

Bendamustine: A “Transversal”* Chemotherapy Agent

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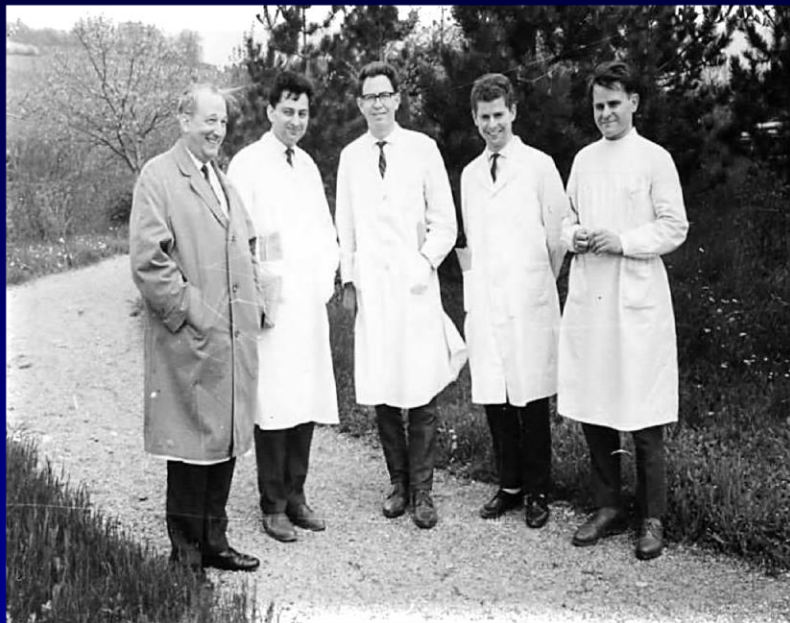
*Def – Cutting across two lines, intersecting

Bendamustine: Background

- Developed in the 1960s in East Germany as a “bifunctional” alkylating agent
- Non-cross resistant with other alkylating agents
- Induces more durable DNA damage than other alkylating agents, resulting in rapid cell death through apoptosis and mitotic catastrophe
- German studies showed single-agent activity in NHL, CLL, multiple myeloma, and breast cancer

Birth certificate of Bendamustine: 1962

„Parents“



Ozegowski & coworkers

die Struktur von Cytostasen u. ähnlichen Derivaten

$$\begin{array}{c}
 \text{Cl-CH}_2\text{CH}_2 \\
 | \\
 \text{N} \\
 | \\
 \text{Cl-CH}_2\text{CH}_2
 \end{array}$$

alkylierende Stickstofflastgruppe

CN1C=NC2=C1C=CC=C2C3=NC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10C11=CC=CC=C11C12=CC=CC=C12C13=CC=CC=C13C14=CC=CC=C14C15=CC=CC=C15C16=CC=CC=C16C17=CC=CC=C17C18=CC=CC=C18C19=CC=CC=C19C20=CC=CC=C20C21=CC=CC=C21C22=CC=CC=C22C23=CC=CC=C23C24=CC=CC=C24C25=CC=CC=C25C26=CC=CC=C26C27=CC=CC=C27C28=CC=CC=C28C29=CC=CC=C29C30=CC=CC=C30C31=CC=CC=C31C32=CC=CC=C32C33=CC=CC=C33C34=CC=CC=C34C35=CC=CC=C35C36=CC=CC=C36C37=CC=CC=C37C38=CC=CC=C38C39=CC=CC=C39C40=CC=CC=C40C41=CC=CC=C41C42=CC=CC=C42C43=CC=CC=C43C44=CC=CC=C44C45=CC=CC=C45C46=CC=CC=C46C47=CC=CC=C47C48=CC=CC=C48C49=CC=CC=C49C50=CC=CC=C50C51=CC=CC=C51C52=CC=CC=C52C53=CC=CC=C53C54=CC=CC=C54C55=CC=CC=C55C56=CC=CC=C56C57=CC=CC=C57C58=CC=CC=C58C59=CC=CC=C59C60=CC=CC=C60C61=CC=CC=C61C62=CC=CC=C62C63=CC=CC=C63C64=CC=CC=C64C65=CC=CC=C65C66=CC=CC=C66C67=CC=CC=C67C68=CC=CC=C68C69=CC=CC=C69C70=CC=CC=C70C71=CC=CC=C71C72=CC=CC=C72C73=CC=CC=C73C74=CC=CC=C74C75=CC=CC=C75C76=CC=CC=C76C77=CC=CC=C77C78=CC=CC=C78C79=CC=CC=C79C80=CC=CC=C80C81=CC=CC=C81C82=CC=CC=C82C83=CC=CC=C83C84=CC=CC=C84C85=CC=CC=C85C86=CC=CC=C86C87=CC=CC=C87C88=CC=CC=C88C89=CC=CC=C89C90=CC=CC=C90C91=CC=CC=C91C92=CC=CC=C92C93=CC=CC=C93C94=CC=CC=C94C95=CC=CC=C95C96=CC=CC=C96C97=CC=CC=C97C98=CC=CC=C98C99=CC=CC=C99C100=CC=CC=C100

$\cdot 4\text{Cl} \cdot \text{H}_2\text{O}$

CH_3

Purinanalogon (2)
Buttersäurerest
Benzimidazol

1964-1970 präklinische u. 1. klinische Pr. Stufe I

1970-1980 klinische Prüf. Stufe I u. II, Produktion bei Jenapharm, Aufnahme in's 2. AB (DDR)

1979 Dr. Ozegowski geht in Ruhestand

1979 Dr. Werner setzt die „Produktpflege“ fort

Entwicklung eines i.v.-Präparates (Lyophilisat Bendamustin + Mannitol)

1980-1990 Ständige Lieferschwierigkeiten von Jenapharm
Klinische Prüfungen in Erfurt, Jena, Potsdam u. Charité weiterhin erfolgreich
Die Streichung von Cytostasen aus dem 2. AB (DDR) konnte erst nach Übernahme der letzten Synthesestufe (Chlorierung zur N-Lost-Verb.) und Lyophilisierung im BCG-Institut des ZIMET verhindert werden.

1990 Jenapharm bekommt neues Profil u.

Conceptual idea:


to improve cytostatic effectivity by combining alkylating and anti-metabolite properties in one substance

Bendamustine: First Clinical Trial 1967



Anger, G., Hesse, P., Köhler, P. et al.
Deutsches Gesundheitswesen 22 (1967) 1079-1084

First clinical trial in 11 patients with leukemias and lymphomas and 4 patients with solid tumors

