



CONNECTING LIFE AND SCIENCE

Targeting and treating: Indolent and Hodgkin lymphoma in 2022

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Disclosures

- **Research Funding:** ADC Therapeutics, Autolus, Bristol-Meyers Squibb, Celgene, Forty Seven, Gilead, Janssen, Kite Pharma, Merck, Millennium, Pharmacyclics, Roche/Genentech, SeaGen
- **Advisory Boards:** ADC Therapeutics, Roche/Genentech, SeaGen

Learning Objectives

- **Follicular lymphoma (FL)**
 - Describe outcomes from FOLL12 trial comparing standard R-Maintenance to MRD based maintenance in first-line therapy of FL
 - Discuss efficacy of CAR-T cell therapy and bispecific antibodies for relapsed FL

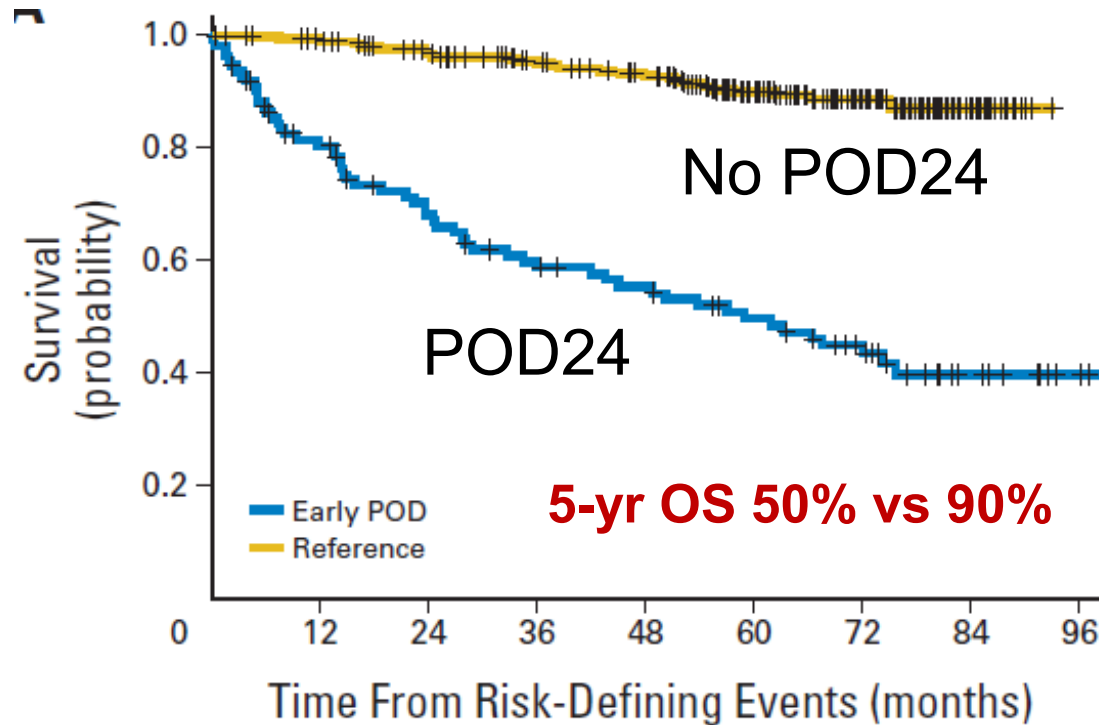
- **Hodgkin lymphoma (HL)**
 - Compare PFS and OS of ABVD and Bv-AVD for first-line therapy of advanced stage HL

Indolent Lymphoma (follicular) 2022

Highlights and controversies

- First-line treatment options
 - R-chemo vs. Obina-chemo
 - Benda vs. CHOP vs. Len
- Maintenance rituximab
- New approaches for relapsed disease
 - **NOT PI3K inhibitors due to worse OS in several randomized trials (Lancet 2022:23:563)**
 - Copanlisib still approved for FL but idelalisib (voluntary), duvelisib (voluntary), umbralisib (FDA) withdrawn
 - Bispecific antibodies
 - CAR-T cell therapy
- Brief summary of marginal zone lymphoma

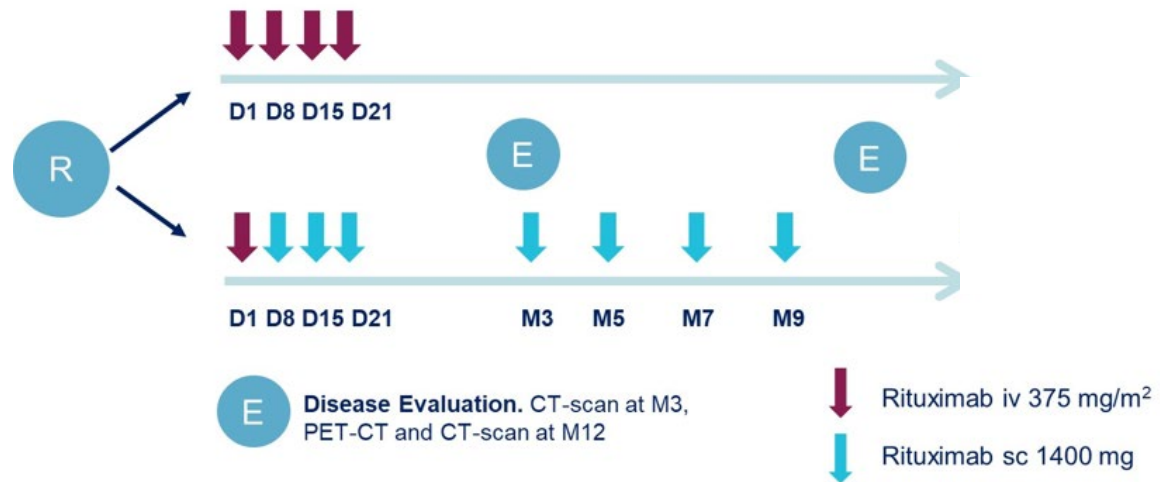
Follicular lymphoma: OS based on POD at 2 yrs



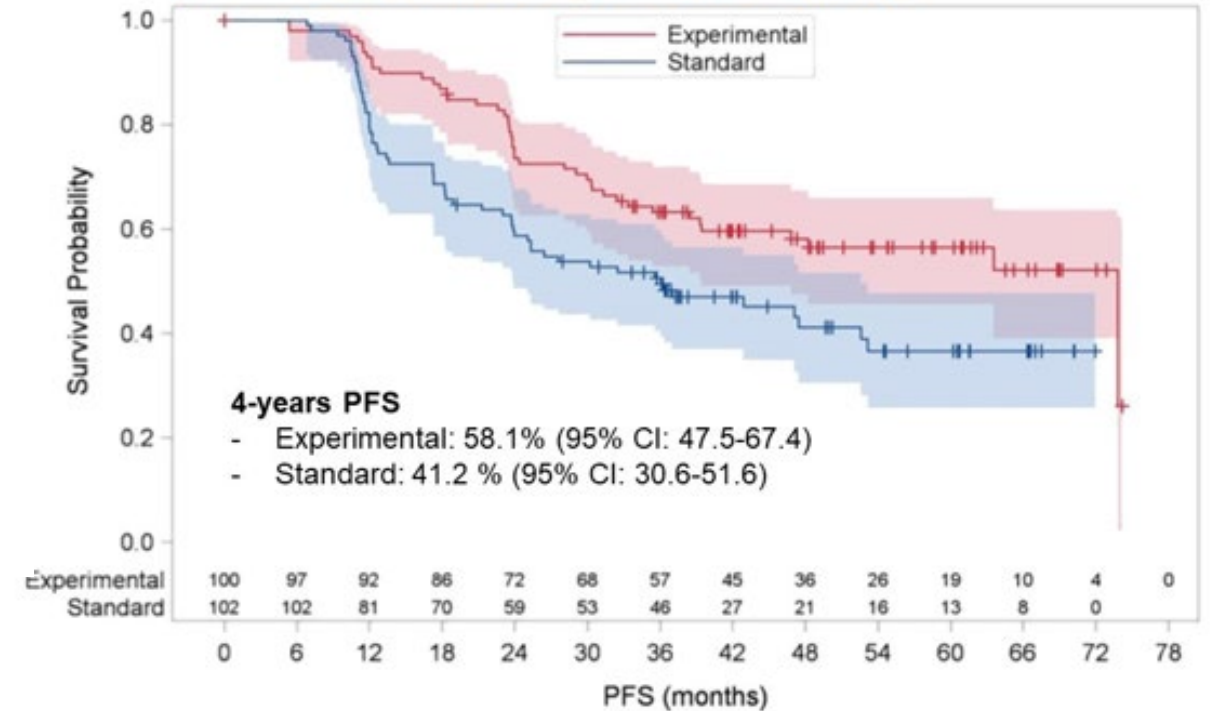
- National Lymphocare Database
- 588 pts with FL, stage II-IV
- Treated with 1st line R-CHOP
- Compared two groups
 - Early POD (progression of dz) within 2 yrs
 - No POD within 2 years
- Trend maintained after FLIPI adjusted

- Pts with early progression (<24 mo) often have transformed DLBCL. BIOPSY
- Pts with 1st remission > 2yrs have OS similar to aged-matched controls.

