Evaluating the Transportability of Efficacy Estimates in Relapsed/Refractory Mantle-Cell Lymphoma

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CONCLUSIONS

- This study suggests that the treatment effect of zanubrutinib observed in BGB-3111-206 in a Chinese-only R/R MCL population is applicable to a European population
- Despite wide confidence intervals, the lower 95% CI bound remained above the prespecified 40% efficacy threshold in both the MAIC and STC primary analyses
- Study robustness was ensured using data from a large, disease-specific, multi-center registry in Europe, allowing for proper replication of BGB-3111-206 inclusion and exclusion criteria. Furthermore, the findings were consistent across both statistical approaches
- The study was limited by the absence of variables such as Ki-67 and TP53, which had a high degree of missingness in the registry and by the low ESS observed across the MAIC analyses which may introduce additional uncertainty

INTRODUCTION

- Mantle-cell lymphoma (MCL) is an aggressive B-cell malignancy characterized by repeated relapses and limited treatment options in the relapsed/refractory (R/R) setting[1]
- Zanubrutinib, a Bruton tyrosine kinase inhibitor (BTKi), while not currently approved for R/R MCL in Europe, demonstrated substantial antitumor activity in the phase 2 BGB-3111-206 study among Chinese patients with R/R MCL, achieving an overall response rate (ORR) of 83.7% (95% confidence interval [CI], 74.2%-90.8%)[2,3]
- As BGB-3111-206 was conducted exclusively in Chinese patients, this study aimed to assess the transportability of the trial findings to a European population with R/R MCL

METHODS

- A high-level overview of the methodology is presented in **Figure 1**
- To transport the efficacy results to a European population, patient data were captured from the European Mantle Cell Lymphoma (EMCL) Network registry
- First, inclusion and exclusion criteria of the BGB-3111-206 study (including but not limited to age, ECOG, no exposure to prior BTKi, number of prior lines of therapy, laboratory measurements and disease history) were applied to patients in the EMCL registry. Aggregate data of eligible target patients, including target covariate information were then generated for the target European population
- ORR was then transported from the source BGB-3111-206 population to the target European population using two different methods: a matching-adjusted indirect comparison[4] (MAIC) and a simulated treatment comparison[5] (STC)
- In the MAIC**,** BGB-3111-206 patients were weighted to match baseline characteristics of the European target population for the core set of variables (**Table 1**). The transported ORR was estimated as the weighted proportion of BGB-3111-206 patients achieving a complete or partial response. Covariate balance was assessed using standardized mean differences (SMD). Effective sample size (ESS) was used to assess the information retained after weighting
- In the STC, a logistic regression model was fitted to BGB-3111-206 individual patient data. The model was applied to a simulated patient-level target population (N=100,000) reproducing the covariate distribution of the target population. The transported ORR was estimated from the mean predicted response probability. Statistical uncertainty was quantified using 1,000 patient-level bootstrap replicates, with 95% CIs derived from the empirical bootstrap distribution
- In all the analyses, the transported ORR was compared to a minimum efficacy threshold of 40%, as BGB-3111-206 trial was designed to rule out a 40% response rate[3]
- Both methods used a set of core (primary analysis) and extended (sensitivity analysis) variables. (**Table 1**) A sensitivity analysis was performed for the MAIC by trimming weights at their 2.5th and 97.5th percentiles

RESULTS

Baseline characteristics

- Clinically meaningful baseline differences were observed between BGB-3111-206 and the target European population, particularly for age, number of prior lines of therapy, ECOG performance status, and disease burden (**Table 1**)

Table 1. Baseline characteristics

Characteristic, n (%)	BGB-3111-206 trial N=86	Target European population N=446
Age ≥65 years	22 (25.6%)	260 (58.3%)
Male	67 (77.9%)	332 (74.4%)
ECOG performance status = 2*	4 (4.7%)	66 (14.8%)
≥3 prior LoT	29 (33.7%)	52 (11.7%)
sMIPI intermediate risk	29 (33.7%)	211 (47.3%)
sMIPI high risk	8 (9.3%)	56 (12.6%)
Blastoid histology	12 (14.0%)	84 (18.8%)
Progressive disease to last LoT	14 (16.3%)	144 (32.3%)
Bulky disease (≥5 cm)*	39 (45.3%)	24 (5.4%)
Extranodal disease*	61 (70.9%)	70 (15.7%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EMCL, European Mantle Cell Lymphoma Network; LoT, line(s) of therapy; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index.
*Extended set of variables; core variables in **bold**

MAIC weighting results

- In the primary MAIC analysis, weighting completely removed baseline imbalances between the source and target populations
- After weighting, the ESS was 18.6, representing a strong sample size reduction indicating poor pre-weighting balance

