Relapsed/Refractory Hodgkin Lymphoma in Pediatric, AYA Patients

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Background

Hodgkin lymphoma in paediatric and AYA age groups has excellent prognosis.

Survival rates above 90% have been achieved.

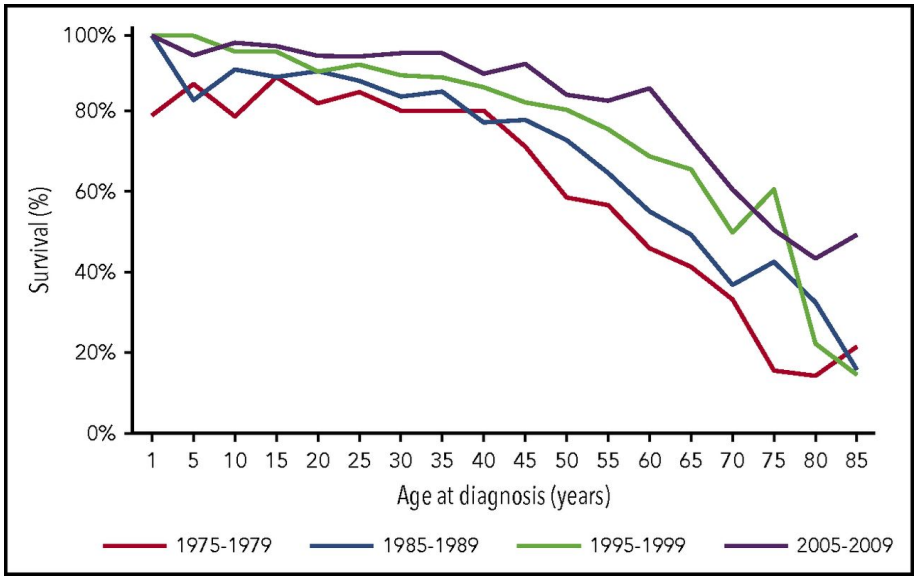
15 to 30% of patients with HL relapse despite optimal primary therapy

Relapsed HL in children also have excellent outcomes, >80% in some series.

Patients with HL - Survival over treatment eras

5-year relative survival rates between the years of 2003 and 2007

- Pediatric (<15 years)- 97.4%
- AYA (15-39 years) - 95.8%
- Adults (≥40 years) - 77.1%



Flerlage JE, Metzger ML, Bhakta N. The management of Hodgkin lymphoma in adolescents and young adults: burden of disease or burden of choice? Blood. 2018 Jul 26;132(4):376–84.

Concerns in the Pediatric/ AYA group

- Long term survivorship is in several decades
- Excess mortality is high in AYA survivors of HL compared to population
- Mortality is contributed by end organ damage, Subsequent malignant neoplasms

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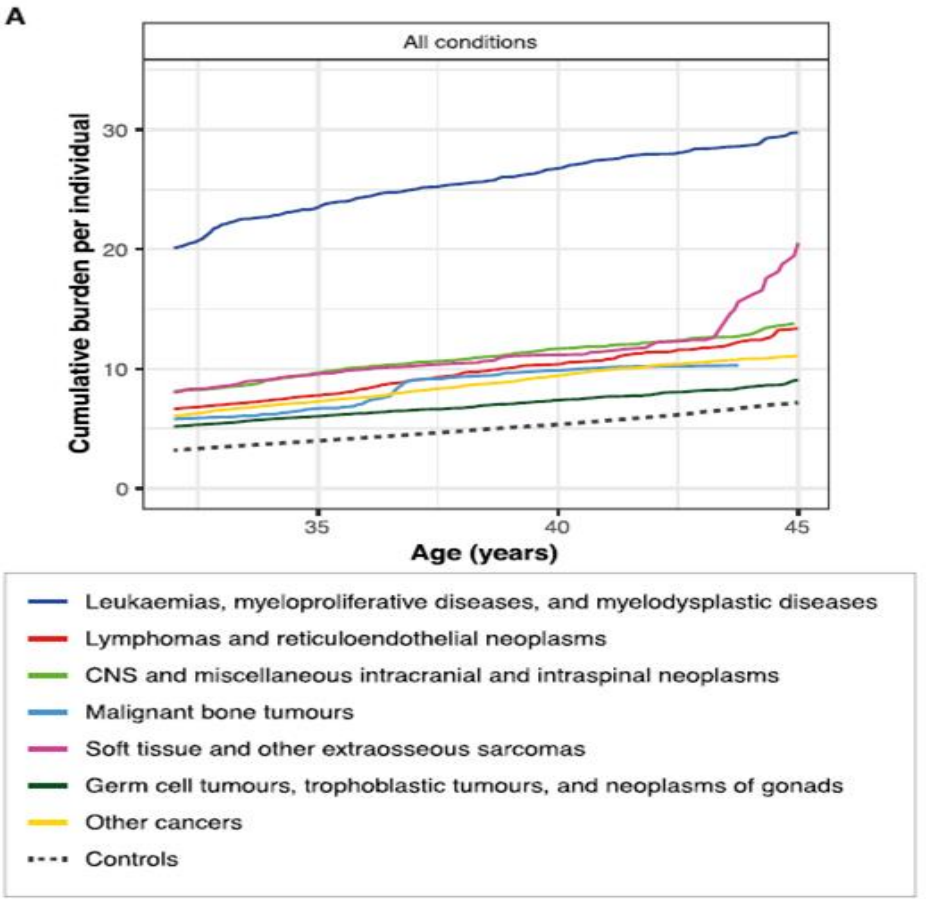
Among 4,063 patients diagnosed with cancer, 3,466 survived ≥ 5 years (85%)

- The cumulative burden of late effects at age 35 was (23.52 per individual [95% CI:19.85–29.33]) to 6.04 [5.32–6.91]).
- Hematological malignancies contributed as a group to the highest burden



Chang WH, Katsoulis M, Tan YY, Mueller SH, Green K, Lai AG. Late effects of cancer in children, teenagers and young adults: Population-based study on the burden of 183 conditions, in-patient and critical care admissions and years of life lost. The Lancet Regional Health – Europe [Internet]. 2022 Jan 1 [cited 2022 Jul 28];12.

In controls, the cumulative burden was 3.99 (CI:3.93–4.08) at age 35 years.

Late effects are associated with excess YLL (i.e., the difference in YLL between survivors with or without late effects)

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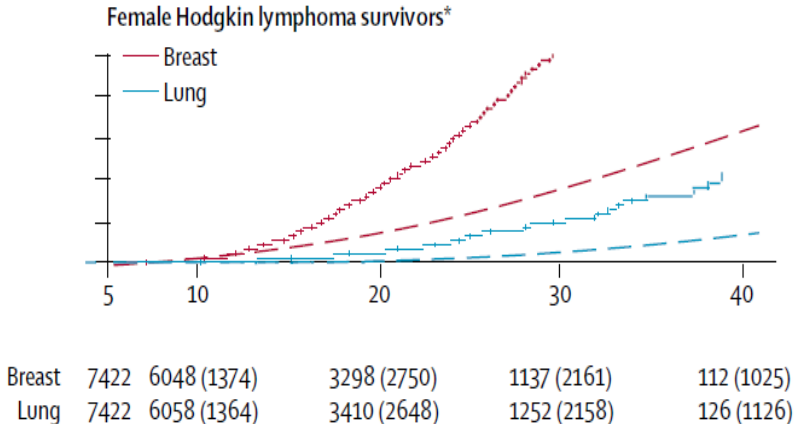
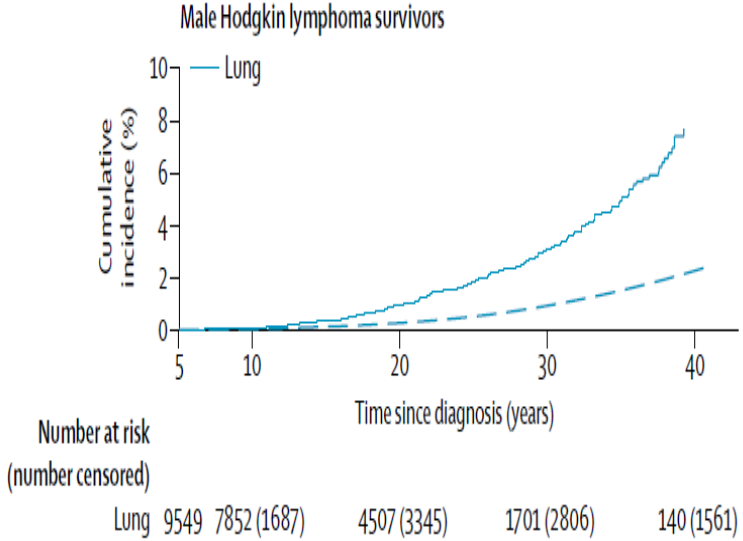
The cumulative incidence of all subsequent primary neoplasms 35 years after diagnosis was **26·6%** (24·7–28·6) in female survivors of Hodgkin lymphoma, and **16·5%** (15·2–18·0) in male survivors of Hodgkin lymphoma.

- 20·2% in survivors of testicular cancer
- 11·9% in survivors of breast cancer,
- 15·8% in survivors of cervical cancer





Additional challenges

- Upfront treatment is not uniform
- Relapse rates continue to drop, making large prospective studies difficult especially in the AYA group
- Most evidence for AYA management is extrapolated from adult studies
- Newer modalities may soon replace, the current approach
- Financial /logistic constraints in LMIC settings

Goal of salvage therapy in Relapsed Hodgkin Lymphoma

- Risk stratified
- Response adapted
- Minimal acute and long term toxicity
- To achieve maximum cure rates

Risk stratification

Response assessment

Optimum Salvage chemotherapy or Immunotherapy?

Role of High dose chemotherapy

Maintenance therapy?

- History of prior treatment, time to relapse /progression, treatment related complications, co-morbidities
- Clinical examination
- Biopsy from appropriate site of relapse
- Restaging- Whole body FDG PET CT is standard of care, Bone Marrow study (as clinically indicated)
- Baseline investigations

Prognostication

-Affected by multiple factors

-Primary progressive/refractory disease, time to relapse, and chemoresistance have been shown to be the most useful prognostic factors at relapse in most series.

