BEST MANAGEMENT OF HODGKIN LYMPHOMA IN THE OLDER ADULT

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CLINICAL CASE

- A 75 year old with a history of smoking but no other co-morbidities presents with fevers, chills, and a 10-lbs weight loss.
- Imaging shows diffuse adenopathy above and below the diaphragm.
- An excisional lymph node biopsy shows classic Hodgkin lymphoma, mixed cellularity subtype.
- Labs demonstrate an elevated erythrocyte sedimentation rate and lactate dehydrogenase, but otherwise no cytopenias.
- PET scan shows no avidity in the bone marrow. Echocardiogram shows a normal ejection fraction with no valvular dysfunction.

Which of the following are potential treatment options?

QUESTION

Which of the following are potential treatment options?

A. escBEACOPP x6

B. AVD x 6

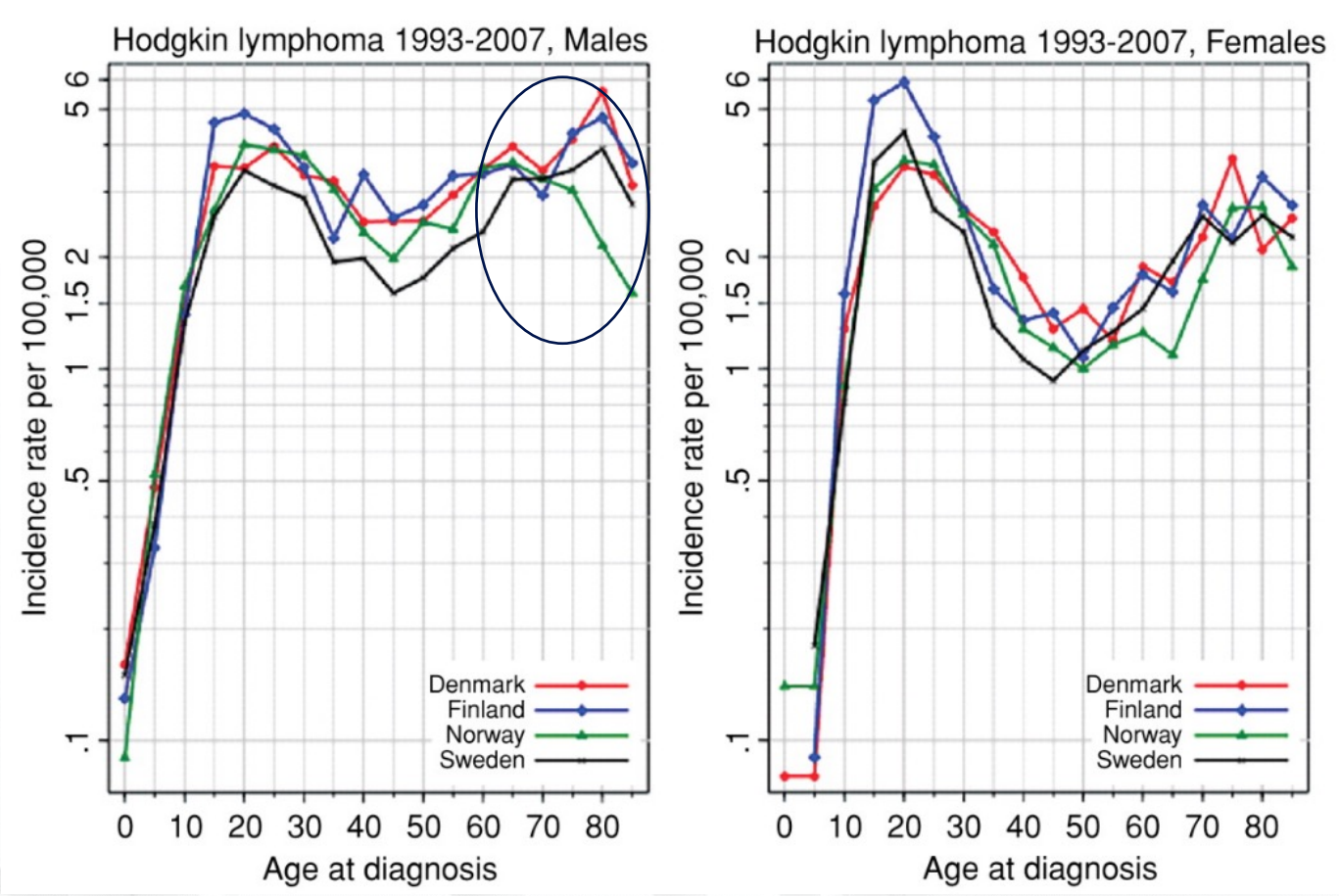
C. Sequential brentuximab and AVD

D. B and C only

OBJECTIVES

- Discuss treatment of older patients with classic Hodgkin lymphoma (cHL)
- Discuss unique toxicities of therapy in older adults
- Discuss the role of brentuximab

BACKGROUND

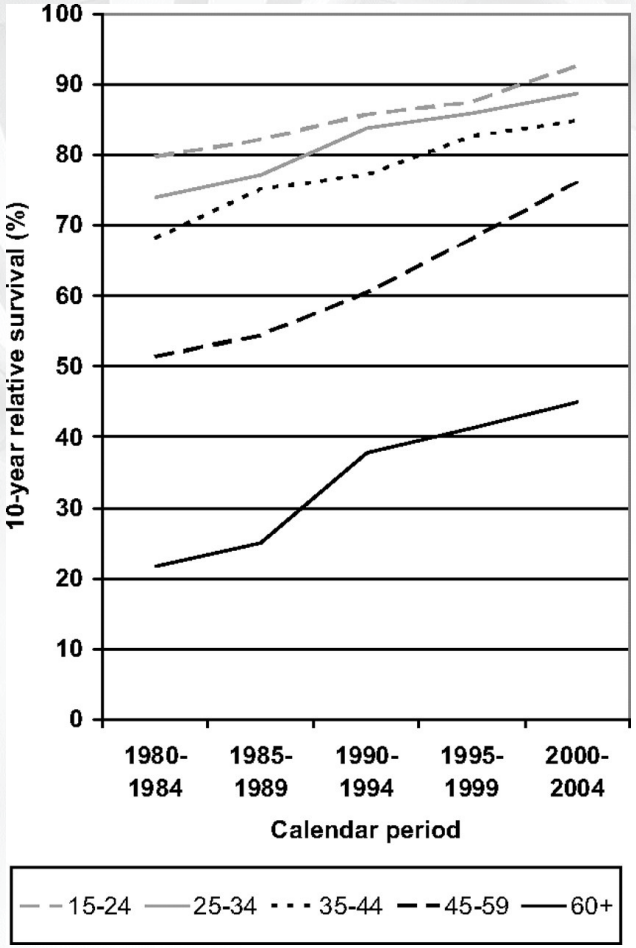


- Older HL: Age > 60
- 20% of HL in the US

CLINICAL PRESENTATION

- More likely to have advanced stage
- Bone marrow involvement
- Extra-nodal disease
- B symptoms
- Higher degree of Mixed Cellularity phenotype
- Less likely to have bulky disease

