HAEMATOLOGICAL CANCER

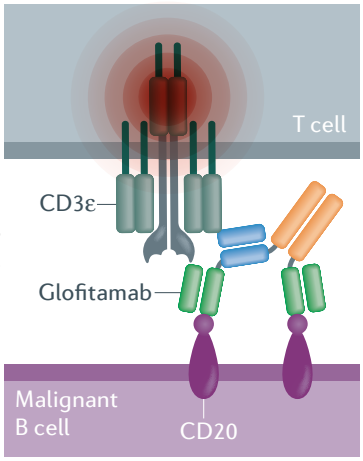
# Engaging results with glofitamab

The prognosis of most patients with relapsed and/or refractory B cell non-Hodgkin lymphoma (R/R B-NHL), particularly those with aggressive histologies such as diffuse large B cell lymphoma or transformed follicular lymphoma, remains dismal. Now, data from the ongoing phase I NP30179 study demonstrate the encouraging activity of glofitamab, a novel bivalent CD20-targeted bispecific T cell-engager antibody, in this setting.

"This trial included 171 heavily pretreated patients with R/R B-NHL, predominantly (74.3%) aggressive lymphoma subtypes; 90.6% had disease refractory to immediate prior therapy," explains study lead Michael Dickinson. These patients received various fixed or step-up doses of glofitamab starting 1 week after a single dose of the anti-CD20 antibody obinutuzumab, which was used to deplete B cells and thereby reduce the risk of a glofitamab-induced cytokine storm.

"The objective response rate (ORR) was 53.8% across all doses tested and 65.7% in 35 patients who received the recommended phase II dose (2.5–10–30 mg step-up dosing), with complete response (CR) rates of 36.8% and 57.1%, respectively," Dickinson summarizes. "Notably, 34 (81.0%) of 42 CRs in patients with aggressive histologies are ongoing at up to 27.4 months." In this group, the median progression-free survival (PFS) was 2.8 months, although PFS plateaued at ~25% beyond 8 months.

Glofitamab-related grade ≥3 adverse events (AEs), mostly cytopenias and infections, occurred in 31.0% of patients. Despite obinutuzumab pretreatment, cytokine-release syndrome occurred in 50.3% of patients, and 5.3% had transient symptoms of immune effector cell-associated neurotoxicity syndrome; however, these AEs were of grade ≥3 in only 3.5% and 1.2%, respectively. Moreover, only 2.9% of patients discontinued treatment owing to AEs, and no treatment-related deaths were reported.




Credit: Simon Bradbrook/Springer Nature Limited

"The safety and preliminary efficacy data of glofitamab compare favourably with those of established third-line treatments — and clear potential for improvement exists in that space," states Dickinson. Multiple CD19-targeted chimeric antigen receptor (CAR) T cell products are approved for third-line treatment of B-NHLs, but challenges related to accessibility, manufacturing, toxicities and resistance continue to limit the benefits of these agents. "Glofitamab is a convenient and readily available non-chemotherapy treatment option," adds Dickinson, concluding that: "this treatment has promising activity against both aggressive and indolent B-NHLs and is well-suited for evaluation in later-phase studies, as a single agent and in combination."

Glofitamab is being tested in various combinations, including with concurrent obinutuzumab as part of the NP30179 study and with gemcitabine plus oxaliplatin in the phase III STARGLO trial (NCT04408638). In addition, a role for glofitamab following, or even in combination with, anti-CD19 CAR T cell therapy can be envisaged, with the aim of overcoming antigen loss and other mechanisms of resistance. Indeed, a trial has been initiated in such a context (NCT04703686).

*David Killock*

**ORIGINAL ARTICLE** Hutchings, M. et al. Glofitamab, a novel, bivalent CD20-targeting T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.20.03175 (2021)

# In the news

## FROM ESMO TAT 2021

March 2021 saw the return of the ESMO Targeted Anticancer Therapies (TAT) Congress, in a virtual format, after a 2-year hiatus caused by the last-minute cancellation of the 2020 Congress as the COVID-19 pandemic spread rapidly around the globe. However, the virtual format might actually have further increased engagement in this meeting focused on early oncology drug development, given that the number of 'attendees' almost tripled, from 380 to 1,127.

Educational sessions covered the breadth of targeted anticancer treatments, from acoustic cluster therapy and antibody–drug conjugates designed to improve the delivery of cytotoxic agents, to a range of molecularly targeted agents, epigenetic drugs and immunotherapies, including engineered T cells, multi-specific T cell engagers, cytokines, oncolytics and microbiota-based interventions. This long list underscores the huge variety and complexity of anticancer strategies that are currently under clinical development. On this background, the 2021 TAT Honorary Award recipient, Ruth Plummer, emphasized the importance of academic–industry partnerships to exploit complementary strengths and overcome weaknesses, thereby improving the adaptability, flexibility and, ultimately, the success of drug development. In his keynote lecture on models for efficient drug development, David Hyman also stressed the importance of approaching this process as a 'team sport'.

The importance of translational research in prioritizing and refining anticancer strategies was highlighted by a series of talks on preclinical studies to identify combination therapies. In this session, René Bernards presented unpublished data from his group indicating that, akin to their findings with BRAF inhibitors in colorectal cancer, EGFR signalling diminishes the efficacy of the tyrosine kinase inhibitor lenvatinib in hepatocellular carcinoma models. Reportedly, combining this agent with the EGFR inhibitor gefitinib resulted in promising activity in a proof-of-concept clinical study.

In oral abstract sessions, attendees were provided with emerging data on intratumoural immunotherapy with liposomes containing IL-12-encoding mRNA (MEDI1191) in patients previously treated with immune-checkpoint inhibitors, revealing a favourable safety profile and shrinkage of both injected and non-injected lesions, even prior to addition of sequential durvalumab. The novel highly selective PI3Kα inhibitor CYH33 also showed promising single-agent activity, including one complete response, in patients with various *PIK3CA*-mutated solid tumours — unlike most other PI3K inhibitors. In the phase II ZENITH20 trial, poziotinib resulted in disease control in almost 90% of patients with *EGFR* or *ERBB2* exon 20-mutant non-small-cell lung cancer, who have a particularly poor prognosis. Importantly, the poor tolerability of this agent could be improved with twice-daily versus once-daily dosing, without compromising efficacy.

Once again, the TAT Congress proved to be an engaging meeting covering many exciting new directions in cancer therapy. We look forwards to returning to Paris next year to discuss the trends in phase I oncology in person.

*David Killock*