13 November 2025
EMADOC-1700519818-2579130
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

MINJUVI

International non-proprietary name: Tafasitamab

Procedure No. EMA/VR/0000255975

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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## List of abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | first-line |
| 2L | second-line |
| 3L | third-line |
| ADA | antidrug antibody |
| ADR | adverse drug reaction |
| AESI | adverse event of special interest |
| AIRTUM | Italian Association of Cancer Registries |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ASCT | autologous stem cell transplantation |
| AST | aspartate aminotransferase |
| BTK | Bruton tyrosine kinase |
| CAR | chimeric antigen receptor |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone |
| CI | confidence interval |
| CMQ | customized MedDRA query |
| COVID-19 | coronavirus disease 2019 |
| CR | complete response |
| CrCl | creatinine clearance |
| CRS | cytokine release syndrome |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVP | cyclophosphamide, vincristine, and prednisone/prednisolone |
| DLBCL | diffuse large B-cell lymphoma |
| DoR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EORTC QLQ | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| E-R | exposure-response |
| ESMO | European Society for Medical Oncology |
| FACT-Lym | Functional Assessment of Cancer Treatment – Lymphoma |
| FAS | full analysis set |
| Fc | fragment crystallizable |
| FDG | fluorodeoxyglucose |

| | |
|---|---|
| FL | follicular lymphoma |
| FLIPI | Follicular Lymphoma International Prognostic Index |
| FMQ | Food and Drug Administration MedDRA query |
| GELF | Groupe d'Etude des Lymphomes Folliculaires |
| HBV | hepatitis B virus |
| HMRN | Haematological Malignancy Research Network |
| HR | hazard ratio |
| ICANS | immune effector cell-associated neurotoxicity |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IKNL/NCR | Netherlands Comprehensive Cancer Organization/Netherlands Cancer Registry |
| IRC | independent review committee |
| IRR | infusion-related reaction |
| IRT | interactive response technology |
| ISI | Integrated Summary of Immunogenicity |
| IV | intravenous(ly) |
| LDH | lactate dehydrogenase |
| mAb | monoclonal antibody |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | minimal residual disease |
| MZL | marginal zone lymphoma |
| NCCN | National Comprehensive Cancer Network |
| NE | not evaluable |
| NHL | non-Hodgkin lymphoma |
| NKCC | natural killer cell count |
| NOS | not otherwise specified |
| NR | not reached |
| OR | odds ratio |
| ORR | overall response rate |
| OS | overall survival |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PI3K | phosphoinositide 3-kinase |
| PK | pharmacokinetic(s) |
| PML | progressive multifocal leukoencephalopathy |
| PO | oral(ly) |
| POD24 | progression of disease within 24 months after initial diagnosis |
| PopPK | population pharmacokinetic(s) |
| PR | partial response |

| | |
|---|---|
| PT | preferred term |
| QD | once daily |
| QoL | quality of life |
| QW | once weekly |
| Q2W | every 2 weeks |
| Q4W | every 4 weeks |
| $R^2$ | lenalidomide (Revlimid®) + rituximab |
| O/R-CHOP | obinutuzumab/rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone |
| R/R | relapsed/refractory |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SCC | squamous cell carcinoma |
| SMQ | standard MedDRA query |
| SOC | system organ class |
| SPM | second primary malignancy |
| TEAE | treatment-emergent adverse event |
| TLS | tumor lysis syndrome |
| TTNT | time to next treatment |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Incyte Biosciences Distribution B.V. submitted to the European Medicines Agency on 25 February 2025 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include in combination with lenalidomide and rituximab treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least one line of systemic therapy for MINJUVI, based on interim results from study INCMOR 0208-301 (inMIND); this is a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of tafasitamab plus lenalidomide and rituximab vs lenalidomide and rituximab in patients with relapsed/refractory (R/R) follicular lymphoma grade 1 to 3a or R/R marginal zone lymphoma. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI. As part of the application, the MAH requested a 1-year extension of the market protection.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information relating to orphan designation*

MINJUVI, was designated as an orphan medicinal product EU/3/25/3027 on 03 March 2025. MINJUVI was designated as an orphan medicinal product in the following indication:

Treatment of follicular lymphoma

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0344/2024 on the granting of a product-specific waiver.

## *Information relating to orphan market exclusivity*

## *Similarity*

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

### *MAH request for additional market protection*

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

### *Scientific advice*

The MAH received scientific advice from the CHMP on 25 June 2020 (EMEA/H/SA/3466/4/2020/II). The scientific advice pertained to clinical aspects of the dossier.

Scientific advice pertaining to INCMOR 0208-301 study design was received from the CHMP. The CHMP scientific advice related to the following clinical aspects:

• The design of the efficacy study MOR208C311 (INCMOR 0208-301), in particular the choice of PFS as primary endpoint, the clinical meaningfulness of a 0.65 HR, the secondary endpoints, the choice of lenalidomide plus rituximab (R2) as active control arm, the selection criteria for the patient population;

• The rationale for tafasitamab dosing regimen and whether the flat dose approach of tafasitamab administered by IV infusion is considered acceptable;

• The proposed safety surveillance methodology.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ehmsen Boje Kvorning Pires Co-Rapporteur: Alexandre Moreau

| Timetable | Actual dates |
|---|---|
| Submission date | 24 February 2025 |
| Start of procedure: | 21 March 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 16 May 2025 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 23 May 2025 |
| Co- Rapporteur's assessment report circulated on: | 27 May 2025 |
| PRAC Outcome: | 05 June 2025 |
| Updated CHMP Rapporteur's assessment report circulated on: | 12 June 2025 |
| 1st CHMP Request for Supplementary Information: | 19 June 2025 |
| Submission of responses: | 06 August 2025 |
| Restart of procedure: | 18 August 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 15 September 2025 |
| Updated PRAC Rapporteur's assessment report circulated on: | 25 September 2025 |
| PRAC Outcome: | 02 October 2025 |
| Updated CHMP Rapporteur's assessment report circulated on: | 09 October 2025 |
| 2nd CHMP Request for Supplementary Information: | 16 October 2025 |

| Timetable | Actual dates |
|---|---|
| Submission of responses: | 21 October 2025 |
| Restart of procedure: | 22 October 2025 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 29 October 2025 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 29 October 2025 |
| Updated PRAC Rapporteur's assessment report circulated on: | 06 November 2025 |
| Updated CHMP Rapporteur's assessment report circulated on: | 06 November 2025 |
| CHMP Opinion: | 13 November 2025 |
| The CHMP adopted a report on similarity of Minjuvi with Yescarta, Lunsumio, Gazyvaro, and Kymriah on date (Appendix I) | 13 November 2025 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

#### *Disease or condition*

Follicular lymphoma (FL) is an indolent form of non- Hodgkin lymphoma and can be described as a heterogeneous clinicopathologic entity that includes tumours derived from germinal center B cells, both centrocytes (small cleaved follicular centre cells) and centroblasts (large noncleaved follicular center cells). FL virtually always has a growth pattern that is partially follicular, giving it a nodular appearance both grossly and microscopically.

#### *State the claimed the therapeutic indication*

MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy.

#### *Epidemiology*

FL is the second most common subtype of non-Hodgkin lymphoma (NHL), comprising 20% to 30% of all NHL diagnoses in developed countries (Cerhan 2020). While there is considerable heterogeneity in the clinical course of FL, it is generally an indolent malignancy, with a prolonged but incurable clinical course. The incidence of FL appears to be increasing, with a documented increase of 0.5 cases per million persons per year between 1992 and 2010. In the EU, the annual incidence of this disease has rapidly increased during recent decades and has risen from 2 to 3 per 100,000 persons during the 1950s to 5 per 100,000 recently. The reported median age at diagnosis for FL in EU is 64.9 years (Casulo 2015). Follicular lymphoma is defined as a lymphoma of germinal center B cells, and virtually always demonstrates a growth pattern that is partially follicular. With modern treatment approaches for FL, median survival exceeds 10 years (Casulo 2015). Over the past several decades, the incorporation of novel active agents into treatment practices has resulted in a decline in FL mortality

trends (Howlader 2016). Yet, FL remains incurable. Its clinical history is typically one of multiple relapses, with successive treatment regimens resulting in progressively shorter disease-control intervals, until fatal, resistant disease emerges. In addition to the morbidity and mortality associated with treatment resistance, cumulative treatment-related toxicity (especially immunosuppression, myelosuppression, and secondary leukaemia related to alkylator exposure) and transformation to diffuse large B-cell lymphoma (DLBCL) remain significant contributors to mortality in patients with FL.

## *Biologic features, aetiology and pathogenesis*

The molecular pathogenesis of FL is a complex process during which a single follicular B cell acquires genetic and epigenetic alterations leading to malignant transformation; the resultant is usually a mixture of centrocytes (small cleaved germinal center cells) and centroblasts (large noncleaved germinal center cells). Some common steps in this pathway have been described, particularly chromosomal rearrangements involving BCL-2 and certain somatic mutations, some of which are also seen in other non-Hodgkin lymphomas. In most cases, FL is associated with a translocation between the long arm of chromosome 18, the site of the BCL-2 oncogene, and one of the three immunoglobulin (Ig) genes. The most common translocation involves the Ig heavy chain gene resulting in the t(14;18)(q32;q21), found in approximately 85 percent of FL. BCL-2 overexpression in itself is not sufficient for FL development and other genetic lesions or host factors are required. Some of the complementary mutations involve genes that regulate the epigenome (for example histone modifications, chromatin structure). Other important factors involve the local host response and tumour microenvironment, and modifications in the B cell receptor that may augment B cell receptor signalling. The tumour cells express monotypic immunoglobulin light chain, CD20 (and CD19), CD10, and BCL-6 and are negative for CD5 and CD23

## *Clinical presentation and diagnosis*

Initially, patients with FL usually present with painless peripheral adenopathy, often with a long history of waxing and waning lymph node enlargement. Widespread disseminated disease is usually present at baseline, but patients are typically asymptomatic aside from their lymphadenopathy. There are no characteristic laboratory abnormalities and, despite the large tumour burden, the majority has a normal serum lactate dehydrogenase (LDH) level. After initial therapy, patients are followed at routine intervals to monitor for relapse or complications related to treatment. On suspicion of relapse it is important to rule out transformation to a more aggressive histologic subtype, most commonly diffuse large B cell lymphoma (NOS). Follicular lymphoma grade 3b and transformed FL generally requires a more intensive treatment approach than FL grade 1-3a.

## *Management*

Significant progress has been made with the introduction of newer targeted agents in R/R FL. However, these new treatments are often associated with significant toxicities and long-term disease control cannot always be achieved, particularly in patients who had received multiple lines of therapy and/or who are highly refractory to treatments (Dreyling 2021).

Rituximab (MabThera) is an anti-CD20 monoclonal antibody, approved in 1998 and well-established in the treatment of patients with R/R FL.

Idelalisib (Zydelig), a selective inhibitor of the PI3K-δ isoform, received EU authorization as monotherapy for the treatment of adult patients with FL that is refractory to 2 prior lines of

treatment in 2014. The approval targets population refractory both to rituximab and to alkylating agent-containing chemotherapy. In 2021, duvelisib (Copiktra), another PI3K inhibitor was approved for patients with FL not responding to two previous treatments.

Obinutuzumab (Gazyvaro) is a second-generation anti-CD20 antibody that was engineered to have a higher affinity for the CD20 receptor and to cause enhanced direct target-cell killing compared with rituximab. Obinutuzumab was approved in 2016 in combination with bendamustine followed by monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen. The approval is based on the progression-free survival results of a Phase III study comparing treatment with obinutuzumab in combination with bendamustine, followed by obinutuzumab alone as maintenance therapy, to bendamustine alone in patients with FL not responding to rituximab. The GADOLIN Study was a multicenter, open-label, randomized Phase 3 study of 396 subjects with indolent NHL refractory to rituximab (Sehn 2016); 321 had R/R FL and were randomised to receive either bendamustine alone or obinutuzumab plus bendamustine followed by 2 years of maintenance with obinutuzumab. Median progression-free survival was significantly longer in the obinutuzumab-bendamustine arm (25.8 months; 95% CI: 19.5, 41.1 months) than in the bendamustine arm (14.1 months; 95% CI: 12.6, 16.0 months); a treatment benefit was also seen for overall survival (Cheson 2018).

The combination of lenalidomide (Revlimid) and rituximab (Leonard 2019) was approved in 2019. The combination of lenalidomide and rituximab is indicated for patients who have relapsed or did not respond to previous treatment (Leonard 2019). In this study, 358 patients with R/R FL or R/R MZL were randomly assigned to lenalidomide plus rituximab (n = 178, 147 patients with R/R FL) or placebo plus rituximab (n = 180, 148 patients with R/R FL). The primary endpoint was progression-free survival assessed by an Independent Review Committee (IRC). For the patients with R/R FL, the median progression-free survival assessed by the IRC was 39.4 months (95% CI: 23.1 months, not reached [NR]) with lenalidomide plus rituximab versus 13.9 months (95% CI: 11.2, 16.0 months) with placebo plus rituximab (hazard ratio [HR], 0.40; 95% CI, 0.29, 0.56; $p < 0.0001$). The median progression-free survival assessed by investigators (R/R FL population) was 27.8 months (95% CI: 22.1 months, NR) with lenalidomide plus rituximab. The data with a median follow-up of 28.3 months were not mature to demonstrate overall survival benefit. Neutropenia (including 50% of patients with Grades 3 to 4), gastrointestinal toxicity, cutaneous reactions, and infections were the most common side effects associated with the combination.

In 2022, mosunetuzumab (Lunsumio), a CD20 x CD3 T-cell bispecific antibody (Budde 2022) received conditional marketing authorization in EU for R/R FL. The pivotal study enrolled 90 patients with R/R FL, and the median study follow-up was 18.3 months. Overall response rate by IRC assessment was 80.0% (95% CI: 70.3%, 87.7%), and the complete response rate was 60.0%. Median duration of response was 22.8 months (95% CI: 9.7 months, NR) and median progression-free survival was 17.9 months (95% CI: 10.1 months, NR).

In 2023, zanubrutinib (Brukinsa) in combination with obinutuzumab was approved for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies. The ORR in patients treated with zanubrutinib in combination with obinutuzumab was 69.0% (95% CI: 60.8%, 76.4%) and the median duration of response was not reached (95% CI: 25.3m, NR) after a median follow-up time of 20.2 months.

