

# Development of a multiepitope mRNA cancer vaccine for glioblastoma - first results of Phase I human study

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## Regina Heidenreich

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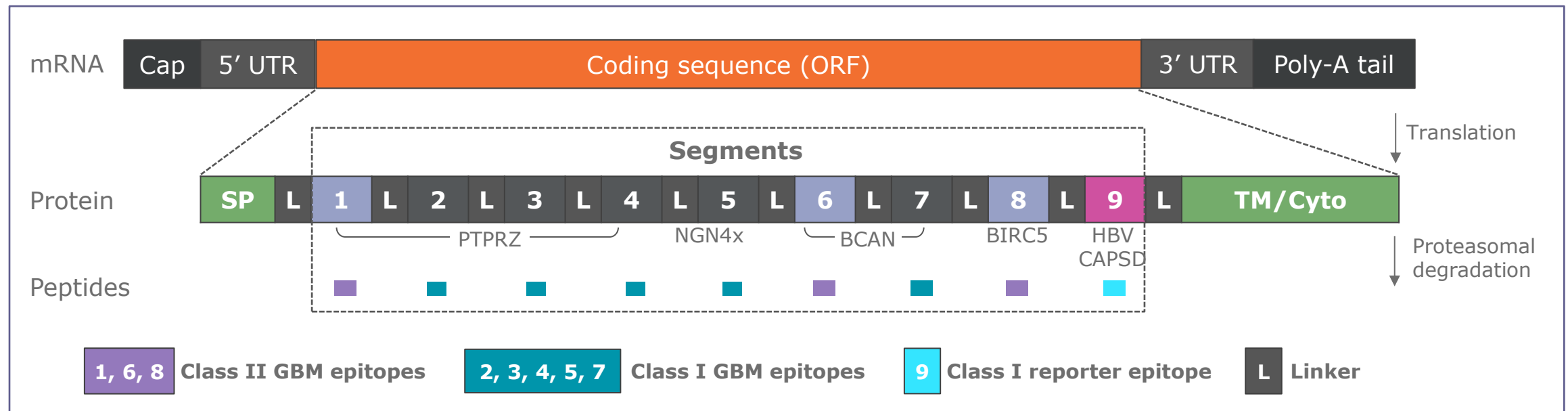
- Employee of: CureVac SE
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- *MGMT*-unmethylated glioblastoma has a poor prognosis, with a median overall survival of approximately 12 months after surgery and chemoradiation with temozolomide<sup>1-3</sup>
- Vaccines based on various platforms (e.g. 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<sup>4-6</sup>
- mRNA vaccines have been shown to induce CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses against a variety of cancer antigens<sup>7</sup> 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.

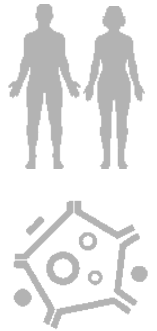
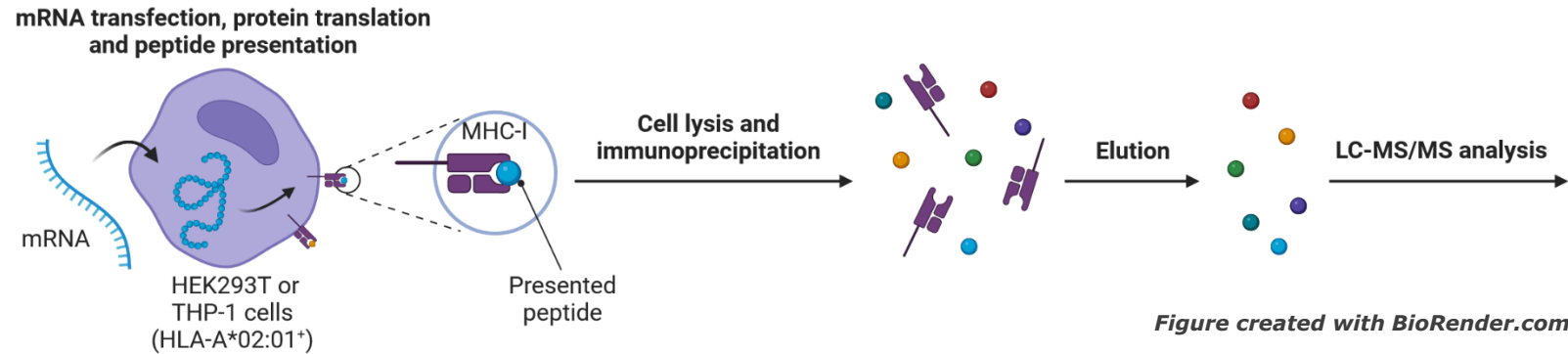
1. Wen PY, et al. *Neuro Oncol.* 2020;22:1073–1113; 2. Alimonti P, Gonzalez Castro LN. *Antibodies (Basel).* 2023;12:27; 3. Stupp R, et al. *Lancet Oncol.* 2009;10(5):459–466; 4. Keskin DB, et al. *Nature.* 2019;565:234–239; 5. Hilf N, et al. *Nature.* 2019;565:240–245; 6. Wen PY, et al. *Clin Cancer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

