Phase 1 Study of ADCT-301 (Camidanlumab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory Classical Hodgkin Lymphoma

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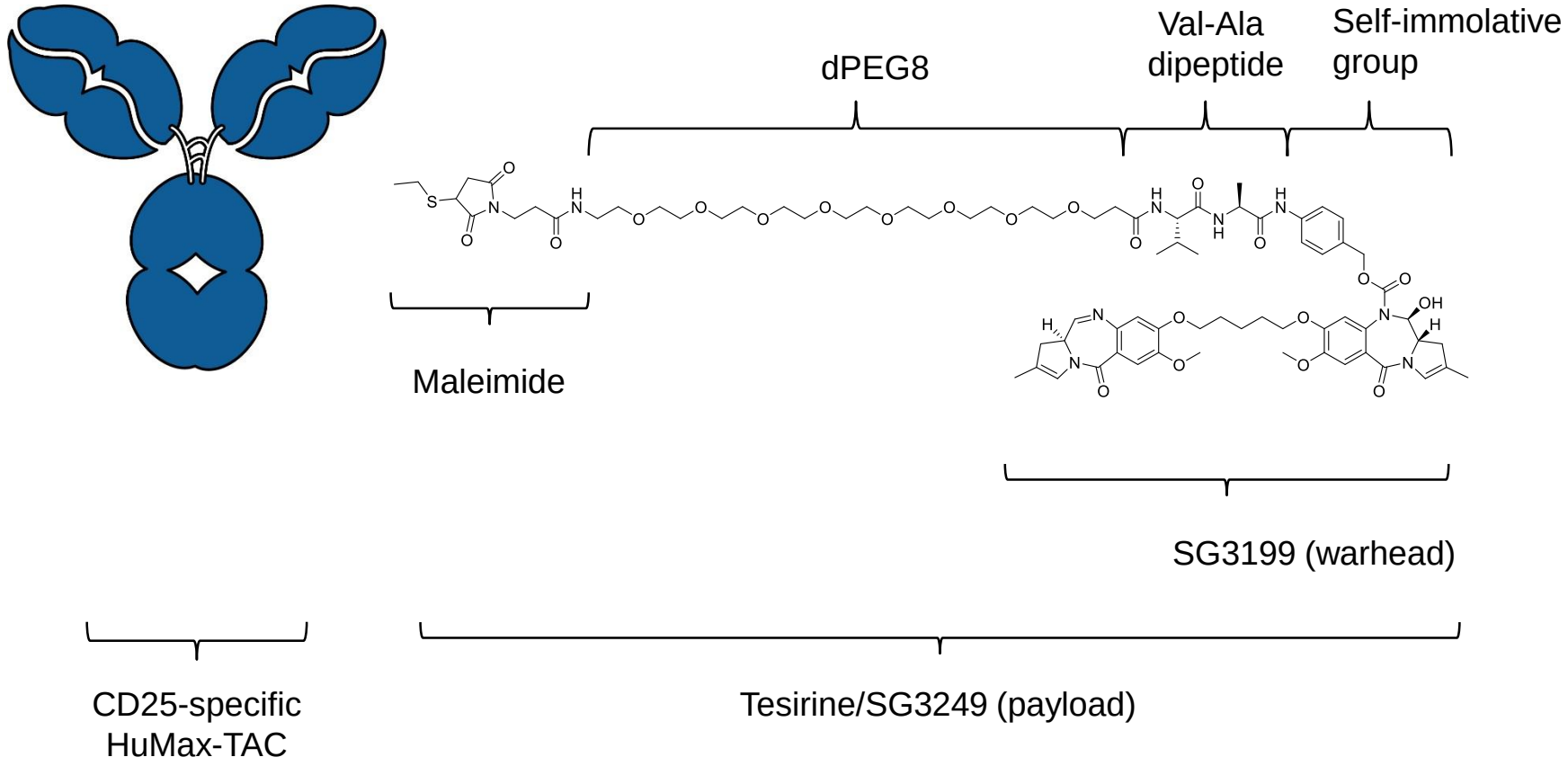
Structure and Components of ADCT-301 (camidanlumab tesirine)



Drug-antibody ratio = 2.0 (± 0.3)

