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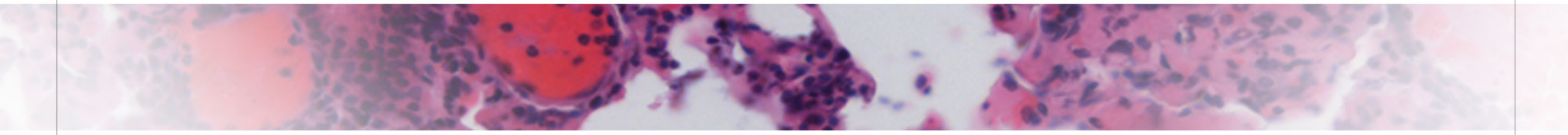

# Cirmtuzumab, an Anti-ROR1 Antibody, in Combination with Ibrutinib: Clinical Activity in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL) from a Phase 1/2 Study

**Hun Ju Lee**[1], Michael Y. Choi, MD[2], Tanya Siddiqi, MD[3*], William G. Wierda, MD, PhD[4], Jacqueline C. Barrientos, MD, MS[5], Nicole Lamanna, MD[6], Alec Goldenberg[7*], Iris Isufi, MD[8], Joseph Tuscano, MD[9*], Sukanthini Subbiah, MD[10], Jean L. Koff, MD[11], Lori A. Leslie, MD[12], Gina G Chung, MD[13*], Elizabeth K Weihe, MD[2*], Xen Ianopulos, MD, PhD[14*], James B. Breitmeyer, MD, PhD[14], Frank J Hsu, MD[14], Michael Wang, MD[1], Catriona Jamieson, MD, PhD[2] and Thomas J. Kipps, MD, PhD[2]

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# Conflicts of Interest Disclosures

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Disclosures:

H.J.L. reports consultancy for Bristol-Myers Squibb and Guidepoint Global; research funding from Bristol-Myers Squibb, Celgene, Oncternal Therapeutics, Seagen, Takeda; and speaker's bureau for Aptitude Health.

Ibrutinib provided by Pharmacyclics LLC, an AbbVie Company

# Background

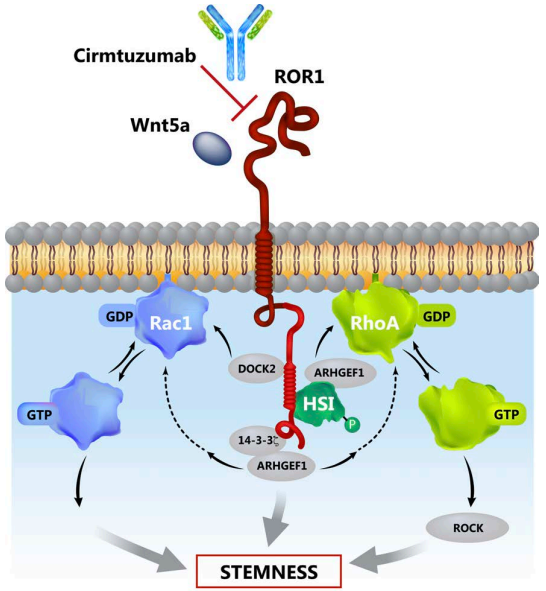
- ROR1 is an onco-embryonic tyrosine kinase receptor that is re-expressed at high levels on many hematologic and solid cancers but not on normal adult tissues. ROR1 binds Wnt5a, resulting in increased tumor growth, survival, metastasis, cancer cell stemness and epithelial mesenchymal transition.

- Cirmtuzumab is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1. In preclinical studies, cirmtuzumab has demonstrated anti-tumor activity as a single agent.

- In preclinical models, ROR1 remained active in MCL or CLL cells treated with BTK inhibitors, and cirmtuzumab had at least additive effects when combined with BTK inhibitors such as ibrutinib. (Yu et al., 2017; Yu et al., 2018)

- In this study, we examined the safety and efficacy of cirmtuzumab in combination with ibrutinib in MCL or CLL.

- *Hypothesis: The combination of cirmtuzumab and ibrutinib results in increased activity and deeper and more durable responses compared to ibrutinib, while maintaining the favorable safety profile of both agents.*

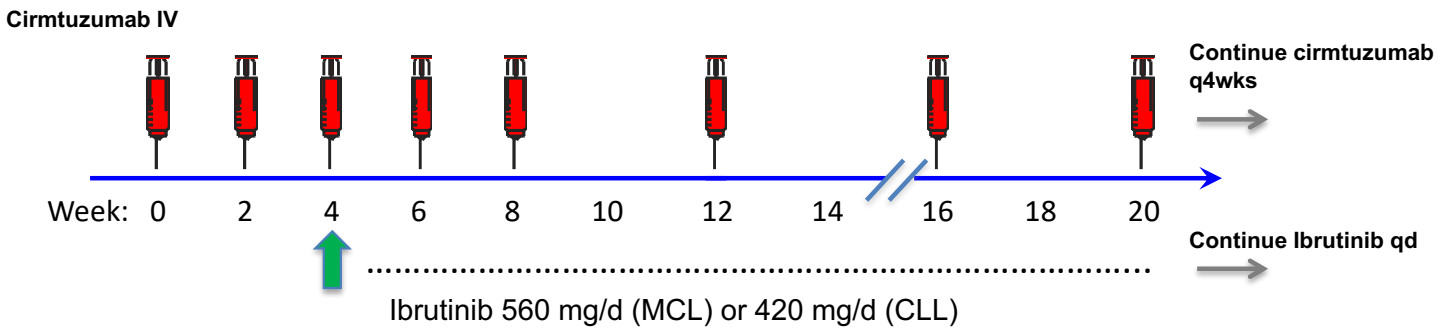


# Study Design

- **Eligibility:** Relapsed/refractory (R/R) MCL or R/R or treatment-naïve (TN) CLL/SLL, age ≥18 years, ECOG <3, radiographically measurable disease and requiring therapy. MCL patients were allowed to have prior ibrutinib therapy; all CLL/SLL patients were BTK-inhibitor naive.

