First-in-human study of the mRNA-based cancer vaccine CVGBM in patients with newly diagnosed and surgically resected *MGMT*-unmethylated glioblastoma (GBM):

First results from the dose-escalation phase

ESMO Congress 2024

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Background

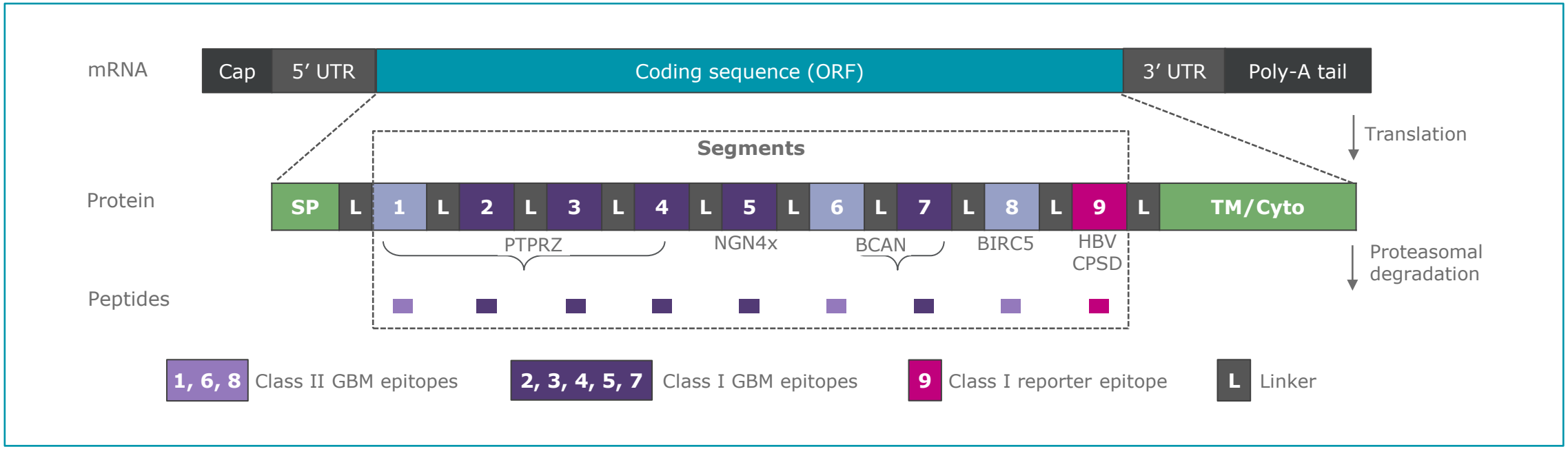
- *MGMT*-unmethylated glioblastoma has a poor prognosis, with a median overall survival of approximately 12 months after surgery and chemoradiation with temozolomide[1–3]
- Vaccines based on various platforms (e.g. peptides, dendritic cells) have been shown to induce T cell responses in patients with glioblastoma, with signals of clinical benefit and tumour immune infiltration reported in some trials[4–6]
- mRNA vaccines have been shown to induce CD4+ and CD8+ T cell responses against a variety of cancer antigens[7] and offer the possibility to encode multiple antigens on a single construct
- Here we report the first results from an ongoing phase 1 clinical trial evaluating the safety and immunogenicity of CVGBM, an investigational multiantigen mRNA vaccine, in patients with newly-diagnosed and surgically resected *MGMT*-unmethylated glioblastoma

MGMT, O6-methylguanine-DNA methyltransferase; mRNA, messenger ribonucleic acid.

