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With the Therapeutic Revolution in First Line, How Will the Second Line be Modified?

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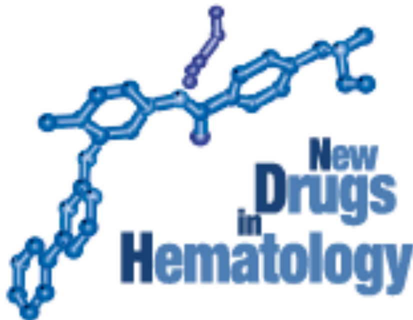
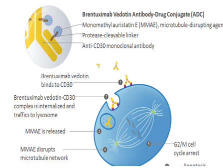


Bologna, May 18-20, 2026

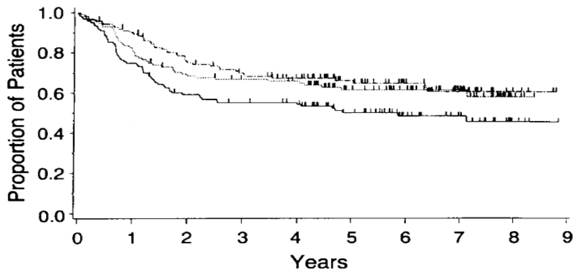
Conflicts of Interest

- Honoraria: Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead Kite, Sanofi, Roche, GenMab, Abbvie, Jazz Pharmaceuticals
- Consultancy: Takeda, BMS/Celgene, Novartis, Janssen, Gilead, Sanofi, GenMab, Abbvie
- Speaker's Bureau: Takeda
- Research Support: Takeda

Advanced Stage HL is a Highly Curable Disease in 2026. More Effective Treatment Strategies and The Introduction of New Drugs



MOPP vs ABVD vs MOPP-ABVD



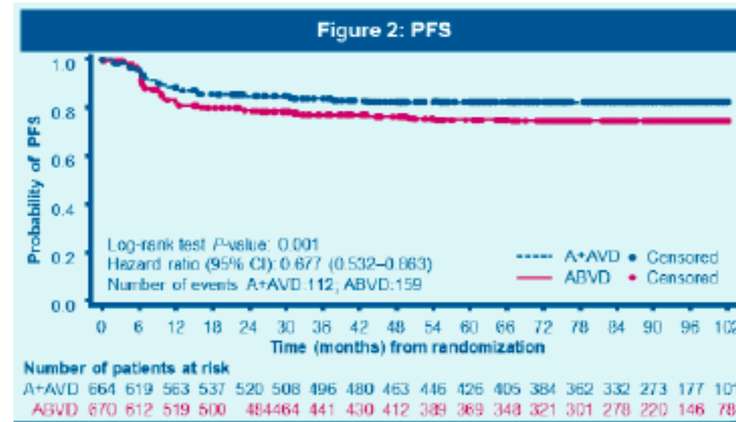
Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
—— MOPP	123	62 (50)	4.84
······ ABVD	115	44 (38)	None
-·-·- MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

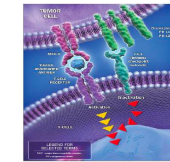
P = 0.02 for the difference between MOPP, ABVD, and MOPP–ABVD. In the column for median years of survival, none indicates that the median survival has not yet been reached.

Canellos G et al, NEJM 1992

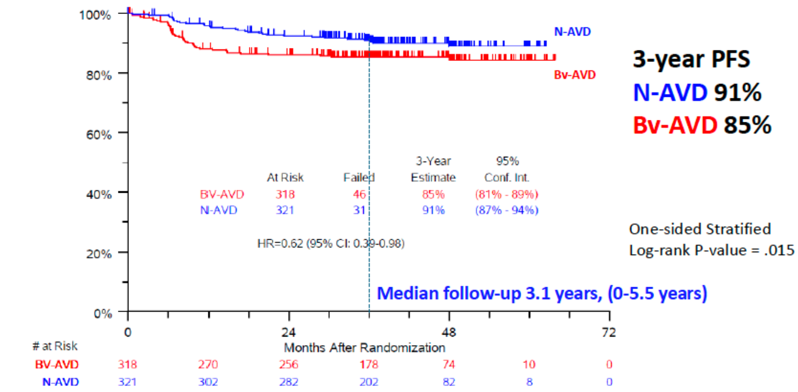
ECHELON-1 7 Years FU. ABVD vs BV-AVD



Ansell S et al, ASCO2024



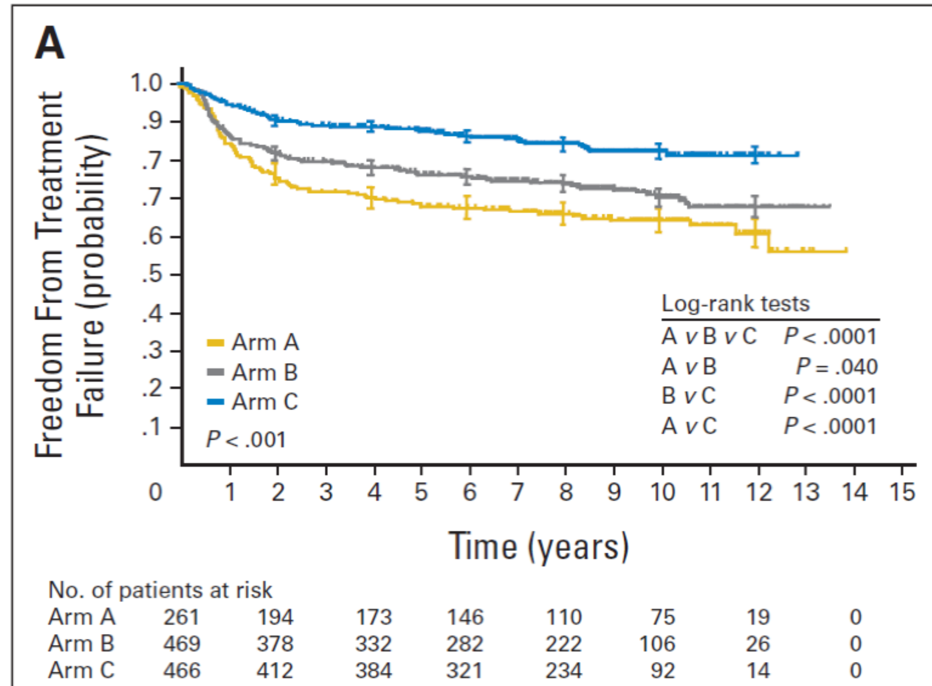
S1826: N-AVD Prolongs PFS in 18–60-year-old Adults



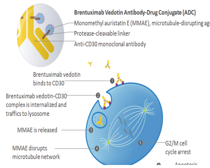
Herrera AF, et al. Blood. 2025;146 (suppl. 1):151.

Advanced Stage HL is a Highly Curable Disease in 2026. More Effective Treatment Strategies and The Introduction of New Drugs

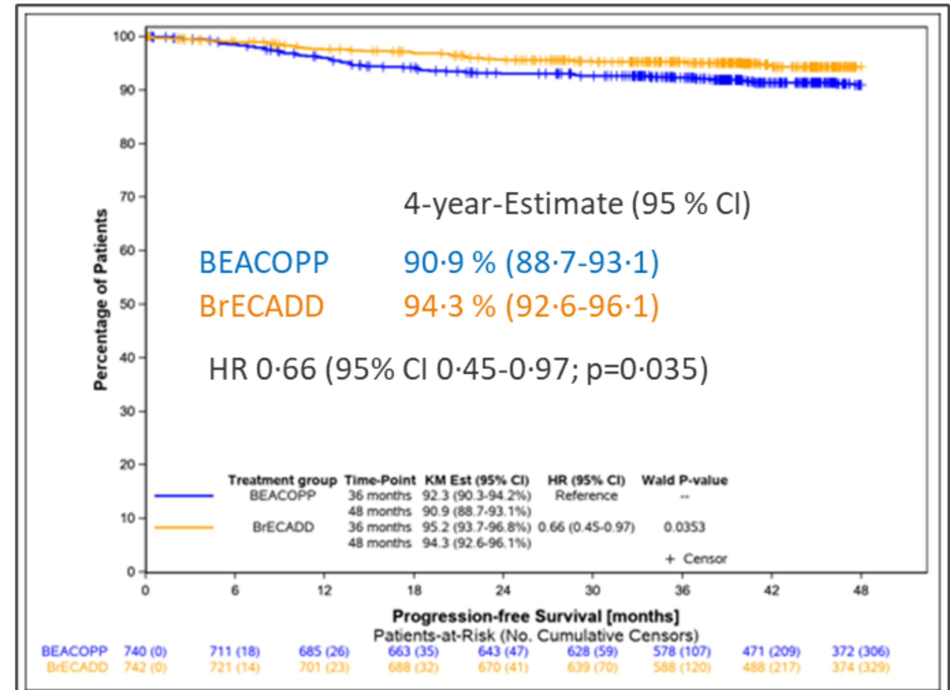
HD9 Trial. COPP/ABVD vs BEACOPP Baseline vs BEACOPP Escalated



Engert A et al, J Clin Oncol 2009



HD21: BrECADD is superior to eBEACOPP (mFU 48 m)

