How I treat plasmablastic lymphoma

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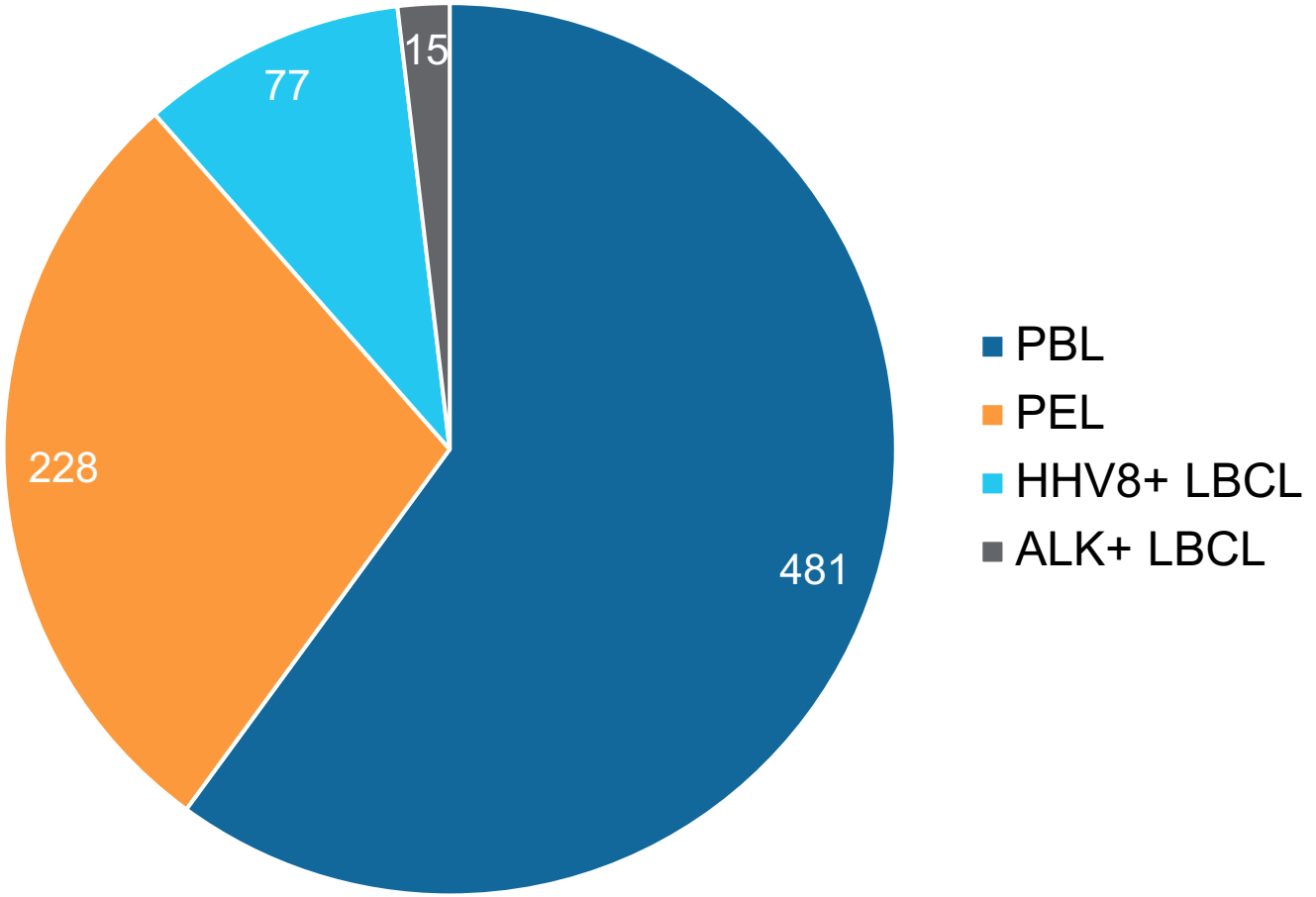
Disclosures

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board
AbbVie	X		X			X
AstraZeneca	X					
BeiGene	X		X			X
Cellectar	X		X			X
Janssen	X		X			
Kite						X
LOXO	X					
Pharmacyclics	X		X			X
Roche			X			
TG Therapeutics	X					

Survival of patients with CD20-negative variants of large B-cell lymphoma: an analysis of the National Cancer Data Base

NCDB

- A joint project of the Commission on Cancer of the American College of Surgeons
- Accounts for 84% of all US cases
- Data on PEL since 2004
- Data on PBL, ALK+ LBCL and HHV8+ LBCL since 2010
- 2008 WHO Classification



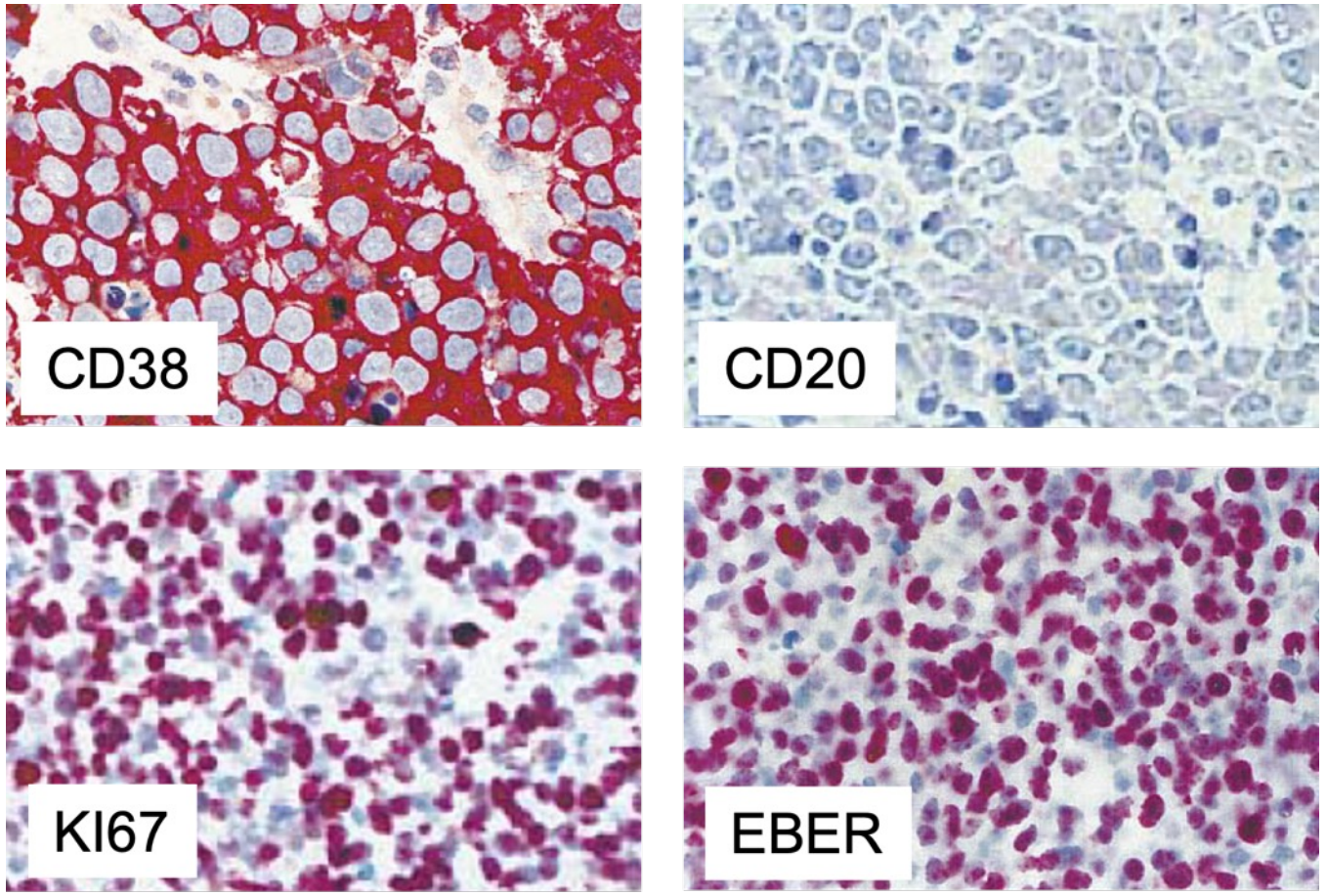
How do we diagnose plasmablastic lymphoma?

Plasmablastic Lymphomas of the Oral Cavity: A New Entity Associated With the Human Immunodeficiency Virus Infection

Patients' characteristics

- n=16
- 14 men
- 15 HIV+
- 11 stage I; 5 stage IV
- 6 chemo; 4 RT; 6 chemo-RT
- 10 died; 2 alive; 4 unknown
- Median OS 6 months

Delecluse et al. Blood 1997



PBL is a real and distinct entity

HIV-associated plasmablastic lymphoma: Lessons learned from 112 published cases

TABLE I. Demographics, HIV Status, and Antiretroviral Therapy of Patients with HIV-Associated PBL

	N	%
Age (n = 112)		
Median (years)	38	
Range (years)	7–65	
Sex (n = 107)		
Male	94	88
Female	13	12
CD4 count (n = 28)		
Median (cells/mm^3)	178	
Range (cells/mm^3)	10–498	
Duration of HIV infection (n = 18)		
Median (years)	5	
Range (years)	0–20	
HAART (n = 25)		
Before	16	64
Concurrent	6	24
After	3	12

Castillo et al. Am J Hematol 2008

TABLE III. Lymphoma and Therapy-Related Characteristics of Patients with HIV-Associated PBL

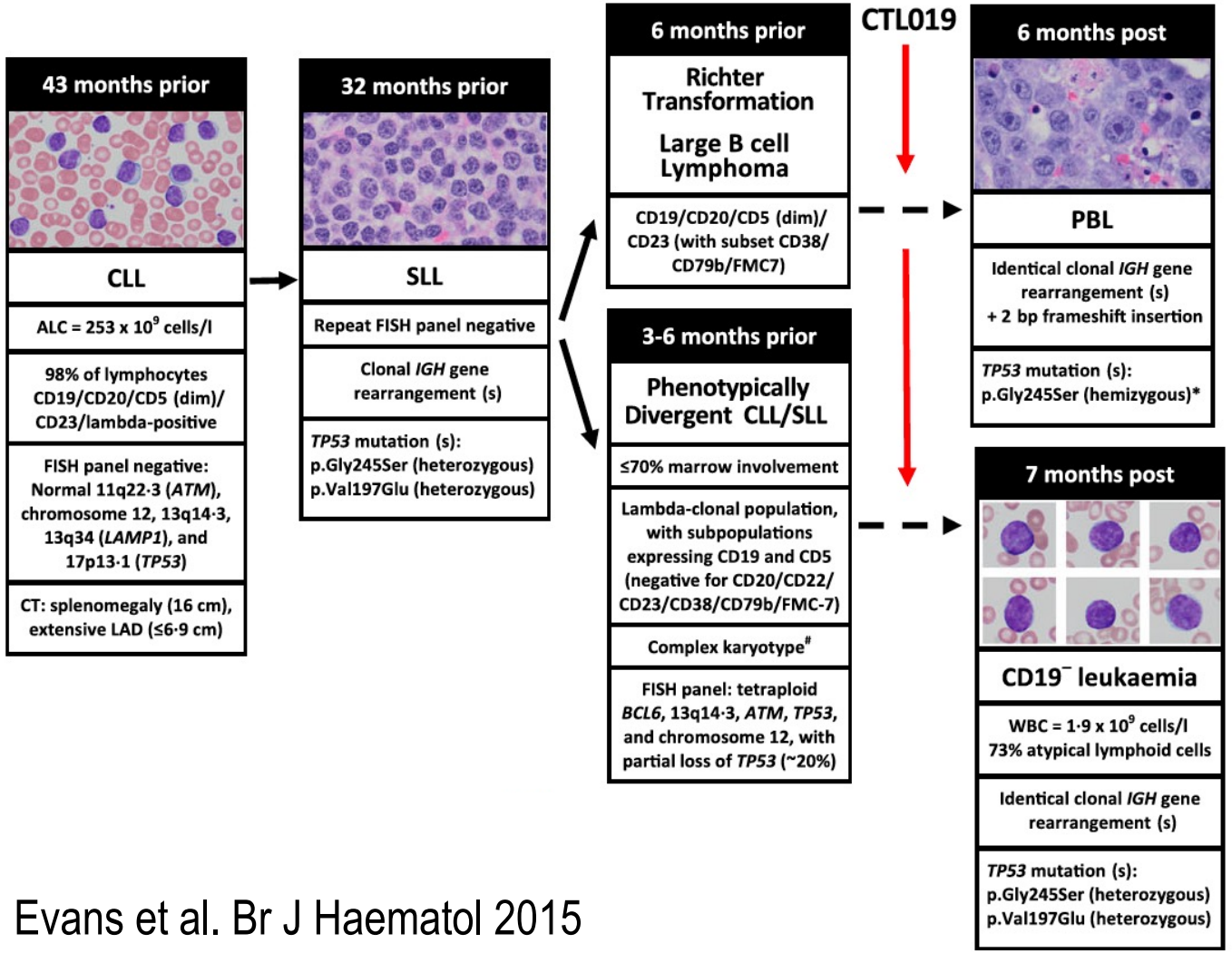
	N	%
Ann arbor stage (n = 85)		
I	49	58
II	2	2
III	0	0
IV	34	40
Primary lymphoma site (n = 112)		
Oral	65	58
Gastrointestinal tract	14	13
Lymph nodes	7	6
Other extranodal nonoral sites[a]	26	23
Therapy (n = 53)		
CHOP alone	16	30
Other chemotherapy regimens	13	25
Chemoradiotherapy (including CHOP)	11	21
Other therapies[b]	7	13
No therapy	6	11
Outcome (n = 55)		
Alive	26	47
Dead	29	53

Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma

	All patients	HIV-positive	HIV-negative	*p*-Value
Total	228 (100%)	157 (69%)	71 (31%)	—
Age ($n=223$)				
Older than 60 years	35 (16%)	2 (1%)	33 (47%)	<0.0001
60 years or younger	188 (84%)	151 (99%)	37 (53%)	
Mean age (range)	45 (1–90)	39 (3–65)	58 (1–90)	<0.0001
Sex ($n=228$)				
Male	172 (75%)	128 (82%)	44 (62%)	0.0026
Female	56 (25%)	29 (18%)	27 (38%)	
Stage ($n=174$)				
I	56 (32%)	42 (37%)	14 (23%)	0.3760*
II	23 (13%)	13 (12%)	10 (16%)	
III	10 (6%)	1 (1%)	9 (15%)	
IV	85 (49%)	57 (50%)	28 (46%)	
Site of involvement ($n=213$)				
Oral	98 (46%)	88 (58%)	10 (16%)	<0.0001
Extraoral	115 (54%)	64 (42%)	51 (84%)	
Bone marrow ($n=83$)				
Involved	25 (30%)	17 (30%)	8 (30%)	0.8511
Not involved	58 (70%)	39 (70%)	19 (70%)	
B symptoms ($n=69$)				
Present	28 (41%)	15 (33%)	13 (54%)	0.1553
Absent	41 (59%)	30 (67%)	11 (46%)	
Therapy ($n=120$)				
Chemotherapy	94 (78%)	59 (77%)	35 (81%)	0.7059
No chemotherapy	26 (22%)	18 (23%)	8 (19%)	
Response to therapy ($n=78$)				
Complete response	38 (49%)	23 (55%)	15 (42%)	0.0208*
Partial response	16 (21%)	11 (26%)	5 (14%)	
Stable disease	6 (8%)	0 (0%)	6 (16%)	
Progressive disease	18 (23%)	8 (19%)	10 (28%)	

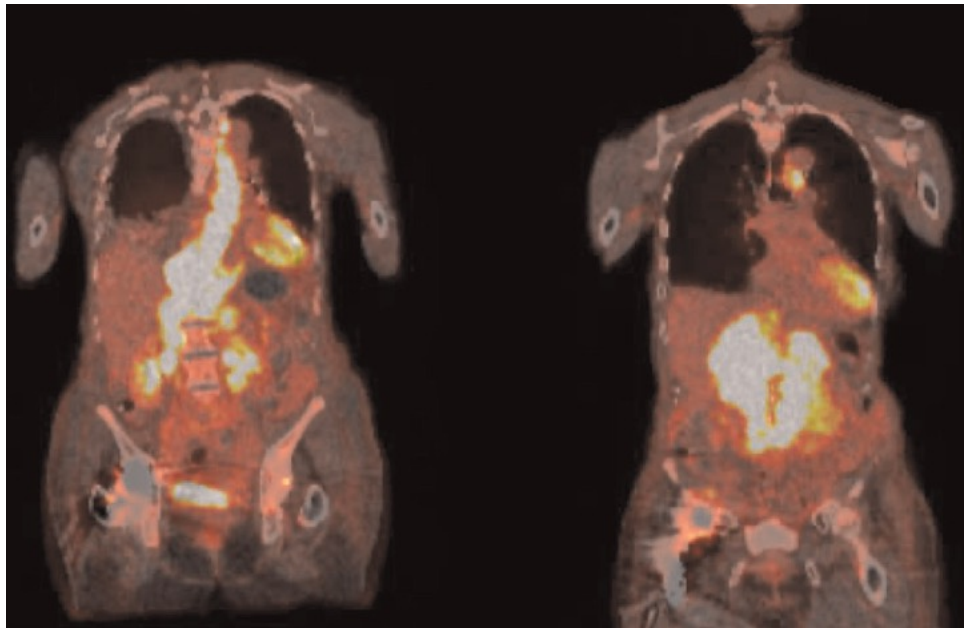
Castillo et al. Leuk Lymphoma 2010

Evolution to plasmablastic lymphoma evades CD19-directed chimeric antigen receptor T cells

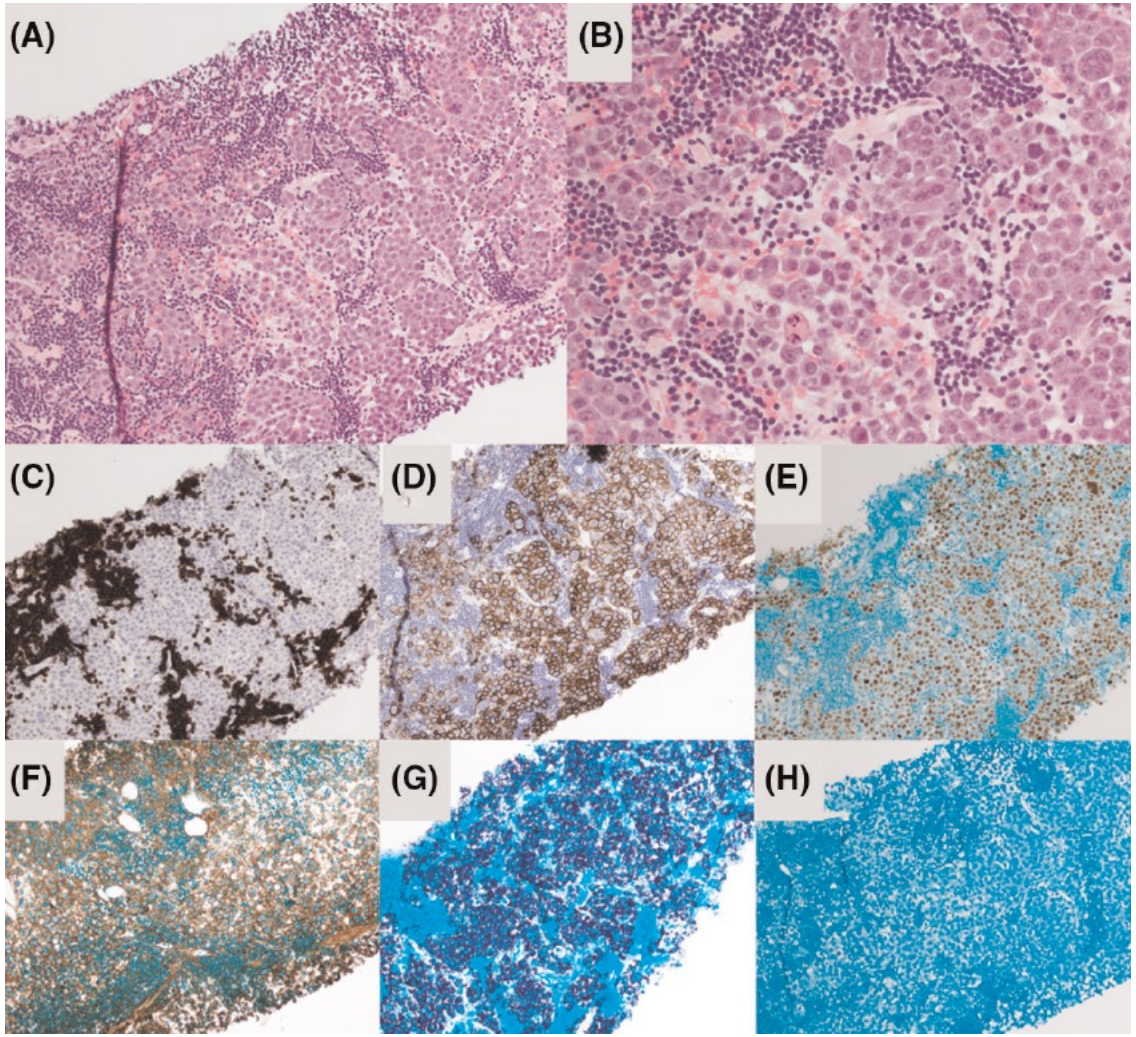


Evans et al. Br J Haematol 2015

Plasmablastic lymphoma transformation in a patient with Waldenström macroglobulinemia treated with ibrutinib



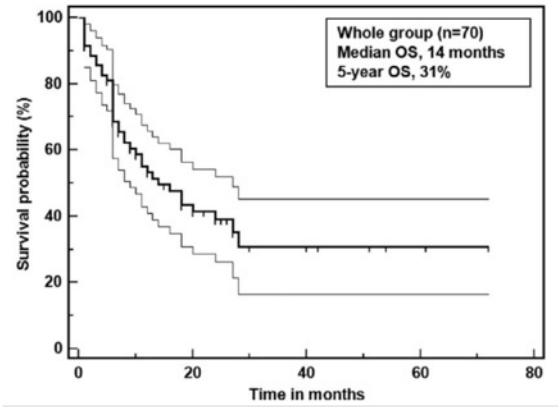
Castillo et al. Br J Haematol 2021

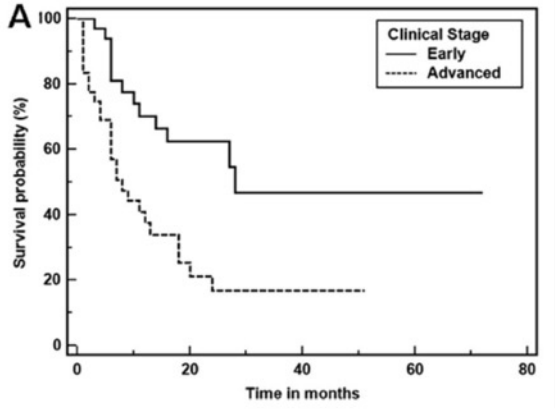


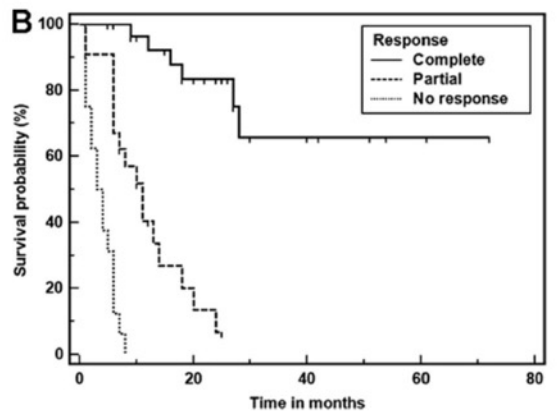
What is the prognosis of plasmablastic lymphoma?