Low-tumor burden follicular lymphoma : FLIRT phase III SC rituximab induction followed by short rituximab maintenance



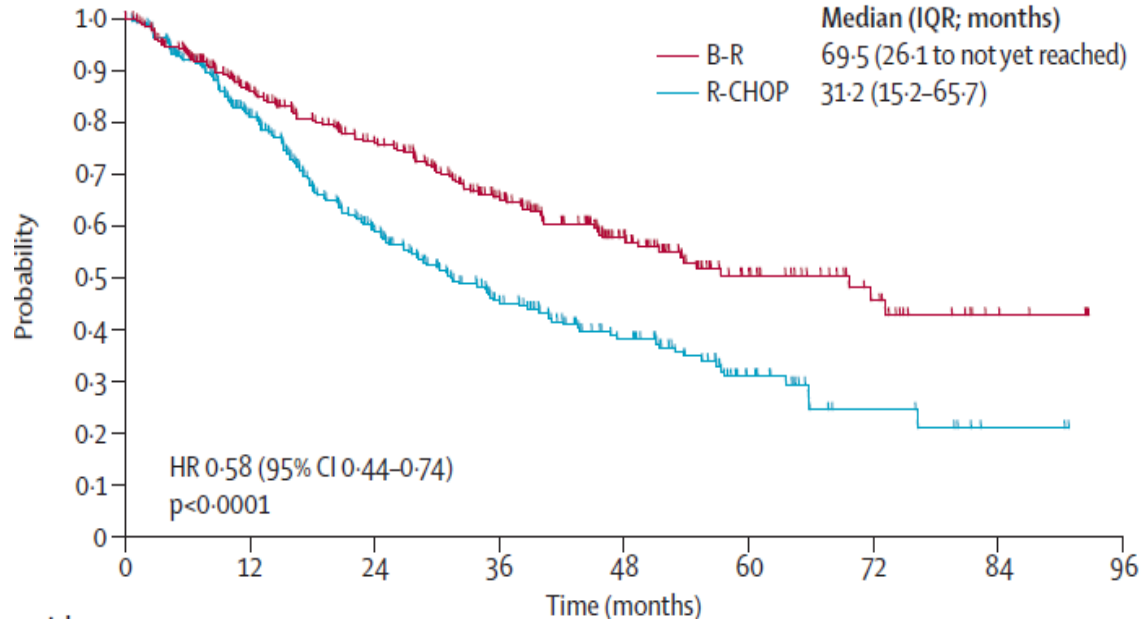
PFS from randomization (ITT)



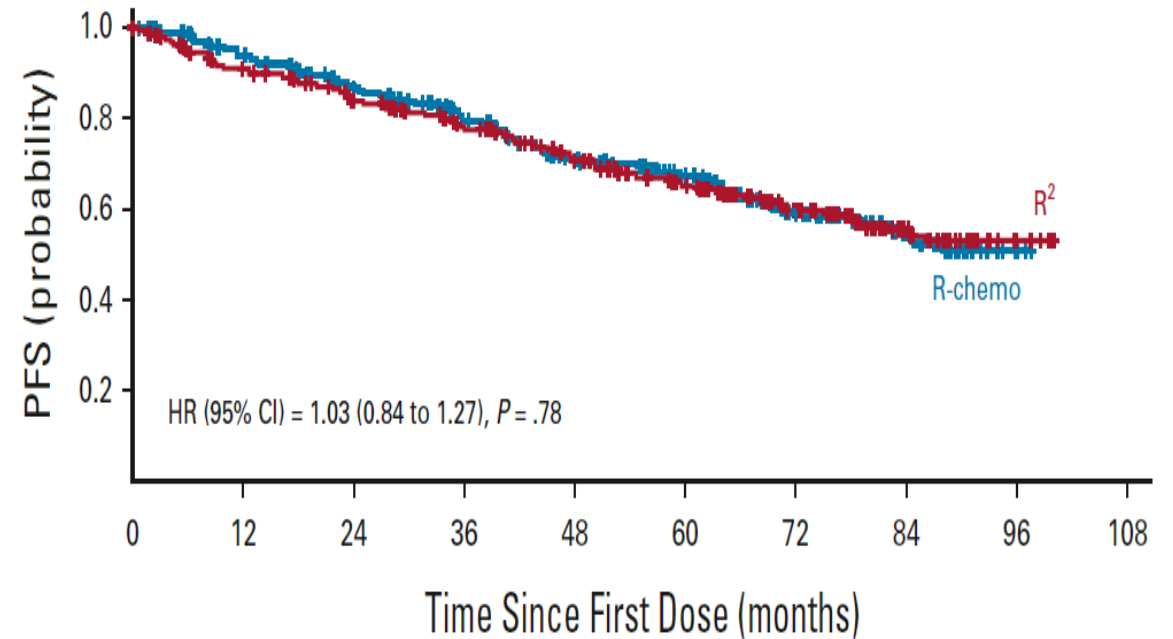
- SC rituximab induction followed by short SC maintenance improves PFS in low tumor burden FL
- 90% of patients in CMR at 12 mo will not require retreatment 4 years after diagnosis

Phase 3 untreated FL: Rituximab based

Bendamustine + rituximab (no Maintenance R)



Lenalidomide + rituximab (R²) vs R-Chemo (Maintenance R/R²)



No difference **10-yr OS**: BR **71%** vs R-CHOP **66%**

6-yr PFS: R-len **60%** vs R-chemo **59%**

6-yr OS: Both **89%**

5-yr OS: **POD 24 60%, no POD24 95%** (both arms)

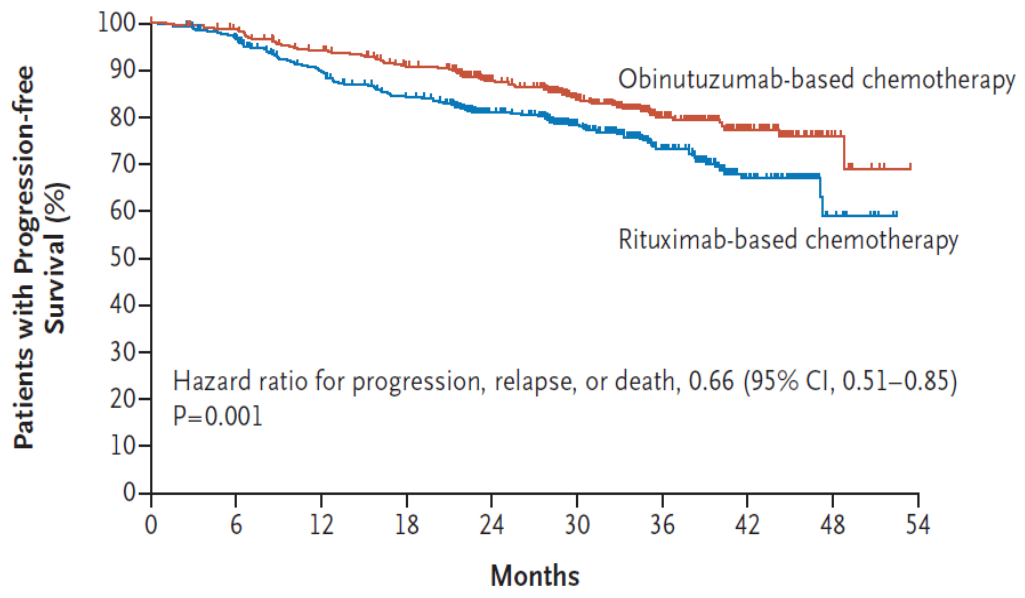
2nd malig: R-len **11%** vs. R-chemo **13%**

