# Management of relapsed or refractory HL

## DGHO Basel 13.10.2024

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mit Hämatologie, internistischer Onkologie, Hämostaseologie, Infektiologie und Rheumatologie

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UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN III
MIT HÄMATOLOGIE, INTERNISTISCHER ONKOLOGIE, HÄMOSTASEOLOGIE, INFEKTIOLOGIE, RHEUMATOLOGIE UND ONKOLOGISCHES ZENTRUM

# Offenlegung potentieller Interessenkonflikte

**1. Anstellungsverhältnis oder Führungsposition**

keine

**2. Beratungs- bzw. Gutachtertätigkeit**

keine

**3. Besitz von Geschäftsanteilen, Aktien oder Fonds**

keiner

**4. Patent, Urheberrecht, Verkaufslizenz**

keine

**5. Honorare**

Speaking fee from Mundipharma, BMS, Takeda, Novartis, Incyte; MSD, Janssen Cilag

**6. Finanzierung wissenschaftlicher Untersuchungen**

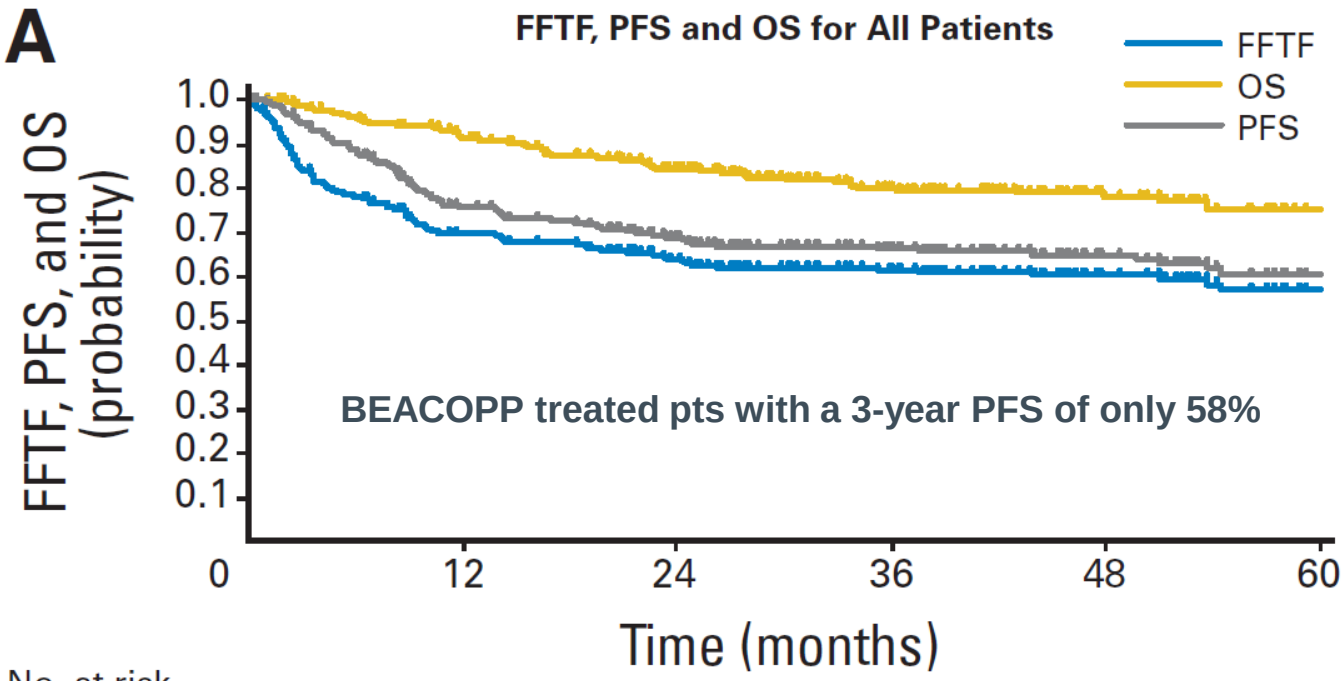
Research support from GSK, Ratiopharm, Roche, MSD, Merck

**7. Andere finanzielle Beziehungen**

Travel support: Amgen, Sanofi Aventis, Roche, Celgene, BMS, Janssen Cilag, Takeda in the last years

# Treatment goals in R/R Hodgkin Lymphoma

•Outcome after induction therapy followed by ASCT with BEAM in the HDR2 trial (n=279 pts)



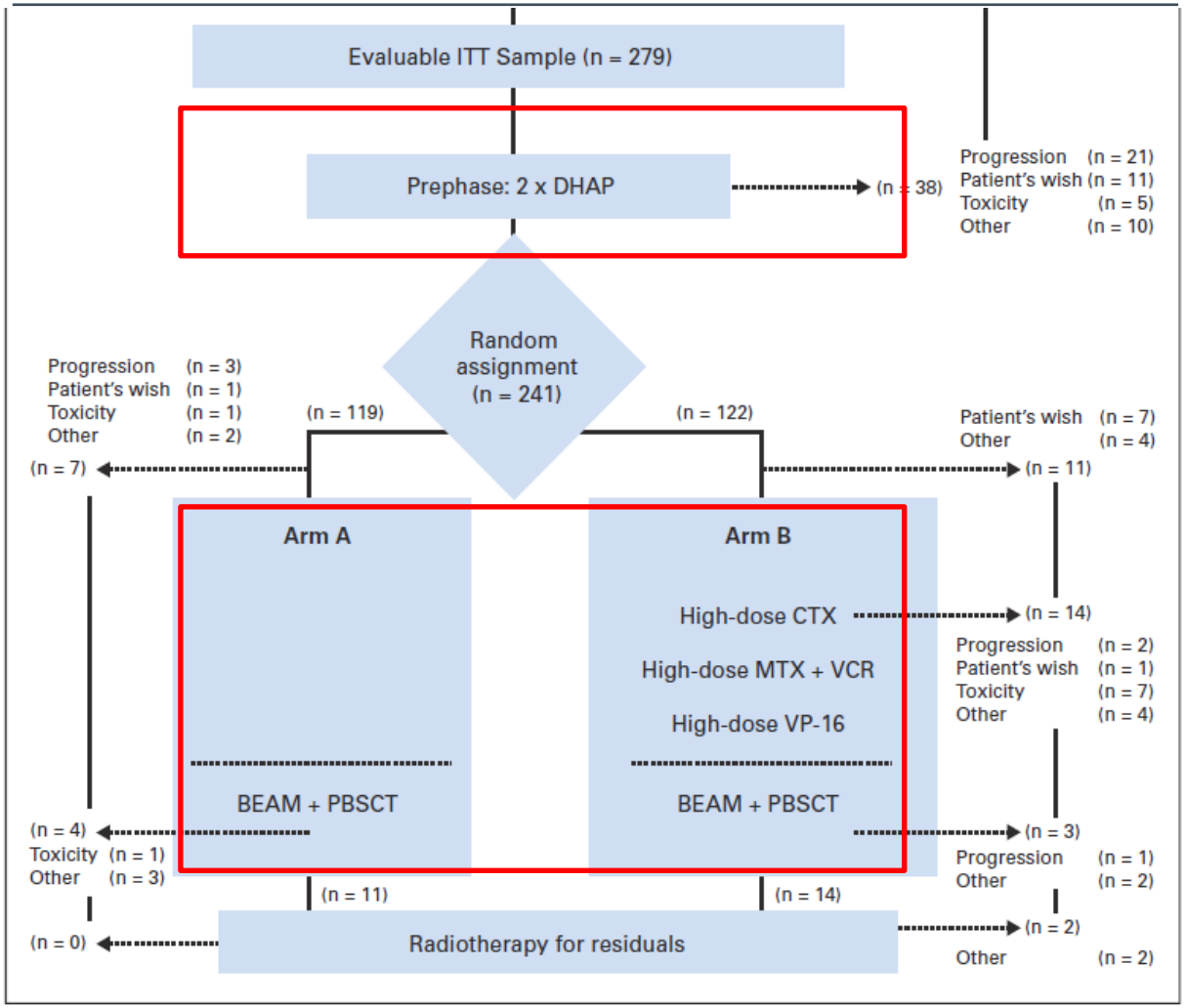

No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| FFTF | 279 | 180 | 149 | 108 | 69 | 44 |
| OS | 279 | 239 | 198 | 138 | 89 | 59 |
| PFS | 279 | 197 | 158 | 112 | 71 | 45 |

JCO 2010 Josting

# Historical standard tested in the HDR2 trial…

**ORR to DHAP:**
CR: 24%
PR: 46%
**ORR: 70%**




JCO 2010 Josting

# A closer look at the HDR2 trial…

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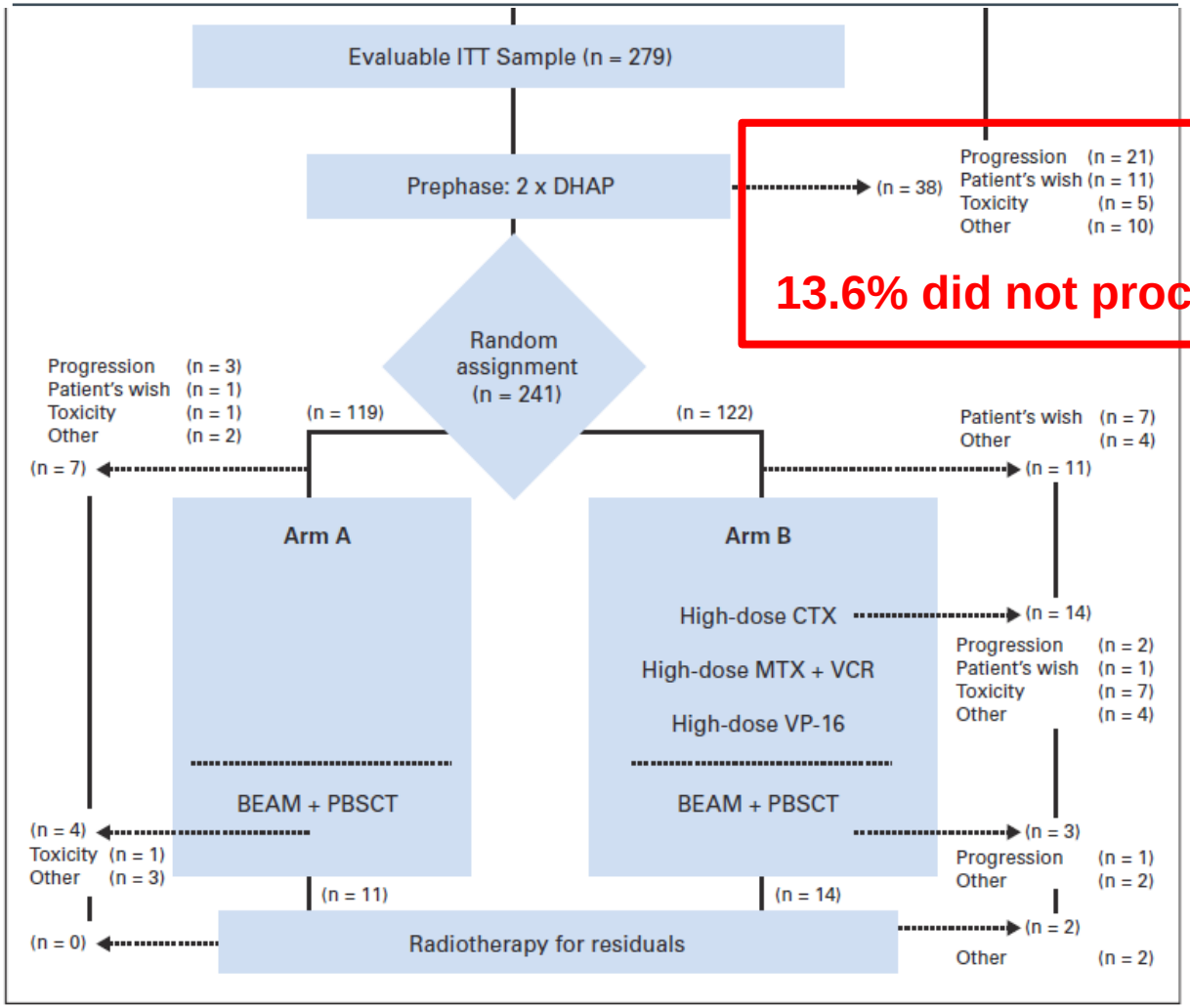



JCO 2010 Josting

# Treatment goals in R/R Hodgkin Lymphoma

- Normalization of Gallium or PET imaging before ATX was highly prognostic in 153 pts

