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Tafasitamab Plus Lenalidomide Versus Pola-BR, R2, and CAR-T in Nontransplant-Eligible Relapsed/Refractory DLBCL: A Post Hoc Analysis of the RE-MIND2 Study Comparing Multiple Cohort-Balancing Approaches

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Introduction

- Tafasitamab (TAFA) is a humanized anti-CD19 monoclonal antibody approved for use in combination with lenalidomide (LEN) in the treatment of nontransplant-eligible (NTE) patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). TAFA+LEN is included in the National Comprehensive Cancer Network (NCCN) treatment guidelines based on the results of the single-arm, phase 2 L-MIND study[1] (NCT02399085)
  - In L-MIND, TAFA+LEN demonstrated efficacy in NTE patients with R/R DLBCL, with an objective response rate of 60% (95% confidence interval [CI], 48-71) after a median follow-up of 13.2 months[1]
  - Outcomes were sustained over ≥35 months' follow-up, as reflected in an objective response rate of 57.5%, median duration of response of 43.9 months (95% CI, 26.1-not reached), median progression-free survival of 11.6 months (95% CI, 6.3-45.7), and median overall survival (OS) of 33.5 months (95% CI, 18.3-not reached)[2]
- In the absence of head-to-head clinical studies directly comparing TAFA+LEN with other therapies routinely used for the treatment of R/R DLBCL, indirect treatment comparisons are required to evaluate the relative efficacy of TAFA+LEN
  - The retrospective observational RE-MIND study, which compared a historical matched control of LEN monotherapy with the L-MIND dataset, indicated improved outcomes with TAFA+LEN compared with LEN alone[3]
  - In a matching-adjusted indirect comparison analysis, OS and progression-free survival outcomes with TAFA+LEN in the L-MIND study were better than in comparator studies of polatuzumab vedotin + bendamustine + rituximab (Pola+BR) and BR[4]
- The retrospective observational cohort study, RE-MIND2 (NCT04697160), compared patient outcomes from L-MIND with those of matched patients treated with NCCN-/European Society for Medical Oncology (ESMO)-recommended therapies[5,6]
  - Here we report a post hoc analysis of RE-MIND2 comparing multiple cohort-balancing approaches, using 2 baseline prognostic factor and/or treatment effect–modifier sets[5,6]

Objectives

- To investigate whether there is an OS benefit of TAFA+LEN vs Pola-BR, rituximab + LEN (R2), and CD19 chimeric antigen receptor T-cell (CAR-T) therapy in RE-MIND2
- To compare multiple cohort-balancing approaches and their impact on the estimation of the OS benefit of TAFA+LEN vs Pola-BR, R2, and CD19 CAR-T in RE-MIND2

Methods

Patient Selection

- RE-MIND2 screened electronic medical records of patients diagnosed with DLBCL (2010-2020) from study sites across Europe, North America, and the Asia-Pacific region
- Patients were eligible for RE-MIND2 if they were ≥18 years of age with histologically confirmed DLBCL and had received ≥2 prior systemic therapies for DLBCL (including ≥1 anti-CD20 therapy)
- Patient cohorts were generated for the NCCN-/ESMO-listed treatments of interest, including Pola-BR, R2, and CAR-T

