LymphomaHub

DLBCL

ASCO 2019 | Smart Start phase 2 trial: Rituximab, lenalidomide & ibrutinib combination for naïve DLBCL

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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 7508 was presented by Jason Westin, MD Anderson Cancer Center, Houston, TX, USA, on the Smart Start clinical trial.[1]

Patients with diffuse large B-cell lymphoma (DLBCL) of the non-germinal center (non-GCB) molecular subtype exhibit an inferior outcome following standard chemotherapy, with < 50% being cured by R-CHOP.[2] This phase II study (NCT02636322) investigated the efficacy of rituximab, lenalidomide, and ibrutinib (RLI) combination prior to standard chemotherapy treatment, in patients with newly-diagnosed non-GCB DLBCL.

The primary objective of this open-label, single-arm, investigator-initiated trial was overall response rate (ORR) after two RLI cycles and complete response (CR) rate following two cycles RLI plus six cycles of RLI in combination with standard chemotherapy.

Study design

- N = 60 newly-diagnosed patients with non-GCB DLBCL, aged ≥18 and with Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Dosing:
  - First two treatment cycles (1–2): RLI (21-day cycles; n = 58 evaluable patients):
    - Rituximab: 375 mg/m^2 intravenously on Day 1
    - Lenalidomide: 25 mg orally on Day 1–10
    - Ibrutinib: 560 mg orally, daily
  - Next treatment cycles (3–8): RLI was combined with R-CHOP or EPOCH for six additional cycles (21-day cycles; n = 56 evaluable patients):
    - RLI: as above
    - Chemotherapy: CHOP (n = 25; 43%) or EPOCH (n = 32; 55%) standard dosing
  - In total, forty-nine patients completed the whole treatment and were evaluable for response assessment
  - **Table 1.** Key baseline characteristics:

Baseline characteristic	Total cohort (N = 60)

Median age (range)	63.5 (29–83)
Male patients	50%
International Prognostic index (IPI) score: Median 0–1 2 3–5	 3 16.7% 31.7% 51.7%
Disease stage III–IV	65%
Double expressor (*Myc, Bcl2 positive by IHC*)	54%
Double hit (*Myc, Bcl6 positive by FISH*)	2.7%
Ki-67: >80% >90%	 77% 49%

Key findings

- Patients who received <5 cycles of chemotherapy: n = 11
- **Table 2**. Key treatment outcomes:

	RLI only **(cycles 1–2; n= 58)**	**RLI + 2 chemotherapy cycles (cycles 1–4; n= 56)**	**End of treatment (cycles 1–8; n= 49)**
ORR	86%	100%	100%
CR	36%	73%	96%
Partial response (PR)	50%	27%	4%
Stable disease (SD)	7%	-	-
Progressive disease (PD)	2%	-	-
Missing response (MR)	5%	-	-

- After the first two RLI cycles:
  - Median tumor burden reduction: 81%
  - One patient who achieved CR withdrew from the study and did not receive further chemotherapy. Two years to date he is still in CR with no need for additional therapy
- At a median follow-up of 362 days:
  - Progression events: n= 3
  - Median time-to-progression (range): not reached (32–938 days)
  - Median overall survival (range): not reached (74–938 days)
  - PFS in double expressor lymphomas: 94%

Safety

- Most common Grade 3 adverse events (AEs) were:
  - Anemia
  - Febrile neutropenia
  - Thrombocytopenia
  - Rash
  - Neutropenia

- Most common any grade AEs seen in >40% of patients were:
  - Nausea
  - Peripheral sensory neuropathy
  - Diarrhea
  - Oral mucositis
- Most common Grade 4 AEs were:
  - Neutropenia
  - Thrombocytopenia
- Grade 5 events:
  - Central nervous system aspergillosis fungal infection (n = 1; due to high-dose corticosteroids and RLI combination)
    - This event led to the prohibition of concomitant corticosteroid treatment (no other similar infections occurred)
  - Febrile neutropenia (n = 1)

Conclusions

- RLI alone led to an ORR of 86%, while the addition of R-CHOP or EPOCH chemotherapy increased the ORR to 100%. These results indicate that RLI ± chemotherapy could be an effective treatment for naive non-GCB DLBCL
- RLI ± chemotherapy showed a manageable toxicity profile
- Further trials are needed to validate the use of RLI in naïve non-GCB DLBCL and explore the efficacy of more RLI cycles with less chemotherapy consolidation

References

1. Westin, J. *et al.* Smart start: Final results of rituximab, lenalidomide, and ibrutinib lead in prior to combination with chemotherapy for patients with newly diagnosed diffuse large B-cell lymphoma. Abstract #7508. 2019 ASCO Annual Meeting, Chicago, Illinois, USA
2. Sehn, L.H. *et al.* 2015. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood* 125, 22–32. https://doi.org/10.1182/blood-2014-05-577189