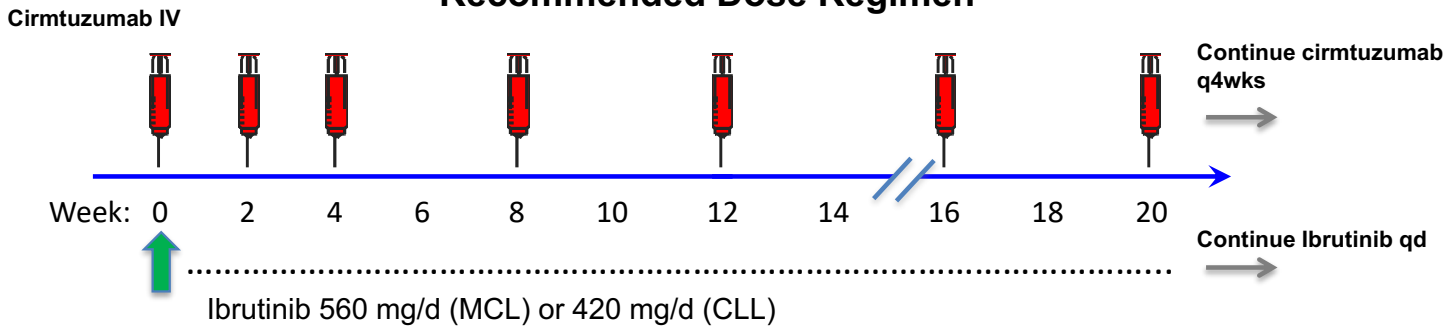
## Treatment Schedule:

**Part 1: Dose Escalation. Cirmtuzumab 2, 4, 8, 16 mg/kg, 300 mg, 600 mg per dose**

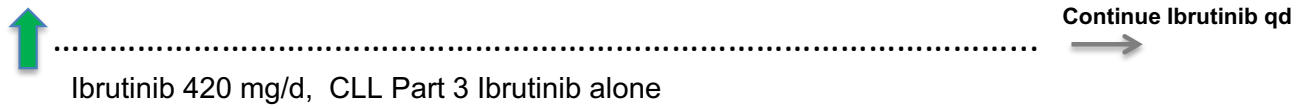



**Part 2: Expansion at RDR. Cirmtuzumab 600 mg per dose**

**Recommended Dose Regimen**




**Part 3: CLL randomized 2:1. Cirmtuzumab 600 mg + Ibrutinib vs Ibrutinib alone**




MCL Part 2 is actively enrolling. CLL Parts 1, 2, 3 have completed enrollment

(ClinicalTrials.gov: NCT03088878)

# Patient Characteristics

| Baseline Characteristics | | | MCL | CLL/SLL |
|---|---|---|---|---|
| | | | **Evaluable Patients: n=15** | **Evaluable Patients[1]: n= 56** |
| **Age (years)** | Median (Range) | | 64 (49 - 73) | 67 (37 - 86) |
| **Gender:** | Male / Female | n (%) | 13 (87%) / 2 (13%) | 37 (66%) / 19 (34%) |
| **MIPI Score[2]:** | Intermediate or High | n (%) | 14 (93%) | NA |
| **Ki-67%[3]:** | Median (range)<br>≥30% expression | (%)<br>n (%) | 35% (10 - 95%)<br>9 (64%) | NA |
| **Prior Systemic Regimens** | | | **Evaluable R/R pts: n= 15** | **Evaluable R/R Pts: n= 32** |
| **Number:** | Median (Range) | | 2 (1 - 5) | 1.5 (1 - 9) |
| **>1 Prior Regimens:** | | n (%) | 11 (73%) | 16 (50%) |
| **Ibrutinib:** | | n | 4 | 0 |
| **Stem Cell Transplant:** | | n | 5 Auto-SCT, 1 Allo-SCT | 1 Auto-SCT |
| **CAR-T:** | | n | 1 | 0 |

(1) CLL: 57% relapsed/refractory, 43% treatment naïve
(2) MIPI-b scores were determined in 14 pts with Ki-67 data, 1 pt had no Ki-67 and used standard MIPI
(3) Ki-67 data available on 14/15 pts

# Safety: All MCL and CLL Patients

## Non-Hematologic Adverse Events in >20% Patients

| N= 71 | Cirmtuzumab and Ibrutinib – Parts 1,2,3 | | |
|---|---|---|---|
| Preferred Term | All Grades % | Grade 1/2 % | Grade 3+ % |
| Subjects with ≥1 TEAE | 97.2 | 39.4 | 57.7 |
| Diarrhea | 40.8 | 38.0 | 2.8 |
| Contusion | 39.4 | 39.4 | 0 |
| Fatigue | 39.4 | 32.4 | 7.0 |
| Upper Resp. Infection | 31.0 | 31.0 | 0 |
| Hypertension | 25.4 | 15.5 | 9.9 |
| Cough | 25.4 | 25.4 | 0 |
| Dyspnea | 23.9 | 22.5 | 1.4 |
| Dizziness | 22.5 | 22.5 | 0 |
| Arthralgia | 22.5 | 21.1 | 1.4 |

## All Treatment-Emergent Hematologic Lab abnormalities

| N= 71 | Cirmtuzumab and Ibrutinib – Parts 1,2,3 | | |
|---|---|---|---|
| | All Grades % | Grade 1/2 % | Grade 3+ % |
| Neutrophils Decreased | 35.2 | 22.5 | 12.7 |
| Platelets Decreased | 43.7 | 42.3 | 1.4 |
| Hemoglobin Decreased | 19.7 | 16.9 | 2.8 |

Data as of Oct 30, 2020, Safety population includes all pts who received at least 1 dose of cirmtuzumab. Data includes all treatment-emergent adverse events regardless of causality; the highest grade/pt is reported using CTCAE v 4.03 per preferred term (MedDRA v 20.1). Lab abnormalities include calculated shifts in grade from baseline and the highest grade/pt.