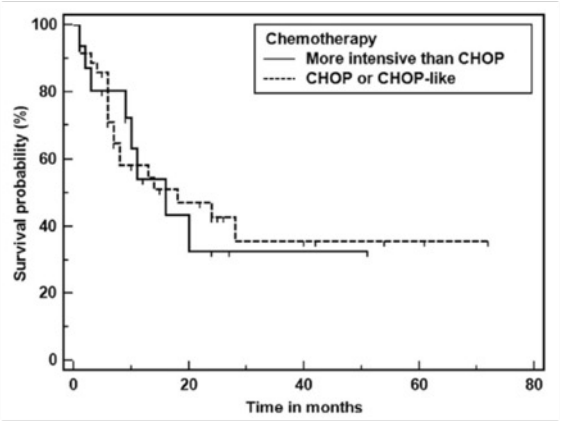
Prognostic Factors in Chemotherapy-Treated Patients with HIV-Associated Plasmablastic Lymphoma

Characteristic	*n*	Percentage
Age ($n = 70$)		
<40 yrs	28	40%
≥40 yrs	42	60%
$CD4^+$ cell count ($n = 29$)		
$<200/mm^3$	18	62%
$<100/mm^3$	13	45%
$<50/mm^3$	11	38%
Clinical stage ($n = 70$)		
Early (1 or 2)	34	49%
Advanced (3 or 4)	36	51%
Chemotherapy ($n = 70$)		
CHOP or CHOP-like	35	50%
More intensive than CHOP	16	23%
Other regimen	19	27%
Response to chemotherapy ($n = 70$)		
Complete response	32	46%
Partial response	22	31%
No response	16	23%



