



Azeliragon, a RAGE inhibitor, in Combination with Temozolomide and Radiotherapy in Patients with Newly Diagnosed Glioblastoma: Phase Ib/II CAN-201 NDG Trial Design

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INTRODUCTION

Glioblastoma (GBM) is the most common malignant primary brain tumor and one of the most aggressive cancers¹. The combination of radiotherapy and temozolomide (TMZ), provided clinical benefits for newly diagnosed glioblastoma (GBM) patients², being the standard of care. However, most GBM patients develop resistance to RT and TMZ³⁻⁴. The high-mobility group box 1 (HMGB1) protein⁵ (involved on glioma cell proliferation) is implicated on TMZ resistance, specifically through binding to the receptor for advanced glycation end-products (RAGE). RAGE may act as an autocrine factor responsible for promoting the growth and migration of tumor cells. Another RAGE-related protein, S100B, promotes macrophage infiltration and promotes tumor growth⁶. Interaction between RAGE and its ligands contributes to tumor progression, invasion and angiogenesis⁷. Azeliragon is a small molecule, known for its ability to disrupt interaction between RAGE and its ligands, including HMGB1 and S100B⁸ (Fig. 1). RAGE and its ligand S100A9 were identified as biomarkers for radiosensitization and RAGE was proposed as potential target to overcome resistance to RT⁹. In a pre-clinical in vivo brain tumor model in which azeliragon was combined with radiation, an improvement in survival derived from the reduction in NFκB-mediated radioresistance in cancer cells was observed⁹⁻¹⁰. In clinical trials in patients with Alzheimer's disease, Azeliragon had a very favorable safety profile.