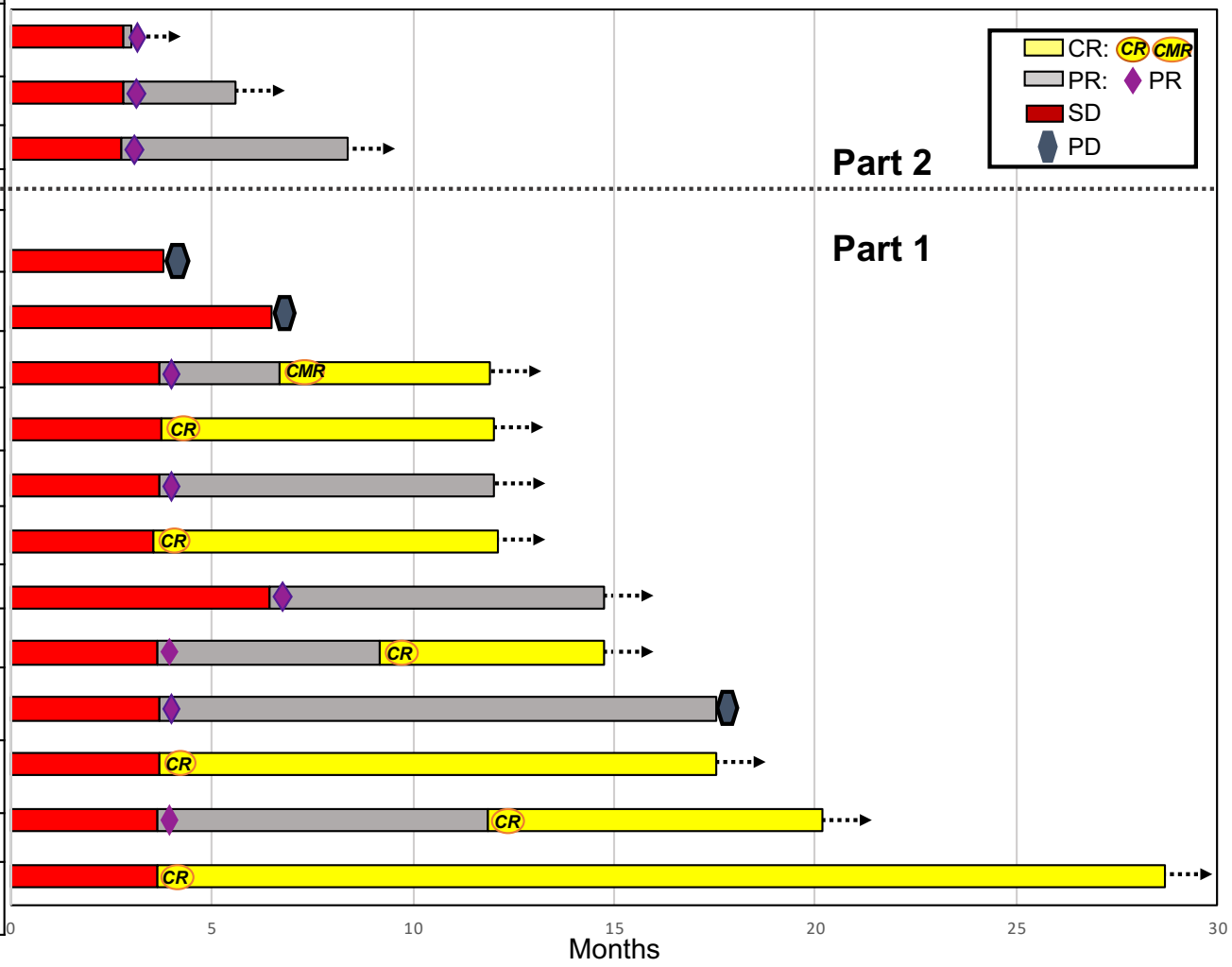
# Best Overall Response

| | Evaluable* Pts N= | Best ORR** (CR & PR) | Clinical Benefit (CR, PR, SD) | CR | PR | SD | PD |
|---|---|---|---|---|---|---|---|
| MCL Part 1 | 12 | 10/12 (83.3%) | 12 (100%) | 7 (58.3%) | 3 (25%) | 2 (16.7%) | 0 |
| Part 2 | 3 | 3/3 (100%) | 3 (100%) | 0 | 3 (100%) | 0 | 0 |
| CLL Parts 1&2 | 34 | 31 (91.2%) | 34 (100%) | 1 (3%) | 30 (88%) 26 PR; 4 PR-L | 3 (8.8%) | 0 |
| Part 3 | 15 Cirm + Ibrutinib | 14 (93.3%) | 15 (100%) | 0 | 14 (93.3%) 12 PR; 2 PR-L | 1 (6.7%) | 0 |
| | 7 ibrutinib | 7 (100%) | 7 (100%) | 0 | 7 PR (100%) | 0 | 0 |

*Evaluable patients for efficacy are those who have completed treatment and have had the planned 3 month post cirmtuzumab + ibrutinib combination therapy imaging studies or had documented or clinical PD following 28 days of therapy. **Includes both confirmed and unconfirmed best responses. For CLL: iwCLL criteria were used. For MCL, Cheson 2007/2014 was used. For MCL, data include one complete metabolic remission (CMR); blinded review of bone marrow biopsy was indeterminant for tumor involvement. Note: One Part 2 MCL patient (PR) met criteria for a CR with a morphologically normal marrow but with minimal marrow disease by flow. Data as of Oct 30, 2020.