-Patients may be classified as

- Very early relapse- < 3 months
- Early relapse - 3 to 12 months
- Late relapse - >12 months

Relapse <1 yr of treatment has the worst outcomes

Harker-Murray PD ***et al, Stratification of treatment intensity in relapsed pediatric Hodgkin lymphoma.*** *Br J Haematol. 2014 May;165(4):534-44*

Other important poor prognostic factors are

- stage at diagnosis
- presence of B symptoms,
- extra-nodal disease at relapse presentation
- residual mediastinal mass immediately prior to ASCT

Ananth Sankar et al,Treatment outcome in children and adolescents with relapsed Hodgkin lymphoma-results of the UK HD3 relapse treatment strategy,Br J Haematol. 2014 May;165(4):534-44

Satwani P, Ahn KW, Carreras J, et al. A Prognostic Model Predicting Autologous Transplantation Outcomes in Children, Adolescents and Young Adults with Hodgkin Lymphoma. Bone marrow transplantation. 2015;50(11):1416-1423. doi:10.1038/bmt.2015.177.

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Ann Hematol. 2016; 95: 695–706.
Published online 2016 Mar 2. doi: 10.1007/s00277-016-2619-9
PMCID: PMC4819743
PMID: 26931115

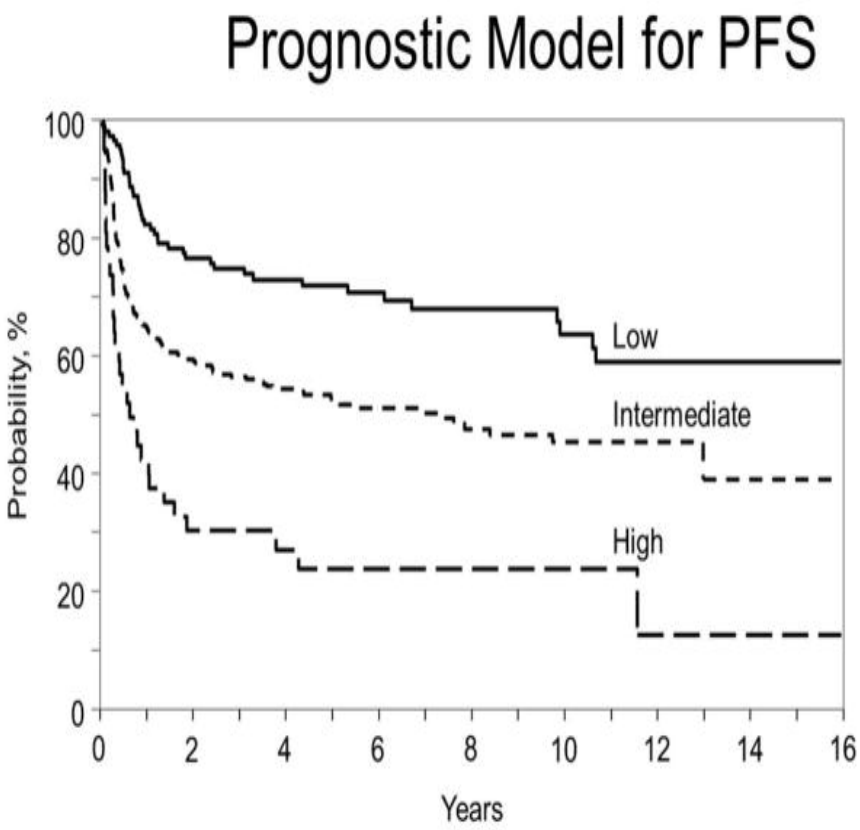
Prognostic value of pretransplant FDG-PET in refractory/relapsed Hodgkin lymphoma treated with autologous stem cell transplantation: systematic review and meta-analysis

Hugo J. A. Adams✉ and Thomas C. Kwee

- Meta-analysis of 745 patients including pediatric, adolescent,adult patients
- Moderate quality evidence of PET as predictive for treatment failure and death post HDCT
- “Considerable number of FI positive have good outcome post HDCT”
- “Considerable number of FI negative have poor outcome post HDCT”
- Pretransplant FDG-PET in predicting treatment failure was 67.2 % sensitive (95 % CI 58.2–75.3 %) and 70.7 % specific (95 % CI 64.2–76.5 %)

Risk factors for reduced survival post-HSCT included

- First remission <12 months,
- Poor performance status
- Chemo-resistance
- Extra-nodal disease at relapse and
- Receipt of first line therapy regimens other than ABVD/ABVD-like



The 3-year PFS probabilities for the

- Low-risk group (score = 0) - **75%**
- Intermediate-risk group (score = 1 or 2) **-56%**
- High-risk group (score = 3 or 4) **-29%**

Is it applicable in the Immunotherapy era?

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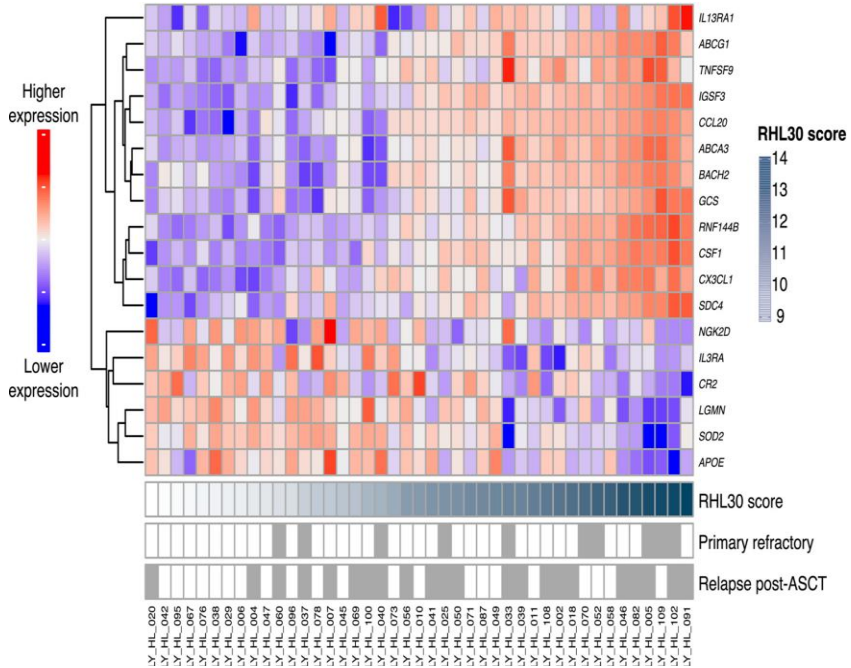
Prognostic Model to Predict Post-Autologous Stem-Cell Transplantation Outcomes in Classical Hodgkin Lymphoma

Fong Chun Chan, Anja Mottok, Alina S. Gerrie, Maryse Power, Marcel Nijland, Arjan Diepstra, Anke van den Berg, Peter Kamper, Francesco d'Amore, Alexander Lindholm d'Amore, Stephen Hamilton-Dutoit, Kerry J. Savage, Sohrab P. Shah, Joseph M. Connors, Randy D. Gascoyne, David W. Scott, and Christian Steidl

- Biology at relapse as measured by digital gene expression profiling
- 5-year PFS: 23.8% RHL30 high-risk vs. 77.5% RHL30 low-risk) and
- Inferior post-ASCT-OS (5-year: 28.7% for RHL 30 high-risk vs. 85.4% for low risk)



Chan FC, Mottok A, Gerrie AS, Power M, Nijland M, Diepstra A, et al. Prognostic Model to Predict Post-Autologous Stem-Cell Transplantation Outcomes in Classical Hodgkin Lymphoma. Journal of Clinical Oncology. 2017 Nov 10;35(32):3722–33

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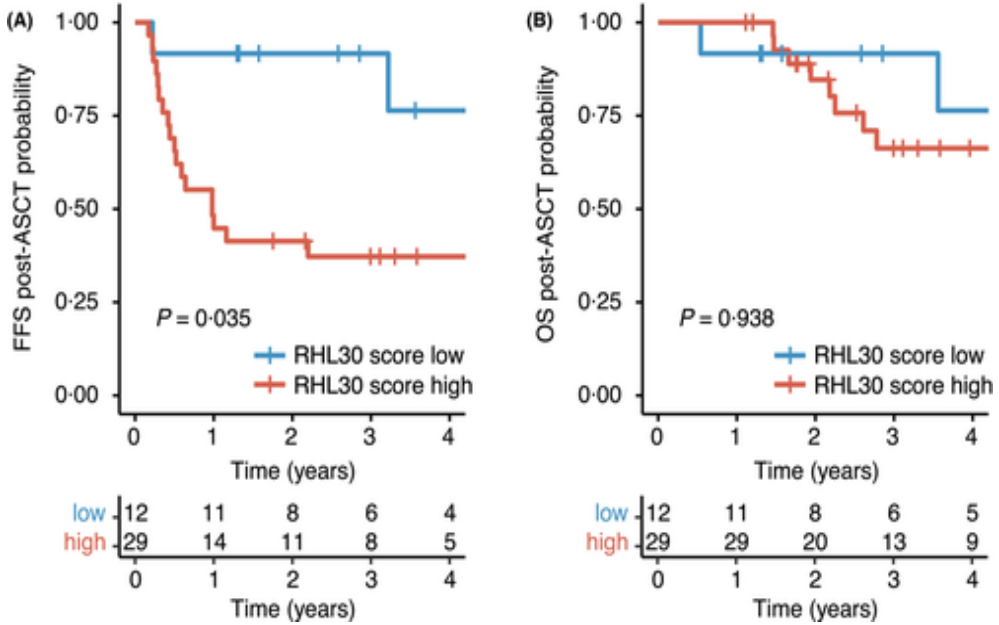
- Patients classified as high-risk by the RHL30 assay had inferior failure-free survival (FFS) after autologous stem cell transplantation (2-year FFS 41% vs. **92%,** P = 0·035).

- "*The RHL30 model is a robust biomarker that risk-stratifies patients considered for autologous stem cell transplantation.*"



Calvente L, Tremblay-LeMay R, Xu W, Chan FC, Hong M, Zhang T, et al. Validation of the RHL30 digital gene expression assay as a prognostic biomarker for relapsed Hodgkin lymphoma. British Journal of Haematology. 2020;190(6):864–8.

LOW RISK RELAPSE:

- Late relapse >1 year
- Stage 1 or 2, No B symptoms
- CR post first line SDCT salvage

High risk disease-

- Early relapse/primary refractory
- Advanced stage, B symtpoms
- Partial/poor response to Salvage chemo

What is the optimum treatment?

Optimal treatment in relapsed pediatric/AYA HL is still debatable.

