Interim Results From the First-in-Human Clinical Trial of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

J Radford[1], B Kahl[2], M Hamadani[3], C Carlo-Stella[4], P. Caimi[5], KM Ardeshna[6], J Feingold[7], S He[7], E Reid[8], M Solh[9], K-Y Chung[10], L Heffner[11], D Ungar[7], OA O'Connor[12]

[1]University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]Department of Medicine, Oncology Division, Washington University, St. Louis, MO, USA; [3]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [4]Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas University, Milan, Italy; [5]Case Western Reserve, University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [6]Department of Haematology, University College London Hospitals, NHS Foundation Trust, London, UK; [7]ADC Therapeutics America Inc., Murray Hill, NJ, USA; [8]Division of Hematology/Oncology, University of California San Diego Moores Cancer Center, La Jolla, CA, USA; [9]Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA; [10]Department of Hematology and Oncology, Greenville Health System, Greenville, SC, USA; [11]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [12]Center for Lymphoid Malignancies, Columbia University Medical Center New York Presbyterian Hospital, New York, NY, USA

60th American Society of Hematology Annual Meeting & Exposition

December 1–4, 2018, San Diego, CA, USA

Acknowledgments

Investigators and affiliations

- **J Radford**, University of Manchester and the Christie NHS Foundation Trust, Manchester, UK
- **B Kahl**, Department of Medicine, Oncology Division, Washington University, St. Louis, MO, USA
- **M Hamadani**, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, USA
- **C Carlo-Stella,** Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas University, Milan, Italy
- **P Caimi**, Case Western Reserve University (CWRU) - University Hospitals Cleveland Medical Center, OH, USA
- **KM Ardeshna**, Department of Haematology, University College London Hospitals, NHS Foundation Trust, London, UK
- **E Reid**, Division of Hematology/Oncology, University of California San Diego Moores Cancer Center, La Jolla, CA, USA
- **M Solh**, Blood and Marrow Transplant Program at Northside Hospital, Atlanta, GA, USA
- **K-Y Chung**, Department of Hematology and Oncology, Greenville Health System, Greenville, SC, USA
- **L Heffner**, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA
- **OA O'Connor**, Center for Lymphoid Malignancies, Columbia University Medical Center New York Presbyterian Hospital, New York, NY, USA

ADC Therapeutics:

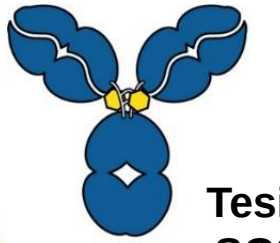
- **JM Feingold**, ADC Therapeutics America, Inc, Murray Hill, NJ, USA
- **S He**, ADC Therapeutics America, Inc, Murray Hill, NJ, USA
- **D Ungar**, ADC Therapeutics America, Inc, Murray Hill, NJ, USA

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 Fishawack Communications Ltd.

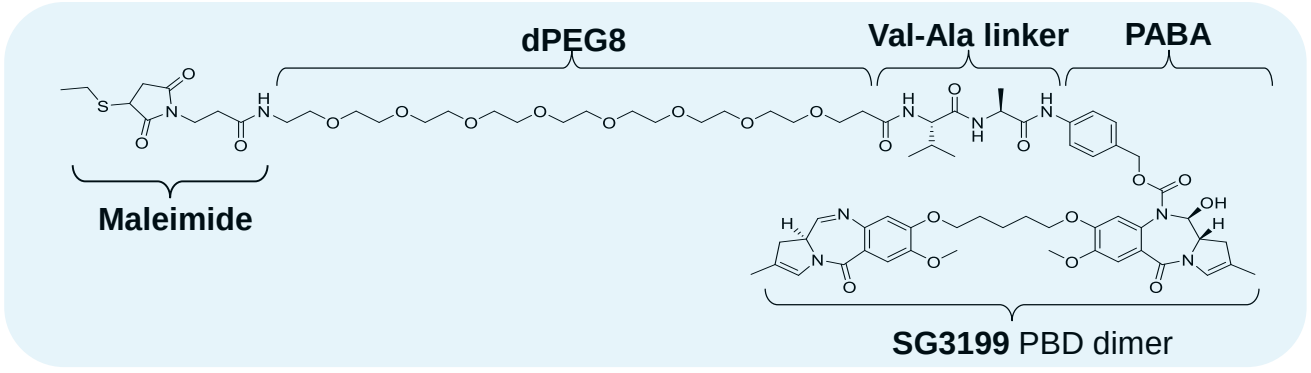
Study sponsored by ADC Therapeutics SA. http://clinicaltrials.gov/show/NCT02669017

