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Comparative effectiveness of immunotherapy alone or with chemotherapy as first-line treatment for marginal zone lymphoma

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Running heads: Outcomes of immunotherapy and chemotherapy in MZL

Author contributions: AJO, TAO, DC and NE designed the study; AJO conducted the statistical analyses and drafted the paper; all authors contributed to the acquisition and interpretation of the data, approved the final version, and agree to be accountable for all aspects of the work.

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Marginal zone lymphoma (MZL) is a heterogeneous indolent B-cell malignancy comprising splenic (SMZL), nodal (NMZL), and extranodal (EMZL) subtypes. (1, 2) Owing to its low incidence and variable presentation, prospective randomized data are limited. Most NMZL regimens mirror those for follicular lymphoma, while localized EMZL is frequently treated with local therapies or antibiotics for *Helicobacter pylori*-associated gastric disease. The IELSG-19 trial remains the only histology-specific phase 3 study of systemic first-line therapy in MZL, demonstrating longer progression-free survival (PFS) with rituximab plus chlorambucil versus either agent alone, but no overall survival (OS) benefit.(3)

Following evidence from trials showing superior PFS with bendamustine-rituximab (BR) compared with cyclophosphamide-based combinations in indolent lymphomas, BR has largely replaced other chemoimmunotherapy regimens in the United States.(4, 5) Small series report 5-year PFS rates of 80–87% across MZL subtypes, yet no study has demonstrated an OS or quality-of-life advantage over rituximab monotherapy, which can yield durable remissions with less toxicity.(6-8) Given bendamustine's prolonged immunosuppression and the indolent nature of relapsed MZL, the comparative survival impact of BR versus rituximab alone warrants clarification.

We evaluated PFS and OS using two large real-world datasets: the U.S. National Cancer Data Base (NCDB), which is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society,(9) and a multi-institutional MZL-real world data (MZL-RWD) retrospective cohort, applying causal-inference methods to minimize treatment-selection bias.(10)

The NCDB 2022 file identified adults (≥18 years) diagnosed with MZL from 2013–2018. This period captures the introduction of rituximab-specific coding and ≥5 years of follow-up. NCDB variables include demographics, stage, B symptoms, and initial treatment categorized as immunotherapy (principally, rituximab) or cytotoxic chemotherapy, without drug-level detail (**Supplemental Table S1**). We excluded patients untreated at the reporting facility, lacking histologic confirmation, not receiving immunotherapy, or with missing diagnosis-to-treatment interval.

The MZL-RWD dataset comprised 878 patients treated at 10 U.S. centers (2010–2020) with detailed clinicopathologic, laboratory, treatment, and survival data,(11, 12) of whom 541 received first-line rituximab or BR. Missing values were imputed by mean substitution. All data

were de-identified and analyses approved by Institutional Review Boards; there was no linkage between datasets.

Analyses were performed separately for NCDB and MZL-RWD using a previously described framework.(4, 13) A logistic model produced propensity scores including all variables from the treatment selection mode and interaction between age (with restricted cubic spline in the NCDB data) and MZL subtype. Patients were matched within a 10% caliper of the propensity-score standard deviation (1:1 matching) in NCDB and inverse-probability-of-treatment weighting [IPTW] in MZL-RWD (validated by 1:1 matching). Covariate balance was defined as standardized difference of means (SDM) <0.1.

Outcomes were OS (NCDB) and PFS plus OS (MZL-RWD), analyzed by Cox models with robust standard errors. Results are reported as hazard ratios (HR) with 95% confidence intervals (95%CI). Double-robust models and stratification by treating hospital confirmed stability. Sensitivity analyses addressed potential unmeasured confounding by: (1) trimming patients with extreme propensity scores (≤25%) and (2) simulating an unmeasured confounder (HR=2.0) with varying prevalence differentials.(14)

In the NCDB dataset (N=8,110), 58% of patients received immunotherapy alone and 42% immunochemotherapy. Median follow-up was 3.9 years. Five-year OS was 75.8% (95%CI: 74.6–76.9), highest for EMZL (79.3%), and lower for NMZL (73.0%) and SMZL (74.0%; **Fig. 1A/B**). Immunochemotherapy recipients were younger, more often male, and more likely to have NMZL, advanced stage, or B symptoms (**Supplemental Table S2**). Treatment proportions remained stable (~60% immunotherapy alone) from 2013–2018 (**Fig. 1C**). Facility-level variation was significant ($P<10^{-}$□) but unrelated to academic versus community status (**Fig. 1D**). EMZL of gastric, pulmonary, cutaneous, salivary, or ocular origin was most often treated with rituximab monotherapy, whereas CNS EMZL most frequently received immunochemotherapy (**Fig. 1E**). Among chemotherapy recipients, 68% had single-agent and 30% multi-agent regimens, consistent with previously reported predominant BR use.(4)

Propensity matching yielded 2,534 pairs with excellent covariate balance (mean SDM 0.018; **Fig. 2A/B/C**). OS did not differ between groups (HR 1.07; 95%CI: 0.94–1.21; *P*=0.30; **Fig. 2D**). Five-year OS was 76.6% (95%CI: 74.4–78.6) for immunotherapy and 76.2% (95%CI: 74.1–78.2) for immunochemotherapy. Results were consistent in hospital-stratified (HR 1.10) and doubly-robust (HR 1.08) models. Subgroup analyses showed no heterogeneity by age or

propensity-score quartile, and low likelihood of significant residual unmeasured confounding, though in SMZL immunochemotherapy use correlated with inferior OS (**Fig. 2E/F**). Histology-specific models confirmed no OS difference for EMZL (HR 1.06; 95%CI: 0.85–1.31) or NMZL (HR 1.08; 95%CI: 0.91–1.28), whereas the SMZL disadvantage (HR 1.42; 95%CI: 1.04–1.96) appeared to be sensitive to moderate simulated confounding. Trimming tails of the propensity-score distribution did not materially alter results (data not shown).

