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GLIOMATCH

Project No. 101136670

The malignant Glioma immuno-oncology matchmaker: towards data-driven precision medicine using spatially resolved radio-multiomics

Deliverable 5.1
Prospective multicentric clinical trial design

WP 5 – Implementation of clinical trial for proof-of-concept

Version 1.0

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Revision history

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Contents

Partner short names

Short name	Partner
KUL	Katholieke Universiteit Leuven
EMC	Erasmus Universitair Medisch Centrum Rotterdam
UM	Universiteit Maastricht
OUS	Oslo Universitetssykehus HF
UDUS	Heinrich-Heine Universität Düsseldorf
FINCB	Fondazione IRCCS Istituto Neuro-logico “Carlo Besta’

Abbreviations

Abbreviation	Term
anti-Gal-1	Anti-Galectin-1 Antibody
anti-PD-L1	Anti-Programmed Cell Death-Ligand 1 Antibody
CD	Cluster of Differentiation
D	Deliverable
DC	Dendritic Cell(s)
DCVax	Dendritic Cell Vaccination
ELISPOT	Enzyme Linked Immuno Spot Assay
EU	European Union
IFNγ	Interferon-γ
i.v.	Intravenous
GBM	Adult Glioblastoma
M	Month
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
MS	Milestone
NDV	Newcastle Disease Virus
OVT	Oncolytic Virus Therapy
RNA	Ribonucleic Acid
RNAseq	RNA Sequencing
siRNA	Small Interfering RNA
TetTox	Tetanus Toxoid
TERT	Telomerase Reverse Transcriptase
WP	Work Package

Executive summary

Background

The deliverable D5.1 is part of Work Package 5 (WP5). In WP5 of the GLIOMATCH project, the partners UDUS, KUL, FINCB, OUS and EMC will conduct explorative, prospective immunotherapy trials on adult glioblastoma patients. To develop the necessary trial documents (milestone 21; MS21) for the ethical and legal approval of the trials (MS22), the clinical trial design, which is reported here, has to be defined.

Objectives

The clinical trial design should provide a common strategy and backbone for the five clinical trials that will be conducted in GLIOMATCH with the aim to obtain informative results on immunotherapy of glioblastoma. It should identify and harmonise critical parameters to reduce factors influencing the outcome, making it more comparable between the individual proof-of-concept trials which use different therapeutic approaches.

Methodology and implementation

The basic trial design summarised in the proposal has been discussed extensively, critical parameters have been defined and the partners involved have agreed on a harmonised clinical trial design.

Outcomes

In the clinical trial design, the target population has been specified. Inclusion and exclusion criteria have been chosen to assure safety and to allocate a homogenous, but still representative group of patients to the trials, which most likely will allow generating informative results. A common therapeutic backbone and a detailed intervention scheme for each of the immunotherapy approaches have been defined, as well as common read-outs to assess safety, clinical outcome and immunological responsiveness comprehensively. Moreover, since there are differences in the protocols to generate dendritic cell vaccines, a strategy has been developed, allowing to delineate potency and detect possible differences in maturation trajectories of the dendritic cells, which may affect efficacy. Finally, on an organisational level, it has been decided that the sponsor as well as trial/project management, data management, quality assurance, pharmacovigilance and biometry will be organised locally by each of the partners.

Impact and next steps

The clinical trial design defined in this deliverable will be translated by each partner into the study protocol as part of the trial documents (D5.3/MS21, M6). It is a pre-requisite for generating the trial documents as well as for obtaining ethical and legal approval to initiate the proposed multicentric clinical trials, as well as for registering the trials in the EU clinical trials register (D5.4/MS22, M12).

1 Introduction

The GLIOMATCH project is a Research and Innovation Action funded by the European Union under Horizon Europe. The project will use state-of-the-art technology to develop a treatment selection platform allowing clinicians to better match adult glioblastoma (GBM) and paediatric high-grade glioma patients with tailored immunotherapy treatments. The project brings together 14 partners from different disciplines, started in January 2024, and will last 5 years.

