ELSEVIER

Blood 142 (2023) 183–185

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Ruxolitinib Promotes Clinical Responses in Large Granular Lymphocytic Leukemia Via Suppression of JAK/STAT-Dependent Inflammatory Cascades

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Background: Large granular lymphocytic leukemias (LGL) are T or NK-cell lymphoproliferative disorders that are characterized by myelosuppression and frequent mutations in STAT3. Commonly used agents include low doses of methotrexate or cyclophosphamide. Among 5 patients (pts) with LGL treated on our phase II study of ruxolitinib in T-cell lymphoma (Moskowitz, et al. Blood 2021), 2 achieved partial response (PR) and 2 achieved stable disease, suggesting oncogenic dependence on JAK/STAT pathway activity in LGL.
Methods: To further explore the efficacy and mechanism of JAK1/2 blockade in LGL, we expanded our phase II study to include 23 pts with relapsed/refractory LGL. This sample size was chosen to allow for narrowing of the 95% confidence interval to 54-87% (Wilson score method) if similar efficacy was observed. Pts received ruxolitinib 20mg PO BID continuously. Responses were assessed after cycles 2, 5, and every 3 cycles thereafter using the response assessment from the ECOG-5998 study for LGL. Furthermore, stable disease (SD) was defined as improvement in cytopenia(s) by 1 grade (without meeting criteria for PR) for a minimum of 6 months. Overall response rate (ORR) included complete response (CR) plus PR; clinical benefit rate (CBR) included ORR plus SD. In parallel, we performed single-cell RNA sequencing (scRNA-seq) on paired C1D1 and C1D8 peripheral blood mononuclear cells (PBMCs) from 7 patients (5 PR, 1 SD, and 1 non-responder) and plasma proteomic profiling on 5 patients (3 PR, 1 SD, and 1 POD).
Results: Among 23 pts, median age was 58 (31-86), 13 (57%) were male, 19 (83%) were white, 1 (4%) was black. Median number of prior therapies was 2 (range 0-5). 12/22 (54%) had STAT3 mutations (of whom 1 also had a JAK1 mutation); 1 had a JAK2 mutation, 1 pt was missing sequencing. Baseline cytopenias included anemia (n=14, 61%), thrombocytopenia (n=12, 52%), and/or neutropenia (n=16, 70%).
Among 20 pts evaluable for response (3 too early), there were 5 (25%) CRs, 6 (30%) PRs, and 4 (20%) SD. ORR and CBR were 55% and 75% respectively. Median event free survival (EFS) was not reached and was 68% (95% CI: 50-93) at 14 months (**Fig. 1A**). STAT3 mutation status predicted for improved EFS (14-month EFS 100% vs 40%, p=0.007). After a median duration of treatment of 13.1 months, there were no unexpected toxicities. Severe adverse events included febrile neutropenia (n=3, 13%) and herpes zoster (n=1, 4%).
To understand the mechanism by which ruxolitinib improved hematologic parameters in LGL, we performed unbiased proteomic analysis of peripheral blood plasma samples using the OLink 96 Inflammation and Immune Response Platforms. Ruxolitinib led to a decrease in several soluble mediators known to be driven by interferon-driven JAK/STAT activation, including CXCL9, CXCL10, and PD-L1, as well as TNF (**Fig. 1B**). Several of these factors have been shown to suppress hematopoi-

etic stem cell function, suggesting a JAK/STAT-dependent paracrine mechanism by which LGL leads to myelosuppression. ScRNA-seq of PBMCs identified LGL cells based on expression of cytotoxic genes, including *NKG7, CST7, CCL5, GZMB* and *PRF1*. Analysis of cell type proportions within the peripheral blood showed that patients achieving a PR to Ruxolitinib showed a decrease in the proportion of circulating myeloid cells. Gene set enrichment analysis (GSEA) of LGL cells revealed substantial downregulation of both JAK/STAT signaling and TNF signaling in LGL cells in PR but not SD patients, whereas persistently elevated TNF signaling was seen not only in LGL cells but also circulating myeloid and naïve T-cells in SD patients, suggesting that LGL cells might promote bone marrow suppression via paracrine effects on the bystander host immune system. Network analysis of LGL cells and non-malignant peripheral blood immune cells is ongoing.
Conclusions: Ruxolitinib induced durable responses in pts with LGL and therefore may represent an option for pts requiring treatment. STAT3 mutation status was predictive of EFS and responses were associated with JAK/STAT pathway downregulation, demonstrating on-target effects. Integrated immune profiling suggests that ruxolitinib may interrupt JAK/STAT-dependent paracrine inflammatory signals that promote bone marrow suppression. An ongoing phase II study of ruxolitinib in LGL will aid in clarifying optimal dosing and confirming both efficacy and mechanism of action (NCT05592015).

Disclosures Moskowitz: *Incyte:* Research Funding; *Merck:* Honoraria, Research Funding; *Beigene:* Research Funding; *Seattle Genetics:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Research Funding; *ADC Therapeutics:* Research Funding. **Dogan:** *Seattle Genetics:* Consultancy; *Physicians' Education Resource:* Consultancy, Honoraria; *EUSA Pharma:* Consultancy; *Loxo:* Consultancy; *Peer View:* Honoraria; *Incyte:* Consultancy; *Takeda:* Other: Research Funding; *Roche:* Other: Research Funding. **Geyer:** *Actinium Pharmaceuticals, Inc:* Research Funding; *Novartis:* Consultancy; *Sanofi:* Consultancy, Research Funding; *Amgen:* Research Funding. **Jacobsen:** *UpToDate:* Patents & Royalties; *BMS:* Honoraria; *Hoffman-LaRoche:* Research Funding; *Bayer:* Honoraria; *Pharmacyclics:* Research Funding; *Merck:* Honoraria, Research Funding; *Celgene:* Research Funding; *Daiichi:* Honoraria. **Kumar:** *BridgeBio:* Current equity holder in publicly-traded company; *Genentech:* Consultancy, Research Funding; *Celgene:* Research Funding; *Kite Pharma:* Consultancy; *Adaptive Biotechnologies:* Research Funding; *Beigene:* Research Funding; *Abbvie Pharmaceuticals:* Research Funding; *Astra Zeneca:* Consultancy, Research Funding; *Seattle Genetics:* Research Funding; *Loxo/Lily Oncology:* Consultancy, Research Funding; *Pharmacyclics:* Research Funding; *Janssen:* Consultancy. **Park:** *Autolus Therapeutics:* Research Funding; *BeiGene:* Consultancy; *Artiva Biotherapeutics:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Incyte:* Research Funding; *Kite:* Consultancy; *Minerva Bio:* Consultancy; *Takeda:* Consultancy, Research Funding; *Sobi:* Consultancy, Research Funding; *Fate Therapeutics:* Research Funding; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Consultancy, Research Funding; *Intella:* Consultancy; *Pfizer:* Consultancy; *GC Cell:* Membership on an entity's Board of Directors or advisory committees; *Curocell:* Consultancy; *Affyimmune:* Consultancy; *Amgen:* Consultancy; *Bright Pharmacetuicals:* Consultancy; *Genentech, Inc.:* Research Funding; *Be Biopharma:* Consultancy. **Thompson:** *Janssen:* Consultancy; *Loxo Oncology at Lilly:* Consultancy; *VJHemOnc:* Honoraria; *Massachusetts Medical Society:* Honoraria; *Curio Science:* Honoraria; *Dava Oncology:* Other: Travel ; *Brazilian Association of Hematology, Hemotherapy and Cellular Therapy (ABHH):* Honoraria; *Intellisphere LLC:* Honoraria; *MJH Life Sciences:* Honoraria; *Genmab:* Research Funding; *AstraZeneca:* Research Funding; *Genentech:* Research Funding; *Abbvie:* Research Funding; *AstraZeneca:* Consultancy; *Nurix Therapeutics:* Research Funding; *Beigene:* Research Funding. **Torka:** *Lilly USA:* Consultancy; *Genentech:* Consultancy; *Seagen:* Consultancy; *ADC Therapeutics:* Consultancy; *TG Therapeutics:* Consultancy; *Genmab:* Consultancy. **Zelenetz:** *BeiGene:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria; *Janssen Pharmaceuticals:* Consultancy, Honoraria; *Abbvie:* Research Funding; *None other than mutual funds (401K):* Current equity holder in publicly-traded company; *SAB:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Honoraria; *MEI Pharma Inc:* Consultancy, Honoraria, Research Funding; *Lymphoma Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding. **Vardhana:** *Immunai:* Consultancy; *Koch Disruptive Technologies:* Consultancy. **Horwitz:** *Cimieo Therapeutics:* Consultancy; *Abcuro Inc.:* Consultancy; *Daiichi Sankyo:* Consultancy, Research Funding; *Auxilius Pharma:* Consultancy; *ONO Pharmaceuticals:* Consultancy; *SecuraBio:* Consultancy; *Takeda:* Consultancy, Research Funding; *Affimed:* Research Funding; *ADC Therapeutics:* Research Funding; *Yingli Pharma Limited:* Consultancy; *Tubulis:* Consultancy; *Crispr Therapeutics:* Research Funding; *Celgene:* Research Funding; *Trillium Therapeutics:* Consultancy, Research Funding; *Millenium:* Research Funding; *Kyowa Hakko Kirin:* Consultancy, Research Funding; *Shoreline Biosciences, Inc.:* Consultancy; *Seattle Genetics:* Research Funding; *Verastem/SecuraBio:* Research Funding.