From the MZL-RWD cohort, we selected 355 patients who received rituximab and 186 who received BR (total N=541; **Fig. 3A**). Overall, in the MZL-RWD study, immunochemotherapy consisted of BR in 75% and cyclophosphamide-based regimens in 25%. Median follow-up was 4.6 years. Median PFS was 5.8 years (95%CI: 4.7–7.1); 5-year OS was 86.5% (95%CI: 82.7–89.6). Unadjusted analyses showed longer PFS and OS with BR, but recipients were younger and had higher stage and LDH (**Supplemental Table S3**). Rituximab use predominated in SMZL (74%) and EMZL (69%). Histologic transformation occurred in 2.8% of rituximab and 4.3% of BR recipients.

The IPTW model balanced all measured covariates (mean SDM 0.022; **Fig. 3A/B**). PFS was significantly superior with BR (HR 0.57; 95%CI: 0.40–0.81; *P*=0.0018), yielding 5-year PFS 66.3% vs 48.7% (**Fig. 3C**). Results remained robust in hospital-stratified and double-robust analyses. No heterogeneity by subtype was observed (**Fig. 3D**), and simulated confounding required ≥30% imbalance to nullify significance (**Fig. 3E**). OS did not differ (HR 0.86; 95%CI: 0.46–1.64; P=0.65; **Fig. 3F**); 5-year OS was 86.2% (BR) vs 87.2% (rituximab). Subset analyses by age, subtype, or propensity quintile were concordant (data not shown). SMZL showed a nonsignificant trend toward worse OS (HR 1.50; 95%CI: 0.51–4.44). Confirmatory 1:1 matching (N = 314) produced similar findings—better PFS with BR (HR 0.50; 95%CI: 0.34–0.73) but no OS difference (HR 0.82; 95%CI: 0.40–1.68). Results were insensitive to alternative missing data handling strategies (data not shown).

Across two complementary real-world datasets, first-line immunochemotherapy and rituximab monotherapy produced comparable OS in MZL, though BR prolonged PFS by roughly 15% at 5 years. These results mirror IELSG-19 trial data, which found longer PFS but no OS benefit for rituximab-chlorambucil versus rituximab monotherapy.(3)

In MZL, where relapses are often indolent and asymptomatic, PFS may not translate into meaningful survival or quality-of-life gains. Demonstrating OS improvement is inherently

difficult given prolonged post-relapse survival and availability of effective retreatment options. Our findings reinforce that BR's toxicity profile—prolonged cytopenias, immunosuppression, and potential for secondary myeloid malignancies—should be weighed against PFS extension. Infectious complications in prior studies reached 13%, including 4% herpes zoster, prompting prophylaxis recommendations.(6) Risks are heightened in older patients and possibly in SMZL, as BR showed better outcomes in EMZL (7-year PFS of 93% in the GELTAMO trial) than in SMZL (5-year PFS of 83% in the BRISMA/IELSG36 trial), where BR induced significant infectious toxicity.(7, 8) Rituximab maintenance or retreatment can prolong PFS, potentially reducing the need for upfront chemotherapy.

The concordance between NCDB (nationwide coverage, limited clinical detail) and MZL-RWD (clinically rich, multi-center) supports external validity. The apparent OS disadvantage of immunochemotherapy in SMZL should be interpreted with caution, as it was not reproduced in MZL-RWD and may reflect unmeasured confounding. Observed PFS benefit with BR was similar to phase 2 trial estimates (66% 5-year PFS in this study vs ~80% in trials), suggesting real-world outcomes may modestly underperform trial benchmarks due to older, less selected populations.

Study limitations include lack of toxicity, quality-of-life data, and causes of death, and incomplete variable coverage compared with MZL prognostic scores.(15) It was also not possible to account for patient preferences for treatment, use of antibiotic therapy for EMZL, or underlying specific comorbidities and frailty. Central pathology review is a critical component of clinical trial approach, but it is not conducted in routine clinical practice, where some degree of histologic misclassification is expected. NCDB lacked treatment specifics, though proportions mirrored contemporary U.S. practice with predominant BR use and exceptionally rare use of chlorambucil.(4) We did not analyze maintenance rituximab or variable bendamustine dosing, as such post-treatment factors would introduce immortal-time bias. An international perspective from countries where the treatment selection process may differ would be of additional value.

In two independent, methodologically robust real-world cohorts, BR achieved longer PFS but no OS advantage over rituximab monotherapy in first-line treatment of MZL. Given similar survival and greater toxicity with chemotherapy, treatment selection should incorporate patient preferences regarding quality of life, tolerance for treatment risks and burden. Rituximab

monotherapy remains a reasonable first-line standard and a platform for future combinations with targeted or biologic agents.

