Recurrent Hematological Toxicity After Second-Line Treatment in Patients with Glioblastoma: Indication of a Potential Predisposition

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Recurrent myelotoxicity in second-line glioblastoma treatment

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1. Abstract

Purpose:

Myelotoxicity is a well-known adverse effect of alkylating chemotherapy for glioblastoma. While risk factors during first-line therapy are established, little is known about myelotoxicity recurrence in second-line treatment. This study investigates whether first-line myelotoxicity therapy predisposes patients to recurrence in the second-line setting.

Patients and Methods:

We conducted a retrospective cohort study of 589 patients with glioblastoma treated at the Brain Tumor Centre Amsterdam (2005-2022). Of these, 178 received second-line lomustine or rechallenge temozolomide. Myelotoxicity severity was predominantly assessed using nadir hematological values and its duration. A log-link generalized linear model evaluated associations between first-line and second-line myelotoxicity severity, adjusting for covariates. Cox proportional hazards models assessed time to myelotoxicity onset.

Results:

We included 151 patients (mean age 57.1 ± 11.8 years; 66.9% male). Lomustine was given to 66.9%. Myelotoxicity occurred in 73.5% of patients, with 19.9% developing severe toxicity. First-line myelotoxicity severity was significantly associated with second-line severity (β=1.3, p<.001). Lomustine correlated with higher myelotoxicity severity than temozolomide (β=1.4, p=.002). Higher first-line myelotoxicity scores predicted earlier onset of any-grade (HR=1.4, p<.001) and severe (HR =2.1, p<.001) myelotoxicity in second-line therapy.

Conclusion:

First-line myelotoxicity for glioblastoma predicts its recurrence and earlier onset in second-line therapy. Patients with toxicity in first-line have an increased risk of severe hematological toxicity upon re-exposure. Lomustine carries a higher risk for myelotoxicity than temozolomide. These findings suggest an inherent predisposition to alkylating

chemotherapy-induced myelotoxicity for a subgroup of patients. Integrating prior myelotoxicity history into second-line treatment decisions may improve risk stratification and guide monitoring.

Implications for Practice

A history of first-line myelotoxicity should guide second-line treatment decisions for glioblastoma. Patients with prior myelotoxicity constitute a high-risk subgroup, prone to developing earlier and more severe hematological toxicity during second-line therapy. Clinicians should implement closer monitoring, especially when considering lomustine over rechallenge temozolomide, which carries a higher risk. Proactively modifying treatment regimens for these patients is a critical step towards safer, more personalized chemotherapy.

2. Introduction

Glioblastoma, the most common adult primary brain tumor (incidence: 3.23 per 100,000), carries a poor prognosis with a 6.8% five-year survival rate.[1] Standard treatment is maximal safe resection, radiotherapy, and temozolomide, while elderly/frail patients often receive hypofractionated radiotherapy.[2] Upon tumor progression, second-line options include lomustine or temozolomide rechallenge, with selection based on performance status, time to progression, and first-line tolerance.[3]

Alkylating agents like temozolomide and lomustine frequently cause myelotoxicity, particularly neutropenia and thrombocytopenia, affecting approximately 25% of patients in a severe grade.[4] Severe forms often impact multiple hematopoietic cell lineages.[5,6] These severe events necessitate treatment modifications, increase unplanned healthcare resource use, may require platelet transfusions, and elevate hospitalization risk due to infection.[7-11] While MGMT methylation, female sex, and older age have been linked to first-line myelotoxicity, predictive biomarkers are lacking, and risk factors for second-line toxicity remain poorly understood.[12-14]

Whether myelotoxicity during first-line treatment predisposes patients to recurrence in second-line therapy remains unclear. Furthermore, it is unknown whether the same hematopoietic lineage (e.g., myeloid vs. lymphoid) is consistently affected across different treatment lines in susceptible patients. Understanding these patterns could improve risk stratification and refine monitoring strategies. This study investigates the occurrence of myelotoxicity during second-line therapy and identifies clinical risk factors. Given limited options for recurrent glioblastoma, identifying higher-risk patients is crucial for tailoring intensive monitoring and pre-emptively adjusting treatments to mitigate complications and optimize care.

3. Materials and Methods

3.1 Study population

Between 2005 and 2022, 589 patients with histologically confirmed glioblastoma were treated at the Brain Tumor Centre Amsterdam. Eligible patients received first-line standard or hypofractionated treatment, followed by second-line therapy upon tumor progression. Further inclusion criteria were planned second-line lomustine (100 mg/m²) or temozolomide (150–200 mg/m²) doses. Of these, 178 patients (30.2%) received second-line chemotherapy (rTMZ and/or lomustine), sometimes after re-resection and/or re-irradiation without chemotherapy. Complete hematological laboratory parameters for both treatment lines were required. Exclusion criteria were unrelated comorbidities influencing hematological parameters or participation in experimental treatment studies.

Data extracted included: general patient characteristics (sex, age, BMI, BSA); clinical data (diagnosis/treatment dates, chemotherapy courses/doses, first-line completion, KPS score pre-second-line); tumor details (location, resection extent, re-resection/re-irradiation); all relevant hematological laboratory values (hemoglobin, thrombocytes, leukocytes, neutrophils, lymphocytes) during both treatment lines; and concomitant second-line medications (seizure-modifying therapies, PPIs, corticosteroids).