SEER Analysis Survival by Age at Diagnosis



Hermann Brenner,Adam Gondos,Dianne Pulte, Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients, Blood, 2008,

OLDER HL LESS LIKELY TO RECEIVE CT OR RT

	Elderly	Younger	
Early Stage	45%	65%	
Advanced Stage	55%	35%	
B symptoms	43	42	
Classification			
NS	**37**	**69**	
LR	5	2	
MC	**18**	**8**	
LD	3	1	
Other	37	20	
Chemotherapy	77	94	
Radiation for Stage 1-2	38	45	P <.001

Erdcamp, Cancer 1992
Evens et al. Blood, 2012
Major, A. et al, Leukemia& Lymphoma, 2019

Table 2. The Number of Patients who Received Incomplete or no Treatment at all in Relation to Age

Age (yr)	No. of patients	No therapy	Incomplete chemotherapy	Incomplete radiation therapy
< 50	142	0	3	0
≥ 50	40	2	7	6

Multicenter analysis of HL > 60

- **Dose intensity = 71%**
- ORR= 92%
- **CR=73%**

BLEOMYCIN LUNG TOXICITY

Retrospective analysis of Elderly patients (n=95)

- The incidence of bleomycin lung toxicity (BLT) = 32%
- Mortality of 25%
- The incidence of BLT was 38% versus 0% among patients receiving G-CSF versus not, respectively

  (P = .0001).

Risk factors for BLT include older age, cumulative bleomycin dose, renal insufficiency, pulmonary radiation, underlying lung disease, and tobacco history.

