7th POSTGRADUATE
Lymphoma
Conference

Updated in Mantle Cell Lymphoma

Clinical Trials & Real World Data

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Donna Camilla Savelli Hotel

President:
P.L. Zinzani

Disclosures

Disclosures of Michael Wang

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Consultant	**AbbVie, Acerta Pharma, ADC Therapeutics America, Amphista Therapeutics Limited, AstraZeneca, Be Biopharma, BeiGene, BioInvent, Deciphera, DTRM Biopharma (Cayman) Limited, Genentech, InnoCare, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Lilly, Merck, Miltenyi Biomedicine, Milken Institute, Oncternal, Parexel, Pepromene Bio, Pharmacyclics, VelosBio**
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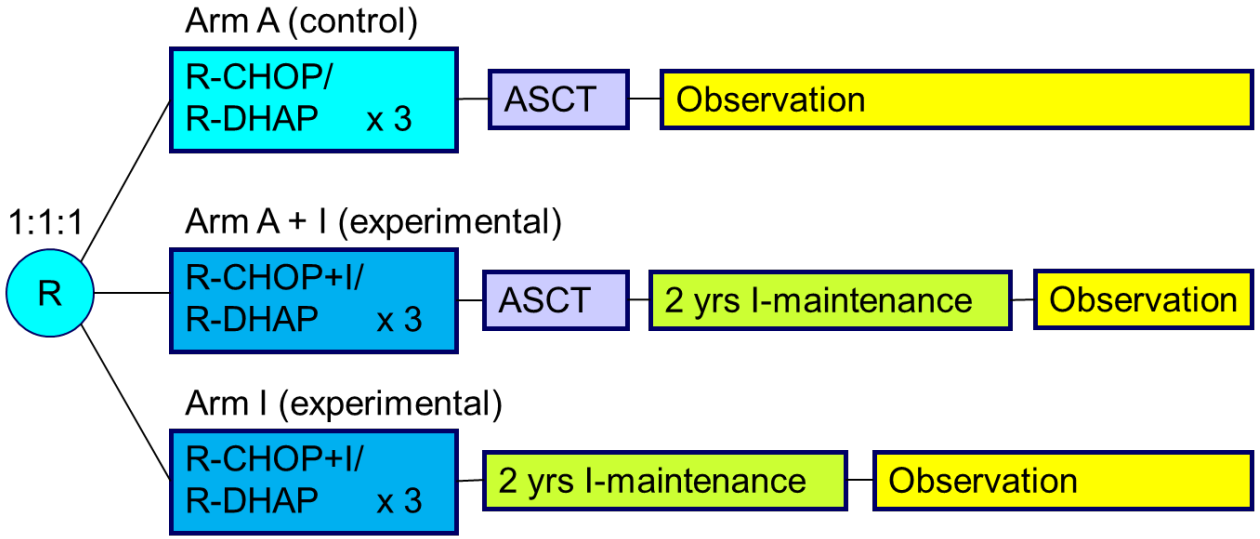
MCL patients
previously untreated
stage II-IV
younger than 66 years
suitable for HA and ASCT
ECOG 0-2

