Hodgkin Lymphoma in Older Patients

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Elderly Hodgkin Disease

- **Defined: age ≥60 years**
- **Under-represented in clinical trials: <5-10% (vs 15-25% population)**

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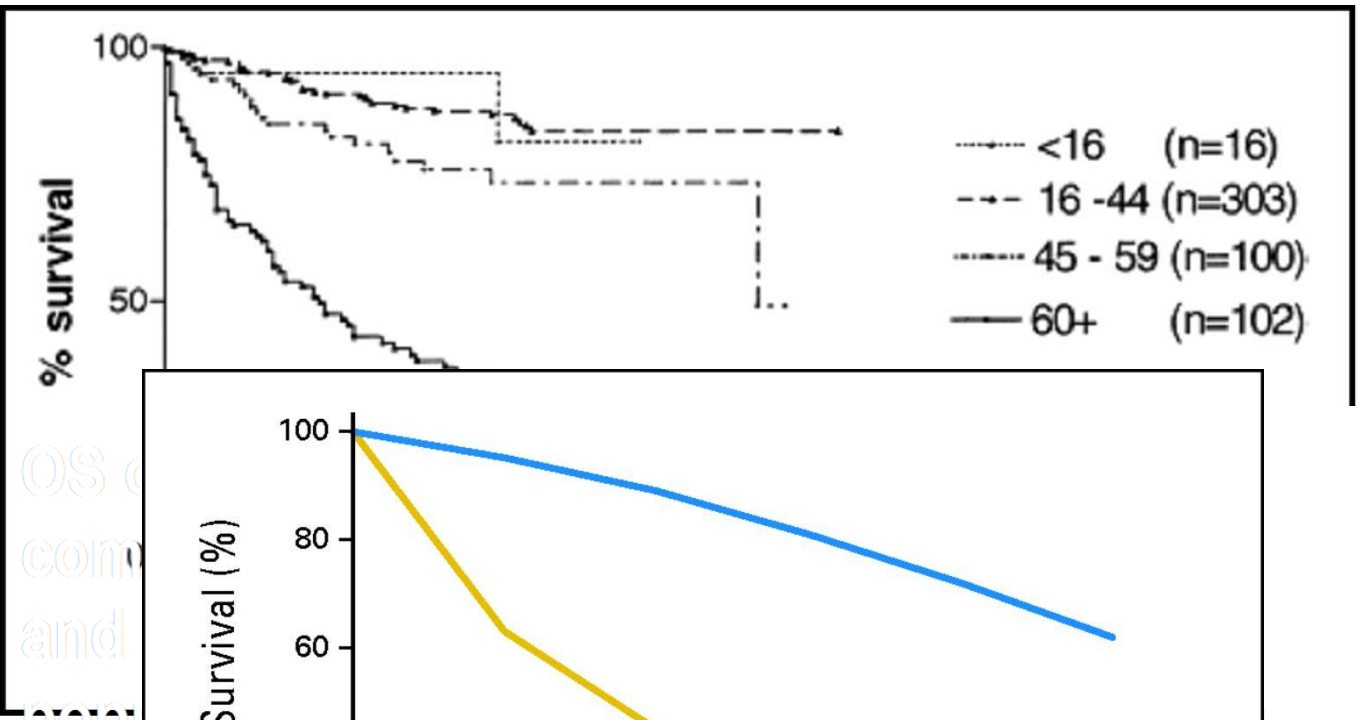
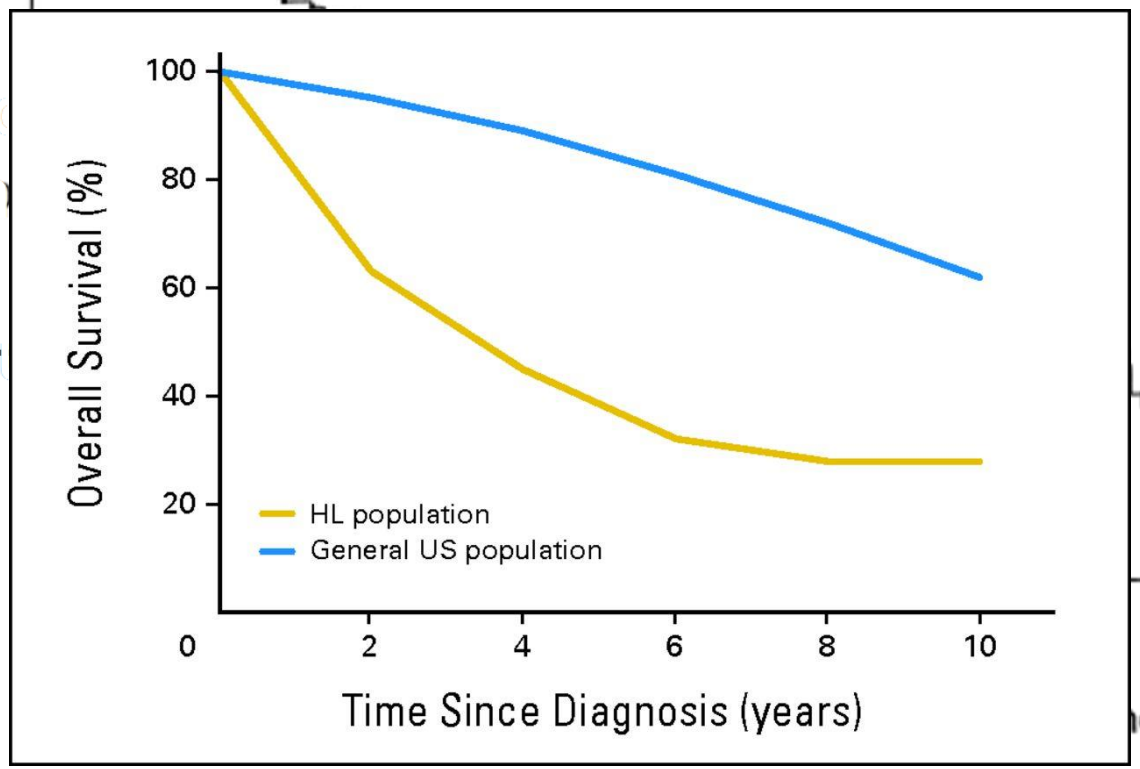
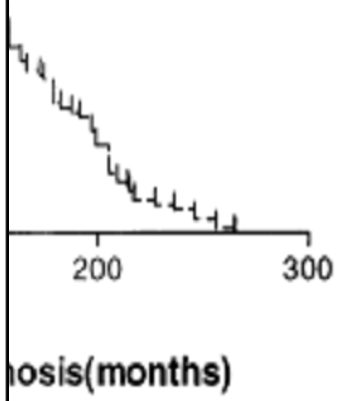
- **Outcomes disproportionately inferior to younger patients (and other cancers): *EFS and OS ~ 40-50% inferior***
- **Standard treatment approach absent**
- **? Why**
  - **Co-morbidities precluding appropriate Rx**
  - **Inadequate treatment delivery/intensity**
  - **Treatment-related toxicities (esp. BLT)**
  - **? Different biology/disease (eg, mix cell, EBV)**