Jenapharm 

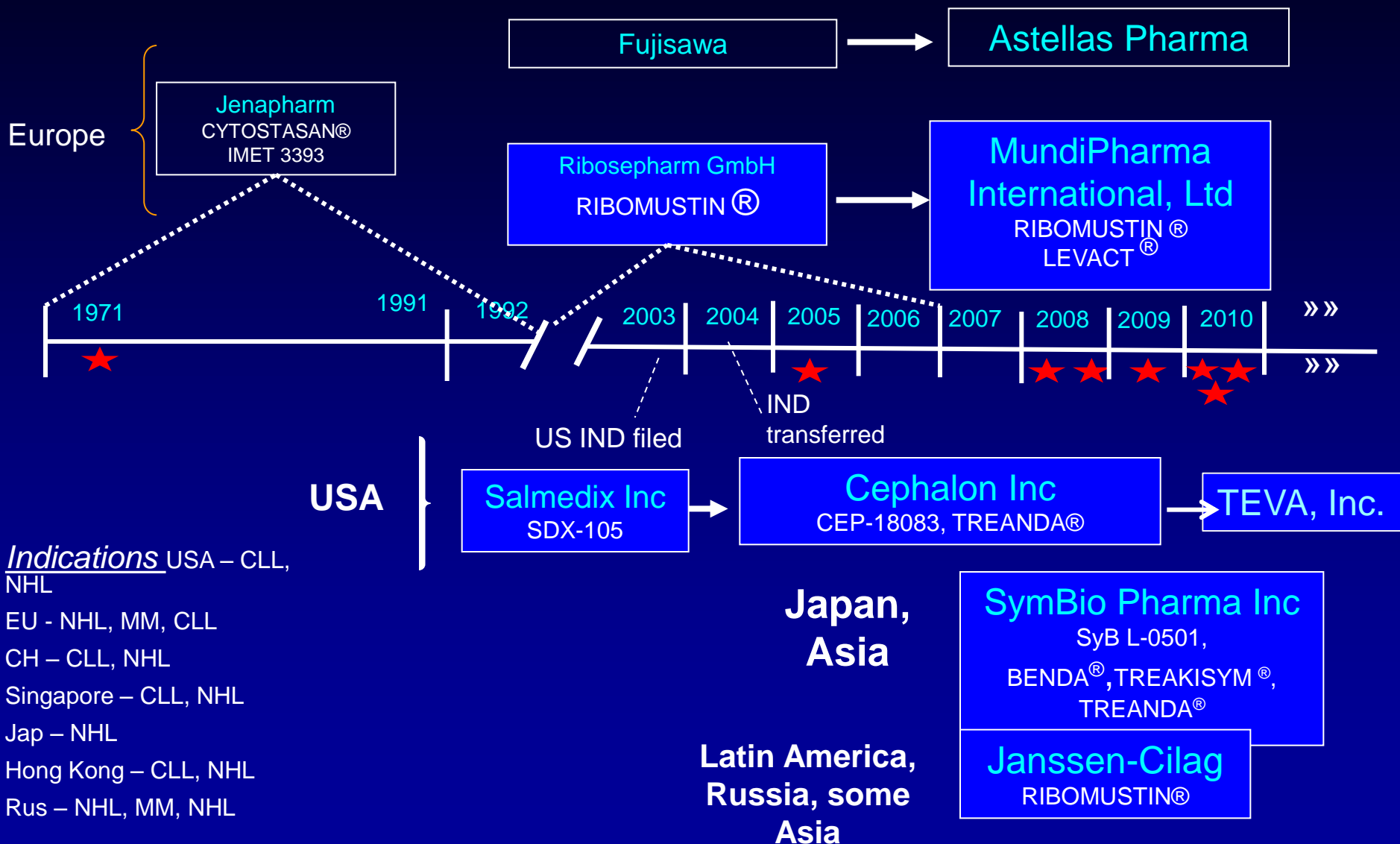
Bendamustine: produced and commercialized by Jenapharm from 1971 to 1992



Bendamustine in the US: Historical Perspective

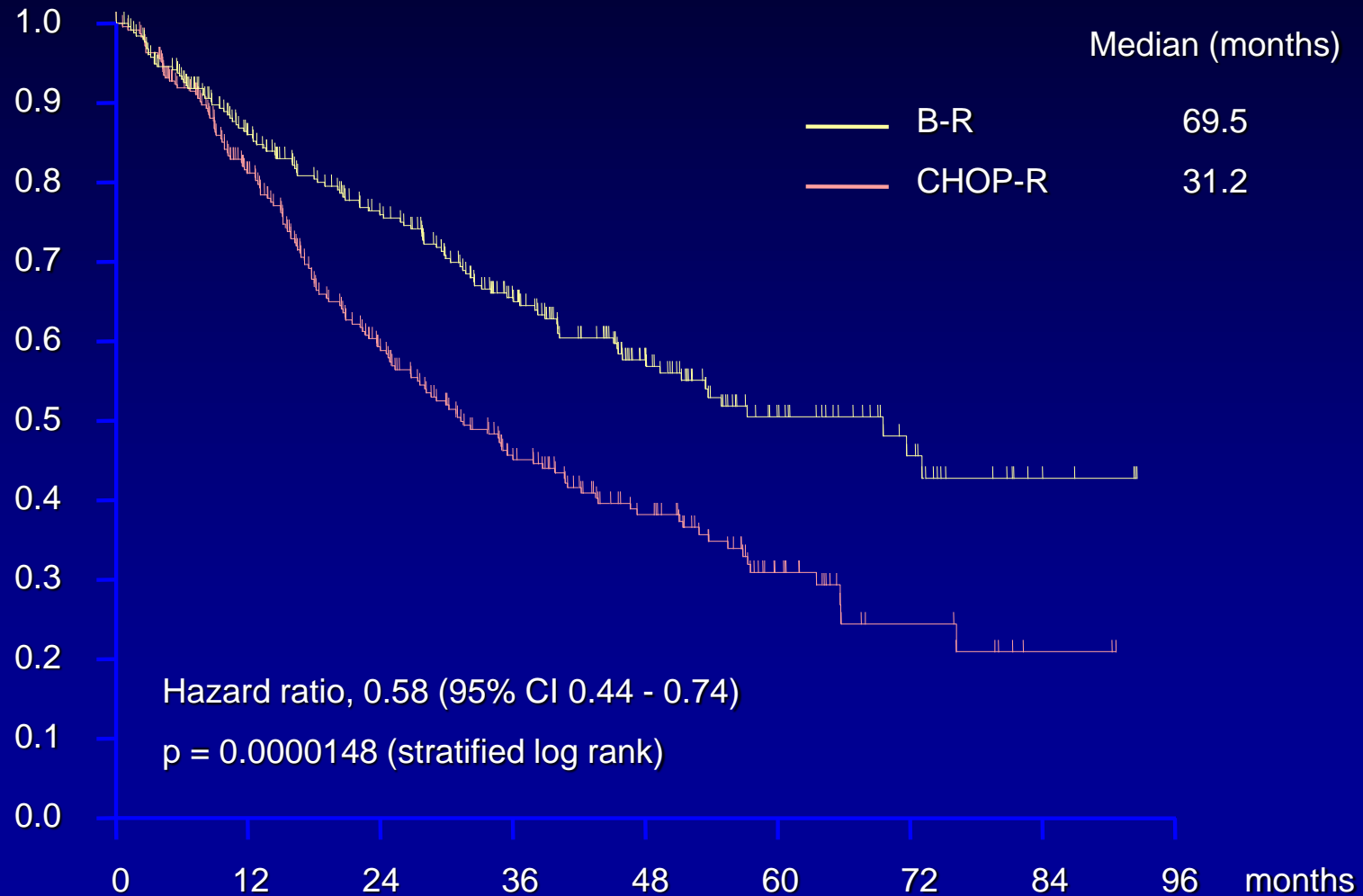
- March 2000 - meeting with Ribosepharm (A. Pieper) at German Cancer Congress in Berlin
- October 2001 - Satellite Symposium to ECCO in Lisbon brought together East/West
- May 2002 - meeting between Ribosepharm and Salmedix
- Sept 29, 2003 - First patient entered onto a clinical trial with bendamustine in the US
- March 30, 2008 - Bendamustine approved by FDA for CLL
- October 31, 2008 – Approved for rituximab refractory F-NHL

Bendamustine: The Long and Winding Road...