1. Wen PY, et al. *Neuro Oncol*. 2020;22:1073–1113; 2. Alimonti P, Gonzalez Castro LN. *Antibodies (Basel).* 2023;12:27; 3. Stupp R, et al. *Lancet Oncol*. 2009;10(5):459–466; 4. Keskin DB, et al. *Nature*. 2019;565:234–239; 5. Hilf N, et al. Nature. 2019;565:240–245; 6. Wen PY, et al. *Clin Cancer Res*. 2019;25:5799–5807; 7. Vishweshwaraiah YL, Dokholyan NV. *Front Immunol*. 2022;13:1029069.

mRNA vaccine candidate CVGBM

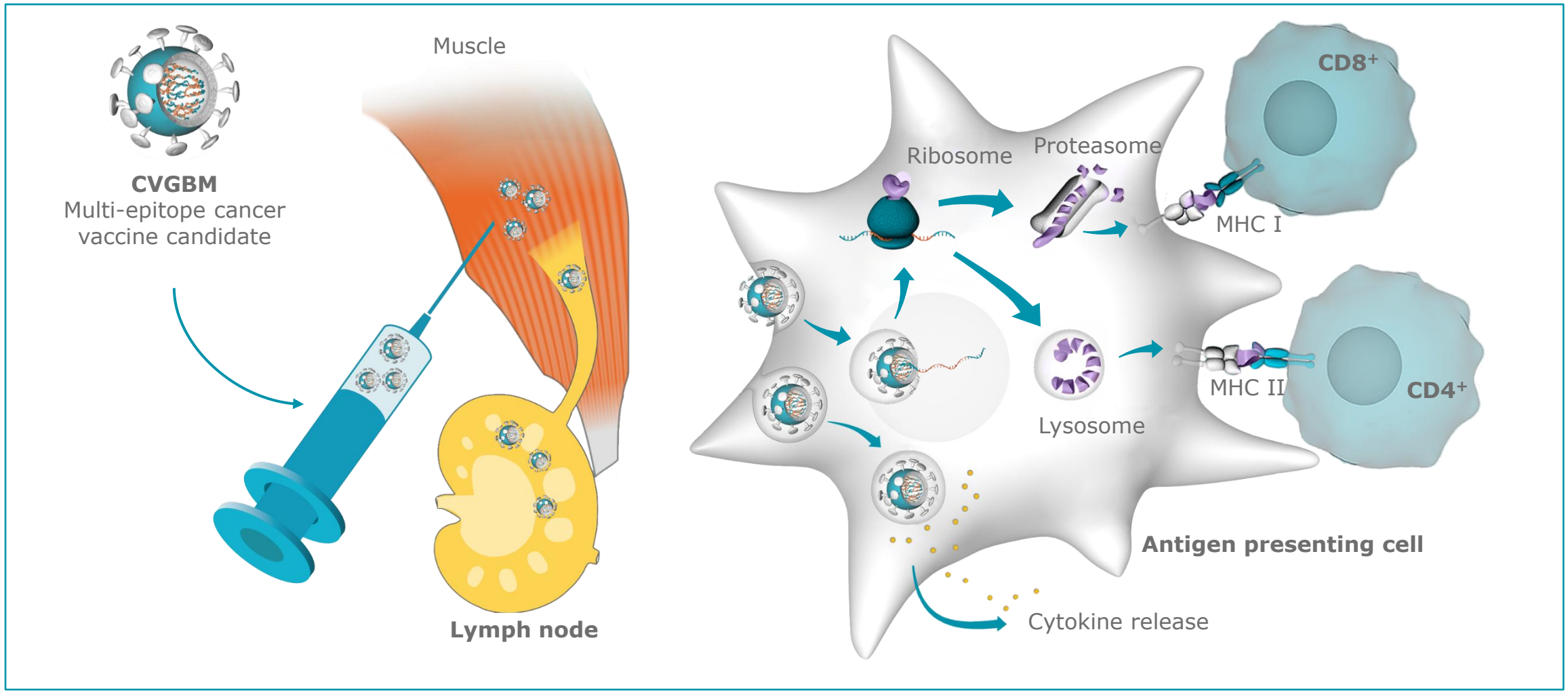
- CVGBM is an investigational cancer vaccine based on chemically-unmodified mRNA for treatment of HLA-A*02:01-positive patients with glioblastoma (GBM)
- The vaccine encodes eight segments derived from four GBM-relevant tumour-associated antigens