Rummel et al Lancet 2013; 381: 1203–10
Rummel et al JCO 2017; 35:7501-7501

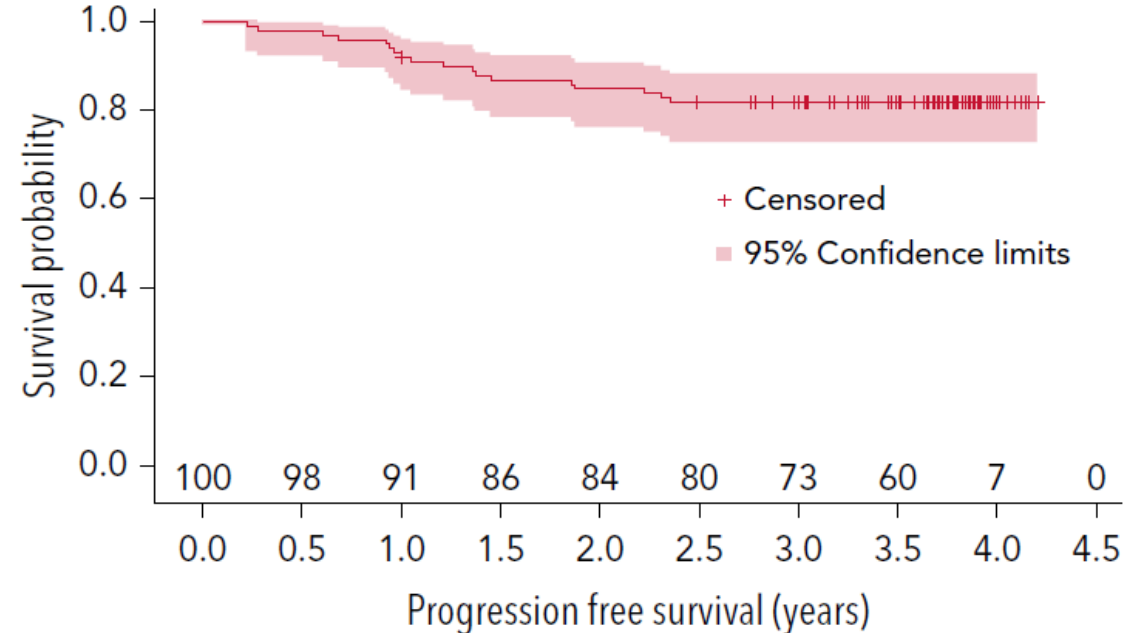
Morschhauser et al NEJM 2018;379:934-47,
Morschhauser et al JCO 2022 doi.org/10.1200/JCO.22.00843

Untreated FL - Obinutuzumab based therapies

Obin+chemo vs + R+chemo



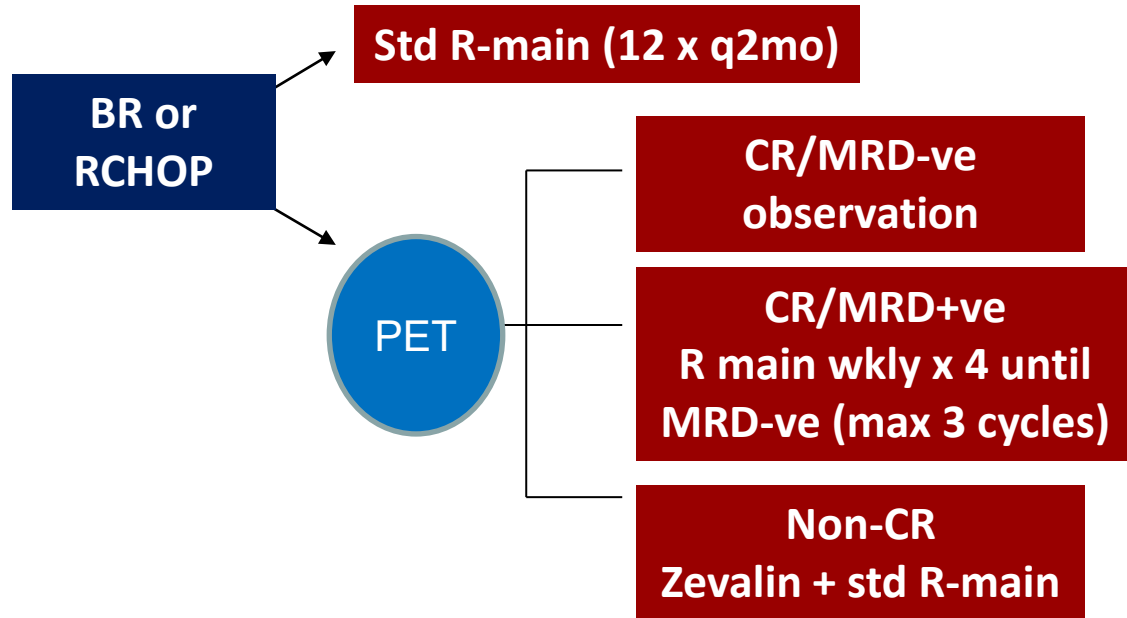
Obin + Len



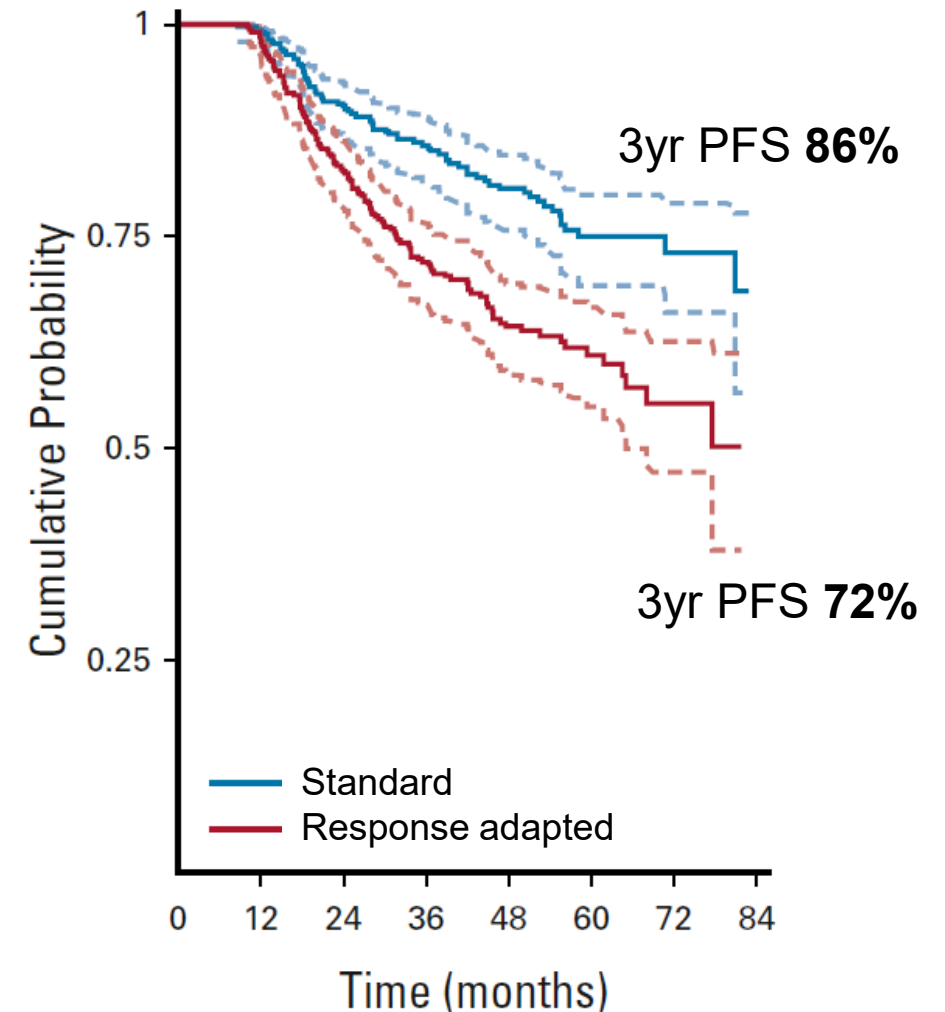
Treatment	Phase	Maintenance	# Pts	ORR (CR)	3-yr PFS	OS	Gr 3+ AE
O+chemo R+chemo	3	2 yrs O or R	1202	89% (20) 87% (24)	80% 73%	94% (5-yr) 92%	76% 68%
O + Len	2	1yr O + Len 1yr O alone	100	92 (47)	82%	94% (3yr)	74%

Marcus et al NEJM 2017;377:1331-44
Bachy et al Blood 2022;139: 2338-46

Response-adapted post-induction rituximab maintenance (FOLL12)