In WP5 of the GLIOMATCH project, 'Implementation of clinical trial for proof-of-concept', the partners UDUS, KUL, FINCB, OUS and EMC will conduct five small-scale, explorative, prospective immunotherapy trials on adult glioblastoma patients, combining dendritic cell (DC) vaccination (DCVax) targeting personalised tumour antigens (autologous whole tumour lysates / tumour stem cell + survivin/TERT mRNA) with strategies tackling factors, which have been identified to affect efficacy (conducted by UDUS, KUL, FINCB, OUS), or Oncolytic Virus Therapy (OVT) using Newcastle Disease Virus (NDV; conducted by EMC) (Figure 1). Thereby, the effect of different factors and different immunotherapeutic approaches can be addressed in parallel, while collecting unique tumour tissue from primary and recurrent tumours as well as tumours at 2nd recurrence after immunotherapy for spatial radio-multiomics analyses and analyses of associations between clinical and immunological outcomes in the respective trial and the results from radio-multiomics analyses.

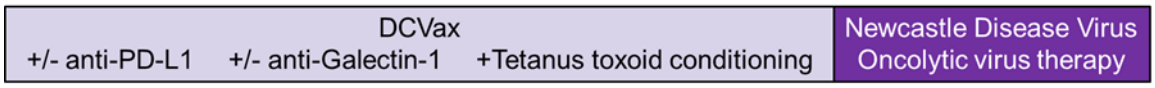

Figure 1. Treatment approaches of GLIOMATCH's clinical trials.

To obtain informative results and make the different approaches more comparable, the partners have identified critical parameters and agreed to harmonise the trial designs accordingly, which will constitute the basis for the individual study protocols (Figure 2).

- Target the same patient population
- Use the same therapeutic backbone and comparable intervention scheme
- Assess the same parameters for dendritic cell vaccines to delineate potency
- Use the same immunological, safety and survival study read-outs
- Collect tissue samples/MRI data (primary – 1st recurrence – 2nd recurrence)

Figure 2. Harmonised parameters for clinical trials between all partners.

2 Harmonisation of Study Parameters for the Development of the Clinical Trial Design

2.1 Patient Population

Inclusion and exclusion criteria have been chosen to ensure safety and to allocate a homogenous, but still representative group of patients to the trials, which most likely will allow generating informative results.

Inclusion criteria

- Adults (18 – 75 years).
- Patients must be in a cognitive state to understand and sign the informed consent, indicating that they are aware of the investigational nature and procedures of the study.
- Glioblastoma at 1st recurrence, qualifying for re-resection (DCVax, OVT) or needle biopsy (OVT).
- Standard radiochemotherapy and six cycles of adjuvant temozolomide chemotherapy completed.
- Primary tumour tissue available for analyses.
- Adequate venous access for leukapheresis (DCVax).
- Near-complete resection (≤ 5 ml residual tumour; DCVax). Second-look surgery is possible.
- Karnofsky Performance Status ≥ 70.

- Corticosteroids ≤ 2 mg dexamethasone/d or equivalent at baseline visit. Use of corticosteroids during the treatment period should be avoided, however it is possible if medically indicated, but may require interruption/delay of DCVax.
- Sufficient tumour tissue available for the preparation of lysate or culture of glioblastoma stem cells (DCVax).
- Successful production of sterile, avital tumour lysate (DCVax).
- Ability to target and inject NDV into tumour tissue (OVT).
- Adequate hepatic, renal and bone marrow function.
- Adequate leukocyte numbers.
- Female patients with reproductive potential and male generative patients and their female partners must agree to be true abstinent or to use a highly effective form of contraception (pearl index < 1%) during the trial.
- Signed informed consent.