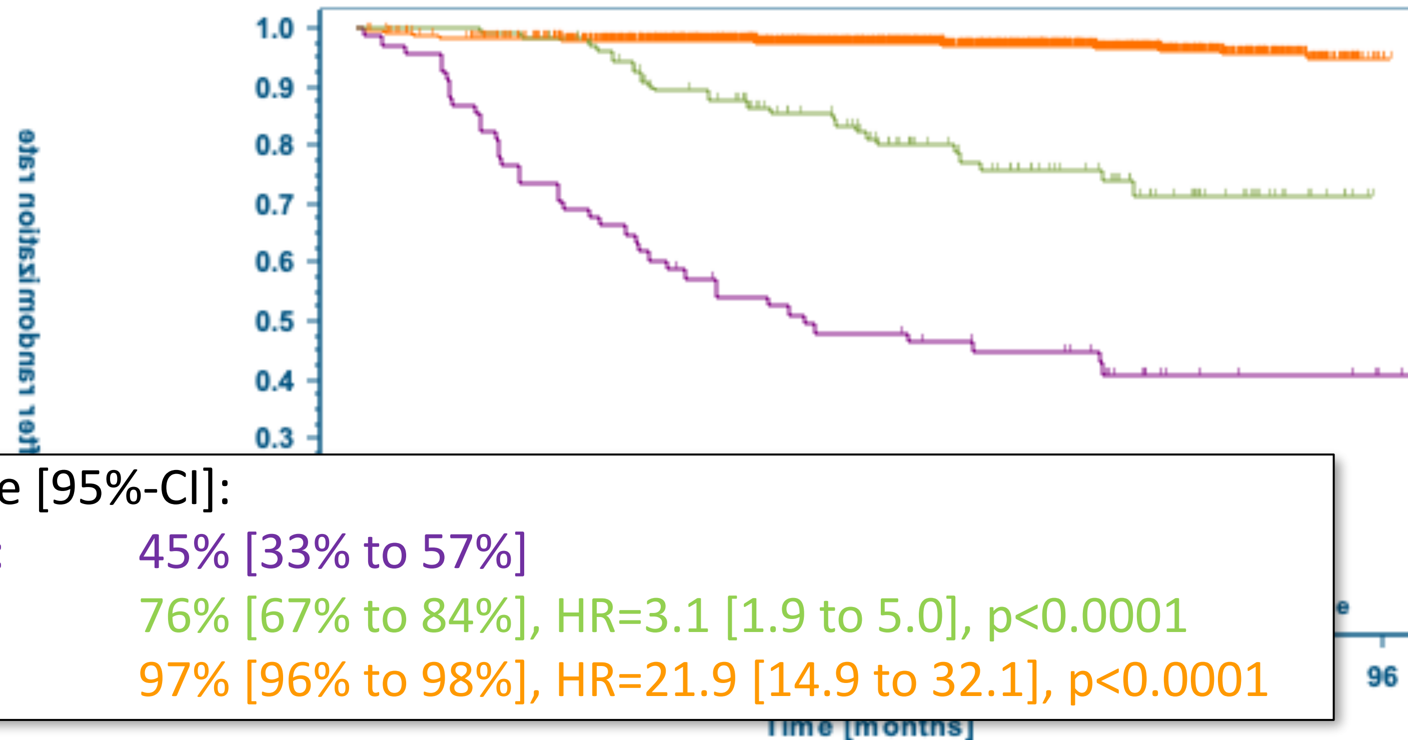


Ferdinandus J et al, J Clin Oncol 2025

Challenges in the Relapsed/Refractory Setting

- Less patients with relapsed / refractory disease
- Frontline BV- and PD-1–based strategies are redefining relapse biology
- Future relapses may represent biologically resistant disease
- Prior treatment exposure increasingly determines salvage selection

Overall Survival After First Diagnosis, BEACOPP-like 1st-Line: Comparison with Complementary Study Cohort, GHSG Database



5-year estimate [95%-CI]:

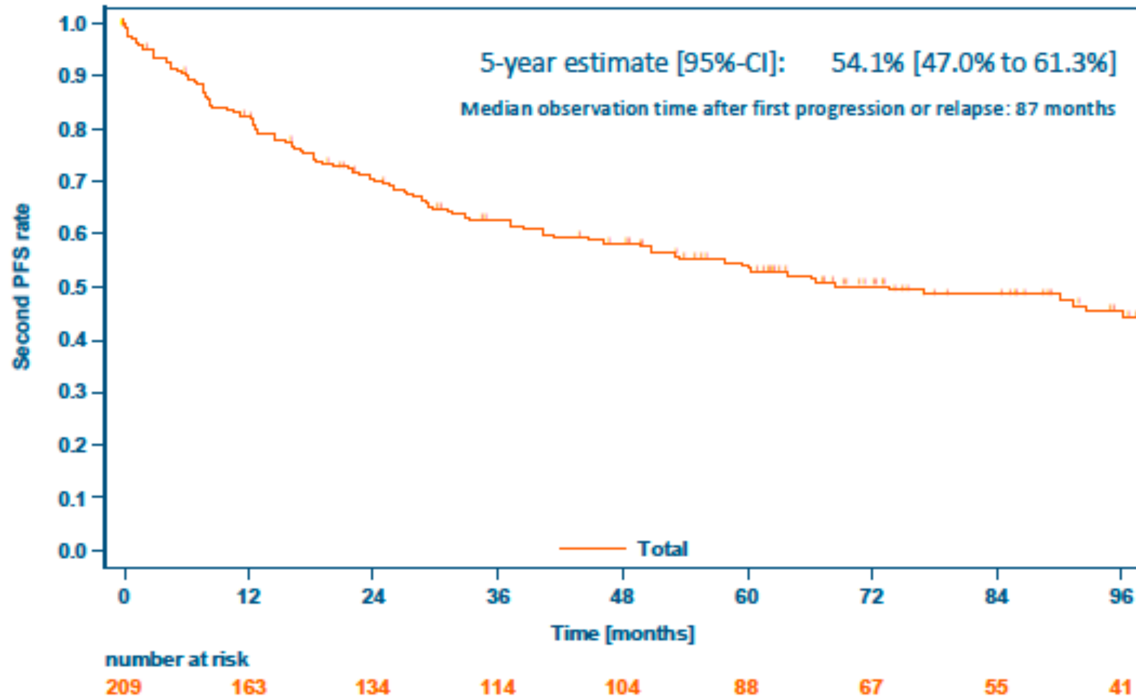
- Progression: 45% [33% to 57%]
- Relapse: 76% [67% to 84%], HR=3.1 [1.9 to 5.0], p<0.0001
- No event: 97% [96% to 98%], HR=21.9 [14.9 to 32.1], p<0.0001

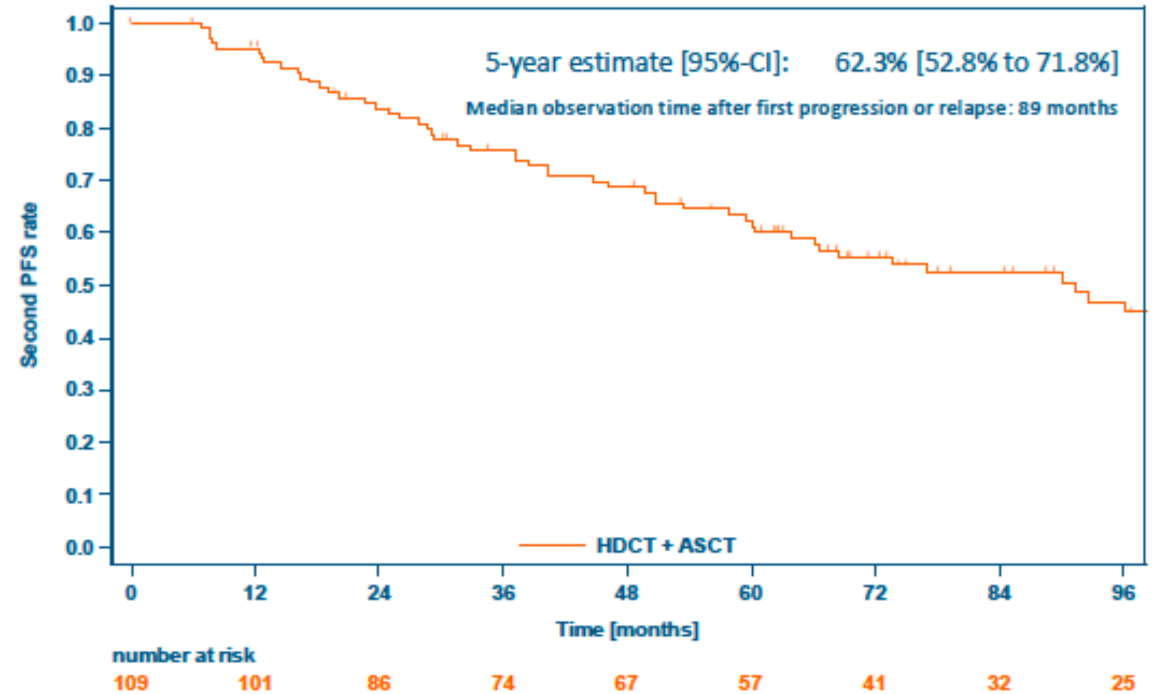
Pts. at risk

No event	2686	2616	2495	2124	1567	1052	563	183	1
Progression	68	56	45	35	31	26	18	11	8
Early or Late Relapse	124	123	115	96	72	51	34	14	0