# MCL Patient Characteristics & Swimmer Plot

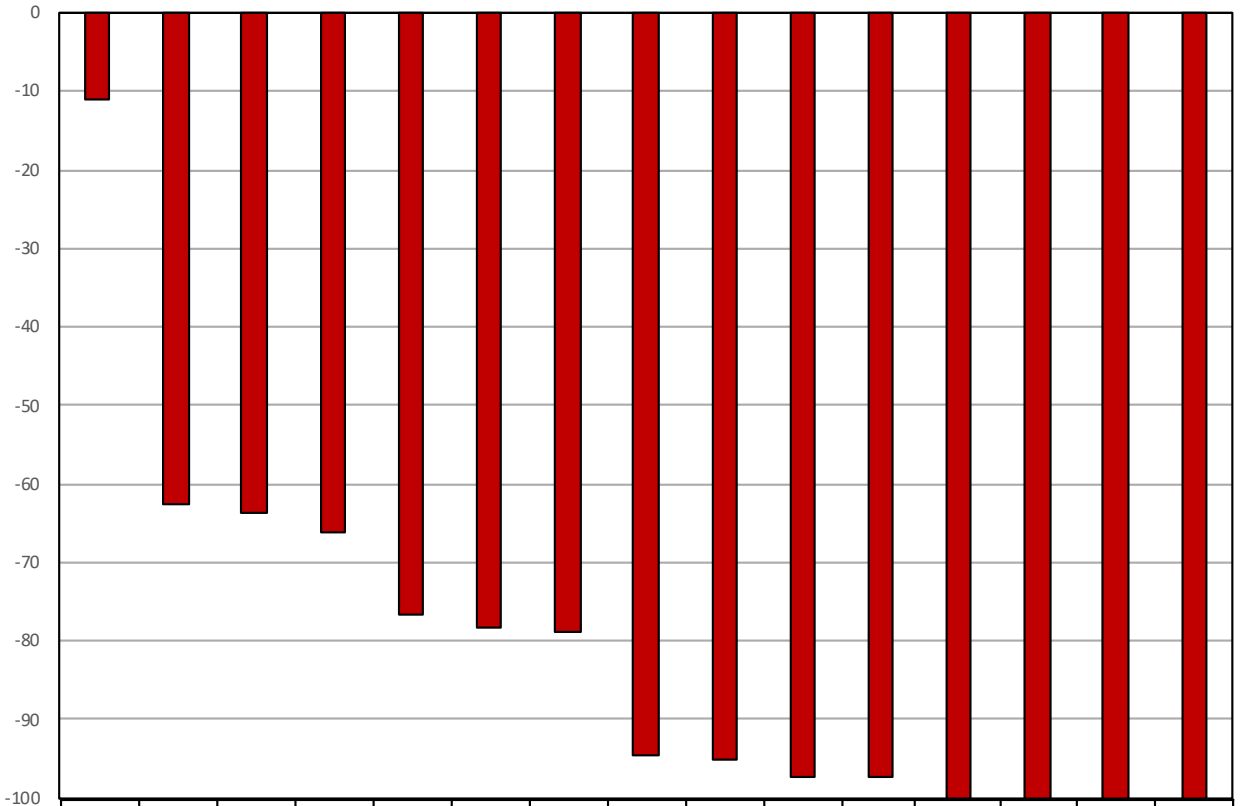
| Resp to Cirm | # Prior Tx | Prior Treatment Regimens | MCL Variant / Ki67 | MIPIb Score at SCR | Bulky >5cm LD | Cirm Dose | Change Tumor Size |
|---|---|---|---|---|---|---|---|
| PR | 2 | R-CHOP/ Lenalidomide; Rituximab/High dose Cytarabine/Lenalidomide | KI67 20% | Int. 6.2 | Yes | 600 mg | -97% |
| PR | 1 | R-HyperCVAD and R-Methotrexate/Cytarabine | Blastoid KI67 95% | High 8.1 | Yes | 600 mg | -64% |
| PR | 1 | Rituximab | KI67 50% | High 6.6 | | 600 mg | -66% |
| | | | | | | | |
| SD* | 2 | RCHOP/ITMTX, R-hyperCVAD | Pleo. Ki67 90% | High 7.1 | (4.8cm) | 8 mg/kg | -79% |
| SD | 2 | RCHOP, R-DHAP | KI67 10% | High 6.7 | | 16 mg/kg | -11% |
| CMR | 2 | RCHOP; R-BEAM/Auto-SCT | KI67 10% | High 6.8 | | 2 mg/kg | -100% |
| CR | 2 | R/Ibrutinib (10mths); R-HyperCVAD | Pleo. KI67 70% | High 7 | Yes | 8 mg/kg | -97% |
| PR | 2 | R/Ibrutinib (10mths); R-HyperCVAD | KI67 40% | High 6.6 | | 4 mg/kg | -54% |
| CR | 2 | R/Ibrutinib (7mths); R-HyperCVAD | Nodular KI67 30% | Int. 5.8 | | 16 mg/kg | -100% |
| PR | 1 | R/Ibrutinib | NA | Int. 5.7 No KI-67 | Yes | 8 mg/kg | -91% |
| CR | 4 | R/hyperCVAD, RCHOP, RICE, BEAM/Auto-SCT | Ki67 ~30% | Int. 5.8 | | 16 mg/kg | -95% |
| PR | 3 | Benda/R, R/AraC/Cisplt/Dex, BEAM/ Auto-SCT | KI67 60% | High 7.8 | | 4 mg/kg | -78% |
| CR | 4 | RCHOP/HDMTX/R, R/velcade/ITMTX, Auto-SCT, CAR-T | Nodular Ki67 ~15% | Low 5.5 | | 4 mg/kg | -100% |
| CR | 1 | RCHOP (Plus RT to orbits) | Blastoid Ki67 75% | High 7.6 | | 2 mg/kg | -77% |
| CR | 5 | RCHOP, BEAMR/ Auto-SCT, Benda/R/Allo-SCT, ICE-R, R | Diffuse KI67 20% | High 7 | Yes | 2 mg/kg | -100% |




Note: Part 1 patients started Ibrutinib on Day 28, and Part 2 patients, on Day 0. Bars represent activity of patients on treatment to last response assessment; arrows indicate pt continues on treatment. Time to first response: 87% (13/15) CR/PR and 57% (4/7) CR occurred by the first evaluation after starting combined cirmtuzumab/ibrutinib

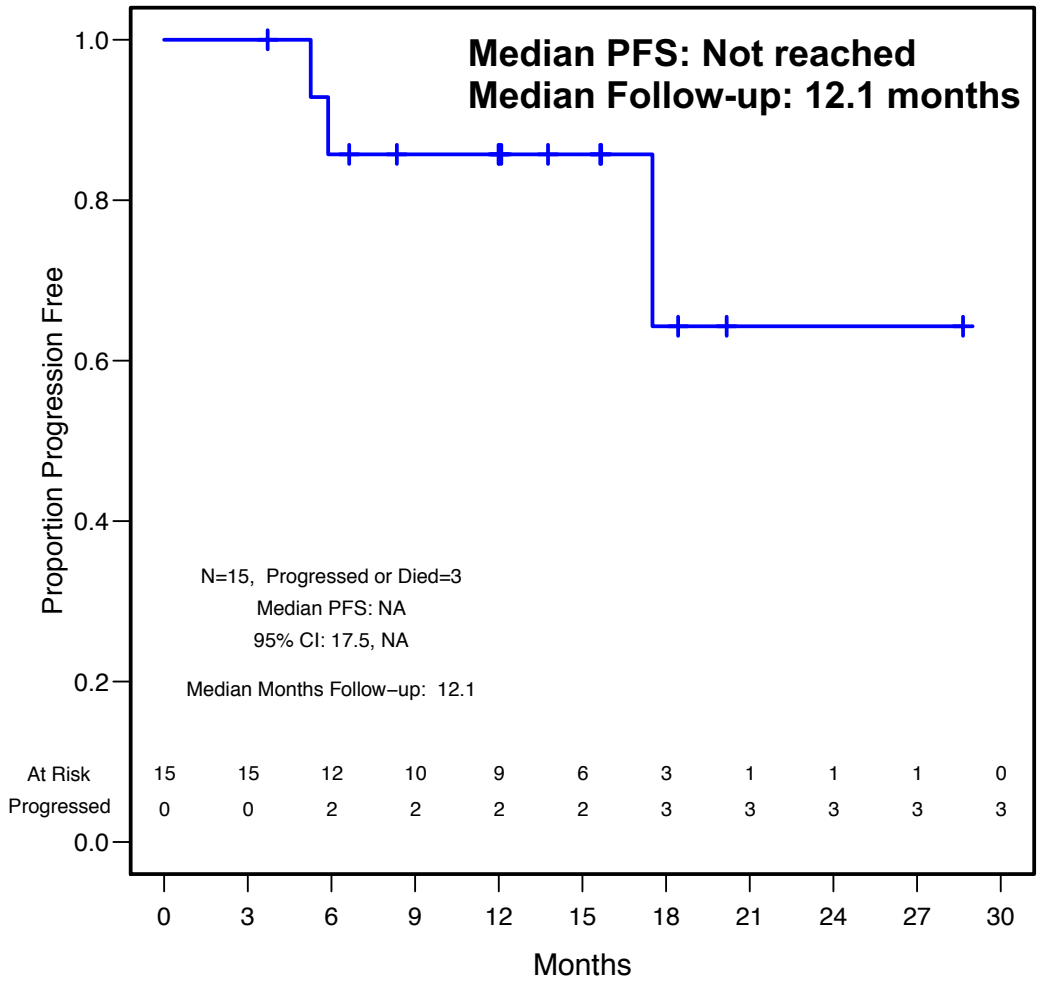
# MCL: Tumor Reduction & Clinical Outcome