Camidanlumab Tesirine Mechanism of Action

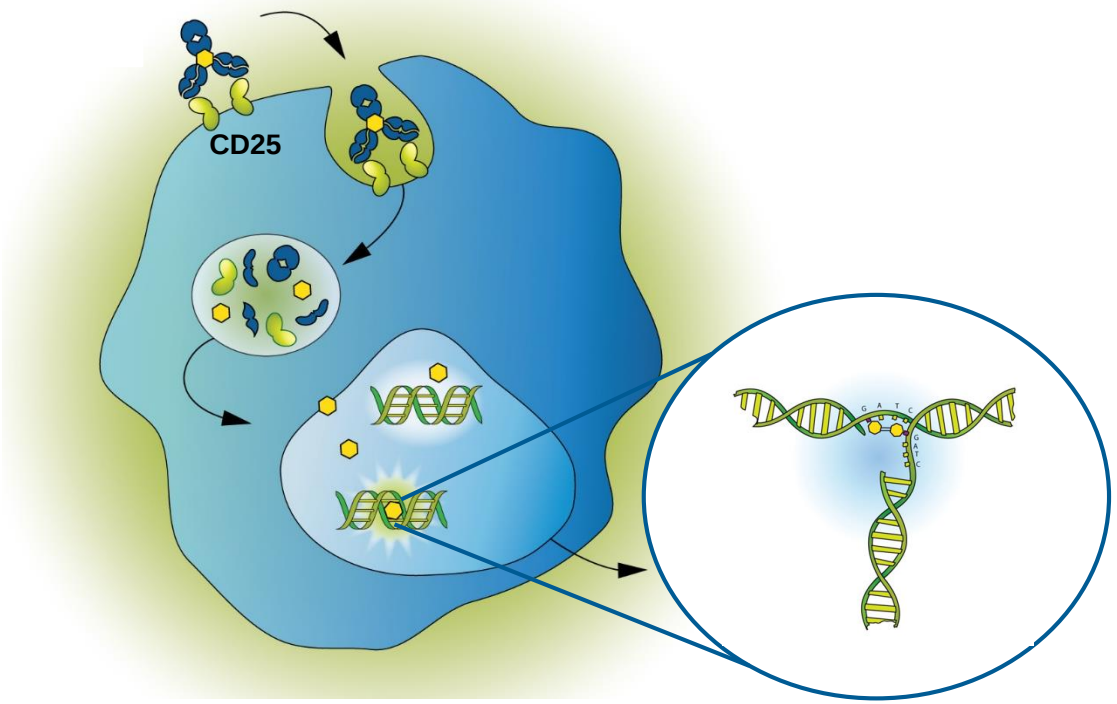
Molecular mode of action

1. **Camidanlumab tesirine binds to the CD25 antigen on the tumor cell surface**
2. **ADC internalization, linker cleavage and PBD release**
3. **Cytotoxic DNA cross-link formation**
   a) Free PBD dimers bind sequence-selectively in the minor groove of cell DNA
   b) PBD dimers form potent cytotoxic DNA cross-links
4. **Stalled DNA replication fork**

   Cross-links stall the DNA replication fork, blocking cell division and causing cancer cell death

Immunological rationale

Targeting of CD25+ Tregs may increase the Teff:Treg ratio, thus promoting immunological tumor eradication[3]



ADC, antibody drug conjugate; PBD, pyrrolobenzodiazepine; Teff, effector T cell; Treg, regulatory T cell

1. Hartley JA. *Expert Opin Investig Drugs.* 2011;20:733–744; 2. Flynn MJ, *et al. Mol Cancer Ther.* 2016;15:2709–21; 3 Sasidharan NV, *et al. Immunol Cell Biol.* 2018;96:21–33.

Study Design

Histologically confirmed relapsed/refractory NHL* or HL
*Including Stage ≥Ib Cutaneous T-cell Lymphoma

2-part study:
- *Part 1*: Dose escalation: continual reassessment method;
- *Part 2*: Dose expansion(s)

1-hour intravenous infusion (3–300 µg/kg); Day 1 every 3 weeks

PRIMARY OBJECTIVE: Safety and tolerability and determine the MTD / RDE of camidanlumab tesirine

SECONDARY OBJECTIVES: Pharmacokinetic profile of camidanlumab tesirine
Clinical activity of camidanlumab tesirine as measured by ORR, DoR, PFS, and OS

For **HL population: MTD was not reached; 2 RDEs** for Part 2 were identified as **30 and 45 µg/kg Q3W**
For **NHL population**: Data were presented at this meeting in **Poster 1658[1] on Saturday, December 1**

DoR, duration of response; HL, Hodgkin lymphoma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RDE, recommended dose for expansion

1. Collins GP, *et al.* 60th American Society of Hematology Annual Meeting & Exposition, December 1–4, 2018, San Diego, CA, USA. **Poster 1658**

Inclusion and Exclusion Criteria

Key inclusion criteria

- Age 18 years or older
- Pathologically confirmed relapsed or refractory lymphoma
- Failed, or intolerant to, any established therapy known to provide clinical benefit at current state of disease
- Prior treatment with brentuximab vedotin and checkpoint inhibitor*
- Measurable disease, as defined by the 2014 Lugano Criteria
- Eastern Cooperative Oncology Group performance status 0 to 2

Key exclusion criteria

- Active graft-versus-host disease
- History of symptomatic autoimmune disease
- History of neuropathy considered of autoimmune origin; other central nervous system autoimmune disease.
- History of recent infection considered to be caused by: HSV1, HSV2, VZV, EBV, Cytomegalovirus, measles, Influenza A, Zika virus, Chikungunya virus, m. pneumonia, C. jejuni, or enterovirus D68
- Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment

HIV, human immunodeficiency virus; HSV 1/2, herpes simplex virus type 1/2; VZV; varicella zoster virus; EBV, Epstein Barr virus

* Introduced with Amendment 7 (Jan 2018)