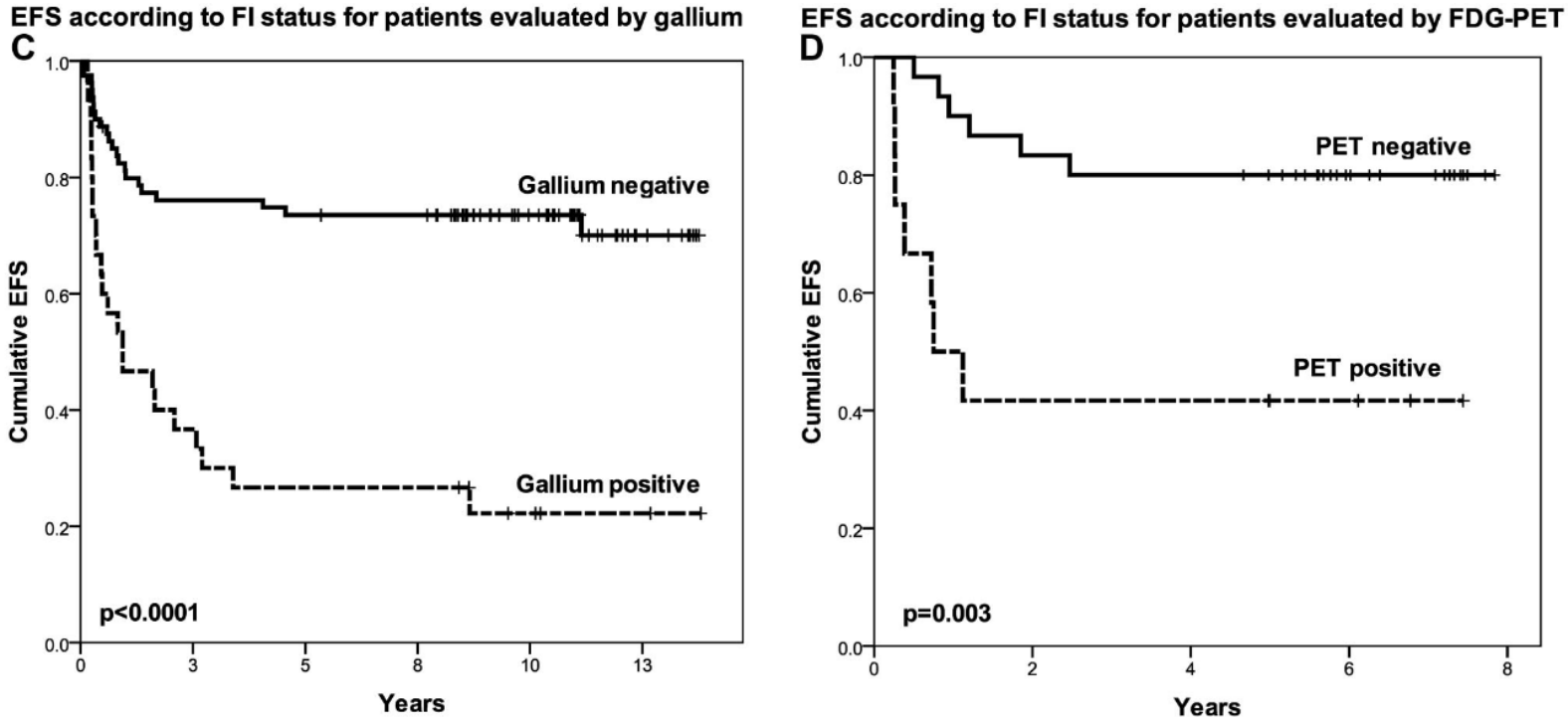



**Figure 1. Patient outcome.** (A) OS and EFS. (B) EFS according to FI status before transplantation. (C) EFS according to FI status for patients evaluated by gallium. (D) EFS according to FI status for patients evaluated by FDG-PET.

Blood 2010 Moskowitz

# Treatment goals in R/R Hodgkin Lymphoma

- Normalization of Gallium or PET imaging before ATX was highly prognostic in 153 pts

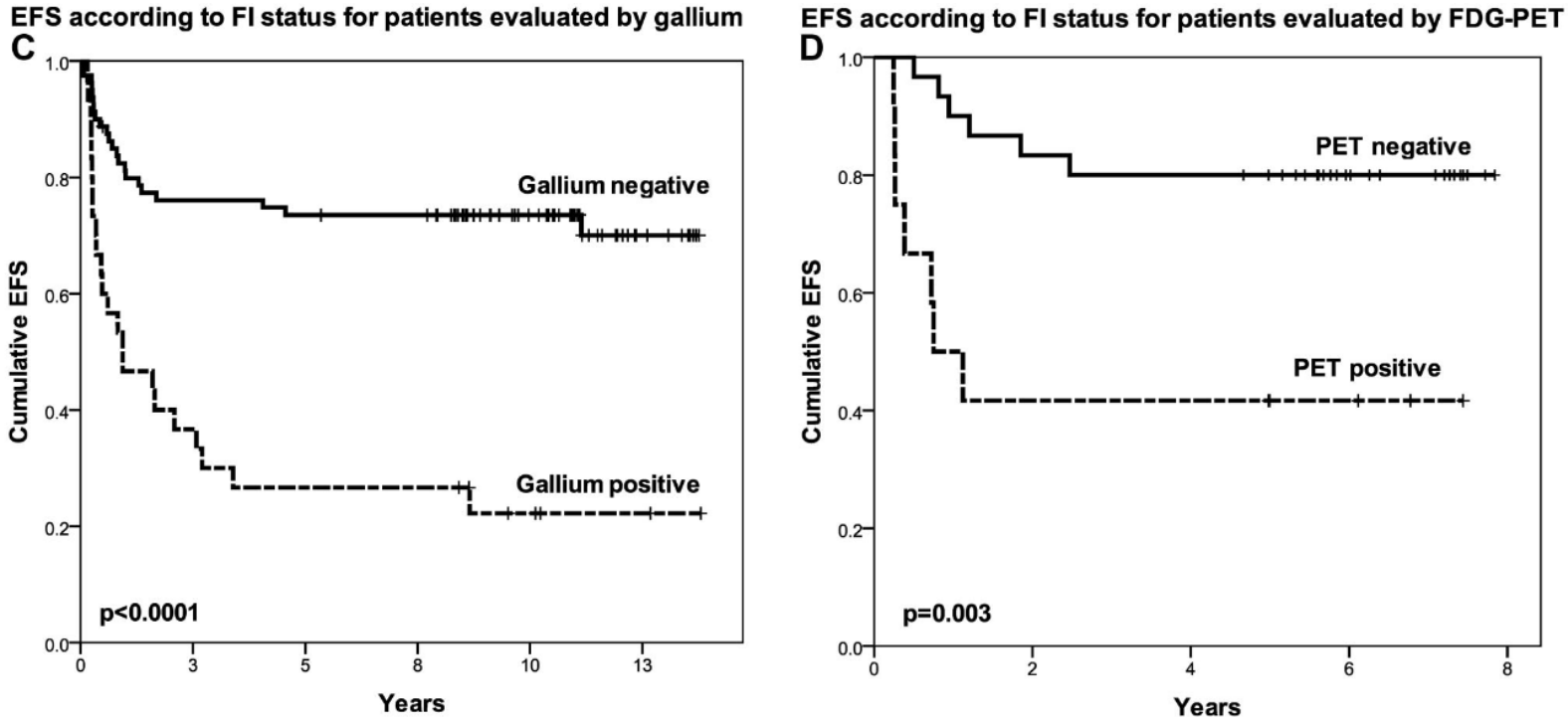


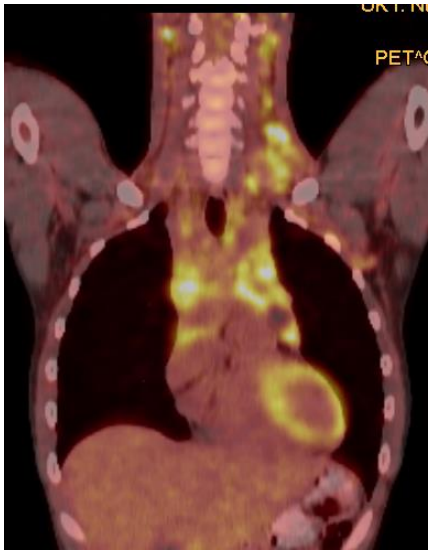

**Figure 1. Patient outcome.** (A) OS and EFS. (B) EFS according to FI status before transplantation. (C) EFS according to FI status for patients evaluated by gallium. (D) EFS according to FI status for patients evaluated by FDG-PET.

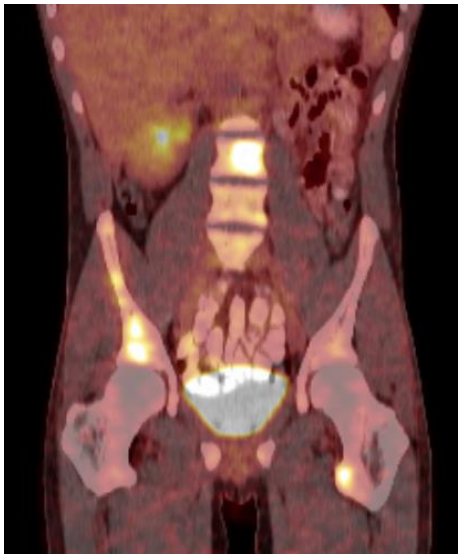
**A negative PET/Scan should be the goal of induction therapy in R/R HL**

Blood 2010 Moskowitz

# Case presentation

**25 year old man was treated in November 2022 for Hodgkin Lymphoma (NSL, Stadium IVA) with BRECADD at our outpatient department. After a negative iPET (DS 1) 4 cycles at all were recommended.**





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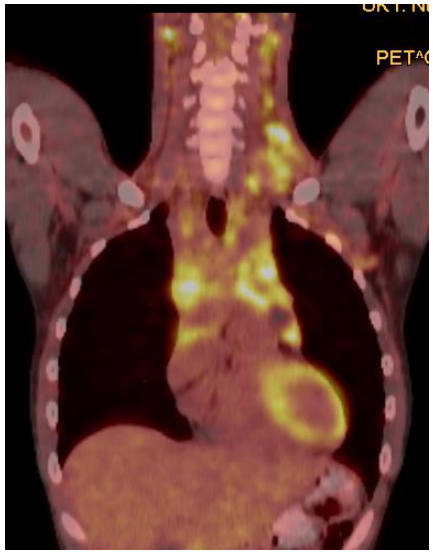
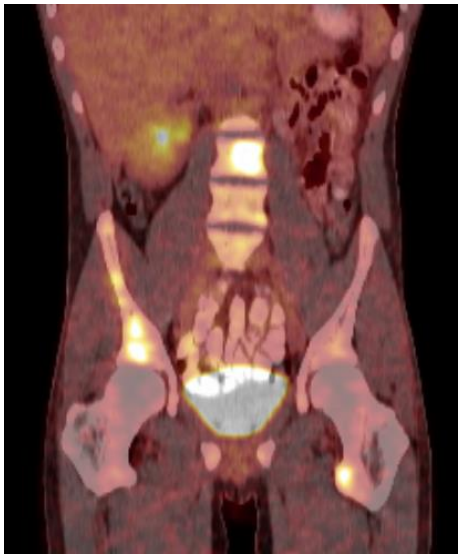
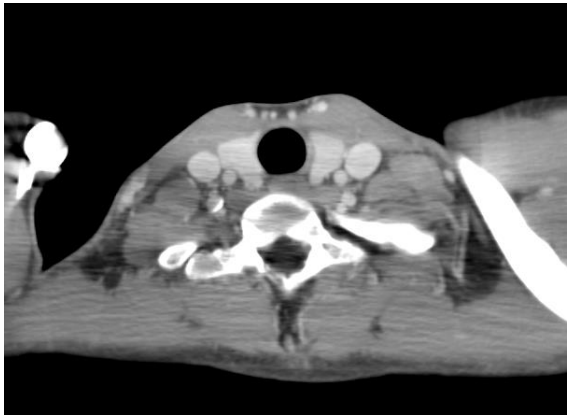
**14 months after end of treatment a new supraclavicular lymph node was palpable.**







# Agenda:

- **Salvagetherapy at first relapse:**
  - ➢**Radiotherapy**
  - ➢**BV +/- chemotherapy**
  - ➢**CPI**
- **Consolidation after stem cell transplant:**
  - ➢**AETHERA**
  - ➢**CPI**
- **Later treatment lines:**
  - ➢**CPI vs BV**
  - ➢**CPI combinations**
- **Allogenic stem cell transplant:**
  - ➢**New data**

# RT should be considered in R/R HL

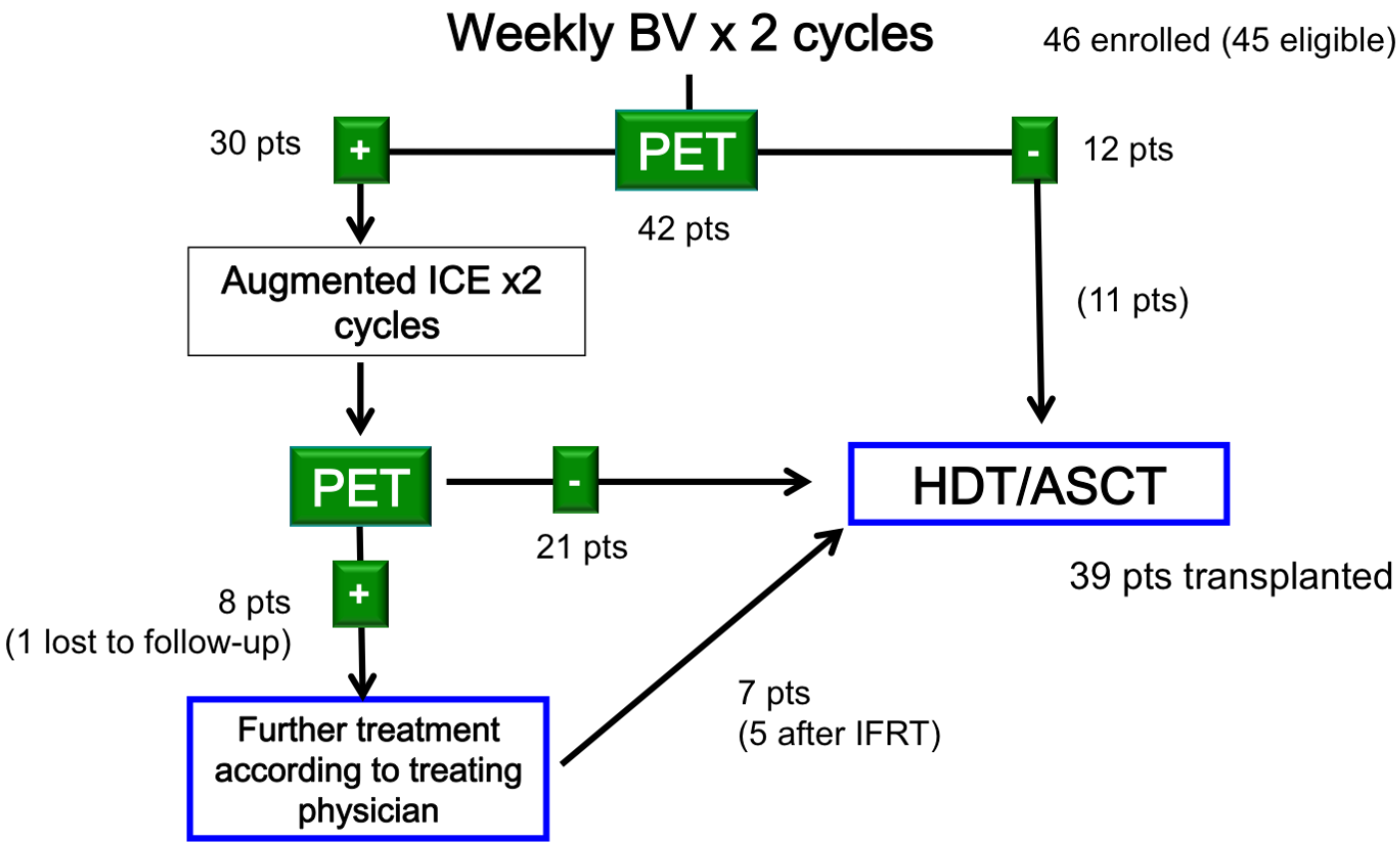
- **ILROG guidelines recommend consideration of IF-RT in R/R HL**
- **Retrospective data from 486 pts show a PFS advantage**
- **RT may be considered after or before ATX**
- **RT as single modality treatment is rarely a curative option**