As chemotherapy dosages based on body surface area (BSA), we assessed initial dosing discrepancy, quantified as the absolute (mg) and relative (%) difference between calculated and received starting doses. Analyses were separate for temozolomide (5 mg increments) and lomustine (40 mg capsules) due to differing capsule availability, which could cause greater dosing discrepancies. The Medical Review Ethics Committee of Amsterdam UMC approved this study (VUMC2020.075).

3.2 Myelotoxicity quantification

Hematological parameters were extracted from electronic health records and laboratory data for all patients during both first- and second-line treatments. Longitudinal measurements were collected from treatment initiation until three months post-discontinuation. Parameters were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For comparison with existing literature, myelotoxicity severity was categorized: no (CTCAE grade 0), moderate (grades 1–2), and severe (grades 3–4) toxicity. Additional stratification was performed for thrombocytopenia and neutropenia, given their clinical relevance. Clinically relevant myelotoxicity was defined as platelet counts $<100 \times 10^9$/L and neutrophil counts $<1.5 \times 10^9$/L. During second-line treatment, duration and frequency of each clinically relevant episode were calculated from the first sub-threshold measurement to the first subsequent supra-threshold value. Baseline laboratory values were defined as those nearest to the start of second-line therapy, within a window from one month prior to two weeks after treatment initiation.

While adhering to the CTCAE classification for categorizing myelotoxicity severity, we also developed a continuous myelotoxicity score. This score, determined for each cell line using CTCAE grade thresholds, integrates the categorical severity with a continuous adjustment within each grade, thereby providing a more nuanced reflection of myelotoxicity that captures variations within a grade while remaining true to standardized categorization. An expanded description of this method can be found in Supplementary Methods 1.

3.3 Statistical analysis

Appropriate statistical tests, based on data characteristics, described demographic differences by second-line treatment type. A generalized linear model (log-link) assessed the association between first- and second-line myelotoxicity using continuous scores. The full model adjusted for all available patient characteristics (e.g., first/second-line treatment

schedules, inter-treatment duration, baseline second-line sex, BSA, and starting myelotoxicity score). A reduced model included only variables improving model fit (determined by backwards variable elimination and AIC reduction ≥5 points). Nadir first and second-line myelotoxicity scores were visualized through scatterplots. If variables were missing in less than 10% of cases and the data were missing at random, multiple imputation by chained equations was used to impute the missing values.

Pearson correlation coefficients were calculated for nadir myelotoxicity scores of all cell lines. Correlations were visualized in correlation matrices to compare both within first- and second-line treatments, as well as between first- and second-line treatment schedules. The Benjamini-Hochberg method adjusted statistical outcomes for multiple comparisons.

The Benjamini-Hochberg method adjusted statistical outcomes for multiple comparisons. The time-to-event was calculated as the number of days between the first day of second-line treatment to the onset of any grade or severe myelotoxicity, respectively. Patients with myelotoxicity at second-line start had an event time of one day. Right sided censoring of patients at the end of second line treatment was applied if no myelotoxicity developed or if patients stopped treatment. Time-to-event findings were visualized through plotting one-minus-Kaplan-Meier curves, showing the proportion of the population that developed the event of interest over time. Forest plots were made to illustrate the direction of the effect of the included variables.

Data handling, univariable comparisons, the fitting of a generalized linear models and time-varying Cox proportional hazards models were done using the Pandas version 2.2.2, statsmodels version 0.14.4 and Lifelines 0.30.0 libraries using Python version 3.13. Statistical significance was set at $p < .05$.

4. Results

4.1 Patient and treatment characteristics

Of 178 eligible patients, 27 (15.2%) lacked sufficient myelotoxicity-related laboratory values for either treatment line, resulting in 151 included patients (84.8%). The average age of the cohort was 57.1 years (SD: 11.8), and 101 patients (66.9%) were male. During first-line treatment, 122 patients (80.8%) received the standard treatment schedule, while 29 (19.2%) followed a hypofractionated schedule. All patients initiated the six-cycle temozolomide monotherapy as first-line adjuvant treatment.

For second-line treatment, baseline patient demographics are presented in Table 1, stratified by treatment type. Supplementary Table 1 provides further details on excluded patients. Tumor re-resection was performed in 37 (24.5%) patients, and 11 (7.3%) patients received re-irradiation. Of the patients included, 101 (66.9%) received lomustine, while 50 (33.1%) received rTMZ. Figure 1 illustrates the flow of patients between different treatment types during first- and second-line therapies. Lomustine patients had a shorter inter-treatment interval (median: 49 days, IQR: 15-168) than rTMZ patients (median: 521 days, IQR: 326-849.2; $p < .001$). Lomustine patients had a mean starting dose of 199.2 mg (SD: 23.3) and relative dosing discrepancy of 5.0% (10.0 mg), versus rTMZ patients with a median 302.5 mg (SD: 30.3) dose and 0.4% (1.1 mg) discrepancy ($p < .001$). In addition, patients treated with second-line lomustine completed fewer cycles of chemotherapy (median: 2 cycles, IQR: 1-2) compared to those receiving rTMZ (median: 4 cycles, IQR: 3-6; $p < .001$).

