Sugemalimab (Cejemly®) with platinum-based chemotherapy for the first-line treatment of metastatic non-small-cell lung cancer (NSCLC)

General information [1]

Drug description

The active substance of Cejemly® is sugemalimab[1], an antineoplastic monoclonal antibody (L01FF11) that potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 ligands.

Indication

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

Incidence [2]

In Austria, in 2022, 5,203 persons were newly diagnosed with cancer of the lung, bronchia and trachea. The age-standardised incidence rate was 68.0/100,000 in men and 45.8/100,000 in women.

Current treatment [3]

- The Onkopedia treatment recommendation for the treatment of NSCLC without activating EGFR-, ROS1-, or ALK aberrations is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On 30 May 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Cejemly®. The full indication is: ❖ Cejemly® in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK, ROS1 or RET genomic tumour aberrations. **Other indications**: none	**Approval status for this indication**: not approved **Other indications**: ❖ According to the manufacturer, sugemalimab has been granted Orphan Drug Designation and Breakthrough Therapy Designation by the FDA for the treatment of T-cell lymphoma and adults with relapsed or refractory extra nodal NK/T-cell lymphoma, respectively.

Manufacturer

Cejemly® is manufactured by CStone Pharmaceutlicals; Marketing authorisation applicant is SFL Pharmaceuticals Deutschland GmbH.

Costs

Currently, there is no cost information available.

Warnings and precautions

Currently, there is no EMA-EPAR Product Information or FDA Label Information available.

Study characteristics [5, 6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

[1] Sugemalimab was previously known as CS1001.

GEMSTONE-302 NCT03789604	479 (2:1)	**sugemalimab** (1200 mg, IV, every 3 weeks) + **platinum-based chemotherapy**[2] for up to 4 cycles, followed by maintenance therapy with **sugemalimab** for squamous NSCLC, and IV **sugemalimab** 500 mg/m^2 + **pemetrexed** for non-squamous NSCLC	**placebo** + **platinum-based chemotherapy**[3] for up to 4 cycles, followed by maintenance therapy with **placebo** for squamous NSCLC, and **IV placebo** + pemetrexed for non-squamous NSCLC	investigator-assessed PFS in the ITT population	**prespecified interim PFS analysis:** 8.6 months (IQR 6.1–11.4) **final PFS analysis:** 17.8 months	**ongoing**, randomised, double-blind[4], phase 3 trial	PD-1	CStone Pharmaceuticals	GEMSTONE-302 [6]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (n=320 vs. n=159)
❖ Written informed consent form (ICF). ❖ 18-75 years of age (18 and 75 included) on the day of signing ICF. ❖ Histologically or cytologically confirmed stage IV NSCLC (staged according to the 8th IASLC classification. ❖ Subjects haven't received systemic treatment for advanced/metastatic NSCLC. ❖ Measurable target lesion evaluated by investigators according to RECIST v1.1. ❖ ECOG PS of 0-1. ❖ Life expectancy ≥ 12 weeks. ❖ Subjects with prior anti-cancer treatment can only be enrolled when all toxicities, except for hearing loss, alopecia and fatigue, of prior anti-cancer treatment have recovered to ≤ Grade 1 according to NCI CTCAE v4.03. ❖ Subjects must have adequate organ function. ❖ Women of childbearing potential (WOBPC, as defined in section 13.5) must have a negative pregnancy test ≤7 days prior to the first dose of the investigational product. WOBCP or fertile men and their WOBCP partners must agree to use an effective method of birth control by providing signed ICF and for six months after last dose of the investigational product.	❖ Histologically confirmed small cell lung cancer or containing small cell components. ❖ Subjects with current active autoimmune disease or prior history of autoimmune disease. ❖ Malignancies other than NSCLC within five years prior to randomisation. ❖ Known history of HIV infection and/or acquired immune deficiency syndrome. ❖ Subject with active hepatitis B or hepatitis C. ❖ Subjects with a known history of alcoholism or drug abuse. ❖ Has a known hypersensitivity to any component of study treatment, for example pemetrexed, cisplatin, carboplatin or other platinum compounds. ❖ Subjects with other conditions that, in the investigator's opinion, may influence the subject's compliance or make subjects not suitable for participating in this trial.	❖ Female sex: 21% vs. 19% ❖ Median age: 62.0 (56.0–67.0) vs. 64.0 (56.0–68.0) years ❖ <65 years: 63% vs. 57% ❖ ≥65 years: 37% vs. 43% ❖ ECOG PS: • 0: 18% vs. 16% • 1: 82% vs. 84% ❖ Smoking status • Never smoked: 27% vs. 25% • Current or former smoker: 73% vs. 75% ❖ Tumour pathological subtype • Squamous: 40% vs. 40% • Non-squamous: 60% vs. 60% ❖ PD-L1 expression • <1%: 39% vs. 40% • ≥1%: 61% vs. 60% ❖ Baseline metastases • Liver: 12% vs. 11% • Brain: 16% vs. 11%