**Table 2** General indications for radiation therapy as part of salvage in patients with relapsed or refractory Hodgkin lymphoma

1. Localized relapse
2. Disseminated relapse but with sites including the following:
   - A. Bulky disease (≥5 cm)
   - B. Persistent FDG-avid disease after salvage chemotherapy or after SCT
   - C. Critical for local control, such as the following:
     - i. Spinal cord compression (vertebral involvement)
     - ii. Nerve root compression
     - iii. Superior vena cava compression
     - iv. Airway compression
     - v. Lymphedema
     - vi. Hydronephrosis

*Abbreviations:* FDG = $^{18}$F fluorodeoxyglucose; SCT = stem cell transplantation.

# FDG-PET Adapted Sequential Therapy With Brentuximab Vedotin and Augmented ICE Followed By ATX




**Courtesy of Moskowitz**

# FDG-PET Adapted Sequential Therapy With Brentuximab Vedotin and Augmented ICE Followed By ATX

- **2 cycles of BV were highly active.**
- **Pts with DS I-II proceeded to ATX.**
- **Pts with DS >II were treated with augICE**
- **Majority of pts (34/45) achieved PET negativity before ATX with BV or augICE**
- **EFS of the PETneg patients: 92%**
- **No difference, if PET negativity was achieved with BV or augICE**

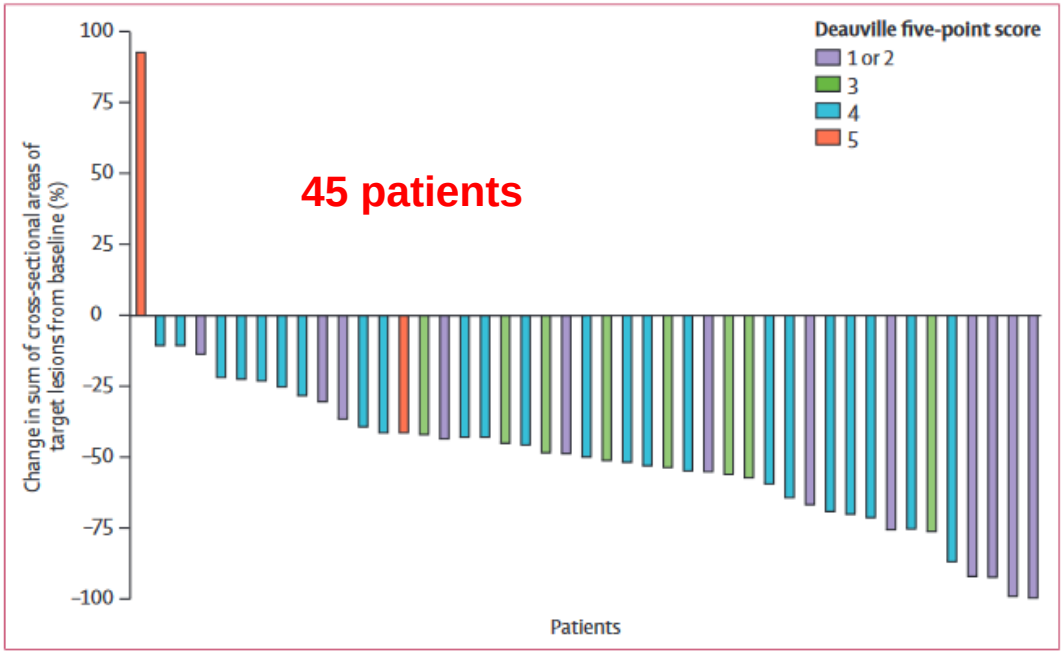



***Figure 2:*** **Tumour reduction after brentuximab vedotin**
Data shows PET status according to the Deauville scores of 1–5.

Lancet Onco 2015 Moskowitz

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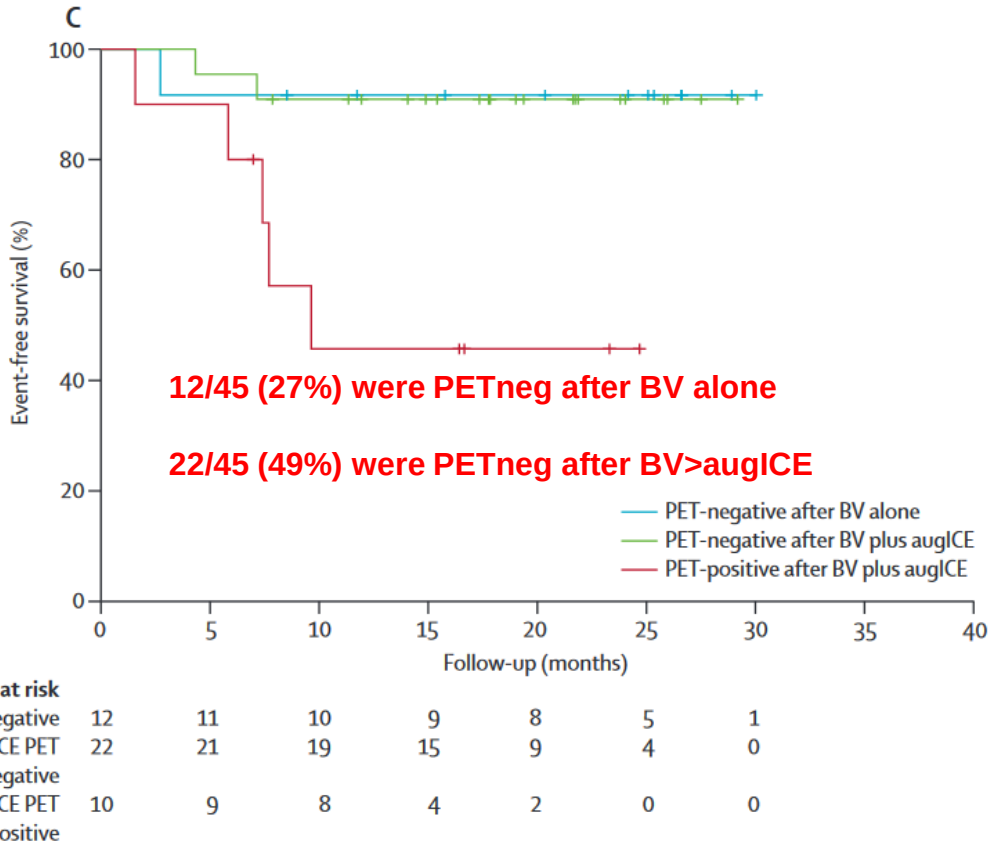


Lancet Onco 2015 Moskowitz

# New combinations in r/r HL

- **Bendamustin + Brentuximab-vedotin:**
  - Phase I/II trial of 64 pts with R/R HL after frontline therapy: ORR 78%
  - Phase II trial of 55 pts with R/R HL after frontline therapy: CR 83%
  - Phase II trial of 40 pts with R/R HL after frontline therapy: CR 79%
  - Retrospective series of 28 patients in Austria: CR 79%
  - Retrospective series of 10 patients in British Columbia: CR 90%
  - Retrospective series of 20 patients in Italy: CR 100%

- **DHAP / ESHAP + Brentuximab-vedotin:**
  - Phase I/II trial of 61 pts with BV+DHAP: CR 79%
  - Phase I/II trial of 66 pts with BV+ESHAP: CR 70%

- **Bendamustine with Gemcitabine and Vinorelbine (BGV):**
  - Phase II trial 59 patients: 73% CR + 10% PR (Jco 2016 Santoro)

Lancet Onco 2018 O´Connor Blood 2018 LaCasce Blood Cancer 2019 Broccoli EJH 2019 Wagner Blood A 2019 Picardi BJH 2016 Kalac ASH 2018 Hagenbeek AnnOnco 2019 Garica-Sanz

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**MEMO:**
**ORR to DHAP: 70%**
**14% do not proceed to ASCT**

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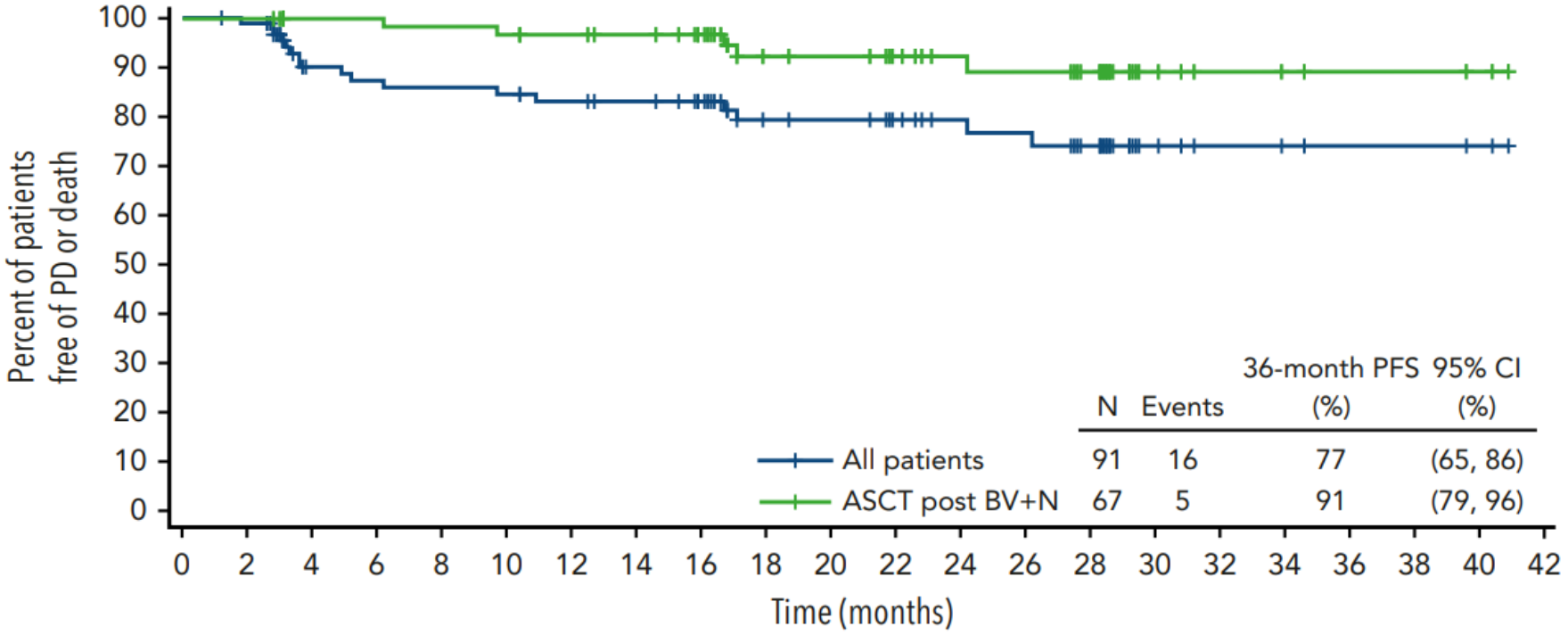
# Brentuximab / Nivo as salvage before ATX