4.2 Severe myelotoxicity is most common among patients receiving lomustine

During first-line treatment (Supplementary Table 2), 132 patients (87.4%) developed myelotoxicity, with 24 (15.9%) experiencing severe forms. Thrombocytopenia was the most prevalent subtype, affecting 81 patients (54.4%).

In second-line treatment (Supplementary Table 3), 114 patients (75.5%) developed myelotoxicity, including 30 patients (19.9%) who experienced severe toxicity. Severe thrombocytopenia remained the most common subtype, occurring in 19 patients (12.7%). Severe myelotoxicity was observed in 23 patients (22.8%) treated with lomustine and in 7 patients (14.0%) treated with rTMZ. Clinically relevant thrombocytopenia occurred in 36 patients (23.8%), with a median duration of 15 days (IQR: 10.5–22.5 days). It typically occurred only once (median), with a maximum of three episodes. Clinically relevant neutropenia was observed in 20 patients (13.2%), with a median duration of 15 days (IQR: 7–42 days), typically occurring once, with a maximum of two episodes.

4.3 Myelotoxicity during first-line treatment associates with increased myelotoxicity score during second-line treatment

To assess whether nadir myelotoxicity severity during first-line treatment predicted severity during second-line treatment, a generalized linear model was applied. A clear pattern emerged (Figure 2C): 10 of the 24 patients (41.7%) with severe first-line myelotoxicity also developed severe second-line myelotoxicity. In comparison, only 20 of the 127 patients (15.8%) without severe first-line myelotoxicity experienced severe toxicity during second-line therapy. Notably, none of the 19 patients with no myelotoxicity during first-line treatment developed severe toxicity during second-line treatment. A corrected analysis of nadir myelotoxicity scores confirmed a significant positive association between first- and second-line severity ($\beta = 1.2$, 95% CI: 1.1–1.3, $p < .001$; Table 2, Figure 2A).

Compared to patients who received rTMZ, those receiving lomustine as second-line treatment had a higher nadir myelotoxicity score ($\beta = 1.4$, 95% CI: 1.1–1.7, $p = .002$, Figure 2B). First-line myelotoxicity score, second-line baseline score, first-line treatment type, female sex, BSA, or age at second-line start were not associated.

4.4 Myeloid-derived myelotoxicity types are correlated within and between first- and second-line treatment

To explore whether population-level differences in myelotoxicity subtypes might reflect selective depletion of hematopoietic progenitor cells, we performed multicollinearity analyses of myelotoxicity scores during second-line treatment. We hypothesized that subtypes originating from a shared progenitor lineage would show positive collinearity. As expected, myeloid-derived toxicities were positively correlated, while lymphocytopenia—arising from a distinct lymphoid lineage—showed no correlation with either thrombocytopenia or neutropenia scores (Figure 3A). Similar patterns were observed during first-line treatment, with strong intercorrelation among myeloid subtypes and a lack of association between lymphoid and myeloid toxicities.

In addition to these analyses, we examined the intercorrelation of myelotoxicity subtypes nadir scores between first- and second-line treatments (Figure 3B). An orthogonal pattern emerged, indicating that each subtype was most strongly correlated with itself across treatment lines. Myeloid-derived toxicities generally showed a positive correlation with their counterparts between treatment lines. In contrast, lymphocytopenia exhibited limited correlation with myeloid subtypes across treatment lines, with second-line anemia being a notable exception.

4.5 Patients who developed severe myelotoxicity during first-line treatment associate with earlier development of myelotoxicity during second-line treatment

Cox Proportional Hazards analyses tested if higher first-line myelotoxicity severity predicted earlier development of any grade and severe second-line myelotoxicity. Both any grade and severe myelotoxicity first occurred during the first week of second-line treatment. Median time to any myelotoxicity was 38 days (IQR: 21-55) and to severe myelotoxicity 82 days (IQR: 40-127). Higher severity of first-line myelotoxicity was independently associated with earlier

development of any grade of myelotoxicity (HR = 1.4, 95%-CI 1.2 – 1.7, p < .001, Figure 4A, B), as well as severe myelotoxicity during second-line treatment (HR = 2.1, 95% CI: 1.5–3.0, p < .001, Figure 4C, D). Additionally, patients who received lomustine - compared to those who received rTMZ - had earlier time to development of any grade of myelotoxicity (HR = 1.7, 95%-CI 1.1 – 2.6, p = .011) and severe myelotoxicity (HR = 2.9, 95% CI: 1.2–7.2, p = .018). A higher myelotoxicity score at baseline was associated with earlier development of any grade of myelotoxicity (HR = 2.5, 95%-CI 1.8 – 3.7, p < .001) but not with the time-to-development of severe myelotoxicity (HR = 1.4 95% - CI 0.67 – 3.1, p = .35). Both patient sex and the type of first-line treatment received was not associated with the time-to-development of myelotoxicity (full results in Supplementary Table 4).