Consensus approach to treatment is *Risk stratified intensification including:*

1. **Salvage combined modality chemo-radiotherapy**
2. **Salvage chemotherapy+/- Immunotherapy followed by high dose chemotherapy and ASCT+/- RT**

Principles of Salvage treatment

- Avoid agents with cross resistance
- Avoid exposure to multiple agents
- Minimize acute complications
- Avoid long term complications

Salvage chemotherapy

Reduce anthracyclines, platinum analogues

Better stem cell mobilization post salvage

Consider resource constraints

Upfront treatment regimens and cumulative doses

	Adult HL therapy			Paediatric HL regimens		
	ABVD	Escalated BEACOPP	Bv-AVD†	ABVE-PC‡	Bv-AVEPC	OEPA/COPDac
Cycles (*n*)	6	6	6	5	5	2/4
Doxorubicin (D)	300	210	300	250	250	160
Bleomycin (B)	120	60	–	75	–	
Vincristine (V; O)	–	12	–	15	7·5	21
Etoposide (E)	–	3600	–	1875	1875	1250
Cyclophosphamide (C)	–	7200	–	6000	6000	4000
Prednisone (P)	–	3360	–	1400	1400	3922
Procarbazine (P)	–	4200	–	–	–	
Vinblastine (V)	72	–	72	–	–	
Dacarbazine (D; Dac)	4500		4500			3000
Brentuximab vedotin (Bv)			14·4		9·0	

Castellino SM, Parsons SK, Kelly KM. Closing the survivorship gap in children and adolescents with Hodgkin lymphoma. British Journal of Haematology. 2019;187(5):573–87.

GDP(Gemcitabine+Dexamethasone+CDDP),DHAP achieves good ORR, with minimal toxicity and cost

PEI+ABVD- Good strategy for non ABVD exposed patients, especially low and intermediate risk groups

Ifosfamide+vinorelbine is effective even in heavily pretreated patients

Ifosfamide and vinorelbine is an effective reinduction regimen in children with refractory/relapsed Hodgkin lymphoma, AHOD00P1: a children's oncology group report, Trippett TM1, Schwartz CL, Guillerman RP, Gamis AS, Gardner S, Hogan S, London WB, Chen L, de Alarcon P.Pediatr Blood Cancer. 2015 Jan;62(1):60-4. doi: 10.1002/pbc.25205.

Response rates of Salvage chemotherapy

Response rates of conventional standard dose salvage chemotherapy regimens

Regimen	Drugs	Patients (n)	ORR (%)	CR Rate (%)
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin	22	73	40
DHAP	Dexamethasone, cytarabine, cisplatin	102	88	21
IEP-ABVD	Ifosfamide, etoposide, prednisolone, Adriamycin, bleomycin, vinblastine, dacarbazine	176	85	Not reported
ICE	Ifosfamide, carboplatin, etoposide	65	88	26
IVE	Ifosfamide, etoposide, epirubicin	51	84	60
IGEV	Ifosfamide, gemcitabine, vinorelbine, prednisolone	91	81	54
BeGEV	Bendamustine, gemcitabine, vinorelbine	59	83	73
GDP	Gemcitabine, dexamethasone, cisplatin	23	70	17
GVD	Gemcitabine, vinorelbine, liposomal doxorubicin	91	70	19

blood advances

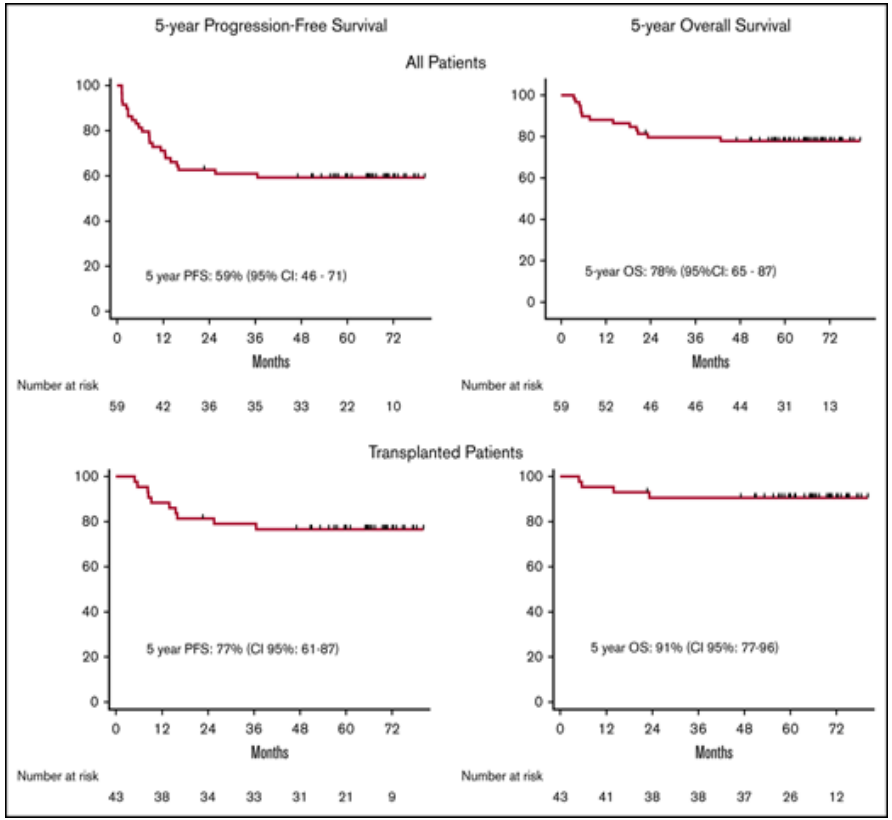
Bendamustine+Gemcitabine regimes

5 years PFS and overall survival (OS) for the whole series (n = 59) were 59% and 78%, respectively.

For patients who received transplants, the 5-year PFS and OS were 77% and 91%

BEGEV- LESS CISPLATIN RELATED NEPHRO/ OTOTOXICITY

Stem cell mobilization is good



Santoro A, Mazza R, Pulsoni A, Re A, Bonfichi M, Zilioli VR, et al. Five- year results of the BEGEV salvage regimen in relapsed/refractory classical Hodgkin lymphoma. Blood Advances. 2020 Jan 14;4(1):136–40.

Immunotherapy in R/R HL

- Significantly improved outcomes in R/R HL in adults
- CAYA studies have confirmed their efficacy in this age group
- Optimal combination therapy , optimal positioning strategy ,however are evolving
- Long term issues are not well studies in children

Brentuximab vedotin

Monoclonal anti-CD30 antibody Brentuximab vedotin is FDA approved for relapsed -refractory HL in children:

- 40 to 70% CR
- Dose- 1.8mg/kg 3 weekly
- Well tolerated, with neutropenia , rash ,transaminitis as the M.C adverse effects

Cole PD, et al, Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial.Lancet Oncol. 2018 Aug 16. pii: S1470-2045(18)30426-1

Neville K,et al Phase I/II study of brentuximab vedotin in pediatric patients (pts) with relapsed or refractory (RR) Hodgkin lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL): interim phase (ph) I safety data. J Clin Oncol 2013;31(Suppl). Abstract 10028

Brentuximab vedotin+Chemotherapy

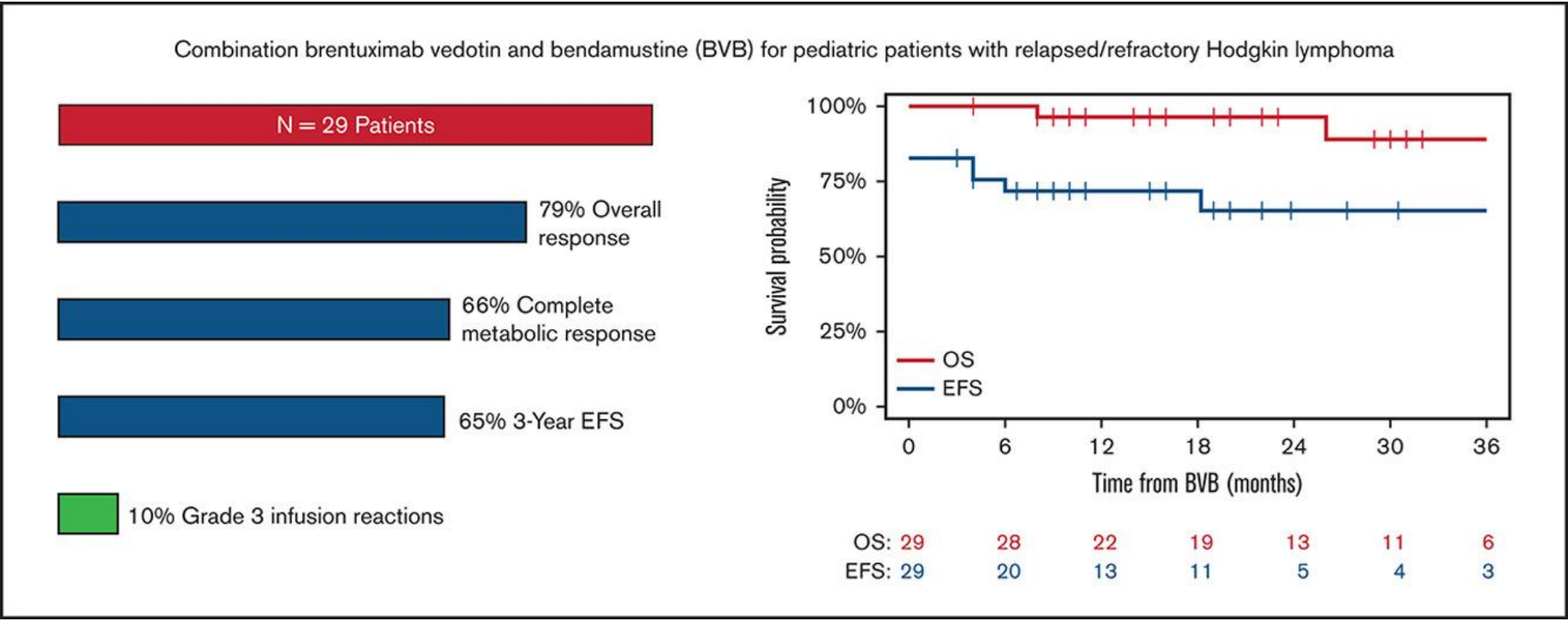
Response rates of Brentuximab vedotin based salvage therapy

Regimen	Drugs	Patients (n)	ORR (%)	CR Rate (%)
BV single agent (adult)	Brentuximab vedotin	37	68	35
BV single agent (pediatric)	Brentuximab vedotin	19	47	33
BV-Bendamustine	Brentuximab vedotin, bendamustine	55	93	74
BV-Nivolumab	Brentuximab vedotin, nivolumab	29	90	62
BV-ESHAP	Brentuximab vedotin, Etoposide, methylprednisolone, cytarabine, cisplatin	66	96	70
BV-ICE	Brentuximab vedotin, Ifosfamide, carboplatin, etoposide	16	94	69
BV-DHAP	Brentuximab vedotin, dexamethasone, cytarabine, cisplatin	12	100	92
BV-IGEV	Brentuximab vedotin, Ifosfamide, gemcitabine, vinorelbine, prednisolone	28	100	71

BV as single agent generally is no longer recommended as second line salvage.