Courtesy of Peter Borchmann

Failing HD15 Prospective Clinical Trial





Courtesy of Peter Borchmann

Historical Standard of Care

- Traditional paradigm: ABVD → salvage chemotherapy → auto-HCT
- Common salvage regimens: ICE, DHAP, GDP, ESHAP
- Goal: PET-negative remission prior to transplant
- 5-year PFS after auto-HCT: ~75% if PET-negative vs ~30–40% if PET-positive
- Most of the patients that received BV / CPIs salvage combinations before auto-HCT, were BV and CPIs naïve

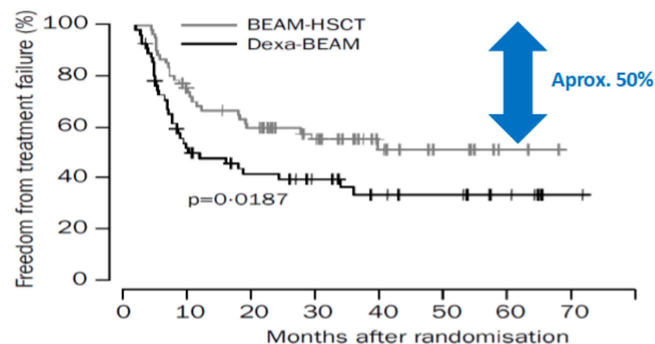
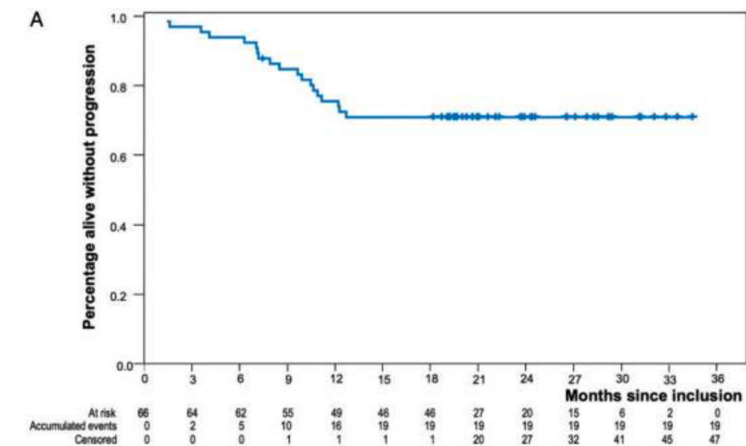
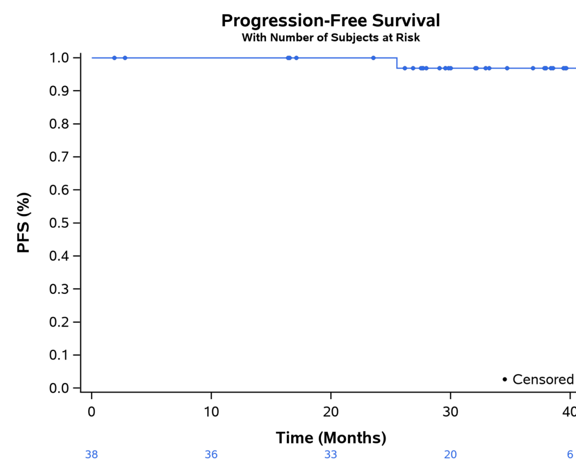


Figure 3: Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin's disease

Schmitz N et al, Lancet 2002



García-Sanz R et al, Ann Oncol 2019



Moscowitz A et al, ISHL22

When Brentuximab Vedotin is Included in 1L, can We Consider Retreatment?

- BV retreatment remains feasible in selected patients
- Published retreatment studies showed ORR ~60% and CR ~30%
- Best candidates: durable prior response and late relapse
- Neuropathy may limit re-exposure
- BV increasingly used in combinations rather than alone
- **BV retreatment could be an option for patients failing BV-containing first line therapies**

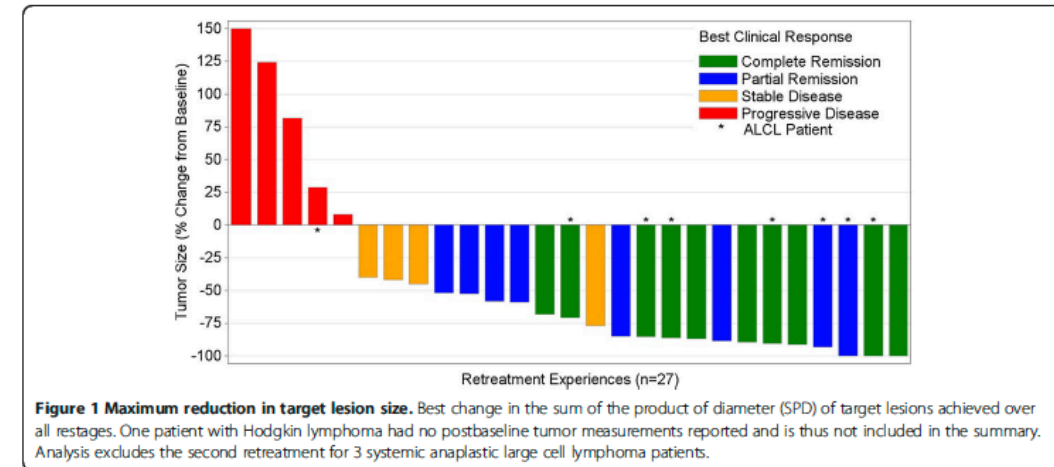


Figure 1 Maximum reduction in target lesion size. Best change in the sum of the product of diameter (SPD) of target lesions achieved over all restages. One patient with Hodgkin lymphoma had no postbaseline tumor measurements reported and is thus not included in the summary. Analysis excludes the second retreatment for 3 systemic anaplastic large cell lymphoma patients.

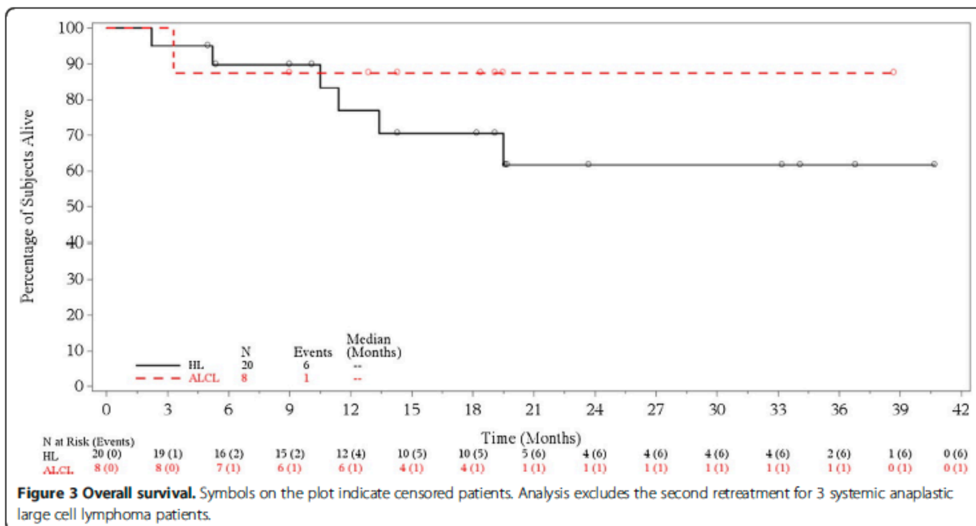


Figure 3 Overall survival. Symbols on the plot indicate censored patients. Analysis excludes the second retreatment for 3 systemic anaplastic large cell lymphoma patients.

Table 3 Treatment-emergent adverse events reported by at least 20% of patients and grade 3 and higher incidence of these events

Event term	Treatment-emergent adverse events (any grade)	Any grade 3 events	Any grade 4 events	Any grade 5 events
Any event, n (%)	28 (97)	8 (28)	3 (10)	3 (10)
Peripheral sensory neuropathy	17 (59)	2 (7)	0	0
Fatigue	12 (41)	3 (10)	1 (3)	0
Nausea	12 (41)	1 (3)	0	0
Diarrhea	11 (38)	0	0	0
Arthralgia	8 (28)	2 (7)	0	0
Headache	8 (28)	0	0	0
Peripheral motor neuropathy	8 (28)	2 (7)	0	0
Pyrexia	8 (28)	0	0	0
Anemia	7 (24)	5 (17)	0	0
Dyspnea	7 (24)	1 (3)	1 (3)	0
Back pain	6 (21)	1 (3)	0	0

Bartlett N et al, J Hematol Oncol 2014

When Brentuximab Vedotin is Included in 1L, can We Consider Retreatment?

