



# **KOL Call on Cirmtuzumab for Treating Patients with Mantle Cell Lymphoma (MCL)**

**Hosted by Oncternal  
Therapeutics, Inc.  
(NASDAQ: ONCT)**

**New Science. New Cancer Therapies. New Hope.**

ONCT KOL Day 29JUL2020

- James Breitmeyer MD PhD  
Oncternal Therapeutics
  - Michael Wang MD  
MD Anderson Cancer Center
  - James Breitmeyer MD PhD
  - Questions & Answers
- Introduction
- Mantle cell lymphoma landscape
- BTK inhibitors therapy of MCL
- CAR-T therapy of MCL
- Clonal evolution of MCL
- Resistance to ibrutinib/venetoclax
- Preclinical evaluation of cirmtuzumab in MCL and DLBCL
- Clinical results with cirmtuzumab + ibrutinib in MCL
- Oncternal pipeline and milestones

## FORWARD LOOKING STATEMENTS

This presentation includes forward-looking statements (including within the meaning of §21E of the U.S. Securities Exchange Act of 1934, as amended, and § 27A of the U.S. Securities Act of 1933, as amended). Forward looking statements, which generally include statements regarding goals, plans, intentions and expectations, are based upon current beliefs and assumptions of Oncternal Therapeutics, Inc. (“Oncternal,” or the “Company”) and are not guarantees of future performance. Statements that are not historical facts are forward-looking statements, and include statements regarding the expected timing for achieving key milestones, including completing and announcing results of clinical trials of the Company’s product candidates, and the anticipated market potential, duration of patent coverage, ability to obtain and maintain favorable regulatory designations and, potentially, accelerated approval pathways for the Company’s product candidates and preclinical programs.

All forward looking statements are subject to risks and uncertainties, which include, but are not limited to: uncertainties associated with the clinical development and process for obtaining regulatory approval of Oncternal’s product candidates, including potential delays in the commencement, enrollment and completion of clinical trials; inherent risks involved in the commercialization of any product, if approved; the risk that results seen in a case study of one patient likely will not predict the results seen in other patients in the clinical trial; the risk that interim results of a clinical trial do not predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, as follow-up on the outcome of any particular patient continues, and as more patient data become available; the risk that unforeseen adverse reactions or side effects may occur in the course of developing and testing Oncternal’s product candidates; risks associated with the COVID-19 outbreak, which may adversely impact our business and clinical trials, including delays in the enrollment of patients; the risk that the regulatory landscape that applies to the development programs for Company’s product candidates may change over time; the risk that competitors may develop technologies or product candidates more rapidly than Oncternal, or that are more effective than Oncternal’s product candidates, which could significantly jeopardize Oncternal’s ability to develop and successfully commercialize its product candidates; the Company’s dependence on the success of its product development programs; and the risk that Oncternal may be unable to obtain sufficient additional capital to continue to advance the development of its product candidates and preclinical programs.

Except as required by applicable law, Oncternal undertakes no obligation to revise or update any forward-looking statement. All forward-looking statements in this presentation are current only as of the date on which the statements were made. Additional factors that could cause actual results to differ materially from those expressed in the forward-looking statements are discussed in reports filed with the SEC by Oncternal, including its most recent Annual Report on Form 10-K, Quarterly Report on Form 10-Q, and Current Reports on Form 8-K filed with the SEC.

Cirmtuzumab, TK216 and Oncternal’s CAR-T targeting ROR-1 are investigational product candidates or preclinical programs that have not been approved by the U.S. Food and Drug Administration for any indication.

# Mantle Cell Lymphoma Landscape



THE UNIVERSITY OF TEXAS  
**MD Anderson**  
**Cancer Center**  
Making Cancer History®

**Michael Wang, MD**

Puddin Clarke Endowed Professor

Department of Lymphoma and Myeloma

Department of Stem Cell Transplantation and Cellular  
Therapy

PI: B Cell Lymphoma Moonshot

Founding Director: MCL Program of Excellence



# Disclosures

## Research Grants

Janssen  
Pharmacyclics  
AstraZeneca  
Acerta Pharma  
Celgene  
Juno Therapeutics  
BeiGene  
Kite Pharma  
Loxo Oncology  
VelosBio  
BioInvent  
Aviara

## Consulting/Advisory Board

Loxo Oncology  
Janssen  
Pharmacyclics  
BioInvent  
Celgene  
Juno Therapeutics  
Pulse Biosciences  
MoreHealth  
Guidepoint Global  
Kite Pharma  
AstraZeneca  
Acerta Pharma  
Oncternal Therapeutics

## Honoraria

Janssen  
Acerta Pharma  
OMI  
Physicians Education  
Resources (PER)  
Oncology News

## Stock

MoreHealth

# Diagnosis of MCL - Immunophenotyping

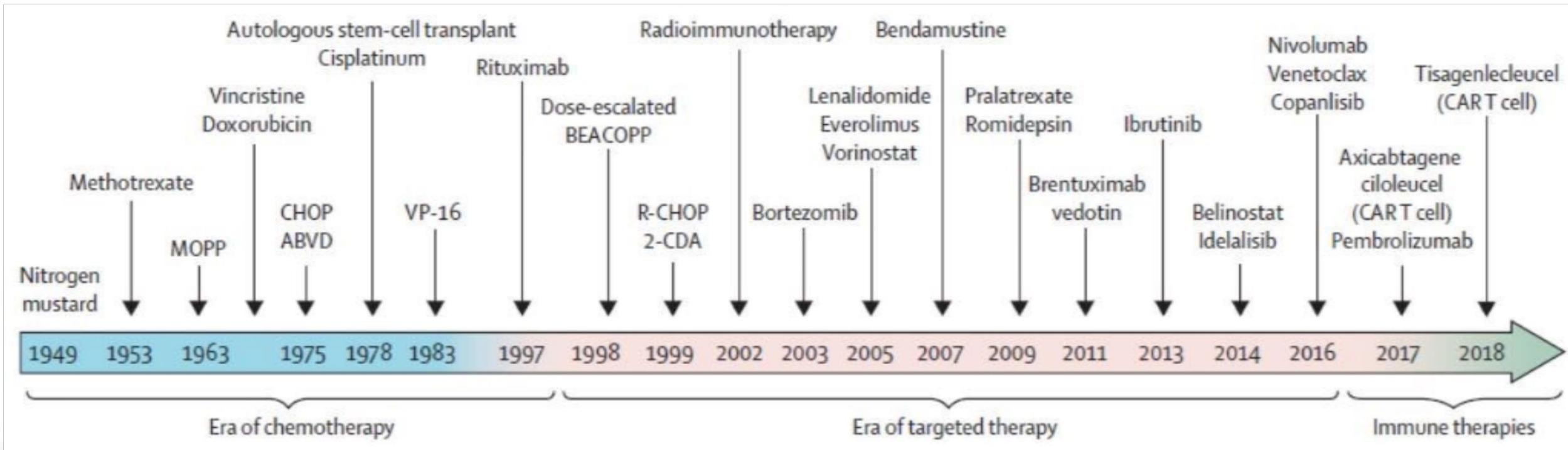
- Important tool in differential diagnosis<sup>1</sup>
- Immunophenotyping can be performed on:<sup>1</sup>
  - Biopsy material
  - Blood
  - Bone marrow
- MCL has characteristic immunophenotype<sup>1</sup>
  - Almost all cases positive for cyclin D1<sup>1</sup>
    - Detected in nucleus of malignant cells<sup>1</sup>

## SOX11 and MCL

Overexpression of the transcription factor SOX11 has been described as a potential differential diagnostic marker in MCL.<sup>2</sup> SOX11 – not normally expressed in B-cells (and infrequently expressed in other B-cell malignancies) – is thought to play an oncogenic role in MCL development.<sup>3,4</sup> Absence of SOX11 is characteristic of MCL that follows an indolent course.<sup>2</sup>

	IHC	FC
CD19		+
CD20	+	+
CD5	+	+
CD10	–	–
FMC7		+
CD23	–	–
Cyclin D1	+	
Bcl-6	–	
Bcl-2	+	
Slg		+ (bright)
IHC – immunohistochemistry FC – flow cytometry		

1. McKay, P., Leach, M., et al. (2012). *Br J Haematol.* **159**(4): 405-26.
2. Vose, J. (2012). *Am J Hematol.* **87**: 605-609.
3. Ferrando, A.A. (2013). *Blood.* 121(12): 2169-70.
4. Mozas, A., Royo, C., et al. (2009). *Haematologica.* 94(11): 1555-62.



**The therapy evolved from chemo therapy to chemo-free targeted therapies then to cellular and immunotherapies.**

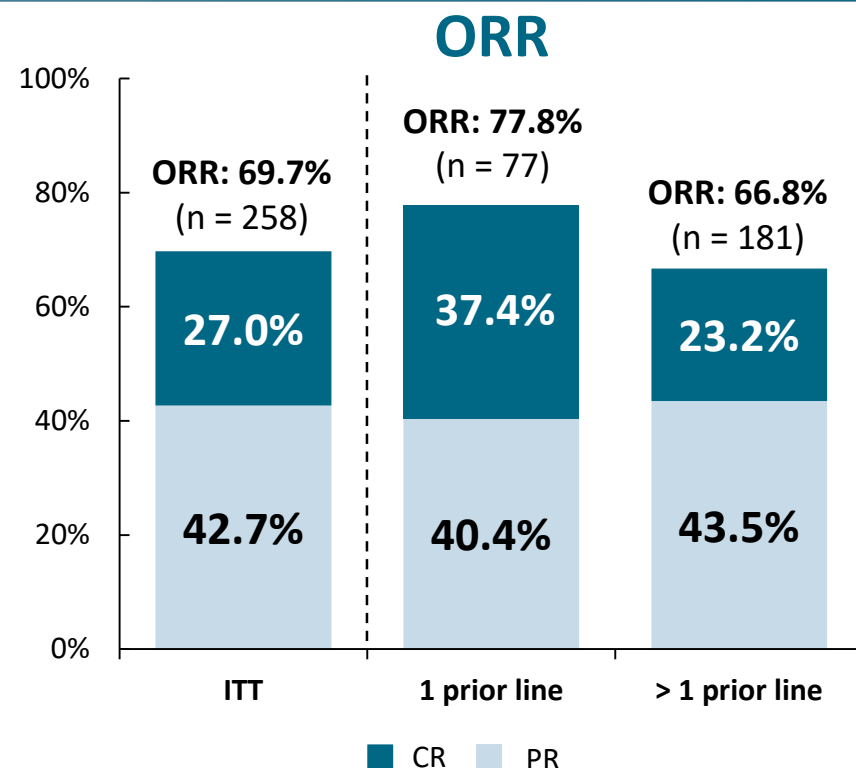
# Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients With Relapsed/Refractory Mantle Cell Lymphoma (MCL): a Pooled Analysis

Simon Rule,<sup>1</sup> Martin Dreyling,<sup>2</sup> Andre Goy,<sup>3</sup> Georg Hess,<sup>4</sup> Rebecca Auer,<sup>5</sup>  
Brad Kahl,<sup>6</sup> José-Ángel Hernandez-Rivas,<sup>7</sup> Keqin Qi,<sup>8</sup> Sanjay Deshpande,<sup>8</sup>  
Lori Parisi,<sup>8</sup> Michael Wang<sup>9</sup>

<sup>1</sup>Department of Haematology, Plymouth University Medical School, Plymouth, UK; <sup>2</sup>Department of Medicine III, Klinikum der Universität München, LMU, Munich, Germany; <sup>3</sup>Department of Hematology & Oncology, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA; <sup>4</sup>Department of Hematology, Oncology and Pneumology, University Medical School of the Johannes Gutenberg University, Mainz, Germany; <sup>5</sup>Centre for Haemato-Oncology, Barts Cancer Institute, London, UK; <sup>6</sup>Department of Medicine, Washington University, St. Louis, MO, USA; <sup>7</sup>Hematology Department, Hospital Universitario Infanta Leonor, Madrid, Spain; <sup>8</sup>Research & Development, Janssen, Raritan, NJ, USA; <sup>9</sup>Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA



# Overall Response and PFS/OS by Best Response



Median, Months (95% CI)	Best Response	
	CR (n = 100)	PR (n = 158)
PFS	NR (47.6-NE)	12.8 (10.4-16.7)
OS	NR (NE-NE)	25.4 (21.3-32.2)

Kaplan-Meier estimate of median.

- CR rate was 37.4% in patients with 1 prior line of therapy
- Median PFS and OS were not reached in patients who achieved a CR (median follow-up 41 months)

PR, partial response.

