AdvanTIG-101: A Phase 1b/2 Study of Ociperlimab (Anti-TIGIT) Plus Tislelizumab (Anti-PD-1) or Rituximab in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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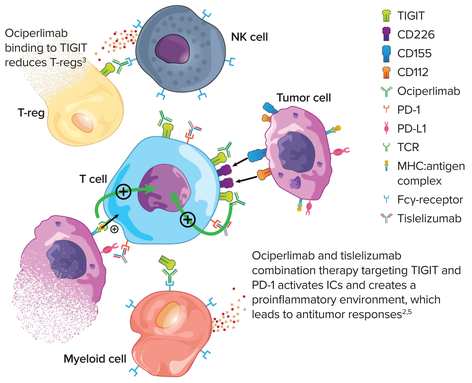
CONCLUSIONS

- Ociperlimab plus tislelizumab or ociperlimab plus rituximab showed acceptable safety and tolerability in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL)
- Limited preliminary antitumor activity was observed in both cohorts; additional combination strategies with selected biomarkers may be explored to expand this benefit

INTRODUCTION

- Programmed cell death-ligand 1 (PD-L1) expression on tumor cells (TCs) is associated with worse clinical outcomes in patients with R/R DLBCL[1]
- In preclinical and clinical studies of solid tumors, co-inhibition of programmed cell death-1 (PD-1) and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitor motif domains (TIGIT) enhanced the antitumor activity of anti-PD-1 therapy[2] (**Figure 1**)
- Ociperlimab (BGB-A1217) is a humanized monoclonal antibody (mAb) that binds TIGIT with high specificity and affinity, blocking the interaction with its ligands on TCs[3]
- TIGIT blockade may promote natural killer (NK) cell activation and could also synergize with therapeutic rituximab-mediated antibody-dependent cellular cytotoxicity activity[4,5]
- Tislelizumab is an anti-PD-1 mAb that blocks the PD-1/PD-L1 immune checkpoint, resulting in T-cell activation[6]
- AdvanTIG-101 (NCT05267054) was a phase 1b/2, open-label, dose-confirmation and dose-expansion study that evaluated the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of ociperlimab in combination with either tislelizumab or rituximab in patients with R/R DLBCL

Figure 1. Mechanism of Action of Ociperlimab and Tislelizumab Combination therapy



Ociperlimab and tislelizumab combination therapy targeting TIGIT and PD-1 activates ICs and creates a proinflammatory environment, which leads to antitumor responses[2,5]

Abbreviations: IC, immune cell; MHC, major histocompatibility complex; TCR, T-cell receptor; T-reg, regulatory T cell.

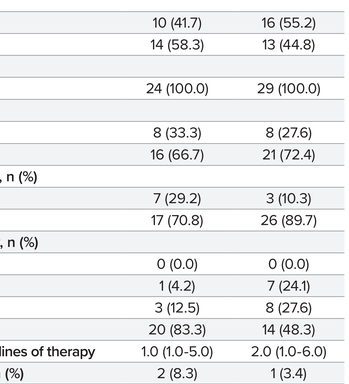
METHODS

Trial Design

- Eligible patients with R/R DLBCL were allocated to two cohorts to receive either ociperlimab plus tislelizumab (Cohort 1) or ociperlimab plus rituximab (Cohort 2) (**Figure 2**)

Figure 2. Study Design

Key Eligibility Criteria
- ≥18 years
- Histologically confirmed DLBCL NOS or EBV+ DLBCL NOS or high-grade B-cell lymphoma with *MYC* and *BCL2*, and/or *BCL6* rearrangements with DLBCL histology (double or triple-hit lymphoma)
- R/R before study entry
- ECOG PS ≤2
- ≥1 prior line of adequate systemic anti-DLBCL therapy[a], unless patients had PD before cycle 2
- Ineligible for high-dose therapy/HSCT



