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## Interim Results of Loncastuximab Tesirine Combined With Ibrutinib in Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)

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**Poster slides, 62nd ASH Annual Meeting and  
Exposition Virtual Meeting, December 5–8, 2020**

**Session 626, Sunday, December 6, 2020,  
7:00 am – 3:30 (Pacific Time)**

# Introduction

- This two-part, open-label, single-arm Phase 1/2 study (NCT03684694) is evaluating Lonca and ibrutinib in patients with R/R DLBCL and patients with R/R MCL
- Patients with R/R DLBCL and patients with R/R MCL have a poor prognosis and the development of an effective and less toxic salvage treatment remains an unmet need<sup>1,2</sup>

**Loncastuximab tesirine (Lonca)** is an ADC comprising a humanized monoclonal anti-CD19 antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, through a protease cleavable valine-alanine linker

**Ibrutinib** is a small-molecule inhibitor of BTK

- Approved for use in MCL, CLL/SLL, WM, MZL, and cGVHD<sup>3</sup>

- We present updated **Phase 1** data for patients receiving the MTD of Lonca 60 µg/kg Q3W and ibrutinib 560 mg/day
  - Initial Phase 1 results identified the MTD<sup>4</sup>

This trial combines an investigational treatment with a licensed drug (ibrutinib) used outside of its label.

1. Levin A, Shah, NN. *Am J Hematol* 2019;94: S18–S23; 2. Maddocks K, *Blood* 2018;132:1647–56; 3. Janssen Biotech, Ibrutinib PI, April 2020; 4. Depaus J, *et al.* EHA 2020. Abstract 1284.

**ADC**, antibody-drug conjugate; **BTK**, Bruton's tyrosine kinase; **cGVHD**, chronic graft-versus-host disease; **CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **Lonca**, loncastuximab tesirine; **MCL**, mantle cell lymphoma;

**MTD**, maximum tolerated dose; **MZL**, marginal zone lymphoma; **PBD**, pyrrolobenzodiazepine; **Q3W**, every 3 weeks; **R/R**, relapsed/refractory; **SLL**, small lymphocytic lymphoma; **WM**, Waldenström's macroglobulinemia.



