Older Patients with Hodgkin Lymphoma: From Frontline to Relapsed/Refractory

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Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy and Honoraria (research or educational): Epizyme; MorphoSys; Hutchmed; Daiichi Sankyo, OncLive; Abbvie; Seattle Genetics, Pharmacyclics; Novartis; Research to Practice
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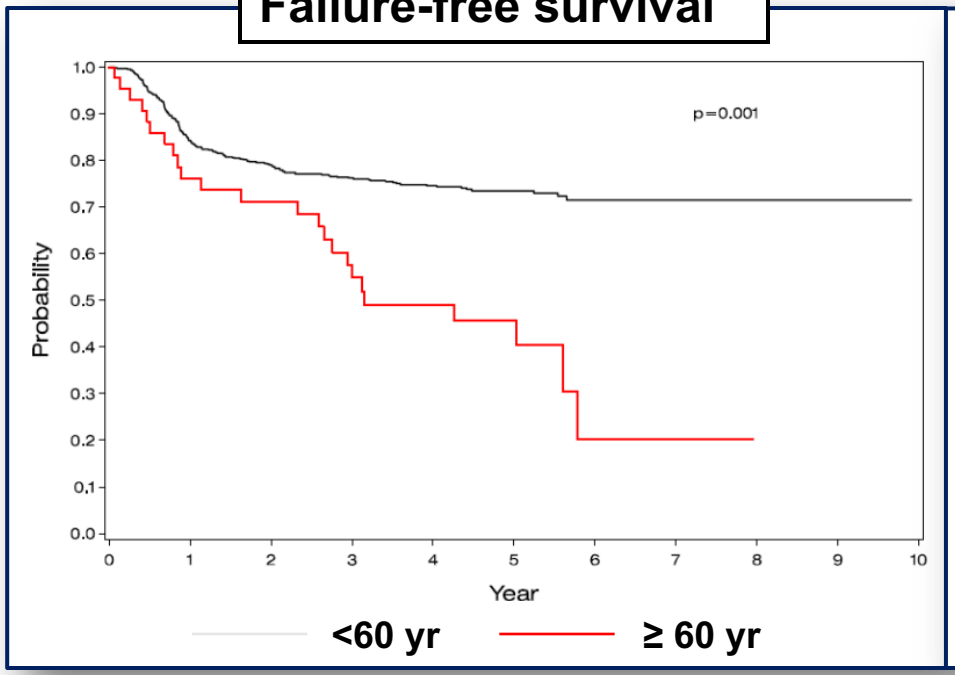
- Discussion of off-label drug use: checkpoint inhibitor therapy in frontline

Older Hodgkin Lymphoma

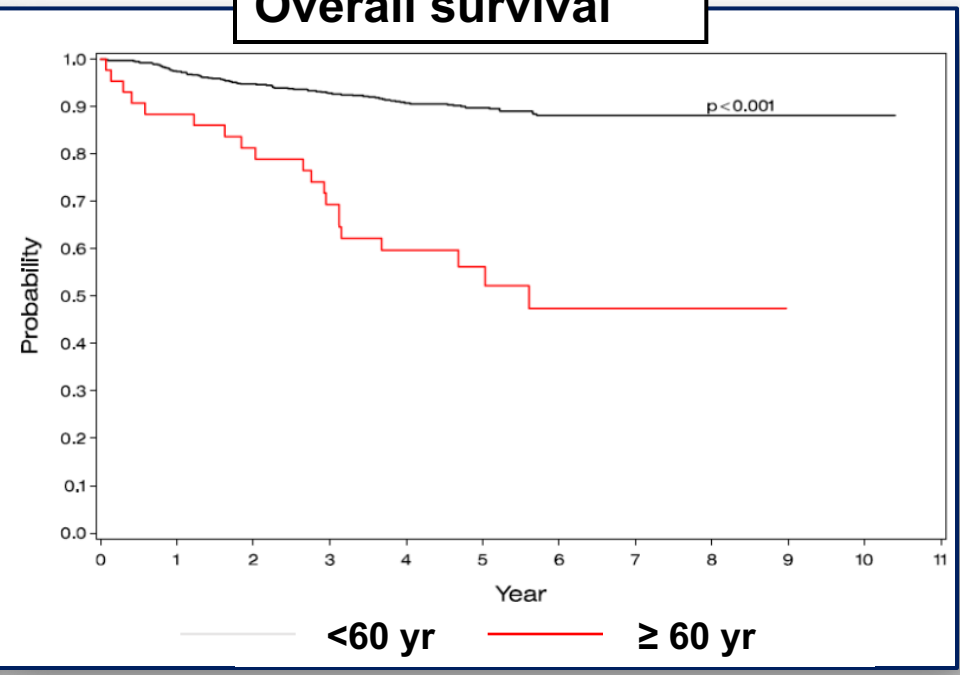
- Defined: ages ≥ 60 years
- Under-represented in clinical trials: <5-10% (vs. 15-25% population)
- Standard treatment approach has been absent
- Outcomes disproportionately inferior to younger pts
- Why?
  - Different biology/disease (e.g., mix cell, EBV)
  - Advanced stage (60-80%)
  - Co-morbidities precluding adequate treatment
  - 'Uniqueness' of ABVD (vs CHOP, etc)
  - Treatment-related toxicities (esp. bleomycin)
  - ? Therapeutic nihilism

E2496 (ABVD vs Stanford V): Older vs Younger HL

Failure-free survival



Overall survival



		< 60 years	=/> 60 years	P
FFS	3-year	76%	56%	0.002
	5-year	74%	48%	
OS	3-year	93%	70%	<0.0001
	5-year	90%	58%	

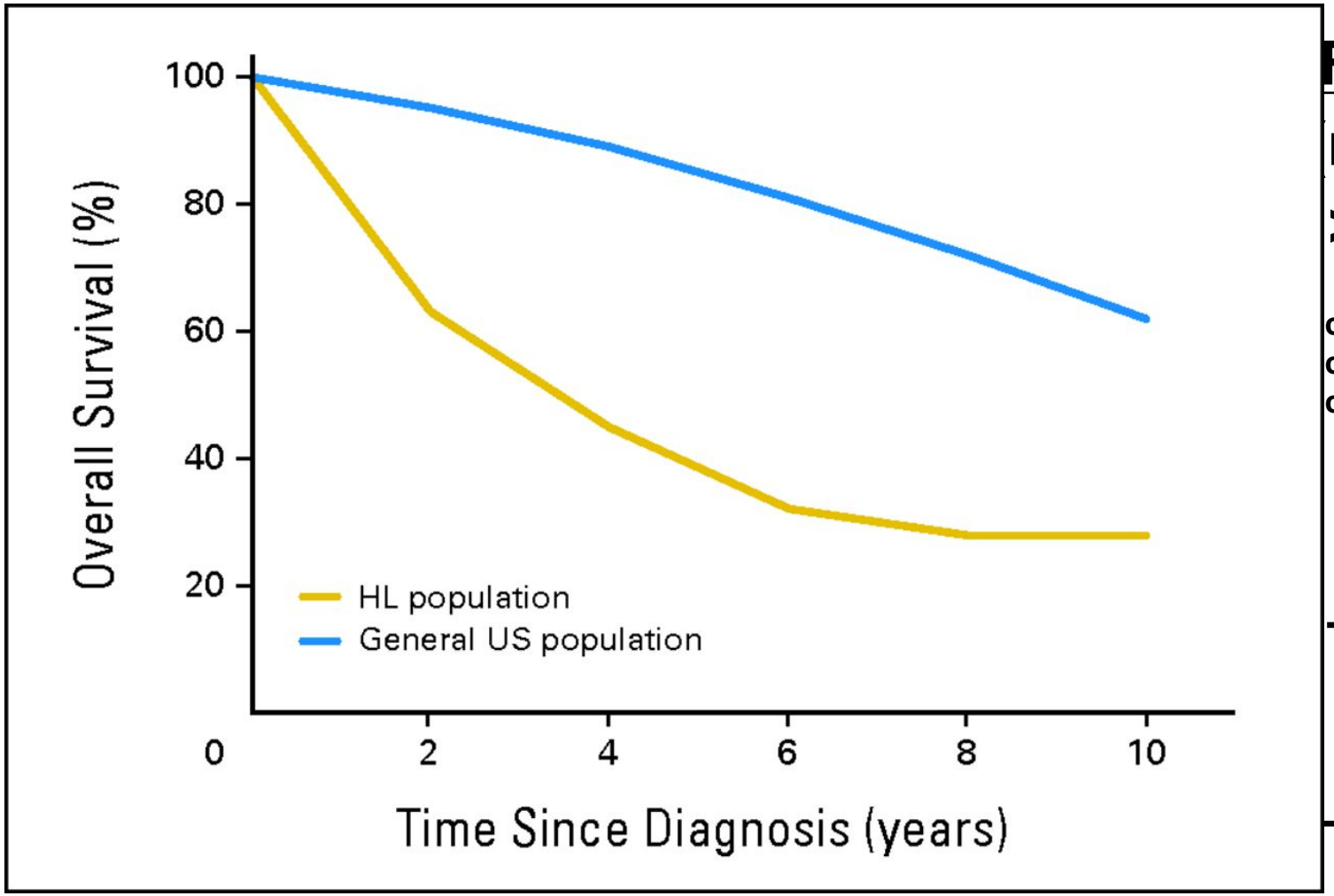
Evens AM et al. BJH 2013

E2496 Older Patients: Toxicity

- **Overall treatment-related mortality: 9.3% (*vs 0.3% <60 years, p<0.001*)**
  - **Grade 5: 2 ABVD (bleomycin lung toxicity n=2) and 2 Stanford V (GI bleed/RF+ colitis/sepsis)**
- **Bleomycin lung toxicity**
  - **CTCAE coding: grade 3 or 4 hypoxia, DLCO, pneumonitis, pulmonary other, etc**
  - **Overall incidence: *26% (fatality rate: 18%)***
  - **Age 69 yrs (61-78) and 50% non-smokers**
  - **91% (10/11) received ABVD**
  - **Timing: Cycle 3 (n=2), cycle 4 (n=2), cycle 5 (n=2), cycle 6 (n=3), month 3 (n=1)**