Appears to be synergy between BV and Bendamustine in the BV-B combination which has reported excellent CR rates of 74% and ORR 94%

blood advances



Forlenza CJ, Gulati N, Mauguen A, Absalon MJ, Castellino SM, Franklin A, et al. Combination brentuximab vedotin and bendamustine for pediatric patients with relapsed/refractory Hodgkin lymphoma. Blood Advances. 2021 Dec 28;5(24):5519–24.

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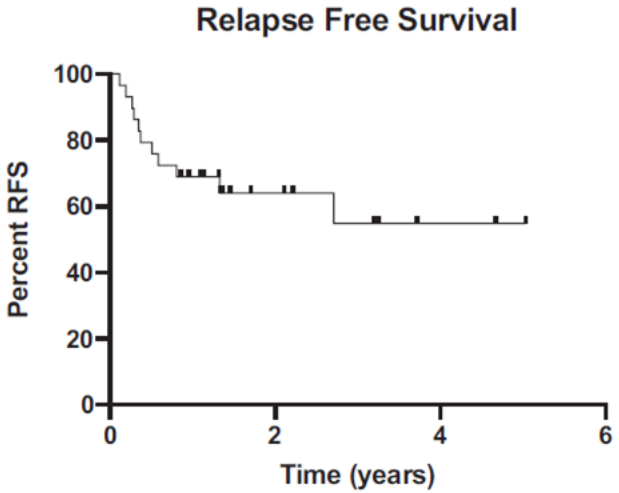
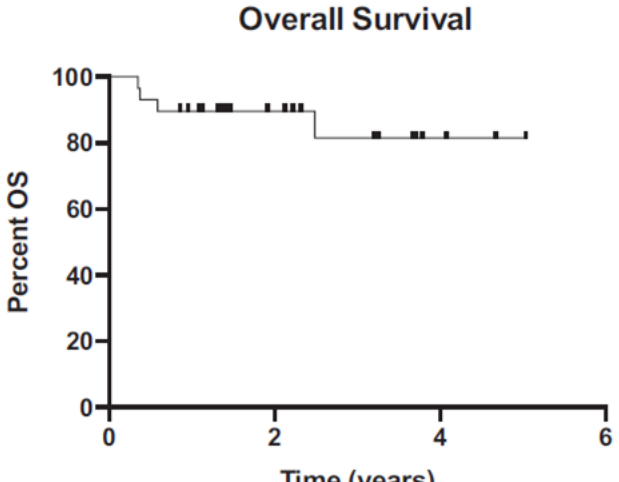
BvB as Salvage in CAYA

- PFS and OS at 24 months are **64% and 90%** respectively
- In total, **66%** experienced grade 3 or 4 (G3/4) toxicity.
- Gr 3/4 cytopenias included neutropenia in 31% (9/29), anaemia in 7% (2/29) and thrombocytopenia in 3% (1/29)
- Neuropathy occurred in **10%** (3/29), all were Gr1
- Infusion-related reactions affected 52% (15/29) of patients: G1/2 in 34% (10/29) and G3/4 in 17% (5/29)
- Bv + B was discontinued due to toxicity in 17%





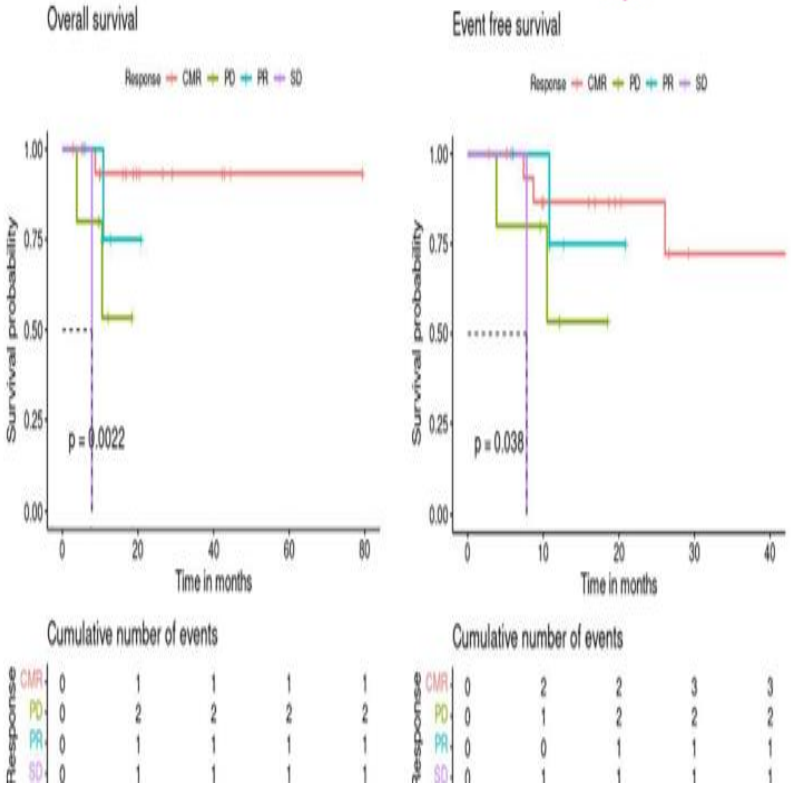
McMillan A et al.The addition of bendamustine to brentuximab vedotin leads to improved rates of complete metabolic remission in children, adolescents and young adults with relapsed and refractory classical Hodgkin lymphoma: a retrospective single-centre series. Br J Haematol. 2021

The median age of the patients was 30 years (15-59 years)
The most common Grade III/IV hematological adverse event was neutropenia 70%, while grade III/IV non-hematological toxicities included infections in 4 (13%), neuropathy in 4(13%), skin rash in 2 (7%)

The ORR and CR rates were **79% and 62%,** respectively.

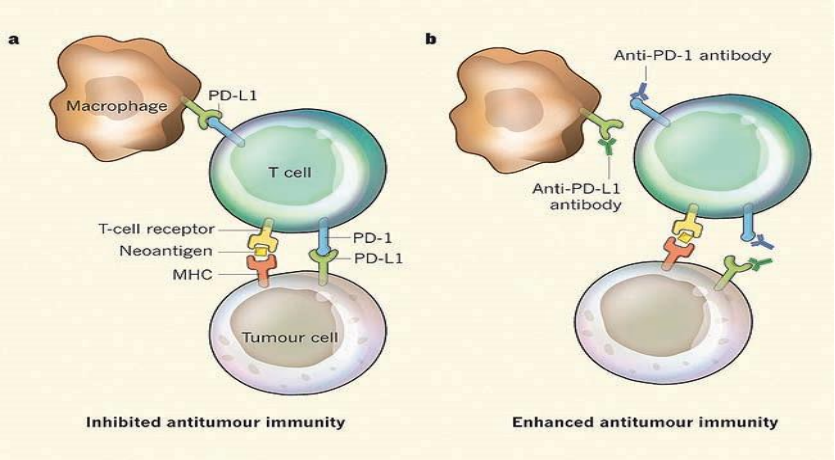
Three year OS and EFS treatment were **75% and 58%,** respectively.

Patients in **CMR** had better survival probability **[93% 3yr-OS and 72% EFS)**



Radhakrishnan VS, Bajaj R, Raina V, Kumar J, Bhave SJ, Sukumaran Nair Reghu, Nag A, Arun I, Zameer L, Dey D, Arora N, Parihar M, Das J, Achari RB, Mishra DK, Chandy M, Nair R. Relapsed Refractory Hodgkin Lymphoma and Brentuximab Vedotin-Bendamustine Combination Therapy as a Bridge to Transplantation: Real-World Evidence From a Middle-Income Setting and Literature Review. Front Oncol. 2022 Jan 21;11:796270.

Check point inhibitors



Pembrolizumab:

FDA approved for pediatric relapsed/refractory Hodgkin Lymphoma

KEYNOTE-051- Pediatric Hodgkin lymphoma -upfront for poor responders

Birgit Geoerger etal, Phase 1/2 KEYNOTE-051 study of pembrolizumab (pembro) in pediatric patients (pts) with advanced melanoma or a PD-L1⁺ advanced, relapsed, or refractory solid tumor or lymphoma,Journal of Clinical Oncology 2017 35:15_suppl, 10525-10525