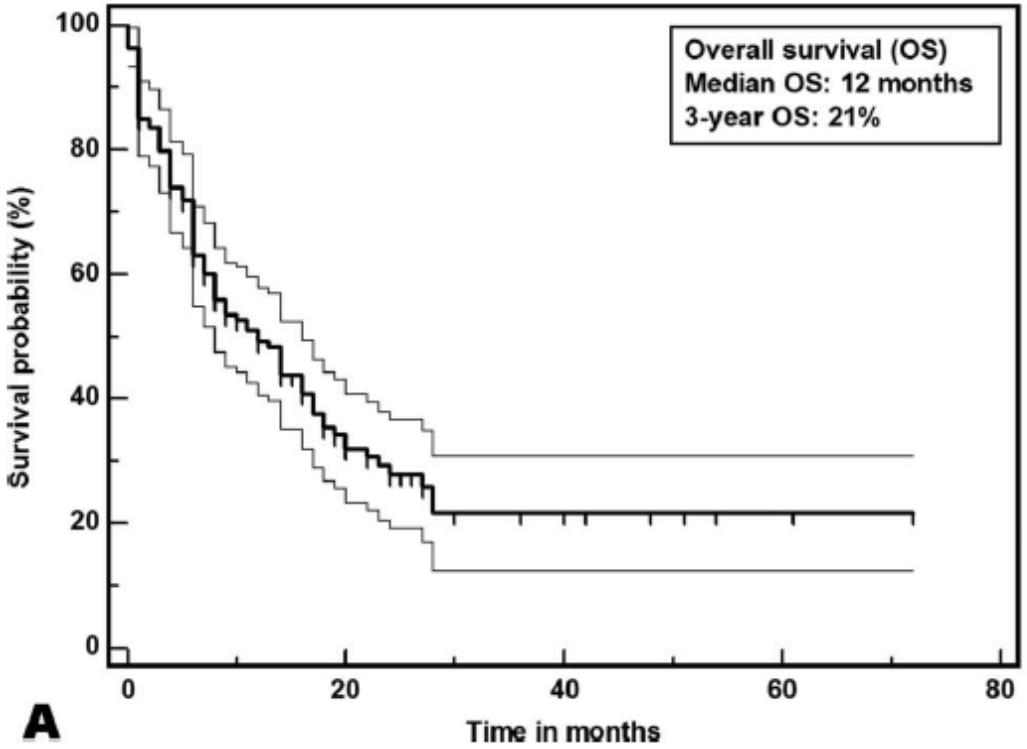


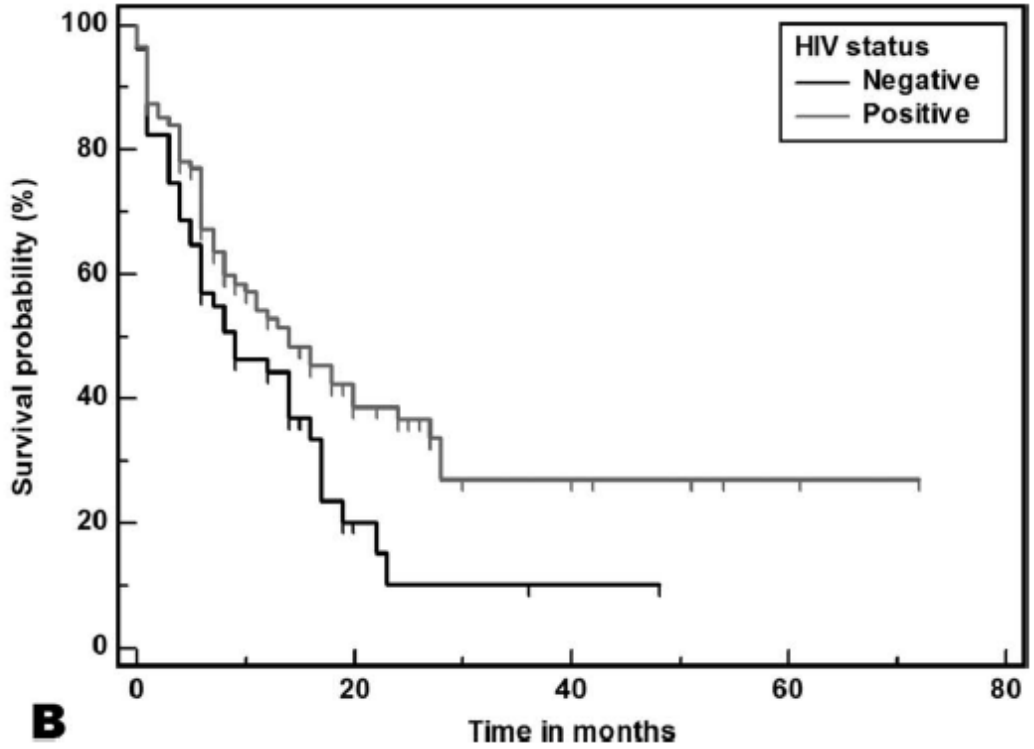




Castillo et al. Oncologist 2010

Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma

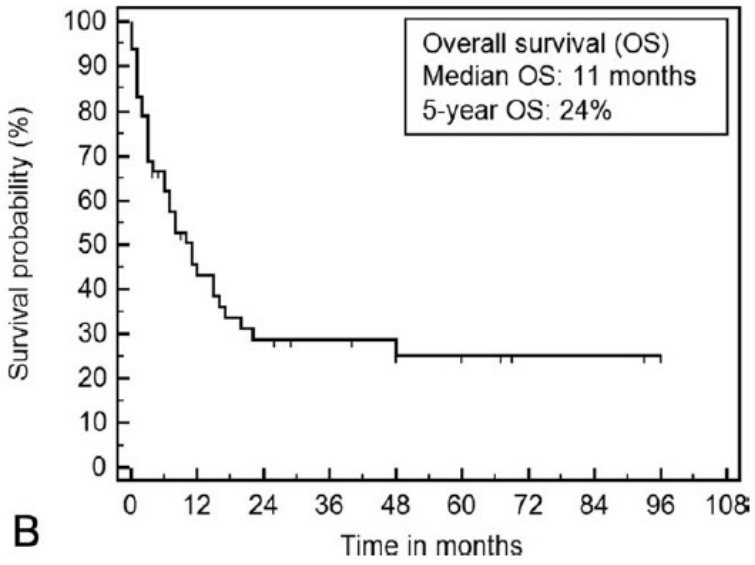


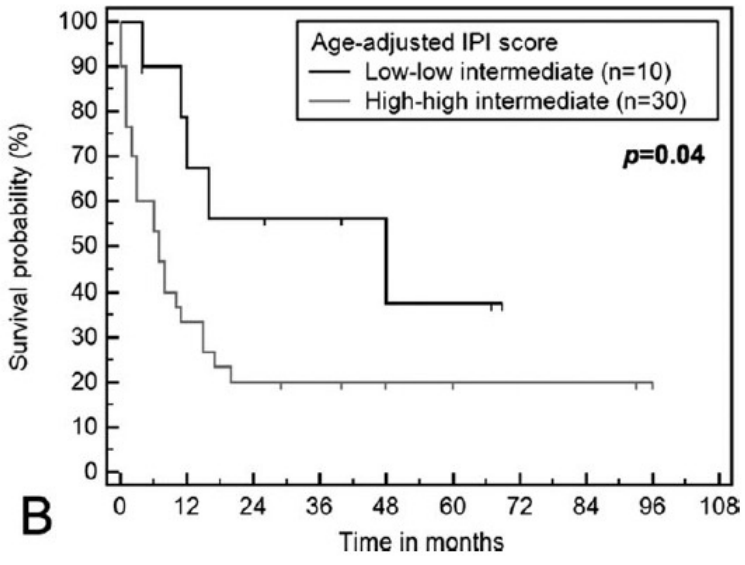


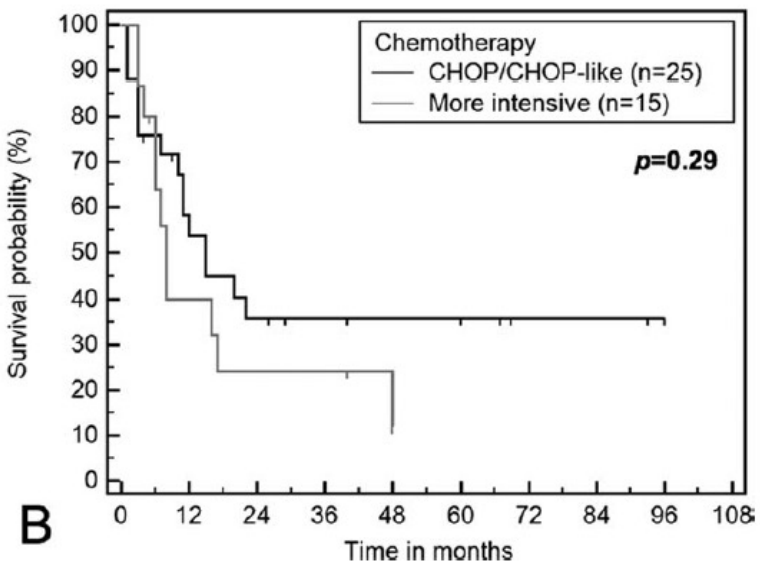
Castillo et al. Leuk Lymphoma 2010

There is PBL also in HIV-negative patients and it might have a worse survival

Human Immunodeficiency Virus-Associated Plasmablastic Lymphoma



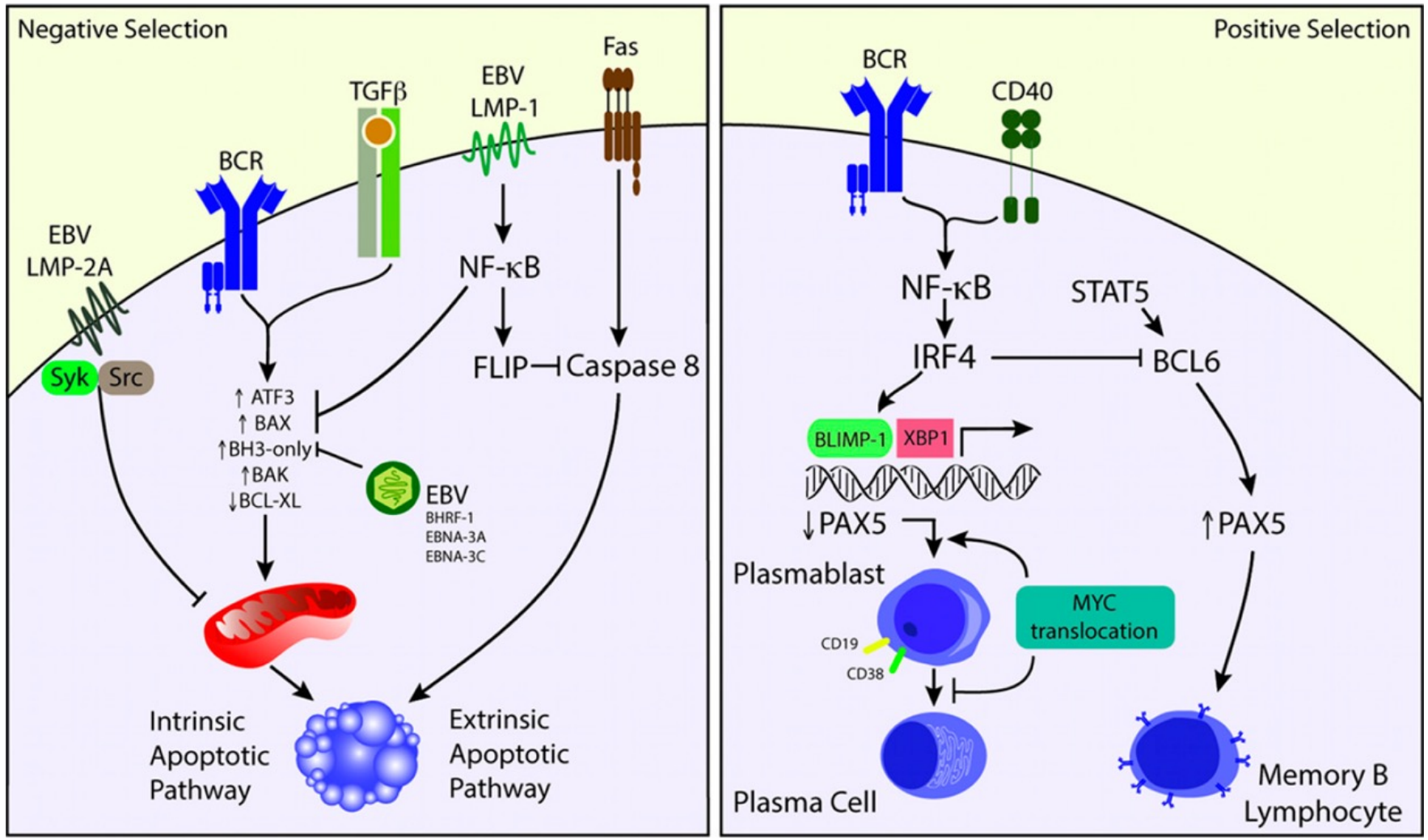




Castillo et al. Cancer 2012

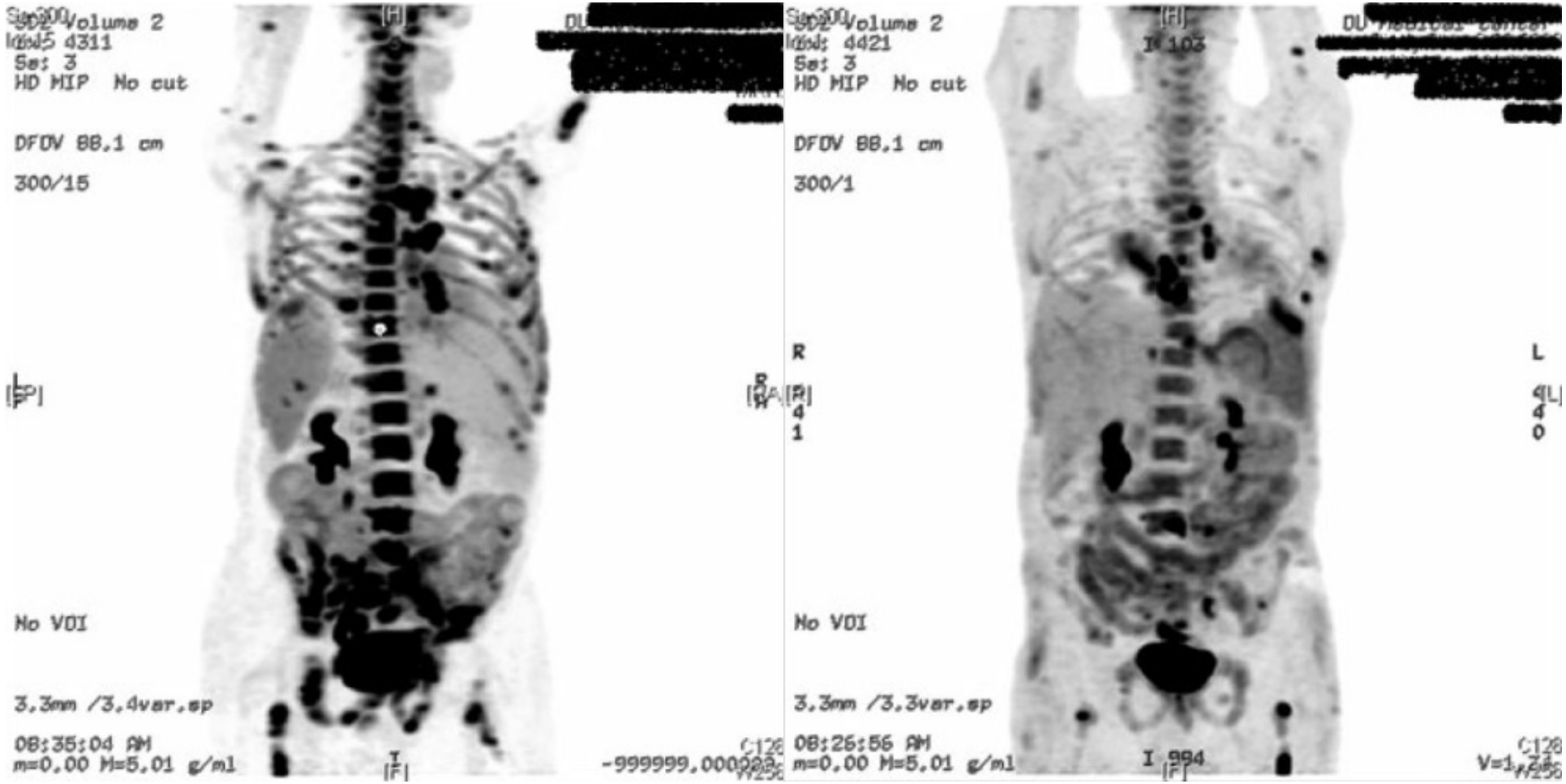
How do we improve outcomes in plasmablastic lymphoma?

The biology and treatment of plasmablastic lymphoma



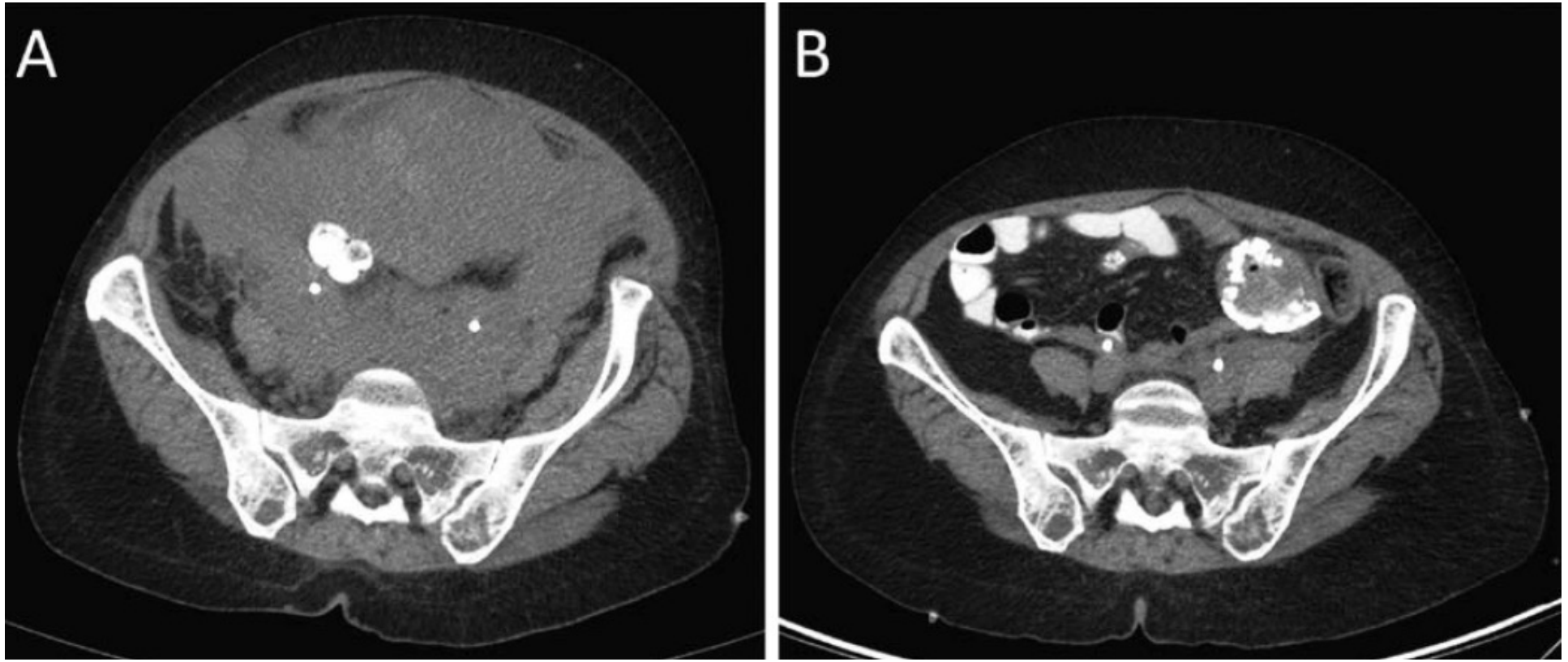
Castillo et al. Blood 2015

AIDS-related plasmablastic lymphoma with dramatic, early response to bortezomib



Bose et al. Eur J Haematol 2009

Bortezomib in Plasmablastic Lymphoma: A Case Report and Review of the Literature



Saba et al. Onkologie 2013

Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma

PATIENTS

Case 1

- 40M, HIV+, CD4 290, stage IV (rectal and pharyngeal), MYC+ 60%, EBER+, alive at 4 years

