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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

A Phase 2 Study of Minimal Residual Disease (MRD)-Adapted Front Line Venetoclax and Obinutuzumab in Fit Patients with Chronic Lymphocytic Leukemia (CLL): Effect of Obinutuzumab on Tumor Lysis Syndrome (TLS) Risk and Safety of Outpatient Venetoclax Dose Escalation

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Introduction: Venetoclax (V) / Obinutuzumab (O) is an effective one-year fixed duration therapy for patients (pts) requiring first-line CLL treatment (tx). In CLL14, tumor lysis syndrome (TLS) risk assessment (including lymph node measurements by imaging and ALC) was required once prior to tx initiation, and O's impact on TLS risk prior to introduction of V was not a pre-planned study endpoint. Therefore, TLS prophylaxis (ppx) and tx setting for V dose escalation did not account for the possibility that O may decrease TLS risk prior to V escalation. Based on this approach, 22% of pts in the CLL14 study were high risk for TLS, thus requiring hospitalization for intensive laboratory monitoring during V dose escalation. (Fischer, NEJM 2019) We hypothesized that cycle (C) 1 of O would significantly decrease TLS risk prior to V escalation and that all pts, regardless of TLS risk category, could safely undergo a standard 5-week V dose escalation in the outpatient setting.

Methods: We are conducting a Phase 2 study (NCT04447768) designed to examine the efficacy of a minimal residual disease (MRD)-adapted approach to V/O combination for fit pts in the front-line setting (study schema, Figure 1). A planned secondary study endpoint is to evaluate the effect of O monotherapy in C1 on TLS risk. Here we present interim results of TLS risk modification for the first 80 patients. Per protocol, TLS risk assessment including CT imaging and ALC measurement was performed at two defined timepoints: (1) prior to C1 day (D) 1 and (2) immediately prior to V initiation on C1D22. Key eligibility criteria: adult pts with CLL requiring first line tx per iwCLL guidelines, CIRS score ≤ 6, adequate heme function (Hgb $\geq$8 g/dL, ANC $\geq 1 \times 10^9$/L, Plt $\geq 30 \times 10^9$/L), creatinine clearance >50 mL/min. O was administered on C1 D1/2, 8 and 15. Per protocol, pts underwent V dose escalation in the outpatient setting, regardless of TLS risk. For pts with low and medium (med) tumor burden, TLS ppx was per FDA label. For pts who remained high TLS risk at the time of V initiation, TLS ppx throughout dose escalation included allopurinol to start at least 3 days prior to V initiation, sevelamer to start 12 hours prior to V initiation, and oral intake of $\geq$2 L water daily. On days of dose escalation, ppx additionally included kayexalate, rasburicase, and IV normal saline on D1 and D2 of each dose escalation. TLS labs were monitored according to FDA label guidance. Statistical analysis of TLS risk and adverse events was descriptive.

Results: As of 5/2023, 80 pts have enrolled in this study. Seventy-eight pts completed the 5-week V ramp-up. Two pts were removed after receiving at least one dose of O but before repeat assessment of TLS risk and initiation of V (1 death unrelated to tx/disease, 1 patient with recurrent grade 3 (G3) O infusion-related reaction (IRR) leading to consent withdrawal). Median pt age was 57.5 years, 68% male, 95% white. Prior to tx initiation, TLS risk categories were low: 16%, med: 58%, and high: 26% (n=80). Change in TLS risk from baseline to C1D22 is detailed in Figure 2. Of the 20 pts who had sequential assessments with high baseline TLS risk, TLS risk after C1 O (C1D22) was low: 55%, med: 35%, high: 10%. For pts with med TLS risk at baseline with sequential assessments (n=45), TLS risk at C1D22 was low: 82%, med: 18%.

