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**Phase 3b study to evaluate debulking regimens prior to initiating venetoclax therapy in untreated patients with** **chronic lymphocytic leukemia**

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**Introduction:** The Bcl-2 inhibitor venetoclax(VEN) demonstrated efficacy in chronic lymphocytic leukemia(CLL) patients. Patients with medium to high tumor burden(TB) are at greater risk for tumor lysis syndrome(TLS) and may require inpatient monitoring. We explore tumor debulking prior to outpatient VEN initiation.

**Methods:** This phase 3b trial(NCT03406156) enrolled 120 untreated adults with CLL/SLL without 17p deletion, having medium to high TB. Patients received at least 2 cycles(C) of debulking therapy (obinutuzumab[G]±bendamustine[B]), receiving additional debulking C(4 or 6 total) if low TB wasn’t achieved. Subsequently, VEN therapy was initiated using a 5-wk ramp-up schedule, as VEN+G for 5mo, then VEN monotherapy until wk53. Interim analysis was planned after 20 patients completed VEN ramp-up to assess safety. Primary endpoints evaluated reduction in TB and IWCLL response rates.

**Results:** As of 12/2/2019, 110 patients were included; 76 received G and 34 G+B for debulking. Majority were male(66%), <75yr(85%). Medium(73%) and high TB(26%) at baseline(BL) was mainly driven by increased ALC, which was ≥25 × 109/L in 85% of patients. After C2, low TB was achieved in 87%(76/87) of evaluable patients; 92%(56/61) with G and 77%(20/26) with G+B. ALC decreased to <25×109/L after C2 in all patients with BL ALC ≥25×109/L on G(59/59) and G+B(18/18). Median decrease in lymph node size was 0.5cm for G and 3cm for G+B from BL to C2 and reduced further with more C of debulking. Grade(Gr) ≥3 adverse events(AEs) were observed more often during G+B(68%) than G(38%). Gr ≥3 AEs were similar during VEN phases(VEN+G/VEN mono; G: 33%/27%, G+B: 35%/27%), but rate of VEN interruptions(G: 24%/17%, G+B: 31%/27%) and dose reductions(G: 6%/10%, G+B: 19%/18%) was higher for those debulked with G+B. AE of TLS was reported for 9/110 patients(8%) during debulking(G: 2 [clinical], G+B: 7 [5 lab/2 unclassified]) and 1/89 debulked patient(1%) with low creatinine clearance rate during VEN+G(lab).

**Conclusions:** Most patients achieved low TB at C2 of debulking with G±B prior to VEN ramp-up. AE of TLS was reported in 1 patient during VEN phase. Similar Gr ≥3 AEs were observed during VEN phases regardless of debulking agents. Debulking reduced TB and may facilitate outpatient VEN initiation.

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