# Most Common Grade $\geq 3$ Treatment-Emergent AEs\*

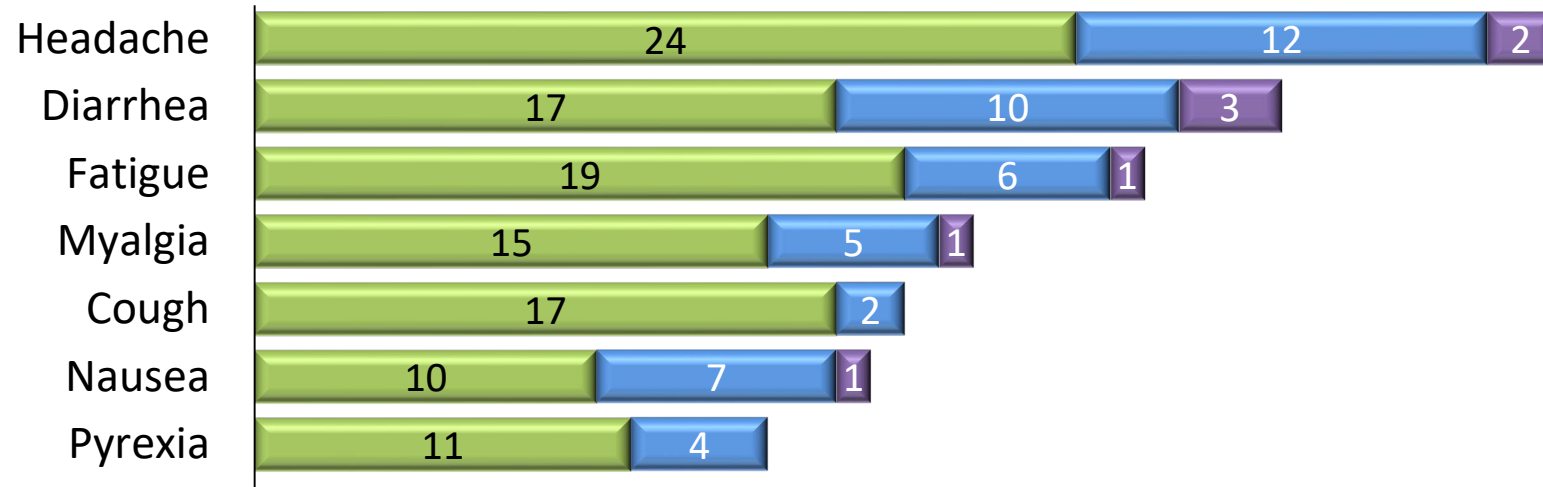
% Patients	Overall (N = 370)	1 Prior Line (n = 99)	> 1 Prior Line (n = 271)
Neutropenia	17.0	7.1	20.7
Thrombocytopenia	12.4	7.1	14.4
Pneumonia	12.7	8.1	14.4
Anemia	10.0	6.1	11.4
Atrial fibrillation	6.2	5.1	6.6
Hypertension	5.1	6.1	4.8

- Generally, grade 3/4 AEs were less common in patients with 1 prior line
- Secondary malignancies: 10.8% (mostly nonmelanoma skin cancers)

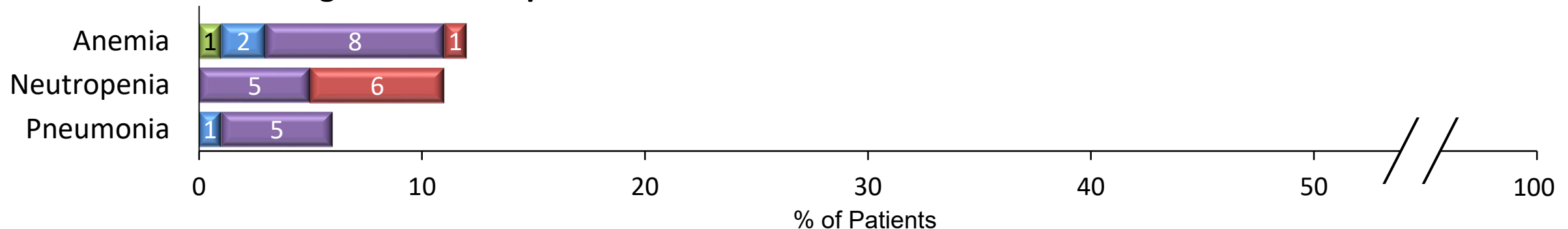
\*Occurring in  $\geq 5\%$  patients in intent-to-treat population.

# Common Adverse Events from acalabrutinib (ORR=80%)

## AEs occurring in $\geq 15\%$ of all patients



## Grade $\geq 3$ AEs occurring in $\geq 5\%$ of all patients



AE = adverse event.

## ORIGINAL ARTICLE

## KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

## ABSTRACT

## BACKGROUND

Patients with relapsed or refractory mantle-cell lymphoma who have disease progression during or after the receipt of Bruton's tyrosine kinase (BTK) inhibitor therapy have a poor prognosis. KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, may have benefit in patients with relapsed or refractory mantle-cell lymphoma.

## METHODS

In a multicenter, phase 2 trial, we evaluated KTE-X19 in patients with relapsed or refractory mantle-cell lymphoma. Patients had disease that had relapsed or was refractory after the receipt of up to five previous therapies; all patients had to have received BTK inhibitor therapy previously. Patients underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 at a dose of  $2 \times 10^6$  CAR T cells per kilogram of body weight. The primary end point was the percentage of patients with an objective response (complete or partial response) as assessed by an independent radiologic review committee according to the Lugano classification. Per the protocol, the primary efficacy analysis was to be conducted after 60 patients had been treated and followed for 7 months.

## RESULTS

A total of 74 patients were enrolled. KTE-X19 was manufactured for 71 patients and administered to 68. The primary efficacy analysis showed that 93% (95% confidence interval [CI], 84 to 98) of the 60 patients in the primary efficacy analysis had an objective response; 67% (95% CI, 53 to 78) had a complete response. In an intention-to-treat analysis involving all 74 patients, 85% had an objective response; 59% had a complete response. At a median follow-up of 12.3 months (range, 7.0 to 32.3), 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively. Common adverse events of grade 3 or higher were cytopenias (in 94% of the patients) and infections (in 32%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 15% and 31% of patients, respectively; none were fatal. Two grade 5 infectious adverse events occurred.

## CONCLUSIONS

KTE-X19 induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma. The therapy led to serious and life-threatening toxic effects that were consistent with those reported with other CAR T-cell therapies. (Funded by Kite, a Gilead company; ZUMA-2 ClinicalTrials.gov number, NCT02601313.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wang at the Department of Lymphoma-Myeloma, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at miwang@mdanderson.org.

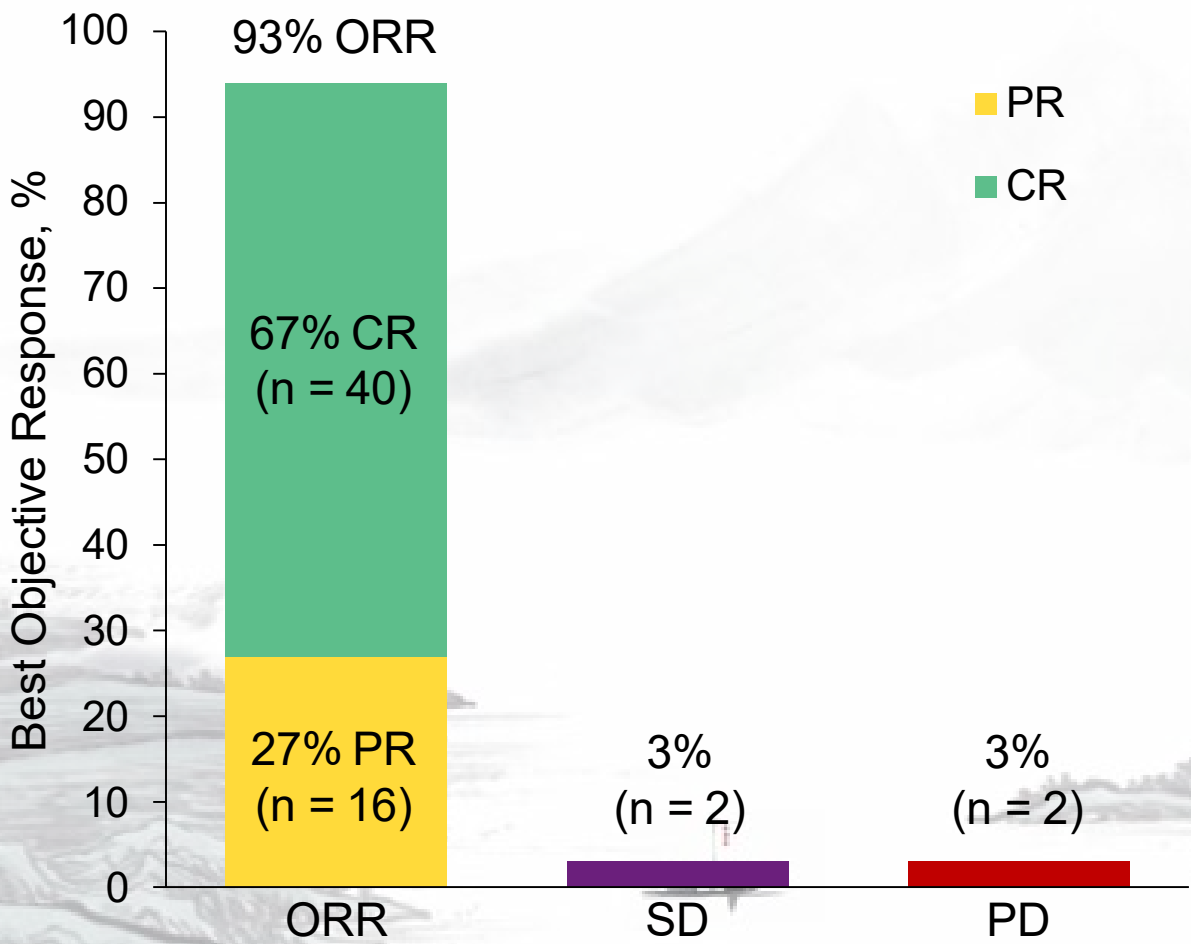
N Engl J Med 2020;382:1331-42.

DOI: 10.1056/NEJMoa1914347

Copyright © 2020 Massachusetts Medical Society.



# ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



Efficacy-Evaluable N = 60	
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

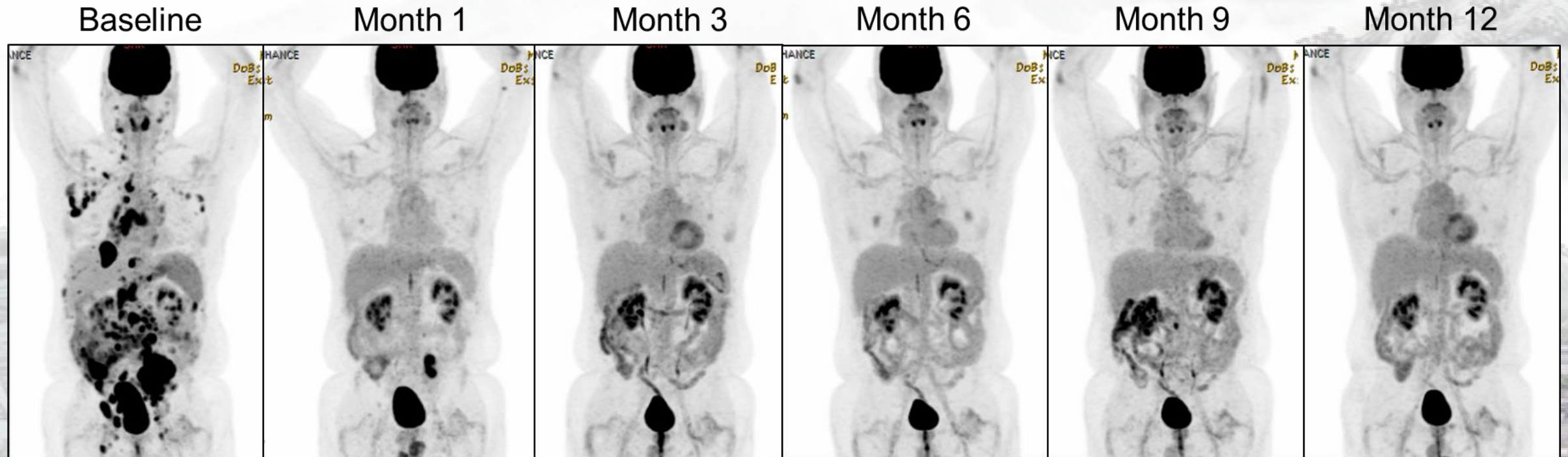
Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).

CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.