## Best Tumor Reduction (SPD cm²)




| Baseline SPD (cm²) | 3.1 | 6.4 | 35 | 12.5 | 7.3 | 11.7 | 21.8 | 38.5 | 10.3 | 26.2 | 31 | 5.9 | 8.4 | 62 | 4.6 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ORR | SD | PR | PR | PR | CR | PR | SD | PR | CR | CR | PR | CMR | CR | CR | CR |

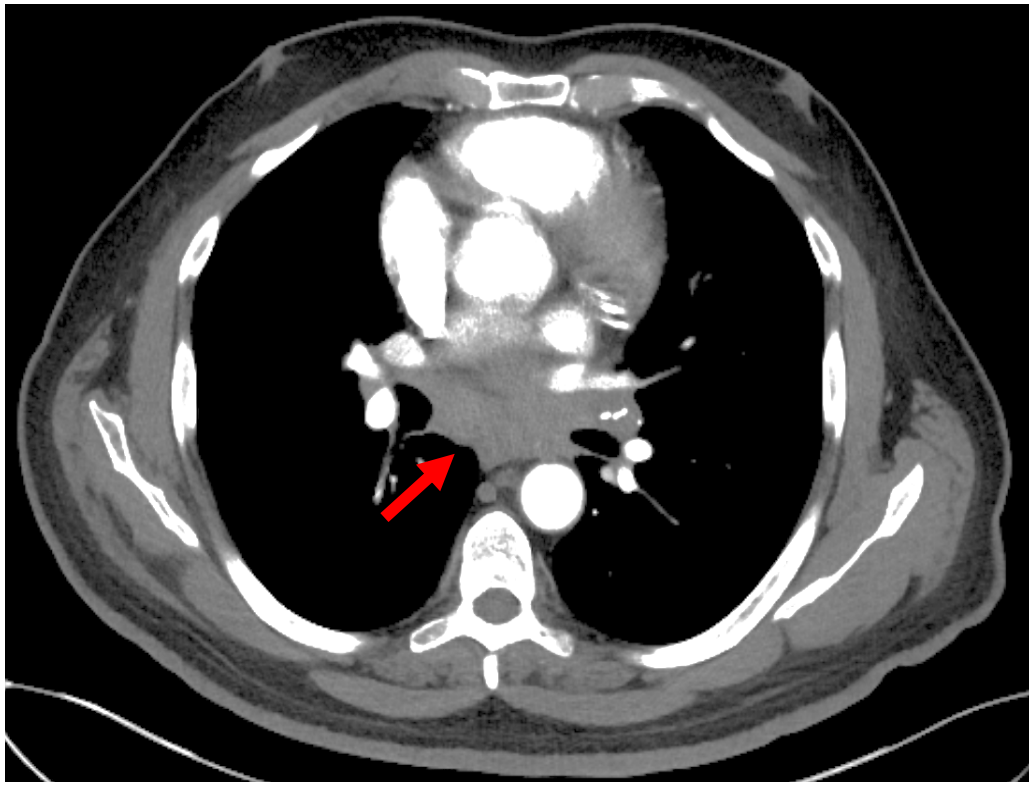
## Progression-Free Survival



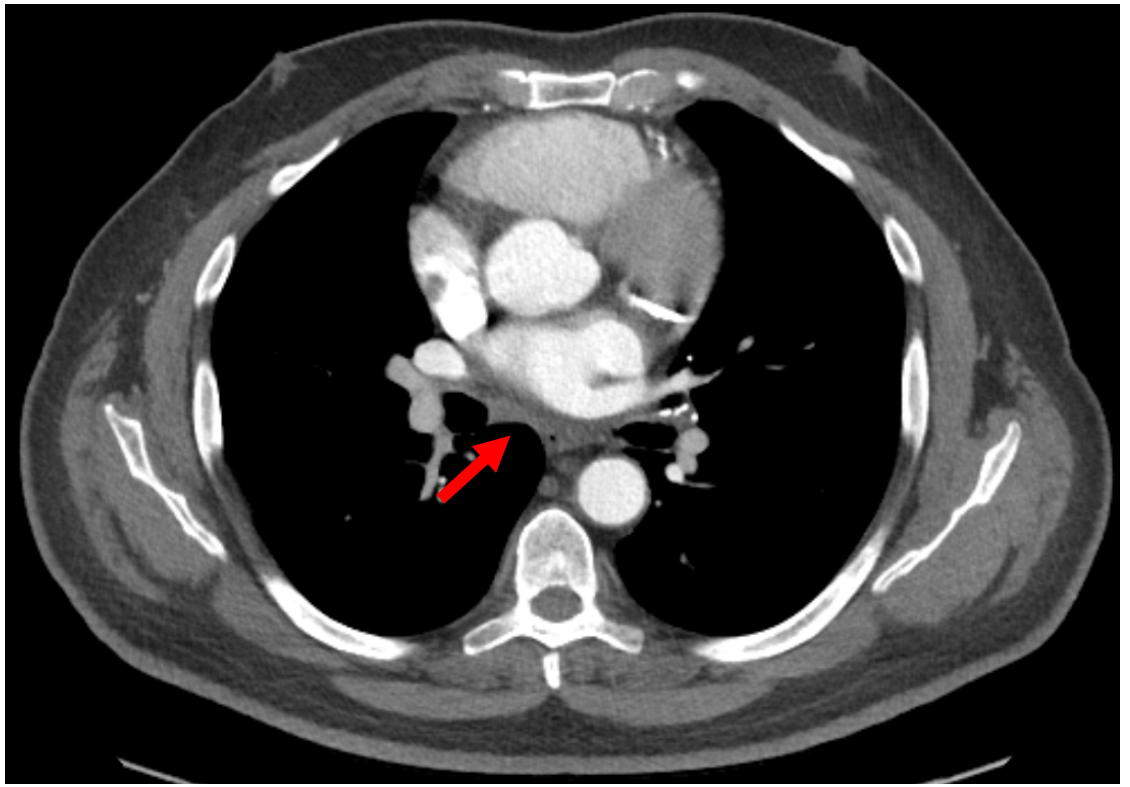
# Case Study, MCL

- 65yo Male initially diagnosed in 2016 with MCL stage IV including involvement of bilateral orbits
- Initial treatment: radiation therapy and R-CHOP
- Recurred and enrolled onto Part 1 Cirmtuzumab/Ibrutinib study in 2019 at the 2mg/kg dose level
- High risk factors:  Blastoid subtype; Ki-67: 75%; High MIPIb score 7.6
- After <4 mos treatment, achieved a PR and after 12 mos, a CR.
- Continues on therapy now >20 months and tolerating treatment well

**Pretreatment**



**<4 months Post Cirmtuzumab/Ibrutinib**



# Summary

## MCL:

- The combination of cirmtuzumab plus ibrutinib is a well-tolerated and active regimen.
  The time to response, depth, and durability of responses are compelling for further development.
- High response rate*: ORR 87% (13/15), clinical benefit 100% (7 CR/CMR, 6 PR, 2 SD).
  Complete responses durable for 5 - 25+ months, with no progressions reported after CR.
- Encouraging PFS: median not reached at median follow-up now >12 months.
- Encouraging efficacy (objective responses) in high-risk sub-populations:
  - Prior SCT or CAR-T (5/15): 4 CR, 1 PR
  - Ki-67 levels ≥30% (9/14): 4 CR, 4 PR
  - Intermediate/high MIPI (14/15): 6 CR, 6 PR
  - Prior ibrutinib (4/15): 100% responded, 2 CR, 2 PR

## CLL/SLL:

- The combination of cirmtuzumab plus ibrutinib is a well-tolerated and active regimen in CLL.
  Parts 1, 2, & 3: ORR 91.8% (45/49) and Clinical Benefit 100% (49/49).
- One patient achieved a CR that was durable for >17 months off all therapy.
- In randomized Part 3, no progressive disease observed on cirmtuzumab/ibrutinib or ibrutinib arms.

*Historical data with single agent ibrutinib in a MCL population with a similar distribution of prior lines of therapy reported an overall ORR 65.7% & CR rate 20% (Rule Br J Haem 2017).

# Cirmtuzumab, an Anti-ROR1 Antibody, in Combination with Ibrutinib: Clinical Activity in Mantle Cell Lymphoma (MCL) or Chronic Lymphocytic Leukemia (CLL) from a Phase 1/2 Study

Abstract #2942

**Hun Ju Lee**[1], Michael Y. Choi, MD[2], Tanya Siddiqi, MD[3*], William G. Wierda, MD, PhD[4], Jacqueline C. Barrientos, MD, MS[5], Nicole Lamanna, MD[6], Alec Goldenberg[7*], Iris Isufi, MD[8], Joseph Tuscano, MD[9*], Sukanthini Subbiah, MD[10], Jean L. Koff, MD[11], Lori A. Leslie, MD[12], Gina G Chung, MD[13*], Elizabeth K Weihe, MD[2*], Xen Ianopulos, MD, PhD[14*], James B. Breitmeyer, MD, PhD[14], Frank J Hsu, MD[14], Michael Wang, MD[1], Catriona Jamieson, MD, PhD[2] and Thomas J. Kipps, MD, PhD[2]

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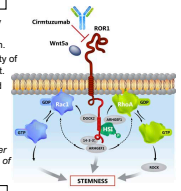
## I. RATIONALE / BACKGROUND

- ROR1 is an onco-embryonic tyrosine kinase receptor that is re-expressed at high levels on many hematologic and solid cancers but not on normal adult tissues. ROR1 binds Wnt5a, resulting in increased tumor growth and survival, cancer cell stemness and epithelial mesenchymal transition.
- Cirmtuzumab is a humanized monoclonal antibody designed to inhibit the tumor promoting activity of ROR1. In preclinical studies, cirmtuzumab has demonstrated anti-tumor activity as a single agent.
- In preclinical models, ROR1 remained active in MCL or CLL cells treated with BTK inhibitors, and cirmtuzumab had at least additive effects when combined with BTK inhibitors such as ibrutinib (Yu et al., 2017; Yu et al., 2018).
- In this study, we examined the safety and efficacy of cirmtuzumab in combination with ibrutinib in MCL or CLL.
- *Hypothesis: The combination of cirmtuzumab and ibrutinib results in increased activity and deeper and more durable responses compared to ibrutinib, while maintaining the favorable safety profile of both agents.*




## II. STUDY DESIGN

Patients (pts) with relapsed/refractory (R/R) MCL or R/R or treatment-naïve (TN) CLL/SLL, age ≥18 years, ECOG <3, radiographically measurable disease and requiring therapy were eligible to participate. MCL pts were allowed to have prior ibrutinib therapy; all CLL/SLL pts were BTK-inhibitor naïve.
(For full entry criteria see ClinicalTrials.gov: NCT03088878).

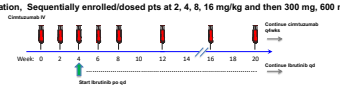
The study was designed in 3 parts:

- **Part 1, Ph1 Dose Escalation of Cirmtuzumab:** Sequential patients (pts) were enrolled at increasing cirmtuzumab dose levels and standard indication specific doses of ibrutinib were initiated on Day 28.
- **Part 2, Pt Expansion:** Following a review of safety and PK/PD data, a recommended dose regimen was chosen as cirmtuzumab 600mg IV per dose and ibrutinib at standard doses of 560mg for MCL or 420mg for CLL/SLL po qd. For MCL, Part 2 is open and actively enrolling pts.
- **Part 3, Ph2 Randomized (2:1) Cirmtuzumab/Ibrutinib vs. Ibrutinib alone in CLL/SLL**: Study was designed to determine efficacy of the recommended combination dose regimen in a comparative study.

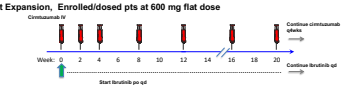
(MCL Part 2 is actively enrolling. CLL Parts 1, 2, 3 have completed enrollment.)

### Treatment Schema for Parts 1, 2, and 3

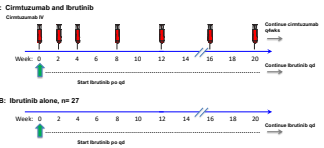
**Part 1: Dose Escalation, Sequentially enrolled/dosed pts at 2, 4, 8, 16 mg/kg and then 300 mg, 600 mg fixed doses**




