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Prognostic Factors and Effect Modifiers in Patients with Relapsed or Refractory Follicular Lymphoma Who Failed At Least 2 Prior Lines of Therapy: A Systematic Literature Review

Christian Hampp[1], Qiufei Ma[1], Alexi N Archambault[1], Jessica J Jalbert[1], Yingxin Xu[1], Srikanth Ambati[1], Hesham Mohamed[1], Yuting Kuang[2], Krystal Cantos[2], Emaan Rashidi[2], Jennifer Uyei[2]

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [2]IQVIA Inc., San Mateo, CA, USA

Background

- Approximately 20% of patients with indolent follicular lymphoma (FL) are expected to experience relapse within 2 years of initial treatment, and the disease tends to become increasingly refractory to treatment with each subsequent line of therapy[1, 2, 3]
- Considering the cumulative toxicity, limited treatment options, and poor outcomes for patients requiring multiple treatment lines, there is a substantial need to identify effective and safe treatments for relapsed/refractory (r/r) FL patients, especially among those requiring third line and above (3L+) treatment
- Despite the rapidly evolving treatment landscape for r/r FL grade 1-3a*, prognostic factors and effect measure modifiers in later line settings in FL have not been assessed systematically
- Considering that r/r FL in later lines affects a relatively small population, and there is no established standard of care to support an ethical randomized controlled trial (RCT), population adjusted indirect comparisons using literature summary data and trial patient-level data is inevitable. Increasingly, patient-level real world data for external control arm studies have been used as supportive evidence of clinical effectiveness. In such comparative studies, pre-specification of prognostic factors for adjustment is required
- The identification of prognostic factors and effect measure modifiers through a systematic literature review (SLR) while leveraging the expertise of subject matter experts is a rigorous approach to pre-specify confounder adjustment in comparative analyses

**Note: FL grade 3b is considered an aggressive lymphoma by most clinical research groups and treated in the same way as diffuse large B-cell lymphoma (DLBCL), therefore not included here*

Objective

- To systematically identify and catalog prognostic factors and effect measure modifiers in adult patients with r/r FL grade 1-3a who failed at least 2 lines of prior therapy as reported in the literature

Methods

- An SLR was conducted using Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), and Cochrane Central Register of Controlled Trials (CENTRAL) between January 1, 2016, and December 13, 2021. Searches were supplemented by conference abstract review (ASCO, ESMO, ASH, EHA in 2021), forward-citation searches, and bibliography review of key publications
- The approach and methods of the SLR followed the guidelines set forth by the Cochrane Handbook for Systematic Reviews of Interventions[4] and PRISMA[5]. Guidelines from EMA,[6] FDA,[7] IQWiG,[8] and NICE[9,10] have also been consulted
- The scope of the research and criteria for including and excluding studies are outlined in Table 1

Table 1. PICOTS criteria

Criteria	Description
Populations	Adult patients with r/r FL grade 1-3a who failed at least 2 lines of therapy (3L+) **Other applicable eligibility criteria:** • **Lymphoma type**: Include only studies with 100% FL patients or if results were stratified for FL; exclude studies with mixed lymphoma types where results were not stratified • **Line of therapy**: Include studies where at least 50% of patients received 3L+ therapy (i.e., median or mean of at least 2 prior lines of therapy); exclude studies that didn't report the number of prior lines of therapy
Interventions	• Any or none
Comparators	• Not applicable
Outcomes***	• Potential prognostic factors* or effect measure modifiers** that were associated with objective response rate (ORR), overall survival (OS), progression free survival (PFS), time to next treatment (TTNT), complete response rate (CR), duration of response (DOR), disease control rate (DCR), or histologic transformation (HT)
Time	• Publication date limit: January 1, 2016 to December 13, 2021
Study design	• Include: RCT, non-randomized trial, observational study • Exclude: Case reports, evidence synthesis studies or reviews (flag for bibliography), health economic modeling/economic/resource use studies
Other	• Exclude: Non-human, pediatric/pregnancy; publication type as editorials, letters, notes, commentaries • Geography: Global • Language: English (journal article or conference abstract)

