EMADOC-1700519818-2465582
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cejemly

International non-proprietary name: Sugemalimab

Procedure No. EMA/VR/0000261157

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{0-\infty}$	area under the serum concentration-time curve extrapolated to infinity
BICR	blinded independent central review
CHO	Chinese hamster ovary
CL	clearance
C_{max} (CV)	maximum serum concentration
C_{trough}	trough serum concentration
$C_{trough,C1}$	trough serum concentration in Cycle 1
CSCO	Chinese Society of Clinical Oncology
CSR	clinical study report
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff
DCO1	data cutoff 1 = 08 Mar 2021
DCO2	data cutoff 2 = 01 Mar 2022
DCO3	data cut off 3 = 03 Apr 2023
DoR	duration of response
ECIS	European Cancer Information System
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ENKTL	extranodal natural killer/T-cell lymphoma
E-R	exposure/response
ESCC	oesophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GEJ	gastro-oesophageal junction
GC	gastric adenocarcinoma
GMR	geometric mean ratios
HCC	hepatocellular carcinoma
HR	hazard ratio
IFN-γ	interferon-γ
IgG4	immunoglobulin G4
IL	interleukin
irAE	immune-related adverse event
ITT	intention-to-treat
IV	intravenous
IxRS	interactive voice response system/interactive web response system

Abbreviation	Definition
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MTD	maximum tolerated dose
NAb	neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCI	(U.S.) National Cancer Institute
NDA	New Drug Application
NE	Not estimable or not evaluable
NICE	National Institute for Health and Care Excellence
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
Q3W	once every 3 weeks
RECIST	response evaluation criteria in solid tumours
RET	rearranged during transfection
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
RP2D	recommended Phase 2 dose
R/R cHL	relapsed or refractory classical Hodgkin lymphoma
R/R ENKTL	relapsed or refractory extranodal natural killer/T-cell lymphoma
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SD	standard deviation
SOC	standard of care
SOC	system organ class
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
V_{ss}	volume of distribution of sugemalimab at steady-state

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Cstone Pharmaceuticals Ireland limited submitted to the European Medicines Agency on 13/03/2025 an application for a variations.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include the treatment of unresectable stage III non-small-cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose disease has not progressed following concurrent or sequential platinum-based chemoradiotherapy for CEJEMLY, based on final results from study CS1001-301; this is a Phase III, multicentre, randomised, double-blind, placebo-controlled study assessing the efficacy and safety of sugemalimab as consolidation therapy versus placebo in participants with locally advanced or unresectable stage III NSCLC who have not progressed after concurrent or sequential chemoradiotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0194/2022 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and PRAC Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	13 March 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 June 2025
PRAC Rapporteur's preliminary assessment report circulated on:	26 June 2025
PRAC outcome	10 July 2025
Joint Rapporteur's updated assessment report circulated on:	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	14 August 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	16 September 2025
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	17 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	9 October 2025
CHMP opinion:	16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

State the claimed therapeutic indication

The claimed therapeutic indication is: "Cejemly as monotherapy is indicated for the treatment of unresectable stage III NSCLC with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose disease has not progressed following concurrent or sequential platinum-based chemoradiotherapy.

Epidemiology

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death across the globe. About 30% of patients diagnosed with NSCLC present with tumour stages IIIA to IIIC, the majority of which are unresectable. Across the EU-27, lung cancer is the leading cause of death among all cancers for men (22.9%) and the second-leading cause for women (15.3%) behind breast cancer (16.7%) with an estimated about 253,000 deaths in 2022.

Management

Platinum-based chemotherapy concurrent with radiotherapy is standard of care for patients with unresectable stage III NSCLC. If concurrent chemoradiotherapy is not possible for any reason, sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative. In this treatment niche, durvalumab is approved as maintenance for patients whose disease did not progress after chemoradiotherapy and whose tumours express PD-L1 on ≥ 1% of tumour cells. Moreover, for patients expressing relevant EGFR driver mutations, osimertinib is approved.

2.1.2. About the product

Sugemalimab is a fully human immunoglobulin G4 monoclonal antibody. It specifically binds to programmed cell death ligand 1 (PD-L1), thus blocking its ligation with PD-1. PD-L1, when expressed on tumour cells and tumour-infiltrating immune cells, can contribute to the inhibition of an anti-tumour immune response. Binding of PD-L1 to the PD-1 and CD80 (B7.1) receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

Currently approved indication:

"Cejemly in combination with platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small -cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations."

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not seek Scientific advice from the CHMP.

2.1.4. General comments on compliance with GCP

The applicant claims that Study CS1001-301 was performed according to GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

Sugemalimab is a natural substance (monoclonal antibody), the use of which will not alter the concentration or distribution of the substance in the environment. As a result no Phase I environmental risk assessment is necessary according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). Sugemalimab is not expected to pose a risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Listing of All Clinical Studies

Phase/Study Identifier; Country(ies)	Objective(s) of the Study (Key Endpoints)	Study Design and Type of Control	Diagnosis of Participants	No. of Participants per Cohort	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment per Protocol [a]	Study Status[b]; Type of Report; DCO/LPLV
Reports of Human Pharmacokinetic (PK) Studies – Patient PK and Initial Tolerability Study Reports							
Phase 1; CS1001-1011a; NCT03312842; China	Safety and tolerability, MTD, and RP2D	Open-label, dose-exploration, not controlled	Participants with metastatic or locally advanced unresectable solid tumours or lymphoma with at least 1 lesion	Sugemalimab: 29	Sugemalimab; 3, 10, 20, and 40 mg/kg or 1200 mg single dose every 3 weeks; IV	Up to 2 years	Completed; Full CSR; LPLV: 30 Nov 2018
Phase 1; CS1001-1011b; NCT03312842; China	Preliminary efficacy (ORR, DCR, DoR, PFS, OS, and Epstein-Barr virus DNA levels)	Open-label, dose-expansion, not controlled	Participants with metastatic or locally advanced unresectable solid tumours or NKTL	Sugemalimab: 217[c]	Sugemalimab as a monotherapy or in combination with chemotherapy drugs, radiation therapy, or targeted therapy; 1200 mg single dose every 3 weeks[d]; IV	Up to 2 years	Ongoing; Full CSR; DCO: 16 Aug 2021
Phase 1; CS1001-102; NCT03744403; US	Safety, tolerability, and RP2D	Open-label, dose-escalation, not controlled	Participants with metastatic or locally advanced unresectable solid tumours	Sugemalimab: 24	Sugemalimab; 10 mg/kg or 1200 mg single dose every 3 weeks; IV	Up to 2 years	Completed; Full CSR; LPLV: 19 Oct 2020
Reports of Efficacy and Safety Studies – Study Reports of Controlled Clinical Studies Pertinent to							

the Claimed Indication							
Phase 3; CS1001-302; NCT03789604; China	Efficacy (PFS and OS)	Randomised, double-blind, placebo-controlled	Participants with metastatic (Stage IV) NSCLC	Sugemalimab: 320 Placebo: 159	Sugemalimab in combination with platinum-based chemotherapy; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 22 Nov 2021
Phase 3; CS1001-301; NCT03728556; China	Efficacy (PFS, OS)	Randomised, double-blind, placebo-controlled	Participants with locally advanced unresectable Stage III NSCLC	Sugemalimab: 255 Placebo: 126	Sugemalimab as a consolidation therapy; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Completed; Full CSR; LPLV: 03 Apr 2023
Reports of Efficacy and Safety Studies – Other Study Reports							
Phase 2; CS1001-201; NCT03595657; China, US[e]	Efficacy (ORR)	Open-label, not controlled	Participants with relapsed or refractory extranodal NKTL	Sugemalimab: 80	Sugemalimab; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 10 Nov 2021
Phase 2; CS1001-202; NCT03505996; China	Efficacy (ORR)	Open-label, not controlled	Participants with relapsed or refractory classical Hodgkin lymphoma	Sugemalimab: 81	Sugemalimab; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 19 Feb 2020
Phase 3; CS1001-301; NCT03728556; China	Efficacy (PFS, OS)	Randomised, double-blind, placebo-controlled	Participants with locally advanced unresectable Stage III NSCLC	Sugemalimab: 255 Placebo: 126	Sugemalimab as a consolidation therapy; 1200 mg single dose every 3 weeks; IV	Up to 2 years	Ongoing; Full CSR; DCO: 08 Mar 2021

[a] Participants who had completed 2 years of study treatment, after consultation with the Investigator and the Sponsor, may have continued treatment until the participant experienced an intolerable adverse reaction, progressive disease, withdrawal of ICF, lost to follow-up, death, or study termination, whichever occurred first.
[b] As of the data cutoff date for each included study.
[c] There were 217 participants enrolled into Cohort 1 to Cohort 9 and Cohort 11. No participant was enrolled into Cohort 10. The data for Cohort 12 and Cohort 13 were not included in the CSR.
[d] Data from Cohort 12 (1800 mg every 4 weeks) were not included in the CSR.
[e] No US participants were enrolled.
CS1001 = sugemalimab; CSR = clinical study report; DCO = data cutoff date (for ongoing studies); DCR = disease control rate; DNA = deoxyribonucleic acid; DoR = duration of response; ICF=informed consent form; IV = intravenous; LPLV = last participant last visit (for completed studies); MTD = maximum tolerated dose; NKTL = natural killer/T-cell lymphoma; No. = number; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK=pharmacokinetic(s); RP2D = recommended Phase 2 dose; US = United States.

2.3.2. Pharmacokinetics

Bioanalytical methods

Human serum samples were analyzed for sugemalimab concentrations using a fully validated specific enzyme-linked immunosorbent assay (ELISA) (Analysis method No. 17BASM127) by WuXi AppTec (Shanghai) Co., Ltd.

Human serum samples were analyzed for anti-sugemalimab antibodies (ADA) using a fully validated electrochemiluminescence (ECL) three-step method (Method No.: 19BASM036) by WuXi AppTec (Shang hai) Co., Ltd.

Human serum samples were analyzed for anti-sugemalimab neutralizing antibodies using a fully validated ECL method (Method No.: ICSH 19-118) by Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd.

Distribution

The empirical Bayes estimates of pharmacokinetic parameters in Stage III NSCLC patients (CS1001-301) showed that the geometric mean (inter subject CV%) for the volume of distribution at steady state (Vss) was 4.74 L (20%).

Elimination

The empirical Bayes estimates of pharmacokinetic parameters in Stage III NSCLC patients (CS1001-301) showed that the geometric mean (inter subject CV%) for the total clearance (CL) at the end of Cycle 1 was 0.214 L/day (23.8%), and the elimination half-life (t 1/2) was 16.6 days (20.8%).

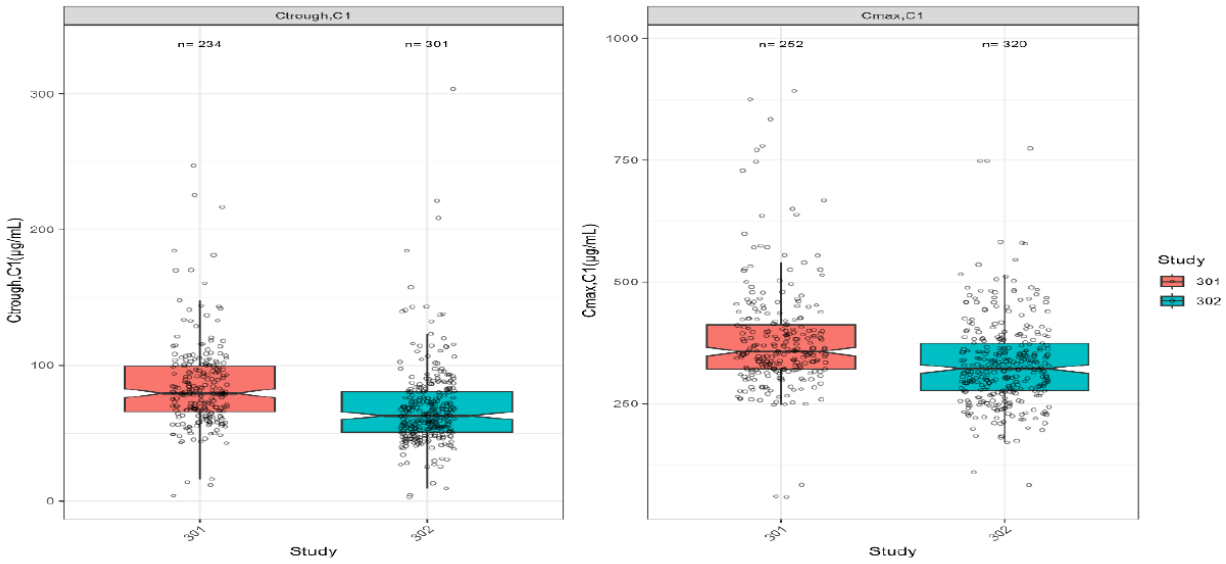
Target population

A PopPK analysis was provided to describe PK in the target population and for performing PK simulations to support the proposed posology. An updated population pharmacokinetic model including patients in the target population (Stage III NSCLC patients) was submitted, compared to the original PopPK model in the initial submission (EMEA/H/C/006088/0000).

As of Apr 3, 2023, a total of 255 participants had received sugemalimab 1200 mg IV Q3W in study CS1001-301. After multiple doses of sugemalimab at 1200 mg IV Q3W, the geometric mean Ctrough,C4 and C_{max},C4 were 130.5 and 546.7 μg/mL, respectively.

Comparisons of the observed C_{trough} and C_{max} at Cycle 1 between Stage III patients (Study CS1001-301) and Stage IV patients (Study CS1001-301) is included in Figure 1.

Figure 1: Box plot of Ctrough,c1 and C_{max},c1 for Studies 301 and 302.



The solid horizontal lines and box heights represent the median, and 25th to 75th percentiles, respectively. The circles are single observed values. Number in each box specifies the number of patients per group.

The baseline demographics/covariates that were identified in the final PopPK model were weight, albumin and sex. The median albumin levels at baseline were comparable between Stage III and IV patients in Phase 3 treated with sugemalimab (Stage III: 42.7 g/L; Stage IV: 40.9 g/L). The median body weights at baseline were comparable between Stage III and IV patients in Phase 3 treated with sugemalimab (Stage III: 62.0 kg, Stage IV: 61.0 kg). The proportions of males/females were comparable between Stage III and IV patients in Phase 3 treated with sugemalimab (Stage III: 92.5% male patients; Stage IV: 79.4% male patients).

PopPK model

The updated sugemalimab PopPK structural model was a two-compartment model with a time-dependent component of clearance (Table 2). The PopPK model identified body weight, sex, albumin, time-varying ADA titre, and disease status as statistically significant covariates; however, the magnitude of these covariate effects on predicted steady-state sugemalimab exposure metrics were generally < 20% and not considered clinically meaningful. Stage III and Stage IV NSCLC disease stage was included as covariates on CL_0 and V_c as a sensitivity analysis despite the limited magnitude of these covariate effects (<20%).

Table 2: Parameter estimates of the Updated PopPK model

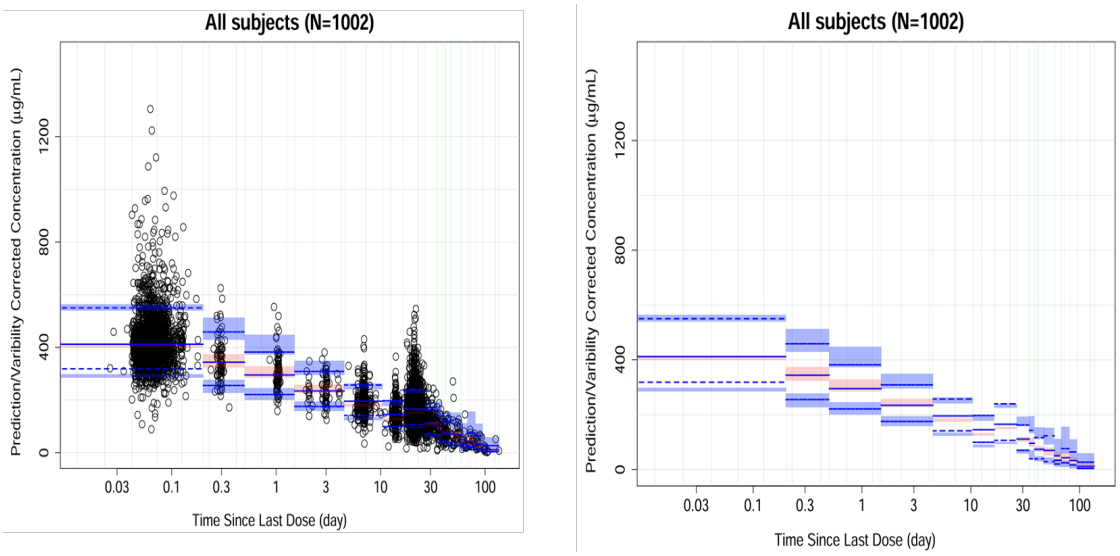
	Updated Model OFV=61797	
Parameter	**Estimates**	**95% CI**
CL0 (L/day)	0.146	[0.141, 0.152]
Effect of Sex on CL0	0.902	[0.861, 0.943]
Effect of Weight on CL0	0.741	[0.637, 0.845]
Effect of Albumin on CL0	-0.852	[-1.01, -0.697]
Effect of NSCLC3 on CL0	**1.02**	**[0.964, 1.08]**

	Updated Model OFV=61797	
Parameter	**Estimates**	**95% CI**
Effect of NSCLC4 on CL0	**1.05**	**[1, 1.1]**
CLT (L/day)	0.109	[0.101, 0.117]
Effect of Sex on CLT	0.722	[0.642, 0.803]
Effect of Time-varying ADA Titer on CLT	0.0856	[0.0649, 0.106]
K_{des} (1/day)	0.0214	[0.0189, 0.0239]
Effect of Lymphoma Disease on K_{des}	0.0426	[0.0322, 0.053]
Central Volume of Distribution (Vc, L)	3.47	[3.36, 3.58]
Effect of Sex on Vc	0.844	[0.813, 0.874]
Effect of Weight on Vc	0.445	[0.369, 0.522]
Effect of Albumin on Vc	-0.252	[-0.364, -0.14]
Effect of Lymphoma on Vc	0.894	[0.858, 0.93]
Effect of NSCLC3 on Vc	**0.918**	**[0.881, 0.955]**
Effect of NSCLC4 on Vc	**1.05**	**[1.01, 1.09]**
Inter-compartmental Clearance (Q, L/day)	0.362	[0.314, 0.411]
Peripheral Volume of Distribution (Vp, L)	0.751	[0.451, 1.05]
Effect of Albumin on Vp	-1.95	[-2.57, -1.33]
Effect of NSCLC Disease on Vp	2.15	[1.31, 2.99]
Between Subject Variability for CL0	23.9	[22.3, 25.5]
Between Subject Variability for Vc	17.8	[16.8, 18.9]
Between Subject Variability for Vp	63.4	[55.9, 70.9]
Between Subject Variability for CLT	36.7	[31.7, 41.6]
Between Subject Variability for K_{des}	93.7	[82.7, 105]
Correlation Between CL0 and Vc	0.431	[0.35, 0.512]
Correlation Between CLT and Vc	0.691	[0.59, 0.791]
Correlation Between CLT and K_{des}	-0.0705	[-0.28, 0.139]
Proportional Residual Unexplained Variability (%)	17	[16.8, 17.3]

The effect of sex is showing the change in parameter for females relative to males.

The ability of the model to describe PK data in the is shown in a pcVPC (Figure 2).

Figure 2: Prediction Variability corrected VPC for the updated PopPK model.



Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red/blue areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles.

In the initial submission, 7054 concentrations from 1002 subjects collected prior to March 8, 2021, were included in the PopPK model. After this date, 312 additional PK samples of CS1001-301 have been collected, consisting of 4 samples from Cycle 4 (from 2 new subjects) and 308 trough concentrations from Cycle 8 and later cycles (from 167 subjects). These additional samples account for less than 5% of the total PopPK dataset.

PopPK simulations

The proposed therapeutic dose of sugemalimab for Stage III NSCLC consolidation treatment is 1200 mg Q3W for patients weighing ≤115 kg and 1500 mg Q3W for those >115 kg. This dosing recommendation is supported by PK simulations for high-body-weight patients.

This dosing approach follows the same modelling & simulation methodology used for the approved indication for stage IV NSCLC indication (EMEA/H/C/006088/0000), which established a regimen of 1200 mg Q3W for patients weighing 115 kg or less and 1500 mg Q3W for those over 115 kg.

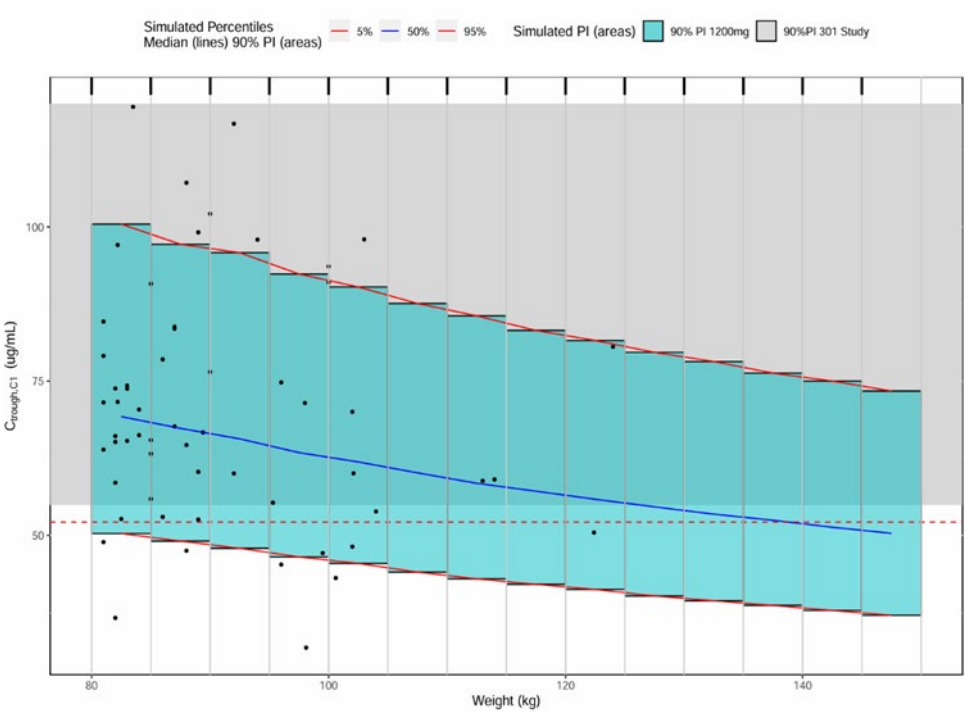
A simulation of exposure metrics across an extended weight range of 80-150 kg following dosages of 1200 mg Q3W and 1500 mg Q3W was conducted, based on the updated PopPK model. The predicted exposure metrics for Cycle 1 of the CS1001-301 study, which serves as the reference for the following analysis, were estimated from individual concentration-time profiles simulated based on individual empirical Bayes estimates (EBE) in the final PopPK model. Simulated body weight values for all 1002 patients included in the PopPK analysis were randomly drawn from a uniform distribution for each 5 kg stratum in the range of 80-150 kg while maintaining the effects of other covariates unchanged.

The predicted sugemalimab exposure metrics at cycle 1 versus body weight for a flat dose of 1200 mg from the final population PK model are shown in Figure 3. The simulations for Ctrough, C1 by dose and body weight strata and for study CS1001-301 are shown in Table 3 and identifies that 1500 mg Q3W in patients with body weights above 115 kg provides exposures comparable with the observed exposure.

Corresponding simulations for AUC and C_{max} were provided (data not shown) which also demonstrated comparable PK exposures between the proposed posology and the observed PK exposures in Study 301.

Corresponding PK simulations were provided for Stage IV patients where the simulated C_{trough} during Cycle 1 for the already approved posology were compared with the observed C_{trough} during Cycle 1 in Study 302. The simulation-based exposure comparisons for Stage IV patients demonstrated that the simulated median and 90% prediction interval of C_{trough} during Cycle 1 overlapped with the observed median and 90% prediction interval, to a similar degree as the simulations for Stage III patients. The geometric mean ratios (GMR) between the simulated and observed C_{trough} during Cycle 1 were 0.74 or higher for the already posology for Stage IV patients across the entire simulated weight range which is similar to the simulations for Stage III patients.

Figure 3: Simulated exposure (Ctrough,C1) following 1200 mg Q3W for high body weight and reference range from study CS1001-301 with proposed target lower limit (from observed data).



Predicted Ctrough,C1 based on the updated population PK model for weight > 80kg population (black circles: individual predictions). The blue and red solid lines are the median and 90% PIs for predicted Ctrough,C1. The blue shaded area encompasses 90% of the simulated patients in each weight stratum (5kg intervals). The grey band encompasses 90% range from Study CS1001-301. The red dotted line represents the 5th percentile of observed Ctrough, C1 in Study CS1001-301 (52.1 µg/mL).

Table 3: Ctrough,C1 (µg/mL) by dose and body weight strata and for Study CS1001-301

Weight (kg)	N	GeoMean	Median(5^{th}-95^{th})	% of $C_{trough,C1}$> 52.1 µg/mL[a]	GMR[b] (90% CI)
From model prediction for study CS1001-301					
43-98	252	80.5	79(54.9-119.9)	97.2	-
From simulated patients dosed 1200mg					
80-85	252	70.6	69(50.3-100.4)	92.9	0.877(0.848-0.907)
85-90	252	68.4	67(49.1-97.2)	89.7	0.850(0.822-0.879)

Weight (kg)	N	GeoMean	Median(5^{th}-95^{th})	% of $C_{trough,C1}$> 52.1 μg/mL[a]	GMR[b] (90% CI)
90-95	252	66.5	66(47.9-95.8)	87.7	0.825(0.798-0.853)
95-100	252	64.6	63.5(46.5-92.4)	84.9	0.802(0.775-0.829)
100-105	252	62.8	62(45.5-90.3)	81.3	0.780(0.755-0.807)
105-110	252	61.1	60(44.1-87.6)	77.8	0.759(0.734-0.785)
110-115	252	59.6	58(43.0-85.6)	74.6	0.740(0.716-0.765)
115-120	252	58.2	57(42.1-83.2)	68.7	0.722(0.698-0.747)
120-125	252	56.7	56(41.2-81.6)	63.9	0.704(0.681-0.728)
125-130	252	55.4	55(40.2-79.7)	59.1	0.688(0.665-0.711)
130-135	252	54.2	53.5(39.4-78.2)	55.6	0.672(0.650-0.695)
135-140	252	53.0	52.5(38.6-76.3)	50.4	0.658(0.636-0.680)
140-145	252	51.8	51(37.8-75.0)	46.8	0.643(0.622-0.665)
145-150	252	50.7	50(37.1-73.4)	42.9	0.629(0.609-0.651)
From simulated patients dosed 1500mg					
80-85	252	88.3	87(62.9-125.6)	99.6	1.096(1.06-1.13)
85-90	252	85.6	84(61.4-121.5)	99.2	1.062(1.03-1.10)
90-95	252	83.1	82(59.9-119.8)	98.8	1.032(0.998-1.07)
95-100	252	80.7	79(58.2-115.5)	98.4	1.002(0.969-1.04)
100-105	252	78.6	77(56.8-112.9)	98.0	0.976(0.944-1.01)
105-110	252	76.5	75(55.1-109.5)	97.2	0.949(0.918-0.981)
110-115	252	74.6	73(53.7-107)	96.8	0.926(0.895-0.957)
115-120	252	72.7	71.5(52.6-104.1)	96.0	0.903(0.873-0.934)
120-125	252	70.9	70(51.6-102)	92.5	0.880(0.852-0.910)
125-130	252	69.3	68(50.3-99.6)	90.5	0.860(0.832-0.889)
130-135	252	67.7	67(49.3-97.8)	89.3	0.841(0.813-0.869)
135-140	252	66.2	65.5(48.3-95.4)	88.1	0.822(0.795-0.850)
140-145	252	64.8	64(47.3-93.8)	84.1	0.805(0.778-0.832)
145-150	252	63.4	63(46.3-91.8)	81.3	0.787(0.761-0.814)

a: 52.1 μg/mL is the 5^{th} percent of observed C_{trough} in Study 301 at cycle 1 within time window of 21±3 days.

b: GeoMean: Geometric Mean;*GMR: the ratio of from two-sample t-test for log-transformed exposure from >80kg and Study CS1001-301 group.

Dose proportionality and time dependencies

No new data regarding dose proportionality was presented.

Regarding time dependencies, in the phase 3 stage III NSCLC study, among 255 patients in the sugemalimab group, the prevalence of anti-drug antibodies (ADA) was 10.6% (27 patients), with 5.9% (15 patients) as treatment-emergent ADA. The total positive rate of NAb was 2.0% (5 patients).

No evidence was observed that ADA had an impact on pharmacokinetics, efficacy or safety, however data are still limited.

2.3.3. Pharmacodynamics

Sugemalimab is a fully human immunoglobulin G4 monoclonal antibody. It specifically binds to programmed cell death ligand 1 (PD L1), thus blocking its ligation with PD 1. PD L1, when expressed on tumour cells and tumour-infiltrating immune cells, can contribute to the inhibition of

an anti-tumour immune response. Binding of PD L1 to the PD 1 and CD80 (B7.1) receptors found on T cells and antigen presenting cells suppresses cytotoxic T cell activity, T cell proliferation, and cytokine production.

2.3.4. PK/PD modelling

New efficacy PKPD analyses in the target population were provided and efficacy simulations were performed to support the proposed posology.

A safety PKPD analysis including patients in the target population (Stage III NSCLC patients) was previously submitted in the initial submission (EMEA/H/C/006088/0000) and is not included in the current assessment report.

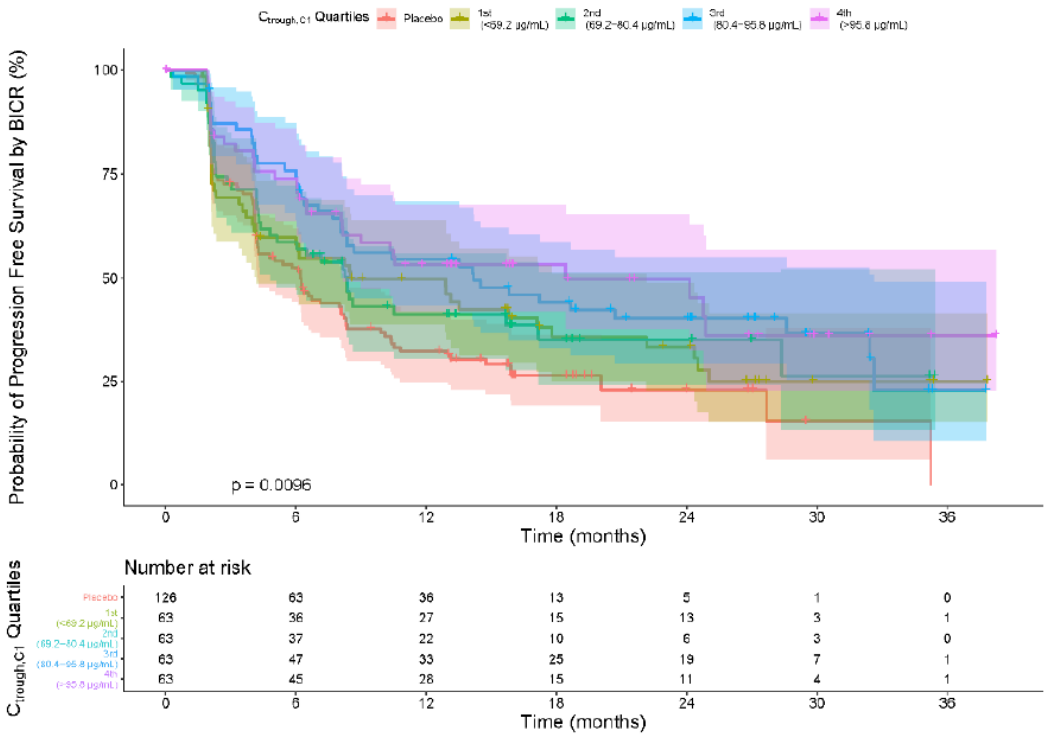
Exposure-efficacy analysis

Exposure metrics taken during Cycle 1 were used in the analysis. Using data from the Phase 3 study, CS1001-301 in participants with Stage III NSCLC, the exposure-efficacy relationship of sugemalimab was explored following a dose of 1200 mg IV Q3W for PFS and OS.