The CD20 x CD3 bispecific antibodies epcoritamab (Tepkinly) and odronextamab (Ordspono) are both approved for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. The ORR in patients treated with epcoritamab was 83% (95% CI: 75.1%, 88.9%) and the median duration of response was 21.4 months (95% CI:

13.7, NR). The ORR in patients treated with odronextamab was 80% (95% CI: 73%, 87%) and the median duration of response was 23 months (95% CI: 18, NR).

Finally, other approved treatments for R/R FL are two CD19-directed CAR-T cell products, axicabtagene ciloleulel, and tisagenlecleucel that are approved after three or The main clinical study supporting the extension of indication for FL was the single arm trial ZUMA-5 (KTE-C19-105), a Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL). Objective response rate (ORR), defined as complete response (CR) plus partial response (PR) per Lugano classification and central assessment, was 91% (95% CI; 82%, 96%) in FL subjects after 3 or more prior lines of therapy (leukapheresed patients). The CR rate was 77% in this population corresponding to the intended indication. Median DOR was 38.6 months (95% CI: 24.7, NE). The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) were evaluated in an open-label, multicentre, single-arm, phase II study (E2202, N=97). The complete response rate in patients after two or more lines of therapy was 68.4 (58.2, 77.4) and The probability for a patient to remain in response (DOR) ≥9 months was 76% (95% CI: 64.9, 84.3), while the probability for a patient who achieved a CR to remain in response ≥9 months was 87% (95% CI: 75.6, 93.3). more or two or more lines of systemic therapy respectively (Fowler 2021; Jacobson 2022).

Given the multiple relapses many patients experience, an unmet need still exists as having many options, less toxic and more efficacious treatments for more or different lines of treatment and individualized choices based on toxicity and mode of administration would be the ultimate goal of clinical development in FL.

## 2.1.2. About the product

Tafasitamab is a Fc-enhanced humanised monoclonal antibody (mAb) that binds to the human B-cell surface antigen, CD19. CD19 is expressed throughout normal and malignant B-cell development up to terminal plasma cell differentiation and is present on all malignant B-cells, including DLBCL (Olejniczak 2006). Alteration of two amino acid residues in the constant region of tafasitamab significantly increases binding to Fc gamma receptors (FcγR), including FcγRIIIa (CD16), and FcγRII (CD32), leading to enhanced in vitro antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and direct cytotoxic effects (apoptosis) on tumour cells relative to the unmodified antibody (Uckun 1988, Tedder 1994, Sato 1997, Otero and Rickert 2003). The major pharmacological effect of tafasitamab is B-cell depletion.

## 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice pertaining to INCMOR 0208-301 study design was received from the CHMP on 25 June 2020 (EMEA/H/SA/3466/4/2020/II). The CHMP scientific advice related to the following clinical aspects:

• The design of the efficacy study MOR208C311 (INCMOR 0208-301), in particular the choice of PFS as primary endpoint, the clinical meaningfulness of a 0.65 HR, the secondary endpoints, the choice of lenalidomide plus rituximab (R2) as active control arm, the selection criteria for the patient population.

• The rationale for tafasitamab dosing regimen and whether the flat dose approach of tafasitamab administered by IV infusion is considered acceptable;• The proposed safety surveillance methodology.

The key recommendations from CHMP are outlined in the Table 1 below.

**Table 1: Key recommendations from CHMP Clinical scientific advice on study INCMOR 0208-301**

| Topic | CHMP recommendation | Implementation |
|---|---|---|
| Choice of primary and key secondary endpoints | - PFS as primary endpoint is acceptable but any improvement in PFS in the FL population would need to be supported by similarly positive improvements in key secondary endpoints, and in particular, no OS detriment would be required to be shown.<br><br>- Use of Lugano 2014 criteria is endorsed.<br><br>- The Applicant is recommended to collect scans so that an independent review can be performed upon request.<br>- EMA censoring rules for the primary analysis of the primary and secondary endpoints should be conducted. | - OS in FL implemented as key secondary endpoint.<br><br>- IRC review of primary and secondary endpoints based on response assessments was implemented in the study.<br><br>- Sensitivity analysis of PFS were conducted according to EMA censoring rules. |
| Choice of lenalidomide plus rituximab (R2) as active control arm | It is acknowledged that there is not one standard treatment regimen for R/R FL and MZL, therefore it is agreed that this combination of lenalidomide and rituximab could be considered an acceptable comparator treatment for R/R FL patients. For MZL, an efficacy benefit was not demonstrated in the R/R MZL population alone in the AUGMENT trial. Thus, in case a treatment benefit is observed for the tafasitamab combination in MZL participants, the contribution of the lenalidomide to the triple combination will remain uncertain | - R2 was used as active control arm.<br>- The Type II variation application is only for the treatment of adult patients with previously treated follicular lymphoma. |
| Patient population for proposed label | - It is acknowledged that patients who develop rituximab refractoriness may still receive rituximab containing regimens in practice.<br><br>- Consider stratification by rituximab refractoriness.<br><br>- Measure CD20 status prior to commencing therapy. If patients known to have lost CD20 surface expression are proposed to be | - Stratification by CD20-refractoriness was implemented.<br><br>- Documentation of positive CD20 and CD19 expression on lymphoma cells was required as per inclusion criteria.<br><br>- Patients were enrolled based on local pathology, but retrospective central pathology review was implemented. |

| | | |
|---|---|---|
| | enrolled, further justification would be required.<br><br>- Investigate feasibility of enrolment based on centrally reviewed histology. | |
| Flat dose approach of tafasitamab | Flat dosing could account for a higher inter-patient variability in exposure than body weight-based dosing for extreme body weight ranges in the event of a strong effect of this covariate on clearance, which seems to apply to tafasitamab PK profile.<br>Considering the expected wide therapeutic window of monoclonal antibodies no concerns are anticipated on the therapeutic efficacy of the intended regimen; however, appropriateness of the chosen dose from a safety perspective cannot be judged. | - Flat dose of tafasitamab was not implemented in the study protocol |

The MAH has, overall, complied with the guidance received concerning the tafasitamab development in FL. In particular, the request to ascertain CD20 expression as a requisite for enrolment was endorsed and has been followed.

### 2.1.4. General comments on compliance with GCP

The MAH claimed that the INCMOR 0208-301 study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Guidelines.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

The MAH submitted an updated environmental risk assessment (ERA) according to the revised EMEA ERA Guideline (EMEA/CHMP/SWP/4447/00 Rev. 1-Corr.; 22 Aug 2024).

Tafasitamab is an Fc-enhanced, humanized monoclonal antibody (mAb) directed against the pan B-cell antigen CD19. Tafasitamab has not been structurally modified using non-natural amino acids, and thus, would not be considered non-natural. As such, tafasitamab would be expected to undergo the same degradation pathways as natural proteins and to have the same environmental impact as naturally occurring human antibodies. Any tafasitamab and/or degradants eliminated by patients will be extensively and rapidly degraded to amino acids. Renal excretion of intact

compound or related fragments is not expected given the large molecular weight. Therefore, it is unlikely that any pharmacologically active antibody will persist in the aquatic compartment. No other environmental concerns are apparent for tafasitamab drug product.

For certain groups of active substances, a tailored testing strategy is required due to their specific mode of action. Tafasitamab is not an antibiotic nor antiparasitic. Tafasitamab does not target endocrine pathways and showed no evidence of endocrine activity in nonclinical studies. So, no tailored testing strategy is required.

Based on these considerations, tafasitamab is unlikely to represent a risk for the environment following its prescribed usage in patients. As a result, in accordance with the EMA revised ERA Guideline, the Risk Assessment was concluded in Phase I and no further assessment or testing is required.

### 2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data was submitted with this application, which is considered acceptable by CHMP. Considering the above data and the relevant guideline, tafasitamab is not expected to pose a risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

**GCP**

The clinical trials were performed in accordance with GCP as claimed by the MAH (see Table 2).

**Table 2: Tabular overview of clinical studies**

| Study | Disease | Dose (mg/kg) | Dose Regimen | No of Participants | PK/PD Endpoints | Sampling | | | Status |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PK | PD | ADA | |
| MOR208C107 | DLBCL | 12 mg/kg body weight by IV on D1, D8, D15 of each 21-day cycle for 6 cycles | 6, 21-day cycles: D1, D8 and D15: Tafasitamab + R-CHOP versus 6, 21-day cycles: D1, D8 and D15: Tafasitamab + LEN (25 mg PO daily on D1 to D10 of each 21-day cycle) + R-CHOP | 66 (33 per arm) | Tafasitamab serum conc ($C_{trough}$ levels and $C_{max}$ levels on D1 of each cycle)<br><br>The number and percentage of participants developing anti-tafasitamab antibodies and semiquantitative titer assessments | Predose and 1 h (± 15 min) postinfusion: C1-C6 on D1 of each cycle, and EOT or discontinued treatment | — | Predose: C1D1, C3D1, C5D1, and EOT or discontinued treatment | Complete |
| INCMOR 0208-102 | NHL | 12 mg/kg tafasitamab or w/ de-escalation to 9 mg/kg per DLTs (Groups 1, 3, 4a, 5)<br><br>LEN: 25 mg QD (Group 3, 5) parsaclisib starting 20 mg QD; (Group 4a) R-CHOP: per standard of care of institution (Group 5) | Tafasitamab:<br>For 28-day cycle IV C1-C3D1, D8, D15, D22 + additional loading dose C1D4. C4 onward, IV infusions occur Q2W on D1, D15, until discontinuation criteria met (Groups 1, 3, 4a). For 21-day cycle IV, D1, 8, and 15 up to 6 cycles. (Group 5)<br><br>LEN: PO D1-D21 up to 12 cycle (Groups 3, 6), D1-D10 up to 6 cycle (Group 5)<br><br>Parsaclisib: 20 mg QD until day 56 followed by 2.5 mg QD (Group 4a)<br><br>R-CHOP: D1-5 each cycle up to 6 cycle (Group 5) | 24 (Phase 1b Groups 1, 3, 4a, and 5) | PK analysis of single agent tafasitamab and tafasitamab + combination treatments<br><br>Descriptive statistics of trough (ie, predose) and $C_{max}$ levels at different timepoints | Groups 1,3,4a: serum samples collected at predose, EOI, and ≈ 1, 4, 24 h after the end of the first infusion Group 5 serum collected predose, postinfusion, and ≈ 1, 4, 24 h postdose, end of first infusion<br><br>For all groups, untimed PK samples were collected at EOS/safety FU<br><br>Additional serum samples were also taken for all groups at varying times[a] | — | None of the participants developed anti-tafasitamab antibody samples in the confirmatory ADA assay | Ongoing |
| INCMOR 0208-301 | FL MZL | Tafasitamab (12 mg/kg IV) C1-C3 D1, D8, D15, D22; C4-C12D1, D15 Rituximab (including biosimilars; 375 mg/m$^2$ IV) on C1D1, D8, D15, D22 and C2-C5D1 LEN (including generics; 20 mg PO QD,10 mg for participants with moderate renal insufficiency) on C1-C12D1 through D21 at approximately the same time every day | Participants are receiving study treatment in 28-cycles for 12 cycles (tafasitamab + LEN) and 5 cycles (rituximab). Treatment was discontinued in case of unacceptable toxicity, disease progression, lack of efficacy, or withdrawal of consent | 654 | PK ($C_{max}$ and $C_{min}$) of tafasitamab in FL and MZL, as well as the overall population (These are exploratory endpoints) | For PK blood sampling: C1D1, D8, D22 (predose and 1 h postdose (± 15 mins); C4 and onward, D1[b]; EOT | — | C1D1, D22 (predose); C4 and onward D1[c] | Ongoing |

[a] Groups 1, 3, and 4, serum samples: predose and 1 h following postinfusion on D4, D8, D16, and D22. Group 5, serum samples: predose and 1 h postdose infusion on C1D8 and D15; for C2-C6D1 serum samples: predose and 1 h postdose.
[b] For C4D1, C8D1, and C12D1, blood should be sampled predose.
[c] For C4D1, C8D1, and C12D1, blood should be sampled predose.
Note: For Studies MOR208C201, MOR208C202, MOR208C203, MOR208C205, and XMAb5574-01, refer the original application for the indication of DLBCL.

## 2.3.2. Pharmacokinetics

### Introduction

This variation includes results of the clinical pharmacology evaluations of the pivotal trial INCMOR 0208-301 (inMIND, ongoing), as well as one Phase 1b/2 study INCMOR 0208-102 (J-MIND, ongoing) and one Phase 1b study MOR 0208C107 (First-Mind, complete) in support of the use of tafasitamab in combination with lenalidomide and rituximab for treatment of participants with relapsed/refractory (R/R) follicular lymphoma (FL). Overall, there are data from a total of 8 studies

included. Of these are 6 complete and 2 ongoing. Data cutoff dates for the ongoing studies are 23 February 2024 (INCMOR 0208-301) and 31 August 2023 (INCMOR 0208-102). Study MOR208C107 was complete on 10 August 2022.

**Bioanalysis**

A second-generation electrochemiluminescent assay on the MSD platform was used in studies MOR208C107 (Study C107), INCMOR 0208-102 (Study 102), and INCMOR 0208-301 (Study 301) for quantification of tafasitamab. For ongoing Study 102, bioanalytical reports for ADA sample analysis (4th-generation assay) and PK sample analysis will be prepared at the conclusion of the study. NAb testing was performed using an antibody-dependent cell-mediated cytotoxicity (ADCC) assay.

**Pharmacokinetic data analyses**

NONMEM® (ICON) version 7.3.0 was used for population PK analysis. Data were analysed with the first order conditional estimation algorithm with interaction (FOCEI). R version 4.3.3 was used for simulations to derive exposure metrics, for graphical analysis, model diagnostics and statistical summaries. Assembly of the population PK dataset and data programming in relation to exposure-response analyses was performed using SAS® software version 9.4.