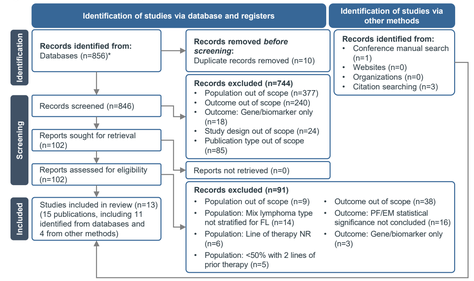
**Defined as variables, including confounders, that are associated with subsequent health outcomes among people with a particular health condition*
***Defined as factors that modify the effect of the putative causal factor(s) under study; effect measure modification occurs when the magnitude of the effect differs depending on the level of a third variable*
****Notes for outcomes: 1) The search and screening were kept broad in order to capture studies reporting on prognostic factors, predictive factors, correlation, association, confounders, effect measure modifiers, subgroups, and other related concepts. 2) Information was extracted for the statistically significant variables only. If multiple models are reported within a study, results were extracted from the most adjusted model. Studies were excluded if statistical significance was not concluded for any model variables*

- Study selection and data extraction were performed by 2 independent reviewers. Risk of bias assessment of individual studies was performed using the quality in prognostic studies (QUIPS) tool[11]
- The protocol for the SLR was registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42022307561

Results

- Overall, 15 publications (9 journal articles and 6 conference abstracts) reporting data on 13 studies were included in the SLR (see Figure 1)

Figure 1. PRISMA flow diagram

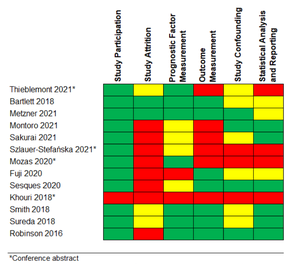


*Search was conducted on December 13, 2021

Study and patient characteristics

- Data sources used among the 13 studies varied, and included non-randomized trials (2 studies) and observational studies (clinical centers or registries, 11 studies)
  - 3 observational studies included overlapping databases, but were all included to capture important sub-populations and to ensure comprehensiveness
- Risk of bias for the included studies (assessed using the QUIPS tool) are presented in Figure 2
  - Most of the included studies were rated high or moderate risk of bias due to lack of reporting, specifically in the "Study Attrition" and "Study Confounding" domains
- The sample size across the included studies varied from 40 to 1567, and the median follow-up time ranged between 17 and 140 months
- Reported treatments included stem cell transplant (SCT; 9 studies), chimeric antigen receptor T-cell therapy (CAR-T; 1 study), targeted therapy (ibrutinib; 1 study), and chemotherapy (1 study). Type of treatment was not reported in 1 study
- Among the 13 studies, all patients had at least 2 lines of prior therapy (6 studies), or at least 50% of the study population received at least 2 lines of prior therapy (3 studies) or had a median/mean of at least 2 lines of prior therapy (4 studies). All studies included 100% FL patients
- Median age of patients ranged from 45 to 64 years, and the proportion of male patients varied from 37% to 70% across the studies

Figure 2. Risk of bias for included studies



*Conference abstract
Red - high risk of bias; yellow - moderate risk of bias; green - low risk of bias

Prognostic factors and effect measure modifiers

- A total of 28 prognostic factors had statistically significant associations (p <0.05) with 7 outcomes:
  - OS (in 9 studies)
  - PFS (in 8 studies)
  - Relapse/progression (in 4 studies)
  - Non-relapse mortality (NRM; in 4 studies)
  - Transplant-related mortality (TRM; in 1 study)
  - ORR (in 1 study)
  - CR (in 1 study)
- Among the identified prognostic factors, older age, having chemorefractory or chemoresistant disease, a greater number of prior lines of therapy, a lower Karnofsky performance score (KPS), a high-risk Follicular Lymphoma International Prognostic Index (FLIPI) composite score, not achieving CR/PR at transplant, use of myeloablative conditioning regimen, and a higher grade of Graft-Versus-Host Disease (GVHD) were associated with worse outcomes in ≥ 2 studies (PFS: 5; OS: 4; others: 6)
- All of the identified prognostic factors showed consistent directionality across studies and outcomes
- See Table 2 for patient demographics and clinical characteristics, Table 3 for disease and treatment characteristics, and Table 4 for imaging and lab measures identified as prognostic factors
- None of the studies identified statistically significant (p <0.05) effect measure modifiers for the population of interest

Table 2. Patient demographics and clinical characteristics – summary of study count, directionality, example characteristics, affected outcomes for statistically significant prognostic factors

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – category with favorable outcomes labeled in green	Clinical outcomes with study counts
Age	N=3§	Older age	• Per year of age (as continuous variable) • ≥45 years (vs. <45 years) • >50 years (vs. ≤50 years)	OS: 2§, PFS: 2, NRM: 3§, TRM: 1, Relapse/ progression: 1
Karnofsky performance score	N=2§	Lower KPS	• <80 (vs. ≥80) • <90 (vs. ≥90)	OS: 1, PFS: 1, NRM: 2§, TRM: 1
ECOG	N=1	Higher ECOG performance score	• 2-4 (vs. 0-1)	OS: 1, PFS: 1
HCT-CI*	N=1	Higher HCT-CI	• High (vs. Low)	PFS: 1, NRM: 1

§Two studies used the same data source and may have overlapping population.