Exclusion criteria

- Severe acute or chronic medical conditions that could increase the risk associated with study participation or study drug administration or could interfere with the interpretation of trial results and, in the opinion of the investigator, would make the patient inappropriate for entry into the study. These include but are not limited to the following:
    - Immunosuppressive disease / immunodeficiency.
    - Chronic renal disease / failure.
    - Cardiovascular: uncontrolled hypertension, unstable angina, myocardial infarction or symptomatic congestive heart failure within the past 12 months or serious uncontrolled cardiac arrhythmia.
    - Severe poorly controlled diabetes.
    - Planned other major surgery.
- Medical history of severe autoimmune disorder or patients with organ allograft.
- Medical history of bleeding diathesis or coagulopathy.
- Prior malignancy during the last three years except non-melanoma skin cancer, in situ cervical cancer, treated superficial bladder cancer or cured, early-stage prostate cancer in a patient with prostate-specific antigen level less than upper limit of normal.
- Known allergy or intolerability to any component of the DC vaccine.
- Current treatment of glioblastoma in another clinical trial with therapeutic intervention or current use of any other investigational agent.
- Known pregnancy or breastfeeding. From pre-menopausal female patients with childbearing potential a negative pregnancy test must be obtained.
- Infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus and Treponema pallidum or others as required by national law.
- Evidence for any active infection requiring hospitalization or i.v. antibiotics or anti-viral treatment within 2 weeks prior to study enrolment.
- Treatment with specific immunostimulatory agents within the last 6 weeks or 5 half-lives of the drug (whichever is longer).
- Accommodation in an institution due to legal orders.
- Evidence of ongoing drug or alcohol abuse.
- Any psycho-social condition hampering compliance with the study protocol.

2.2 Therapeutic Backbone and Intervention Scheme

All patients should have received the same previous therapeutic interventions:

- Glioblastoma at 1st recurrence after standard radiochemotherapy and six cycles of adjuvant temozolomide chemotherapy.
- Re-resection (DCVax, OVT) or needle biopsy (OVT) at 1st recurrence.
- Re-resection at 2nd recurrence after immunotherapy (if medically indicated and possible)
- Further therapy after 2nd recurrence is at the physician's discretion.

The specific intervention schemes for the different treatment approaches include:

- UDUS: Vaccination with autologous tumour lysate-loaded DC in combination with the anti-PD-L1 antibody Atezolizumab (2 groups, DCVax / DCVax + anti-PD-L1, 3 patients each group).
- KUL: Vaccination with autologous tumour lysate-loaded DC in combination with siRNA specific for Galectin-1 (3 groups, anti-Gal-1 / DCVax / anti-Gal-1 + DCVax, 3 patients each group).
- OUS: Vaccination with autologous cancer stem cell, survivin and TERT mRNA transfected DC in combination with the anti-PD-L1 antibody Atezolizumab (2 groups, 3 patients each).
- FINCB: Vaccination with autologous tumour lysate-loaded DC in combination with tetanus toxoid preconditioning of the vaccination site (1 group, 6 patients).
- EMC: OVT using NDV (4 dose escalation groups with 3 allocated patients each and a one-off 3 additional patients in case of a dose-limiting toxicity, 1 expansion group at maximum tolerated dose with 10 allocated patients; in total a maximum of 25 patients).

Details on timing and dosing of the treatments are provided in Figure 3:

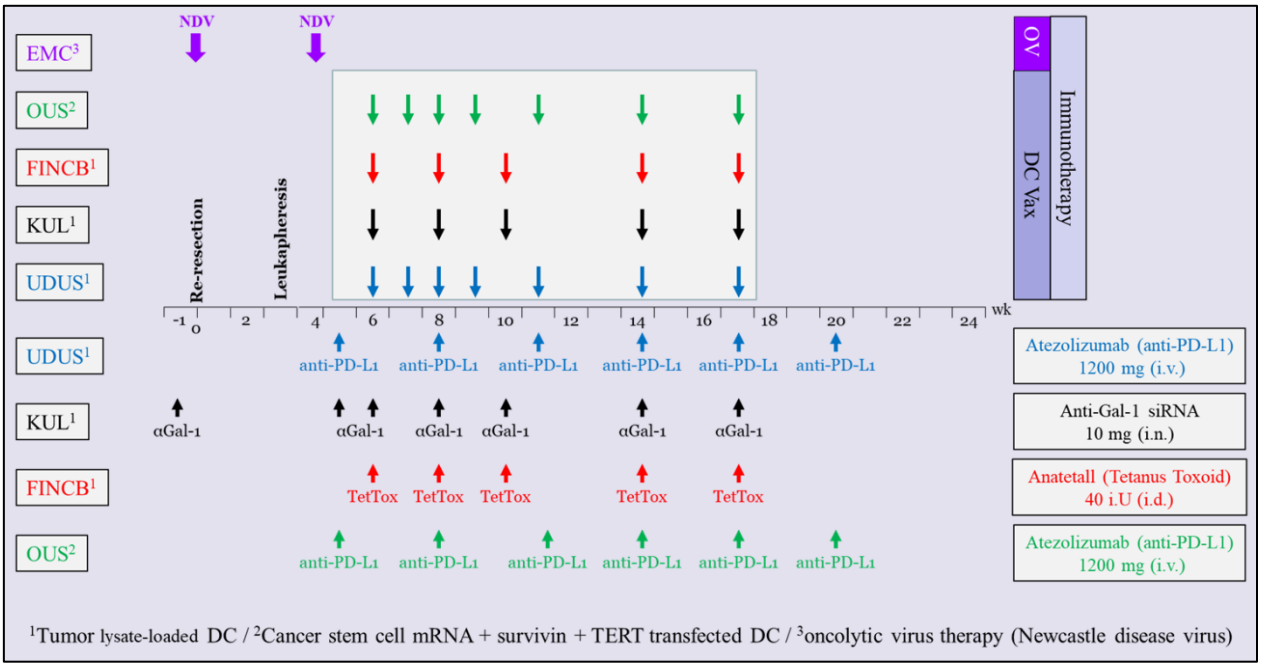

Figure 3. Intervention schemes for GLIOMATCH's clinical trials treatment approaches.

Dosing and schedules still may be changed due to scientific or local regulatory reasons.

2.3 Assessment of Dendritic Cell Vaccines

For the generation of DC vaccine cells, the individual centres have so far used similar but still different protocols. It has been decided that each centre will continue to use the protocol which has been used in previous trials and for which regulatory approval has been obtained. Release criteria for the cellular products will remain unchanged according to the local regulations. However, characterisation of vaccine cells will be harmonised and extended to better delineate potency of vaccines, which may differ between different DC preparations and between individual patients [1]:

- Expression of classical DC maturation markers: CD25, CD40, CD80, CD83, CD86, HLA-DR and IL-12.
- Expression of markers identifying characteristics of regulatory DC: CD200, CD273 and CD279.
- Expression of markers which have been reported to discriminate different DC maturation trajectories with different therapeutic potency [1]: CD58, CD197, CD223, CD252, CD278, CD327, interleukin-23 receptor, interferon-γ and Toll-like receptor 5.
- Bulk-RNAseq of loaded/unloaded DC.

2.4 Safety, Clinical and Immunological Read-outs

Patients will be followed up for one year from surgery, with MRI scans every 2-3 months. A standard operation procedure for MRI scans to allow for radio-multiomics analyses will be provided by UM.

The minimum study read-outs will be:

Safety

- Frequency and severity of adverse events with toxicity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Clinical

- Feasibility (production and application of therapeutics).
- Overall survival rates at 6 and 12 months.
- Progression-free survival rate at 6 months.

Immunological responsiveness

Systemic immunological responsiveness (Interferon-γ (IFNγ)-ELISPOT, multi-cytokine response, serum-functional immunodynamic status [2]).

- Local immunological responsiveness (T-cell subsets including IFNγ-producing tumour-infiltrating effector T cells - if patients are re-resected after immunotherapy).
- Composition and changes (primary → 1st recurrence → 2nd recurrence (after therapy)) in tumour cells/microenvironment (longitudinal spatial-multiomics).

Overall (Consortium)

- Association of survival and immunological responsiveness with spatial/radio-multiomics data.

Systemic and local immunological responsiveness will serve as the primary study endpoint.

2.5 Collection of Tissue Samples

A standard operation procedure for tissue collection and transfer will be provided by KUL. Collection of tumour material for spatial-multiomics analyses will not hamper vaccine production or diagnosis nor will the surgical approach be changed due to tissue procurement needs.

2.6 General Aspects of Trial

For all trials, there will be an individual local sponsor, and it is the trial site's responsibility to organise locally trial/project management, data management, quality assurance, pharmacovigilance and biometry. The biostatistical approaches will be exchanged between partners in a harmonisation attempt. Trial documents will be made available between partners to simplify and speed up generation of the final trial documents and applications for ethical and regulatory approval.

3 Future Work

The definition of the clinical trial design (D5.1) is the pre-requisite for generating the trial documents (D5.3/MS21, M6) and obtaining ethical and legal approval to initiate the proposed multicentric clinical trials as well as registration of the trials at the EU clinical trials register (D5.4/MS22, M12).

4 References

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