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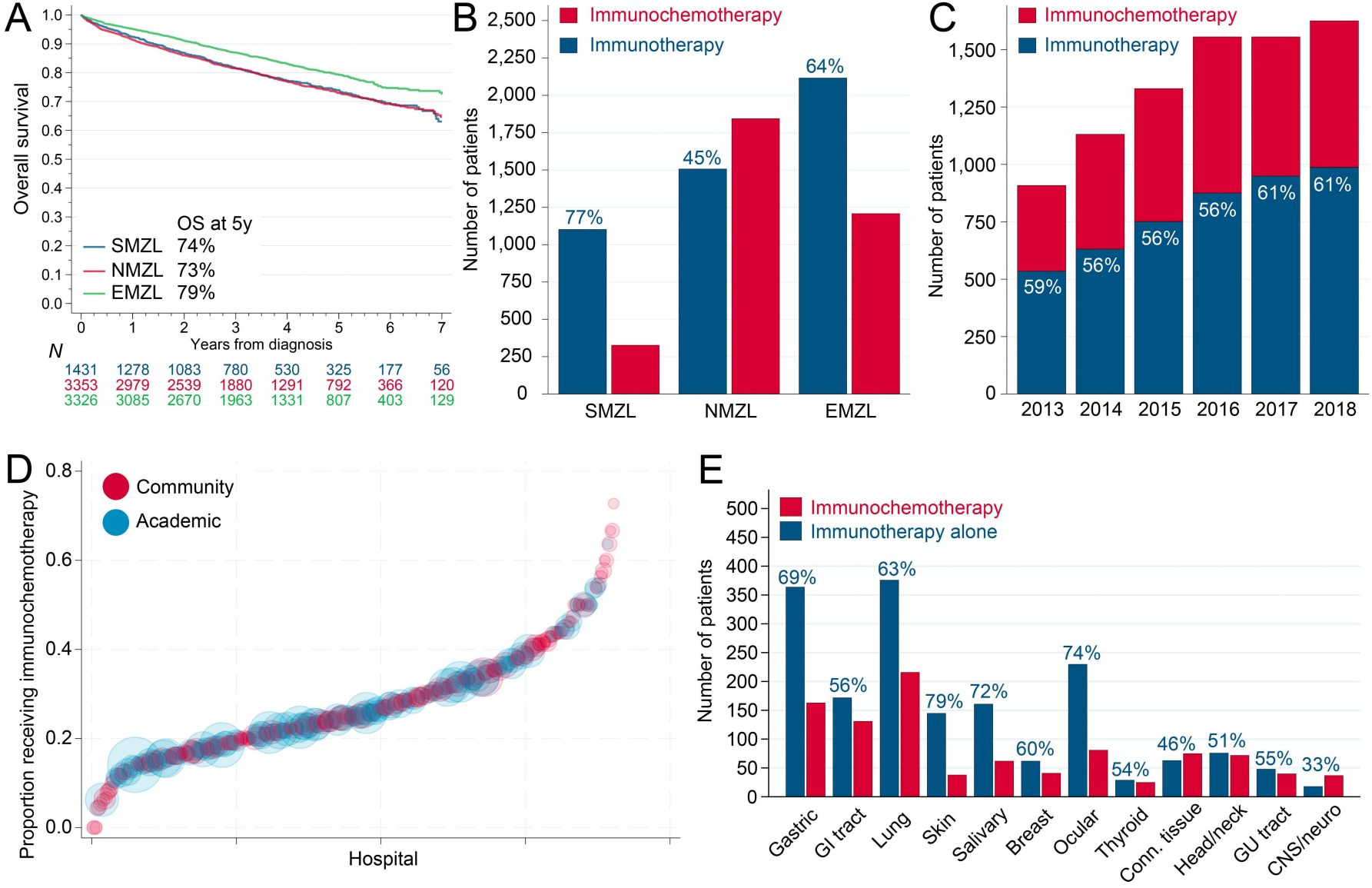
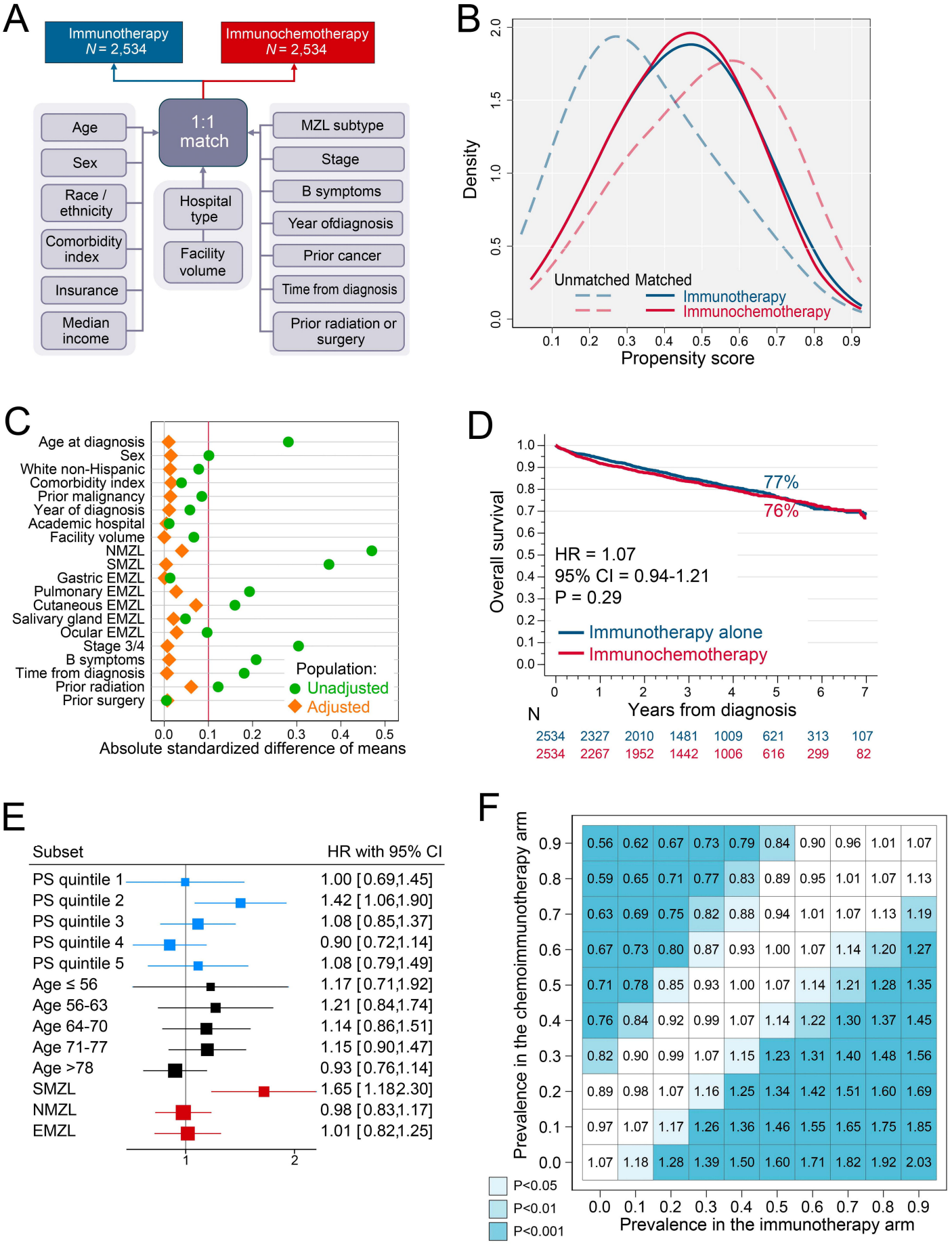
Figure 1. **Treatments and outcomes of MZL in the NCDB data, 2013-2018: (A)** OS of patients, stratified by MZL histology; **(B)** use of immunochemotherapy or immunotherapy alone in MZL histologic subtypes (percent of patients with each histology receiving immunotherapy is listed); **(C)** use of immunochemotherapy and immunotherapy in each calendar year (percent of patients receiving immunotherapy is listed); **(D)** Variation in the relative use of immunochemotherapy (versus immunotherapy) in each reporting hospital; the size of the circle corresponds to the number of reported MZL cases from each hospital; facilities are ranked according to the increasing proportion of patients treated with combination immunochemotherapy, and only facilities reporting at least 6 MZL cases are included; (E) Number of patients with EMZL of specific primary anatomic locations receiving immunochemotherapy or immunotherapy alone.