The E-R relationships including PFS and OS were explored by Kaplan-Meier plots and time to events (TTEs) models.

Graphical analysis for PFS indicated a possible relationship between Ctrough,C1 and PFS, as assessed by both BICR and the Investigator (Kaplan-Meier curves by quartiles of Ctrough,C1,Figure 4).

Figure 4: Progression-free Survival by Quartiles of Ctrough,C1.

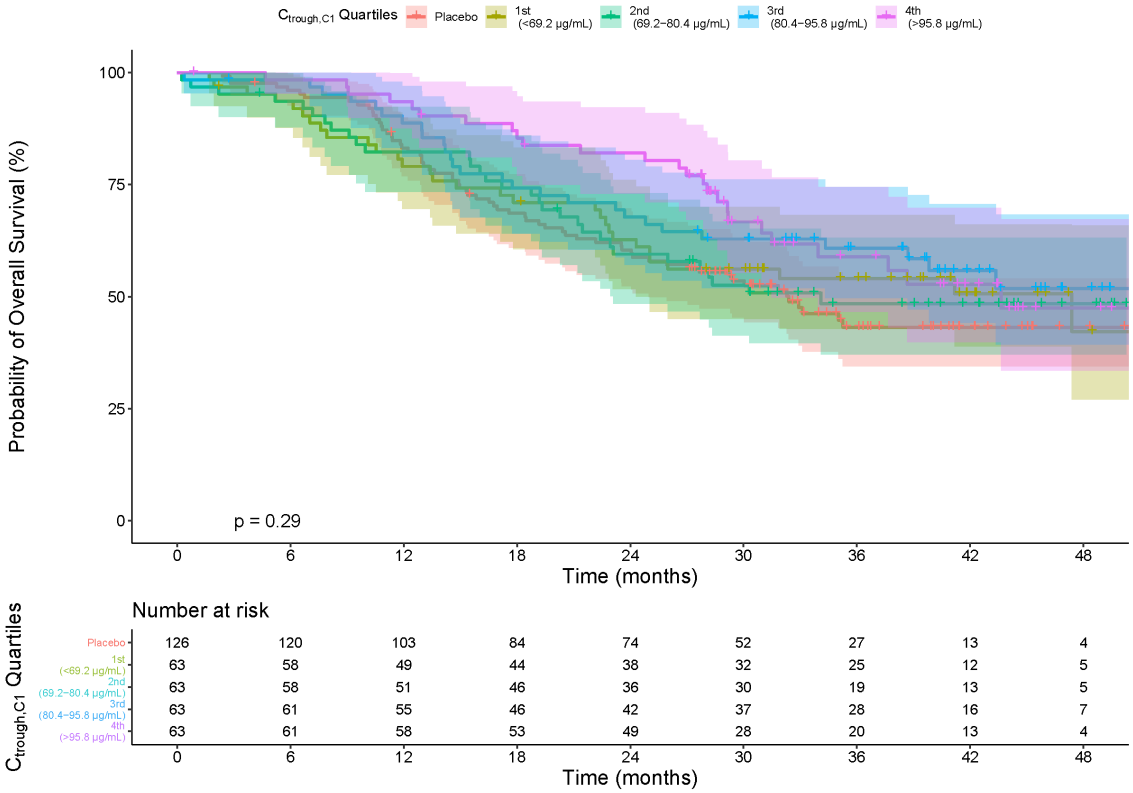


Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CI, and P value is derived from a log-rank test. BICR = blinded independent central review; CI = confidence interval; Ctrough,C1 = trough serum concentration in Cycle 1.

The TTE model for PFS as assessed by BICR showed an estimated 7.9% reduction in the hazard of disease progression or death per increase in Ctrough,C1 of 10 µg/mL, indicating an improvement in PFS with increasing sugemalimab Cycle 1 trough concentration.

The graphical analysis using Kaplan-Meier plots for OS indicated no significant relationship present between sugemalimab exposure (Ctrough,C1) and OS (p>0.05) (Figure 5).

Figure 5: Overall Survival by Quartiles of Ctrough,C1.



Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CI, and P value is derived from a log-rank test. CI = confidence interval; Ctrough,C1 = trough serum concentration in Cycle 1.

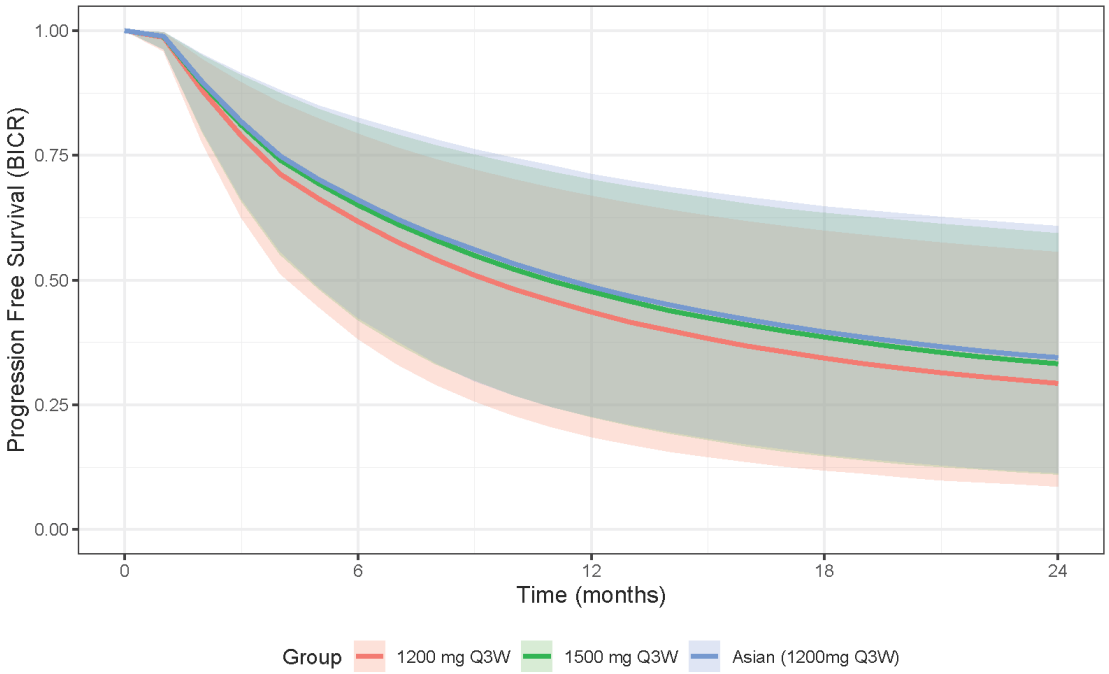
Exposure-efficacy simulations

Since all participants with stage III NSCLC were of Asian race, simulations based upon developed exposure-response analysis were carried out to understand expected exposure-response relationships for different patient characteristics to help support dose selection in the high body weight demographic. Specifically, these simulations accounted for differences in PK due to patient characteristics to allow for prediction of outcomes in NSCLC patients with demographics representative of the high body weight population under the 1200 mg and 1500mg dose IV Q3W regimen.

The final PopPK model was used to simulate exposure metrics AUCC1, Ctrough,C1, and C_{max},C1 for virtual patients under both 1200 mg IV Q3W and 1500mg IV Q3W. These exposure metrics were then incorporated into the exposure-efficacy models to compute the cumulative expected probability of PFS every 3 months up to 24 months.

Simulations of the probability of PFS, stratified by body weight, examined differences in PFS between participants with high body weights in the range of 90 to 120 kg receiving a 1200 mg and higher dose 1500 mg compared to Asian participants with body weights in the range of 43 to 98 kg (Figure 6).

Figure 6: Exposure-response Simulations: Progression-free Survival.



Note: Solid lines represent median., shaded area = 90% PI , red: high body weight population (90 to 120 kg) at 1200 mg; green: high body weight population (90 to 120 kg) at 1500 mg; blue: Asian at 1200 mg.

2.3.5. Discussion on clinical pharmacology

PK information in the target population was collected in Study CS1001-301. The PK data in Study CS1001-301 were included in the initial submission (EMEA/H/C/006088/0000) as supportive evidence. The PK data was also used to support dosing recommendations in patients with high body weight using a PopPK-based PK-bridge.

The bioanalytical methods used in this study are acceptable. The bioanalysis methods as well as the methods for detecting anti-sugemalimab antibodies and anti-sugemalimab neutralizing antibodies were already assessed and found acceptable in the initial submission (EMEA/H/C/006088/0000).

Information on the PK parameters (distribution and elimination) in Stage III patients have been included in section 5.2 of the SmPC which is acceptable.

An updated PopPK model was included compared to the initial submission (EMEA/H/C/006088/0000). The updated PopPK model included NSCLC disease stage (Stage III vs Stage IV) as a new covariate on CL and Vc. The updated PopPK model predicted similar CL between Stage III and Stage IV patients whereas the Vc was slightly lower (~10-15%) for Stage III patients compared to Stage IV patients.

A weight cut-off of 115 kg (1200 mg Q3W ≤115 kg and 1500 mg Q3W >115 kg) was proposed for both Stage III and Stage IV patients which is acceptable. There is a numerical difference in the observed PK exposure between Studies 301 (Stage III) and 302 (Stage IV) (Figure 1) but the difference is not clinically relevant. Furthermore, there is no biological rationale that the dosage of sugemalimab should differ between these patient groups.

The proposed posology weight cut-off was further supported by updated PopPK simulations. The updated simulations for Stage III patients demonstrated that the simulated C_{trough} during Cycle 1 following the proposed posology (1200 mg Q3W ≤115 kg and 1500 mg Q3W >115 kg) are comparable to the corresponding observed C_{trough} during Cycle 1 in Study 301. The simulated median and 90% prediction interval for C_{trough} during Cycle 1 for the proposed posology overlapped with the observed median and 90% prediction interval for C_{trough} during Cycle 1 in study 301. A geometric mean ratio (GMR) was also calculated between the simulated and observed C_{trough} during Cycle 1 which were 0.74 or higher for the proposed posology across the entire simulated weight range which is adequate.

The PK comparisons focused on C_{trough} during Cycle 1 which is acceptable since it is the most relevant exposure metric from an efficacy perspective for a checkpoint inhibitor. Corresponding simulations for AUC and C_{max} (data not shown) also demonstrated comparable PK exposures between the proposed posology and the observed PK exposures in Study 301.

Corresponding PK simulations were provided for Stage IV patients where the simulated C_{trough} during Cycle 1 for the already approved posology were compared with the observed C_{trough} during Cycle 1 in Study 302. The simulation-based exposure comparisons for Stage IV patients demonstrated that the simulated median and 90% prediction interval of C_{trough} during Cycle 1 overlapped with the observed median and 90% prediction interval, to a similar degree as the simulations for Stage III patients. The GMR between the simulated and observed C_{trough} during Cycle 1 were 0.74 or higher for the already posology for Stage IV patients across the entire simulated weight range which is similar to the simulations for Stage III patients. Regarding immunogenicity, there are no clinically relevant differences between Stage III and Stage IV patients which is acceptable. The SmPC section 5.1 has been adequately updated with the ADA results from Study CS1001-301.

The exposure-efficacy analyses and corresponding simulations were only considered supportive evidence with limited impact on the overall benefit-risk. The exposure-efficacy analyses were based on PKPD data from Study CS1001-301 which only included one dose level (1200 mg Q3W). This is a significant limitation of the exposure-efficacy analyses since a single dose level gives a too narrow exposure range to adequately characterise the true exposure-response relationship. This issue is not pursued since the PopPK analysis and PK simulations are considered sufficient to support the proposed posology.

A safety PKPD analysis including patients in the target population (Stage III NSCLC patients) was previously submitted in the initial marketing authorisation application (EMEA/H/C/006088/0000) and is not included in the current assessment report which is acceptable.

2.3.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology package suffices to support the proposed use.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study CS1001-301

Study CS1001-301 (GEMSTONE-301): a randomised, double-blind, placebo-controlled, multicentre Phase III study conducted in China, to evaluate the efficacy and safety of sugemalimab as

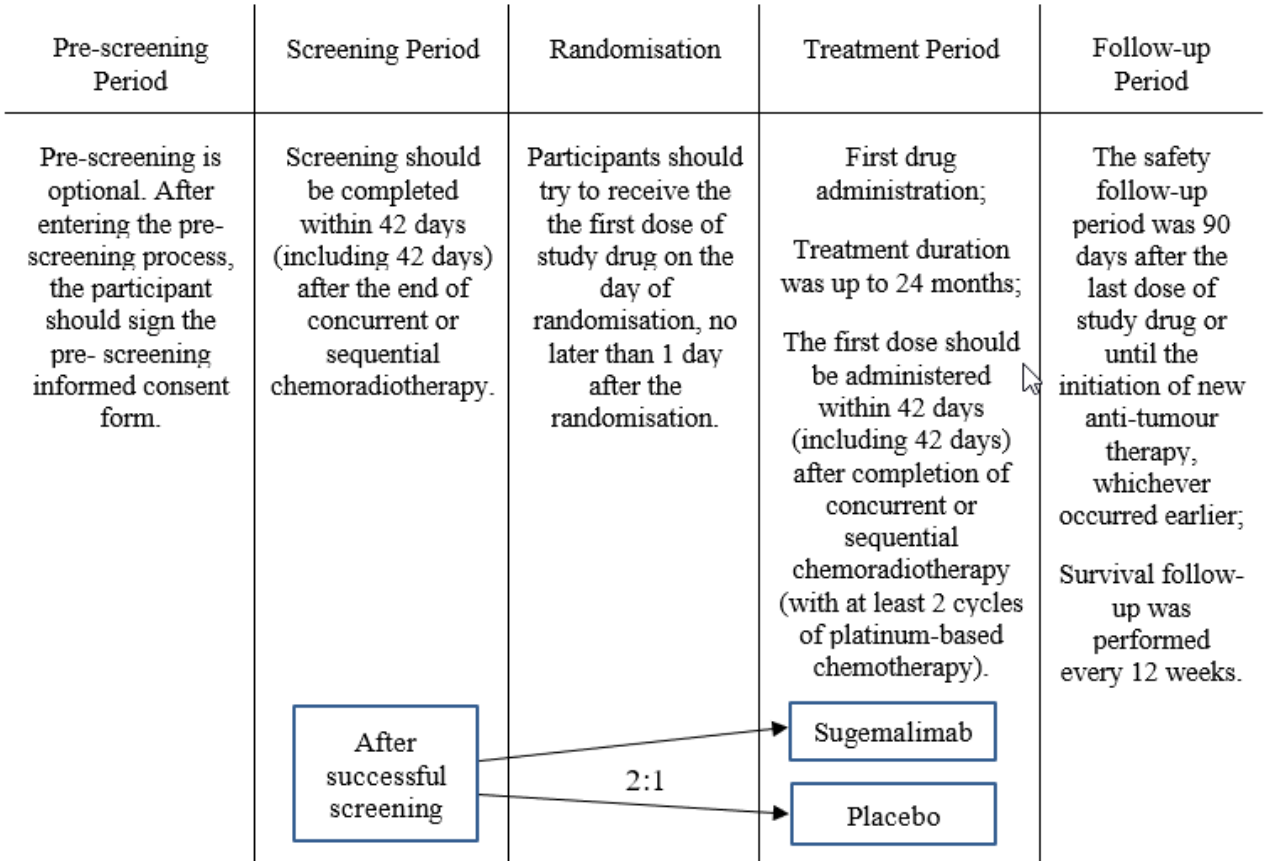
consolidation therapy versus placebo in participants with locally advanced or unresectable stage III NSCLC who have not progressed after concurrent or sequential chemoradiotherapy.

The results from the first interim analysis for PFS (DCO 08 March 2021) from Study CS1001-301 were claimed as supportive in the initial MAA and were described briefly in the EPAR of procedure EMEA/H/C/006088/0000.

The study has been terminated.

Methods

Figure 7: Study flow chart



Study participants

Inclusion criteria

1. Willing to participate in this trial; fully understand and get informed of this trial and have signed the master informed consent form (ICF).
2. ≥ 18 years of age on the day of signing ICF.
3. Have histologically or cytologically confirmed locally advanced, unresectable stage III non-small cell lung cancer (staged according to the International Association for the Study of Lung Cancer [IASLC] classification, version 8; refer to section 14.8).
    - Non-squamous-cell cancer:

- About epidermal growth factor receptor (EGFR) mutation status: subjects with known EGFR mutation must be excluded (testing method and results are acceptable as evaluated by the site and sponsor; methods described in NCCN or CSCO guidelines are recommended). Subjects with unknown EGFR mutation status must receive tests which method must be acceptable as evaluated by site or sponsor; subjects with confirmed EGFR mutation will be excluded.
- About anaplastic lymphoma kinase (ALK) translocation and c-ros pro-oncogene 1-receptor tyrosine kinase (ROS1) translocation: subjects with known ALK or ROS1 translocation will be excluded; subjects with unknown ALK and ROS1 translocation may directly undergo screening without having translocation tests.

• Squamous-cell cancer:

– Subjects with known EGFR mutation, ALK translocation or ROS1 translocation will be excluded; subjects with unknown EGFR, ALK or ROS1 status may directly undergo screening without having tests for these factors.

4. The first dose of CS1001 will be administered within 1 - 42 days (including 42 days) after concurrent/sequential chemoradiotherapy (including at least 2 cycles of platinum-containing chemotherapy) is completed.

   Note: Concurrent chemoradiotherapy is required to be at least 2 cycles of platinum-based chemotherapy concurrent with radiotherapy.

   Note: If a subject was receiving weekly chemotherapy regimen, platinum-based chemotherapy of at least 4 weeks should be completed.

   Note: Screening of subjects within 14 days after concurrent / sequential chemoradiotherapy is recommended.

5. Platinum-containing chemotherapy: Platinum must be one of cisplatin, carboplatin or nedaplatin. Chemotherapy must contain at least one of the following drugs: etoposide, vinorelbine, vinblastine, pemetrexed, taxanes (e.g., paclitaxel, docetaxel, albumin-bound paclitaxel, paclitaxel liposome) or gemcitabine (gemcitabine must not be used as chemotherapy in the chemoradiotherapy).

   Note: Chemotherapy shall follow instructions in the Chinese Society of Clinical Oncology (CSCO) Guideline for Diagnosis and Treatment of Primary Lung Cancer 2017 V1.

6. The last chemotherapy must be administered no later than the last radiotherapy. Consolidation chemotherapy is not allowed after radiotherapy; but induction chemotherapy before concurrent chemoradiotherapy is allowed.

   Note: Interval between the end of chemotherapy cycle and beginning of radiotherapy must not exceed 35 days for sequential chemoradiotherapy.

7. Total dose of radiotherapy is 60 Gy ± 10% (54 Gy - 66 Gy). The minimum technical standard for radiotherapy is three-dimensional conformal radiotherapy (3D-CRT) with CT planning.

   Note: Study RTOG 0617 proved that total dose of radiotherapy increased to 74 Gy would not improve efficacy.

   Note: Dose received by organs is recommended to be as close to the following principles as possible:

   • Average dose in lungs ≤ 20 Gy and/or V20 ≤ 35%

- Average dose in esophagus ≤ 34 Gy
- Average dose in heart ≤ 20 Gy or V50 ≤ 25%

8. Absence of progression after concurrent/sequential chemoradiotherapy (responses should be complete response [CR], partial response [PR] and stable disease [SD]).
9. ECOG PS of 0 or 1.
10. Life expectancy ≥ 12 weeks.
11. Provide unstained tumor tissue sections for TMB assay and provide the relevant pathology report. Subjects with no available archived tumor tissue samples should be willing to receive tumor lesion biopsy for obtaining tumor sample before receiving any study treatment (number of samples will be determined according to the biopsy status). If due to medical reasons, a subject is unable to receive tumor lesion biopsy, the investigator should discuss with the Sponsor to determine the eligibility of the subject.
12. Subject with prior anti-cancer treatment can only be enrolled when all toxicities except for hearing loss, alopecia and fatigue, of prior anti-cancer treatment has recovered to baseline or ≤ Grade 1 (according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03).

    Note: Subjects with > Grade 1 irreversible toxicity that is not expected to get worse after the initiation of study treatment may be eligible after consultation with the Sponsor.
13. Subjects must have adequate organ function as assessed in the following laboratory tests (subjects must not receive any blood transfusion, erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF) or other medical supportive treatment within 7 days prior to the investigational product administration):

Systems	**Laboratory Tests**
Hematology	
Absolute neutrophil count (ANC)	≥ 1.5 X 109/L
Platelets	≥ 100 X 109/L
Hemoglobin	≥ 90 g/L or ≥ 5.6 mmol/L
Kidney	
Serum creatinine or serum creatinine clearance	< 1.5 X ULN ≥ 40 mL/min (according to Cockcroft-Gault equation; refer to Section 14.9; creatinine clearance is only calculated if serum creatinine > 1.5 X ULN)
Liver	
Total bilirubin	**≤** 1.5 X ULN (not applicable for subjects with Gilbert's Syndrome, whose eligibility will be determined after consultation with sponsor).
Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT])	**≤** 3 X ULN
Coagulation	

International normalized ratio (INR) or prothrombin time (PT)	≤ 1.5 X ULN

14. Women of childbearing potential or fertile men must agree to use an effective contraceptive method from signing the master ICF until 180 days after the last dose of investigational product. Women of childbearing potential include premenopausal women and women who became menopausal less than 2 years ago. Women of childbearing potential must have a negative pregnancy test ≤7 days prior to the first dose of investigational product.

Exclusion criteria

1. Histologically identified to have mixed small cell lung cancer component.
2. Disease progression after concurrent/sequential chemoradiotherapy.
3. Major surgical procedure (as determined by investigators) within 28 days prior to the first dose of investigational product.
4. Has received a live vaccine within 28 days prior to the first dose of investigational product.
5. Any use of traditional Chinese medicine or herbal preparations with anti-tumor indications within 14 days prior to the first dose of investigational product.
6. Current participation in another clinical study or use of any investigational drug within 28 days prior to the first dose of investigational product in this trial. (Participation in the overall survival follow-up of a study is allowed.)
7. Any prior treatment of antibody/drug that targets at T-cell coregulatory proteins (immune checkpoints, including PD-1, PD-L1, CTLA4, TIM3 and LAG3, etc.).
8. Subjects with squamous cell lung cancer who had prior treatment of antiangiogenic drugs.
9. Subjects with current active autoimmune disease or prior history of autoimmune disease that probably will relapse (for example, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroid conditions, vasculitis, psoriasis, etc.) or at risk of having these conditions (for example having received organ transplantation or immune suppressant treatment). Subjects with the following conditions are allowed to be screened: type I diabetes mellitus, hypothyroidsm that can be managed with thyroxine replacement only, dermatological condition that doesn't require systemic treatment (for example leukoderma, psoriasis or alopecia) or the condition is expected not to relapse without external trigger.
10. Immune deficient disease or currently under systemic corticosteroid treatment (equivalent to > 10 mg/day prednisone) or any other form of immune suppressing treatment within 7 days prior to the first dose of investigational product.

    Note: Subjects with no active autoimmune disease is allowed to use corticosteroid equivalent to ≤ 10 mg/day prednisone as adrenal replacement treatment. Topical, ophthalmic, intra-articular, nasal or inhaled corticosteroid (with very low systemic absorption) is allowed. Short-term corticosteroid for prevention (for example for contrast allergy) or treating non-autoimmune conditions (for example delayed hypersensitivity caused by contrast allergy).
11. A known additional malignancy within 5 years prior to the first dose of investigational product. Subjects with locally curable malignancies (including basal cell carcinoma of skin, squamous cell carcinoma of skin, breast cancer in situ or cervical cancer in situ) that have undergone curative therapy are permitted to enroll.

12. Pneumonitis ≥ grade 2 caused by chemoradiotherapy (Subjects with Grade 2 pneumonitis not treated with systemic corticosteroid which has recovered to ≤ Grade 1 within 14 days and without risk of recurrence as per investigator's judgment can be screened).

13. Symptomatic interstitial lung disease; subjects with past history of lung disease that in the investigator's judgment may interfere with judgment of treatment of drug-related lung toxicity will also be excluded.

14. Active pulmonary tuberculosis in 1 year prior to first dose of investigational product. Subjects whose active pulmonary tuberculosis occurred at least 1 year ago, who have no evidence of active pulmonary tuberculosis as determined by the investigators are permitted to enroll.

15. History of inflammatory bowel disease or active inflammatory bowel disease (for example Crohn's disease or ulcerative colitis).

16. Known history of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome.

17. Subjects at active phase of chronic hepatitis B or with active hepatitis C. Subjects who are hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody positive at screening must receive hepatitis B virus (HBV) DNA quantitative test (excluded if > 2500 copies/mL or 500 IU/mL) and HCV RNA test (excluded if > lower limit of detection) for confirmation. The subjects can only be enrolled when presence of active hepatitis B or C that requires treatment is ruled out, respectively. Subjects that carry hepatitis B virus, with stable hepatitis B (HBV DNA titer ≤ 2500 copies/mL or 500 IU/mL) after medical treatment or with cured hepatitis C are permitted to enroll.

    Note: If the lower detection limit of HBV DNA test performed locally at the Site is higher than 2500 cps/mL or 500 IU/mL, the subject in that site is eligible as long as the HBV DNA quantitative test result is lower than the lower detection limit.

18. Active infection that necessitates systemic treatment within 14 days prior to the first dose of investigational product.

19. History of organ transplantation.

20. Subjects with known history of alcoholism or drugs abuse.

21. Severe allergic reaction (≥ grade 3 according to CTCAE v4.03) to other monoclonal antibodies.

22. Uncontrollable concomitant diseases which include but may not be limited to: symptomatic congestive heart failure, uncontrollable hypertension, arrhythmia, active peptic ulcer or hemorrhagic disease.

23. QTc interval > 480 msec on the screening electrocardiogram (ECG) (as calculated by Fridericia formula).

24. Subjects with other conditions that in the investigator's opinion may influence subject's compliance or make subjects not suitable for participating in this trial.

Treatments

The investigational treatment regimen was CS1001, 1200 mg, i.v. infusion every 3 weeks. For the placebo group, corresponding placebo was used.

Treatment was to be continued until disease progression or unacceptable toxicity.

Dose increase or reduction of investigational product was not permitted in this trial.

Objectives

Primary objective

To compare the efficacy of sugemalimab vs. placebo in terms of PFS evaluated by BICR according to RECIST v1.1.

Secondary objectives

To compare efficacy of sugemalimab vs. placebo in terms of OS, PFS by INV according to RECIST v1.1, ORR, DoR and time to death/distant metastasis (TTDM) by BICR and INV according to RECIST v1.1.

Outcomes/endpoints

Primary endpoint

Study CS1001-301 had one primary efficacy endpoint, PFS evaluated by BICR according to RECIST v1.1.

PFS was defined as the time from randomization to the first recorded progression or all-cause death, whichever occurred first.

The date of disease progression was the date of the subject's first disease progression whether or not that disease progression is confirmed. Subjects without event (no disease progression or death) will be censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline was censored at the date of randomization. Subjects with two or more missed tumour evaluations and subjects who initiated a new therapy before progression were not censored.

Secondary endpoints

OS (key secondary endpoint):

Overall survival was defined as the time interval between the date of randomization to the date of all-cause death.

ORR:

The number and percentage of subjects who achieve objective tumour response (CR or PR). A subject who failed to receive any tumour assessment after baseline was considered as a non-responder.

DoR:

Duration of response for responders (CR or PR) was defined as the time interval between the date of the earliest qualified response and the date of PD or all-cause death, whichever occurred first. For subjects who were alive without progression following the qualified response, duration of response was censored on the date of last evaluable tumour assessment or last follow up for progression of disease. If no tumour assessment was performed after the first occurrence of CR or PR, duration of response (DoR) was censored at the date when CR or PR first occurs. Subjects with two or more missed tumour evaluations and subjects who initiated a new therapy before progression were not censored.

TTDM:

TTDM was defined as the time from the date of randomization to distant metastasis or death, whichever occurred first. Distant metastasis was defined as new lesion outside the radiation field (as evaluated according to RECIST v1.1 or tissue biopsy). Subjects without event (no distant metastasis or death) were censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline were censored at the date of randomization.

Imaging assessments:

During the first year of the treatment period, imaging assessments were performed every 9 weeks; after 1 year: imaging assessments were performed every 12 weeks until disease progression, loss to follow-up, death, or end of study, whichever occurred first.

Sample size

Sample size and number of events of the study were estimated based upon the following assumptions:

- PFS tested in a two-sided log-rank test at a significance level of 5%
- A power of 97.6% to detect a PFS hazard ratio (HR) of 0.6, corresponding to extension of median PFS from 6 months to 10 months
- The randomization ratio of treatment and control groups was 2:1
- Time-to-event variable assumed to follow exponential distribution
- The average enrolment rate assumed to be 13.6 subjects per month, and approximately 27 months needed to complete study enrolment
- Interim analysis conducted for PFS and type I error controlled by using O'Brien-Fleming method
- Drop-out rate for PFS in the two treatment groups assumed to be 5% every 12 months.

Based on the above assumptions, approximately 368 patients were planned to be randomised, and approximately 262 PFS events were needed to detect the maximum HR of 0.774.

If PFS result is positive, overall survival (OS) is tested in a two-sided log-rank test at a significance level of 5%. Number of events needed for OS analysis were estimated based on the following assumptions:

    - A power of 83% to detect the OS HR of 0.67, corresponding to extension of median OS from 22 months to 32.8 months
    - Time-to-event data assumed to follow exponential distribution
    - Interim analysis to be conducted for OS with approximate Pocock boundary
- Drop-out rate for OS in the two treatment groups assumed to be 2% every 12 months.

Based on this sample size and the above assumptions, the final OS analysis was planned to be performed when approximately 260 deaths occurred. The maximum detectable HR for this event quantity was about 0.75.

Randomisation

Eligible subjects were randomized in 2:1 to receive sugemalimab or placebo by stratification block randomization by IVRS/IWRS (Interactive Voice/Web Response System).

Stratification factors for randomization were: ECOG status (0 versus 1), chemoradiotherapy (concurrent versus sequential) and total radiotherapy dose (<60 Gy and ≥ 60 Gy).

Patients were to be randomized within 42 days after the last radiotherapy. No more than 40% of randomized subjects were to have received sequential chemoradiotherapy

Blinding (masking)

Study CS1001-301 was a double-blinded study.

Statistical methods

Analysis populations

The ITT set included all randomized patients with treatment groups assigned in accordance with the randomization. The analysis of PFS, OS and TTDM was based on the ITT set. ORR analysis was based on ITT population with measurable disease at baseline. Duration of response analysis was based on ITT population who achieved objective response.

The safety analysis set included all subjects who have received at least one dose of study treatment.

