20TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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Caring for Older Patients with Hodgkin Lymphoma

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Disclosures

- 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

➢ Research Funding: LLS, ORIEN, and NCI/NIH

➢ Patents and Royalties: none

➢ Membership on an Entity's Board of Directors or Advisory Committees: none

➢ Discussion of off-label drug use: checkpoint inhibitor therapy in frontline

Older Hodgkin Lymphoma

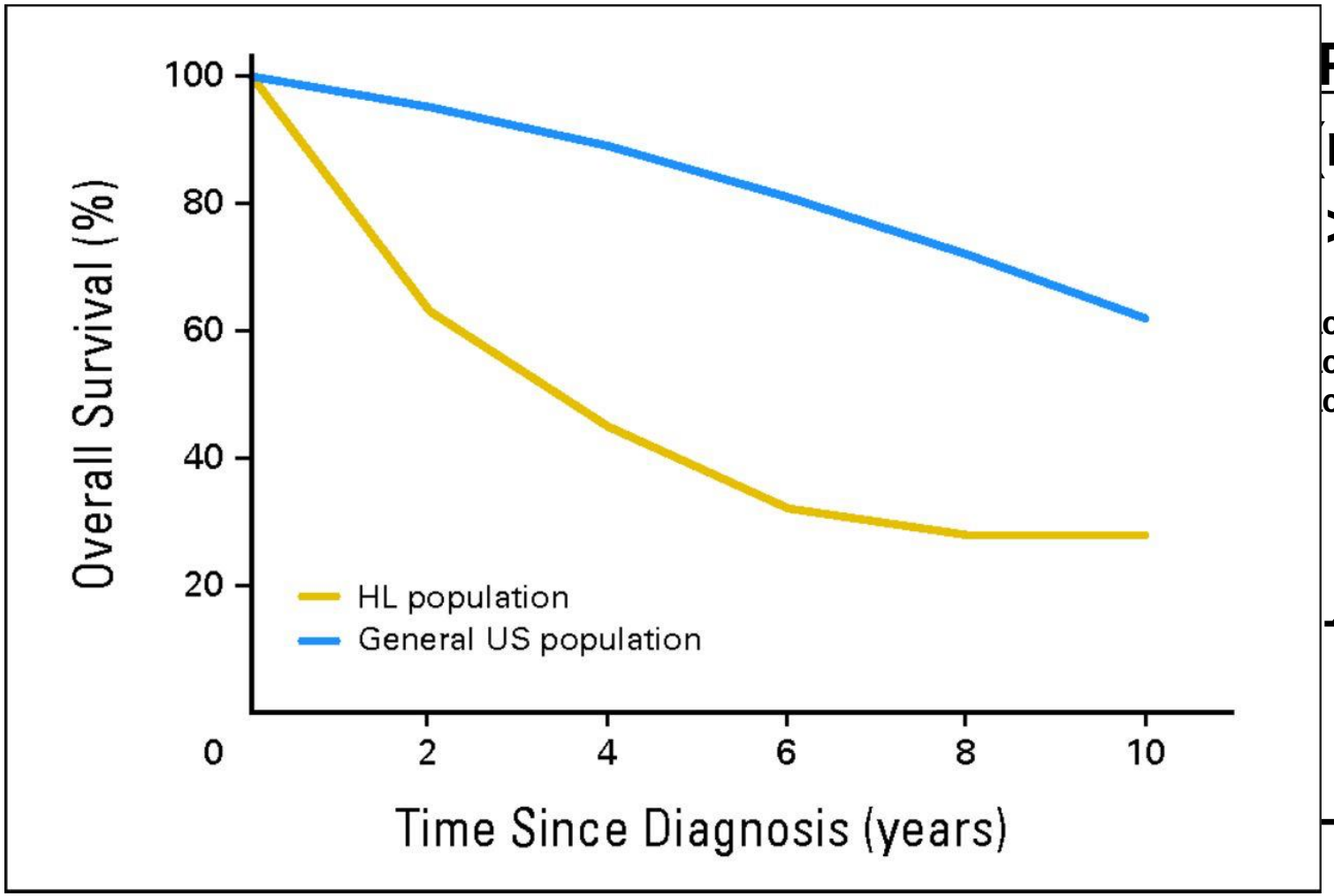
- **Defined: ages ≥ 60 years**
- **Under-represented in clinical trials: <5-10% (vs. 15-25% population)**
- **Standard treatment approach has been absent**
- **Outcomes disproportionately inferior to younger pts**
- **Why?**
  - **Different biology/disease (e.g., mix cell, EBV)**
  - **Advanced stage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

Treatment of Elderly HL (1970 to 2000)

- **Decreased intensity of chemotherapy and individualized dosing**
  - **e.g., CVP/CEB, ChlVPP +/- OEPA, VEPEMB**
- **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;

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



Percent survival

FS: 53% & 36%
mortality: 31%)
>70 & loss ADLs

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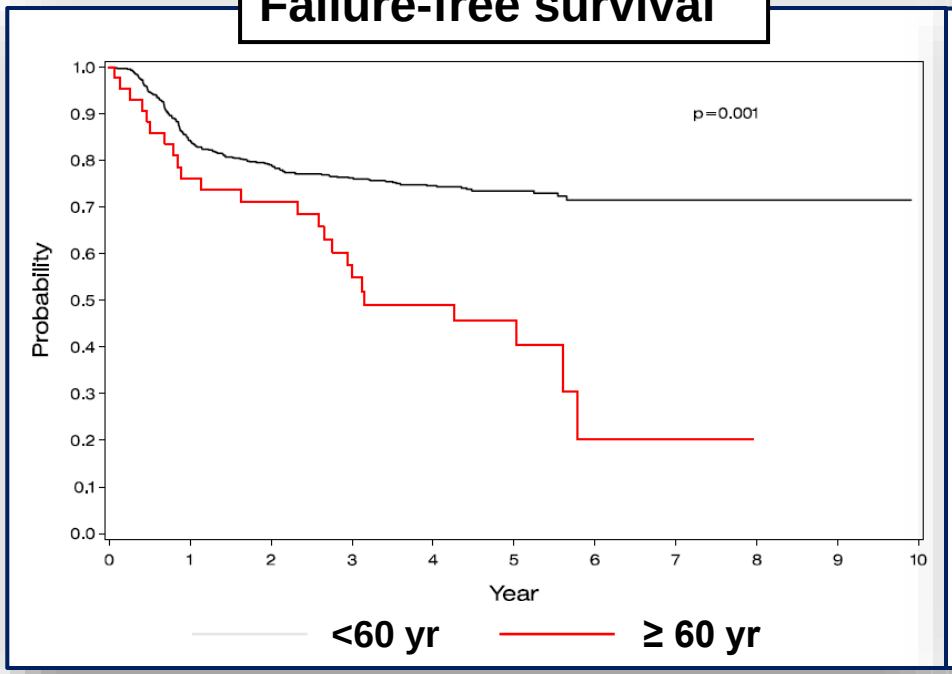
150 180