HL population: Baseline Characteristics

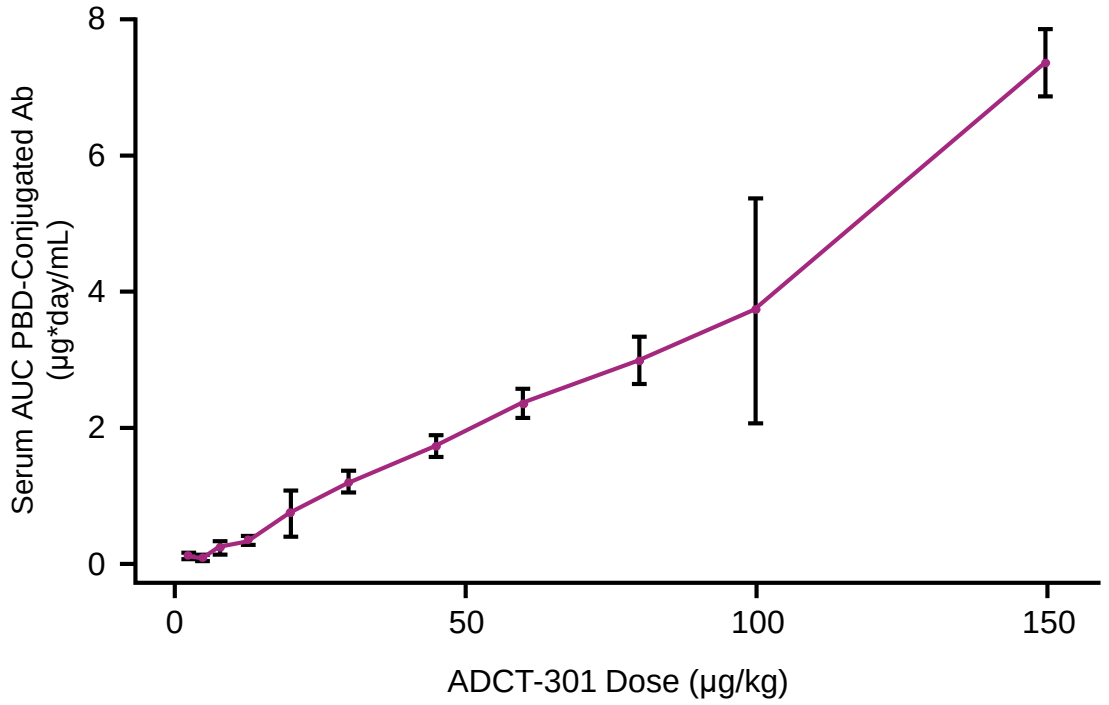
Patient characteristic	Total (N=67)
Sex, n (%)	
Male	40 (59.7)
Female	27 (40.3)
Race, n (%)	
White	55 (82.1)
Black or African American	4 (6.0)
Asian	3 (4.5)
Other	5 (7.5)
Age, years, median (min, max)	38.0 (19, 80)
Number of previous systemic therapies, median (min, max)	**5.0 (2, 15)**
Prior brentuximab vedotin (BV), n (%)	65 (97.0)
Prior checkpoint inhibitor (CHPi), n (%)	47 (70.1)
Prior BV and CHPi, n (%)	47 (70.1)
Prior stem cell transplantation, n (%)	40 (59.7)
• Allogeneic stem cell transplantation, n (%)	7 (10.4)

Data shown as of 16 Oct 2018

Pharmacokinetic Analysis Data

- **Exposure in serum increases with dose**
- **Half-life in patients with lymphoma is reasonably long[a]**
  - PBD-conjugated antibody – 9.1 days (4.3, 25 days)
  - Total antibody – 12.0 days (4.4, 62 days)
- **Modest to moderate drug accumulation expected with multiple (Q3W) doses**
  - At 45 µg/kg dose (for n=29 patients),
    - ~1.4x (CV=22%) for PBD-conjugated Ab
    - ~2.1x (CV=63%) for total Ab
- **PBD (SG3199) exposure predominantly below quantifiable limits; no accumulation is evident**
- **No significant anti-drug antibody formation apparent** (n=56 patients evaluated)

Camidanlumab tesirine mean (SE) AUC versus dose



[a]Presented as median (min, max)
Ab, antibody; AUC, area under the curve; CV, coefficient of variation; Q3W, every 3 weeks; SE, standard error of the mean

Data shown as of 16 Oct 2018

HL population: Most Common All Grades TEAEs *(≥20% Patients)* (Safety Analysis Set)

TEAEs, n (%)	Dose (µg/kg)					
	≤20 (n=3)	30 (n=10)	45 (n=37)	60 (n=12)	≥80 (n=5)	Total (N=67)
Patients with any grade TEAE	3 (100)	10 (100)	37 (100)	12 (100)	5 (100)	67 (100)
Fatigue	1 (33.3)	5 (50.0)	16 (43.2)	6 (50.0)	2 (40.0)	30 (44.8)
Maculopapular rash	1 (33.3)	5 (50.0)	14 (37.8)	4 (33.3)	2 (40.0)	26 (38.8)
Pyrexia	1 (33.3)	2 (20.0)	12 (32.4)	4 (33.3)	1 (20.0)	20 (29.9)
Gamma-glutamyltransferase increased	2 (66.6)	1 (10.0)	7 (18.9)	5 (41.7)	4 (80.0)	19 (28.4)
Alanine aminotransferase increased	1 (33.3)	0 (0)	9 (24.3)	5 (41.7)	3 (60.0)	18 (26.9)
Aspartate aminotransferase increased	0 (0)	0 (0)	7 (18.9)	5 (41.7)	4 (80.0)	16 (23.9)
Nausea	1 (33.3)	0 (0)	10 (27.0)	0 (0)	4 (80.0)	15 (22.4)
Cough	1 (33.3)	1 (10.0)	9 (24.3)	2 (16.7)	1 (20.0)	14 (20.9)
Dyspnea	1 (33.3)	0 (0)	8 (21.6)	3 (25.0)	2 (40.0)	14 (20.9)
Rash	0 (0)	4 (40.0)	8 (21.6)	2 (16.7)	0 (0)	14 (20.9)

Grey shading indicates liver test abnormalities; blue indicates other toxicities

HL, Hodgkin lymphoma; TEAE, treatment-emergent adverse event

Data shown as of 16 Oct 2018

HL population: Most Common TEAEs ≥Grade 3 (≥5% *Patients*) (Safety Analysis Set)