**Pop PK analysis**

Previously, a population PK model for tafasitamab was developed based on data of four clinical studies (XmAb5574-01, MOR208C201, MOR208C202, and MOR208C203 [LMIND]) with a 2-compartment structure, linear disposition and time-dependent elimination. The previous Pop PK model was updated with PK data from studies C205 (COSMOS), C107 (firstMIND), 301 (inMIND), and 102 (J-MIND) Part 1 and 2 (excluding Group 2) and re-estimated. Cancer type and number of treated participants in the different studies are listed below:

- XmAb5574-01 (Phase 1 dose escalation; CLL/SLL; N = 27 PK evaluable participants)
- MOR208C201 (Phase 2; NHL; N = 91)
- MOR208C202 (Phase 2; ALL; N = 22)
- MOR208C203 (Phase 2; DLBCL; N = 81)
- MOR208C205 (Phase 2; CLL/SLL; N = 24)
- MOR208C107 (Phase 1b; DLBCL; N = 66)
- INCMOR0208-301 (Phase 3 ongoing; R/R FL or MZL; N = 329)
- INCMOR0208-102 (Phase 1b/2 ongoing; NHL; N = 24)

The full PK analysis dataset included 8758 PK observations from 664 participants. Five participants had no PK data. A total of 707 samples were BLQ and excluded, of which 70 were post-first dose. In addition, 80 observations were excluded as non-evaluable, clearly erratic, deemed outliers based on CWRES >5 (n=14) or were non-zero pre-first dose.

The function describing time-dependency in CL was updated to increase stability of the base structural model, the sigmoidicity factor γ was fixed to 1 (i.e., removed), and a maximum decline in CL (Imax) was estimated. In addition, IIV on Imax was introduced, applying a logit transformation. Both additive and multiplicate error models were applied.

The population PK analysis in the MAA had identified baseline body weight, baseline albumin, sex and disease type as statistically significant covariates. Additional covariates were tested on

disposition parameters by a step-wise inclusion and backwards exclusion approach. The final updated model included effects of WT, serum albumin, sex, race (Asian versus non-Asian), LEN co-administration and CRCL on CL; and WT, disease type (NHL and ALL versus CLL or SLL), race (Asian versus non-Asian) on Vc.

A sensitivity test was performed re-including excluded outliers. The parameter estimates for the final population PK model are presented in Table 15. Most parameters were estimated with good precision except T50. Both unexplained IIV (%CV) and eta shrinkage was low for CL, moderate for Vc and high for Imax, respectively.

**Table 3: Final population PK parameter estimates**

| Parameter | Estimate | RSE(%) | Bootstrap 95% CI | IIV (CV%)[a] | Shrinkage (%) |
|---|---|---|---|---|---|
| CL [L/day] | 0.481 | 6.47 | 0.416 – 0.535 | 28.2 | 9.62 |
| Vc [L] | 5.10 | 3.24 | 4.81 – 5.43 | 19.7 | 11.3 |
| Q [L/day] | 0.875 | 10.2 | 0.722 – 1.06 | – | – |
| Vp [L] | 2.80 | 7.94 | 2.47 – 3.34 | 44.8 | 22.5 |
| Imax | 0.387 | 7.93 | 0.344 – 0.646 | 87.4 | 44.3 |
| $T_{50}$ [day] | 78.8 | 51.4 | 42.6 – 590 | – | – |
| CL/Q-WT | 0.493 | 14.4 | 0.367 – 0.623 | – | – |
| CL-ALB | -0.706 | 13.9 | -0.923 – -0.525 | – | – |
| CL-SEX | -0.136 | 18.4 | -0.183 – -0.0854 | – | – |
| CL-RACE | -0.203 | 16.0 | -0.266 – -0.145 | – | – |
| CL-LEN | 0.139 | 33.1 | 0.0388 – 0.224 | – | – |
| CL-CRCL | 0.130 | 33.5 | 0.0397 – 0.212 | – | – |
| Vc/Vp-WT | 0.427 | 10.4 | 0.350 – 0.517 | – | – |
| Vc-SEX | -0.154 | 11.1 | -0.184 – -0.119 | – | – |
| Vc-RACE | -0.129 | 20.1 | -0.173 – -0.0778 | – | – |
| Vc-DIS23 | -0.231 | 10.4 | -0.282 – -0.188 | – | – |
| PROP | 0.167 | 5.26 | 0.152 – 0.183 | – | – |
| ADD [µg/mL] | 2.55 | 44.6 | 0.655 – 4.63 | – | – |
| EPS | 1 FIX | – | – | – | 8.83 |

Source: GOFmodelCompare_INCY-PMX-TAFASITAMAB-6058-20241012.Rmd, Table_15_Final_Model_Parameter.csv, run_rmv_ALT.lst

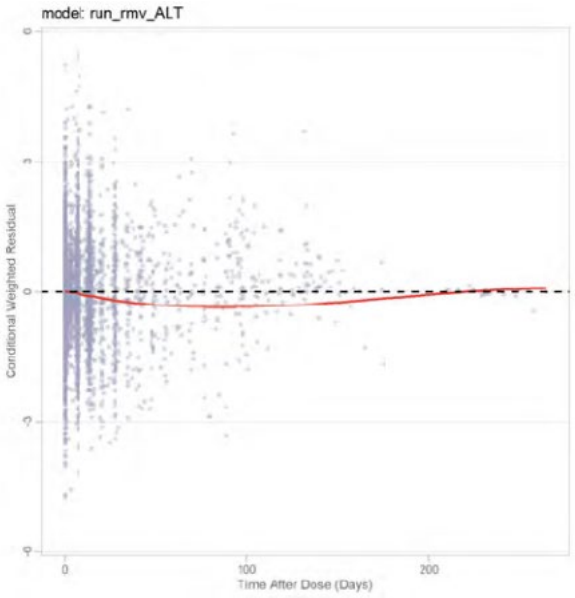
Note: IIV (CV%) is calculated as $(100 \times \sqrt{e^{\omega^2} - 1})$, where $\omega$ is the variance of a normal distribution with mean 0.

[a] Covariances: CL-Vc: 0.0232, Vc-Vp:0.0526, CL-Vp: 0.0124

Abbreviations: ADD=additive error; ALB=serum albumin; ALL=acute lymphoblastic leukemia; CI=confidence interval; CL=clearance; CLL=chronic lymphocytic leukemia; CRCL=creatinine clearance; CV=coefficient of variation; DIS23=NHL and ALL versus CLL or SLL; EPS=residual error: variance of a normal distribution with mean 0; FIX=fixed parameter; IIV=inter-individual variability; Imax=maximum decline in CL (expressed as fraction); LEN=co-administration of lenalidomide; NHL=non-Hodgkin's lymphoma; PK=pharmacokinetic; PROP=proportional error; Q=inter-compartmental clearance; RSE=relative standard error; SLL=small lymphocytic leukemia; $T_{50}$=time to half of the maximum decline in CL; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=body weight.

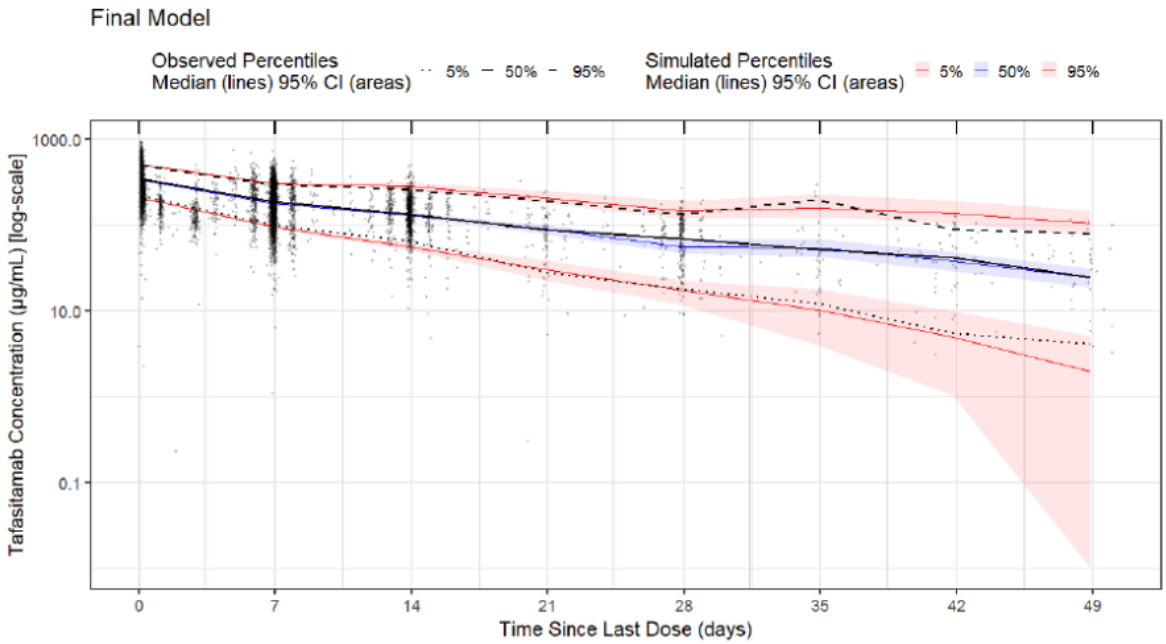
The final Pop PK model was evaluated by GoF plots, bootstrap (n=200 replicates) and pcVPCs (n=500 replicates) of pooled studies.

**Figure 1 CWRES vs Time since most recent dose**



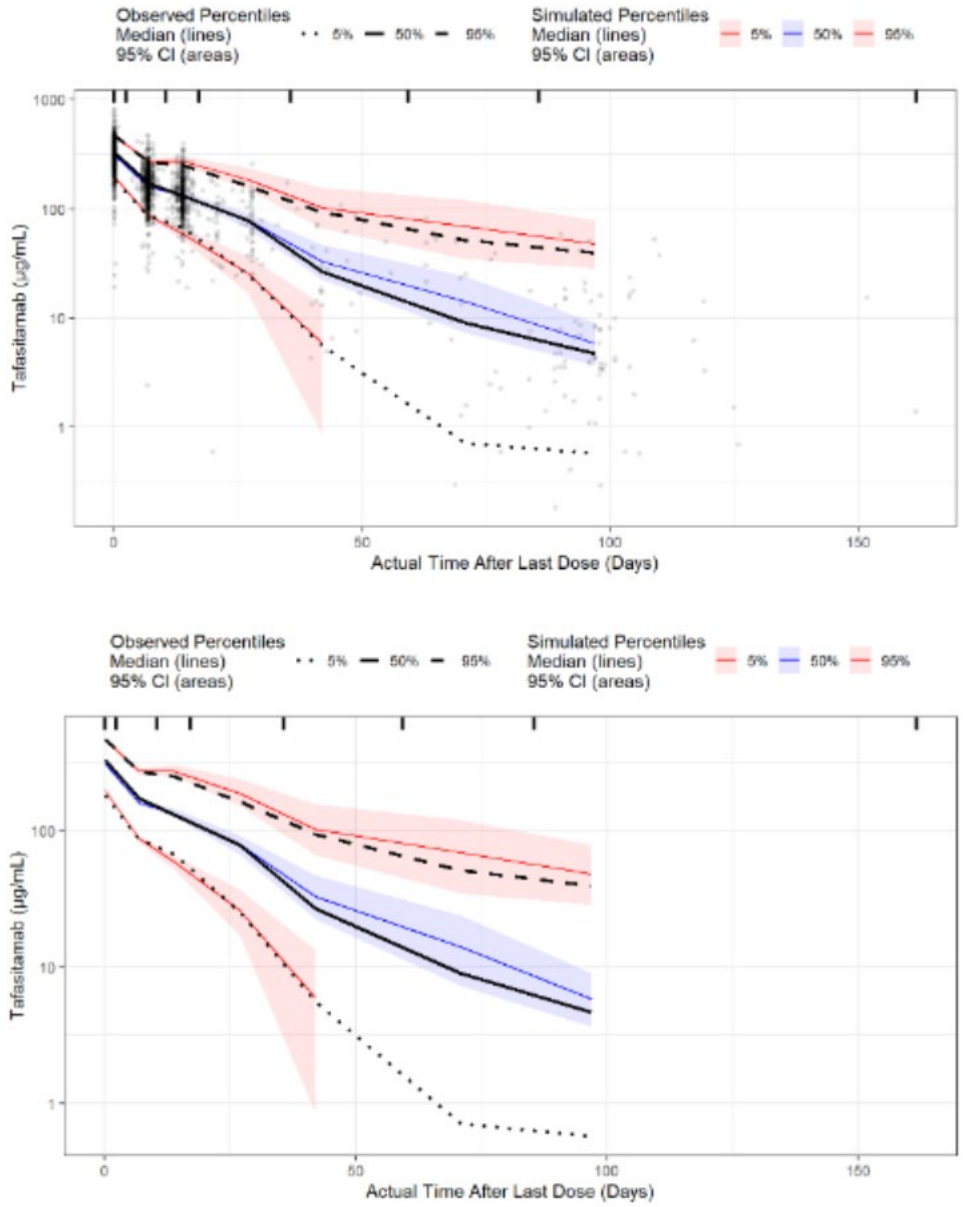

Source: GOFmodelCompare_INCY-PMX-TAFASITAMAB-6058-20241012.Rmd; GOF-8.jpg
Notes: Dots are individual data points. The red solid line is a smoothed LOESS line. Black dashed lines show the y=0 line and the boundaries of the CWRES ± 3 interval.
Abbreviations: CWRES=conditional weighted residuals; LOESS=locally weighted scatterplot smoothing.

**Figure 2 Prediction-corrected VPC**




Source: VPC_INCY-PMX-TAFASITAMAB-6058-20241021.R; trunc_vpc_finalmodel_tad_overall_logy_pam10.png.png
Notes: Grey dots are observed data points; the black solid line is the observed median; black dotted / dashed lines are observed p5 and p95. The blue area is the 95% PI of the simulated median, and pink areas are the 95% PI of the simulated p5 and p95. X-axis truncated at 7 weeks after dose administration, as data get too sparse and uncertainty too high after this point in time.
Abbreviations: CI=confidence interval; p5=5th percentile; p95=95th percentile; PI=prediction interval; VPC=visual predictive check.

**Figure 3 Prediction-corrected Visual Predictive Check of study 301 (log scale)**




Lenalidomide was identified as a statistically significant but not clinically relevant covariate on tafasitamab clearance in the reported population PK analysis. A data programming error was discovered in the Pop PK analysis dataset, in which all participants of Study 301 (inMIND) were denoted as not having received lenalidomide coadministration, which was not correct. Upon correction of the data programming error, lenalidomide was no longer identified as a statistically significant covariate on tafasitamab clearance and the effect was removed. The re-estimated parameters without the lenalidomide effect on CL are presented below. The removal of lenalidomide effect had greatest impact on Imax and T50 estimates.