Evens AM and Hong F. JCO 2013

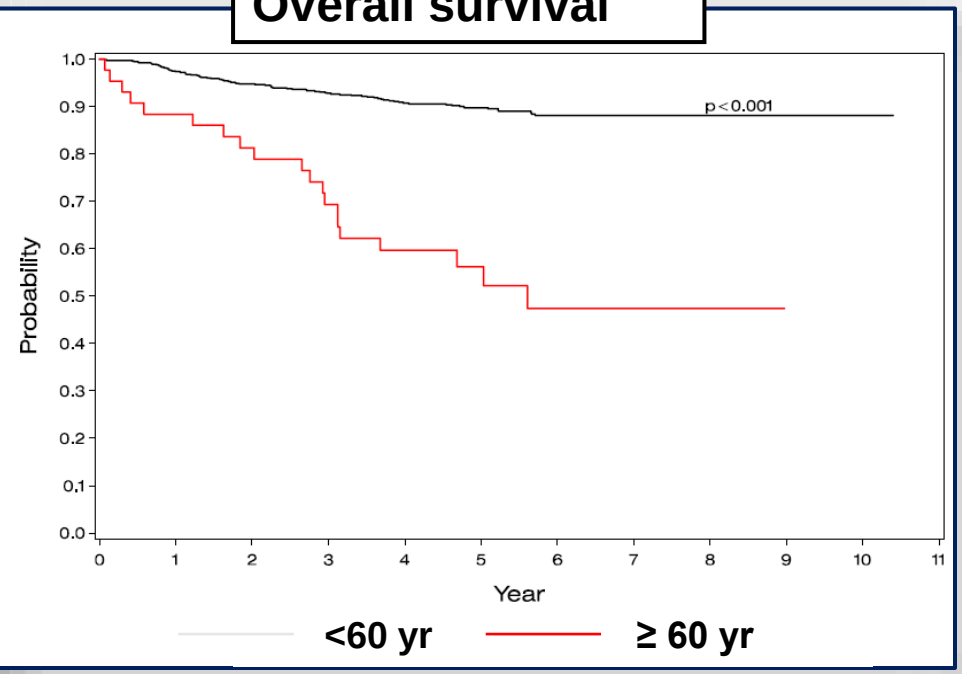
2012; 119:692-5

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

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.

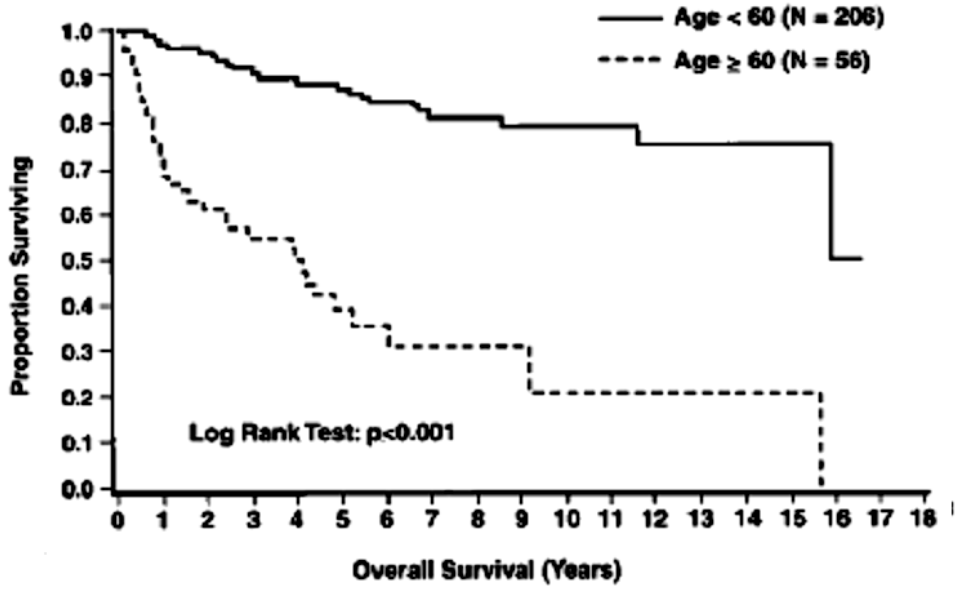


Fig 1. Overall survival by age group. The difference between the curves is significant (log-rank test; $P < .001$).