For further information on the preclinical development of CVGBM, see Poster 22P presented by Mülfarth *et al* on Sunday 15 September

BCAN, brevican; BIR5C, Survivin; GBM, glioblastoma; HBV, hepatitis B virus; HBV CAPSD, hepatitis B virus Capsid protein; HLA, human leukocyte antigen; mRNA, messenger ribonucleic acid; NLGN4X, neuroligin; ORF, open reading frame; PTPRZ, receptor-type tyrosine-protein phosphatase zeta B; SP, signal peptide; TM/Cyto, transmembrane and cytosolic domain; UTR, untranslated region.

CVGBM mechanism of action



MHC, major histocompatibility complex.

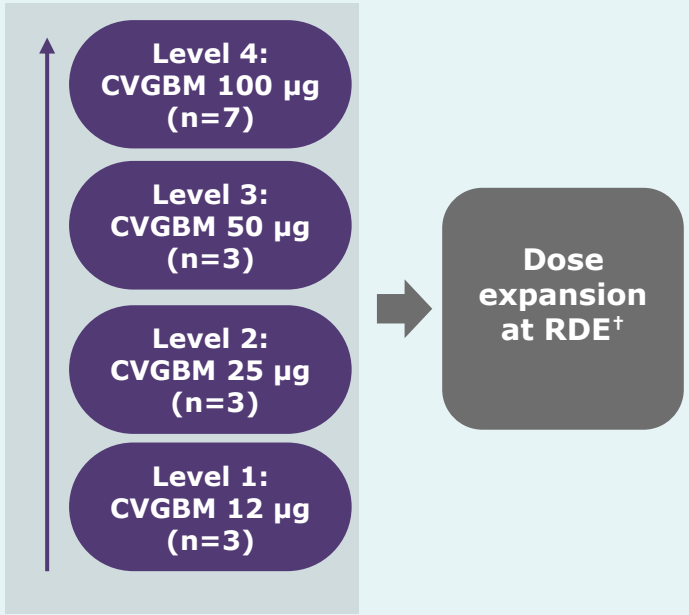
Study overview

CV-GBLM-001 (NCT05938387) is an open-label, phase 1 trial consisting of two parts: dose-escalation (Part A) and dose-expansion (Part B)

Key inclusion criteria

- Newly-diagnosed *MGMT*-unmethylated GBM
- HLA-A*02:01-positive
- Gross total or partial resection (≥50% of tumour volume resected)
- Completed post-surgery radiotherapy with or without chemotherapy
- ALC >0.5 x 10^9/L

Study design



Study objectives

Primary

- **Safety and tolerability**
- Determine the highest tolerable dose and/or RDE of CVGBM

Secondary

- Time to relapse
- Progression-free survival
- Overall survival
- Quality of life

