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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Copanlisib in Combination with Nivolumab in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Primary Mediastinal Large B-Cell Lymphoma: A Phase II Study

N. Nora Bennani, MD[1], Pamela Atherton[1], Kimberly O Steinert[1], Lisa M. Rimsza, MD[2], Aung M. Tun, MD[3], Marc S. Hoffmann, MD[4], Mayur S. Narkhede, MBBS[5], Rakhee Vaidya, MD[6], Rabih Said[7], Geoffrey I Shapiro, MD[8], Brian A Costello, MD[9], Stephen M Ansell, MD PhD[10], Grzegorz S. Nowakowski, MD[10]

[1] Mayo Clinic, Rochester, MN
[2] Department of Laboratory Medicine and Pathology, Mayo Clinic, Phoenix, AZ
[3] Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas, Westwood, KS
[4] The University of Kansas Medical Center, Kansas City, KS
[5] Department of Hematology Oncology, University of Alabama at Birmingham, Birmingham, AL
[6] Wake Forest, Winston-Salem, NC
[7] Investigational Drug Branch, CTEP, NCI, Rockville, MD
[8] Dana-Farber Cancer Institute, Boston
[9] Medical Oncology, Mayo Clinic, Rochester, MN
[10] Division of Hematology, Mayo Clinic, Rochester, MN

Introduction: Diffuse Large B-cell Lymphoma (DLBCL) are aggressive B-cell non-Hodgkin lymphomas (NHL). One particular subtype, Primary Mediastinal B-cell Lymphoma (PMBCL), is often grouped with DLBCL, but it possesses distinct biological and clinical characteristics. While initial therapy successfully cures approximately two-thirds of patients (pts), those who do not respond or experience progression within the first two years have a poor prognosis despite novel cellular therapies and bispecifics and ultimately succumb to their disease. There is a pressing need for more effective therapeutic approaches in this patient population.

Recent advances in the understanding of DLBCL pathogenesis have led to the targeting of various signaling pathways, including the PI3K-AKT-mTOR pathway. One such drug, copanlisib (C), a pan-PI3K inhibitor with potent PI3K-α/PI3K-δ inhibition, exhibited activity in both indolent and aggressive NHL. In preclinical studies using a DLBCL mouse model, treatment with C effectively reduced the immunosuppressive tumor-infiltrating T-regulatory cells (Tregs). Moreover, when combined with a surrogate anti-mouse programmed death -1 (PD-1) blocker, C demonstrated significant in vivo responses (75%) compared to the monotherapy groups (0%).

These findings support the rationale for exploring the combination of nivolumab, a PD-1 blocker, and copanlisib (C-N) in DLBCL. Thus, a phase 2 prospective study has been developed, focusing on two relapsed/refractory (RR) cohorts (DLBCL and PMBCL), treated with the combination of C-N. A prespecified interim analysis was planned upon enrollment of 14 pts. Herein, we report outcomes of the 12 enrolled pts, as the study was halted prematurely due to a safety signal deemed possibly related to the combination.

Study design: C 60 mg was given intravenously on days 1, 8, and 15 during cycles 1-8, and on days 1 and 15 in subsequent cycles. N 240 mg IV was given on days 1 and 15 during cycles 1-8, and 480 mg on day 1 on subsequent cycles. Each treatment cycle is 28 days. Therapy was given for up to 2 years, as long as there is no disease progression or unacceptable side effects. The primary objective of the study is to determine the ORR, which includes complete and partial responses (CR+PR). Secondary objectives include evaluating the safety of the combination, as well as assessing progression-free survival (PFS), duration of response (DOR), CR, and overall survival (OS). The study plan was to enroll a maximum of 106 pts, including a safety cohort of 6 pts. The study received funding from Bayer and conducted through NCI-CTEP (NCI Protocol #10193; NCT03484819).

Results: Twelve pts who received at least one cycle of C-N were included in this analysis. Pt characteristics are illustrated in table 1. All enrolled pts had DLBCL histology. Only one patient received a prior autologous stem cell transplant. Interestingly 4/12 received prior chimeric antigen receptor T-cell therapy (CART). Of the 12 enrolled pts, seven were evaluated for response. The ORR was 25% (3/12) (95% CI: 5 - 57%), all CR. The median number of cycles received was 2.5 (range 1-24) with two pts

receiving 23 and 24 cycles. Observed grade 3 and higher adverse events (AEs) were as follows: non-hematologic AEs in 10/12 (83.3%), while hematologic AEs were seen in 5/12 (41.7%) pts. A relatively higher incidence of cardiac events (4/12) were noted including one cardiac arrest after one cycle of therapy, and four atrial fibrillation events, all grade 3, but only two were deemed possibly attributed to therapy. The cardiac arrest was deemed unrelated to therapy.

Conclusions: C-N combination had modest clinical activity in pts with R/R DLBCL with some prolonged responses. However, due to the relatively high number of cardiac events and the changing therapeutic landscape with recent approvals, a decision was made to halt the study. These findings likely reflect possibly older and sicker patient population. Biomarker studies for predictors of response are under consideration.

Disclosures Bennani: *Astellas Pharma:* Other: Advisory board; No personal compensation; *Affimed:* Other: Advisory board; No personal compensation; *Secura Bio:* Other: Advisory board; No personal compensation; *Kymera:* Other: Advisory board; No personal compensation; *Acrotech:* Other: Advisory board; No personal compensation; *Acrotech:* Other: Scientific Advisory Committee, No personal compensation . **Rimsza:** *Roche:* Other: Consulting; *NanoString:* Other: Licensed intellectual property. **Hoffmann:** *Genentech:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *TG Therapeutics:* Consultancy, Honoraria; *Kite:* Consultancy, Honoraria. **Ansell:** *Takeda Pharmaceuticals USA Inc:* Other: Contracted Research; *Seagen Inc:* Other: Contracted Research; *Regeneron Pharmaceuticals Inc:* Other: Contracted Research; *Pfizer, Inc:* Other: Contracted Research; *Bristol-Myers Squibb:* Other: Contracted Research; *Affirmed:* Other: Contracted Research; *ADC Therapeutics:* Other: Contracted Research. **Nowakowski:** *MorphoSys:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Fate Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol-Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Curis:* Consultancy; *TG Therapeutics:* Consultancy; *Abbvie:* Consultancy; *Selvita Inc:* Consultancy; *Incyte:* Consultancy; *Celgene Corporation:* Consultancy; *MEI Pharma:* Consultancy; *ADC Therapeutics:* Consultancy; *Bantam Pharmaceutical LLC:* Consultancy; *Kite Pharma:* Consultancy; *Karyopharm Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Kymera Therapeutics:* Consultancy; *Blueprint Medicines:* Consultancy; *Seagen:* Consultancy; *F Hoffmann-La Roche Limited:* Consultancy; *Genentech:* Consultancy; *Debiopharm:* Consultancy; *Ryvu Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Zai Lab Limited:* Consultancy.

Table 1: Patient Characteristics	Total N=12
Age	
Median (Range), years	72.5 (54 - 85)
Male Gender, n (%)	7 (58.3)
Race, n (%)	
White	11 (91.7)
Black or African American	1 (8.3)
Performance Score, n (%)	
0	3 (25)
1	6 (50)
2	3 (25)
Lines of Therapy, Median (Range)	3 (1-6)
Prior Autologous Stem Cell Transplant, n (%)	1 (8.3)
Prior CART cell Therapy, n (%)	4 (33.3)

Figure 1

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