Primary analysis

The primary efficacy endpoint was the PFS evaluated by BICR according to RECIST v1.1. Comparison between CS1001 and placebo was performed using a two-sided stratified log-rank test at a significance level of 5%. Stratified Cox regression model was used for estimating efficacy, and PFS hazard ratio (HR) and its 95% confidence interval (CI) was provided. Stratification factors were the same as those used for randomisation, and the order of the three stratification factors were specified as ECOG status, mode of prior chemoradiotherapy, and total dose of baseline radiotherapy. In stratified analysis, if the number of patients in a stratum did not meet the requirement of analytical test, for example, less than 10 patients, then the relevant stratified groups would be combined for analysis. A sensitivity test for the unstratified analysis would also be performed. Kaplan-Meier method was used to estimate median PFS (by Brookmeyer Crowley method), PFS rate at different time points and their 95% CIs (by Greenwood method). A Kaplan-Meier curve was provided to visually describe PFS changes over time.

Secondary analysis

Secondary endpoints: OS, PFS (by investigators according to RECIST v1.1), Duration of response (DoR, by BICR and investigators), and Time to death/distant metastasis (TTDM, by BICR and investigators) were also analysed using the same statistical analysis method as that for the primary efficacy endpoint. Censoring rules according to the statistical analysis plan are summarized in the table:

Endpoint	***Censoring rules***
PFS	Subjects without event (no disease progression or death) were censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline were censored at the date of randomization. Subjects with two or more missed tumour evaluations and subjects who initiated a new therapy before progression were not censored
OS	Subjects without death report before data cutoff were censored at the date of last survival confirmation. Subjects without any data after baseline were censored at the date of randomization.
DoR	For subjects who were alive without progression following the qualified response, duration of response was censored on the date of "last tumour assessment". If no tumour assessment was performed after the first

	occurrence of CR or PR, DoR was censored at the date when CR or PR first occurs. Subjects with two or more missed tumour evaluations and subjects who initiated a new therapy before progression were not censored
TTDM	Subjects without event (no distant metastasis or death) were censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline were censored at the date of randomization.

Objective response rate (ORR, by BICR and investigators) was analysed using stratified Mantel-Haenszel test. A subject who failed to receive any tumour assessment after baseline was considered as a non-responder.

Sensitivity analyses

The following sensitivity analyses of the primary efficacy endpoint and secondary efficacy endpoint were carried out with the same statistical method as used in the primary analysis.

Based on the number of subjects using anti-cancer treatment not permitted by this protocol, the impact of anti-cancer treatment on the PFS (by BICR according to RECIST v1.1) and OS were assessed. Sensitivity analysis was performed when more than 5% of subjects in either treatment group use unallowed anti-neoplastic treatment. Subjects who used non-protocol permitted anti-cancer treatment before any PFS event (by BICR according to RECIST v1.1) were censored at the date of "last tumour assessment" prior to the non-protocol permitted anti-cancer treatment. Subjects without event (no disease progression or death) were censored at the date of "last tumour assessment" prior to the non-protocol permitted anti-cancer treatment. Subjects who had no post-baseline tumour were censored on the randomization day. Subjects who used non-protocol permitted anti-cancer treatment before any OS event were censored at the date of the non-protocol permitted anti-cancer treatment using day. Subjects without death report before data cutoff were censored on the date of non-protocol permitted anti-cancer treatment using day. Subjects without any data after baseline were censored at the date of randomization.

Sensitivity analysis was performed for the impact of missing tumour assessments on PFS (as per BICR's evaluation according to RECIST v1.1). Subjects who had two or more missing tumour assessments prior to PFS event were censored at the day of "last tumour assessment" prior to the relevant event. Subjects without event (no disease progression or death) were censored at the date of "last tumour assessment". Subjects without any data after baseline were censored at the date of randomization.

The impact of COVID-19 on PFS (by BICR according to RECIST v1.1) was analysed as follows: The patients with a delay of CS1001/placebo administration > 9 weeks due to COVID-19 (the delay duration is calculated according to IxRS scheduled visit date) were censored on the day of "last tumour assessment" prior to the start of COVID-19. The start time of COVID-19 was set as 22Jan2020. For other patients, those who did not have an event were censored at the "last tumour assessment". Subjects without tumour assessment data after baseline were censored at the date of randomization.

Subgroup analyses

Subgroup analyses were performed for PFS (by BICR according to RECIST v1.1), OS, and ORR (by BICR) providing a forest plot containing each subgroup factor as follows: demographics, stratification factors, histopathological type, best response of chemoradiotherapy, and prior anti-cancer treatment other than chemoradiotherapy, to evaluate the consistency of study results between each subgroup.

Multiplicity

The sequential testing method was used to control overall type I error. If PFS (evaluated by BICR according to RECIST v1.1) interim or final analysis show that the null hypothesis was rejected, i.e. CS1001 is superior to placebo, the sequential testing of secondary efficacy endpoints was conducted in the following order:
1) OS
2) TTDM by BICR
3) ORR by BICR.
First, OS hypothesis testing (at a significance level of 0.05) was conducted; if OS interim analysis results indicate the null hypothesis is rejected, hypothesis testing (at a significance level of 0.05) of TTDM final analysis was to be conducted, and the data cutoff is consistent with that of the OS interim analysis; if final TTDM analysis results indicate the null hypothesis is rejected, hypothesis testing (at a significance level of 0.05) of ORR final analysis was to be conducted, and the data cutoff is consistent with that of the OS interim analysis; if OS interim analysis results indicate the null hypothesis is not rejected, while the final analysis results indicate the null hypothesis is rejected, the hypothesis testing (at a significance level of 0.05) of TTDM and ORR final analysis was to be conducted using the data cutoff that of the OS interim analysis; if TTDM final analysis results indicate the null hypothesis is rejected, hypothesis testing (at a significance level of 0.05) of ORR final analysis was to be conducted.

Interim analysis

Interim PFS analysis was planned to be conducted when approximately 194 PFS events (74% of data information) were observed or last patient is enrolled, whichever occurs later. The interim analysis was estimated to be conducted at around 27 months after the first patient enrolment. Final PFS analysis was planned to be performed when approximately 262 PFS events are observed, which was estimated to be at around 33 months after the first patient enrolment. O'Brien-Fleming method was used to control two-sided overall type I error < 0.05. The PFS interim analysis was conducted with a total of 197 PFS events as of the data cutoff date (08 March 2021). The PFS final analysis was conducted with a total of 244 PFS events as of the data cutoff date (01 March 2022).

If the interim or final PFS analysis result was positive, interim OS analysis was performed when approximately 175 deaths (67% of data information) occur, which was estimated to be around 40 months after the first subject enrolment. The final OS analysis was to be performed when approximately 260 OS events were observed. This analysis was estimated to be done at 68 months after the first subject enrolment. Lan-DeMets method with an approximation Pocock boundary were to be used to control overall type I error <0.05. The OS interim analysis was conducted with a total of 180 OS events as of the data cutoff date (03 April 2023).

Independent data monitoring committee (iDMC) evaluated the safety data collected in the trial regularly every 6 months after the first patient enrolment. Members of iDMC were from outside the sponsor, who must follow the guidance about duties and responsibilities. Any safety monitoring result that may affect the conduct of this trial must be notified to the investigator so that Ethics Committee (EC) will be informed. iDMC monitored the data for interim PFS analysis and made recommendations to sponsor according to the following ending boundaries. Constitution, roles and responsibilities and execution of iDMC were described in iDMC guidance.

Table 4: Boundaries for PFS and OS analyses (for the planned number of events)

	Sample size	Number of events	Time (months)	Boundary of hazard ratio	Median difference for hazard ratio boundary	Boundary of P value	Power
PFS							
Interim analysis	368	194	27	0.707	2.5	0.0183	0.854
Final analysis	368	262	33	0.774	1.8	0.0445	0.976
OS							
Interim analysis	368	175	40	0.726	8.3	0.0384	0.677
Final analysis	368	260	68	0.750	7.3	0.0246	0.830

The boundary values were updated according to the observed number of events.

Changes of the planned analyses

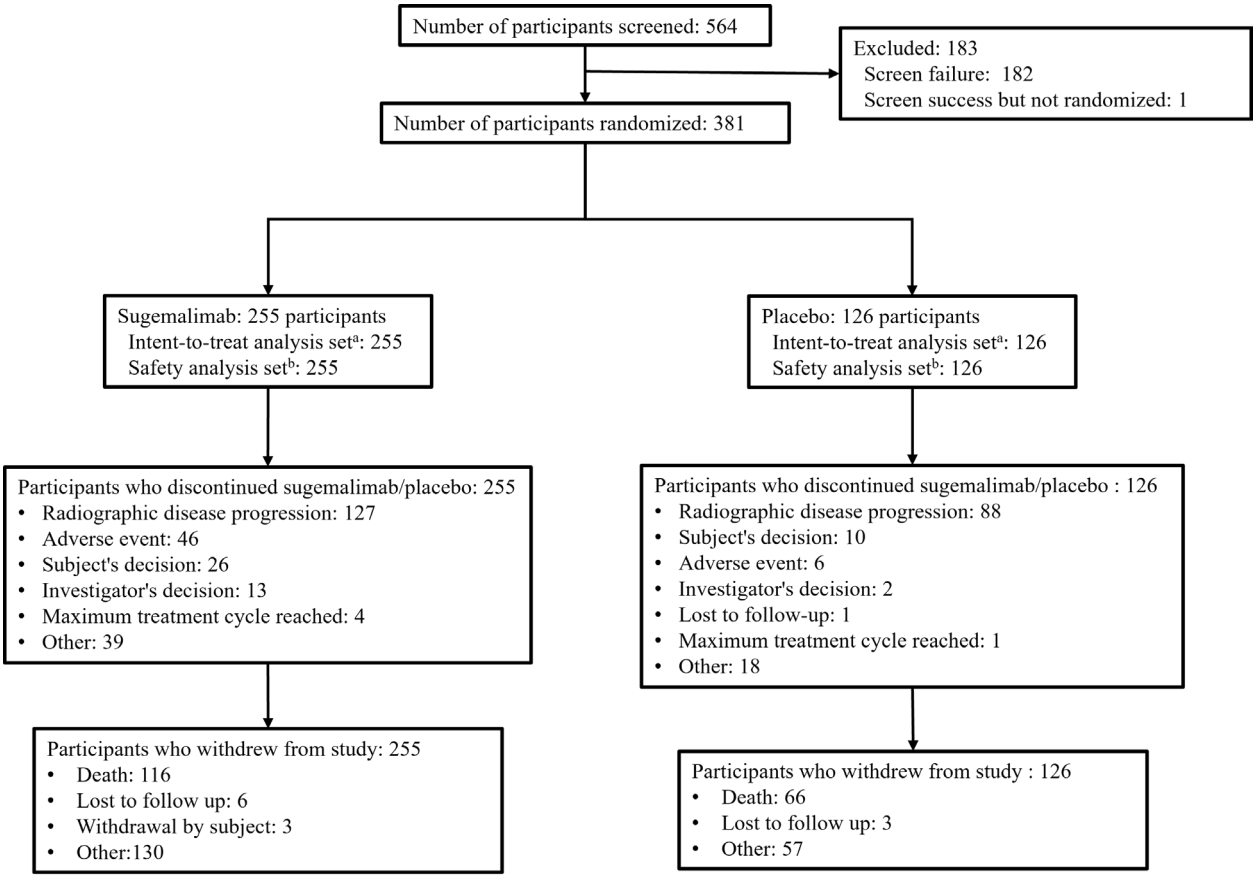
The statistical analysis plan (SAP) was authored on 12 April 2021, based on the protocol version 5 (from 20 November 2020). No changes were made in the SAP.

In the protocol version 5, the primary objective and endpoint of the study were revised from "Progression-free Survival (PFS) by the investigator according to RECIST v1.1" to "PFS by Blinded Independent Central Review (BICR) according to RECIST v1.1". Also, the planned study sample size was changed from 402 to 368. In an earlier protocol version, a section on multiple comparisons was added.

Results

Participant flow

Figure 8: Participant Disposition – Study CS1001-301 (OS Interim Analysis DCO3 – 03 April 2023)



DCO3 date: 03 April 2023
Abbreviation: ITT = intention-to-treat.
[a] All participants who were randomised into the study.
[b] All participants who were randomised and received at least one dose of the study drug.

Table 5: Patient disposition

	CS1001	Placebo	Total
Screened			564
Screen failure			182
Screen success but not randomized			1
Randomized	255 (100.0%)	126 (100.0%)	381 (100.0%)
Treated	255 (100.0%)	126 (100.0%)	381 (100.0%)
Discontinued from study treatment	255 (100.0%)	126 (100.0%)	381 (100.0%)
Adverse event	46 (18.0%)	6 (4.8%)	52 (13.6%)
Radiographic disease progression	127 (49.8%)	88 (69.8%)	215 (56.4%)
Symptomatic deterioration without radiographic evidence	0	0	0
Subject's decision	26 (10.2%)	10 (7.9%)	36 (9.4%)
Investigator's decision	13 (5.1%)	2 (1.6%)	15 (3.9%)
Study terminated by sponsor	0	0	0
Need for prohibited medications	0	0	0
Severe non-compliance with the study and/or study procedures	0	0	0
Lost to follow-up	0	1 (0.8%)	1 (0.3%)
Death	0	0	0
Pregnancy	0	0	0
Maximum treatment cycle reached	4 (1.6%)	1 (0.8%)	5 (1.3%)
Other	39 (15.3%)	18 (14.3%)	57 (15.0%)
Discontinued from study	255 (100.0%)	126 (100.0%)	381 (100.0%)
Death	116 (45.5%)	66 (52.4%)	182 (47.8%)
Lost to follow up	6 (2.4%)	3 (2.4%)	9 (2.4%)
Withdrawal by subject	3 (1.2%)	0	3 (0.8%)
Other	130 (51.0%)	57 (45.2%)	187 (49.1%)

All patients that discontinued from study under “other” did so due to the termination of the study by the sponsor.

Recruitment

A total of 564 patients were screened at 50 study sites, all in China, and a total of 381 patients were randomised in a 2:1 ratio to the sugemalimab group (255 patients) and the placebo group (126 patients) from 26 October 2018 to 30 December 2020.

Conduct of the study

Protocol amendments

Latest protocol version 5.1 – 15 July 2022

Updated procedures at the completion of the study following the termination after the OS interim analysis. This included the termination of BICR evaluation and PK and ADA samples.

Added guidance for immune-related myocarditis.

Protocol version 5.0 – 30 November 2020 updates

Increased number of sites from 40 to 50.

Primary endpoint updated from INV to BICR and revision of secondary endpoints in line with this.

Decreased sample size from 402 to 368 patients, reduced number of events for the IA and final PFS analysis, the method for controlling the type I error was changed from Hwang-Shil-DeCani to O'Brien-Fleming.

Updated the evaluation of PD to be consistent with RECIST v1.1.

Protocol version 4.0 – 11 May 2020 updates

Added requirement concerning concurrent chemoradiotherapy.

Added sequential testing of secondary endpoints.

Added the requirement to obtain routine laboratory tests and thyroid function tests within 3 days prior to study drug administration from Cycle 2 and onwards.

Revised safety follow-up to include "or initiation of new anti-cancer therapy.

Added confirmation criteria for disease progression.

Added the value of Gamma parameter of Hwang-Shil-DeCani methods and the precision of p-value bound.

Added that irradiated lesions were to be considered as measurable disease if the criteria for measurable disease and target lesion selection requirements were met considering consistent assessment of anti-tumour efficacy according to RECIST (v1.1)

Protocol version 3.1 – 29 October 2019 updates

Added exclusion criteria 8: "Subjects with squamous cell lung cancer who had prior treatment of antiangiogenic drugs"

Protocol version 3.0 – 12 September 2019 updates

The pre-screening phase were added to the study procedures.

The TMB-related study objectives and endpoints were adjusted to lower the requirements on tumour tissue sections for TMB test.

Removed efficacy comparison in the subgroup with tumour mutational burden $\geq$10.

Patients with cytologically confirmed locally advanced, unresectable stage III NSCLC were included in the enrolled population.

Requirement for patients with unknown EGFR, ALK or ROS status to be tested centrally were removed.

Inclusion criteria of radiation received in the heart was reduced in accordance with NCCN NSCLC guideline for organ-specific radiation dose.

Modified inclusion criteria 13 regarding supportive treatment before assessment of adequate organ function from 14 days to 7 days.

Modified exclusion criteria 9 reducing the wash-out time of systemic corticosteroid treatment from 14 days to 7 days.

No patients were included under previous protocol versions; hence these are not commented further.

Protocol deviations

Table 6: Summary of Important Protocol Deviations-Intent-to-Treat Analysis Set

Deviation Category Types of Deviations	**Sugemalimab (N=255)**	**Placebo (N=126)**	**Total (N=381)**
Number of patients with at least one important protocol deviation	50 (19.6%)	16 (12.7%)	66 (17.3%)
Overall total number of important protocol deviations	54	22	76
Study Conduct/Procedures	**31 (12.2%)**	**9 (7.1%)**	**40 (10.5%)**
Screening	9 (3.5%)	2 (1.6%)	11 (2.9%)
Inclusion/Exclusion Criteria	8 (3.1%)	2 (1.6%)	10 (2.6%)
Study Restrictions/Withdrawal Criteria	5 (2.0%)	3 (2.4%)	8 (2.1%)
Sample Processing/Storage	3 (1.2%)	1 (0.8%)	4 (1.0%)
Study Assessment	2 (0.8%)	2 (1.6%)	4 (1.0%)
Dose Formulation/Dose Administration	2 (0.8%)	0	2 (0.5%)
Sample Collection	2 (0.8%)	0	2 (0.5%)
Safety	**11 (4.3%)**	**5 (4.0%)**	**16 (4.2%)**
Reporting/Follow-up	11 (4.3%)	5 (4.0%)	16 (4.2%)
Recording	1 (0.4%)	0	1 (0.3%)
Informed Consent	**7 (2.7%)**	**3 (2.4%)**	**10 (2.6%)**
Presence/Absence	6 (2.4%)	2 (1.6%)	8 (2.1%)
Signature/Date	1 (0.4%)	0	1 (0.3%)
Version	0	1 (0.8%)	1 (0.3%)
Investigational Product	**1 (0.4%)**	**2 (1.6%)**	**3 (0.8%)**
Handling/Storage/Retention	1 (0.4%)	2 (1.6%)	3 (0.8%)

Source: Table t_dv_ITT_2
A patient was only counted once if experiencing more than one deviation of the same type.

Important protocol deviations due to the COVID-19 pandemic occurred in 2 (0.8%) patients in the sugemalimab group and 1 (0.8%) patient in the placebo group, which were categorized as study conduct/procedures and informed consent.

Baseline data

Table 7: Demographic and Baseline Characteristics-Intent-to-Treat Analysis Set

	Sugemalimab (N=255)	Placebo (N=126)	Total (N=381)
Sex			
Male	236 (92.5%)	115 (91.3%)	351 (92.1%)
Female	19 (7.5%)	11 (8.7%)	30 (7.9%)
Age (years)			
n	255	126	381
Mean (SD)	60.5 (6.62)	59.9 (6.72)	60.3 (6.65)
Median	61.0	60.0	61.0
Min, Max	46, 78	42, 73	42, 78
Age category			
<65 years	182 (71.4%)	94 (74.6%)	276 (72.4%)
>=65 years	73 (28.6%)	32 (25.4%)	105 (27.6%)
Race			
Asian	255 (100.0%)	126 (100.0%)	381 (100.0%)
Height (cm)			
n	252	125	377
Mean (SD)	166.9 (6.64)	166.8 (6.43)	166.9 (6.57)
Median	168.0	168.0	168.0
Min, Max	143, 185	150, 188	143, 188
Weight at baseline (kg)			
n	255	126	381
Mean (SD)	63.8 (10.07)	63.7 (9.91)	63.8 (10.00)
Median	62.0	63.0	62.0
Min, Max	43, 98	43, 93	43, 98
BMI at baseline (kg/m^2)			
n	252	125	377
Mean (SD)	22.9 (3.07)	22.9 (2.93)	22.9 (3.02)
Median	22.7	22.7	22.7
Min, Max	15, 32	17, 32	15, 32
Smoking history			
Never	42 (16.5%)	16 (12.7%)	58 (15.2%)
Former	195 (76.5%)	101 (80.2%)	296 (77.7%)
Current	18 (7.1%)	9 (7.1%)	27 (7.1%)
ECOG PS			
0	78 (30.6%)	38 (30.2%)	116 (30.4%)
1	177 (69.4%)	88 (69.8%)	265 (69.6%)
Prior platinum treatment			
Cisplatin	130 (51.0%)	61 (48.4%)	191 (50.1%)
Carboplatin	82 (32.2%)	47 (37.3%)	129 (33.9%)
Nedaplatin	56 (22.0%)	20 (15.9%)	76 (19.9%)

Source: Table t_dm_ITT_2
Abbreviation: BMI = body mass index; ECOG = eastern cooperative oncology group; PS = performance status; SD = standard deviation.

Table 8: Baseline Disease Characteristics – Intent-to-Treat Analysis Set

	Sugemalimab (N=255)	Placebo (N=126)	Total (N=381)
Time since initial diagnosis (months)			
n	255	126	381
Mean (SD)	5.2 (3.85)	7.6 (21.79)	6.0 (12.94)
Median	4.4	4.6	4.5
Min, Max	2, 41	2, 219	2, 219
Stage of non-small cell lung cancer before chemoradiotherapy			
Stage IIIA	74 (29.0%)	32 (25.4%)	106 (27.8%)
Stage IIIB	146 (57.3%)	65 (51.6%)	211 (55.4%)
Stage IIIC	33 (12.9%)	28 (22.2%)	61 (16.0%)
Other	2 (0.8%)	1 (0.8%)	3 (0.8%)
Histology type			
Squamous cell carcinoma	177 (69.4%)	89 (70.6%)	266 (69.8%)
Non-squamous cell carcinoma	76 (29.8%)	37 (29.4%)	113 (29.7%)
Missing	2 (0.8%)	0	2 (0.5%)
Chemoradiotherapy type			
Sequential chemoradiotherapy	86 (33.7%)	41 (32.5%)	127 (33.3%)
Concurrent chemoradiotherapy	169 (66.3%)	85 (67.5%)	254 (66.7%)
Best response to chemoradiotherapy			
CR	4 (1.6%)	2 (1.6%)	6 (1.6%)
PR	172 (67.5%)	77 (61.1%)	249 (65.4%)
SD*	79 (31.0%)	47 (37.3%)	126 (33.1%)

Source: Table t_dm_dx_ITT_2
Abbreviation: CR = complete response; PD = disease progression; PR = partial response; SD* = stable disease; SD = standard deviation.

Table 9: Prior Treatment History of Non-small Cell Lung Cancer – Intent-to-Treat Analysis Set

	Sugemalimab (N=255)	Placebo (N=126)
Duration of chemotherapy in prior chemoradiotherapy (months)		
n	255	126
Mean (SD)	2.0 (1.20)	2.0 (1.20)
Median	1.5	1.5
Min, Max	0, 13	1, 8
Whether induction chemotherapy was received in prior concurrent chemoradiotherapy		
Yes	103 (40.4%)	60 (47.6%)
No	66 (25.9%)	25 (19.8%)
Duration of induction chemotherapy in prior concurrent chemoradiotherapy (months)		
n	103	60
Mean (SD)	1.5 (1.30)	1.8 (1.24)
Median	1.3	1.5
Min, Max	0, 12	0, 6
Anatomic sites receiving radiotherapy in prior chemoradiotherapy		
Lung	246 (96.5%)	124 (98.4%)
Regional lymph node	113 (44.3%)	50 (39.7%)
Distant lymph nodes	1 (0.4%)	0
Trachea	1 (0.4%)	0
Other	2 (0.8%)	2 (1.6%)
Cumulative total dose of radiotherapy received in prior chemoradiotherapy (Gy)		
Dose<60	43 (16.9%)	21 (16.7%)
Dose≥60	212 (83.1%)	105 (83.3%)
Prior anti-tumour drug therapy other than chemoradiotherapy		
Yes	22 (8.6%)	6 (4.8%)
No	233 (91.4%)	120 (95.2%)
Other prior radiotherapy other than chemoradiotherapy		
Yes	0	0
No	255 (100.0%)	126 (100.0%)
Prior cancer-related surgery		
Yes	13 (5.1%)	6 (4.8%)
No	242 (94.9%)	120 (95.2%)

Source: Table t_pr_pchemrad_ITT_2
Abbreviation: SD = standard deviation.

Table 10: Frequency of PD-L1 results – Intent-to-Treat Analysis Set

	Sugemalimab (N=255)	Placebo (N=126)	Total (N=381)
PD-L1 (TC%)			
< 1%	51 (20.0%)	29 (23.0%)	80 (21.0%)
>= 1%	72 (28.2%)	23 (18.3%)	95 (24.9%)
Not tested	132 (51.8%)	74 (58.7%)	206 (54.1%)

Information on other actionable mutations is not available because these were not tested.

Numbers analysed

Table 11: Summary of Analysis Sets

	Sugemalimab	Placebo	Total
Intent-to-Treat Analysis Set (ITT)	255	126	381
Safety Analysis Set (SAS)	255	126	381
Pharmacokinetic Analysis Set (PKAS)	252	0	252
Anti-drug Antibody Analysis Set (ADAAS)	255	0	255

Intent-to-treat analysis set consisted of all patients who were randomised.
Safety analysis set consisted of all patients who received at least one dose of study drug, and patients would be assigned as treated.
Pharmacokinetic analysis set consisted of all patients who received at least one dose of study drug and had at least one post-baseline pharmacokinetic assessment.
Anti-drug antibody analysis set consisted of all patients who received at least one dose of study drug and had at least one post-baseline anti-drug antibody assessment.

Outcomes and estimation

As of the data cutoff date (03 April 2023) for the OS interim analysis, the median follow-up time (range) was 40.4 (0.23+ -53.26) months in the sugemalimab group and 35.4 (2.40+-51.19) months in the placebo group.

Primary endpoint, Progression Free Survival

The alpha-protected final PFS was reported for the final PFS analysis (DCO 01 March 2022) and also for the OS interim analysis (DCO 03 April 2023).

As of the data cutoff date for PFS final analysis, 154 (60.4%) PFS events (129 disease progression and 25 deaths) had occurred in the sugemalimab group and 90 (71.4%) PFS events (85 disease progression and 5 deaths) had occurred in the placebo group. The median PFS assessed by BICR in the sugemalimab group was 10.5 (95% CI: 8.3, 17.1) versus 6.2 months (95% CI: 4.2, 8.1) in the placebo group. The stratified HR was 0.65 (95% CI: 0.50, 0.84) and a two-sided stratified log-rank test p=0.0012). The final PFS analysis was also multiplicity controlled, and the result was statistically significant.

Table 12: Summary of Progression-free Survival by BICR – Intent-to-Treat Analysis Set (DCO 01 March 2022, PFS final analysis)

	Sugemalimab (N=255)	Placebo (N=126)
Participants with event	**154 (60.4%)**	**90 (71.4%)**
Progressive disease	129	85
Death	25	5
Participants censored	**101 (39.6%)**	**36 (28.6%)**
Progression-free survival (months)		
Median	10.51	6.21
95% CI	(8.25, 17.12)	(4.21, 8.08)
25% and 75% percentiles	4.01, -	2.33, 20.04

	Sugemalimab (N=255)	Placebo (N=126)
Range	0.03+ to 38.24+	0.03+ to 35.25
Stratified analysis*		
2-sided p-value (log-rank)	0.0012	
Hazard ratio	0.65	
95% CI	(0.50, 0.84)	
Unstratified analysis		
2-sided p-value (log-rank)	0.0014	
Hazard ratio	0.65	
95% CI	(0.50, 0.85)	
Progression-free survival rate		
6 months	67.0%	52.4%
95% CI	(60.84%, 72.46%)	(43.29%, 60.80%)
Difference	14.6%	
95% CI	(4.04%, 25.14%)	
12 months	49.5%	32.3%
95% CI	(43.09%, 55.59%)	(24.11%, 40.84%)
Difference	17.2%	
95% CI	(6.64%, 27.67%)	
18 months	41.4%	26.4%
95% CI	(34.94%, 47.81%)	(18.41%, 35.03%)
Difference	15.1%	
95% CI	(4.46%, 25.67%)	
24 months	38.6%	23.1%
95% CI	(32.04%, 45.16%)	(14.34%, 33.07%)
Difference	15.5%	
95% CI	(3.96%, 27.12%)	
30 months	30.7%	15.4%
95% CI	(23.55%, 38.02%)	(4.84%, 31.45%)
Difference	15.3%	
95% CI	(-0.39%, 30.92%)	
36 months	26.1%	0
95% CI	(18.02%, 34.87%)	(-, -)
Difference	26.1%	
95% CI	(-, -)	

DCO2 date: 01 March 2022

Abbreviations: BICR = blinded independent central review; CI = confidence interval.

Summaries of progression-free survival (median, percentiles) were Kaplan-Meier estimates.
Confidence interval for the median was computed using the method of Brookmeyer and Crowley.
Confidence interval for event-free rate was computed using the Greenwood method.
Confidence interval for difference in rates was computed based on normal approximation with pooled standard error.
Hazard ratios were estimated by Cox regression.

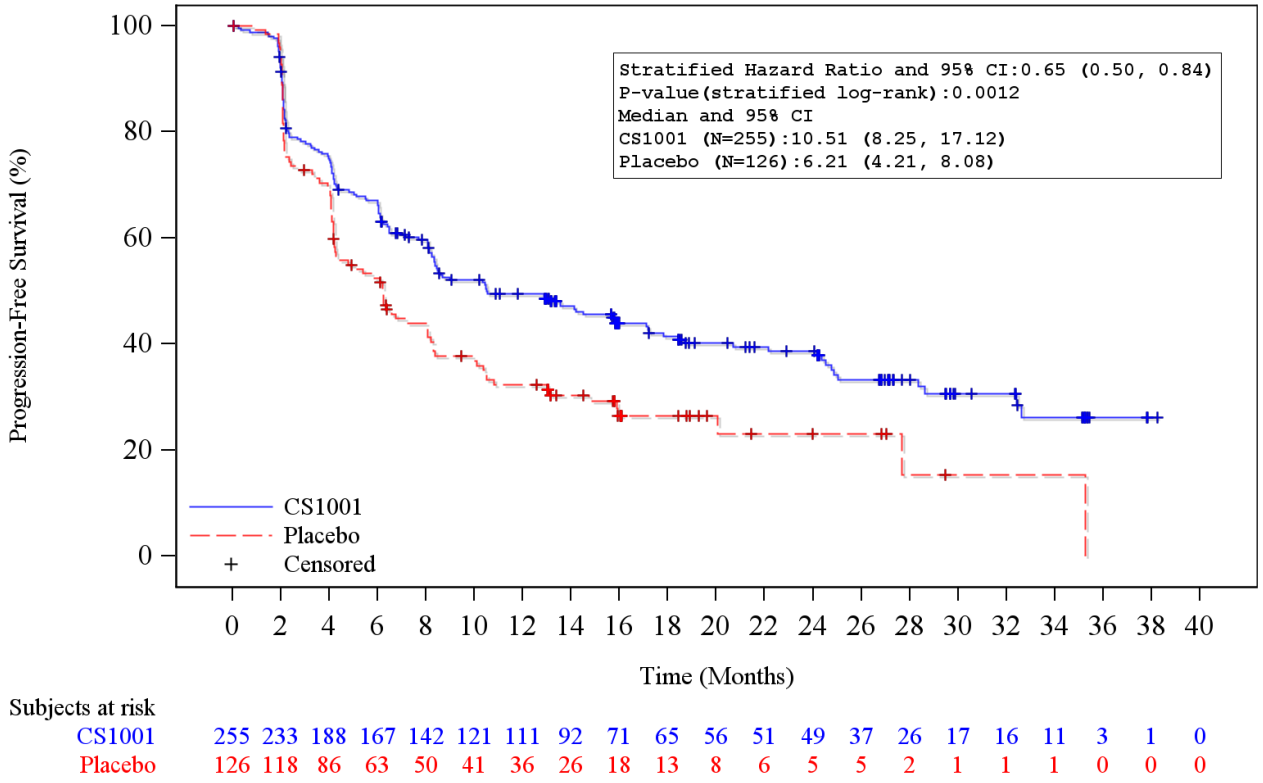
+ was for the minimum or maximum value from censored participants.