Progression free survival

45 months follow-up

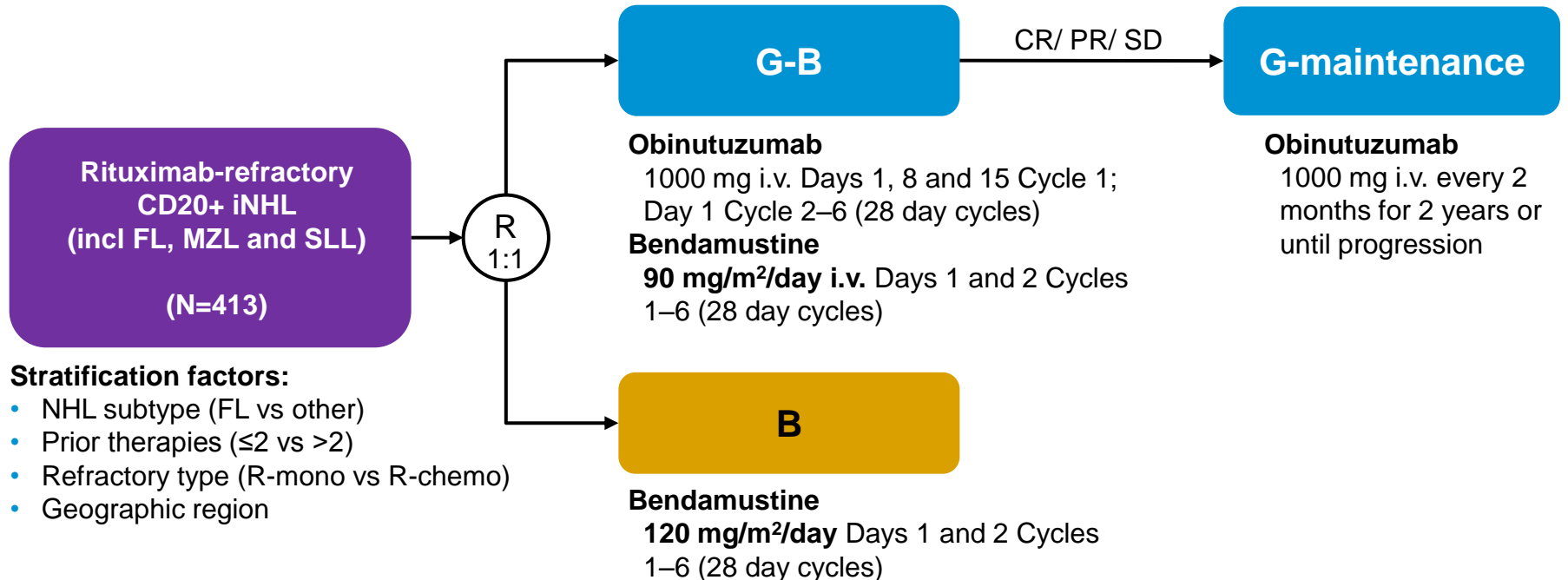


BRIGHT: Response Rates

IRC Assessment of Response by Histology, n/N (%)	CR		CR + PR	
	BR	R-CHOP/R-CVP	BR	R-CHOP/R-CVP
iNHL	49/178 (28)	43/174 (25)	173/178 (97)	160/174 (92)
FL	45/148 (30)	37/149 (25)	147/148 (> 99)	140/149 (94)
MZL	5/25 (20)	4/17 (24)	23/25 (92)	12/17 (71)
LPL	0/5	1/6 (17)	3/5 (60)	6/6 (100)
MCL	17/34 (50)	9/33 (27)*	32/34 (94)	28/33 (85)*

*R-CHOP, n=22.

GADOLIN: Study design (NCT01059630)



Stratification factors:

- NHL subtype (FL vs other)
- Prior therapies (≤ 2 vs > 2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

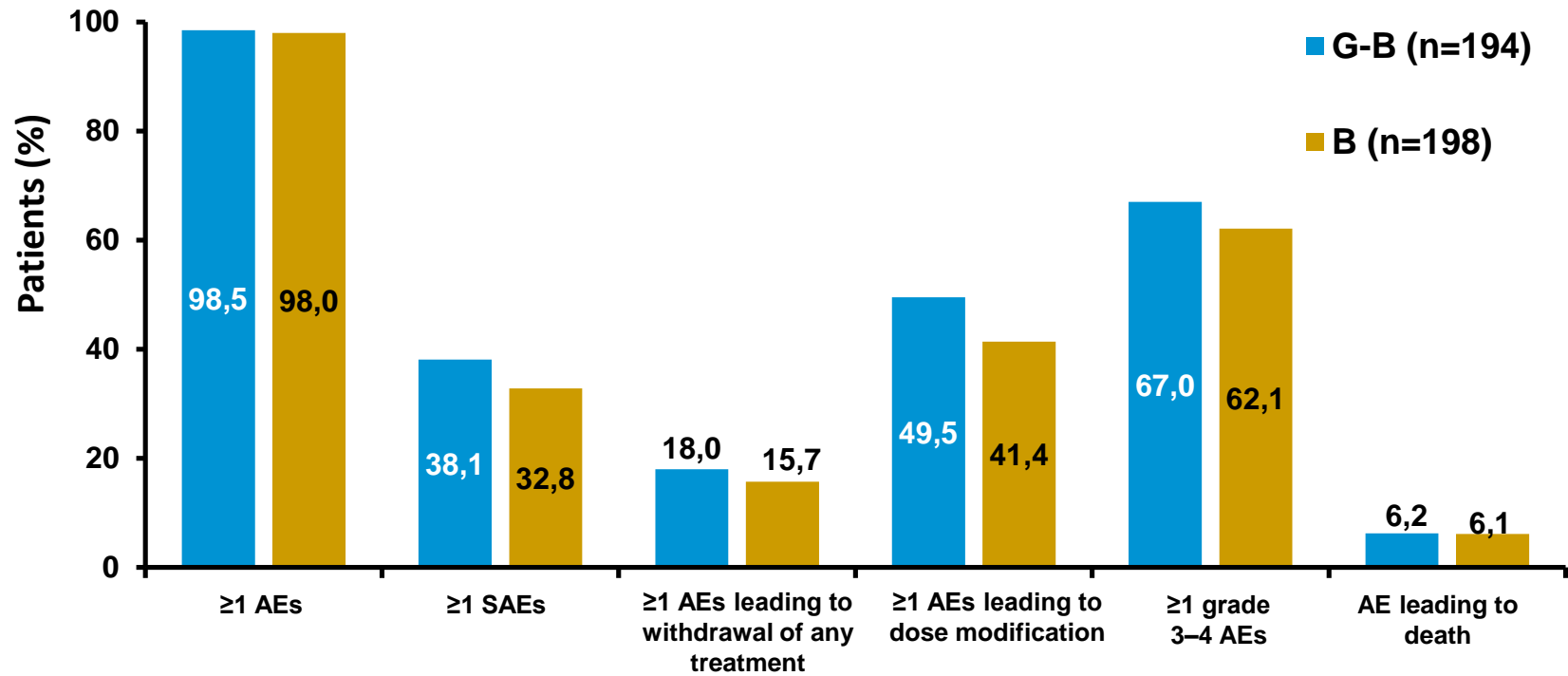
- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months (modified Cheson criteria 2007)

GADOLIN: Baseline characteristics

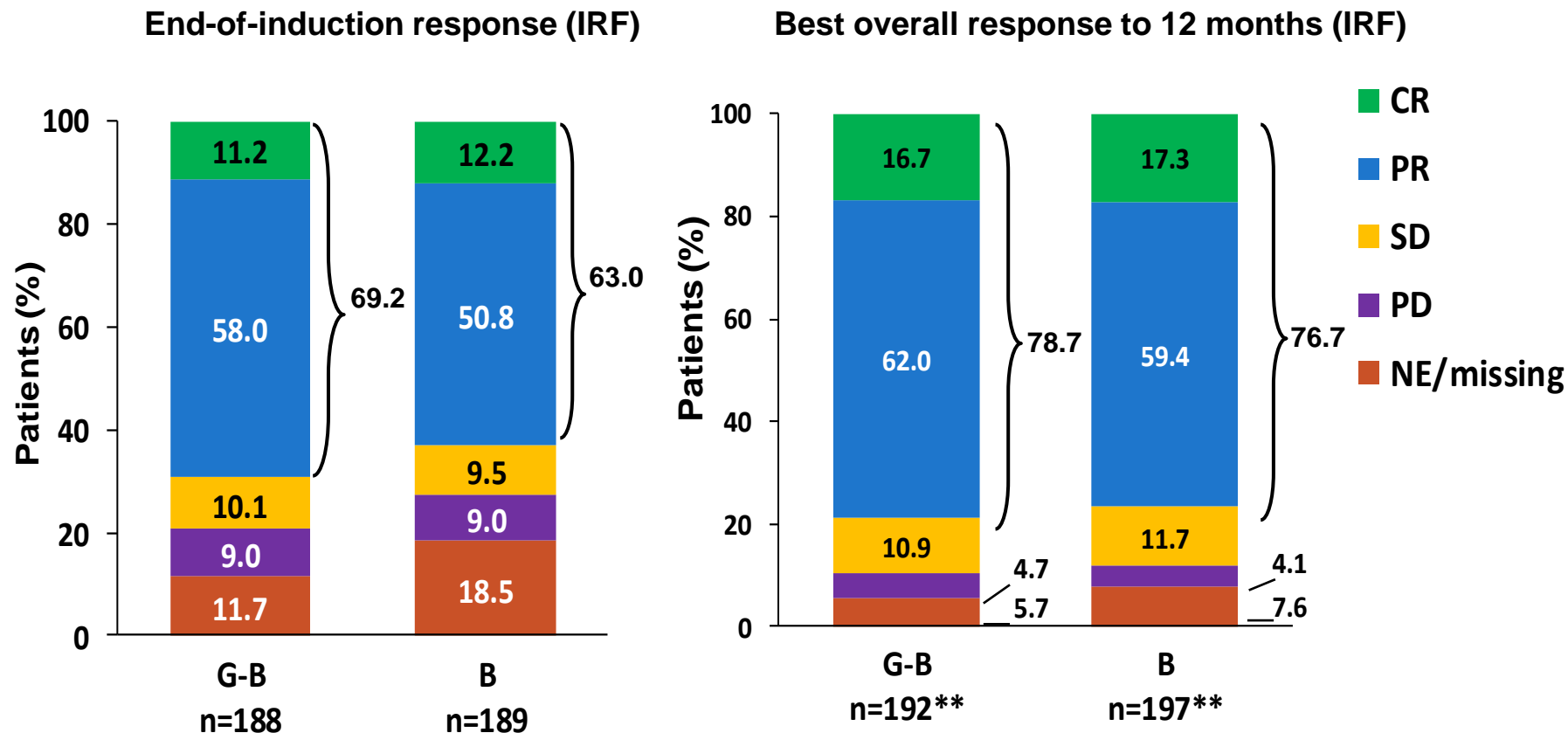
Characteristic	G-B (n=194)	B (n=202)
Mean time from diagnosis to randomization, years (range)	4.2 (0.3–32)	4.2 (0.3–30)
Median prior lines of therapy, n (range)	2 (1–10)	2 (1–7)
Median time since last prior regimen, months (maximum)	4.0 (128.4)	3.7 (64.0)
Number of patients refractory to last treatment, n (%)	178 (92)	187 (93)
Patients double refractory to rituximab and alkylators, n (%)*	147 (76)	164 (81)