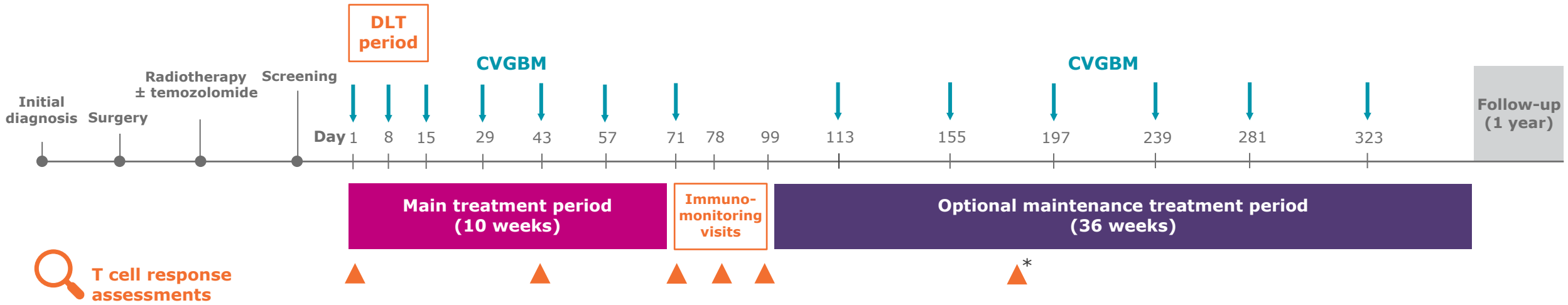
Exploratory

- **Immunogenicity based on antigen-specific cellular immune responses**
- Changes in peripheral blood biomarkers of the innate and adaptive immune responses
- Humoral immunogenicity against PEG components of CVGBM

ALC, absolute lymphocyte count, GBM, glioblastoma; HLA, human leukocyte antigen; MGMT, O6-methylguanine-DNA methyltransferase; PEG, polyethylene glycol; RDE, recommended dose for expansion.
*Dose escalation was guided by a Bayesian Logistic Regression Model; †RDE confirmed by an independent Data and Safety Monitoring Board (DSMB).

Study treatment and assessments

Dose escalation (Part A)



- Patients received 7 intramuscular vaccinations within 10 weeks and optional maintenance vaccinations in case of non-progression/potential benefit (at the investigator's discretion)
- Antigen-specific CD4+ and CD8+ T cell responses in the peripheral blood were assessed by IFNy ELISPOT (ex vivo and after IVS) at relevant pre-determined timepoints till day 99

*T cell assessment only performed in patients without optional maintenance treatment period.
DLT, dose-limiting toxicity; IFN-γ, interferon gamma; IVS, *in vitro* stimulation.

Patient baseline characteristics

	Dose level 1 12 µg (n=3)	Dose level 2 25 µg (n=3)	Dose level 3 50 µg (n=3)	Dose level 4 100 µg (n=7)	Total (N=16)
Sex, n (%)					
Female	0 (0.0)	2 (66.7)	0 (0.0)	2 (28.6)	**4 (25.0)**
Male	3 (100.0)	1 (33.3)	3 (100.0)	5 (71.4)	**12 (75.0)**
Age, years, mean (SD)	59.7 (2.5)	69.7 (7.6)	46.3 (8.3)	48.4 (12.5)	**54.1 (12.7)**
Age group, n (%)					
<65 years	3 (100.0)	1 (33.3)	3 (100.0)	7 (100.0)	**14 (87.5)**
≥65 years	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	**2 (12.5)**
Karnofsky performance status (%), mean (SD)	83.3 (15.3)	90.0 (10.0)	90.0 (10.0)	90.0 (8.2)	**88.8 (9.6)**
Resection history, n (%)					
Partial	1 (33.3)	1 (33.3)	2 (66.7)	3 (42.9)	**7 (43.8)**
Complete	2 (66.7)	2 (66.7)	1 (33.3)	4 (57.1)	**9 (56.3)**
Baseline steroid use, n (%)					
Yes	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	**2 (12.5)**
No	3 (100.0)	2 (66.7)	2 (66.7)	7 (100.0)	**14 (87.5)**

SD, standard deviation.

Treatment-related adverse events (TRAEs)

All patients completed the 2-week dose-limiting toxicity (DLT) evaluation period without any DLT reported

	Dose level 1 12 µg (n=3)	Dose level 2 25 µg (n=3)	Dose level 3 50 µg (n=3)	Dose level 4 100 µg (n=7)	Total (N=16)
Duration of exposure, days, mean (SD)	141.0 (64.2)	103.0 (55.7)	100.7 (25.8)	48.7 (11.2)	**85.9 (49.6)**
Patients experiencing ≥1 event, n/n (total number of events)					**n/N (%)**
Any TRAE	3/3 (9)	3/3 (9)	3/3 (28)	7/7 (59)	**16/16 (100.0)**
Most commonly reported TRAEs; patients experiencing ≥1 event, n/n (total number of events)					**n/N (%)**
Nervous system disorders					
Headache	1/3 (1)	1/3 (1)	2/3 (4)	2/7 (6)	**6/16 (37.5)**
General disorders and administration site conditions					
Chills	0	1/3 (2)	3/3 (4)	3/7 (7)	**7/16 (43.8)**
Pyrexia	2/3 (2)	0	1/3 (1)	5/7 (9)	**8/16 (50.0)**
Fatigue	1/3 (1)	2/3 (2)	1/3 (1)	2/7 (7)	**6/16 (37.5)**
Malaise	1/3 (1)	1/3 (1)	0	2/7 (3)	**4/16 (25.0)**