Outcomes of elderly HD



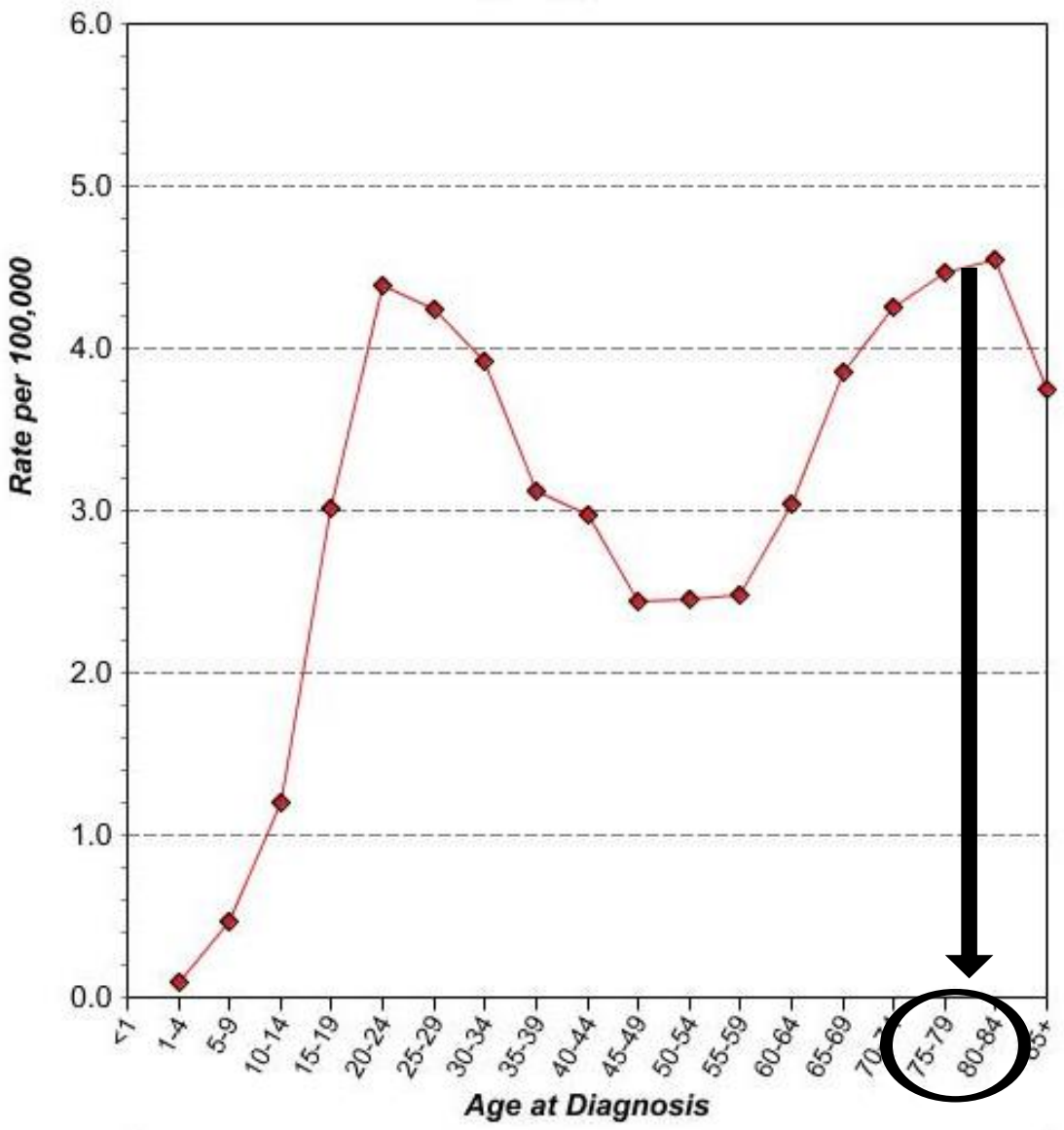




Evens AM et al. Blood 2012; Evens AM and Hong F. JCO 2013

Stark et al. BJH, 2002; 19:432

US Age-Specific SEER Incidence Rates



SEER Stat Database: Incidence-SEER 17 regs public use (2000-2008), NCI, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010.

Elderly HD: patient characteristics

Author/Series (country)	No. pts	Data source	Median age, years (range)	Gender	Stage	B symptoms	Bulky mediastinum	Histology
Levis, 1994 (Italy)	65	Retrospective (registry) 1982-1989	72 (66-80)	NR	I/II 57% III/IV 43%	41%	2%	MC 62% NS 29%
Weeks, 2002 (United States)	56	Retrospective (1982-1998)	NR	M 57% F 43%	I/II 27% III/IV 73%	59%	7%	NS 39% MC 34%
Stark, 2002 (United Kingdom)	102	Prospective (popul. based)	M: 69 (60-85) F: 72 (60-91)	M 51% F 49%	IA/IIA 36% IIB/IV 64%	51%	NR	NS 42% MC 32%
Landgren, 2003 (Sweden)	88	Retrospective 1973-1994	72 (60-92)	M 55% F 45%	I/II 31% III/IV 69%	64%	2%	MC 42% NS 17%
Levis, 2004 (Italy)	111	Prospective phase II	71 (66-83)	M 53% F 47%	I/II 56% III/IV 44%	39%	8%	MC 47% NS 34%
Engert, 2005 (Germany)	372	Clinical trials 1988-1998	65 (60-75)	F 52%, M 48%	I/II 53% III/IV 47%	50%	9%	NS 41% MC 35%
Feltl, 2006 (Prague, Czech)	52	Retrospective (1973-1993)	65 (60-84)	NR	I/IIA 19% IIB-IV 81%	83%	NR	MC 40% NS 31%

Adapted from: Evens A, Sweetenham J, Horning S. Oncology, 2008.

Prognostic features (IPS): Advanced Stage Disease

- ***Age >45***
- **Stage IV**
- **Hgb < 10.5 gm/dL**
- **Lymphocyte count < 600/mm^3 or < 8%**
- **Male gender**
- **Albumin < 4 gm/dL**
- **WBC > 15,000/mm^3**

N Engl J Med. 1998; 339:1506.

