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DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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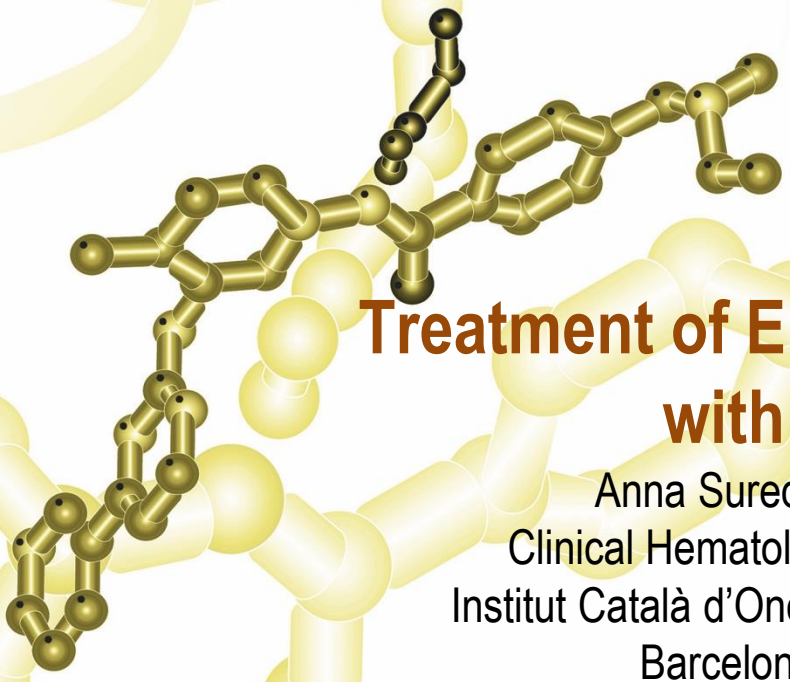

New Drugs in Hematology

Treatment of Elderly Patients with cHL

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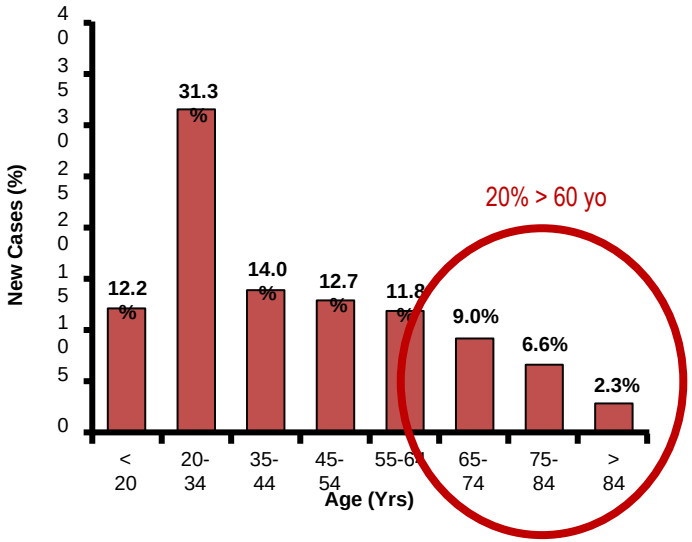
Disclosures of Anna Sureda Balari

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
Takeda	x		x		x		x
BMS/Celgene	x		x				x
MSD							x
Jansen			x				x
Amgen							x
Novartis			x				x
Gilead Kite			x				x
Sanofi			x				x
Roche							x
Alexion							x

Classical HL Has a Bimodal Age Pattern

SEER 2017
Estimated 8260 New Cases of Classic HL in US/Yr With 1070 Deaths

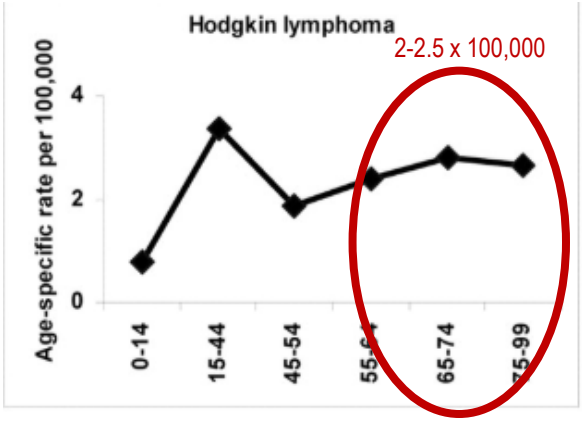
New HL Cases in 2017 by Age Group



Hodgkin Lymphoma Cancer Stat Facts. 2017. https://seer.cancer.gov/statfacts/html/hodg.html.

HAEMACARE groupings(1)

Age-specific incidence rates (per 100 000) for HMs diagnosed in 2000-2002 and archived by 44 European CRs by age class and morphologic type



HL incidence was significantly higher in Southern Europe (2.97) and significantly lower in Eastern Europe (2.12) and Northern Europe (2.04).