Phase I/II study at first relapse before ASCT:

n=91, median age: 34 years, all patients received 4 cycles BV/Nivo

CR rate: 67%, 67 patients received ASCT after BV/Nivo without further salvage

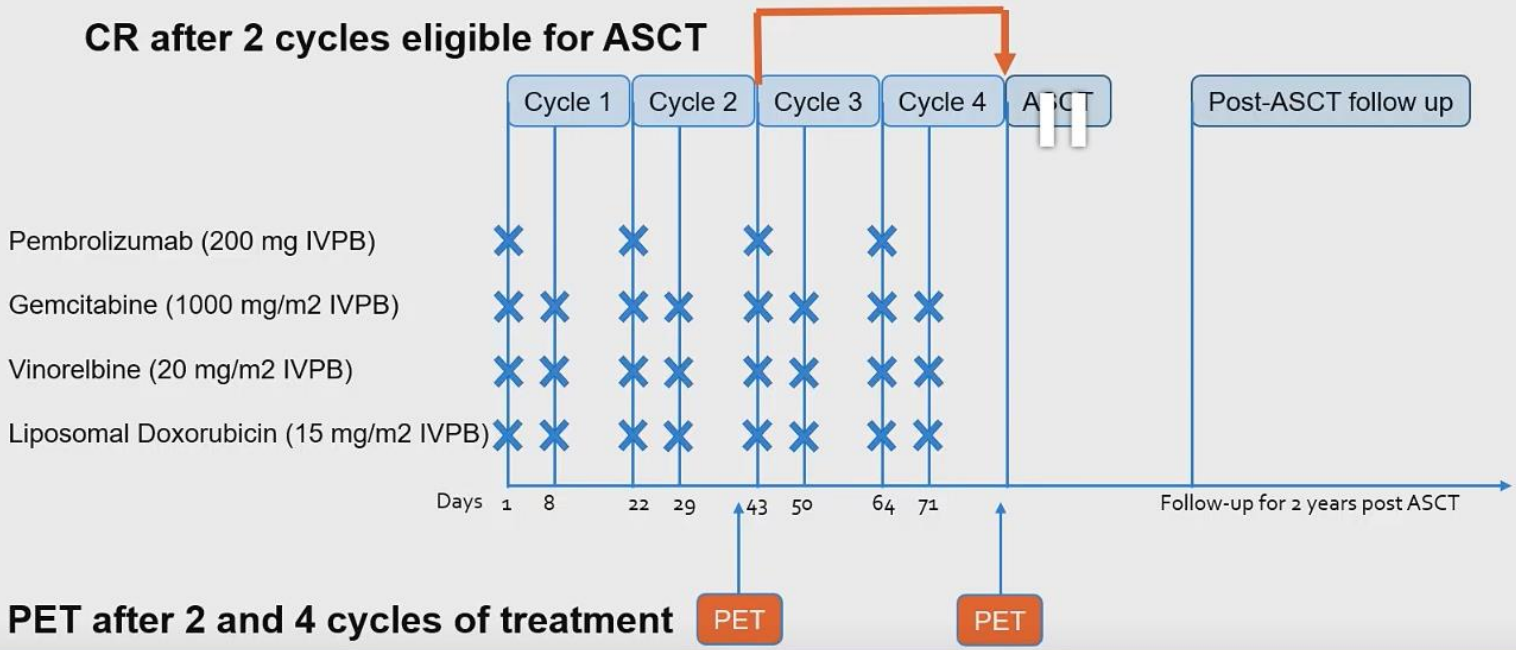



Blood 2021 Advani

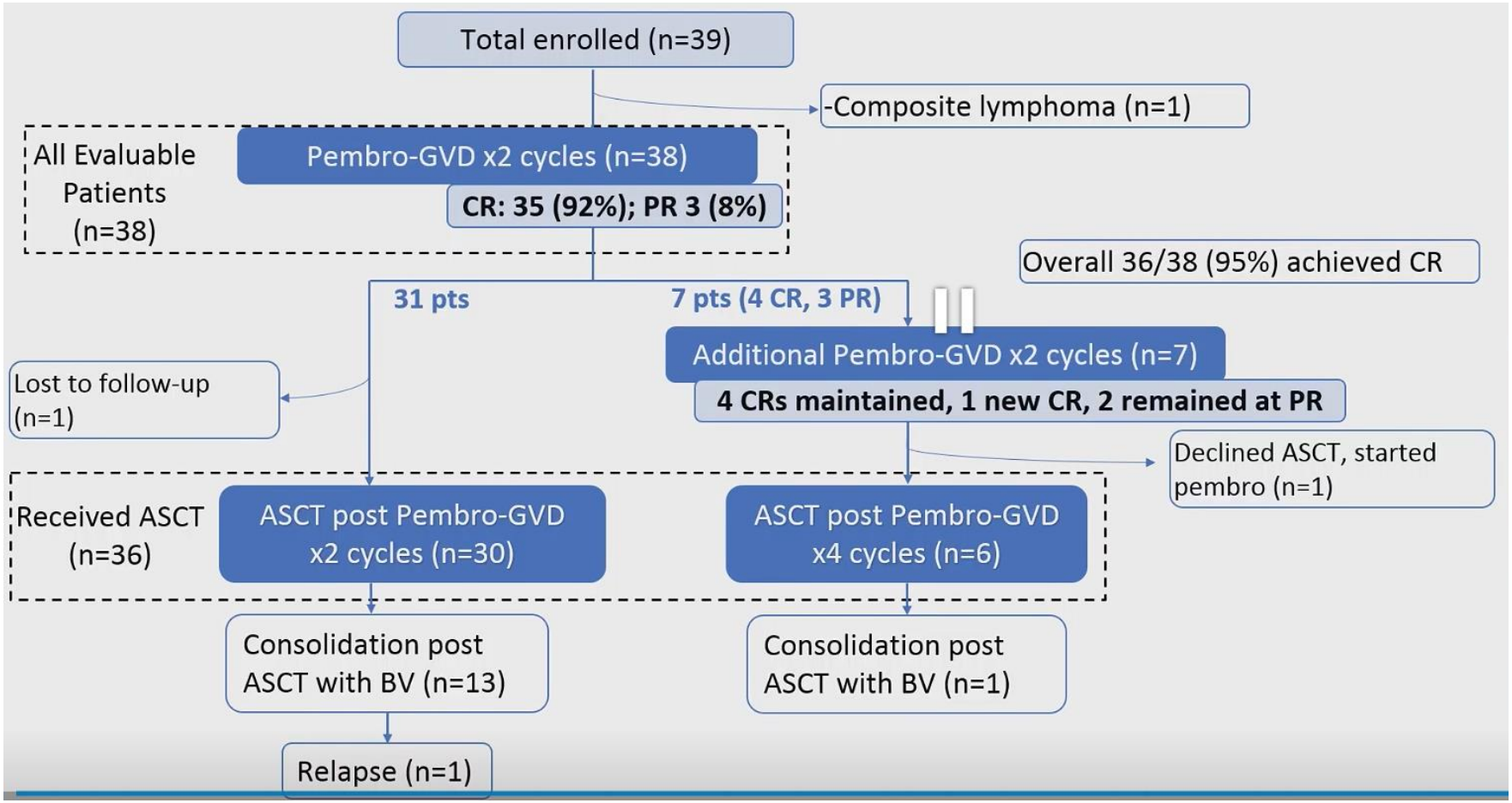
# Pembro-based salvage treatment

## 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



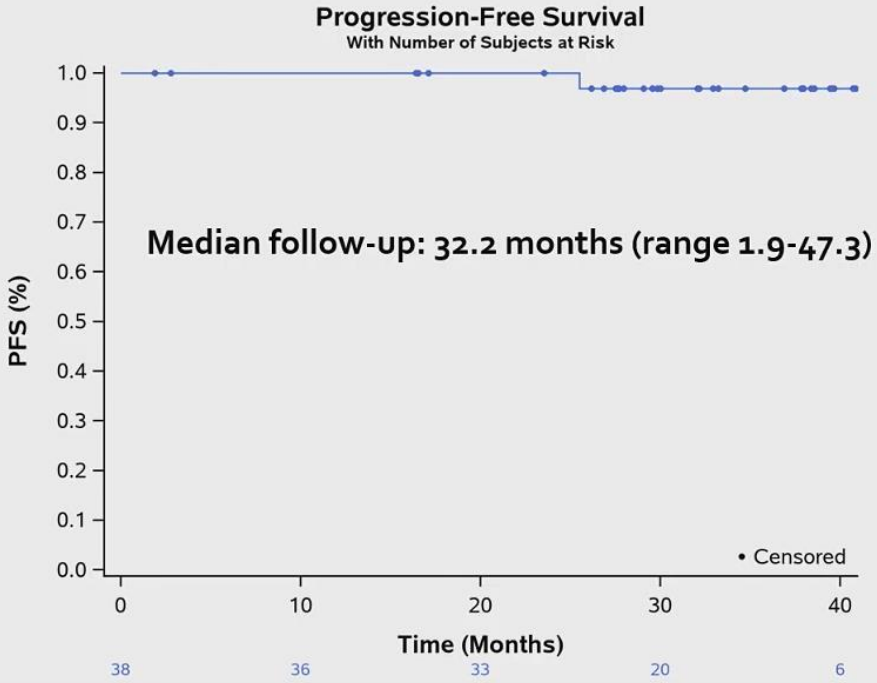
# Pembro-based salvage treatment



# Pembro-based salvage treatment

## Results of long-term follow up in the ITT cohort

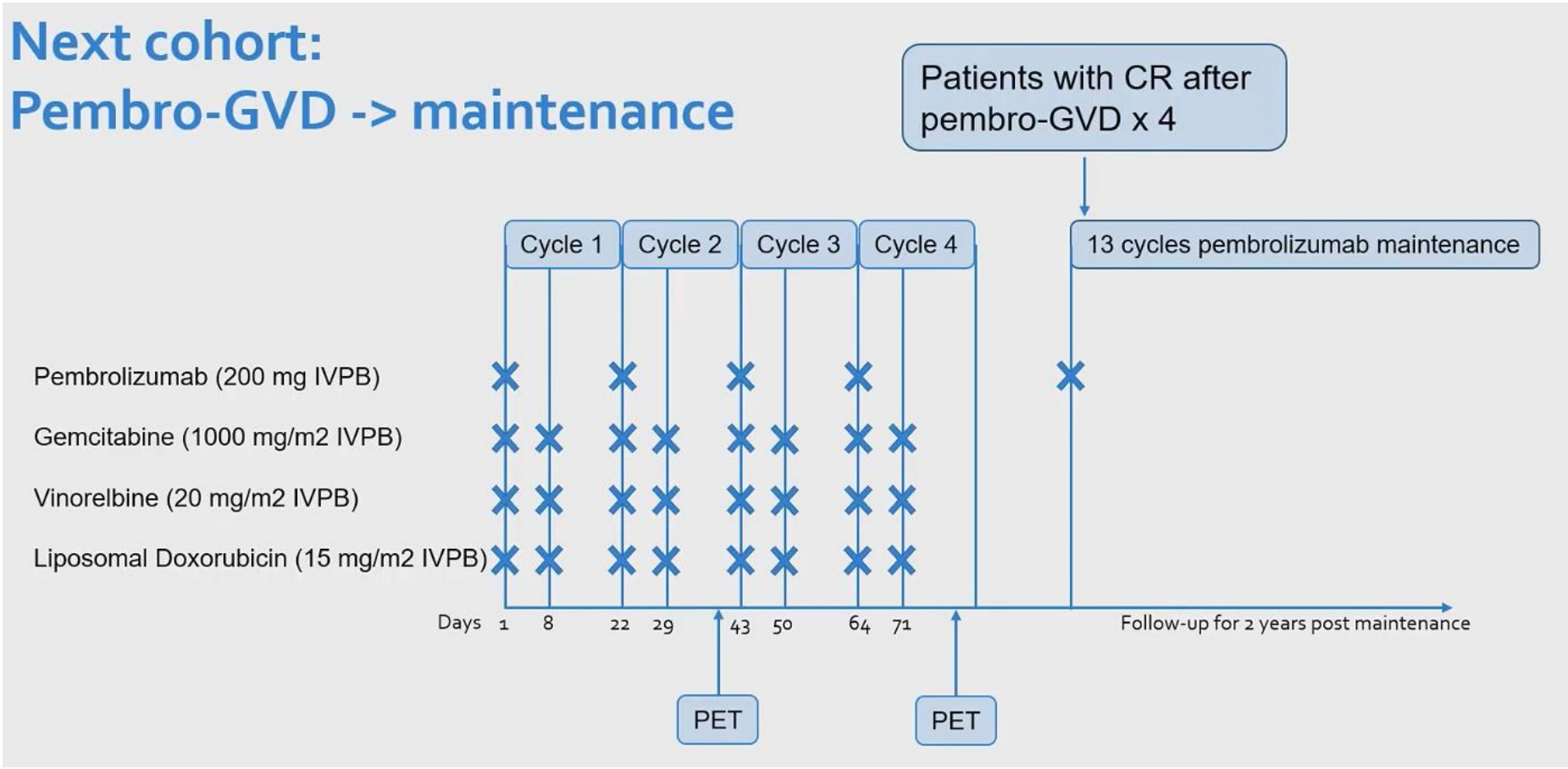
- 38 evaluable patients
- ORR: 100%
- CR: 95% (92% after 2 cycles)
- 36 pts proceeded to ASCT
- 1 relapse, 1 death (unrelated)
- 30 month PFS: 96%