Only 9% pts age >55 years (55-65); *none* over age 65

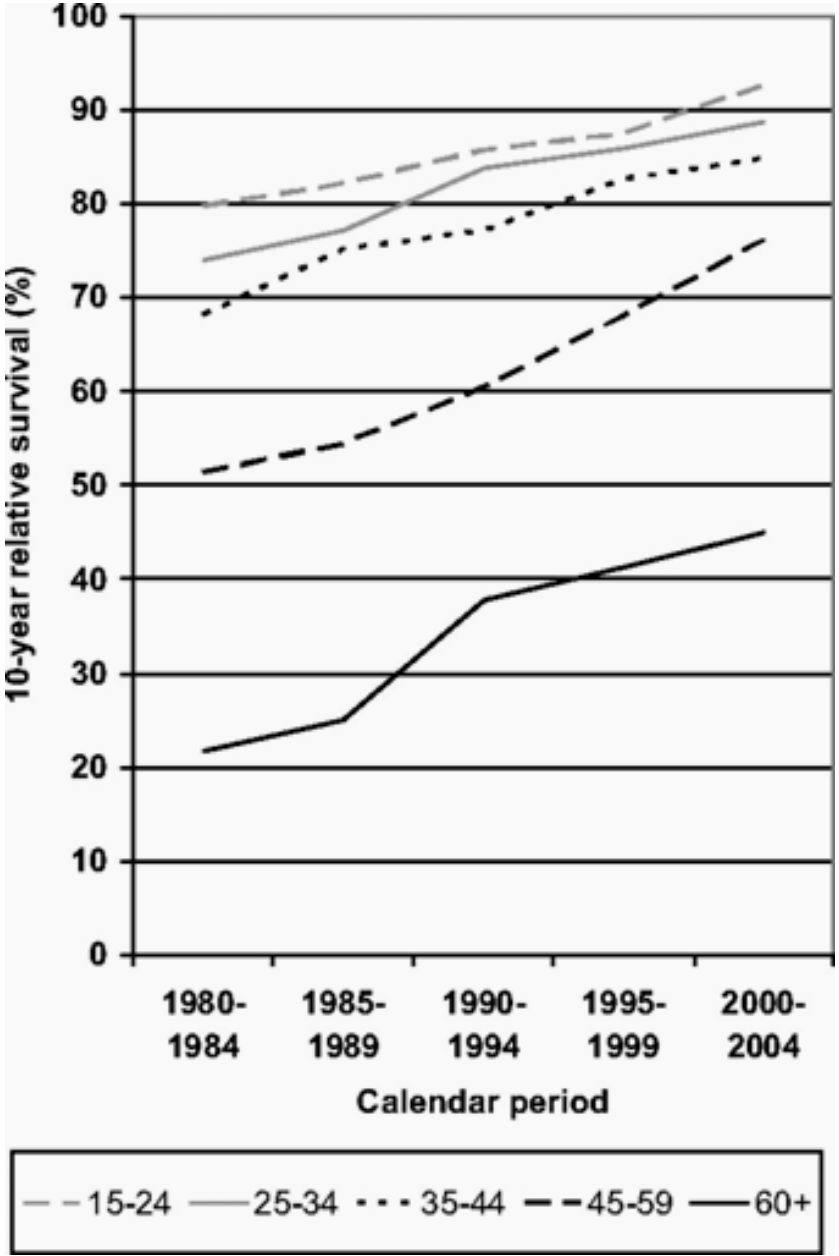
Personal communication, V.Diehl

Treatment of Elderly HD (1970 to 2000):

- **TRM (ABVD 23%, BEA_{base} 21%, BACOPP 12%)**
- **Decreased intensity of chemotherapy and individualized dosing**
  - **e.g., CVP/CEB, ChlVPP +/- OEPA**
- **Dose intensity important?**
  - **5-year CSS 51%, OS 39% (MOPP/ABV)**
  - **RDI > 65% improved OS (P=0.001)**
- **Non-anthracycline options**
  - **e.g., VBM and ChlVPP: sub-optimal outcomes**

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. Haematologi;a. 2003

“Catch up” for older HD pts?



- **Pts age 45-59 years and ≥60 years with increased 10-year relative survival by 25% and 23%, respectively.**

- **A strong age gradient <u>persists</u> (in 2000-2004), with 10-year relative survival of:**

Age 15-24 yrs: 93%
Age 25-34 yrs: 89%
Age 35-44 yrs: 85%
Age 45-54 yrs: 76%
<u>Age 60+ yrs: 45%</u>

Brenner, H. et al. Blood 2008;111:2977-2983

Chicago Elderly HD (2000-2009)

- **Retrospective analysis (1/00-1/10), n=95 HD pts ≥ age 60 years (median 67 yrs; 60-89; 33% ≥ age 70)**
  - **U Chicago, Rush, Northwestern, LGH, Loyola**
- **Characteristics**
  - **NOS 42%, NS 34%, MC 18%, and LP 6%**
  - **Prior malignancy 27%, Hx CAD 20%, B sx 52%, Wt loss 35%, PS >1 29%, and stage III/IV 65%, and IPS 4-7 in 64%**
- **Functional status**
  - **61% with any grade 3-4 co-morbidity (CIRS-G), 29% "not fit", 13% loss ADLs, and 18% w/ geriatric syndrome**

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

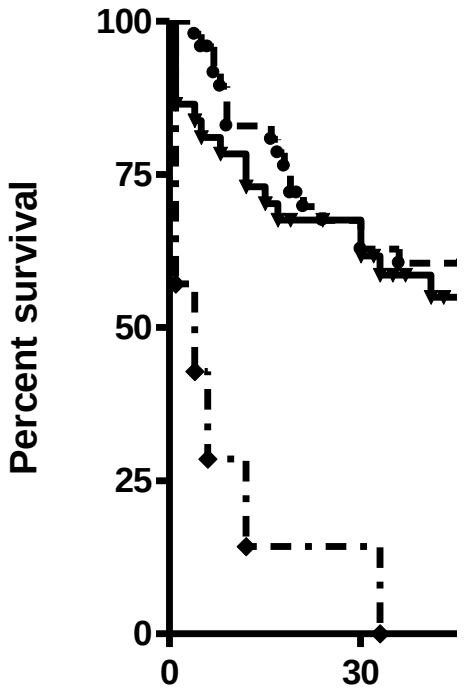
Chicago Elderly HD (2000-2009)