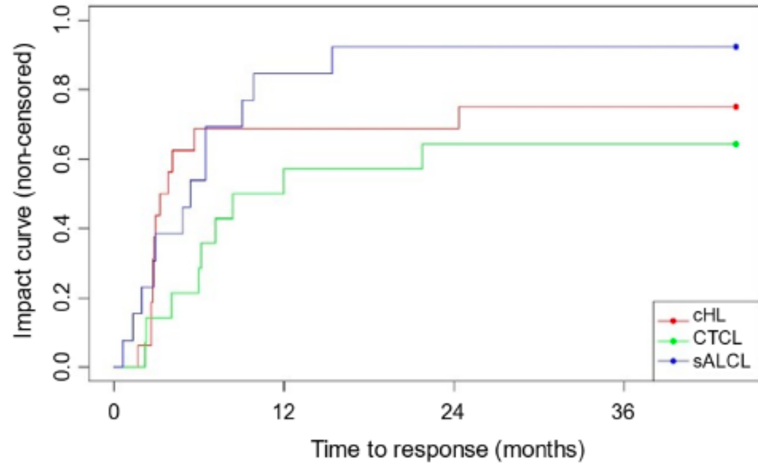
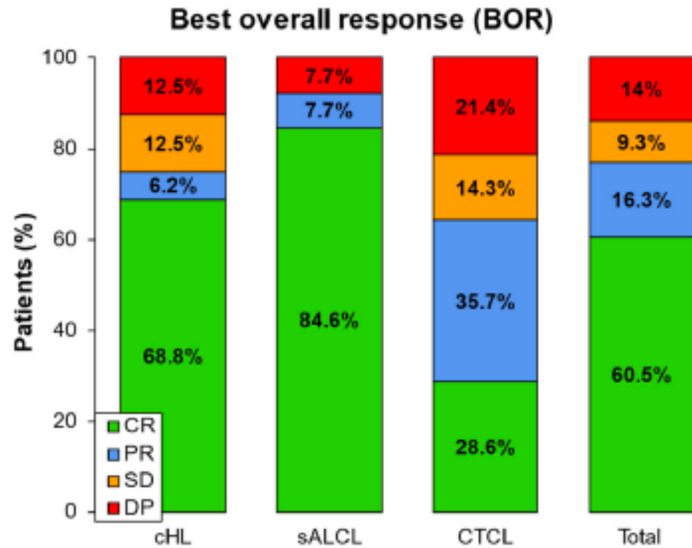
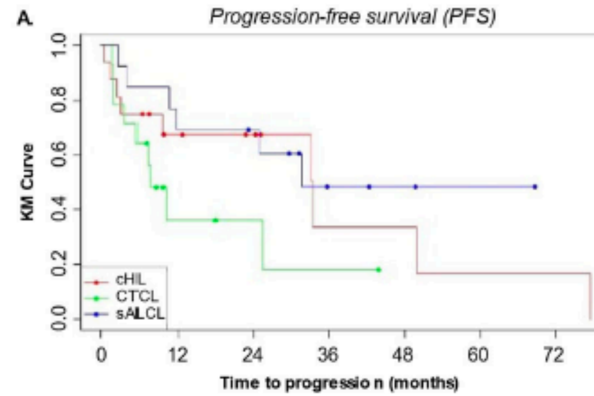
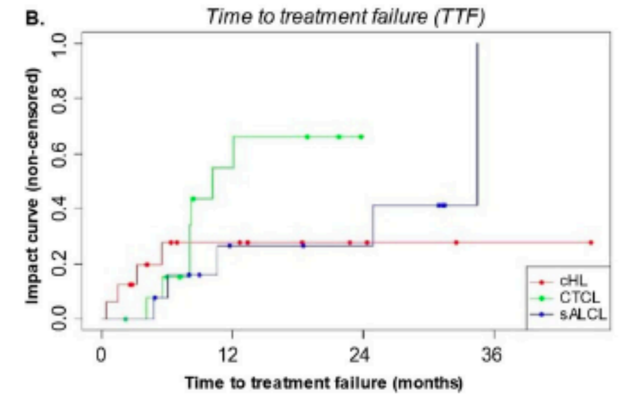


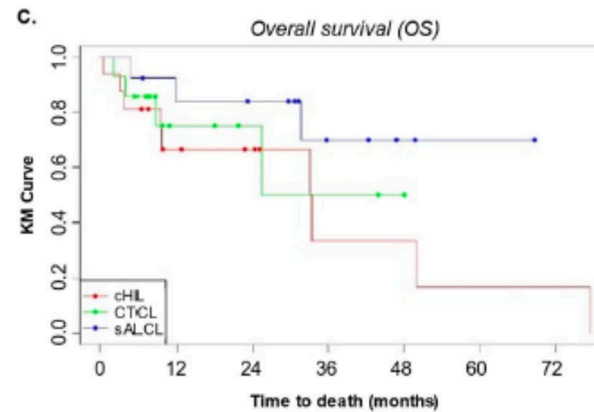
Figure 2. Kaplan–Meier estimates of ORR.



N: 43 patients (16 cHL, 13 sALCL, and 14 CTCL)







Sureda A et al, Cancer 2025

Treating Failures to First Line BV-Containing Regimens

Characteristic	All (n=104)
Sex	
Female	48
Male	52
Stage at diagnosis	
II	24
III	20
IV	54
Unknown	2
Frontline therapy	
A+AVD	76
ABVD with AAVD	16
Brentuximab in other combinations	8
Response to frontline treatment	
Complete response	45
Partial response	23
Progressive disease	28
Unknown	4
Days to relapse (from end-of-frontline treatment)	
≤90	57
91-365	28
366+	15
Stage at relapse	
I	5
II	31
III	18
IV	38
Unknown	8
B symptoms at relapse	
Yes	17
No	80
Unknown	3
Bulk ≥ 5 cm at relapse	
No	70
Yes	18
Unknown	12

- Median age at first relapse was 35 years.
- The most frequently used salvage regimens were anti-PD1+chemotherapy combinations (55%), followed by chemotherapy alone (29%), BV+nivolumab (8%), anti-PD1 monotherapy (7%), and RT only (1%).
- In all pts, the overall response rate (ORR) to first salvage tx was 88%, the complete response (CR) rate was 66%.
- First salvage tx that included PD-1 blockade (n=73) led to an ORR of 96% with 72% CR versus ORR 84% and 61% CR for chemotherapy-only salvage (n=31)
- 87 pts (83%) underwent autologous stem cell transplantation (ASCT).

Yeu Ong S et al, ISHL13

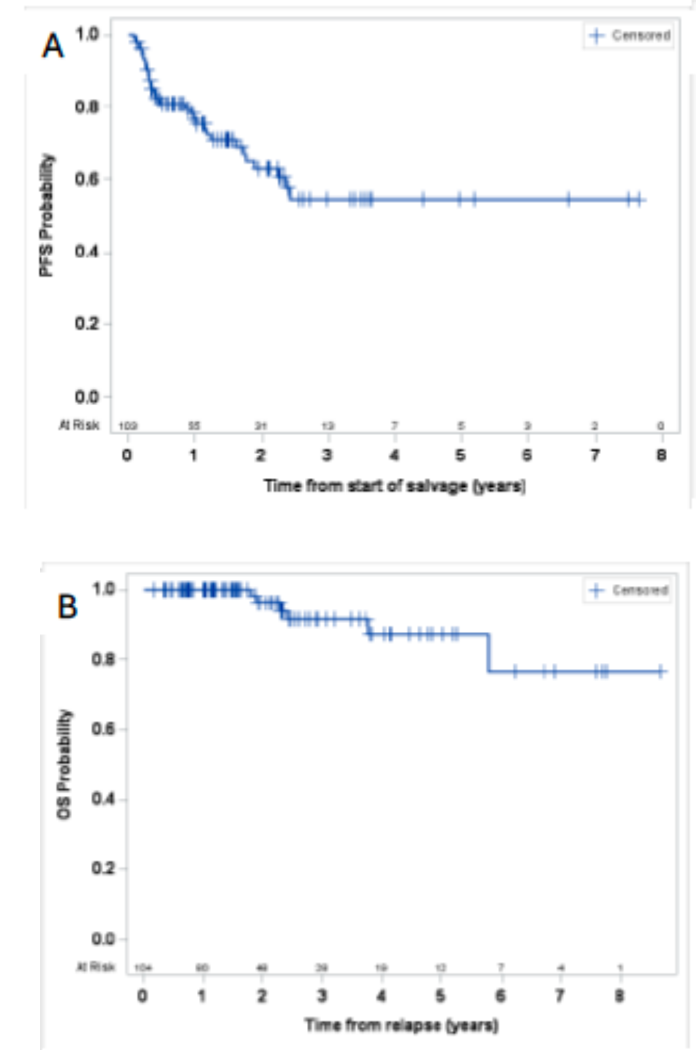
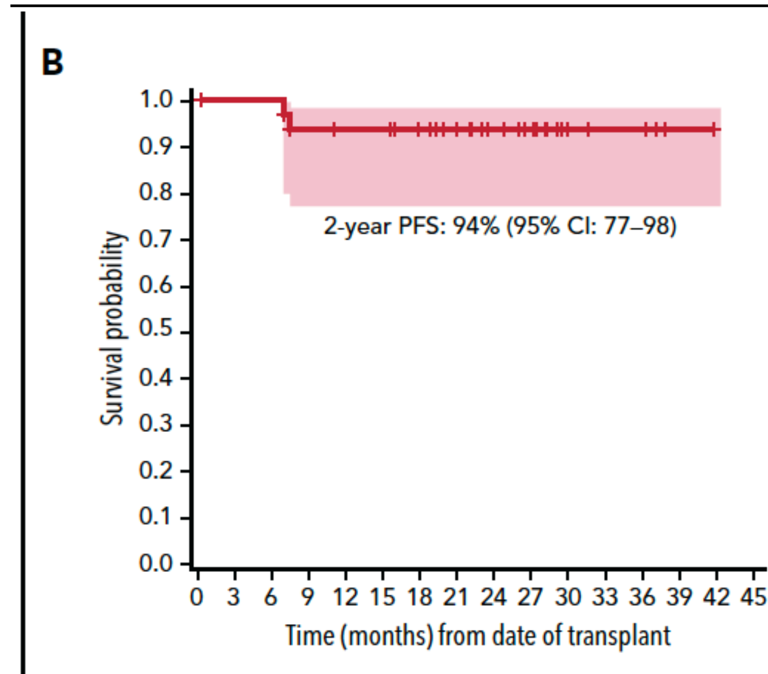
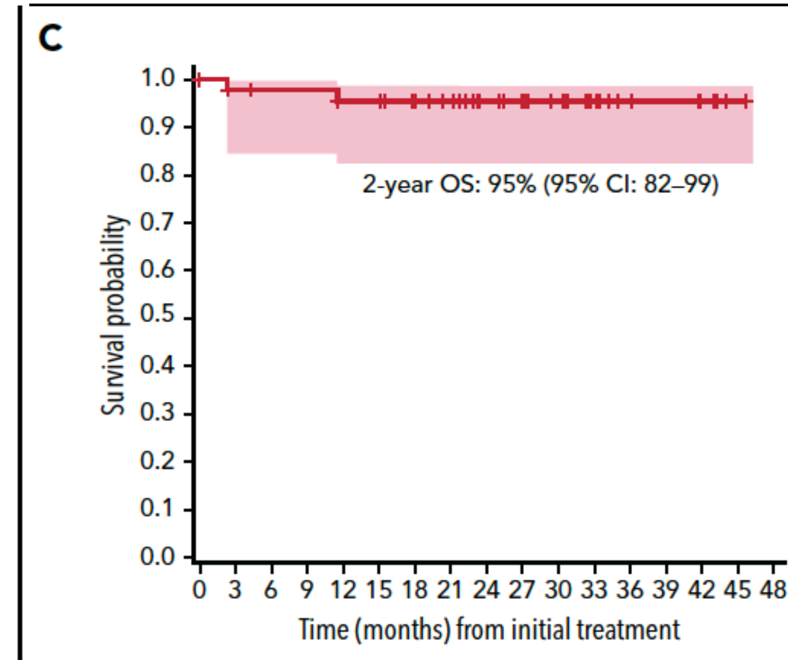