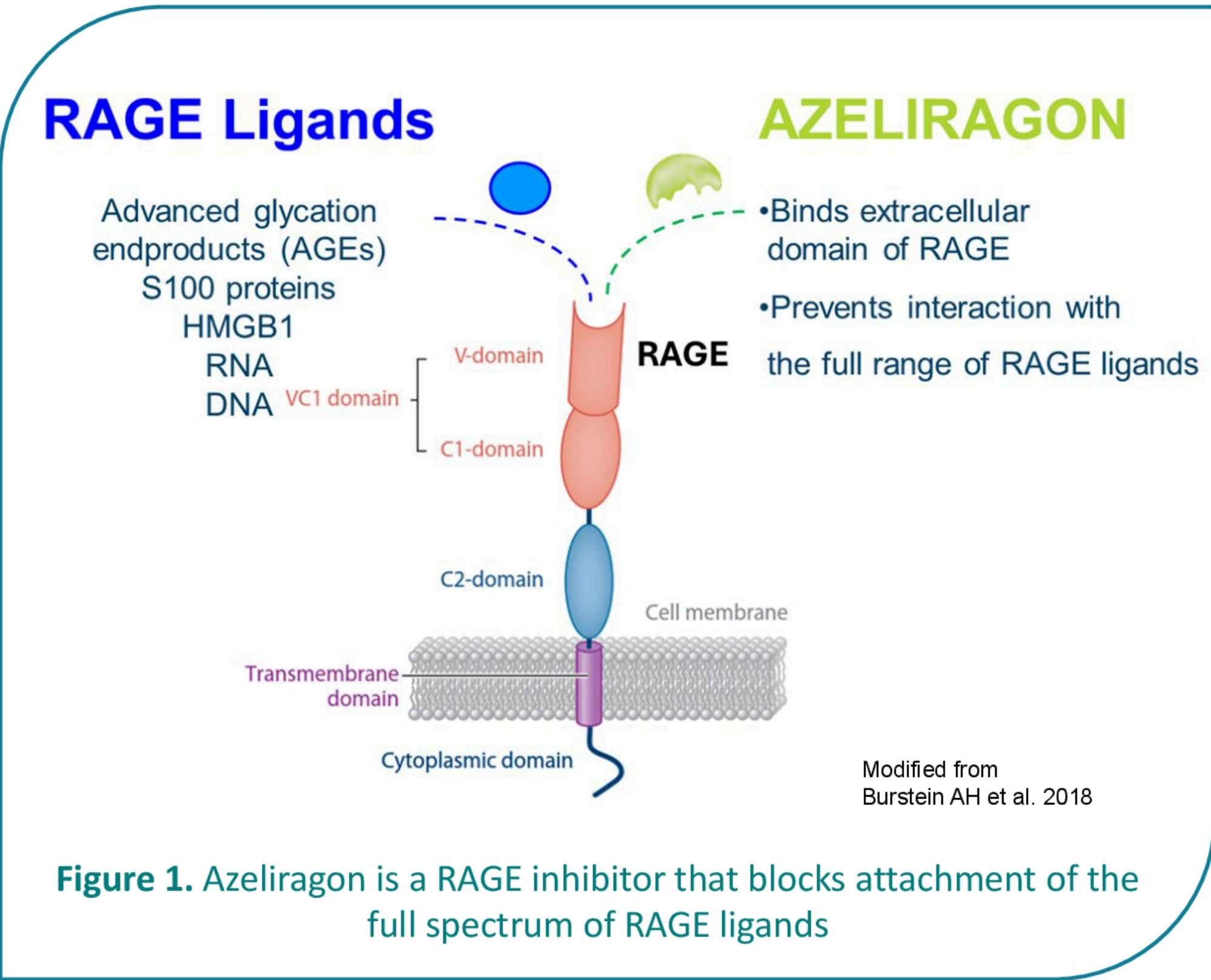


Figure 1. Azeliragon is a RAGE inhibitor that blocks attachment of the full spectrum of RAGE ligands

