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# POSTER ABSTRACTS

## 626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

### Trial in Progress: A Phase I/II Study of Tafasitamab Plus Lenalidomide in Patients with Relapsed CNS Lymphoma

*Michael P Randall, MD[1], Andreas Rauschecker, MD, PhD[2], Liam Gima-Lange, B.S.[1], Jenai Wilmoth, RN[1], Lingjing Chen[1], Ming Lu[1], Huimin Geng, PhD[3], Haifaa Abdulhaq, MD[4,5], James L. Rubenstein, MD PhD[6]*

[1] Hematology/Oncology Department of Medicine, University of California, San Francisco, San Francisco, CA
[2] Radiology and Biomedical Imaging, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA
[3] Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA
[4] University of California San Francisco, Fresno/Community Cancer Institute, Clovis, CA
[5] Hematology/Oncology, University of California, San Francisco, Fresno, CA
[6] Hematology/Oncology Department of Medicine, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

**Background and Significance**

The development of novel, more effective biological strategies to prevent secondary CNS lymphoma (CNSL) and to treat primary and secondary CNSL would have significant impact.

It is well established that the CD19 transmembrane glycoprotein is expressed by B-cells throughout differentiation, by the majority of B cell malignancies, and by follicular dendritic cells. Given the high incidence of neurotoxicity associated with blood-brain barrier disruption with CD19-directed CAR-T cells and bi-specific T-cell engager antibodies, Parker et al. recently investigated the possibility of CD19 expression by previously unrecognized cell population(s) in the brain. Single-cell RNA sequencing data demonstrated CD19 expression in brain mural cells, an integral component of the neurovascular unit that regulates integrity of the blood-brain barrier.(Cell, 2020; 183:126-42).

Given these observations and the compelling problem of relapsed primary and secondary CNS lymphoma, we are evaluating tafasitamab, an anti-CD19 humanized monoclonal antibody, as a novel therapeutic for refractory CNS lymphomas. We hypothesize that tafasitamab may modulate blood-brain barrier integrity by perturbation of CD19 expressed on mural cells; but without recruitment of cytotoxic T cells and resultant cytokine release syndrome. Our rationale is supported by the Phase II L-MIND study, in which tafasitamab plus lenalidomide exhibited synergistic efficacy against relapsed/refractory aggressive non-Hodgkin lymphoma, with overall response rate of 60%, complete response rate of 43%, and a favorable toxicity profile compared to CAR-T without neurotoxicity. Notably, the L-MIND trial excluded patients previously treated with immunomodulatory drugs as well as CNS lymphoma. (Lancet Oncology 2020: 21:978-88). We also recently reported that tafasitamab plus lenalidomide induced brain parenchymal regressions in two consecutive CNS lymphoma patients with disease refractory to lenalidomide, pomalidomide and rituximab. (British Journal of Haematology 2023 201(1):154-157).

**Study Design and Methods**

This single-arm, open-label, multicenter Phase I/II study (NCT05351593) assesses safety, CNS pharmacokinetics and preliminary efficacy of tafasitamab plus lenalidomide in patients with relapsed primary and secondary CNSL.

The Phase I portion of the study will determine tolerated dose (MTD) and recommended Phase II dose (RP2D) of lenalidomide in combination with tafasitamab. We are applying 3+3 dose escalation rules to examine lenalidomide 10mg, 15mg and 20 mg plus tafasitamab at 12 mg/kg. After the RP2D is identified, the Phase II portion of the study will begin. The primary objective of the Phase II expansion is to evaluate the clinical benefit rate (stable disease or better) via Simon's minimax two-stage design. Exploratory endpoints include assessment of effect of tafasitamab on blood-brain barrier permeability, correlation of the relationships between tumor response or resistance with tumor mutational profile, and changes in CSF and blood immune cell phenotypes.

The study plans to enroll up to 35 patients. Eligibility mandates age $\geq$ 18 years, anticipated survival >2 months, ECOG PS 0-1, and receipt of at least one prior systemic therapy. Patients with prior exposure to lenalidomide or pomalidomide or concomitant systemic lymphoma are allowed. Patients with HIV infection, CNS PTLD, and those who previously received a CD19-targeting CAR-T product are ineligible.

The study is currently enrolling at the University of California San Francisco, with plans to expand enrollment to other institutions within the United States.

**Disclosures Abdulhaq:** *Genentech:* Speakers Bureau; *Amgen, MorphoSys, Genentech, BMS, Novartis, Pfizer, AbbVie:* Consultancy; *Oncopeptide, Morphosys, Genentech, Pfizer:* Research Funding. **Rubenstein:** *Gilead:* Consultancy; *NURIX:* Research Funding; *Incyte:* Research Funding.

**OffLabel Disclosure:** We are studying the off-label use of tafasitamab, in combination with lenalidomide in relapsed CNS lymphomas.

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