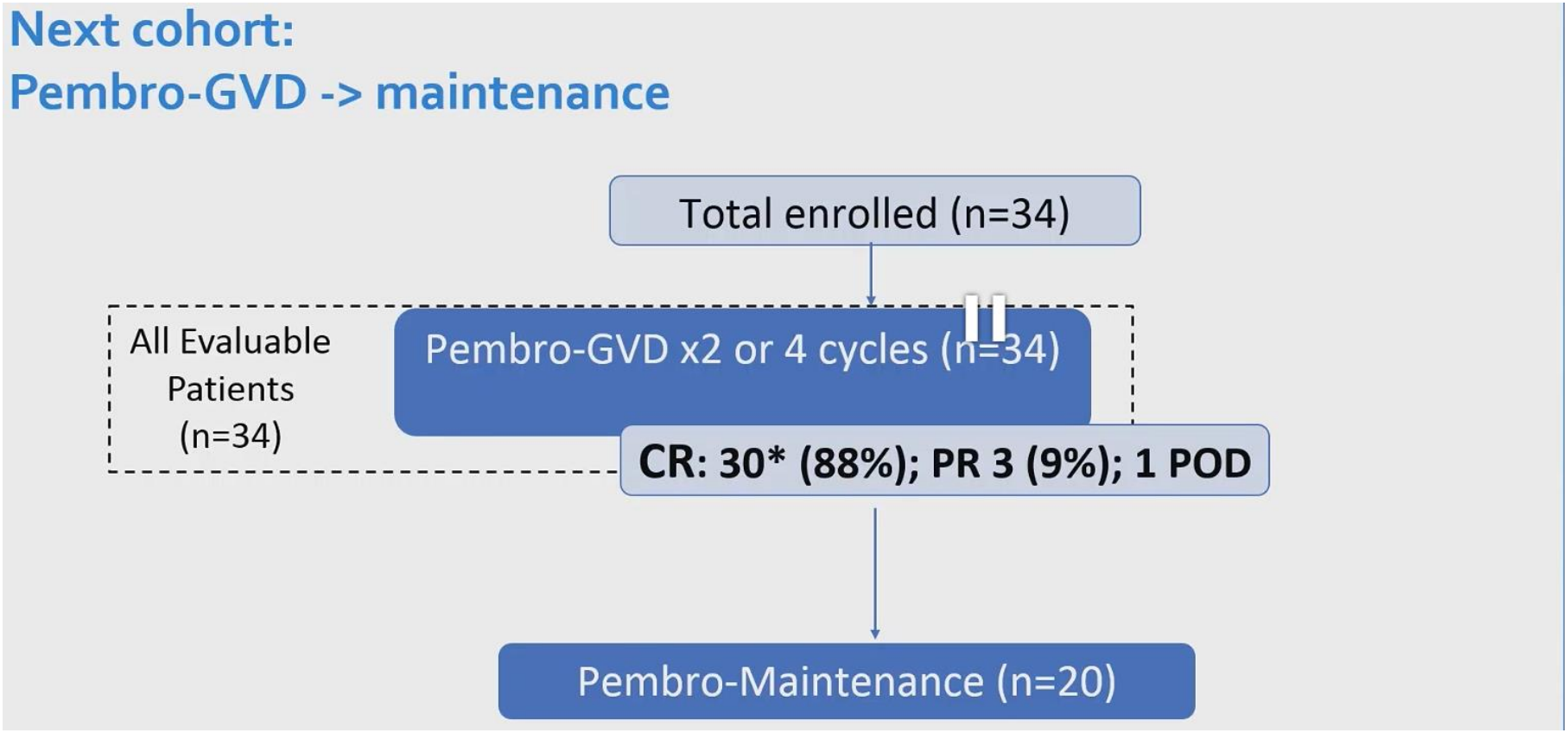

Memorial Sloan Kettering Cancer Center

Data cut off: 10/6/2022

# Pembro-based salvage treatment



# Pembro-based salvage treatment

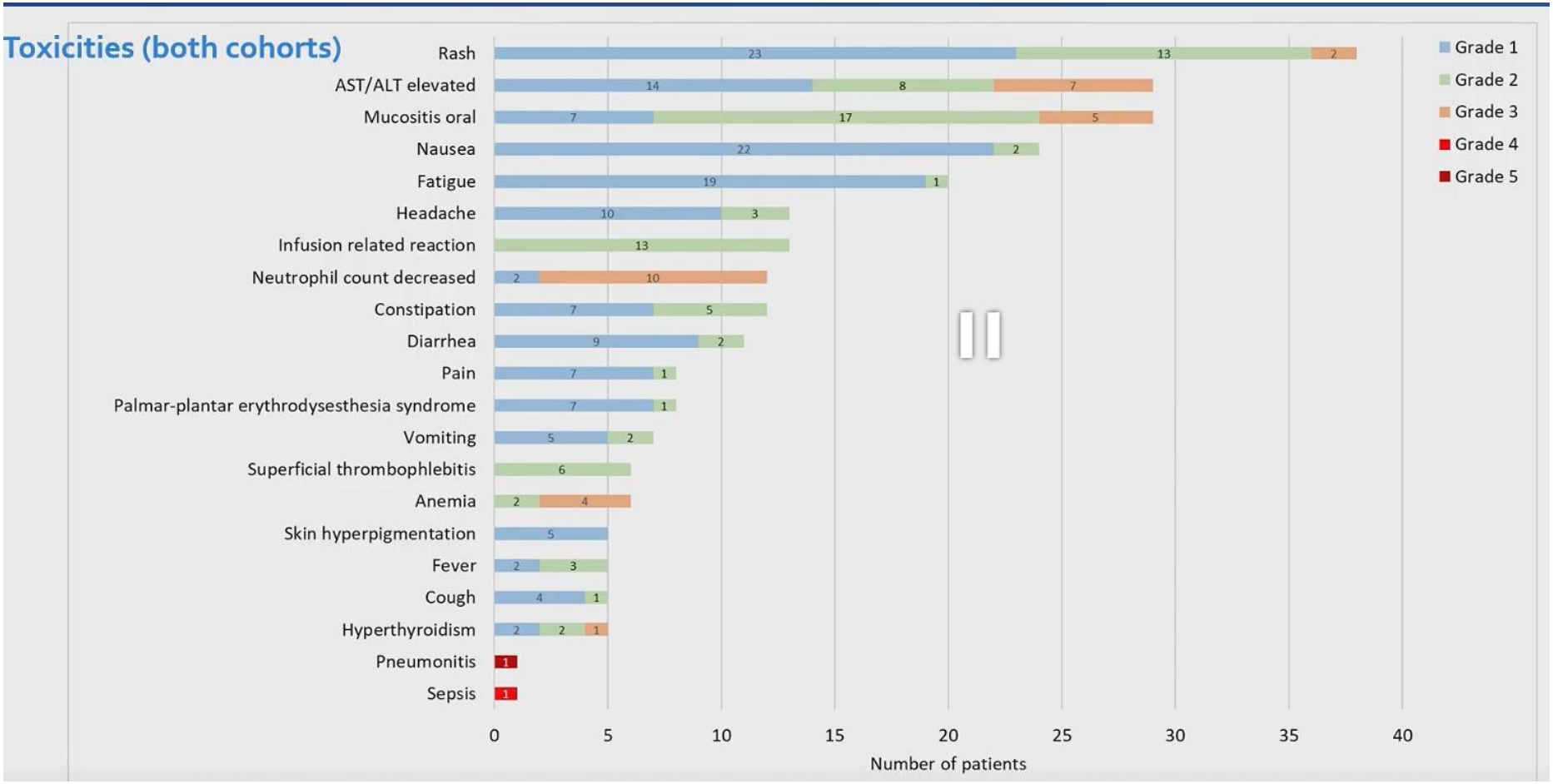


# Pembro-based salvage treatment

## Efficacy of pembro-GVD across both cohorts

| Characteristics | n (%) |
|---|---|
| Total treated with p-GVD | 73 |
| Evaluable for toxicity: | 73 |
| Evaluable for response: | 72 |
| ORR: | 69 (96%) |
| **CR:** | **66 (92%)** |

# Pembro-based salvage treatment



# Pembro-based salvage treatment

## Engraftment syndrome (ES)

- **23 of 34 (67%)** pts transplanted at MSKCC experienced engraftment syndrome
- Time to development of ES: **median 10 days (range 8-17) post transplant**
- Signs/symptoms
  - **Fevers, n=14 (61%)**
  - **Transaminitis, n=14 (61%),** G3, n=3
  - **Diarrhea, n=12 (52%),** G3, n=3
  - **Rash, n=8 (35%),** G3, n=4
- All patients recovered with steroids

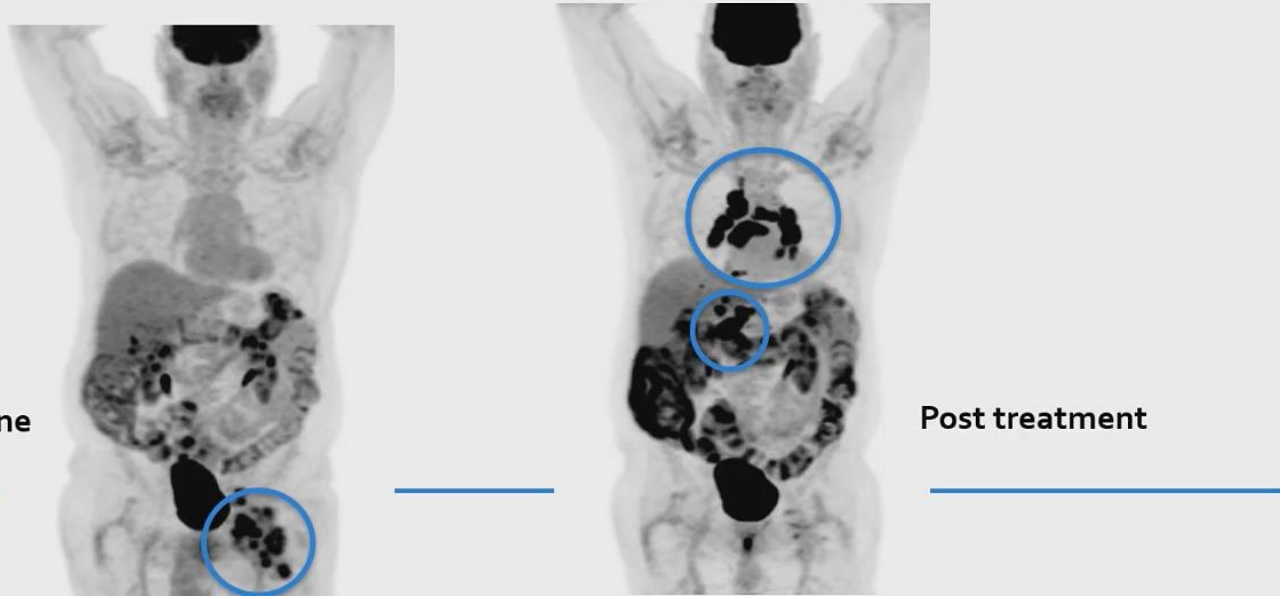
## Recognizing and treating Engraftment Syndrome

- **Presents with any of following symptoms, days 8-11 post ASCT:**
  - High grade fever >38.5°C
  - Skin rash (covering >25% body surface area)
  - Diarrhea (>2 watery BM/24 hrs)
  - May also be associated with
    - Hepatitis, pulmonary infiltrates, acute kidney injury, neurologic dysfunction
- Management:
  - **Any new onset fever, rash, and/or diarrhea occurring days 8-11 days post ASCT:**
    - **Obtain cultures, initiate broad spectrum antibiotics AND corticosteroids**
    - Dexamethasone 0.2mg/kg IV daily x 3 days (or symptom resolution) followed by 20-30% oral taper every 3 days over 14 days

# Pembro-based salvage treatment

## Pseudo-progressions (5 on ASCT cohort)

- 2 pts with FDG-avid hilar LAN 7 & 9 months post ASCT -> **non-necrotizing granulomas**
- 2 pts with FDG-avid axillary and mediastinal LAN 13 & 15 months post ASCT -> **reactive changes**
- 1 pt with FDG-avid terminal ileum 12 months post ASCT -> **follicular hyperplasia**

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# CPI with chemotherapy as salvage treatment

**Pembro-GVD trial:**

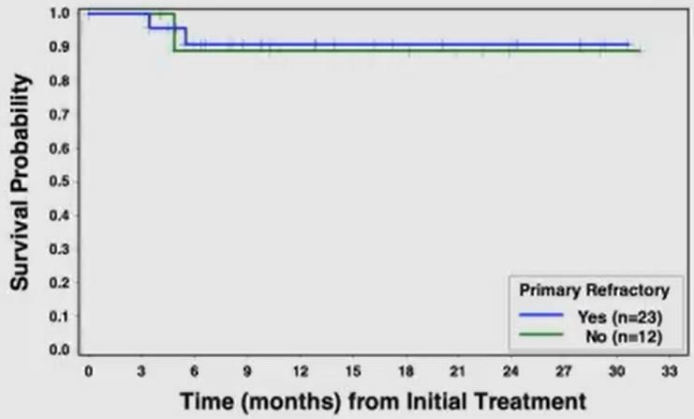
**This new combination shows very high CR rates as salvage before ASCT. A cohort without transplantation is ongoing and will show the potential of salvage treatment without ASCT.**

**Nivo-ICE trial:**

**Nivo in combination with 2-3 cycles ICE resulted in 38 patient in CR rate of 89% before ASCT.**

1-year PFS: 90%
- Primary refractory: 95%

10-month Post-HCT PFS: 96%
- Primary refractory: 100%




ASH & ISHL 2022 Moskowitz

ASH 2022 Mei

# Case presentation

**Before salvage treatment we performed a new biopsy. Due to previous BV exposure the patient received 2 cycles Pembro and GVD and a new PET scan showed complete metabolic response in June 2024.**