2 Fatalities

Chicago Elderly HL: EFS + OS (2000-2009): A Prognostic Model



Percent survival

1

FS: 53% & 36%

mortality: 31%)

>70 & loss ADLs

ctor(s)

ctor(s)

ctor(s)

150

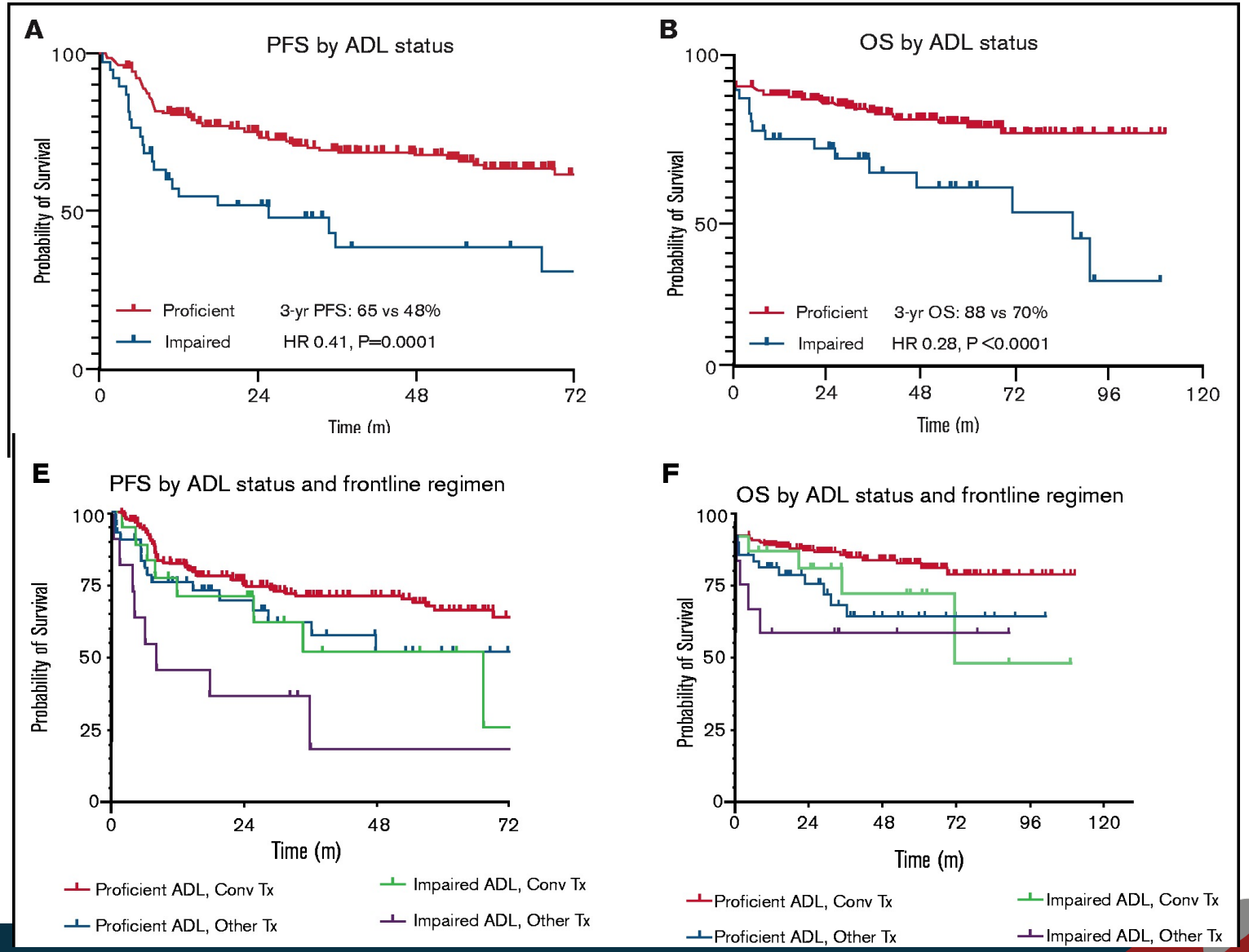
180

Evens AM and Hong F. JCO 2013

2012; 119:692-5

Threading the Older Patient Needle

- Multicenter analysis of geriatric fitness and real-world outcomes in older patients with classical Hodgkin lymphoma (2010-2018)
  - 244 pts, median age 68 yrs, 63% stage III/IV, 12% loss of ≥1 ADL, 18% CIRS-G score ≥10 (*conventional Tx* = anthracycline-based)

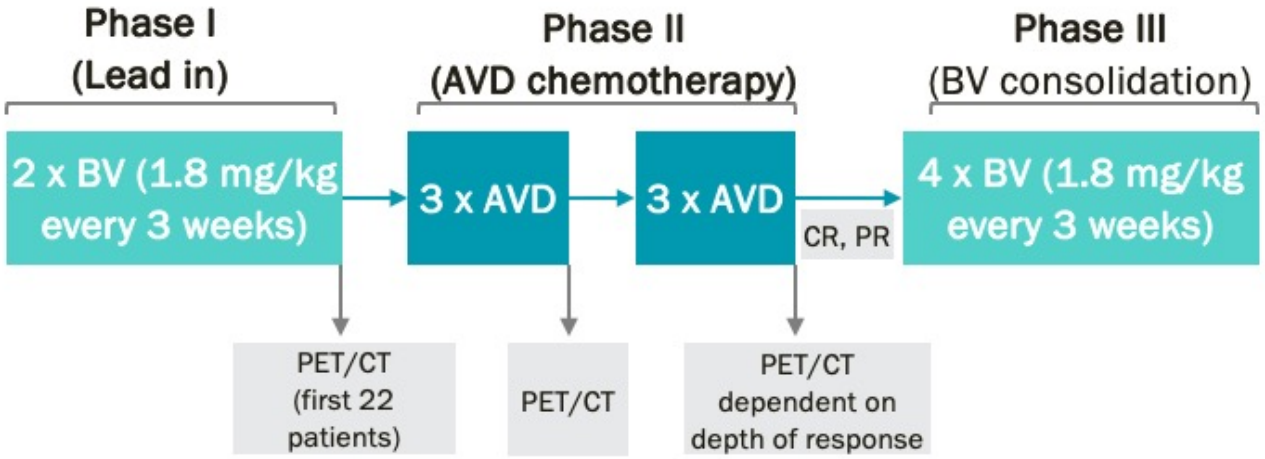


Orellana-Noia V et al. Blood Adv 2021

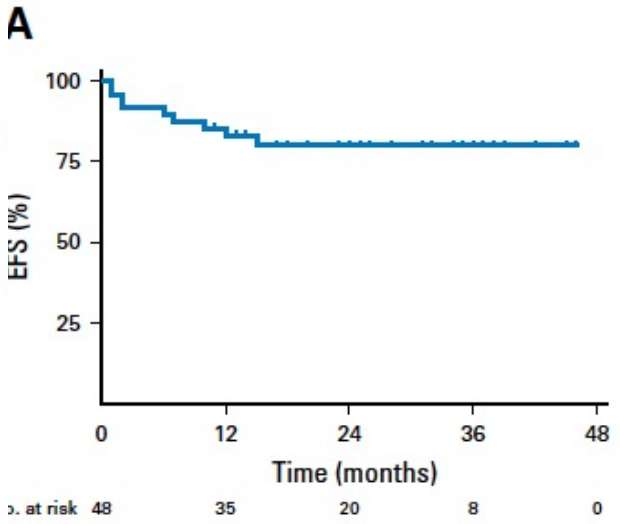
2018 to Current:

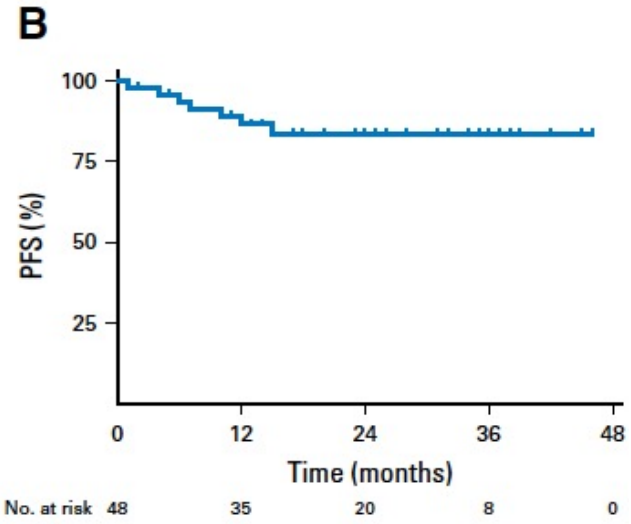
Clinical Trial Data with Targeted Therapeutic Platforms (Fit vs Unfit/Frail)

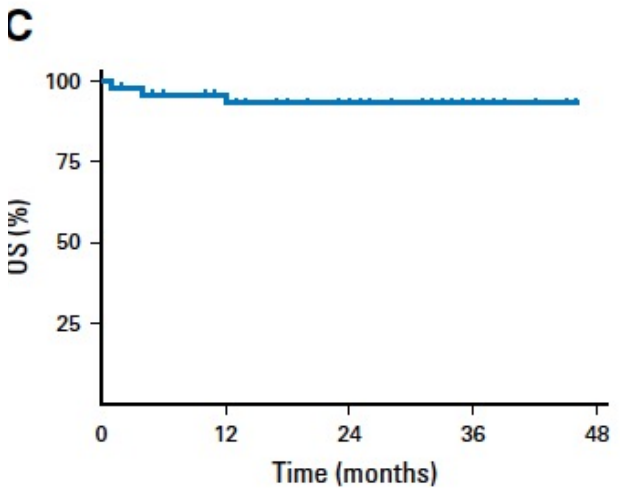
Phase 2 1L BV-AVD in Older HL Patients: Efficacy/Safety