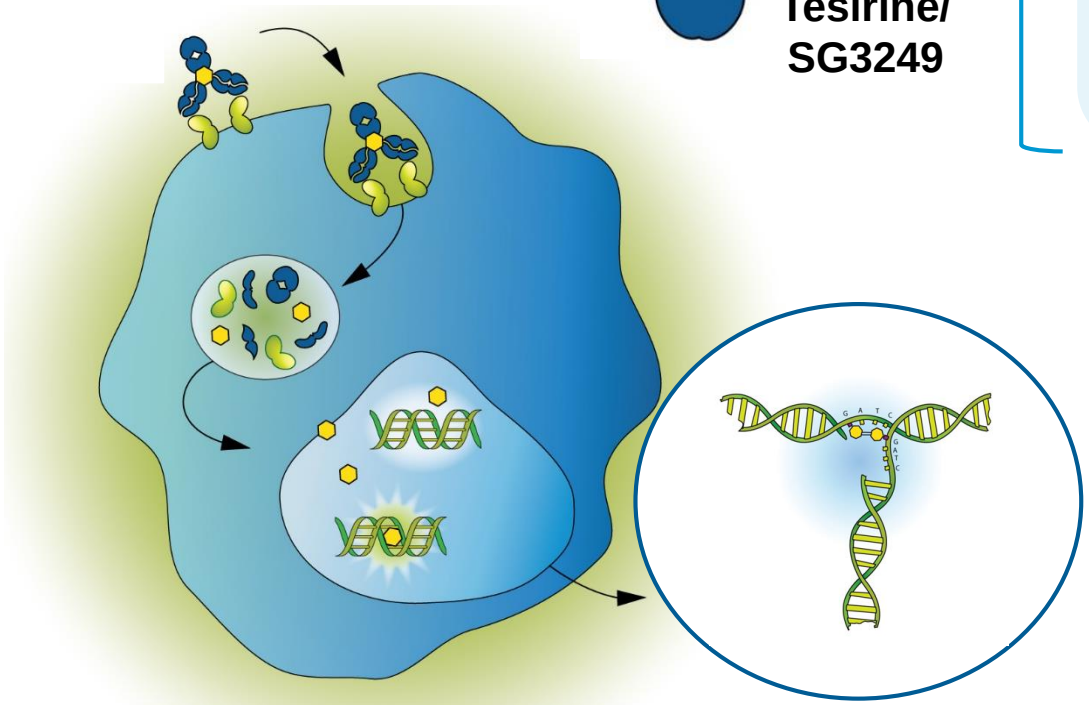
ADCT-402 (Loncastuximab Tesirine)
PBD-Based Molecular Structure and Mechanism of Action

Loncastuximab tesirine
is a CD19-specific antibody
+ tesirine/SG3249 payload



Tesirine/ SG3249





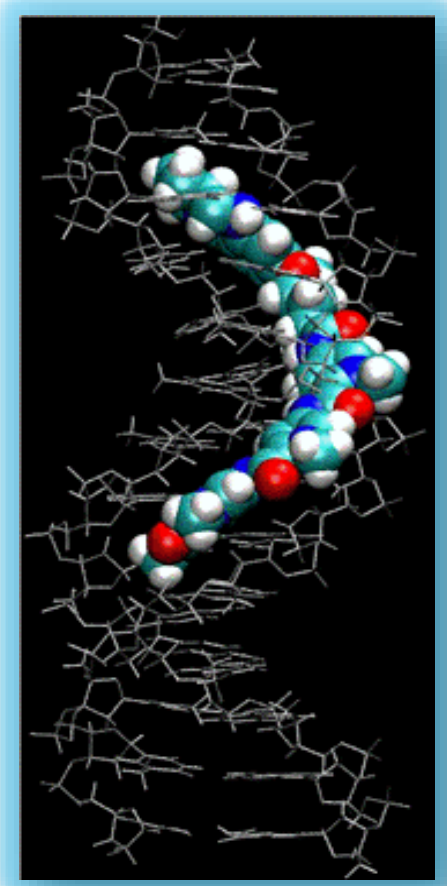
1. **Loncastuximab tesirine binds to CD19 antigen on the tumor cell surface**
2. **ADC is internalized, the linker is cleaved and PBD dimers are released**
3. **Cytotoxic DNA cross-link formation**
4. **Stalled DNA replication fork**
5. **Cell goes into apoptosis**

ADC, antibody-drug conjugate; PABA, para-aminobenzoic acid; PBD, pyrrolobenzodiazepine.

Zammarchi F. *Blood.* 2018; 131: 1094–1105

PBD Dimers as Anti-Tumor Agents

- PBD is a DNA cross-linking agent
- Non-tubulin approach
- Minor groove binding is less distortive of DNA[1]
  - Less visible to DNA repair mechanisms
- IC_{50} potency in picomolar (10^{-12}) range[2]
- Effective in multidrug-resistant (+) cell lines[3]
- Active in slowly proliferating cancers[4]



IC_{50}, half maximal inhibitory concentration; PBD, pyrrolobenzodiazepine.

1. Clingen PH *et al. Nucleic Acids Res.* 2005; 33: 3283–3291. 2. Tiberghien AC *et al. ACS Med Chem Lett.* 2016; 7: 983−987. 3. Kung Sutherland MS *et al. Blood.* 2013; 122: 1455–1463. 4. Hartley JA *et al. Cancer Res.* 2010; 70: 6849–6858.