DLT, dose-limiting toxicity; TRAE, treatment-related adverse event (based on investigator causality assessment).
Data cut-off: 29 February 2024, at time of recommended dose for expansion (RDE) selection.

TRAEs (Grade ≥3; investigator assessments)

Event, n/n (total number of events)	Dose level 1 12 µg (n=3)	Dose level 2 25 µg (n=3)	Dose level 3 50 µg (n=3)	Dose level 4 100 µg (n=7)	Total (N=16), n/N (%)
Any TRAE Grade 3[a]	1/3 (1)	2/3 (2)	2/3 (3)	2/7 (3)	**7/16 (43.8)**
Patients experiencing ≥1 TRAE Grade 3 (all were Grade 3, no Grade 4/5 events reported)					
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
Tumour pseudoprogression	0	1/3 (1)	0	0	**1/16 (6.3)**
Nervous system disorders					
Brain oedema[b]	**1/3 (1)***	0	1/3 (1)[c]	0	**2/16 (12.5)**
Worsening of pre-existing leukoencephalopathy	0	**1/3 (1)***	0	0	**1/16 (6.3)**
Epilepsy	0	0	**1/3 (1)*[c]**	0	**1/16 (6.3)**
Ataxia	0	0	0	**1/7 (1)*[d]**	**1/16 (6.3)**
Vascular disorders					
Hypertension	0	0	1/3 (1)	0	**1/16 (6.3)**
General disorders and administration site conditions					
Pyrexia	0	0	0	1/7 (1)[e]	**1/16 (6.3)**
Malaise	0	0	0	1/7 (1)[e]	**1/16 (6.3)**

*Reported as serious adverse event.

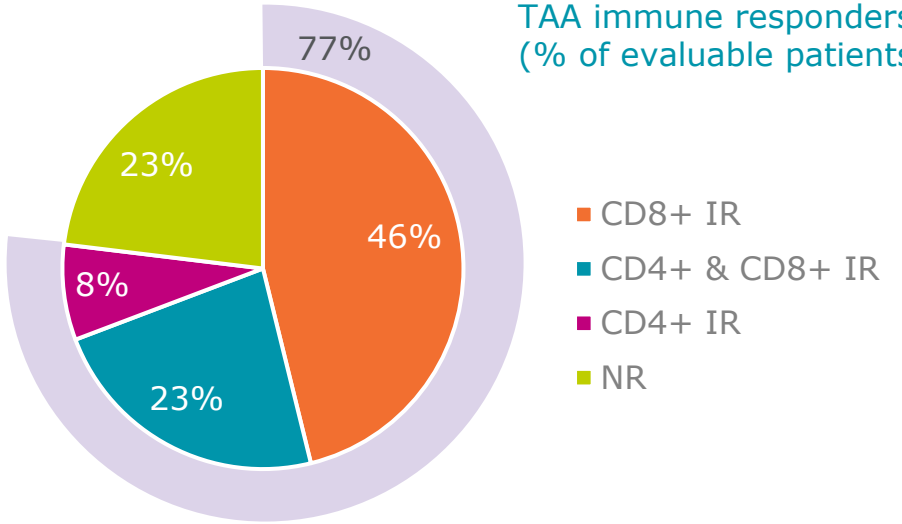
[a]Graded according to NCI-CTCAE Version 5.0; [b] Any Cerebral Oedema (new onset and worsening from baseline) is considered Grade 3 according to NCI-CTCAE; [c,e]Occurred in the same patient;
[d]At the data cut-off on 29 February 2024, ataxia Grade 3 was reported associated with worsening of pre-existing leukoencephalopathy (Grade 2), upgraded to Grade 3 on 4 March 2024. MRI, magnetic resonance imaging; NCI-CTAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event.
Data cut-off: 29 February 2024, at time of recommended dose for expansion (RDE) selection. From the cut-off date until 31 July 2024, no additional Grade ≥3 events or serious adverse events occurred.