5. Discussion

Our analyses revealed a strong correlation between first-line myelotoxicity and its second-line recurrence in progressive glioblastoma, with higher initial toxicity predicting earlier subsequent onset. This underrecognized relationship underscores the need for improved risk stratification and monitoring, particularly with widespread alkylating agent use. Identifying patients at higher risk of recurrent myelotoxicity could help optimize treatment decisions and mitigate toxicity-related complications.

Treatment selection for patients with progressive glioblastoma is based on response to initial therapy, patient performance at tumor progression, and treatment tolerability, including prior myelotoxicity. While one study found no recurrence link for non-hematological toxicities with tyrosine kinase inhibitors [15], myelotoxicity recurrence, despite its prognostic and treatment response relevance, has not been specifically examined. As a result, it remains unclear whether prior hematological toxicity should guide second-line treatment selection or influence the starting dose. Our findings indicate first-line myelotoxicity strongly predicts second-line risk; moreover, patients with more severe first-line myelotoxicity developed it

more rapidly upon re-exposure in the recurrent setting. *These findings suggest that clinicians may wish to incorporate prior myelotoxicity history into their assessment when initiating second-line therapy, especially when considering lomustine. In patients with previous severe toxicity, intensified monitoring—such as weekly blood counts during the initial treatment cycles—may help detect early complications. Moreover, in scenarios where efficacy is comparable, these risk profiles may support choosing temozolomide rechallenge over lomustine to minimize the likelihood of severe hematological events.*

Myelotoxicity risk in patients receiving alkylating agents has been associated with patient characteristics in prior studies. For instance, MGMT promoter methylation status and baseline patient factors such as female sex and BSA have been linked to increased myelotoxicity risk.[5,13,16] Predictive models using demographic and baseline clinical factors showed limited performance and no prospective clinical application.[17,18] However, models incorporating biological parameters (e.g., myelotoxicity-associated SNPs) show improved accuracy, suggesting a biological predisposition to myelotoxicity missed by conventional clinical assessments.[13,19] This aligns with our findings of recurrent hematological toxicity after first-line treatment, further indicating a potential predisposition that extends beyond conventional clinical risk factors. Notably, frequently reported risk factors such as BSA, female sex, and age were not associated with myelotoxicity in our study. This finding suggests that prior myelotoxicity status may be a more relevant predictor of toxicity recurrence than previously described demographic factors.

Patients receiving lomustine in second-line treatment experienced greater myelotoxicity severity. This may be due to the shorter inter-treatment interval (also seen in our cohort), as lomustine is typically prescribed for tumor progression within six months. Moreover, pharmacokinetics differs between lomustine and temozolomide, with prolonged bone marrow suppression in lomustine that may exacerbate myelotoxicity and lomustine being

highly lipophilic where temozolomide is more hydrophilic.[20-22] Limited recovery time from first-line treatment may place additional strain on hematopoietic progenitor cells before second-line therapy, suggesting hematopoietic reserve plays a critical role in determining toxicity severity with sequential alkylating chemotherapy. Chemotherapy doses are also calculated based on BSA, introducing inherent discrepancies between calculated and received doses due to drug capsule availability. We observed this discrepancy to be greater for lomustine (40 mg capsule increments) compared to temozolomide (5 mg increments) in our cohort. This dose variability could contribute to differing myelotoxicity severity between regimens. Therefore, initiating second-line treatment, particularly lomustine, shortly after first-line therapy warrants careful consideration and potentially stricter monitoring, as compromised hematopoietic reserve and dosing nuances appear relevant contributors to subsequent myelotoxicity risk.

Analyses revealed collinear patterns in myelotoxicity types between first- and second-line treatment. First-line myelotoxicity correlated with the same type in second-line, and specific lineage relationships were observed across treatments. For instance, severe thrombocytopenia in first-line aligned with myeloid-related toxicities (thrombocytopenia, anemia, neutropenia) in second-line, but not lymphoid (lymphocytopenia). This suggests myelotoxicity risk may be driven by lineage-specific vulnerabilities. Recognizing early signs of less severe myelotoxicity, such as anemia, could allow for proactive interventions and potentially reduce unplanned healthcare utilization. We hypothesize that early myelotoxicity within a specific hematopoietic lineage predicts the later occurrence of severe toxicity in that same lineage.

A key strength is using a continuous CTCAE-based severity score, capturing more myelotoxicity nuance than binary cutoffs. This approach integrates multiple myelotoxicity types into a single, detailed measure. Our real-world clinical cohort further enhances the

generalizability of the findings. Given the limited treatment options for glioblastoma, tailoring treatment schedules to individual myelotoxicity patterns may improve both safety and efficacy. Importantly, our results indicate that early-onset myelotoxicity could serve as a biomarker for recurrence risk, supporting its potential role in personalized treatment strategies. However, as a single-centre retrospective study, our results should be interpreted cautiously due to potential biases. Specifically, selection bias may be present: patients with severe prior myelotoxicity might have been offered second-line chemotherapy less frequently, potentially reducing the observed incidence and underestimating the strength of the association. Consequently, the strong association we observed likely represents a conservative estimate of the true risk in the general glioblastoma population. Additionally, due to the retrospective design, hematological monitoring followed routine clinical practice rather than a standardized trial protocol. This may have resulted in variations in sampling intervals and potentially missed transient nadirs between visits; however, these undetected episodes are likely of limited clinical significance, and our use of continuous CTCAE-based scoring mitigates the impact of isolated missed peak values. Moreover, the initial exclusion of patients lacking sufficient myelotoxicity-related laboratory values for analysis could introduce bias if these individuals were systematically different from the included cohort. External validation in additional cohorts, particularly among patients treated with rTMZ, is preferable to confirm these associations and enhance their clinical applicability.

