New Strategies for MCL

Bijal Shah

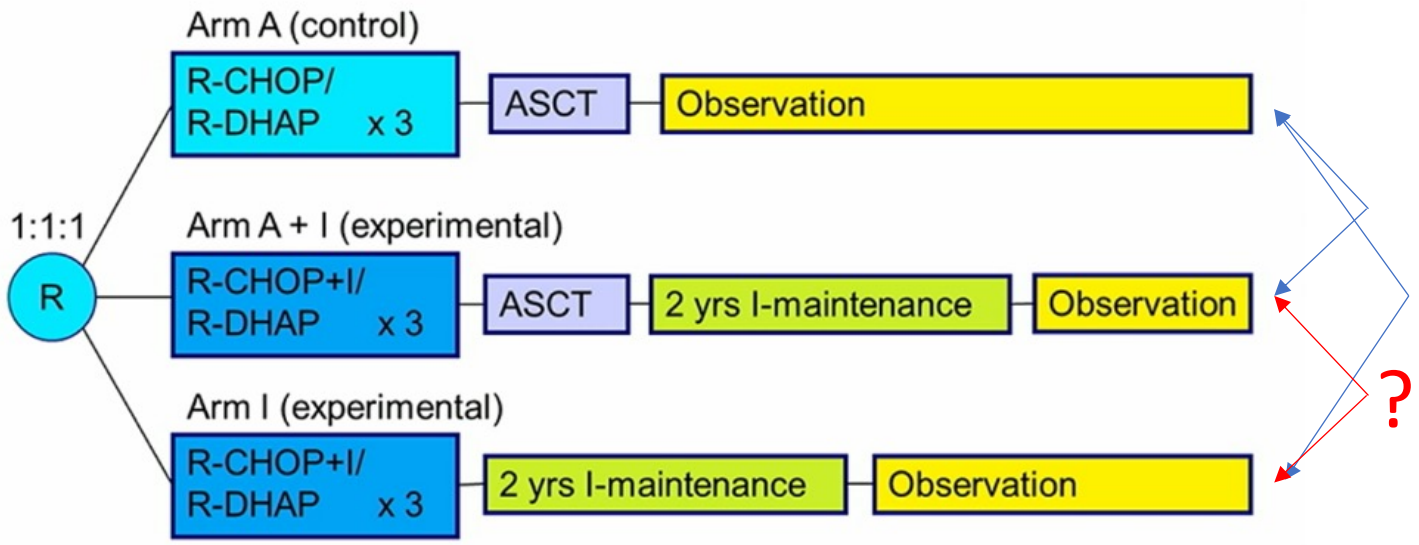
Objective

- Review updates in Mantle Cell Lymphoma highlighted at the 2022 American Society of Hematology Meeting

Newly Diagnosed MCL

Ibrutinib + Autologous Transplant

TRIANGLE: Ibrutinib plus standard first-line treatment or as a substitute for ASCT in younger MCL patients



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

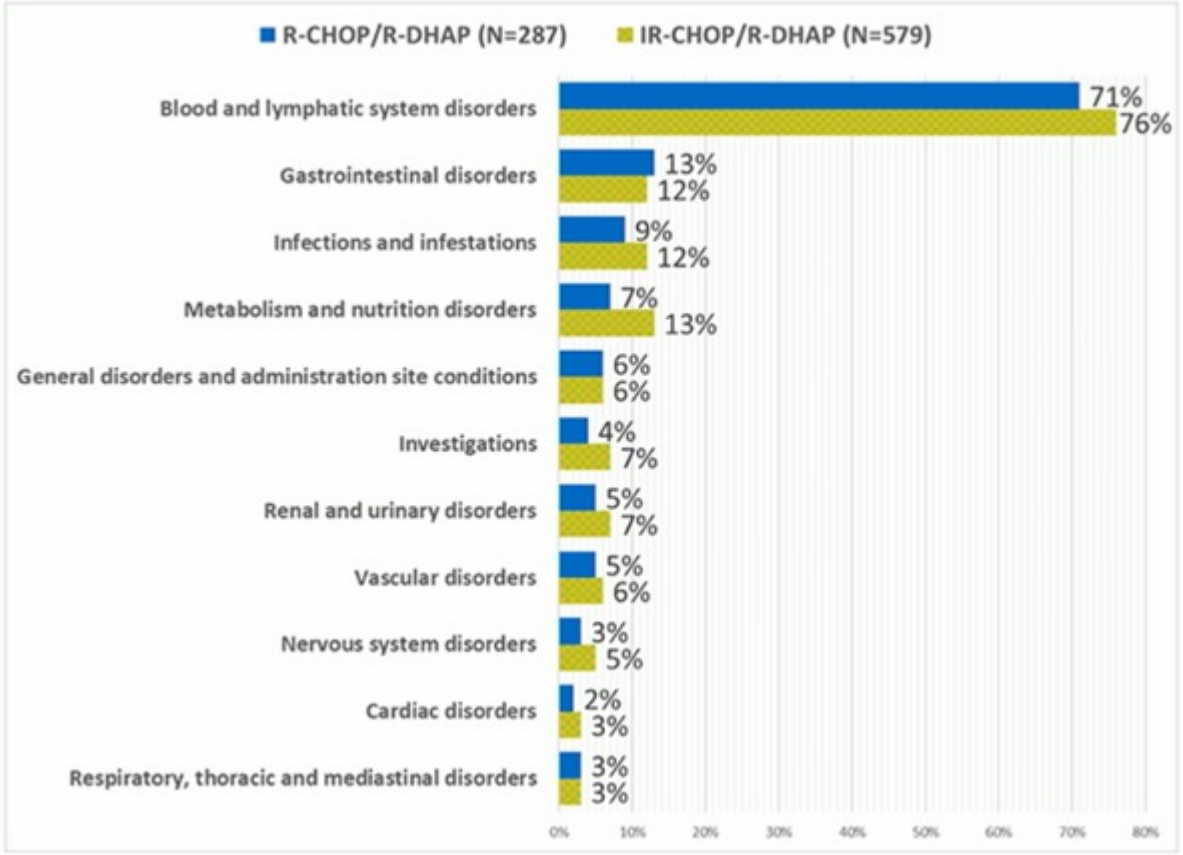
- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

