News dal mondo "LINFOMI"

NAPOLI - 18 SETTEMBRE 2023 - ROYAL HOTEL CONTINENTAL

IL RUOLO DEL PEMBROLIZUMAB NEL LINFOMA DI HODGKIN

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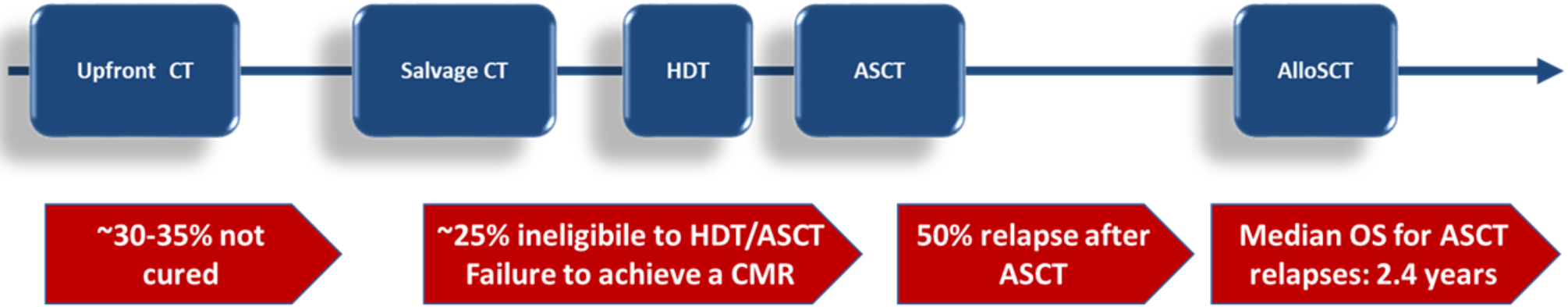
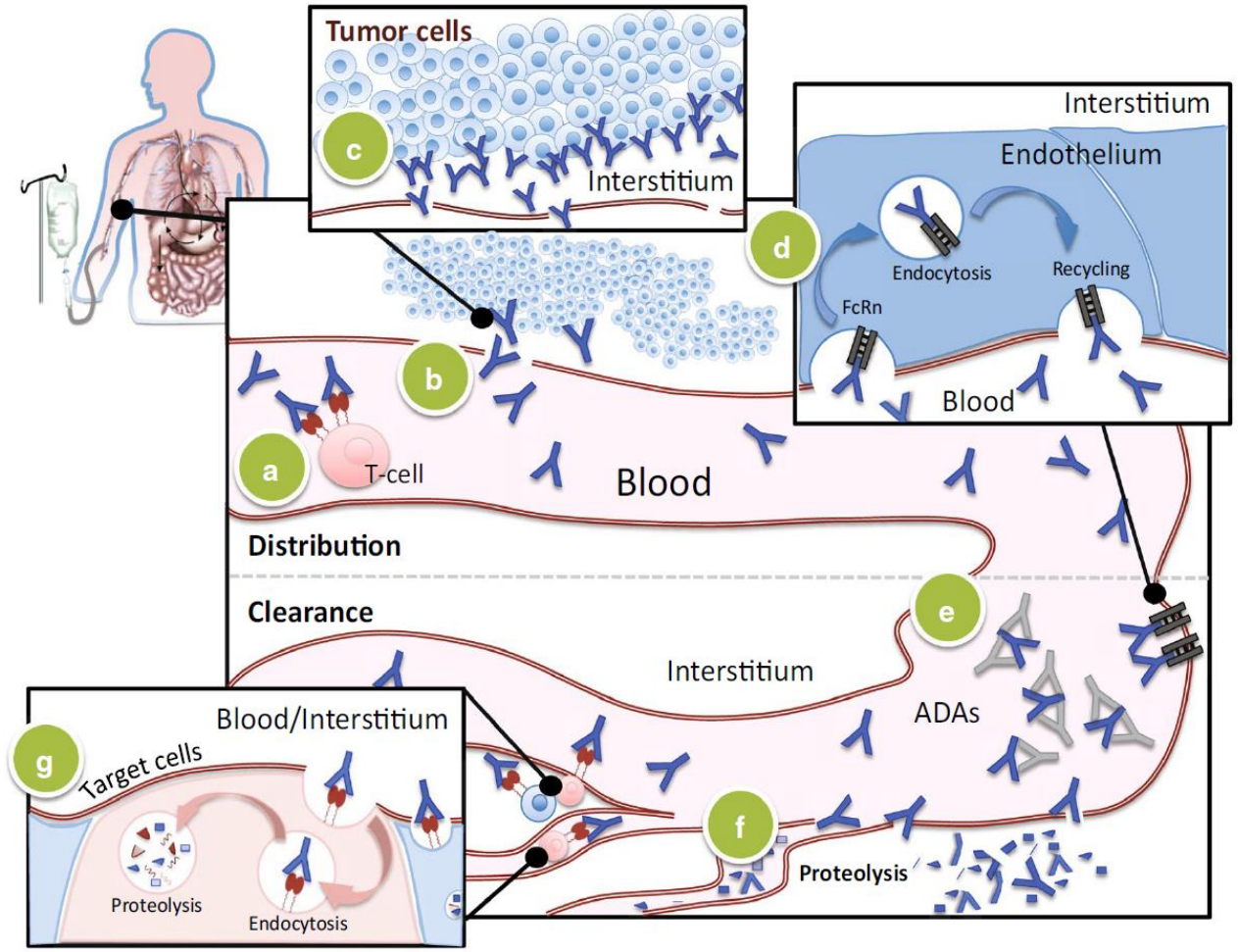
The *classic* therapeutic sequence for advanced stage Hodgkin Lymphoma



2010 ···▶ 2011 ···▶ 2023 ?



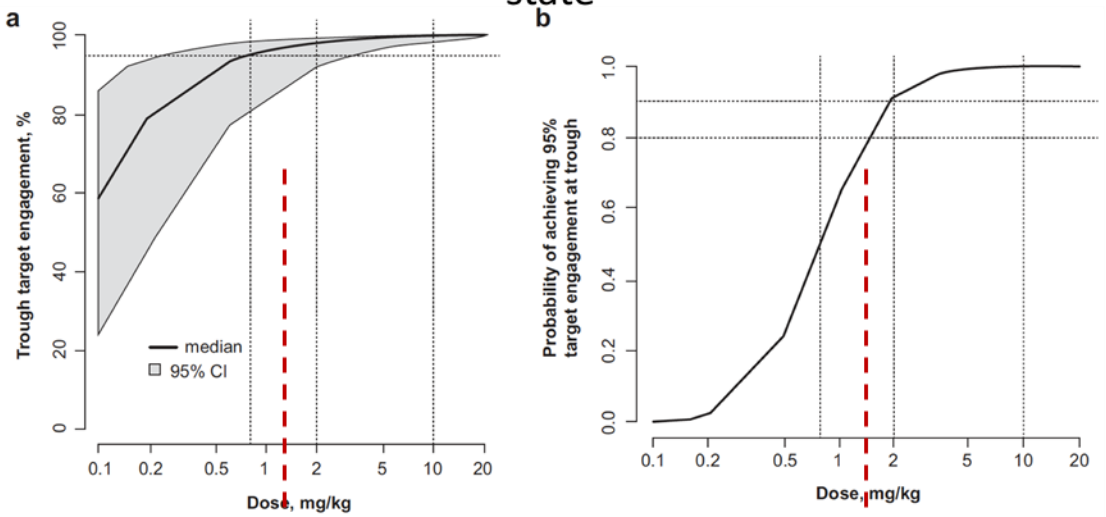
Target-mediated drug disposition (TMDD)
Receptor mediated endocytosis and degradation

Plateau PD1 receptor occupancy maintaned @ serum levels < 1.2 μg/mL

Pembrolizumab:

- **Fully humanized IgG4 mAb against the PD-1 antigen**
- **Recommended (original) dosing: 2 mg/kg or 200 mg (30 min *i.v.*) q3 weeks**
- **Steady state reached after approximately 18 weeks**
- **Average half-life in the range of 14–27.3 days**
- **Exposure-response relationship for efficacy and safety is flat between 2 mg/kg to 10 mg/kg**

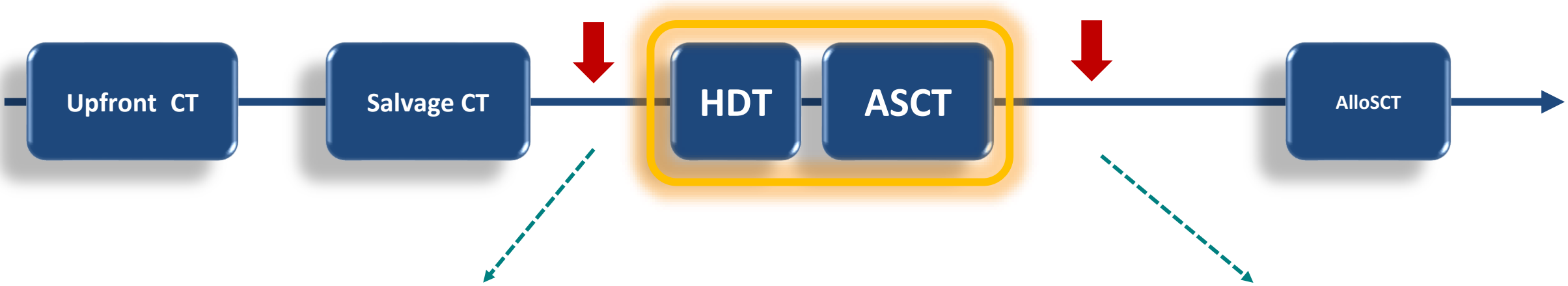
Target engagement as a function of concentration at steady state



Pembrolizumab as a single agent for RR-HL

The current therapeutic sequence for patients with Hodgkin Lymphoma

The best salvage option ***today remains HDT-ASCT (tomorrow ?)***



- **Increase 'candidability'**
  functional eligibility
- **Achieve the best pre-ASCT CR**
- *'CR is good but not all CRs are equal'*
- Avoid or delay ASCT ?

After ASCT Failure

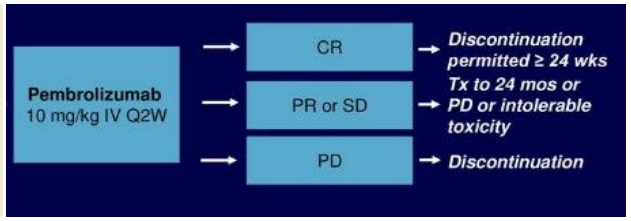
Prevent ASCT failure

Pinto A 2022)

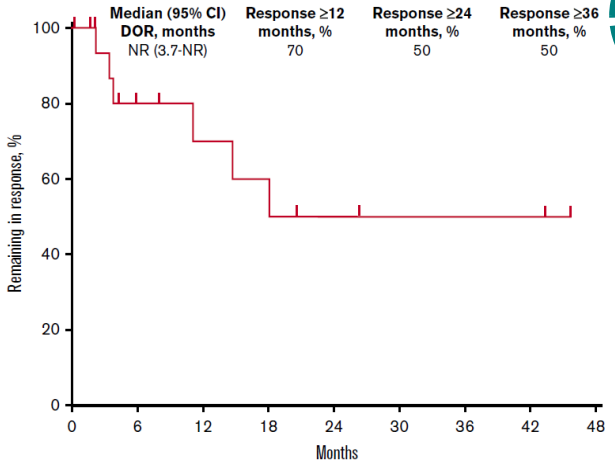
The '*early days*': Keynote-013 (Phase Ib) & Keynote-087

Keynote-013

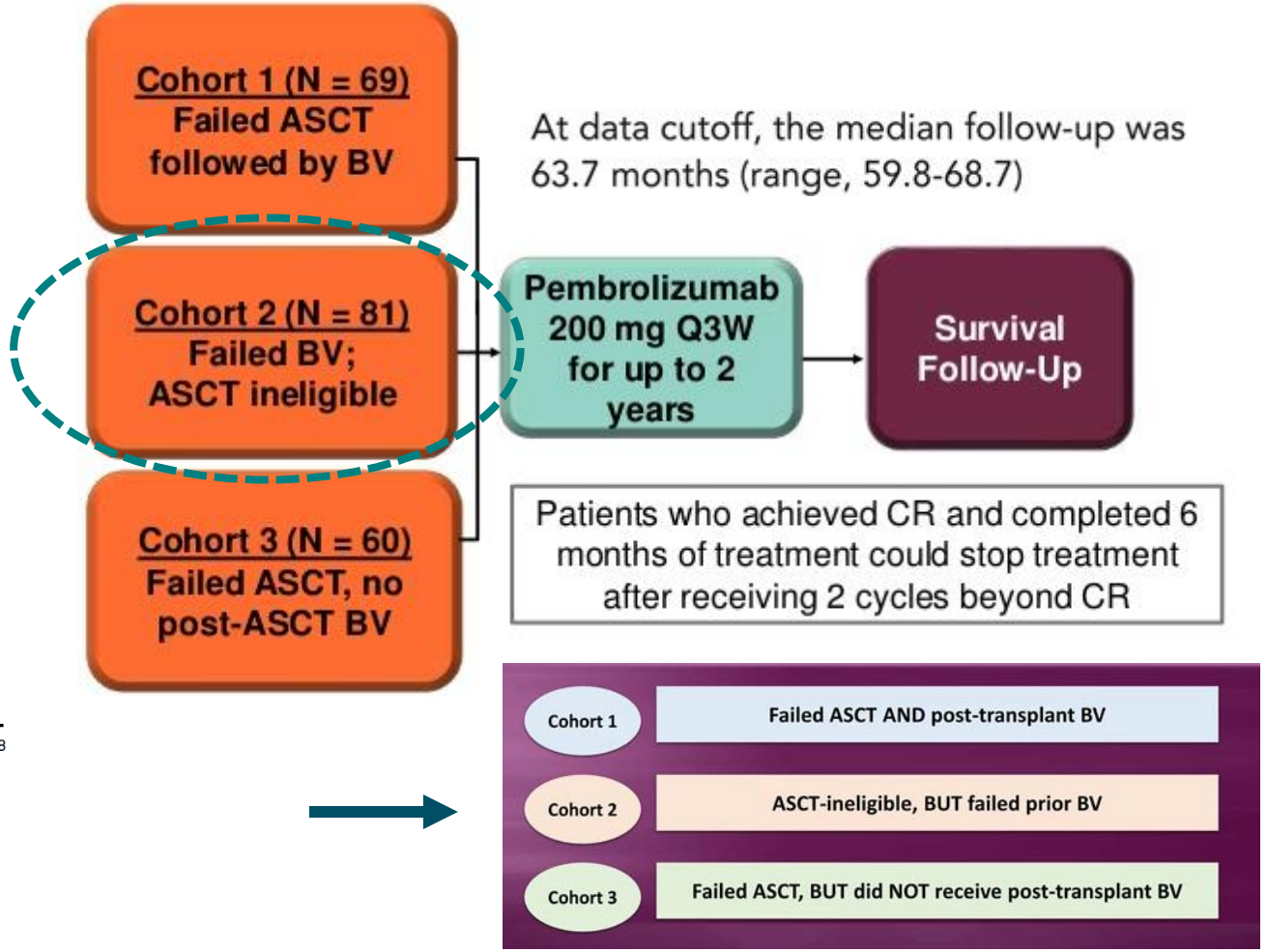
- Nodular sclerosing or mixed cellularity HL
- Relapsed or refractory to brentuximab vedotin
- Failure of ASCT or transplant ineligible



	Total population, N = 31
ORR (CR + PR), % (95% CI)	58.1 (39.1-75.5)
Response, n (%)	
CR	6 (19.4)
PR	12 (38.7)
SD	7 (22.6)
PD	6 (19.4)