KEYNOTE-087 followup report

2 year OS

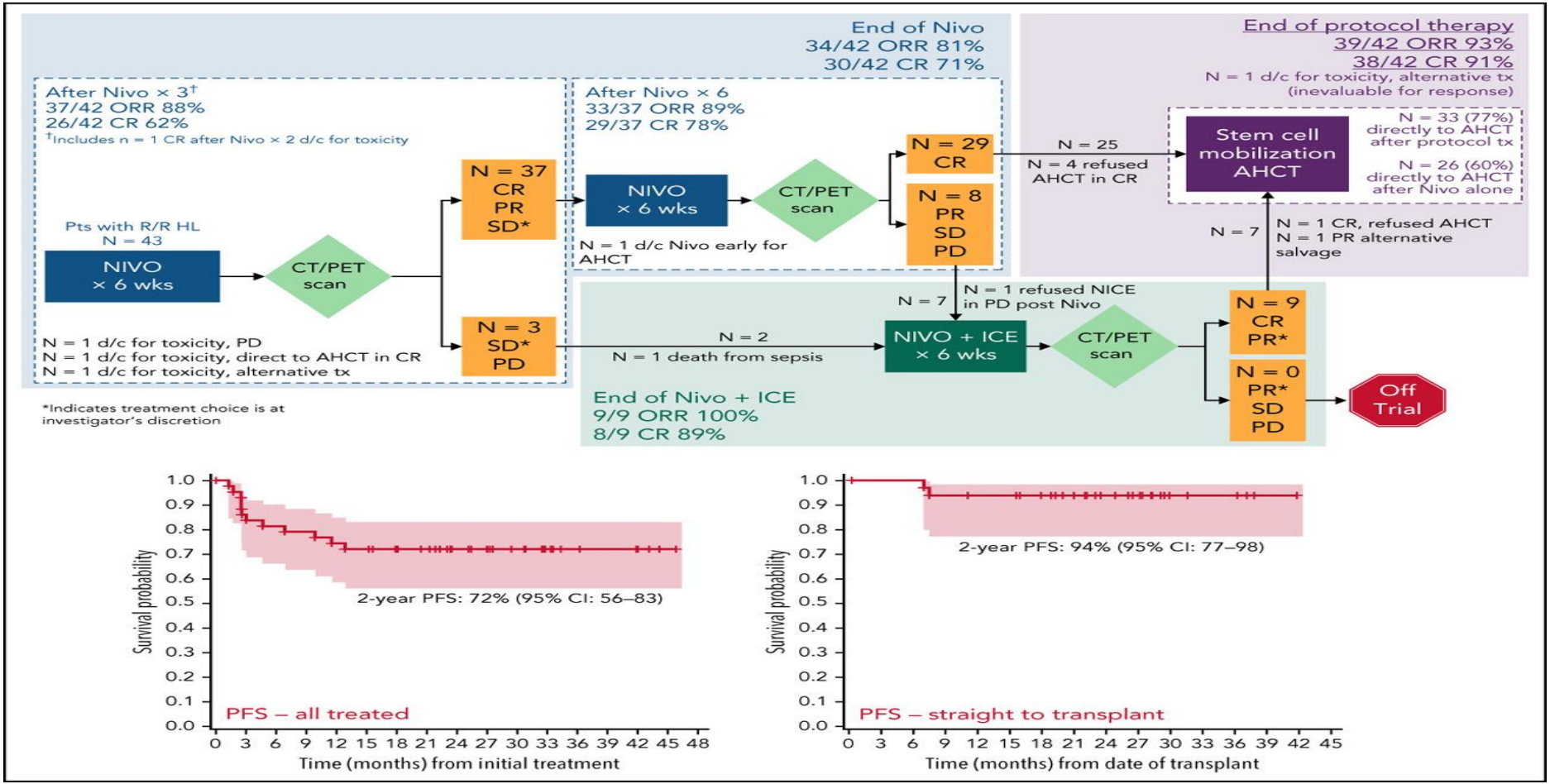
- Subsequent brentuximab vedotin (BV) therapy (cohort 1)- 92.5%
- Salvage chemotherapy and BV (cohort 2) - 90.6%
- ASCT but not treated with BV after ASCT (cohort 3) - 89.4%

Zinzani PL, Chen RW, Lee HJ, Armand P, Johnson NA, Brice P, et al. Two-Year Follow-up of Keynote-087 Study: Pembrolizumab Monotherapy in Relapsed/Refractory Classic Hodgkin Lymphoma. Blood. 2018 Nov 29;132:2900.

Nivolumab and Brentuximab Vedotin (BV)–Based, Response-Adapted Treatment in Children, Adolescents, and Young Adults (CAYA) With Standard-Risk Relapsed/Refractory Classical Hodgkin Lymphoma (R/R cHL): Primary Analysis of the Standard-Risk Cohort of the Phase 2 **CheckMate 744 Study**

- 44 patients
- Median age was 16 years (range, 9–30);
- CMR rate (90% CI) any time before consolidation was 88%; objective response rate (ORR) was 98%
- One-year progression-free survival rate by BICR was 91% (90% CI, 77–96)
- Most common any-grade TRAEs were nausea and hypersensitivity (20% each)

NICE study- Nivo+ICE



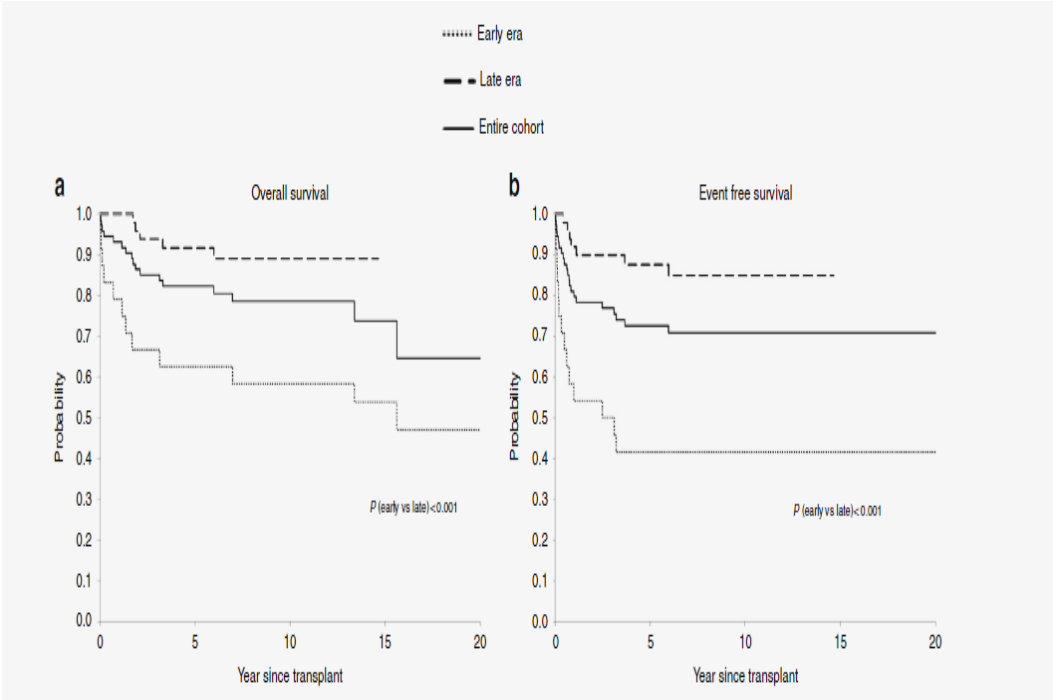
The role of high dose chemo with ASCT

- Has been the standard of care as consolidation chemotherapy in R/R HL
- Established evidence to support its use
- Questions remain regarding pre transplant remission status and use in all cases

ASCT outcomes in CAYA group

5-year overall survival improved from **62.5 ± 9.6% to 91.8 ± 4.4%** ($p < 0.001$) and

Event free survival improved from **41.7 ± 9.6% to 87.7 ± 5.3%** for patients treated in a later era (2002–2015).



Talleur, A.C., Flerlage, J.E., Shook, D.R. et al. Autologous hematopoietic cell transplantation for the treatment of relapsed/refractory pediatric, adolescent, and young adult Hodgkin lymphoma: a single institutional experience. Bone Marrow Transplant 55, 1357–1366 (2020).

Schellong G et al from pediatric DAL/GPOH-HD group(n=176) and *Shankar A et al (n=80)*from UK HD3 relapse treatment group published the largest pediatric studies for relapsed HD

- Low risk groups did not show much benefit over salvage chemo+RT
- OS of 90% without HSCT in favorable risk group
- Best improvement in outcomes were for patients who were in the high risk group.

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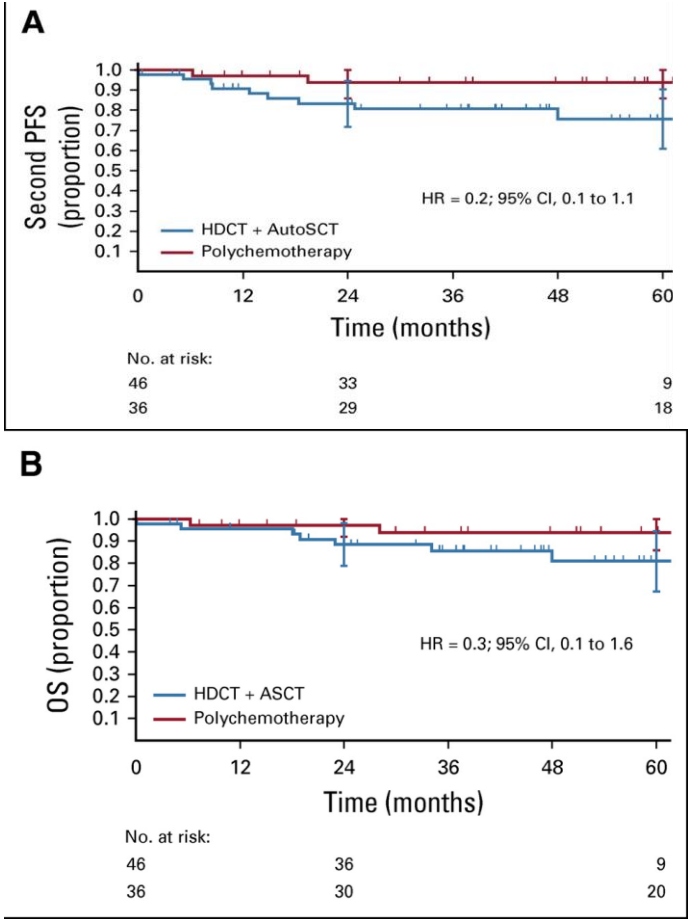
- 2-year second PFS rate with **SDCT 94.0%** (95% CI, 85.7% to 100%) versus **83.3% with ASCT** (95% CI, 71.8% to 94.8%).

- The 2-year OS rate was **97.2% with CTx** (95% CI, 91.7% to 100%) versus **88.4% with ASCT** (95% CI, 78.7% to 98.1%)

"***CTx may constitute a reasonable therapeutic option and potential alternative to ASCT in selected patients with relapse after initial treatment of ES-HL, especially in case of contraindications to ASCT or a resource-constrained setting..***"



Bröckelmann PJ, Müller H, Guhl T, Behringer K, Fuchs M, Moccia AA, et al. Relapse After Early-Stage, Favorable Hodgkin Lymphoma: Disease Characteristics and Outcomes With Conventional or High-Dose Chemotherapy. JCO. 2021 Jan 10;39(2):107–15.