* The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from IxRS (Interactive Voice/Web Response System).

Table 13: Reasons for censoring of PFS - Intent-to-Treat Analysis Set (DCO 01March 2022, PFS final analysis)

	Sugemalimab (N=255)	Placebo (N=126)
Patients Censored	101 (39.6%)	36 (28.6%)
Alive without documented progression	99 (38.8%)	35 (27.8%)
No post-baseline assessment	0	1 (0.8%)
Withdrawal by subject	2 (0.8%)	0

Figure 9: Kaplan-Meier Curve of Progression-free Survival (PFS) by BICR – Intent-to-Treat Analysis Set (DCO 01March 2022, PFS final analysis)



DCO2 date: 01 March 2022
Abbreviation: BICR = blinded independent central review; CI = confidence interval.

Medians were Kaplan-Meier estimates. Confidence interval for the median was computed using the method of Brookmeyer and Crowley.

Hazard ratio was estimated by stratified Cox regression model with stratification factors from IxRS (Interactive Voice/Web Response System).

P-value was from stratified log rank test with stratification factors from IxRS.

The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy.

Table 14: Summary of Progression-free Survival by BICR (descriptive PFS analysis – Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)

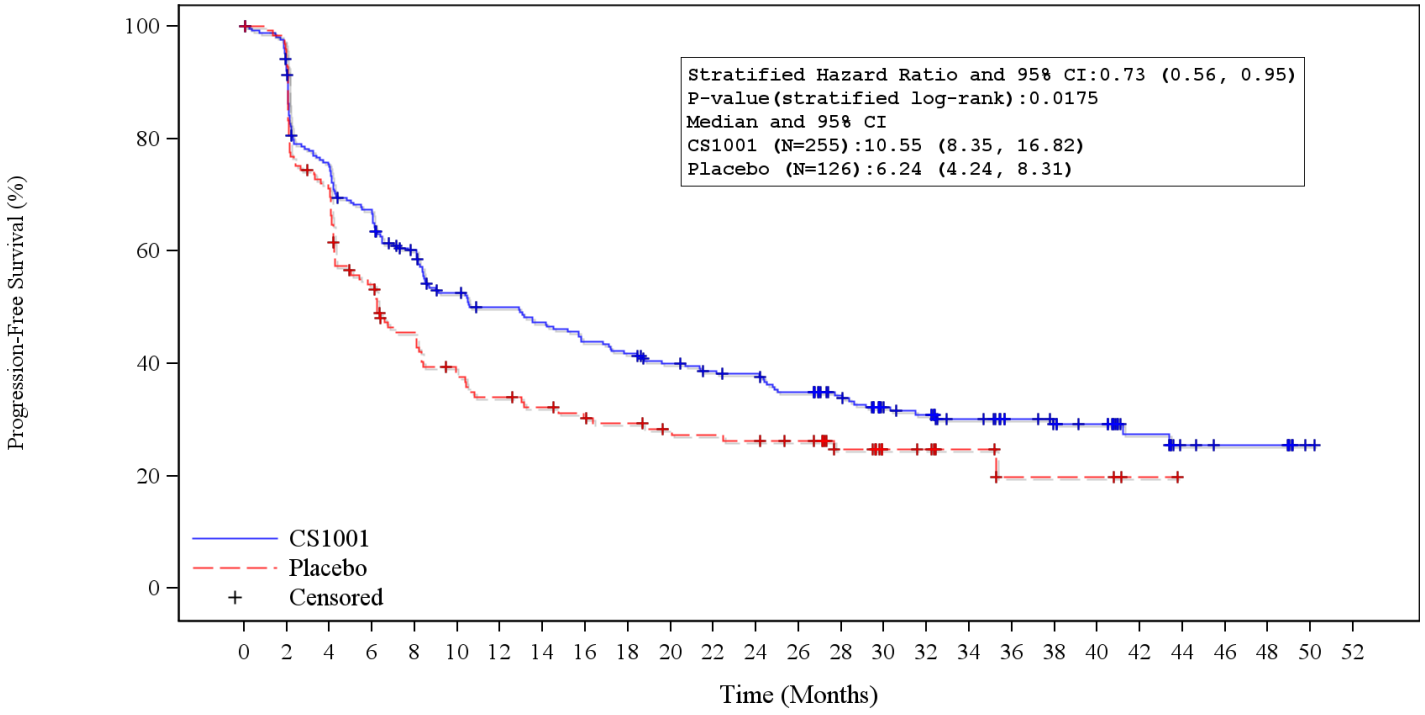
	Sugemalimab (N=255)	Placebo (N=126)
Patients with event	**169 (66.3%)**	**90 (71.4%)**
Progressive disease	137	85
Death	32	5
Patients censored	**86 (33.7%)**	**36 (28.6%)**
Progression-free survival (months)		
Median	10.55	6.24
95% CI	(8.35, 16.82)	(4.24, 8.31)
25% and 75% percentiles	4.01, -	2.66, 27.66
Range	0.03^{+} to 50.17^{+}	0.03^{+} to 43.76^{+}
Stratified analysis*		
2-sided p-value (log-rank)[a]	0.0175	
Hazard ratio	0.73	
95% CI	(0.56, 0.95)	

Abbreviation: BICR = blinded independent central review; CI = confidence interval.
Summaries of progression-free survival (median, percentiles) were Kaplan-Meier estimates.
Hazard ratios were estimated by Cox regression.
$^{+}$ was for the minimum or maximum value from censored patients.
* The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from IxRS (Interactive Voice/Web Response System).
[a)] Descriptive p-value.

Table 15: Reasons for censoring of PFS - Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)

	Sugemalimab (N=255)	Placebo (N=126)
Patients Censored	86 (33.7%)	36 (28.6%)
Alive without documented progression	83 (32.5%)	35 (27.8%)
No post-baseline assessment	0	1 (0.8%)
Withdrawal by subject	2 (0.8%)	0
Lost to follow-up	1 (0.4%)	0

Figure 10: Kaplan-Meier Curve of Progression-free Survival (PFS) by BICR – Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)



Subjects at risk

CS1001	255	233	188	168	144	123	115	109	101	96	89	84	82	74	65	51	48	39	32	28	25	15	9	7	7	1	0
Placebo	126	118	88	65	52	43	38	35	32	30	27	26	25	23	16	10	9	6	3	3	3	1	0	0	0	0	0

Abbreviation: BICR = blinded independent central review; CI = confidence interval.

Medians were Kaplan-Meier estimates. Confidence interval for the median was computed using the method of Brookmeyer and Crowley. Hazard ratio was estimated by stratified Cox regression model with stratification factors from IxRS (Interactive Voice/Web Response System). P-value was from stratified log rank, test with stratification factors from IxRS, descriptive.

The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy.

Secondary endpoints

Overall survival

OS did not reach statistical significance at the OS interim analysis.

Table 16: Summary of Overall Survival - Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)

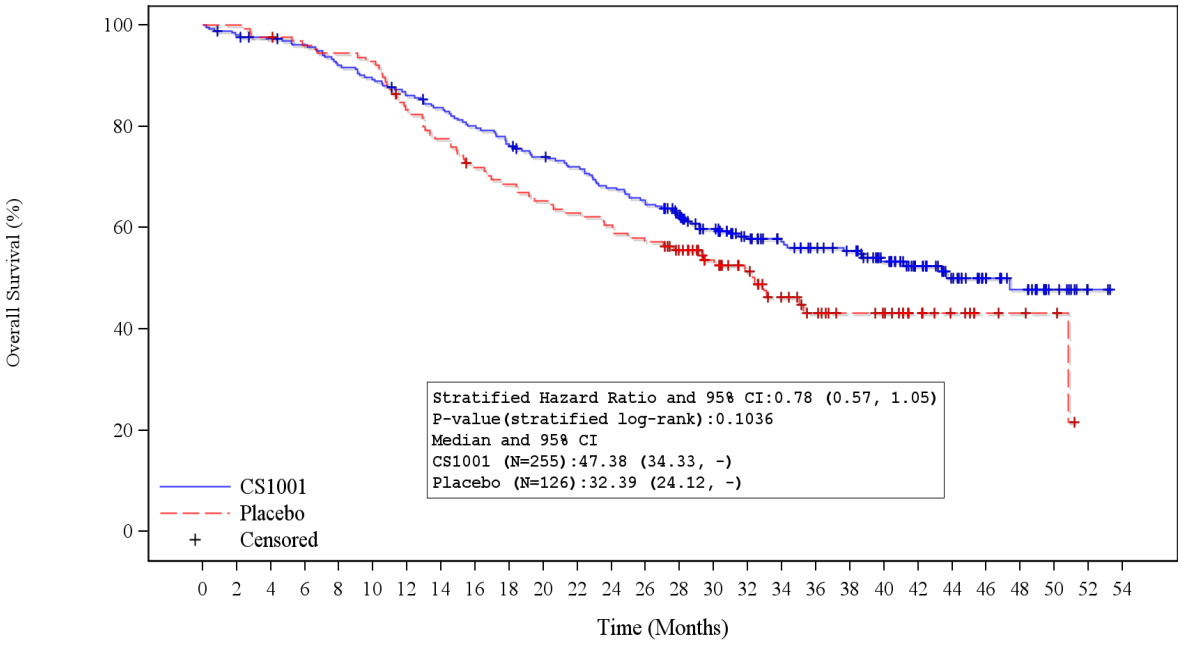
	Sugemalimab (N=255)	Placebo (N=126)
Patients with event	**114 (44.7%)**	**66 (52.4%)**
Death	114	66
Patients censored	**141 (55.3%)**	**60 (47.6%)**
Overall survival (months)		
Median	47.38	32.39
95% CI	(34.33, -)	(24.12, -)
25% and 75% percentiles	19.19, -	14.95, 50.79
Range	0.23 to 53.26+	2.40 to 51.19+
Stratified analysis*		
2-sided p-value (log-rank)	0.1036	
Hazard ratio	0.78	
95% CI	(0.57, 1.05)	
Unstratified analysis		
2-sided p-value (log-rank)	0.0872	
Hazard ratio	0.77	
95% CI	(0.57, 1.04)	
Overall survival rate		
6 months	96.0%	96.0%
95% CI	(92.78%, 97.86%)	(90.70%, 98.32%)
Difference	0.0%	
95% CI	(-4.15%, 4.21%)	
12 months	86.1%	83.2%
95% CI	(81.15%, 89.80%)	(75.39%, 88.70%)
Difference	2.9%	
95% CI	(-4.94%, 10.73%)	
18 months	76.4%	68.6%
95% CI	(70.66%, 81.21%)	(59.64%, 75.98%)
Difference	7.8%	
95% CI	(-1.89%, 17.54%)	
24 months	67.9%	60.4%
95% CI	(61.67%, 73.28%)	(51.25%, 68.43%)
Difference	7.4%	
95% CI	(-2.97%, 17.82%)	
30 months	59.8%	53.5%
95% CI	(53.36%, 65.64%)	(44.27%, 61.93%)
Difference	6.3%	
95% CI	(-4.53%, 17.07%)	
36 months	56.0%	43.2%
95% CI	(49.41%, 62.12%)	(33.40%, 52.59%)
Difference	12.8%	
95% CI	(1.24%, 24.43%)	
42 months	52.5%	43.2%
95% CI	(45.54%, 58.90%)	(33.40%, 52.59%)
Difference	9.3%	
95% CI	(-2.52%, 21.04%)	
48 months	47.8%	43.2%
95% CI	(39.48%, 55.61%)	(33.40%, 52.59%)
Difference	4.6%	
95% CI	(-8.05%, 17.23%)	

Table 17: Reasons for censoring of OS - Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)

	Sugemalimab (N=255)	Placebo (N=126)
Alive	130 (51.0%)	57 (45.2%)
Death date not available*	2 (0.8%)	0

Withdrawal by subject	3 (1.2%)	0
Lost to follow-up	6 (2.4%)	3 (2.4%)

Figure 11: Kaplan-Meier Curve of Overall Survival – Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)



Abbreviation: CI = confidence interval.

Medians were Kaplan-Meier estimates. Confidence interval for the median was computed using the method of Brookmeyer and Crowley. Hazard ratio was estimated by stratified Cox regression model with stratification factors from IxRS (Interactive Voice/Web Response System). P-value was from stratified log rank test with stratification factors from IxRS.

Post-progression anti-cancer treatment

137 (53.7%) of patients treated with sugemalimab and 85 (67.5%) of patients treated with placebo received follow-up anti-cancer treatment. Platinum compounds and taxanes were used to treat 69 (27.1%) and 69 (27.1%) patients previously treated with sugemalimab and 47 (37.3%) and 44 (34.9%) patients previously treated with placebo. More patients previously treated with placebo received PD-1/PD-L1 inhibitor as follow-up anti-cancer treatment, 52 (41.3%) compared to 30 (11.8%) patients from the sugemalimab group. Several different PD-1/PD-L1 inhibitors were used, most common was sintilimab.

Progression free survival by INV

At the OS interim analysis (03 April 2023), 182 (71.4%) PFS events (170 disease progression and 12 deaths) had occurred in the sugemalimab group and 103 (81.7%) PFS events (100 disease progression and 3 deaths) had occurred in the placebo group. The median PFS assessed by Investigator was 10.4 months (95% CI: 8.3, 12.8) in the sugemalimab group and 7.1 months (95% CI: 5.3, 8.3) in the placebo group, with a stratified HR 0.70 (95% CI: 0.55, 0.90) and a nominal two-sided stratified log-rank test P = 0.0053.

Table 18: Concordance Analysis between the BICR Determined and the Investigator Determined PD Status - Intent-to-Treat Analysis Set (DCO 03 April 2023, OS interim analysis)

	CS1001 (N=255)	Placebo (N=126)
Patients included in the analysis*	243	123
PD occurrence		
Concordance	180 (74.1%)	98 (79.7%)
PD per BICR and PD per investigator	121 (49.8%)	80 (65.0%)
No PD per BICR and no PD per investigator	59 (24.3%)	18 (14.6%)
Discordance	63 (25.9%)	25 (20.3%)
PD per BICR and no PD per investigator	15 (6.2%)	5 (4.1%)
No PD per BICR and PD per investigator	48 (19.8%)	20 (16.3%)
PD occurrence and timing of PD		
Concordance	146 (60.1%)	80 (65.0%)
PD per BICR and PD per investigator, dates within 10 weeks	87 (35.8%)	62 (50.4%)
No PD per BICR and no PD per investigator	59 (24.3%)	18 (14.6%)
Discordance	97 (39.9%)	43 (35.0%)
PD per BICR and no PD per investigator	15 (6.2%)	5 (4.1%)
No PD per BICR and PD per investigator	48 (19.8%)	20 (16.3%)
PD per BICR and PD per investigator, dates differ by > 10 weeks	34 (14.0%)	18 (14.6%)
Differences in timing between BICR and investigator PD dates > 10 weeks		
BICR PD earlier than investigator PD	30 (12.3%)	15 (12.2%)
10 to 20 weeks	13 (5.3%)	9 (7.3%)
20 to 30 weeks	7 (2.9%)	3 (2.4%)
> 30 weeks	10 (4.1%)	3 (2.4%)

Abbreviation: BICR = blinded independent central review; PD = progressive disease.
* was defined as patients evaluable for concordance, which was intent-to-treat analysis set with at least one post-baseline tumor assessments available.
Percentages were based on the number of patients included in the analysis.

Overall response rate

The ORR analysis set was all randomised patients with measurable disease at baseline.

The sugemalimab group and the placebo group had 204 and 101 patients, respectively, who were included in the ORR analysis set. A total of 51 patients in the sugemalimab group and 25 patients in the placebo group were not included in the ORR analysis set, as they did not have measurable lesions at baseline according to the BICR assessment.

Table 19: Overall Response Assessed by BICR - Intent-to-Treat Analysis Set with Measurable Disease at Baseline (03 April 2023, OS interim analysis)

	Sugemalimab (N=204)	Placebo (N=101)
Objective response rate (CR+PR)	**50 (24.5%)**	**25 (24.8%)**
95% CI	(18.77%, 31.00%)	(16.70%, 34.33%)
Rate difference (sugemalimab-Placebo)	-0.2%	
95% CI	(-10.52%, 10.04%)	
2-sided P-value	0.9648	
Best overall response		
Complete response (CR)	1 (0.5%)	1 (1.0%)
95% CI	(0.01%, 2.70%)	(0.03%, 5.39%)
Partial response (PR)	49 (24.0%)	24 (23.8%)
95% CI	(18.33%, 30.48%)	(15.86%, 33.26%)
Stable disease (SD)	104 (51.0%)	48 (47.5%)
95% CI	(43.90%, 58.03%)	(37.49%, 57.70%)
Disease progression (PD)	43 (21.1%)	26 (25.7%)
95% CI	(15.69%, 27.32%)	(17.56%, 35.40%)
Not evaluable	0	0
Not applicable*	7 (3.4%)	2 (2.0%)

Source: Table t_ef_bor_bicr_ITT_m2_2
Abbreviation: BICR = blinded independent central review; CI = confidence interval.
Best overall response was defined as the best response during the period between the first dose and the first documented PD, death, or date of subsequent therapy, whichever occurs first.
*Patients were classified as not applicable if no post-baseline response assessments were available.
Confidence interval for rate was calculated using Clopper-Pearson method.
Confidence interval for rate difference was calculated using the normal approximation of binomial distribution.
P-value was calculated using stratified Mantel-Haenszel method with stratification factors from IxRS (Interactive Voice/Web Response System).
The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy.

The median DoR assessed by BICR was 24.1 months (95% CI: 11.6, not reached) and 8.4 months (95% CI: 4.2, not reached) in the sugemalimab group and placebo group, respectively.

Time to death/distant metastasis

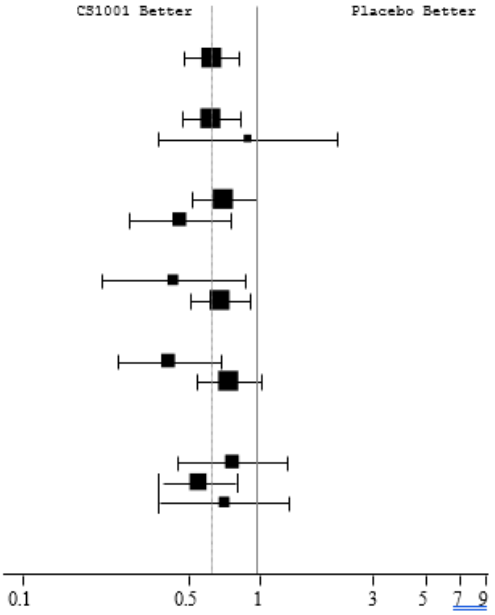
As of the data cutoff date for the OS interim analysis (03 April 2023), the sugemalimab group experienced 173 (67.8%) TTDM events, comprising 111 distant metastases and 62 deaths. In contrast, the placebo group had 92 (73.0%) TTDM events, consisting of 59 distant metastases and 33 deaths. The median TTDM, as assessed by BICR, was found to be 15.2 months (95% CI: 10.3, 19.1) in the sugemalimab group and 10.5 months (95% CI: 7.1, 17.0) in the placebo group. A stratified analysis yielded a hazard ratio of 0.83 (95% CI: 0.64, 1.07) for the sugemalimab group compared to the placebo group.

Ancillary analyses

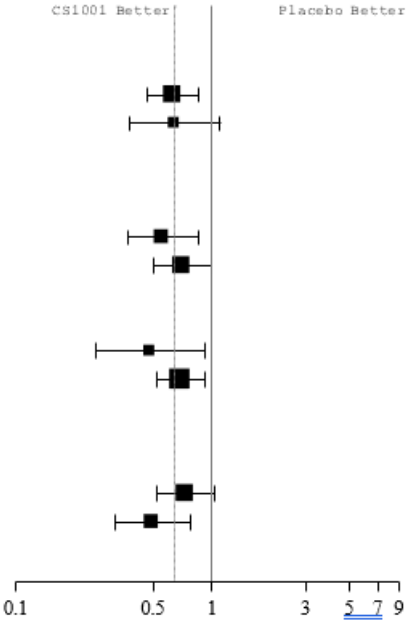
Subgroup analysis PFS

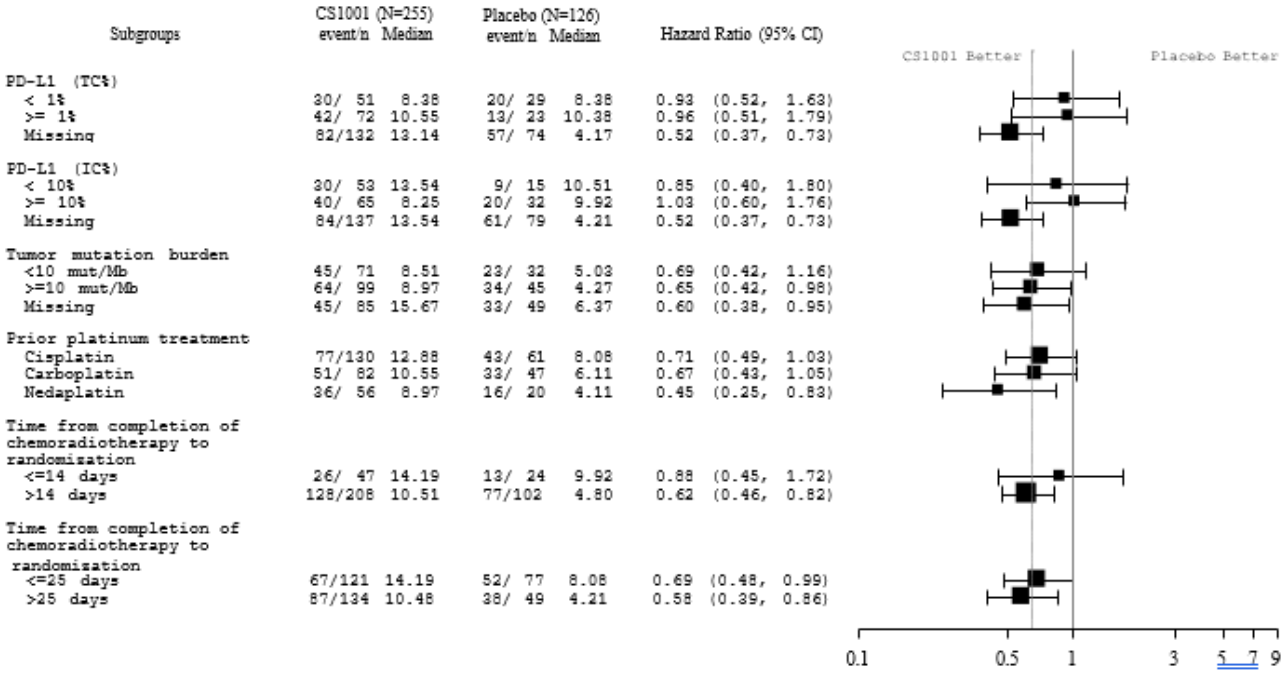
Figure 12: Forest Plot of Hazard Ratio of Progression-free Survival Assessed by BICR–Intent-to-Treat Analysis Set (DCO 01 March 2022, PFS final analysis)

Subgroups	CS1001 (N=255) event/n	CS1001 (N=255) Median	Placebo (N=126) event/n	Placebo (N=126) Median	Hazard Ratio (95% CI)
All patients	154/255	10.51	90/126	6.21	0.65 (0.50, 0.84)
Sex					
Male	142/236	12.91	81/115	6.21	0.64 (0.49, 0.84)
Female	12/ 19	6.47	9/ 11	7.13	0.91 (0.38, 2.17)
Age					
<65 years	108/182	12.88	64/ 94	7.13	0.72 (0.53, 0.99)
>=65 years	46/ 73	10.51	26/ 32	4.07	0.47 (0.29, 0.78)
Smoking history					
Never	22/ 42	14.13	13/ 16	5.75	0.45 (0.22, 0.90)
Former or current	132/213	10.45	77/110	6.24	0.70 (0.53, 0.93)
ECOG PS					
0	40/ 78	24.51	28/ 38	8.08	0.43 (0.26, 0.70)
1	114/177	8.35	62/ 88	6.11	0.76 (0.56, 1.04)
Cancer stage before chemoradiotherapy					
Stage IIIA	41/ 74	13.14	20/ 32	6.21	0.79 (0.46, 1.35)
Stage IIIB	92/146	10.48	50/ 65	6.21	0.57 (0.40, 0.81)
Stage IIIC	21/ 33	8.38	20/ 28	5.39	0.73 (0.39, 1.36)
Unknown	0/ 2	-	0/ 1	-	- (-, -)



Subgroups	CS1001 (N=255) event/n	CS1001 (N=255) Median	Placebo (N=126) event/n	Placebo (N=126) Median	Hazard Ratio (95% CI)
Histology type					
Squamous cell carcinoma	115/177	8.38	67/ 89	4.27	0.63 (0.47, 0.86)
Non-squamous cell carcinoma	37/ 76	24.51	23/ 37	9.92	0.65 (0.38, 1.10)
Missing	2/ 2	3.02	0/ 0	-	- (-, -)
Chemoradiotherapy type					
Sequential	63/ 86	8.08	38/ 41	4.07	0.56 (0.37, 0.85)
Concurrent	91/169	15.67	52/ 85	8.31	0.70 (0.50, 0.99)
Radiotherapy dose					
<60 Gy	25/ 43	15.80	17/ 21	4.27	0.49 (0.26, 0.92)
>=60 Gy	129/212	10.48	73/105	6.24	0.69 (0.52, 0.93)
Best response to prior CRT					
Complete response	3/ 4	5.82	1/ 2	-	- (-, -)
Partial response	104/172	10.51	51/ 77	8.02	0.73 (0.52, 1.03)
Stable disease	47/ 79	13.54	38/ 47	4.24	0.50 (0.32, 0.77)
Non-CR/non-PD	0/ 0	-	0/ 0	-	- (-, -)





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Abbreviation: BICR = blinded independent central review; CI = confidence interval; CR = complete response; CRT = chemoradiotherapy; ECOG = eastern cooperative oncology group; PD = disease progression; PD-L1 = programmed death ligand-1; PS = performance status.

Medians were Kaplan-Meier estimates.

Hazard ratio and 95% CI were calculated using unstratified univariate Cox regression, except for the analysis for all patients which used stratified Cox regression with the stratification factors from the IxRS (Interactive Voice/Web Response System), the stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy.

For subgroup analysis, ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from EDC (Electronic Data Capture).

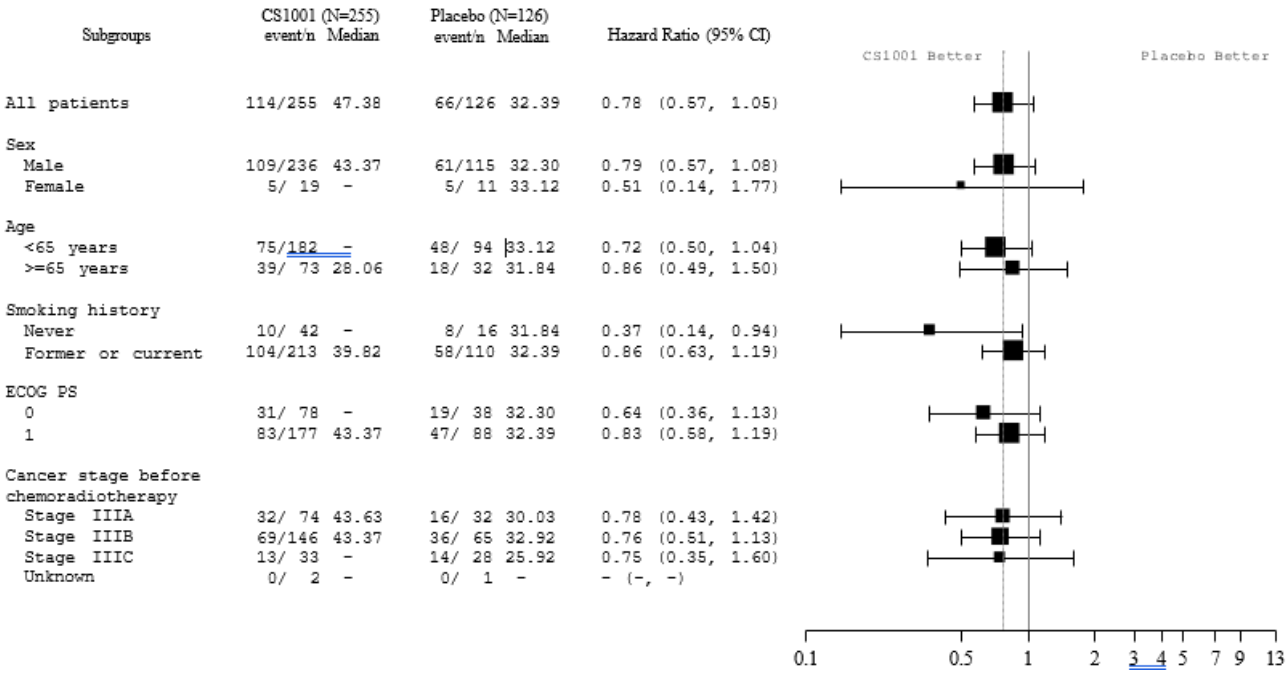
The dotted line is the hazard ratio from all patients. The area of square is proportion with the number of patients within per subgroup.

If total event number <10 within one subgroup, hazard ratio (95% CI) is not displayed.

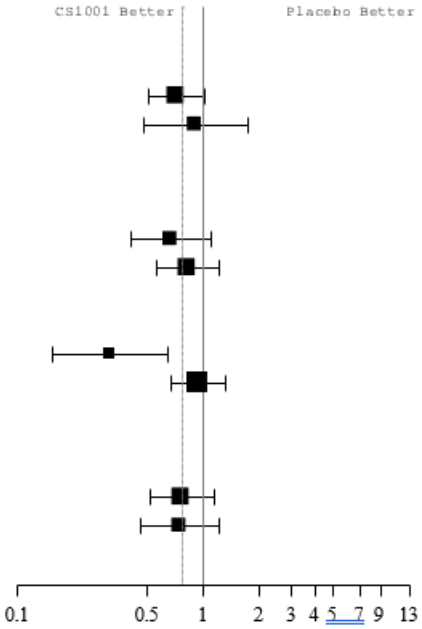
Stage of non-small cell lung cancer before chemoradiotherapy is categorized as "Unknown?if no further category is available. There may be patients receiving more than one type of platinum.