Sant M et al. Blood 2010

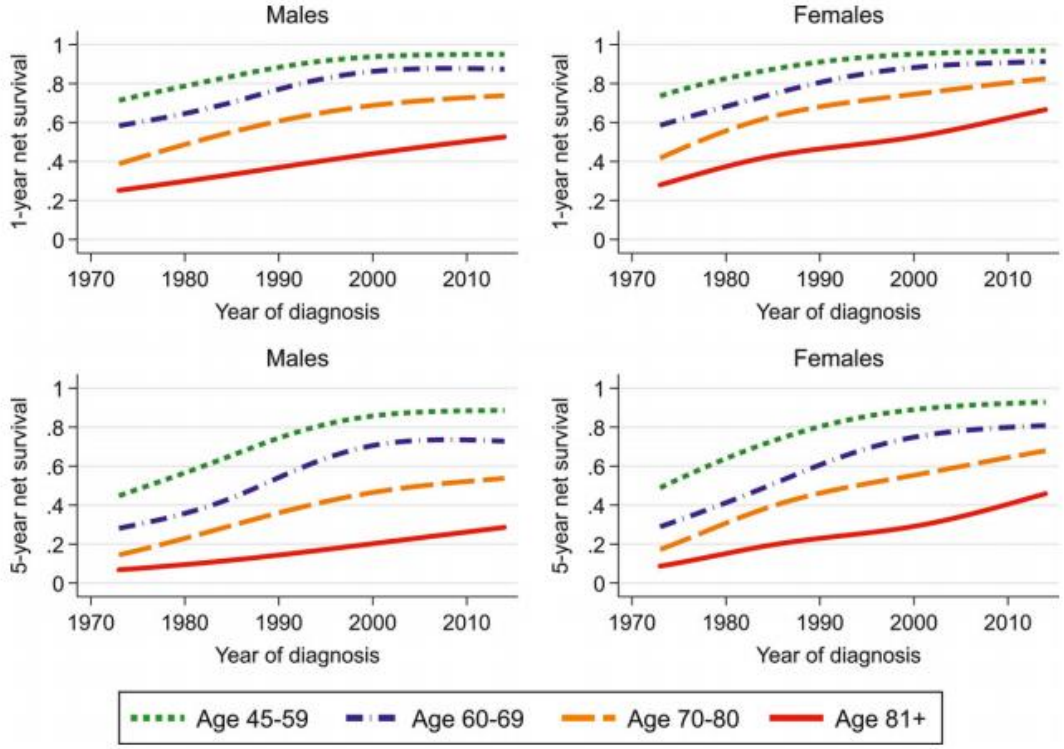


Fig 1. Temporal trends in 1- and 5-year net survival for Hodgkin lymphoma patients in Sweden. Estimates are from a flexible parametric model fitted to the first 6 years of follow-up for patients aged 45 years and older at diagnosis. Reproduced with permission from Björkholm *et al.* (2018). ©2018 John Wiley and Sons.

Survival is Poorer in the Elderly Population of Patients

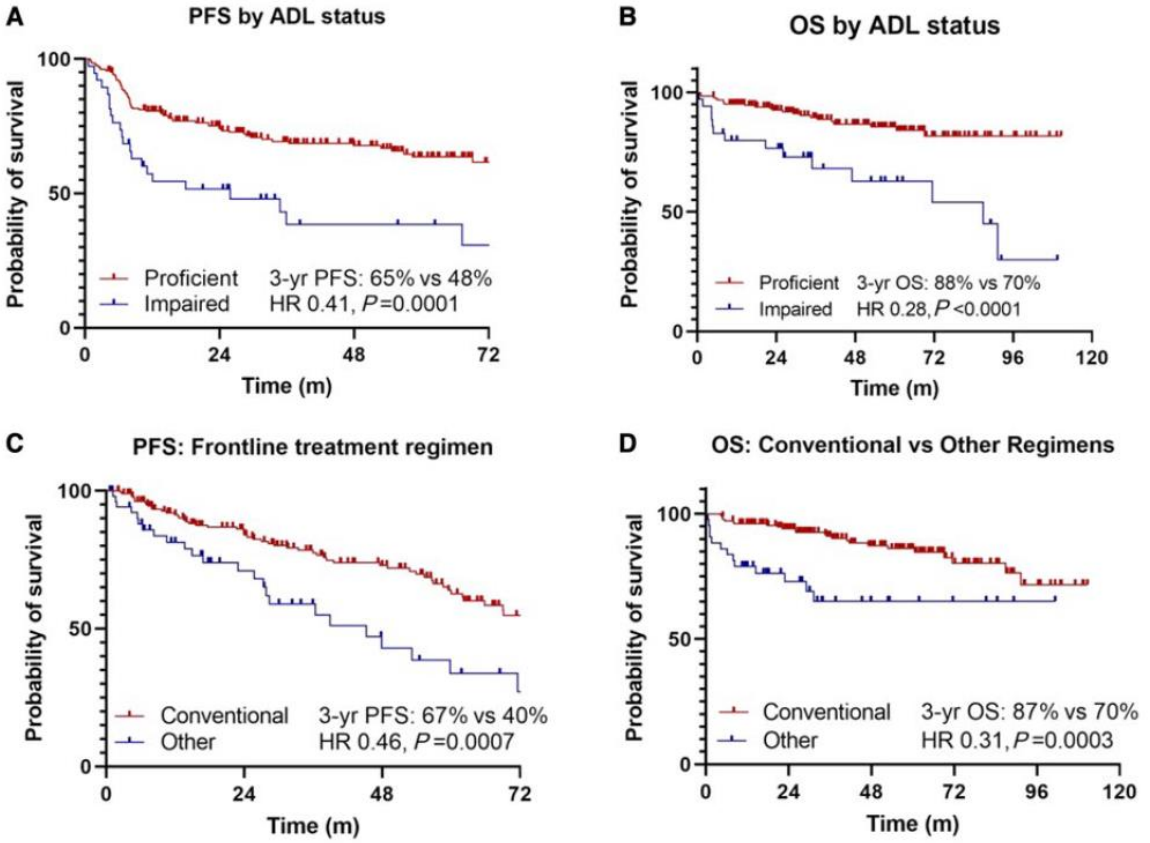
Björkholm M et al. Eur J Haematol 2018

Why?

- Different biology of the disease (more mixed cellularity, more EBV positive cases)
- Advanced stage more frequently present
- Higher incidence of co-morbidities
- Less capacity to receive full dose ABVD; higher incidence of treatment related toxicity (bleomycin)
- Small representation of elderly patients in prospective clinical trials

Impact of Functional Status & Conventional Tx in cHL

- Multicenter US RWE of geriatric fitness and real world outcomes in older patients with cHL (2010-2018)
- 244 pts, median age 68 yrs, 63% stage III/IV, 12% loss of >= 1 ADL, 18% CIRS-G score >= 10 (conventional treatment = anthracycline based)