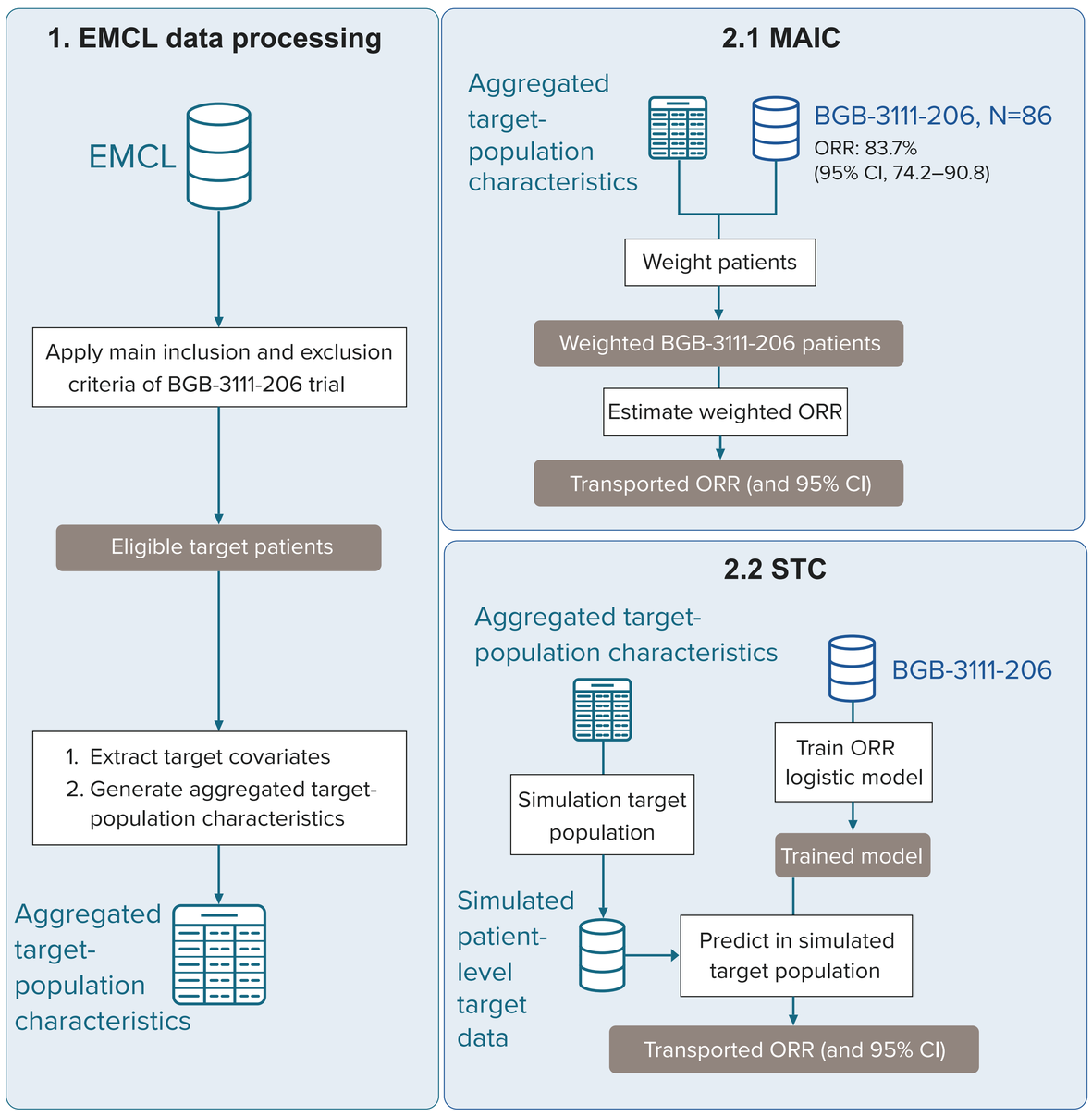
STC model performance

- Models fit on the core and extended sets of variables showed good discrimination (area under the receiver operating characteristic [ROC] curve of 0.851 and 0.929, respectively) and satisfactory calibration (Hosmer–Lemeshow p-value of 0.805 and 0.904, respectively)