**Table 4 Re-estimated parameters without the lenalidomide effect for tafasitamab based on the corrected analysis dataset**

| Parameter | Estimate | RSE(%) | IIV (CV%)[a] | Shrinkage (%) |
|---|---|---|---|---|
| CL [L/day] | 0.441 | 2.27 | 29.2 | 7.80 |
| Vc [L] | 5.14 | 3.05 | 19.7 | 11.4 |
| Q [L/day] | 0.866 | 8.36 | – | – |
| Vp [L] | 3.16 | 3.23 | 44.7 | 20.1 |
| Imax | 0.497 | 3.16 | 295 | 50.7 |
| $T_{50}$ [day] | 326 | 16.0 | – | – |
| CL/Q-WT | 0.501 | 14.7 | – | – |
| CL-ALB | -0.750 | 13.1 | – | – |
| CL-SEX | -0.124 | 20.1 | – | – |
| CL-RACE | -0.198 | 16.1 | – | – |
| CL-CRCL | 0.147 | 29.7 | – | – |
| Vc/Vp-WT | 0.437 | 10.2 | – | – |
| Vc-SEX | -0.15 | 11.1 | – | – |
| Vc-RACE | -0.122 | 20.4 | – | – |
| Vc-DIS23 | -0.238 | 9.82 | – | – |
| PROP | 0.167 | 4.65 | – | – |
| ADD [µg/mL] | 2.44 | 38.8 | – | – |
| EPS | 1 FIX | – | – | 8.86 |

Source: tafa-final-wo-len.lst; tafa-final-wo-len.ext; parameters-tafa-final-wo-len.csv

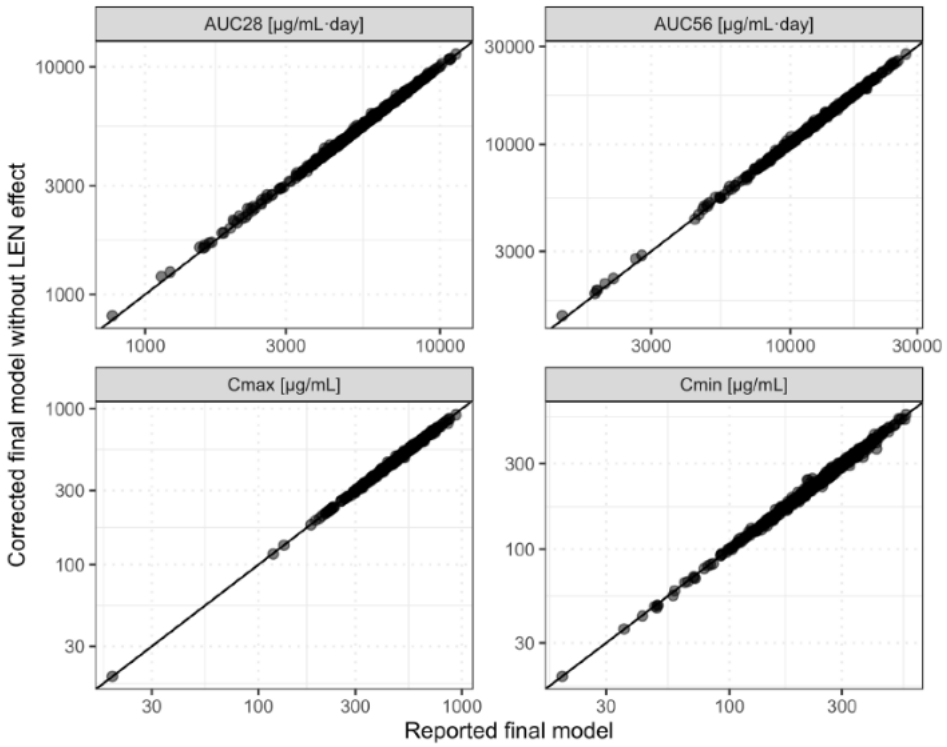
Note: IIV (CV%) is calculated as $(100 \times \sqrt{e^{\omega^2} - 1})$, where $\omega$ is the variance of a normal distribution with mean 0.

[a] Covariances: CL-Vc: 0.0214, Vc-Vp:0.0552, CL-Vp: 0.0128

Abbreviations: ADD=additive error; ALB=serum albumin; ALL=acute lymphoblastic leukemia; CI=confidence interval; CL=clearance; CLL=chronic lymphocytic leukemia; CRCL=creatinine clearance; CV=coefficient of variation; DIS23=NHL and ALL versus CLL or SLL; EPS=residual error: variance of a normal distribution with mean 0; FIX=fixed parameter; IIV=inter-individual variability; Imax=maximum decline in CL (expressed as fraction); LEN=co-administration of lenalidomide; NHL=non-Hodgkin's lymphoma; PK=pharmacokinetic; PROP=proportional error; Q=inter-compartmental clearance; RSE=relative standard error; SLL=small lymphocytic leukemia; $T_{50}$=time to half of the maximum decline in CL; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=body weight.

Exposure metrics were predicted with the corrected final model without lenalidomide effect and compared with exposure metrics predicted by the reported final model. The respective correlation plots are shown below.

**Figure 4 Comparison of exposure metrics based on reported vs corrected dataset**

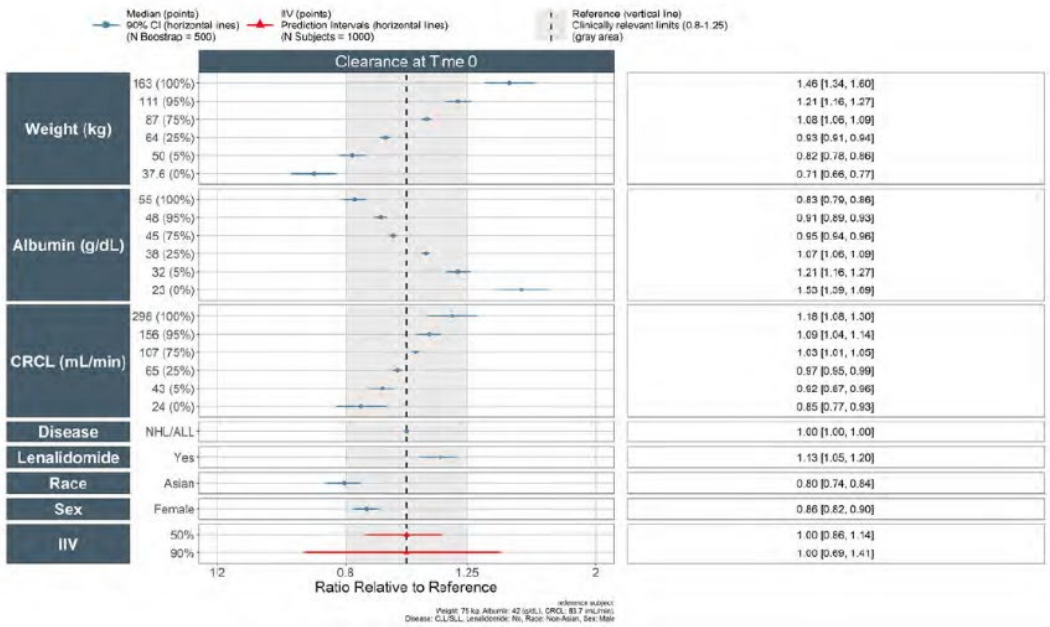



Source: compare-exposure.r; figure3-exposure-comparisons.png
Abbreviations: AUC28=area under the concentration-time curve in Treatment Cycle 1, i.e., from 0-28 days; AUC56=area under the concentration-time curve in Treatment Cycles 1 and 2, i.e., from 0-56 days; Cmax=simulated overall maximum concentration; Cmin=simulated maximum trough concentration; LEN=lenalidomide

Model estimations

The final reported Pop PK model was used to estimate individual exposure parameters by posterior Bayesian estimation or simulation in R. The effect of intrinsic and extrinsic factors on derived exposures were evaluated by Forest plots. In addition, a subgroup analysis by ethnicity (Japanese versus non-Japanese or Japanese versus Caucasian) were performed.

**Figure 5 Univariate impact of covariates on tafasitamab CL**




Source: Foresplot_FINALmodel_INCY-PMX-TAFASITAMAB-6058-20241013.R, ForestPlot_univariate-final-cl.png

Note: Chosen covariate values (y-axis) represent the minimum, 1st quartile, median, 3rd quartile and maximum of the respective covariate in the data set. The CL point estimate and error bars for each covariate level are the median and 95% CI of 500 bootstrap replicates. Note that the error bars represent uncertainty in the population estimates, not IIV. Values are not necessarily identical with values in Table 17, since Table 17 is based on population estimates and this figure is based on bootstrap estimates.

Abbreviations: ALL=acute lymphoblastic leukemia; CI=confidence interval; CL=clearance; CLL=chronic lymphocytic leukemia; CRCL=creatinine clearance; IIV=inter-individual variability; N=number; NHL=non-Hodgkin's lymphoma; SLL=small lymphocytic leukemia.

Covariate effects were also assessed for their impact on exposure (simulating weekly dosing at 12 mg/kg for three 28-day cycles). P5 and p95 of WT were associated with a change of -20% to +24% in AUC0−28 and -19% to +23% in maximal serum concentration (max Cmax) compared to a participant with median WT. P5 and p95 of ALB were associated with a change in AUC0−28 of -9% to +4% and max Cmax by -12% to +6% compared to a participant with median ALB levels.

| | | | | |
|---|---|---|---|---|
| Mean (CV%) | 194 (39.1%) | 163 (41.4%) | 151 (45.6%) | 151 (45.3%) |
| Median [Min, Max] | 194 [55.1, 373] | 164 [68.1, 398] | 143 [20.2, 444] | 144 [20.2, 444] |
| Geo. mean (Geo. CV%) | 179 (44.9%) | 152 (39.4%) | 134 (56.7%) | 135 (55.5%) |
| Missing | 7 (14.6%) | 3 (11.5%) | 166 (34.7%) | 182 (34.0%) |
| **Average $Cmin_{169\text{-}ast}$ (µg/L)** | | | | |
| Mean (CV%) | 158 (33.9%) | 143 (37.5%) | 127 (43.2%) | 129 (42.4%) |
| Median [Min, Max] | 170 [66.2, 294] | 142 [38.7, 293] | 122 [16.1, 346] | 125 [16.1, 346] |
| Geo. mean (Geo. CV%) | 149 (38.0%) | 132 (45.4%) | 115 (52.2%) | 117 (51.5%) |
| Missing | 19 (39.6%) | 4 (15.4%) | 204 (42.7%) | 225 (42.0%) |
| **Maximum Cmax (all doses) (µg/L)** | | | | |
| Mean (CV%) | 545 (20.7%) | 590 (23.0%) | 483 (27.1%) | 488 (26.8%) |
| Median [Min, Max] | 529 [358, 864] | 596 [306, 856] | 482 [19.2, 935] | 490 [19.2, 935] |
| Geo. mean (geo. CV%) | 534 (20.6%) | 574 (25.0%) | 462 (33.8%) | 467 (33.1%) |
| **Maximum Cmax ($1^{st}$ dose) (µg/L)** | | | | |
| Mean (CV%) | 255 (16.6%) | 293 (22.8%) | 215 (44.5%) | 220 (43.1%) |
| Median [Min, Max] | 252 [191, 368] | 284 [181, 455] | 236 [0.866, 449] | 240 [0.866, 455] |
| Geo. mean (geo. CV%) | 251 (16.3%) | 286 (22.8%) | 167 (123.9%) | 173 (119.5%) |
| Missing | 0 (0%) | 2 (7.7%) | 142 (29.7%) | 158 (29.5%) |

Source: Sub-population INCY-PMX-TAFASITAMAB-6058-20241025.rmd; table21_Exposures_EHN_Race.csv

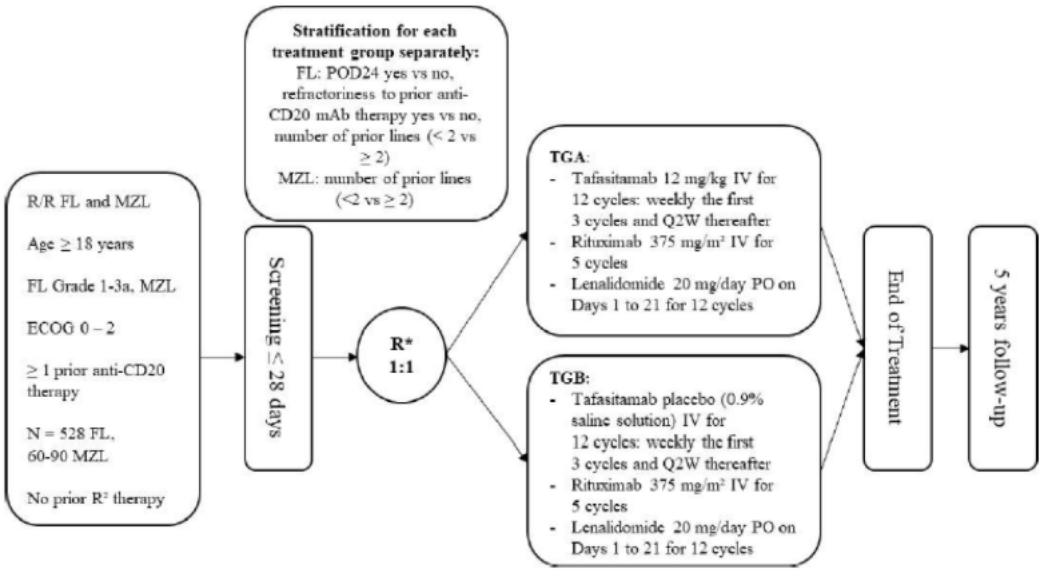
Note: N is not expected to be identical in Table 19, Table 20, and Table 21. Not all participants have PK parameters, and of those who have, not all have exposures (actual dosing was used in simulations, i.e., if participants dropped out before the end of Cycle 1, they do not have $AUC_{0\text{-}28}$ values. In addition, only exposures of participants receiving a dose of 12 mg/kg are reported.)

