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An External Control for Mosunetuzumab Using Real-World Data in Follicular Lymphoma in the Third or Subsequent Lines of Systemic Therapy

Sarah F. McGough,[1*†] Natasha Shamas,[1†] Jue Wang,[1] Mahmoud Jaber,[2] Binay Swarup,[2] Marie-Helene Blanchet Zumofen,[2] Bertrand Lautié,[2] Joana Parreira,[2] Michael C. Wei,[1] Ashwini Shewade[1]

*Presenting author: mcgough.sarah@gene.com; †equal contribution

Summary

Mosunetuzumab (M) has shown significantly high rates of complete response with manageable safety in a single-arm trial (SAT)[1]

Real-world data (RWD) from the US were used to build an external control to provide additional context to evidence from the M SAT

These findings support a clinically meaningful benefit of fixed-duration M monotherapy as a chemotherapy-free option for the ≥3 lines of therapy (3L+) follicular lymphoma (FL) patient population.

Comparison with a RWD-based external control suggested higher complete response (CR) rate and longer overall survival (OS) for M

Background

- FL is an incurable indolent disease characterized by a series of remissions and relapses, with generally increasing refractoriness and decreasing duration of response to therapy.
- Despite the availability of many new therapeutic options, there is no clear standard of care in the relapsed/refractory (R/R) FL setting, especially in 3L+ FL.
- M is a CD20xCD3 T-cell engaging bispecific antibody that showed manageable safety and a significantly higher rate of CR after a fixed duration of treatment compared to a historical control in a Phase II SAT (NCT02500407).[1]
- Additional evidence, such as RWD, can provide context related to the comparative treatment benefit of M in the heterogeneous treatment landscape of 3L+ FL.
- This study aims to compare clinical outcomes in 3L+ FL patients treated in the M SAT to those treated with commonly available treatments in routine clinical practice, particularly in the community setting, in the United States (US).

[1]Genentech, Inc., South San Francisco, USA; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Methods.

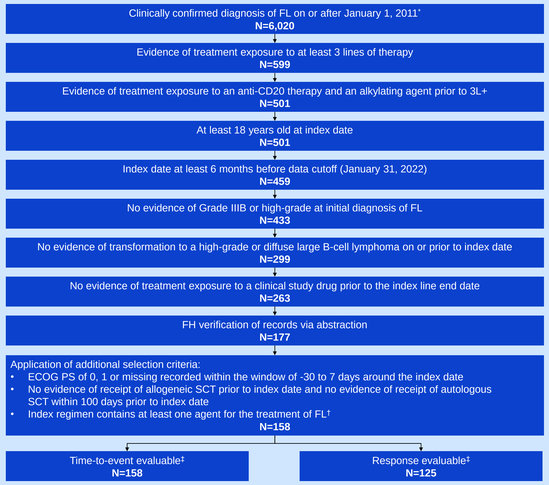
Study design and data sources

- This observational study compared efficacy outcomes of M in 3L+ R/R FL from the SAT with those observed in the real-world using a nationwide Flatiron Health (FH) database of FL patients derived from electronic health records.
- FH is a longitudinal, de-identified, patient-level database capturing data from over 280 cancer clinics (800 sites of care) representing over 2 million active US cancer patients.[2,3]
- Data from a cohort of 3L+ R/R FL patients from FH were used to develop an external control arm meeting key eligibility criteria of the M SAT and balanced on key confounders using the propensity score method (PSM).

Cohort selection

- The RWD cohort was selected from patients in the FH database with a confirmed diagnosis of FL, on or after January 1, 2011, and evidence of ≥3 lines of therapy for FL on or before July 31, 2021 (**Figure 1**).

Figure 1. Cohort selection in FH.



*Patients were probabilistically sampled from an overall cohort of 207,263 patients with an ICD code for FL in the FH network.
†Defined as a regimen including at least one agent recommended by the National Comprehensive Cancer Network for the treatment of FL.
‡Of 158 patients, all had progression and/or survival data available but 33 did not have response data available in their index line of systemic therapy, resulting in 125 response-evaluable patients and 158 time-to-event evaluable patients.
ECOG, Eastern Cooperative Oncology Group Performance Status; SCT, stem cell transplant.

Statistical analyses.