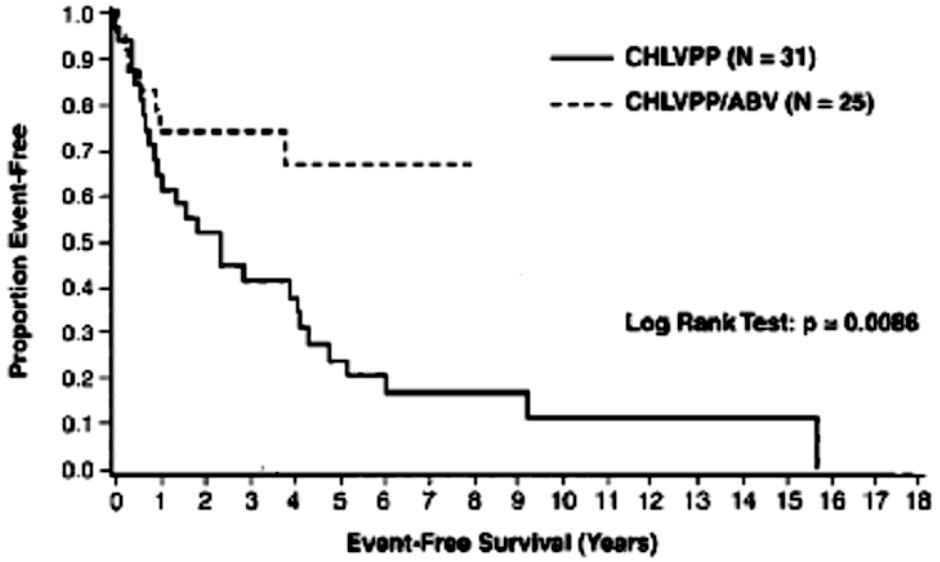


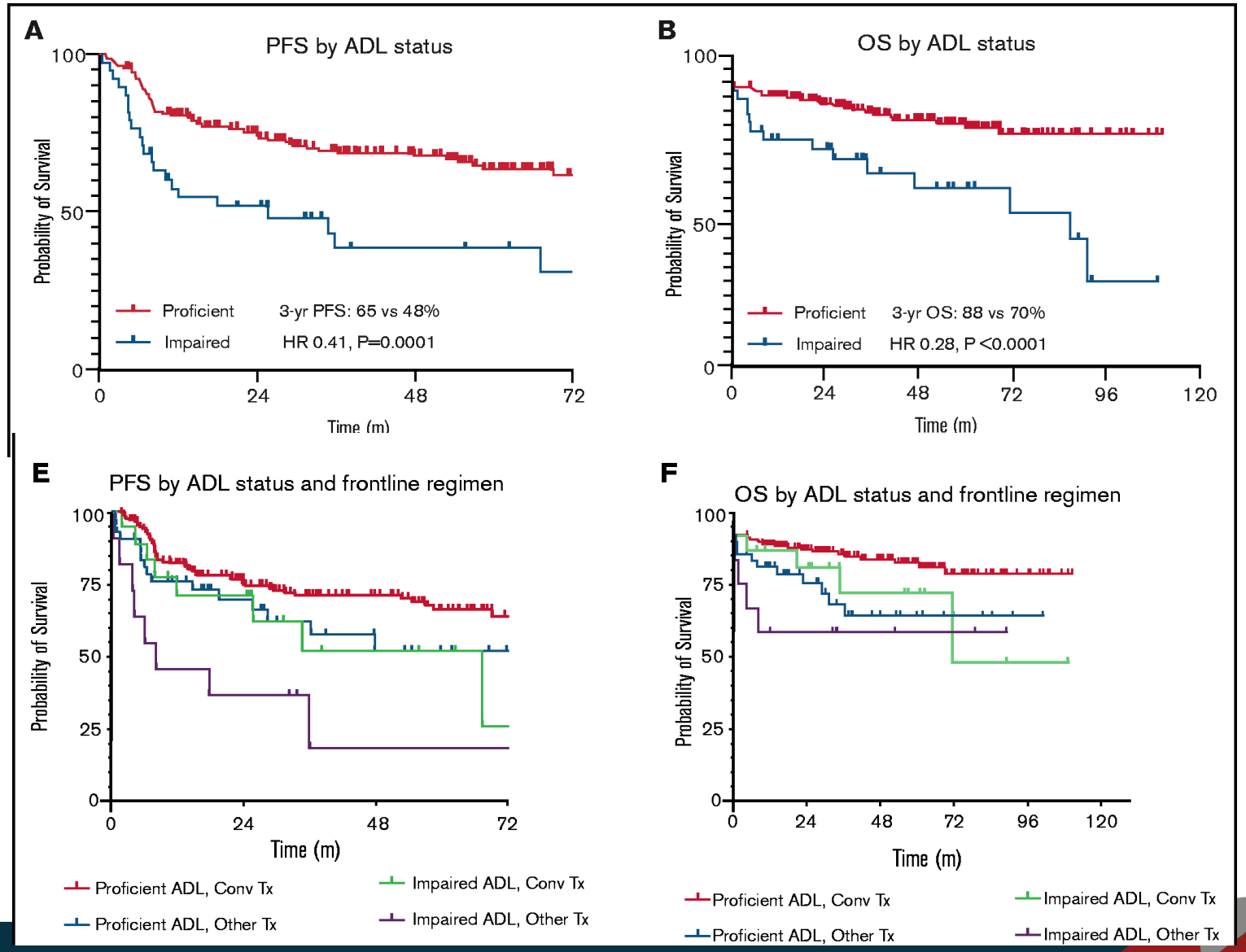
Fig 3. Overall survival of patients ≥ 60 years old segregated on the basis of treatment regimen. The difference between the curves was significant (log-rank test; $P = .0086$).

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)

Goh Z et al. Clin Lymphoma Myeloma Leuk. 2023 Feb 1;S2152-2650.

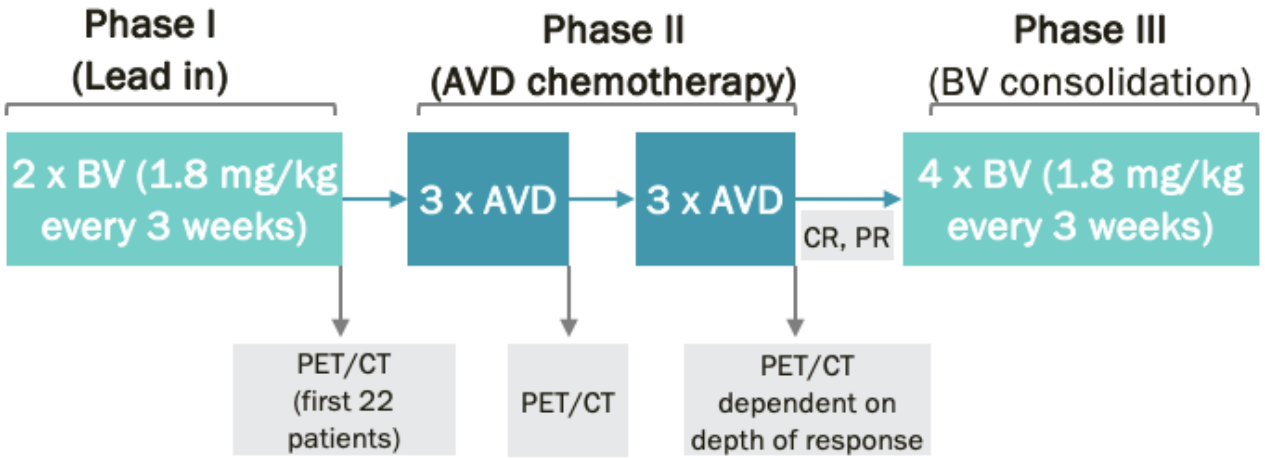
Orellana-Noia V et al. Blood Adv 2021



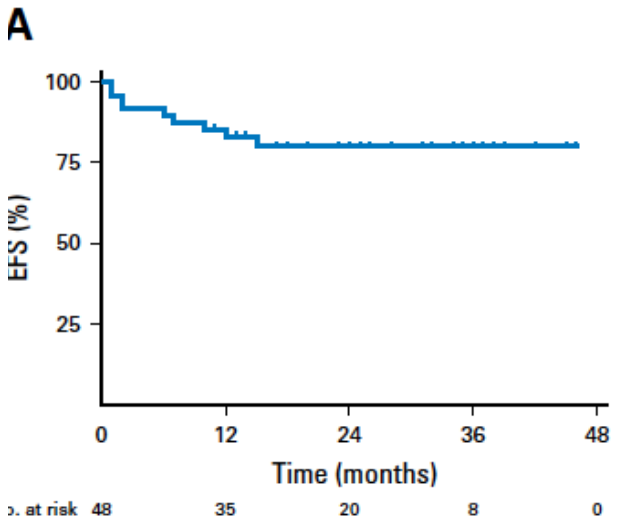
2018 to Current:

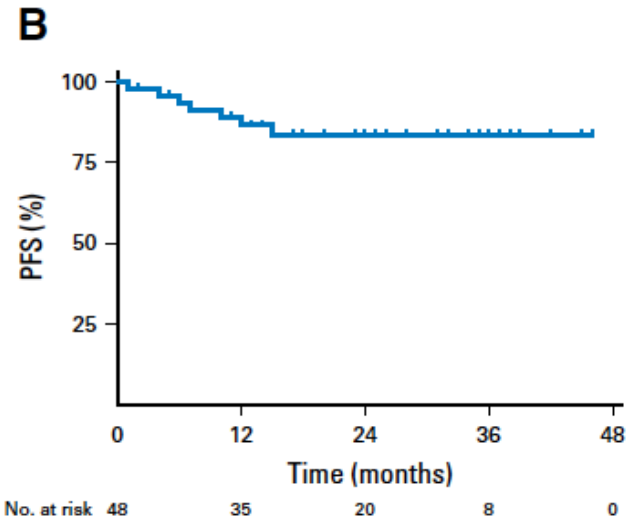
Clinical Trial Data with Targeted Therapeutic Platforms (Fit vs Unfit/Frail)

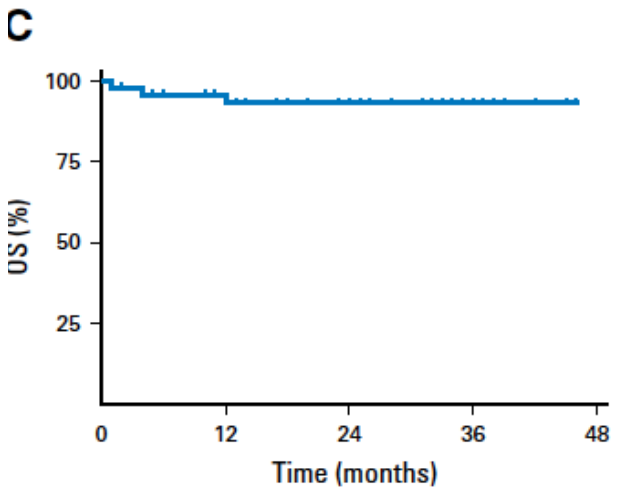
Phase 2 1L BV-AVD in Older HL Patients: Efficacy/Safety