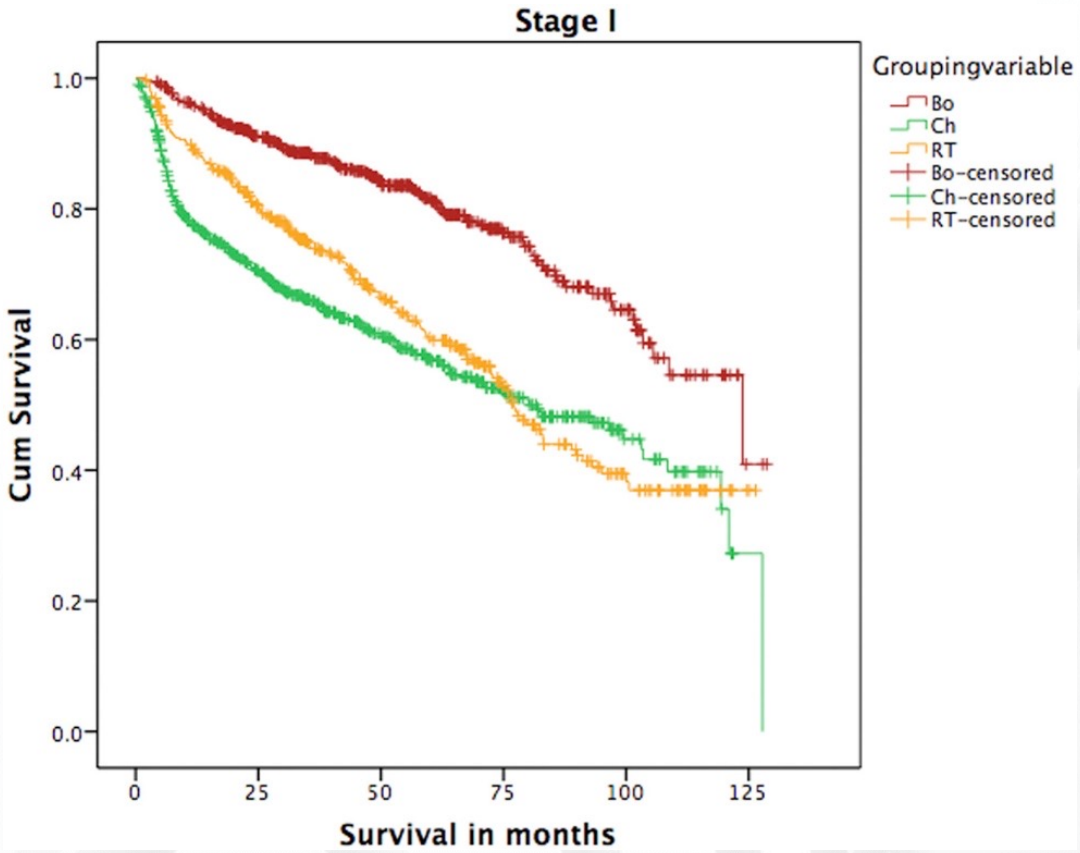
Anderson, Leukemia & Lymphoma, 2019

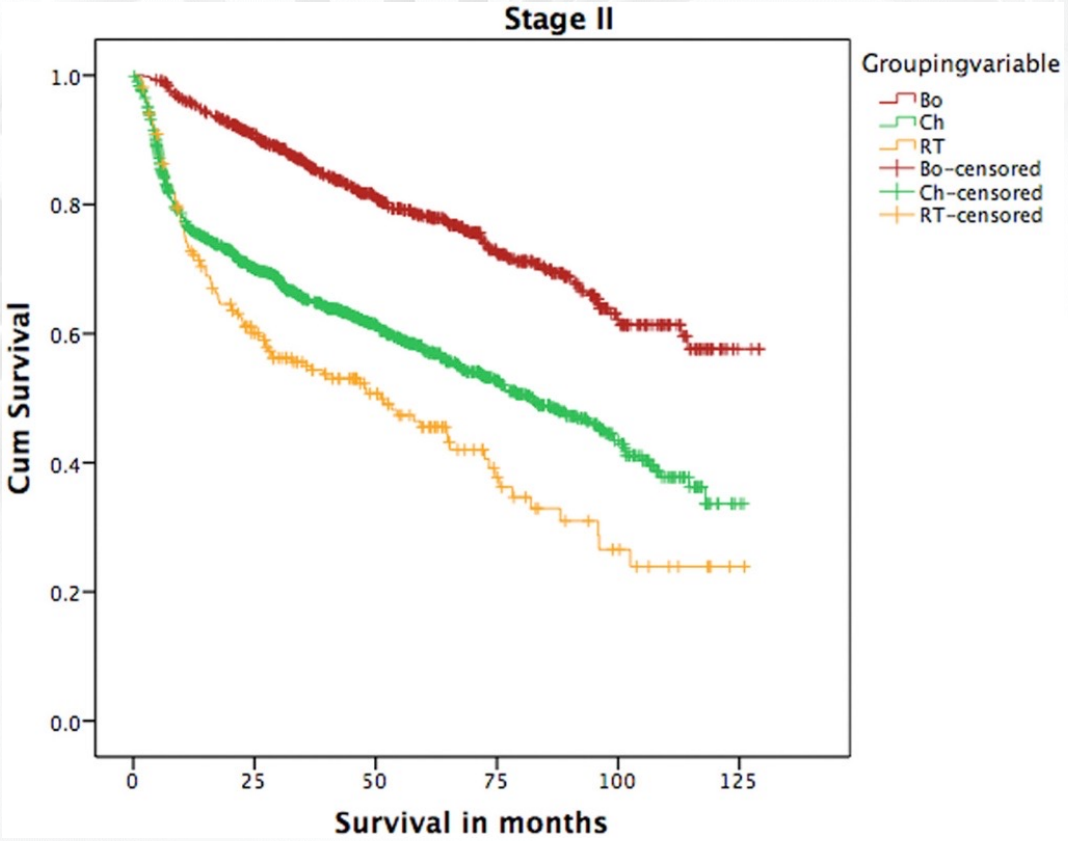
HOW DO WE TREAT OLDER HL PATIENTS?

- ABVD
- AVD
- BV + AVD
- Sequential BV AVD
- BV + dacarbazine
- BV alone
- BV nivolumab
- Palliative

LIMITED STAGE HL

IMPROVED OUTCOMES WITH CMT AMONG OLDER ADULTS WITH LIMITED STAGE HL

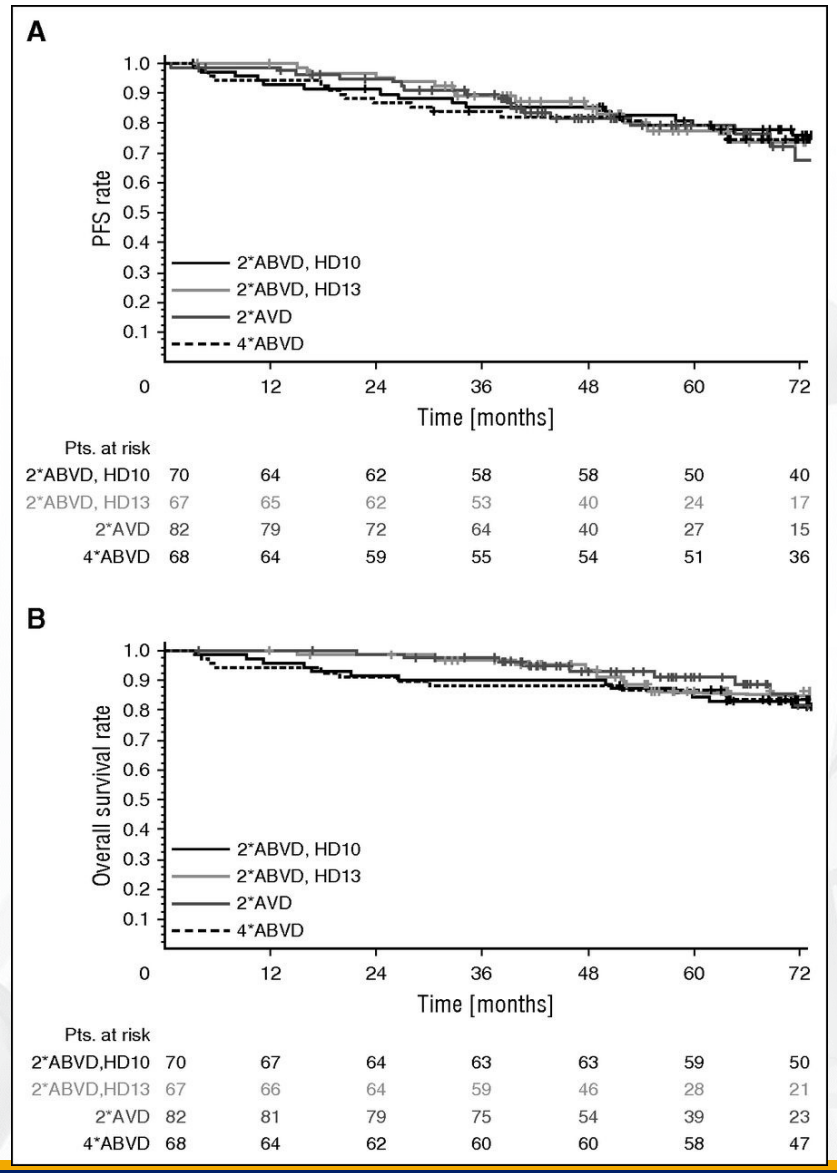




OS rates for patients receiving CT, RT, or CT plus RT were 58.1%, 54%, and 77.7%

Goyal et al. Clin Leukemia, Lymphoma, Myeloma, 2017

NO SIGNIFICANT DETRIMENT WITH OMITTING BLEOMYCIN IN OLDER EARLY-STAGE FAVORABLE HL



Analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials

N= 287 older early-stage favorable HL

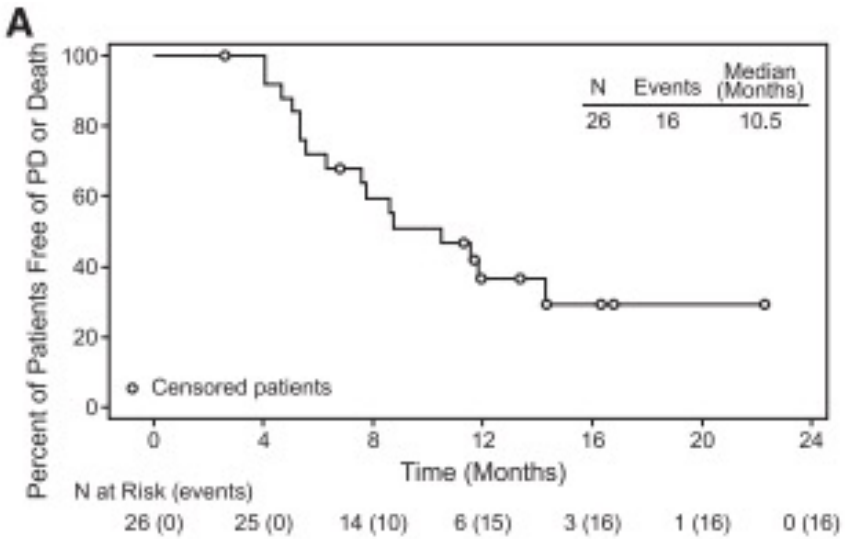
Treatment:

- 2×ABVD; n = 137
- 2×AVD; n = 82, followed by IF-RT
- 4×ABVD+IF-RT n = 68.