- Patients in the FH database could meet the eligibility criteria of the M trial at multiple lines in the 3L+ setting because of the retrospective nature of the database. For each patient in the RWD cohort, the latest eligible line with complete data on all prognostic factors and availability of outcomes was selected as the index line.
- The M and RWD cohorts were balanced on key pre-specified prognostic factors (**Table 1**). The RWD cohort was re-weighted using inverse probability of treatment weights to estimate the average treatment effect in the treated population.
- Comparative analyses between the M and RWD cohorts were conducted for overall response rate (ORR; primary endpoint), CR rate, progression-free survival (PFS), OS as secondary endpoints, and time-to-next treatment (TTNT; exploratory endpoint).
- Sensitivity analyses were conducted to assess the robustness of the findings: 1) Adjudicated line of therapy: using abstracted line confirmation information to update the FH default line of therapy data; 2) Earliest line: selecting each patient's earliest eligible index line; 3) Strict inclusion/exclusion (I/E): applying a set of stricter trial eligibility criteria; 4) Anti-CD20 + chemotherapy (anti-CD20 + chemo): subsetting to a cohort of patients treated with anti-CD20 + chemo only; 5) Tumor grade: using abstracted tumor grade information; 6) Full follow-up: modelling the full available follow-up time in the RWD cohort.

The M SAT enrolled 90 patients;[1] all were included in the analysis.

- The RWD cohort included 158 patients for time-to-event endpoints and 125 for response-based endpoints (**Figure 1**).
- RWD patients received one of 5 regimen categories as their 3L+ index regimen: anti-CD20 + chemo (37%), anti-CD20+ lenalidomide (16%), anti-CD20 monotherapy (15%), phosphoinositide 3-kinase inhibitors (16%), and other (16%).

- The M cohort was more heavily pretreated with a higher proportion of patients with 4+ prior lines of systemic therapy than the RWD cohort, which had a higher proportion of double-refractory patients (**Table 1**).
- PSM addressed the imbalance between cohorts on the prognostic factors (standardized mean difference [SMD], <0.10, **Table 1**).

Table 1. Baseline characteristics in M SAT versus RWD.

	M SAT N=90*	Weighted RWD		SMD‡	
		Pre, N=158*†	Post, N=88*	Pre	Post
Prognostic factors included in the PSM					
Age at index line (years)	60 (53–66)	68 (57–75)	59 (53–69)	0.44	0.01
POD24	47 (52%)	74 (47%)	42 (48%)	0.11	0.08
Refractory to last prior line	62 (69%)	102 (65%)	59 (67%)	0.09	0.04
Double refractory	48 (53%)	121 (77%)	48 (55%)	0.50	0.03
Number of prior lines					
2	34 (38%)	111 (70%)	33 (37%)	0.75	0.07
3	28 (31%)	34 (22%)	30 (34%)		
4+	28 (31%)	13 (8.2%)	25 (29%)		
Factors not included in the PSM§					
Time from initial FL diagnosis to index (months)	81 (51–129)	44 (22–64)	40 (19–76)	–	–

*Median (interquartile range) or n (%).
†A subset of 125 patients were included in the response-evaluable cohort; a separate PSM was run for this subset and good balance was achieved on all prognostic variables (SMD <0.10).
‡Balance between the RWD and M cohorts was considered achieved if the SMD of at least half of the prognostic variables in the PSM was <0.25.
§Due to lack of adequate balance between cohorts as well as to improve balance on the other prognostic factors, time from initial diagnosis to initiation of index was omitted from the PSM post-hoc and instead adjusted for in the outcome models.
To make an objective assessment with the M SAT, all endpoints were assessed in the RWD cohort up to the maximum observed follow-up for M. At the August 21, 2021 data cut-off date, the maximum follow-up was 27.5 months.
POD24, progression of disease within 24 months.

Comparative analyses of clinical outcomes between M SAT and RWD cohorts.

- There was a significant treatment benefit associated with M for CR rate (odds ratio [OR], 3.18; 95% confidence interval [CI]: 1.41–7.17) and OS (hazard ratio [HR], 0.43; 95% CI: 0.19–0.94) (**Table 2**).
- 12-month OS was 93% (95% CI: 88–98) in M SAT and 76% (95% CI: 64–88) in RWD.
- ORR, PFS, and TTNT were comparable between the M SAT and RWD cohorts.

Table 2. Summary of weighted comparative outcomes.