# Representative PET Scans of Complete Response

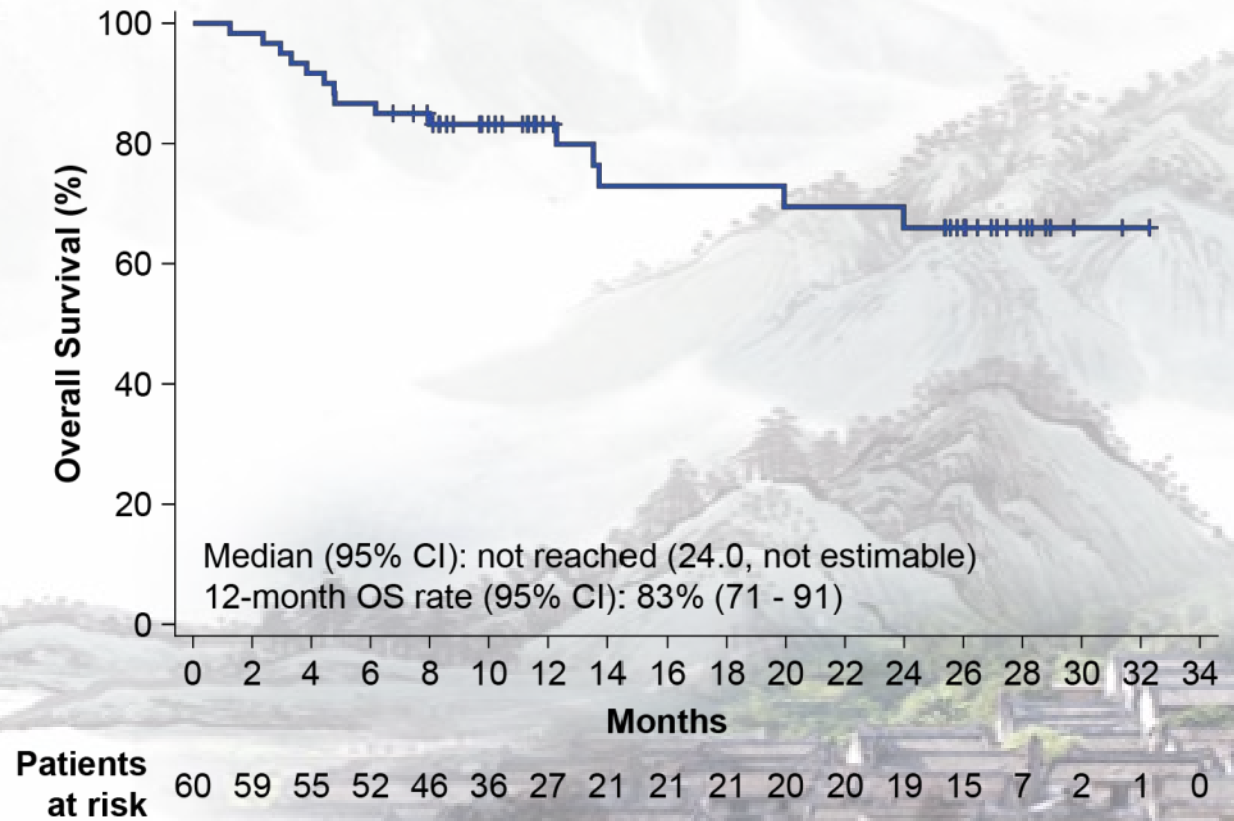
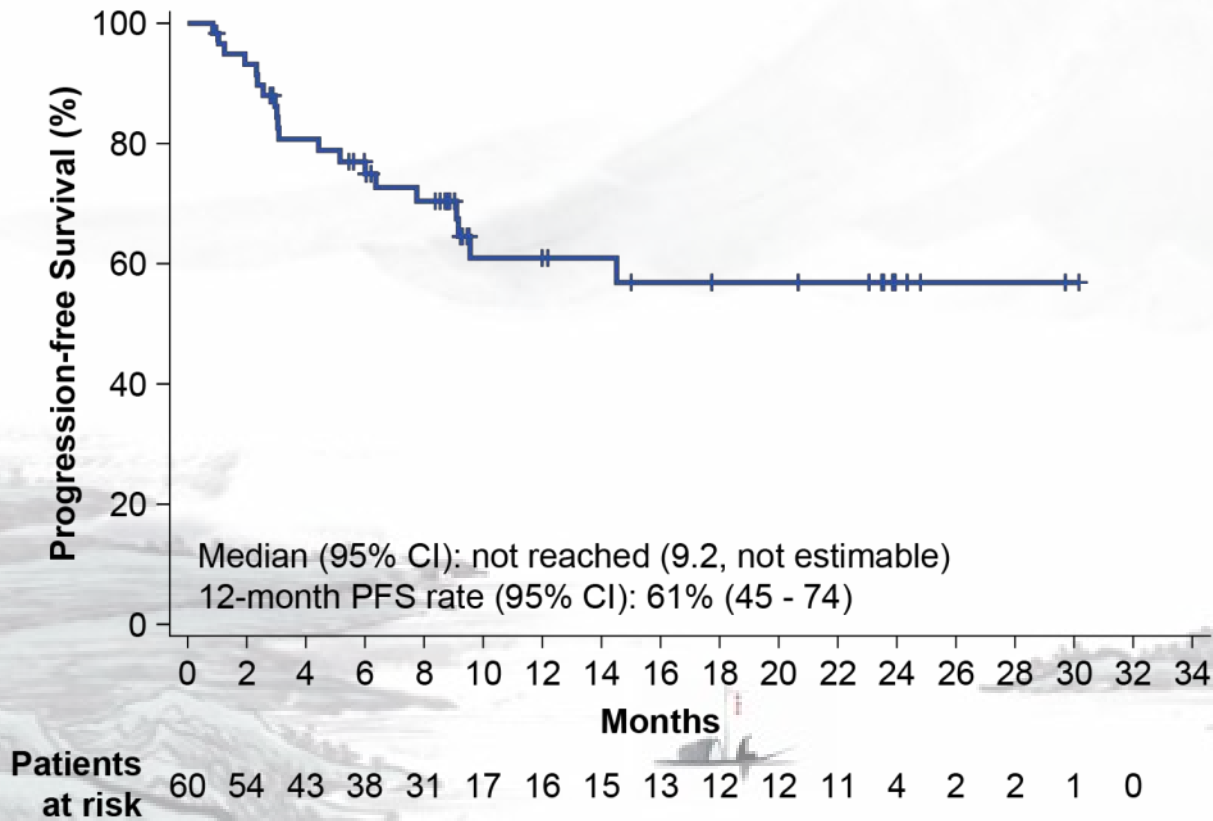
- 50-year-old male patient with 3 prior therapies who presented with multi-compartmental MCL
- With KTE-X19, he achieved PR at Month 1 and CR at Month 3 and remains in remission 18 months later



CR, complete response; MCL, mantle cell lymphoma; PET, positron emission tomography; PR, partial response.

# Progression-Free Survival and Overall Survival

- Median PFS and median OS were not reached after a median follow-up of 12.3 months



OS, overall survival; PFS, progression-free survival.

# Cytokine Release Syndrome

- No Grade 5 CRS occurred

Parameter	N = 68
CRS, n (%) <sup>a</sup>	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

<sup>a</sup> CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.

# Neurologic Events

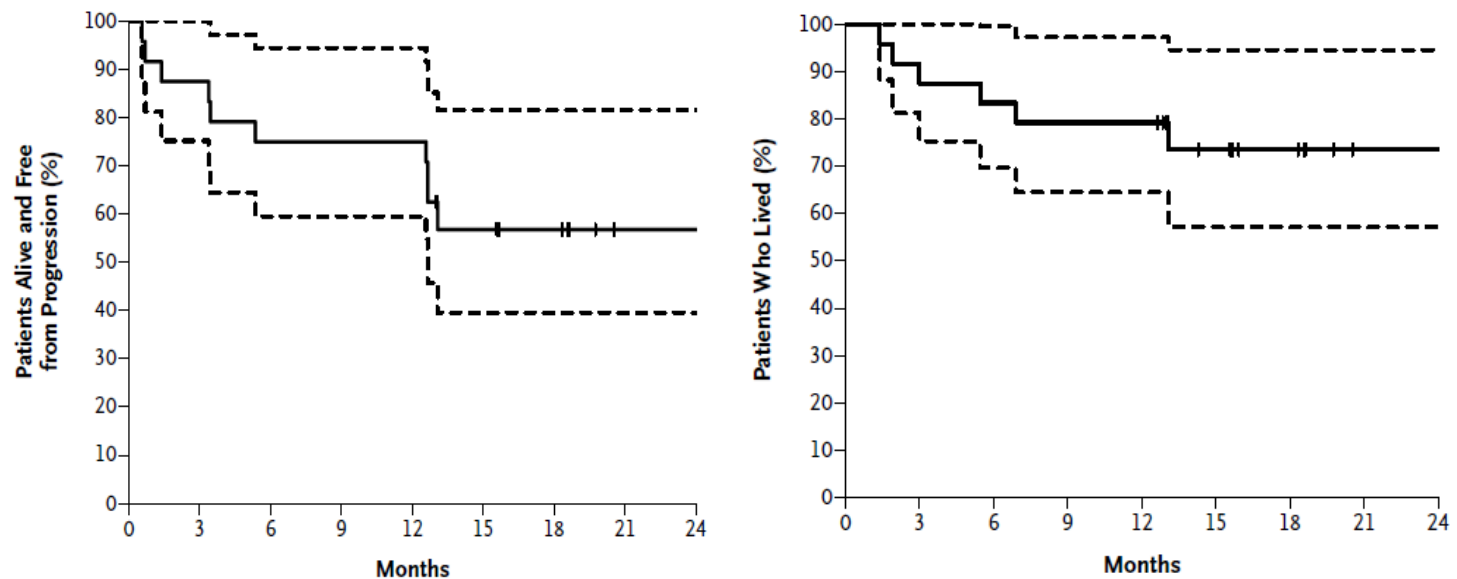
Parameter	N = 68
Neurologic events, n (%) <sup>a</sup>	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86) <sup>b</sup>

- No Grade 5 neurologic events occurred
- One patient had Grade 4 cerebral edema confirmed by MRI of the brain
  - The patient was intubated and treated with aggressive multimodality therapies including tocilizumab, siltuximab, high-dose steroids, intrathecal Ara C plus dexamethasone, mannitol, ventriculostomy and IV ATG<sup>c</sup>
  - The neurotoxicities fully resolved and the patient remains in CR 24 months later
  - This is the first reported use of ATG in treating CAR T cell-related toxicities

<sup>a</sup> Neurologic events were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03. <sup>b</sup> Four patients had ongoing neurologic events at data cutoff: Grade 1 tremor (n = 3), Grade 2 concentration impairment (n = 1), and Grade 1 dysesthesia (n = 1). Two patients died from unrelated AEs (organizing pneumonia and staphylococcal bacteremia) prior to the resolution of the neurologic events. <sup>c</sup> Rabbit ATG.

# Ibrutinib/Venetoclax for Rel/Ref MCL

- Phase 2 study in 23 with Rel/Ref MCL, 1 untreated
- Ibrutinib 560/day for 4 wks, then add Venetoclax, ramp-up to 400 mg daily until PD
- # Prior TX: 0-6, 9 (43%) with Ki67 > 30; 50% had p53 mutated and/or deleted
- CR at 16 wk: 70% (vs historical 9% Ibrutinib alone)
- Clearance by flow in 67%, 16/19 became MRD negative



*Tam et al. NEJM 378: 1211-1223, 2018.*

**Only 2 had TLS (Chemical only).**





## 1592 Updated Safety and Activity of the Investigational Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) in Patients with Mantle Cell Lymphoma

Constantine S. Tam, MBBS (Hons), MD, FRACP, FRCPA<sup>1,2,3,4</sup>, Michael Wang, MD<sup>5</sup>, David Simpson, MBChB, FRACP, FRCPA<sup>6</sup>, Stephen Opat, FRACP, FRCPA, MBBS<sup>7,8</sup>, Gavin Cull, MB, BS, DM, FRACP, FRCPA<sup>9,10</sup>, Javier Munoz, MD<sup>11</sup>, Tysel J. Phillips, MD<sup>12</sup>, Won-Seog Kim, MD, PhD<sup>13\*</sup>, James Hilger, PhD<sup>14\*</sup>, Jane Huang, MD<sup>14</sup>, William Novotny, MD<sup>14\*</sup> and Judith Trotman<sup>15,16</sup>

### Results:

43 patients were enrolled: 38 relapsed/refractory and 5 treatment-naïve (Table). Median follow-up was 10.3 months (range, 0.1–39.2).

20 patients have discontinued treatment (12 due to progressive disease; 8 due to TEAEs).

**Table. Patient Characteristics, Safety, and Efficacy**

Patient characteristics	N = 43
Median (range) age, y	71 (42–87)
ECOG PS, n (%)	
0	21 (48.8)
1	19 (44.2)
2	3 (7.0)
Median (range) no. of prior therapies	1 (0–4)
Median (range) follow-up, mo	10.3 (0.1–39.2)
Disease status, n (%)	
Treatment-naïve	5 (11.6)
Relapsed/refractory	38 (88.4)
Bulky disease >10 cm, n (%)	3 (7.0)

Overall response rate was 90.0% (n=36/40) including 20.0% (n=8) with complete response.

Efficacy	
<b>Best response per investigator</b>	<b>n = 40<sup>a</sup></b>
Overall response rate, n (%); 95% CI	36 <sup>b</sup> (90.0); 76.3, 97.2
Complete response, n (%)	8 (20.0)
Partial response, n (%)	28 (70.0)
Stable disease, n (%)	1 (2.5)
Progressive disease, n (%)	1 (2.5)
Discontinued before first assessment due to AE, n (%)	2 (5.0)
<b>Duration of response (months)</b>	<b>n = 36</b>
Number of events, n (%)	12 (33.3)
Median (95% CI)	15.4 (11.5, 28.2)
<b>Progression-free survival (months)</b>	<b>n = 40</b>
Number of events, n (%)	16 (40.0)
Median (95% CI)	18.0 (12.7, 30.7)

# Targeting BTK With Reversible BTK Inhibitors

## Selective BTK Inhibitors

### **GDC0853**

- Pre-clinical (Reif S and Woyach J, ASCO 2016)
- Clinical trial prematurely discontinued due to prioritization toward other indications (Byrd JC et al. *Oncotarget*. 2018)

### **SNS-062**

- Fabian C and Johnson AJ (AACR 2017)
- Initiating phase 1 clinical trial

### **LOXO-305**

- Pre-clinical study CLL 200 (Brandhuber B, SOHO 2018)
- Initiating Phase 1 clinical trial in 2018

## Less Selective BTK Inhibitors

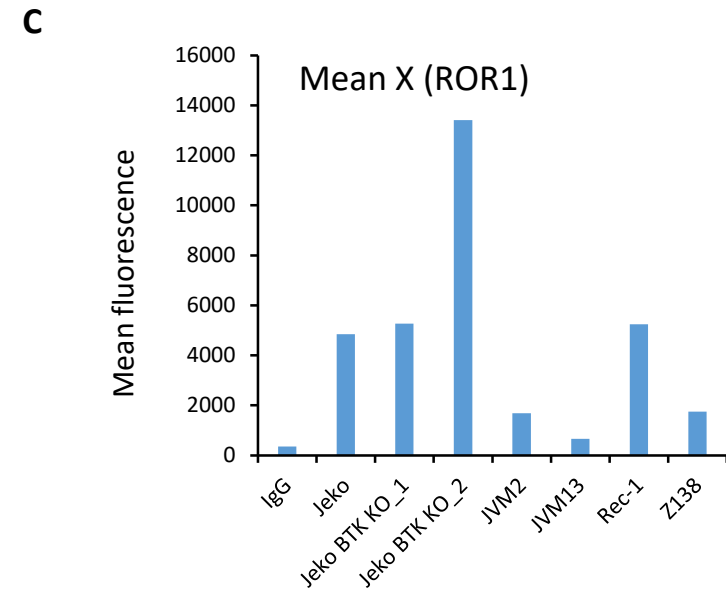
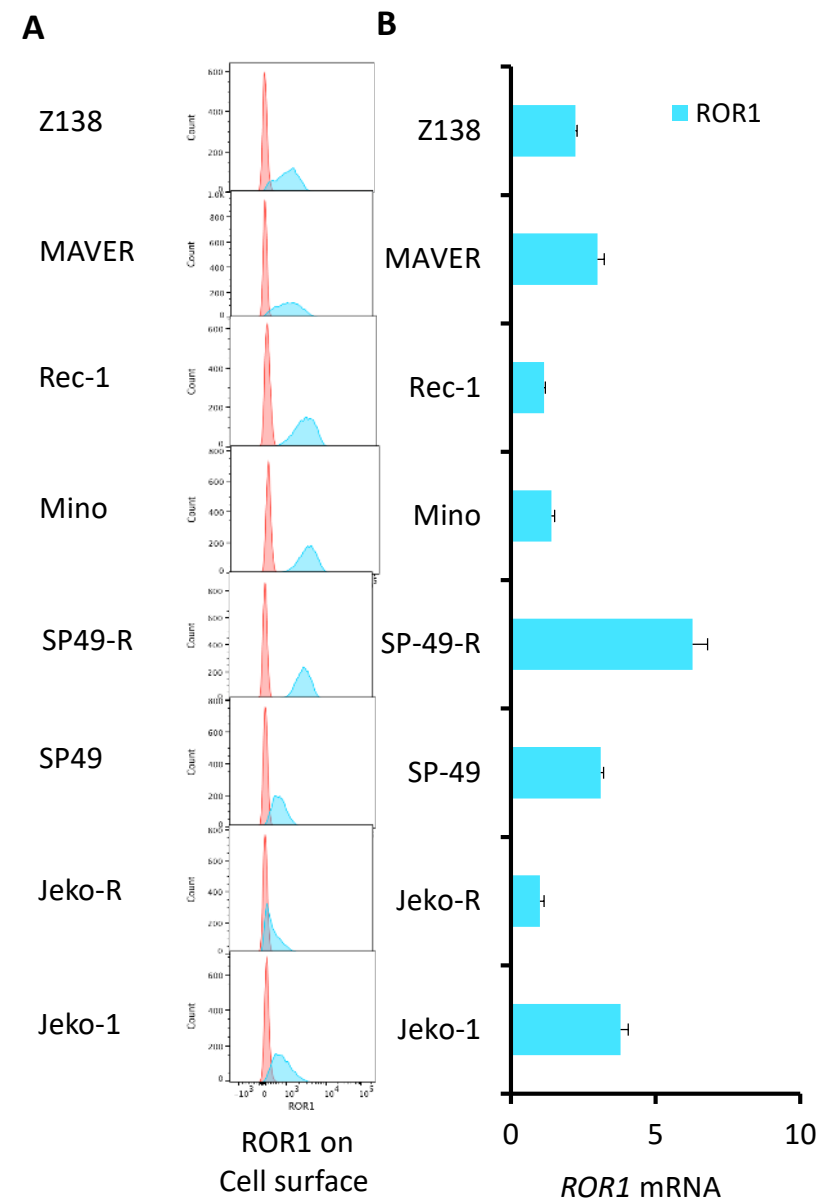
### **ARQ531**