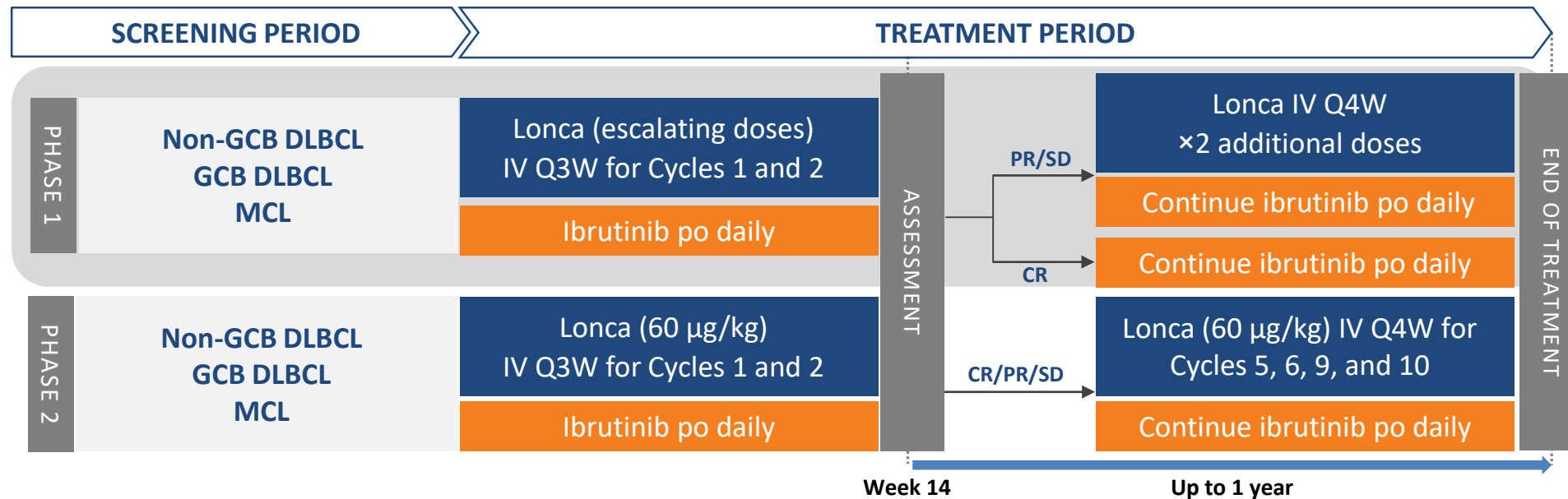
# Objectives and Study Design

## Primary objective for Phase 1:

- Characterize safety/tolerability and identify the RP2D and schedule for use in Phase 2

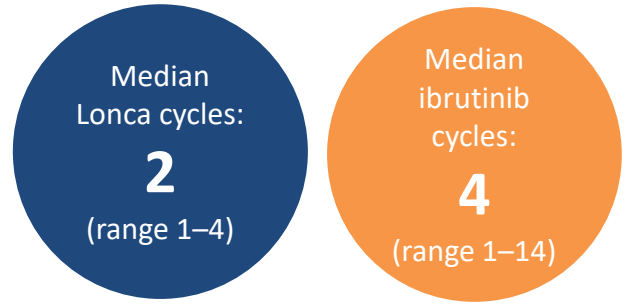
## Secondary objectives for Phase 1:

- Evaluate antitumor effect
- Characterize pharmacokinetics
- Evaluate immunogenicity



CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; IV, intravenous; Lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; po, taken orally; PR, partial response; RP2D, recommended Phase 2 dose; SD, stable disease; Q3W, every 3 weeks; Q4W, every 4 weeks.

# Baseline Characteristics



As of August 20, 2020, **37 patients** had received Lonca 60 µg/kg plus ibrutinib 560 mg

| Characteristic                     | DLBCL (n=30) | MCL (n=7)  | All patients (n=37) |
|------------------------------------|--------------|------------|---------------------|
| Sex, n (%)                         |              |            |                     |
| Male                               | 21 (70.0)    | 6 (85.7)   | 27 (73.0)           |
| Age, years, median (range)         | 72 (40–91)   | 69 (54–89) | 72 (40–91)          |
| ECOG status, n (%)                 |              |            |                     |
| 0                                  | 16 (53.3)    | 4 (57.1)   | 20 (54.1)           |
| 1                                  | 11 (36.7)    | 3 (42.9)   | 14 (37.8)           |
| 2                                  | 3 (10.0)     | 0          | 3 (8.1)             |
| NHL subtype, n (%)                 |              |            |                     |
| Non-GCB DLBCL                      | 24 (80.0)    | -          | 24 (64.9)           |
| GCB DLBCL                          | 6 (20.0)     | -          | 6 (16.2)            |
| MCL                                | -            | 7 (100)    | 7 (18.9)            |
| Disease stage <sup>a</sup> , n (%) |              |            |                     |
| Stage II                           | 3 (10.0)     | 0          | 3 (8.1)             |
| Stage III                          | 5 (16.7)     | 1 (14.3)   | 6 (16.2)            |
| Stage IV                           | 22 (73.3)    | 6 (85.7)   | 28 (75.7)           |