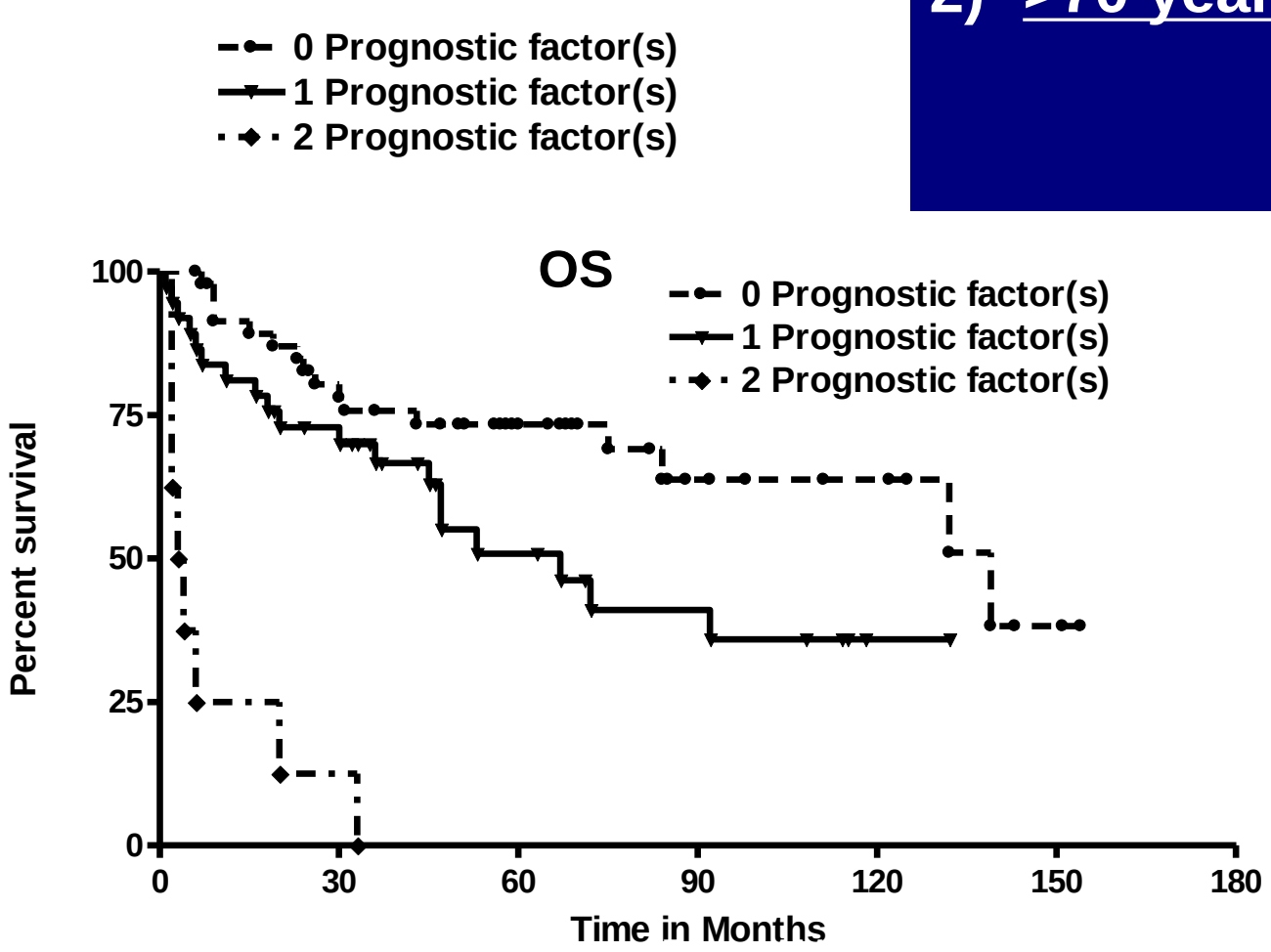
	N	2-yr	5-yr	P
EFS				
All pts	95	63%	47%	
Stage				
I/II	32	81%	65%	
III/IV	61	52%	37%	0.007
OS				
All pts	95	73%	58%	
Stage				
I/II	32	90%	79%	
III/IV	61	63%	46%	0.001

- ORR 88% (75% CR)
- BLT 33% (Death: 31%)
- Inferior EFS and OS (on univariate): age >70, B symptoms, weight loss, PS >1, albumin, Hx CAD, stage III/IV, any CIRS-G 3/4, and ADL loss
- Multivariate: Age >70 (OR 2.24, p=0.02) loss of ADL's (HR 2.71, p=0.04), and lack of CR (HR 8.1, p<0.0001),

Chicago Elderly HD: EFS + OS Prognostic Model

1) ADL loss
2) >70 years





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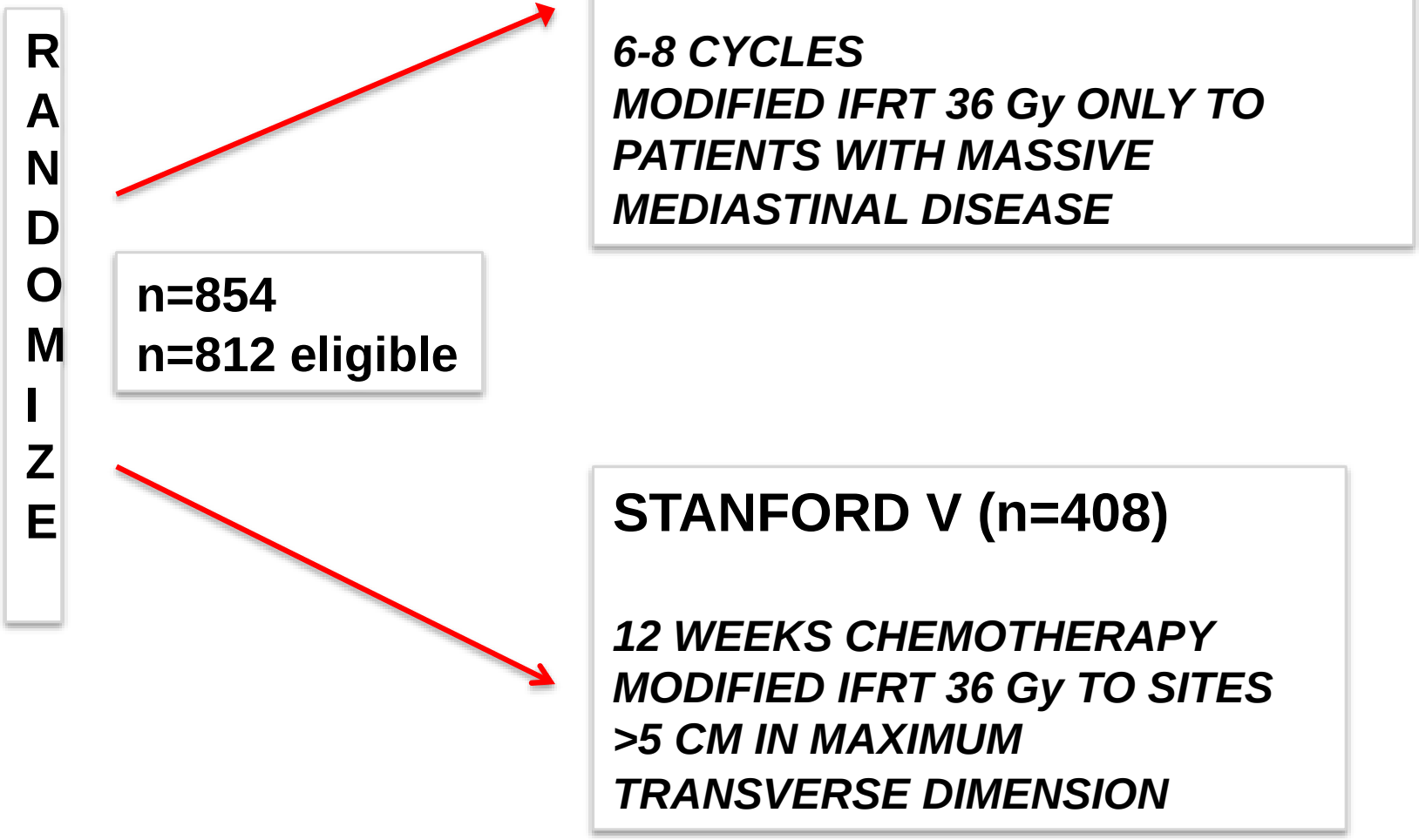