One patient developed laboratory TLS on C1D3 following administration of O; no clinical TLS was observed. All pts accomplished V dose escalation in the outpatient setting with no observed laboratory or clinical TLS as defined by Howard Criteria. Grade 3 / 4 tx emergent AEs that occurred in >5% between C1D1 and C3D1 included neutropenia (35% G3, 11% G4), IRR (11% G3, 0% G4), and thrombocytopenia (9% G3, 3% G4).

Conclusions: A single cycle of O effectively reduced TLS risk prior to introduction of V escalation with most pts achieving low or med TLS risk by C1D22. Notably, 90% of pts with high pre-tx TLS risk converted to low or med risk following C1 of O allowing for outpatient V escalation per FDA label. Further, we demonstrate that V dose escalation can be safely accomplished in the outpatient setting with close monitoring regardless of TLS risk. With this strategy, we observed no laboratory or clinical TLS during V dose escalation. Eliminating the need for hospitalization during V dose escalation may enhance patient and provider convenience and decrease the economic burden of this regimen. This study is ongoing; efficacy results of this MRD-guided approach to V/O are forthcoming.

Disclosures Roeker: *Ascentage:* Consultancy; *Janssen:* Consultancy; *TG Therapeutics:* Consultancy; *Adaptive Biotechnologies:* Research Funding; *DAVA:* Other: CME speaker; *Curio:* Other: CME speaker; *Pharmacyclics:* Consultancy; *AbbVie:* Consultancy, Research Funding; *Loxo Oncology:* Consultancy, Other: travel support, Research Funding; *Abbott Laboratories:* Current equity holder in publicly-traded company; *Medscape:* Other: CME speaker; *Genentech:* Research Funding; *AstraZeneca:* Consultancy, Research Funding; *Beigene:* Consultancy; *Pfizer:* Consultancy, Research Funding; *PeerView:* Other: CME speaker; *Dren Bio:* Research Funding; *Aptose Biosciences:* Research Funding; *Qilu Puget Sound Biotherapeutics:* Research Funding. **Zelenetz:** *F. 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Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Janssen:* Consultancy, Research Funding; *Genmab:* Consultancy; *Incyte:* Consultancy; *Owkin:* Current holder of *stock options* in a privately-held company; *Nordic Nanovector:* Consultancy; *Orna:* Consultancy. **Lue:** *Merck:* Consultancy; *OncLive:* Consultancy. **Goldberg:** *AROG:* Research Funding; *Celularity:* Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Aptose:* Research Funding; *Trillium:* Research Funding; *ADC Therapeutics:* Research Funding; *Aprea:* Research Funding; *Prelude:* Research Funding; *Pfizer:* Research Funding; *DAVA Oncology:* Honoraria; *Astellas Pharma:* Consultancy; *Abbvie:* Consultancy, Research Funding; *Genentech:* Consultancy. **Fakhri:** *BMS/Juno:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Genetech:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Genmab/Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *LOXO/Lilly:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pharmacyclics:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Coombs:** *AbbVie, Genentech, Beigene, AstraZeneca, Lilly, Octapharma:*

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OffLabel Disclosure: This study examines alternate (off-label) strategy for TLS prophylaxis and monitoring during venetoclax dose escalation as outlined in the protocol.