* Double refractory to rituximab and an alkylating agent from same or different regimens

GADOLIN: Overview of AEs



GADOLIN: Response to therapy



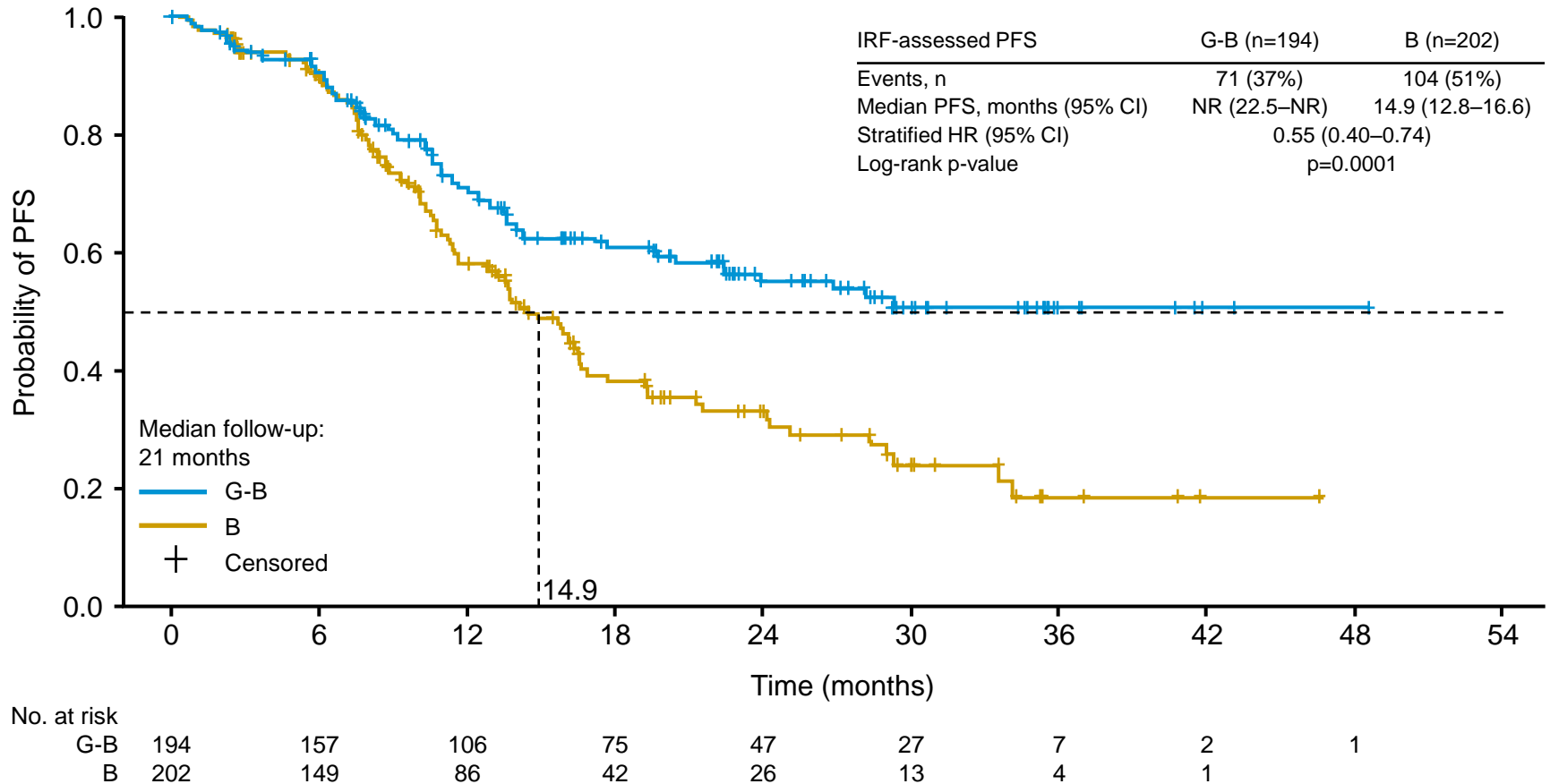
- 19 patients still in induction (G-B, n=6; B, n=13)*

* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

GADOLIN primary outcome: IRF-assessed PFS



Bendamustine: Other Potential Lymphoma Indications

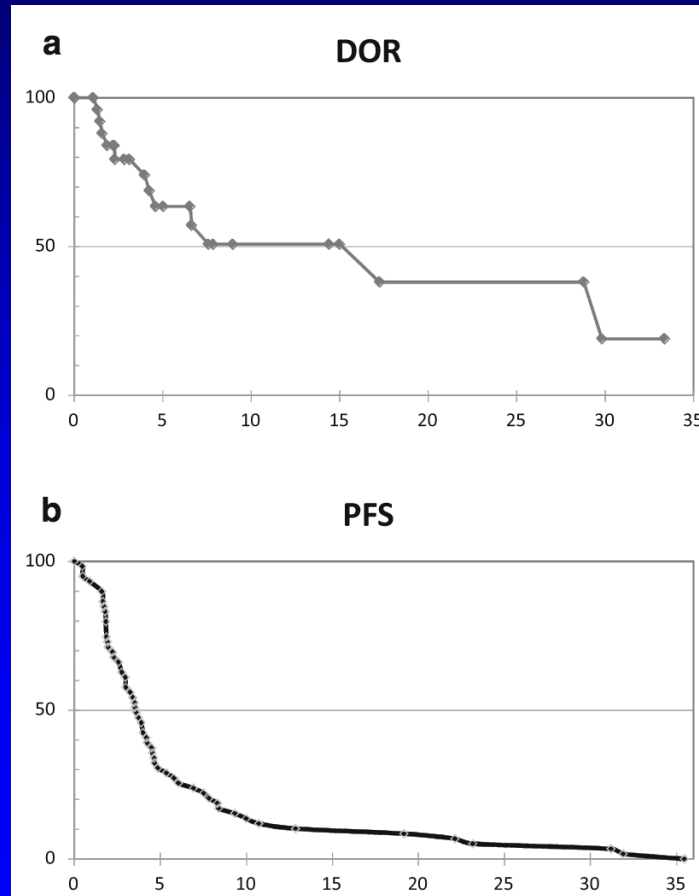
- Diffuse large B-cell lymphoma
- Hodgkin lymphoma
- PTCL

Bendamustine in Aggressive NHL (n=18)

<u>Response</u>	<u>Percent</u>	<u>Duration (mo)</u>
ORR	44	
CR	17	6, 8+, 27+
PR	28	2,2,2,3,10