Post Hoc Analysis

- To address differences in baseline demographic and clinical characteristics between the L-MIND and RE-MIND2 treatment cohorts, propensity score methods based on prespecified sets of either 6 or 9 baseline prognostic factors and/or treatment effect modifiers (covariates) **(Table 1)** were estimated
- Propensity score methods employed to balance covariates across treatment cohorts comprised inverse probability of treatment weighting (IPTW) and 1:1 nearest neighbor (1:1 NN) matching (see additional details in **Supplemental Methods**)
- For IPTW, probability weights were assigned to both cohorts, with probability weight in the L-MIND cohort set at 1, and probability weight in the RE-MIND2 cohort (denoted as $w(c)$) estimated from $w(c)=p_i/(1-p_i)$, where p_i represents individual propensity score, obtained using the abovementioned baseline covariates in a logistic regression model
  - Patients with probability weight >30 were excluded from the analysis
  - To provide further balance, a sensitivity analysis with propensity score weighting using overlap weights[7] was applied
- For propensity score matching, if the number of eligible patients for matching was smaller in the RE-MIND2 cohort than in the L-MIND cohort, 1:1 NN matching was performed using the RE-MIND2 cohort in a random ordered fashion for selecting the closest matching patient from the L-MIND cohort in terms of estimated propensity score
- Multiple imputation (MI) was applied to reduce bias caused by missing data
  - Estimated propensity scores were imputed for prespecified treatments separately, using the 2 sets of covariates
  - Following imputation, IPTW and 1:1 NN matching were performed to balance cohort covariates
- For each comparator treatment, 5 cohort-balancing methods were used:
  - I. 1:1 NN matching with 9 covariates with MI
  - II. 1:1 NN matching with 6 covariates, excluding patients with missing values
  - III. 1:1 NN matching with 6 covariates with MI
  - IV. IPTW with 9 covariates, excluding patients with missing values
  - V. IPTW with 9 covariates with MI
- Cohort balance was assessed from the standardized mean difference (SMD) of the individual covariates after matching/IPTW of estimated propensity scores in each treatment cohort. Balance was assumed if the SMD was <0.2
- Cohort balance under MI was assessed using the maximized standardized difference (MSD) and averaged standardized difference (ASD) of individual covariates using the method of Frank et al.[8] Balance was assumed if, after weighting, the MSD or ASD was <0.2
- For cohort-balancing methods using NN 1:1 matching, OS hazard ratios (HRs) and 95% CIs were estimated using the Cox proportional hazards model with cohort status as covariate
  - Difference in OS between the cohorts was compared using the 2-sided log-rank test
  - For balancing using overlap weights on estimate propensity scores, OS analyses were weighted by the selected balancing weight to estimate treatment effect

