Targeting and treating: Indolent, mantle cell, and Hodgkin lymphoma in 2022

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- **Advisory Boards**: ADC Therapeutics, Roche/Genentech, SeaGen

Learning Objectives

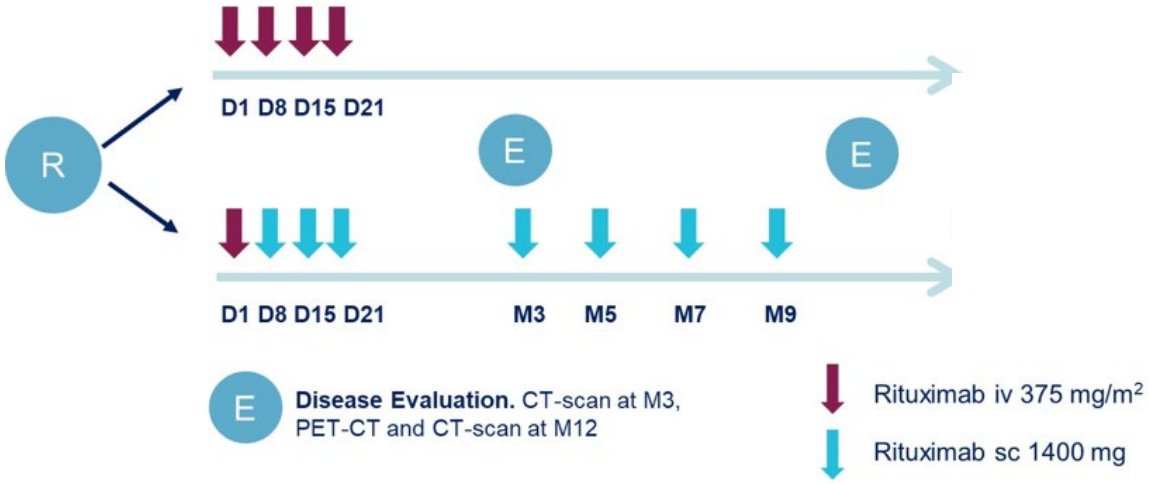
- **Follicular lymphoma (FL)**
  - Describe outcomes from FOLL12 trial comparing standard R-Maintenance to MRD based maintenance in first-line therapy of FL
  - Discuss efficacy of CAR-T cell therapy and bispecific antibodies for relapsed FL
- **Mantle cell lymphoma (MCL)**
  - Review recent data on BTK-based approaches in first and later-lines of therapy for MCL
  - Discuss efficacy of CAR-T cell therapy and bispecific antibodies for relapsed MCL
- **Hodgkin lymphoma (HL)**
  - Compare PFS and OS of ABVD and Bv-AVD for first-line therapy of advanced stage HL

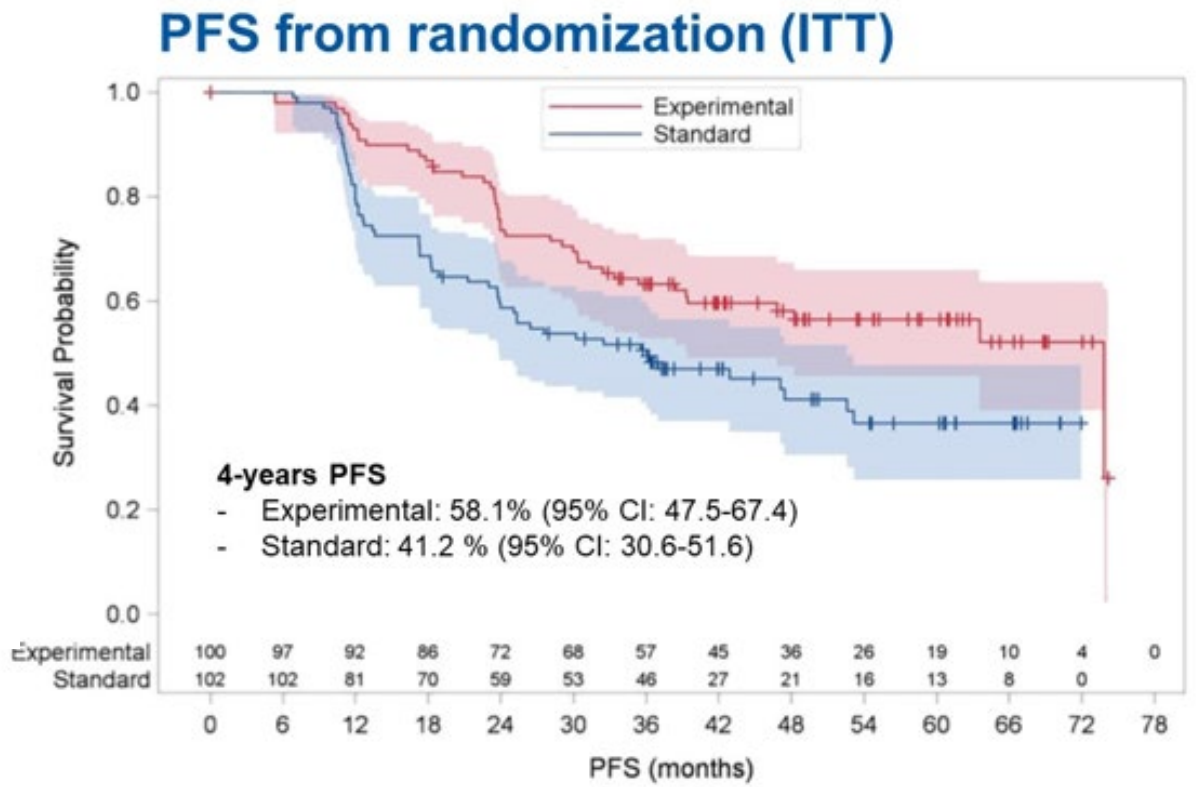
Indolent Lymphoma (follicular) 2022

Highlights and controversies

- First-line treatment options
  - R-chemo vs. O-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    - *Copanlisib still approved for FL but idelalisib (voluntary), duvelisib (voluntary), umbralisib (FDA) withdrawn*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

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



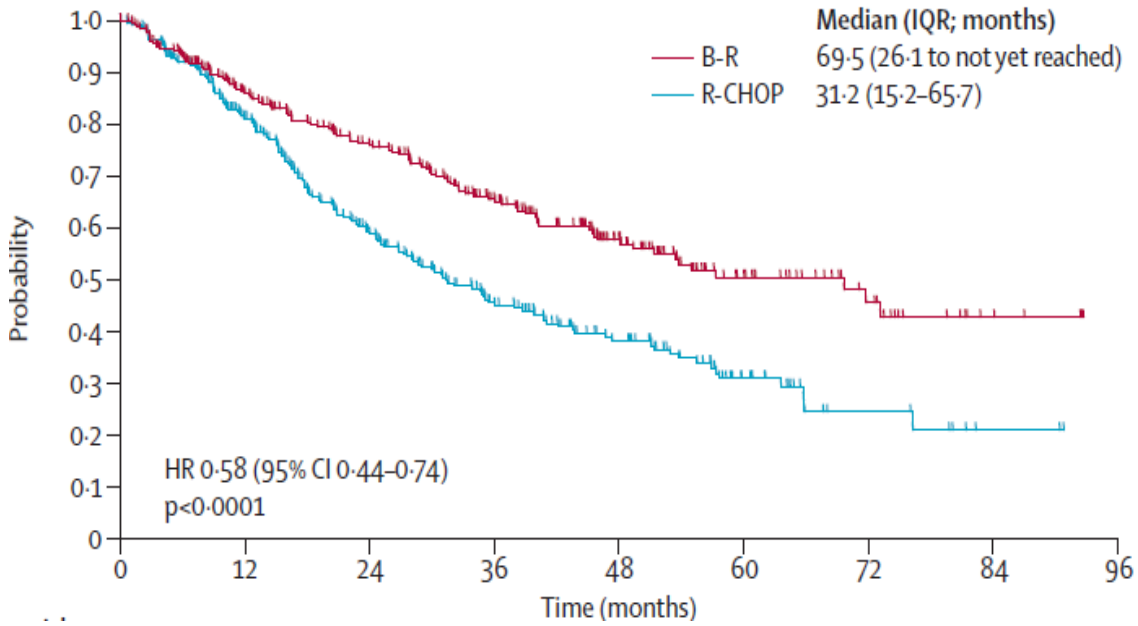


- SC rituximab induction followed by short SC maintenance improves PFS in low tumor burden FL
- 90% of patients in CMR at 12 mo will not require retreatment 4 years after diagnosis

Carton et al ASCO 2022 JCO:;40: 7512-7512

Phase 3 untreated FL: Rituximab based

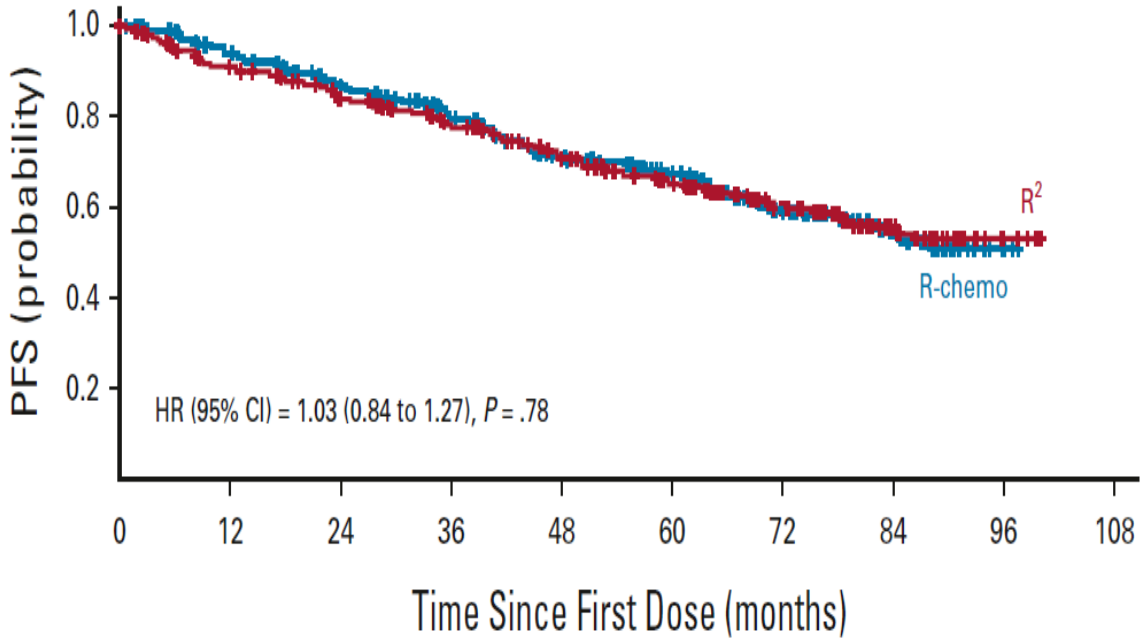
Bendamustine + rituximab (no Maintenance R)



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

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

Lenalidomide + rituximab (R^2) vs R-Chemo (Maintenance R/R^2)