Dreyling et al, ASH 2022

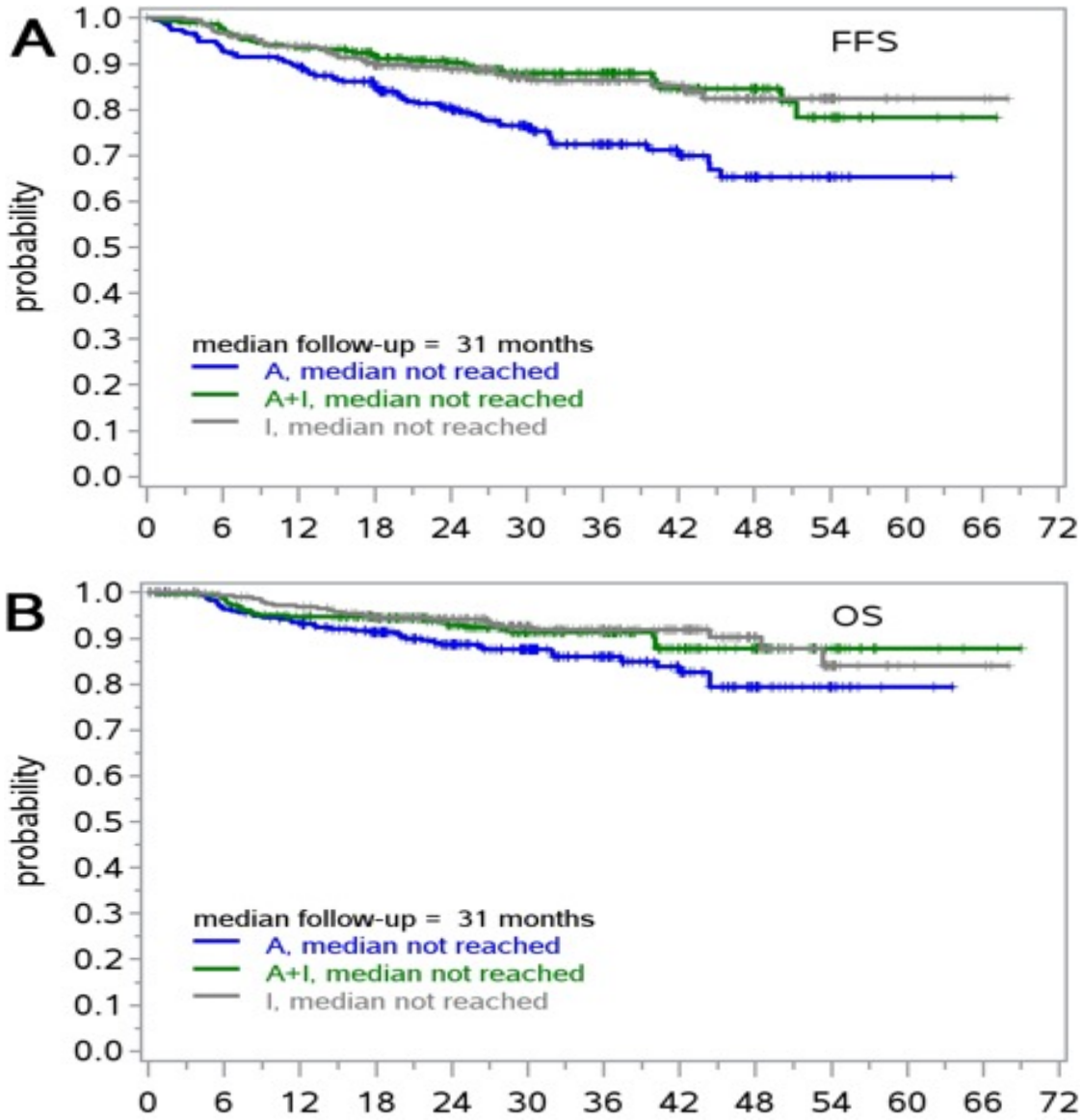
Induction Response and Toxicity



	Ibrutinib +/- AutoSCT (n=559)	AutoSCT (n=272)	P-Value
ORR	**98%**	94%	p=0.0025
CR	**45%**	36%	p=0.0203

The inclusion of Ibrutinib was associated with a modest increase in toxicity during induction, but was associated with a significant improvement in ORR and CR

Dreyling et al, ASH 2022



	Ibrutinib + AutoSCT (n=292)	AutoSCT (n=288)	P-Value
3y FFS	**88%**	72%	HR 0.52, p=0.0008
3y OS	91%	86%	-

	AutoSCT (n=288)	Ibrutinib (n=290)	P-Value
3y FFS	**72%**	86%	HR 1.77, p=0.9979
3y OS	86%	92%	-

The inclusion of Ibrutinib was associated with an improvement in FFS

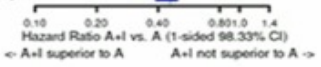
There is no clear benefit of AutoSCT in FFS or OS

Dreyling et al, ASH 2022

FFS Superiority of A+I vs. A

??

Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	580	103	0.46 (0 - 0.72)
Sex (p=0.0016)			
Female	146	23	0.62 (0 - 1.51)
Male	434	80	0.43 (0 - 0.71)
MIPI			
Low	336	40	0.49 (0 - 0.99)
Intermediate (p=0.49)	159	35	0.35 (0 - 0.77)
High (p=0.69)	85	28	0.58 (0 - 1.32)
Cytology (p=0.48)			
Non-blastoid	426	68	0.36 (0 - 0.65)
Blastoid	60	18	0.57 (0 - 1.56)
Ki-67 (p=0.82)			
Low	234	39	0.50 (0 - 1.02)
High	150	38	0.47 (0 - 0.90)
P53 expression (p=0.039)			
Low	284	36	0.64 (0 - 1.32)
High	44	16	0.15 (0 - 0.60)
High risk biology (p=0.19)			
Low	270	31	0.63 (0 - 1.38)
High	64	25	0.32 (0 - 0.79)
R maintenance ITT (p=0.96)			
No	191	48	0.44 (0 - 0.84)
Yes	389	55	0.46 (0 - 0.85)
R maintenance mAT (p=0.94)			
No	217	55	0.45 (0 - 0.81)
Yes	363	48	0.44 (0 - 0.86)



A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I

- No difference in efficacy according to cytology and Ki-67
- More effective in high p53 expressors
- Trend towards higher efficacy in high-risk biology
- No differential efficacy by R maintenance

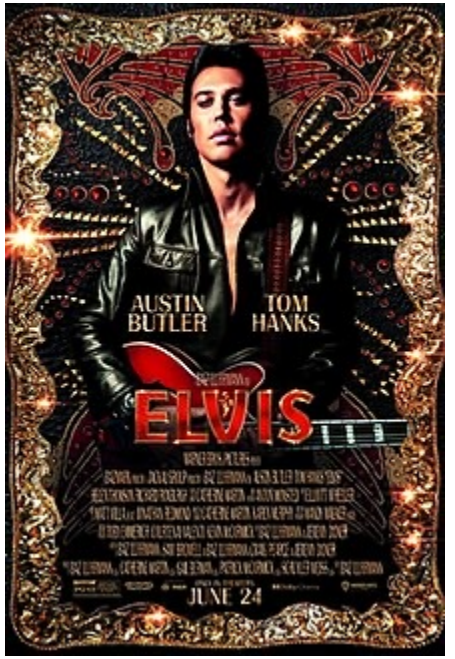
Dreyling et al, ASH 2022

Cause of Death

Cause of death	A n=39/288 (13,5%)		A+I n=25/292 (8,6%)		I n=23/290 (7,9%)	
Lymphoma	16	5,6%	4	1,4%	11	3,8%
Concomitant disease	11	3,8%	7	2,4%	5	1,7%
Lymphoma and concomitant disease	0	0%	1	0,3%	1	0,3%
Secondary malignancy	1	0,3%	2	0,7%	0	0%
Therapy	4	1,4%	3	1,0%	0	0%
Therapy and concomitant disease	1	0,3%	0	0%	0	0%
Unknown	6	2,1%	8	2,7%	6	2,1%

Dreyling et al, ASH 2022

Dose De-intensified Chemotherapy with Venetoclax



Study Schema

Key Inclusion Criteria
- Adult patients with untreated MCL
- ECOG PS 0-2

Venetoclax
- PO Days 8-28 of first cycle (ramp up) and days 1-10 of cycles 2-6

Obinutuzumab
- IV on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2-6

Bendamustine
- 90mg/m^2 on days 1 & 2 for 6 cycles

Primary endpoint
- Efficacy

Secondary endpoints
- Safety
- Methods for determining molecular remission
- Long-term PFS and OS

https://clinicaltrials.gov/ct2/show/NCT03872180 (Accessed 5 Jan 2023)

Greenwell et al., ASH. 2022

Efficacy

Median age: 62 (range 41 – 80)

	ORR	CR
BR (n=151)	88.5%	57.6%
BR + Ibrutinib (n=171)	89.7%	65.5%
BO + Venetoclax (n=23)	**86%**	**83%**

Patients without Complete Response	TP53 mutation & del17p	Complex Karyotype	Blastoid	MIPI	Ki67
1. Progressive Disease	No	-	No	Intermediate	20%
2. Progressive Disease	Yes	-	-	High	-
3. Progressive Disease	Yes	Yes	Yes	Intermediate	80%
4. Partial Response	No	Yes	(noted at prog.)	Low	40%