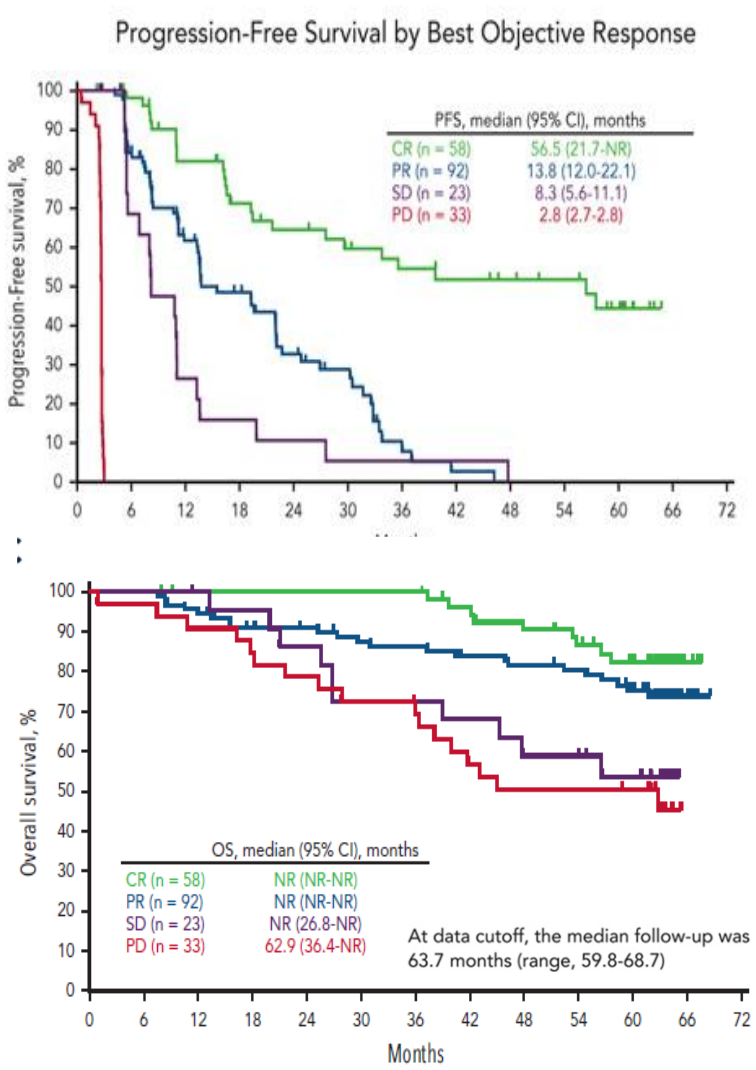


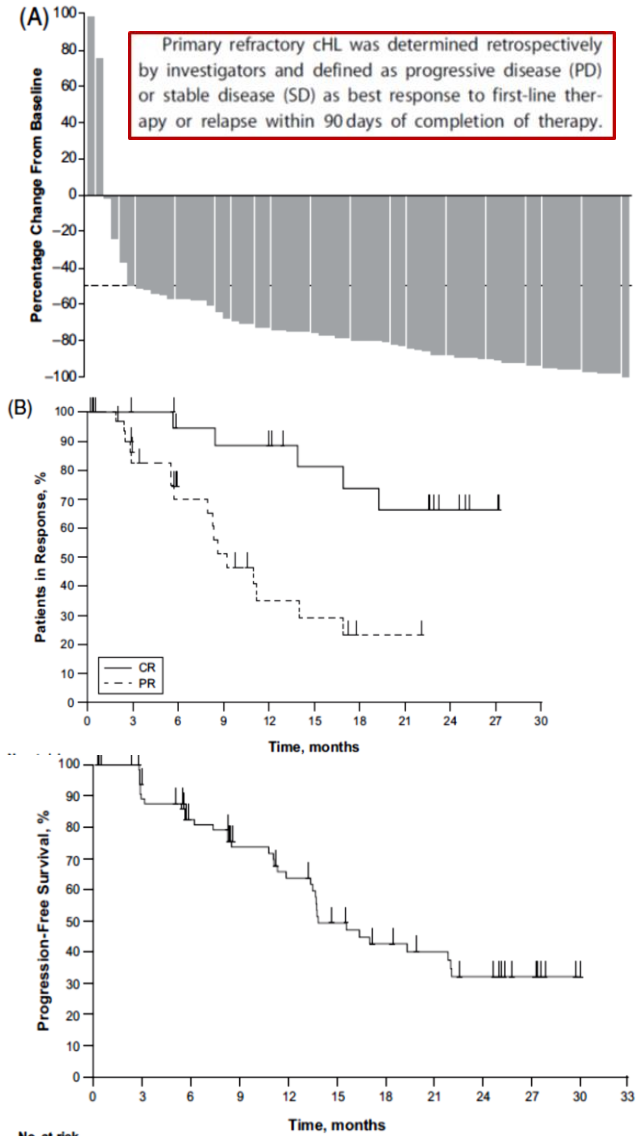
Keynote-087

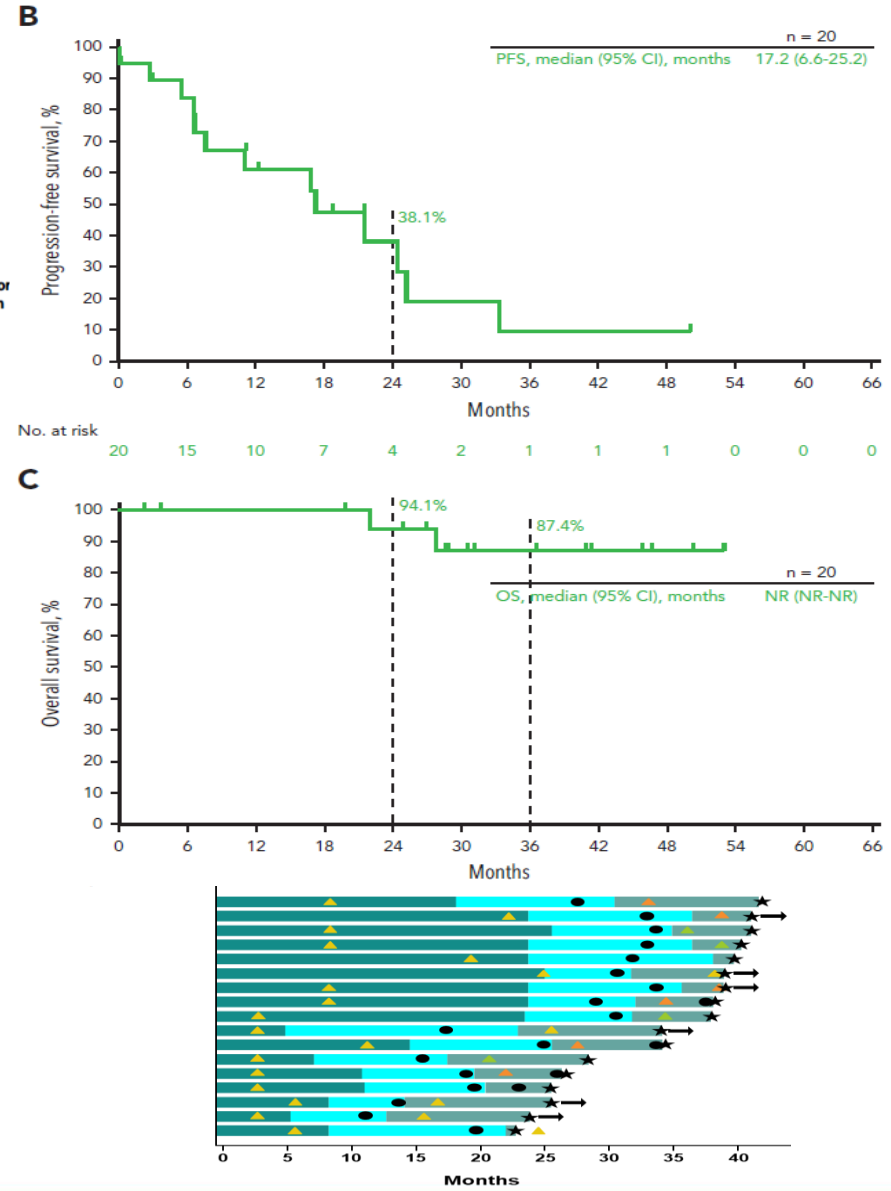


Keynote-087: 3 key findings

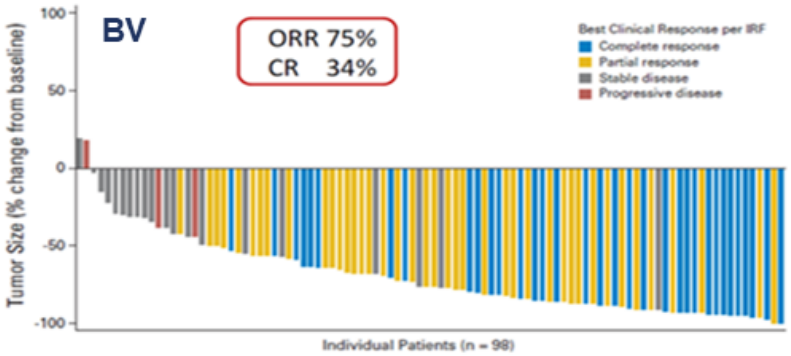
Armand et al. *Blood Adv* (2020) 4: 420
Armand *et al. Blood* (2023) 142: 878
Zinzani PL *et al. Leuk Lymphoma* (2020) 61:950

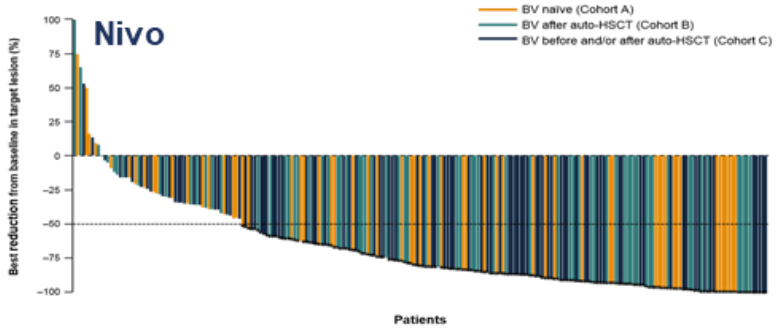


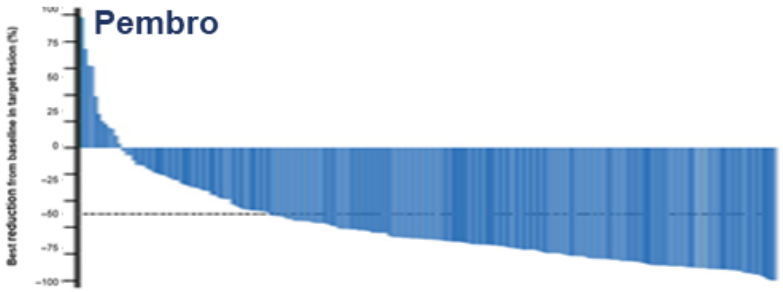




PD1-blockade…after ASCT failure….







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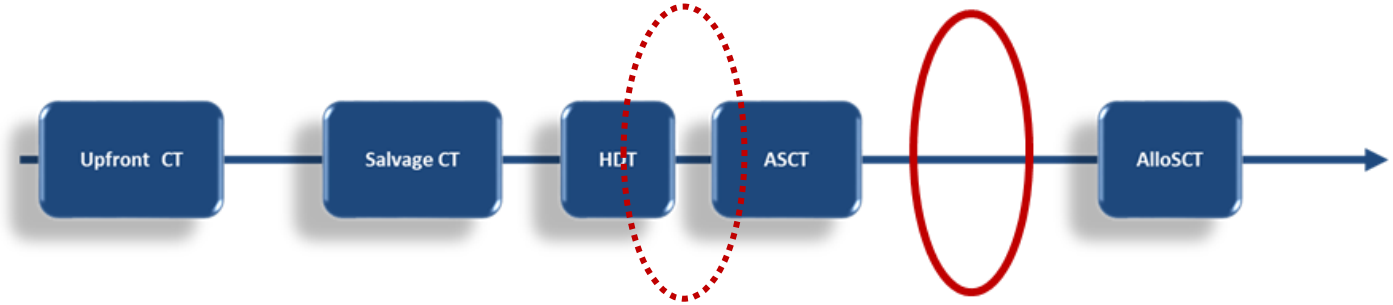


?

Efficacy in relapsed/refractory patients:

Brentuximab vedotin

ORR 76%

CR 36%

Nivolumab

ORR 66% mDOR 18 months

CR 22% mDOR 30 months

Pembrolizumab

ORR 72% mDOR 16.5 months

CR 22% mDOR 30 months

Younes at al. J Clin Oncol 2012
Younes et al., Lancet Oncol 2016
Chen et al. J Clin Oncol 2017

Keynote-204: Study design

Key Eligibility Criteria

- Relapsed or refractory cHL
- Relapse after auto-SCT or ineligible for auto-SCT and failed 1 prior line of therapy
- Measurable disease per IWG 2007 criteria[1]
- ECOG PS 0-1
- BV-naive and BV-exposed patients eligible

R 1:1

- Pembrolizumab 200 mg IV Q3W Up to 35 cycles
- Brentuximab vedotin 1.8 mg/kg IV Q3W Up to 35 cycles

- Response assessed Q12W per IWG 2007 Revised Response Criteria for Malignant Lymphoma[1]
- AEs evaluated Q3W throughout the trial period, and Q12W during follow-up

Stratification Factors

- Prior auto-SCT (yes vs no)
- Status after 1L therapy (primary refractory vs relapsed <12 months vs relapsed ≥12 months after end of 1L therapy)

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 transplantation (allo-SCT); OS

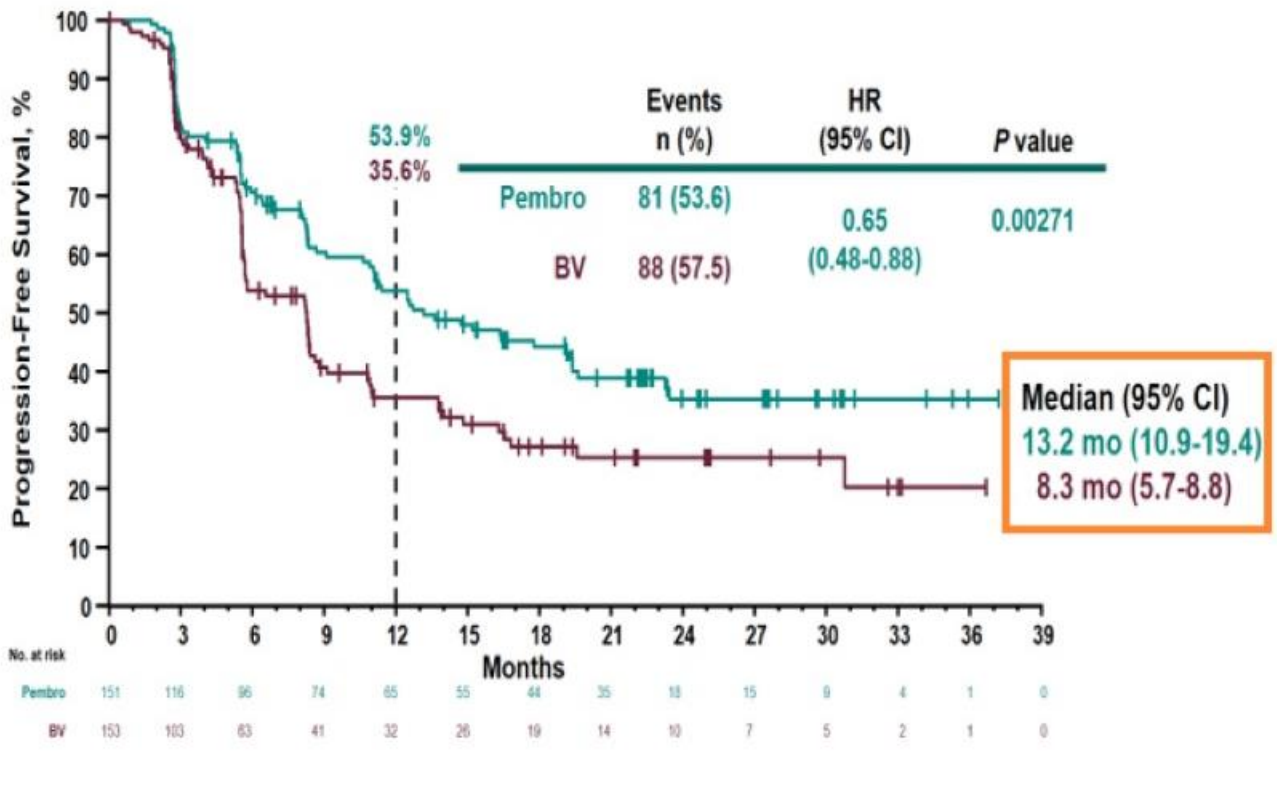
Secondary End Points: PFS per BICR by IWG 2007 criteria excluding clinical and imaging data following auto-SCT or allo-SCT; ORR by BICR per IWG 2007; PFS per investigator review; DOR; safety

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

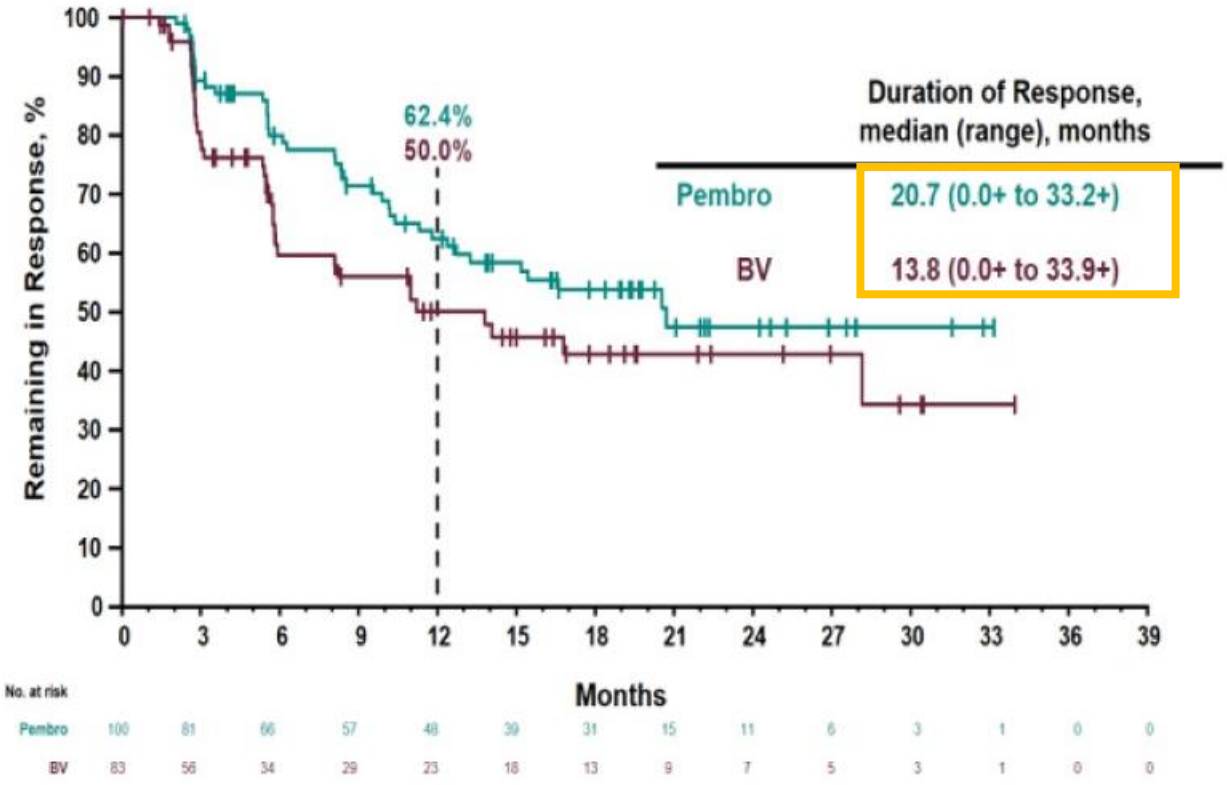
Keynote-204: PFS & DOR

Superior PFS With Pembrolizumab vs Brentuximab Vedotin

Per Blinded Independent Investigator Central Review*



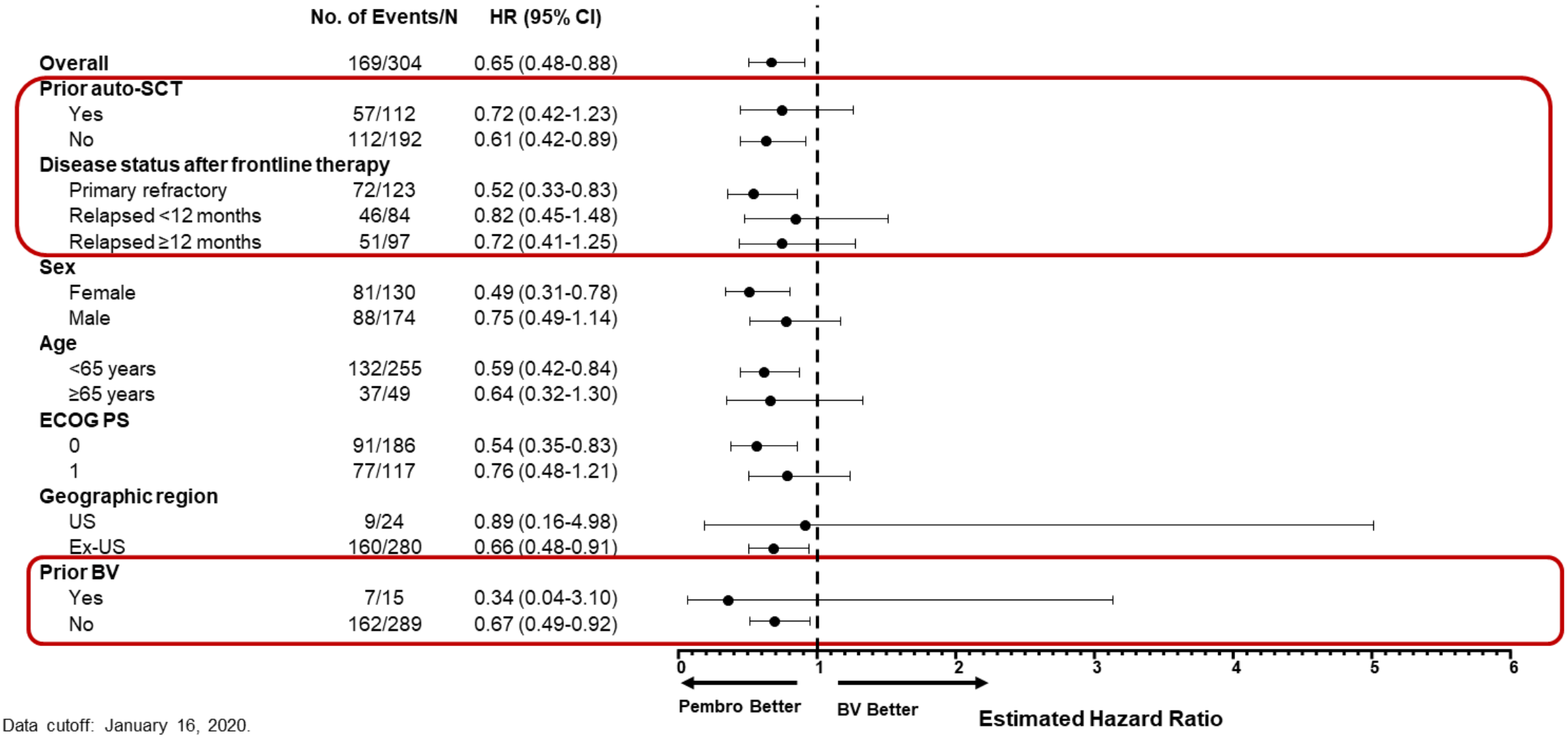
Per Investigator Review



*Including clinical and imaging data following auto-SCT or allo-SCT

Kuruvilla J, et al. J Clin Oncol. 2020;38(suppl); abstract 8005; Kuruvilla J, et al. Lancet Oncol. 2021;22:512-524.