Table 1. Groups of Covariates Used to Balance Cohorts

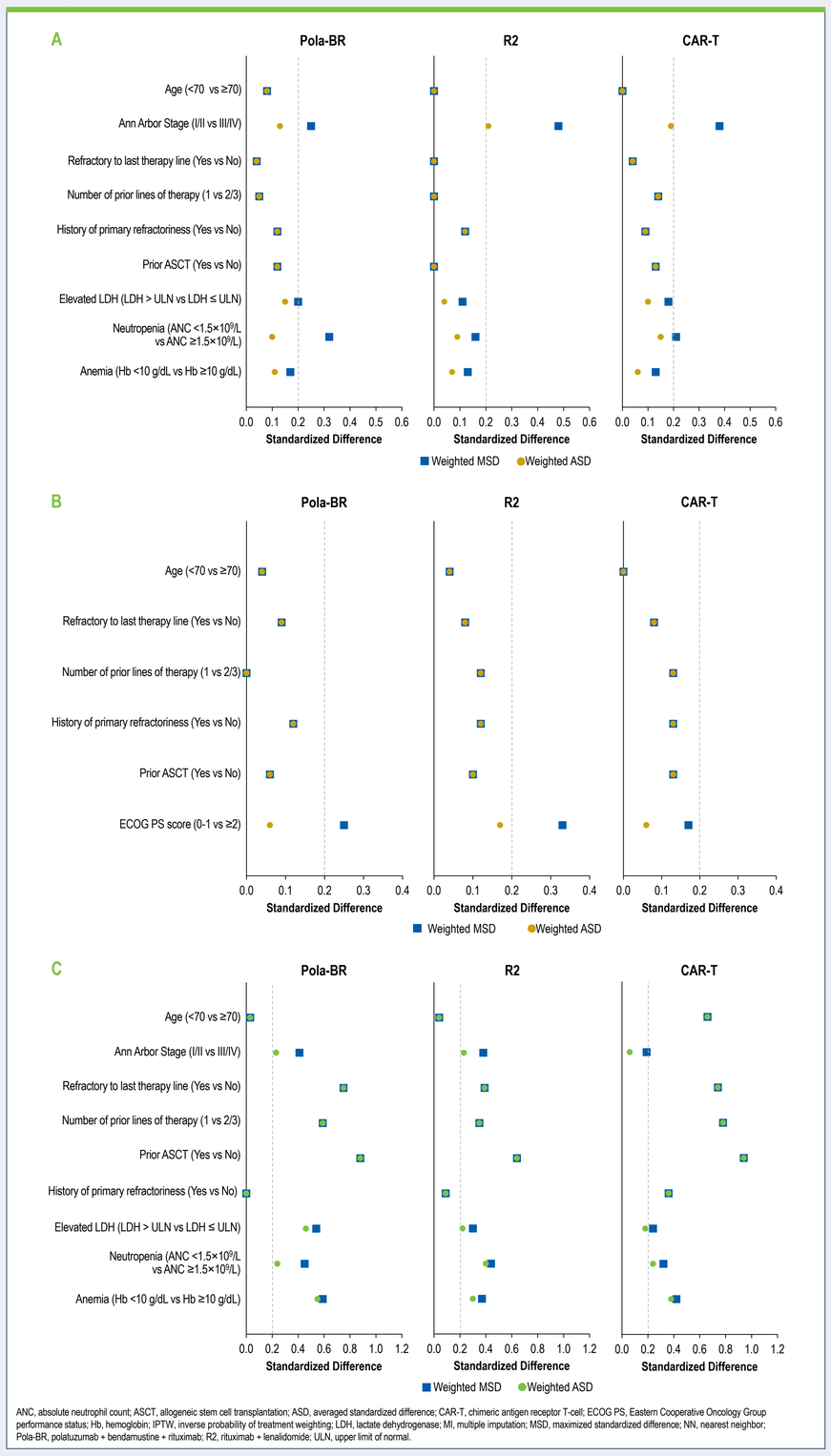
9-Covariate Set	6-Covariate Set
Age (as categorical variable with subgroups <70 vs ≥70 years of age)	Number of prior lines of therapy (1 vs 2/3)
Ann Arbor Stage (I/II vs III/IV)	Refractoriness to last therapy line (Yes vs No)
Refractoriness to last therapy line (Yes vs No)	History of primary refractoriness (Yes vs No)
Number of prior lines of therapy (1 vs 2/3)	ECOG PS score (0-1 vs ≥2)
History of primary refractoriness (Yes vs No)	Prior ASCT (Yes vs No)
Prior ASCT (Yes vs No)	Age (as categorical variable with subgroups <70 vs ≥70 years of age)
Elevated LDH (LDH > ULN vs LDH ≤ ULN)	
Neutropenia (ANC <1.5×10⁹/L vs ANC ≥1.5×10⁹/L)	
Anemia (Hb <10 g/dL vs Hb ≥10 g/dL)	

ANC, absolute neutrophil count; ASCT, allogeneic stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Results