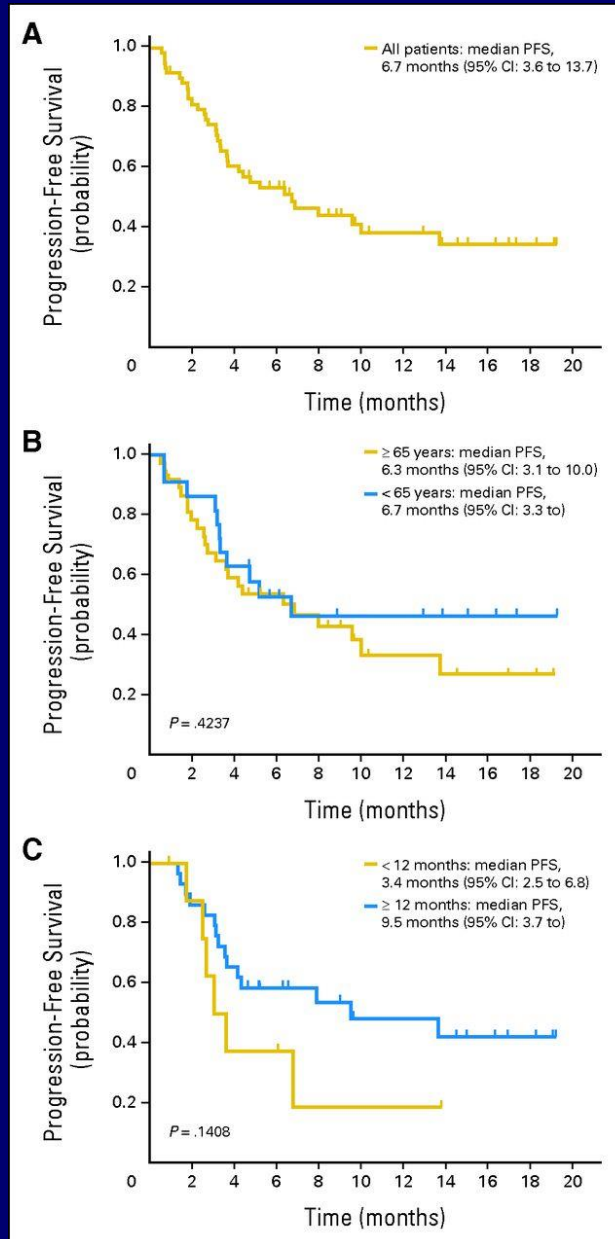
Bendamustine+Rituximab in Elderly Relapsed/Refractory DLBCL

- Benda – 120 mg/m², d 1, 2 + rituximab 375 mg/m² q 28 d
- 59 pts enrolled
- Median age 74 yrs
- ORR 45.8%, CR 15.3%



PFS with BR in R/R DLBCL

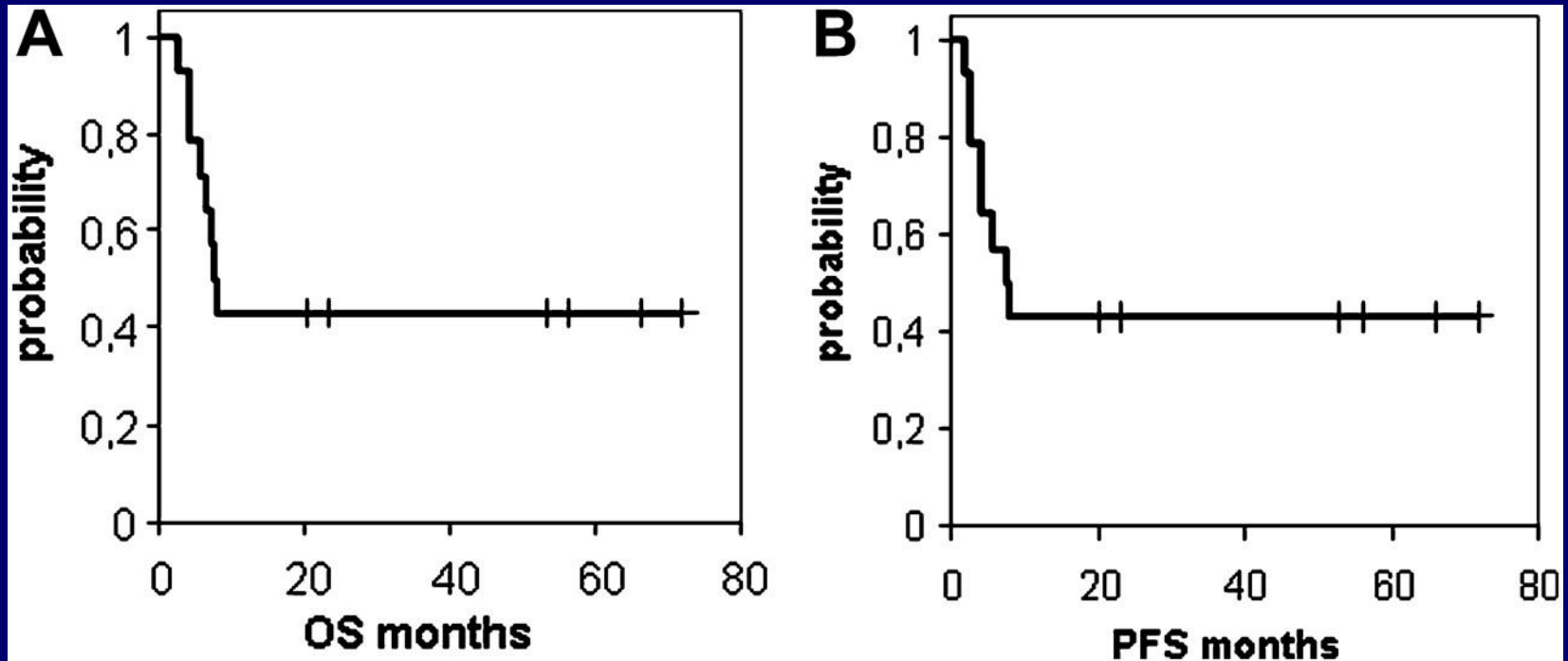
- 63 enrolled, 59 treated
- Median age 67 yrs
- ORR 62.7% (CR 37.3%)