STUDY SCHEME

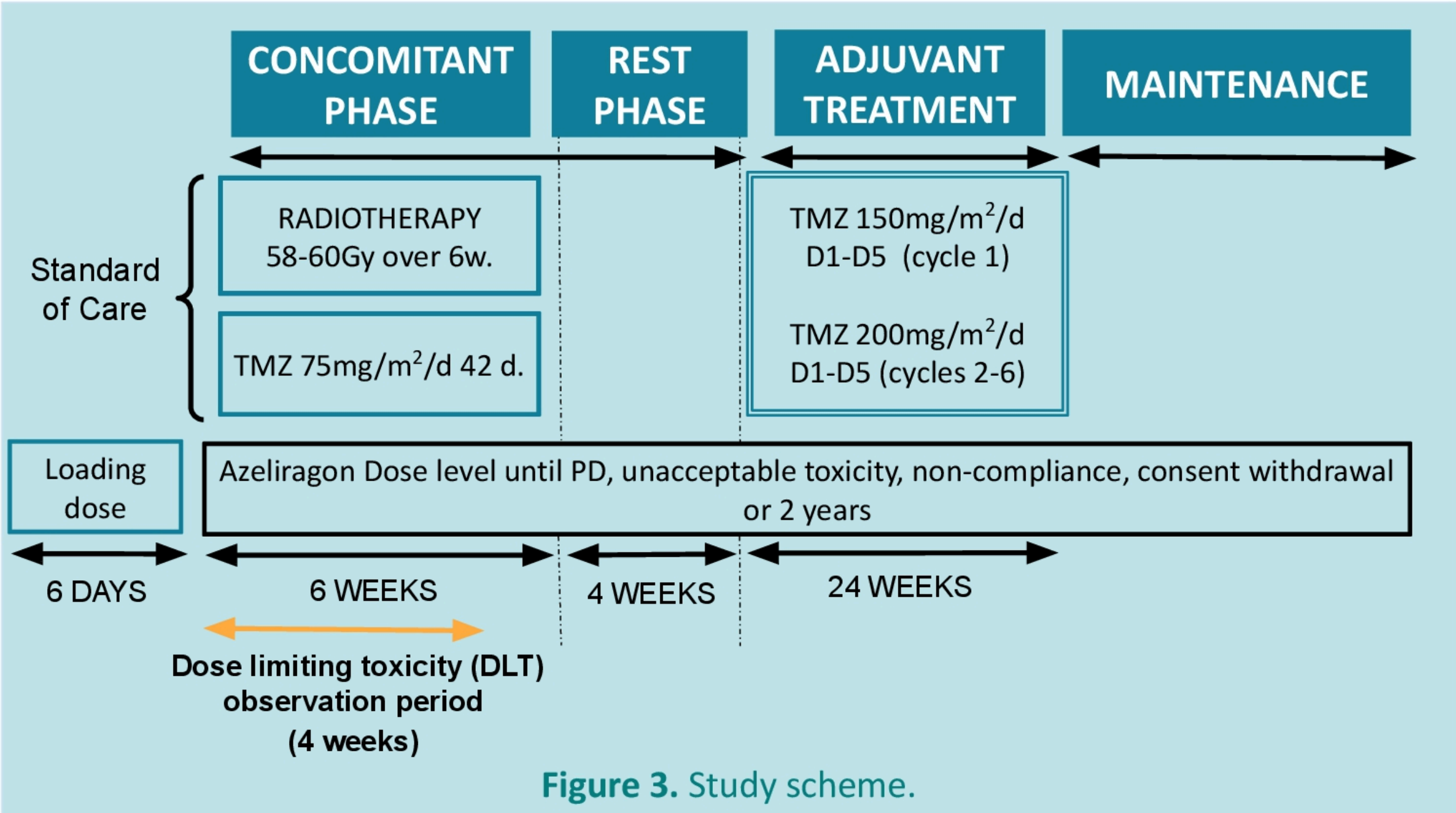


Figure 3. Study scheme.

OBJECTIVES

Primary:

- To determine the Recommended Phase 2 Dose (RP2D) of Azeliragon in patients with newly diagnosed GBM receiving concurrent RT and TMZ. RP2D is defined as the dose for which <33% patients experience a dose limiting toxicity (DLT) within 28 days from initiation of dosing.

Secondary:

- To assess preliminary evidence of an effect of azeliragon in patients with newly diagnosed GBM receiving concurrent RT and TMZ:
 - The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, v5.0), seriousness, duration, and relationship to study treatment.
 - Disease control as indicated by RANO criteria.
 - Progression-free survival (PFS).
 - Overall survival.
 - Change in ECOG status.
 - Changes in requirement of dexamethasone to control peritumoral edema

Exploratory:

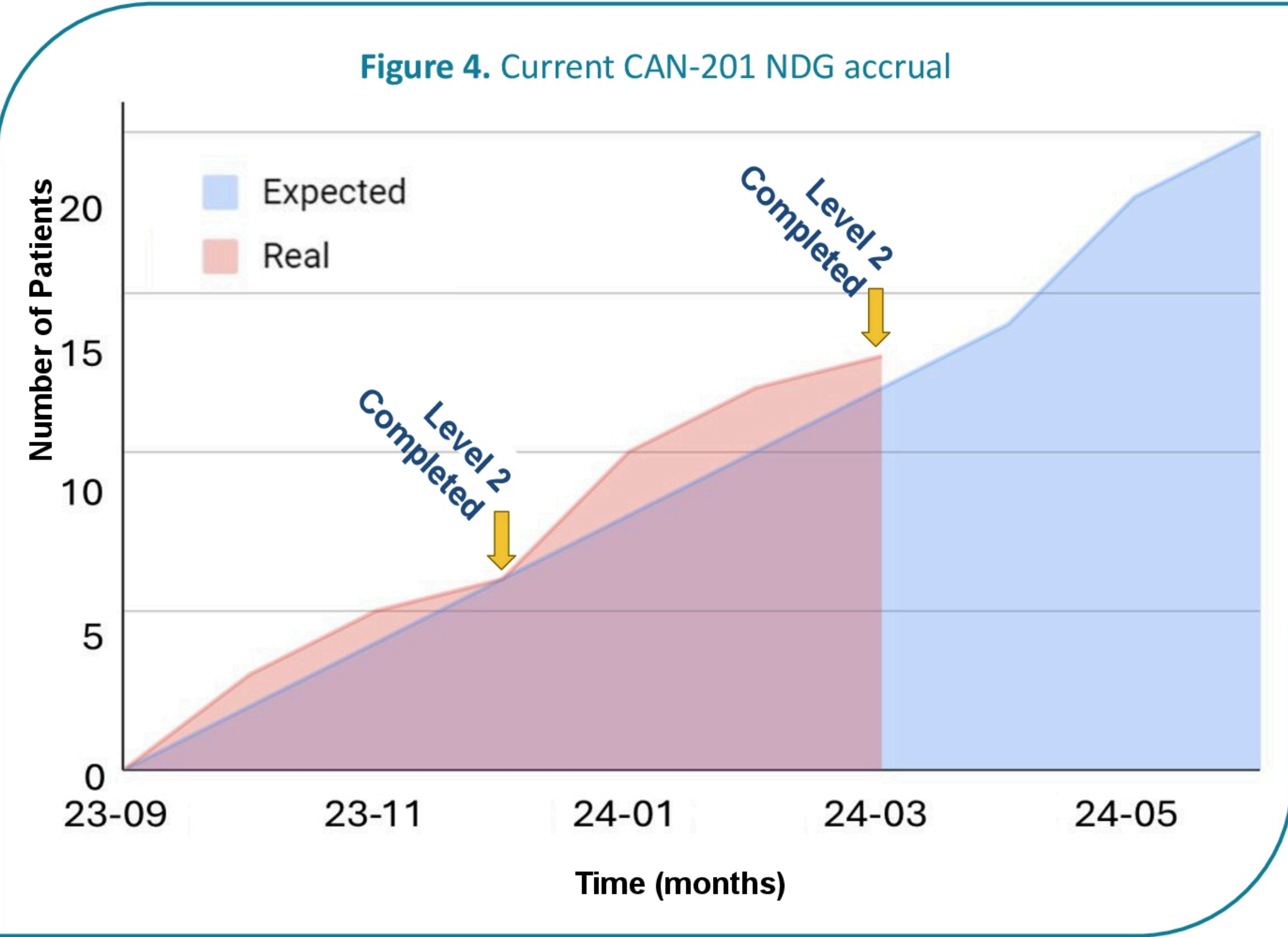
- To determine if response to RAGE inhibitors could be predicted by a liquid biopsy measuring circulating levels of S100A9 or other molecular biomarkers in the blood.

PATIENT ELIGIBILITY

Eligible patients must be male or female (non-pregnant and non-lactating), ≥ 18 to ≤ 70 years old, ECOG ≤ 2, and have a histologically confirmed newly diagnosed glioblastoma (GBM, WHO grade IV). Patients should have had a gross total or subtotal resection performed < 7 weeks prior to enrollment, documented at postoperative MRI. Patients who have had a biopsy only without resection are not eligible. The histological diagnosis must have been made after biopsy or neurosurgical tumor resection; the local MGMT report determination should be available and uploaded to the eCRF. Patients should be treatment-naïve and deemed suitable by the treating physician to receive the standard RT / TMZ scheme. Corticosteroid treatment must be on a stable or decreasing dose for at least 14 days prior to first dose of study treatment. Patients must have adequate blood counts including absolute neutrophil count (ANC) ≥ 1.0 × 10⁹/L; Platelet count ≥ 75,000/mm³ (75 × 10⁹/L); Hemoglobin (Hgb) ≥ 9 g/dL without transfusion or growth factor support; liver enzymes including aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal range (ULN); total bilirubin ≤ 1.5 × ULN; and estimated creatinine clearance of > 60 mL/min (Cockcroft-Gault formula).

SAMPLE SIZE

During dose escalation phase, up to 6 patients can be enrolled at a time and accrual is only stopped when awaiting data from those 6 patients. The subsequent expansion phase may include up to 14 additional patients at the RP2D. No formal size calculations were used for expansion phase.



- Accrual started in September 2023.
- To date, 13 patients have been enrolled (Fig.4).
- As of April 2024, recruitment in dose level 1 and 2 were completed with 6 patients. Recruitment in Level 3 is started and is expected to be completed by July 2024.