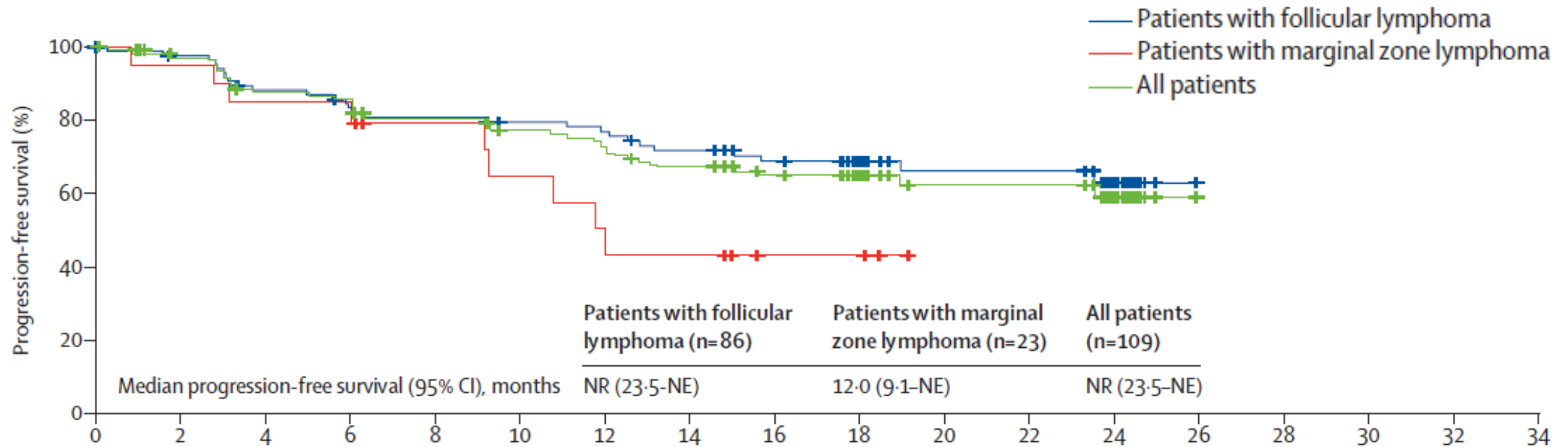


- Ph 3, n= 786
- Investigator choice: **R-CHOP** (n=445) or **R-Benda** (n=341)
- 3-yr PFS for MRD-ve: **92%** (ref arm) vs **78%** (exp arm)
- PFS favored ref arm in R-CHOP and R-Benda subsets
- 3-year OS **98%** (standard) vs **97%** (response adapted)



Luminari et al JCO 2021;40:729-739.

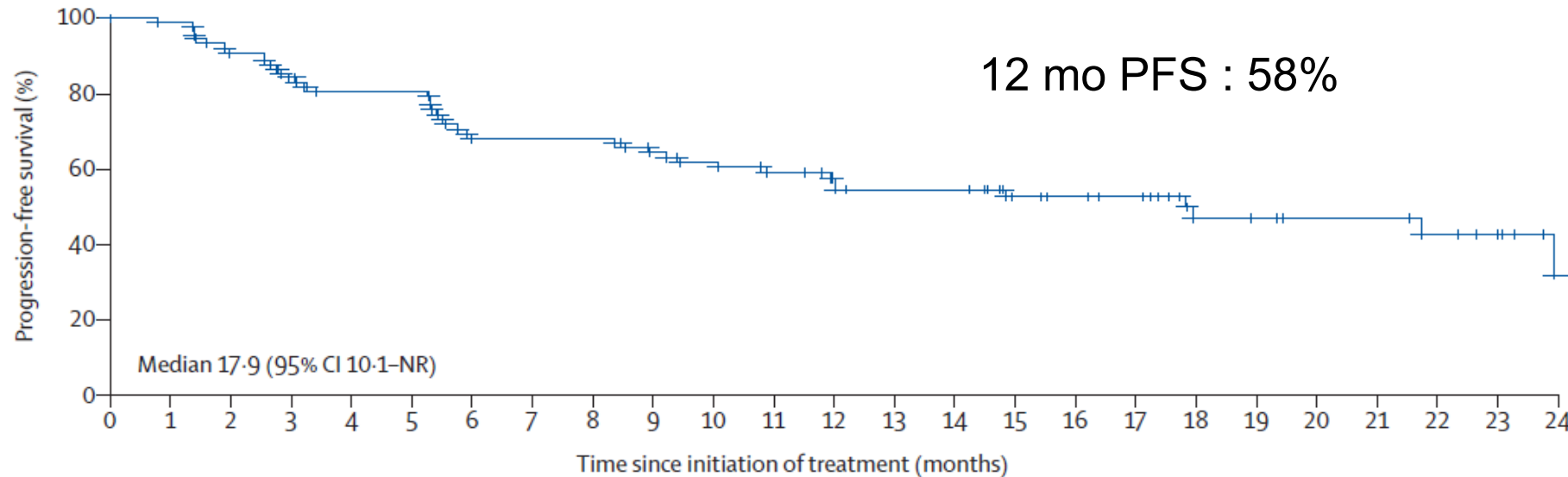
CAR-T therapy at relapse – iNHL



- Ph2; n= 148, 124 FL, 24 MZL
- FL: ORR: 94%, CR 79%
- Median PFS: 23.5 mo, 18 mo PFS 64.8%
- Median OS: NR, 18-mo OS 87.4%
- Gr \geq 3 CRS 7%; neurotoxicity 19%

Bispecific Ab for relapsed FL

Mosunetuzumab CD20 x CD3



- Phase 1: n=90
- ORR: 80%; **CR 60%**
- AEs: Gr \geq 3 neutropenia (27%),
- CRS occurred in 44%, Gr \geq 3 **2%**

Approved for R/R FL by EMA 4/25/22
 FDA to make decision by end of 2022

Ongoing Ph 3 Mosun + Len vs Rituxan + Len (NCT04712097)

Marginal Zone Lymphoma

Extranodal

- Gastric, *H.pylori* positive, antibiotic therapy³
- Localized disease, radiotherapy (4-24 Gy)^{4,5}

Splenic

- Active surveillance¹
- If HCV+, treat HCV²
- Rituximab⁶
- Chemotherapy⁶

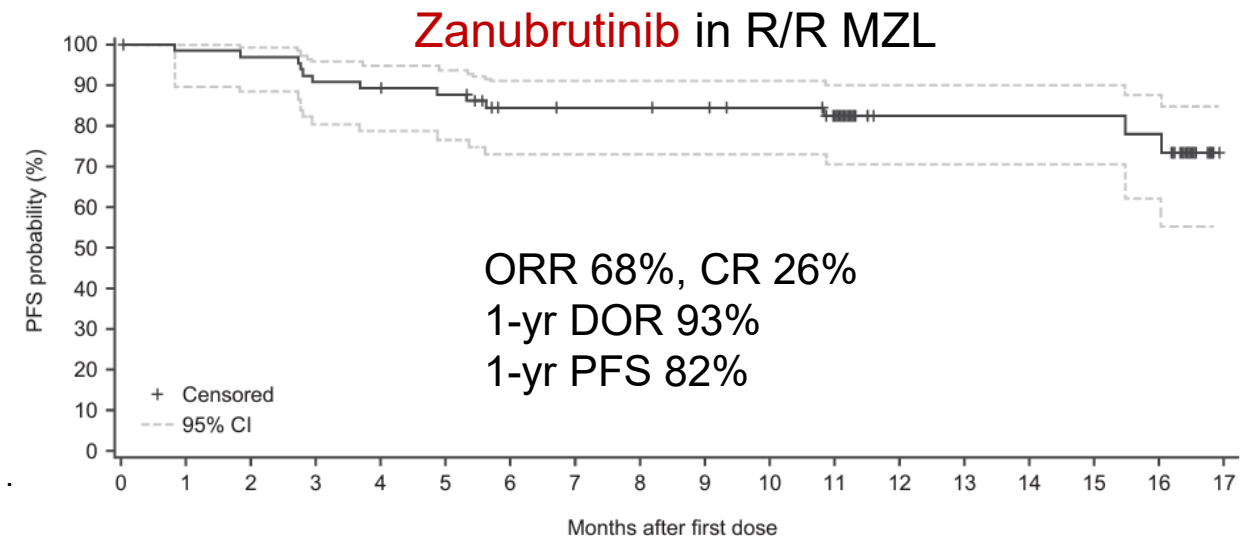
Nodal

- Localized disease, radiotherapy (4-24 Gy)⁵
- Advanced disease, rituximab based i.e. BR⁶

Relapse:

- If asymptomatic – active surveillance¹
- Rituximab, R-chemo, R-len, **BTKi**⁷

1. Chey Am J Gastroenterol 2017; 112: 212-39.
2. Wirth et al Ann Oncol 2013;24:1344-51
3. Imber et al Blood Adv 2021;5:4185-419
4. Florindez et al Cancer 2020;126:4706-16
5. Arcaini et al Blood 2016;128:2527-32
6. Salar et al Blood 2017;130:1772-4
7. Rossi et al NEJM 2022;386:568-81.