Figure 1. (A) Progression-free survival (PFS) post salvage tx 1; (B) Overall survival (OS) post relapse after frontline treatment with BV-based treatment.

Response-Adapted Anti-PD1 Based Salvage Therapy for HL with Nivolumab Alone or in Combination with ICE

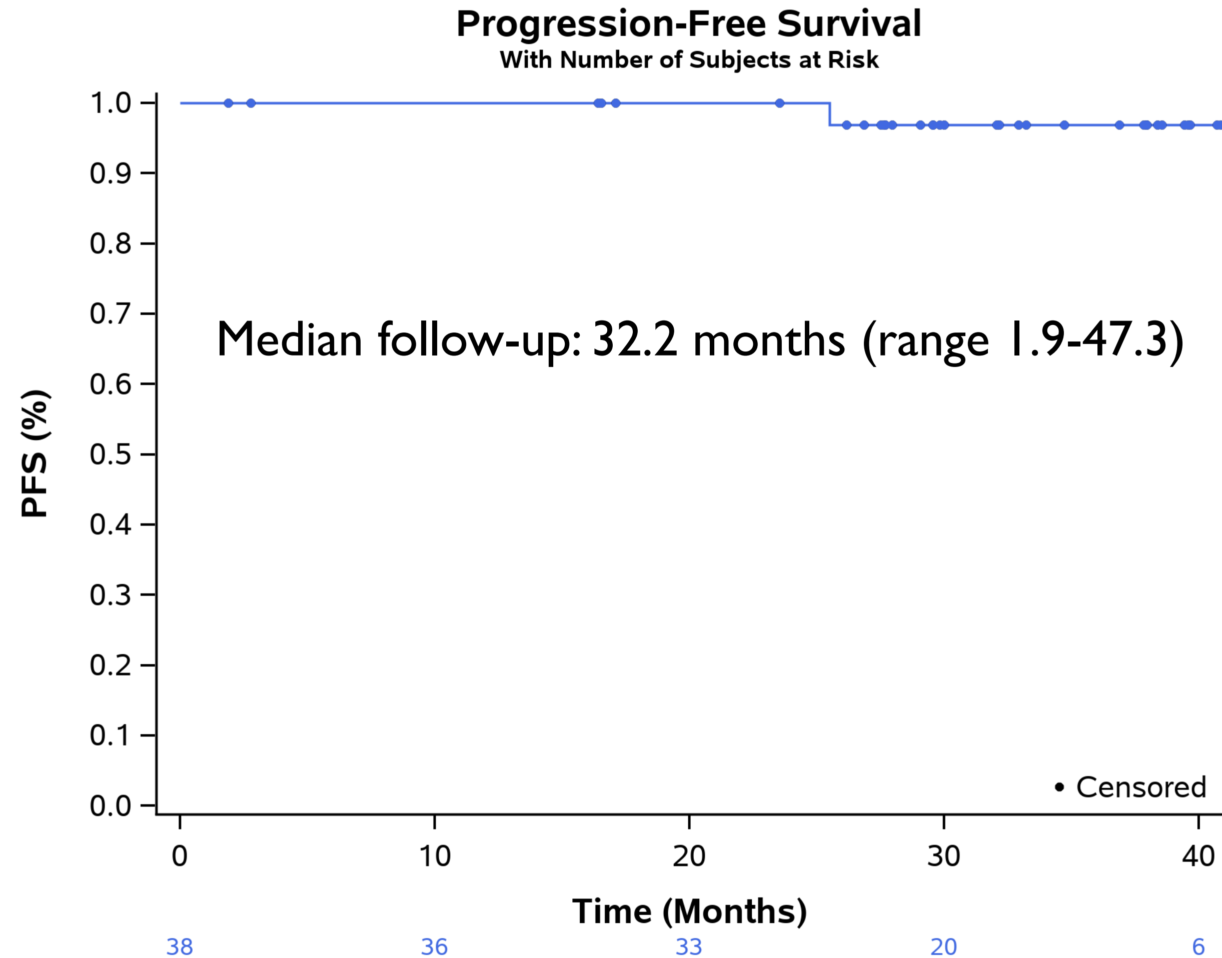




Mei MG et al, Blood 2022

Pembro-GVD as Salvage Treatment Strategy. 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%



Moskowitz A et al, ISHL2022 (with permission)

Data cut off: 10/6/2022

PD-1 Based Salvage Therapy for RR cHL: A Multicenter Real-World Analysis

Table 1 Patient characteristics

		N	%
Age at start of PD1	Median (min-max)	31 (19-69)	
Sex	Male	30	63.8
	Female	17	36.2
Number of prior therapy lines	Median (min-max)	2 (1-4)	
Salvage regimen	ICI mono	10	21.3
	Nivolumab	4/10	40
	Pembrolizumab	6/10	60
	ICI + Chemo	34	75.6
	P-GVD	30/34	88.2
	P-ICE	3/34	8.8
	N-ICE	1/34	2.9
	ICI + BV	3	6.4
	Pembro + Bv	1/3	33.3
	Nivo + Bv	2/3	66.7
Consolidation [a]	Allogenic SCT [b]	6	12.8
	Autologous SCT	37	78.7
	No SCT [c]	4	8.5
Consolidating regimen *(of auto/allo pts.)*	BEAM	36	83.7
	TEAM	1	2.3
	TBI + Cyclo + ATG	2	4.7
	Flu + Treo + ATG	4	9.3
Ann Arbor stage at relapse	II	12/34	35.3
	III	08/34	23.5
	IV	14/34	41.2
B-Symptoms at relapse	yes	13/32	40.6
	no	19/32	59.4
ECOG at relapse	0	21/33	63.6
	1	12/33	36.4
Bulky disease at relapse	yes	11/34	32.4
	no	23/34	67.6

[a] None of the patients had a second HDCT; [b] 5/6 allogeneic SCT patients had prior HDCT; [c] Of the 4 patients without consolidation: 2 withdrew consent, 1 had toxicity (pneumonitis), 1 died prior allo-SCT.