Orellana-Noia V et al, Blood Adv 2021

Impact of Functional Status & Conventional Tx in cHL

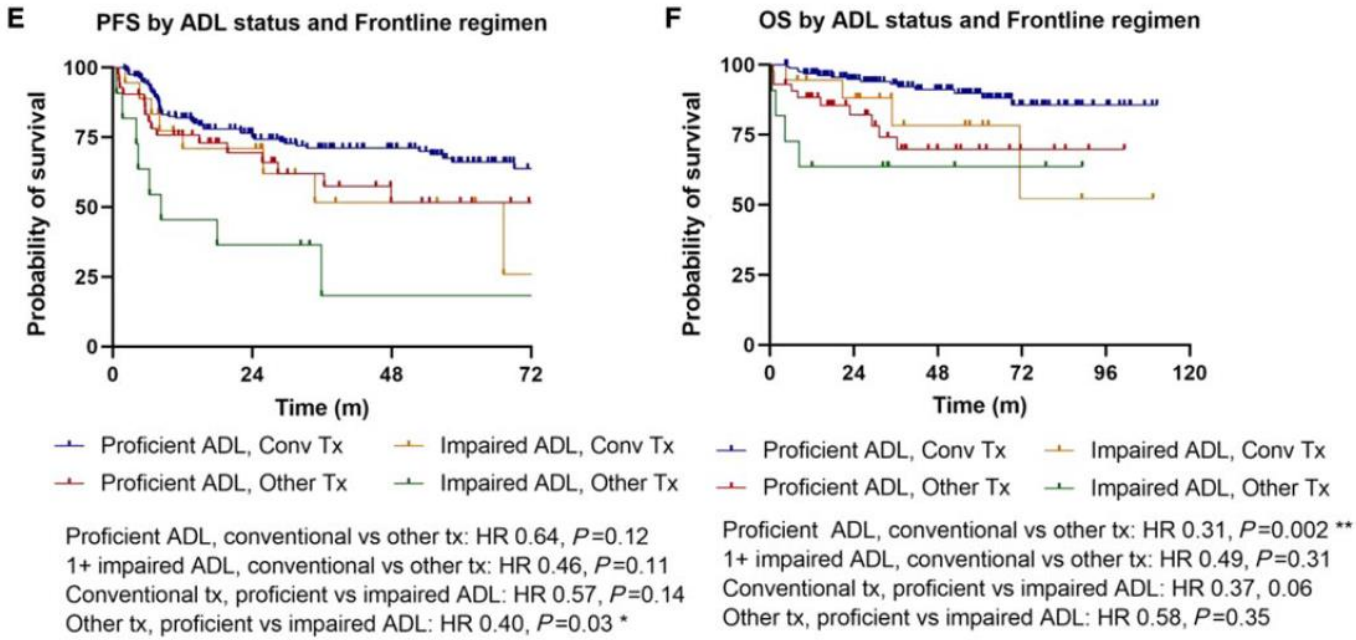
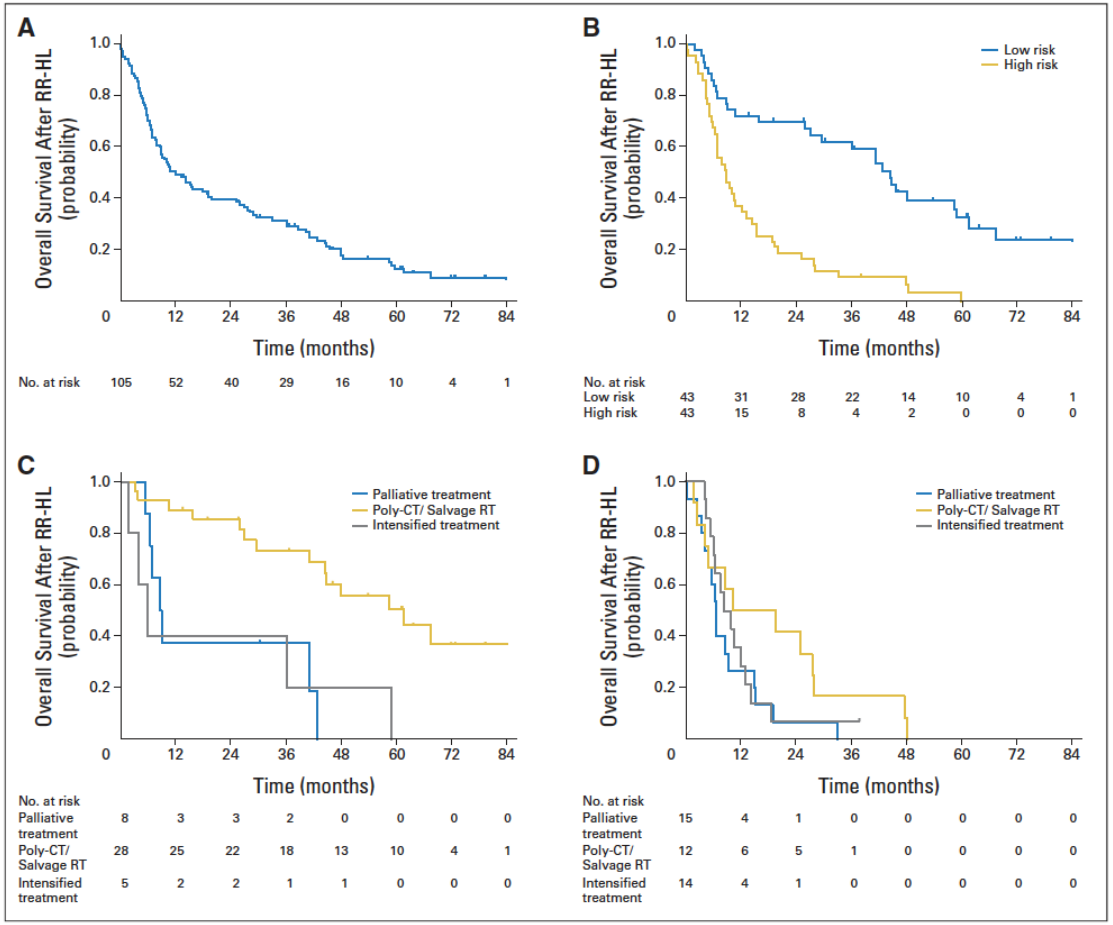


Figure 1. Outcomes of older HL patients based on functional status and conventional therapy. PFS and OS by geriatric fitness measures in stage II to IV disease. Time is listed in months for all figures. (A) PFS by ADL status. (B) OS by ADL status. (C) PFS by frontline treatment regimen. (D) OS by treatment regimen. (E) PFS by ADL status and frontline regimen. (F) OS by ADL status and frontline regimen. Tx, treatment. Reprinted with permission.[28]

Orellana-Noia V et al, Blood Adv 2021



Elderly Patients with Relapsed Disease Have a Very Poor Outcome

Böll B et al, J Clin Oncol 2013

Characterizing the Elderly Population of Patients. Frailty Assesment Tools

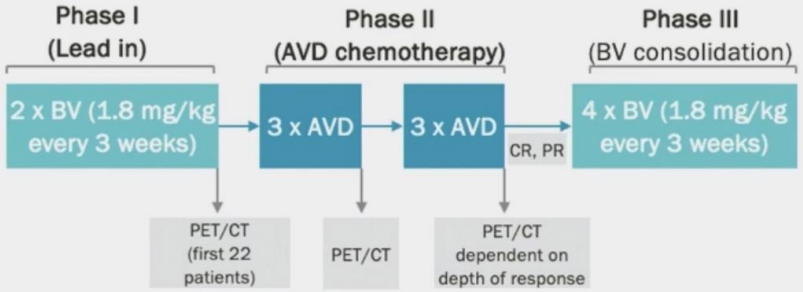
Older Hodgkin Lymphoma Patient (Advanced Stage)