Subgroup analysis OS

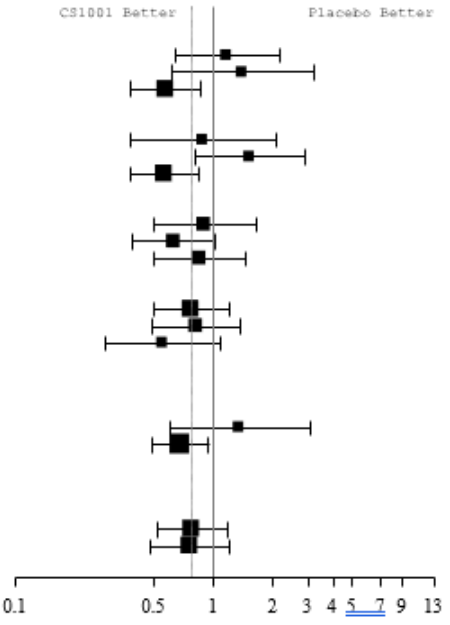
Figure 13: Forest Plot of Hazard Ratio of Overall Survival– Intent-to-Treat Analysis Set(03 April 2023, OS interim analysis)



Subgroups	CS1001 (N=255) event/n	Median	Placebo (N=126) event/n	Median	Hazard Ratio (95% CI)
Histology type					
Squamous cell carcinoma	86/177	38.70	52/ 89	27.66	0.73 (0.51, 1.02)
Non-squamous cell carcinoma	27/ 76	-	14/ 37	-	0.92 (0.48, 1.75)
Missing	1/ 2	-	0/ 0	-	- (-, -)
Chemoradiotherapy type					
Sequential	42/ 86	41.17	25/ 41	24.12	0.68 (0.41, 1.11)
Concurrent	72/169	47.38	41/ 85	32.92	0.83 (0.57, 1.22)
Radiotherapy dose					
<60 Gy	15/ 43	-	17/ 21	20.40	0.32 (0.16, 0.64)
>=60 Gy	99/212	43.37	49/105	35.25	0.94 (0.67, 1.32)
Best response to prior CRT					
Complete response	1/ 4	-	0/ 2	-	- (-, -)
Partial response	74/172	47.38	38/ 77	32.92	0.77 (0.52, 1.14)
Stable disease	39/ 79	34.33	28/ 47	29.40	0.76 (0.46, 1.23)
Non-CR/non-PD	0/ 0	-	0/ 0	-	- (-, -)



Subgroups	CS1001 (N=255) event/n	Median	Placebo (N=126) event/n	Median	Hazard Ratio (95% CI)
PD-L1 (TC%)					
< 1%	31/ 51	27.79	16/ 29	29.40	1.17 (0.64, 2.14)
>= 1%	29/ 72	-	7/ 23	-	1.40 (0.62, 3.21)
Missing	54/132	-	43/ 74	27.66	0.57 (0.38, 0.86)
PD-L1 (IC%)					
< 10%	22/ 53	-	7/ 15	33.12	0.88 (0.38, 2.07)
>= 10%	36/ 65	28.62	13/ 32	-	1.53 (0.81, 2.90)
Missing	56/137	-	46/ 79	27.04	0.56 (0.38, 0.83)
Tumor mutation burden					
<10 mut/Mb	34/ 71	43.37	16/ 32	33.12	0.90 (0.50, 1.63)
>=10 mut/Mb	46/ 99	39.82	27/ 45	24.97	0.63 (0.39, 1.01)
Missing	34/ 85	-	23/ 49	50.79	0.85 (0.50, 1.46)
Prior platinum treatment					
Cisplatin	57/130	43.63	31/ 61	33.12	0.77 (0.50, 1.19)
Carboplatin	37/ 82	-	24/ 47	31.84	0.82 (0.49, 1.37)
Nedaplatin	26/ 56	39.82	13/ 20	23.56	0.55 (0.28, 1.08)
Time from completion of chemoradiotherapy to randomization					
<=14 days	21/ 47	43.37	8/ 24	-	1.35 (0.60, 3.08)
>14 days	93/208	47.38	58/102	29.31	0.68 (0.49, 0.94)
Time from completion of chemoradiotherapy to randomization					
<=25 days	54/121	43.37	40/ 77	32.92	0.78 (0.51, 1.17)
>25 days	60/134	47.38	26/ 49	32.30	0.76 (0.48, 1.20)



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Abbreviation: CI = confidence interval; CR = complete response; CRT = chemoradiotherapy; ECOG = eastern cooperative oncology group; PD = disease progression; PD-L1 = programmed death ligand-1; PS = performance status.

Medians were Kaplan-Meier estimates.

Hazard ratio and 95% CI were calculated using unstratified univariate Cox regression, except for the analysis for all patients which used stratified Cox regression with the stratification factors from the IxRS (Interactive Voice/Web Response System), the stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy.

For subgroup analysis, ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from EDC (Electronic Data Capture).

The dotted line is the hazard ratio from all patients. The area of square is proportion with the number of patients within per subgroup.

If total event number <10 within one subgroup, hazard ratio (95% CI) is not displayed.

Stage of non-small cell lung cancer before chemoradiotherapy is categorized as 'Unknown' if no further category is available. There may be patients receiving more than one type of platinum.

Analysis of OS adjusted by rank preserving structural failure time models

Table 20: Overall Survival Adjusted by Rank Preserving Structural Failure Time Models - ITT Analysis Set – Study CS1001-301 (OS Interim Analysis DCO3 - 03 April 2023)

	Sugemalimab (N=255)	Placebo adjusted by RPSFTM (N=126)
Participants with event	**114 (44.7%)**	**65 (51.6%)**
Death	114	65
Participants censored	**141 (55.3%)**	**61 (48.4%)**
Overall survival (months)		
Median	47.38	29.31
95% CI	(34.33, -)	(21.16, -)
25% and 75% percentiles	19.19, -	14.59, 50.79
Range	0.23 to 53.26+	2.40 to 50.79
Stratified analysis*		
2-sided p-value (log-rank)		0.0166
Hazard ratio		0.69
95% CI		(0.50, 0.94)
Unstratified analysis		
2-sided p-value (log-rank)		0.0134
Hazard ratio		0.68
95% CI		(0.50, 0.92)

DCO3 date: 03 April 2023

Abbreviation: CI = confidence interval.

Summaries of overall survival (median, percentiles) were Kaplan-Meier estimates.

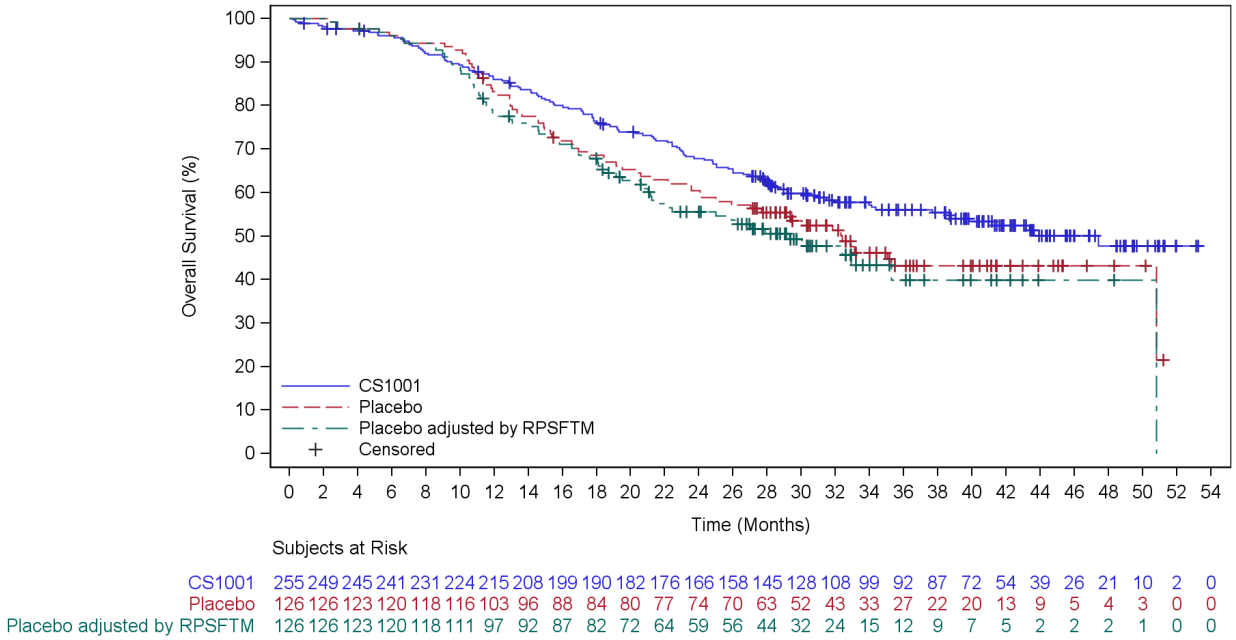
Confidence interval for the median was computed using the method of Brookmeyer and Crowley.

Hazard ratios were estimated by Cox regression.

+ was for the minimum or maximum value from censored participants.

* The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from IxRS (Interactive Voice/Web Response System).

Figure 14: Kaplan-Meier Curve of Overall Survival Adjusted by Rank Preserving Structural Failure Time Models - ITT Analysis Set – Study CS1001-301 (OS Interim Analysis DCO3 - 03 April 2023)



Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of Efficacy for trial CS1001-301

Title: A Randomized, Double-Blind, Placebo-Controlled Phase III Study of CS1001-301 as Consolidation Therapy in Patients with Locally Advanced/unresectable (Stage III) Non-small Cell Lung Cancer Who Have Not Progressed After Concurrent/Sequential Chemoradiotherapy		
Study identifier	CS1001-301 (GEMSTONE-301)	
Design	This is a randomised, double-blind, placebo-controlled, multicenter Phase III study to compare the efficacy and safety between sugemalimab versus placebo as consolidation therapy in patients with locally advanced/unresectable stage III NSCLC who have not progressed after concurrent or sequential chemoradiotherapy. Eligible patients were randomised to receive sugemalimab or placebo by stratified block randomisation with a 2:1 ratio until disease progression, intolerable toxicity, withdrawal of informed consent, death, or other reasons specified in the protocol.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 months not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Sugemalimab	1200 mg sugemalimab Q3W Up to 24 months N- 255
	Placebo	Placebo Q3W Up to 24 months N- 126

Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	PFS assessed by blinded independent central review committee (BICR) according to RECIST v1.1. PFS was defined as the time from the date of randomisation to first documented disease progression or all-cause death, whichever occurred first.
	Secondary endpoint	Overall survival (OS)	OS defined as the time interval between the date of randomisation to the date of all-cause death. Patients alive were censored at the last known alive date.
	Secondary endpoint	Progression-free survival – Investigator assessed (PFS-Inv)	PFS assessed by investigator according to RECIST v1.1.
	Secondary endpoint	Objective response rate (ORR, ORR-Inv)	Assessed by BICR and investigator according to RECIST v1.1; the number and proportion of patients who achieved objective tumours response (CR or PR).
	Secondary endpoint	Duration of Response (DoR, DoR-Inv)	Assessed by BICR and investigator according to RECIST v1.1; duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualified response and the date of disease progression or all-cause death, whichever occurs first.
	Secondary endpoint	Time to death/distant metastasis (TTDM, TTDM-Inv)	Assessed by BICR and investigator according to RECIST v1.1; Defined as the time from the date of randomisation to distant metastasis or all-cause death, whichever occurs first.
Database lock	01 March 2022 for PFS final analysis 03 April 2023 for OS interim analysis		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat; defined as all randomised patients The PFS interim analysis was conducted based on a 08 March 2021 data cut-off date. The final PFS analysis was conducted based on a 01 March 2022 data cut-off date. The pre-specified OS interim analysis was conducted based on a 03 April 2023 data cut-off date and used to support analyses of OS and other secondary endpoints		
Descriptive statistics and estimate variability	Treatment group	Sugemalimab	Placebo
	Number of subjects	255	126
	PFS*, patients with event (%)	154 (60.4)	90 (71.4)
	PFS*, Median (months) 95% CI	10.51 (8.25, 17.12)	6.21 (4.21, 8.08)
	OS**, patient with event	114 (44.7)	66 (52.4)

	OS**, Median (months) 95% CI	47.38 (34.33, NR)	32.39 (24.12, NR)
	ORR** (%) 95% CI	50 (24.5) (18.77, 31.00)	25 (24.8) (16.70, 34.33)
	DoR**, Median (months) 95% CI	24.05 (11.60, NR)	8.44 (4.21, NR)
	TTDM**, Median (months) 95% CI	15.18 (10.28, 19.12)	10.51 (7.13, 16.95)

Effect estimate per comparison	Comparison groups		Sugemalimab vs. placebo
	Primary endpoint **PFS***	Hazard ratio§	0.65
		95% CI	(0.50, 0.84)
		P-value 2-side (log rank) §	0.0012
	Secondary endpoint **OS****	Comparison groups	Sugemalimab vs. placebo
		Hazard ratio§	0.78
		95% CI	(0.57; 1.05)
		P-value 2-side (log rank) §	0.1036

*Data based on data cut-off date of 01 March 2022 (PFS final analysis)
**Data based on data cut-off date of 03 April 2023 (OS interim analysis)
§ Hazard ratio is based on the stratified Cox regression model. P-value is based on the stratified log-rank test. The stratification factors are ECOG performance status, chemoradiotherapy type, and total dose of prior radiotherapy from Interactive Voice/Web Response System.
NR: Not reached.

In vitro biomarker test for patient selection for efficacy

Any patients who signed the master ICF needed to provide tumour tissue sections and blood sample (2 mL whole blood) for TMB test (10 sections) and PD-L1 expression assay (3 sections), if permitted by the Ethics Committee. Requirements for biomarker sample collection were detailed in the study protocol. PD-L1 expression levels were measured by VENTANA PD-L1 (SP263) immunohistochemistry in a central laboratory. The evaluation method is the proportion of tumour cells with PD-L1 membrane staining of any intensity above background staining.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study supporting this application is Study CS1001-301 (GEMSTONE-301). This study was terminated following the OS interim analysis (DCO 03 April 2023).

This was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, study of sugemalimab in participants with locally advanced/unresectable (Stage III) NSCLC that had not progressed after prior concurrent/sequential chemoradiotherapy. Both squamous and non-squamous NSCLC patients were included. Patients with known mutation/translocation status of EGFR, ALK and ROS1 were excluded. PD-L1 status was not systematically assessed.

Platinum-containing chemotherapy were to include platinum (either cisplatin, carboplatin or nedaplatin) and at least one of: etoposide, vinorelbine, vinblastine, pemetrexed, a taxane, or gemcitabine. Nedaplatin (used in prior chemotherapy by 20% of the study population) is not approved in the EU, but is deemed sufficiently similar to carboplatin based on available literature. The chemotherapy was to follow instructions of the Chinese Society of Clinical Oncology (CSCO) Guideline for Diagnosis and Treatment of Primary Lung Cancer 2017 V1. The total dose of radiotherapy was to be 60 Gy ± 10% (54 Gy - 66 Gy). Prior treatment of antibody/drug that targets at T-cell coregulatory proteins (immune checkpoints, including PD-1, PD-L1, CTLA4, TIM3 and LAG3, etc.) was not allowed. The chemoradiation therapy given is broadly in line with ESMO guidance.

Patients were randomised 2:1 to sugemalimab or placebo. Randomisation stratification factors included ECOG performance status (PS) (0 vs 1), mode of prior chemoradiotherapy (sequential chemoradiotherapy vs concurrent chemoradiotherapy), and the total dose of baseline radiotherapy (< 60 Gy vs ≥ 60 Gy).

Participants received sugemalimab (1200 mg, intravenous infusion [IV], every 3 weeks [Q3W]) or placebo, and the treatment was continued until disease progression, intolerable toxicity, withdrawal of consent, death, or other reasons specified in the protocol. Treatment duration of sugemalimab was up to 24 months.

The primary endpoint was PFS assessed by BICR per RECIST v1.1 defined as the time from randomisation to disease progression or all-cause death, whichever occurred first.

The secondary efficacy endpoints were OS, PFS (by INV per RECIST v1.1), ORR, DoR and Time to death/distant metastasis (TTDM). The secondary efficacy endpoints were tested sequentially in the order of OS, TTDM, and ORR, as prespecified in the Statistical Analysis Plan (SAP).

Overall, the study design, including comparators and endpoints, are considered appropriate.

Statistical/methodological considerations

The primary endpoint PFS (evaluated by BICR) was evaluated by conventional time-to-event analysis methods. A stratified log-rank test was used for statistical testing between CS1001 and placebo, while stratified Cox regression model was used for estimation of efficacy. The model included same stratification factors as those used for randomisation. For PFS, subjects without event (no disease progression or death) were censored at the date of "last tumour assessment". Subjects without tumour assessment after baseline were censored at the date of randomization. Subjects with two or more missed tumour evaluations and patients who initiated a new therapy before progression were not censored.

Secondary variables: OS, Duration of response, and TTDM were analysed using the same statistical analysis methods as that for the primary efficacy endpoint.

The overall Type I error rate was controlled dually, i.e. by using error spending methods due to interim analyses in a group-sequential study design, and by using hierarchical testing procedure for the 4 efficacy endpoints that were tested in a prespecified order. The PFS (evaluated by BICR) and OS had an interim and a final analysis planned each, with boundary values derived using O'Brien-Fleming method and Lan-DeMets method with Pocock boundary, respectively. The primary and the main secondary endpoints were tested in a prespecified order (PFS by BICR, OS, TTDM by BICR, ORR by BICR). With these methods, the Type I error is considered controlled at 5% two-sided.

Since the OS was not statistically significant at the interim analysis, testing of TTDM and ORR is considered to fall outside multiplicity control.

Major changes in the planned statistical analyses were documented in the protocol version 5, where the primary objective and endpoint of the study were revised from "Progression-free Survival (PFS) by the investigator according to RECIST v1.1" to "PFS by Blinded Independent Central Review (BICR) according to RECIST v1.1". Also, the planned study sample size was changed from 402 to 368, and the required number of events and the alpha spending function were updated. Since the study was double-blind and the changes documented prior to the interim PFS analysis, these changes are deemed acceptable.

Recruitment and conduct

The study was conducted exclusively in China. A total of 564 patients were screened and 381 patients were randomised in a 2:1 ratio to sugemalimab group (255 patients) and placebo group (126 patients) from 26 October 2018 to 30 December 2020. All patients received the allocated treatment. Cross-over was not permitted.

The proportion of patients with at least one important protocol deviation is high, 19.6% (n=50) for the sugemalimab arm and 12.7% (n=16) for the placebo arm. Most of these are due to study conduct/procedures and safety, e.g. deviations from screening procedure, not fulfilling inclusion/exclusion criteria, deviations from sample collection/processing/storage and deviations from safety reporting/follow-up. It is noted that 2.6% (n=10) of patients had important protocol deviations for informed consent. Important protocol deviations related to the COVID-19 pandemic were reported for a total of 3 patients.

Efficacy data and additional analyses

BICR-assessed PFS was analysed in the ITT population, which included all randomly assigned participants, at 2 prespecified time points: (1) an interim PFS analysis and (2) a final PFS analysis. The PFS analysis was also updated at the interim OS analysis data cut.

Overall distribution of baseline characteristics is generally well balanced between the two treatment arms. Patients were exclusively of Asian origin. The median age of included patients was 61 years. 72.4% of patients were younger than 65 years. It is notable that there is a very strong male dominance with 92.1% males, hampering the assessment of efficacy in females. However, gender is not a known effect modifier in this clinical situation, or when treating with PD-L1 targeting agents.

PD-L1 testing was not mandatory but results are available for a subpopulation of patients (n=175). Section 5.1 of the SmPC clearly states that Test for PD-L1 status was not mandatory and was not systematically assessed. Apart from testing for EGFR mutational status in participants with non-squamous NSCLC, no further information of other actionable mutations is available as it was not tested. The exclusion of patients with known actionable mutations is acceptable.

69.8% of the patients had squamous cell carcinoma. 66.7% of all patients were treated following concurrent chemoradiotherapy. The proportion of patients that were treated after sequential chemoradiotherapy were capped at 40%.

The study was performed exclusively in China. Several agents targeting PD-1 or PD-L1 have been approved for use in NSCLC in the EU based on global studies including predominantly Caucasian patients (e.g., pembrolizumab, atezolizumab, durvalumab). Moreover, several agents, including Cejemly, have been approved for similar use based on studies performed exclusively in China, which have shown similar benefits. The present application for Cejemly is in a similar niche where the positive B/R of durvalumab was shown in a study with centers in North and Latin America,

Europe, and Asia Pacific, including approximately 70% Caucasian patients. Thus, the external validity for EU patients of the present pivotal study is accepted.

Results

At the final PFS analysis (DCO: 01 March 2022) were a total of 154 PFS events observed in the sugemalimab group, compared to 90 in the placebo group. Median PFS was 10.5 months (95% CI: 8.3, 17.1) in the sugemalimab group versus 6.2 months (95% CI: 4.2, 8.1) in the placebo group (stratified HR 0.65; [95% CI: 0.50, 0.84]; two-sided P = 0.0012). The median follow-up was 27.1 months and 23.5 months for the sugemalimab group and placebo group, respectively.

At the time of the OS interim analysis (DCO: 03 April 2023) were the median PFS 10.6 months (95% CI: 8.4, 16.8) in the sugemalimab group versus 6.2 months (95% CI: 4.2, 8.3) in the placebo group (stratified HR 0.73 [95% CI: 0.56, 0.95]; two-sided P = 0.0175 (nominal p-value)). The median follow-up was 40.4 months and 35.4 months for the sugemalimab group and placebo group, respectively.

OS did not reach statistical significance at the OS interim analysis (DCO: 03 April 2023). The study was subsequently terminated, hence there will not be any more updates from this study.

The OS interim analysis was performed after 180 OS events had occurred (47% maturity). A total of 114 OS events were observed in the sugemalimab, compared to 66 in the placebo group. The median OS was 47.4 months (95% CI: 34.3, NR [not reached]) in the sugemalimab group and 32.4 months (95% CI: 24.1, NR) in the placebo group (stratified HR 0.78 [95% CI: 0.57, 1.05], two-sided P = 0.1036) and the actual statistical superiority boundary of 0.0392 was not reached.

More patients previously treated with placebo received PD-1/PD-L1 inhibitor as follow-up anti-cancer treatment, 52 (41.3%) compared to 30 (11.8%) patients from the sugemalimab group. A rank preserving structural failure time models (RPSFTM) was performed ad-hoc to investigate the potential impact of this imbalance. After adjustment, the median OS for the placebo group was 29.3 months compared to 32.4 months unadjusted. This adjustment also presented a stratified HR of 0.69 [95% CI: 0.50, 0.94], two-sided nominal of P = 0.0166. Given the uncertainties about bias control when modelling OS to account for the impact of post-progression therapies, no claims can be made on this basis.

Overall, subgroup analyses of PFS and OS do not raise concerns regarding lack of efficacy in any subgroup presented. However, PD-L1 expression status is missing in more than 50% of patients. Moreover, there is substantial heterogeneity of effects between those with PD-L1 expression data and those for whom this is missing – with no apparent effect of sugemalimab in those patients for whom PD-L1 status data are available. Therefore, these data are not representative of the full study population, and do not allow for any conclusion of the impact of PD-L1 expression on efficacy.

In a previous decision for the use of Imfinzi for similar use, the CHMP considered that interpretable data on PD-L1 expressors did not support use in these patients. Similar to sugelimumab, durvalumab is an inhibitor of PD-L1, which is dosed at a roughly similar intensity. Hence, the indication for sugemalimab is restricted to patients with PD-L1 ≥1% in line with the only relevant precedent (Imfinzi) where the indication was restricted to patients expressing PD-L1 ≥1%.

As a result of this restriction of indication to patients expressing PD-L1 ≥1%, section 4.2 of the SmpC was updated in order to include information on PD-L1 testing. To determine eligibility for treatment, tumour cell PD-L1 expression should be assessed with a CE-marked IVD with the corresponding intended purpose. If a CE-marked IVD is not available, an alternative validated test should be used.

PFS assessed by INV exhibits a similar hazard ratio (stratified HR 0.70, 95% CI: 0.55, 0.90) at the OS interim analysis compared to PFS assessed by BICR. However, the concordance between BICR and INV is less than 80% for both the sugemalimab and placebo arms. Despite this, PFS by INV achieves nominal significance, and since the robustness of the PFS estimate is not compromised, this issue is not further investigated.

The ORR analysis set was all randomised patients with measurable disease at baseline. 204 patients in the sugemalimab group and 101 patients in the placebo group were included in the ORR analysis set based on BICR assessment. ORR (CR + PR, DCO: 03 April 2023, OS IA) assessed by BICR was 24.5% (95% CI: 18.8%, 31.0%) in the sugemalimab group and 24.8% (95% CI: 16.7%, 34.3%) in the placebo group. The median DoR assessed by BICR was 24.1 months (95% CI: 11.6, NR) in the sugemalimab group and 8.4 months (95% CI: 4.2, NR) in the placebo group at the OS IA.

The time to TTDM analysis at the OS IA (DCO 03 April 2023) included 173 (67.8%) TTDM events (111 distant metastases and 62 deaths) that occurred in the sugemalimab group, and 92 (73.0%) TTDM events (59 distant metastases and 33 deaths) that occurred in the placebo group. The median TTDM (95% CI) assessed by BICR was 15.2 months (10.3, 19.1) and 10.5 months (7.1, 17.0) in the sugemalimab and placebo groups, respectively, with a stratified analysis HR 0.83 (95% CI: 0.64, 1.07). No difference was shown for TTDM that would support the primary endpoint.

PFS2 was not reported.

2.4.3. Conclusions on the clinical efficacy

Sugemalimab treatment for patients with unresectable NSCLC without EGFR mutations or ALK, ROS1 genomic tumour aberrations who have not progressed following platinum-based chemoradiotherapy has shown statistically significant PFS improvement over placebo in Study CS1001-301. OS did not reach statistical significance at the interim analysis. The study was subsequently terminated, hence there will not be any more OS updates from this study. Notably, given the extent of use of PD-L1 targeting agents on progression in the placebo control arm, the sensitivity of the study to show an OS gain was limited.

It is recognised that the ability to demonstrate an OS gain in this treatment niche may be limited due to post-progression use of the same drug class. Given available knowledge, a prolongation of PFS of the present magnitude after chemoradiotherapy for unresectable stage III NSCLC is considered to isolate clinical benefit, in the absence of any signal of a detrimental effect on OS.

Notably efficacy cannot be determined for PD-L1 low expressors as PD-L1 testing was lacking for the majority of patients in the study. Hence, the indication for sugemalimab is restricted to patients with PD-L1 ≥1%. As outlined, this is in line with the relevant precedent.

2.5. Clinical safety

Introduction

The key safety data in support of this application were derived from study CS1001-301 (hereafter referred to as study 301). A total of 255 patients were exposed to sugemalimab monotherapy and 126 to placebo in study 301.

The full safety data set derives from a sugemalimab monotherapy pool consisting of 568 patients with advanced solid or haematologic malignancies exposed to the recommended sugemalimab dose of 1,200 mg/kg Q3W in two phase 1, two phase 2, and two phase 3 studies including study 301.

Table 22: List of clinical studies with sugemalimab included in the summary of clinical safety

Study ID NCT Number Phase (Study Status[a])/ Countries/ DCO/LPLV (Report Type)	Study Design	Drug Product(s)/ Route of Administration/ Dosing Cycle	Number of Participants Treated (Safety Analysis Set)
Pivotal Phase 3 Study			
CS1001-301/ NCT03728556 Phase 3 (Completed)/ China/ 03 Apr 2023 LPLV (Full CSR)	Randomised, double-blind, placebo-controlled study of sugemalimab in participants with locally advanced/unresectable Stage III NSCLC who have not progressed after prior concurrent/sequential chemoradiotherapy	Sugemalimab 1200 mg fixed dose or placebo/ IV infusion/ Q3W	Total: 381 Sugemalimab: 255 Placebo: 126
Supportive Studies			
CS1001-302 NCT03789604 Phase 3 (Ongoing)/ China/ 22 Nov 2021 DCO (Full CSR)	Randomised, multicentre, double-blind, placebo-controlled study of sugemalimab in combination with chemotherapy as first-line treatment in participants with Stage IV NSCLC	Double-blind phase: Sugemalimab 1200 mg fixed dose in combination with platinum-based chemotherapy or placebo in combination with platinum-based chemotherapy/ IV infusion/ Q3W; 4 cycles for platinum-based chemotherapy Maintenance: Up to a total of ~35 cycles of sugemalimab or placebo Crossover phase: Sugemalimab 1200 mg fixed dose/ IV infusion/ Q3W	Total: 479 Double-blind phase: Sugemalimab: 320 Placebo: 159 Crossover phase: Sugemalimab: 45 (received placebo during the double-blind phase)
CS1001-101a/CS1001-101b NCT03312842 Phase 1a (Completed)/ China/ 30 Nov 2018 DCO (Full CSR) Phase 1b (Ongoing)/ China/ 16 Aug 2021 DCO (Full CSR; excludes Cohort 12 and Cohort 13)	Phase 1a: Open-label, first-in-human, multiple-dose, dose-escalation, dose-expansion study of sugemalimab in participants with advanced solid tumours or lymphomas Phase 1b: Indication expansion phase for preliminary evaluation of antitumour efficacy of sugemalimab in monotherapy and in combination with standard therapies in participants with multiple types of solid tumours or lymphomas	Phase 1a: Sugemalimab 3, 10, 20, and 40 mg/kg and 1200 mg fixed dose IV infusion/ Q3W Phase 1b: Sugemalimab 1200 mg fixed dose (as monotherapy [Cohorts 1 to 4] or in combination with chemotherapy [Cohorts 5 to 9], targeted therapy [Cohorts 10 to 12], or radiotherapy [Cohort 13])/ IV infusion/ Q3W	Total: 246 Phase 1a: 29 3 to 40 mg/kg: 13 1200 mg: 16 Phase 1b: 217 Cohorts 1 to 4: 79 Cohorts 5 to 9: 115 Cohort 11: 23
CS1001-102/ NCT03744403 Phase 1 (Completed)/ US/ 19 Oct 2020 LPLV (Full CSR)	Open-label, multiple-dose, dose-escalation bridging study of sugemalimab in participants with advanced solid tumours	Sugemalimab 10 mg/kg and 1200 mg fixed dose/ IV infusion/ Q3W	Total: 24 10 mg/kg: 12 1200 mg: 12
CS1001-201/ NCT03595657 Phase 2 (Ongoing)/ China, US[b]/ 10 Nov 2021 DCO (Full CSR)	Single-arm, multicentre study of sugemalimab in participants with relapsed or refractory ENKTL	Sugemalimab 1200 mg fixed dose/ IV infusion/ Q3W	Total: 80
CS1001-202/ NCT03505996 Phase 2 (Ongoing)/ China/ 19 Feb 2020 DCO (Full CSR)	Single-arm, multicentre study of sugemalimab in participants with relapsed or refractory classical Hodgkin lymphoma	Sugemalimab 1200 mg fixed dose/ IV infusion/ Q3W	Total: 81

[a] As of the data cutoff date for each included study.
[b] No US participants were enrolled.
The data cutoff dates for the clinical studies included in sugemalimab monotherapy pool were 16 Aug 2021 for CS1001-101a/CS1001-101b, 08 Feb 2021 for CS1001-102, 10 Nov 2021 for CS1001-201, 19 Feb 2020 for CS1001-202, 08 Mar 2021 for CS1001-301, and 22 Nov 2021 for CS1001-302.
CSR = clinical study report; DCO = data cutoff date (for ongoing studies); ENKTL = extranodal natural killer/T cell lymphoma; ID = identification; IV = intravenous; LPLV = last participant last visit (for completed studies); NCT = National Clinical Trial; NSCLC = non-small cell lung cancer; Q3W = once every 3 weeks; US = United States
Sources: Study CS1001-301 CSR, Study CS1001-302 CSR, Study CS1001-101a CSR, Study CS1001-101b CSR, Study CS1001-102 CSR, Study CS1001-201 CSR, and Study CS1001-202 CSR

Patient exposure

Sugemalimab IV was administered Q3W until disease progression or unacceptable toxicity.