| Characteristic   | DLBCL (n=30) | MCL (n=7) | All patients (n=37) |
|--|--------------|-----------|---------------------|
| Number of prior systemic therapies <sup>b</sup>        |              |           |                     |
| Median (range)   | 2 (1–6)      | 2 (1–4)   | 2 (1–6)             |
| First-line prior therapy response, n (%) <sup>c</sup>  |              |           |                     |
| Relapsed   | 20 (66.7)    | 4 (57.1)  | 24 (64.9)           |
| Refractory   | 7 (23.3)     | 1 (14.3)  | 8 (21.6)            |
| Other  | 3 (10.0)     | 2 (28.6)  | 5 (13.5)            |
| Last-line prior therapy response, n (%) <sup>c,d</sup> |              |           |                     |
| Relapsed   | 13 (43.3)    | 4 (57.1)  | 17 (45.9)           |
| Refractory   | 17 (56.7)    | 1 (14.3)  | 18 (48.6)           |
| Other  | 0            | 2 (28.6)  | 2 (5.4)             |
| Prior SCT, n (%)                                       |              |           |                     |
| Autologous   | 2 (6.7)      | 1 (14.3)  | 3 (8.1)             |
| Allogeneic   | 0            | 1 (14.3)  | 1 (2.7)             |

Data cut: August 20, 2020. <sup>a</sup>Ann Arbor Criteria; <sup>b</sup>Prior SCT is included. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. <sup>c</sup>Systemic therapy; Relapsed: complete or partial response, followed by relapse; Refractory: stable disease or progressive disease; Other: missing data or not evaluable. <sup>d</sup>If SCT is most recent line, the variable is defined as response to the therapy immediately preceding SCT.

**DLBCL**, diffuse large B-cell lymphoma; **ECOG**, Eastern Cooperative Oncology Group; **GCB**, germinal center B-cell; **Lonca**, loncastuximab tesirine; **MCL**, mantle cell lymphoma; **NHL**, non-Hodgkin lymphoma; **SCT**, stem cell transplant.

# Safety Results

| TEAE (all grades) by preferred term in ≥20% of patients | n (%)     |
|---|-----------|
| Any TEAE  | 37 (100)  |
| Thrombocytopenia  | 11 (29.7) |
| Anemia  | 8 (21.6)  |
| Fatigue   | 8 (21.6)  |
| Diarrhea  | 8 (21.6)  |

| TEAE (Grade ≥3) by preferred term in ≥5% of patients | n (%)     |
|--|-----------|
| Any TEAE   | 23 (62.2) |
| Anemia   | 4 (10.8)  |
| Neutropenia  | 4 (10.8)  |
| Thrombocytopenia                                     | 2 (5.4)   |
| Fatigue  | 2 (5.4)   |

Combination of Lonca plus ibrutinib had manageable toxicity

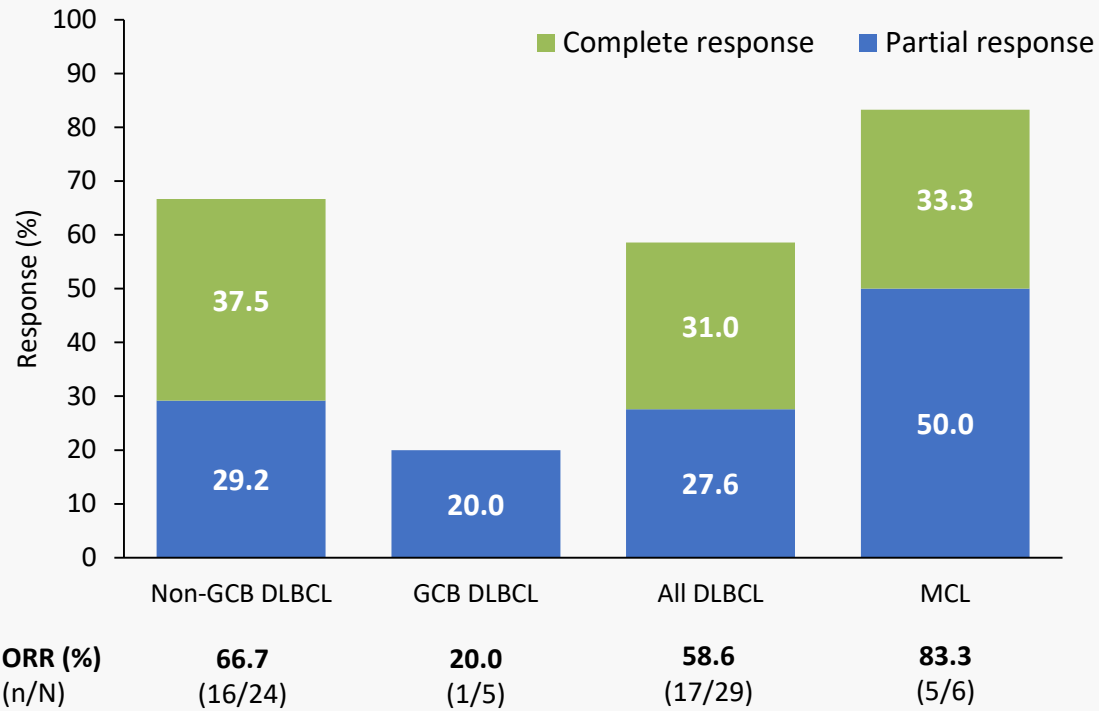
Data cut: August 20, 2020.

**Lonca**, loncastuximab tesirine; **TEAE**, treatment-emergent adverse event.



# Efficacy Results

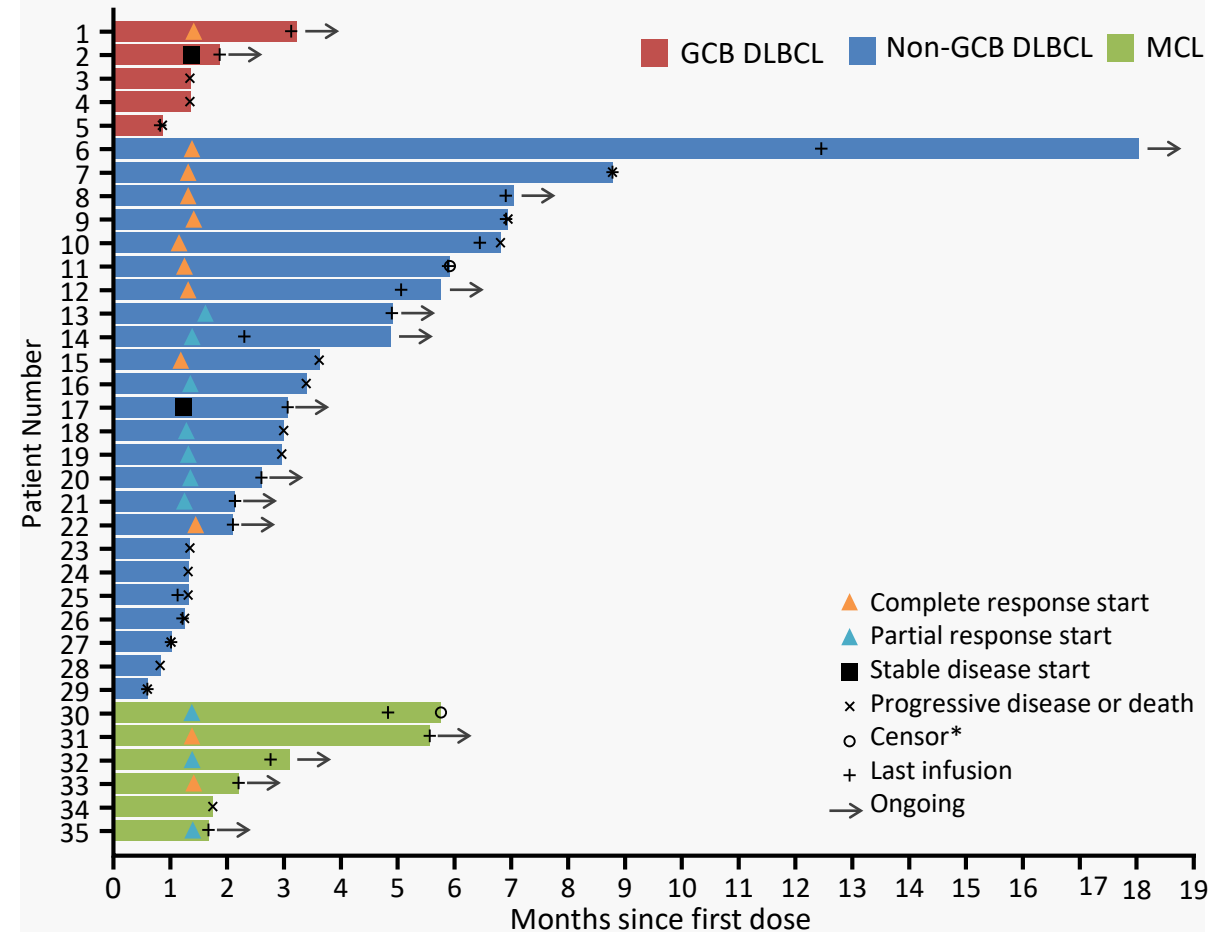
Total population: ORR: 62.9% CRR: 31.4%



Data cut: August 20, 2020; 35/37 patients were evaluable for efficacy; 1 with GCB DLBCL and 1 with MCL were non-evaluable. \*Only for censored patients who discontinue trial due to reasons other than progression or who go onto a different anticancer treatment.

**CRR**, complete response rate; **DLBCL**, diffuse large B-cell lymphoma; **GCB**, germinal center B-cell; **MCL**, mantle cell lymphoma; **ORR**, overall response rate.

Median treatment duration: 70 days (range 18–379 days)