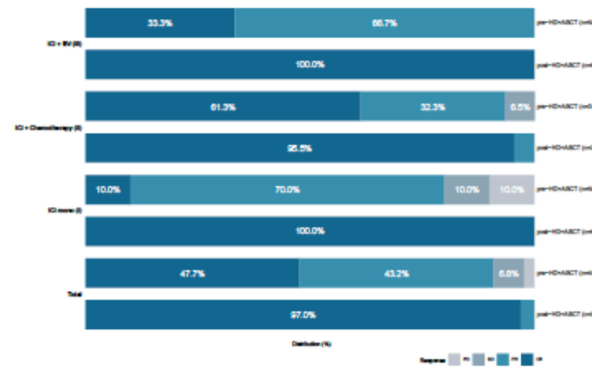
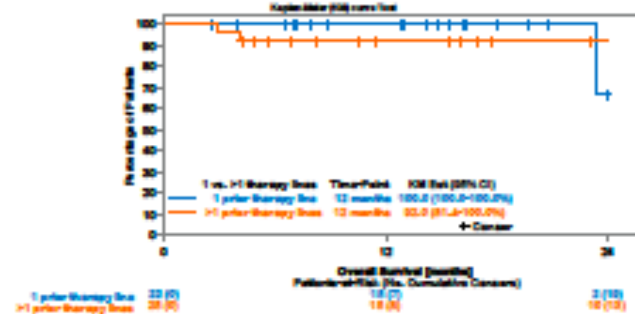
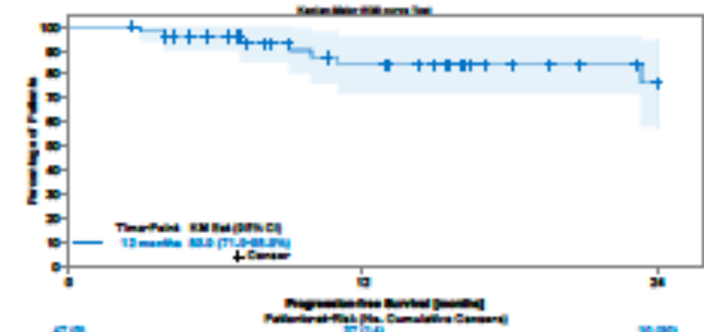


Figure 3 Best overall response, split by treatment group

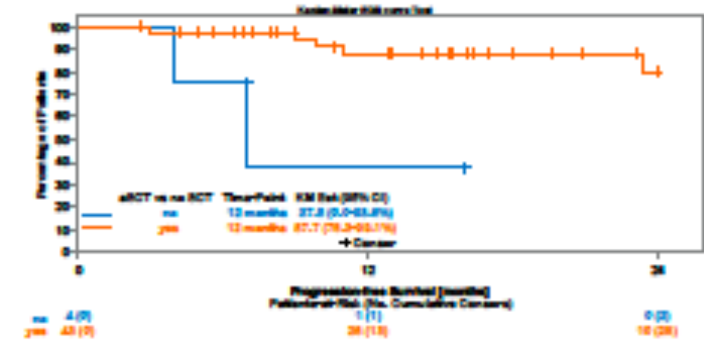
Overall survival, split by treatment lines



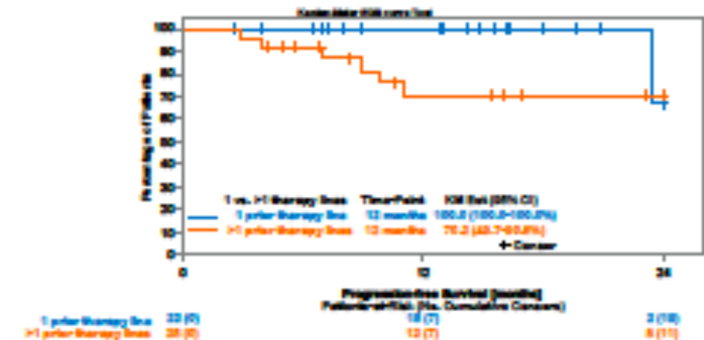
Progression-free survival of all patients



Progression-free survival, split by consolidating HD-CT/allo vs. none



Progression-free survival, split by treatment lines



Tharmaseelan H et al, EHA2025

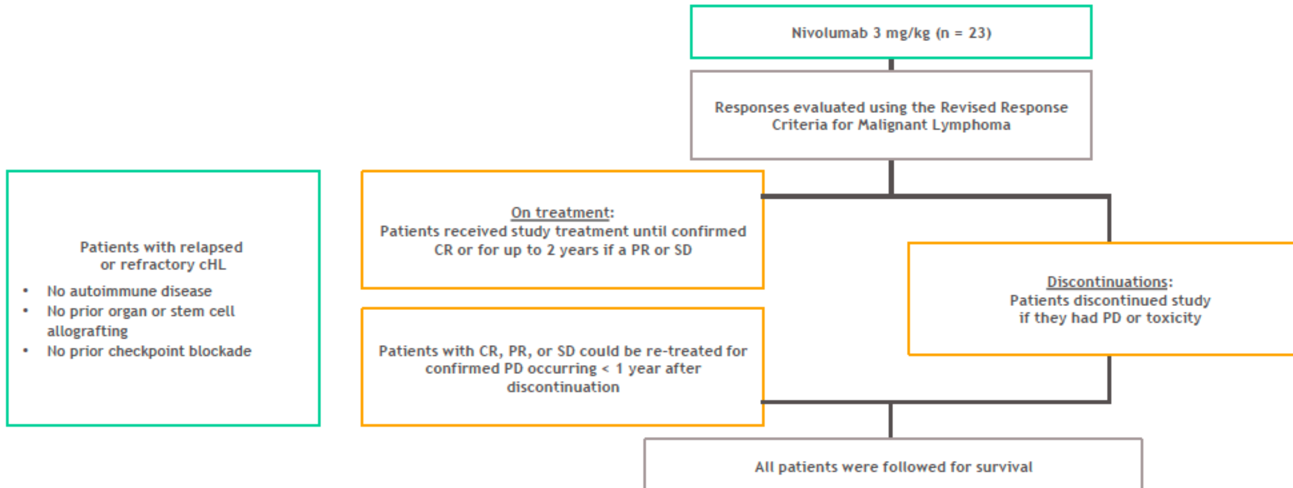
We do not Have Data on How Failures after BRECADD Can Be Rescued!!!

CPIs Based Therapies

When CPIs are Included in 1L, can We Consider Retreatment?

- PD-1 retreatment is an important emerging concept
- Patients relapsing after elective discontinuation may respond again
- Retreatment appears more effective after treatment discontinuation than progression on therapy
- PD-1 exposed disease is not equivalent to PD-1 refractory disease
- True PD-1 resistance remains a major unmet need

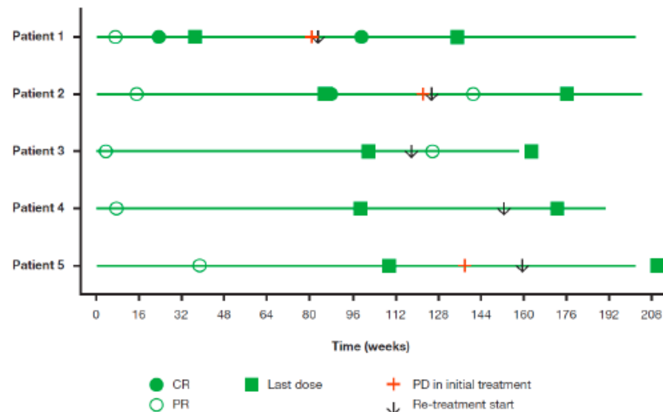
Retreatment with CPIs. Lessons from Study 039



Treatment Outcomes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Initial treatment period					
BOR	CR	CR	PR	PR	PR
DOR (weeks)	74	107	110	169	99
DOT (weeks)	37	85	102	98	109
Off-therapy time to progression (weeks)	44	37	12	< 54	29
Re-treatment					
BOR	CR	PR	PR	NA	NA
Duration of response (weeks)	34	8	15	NE	NE
Time to best response (weeks)	18	16	9	NE	NE
Duration of re-treatment (weeks)	52	24	30	20	51
Total time from start of nivolumab treatment to last re-treatment dose (weeks)	135	149	148	172	210

Duration of Response



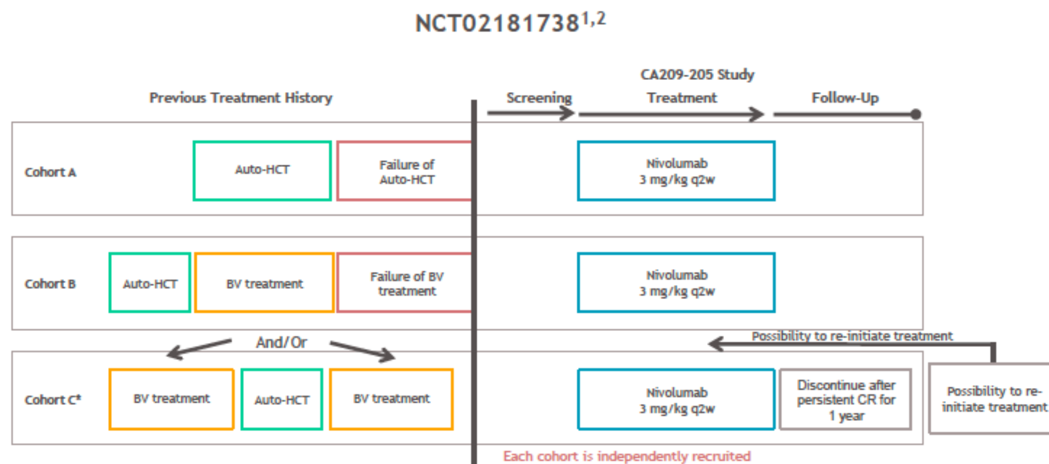
Adverse Events

Phase	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Initial	Lymphopenia (G3) Fatigue (G1)	Pruritus (G1)	GERD (G2) Increased lipase (G1)	Anorexia (G1) Asthenia (G1, G2) Bronchospasm (G1) Dyspnea (G1) Increased ALK (G1) Lung infection (G2) Peripheral neuropathy (G2) Pneumonia (G2) Stomatitis (G1) Thrombocytopenia (G1, G2)	Nausea (G2) Increased lipase (G1, G2)
Re-treatment	Decreased neutrophil count (G1, G2)	-	Increased CPK (G1) Increased amylase (G1) Increased lipase (G1)	-	-