TEAEs ≥Grade 3, n (%)	Dose (µg/kg)					
	≤20 (n=3)	30 (n=10)	45 (n=37)	60 (n=12)	≥80 (n=5)	Total (N=67)
Patients with grade ≥3 TEAE	2 (66.6)	6 (60.0)	24 (64.9)	7 (58.3)	5 (100)	44 (65.7)
Maculopapular rash	1 (33.3)	2 (20.0)	7 (18.9)	1 (8.3)	1 (20.0)	12 (17.9)
Gamma-glutamyltransferase increased	1 (33.3)	1 (10.0)	3 (8.1)	3 (25.0)	4 (80.0)	12 (17.9)
Alanine aminotransferase increased	0 (0)	0 (0)	3 (8.1)	2 (16.7)	2 (40.0)	7 (10.4)
Aspartate aminotransferase increased	0 (0)	0 (0)	1 (2.7)	2 (16.7)	2 (100)	5 (7.5)
Anemia	1 (33.3)	1 (10.0)	3 (8.1)	0 (0)	0 (0)	5 (7.5)
Guillain–Barré syndrome/Radiculopathy	0 (0)	1 (10.0)	3 (8.1)	1 (8.3)	0 (0)	5 (7.5)
Increased lipase	0 (0)	1 (10.0)	3 (8.1)	0 (0)	0 (0)	4 (6.0)

Grey shading indicates liver test abnormalities; red shading indicates hematologic abnormalities; blue indicates other toxicities

HL, Hodgkin lymphoma; TEAE, treatment-emergent adverse event

Data shown as of 16 Oct 2018

HL population: Selected Toxicities Summary All Grades (Safety Analysis Set),

Potentially PBD-related toxicities (SMQ)	Dose (µg/kg)					
	≤20 (n=3)	30 (n=10)	45 (n=37)	60 (n=12)	≥80 (n=5)	Total (N=67)
Edema or effusion	1 (33.3)	3 (30.0)	10 (27.0)	2 (16.7)	1 (20.0)	17 (25.4)
Skin related	1 (33.3)	9 (90)	25 (67.6)	10 (83.3)	4 (80.0)	49 (73.1)
Liver function test	3 (100)	1 (10.0)	13 (35.1)	8 (66.7)	4 (80.0)	29 (43.3)
Selected autoimmune toxicities						
Guillain–Barré syndrome/Radiculopathy	0 (0)	1 (10.0)	3 (8.1)	1 (8.3)	0 (0)	5 (7.5)
Colitis	1 (33.3)	0 (0)	1 (2.7)	0 (0)	0 (0)	2 (3.0)
Hypothyroidism	0 (0)	0 (0)	2 (5.4)	1 (8.3)	1 (20.0)	4 (6.0)
Hyperthyroidism	0 (0)	0 (0)	2 (5.4)	0 (0)	0 (0)	2 (3.0)
Thyroiditis	0 (0)	0 (0)	0 (0)	0 (0)	1 (20.0)	1 (1.5)

TEAEs leading to treatment discontinuation occurred in 19/67 (28.4%) patients

PBD, pyrrolobenzodiazepine; SMQ, standardised MedDRA query; TEAEs, treatment-emergent adverse events