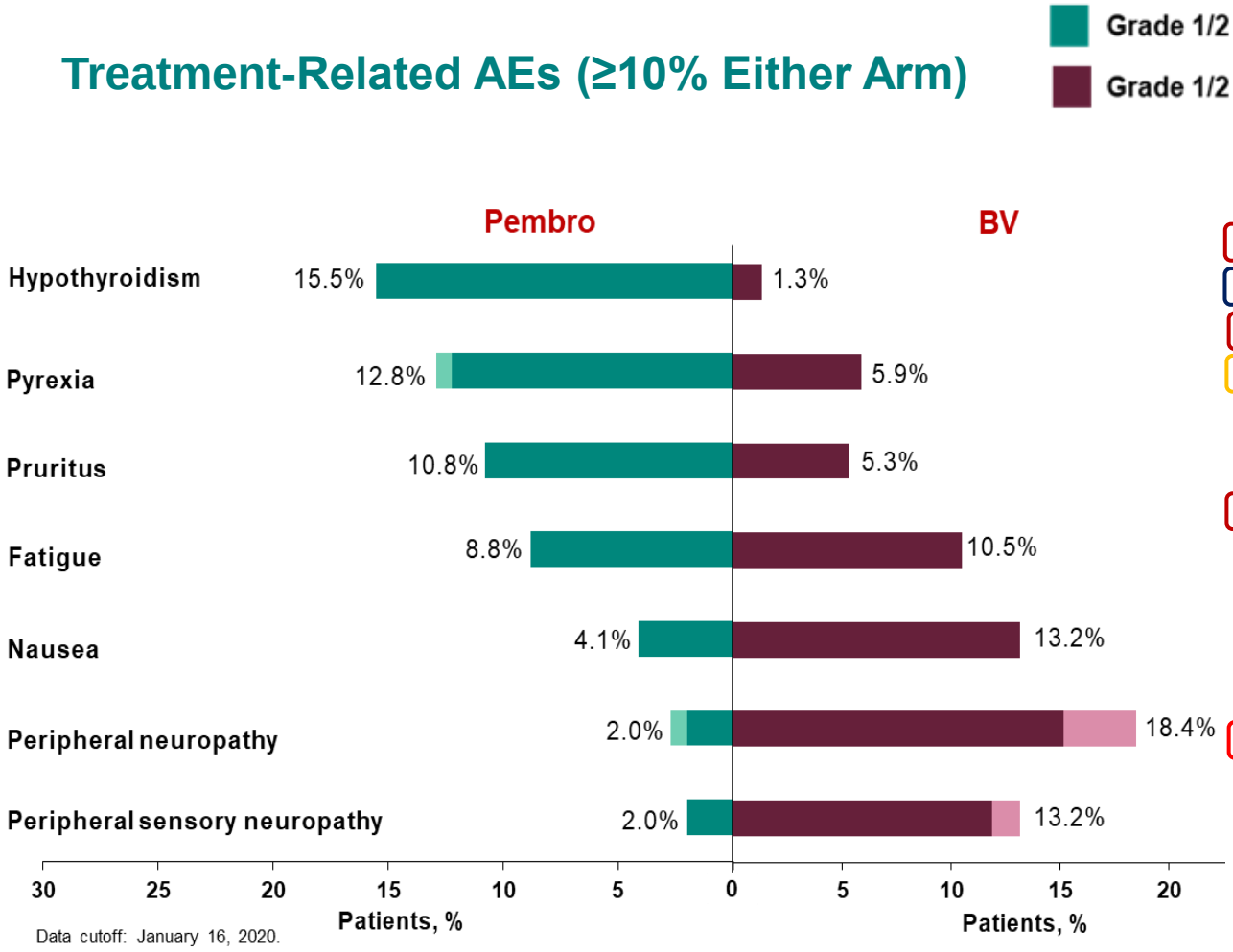
Keynote-204: PFS in Key Subgroups



Data cutoff: January 16, 2020.

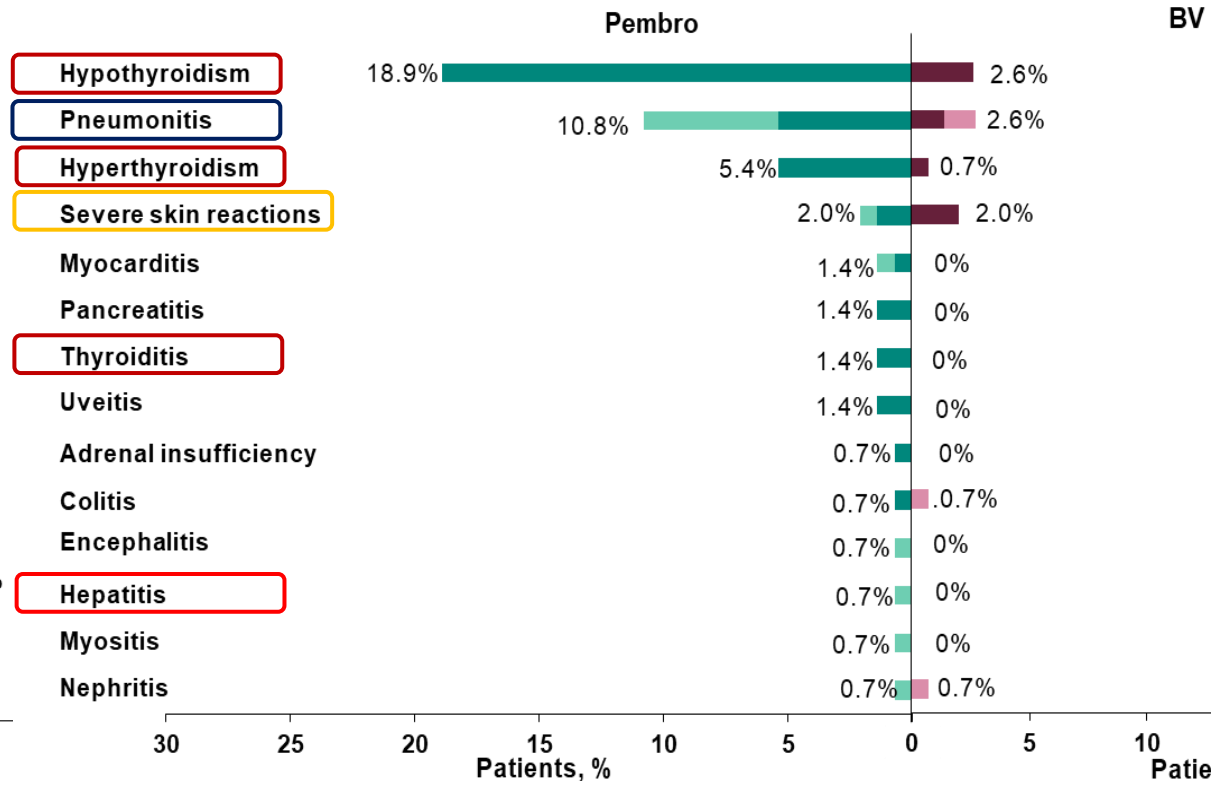
Keynote-204: Safety

Treatment-Related AEs (≥10% Either Arm)

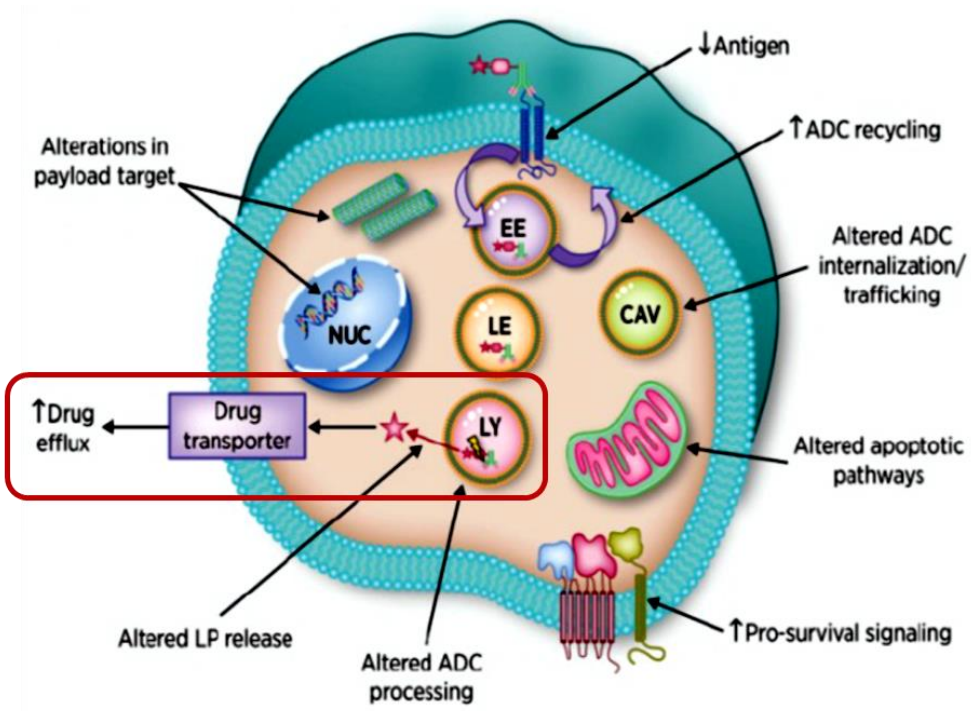


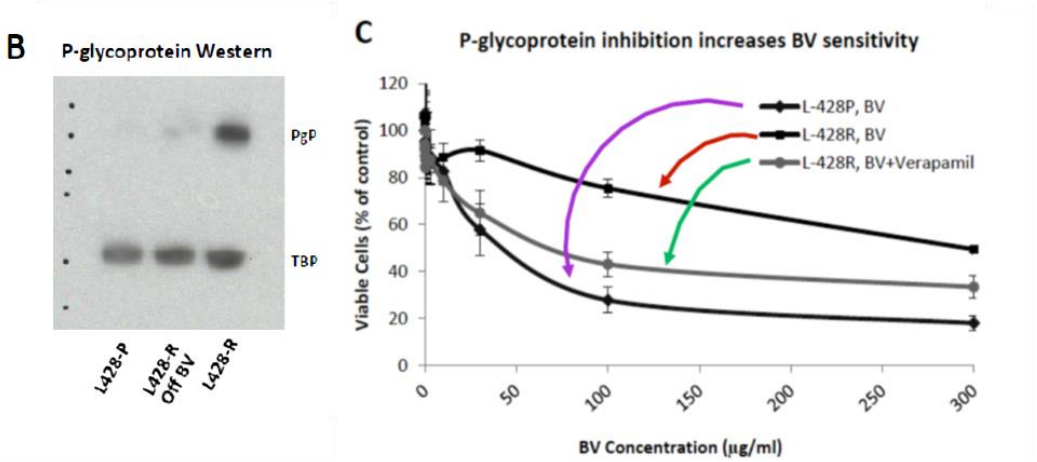
Data cutoff: January 16, 2020.

Immune-Mediated AEs

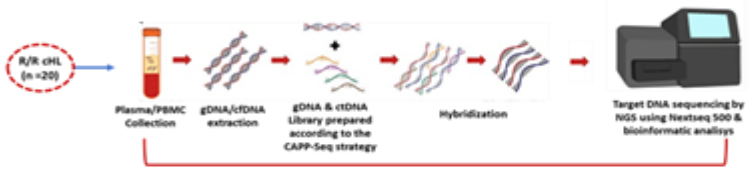


Brentuximab vedotin

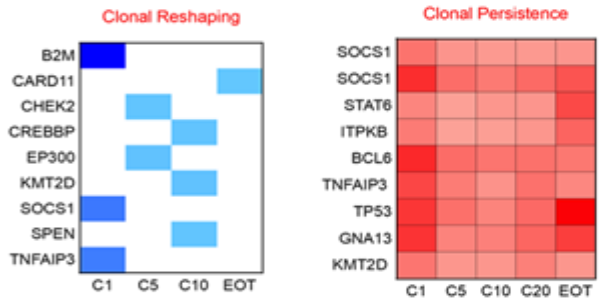




PD1 blockade



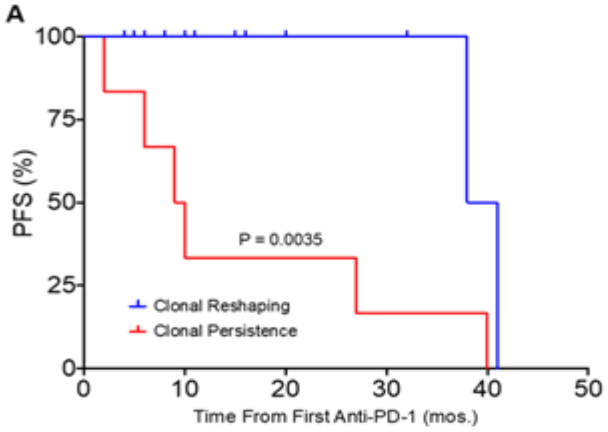
Sequencing was performed to obtain a depth of coverage >2000x in >80% of the target region. Sensitivity of 3x10-3



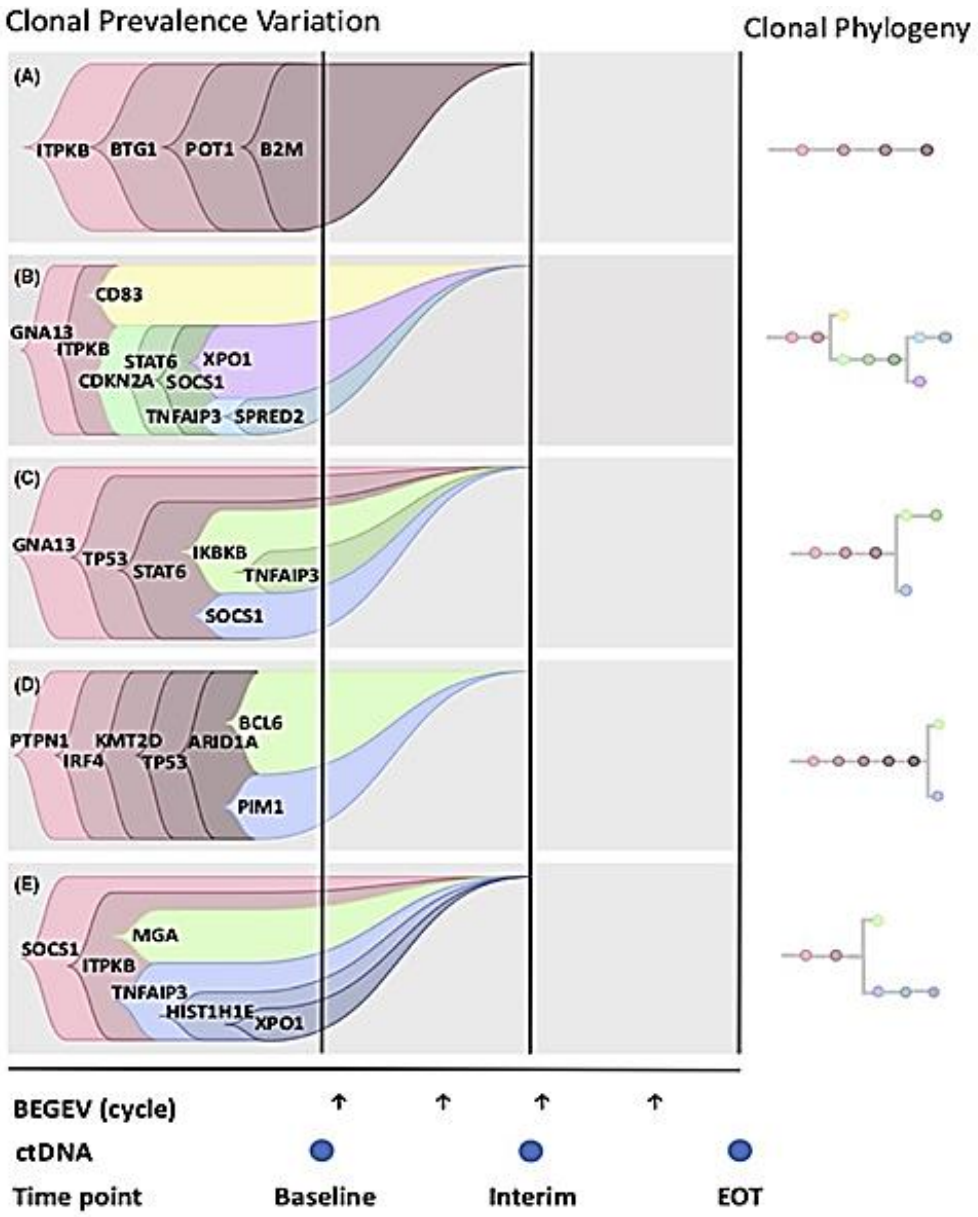
1. Complete change of mutations @ each therapy cycle Clonal Reshaping modality

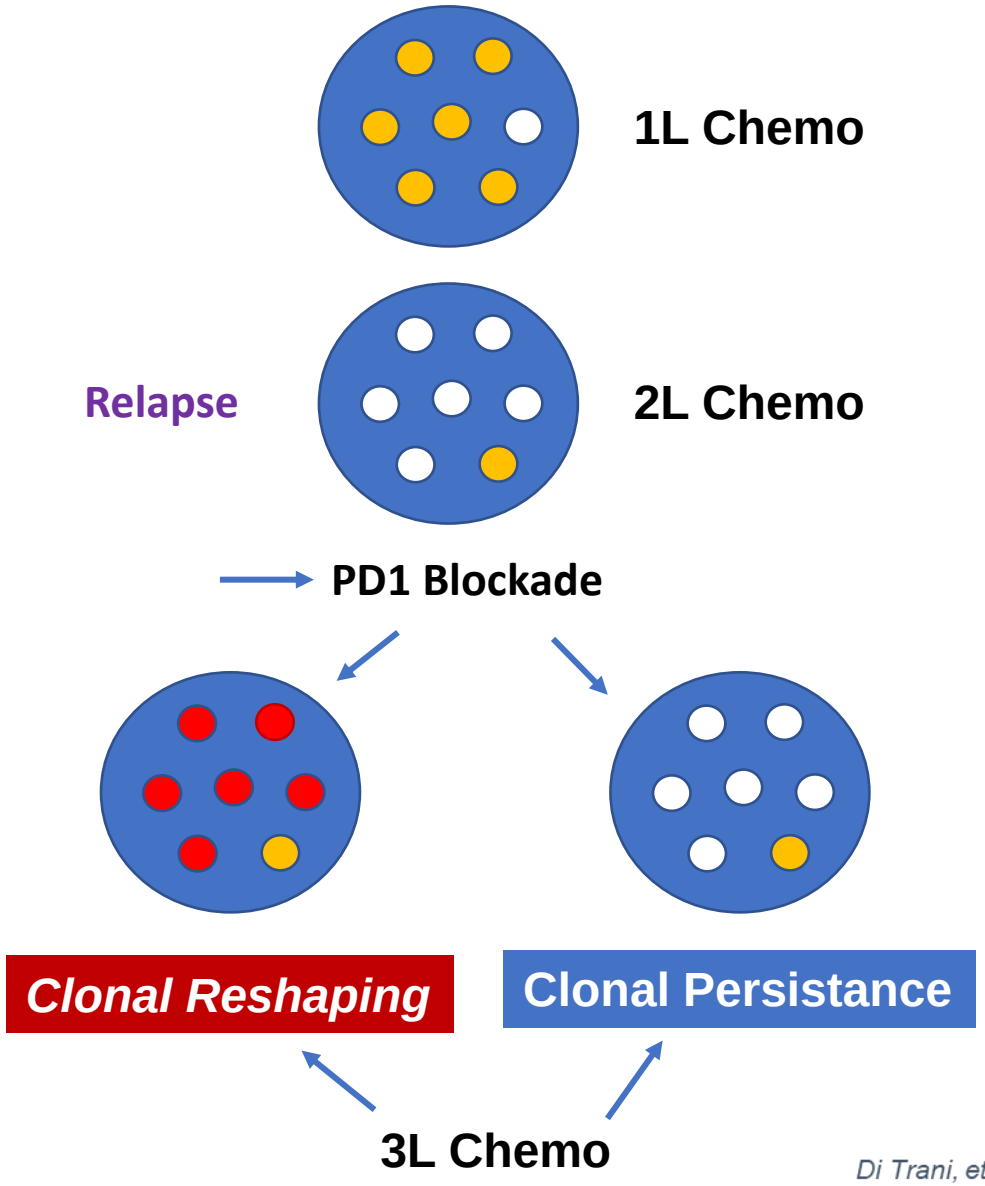
2. Persistence of mutations overtime. Clonal Persistence modality

Longitudinal Analysis of ctDNA
PFS by Patterns of Mutations (*Reshaping vs Persistance*)



Br J Haematol. 2022;198:82–92.