Boris Böll et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials, Blood, 2016

ADVANCED STAGE HODGKIN THERAPY

BRENTUXIMAB MONOTHERAPY



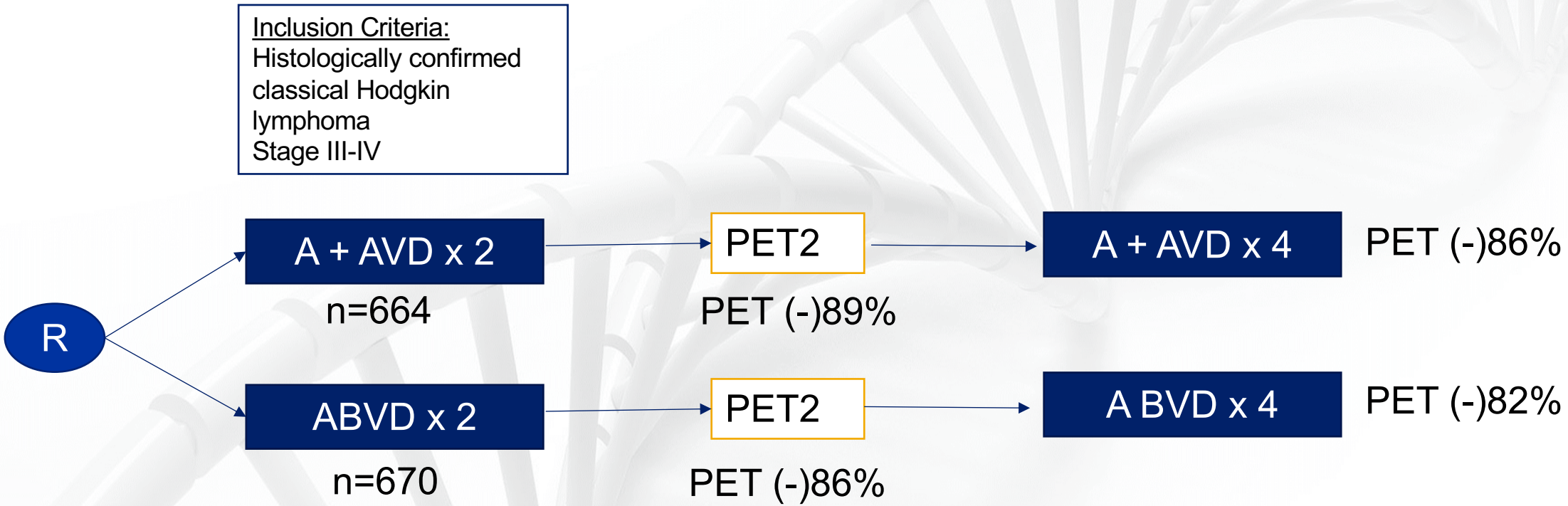
- N=27
- BV up to 16 cycles
- Comprehensive GA: 67% impaired

Table 3. Best clinical response to frontline brentuximab vedotin monotherapy

	N = 26*		
	n	%	95% CI†
ORR (CR + PR)	24	92	(74.9, 99.1)
Best clinical response			
CR	19	73	(52.2, 88.4)
PR	5	19	—
SD	2	8	—
Disease control rate (CR + PR + SD)	26 (100)	100	(86.9, 100)

Forrero-Tores, Blood 2015

BRENTUXIMAB AND CHEMOTHERAPY: ECHELON-1



Primary Endpoint: Modified PFS

1. Progression
2. Death
3. Modified progression
   DV 3-5 followed by anti-cancer therapy (i.e. radiation)

Johnson, NEJM, 2016

ECHELON-1 ELDERLY DATA

Table 1.

	Pts aged ≥60 yrs (n=186)		Pts aged <60 yrs (n=1148)	
	A+AVD (n=84)	ABVD (n=102)	A+AVD (n=580)	ABVD (n=568)
2-yr mPFS per IRF, % (95% CI)	70.3 (58.4, 79.4)	71.4 (60.5, 79.8)	83.7 (80.2, 86.6)	78.2 (74.4, 81.6)
HR (95% CI) [p-value]	1.00 (0.58, 1.72) [0.993]		0.73 (0.56, 0.96) [0.025]	
2-yr PFS per INV, % (95% CI)	73.8 (62.3, 82.2)	68.9 (58.1, 77.5)	85.6 (82.3, 88.4)	79.6 (75.9, 82.8)
HR (95% CI) [p-value]	0.85 (0.49, 1.48) [0.576]		0.67 (0.50, 0.90) [0.006]	

Table 2.

	Pts aged ≥60 yrs evaluable for safety* (n=181)		Pts aged <60 yrs evaluable for safety* (n=1140)	
	A+AVD (n=83)	ABVD (n=98)	A+AVD (n=579)	ABVD (n=561)
G3/4 AEs, n (%)	73 (88)	78 (80)	476 (82)	356 (63)
Fatal AEs	3 (4)	5 (5)	6 (1)	8 (1)
Any-grade neutropenia	61 (73)	65 (66)	393 (68)	296 (53)
Any-grade FN	31 (37)	17 (17)	97 (17)	35 (6)
Any-grade PN	54 (65)	42 (43)	388 (67)	244 (43)
Any-grade pulmonary AEs	2 (2)	13 (13)	10 (2)	31 (6)

*Received ≥1 dose of study therapy.

Evens, ASH 2018

SUMMARY OF ECHELON-1 IN OLDER HL

- For older ECHELON-1 pts, mPFS and PFS were similar in both arms.