At the data cut-off (DCO) of 03 April 2023 all patients in study 301 had discontinued sugemalimab or placebo treatment and discontinued from the study.

Table 23: Summary of exposure to sugemalimab or placebo, study CS1001-301 (safety analysis set)

	Sugemalimab (N = 255)	Placebo (N = 126)
Treatment Duration (months)		
Mean (SD)	14.7 (13.33)	12.1 (10.47)
Median	9.0	7.6
Min, max	0.2, 50.7	0.7, 42.2
Number of Cycles		
Mean (SD)	19.8 (18.08)	16.3 (14.10)
Median	12.0	10.0
Min, max	1, 72	1, 60
Total Cumulative Dose (mg)		
Mean (SD)	23760.0 (21699.35)	19561.9 (16923.84)
Median	14400.0	12000.0
Min, max	1200, 86400	1200, 72000

Treatment duration is defined as minimum of (treatment end date of study drug - treatment start date of study drug + 21, clinical cutoff date - treatment start date of study drug + 1, study discontinue date - treatment start date of study drug + 1) / 30.4375.
Total cumulative dose is defined as the sum of actual dosage administered during each cycle.
CSR = clinical study report; max = maximum; min = minimum; SD = standard deviation.
Source: Study CS1001-301 CSR, Table t_ex_SA_2

Adverse events

Table 24: Overview of treatment-emergent adverse events, study CS1001-301 (safety analysis set)

	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of participants with at least one		
TEAE	**248 (97.3)**	**121 (96.0)**
Treatment-related TEAE	201 (78.8)	81 (64.3)
Serious TEAE	**94 (36.9)**	**37 (29.4)**
Treatment-related serious TEAE	49 (19.2)	12 (9.5)
Grade 3-5 TEAE	**87 (34.1)**	**38 (30.2)**
Treatment-related Grade 3-5 TEAE	37 (14.5)	8 (6.3)
Immune-related TEAE assessed by investigator[a]	**150 (58.8)**	**49 (38.9)**
Immune-related TEAE Grade 3-5 assessed by investigator	21 (8.2)	0
Infusion-related reaction	**1 (0.4)**	**2 (1.6)**
TEAE leading to drug permanently discontinued	**47 (18.4)**	**6 (4.8)**
TEAE leading to infusion interruption	**1 (0.4)**	**1 (0.8)**
TEAE leading to treatment cycle delay	**101 (39.6)**	**36 (28.6)**
TEAE leading to death	**12 (4.7)**	**3 (2.4)**

[a] Immune-related AEs by Sponsor assessment are provided in Study CS1001-301 CSR, Section 12.10.
Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
NCI-CTCAE version 4.03.

"Related" is defined as the relationship to the study drug is related or missing.
AE = adverse event; CSR = clinical study report; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event
Source: Study CS1001-301 CSR, Table t_ae_sum_SA_2, Module 5.3.5.3, Study CS1001-301 Ad hoc, Table t_ae_iirae_sum_SA

Adverse events by system organ class and preferred term

Table 25: Most frequently reported treatment-emergent adverse events (≥ 10%) by system organ class and preferred term, study CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	248 (97.3)	121 (96.0)
Investigations	**173 (67.8)**	**78 (61.9)**
Alanine aminotransferase increased	63 (24.7)	20 (15.9)
Aspartate aminotransferase increased	52 (20.4)	13 (10.3)
Weight increased	41 (16.1)	14 (11.1)
White blood cell count decreased	28 (11.0)	15 (11.9)
Platelet count decreased	19 (7.5)	13 (10.3)
Respiratory, thoracic and mediastinal disorders	**147 (57.6)**	**72 (57.1)**
Cough	54 (21.2)	34 (27.0)
Pneumonitis	37 (14.5)	24 (19.0)
Metabolism and nutrition disorders	**115 (45.1)**	**67 (53.2)**
Hyperglycaemia	34 (13.3)	13 (10.3)
Hypercholesterolaemia	31 (12.2)	12 (9.5)
Hypertriglyceridaemia	27 (10.6)	16 (12.7)
Hypoalbuminaemia	27 (10.6)	19 (15.1)
Hyperuricaemia	23 (9.0)	18 (14.3)
Infections and infestations	**107 (42.0)**	**54 (42.9)**
Pneumonia	42 (16.5)	17 (13.5)
Upper respiratory tract infection	27 (10.6)	19 (15.1)
Blood and lymphatic system disorders	**78 (30.6)**	**43 (34.1)**
Anaemia	62 (24.3)	31 (24.6)
Injury, poisoning and procedural complications	**77 (30.2)**	**32 (25.4)**
Radiation pneumonitis	63 (24.7)	25 (19.8)
Endocrine disorders	**75 (29.4)**	**19 (15.1)**
Hypothyroidism	53 (20.8)	15 (11.9)
Hyperthyroidism	40 (15.7)	6 (4.8)
Skin and subcutaneous tissue disorders	**60 (23.5)**	**14 (11.1)**
Rash	27 (10.6)	9 (7.1)

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 26.0.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Source: Study CS1001-301 CSR, Table t_ae_SA_2

Infusion-related reactions (IRRs) occurred in one (0.4%) patient in the sugemalimab arm vs. two (1.6%) patients in the placebo arm.

Treatment-related adverse events by system organ class and preferred term

Table 26: Most frequently reported sugemalimab/placebo-related treatment-emergent adverse events (≥ 5%) by system organ class and preferred term, study CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	201 (78.8)	81 (64.3)
Investigations	**119 (46.7)**	**48 (38.1)**
Alanine aminotransferase increased	42 (16.5)	14 (11.1)
Aspartate aminotransferase increased	35 (13.7)	7 (5.6)
Blood thyroid stimulating hormone increased	22 (8.6)	4 (3.2)
Blood thyroid stimulating hormone decreased	20 (7.8)	7 (5.6)
Blood bilirubin increased	15 (5.9)	5 (4.0)
Gamma-glutamyltransferase increased	13 (5.1)	3 (2.4)
White blood cell count decreased	12 (4.7)	8 (6.3)
Endocrine disorders	**72 (28.2)**	**16 (12.7)**
Hypothyroidism	50 (19.6)	12 (9.5)
Hyperthyroidism	40 (15.7)	5 (4.0)
Respiratory, thoracic and mediastinal disorders	**71 (27.8)**	**27 (21.4)**
Immune-mediated lung disease	25 (9.8)	4 (3.2)
Pneumonitis	25 (9.8)	18 (14.3)
Interstitial lung disease	16 (6.3)	4 (3.2)
Metabolism and nutrition disorders	**50 (19.6)**	**19 (15.1)**
Hyperglycaemia	19 (7.5)	6 (4.8)
Hypertriglyceridaemia	14 (5.5)	6 (4.8)
Hypercholesterolaemia	13 (5.1)	2 (1.6)
Skin and subcutaneous tissue disorders	**49 (19.2)**	**8 (6.3)**
Rash	22 (8.6)	6 (4.8)
Pruritus	17 (6.7)	3 (2.4)
Blood and lymphatic system disorders	**24 (9.4)**	**10 (7.9)**
Anaemia	17 (6.7)	7 (5.6)

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 26.0.
"Related" is defined as the relationship to sugemalimab or placebo is related or missing.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Source: Study CS1001-301 CSR, Table t_ae_rel_SA_2

Adverse reactions

The following methodology was used for classification of ADRs:

All TEAEs observed in > 2 patients or ≤ 2 patients for immune-related class effect events and/or events falling into an EMA Designated Medical event (DME) category in the sugemalimab + chemotherapy combination safety pool (n=435) and the sugemalimab monotherapy safety pool

(n=568), were selected for individual medical review. The Bradford-Hill criteria were used for assessment and ADR identification and if a reasonable possibility of a causal relationship with sugemalimab was present, the TEAE was included as an ADR. ADRs representing the same or similar medical concepts were grouped.

Of note, the change in frequencies of ADRs pertaining to Cejemly in combination with chemotherapy for the ADRs haemolytic, anaemia, ANCA-positive vasculitis, colitis, and myositis were originally added to the ADR table during the initial approval of Cejemly for the combination therapy indication ((EMEA/H/C/006088/0000) although these specific ADRs were only observed for Cejemly monotherapy. Since there is now a separate ADR column for monotherapy ADRs, these specific ADRs have been moved to the new column and the footnote removed, changing the frequencies overall of some of the ADR observed in the combination therapy pool.

Table 27*:* combination therapy adverse reactions table

Grouped Term	**All Grade CS1001 + Chemo (N=435)**	**Grade 3-5 CS1001 + Chemo**
Number of Patients with at least one event listed below	416(95.6%)	144(33.1%)
Anaemia	337(77.5%)	76(17.5%)
Hepatic enzyme increased	185(42.5%)	10(2.3%)
Rash	114(26.2%)	6(1.4%)
Hyperlipidaemia	94(21.6%)	10(2.3%)
Hyperglycaemia	80(18.4%)	7(1.6%)
Hyponatraemia	73(16.8%)	19(4.4%)
Hypokalaemia	68(15.6%)	13(3.0%)
Hypothyroidism	68(15.6%)	1(0.2%)
Hyperthyroidism	66(15.2%)	0
Proteinuria	61(14.0%)	0
Abdominal pain	60(13.8%)	3(0.7%)
Fatigue	58(13.3%)	6(1.4%)
Arthralgia	53(12.2%)	1(0.2%)
Hypoaesthesia	50(11.5%)	1(0.2%)
Hypocalcaemia	44(10.1%)	1(0.2%)
Blood creatinine increased	38(8.7%)	2(0.5%)
Hyperuricaemia	38(8.7%)	0
Hypochloraemia	37(8.5%)	3(0.7%)
Stomatitis	31(7.1%)	4(0.9%)
Blood creatine phosphokinase increased	30(6.9%)	1(0.2%)
Hypomagnesaemia	27(6.2%)	1(0.2%)
Hepatic function abnormal	25(5.7%)	8(1.8%)
Hypertension	25(5.7%)	6(1.4%)
Amylase increased	24(5.5%)	9(2.1%)
Blood bilirubin increased	22(5.1%)	2(0.5%)
Myalgia	22(5.1%)	0

Tachycardia	21(4.8%)	1(0.2%)
Pneumonitis	18(4.1%)	5(1.1%)
Conjunctivitis	14(3.2%)	0
Nephritis	12(2.8%)	4(0.9%)
Neuropathy peripheral	12(2.8%)	0
Diabetes mellitus	7(1.6%)	3(0.7%)
Bone pain	6(1.4%)	0
Dry eye	6(1.4%)	0
Hepatitis	6(1.4%)	4(0.9%)
Dry mouth	5(1.1%)	0
Infusion related reaction	5(1.1%)	0
Lipase increased	5(1.1%)	3(0.7%)
Skin hypopigmentation	5(1.1%)	0
immune-related hypophysitis	5(1.1%)	0
Anaphylactic reaction	4(0.9%)	1(0.2%)
Dyslipidaemia	4(0.9%)	0
Adrenal insufficiency	2(0.5%)	0
Troponin T increased	2(0.5%)	0
Cortisol decreased	1(0.2%)	0
Immune-mediated arthritis	1(0.2%)	0
Immune-mediated encephalitis	1(0.2%)	0
Immune-mediated myocarditis	1(0.2%)	0
Immune-mediated thyroiditis	1(0.2%)	0
Pancreatitis	1(0.2%)	0
Proctitis	1(0.2%)	0

Table 28: Monotherapy adverse reactions table

Grouped Term	**All Grade CS1001 (N=568)**	**Grade 3-5 CS1001**
Number of Patients with at least one event listed below	463(81.5%)	95(16.7%)
Hepatic enzyme increased	161(28.3%)	17(3.0%)
Anaemia	130(22.9%)	18(3.2%)
Hypothyroidism	128(22.5%)	5(0.9%)
Rash	97(17.1%)	7(1.2%)
Pyrexia	87(15.3%)	2(0.4%)
Hyperthyroidism	82(14.4%)	1(0.2%)
Blood bilirubin increased	74(13.0%)	10(1.8%)
Hyperlipidaemia	73(12.9%)	7(1.2%)
Proteinuria	70(12.3%)	0
Hyperglycaemia	62(10.9%)	4(0.7%)

Pneumonitis	52(9.2%)	5(0.9%)
Hypokalaemia	41(7.2%)	8(1.4%)
Hyponatraemia	40(7.0%)	8(1.4%)
Diarrhoea	28(4.9%)	0
Arthralgia	27(4.8%)	0
Blood creatine phosphokinase increased	27(4.8%)	4(0.7%)
Hypertension	23(4.0%)	9(1.6%)
Blood creatinine increased	22(3.9%)	0
Tachycardia	17(3.0%)	1(0.2%)
Fatigue	16(2.8%)	2(0.4%)
Hepatic function abnormal	11(1.9%)	4(0.7%)
Stomatitis	10(1.8%)	1(0.2%)
Amylase increased	8(1.4%)	0
Myalgia	7(1.2%)	0
Nephritis	7(1.2%)	2(0.4%)
Myocarditis	5(0.9%)	1(0.2%)
Myositis	5(0.9%)	1(0.2%)
Conjunctivitis	3(0.5%)	0
Diabetes mellitus	3(0.5%)	1(0.2%)
Hepatitis	2(0.4%)	0
Hypersensitivity	2(0.4%)	0
Infusion related reaction	2(0.4%)	0
Troponin T increased	2(0.4%)	0
immune-related hypophysitis	2(0.4%)	0
Anti-neutrophil cytoplasmic antibody positive vasculitis	1(0.2%)	0
Colitis	1(0.2%)	1(0.2%)
Haemolytic anaemia	1(0.2%)	1(0.2%)
Immune-mediated arthritis	1(0.2%)	0

Adverse events by severity

Table 29: Grade 3-5 treatment-emergent adverse events (> 1%) by system organ class and preferred term, study CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	87 (34.1)	38 (30.2)
Infections and infestations	**26 (10.2)**	**13 (10.3)**
Pneumonia	23 (9.0)	8 (6.3)
Upper respiratory tract infection	1 (0.4)	2 (1.6)
Metabolism and nutrition disorders	**22 (8.6)**	**14 (11.1)**
Hyperuricaemia	6 (2.4)	5 (4.0)
Hyponatraemia	6 (2.4)	0
Hypertriglyceridaemia	5 (2.0)	3 (2.4)
Hypercalcaemia	0	3 (2.4)
Hypokalaemia	0	3 (2.4)
Investigations	**21 (8.2)**	**10 (7.9)**
Lymphocyte count decreased	4 (1.6)	0
Neutrophil count decreased	4 (1.6)	0
Blood cholesterol increased	3 (1.2)	0
Weight increased	3 (1.2)	2 (1.6)
Gamma-glutamyltransferase increased	2 (0.8)	3 (2.4)
Platelet count decreased	2 (0.8)	2 (1.6)
Respiratory, thoracic and mediastinal disorders	**18 (7.1)**	**4 (3.2)**
Immune-mediated lung disease	8 (3.1)	0
Vascular disorders	**7 (2.7)**	**2 (1.6)**
Hypertension	5 (2.0)	1 (0.8)
Skin and subcutaneous tissue disorders	**6 (2.4)**	**0**
Rash	3 (1.2)	0
Blood and lymphatic system disorders	**5 (2.0)**	**5 (4.0)**
Leukopenia	3 (1.2)	0
Anaemia	2 (0.8)	4 (3.2)

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once at the highest grade for unique SOC or PT.
MedDRA version 26.0. NCI-CTCAE version 4.03.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PT = preferred term; SOC = system organ class.
Source: Study CS1001-301 CSR, Table t_ae_ctc345_SA_2

Table 30: Summary of treatment-emergent adverse events by grade 3, 4, and 5 (≥ 1% of participants in either treatment group), study CS1001-301

	Sugemalimab (N=255)			Placebo (N=126)		
MedDRA Preferred Term	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Number of patients with at least one event	64 (25.1%)	11 (4.3%)	12 (4.7%)	27 (21.4%)	8 (6.3%)	3 (2.4%)
Pneumonia	19 (7.5%)	0	4 (1.6%)	7 (5.6%)	0	1 (0.8%)
Immune-mediated lung disease	5 (2.0%)	2 (0.8%)	1 (0.4%)	0	0	0
Hyperuricaemia	0	6 (2.4%)	0	0	5 (4.0%)	0
Hyponatraemia	6 (2.4%)	0	0	0	0	0
Hypertriglyceridaemia	5 (2.0%)	0	0	2 (1.6%)	1 (0.8%)	0
Hypertension	5 (2.0%)	0	0	1 (0.8%)	0	0
Lymphocyte count decreased	3 (1.2%)	1 (0.4%)	0	0	0	0
Neutrophil count decreased	4 (1.6%)	0	0	0	0	0
Weight increased	3 (1.2%)	0	0	2 (1.6%)	0	0
Blood cholesterol increased	3 (1.2%)	0	0	0	0	0
Leukopenia	2 (0.8%)	1 (0.4%)	0	0	0	0
Rash	3 (1.2%)	0	0	0	0	0
Anaemia	2 (0.8%)	0	0	4 (3.2%)	0	0
Gamma-glutamyltransferase increased	2 (0.8%)	0	0	3 (2.4%)	0	0
Platelet count decreased	1 (0.4%)	1 (0.4%)	0	1 (0.8%)	1 (0.8%)	0
Hypophosphataemia	2 (0.8%)	0	0	0	1 (0.8%)	0
Pneumonitis	2 (0.8%)	0	0	1 (0.8%)	0	0
Radiation pneumonitis	1 (0.4%)	1 (0.4%)	0	1 (0.8%)	0	0
Coronary artery disease	2 (0.8%)	0	0	0	0	0
Haemoptysis	0	0	2 (0.8%)	0	0	0
Hyperglycaemia	2 (0.8%)	0	0	0	0	0
Hypothyroidism	2 (0.8%)	0	0	0	0	0
Inguinal hernia	2 (0.8%)	0	0	0	0	0
Neutropenia	1 (0.4%)	1 (0.4%)	0	0	0	0
Rectal cancer	2 (0.8%)	0	0	0	0	0
Upper respiratory tract infection	1 (0.4%)	0	0	2 (1.6%)	0	0
Hypercalcaemia	0	0	0	2 (1.6%)	1 (0.8%)	0
Hypokalaemia	0	0	0	2 (1.6%)	1 (0.8%)	0

Treatment-related adverse events by severity

Table 31: Most common (≥ 5%) treatment-related treatment-emergent adverse events by highest NCI-CTCAE grade grouped by all grades and grade 3-5, study CA1001-301 (safety analysis set)

	CS1001 (N=255)		Placebo (N=126)	
MedDRA System Organ Class MedDRA Preferred Term	All Grades	Grade 3-5	All Grades	Grade 3-5
Number of patients with at least one event	201 (78.8%)	37 (14.5%)	81 (64.3%)	8 (6.3%)
Investigations	119 (46.7%)	9 (3.5%)	48 (38.1%)	1 (0.8%)
Alanine aminotransferase increased	42 (16.5%)	0	14 (11.1%)	0
Aspartate aminotransferase increased	35 (13.7%)	1 (0.4%)	7 (5.6%)	0
Blood thyroid stimulating hormone increased	22 (8.6%)	0	4 (3.2%)	0
Blood thyroid stimulating hormone decreased	20 (7.8%)	0	7 (5.6%)	0
Blood bilirubin increased	15 (5.9%)	0	5 (4.0%)	0
Gamma-glutamyltransferase increased	13 (5.1%)	1 (0.4%)	3 (2.4%)	0
White blood cell count decreased	12 (4.7%)	0	8 (6.3%)	0
Endocrine disorders	72 (28.2%)	2 (0.8%)	16 (12.7%)	0
Hypothyroidism	50 (19.6%)	2 (0.8%)	12 (9.5%)	0
Hyperthyroidism	40 (15.7%)	0	5 (4.0%)	0
Respiratory, thoracic and mediastinal disorders	71 (27.8%)	11 (4.3%)	27 (21.4%)	1 (0.8%)
Immune-mediated lung disease	25 (9.8%)	8 (3.1%)	4 (3.2%)	0
Pneumonitis	25 (9.8%)	2 (0.8%)	18 (14.3%)	1 (0.8%)
Interstitial lung disease	16 (6.3%)	0	4 (3.2%)	0
Metabolism and nutrition disorders	50 (19.6%)	6 (2.4%)	19 (15.1%)	2 (1.6%)
Hyperglycaemia	19 (7.5%)	0	6 (4.8%)	0
Hypertriglyceridaemia	14 (5.5%)	3 (1.2%)	6 (4.8%)	1 (0.8%)
Hypercholesterolaemia	13 (5.1%)	0	2 (1.6%)	0
Skin and subcutaneous tissue disorders	49 (19.2%)	6 (2.4%)	8 (6.3%)	0
Rash	22 (8.6%)	3 (1.2%)	6 (4.8%)	0
Pruritus	17 (6.7%)	1 (0.4%)	3 (2.4%)	0
Blood and lymphatic system disorders	24 (9.4%)	2 (0.8%)	10 (7.9%)	1 (0.8%)
Anaemia	17 (6.7%)	1 (0.4%)	7 (5.6%)	1 (0.8%)

Grade 4 sugemalimab- or placebo-related TEAEs were reported in three (1.2%) and two (1.6%) participants, respectively. Grade 4 sugemalimab-related TEAEs were immune-mediated lung disease (two [0.8%] participants), metabolic acidosis (one [0.4%] participant) and respiratory alkalosis (one [0.4%] participant). Grade 4 placebo-related TEAEs were hypercalcaemia, hypophosphatemia and platelet count decreased (one [0.8%] participant each).

Grade 5 (fatal) TEAEs considered related to sugemalimab or placebo by the Investigator were reported in three (1.2%) participants in the sugemalimab group and none in the placebo group.

Adverse events leading to dose interruption

TEAEs leading to infusion interruption of sugemalimab or placebo were reported in one participant in each study arm (0.4% vs 0.8%). The reasons were vomiting and dizziness (sugemalimab) and dizziness (placebo), respectively.

Averse events leading to treatment cycle delay

Table 32: Treatment-emergent adverse events leading to treatment cycle delay, study CS1001-301 (safety analysis set)

MedDRA System Organ Class MedDRA Preferred Term	CS1001 (N=255)	Placebo (N=126)
Number of patients with at least one event	101 (39.6%)	36 (28.6%)
Respiratory, thoracic and mediastinal disorders	35 (13.7%)	19 (15.1%)
Pneumonitis	16 (6.3%)	14 (11.1%)
Immune-mediated lung disease	9 (3.5%)	2 (1.6%)
Interstitial lung disease	9 (3.5%)	2 (1.6%)
Chronic obstructive pulmonary disease	2 (0.8%)	0
Dyspnoea	1 (0.4%)	0
Tracheal fistula	1 (0.4%)	0
Pleural effusion	0	1 (0.8%)
Infections and infestations	28 (11.0%)	13 (10.3%)
Pneumonia	15 (5.9%)	4 (3.2%)
COVID-19	12 (4.7%)	5 (4.0%)
Herpes zoster	2 (0.8%)	1 (0.8%)
Lower respiratory tract infection	1 (0.4%)	1 (0.8%)
Laryngopharyngitis	0	1 (0.8%)
Upper respiratory tract infection	0	2 (1.6%)
Injury, poisoning and procedural complications	25 (9.8%)	9 (7.1%)
Radiation pneumonitis	22 (8.6%)	8 (6.3%)
Joint injury	1 (0.4%)	0
Pulmonary radiation injury	1 (0.4%)	0
Radiation fibrosis - lung	1 (0.4%)	0
Clavicle fracture	0	1 (0.8%)
Fracture	0	1 (0.8%)

Abbreviation: MedDRA = medical dictionary for regulatory activities.
MedDRA version 26.0.
Treatment-Emergent adverse event (TEAE) was defined as any AE that occurred or worsened on or after the initiation of study drug.
For frequency counts by system organ class or preferred term, multiple occurrences of the same condition in an individual were counted only once.

Adverse events of special interest

Immune-related AEs (irAEs) are considered adverse events of special interest (AESIs) in the sugemalimab clinical studies.

Table 33: Summary of immune-related adverse events from Investigator assessment by category, study CS1001-301

	CS1001 1200 mg (N=255)	Placebo (N=126)
Number of Patients with at Least One Event	150(58.8%)	49(38.9%)
Number of Patients with at Least One		
Grade 3-5 Event	21(8.2%)	0(0.0%)
Serious Event	40(15.7%)	7(5.6%)
Investigator Assessed as irAE	150(58.8%)	49(38.9%)
Event Leading to Drug Permanently Discontinued	26(10.2%)	1(0.8%)
Event Leading to Drug Interruption	41(16.1%)	13(10.3%)
Event Leading to Death	1(0.4%)	0(0.0%)
Event Treated with Systemic Corticosteroid	54(21.2%)	11(8.7%)
Event Treated with High Dose Systemic Corticosteroid	47(18.4%)	7(5.6%)

Abbreviations: AESI=Investigator Identified irAE; irAE=immune related adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NCI-CTCAE= National Cancer Institute - Common Terminology Criteria for Adverse Events.
MedDRA Version 26.0.
NCI-CTCAE Version 4.03.
Drug in this table indicates CS1001/Placebo; Drug interruption includes action taken associated with infusion interrupted or treatment cycle delayed.

Table 34: Immune-related adverse events from investigator assessment by category, preferred term, study CS1001-301 (safety analysis set)

Category	CS1001 1200 mg (N=255)	Placebo (N=126)
Number of Patients with at Least One Event	150(58.8%)	49(38.9%)
Hepatitis	22(8.6%)	6(4.8%)
Alanine aminotransferase increased	18(7.1%)	6(4.8%)
Aspartate aminotransferase increased	14(5.5%)	4(3.2%)
Bilirubin conjugated increased	5(2.0%)	1(0.8%)
Blood bilirubin increased	6(2.4%)	1(0.8%)
Immune-mediated hepatitis	1(0.4%)	0(0.0%)
Transaminases increased	1(0.4%)	0(0.0%)
Pneumonitis	55(21.6%)	20(15.9%)
Immune-mediated lung disease	25(9.8%)	4(3.2%)
Interstitial lung disease	14(5.5%)	4(3.2%)
Pneumonitis	18(7.1%)	12(9.5%)
Colitis	5(2.0%)	1(0.8%)
Colitis ulcerative	1(0.4%)	0(0.0%)
Diarrhoea	4(1.6%)	1(0.8%)
Nephritis (including renal failure)	5(2.0%)	2(1.6%)
Blood creatinine increased	2(0.8%)	2(1.6%)
Blood urea increased	1(0.4%)	0(0.0%)
Renal impairment	1(0.4%)	0(0.0%)
Renal injury	1(0.4%)	0(0.0%)
Hyperthyroidism	54(21.2%)	12(9.5%)
Blood thyroid stimulating hormone decreased	14(5.5%)	4(3.2%)
Hyperthyroidism	37(14.5%)	5(4.0%)
Thyroxine free increased	4(1.6%)	1(0.8%)
Thyroxine increased	2(0.8%)	0(0.0%)
Tri-iodothyronine free increased	8(3.1%)	2(1.6%)
Tri-iodothyronine increased	1(0.4%)	0(0.0%)
Hypothyroidism	63(24.7%)	16(12.7%)
Blood thyroid stimulating hormone increased	18(7.1%)	4(3.2%)
Hypothyroidism	47(18.4%)	11(8.7%)
Thyroxine decreased	1(0.4%)	0(0.0%)
Thyroxine free decreased	7(2.7%)	2(1.6%)
Tri-iodothyronine decreased	0(0.0%)	1(0.8%)
Tri-iodothyronine free decreased	2(0.8%)	0(0.0%)
Thyroiditis	2(0.8%)	0(0.0%)
Thyroid disorder	2(0.8%)	0(0.0%)
Diabetes Mellitus	9(3.5%)	0(0.0%)
Blood glucose increased	3(1.2%)	0(0.0%)
Hyperglycaemia	6(2.4%)	0(0.0%)
Severe skin adverse reactions	6(2.4%)	0(0.0%)
Pruritus	1(0.4%)	0(0.0%)
Rash	3(1.2%)	0(0.0%)
Rash maculo-papular	1(0.4%)	0(0.0%)
Urticaria	1(0.4%)	0(0.0%)
thrombocytopenia	1(0.4%)	0(0.0%)
Platelet count decreased	1(0.4%)	0(0.0%)
Rhabdomyolysis/Myopathy	1(0.4%)	0(0.0%)
Myoglobin blood increased	1(0.4%)	0(0.0%)
Myocarditis	8(3.1%)	1(0.8%)
Atrial fibrillation	1(0.4%)	0(0.0%)
Blood creatine phosphokinase MB increased	1(0.4%)	1(0.8%)
Immune-mediated myocarditis	2(0.8%)	0(0.0%)
Myocarditis	2(0.8%)	0(0.0%)
Supraventricular tachycardia	1(0.4%)	0(0.0%)
Troponin I increased	1(0.4%)	0(0.0%)
Ventricular extrasystoles	1(0.4%)	0(0.0%)
Myositis	11(4.3%)	3(2.4%)
Blood creatine phosphokinase increased	7(2.7%)	3(2.4%)
Immune-mediated myositis	2(0.8%)	0(0.0%)
Myalgia	2(0.8%)	0(0.0%)
Skin reaction (excluding severe)	36(14.1%)	5(4.0%)
Dermatitis	2(0.8%)	0(0.0%)
Dermatitis acneiform	1(0.4%)	0(0.0%)
Eczema	2(0.8%)	0(0.0%)
Immune-mediated dermatitis	3(1.2%)	0(0.0%)
Leukoderma	1(0.4%)	0(0.0%)
Pruritus	14(5.5%)	2(1.6%)
Rash	21(8.2%)	4(3.2%)
Rash maculo-papular	1(0.4%)	1(0.8%)
Arthritis	1(0.4%)	0(0.0%)
Immune-mediated arthritis	1(0.4%)	0(0.0%)
Upper Gastrointestinal Disorders	2(0.8%)	0(0.0%)
Mouth ulceration	2(0.8%)	0(0.0%)

Abbreviations: NCI-CTCAE= National Cancer Institute - Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; AESI=Investigator Identified irAE.
MedDRA Version 26.0.

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irAEs by severity

Grade 1 irAEs: 59 (23.1%) in the sugemalimab arm vs. 32 (25.4%) in the placebo arm.

Grade 2 irAEs: 70 (27.5%) sugemalimab vs. 17 (13.5%) placebo.

Grade 3 irAEs: 18 (7.1%) sugemalimab vs. 0 placebo.

Grade 4 irAEs: 2 (0.8%) sugemalimab vs. 0 placebo.

Grade 5 irAEs: 1 (0.4%) sugemalimab vs. 0 placebo.

The grade 3 irAEs in the sugemalimab arm were pneumonitis and severe skin adverse reactions (six [2.4%] each), hepatitis (two [0.8%]), colitis, hypothyroidism, thrombocytopenia, and myocarditis (one [0.4%] each).

The two grade 4 and the one case of grade 5 irAEs pertained to pneumonitis.

Serious irAEs

Serious irAEs were reported in 15.7% of patients: pneumonitis (32 [32.5%]), myocarditis (4 [1.6%]), myositis and colitis (2 [0.8%] each), and severe skin reaction 1 [0.4%]).

Dose modifications due to irAEs

Interruption of sugemalimab treatment due to irAEs was reported in 41 pneumonitis (22 [8.6%]), severe skin reaction (4 [1.6%]), myositis (3 [1.2%]), hypothyroidism, hepatitis, myocarditis and colitis (2 [0.8%] each), hyperthyroidism, skin reaction (not severe), nephritis, and thrombocytopenia (1 [0.4%] each).