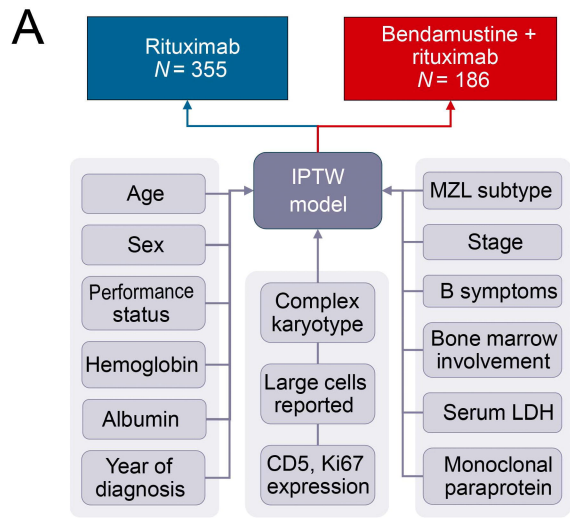
Figure 2. **Analysis of the NCDB dataset: (A)** variables used for 1:1 propensity score matching, the final propensity score model included all variables listed, with age and time from diagnosis modeled using restricted cubic splines, and with an interaction between age and MZL subtype; **(B)** distribution of the propensity score before and after matching; **(C)** absolute standardized differences of means for the main confounders included in the propensity score model; insurance categories and median income omitted but were adequately balanced (maximum SDM 0.021); **(D)** OS in the matched cohort comparing patients treated with immunotherapy alone or with combination immunochemotherapy; OS at 5 years are listed; **(E)** subset analysis evaluating heterogeneity of OS outcome according to propensity score (PS) quintile, age quintile, or MZL histology; **(F)** sensitivity analysis investigating change in the model HR and statistical significance (denoted by shading) in models additionally adjusting for a putative unobserved confounder associated with a HR of 2.0, while varying its prevalence in both study arms.

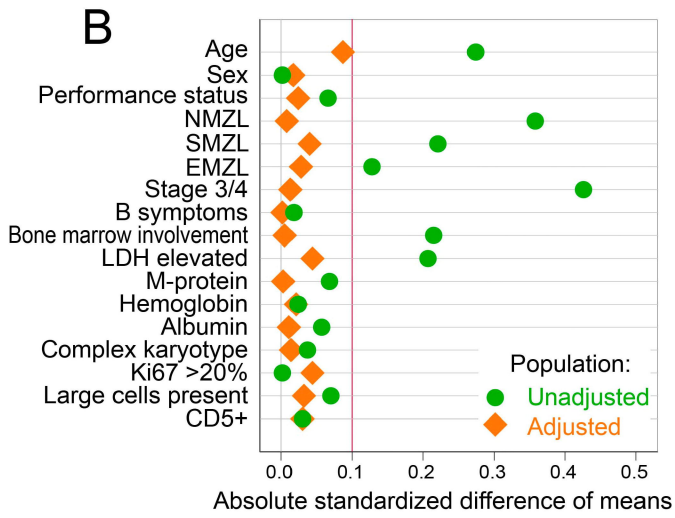
Figure 3. Analysis of the MZL-RWD dataset: (A) variables used for IPTW propensity score model; the final propensity score model included all variables listed, and an interaction between age and MZL subtype; **(B)** absolute standardized differences of means for the main confounders included in the propensity score model; **(C)** PFS in the adjusted cohort comparing patients treated with rituximab or BR; PFS estimates at 5 years are listed; **(D)** subset analysis evaluating heterogeneity of the PFS outcome according to propensity score (PS) quintile, age quintile, or MZL histology; **(E)** sensitivity analysis investigating change in the model HR and statistical significance (denoted by shading) in models additionally adjusting for a putative

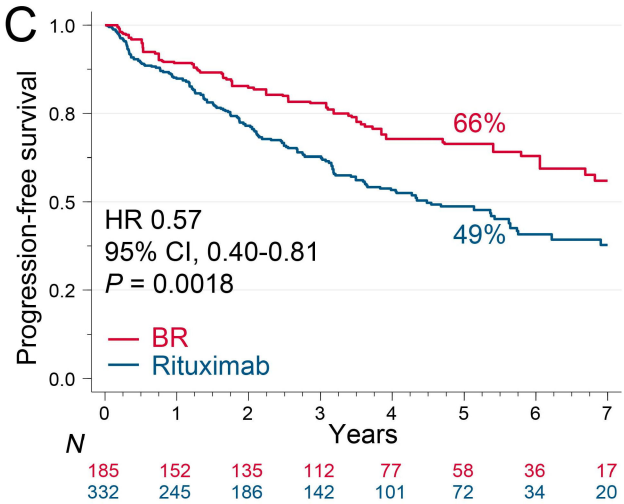
unobserved confounder associated with a HR of 2.0 while varying its prevalence in both study arms; **(F)** OS in the adjusted cohort comparing patients treated with rituximab or BR; OS estimates at 5 years are listed.