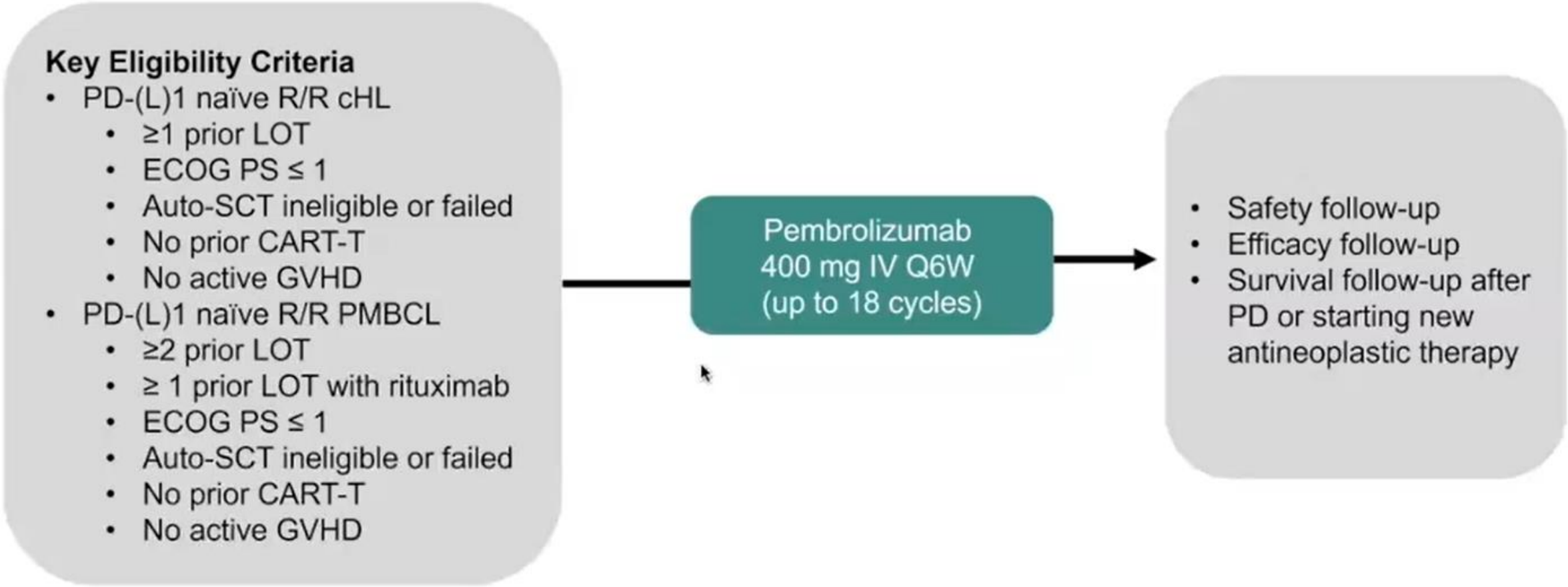




Di Trani, et al. ASH 2019
Calabretta, et. al. BJH 2022

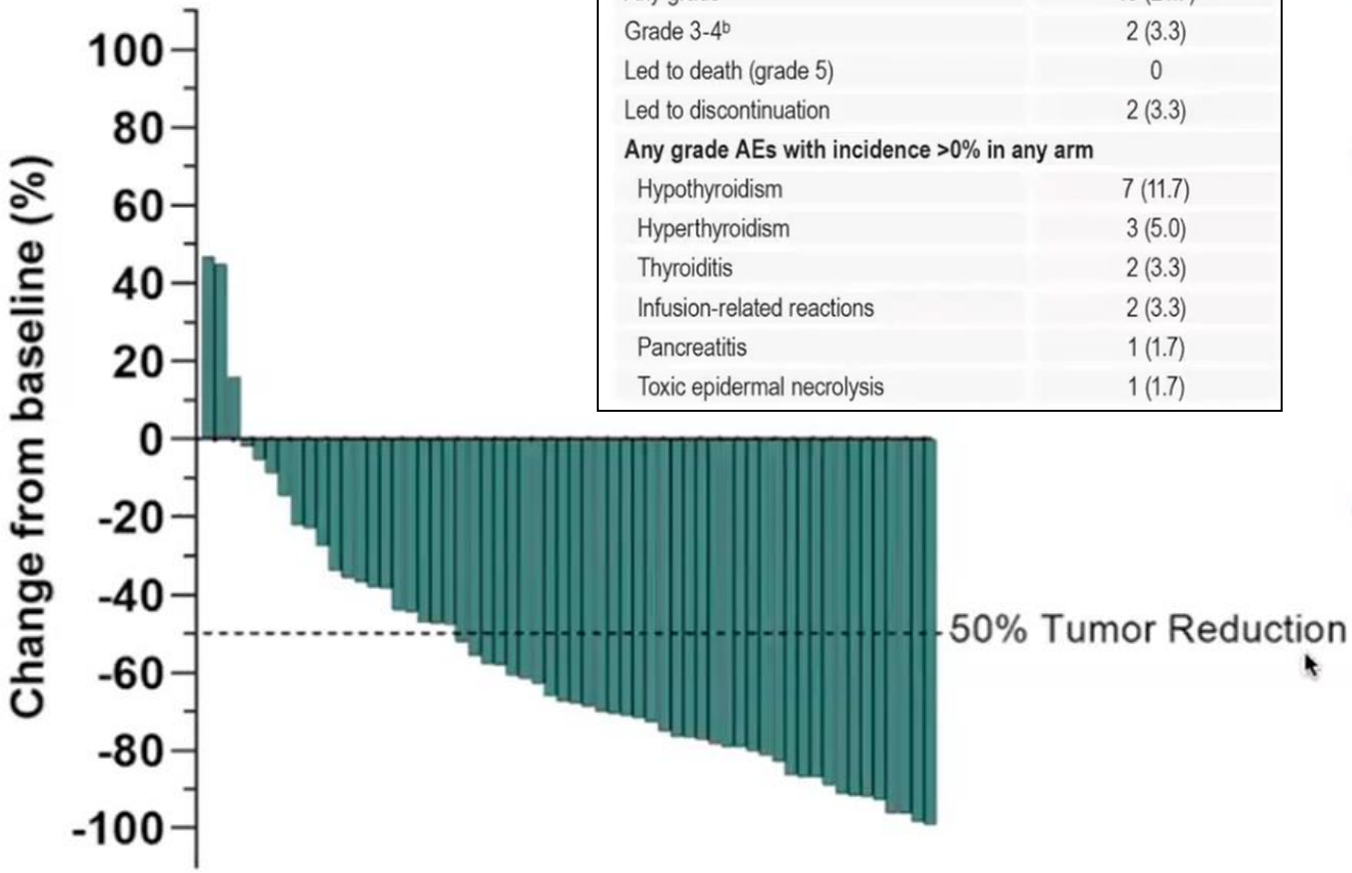
Phase 2 KEYNOTE-B68 trial

Study Design



Best Percentage Change From Baseline (Lugano) for Target Lesions in Patients with R/R cHL

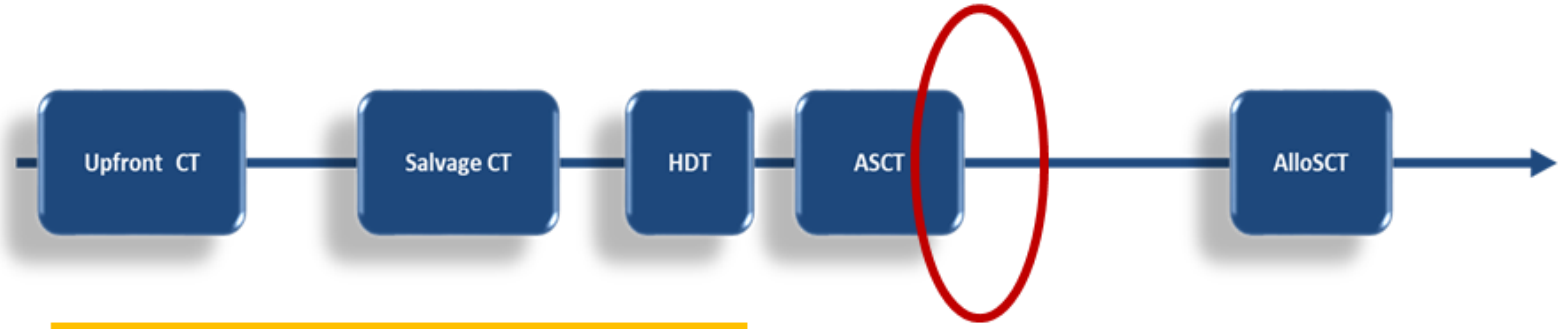
Events, n (%)	R/R cHL N = 60
Any grade	13 (21.7)
Grade 3-4[b]	2 (3.3)
Led to death (grade 5)	0
Led to discontinuation	2 (3.3)
Any grade AEs with incidence >0% in any arm	
Hypothyroidism	7 (11.7)
Hyperthyroidism	3 (5.0)
Thyroiditis	2 (3.3)
Infusion-related reactions	2 (3.3)
Pancreatitis	1 (1.7)
Toxic epidermal necrolysis	1 (1.7)



- Median duration of follow-up: 8.9 months (range, 1.0-15.9)
- **ORR for R/R cHL: 65% (95% CI, 52%-77%)**
  - **20 complete responses, 19 partial responses**
- Median duration of response[a]: not reached (0+ to 8.6+ months)
  - 7 patients had duration of response ≥6 months[a]

Pembrolizumab 400 mg Q6W had no new safety concerns, confirming Q6W dosing in hematologic indications

Pembrolizumab to prevent ASCT failure: post-ASCT consolidation



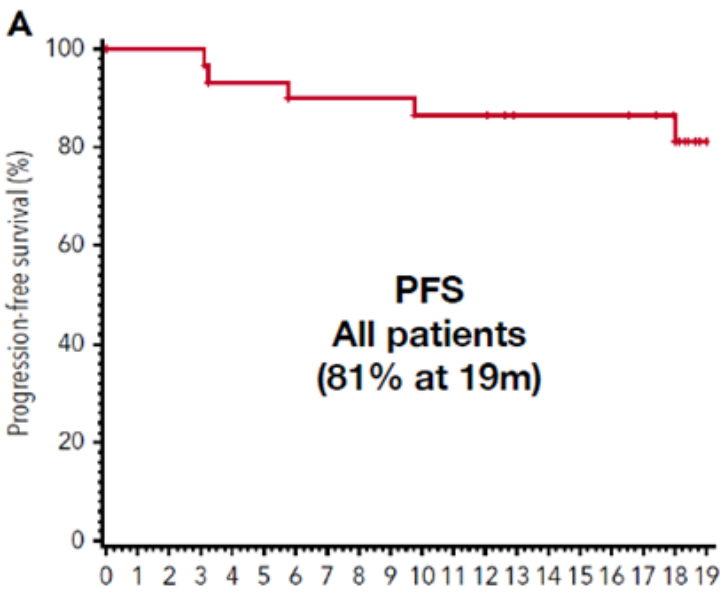
PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation

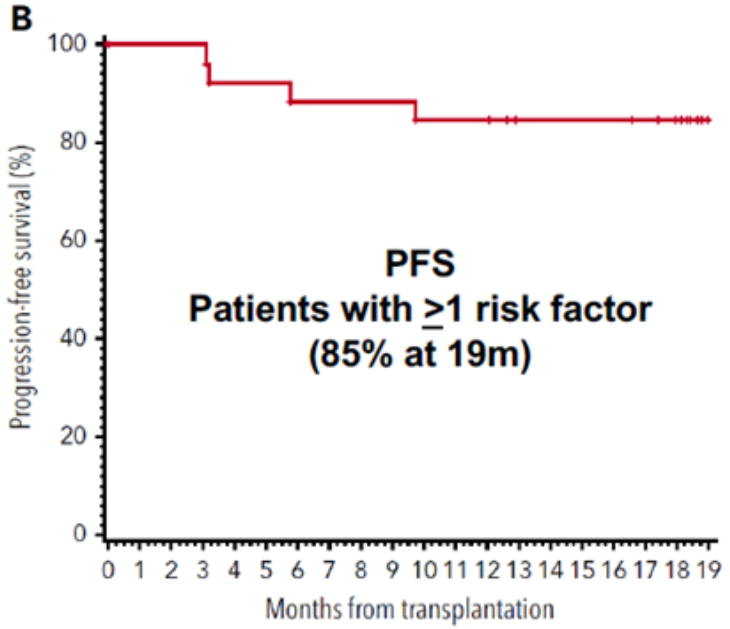
Risk factors	
Primary refractory disease	17 (57)
Relapse within 12 mo	5 (17)
Extranodal disease at relapse	8 (27)
At least 1 of above 3 factors	26 (87)
Residual disease after salvage	3 (10)
B symptoms at relapse	2 (7)
>1 salvage therapy	5 (17)
At least 1 of above 6 factors	27 (90)
At least 2 of above 6 factors	12 (40)

Multicohort phase 2 study

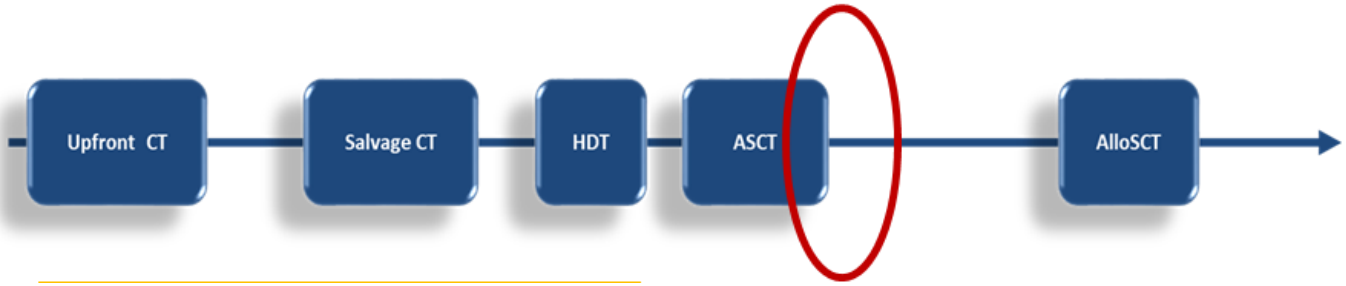
Inclusion criteria:

- **Previous ASCT and chemosensitive disease (metabolic PR or CR)**
- **No more than 3 previous line of therapy**
- **Allow prior PD-1 blockade**



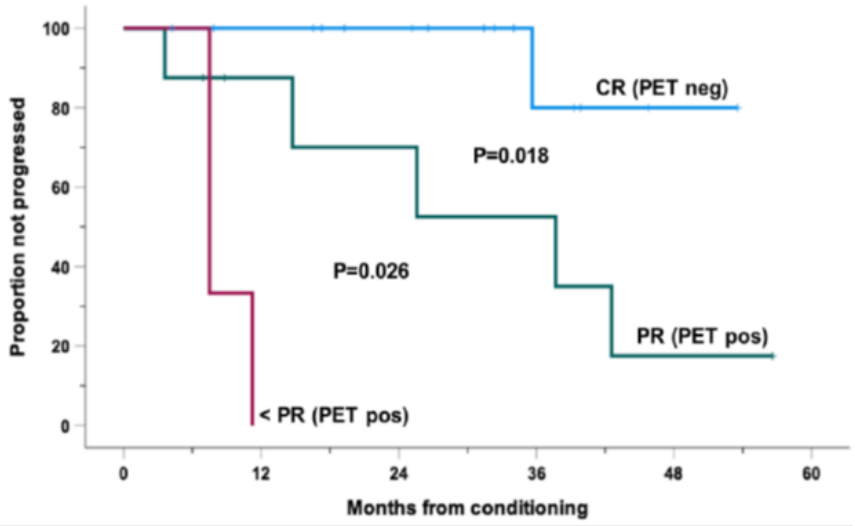


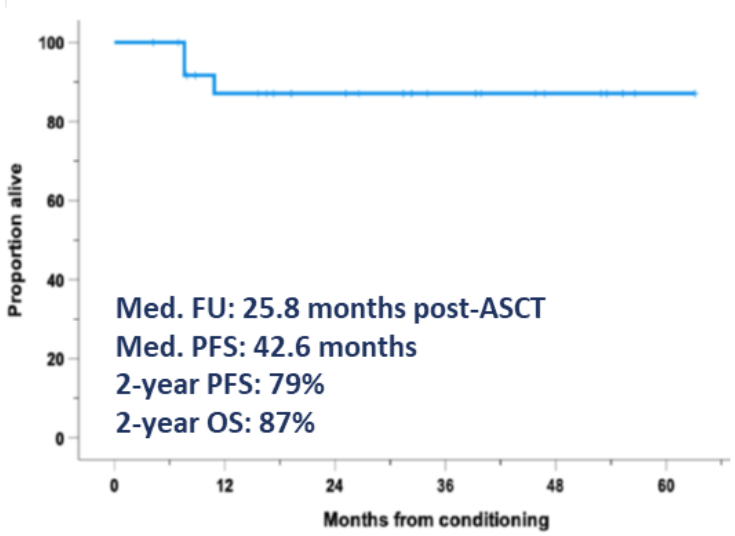
Pembrolizumab to prevent ASCT failure: post-ASCT consolidation

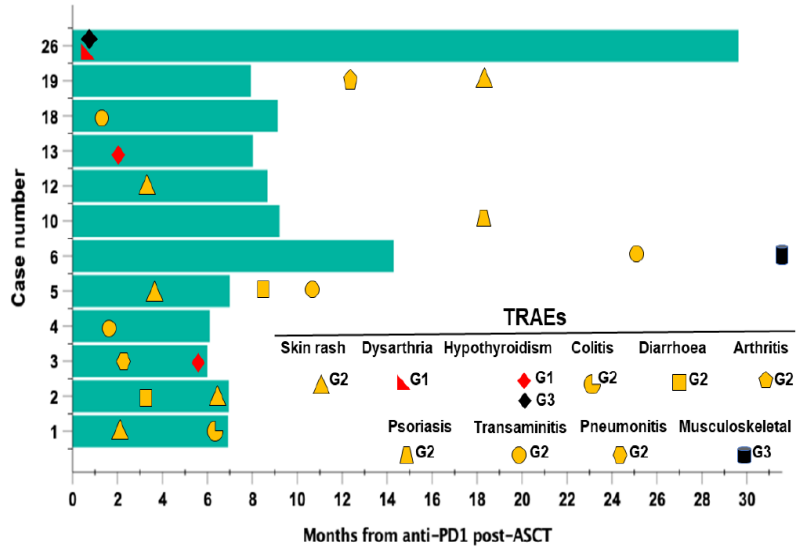


Anti-PD1 Consolidation in Patients with Hodgkin Lymphoma at High Risk of Relapse after Autologous Stem Cell Transplantation: A Multicenter Real-Life Study

Disease status after frontline therapy	
Primary refractory	18 (69)
Relapse <12 months	4 (15)
Failure after interim PET-driven escalation (BEACOPP esc)	5 (19)