- Baseline Objective Geriatric Assessment (MINIMUM: comorbidities (eg, CIRS-G or CCI) and assessment of self-care ADLs & IADLs)
- Proactive multidisciplinary medical management (eg, geriatrics, PCP, cardiology, endocrinology, etc)

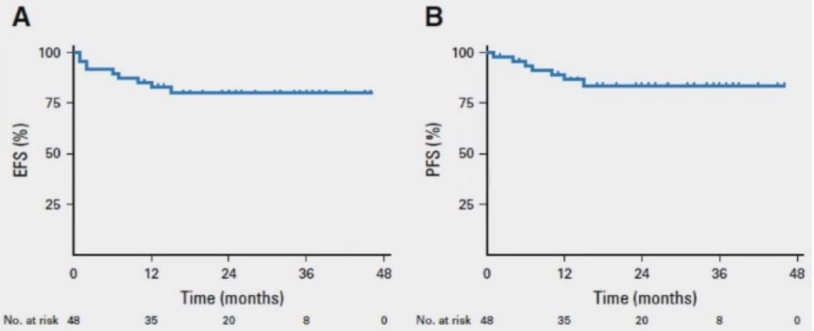
Criteria	Fit	Unfit	Frail
ADL	6	5	≤4
IADL	8	6-7	≤5
CIRS-G	0 score of 3-4 and <5 of score 2	0 score of 3-4 and 5-8 of score 2	≥1 score of 3-4 and/or >8 of score 2
Age	<80 years	≥80 years FIT	≥80 years UNFIT

Evens AM et al, ASH 2023 Educational Program

Phase 2, 1L Sequential BV-AVD in Ederly cHL Patients



- Among all 48 patients, 77% completed all 6 cycles of AVD therapy
- Grade 3 or 4 adverse events occurred in 42% of patients, with the highest incidence of neutropenia (44%)
  - 4% of patients grade 3 peripheral neuropathy (27% grade 2); 69% events were reversible to grade 1 or lower at 90 days after completion of treatment
- **ORR/CR: BV lead 82% (38%); Post-AVD 95% (90%)**

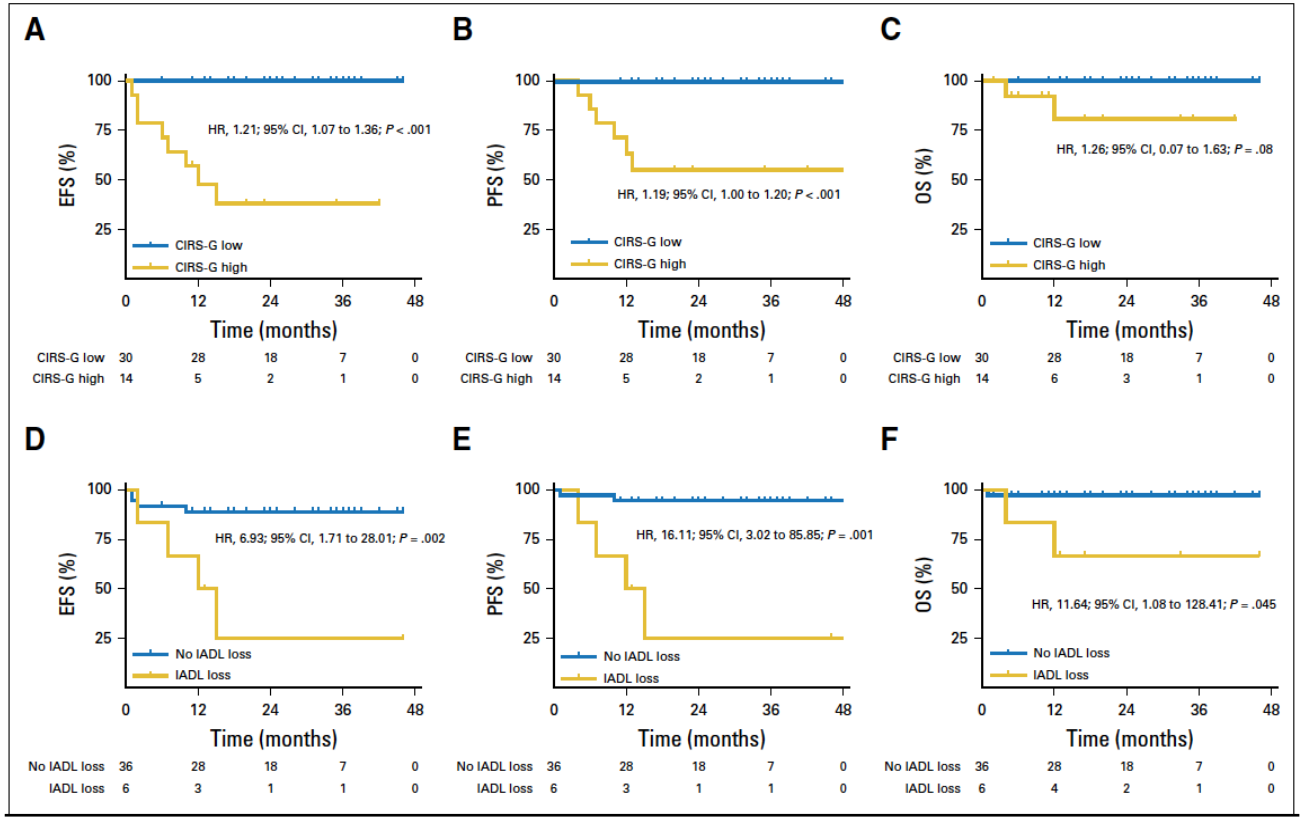


2-year EFS: 84%

2-year PFS: 90%

2-year OS: 92%

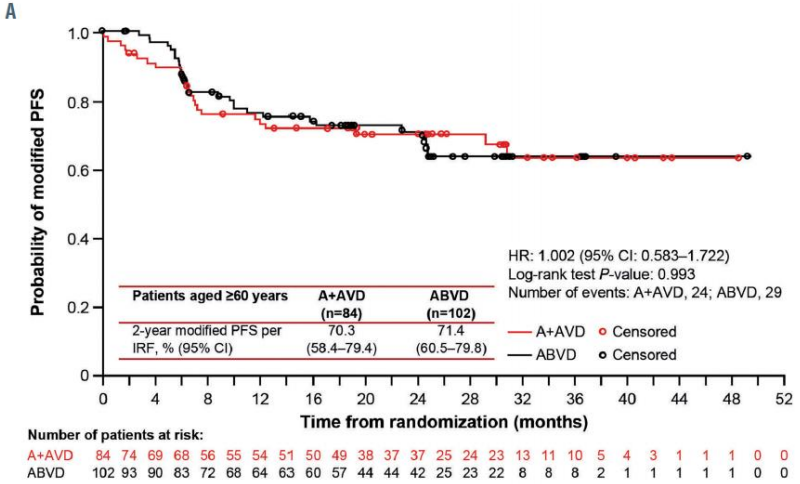
Evens AM et al, ASH 2023 Educational Program (Evens AM et al, J Clin Oncol, 2018)