- 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







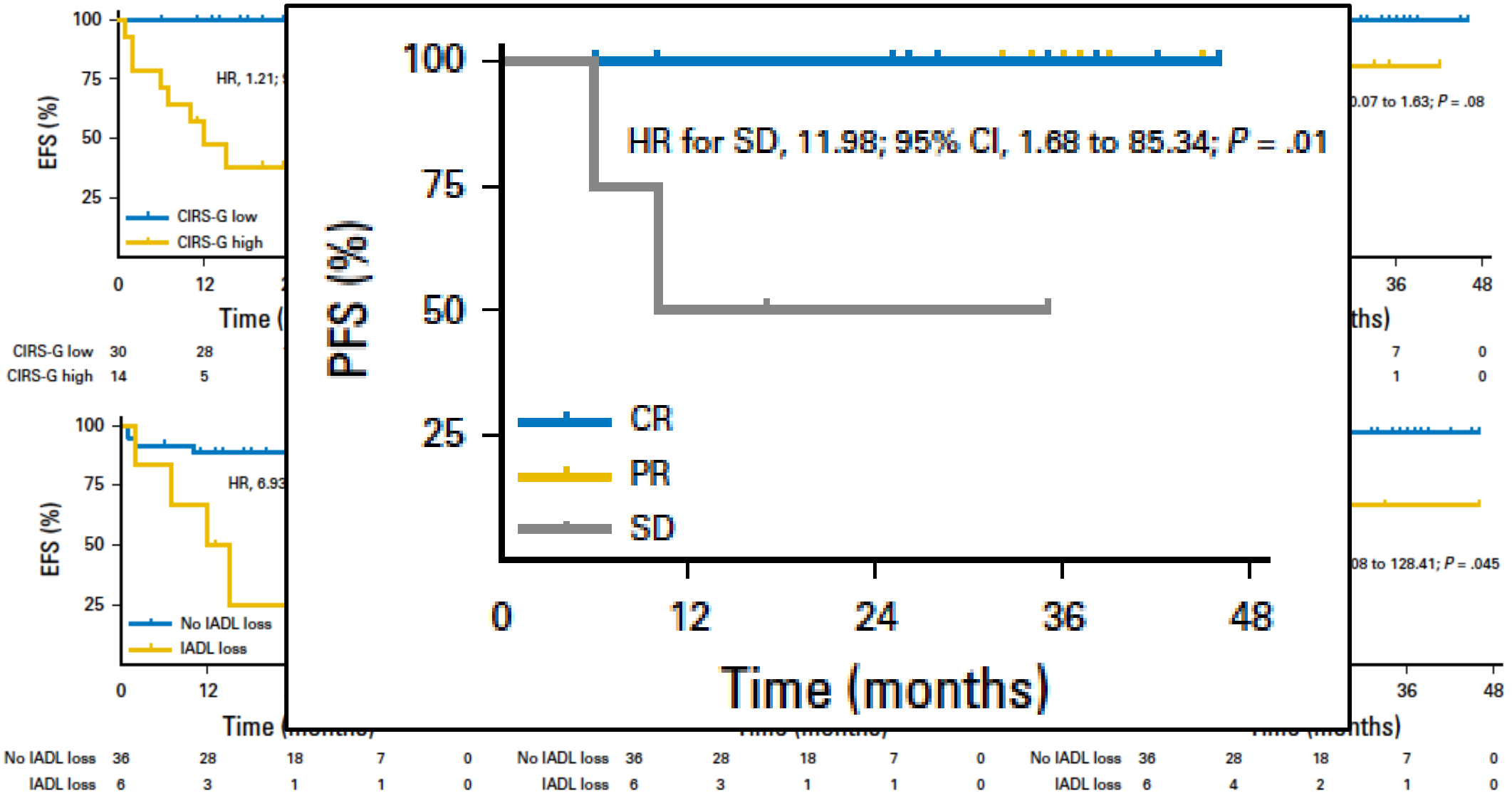
2-year EFS: 90%

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%**

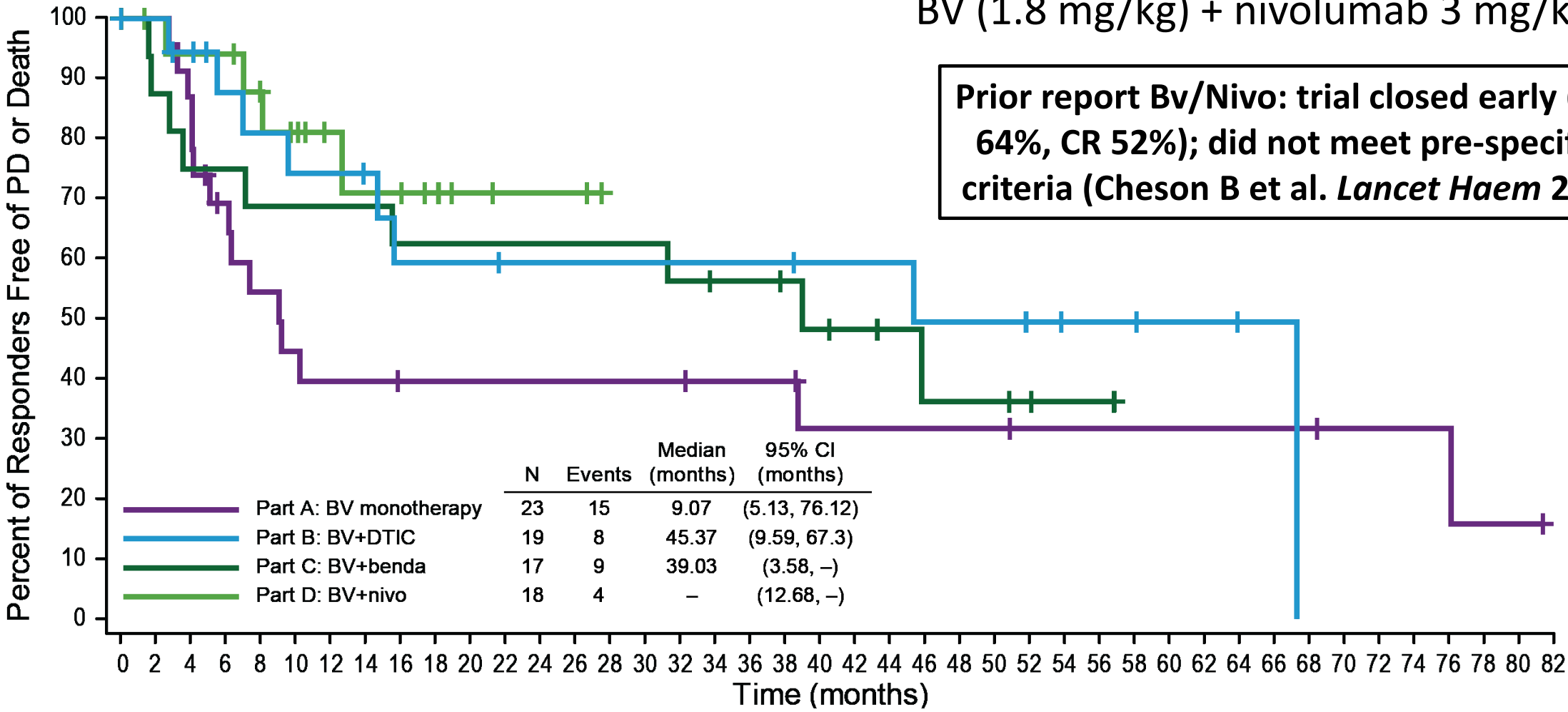
Closed early due to toxicity (2 toxic deaths)