Opat et al. Clin Cancer Res 2021;27:6323-32

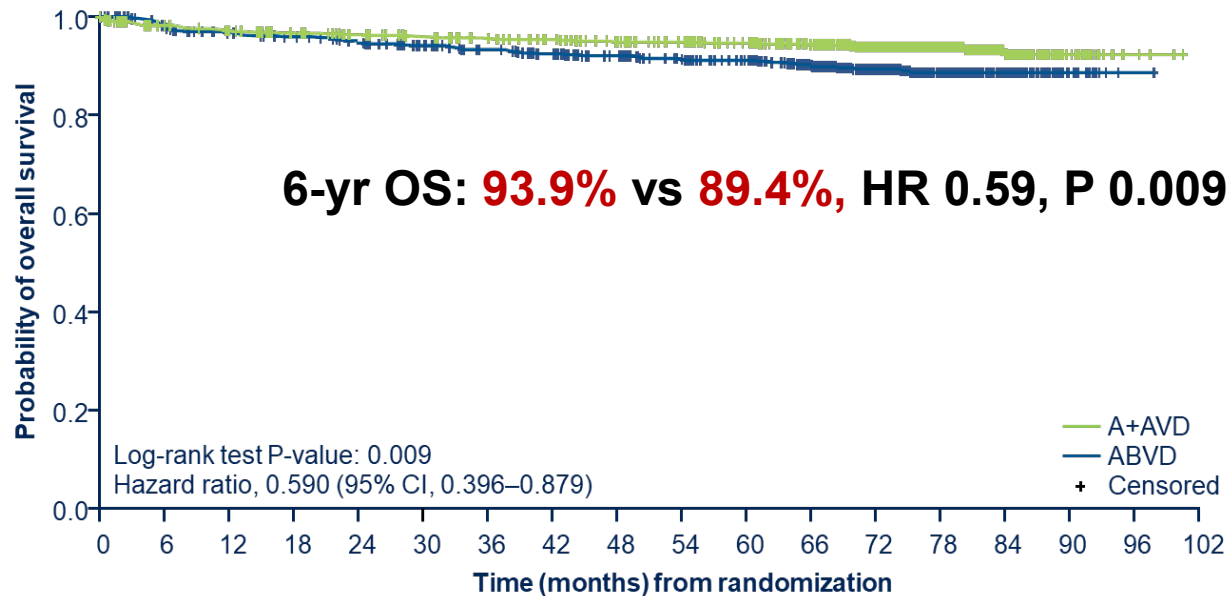
Hodgkin Lymphoma 2022

Highlights and controversies

- Advanced stage
 - Should everyone receive Bv as 1st line therapy?
 - Role for PD1 inhibitors in 1st line therapy?
 - Instead of Bv or in addition to Bv
 - Optimal management of older patients
- Early stage
 - Preliminary data incorporating Bv ± PD-1 inhibitors in 1st line therapy
- Relapsed disease
 - 2nd line options

An updated analysis of ECHELON-1

OS advantage with Bv-AVD (AAVD)



6-yr PFS update **82.3% vs 74.5% HR 0.68**

Significant HR favoring AAVD

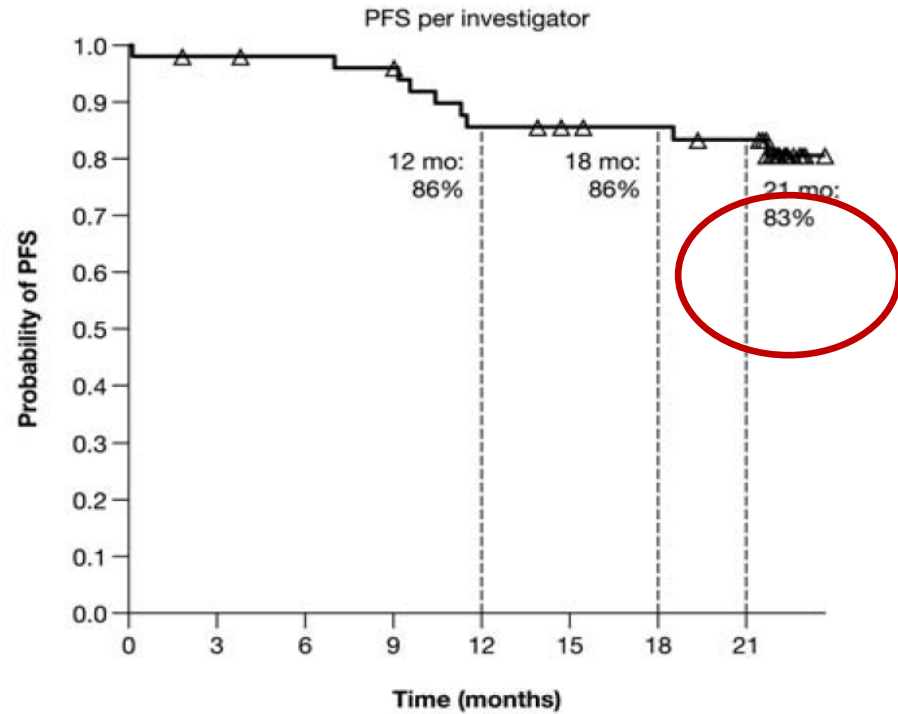
Subgroup	HR (CI)
Age <60	0.51 (0.29 - 0.89)
IPS 2-3	0.62 (0.33 - 1.14)
IPS 4-7	0.48 (0.26 - 0.88)
Stage 4	0.48 (0.29 - 0.80)
EN site >1	0.30 (0.14 - 0.67)
Male	0.43 (0.25 - 0.73)

- *Second Malignancies*
 - AAVD 23 (14 ST, 9 heme - **6 NHL**)
 - ABVD 32 (14 ST, 17 heme - **13 NHL**)
- *Pregnancies among patients and their partners*
 - AAVD 113, ABVD 78

Ansell et al JCO 2022;40;7503-7503.

Adding PD-1 inhibitors to initial treatment for advanced stage HL

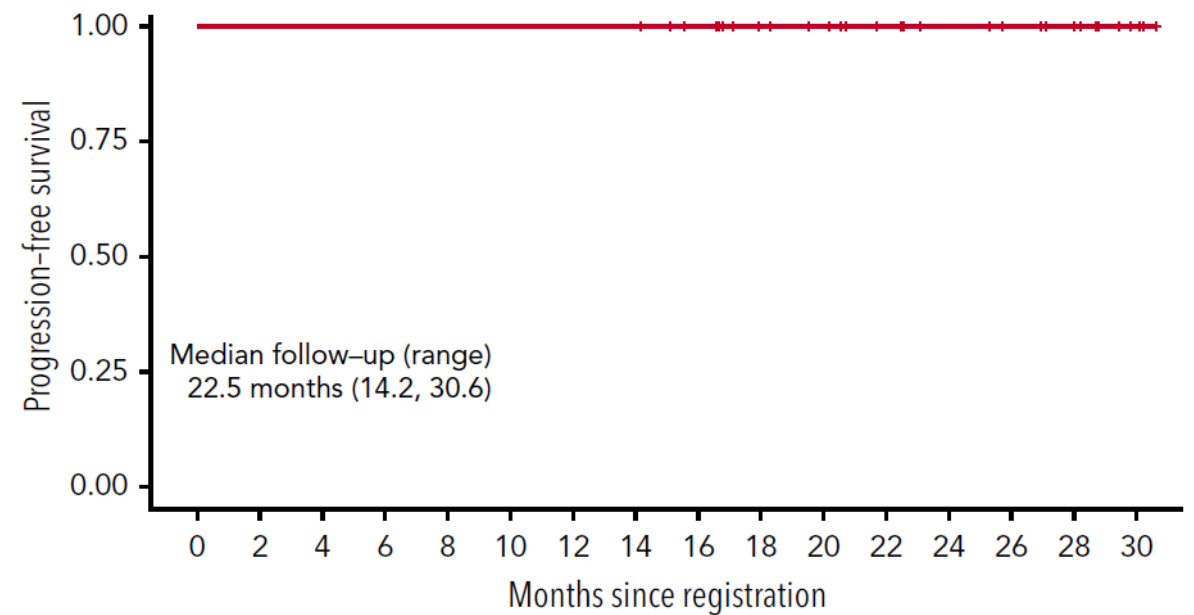
Nivo-AVD (Checkmate 205)



- Stage 3-4 (n=41), 2B (n=10)

Ramchandren et al JCO 2019;37:1997-2007
Ansell et al. Hematol Oncol 2019;37:146-147