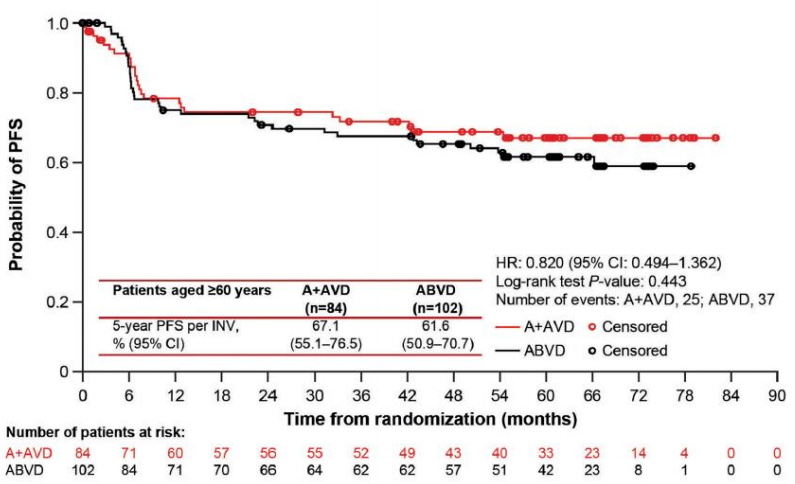


What is the Impact of Functional Status?

Evens AM et al, J Clin Oncol 2018

The Impact of BV-AVD vs ABVD in 1st Line Tx Advanced Stage Elderly Patients with cHL. The ECHELON 1 Prospective Clinical Trial





Evens AM et al, Haematol 2022

The Impact of BV-AVD vs ABVD in 1st Line Tx Advanced Stage Elderly Patients with cHL. The ECHELON 1 Prospective Clinical Trial. Efficacy

	Aged ≥60 years (n=186)		Aged ≥60 years with stage III disease (n=65)*		Aged ≥60 years with stage IV disease (n=118)*		Aged <60 years (n=1,148)		ITT population (n=1,334)	
	A+AVD (n=84)	ABVD (n=102)	A+AVD (n=31)	ABVD (n=34)	A+AVD (n=51)	ABVD (n=67)	A+AVD (n=580)	ABVD (n=568)	A+AVD (n=664)	ABVD (n=670)
24-month modified PFS† per IRF, % (95% CI)[20]	70.3 (58.4-79.4)	71.4 (60.5-79.8)	67.7 (44.9-82.6)	80.9 (66.2-90.9)	71.3 (56.3-81.9)	66.1 (51.8-77.1)	83.7 (80.2-86.6)	78.2 (74.4-81.6)	82.1 (78.8-85.0)	77.2 (73.7-80.4)
24-month PFS‡ per INV, % (95% CI)	74.4 (62.2-82.7)	70.8 (60.6-78.8)	74.8 (54.2-87.1)	85.3 (68.2-93.6)	74.1 (59.6-84.1)	62.7 (49.5-73.5)	86.5 (83.4-89.1)	80.4 (76.8-83.5)	84.5 (81.4-87.1)	78.3 (74.9-81.4)
60-month PFS‡ per INV, % (95% CI)	67.1 (55.1-76.5)	61.6 (50.9-70.7)	70.1 (48.7-83.9)	69.9 (51.3-82.6)	65.1 (49.9-76.8)	57.0 (43.5-68.5)	84.3 (81.0-87.1)	77.8 (74.0-81.1)	80.7 (77.1-83.8)	73.1 (69.0-76.7)

Evens AM et al, Haematol 2022

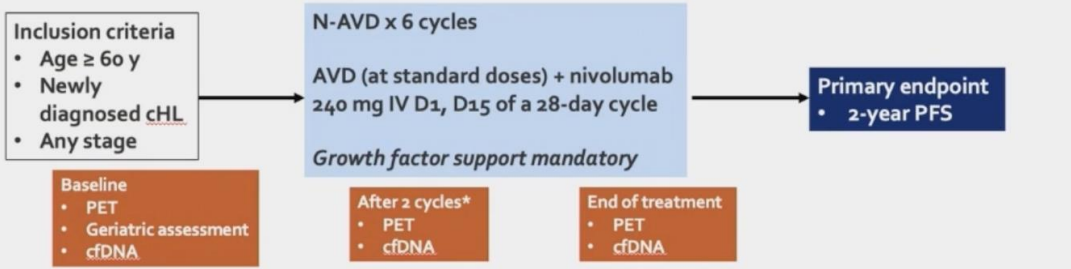
The Impact of BV-AVD vs ABVD in 1st Line Tx Advanced Stage Elderly Patients with cHL. The ECHELON 1 Prospective Clinical Trial. Safety and Toxicity

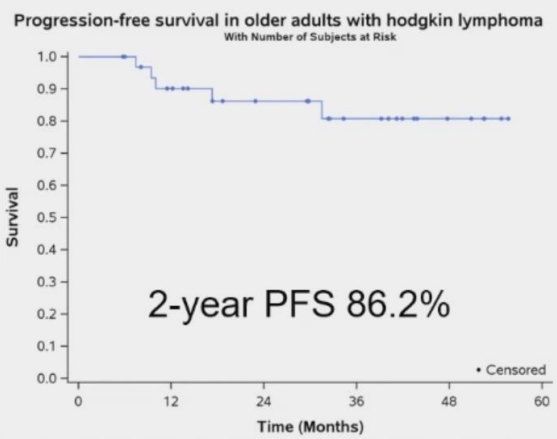
	Patients aged ≥60 years evaluable for safety* (n=181)		Patients aged <60 years evaluable for safety* (n=1,140)		Safety population*,[38] (n=1,321)	
	A+AVD (n=83)	ABVD (n=98)	A+AVD (n=579)	ABVD (n=561)	A+AVD (n=662)	ABVD (n=659)
Grade ≥3 AE, n (%)	73 (88)	78 (80)	476 (82)	356 (63)	549 (83)	434 (66)
On-study deaths,† n (%)	3 (4)	5 (5)	6 (1)	8 (1)	9 (1)	13 (2)
Grade ≥3 neutropenia,‡ n (%)	58 (70)	58 (59)	372 (64)	259 (46)	430 (65)	317 (48)
Any-grade FN on study, n (%)	31 (37)	17 (17)	97 (17)	35 (6)	128 (19)	52 (8)
Any-grade pulmonary AE, n (%)	2 (2)	13 (13)	10 (2)	31 (6)	12 (2)	44 (7)

