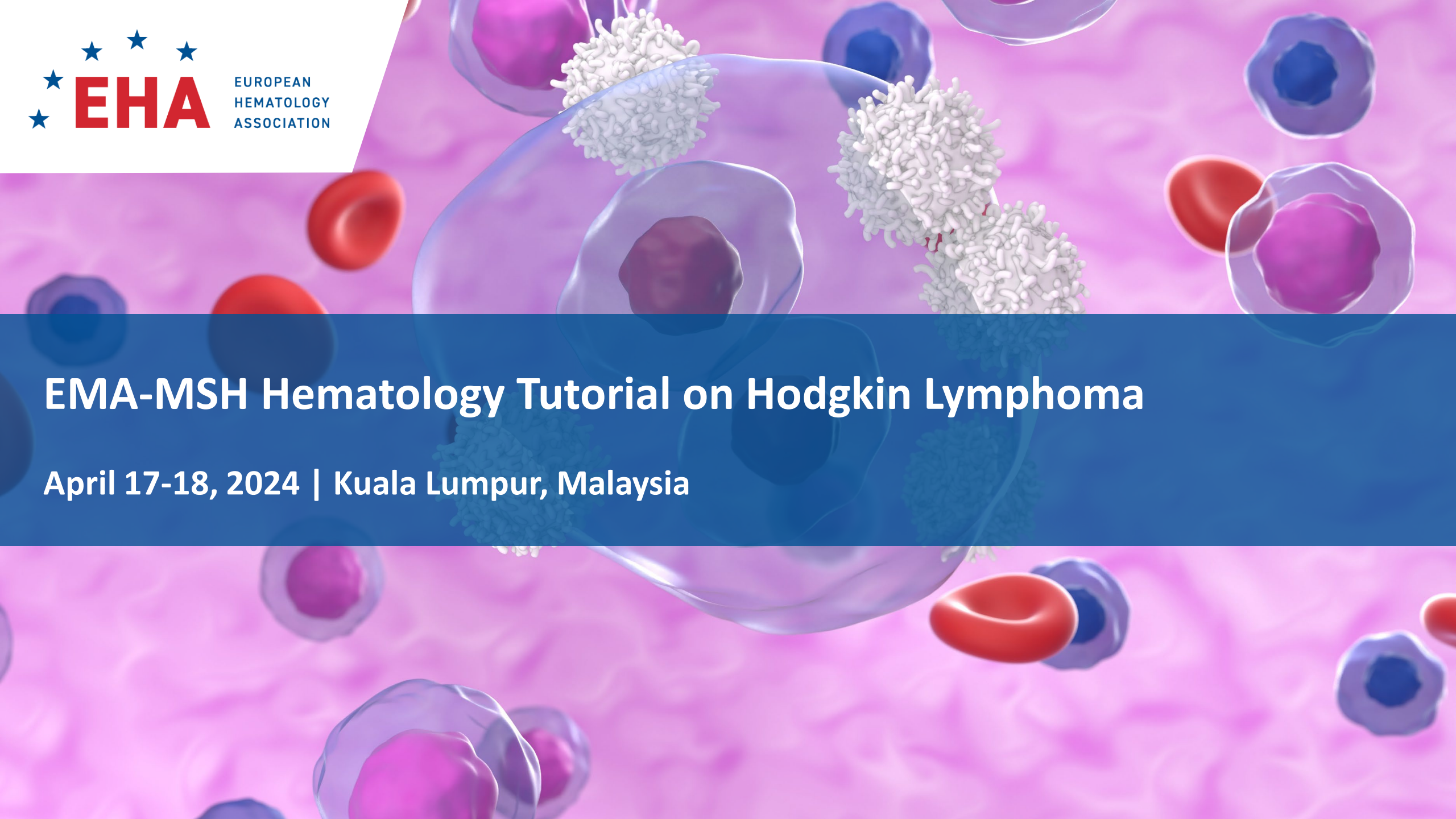

EUROPEAN HEMATOLOGY ASSOCIATION

EMA-MSH Hematology Tutorial on Hodgkin Lymphoma

April 17-18, 2024 | Kuala Lumpur, Malaysia

Classical Hodgkin Lymphoma: not always a good prognosis disease

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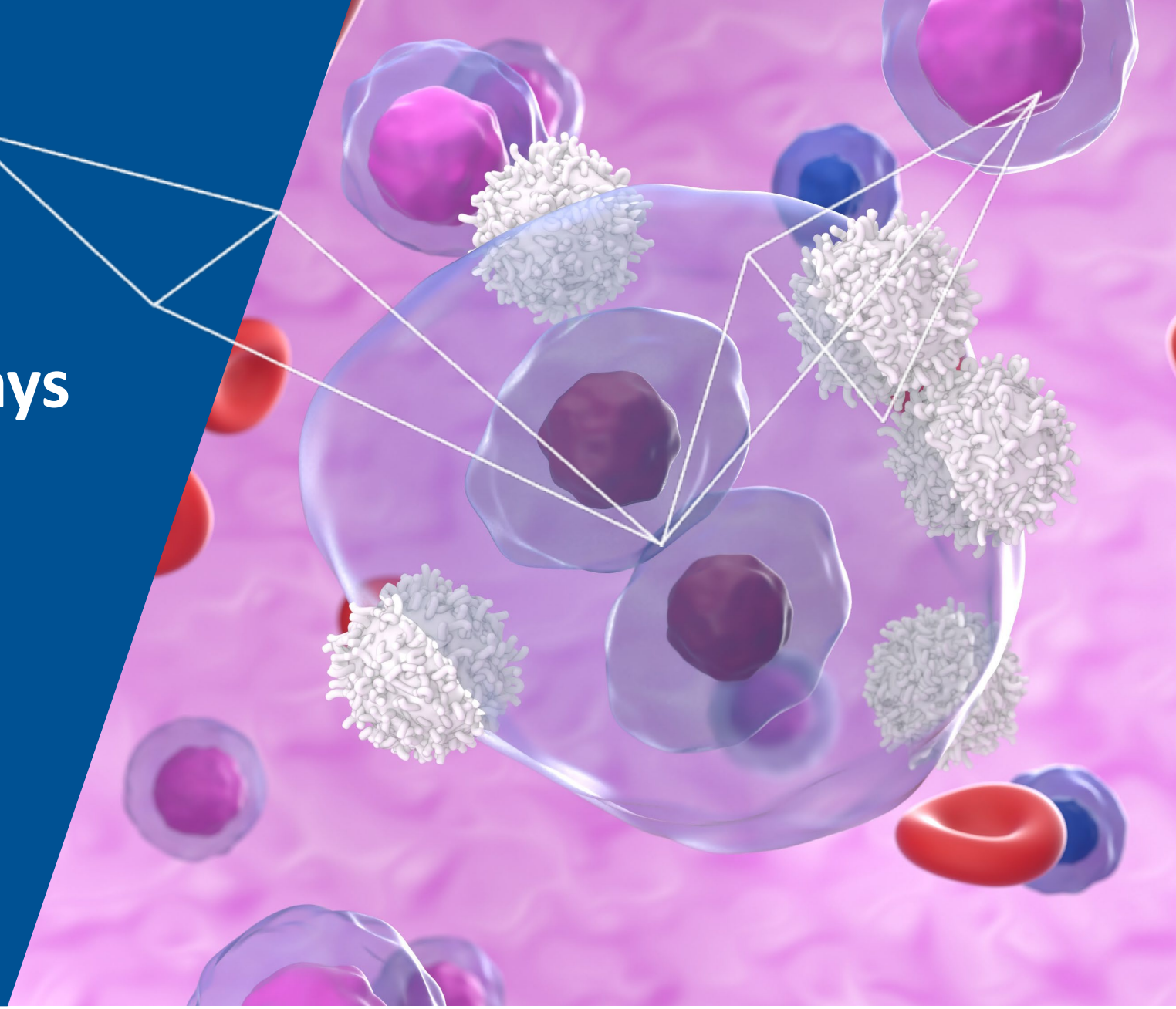
Division of Hematology and Stem Cell Transplantation

IRCCS Istituto Nazionale Tumori

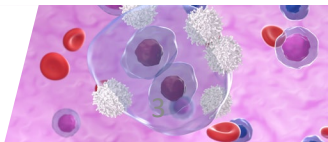
Milan, Italy

April 17, 2024



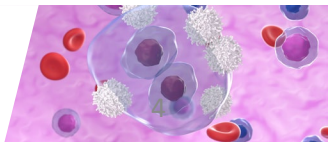
Disclosures

Research support PI	Celgene
Consultant	–
Major stockholder	–
Honoraria	Celgene, Gilead, Lilly, Takeda
Scientific advisory board	Lilly, Takeda



Agenda & learning objectives

- To stratify patients affected by relapsed/refractory (r/r) classical Hodgkin lymphoma (HL) accordingly to risk factors
- To optimize the choice of second line treatment intended as bridge to autologous stem cell transplantation (ASCT)
- To consolidate high-risk patients after ASCT
- To choose salvage treatment for transplant ineligible r/r patients



How many patients require salvage therapy?

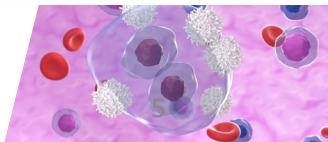
Stage	pts	refractory N	(%)	relapsed N	(%)
Limited (I-II)	241	0	0	6	**2,5**
Advanced	460	32	**7**	87	**19**

British Columbia dataset 1990-2000

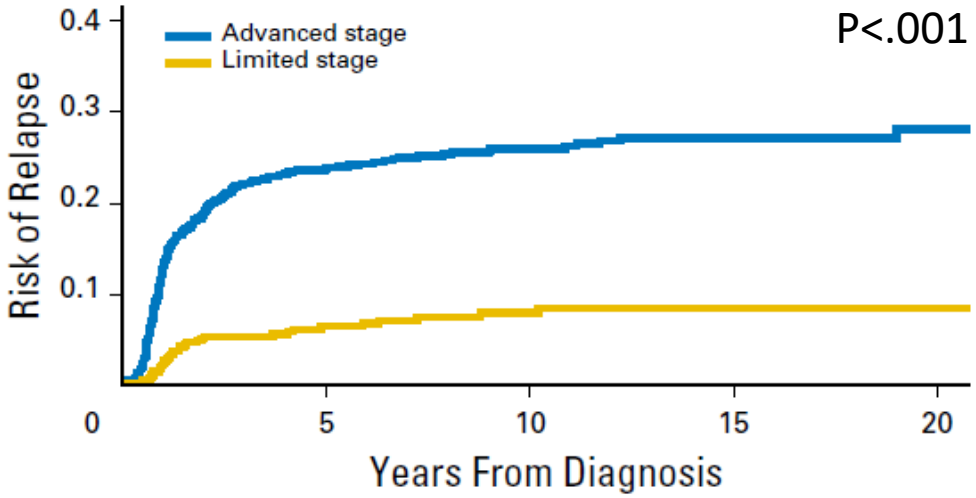
Connors JM, Blood 2003

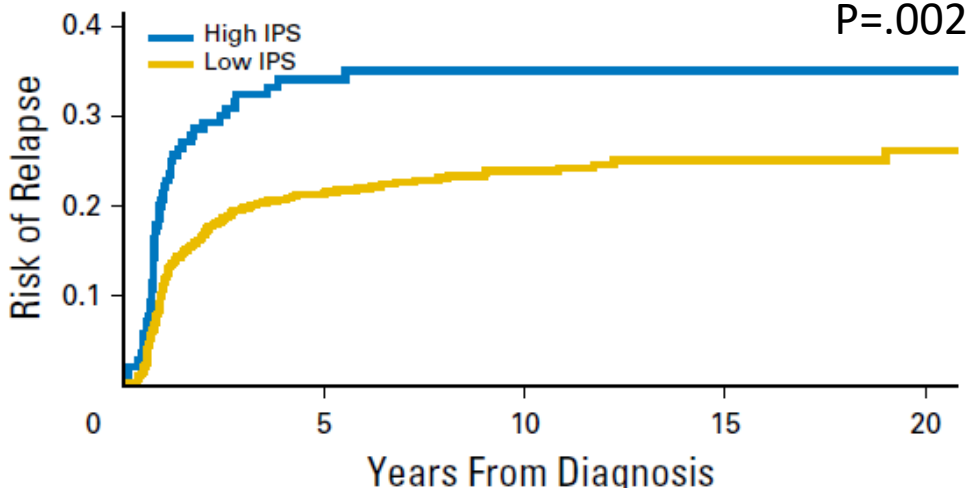
5-10% of patients are refractory to front-line treatment and 10-30% of patients experience relapse after achieving a complete response

Diehl V, Principles and Practice of Oncology 6th ed 2000



Risk of relapse

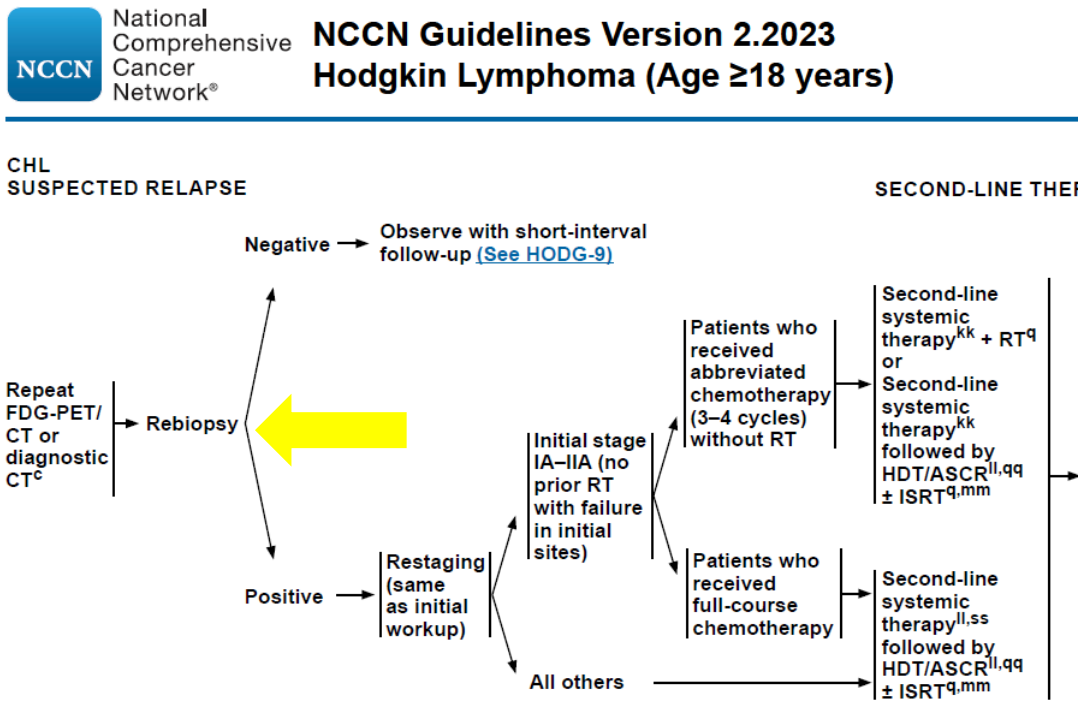




Hapgood G et al, JCO 2016

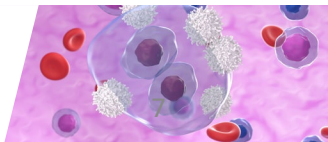
Risk of relapse is higher for patients presenting with advanced stage and high Hasenclever score (IPS)

Repeat biopsy whenever possible



I consider to skip histological confirmation if the case of:

- difficult to reach suspected site of relapse/persistence of disease
- surgical intervention that can significantly delay the start of salvage therapy (surgical waiting list, complications)
- suspected site was involved at initial diagnosis and patient is refractory (never achieved PET negative)
- patient refusal



Patients' stratification at relapse

Treatment for r/r cHL differs between **young, fit patients** who are eligible for high-dose chemotherapy and autologous stem cell transplants and **older adults** who are not eligible for intensive therapies

Patient characteristics:

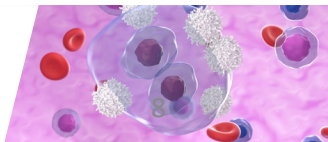
- Age (cut-off: 65 years old; 70 if the patients is fit?)
- Co-morbidities (adequate pulmonary, cardiac, liver and renal function; pre-existing autoimmune diseases and neuropathy)