Loncastuximab Tesirine Phase 1 Lymphoma Study (NCT02669017)

R/R B-cell NHL,
failed, or intolerant to, any established therapy

1-hour intravenous infusion (15–200 µg/kg)
Day 1 every 3 weeks (q3w)
Dose escalation – 3+3 design
(Cycle 1 dose-limiting toxicity observation period)

PRIMARY STUDY OBJECTIVES

- Evaluate the safety and tolerability and determine the maximum tolerated dose of loncastuximab tesirine
- **Part 1 (dose escalation)**: Determine the recommended dose of loncastuximab tesirine for dose expansion (Part 2)
- **Part 2 (dose expansion)**: Evaluate the safety and tolerability of loncastuximab tesirine at the dose level recommended in Part 1

SECONDARY STUDY OBJECTIVES

- Evaluate the clinical activity of loncastuximab tesirine as measured by ORR, DoR, PFS, and OS
- Characterize PK profile of loncastuximab tesirine and free warhead SG3199

Enrollment for both parts of the study is complete
Part 2 was conducted using doses 120 µg/kg and 150 µg/kg (q3w)

DoR, duration of response; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; R/R, relapsed/refractory

Patient Population

KEY INCLUSION CRITERIA

- Relapsed/refractory B-cell NHL
- Measurable disease, as defined by the 2014 Lugano Classification
- Eastern Cooperative Oncology Group performance status 0 to 2
- Absolute neutrophil count ≥1000/μL
- Platelet count ≥75,000/μL
- Hb ≥9.0 g/dL without transfusion within 2 weeks prior to Day 1
- Serum/plasma creatinine ≤1.5 mg/dL. If creatinine >1.5 mg/dL, creatinine clearance must be >60 mL/min as calculated by the Cockcroft and Gault equation
- Serum/plasma ALP, ALT, and AST ≤2 times ULN; ≤5 times ULN if there is liver or bone involvement
- Total serum/plasma bilirubin ≤1.5 times ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 times ULN)

KEY EXCLUSION CRITERIA

- Active graft-versus-host disease
- Autologous or allogeneic transplant within the 60 days prior to screening
- Known seropositive for human immunodeficiency virus, hepatitis B surface antigen, or antibody to hepatitis C virus
- Major surgery, chemotherapy, systemic therapy (excluding steroids), radiotherapy, or any other experimental medications within 14 days prior to Cycle 1, Day 1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; ULN, upper limit of normal

Safety and Efficacy of Loncastuximab Tesirine in Patients with Mantle Cell Lymphoma or Follicular Lymphoma

Presented in Poster #2874 (Caimi *et al.*)

Safety and Efficacy of ADCT-402 (Loncastuximab Tesirine), a Novel Antibody Drug Conjugate, in Relapsed/Refractory Follicular Lymphoma and Mantle Cell Lymphoma: Interim Results From the Phase 1 First-in-Human Study

Date:	**Sunday, December 2, 2018**
Presentation time:	**6:00 PM – 8:00 PM**
Session name:	**623. Mantle Cell, Follicular, and Other Indolent B-Cell Lymphoma—Clinical Studies: Poster II**
Location:	**San Diego Convention Center, Hall GH**

Patients with DLCBL: Baseline Characteristics (Safety Analysis Set; n=139)

Patient Characteristic		Total (n=139)
Sex, n (%)	**Male** **Female**	80 (57.6) 59 (42.4)
Race, n (%)*	**White** **Black/African American** **Asian** **Other**	126 (90.6) 7 (5.0) 3 (2.2) 2 (1.4)
Age, years, median (min, max)		63 (20, 86)
Stage, n (%)*	**I–II** **III** **IV**	27 (19.4) 23 (16.5) 89 (64.0)
Bulky disease, n (%)		19 (13.7)
Serum lactate dehydrogenase, U/L		350 (109–9348)

Patient Treatment History		Total (n=139)
Last line chemotherapy response, n (%)*	**Relapsed** **Refractory**	48 (34.5) 90 (64.7)
No. of previous systemic therapies, median (min, max)		3 (1, 10)
No. of previous systemic therapies, n (%)	**≤3** **4–6** **7–10**	85 (61.2) 47 (33.8) 7 (5.0)
Prior stem cell transplantation, n (%)	**Yes** **No**	27 (19.4) 112 (80.6)

*Data missing for 1 patient
Data shown as of 16 Oct 2018

Patients with DLBCL: Drug Exposure (Safety Analysis Set; n=139)

- The median (min, max) number of cycles received is 2 (1, 13)
- The median (min, max) duration of treatment with loncastuximab tesirine is 43 (1, 253) days

Dose (µg/kg)	n	Number of Cycles Dosed, Median (Min, Max)	Duration of Treatment (days), Median (Min, Max)
15	2	2 (2, 2)	22 (22, 22)
30	3	2 (2, 13)	22 (22, 253)
60	3	2 (1, 2)	22 (1, 22)
90	2	6 (4, 8)	122 (66, 178)
120	32	3 (1, 9)	42 (1, 238)
150	70	3 (1, 12)	44 (1, 238)
200	27	2 (1, 5)	43 (1, 177)
Total	139	**2 (1, 13)**	**43 (1, 253)**

Data shown as of 16 Oct 2018

Patients with DLBCL: TEAEs (Any Grade) Reported by ≥20% of Patients (Safety Analysis Set; n=139)

