Outcomes in grade 3B follicular lymphoma: an international study led by the Australasian Lymphoma Alliance

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Abstract

Grade (G) 3B follicular lymphoma (FL) is a rare FL subtype which exists on a histological continuum between 'low-grade' (Grade 1, 2 and 3A FL) and diffuse large B-cell lymphoma (DLBCL) appearing to share features with each. Clinical characteristics and outcomes are poorly understood due to lack of adequate representation in prospective trials and large-scale analyses. We analyzed 157 G3BFL cases from 18 international centers, and two comparator groups; G3AFL (n=302) and DLBCL (n=548). Composite histology with DLBCL or low-grade FL occurred in approximately half of the G3BFL cases. With a median of 5 years follow-up, the overall survival and progression-free survival of G3BFL patients was better than that of DLBCL patients (P<0.001 and P<0.001, respectively); however, G3BFL patients were younger (P<0.001) with better performance status (P<0.001), less extranodal disease (P<0.001) and more frequently had normal lactate dehydrogenase (P<0.001) at baseline. The overall and progression-free survival of patients with G3BFL and G3AFL were similar (P=0.83 and P=0.80, respectively). After frontline immunochemotherapy, 24% of G3BFL relapsed; relapse rates were 63% in the DLBCL cohort and 19% in the low-grade FL cohort. Eight percent of relapses occurred beyond 5 years. In this G3BFL cohort, the revised International Prognostic Index successfully delineated risk groups, but the Follicular Lymphoma International Prognostic Index did not. We conclude that patients with immunochemotherapy-treated G3BFL have similar survival outcomes to those with G3AFL, yet a favorable baseline profile and distinctly superior prognosis compared to patients with DLBCL.

Introduction

Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin lymphoma, constituting 20-30% of all cases.[1] World Health Organization (WHO) morphological grading is according to the relative proportion of centrocytes to centroblasts.[2] WHO grade 3B follicular lymphoma (G3BFL), the highest grade, accounts for only 5-10% of cases[1,3-6] and is differentiated from its lower grade counterpart, grade 3A FL (G3AFL), by the presence of follicles comprised exclusively of centroblasts.[7] While the 2022 revision of the International Consensus Classification of Mature Lymphoid Neoplasms has retained this grading strategy,[8] the recent 5th edition of the WHO diagnostic criteria has revised FL nomenclature, with G1-3FL now being referred to as classic FL and G3BFL as follicular large cell lymphoma.[9]

Low-grade FL (grade 1, 2 and 3AFL) typically follows a relapsing-remitting disease course potentially spanning decades, whereas G3BFL is thought to follow a more aggressive clinical course. Published data, however, conflict with some G3BFL reports describing an indolent, incurable natural history while others describe rapid initial progression followed by long remissions and potential cure from combination chemotherapy, more akin to diffuse large B-cell lymphoma (DLBCL).[3,4,6,10-15]

Despite histological similarities between G1-G3AFL and G3BFL, treatment guidelines largely recommend rituximab and anthracycline-containing regimens for G3BFL,[16] analogous to the clinical management for DLBCL. In contrast, low-grade FL management predominantly utilizes therapy to control symptomatic disease and achieve durable remission as opposed to cure.[17,18] While historical variation exists for G3AFL therapeutic paradigms,[19,20] G3AFL is currently considered an indolent lymphoma and regularly included in modern-era low-grade FL trials.[17,21,22] Yet exclusion of G3BFL from both DLBCL and low-grade FL clinical trials and the small heterogeneous cohorts in published retrospective series have limited our understanding of this high-grade FL subgroup and the optimal treatment approach.

Here we describe outcomes in the first large international G3BFL study from the rituximab era. We utilized contemporaneous comparator G3AFL and DLBCL cohorts to establish prognostic information, survival outcomes and relapse patterns of this rare FL subtype.

Methods

We developed a database of consecutively treated adult G3BFL patients diagnosed between 2002 and 2019 from 18 expert lymphoma centers in Australia, UK and Canada. Composite G3AFL/G3BFL and G3BFL/DLBCL were included in the G3B group. Treatment consisted of rituximab/obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R/O-CHOP)-like chemotherapy with or without radiotherapy. Those receiving radiotherapy alone (n=2) or alternate chemotherapy regimens (n=6) were excluded. In this study, FL grading was according to the 4th edition WHO criteria.[7]

Consecutive G3AFL and DLBCL cases from participating institutions were collected for comparison because of the close histological relationships and to establish clinical similarities and differences between these and G3BFL. The G3AFL comparator cases were collected consecutively in the same time-frame and by the same contributing sites as the G3BFL group. Treatment was with R-CHOP-like chemotherapy with or without radiotherapy or bendamustine-rituximab. The DLBCL cohort were treated with R-CHOP, with or without radiotherapy, from 2008-2018 (inclusive), and were identified from three of the Australian sites.

The majority of participating sites follow the standard international recommendation of 5 years' follow-up in aggressive lymphoma, after which time patients were discharged back to their primary care physician and at which point no further outcome data could be extracted from external sources.

Retrospective data including baseline characteristics, treatment details and outcomes were obtained from registries and tertiary institution medical records. Cases were sourced from centers with established expert lymphoma multidisciplinary meeting histopathology review, as central histological review of all archived cases from the large number of international participating sites was not feasible. Additionally, in order to ensure homogeneity of diagnosis and grading between contributing countries, we analyzed progression-free survival (PFS) according to regions (Australia *vs*. Canada *vs*. UK) for G3AFL and G3BFL, and demonstrated no statistical difference between regions (G3AFL P=0.78, G3BFL P=0.58). Furthermore, the proportions of G3AFL and G3BFL in our series are similar to those reported elsewhere.[4,6,15]

Overall survival (OS) was defined as the time from the date of diagnosis until death from any cause, and PFS as the time from diagnosis until relapse/progression (to any B-cell lymphoma subtype) or death from any cause, both calculated using the Kaplan-Meier method with patients censored at last known follow-up if no date of death or progression was recorded.[23] Differences in patient and disease-related characteristics among groups (G3AFL, G3BFL and DLBCL) were analyzed using the Fisher exact test for discrete variables and the Kruskal-Wallis H test for continuous variables. Differences in OS and PFS were compared using log-rank tests, and associations between prognostic factors, histological subgroup and outcomes were analyzed using Cox proportional hazard models. Variables with P<0.1 on univariable analysis were included in the multivariable analysis, with two-tailed P values ≤0.05 considered statistically significant. This study was conducted in accordance with the ethical standards of the responsible committee on human experi-

mentation and with the Declaration of Helsinki of 1975, as revised in 2008 and was approved by institutional review boards at all participating institutions.