# Pharmacokinetics Results

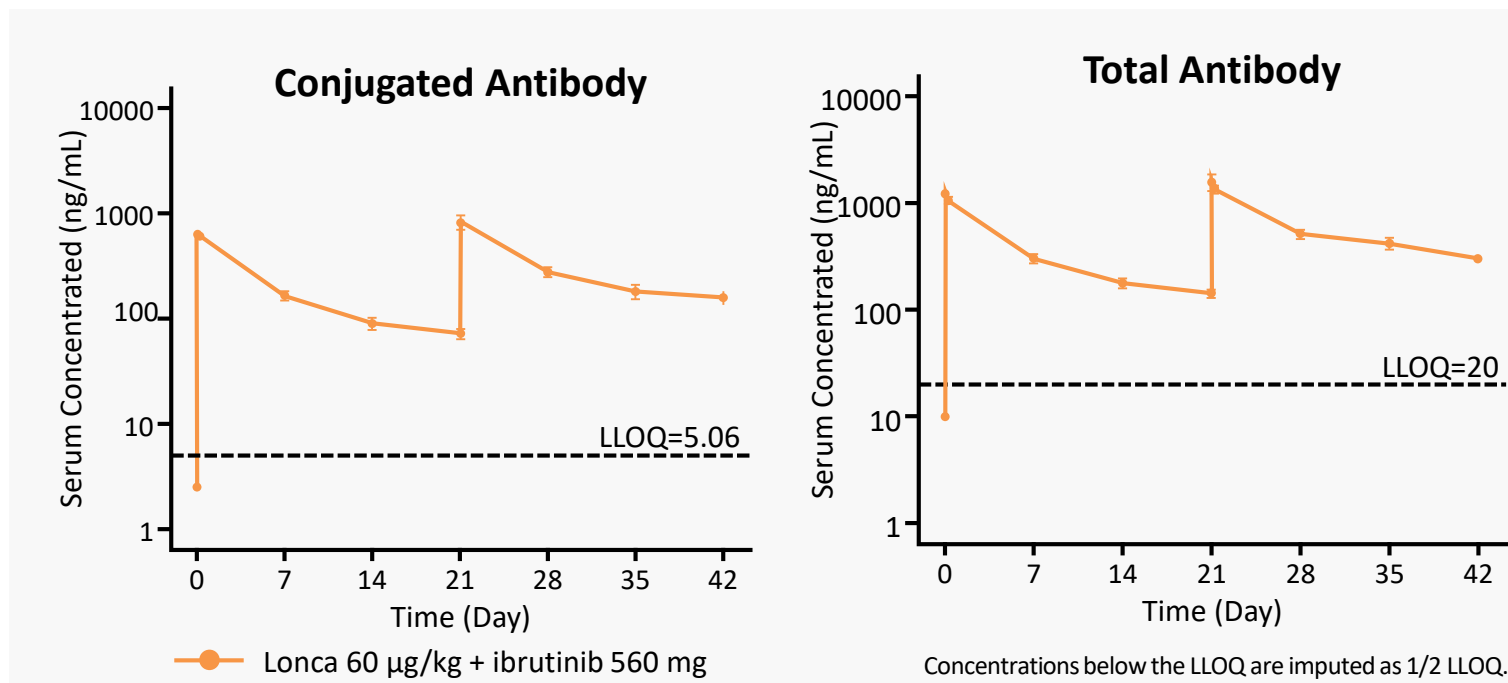
| PK parameters                                       | Conjugated Ab     | Total Ab           |
|---|-------------------|--------------------|
| <b>Cycle 1: Lonca 60 µg/kg and ibrutinib 560 mg</b> |                   |                    |
| <b>C<sub>max</sub> (ng/mL)</b>                      | 659 (45.3) [26]   | 1280 (41.4) [26]   |
| <b>AUC<sub>inf</sub> (ng·day/mL)</b>                | 4364 (61.9) [8]   | 7449 (54.8) [9]    |
| <b>T<sub>half</sub> (day)</b>                       | 6.31 (46.7) [8]   | 5.65 (38.2) [9]    |
| <b>CL (L/day)</b>                                   | 0.893 (60.4) [8]  | 0.590 (50.1) [9]   |
| <b>V<sub>ss</sub> (L)</b>                           | 5.52 (47.2) [8]   | 3.43 (43.6) [9]    |
| <b>Cycle 2: Lonca 60 µg/kg and ibrutinib 560 mg</b> |                   |                    |
| <b>C<sub>max</sub> (ng/mL)</b>                      | 761 (91.7) [21]   | 1461 (80.8) [21]   |
| <b>AUC<sub>tau</sub> (ng·day/mL)</b>                | 5582 (65.0) [15]  | 10,423 (60.1) [13] |
| <b>T<sub>half</sub> (day)</b>                       | 7.57 (43.0) [11]  | 7.79 (33.0) [6]    |
| <b>CL (L/day)</b>                                   | 0.705 (63.3) [15] | 0.451 (58.8) [13]  |
| <b>V<sub>ss</sub> (L)</b>                           | 7.85 (64.0) [11]  | 6.01 (50.0) [6]    |
| <b>AI</b>   | 1.21 (15.9) [11]  | 1.20 (10.4) [6]    |

Blood samples for PK analysis were drawn on Day 1 (pre-dose), Day 8 and Day 15 of treatment Cycles 1 and 2.

Data shown as geometric mean (geometric % coefficient of variation) [n].

Data cut: August 20, 2020.