- Reif S and Woyach J (ASH 2017)
- Phase 1 clinical trial ongoing

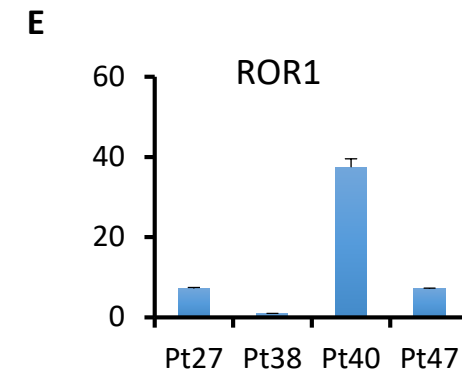
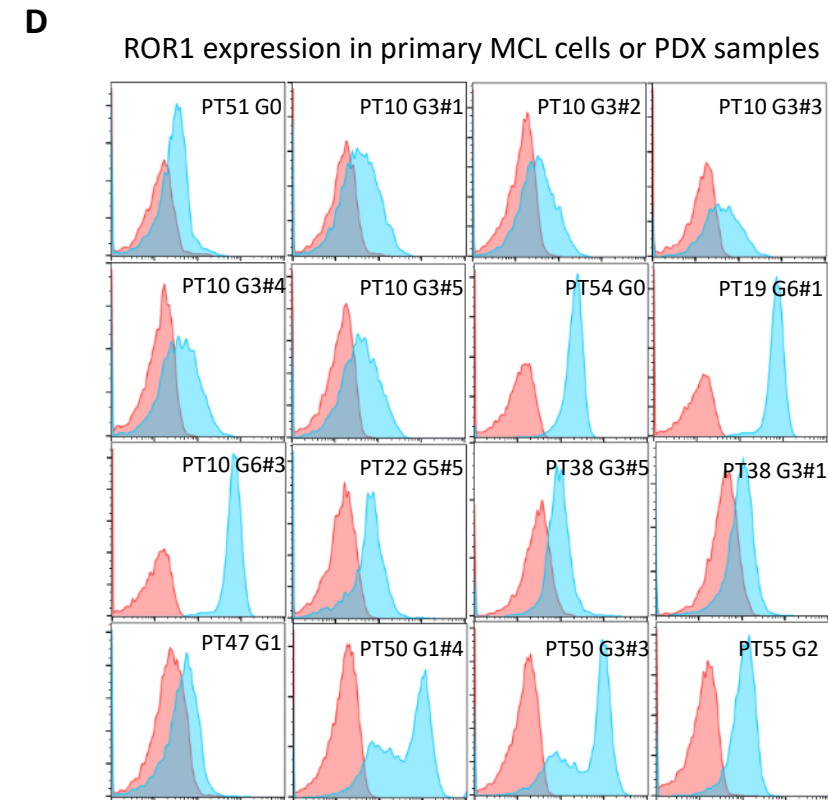
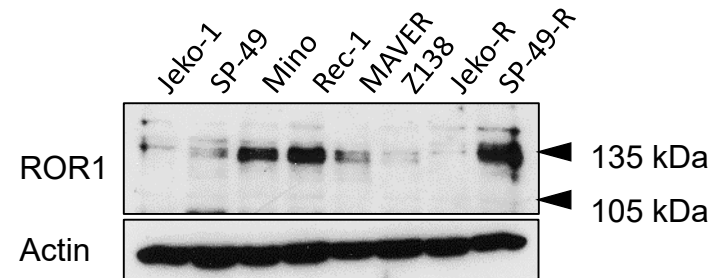
# Cirmtuzumab Enhances Ibrutinib Cytotoxicity in MCL Cells

Vivian Jiang, Wang Lab

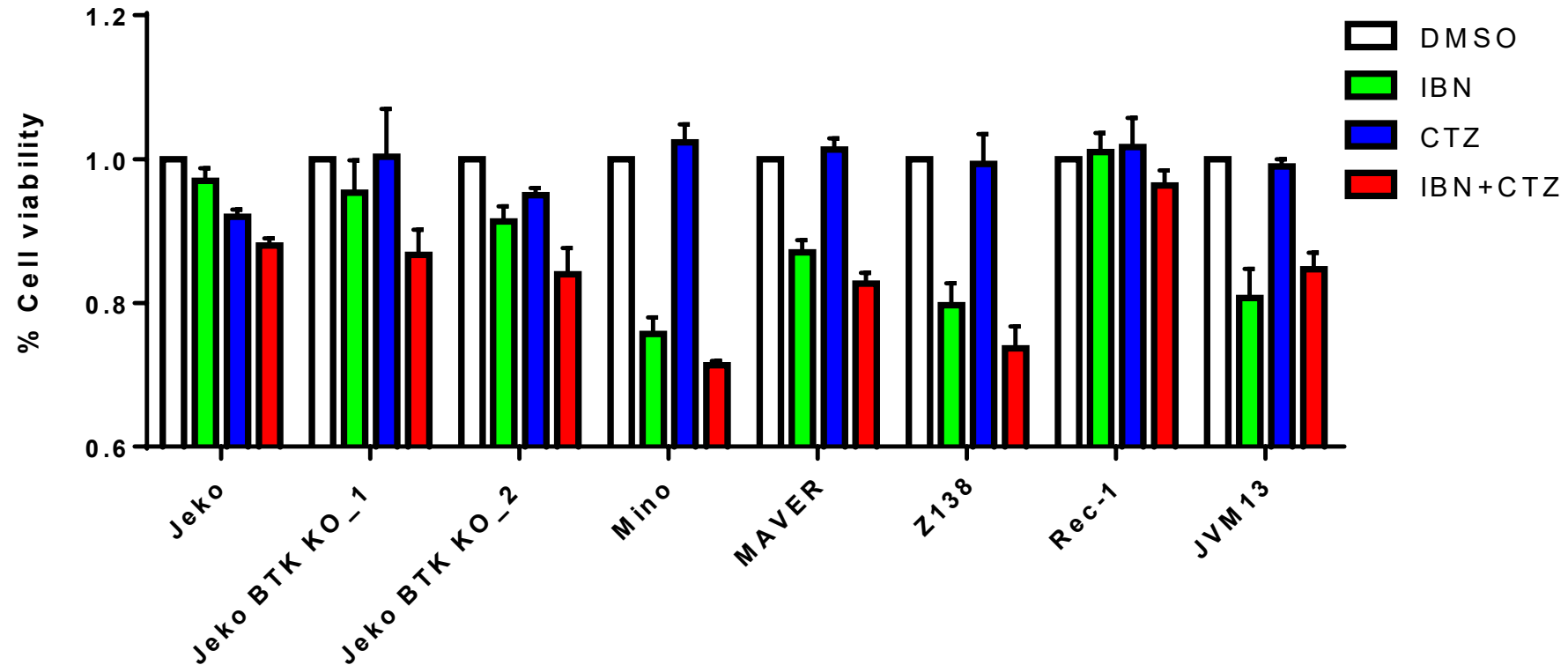
# ROR1 expression in MCL cells



**E** ROR1 protein expression in MCL cell lines



## Cirmtuzumab enhanced IBN induced-cytotoxicity in MCL cells



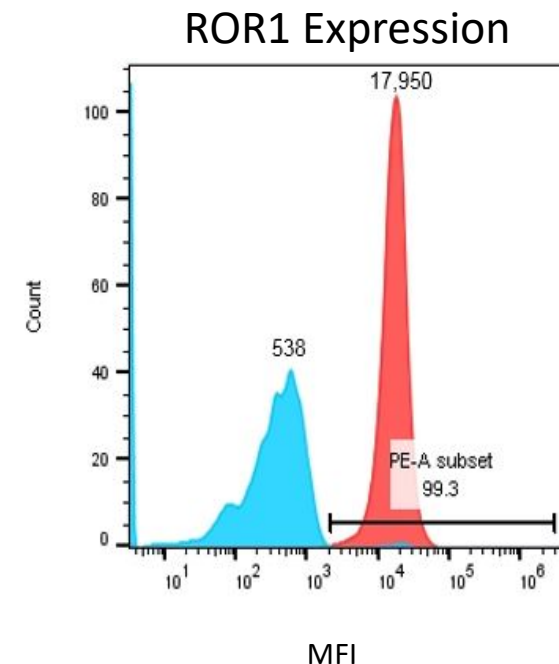
### Treatment (24h)

- Low IBN: 1uM (Jeko), 0.5uM (Rec-1)
- High IBN: 10uM (Jeko BTK KO\_1, Jeko BTK KO\_2, Mino, MAVER, Z138, JVM13)
- Cirmtuzumab: 2mg/ml

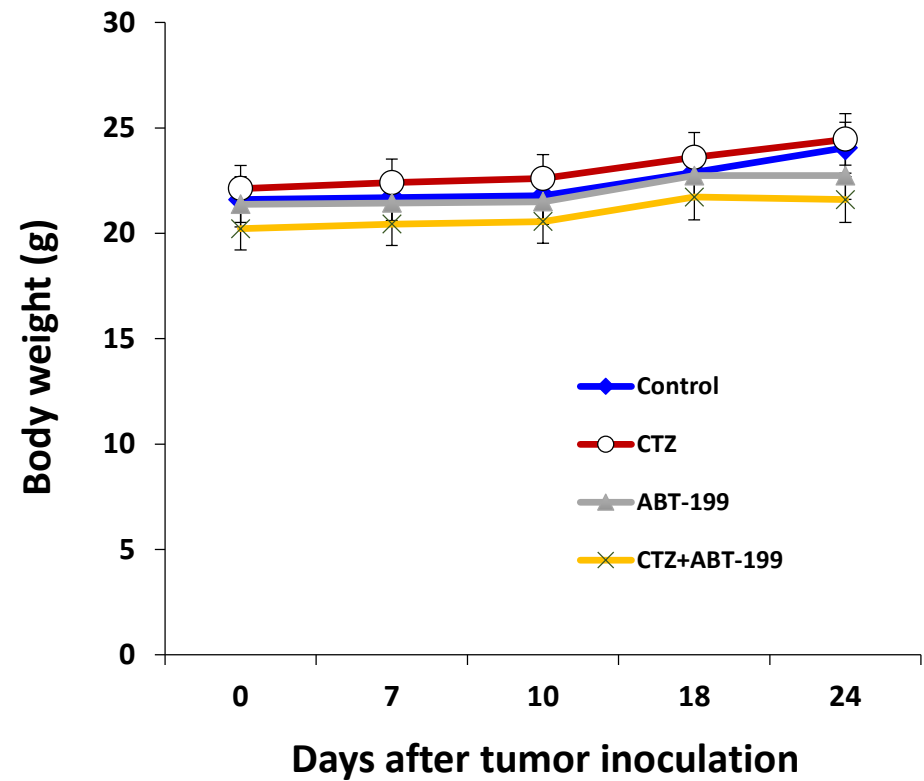
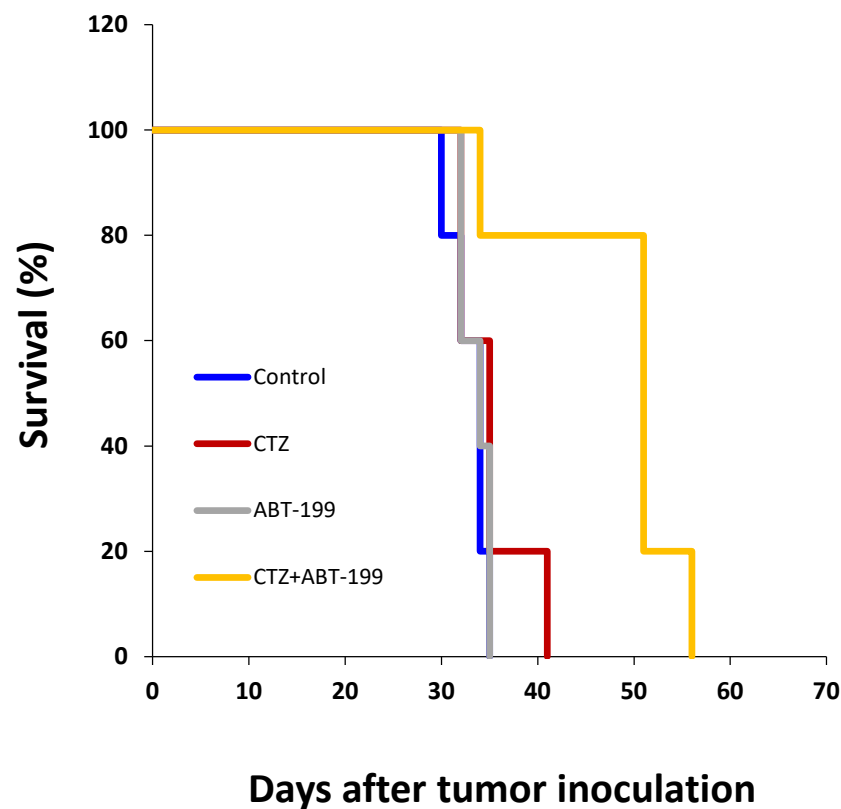