Response to salvage therapy:

- Clinical
- Radiological
- Functional imaging

Assess underlying co-morbidities, inflammatory/infectious conditions

DOI: 10.1002/pbc.26707

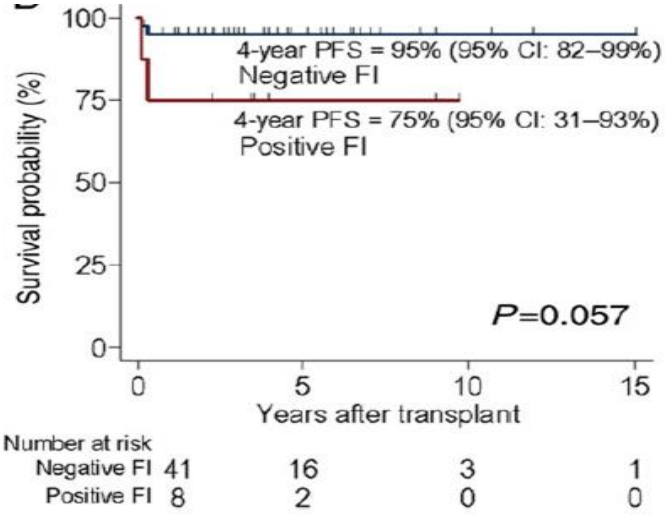
RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer
SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
aspho The American Society of Pediatric Hematology/Oncology

Pretransplant functional imaging and outcome in pediatric patients with relapsed/refractory Hodgkin lymphoma undergoing autologous transplantation

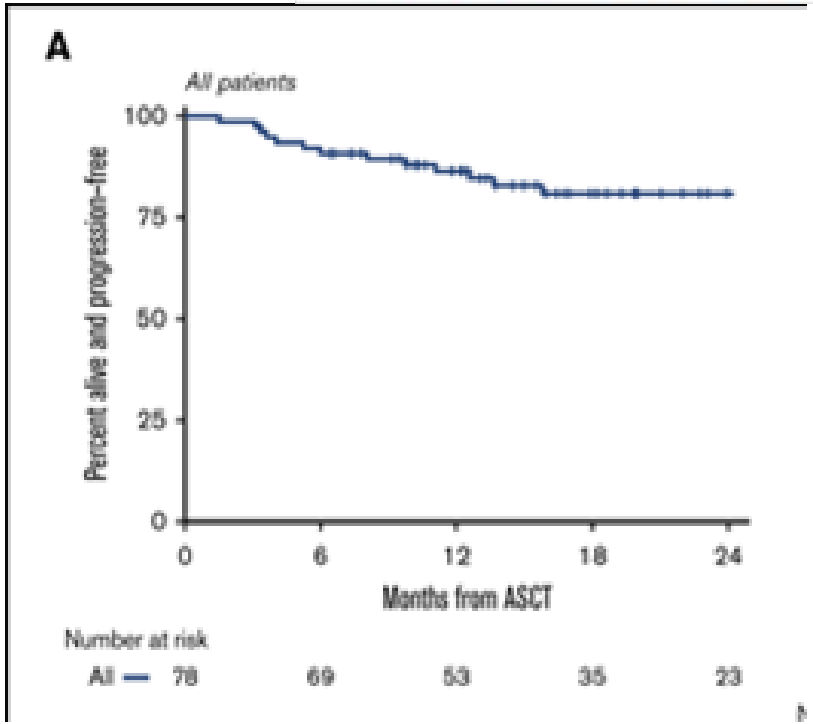
- The 4-year PFS for the entire cohort **was 92%** (95% confidence interval [CI]: 78–97)

- PFS based on pretransplant disease status was **95% (95% CI: 82–99%) in the negative** FI group versus **75% (95%CI: 31–93) if positive** FI (P = 0.057).



ASCT post CPI

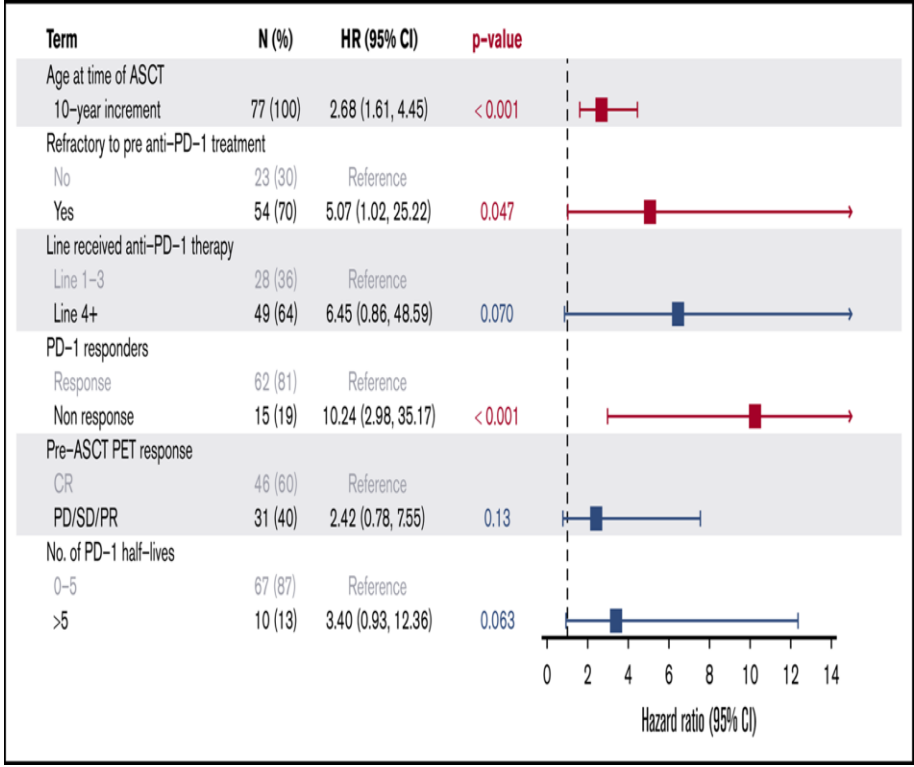
- Cohort of heavily pretreated patients.
- Median post-ASCT follow-up of 19.6 months, the 18-month progression-free survival (PFS) and overall survival were 81% (95% CI, 69-89) and 96% (95% confidence interval [CI], 87-99),



Merryman RW, Redd RA, Nishihori T, Chavez J, Nieto Y, Darrah JM, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. Blood Advances. 2021 Mar 12;5(6):1648–59.

Significant predictors of inferior PFS,

- Age (HR, 2.7 for increasing 10-year increments; *P* < .001)
- Lack of response to anti-PD-1 therapy (HR, 10.2; *P* < .001)
- Refractory disease to the line prior to anti-PD-1 therapy (HR, 5.1; *P* = .047)



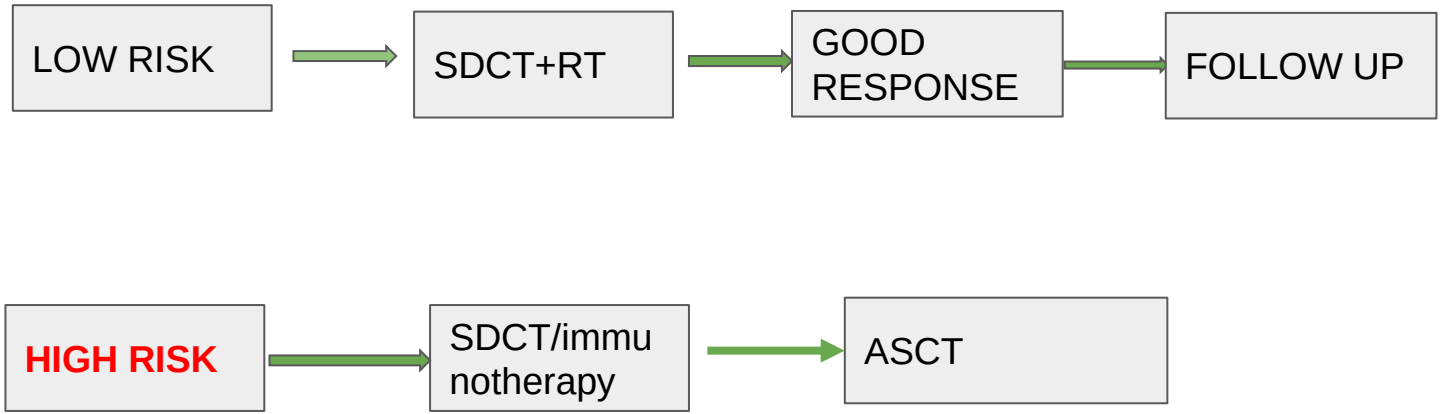
"ASCT has traditionally been reserved for chemosensitive patients, preliminary evidence suggests that treatment with PD-1 blockade may result in higher than-expected response rates to subsequent cytotoxic therapy."

Conditioning regimes for ASCT:

Most common are BEAM, LEAM and CBV.

BEAM has been accepted as standard in most centres

Center experience and patient population are important in choosing conditioning regime.


LOW RISK
SDCT+RT
GOOD RESPONSE
FOLLOW UP
HIGH RISK
SDCT/immunotherapy
ASCT

Role of radiation therapy

- Current chemointense upfront therapy in children and AYA has reduced need for upfront radiation
- RT naïve patients on relapse may be considered for consolidation RT in post SDCT a s the only consolidation modality
- Post ASCT consolidation RT may be considered to limited extent in sites of partial response.

Sureda et al. BMC Cancer (2020) 20:1088
https://doi.org/10.1186/s12885-020-07561-2

BMC Cancer

REVIEW Open Access

Improving outcomes after autologous transplantation in relapsed/refractory Hodgkin lymphoma: a European expert perspective

In the post-ASCT consolidation setting, radiotherapy improves local control at 36 months post-ASCT (78% with RT vs 48% without RT) (Jauhari et al,2015)

Significant improvements in 2-year PFS (67% vs 42%, $p < 0.01$),in patients with

- Bulky disease (62% vs 39%)
- B-symptoms (48% vs 28%)
- Primary-refractory disease (47% vs 32%)
- Partial response per pre-transplant imaging (47% vs 32%) *Wilke et al,2017*

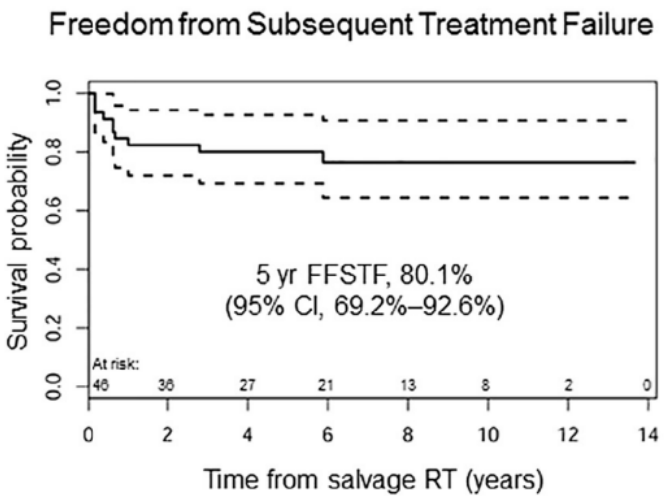
However significant improvement in OS with consolidative radiotherapy is not proved