In conclusion, more severe first-line myelotoxicity in glioblastoma patients predicts earlier and more severe second-line myelotoxicity. This association highlights that myelotoxicity in first-line treatment suggests more stringent follow-up during second-line treatment, especially if lomustine is given.

Author contributions

All authors contributed to the study conception and design. Data collection was performed by Leon van Hout, Femke E. L. van den Elzen, Zoë de Jong, and Nienke Grun. Formal analysis and methodology were performed by Leon van Hout and Birgit I. Lissenberg – Witte. Visualization was performed by Leon van Hout and Femke E. L. van den Elzen. The first draft of the manuscript was written by Leon van Hout and Femke E. L. van den Elzen. All authors commented on previous versions of the manuscript and contributed to its review and editing. Supervision was provided by Mathilde C. M. Kouwenhoven. All authors read and approved the final manuscript.

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Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Data availability

The datasets collected during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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7. Figures

7.1 Figure captions

Figure 1 Patient treatment type flowchart showing patient flow and exclusions

Figure 2 Nadir myelotoxicity score during first-line treatment is positively associated with the nadir myelotoxicity score during second-line treatment. A. Scatterplot overlay showing the nadir myelotoxicity score developed during second-line treatment (y-axis) by the nadir myelotoxicity score developed during first-line treatment (x-axis). The blue line shows the predicted effect of first-line myelotoxicity score on the second-line myelotoxicity score. With continuous variables set to the mean population value and categorical variables set to the most common value: first-line treatment, standard treatment; second-line treatment, lomustine; sex, male. B. Boxplots showing the nadir myelotoxicity score for both treatment lines during second-line treatment. Patients who received lomustine had a higher median nadir myelotoxicity score during second-line treatment in comparison to the median nadir myelotoxicity score during first-line treatment. C. Bar charts showing the occurrence of different severities of myelotoxicity during second-line treatment, by the severity of myelotoxicity during first-line treatment. D. Scatterplots overlaying boxplots showing the duration in days of the first clinically relevant episode a patient developed during second-line treatment. Episode duration plots are stratified based on the nadir first-line myelotoxicity severity. A clinically relevant episode of thrombocytopenia is defined as a thrombocyte count of $< 100 \times 10^9$/L, and a clinically relevant episode of neutropenia is defined as a neutrophile count of $< 1.5 \times 10^9$/L. No myelotoxicity: grade 0, moderate myelotoxicity: grades 1 & 2, and severe myelotoxicity: grades 3 & 4. **, $p < .01$

Figure 3 Development of different cell line myelotoxicities are associated with in first-line, within second-line and between first- and second-line treatment phases. A. Heatmap representation of two correlation matrices, correlations between specific cell lines within

first-line treatment are shown in the bottom left half, correlations between specific cell lines within second-line treatment are shown in the top right half. B. Heatmap representation of a correlation matrix between the occurrence of specific cell line myelotoxicities during first-line and second-line treatment phases. Top values in the cell are the Pearson correlation coefficient; bottom values are the significance values as corrected for multiple testing using the Benjamini Hochberg method. Dotted lines indicate correlations between lymphoid progenitor derived cell lines with myeloid progenitor derived cell lines. Abbreviations: Thr, thrombocytopenia; Ane, anemia; Lym, lymphocytopenia; Neu, neutropenia; Leuk, leukocytopenia

Figure 4 Nadir first-line myelotoxicity severity correlates with time-to-development of both any and severe myelotoxicity during second-line treatment. A. One-minus Kaplan-Meier curve showing the time-to-development of any severity of myelotoxicity during second-line treatment, per CTCAE grade of myelotoxicity at nadir during first-line treatment. B. Forest-plot showing the Cox-Proportional Hazards analyses outcomes for the time-to-development of any severity of myelotoxicity during second-line treatment. C. One-minus Kaplan-Meier curve showing the time-to-development of severe myelotoxicity during second-line treatment, per CTCAE grade of myelotoxicity at nadir during first-line treatment. D. Forest-plot showing the Cox-Proportional Hazards analyses outcomes for the time-to-development of severe myelotoxicity during second-line treatment

8. Tables

8.1 Table captions

Table 1: Patients demographics stratified by received second line treatment type.

Table 2: Final reduced generalized linear model, fit for nadir myelotoxicity score during second-line treatment.

Table 1: Patients demographics stratified by received second line treatment type.