Abbreviations: $AUC_{0\text{-}28}$=area under the concentration-time curve in Treatment Cycle 1, i.e., from 0-28 days; $AUC_{0\text{-}56}$=area under the concentration-time curve in Treatment Cycles 1 and 2, i.e., from 0-56 days; Cmax=maximum concentration; Cmin=trough concentration; $Cmin_{0\text{-}84}$= average trough concentration from 0-84 days (Cycle 1-3); $Cmin_{85\text{-}168}$=average trough concentration from 85-168 days (Cycle 4-6); $Cmin_{169\text{-}last}$=average trough concentration from day 169 to end of treatment (from Cycle 7 onwards); CV=coefficient of variation; geo.=geometric; PK=pharmacokinetic; Max=maximum; Min=minimum; N=number of participants; PK=pharmacokinetic.

## *Absorption, Distribution, Elimination*

The treatment regimens applied in Study 301 are shown in the figure below. The PK data from Study 301 were pooled with other clinical studies. Only sparse PK samples were collected.

Figure 6 Treatment algorithm of study INCMOR 0208 - 301




*Randomization will apply separately for FL versus MZL populations.

Source: Clinical study protocol of Study INCMOR0208-301[7]
Abbreviations: CD20=cluster of differentiation 20; ECOG=Eastern Cooperative Oncology Group; FL=follicular lymphoma; IV=intravenous; mAb=monoclonal antibody; MZL=Marginal Zone Lymphoma; N=number of participants; PO=oral; POD24=progression of disease within 24 months after initial diagnosis; Q2W=every 2 weeks; R=randomization; R/R=relapsed/refractory; R²=rituximab + lenalidomide (Revlimid®); TG=treatment group.

Study INCMOR 0208-102 is an ongoing, open-label, multicenter, Phase 1b/2 study of tafasitamab, tafasitamab + LEN, tafasitamab + parsaclisib, and tafasitamab + LEN in combination with R-CHOP. Phase 1b include Japanese participants with R/R NHL. Phase 2 include Japanese participants with R/R DLBCL. As of the data cutoff date of 31 AUG 2023, a total of 24 participants were enrolled in Groups 1, 3, 4a, and 5, and received at least 1 dose of tafasitamab.

The PK data from Study INCMOR 0208-102 were compared to the PK data from corresponding studies conducted in non-Japanese participants.

PK across studies

The concentration-time profiles of the 8 clinical studies included in the Pop PK population are shown below. The following tables show the secondary PK parameters for the final reported model and the model estimated exposure metrics from subjects receiving 12 mg/kg (estimated across studies), respectively.

Figure 7 Summary statistics of simulated exposure metrics across studies at 12mg/kg

| Metric | Mean | SD | CV% | Median | Min | Max | Geo mean | Geo CV% |
|---|---|---|---|---|---|---|---|---|
| $AUC_{0\text{-}28}$ [µg/mL*day] | 5624.2 | 1691.6 | 30.1 | 5572.4 | 773.4 | 11325.2 | 5332.9 | 41.8 |
| $AUC_{0\text{-}56}$ [µg/mL*day] | 13518.6 | 4098.8 | 30.3 | 13672.6 | 1388.2 | 27226.3 | 12741.9 | 46.4 |
| maxCmin | 250.6 | 90.0 | 35.9 | 243.6 | 19.6 | 559.5 | 232.2 | 52.3 |
| average $Cmin_{0\text{-}84}$ [µg/mL] | 176.9 | 65.5 | 37.0 | 173.7 | 2.3 | 421 | 162.3 | 59.0 |
| average $Cmin_{85\text{-}168}$ [µg/mL] | 165.5 | 75.1 | 45.4 | 154.6 | 20.2 | 445.5 | 147.3 | 68.0 |
| average $Cmin_{169\text{-}last}$ [µg/mL] | 131.8 | 55.3 | 41.9 | 127.2 | 16.1 | 346.3 | 119.2 | 61.6 |
| max Cmax overall [µg/mL] | 491 | 127.9 | 26.1 | 491.6 | 19.2 | 935.3 | 471.7 | 36.1 |
| max Cmax 1st dose [µg/mL] | 201.1 | 105.3 | 52.3 | 229.6 | 0.9 | 454.8 | 147.2 | 175.4 |

Source: Exposure_table6_INCY-PMX-TAFASITAMAB-6058-20241009.rmd; allMetrics_summaries.csv_20241014.csv

Abbreviations: $AUC_{0\text{-}28}$=area under the concentration-time curve in Treatment Cycle 1, i.e., from 0-28 days; $AUC_{0\text{-}56}$=area under the concentration-time curve in Treatment Cycles 1 and 2, i.e., from 0-56 days; $Cmin_{0\text{-}84}$= average trough concentration from 0-84 days (Cycle 1-3); $Cmin_{85\text{-}168}$=average trough concentration from 85-168 days (Cycle 4-6); $Cmin_{169\text{-}last}$=average trough concentration from day 169 to end of treatment (from Cycle 7 onwards); CV=coefficient of variation; maxCmax=simulated maximum Cmax concentration; maxCmin=simulated maximum trough concentration; geo=geometric; Max=maximum; Min=minimum; SD=standard deviation.

## 2.3.3. Pharmacodynamics

### *Primary and secondary pharmacology*

**Dose**

The 12 mg/kg dose is approved in combination with LEN for the treatment of R/R DLBCL. The approved dose of 12 mg/kg tafasitamab was further evaluated in the placebo controlled INCMOR 0208-301 in participants with R/R FL or R/R MZL, in combination with lenalidomide and rituximab. The treatment resulted in prolonged PFS in R/R FL with an acceptable safety profile compared to placebo (lenalidomide and rituximab). The approved dose level of 12 mg/kg tafasitamab in combination with lenalidomide and rituximab seems appropriate for participants with R/R FL.

**Immunogenicity**

As of the data cutoff date for Study INCMOR 0208-301, 3905 human serum samples from 652 evaluable participants (325 from placebo + LEN +R-CHOP and 327 from tafasitamab + LEN + R-CHOP) were analysed for anti-tafasitamab antibodies.

A total of 36 samples were confirmed ADA-positive. At the participant level, 17 (2.6%) ADA-positive participants were identified. Eight (1.2%) of the 17 ADA-positive participants had nontreatment-emergent ADAs with only baseline-positive ADAs and 9 (1.4%) had treatment-emergent ADAs. Out of the 9 treatment-emergent positive participants, only 1 (0.2%) had persistent positive treatment-emergent ADAs. Among the 9 treatment-emergent positive participants, 6 were from the placebo group. No ADA-positive samples had detectable NAbs.

In Study 301, 36 ADA-evaluable samples from 17 participants were confirmed positive. None had detectable NAbs. Nine participants had treatment-emergent (post-baseline) ADAs of which 6 participants were placebo treated.

## 2.3.4. PK/PD modelling

**Exposure-response modelling**

The exposure-response relations for selected efficacy and safety endpoints were investigated in participants with R/R follicular lymphoma (FL) and Grade 1 to 3a or R/R marginal zone lymphoma (MZL) enrolled in Study 301 (inMIND) through graphical assessment, logistic regression analysis and/or time-to-event analysis. The reported population PK model was used to simulate concentration-time profiles from the dataset, comprised of all available dosing and covariate information. Post-hoc exposure estimates were obtained for 327 participants from Study 301. Model-derived exposure metrics AUC28, AUC56, overall Cmax, and highest Cmin were all highly correlated.

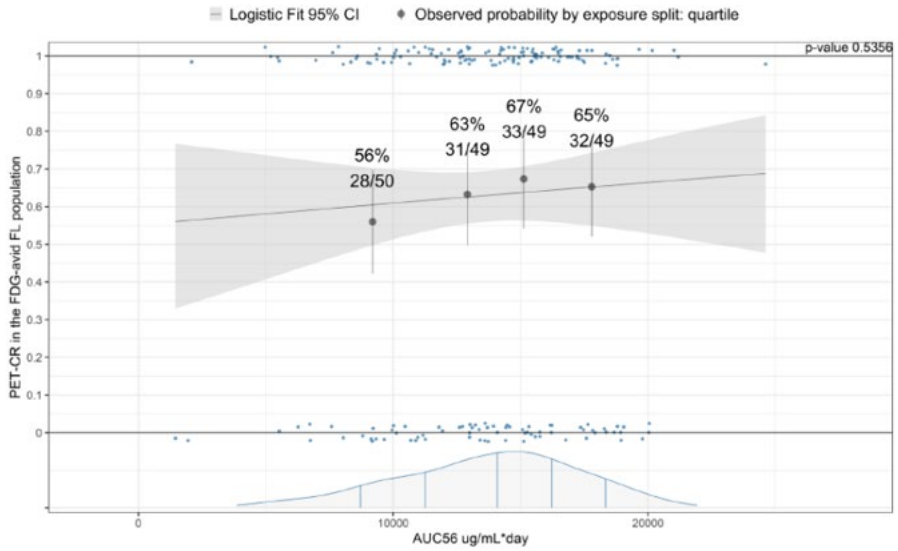
Initially exploratory exposure-efficacy analyses were performed to identify any trends. For significant E-R relationships ($p<0.01$), further analyses were conducted by quantitative E-R modelling including covariate testing. For logistic regression, covariates were added on the intercept as linear predictors on the logit scale, starting with a full model followed by backward elimination of insignificant covariates at a significance level of 0.001, using the likelihood ratio test. For Cox PH functions, covariates were added as linear predictors on the log of the hazard, again starting with a full model followed by backward elimination of insignificant covariates at a significance level of 0.001. Logistic regression models were evaluated by plots of model-predicted response compared to observations stratified by (binned) exposure. Time-to-event models were evaluated by KM curves stratified by tafasitamab exposure quantiles.

Efficacy:

A total of 326 participants were included in the efficacy E-R analysis, of which 273 were patients with FL. PFS and OS were available for all FL participants. PET-CR information was available for 201 FL participants. For efficacy endpoints if a trend was detected, the following baseline covariates were tested: age, gender, weight, race, ECOG, FL-IPI, NK-cell count, primary refractory, refractory to prior treatment, number of prior lines, progression within 24 months and B-cell count.

The only statistically significant E-R relation ($p<0.01$) identified for an efficacy endpoint was for PFS. For OS, the data was too limited. No exposure trend was identified for PET-CR.

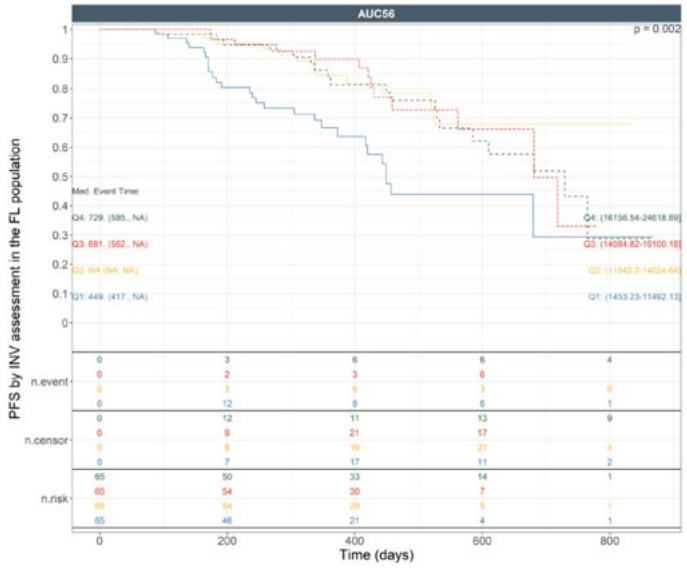
**Figure 8 Relationship of PET-CR vs. AUC56, with PET-CR grouped by AUC56 quartiles and a linear logistic regression Fit**




Source: exposure-efficacy-v06.qmd, exposure-efficacy-v06.html, quick-binary-3.png
Note: Blue dots represent individual participants with event (at the top) and participants with no event (at the bottom). Observations were jittered for improved visualization. Numbers depict n/N and percentage for each exposure quartile, with n being the number of participants with an event and N being the total number of participants. Solid grey dots and vertical lines represent incidence and 95% CI of observations at median exposure within quartile; the solid line represents the logistic regression fit of the form logit(prob[event]) AUC × slope + intercept; the grey area represents the 95% CI; vertical lines under the density curve represent the width of exposure quartiles.
Abbreviations: AUC=area under the serum concentration-time curve; AUC56=area under the serum concentration-time curve from Day 1 to Day 56 (Cycle 1 and Cycle 2); CI=confidence interval; FDG=fluorodeoxyglucose; FL=follicular lymphoma; PET-CR=positron emission tomography-negative complete response; prob=probability

A total of 71 (27.3%) out of the 260 participants with FL from Study 301, for whom AUC56 could be calculated, experienced disease progression or death. The KM curves for PFS in FL showed significant exposure-dependency of PFS (cox-regression P-value < 0.001), driven by the lowest exposure quartile.

**Figure 9 Kaplan – Meier curves by AUC56 quartile for PFS in the FL population**




Source: exposure-efficacy-v06.qmd, exposure-efficacy-v06.html; quick-tte-2.png
Notes: curves are Kaplan-Meier curves stratified by exposure quartiles. P-value is for the log-rank test.
Abbreviations: AUC56=area under the serum concentration-time curve from Day 1 to Day 56 (Cycle 1 and Cycle 2); FL=follicular lymphoma; INV=investigator; n.=number; NA=not available; PFS=progression-free survival; Q=quartile

A Cox PH model was established, and a covariate analysis was performed with addition of all covariates followed by backward deletion (p<0.001). Only primary refractory remained a significant predictor.

**Table 5 Parameter estimates of the Cox PH model for PFS in the FL population**

| Predictor | Estimate | Standard Error | *P* value |
|---|---|---|---|
| Primary refractory | 0.791 | 0.241 | 0.00103 |

Source: exposure-efficacy-v06.qmd, exposure-efficacy-v06.html
Abbreviations: AUC56=area under the serum concentration-time curve from Day 1 to Day 56 (Cycle 1 and Cycle 2); FL=follicular lymphoma; PH=proportional hazard; PFS=progression-free survival

In the overall population (FL+ MZL) KM curves showed significant exposure-dependency of PFS (cox-regression P-value < 0.001), driven by the lowest exposure quartile.

A Cox PH model covariate analysis was performed where only AUC56 remained a significant predictor.

Safety:

A total of 327 participants were included in the safety E-R analysis dataset. Five safety endpoints with incidence >10%, TEAE leading to dose modification, Grade ≥ 3 TEAE, Grade ≥ 3 neutropenia, SAE, and Grade ≥ 3 infections and infestations were evaluated. For safety endpoints the following covariates were tested if a trend was detected: time on treatment, number of prior treatment lines, age, gender, race, weight, ECOG status, Ann Arbor stage and refractory to prior treatment.