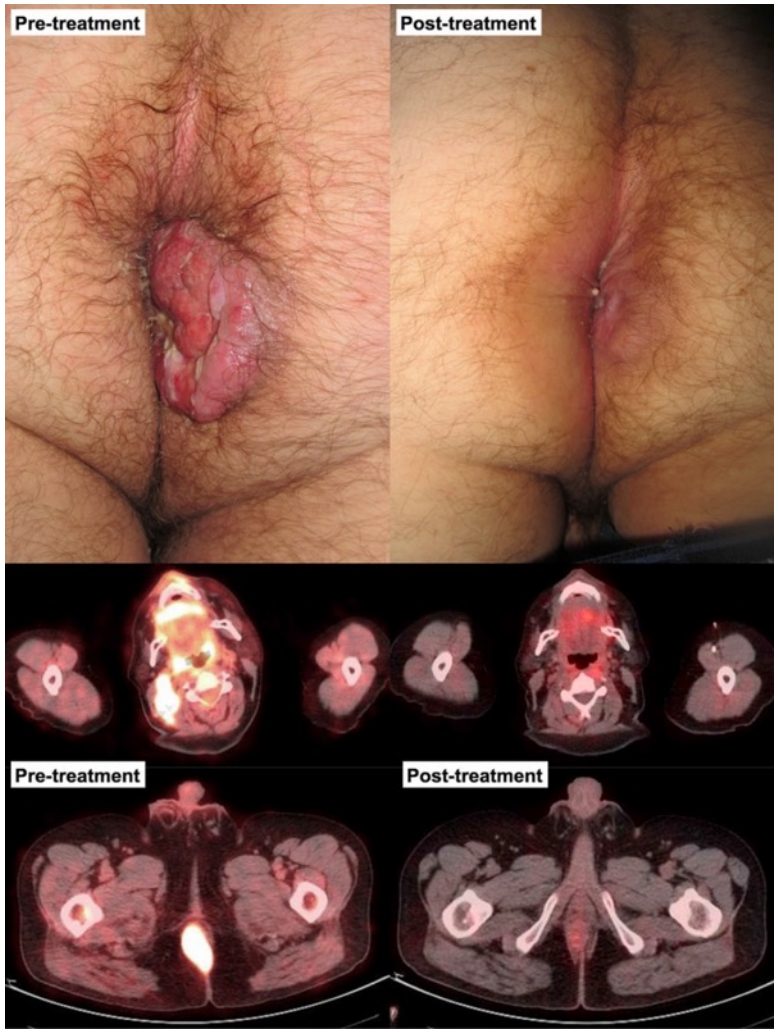
Case 2

- 36M, HIV+, CD4 34, stage IV (rectal and lung nodules), EBER+, alive at 3 years

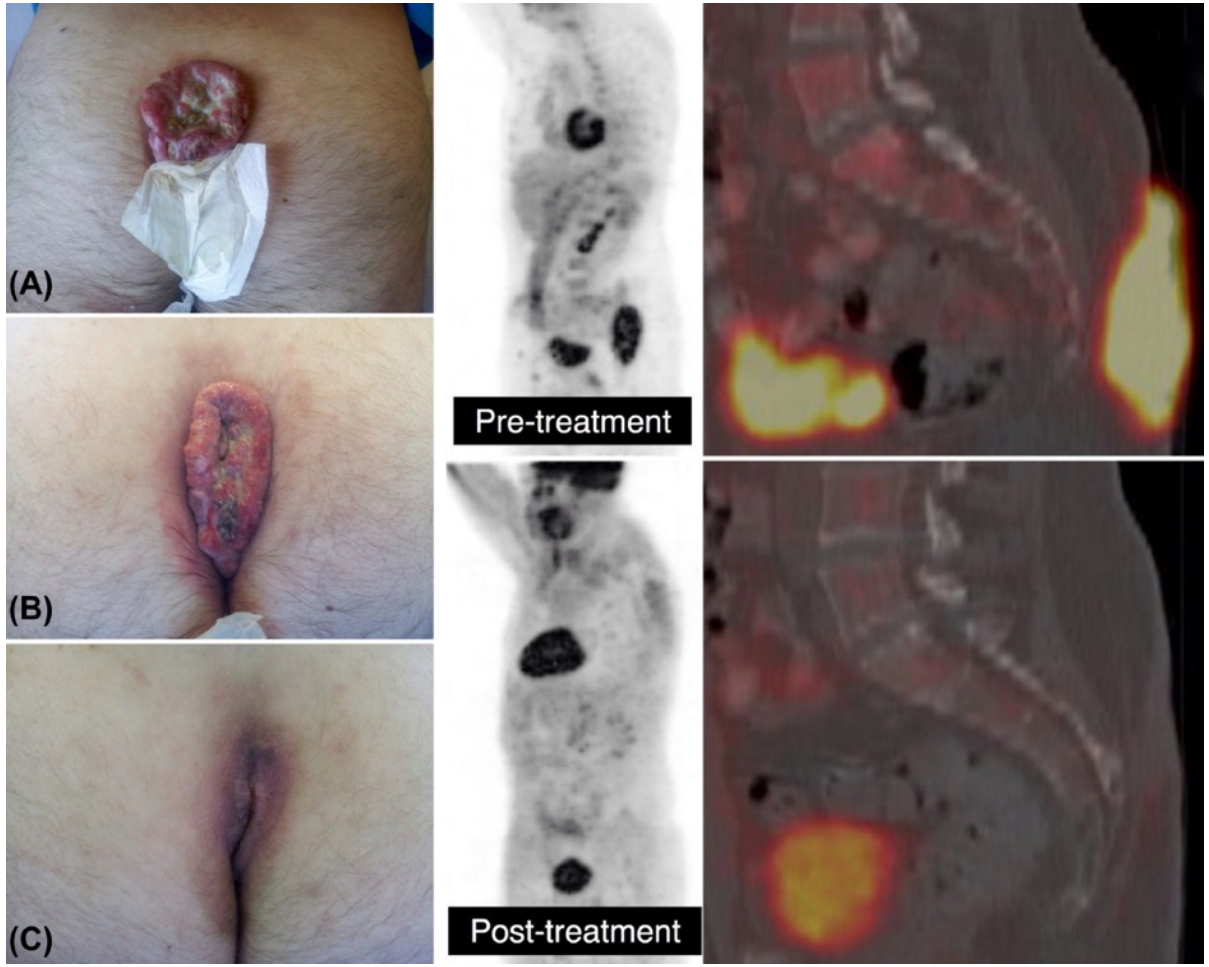
Case 3

- 66M, HIV-, stage II (non-obstructing colonic mass), MYC+ 15%, alive at 2.5 years

Castillo et al. Br J Haematol 2015



Bortezomib plus CHOP for the treatment of HIV-associated plasmablastic lymphoma: clinical experience in three patients



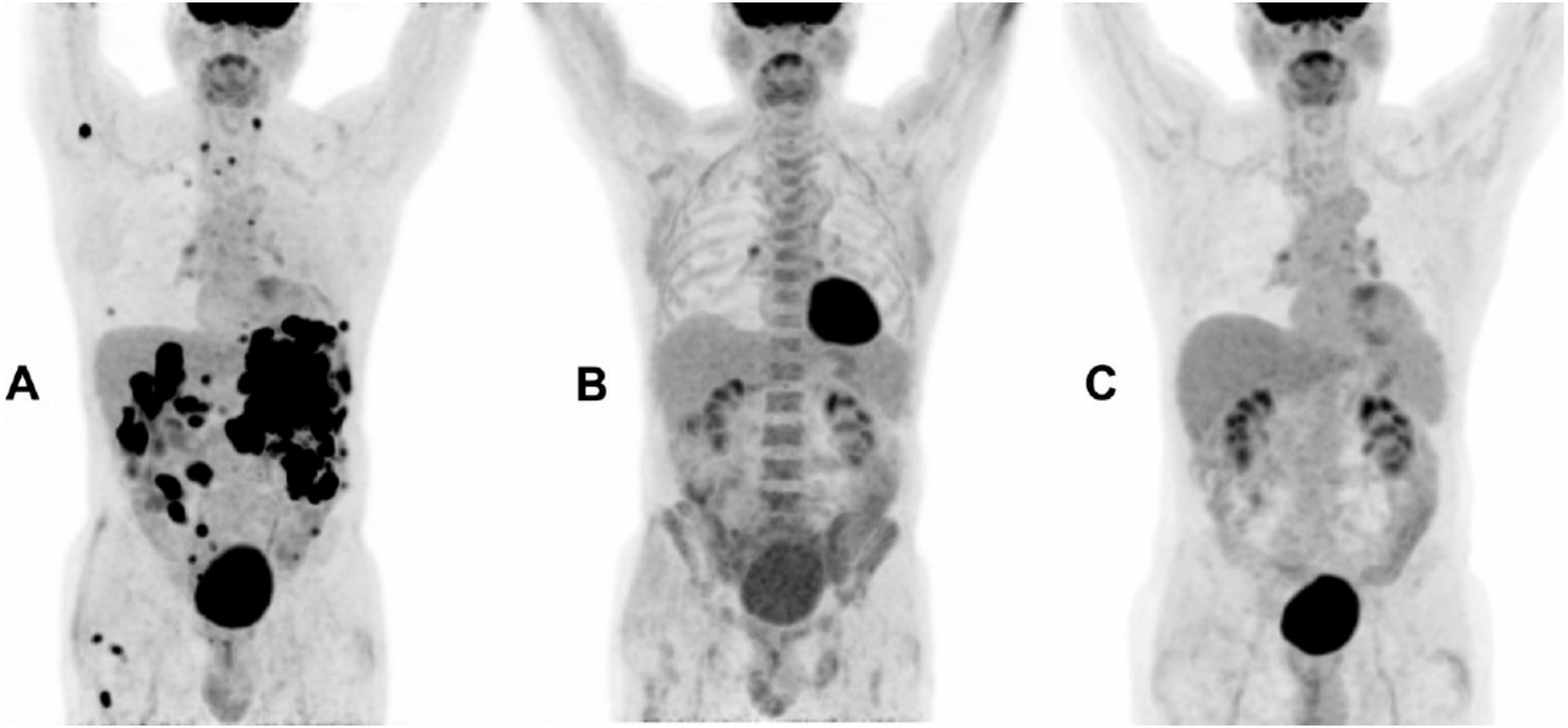
2 patients alive at 12 and 24 months

1 patient died at 12 months

Fernandez-Alvarez et al.
Leuk Lymphoma 2016

Infusional dose-adjusted epoch plus bortezomib for the treatment of plasmablastic lymphoma

Patient alive at 2 years



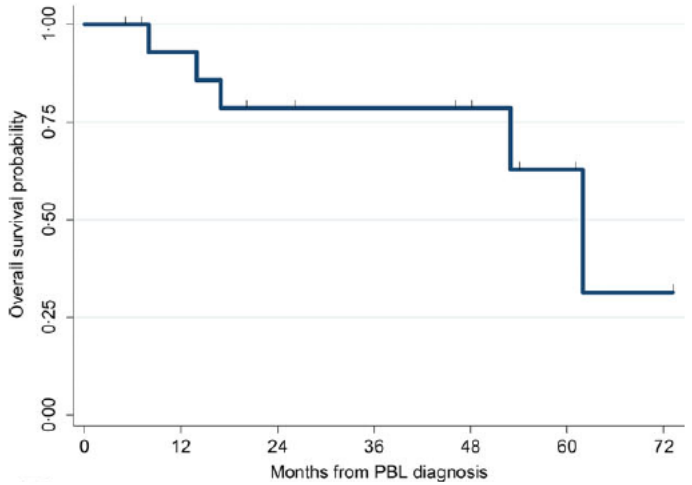
Fedele et al. Ann Hematol 2016

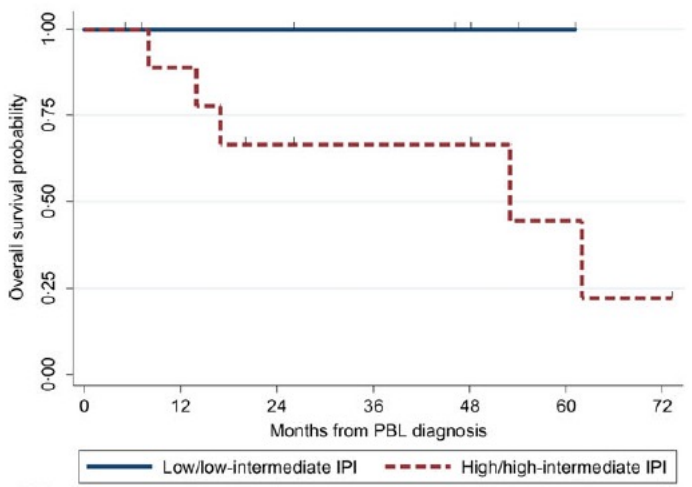
Bortezomib plus EPOCH is effective as frontline treatment in patients with plasmablastic lymphoma

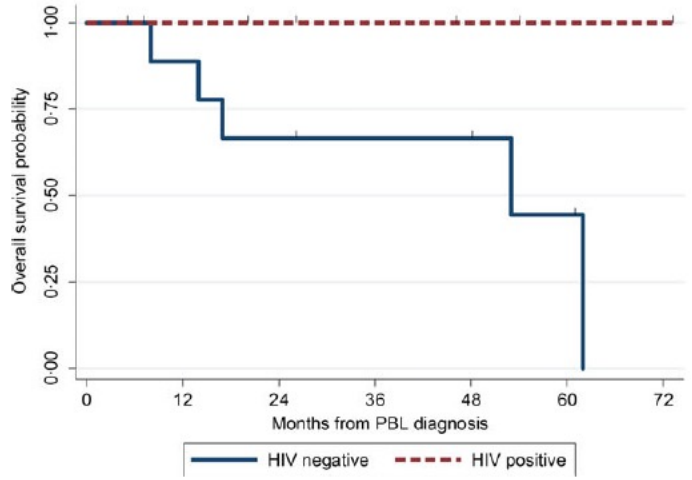
Table I. Patients' clinicopathological characteristics.

Characteristic	Number	Percentage
Age ≥60 years	6/16	38
Male sex	15/16	94
ECOG performance score >1	7/16	44
Increased LDH level	8/16	50
Advanced stage	14/16	88
Extranodal involvement	16/16	100
Low/low intermediate IPI score	5/16	37
High/high intermediate IPI score	10/16	63
HIV infection	6/16	38
CD20 expression	0/16	0
CD38/CD138 expression	16/16	100
HHV8 LANA expression	0/10	0
ALK expression	0/10	0
Ki67 expression ≥80%	14/16	88
EBER ISH positive	9/14	64
MYC rearrangements	8/10	80

Castillo et al. Br J Haematol 2019







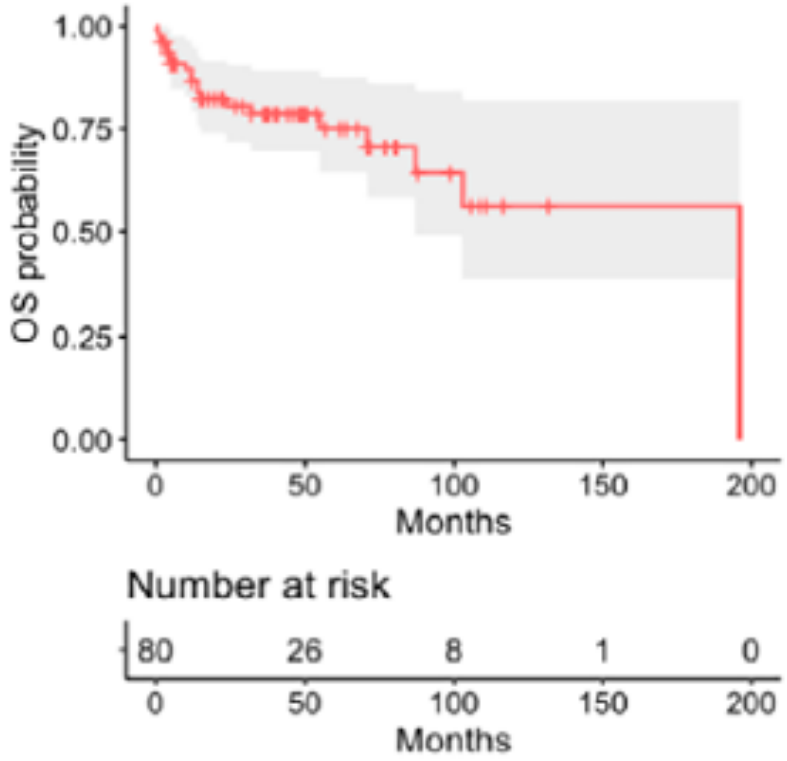
Hematopoietic Cell Transplantation for Plasmablastic Lymphoma: A Review