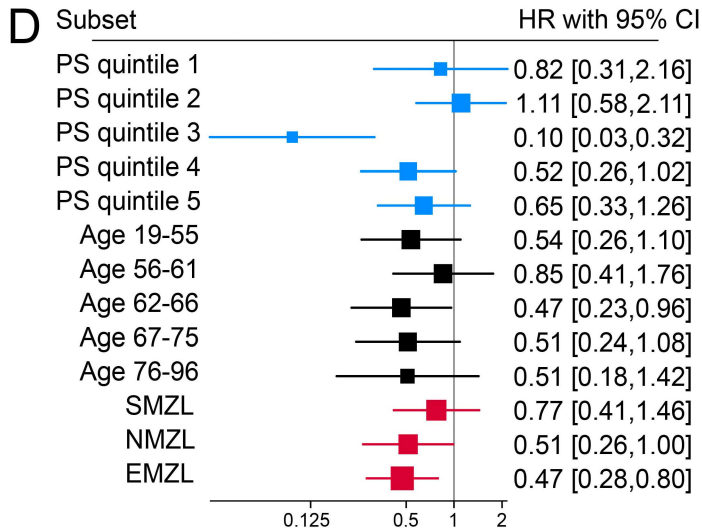

A
Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
OS at 5y
SMZL 74%
NMZL 73%
EMZL 79%
0 1 2 3 4 5 6 7
Years from diagnosis
N
1431 1278 1083 780 530 325 177 56
3353 2979 2539 1880 1291 792 366 120
3326 3085 2670 1963 1331 807 403 129
B
Immunochemotherapy
Immunotherapy
Number of patients
2,500
2,250
2,000
1,750
1,500
1,250
1,000
750
500
250
0
77%
45%
64%
SMZL
NMZL
EMZL
C
Immunochemotherapy
Immunotherapy
Number of patients
1,500
1,250
1,000
750
500
250
0
59%
56%
56%
56%
61%
61%
2013
2014
2015
2016
2017
2018
D
Community
Academic
Proportion receiving immunochemotherapy
0.8
0.6
0.4
0.2
0.0
Hospital
E
Immunochemotherapy
Immunotherapy alone
Number of patients
500
450
400
350
300
250
200
150
100
50
0
69%
56%
63%
79%
72%
60%
74%
54%
46%
51%
55%
33%
Gastric
GI tract
Lung
Skin
Salivary
Breast
Ocular
Thyroid
Conn. tissue
Head/neck
GU tract
CNS/neuro

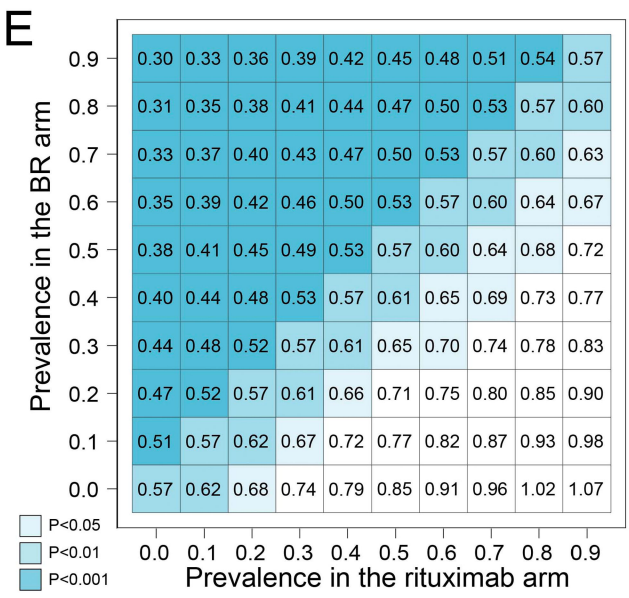

A
Immunotherapy N = 2,534
Immunochemotherapy N = 2,534
1:1 match
Age
Sex
Race / ethnicity
Comorbidity index
Insurance
Median income
Hospital type
Facility volume
MZL subtype
Stage
B symptoms
Year ofdiagnosis
Prior cancer
Time from diagnosis
Prior radiation or surgery
B
Density
Unmatched Matched
Immunotherapy
Immunochemotherapy
Propensity score
C
Age at diagnosis
Sex
White non-Hispanic
Comorbidity index
Prior malignancy
Year of diagnosis
Academic hospital
Facility volume
NMZL
SMZL
Gastric EMZL
Pulmonary EMZL
Cutaneous EMZL
Salivary gland EMZL
Ocular EMZL
Stage 3/4
B symptoms
Time from diagnosis
Prior radiation
Prior surgery
Population:
Unadjusted
Adjusted
Absolute standardized difference of means
D
Overall survival
77%
76%
HR = 1.07
95% CI = 0.94-1.21
P = 0.29
Immunotherapy alone
Immunochemotherapy
Years from diagnosis
N
2534 2327 2010 1481 1009 621 313 107
2534 2267 1952 1442 1006 616 299 82
E
Subset
HR with 95% CI
PS quintile 1 1.00 [0.69,1.45]
PS quintile 2 1.42 [1.06,1.90]
PS quintile 3 1.08 [0.85,1.37]
PS quintile 4 0.90 [0.72,1.14]
PS quintile 5 1.08 [0.79,1.49]
Age ≤ 56 1.17 [0.71,1.92]
Age 56-63 1.21 [0.84,1.74]
Age 64-70 1.14 [0.86,1.51]
Age 71-77 1.15 [0.90,1.47]
Age >78 0.93 [0.76,1.14]
SMZL 1.65 [1.18,2.30]
NMZL 0.98 [0.83,1.17]
EMZL 1.01 [0.82,1.25]
F
Prevalence in the chemoimmunotherapy arm
Prevalence in the immunotherapy arm
0.9 0.56 0.62 0.67 0.73 0.79 0.84 0.90 0.96 1.01 1.07
0.8 0.59 0.65 0.71 0.77 0.83 0.89 0.95 1.01 1.07 1.13
0.7 0.63 0.69 0.75 0.82 0.88 0.94 1.01 1.07 1.13 1.19
0.6 0.67 0.73 0.80 0.87 0.93 1.00 1.07 1.14 1.20 1.27
0.5 0.71 0.78 0.85 0.93 1.00 1.07 1.14 1.21 1.28 1.35
0.4 0.76 0.84 0.92 0.99 1.07 1.14 1.22 1.30 1.37 1.45
0.3 0.82 0.90 0.99 1.07 1.15 1.23 1.31 1.40 1.48 1.56
0.2 0.89 0.98 1.07 1.16 1.25 1.34 1.42 1.51 1.60 1.69
0.1 0.97 1.07 1.17 1.26 1.36 1.46 1.55 1.65 1.75 1.85
0.0 1.07 1.18 1.28 1.39 1.50 1.60 1.71 1.82 1.92 2.03
P<0.05
P<0.01
P<0.001

