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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Pharmacodynamic Biomarkers and CtDNA Support the Mechanism of Action and Clinical Efficacy of Golcadomide (CC-99282) Combined with R-CHOP in Previously Untreated Aggressive B-Cell Lymphoma

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Introduction

Golcadomide (GOLCA, CC-99282) is an orally available cereblon E3 ligase modulator (CELMoD ®) that potently degrades target proteins Ikaros and Aiolos, enhancing antiproliferative, apoptotic, and immunomodulatory activity and preferentially distributing to lymphoid organs. In a phase 1 study, GOLCA monotherapy previously demonstrated a manageable safety profile with promising clinical activity in relapsed/refractory non-Hodgkin lymphoma (Michot *Blood* 2021). In the ongoing CC-220-DLBCL-001 study (NCT04884035), GOLCA dose finding is underway in patients with previously untreated aggressive B-cell lymphoma (BCL), in combination with R-CHOP in 21-day (D) cycles (C), at a variety of GOLCA dose levels (DLs) and schedules: DL-1 = 0.2 mg D1-7, DL1 = 0.4 mg D1-7, and DL2 = 0.4 mg D1-10. Here, we report Ikaros degradation, immune modulation, circulating tumor DNA (ctDNA) assessment, and baseline tumor genomics.

Methods

Peripheral blood was collected to analyze Ikaros and Aiolos levels in T cells by flow cytometry (C1D1, C1D7, and C2D1). Immune phenotyping of T and natural killer (NK) cells was performed by flow cytometry (C1D1, C1D15, C2D1, and C3D1). ctDNA levels were analyzed by the PhasED-Seq assay (timepoints C1D1, C2D1, C3D1, and end of treatment [EOT]; Kurtz *Nat Biotechnol* 2021); somatic variants were filtered by performing PhasED-seq on buffy coats. Pretreatment biopsies were analyzed by whole genome sequencing and whole transcriptome sequencing. DL1 (0.4 mg D1-7) and DL2 (0.4 mg D1-10) data were pooled.

Results

Ikaros levels in T cells at 5 hours after the first dose had a 1.1% median increase with 0.2 mg and 44% median decrease with 0.4 mg; by C1D7 pretreatment, Ikaros substantially decreased with both DLs (median: 0.2 mg, 87% decrease; 0.4 mg, 83% decrease). Ikaros differences between 0.2 mg and 0.4 mg were not substantial. By C2D1, Ikaros levels recovered to baseline. Based on preclinical benchmarks, steady-state Ikaros degradation in T cells suggested that direct tumor cell killing by GOLCA was achieved.

Changes in T and NK cell phenotypes in peripheral blood included activation, increased proliferation, increased T effector memory and regulatory cell levels, and decrease in naive T cells. Changes were seen by C1D15 and maintained at C2D1 and C3D1. Overall, immune changes between 0.2 mg and 0.4 mg dose levels were not substantially different.

Phased variant data from ctDNA and buffy coats were evaluable for 34 patients (0.2 mg, n =15; 0.4 mg, n = 19). Baseline ctDNA levels were similar between the 0.2 mg and 0.4 mg cohorts and, consistent with prior studies, correlated with International Prognostic Index and cell of origin. Previously reported landmarks such as early molecular response (EMR; ≥ 2 log decrease) at C2D1 and major molecular response (MMR; ≥ 2.5 log decrease) at C3D1 were assessed (Kurtz *J Clin Oncol* 2018) . A high fraction of patients designated high risk by pretreatment ctDNA (≥ 2.5 log haploid genome equivalents [HGE]/mL; Kurtz *J Clin Oncol* 2018) were clinical responders. Patients who achieved minimal residual disease (MRD) negativity on treatment generally remained MRD negative at subsequent timepoints. At C2D1, the EMR and MRD negativity rates for 0.2 mg were 73% (11/15) and 20% (3/15), respectively; for 0.4 mg these rates were 83% (15/18) and 44% (8/18). At C3D1, the MMR and MRD negativity rates for 0.2 mg were 83% (10/12) and 42% (5/12), respectively; for 0.4 mg these were 83% (10/12) and 58% (7/12). Although ctDNA differences between 0.2 mg and 0.4 mg were not substantial, numerically greater ctDNA changes were seen

with 0.4 mg GOLCA + R-CHOP vs 0.2 mg GOLCA + R-CHOP and vs R-CHOP and R-CHOP-like regimens from other cohorts (**Figure**). Insufficient samples were available to draw conclusions about EOT, but additional ctDNA data will be presented. Whole genome and transcriptome sequencing data from GOLCA + R-CHOP-treated patients will be shown.

