LymphomaHub

CLL/SLL

ASCO 2019 | Obinutuzumab plus venetoclax is superior than combination with chlorambucil in naïve CLL with comorbidities

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On Tuesday 4th June an oral abstract session took place at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting. During that session, Abstract 7502 was presented by Kirsten Fischer, University of Cologne, Cologne, DE, on the phase III CLL14 clinical trial.

This study (NCT02242942) compared the efficacy and safety of fixed-duration venetoclax plus obinutuzumab (VenG) against treatment with chlorambucil and obinutuzumab (ClbG) in patients with naïve chronic lymphocytic leukemia (CLL) and comorbidities. The primary endpoint of this multinational, open-label, phase III trial was progression-free survival (PFS). Secondary endpoints included, minimal residual disease (MRD) in peripheral blood (PB) or bone marrow (BM) three months after treatment completion, overall survival (OS), and response rates.

Study design & baseline characteristics

- N = 432 patients with previously-untreated CLL and comorbidities, with a cumulative illness rating scale (CIRS) score > 6 and/or estimated creatine clearance (CrCl) < 70 mL/min
- Patients were 1:1 randomized to six cycles of VenG or ClbG with six additional cycles of venetoclax or chlorambucil, respectively:
  - VenG dosing:
    - Ven: administered orally in a 5-week ramp-up: 20 mg > 50 mg > 100 mg > 200 mg > 400 mg, starting at cycle 1, day 22; thereafter at 400 mg until the end of cycle 12
    - G: administered intravenously at 1000 mg on day 1 (or 100 mg day 1 and 900 mg day 2), day 8, and day 15 of cycle 1; thereafter 1000 mg on day 1 of cycles 2–6, every 28 days
  - ClbG dosing:
    - Clb: administered orally at 0.5 mg/kg on day 1 and 15 of cycles 1–12, every 28 days
    - G: same as above
  - **Table 1.** Key baseline characteristics:

Baseline characteristic	**VenG cohort** (n = 216)	**ClbG cohort** (n = 216)

Median age (years)	72	71
Binet stage:		
A	21%	20%
B	36%	37%
C	43%	43%
Median total CIRS score	9	8
Median estimated CrCl (ml/min)	65.2	67.5
Risk of tumor lysis syndrome (TLS):		
Low	13%	12%
Intermediate	64%	68%
High	22%	20%
Immunoglobulin heavy variable (*IGHV)* unmutated status	61%	59%
TP53 deletion and/or mutation	12%	12%
Deletion in 17p	9%	7%

Key results

- After a median follow-up of 29 months:
  - PFS was significantly longer in the VenG cohort when compared to ClbG (HR = 0.35; [95% CI, 0.23–0.53]; $p < 0.0001$)
  - In *IGHV* unmutated patients, treatment with VenG led to improved PFS and abrogated the inferior outcome seen with ClbG. A similar trend was seen for patients with *TP53* deletion or mutation.
  - OS was not significantly different between the two cohorts (HR = 1.24; [95% CI, 0.64–2.40]; $p = 0.52$)

- Negative MRD rates
  - At 3 months after treatment completion, MRD negativity was significantly higher with VenG than ClbG, in both PB ($p < 0.001$) and BM ($p < 0.001$):
    - VenG: 76%, PB & 57%, BM
    - ClbG: 35%, PB & 17%, BM
  - At 12 months after treatment completion, higher negative MRD rates were maintained with VenG (81%) compared to ClbG (27%)

- **Table 2**. Key response outcomes:

Response	**VenG cohort (n = 216)**	**ClbG cohort (n = 216)**	***P* value**
Overall response rate (ORR)	85%	71%	0.0007
Complete response (CR)	50%	23%	< 0.0001
Partial response (PR)	35%	48%	

Safety

- Grade 3–4 hematological toxicities occurred in:
  - VenG cohort (n = 212): 60% of patients
  - ClbG cohort (n = 216): 55% of patients
- The most common haematological toxicities observed in VenG *versus* ClbG, were:
  - Neutropenia: 53% *versus* 48%
  - Thrombocytopenia: 14% *versus* 15%
  - Anemia: 8% *versus* 7%
  - Febrile neutropenia: 5% *versus* 4%
- Grade 3–4 infections and manifestations occurred in:
  - VenG cohort (n = 212): 18% of patients
  - ClbG cohort (n = 216): 15% of patients
- Grade 5 reported deaths during study:
  - VenG cohort (n = 212): 2% (n = 5; infections and manifestations, 4 and neoplasms, 1)

    - ClbG cohort (n = 216): 2% (n = 4; infections and manifestations, 3 and neoplasms, 1)
- Grade 5 reported deaths after study completion:
    - VenG cohort (n = 212): 5% (n = 11)
    - ClbG cohort (n = 216): 2% (n = 4)

Conclusions

- Fixed duration VenG treatment led to significantly superior PFS, ORR and CR rates than ClbG treatment in patients with previously-untreated CLL with comorbidities
- A better outcome was seen for high-risk patients with unmutated *IGVH* and *TP53* mutations after VenG treatment
- The rate of MRD negativity observed in VenG treated patients is the highest so far reported in a randomized clinical trial in this patient population
- VenG showed a manageable safety profile in patients with CLL and comorbidities

References

1. Fischer K. *et al*. Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD−) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. *J Clin Oncol* 37, 2019 (suppl; abstract 7502). 2019 ASCO Annual Meeting, Chicago, Illinois, USA