**The hematopoietic cell transplant-comorbidity index (HCT-CI) is a comorbidity index that comprises 17 different categories of organ dysfunctions, including arrhythmia, cardiac comorbidity, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric disturbance, mild hepatic comorbidity, obesity, infection, rheumatologic comorbidity, peptic ulcer, moderate/severe renal comorbidity, moderate pulmonary comorbidity, prior solid tumor, heart valve disease, severe pulmonary comorbidity, moderate/severe hepatic comorbidity*

Table 3. Disease and treatment characteristics – summary of study count, directionality, example characteristics, directionality, affected outcomes for statistically significant prognostic factors

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – Category with favorable outcomes labeled in green	Clinical outcomes with study counts
Chemo-sensitivity	N=3§	Chemorefractory or chemoresistant disease	• Chemoresistant (vs. chemosensitive) • Chemorefractory (vs. chemosensitive) • Rituximab-refractory disease (vs. Rituximab-sensitive disease)	OS: 2§, PFS: 2§, NRM: 2§, TRM: 1, ORR: 1, Relapse/ progression: 2§
Prior lines of therapy	N=2	Higher number of prior lines of therapy	• 3-4 (vs. 1-2) • ≥5 (vs. 1-2) or (vs. 3-4) • >3 (vs. ≤3)	OS: 1, PFS: 2, NRM: 2, TRM: 1
FLIPI score	N=2	High-risk FLIPI score	• High-risk (vs. low-risk) • High-risk (vs. low-risk/Intermediate)	OS: 1, PFS: 1

Table 3. Disease and treatment characteristics – summary of study count, directionality, example characteristics, directionality, affected outcomes for statistically significant prognostic factors (cont'd)

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – category with favorable outcomes labeled in green	Clinical outcomes with study counts
Disease status at transplant	N=2	Not achieving CR/PR at transplant	• No complete remission (vs. complete remission) • Others (vs. CR/PR)	PFS: 1, Relapse/ progression: 1
Conditioning regimen	N=2	The use of myeloablative conditioning regimen	• MAC (vs. Reduced intensity/non-myeloablative) • Myeloablative (vs. Reduced intensity)	OS: 1, PFS: 2, TRM: 1
GVHD grade	N=2	Higher grade of GVHD	• Acute II-IV (vs. Others) • III-IV (vs. I-II)	OS: 1, NRM: 1
Histology	N=1	Higher histology grade	• Grade 3 (vs. Grade 1) • Missing (vs. Grade 1)	OS: 1, PFS: 1, Relapse/ progression: 1
Ann Arbor stage	N=1	Higher Ann Arbor stage	• III/IV (vs. I/II)	OS: 1
Disease stage at diagnosis	N=1	Higher disease stage	• III/IV (vs. I/II)	Relapse/ progression: 1
Extranodal involvement at HCT	N=1	Extranodal involvement	• Yes (vs. No) • Missing (vs. No)	OS: 1
Nodal sites involved	N=1	Higher number of nodal sites	• ≥4 (vs. <4)	OS: 1
PFS2	N=1	Shorter PFS2	• <2 years (vs. >5 years or 2-5 years)	OS: 1, CR after 3rd line treatment: 1
POD24	N=1	Presence of POD24	• Yes (vs. No)	PFS: 1
History of early treatment failure	N=1	History of early treatment failure	• Yes (vs. No)	OS: 1
Duration of last remission prior to alloSCT	N=1	Shorter duration of remission	• <1 year (vs. >1 year)	OS: 1
Time between ASCT and relapse	N=1	Early relapse after ASCT	• <2 years (vs. >2 years)	OS: 1
Treatment line for ASCT	N=1	Higher treatment line for ASCT	• 3rd/4th (vs. 1st)	OS: 1
Histological transformation at relapse after ASCT	N=1	Histological transformation at relapse after ASCT	• Yes (vs. No)	OS: 1

§Two studies used the same data source and may have overlapping population.