Permanent discontinuation of sugemalimab due to irAEs was reported in 26 patients: pneumonitis (21 [8.2%]) and skin reaction, severe skin reaction, myositis, myocarditis, and thrombocytopenia (1 [0.4%] each).

Time to onset

Median time to onset (TTO) of first irAE event regardless of category was 125,0 days but varied between 61,0 days (range 20, 976) for ir-hyperthyroidism and 598,5 days (range 546, 651) days) for ir-thyroiditis.

The majority (67.3%) of all irAE events were resolved at DCO. The resolution rate for the individual irAEs where not all events were resolved was 20/22 (90.9%) for hepatitis, 20/55 (36.4%) for pneumonitis, 45/54 (83.3%) for hyperthyroidism, 32/63 (50.8%) for hypothyroidism, 0/2 (0%) for thyroiditis, 8/9 (88.9%) for diabetes mellitus, 4/8 (50.0%) for myocarditis, and 30/36 (83.3%) for myositis.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 35: Serious treatment-emergent adverse events (≥ 1% of participants in either treatment group) by system organ class and preferred term, study CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	94 (36.9)	37 (29.4)
Respiratory, thoracic and mediastinal disorders	**39 (15.3)**	**12 (9.5)**
Immune-mediated lung disease	17 (6.7)	1 (0.8)
Pneumonitis	11 (4.3)	8 (6.3)
Interstitial lung disease	9 (3.5)	3 (2.4)
Infections and infestations	**30 (11.8)**	**12 (9.5)**
Pneumonia	24 (9.4)	8 (6.3)
Injury, poisoning and procedural complications	**19 (7.5)**	**9 (7.1)**
Radiation pneumonitis	16 (6.3)	6 (4.8)
Hepatobiliary disorders	**1 (0.4)**	**3 (2.4)**
Cholecystitis	0	2 (1.6)
Nervous system disorders	**1 (0.4)**	**2 (1.6)**
Cerebral infarction	0	2 (1.6)

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 26.0.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Source: Study CS1001-301 CSR, Table t_ae_ser_SA_2

Treatment-related serious adverse events

Table 36: Sugemalimab- or placebo-related serious treatment-emergent adverse events (≥ 2 participants in either treatment group) by system organ class and preferred term, study CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	49 (19.2)	12 (9.5)
Respiratory, thoracic and mediastinal disorders	**33 (12.9)**	**10 (7.9)**
Immune-mediated lung disease	17 (6.7)	1 (0.8)
Pneumonitis	9 (3.5)	7 (5.6)
Interstitial lung disease	8 (3.1)	2 (1.6)
Infections and infestations	**10 (3.9)**	**1 (0.8)**
Pneumonia	8 (3.1)	1 (0.8)
Cardiac disorders	**3 (1.2)**	**0**
Immune-mediated myocarditis	2 (0.8)	0

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 26.0.
"Related" is defined as the relationship to sugemalimab or placebo is related or missing.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Source: Study CS1001-301 CSR, Table t_ae_rel_ser_SA_2

Deaths

In study 301, any death resulting from a non-drug related event that occurred ≥ 90 days after the last dose of study drug was not recorded as an AE but was recorded as a death due to other causes.

Table 37: Summary of deaths, study CS1001-301 (safety analysis set)

	Sugemalimab (N=255)	Placebo (N=126)	Total (N=381)
Number of Patient Deaths	**116 (45.5%)**	**66 (52.4%)**	**182 (47.8%)**
Primary cause of death			
Adverse Event	12 (4.7%)	3 (2.4%)	15 (3.9%)
Progression of Disease	87 (34.1%)	58 (46.0%)	145 (38.1%)
Other	17 (6.7%)	5 (4.0%)	22 (5.8%)

Source: Table t_dd_SA_2

Table 38: Treatment-emergent adverse events leading to death by system organ class and preferred term, study CS1001-301 (safety analysis set)

MedDRA System Organ Class MedDRA Preferred Term	Sugemalimab (N=255)	Placebo (N=126)
Number of patients with at least one event	12 (4.7%)	3 (2.4%)
Infections and infestations	**5 (2.0%)**	**1 (0.8%)**
Pneumonia	4 (1.6%)	1 (0.8%)
Infection	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	**4 (1.6%)**	**1 (0.8%)**
Haemoptysis	2 (0.8%)	0
Immune-mediated lung disease	1 (0.4%)	0
Interstitial lung disease	1 (0.4%)	1 (0.8%)
Cardiac disorders	**1 (0.4%)**	**1 (0.8%)**
Atrial flutter	1 (0.4%)	0
Cardiac failure	1 (0.4%)	0
Cardio-respiratory arrest	0	1 (0.8%)
General disorders and administration site conditions	**1 (0.4%)**	**0**
Death	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4%)**	**0**
Acute myeloid leukaemia	1 (0.4%)	0
Nervous system disorders	**1 (0.4%)**	**0**
Haemorrhage intracranial	1 (0.4%)	0
Vascular disorders	**0**	**1 (0.8%)**
Shock	0	1 (0.8%)

Source: Table t_ae_fatal_SA_2
Abbreviation: MedDRA = medical dictionary for regulatory activities.
MedDRA version 26.0.
Treatment-Emergent adverse event (TEAE) was defined as any AE that occurred or worsened on or after the initiation of study drug.
For frequency counts by system organ class or preferred term, multiple occurrences of the same condition in an individual were counted only once.

Two cases of death due to pneumonia and the one case of death due to immune-mediated lung disease were assessed as related to sugemalimab by the investigator. In all three cases, patients had onset of symptoms shortly (<1 month) after treatment with sugemalimab started.

Laboratory findings

Clinical chemistry

Table 39: Laboratory abnormalities worsening from baseline – clinical chemistry safety analysis set

		CS1001 (N=255)		Placebo (N=126)	
Parameter	Direction	All Grade	Grade 3-4	All Grade	Grade 3-4
Alanine Aminotransferase (U/L)	High	82 (32.2%)	2 (0.8%)	31 (24.6%)	0
Albumin (g/L)	Low	100 (39.2%)	0	42 (33.3%)	0
Alkaline Phosphatase (U/L)	High	45 (17.6%)	0	28 (22.2%)	0
Aspartate Aminotransferase (U/L)	High	84 (32.9%)	2 (0.8%)	22 (17.5%)	1 (0.8%)
Bilirubin (umol/L)	High	48 (18.8%)	0	16 (12.7%)	0
Cholesterol (mmol/L)	High	97 (38.0%)	5 (2.0%)	53 (42.1%)	0
Correct Calcium (mmol/L)	Low	39 (15.3%)	0	7 (5.6%)	0
	High	39 (15.3%)	2 (0.8%)	18 (14.3%)	3 (2.4%)
Creatinine (umol/L)	High	224 (87.8%)	0	107 (84.9%)	0
Fasting Glucose (mmol/L)	Low	15 (5.9%)	1 (0.4%)	4 (3.2%)	0
	High	126 (49.4%)	8 (3.1%)	65 (51.6%)	5 (4.0%)
Magnesium (mmol/L)	Low	45 (17.6%)	0	28 (22.2%)	1 (0.8%)
Magnesium (mmol/L)	High	38 (14.9%)	7 (2.7%)	20 (15.9%)	5 (4.0%)
Phosphate (mmol/L)	Low	89 (34.9%)	11 (4.3%)	45 (35.7%)	3 (2.4%)
Potassium (mmol/L)	Low	59 (23.1%)	12 (4.7%)	23 (18.3%)	4 (3.2%)
	High	17 (6.7%)	3 (1.2%)	3 (2.4%)	0
Sodium (mmol/L)	Low	80 (31.4%)	11 (4.3%)	36 (28.6%)	2 (1.6%)
	High	9 (3.5%)	0	5 (4.0%)	0

Laboratory results were graded using Common Terminology Criteria for Adverse Events Version 4.03.

Program Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\t_lb_chem_abnorm_SA.sas
Output Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\output\t_lb_chem_abnorm_SA.rtf

Table 40: Liver function laboratory findings

Laboratory Findings	CS1001 (N=255)	Placebo (N=126)
ALT and/or AST>3*ULN and TBIL>=2*ULN, and ALP < 2*ULN	0	0
ALT and/or AST>3*ULN, and TBIL>=2*ULN	0	0
ALT and/or AST>3*ULN, and TBIL>=1.5*ULN	0	0
ALT and/or AST		
>3*ULN	9 (3.5%)	2 (1.6%)
>=5*ULN	3 (1.2%)	1 (0.8%)
>=10*ULN	0	0
>=20*ULN	0	0
ALT		
>3*ULN	8 (3.1%)	0
>=5*ULN	2 (0.8%)	0
>=10*ULN	0	0
>=20*ULN	0	0
AST		
>3*ULN	7 (2.7%)	2 (1.6%)
>=5*ULN	2 (0.8%)	1 (0.8%)
>=10*ULN	0	0
>=20*ULN	0	0
TBIL		
>=1.5*ULN	9 (3.5%)	1 (0.8%)
>=2*ULN	5 (2.0%)	0
ALP		
>=1.5*ULN	9 (3.5%)	8 (6.3%)

Abbreviation: ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; TBIL = Total Bilirubin; ALP = Alkaline Phosphatase; ULN = upper limit of normal.
Number of patients with post-baseline test results (or combination of test results from the same visit) that met the predetermined criteria were counted.

Program Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\t_lb_liver_SA.sas
Output Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\output\t_lb_liver_SA.rtf

No cases met the criteria for Hy's law.

Haematology

Table 41: Laboratory abnormalities worsening from baseline – haematology safety analysis set

		CS1001 (N=255)		Placebo (N=126)	
Parameter	Direction	All Grade	Grade 3-4	All Grade	Grade 3-4
Hemoglobin (g/L)	Low	42 (16.5%)	7 (2.7%)	22 (17.5%)	5 (4.0%)
	High	11 (4.3%)	0	4 (3.2%)	0
Leukocytes (10^9/L)	Low	49 (19.2%)	5 (2.0%)	32 (25.4%)	4 (3.2%)
Lymphocytes (10^9/L)	Low	108 (42.4%)	33 (12.9%)	51 (40.5%)	14 (11.1%)
	High	7 (2.7%)	2 (0.8%)	0	0
Neutrophils (10^9/L)	Low	33 (12.9%)	7 (2.7%)	19 (15.1%)	3 (2.4%)
Platelets (10^9/L)	Low	39 (15.3%)	3 (1.2%)	22 (17.5%)	2 (1.6%)

Laboratory results were graded using Common Terminology Criteria for Adverse Events Version 4.03.

Program Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\t_lb_chem_abnorm_SA.sas
Output Location:
P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\output\t_lb_hema_abnorm_SA.rtf

Thyroid function tests

In study 301, thyroid function tests (thyrotropin, free triiodothyronine, free thyroxine) were performed regularly as part of the monitoring for immune-related thyroid disorders. Baseline values represent the patients' last observations prior to initiation of study drug.

The majority of patients hade normal thyrotropin, free triiodothyronine, and free thyroxine values at baseline (90.2%, 96.1%, and 97.3% of patients, respectively).

For each thyroid parameter, comparable proportions of patients experienced either high or low values post-baseline compared to baseline (thyrotropin 31.0% high vs. 32.5% low, free triiodothyronine 27.5% high vs. 20.4% low, free thyroxine 20.8% high vs. 27.1% low, respectively).

Vital signs and physical findings

Vital signs and weight

There were no clinically meaningful changes in vital signs (blood pressure, pulse rate, respiratory rate, body temperature) and weight from baseline and across treatments.

Electrocardiogram

Abnormal ECG values determined by the Investigator to be clinically significant were reported as AEs. None of the TEAEs associated with abnormal ECG findings were grade $\geq$ 3 in severity, serious, or led to discontinuation of sugemalimab or placebo treatment.

Table 42: 12-lead ECG results (safety analysis set)

Treatment	Worst Post-Baseline 12-Lead ECG Result	Baseline 12-Lead ECG Result: Normal	Abnormal, not clinically significant	Abnormal, clinically significant	Not evaluable	Missing	Total
CS1001 (N=255)	Normal	2 (0.8%)	2 (0.8%)	0	0	0	4 (1.6%)
	Abnormal, not clinically significant	4 (1.6%)	6 (2.4%)	3 (1.2%)	0	0	13 (5.1%)
	Abnormal, clinically significant	8 (3.1%)	8 (3.1%)	1 (0.4%)	1 (0.4%)	0	18 (7.1%)
	Not evaluable	0	0	0	0	0	0
	Missing	132 (51.8%)	75 (29.4%)	8 (3.1%)	5 (2.0%)	0	220 (86.3%)
	Total	146 (57.3%)	91 (35.7%)	12 (4.7%)	6 (2.4%)	0	255 (100.0%)
Placebo (N=126)	Normal	3 (2.4%)	1 (0.8%)	1 (0.8%)	0	0	5 (4.0%)
	Abnormal, not clinically significant	2 (1.6%)	2 (1.6%)	0	0	0	4 (3.2%)
	Abnormal, clinically significant	1 (0.8%)	2 (1.6%)	0	0	0	3 (2.4%)
	Not evaluable	0	0	0	0	0	0
	Missing	61 (48.4%)	37 (29.4%)	10 (7.9%)	6 (4.8%)	0	114 (90.5%)
	Total	67 (53.2%)	42 (33.3%)	11 (8.7%)	6 (4.8%)	0	126 (100.0%)

Abbreviation: ECG = electrocardiograph; N = number of patients in specified group.

Program Location: P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\t_eg_SA.sas
Output Location: P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\output\t_eg_SA.rtf

ECOG performance status

Table 43: Table of ECOG performance status (safety analysis set)

Treatment	Highest Post-Baseline ECOG Performance Status	Baseline ECOG Performance Status: 0	1	>= 2	Missing	Total
CS1001 (N=255)	0	46 (18.0%)	0	0	0	46 (18.0%)
	1	27 (10.6%)	166 (65.1%)	0	0	193 (75.7%)
	>= 2	3 (1.2%)	6 (2.4%)	0	0	9 (3.5%)
	Missing	2 (0.8%)	5 (2.0%)	0	0	7 (2.7%)
	Total	78 (30.6%)	177 (69.4%)	0	0	255 (100.0%)
Placebo (N=126)	0	25 (19.8%)	0	0	0	25 (19.8%)
	1	9 (7.1%)	85 (67.5%)	0	0	94 (74.6%)
	>= 2	3 (2.4%)	2 (1.6%)	0	0	5 (4.0%)
	Missing	1 (0.8%)	1 (0.8%)	0	0	2 (1.6%)
	Total	38 (30.2%)	88 (69.8%)	0	0	126 (100.0%)

Abbreviation: ECOG = eastern cooperative oncology group.

Program Location: P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\t_ecog_shift_SA.sas
Output Location: P:\01_OngoingProjects\C_092_ONC_CS1001_301\Final\Original\Programs\tfl\output\t_ecog_shift_SA.rtf

Safety in special populations

Table 44: Overview of safety by sex and age groups, study CS1001-301

	Sugemalimab (N=255)		Placebo (N=126)		Sugemalimab (N=255)		Placebo (N=126)	
	Female (N=19)	Male (N=236)	Female (N=11)	Male (N=115)	Age < 65 (N=182)	Age >= 65 (N=73)	Age < 65 (N=94)	Age >= 65 (N=32)
TEAEs (all grades)	18 (94.7%)	230 (97.5%)	11 (100.0%)	110 (95.7%)	178 (97.8%)	70 (95.9%)	90 (95.7%)	31 (96.9%)
TEAEs grade > 3	5 (26.3%)	82 (34.7%)	0	38 (33.0%)	58 (31.9%)	29 (39.7%)	28 (29.8%)	10 (31.3%)
SAEs	6 (31.6%)	88 (37.3%)	2 (18.2%)	35 (30.4%)	70 (38.5%)	24 (32.9%)	24 (25.5%)	13 (40.6%)
immune-related TEAEs	12 (63.2%)	138 (58.5%)	7 (63.6%)	42 (36.5%)	113 (62.1%)	37 (50.7%)	39 (41.5%)	10 (31.3%)
TEAEs leading to death	0	12 (5.1%)	0	3 (2.6%)	7 (3.8%)	5 (6.8%)	2 (2.1%)	1 (3.1%)
TEAEs leading to treatment discontinuation	2 (10.5%)	45 (19.1%)	0	6 (5.2%)	32 (17.6%)	15 (20.5%)	4 (4.3%)	2 (6.3%)

Table 45: Overview of safety by weight groups and ECOG performance status, study CS1001-301

	Sugemalimab (N=255)		Placebo (N=126)		Sugemalimab (N=255)		Placebo (N=126)	
	Weight<= 62 (N=132)	Weight > 62 (N=123)	Weight <= 62 (N=60)	Weight > 62 (N=66)	ECOG = 0 (N=78)	ECOG =1 (N=177)	ECOG = 0 (N=38)	ECOG = 1 (N=88)
TEAEs (all grades)	129 (97.7%)	119(96. 7%)	59 (98.3%)	62 (93.9%)	78 (100.0%)	170 (96.0%)	34 (89.5%)	87 (98.9%)
TEAEs grade > 3	43 (32.6%)	44 (35.8%)	16 (26.7%)	22 (33.3%)	26 (33.3%)	61 (34.5%)	10 (26.3%)	28 (31.8%)
SAEs	46 (34.8%)	48 (39.0%)	17 (28.3%)	20 (30.3%)	29 (37.2%)	65 (36.7%)	11 (28.9%)	26 (29.5%)
immune-related TEAEs	73 (55.3%)	77 (62.6%)	22 (36.7%)	27 (40.9%)	43 (55.1%)	107 (60.5%)	11 (28.9%)	38 (43.2%)
TEAEs leading to death	7 (5.3%)	5 (4.1%)	1 (1.7%)	2 (3.0%)	4 (5.1%)	8 (4.5%)	1 (2.6%)	2 (2.3%)
TEAEs leading to treatment discontinuation	24 (18.2%)	23 (18.7%)	2 (3.3%)	4 (6.1%)	15 (19.2%)	32 (18.1%)	2 (5.3%)	4 (4.5%)

Table 46: Overview of safety by PD-L1 and ADA status, study CS1001-301

	Sugemalimab (N=255)		Placebo (N=126)		Sugemalimab (N=255)	
	PDL1 < 1% (N=51)	PDL1 >= 1% (N=72)	PDL1 < 1% (N=29)	PDL1 >= 1% (N=23)	ADA Negative (N=228)	ADA Positive (N=27)
TEAEs (all grades)	49 (96.1%)	71 (98.6%)	26 (89.7%)	22 (95.7%)	222 (97.4%)	26 (96.3%)
TEAEs grade > 3	18 (35.3%)	22 (30.6%)	6 (20.7%)	5 (21.7%)	80 (35.1%)	7 (25.9%)
SAEs	12 (23.5%)	31 (43.1%)	6 (20.7%)	7 (30.4%)	86 (37.7%)	8 (29.6%)
immune-related TEAEs	31 (60.8%)	48 (66.7%)	11 (37.9%)	11 (47.8%)	132 (57.9%)	18 (66.7%)
TEAEs leading to death	3 (5.9%)	1 (1.4%)	0	0	12 (5.3%)	0
TEAEs leading to treatment discontinuation	7 (13.7%)	12 (16.7%)	0	0	42 (18.4%)	5 (18.5%)

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with sugemalimab.

Discontinuation due to adverse events

Table 47: Treatment-emergent adverse events leading to permanent discontinuation of sugemalimab or placebo treatment by system organ class and preferred term, CS1001-301 (safety analysis set)

System Organ Class Preferred Term	Sugemalimab (N = 255) n (%)	Placebo (N = 126) n (%)
Number of Participants With at Least One Event	47(18.4)	6 (4.8)
Respiratory, thoracic and mediastinal disorders	**25 (9.8)**	**3 (2.4)**
Immune-mediated lung disease	13 (5.1)	0
Pneumonitis	7 (2.7)	2 (1.6)
Interstitial lung disease	3 (1.2)	1 (0.8)
Haemoptysis	2 (0.8)	0
Infections and infestations	**6 (2.4)**	**1 (0.8)**
Pneumonia	5 (2.0)	1 (0.8)
Infection	1 (0.4)	0
Pulmonary tuberculosis	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (2.0)**	**0**
Acute myeloid leukaemia	1 (0.4)	0
Hepatic cancer	1 (0.4)	0
Oesophageal cancer metastatic	1 (0.4)	0
Oesophageal squamous cell carcinoma	1 (0.4)	0
Rectal cancer	1 (0.4)	0
Metabolism and nutrition disorders	**3 (1.2)**	**0**
Hypertriglyceridaemia	2 (0.8)	0
Diabetic ketoacidosis	1 (0.4)	0
Cardiac disorders	**2 (0.8)**	**0**
Atrial flutter	1 (0.4)	0
Cardiac failure	1 (0.4)	0
Immune-mediated myocarditis	1 (0.4)	0
Injury, poisoning and procedural complications	**2 (0.8)**	**2 (1.6)**
Radiation pneumonitis	2 (0.8)	1 (0.8)
Thoracic vertebral fracture	0	1 (0.8)
Investigations	**2 (0.8)**	**0**
Blood creatine phosphokinase increased	1 (0.4)	0
Platelet count decreased	1 (0.4)	0
System Organ Class Preferred Term	**Sugemalimab** **(N = 255)** **n (%)**	**Placebo** **(N = 126)** **n (%)**
Skin and subcutaneous tissue disorders	**2 (0.8%)**	**0**
Rash	2 (0.8%)	0
General disorders and administration site conditions	**1 (0.4%)**	**0**
Death	1 (0.4%)	0
Nervous system disorders	**1 (0.4%)**	**0**
Haemorrhage intracranial	1 (0.4%)	0

Treatment-emergent adverse event is defined as any adverse event that occurred or worsened on or after the start of study treatment.
The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 26.0.
CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class
Source: Study CS1001-301 CSR, Table t_ae_disc_SA_2

Sugemalimab-related TEAEs leading to treatment discontinuation also led to death in 3 participants: immune-mediated lung disease in 1 participant and pneumonia in 2 participants (Table 15). No participant had placebo-related TEAEs leading to treatment discontinuation that resulted in death. Additional details on TEAEs leading to death are provided in Section 2.1.2.1.

Supportive sugemalimab monotherapy pool

Introduction

The sugemalimab monotherapy pool consisted of 568 patients with advanced or metastatic NSCLC, other solid tumours, and haematological malignancies who received at least one dose of sugemalimab 1,200 mg Q3W.

The sugemalimab arm of study 301 (n=255) accounted for 44.9% of the patients in the sugemalimab monotherapy pool.

It is noted that the TEAE incidences presented for the sugemalimab arm of study 301 in the pivotal study differs from the incidence numbers presented for the same study arm in the sugemalimab monotherapy pool tables. This is due to different DCOs. Study data 301 are presented as of DCO 03 April 2023 whereas the DCO of the studies included in the sugemalimab monotherapy pool, including study 301, was 08 March 2021.

Overall, the study 301 safety population and the sugemalimab monotherapy pool population were comparable as regards variables such as sex (majority male participants), race (Asian), median age at diagnosis (< 65 years), median weight (< 65 kg), and ECOG performance status (majority ECOG 1). Other factors, such as distribution of disease stage or histology were not comparable due to different study inclusion criteria. This also regarded prior treatments. Patients in the monotherapy pool were generally more heavily pretreated, with 41.4% having received 1st line and 28.9% 2nd line treatment, and 48.8% having underwent prior cancer-related surgery, whereas only 8.6% of the patients in the study 301 safety population had received prior cancer therapy other than chemoradiotherapy and 5.1% having underwent prior cancer-related surgery.

Patient exposure

As of DCO 08 March 2021 for the studies included in the sugemalimab monotherapy pool, 164 (28.9%) of the patients were still on treatment and 404 (70.1%) had discontinued treatment. A total of 373 (65.7%) of the patients were still on study, whereas 195 (34.3%) had discontinued from study.

Table 48: Summary of exposure to sugemalimab, sugemalimab monotherapy pool (safety analysis set)

	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Treatment Duration (months)							
Mean (SD)	6.76 (8.708)	4.72 (5.987)	8.62 (9.593)	7.67 (4.407)	8.66 (6.884)	5.67 (4.630)	7.87 (7.272)
Median	3.65	2.07	5.19	6.24	6.34	4.34	5.59
Min, max	0.7, 36.3	0.7, 20.0	0.7, 37.4	0.1, 19.8	0.2, 28.4	0.4, 16.6	0.1, 37.4
Number of Cycles							
Mean (SD)	9.2 (11.57)	6.8 (8.62)	12.3 (13.65)	11.0 (6.37)	11.7 (9.40)	7.9 (6.58)	10.9 (10.02)
Median	5.0	3.0	7.5	9.0	9.0	6.0	8.0
Min, max	1, 50	1, 29	1, 54	1, 29	1, 41	1, 24	1, 54
Total Cumulative Dose (mg)							
Mean (SD)	11002.1 (13880.69)	8200.0 (10346.01)	14733.1 (16377.82)	13192.3 (7658.66)	14075.3 (11279.22)	9493.3 (7901.39)	13040.9 (12024.29)
Median	6000.0	3600.0	9000.0	10800.0	10800.0	7200.0	9600.0
Min, max	1200, 60000	1200, 34800	1200, 64800	579, 34800	1200, 49200	1200, 28800	579, 64800
Duration of Exposure, n (person-years)							
< 1 month	12 (0.698)	2 (0.115)	7 (0.402)	2 (0.063)	16 (0.854)	2 (0.088)	41 (2.220)
1 to < 3 months	32 (5.008)	7 (1.188)	29 (5.185)	11 (2.346)	42 (7.422)	17 (2.943)	138 (24.093)
3 to < 6 months	20 (7.053)	0	12 (5.218)	24 (10.349)	57 (21.344)	9 (3.521)	122 (47.485)
6 to < 9 months	14 (8.019)	1 (0.698)	7 (4.594)	19 (11.537)	53 (32.539)	9 (5.273)	103 (62.661)
9 to < 12 months	1 (0.890)	0	6 (5.394)	11 (9.520)	18 (15.483)	2 (1.788)	38 (33.073)
12 to < 15 months	3 (3.384)	1 (1.051)	3 (3.231)	8 (9.287)	19 (21.175)	2 (2.171)	36 (40.298)
15 to < 18 months	3 (4.186)	0	6 (8.493)	4 (5.405)	16 (22.220)	4 (5.487)	33 (45.791)
18 to < 21 months	1 (1.708)	1 (1.667)	1 (1.569)	2 (3.274)	15 (24.608)	0	20 (32.827)
≥ 21 months	9 (22.593)	0	9 (23.357)	0	19 (38.330)	0	37 (84.279)
Total	95 (53.539)	12 (4.720)	80 (57.443)	81 (51.781)	255 (183.975)	45 (21.270)	568 (372.728)

Treatment duration is defined as minimum of (treatment end date of study drug - treatment start date of study drug + 21, clinical cutoff date - treatment start date of study drug + 1, study discontinue date - treatment start date of study drug + 1) /30.4375.
Total cumulative dose is defined as the sum of actual dosage administered during each cycle.
The cumulative exposure in person-years = sum (total treatment duration [days]) / 365.25.
max = maximum; min = minimum; SD = standard deviation
Sources: Module 5.3.5.3, Table 2.1.1 and Table 2.4.1

Adverse events

Table 49: Overview of treatment-emergent adverse events, sugemalimab monotherapy pool (safety analysis set)

	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participants With							
Any TEAE	**93 (97.9)**	**12 (100.0)**	**77 (96.3)**	**73 (90.1)**	**246 (96.5)**	**40 (88.9)**	**541 (95.2)**
Any TEAE of Grade 3 to 5	46 (48.4)	9 (75.0)	31 (38.8)	22 (27.2)	62 (24.3)	11 (24.4)	181 (31.9)
Any serious TEAE	26 (27.4)	6 (50.0)	18 (22.5)	15 (18.5)	72 (28.2)	7 (15.6)	144 (25.4)
Any TEAE leading to infusion interruption	0	0	4 (5.0)	0	1 (0.4)	0	5 (0.9)
Any TEAE leading to treatment cycle delayed	27 (28.4)	0	13 (16.3)	14 (17.3)	82 (32.2)	5 (11.1)	141 (24.8)
Any TEAE leading to treatment discontinuation	11 (11.6)	3 (25.0)	10 (12.5)	6 (7.4)	29 (11.4)	2 (4.4)	61 (10.7)
Any TEAE leading to death	2 (2.1)	1 (8.3)	5 (6.3)	0	10 (3.9)	1 (2.2)	19 (3.3)
Any Treatment-Related TEAE	**82 (86.3)**	**8 (66.7)**	**61 (76.3)**	**62 (76.5)**	**193 (75.7)**	**29 (64.4)**	**435 (76.6)**
Any treatment-related TEAE of Grade 3 to 5	17 (17.9)	1 (8.3)	13 (16.3)	10 (12.3)	26 (10.2)	5 (11.1)	72 (12.7)
Any treatment-related serious TEAE	10 (10.5)	1 (8.3)	5 (6.3)	5 (6.2)	38 (14.9)	4 (8.9)	63 (11.1)
Any treatment-related TEAE leading to infusion interruption	0	0	4 (5.0)	0	1 (0.4)	0	5 (0.9)
Any treatment-related TEAE leading to treatment cycle delayed	13 (13.7)	0	9 (11.3)	9 (11.1)	49 (19.2)	4 (8.9)	84 (14.8)
Any treatment-related TEAE leading to treatment discontinuation	7 (7.4)	1 (8.3)	4 (5.0)	5 (6.2)	24 (9.4)	1 (2.2)	42 (7.4)
Any treatment-related TEAE leading to death	1 (1.1)	1 (8.3)	0	0	4 (1.6)	1 (2.2)	7 (1.2)
Any Infusion-Related Reaction TEAE	**1 (1.1)**	**0**	**4 (5.0)**	**13 (16.0)**	**1 (0.4)**	**0**	**19 (3.3)**
Immune-Related AEs by Investigator Assessment[a]	**39 (41.1)**	**0**	**22 (27.5)**	**32 (39.5)**	**137 (53.7)**	**8 (17.8)**	**238 (41.9)**

[a] Immune-related AEs by Sponsor assessment are provided in the individual CSRs.
MedDRA version 24.1.
AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Sources: Module 5.3.5.3, Table 3.1.1 and Table 3.2.11.1

Adverse events by system organ class and preferred term

Table 50: Most commonly reported treatment-emergent adverse events (≥ 10% of participants overall) by system organ class and preferred term, sugemalimab monotherapy pool (safety analysis set)

System Organ Class Preferred Term	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participants With at Least One Event	93 (97.9)	12 (100.0)	77 (96.3)	73 (90.1)	246 (96.5)	40 (88.9)	541 (95.2)
Investigations	**78 (82.1)**	**6 (50.0)**	**57 (71.3)**	**46 (56.8)**	**163 (63.9)**	**28 (62.2)**	**378 (66.5)**
Aspartate aminotransferase increased	39 (41.1)	1 (8.3)	19 (23.8)	9 (11.1)	46 (18.0)	6 (13.3)	120 (21.1)
Alanine aminotransferase increased	34 (35.8)	1 (8.3)	13 (16.3)	14 (17.3)	51 (20.0)	4 (8.9)	117 (20.6)
White blood cell count decreased	13 (13.7)	0	24 (30.0)	5 (6.2)	19 (7.5)	4 (8.9)	65 (11.4)
Blood bilirubin increased	31 (32.6)	2 (16.7)	5 (6.3)	2 (2.5)	16 (6.3)	3 (6.7)	59 (10.4)
Respiratory, Thoracic and Mediastinal Disorders	**23 (24.2)**	**1 (8.3)**	**18 (22.5)**	**13 (16.0)**	**133 (52.2)**	**7 (15.6)**	**195 (34.3)**
Cough	14 (14.7)	0	5 (6.3)	7 (8.6)	47 (18.4)	1 (2.2)	74 (13.0)
Infections and Infestations	**18 (18.9)**	**3 (25.0)**	**30 (37.5)**	**35 (43.2)**	**78 (30.6)**	**11 (24.4)**	**175 (30.8)**
Upper respiratory tract infection	5 (5.3)	0	10 (12.5)	22 (27.2)	22 (8.6)	1 (2.2)	60 (10.6)
Pneumonia	1 (1.1)	1 (8.3)	9 (11.3)	8 (9.9)	33 (12.9)	7 (15.6)	59 (10.4)
General Disorders and Administration Site Conditions	**33 (34.7)**	**4 (33.3)**	**33 (41.3)**	**33 (40.7)**	**58 (22.7)**	**9 (20.0)**	**170 (29.9)**
Pyrexia	15 (15.8)	1 (8.3)	24 (30.0)	28 (34.6)	15 (5.9)	4 (8.9)	87 (15.3)
Blood and Lymphatic System Disorders	**37 (38.9)**	**1 (8.3)**	**20 (25.0)**	**16 (19.8)**	**69 (27.1)**	**15 (33.3)**	**158 (27.8)**
Anaemia	34 (35.8)	0	13 (16.3)	12 (14.8)	56 (22.0)	15 (33.3)	130 (22.9)
Endocrine Disorders	**12 (12.6)**	**1 (8.3)**	**19 (23.8)**	**20 (24.7)**	**65 (25.5)**	**5 (11.1)**	**122 (21.5)**
Hypothyroidism	8 (8.4)	1 (8.3)	17 (21.3)	15 (18.5)	44 (17.3)	4 (8.9)	89 (15.7)
Injury, Poisoning and Procedural Complications	**3 (3.2)**	**0**	**2 (2.5)**	**0**	**72 (28.2)**	**1 (2.2)**	**78 (13.7)**
Radiation pneumonitis	0	0	0	0	61 (23.9)	0	61 (10.7)

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class
Source: Module 5.3.5.3, Table 3.2.1

The incidence of IRRs in the sugemalimab monotherapy pool was 3.3%.