Efficacy (I vs. C) in the ITT population	**Safety** (I vs. C)
<u>Prespecified interim analysis (data cutoff 8 June 2020)</u> **Progression or death events:** 48% vs. 71% **Median PFS:** 7.8 months (95% CI, 6.9–9.0) vs. 4.9 (4.7–5.0); stratified HR 0.50 (95% CI, 0.39–0.64), p<0.0001 **<u>Prespecified PFS final analysis (data cutoff 15 March 2021)</u>**	**TEAEs:** >99% vs. 99% **Any TRAEs:** 99% vs. 96% **Grade 3–4 TRAEs:** 54% vs. 56% **Any serious TRAEs:** 23% vs. 20%

[2] Carboplatin (AUC 5 mg/mL per min, IV) and paclitaxel (175 mg/m^2, IV) for squamous NSCLC, or carboplatin (AUC 5 mg/mL per min, IV) and pemetrexed (500 mg/m^2, IV) for non-squamous NSCLC.
[3] Patients received the same platinum-based chemotherapy regimens for squamous or non-squamous NSCLC as in the sugemalimab group.
[4] Chemotherapy is open-label, but information regarding the investigational products received is blinded.

Progression or death events: 70% vs. 85%
Median PFS: 9.0 months (95% CI, 7.4–10.8) vs. 4.9 months (4.8–5.1); stratified HR 0.48, 95% CI, 0.39–0.60; p<0.0001
Estimated 12-month PFS: 36.4% (95% CI, 31.0–41.8) vs. 14.8% (9.7–21.1)
OS data: immature
OS rates at 12 months: 72.4% vs. 62.0%
OS rates at 14 months: 47.1% vs. 38.1%
ORR (CR + PR): 63.4% vs. 40.3%

Cross over:
In the placebo group, 44 (28%) of 159 patients crossed over to receive at least one dose of sugemalimab monotherapy and 20 (13%) of 159 received subsequent immunotherapy other than sugemalimab[5].

TRAEs leading to discontinuation of any treatment: 14% vs. 9%
Deaths from AEs irrespective of attribution: 6% vs. 6%
Fatal adverse events attributed to any treatment: 3%[6] vs. 1%[7]
Immune-related TEAEs: 25% vs. 3%

Patient-reported outcomes

The evaluation of patient-reported outcomes is not provided in GEMSTONE-302 trial.

ESMO-MCBS version 1.1 [7]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: +4.1 months	0.48 (0.39–0.60)	HR ≤0.65 AND gain ≥1.5 months	3	-	NA	-	3
Adapted	NC	2B	≤6 months	PFS: +4.1 months	0.48 (0.39–0.60)	HR ≤0.65 AND gain ≥1.5 months	3	+22% immune-related TEAEs	NA	-1[8]	2

Risk of bias (RCT) [8]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	unclear[9] unclear risk	yes low risk	unclear[10] unclear risk	yes[11] high risk	unclear

Ongoing trials [9]

NCT number/trial name	Description	Estimated study completion date
NCT03789604 / GEMSTONE-302	Please see above.	06/2025

Available assessments

- No assessments were identified via NICE, NIHR, CDA-AMC, ICER and G-BA.