Antigen-specific T cell responses to CVGBM

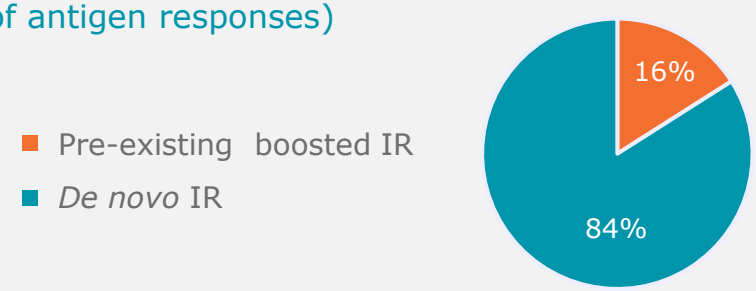
Antigen-specific T cell responses detected by IFNγ ELISpot in PBMC

13 evaluable patients out of a total of 16 (81%)

	n (%)
TAA-specific T cell responders (CD4+ and/or CD8+)[a]	**10 (77)**
TAA-specific CD8+ T cell responders[a]	9 (69)
TAA-specific CD4+ T cell responders[a]	4 (31)
TAA-specific CD4+ and CD8+ T cell responders[a]	3 (23)
HBV (reporter antigen) CD8+ T cell responders[b]	6 (46)
TAA-specific T cell responders against ≥ 2 out of 4 encoded TAAs[c]	6/9 (67)



Immune responses against individual TAAs (% of antigen responses)