Ansell S et al, ISHL11

CheckMate 205 Cohort C Allowed Patients in Persistent CR for 1 Year to Stop Therapy. Retreatment Strategy

- In Cohort C, patients discontinue treatment after persistent CR for 1 year



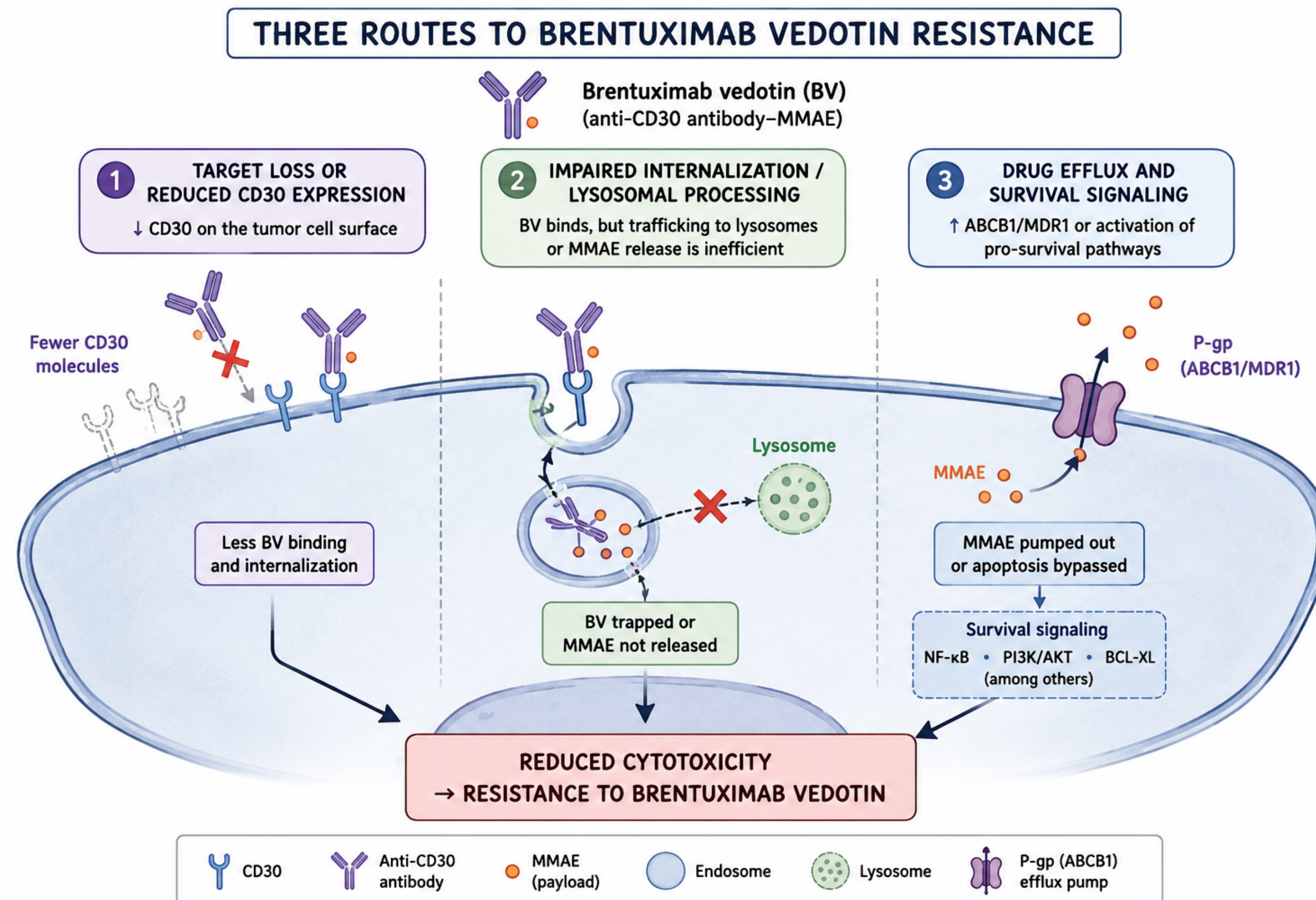
	CM205 Cohort C	
	Patient 1	Patient 2
Baseline		
Age, years	53	30
Sex	F	F
ECOG performance status	1	1
Initial treatment period		
BOR	PR	CR
Re-treatment		
BOR	PR	PR

Ansell S et al, ISHL11

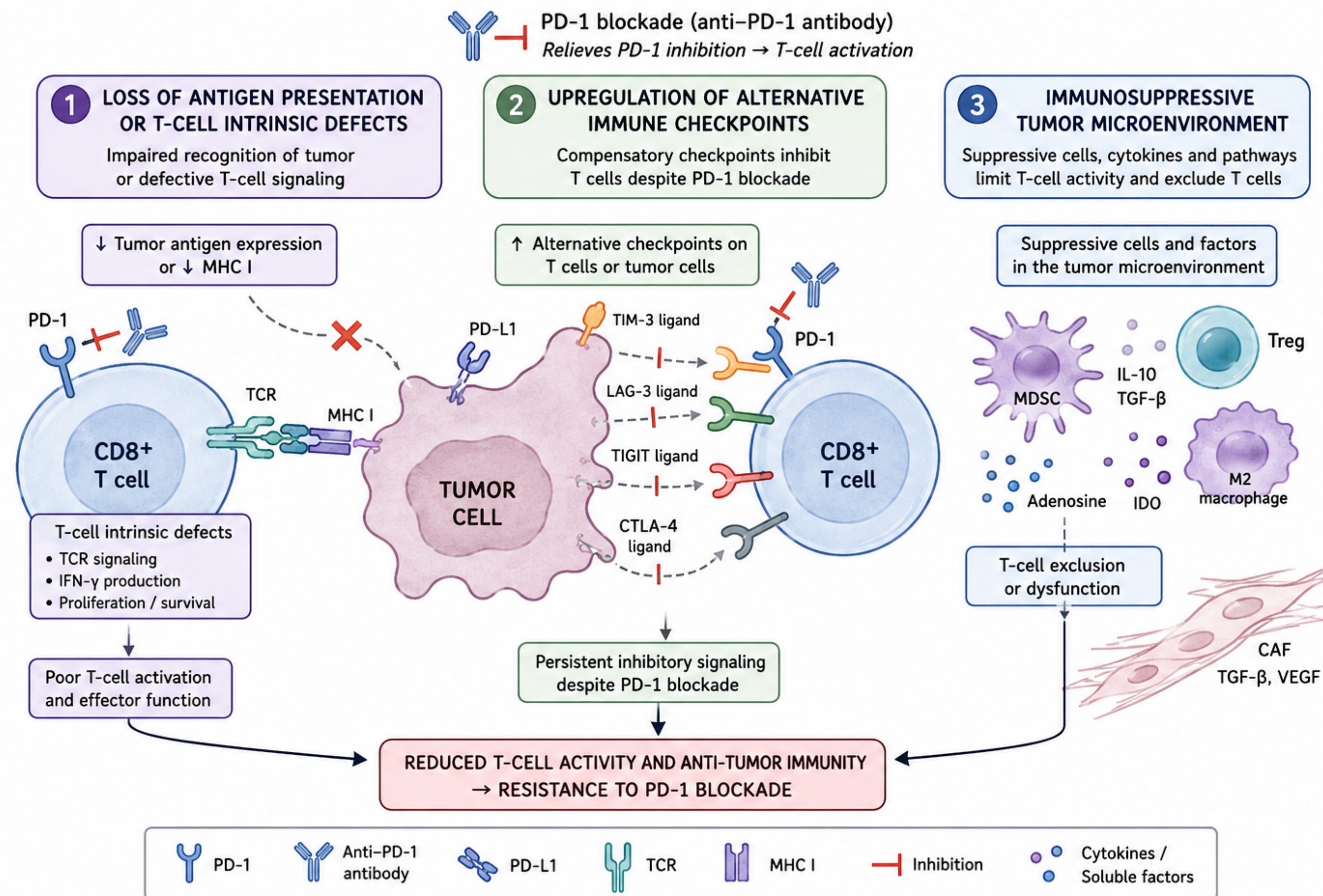
We do not Have Data on How Failures after N-AVD Can Be Rescued!!!

BV Containing Protocols (?)
CPIs Based Therapies (?)