Elegibility for transplantation

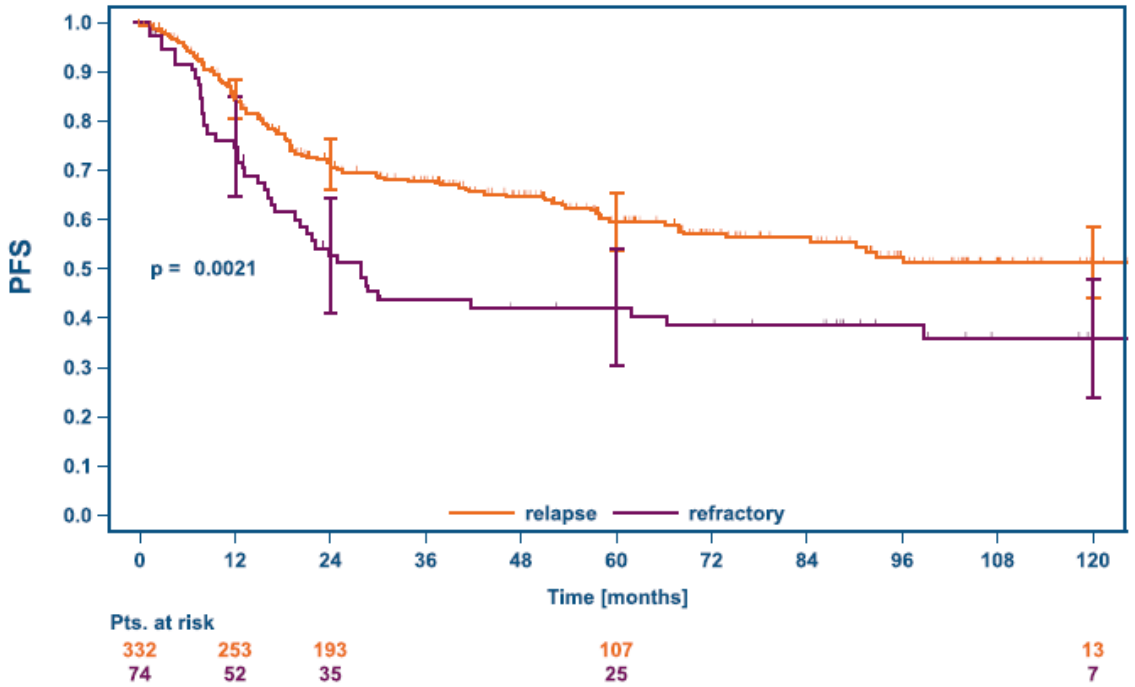
Disease characteristics:

- Time to relapse
- Tumor burden

First-line therapy



Time to first treatment failure

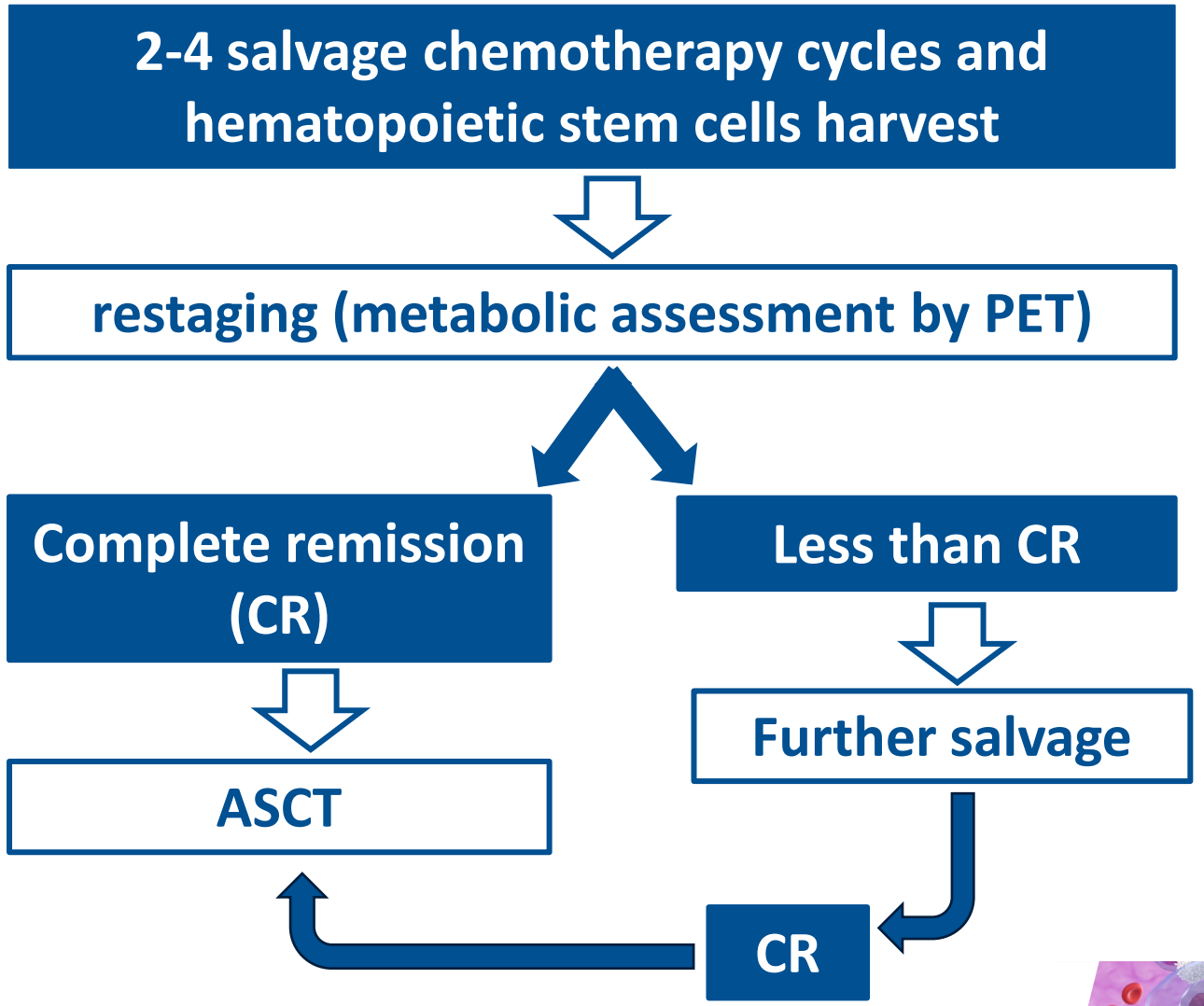


Cut-off for refractory: time to relapse ≤ 3 months

Bröckelmann PJ et al, Leukemia 2022

Standard of care for younger r/r HL patients

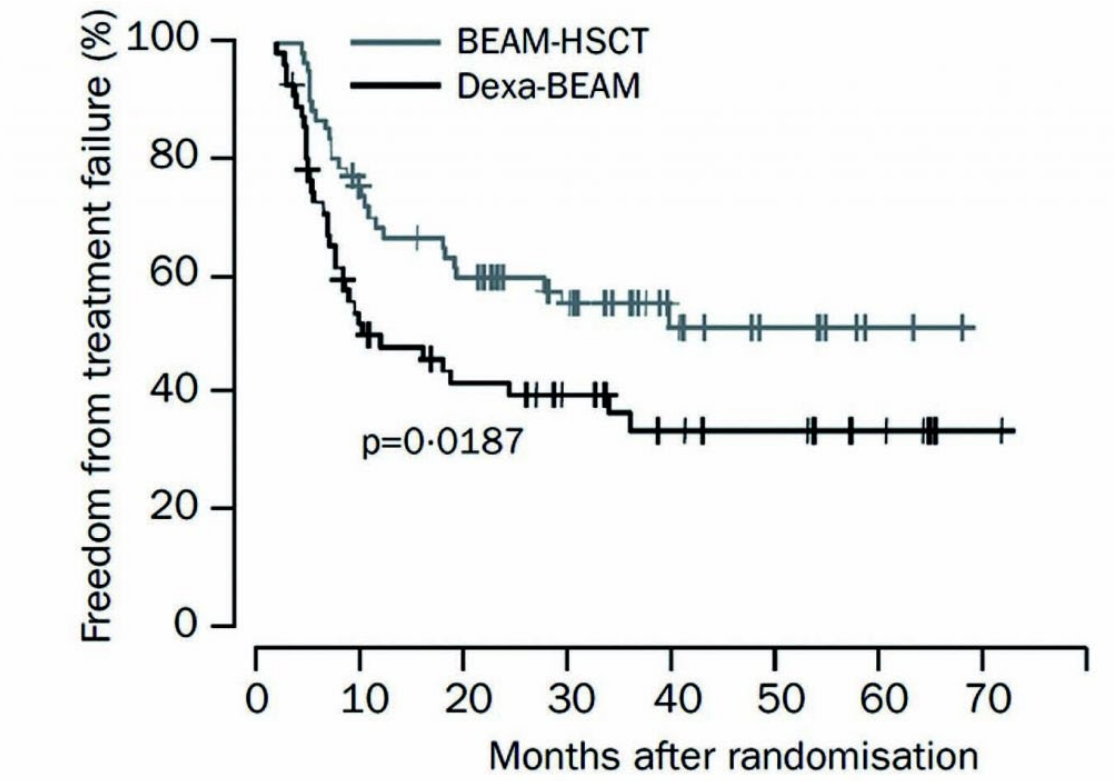
The current **standard of care** for patients with Hodgkin's lymphoma (HL) who relapse from or are refractory to primary chemotherapy is **salvage chemotherapy** with cytotoxic drugs not-cross-resistant and alternative to those used in front-line, and in those who demonstrate chemotherapy-sensitive disease, **ASCT**



ASCT@relapse: randomized clinical trials

TRIAL	PTS (N)	TREATMENT	OUTCOME
BNLI Linch DC, Lancet 1993	40	A: mini-BEAM B: HD-BEAM+SCT	A: 3y-EFS 10% B: 3y-EFS 58%
HD-R1 Schmitz N, Lancet 2002	161	A: Dexa-BEAMx4 B: Dexa-BEAMx2+HD-BEAM+SCT	A: FFTF 34% B: FFTF 55%

HD-R1



Number of patients

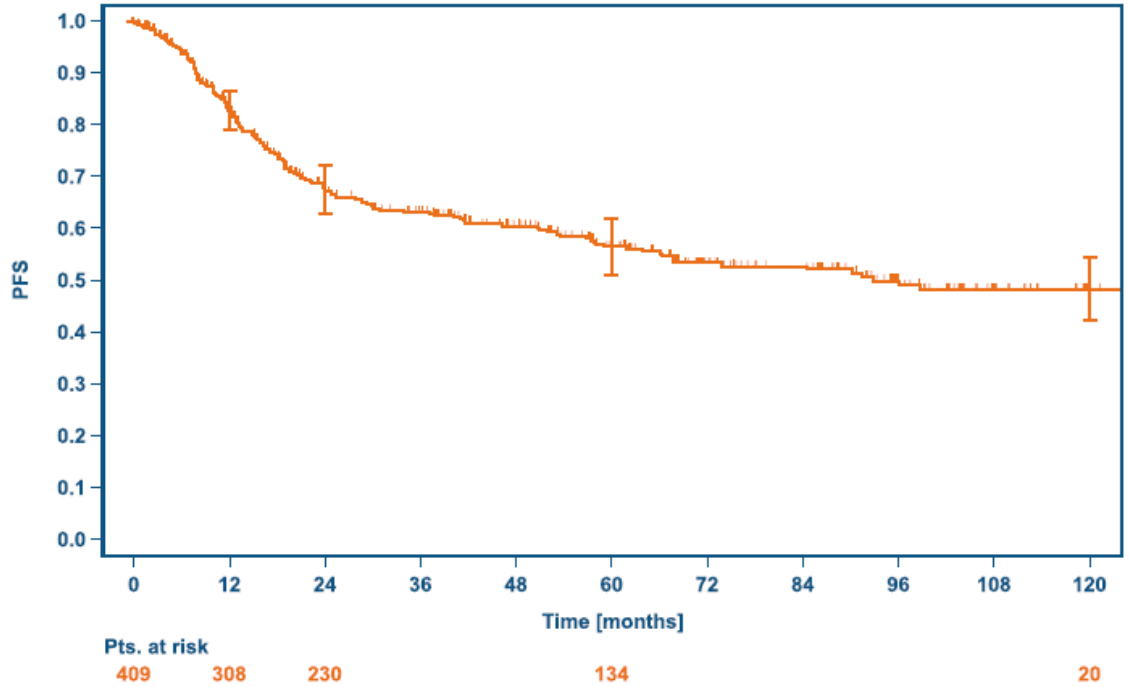
BEAM-HSCT	61	43	34	25	13	8	7	0
Dexa-BEAM	56	27	20	15	10	8	5	1

ASCT is associated with significantly greater freedom from treatment failure, which is achieved in around **50%** of patients

Thus, about 50% of patients relapse after ASCT, and the post-progression survival for this group is poor

Schmitz N et al, Lancet 2002

Long-term post ASCT outcome: contemporary era



409 patients with first r/r HL (HD13 HD14 HD15)

Even in the present era, the long-term **cure rate** of r/r HL after ASCT does not exceed 50%

Bröckelmann PJ et al, Leukemia 2022

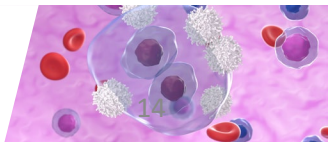
Salvage therapy as bridge to ASCT: how to choose?

Randomized prospective clinical trials comparing different regimens of conventional chemotherapy are **lacking**

Choose your favorite option among cycles tested in phase 2 trials

The **main goals** of salvage therapy for r/r HL are:

- achieve complete metabolic response → **negative PET** (Deauville Score: 1-3) before ASCT
- **mobilize** (with addition of G-CSF) hematopoietic stem cells in the peripheral blood (PBSC)
- **minimize toxicity**

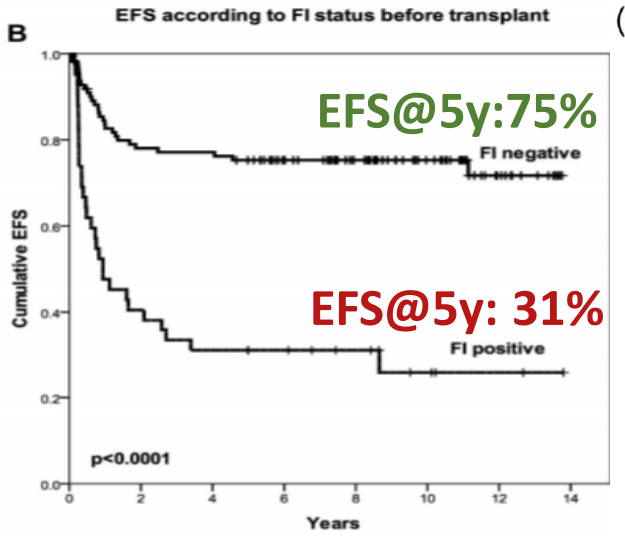


Complete metabolic remission@ASCT and outcome

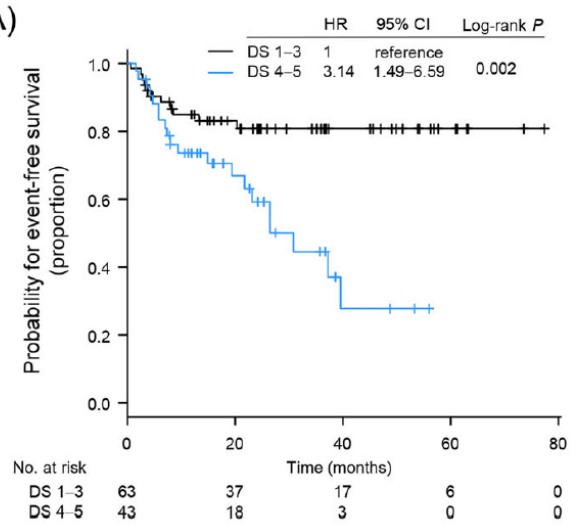
PET/CT before high-dose salvage therapy in relapsed HL

Duration of remission before relapse, and the response to induction therapy are important prognostic factors that predict a good outcome after high-dose chemotherapy with autologous stem cell support (HD + ASCT). Several studies have shown that PET/CT performed after induction therapy and before HD + ASCT can predict which HL patients will achieve long-term remission after the salvage regimen.[39-41] These studies all report a poor long-term PFS (after 2-5 years) in patients who are PET^{+} after induction chemotherapy (31%-41%) compared with a PFS of 73%-82% in the patients who reach a PET^{-} remission before HD + ASCT. How-