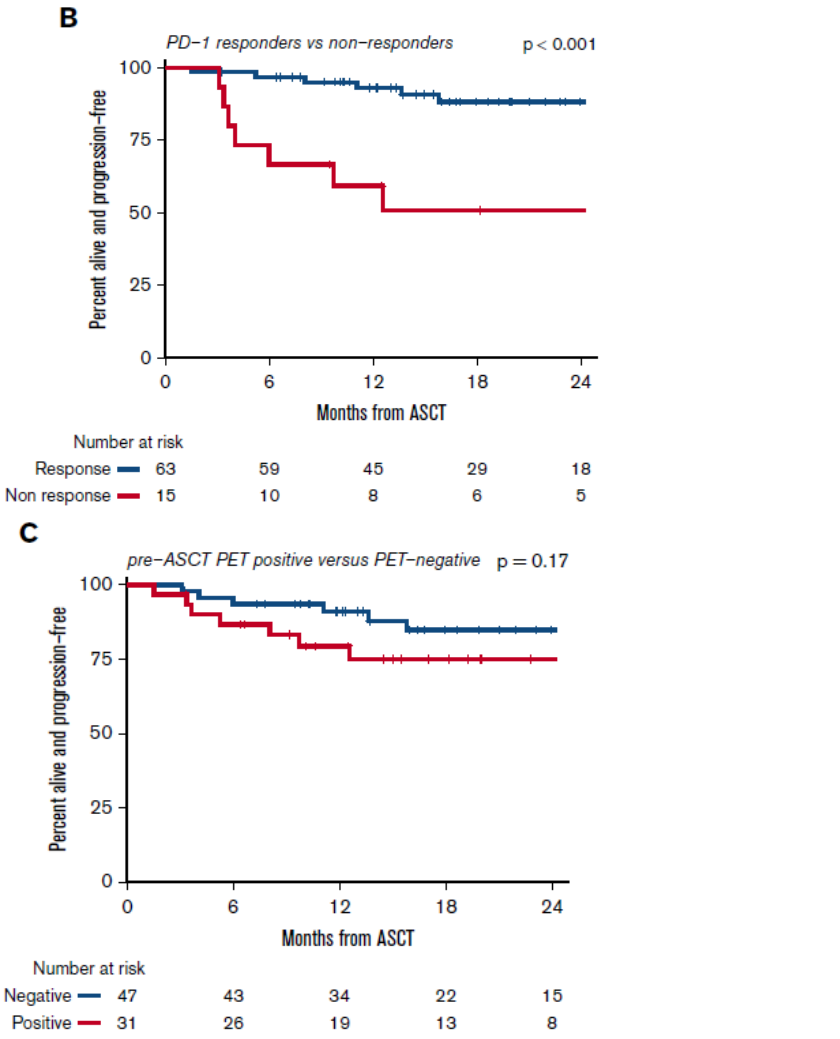




Rosaria De Filippi *Cancers* **2022**, *14*, 5846

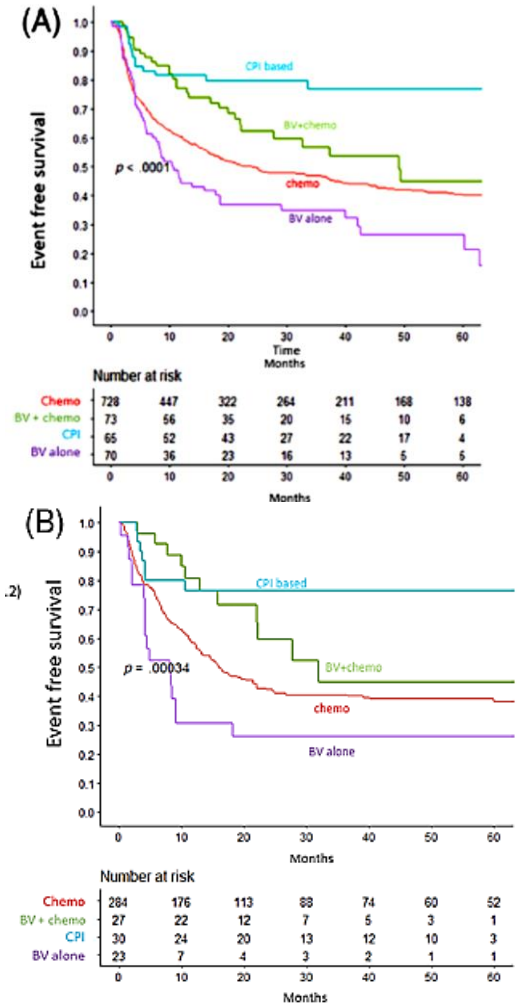
PD1-blockade as last treatment line before ASCT (single agent or combined)

Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma



blood advances 23 MARCH 2021 • VOLUME 5, NUMBER 6

Checkpoint inhibitor-based salvage regimens prior to autologous stem cell transplant improve event-free survival in relapsed/refractory classic Hodgkin lymphoma



Am J Hematol. 2023;98:464-471.

Improved outcomes for relapsed/refractory Hodgkin lymphoma after autologous transplantation in the era of novel agents

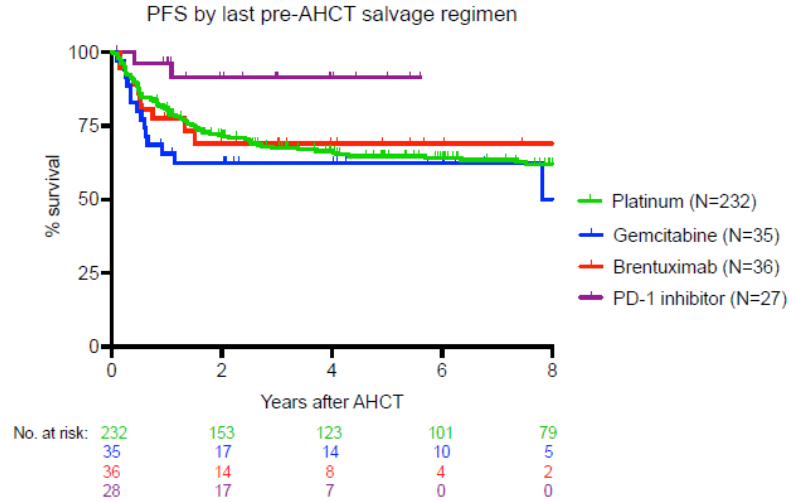
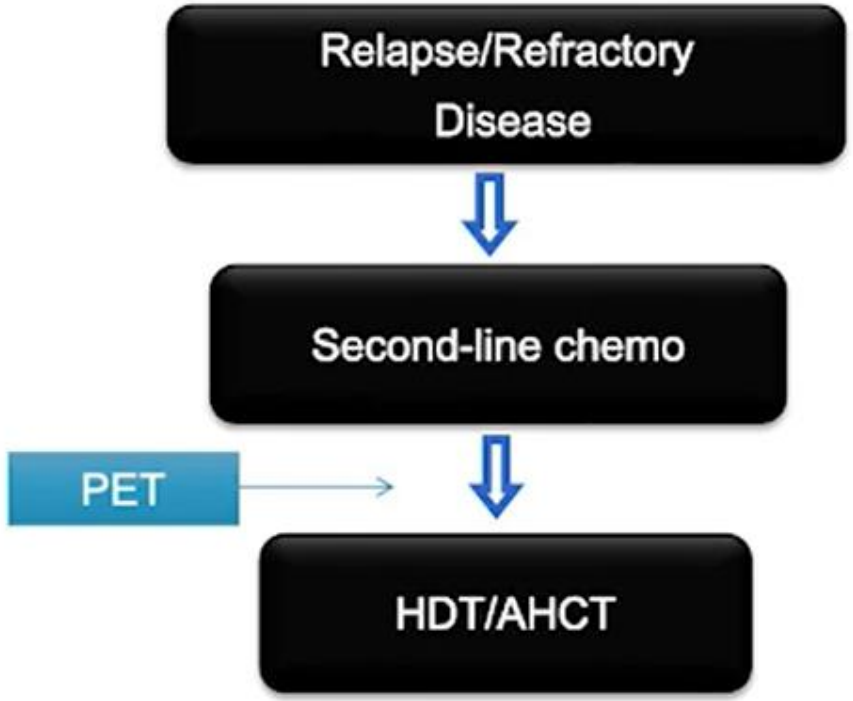


Table 4. Multivariable analysis for progression-free survival in the modern era

Variable	N (%)	Hazard ratio (95% CI)	P value
Age <45	146 (80%)	Reference	--
Age ≥45	37 (20%)	**1.96 (1.01-3.84)**	**0.049**
Relapsed	133 (73%)	Reference	--
Refractory	50 (27%)	**2.58 (1.44-4.63)**	**0.0014**
Metabolic CR	111 (61%)	Reference	--
Not in CR	72 (39%)	**1.93 (1.06-3.50)**	**0.031**
Chemotherapy pre-AHCT[1]	156 (85%)	Reference	--
PD-1 inhibitor pre-AHCT[2]	27 (15%)	**0.21 (0.05-0.86)**	**0.030**

Spinner et al. Blood. 2023 Mar 1:blood.2022018827.
doi: 10.1182/blood.2022018827.

Second-Line Therapy and Autologous Transplant



Newer Second-Line Therapies

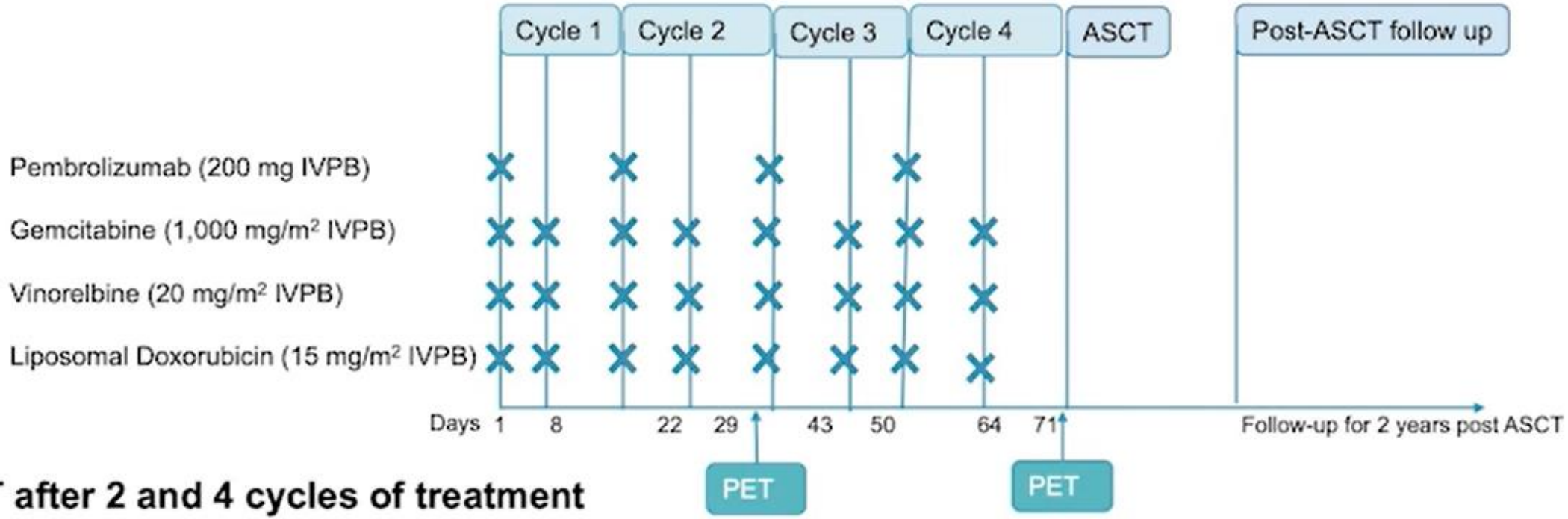
Regimen	n	% PET-neg
BV->augICE[2]	65	83%
BV->ICE[3]	56	66%
BV-benda[4]	55	74%
BV plus:		
ICE[5]	39	69%
DHAP[6]	61	81%
ESHAP[7]	66	70%
Gem[8]	42	67%
BV-nivolumab[9]	91	67%
BEGEV[10]	59	75%
Pembro-GVD[11]	38	95%

[1]Moskowitz AJ et al: Blood 116:4934-7, 2010; [2]Moskowitz AJ, et al: ASH 2019; [3]Herrera et al: Ann Oncol 2018; [4]LaCasce et al: Blood 2018; [5]Stamatoullas et al: ASH 2019; [6]Kersten et al: Haematologica 2020; [7]Garcia-Sanz, et al: Ann Oncol 2019; [8]Cole, et al: Lancet Oncol 2018; [9]Advani, et al: Blood 2021; [10]Santoro, et al: Blood Advances 2020; [11]Moskowitz AJ, et al: J Clin Oncol 2021

Phase II Study of Pembro-GVD as Second-Line Therapy for Classical Hodgkin Lymphoma

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

CR After 2 cycles Eligible for ASCT



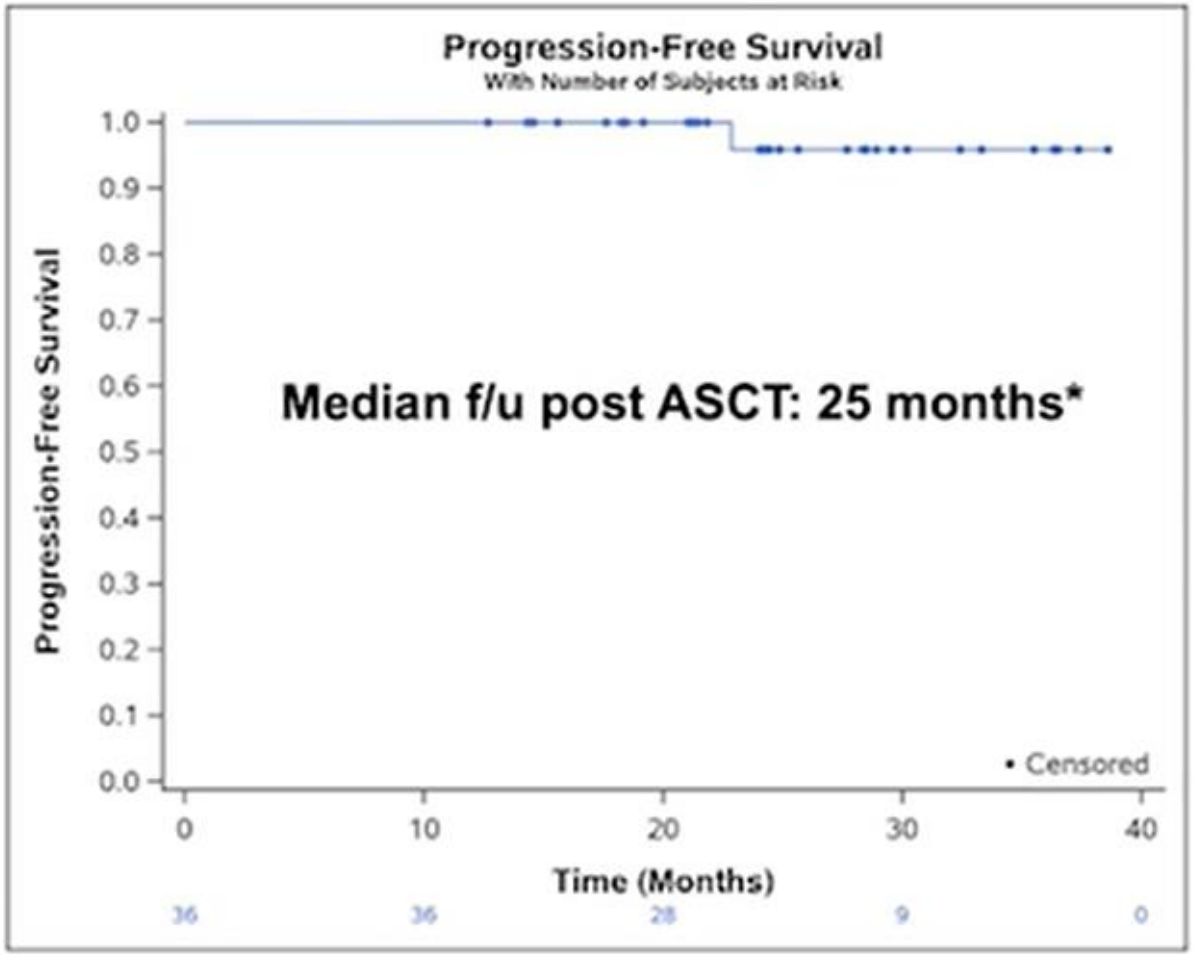
PET after 2 and 4 cycles of treatment

ASCT = autologous stem cell transplant; IVPB = intravenous piggyback; Pembro-GVD = pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin

Moskowitz AJ, et al: J Clin Oncol 39:3109-3117, 2021

Phase II Study of Pembro-GVD as Second-Line Therapy for Classical Hodgkin Lymphoma

- n = 38 evaluable patients
- ORR: 100%
- CR: 95% (92% after 2 cycles)
- 36 pts proceeded to ASCT
- 1 relapse



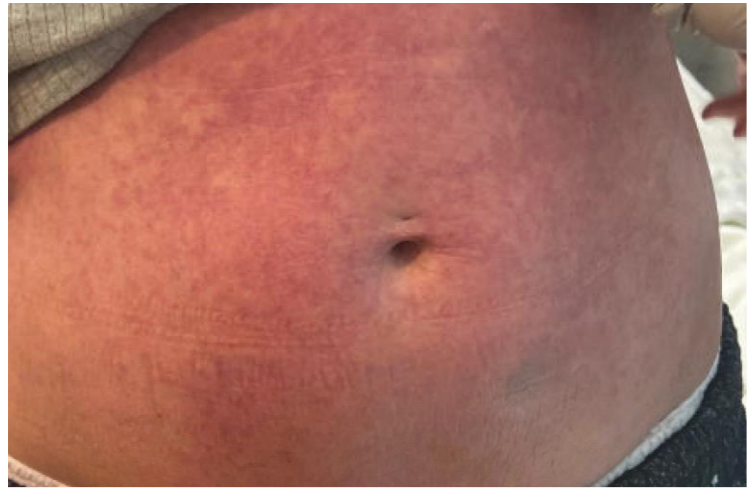
f/u = follow-up; ORR = objective response rate