Primary outcome: FFS

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

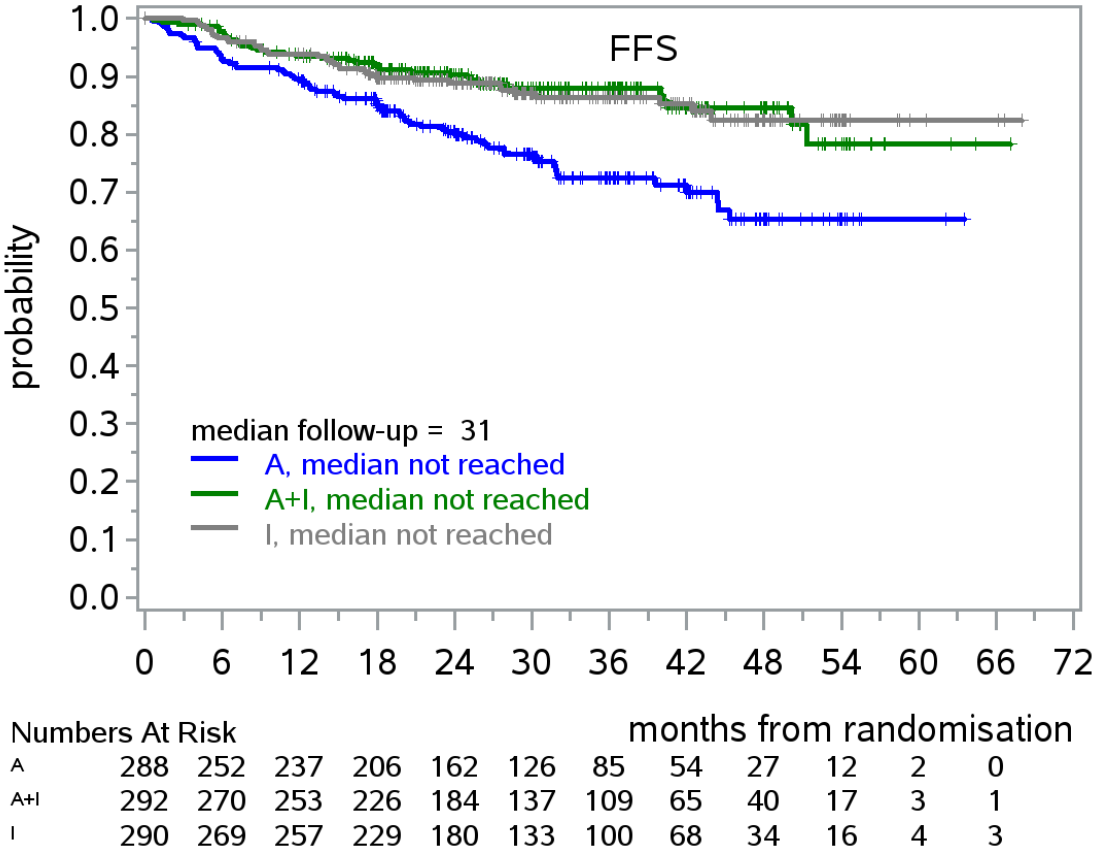


- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

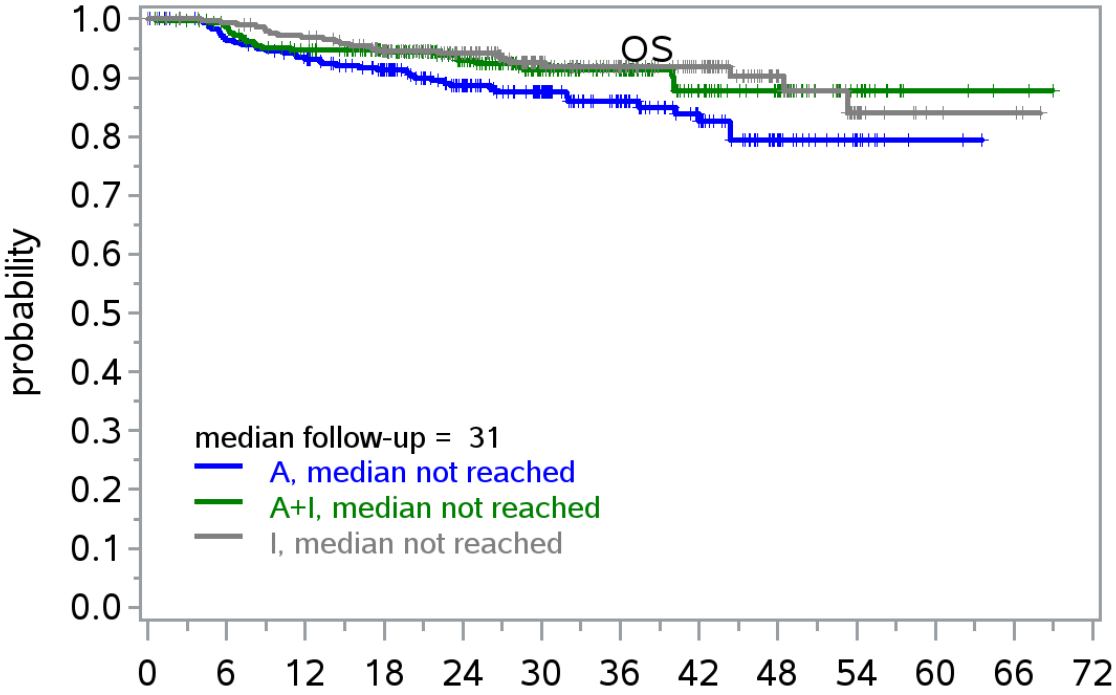
- CR- and OR-Rates significantly higher in the combined I induction (A+I/I) versus control (A) (CR: p=0.0203, OR: p=0.0025)
- MCL Younger R-CHOP/R-DHAP group: 38% (CR), 94% (OR)