Response

	ABVD		Stanford V	
	N	%	N	%
CR	6	26	4	20
Clinical CR	9	39	9	45
PR	2	9	0	0
SD	4	17	2	10
PD	0	0	2	10
Not eval.	2	9	3	15

Older vs Younger Subjects

CR/clinical CR:
65% vs 71%
(p=0.49)

ORR:
70% vs 78%
(p=0.19)

Evens AM et al. Brit J Haem, 2013

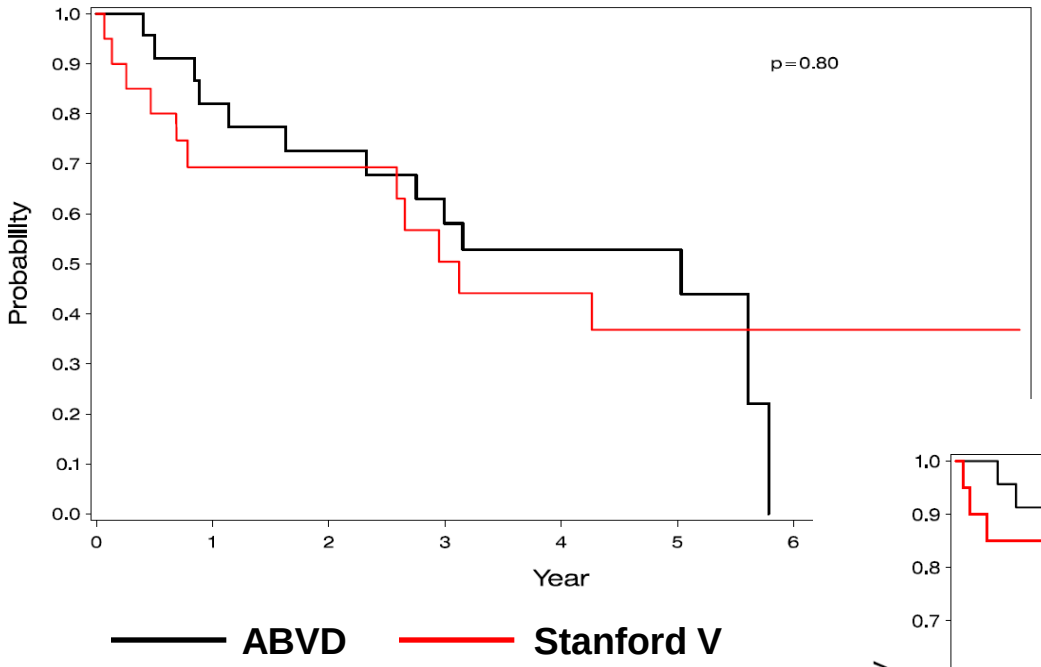
Toxicity (non-hematologic)

- **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% (5/10) 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)**