- 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







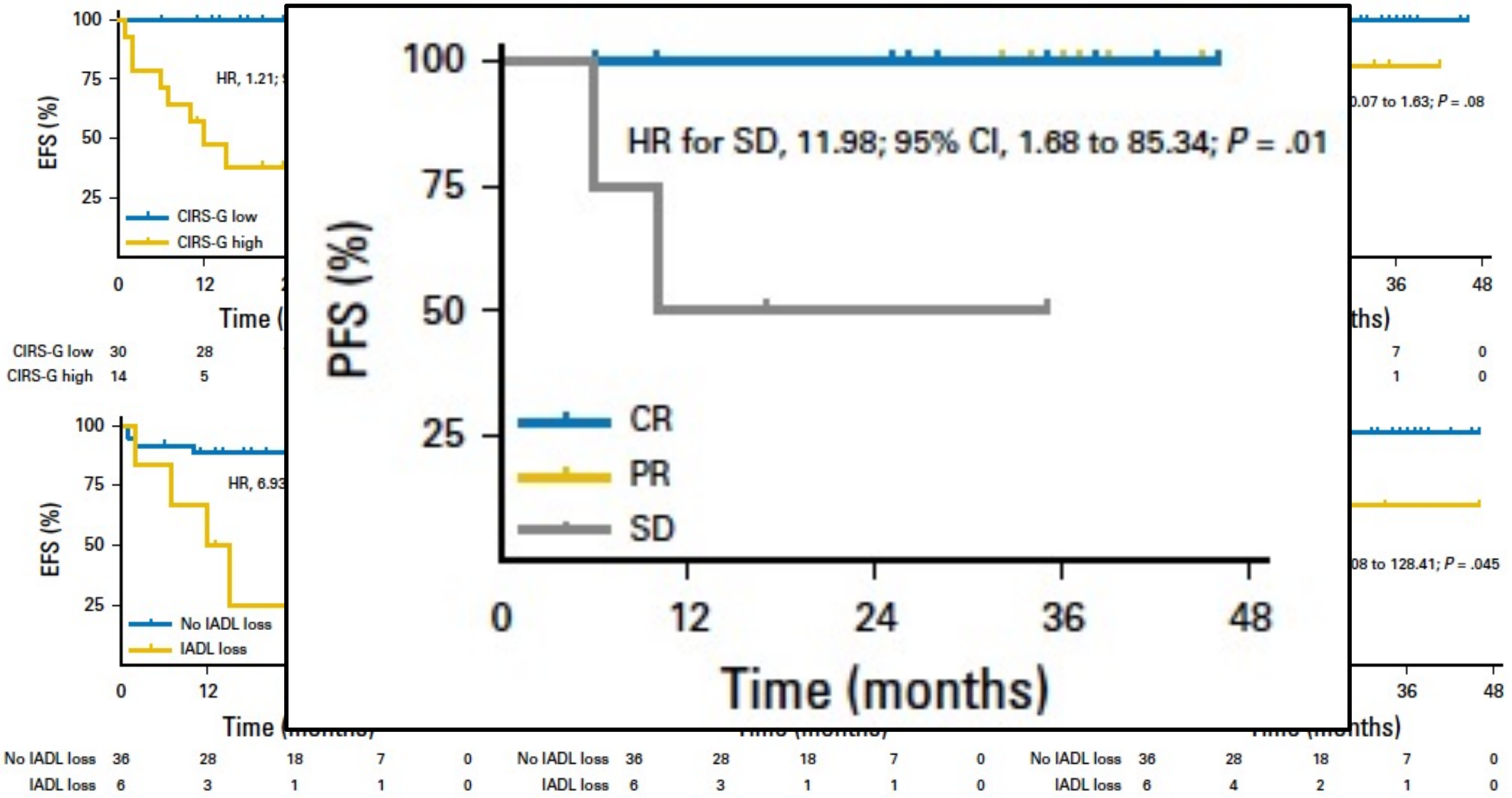
2-year EFS: 90%

2-year PFS: 84%

2-year OS: 92%

Evens AM, et al. *J Clin Oncol*. 2018; 36:3015-3022

Was “functional status” prognostic of outcome?



ECHELON-1 Older HL Patients (n=186)

	≥60 yrs A+AVD	≥60 yrs ABVD	<60 yrs A+AVD	<60 yrs ABVD
24-month PFS	70.3%	71.4%	83.7%	78.2%
60-month PFS	67.1%	61.6%	84.3%	77.8%

- Toxicity Older pts (A+AVD vs ABVD)
  - Fatal AEs: 4% vs 5%, respectively
  - Any grade febrile neutropenia: 37% vs 17%, respectively
  - Pulmonary AE: 2% vs. 13%, respectively

	≥60 yrs A+AVD	≥60 yrs ABVD	<60 yrs A+AVD	<60 yrs ABVD
Any grade PN	65%	43%	67%	43%
Grade 2 PN	19%	13%	20%	8%
Grade 3/4 PN	18%	3%	9%	1%
Resolution/Imp	80% (56%/24%)	83% (71%/12%)	86% (74%/12%)	86% (81%/5%)

“Unfit” Older HL: BV +/- DTIC or Bendamustine or Nivo

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%**

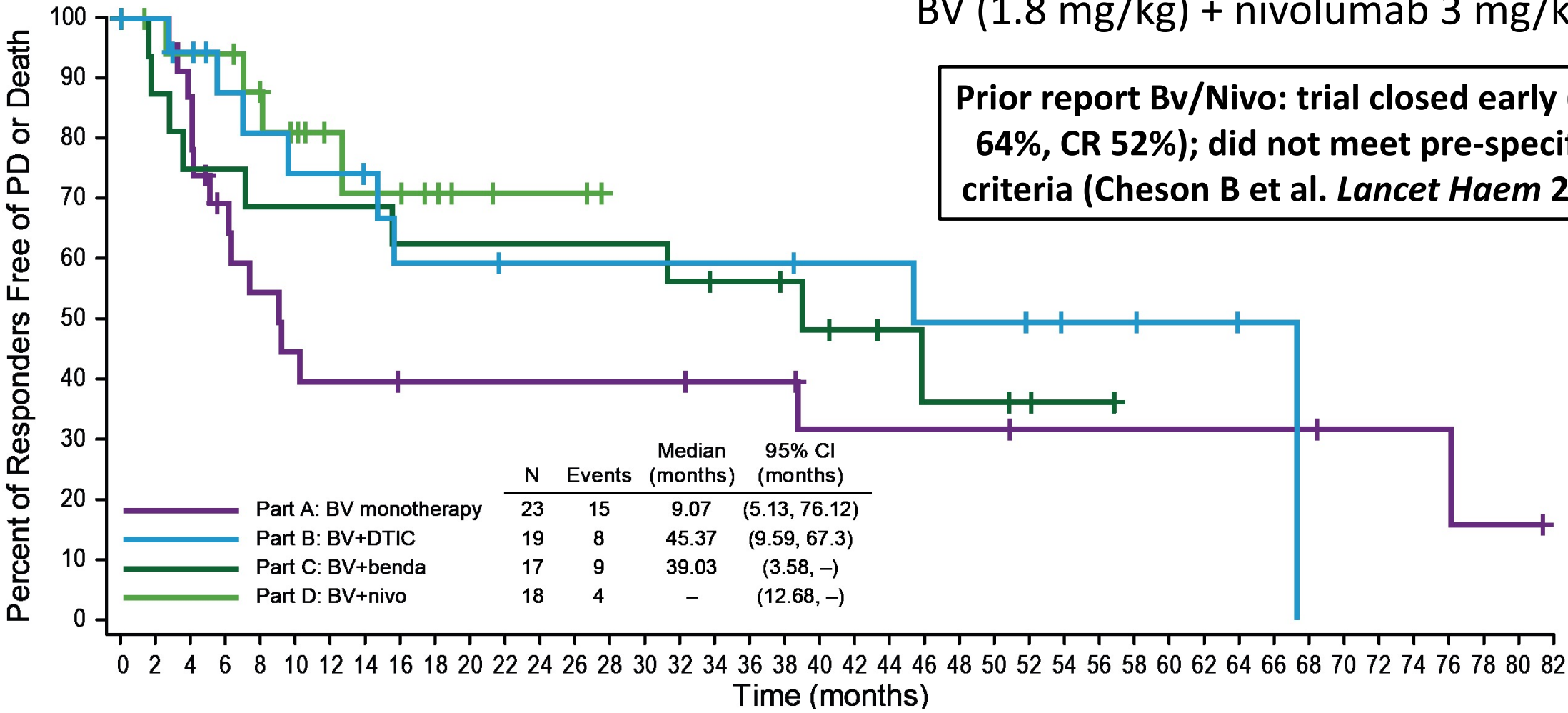
Closed early due to toxicity (2 toxic deaths)

Friedberg J et al. Blood, 2017
Yasenchak CA et al. ASH 2020; Abstract 471.