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



- Test A+I vs. I ongoing, no decision yet

Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	



Numbers At Risk

A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

- 3-year OS:
  - A: 86% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

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

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

Response Rates & Grade 3+ Toxicity

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=21)	
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)

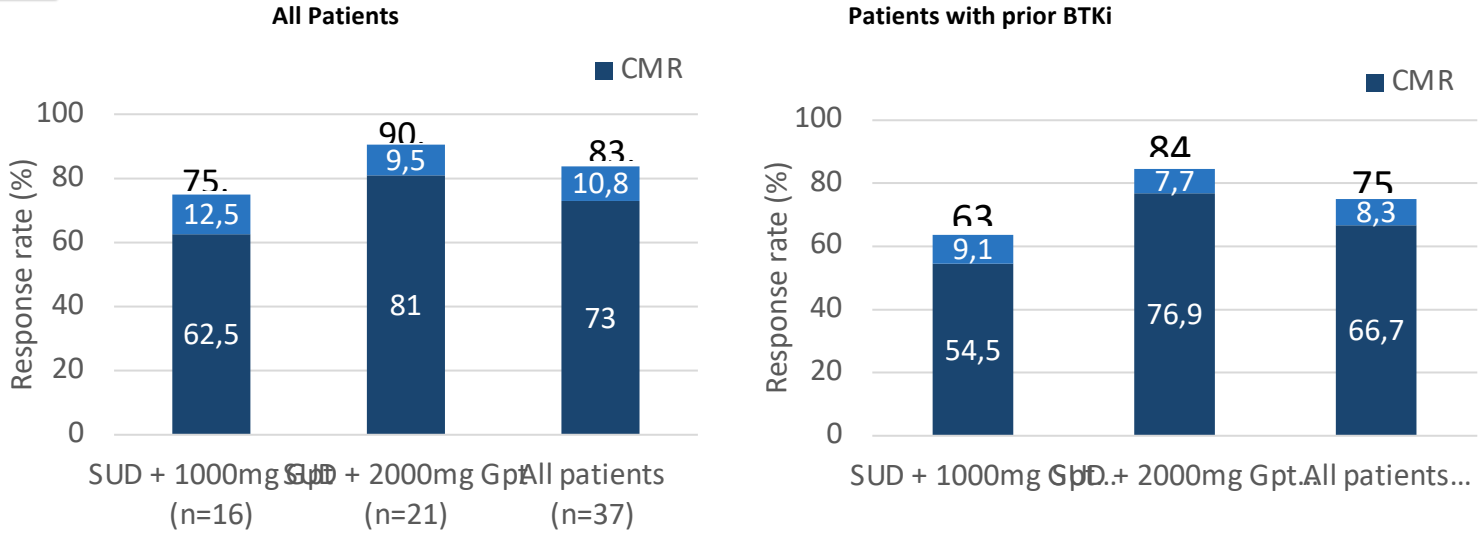
ALR (n=24)	
Neutropenia	38%
Infections	29%
COVID-19 (g5)	13% (0%)
Discontinuation (non PD) by 24mo	Acala (0), Len (0)

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

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

Phillips et al., ASH. 2022

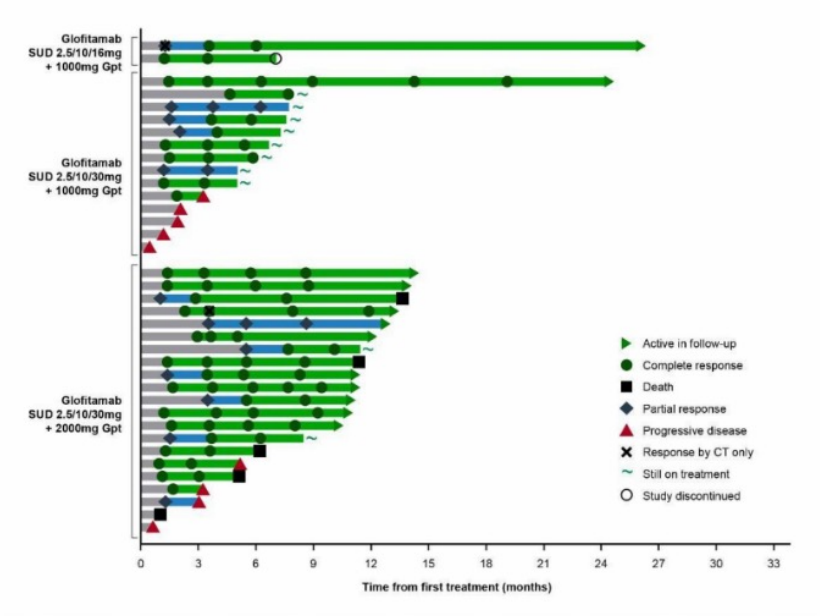
High response rates with glofitamab monotherapy in patients with R/R MCL