TEAEs (Any Grade), n (%)	Dose (µg/kg)				
	≤90 (n=10)	120 (n=32)	150 (n=70)	200 (n=27)	Total (n=139)
Patients with any TEAE	10 (100)	32 (100)	69 (98.6)	27 (100)	138 (99.3)
Any edema or effusion	**2 (20.0)**	**17 (53.1)**	**35 (50.0)**	**14 (51.9)**	**68 (48.9)**
Fatigue	4 (40.0)	19 (59.4)	25 (35.7)	11 (40.7)	59 (42.4)
Nausea	2 (20.0)	9 (28.1)	23 (32.9)	12 (44.4)	46 (33.1)
Peripheral edema	1 (10.0)	10 (31.3)	23 (32.9)	11 (40.7)	45 (32.4)
Anemia	3 (30.0)	6 (18.8)	24 (34.3)	10 (37.0)	43 (30.9)
Gamma-glutamyltransferase increased	**2 (20.0)**	**10 (31.3)**	**16 (22.9)**	**11 (40.7)**	**39 (28.1)**
Skin-related changes (rash)	**1 (10.0)**	**5 (15.6)**	**25 (35.7)**	**5 (18.5)**	**36 (25.9)**
Constipation	0 (0.0)	10 (31.3)	17 (24.3)	4 (14.8)	31 (22.3)
Neutropenia	1 (10.0)	4 (12.5)	17 (24.3)	9 (33.3)	31 (22.3)
Dyspnea	0 (0.0)	8 (25.0)	16 (22.9)	6 (22.2)	30 (21.6)
Pleural effusion	1 (10.0)	8 (25.0)	14 (20.0)	6 (22.2)	29 (20.9)
Decreased appetite	2 (20.0)	6 (18.8)	11 (15.7)	9 (33.3)	28 (20.1)
Thrombocytopenia	1 (10.0)	7 (21.9)	13 (18.6)	7 (25.9)	28 (20.1)

TEAE, treatment-emergent adverse event
Data shown as of 16 Oct 2018

Patients with DLBCL: Grade ≥3 TEAEs Reported By ≥5% of Patients (Safety Analysis Set; n=139)

TEAEs (Grade ≥3), n (%)	Dose (µg/kg)				
	≤90 (n=10)	120 (n=32)	150 (n=70)	200 (n=27)	Total (n=139)
Patients with any Grade ≥3 TEAE	4 (40.0)	23 (71.9)	55 (78.6)	24 (88.9)	106 (76.3)
Neutrophil count decreased[a]	**2 (20.0)**	**9 (28.1)**	**24 (34.3)**	**16 (59.3)**	**51 (36.7)**
Platelet count decreased[a]	**1 (10.0)**	**7 (21.9)**	**17 (24.3)**	**11 (40.7)**	**36 (25.9)**
Gamma-glutamyltransferase increased	1 (10.0)	7 (21.9)	12 (17.1)	7 (25.9)	27 (19.4)
Anemia	**2 (20.0)**	**3 (9.4)**	**9 (12.9)**	**3 (11.1)**	**17 (12.2)**
Disease progression	0 (0.0)	2 (6.3)	7 (10.0)	0 (0.0)	9 (6.5)
Alkaline phosphatase increased	1 (10.0)	3 (9.4)	3 (4.3)	1 (3.7)	8 (5.8)
Lymphocyte count decreased	**0 (0.0)**	**2 (6.3)**	**4 (5.7)**	**2 (7.4)**	**8 (5.8)**
Alanine aminotransferase increased	0 (0.0)	1 (3.1)	4 (5.7)	2 (7.4)	7 (5.0)
Fatigue	0 (0.0)	2 (6.3)	2 (2.9)	3 (11.1)	7 (5.0)
Hypokalemia	0 (0.0)	0 (0.0)	6 (8.6)	1 (3.7)	7 (5.0)
White blood cell count decreased	**0 (0.0)**	**2 (6.3)**	**3 (4.3)**	**2 (7.4)**	**7 (5.0)**