BV +/- DTIC or Bendamustine or Nivolumab

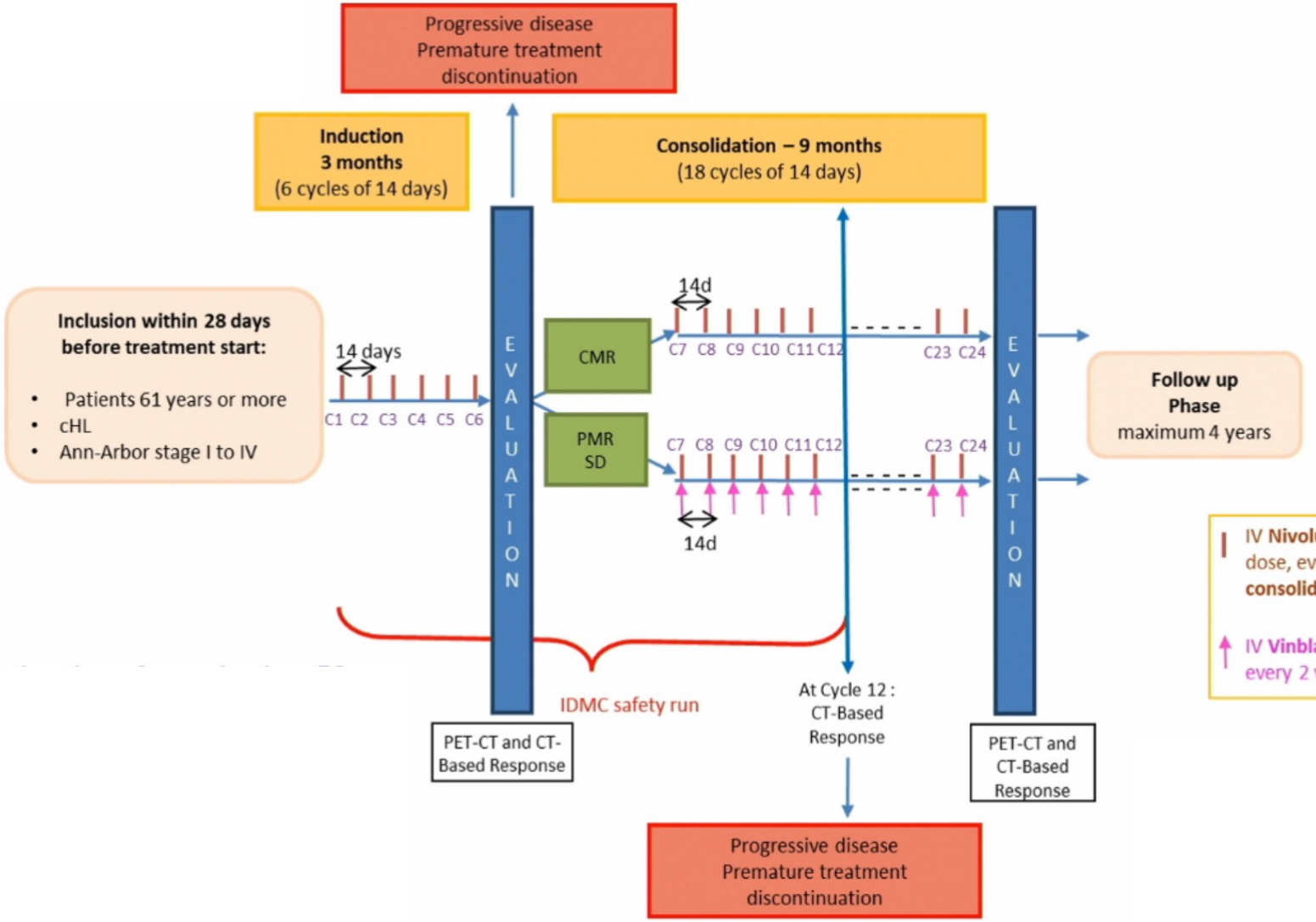
BV (1.8 mg/kg) + nivolumab 3 mg/kg

Prior report Bv/Nivo: trial closed early (ORR 64%, CR 52%); did not meet pre-specified criteria (Cheson B et al. *Lancet Haem* 2020)



Yasenchak C. ASH 2020

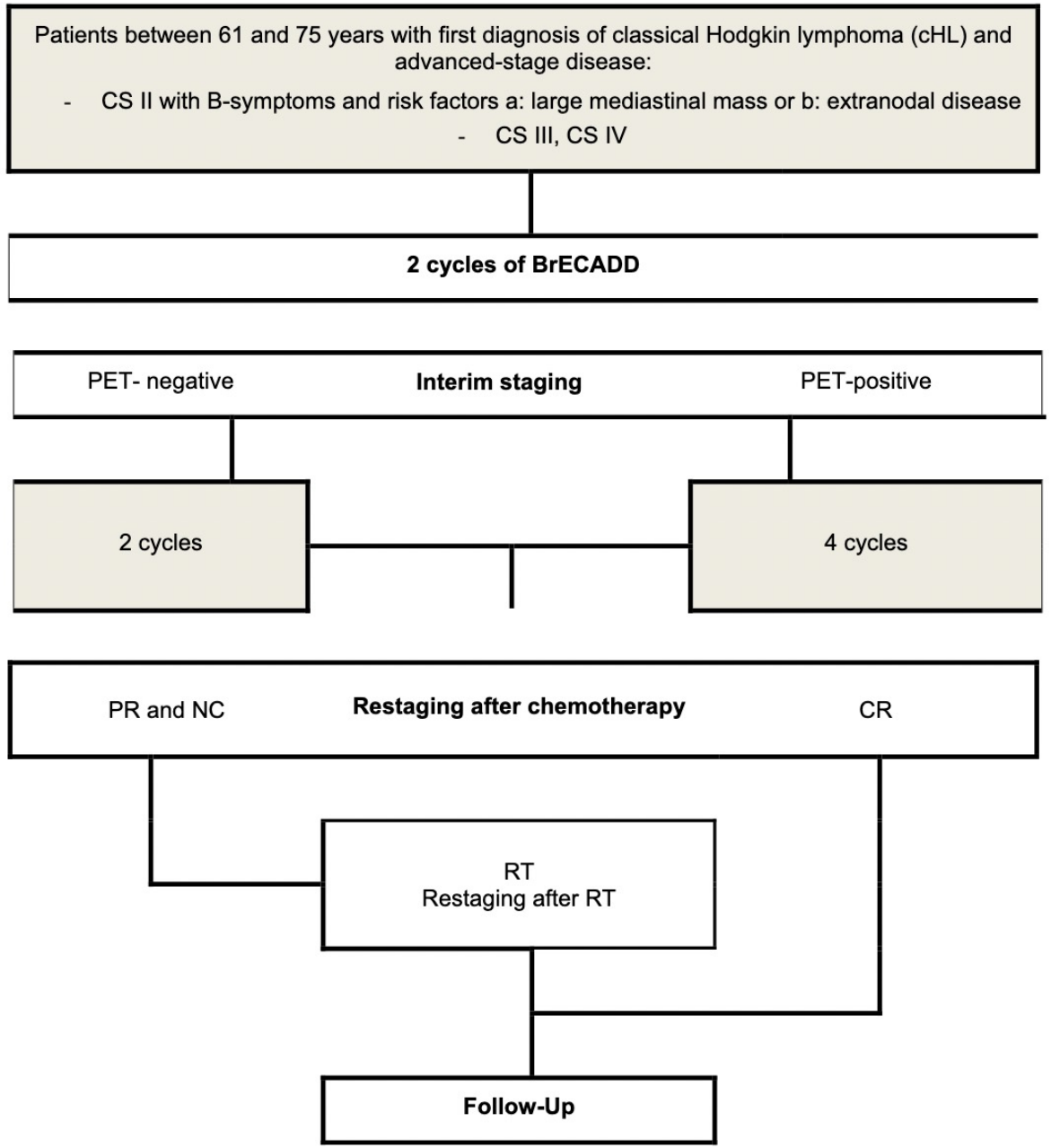
Nivolumab for untreated frail older HL pts: NIVINIHO trial, Ph 2 LYSA group study



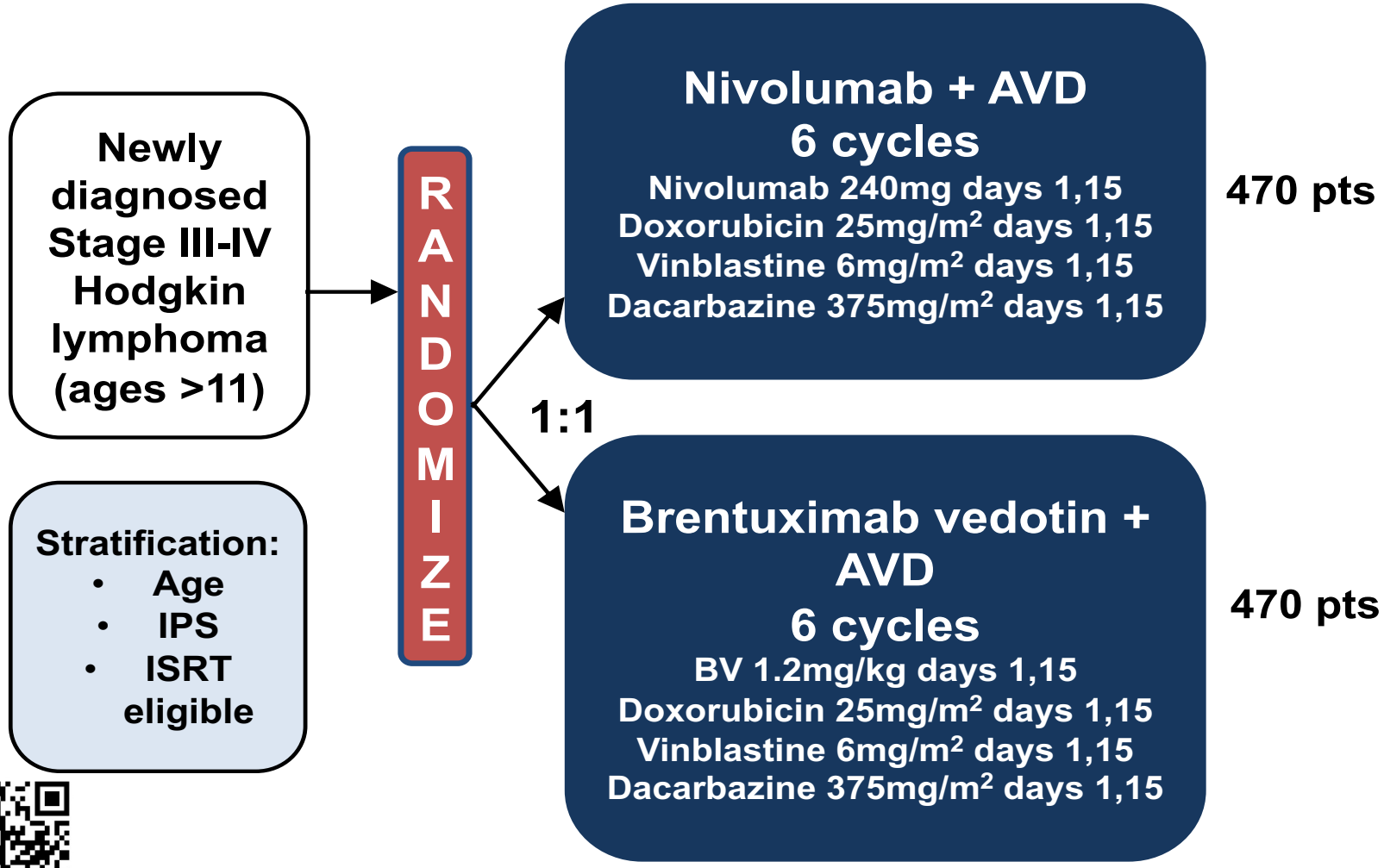
- N=56 pts efficacy
- Med age 75 yrs, med CIRS-G 10 (6-18)
- EOT ORR 47% w/ CR 29% (16% EOI)
- Median PFS 9.8 mos