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

BV +/- DTIC or Bendamustine or Nivolumab

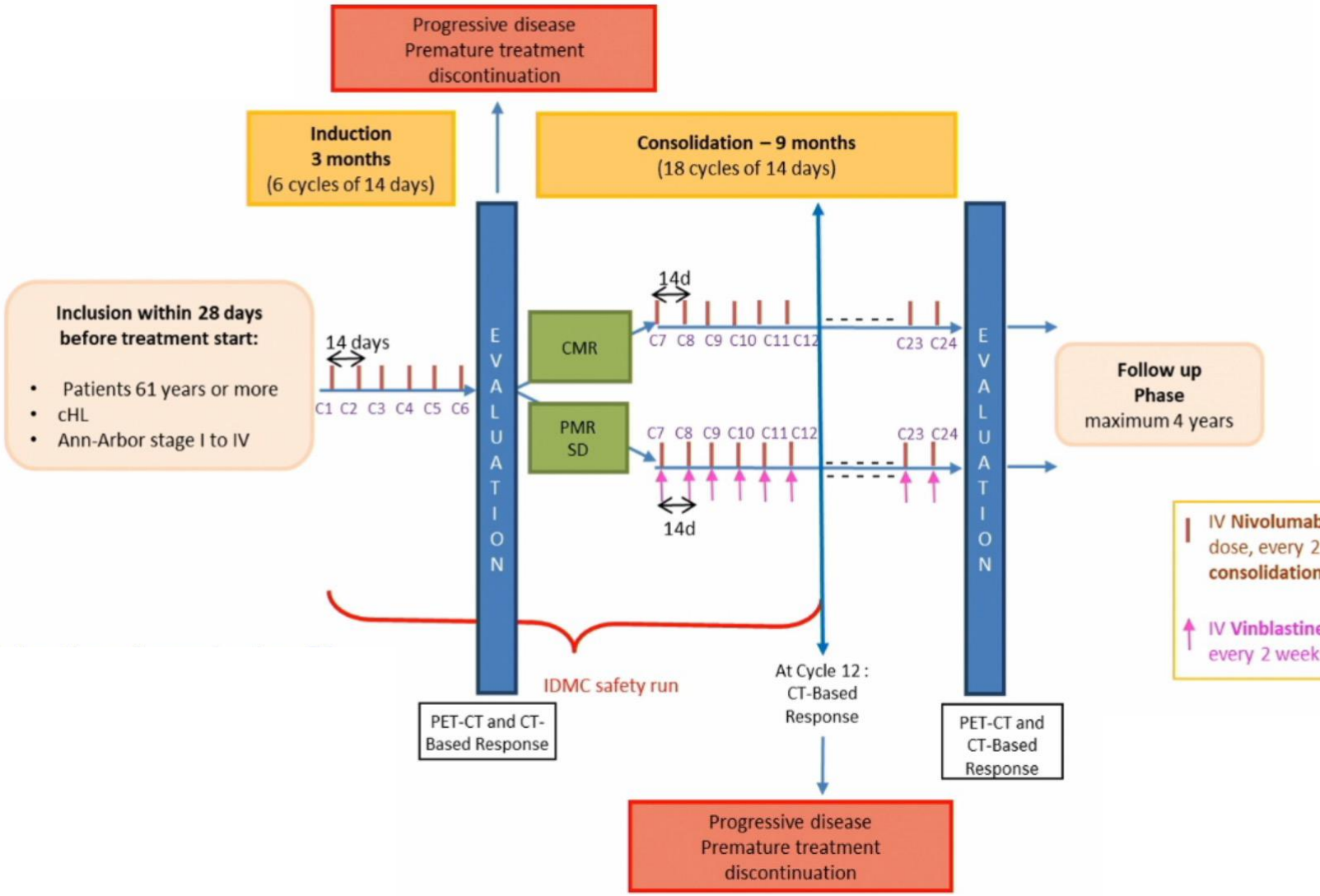
BV (1.8 mg/kg) + nivolumab 3 mg/kg

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



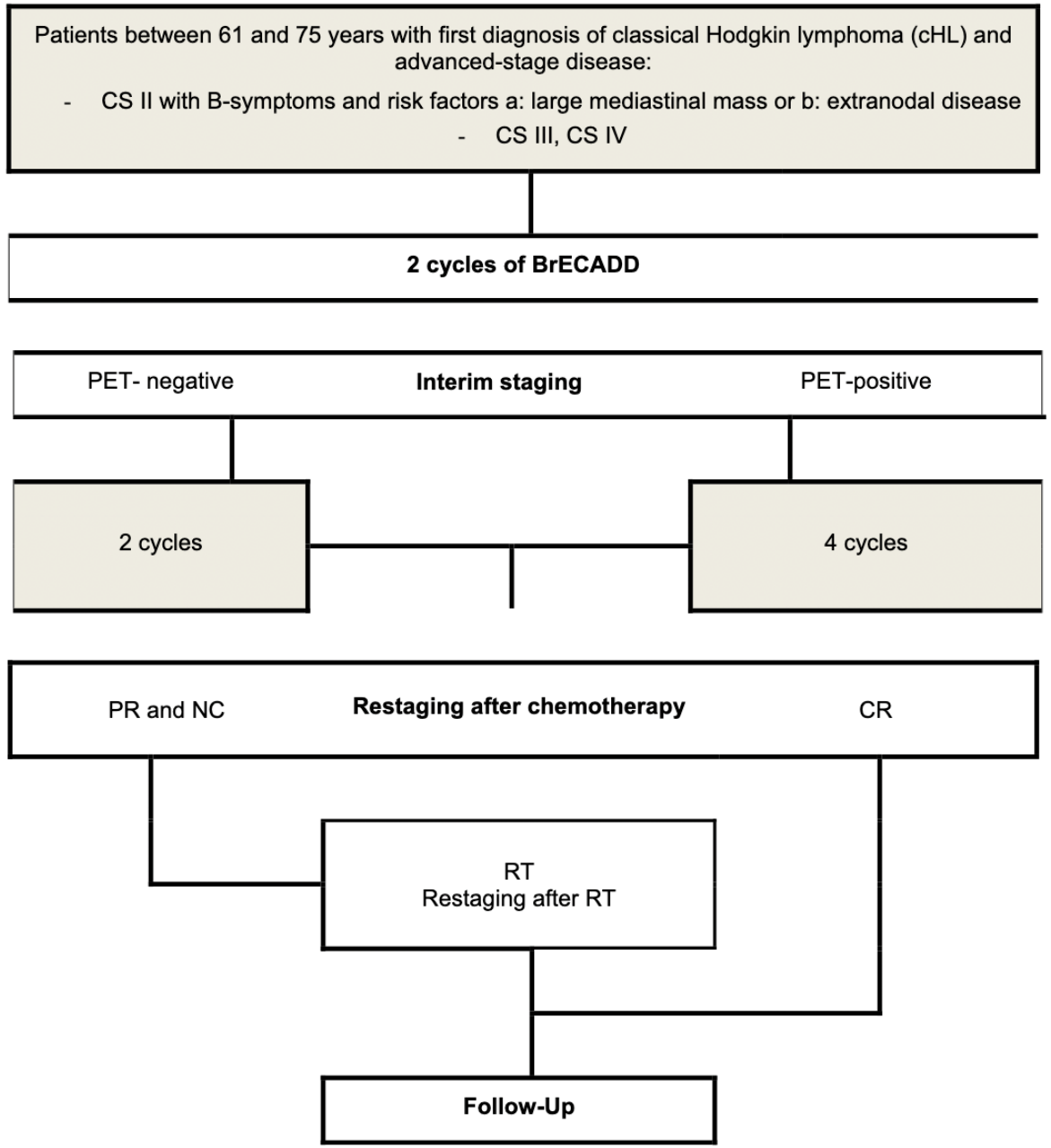
IV **Nivolumab** administration 240mg/flat dose, every 2 weeks on the **induction and consolidation phases**

IV **Vinblastine** administration : 6 mg/m² every 2 weeks on **consolidation phase**

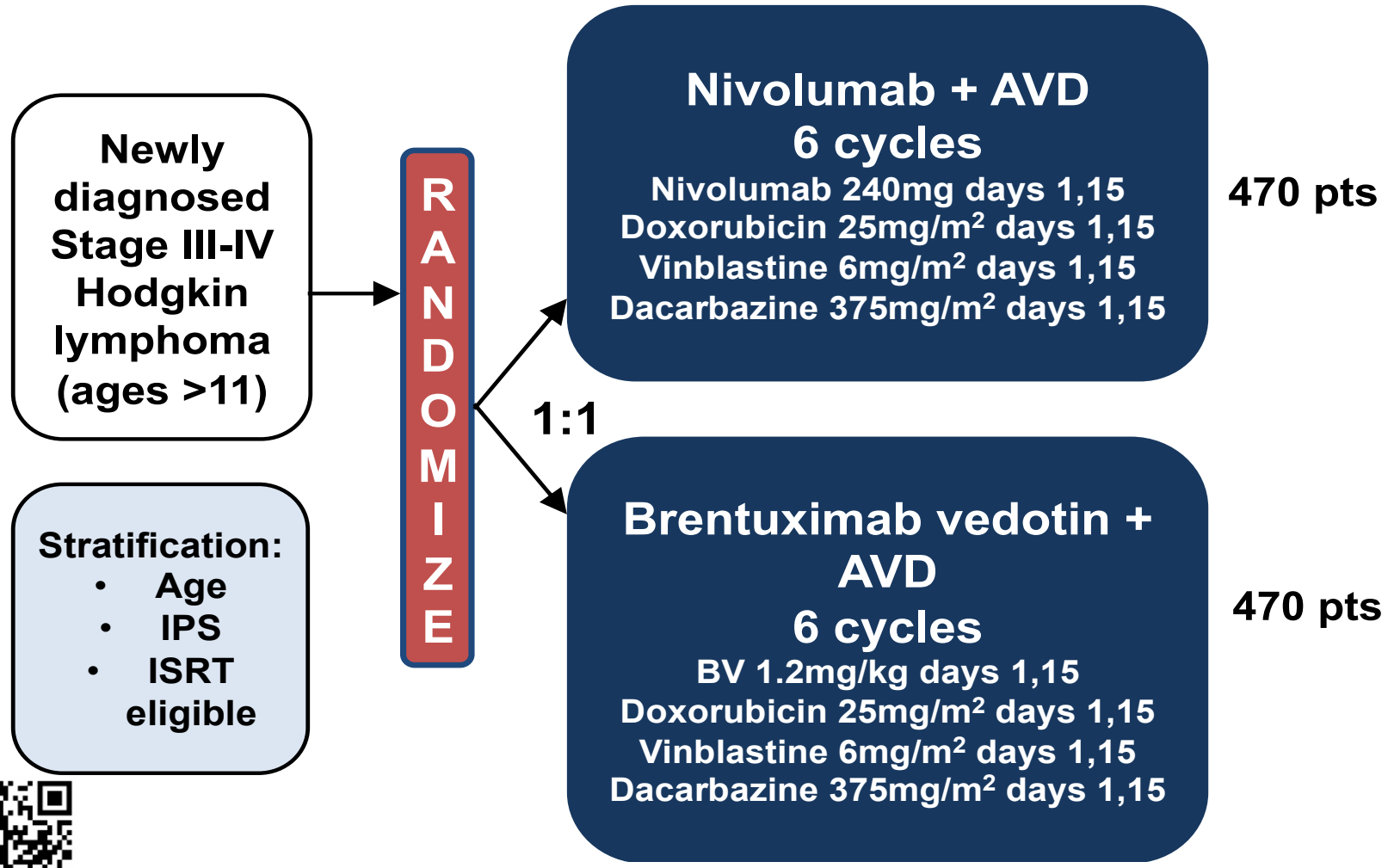
- N=56 pts efficacy
- Med age 75 yrs, med CIRS-G 10 (6-18)
- EOT ORR 47% w/ CR 29% (16% EOI)
- Median PFS 9.8 mos