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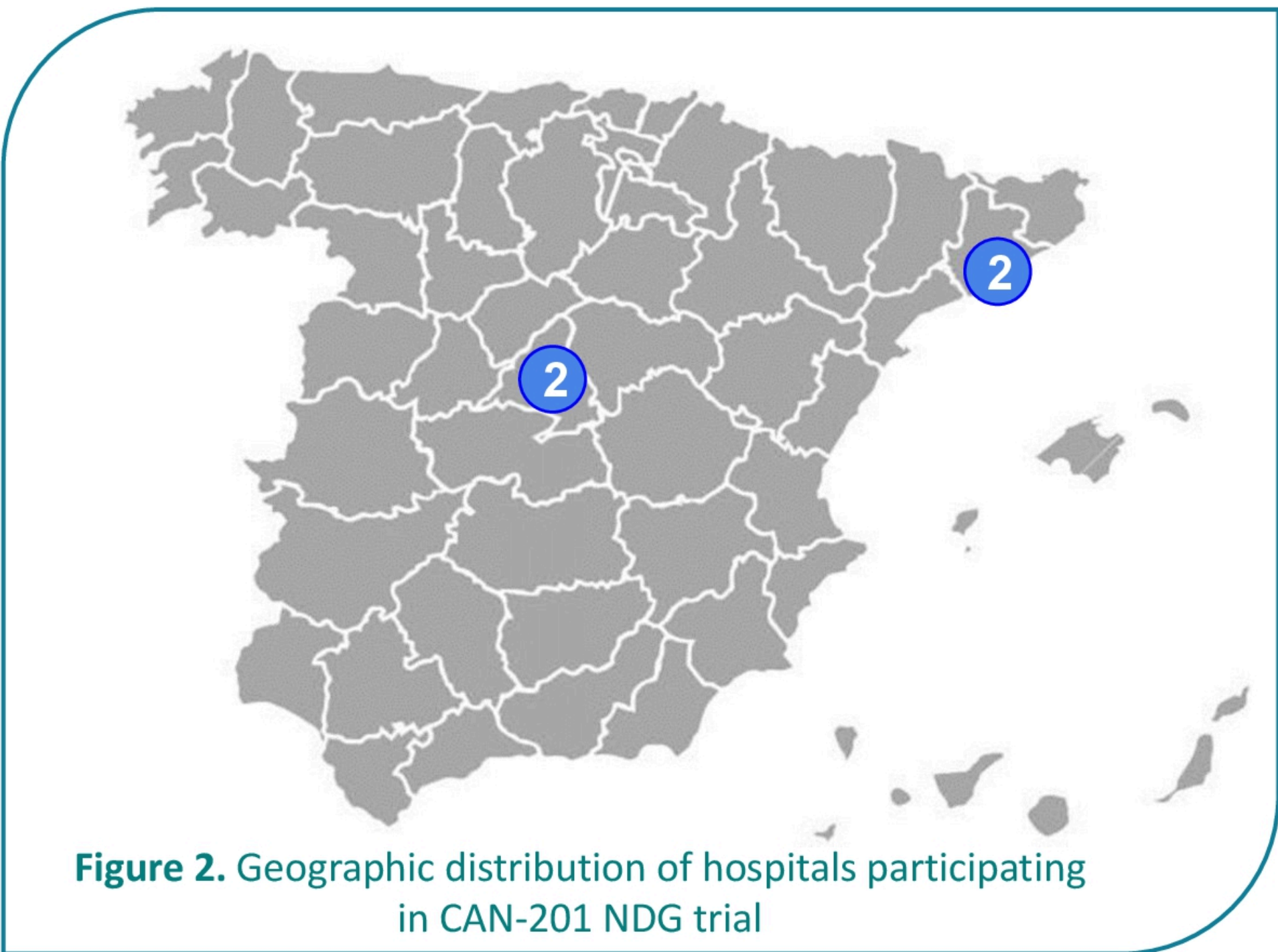


Figure 2. Geographic distribution of hospitals participating in CAN-201 NDG trial

Table 1. Dose Levels

Dose	Loading Dose for 6 days	Continuous Dose
Level 1	15 mg once daily	5 mg once daily
Level 2	15 mg twice daily	10 mg once daily
Level 3	30 mg twice daily	20 mg once daily

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