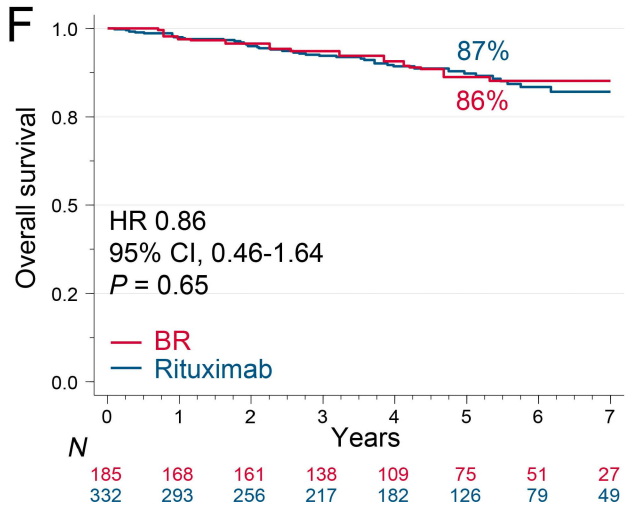

A
Rituximab
N = 355
Bendamustine + rituximab
N = 186
IPTW model
Age
Sex
Performance status
Hemoglobin
Albumin
Year of diagnosis
Complex karyotype
Large cells reported
CD5, Ki67 expression
MZL subtype
Stage
B symptoms
Bone marrow involvement
Serum LDH
Monoclonal paraprotein


B
Age
Sex
Performance status
NMZL
SMZL
EMZL
Stage 3/4
B symptoms
Bone marrow involvement
LDH elevated
M-protein
Hemoglobin
Albumin
Complex karyotype
Ki67 >20%
Large cells present
CD5+
Population:
Unadjusted
Adjusted
0.0 0.1 0.2 0.3 0.4 0.5
Absolute standardized difference of means


C
Progression-free survival
1.0 0.8 0.5 0.2 0.0
66%
49%
HR 0.57
95% CI, 0.40-0.81
P = 0.0018
BR
Rituximab
0 1 2 3 4 5 6 7
Years
N
185 152 135 112 77 58 36 17
332 245 186 142 101 72 34 20


D
Subset
HR with 95% CI
PS quintile 1 0.82 [0.31,2.16]
PS quintile 2 1.11 [0.58,2.11]
PS quintile 3 0.10 [0.03,0.32]
PS quintile 4 0.52 [0.26,1.02]
PS quintile 5 0.65 [0.33,1.26]
Age 19-55 0.54 [0.26,1.10]
Age 56-61 0.85 [0.41,1.76]
Age 62-66 0.47 [0.23,0.96]
Age 67-75 0.51 [0.24,1.08]
Age 76-96 0.51 [0.18,1.42]
SMZL 0.77 [0.41,1.46]
NMZL 0.51 [0.26,1.00]
EMZL 0.47 [0.28,0.80]
0.125 0.5 1 2


E
Prevalence in the BR arm
0.9 0.30 0.33 0.36 0.39 0.42 0.45 0.48 0.51 0.54 0.57
0.8 0.31 0.35 0.38 0.41 0.44 0.47 0.50 0.53 0.57 0.60
0.7 0.33 0.37 0.40 0.43 0.47 0.50 0.53 0.57 0.60 0.63
0.6 0.35 0.39 0.42 0.46 0.50 0.53 0.57 0.60 0.64 0.67
0.5 0.38 0.41 0.45 0.49 0.53 0.57 0.60 0.64 0.68 0.72
0.4 0.40 0.44 0.48 0.53 0.57 0.61 0.65 0.69 0.73 0.77
0.3 0.44 0.48 0.52 0.57 0.61 0.65 0.70 0.74 0.78 0.83
0.2 0.47 0.52 0.57 0.61 0.66 0.71 0.75 0.80 0.85 0.90
0.1 0.51 0.57 0.62 0.67 0.72 0.77 0.82 0.87 0.93 0.98
0.0 0.57 0.62 0.68 0.74 0.79 0.85 0.91 0.96 1.02 1.07
P<0.05
P<0.01
P<0.001
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9
Prevalence in the rituximab arm


F
Overall survival
1.0 0.8 0.5 0.2 0.0
87%
86%
HR 0.86
95% CI, 0.46-1.64
P = 0.65
BR
Rituximab
0 1 2 3 4 5 6 7
Years
N
185 168 161 138 109 75 51 27
332 293 256 217 182 126 79 49

Data supplement

Outcomes of immunotherapy or combination immunochemotherapy in first-line treatment of marginal zone lymphoma

Table of contents:

Supplemental Table S1. Specification of variables derived from the NCDB 2022 Participant User File and the MZL-RWD datasets. The detailed specification of all NCDB variables is provided at: https://www.facs.org/media/fowa425u/2022-data-dictionary.pdf