- 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

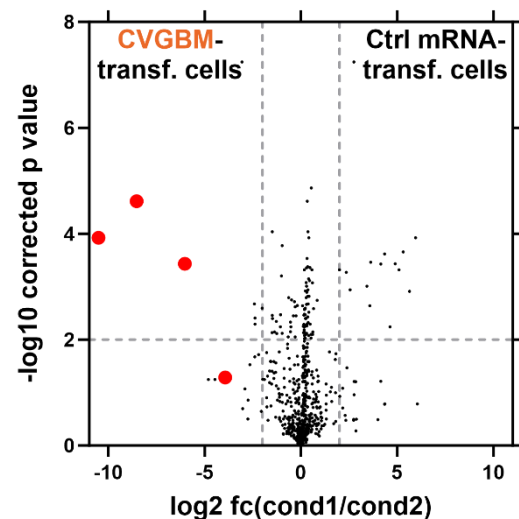


BCAN, brevican; BIRC5, Survivin; GBM, glioblastoma; HBV, hepatitis B virus; HBV CAPSD, hepatitis B virus Capsid protein; HLA, human leukocyte antigen; mRNA, messenger ribonucleic acid; NLGN4X, neuroligin; ORF, open reading frame; PTPRZ, receptor-type tyrosine-protein phosphatase zeta B; SP, signal peptide; TM/Cyto, transmembrane and cytosolic domain; UTR, untranslated region.

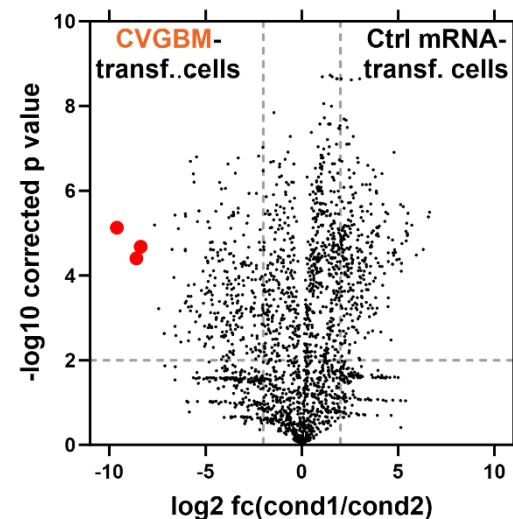
# CVGBM-encoded peptides are presented on HLA class I on human cells *in vitro*