Purple text indicates liver test abnormalities

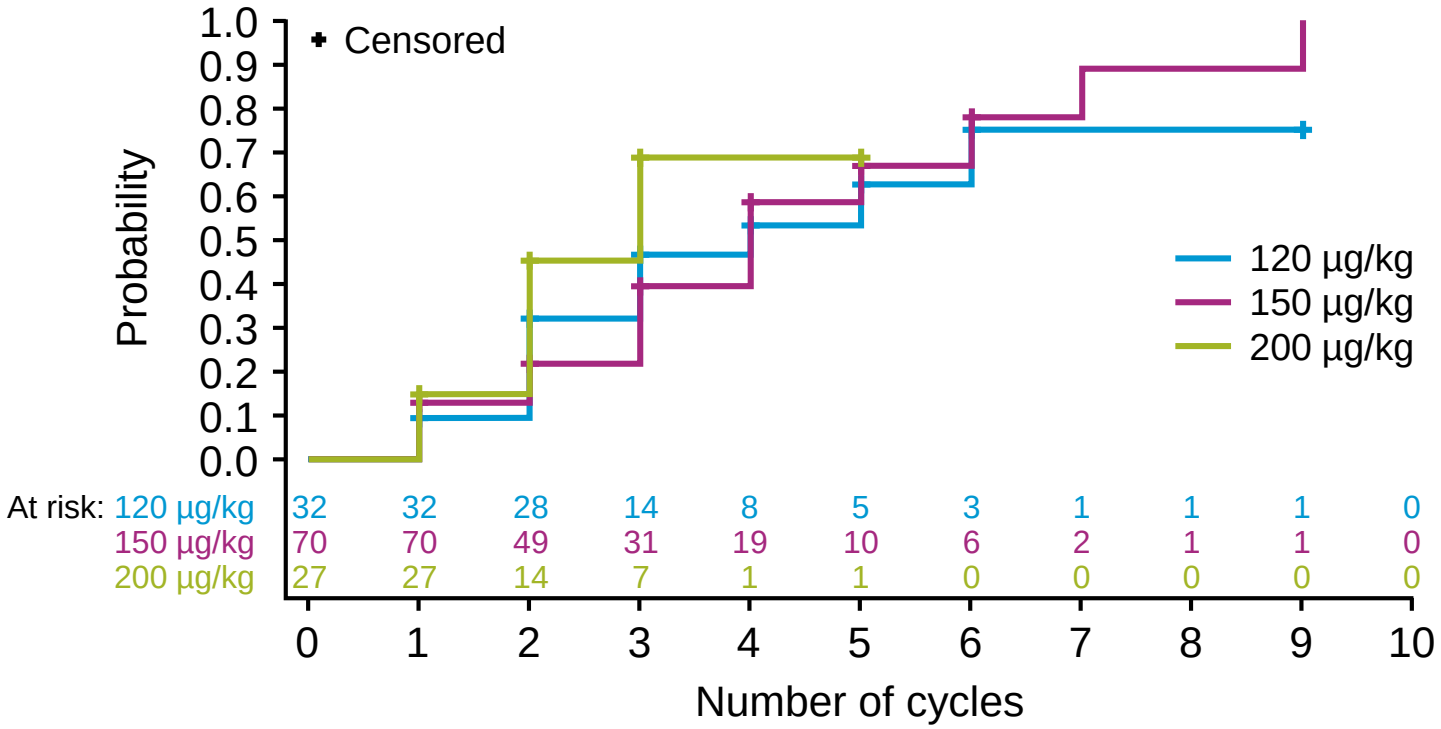
[a]Data on decreased platelet count (thrombocytopenia) and neutrophil count decreased (neutropenia) are based on laboratory abnormality reporting.

TEAE, treatment-emergent adverse event.

Data shown as of 16 Oct 2018

Patients with DLBCL: TEAEs Leading to Dose Modification (Safety Analysis Set; n=139)

~68% and 78% of patients in the 120 µg/kg and 150 µg/kg groups, respectively, tolerated ≥2 cycles before occurrence of any TEAE leading to dose reduction/delay