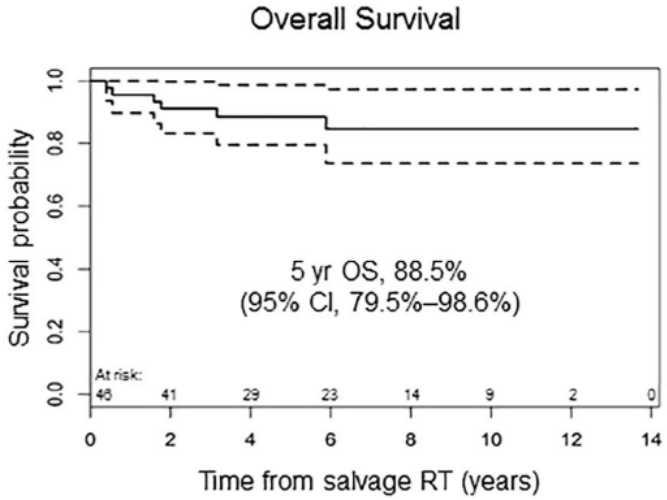
Orignal Article

Treatment patterns and disease outcomes for pediatric patients with refractory or recurrent Hodgkin lymphoma treated with curative-intent salvage radiotherapy

Christopher L. Tinkle [a,*], Noelle L. Williams [b], Huiyun Wu [c], Jianrong Wu [d], Sue C. Kaste [e,f,g], Barry L. Shulkin [e,f], Aimee C. Talleur [h], Jamie E. Flerlage [g], Melissa M. Hudson [g], Monika L. Metzger [g], Matthew J. Krasin [a]

- The 5-year CIN of local failure after salvage RT was 17.7% (95% confidence interval [CI], 8.2–30.2%).
- The 5-year freedom from subsequent treatment failure was 80.1% (95% CI, 69.2–92.6%) and OS was 88.5% (95% CI, 79.5–98.6%)
- Inadequate response to salvage systemic therapy (p = 0.048) and male sex (p = 0.049) were significantly associated with local failure after salvage RT.





Maintenance therapy after HDCT consolidation

- Who benefits from maintenance?
- What is the optimal maintenance?
- Duration of maintenance?
- Evidence in Pediatric/AYA group

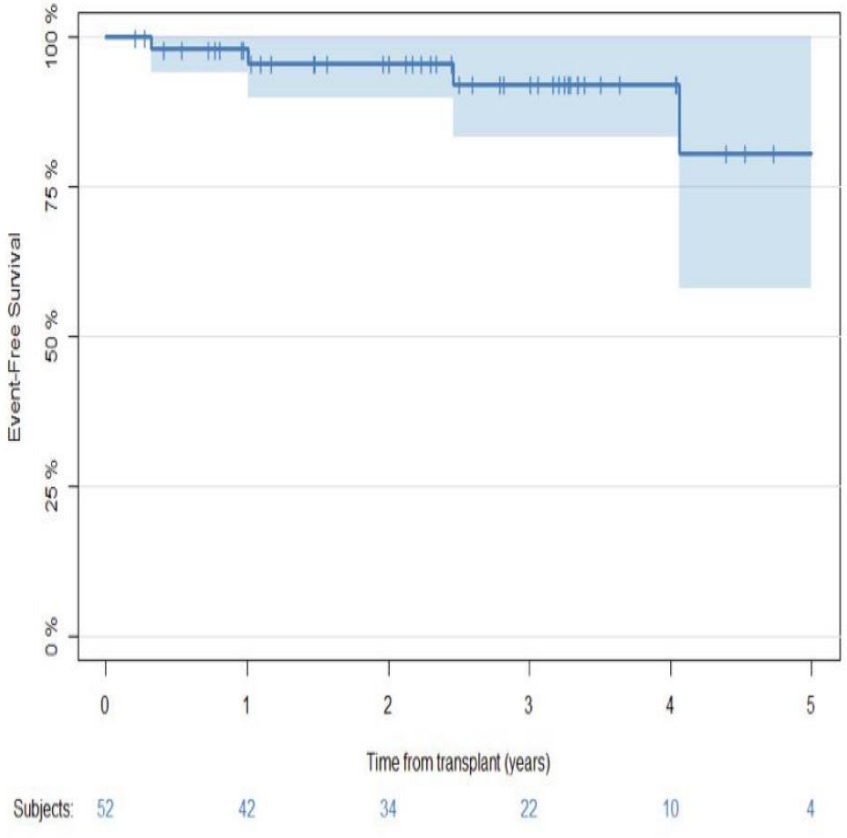
High-risk disease with any one factor-

- Primary refractory disease,
- Relapse within 1 year of completing therapy,
- Extranodal disease at relapse,
- B symptoms at relapse, or
- >1 salvage regimen prior to autoHCT

NCCN recommend brentuximab vedotin maintenancepost ASCT for patients with a high risk of relapse, defined as ≥ 2 of the following risk factors:

- Remission lasting < 1 year,
- Extranodal involvement,
- PET-positive response at time of transplant,
- B symptoms, and/or > 1 salvage/subsequent therapy regimen.

- **Three-year EFS - 92%** [95%CI: 83-100].
- Patients with 0-1 risk factors and 2 risk factors had a 3-year EFS of 100% and 90% [95%CI: 79-100], respectively
- **96%** are alive with no evidence of disease, while 4% patients are alive with disease.
- No deaths have occurred.



Forlenza CJ, Rosenzweig J, Mauguen A, Buhtoiarov I, Cuglievan B, Dave H, et al. Brentuximab Vedotin As Consolidation Therapy Following Autologous Stem Cell Transplantation in Children and Adolescents with Relapsed/Refractory Hodgkin Lymphoma: A Multi - Center Retrospective Analysis. Blood. 2021 Nov 23;138:2465.

PD-1 blockade in maintenance

- Data is limited in children and adolescent maintenance with CPI though most studies have included Young adult patients
- Pembrolizumab 200 mg IV was given every 3 weeks for up to eight cycles as consolidation therapy starting within 60 days of autoHCT
- PFS was 82% at 18 months, and **43%** experienced an immune-related adverse event

A Phase II Single Arm Study of Nivolumab As Maintenance Therapy after Autologous Stem Cell Transplantation in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

blood®
Volume 138, Supplement 1, 23 November 2021, Page 2455

Nivolumab (240 mg IV every 2 weeks) starting 45-180 days post-transplant for a maximum of 6 months of treatment.

With a median follow up of 9.2 months, the median PFS and overall survival (OS) have not been reached.

6 month PFS 92.1% and the 12-month OS is 100%.

Figure 1a Progression-free survival

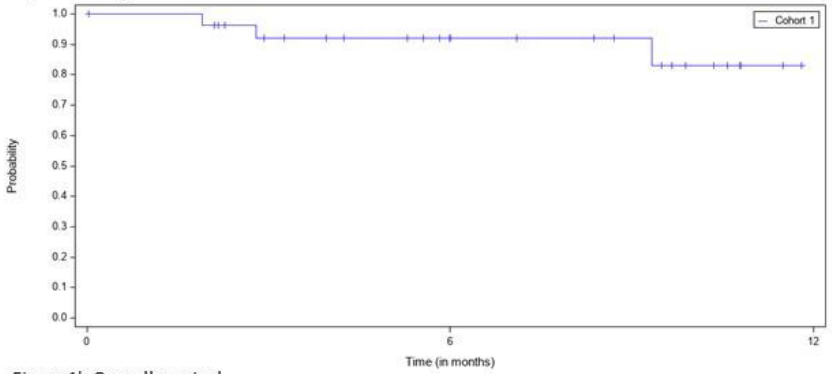
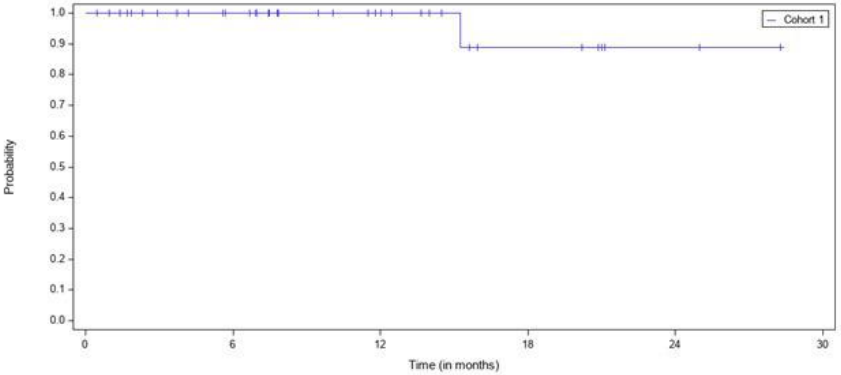


Figure 1b Overall survival

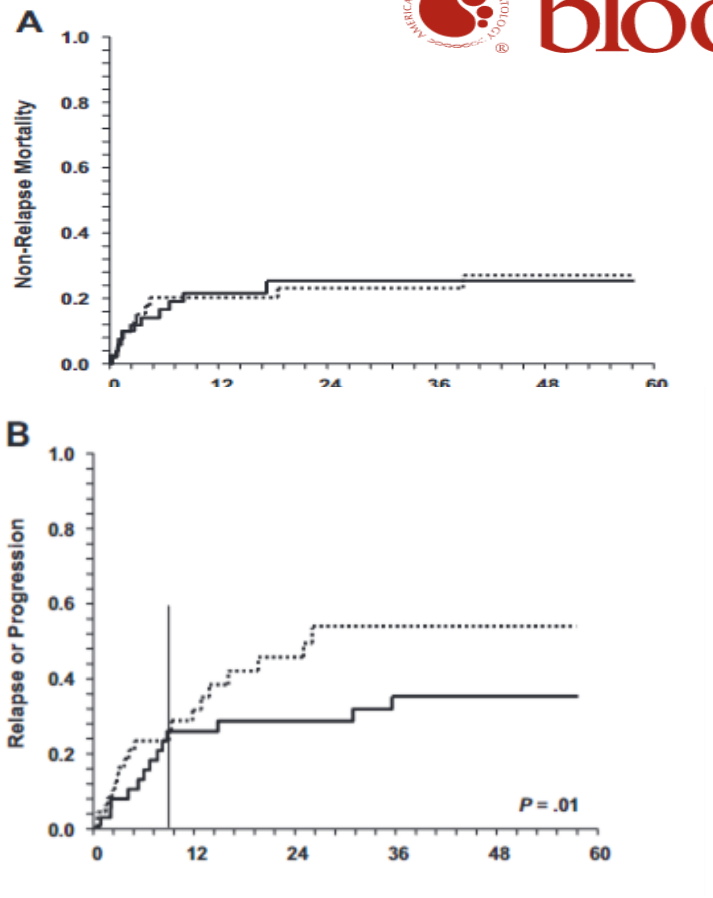


- Prolonged use of BV may be associated with increased peripheral neuropathy
- IRAEs may increase with prolonged use may of checkpoint inhibitors
- Data on long term issues with prolonged use of these agents in children are not known

Allogeneic transplant in R/R HL

- Reserved for patients who relapse following ASCT or refractory disease after multiple lines of salvage
- Graft versus lymphoma effect
- Risk of GVHD and good outcomes with ASCT limits its upfront use.