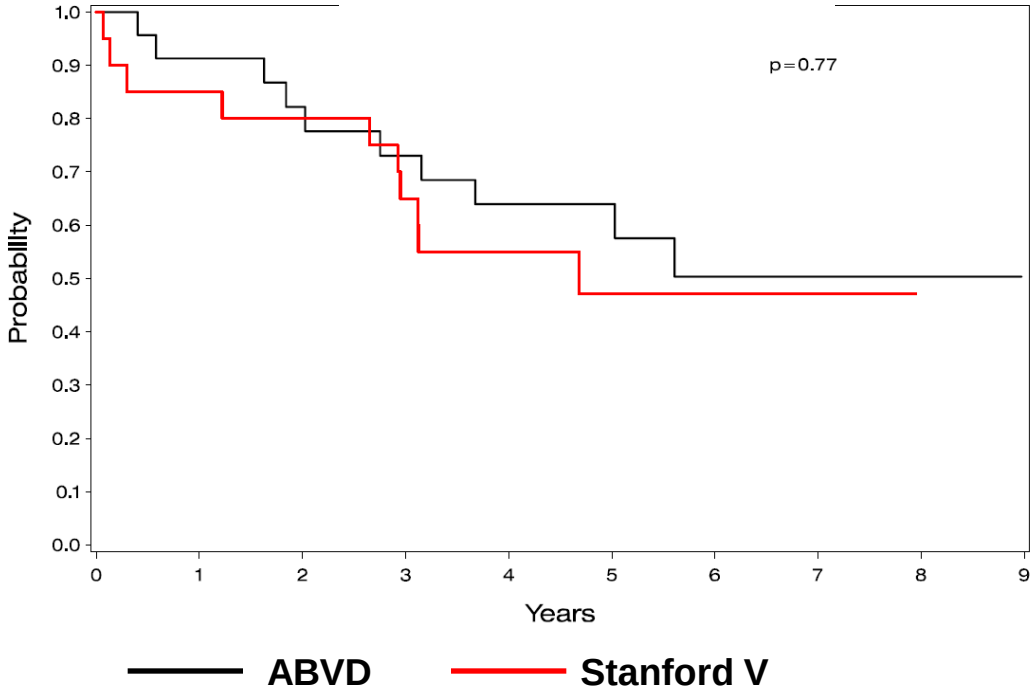
2 Fatalities

Survival: ABVD vs Stanford V

Failure-free survival

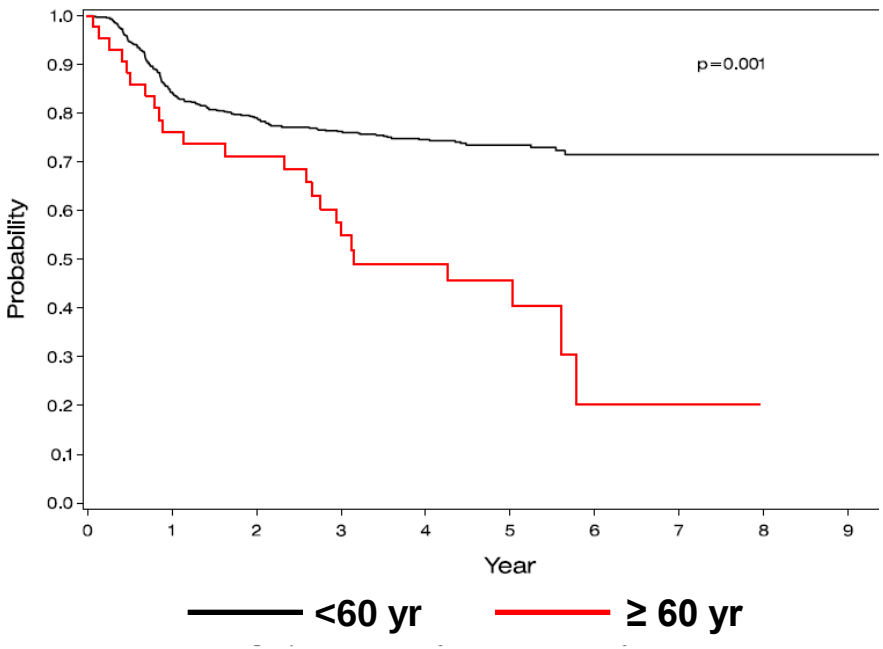


Overall survival

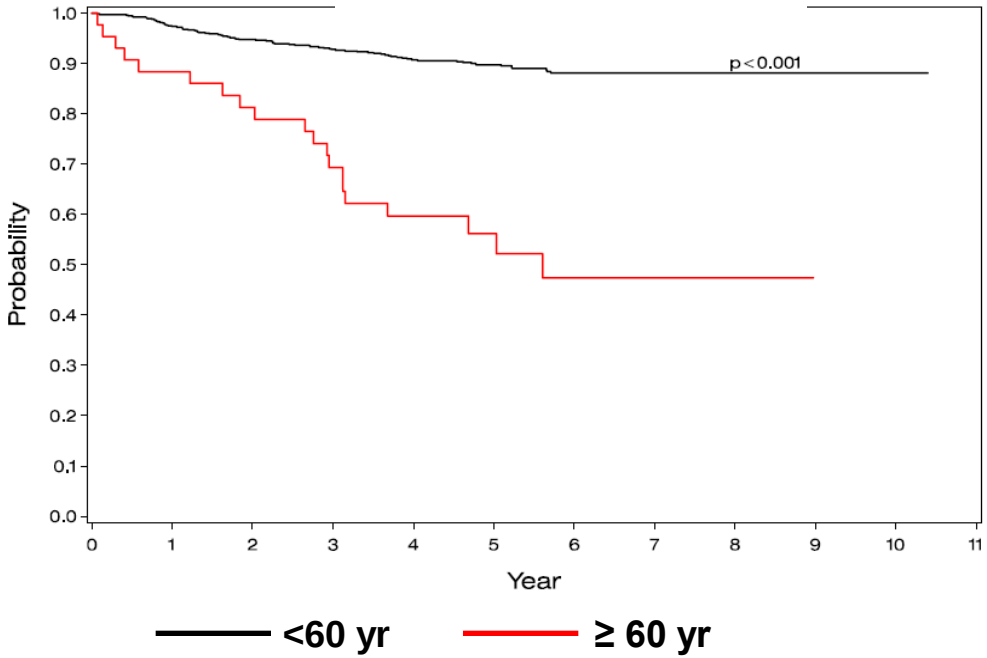


Survival: Older vs Younger HD

Failure-free survival



Overall survival



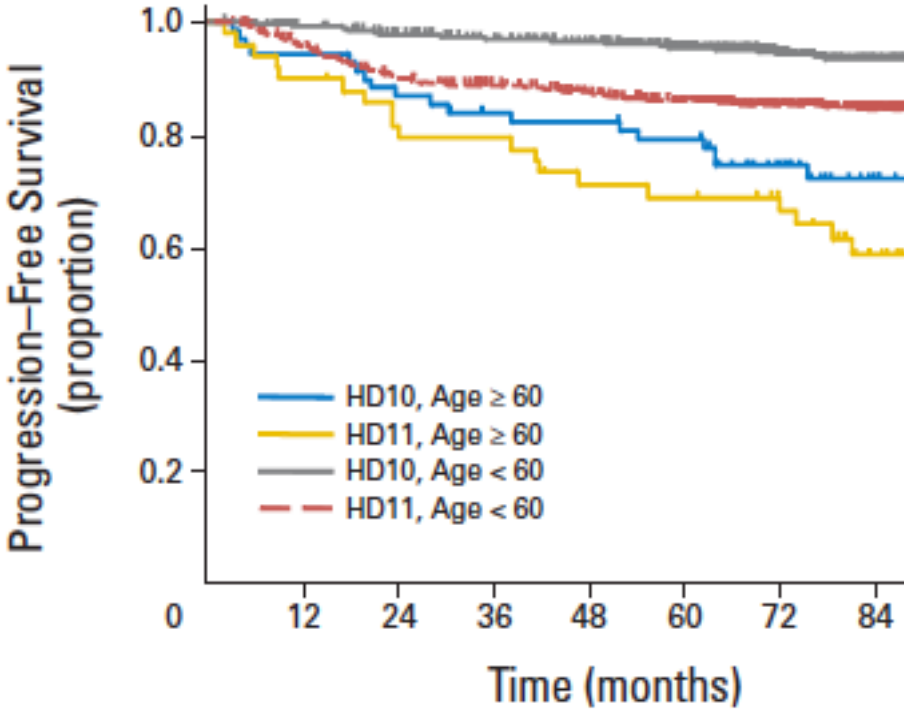
		< 60 years	=/> 60 years	P
FFS	3-year	76%	56%	0.002
	5-year	74%	48%	
OS	3-year	93%	70%	<0.0001
	5-year	90%	58%	

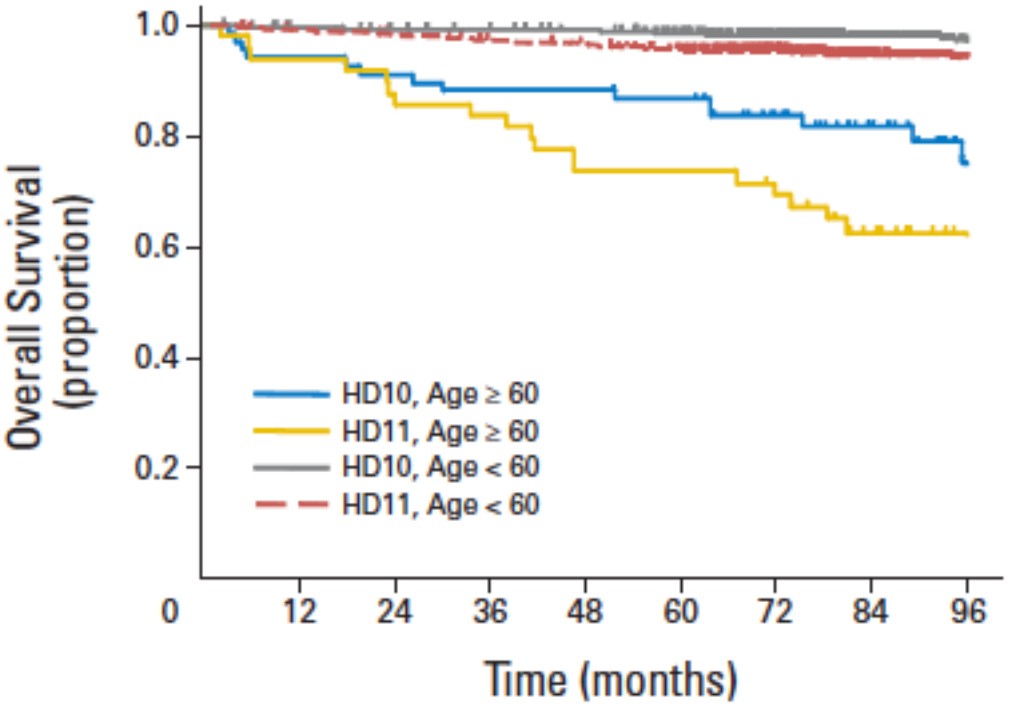
Early-stage HD: GHSG

- **HD10 and HD11: 68 and 49 elderly HD pts (median ages 65 and 64 years)**
- **HD10: 2-4 ABVD + 20-30 Gy**
- **HD11: ABVD vs BEACOPP(base) + 20/30Gy**
- **WHO grade 3/4 toxicities: 68% (grade 4) 18%**
- **TRM of 5% (vs 0.4% in age <60 years)**
- **CR rate 89% (vs 95% younger pts, p=0.001)**