Ongoing and New Studies

Ongoing / future studies in older HL: GHSG HD21

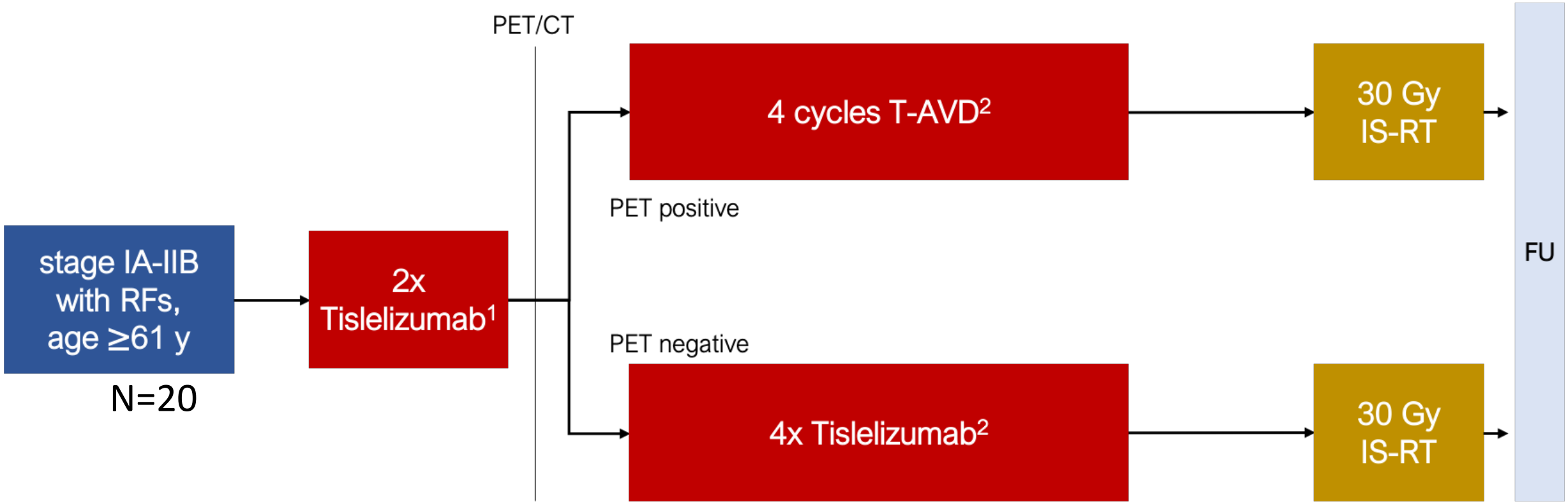


North American Cooperative Group Study for Advanced Stage HL: S1826



SWOG: A.Herrera; COG: K.Kelly; Alliance: S.Rutherford; ECOG: A.Evens

INDIE: Elderly Cohort



*chemotherapy should start as soon as central PET evaluation is available. Up to 1 further dose tislelizumab is allowed in case of severe delay of PET panel assessment. [1]Tislelizumab 200mg Q3W [2]Tislelizumab 300mg Q4W, on day 1 of each 28-day AVD cycle if combined with AVD. RFs: GHSG risk factors for early-stage unfavorable; y: years

Supported with drug & funding by BeiGene. [1] 200mg 3-weekly [2] 400mg 4-weekly.
Abbreviations: RF: risk factors, y: years, T-AVD: tislelizumab and AVD, FU: follow-up

UK Older cHL Patient Study

Early (fav):
- **stage I/II with no bulk;**
- **ESR < 50 (or < 30 with B Symptoms),**
- **no E-disease;**
- **1-2 nodal sites involved**

Newly diagnosed cHL > 60 chemo fit but for whom ABVD not recommended by the investigators

Tislelizumab x3

PET

CMR

Early stage (fav) T x2 → **RT[1]** → **PET** → **T every 3 weeks until PD, tox or 2y from first dose**

Early stage (unfav) T+AVD x2 → **RT[1]** → **PET**

Advanced stage T+AVDx4 → **RT[1]** → **PET**

PMR, SD, PD

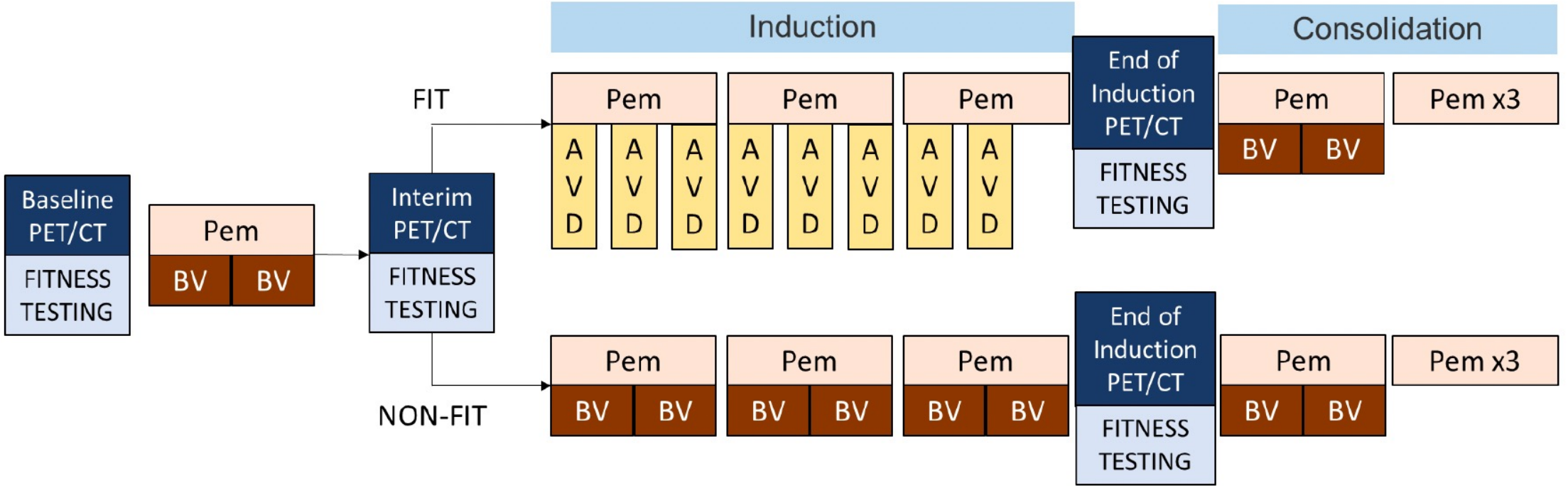
Early stage T+AVD x4 → **PET** → **RT[1]** → **PET**

Advanced stage T+AVDx6 → **PET** → **RT[1]** → **PET**

RATiFY

[1]Radiotherapy integrated as per local recommendations

New 1L Ph. 2 Study for Older HL pts



Pem: Pembrolizumab 400mg IV q6W

BV: Brentuximab vedotin 1.8 mg/kg IV q3W

4 week cycles:
A: Doxorubicin/Adriamycin 25 mg/m^2 IV q2W
V: Vinblastine 6 mg/m^2 IV q2W
D: Dacarbazine 375 mg/m^2 IV q2W

NON-FIT - Any of the following:
ECOG Performance Status ≥ 3
CIRS-G total score ≥10
LVEF < 40% at screening or anytime after
Loss of ≥ 1 basic ADL
Loss of ≥2 instrumental ADLs

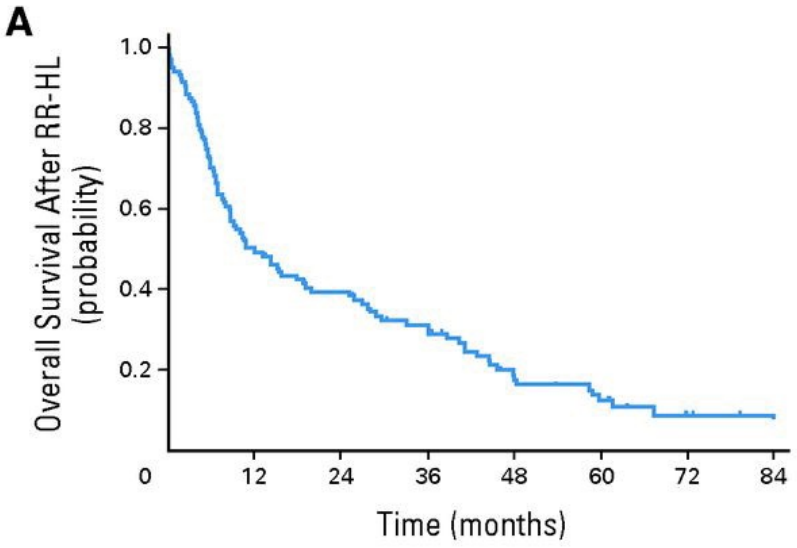
NCT05404945

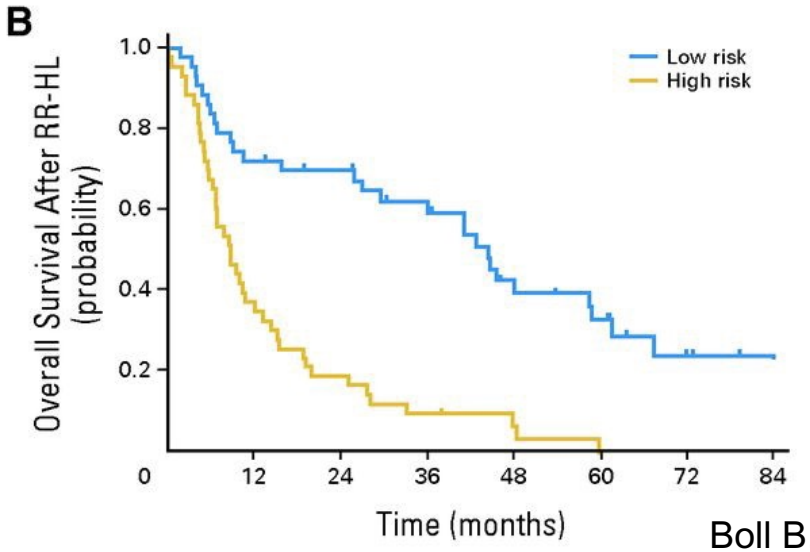
How I Treat Newly-Diagosed Older HL Patients