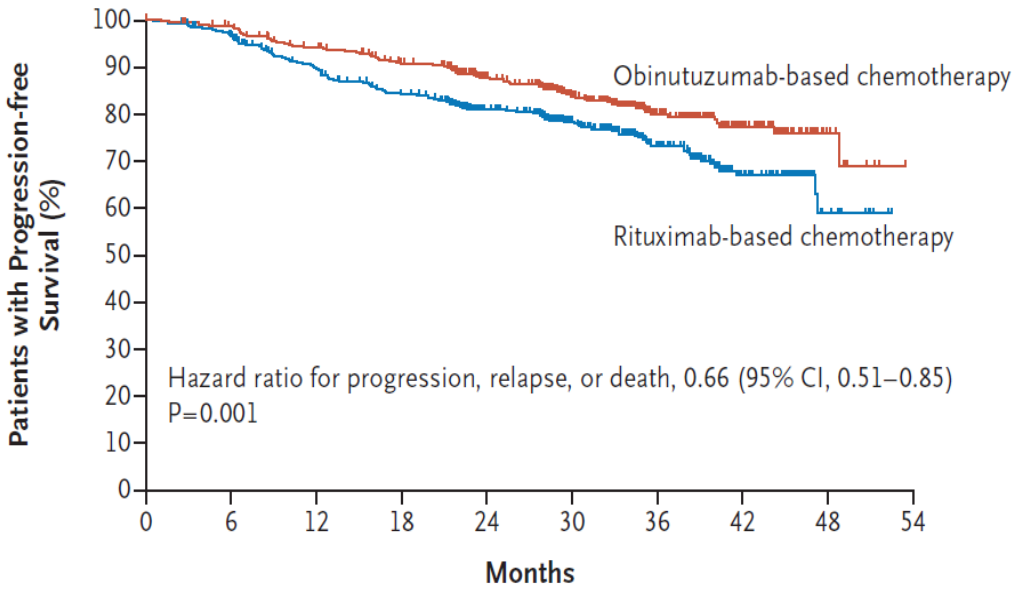


6-yr PFS: R-len **60%** vs R-chemo **59%**
6-yr OS: Both **89%**
5-yr OS: POD 24 **60%,** no POD24 **95%** (both arms)
2nd malig: R-len **11%** vs. R-chemo **13%**

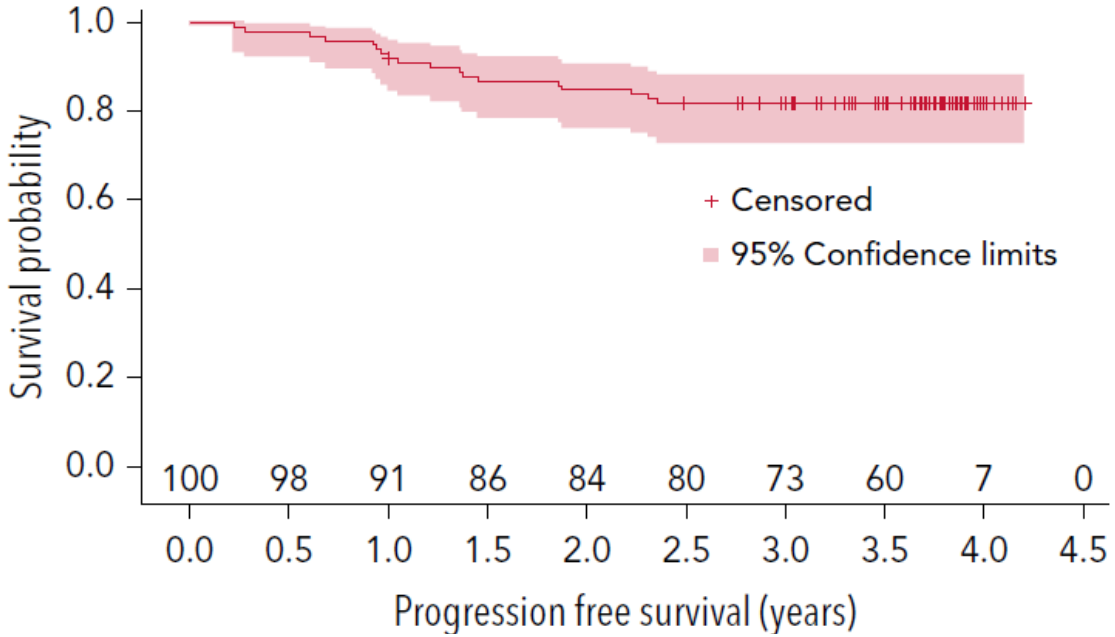
Morschhauser et al NEJM 2018;379:934-47,
Morschhauser et al JCO 2022 doi.org/10.1200/JCO.22.00843

Untreated FL - Obinutuzumab based therapies

Obin+chemo vs + R+chemo



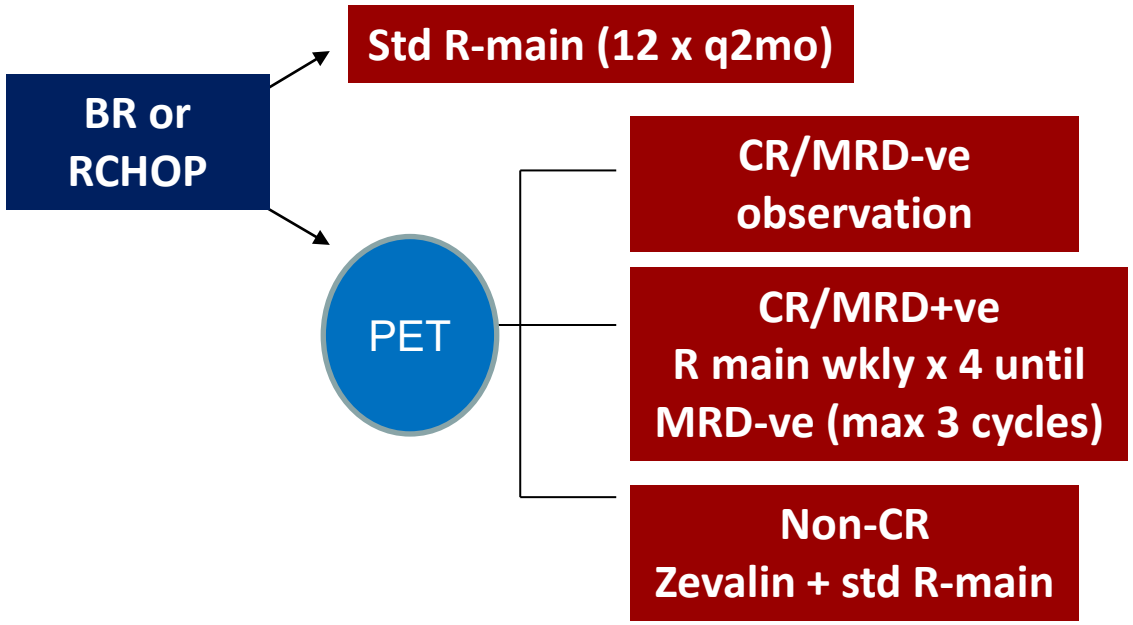
Obin + Len



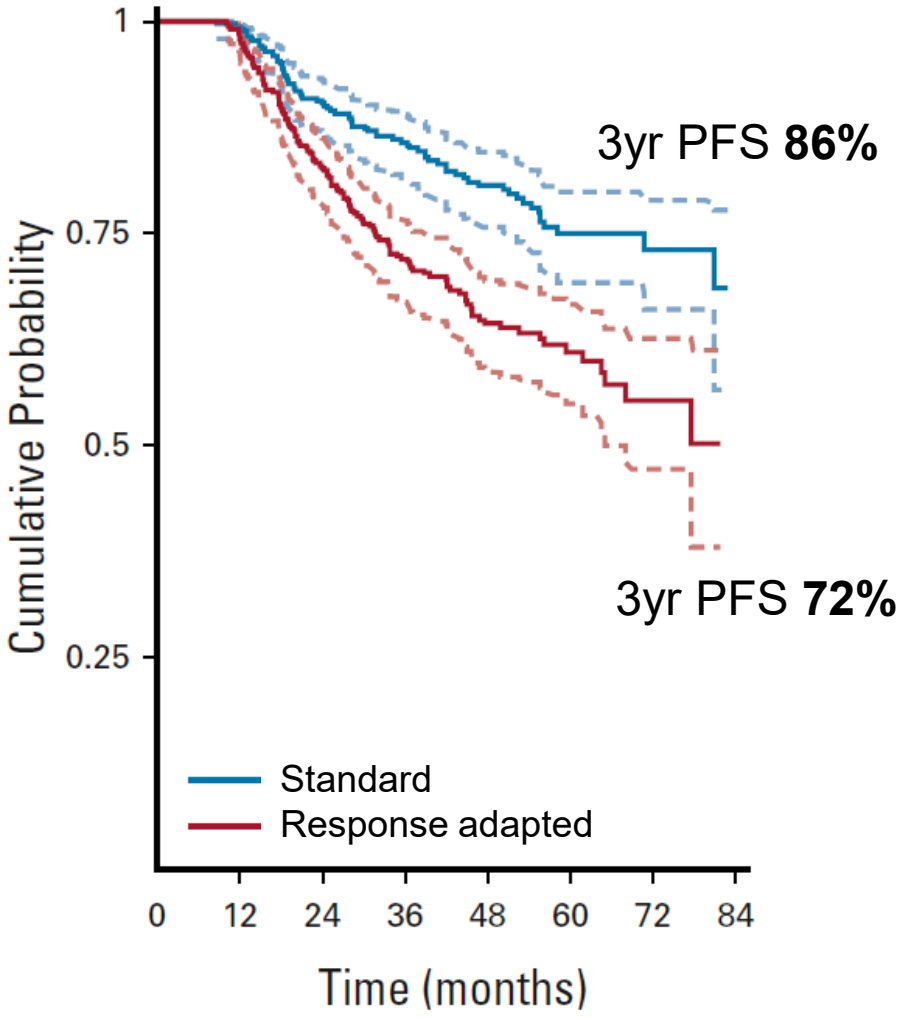
Treatment	Phase	Maintenance	# Pts	ORR (CR)	3-yr PFS	OS	Gr 3+ AE
O+chemo R+chemo	3	2 yrs O or R	1202	89% (20) 87% (24)	**80%** **73%**	94% (5-yr) 92%	**76%** **68%**
O + Len	2	1yr O + Len 1yr O alone	100	92 (47)	**82%**	94% (3yr)	**74%**

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

Response-adapted post-induction rituximab maintenance (FOLL12)

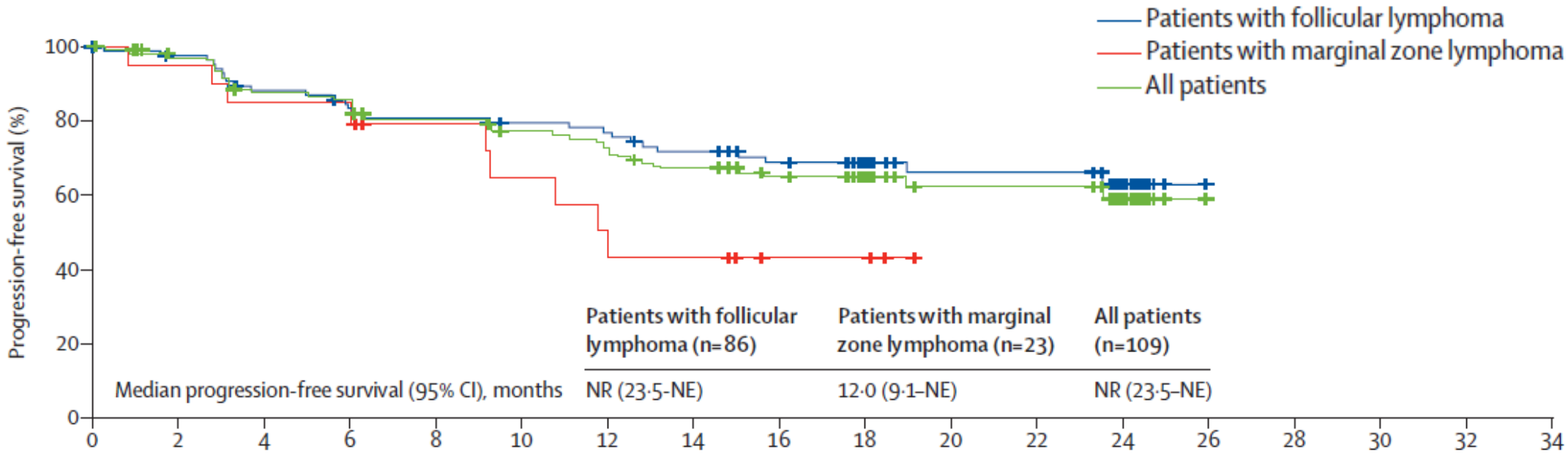


- Ph 3, n= 786
- Investigator choice: R-CHOP (n=445) or R-Benda (n=341)
- 3-yr PFS for MRD-ve: 92% (ref arm) vs 78% (exp arm)
- PFS favored ref arm in R-CHOP and R-Benda subsets
- 3-year OS 98% (standard) vs 97% (response adapted)