Ongoing and New Studies

Ongoing / future studies in older HL: GHSG HD21

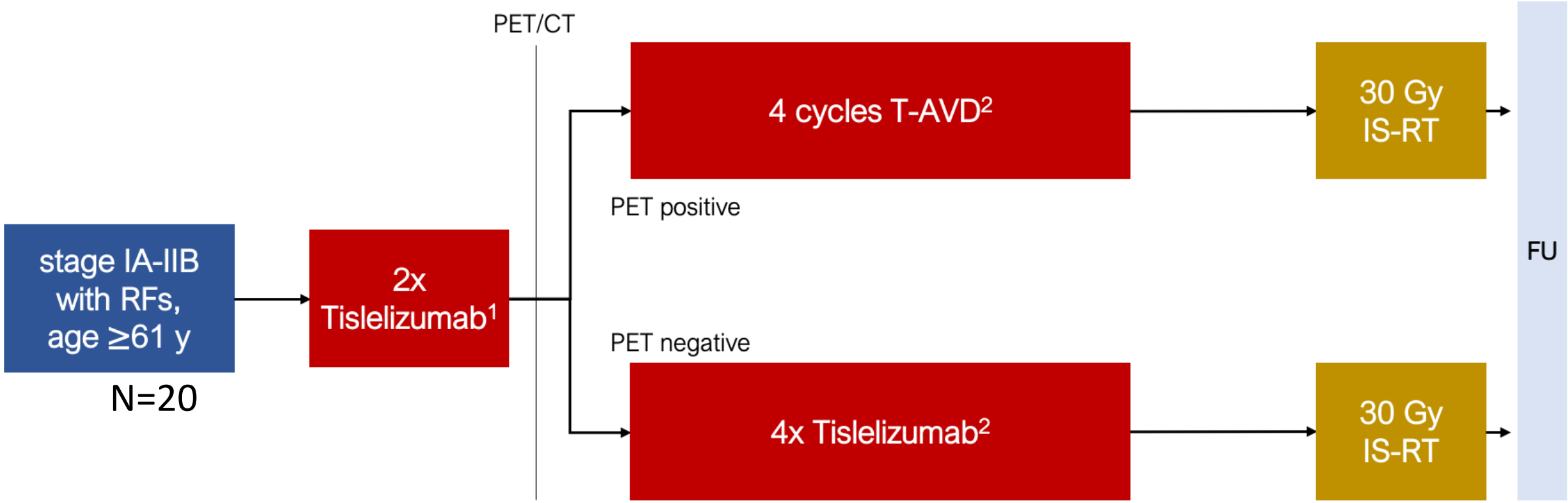


North American Cooperative Group Study for Advanced Stage HL: S1826



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

INDIE: Elderly Cohort

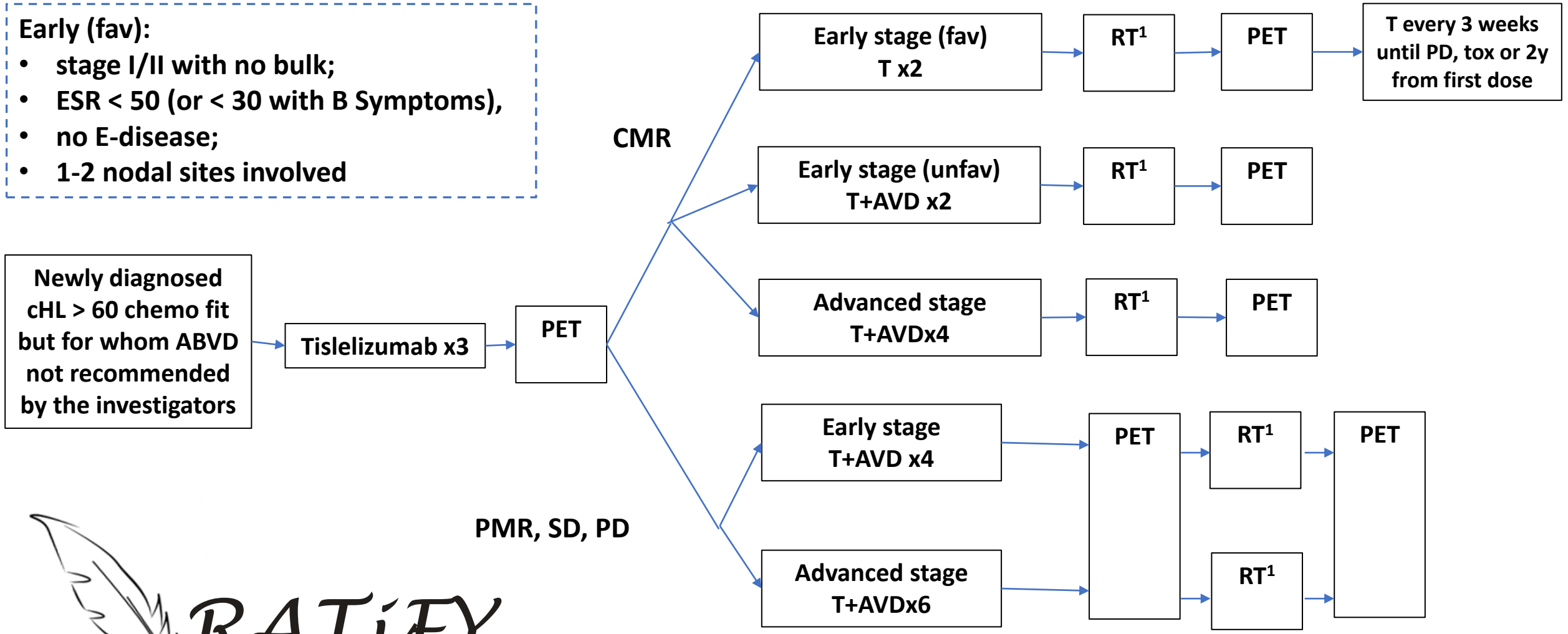


*chemotherapy should start as soon as central PET evaluation is available. Up to 1 further dose tislelizumab is allowed in case of severe delay of PET panel assessment. [1]Tislelizumab 200mg Q3W [2]Tislelizumab 300mg Q4W, on day 1 of each 28-day AVD cycle if combined with AVD. RFs: GHSG risk factors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

