Encouraging Early Results from the First-in-Human Clinical Trial of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory B-Cell Lineage Non-Hodgkin Lymphoma

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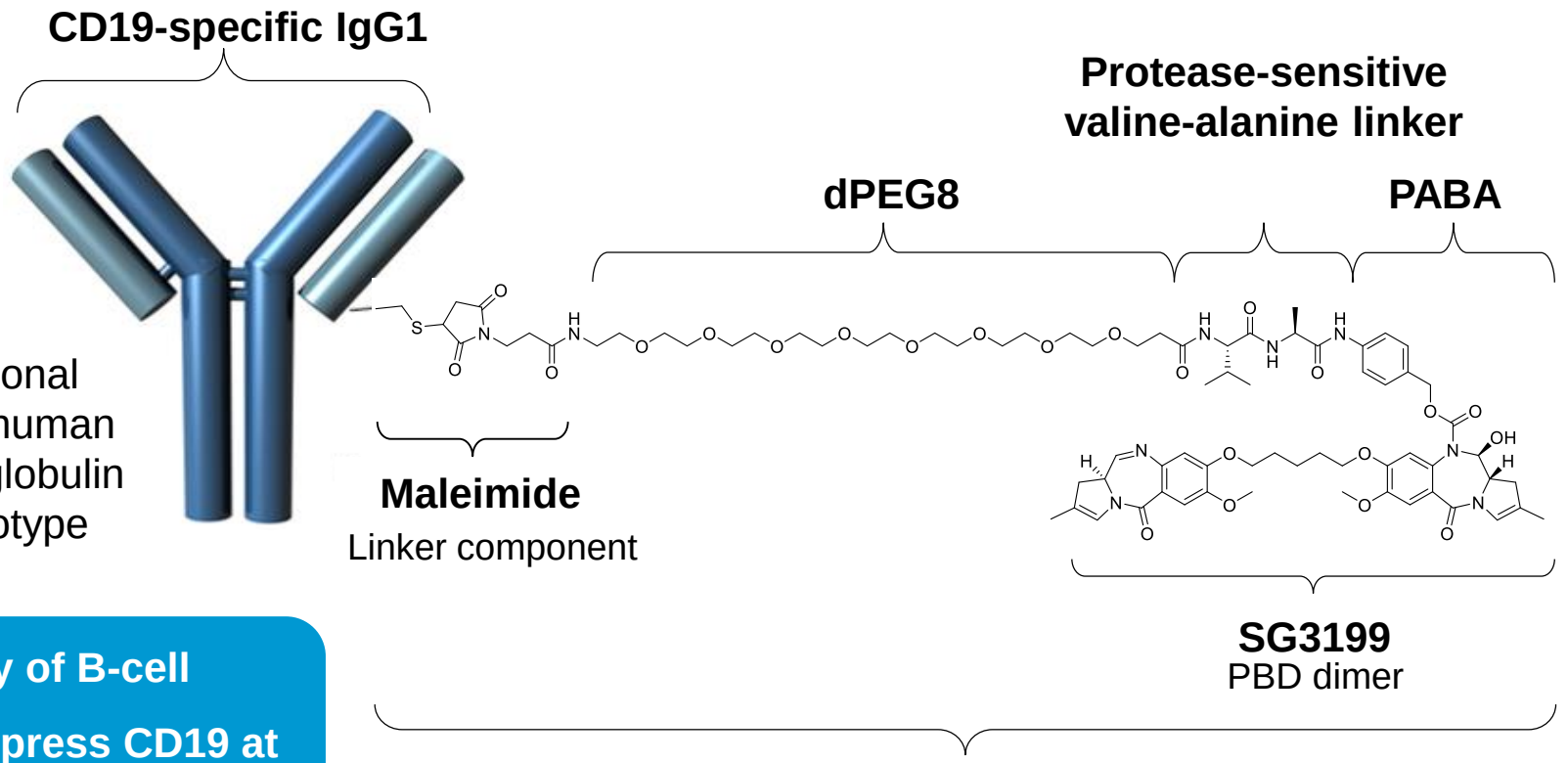
ADCT-402 (loncastuximab tesirine; Lonca-T)
PBD-Based ADC Molecular Structure



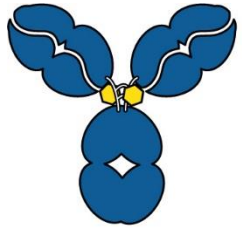
The majority of B-cell malignancies express CD19 at normal to high levels[1]

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

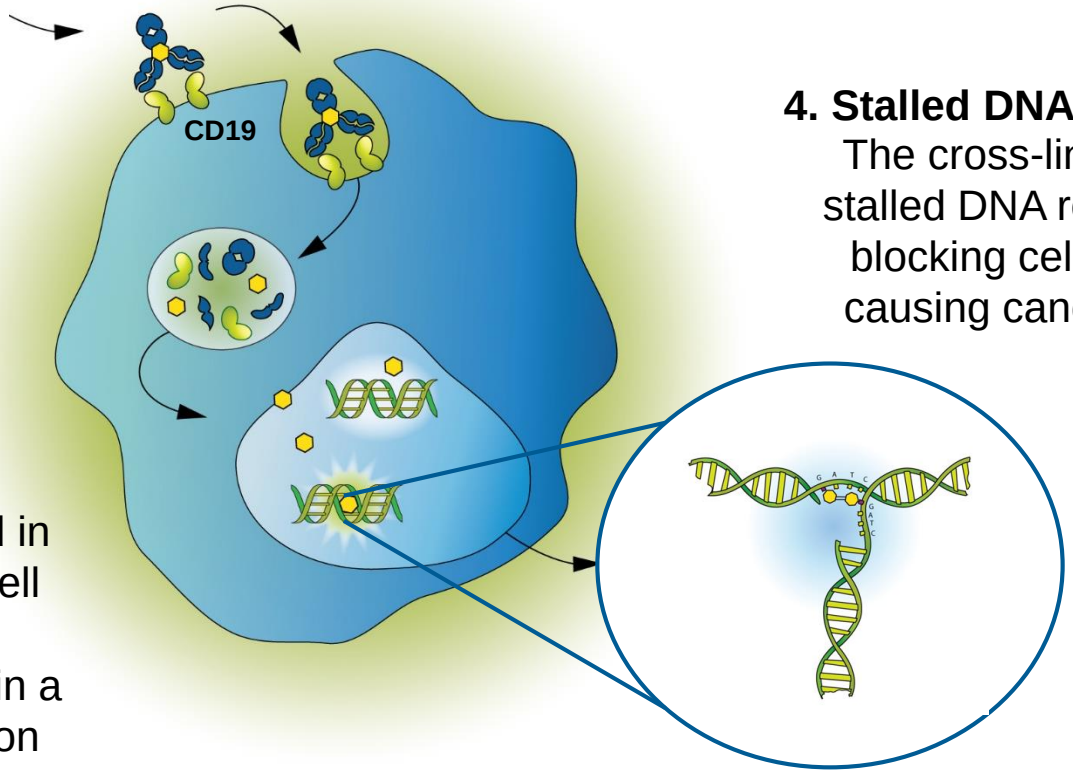
1. Wang K *et al*. *Exp Hematol Oncol*. 2012; 1: 36.