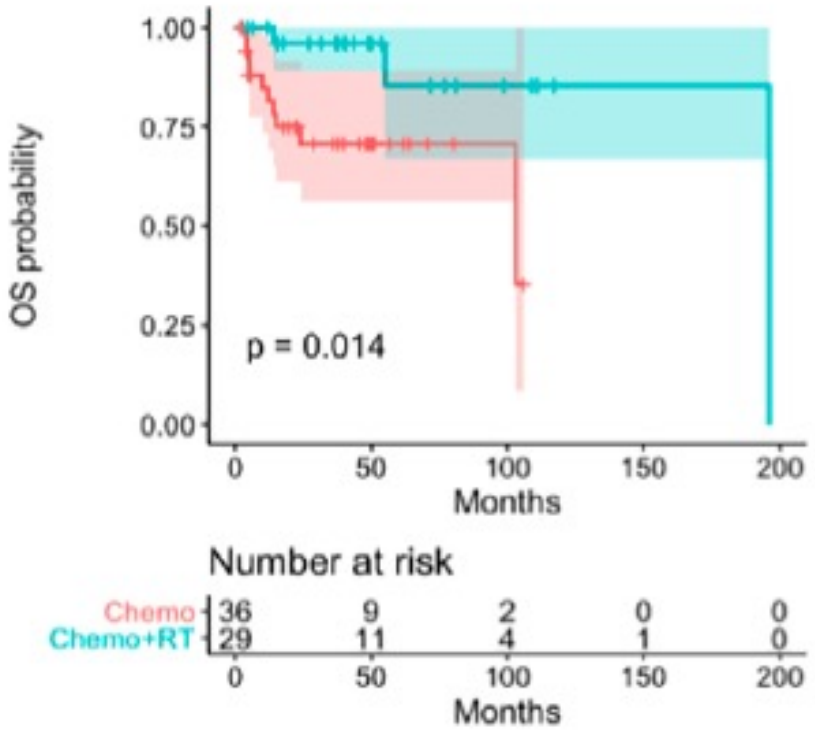
Case Reports of HIV-Negative Patients with PBL and Their Reported Outcome in Literature

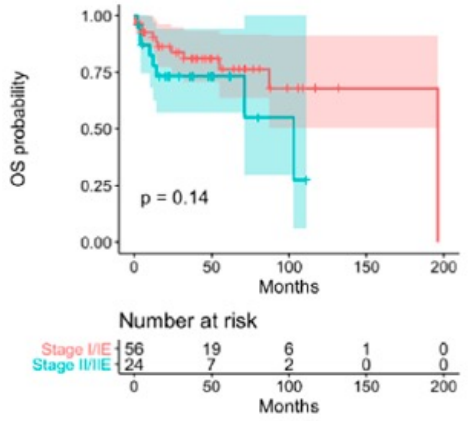
Patient No. [Ref]	Age, yr	Gender (M/F)	Stage	Immune Status	aaIPI	Induction Regimen	Disease Status before AHCT	Conditioning Regimen	Disease Status after AHCT	DFS after AHCT, mo	OS at Last follow-up, mo
1 [18,21]	23	M	IV	Competent	2	HyperCVAD × 2 PD: IVAC × 3	PR2	BEAM	CR	5	12 (died)
2 [18,75]	57	M	IV	Cardiac transplant (cyclosporine)	2	Cyclosporine w/d Cy/MTX PD: ICE × 3	PR2	Chemo-based	PD	PD	6 (died)
3 [18]	63	F	IV	Competent	5	HyperCVAD × 4	CR1	BEAM	CR	2	13.3 (died)
4 [18]	60	F	IV	Competent	3	HyperCVAD × 4	PR1	BEAM	CR	14	36.5 (died)
5 [18]	64	M	IIE	Competent	2	R-CHOP × 6	CR1	BEAM	CR	A-NED	25.3
6 [18]	67	M	IV	Competent	3	CHOP × 1 R-CHOP × 5	CR1	BEAM	CR	A-NED	46.7
7 [60]	36	M	IV	Competent	2	ProMACE/CytaBOM	CR1	BEAM	CR	NR	16.9 (died)
8 [60]	52	F	II	Competent	1	CHOP × 6 PD: MiniBEAM	PR2	Cy-TBI	CR	2.5	17.2 (died)
9 [60]	50	M	II	Competent	0	CHOP: RD MiniBEAM: RD ICE	RD/CR1	BEAM	PD	PD	14 (died)

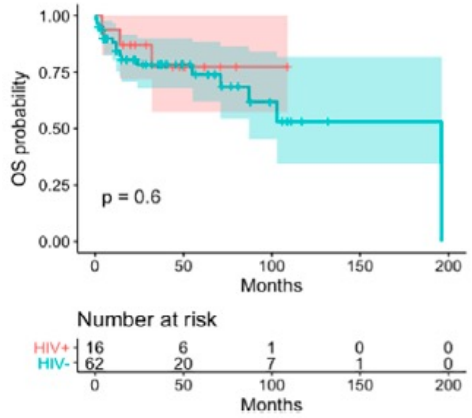
Al-Malki et al. Biol Blood Marrow Transplant 2014

Outcomes of patients with limited-stage plasmablastic lymphoma: A multi-institutional retrospective study





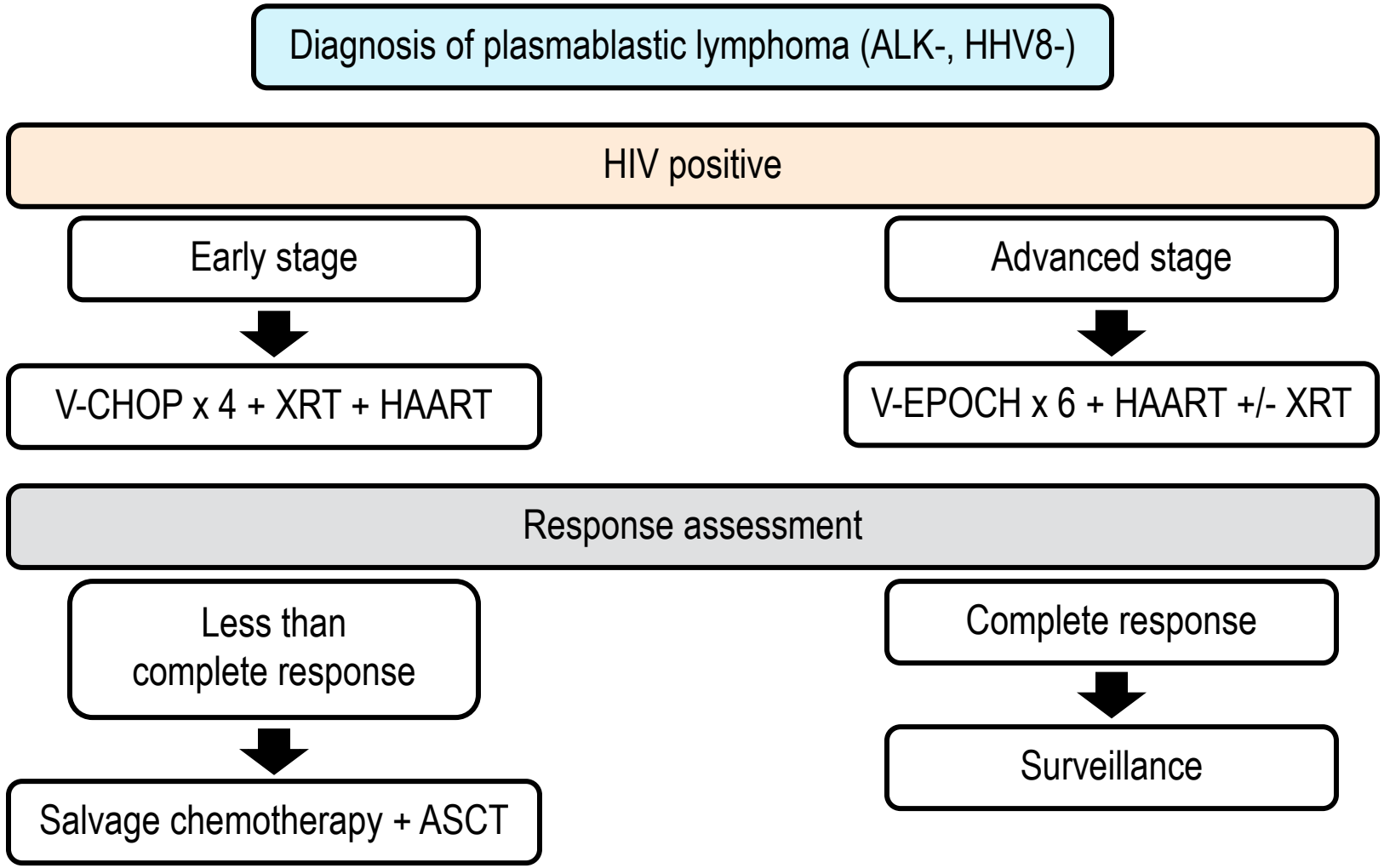




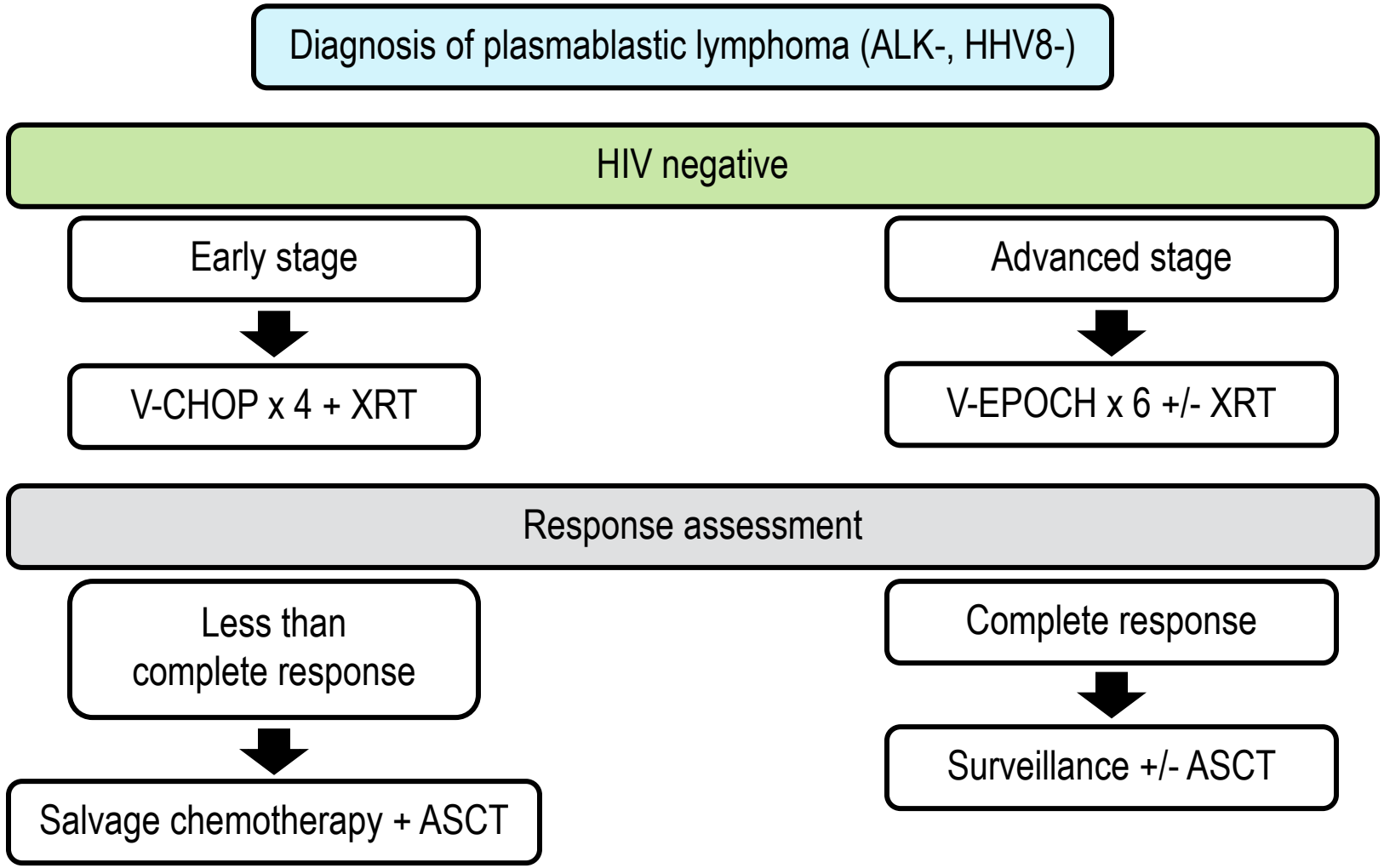
Hess et al. Am J Haematol 2023

How do I treat plasmablastic lymphoma in 2023?