CVGBM-derived peptides presented on HLA class I on **HEK293T cells**



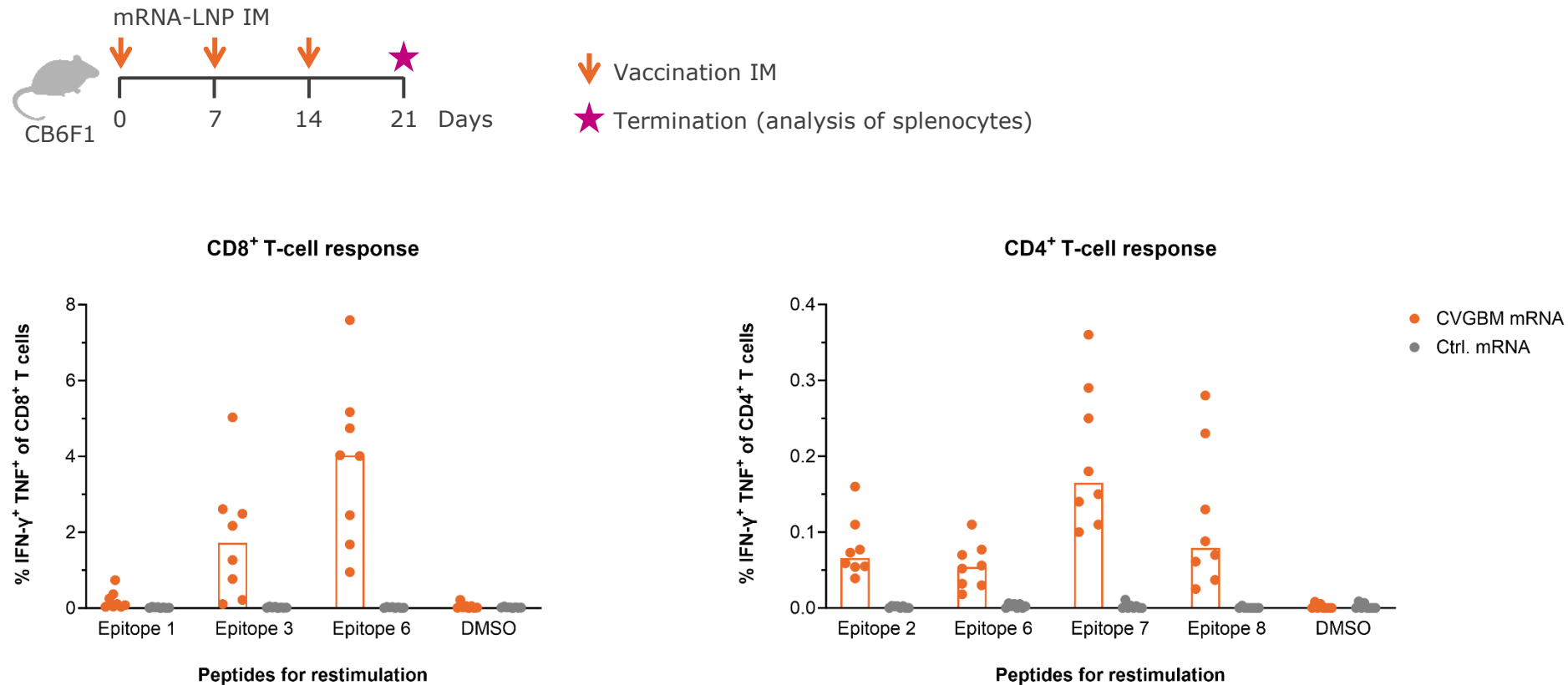
CVGBM-derived peptides presented on HLA class I on **THP-1 cells**



- Presentation of four of the six HLA-A\*02:01-restricted peptides.
- No additional peptides from other parts of fusion protein (e.g. epitopes from junctions) detected.

# Immunogenicity of CVGBM vaccine demonstrated *in vivo*

Translation of CVGBM mRNA, correct processing of encoded fusion protein and presentation of contained peptides is demonstrated via immunogenicity *in vivo*.



# First in-human study of CVGBM: 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)



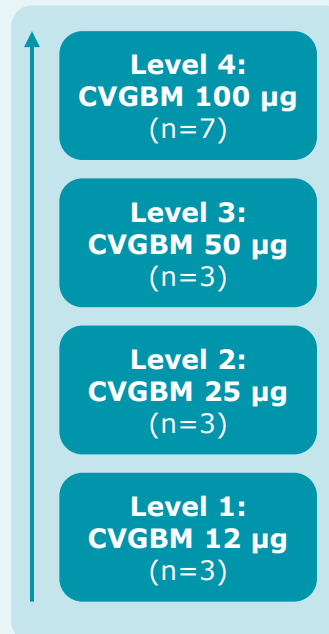
## Key inclusion criteria

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



## Study design

### Part A (N=16)\*



### Part B (N= $\sim 20$ )



## Study objectives

### Primary

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

### Secondary

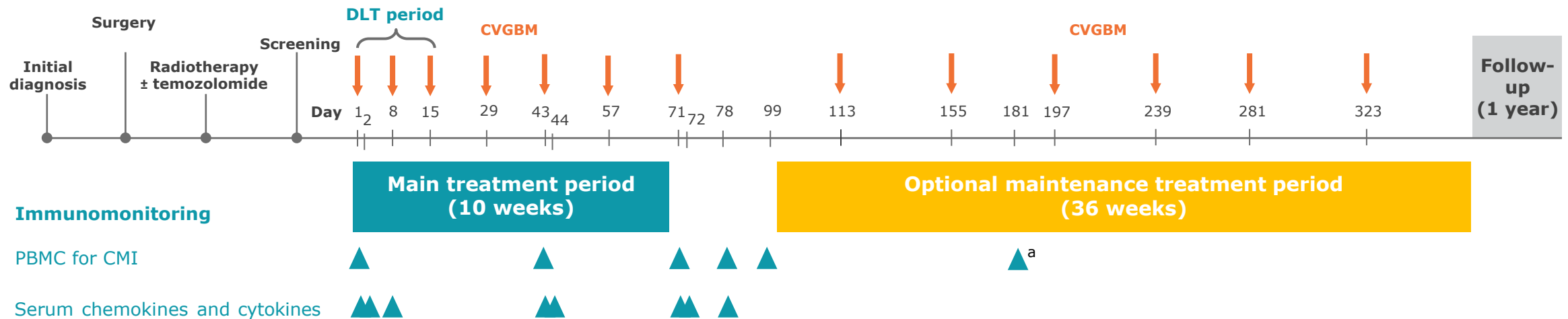
- Time to relapse
- Progression-free survival
- Overall survival
- Quality of life

### 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; <sup>†</sup>RDE confirmed by an independent Data and Safety Monitoring Board (DSMB).

## 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<sup>+</sup> and CD8<sup>+</sup> T cell responses in the peripheral blood were assessed by IFN $\gamma$  ELISPOT (ex vivo and after IVS) at relevant pre-determined timepoints till day 99

<sup>a</sup>T cell assessment on Day 181 only performed in patients who did not continue into the optional maintenance treatment period. CMI, cell-mediated immunity; DLT, dose-limiting toxicity; PBMC, peripheral blood mononuclear cell.

# Treatment-related adverse events (TRAEs)

All patients completed the 2-week dose-limiting toxicity (DLT) evaluation period without any DLT reported; 91% of reported TRAEs were grade 1/2

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

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)

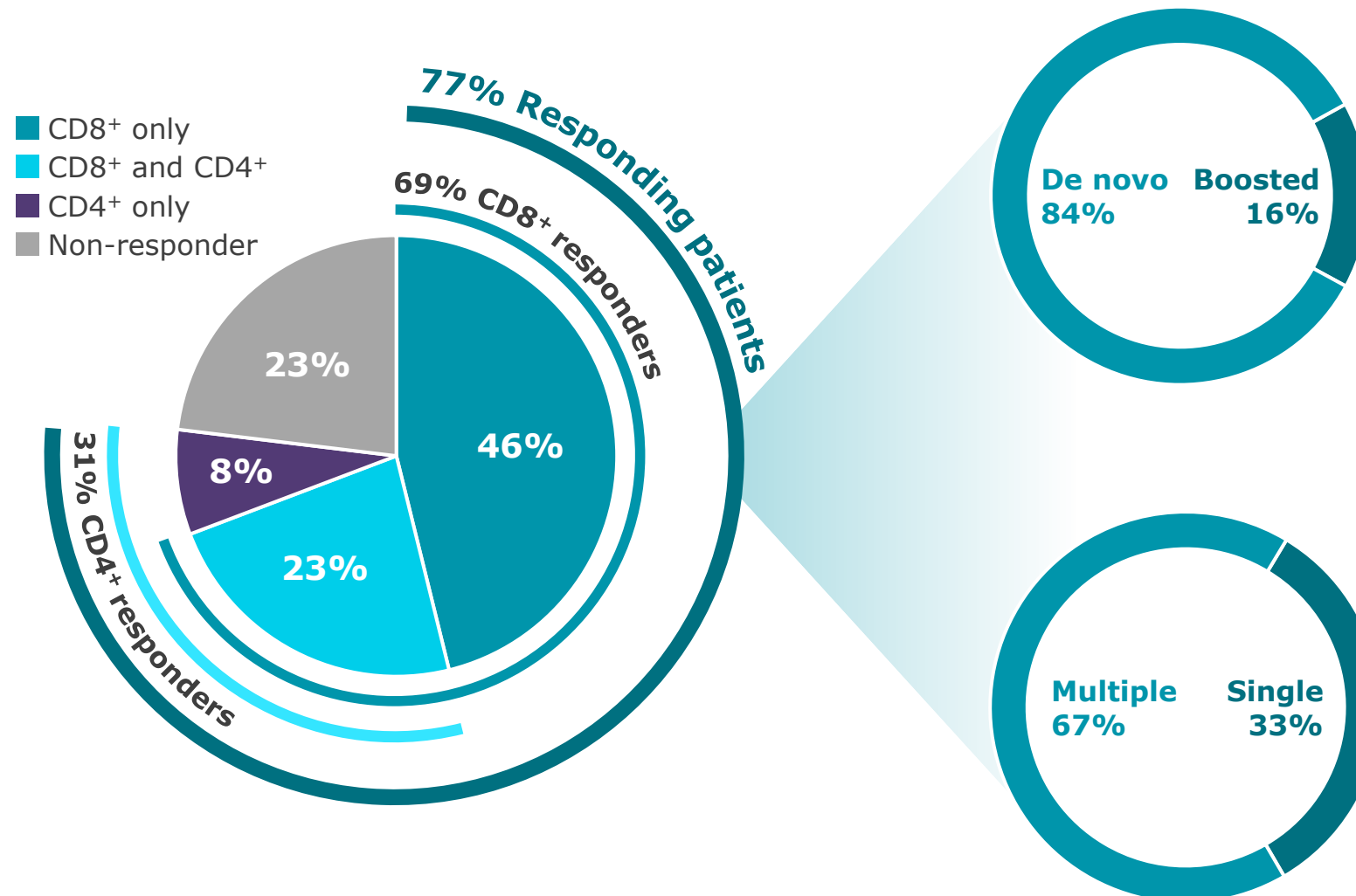
Event, n/n (total number of events)	Dose level 1 12 µg (n=3)	Dose level 2 25 µg (n=3)	Dose level 3 50 µg (n=3)	Dose level 4 100 µg (n=7)	Total (N=16), n/N (%)
<b>Any TRAE Grade 3<sup>a</sup></b>	1/3 (1)	2/3 (2)	2/3 (3)	2/7 (3)	<b>7/16 (43.8)</b>
<b>Patients experiencing ≥1 TRAE Grade 3 (all were Grade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

**\*Reported as serious adverse event.**

<sup>a</sup>Graded according to NCI-CTCAE Version 5.0; <sup>b</sup> Any Cerebral Oedema (new onset and worsening from baseline) is considered Grade 3 according to NCI-CTCAE; <sup>c</sup>Occurred in the same patient; <sup>d</sup>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.

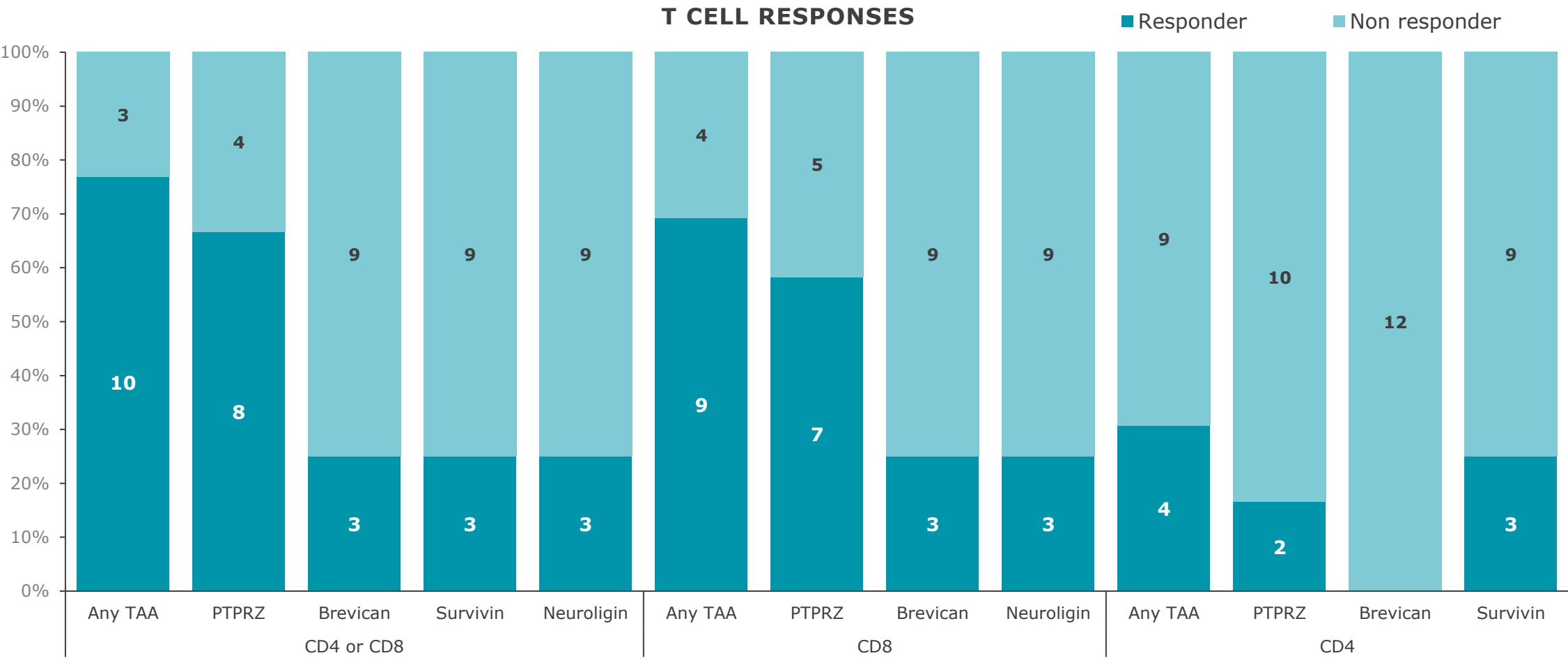
# CVGBM Induced De Novo Antigen-specific T cell Responses in Majority of Responding Patients in Glioblastoma



- **84%** of detected T cell responses against individual TAAs were induced **de novo**
- **16%** of detected T cell responses were induced by **boosting** of pre-existing T cells
- **67%** of responding patients showed T cell responses against **multiple cancer antigen**
- **33%** of responding patients showed T cell responses to **one cancer antigen**

TAA, tumour-associated antigen. Data cut-off: 23 July 2024; data are preliminary and partially cleaned.

# CVGBM-specific immune responses were demonstrated against all encoded TAAs



Analysis performed on response level, the number of responses might vary between TAA or cell type due to assay acceptance criteria or available cell numbers. TAA, tumor-associated antigen. Data cut-off: 23 July 2024; data are preliminary and partially cleaned.



- CVGBM was generally well tolerated up to a dose level of 100 µg in patients with newly-diagnosed and surgically resected *MGMT*-unmethylated glioblastoma
- Majority of reported AEs were transient Grade 1/2 events, 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 tumor-associated antigen-specific T cell responses in 77% of evaluable patients, of which 84% were primed and activated de novo by CVGBM.
- Majority of patients (67%) showed immune responses against more than 2 encoded TAAs
- CVGBM-specific immune responses were demonstrated against all encoded TAAs
- 100 µg was selected as the recommended dose for the dose expansion phase, which recently started enrolment

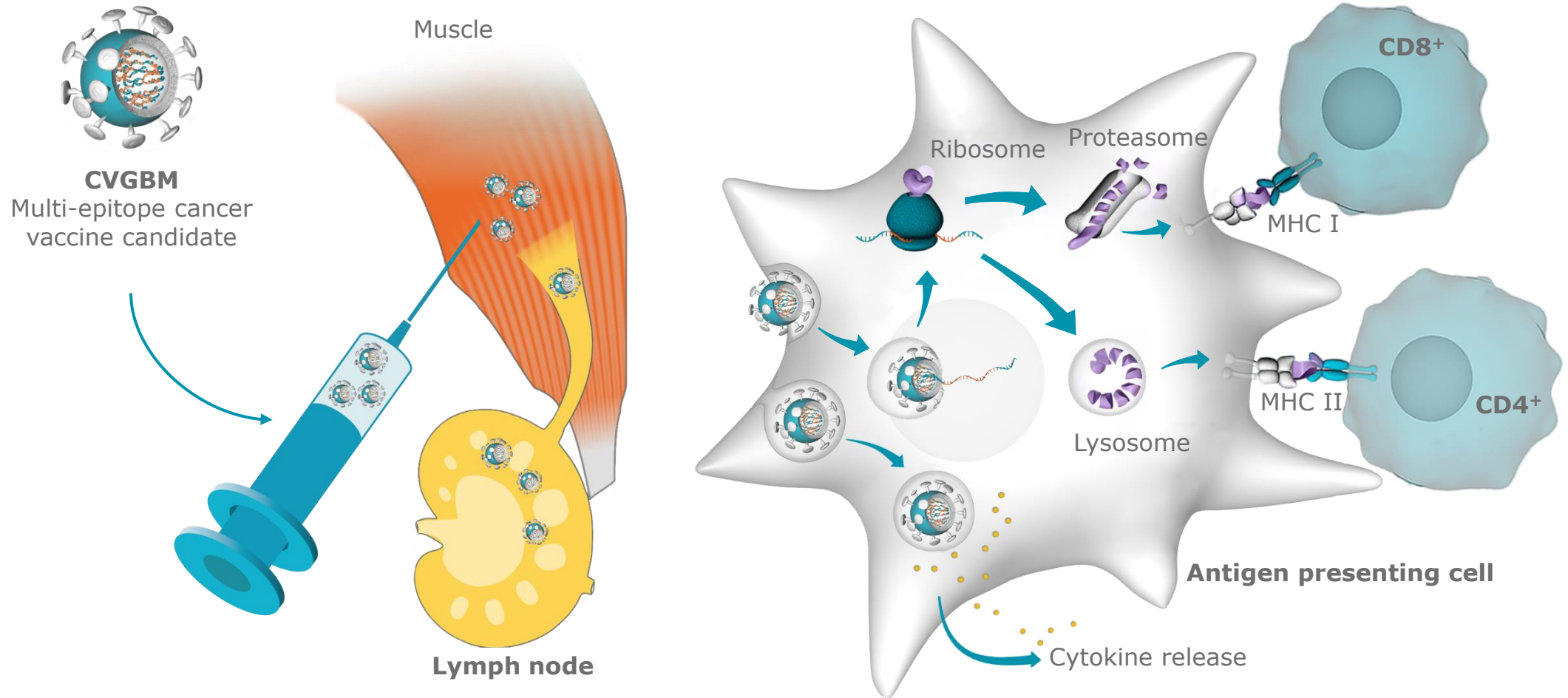
Thank you to the patients and their families, the participating study sites that enrolled patients and the clinical and laboratory team at CureVac

- Department of Neurology and Interdisciplinary Neuro-Oncology, University Hospital Tübingen, Hertie Institute for Clinical Brain Research, Eberhard Karls University Tübingen, Tübingen, Germany
- University Hospital Regensburg, Regensburg, Germany
- University Hospital Leipzig, Leipzig, Germany
- Department of Neurosurgery, Division of Neuro-oncology, LMU, Munich, Germany
- Senckenberg Institute of Neurooncology, Goethe University Hospital, Frankfurt, Germany
- Division of Clinical Neurooncology, Department of Neurology and Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Medicine Essen, University Duisburg-Essen, Essen, Germany
- Liège University Hospital, Liège, Belgium
- Erasmus MC Cancer Institute, Rotterdam, The Netherlands



**Back-up**

# CVGBM mechanism of action



MHC, major histocompatibility complex.