Updated from Moskowitz AJ, et al: J Clin Oncol 39:3109-3117, 2021

Caution: Engraftment syndrome with PD-1 blockade -> HDT/AHCT

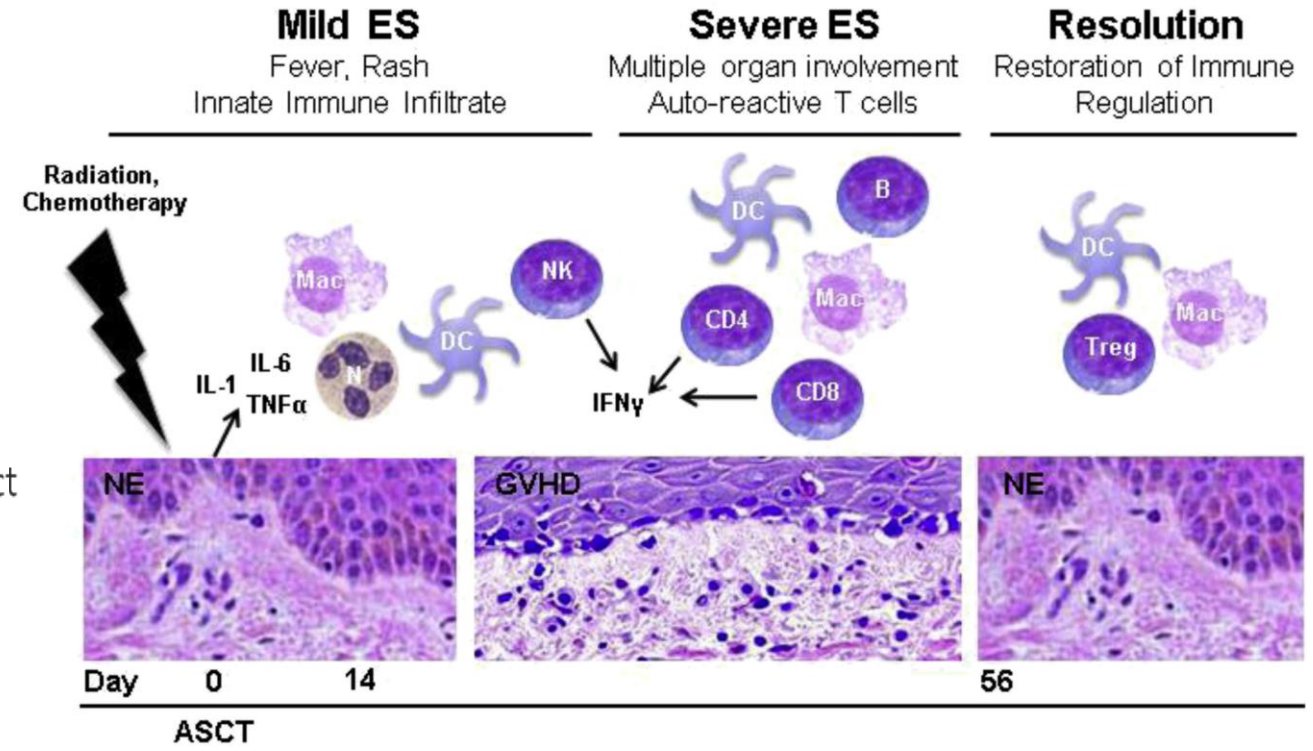
Experience from pembro-GVD study

- **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 dysfunct



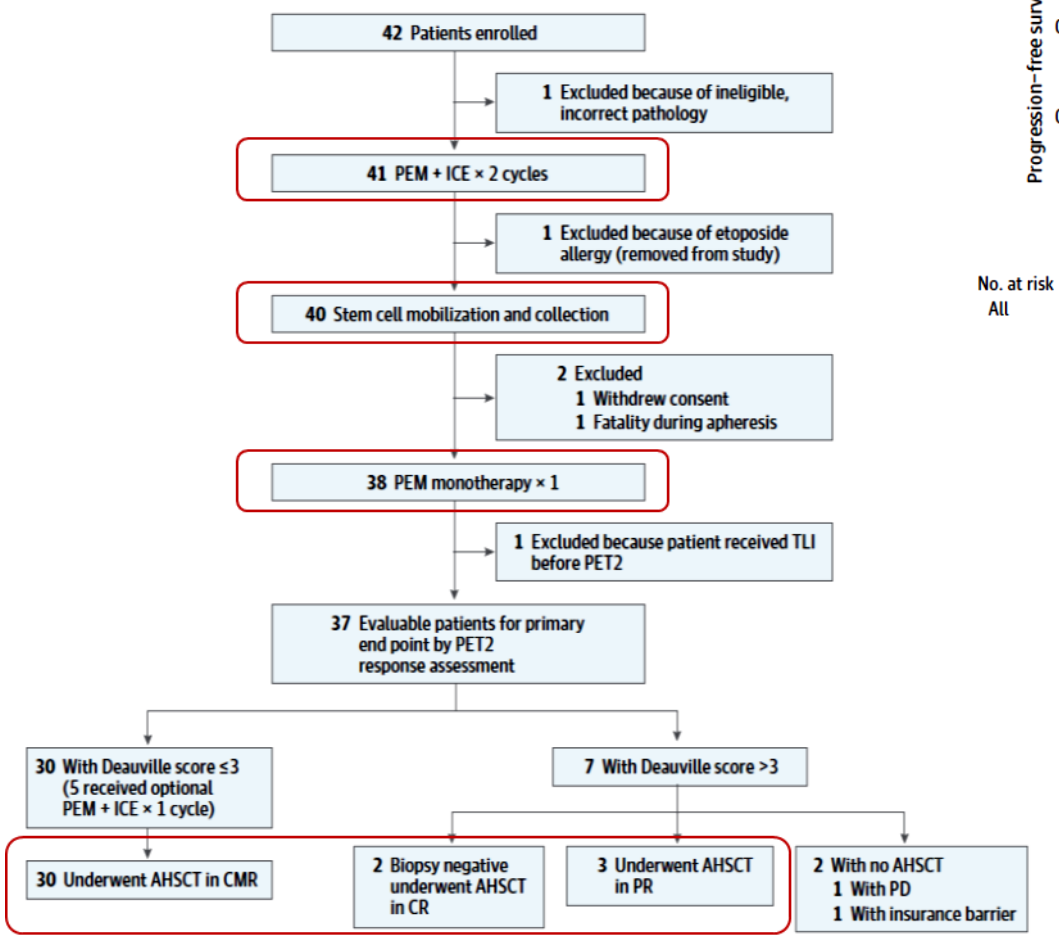
- Management:
  - **Any new onset fever, rash, and/or diarrhea occurring days 8-11 days post ASCT:**
    - **Obtain cultures, initiate broad spectrum antibiotics AND corticosteroids**
    - Dexamethasone 0.2mg/kg IV daily x 3 days (or symptom resolution) followed by 20-30% oral taper every 3 days over 14 days

JAMA Oncology | Original Investigation

Pembrolizumab Added to Ifosfamide, Carboplatin, and Etoposide Chemotherapy for Relapsed or Refractory Classic Hodgkin Lymphoma

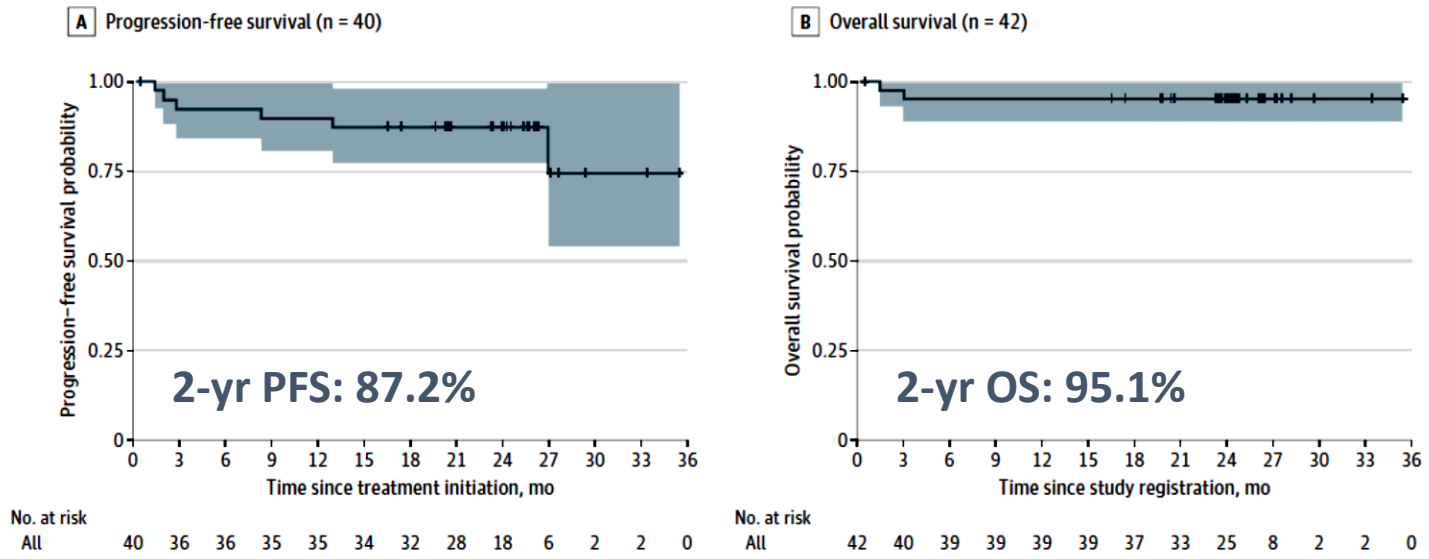
A Multi-institutional Phase 2 Investigator-Initiated Nonrandomized Clinical Trial

Locke J. Bryan, MD; Carla Casulo, MD; Pamela B. Allen, MD; Scott E. Smith, MD; Hatice Savas, MD; Gary L. Dillehay, MD; Reem Karmali, MD; Barbara Pro, MD; Kaitlyn L. Kane, MS; Latifa A. Bazzi, MPH; Joan S. Chmiel, PhD; Brett A. Palmer, MS; Jayesh Mehta, MD; Leo I. Gordon, MD; Jane N. Winter, MD



JAMA Oncol. 2023;9(5):683-691. doi:10.1001/jamaoncol.2022.7975
Published online March 16, 2023.

Figure 2. Outcomes Data With Median Follow-up of 24 Months (Range, 0.5-35.4 Months)

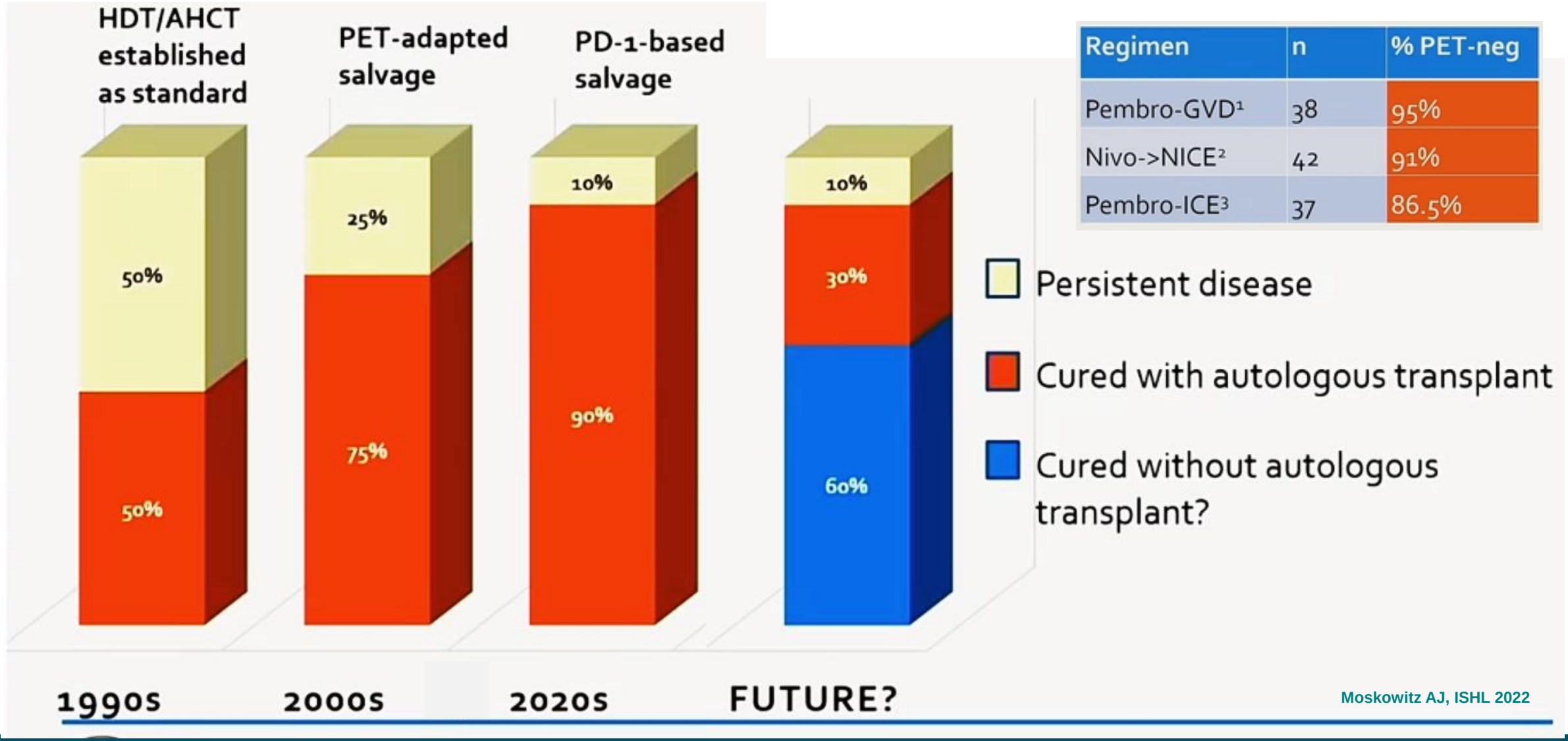


22 patients (52.4%) G3/G4 AEs:

Thrombocytopenia, n = 15;
Anemia, n = 11;
Neutropenia, n = 9;
Lymphopenia, n = 10;
Transaminitis, n = 2

Acute respiratory failure during white blood cell count recovery after AHSCT, possibly associated with Engraftment Syndrome (n = 1)

Are we about to abandon transplant in Hodgkin lymphoma?

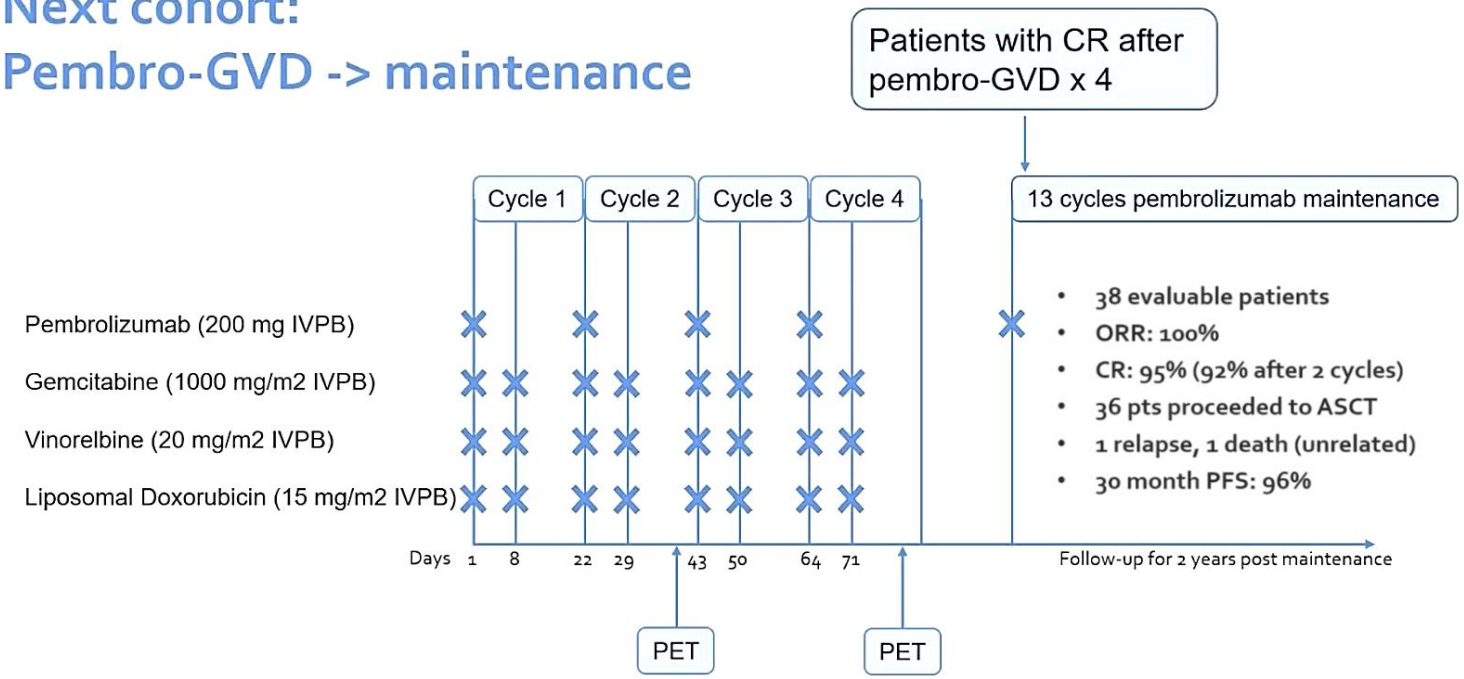


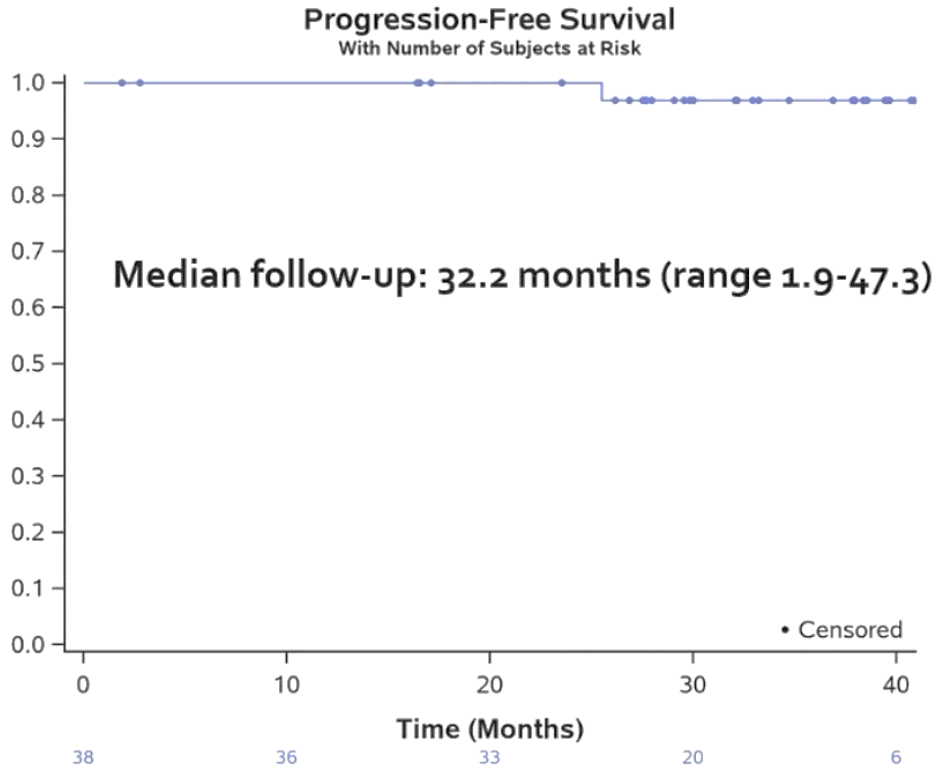
Regimen	n	% PET-neg
Pembro-GVD[1]	38	95%
Nivo->NICE[2]	42	91%
Pembro-ICE[3]	37	86.5%

Moskowitz AJ, ISHL 2022

NCT03618550 - Phase II Study of Second- Line Pembrolizumab Plus GVD for Relapsed or Refractory Hodgkin Lymphoma

Next cohort: Pembro-GVD -> maintenance

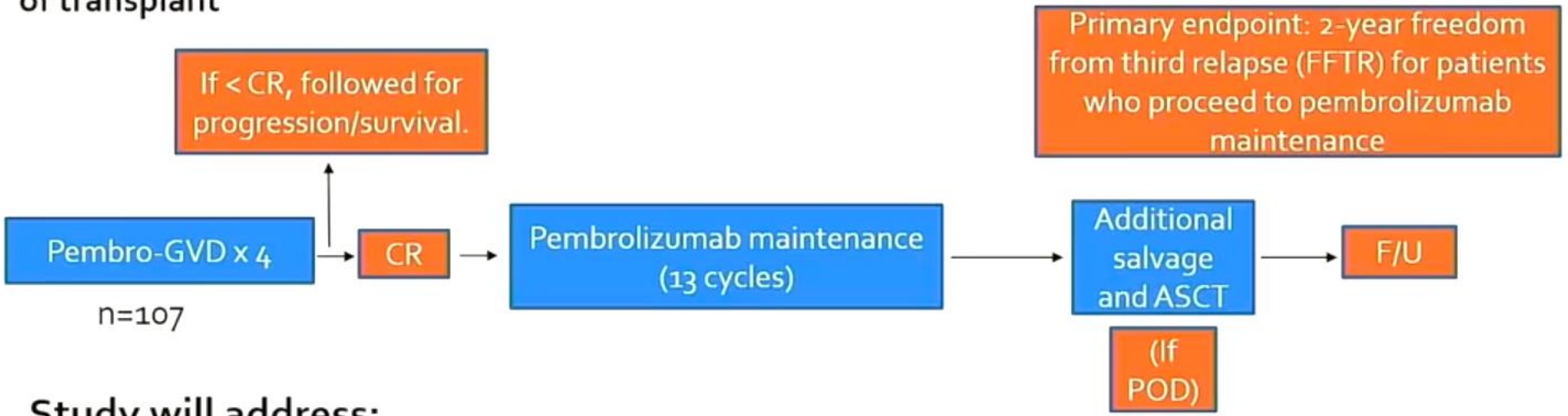




Moskowitz AJ, ISHL 2022

Is transplant needed for everyone in second-line setting?

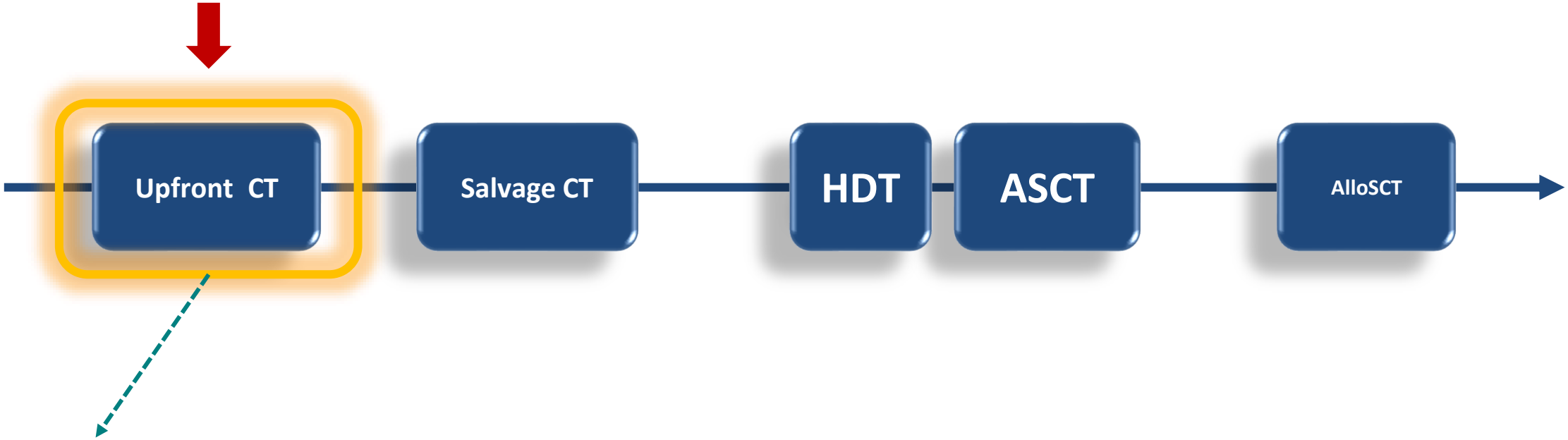
Single-arm, non-inferiority study aimed to show that cure rates can be maintained despite reduced use of transplant



Study will address:

- How many patients can avoid transplant?
- Is transplant effective if delayed to 3rd line setting?
- What predicts who can avoid transplant?
  - MTV? ctDNA? Clinical factors?