Greenwell et al., ASH. 2022, Wang et al, NEJM 2022

Safety Results

Grade 3-4 Toxicity	Number
Neutropenia	6
Leukopenia	6
Thrombocytopenia	4
Hypophosphatemia	3
Anemia	2
Infusion reaction	2
Tumor lysis syndrome	2

Other Gr3-4 Tox (1 each): Appendicitis Fatigue, Foot pain, Hemorrhage, MI, Pneumonitis, SVT, Hyperkalemia

7 patients discontinued treatment prior to completion of therapy due to

- Disease progression (n=3)
- Recurrent Gr3 thrombocytopenia (n=1)
- Recurrent Gr3 neutropenia (n=2)
- CMV viremia without CMV disease (n=1)

- All patients who came off protocol therapy early due to toxicity achieved a CR on their interim restaging

- There were no deaths attributable to therapy

Chemotherapy Free Combinations

2884 Acalabrutinib Plus Venetoclax and Rituximab in Patients with Treatment-Naïve (TN) Mantle Cell Lymphoma (MCL): 2-Year Safety and Efficacy Analysis

Acalabrutinib	**Until PD**
+	
Rituximab	**24mo (monthly x6, then q2mo)**
+	
Venetoclax	**24mo (starting in c2)**

1º: Safety
2º: ORR, DOR/PFS/OS
Exploratory: MRD

Median Age: 66 (51-85)
sMIPI High: 19%
Ki67 ≥30%: 48%

73 Phase 2 Trial of Acalabrutinib-Lenalidomide-Rituximab (ALR) with Real-Time Monitoring of MRD in Patients with Treatment-Naïve Mantle Cell Lymphoma

Acalabrutinib	**Optional DC at 24mo if MRD negative**
+	
Rituximab	**Until PD (weekly x4, then 2mo)**
+	
Lenalidomide	**Optional DC at 24mo if MRD negative**

1º: 12mo CR Rate
2º: ORR, Safety, DOR/PFS/OS
Exploratory: MRD

Median Age: 64 (35-77)
MIPI High: 21%
Ki67 >30%: 29%

Wang et al., ASH. 2022, Ruan et al. ASH 2022

Safety and Efficacy

AVR (n=21)	
ORR / CR	100% / 90%
6mo MRD^{neg}	12 of 12 evaluable (100%)
12mo MRD^{neg}	12 of 14 evaluable (86%)
24mo MRD^{neg}	Not reported

ALR (n=24)	
ORR / CR	100% / 83%
6mo MRD^{neg}	12 of 24 evaluable (50%)
12mo MRD^{neg}	16 of 24 evaluable (67%)
24mo MRD^{neg}	10 of 12 evaluable (83%)

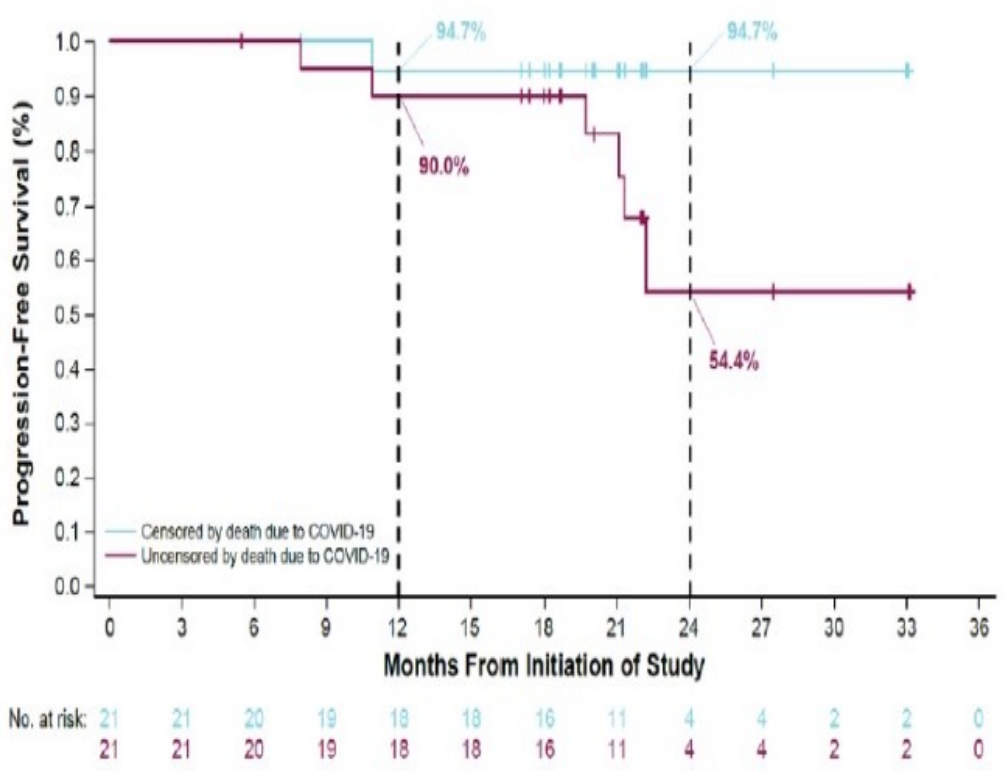
AVR (n=21)	
Neutropenia	33%
Infections	38%
COVID-19 (g5)	24% (24%)
Discontinuation (non-PD) by 25mo	Acala (4), Ven (6)