Dataset / Variable	Specification
NCDB	
Patient characteristics	
Age	Per year, capped at 90 per the NCDB policy. Specified using a restricted cubic spline.
Sex	Patient's sex
Race / ethnicity	Combines the NCDB "Race" variable (as recorded by the registry using the hospital record) and "Spanish Origin". Reclassified as White (non-Hispanic), Hispanic (of any race), Black, Asian/Other, and Unrecorded.
Comorbidity index	Using the Charlson Comorbidity Index as recorded in the NCDB. Classified as 0, 1, 2, or ≥3.
Year of diagnosis	2013 to 2018
Health insurance	As recorded by the NCDB, classified as private insurance, Medicaid, Medicare, other government-sponsored, uninsured, or unknown status.
Income	Median household income for each patient's area of residence is estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from the 2012 American Community Survey data, spanning years 2008-2012 and adjusted for 2012 inflation; Household income is categorized as quartiles based on equally proportioned income ranges among all US zip codes.
Urban / rural status	Indicator derived from the patient's county code recorded at the time of diagnosis, based on the 2013 designation by the US Department of Agriculture Economic Research Service
Disease characteristics	
MZL histology	Determined using the ICD-O-3 histology code and the primary anatomical site code.
Prior malignancy	Derived from the registry "sequence number", which indicates whether the MZL record is the first or subsequent malignancy for the patient.
EMZL primary site	ICD-O-3 primary site code
Ann Arbor stage	As recorded by the NCDB, classified as 1, 2, 3, 4, or unrecorded.
B symptoms	As recorded by the NCDB, classified as present, absent, or unrecorded.
Treatment characteristics	
Diagnosis-to-treatment interval	In days. Specified using a restricted cubic spline.
Surgery prior to systemic therapy	As recorded in the NCDB, for patients whose MZL may have been treated with excision prior to systemic therapy
Radiation therapy prior to systemic therapy	As recorded in the NCDB, for patients whose MZL may have been treated with excision prior to systemic therapy
Facility characteristics	
Academic or community	According to the Commission on Cancer (CoC) designation, based on the type of facility, program structure, services provided, and the number of cases accessioned each year.

	Of the n=1038 facilities included in this analysis, 202 (19.4%) were designated as academic
Facility volume	Calculated for each facility as the total number of MZL cases reported to NCDB divided by the number of calendar years included. Categorized as average ≤ or >5 cases per year. Median volume was 1.7 (interquartile range, 0.9 to 3.0), and 119 (11.5%) of facilities were classified as higher volume.
MZL-RWD	
Patient characteristics	
Age	Per year, specified as a restricted cubic spline
Sex	Patient's sex
Performance status	According to the Eastern Cooperative Oncology Group (ECOG) scale, classified as good (0-1) or poor (2-4).
Disease characteristics	
MZL histology	Classified as EMZL, NMZL, or SMZL according to the WHO diagnosis on the pathology report and clinical assessment of the investigator.
Stage	Derived from the medical record, classified as early (1/2) or advanced (3/4).
B symptoms	Present or absent, derived from the medical record.
Bone marrow involvement	Derived from the medical record, when a staging bone marrow biopsy was performed.
Lactate dehydrogenase (LDH)	Serum LDH recorded at diagnosis.
Monoclonal paraprotein	Present or absent/unrecorded.
Albumin	Classified as normal or low according to the institutional reference range.
Hemoglobin	In g/dL (continuous variable) at the time of diagnosis
Ki-67 staining	Classified as < or ≥20%, when staining performed on the diagnostic biopsy
Complex cytogenetics	When recorded at the time of initial diagnosis
Large cell tumor content	Presence of increased or prominent large cells recorded on the initial diagnostic biopsy by the pathologist.
CD5 expression	Positive or negative, as recorded on the initial diagnostic biopsy or flow cytometry.

Supplemental Table S2. Characteristics of patients with MZL in the NCDB dataset according to first-line therapy administered.

	Immunotherapy N = 4,728 (58.3%)	**Immunochemotherapy N = 3,382 (41.7%)**	**Total N = 8,110**	***P***
Age at diagnosis, median (range)	69 (19-90)	65 (20-90)	67 (19-90)	<0.001
Sex, N (%)				
Male	2,002 (42.3%)	1,601 (47.3%)	3,603 (44.4%)	<0.001
Female	2,726 (57.7%)	1,781 (52.7%)	4,507 (55.6%)	
Race/ethnicity, N (%) [a]				
White non-Hispanic	3,945 (83.4%)	2,720 (80.4%)	6,665 (82.2%)	<0.001
Hispanic	246 (5.2%)	203 (6.0%)	449 (5.5%)	
Black	349 (7.4%)	316 (9.3%)	665 (8.2%)	
Asian/other	148 (3.1%)	128 (3.8%)	276 (3.4%)	
Unknown	40 (0.8%)	15 (0.4%)	55 (0.7%)	
Charlson-Deyo comorbidity index [a]				
0	3,586 (75.8%)	2,626 (77.6%)	6,212 (76.6%)	0.309
1	749 (15.8%)	497 (14.7%)	1,246 (15.4%)	
2	233 (4.9%)	155 (4.6%)	388 (4.8%)	
≥3	160 (3.4%)	104 (3.1%)	264 (3.3%)	
Median income quartiles, N (%) [a]				
< $38,000	532 (11.3%)	426 (12.6%)	958 (11.8%)	0.029
$38,000 - $47,999	834 (17.6%)	628 (18.6%)	1,462 (18.0%)	
$48,000 - $62,999	1,115 (23.6%)	823 (24.3%)	1,938 (23.9%)	
$63,000 +	1,582 (33.5%)	1,023 (30.2%)	2,605 (32.1%)	
Unrecorded	665 (14.1%)	482 (14.3%)	1,147 (14.1%)	
Health insurance, N (%) [a]				
Uninsured	68 (1.4%)	87 (2.6%)	155 (1.9%)	<0.001
Private	4,026 (85.2%)	2,721 (80.5%)	6,747 (83.2%)	
Medicaid	207 (4.4%)	207 (6.1%)	414 (5.1%)	
Medicare	323 (6.8%)	260 (7.7%)	583 (7.2%)	
Other government	46 (1.0%)	35 (1.0%)	81 (1.0%)	
Unknown	58 (1.2%)	72 (2.1%)	130 (1.6%)	
MZL subtype, N (%)				
SMZL	1,103 (23.3%)	328 (9.7%)	1,431 (17.6%)	<0.001
NMZL	1,508 (31.9%)	1,845 (54.6%)	3,353 (41.3%)	
EMZL	2,117 (44.8%)	1,209 (35.7%)	3,326 (41.0%)	
Stage, N (%) [a]				
1/2	1,661 (35.1%)	814 (24.1%)	2,475 (30.5%)	<0.001
3/4	2,626 (55.5%)	2,370 (70.1%)	4,996 (61.6%)	
Unrecorded	441 (9.3%)	198 (5.9%)	639 (7.9%)	
B symptoms, N (%) [a]				
No B-symptoms	3,395 (71.8%)	2,140 (63.3%)	5,535 (68.2%)	<0.001
B-symptoms	887 (18.8%)	904 (26.7%)	1,791 (22.1%)	
Unknown	446 (9.4%)	338 (10.0%)	784 (9.7%)	
Prior malignancy, N (%)				
No	3,743 (79.2%)	2,791 (82.5%)	6,534 (80.6%)	<0.001
Yes	985 (20.8%)	591 (17.5%)	1,576 (19.4%)	
Diagnosis-to-treatment interval in days, median (range) [a]	45 (0-1375)	39 (0-728)	42 (0-1375)	<0.001
Prior radiation, N (%)				
No	4,568 (96.6%)	3,331 (98.5%)	7,899 (97.4%)	<0.001
Yes	160 (3.4%)	51 (1.5%)	211 (2.6%)	
Prior surgery, N (%)				
No	4,049 (85.6%)	2,902 (85.8%)	6,951 (85.7%)	0.831
Yes	679 (14.4%)	480 (14.2%)	1,159 (14.3%)	