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

CAR-T therapy at relapse – iNHL

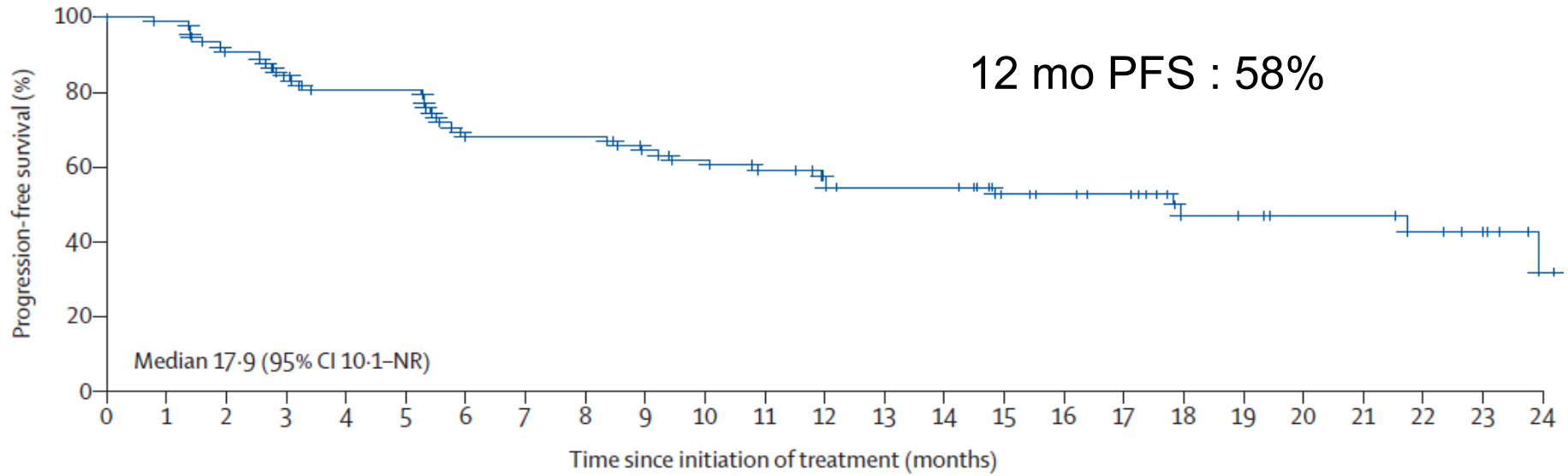


- Ph2; n= 148, 124 FL, 24 MZL
- FL: ORR: 94%, CR 79%
- Median PFS: 23.5 mo, 18 mo PFS 64.8%
- Median OS: NR,18-mo OS 87·4%
- Gr≥3 CRS 7%; neurotoxicity 19%

Jacobson et al Lancet Oncol 2022; 23: 91–103

Bispecific Ab for relapsed FL

Mosunetuzumab CD20 x CD3



12 mo PFS : 58%

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

Budde et al Lancet Oncol 2022; doi.org/10.1016/S1470-2045(22)00335-7

Marginal Zone Lymphoma

Extranodal

- Gastric, *H.pylori* positive, antibiotic therapy[3]
- Localized disease, radiotherapy (**4**-24 Gy)[4,5]

Splenic

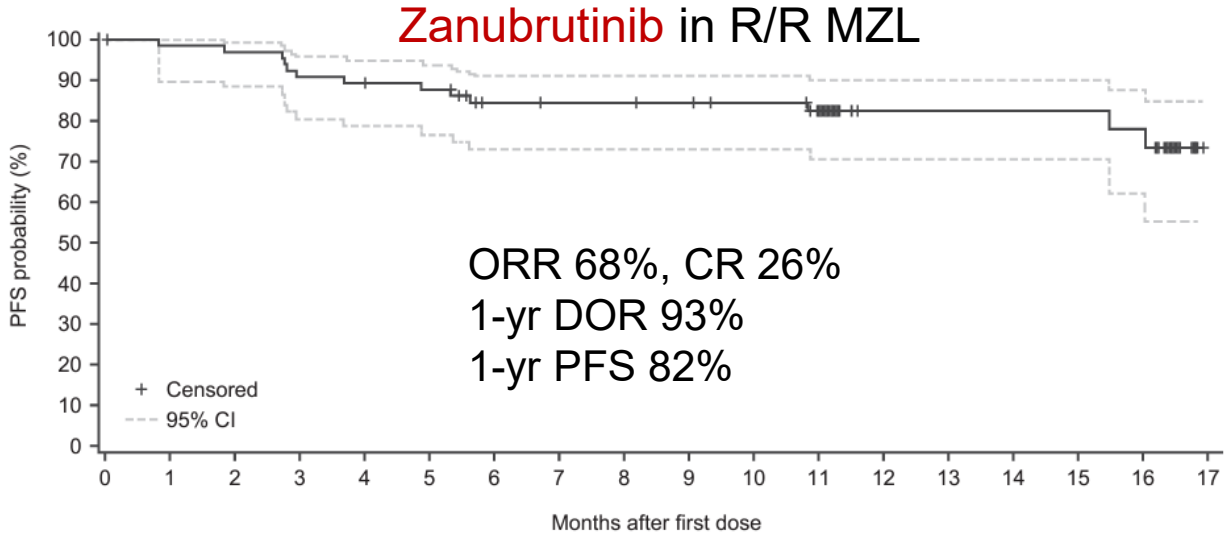
- Active surveillance[1]
- If HCV+, treat HCV[2]
- Rituximab[6]
- Chemotherapy[6]

Nodal

- Localized disease, radiotherapy (4-24 Gy)[5]
- Advanced disease, rituximab based i.e. BR[6]

Relapse:

- If asymptomatic – active surveillance[1]
- Rituximab, R-chemo, R-len, **BTKi**[7]



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

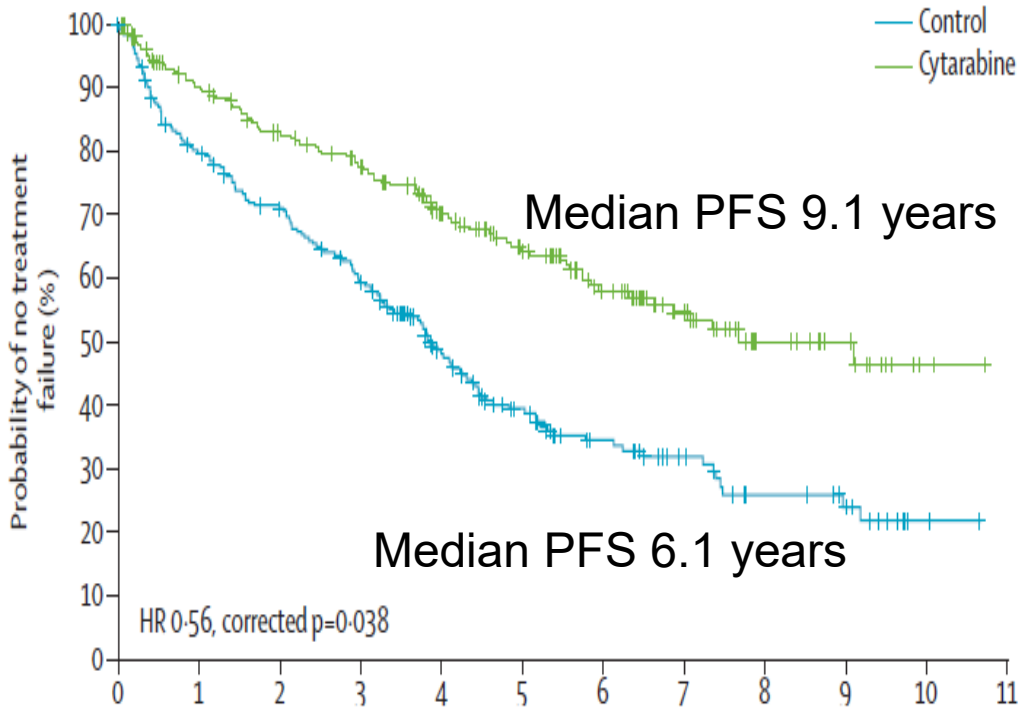
1. Chey Am J Gastroenterol 2017; 112: 212-39.
2. Wirth et al Ann Oncol 2013;24:1344-51
3. Imber et al Blood Adv 2021;5:4185-419
4. Florindez et al Cancer 2020;126:4706-16
5. Arcaini et al Blood 2016;128:2527-32
6. Salar et al Blood 2017;130:1772-4
7. Rossi et al NEJM 2022;386:568-81.

Mantle cell lymphoma 2022
Highlights and controversies

- Watch and wait
  - ≈ 10% of patients can be safely observed (low volume LAD or spleen/PB only)
  - can usually establish tempo in first 3-6 mo
- Initial Therapy
  - Is age a determinant?
  - Induction regimen? Ara-C? non-chemo?
  - Transplant?
  - Maintenance?
- Relapse Therapy
  - BTK inhibitors
  - CAR-T
  - On the near horizon: Bispecific antibodies
- Special consideration: TP53 deletion/mutation

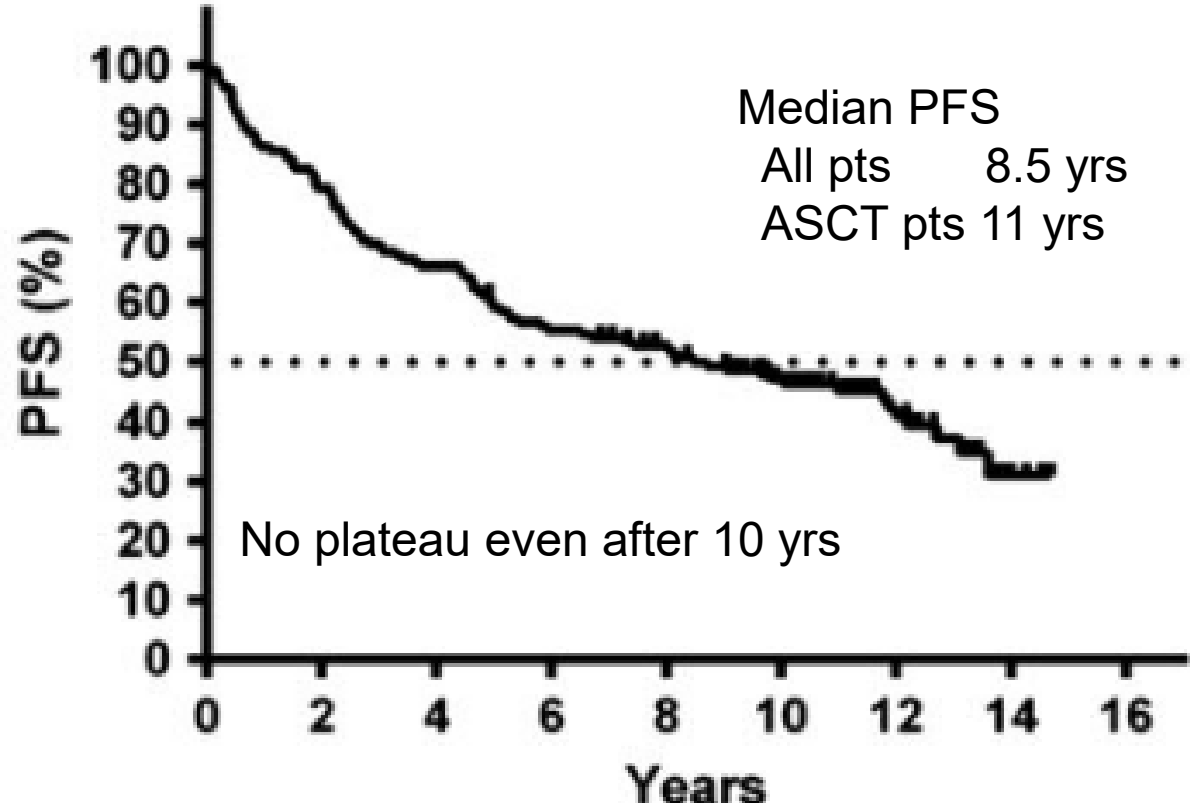
Pre-transplant induction for MCL: Ara-C improves outcomes (Pre-Benda era)