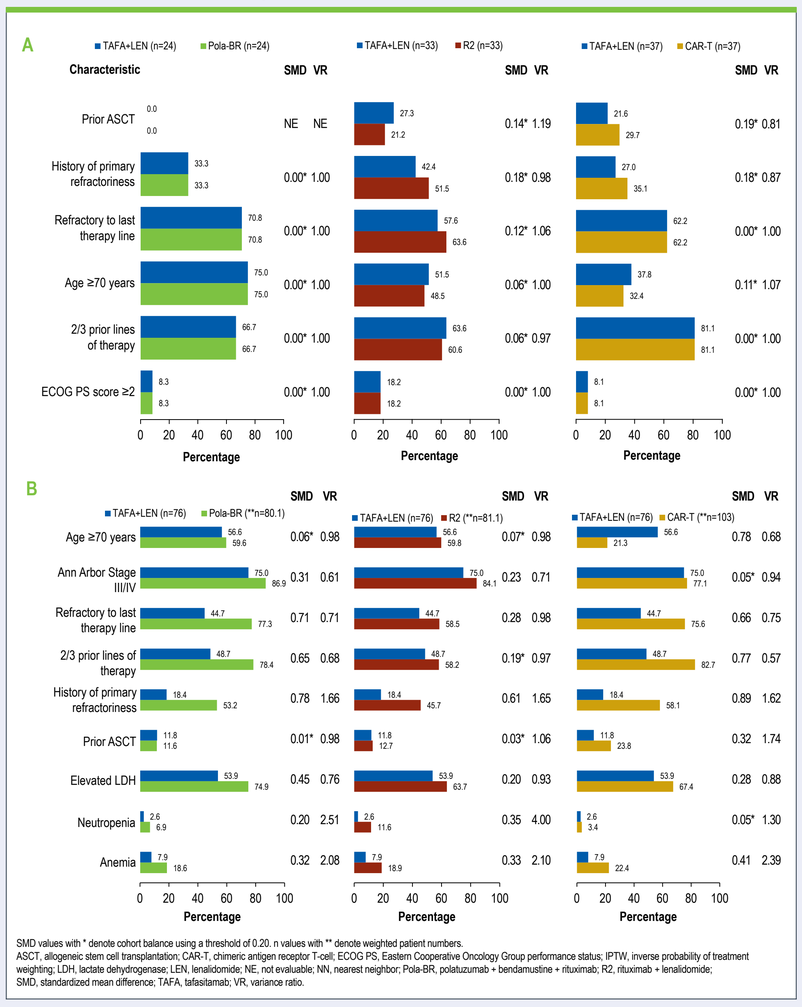
- There were 76 patients from L-MIND eligible for analysis for TAFA+LEN, and 92, 92, and 140 from RE-MIND2 for Pola-BR, R2, and CAR-T, respectively
- Analyses based on 6- and 9-covariate 1:1 NN matching achieved greater cohort balance compared with analyses based on IPTW
- Balance summary of covariates used for matching and weighting are shown in **Figure 1** and **Figure 2**; for analyses relying on MI, only MSD and ASD are reported
  - 1:1 NN matching based on 6 covariates resulted in the best cohort balance on the included covariates
  - 1:1 NN matching based on 9 covariates with MI achieved a high degree of cohort balance on all covariates except for Ann Arbor Stage
- OS HRs for the comparison of TAFA+LEN with each of the 3 comparator treatments using all 5 cohort-balancing methods are shown in **Table 2**
- Similar results were obtained with method I 1:1 NN matching on 6 complete covariates and method V 1:1 NN matching on 9 covariates with MI, across each comparator
- **Figure 3** and **Supplemental Figure 1** show representative Kaplan-Meier curves for OS for TAFA+LEN and each of the comparator treatments using all 5 cohort-balancing methods
- OS was improved with TAFA+LEN compared with Pola-BR using 5 of 5 cohort-balancing methods, and in 4 of 5 (methods I, II, IV, V), it was statistically significantly improved **(Table 2, Figure 3, Supplemental Figure 1)**
- OS was statistically significantly improved with TAFA+LEN compared with R2 in all 5 analyses **(Table 2, Figure 3, Supplemental Figure 1)**
- OS was numerically improved with TAFA+LEN compared with CAR-T using all 5 cohort-balancing methods, but no analysis showed a statistically significant difference between the treatments **(Table 2, Figure 3, Supplemental Figure 1)**

Figure 1. Covariate Balance for (A) 1:1 NN Matching With MI in 9-Covariate Matched Analysis Set; (B) 1:1 NN Matching With MI in 6-Covariate Matched Analysis Set; (C) IPTW Analyses With MI in 9-Covariate Full Analysis Set



ANC, absolute neutrophil count; ASCT, allogeneic stem cell transplantation; ASD, averaged standardized difference; CAR-T, chimeric antigen receptor T-cell; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase; MI, multiple imputation; MSD, maximized standardized difference; NN, nearest neighbor; Pola-BR, polatuzumab + bendamustine + rituximab; R2, rituximab + lenalidomide; ULN, upper limit of normal.