# Experimental design for cirmtuzumab and ABT-199 alone or in combination in a GCB-DLBCL PDX model

- A GCB-DLBCL PDX model was derived from a DLBCL GC type patient and established in the Wang Lab at MDACC.
- The NSG mice carrying the PDX models were randomly divided into 4 groups (n=5) and treated with the cirmtuzumab and ABT-199 alone or in combination:
  1. Control
  2. Cirmtuzumab (CTZ): 10 mg/kg, i.v., twice per week
  3. ABT-199 (venetoclax): 50mg/kg, oral gavage, daily
  4. CTZ+ABT-199



The treatments had no toxicity in the first 4 doses and prolonged survival of DLBCL-PDX mice



CTZ = cirmtuzumab  
ABT-199 = venetoclax



# **scRNA-seq reveals heterogeneity, clonal evolution and strategies to overcome ibrutinib-venetoclax dual resistance in mantle cell lymphoma**

Vivian Changying Jiang, PhD; Michael Wang, MD  
MD Anderson Cancer Center, Houston, TX

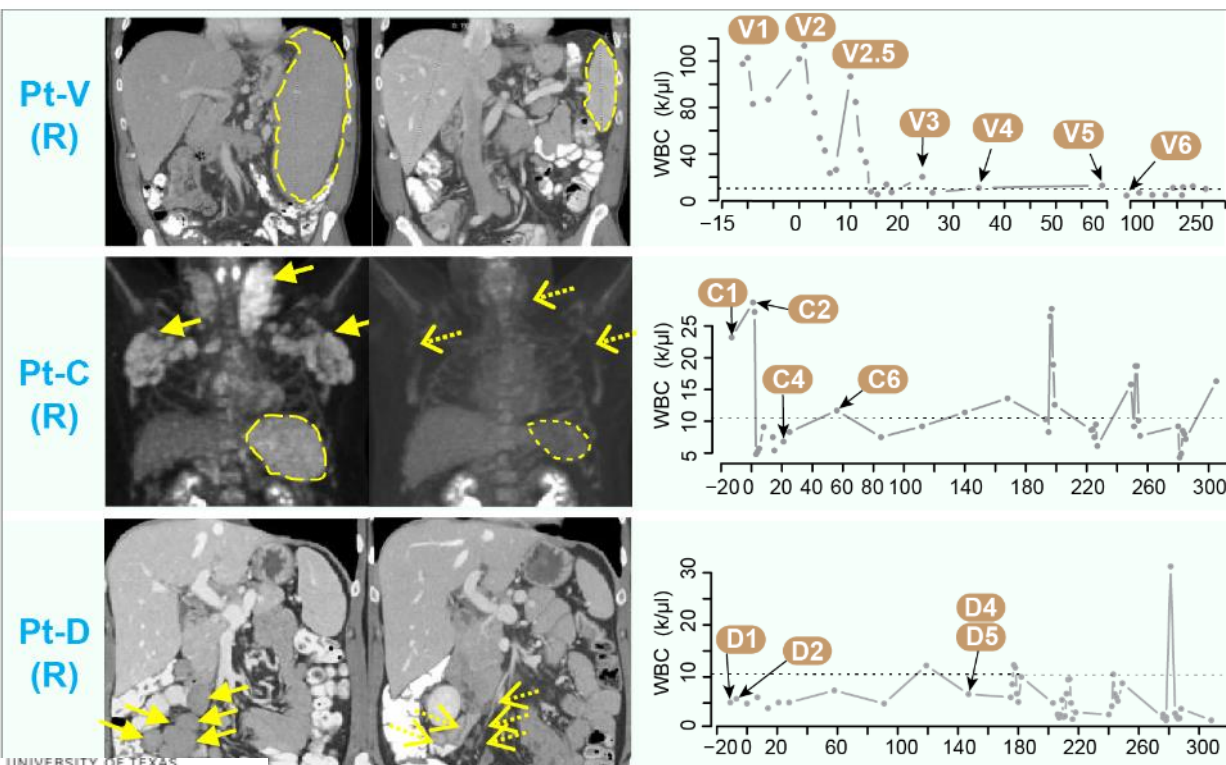
# Patient clinical responses and longitudinal sampling for scRNA-seq analysis

**A**

## Ibrutinib-responders

3 Pt, 15 samples

Baseline Post-treatment

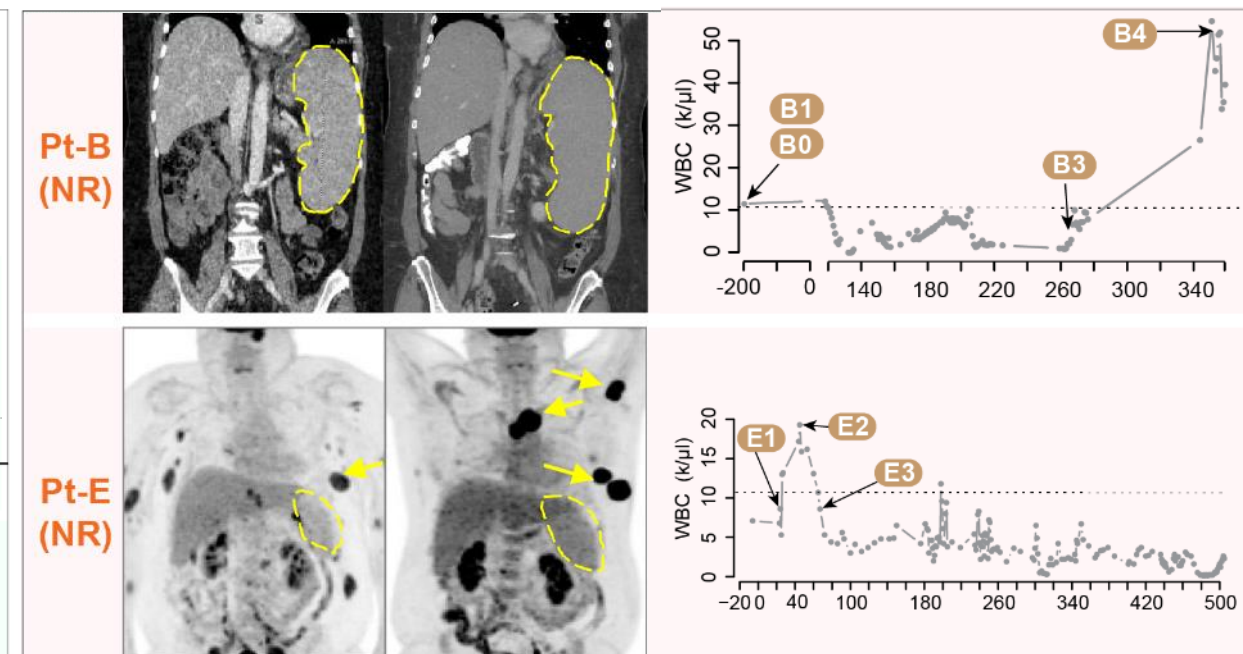


**B**

## Ibrutinib-venetoclax non-responders

2 Pt, 6 samples

Baseline Post-treatment

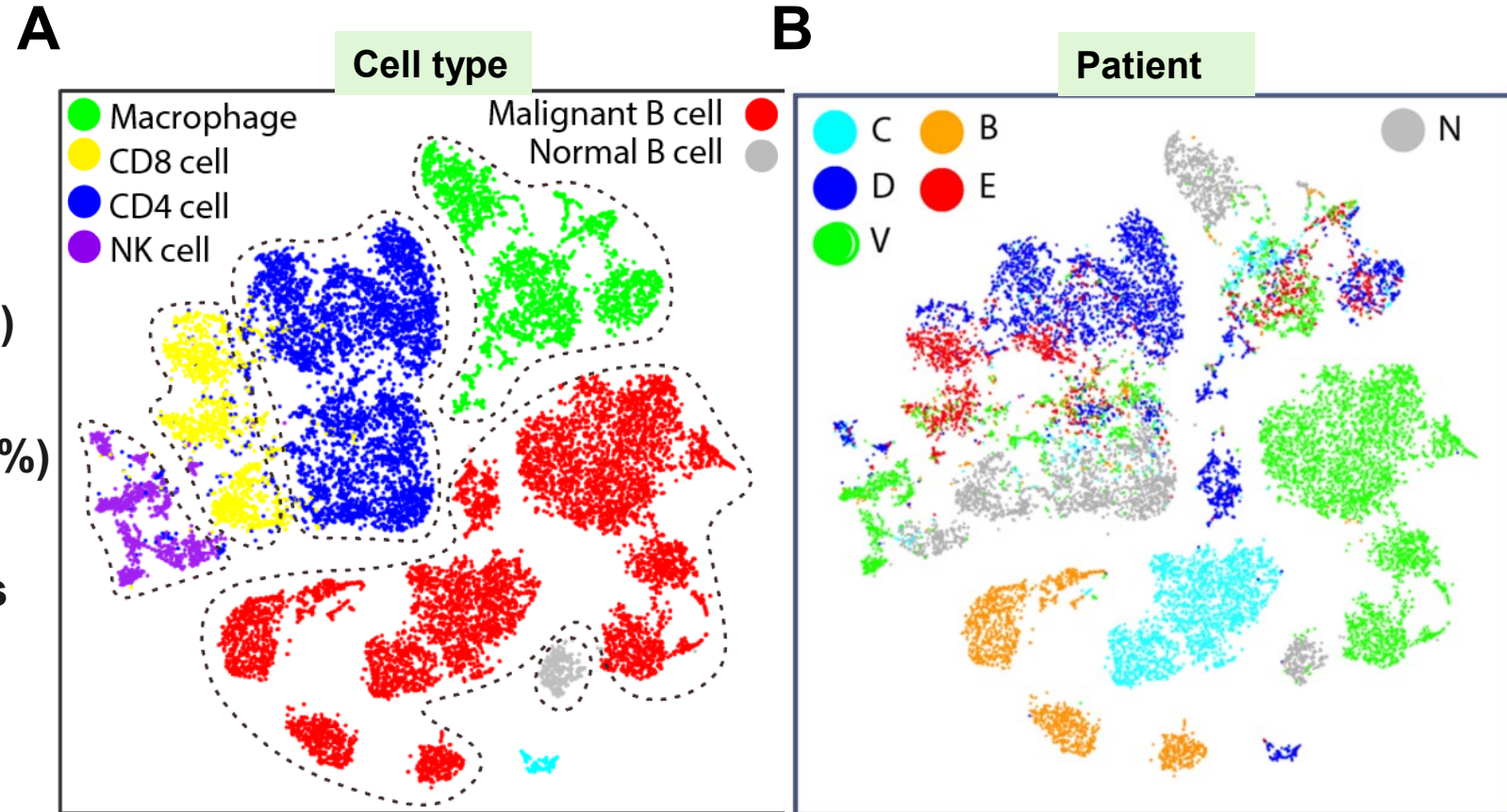




# Unsupervised clustering of 21 patient specimens via scRNA-seq analysis

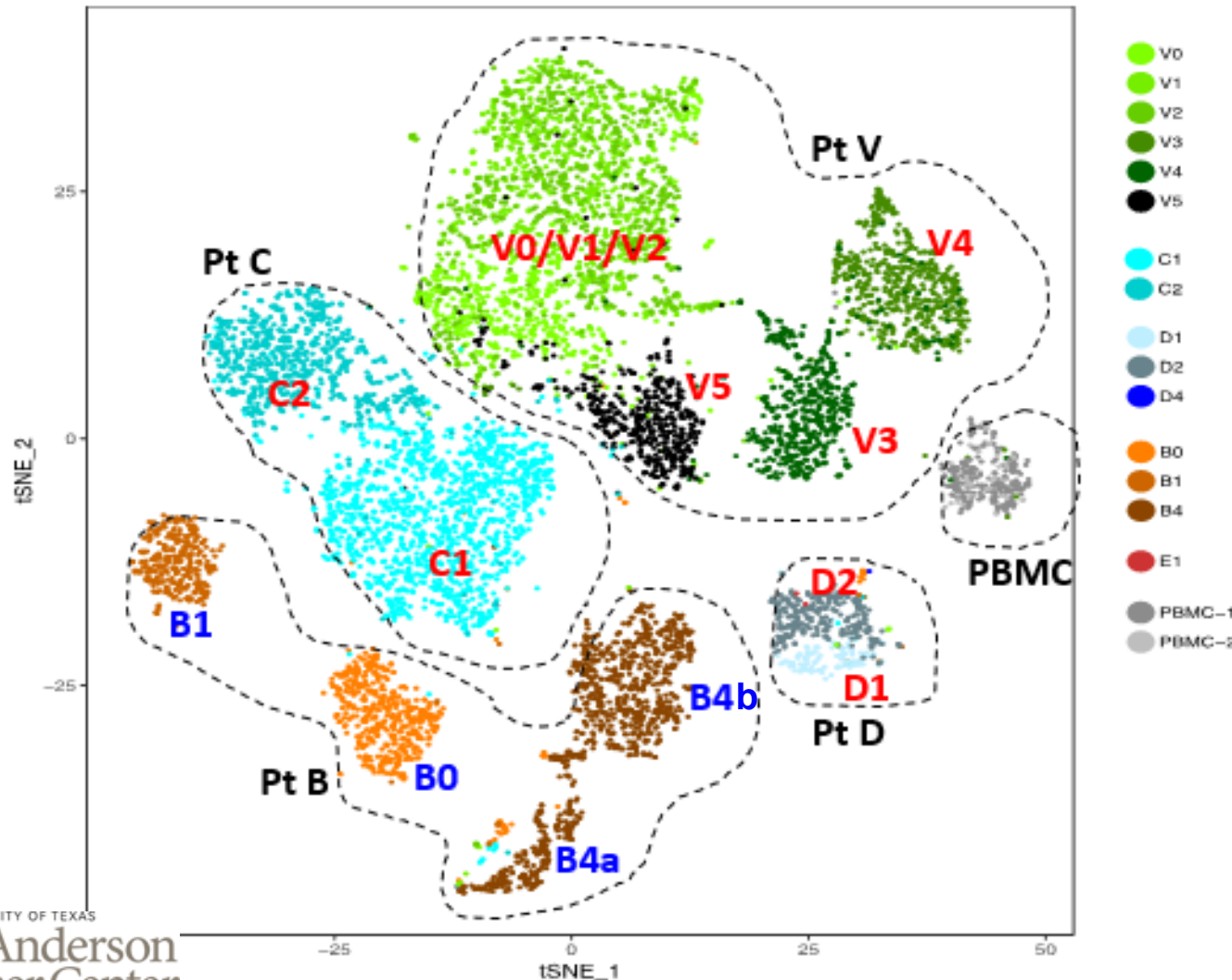
18,794 single cells:

- Malignant B cells (10,464, 56%)
- Non-malignant cells (8,330, 44%)
- Clustered closely by cell types





# MCL cells: inter-patient heterogeneity and intra-patient heterogeneity (IPH)



## MCL cells clustered

- By patient
- By sample from the same patient

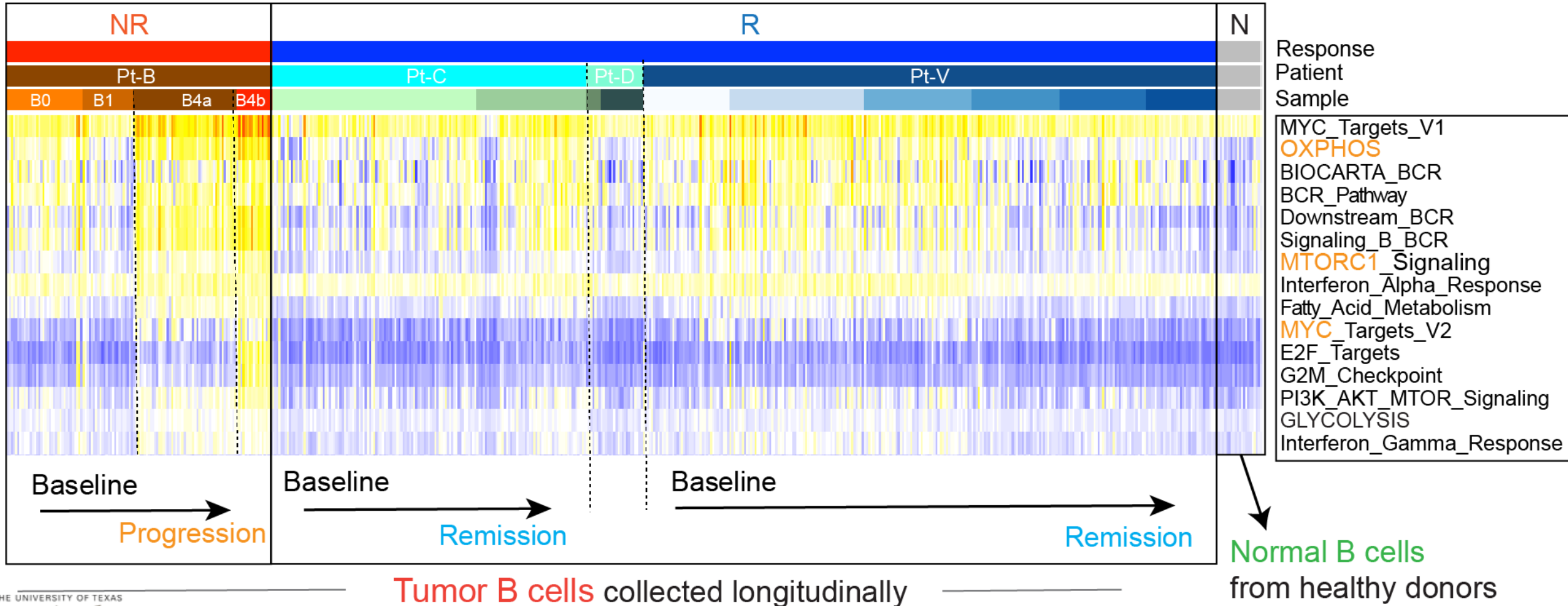
## Ibrutinib-responders:

- Pt V: V0/V1/V2, V3, V4 and V5
- Pt C: C1 and C2
- Pt D: D1 and D2

## Ibrutinib-venetoclax nonresponder:

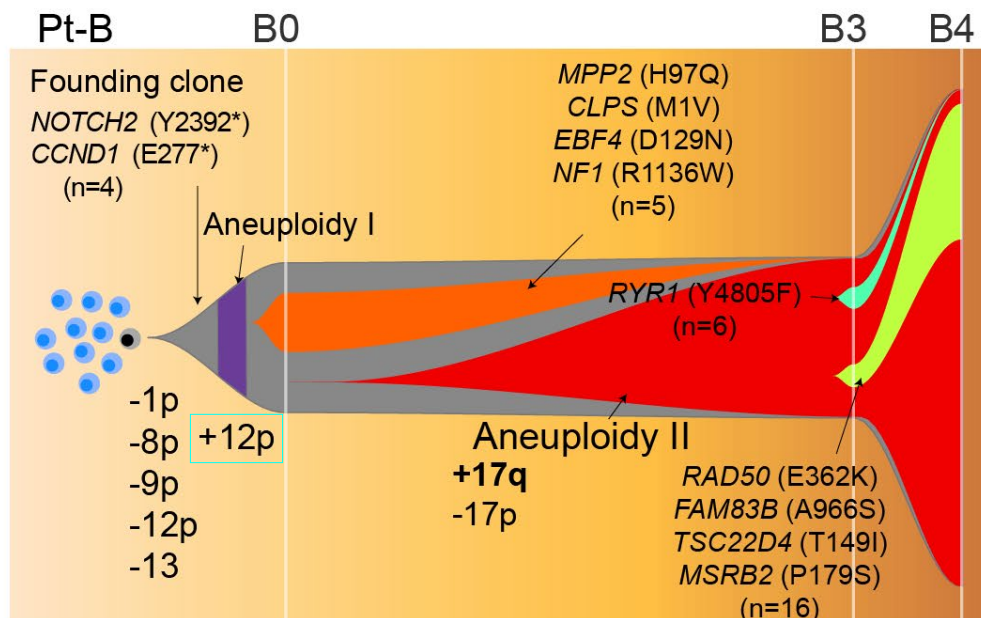
- Pt B: B0, B1 and **B4 (B4a and B4b)**

# Transcriptomic heterogeneity and evolution of cancer hallmarks

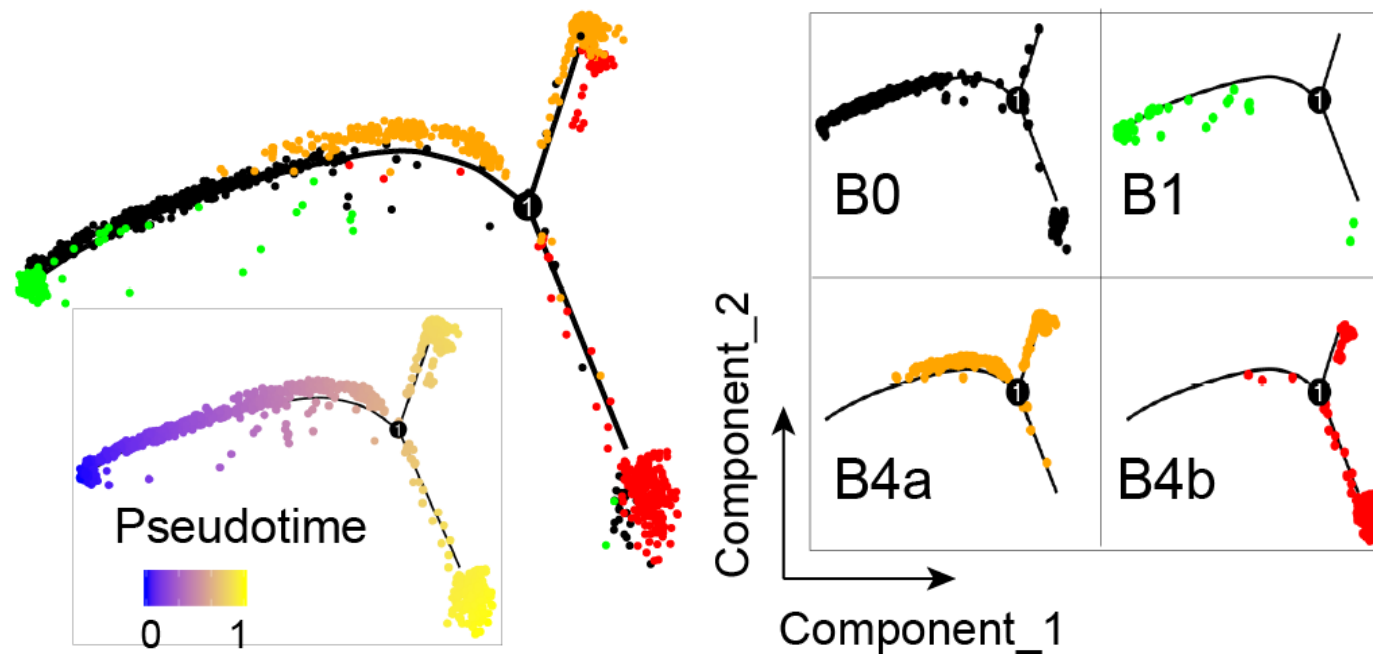


# Clonal evolution along disease progression in the ibrutinib-venetoclax non-responder Pt-B

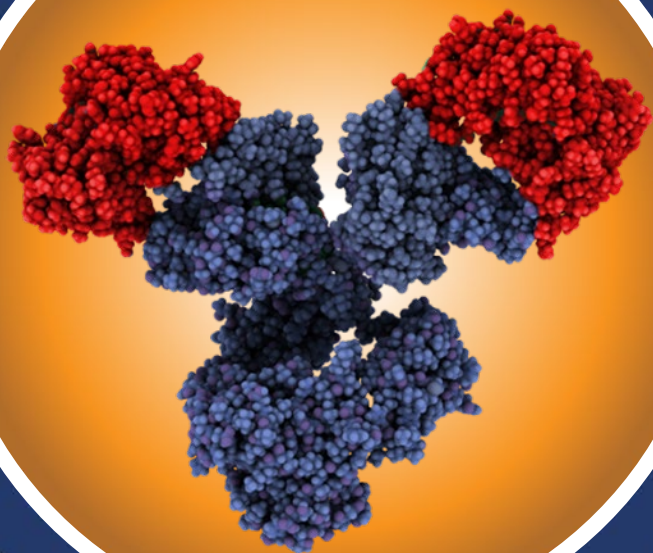
**A**



**B**



- Deep WES sequencing confirmed that 12p and 17q gain in patient B associated with disease progression.
- Single-cell trajectory analysis showed tumor cells in B0 (BM) and B1 (PB) at baseline evolved into two individual subpopulations B4a and B4b at disease progression



## CIRMTUZUMAB

ROR1 monoclonal antibody



## OPPORTUNITY

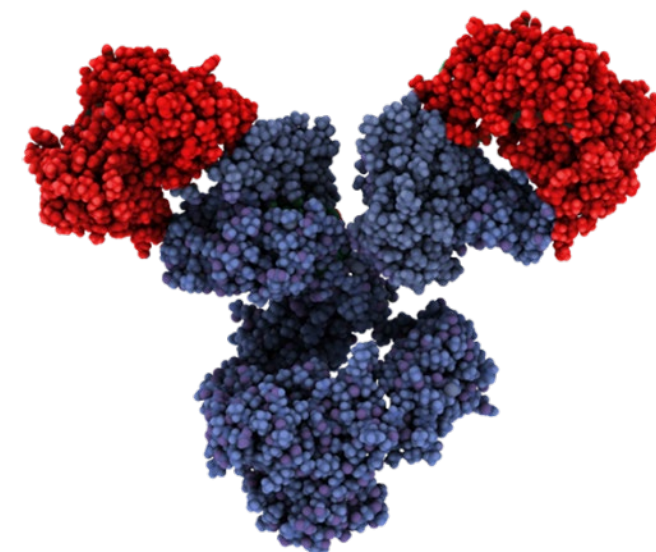
- Potential in multiple hematologic and solid cancers
- Supported by ~\$14M non-dilutive CIRM grant
- Patent coverage through 2033

## MECHANISM OF ACTION

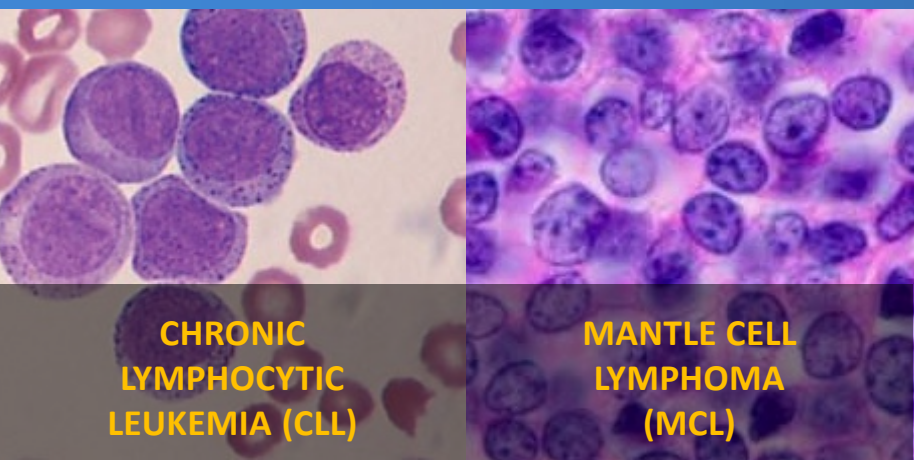
- High-affinity humanized ROR1 monoclonal antibody
- Inhibits Wnt5a stimulated ROR1 signaling
  - Decreased proliferation, invasion, metastasis, stemness
- Preclinical synergy observed with ibrutinib or paclitaxel