R-CHOP x 6 + ASCT vs
R-CHOP x 3 alt R-DHAP x 3 + ASCT



Hermine et al Lancet 2016; 388: 565–75

NORDIC
R-Maxi-CHOPx3 alt with HDAra-Cx3 + ASCT



Eskelund et al BJH 2016;175:410–418
Geisler et al Blood 2006;112:2687–2693

Bendamustine-based regimens as 1st line therapy in MCL

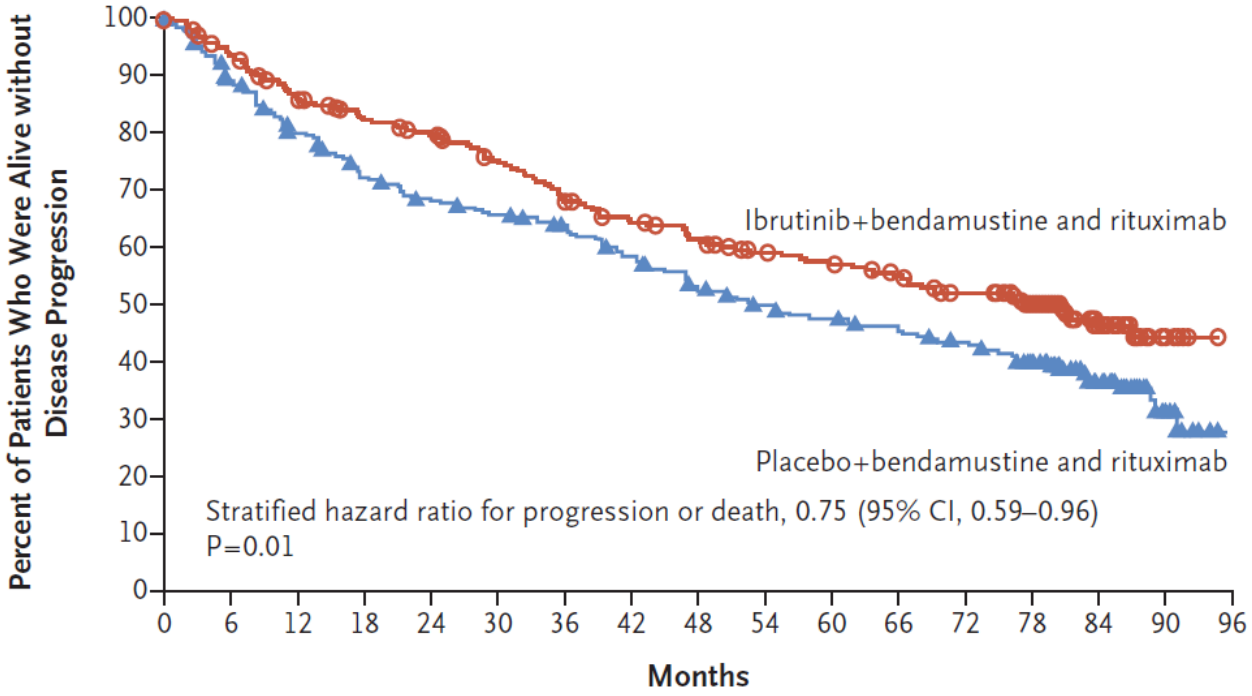
Regimen	Phase	PFS	P	OS
R-Benda vs R-CHOP[1]	3 (STiL)	Med 35 mo vs 22 mo	0.0044	
R-Benda vs. R-CHOP[2]	3 (BRIGHT)	3-yr ≈ 60% vs ≈ 30%	0.0035	Med NR at 5 yrs either arm
R-BAC 500[3]	2 (≥ age 65 or inelig for ASCT)	2-yr 81%		2-yr 86%
R-BAC 500 vs R-Benda[4]	Retrospective (inelig for ASCT)	2-yr 87% vs 64%		Med 10 yrs vs 6.5 yrs
R-Benda vs R-HyperCVAD[5]	2 (SWOG 1106)	5-yr 69% vs 62%		5-yr 80%* vs 74%
R-Benda vs **R-Benda-Bortez**	3 (E1411) MR vs. MR + len	2-yr 75% vs 80%	NS	

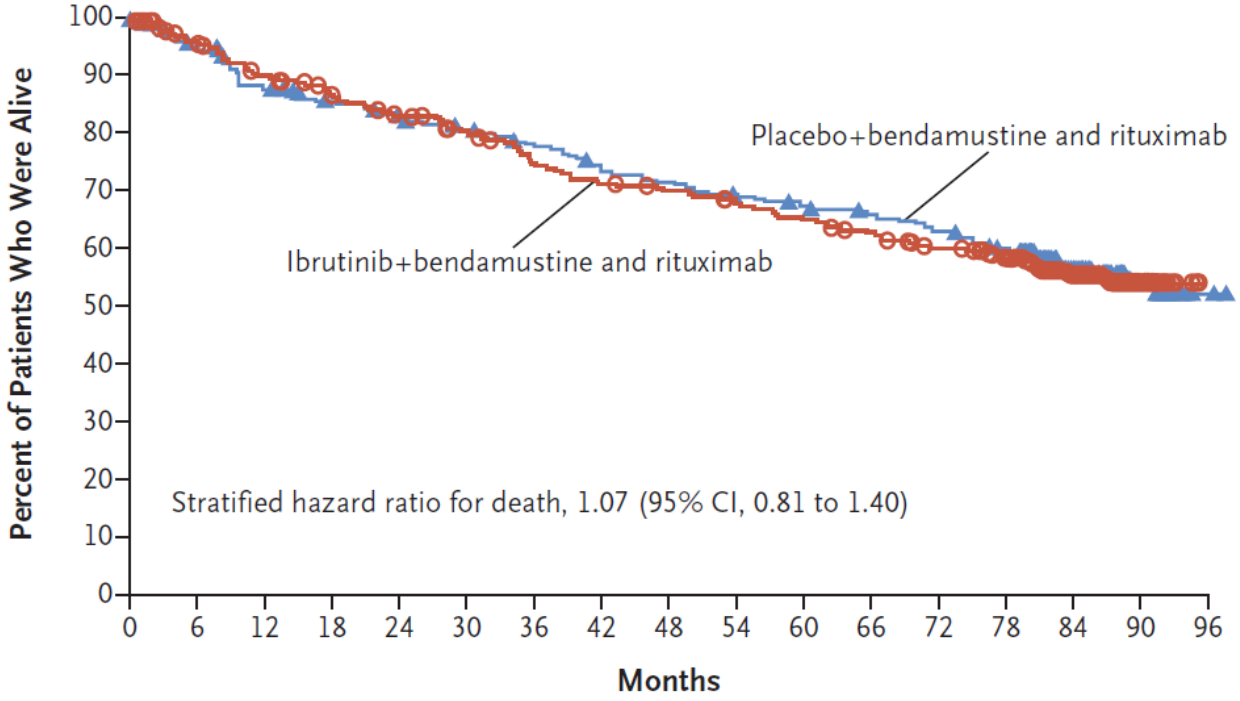
* 91% ASCT vs 60% no ASCT

1. Rummel et al Lancet 2013;381:1203–10
2. Flinn et al JCO 2019;37:984-991
3. Visco et al Lancet Haem 2017;4:e15
4. Bega et al Cancers 2021:13;6089
5. Kamdar et al Blood Adv 2019;3:3132-3135
6. Smith et al ASCO 2021, abstr 7503

Phase 3: Ibrutinib + BR + R main. vs. BR + R main.

1st line tx in older pts with MCL (SHINE)





Ibrutinib + BR + R main

- Improves median PFS by 2.3 years (80.6 mo vs 52.9 mo)
- No improvement in pts with del17p

- No difference in OS at med f/u 7 yrs
- Deaths due to AE 10.7% ibr arm vs 6.1%

Results of Phase 3 BR +/- Acala pending

Wang et al NEJM 2022 DOI: 10.1056/NEJMoa2201817

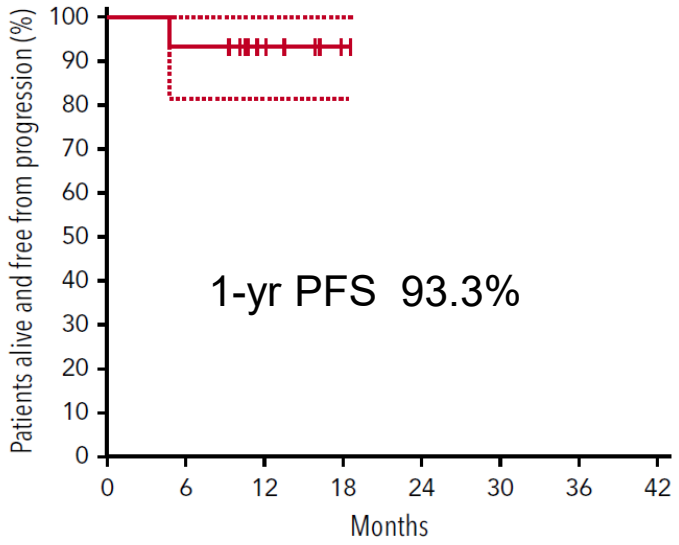
Maintenance Therapy in 1st Line MCL

- Maintenance R vs IFN **after R-CHOP** (MR until PD or intolerance)[1]
  - Med PFS 5.4 vs 1.9 yrs, P < 0.001
  - Med OS 9.8 vs 7.1 yrs, P = 0.0026
- Maintenance R vs. Obs **after ASCT** (Q2m x 3 yrs)[2]
  - 4-yr PFS 83% vs. 64%, P < 0.001
  - 4-yr OS 89% vs. 80%, P = 0.04
- Maintenance R vs Obs **after R-Benda,** STiL MAINTAIN trial (Q2m x 2 yrs)[3]
  - No difference PFS/OS at median f/u 4.5 yrs
  - Median PFS: NR (MR) vs 55 mo and median OS 70 mo (MR) vs. NR
- Maintenance Len vs Obs **after ASCT** (2 yrs of len)[4]
  - 3-yr PFS 80% vs. 64%, P = 0.001
  - No difference OS

1. Hanneke et al JCO 2019;38:248-256
2. Gouill et al. NEJM 2017;377:1250-1260
3. Rummel et al. JCO 2016:35, 15 Supp
4. Ladetto et al. Lancet Haem 2021:8;e34-44