The five safety endpoints with an incidence rate >10% underwent logistic regression to quantify the relationship to exposure (AUC56, AUC28 and Cmax). The only statistically significant relationship (p< 0.01) between a safety endpoint and exposure identified, was the inverse relation of TEAE leading to dose modification vs. AUC56 (Figure 12).

The incidence of TEAE leading to dose modification was 76.6% (N = 251). Subsequently, logistic regression was performed on incidence of TEAE leading to dose modification, including both AUC56 and the listed covariates. All tested covariates were removed as insignificant during the backward elimination step, and AUC56 remained as the only significant predictor of TEAE leading to dose modification in the model.

All five safety endpoints with incidences >10% also underwent time-to-event analysis illustrated by KM plots stratified by tafasitamab exposure quartiles. KM curves showed a significant exposure-dependency of first occurrence of an incident for all safety endpoints (Cox-regression p-value < 0.001) except for Grade≥3 infections and infestations. TEAE leading to dose modification, Grade ≥ 3 TEAE, first occurrence of Grade ≥ 3 neutropenia and first occurrence of SAE were all driven by the lowest exposure quartile (Figures 22-25).

Cox PH modelling was established and covariate analysis performed for each endpoint. For TEAE leading to dose modification, AUC56 remained significant. For first occurrence of Grade ≥ 3 TEAE, both age and AUC56 remained significant. For first occurrence of SAE, time on treatment remained significant. For first occurrence of Grade ≥ 3 neutropenia, no significant covariates were identified and AUC56 was removed from the model during the backward elimination step. Parameter estimates of the final CPH models for the respective safety endpoint are shown below.

**Table 6 Parameter estimates of the Cox PH model for grade ≥ 3 TEAE**

| Predictor | Estimate | Standard Error | *P* value |
|---|---|---|---|
| AUC56 | -0.0000825 | 0.0000177 | <0.001 |
| Age | 1.44 | 0.423 | <0.001 |

Source: exposure-safety-v04.qmd, exposure-safety-v04.html
Abbreviations: AUC56=area under the serum concentration-time curve from Day 1 to Day 56 (Cycle 1 and Cycle 2); PH=proportional hazard; TEAE=treatment-emergent adverse event

**Table 7 Parameter estimates of the Cox PH model for SAE**

| Predictor | Estimate | Standard Error | *P* value |
|---|---|---|---|
| Time on treatment | -2.16 | 0.405 | <0.001 |

Source: exposure-safety-v04.qmd, exposure-safety-v04.html
Abbreviations: PH=proportional hazard; SAE=serious adverse event

## 2.3.5. Discussion on clinical pharmacology

Previous assessed and validated methods based on electrochemiluminescent assay (ECLA) were applied for ADA testing and for quantification of tafasitamab. NAb testing was performed using an antibody-dependent cell-mediated cytotoxicity (ADCC) assay. All final data reports will be submitted once Study 301 and 102 are complete, as recommended by the CHMP.

The PK of tafasitamab 12 mg/kg in combination with lenalidomide and rituximab intended for treatment of R/R FL patients were investigated in Phase 3 Study INCMOR 0208-301. Study INCMOR 0208-102 is an ongoing Phase 1b/2 study of tafasitamab mono- and combination therapy in Japanese participants with R/R NHL (Phase 1b) or DLBCL (Phase 2). At the time of data-cutoff only 24 participants were dosed. Most participants were diagnosed with R/R FL (83.9%). PK sampling was sparse and exposure metrics model-derived. Comparison of t½ and Vss across studies in which participants received tafasitamab 12 mg/kg, did not indicate any impact of combination treatment or disease type on PK. The values derived from Study 301 were close to the mean estimates of all studies. Comparing the exposure in these participants to non-Japanese participants from other studies indicated Japanese participants have slightly higher exposure. However, as the number of Japanese participants in each treatment group is low, no firm conclusions can be drawn and the results regarding Japanese race should be interpreted with caution.

The indication is primarily supported by data from Study 301 of which 276 participants out of 329 was diagnosed with R/R FL. Alle were treated with tafasitamab 12 mg/kg in combination with lenalidomide and rituximab.

A previous Pop PK model was updated to include data from studies C205 (COSMOS), C107 (firstMIND), 301 (inMIND), and 102 (J-MIND) Part 1 and 2 (excluding Group 2) and re-estimated. Covariate effects included were: WT, serum albumin, sex, race (Asian versus non-Asian), CRCL on CL; and WT, disease type (NHL and ALL versus CLL or SLL), race (Asian versus non-Asian) on Vc. Effect of concomitant lenalidomide was initially included on CRCL and CL but was wrongly computed in Study 301 (inMIND). After re-estimation with corrected 301 data, the effect of lenalidomide use was removed. The erroneous "reported" model with lenalidomide effect was used for estimation of exposure metrics and for E-R analyses.

Effect of body weight (37.5 – 163 kg) and serum albumin (23-55 g/L) had the greatest impact on tafasitamab CL. Clearance and Vc increased with body weight and clearance increased with lower serum albumin. A Forest plot of univariate impact of body weight on exposure, however, indicated

the reverse effect with exposure increasing with body weight. The exponent of weight effect on V was estimated to 0.427 in the final Pop PK model for tafasitamab.

A subgroup analysis of Asian/Japanese vs Caucasian indicated that exposure was slightly higher in Asians compared to non-Asians which is in line with a general lower body weight in people from Asia. However, the number of Japanese participants in each treatment group is low and the results should be interpreted with caution.

The approved dose level of 12 mg/kg tafasitamab in combination with lenalidomide and rituximab seem appropriate for participants with R/R FL. Section 4.2 of the SmPC was updated to reflect the recommended starting dose for lenalidomide and rituximab; Section 5.2 was also updated with model-derived PK information pooled across studies at 12 mg/kg, that included new data in participants diagnosed with DLBCL, FL and MZL. All proposed changes to Section 5.2 were updated using the correct Pop PK model. In Study 301, 9 participants had treatment-emergent (post-baseline) ADAs of which 6 participants were placebo treated. None had detectable NAbs.

For exposure-response analyses, all model-derived exposure metrics were highly correlated (AUC28, AUC56, overall Cmax, and highest Cmin). For efficacy endpoints PFS, OS and PET-CR, only Kaplan Meier curves for PFS in FL and in the overall population (FL+MZL) showed significant exposure-dependency. Cox PH modelling determined primary refractory to be predictor for PFS in FL and AUC56 to be predictor in the overall population.

For safety, TEAE leading to dose modification had a statistically significant inverse relation to exposure with AUC56 as predictor. In the time-to-event analyses, Cox PH modelling identified AUC56 as significant predictor for TEAE leading to dose modification; age and AUC56 were significant for first occurrence of Grade ≥ 3 TEAE while time on treatment remained significant for first occurrence of SAE. For first occurrence of Grade ≥ 3 neutropenia, no significant covariates including exposure (AUC56) were identified.

The SmPC Section 5.2 was updated with model-derived PK information pooled across studies at 12 mg/kg, that included new data in participants diagnosed with DLBCL, FL and MZL.

### 2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of tafasitamab for treatment of patients with R/R FL seems overall well described. The PI has been updated with the relevant information.

Following a recommendation by the CHMP the MAH will submit all final clinical pharmacology data reports from Study INCMOR 0208-301 and study INCMOR 0208-102, once these studies are completed.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

No dose response studies have been performed.

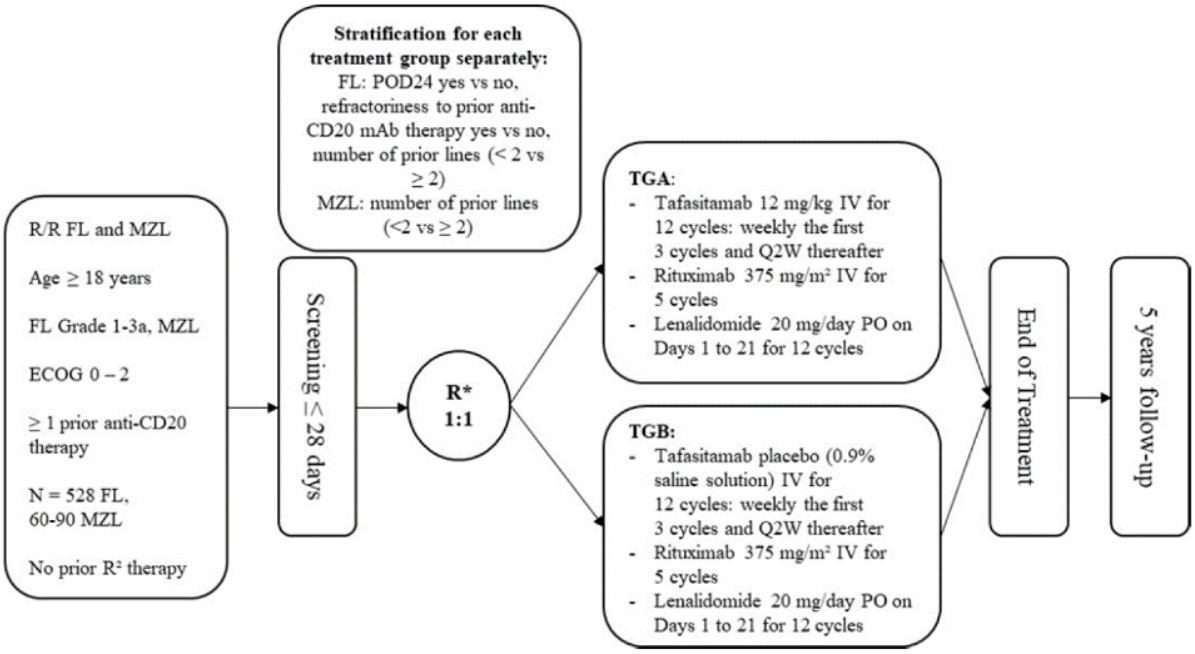
Please see clinical pharmacology sections.

### 2.4.2. Main studyies

**INCMOR 0208-301 ("inMIND"):** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition

to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma.

**Figure 10 INCMOR 0208-301 study design schema**




Q2W = every 2 weeks.

Note 1: TGA (Treatment Group A) refers to tafasitamab+R2, and TGB (Treatment Group B) refers to placebo+R2.

Note 2: The primary analysis for PFS will occur after EOT and prior to the completion of the 5-year follow-up period.

* Randomization applied separately for FL and MZL Populations.

## Methods

Study INCMOR 0208-301 is a randomized, double-blind, placebo-controlled, parallel-group study in participants at least 18 years of age with histologically confirmed R/R FL or R/R MZL. Participants were randomized 1:1 to receive tafasitamab+R2 or placebo+R2. Randomization occurred separately for the FL and MZL populations.

### *Study participants*

**Inclusion criteria:**

Participants are eligible to be included in the study only if all of the following criteria apply:

- Age ≥ 18 years at the time of signing the ICF.
- Ability to comprehend and willingness to sign a written ICF for the study.
- Histologically confirmed Grade 1, 2, or 3a FL or histologically confirmed nodal MZL, splenic MZL, or extranodal MZL as assessed locally (Swerdlow et al 2016); expression of CD19+ and CD20+ on lymphoma cells **must be documented** for all participants, FL and MZL, prior to randomization.

**NOTE**: Participants with gastric MZL and evidence of Helicobacter pylori must have a documented nonresponse to antibiotic therapy prior to randomization.

- Willingness to avoid pregnancy or fathering children based on the criteria below.
- Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 180 days (6 months) after the last dose of study treatment, even if they have undergone a successful vasectomy, and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed.
- WOCBP participants must commit either to abstain continuously from heterosexual sexual intercourse or agree to take appropriate precautions to avoid pregnancy (by using 2 different methods of birth control: one with at least 99% certainty and an additional effective [barrier] method) starting at least 4 weeks before taking the study treatment, while taking the study treatment, during breaks (dose interruptions), and for at least 180 days (6 months) after stopping the study treatment. Permitted methods that are at least 99% effective in preventing pregnancy and the permitted additional effective (barrier) methods should be communicated to the participants and their understanding confirmed.

  *Note*: Because of the increased risk of venous thromboembolism, combined oral contraceptive pills are not recommended. If a participant is currently using combined oral contraception, the participant should switch to a protocol-specified effective method. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception.

- Must have a negative **serum** pregnancy test at screening (within 10-14 days of the first study drug treatment) and before the first dose on Day 1 (within 24 hours of initiating treatment with lenalidomide).
- Agree to ongoing pregnancy testing during the course of the study; weekly during the first month of study drug treatment, then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles (even if true abstinence is the chosen method of birth control) up to and including the EOT visit.
- Must refrain from breastfeeding and donating oocytes during the course of study and for 180 days (6 months) after the last dose of study treatment.
- A woman not considered to be of childbearing potential as defined in the protocol is eligible.

*Note*: The participants should be informed about the option of donation and cryopreservation of germ cells before the study if applicable.

All participants must

- have been previously treated with at least 1 prior **systemic** anti-CD20 immunotherapy or chemo-immunotherapy. This includes treatments such as the following: rituximab monotherapy or chemotherapy plus immunotherapy with rituximab or obinutuzumab, with or without maintenance.
- Must have **documented** relapsed, refractory, or PD after treatment with systemic therapy (a participant in remission [in CR or PR] after the last prior treatment line would not be eligible).

- Relapsed lymphoma: relapsed after initial response of CR or PR ≥ 6 months after prior therapy.
- Refractory lymphoma: achieved less than PR to the last treatment or achieved a CR or PR that lasted less than 6 months.
- Progressive lymphoma: PD after initial response of SD to prior therapy.

- Must be in need of treatment for relapsed, refractory, or PD as assessed by the investigator. NOTE: For FL only, refer to GELF criteria as a guidance.
- Participants must have at least 1 measurable disease site. A radiographically measurable lymphadenopathy is defined as at least 1 nodal lesion > 1.5 cm in longest diameter or at least 1 extranodal lesion > 1.0 cm in longest diameter (Cheson et al 2014). The lesion must be confirmed to be measurable by CT, MRI, or PET-CT, at the latest at the time of randomization.

*Note*: Participants with PET-negative lesions that are measurable by CT or MRI are eligible and followed up with CT or MRI only.