TEAE, treatment-emergent adverse event

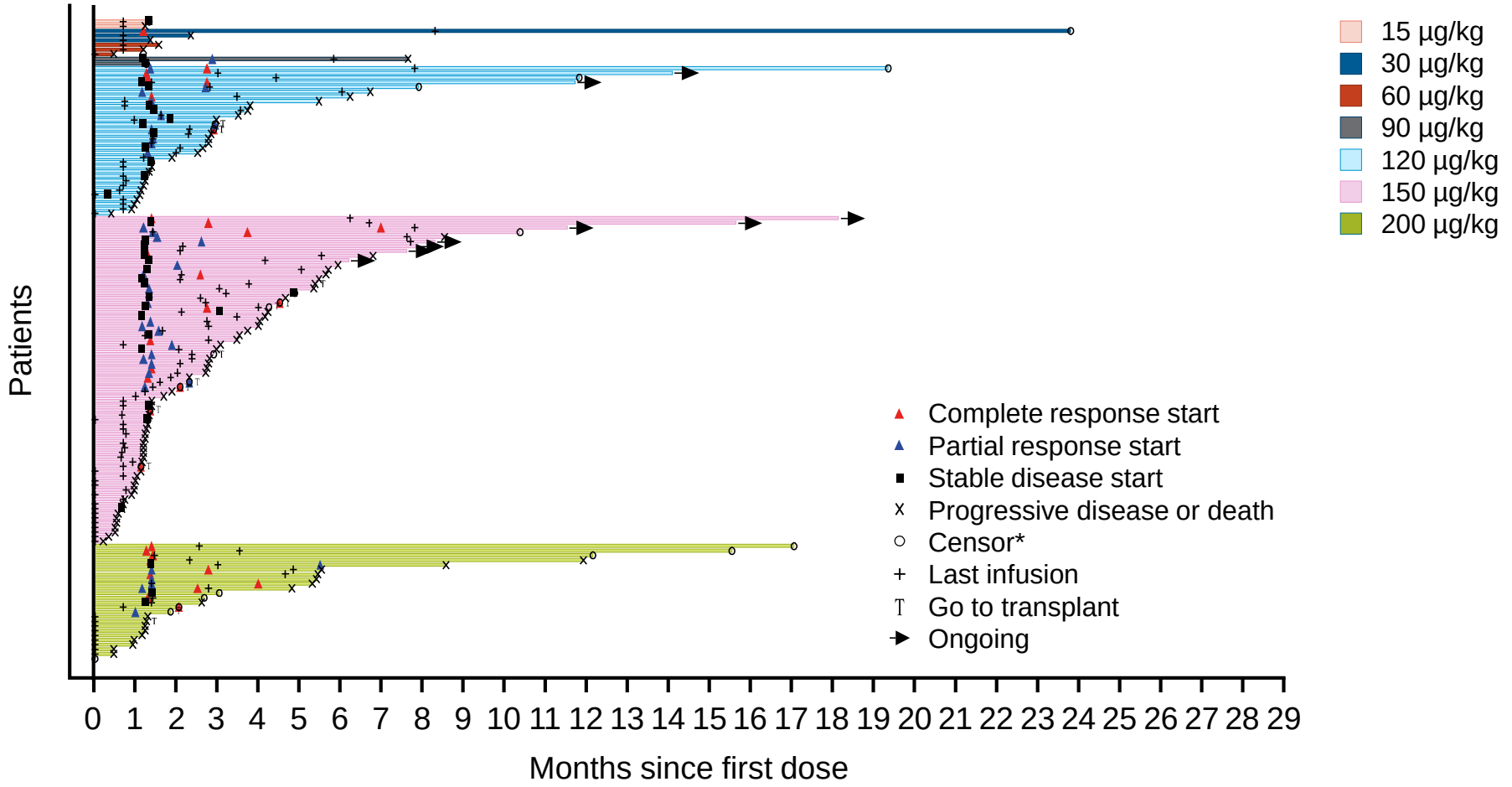
Data shown as of 16 Oct 2018

Patients with DLBCL: Response Rates (Efficacy Analysis Set)

Response, n (%)	Total (All Doses) (n=137)	Non-bulky disease (n=119)	Bulky disease (n=18)	Dose ≥120 µg/kg (n=127)
Complete response (CR)	31 (22.6)	29 (24.4)	2 (11.1)	30 (23.6)
Partial response (PR)	26 (19.0)	24 (20.2)	2 (11.1)	25 (19.7)
Stable disease	24 (17.5)	21 (17.6)	3 (16.7)	22 (17.3)
Progressive disease	54 (39.4)	43 (36.1)	11 (61.1)	48 (37.8)
Not evaluable	2 (1.5)	2 (1.7)	0	2 (1.6)
Overall response rate (CR + PR)	**57 (41.6)**	**53 (44.5)**	**4 (22.2)**	55 (43.3)