## DEVELOPMENT STATUS

- Well-tolerated and active in completed CLL Phase 1
- Phase 2 enrolling in MCL in combination with ibrutinib
- Randomized Phase 2 enrolled in CLL in combination with ibrutinib
- Phase 1b enrolling in HER2-negative breast cancer
- Orphan Drug Designations for MCL and CLL granted by FDA



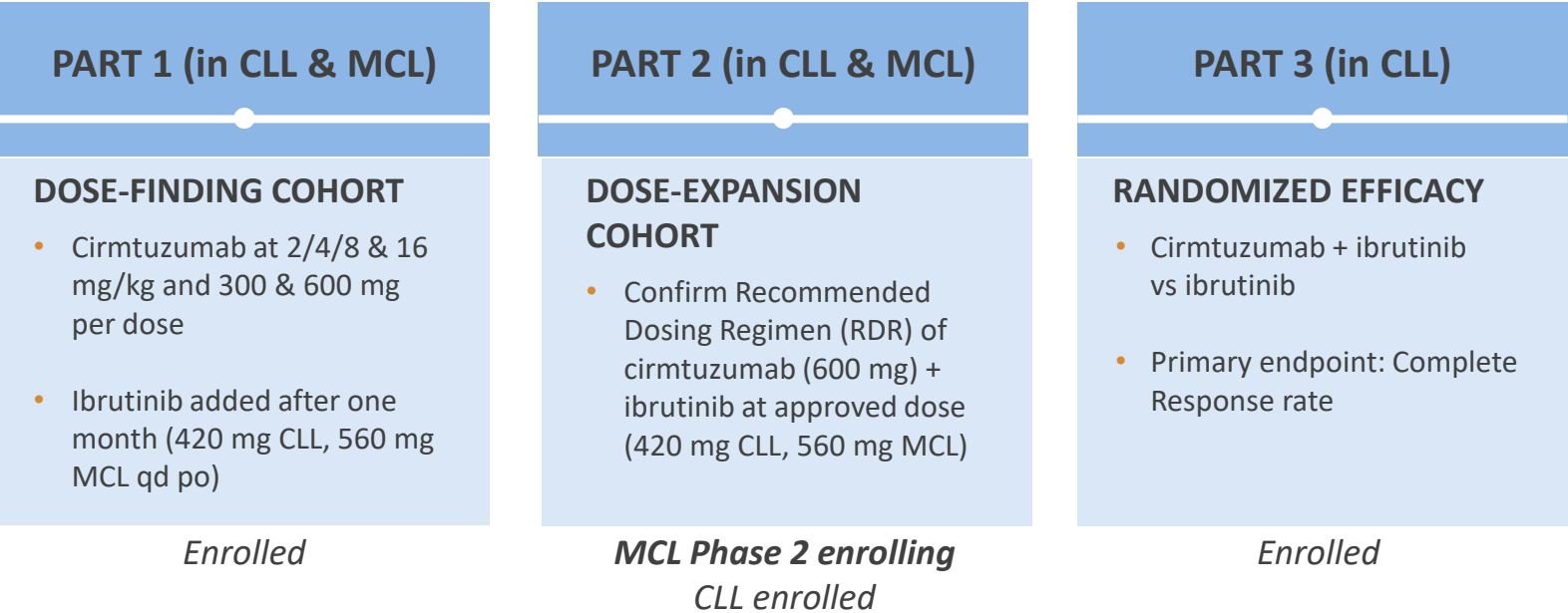
**ROR1** = Receptor tyrosine kinase-like Orphan Receptor 1  
**CIRM** = California Institute for Regenerative Medicine



## CIRLL Study:

- Cirmtuzumab and Ibrutinib targeting ROR1 for Leukemia and Lymphoma
- MCL enrollment recently expanded

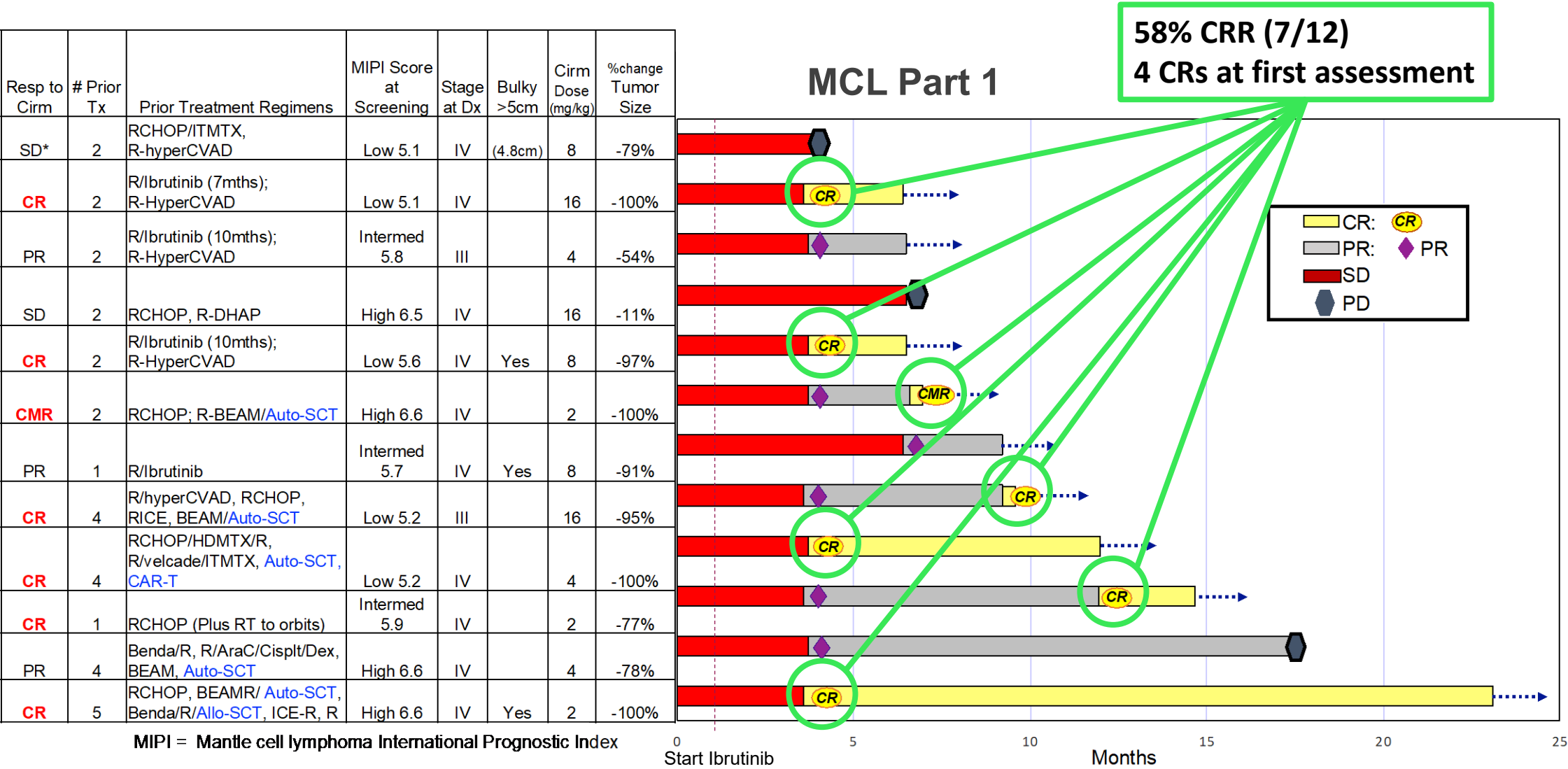
## STUDY DESIGN





# CIRLL Trial: Interim MCL Part 1 Data

## Best Tumor Response Over Time ORR = 83%, CR Rate 58%

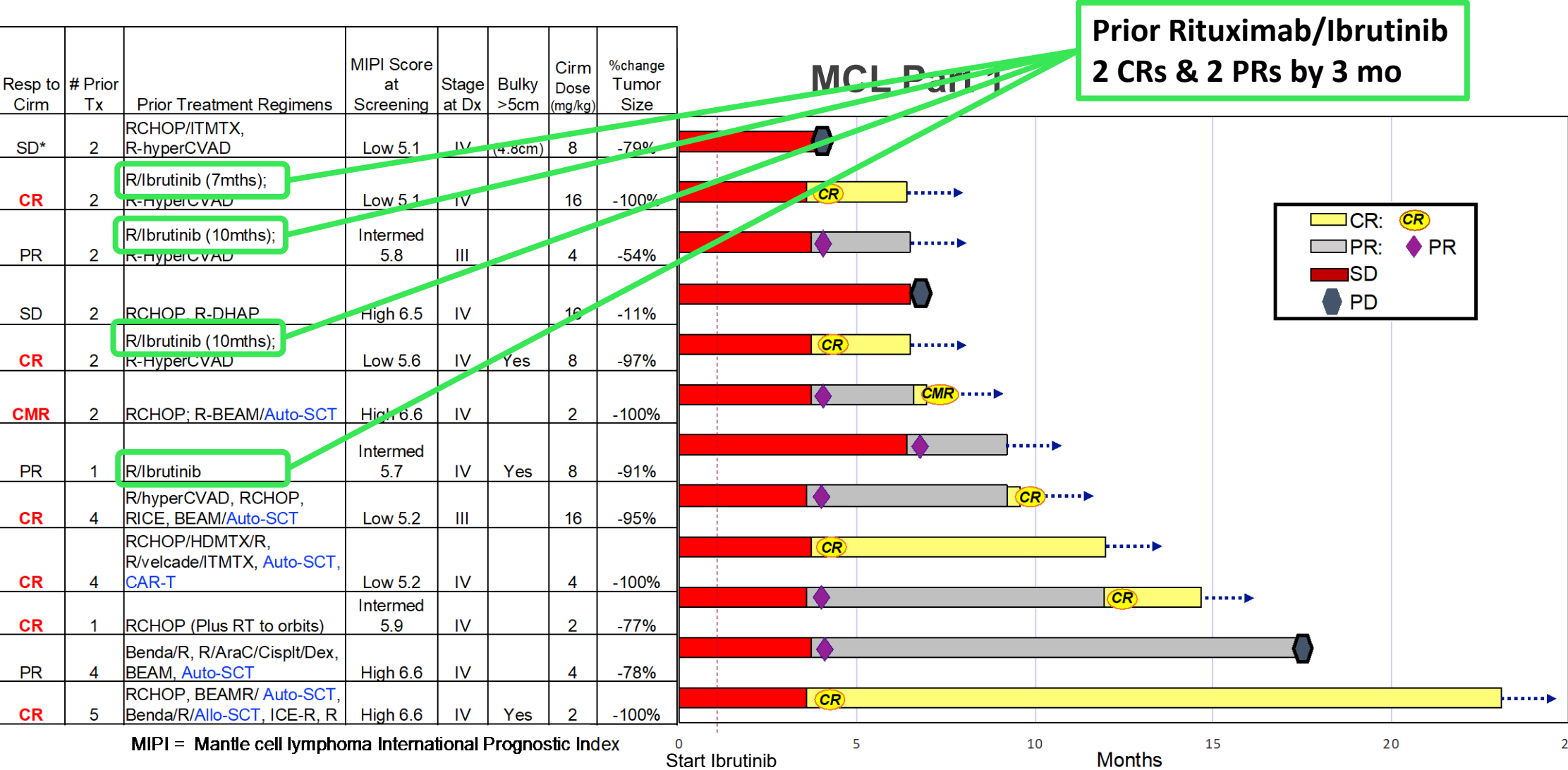


Simon Rule Haematologica 2019: ORR 67% and CR rate 23% for ibrutinib in MCL with >1 prior lines of therapy in a pooled analysis across three third-party clinical studies

**Higher than expected 23% CR rate**

# CIRLL Trial: Interim MCL Part 1 Data

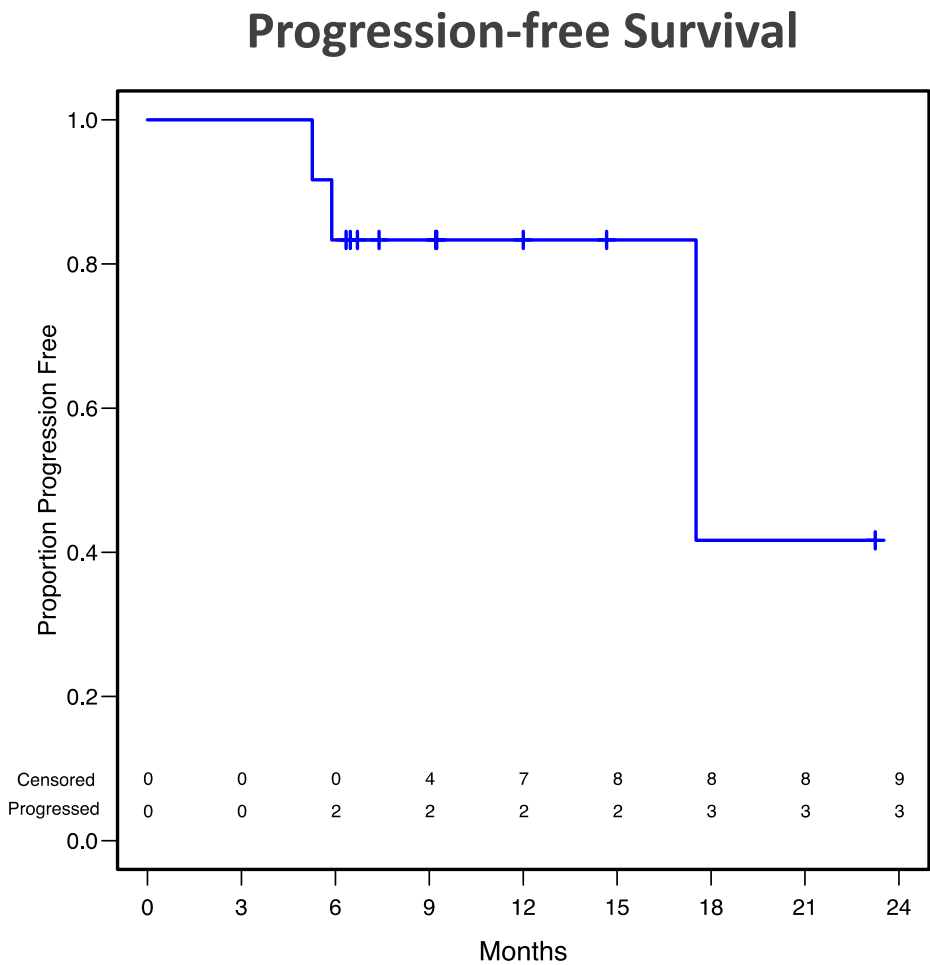
## Best Tumor Response Over Time ORR = 83%, CR Rate 58%