Pembro x 3 → AVD x 4-6

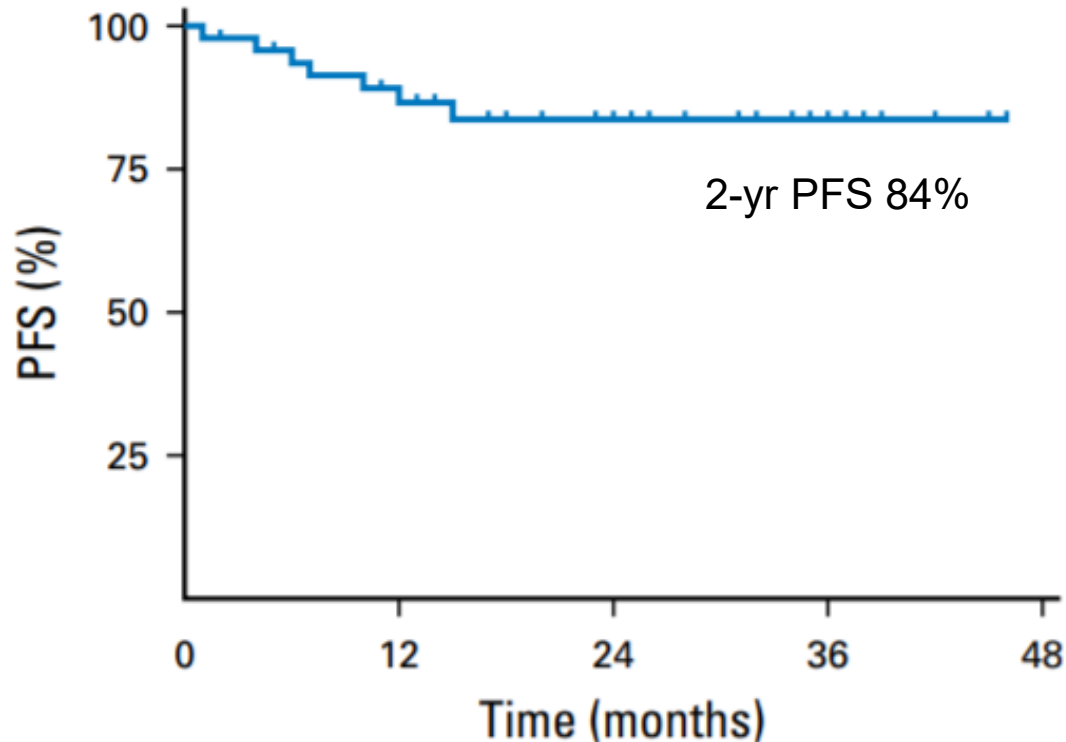


- Stage 3-4 (n=18), 2B (n=12)

Allen et al Blood. 2021;137:1318-1326

Potential approaches for older pts with HL (No Bleo)