ALR (n=24)	
Neutropenia	38%
Infections	29%
COVID-19 (g5)	13% (0%)
Discontinuation (non PD) by 24mo	Acala (0), Len (0)

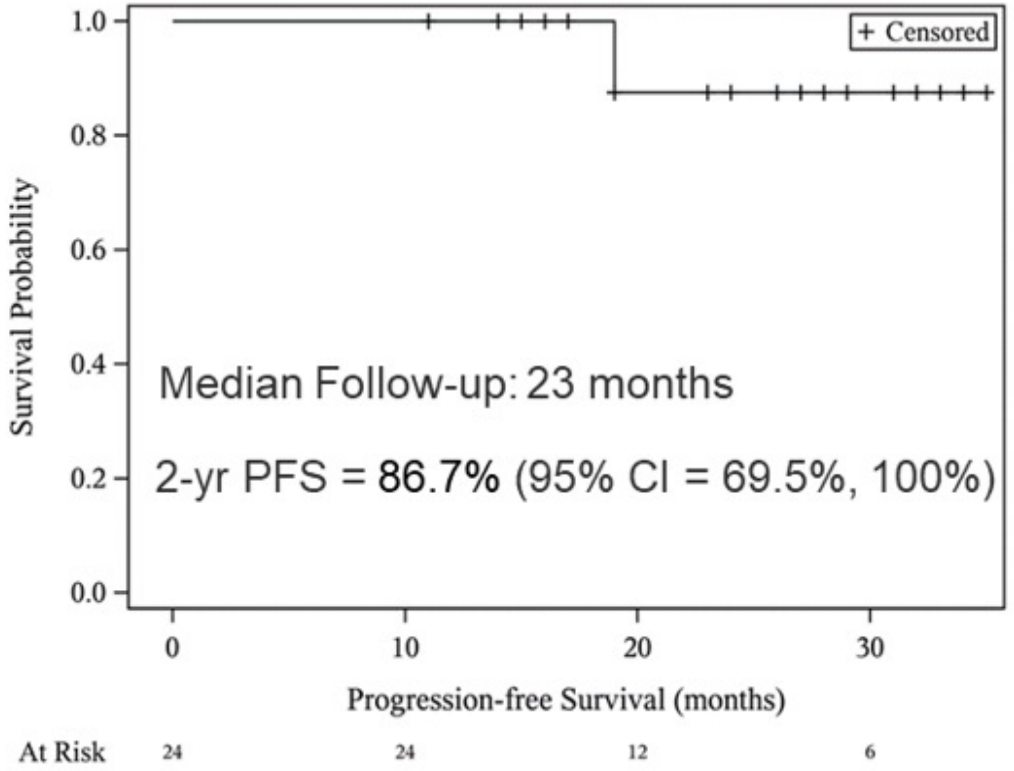
Wang et al., ASH. 2022, Ruan et al. ASH 2022

Progression Free Survival

AVR



ALR



Wang et al., ASH. 2022, Ruan et al. ASH 2022

Relapsed/Refractory MCL

Bispecifics in MCL

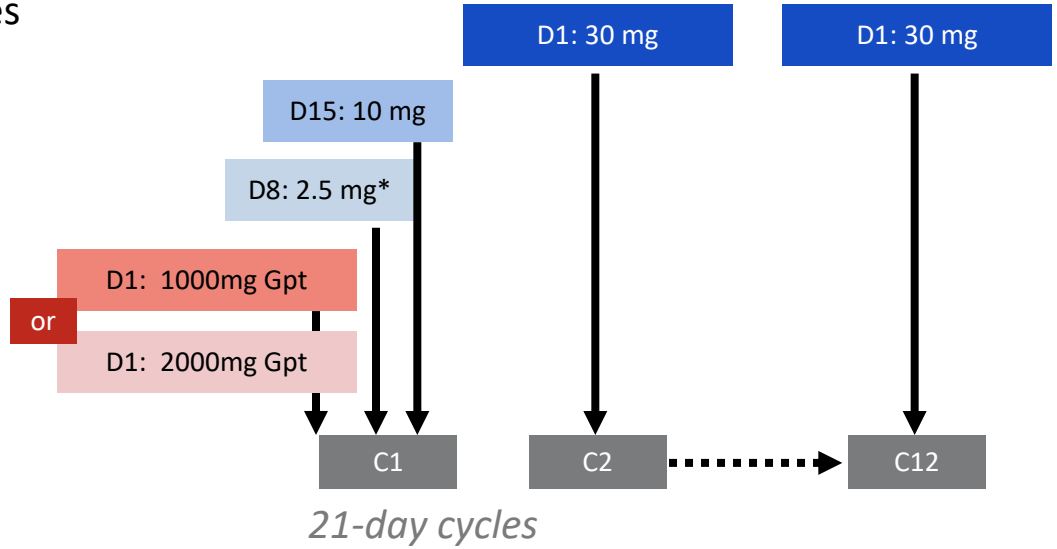
Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated R/R MCL

Glofitamab IV administration
- Fixed-duration treatment: maximum 2 cycles

CRS mutation
- Obinutuzumab pretreatment
- (1 x 1000mg or 1 x 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