Non-"chemotherapy" approaches as 1st line therapy in MCL

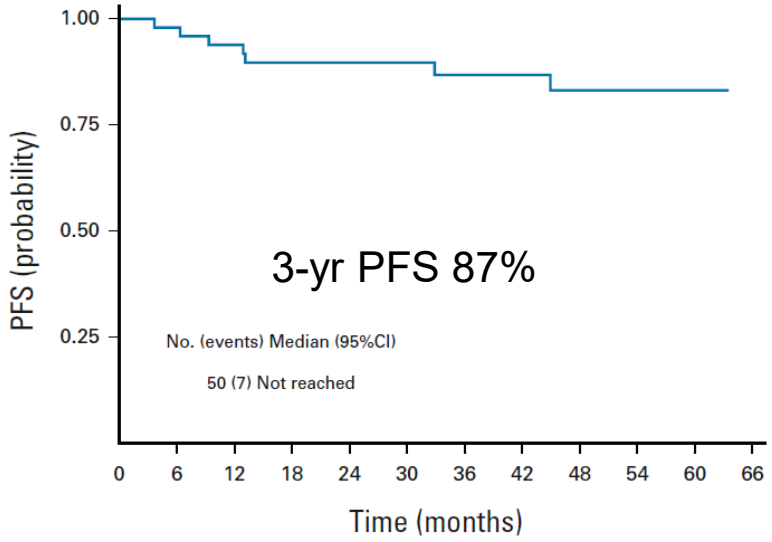
Obina-Ibrutinib-venetoclax



- Ph1/2, **pts ≤65**, n=15
- ORR 93%, CR 87%

Le Gouill et al Blood. 2021;137:877-887

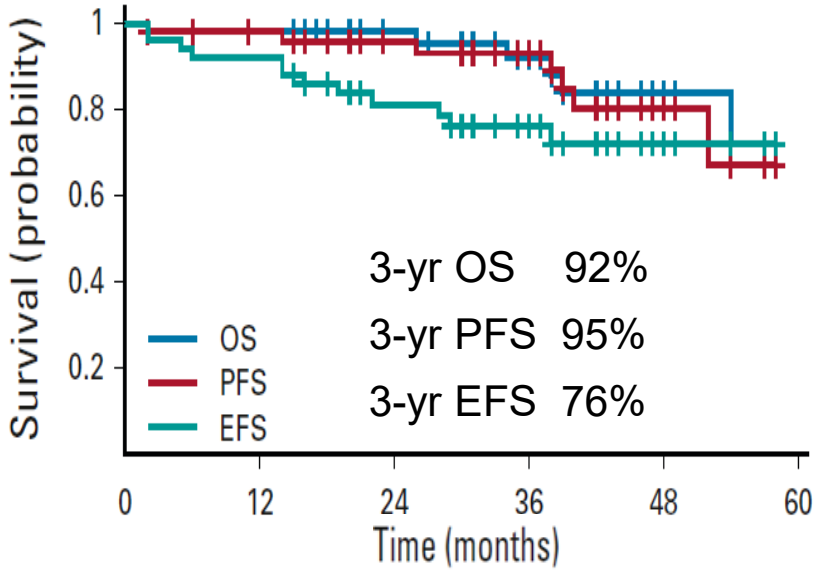
R-Ibrutinib in pts ≥65



- Ph2, n=50
- ORR 87%, CR 71%

Jain et al JCO 2021;40:202-212

R-Ibrutinib in indolent MCL



- Ph2, n=50
  - No dx-related symptoms, nonblastoid, Ki-67 <30%, tumor diameter ≤3 cm
- ORR 94%, CR 86%
- 69% MRD neg at 2-yrs & elig to d/c Ibr

Giné et al JCO 2022;40:1196-1205.

Results of large "real world" cohorts in 1st line MCL
Role of ASCT and Maintenance R

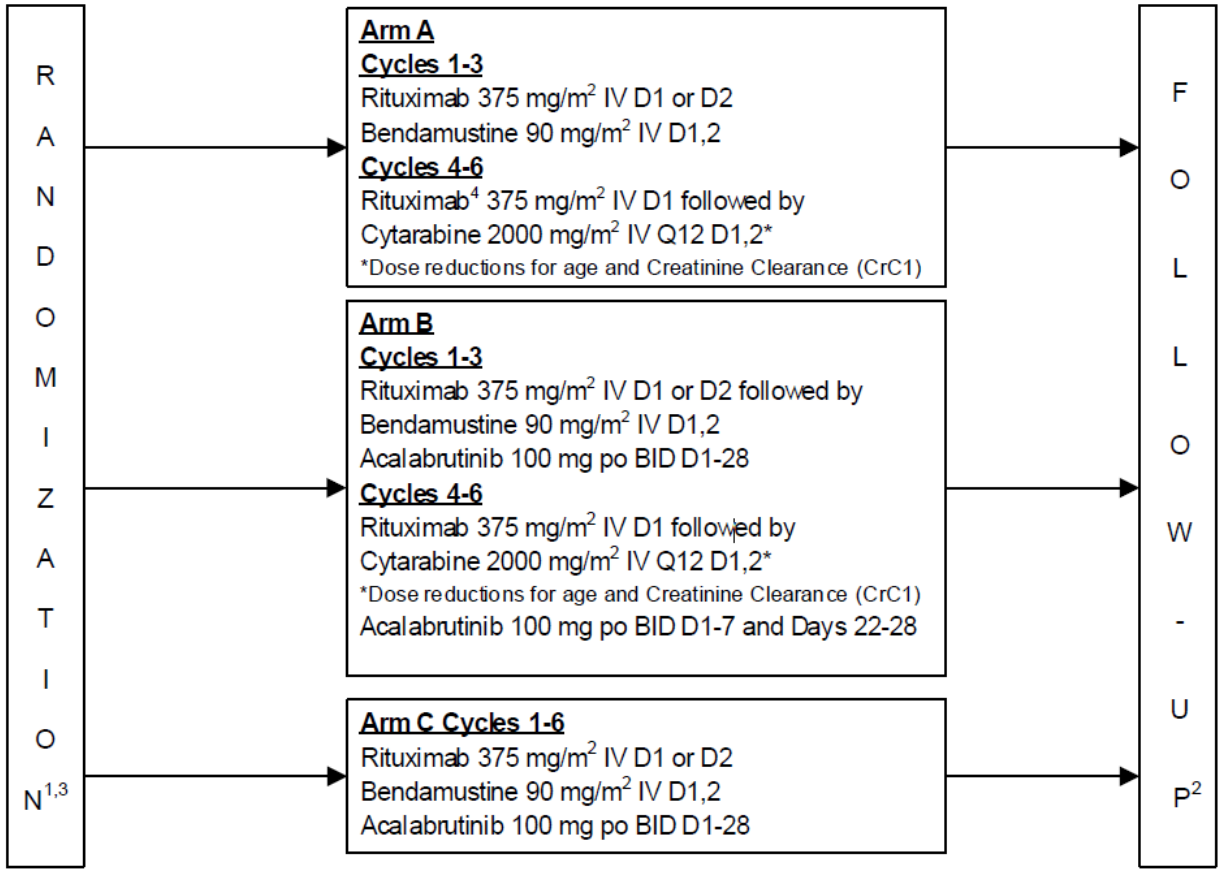
- Retrospective data from 4,216 pts with MCL in Flatiron Health electronic record, mostly US community oncology practices, treated 2011-2020
- 3614 pts with documented 1st line treatment
  - R-Benda most common regimen (increased 19% 2011 to 53% 2020)
- 1265 pts < 65 yrs
  - 30% Ara-C-based induction
  - 23.5% received ASCT
  - No difference in TTNT or OS with ASCT versus no ASCT
- Maintenance R vs. Obs after R-Benda
  - Med TTNT 65 mo (MR) vs 38 mo, P < .001
  - Med OS 89 mo (MR) vs 78 mo, P < 0.001

Martin et al. JCO 2022; doi.org/10.1200/JCO.21.02698

Ongoing Phase 3 trials to address 1st line BTK and ASCT in MCL

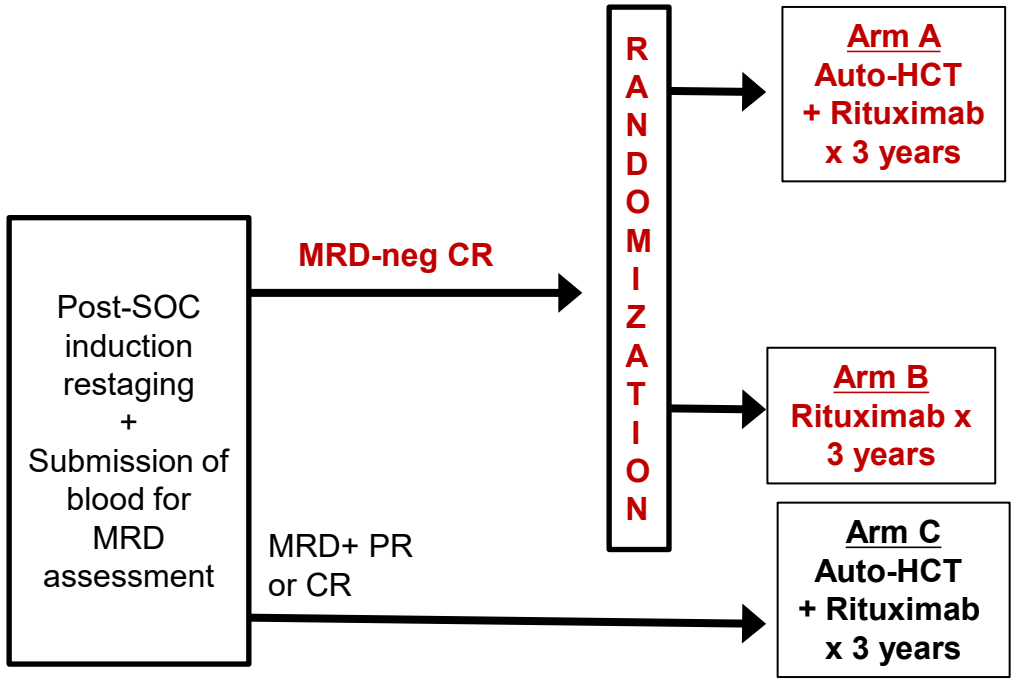
EA4181: Untreated MCL

BR/R-AraC vs BR/R-AraC+Acala vs BR + Acala



EA4151: Consolidation after initial therapy

Auto-HST + MR vs MR



BTK inhibitors in relapsed MCL

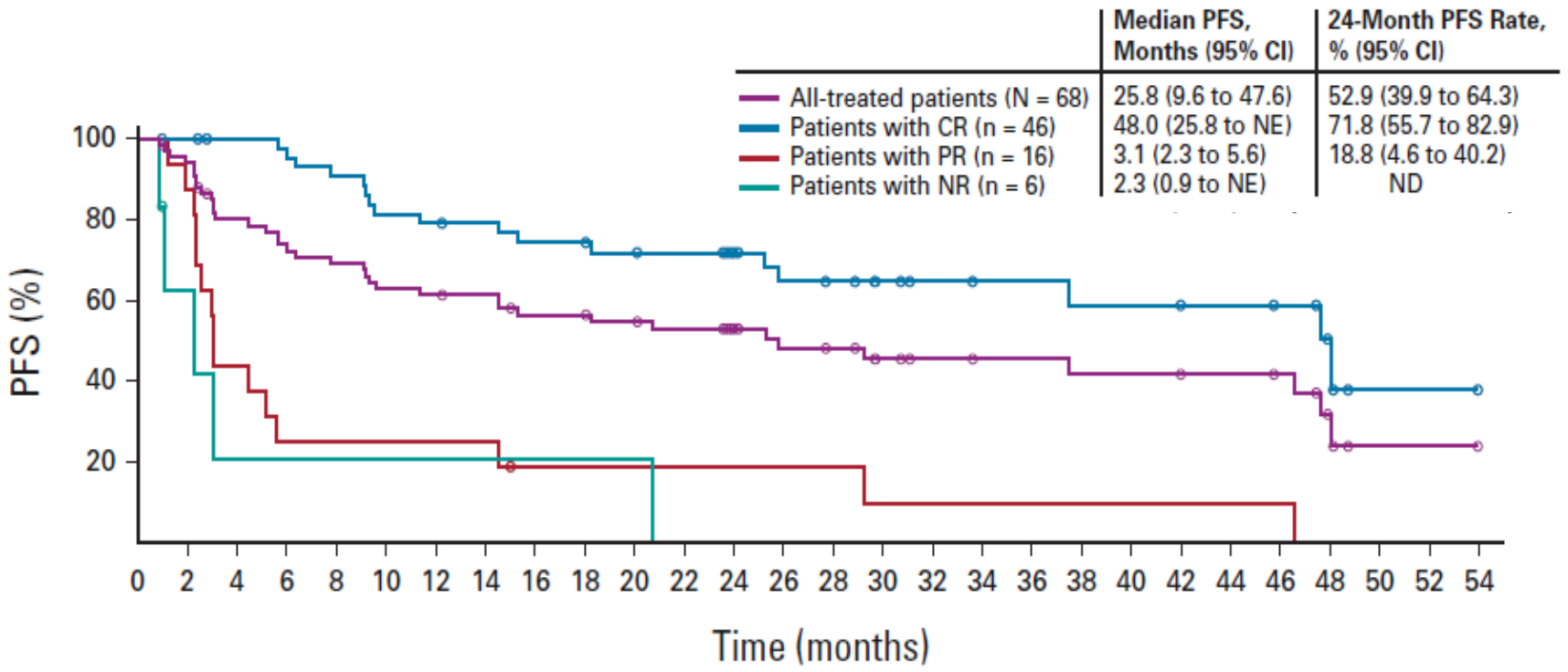
Approved Agents	# Pts	ORR	CR	PFS	Arrhythmia
Ibrutinib[1]	111	67%	23%	2-yr 31%	11%, 6% Gr3
Acalabrutinib[2]	124	81%	40%	1-yr 67%	0
Zanubrutinib[3]	86	84%	80%	3-yr 48%	0
Zanubrutinib[4]	32	84%	25%	Med 21 mo	6.3%
Investigational					
Pirtobrutinib[5] (LOXO-305)*	56 (93% prior BTK)	52%	25%		<1%