Phillips et al., ASH. 2022

Glofitamab monotherapy produces a high CR rate and durable remissions in heavily pretreated MCL

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

Results from a Phase 1/2 Study of Tandem, Bispecific Anti-CD20/Anti-CD19 (LV20.19) CAR T-Cells for MCL

Shah et al., ASH. 2022

Among MCL patients with a median of 4 prior lines of therapy, the anti-CD20/CD19 CAR-T maintained a durable remission for nearly all patients

Figure 1

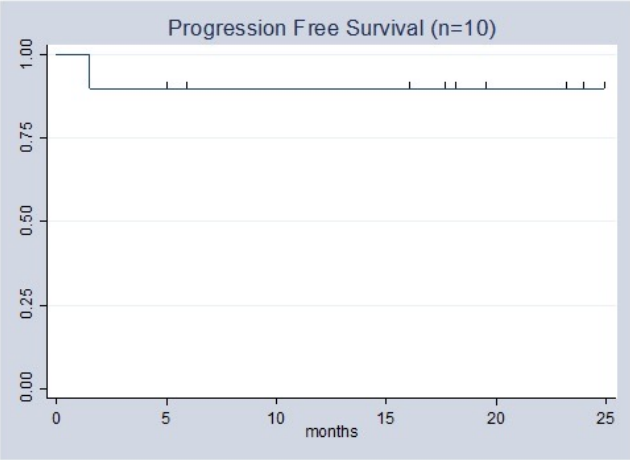


Table 1: Clinical characteristics of patients receiving LV20.19 CAR T-cells

	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

Three-Year Follow-Up of Outcomes With KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma in ZUMA-2

Michael L. Wang, MD[1]; Javier Munoz, MD, MS, FACP[2]; Andre Goy, MD[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA, FACP[8]; Ian W. Flinn, MD, PhD[9]; David B. Miklos, MD, PhD[10]; John M. Pagel, MD, PhD, DSc[11]; Marie José Kersten, MD, PhD[12]; Roch Houot, MD, PhD[13]; Amer Beitinjaneh, MD[14]; Weimin Peng, PhD[15]; Xiang Fang, PhD[15]; Rhine R. Shen, PhD[15]; Rubina Siddiqi, PhD[15]; Ioana Kloos, MD[15]; Patrick M. Reagan, MD[16]

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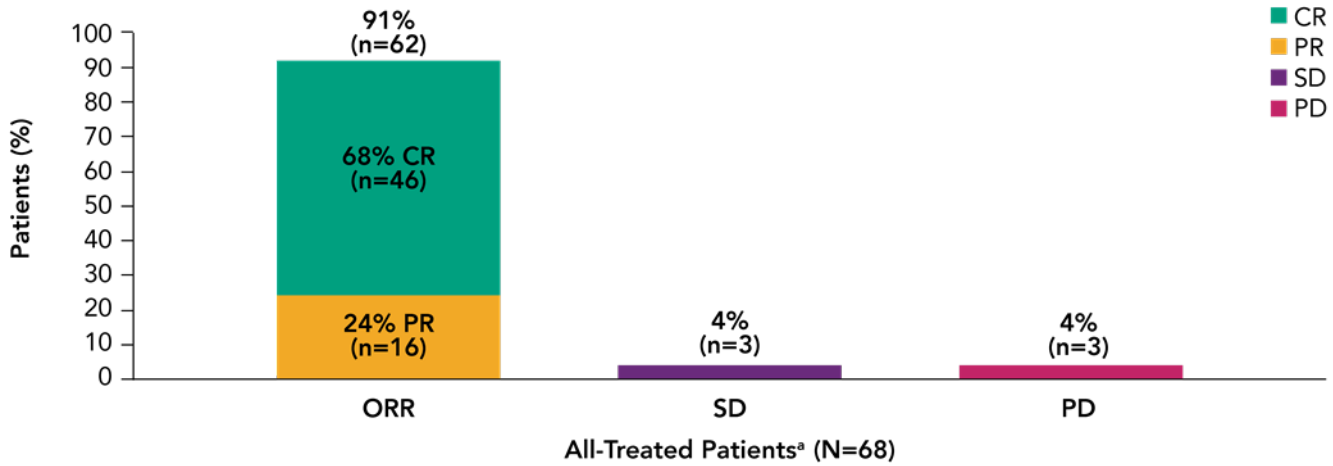
Wang ML et al. ASCO 2022. Abstract 7518.