[a] see Table S1 for details of the specification.

Supplemental Table S3. Characteristics of patients with MZL in the RWD-MZL dataset according to first-line rituximab or BR therapy administered.

	Rituximab N = 355 (65.6%)	**BR N = 186 (34.4%)**	**Total N = 541 (100.0%)**	***P*** [b]
Age, median (range)	65 (19-96)	61 (35-91)	64 (19-96)	0.001
Sex, N (%)				
Male	174 (49.0%)	91 (48.9%)	265 (49.0%)	0.99
Female	181 (51.0%)	95 (51.1%)	276 (51.0%)	
Poor performance status, N (%) [a]				
No	284 (80.0%)	151 (81.2%)	435 (80.4%)	0.59
Yes	27 (7.6%)	11 (5.9%)	38 (7.0%)	
Missing	44 (12.4%)	24 (12.9%)	68 (12.6%)	
MZL subtype, N (%)				
SMZL	102 (28.7%)	36 (19.4%)	138 (25.5%)	<0.001
NMZL	70 (19.7%)	66 (35.5%)	136 (25.1%)	
EMZL	183 (51.5%)	84 (45.2%)	267 (49.4%)	
Stage, N (%)				
1/2	119 (33.5%)	29 (15.6%)	148 (27.4%)	<0.001
3/4	236 (66.5%)	157 (84.4%)	393 (72.6%)	
B symptoms, N (%)				
No	274 (77.2%)	148 (79.6%)	422 (78.0%)	0.90
Yes	60 (16.9%)	34 (18.3%)	94 (17.4%)	
Missing	21 (5.9%)	4 (2.2%)	25 (4.6%)	
Bone marrow involvement, N (%)				
No	130 (36.6%)	53 (28.5%)	183 (33.8%)	0.023
Yes	141 (39.7%)	94 (50.5%)	235 (43.4%)	
Not tested	84 (23.7%)	39 (21.0%)	123 (22.7%)	
LDH elevated, N (%) [a]				
No	218 (61.4%)	133 (71.5%)	351 (64.9%)	0.027
Yes	88 (24.8%)	32 (17.2%)	120 (22.2%)	
Missing	49 (13.8%)	21 (11.3%)	70 (12.9%)	
Serum M-protein, N (%) [a]				
Absent	99 (27.9%)	60 (32.3%)	159 (29.4%)	0.46
Present	70 (19.7%)	51 (27.4%)	121 (22.4%)	
Missing	186 (52.4%)	75 (40.3%)	261 (48.2%)	
Serum albumin, N (%) [a]				
Normal	280 (78.9%)	145 (78.0%)	425 (78.6%)	0.56
Low	37 (10.4%)	23 (12.4%)	60 (11.1%)	
Missing	38 (10.7%)	18 (9.7%)	56 (10.4%)	
Hemoglobin, g/dL, median (range)	12.6 (3.7-18.9)	12.3 (3.7-16.6)	12.5 (3.7-18.9)	0.53
Ki67 expression >20%, N (%) [a]				
<20%	128 (36.1%)	78 (41.9%)	206 (38.1%)	0.99
≥20%	38 (10.7%)	23 (12.4%)	61 (11.3%)	
Not tested	189 (53.2%)	85 (45.7%)	274 (50.6%)	
Large cells present, N (%) [a]				
No	275 (77.5%)	149 (80.1%)	424 (78.4%)	0.43
Yes	29 (8.2%)	20 (10.8%)	49 (9.1%)	
Not reported	51 (14.4%)	17 (9.1%)	68 (12.6%)	
CD5 expression, N (%) [a]				
No	268 (75.5%)	148 (79.6%)	416 (76.9%)	0.88
Yes	36 (10.1%)	18 (9.7%)	54 (10.0%)	
Not tested	51 (14.4%)	20 (10.8%)	71 (13.1%)	
Complex cytogenetics				
No	174 (49.0%)	80 (43.0%)	254 (47.0%)	0.87
Yes	16 (4.5%)	6 (3.2%)	22 (4.1%)	
Not tested	165 (46.5%)	100 (53.8%)	265 (49.0%)	

[a] see Table S1 for details of the specification.

[b] statistical tests compare only groups with non-missing values.