Results

A total of 157 G3BFL cases were eligible including 85 cases of pure G3BFL, 24 of composite G3A/G3BFL, and 48 of composite G3B/DLBCL, collectively termed the "G3BFL" group. The comparator groups consisted of 302 G3AFL and 548 DLBCL consecutive cases. Baseline clinical and tumor characteristics, treatment and relapse data are summarized in Table 1.

For G3BFL, all patients received R- or O-CHOP-like chemotherapy with 17% receiving consolidative radiotherapy. Fifty-nine patients (37%) received maintenance rituximab or obinutuzumab for a median of 8 cycles (range 1-24). Of the G3AFL patients, 74% received R- or O-CHOP-like chemotherapy with or without radiotherapy and 26% received bendamustine-rituximab, with 68% receiving maintenance therapy for a median of eight cycles (range, 1-24).

The median follow-up of the entire cohort was 5 years (range, 0.03-16.11 years). The 5-year survival rates of patients with pure G3BFL, composite G3A/3BFL or G3BFL/DLBCL were not significantly different (PFS: G3BFL 60% [95% CI: 46-71%], G3AFL/G3BFL 79% [95% CI: 54-92%], and G3BFL/DLBCL 70% [95% CI: 51-83%] *P*=0.51; OS: G3BFL 80% [95% CI: 67-88%], G3AFL/G3BFL 86% [95% CI: 54-96%], G3BFL/DLBCL 87% [95% CI: 71-95%] *P*=0.37) and therefore this group was analyzed together. The 5-year PFS of the G3BFL group was 66% (95% CI: 57-75%) and the OS was 84% (95% CI: 76-89%). While outcomes were similar in the G3AFL and G3BFL groups (OS: HR=1.04 [95% CI: 0.67-1.65] *P*=0.84; PFS: HR=1.04 [95% CI: 0.75-1.46] *P*=0.81), the G3BFL group had superior PFS and OS compared to those of the DLBCL group (OS: HR=2.19 [95% CI 1.45-3.29] *P*<0.001; PFS: HR=1.73 [95% CI: 1.27-2.63] *P*=0.001). No plateau was observed on the G3BFL PFS curve (Figure 1A, B). No difference in survival was demonstrated between R-CHOP-treated G3AFL and G3BFL (OS: HR=0.98 [95% CI: 0.60-1.60] *P*=0.93; PFS HR 0.98 [95% CI 0.68-1.40] *P*=0.89) (Figure 2A, B).

On univariate analysis of the entire cohort, candidate factors that were statistically significant for PFS and OS were age >60 years, male gender, elevated baseline lactate dehydrogenase, stage III/IV disease, Eastern Cooperative Oncology Group (ECOG) performance status 3-4 and extranodal involvement. Stage III/IV disease and extranodal involvement did not retain significance on multivariable analysis. DLBCL was associated with inferior PFS and OS on both univariate and multivariate analyses, whereas G3AFL and G3BFL did not display a difference in outcome. The DLBCL cohort PFS and OS HR were 1.27 (95% CI: 1.00-1.62; *P*=0.05) and 1.53 (95% CI: 1.12-2.08; *P*=0.007) respectively, whereas the G3AFL PFS and OS HR were 0.97 (95% CI: 0.69-1.35; *P*=0.84), and 0.96 (95% CI: 0.61-1.51; *P*=0.86) respectively. The G3BFL PFS HR was 0.81 (95% CI: 0.54-1.2; *P*=0.30) and the OS HR was 0.86 (95% CI: 0.51-1.47; *P*=0.59) (Table 2).

The proportions of relapses and those progressing within 24 months of diagnosis (POD24)[24] were similar in the G3AFL and G3BFL groups with total relapse proportions and POD24 as follows: G3AFL 29% and 18%, G3BFL 25% and 19%. The median time to relapse was 19 months (range, 1-155) for G3AFL and 13 months (range, 4-138) for G3BFL. In those who relapsed, no difference in outcomes was seen according to baseline histological grade: PFS HR=1.04 (95% CI: 0.71-1.54) *P*=0.81; OS: HR=1.10 (95% CI: 0.62-1.95) *P*=0.75. At 2 years, G3BFL patients experiencing POD24, had an inferior OS compared with G3AFL patients: 2-year OS G3AFL 66% (95% CI: 51-78%), G3BFL 34% (95 CI: 14-57%) *P*=0.05.

Of the 39 relapses in the G3BFL group, 27 had biopsy confirmation. Histology at relapse was G1FL or G2FL in two (7%), G3AFL in three (11%), G3BFL in five (18%) and DLBCL in 17 (63%). Of those who relapsed/transformed to DLBCL, diagnostic histology was composite G3AFL/G3BFL in two patients (12%), G3BFL in ten patients (59%) and G3BFL/DLBCL in five patients (29%). The median time to relapse with FL histology was 28 months (range, 5-138) and with DLBCL 18 months (range, 4-59). Patterns of relapse according to histological subtype are presented in Figure 3. Three of 39 relapses in G3BFL occurred beyond 5 years at 6, 7.5 and 11.5 years and histology was G1FL/G2FL, G3AFL and G3BFL.

Twenty-seven deaths were reported in the G3BFL group. Of these, 15 were attributable to lymphoma. Six deaths occurred beyond 5 years from the initial G3BFL diagnosis, all due to non-lymphomatous causes. In the G3AFL cohort, 62 deaths were recorded, of which 38 were due to lymphoma. Nineteen deaths occurred more than 5 years after the initial diagnosis of lymphoma, of which six were caused by lymphoma. In the DLBCL cohort, 179 deaths occurred. Lymphoma was the cause of death in 118 cases with 19 deaths occurring beyond 5 years, nine of which were caused by lymphoma.