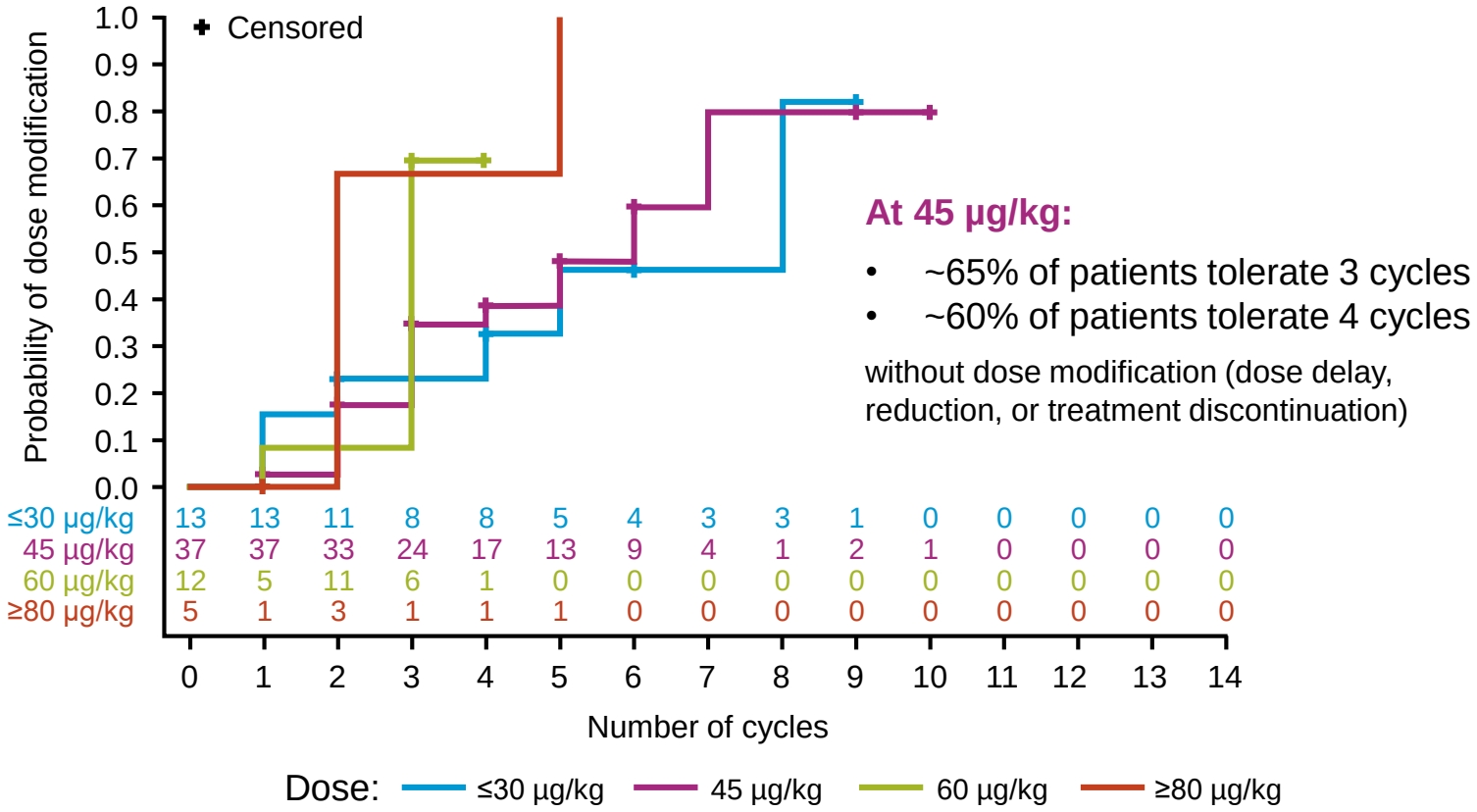
Data shown as of 16 Oct 2018

HL population: Drug Exposure

Camidanlumab tesirine exposure

Median (min, max) no. of cycles received	
30 µg/kg	4.5 (1, 9)
45 µg/kg	4.0 (1, 10)
60 µg/kg	2.5 (2, 8)
80 µg/kg	4.0 (1, 5)
All dose levels	**3 (1, 15)**

Time to first AE leading to dose modification



At 45 µg/kg:

- ~65% of patients tolerate 3 cycles
- ~60% of patients tolerate 4 cycles

without dose modification (dose delay, reduction, or treatment discontinuation)

Data shown as of 16 Oct 2018

HL population: Response Rates (Efficacy Analysis Set)

Response*, n (%)	Dose (µg/kg)					
	≤20 (n=3)	30 (n=10)	45 (n=37)	60 (n=12)	≥80 (n=5)	Total (N=67)
Overall response rate (CR+PR)	**1 (33.3)**	**5 (50.0)**	**32 (86.5)**	**7 (58.3)**	**4 (80.0)**	**49 (73.1)**
Complete response (CR)	0 (0)	4 (40.0)	16 (43.2)	5 (41.7)	2 (40.0)	27 (40.3)
Partial response (PR)	1 (33.3)	1 (10.0)	16 (43.2)	2 (16.7)	2 (40.0)	22 (32.8)
Stable disease	1 (33.3)	3 (30.0)	0 (0)	1 (8.3)	0 (0)	5 (7.5)
Progressive disease	0 (0)	1 (10.0)	5 (13.5)	4 (33.3)	0 (0)	10 (14.9)
Not evaluable	1 (33.3)	1 (10.0)	0 (0)	0 (0)	1 (20.0)	3 (4.5)

***Best visit response based on 2014 Lugano Criteria

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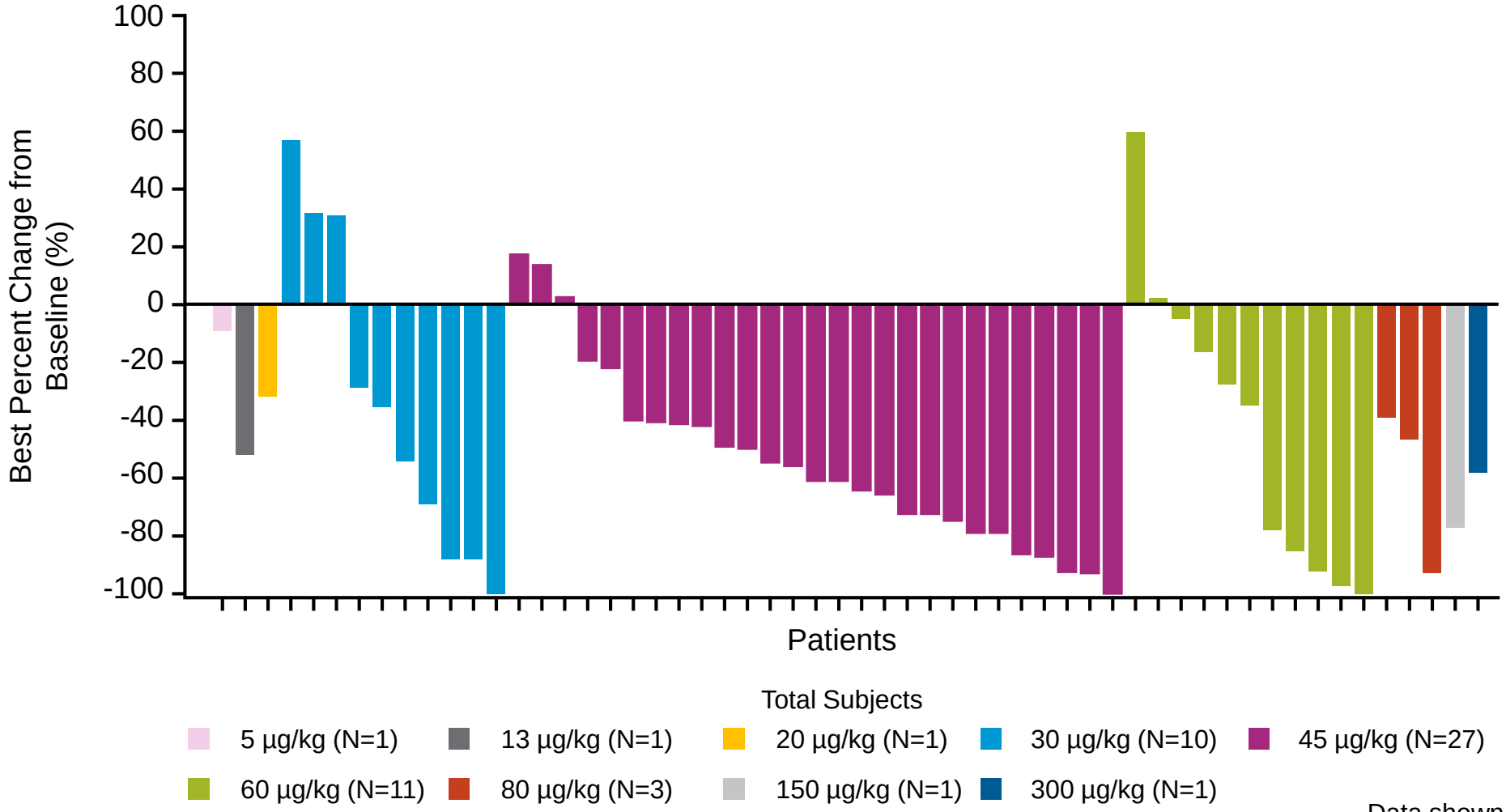
HL population: Waterfall Plot Showing Responses for Individual Patients (Efficacy Analysis Set)