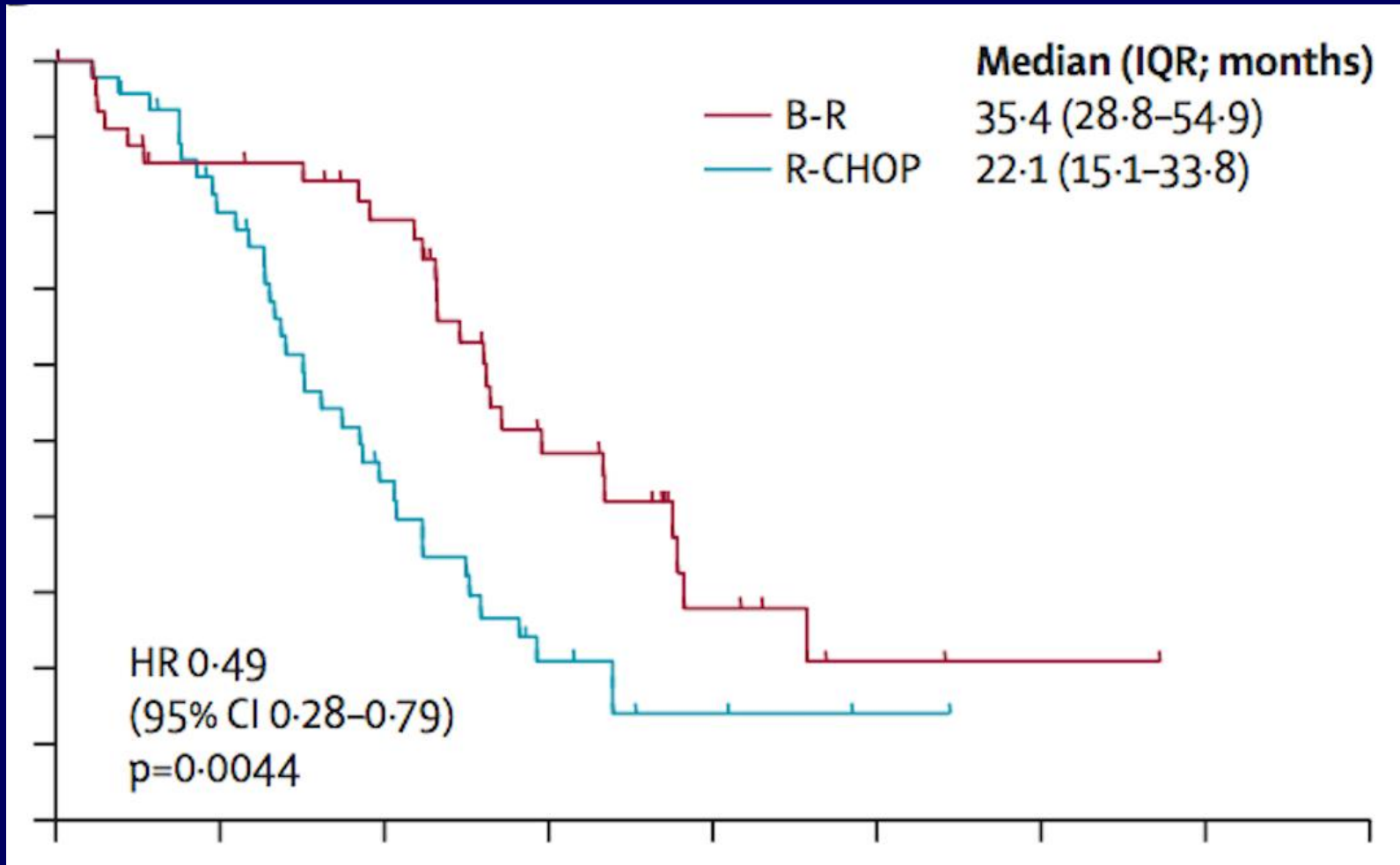
R-Bendamustine in Untreated DLBCL

- 14 pts (\geq 80 yrs; median 85 yrs, 80-95 yrs)
- Not eligible for R-CHOP or refused aggressive tx
- AAIP: 0 (5), 1(3), 2 (6)
- B (120 mg/m² d 2,3), R (375 mg/m² d1), q 21 d
 - Stage I-II – 4 cycles + IFRT
 - Stage III-IV – 6 cycles – 2 doses R
- ORR – 69%, CR 54%
- Mean PFS and OS 7.7 mo
- Well-tolerated (6% gr 4 neutropenia)

Outcome with BR As Initial Treatment of Elderly Patients with DLBCL



BR vs R-CHOP in Untreated MCL



Intergroup Randomized Phase 2 Four-Arm Study in Patients ≥ 60 With Previously Untreated Mantle Cell Lymphoma

- BR \longrightarrow R
- BR \longrightarrow R²
- BVR \longrightarrow R
- BVR \longrightarrow R²

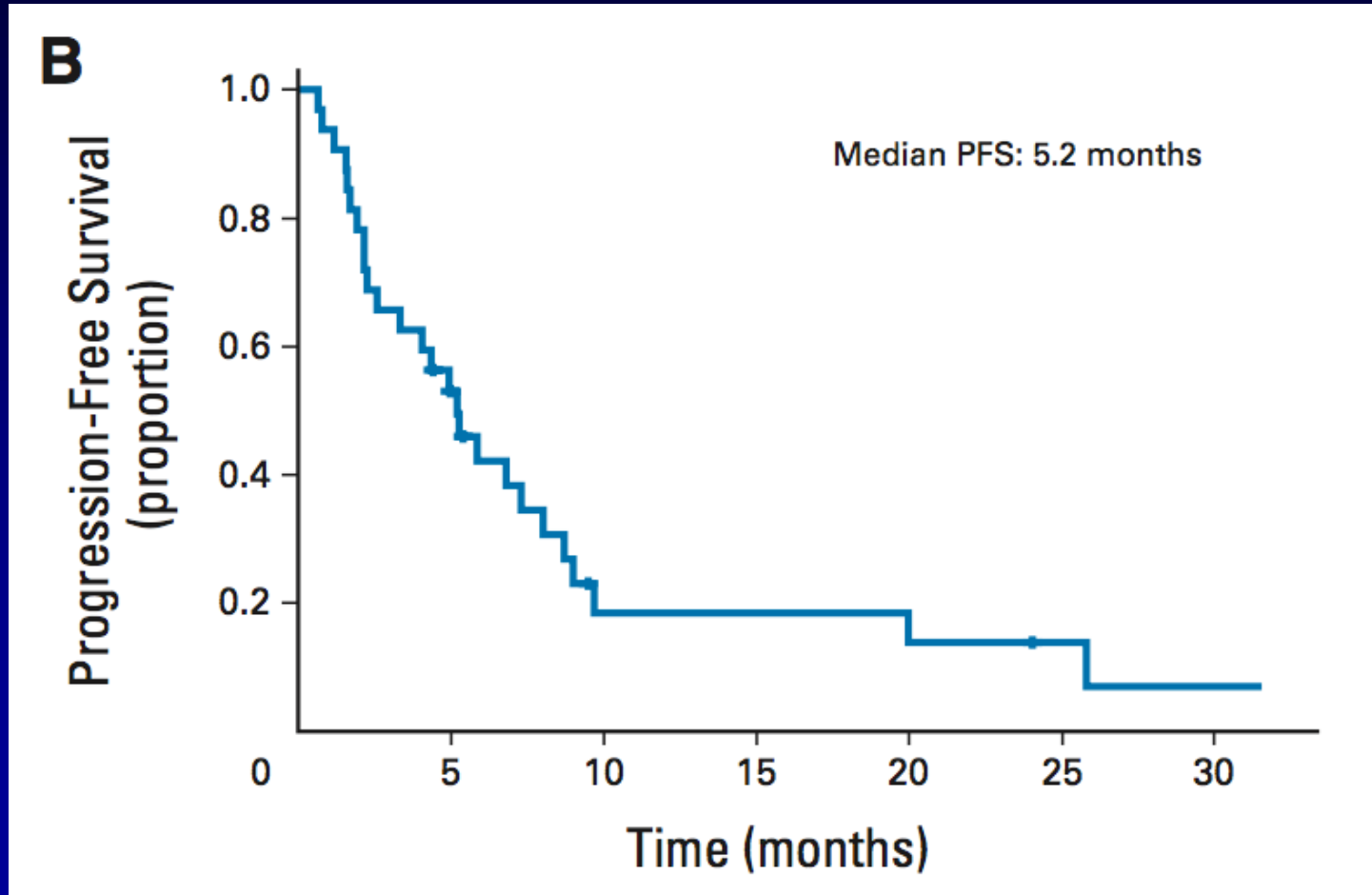
BR vs R-HyperCVAD in MCL

	RHCVAD	BR
Pts	16	35
ORR (%)	94.1	82.9
CR (%)	35	40
2 yr PFS (%)	81	81
2 yr OS (%)	87	87
Failure to collect SCs	5	1

Bendamustine in Hodgkin Lymphoma

- 36 pts, who failed ASCT (75%) or ineligible
- ORR 56%(CR 33%)(No responses if relapse <3 m)
- 5 pts previously ineligible for NMT underwent procedure
- Well-tolerated