- Treatment-emergent AEs was higher in older pts,
  - Higher fatal pulmonary events in ABVD pts.
  - The high incidence of FN in older A+AVD pts points to the need for G-CSF prophylaxis

SEQUENTIAL BRENTUXIMAB AND AVD

Inclusion Criteria:
classical Hodgkin lymphoma
Stage III-IV
Age > 60

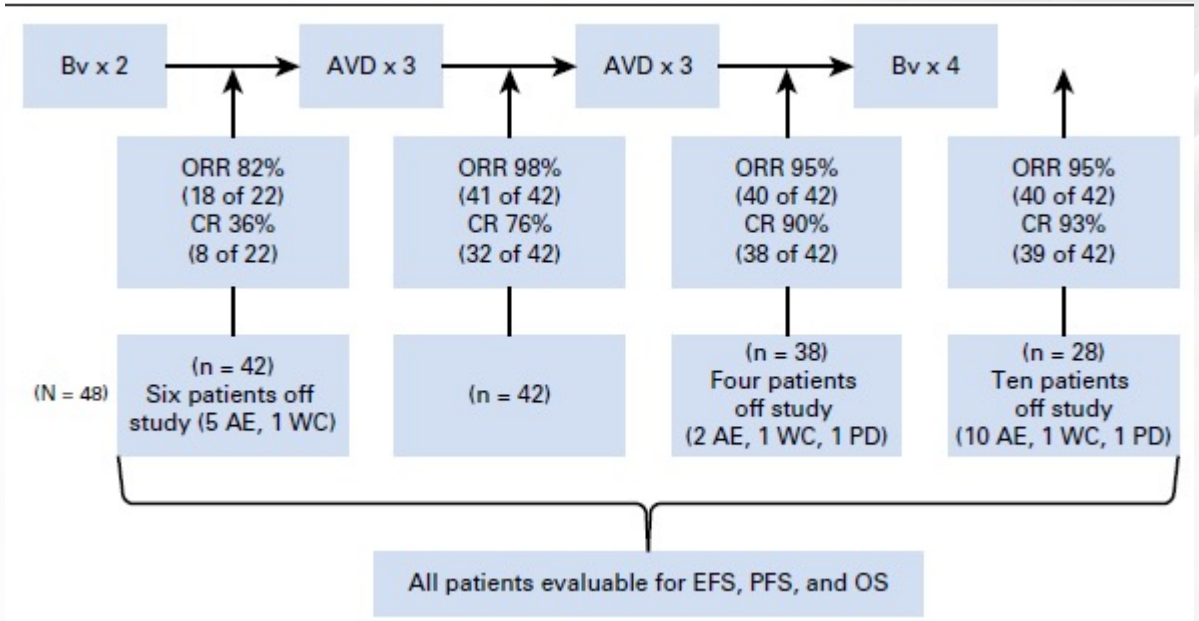


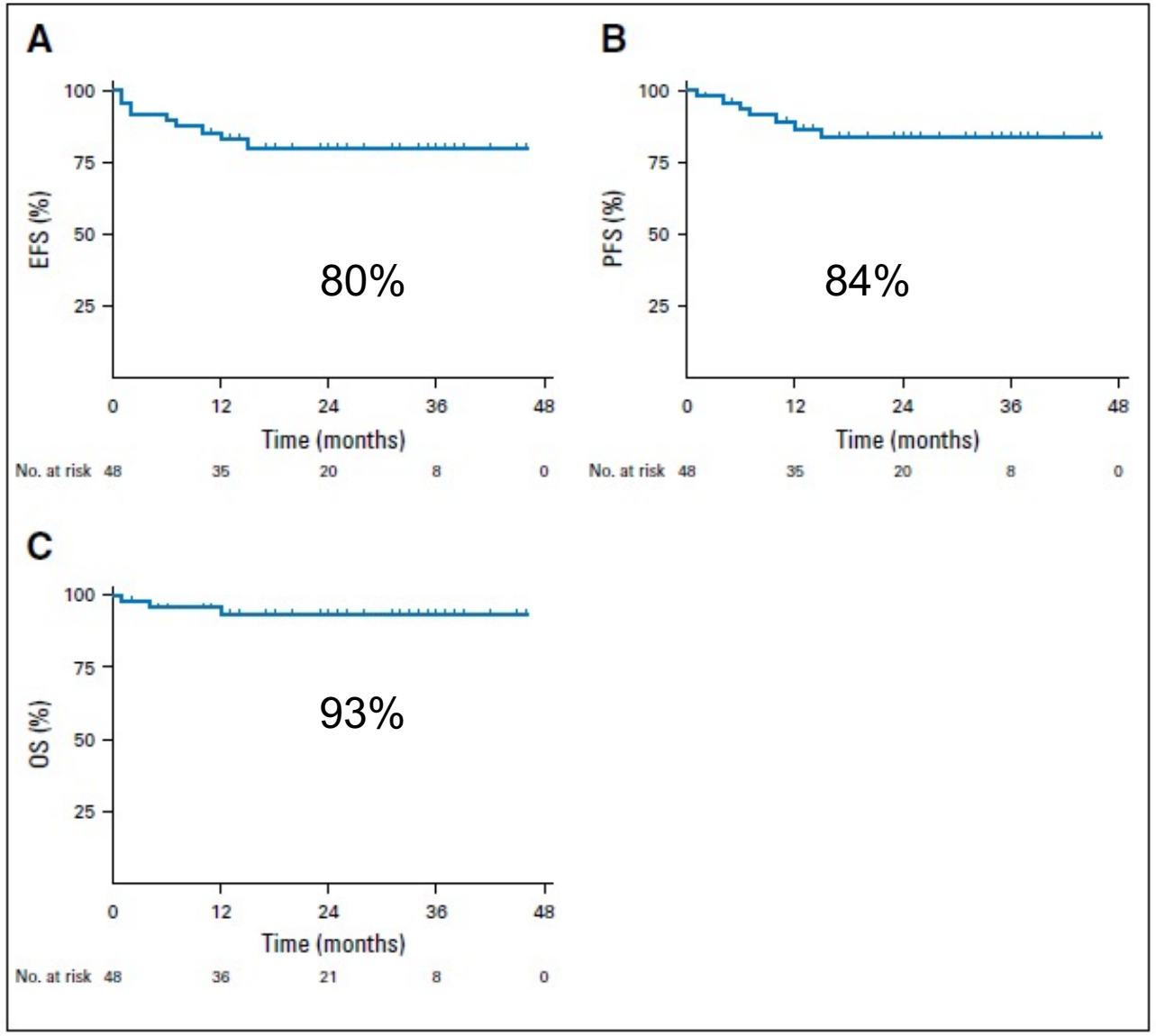
Table 1. Patient Characteristics

Characteristic	No. (N = 48)*	%
Age, years		
60-70	25	52
71-80	15	31
> 80	8	17
Sex		
Female	18	37
Male	30	63
Histology		
Nodular sclerosis	22	46
Mixed cellularity	12	25
Classic, not otherwise specified	12	25
Lymphocyte rich	2	4
ECOG PS		
0	19	40
1	20	41
2	9	19
B symptoms	18	37
Albumin		
Low (< 4.0 g/dL)	22	46
International Prognostic Score		
0-2	20	42
3-7	28	58
Bone marrow		
Involved	11	23
Bulky disease (≥ 10 cm)	5	10
Stage		
II†	9	19
III	18	37
IV	21	44
Median CIRS-G score (range)	7 (0-20)	