Bv x 2 → AVD x 6 → Bv x 4

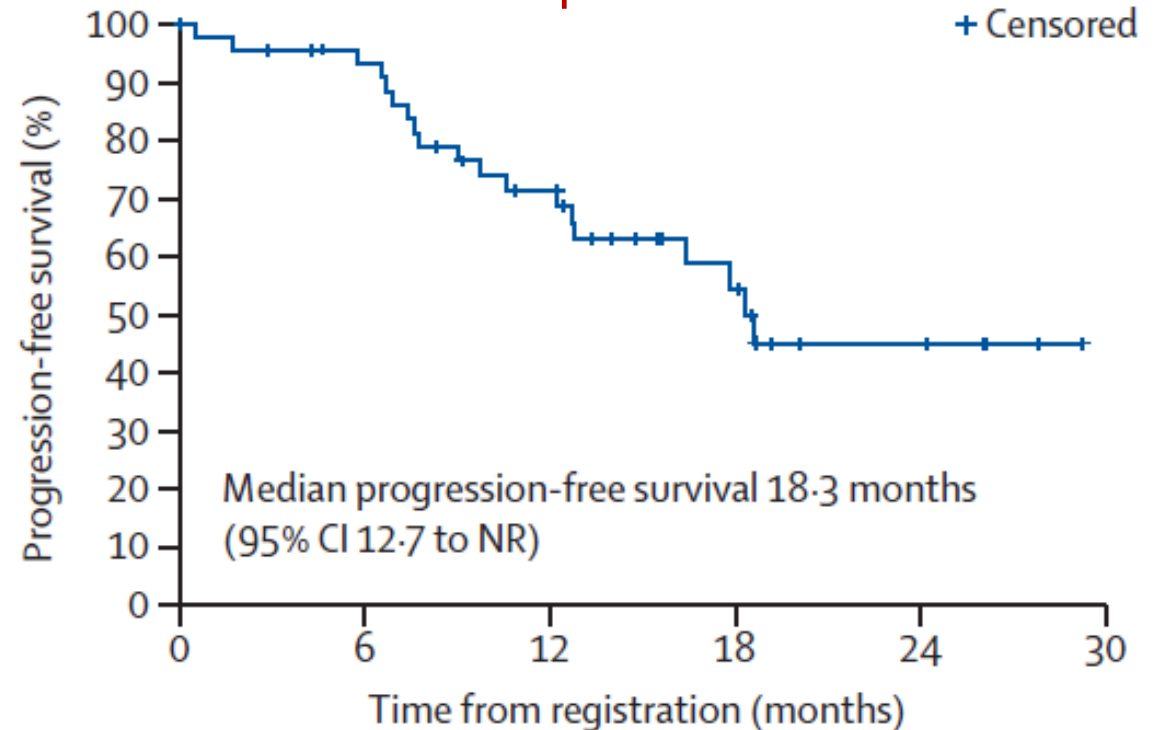


Neuropathy: Gr3 4%; Gr 2 27%

Evens et al JCO 2018;36:3015-22

Bv-Nivo x 8

Suboptimal

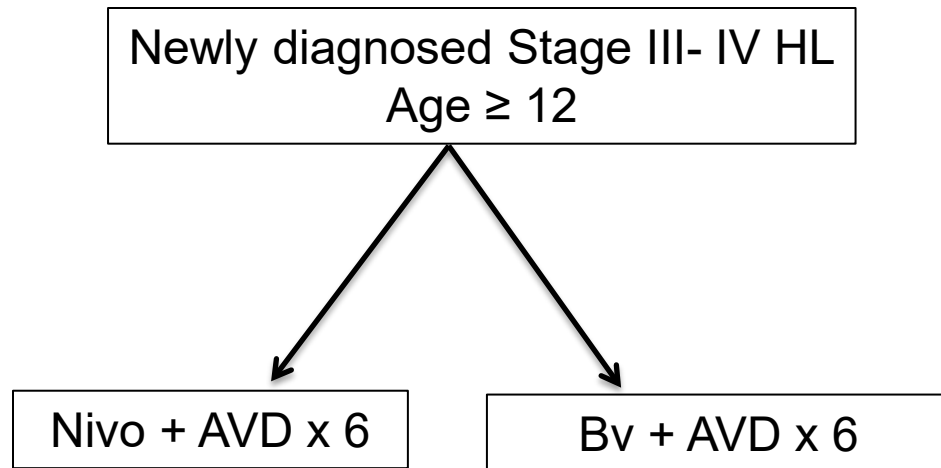


Neuropathy: Gr3 11%; Gr 2 35%

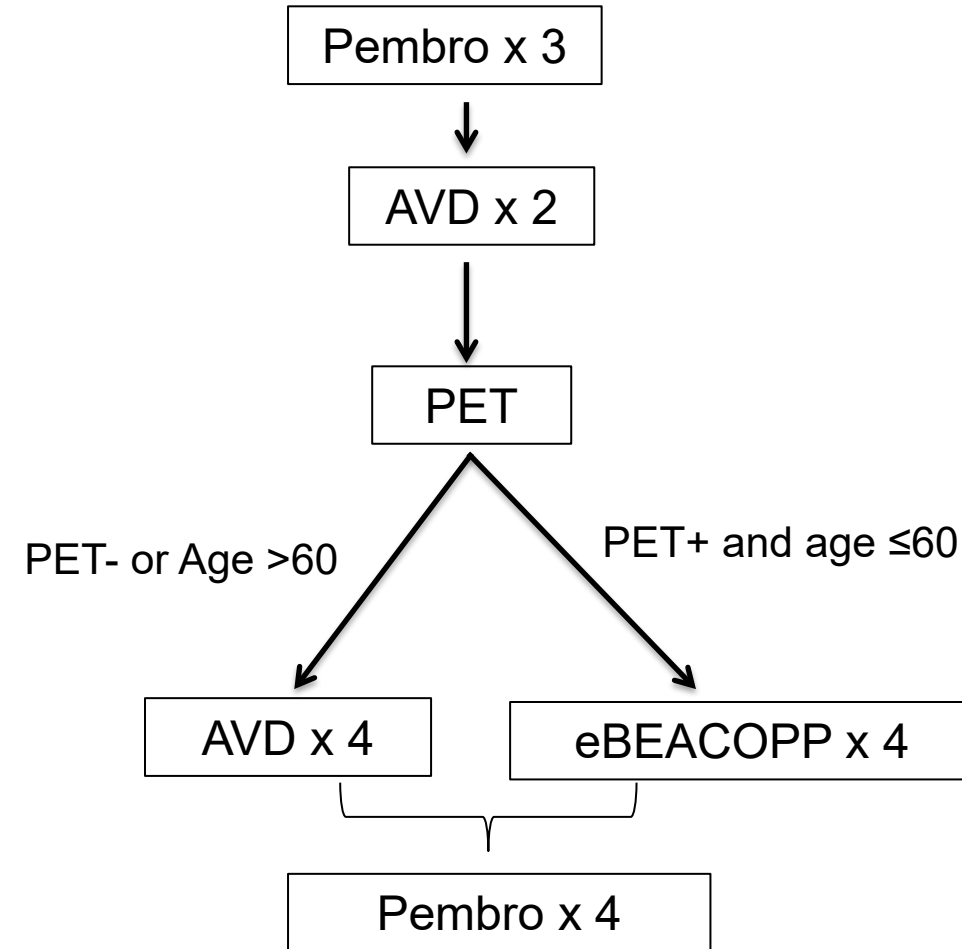
Cheson et al Lancet Haem 2020;7:e808–15

Advanced stage: *ongoing trials*

S1826

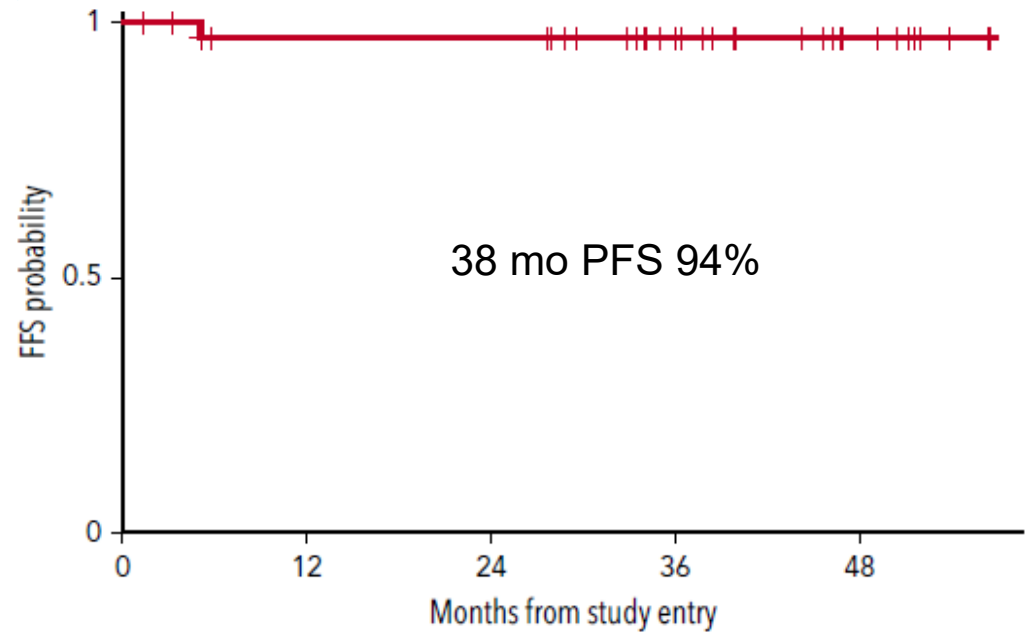


KEYNOTE –C11



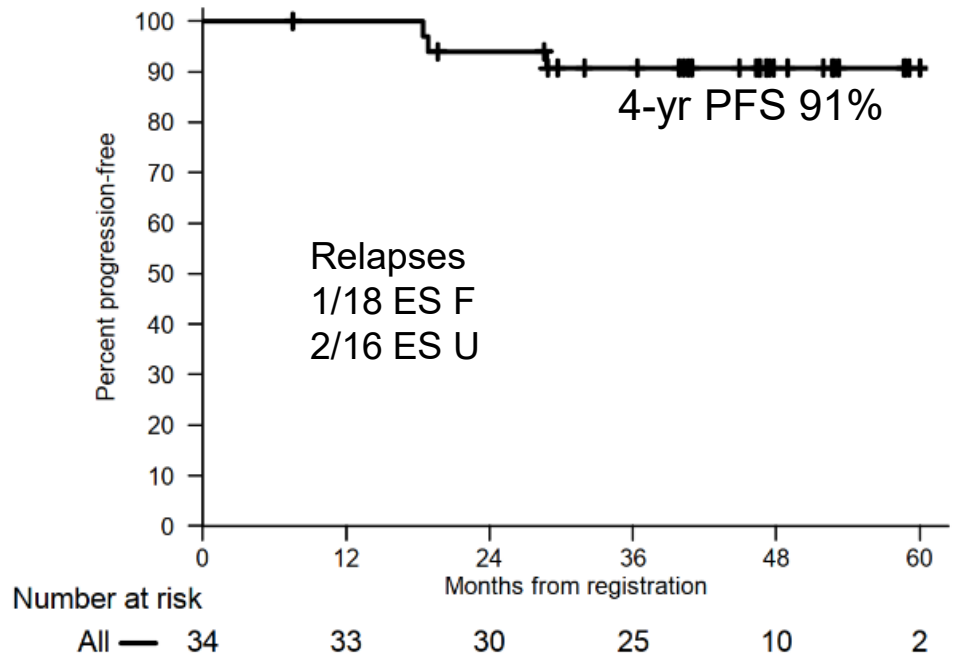
Published *pilot/Phase 2* trials incorporating Bv: Early stage

Bv-AVD x 4 (non-bulky)



Abramson et al Blood. 2019;134:606-613

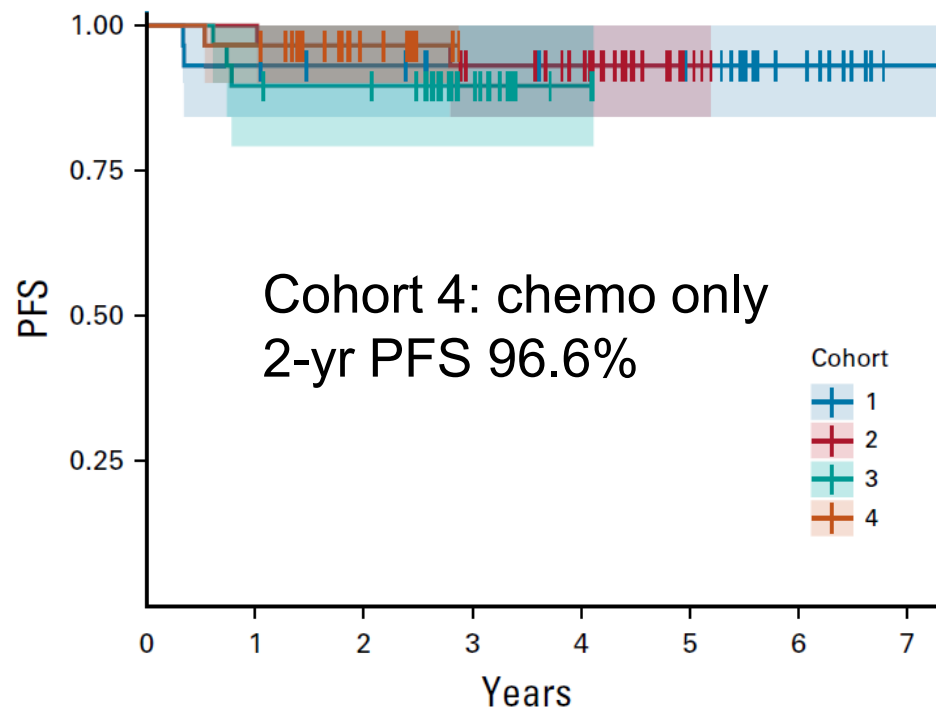
Bv-AD x 4- 6 (non-bulky) Eliminate velban