Pembrolizumab as a upfront strategy for Hodgkin Lymphoma



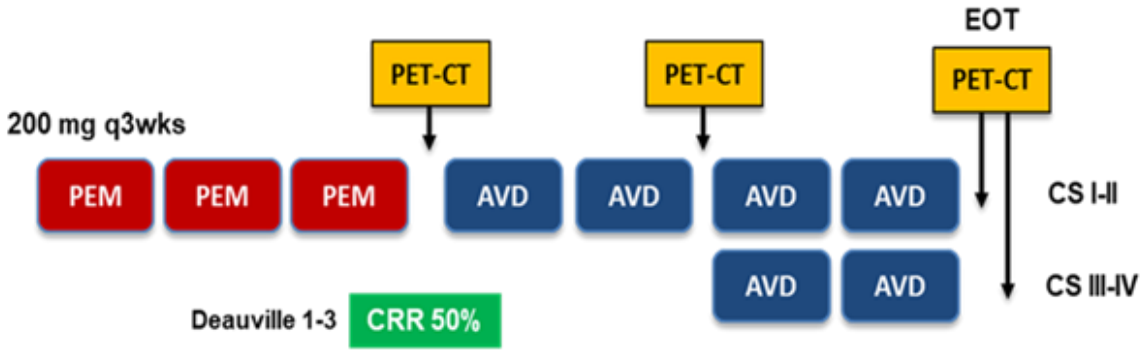
- ***SEQUENTIAL***
- ***COMBINED***

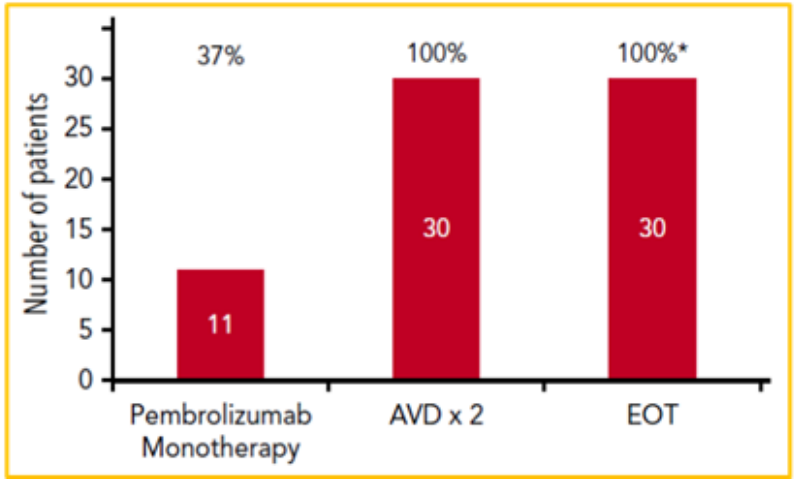
Pinto A 2022)

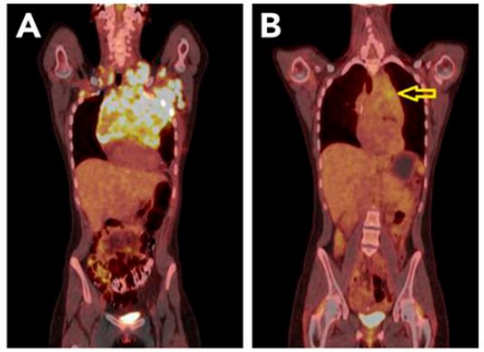
blood Regular Article

Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma

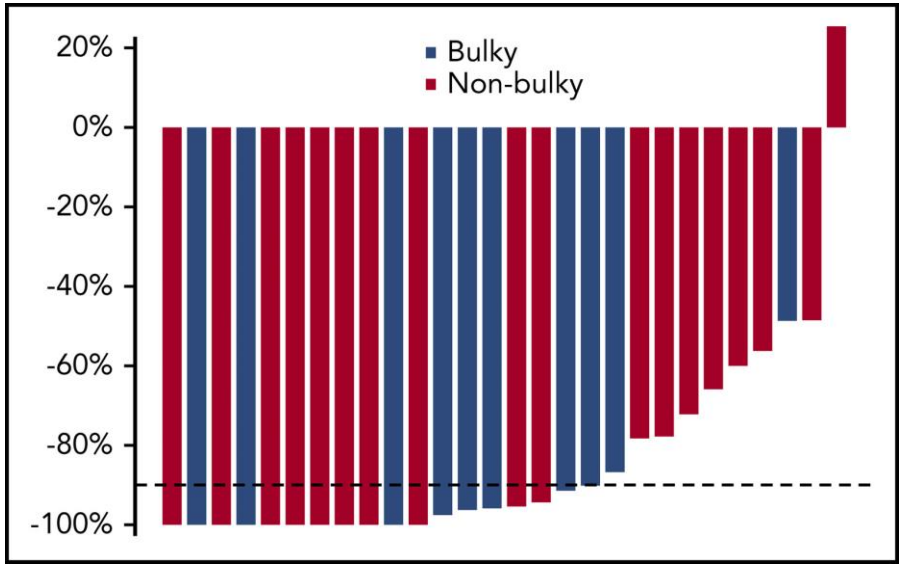
Pamela B. Allen,[1] Hatice Savas,[2,3] Andrew M. Evens,[4] Ranjana H. Advani,[5] Brett Palmer,[3] Barbara Pro,[3] Reem Karmali,[3] Eric Mou,[5] Jeffrey Bearden,[3] Gary Dillehay,[2,3] Robert A. Bayer,[3] Robert M. Eisner,[3] Joan S. Chmiel,[3,6] Kaitlyn O'Shea,[3,6] Leo I. Gordon,[3] and Jane N. Winter[3]

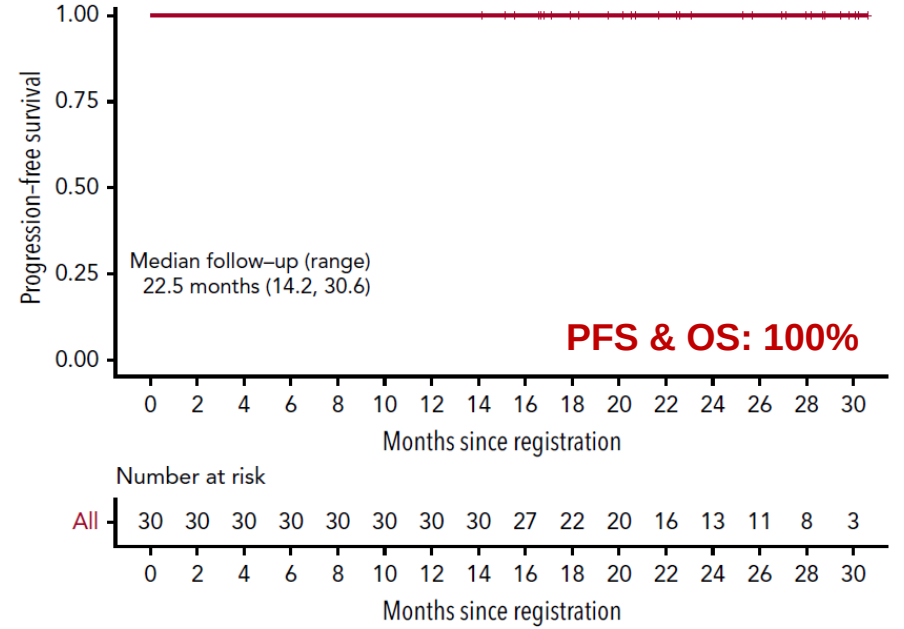






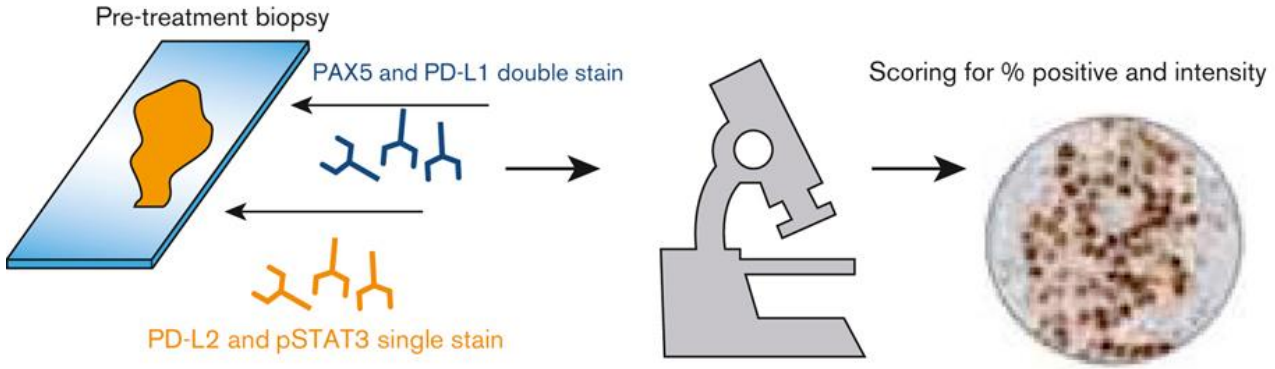
Response to single-agent pembrolizumab



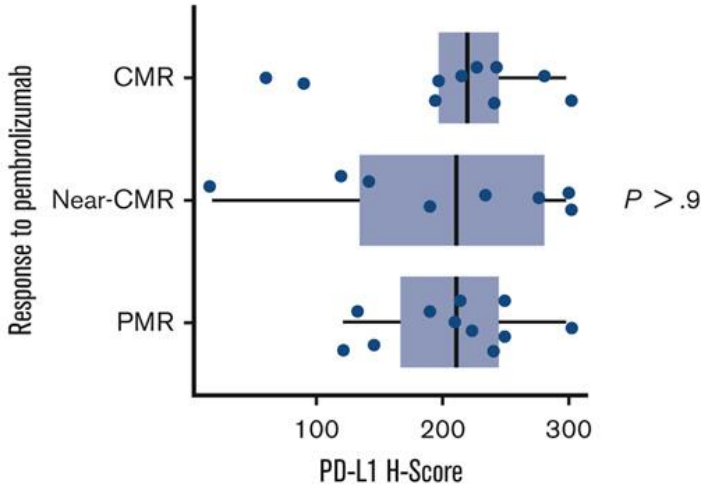


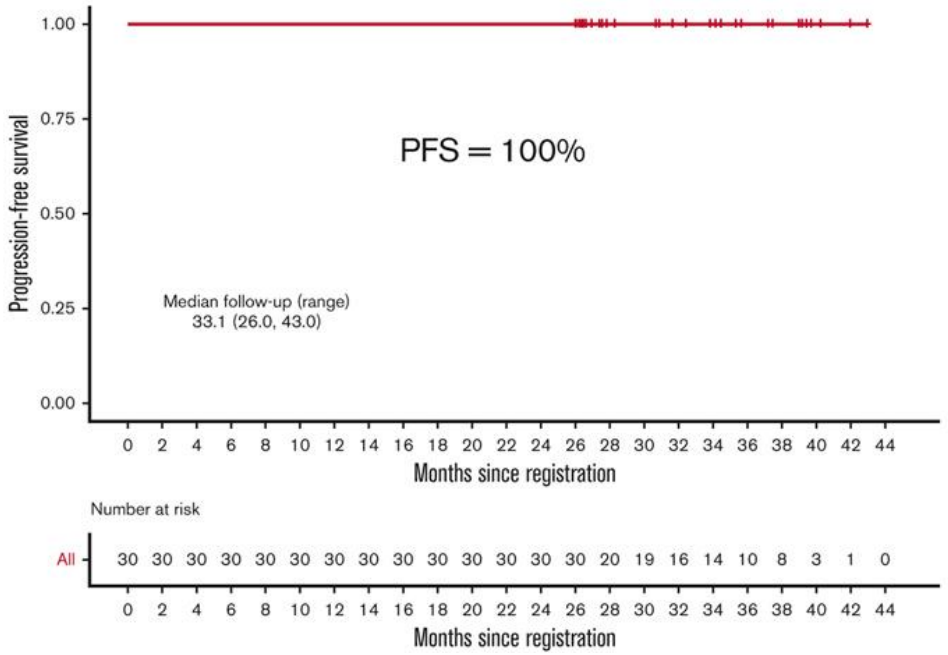
Allen PB, et al. Blood. 2017;129(26):3416-3418

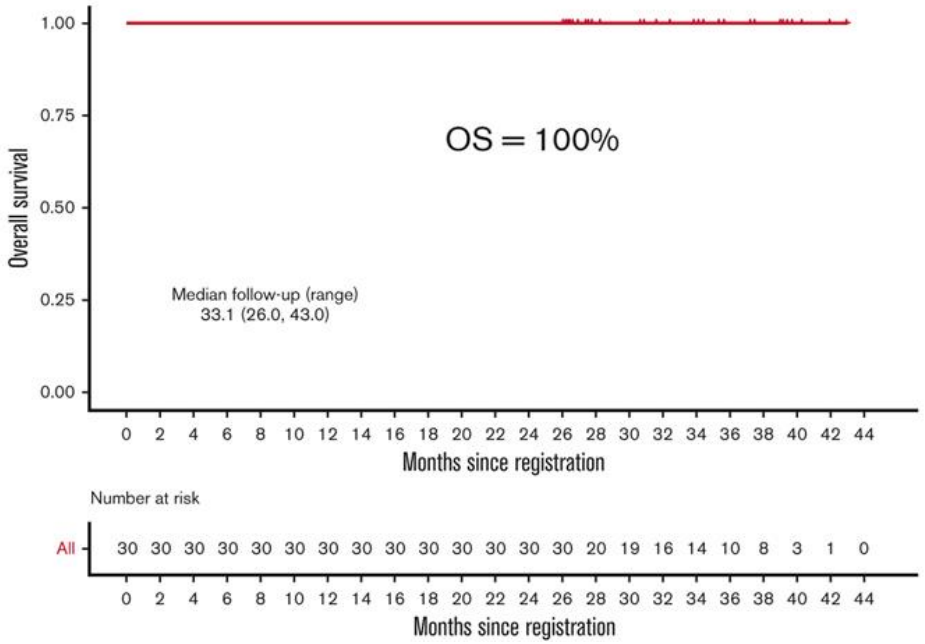
Sequential Pembrolizumab and AVD is Highly Effective at any PD-L1 Expression Level in Untreated Hodgkin Lymphoma



H score = staining intensity (0-3) x % positive tumor cells (0-100%)
Range = 0-300



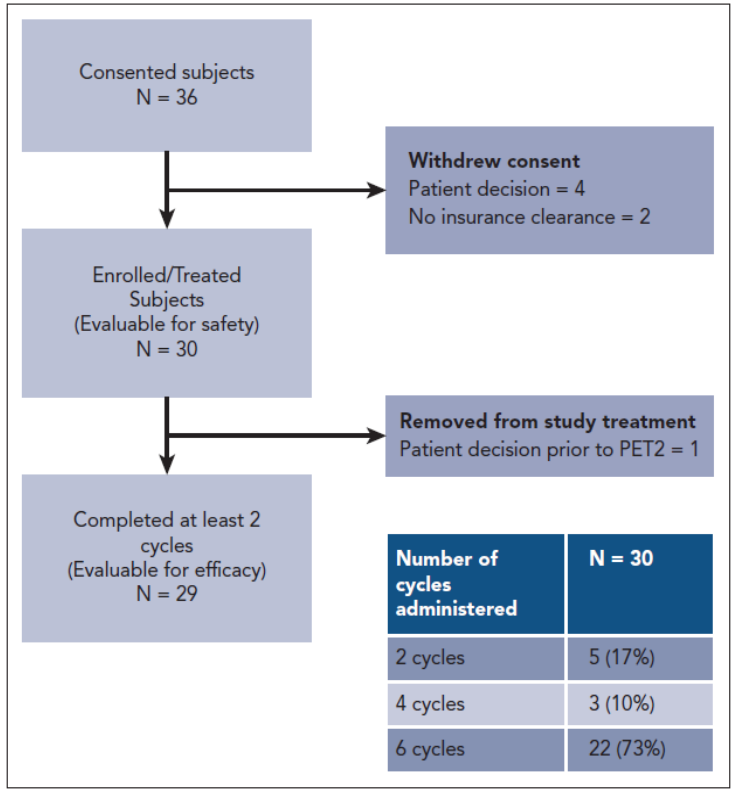




Concurrent pembrolizumab with AVD for untreated classic Hodgkin lymphoma

Ryan C. Lynch,[1,2] Chaitra S. Ujjani,[1,2] Christina Poh,[1] Edus H. Warren,[1,2] Stephen D. Smith,[1,2] Mazyar Shadman,[1,2] Brian Till,[1,2] Vikram M. Raghunathan,[1] Stefan Alig,[3] Ash A. Alizadeh,[3] Avanti Gulhane,[4] Delphine L. Chen,[4] Yolanda Tseng,[2,5] Hilary Coye,[1] Megan Shelby,[1] Susan Ottemiller,[1] Sarith Keo,[1] Kaitlin Verni,[1] Hongyan Du,[1] Jacquelin Vandermeer,[1] Ashley Gaston,[1] Heather Rasmussen,[1] Paul Martin,[1] Edmond Marzbani,[1] Jenna Voutsinas,[2] and Ajay K. Gopal[1,2]

Characteristic	n = 30
Male sex, n (%)	12 (40)
Age, median (range), y	33 (18-69)
Stage, n (%)	
I	1 (3)
II	11 (37)
III	7 (23)
IV	11 (37)
B symptoms, n (%)	13 (43)
Mediastinal bulk, >10 cm, n (%)	6 (20)
Elevated erythrocyte sedimentation rate, >50, n (%)	11 (37)
Extranodal involvement, n (%)	11 (37)
Spleen involvement, n (%)	7 (23)
Early-stage unfavorable, National Comprehensive Cancer Network (n = 12), n (%)	6 (50)
International Prognostic Score (advanced stage, n = 18), n (%)	
0-1	6 (33)
2 and 3	7 (39)
4, 5, 6, and 7	5 (28)