- ECOG performance status of 0 to 2.
- Participants with laboratory values at screening defined as follows:

**Table 6: Inclusionary Laboratory Values**

| Laboratory Parameter | | Inclusion Criterion |
|---|---|---|
| **Hematology (hematological laboratory values should be considered in the absence of growth factors or transfusions)** | | |
| a | Platelets | ≥ 75 × $10^9$/L (unless secondary to BM involvement as demonstrated by BM biopsy). |
| b | ANC | ≥ 1.5 × $10^9$/L (unless secondary to BM involvement as demonstrated by BM biopsy). |
| c | Hemoglobin | ≥ 8.0 g/dL (unless secondary to BM involvement as demonstrated by BM biopsy). |
| **Hepatic** | | |
| d | ALT | ≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement. |
| e | AST | ≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement. |
| f | Total serum bilirubin | ≤ 1.5 × ULN unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Participants with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤ 5 × ULN. |
| g | Alkaline phosphatase | ≤ 3 × ULN or < 5 × ULN in cases of documented liver involvement. |
| **Renal** | | |
| h | Serum creatinine clearance | ≥ 30 mL/min either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976). |

**Exclusion Criteria**

Participants are excluded from the study if any of the following criteria apply:

- Women who are pregnant or breastfeeding. For Japan, women who are breastfeeding and wish to enroll must discontinue breastfeeding at least 90 days before receiving study drug/treatment. They must also refrain from breastfeeding during the course of study and for 90 days after the last dose of study treatment.
- History of or current histology other than FL and MZL or clinical evidence of transformed lymphoma by INV assessment.
- History of radiation therapy to ≥ 25% of the BM for other diseases.
- History of prior nonhematologic malignancy except for the following:

a) Malignancy treated with curative intent and with no evidence of active disease for more than 2 years before screening.

b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.

c) Adequately treated carcinoma in situ without current evidence of disease.

- Congestive heart failure (left ventricular ejection fraction of < 50%, assessed by 2D-echocardiography or MUGA scan.
- Participants with:

a) Known positive test result for HCV (with anti-HCV serology testing) and a positive test for HCV RNA.

*Note*: Participants with positive serology must have been tested for HCV RNA and are eligible only in the case of negative HCV RNA.

b) Known positive test result for chronic HBV infection (defined by HBsAg positivity).

*Note*: Participants with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA was undetectable, provided that they are willing to undergo monthly ongoing DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Participants who have protective titers of HBsAb (HBsAb positive, HBcAb negative, and HBsAg negative) after vaccination or previously cured hepatitis B are eligible.

c) Seropositivity for or history of active viral infection with human immunodeficiency virus (HIV).

- Active systemic infection (including SARS-CoV-2–positive test).
- Participants in a severely immunocompromised state.
- Known CNS lymphoma involvement.
- Uncontrolled concurrent illness.
- History or evidence of clinically significant cardiovascular, CNS, and/or other systemic disease that would, in the investigator's opinion, preclude participation in the study or compromise the participant's ability to give informed consent.

- Life expectancy < 6 months.
- History or evidence of rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
- Major surgery (excluding lymph node biopsy) within 28 days prior to signing the ICF unless the participant is recovered at the time of signing the ICF.
- Any systemic antilymphoma and/or investigational therapy within 28 days prior to the start of Cycle 1.
- Administration of a **live** vaccine within 28 days prior to the start of study treatment (Cycle 1 Day 1).
- Prior use of lenalidomide in combination with rituximab.
- History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, immunomodulatory drugs, rituximab, other mAbs, and/or the excipients contained in the study drug formulations.
- Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

***Treatments***

A treatment cycle is defined as 28 calendar days and includes treatment with tafasitamab/placebo, lenalidomide, and rituximab. The treatment period for each participant starts with the first administration of study treatment on Cycle 1, Day 1 (C1D1). Study drugs are tafasitamab/placebo, lenalidomide, and rituximab.

Tafasitamab (12 mg/kg IV) or placebo (0.9% saline solution IV)

1. Administered Cycles 1 to 3 on Days 1, 8, 15, and 22, and Cycles 4 to 12 on Days 1 and 15.
2. Tafasitamab will be supplied by the sponsor to an unblinded pharmacy. The placebo will be locally sourced and delivered to an unblinded pharmacy. In case of changes in body weight, tafasitamab dosing should be based on the participant's weight as assessed at the most recent treatment cycle.

Rituximab (including biosimilars; 375 mg/m2 IV)

1. Administered Cycle 1 on Days 1, 8, 15, and 22, and Cycles 2 to 5 on Day 1.
2. Rituximab should be administered approximately 30 minutes after the tafasitamab/placebo infusion is completed but no less than 15 minutes. For logistical reasons, rituximab may be administered on the day after the tafasitamab infusion, or administration may be split over 2 consecutive days, according to local practice and the institution's standard of care.

Lenalidomide (including generics) (20 mg PO QD*)

- Administered Cycles 1 to 12 on Days 1 to 21 at approximately the same time every day. Lenalidomide will be provided by the sponsor to the sites.
- *For participants with moderate renal insufficiency (creatinine clearance ≥ 30 mL/min to < 60 mL/min), the starting dose of lenalidomide must be reduced to of 10 mg daily using the

same schedule. The dose of lenalidomide may be increased to 15 mg QD on Days 1 to 21 of each cycle if no Grade 3/4 lenalidomide-related toxicities occur after 2 cycles.

***Objectives***

The primary objective of the study is to compare the efficacy of tafasitamab versus placebo, each administered in combination with lenalidomide and rituximab, based on investigator-assessed PFS in patients with R/R FL. The key secondary objectives are to assess PFS in the overall study population (including FL and MZL), PET-CR in the FDG-avid FL population, and OS in the FL population. Additional secondary objectives include evaluation of safety, quality of life, and other efficacy measures such as ORR, DOR, TTNT and PFS2. The objectives are considered clinically relevant.
The first key secondary endpoint (PFS in the overall population: FL & MZL) is not directly relevant to the present application but had to succeed in order to allow hierarchical testing of the remaining key secondary endpoints.

***Outcomes/endpoints***

Primary endpoint

Progression-free survival by INV assessment is defined as the time from the date of randomization to the date of first documented disease progression, as determined by disease assessment per the Lugano classification or death due to any cause, whichever occurs earlier. For the primary analysis, PFS will be censored if no PFS event is observed before the cutoff date or the date that a new anti-lymphoma therapy is started.

Key secondary endpoint

Progression-free survival by INV assessment in the overall population (FL and MZL) will be compared and analyzed in the same manner as the primary endpoint.

The PET-CR rate is defined as the proportion of FDG-avid participants who achieved a CR as per Lugano classification with a PET-negative result defined as a complete metabolic response at any time after start of treatment over the FDG-avid FL population at baseline. FDG-avid FL participants with no postbaseline assessment by PET or those who did not achieve a PET-CR will be classified as "non–CR-responder."

Overall survival is defined as the time from randomization until death from any cause. All participants should be followed until death or until the end of study, whichever comes first, as specified in the Protocol. The cause of death ("disease progression," "adverse event," or "other") will be summarized. Participants who are not reported as a death at the time of the analysis cutoff will be censored at the earlier of the analysis cutoff and date of last known alive.

Change in Censoring Rules in Sensitivity Analysis

1. For the primary and key secondary endpoint of PFS in the FL and overall populations, the analysis may be performed considering participants having an event after 2 or more missed visits as having a PFS event.

2. For the primary and key secondary endpoint of PFS in the FL and overall populations, the analysis will correct for potential bias in the follow-up schedules for disease assessment by assigning the dates for censoring and events only at scheduled

visit dates. It is the same as the primary analysis except that the date of progression is approximated as the date of the Protocol-scheduled visit immediately after the radiologic assessment of PD.

- For the primary and secondary efficacy endpoints, sensitivity analyses may be performed to evaluate the impact of subsequent anti-lymphoma therapy. For the PFS and DoR endpoints, sensitivity analyses may be performed per EMA guidelines to consider new anti-lymphoma treatment as an event or consider all disease progressions and deaths as events regardless of whether they occur after initiating new anti-lymphoma treatment.

***Sample size***

It was planned to randomize approximately 528 participants with FL and 60 to 90 participants with MZL. The overall recruitment is completed if the required 528 participants with FL for the primary analysis and at least 60 participants with MZL are randomized. The recruitment of participants with MZL is limited to a maximum of 90 participants. The number of participants with MZL is based on the expected enrollment proportion of participants with FL and MZL.
A total number of 174 PFS events in the FL population are required to detect a HR of 0.65 with 80% power at the primary analysis, using a 2-sided log-rank test at an alpha level of 5%. Assuming a median PFS of 27.8 months for lenalidomide in addition to rituximab (TGB), 21 months of enrollment, 12 months of follow-up for PFS, and 15% of dropouts, 528 evaluable FL participants need to be randomized.

***Randomisation***

Participants were randomized (separately for FL and MZL) at a 1:1 ratio to 1 of the following 2 treatment groups:

- TGA: tafasitamab + lenalidomide + rituximab
- TGB: placebo + lenalidomide + rituximab

Stratified randomization was done through IRT using the stratification factors described below. Stratified randomization will be performed separately for participants with FL and MZL.

Participants with FL were to be stratified at the time of randomization for the following factors:
- POD24 (yes vs no)
- Refractoriness to prior anti-CD20 mAb therapy (yes vs no)
- The number of prior lines of therapy (< 2 vs ≥ 2).

Participants with MZL were to be stratified at the time of randomization for the following factor:
- The number of prior lines of therapy (< 2 vs ≥ 2).

***Blinding (masking)***

This is a double-blind study; therefore, participants, investigators, and the study team members will remain blinded to treatment assignment.
Data that may potentially unblind the treatment assignment (ie, study treatment concentrations) will be handled with special care to ensure that the integrity of the blind is maintained, and the potential for bias is minimized. This will include making special provisions such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and/or unblinding. Participants, investigators, and the study team members will remain blinded to treatment assignment until the time of the primary analysis. The endpoints PFS, ORR, and DOR, as determined by IRC assessment using International Working Group 2014 response criteria will be analyzed in the FL, MZL, and overall populations.

**Analysis sets**

Multiple analysis sets were implemented in this study across the FL, overall, and MZL populations. These included the full analysis set (FAS), per-protocol set (PPS), safety analysis set (SAF), MRD-evaluable subsets, and the FDG-avid population. The FAS comprised all randomized participants, PPS included over 95% of FAS participants, the SAF included nearly all participants who received at least one dose. The FDG-avid population represented approximately 89% of the overall population, and among these, 505 participants from the FL population (77.2% of the overall study population) were used for the analysis of the key secondary endpoint assessing PET-CR rate. The main efficacy analyses were conducted using the FAS, while the PPS, SAF, and predefined subpopulations were used for sensitivity and supporting analyses.

***Statistical methods***

Primary endpoint

The distribution of PFS by INV assessment will be compared between the 2 treatment groups using a stratified log-rank test at 2-sided 5% level of significance. The strata information will be based on the data obtained from IRT that was used for randomization.

A stratified Cox proportional hazard model will be used to estimate the HR between TGA (tafasitamab + lenalidomide + rituximab) versus TGB (placebo + lenalidomide + rituximab), along with 2-sided 95% CI. The distribution of PFS estimated using the Kaplan-Meier method and the number of events, censoring, and censoring reasons would be summarized. The median along with 2-sided 95% CIs by treatment group along with the 95% CI calculated using the generalization of Brookmeyer and Crowley's method with log-log transformation and PFS rates at 6, 12, 18, 24, 36, and 48 months may be provided along with the corresponding 2-sided 95% CIs would be presented. All analyses mentioned above are to be performed for participants with FL in the FAS. If the null hypothesis is rejected at a 2-sided significance level of 5%, the primary endpoint is met.

Key secondary endpoint

Progression-free survival by INV assessment in the overall population (FL and MZL) will be compared and analyzed in the same manner as the PFS in the FL population. The strata information for the stratified log-rank test will be based on the randomization factor used for both cohorts, FL and MZL: number of prior lines of therapy (< 2 versus ≥ 2).

The PET-CR rate is defined as the proportion of FDG-avid participants who achieved a CR as per Lugano classification with a PET-negative result defined as a complete metabolic response at any time after start of treatment over the FDG-avid FL population at baseline. FDG-avid FL participants with no postbaseline assessment by PET or those who did not achieve a PET-CR will be classified as "non–CR-responder."
The CR rate will be compared between the 2 treatments groups using a stratified CMH test. The odds ratio and its 95% CIs calculated from the stratified CMH test will also be presented. The number of participants classified as PET-CR responders and the respective rates as well as 95% CIs (using Clopper-Pearson) will be presented. Analysis of the key secondary endpoint of PET-CR will be performed for participants with FDG-avid FL in the FAS.
Overall survival will be compared and analyzed using stratified tests as described for PFS with FL in the FAS at the time of interim, primary, and final analysis. Participants will be censored at the last date they were known to be alive, regardless if a new anti-lymphoma therapy was started.

Sensitivity analysis

- All primary and key secondary efficacy analyses and the corresponding subgroup analyses may be performed on the PPS.
- For time to event endpoints, the assumption of proportional hazard may be tested. If the assumption is not met, a Renyi test may be performed. Additional details will be provided in the SAP.
- For time to event endpoints, unstratified log-rank test may be performed and unadjusted HR may be obtained using unstratified Cox PH model.
- Stratified analyses may be performed using stratification factors from the eCRF.
- For binary endpoints like PET-CR rate and ORR, Fisher's exact test may be performed.

Subgroup analysis

Primary and key secondary endpoints will be analyzed in the following subgroups:

- Baseline NKCC in the FL population and the overall population. Natural killer cell categories are defined using a cut-off of 100 NK cells/μL (≤ 100 cells/μL vs > 100 cells/μL).
- POD24 in the FL population and the overall population
- Japanese FL and overall Japanese population

The MZL population is considered as a subpopulation of interest. Primary and key secondary endpoints assessed by investigator, DOR and ORR by investigator, MRD and PFS, ORR and DOR assessed by IRC, will be analyzed in the MZL population. Subgroup analyses when conducted for the FL and overall population will also be conducted on MZL population.

Additional subgroup analyses may include the following:

- Age group (< 65 years of age versus ≥ 65 years of age)
- Sex
- Race
- Ethnicity
- Geographic region
- Other stratification factors including refractoriness to prior anti-CD20 mAb therapy and number of prior lines of therapy.

