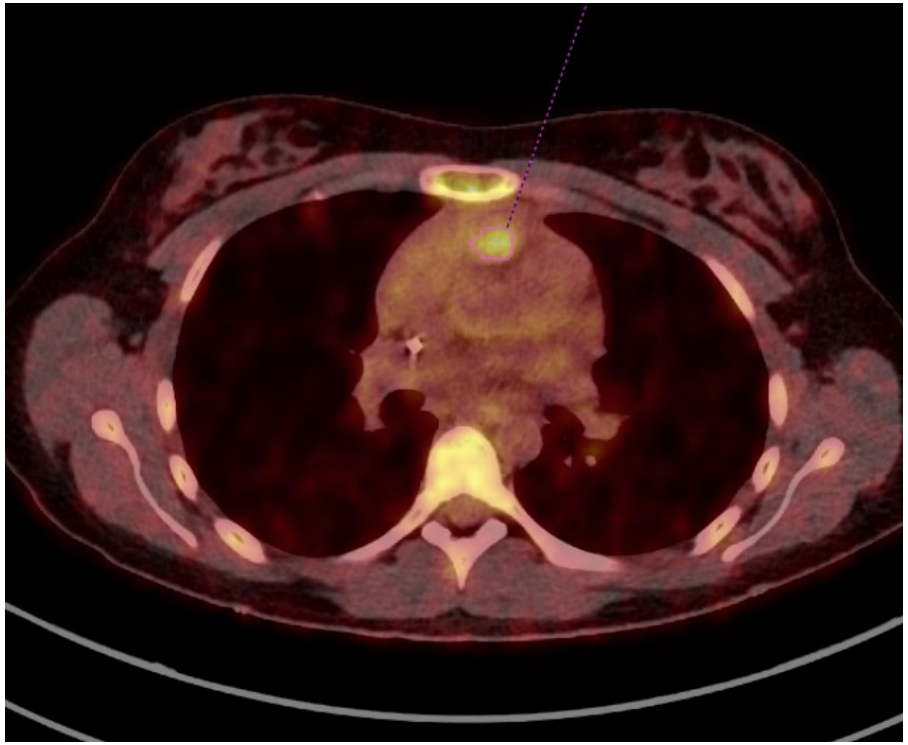
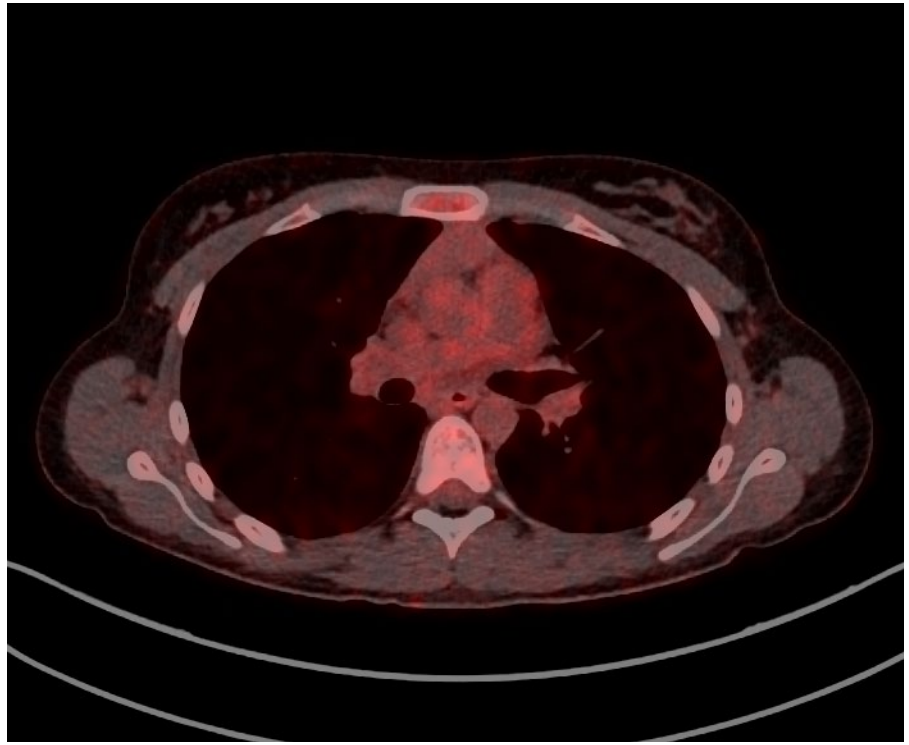
Fig. 5 Patient received P-GVD + HDCT



Reinduction



After HD-CT

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5.6 Which maintenance therapy is suitable?