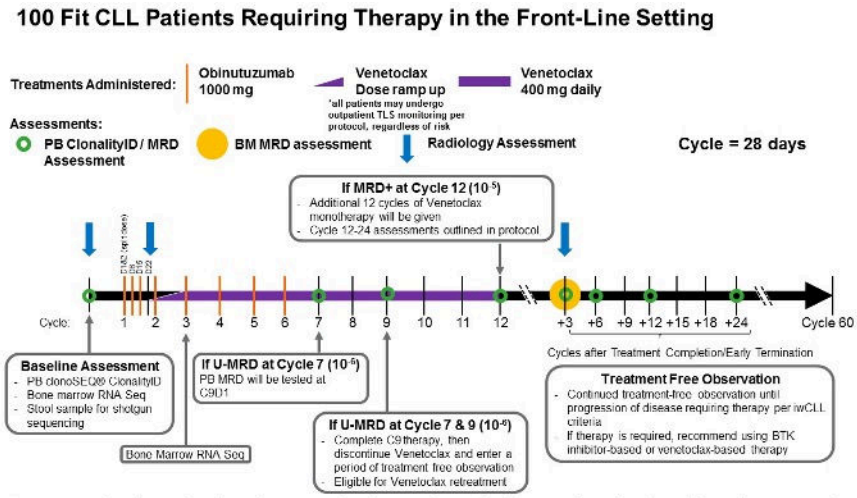

Figure 1. Study schema for this phase 2 study of minimal residual disease (MRD)-adapted front line venetoclax and obinutuzumab in fit patients with CLL (NCT04447768). TLS risk is assessed at baseline and following completion of 1 cycle of obinutuzumab (C1D22).

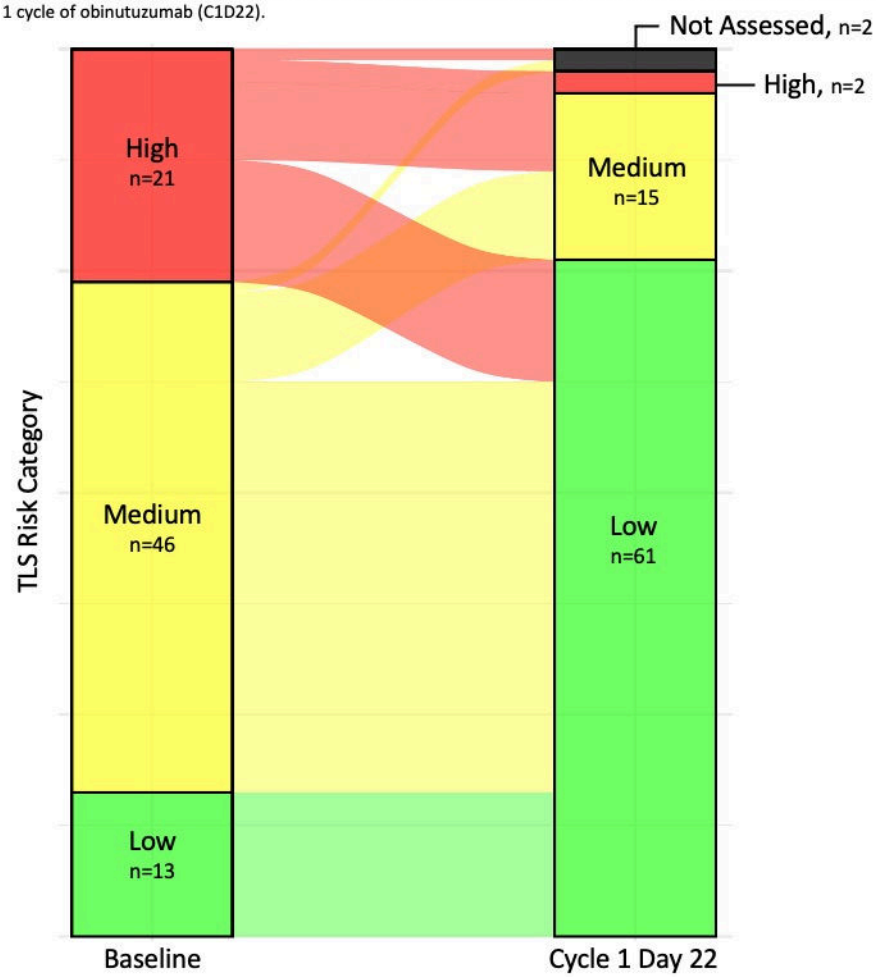

Figure 2. Change in TLS risk from baseline (prior to any therapy) to cycle 1 day 22 (following completion of cycle 1 of obinutuzumab, prior to initiation of venetoclax dose escalation). 90% of patients with high TLS risk at baseline are found to have low or medium TLS risk following 1 cycle of obinutuzumab ($p<0.001$ using McNemar's χ^2 test).

Figure 1

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