Assessed Response, PFS, and Comprehensive Geriatric Assessment

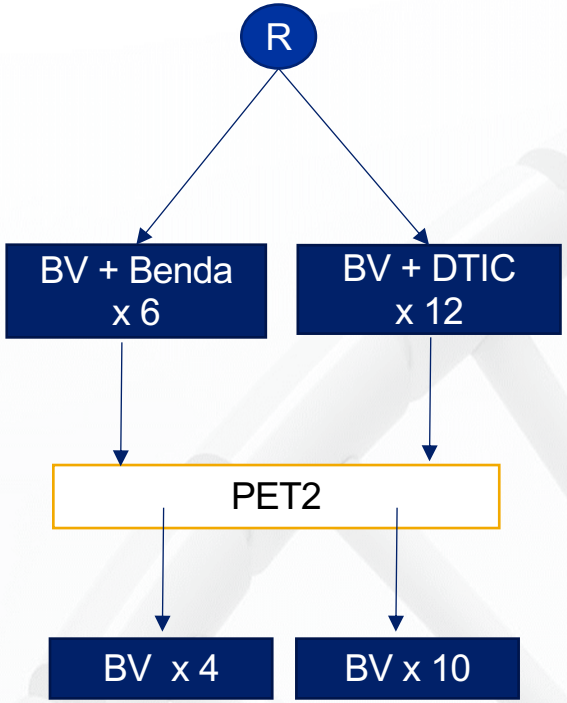
Evens, Blood 2018

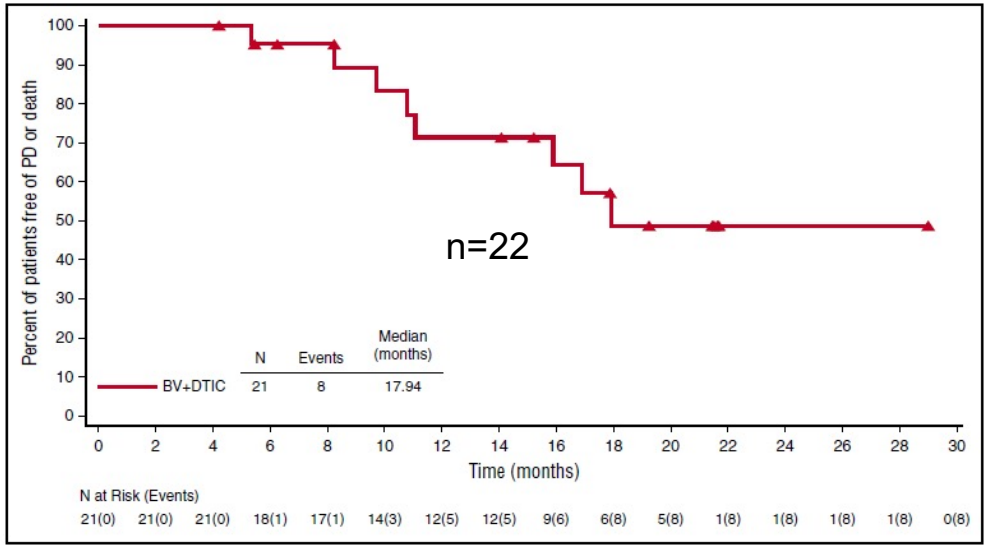
RESULTS


A
100
75
50
25
EFS (%)
80%
0
12
24
36
48
Time (months)
No. at risk 48 35 20 8 0
B
100
75
50
25
PFS (%)
84%
0
12
24
36
48
Time (months)
No. at risk 48 35 20 8 0
C
100
75
50
25
OS (%)
93%
0
12
24
36
48
Time (months)
No. at risk 48 36 21 8 0

OLDER CHL: BRENTUXIMAB WITH DACARBAZINE OR BENDAMUSTINE

Inclusion Criteria:
Histologically confirmed classical Hodgkin lymphoma
Age ≥60





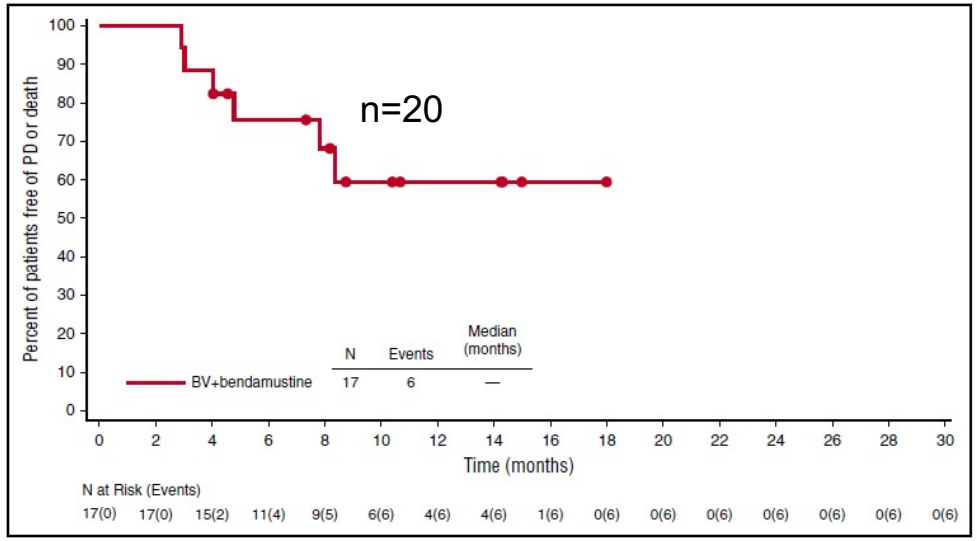


Table 4. Summary of AEs

	BV+DTIC (n = 22)	BV+bendamustine (n = 20)
Any TEAE*	22 (100)	20 (100)
Treatment-related AEs	22 (100)	19 (95)
Grade ≥3 AEs	10 (45)	18 (90)
SAEs	4 (18)	13 (65)
AEs leading to treatment discontinuation	12 (55)	12 (60)
Deaths within 30 d of last dose	0	2 (10)†

Table 3. Summary of best clinical response

	BV+DTIC (n = 21)	BV+bendamustine (n = 17)
ORR*	21 (100)	17 (100)
95% CI†	83.9, 100	80.5, 100
Best clinical response		
CR	13 (62)	15 (88)
PR	8 (38)	2 (12)
95% CI† for CR rate	38.4, 81.9	63.6, 98.5

Friedberg, Blood

ACCRU: BRENTUXIMAB AND NIVOLUMAB IN OLDER HODGKIN LYMPHOMA

Eligibility:

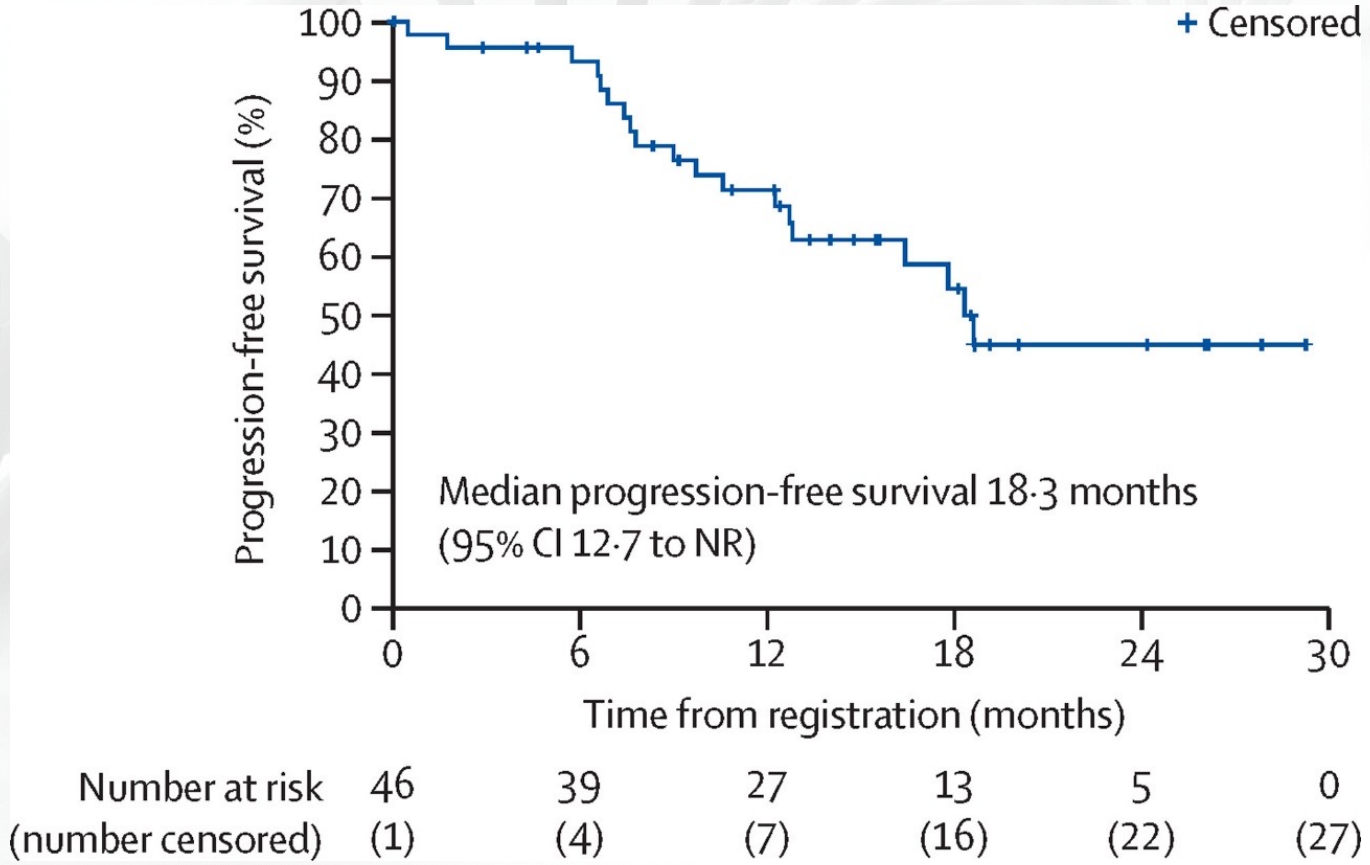
≥60 years or < 60 years but unsuitable for standard chemotherapy due to EF <50%, DLCO < 80%, or CrCl 30 mL/min-60 mL/min, or those who refused chemotherapy.

Treatment:

Brentuximab vedotin at 1·8 mg/kg (dose cap at 180 mg) and nivolumab at 3 mg/kg both intravenously every 21 days for 8 cycles.

Response:

- N=46 patients
- ORR 64%
- Failed to meet primary endpoint.