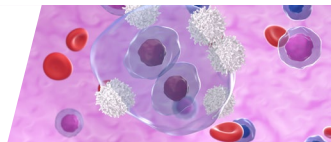
Hutchings M, ASH Edu 2012



Moskowitz A et al, Blood 2010



Yhim HY et al, Am J Hematol 2022

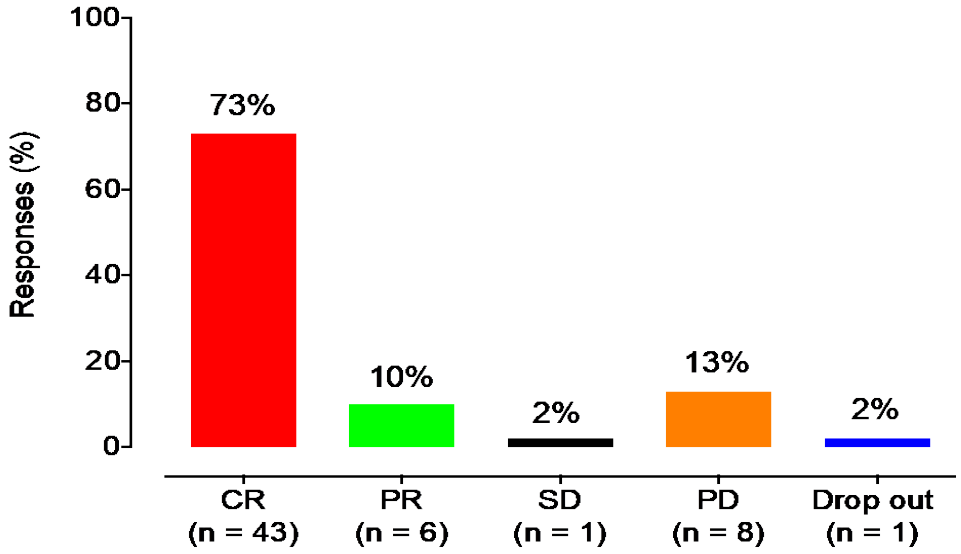


Conventional chemotherapy regimens

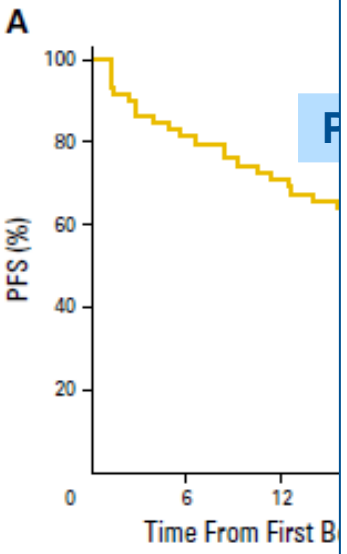
Regimen	Pts N	ORR (%)	CR (%)	Survival	Reference
ICE	65	88	26	@43 ms EFS, 82% in CR pts	Moskowitz, Blood 2001
DHAP	279	71	24	@3 yrs PFS 69%, OS 85%	Josting, Ann Oncol 2003
IGEV	91	81	54	@3yrs FFP 53%, OS 70%	Santoro, Haematol 2007
BeGEV	59	83	73	@2yrs OS 62%, PFS 78%	Santoro, JCO 2016
GDP	23	59	17	NA	Baetz T, Ann Oncol 2003
GVD	91	70	19	@4yrs EFS 52%, OS 70%	Bartlett N et al, Ann Oncol 2007
ESHAP	82	67	50	@5 yrs PFS 83%, OS 59%	Labrador, Ann Hematol 2014

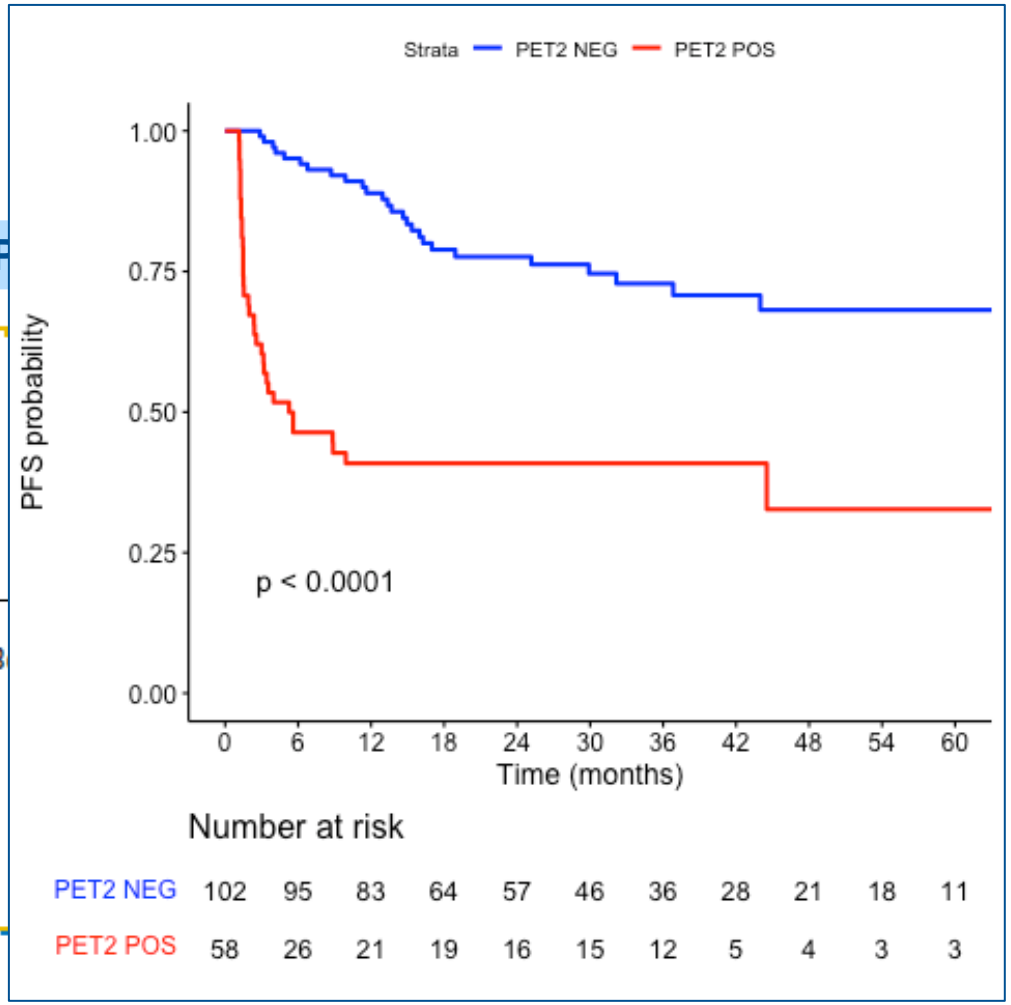
BeGEV

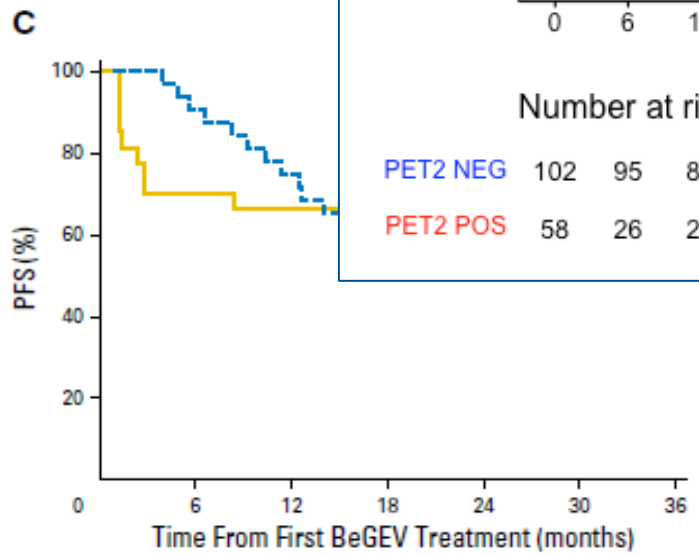
Bendamustine 90 mg/mq d 2-3, Gemcitabine 800 mg/mq d 1-4, Vinorebine 20 mg/mq d 1



Median CD34+ cells/kg 8.8 x 10^6







Santoro A et al, JCO 2016
Santoro A et al, Blood Adv 2020
Rusconi C et al, EHA 2023

EHA EUROPEAN HEMATOLOGY ASSOCIATION

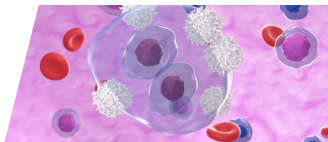
New drugs

Brentuximab-vedotin (BV) and immune check-point inhibitors (CPI), nivolumab and pembrolizumab, proved to be effective in the r/r HL setting when used as single agent beyond first salvage

Younes A et al, NEJM 2012
Chen R et al, Blood 2016
Ansell S et al, NEJM 2015
Armand P et al, Blood Adv 2023

BV and CPI single agent can rescue some of the patients who failed first-salvage with conventional chemo thus allowing to proceed to ASCT

Eyre T et al, BJH 2017
Chen R et al, Biol Blood Marrow Transplant 2015
Zinzani PL et al, The Oncologist 2015
Merryman RW et al, Blood Adv 2021

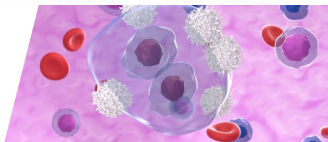


Incorporating new drugs in first salvage

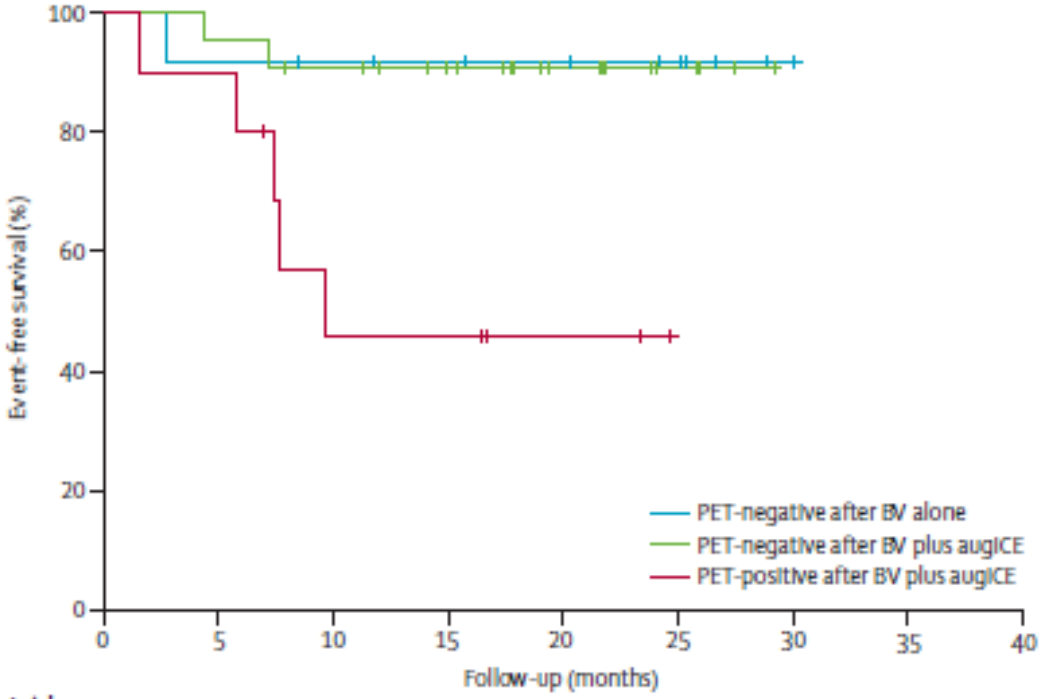
BV and CPI can be combined to first-salvage chemotherapy with the aim to improve CR rate and therefore post-ASCT outcome

	Sample size	Regimen		PET-Neg	PFS	Study
Sequential BV and chemo	65	BV-> augICE		83% 27% (BV alone)	73% @ 6 yr	Moskowitz et al. (74)
	45	DD-BV-ICE		74%	80.4% @ 2 yr	Lynch et al. (90)
Combined BV and chemo	55	BV-benda		74%	62.6% @ 2 yr 69.8% for ASCT pts	LaCasce et al. (75)
	39	ICE	plus BV	69%	69% @ 1 yr	Stamatoullas et al. (91)
	61	DHAP		81%	74% @ 2 yr	Kersten et al. (78)
	66	ESHAP		70%	71% @ 30 mo	Garcia-Sanz et al. (77)
BV plus CPI	91	BV-nivolumab		67%	79% @ 2 yr	Moskowitz et al. (92)
Combined CPI/chemo	43	Nivo-ICE		91% 71% (Nivo alone)	72% @ 2 yr for all 94% @ 2 yr for ASCT	Mei et al. (82)
	39	Pembro-GVD		92%	100% @ 1 yr post-ASCT	Moskowitz et al. (83)

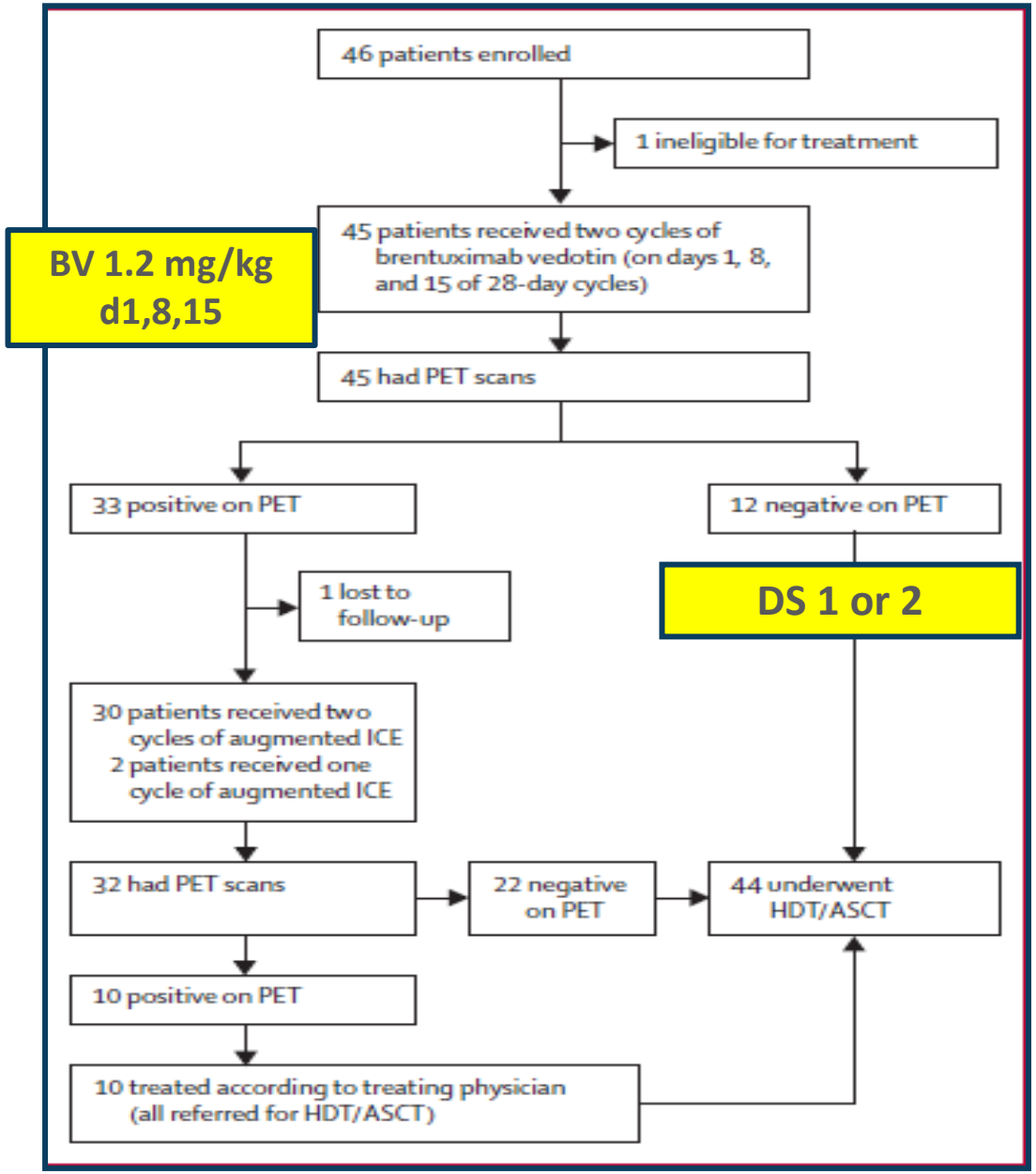
Modified form Ullah F et al, Frontiers 2023



BV +/- augmented ICE pre-ASCT



Number at risk							
BV PET negative	12	11	10	9	8	5	1
BV-augICE PET negative	22	21	19	15	9	4	0
BV-augICE PET positive	10	9	8	4	2	0	0



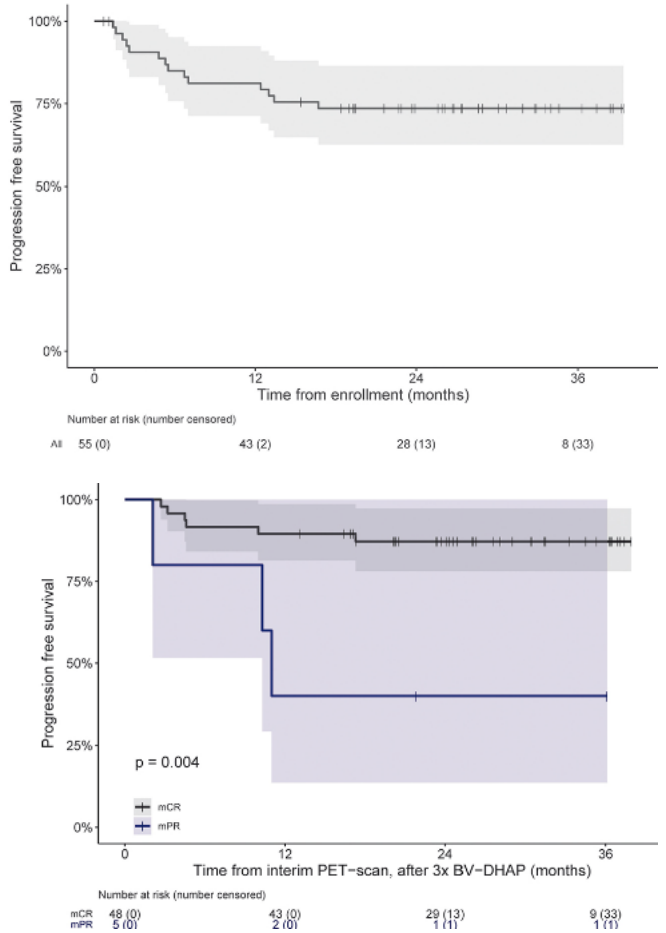
Mosckowitz AJ et al, Lancet Oncol 2015

BRaVE study

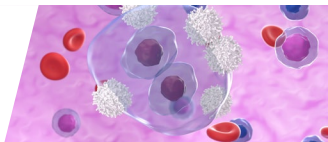
BV (1.8 mg/kg) combined with DHAP (full dose) for 3 cycles every 21 days before ASCT