Lonca-T Mechanism of Action

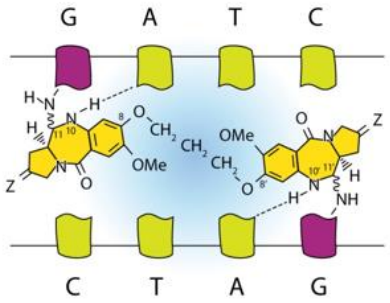
Lonca-T



1. Lonca-T binds to the CD19 antigen on the tumor cell surface



2. ADC internalization and PBD release
Following internalization of the ADC, the protease-sensitive linker is cleaved and the cytotoxic PBD dimer is released inside the cell



3. Cytotoxic cross-links
The free PBD dimers bind in the minor groove of the cell DNA and forms potent cytotoxic DNA cross-links in a sequence-selective fashion

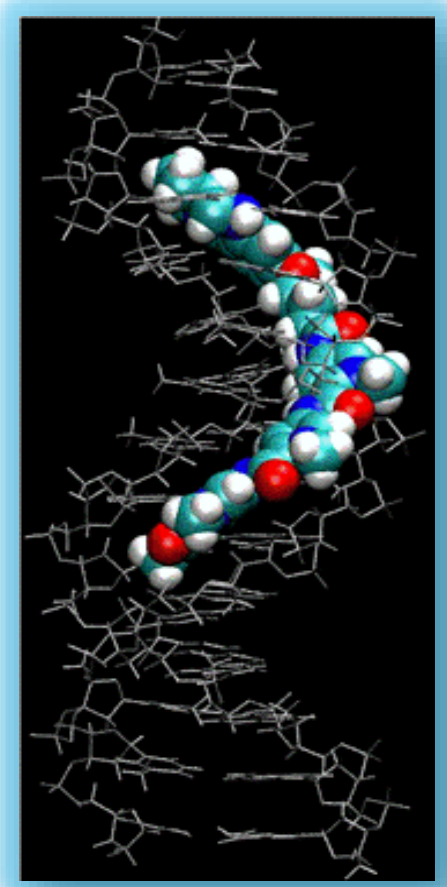
4. Stalled DNA replication fork
The cross-links result in a stalled DNA replication fork, blocking cell division and causing cancer cell death

ADC, antibody drug conjugate; PBD, pyrrolobenzodiazepine.

1. Hartley JA. *Expert Opin Investig Drugs.* 2011; 20: 733–744.

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
- Measurable pharmacodynamic endpoints
- Demonstrable Therapeutic Index
- IC_{50} potency in picomolar range (10^{-12})[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: 3283–91. 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.

Lonca-T Phase 1 Lymphoma Study (NCT02669017)

R/R B-cell non-Hodgkin lymphoma[a]

Failed, or intolerant to, any established therapy

1-hour intravenous infusion (15–200 µg/kg)
Day 1 every 3 weeks

Dose escalation – 3+3 method
(Cycle 1 dose-limiting toxicity observation period)

PRIMARY STUDY OBJECTIVES

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

SECONDARY STUDY OBJECTIVES

- Evaluate the clinical activity of Lonca-T as measured by overall response rate, duration of response, progression-free survival, and overall survival
- Characterize the pharmacokinetic profile of Lonca-T

Enrollment for part 1 is complete
Enrollment for part 2 is ongoing at study centers in the USA, UK, and Italy at doses 120 µg/kg and 150 µg/kg (q3w)

Patient Population

KEY INCLUSION CRITERIA

- Relapsed 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
- Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1

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 biotherapy-targeted therapies within 21 days prior to Cycle 1, Day 1

Patient Baseline Characteristics: Safety Analysis Set Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

Patient Characteristic	Total (N=138)
Sex, n (%)	
Female	43 (31.2)
Male	95 (68.8)
Race, n (%)[a]	
White	123 (89.1)
Black or African American	7 (5.1)
Asian	3 (2.2)
Other	3 (2.2)
Age, years, median (min, max)	63.5 (23, 86)
Prior chemotherapy response status, (n %)	
Relapsed	57 (41.3)
Refractory	80 (58.0)
Number of previous chemotherapies, median (min, max)	3 (1,10)
Prior stem cell transplantation, n (%)	
Yes	35 (25.4)
No	103 (74.6)

Data shown as of 1 Nov 2017. [a]n=2 missing data in total population.

Patient Diagnosis at Baseline: Safety Analysis Set Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

Patient Diagnosis at Baseline	Total (N=138)
Non-Hodgkin lymphoma, n (%)	
Diffuse large B-cell lymphoma (DLBCL)	95 (68.8)
Mantle cell lymphoma	12 (8.7)
Follicular lymphoma (FL)	12 (8.7)
Marginal zone B-cell lymphoma	5 (3.6)
Chronic lymphocytic leukemia (CLL)	4 (2.9)
Waldenström macroglobulinemia	1 (0.7)
Transformed follicular lymphoma	1 (0.7)
High-grade B-cell lymphoma	1 (0.7)
Primary mediastinal B-cell lymphoma	1 (0.7)
Mixed DLBCL-Burkitt's lymphoma	1 (0.7)
Small lymphocytic lymphoma (SLL)/CLL	1 (0.7)
CLL/SLL recurrence and simultaneous FL	1 (0.7)
Mediastinal (thymic large B-cell lymphoma)	1 (0.7)
Sarcoid	1 (0.7)
Aggressive B-cell lymphoma with features intermediate between DLBCL and Burkitt's lymphoma	1 (0.7)

Data shown as of 1 Nov 2017.

Drug Exposure: Safety Analysis Set
Part 1 (Dose Escalation) / Part 1 and Part 2 (Dose Expansion)

- The median number of Lonca-T cycles received is 2

	Dose (µg/kg)	n	Total Number of Cycles Dosed, Median (Min, Max)	Duration of Treatment (Days), Median (Min, Max)
Part 1 (dose escalation)	15	4	2 (2, 7)	43 (34, 147)
	30	4	2 (2, 13)	44 (43, 274)
	60	4	2 (1, 22)	43 (22, 471)
	90	5	4 (3, 11)	87 (64, 231)
	120	16	3 (2, 9)	87 (43, 259)
	150	19	3 (1, 6)	72 (22, 203)
	200	36	2 (1, 5)	54 (3, 198)
Parts 1 & 2 (dose escalation and dose expansion)	120	41	2 (1, 9)	49 (8, 259)
	150	44	2 (1, 6)	43 (2, 203)
	Total	**138**	**2 (1, 22)**	**44 (2, 471)**

Data shown as of 1 Nov 2017.

Most Common TEAEs: Safety Analysis Set
Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

TEAEs (Any Grade) Reported By ≥20% of Patients, n (%)	Dose (µg/kg)				
	≤90 (n=17)	120 (n=41[a])	150 (n=44[b])	200 (n=36)	Total (N=138)
Patients with any TEAE	**16 (94.1)**	**41 (100)**	**42 (95.5)**	**36 (100)**	**135 (97.8)**
Skin related changes	8 (47.1)	21(51.2)	22 (50.0)	21(58.3)	72 (52.2)
Fatigue	8 (47.1)	21 (51.2)	16 (36.4)	16 (44.4)	61 (44.2)
Nausea	3 (17.6)	11 (26.8)	9 (20.5)	16 (44.4)	39 (28.3)
Increased gamma-glutamyltransferase	5 (29.4)	8 (19.5)	8 (18.2)	16 (44.4)	37 (26.8)
Anemia	4 (23.5)	8 (19.5)	10 (22.7)	13 (36.1)	35 (25.4)
Peripheral edema	1 (5.9)	11 (26.8)	10 (22.7)	13 (36.1)	35 (25.4)

Data shown as of 1 Nov 2017. [a]Includes 16 patients from part 1 and 25 patients from part 2. [b]Includes 19 patients from part 1 and 25 patients from part 2.
TEAE, treatment-emergent adverse event.

Most Common Grade ≥3 TEAEs: Safety Analysis Set Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

TEAEs (Grade ≥3) Reported By ≥5% of Patients, n (%)	Dose (µg/kg)				
	≤90 (n=17)	120 (n=41[a])	150 (n=44[b])	200 (n=36)	Total (N=138)
Patients with any Grade ≥3 TEAE	**9 (52.9)**	**23 (56.1)**	**27 (61.4)**	**29 (80.6)**	**88 (63.8)**
Neutropenia	1 (5.9)	4 (9.8)	8 (18.2)	8 (22.2)	21 (15.2)
Increased gamma-glutamyltransferase	4 (23.5)	4 (9.8)	4 (9.1)	8 (22.2)	20 (14.5)
Anemia	3 (17.6)	4 (9.8)	6 (13.6)	4 (11.1)	17 (12.3)
Thrombocytopenia	0	2 (4.9)	7 (5.9)	8 (22.2)	17 (12.3)
Increased alkaline phosphatase	4 (23.5)	2 (4.9)	0	1 (2.8)	7 (5.1)
Fatigue	0	1 (2.4)	3 (6.8)	3 (8.3)	7 (5.1)

Data shown as of 1 Nov 2017. [a]Includes 16 patients from part 1 and 25 patients from part 2. [b]Includes 19 patients from part 1 and 25 patients from part 2.
TEAE, treatment-emergent adverse event.

TEAEs Leading to Treatment Withdrawal: Safety Analysis Set Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

One dose-limiting toxicity (thrombocytopenia at 200 µg/kg) has been reported; the maximum tolerated dose has not yet been reached

TEAEs Leading to Withdrawal By Preferred Term, n (%)	Dose (µg/kg)				
	≤90 (n=17)	120 (n=41[a])	150 (n=44[b])	200 (n=36)	Total (N=138)
Total patients withdrawn	**1[c] (5.9)**	**4[a] (9.8)**	**4 (9.1)**	**7[c] (19.4)**	**16 (11.6)**
Increased gamma-glutamyltransferase	1 (5.9)	1 (2.4)	0	1 (2.8)	3 (2.2)
Increased alkaline phosphatase	1 (5.9)	1 (2.4)	0	1 (2.8)	3 (2.2)
Thrombocytopenia	0	0	1 (2.3)	2 (5.6)	3 (2.2)
Fatigue	0	1 (2.4)	0	0	1 (0.7)
Abdominal pain	0	0	1 (2.3)	0	1 (0.7)
Decreased platelet count	0	0	0	1 (2.8)	1 (0.7)
Periorbital edema	0	1 (2.4)	0	0	1 (0.7)
Injection site extravasation	0	0	0	1 (2.8)	1 (0.7)
Fluid overload	0	0	0	1 (2.8)	1 (0.7)
Central nervous system lesion	0	0	0	1 (2.8)	1 (0.7)
Intestinal perforation	0	1 (2.4)	0	0	1 (0.7)
Lung infection	0	0	1 (2.3)	0	1 (0.7)
Sepsis	0	0	1 (2.3)	0	1 (0.7)

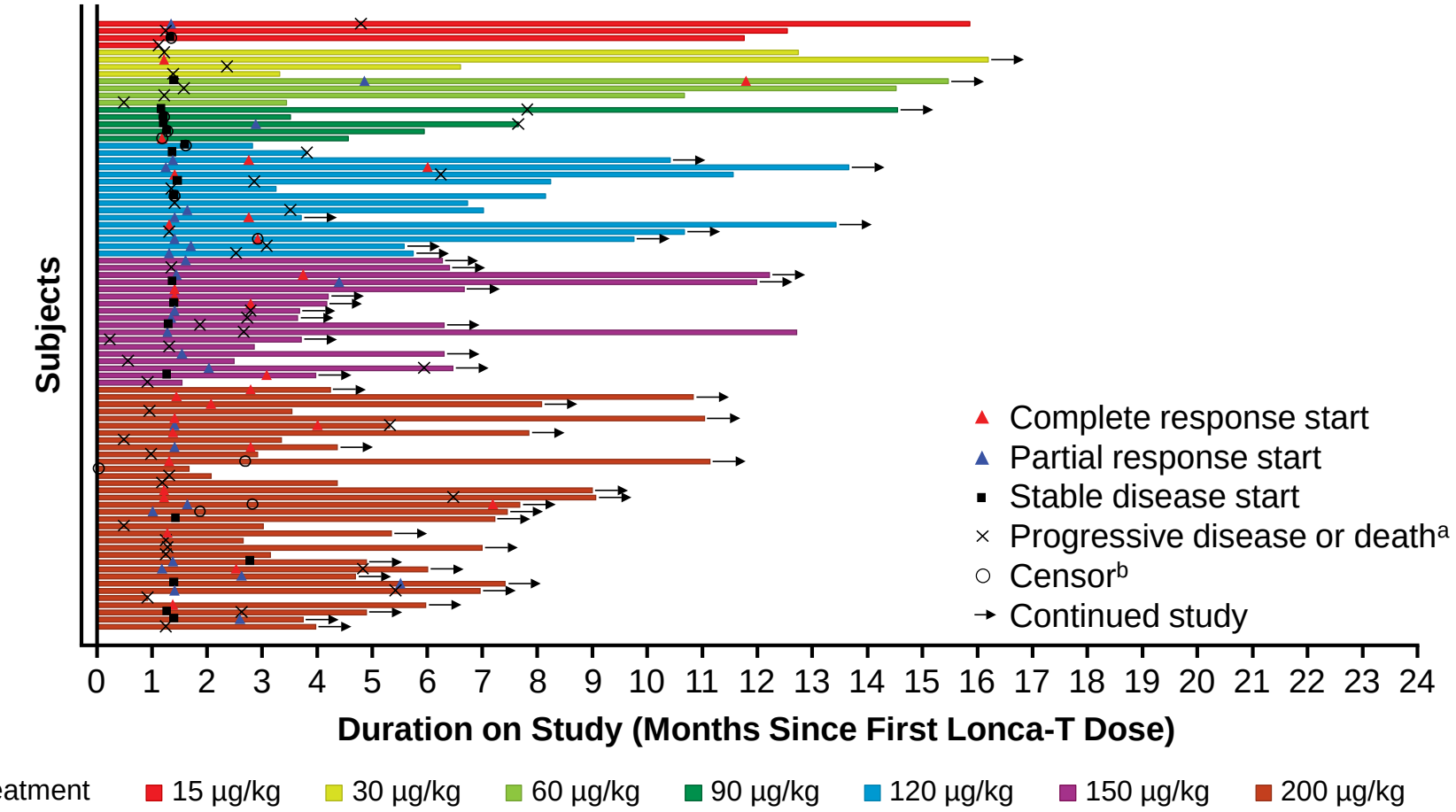
Data shown as of 1 Nov 2017. [a]Includes 16 patients from part 1 and 25 patients from part 2. [b]Includes 19 patients from part 1 and 25 patients from part 2. [c]One patient had 2 TEAEs reported. TEAE, treatment-emergent adverse event.

NHL Response Rates: Efficacy Analysis Set Part 1 (Dose Escalation)

Response, n (%)	**Total (N=85)**	**Dose ≥120 µg/kg (n=68)**
Complete response (CR)	27 (31.8)	24 (35.3)
Partial response (PR)	19 (22.4)	17 (25.0)
Stable disease	11 (12.9)	7 (10.3)
Progressive disease	28 (32.9)	20 (29.4)
Overall response rate (CR + PR)	**46 (54.2)**	**41 (60.3)**

Data shown as of 1 Nov 2017.

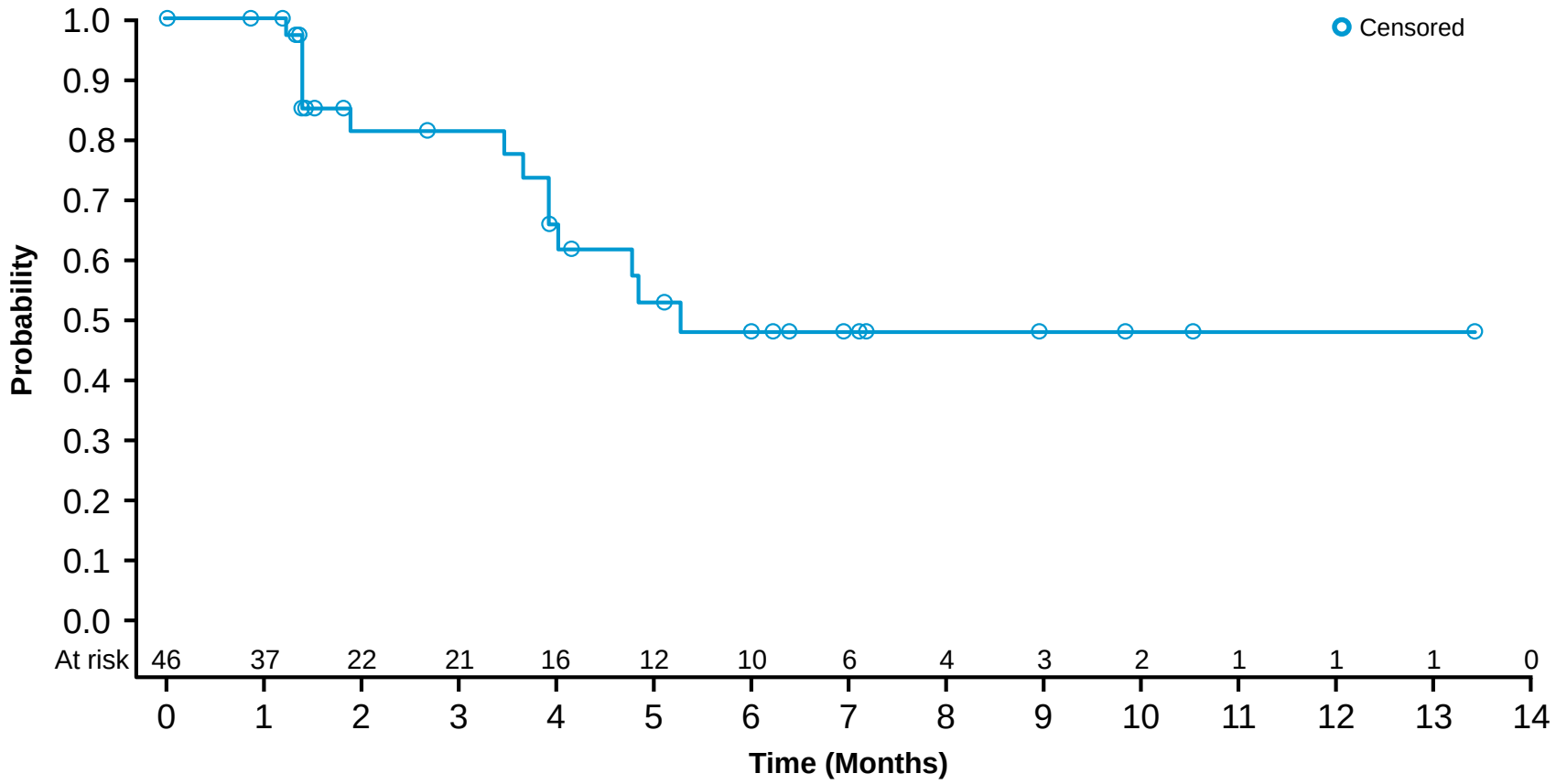
Non-Hodgkin Lymphoma (NHL) Swimmer Plot: Efficacy Analysis Set Part 1 (Dose Escalation)



Data shown as of 1 Nov 2017. Each bar represents 1 patient. [a]Study drug was discontinued at "x" for progression but patients continued to be followed.
[b]Exclude censors by cutoff date.

NHL Duration of Response: Efficacy Analysis Set Part 1 (Dose Escalation)

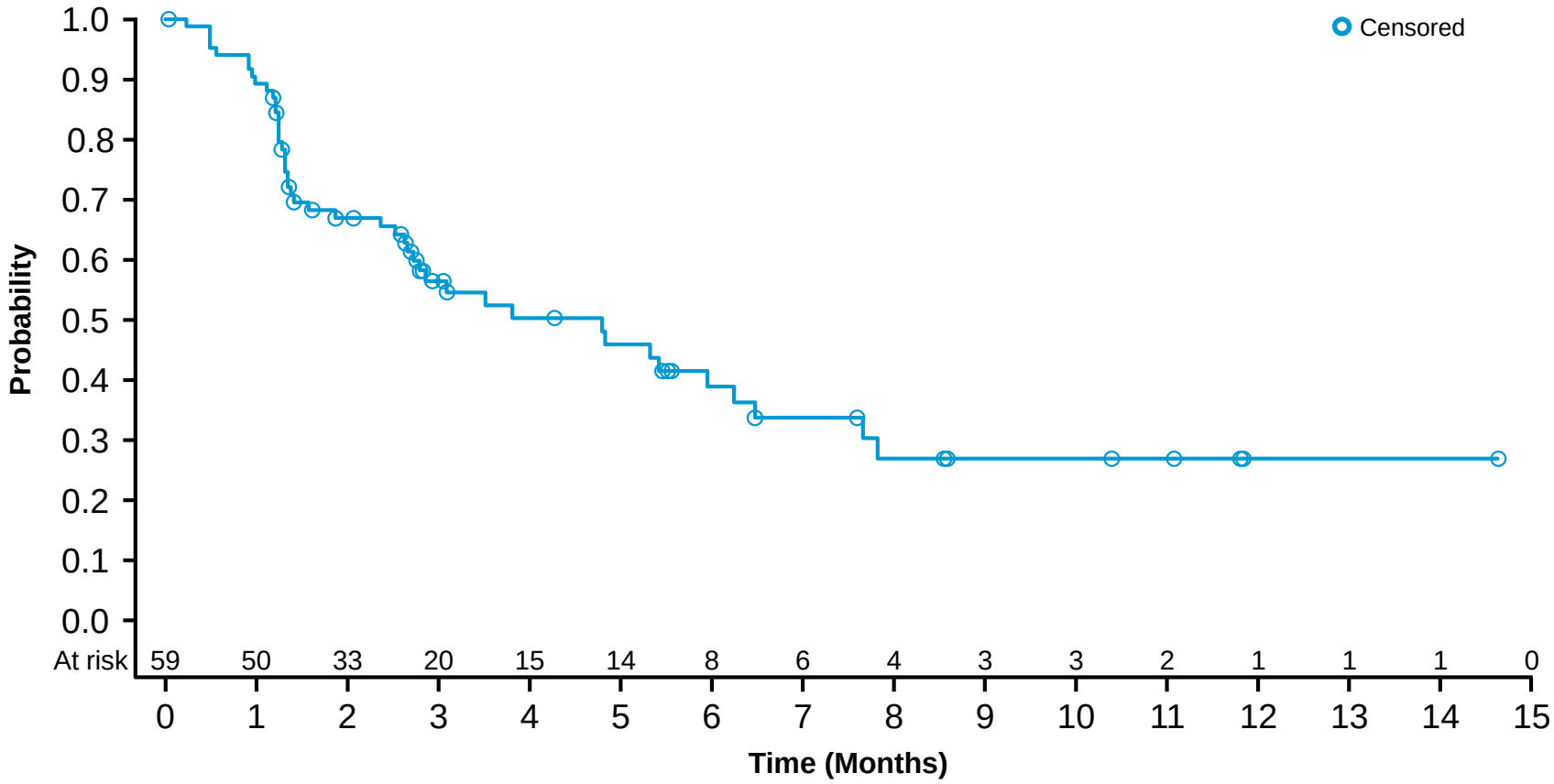
Median duration of response: 5.3 months



Data shown as of 1 Nov 2017.

NHL Progression-Free Survival: Efficacy Analysis Set Part 1 (Dose Escalation)

Median progression-free survival: 4.8 months



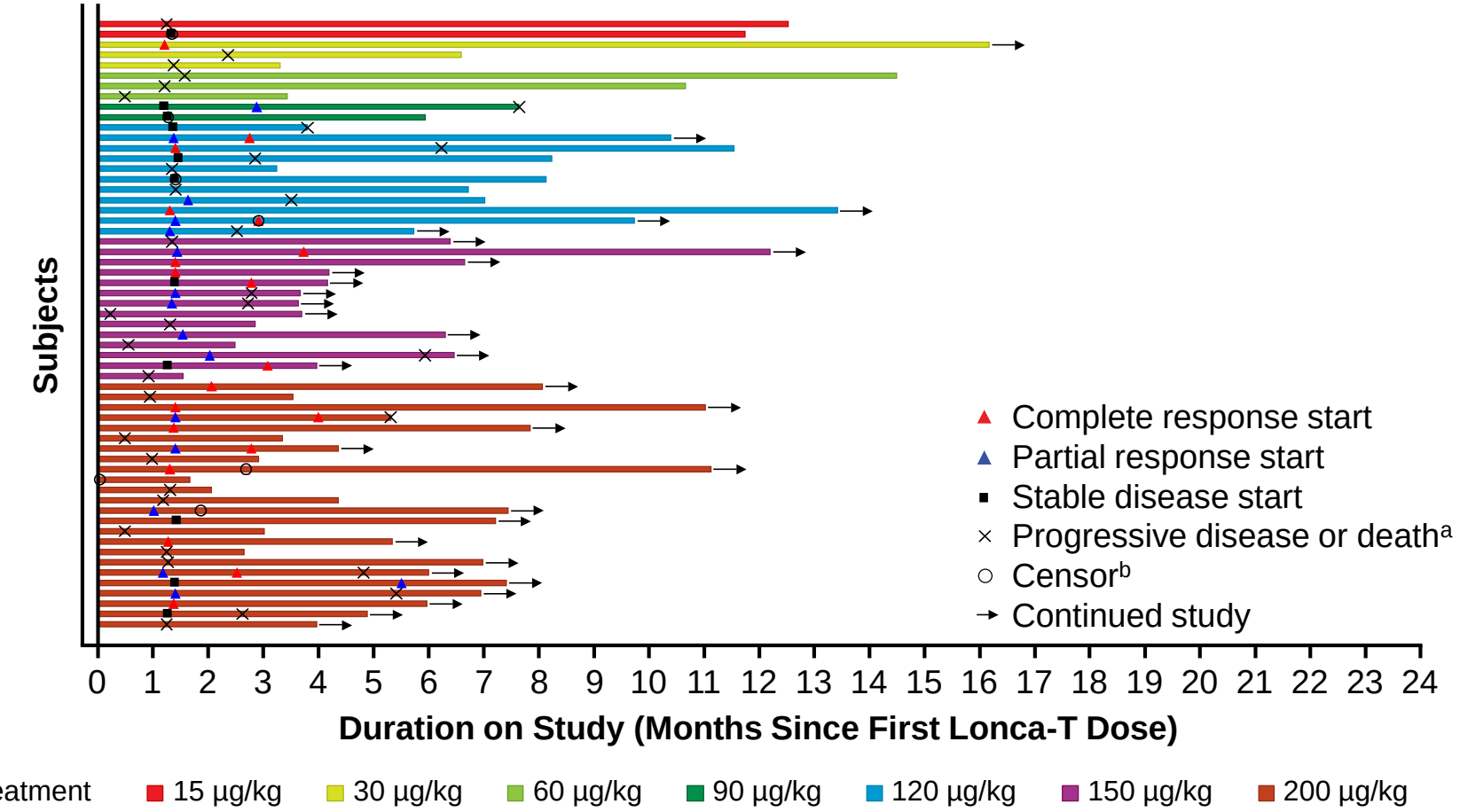
Data shown as of 1 Nov 2017.

DLBCL Response Rates: Efficacy Analysis Set Part 1 (Dose Escalation)

Response, n (%)	Total (N=59)	Dose ≥120 µg/kg (n=49)
Complete response (CR)	19 (32.2)	18 (36.7)
Partial response (PR)	10 (16.9)	9 (18.4)
Stable disease	7 (11.9)	5 (10.2)
Progressive disease	23 (39.0)	17 (34.7)
Overall response rate (CR + PR)	**29 (49.1)**	**27 (55.1)**

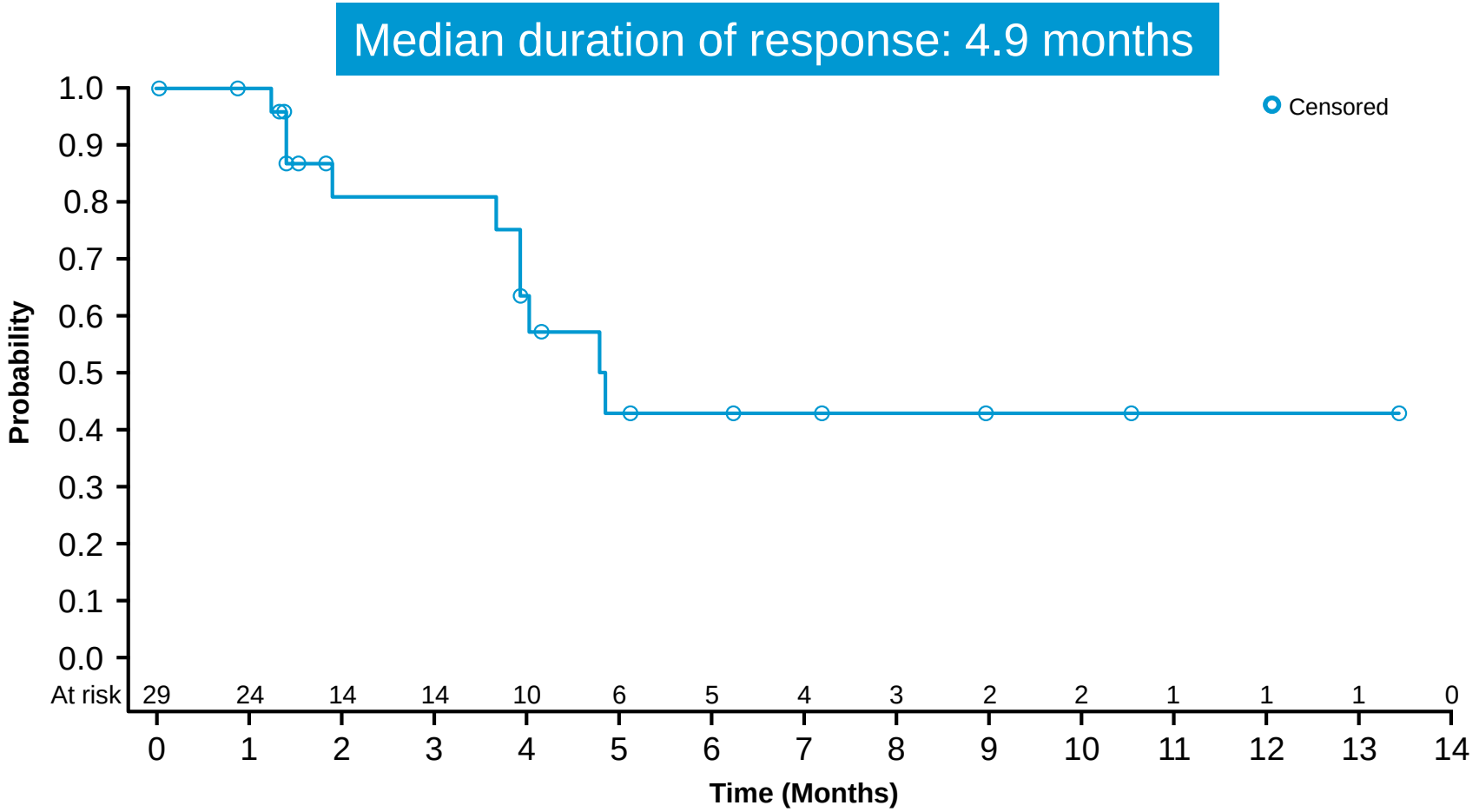
Data shown as of 1 Nov 2017.

Diffuse Large B-Cell Lymphoma (DLBCL) Swimmer Plot: Efficacy Analysis Set Part 1 (Dose Escalation)



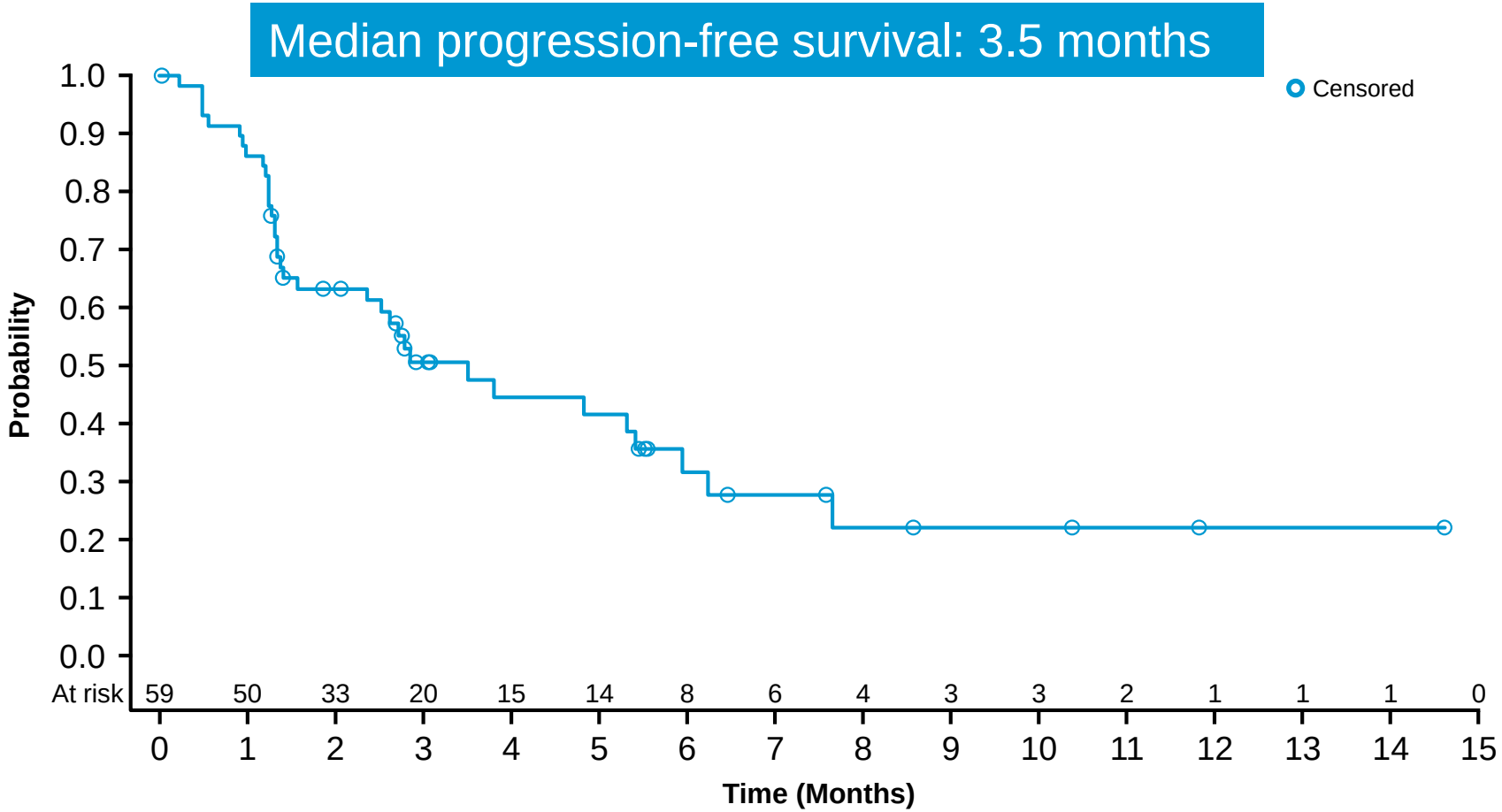
Data shown as of 1 Nov 2017. Each bar represents 1 patient. [a]Study drug was discontinued at "x" for progression but patients continued to be followed.
[b]Exclude censors by cutoff date.

DLBCL Duration of Response: Efficacy Analysis Set Part 1 (Dose Escalation)



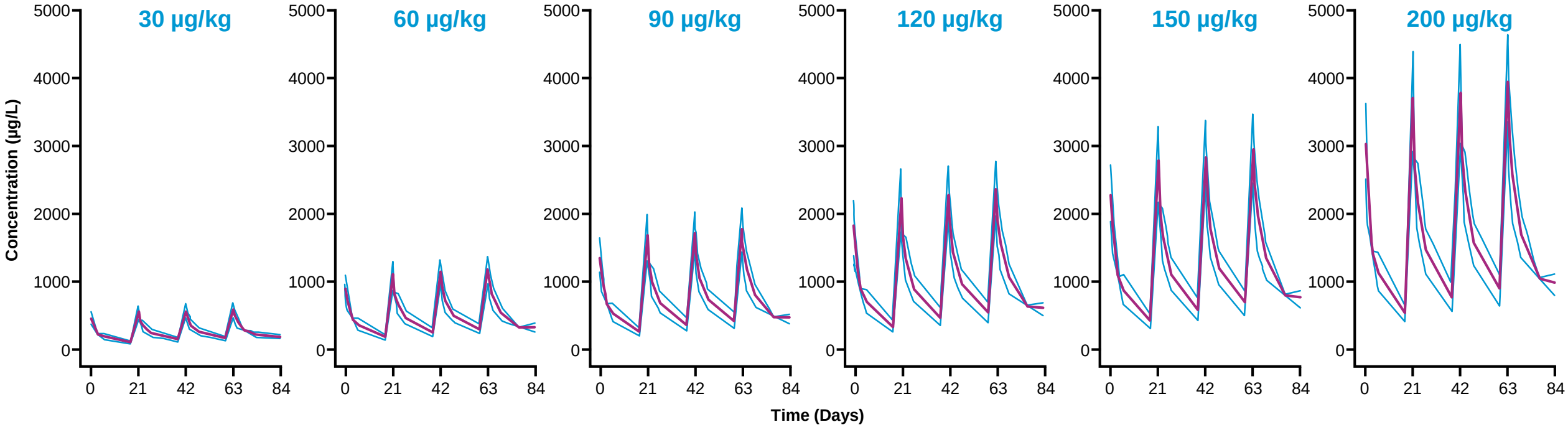
Data shown as of 1 Nov 2017.

DLBCL Progression-Free Survival: Efficacy Analysis Set Part 1 (Dose Escalation)



Data shown as of 1 Nov 2017.

Lonca-T PBD-Conjugated Antibody Predicted Concentration vs Time in Serum



Exposure to PBD-conjugated antibody increases with dose
Total antibody profiles are comparable (not shown)

Variability increases proportionately with exposure

Modest accumulation seen for 90, 120, and 200 µg/kg with multiple doses

Concentrations of unconjugated warhead predominantly below limit of quantification for all patients and doses

Data shown as median (bold red line) and 10th, 90th percentile (blue lines) of population predicted values.
PBD, pyrrolobenzodiazepine.

Relationship Between Lonca-T Exposure and Safety and Efficacy

Presented in Poster #2543 (O'Connor *et al.*)

Elucidating Exposure-Response (Safety and Efficacy) of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Containing Antibody Drug Conjugate, for Recommended Phase 2 Dose Determination in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma

Date:	**Sunday, December 10, 2017**
Presentation time:	**6:00 PM – 8:00 PM**
Session name:	**605. Molecular Pharmacology, Drug Resistance—Lymphoid and Other Diseases: Poster II**
Location:	**Georgia World Congress Center, Bldg A, Lvl 1, Hall A2**

Summary

- In this first-in-human study, Lonca-T has demonstrated encouraging single-agent anti-tumor activity and manageable toxicity in patients with recurrent B-cell NHL who had failed or were intolerant to established therapies.
- One dose-limiting toxicity (worsening thrombocytopenia at 200 µg/kg) has been reported; the maximum-tolerated dose was not reached during dose escalation
- Major toxicities are persistent grade 1-2 toxicity; (fluid 3rd spacing, rash, fatigue)
- At doses ≥120 µg/kg in part 1, the overall response rate was:
  - 60.3% in the total relapsed/refractory (R/R) B-cell NHL patient population (comprising 35.3% complete response [CR] and 25.0% partial response [PR])
  - 55.1% in patients with R/R DLBCL (comprising 36.7% CR and 18.4% PR)
- Expansion cohorts using doses of 120 µg/kg once every 3 weeks (q3w) and 150 µg/kg q3w are currently enrolling

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  - all study co-investigators and research coordinators

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