**Part 2: Patient Expansion, Enrolled/dosed pts at 600 mg flat dose**




**Part 3: Randomized (2:1) Cirmtuzumab/Ibrutinib vs. Ibrutinib alone in CLL/SLL at recommended dose regimen**




### Patient Characteristics

| Baseline Characteristics | | | MCL | CLL/SLL |
|---|---|---|---|---|
| | | | Evaluable Patients: n=15 | Evaluable Patients[1]: n= 56 |
| **Age (years)** | Median (Range) | | 64 (49 - 73) | 67 (37 - 86) |
| **Gender:** | Male / Female | n (%) | 13 (87%) / 2 (13%) | 37 (66%) / 19 (34%) |
| **MIPI Score[2]:** | Intermediate or High | n (%) | 14 (93%) | NA |
| **Ki-67%[3]:** | Median (range) | (%) | 35% (10 - 95%) | NA |
| | ≥30% expression | n (%) | 9 (64%) | |
| **Prior Systemic Regimens** | | | **Evaluable R/R pts: n= 15** | **Evaluable R/R Pts: n= 32** |
| **Number:** | Median (Range) | | 2 (1 - 5) | 1.5 (1 - 9) |
| **>1 Prior Regimens:** | | n (%) | 11 (73%) | 16 (50%) |
| **Ibrutinib:** | | n | 4 | 0 |
| **Stem Cell Transplant:** | | n | 5 Auto-SCT, 1 Allo-SCT | 1 Auto-SCT |
| **CAR-T:** | | n | 1 | 0 |

(1) CLL: 57% relapsed/refractory, 43% treatment naïve (2) MIPI-b scores were determined in 14 pts with Ki-67 data, 1 pt had no Ki-67 and used standard MIPI (3) Ki-67 data available on 14/15 pts

## III. CLINICAL RESULTS

### Safety of Cirmtuzumab and Combination With Ibrutinib

- Cirmtuzumab was well tolerated in both MCL and CLL patients. During dose escalation, no DLTs or grade 3 events occurred that were possibly related to cirmtuzumab alone.
- Most common events reported for both MCL and CLL regardless of attribution to cirmtuzumab or the combination of cirmtuzumab/ibrutinib included fatigue, diarrhea, contusion, URI, cough, dyspnea
- Non-hematologic grade ≥ 3 events occurring in >3 pts regardless of attribution included diarrhea, fatigue, hypertension, and Afib (includes patients with pre-existing conditions)
- Hematologic lab abnormalities of decreased neutrophils, platelets and Hgb were examined for worsening CTCAE ver 4.03 grade compared to pre-treatment values and the highest grades are indicated in the table below.
- Overall, the addition of cirmtuzumab to ibrutinib was without any new grade 3 or higher adverse events and was consistent with the safety profile reported for ibrutinib alone

### Safety: All MCL and CLL Patients Non-Hematologic Adverse Events in >20% Patients

| N= 71 | Cirmtuzumab and Ibrutinib – Parts 1,2,3 | | |
|---|---|---|---|
| **Preferred Term** | **All Grades %** | **Grade 1/2 %** | **Grade 3+ %** |
| Subjects with ≥1 TEAE | 97.2 | 39.4 | 57.7 |
| Diarrhea | 40.8 | 38.0 | 2.8 |
| Contusion | 39.4 | 39.4 | 0 |
| Fatigue | 39.4 | 32.4 | 7.0 |
| Upper Resp. Infection | 31.0 | 31.0 | 0 |
| Hypertension | 25.4 | 15.5 | 9.9 |
| Cough | 25.4 | 25.4 | 0 |
| Dyspnea | 23.9 | 22.5 | 1.4 |
| Dizziness | 22.5 | 22.5 | 0 |
| Arthralgia | 22.5 | 21.1 | 1.4 |

### All Treatment-Emergent Hematologic Lab abnormalities

| N= 71 | Cirmtuzumab and Ibrutinib – Parts 1,2,3 | | |
|---|---|---|---|
| | **All Grades %** | **Grade 1/2 %** | **Grade 3+ %** |
| Neutrophils Decreased | 35.2 | 22.5 | 12.7 |
| Platelets Decreased | 43.7 | 42.3 | 1.4 |
| Hemoglobin Decreased | 19.7 | 16.9 | 2.8 |

Data as of Oct 30, 2020. Safety population includes all pts who received at least 1 dose of cirmtuzumab. Data includes all treatment-emergent adverse events regardless of causality; the highest grade/pt is reported using CTCAE v 4.03 per preferred term (MedDRA v 20.1). Lab abnormalities include calculated shifts in grade from baseline and the highest grade/pt.

### Disposition After Enrollment

| Indication | Dosed | Evaluable For Efficacy | 24 Weeks Combo Tx | Completed ≥ 48 weeks Tx | Extended Tx |
|---|---|---|---|---|---|
| CLL Part 1 | 18 | 18 | 18 | 15 | 12 |
| CLL Part 2 | 16 | 16 | 16 | 15 | 14 |
| CLL Part 3 Cirmuzumab + Ibrutinib | 18 | 15 | 12 | 3 | 1 |
| Ibrutinib alone | 10 | 7 | 7 | 2 | 0 |
| MCL Part 1 | 12 | 12 | 11 | 10 | 10 |
| MCL Part 2 | 7 | 3 | 2 | 0 | 0 |

- Most patients have stayed on study and completed the planned initial 1 year of therapy. Pts then had the option of Extended Treatment and could receive another year of therapy (earlier pts may have received more).
- Evaluable patients for efficacy are those who have completed treatment and have had the planned 3 month post cirmtuzumab + ibrutinib combination therapy imaging studies or had documented or clinical PD following 28 days of therapy.
- Reasons for discontinuations during planned therapy:
  - MCL Part 1: 3 discontinuations due to progressive disease – Days 140, 196, and 560. Part 2: 2 pts withdrew early and before receiving a full planned first cycle due to 1) an exacerbation of a pre-existing acoustic neuroma and 2) small bowel obstruction
  - CLL Part 1: 3 came off due to AEs (none related to cirmtuzumab); 2 sought alternative therapy; 1 required therapy for known history of prostate cancer. CLL Part 2: 1 discontinued due to an AE thought possibly related to ibrutinib
  - CLL Part 3: 3 discontinued due to AEs – 2 unrelated to study agents; 1 possibly related to ibrutinib. 6 pts withdrew early and before receiving a full planned first cycle due to AEs including: exacerbation of pre-existing condition – Afib, anemia, weakness. Infection: pneumonia bacterial (2)/ COVID (1) and urticaria thought to be related to ibrutinib
  - COVID-19: 1 Part 3 CLL patient on ibrutinib alone developed COVID-19 infection and withdrew. 3 pts from Parts 1&2 and one from Part 3 CLL have discontinued due to fear of contracting COVID at the hospital. Sponsor has been working with the sites to minimize disruption of patient visits and treatments.

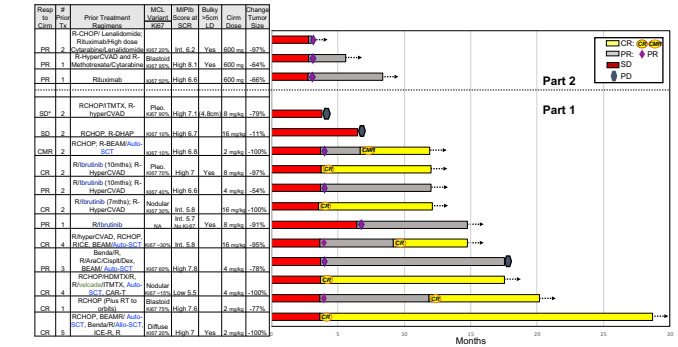
### Best Overall Response

| | Evaluable Pts N= | Best ORR* (CR & PR) | Clinical Benefit (CR, PR, SD) | CR | PR | SD | PD |
|---|---|---|---|---|---|---|---|
| **MCL Part 1** | 12 | 10/12 (83.3%) | 12 (100%) | 7 (58.3%) | 3 (25%) | 2 (16.7%) | 0 |
| **Part 2** | 3 | 3/3 (100%) | 3 (100%) | 0 | 3** (100%) | 0 | 0 |
| **CLL Parts 1&2** | 34 | 31 (91.2%) | 34 (100%) | 1 (3%) | 30 (88%) 26 PR; 4 PR-L | 3 (8.8%) | 0 |
| **Part 3** | 15 Cirm + Ibrutinib | 14 (93.3%) | 15 (100%) | 0 | 14 (93.3%) 12 PR; 2 PR-L | 1 (6.7%) | 0 |
| | 7 ibrutinib | 7 (100%) | 7 (100%) | 0 | 7 PR (100%) | 0 | 0 |

*Includes both confirmed and unconfirmed best responses. For CLL: iwCLL criteria were used. For MCL, Cheson 2007/2014 was used. For MCL, data include 1 complete metabolic remission (CMR); blinded review of bone marrow biopsy was indeterminant for tumor involvement. Note: One Part 2 MCL patient (PR) met criteria for a CR with a morphologically normal marrow but with minimal marrow disease by flow. Data as of Oct 30, 2020.

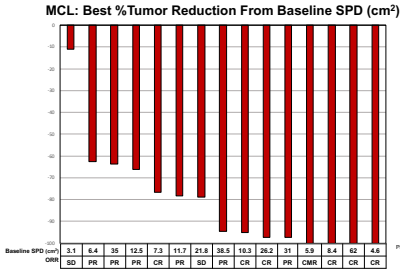
### MCL PARTS 1 & 2

### Clinical Characteristics and Response Over Time

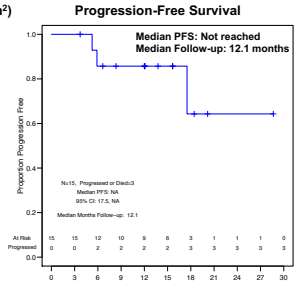



Note: Part 1 patients started Ibrutinib on Day 28, and Part 2 patients, on Day 0. Bars represent activity of patients on treatment to last response assessment; arrows indicate pt continues on treatment. Time to first response: 87% (13/15) CR/PR and 57% (4/7) CR occurred by the first evaluation after starting combined cirmtuzumab/ibrutinib

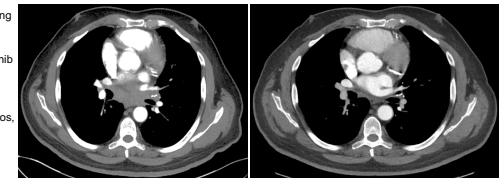
### MCL: Best %Tumor Reduction From Baseline SPD (cm²)




### Progression-Free Survival

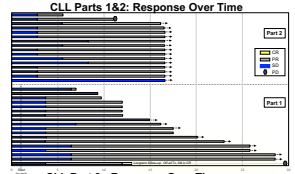


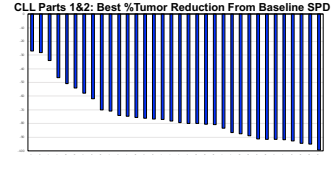

### Rapid Response in an MCL Patient with Bulky Disease

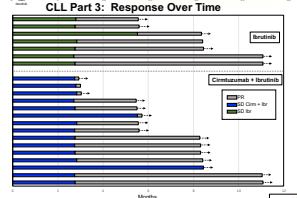


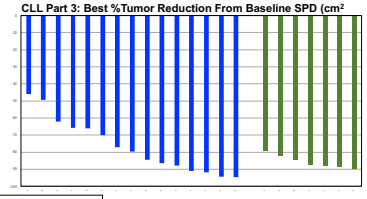

- 65yo Male initially diagnosed in 2016 with MCL including involvement of bilateral orbits
- Initial treatment: radiation therapy and R-CHOP
- Recurred and enrolled onto Part 1 Cirmtuzumab/Ibrutinib study in 2019 at the 2mg/kg dose level
- High risk factors: Blastoid subtype; Ki-67: 75%; High MIPIb score 7.6
- After <4 mos treatment, achieved a PR and after 12 mos, a CR.
- Continues on therapy now >20 months and tolerating treatment well

### CLL PARTS 1, 2 & 3

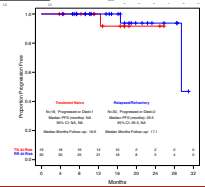



**CLL Parts 1&2: Progression Free Survival**




**Treatment Naive: n= 19**
**Median PFS: Not reached**
**Median Follow-up 16.6 mos**

**Relapsed/ Refractory: n=30**
**Median PFS: 29.5 mos**
**Median Follow-up 17.1 mos**

## IV. SUMMARY

**MCL:**

- The combination of cirmtuzumab plus ibrutinib is a well-tolerated and active regimen. The time to response, depth, and durability of responses are compelling for further development.
- High response rate*. ORR 87% (13/15), clinical benefit 100% (7 CR/CMR, 6 PR, 2 SD). Complete responses have been durable for 5 - 25+ months, with no progressions reported after CR.
- Encouraging PFS, median not reached at median follow-up now >12 months.
- Encouraging efficacy (objective responses) in high-risk sub-populations:
  - Prior SCT or CAR-T (5/15): 4 CR, 1 PR
  - Ki-67 levels ≥30% (9/14): 4 CR, 4 PR
  - Intermediate/high MIPI (14/15): 6 CR, 6 PR
  - Prior ibrutinib (4/15): 100% responded, 2 CR, 2 PR

**CLL/SLL:**

- Cirmtuzumab plus ibrutinib is a well-tolerated and active regimen in CLL. Parts 1, 2, & 3: ORR 91.8% (45/49) and Clinical Benefit 100% (49/49).
- One patient achieved a CR that was durable for >17 months off all therapy.
- In randomized Part 3, no progressive disease observed on cirmtuzumab/ibrutinib or ibrutinib arms.

*Historical data with single agent ibrutinib in a MCL population with a similar distribution of prior lines of therapy reported an overall ORR 65.7% & CR rate 20% (Rule Br J Haem 2017).