Bendamustine in HL

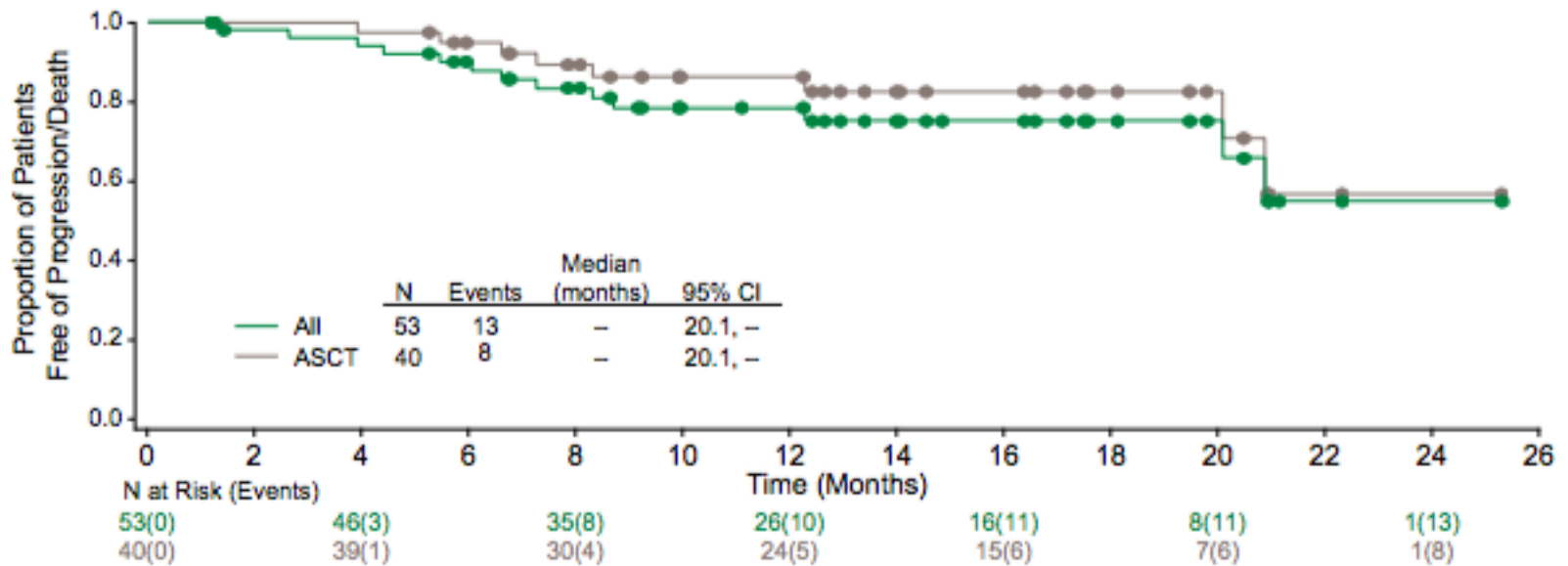


Best Response on Combination Therapy

N=53	n (%)	95% CI
Best clinical response		
Complete remission (CR)	40 (76)	61.7, 86.2
Partial remission (PR)	9 (17)	
Stable disease (SD)	3 (6)	
Progressive disease (PD)	1 (2)	
Objective response rate (ORR [CR + PR])	49 (93)	81.8, 97.9

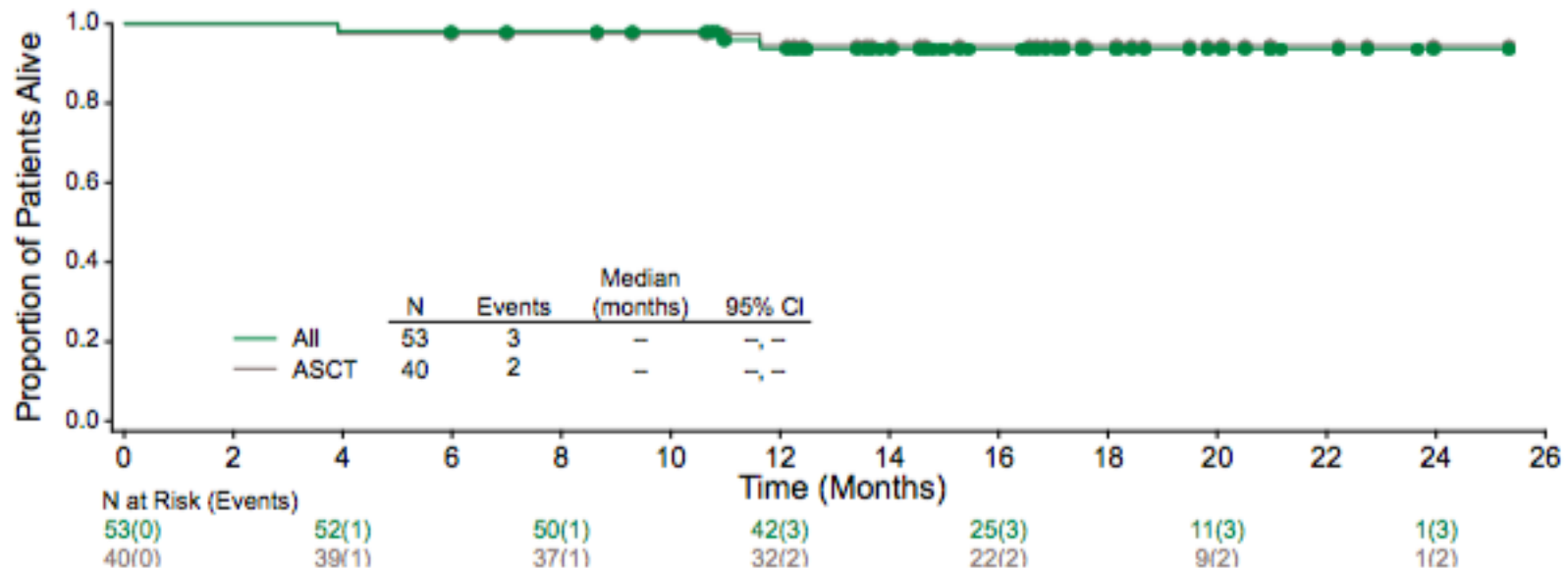
- 76% CR rate and 93% ORR
- CR rates were 88% in relapsed pts and 64% in primary refractory pts

Progression-Free Survival – All Patients and in ASCT Subset



- Overall 18-month PFS rate of 75% (95% CI: 59, 86), 83% in ASCT subset
- 9 of 11 pts (82%) observed ≥ 18 months remain free of progression

Overall Survival – All Patients and in ASCT Subset

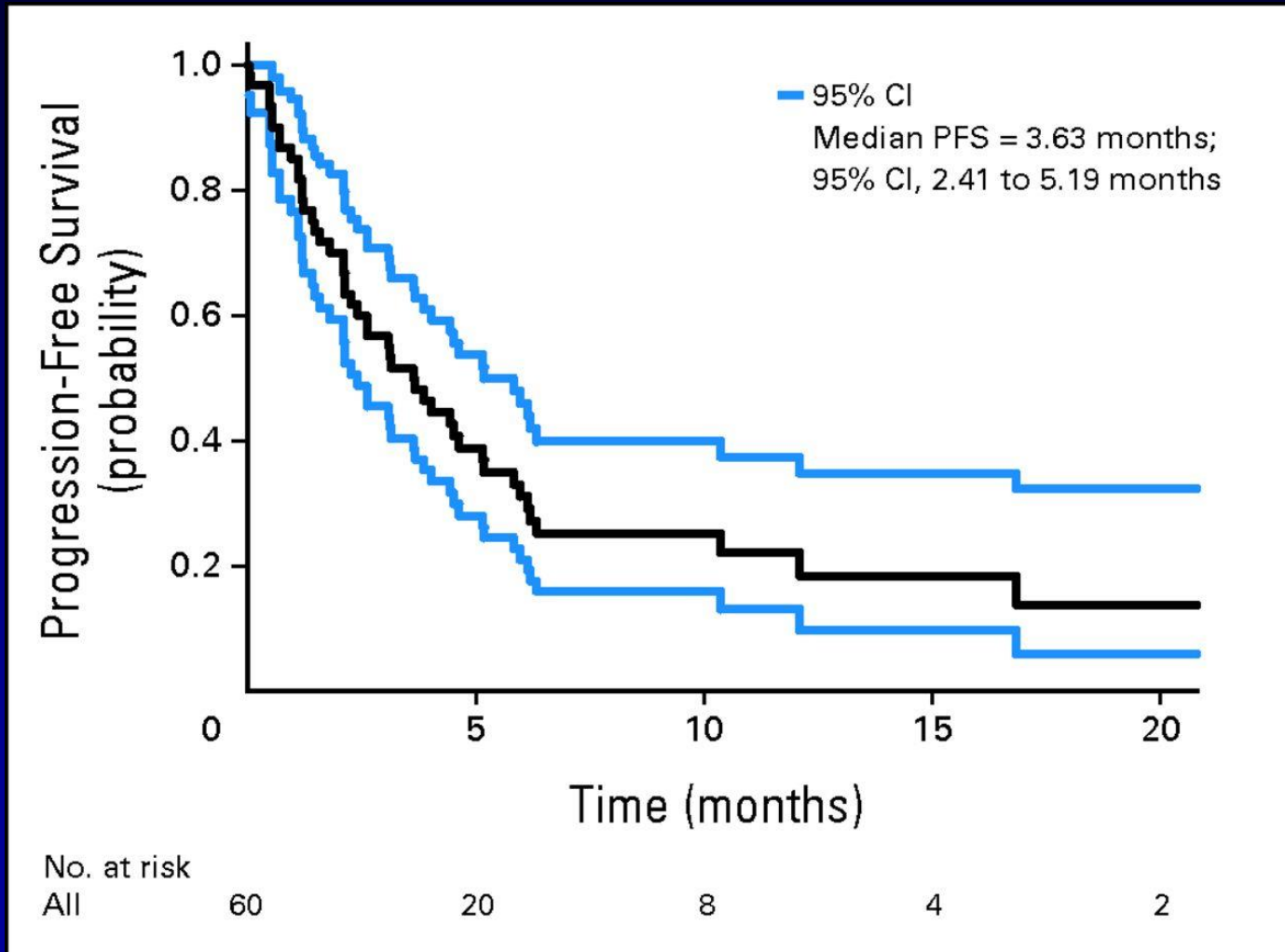


- 3 patient deaths have occurred: 2 pts died from progression of their HL and 1 pt died from septic shock after transplant