Boll B et al. JCO 2013; 31:1522-29

Early-stage HD: GHSG



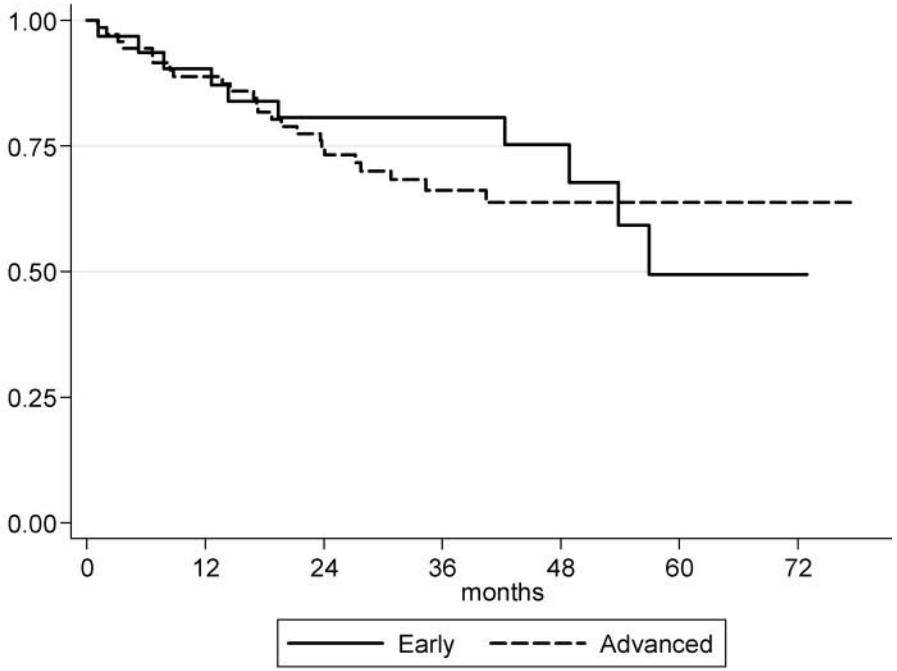


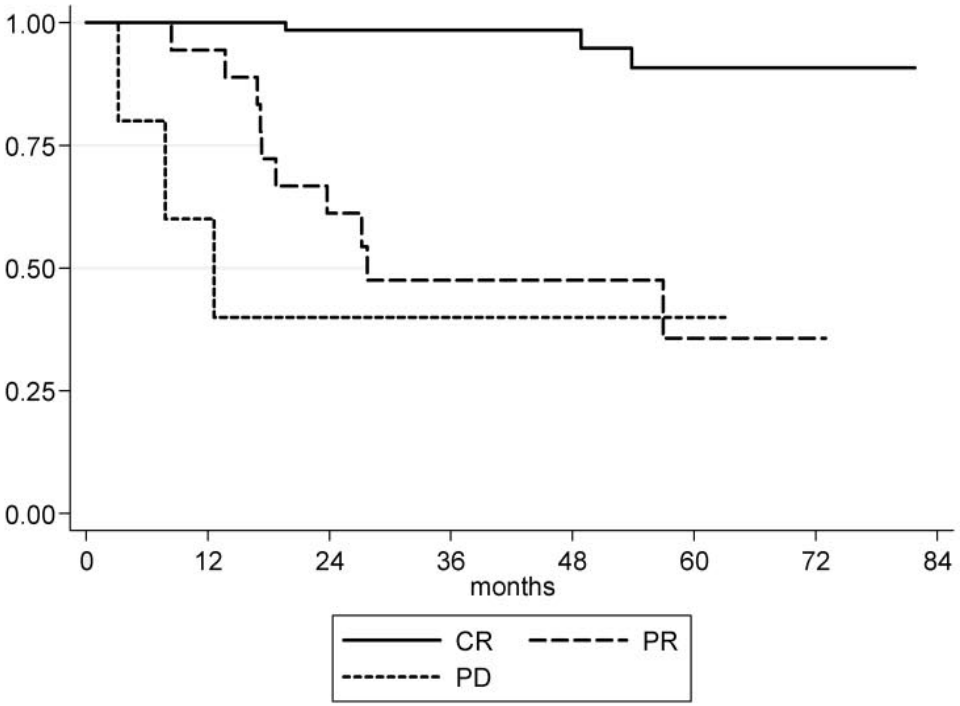
Boll B et al. JCO 2013; 31:1522-29

Current/Future Directions

SHIELD Programme

- **VEPMB (n=103): median age 72 years**
- **CR rate: 75% for ES and 61% for AS**
- **3-year OS and PFS of 66% and 58%,**





CR: Hgb, ADL, IDL, Comorbid, PS, albumin

Proctor S et al. Blood 2012

Other Regimens for Older Patients

- **CHOP**
  - **29 pts (11 stage I/II; 18 stage III/IV); median age 71 years (60–91) treated with 2-4 cycles + XRT or 6-8 cycles of CHOP**
- **PVAG**
  - **RDI 88%; ORR 81% (CR 78%); TRM 2%**
  - **Advanced stage pts: 3-year PFS 58% and 30-year OS 64%**