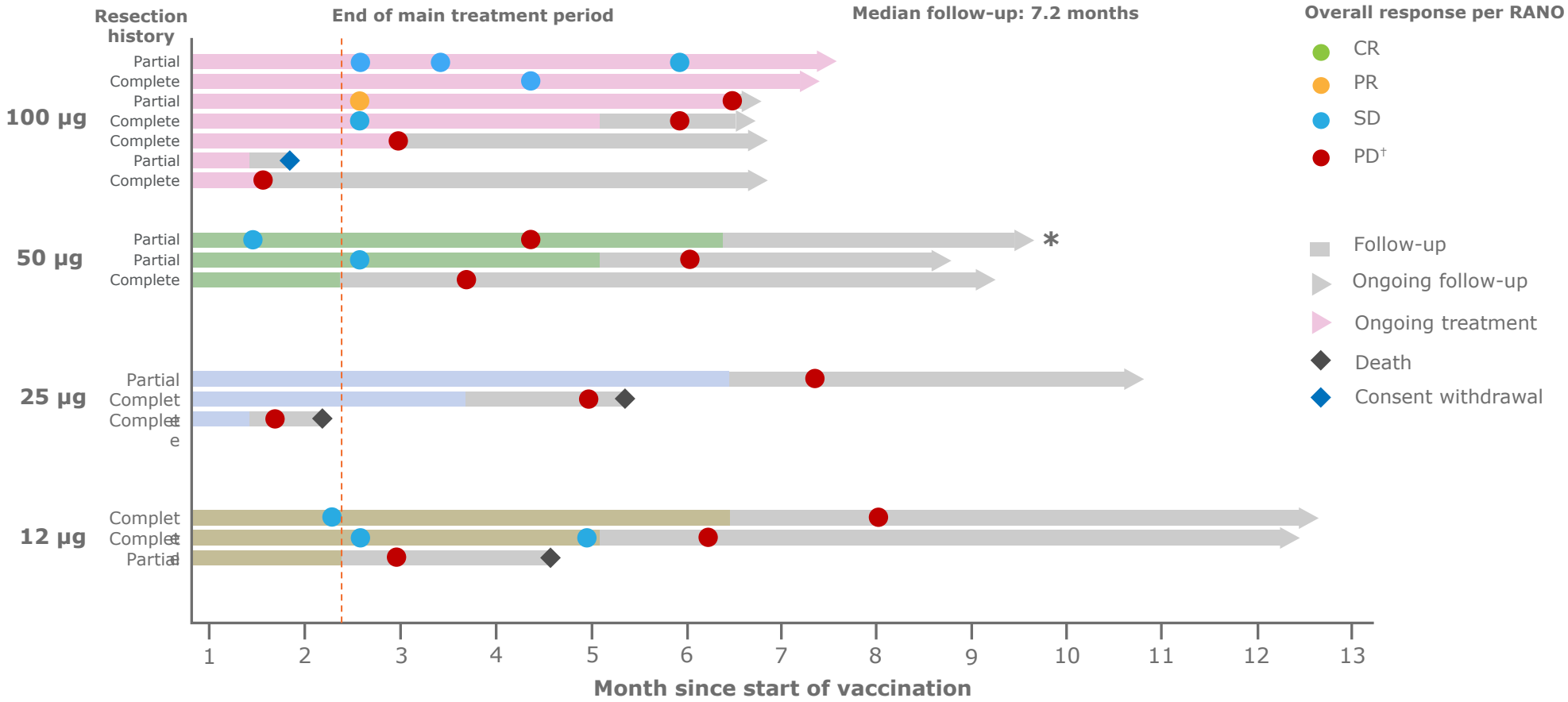
19 T cell responses against individual TAAs detected in 10 responders

Composition of immune responses against individual TAAs	Responses,[d,e] n/n (%)
Pre-existing boosted TAA-specific T cell response[d]	**3/19 (16)**
De novo TAA-specific CD4+ and CD8+ T cell response[e]	**16/19 (84)**

[a]Patients with immune response against ≥1 TAA; [b]HBV reporter antigen, detected by IFN-γ ELISpot in ≥1 timepoint after baseline; [c]Patients with immune response against ≥2 out of 4 encoded TAAs (only 9 patients could be evaluated for multiple responses); [d]Pre-existing immune response against ≥1 TAA at baseline; [e]*De novo* post-baseline immune response without detectable pre-existing immune response at baseline. HBV, hepatitis B virus; IR, immune response; NR, non-responder; PBMC, peripheral blood mononuclear cell; TAA, tumour-associated antigen.
Data cut-off: 23 July 2024; data are preliminary and partially cleaned.

Response assessment

13/16 (81%) patients completed the main treatment period



Solid bars represent the treatment period. *This patient had pseudoprogression/preliminary PD, which did not lead to discontinuation from study drug treatment as per iRANO and the study protocol;
†Only cases of PD according to RANO or confirmed PD according to iRANO (not unconfirmed PDs per iRANO) are shown.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; (i)RANO, (immunotherapy) response assessment for neuro-oncology.
Data cut-off: 31 July 2024 (preliminary and partially cleaned data).

Conclusions

- CVGBM was generally well tolerated up to a dose level of 100 µg in patients with newly-diagnosed and surgically resected *MGMT*-unmethylated glioblastoma
- Most common AEs were mild to moderate systemic reactions such as headache, fever and chills that resolved within 1–2 days post injection
- There was no obvious dose-dependency of neurological AEs or serious AEs
- Preliminary immunogenicity results demonstrate induction of tumour-associated antigen-specific T cell responses in 77% of evaluable patients, of which 84% were primed and activated de novo by CVGBM
- 100 µg was selected as the recommended dose for the dose expansion phase, which recently started enrolment

AE, adverse event.

Thank you for your attention

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