ORR

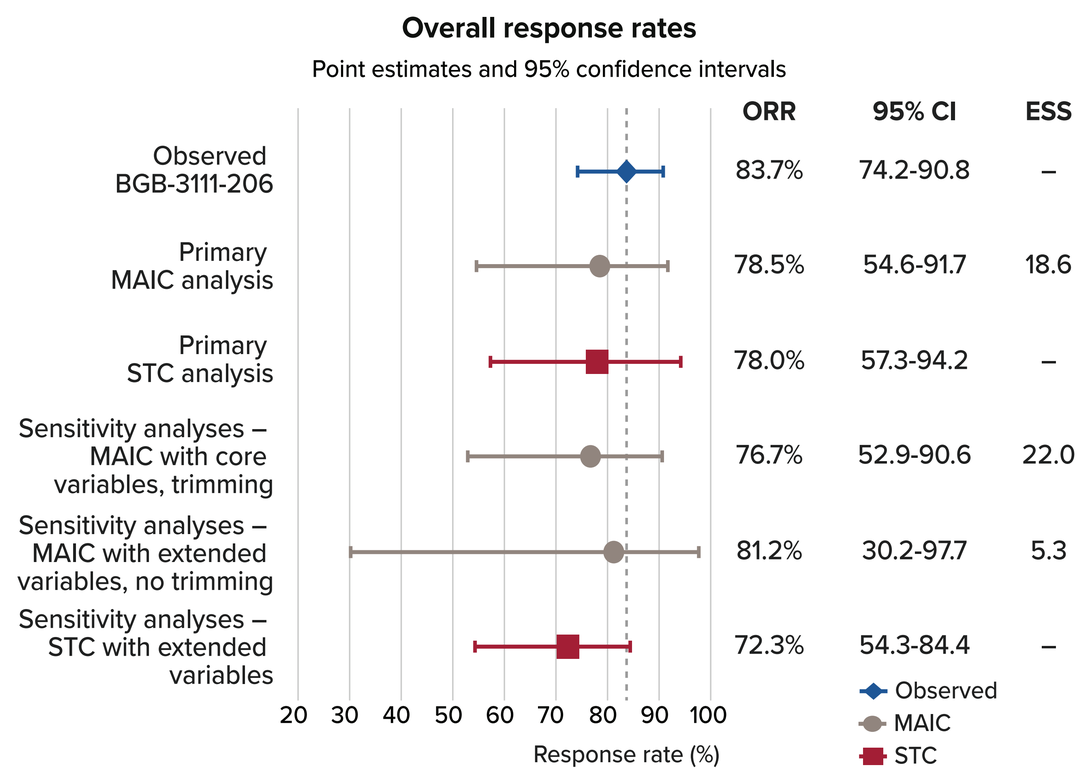
- The transported results for the European population remained consistent with the observed ORR from BGB-311-206 (83.7%, 95% CI: 74.2%-90.8%) with the core set of variables across both the MAIC (78.5%, 95% CI: 54.6%-91.7%) and STC (78.0%, 95% CI: 57.3%-94.2%) (**Figure 2**)
- Using the extended set of variables decreased ESS significantly in the MAIC (ESS=5.3) and had little impact on the STC results (**Figure 2**)
- The weight trimming sensitivity analysis for the MAIC had little impact on the transported ORR and modestly increased ESS (ESS=22.0)

Figure 1. Methodology overview



Abbreviations: CI, confidence interval; EMCL, European Mantle Cell Lymphoma Network; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; STC, simulated treatment comparison.

Figure 2. Observed and transported ORRs



Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; STC, simulated treatment comparison.
Core set variables: age, sex, number of prior line(s) of therapy (LoT), simplified Cell Lymphoma International Prognostic Index (sMIPI), blastoid histology, and progressive disease during the last LoT.
Extended set variables: core variables plus Eastern Cooperative Oncology Group (ECOG) performance status, bulky disease, and extranodal disease.

References

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Acknowledgments

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Editorial assistance was provided by SNELL Medical Communication Inc.

Disclosures

GH: Consulting or advisory role: AbbVie, AstraZeneca, BeiGene/BeOne, BMS, Gilead/Kite, Incyte, Janssen, Miltenyi, MSD, Pierre-Fabre, Regeneron, Roche, Sobi; Honoraria: AbbVie, ADC, AstraZeneca, BeiGene, BMS, Gilead/Kite, Incyte, Janssen, Lilly, MSD, Novartis, Roche, Sobi; Research support: AbbVie, Gilead/Kite, Janssen, Lilly, Roche; Travel support: Incyte, Janssen, Pierre-Fabre; **LB, LM:** Employees and equity holders: BeOne Medicines, Ltd.**; SZ, AM, PL:** Employees: Quinten Health**;** Research support: BeOne Medicines, Ltd.; **AO:** Nothing to disclose.

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Presented at ISPOR EU-26; November 8-11, 2026, Vienna, Austria