Objective Response Rate (ORR) in All Treated Patients (N=68)



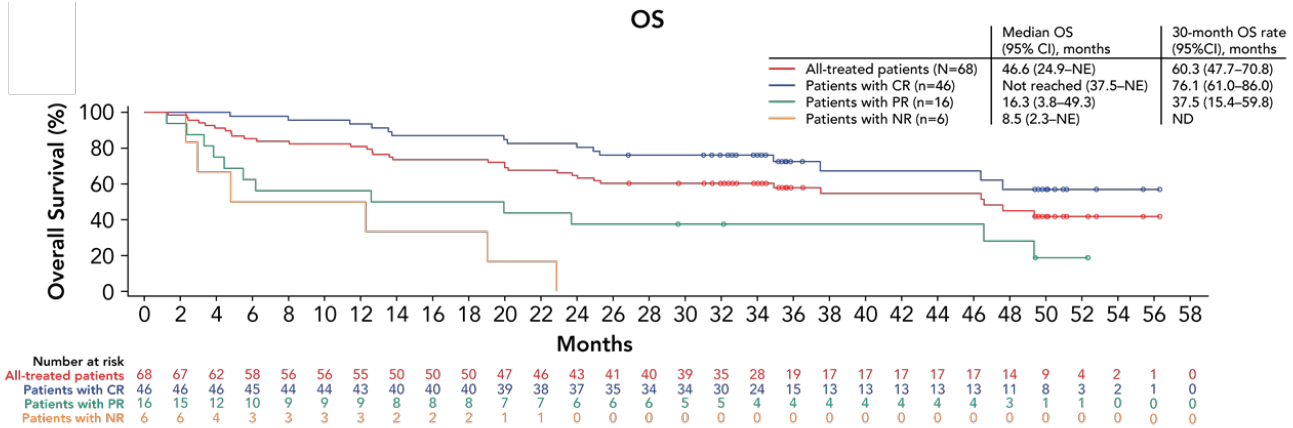
After a median follow-up of 35.6 months (range, 25.9-56.3), the ORR (CR + partial response [PR]) was 91% (95% CI, 81.8-96.7), with a 68% CR rate (95% CI, 55.2-78.5) and a median DOR of 28.2 months (95% CI, 13.5-47.1)
In the ITT population, ORR was 84% (95% CI, 73.4-91.3), with a 62% CR rate (95% CI, 50.1-73.2)

With 3-years of follow-up, these data demonstrate that a single infusion of KTE-X19 resulted in high rates of durable responses in R/R MCL.

Assessed by an IRRC according to the Lugano Classification.[1] [a] Since the previous report,[2] IRRC review determined that 1 patient who was previously reported as best response of PR had no disease at baseline; this patient is reported as PD in the current report. 1. Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068. 2. Wang M, et al. *Blood*. 2020;136(suppl 1):20-22.

Wang ML et al. ASCO 2022. Abstract 7518.

Overall Survival (OS) in All Treated Patients (N=68)



- The median progression-free survival (PFS) was 25.8 months, as shown in the full poster
- In the ITT population (data not shown), the median PFS was 24.0 months and the median OS was 47.4 months

Median OS among treated patients was 46.6 months and was not reached among those who achieved CR.

Median follow-up 35.6 months.
CR, complete remission; mo, month; NE, not estimable; NR, no response; OS, overall survival; PFS, progression-free survival.

Wang ML et al. ASCO 2022. Abstract 7518.

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

Michael L. Wang[1], Nirav N. Shah[2], Alvaro J. Alencar[3], James N. Gerson[4], Manish R. Patel[5], Bita Fakhri[6], Wojciech Jurczak[7], Xuan Tan[8], Katharine Lewis[8], Timothy Fenske[2], Catherine C. Coombs[9], Ian W. Flinn[10], David J. Lewis[11], Steven Le Gouill[12], M. Lia Palomba[13], Jennifer A. Woyach[14], John M. Pagel[15], Nicole Lamanna[16], Jonathon B. Cohen[17], Minal A. Barve[18], Paolo Ghia[19], Toby A. Eyre[20], Pier Luigi Zinzani[21], Chaitra S. Ujjani[22], Youngil Koh[23], Koji Izutsu[24], Ewa Lech-Maranda[25], Constantine S. Tam[26], Suchitra Sundaram[27], Ming Yin[28], Binoj Nair[28], Donald E. Tsai[28], Minna Balbas[28], Anthony R. Mato[13], Chan Y. Cheah[8]