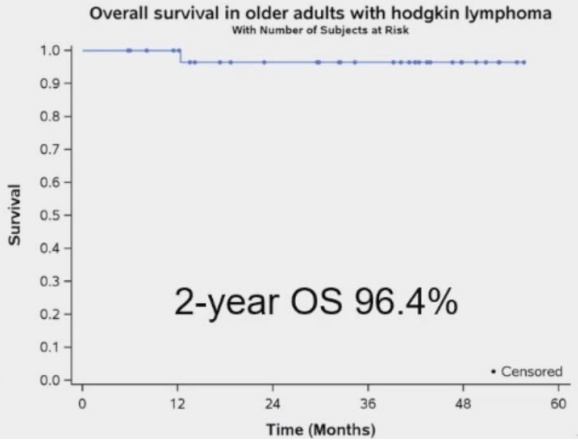
Evens AM et al, Haematol 2022

Integrating CPIs in 1st Line Therapy of Advanced Stage Elderly cHL

- N=40 pts efficacy (n=37 in phase 2, and n=33 efficacy)
- Med age 66 yrs, 78% stage III/IV

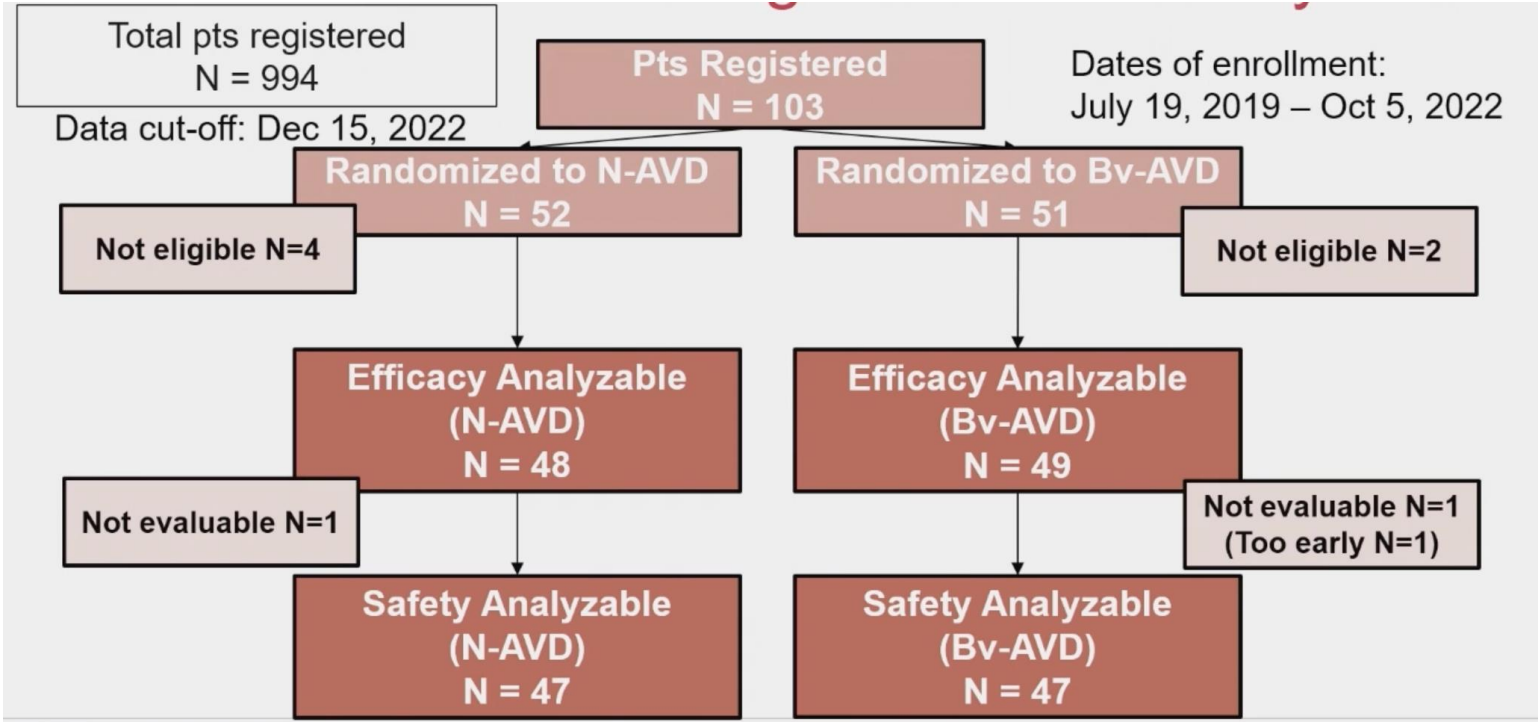






Torka P et al, ICML 2023

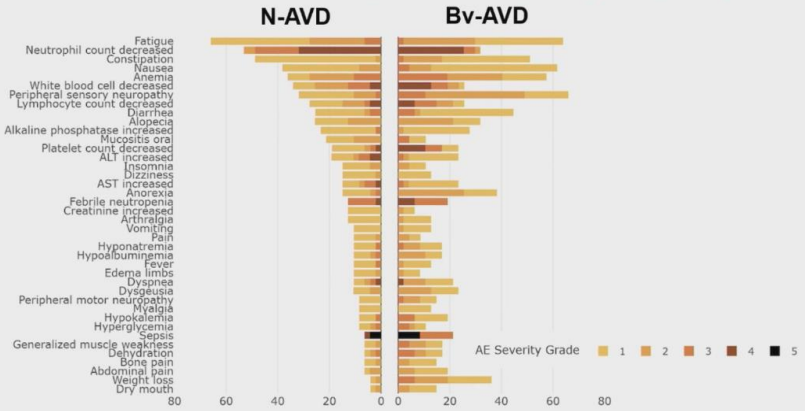
S1826 CONSORT Diagram for Patients >= 60 years



Rutherford S et al, ASH2023

Adverse Event Profile

More AEs with Bv-AVD (GI, neuropathy, sepsis)



Adverse Events (AEs) in ≥10% of Older Pts

Toxicity	N-AVD N = 47		Bv-AVD N = 47	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	25 (53%)	23 (49%)	15 (32%)	14 (30%)
Anemia	17 (36%)	5 (11%)	27 (57%)	9 (19%)
Thrombocytopenia	9 (19%)	2 (4%)	11 (23%)	8 (17%)
Received G-CSF	33 (69%)#		45 (92%)#	
Bone pain	3 (6%)		7 (15%)	