Kolstad et al. Leuk Lymphoma. 2007; 48:570

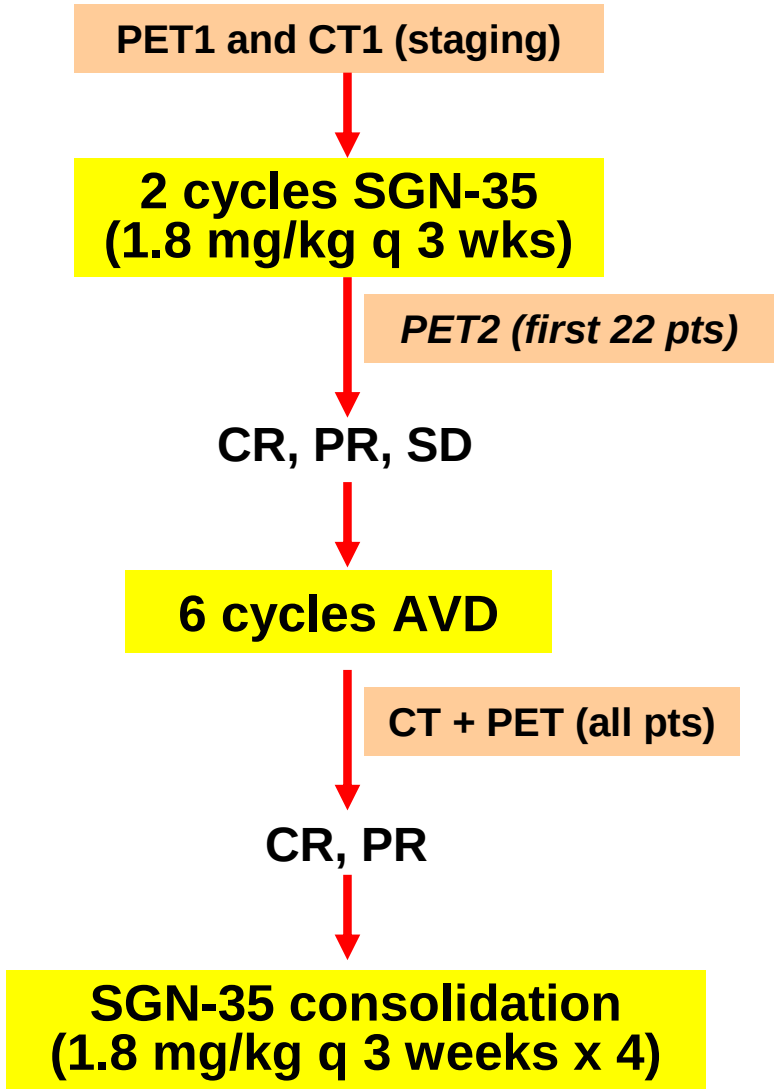
Boll B et al. Blood 2011

Brentuximab vedotin in older HD pts

- **Clinical trials SG035-0001 to SGN35-008**
- **N=16 pts (median age 66, range 60-82)**
- **Versus young pts: worse PS, creatinine, co-morbidities, con meds, and prior cancer Rx**
- **More anemia (30% vs 10%), sensory PN (60% vs 46%), fatigue (58% vs 43%), and any grade 3/4 (70% vs 56%)**
- **ORR 56%, median OS 12.4 months (2-yr 48%)**
- **No factors predicted response or toxicity (besides prior hx of AEs)**

Gopal A. Leuk and Lymph 2014

Incorporation of SGN-35 into Frontline Therapy



- Phase II investigator-initiated study
- Untreated advanced-stage elderly HD (=/> 60 yo)
- Participating institutions: Tufts, Northwestern, Univ. of Chicago, MSKCC, Ohio State, MDACC, Stanford Nebraska, and UMass
- Window (lead in) study with SGN-35
- Tissue based studies
- CGA (CIRS-G) and HRQL assessments
- Study of “early” FDG-PET

Pancreatitis in patients treated with brentuximab vedotin: a previously unrecognized serious adverse event

Characteristics	*Data*
Median age (years)	45 (range: 23-65)
Gender	Male (n=4); female (n=4)
Indication	cHL (n=7); ALCL (n=1)
Median number of BV doses	2 (range, 1-3)
Median BV dose	150 mg (range: 85-180 mg)
Median onset from most recent dose	12 days (range: 9-16 days)
Median lipase (u/L)	599 (range: 169-1143)
Severity of pancreatitis AE	Grade 5 (n=2); Grade 4 (n=1); Grade 3 (n=6)

Ghandi MD, et al. Blood. 2014; 123:2895-7

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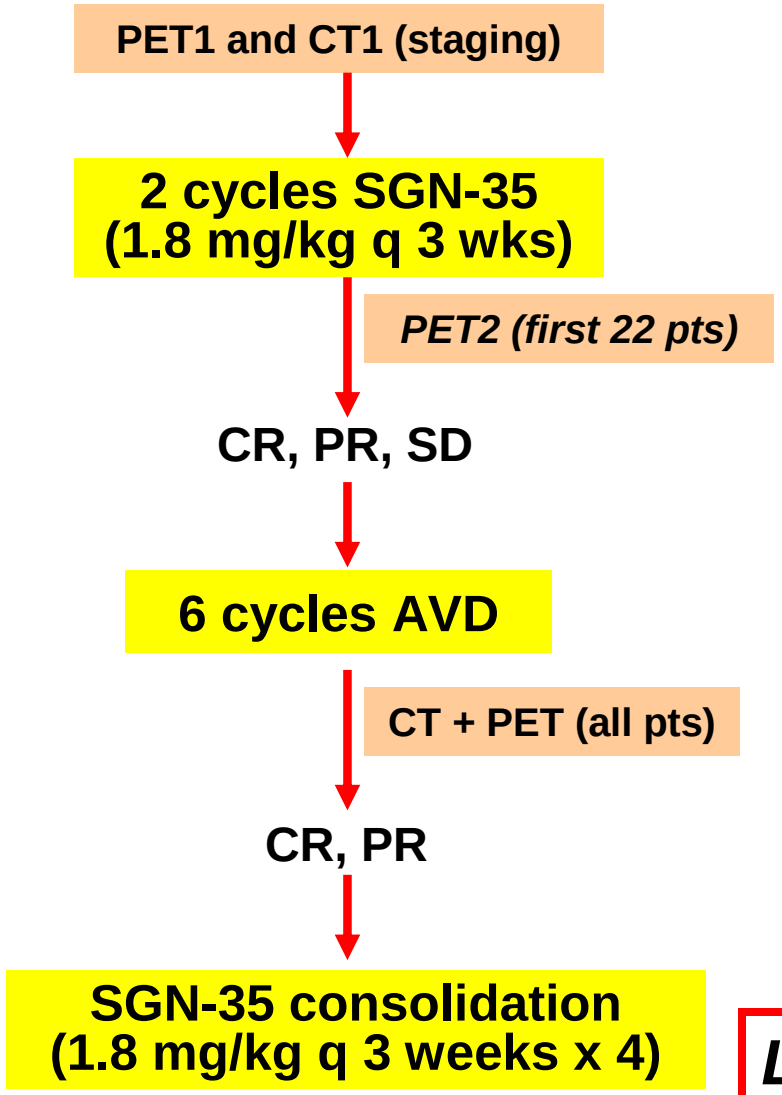

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Lugano, June 2015

Older HD Summary

- Different characteristics/epidemiology
- Outcomes suboptimal with conventional Tx
- Toxicity and TRM (caution re: bleomycin-lung toxicity)
- Recent retrospective prognostic/outcomes
- Ph. II studies: VEPEMB, CHOP, and PVAG
- Need more prospective studies and improved therapeutic options
  - Examine functional tools in elderly (i.e., ? PET)
  - Incorporate co-morbidity and ADL assessments
  - Trials examining integration of novel agents


Ciao, Grazie