Recommended treatment algorithm



Recommended treatment algorithm



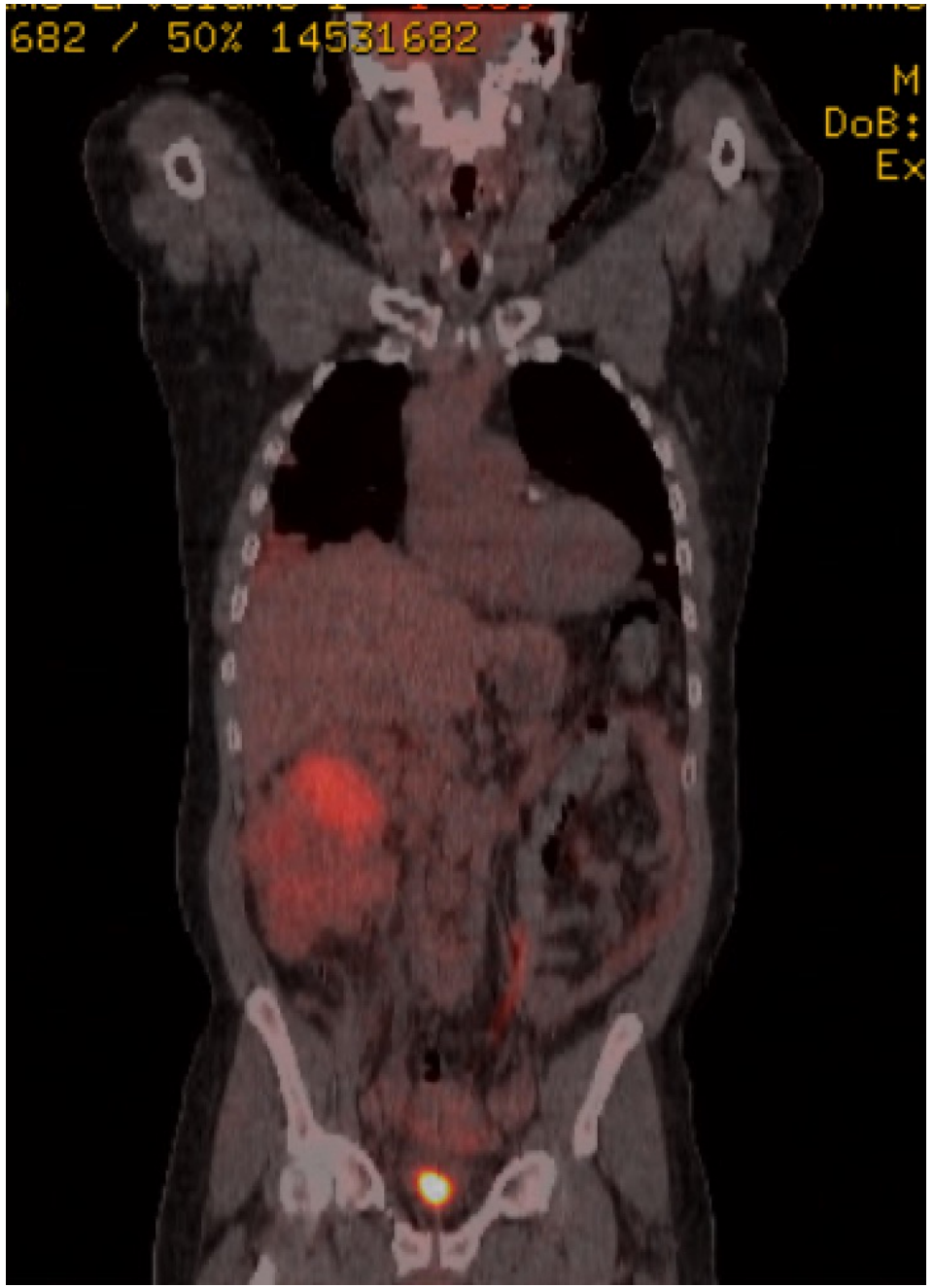
What novel agents can be used in relapsed plasmablastic lymphoma?

Daratumumab

55-year-old HIV+ man presented with severe RLQ pain

The patient had HAART adjusted and received 6 cycles of V-EPOCH attaining a CR

Two months later, he presented with recurrent right flank pain

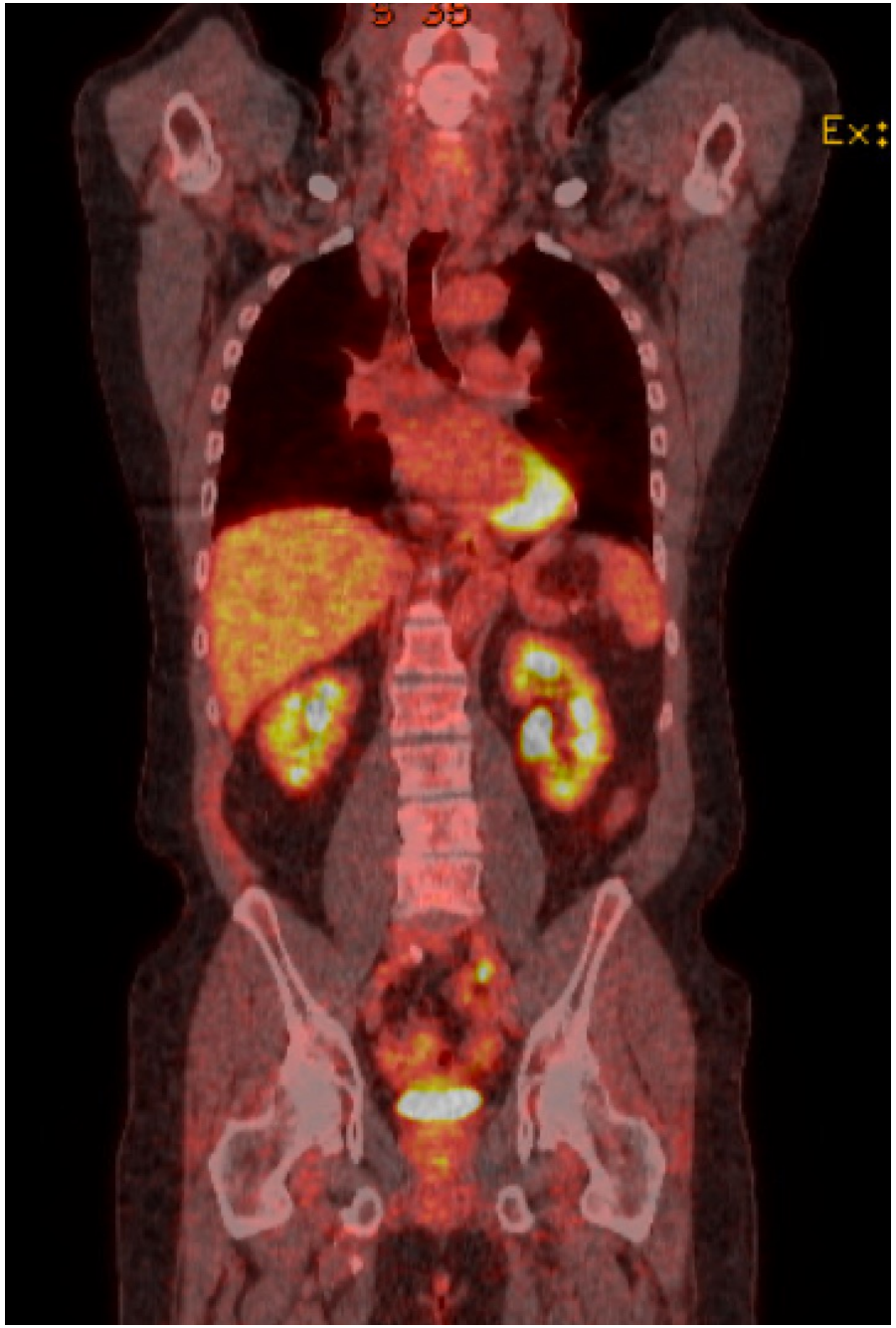


Clinical course

The patient was started on ICE in combination with daratumumab 16 mg/kg IV every week for 8 weeks

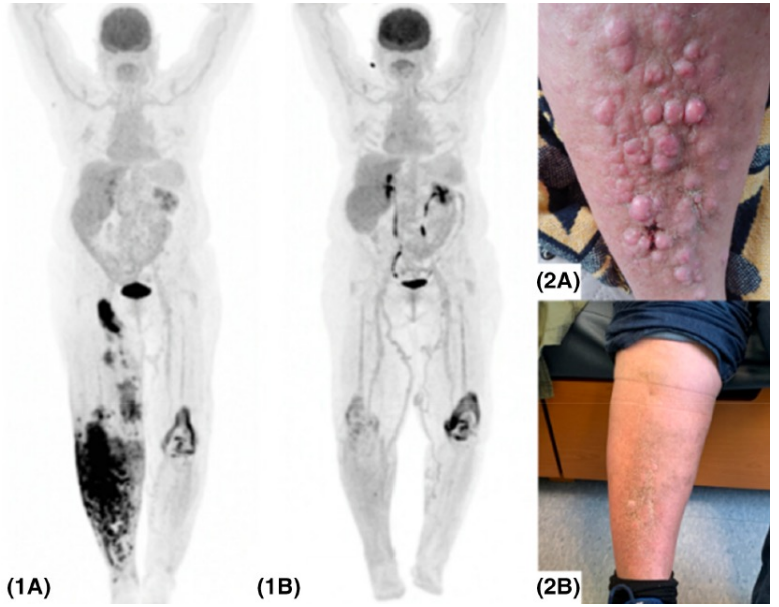
Attained CR and underwent ASCT

Alive in CR, 6 years after diagnosis



Daratumumab with ifosfamide, carboplatin and etoposide for the treatment of relapsed plasmablastic lymphoma

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	64	55	38	42
Gender	F	M	M	M
HIV	Negative	Positive	Positive	Positive
CD4 count at diagnosis, $\times 10^9$/l	N/A	0.154	0.180	0.192
Stage	IV	IV	IV	IV
Extranodal site(s)	Soft tissue	Kidney	Rectum	Testicular
CD138	+	+	+	+
MYC rearrangement	No	No	Yes	Yes
Front-line treatment	V-EPOCH	V-EPOCH	V-EPOCH	V-EPOCH
Daratumumab dose	16 mg/kg IV weekly	16 mg/kg IV weekly	1800 mg subcutaneous weekly	16 mg/kg IV weekly
Cycles D-ICE, *n*	3	4	3	3
Toxicity	Grade 4 myelosuppression	Grade 4 myelosuppression	Grade 4 neutropenia	Grade 4 febrile neutropenia
Consolidation	N/A	AutoSCT	Plan for AutoSCT	AutoSCT
Best response to D-ICE	CR	CR	CR	CR
PFS, months	5	73	4	8
OS, months	8 (died)	73 (alive)	4 (alive)	8 (alive)