Study Objectives
Primary: Safety and tolerability, RP2D
Secondary: Preliminary antitumor activity, PK, host immunogenicity
Exploratory: Association of PD-L1 expression and other exploratory biomarkers with antitumor activity

[a]Defined as an anti-CD20 antibody-based chemoimmunotherapy for ≥2 consecutive cycles.
At enrollment, the PD-L1 IHC expression on TCs was tested and determined locally.
All antitumor endpoints were assessed by investigator per Lugano Classification.
Abbreviations: D, day; EBV+, Epstein–Barr virus positive; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HSCT, hematopoietic stem cell transplantation; IHC, immunohistochemistry; IV, intravenous; NOS, not otherwise specified; OCI, ociperlimab; PD, progressive disease; Q3W, once every 3 weeks; ritux, rituximab; RP2D, recommended phase 2 dose; TIS, tislelizumab.

RESULTS

Baseline Characteristics and Patient Disposition

- As of August 30, 2024, 53 patients (n=24, Cohort 1; n=29, Cohort 2) were enrolled and treated. Baseline characteristics are shown in **Table 1**
- Median age (range) was 65.0 years (21.0-80.0), and all patients had an ECOG PS of 0 or 1 at baseline
- Median (range) study follow-up was 9.0 months (0.2-28.0)

Table 1. Baseline Characteristics (Safety Analysis Set)

	Cohort 1 OCI + TIS (N=24)	Cohort 2 OCI + ritux (N=29)
Age, median (range), years	64.0 (40.0-79.0)	66.0 (21.0-80.0)
Sex, n (%)		
Male	10 (41.7)	16 (55.2)
Female	14 (58.3)	13 (44.8)
Race, n (%)		
Asian	24 (100.0)	29 (100.0)
ECOG PS, n (%)		
0	8 (33.3)	8 (27.6)
1	16 (66.7)	21 (72.4)
DLBCL IHC subtype, n (%)		
GCB	7 (29.2)	3 (10.3)
Non-GCB	17 (70.8)	26 (89.7)
Stage at study entry, n (%)		
Stage I	0 (0.0)	0 (0.0)
Stage II	1 (4.2)	7 (24.1)
Stage III	3 (12.5)	8 (27.6)
Stage IV	20 (83.3)	14 (48.3)
Median (range) prior lines of therapy	1.0 (1.0-5.0)	2.0 (1.0-6.0)
Prior radiotherapy, n (%)	2 (8.3)	1 (3.4)
Prior autologous stem cell transplant, n (%)	1 (4.2)	0 (0.0)
Prior allogeneic stem cell transplant, n (%)	0 (0.0)	0 (0.0)
Prior chimeric T-cell therapy, n (%)	2 (8.3)	1 (3.4)
Refractory to last prior systemic therapy, n (%)	12 (50.0)	17 (58.6)

Abbreviations: GCB, germinal center B cell.

Safety and Tolerability

- Ociperlimab plus tislelizumab (Cohort 1) or ociperlimab plus rituximab (Cohort 2) were generally well tolerated, and toxicities were manageable (**Table 2**)
- Of the 12 dose-limiting toxicity (DLT)-evaluable patients (n=6 in each cohort), one patient in Cohort 1 experienced a DLT (grade 3 febrile neutropenia). During the dose-confirmation stage, all patients received ociperlimab 900 mg, which was used as the RP2D
- In Cohort 1, the most common treatment-emergent adverse events (TEAEs) were neutrophil count decreased (33.3% [n=8]; grade ≥3 [n=4]), white blood cell count decreased (29.2% [n=7]; grade ≥3 [n=3]), and lymphocyte count decreased (25.0% [n=6]; grade ≥3 [n=1])
- In Cohort 2, the most common TEAEs were neutrophil count decreased (31.0% [n=9]; grade ≥3 [n=3]), anemia (31.0% [n=9]; grade ≥3 [n=1]), white blood cell count decreased (24.1% [n=7]; grade ≥3 [n=1]), and platelet count decreased (24.1% [n=7]; grade ≥3 [n=0])

Table 2. Overall Safety Summary (Safety Analysis Set)

	Cohort 1 OCI + TIS (N=24)	Cohort 2 OCI + ritux (N=29)
Any TEAE	24 (100.0)	28 (96.6)
Grade ≥3	10 (41.7)	13 (44.8)
Serious	9 (37.5)	8 (27.6)
Leading to death	2 (8.3)	2 (6.9)
Leading to treatment discontinuation	1 (4.2)	4 (13.8)
Any TR-TEAE	18 (75.0)	25 (86.2)
Grade ≥3	5 (20.8)	11 (37.9)
Serious	5 (20.8)	6 (20.7)
Leading to death	0 (0.0)	1 (3.4)
Leading to treatment discontinuation	0 (0.0)	3 (10.3)
DLT	1 (16.7)[a]	0 (0.0)[b]
Any immune-mediated AE	4 (16.7)	5 (17.2)
Grade ≥3	0 (0.0)	3 (10.3)
Serious	0 (0.0)	2 (6.9)
Leading to death	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	0 (0.0)	2 (6.9)
Any IRR	4 (16.7)	1 (3.4)

TR-TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. AEs were graded for severity using NCI-CTCAE v5.0.
[a]One case of grade 3 febrile neutropenia among the 6 DLT-evaluable patients. [b]Among the 6 DLT-evaluable patients.
Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; IRR, infusion-related reaction; TR-TEAE, treatment-related TEAE.

- In Cohort 1, TR-TEAEs occurred in 75.0% (n=18) of patients; 20.8% (n=5) of patients experienced grade ≥3 TR-TEAEs (**Table 3**)
- In Cohort 2, TR-TEAEs occurred in 86.2% (n=25) of patients; 37.9% (n=11) of patients experienced grade ≥3 TR-TEAEs
- Three patients (10.3%) in Cohort 2 experienced TR-TEAEs leading to treatment discontinuation (cardiac failure [grade 5], immune-mediated enterocolitis [grade 3], interstitial lung disease [grade 3])
- One patient in Cohort 2 experienced a TR-TEAE leading to death (cardiac failure)
- No patients in either cohort experienced immune-mediated AEs leading to death or any grade ≥3 IRRs

Table 3. TR-TEAEs Occurring in ≥10% of Patients (Safety Analysis Set)

	Cohort 1 OCI + TIS (N=24)		Cohort 2 OCI + ritux (N=29)	
Preferred term	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutrophil count decreased	6 (25.0)	3 (12.5)	9 (31.0)	3 (10.3)
White blood cell count decreased	5 (20.8)	3 (12.5)	7 (24.1)	1 (3.4)
Blood lactate dehydrogenase increased	4 (16.7)	0 (0.0)	2 (6.9)	0 (0.0)
Pyrexia	4 (16.7)	0 (0.0)	1 (3.4)	0 (0.0)
Lymphocyte count decreased	3 (12.5)	0 (0.0)	5 (17.2)	3 (10.3)
Anemia	2 (8.3)	0 (0.0)	5 (17.2)	1 (3.4)
Aspartate aminotransferase increased	1 (4.2)	0 (0.0)	3 (10.3)	0 (0.0)
Platelet count decreased	1 (4.2)	0 (0.0)	5 (17.2)	0 (0.0)
Rash	1 (4.2)	0 (0.0)	4 (13.8)	1 (3.4)

TR-TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. AEs were graded for severity using NCI-CTCAE v5.0.

Preliminary Antitumor Activity

- Ociperlimab plus tislelizumab (Cohort 1) or ociperlimab plus rituximab (Cohort 2) showed limited antitumor activity (**Table 4**)
- Overall response rate (ORR) (95% confidence interval [CI]) was 17.4% (5.0-38.8) in Cohort 1 (complete response [CR]; n=3), partial response [PR]; n=1) and 18.5% (6.3-38.1) in Cohort 2 (CR [n=2]; PR [n=3])
- The median (range) time to response was 2.1 months (2.1-2.2) for Cohort 1 and 2.0 months (1.9-4.2) for Cohort 2

Table 4. Efficacy Data (Efficacy Evaluable Analysis Set)

	Cohort 1 OCI + TIS (N=23)	Cohort 2 OCI + ritux (N=27)
ORR, n (% [95% CI])[a]	4 (17.4 [5.0-38.8])	5 (18.5 [6.3-38.1])
Best overall response, n (%)		
CR	3 (13.0)	2 (7.4)
PR	1 (4.3)	3 (11.1)
SD	1 (4.3)	4 (14.8)
PD	17 (73.9)	17 (63.0)
Not assessable	1 (4.3)	1 (3.7)
Time to response, median (range), months	2.1 (2.1-2.2)	2.0 (1.9-4.2)
Duration of response, median (range), months	13.3 (6.2-18.7)	7.8 (0.0-8.5)

Two patients died before the first post-baseline tumor assessment, and their best overall response is not available.
All antitumor endpoints were confirmed responses assessed by the investigator using the Lugano Classification.
[a]95% CI was estimated using the Clopper–Pearson method.
Abbreviations: SD, stable disease.

PK and Biomarkers

- PK data for ociperlimab were available for all 53 patients and were consistent with previously reported ociperlimab PK data
- Of 47 tested patients, 70.2% (n=33) had ≥1% PD-L1-positive TCs, including 10.6% (n=5) of patients with high expression of PD-L1 (≥50%) (**Table 5**)
- Of 44 tested patients, 93.2% (n=41) had ≥1% TIGIT-positive ICs. Although TIGIT was rarely expressed on TCs in previous reports, 40.9% (n=18) of patients had TIGIT-positive staining in ≥1% TCs, and 6.8% (n=3) patients had ≥50% TIGIT-positive TCs (**Table 5**)
- Of the four patients in Cohort 1 who achieved a CR or PR, two patients had a high PD-L1 expression on TCs of 90.0% and 100.0%, respectively (**Table 6**)
- Of the seven patients across both cohorts with a CR or PR and evaluable data, 71.4% (n=5) had TIGIT-positive ICs (**Table 6**)
- In Cohort 2, three patients who achieved a CR or PR with evaluable data had TIGIT-positive TCs, including one patient with 70.0% TIGIT-positive TCs (**Table 6**)

Table 5. PD-L1 and TIGIT Expression in Baseline Tumor Tissue

	PD-L1 on TCs	TIGIT on TCs	TIGIT on ICs
Patients with evaluable data	n=47	n=44	n=44
Expression level, n (%)			
<1% (negative)	14 (29.8)	26 (59.1)	3 (6.8)
1-<50%	28 (59.6)	15 (34.1)	37 (84.1)
≥50%	5 (10.6)	3 (6.8)	4 (9.1)

Table 6. PD-L1 and TIGIT Expression in Baseline Tumor Tissue in Patients with a CR or PR

	Best overall response	PD-L1-positive TCs (%)	TIGIT-positive TCs (%)	TIGIT-positive ICs (%)
Cohort 1	PR	90.0	0.0	4.0
	CR	1.0	0.0	8.0
	CR	NA	0.0	0.0
	CR	100.0	0.0	30.0
Cohort 2	CR	5.0	35.0	0.0
	CR	NA	NA	NA
	PR	0.0	1.0	10.0
	PR	5.0	70.0	1.0
	PR	NA	NA	NA

Each row represents an individual patient. Expression level <1% was considered negative.
Abbreviations: NA, not available.

Immunogenicity

- The incidence of treatment-emergent anti-drug antibodies (ADAs) was 2.3% (n=1) for ociperlimab (n=43 ADA-evaluable) and 5.3% (n=1) for tislelizumab (n=19 ADA-evaluable). However, both patients had negative neutralizing antibody tests

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DISCLOSURES

YS: No disclosures.

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