Serious Adverse Event	Cycle 1 (n=55)		Cycle 2 (n=53)		Cycle 3 (n=51)		Total** (n=55)		Recovered
CTCAE grade (n)	3	4	3	4	3	4	3	4	
Febrile neutropenia	5	1	0	0	3	0	8	1	All
Infection	0	0	1	0	1	0	2	0	All
Renal function disorder	0	0	0	0	2	0	2	0	With sequela*
Sepsis	0	0	0	1	1	0	1	1	All
Epistaxis	0	0	1	0	0	0	1	0	All
Fever	0	0	0	0	1	0	1	0	All
Elevated liver enzymes	0	0	0	1	0	0	0	1	All
Infusion related reaction	0	0	1	0	0	0	1	0	All
Malaise	1	0	1	0	0	0	1	0	All
Nausea/vomiting	1	0	0	0	1	0	1	0	All
Periodic paralysis (hypokalemia)	1	0	0	0	0	0	1	0	All
Total	**8**	**1**	**4**	**2**	**9**	**0**	**19**	**3**	
Individual patients†	*7*	*1*	*4*	*2*	*7*	*0*	*15*	*3*	
Individual patients total‡	*8 (15%)*		*6 (11%)*		*7 (14%)*		*18 (33%)*		

	Pre-ASCT response	Post ASCT response
mCR	42 (81%)	46
mPR	5 (10%)	1
PD	5 (10%)	

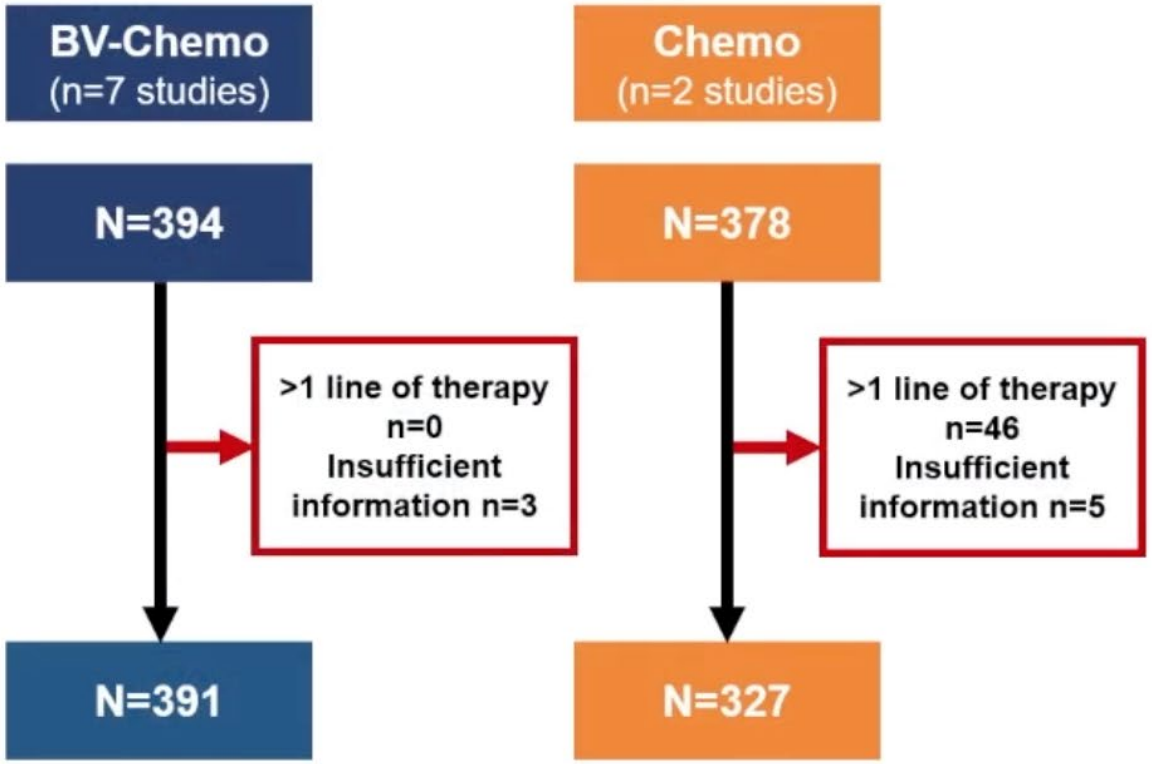


Kersten MJ et al, Haematologica 2021



BV combined with chemio vs chemio only (multi-trial analysis)

Flow-chart of inclusion

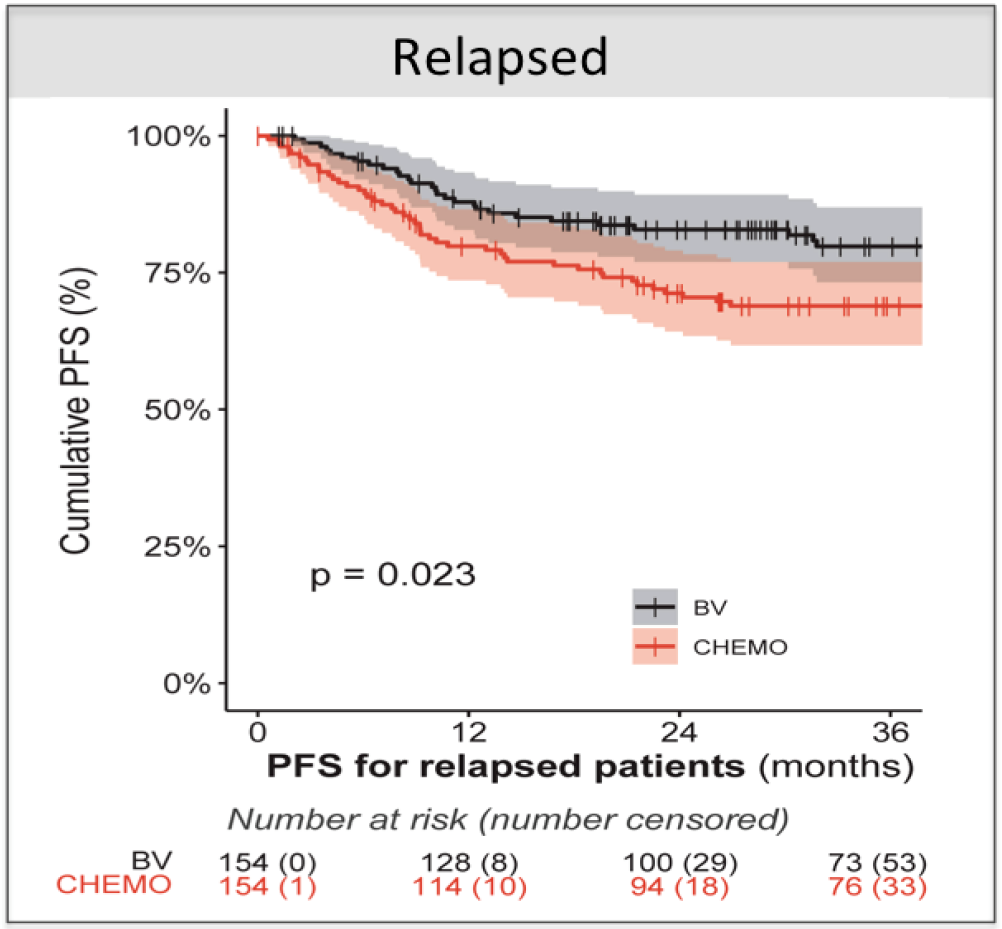


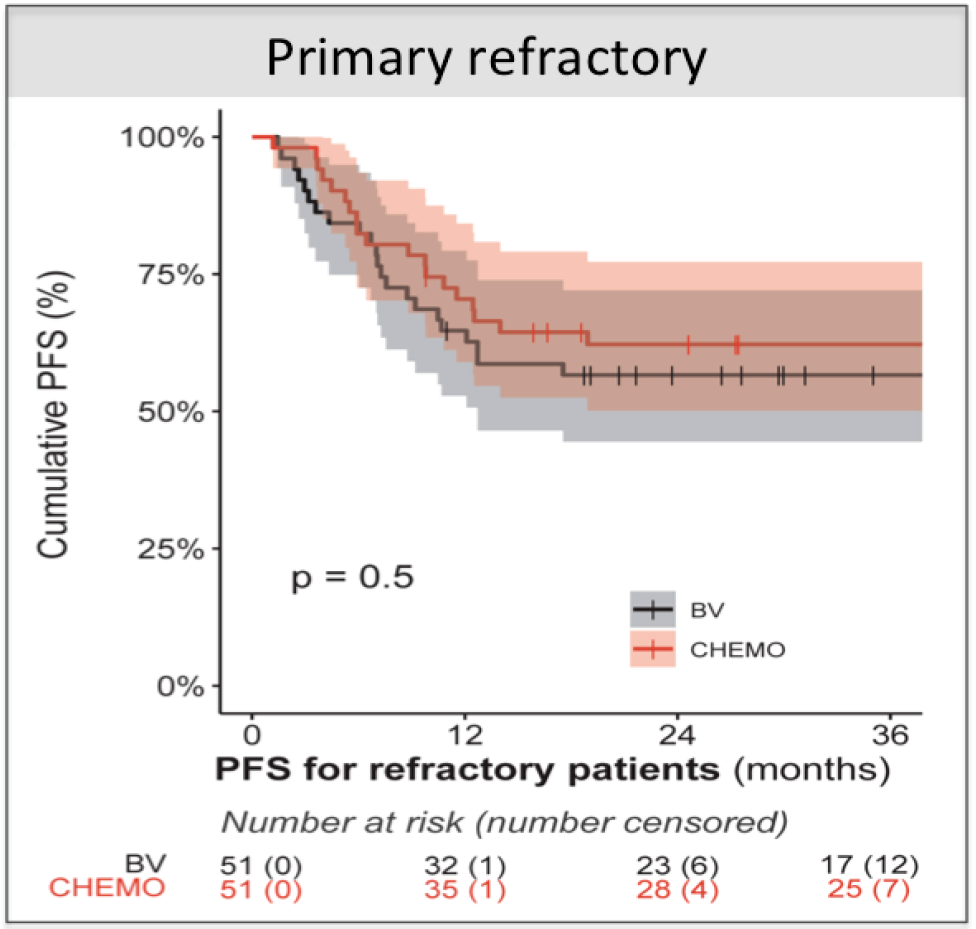
Study characteristics

Study	Regimen	N	Primary refractory
Kersten, 2020	BV-DHAP	65	39%
Garcia-Sanz, 2019	BV-ESHAP	65	60%
Broccoli, 2019	BV-Benda	40	70%
LaCasce, 2018	BV-Benda	55	51%
Cole, 2018	BV-Gem	45	64%
Herrera, 2018	BV-ICE (seq)	57	54%
Moskowitz, 2017	BV-ICE (seq)	64	53%
Moskowitz, 2012	ICE/GVD	94	43%
Jostings, 2010	DHAP	233	5%

Driessen J et al, Blood Adv 2024

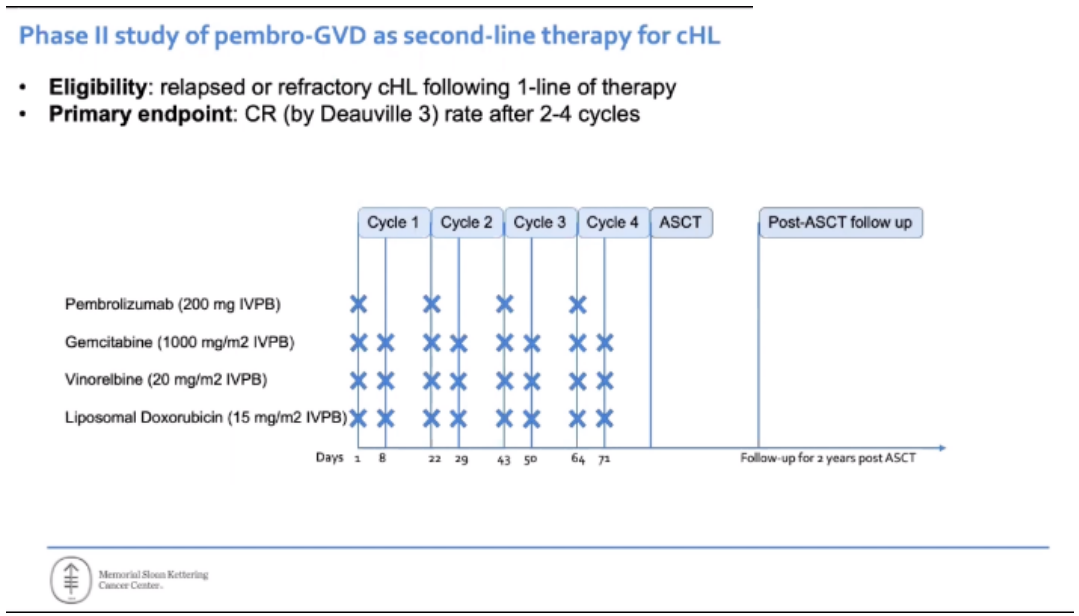
BV combined with chemio vs chemio only: PFS

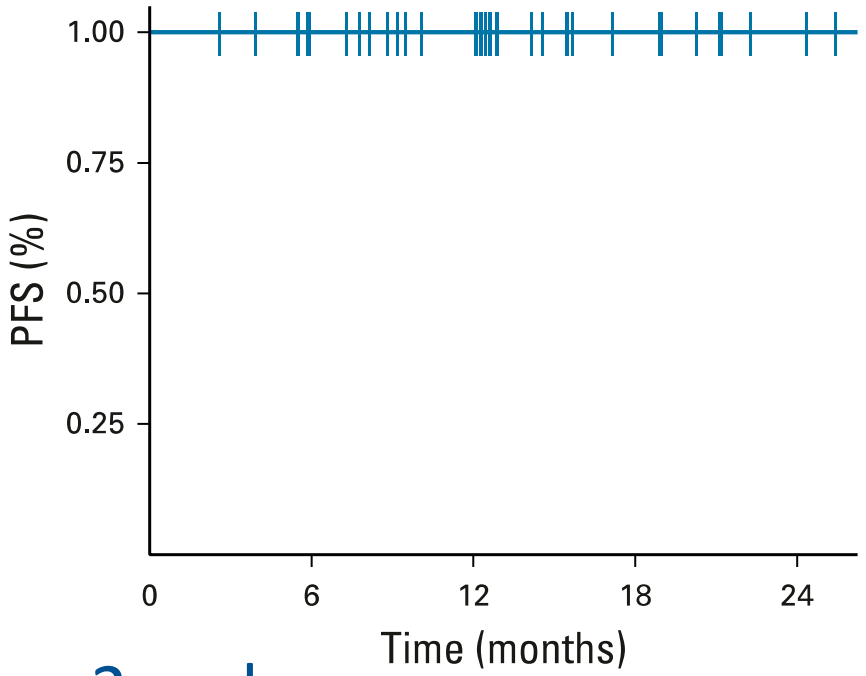




Driessen J et al, Blood Adv 2024

Pembro plus GVD as first salvage





30/39 pts (77%) proceeded to ASCT after 2 cycles

CR rate for the whole study population was 94%

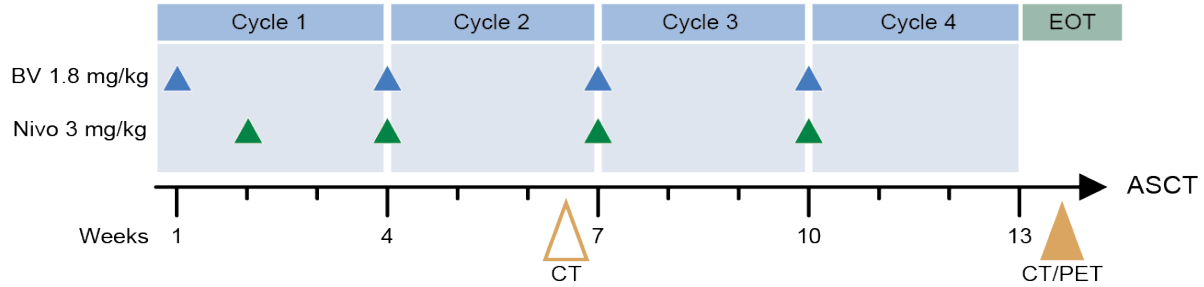
No safety alarms after ASCT

Is it time to identify a subgroup of patients who can spare transplantation?

