Analysis of Clinical Determinants Driving Safety and Efficacy of Camidanlumab Tesirine (ADCT-301, Cami) in Relapsed/Refractory (R/R) Classical Hodgkin Lymphoma (cHL)

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Conflict of Interest Disclosures

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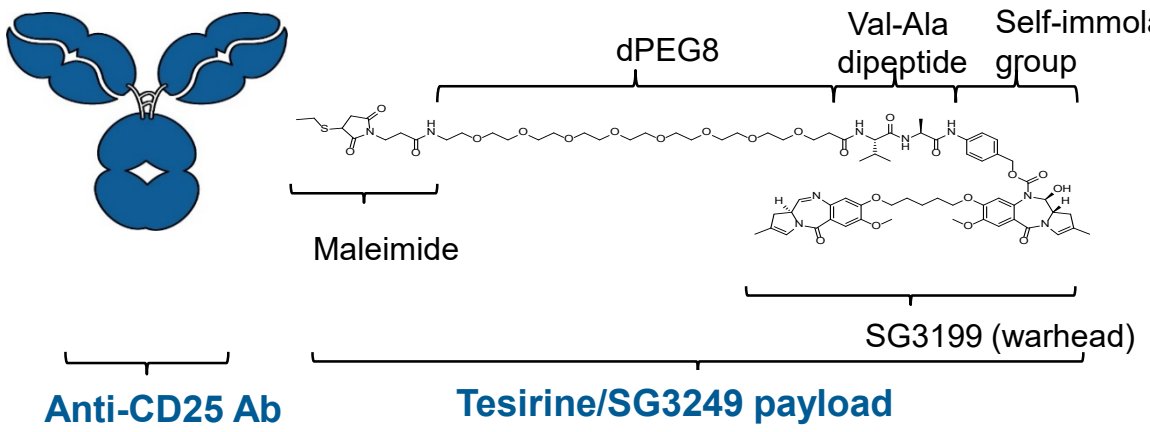
Introduction

Structure and components of camidanlumab tesirine (Cami)

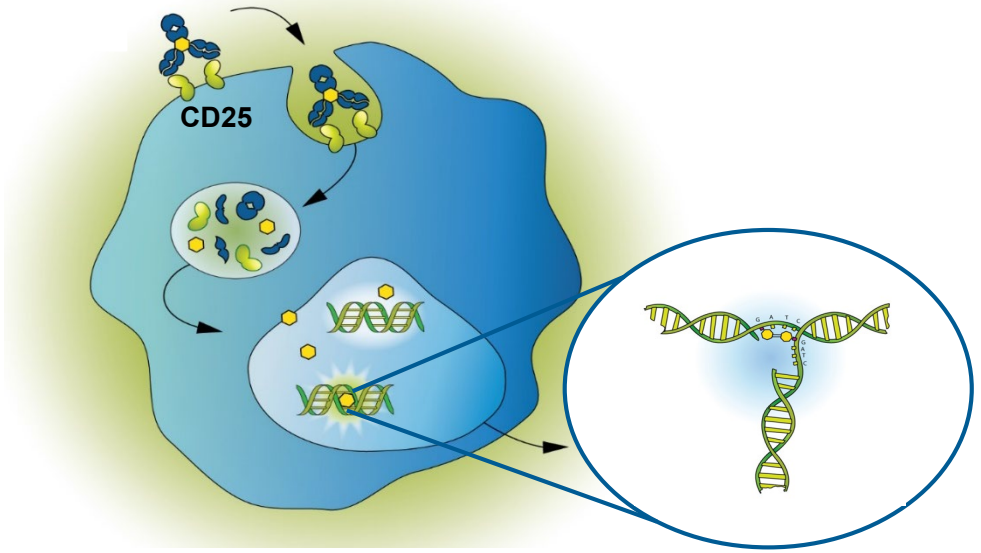


Immunological rationale

- Targeting of CD25+ Tregs may increase the Teff:Treg → immunologic tumour eradication[1]
- Anti-CD25 therapies synergise with PD-1 blockade to eradicate established tumours[2]

Mode of action

1. Cami binds to the CD25 antigen on the tumor cell surface
2. ADC internalisation, linker cleavage, and PBD release
3. Cytotoxic DNA cross-link formation
4. Stalled DNA replication fork causing cell death[3,4]



1. Sasidharan NV, et al. *Immunol Cell Biol*. 2018;96:21–33. 2. Arce Vargas F, et al. *Immunity*. 2017;46:577–86. 3. Hartley JA. *Expert Opin Investig Drugs*. 2011;20:733–44. 4. Flynn MJ, et al. *Mol Cancer Ther*. 2016;15:2709–21.

ADC, antibody drug conjugate; CD25, cluster of differentiation 25; PBD, pyrrolobenzodiazepine; Teff, effector T cell; Treg, regulatory T cell; Val-Ala, valine-alanine..

Phase 1 Study in Patients With Histologically Confirmed R/R NHL or cHL

STUDY DESIGN

- **Part 1:** Dose escalation; continual reassessment method
- **Part 2:** Dose expansion

1-hour intravenous infusion (3–300 µg/kg); once every 3 weeks (Q3W)

PRIMARY OBJECTIVE

Evaluate safety and tolerability and determine the MTD/RDE of camidanlumab tesirine

KEY INCLUSION CRITERIA FOR PATIENTS WITH cHL

- Male or female aged 18 years or older
- ECOG Performance Status 0 to 2
- Failed, or intolerant to, any established therapy known to provide clinical benefit at current state of disease
- Prior treatment with brentuximab vedotin and CHPi*

For cHL population: Enrollment complete. MTD not reached; 2 RDEs for Part 2, 30 and 45 µg/kg Q3W
For NHL population: Enrollment of patients with T-cell lymphoma continues in Part 2 at 80 µg/kg Q3W

*Introduced with Amendment 7 (Jan 2018). cHL, classical Hodgkin lymphoma; CHPi, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; RDE, recommended dose for expansion; R/R, relapsed/refractory.

Camidanlumab Tesirine in Classical Hodgkin Lymphoma

Patient Characteristics

Patient Baseline Characteristics All Lymphoma Types	Total (N=128*)
Sex, n (%)	
Female	52 (40.6)
Male	76 (59.4)
Race, n (%)	
White	104 (81.3)
Black or African American	14 (10.9)
Asian	4 (3.1)
Other	6 (4.7)
Age, years, median (min, max)	52 (19, 88)
Number of previous systemic therapies, median (min, max)	**5 (1, 15)**
Prior stem cell transplant, n (%)	57 (44.5)

Previous systemic therapies included prior SCT. *Safety analysis set.
DLBCL, diffuse large B-cell lymphoma; SCT, stem cell transplantation.

Patient Diagnosis at Baseline	N (%)
All patients*	128
Classical Hodgkin lymphoma	**77 (60.2)**
DLBCL	14 (10.9)
Mantle cell lymphoma	3 (2.3)
Burkitt lymphoma	1 (0.8)
Mediastinal (thymic) large B-cell lymphoma	1 (0.8)
Follicular lymphoma	1 (0.8)
Cutaneous T-cell lymphoma	13 (10.2)
Peripheral T-cell lymphoma	5 (3.9)
Adult T-cell leukemia/lymphoma	8 (6.3)
Angioimmunoblastic T-cell lymphoma	2 (1.6)
Other	3 (2.3)

Data shown as of Apr 14, 2019.

cHL Population:
Selected Toxicities Summary, All Grades

Potentially PBD-Related TEAEs (SMQ), n (%)*	30 µg/kg (n=20)	45 µg/kg (n=37)	Total (N=77)
Edema or effusion	5 (25.0)	10 (27.0)	19 (24.7)
Skin related	10 (50.0)	25 (67.6)	50 (64.9)
Liver function test	2 (10.0)	13 (35.1)	30 (39.0)
Selected autoimmune and neurologic toxicities, n (%)*			
Peripheral sensory neuropathy	1 (5.0)	5 (13.5)	7 (9.1)
Guillain–Barré syndrome/radiculopathy	1 (5.0)	3 (8.1)	5 (6.5)
Colitis	0	1 (2.7)	2 (2.6)
Hypothyroidism	0	2 (5.4)	4 (5.2)
Hyperthyroidism	0	2 (5.4)	2 (2.6)
Pneumonitis	0	0	1 (1.3)
Thyroiditis	0	0	1 (1.3)

One additional patient died of multiple cranial nerve palsy/polyneuropathy considered possibly related to camidanlumab tesirine, but this patient received two cycles of BV after camidanlumamb tesirine and prior to symptom deterioration

Safety analysis set. *Patients may have experienced one or more of these toxicities and may appear more than once in the table.
BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; PBD, pyrrolobenzodiazepine; TEAE, treatment-emergent adverse event.

cHL Population:
Most Common (≥5% Total) Grade ≥3 TEAEs

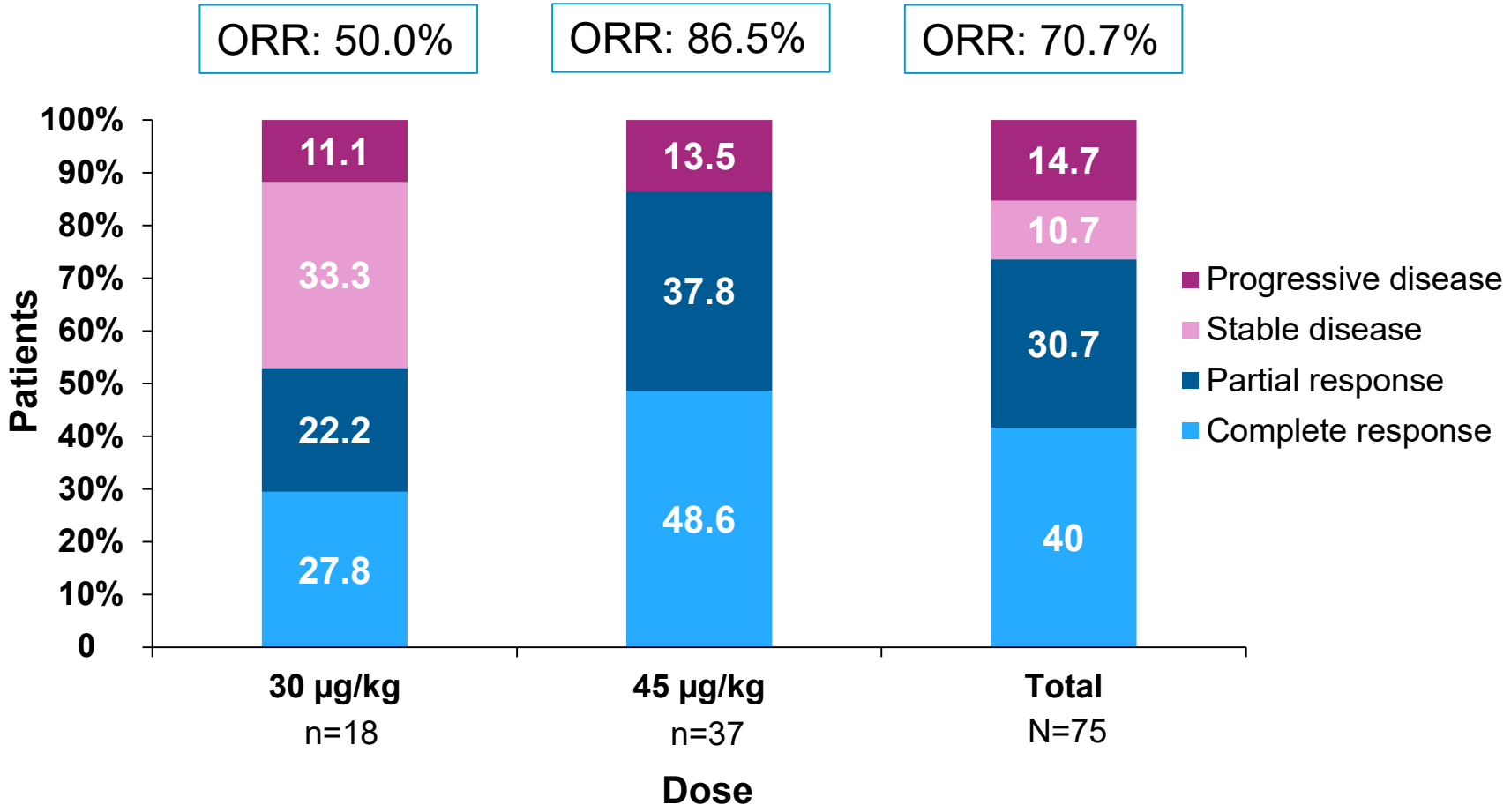
TEAEs, n (%)*	30 µg/kg (n=20)	45 µg/kg (n=37)	Total (N=77)
Patients with any Grade ≥3 TEAEs	12 (60.0)	25 (67.6)	51 (66.2)
GGT increased	2 (10.0)	3 (8.1)	13 (16.9)
Maculopapular rash	2 (10.0)	8 (21.6)	13 (16.9)
ALT increased	0 (0.0)	3 (8.1)	7 (9.1)
Anemia	2 (10.0)	3 (8.1)	6 (7.8)
AST increased	0 (0.0)	1 (2.7)	5 (6.5)
Guillain–Barré syndrome/radiculopathy	1 (5.0)	3 (8.1)	5 (6.5)
Lipase increased	1 (5.0)	3 (8.1)	4 (5.2)
Patients with any TEAEs leading to treatment discontinuation, (%)	20.0	27.0	26.0

*Only 1 Grade 5 event (death) due to unspecified cause was reported in the 45 µg/kg treatment group.

The most common all grade TEAEs (≥20%) in the total cHL population were fatigue, maculopapular rash, pyrexia, GGT increased, nausea, ALT increased, AST increased, and cough

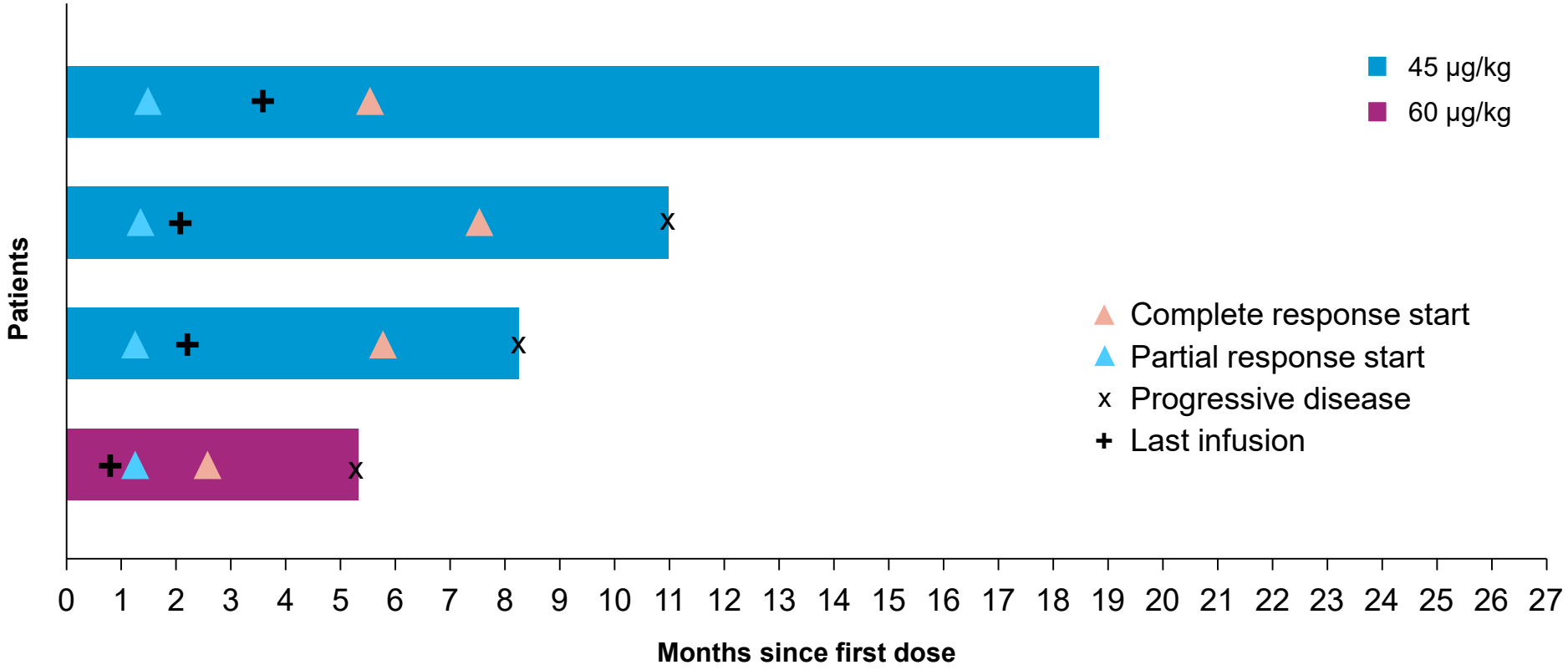
Data shown as of Apr 14, 2019. Safety analysis set. For each preferred term, patients are included only once.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; cHL, classical Hodgkin lymphoma; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

cHL Population:
Response Rates (Lugano Classification 2014)



Data shown as of Apr 14, 2019. Efficacy analysis set. Data are presented as % of patients that showed complete response, partial response, stable disease, or progressive disease in different groups. cHL, classical Hodgkin lymphoma; ORR, overall response rate.

cHL Population:
Late Responses Without Further Dosing



4 patients had improved responses to camidanlumab tesirine ≥6 weeks after their last infusion

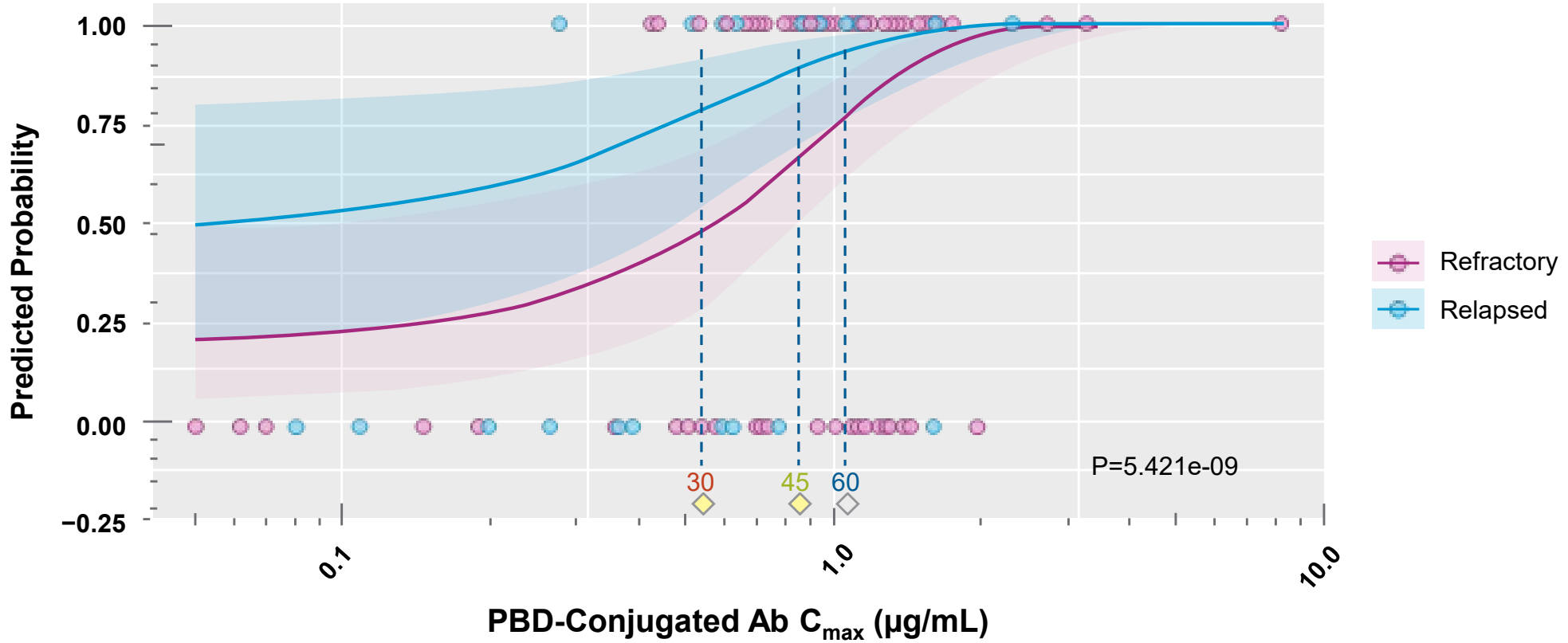
Data shown as of Apr 14, 2019. Efficacy analysis set. Each bar represents 1 patient in the study. *Only for censored patients who discontinued due to reasons other than progression or who go onto a different anticancer treatment.
cHL, classical Hodgkin lymphoma.

cHL Population:
Response Rates by Clinical Characteristics

Characteristic	Subgroups	45 µg/kg Cohort (N=37)	
		ORR n/N, %	CR n/N, %
Overall	–	32/37, 86.5	18/37, 48.6
Age group, years	≤55	25/28, 89.3	14/28, 50.0
	>55	7/9, 77.8	4/9, 44.4
Disease stage at study entry	I–II	12/14, 85.7	8/14, 57.1
	III	8/8, 100.0	5/8, 62.5
	IV	12/15, 80.0	5/15, 33.3
Number of prior therapies	<4	6/6, 100.0	3/6, 50.0
	≥4	26/31, 83.9	15/31, 48.4
Response to first-line systemic anticancer therapy	Refractory	11/13, 84.6	6/13, 46.2
	Relapsed	21/24, 87.5	12/24, 50.0
Response to most recent prior systemic anticancer therapy	Refractory	22/25, 88.0	11/25, 44.0
	Relapsed	8/10, 80.0	6/10, 60.0

Data shown as of Apr 14, 2019. Efficacy analysis set. Dark blue: Similar CR rate irrespective of variable. Purple: Trend for reduced CR rate in refractory patients compared with relapsed patients; confirmed by PK modeling (next slide).
cHL, classical Hodgkin lymphoma; CR, complete response; ORR, overall response rate; PK, pharmacokinetic.

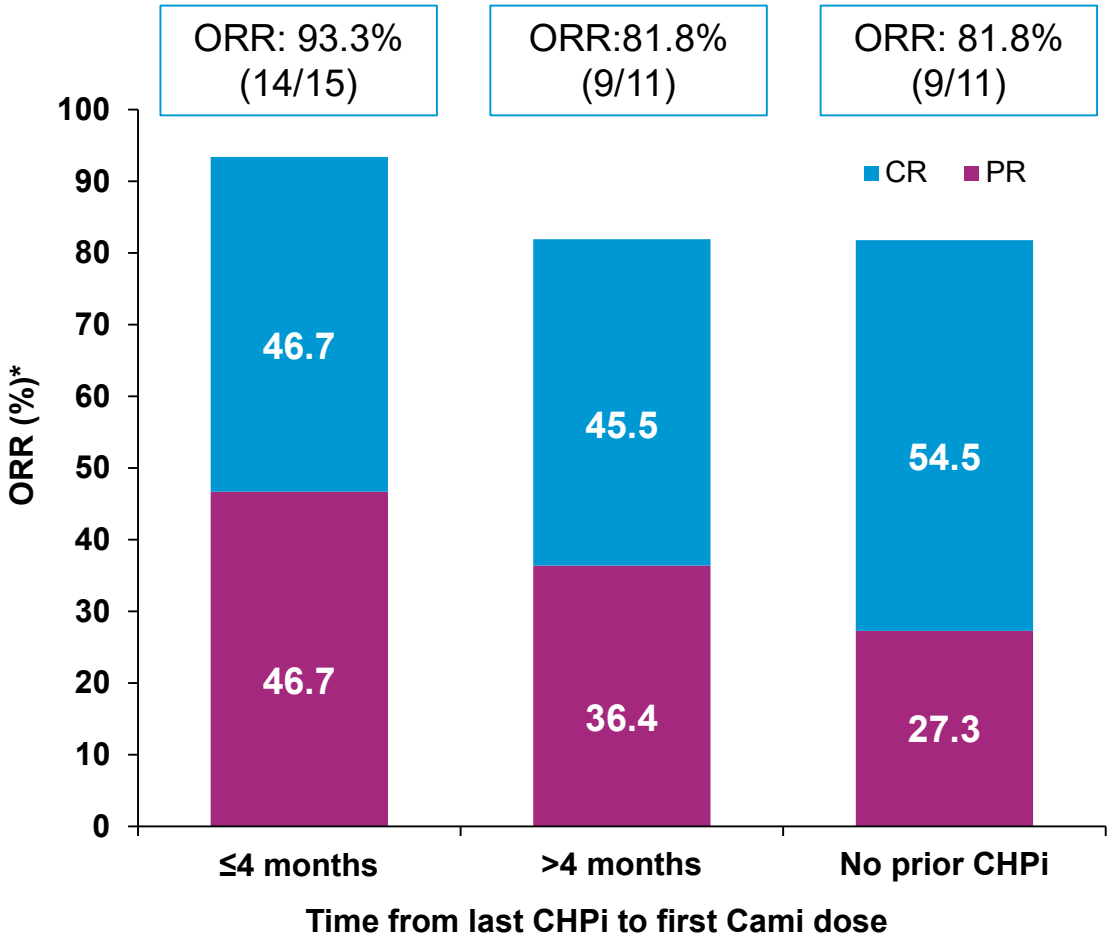
Probability of Objective Response vs C_{max} in Patients With cHL Receiving Camidanlumab Tesirine



- **Median exposures from 30 to 60 µg/kg increased and indicated a positive exposure-response relationship**
- **Mean predicted probabilities of response for typical patients were 0.87 for relapsed and 0.67 for refractory patients**

Graphics depict mean and 95% confidence intervals of predicted probabilities. Coloured numbers denote the dose (µg/kg) groups administered; yellow diamonds and vertical dotted lines denote the median respective exposures. P-value is overall significance of model with predictors compared with intercept alone. Ab, antibody; cHL, classical Hodgkin lymphoma; C_{max}, concentration maximum; PBD, pyrrolobenzodiazepine.

cHL Population:
Responses by Prior CHPi (45 µg/kg Cohort): Safety and Efficacy



Selected TEAE Groups, n (%)†	45 µg/kg Cohort (N=37)		
	≤4 Months (n=15)	>4 Months (n=11)	None (N=11)
Edema or effusion	5 (33.3)	2 (18.2)	3 (27.3)
Liver function test	6 (40.0)	4 (36.4)	3 (27.3)
Skin related	10 (66.7)	8 (72.7)	7 (63.6)
Autoimmune	5 (33.3)	4 (36.4)	2 (18.2)
Neurologic	4 (26.7)	3 (27.3)	3 (27.3)
Guillain–Barré syndrome/radiculopathy‡	1 (6.7)	1 (9.1)	1 (9.1)

Data shown as of Apr 14, 2019. For each common adverse event group and preferred term in table, patients are included only once at the maximum severity. *Efficacy analysis set. †Safety analysis set. ‡Two other events occurred at 30 and 60 µg/kg doses in the >4 months and none groups, respectively.
CHPi, checkpoint inhibitor; CR, complete response; ORR, overall response rate; PR, partial response; TEAE, treatment-emergent adverse event.

Conclusions

The recommended dose for Phase 2 in cHL (NCT02432235) has been determined as 45 µg/kg Q3W dosed for two cycles (optimal ORR), followed by 30 µg/kg Q3W (to improve tolerability while maintaining significant anticancer activity)

ORR to camidanlumab tesirine was high across all subgroups, suggesting **robust antitumour activity across the R/R cHL population**

Significant difference in relapsed (higher predicted probability of response) vs refractory to last line of therapy was seen in PK modeling

Reported cases of Guillain–Barré syndrome/radiculopathy did not appear related to prior CHPi

cHL, classical Hodgkin lymphoma; CHPi, checkpoint inhibitor; CR, complete response; ORR, overall response rate; PK, pharmacokinetic; Q3W, once every 3 weeks; R/R, relapsed/refractory.