**Ab**, antibody; **AI**, accumulation index; **AUC<sub>inf</sub>**, area under the curve vs time curve from 0 to infinity; **AUC<sub>tau</sub>**, area under the curve from 0–21 days; **CL**, apparent clearance; **C<sub>max</sub>**, maximum observed concentration; **LLOQ**, lower limit of quantification; **Lonca**, loncastuximab tesirine; **PK**, pharmacokinetic; **SE**, standard error; **T<sub>half</sub>**, apparent terminal half-life; **V<sub>ss</sub>**, apparent steady-state volume of distribution



- Good exposure coverage seen throughout dosing interval
- Cycle-related increases in PK parameters apparent
- Exposure variability among patients appears moderate

# Conclusions

## Study conclusions

Lonca 60 µg/kg plus ibrutinib 560 mg continues to have encouraging antitumor activity and manageable toxicity in patients with R/R DLBCL and with R/R MCL

**ORR for all patients was 62.9%**

- Non-GCB DLBCL **66.7%**
- GCB DLBCL **20.0%**
- MCL **83.3%**

**CRR for all patients was 31.4%**

- Non-GCB DLBCL **37.5%**
- GCB DLBCL **0%**
- MCL **33.3%**

Safety data were consistent with those reported previously<sup>1</sup>

Good Lonca exposure coverage obtained over the Q3W dosing interval

1. Depaus J, et al. EHA 2020. Abstract 1284.

**CRR**, complete response rate; **DLBCL**, diffuse large B-cell lymphoma; **GCB**, germinal center B-cell; **Lonca**, loncastuximab tesirine; **MCL**, mantle cell lymphoma; **ORR**, overall response rate; **Q3W**, every three weeks; **R/R**, relapsed/refractory.



# Disclosures and Acknowledgments

- **J. Depaus:** consultancy for Takeda, Novartis, and Janssen
- **N. Wagner-Johnston:** Board of directors, speakers' bureau, or advisory committee for ADC Therapeutics, Regeneron, CALIB-R, Verastem, and Karyopharm
- **P. Luigi Zinzani:** consultancy for Verastem, MSD, Eusapharma, Sanofi; board of directors, speakers' bureau, or advisory committee for Verastem, Celltrion, Gilead, Janssen-Cilag, Bristol-Myers Squibb, Servier, Sandoz, MSD, Immune Design, Celgene, Portola, Roche, Eusapharma, Kyowa Kirin, and ADC Therapeutics (advisory board agreement)
- **T. J. Phillips:** board of directors, speakers' bureau, or advisory committee for Celgene/Bristol-Myers Squibb, Kite/Gilead, Seattle Genetics, AbbVie/Pharmacyclics, Incyte, and Genentech
- **E. Bachy:** employee of Université Claude Bernard Lyon 1, Lyon, France; consultancy for Roche and Gilead; research funding from Amgen; honoraria from Roche, Celgene, Amgen, Janssen, Gilead, Novartis, and Sanofi; board of directors, speakers' bureau, or advisory committee for Beigene
- **M. Janakiram:** Research funding from ADC Therapeutics, FATE therapeutics, Takeda pharmaceuticals
- **J. Adeleye, K. Havenith, J. Boni, L. Wang, and A. Ervin-Haynes:** employees of ADC Therapeutics with stock options
- **C. Carlo-Stella:** consultancy for Boehringer Ingelheim and Sanofi; research funding from ADC Therapeutics and Rhizen Pharmaceuticals; honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology, AstraZeneca; board of directors, speakers' bureau, or advisory committee for Servier, Novartis, Genenta Science SRL, ADC Therapeutics, Roche, and Karyopharm
- **J. Maly, S. Ferrari, L. J. Bryan, V. Delwail, S. de Guibert, and M. Tani:** nothing to disclose
- **X. Zhang,** who contributed to the abstract, was previously an employee of ADC Therapeutics with stock options

This study was funded by ADC Therapeutics SA (NCT03684694); with supply of ibrutinib from Pharmacyclics LLC, an AbbVie company

## Acknowledgments

- The authors would like to thank all the participating patients and their families, all study co-investigators and research coordinators.
- Editorial support was provided by Louise Gildea, PhD, of Fishawack Communications Ltd, part of Fishawack Health.