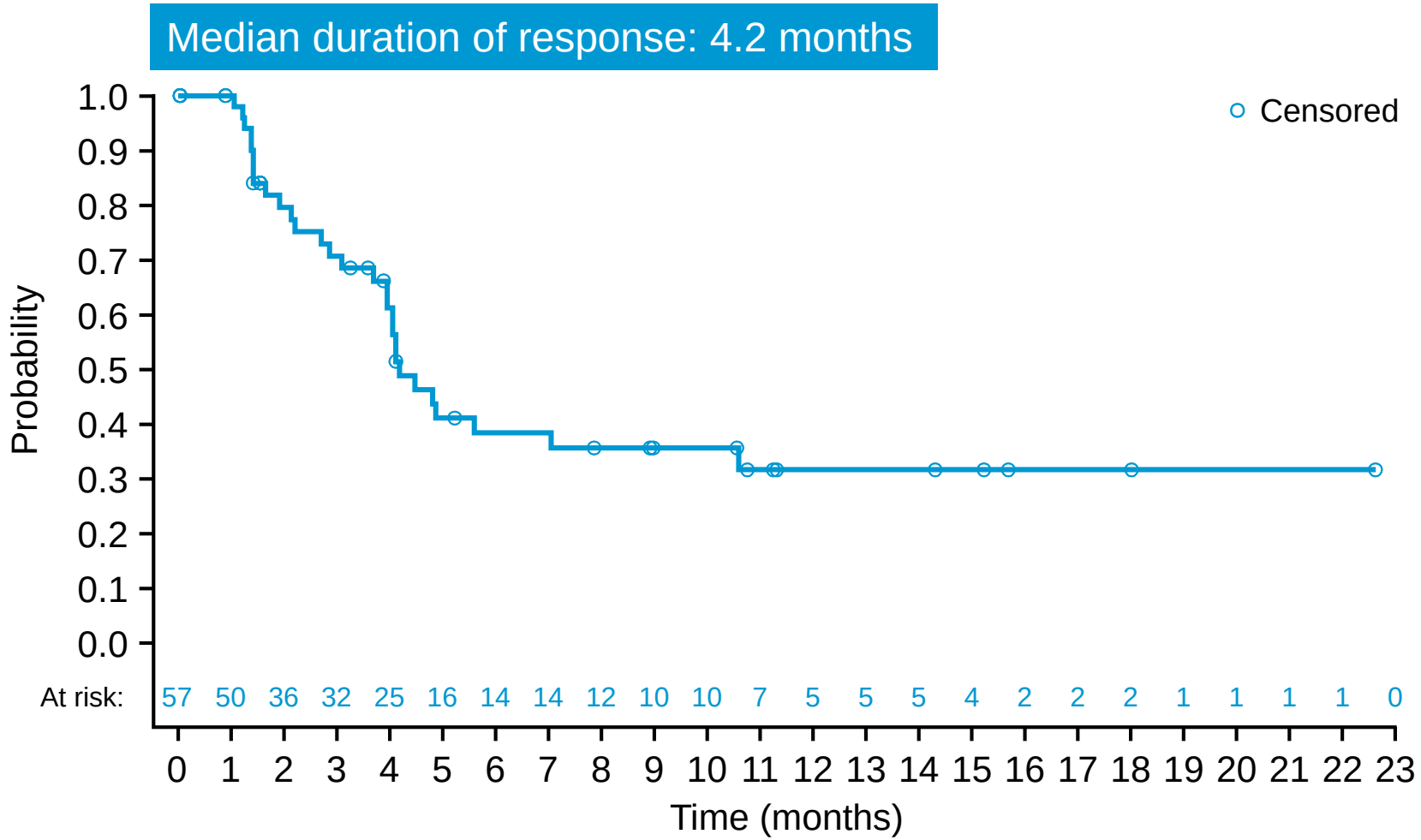
Data shown as of 16 Oct 2018

Patients with DLBCL: Swimmer Plot (Efficacy Analysis Set; n=137)



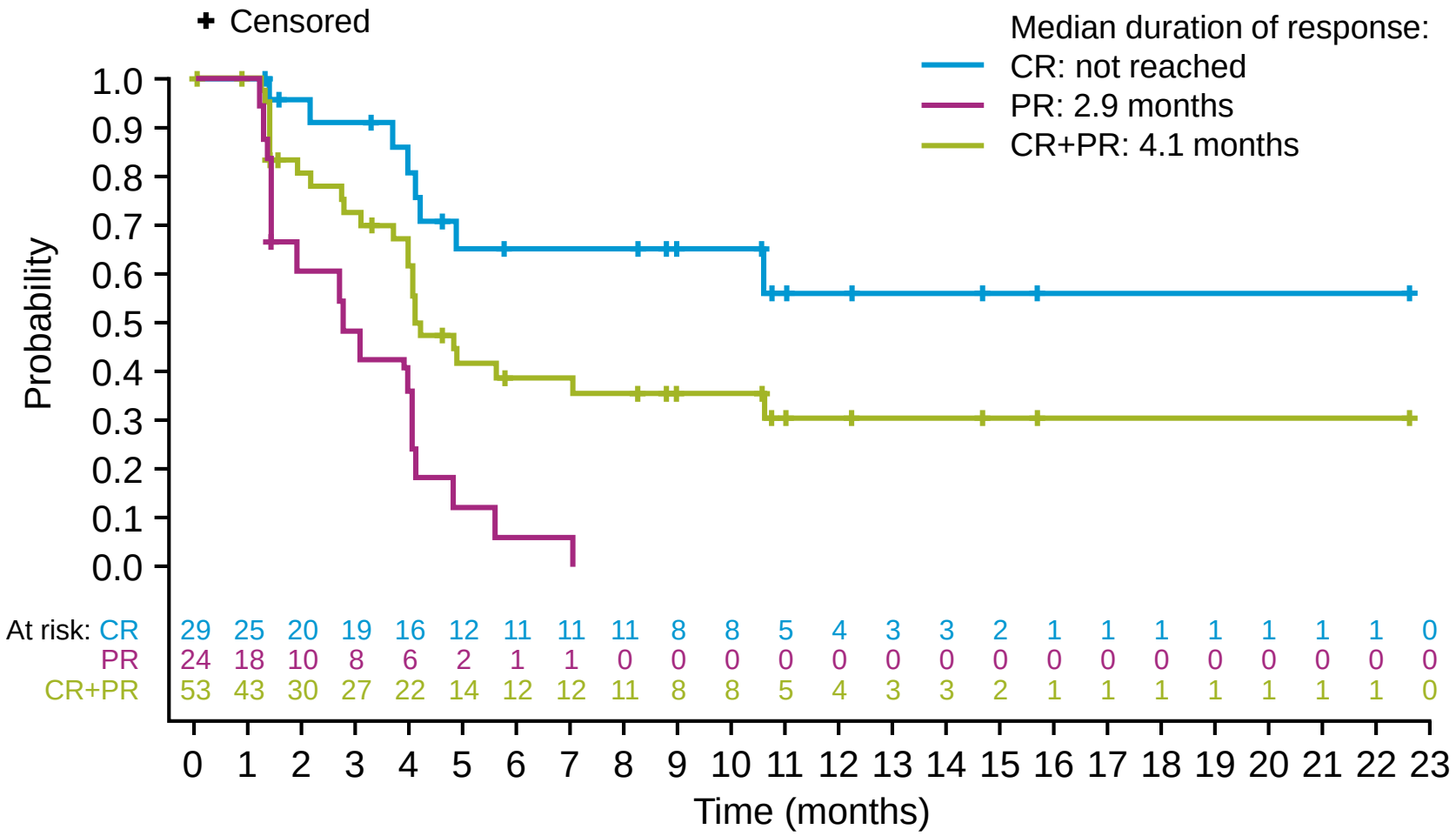
Each bar represents 1 patient. *Only for censored patients who discontinue trial due to reasons other than progression or who go onto a different anticancer treatment
Data shown as of 16 Oct 2018