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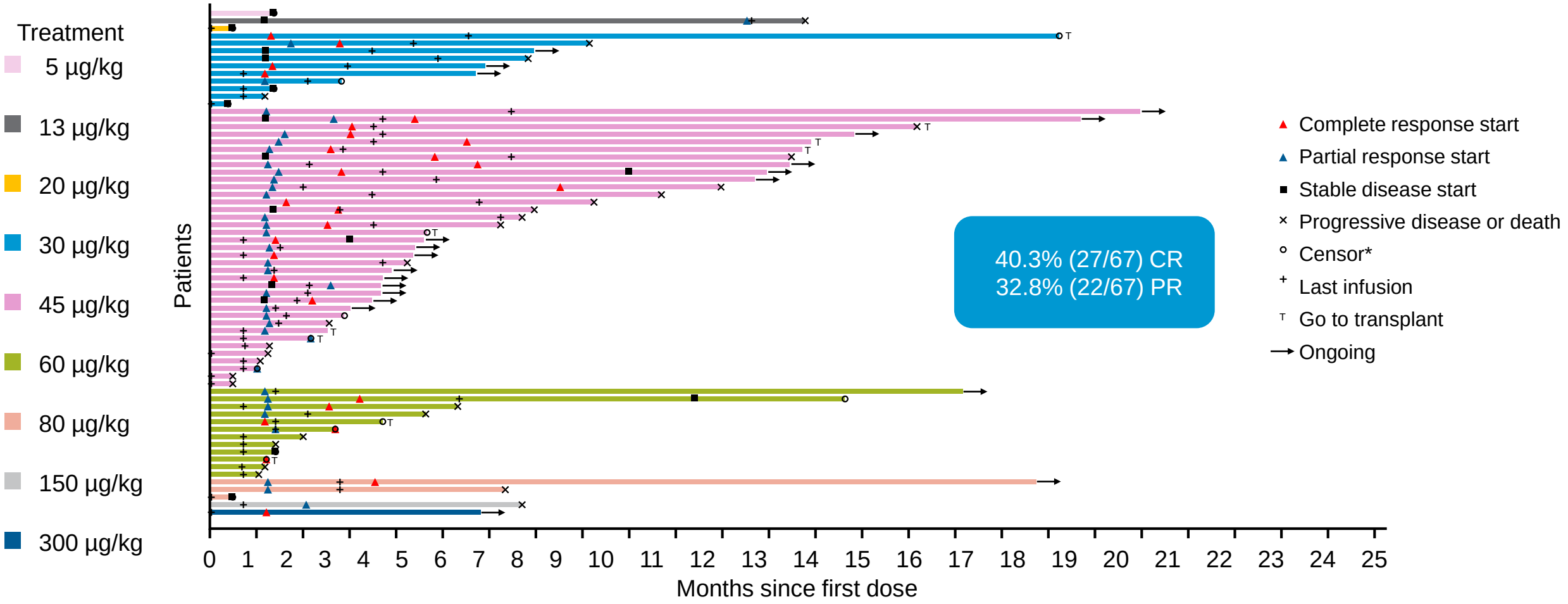
HL population: Swimmer Plot Showing Responses for Individual Patients (Efficacy Analysis Set)



*Patients who discontinue study due to reasons other than progression or who go onto a different anticancer treatment

Data shown as of 16 Oct 2018

Overall Response Rate by Prior Treatment (Efficacy Analysis Set), 45 µg/kg and All Doses Groups

Prior Treatments	45 µg/kg dose (n=37)	All doses (n=67)
Brentuximab vedotin	ORR 86.5% (32/37 patients)	ORR 73.8% (48/65 patients)
Brentuximab vedotin Checkpoint Inhibitor	ORR 88.5% (23/26 patients)	ORR 72.3% (34/47 patients)
Stem Cell Transplant	ORR 88.9% (16/18 patients)	ORR 67.5% (27/40 patients)
Brentuximab vedotin Checkpoint Inhibitor Stem Cell Transplant	ORR 92.9% (13/14 patients)	ORR 67.9% (19/28 patients)

BV, brentuximab vedotin; CHPi, checkpoint inhibitor; SCT, stem cell transplantation

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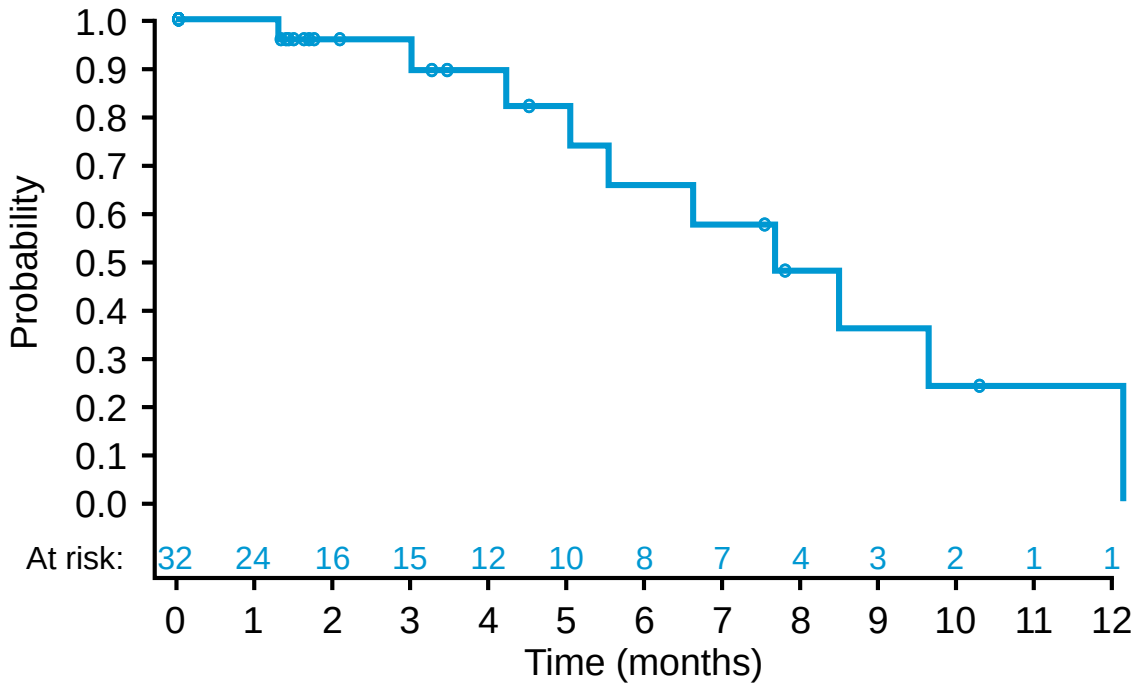
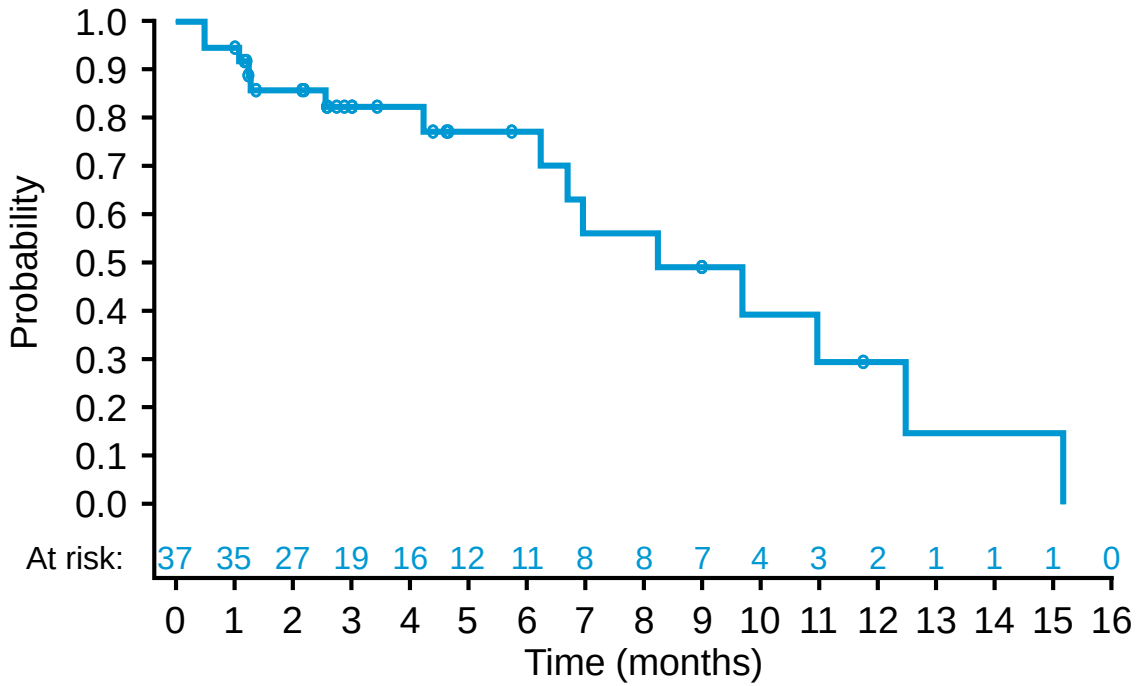
HL population, 45 µg/kg dose group: Duration of Response and Progression-free Survival

Median duration of response: 7.69 months



Median progression-free survival: 8.25 months



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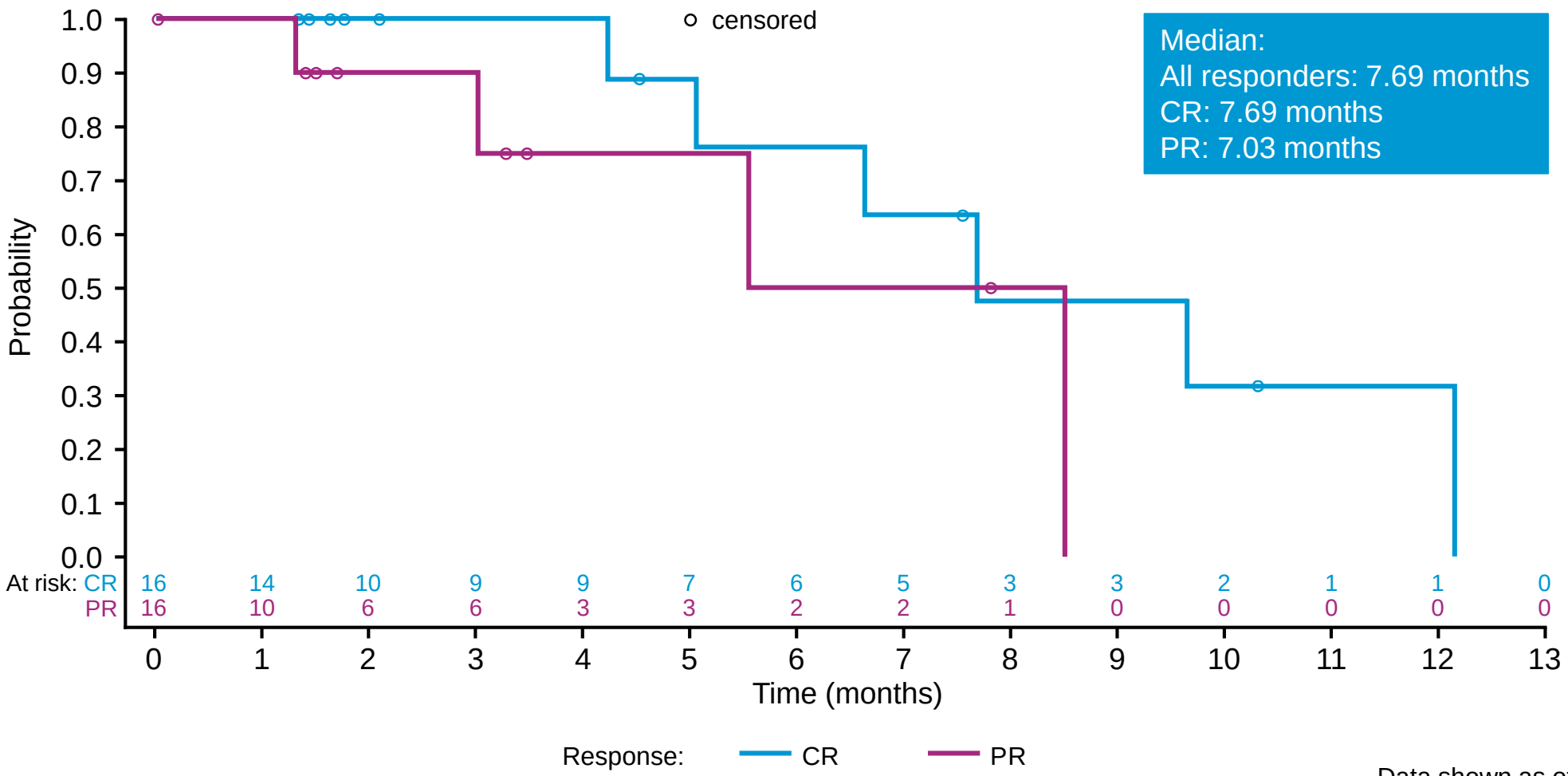
Duration of Response by PR/CR – 45 µg/kg

HL patients



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Conclusions

- **In patients with R/R HL, therapy with camidanlumab tesirine provided impressive OR and CR rates in a heavily pre-treated patient population**
  - This includes ORR 88.5% in patients in the 45 µg/kg dose group who had received prior BV and CHPi
- **Camidanlumab tesirine has shown encouraging activity in heavily pretreated patients with HL including the challenging subset of dual BV/CHPi failure**
- **Careful investigation for early identification of patients at high risk of autoimmune events, including Guillain–Barré Syndrome, are ongoing**
- **Enrolment of patients with HL is ongoing in Part 2 at doses 30 µg/kg and 45 µg/kg Q3W**
- **These data support further investigation in a planned Phase 2 study**

BV, brentuximab vedotin; CHPi, checkpoint inhibitor; CR, complete response; HL, Hodgkin lymphoma; ORR, overall response rate; R/R, relapsed/refractory

Data shown as of 16 Oct 2018

Acknowledgments

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http://clinicaltrials.gov/show/NCT02432235