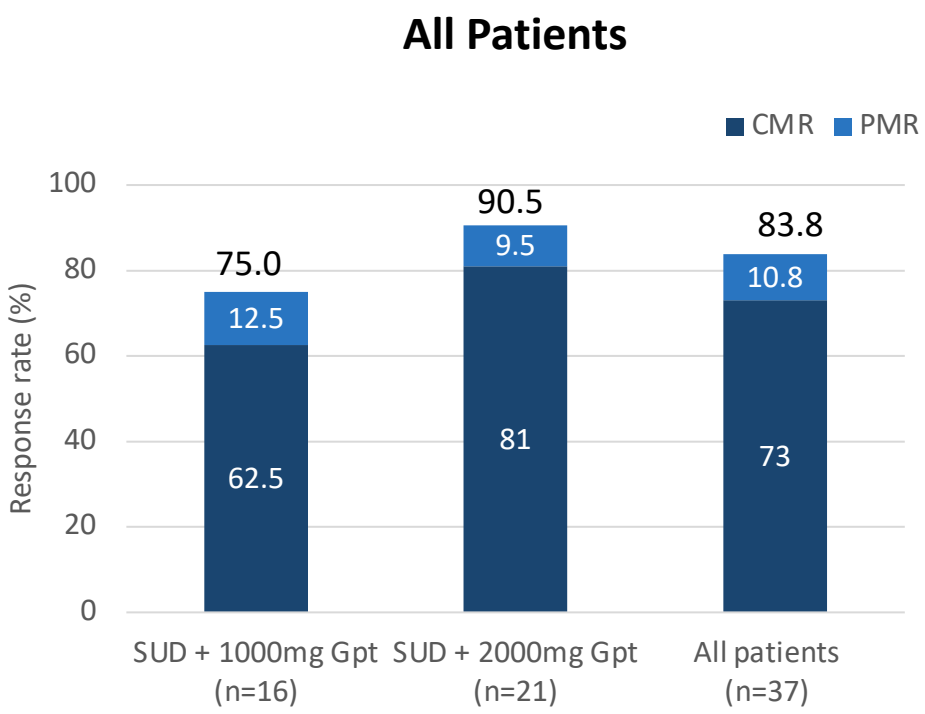
Population characteristics
- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1

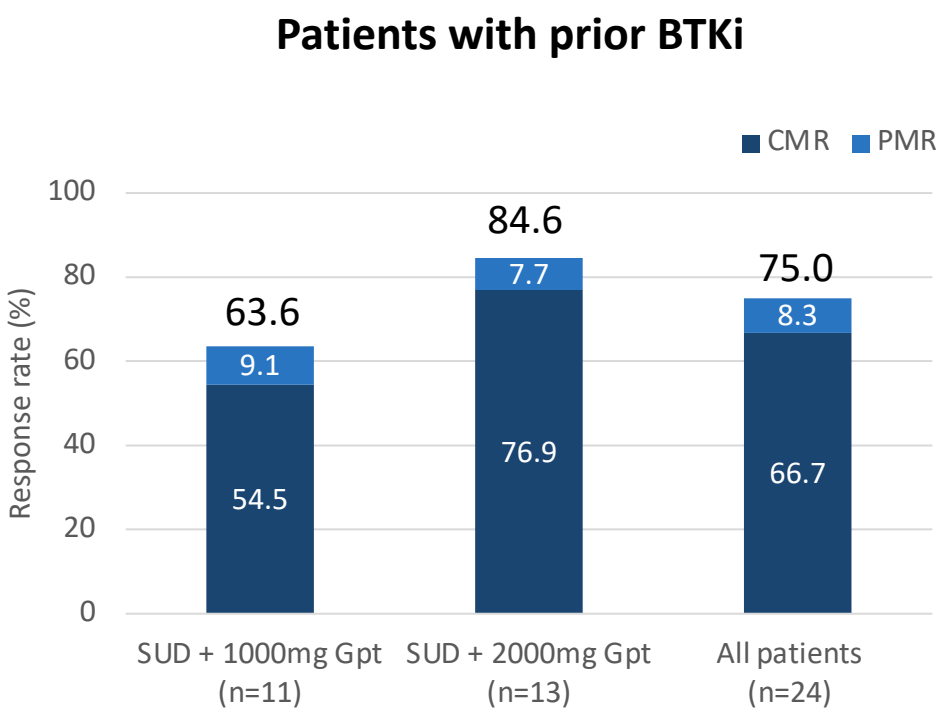
Clinical cutoff date: March 14, 2022



Phillips et al., ASH. 2022

Efficacy

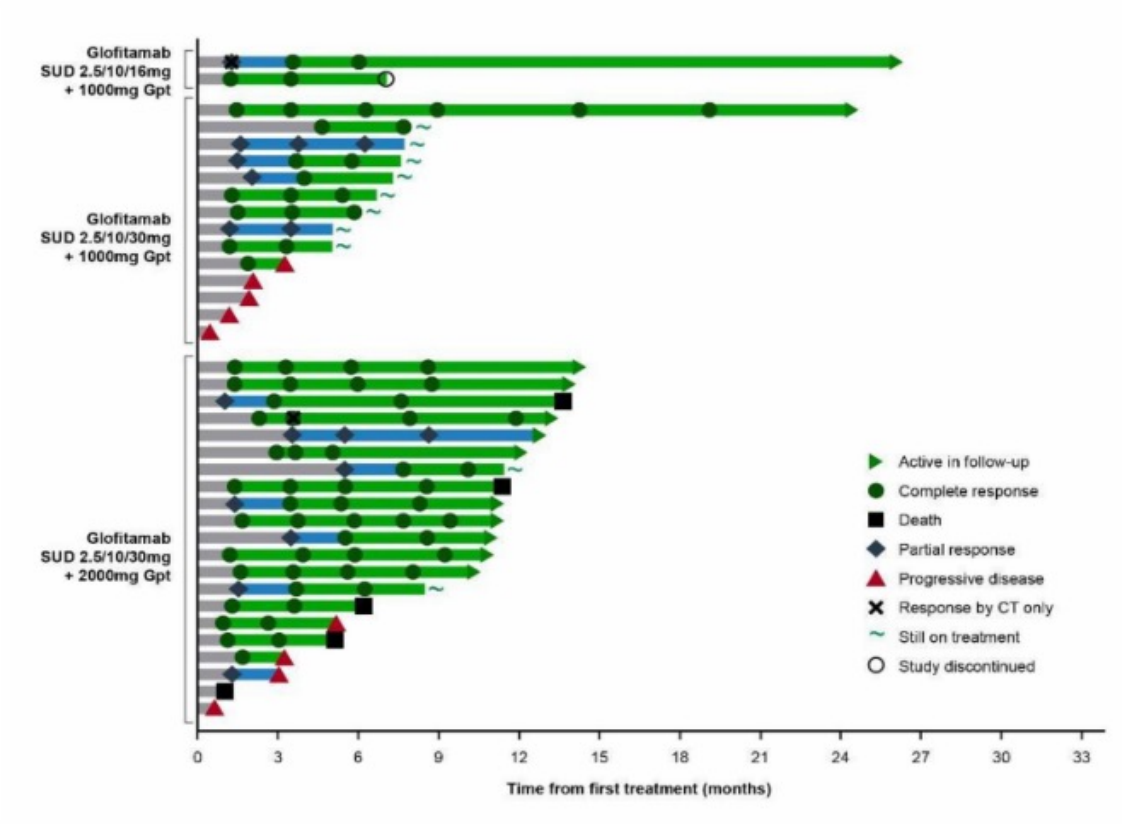




Phillips et al., ASH. 2022

Duration of Response

Figure. Duration of response and time on study by glofitamab dosing cohort



CT, computed tomography; Gpt, obinutuzumab pretreatment; SUD, step-up dose.

Phillips et al., ASH. 2022

Safety

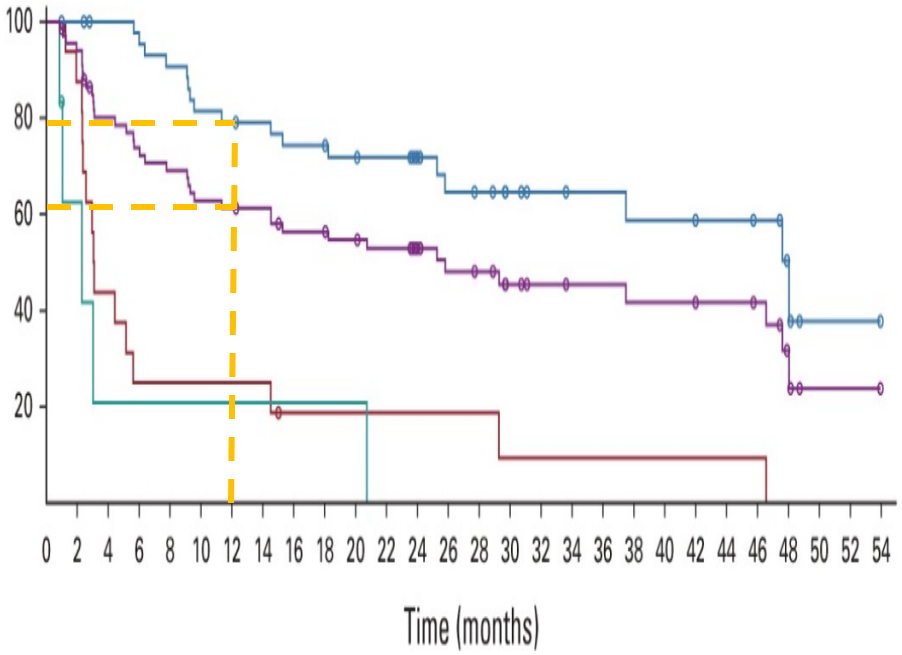
Cytokine Release Syndrome		
	Obi @1000mg (n=16)	**Obi @2000mg (n=21)**
CRS Grade 1+2	62.5% (n=10)	56.8% (n=12)
CRS Grade 3+4	25% (n=4)	9.5% (n=2)
Grade3+ CRS timing	cycles 1 & 2	cycle 1
CRS onset	7.55hr (4.4-14hr)	9.77hr (5-20.8hr)

Other Notable Toxicities		
	All Grades	Grade 3+
Neutropenia	45.9% (n=17)	27% (n=10)
Infections	64.9% (n=24)	32.4% (n=12)*
Neurologic	48.6% (n=18)	2.7% (n=1)

CAR T-Cell Therapy in MCL

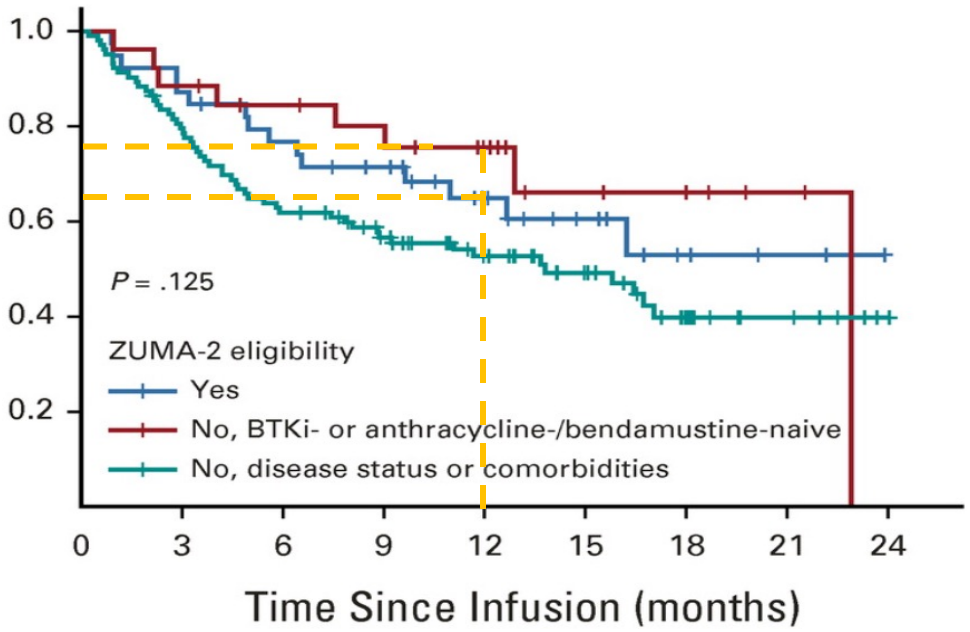
CAR T-cell Therapy in MCL

ZUMA 2



CR in Z2: 68%

Real World



CR in Z2 Eligible: 85%
CR in BTK/Chemo Naïve: 96%

J Clin Oncol. 2023 Jan 20;41(3):555-567, J Clin Oncol. 2023 Feb 8 [ahead of print]

Dual Antigen Targeting in MCL: CD19 + CD20

Figure 1

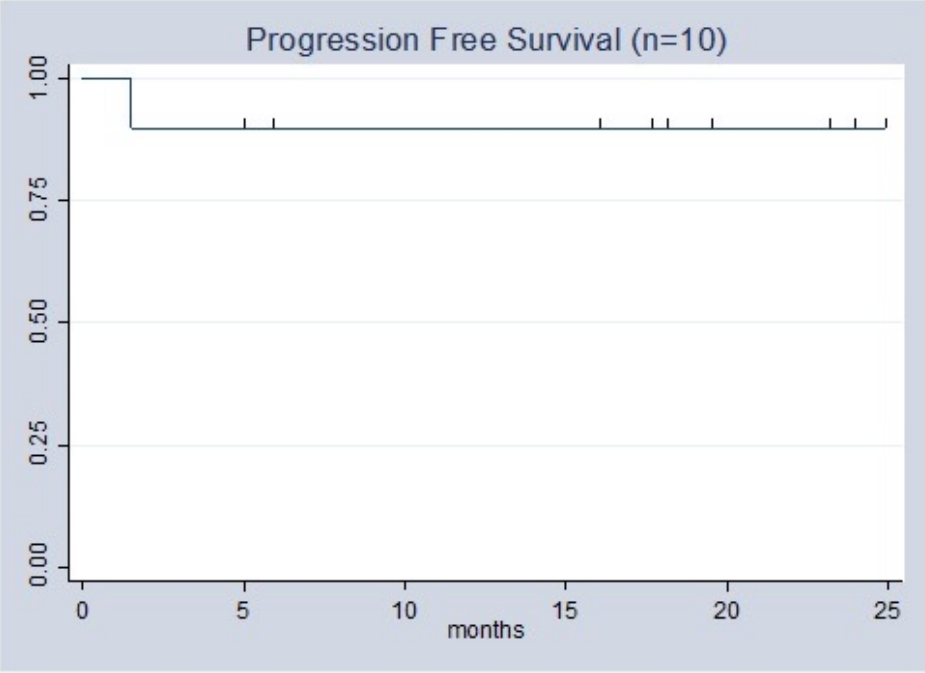


Table 1: Clinical characteristics of patients receiving LV20.19 CAR T-cells

	MCL patients (n=10)
Median Age, years	62 (50-74)
Male % (n)	90% (9)
Prior auto-HCT % (n)	30% (3)
Prior allo-HCT % (n)	20% (2)
Median LDH (Day 0)	220 (152-393)
BTKi exposed % (n)	100% (10)
BTKi progressed % (n)	80% (8)
Non-covalent BTKi progressed % (n)	40% (4)
Median Prior Lines (including transplant)	4 (3-8)
MIPI at Diagnosis (n=9) Low Intermediate High	 4 patients 3 patients 2 patients
Complex Cytogenetics	3 patients
p53 aberrations (not uniformly assessed)	2 patients with p53 deletion 1 patient with p53 somatic mutation

Abbreviations: MCL: mantle cell lymphoma, LDH=Lactate Dehydrogenase, BTKi=bruton kinase inhibitor, MIPI=mantle cell international prognostic index

Shah et al., ASH. 2022

Thank You