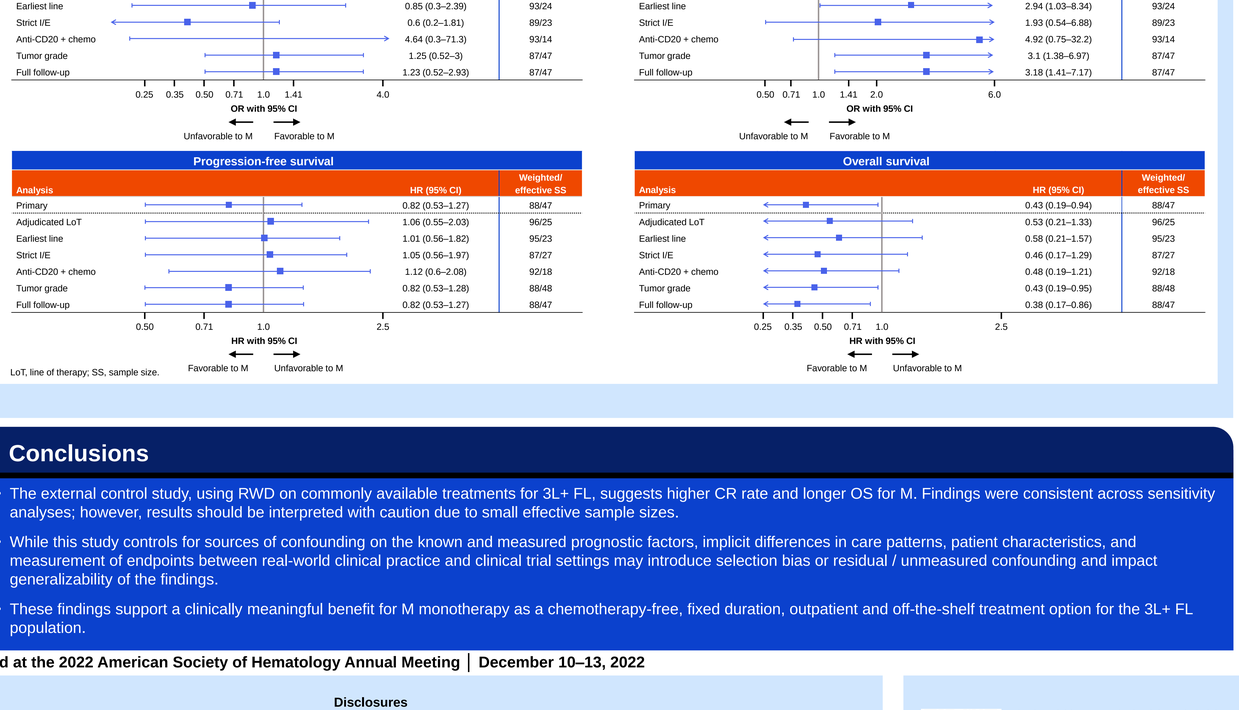
Endpoint	Treatment arm		M vs RWD
	M SAT	RWD	
Response rate	N=90	N=87*	OR (95% CI)†
	Proportion responding (95% CI)		
Primary: ORR	80% (72–88%)	75% (63–86%)	1.23 (0.52–2.93)
Secondary: CR rate	60% (50–70%)	33% (19–47%)	3.18 (1.41–7.17)
Time-to-event	N=90	N=88‡	HR (95% CI)§
	Median time-to-event (months, 95% CI)		
Secondary: PFS	17.9 (10.1–NR)	10.1 (6.54–22.8)	0.82 (0.53–1.27)
Secondary: OS	NR	NR	0.43 (0.19–0.94)
Exploratory: TTNT	NR (16.2–NR)	19.4 (8.98–22.6)	0.77 (0.47–1.26)

*Sample size in the response-evaluable cohort after weighting (i.e. the sum of weights). The effective sample size was 47.
†Weighted logistic regression and ‡Cox proportional hazards model as a function of study cohort and time from FL diagnosis to index line initiation. 95% CIs constructed using a robust estimator for the standard error.
§Sample size in the time-to-event evaluable cohort after weighting. The effective sample size was 47. For OS and TTNT, 2 patients (with a total weight of 5) were excluded due to inadequate capture of dates.
NR, not reached.

Sensitivity analyses show consistency in findings for all endpoints.

- Estimates for CR rate and OS were consistent with those of the primary analysis in directionality and magnitude. Estimates for ORR and PFS fluctuated but remained comparable between the M and RWD cohorts (**Figure 2**).

Figure 2. Forest plots of sensitivity analyses for M SAT vs RWD.



LoT, line of therapy; SS, sample size.

Conclusions

- The external control study, using RWD on commonly available treatments for 3L+ FL, suggests higher CR rate and longer OS for M. Findings were consistent across sensitivity analyses; however, results should be interpreted with caution due to small effective sample sizes.
- While this study controls for sources of confounding on the known and measured prognostic factors, implicit differences in care patterns, patient characteristics, and measurement of endpoints between real-world clinical practice and clinical trial settings may introduce selection bias or residual / unmeasured confounding and impact generalizability of the findings.
- These findings support a clinically meaningful benefit for M monotherapy as a chemotherapy-free, fixed duration, outpatient and off-the-shelf treatment option for the 3L+ FL population.

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Disclosures
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