Overall, the incidences of treatment-related TEAEs by PT, adverse events grade 3-5, and treatment-related adverse events grade 3-5 in the sugemalimab arm of study 301 were consistent with the findings in the sugemalimab monotherapy pool.

Adverse events of special interest

Table 51: Overall summary of immune-related adverse events from investigator assessment, sugemalimab monotherapy pool (safety analysis set)

	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participants With at Least One Event	**39 (41.1)**	**0**	**22 (27.5)**	**32 (39.5)**	**137 (53.7)**	**8 (17.8)**	**238 (41.9)**
Grade 3 to 5 event	7 (7.4)	0	3 (3.8)	5 (6.2)	14 (5.5)	1 (2.2)	30 (5.3)
Serious event	6 (6.3)	0	1 (1.3)	4 (4.9)	29 (11.4)	1 (2.2)	41 (7.2)
Event leading to sugemalimab permanently discontinued	4 (4.2)	0	0	3 (3.7)	19 (7.5)	1 (2.2)	27 (4.8)
Event leading to sugemalimab interruption (cycle delayed/ infusion interruption)	8 (8.4)	0	4 (5.0)	3 (3.7)	35 (13.7)	0	50 (8.8)
Event leading to death	0	0	0	0	2 (0.8)	1 (2.2)	3 (0.5)
Event treated with systemic corticosteroid	0	0	1 (1.3)	1 (1.2)	44 (17.3)	1 (2.2)	47 (8.3)
Event treated with high-dose systemic corticosteroid	0	0	1 (1.3)	1 (1.2)	38 (14.9)	1 (2.2)	41 (7.2)

MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities
Source: Module 5.3.5.3, Table 3.2.11.1

Table 52: Immune-related adverse events from investigator assessment by category, sugemalimab monotherapy pool (safety analysis set)

Category	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participants With at Least One Event	**39 (41.1)**	**0**	**22 (27.5)**	**32 (39.5)**	**137 (53.7)**	**8 (17.8)**	**238 (41.9)**
Immune-related hypothyroidism	15 (15.8)	0	13 (16.3)	14 (17.3)	49 (19.2)	4 (8.9)	95 (16.7)
Immune-related hyperthyroidism	8 (8.4)	0	5 (6.3)	3 (3.7)	45 (17.6)	3 (6.7)	64 (11.3)
Immune-related pneumonitis	2 (2.1)	0	1 (1.3)	0	49 (19.2)	1 (2.2)	53 (9.3)
Immune-related skin adverse reactions (excluding severe)	4 (4.2)	0	7 (8.8)	8 (9.9)	32 (12.5)	1 (2.2)	52 (9.2)
Immune-related hepatitis	13 (13.7)	0	2 (2.5)	9 (11.1)	20 (7.8)	2 (4.4)	46 (8.1)
Immune-related myocarditis	6 (6.3)	0	1 (1.3)	3 (3.7)	5 (2.0)	1 (2.2)	16 (2.8)
Immune-related diabetes mellitus	2 (2.1)	0	1 (1.3)	2 (2.5)	8 (3.1)	0	13 (2.3)
Immune-related myositis	3 (3.2)	0	2 (2.5)	1 (1.2)	5 (2.0)	2 (4.4)	13 (2.3)
Immune-related colitis	2 (2.1)	0	2 (2.5)	0	4 (1.6)	0	8 (1.4)
Immune-related nephritis (including renal failure)	1 (1.1)	0	0	1 (1.2)	5 (2.0)	0	7 (1.2)
Immune-related pancreatitis	7 (7.4)	0	0	0	0	0	7 (1.2)
Immune-related severe skin adverse reactions	0	0	1 (1.3)	1 (1.2)	4 (1.6)	0	6 (1.1)
Immune-related upper gastrointestinal disorders	1 (1.1)	0	0	0	2 (0.8)	0	3 (0.5)
Immune-related thyroiditis	0	0	0	2 (2.5)	1 (0.4)	0	3 (0.5)
Immune-related hypophysitis	2 (2.1)	0	0	0	0	0	2 (0.4)
Immune-related pancytopenia/bicytopenia	1 (1.1)	0	0	1 (1.2)	0	0	2 (0.4)
Immune-related adrenal insufficiency	1 (1.1)	0	0	0	0	0	1 (0.2)
Immune-related arthritis	0	0	0	0	1 (0.4)	0	1 (0.2)
Immune-related haemolytic anaemia	0	0	0	1 (1.2)	0	0	1 (0.2)
Immune-related ocular toxicities	0	0	1 (1.3)	0	0	0	1 (0.2)
Immune-related rhabdomyolysis/myopathy	0	0	0	0	0	1 (2.2)	1 (0.2)
Immune-related vasculitis	0	0	0	1 (1.2)	0	0	1 (0.2)

MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities
Source: Module 5.3.5.3, Table 3.2.12.3

Serious adverse events

Table 53: Serious treatment-emergent adverse events (≥ 2% of participants overall by preferred term) by system organ class and preferred term, sugemalimab monotherapy pool (safety analysis set)

System Organ Class Preferred Term	CS1001-101a/b (N = 95) n (%)	CS1001-102 (N = 12) n (%)	CS1001-201 (N = 80) n (%)	CS1001-202 (N = 81) n (%)	CS1001-301 (N = 255) n (%)	CS1001-302 Crossover (N = 45) n (%)	Total (N = 568) n (%)
Number of Participants With at Least One Event	26 (27.4)	6 (50.0)	18 (22.5)	15 (18.5)	72 (28.2)	7 (15.6)	144 (25.4)
Infections and Infestations	**5 (5.3)**	**2 (16.7)**	**8 (10.0)**	**9 (11.1)**	**24 (9.4)**	**3 (6.7)**	**51 (9.0)**
Pneumonia	1 (1.1)	0	4 (5.0)	6 (7.4)	20 (7.8)	3 (6.7)	34 (6.0)
Respiratory, Thoracic and Mediastinal Disorders	**2 (2.1)**	**0**	**0**	**3 (3.7)**	**34 (13.3)**	**1 (2.2)**	**40 (7.0)**
Immune-mediated lung disease	0	0	0	0	14 (5.5)	1 (2.2)	15 (2.6)
Pneumonitis	1 (1.1)	0	0	0	11 (4.3)	0	12 (2.1)
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**0**	**17 (6.7)**	**0**	**17 (3.0)**
Radiation pneumonitis	0	0	0	0	15 (5.9)	0	15 (2.6)

The participant is counted only once per unique SOC and once per unique PT within SOC.
MedDRA version 24.1.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class
Source: Module 5.3.5.3, Table 3.2.4.1

Post marketing experience

At DCO for the current applicant, sugemalimab was only authorised for marketing in China. As of 24 July 2024, sugemalimab is authorised for marketing in the EU.

Cumulatively, as of 19 December 2024, the estimated patient exposure for the cumulative period is based on worldwide sales of 4,210 Standard Units while the patient exposure is approximately 121 patient-years.

2.5.1. Discussion on clinical safety

The safety assessment is focused on data from the pivotal study CS1001-301 (study 301) in patients with unresectable stage III NSCLC without sensitising EGFR mutations, or ALK or ROS1 genomic aberrations whose disease had not progressed following concurrent or sequential platinum-based chemoradiotherapy.

Data are presented as of DCO date 03 April 2023, when all patients in study 301 had discontinued sugemalimab or placebo treatment and discontinued from the study.

In study 301, 255 patients were exposed to sugemalimab monotherapy and 126 to placebo.The size of the safety database is considered acceptable. As expected in a placebo-controlled study, the median duration of treatment exposure in the active sugemalimab arm was longer (9.0 months) than in the placebo arm (7.6 months). The patient exposure is acceptable and evokes no concern. Safety data from study 301 is the focus of this assessment, however the full safety database for sugemalimab monotherapy encompasses 568 patients exposed to the recommended sugemalimab dose of 1,200 mg/kg Q3W as presented in section 4.8 of the SmPC.

Almost all patients in study 301 experienced TEAEs of any grade (97.3% sugemalimab vs. 96.0% placebo). Overall, the incidences of the most commonly occurring TEAEs by SOC and PT were comparable between the sugemalimab and placebo arm in study 301.

TEAEs by PT with ≥ 5.0% higher incidence in the sugemalimab vs. the placebo arm were `ALT´ and `AST increased´ (24.7% and 20.4% sugemalimab vs. 15.9% and 10.3% placebo, respectively), `weight increased´(16.6% vs. 11.1%), and `hypo-´ and `hyperthyroidism´ (20.8% and 15.7% vs. 11.9% and 4.8%, respectively).

Infusion-related reactions (IRRs) were rare and occurred in one (0.4%) patient in the sugemalimab arm. This patient experienced a total of two events of vomiting and dizziness. In the placebo arm, two (1.6%) patients experienced IRRs.

IRR is an established adverse reaction pertaining to sugemalimab and cases of e.g., anaphylactic reactions have been reported in clinical studies. This is reflected in the SmPC sections 4.2, 4.4. and 4.8.

It is noted that different terms for reporting TEAE pneumonitis are used. In the SmPC 4.8 the terms pneumonitis (not otherwise specified), immune-mediated lung disease and interstitial lung disease, which are listed separately in the CSR, are grouped together as ADR pneumonitis. This is outlined with a footnote under the ADR table, which was introduced at the time of approval. According to the Applicant, merging of these terms is made because they are difficult to clinically differentiate. This is acknowledged. Radiation pneumonitis, however, is not included in the ADR term pneumonitis due to its different aetiology and is not considered an ADR pertaining to sugemalimab. Although it may be clinically difficult to distinguish between radiation pneumonitis and `other´ cases of pneumonitis, this is considered acceptable.

Dose modification recommendations for radiation pneumonitis and a warning for radiation pneumonitis, in addition to the existing warning pertaining to immune-mediated pneumonitis, are included in the SmPC 4.2 and 4.4. Patients should be monitored for signs and symptoms of radiation pneumonitis. Suspected radiation pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded. In case of grade 2 and 3 radiation pneumonitis, treatment should be withheld until radiation pneumonitis recovers to Grade 0 to 1. In case of grade 4 radiation pneumonitis, treatment should be permanently discontinued. This is acknowledged.

In the table of ADRs of SmPC section 4.8, some ADRs are presented as immune-mediated, but for some ADRs this association is only indicated with a footnote. It was clarified that this is because some MedDRA PT terms have `immune-related/mediated´ in the name. For those without this specification, the immune-mediated relationship is clarified in a footnote. This is acknowledged.

Grade 3-5 TEAE incidences were comparable between the sugemalimab arm (34.1%) and the placebo arm (30.2%) of study 301. The majority of AEs by PT occurred in < 1% of participants. In both study arms, the most common grade 3 and 4 TEAEs respectively were pneumonia and hyperuricaemia. Grade 5 TEAEs were twice as common in the sugemalimab arm (n=12 [4.7%]) than in the placebo arm (n=3 [2.4%]).

TEAEs leading to study treatment interruption were equally uncommon in the sugemalimab and placebo arms of study 301 (one patient each). TEAEs leading to study cycle delay were reported for 39.6% of the patients in the sugemalimab arm and 28.6% in the placebo arm, respectively.

In the sugemalimab arm, the most common reasons for study cycle delay were related to pulmonary events, e.g., radiation pneumonitis (8.6%), pneumonitis (6.3%), pneumonia (5.9%), and immune-mediated and interstitial lung disease (3.5% each). This is acknowledged considering the primary disease location and previous irradiation of the lungs. Treatment cycle delays in the placebo arm were mainly due to pneumonitis (11.1%).

In line with the reasons for treatment cycle delay, all but two of the in total 36.9% SAEs in the sugemalimab arm were pulmonary events: pneumonia (9.4%), immune-mediated lung disease (6.7%), radiation pneumonitis (6.3%), pneumonitis (4.3%), and interstitial lung disease (3.5%). As expected, SAEs occurred less frequently in the placebo arm (29.4%).

A total of 116 (45.5%) of the patients in the sugemalimab arm and 66 (52.4%) of the patients in the placebo arm died while on study. Of these deaths, 12 (4.7%) and three (2.4%), respectively, were due to TEAEs. The only deaths due to TEAEs occurring in $\geq$ 1 patient in the sugemalimab arm were pneumonia (n=4 patients) and haemoptysis (n=2 patients). The Investigator assessed three cases of deaths due to TEAEs as related to sugemalimab (pneumonia n=2 and immune-mediated lung disease n=1).

Immune-related AEs (irAEs) were considered AESIs in all sugemalimab clinical studies. As expected, the incidence of irAEs was higher in the sugemalimab than in the placebo arm (58.8% vs. 38.9%) of study 301, although the incidence of supposedly irAEs reported in the placebo arm was surprisingly high. The most frequently reported Investigator-assessed irAE categories were ir-hypothyroidism (sugemalimab 24.7% vs. placebo 12.7%), ir-pneumonitis (21.6% vs. 15.9%), ir-hyperthyroidism (21.2% vs. 9.5%), ir-skin adverse reaction (excluding severe) (14.1% vs. 4.0%) and ir-hepatitis (8.6% vs. 4.8%, respectively). All other irAE categories were reported in < 5% of participants in each treatment arm.

In the sugemalimab arm, the majority of all irAEs were grade 1-2. There was a total of 18 (7.1%) grade 3 irAEs in the sugemalimab arm, of which pneumonitis and severe skin adverse reactions were the most common (six cases [2.4%] each). There were two grade 4 (0.8%) and one grade 5 irAE (0.4%), all pertaining to pneumonitis. At the time of DCO, most of the irAEs (67.3%) had resolved completely.

Novel dose modifications for immune-related ADRs are outlined in the SmPC 4.2 and extensive warnings are presented in 4.4. Moreover, a novel dose modification recommendation for non-immune mediated adverse reactions is introduced. This is endorsed.

The most commonly reported abnormal clinical chemistry parameters in the sugemalimab arm were ALT and AST high (32.2% and 32.9%, respectively), cholesterol high (38.0%), creatinine high (87.8%), and fasting glucose high (49.4%), as well as albumin low (39.2%), phosphate low (34.9%), potassium low (23.1%), and sodium low (31.4%). The majority of the laboratory changes were grade 1-2.

There were no case reports meeting the criteria for Hy's law. Hepatic enzyme increased, hepatic function abnormal, and hepatitis are established ADRs pertaining to sugemalimab and dose modification and warnings are for immune-related hepatitis were already included in the SmPC 4.2 and 4.4.

Thyroid function tests were regularly performed, with baseline values representing the patients' last observations prior to initiation of study drug. The majority of patients ($\geq$ 90%) had normal thyrotropin, free triiodothyronine, and free thyroxine values at baseline.

In line with the higher incidence of immune-related thyroid disorders in the sugemalimab arm (please refer to irAEs above), the shifts in thyroid parameters were overall greater in patients exposed to sugemalimab compared to placebo.

According to the Applicant there were no clinically meaningful changes in vital signs (blood pressure, pulse rate, respiratory rate, body temperature) and weight from baseline and across treatments. Most patients (93.7%) maintained an ECOG performance status of 0-1 post-baseline.

At baseline, 12 (4.7%) patients in the sugemalimab arm had an abnormal, clinically significant ECG and post-baseline the number of patients had increased to 18 (7.1%). It is not outlined what kind of clinically significant ECG findings that were reported. It is also noted that post-baseline ECGs were missing for 132 (51.8%) of the patients and that no information on potential cases with QTcF > 500 msec at baseline and post-baseline or cases with a maximum change in QTcF > 60 msec were provided. Since QTcF prolongation has not been identified as a problem for other PD-L1 inhibitors, though, this issue is not pursued further.

The TEAE incidences (TEAEs all grade, TEAEs grade $\geq$ 3, SAEs, irTEAEs, TEAEs leading to death, and TEAEs leading to treatment discontinuation) by special populations sex, age groups, weight groups, ECOG performance status, PD-L1 status, and ADA status were overall comparable between subgroups.

A total of 47 (18.4%) of the patients in the study 301 sugemalimab arm and six (4.8) in the placebo arm discontinued study treatment due to TEAEs. In line with the SAEs and TEAEs leading to dose modifications, the most common TEAEs leading to discontinuation in the sugemalimab arm were pulmonary events (immune-mediated lung disease 5.1%, pneumonitis 2.7%, pneumonia 2.0%, interstitial lung disease 1.2%, and haemoptysis and radiation pneumonitis 0.8% each).

Generally, the TEAE incidence in the placebo arm of study 301 was surprisingly high. Except for lung related side effects and symptoms, which may be explained by the tumour location and prior lung irradiation, the incidences of e.g., hypothyroidism (11.9%), and ALT and AST increased (15.9% and 10.3%, respectively), in the placebo arm were intriguing. The worldwide annual incidence of hypothyroidism is estimated to be 1-1.5% (prevalence approximately 3-4%) and, thus, the incidence in the placebo arm was 8-10 times higher than expected. It is noted that almost all patients in both the sugemalimab arm and the placebo arm used concomitant medications, with 51.85% in the sugemalimab arm vs. 53.2% in the placebo arm using preparations against cough and cold (including herbal medicines) and 35.7% vs. 40.5%, respectively, using unspecified herbal and traditional medicines. This may possibly contribute to the high TEAE incidences. However, since the TEAE incidence, as expected, was consistently higher in the sugemalimab arm than in the placebo arm of study 301 and the safety profile overall appeared manageable, this issue is not pursued further.

A sugemalimab monotherapy pool was provided as support for the overall sugemalimab safety profile. This comparison was limited by the fact that a) the monotherapy pool consisted of various advanced tumours with different pre-treatments and toxicity and b) approximately half of the monotherapy pool was based on the study 301 sugemalimab arm. Overall, though, the findings in the sugemalimab arm of study 301 were consistent with known findings in other sugemalimab monotherapy studies, apart from irAEs which were more commonly reported in the study 301 sugemalimab arm. This pool consisting of 568 patients has been used for the ADR table in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

Overall, the safety profile is considered acceptable and as anticipated for a compound of this well-known class.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Important identified risks	Immune-mediated adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	None

No changes to the list of safety concerns were needed as a result of this extension of indication. The list of safety concerns remains unchanged.

Pharmacovigilance plan

None.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune-mediated adverse reactions	**Routine risk minimisation measures:** *SmPC Section 4.2* *SmPC Section 4.4* *SmPC Section 4.5* *SmPC Section 4.8* *PL Section 2* PL Section 4 Restricted medical prescription. **Additional risk minimisation measures:** Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*
Reproductive and developmental toxicity	**Routine risk minimisation measures:** *SmPC Section 4.6* *PL Section 2* *Restricted medical prescription.* **Additional risk minimisation measures:** *None proposed.*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: *None proposed.* **Additional pharmacovigilance activities**: *None proposed.*

No changes to risk minimisations measures were needed as a result of this extension of indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to radiation pneumonitis has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

1. The proposed indication extension is for the medicinal product of same route of administration, targeting the same patient population – NSCLC just at different stage of disease.

2. The overall design, layout and style of writing in PIL will not be changed.

3. The proposed PIL will only introduce the changes below to the approved PIL:

- Section 1 What Cejemly is and what it is used for:
    - In subsection "What CEJEMLY is used for" the sentence CEJEMLY is used in combination with platinum-based chemotherapy will be updated to include the proposed indication. CEJEMLY is used in combination with platinum-based chemotherapy or as monotherapy.
- Section 3: How you are given CEJEMLY
    - The subsection "How much is given" is updated to reflect the dosage recommendation of stage III NSCLC patients.
- Section 4: Possible side effects
    - The subsections "Side effects" may trigger immediate medications and other side effects will be updated to reflect the overall side effects when used as monotherapy for stage III NSCLC patients.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for sugemalimab, revised during the procedure is, as monotherapy for the treatment of unresectable stage III NSCLC with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose tumours express PD-L1 on ⩾ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiotherapy.

3.1.2. Available therapies and unmet medical need

Platinum-based chemotherapy concurrent with radiotherapy is standard of care for patients with unresectable stage III NSCLC. If concurrent chemoradiotherapy is not possible—for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative. In this treatment niche, durvalumab is approved as maintenance for patients whose disease did not progress after chemoradiotherapy and whose tumours express PD-

L1 on ≥ 1% of tumour cells. Moreover, for patients expressing relevant EGFR driver mutations, osimertinib is approved.

3.1.3. Main clinical studies

The pivotal study CS1001-301 was a randomised, double-blind, placebo-controlled, multicentre Phase III study conducted in China, to evaluate the efficacy and safety of sugemalimab or placebo as consolidation therapy, in patients with locally advanced or unresectable stage III NSCLC who have not progressed after concurrent or sequential chemoradiotherapy.

Patients had to have confirmed locally advanced, unresectable stage III-NSCLC and both squamous and non-squamous patients were included. Patients with known mutation/translocation status of EGFR, ALK and ROS1 were excluded. Importantly, testing for PD-L1 expression status was not mandatory.

3.2. Favourable effects

At the pre-planned PFS interim analysis and at the final PFS analysis sugemalimab showed a statistically significant improvement in PFS compared to placebo. At the final PFS analysis a total of 154 PFS events were observed in the sugemalimab group, compared to 90 in the placebo group, with a median follow-up of 27.1 months and 23.5 months for the sugemalimab group and placebo group, respectively. The median PFS was 10.5 months in the sugemalimab group versus 6.2 months in the placebo group (stratified HR 0.65 [95% CI: 0.50, 0.84], two-sided p = 0.0012).

OS did not reach statistical significance at the OS interim analysis (DCO: 03 April 2023). A total of 114 OS events were observed in the sugemalimab group, compared to 66 in the placebo group. The median OS was 47.4 months (95% CI: 34.3, NR [not reached]) in the sugemalimab group and 32.4 months (95% CI: 24.1, NR) in the placebo group (stratified HR 0.78 [95% CI: 0.57, 1.05], two-sided P = 0.1036) and the actual statistical superiority boundary of 0.0392 was not reached.

The study was terminated and all patients discontinued the study on DCO of 03 April 2023.

3.3. Uncertainties and limitations about favourable effects

The study was closed after the abovementioned OS interim analysis. This was due to futility with respect to the likelihood of a statistically significant read-out. Notably, 41% (n=52) of patients in the control arm were treated with a PD-L1 targeting agent after progression.

For more than 50% of patients in both study arms, PD-L1 expression status was not determined. For patients with reported PD-L1 status there was no trend for efficacy as a function of PD-L1 expression. Hence, no conclusions regarding PD-L1 status as an effect modifier can be drawn based on the pivotal study. This is reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

The safety database in the sought indication consists of 381 participants included in study CS1001-301 (study 301). Participants were randomised 2:1 to either sugemalimab monotherapy (n=255) or placebo (n=126). The full safety database for sugemalimab monotherapy comprises 568 treated patients.

The median duration of treatment in the sugemalimab arm was 9.0 months (range: 0.2, 50.7) compared to 7.6 months (range: 0.7, 42.2) in the placebo arm. The median duration of follow-up

had then reached 40.4 months (range: 38.67, 45.47) and 35.4 months (range: 32.59, 39.92) in the sugemalimab and placebo arms, respectively.

Overall, the reported TEAEs in the sugemalimab arm were in line with the established safety profile pertaining to sugemalimab + platinum-based chemotherapy. The most common TEAEs in the sugemalimab arm which are also proposed ADRs were ALT and AST increased (24.7% and 20.4%, respectively), anaemia (24.3%), radiation pneumonitis (24.7%), and hypothyroidism (20.8%).

Grade $\geq$ 3 TEAEs were reported for 34.1% and 30.2% of the patients in study 301, respectively. In the sugemalimab arm, the most commonly occurring TEAE grade $\geq$ 3 which is also an ADR pertaining to sugemalimab was immune-mediated lung disease (3.1%).

SAEs were reported for 36.9% of the patients in the sugemalimab arm vs. 29.4% in the placebo arm. The vast majority were lung related (immune-mediated lung disease, pneumonitis and radiation pneumonitis, interstitial lung disease, and pneumonia). A warning on radiation pneumonitis has been added to section 4.4 of the SmPC to include recommendations on how to monitor and manage it.

TEAEs leading to treatment infusion interruption was uncommon (one patient in each study arm), whereas treatment cycle delay was reported for 39.6% vs. 28.6% of participants, respectively. As for SAEs, the most common reasons were lung related.

A total of 18.4% of patients in the sugemalimab arm discontinued treatment due to TEAEs vs. 4.8% in the placebo arm. The most common TEAEs leading to treatment discontinuation were lung related.

Of the in total 12 (4.7%) deaths due to TEAEs reported in the sugemalimab arm, three were considered related to sugemalimab treatment by the investigator. These were pneumonia (n=2) and immune-meditated lung disease (n=1). In all three cases, onset of symptom occurred shortly after initiation of sugemalimab treatment.

The key safety issues for sugemalimab treatment were immune-related (ir) adverse reactions. Several such reactions are established ADRs pertaining to sugemalimab + chemotherapy and were also confirmed to pertain to sugemalimab monotherapy. The most frequently reported irADRs in the sugemalimab arm were ir-hypothyroidism (24.7%), ir-pneumonitis (21.6%), and ir-hyperhyroidism (21.2%).

Overall, the safety profile of sugemalimab monotherapy was in line with that pertaining to sugemalimab + platinum-based chemotherapy, as well as other PD-L1 targeting agents. No new safety concerns were identified.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 54: Effects Table for study CS1001-301, DCO 03 April 2023

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			Sugemalimab N=255	Placebo N=126		
PFS, median	Time from randomisation to first tumour progression or death	months	10.6	6.2		CSR
		HR, 95% CI	0.73 (0.56, 0.95)			
OS, median	Time from randomisation until death	months	47.4	32.4	Not statistically significant. p=0.1036 (actual statistical superiority boundary=0.0392)	
		HR, 95% CI	0.78 (0.57, 1.05)			
Unfavourable Effects						
AEs	Grade 3-4 Grade 5 SAEs Leading to treatment discontinuation	%	29.4 4.7 36.9 18.4	27.8 2.4 29.4 4.8	Asia-only study, limited follow-up time, unexpectedly high AE incidence in the placebo arm	
Immune-related AEs	Any Grade 3-4 Grade 5 SAEs Leading to treatment discontinuation	%	58.8 7.8 0.4 15.7 10.2	38.9 0 0 5.6 0.8		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study for this application was performed exclusively in China. As has been the case for several previous applications conducted exclusively in China, there is a notable dominance of men in the study population, who are also quite young. However, given the extensive experience of products in the class, sharing the same mechanism of action, with several products showing similar results in China only studies, as was seen in the rest of the world, extrapolation of effects is considered possible provided similar exposure.

The study met the primary endpoint with a statistically significant improvement in PFS assessed by BICR at the PFS analyses (DCO: 08 March 2021 and 01 April 2022). OS did not reach statistical significance at the OS interim analysis (DCO: 03 April 2023). The study was subsequently terminated, hence there will not be any more OS updates from this study. Notably, given the extent of use of PD-L1 targeting agents on progression in the placebo control arm, the sensitivity of the study to show an OS gain was limited.

Given available knowledge, a prolongation of PFS of the present magnitude after chemoradiotherapy for unresectable stage III NSCLC after chemoradiotherapy is considered to isolate clinical benefit, in the absence of any signal of a detrimental effect on OS.

PD-L1 expression status is unknown for over 50% of patients in both study arms. For patients with reported PD-L1 status there was no trend for efficacy as a function of PD-L1 expression. Hence, no conclusions regarding PD-L1 status as an effect modifier can be drawn based on the pivotal study. In light of the relevant precedent (Imfinzi) where the indication has been restricted to patients expressing PD-L1 ≥1%, specific data would be required to support an inference of efficacy also in patients expressing PD-L1 <1%. Thus, the indication has been restricted to patients expressing PD-L1 ⩾ 1%. The key risks identified for sugemalimab monotherapy were immune-related adverse reactions, especially hypo- and hyperthyroidism, and pneumonitis. These are all established ADRs pertaining to sugemalimab + platinum-based chemotherapy, as well as for PD-L1 targeting agents in general, and included as important identified risks in the EU RMP. Overall, the safety profile of sugemalimab monotherapy was manageable and no new safety concerns were identified.

3.7.2. Balance of benefits and risks

A prolongation of PFS has been demonstrated, with a trend towards increased overall survival. Tolerability is acceptable. However, in view of the missing PD-L1 expression status in a majority of the patients randomised in the pivotal study, and the precedent of Imfinzi in the same setting, the indication is restricted to patients expressing PD-L1 ⩾ 1% as efficacy in patients with PD-L1 expression (<1%) could not be demonstrated.

3.8. Conclusions

The overall B/R of Cejemly is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include the treatment of unresectable stage III non-small-cell lung cancer (NSCLC) with no sensitising EGFR mutations, or ALK, ROS1 genomic tumour aberrations in adults whose disease has not progressed following concurrent or sequential platinum-based chemoradiotherapy for CEJEMLY, based on final results from study CS1001-301; this is a Phase III, multicentre, randomised, double-blind, placebo-controlled study assessing the efficacy and safety of sugemalimab as consolidation therapy versus placebo in participants with locally advanced or unresectable stage III NSCLC who have not progressed after concurrent or sequential chemoradiotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Cejemly is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Cejemly have access to/are provided with the patient card.

The patient card shall contain the following key elements:

-Description of the main signs and symptoms of the irARs and the importance of notifying their treating physician immediately when symptoms occur.

-Reminder to carry the patient card at all times.

-Contact details of the Cejemly prescriber.