	Patient Demographics per Second Line Treatment Type			P-value[1]
	All patients, (%)	Lomustine, (%)	Temozolomide (%)	
Total n. patients, (%)	151 (100.0)	101 (66.9)	50 (33.1)	
Sex				
Male	101 (66.9)	69 (68.3)	32 (64.0)	.84
Female	50 (33.1)	32 (31.7)	18 (36.0)	
Age at diagnosis				
Mean	57.1	57.9	55.5	.31
Standard deviation	11.8	11.0	13.2	
BSA				
Mean	2.0	2.0	2.0	.31
Standard deviation	0.20	0.20	0.20	
Duration between first-line and second-line treatment (days)				
Median	154	49	521.5	< .001
25-75% range	29.5 - 393	15 - 168	326 - 849	
Second-line number of received chemotherapy cycles				
Median	2.0	2.0	4.0	< .001
25-75% range	1.0 - 4.0	1.0 - 2.0	3.0 - 6.0	
Received reresection				
No	114 (75.5)	81 (80.2)	33 (66.0)	.11
Yes	37 (24.5)	20 (19.8)	17 (34.0)	
Tumour location				
Frontal	44 (29.1)	29 (28.7)	15 (30.0)	.60
Not frontal	107 (70.9)	72 (71.3)	35 (70.0)	
Tumour side				
Right	71 (47.0)	46 (45.5)	25 (50.0)	.97
Left	80 (53.0)	55 (54.5)	25 (50.0)	
KPS before Second Line				
<70%	9 (6.0)	5 (5.0)	4 (8.0)	.80
≥70%	142 (94.0)	96 (95.0)	46 (92.0)	
First-line treatment received				

Standard	122 (80.8)	79 (78.2)	43 (86.0)	.28
Hypofractionated	29 (19.2)	22 (21.8)	7 (14.0)	
First-line treatment completed				
No	30 (19.9)	26 (25.7)	4 (8.0)	.012
Yes	106 (70.2)	67 (66.3)	39 (78.0)	
Missing	15.0 (9.9)	8.0 (7.9)	7.0 (14.0)	
Second-Line PPI				
No	81 (53.6)	51 (50.5)	30 (60.0)	.23
Yes	66 (43.7)	47 (46.5)	19 (38.0)	
Missing	4.0 (2.6)	3.0 (3.0)	1.0 (2.0)	
Second-Line Seizure Modulating Drug				
No	50 (33.1)	29 (28.7)	21 (42.0)	.095
Yes	98 (64.9)	70 (69.3)	28 (56.0)	
Missing	3.0 (2.0)	2.0 (2.0)	1.0 (2.0)	
Second-Line Corticosteroids				
No	48 (31.8)	22 (21.8)	26 (52.0)	< .001
Yes	99 (65.6)	76 (75.2)	23 (46.0)	
Missing	4.0 (2.6)	3.0 (3.0)	1.0 (2.0)	

BSA, Body Surface Area; PPI, Protonpumpt inhibitor

[1]P-value is for Students' t-test (continuous variables) or $\chi 2$ test (categorical variables)

Table 2: Final reduced generalized linear model, fit for nadir myelotoxicity score during second-line treatment.

	β	z	Sig.	Exp. 95% confidence interval	
				2.5%	97.5%
Intercept	0.25	-2.1	.04	0.07	0.9
First-Line nadir Myelotoxicity score	1.2	4.8	<.001	1.1	1.3
Baseline Myelotoxicity score	1.1	1.7	.09	0.98	1.3
Second-line treatment type					
Temozolomide	-	-	-	-	-
Lomustine	1,4	1.7	.002	1.1	1.7
First-line treatment type					
Standard	-	-	-	-	-
Hypofractionated	0.88	-1.0	.30	0.69	1.1
Sex					
Male	-	-	-	-	-
Female	1.2	1.4	.15	0.94	1.4
BSA	1.5	1.6	.11	0.91	2.5
Age at Start of Second-line	1.0	1.8	.08	0.99	1.0