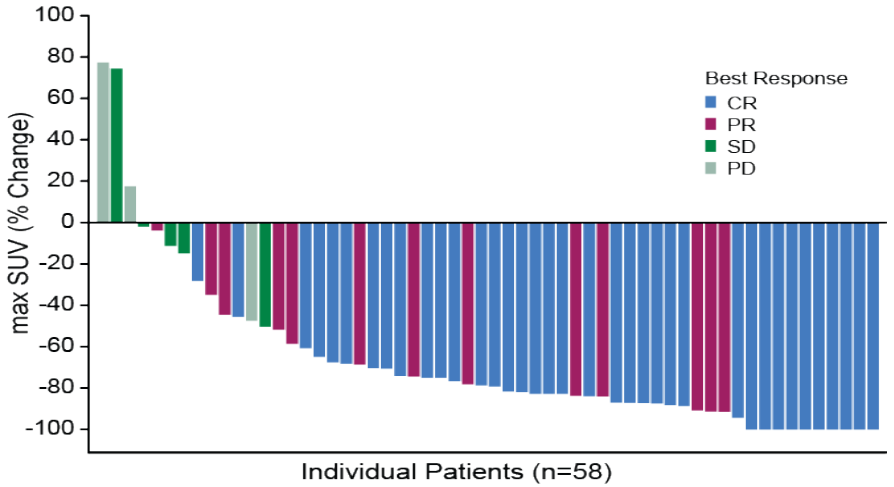
Moskowitz AJ et al, J Clin Oncol 2021

Nivo&BV as *chemo-free* bridge to ASCT

ORR: 83%, CR 62%;
54/62 pts underwent ASCT.
6-months PFS: 89%



Patient demographics and disease characteristics	N = 62
Median age, years (range)	36 (18-69)
Gender (M/F)	30/32
Disease status relative to frontline tx, n (%)	
Primary refractory	28 (45)
Relapsed, remission duration ≤1 yr / >1 yr	19 (31) / 15 (24)
Bulky disease at baseline, n (%)	8 (13)
Extranodal disease at baseline, n (%)	16 (26)
Disease stage at initial diagnosis, n (%)	
I/II	37 (60)
III/IV	24 (39)
Unknown	1 (2)
Median prior therapies[a] (range)	1 (1-3)
Prior chemotherapy regimens, n (%)	
ABVD	56 (90)
BEACOPP	2 (3)
Stanford V	2 (3)
Other[b]	6 (10)
Prior radiation	9 (15)



IRRs occurred in 25 pts (41%), most frequently during the Cycle 2 BV infusion→mandatory premedication

Herrera AF et al, Blood 2018

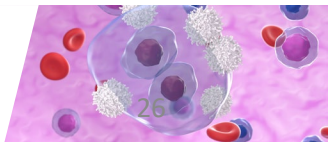
Post-ASCT consolidation

2-4 salvage chemotherapy cycles and hematopoietic stem cells harvest

ASCT

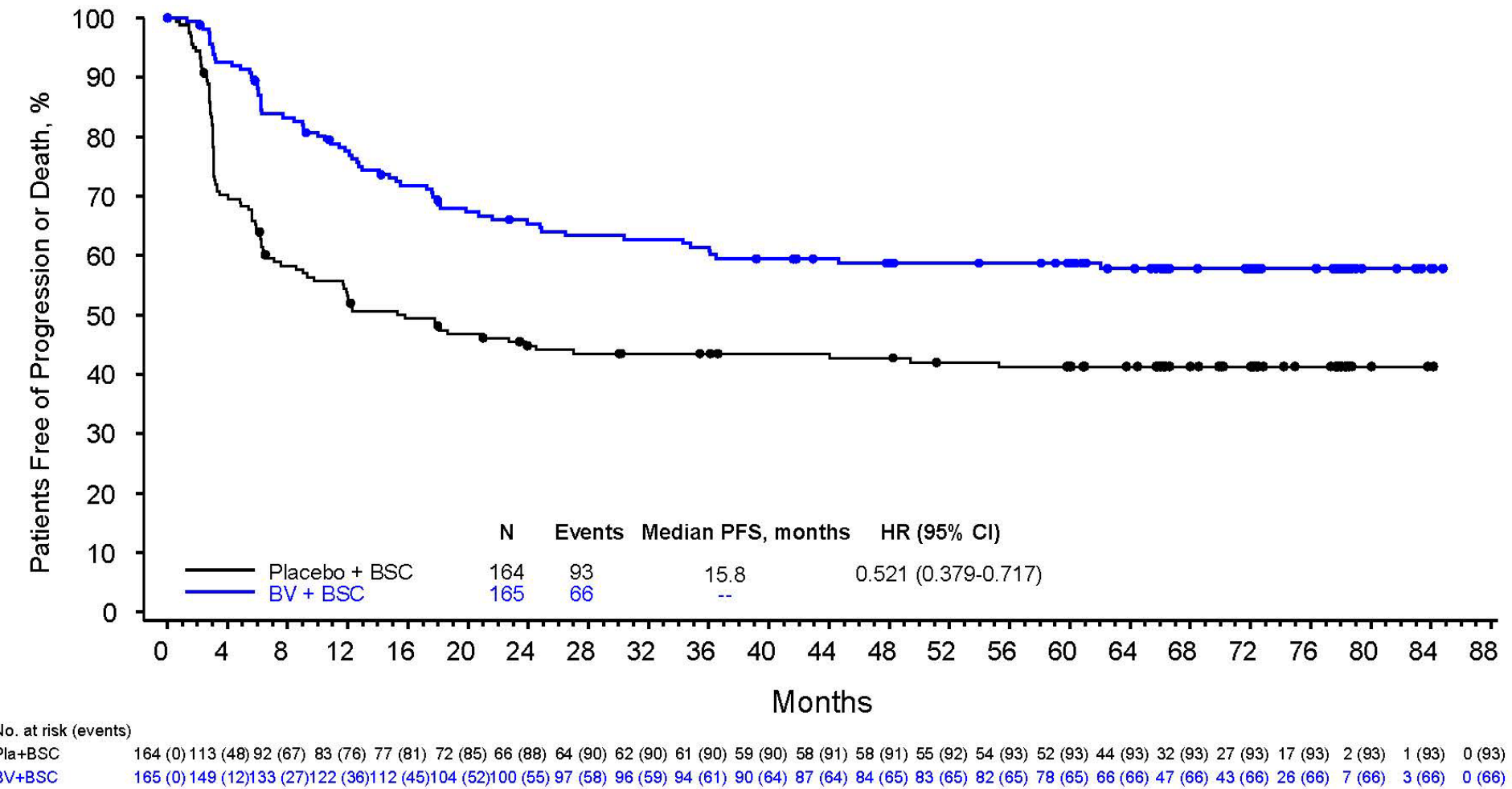
Consider consolidation for High-risk patients : Radiotherapy/ Brentuximab-Vedotin/CPI

Follow-up



Brentuximab-Vedotin consolidation for high-risk patients

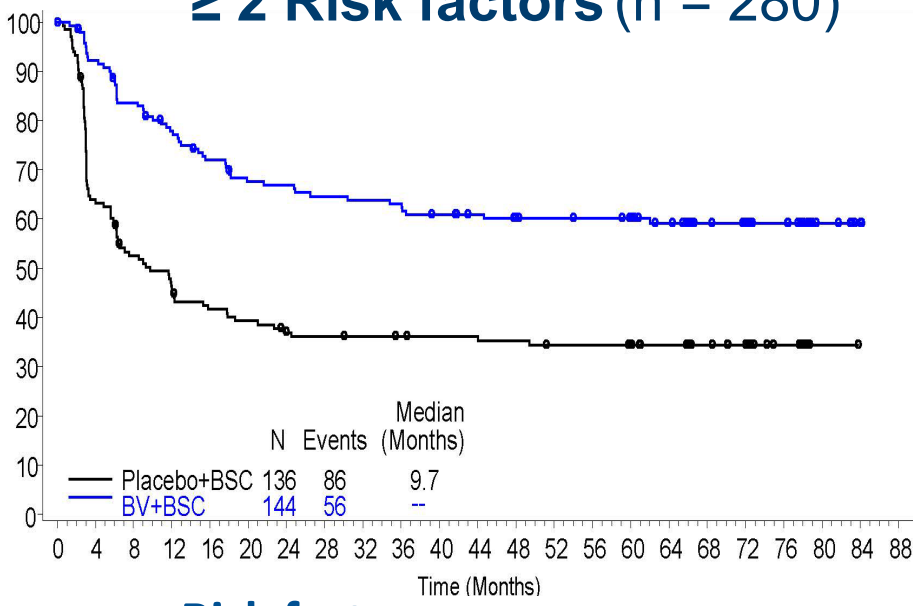
AETHERA Trial



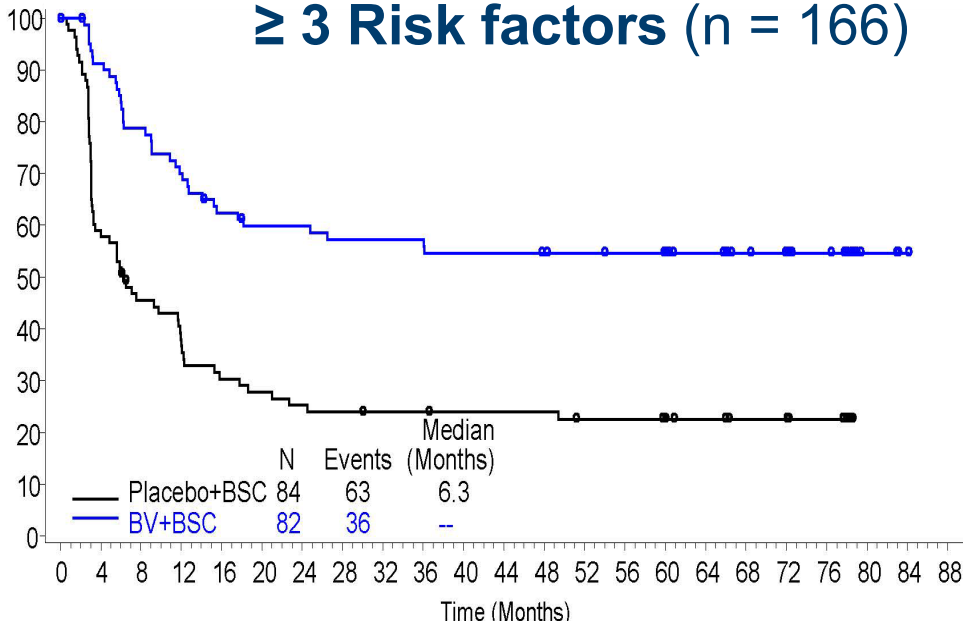
Moskowitz CH, et al. Blood 2018

AETHERA Trial

≥ 2 Risk factors (n = 280)



≥ 3 Risk factors (n = 166)



Risk factors:

- Primary refractory or relapse < 12 months from completion of front-line tx
- Less than CR achieved with salvage treatment
- >1 previous salvage treatment
- Extranodal disease at relapse or progression after frontline therapy
- B symptoms before starting salvage therapy

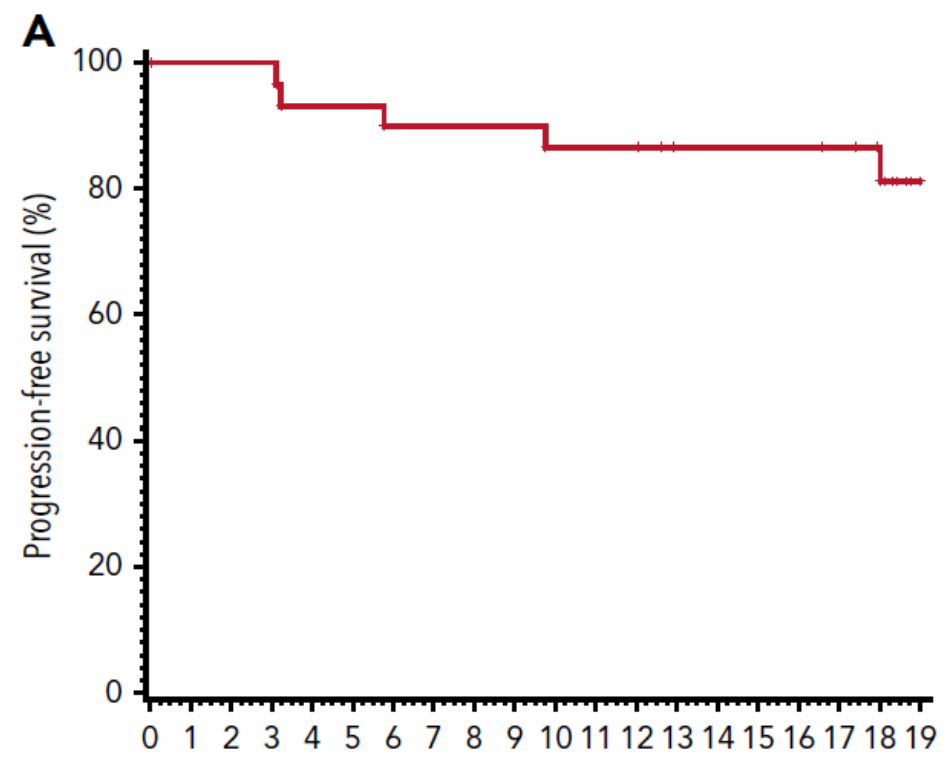
Moskowitz CH, et al. Blood 2018

Pembro as post ASCT consolidation

Phase 2 study of pembrolizumab in 30 pts. Pembrolizumab was administered at 200 mg IV every 3 weeks for up to 8 cycles, starting within 21 days of post-ASCT discharge

KEY POINTS

- PD-1 blockade using pembrolizumab administered after ASCT has an acceptable safety profile.
- This treatment results in a high PFS in patients with cHL, including in high-risk patients

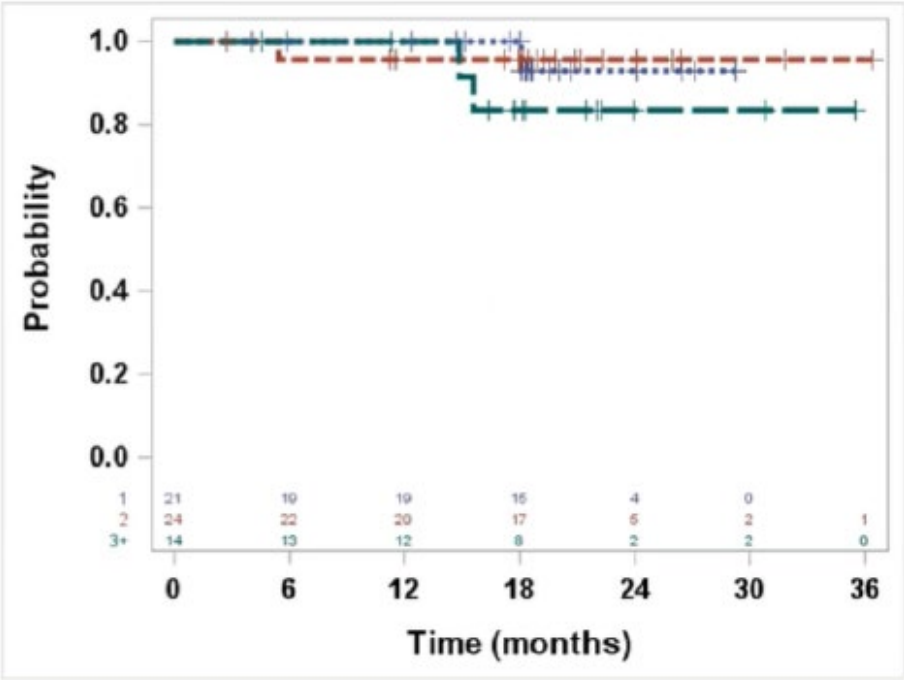


Armand P et al, Blood 2019

Nivo&BV as post-ASCT consolidation

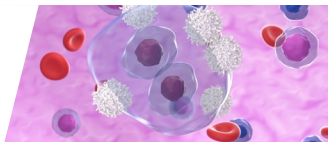
- **59 r/r HL** patients enrolled after ASCT
- Post-ASCT **therapy**: brentuximab vedotin (1
(3 mg/kg) intravenously starting 30–60 days
day 1 of each 21-day cycle for up to 8 cycles
- The most common adverse events w
neuropathy (31 [53%] of 59) and **neutropeni**
- **Immune-related adverse events** requiring c
17 (29%) of 59 patients. No treatment-relate
- The **18-month PFS** in all 59 patients was **94%** (95% CI 84–98)