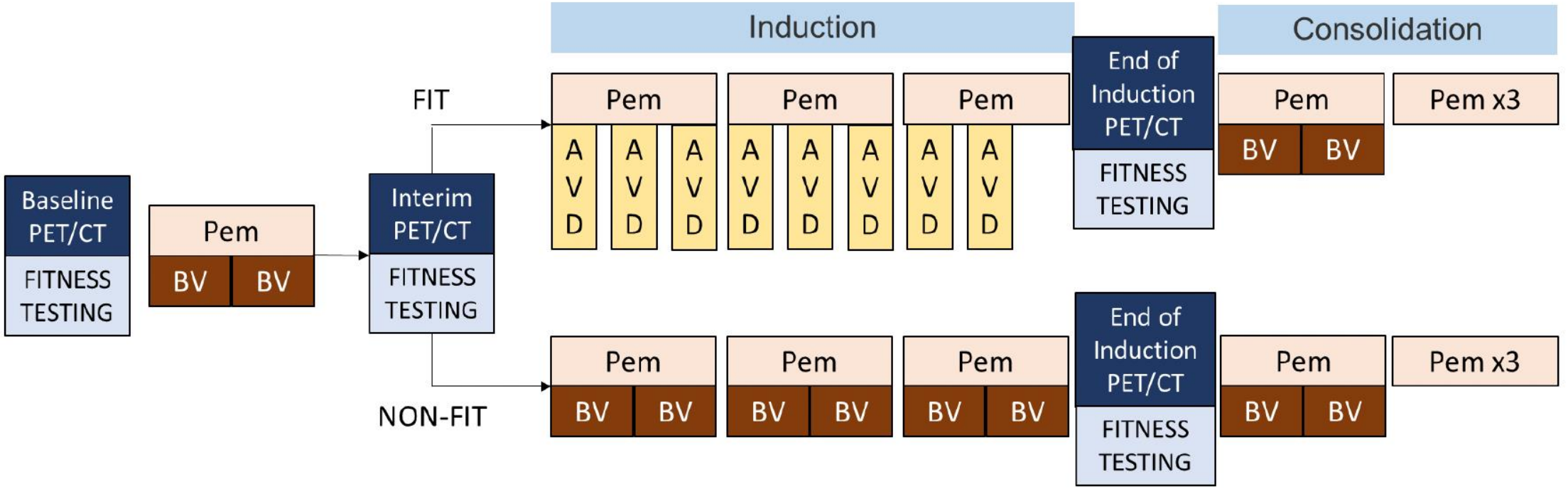
Early (fav):
- **stage I/II with no bulk;**
- **ESR < 50 (or < 30 with B Symptoms),**
- **no E-disease;**
- **1-2 nodal sites involved**



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

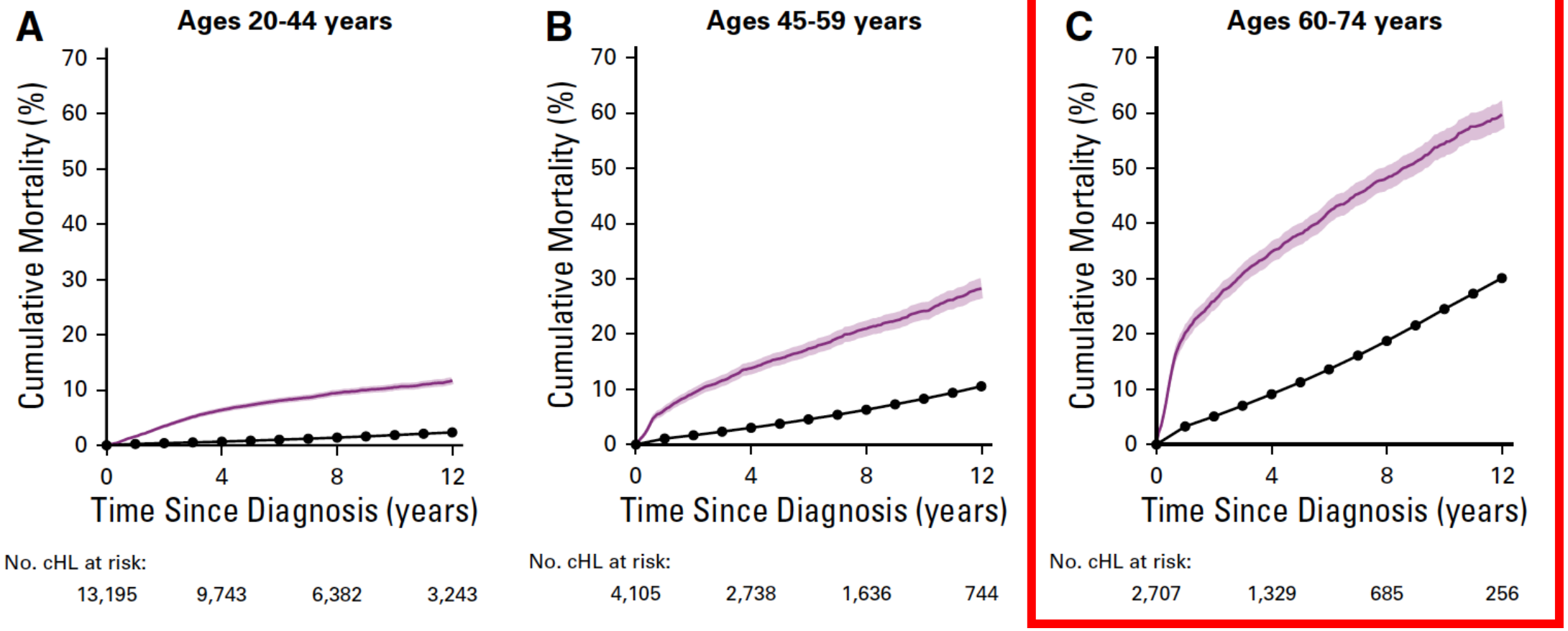
NON-FIT - Any of the following:
ECOG Performance Status ≥ 3
CIRS-G total score ≥10
LVEF < 40% at screening or anytime after
Loss of ≥ 1 basic ADL
Loss of ≥2 instrumental ADLs

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: Stanford V (low EF), ?? mini-AVD

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

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