* **Highly selective BTK inhibitor with equal potency against WT and C481-mutated BTK**

1. Wang et al Blood 2015; 126:739–745.
2. Wang et al Lancet 2018; 391:659–67
3. Song et al Blood 2022; 139:3148-3158
4. Tam et al Blood Adv 2021; 5:2577-2585
5. Mato et al Lancet 2021;397;892-901

CAR-T therapy for relapsed MCL (KTE-X19)

- Phase 2, n = 68
- ORR 91%, CR 68%
- Median PFS 25.8 mo
- Median OS 46.6 mo
- Gr ≥3 CRS 15%
- Gr ≥3 neurotoxicity 31%
- Worse outcomes if prior bendamustine
  - < 6 mo is worst
  - lower peak CAR-T#

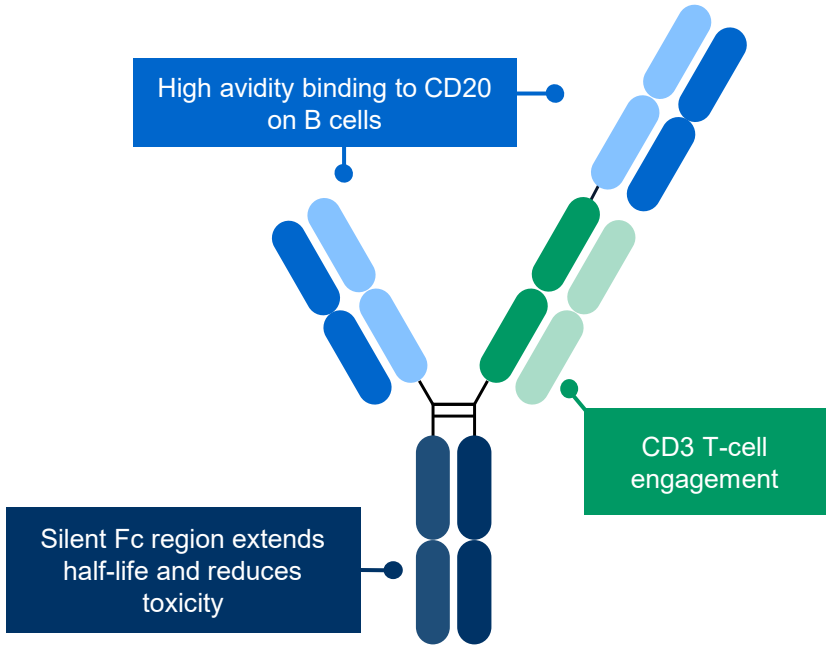


Wang et al N Engl J Med 2020;382:1331-42
Wang et al J Clin Oncol 2022; https://doi.org/10.1200/JCO.21.02370

Bispecific Ab Glofitamab for relapsed MCL

- Phase 1-2, n= 21
- Obinatuzumab Day -7
- Step up dosing over 3 weeks to mitigate CRS
- **ORR: 81%, CR 68%**
- ORR similar with or without prior BTKi
- CRS mostly low grade, 1 Gr 4 CRS was reported in pt with rapid progression
- ICANS-like AEs infrequent, low grade and resolved within 1 day.

Glofitamab: *CD20 ×CD3 bispecific antibody with 2:1 configuration for increased potency vs 1:1 configuration*



Philips et al ASH 2021 Blood;138:130-133

MCL and *TP53*

- *TP53* deletion (FISH)
- *TP53* mutation (next-generation sequencing)
- *TP53* deletions: worse prognosis post-ASCT
  Median OS: 7-yr vs 5.1-yr (*TP53*)[1]
- ***TP53* mutations** associated with **dismal prognosis** even after intensified treatment (Nordic trial)
  - Median OS: 12.7-yr vs 1.8-yr[2]
- Combined *TP53* and *CDKN2A,* or complex karyotype are associated with even worse OS[3]
- **BTK inhibitors, CAR-T cells may improve outcomes of del17p/TP53 mutated MCL**

Agent	# Pts	ORR (%)		Med OS (mo)		Med PFS (mo)	
	TP53	TP53	WT	TP53	WT	TP53	WT
BR+Len[4]	9	NR		35	69	10	42
Zanubrutinib[5]	15	80	90	86% 3-y	42% 3-y	NR	15
Ven+ ibrut[6]	12	50	75	N/A		26	29
Ibrut+len+R[7]	11	73	79	N/A			
CAR-T[8]	6	100	100	NR	NR	NR*	48

* 2/6 remain in remission (4-78 mo)

Consider FISH and NGS testing in all newly dx MCL

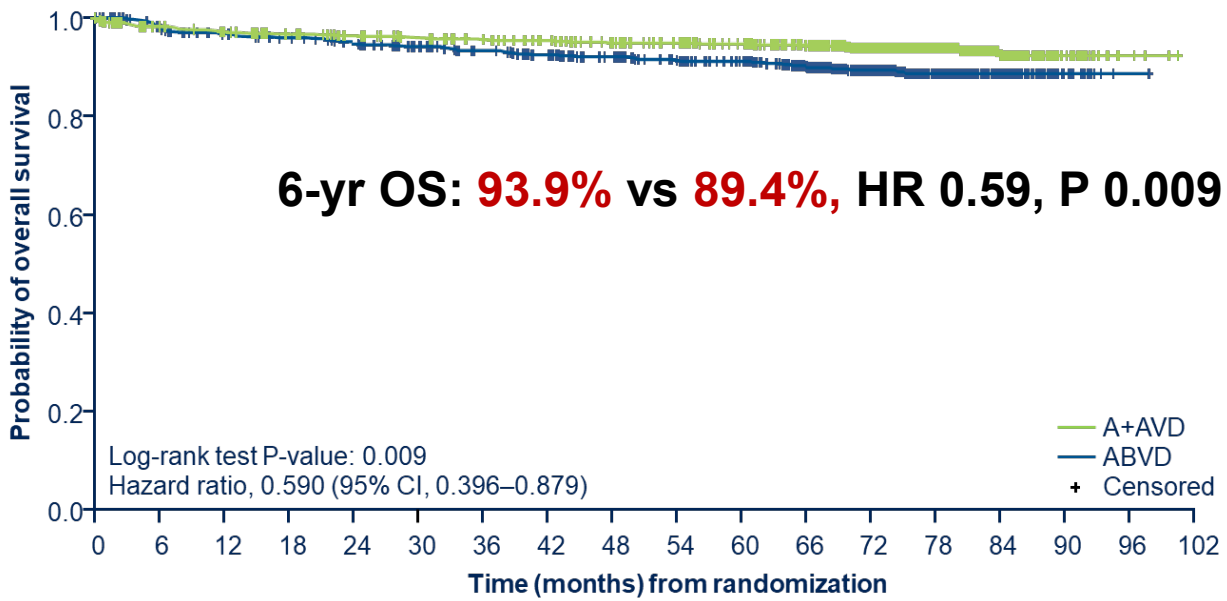
1. Delfau-Larue et al Blood. 2015;126:604-611
2. Eskelund et al Blood. 2017;130:1903-1910
3.Obr et al Clin Lymphoma Myeloma Leuk.2018;18:762-76
4. Eskelund et al Haematologica 2018; 103:e534
5.Song et al Blood 2022; 139:3148-3158
6. Tam 2018 NEJM 2018;378:1211-23
7.Jerkeman et al Lancet Haem 2018;5:e109-16
8. Wang et al J Clin Oncol 2022;doi/10.1200/JCO.21.02370

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

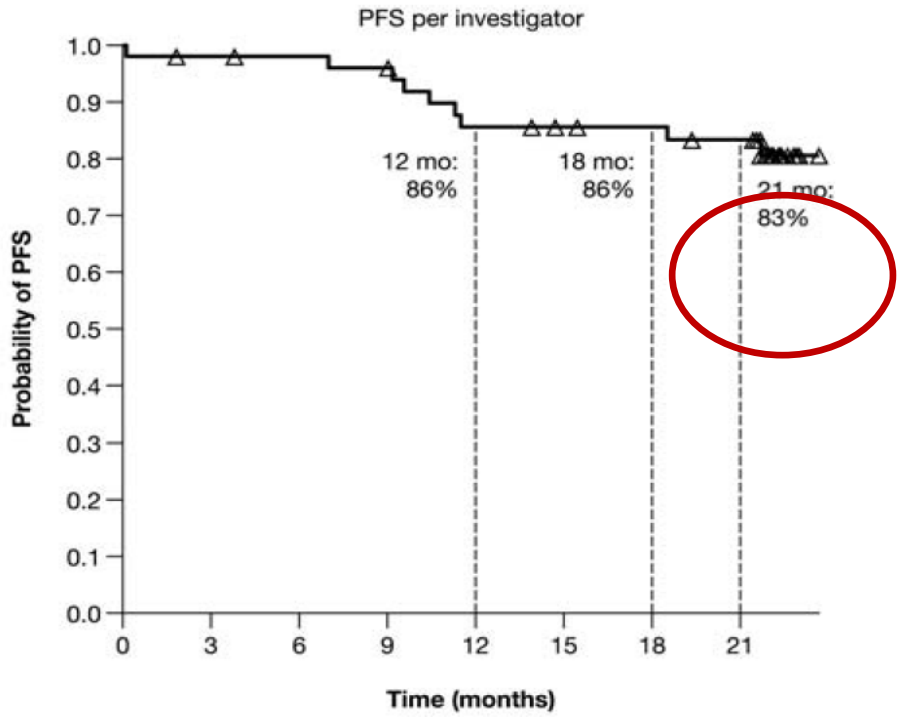
Subgroup	HR (CI)
Age <60	0.51 (0.29 - 0-89)
IPS 2-3	0.62 (0.33 - 1.14)
IPS 4-7	0.48 (0.26 – 0.88)
Stage 4	0.48 (0.29 – 0.80)
EN site >1	0.30 (0.14 – 0.67)
Male	0.43 (0.25 – 0.73)

- *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

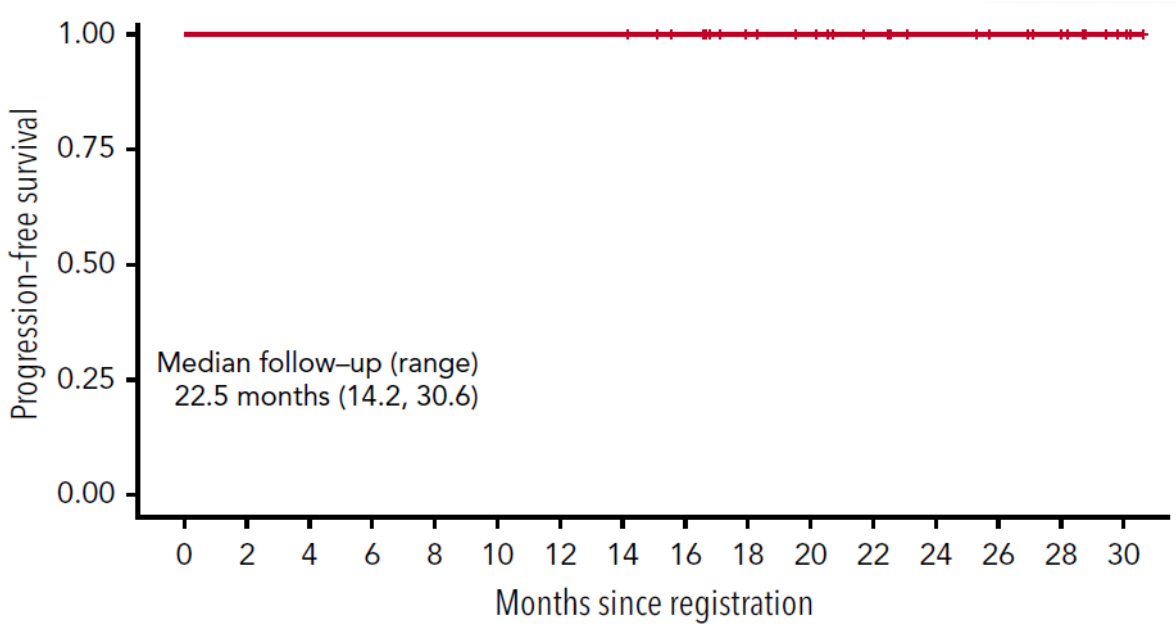
Nivo-AVD (Checkmate 205)



- 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

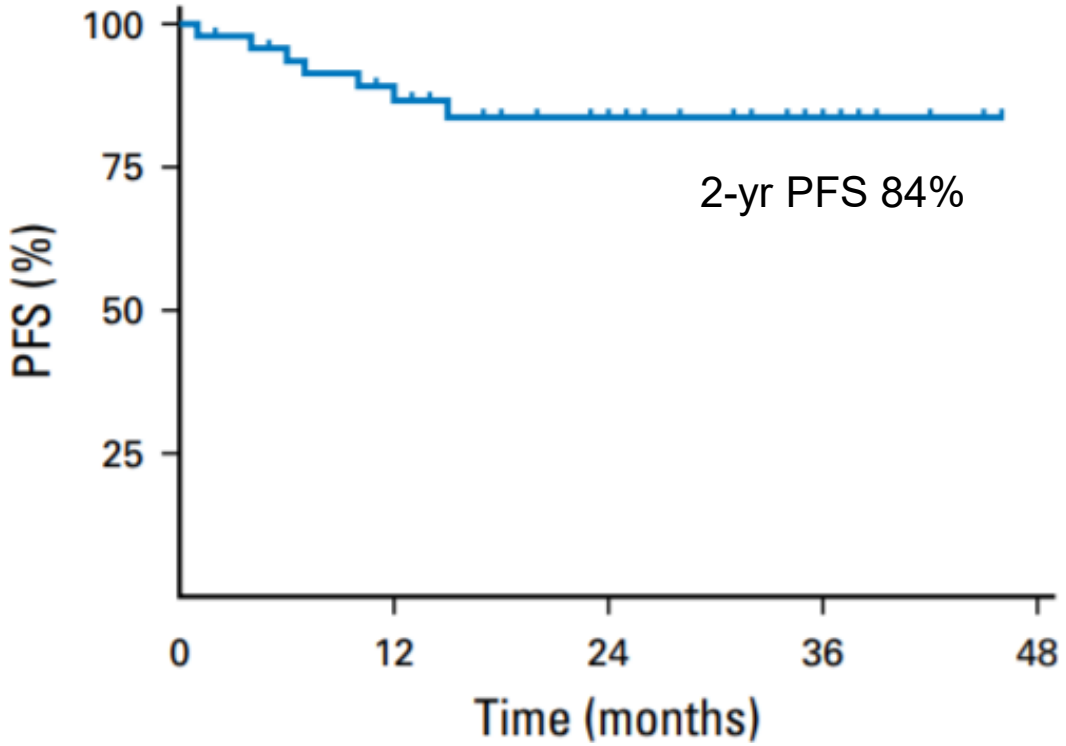


- Stage 3-4 (n=18), 2B (n=12)