OffLabel Disclosure: ruxolitinib for LGL

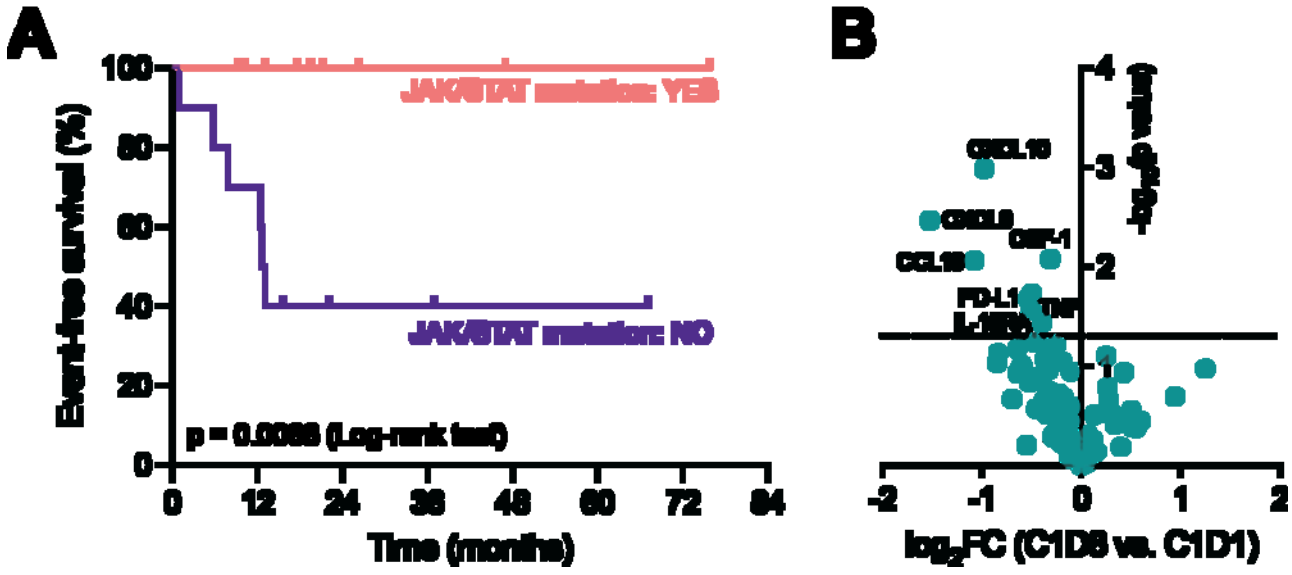

Figure 1

https://doi.org/10.1182/blood-2023-181922