**He received high dose chemotherapy with stem cell support in July 2024.**

# Agenda:

- **Salvagetherapy at first relapse:**
  - ➢**Radiotherapy**
  - ➢**BV +/- chemotherapy**
  - ➢**CPI**
- **Consolidation after stem cell transplant:**
  - ➢**AETHERA**
  - ➢**CPI**
- **Later treatment lines:**
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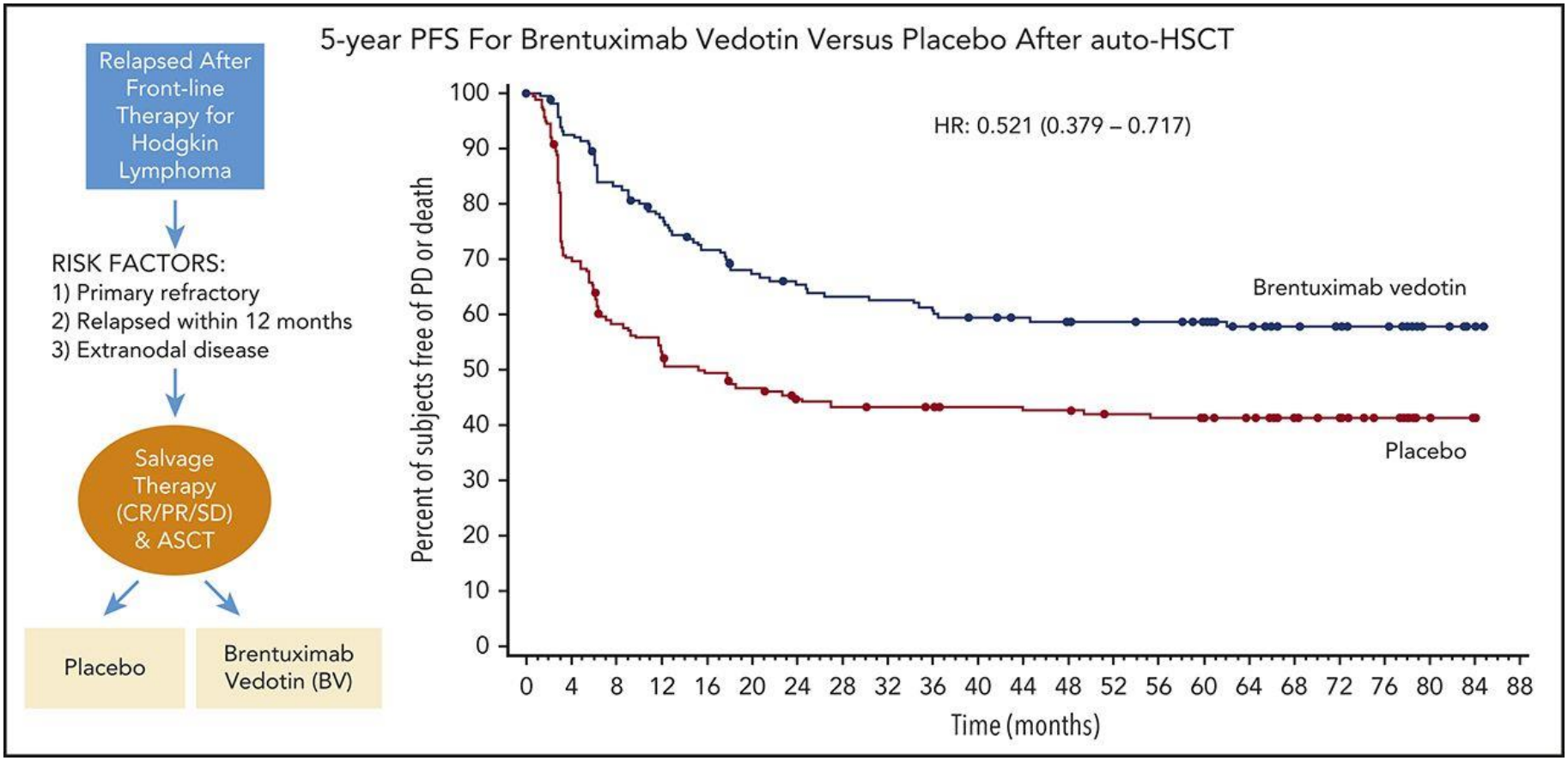
  - ➢**CPI combinations**
- **Allogenic stem cell transplant:**
  - ➢**New data**

# Brentuximab maintenance improves PFS




**Maintenance für 48 weeks increases rate of curation in first relapse**

Blood 2018 Moskowitz

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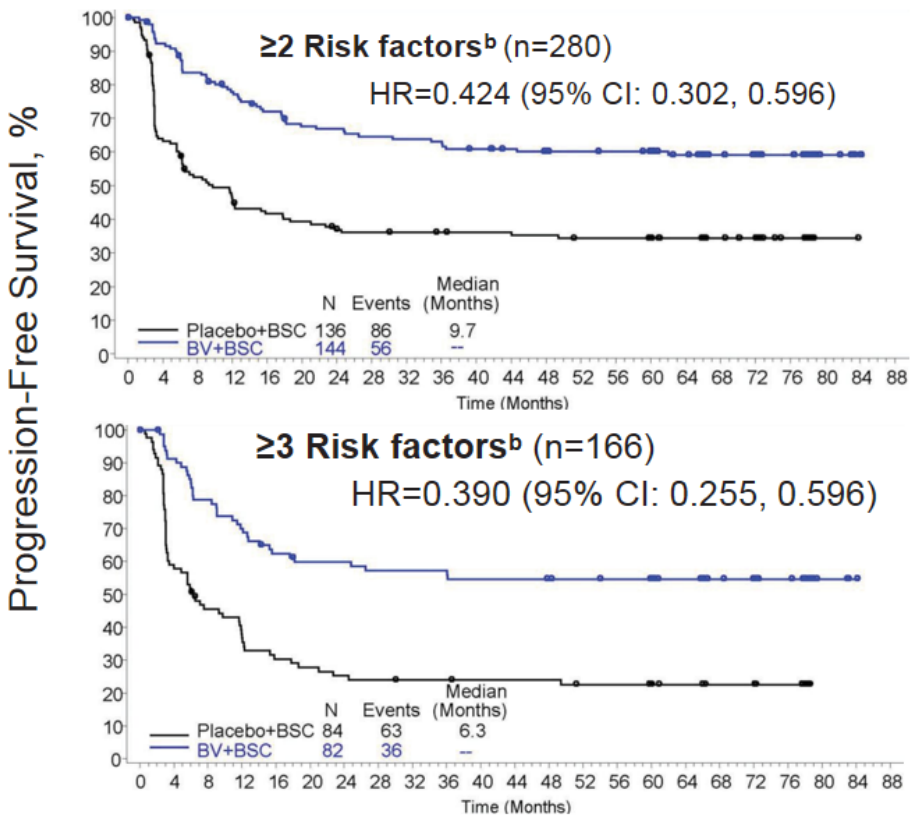



**Risk Factors**

- Primary-refractory HL or relapse <12 months from completion of frontline therapy
- PR or SD as best response to salvage therapy pre-ASCT
- ≥2 previous salvage therapies
- Extranodal disease at pre-ASCT relapse
- B symptoms after failure of frontline therapy

[a]Small number of patients with 1 risk factor precludes an assessment of group
[b]Post hoc analysis

Blood 2018 Moskowitz

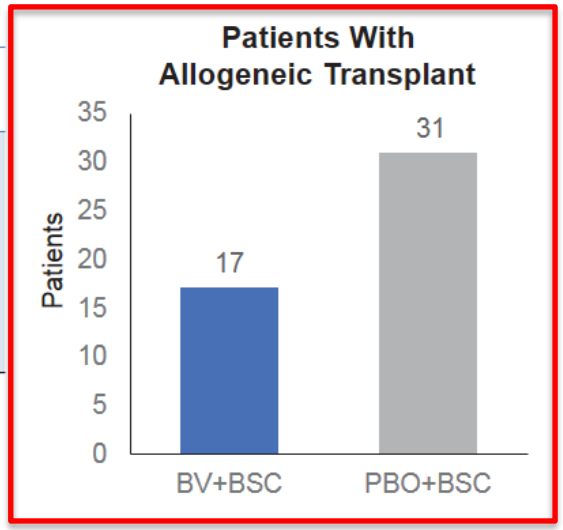
# Brentuximab maintenance improves PFS

## Subsequent Anticancer Therapy

- 87% of patients on PBO received single-agent BV as subsequent therapy
- 10 patients on the BV arm were subsequently retreated with BV (ORR=60%)
  - 4 CRs, 2 PRs, 1 SD, 1 PD, and 1 unknown
- Fewer allogeneic transplants on BV arm (n=17) versus PBO (n=31)

| Regimen type | BV+BSC (n=165) n (%) | PBO+BSC (n=164) n (%) |
|---|---|---|
| Any subsequent therapy | 53 (32) | 89 (54) |
| Single-agent BV | 10 (6) | 77 (47) |
| Multi-agent regimen[a] | 38 (23) | 46 (28) |
| Single-agent therapy | 24 (15) | 33 (20) |
| Radiation | 25 (15) | 29 (18) |
| Stem cell transplant[b] | 19 (12) | 35 (21) |
| Other[c] | 3 (2) | 4 (2) |

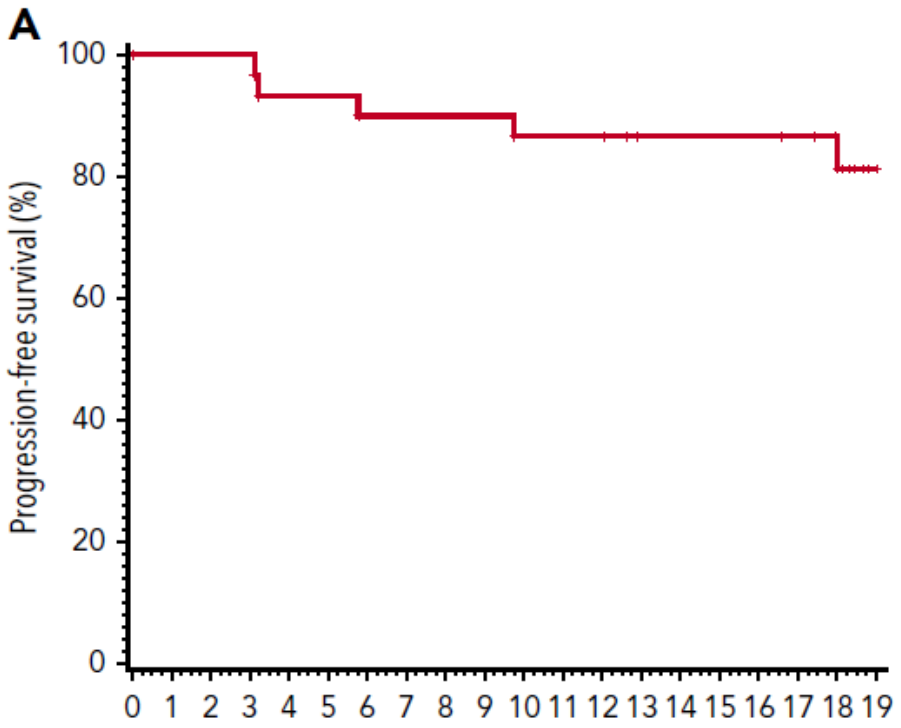
[a]Includes multi-agent regimens with BV (n = 2 in each treatment group)
[b]Allogeneic transplants (n=17 in BV arm and n=31 in PBO )
[c]Other includes donor lymphocyte fusion (n=2 in each group) and unknown (n=1 in BV, n=2 in PBO)




Blood 2018 Moskowitz

# Pembrolizumab consolidation after ATX

Phase II study of consolidative pembrolizumab after ASCT:
n=30, median age: 33 years, 8 cycles pembrolizumab




Blood 2020 Armand

# Brentuximab / Nivo as consolidation after ATX

## Study Design/Treatment Plan

- AHCT according to institutional standards
- Starting 30-75 days after AHCT:
  - 1.8mg/kg BV and 3mg/kg Nivo every 21 days for planned 8 cycles
  - If one drug discontinued for toxicity, other could be continued
- PET-CT after AHCT/baseline, C4D15, EOT, 12 and 18 mo after treatment
- Primary endpoint: 18-month progression-free survival (PFS)
  - A sample size of 59 evaluable patients will provide approximately 81% power for detecting the increase in 18-month PFS from the baseline of 65% to 80% in this study at 1-sided type I error of 0.05
- Secondary endpoints: overall survival, safety, response rate for pts not in CR
- PFS and response assessed by investigators according to 2014 Lugano classification

# Brentuximab / Nivo as consolidation after ATX

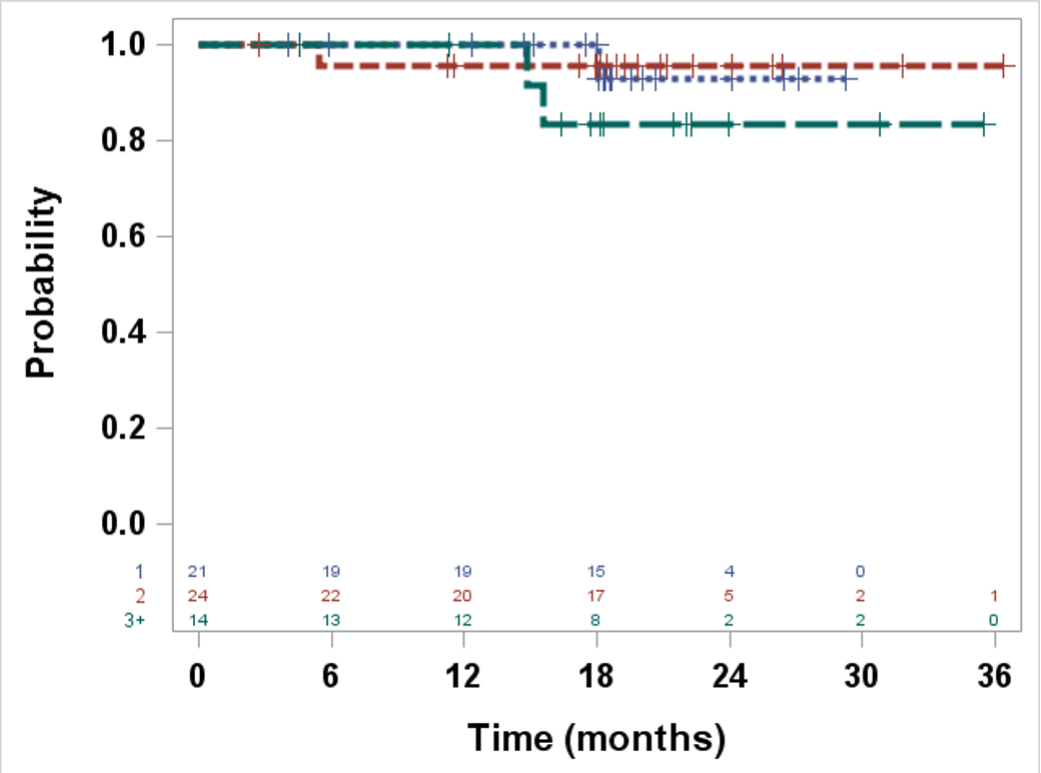
## PFS according to number of risk factors

19-month PFS in pts with:

1 risk factor (n=21) – 93%
(95 CI 59-99%)

2 risk factors (n=24) – 96%
(95 CI 73-99%)

3+ risk factors (n=14) – 83%
(95 CI 48-96%)



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  - ➢**CPI**
- **Consolidation after stem cell transplant:**
  - ➢**AETHERA**
  - ➢**CPI**
- **Later treatment lines:**
  - ➢**CPI vs BV**
  - ➢**CPI combinations**
- **Allogenic stem cell transplant:**
  - ➢**New data**