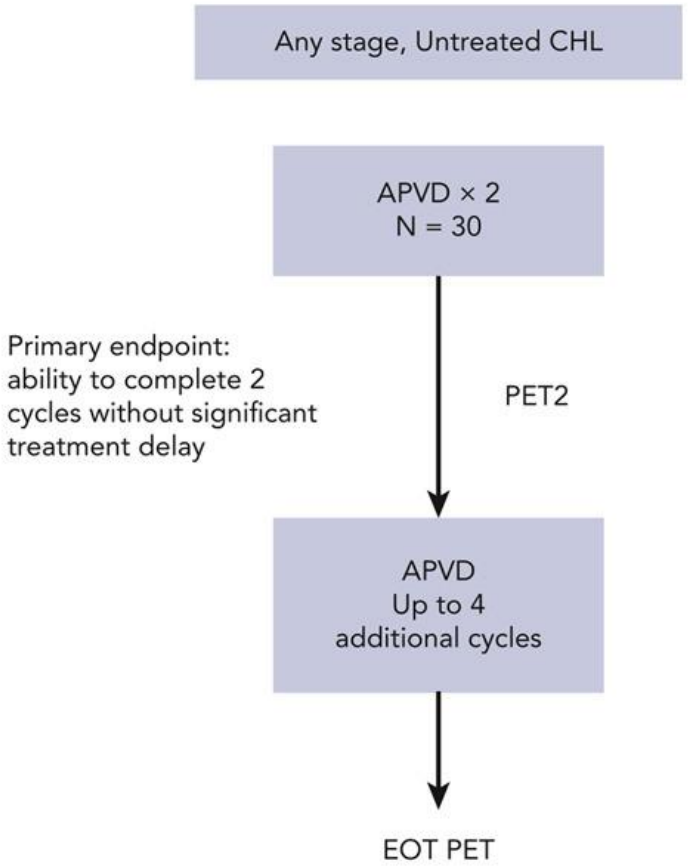


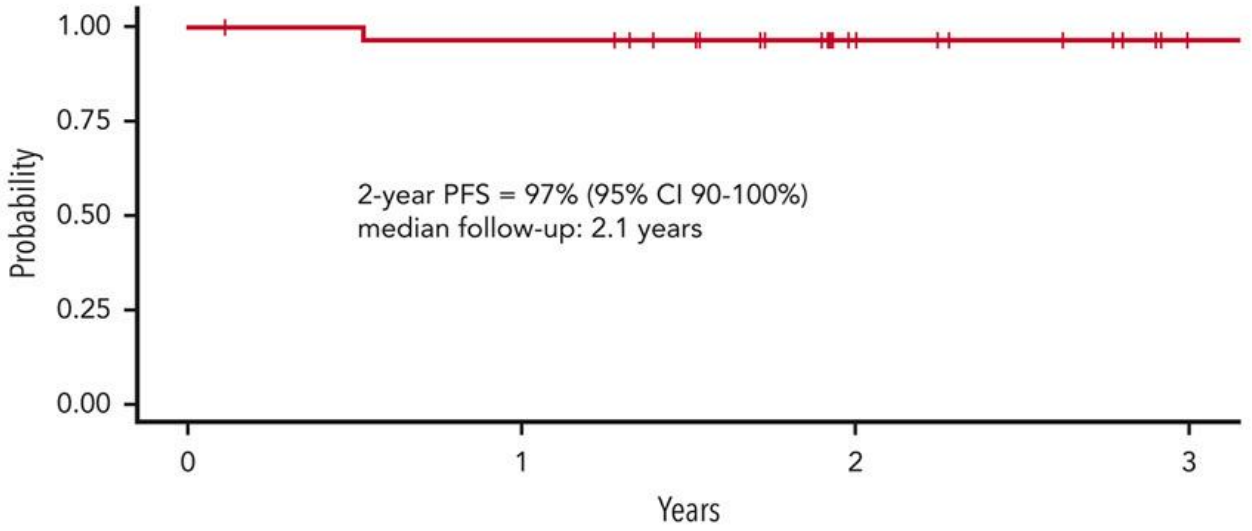
Number of cycles administered	N = 30
2 cycles	5 (17%)
4 cycles	3 (10%)
6 cycles	22 (73%)

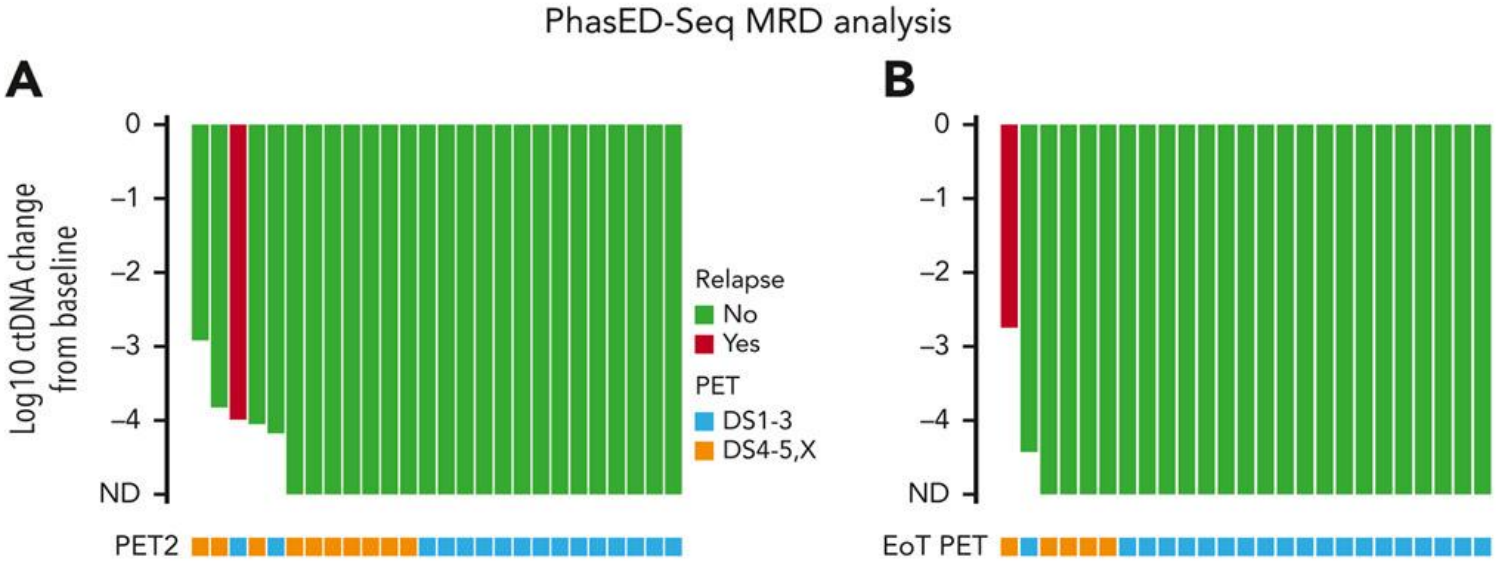
Table 3. IRAEs of any grade

AE	Any grade, n	%	Grade 3, n	%	Grade 4, n	%
Elevated ALT	20	67	2	7	1	3%
Elevated AST	10	33	—	—	1	3%
Rash	12	43	1	3	—	—
Hypothyroidism	2	7	—	—	—	—
Arthritis	1	3	—	—	—	—
Colitis	1	3	—	—	—	—
Total	26	87	3	10	1	3

Concurrent pembrolizumab with AVD (APVD) in untreated classical Hodgkin lymphoma







blood® 25 MAY 2023 | VOLUME 141, NUMBER 21

Single arm phase 2 trial of pembrolizumab as a first therapy for Hodgkin lymphoma

Prior to Treatment

Screening 28 Days

Treatment Phase

Pembrolizumab 200mg IV q3 weekly

Up to 35 cycles or 2 years

Follow-up Phase

Follow-up 1 year

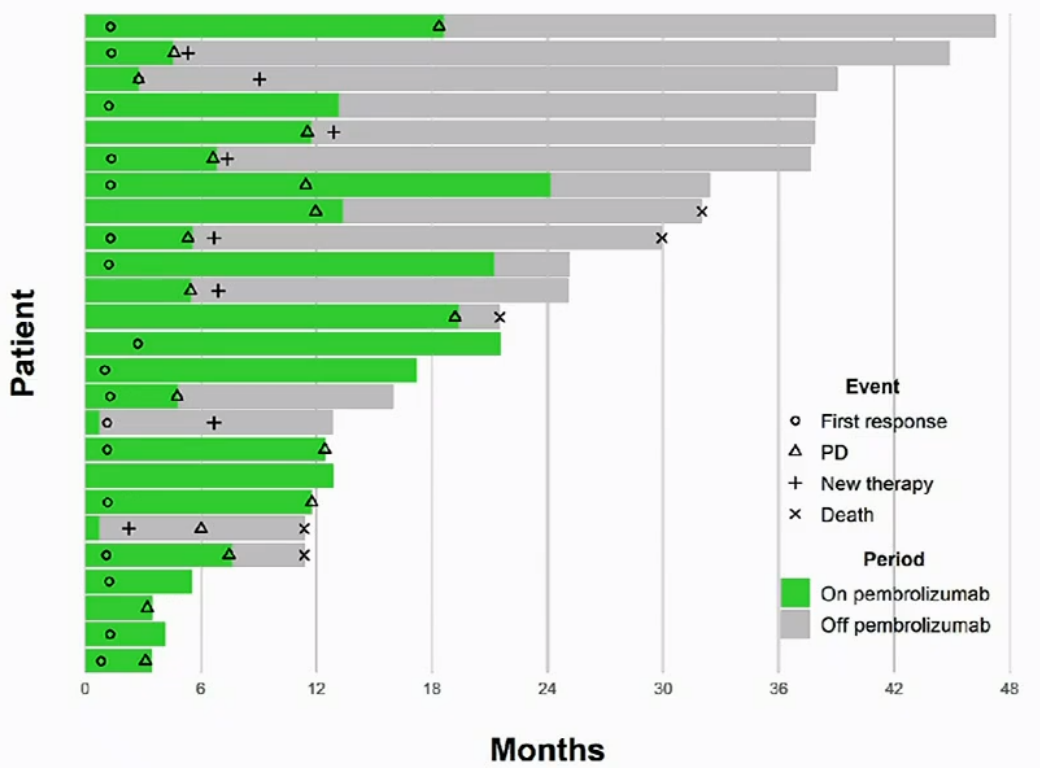
N=25

Key inclusion:

- Either
  - considered to be ineligible for frontline ABVD for reasons of fitness or comorbidity
  - **or** be aged ≥65;
- have an ECOG<3,
- adequate organ function (platelets ≥75, neutrophils ≥1.0, GFR ≥30ml/min)
- Age-associated low-risk concomitant malignancies were allowed

Response	Lugano	LYRIC
CMR/CR	8 (32%)	8 (32%)
PMR/PR	10 (40%)	10 (40%)
NMR/SD	5 (20%)	5 (20%)
IR	-	2 (8%)
PMD/PD	2 (8%)	0 (0%)

- A median of 11 treatment cycles were delivered (range 1-35)
- The median duration of response was 10.6 months



Clinical Haematology

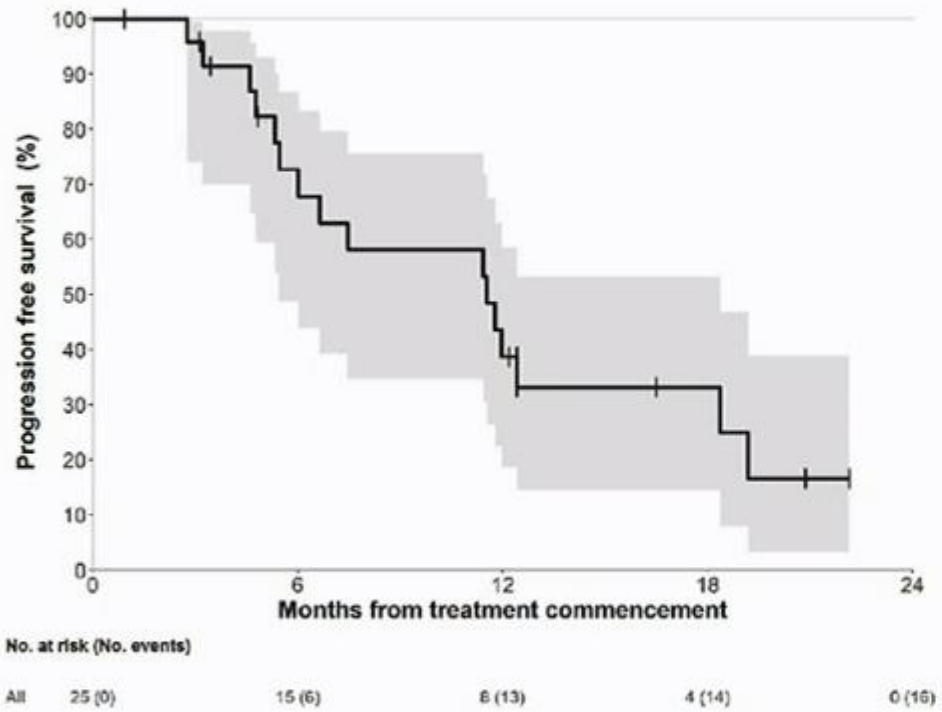
PeterMac

The Royal Melbourne Hospital

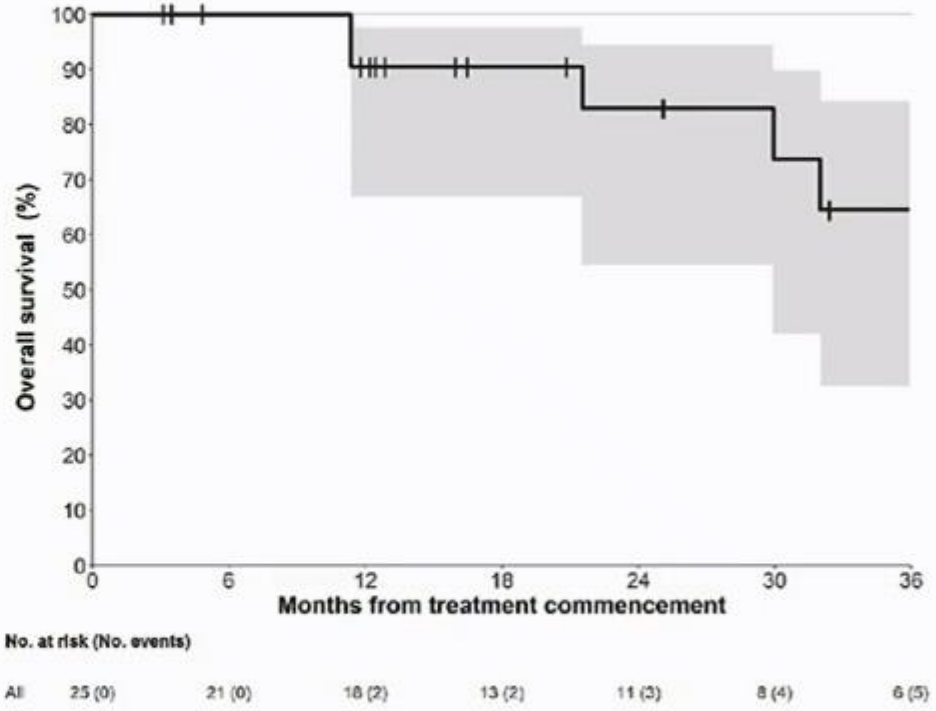
Dickinson MJ, et al EHA & Lugano 2023

Survival outcomes

Progression Free Survival



Overall Survival

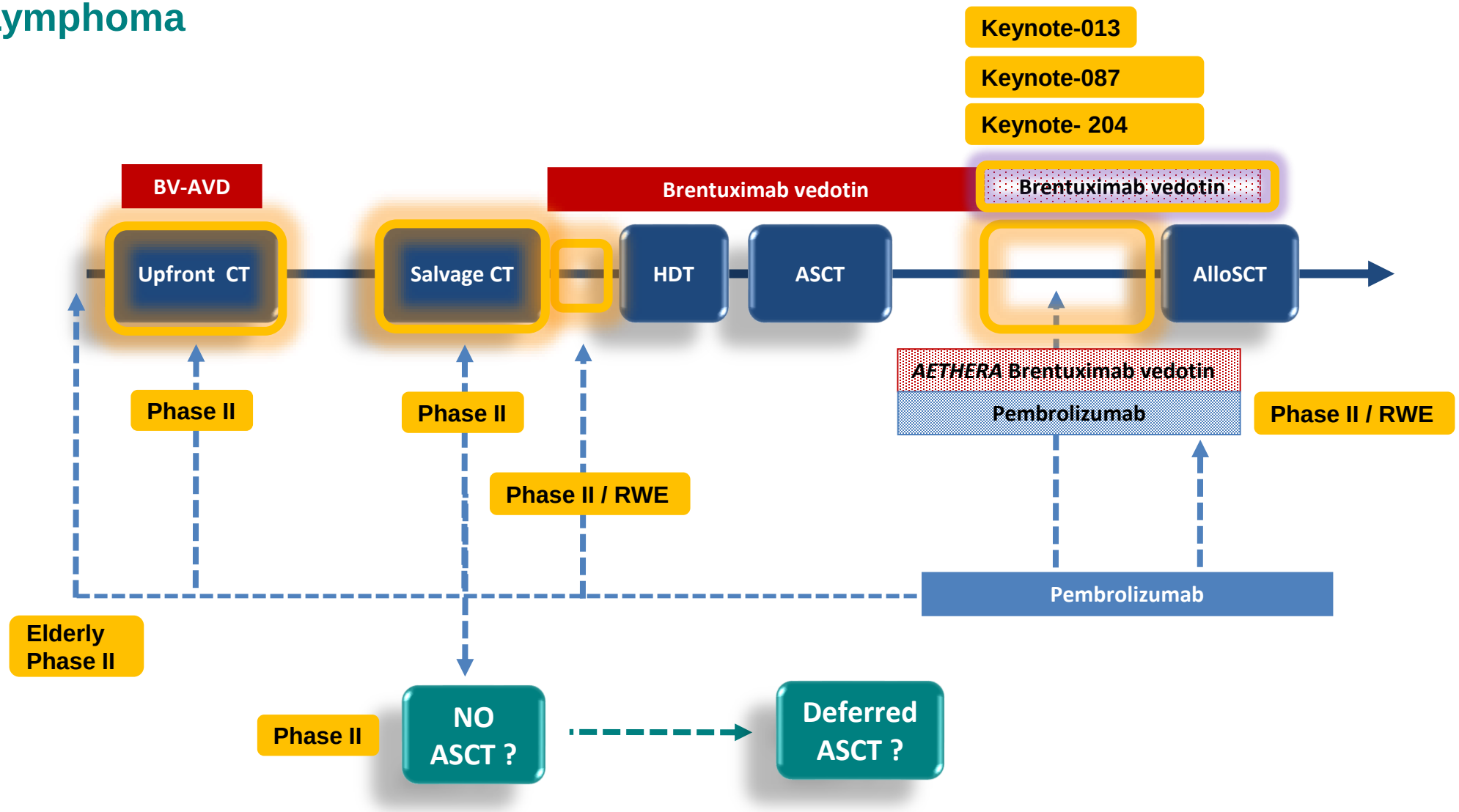


Median follow up 2 years:
12m survival 90%; 2y survival 83%

Clinical Haematology

PeterMac
The Royal Melbourne Hospital

How Pembrolizumab (& PD1-blockade) is changing the treatment paradigm for Hodgkin Lymphoma



Grade III+ toxicity attributed to pembrolizumab

	Number	Total
Ggt Increased	4	4 (16%)
Immune System Disorders - Hepatitis	2	2 (8%)
Alkaline Phosphatase Increased	1	1 (4%)
Arthritis	1	1 (4%)
Aspartate Aminotransferase Increased	1	1 (4%)
Heart Failure	1	1 (4%)
Lipase Increased	1	1 (4%)
Musculoskeletal And Connective Tissue Disorder - Synovitis	1	1 (4%)
Skin And Subcutaneous Tissue Disorders - Cutaneous Reaction	1	1 (4%)
Any Adverse Event	**8**	**8 (32%)**

	Pembro n = 151	BV n = 153
Age, median (range)	36 (18-84)	35 (18-83)
≥65 years, n (%)	27 (17.9)	22 (14.4)
Male, n (%)	84 (55.6)	90 (58.8)
White, n (%)	119 (78.8)	115 (75.2)
ECOG PS 0, n (%)	86 (57.0)	100 (65.3)
Prior auto-SCT, n (%)		
Yes	56 (37.1)	56 (36.6)
No	95 (62.9)	97 (63.4)

	Pembro n = 151	BV n = 153
Disease status after frontline therapy, n (%)		
Primary refractory	61 (40.4)	62 (40.5)
Relapsed <12 months	42 (27.8)	42 (27.5)
Relapsed ≥12 months	48 (31.8)	49 (32.0)
Prior BV, n (%)	5 (3.3)	10 (6.5)
Prior radiation, n (%)	58 (38.4)	61 (39.9)
Bulky disease, n (%)	35 (23.2)	25 (16.3)
Baseline B-symptoms, n (%)	43 (28.5)	36 (23.5)
Baseline bone marrow involvement, n (%)	12 (7.9)	5 (3.3)

Data cutoff: January 16, 2020.

PEMBROLIZUMAB AND HODGKIN LYMPHOMA

- **<u>Brief</u> pharmacokinetics of Pembrolizumab**
- **Pembrolizumab as a single agent for RR-HL**
- **Pembrolizumab maintenance strategies (post-ASCT & without ASCT)**
- **Pembrolizumab as a salvage treatment pre-ASCT (alone & combined with chemo**
- **Pembrolizumab as a salvage treatment pre-ASCT (*alone & combined with chemo*)**