TPS7094 **Poster Session**

Optimizing frontline therapy for diffuse large B cell lymphoma (DLBCL) in older adults: A glofitamab-based, response-adapted, window-style study (GLORY).

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Background: Older adults (OA) with DLBCL classified as unfit or frail based on simplified geriatric assessment (sGA) do poorly with standard doses of anthracycline based chemotherapy. Bispecific antibodies have a preserved risk-benefit profile in OA and their combination with chemotherapy represents a promising strategy to increase cure rates in DLBCL. Interim PET scans have a high negative predictive value and can be harnessed to guide response adapted therapy in this setting to minimize exposure to chemotherapy for responsive patients. GLORY is a window-style, glofitamab-based, response-adapted study with polatuzumab-rituximab-miniCHP (pola-R-miniCHP) backbone specifically designed for unfit and frail older adults with DLBCL who are being treated with curative intent. The dual goals of this personalized strategy are: 1. To improve cure rates in patients with iPET2 positivity, 2. To reduce chemotherapy dosage and ensuing toxicities in patients with iPET2 negativity while maintaining/improving cure rate. **Methods:** In this Phase II, prospective, open label, single arm, single institution study, OA $\geq$ 65 years of age with newly diagnosed DLBCL, high grade or transformed B-cell lymphoma, classified as unfit or frail by simplified geriatric assessment (sGA) will be included. All patients will receive 2 cycles of glofitamab and polatuzumab followed by an interim PET scan (iPET2). If iPET2 is negative (Deauville 1-3), patients will receive 4 cycles of glofitamab-pola-R-miniCHP. If iPET2 is positive without progression, patients receive 6 cycles of glofitamab-pola-R-miniCHP. All patients undergo end of treatment (EOT) PET and are followed for 5 years. ctDNA and dynamic changes in aging biomarkers [epigenetic aging clock, senescence associated secretory phenotype (SASP)] will be measured at baseline, after cycle 1 (C1), after C2 and at the EOT and correlated with outcomes. On therapy tumor biopsy after cycle 1 of glofitamab+-polatuzumab is optional. The trial has been thoughtfully designed to be OA-friendly with pragmatic eligibility criteria and stepwise strategies (eg. prephase) to mitigate the risk of toxicities. The primary endpoints are complete response rate (CRR) after 2 cycles of glofit-pola and CRR after completion of therapy. Key secondary end points include other measures of efficacy such as overall response rate (ORR), progression free survival (PFS) and overall survival (OS) and safety. The target CRR at the end of therapy is 60% with an unacceptably low rate of 40%. Based on these assumptions, a sample size of 42 patients provides a 5% one sided type 1 error and 80% power. This is a single stage design, and the study will be considered positive if 23 of 42 patients achieve a CR at the end of therapy. Additionally, the coprimary endpoint of CR rate after 2 cycles of glofitamab+polatuzumab will be used to stop for futility. Clinical trial information: NCT06765317. Research Sponsor: Genentech; Memorial Sloan Kettering Cancer Center.