Figure 2. Weighted Baseline Characteristic Balance, SMD, and VR for (A) 1:1 NN Matching Analyses Based on Complete Covariates in 6-Covariate Matched Analysis Set and (B) IPTW Analyses Based on Complete Covariates in 9-Covariate Full Analysis Set



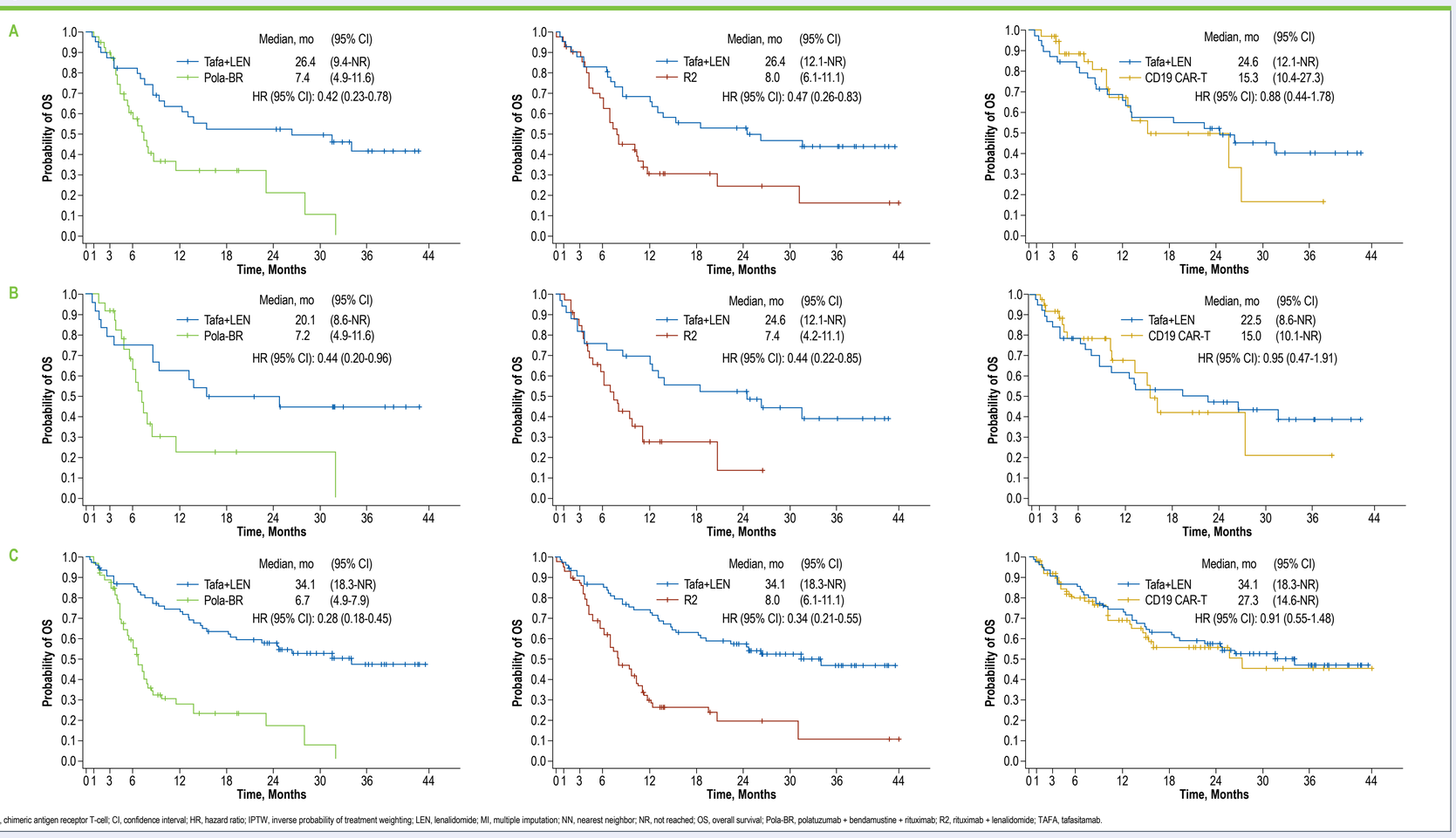
SMD values with * denote cohort balance using a threshold of 0.20. n values with ** denote weighted patient numbers.
ASCT, allogeneic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; ECOG PS, Eastern Cooperative Oncology Group performance status; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase; LEN, lenalidomide; MI, multiple imputation; NE, not evaluable; NN, nearest neighbor; Pola-BR, polatuzumab + bendamustine + rituximab; R2, rituximab + lenalidomide; SMD, standardized mean difference; TAFA, tafasitamab; VR, variance ratio.