PFS according to number of risk factors



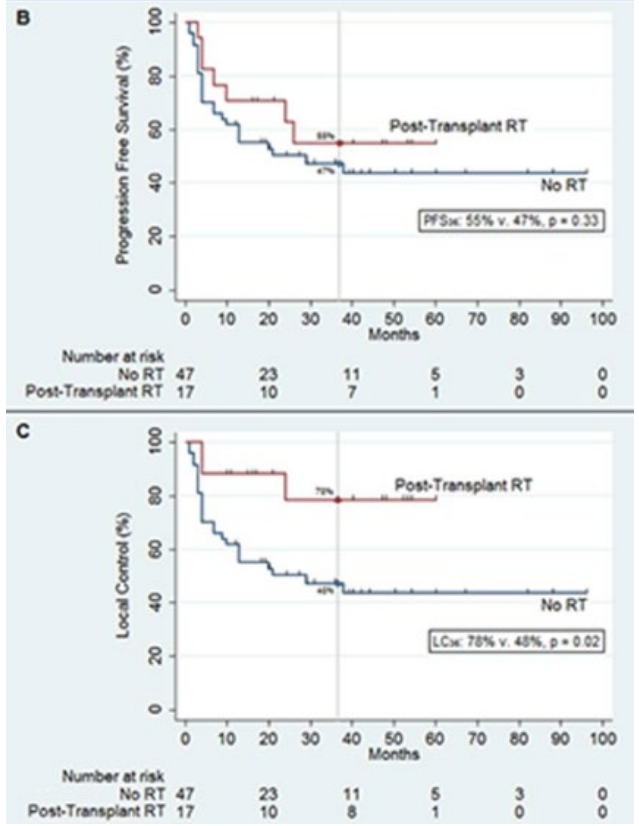
19-month PFS in patients with:
- 1 risk factor (n=1): 93% (95 CI: 59–99)
- 2 risk factors (n=24): 96% (95 CI: 73–99)
- 3+ risk factors (n=14): 83% (95 CI: 48–96)

Herrera AF et al, Lancet Hematol 2023



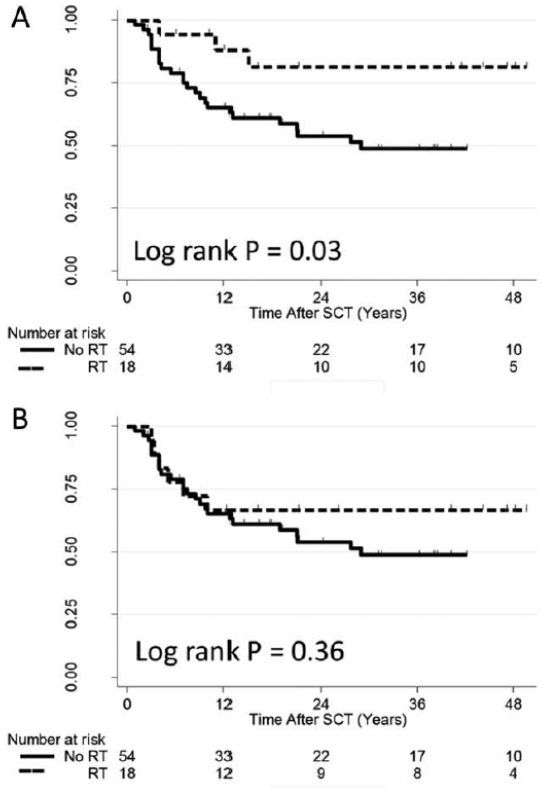
Radiotherapy consolidation after ASCT

UPENN



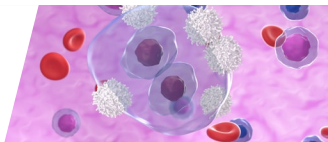
Jauhari S et al, Blood 2015

MD Anderson



Milagros S et al, Cancer 2016

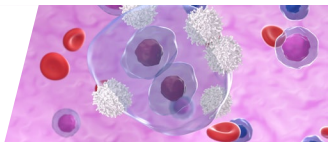
Two retrospective studies from US showing similar results: peri-transplant **RT** achieve a **superior local control** that does not translate into a benefit in survival



Radiotherapy consolidation after ASCT

There is **no randomized prospective trial** evaluating the role of post-transplant radiotherapy (RT) consolidation in R/R cHL; however, several retrospective studies support this strategy, particularly for patients with early-stage disease and bulky sites.

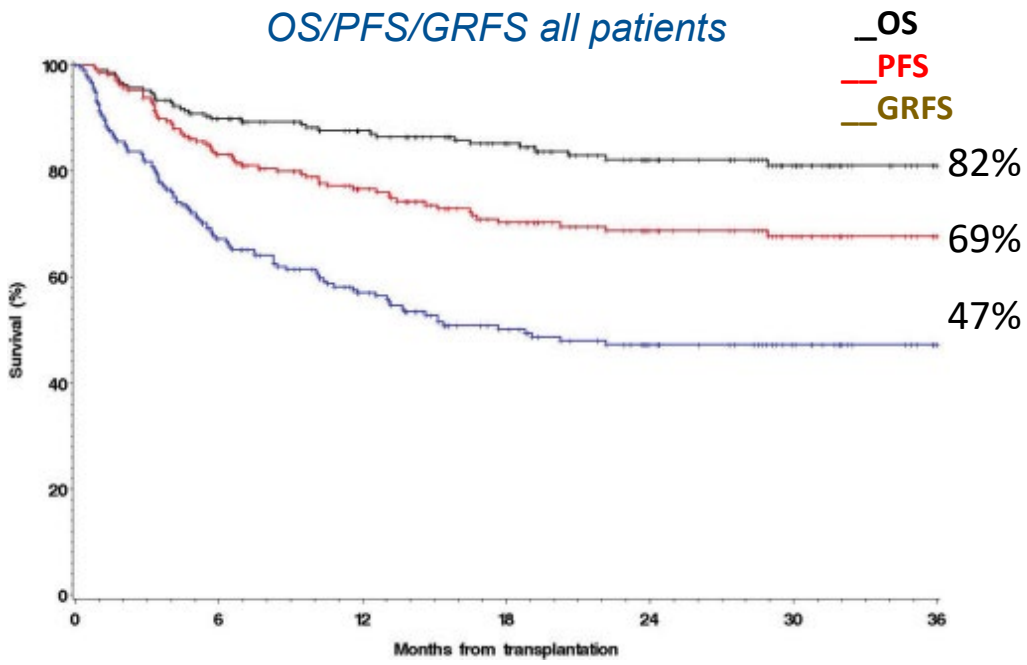
- Consider RT consolidation for patients who are **RT-naïve** with **localized bulky disease**, particularly for those in PR pre-transplant not eligible to further bridge therapy and/or those who are poor candidates for BV maintenance
- Plan and deliver the lowest dose supposed to be effective and limit fields' extension in order to not increase late toxicity in a population considered at high risk for second neoplasia
- Do not exceed **30 Gy for PET negative** and **36 Gy for PET positive** sites



The role of AlloSCT in the era of new drugs

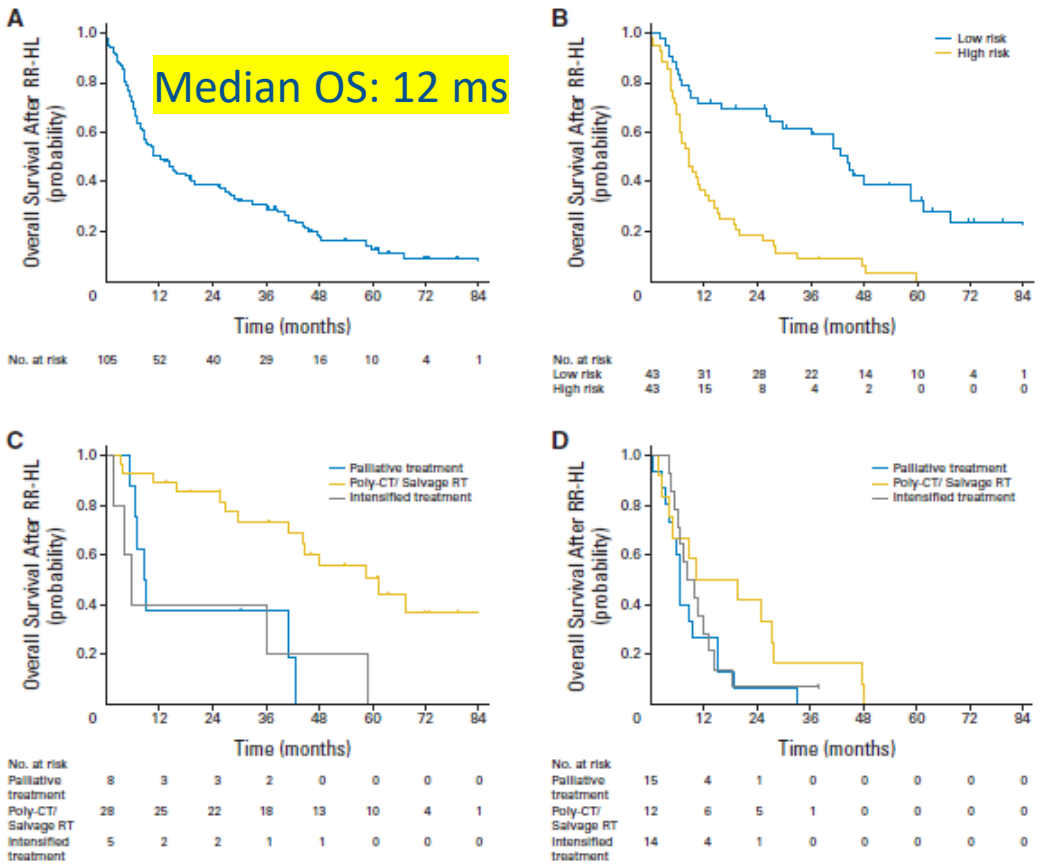
Allogeneic is the only potentially curative approach in younger, fit, very high-risk patients since triple **refractory (to ASCT, BV and CPI).** Major limitations of allogeneic transplantation are acute and late toxicity, failure to achieve metabolic response and donor availability

- Consider **early search for donor** in high-risk situation
- Refer patient to a transplant unit with expertise in lymphoma
- Make sure that **wash-out** period from last **CPI** dose is adequate to reduce graft incidence and severity
- Use **reduce-intensity conditioning (RIC)**
- Use post-transplant cyclophosphamide for graft prophilaxis **(PTCy)**

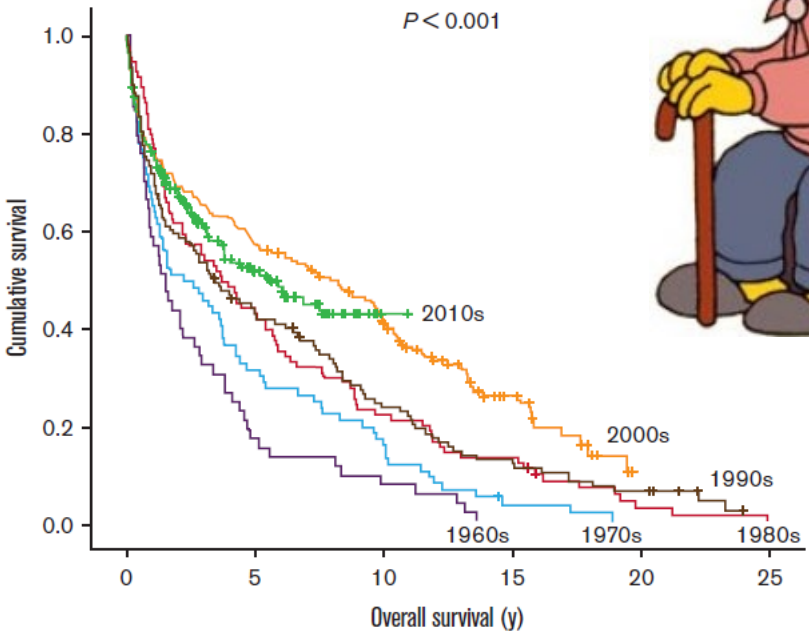


Merryman et al. Leukemia, 2021

The elderly r/r HL: an unmet need



Boll B et al, JCO 2013



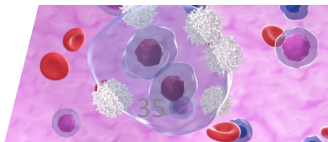
Number at risk = 744

1960s	53	9	4	0	0	0
1970s	77	24	12	2	0	0
1980s	93	39	20	12	2	0
1990s	120	50	26	14	7	0
2000s	183	105	69	20	0	-
2010s	218	56	1	0	-	-

Cheng PTM et al, Blood Adv 2022

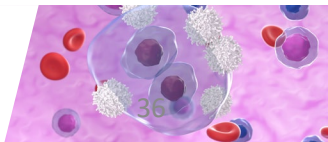
The elderly r/r HL: treatment options

- Bendamustine alone (be careful to infection rate and keep in mind antimicrobical prophilaxis)
- Brentuximab-vedotin single agent (fit patients, excluded if severe pre-existing polineuropathy)
- CPI single agent (fit and unfit patients, excluded if previous history of autoimmune disease)
- Combos to be carefully considered due to increased toxicity
- Radiotherapy (but very often the elderly present with advanced stage disease)
- Waiting for a valid option *per os* (CPI)…



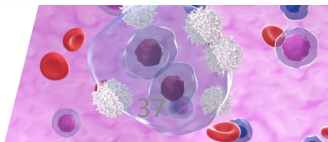
Relapsed/refractory HL: summary and conclusion-I

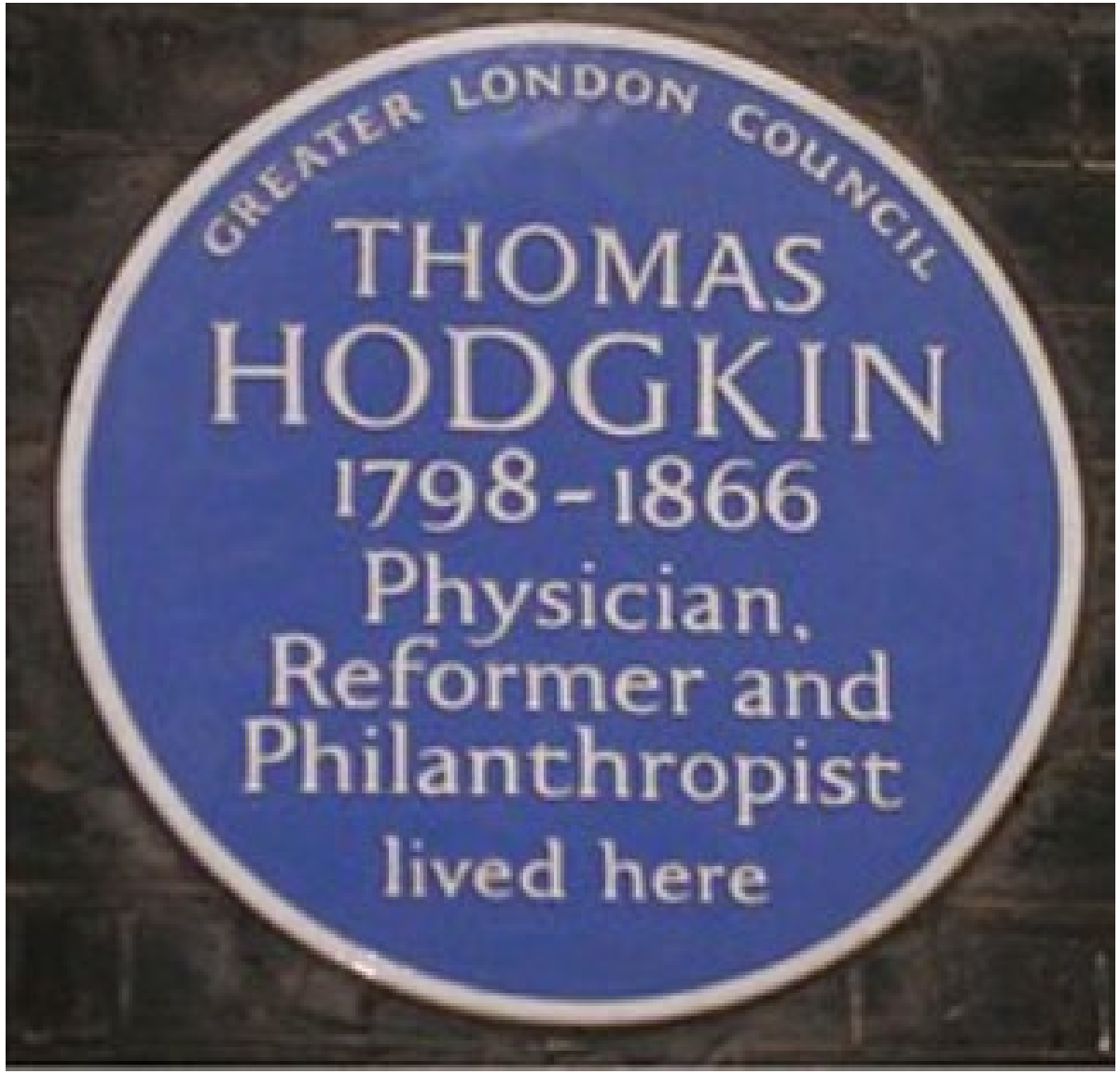
- 10-40% of HL patients require salvage therapy due to refractory or relapsed disease
- Biopsy should be repeated at relapse whenever possibile
- For younger fit patients, the standard of care is salvage therapy followed by ASCT
- Salvage therapy can be choosen among strategies tested in phase 2 trials and randomized data on head-to-head comparison between different regimens are lacking
- The main goal of salvage therapy is to achieve complete metabolic response before transplantation



Relapsed/refractory HL: summary and conclusion-I

- Efficacy of salvage regimens can increase when new drugs (BV and/or CPI) are combined to conventional chemotherapy
- Are we ready to spare ASCT in super-selected patients achieving complete remission after salvage with new combos? Experimental!
- High-risk patients should be offered post-autologous consolidation (BV and/or CPI, radiotherapy)
- For elderly r/r HL patients a standard of care is lacking and they represent an unmet medical need: clinical trial are encouraged in this setting
- The landscape of salvage therapy is partially determined by changes in first-line therapy



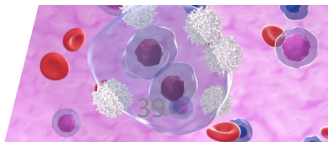


chiara.rusconi@istitutotumori.mi.it

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Thanks for your attention!