Abramson et al Lugano 2021;279: abstr 198

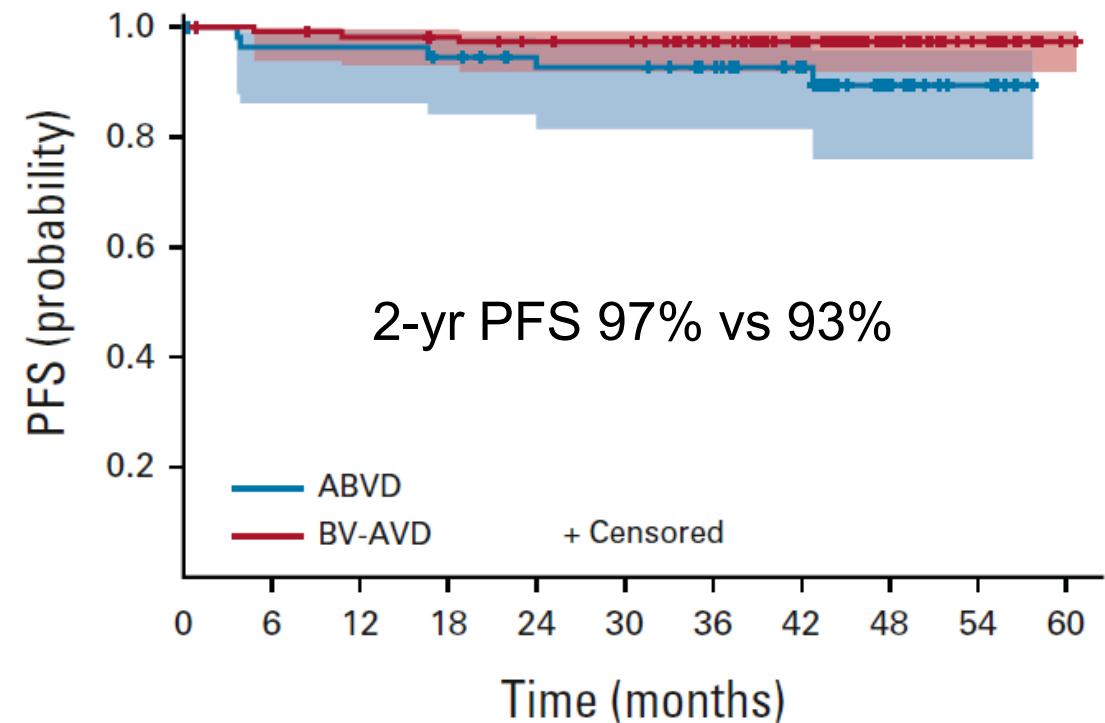
Published pilot/Ph2 trials incorporating Bv: Early stage

Bv-AVD x 4 (GHSG unfavorable)



Kumar et al. JCO 2021;39:2257-2265

Bv-AVD x 4 + RT (EORTC unfavorable)



Fornecker et al. JCO 2022; doi.org/10.1200/JCO.21.01281

Rel/ref HL: incorporating new agents into second line therapy

Regimen	No. of Patients	ORR (%)	CR Rate (%)	Imaging Modality	PFS or EFS (all patients)	PFS or EFS (SLT plus ASCT)	
BV	56	75	43	PET	NR	77% (2-year)	1
BV → ICE	45	76	69	PET	NR	80% (2-year)	2
BV-Benda	55	93	74	PET	63% (2-year)	70% (2-year)	3
	40	84	79	PET	67% (3-year)	NR	4
BV-DHAP	55	90	81	PET	74% (2-year)	NR	5
BV-ESHAP	66	91	70	PET	71% (2.5-year)	NR	6
BV-Gem ^a	42	74	67	PET	NR	NR	7
BV-ICE	39	95	69	PET	69% (1-year)	NR	8
	45	91	74	PET	82% (2-year)	NR	9
BV-Nivo	61	85	67	PET	77% (3-year)	91% (3-year)	10
Nivo → ICE	37	89	86	PET	79% (1-year)	NR	11
Pembro-GVD	38	100	95	PET	100% (1-year)	100% (1-year)	12

1 Herrera et al Ann Oncol 2018;29:724-730

2 Moskowitz et al Lancet Oncol 2015;16:284-292

3 LaCasce et al Blood 2018;132:40-48,

4 Broccoli et al Blood Cancer J 2019;9:100

5 Kersten et al Haematologica 2021;106:1129-1137

6 Garcia-Sanz et al 2019; Ann Oncol 30:612-620

7 Cole et al Lancet Oncol 2018;19:1229-1238

8 Stamatoullas et al Blood 2019;134:132

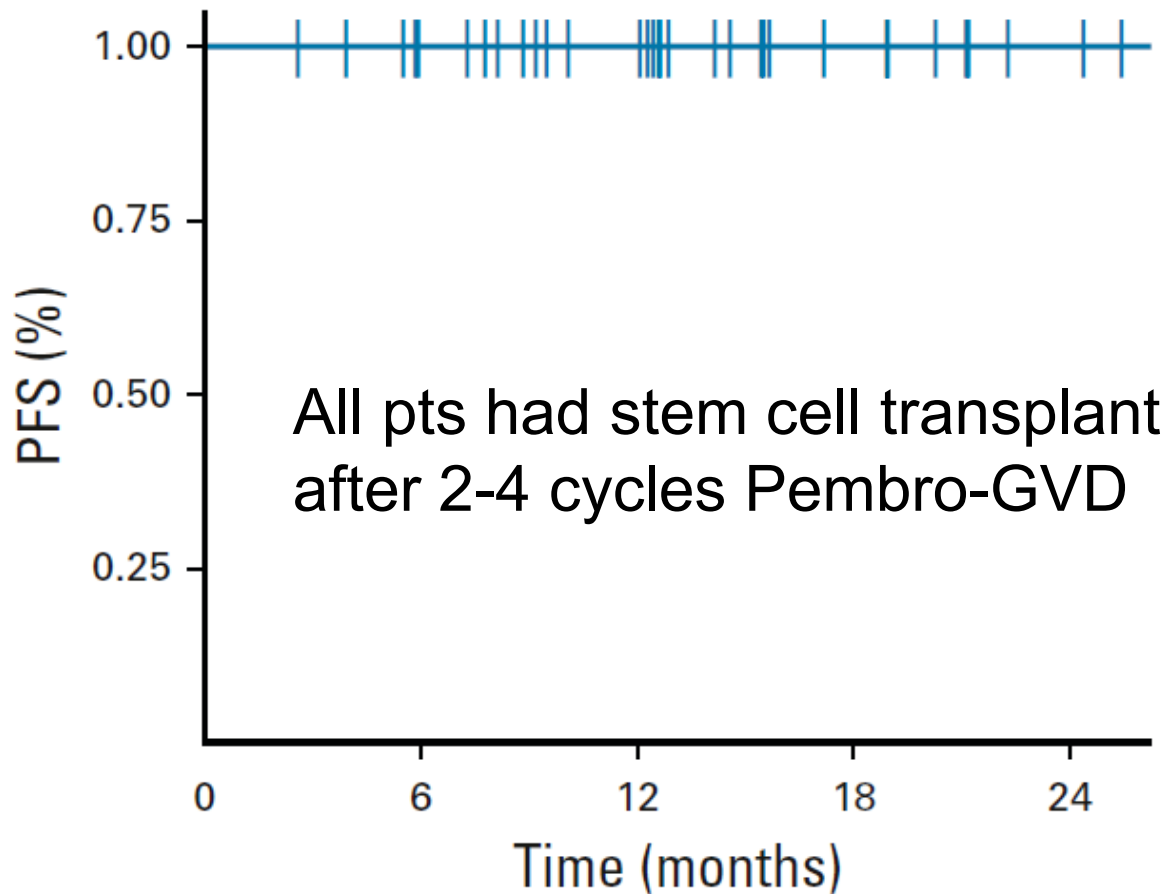
9 Lynch et al Blood 2019;136:16-18

10 Advani et al Blood 2021;138: 427-438,

11 Herrera et al Blood 2018;131:1183-1194

12 Moskowitz et al JCO 2021; 39:3109-3117

Pembro-GVD* for relapsed HL; N=39



Toxicity

- Gr3:
 - neutropenia (10%)
 - transaminitis (10%)
- Gr 1-2
 - rash (46%)
 - mucositis (33%)
 - transaminitis (31%)
 - infusion related rxn IDoxil (21%)
- Frequent engraftment syndrome (68%) at median of 10 days following ASCT
 - Manifested as transaminitis, rash, and/or diarrhea, responded to 3 days high-dose steroids with rapid 1-2 wk taper

*gemcitabine, vinorelbine, liposomal doxorubicin

Take Home Messages

- Low burden FL - consider single agent rituximab with short course maintenance R
- Multiple equivalent options for 1st-line treatment of FL, nearly half expected to be “cured”
- Maintenance R prolongs PFS in FL, but not OS, regardless of disease status at end of induction
- Approval of bispecific Ab Mosunetuzumab for R/R FL expected late 2022
- Zanubrutinib treatment of choice for relapsed MZL
- Bv-AVD improves OS in higher risk advanced stage HL
- **Liberal use of Covid Vax, Pax, Evusheld in all NHL pts**