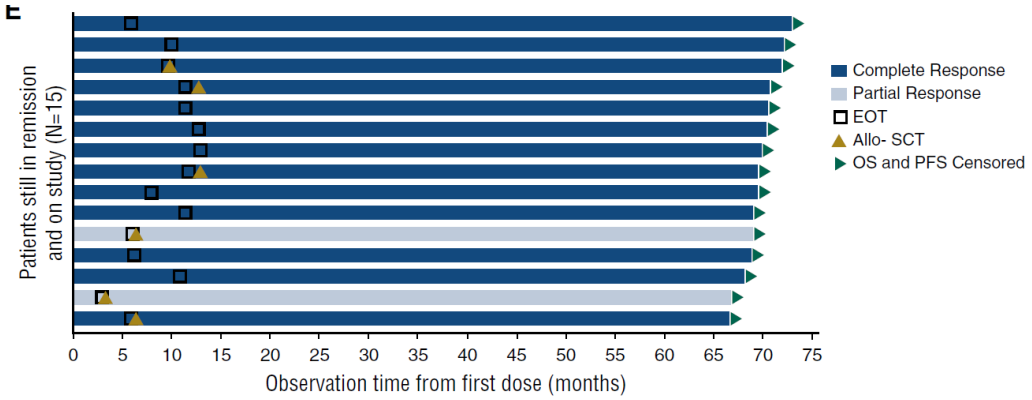
# Possible cure with BV in heavily pretreated patients

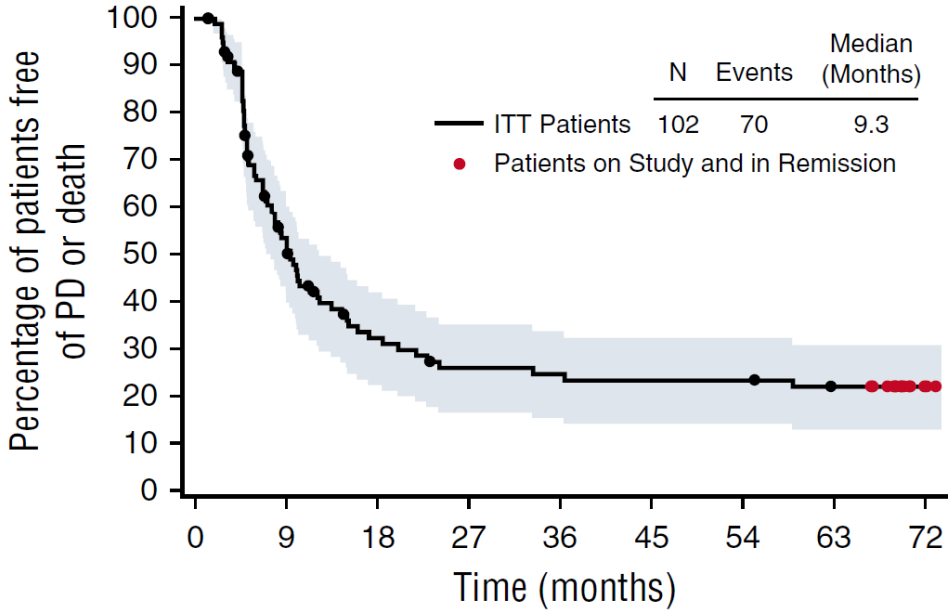
- **Phase II trial**
- **n=102 patients**

- **Median previous regimens: 3.5**
- **ORR: 75%**
- **Median PFS: 5.6 months**

- 38% of pts who achieved CR (13/34) remained in remission for.5 years and may be cured.

- 9 of these 13 long-term CRs did not underwent Allo-TX.




Blood 2016 Chen

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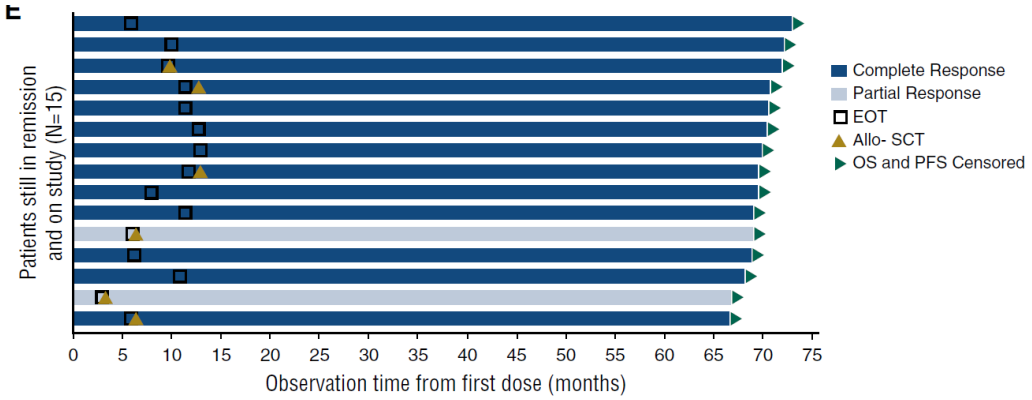


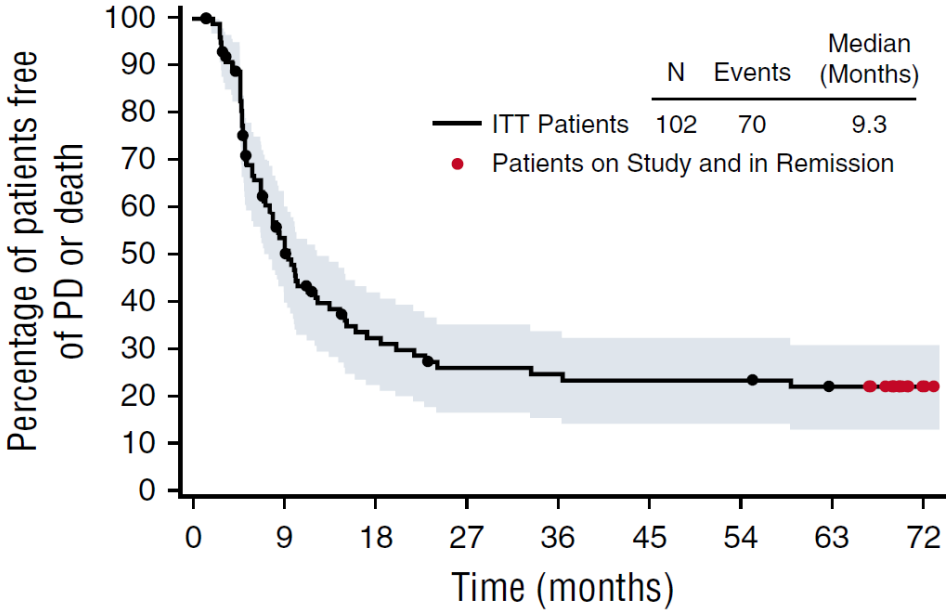


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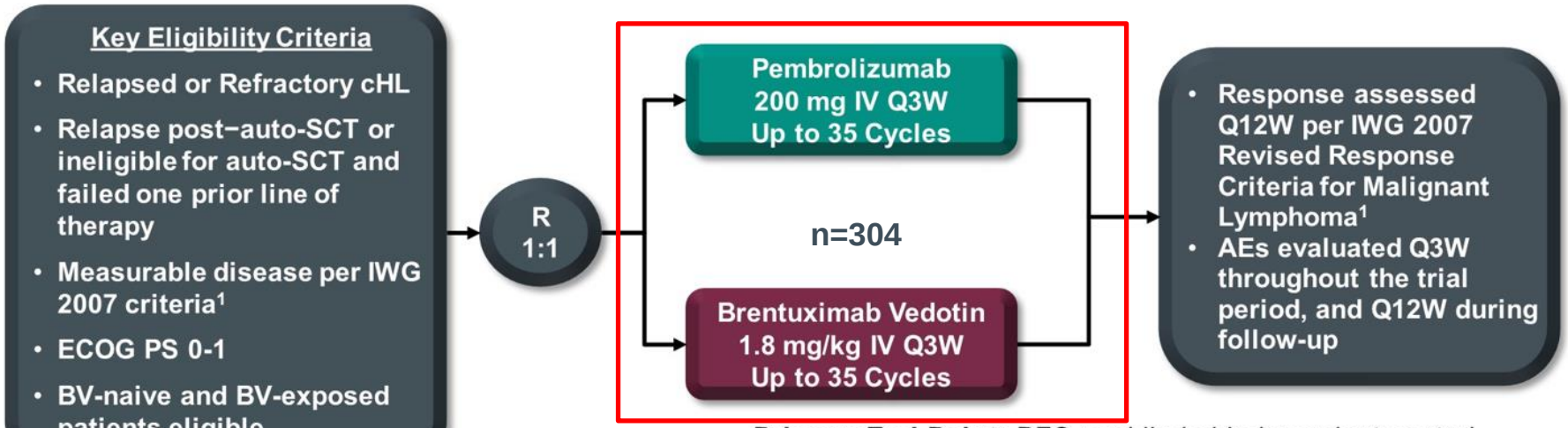
# KN-204: Pembrolizumab vs BV

## KEYNOTE-204 Study Design (NCT02684292)




**Primary End Point:** PFS per blinded independent central review (BICR) by IWG 2007 criteria including clinical and imaging data following auto-SCT or allogeneic stem cell transplant (allo-SCT); OS

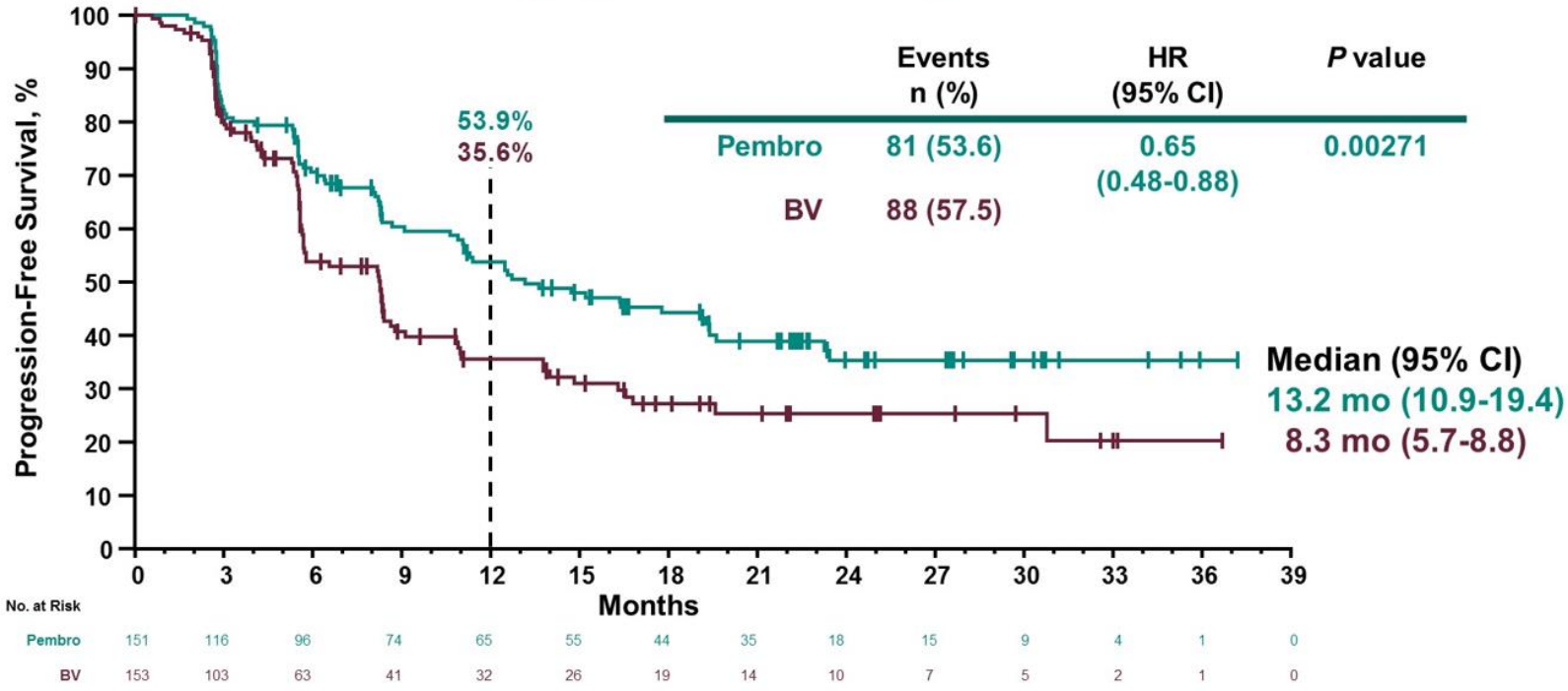
**Secondary End Points:** PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