Dittus et al. Br J Haematol 2022

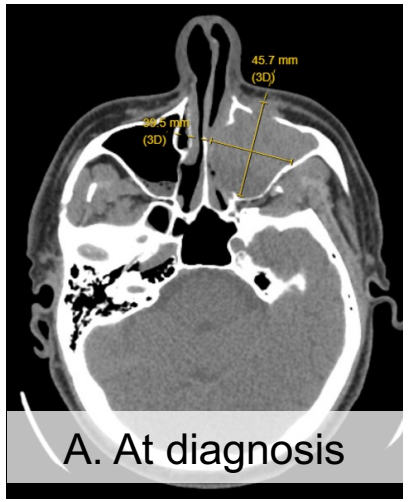
Pembrolizumab

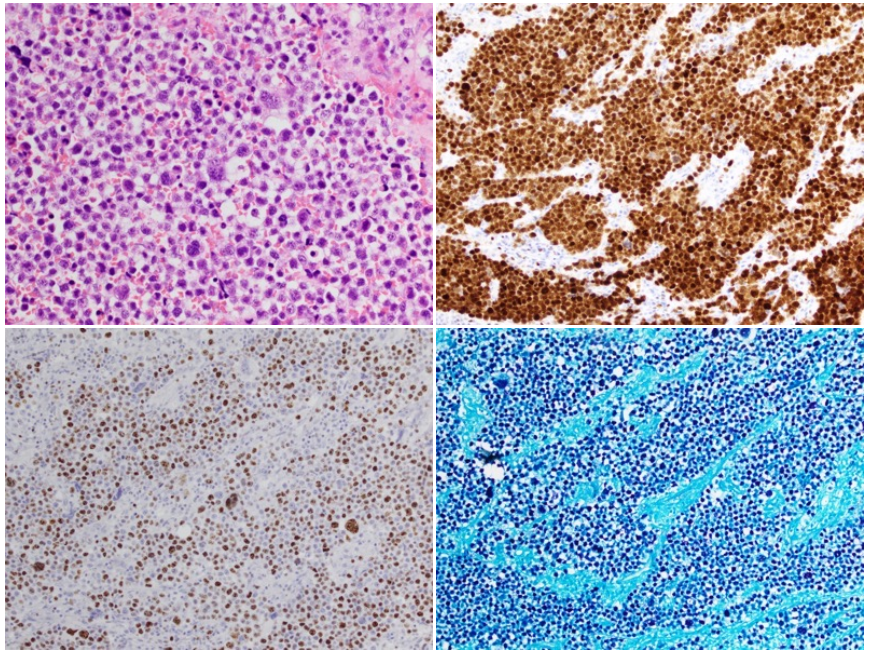
79-year-old man presents with nasal discharge, left-sided facial numbness and bulging of left cheek

V-CHOP for 4 cycles → CR based on PET/CT scans

Planned for XRT but 4 weeks later, symptoms recurred

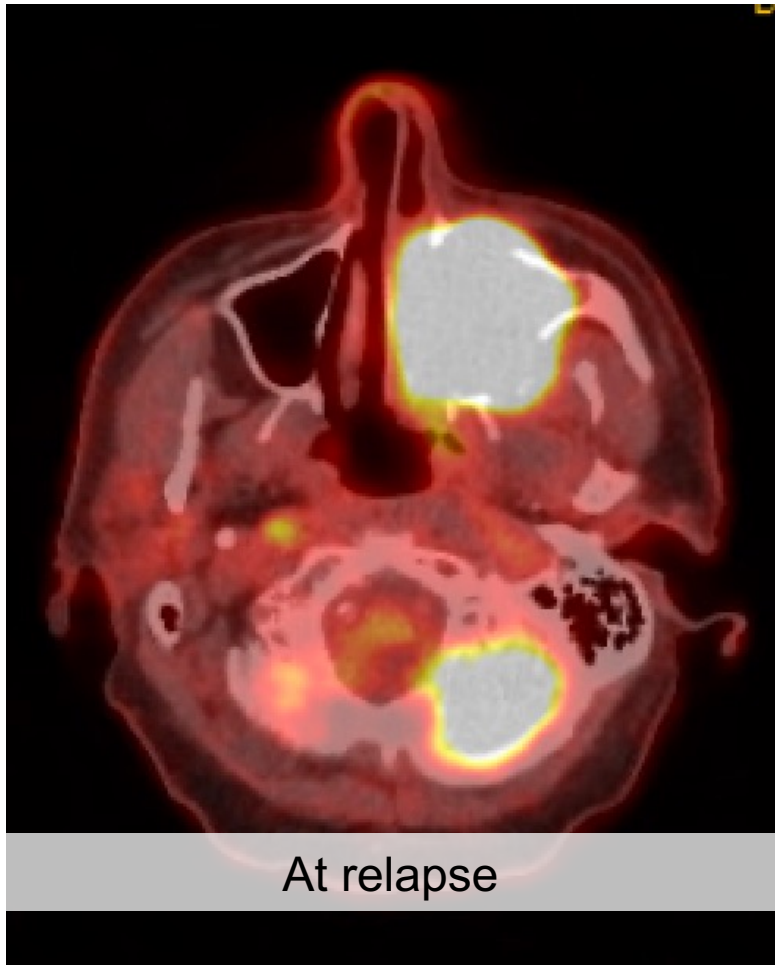
The patient received daratumumab, lenalidomide and dexamethasone without response

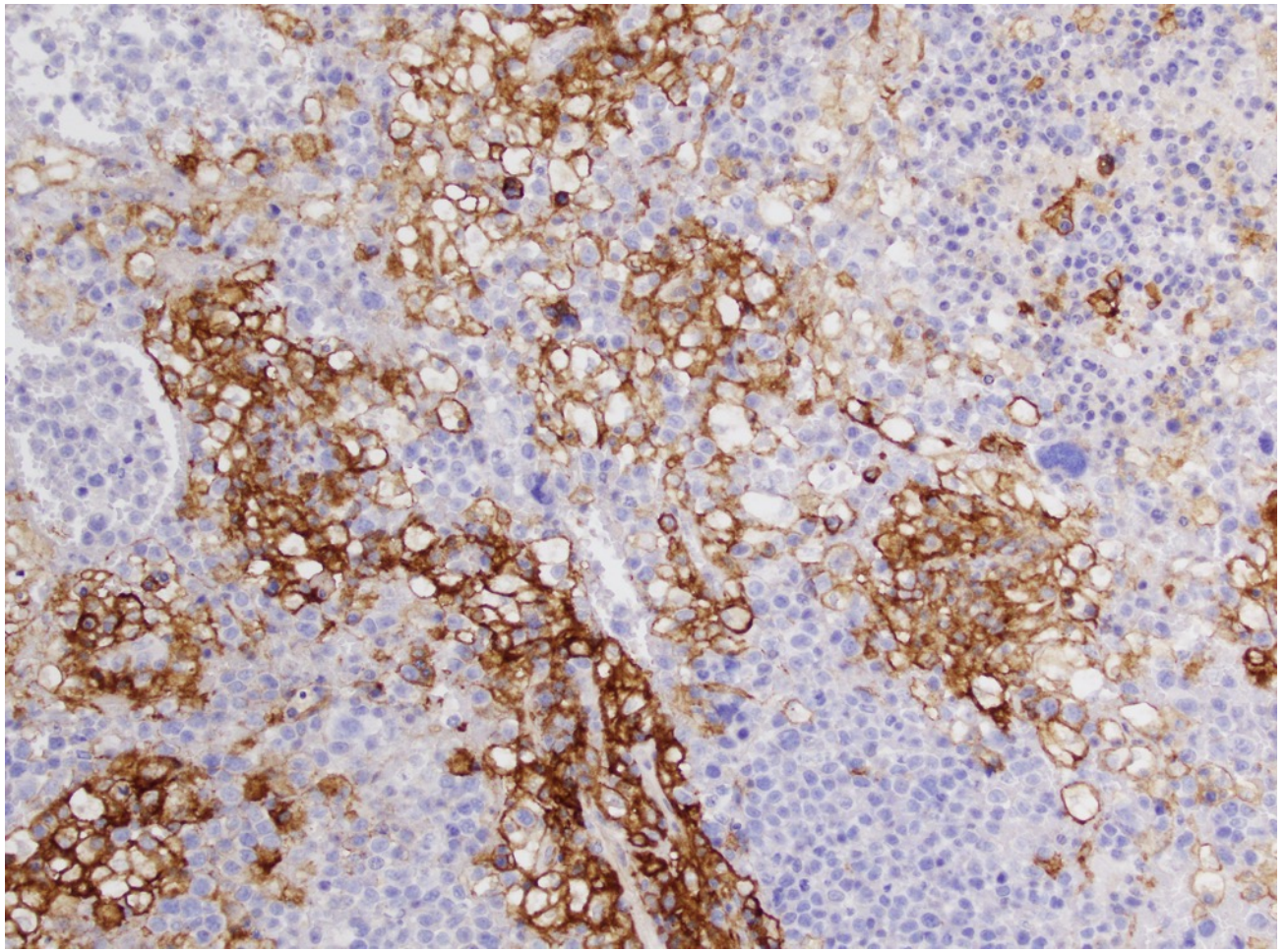




Castillo et al. Am J Hematol 2021

PD1 expression in PBL cells and TAMs





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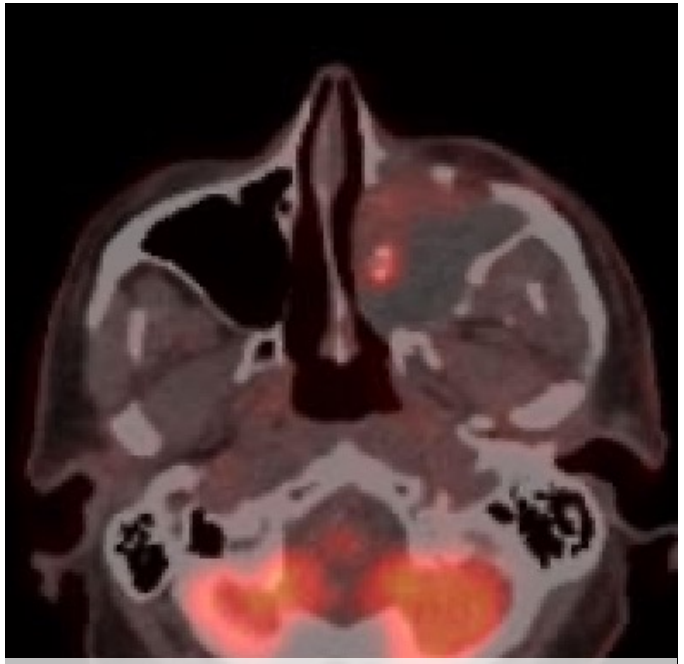
Clinical course (2)



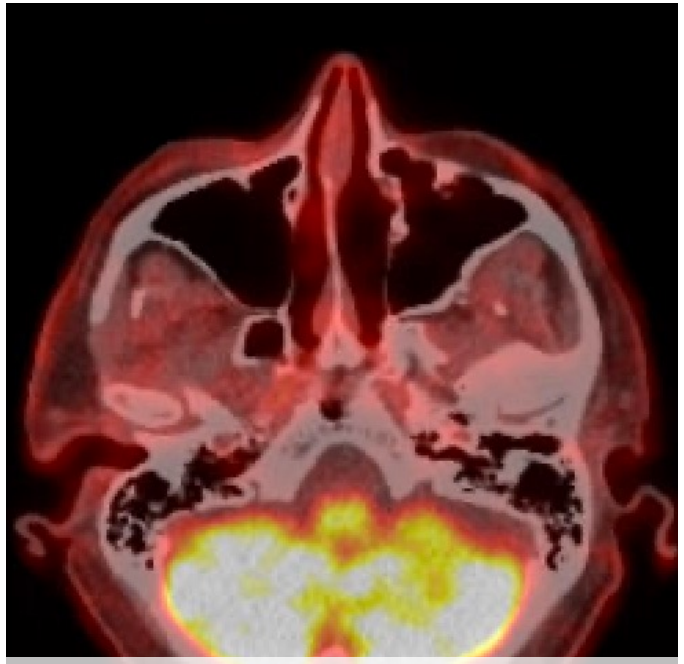
Within 6 cycles of pembrolizumab

Received XRT + pembrolizumab x 18 cycles

Course complicated by:
- UTIs
- Pneumonia
- Zoster ophthalmicus
- Heart failure - LVEF 10%

Pembrolizumab was stopped

Alive in CR, 48 months from diagnosis - LVEF 45%



12 months after pembrolizumab

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Clinical trials

- Belantamab Mafodotin In Plasmablastic Lymphoma & ALK+ Large B-Cell Lymphoma (NCT04676360) – DFHCC, MDACC, MSKCC
- A Study of Daratumumab and Dose-Adjusted EPOCH in Plasmablastic Lymphoma (NCT04139304) – Hopkins, UNC, UPENN, MSKCC
- Study to Evaluate Combined Treatment of Daratumumab, Bortezomib and Dexamethasone in PBL Patients (NCT04915248) - Istituto Scientifico San Raffaele, Milano

Conclusions

- PBL is a distinct entity with poor prognosis.
- Associated with EBV infection and *MYC* gene rearrangement.
- Bortezomib-chemotherapy might improve outcomes in the front line.
- Anti-CD38 and anti-PDL1 therapy might be of value in relapsed disease.

How I treat plasmablastic lymphoma

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