The univariable analysis of candidate prognostic factors in G3BFL for PFS and OS is presented in Table 3. CD10 immunohistochemical negativity and Ann Arbor stage III/IV disease were associated with inferior PFS, while elevated lactate dehydrogenase, ECOG performance status 3-4 and age >60 years were associated with inferior OS. Factors that retained significance on multivariable analysis were ECOG performance status 3-4 for PFS and OS and stage III/IV disease for PFS. Of note, our series did not show an OS or PFS advantage with the addition of maintenance rituximab or obinutuzumab to front-line immunochemotherapy in G3BFL (OS HR=0.32 [95% CI: 0.07-1.59] *P*=0.17; PFS HR=0.91 [95% CI: 0.38-2.18] *P*=0.84), with the caveat

of non-uniform administration and treatment cycle length (Table 3).

The prognostic utility of the Follicular Lymphoma International Prognostic Index (FLIPI)[25] and the revised International Prognostic Index (R-IPI)[26] for G3BFL were assessed. The FLIPI showed poor discrimination of risk groups with low, intermediate and high-risk 5-year OS of 100%, 80% and 81%, respectively (*P*=0.19). The R-IPI showed a statistically significant difference between risk groups with low, intermediate and high-risk 5-year OS of 100%, 85% and 64% respectively (*P*<0.001) (Figure 4A, B).

Discussion

This international analysis of G3BFL patients, uniformly

Table 1. Clinical characteristics, treatment and outcome summary.

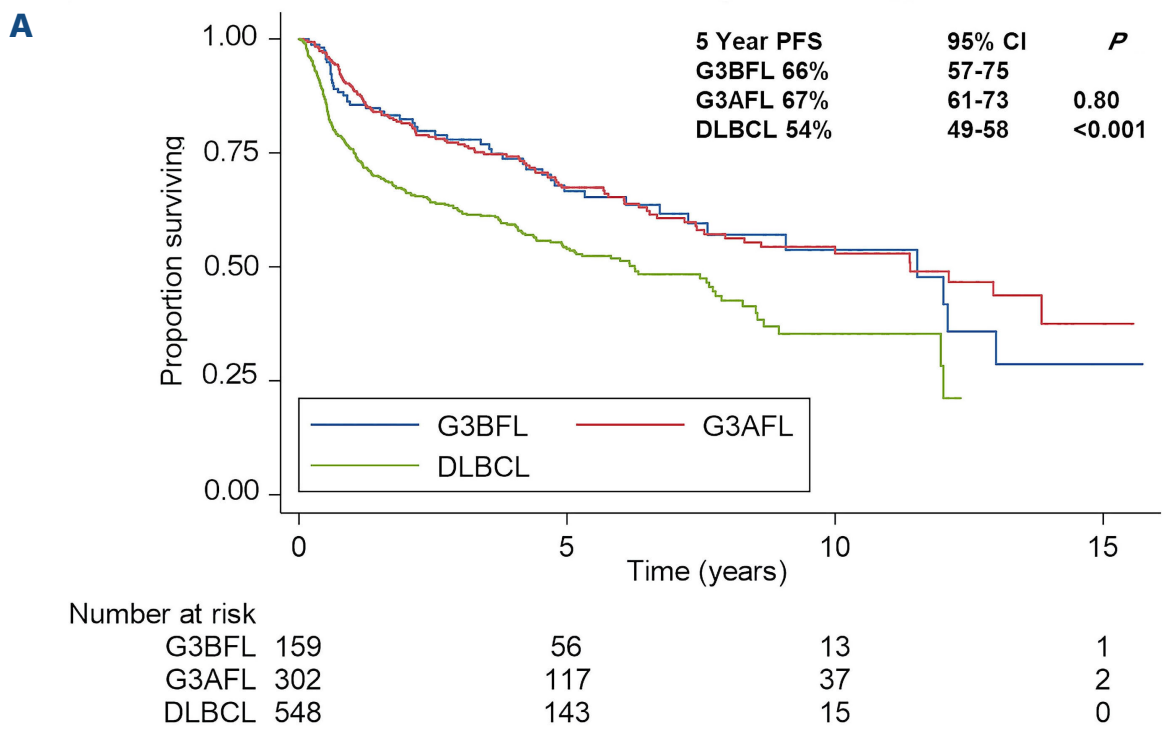
Characteristic	G3AFL (N=302)	G3BFL (N=157)	DLBCL (N=548)	*P*
Age in years				
Median (range)	62 (22-86)	63 (18-86)	68 (20-92)	<0.001
>60 years, N (%)	169 (56)	85 (54)	394 (72)	<0.001
Sex, N (%)				
Male	150 (50)	87 (55)	317 (58)	0.07
Stage at diagnosis, N (%)				
I/II	51 (17)	48 (31)	176 (32)	<0.001
III/IV	247 (83)	109 (69)	371 (68)	
Performance status, N (%)				
ECOG 1-2	255 (94)	147 (95)	448 (87)	<0.001
ECOG 3-4	15 (6)	7 (5)	65 (13)	
LDH > ULN, N (%)	70 (28)	59 (38)	306 (62)	<0.001
Ki67 positive, median (range)	50 (5-99)	72 (30-100)	85 (5-100)	<0.001
Extranodal site, N (%)	157 (52)	76 (49)	366 (67)	<0.001
Bulk >7 cm, N (%)	77 (33)	38 (27)	NA	0.25
CD10 positive by IHC, N (%)	255 (91)	116 (78)	NA	<0.001
BCL2 positive by IHC, N (%)	250 (90)	112 (76)	NA	0.001
FLIPI (points), N (%)				
Low (0-1)	11 (5)	25 (17)	NA	0.002
Intermediate (2)	59 (29)	41 (27)	NA	
High (3-4)	139 (66)	83 (56)	NA	
R-IPI (points), N (%)				
Low (0)	8 (5)	24 (16)	35 (7)	<0.001
Intermediate (1-2)	138 (71)	89 (59)	215 (42)	
High (3-5)	47 (24)	38 (25)	262 (51)	
Treatment, N (%)				
R/O-CHOP (like) ± RT	223 (74)	157 (100)	548 (100)	<0.001
Bendamustine-rituximab	79 (26)	0 (0)	0 (0)	
Anthracyclines, N (%)	217 (72)	151 (96)	548 (100)	<0.001
No anthracyclines, N (%)	85 (28)	6 (4)	0 (0)	
Maintenance therapy, N (%)	205 (68)	59 (37)	NA	<0.001
Relapse, N (%)	87 (29)	39 (25)	NA	0.21
POD24, N (%)	48 (18)	22 (19)	NA	0.89
Histology at relapse, N (%)				
Grade 1/2	9 (17)	2 (7)	NA	0.02
Grade 3A	14 (26)	3 (11)		
Grade 3B	1 (2)	5 (18)		
DLBCL	30 (56)	17 (63)		