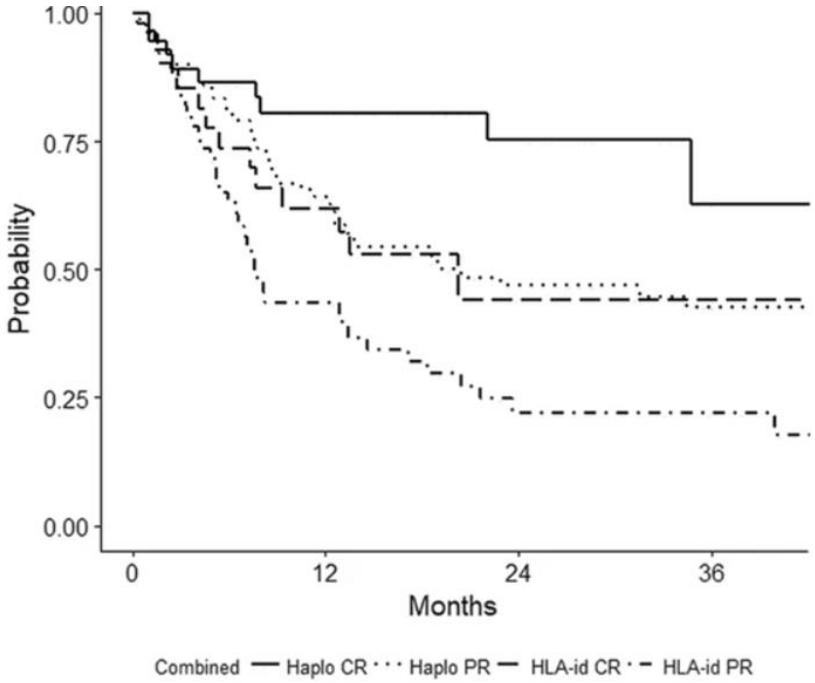
- PFS: 60% ± 27%, OS: 83% ± 15% at 3 years
- Nonrelapse mortality (NRM) at 1 year was 21% (± 4%), with comparable results after RIC or MAC



Claviez A, Canals C, Dierickx D, Stein J, Badell I, Pession A, et al. Allogeneic hematopoietic stem cell transplantation in children and adolescents with recurrent and refractory Hodgkin lymphoma: an analysis of the European Group for Blood and Marrow Transplantation. Blood. 2009 Sep 3;114(10):2060–7.

Haploidentical vs HLA matched transplant

- The 2-year **PFS** was significantly better for HAPLO than HLA-matched (**63%** vs **37%,** $p = 0.03$), without difference in OS.
- Patients in CR had better PFS
- Patients in CR receiving haplo HSCT showed higher 2-year PFS and lower 2-year RI with HLA-id donor (**75%** vs **47%**, $p < 0.001$ and 11% vs 34%, $p < 0.001$, respectively).
- 1-year **NRM** was similar (**15%** vs 16% $p = 0.9$).



Castagna L, Busca A, Bramanti S, Raiola Anna M, Malagola M, Ciceri F, et al. Haploidentical related donor compared to HLA-identical donor transplantation for chemosensitive Hodgkin lymphoma patients. BMC Cancer. 2020 Nov 24;20(1):1140.

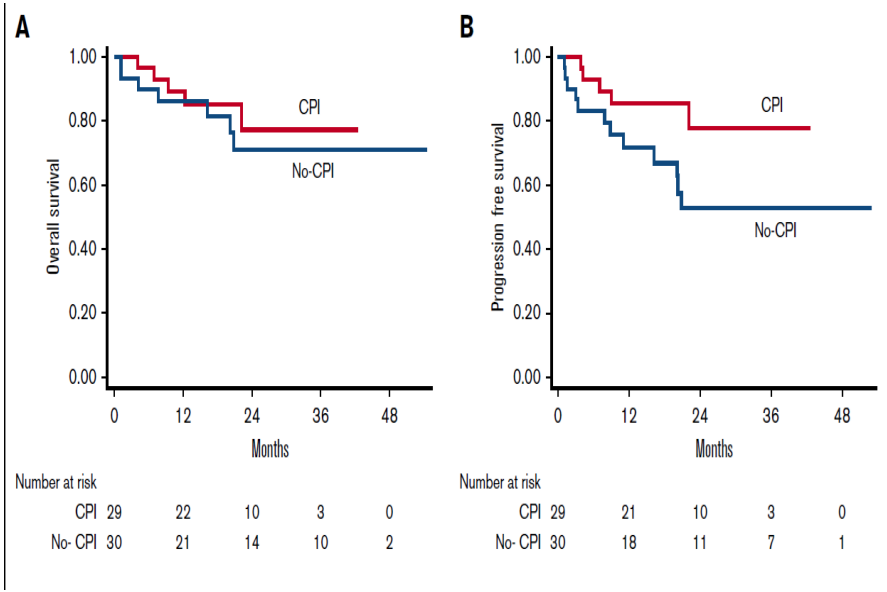
REGULAR ARTICLE

blood advances

Check for updates

Checkpoint inhibition before haploidentical transplantation with posttransplant cyclophosphamide in Hodgkin lymphoma

- 100 day cumulative incidence of grade 2-4 **aGVHD** was not significantly different between CPI (41%) and no-CPI (33%) cohorts
- Two-year **NRM** rate was 18% for all patients with no difference between CPI and no-CPI cohorts (15% vs 21%; P =0.578)



Precautions for Allo SCT post CPI

- “Adequate” time after CPI and Allo HSCT
- Use of PTCy
- Use of Reduced intensity conditioning
- Avoiding CPI maintenance post Allo-SCT

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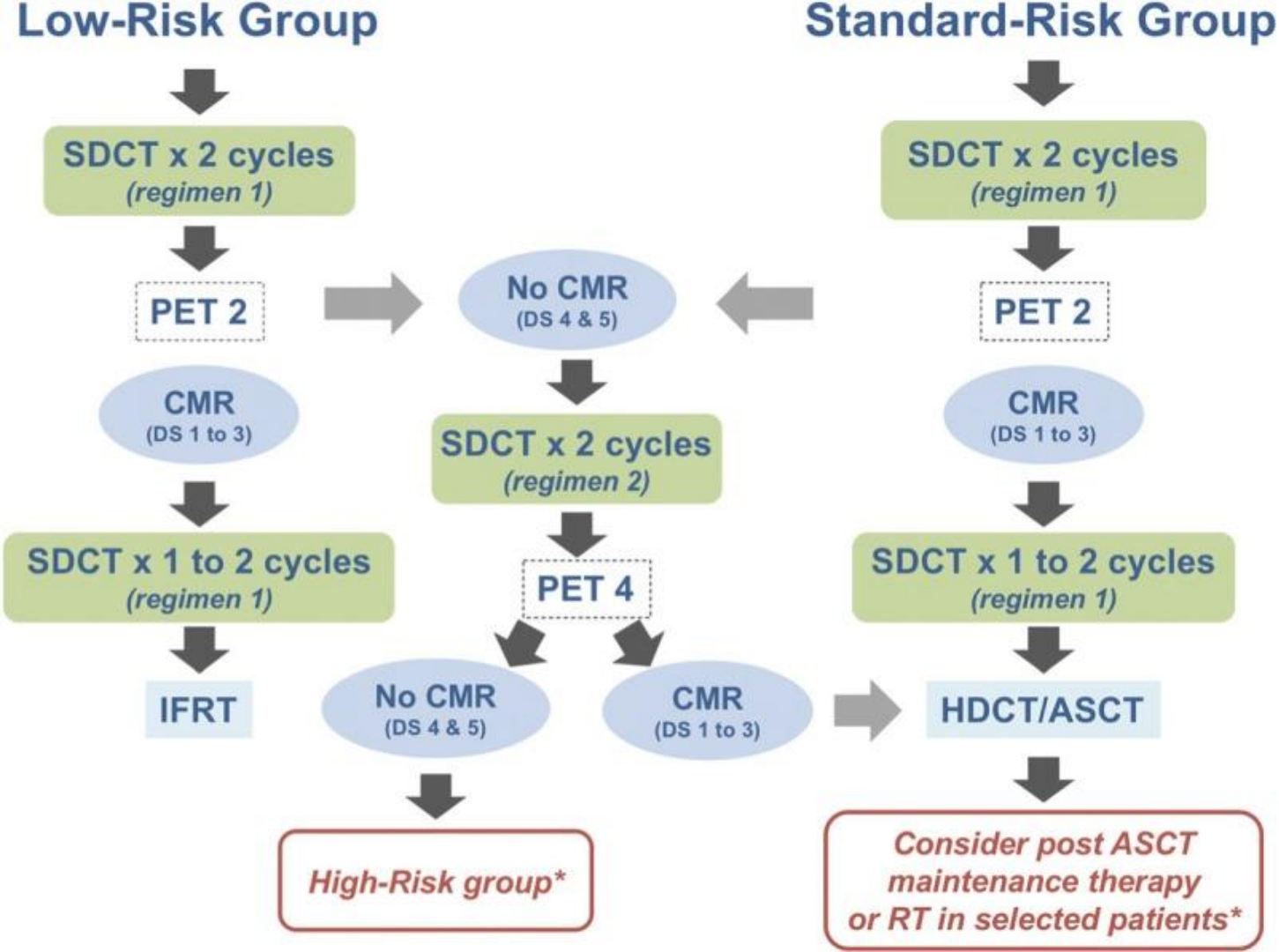
Guideline Article - Expert opinion

OPEN ACCESS

Risk and Response Adapted Treatment Guidelines for Managing First Relapsed and Refractory Classical Hodgkin Lymphoma in Children and Young People. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group


Low-Risk Group
Standard-Risk Group
SDCT x 2 cycles
(regimen 1)
SDCT x 2 cycles
(regimen 1)
PET 2
No CMR
(DS 4 & 5)
PET 2
CMR
(DS 1 to 3)
SDCT x 2 cycles
(regimen 2)
CMR
(DS 1 to 3)
SDCT x 1 to 2 cycles
(regimen 1)
PET 4
SDCT x 1 to 2 cycles
(regimen 1)
IFRT
No CMR
(DS 4 & 5)
CMR
(DS 1 to 3)
HDCT/ASCT
High-Risk group*
Consider post ASCT
maintenance therapy
or RT in selected patients*

Humani nihil a se alienum putabat

(Nothing of Humanity was Foreign to Him)