Table 2. OS HRs for Cohort-Balancing Methods for TAFA+LEN vs Pola-BR, R2, and CAR-T

TAFA+LEN vs Comparator	Cohort-Balancing Method I: 1:1 NN Matching With MI 9-Covariate Set	II: 1:1 NN Matching 6-Covariate Set	III: 1:1 NN Matching With MI 6-Covariate Set	IV: IPTW 9-Covariate Set	V: IPTW With MI 9-Covariate Set
Pola-BR	n=39	n=24	n=39	n=36	n=63
HR (95% CI)	**0.42 (0.23-0.78)**	**0.44 (0.20-0.96)**	**0.35 (0.19-0.66)**	0.50 (0.20-1.25)	**0.28 (0.18-0.45)**
P value	**0.0061**	**0.0381**	**0.0012**	0.1389	**<0.0001**
R2	n=41	n=33	n=39	n=35	n=60
HR (95% CI)	**0.47 (0.26-0.83)**	**0.44 (0.22-0.85)**	**0.42 (0.23-0.76)**	**0.35 (0.17-0.73)**	**0.34 (0.21-0.55)**
P value	**0.0093**	**0.0143**	**0.0042**	**0.0050**	**<0.0001**
CAR-T	n=39	n=37	n=40	n=50	n=95
HR (95% CI)	0.88 (0.44-1.78)	0.95 (0.48-1.91)	0.98 (0.48-2.03)	0.52 (0.25-1.07)	0.91 (0.55-1.48)
P value	0.7302	0.8915	0.9635	0.0735	0.6934

Statistically significant values are shown in bold.
CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; MI, multiple imputation; NN, nearest neighbor; OS, overall survival; Pola-BR, polatuzumab + bendamustine + rituximab; R2, rituximab + lenalidomide; TAFA, tafasitamab.

Figure 3. Kaplan-Meier Plots of OS for TAFA+LEN and Pola-BR, CAR-T, R2 Using Cohort-Balancing Methods: (A) 1:1 NN Matching With 9 Covariates With MI; (B) 1:1 NN Matching With 6 Covariates, Excluding Patients With Missing Values; (C) IPTW With 9 Covariates With MI



CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; MI, multiple imputation; NN, nearest neighbor; NR, not reached; OS, overall survival; Pola-BR, polatuzumab + bendamustine + rituximab; R2, rituximab + lenalidomide; TAFA, tafasitamab.

Conclusions

- **Different combinations of prognostic covariates and multiple cohort-balancing approaches consistently showed TAFA+LEN to be associated with better OS outcomes compared with the NCCN-/ESMO-listed treatment regimens of interest for patients with NTE R/R DLBCL**
  - **TAFA+LEN was associated with better OS outcomes than Pola-BR and R2, and similar OS outcomes to CAR-T therapy**
- **In general, results associated with IPTW were affected by larger uncertainty and higher risk of bias compared with those associated with 1:1 NN matching**
- **Limitations owing to sample size, retrospective comparator data, and known methodological features of indirect comparisons warrant further investigation**

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Disclosures

About Tafasitamab: Tafasitamab is a humanized Fc-modified cytolytic CD19-targeting monoclonal antibody. In 2010, MorphoSys licensed exclusive worldwide rights to develop and commercialize tafasitamab from Xencor, Inc. Tafasitamab incorporates an XmAb® engineered Fc domain, which mediates B-cell lysis through apoptosis and immune effector mechanism including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In January 2020, MorphoSys and Incyte entered into a collaboration and licensing agreement to further develop and commercialize tafasitamab globally. Following accelerated approval by the US Food and Drug Administration in July 2020, tafasitamab is being co-commercialized by MorphoSys and Incyte in the United States. Incyte has exclusive commercialization rights outside the United States. XmAb® is a trademark of Xencor, Inc.

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