NA: not available. G3AFL: grade 3A follicular lymphoma; G3BFL: grade 3B follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; ECOG Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal; IHC: immunohistochemistry; FLIPI: Follicular Lymphoma International Prognostic Index; R-IPI: Revised International Prognostic Index, R/O-CHOP, rituximab or obinutuzumab with cyclophosphamide, doxorubicin, vincristine and prednisolone; RT: radiotherapy; POD24: progression of disease within 2 years.

treated with R-CHOP-like chemotherapy, is the largest and most comprehensive of its kind. By comparisons with contemporaneous G3AFL and DLBCL cohorts, of which the vast majority were also treated with R-CHOP-like therapy, we found that patients with G3BFL have a better prognosis than those with DLBCL. Moreover, G3AFL and G3BFL had very similar PFS and OS outcomes. These key findings indicate that G3BFL behaves similarly to G3AFL, but is distinct from DLBCL.

The historically described aggressive behavior of G3BFL is based on small (n<25), retrospective cohorts predominantly treated in the pre-rituximab era.[5,11,13,14] However, in our dataset, both PFS and OS for G3BFL were markedly superior to those for DLBCL. Interestingly, patients with composite G3BFL and DLBCL histology experienced similar survival outcomes to patients with pure G3BFL, rather than DLBCL. This was not due to treatment, as both cohorts uniformly received R/O-CHOP. This contrasts with the series reported by Yuen *et al.*[27] showing that outcomes of 17 G3BFL and DLBCL patients were similar (OS *P*=0.42; event-free survival, *P*=1.0). Our results may in part be due to the more favorable baseline clinical prognostic profile of G3BFL compared to DLBCL. G3BFL patients were found to be younger with a better performance status, less frequent extranodal involvement and/or baseline elevated lactate dehydrogenase. However, our multivariable analysis, accounting for these differences, demonstrated that only DLBCL patients had inferior outcomes.

In addition to the similar survival outcomes of patients with



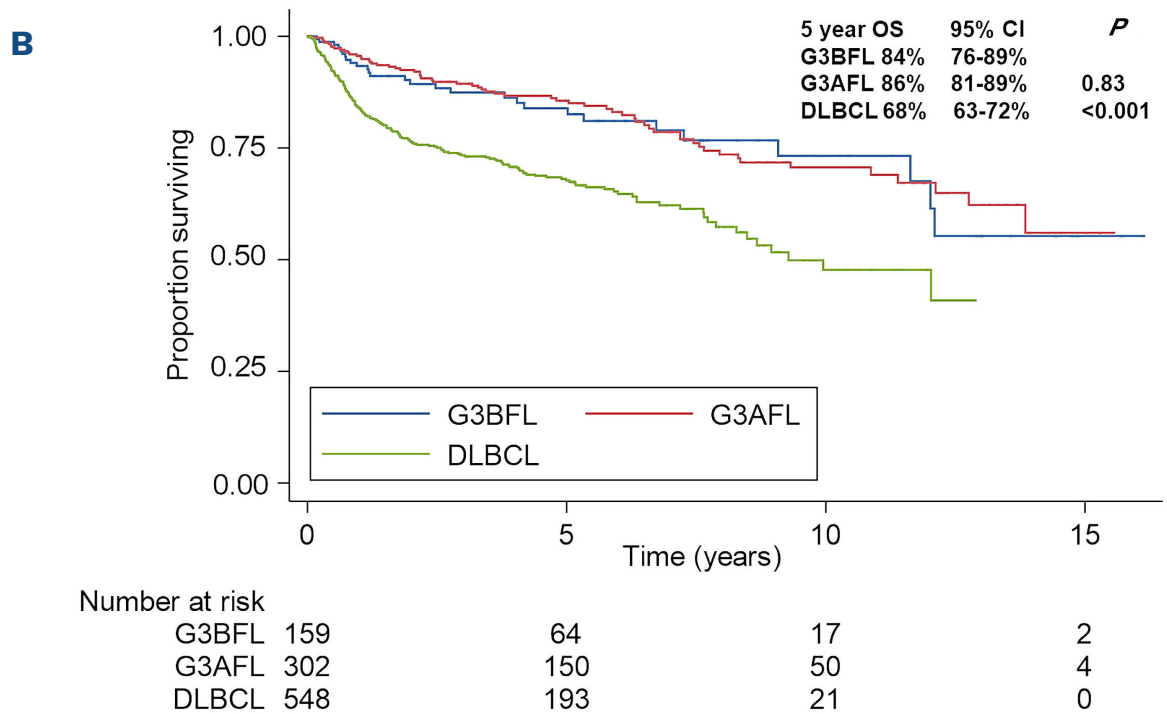


Figure 1. Survival outcomes according to histology. (A) Progression-free survival (PFS) according to histology. (B) Overall survival (OS) according to histology. 95% CI: 95% confidence interval; G3BFL: grade 3B follicular lymphoma; G3AFL: grade 3A follicular lymphoma; DLBCL: diffuse large B-cell lymphoma.

G3AFL or G3BFL, the POD24 rate and continuous pattern of relapse were also similar for the follicular histologies. This was despite the use of bendamustine for around 25% of G3AFL patients, compared to nearly all G3BFL patients receiving R/O-CHOP. The proportion of relapses with DLBCL histology was similar for G3AFL and G3BFL. Baseline clinical characteristics were well balanced, as were FLIPI and R-IPI profiles. While outcomes of G3BFL and G3AFL were equivalent with R-CHOP, it is not known if bendamustine-based therapy for G3BFL would have yielded equivalent outcomes. Unlike previous small series,[4,15] our data suggest that G3BFL may not consistently be curable as evidenced by the continuous pattern of relapse.