Link type: Log-Link

Figure 4

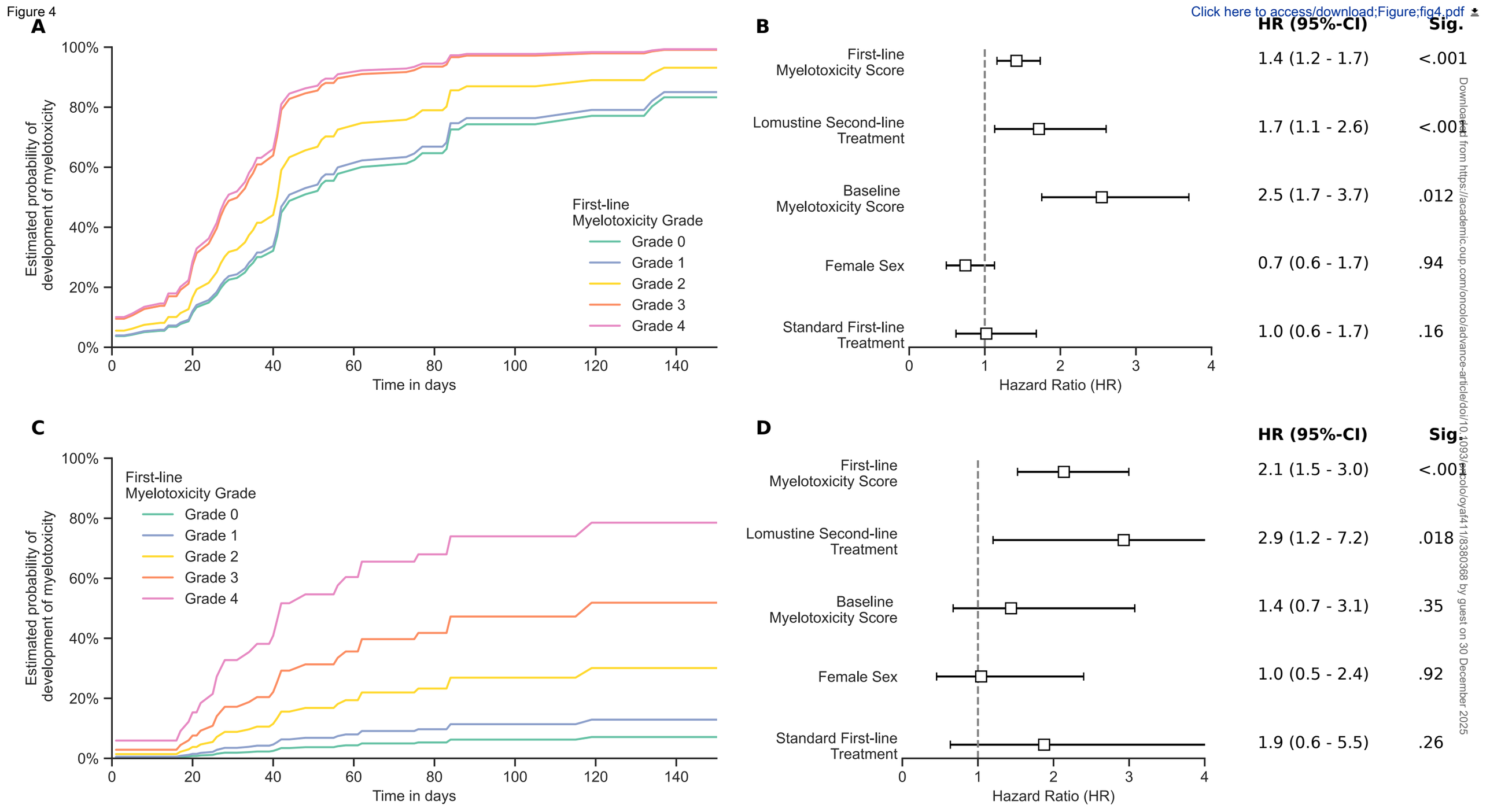

Figure 1