DLBCL: Duration of Response



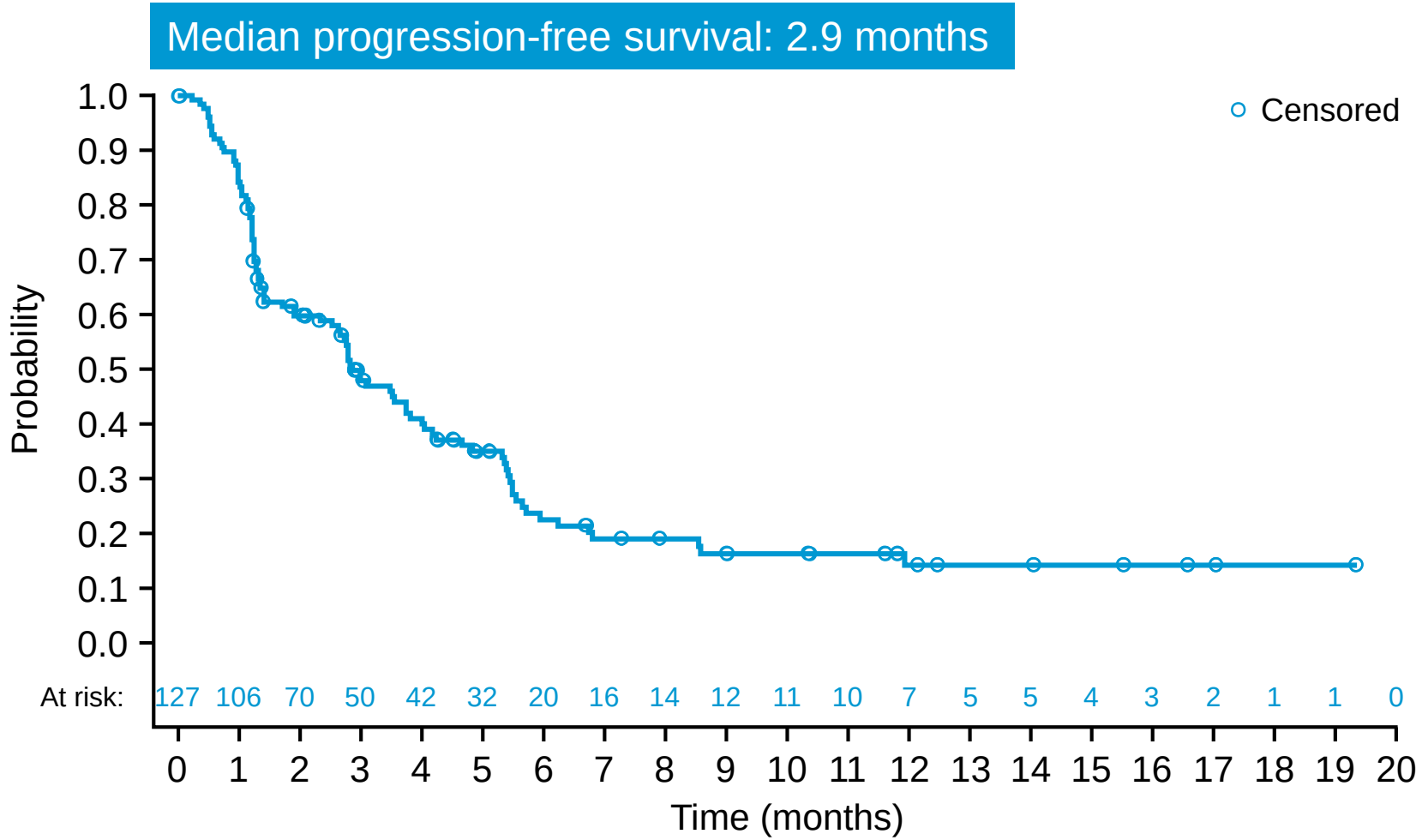
Data shown as of 16 Oct 2018

DLBCL: Duration of Response, by Response, at Dose ≥120 µg/kg



Data shown as of 16 Oct 2018

DLBCL: Progression-Free Survival at Dose ≥120 µg/kg (Efficacy Analysis Set)



Data shown as of 16 Oct 2018

Summary

- **In a Phase I study in patients with recurrent R/R DLBCL who had failed or were intolerant to established therapies, treatment with loncastuximab tesirine showed encouraging single-agent anti-tumor activity and manageable toxicity**
- **Notable toxicities include peripheral edema and serosal effusion (pleural, pericardial, and ascitic), GGT increased, thrombocytopenia, neutropenia, and rash**
- **At doses ≥120 µg/mL, the ORR was 43.3% (55/127 patients), CR rate was 23.6% and PR rate was 19.7%**
  - After a median follow-up of 5.5 months, median DoR was not reached in patients achieving a CR
- **A Phase II study is enrolling patients with R/R DLBCL (n=20 recruited to date) to evaluate the efficacy and safety of loncastuximab tesirine at dose 150 µg/kg Q3W for 2 cycles followed by dose 75µg/kg Q3W (NCT03589469)**

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; GGT, gamma glutamyltransferase; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory