3023: *A phase 1a/b, multi-regional, first-in-human study of CS5001, a novel anti-ROR1 ADC, in patients with advanced solid tumors and lymphomas*

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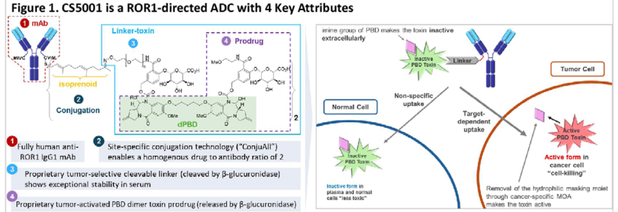
BACKGROUND

- Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an embryonic tyrosine kinase-like molecule implicated in multiple pathways promoting oncogenic signaling. ROR1 is overexpressed in a broad spectrum of solid tumors and hematological malignancies while notably absent in normal tissues[1-3].
- CS5001 is an antibody-drug conjugate (ADC) composed of a human anti-ROR1 IgG1 monoclonal antibody which is site-specifically conjugated to a tumor-activate pyrrolobenzodiazepine dimer (PBD) prodrug through a tumor-selective proprietary lysosomal cleavable β-glucuronide linker. Preclinical studies have shown potent anti-tumor activities in various lymphoma and solid tumor models[4-5].
- A first-in-human phase 1a/1b study is being conducted to evaluate the safety, pharmacokinetics (PK) profiles, and anti-tumor activities of CS5001 in patients with advanced solid tumors and B-cell lymphomas. Here, we report preliminary phase 1a results.

Figure 1. CS5001 is a ROR1-directed ADC with 4 Key Attributes



ADC=antibody-drug conjugate; mAB=monoclonal antibody; MOA=mechanism of action; PBD=pyrrolobenzodiazepine; ROR1=receptor tyrosine kinase-like orphan receptor 1

METHODS

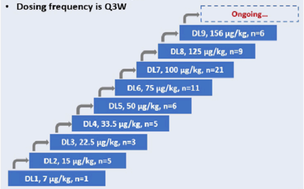
Figure 2. Phase 1a/1b Study Design

Phase 1a Dose Escalation (BOIN Design) + Backfill

Key eligibility criteria

- Age 18 years or older
- Patients with advanced solid tumor or lymphoma who progressed or were intolerant to all available standard therapies known to confer clinical benefit
- ≥1 evaluable lesion
- Adequate organ function
- Available tumor samples for biomarker analysis

- MRCT phase 1 trial is ongoing in the USA, AUS and China
- BOIN dose escalation design
- Dosing frequency is Q3W



Primary objective:

- Safety and tolerability of CS5001, MTD, and tentative RP2D

Secondary objective:

- PK profile of CS5001, total antibody, prodrug and the free cytotoxin
- Preliminary anti-tumor activity of CS5001

Exploratory objective:

- ROR1 expression on treatment response to CS5001

Tentative RP2D

Phase 1b Dose Expansion

Further exploring efficacy and safety in selected solid tumors and lymphomas

ADC=antibody-drug conjugate; BOIN=Bayesian optimal interval; DL=dose level; MTD=maximum tolerated dose; MRCT=multi-regional clinical trial; PK=Pharmacokinetics; Q3W=once every 3 weeks; ROR1=receptor tyrosine kinase-like orphan receptor 1; RP2D=recommended phase 2 dose

RESULTS

Baseline Characteristics

- As of 1 April 2024, 67 patients with lymphomas (n=21) or solid tumors (n=46) regardless of ROR1 expression status were treated across 9 dose levels (7 to 156 μg/kg) (Table 1).
- Fifty-five (82.1%) patients had received ≥3 lines of prior anti-tumor treatment.
- Sixteen (23.9%) patients remained on CS5001 treatment, and 51 (76.1%) patients discontinued treatment.
- Dose escalation is ongoing with continued backfilling additional patients to selected higher dose levels (DLs) for determination of preliminary RP2D.

Table 1. Baseline Characteristics (Safety Analysis Set)

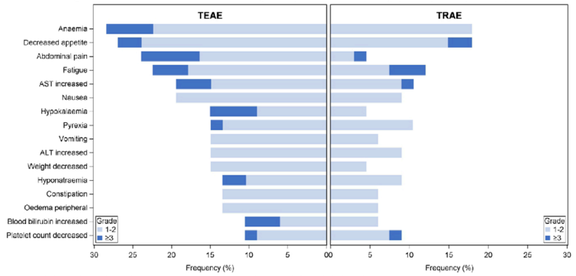
Characteristics	Total N = 67	Characteristics	Total N = 67
Age, Median (range) (years)	57.0 (20-83)	**Tumor type, n (%)**	
Sex, n (%)		**Lymphomas**	**21 (31.3%)**
Female	35 (52.2%)	Diffuse large B-cell lymphoma	10 (14.9%)
Male	32 (47.8%)	Hodgkin lymphoma	10 (14.9%)
Race, n (%)		Follicular lymphoma	1 (1.5%)
Asian	36 (53.7%)	**Solid Tumors**	**46 (68.7%)**
Non-Asian	31 (46.3%)	Colorectal cancer	11 (16.4%)
ECOG PS, n (%)		Breast cancer	11 (16.4%)
0	24 (35.8%)	Non-small cell lung cancer	8 (11.9%)
1	43 (64.2%)	Pancreatic cancer	5 (7.5%)
Prior systemic anti-cancer therapy, n (%)		Ovarian cancer	2 (3.0%)
<3	12 (17.9%)	Others	9 (13.4%)
≥3	55 (82.1%)		

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

Safety and Tolerability

- No dose-limiting toxicity (DLT) has been reported up to DL9 (156 μg/kg), and maximum tolerated dose (MTD) has not been reached.
- Sixty (89.6%) patients experienced at least one treatment-emergent adverse events (TEAEs); 32 (47.8%) had ≥ grade 3 TEAEs. The most common (≥20%) TEAEs were anaemia (n=19, 28.4%), decreased appetite (n=18, 26.9%), abdominal pain (n=16, 23.9%), and fatigue (n=15, 22.4%).
- Treatment-related adverse events (TRAEs) occurred in 45 (67.2%) patients; 13 (19.4%) had ≥ grade 3 TRAEs. The most common (≥10%) TRAEs were anaemia (n=12, 17.9%), decreased appetite (n=12, 17.9%), fatigue (n=8, 11.9%), pyrexia (n=7, 10.4%), and aspartate aminotransferase increased (n=7, 10.4%).

Figure 3. The Most Common TEAEs (≥10%) and TRAEs (≥2%) (Safety Analysis Set)



AEs were graded according to National Cancer Institute Common Terminology Criteria for AE (NCI-CTCAE) v5.0.
TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event; AST=aspartate aminotransferase increased; ALT=alanine aminotransferase increased.

Pharmacokinetics (PK)

Figure 4. Mean Serum Concentration of CS5001 and Total Antibody vs. Time Profiles at Cycle 1 (Semi-Log Scale)

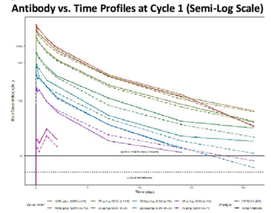
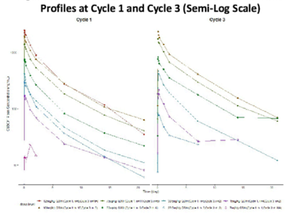


Figure 5. Mean Serum Concentration of CS5001 vs. Time Profiles at Cycle 1 and Cycle 3 (Semi-Log Scale)



Blood specimens were collected for PK analysis at predefined timepoints. PK parameters were derived from non-compartmental analysis from the serum concentration-time profile of CS5001.

PK, cont.

- As of 1 April 2024, PK data were collected from 52 patients across 8 dose levels.
- Exposure of CS5001 was overall proportional to dose, with an apparent half-life of about 5 days.
- PK profile of CS5001 was similar to that of total antibody (Figure 4).
- Despite fewer patients evaluable for PK from Cycle 3, no significant accumulation was observed at Cycle 3 (Figure 5).
- Plasma concentration of free toxin was below the limit of quantification in all samples (lower limit of quantification was 10pg/mL).

Efficacy

In all Evaluable Patients (Table 2)

- Among all 59 evaluable patients (lymphoma, n=21; solid tumor, n=38) from DL1 to DL9, encouraging anti-tumor activity was observed across various tumor types from DL5 to DL9. Correlation between anti-tumor activity and ROR1 expression is currently under evaluation.

In Lymphomas (Table 3)

- For diffuse large B-cell lymphoma (DLBCL), objective responses were observed from DL7 (100 μg/kg) and above, i.e. 1 complete response (CR) and 2 partial responses (PRs) among 6 evaluable patients at DL7-9 (ORR: 50.0%).
- For Hodgkin lymphoma (HL), objective responses were observed from DL5 (50 μg/kg) and above, i.e. 1 CR and 4 PRs among 9 evaluable patients at DL5-9 (ORR: 55.6%).

In Solid Tumors (Table 4)

- PRs and stable diseases (SDs) with reduced tumor burden were emerging in various types of solid tumors at higher doses, notably in non-small cell lung cancer (NSCLC) (1 PR and 3 SDs), triple-negative breast cancer (TNBC) (1 SD), pancreatic cancer (1 PR), and ovarian cancer (1 SD). Most of these patients remain on study for continued treatment and tumor assessment.

Table 2. BOR in All Evaluable Patients (Efficacy Analysis Set)

BOR	DL1–4 7-33.5 μg/kg (n=11)	DL5 50 μg/kg (n=6)	DL6 75 μg/kg (n=11)	DL7 100 μg/kg (n=18)	DL8 125 μg/kg (n=9)	DL9 156 μg/kg (n=4)	All DLs (N=59)
CR	0	0	0	2 (11.1%)	0	0	2 (3.4%)
PR	0	1 (16.7%)	1 (9.1%)	1 (5.6%)	4 (44.4%)	1 (25.0%)	8 (13.6%)
SD	1 (9.1%)	1 (16.7%)	1 (9.1%)	2 (11.1%)	2 (22.2%)	2 (50.0%)	9 (15.3%)
PD	10 (90.9%)	4 (66.7%)	9 (81.8%)	13 (72.2%)	3 (33.3%)	1 (25.0%)	40 (67.8%)

Table 3. BOR in Evaluable Patients with Lymphomas

BOR	DL1–4 7-33.5 μg/kg (n=2)	DL5 50 μg/kg (n=2)	DL6 75 μg/kg (n=5)	DL7 100 μg/kg (n=8)	DL8 125 μg/kg (n=3)	DL9 156 μg/kg (n=1)	All DLs (N=21)
CR	0	0	0	2 (25.0%)	0	0	2 (9.5%)
PR	0	1 (50.0%)	1 (20.0%)	0	3 (100.0%)	1 (100.0%)	6 (28.6%)
SD	0	0	0	0	0	0	0
PD	2 (100.0%)	1 (50.0%)	4 (80.0%)	6 (75.0%)	0	0	13 (61.9%)

Table 4. BOR in Evaluable Patients with Solid Tumors

BOR	DL1–4 7-33.5 μg/kg (n=9)	DL5 50 μg/kg (n=4)	DL6 75 μg/kg (n=6)	DL7 100 μg/kg (n=10)	DL8 125 μg/kg (n=6)	DL9 156 μg/kg (n=3)	All DLs (N=38)
CR	0	0	0	0	0	0	0
PR	0	0	0	1 (10.0%)	1 (16.7%)	0	2 (5.3%)
SD	1 (11.1%)	1 (25.0%)	1 (16.7%)	2 (20.0%)	2 (33.3%)	2 (66.7%)	9 (23.7%)
PD	8 (88.9%)	3 (75.0%)	5 (83.3%)	7 (70.0%)	3 (50.0%)	1 (33.3%)	27 (71.1%)

Anti-tumor activity was assessed using RECIST v1.1 for solid tumors and Lugano 2014 for lymphomas. Data cutoff for efficacy analysis was 10 May 2024.
Patients were considered evaluable if he/she was treated with CS5001 and accepted post-baseline tumor assessment. DL=dose level; BOR=best overall response; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Case Reports

1. 78-year-old female with DLBCL (Figure 6)

After receiving 3 cycles of CS5001 treatment (100 μg/kg Q3W), a CR was achieved per Lugano 2014.

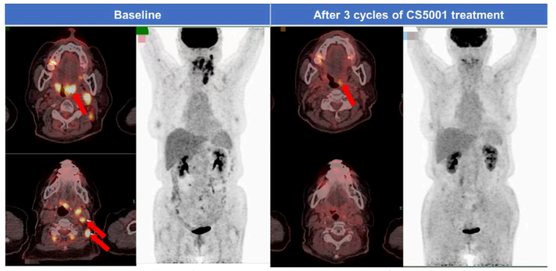


Figure 6 (Red arrows pointing to the target lesions)

2. 64-year-old male with NSCLC (Figure 7)

After receiving 3 cycles of CS5001 treatment (125 μg/kg Q3W), the sum of longest diameter of target lesion reduced from baseline 91.4 mm to 55.1 mm (39.7% reduction), and overall response was PR per RECIST v1.1.

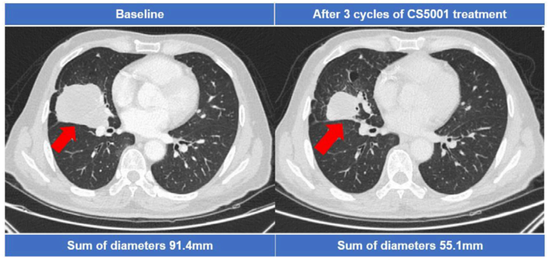


Figure 7 (Red arrows pointing to the target lesions)

CONCLUSION

- CS5001 is well tolerated in heavily pre-treated patients with advanced solid tumors and lymphomas across doses from 7 to 156 μg/kg. No DLT was observed and MTD was not reached.
- PK profile of CS5001 was similar to that of total antibody, indicating good stability of the ADC in circulation.
- Encouraging anti-tumor activity was observed across various tumor types regardless of ROR1 expression.
- Dose escalation and backfilling at higher doses are still ongoing to determine preliminary RP2D, followed by phase 1b dose expansion in indication of interest for dose optimization and potential registration.

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DISCLOSURES

L. Charlotte: advisor for Sanofi; received travel accommodations, or other expenses paid or reimbursed by Amgen.

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