- Pre-treatment Geriatric Assessment (and pre-phase Rx!)
- Early-stage
  - FIT: AVD x 2-4 cycles + ISRT (other: VEPEMB)
  - UNFIT/FRAIL: ChlVPP + ISRT, Bv +/- Nivo + ISRT
- Advanced-stage
  - FIT: sequential Bv-AVD-Bv (AVD, PVAG, ? CHOP/Bv-CAP)
    - With full supportive care measures (PCP, HSV, GCSF, etc)
  - FRAIL: Bv +/- DTIC or Nivo (other: ChlVPP)
  - UNFIT: ? mini-AVD, Stanford V (low EF)

Relapsed Older HL Patients

- 105 pts (median age 66 years)
  - 28%, 31%, and 41% had primary PD, early relapse, or late relapse, respectively
  - 2nd line Tx: intensified regimens (22%), conventional polychemotherapy and/or salvage-radiotherapy w/ curative intent (42%), and palliative (31%)
  - *Prognostic (2-3)*: early relapse, stage III/IV, anemia





Boll B. J Clin Onc 2013

Overall Summary

- Outcomes historically suboptimal; recent data suggest survival improvement
- Geriatric measures important (*minimum to evaluate:* co-morbidities & ADLs)
- Extreme caution (or avoid) bleomycin lung toxicity!
- Importance of anthracycline
  - More nuance than 6 cycles chemotherapy vs. none (? mini-AVD)
- Need continued prospective studies
  - More translational studies (eg, immunosenescence, EBV, etc)
  - Incorporate geriatric assessments to evaluate tailored Rx
  - Integrate newer targeted therapeutics (vis-à-vis Intl collaborations)
  - Surveillance of older cHL patient survivors (esp. cardiac)

Acknowledgements

- HL mentors: Leo Gordon, Sandra Horning, Jane Winter, and Volker Diehl
- International collaborators (HoLISTIC: hodgkinconsortium.com)
- NCI R01 CA262265, NCI R01 CA261752, NCI R01 CA260064, LLS TRP, and ORIEN
- Our Patients

Back Up

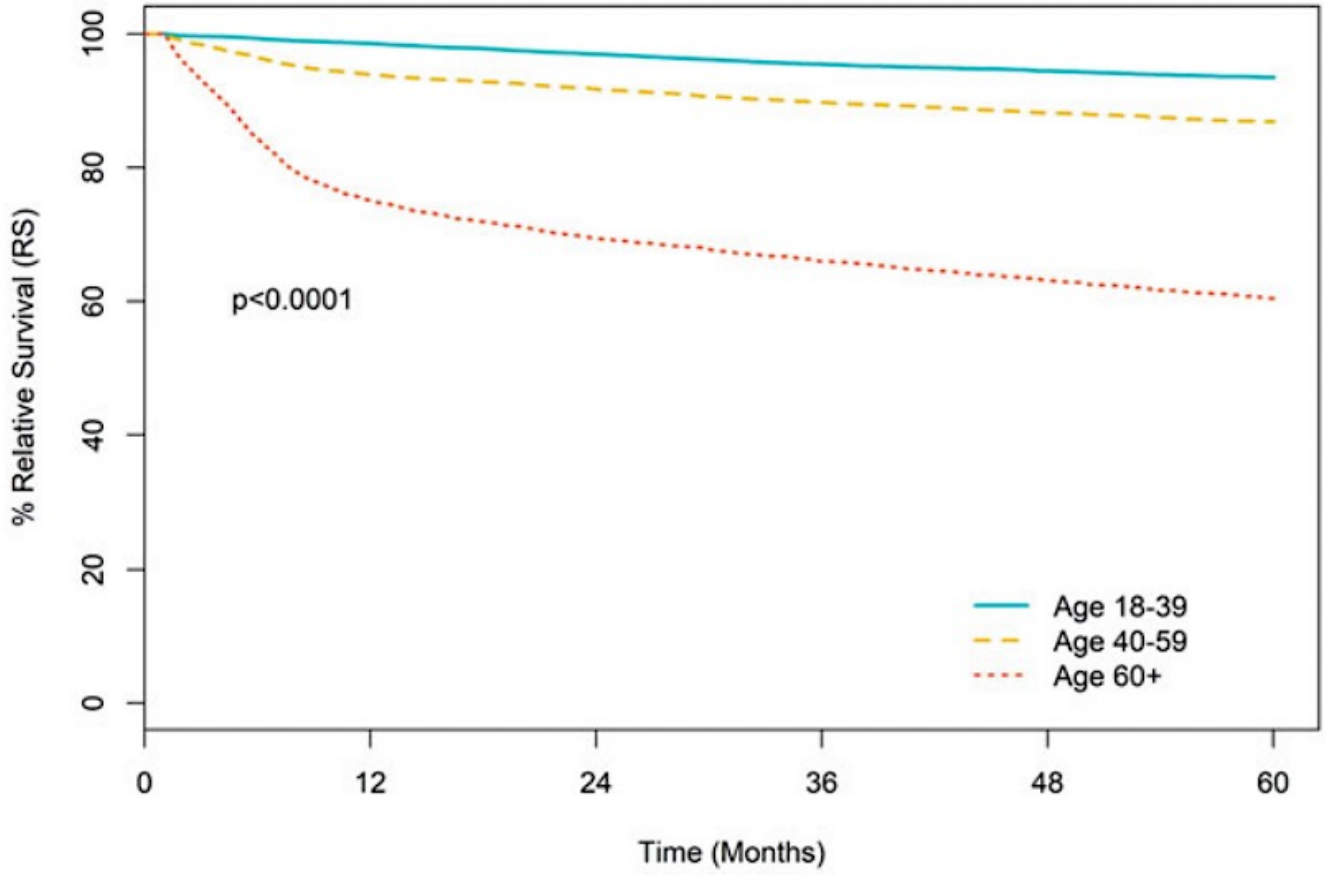
Treatment of Elderly HL (1970 to 2000)

- Decreased intensity of chemotherapy and individualized dosing
  - e.g., ChlVPP +/- OEPA, VEPEMB, CHOP
- Non-anthracycline options
  - e.g., VBM, ChlVPP, BCVPP
- Dose intensity important?
  - 5-year CSS 51%, OS 39% (MOPP/ABV)
  - RDI > 65% improved OS (P=0.001)
- BEACOPP *baseline*: 21% TRM

Levis A et al. Haematologica 1996; Enblad G et al. Acta Oncol 2002; Bakemeier RF et al. Ann Intern Med 1984; Zinzani PL et al. Haematologica 2000; McElwain TJ et al. Br J Cancer. 1977; Levis et al Ann Oncol. 2004; Weekes, et al. JCO. 2002; Landren et al. Haematologica. 2003;

Inferior outcomes and treatment disparities in older cHL patients

- National Cancer Data Base: 10,873 age ≥60 yrs diagnosed 2004–2013
- 2-yr OS 97%, 91%, and 65% for 18-39, 40-59, and ≥60 yrs, respectively
- Older pts with more advanced comorbidity scores, stage III–IV disease; treated less with chemotherapy and less at academic/research centers



Why?

- Different biology/disease (e.g., mix cell, EBV)
- Advanced stage (70-80%)
- Co-morbidities precluding adequate treatment
- Treatment-related toxicities (esp. bleomycin)
- 'Uniqueness' of ABVD (vs CHOP, etc)
- ? Therapeutic nihilism

Major A et al. Leuk Lymphoma . 2019; 60:1234-1243

Geriatric Assessment 101

Domain	Components
Functional Status	Katz Activities of Daily Living (ADL)
	Lawton Instrumental ADLs (IADL)
	Falls
	Objective physical performance (e.g., Timed “Up and Go”)
Comorbidities	Cumulative Illness Rating Scale-Geriatric (CIRS-G)
	Charlson Comorbidity Index
Psychologic Health	Depression (e.g., Geriatric Depression Scale-15, GDS-15)
Cognition	Mini-Cog
	Blessed Orientation-Memory-Concentration (BOMC)
Nutritional status	Weight loss
	Body mass index
Polypharmacy	Number of medications
	Potentially inappropriate medications
Social support	Presence of caregivers
	Medical Outcomes Study Social Support & Social Activity Survey
Geriatric syndromes	Dementia, delirium, osteoporosis, falls, failure to thrive, sarcopenia, pressure ulcer, incontinence, neglect/abuse
Other measures: Chemotherapy toxicity (e.g., Cancer and Age Research Group (CARG) Score; Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score)	

Adapted from Mohile SG et al. J Clin Oncol 2018

Geriatric Measures (minimum)

- **ADLs: Instrumental vs self care ADLs**
  - **Instrumental: Housework, Meal Prep, Manage money, Take meds, Shopping, Laundry, Use phone, Use transportation**
  - **Self care: bathing, dressing, transferring, toileting, feeding, continence**
- **Co-Morbidities: Cumulative Illness Rating Scale-Geriatrics (CIRS-G)**
  - **14 organs (cardiac, vascular, heme, respiratory, ENT, upper/lower GI, hepatobil, renal, GU, bone-skin, neuro, endocrine, psych)**

https://www.mdcalc.com/cumulative-illness-rating-scale-geriatric-cirs-g

Estimates on non-cancer life expectancy (e.g., the Schonberg Index or Lee Index): https://eprognosis.ucsf.edu/leeschonberg.php

How to define Fit vs Unfit (or frail)?