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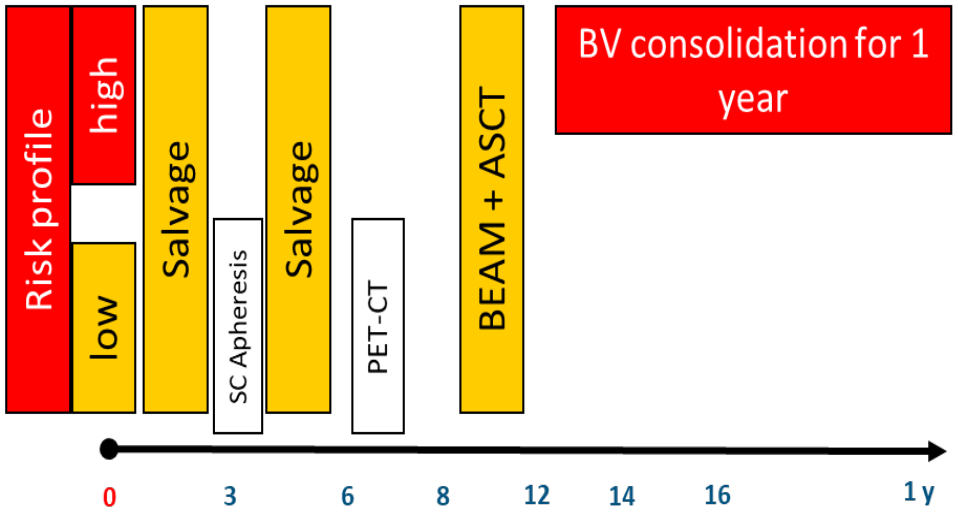
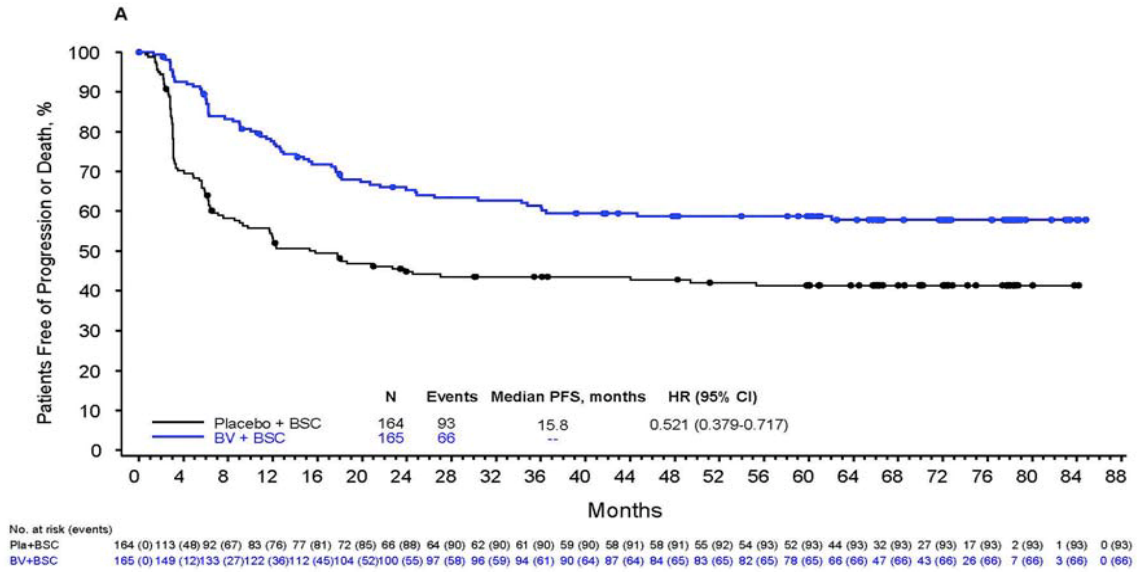
2nd consolidation/maintenance with brentuximab vedotin (BV)



Key inclusion/exclusion criteria:

- relapsed HL, max. 45 days after ASCT
- high risk of recurrence
- ECOG 0-1
- No prior BV or allo
- No PD after salvage

AETHERA - PFS per Investigator: 5-year follow-up



Follow up and discussion

- The patient received 12 doses BV maintenance therapy and is relapse-free since February 2021 until today
- Novel agents offer a huge potential for r/r HL and may help to further reduce treatment related morbidity
- PD1-antibody-based therapies are effective in r/r HL, despite immune-related side effects there is a positive risk/benefit ratio
- Currently, bispecific antibodies and dual checkpoint inhibtion are under investigation

References

- Younes et al., Lancet Oncol. 2016 Sep 17; (9): 1283–94
- Ansell et al., Blood Adv. 2023 Aug 2:bloodadvances.2023010334
- Armand et al., Blood. 2023 Sep 7;142(10):878-886.
- Merryman et al., Blood Adv. 2021 Mar 23;5(6):1648-165
- Timmermann et al., Blood (2023) 142 (Supplement 1): 4440.