AEs of interest: Hematologic

*Growth factor required with Bv-AVD

#Calculation by intent-to-treat

Toxicity	N-AVD N = 47	Bv-AVD N = 47	p-value*	N-AVD N = 47	Bv-AVD N = 47	p-value*
	Any grade N (%)	Any grade N (%)		Gr ≥ 3 N (%)	Gr ≥ 3 N (%)	
Febrile Neutropenia	6 (13%)	9 (19%)	0.57	6 (13%)	9 (19%)	0.57
Sepsis	3 (6%)	10 (21%)	0.07	3 (6%)	10 (21%)	0.07
Infections/ Infestations	9 (19%)	16 (34%)	0.16	3 (6%)	10 (21%)	0.07

AEs of interest: Infectious

*Two-sided Fisher's exact test

Rutherford et S al, ASH 2023

Adverse Event Profile

Toxicity	N-AVD N = 47 Any grade N (%)	Bv-AVD N = 47 Any grade N (%)	p-value*	N-AVD N = 47 Gr ≥ 3 N (%)	Bv-AVD N = 47 Gr ≥ 3 N (%)	p-value*
Peripheral sensory neuropathy#	15 (32%)	31 (66%)	0.0018	1 (2%)	5 (11%)	0.20
Peripheral motor neuropathy+	4 (9%)	7 (15%)	0.52	0 (0%)	1 (2%)	1.00

AEs of interest: Peripheral Neuropathy

#N-AVD, gr 1: 21%, gr 2: 9%, gr 3: 2%; Bv-AVD, gr 1: 17%, gr 2: 38%, gr 3: 11%.

+N-AVD, gr 1: 9%; Bv-AVD gr 1: 6%, gr 2: 6%, gr 3: 2%.

*Two-sided Fisher's exact test

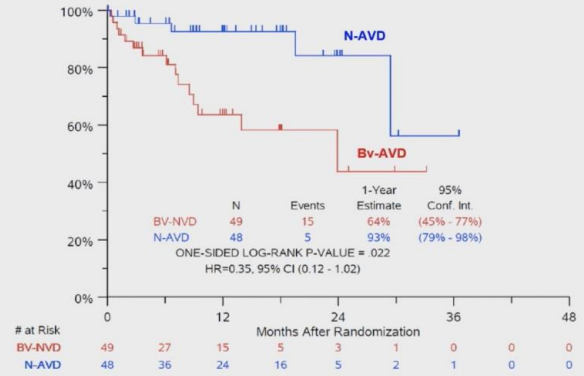
Sutherland S et al, ASH 2023

Disposition	N-AVD N = 48, N (%)	Bv-AVD N = 49, N (%)
Treatment ongoing	1 (2%)	2 (4%)
Completed treatment	42 (88%)	31 (63%)
Discontinued all treatment early	**5 (10%)**	**16 (33%)**
Adverse event	2 (4%)	7 (14%)
Refusal unrelated to AE	1 (2%)	2 (4%)
Progression/relapse	0 (0%)	1 (2%)
Death on treatment	1 (2%)	5 (10%)
Other – not protocol specified	1 (2%)	1 (2%)
Received protocol radiotherapy	0 (0%)	0 (0%)

15% discontinued nivolumab and 39% discontinued Bv early, primarily due to AEs

EFS event	N-AVD	Bv-AVD
Progression/Relapse	**3**	**8**
Death without progression	2	6
Non-protocol chemotherapy before PD	0	1
Non-protocol immunotherapy before PD	0	0
Non-protocol RT prior to PD	0	2
Total EFS Event	**5**	**17**

N-AVD markedly improves PFS over Bv-AVD in older patients with cHL



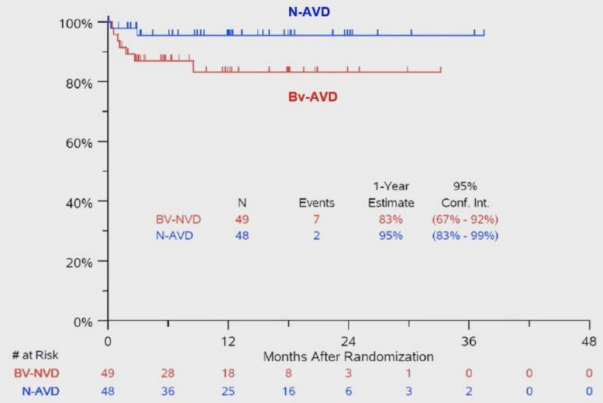
1-year PFS
N-AVD 93%
Bv-AVD 64%

Median follow-up
12.1 months

p-value = 0.022
HR=0.35,
95% CI (0.12-1.02)

Sutherland S et al, ASH 2023

Fewer deaths occurred on N-AVD vs Bv-AVD



1-year OS
N-AVD 95%
Bv-AVD 83%

Median follow-up
12.1 months

p-value = 0.091
HR=0.35,
95% CI (0.07-1.75)

Majority of deaths on Bv-AVD due to infection/sepsis

Cause of death	N-AVD	Bv-AVD
Infection	1	3
Sepsis	1	2*
Pneumonitis	0	1
Unknown	0	1
Total OS events	**2**	**7**