Bruce Cheson, Lancet Haematol 2020;7: e808–15

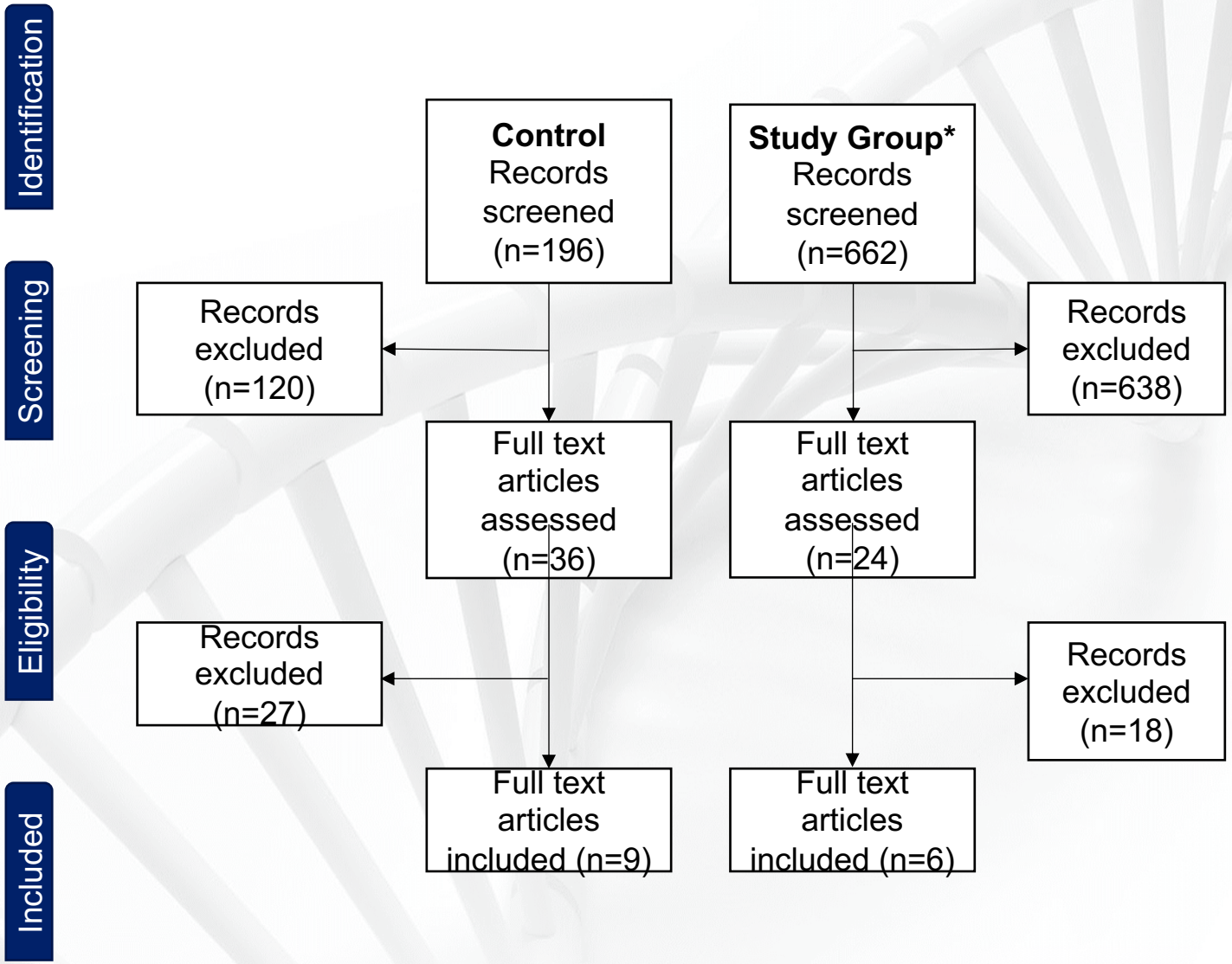
PUTTING ALL THE DATA TOGETHER

- How should we treat older HL patients in the era of novel therapy?

Efficacy

Toxicity

SYSTEMATIC REVIEW: ASSESS TOXICITY OF CHEMOTHERAPY VS. NOVEL AGENTS



***Study Group:**

Brentuximab
- Articles= 41
- Abstracts= 208

Nivolumab
- Articles =118
- Abstracts = 122

Pembrolizumab
- Articles=78
- Abstracts= 95

Abbreviation PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-analyses.

TOXICITY OF BLEOMYCIN IN OLDER ADULTS

Pulmonary events (control arm)

- ≤ 2 cycles of a bleomycin-containing regimen:
  - only 4 patients across 4 studies (rate < 1%).
- > 2 cycles of bleomycin:
  - 3.7% in the VEPEMB trial to 44% in patients receiving 4-8 cycles of bleomycin on E2496.
  - Overall, the rate of pulmonary toxicity in patients receiving >2 cycles of bleomycin was 10%

Allen et al. Leukemia & Lymphoma, 2018

ADVANCED STAGE BRENTUXIMAB-BASED OPTIONS FOR OLDER HODGKIN'S

	Concurrent Bv + AVD (ECHELON)		Sequential Bv and AVD	Bv + Dacarbazine (or Bendamustine)		Bv + Nivolumab (ACCRU)
Regimen	**ABVD**	**Bv + AVD**	2Bv →6AVD→ 4Bv	**Bv + DTIC**	**Bv + Benda**	**Bv + Nivo**
Brentuximab dose	0	1.2 mg/kg q 15 days x 6 cycles (12 doses)	1.8 mg/kg q 21 days x 6 total	1.8 mg/kg A and q 21d x 12	1.8 mg/kg A and q 21d x 12	1.8 mg/kg + nivolumab q 21 days
Outcomes	2-yr mPFS 71.4%	2-yr mPFS 70.3%	2-year EFS 80%, PFS 84% 2-year OS 93%	ORR 100%, CR 66% 2- yr PFS 50%	ORR 100%, CR 88.2% 1-yr PFS 63%	ORR 61%, CMR 48% 18.3 month median PFS
Gr 3/4 AE	80%	88%	41.7%	45%	90%	80%
Pulmonary AE	2%	13%	0%	0%	5%	4%
Peripheral Neuropathy	43%	65%	33.3%	77%	40%	48%
Febrile Neutropenia	17%	37%	6.3%	13.6%	25%	3%*

*Grade 3 leukopenia

Evens, JCO 2018; Freidberg, Blood, 2017; Bruce Cheson, Lancet Haematol 2020;7

KEY POINTS

- > 2 cycles of bleomycin excess pulmonary toxicity in HL > 60 years.
- Peripheral neuropathy was more frequent in BV-containing regimens and was associated with total BV exposure.
- There are multiple options of safe and efficacious therapy for older HL

HOW I TREAT OLDER HODGKIN LYMPHOMA

	Early stage favorable	Early stage unfavorable	Advanced Stage
FIT	AVD x 2 + RT	A(B)VD x 4	Sequential Bv AVD
UNFIT	AVD x 2 + RT	AVD x 4	Nivolumab or dacarbazine + Bv
FRAIL	RT	Bv monotherapy or checkpoint blockade	Bv monotherapy or checkpoint blockade

THANK YOU!





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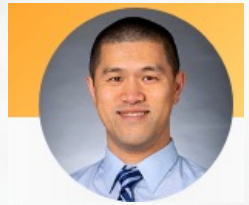

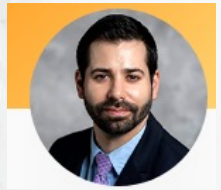


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TREATMENT OUTCOMES WITH BRENTUXIMAB AMONG OLDER CHL

Treatment	N	ORR %	CR %	PFS %	Median OS
BV + Nivo	46	61	48	Median 18.4 mo	94% @ 21 mo
BV + DTIC	22	100	61.9	50 (2 yr)	Not Reached
BV + Bendamustine	20	100	88.2	63 (1 yr)	Not Reached
BV Monotherapy	27	92	73.1	Median PFS 10.5 mo.	Not Reached
BV + Bendamustine	15	NA	NA	NA	N/A
Sequential A + AVD	48	95	93.8	84 (2 yr)	Not Reached (95% 2-yr)
B-CAP	50	98	98	N/A	N/A
Concurrent A + AVD	84	NA	NA	70.3 (2 yr)	N/A

Evens, JCO 2018; Freidberg, Blood, 2017; Bruce Cheson, Lancet Haematol 2020;7