Previous studies comparing G3AFL and G3BFL have yielded conflicting results. In a study of 345 FL patients, patients with G3BFL (n=23) had a higher mortality compared with G1-3AFL patients, independently of clinical factors (P<0.01).[4] However, only 9% of G3BFL patients received front-line rituximab, although anthracycline was used in 70% compared with 30% of G1-2FL and 43% of G3AFL cases. Another small study (17 G3BFL) displayed inferior outcomes for these patients compared to those with G3AFL using rituximab and anthracycline therapy (P=0.043).[27] In contrast, Shustik *et al.*[6] found equivalent outcomes in G3AFL and G3BFL (n=22); again, not all received rituximab. Interpretation of these three studies is hampered by small numbers of G3BFL cases and non-uniform rituximab use.

In our study the proportion of G3BFL patients expressing

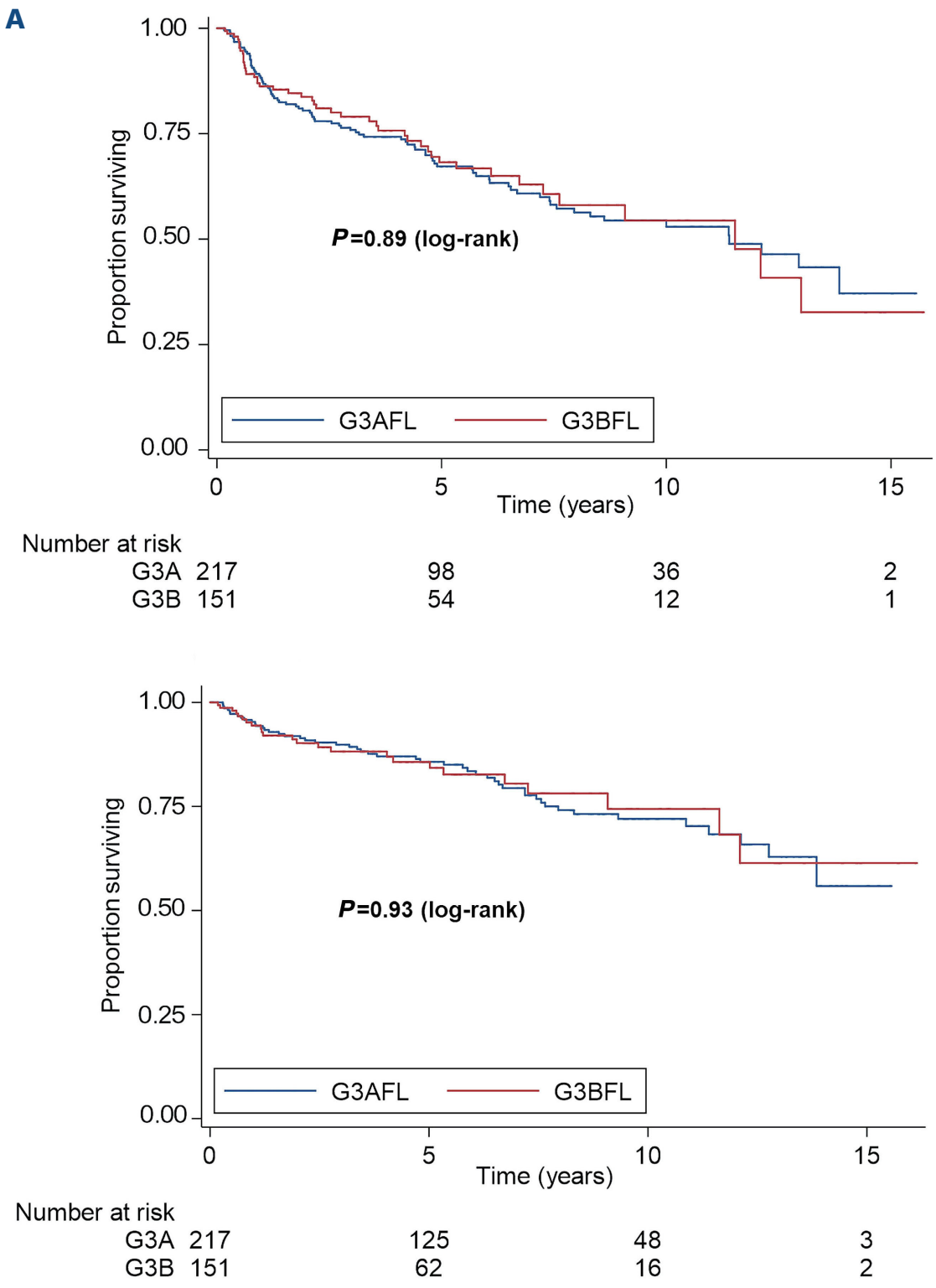


Figure 2. Survival outcomes with R-CHOP by histology. (A) Progression free survival with R-CHOP by histology. (B) Overall survival with R-CHOP by histology. R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; G3AFL: grade 3A follicular lymphoma; G3BFL: grade 3B follicular lymphoma.

CD10 and BCL2, as assessed by immunohistochemistry, was significantly lower than the proportion of G3AFL. This is corroborated by prior studies, demonstrating that pure G3BFL and composite G3B/DLBCL can lack CD10 and BCL2 contrasting with G1-3AFL, which typically has uniform CD10, BCL2 and BCL6 expression.[28,29] Additionally, our data and others have shown that the median Ki-67 proliferation index increases proportionally with FL grade[28] but is lower than that seen with DLBCL. To further characterize these laboratory-based differences, two recent studies utilized gene expression profiling techniques with differing results. Horn *et al.* failed to observe a significant difference in the gene expression patterns between G3AFL and G3BFL, while in a supervised analysis approach[30], Piccaluga *et al.* demonstrated G3BFL formed a single cluster, distinct from FLG1/2 and G3AFL[31]. Low case numbers (6 and 4, respectively) and differing gene sets likely contributed to this discrepancy. Further molecular studies are needed to examine the biological differences between these FL subgroups.

The original FLIPI[25] and R-IPI[26] score studies did not include G3BFL in their primary analyses, hence their utility is not clear in this group. For the first time, we have shown that the R-IPI retains prognostic significance with G3BFL, while the FLIPI score does not. Given the excellent delineation between risk groups using the R-IPI, our results support the use of the R-IPI as an accurate baseline prognostication tool for G3BFL.

Our study shows a higher rate of R-IPI high-risk patients in the DLBCL cohort than in the G3AFL and G3BFL cohorts. Ad-

Table 2. Univariable and multivariable analyses of the entire cohort.