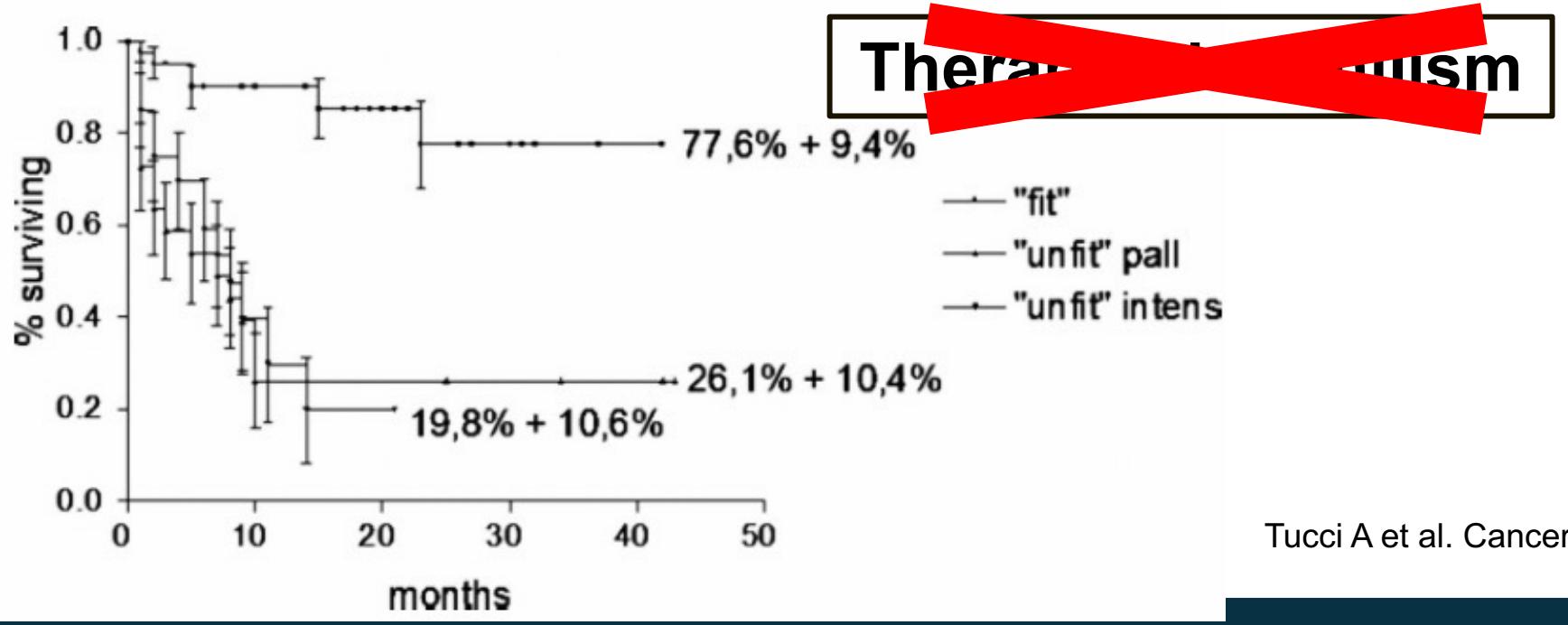
	Fit	Unfit	Frail
ADL	6	5*	4*
IADL	8	6-7*	≤5*
CIRS-G	No score 3-4 and <5 comorbidities score 2	No score 3-4 and 5-8 comorbidities score 2	≥1 score 3-4 or >8 comorbidities 2
Age		≥80 fit	≥80 unfit
	**Number of residual functions*		

Tucci A et al. Leuk Lymphoma 2015

ADL/IADL	Evens AM. *Blood* 2012; Evens AM. J Clin Oncol 2018
CIRS-G	Levis A. *Ann Oncol* 2004; van Spronsen D. E*ur J Cancer* 2005; Wrobel T. *Leuk Lymphoma* 2018; Evens A. J Clin Oncol 2018
Age	Enblad G *Acta Oncol* 2002; Landgen O *Haematologica* 2003; Evens AM. *Blood* 2012; Wrobel T. *Leuk Lymphoma* 2018

Clinical Judgment vs GA

- CGA performed in 84 DLBCL pts aged >65 years
- Treatment w/ curative vs palliative intent chosen according to clinical judgment
- 50% deemed fit by GA (ORR 93% vs 48% for unfit)
- 50% unfit by GA: half treated with curative and half palliative Rx — outcomes not different



Tucci A et al. Cancer 2009

Chicago Elderly HL (2000-2009)

- Retrospective analysis, n=95 HD pts ≥ ages 60 years (median 67 yrs; 60-89; 33% ≥ ages 70)
  - Northwestern, U Chicago, Rush, LGH, Loyola
- Characteristics
  - NOS 42%, NS 34%, MC 18%, and LP 6%
  - Prior/recent malignancy 27%, Wt loss 35%, PS >2-4 29%, stage III/IV 65%, IPS 4-7 in 64%
- Functional status
  - 61% any grade 3-4 co-morbidity (CIRS-G); 29% “not fit”; 13% loss ADLs; and 18% geriatric syndrome

Evens AM et al. Blood 2012; 119:692-5

Are anthracyclines important?

- From 1982 to 1998: 56 pts ages ≥60 years with ChlVPP or ChlVPP/ABV
  - 5-year EFS & OS pts <60: 75% & 87% *vs* ≥60 yrs: 31% & 39%
  - 5-year OS ages >60: 30% w/ ChlVPP (n=31) vs 67% w/ ChlVPP/ABV (n=25), *P* 0.0086

Weekes, et al. JCO. 2002.

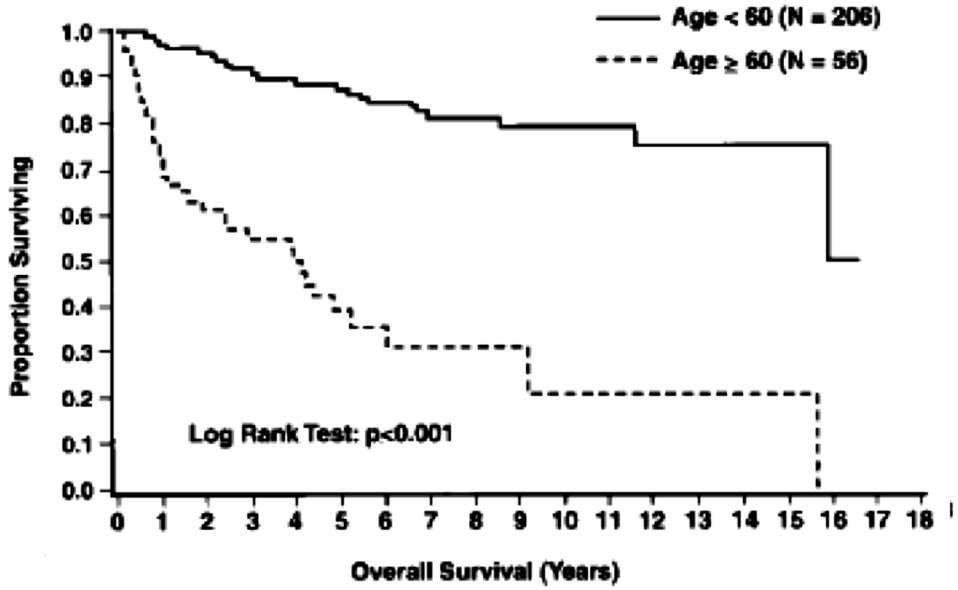


Fig 1. Overall survival by age group. The difference between the curves is significant (log-rank test; $P < .001$).