Table 4. Imaging and lab measures – summary of study count, directionality, example characteristics, directionality, affected outcomes for statistically significant prognostic factors

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – category with favorable outcomes labeled in green	Clinical outcomes with study counts
Hemoglobin	N=1	Lower level of hemoglobin	• ≤12 g/dL (vs. >12 g/dL)	OS: 1, PFS: 1
LDH	N=1	Elevated LDH	• High (vs. Normal)	OS: 1, NRM: 1
Serum soluble interleukin 2-receptor level at third line	N=1	Lower level of sIL2R	• ≤ 1080 IU/mL (vs. >1080 IU/mL)	PFS: 1

Table 4. Imaging and lab measures – summary of study count, directionality, example characteristics, directionality, affected outcomes for statistically significant prognostic factors (cont'd)

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – category with favorable outcomes labeled in green	Clinical outcomes with study counts
SUVmax in PET/CT	N=1	Higher values of SUVmax high-risk	• At cycle 1 day 8 PET/CT (as continuous variable) • At cycle 1 day 8 PET/CT ≥13.78 (vs. <13.78)	PFS: 1, ORR: 1
TMTV	N=1	Higher TMTV	• High (>510 cm^3, vs. Low)	PFS: 1
Deauville score*	N=1	Higher Deauville score	• ≥3 (vs. <3)	OS: 1

**The Deauville 5-point scale is based on a visual comparison between the uptake of lymphoma tissue and that of the liver and mediastinum in PET/CT.*

Abbreviations *-- ASCT: Autologous stem cell transplantation; allo-HSCT: allogenic hematopoietic stem cell transplantation; allo-SCT: allogenic stem cell transplantation; CR: Complete remission/response; ECOG: Eastern Cooperative Oncology Group; FLIPI: Follicular Lymphoma International Prognostic Index; GVHD: Graft versus host disease; HCT: Hematopoietic cell transplant; HCT-CI: Hematopoietic cell transplant-comorbidity index; KPS: Karnofsky performance score; LDH: Lactate dehydrogenase; NRM: Non-relapse mortality; OS: Overall survival; ORR: Objective response rate; PET/CT: Positron emission tomography/computed tomography; PFS: Progression free survival; PFS2: Interval between frontline treatment and the second relapse; POD24: Progression of disease within 24 months from first immunochemotherapy; PR: Partial remission; sIL2R: soluble interleukin 2-receptor; SUV: Standardized uptake value; TRM: Transplant related mortality; TMTV: Total metabolic tumor volume*

Limitations

- For 20 of the prognostic factors, evidence was only observed in one study, and additional research is required to further validate the association
- Patient clinical and treatment characteristics, as well as treatment received during the study period varied across the included studies. While considered a strength of real-world studies, presence of heterogeneity has the potential to complicate interpretations of prognostic association estimates, particularly since not all patients were necessarily 3L+
- Across studies, there were some overlap in data sources, which may cause some factors to be represented more than once and appear more important
- Only variables and clinical outcomes with statistically significant associations (p <0.05) were extracted. Given that statistical significance is highly influenced by sample and effect size, this study may not include an exhaustive list of every prognostic factor or effect measure modifier relevant to the patient population. This SLR also did not report variables that were non-significant
- The risk of bias assessment showed a lack of reporting for the prognostic factor studies, specifically in the "Study Attrition" and "Study Confounding" domains. This may be due to insufficient reporting especially in conference abstracts, and the fact that many prognostic factor analyses were exploratory in nature and not typically the primary objective of the included studies

Conclusion

- To the best of our knowledge, this SLR is the first to provide a systematic, comprehensive assessment of prognostic factors and potential confounders in patients treated for 3L+ r/r FL, on the basis of scientific literature
- Twenty-eight patient clinical characteristics and disease and treatment characteristics were found to be important prognostic factors of clinical outcomes for patients with r/r FL. However, no statistically significant effect measure modifiers were identified based on the SLR
- Older age, having chemorefractory or chemoresistant disease, a greater number of prior lines of therapy, a lower KPS, a high-risk FLIPI composite score, not achieving CR/PR at transplant, use of myeloablative conditioning regimen, and a higher grade of GVHD were associated with worse survival or response outcomes in ≥ 2 studies
- The prognostic factors identified through this SLR in r/r FL can inform the selection of variables in pre-specified comparative analyses especially between clinical trial populations and real-world data derived cohorts

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Disclosures

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