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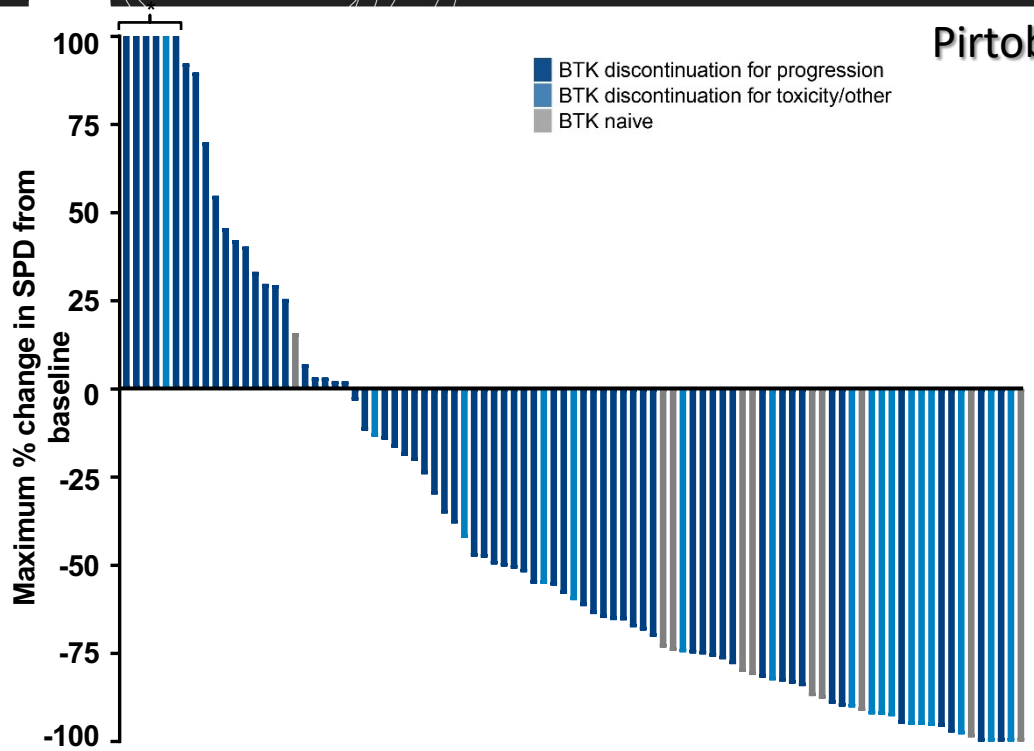
Pirtobrutinib Efficacy in Mantle Cell Lymphoma



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma: Real World Experience from the US Lymphoma CAR T Consortium

• Yucai Wang,[1,*] Preetesh Jain,[2,*] Frederick L. Locke,[3,*] Javier L. Munoz,[4] Matthew Maurer,[1] Amer M. Beitinjaneh,[5] Matthew J. Frank,[6] Saurabh Dahiya,[7] Joseph P. Mcguirk,[8] Miriam T. Jacobs,[9] Andre Goy,[10] Julie M. Vose,[11] Brian T. Hill,[12] Olalekan O. Oluwole,[13] Abhinav Deol,[14] Bijal Shah,[3] Jonas Paludo,[1] Trent Wang,[5] Lazaros Lekakis,[5] David B. Miklos,[6] Aaron P. Rapoport,[7] Armin Ghobadi,[9] Sattva S. Neelapu,[3] Yi Lin,[1,#] Michael Wang,[2,#] Michael D. Jain[3,#]

[1]Mayo Clinic, Rochester, MN; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Moffitt Cancer Center, Tampa, FL; [4]Mayo Clinic, Phoenix, AZ; [5]University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL; [6]Stanford University Medical Center, Stanford, CA; [7]University of Maryland School of Medicine, Greenebaum Comprehensive Cancer Center, Baltimore, MD; [8]University of Kansas Medical Center, Kansas City, KS; [9]Washington University School of Medicine, Siteman Cancer Center, St Louis, MO; [10]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ; [11]University of Nebraska Medical Center, Buffett Cancer Center, Omaha, NE; [12]Cleveland Clinic, Cleveland, OH; [13]Vanderbilt-Ingram Cancer Center, Nashville, TN; [14]Wayne State University, Karmanos Cancer Institute, Detroit, MI;
[*]Co-first authors; [#]Co-senior authors.