Back-up slides

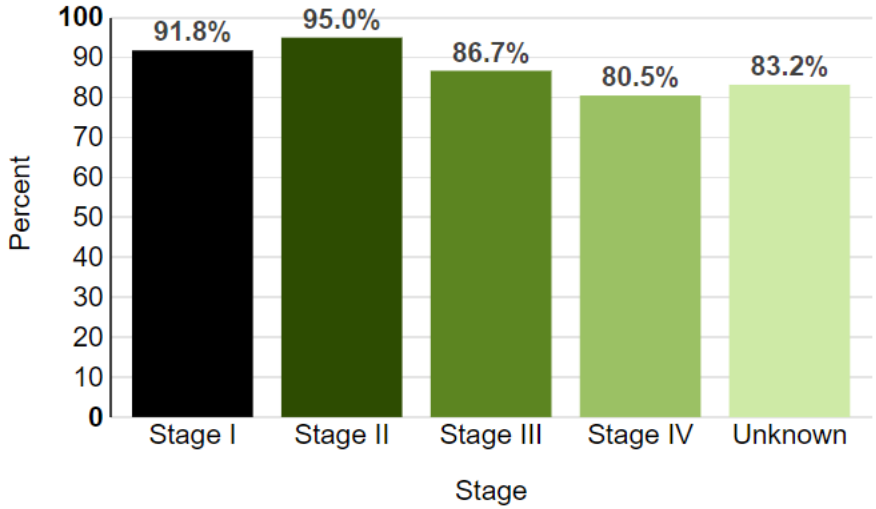


Hodgkin lymphoma and prognosis

5-Year
Relative Survival

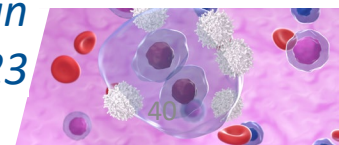
88.9%

HL prognosis is favourable and long-term relative survival is excellent

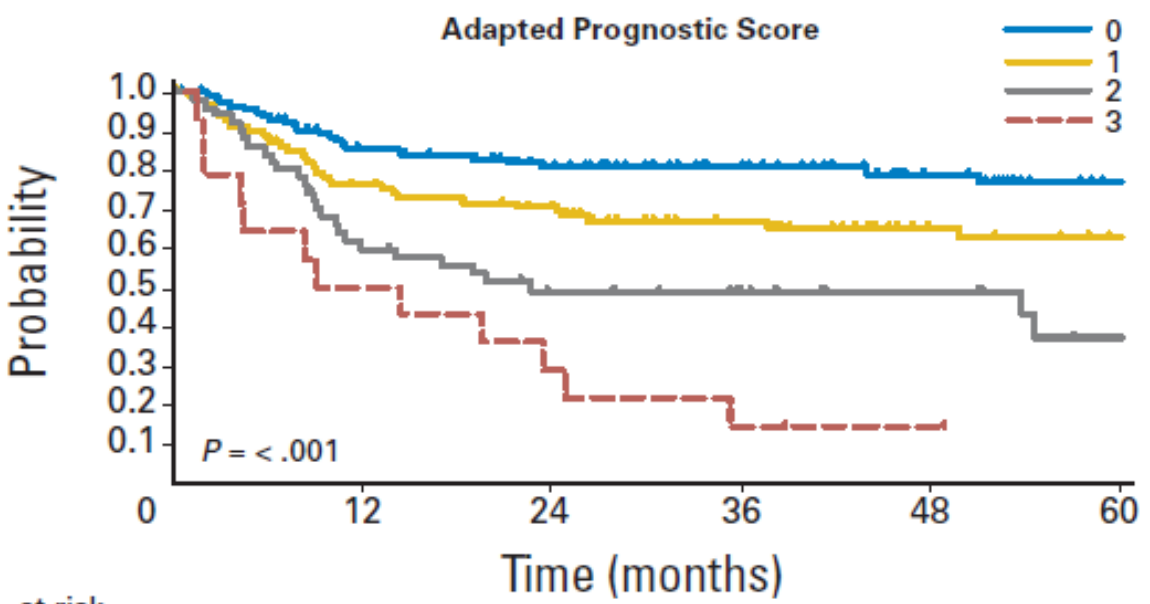


5-year survival is over 80% also in patients presenting with advanced stage disease at diagnosis

Surveillance, Epidemiology and End Results Program, National Cancer Institute. Cancer Stat Facts: Hodgkin Lymphoma. Accessed at https://seer.cancer.gov/statfacts/html/hodg.html on 24 July 2023



Prognosis at relapse: progression-free survival



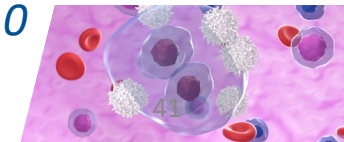
No. at risk

0	117	92	74	53	35	21
1	96	69	59	42	25	19
2	52	29	21	15	10	5
3	14	7	4	2	1	0

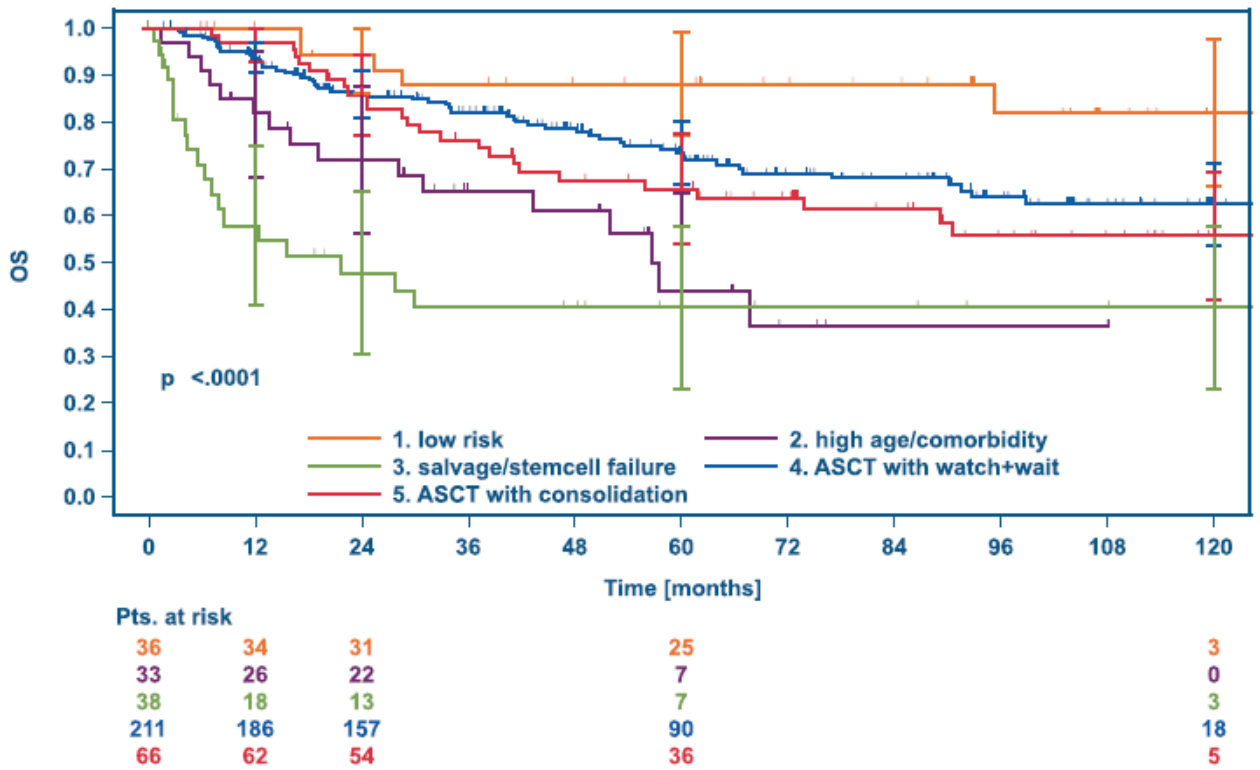
Prognostic score based on 3 simple clinical variables at relapse predicts PFS:

- Stage IV
- Early relapse (≤ 12 months)
- Anemia (<10.5 g/dl female or <12 g/dl male)

Josting A et al, JCO 2010



Inferior survival for not transplanted r/r HL patients



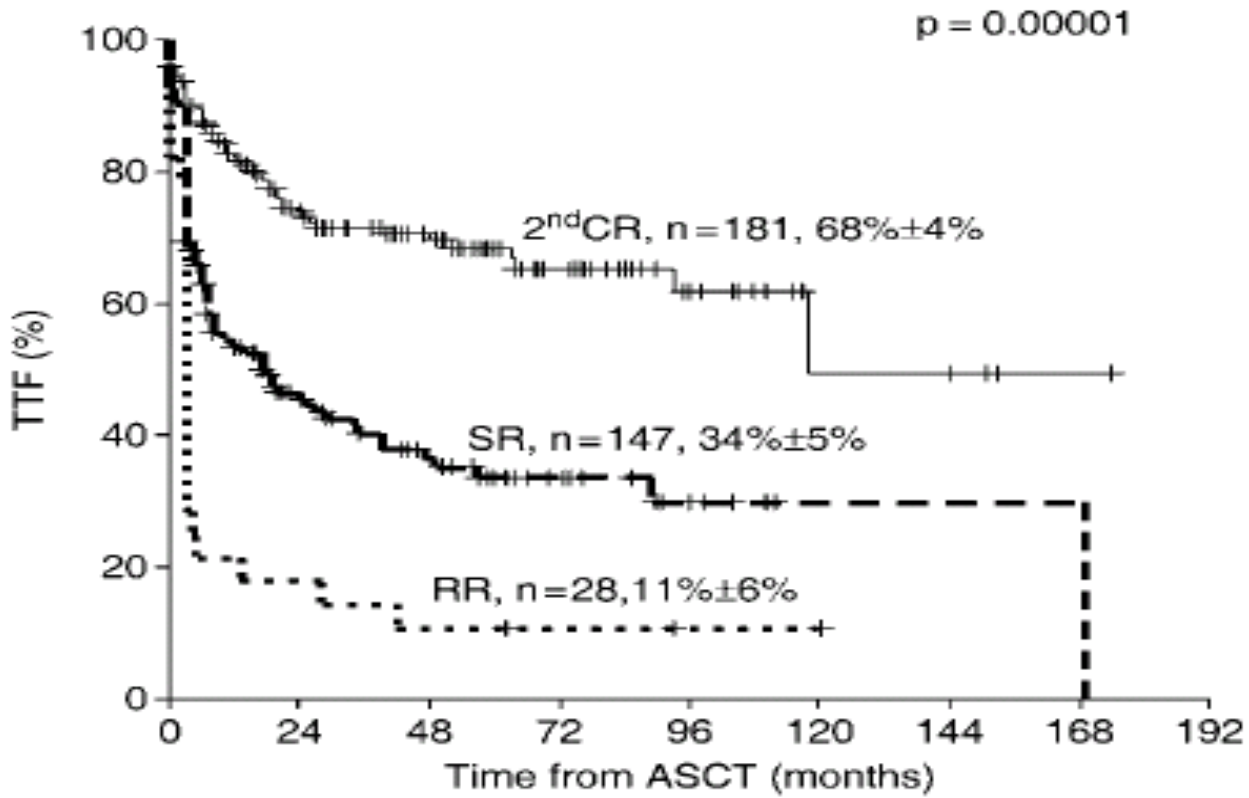
Inferior OS for:

- elderly patients and/or patients with co-morbidities
- patients not proceeding to ASCT due to refractoriness to salvage treatment

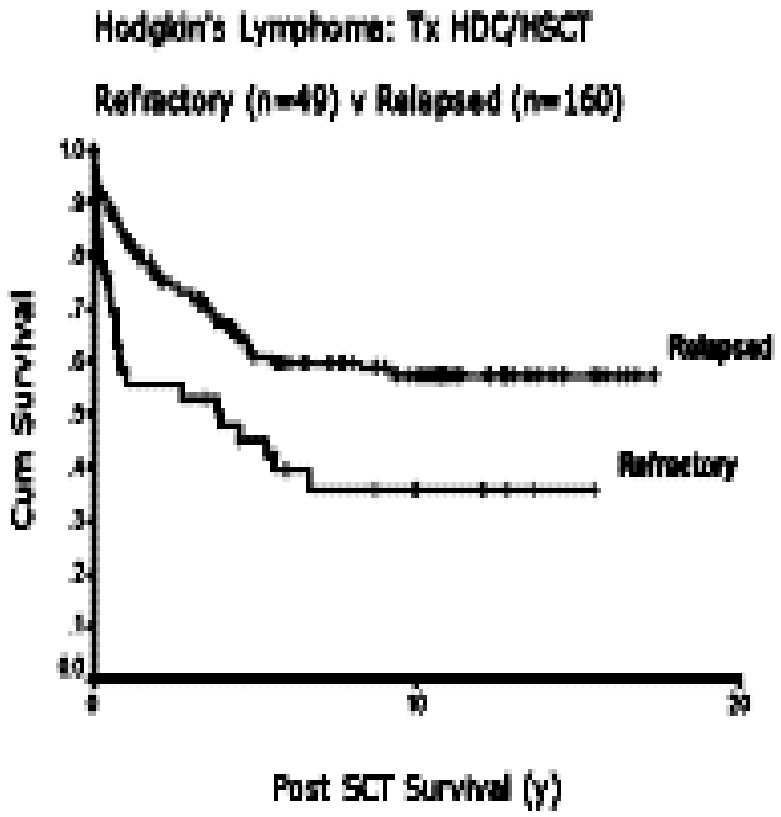
Bröckelmann PJ et al, Leukemia 2022

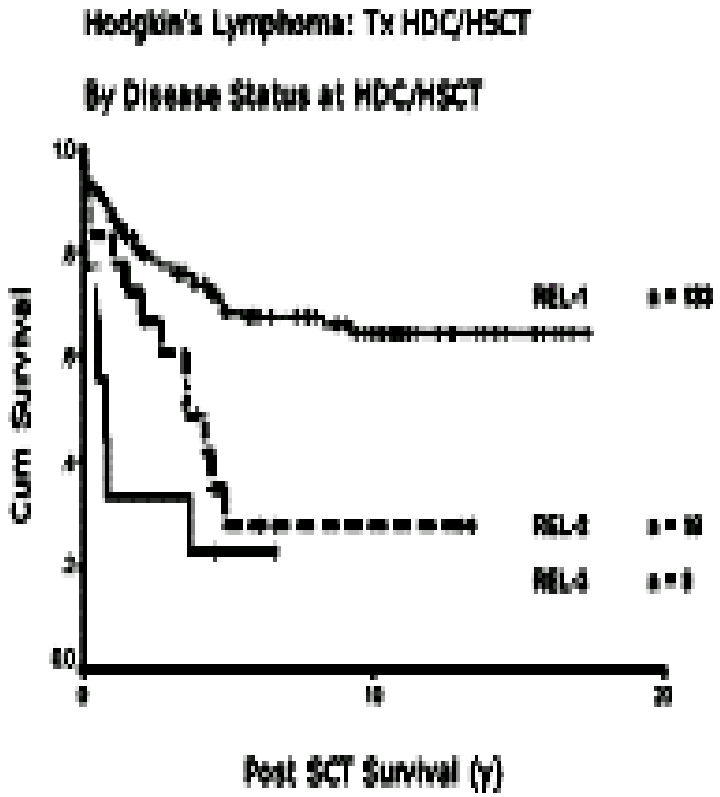
TTF according to disease status

Sureda, 2005



ASCT and OS: British Columbia experience





Connors, Blood 2003

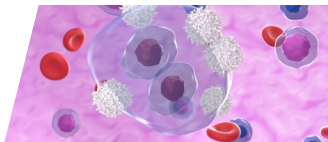
First salvage therapy: conventional CT schemes

Goals:

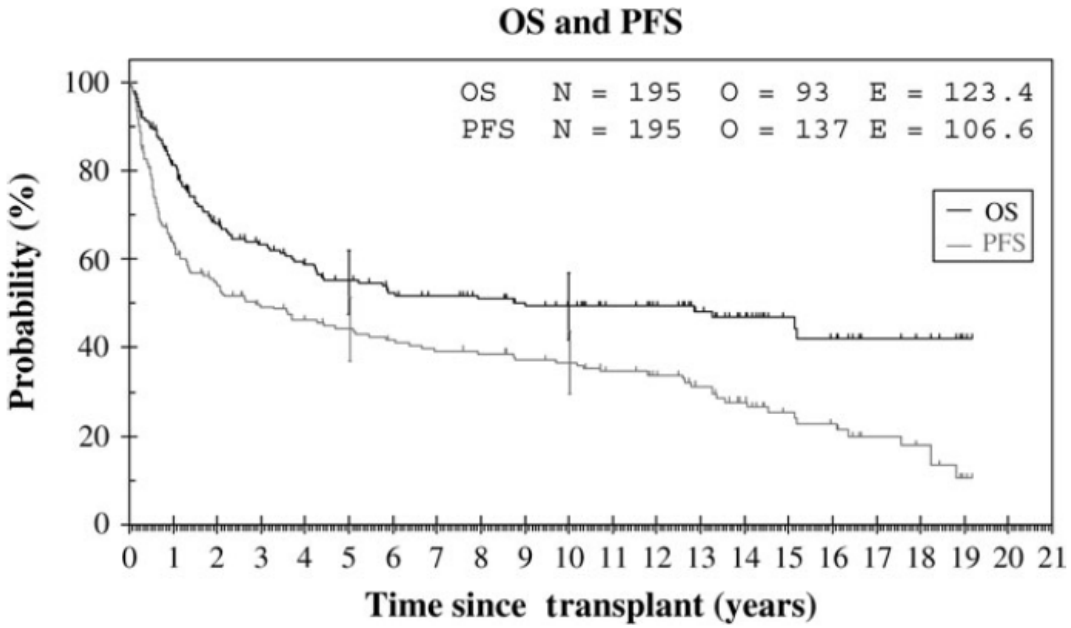
- **Achieve CR = negative PET before ASCT**
- **Mobilize adequate PBSC**
- **Minimize toxicity**

Chemotherapy Regimen	N pts	% CR	% ORR
BeGEV	**59**	**73**	**83**
ICE	65	26	85
ICE/AugICE	97	60	n/a
DHAP	102	21	89
GVD	91	19	70
IGEV	91	54	81
IEV	51	76	84
GDP	23	17	69

No randomized prospective clinical trials available



Long-term post-ASCT outcome: historical data



Single center (Royal Marsden Hospital, UK) retrospective analysis on 195 consecutive HL who were autografted from 1985 to 2005. Five-year OS/PFS was 55% of 44% and **10-year OS/PFS was 49.4% of 37%** for whole group

Twenty (10%) patients developed **second cancer** (seven secondary acute myeloid leukaemia/myelodysplastic syndrome). Probability of developing second cancer at 10 years was 14.7% and 24.8% at 19 years

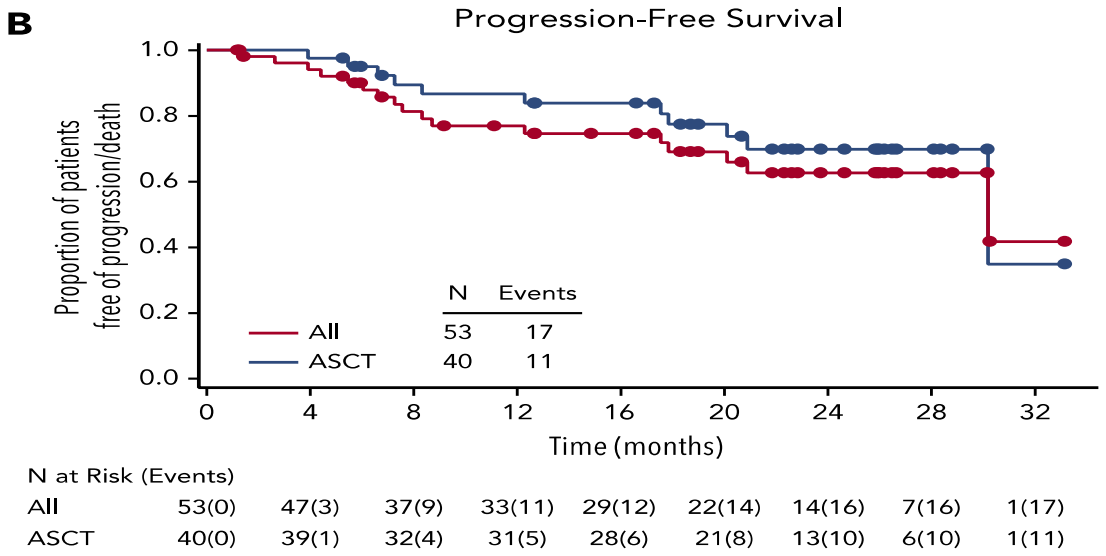
Sirohi B et al, Annals of Oncol 2008

Regimen	Nr patients	ORR (%)	CR (%)	Survival	Biblio
ICE	65	88	26	@43 ms EFS 82% se CR	Moskowitz, Blood 2001
DHAP	102	89	21		Josting, Ann Oncol 2003
IGEV	91	81	54	@3yrs FFP 53%, OS 70%	Santoro, Haematol 2007
BeGEV	59	83	73	@2yrs OS 62%, PFS 78%	Santoro, JCO 2016
BV	37	68	35		Chen, Biol Blood Marrow Transplant 2015
BV ICE	44	NR	27	@2yrsEFS 80%, OS 95%	Cassaday, Blood 2016

Benda-BV

Characteristic	N = 55
Age, median (range), y	36 (19-79)
Male, n (%)	24 (43.6)
White, n (%)	46 (83.6)
ECOG status, n (%)	
0	36 (65.5)
1	18 (32.7)
2	1 (1.8)
Months since HL diagnosis, median (range)	13.8 (3-98)
Disease stage at diagnosis, n (%)	
I	3 (5.5)
II	23 (41.8)
III	14 (25.5)
IV	15 (27.3)
Frontline therapy received, n (%)*	
ABVD†	50 (90.9)
Stanford V	3 (5.5)
AVD	1 (1.8)
VAMP	1 (1.8)
Response to frontline therapy, n (%)	
Primary refractory‡	28 (50.9)
Relapsed	27 (49.1)
CR > 1 y	17
CR ≤ 1 y	10
Prior cancer-related radiotherapy, n (%)	15 (27.3)
Baseline disease characteristics, n (%)	
B symptoms	12 (21.8)
Bulky disease§	5 (9.1)
Extranodal disease	17 (30.9)
Bone marrow involvement	9 (16.4)

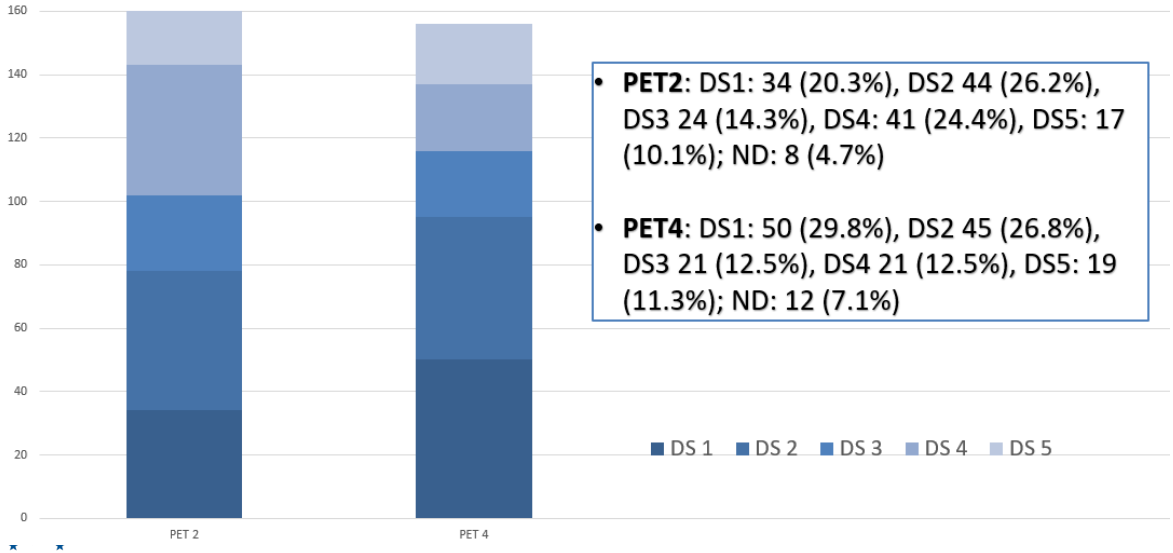
Best clinical response in 53 pts	%
ORR	92.5
CR	73.6
Refractory	64
Relapsed	84



LaCasce A et al, Blood 2018

BeGEV and interim PET

Tab.1 Patients' characteristics at BEGEV start	
Number of pts (%)	168 (100)
M (%)	89 (53)
Median age (range)	37 (18-72)
Stage N (%): I-II	86 (51.2)
III	29 (17.3)
IV	53 (31.5)
B symptoms	28 (17)
EN sites	57 (34)
Second line indication: primary refractory	93 (55)
early relapse (≤ 12 ms)	37 (22)
late relapse (>12 ms)	38 (23)



- **PET2**: DS1: 34 (20.3%), DS2 44 (26.2%), DS3 24 (14.3%), DS4: 41 (24.4%), DS5: 17 (10.1%); ND: 8 (4.7%)
- **PET4**: DS1: 50 (29.8%), DS2 45 (26.8%), DS3 21 (12.5%), DS4 21 (12.5%), DS5: 19 (11.3%); ND: 12 (7.1%)

Multivariate Cox regression model of PFS evaluating PET2 result and presence of adverse clinical characteristics at relapse such as EI (HR 1.01 , CI 95%: 0.59-1.73), time to relapse (primary refractory and early relapse vs late relapse, HR 0.67, CI 95%: 0.37-1.22) and presence of B symptoms (HR 0.97, CI 95%: 0.51-1.85), identified **PET2 positivity as the only predictive factor for PFS** (HR 4.31, CI 95%: 2.54-7.31, p<0.001).

Rusconi C et al, EHA 2023

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Pembrolizumab vs Brentuximab for transplant ineligible r/r HL: KEYNOTE-204

Stratified by prior autologous SCT (yes vs no), status after first-line therapy (primary refractory vs relapsed < 12 mos vs relapsed ≥ 12 mos after end of first-line therapy)

Patients with R/R cHL who relapsed after or are ineligible for autologous SCT and failed 1 prior therapy line*; measurable disease per IWG 2007 criteria; ECOG PS 0/1 (N = 304)

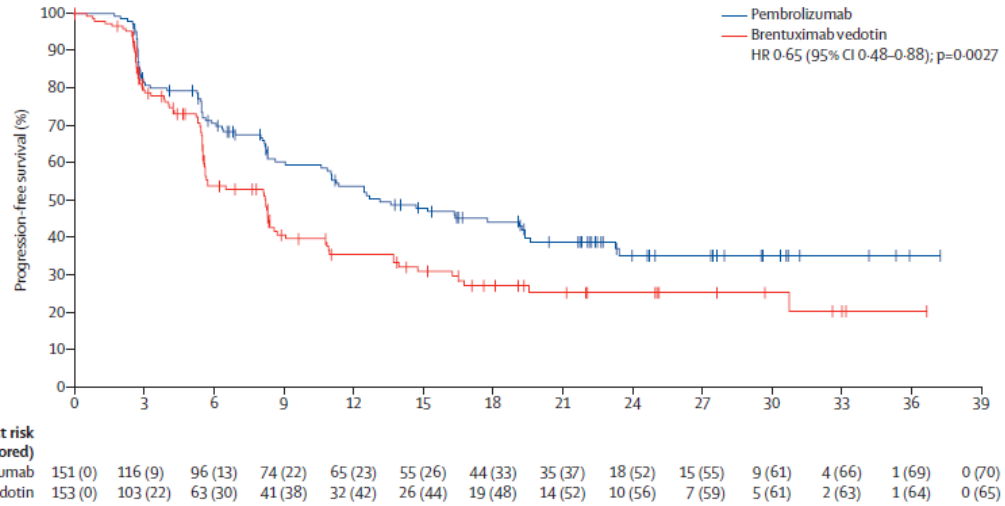
Pembrolizumab 200 mg IV Q3W (n = 151)

Brentuximab Vedotin 1.8 mg/kg IV Q3W (n = 153)

Up to 35 cycles

Follow-up: response, AEs assessed Q12W

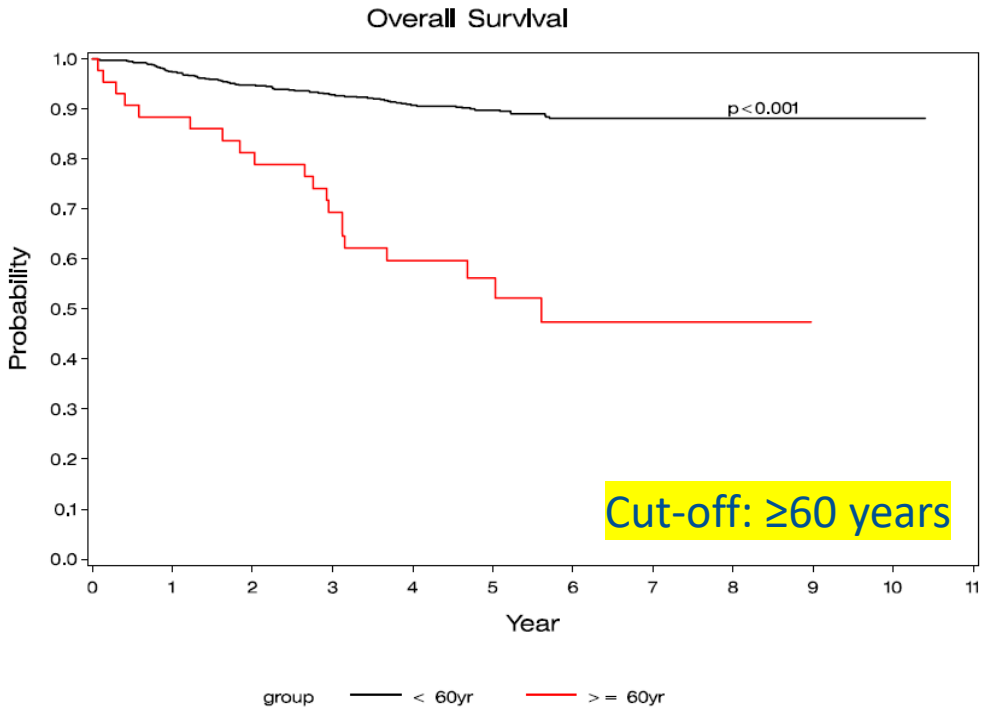
*Prior use of brentuximab vedotin permitted. AEs assessed Q3W during trial period.



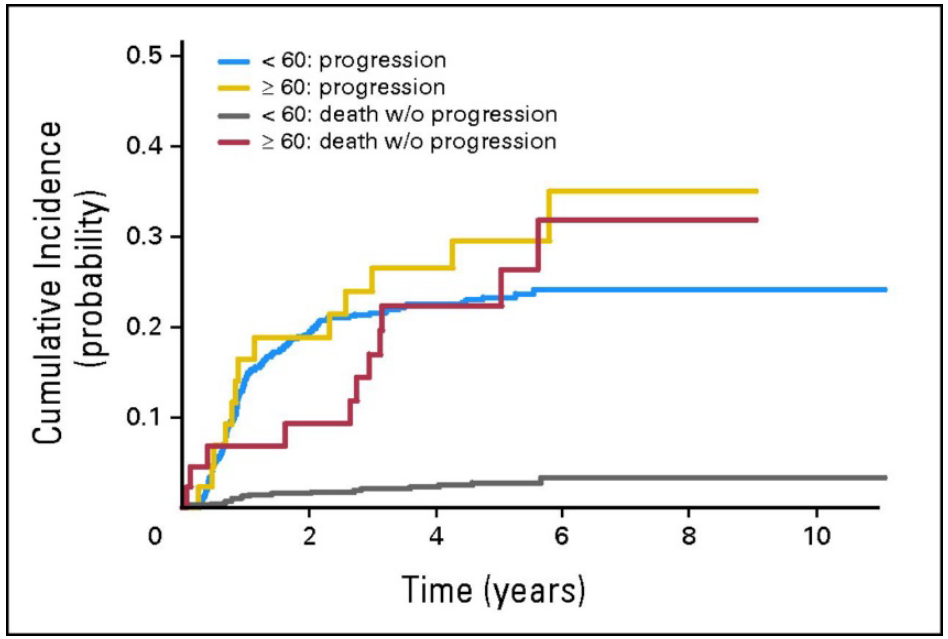
Serious treatment-related adverse events occurred in 24 (16%) of 148 patients receiving pembrolizumab and 16 (11%) of 152 patients receiving brentuximab vedotin.
One treatment-related death due to pneumonia occurred in the **pembrolizumab** group

Kuruvilla J et al, Lancet Oncol 2021

The elderly



Evens AM et al, BJH 2013



Evens AM et al, JCO 2013

- Under-represented in clinical trials: <5-10% (vs 15-25% population)
- Outcomes disproportionately inferior to younger patients (and other cancers)
- Toxicity is a major limit for survival
- Growing scientific interest for this population

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