Bendamustine in Relapsed/Refractory T-NHL: BENTLEY Trial

- 60 pts: NOS–23; AILD–32; ALCL–2; MF-1; EATL-1
- Median age 66 yr
- Tx – 120 mg/m² d 1,2 q 3 wks
- ORR 50%, 28% CR

PFS With Bendamustine in PTCL

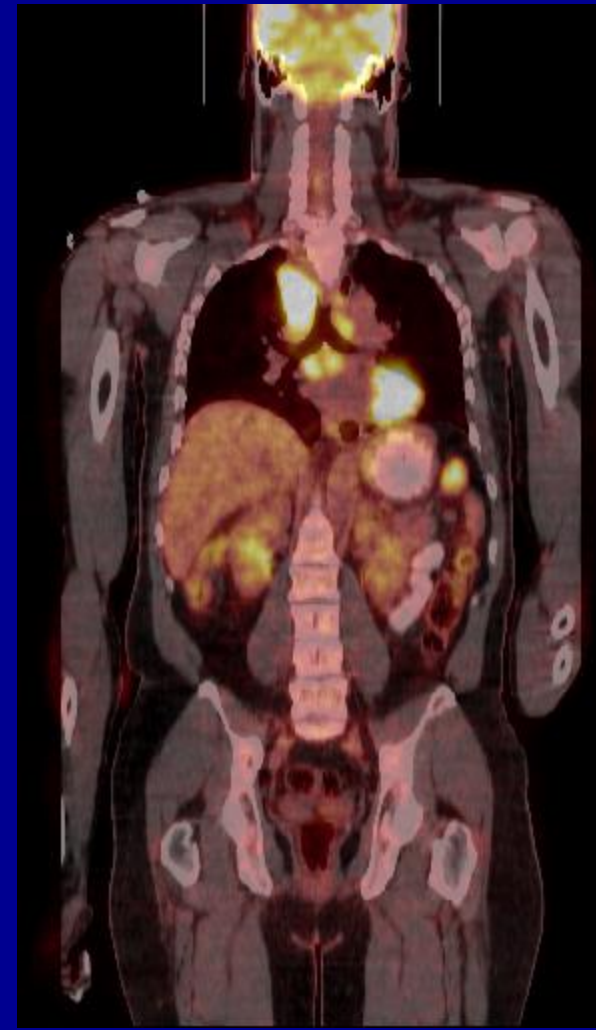
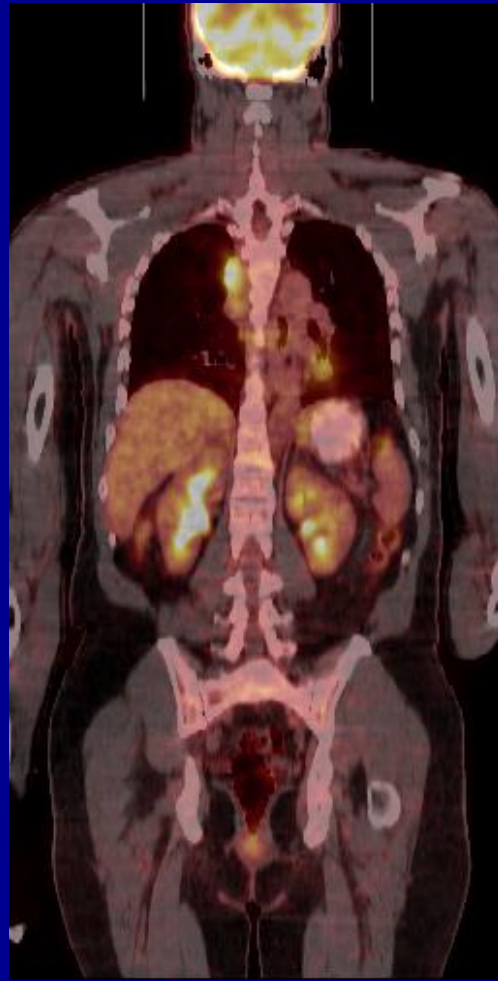
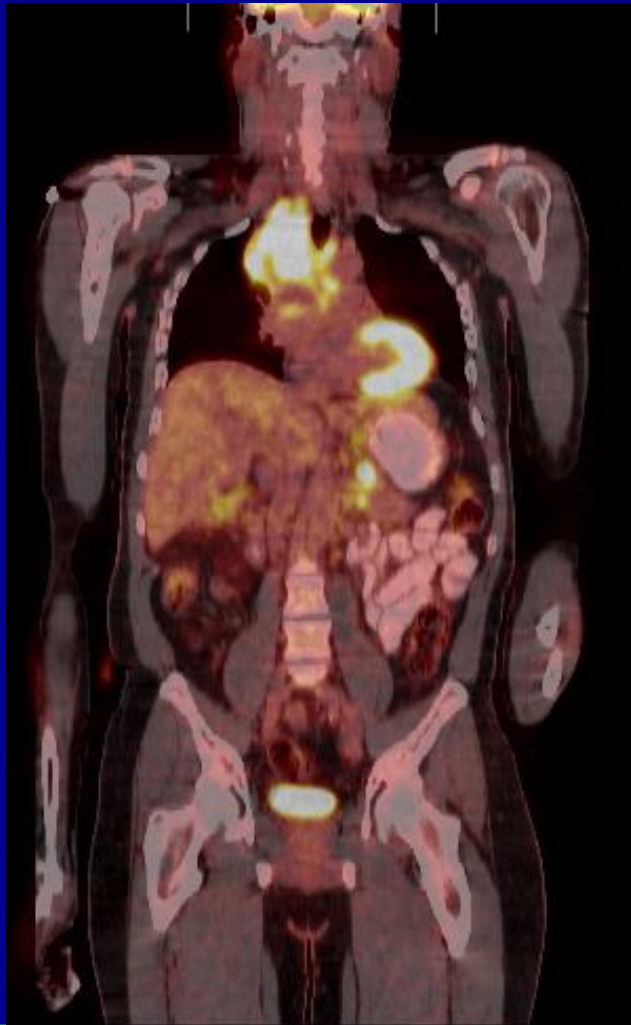


Case – Upfront Follicular



- 51-year-old African American jazz vocalist
- In 2001 a routine CXR for a pre-employment physical revealed a mediastinal mass
 - Biopsy consistent with follicular lymphoma
- CVP to a <PR
- A watch and wait approach was taken
- December, 2011 he returned with hoarseness, fatigue, weight loss, abdominal pain and jaundice.

PET CT



Labs



- Labs
 - total serum bilirubin of 23.4 mg/dL.
 - ALT 93 mg/dL ; AST 74 mg/dL; alk phos 617 mg/dL
 - LDH: 915 mg/dL
- Biopsy – transformed FL to DLBCL
- Bendamustine 90mg/m² on Days 1 and 2, with rituximab 375 mg/m²
- Total bilirubin improved from 24.3 mg/dL at the time of admission to 11 mg/dL at the time of discharge
- Normalized within 2-3 months

Continued Treatment



- Mr. S completed 6 cycles of BR q28 days
- His fatigue, and night sweats resolved completely, as did his hoarseness such that he was able to sing again.
- Refused transplant
- Remains in CR 5 years later

Bendamustine Combinations

- BRL – too toxic Cheson BJH 169:528, 2015
- BOfa – too toxic Ujjani and Cheson Leuk Lymph 56:925, 2015
- BVR – no more effective Fowler et al JCO 29:3389, 2011
- BR-idela – too toxic
- BR-ibrutinib – tolerable
- BR-venetoclax - tolerable

Conclusions

- Bendamustine is newest old/oldest new drug with major activity in hematologic malignancies
- Dominant chemotherapy drug for F-NHL, SLL, MCL
- Backbone of many new regimens in development
- Critical to carefully develop combinations with targeted agents
- Increase its role in improving patient outcome