Brexu-Cel RWE: Patient demographics

Variables	Number	Variables	Number
Age, median (range)	67 (34-89)	**Prior therapies**	
Sex, male	76 (80%)	Total lines, median (range)	3 (1-10)
ECOG PS ≥2	8 (8%)	Prior CD20 antibody	94 (99%)
Simplified MIPI		Prior anthracycline or bendamustine	82 (86%)
Low risk (0-3)	30 (32%)	Prior cytarabine	43 (45%)
Intermediate risk (4-5)	54 (57%)	Prior AutoSCT	27 (28%)
High risk (6-11)	11 (12%)	Prior rituximab maintenance	41 (43%)
Ki-67, ≥50%	50/88 (57%)	Prior BTKi	78 (82%)
Blastoid/pleomorphic	39 (41%)	BTKi-refractory n=69 (73%), BTKi-intolerant n=5 (5%)	
***TP53* mutation or deletion**	31/70 (44%)	Prior lenalidomide	22 (23%)
Complex karyotype	8/28 (29%)	Prior venetoclax	33 (35%)
Stage III-IV	83 (87%)	**Disease status**	
CNS involvement	7 (7%)	Relapsed after last line	53 (56%)
Bone marrow involvement	30/67 (45%)	Refractory to last line	42 (44%)
Bulky disease (≥10 cm)	10 (11%)	**Total (received CAR T infusion)**	**95**

Brexu-Cel RWE: ZUMA-2 ineligibility

Reasons for ZUMA-2 ineligibility	Number (%)	Reasons for ZUMA-2 ineligibility	Number (%)
ECOG PS ≥2	8 (8%)	Total bilirubin >1.5 mg/dL	3 (3%)
CNS involvement by lymphoma	7 (7%)	AST/ALT >2.5xULN	1 (1%)
Prior lines of therapy >5	12 (13%)	LVEF ≤50%	3 (3%)
No prior BTKi	17 (18%)	Significant cardiac disease <12 months	6 (6%)
No prior CD20 antibody/ anthracycline/bendamustine	13 (14%)	Pericardial effusion	3 (3%)
Prior AlloSCT	4 (4%)	Pleural effusion	5 (5%)
Prior anti-CD19 therapy	1 (2%)	SaO2 <92% on room air	1 (1%)
Prior CAR T-cell therapy	1 (1%)	HIV/Hepatitis B/ Hepatitis C	2 (2%)
ANC <1000/µL	8 (8%)	Active infection requiring IV antibiotics	2 (2%)
ALC <100/µL	1 (1%)	Autoimmune disease requiring therapy	2 (2%)
Platelet <75,000/µL	5 (5%)	Requiring >5 mg/day of prednisone	2 (2%)
Creatinine >1.5 mg/dL	8 (8%)	CNS disorder (e.g., seizure, stroke, etc.)	2 (2%)
Creatinine clearance <60 mL/min	19 (20%)	Another malignancy	4 (4%)

- **A total of 74 (78%) patients would not have met ZUMA-2 eligibility criteria.**
- Main reasons for ineligibility included prior therapies, renal dysfunction, cytopenias, ECOG PS, and CNS involvement.

Brexu-Cel: CRS and ICANS

	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	86 (91%)	57 (60%)	91%	63%
Max Grade*				
1-2	78 (82%)	24 (25%)	76%	32%
3-4	8 (8%)	33 (35%)	15%	31%
Days to onset	4 (0-11)	6 (1-15)	2 (1-13)	7
Days to max Grade	5 (0-7)	7 (3-15)	-	-
Duration	5 (1-33+)	6 (2-144+)	11	12

*CRS grading: ASTCT (n=11), Lee (n=2), CARTOX (n=1); ICANS grading: ASTCT (n=12), CTCAE (n=1), CARTOX (n=1)
CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; NE = neurological events.