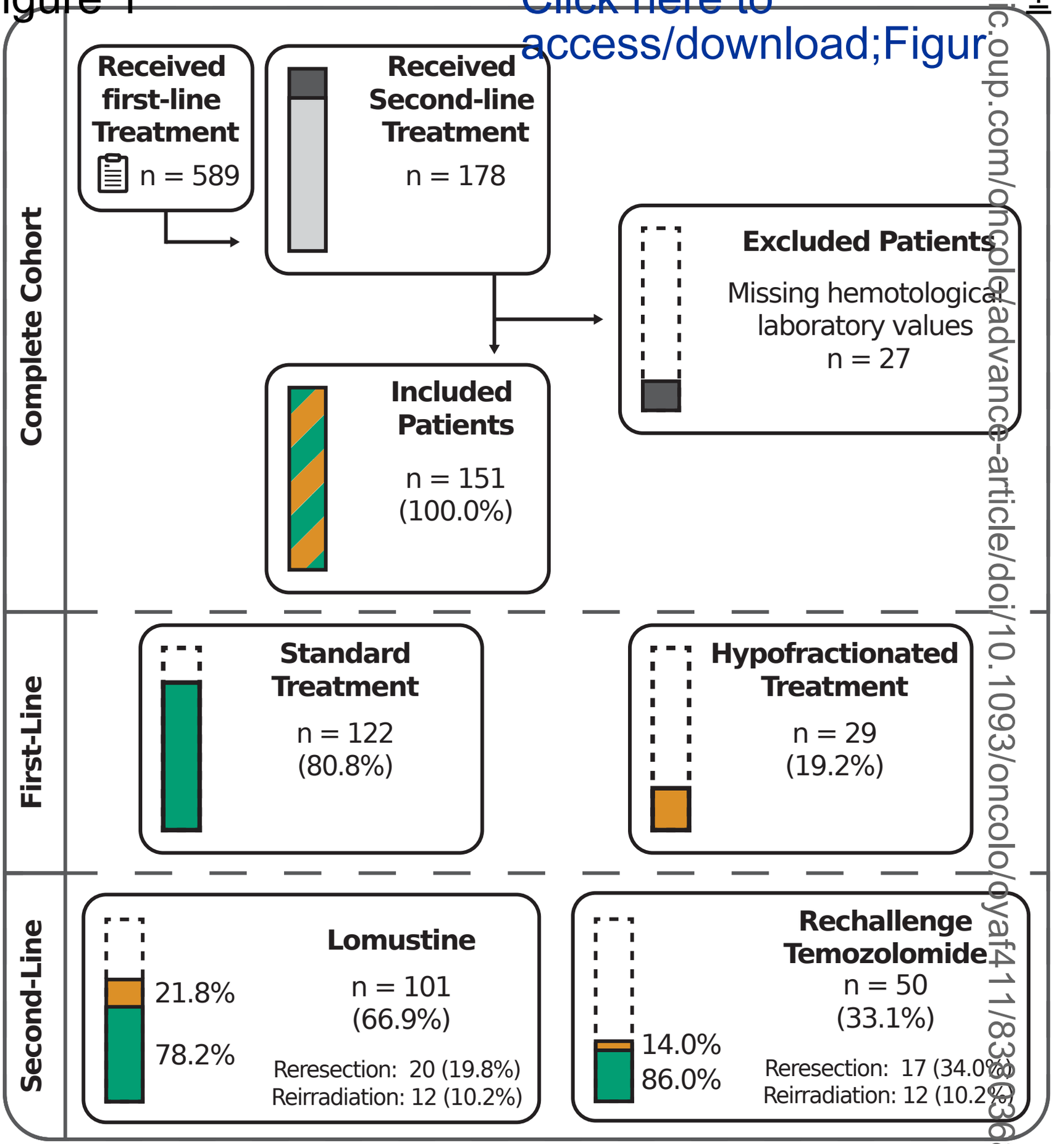

Figure 2

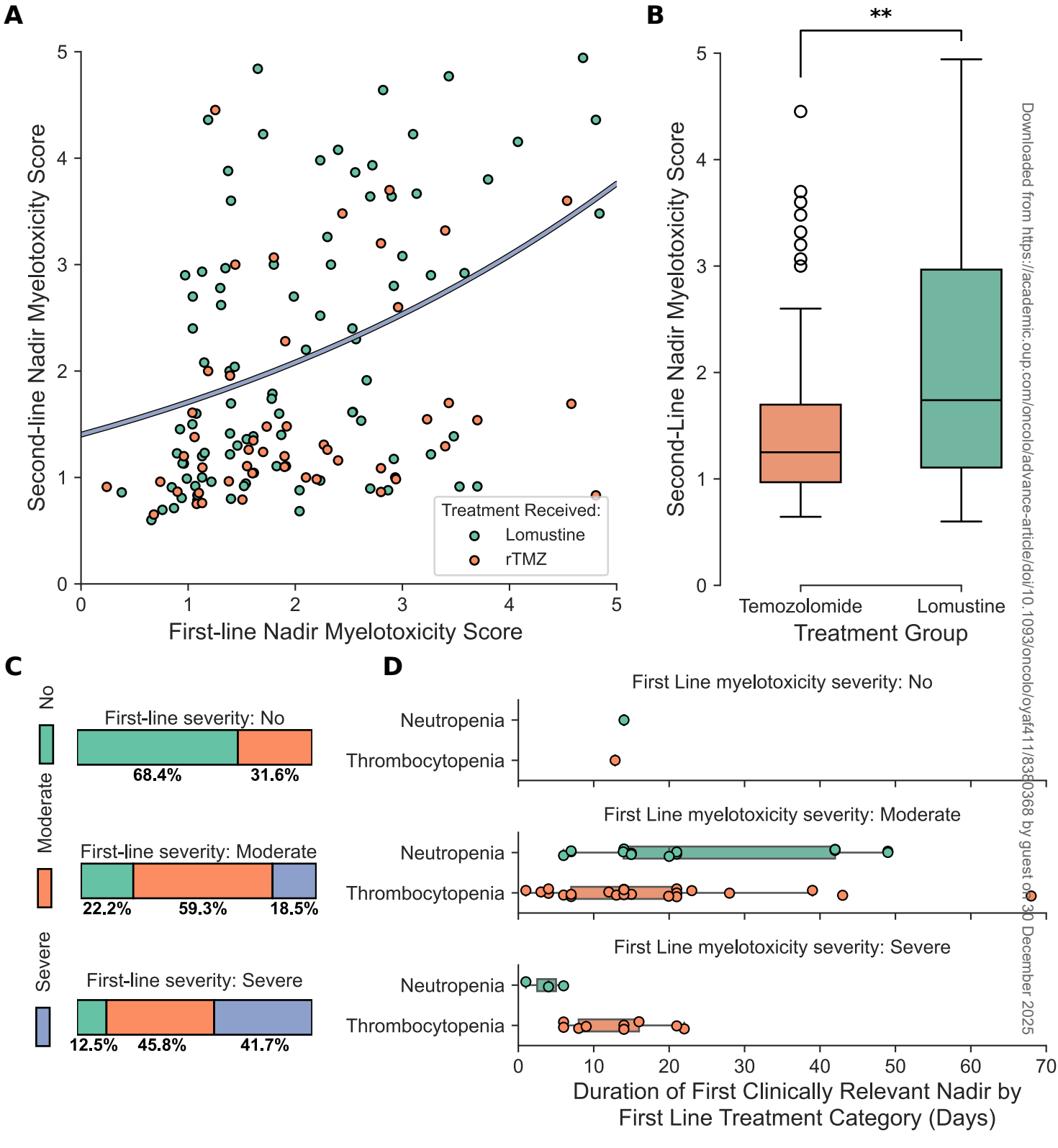

Figure 3