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

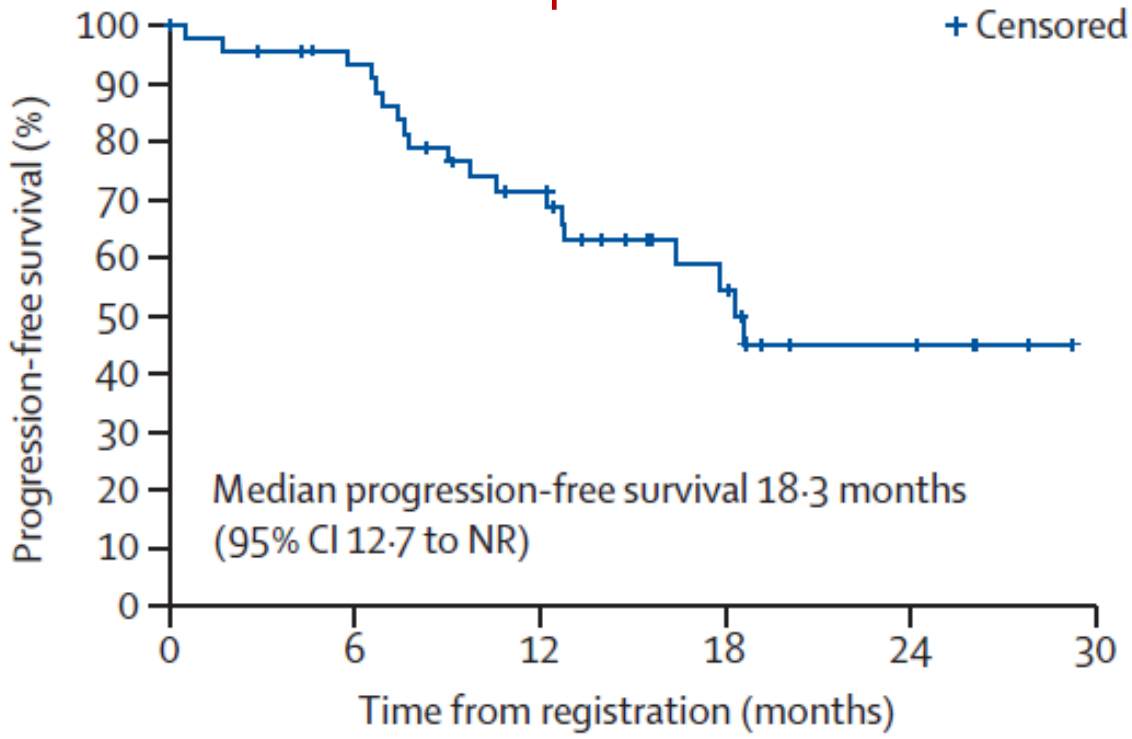


Neuropathy: Gr3 4%; Gr 2 27%

Evens et al JCO 2018;36:3015-22

Bv-Nivo x 8

Suboptimal

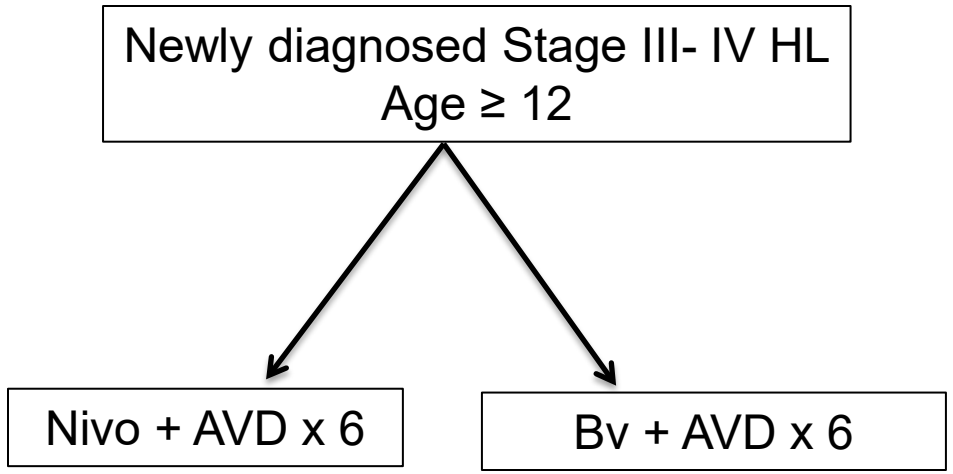


Neuropathy: Gr3 11%; Gr 2 35%

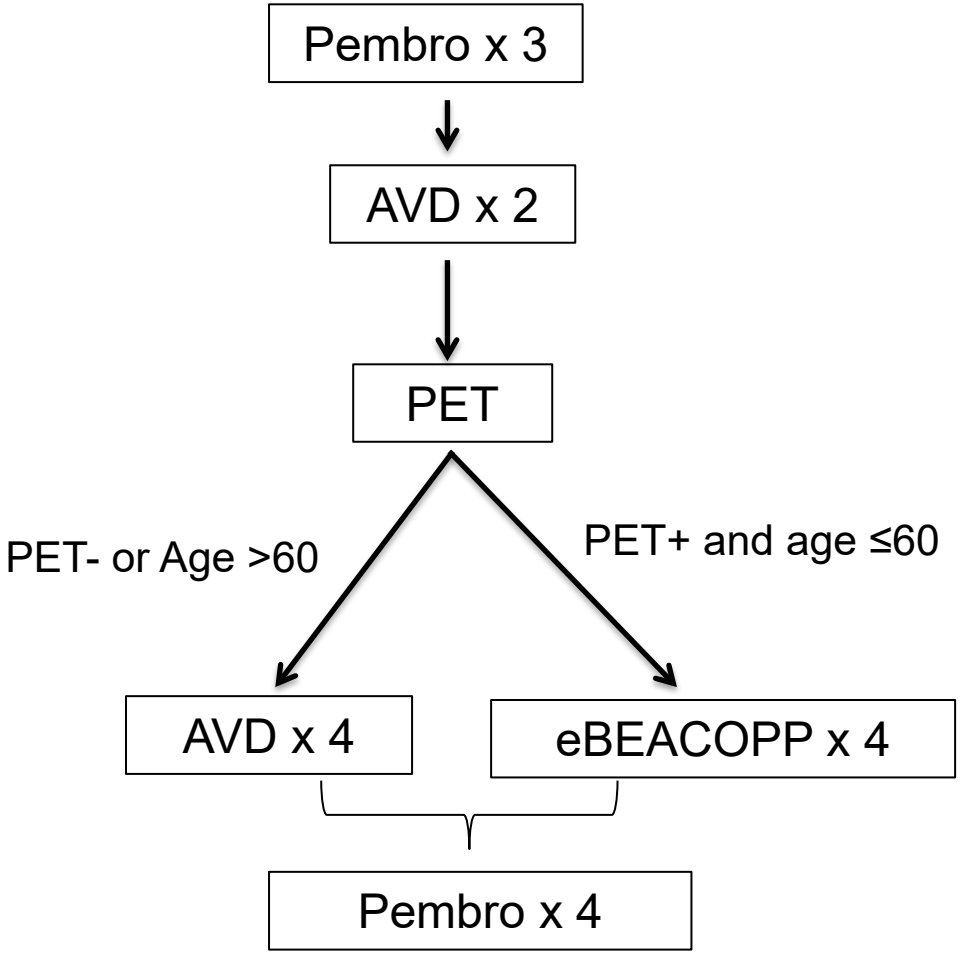
Cheson et al Lancet Haem 2020;7:e808–15

Advanced stage: *ongoing trials*

S1826

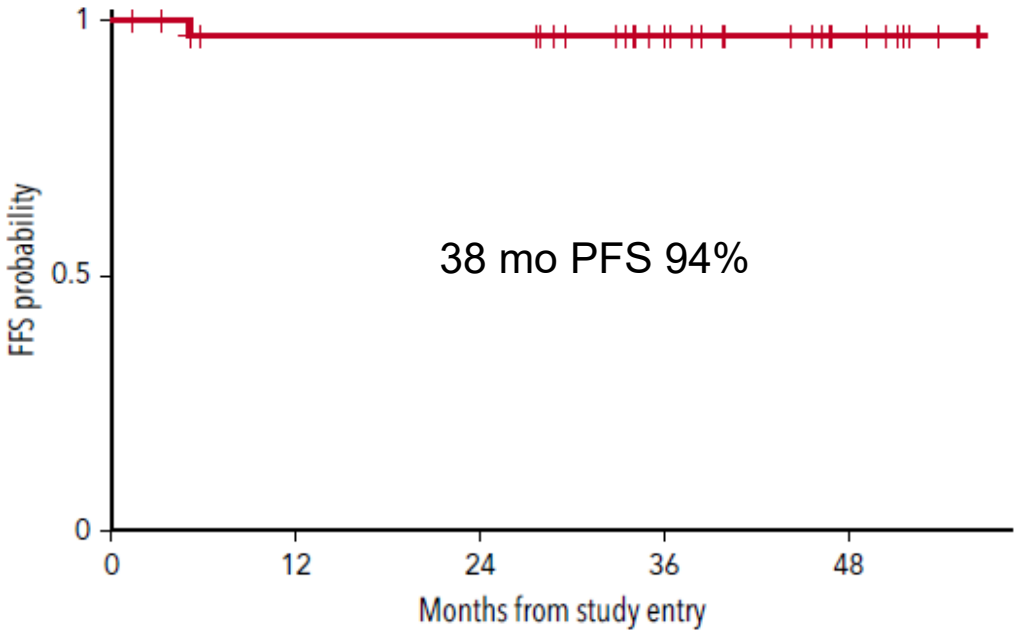


KEYNOTE –C11



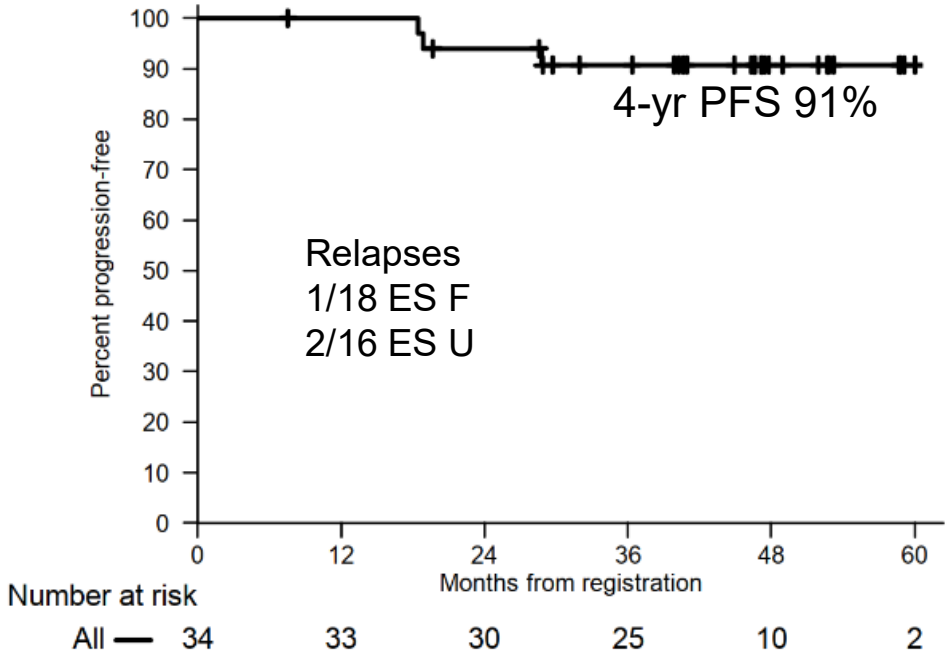
Published *pilot/Phase 2* trials incorporating Bv: Early stage

Bv-AVD x 4 (non-bulky)



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

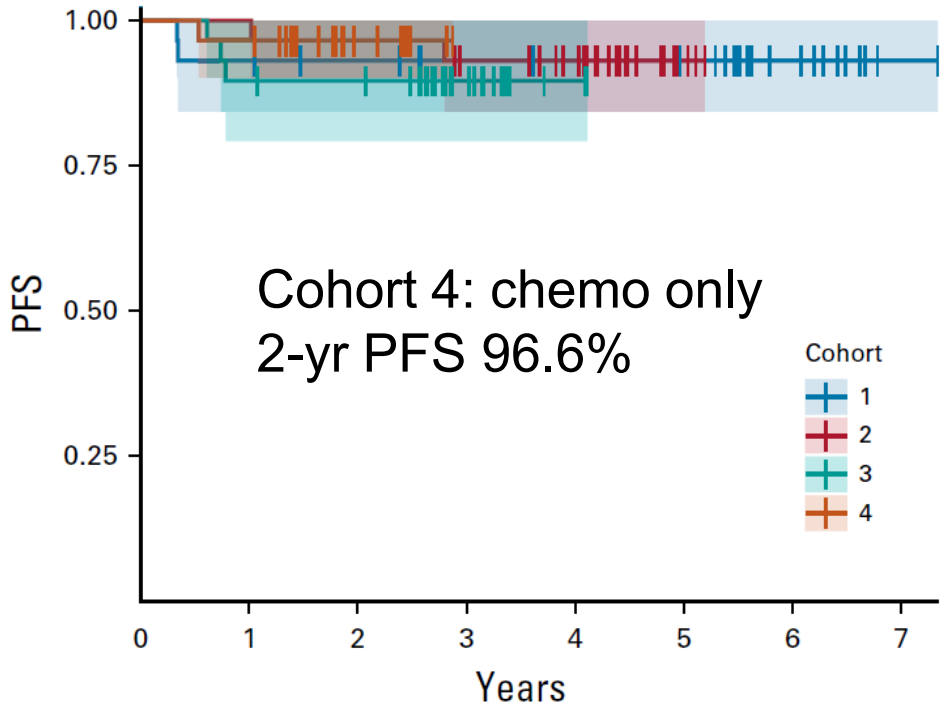
Bv-AD x 4- 6 (non-bulky)
Eliminate velban



Abramson et al Lugano 2021;279: abstr 198

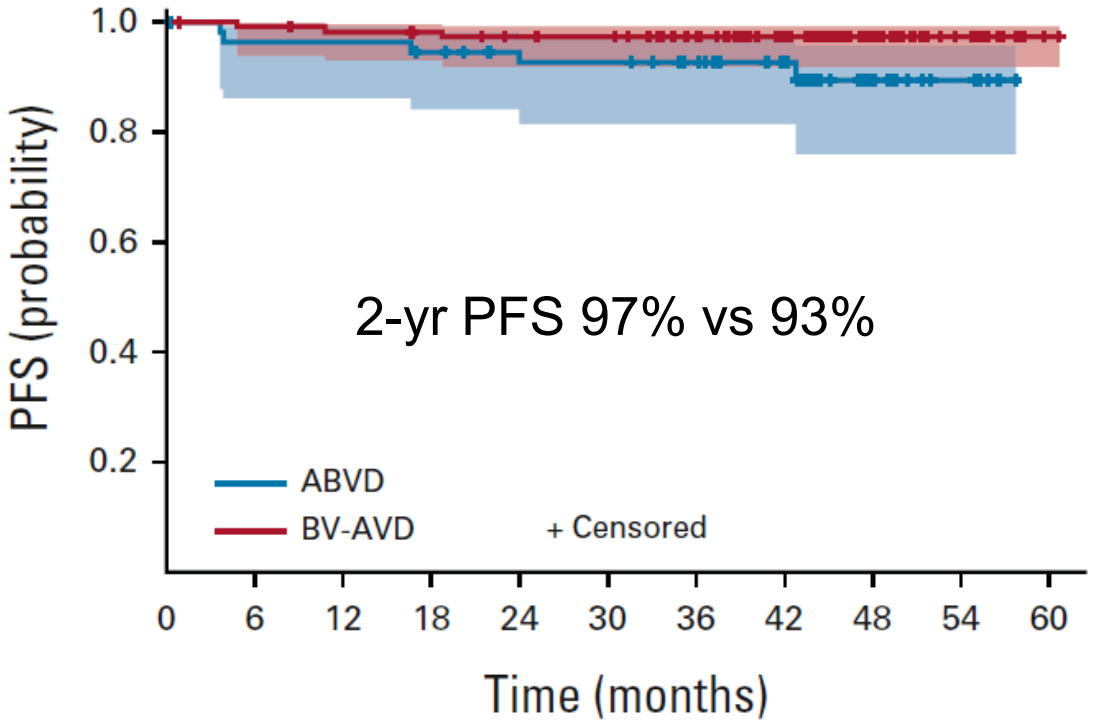
Published pilot/Ph2 trials incorporating Bv: Early stage

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

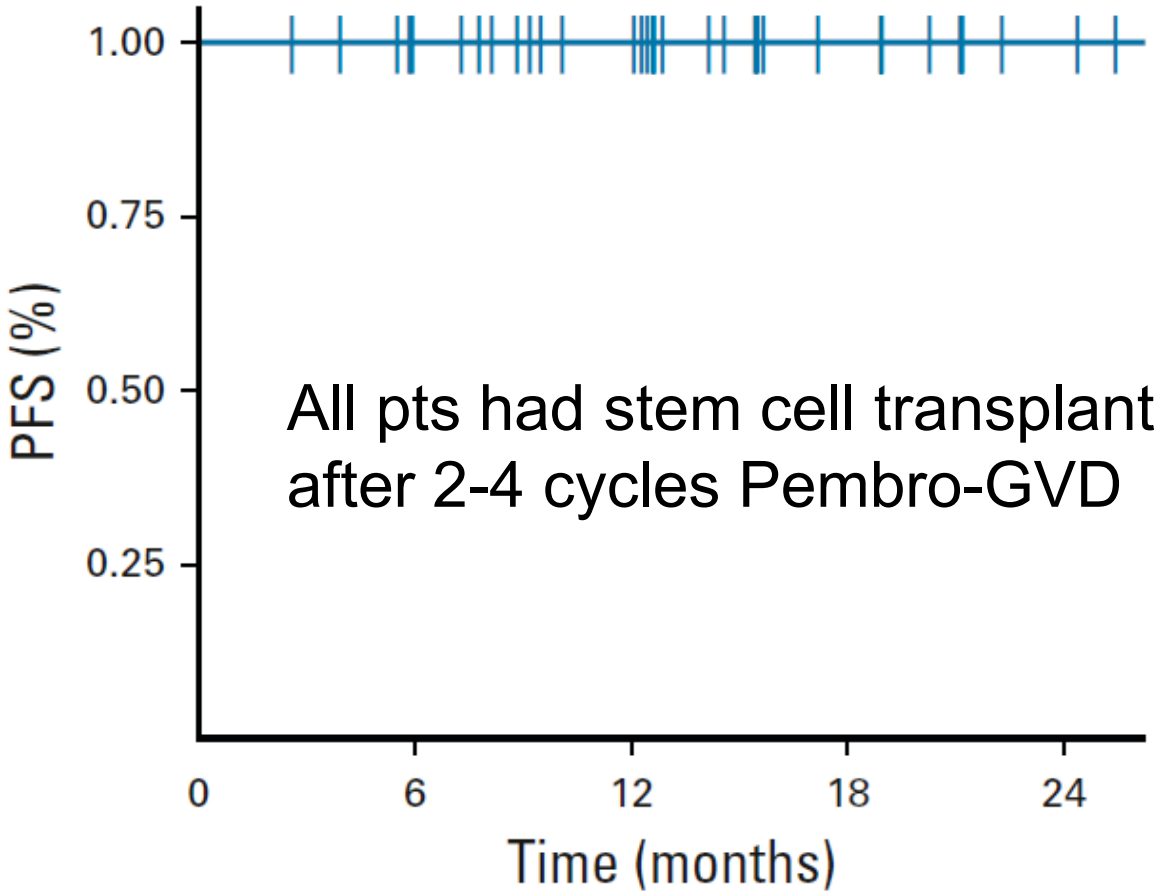
Rel/ref HL: incorporating new agents into second line therapy

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

Bartlett JCO Grand Rounds 2021;39:3097-3103

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



*gemcitabine, vinorelbine, liposomal doxorubicin

Toxicity

- Gr3:
  - neutropenia (10%)
  - transaminitis (10%)
- Gr 1-2
  - rash (46%)
  - mucositis (33%)
  - transaminitis (31%)
  - infusion related rxn lDoxil (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

Moskowitz et al JCO 2021;39:3109

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
- Ara-C improves outcomes in 1st-line MCL compared to anthracycline-based tx (role with benda-based induction under investigation in E4181)
- Non-randomized trials suggest benefit to consolidative ASCT as 1st-line tx in MCL (Phase 3 E4151 ongoing)
- Test patients with symptomatic MCL for TP53 mutation and consider early BTK, CAR-T
- Bv-AVD improves OS in higher risk advanced stage HL

- **Liberal use of Covid Vax, Pax, Evusheld in all NHL pts**