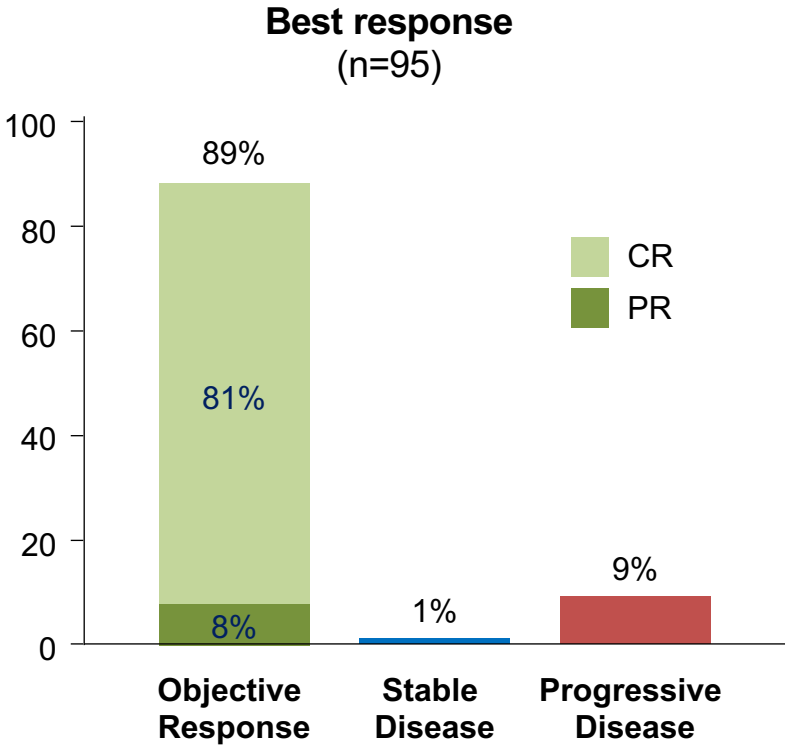
- The incidences of CRS and ICANS were comparable to those reported in ZUMA-2.
- Tocilizumab and corticosteroids use appeared to be more frequent in this Consortium study cohort.

Management	Number	ZUMA-2 (%)
Tocilizumab	75 (79%)	CRS: 59% NE: 26%
Tocilizumab doses, median	2 (1-4)	
Steroid	66 (69%)	CRS: 22% NE: 38%
Anakinra	16 (17%)	
ICU admission	20 (21%)	
ICU days, median	3 (1-12)	
Vasopressors	10 (11%)	16%
Mechanical ventilation	4 (4%)	
Dialysis	3 (3%)	

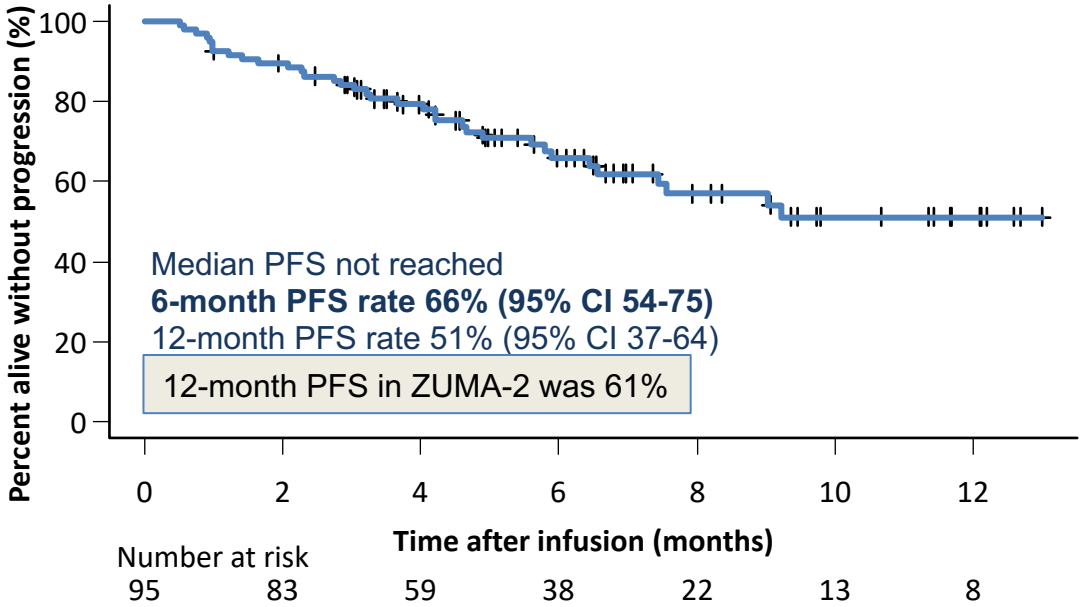
Wang M, et al. NEJM 2020.

Brexu-Cel RWE: Clinical response

- **Median time to initial response was 30 days (range 16-104).**
- Day 30 ORR (n=92 evaluated) was 88%, including 66% CR and 22% PR.
- 12 of 20 patients with PR and 1 of 2 patients with SD at day 30 achieved CR after a median of 64 days (range 22-135).
- Median time to best response was 30 days (range 16-168).
- **The best ORR was comparable to that reported in ZUMA-2 (93%).**



Brexu-cel RWE: Progression-free survival



Brexu-cel RWE: Overall survival