Simon Rule Haematologica 2019: ORR 67% and CR rate 23% for ibrutinib in MCL with >1 prior lines of therapy in a pooled analysis across three third-party clinical studies

# CIRLL Trial: Interim MCL Part 1 Data

## Progression-free Survival



- Median PFS 17.5 months
- Median follow-up 8.3 months

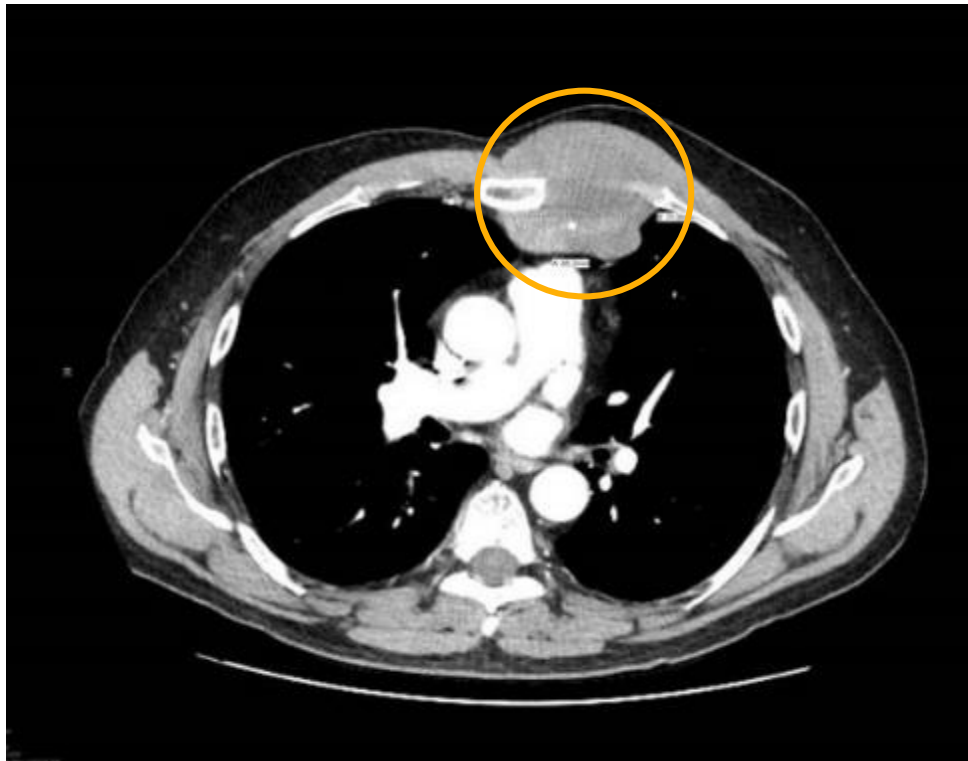
*Simon Rule Haematologica 2019: PFS 10.3 months for ibrutinib in MCL with >1 prior lines of therapy in a pooled analysis across three third-party clinical studies*

# Patient Story: Durable Complete Response in Patient with Relapsed Mantle Cell Lymphoma in Clinical Trial of Cirmtuzumab and Ibrutinib

- 67-year old male, Diagnosed with MCL in 2009
- Five prior therapies including 2 stem cell transplants

- Rapid clinical response with confirmed CR after 3 months cirmtuzumab + ibrutinib
- CR confirmed and durable at 23+ months on study

**Baseline**

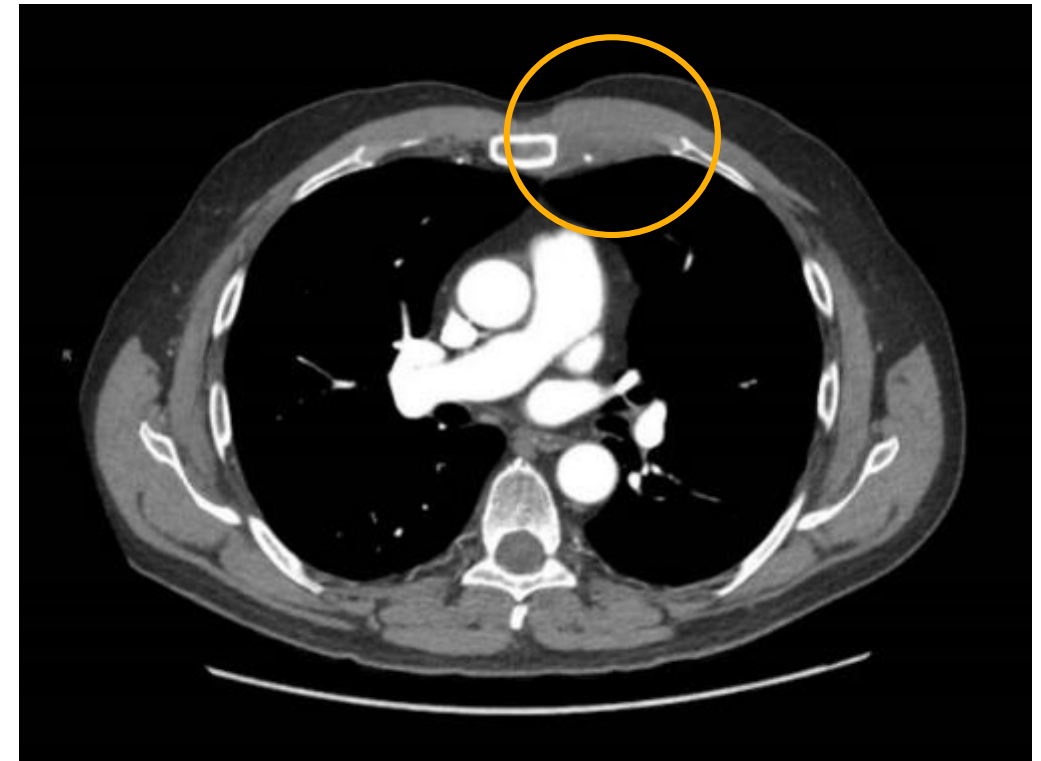


3 months



Complete  
Response

**Cirmtuzumab + Ibrutinib**



Source: Choi, 2019 ASCO and Lee, 2020 ASCO

# CIRLL Trial Cirtuzumab + Ibrutinib: MCL Interim Data

## 58% Complete Response Rate

Results from 12 evaluable patients with relapsed/refractory MCL treated with cirtuzumab + ibrutinib:

- Heavily pretreated: Auto-SCT (n=5), allo-SCT (n=1), CAR-T (n=1), ibrutinib (n=4)
- Efficacy: CR rate 58%, ORR 83%, median PFS 17.5 months
- All 4 patients previously treated with ibrutinib responded (2 CRs, 2 PRs)
- Based on results, increasing enrollment in MCL Phase 2 to at least 20 patients & Allowing enrollment of patients with broader range of prior ibrutinib treatment
- Meeting requested with FDA to explore potential accelerated approval pathway in MCL

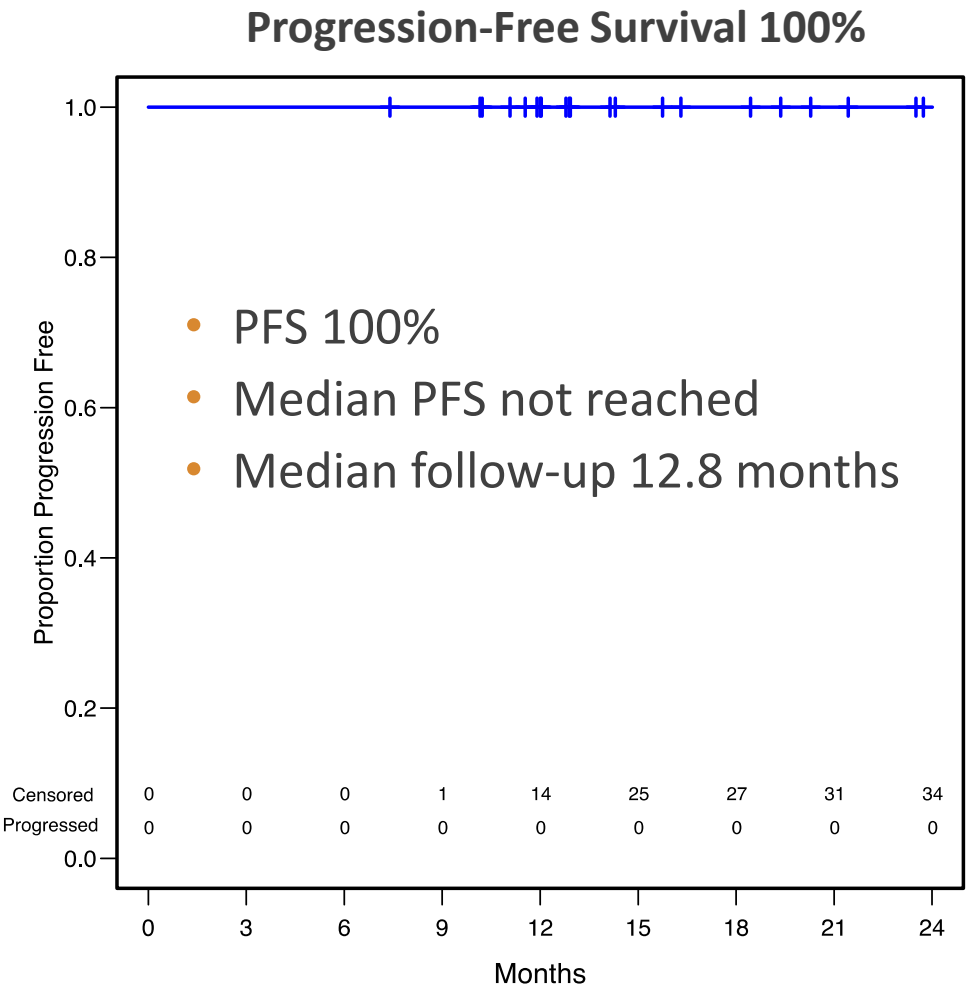
\*One patient with CMR: Complete Metabolic Response by PET scan (Cheson2014), BM pending  
MIPI - Mantle Cell Lymphoma International Prognostic Index

Source: Lee, 2020 ASCO, data cut-off April 30, 2020

# CIRLL Trial Cirmtuzumab + Ibrutinib: CLL Interim Data

## 100% PFS

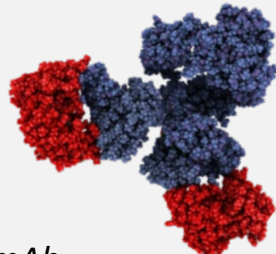
- 34 evaluable patients (22 relapsed/refractory, 12 treatment naïve)
  - Average 2.6 prior therapies (range 1-9) for r/r patients
- Median follow-up 12.8 months
- Efficacy: 1 CR (3%), 29 PR (85%), 4 SD (12%)
  - Best ORR 88% (30 of 34)
  - Clinical Benefit (CR, PR or SD) seen in 100% of subjects
  - No progressive disease observed on study (PFS=100%)
- Adverse events typical for ibrutinib alone
  - No dose limiting toxicities or discontinuations due to cirmtuzumab
  - No Grade 3 or higher common adverse events attributed to cirmtuzumab alone
  - Neutropenia 8.6% across CLL and MCL cohorts
    - Neutropenia 50-60% (Grade 3-4: 23%) in Imbruvica Prescribing Information
- Limiting total enrollment in randomized Phase 2 CLL cohort to ~30 patients



Note: 1 patient died of complications of acute cholecystitis off study without evidence of CLL progression



# Robust Pipeline – Novel Product Candidates in Multiple Indications

Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Modality
Cirmtuzumab	Mantle Cell Lymphoma (MCL)					 <i>ROR1 mAb</i>
	Chronic Lymphocytic Leukemia (CLL)					
	Breast Cancer					
TK216	Ewing Sarcoma					 <i>ETS oncoprotein inhibitor</i>
	Acute Myeloid Leukemia (AML)					
	Prostate Cancer					
ROR1 CAR-T	Heme Cancers					 <i>ROR1 CAR-T cell therapy</i>
	Solid Tumors					

- **TK216**
  - **Ewing sarcoma** Phase 1 expansion cohort data for 12-16 patients **2H 2020**
  - IND-enabling data in additional **ETS-driven tumors** **2H 2020**
- **Cirmtuzumab**
  - **MCL** clinical data update for ongoing Phase 1/2 **4Q 2020**
  - **CLL** clinical data update for ongoing Phase 1/2 **4Q 2020**
  - **HER2-negative breast cancer** clinical data update for ongoing Phase 1b **1H 2021**
  - IND-supporting data in additional **ROR1 expressing tumors** **2H 2020**
- **ROR1 CAR-T** first-in-human dosing in China **2021**

## THREE NOVEL ONCOLOGY PRODUCT CANDIDATES IN DEVELOPMENT

### TK216: TARGETED ETS INHIBITOR

- Deep partial responses observed in two patients in Ewing sarcoma Phase 1
- Additional opportunities in other cancers with ETS alterations

### CIRMTUZUMAB: ROR1 INHIBITORY MONOCLONAL ANTIBODY

- Enrollment in Phase 2 study of cirmtuzumab plus ibrutinib in MCL expanded based on encouraging interim ASCO results
- Meeting with FDA requested to discuss potential accelerated approval pathway
- Ongoing clinical studies in CLL and breast cancer, and preclinical studies in additional cancer indications

### ROR1 CAR-T: PRECLINICAL DEVELOPMENT WITH CIRM AND SHANGHAI PHARMA

- Potential to improve on CAR-T efficacy and safety

### MULTIPLE DATA CATALYSTS EXPECTED IN NEXT 12 MONTHS

- Clinical data updates expected in Ewing sarcoma, MCL, CLL and breast cancer
- ROR1 CAR-T expected to reach clinic in 2021 in China

## EXPERIENCED MANAGEMENT AND BOARD OF DIRECTORS