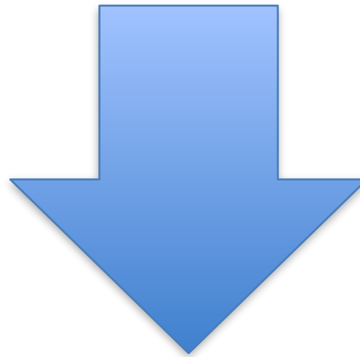
We Need to Better Understand the Mechanisms of Brentuximab Vedotin Resistance



We Need to Better Understand the Mechanisms of PD-1 Resistance



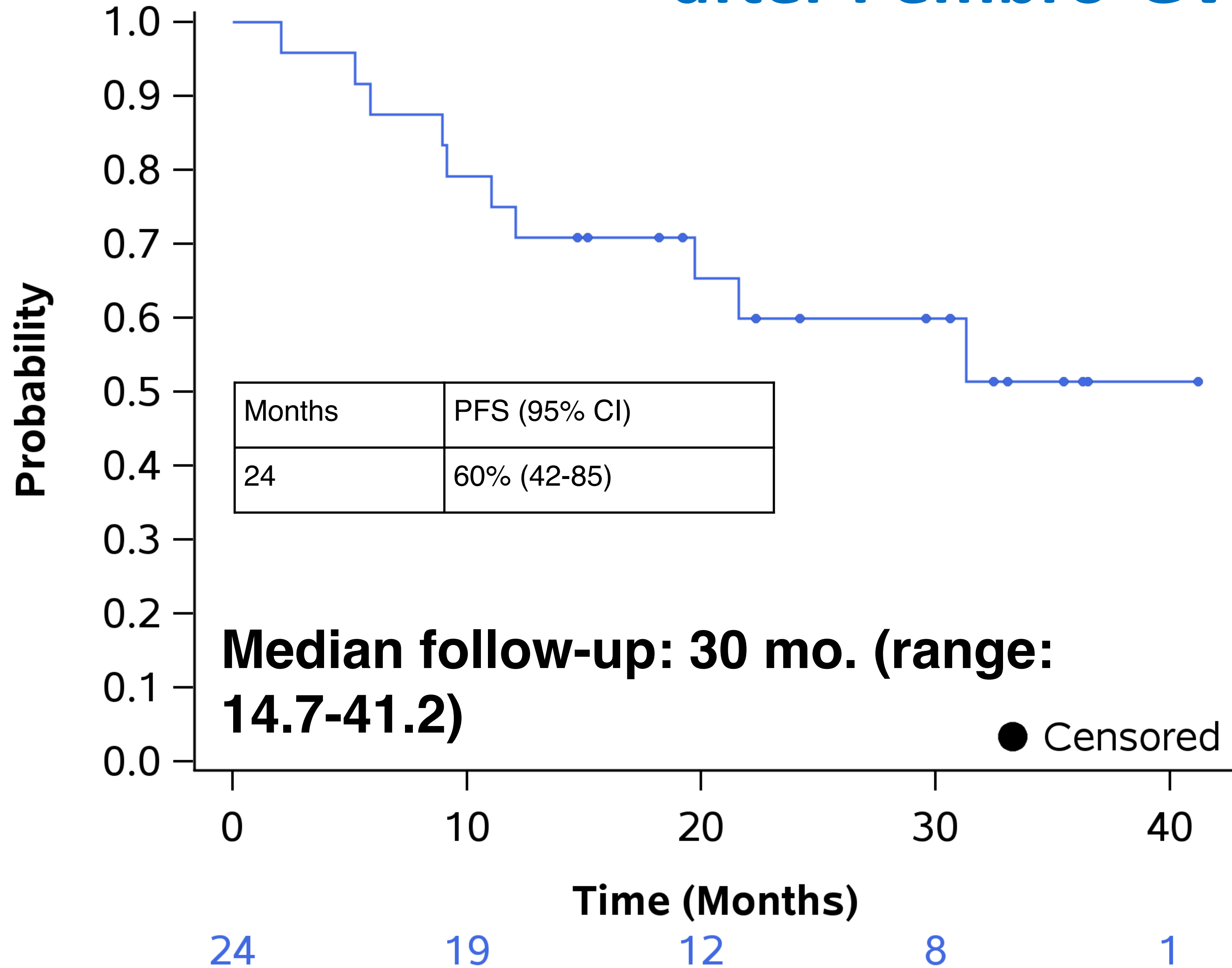
We Need to Better Understand the Mechanisms of Resistance



Relapse biology may increasingly guide salvage therapy decisions

Is Still Auto-HCT Mandatory in RR Patients in the Era of New Drugs?

Pembro Maintenance Instead of Transplant for pts in CR after Pembro-GVD: PFS



Months	PFS (95% CI)
24	60% (42-85)

10 relapses:

- 4 pts during pembro maintenance
- 3 pts within 6 months of last pembro
- 3 pts beyond 6 months of last pembro

9 pts proceeded to transplant following:

- BV/benda (n=1)
- BV-ICE (n=1)
- ICE (n=1)
- BV/nivo, ICE, RT (n=2)
- Pembro-GVD (n=2)
- Pembro-GVD, ICE (n=1)

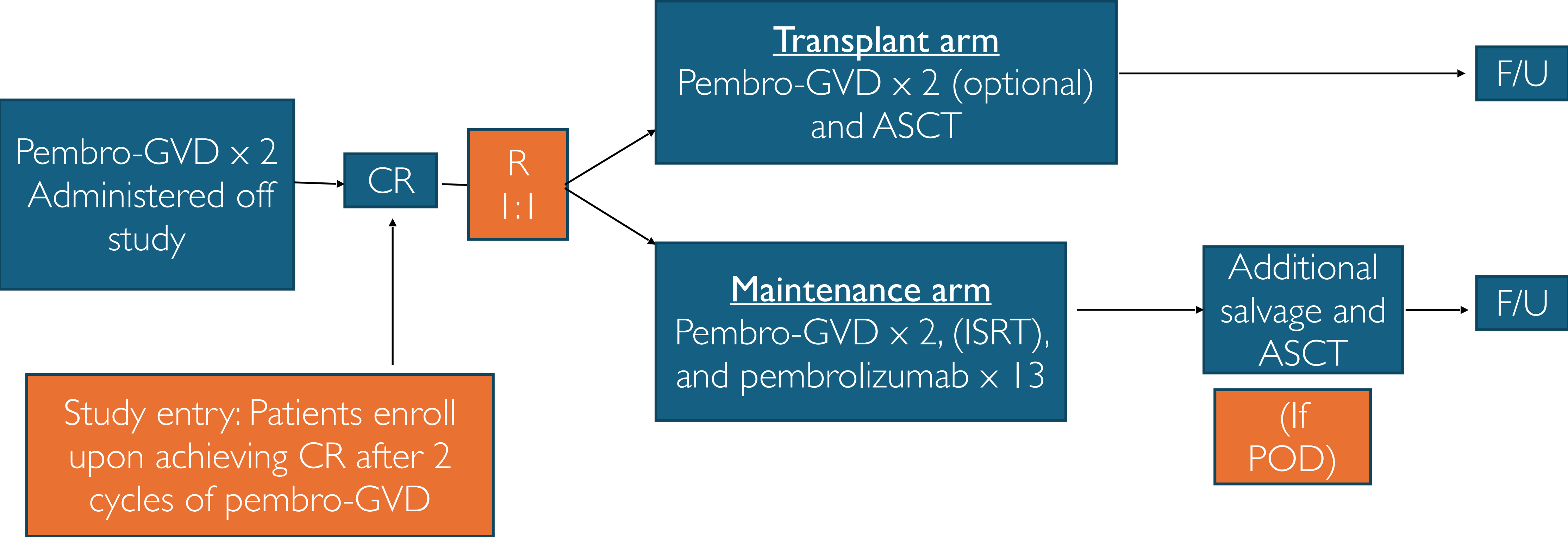
1 pt not transplanted due to comorbidities

- receiving palliative pembro plus gemcitabine, achieved CR

Moskowitz A et al, ISHL13

Data cut off: 9/20/2024

Phase II Randomized, Non-Inferiority Study Evaluating Immediate vs Delayed Transplant for Stage I-III rel/ref HL



Primary endpoint: Freedom from disease at 5 years post-randomization. Patients to be stratified according to use of front-line PD-1 blockade n=178

Moskowitz A (with permission)

Long Term Outcome of Patients Undergoing Consolidation with BV (n = 80). The BRESELIBET Trial

Sureda A et al, ISHL13

Toward Personalized Salvage Therapy

Future salvage strategies may depend on:

- Prior frontline exposure
- PET kinetics
- ctDNA
- Immune profiling

The era of 'one salvage fits all' is ending

Potential Future Treatment Algorithm

- ABVD relapse → BV / PD-1–based salvage ± auto-HCT
- BV-exposed relapse → checkpoint inhibitor combinations
- PD-1–exposed relapse → chemotherapy (?), cellular therapies (?) or clinical trials (?)
- Double-refractory disease remains a major unmet need
- Treatment sequencing will become increasingly individualized

Take-Home Messages

- Frontline advances are redefining relapse management in cHL
- Second-line therapy is becoming more immune-based and personalized
- Retreatment with BV or PD-1 blockade may remain feasible in selected patients
- Auto-HCT remains important but its role may evolve
- Future progress depends on precision medicine and novel immune strategies
- The selection of second line treatment strategies is still highly dependent on geographical access and reimbursement to targetted therapies