Candidate factor	Univariable analysis				Multivariable analysis			
	PFS HR (95% CI)	*P*	OS HR (95% CI)	*P*	PFS HR (95% CI)	*P*	OS HR (95% CI)	*P*
Age >60 years	3.14 (2.28-4.31)	<0.001	3.14 (2.28-4.31)	<0.001	1.38 (1.09-1.76)	0.008	3.02 (2.11-4.32)	<0.001
Male	1.33 (1.04-1.70)	0.02	1.33 (1.04-1.70)	0.02	1.40 (1.13-1.74)	0.002	1.46 (1.12-1.91)	0.005
Elevated serum LDH	2.54 (1.95-3.32)	<0.001	2.54 (1.95-3.32)	<0.001	1.93 (1.53-2.44)	<0.001	2.01 (1.51-2.68)	<0.001
Stage (III/IV *vs.* I/II)	1.55 (1.16-2.07)	0.003	1.55 (1.16-2.07)	0.003	1.45 (1.10-1.92)	0.009	1.20 (0.87-1.66)	0.27
Extranodal site(s)	1.75 (1.42-2.15)	<0.001	1.40 (1.09-1.80)	0.008	1.43 (1.13-1.81)	0.003	1.10 (0.83-1.46)	0.68
ECOG (3-4 *vs.* 0-2)	3.62 (2.61-5.02)	<0.001	3.62 (2.61-5.02)	<0.001	2.10 (1.54-2.86)	<0.001	2.36 (1.67-3.32)	<0.001
Grade 3A FL	0.97 (0.69-1.35)	0.84	0.96 (0.61-1.51)	0.86	-	-	-	-
Grade 3B FL	0.81 (0.54-1.21)	0.30	0.86 (0.51-1.47)	0.59	-	-	-	-
DLBCL	1.73 (1.41-2.13)	<0.001	2.26 (1.74-2.93)	<0.001	1.27 (1.00-1.62)	0.05	1.53 (1.12-2.08)	0.007

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; ECOG Eastern Cooperative Oncology performance status; FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma.

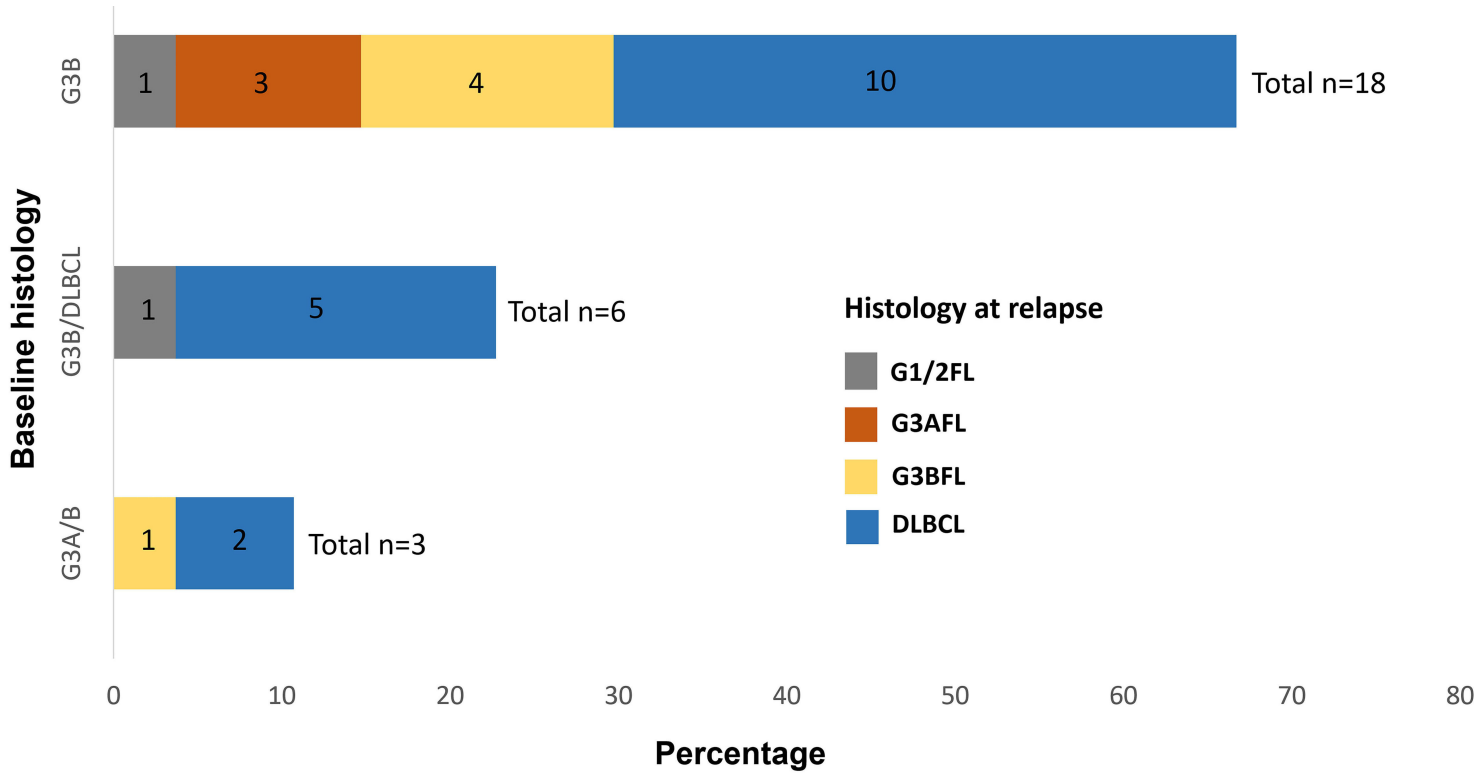
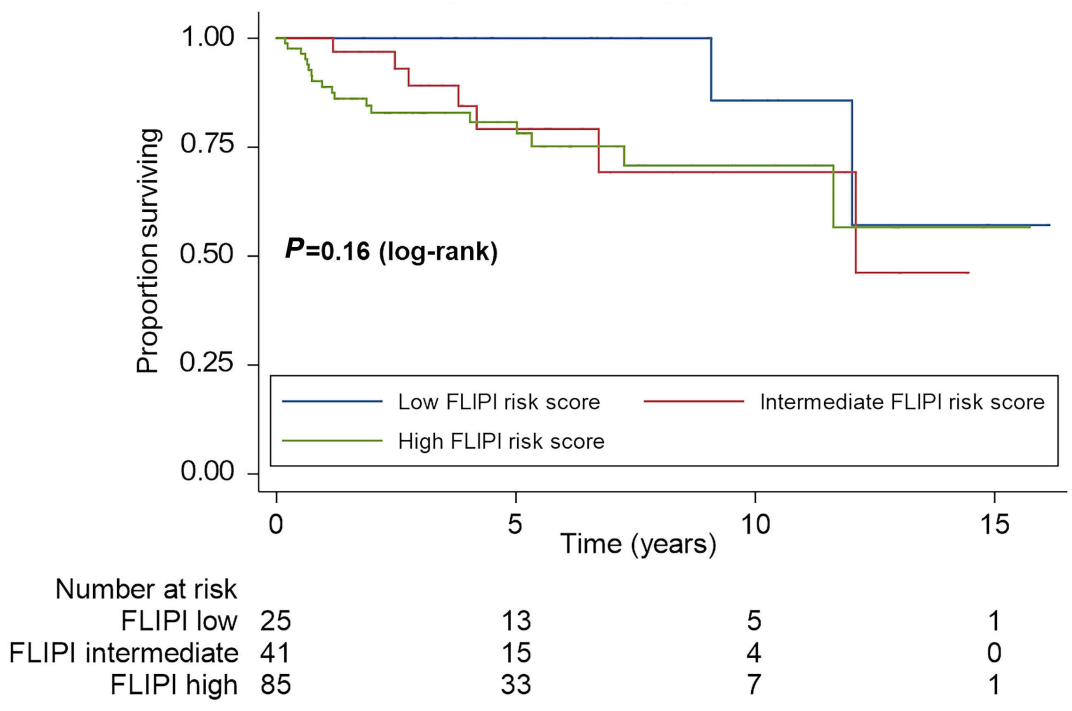