Other aspects and conclusions

[5] Data for the crossover phase and the pharmacokinetics and immunogenicity of sugemalimab were not mature at the recent data cutoff; therefore, those outcomes will be reported subsequently.
[6] Pneumonia with respiratory failure (n=1); myelosuppression with septic shock (n=1); pneumonia (n=2); respiratory failure, abdominal pain, cardiac failure, and immune-mediated pneumonitis (n=1 each); the other two deaths had an unspecified cause.
[7] Pneumonia and multiple organ dysfunction syndrome.
[8] Toxicity adjustment.
[9] No information found.
[10] The trial is currently ongoing.
[11] The funder participated in the data collection, data analysis, and data interpretation in collaboration with the authors, and contributed to the writing of the report by funding professional medical writing assistance.

- In May 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Cejemly®, in combination with platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations, or ALK, ROS1 or RET genomic tumour aberrations. The FDA has not yet approved this indication.
- GEMSTONE-302 is an ongoing, randomised, double-blind, phase 3 trial to evaluate the efficacy and safety of sugemalimab plus chemotherapy for patients with metastatic squamous or non-squamous NSCLC. Eligible patients were aged 18–75 years, had histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC without known EGFR sensitising mutations, ALK, ROS1, or RET fusions, no previous systemic treatment for metastatic disease, and an ECOG PS of 0 or 1. Patients were excluded if they had pathologically confirmed small-cell lung cancer or tumours with a small cell component, symptomatic central nervous system metastases, or autoimmune disease, or if they had received previous treatment with immune-checkpoint blockade therapies.
- The primary endpoint was investigator-assessed PFS in the ITT population. At the preplanned interim analysis (median follow-up 8.6 months, PFS was significantly longer in the sugemalimab group compared with the placebo group: median 7.8 months vs. 4.9 months; stratified HR was 0.50 (95% CI, 0.39–0.64, p<0.0001). At the final analysis (median follow-up 17.8 months), median PFS was 9.0 months vs. 4.9 months; stratified HR was 0.48 (95% CI, 0.39–0.60, p<0.0001).
  The evaluation of patient-reported outcomes is **not provided** in the GEMSTONE-302 trial.
- The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit **grade of 3 and 2**, respectively.
  Due to the ongoing status of the trial, the **risk of bias** was considered **unclear**. However, the **risk is increased** by the role of the sponsor in collection, analysis and interpretation of data.
- Besides GEMSTONE-302, **no further trials** were identified assessing sugemalimab in patients with stage IV NSCLC.
- Conclusion/requirements

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, AUC=area under the curve C=comparator, CDA-AMC=Canada's Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTCAE= Common Terminology Criteria for Adverse Events, ECOG PS= Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EPAR= European public assessment report, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HIV= human immunodeficiency virus, HR=hazard ratio, I=intervention, IASLC= International Association for the Study of Lung Cancer, ICER=Institute for Clinical and Economic Review, ICF=informed consent form, Int.=intention, ITT=intention-to-treat, IV=intravenous(ly), MG=median gain, n=number of patients, NA=not available, NCI=National Cancer Institute, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=programmed cell death protein 1, PD-L1=programmed cell death protein ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event, WOCBP=women of childbearing potential

References:

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3. Onkopedia, Griesinger F, et al. Onkopedia Guidelines. Lung Cancer, non small lung cancer (NSCLC). [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/lung-cancer-non-small-lung-cancer-nsclc/@@guideline/html/index.html#ID0EASAI].
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6. Zhou C, Wang Z, Sun Y, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. Lancet Oncol 2022; 23:220–33.
7. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
8. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
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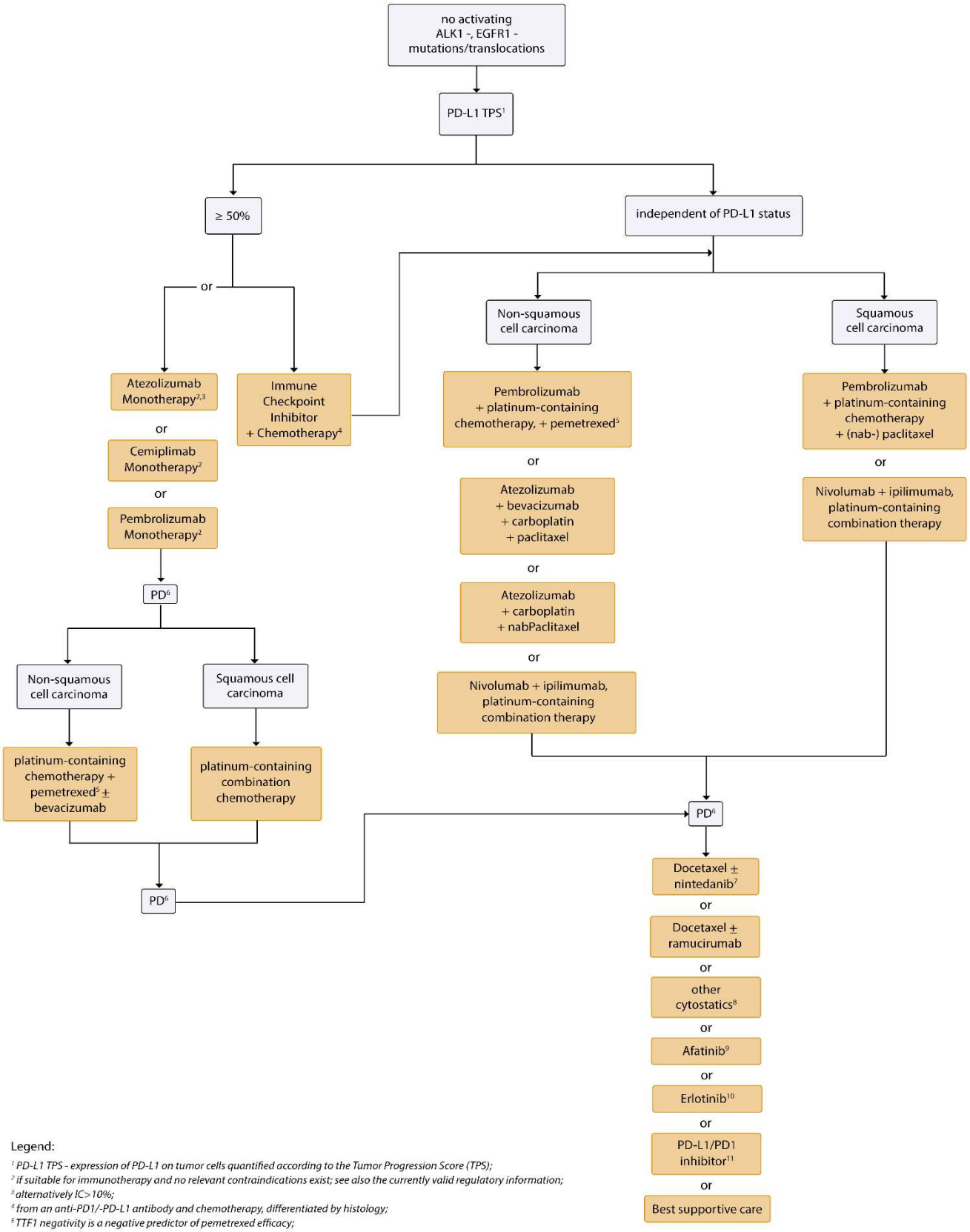
Appendix – Figure 1:



Legend:

[1] *PD-L1 TPS - expression of PD-L1 on tumor cells quantified according to the Tumor Progression Score (TPS);*
[2] *if suitable for immunotherapy and no relevant contraindications exist; see also the currently valid regulatory information;*
[3] *alternatively IC>10%;*
[4] *from an anti-PD1/-PD-L1 antibody and chemotherapy, differentiated by histology;*
[5] *TTF1 negativity is a negative predictor of pemetrexed efficacy;*
[6] *PD - progressive disease;*
[7] *Nintedanib only in adenocarcinoma;*
[8] *3rd generation cytostatic. Generation: gemcitabine, pemetrexed, vinorelbine; pemetrexed only in non-squamous cell carcinoma;*
[9] *afatinib only in squamous cell carcinoma;*
[10] *the indication was removed by the FDA in 2016;*
[11] *PD-1/PD-L1 inhibitor: atezolizumab (independent of PD-L1 expression), nivolumab (independent of PD-L1 expression), pembrolizumab (only in TPS >1%); evidence of efficacy is not established in patients, who have been pre-treated with an immune checkpoint inhibitor in first-line therapy;*