Non-relapse mortality
N-AVD 4% vs Bv-AVD 14%

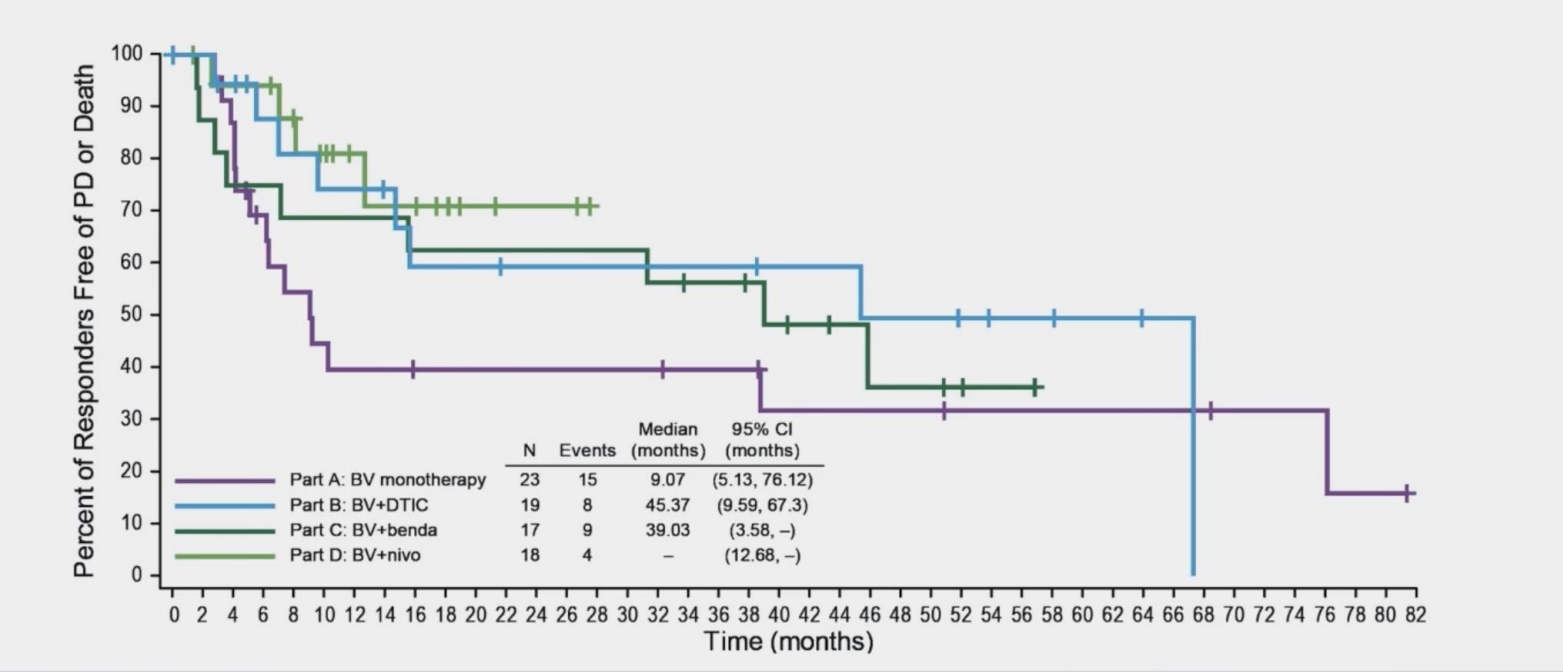
Rutherford S et al, ASH 2023

"Unfit" Older cHL Patients. BV +/- DTIC or Bendamustine or Nivolumab

Efficacy Evaluable Set	Part A BV mono N=25	Part B BV+DTIC N=19	Part C BV+benda N=17	Part D BV+nivo N=19
ORR, n (%)	**23 (92)**	**19 (100)**	**17 (100)**	**18 (95)**
Best overall response				
Complete response	18 (72)	13 (68)	15 (88)	15 (79)
Partial response	5 (20)	6 (32)	2 (12)	3 (16)
Stable disease	2 (8)	0	0	1 (5)
Progressive disease	0	0	0	0
Duration of response, n	23	19	17	18
Median (min, max)	9.1 (2.8, 81.4+)	45.4 (0.0+, 67.3)	39.0 (0.0+, 56.8+)	NR (1.4+, 27.5+)
Grade 3 PN	**35%**	**25%**	**20%**	**33%**

Friedberg J et al, Blood 2017; Yasenchak CA et al, ASH 2000; Abstract 471

"Unfit" Older cHL Patients. BV +/- DTIC or Bendamustine or Nivolumab



Cheson B et al, Lancet Haem 2020; Yasenchak CA et al, ASH 2000; Abstract 471

Ongoing or Planned Prospective Clinical Trials for Older Patients

Trial title	Trial phase	Study number	Disease stage	GA-based inclusion/ GA-directed therapy	Study design
Phase II Trial of Individualized Immunotherapy in Early-Stage Unfavorable Classical Hodgkin Lymphoma *(INDIE)*	2	NCT04837859	IA-IIB	Yes (CIRS-G)/no	2 cycles tislelizumab; PET neg: 4 cycles tislelizumab +30 gy ISRT; PET pos: 4 cycles T-AVD +30 gy ISRT
Response Adapted Incorporation of Tislelizumab Into the Front-line Treatment of Older Patients With Hodgkin Lymphoma *(RATiFY)*	2	NCT05627115	I-IV	No/no	3 cycles tislelizumab; PET neg: 2 cycles T +/− RT followed by tislelizumab until PD or toxicity for fav ES or 2–4 cycles T+AVD +/− RT for unfav ES and AS; PET pos: 4–6 cycles T+AVD +/− RT for ES and AS
Fitness-Adapted, Pembrolizumab-Based Therapy for Untreated Classical Hodgkin Lymphoma Patients 60 Years of Age and Above	2	NCT05404945	II-IV	Yes/yes (CIRS-G + ADLs)	Pembro + BV followed by repeat GA/ fitness; fit induction: 3 cycles Pembro q6w + 4 cycles AVD; unfit induction: 3 cycles Pembro q6w + 3 cycles BV; consolidation for all: Pembro +2 doses BV
A Study of Brentuximab Vedotin With Hodgkin Lymphoma (HL) and CD30-Expressing Peripheral T-cell Lymphoma (PTCL)	2	NCT01716806	II-IV	Yes/yes (CIRS-G + ADLs)	Cohorts E and F: single-agent BV for patients unsuitable or unfit for initial conventional combination chemotherapy by GA (ie, CIRS-G ≥10 and/or loss of any instrumental ADL)
BrEPEM-LH-22017 for Older Patients With Untreated Hodgkin Lymphoma (HL)	1/2	NCT03576378	IIB-IV	No/no	6 cycles BV-EPEM
HD21 for Advanced Stages Treatment Optimization Trial in the First-line Treatment of Advanced Stage Hodgkin Lymphoma; Comparison of 6 Cycles of Escalated BEACOPP With 6 Cycles of BrECADD (elderly extension)	2	NCT02661503	IIB with LMM or EN, III/IV	Yes (CIRS-G)/no	2 cycles BrECADD; PET neg: 2 cycles BrECADD; PET pos: BrECADD 4 cycles +/− RT
Immunotherapy (Nivolumab or Brentuximab Vedotin) Plus Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage III-IV Classic Hodgkin Lymphoma *(S1826)**	3	NCT03907488	III/IV	No/no	6 cycles Nivo + AVD vs 6 cycles BV + AVD

Evens AM et al,
ASH 2023 Educational Program

Conclusions

- Outcomes of older patients still sub-optimal but the introduction of new drugs suggest that results have improved
- Geriatric assesments are important
- Anthracycline-based therapy remains the SoC (especially for fit patients)
  - Although FU is short, N-AVD seems to be better than BV-AVD
  - More studies are needed for the unfit / frail population of patients
- Special consideration of side effects
- Additional prospective clinical trials are needed