Figure 3. Histological grade at relapse of grade 3B follicular lymphoma. G: grade; FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma.

Table 3. Univariable and multivariable analyses for grade 3B follicular lymphoma.

Candidate factor	Univariable analysis				Multivariable analysis			
	PFS HR (95% CI)	*P*	OS HR (95% CI)	*P*	PFS HR (95% CI)	*P*	OS HR (95% CI)	*P*
Age >60 years	1.00 (0.57-1.74)	1.00	2.14 (0.96-4.79)	0.05	0.96 (0.42-2.19)	0.92	1.90 (0.53-6.87)	0.33
Male	0.76 (0.43-1.32)	0.33	0.96 (0.45-2.04)	0.91	-	-	-	-
Elevated serum LDH	2.43 (1.39-4.26)	0.002	2.00 (0.94-4.26)	0.05	1.68 (0.69-4.09)	0.25	1.98 (0.57-6.94)	0.28
Stage (III/IV *vs.* I/II)	2.76 (1.34-5.72)	0.006	1.90 (0.77-4.73)	0.17	3.71 (1.08-12.78)	0.04	3.67 (0.45-29.59)	0.22
Extranodal site(s)	1.20 (0.69-2.09)	0.53	0.65 (0.30-1.42)	0.28	-	-	-	-
ECOG (3-4 *vs.* 0-2)	7.11 (2.96-17.08)	<0.001	18.25 (6.92-48.08)	<0.001	3.92 (0.94-16.28)	0.05	6.45 (1.34-31.08)	0.02
Bulky disease	0.13 (0.62-2.11)	0.68	1.13 (0.49-2.61)	0.77	-	-	-	-
CD10 positive by IHC	0.50 (0.26-0.93)	0.02	0.49 (0.21-1.14)	0.10	0.63 (0.25-1.57)	0.32	0.65 (0.19-2.28)	0.50
BCL2 positive by IHC	1.78 (0.83-3.82)	0.14	1.06 (0.44-2.66)	0.90	-	-	-	-
Maintenance rituximab/obinutuzumab	0.69 (0.36-1.28)	0.23	0.40 (0.15-1.07)	0.07	0.91 (0.38-2.18)	0.84	0.32 (0.07-1.59)	0.17

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; LDH: lactate dehydrogenase; ECOG Eastern Cooperative Oncology performance status; IHC: immunohistochemistry.