1. Cheson BD et al. *J Clin Oncol*. 2007;25:579-586.

# KN-204: Pembrolizumab vs BV

## Primary End Point: Progression-Free Survival Per Blinded Independent Central Review

### Including Clinical and Imaging Data Following Auto-SCT or Allo-SCT



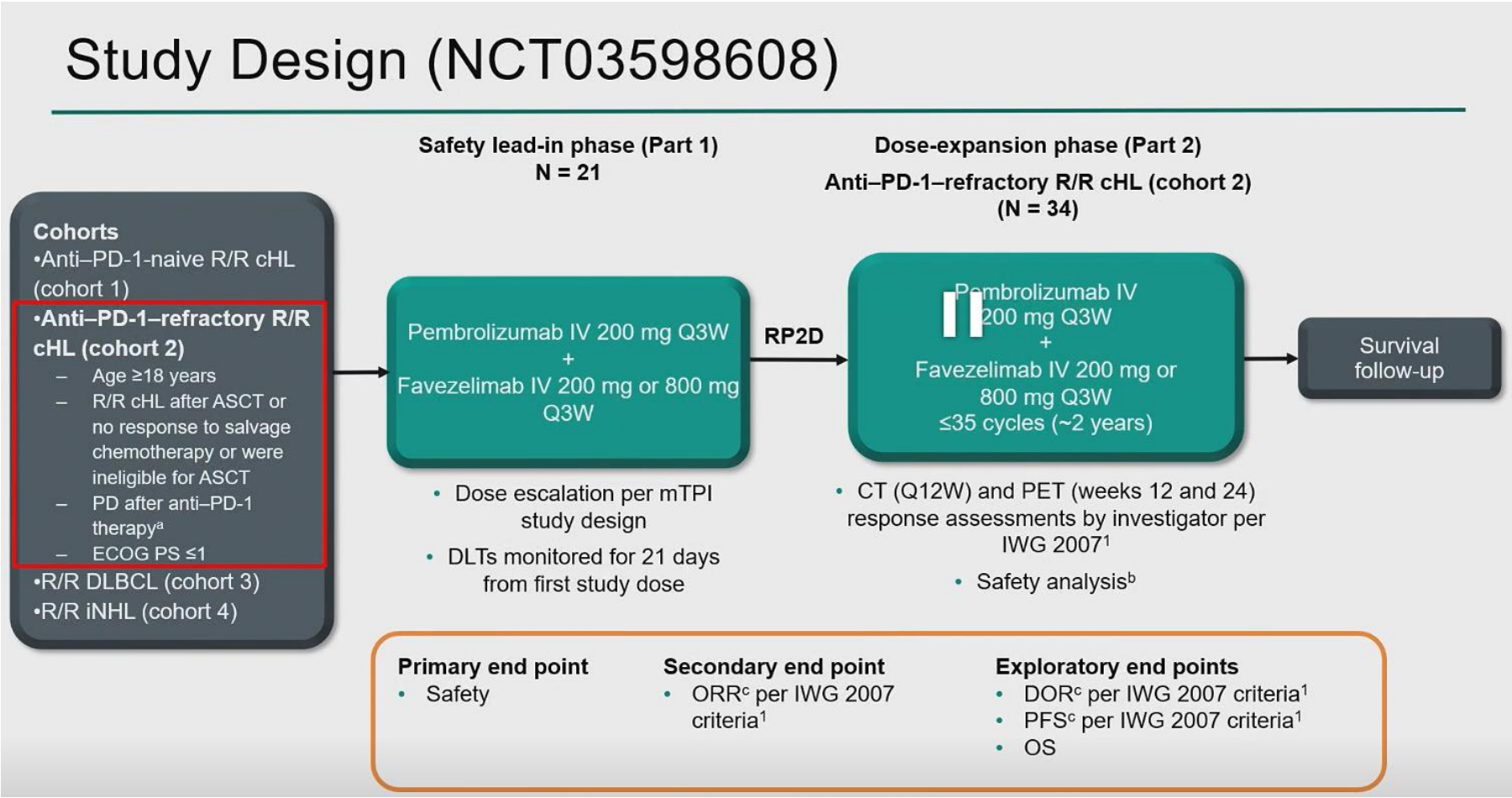

Data cutoff: January 16, 2020.

# Safety and Dose-Expansion Study of Combination Favezelimab (anti–LAG-3) Plus Pembrolizumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma Refractory to Anti–PD-1 Treatment

John Timmerman[1]; David Lavie[2]; Nathalie A. Johnson[3]; Abraham Avigdor[4]; Peter Borchmann[5]; Charalambos Andreadis[6]; Ali Bazargan[7]; Gareth P. Gregory[8]; Colm Keane[9]; Inna Tzoran[10]; Vladan Vucinic[11]; Pier Luigi Zinzani[12]; Hong Zhang[13]; Pallavi Pillai[13]; Akash Nahar[13]; Alex F. Herrera[14]

[1]UCLA Medical Center, Los Angeles, CA, USA; [2]Hadassah Medical Center, Jerusalem, Israel; [3]Jewish General Hospital, Montreal, QC, Canada; [4]Sheba Medical Center–Tel HaShomer, Ramat Gan, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]University Hospital of Cologne, Cologne, Germany; [6]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [7]University of Melbourne, Melbourne, VIC, Australia; St Vincent's Hospital, Fitzroy, VIC, Australia; [8]School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia; [9]Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Rambam Health Care Campus, Haifa, Israel; [11]University of Leipzig Medical Center, Leipzig, Germany; [12]IRCCS-University of Bologna Seragnoli Institute of Hematology and Department of Specialized, Diagnostic, and Experimental Medicine, University of Bologna, Bologna, Italy; [13]Merck & Co., Inc., Rahway, NJ, USA; [14]City of Hope, Duarte, CA, USA

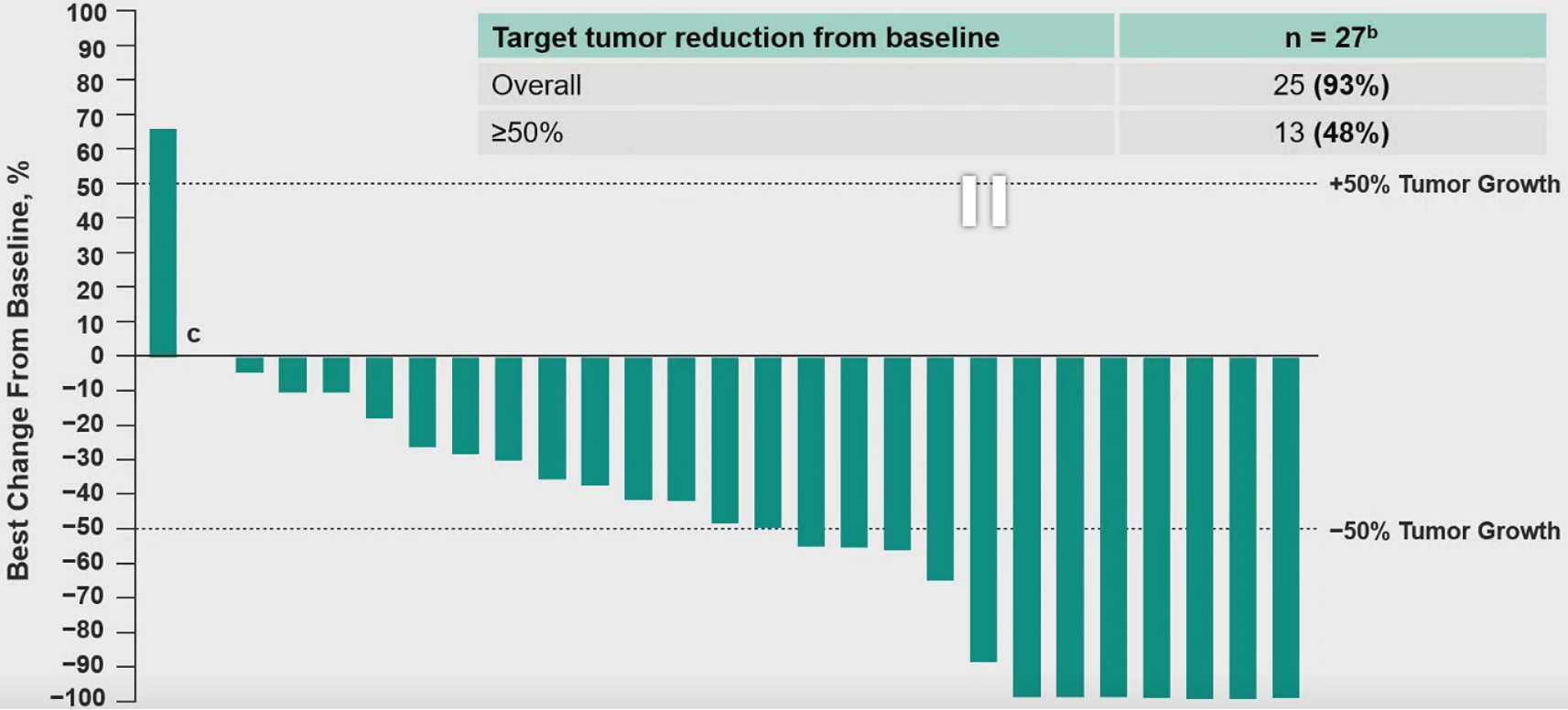
# Favezelimab with pembrolizumab



# Favezelimab with pembrolizumab

## Best Change From Baseline in Target Lesion Size[a]

| Target tumor reduction from baseline | n = 27[b] |
|---|---|
| Overall | 25 **(93%)** |
| ≥50% | 13 **(48%)** |



# Favezelimab with pembrolizumab

## Conclusions

- The RP2D was determined to be favezelimab 800 mg Q3W + pembrolizumab 200 mg Q3W
  - Only 1 DLT was observed across all cohorts
  - No DLTs were observed with the favezelimab 800 mg dose
- The combination had a manageable safety profile in patients with cHL refractory to anti–PD-1 therapy
- Favezelimab + pembrolizumab demonstrated promising antitumor activity in patients with cHL refractory to anti–PD-1 therapy
  - ORR, 30% (CR, 9%; PR, 21%)
  - 25 of 27 (93%) patients who had both baseline and postdose assessments by the data cutoff date had a baseline reduction in target lesions
- A phase 3 study investigating a coformulation of favezelimab/pembrolizumab in patients with cHL refractory to anti–PD-1 therapy is under way (NCT05508867)

# Case presentation

**Before salvage treatment we performed a new biopsy. Due to previous BV exposure the patient received 2 cycles Pembro and GVD and a new PET scan showed complete metabolic response in June 2024.**

**He received high dose chemotherapy with stem cell support in July 2024.**

**After engraftment and demission from stem cell ward he proceeded to radiotherapy and then to consolidative pembrolizumab for 6 months.**

# Agenda:

- **Salvagetherapy at first relapse:**
  - ➢**Radiotherapy**
  - ➢**BV +/- chemotherapy**
  - ➢**CPI**
- **Consolidation after stem cell transplant:**
  - ➢**AETHERA**
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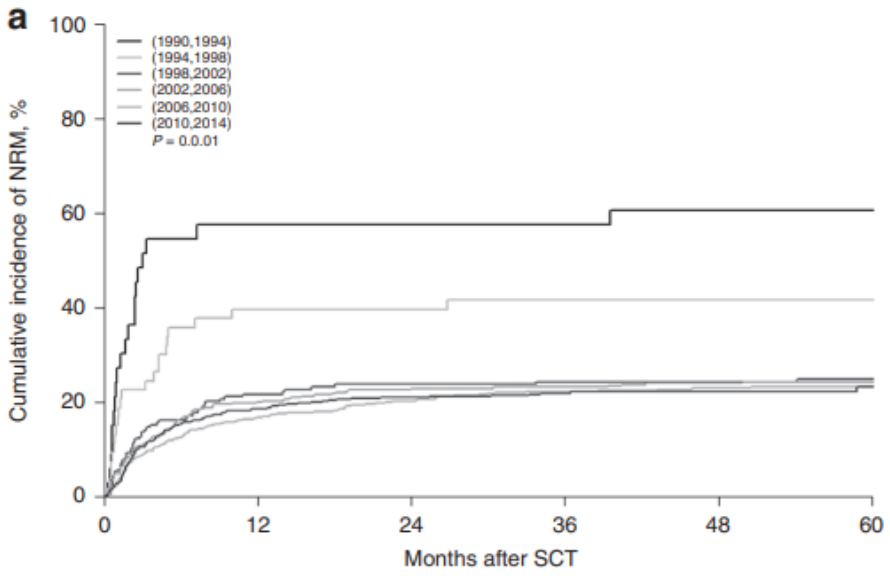
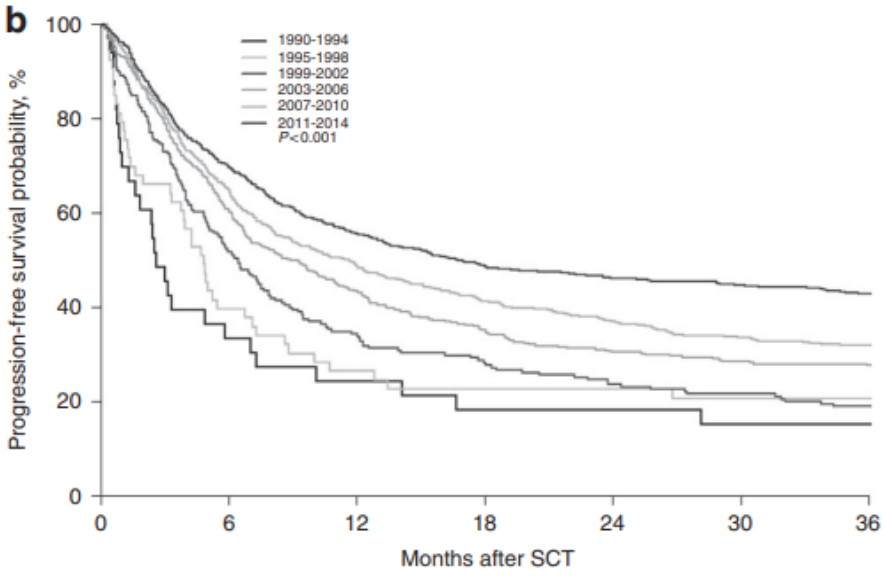
- **Later treatment lines:**
  - ➢**CPI vs BV**
  - ➢**CPI combinations**
- **Allogenic stem cell transplant:**
  - ➢**New data**

# Allogenic TX in R/R Hodgkin Lymphoma

**EBMT retrospective anaylsis of 2204 patients from 1990 to 2014:**

- Number increaed over time including Haplo-TX
- RIC > MAC in last decade
- More chemosensitive disease before TX




BMT 2020 Sureda

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**Sandro Wagner**
**Dominik Kiem**
**Marie Mayer**
**Lukas Weiss**
**Richard Greil**
**Alexander Egle**

Hämatologische / Hämostaseologische Ambulanz C4 EG

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# Unseren Patienten

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