Conclusions

Pharmacodynamic biomarkers and ctDNA levels indicate that both tumor-intrinsic and immune-modulating mechanisms of action of GOLCA remain relevant in combination with R-CHOP in previously untreated aggressive BCL. ctDNA data during treatment are consistent with the efficacy noted on clinical restaging. Translational data demonstrate the potency of GOLCA and will support future frontline clinical trial designs in patients with untreated aggressive BCL.

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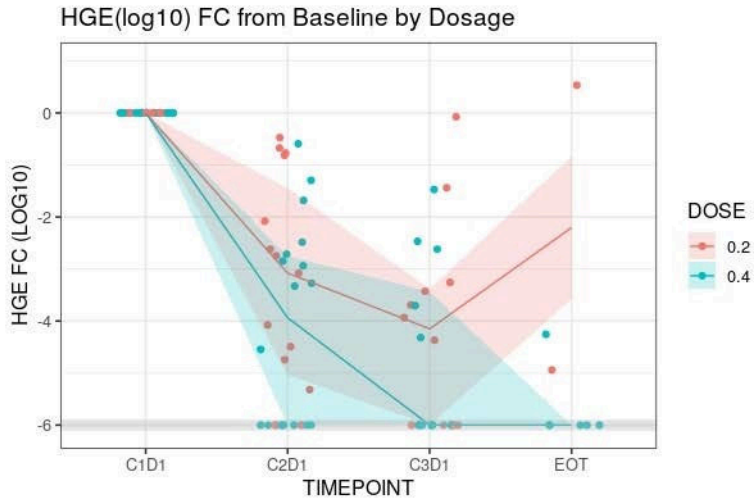
Disclosures Kaplan: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Basavanhally:** *Bristol Myers Squibb:* Current Employment, Current holder of *stock options* in a privately-held company. **Nakayama:** *BMS:* Current Employment. **Kyriakopoulos:** *Bristol Myers Squibb:* Current Employment. **Amzallag:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Gkasiamis:** *Bristol Myers Squibb:* Current Employment. **Patel:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Sudhindra:** *Bristol Myers Squibb:* Current Employment, Current holder of *stock options* in a privately-held company. **Nowakowski:** *Curis:* Consultancy; *Zai Lab Limited:* Consultancy; *Selvita Inc:* Consultancy; *Kymera Therapeutics:* Consultancy; *Kite Pharma:* Consultancy; *MEI Pharma:* Consultancy; *Bantam Pharmaceutical LLC:* Consultancy; *Bristol-Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Ryvu Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Debiopharm:* Consultancy; *TG Therapeutics:* Consultancy; *Genentech:* Consultancy; *Celgene Corporation:* Consultancy; *Fate Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Blueprint Medicines:* Consultancy; *ADC Therapeutics:* Consultancy; *Abbvie:* Consultancy; *F Hoffmann-La Roche Limited:* Consultancy; *MorphoSys:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Incyte:* Consultancy; *Karyopharm Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Seagen:* Consultancy. **Westin:** *Genentech:* Consultancy, Research Funding; *MonteRosa:* Consultancy; *Kite/Gilead:* Consultancy, Research Funding; *Nurix:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *SeaGen:* Consultancy; *ADC Therapeutics:* Consultancy, Research Funding; *Abbvie:* Consultancy; *Novartis:* Consultancy, Research Funding; *Morphosys/Incyte:* Consultancy, Research Funding; *BMS:* Consultancy, Research Funding; *Calithera:* Research Funding; *Kymera:* Research Funding. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

Figure. Longitudinal FC in ctDNA with 0.2 mg (red) and 0.4 mg (blue) GOLCA + R-CHOP.



Each dot represents an individual measurement from a single patient.
Solid lines = median, shading = interquartile range.
FC, fold change.

Figure 1

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