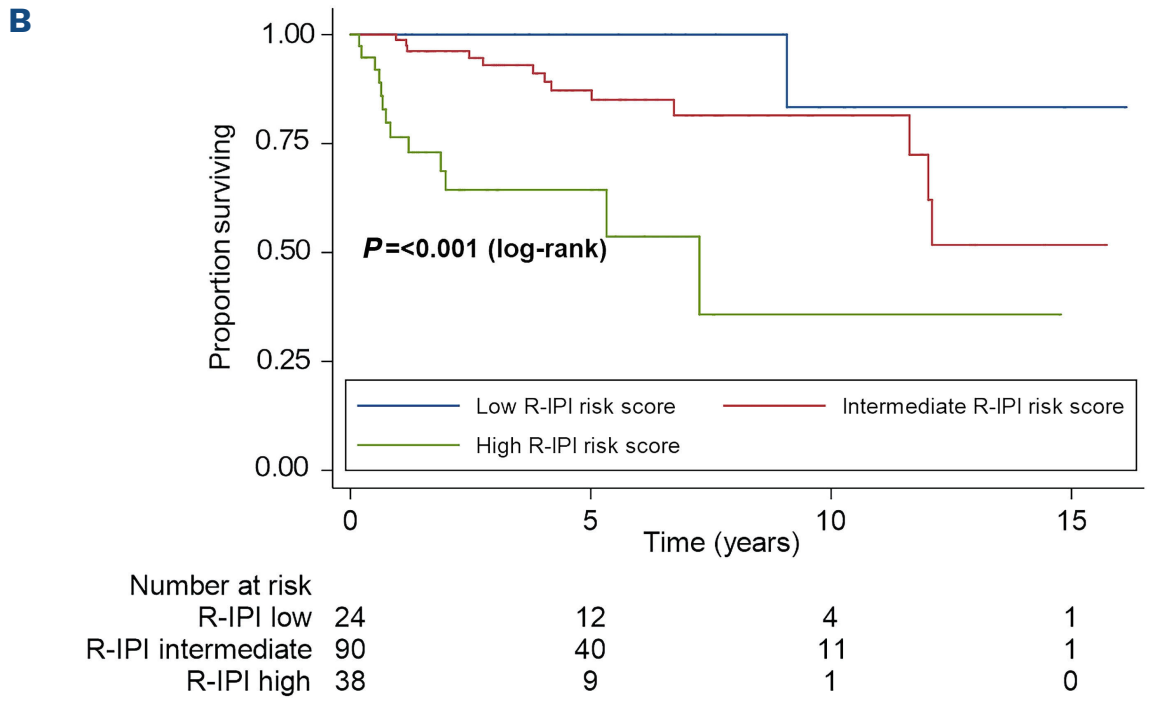


Figure 4. Survival of patients with grade 3B follicular lymphoma according to prognostic risk scores. (A) Overall survival according to Follicular Lymphoma International Prognostic Index (FLIPI) risk score. (B) Overall survival according to Revised International Prognostic Index (R-IPI).

ditionally, compared to DLBCL patients, G3BFL patients presented more commonly with lactate dehydrogenase within the normal range, a lower median ki67 and less frequently with extranodal site involvement, reflecting a more favorable disease "signature". These factors likely contribute to the favorable outcomes of G3AFL and G3BFL described in our study compared to DLBCL.

There are a number of limitations to this study. We acknowledge the inherent limitations of retrospective data collection and analyses. The practice of discharging patients with aggressive lymphoma after 5 years of follow-up and the inability to collect ongoing outcome data after this time-point may contribute to survivorship bias. While it is recognized that relapses after 5 years are rare for DLBCL, this may not be the case with G3BFL, so longer-term conclusions should be made with caution. Another problem is that central pathology review of the entire cohort by a single pathologist was not possible; however, we limited study participation to institutions with local lymphoma pathological expertise and routine lymphoma multidisciplinary meeting case reviews. Even with the harmonization of criteria for FL grading we acknowledge concordance and reproducibility challenges in grading of G3FL.[1,29] Nonetheless, with global central review not feasible in routine care, our international collaboration, with designated expert centers presents a large, real-world international cohort. Furthermore, while relapse proportions were reported, follow-up was not uniform between patients and not all cases had biopsy information available, so these results should be interpreted with caution. Additionally, limited immunohistochemistry and fluorescent *in situ* hybridization diagnostic data were available/provided and this precluded a detailed analysis in this regard. We also acknowledge that the DLBCL cases were collected from 2008 onwards from a limited number of representative centers, while the indolent cases were from 2002 onwards. This decision was due to feasibility of collecting thousands of DLBCL cases as DLBCL is far more common, and due to the stable outcomes of DLBCL seen in both trials and retrospective cohorts across the rituximab era. The similar outcomes from our cohort compared to other large DLBCL real-world studies are reassuring.[26,32,33]

On the basis of this analysis, G3BFL should be considered to have a prognosis similar to that of G3AFL, and distinct from that of DLBCL. Because our G3BFL cohort was uniformly treated with R/O-CHOP, we cannot currently recommend alternative regimens used for lower grade FL. Nevertheless, we suggest that upfront clinical trials for FL that incorporate anti-CD20 monoclonal antibody and CHOP include both G3AFL and G3BFL cases. Due to the marked difference in outcomes compared to those of DLBCL, it seems appropriate to exclude G3BFL from front-line DLBCL clinical trials. Further research to improve the molecular classification of G3BFL may assist in developing specific treatments for this rare subgroup.

Disclosures

HC, MG, MN, JTE, GH, JC, MG, BS, MS, SR, CA, SHW, KF, GD, ZN and TR have no conflicts of interest to disclose. AB has received speakers fees from Roche and sat on an advisory board for Gilead. DV has received honoraria from and sat on advisory boards for Roche, Kite/Gilead, BMS/Celgene, BeiGene, Janssen, Abbvie, AstraZeneca, and Kyowa Kirin; and had received research funding from Roche and AstraZeneca; JW has received honoraria, travel support, and speakers fees from and sat on advisory boards for Abbvie; has received honoraria and travel support from Janssen; and sat on advisory boards for Alexion. MJB has received honoraria from Celltrion, Tevapharma, Gilead, and F. Hoffmann-La Roche; has sat on advisory boards for F. Hoffmann-La Roche; and has received travel expenses from BMS. GC has sat on advisory boards for BMS; and has received research funding from BMS, HutchMed, Pharmacyclics, Merck Serono, AstraZeneca, MorphoSys, Incyte, SeaGen, Isofol, Bayer, and Amgen. MK has sat on advisory boards for Roche and Antengene. H-PL has sat on advisory boards for Roche; and has received honoraria from BeiGene. CT has received honoraria and research funding from Abbvie, Janssen, and BeiGene. CYC has provided consulting services for, has sat on advisory boards for, and has received honoraria from Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG therapeutics, Beigene, Novartis, and BMS; and has received research funding from BMS, Roche, Abbvie, and MSD. AKM has received speaker's fees from Abbvie; has sat on advisory boards for SOBI and Novartis; and had meeting sponsorship from Amgen and MSD. NH has sat on advisory boards for Roche, Gilead, Abbvie, Novartis, Janssen, and Jazz pharma. EAH has received research funding* from Bristol Myers Squibb/Celgene, Merck KgA, AstraZeneca, and Roche; has sat on advisory boards for Roche*, Antigene*, Bristol Myers Squibb, AstraZeneca, Novartis*, Merck Sharpe Dohme*, Gilead*, and Beigene*; has received speaker's fees from Roche*, AstraZeneca*, Abbvie*, Janssen, and Regeneron; and provided consultancy services to Specialised therapeutics. (*Paid to institution).*

Contributions

AB designed the research study, contributed and analyzed the data and wrote the paper. EAH designed and supervised the research study, analyzed the data and wrote the paper. JTE, JW, GH, JC, MG, BS, MJB, MS, SR, CA, GC, SHW, MK, H-PL, KF, CT, GD, CYC, ZN, TR, AKM, NH, HC, MG, MN and DV contributed data and wrote the paper.

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Data-sharing statement

The authors will willingly share the original data on request made by e-mail to the corresponding author.

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