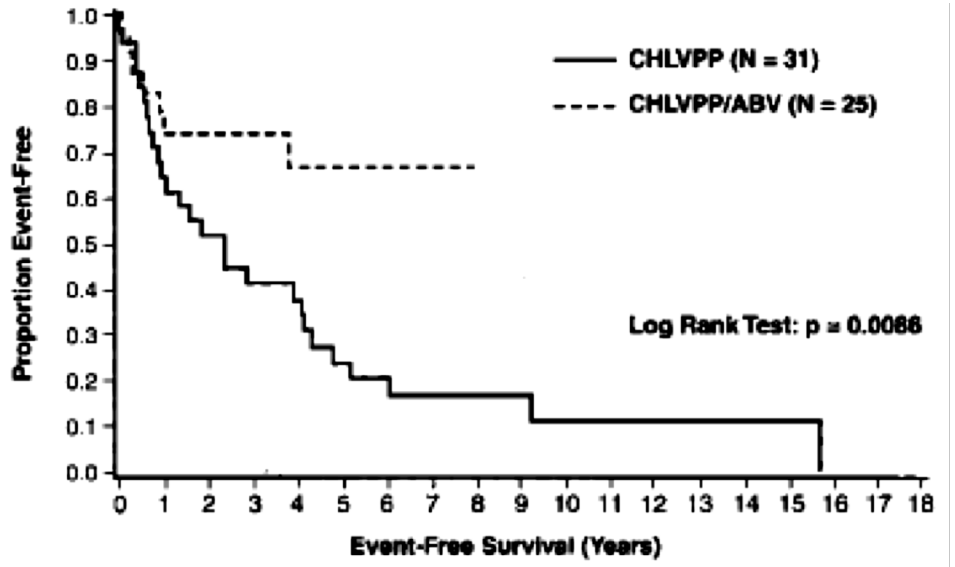
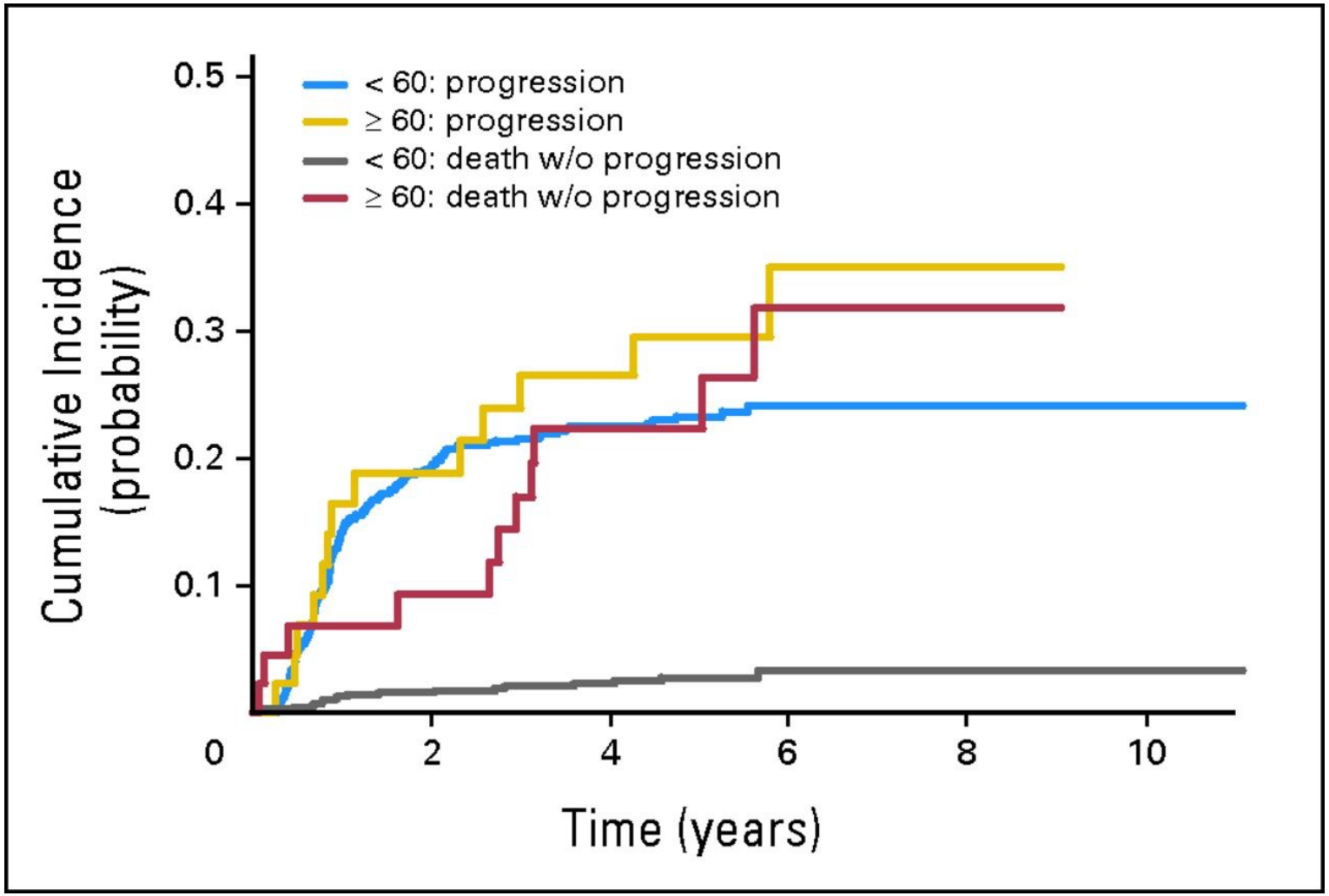


Fig 3. Overall survival of patients ≥ 60 years old segregated on the basis of treatment regimen. The difference between the curves was significant (log-rank test; $P = .0086$).

Competing risk analysis



Evens AM et al. Brit J Haem 2013; Evens AM and Hong F, JCO 2013; 31:1502-1505

Early-stage disease: GHSG

- HD10 and HD13 (median 65 yrs)
  - 2 cycles ABVD (n=137) or AVD (n=82) + IFRT; vs. 4 × ABVD + IFRT (n=68)
- Any WHO grade 3/4 toxicities: 29% w/ 2 x ABVD vs. 65% w/ 4 x ABVD
- Risk BLT: 2 x ABVD 1.3% vs. 4 x ABVD 10% (43% of these being lethal)
- France n=147 older pts (43% ages >70 yrs): 27% incidence of BLT
  - 33% fatality rate (71% > 2 ABVD cycles)

Stamatoullas A. BJH 2015

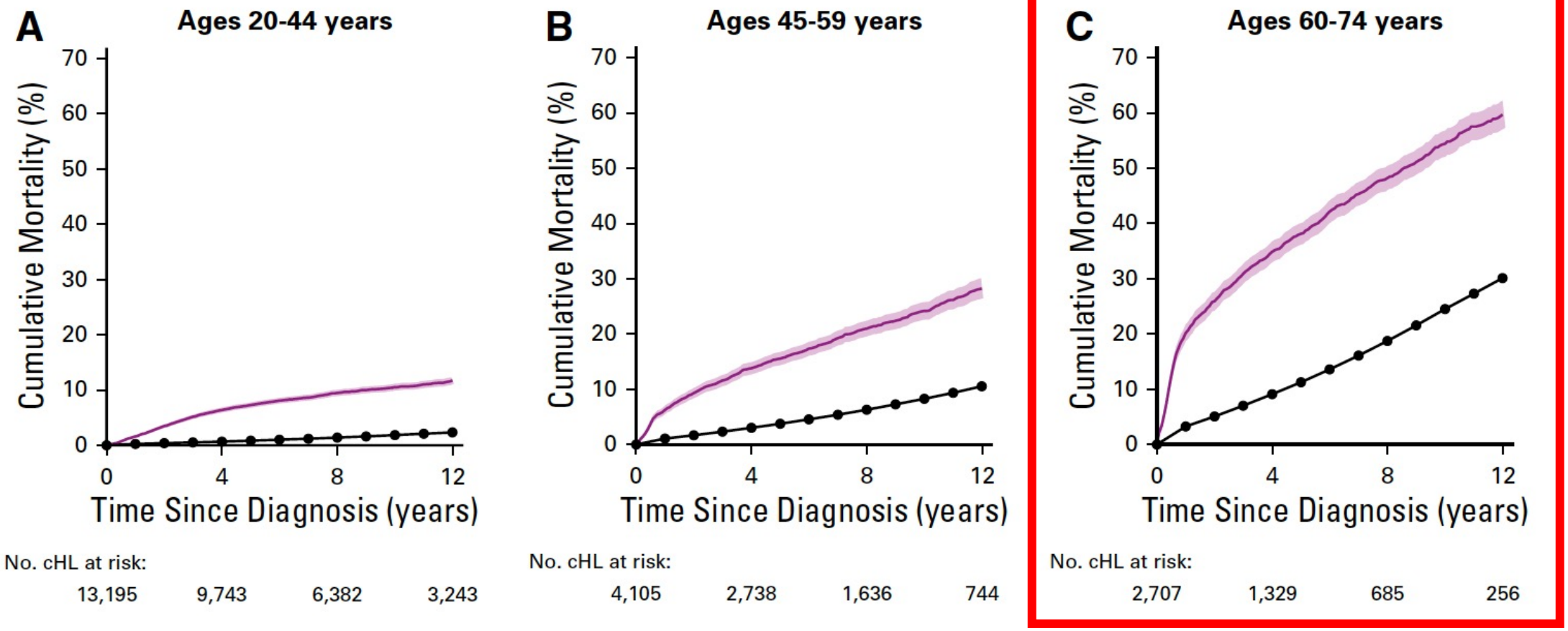
Boll B et al. Blood 2013.

Bleomycin lung toxicity (BLT): potentially life threatening

- **Risk factors**
  - ***OLDER AGE,*** **Renal insufficiency, pulm. RT, underlying lung disease, # doses, supplemental O_2 and G-CSF (infiltration alveolar neutrophils with pro-inflammatory cytokines + free radicals)**
- **Incidence**
  - **5% to 31% (assoc. mortality rate 3% to 27%)**
  - **VA: ≤ 49, 50-59, 60-69 & ≥ 70 yrs: 3%, 7%, 13% & 24%**
  - **Mayo Series, BLT: 26% +G-CSF vs. *no* G-CSF 9% (24% mortality rate)**

Stamatoullas A. BJH 2015; Adachi. Tox Path 2003; Thomas TS. J Geriatr Oncol. 2019; Martin WG JCO 2005

Cumulative mortality: US population vs 20,007 individuals with cHL (SEER 17, 2000-2015)



EARs heart disease 60-74 yrs *SMR stage I/II 38.5; and stage III/IV 59.6*

Cumulative mortality as a result of all causes in the general population and classical Hodgkin lymphoma (cHL) population according to age group

Dores GM et al. *JCO.* 2020

Bv-CAP phase 2 study by the GHSG and NLG

- cHL ages ≥60 yrs
  - Bv-CAP (Bv 1.8 mg, Cytoxan 750 mg/m2, adriamcyin 50 mg/m2, prednisone 100mg)
  - Primary objective: ORR s/p 6 cycles
- 48 pts per protocol; median 66 yrs, 96% stage III/IV
- 20% G2 neuropathy (0 G3), TRM 2%
- RDI 92.9%, ORR 98% (CR 65%)
- 1-yr PFS 74% & OS 93%
  - Metabolic PR 1-yr PFS 47%

Boll B et al. ASH 2020