When subgroups are corresponding to stratification factors, the CRF strata information should be used. No adjustment for multiplicity will be performed for subgroup analyses. All the subgroup analyses will be performed using CRF data and analyzed using an unstratified test. The HR for PFS and OS between treatment groups will be estimated using an unstratified Cox proportional hazard model at each subgroup level along with 2-sided 95% CI. The unstratified odds ratio for PET-CR rate between treatment groups along with its 95% CI will be estimated at each subgroup level. The HR or odds ratio and corresponding 95% CI by subgroups will be presented graphically in forest plots.

**Interim analysis**

A PFS interim analysis for futility will be performed after 20% (approximately 35) of the required INV-assessed PFS events have been observed in participants with FL in the FAS. This is expected to occur approximately 15 months after the first participant is randomized and approximately 338 (out of 528 total) participants with FL have been randomized in the study.
The PFS HR will be calculated, and the IDMC may recommend to stop the study if the observed HR of tafasitamab plus lenalidomide in addition to rituximab (TGA) over placebo plus lenalidomide in addition to rituximab (TGB) is ≥ 1.05 for participants with FL in the FAS (nonbinding futility boundary). Early stop for efficacy is not planned.

The false negative rate for a futility stops with a futility boundary of HR = 1.05 is

- Approximately 8% if the true HR is 0.65, and
- Approximately 15% if the true HR is 0.74.

The false positive rate for continuation of the study with a futility boundary of HR = 1.05 is

- Approximately 62% if the true HR is 0.95.

At the time of the PFS primary analysis, an interim futility analysis of OS will be conducted.

The median OS of 10 years in the control group, a PFS HR of 0.65, a 21-month accrual rate, a 12-months follow up, and a 15% drop out rate would result in approximately 47 deaths at the time of the PFS primary analysis estimated 33.5 months after the first participant is randomized.
The final analysis for the study will still be expected to occur approximately 96 months after the first participant is randomized. The OS interim futility analysis will be implemented using an O'Brien and Fleming beta
spending function.

**Multiplicity**

In order to control the study-wise type I error due to the multiple testing of the primary and key secondary endpoints, a hierarchical order of testing will be implemented.
The primary endpoint analysis will serve as a gatekeeper:

- PFS by INV in the FL population

If the primary null hypothesis is rejected, the key secondary endpoints can be tested with the following fixed order:

- PFS by INV in the overall population (FL and MZL)
- PET-CR rate by INV in the FDG-avid FL population
- OS in the FL population

If a null hypothesis is not rejected, the formal sequential testing will be stopped, and the p-values for the remaining key secondary endpoints will be reported for exploratory and illustrative purposes.

**SAP amendments**

Changes to Protocol-Defined Analyses
The MRD-evaluable set analysis population was added in the SAP to support the sensitivity analysis for the summary of MRD-negativity rate.
The following analyses were added in the SAP to provide additional study information:

-Summary of currentness of PFS and OS data
-Summary of PFS and OS follow-up time
-Summary of time to objective response
-Overall survival for PFS with FL for interim analysis

As of SAP Amendment 2, the MRD-negativity rate threshold used other secondary efficacy analysis will be $10^{-5}$ and the threshold of $10^{-4}$ will be used for sensitivity.

**Changes to the Statistical Analysis Plan**

Amendment 1: the SAP was updated to clarify the stratification factors to be included in the analysis and to clarify the censoring rules for overall survival.

Amendment 2 The SAP was updated to describe an OS futility interim analysis to be performed at the time of the PFS primary analysis; to include the Japanese population as a subgroup analysis.; to specify the cut-off to be used to classify the NKCC, added information about CRF strata information and clarified subgroup analyses.; to clarify the origin of the MRD samples, the definition of sample stability, the threshold to be used to define negativity, and the denominator to calculate the MRD negativity rates; to clarify the definition of PFS on next treatment; to specify the interim analysis described in the section will be for PFS and to discuss PFS and OS interim analysis separately.

Amendment 3 The SAP was updated with clarifications in the MZL population removal of the sensitivity analysis using peripheral blood sample at EOT with a $10^{-4}$ as threshold to define negativity (in the MRD-blood evaluable population) and minor amendments. The following post hoc analyses were performed:

-Tafasitamab exposure was summarized by region (ie, North America, Europe, rest of world) in the FL and Overall populations.

-Subgroup analyses of ORR in the FL, MZL, and Overall Populations by investigator assessment and IRC assessment were summarized and presented graphically in forest plots.

## Results

### *Participant flow*

**Table 8 Summary of participants disposition (FL FAS)**

| Variable, n (%) | Tafasitamab+R$^2$ (N = 273) | Placebo+R$^2$ (N = 275) | Total (N = 548) |
|---|---|---|---|
| Participants randomized | 273 (100.0) | 275 (100.0) | 548 (100.0) |
| Participants treated | 273 (100.0) | 273 (99.3)[a] | 546 (99.6) |
| Participants with ongoing treatment | 51 (18.7) | 42 (15.3) | 93 (17.0) |
| Participants who discontinued treatment | 222 (81.3) | 231 (84.0) | 453 (82.7) |
| Primary reason for treatment discontinuation | | | |
| Completed | 146 (53.5) | 118 (42.9) | 264 (48.2) |
| AE | 24 (8.8) | 15 (5.5) | 39 (7.1) |
| Death | 2 (0.7) | 3 (1.1) | 5 (0.9) |
| Lost to follow-up | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Lack of efficacy | 7 (2.6) | 5 (1.8) | 12 (2.2) |
| Physician decision | 4 (1.5) | 0 (0.0) | 4 (0.7) |
| PD | 30 (11.0) | 84 (30.5) | 114 (20.8) |
| Withdrawal by participant | 7 (2.6) | 5 (1.8) | 12 (2.2) |
| Other | 1 (0.4) | 1 (0.4) | 2 (0.4) |
| Participants ongoing in study | 244 (89.4) | 229 (83.3) | 473 (86.3) |
| Participants who withdrew from study | 29 (10.6) | 46 (16.7) | 75 (13.7) |
| Primary reason for withdrawal from study | | | |
| Death | 15 (5.5) | 22 (8.0) | 37 (6.8) |
| Lost to follow-up | 3 (1.1) | 2 (0.7) | 5 (0.9) |
| Withdrawal by participant | 11 (4.0) | 19 (6.9) | 30 (5.5) |
| Other | 0 (0.0) | 2 (0.7) | 2 (0.4) |
| Missing | 0 (0.0) | 1 (0.4) | 1 (0.2) |

[a] Two participants randomized to the placebo+R$^2$ group were not treated due to confirmation of rituximab hypersensitivity and withdrawal by participant (refer to Listing 2.1.1.1).

**Table 9 : Summary Table of Screen Failures in Study inMIND**

| | |
|---|---|
| Participants screened | 817 |
| Participants not randomized | 163 (100.0) |
| Main reason for non-enrolment (%)[a] | |
| Screen failure (%)[a] | 152 (93.3) |
| Inclusion criterion not met [a,b] | 88 (54.0) |
| Exclusion criterion not met [a,b] | 71 (43.6) |
| Other reasons for non-enrolment (%)[a] | 11 (6.7) |
| Other | 5 (3.1) |

| | |
|---|---|
| Withdrawal by participant | 4 (2.5) |
| Lost to follow-up | 1 (0.6) |
| Physician decision | 1 (0.6) |

[a] percentages based on the number of participants not randomized
[b] categories are not mutually exclusive.

**Table 10: Summary of participants not meeting CD19 and/or CD20 requirement of inclusion criterion #3**

| | Number of Participants |
|---|---|
| Lack of CD19 expression | 5 |
| Lack of CD20 expression | 6 |
| Lack of CD19 and CD20 expression | 0 |

***Recruitment***

First patient dosed: 16 APR 2021

Last patient enrolled: 10 AUG 2023

Data cut-off: 23.02.2024

This study was conducted at 210 study centres overall (199 for the Follicular Lymphoma [FL] Population and 65 for the Marginal Zone Lymphoma [MZL] Population) in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, the Netherlands, Norway, Poland, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, the United Kingdom, and the United States.

***Conduct of the study***

Study INCMOR 0208-301 was conducted in compliance with Good Clinical Practice and ethical principles that have their origin in the Declaration of Helsinki and were consistent with US, European, and ICH guidelines on drug development. The study was closely monitored by the study sponsor's personnel or contract organizations for compliance with the study Protocol and procedures described herein. Participant enrolment into this study started in 2021 during the COVID-19 pandemic, when highly transmissible SARS-CoV-2 strains were prevalent and vaccines and treatments were available, although to a different extent across participating countries.

**Table 11: Summary of important protocol deviations – FL FAS**

| | **Tafasitamab + $R^2$ (N=273)** | **Placebo + $R^2$ (N=275)** | **Total (N=548)** |
|---|---|---|---|
| Number (%) of participants who had an important protocol deviation | 49 (17.9) | 47 (17.1) | 96 (17.5) |
| Administrative issue | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Inclusion/exclusion | 6 (2.2) | 4 (1.5) | 10 (1.8) |
| Informed consent | 2 (0.7) | 7 (2.5) | 9 (1.6) |
| Safety reporting | 19 (7.0) | 21 (7.6) | 40 (7.3) |
| Study intervention | 3 (1.1) | 1 (0.4) | 4 (0.7) |

| | | | |
|---|---|---|---|
| Trial procedures | 25 (9.2) | 18 (6.5) | 43 (7.8) |

***Baseline data***

**Table 12 Summary of demographics and baseline characteristics**

| Variable | Tafasitamab+R$^2$ (N = 273) | Placebo+R$^2$ (N = 275) | Total (N = 548) |
|---|---|---|---|
| Region, n (%) | | | |
| North America | 38 (13.9) | 24 (8.7) | 62 (11.3) |
| Europe | 176 (64.5) | 193 (70.2) | 369 (67.3) |
| Rest of the world | 59 (21.6) | 58 (21.1) | 117 (21.4) |
| Age (years) | | | |
| Mean (STD) | 64.6 (10.89) | 63.7 (11.69) | 64.2 (11.29) |
| Median (min, max) | 64.0 (36, 88) | 64.0 (31, 85) | 64.0 (31, 88) |
| Age group, n (%) | | | |
| < 65 years | 137 (50.2) | 139 (50.5) | 276 (50.4) |
| ≥ 65 years | 136 (49.8) | 136 (49.5) | 272 (49.6) |
| < 75 years | 219 (80.2) | 221 (80.4) | 440 (80.3) |
| ≥ 75 years | 54 (19.8) | 54 (19.6) | 108 (19.7) |
| Sex, n (%) | | | |
| Male | 150 (54.9) | 149 (54.2) | 299 (54.6) |
| Female | 123 (45.1) | 126 (45.8) | 249 (45.4) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 31 (11.4) | 24 (8.7) | 55 (10.0) |
| Not Hispanic or Latino | 228 (83.5) | 226 (82.2) | 454 (82.8) |
| Not reported | 11 (4.0) | 23 (8.4) | 34 (6.2) |
| Unknown | 3 (1.1) | 2 (0.7) | 5 (0.9) |

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) | Total (N = 548) |
|---|---|---|---|
| Race, n (%) | | | |
| White | 219 (80.2) | 219 (79.6) | 438 (79.9) |
| Black or African American | 1 (0.4) | 0 (0.0) | 1 (0.2) |
| Asian | 40 (14.7) | 42 (15.3) | 82 (15.0) |
| American Indian or Alaska Native | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian or Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Not reported | 11 (4.0) | 10 (3.6) | 21 (3.8) |
| Other | 2 (0.7) | 4 (1.5) | 6 (1.1) |
| Body weight (kg) at screening visit | | | |
| n | 271 | 273 | 544 |
| Mean (STD) | 76.70 (17.556) | 77.16 (19.525) | 76.93 (18.555) |
| Median (min, max) | 76.70 (37.2, 144.5) | 76.10 (45.0, 199.0) | 76.25 (37.2, 199.0) |
| ECOG score at screening visit, n (%) | | | |
| 0 | 181 (66.3) | 192 (69.8) | 373 (68.1) |
| 1 | 85 (31.1) | 75 (27.3) | 160 (29.2) |
| 2 | 7 (2.6) | 8 (2.9) | 15 (2.7) |

**Table 13 Summary of baseline characteristics and disease history (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) | Total (N = 548) |
|---|---|---|---|
| Time since initial diagnosis, years | | | |
| Median (min, max) | 5.2 (0, 34) | 5.5 (1, 33) | 5.3 (0, 34) |
| FL grade at study entry, n (%) | | | |
| Grade 1 | 61 (22.3) | 51 (18.5) | 112 (20.4) |
| Grade 2 | 142 (52.0) | 152 (55.3) | 294 (53.6) |
| Grade 3a | 67 (24.5) | 71 (25.8) | 138 (25.2) |
| Missing | 3 (1.1) | 1 (0.4) | 4 (0.7) |
| Ann Arbor staging at study entry, n (%) | | | |
| Stage I | 10 (3.7) | 13 (4.7) | 23 (4.2) |
| Stage II | 42 (15.4) | 37 (13.5) | 79 (14.4) |
| Stage III | 72 (26.4) | 63 (22.9) | 135 (24.6) |
| Stage IV | 149 (54.6) | 162 (58.9) | 311 (56.8) |

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) | Total (N = 548) |
|---|---|---|---|
| Time since initial diagnosis, years | | | |
| Median (min, max) | 5.2 (0, 34) | 5.5 (1, 33) | 5.3 (0, 34) |
| FL grade at study entry, n (%) | | | |
| Grade 1 | 61 (22.3) | 51 (18.5) | 112 (20.4) |
| Grade 2 | 142 (52.0) | 152 (55.3) | 294 (53.6) |
| Grade 3a | 67 (24.5) | 71 (25.8) | 138 (25.2) |
| Missing | 3 (1.1) | 1 (0.4) | 4 (0.7) |
| Ann Arbor staging at study entry, n (%) | | | |
| Stage I | 10 (3.7) | 13 (4.7) | 23 (4.2) |
| Stage II | 42 (15.4) | 37 (13.5) | 79 (14.4) |
| Stage III | 72 (26.4) | 63 (22.9) | 135 (24.6) |
| Stage IV | 149 (54.6) | 162 (58.9) | 311 (56.8) |

**Table 14 : Summary of Prior Cancer Therapy (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) | Total (N = 548) |
|---|---|---|---|
| **Number of prior systemic anticancer therapy lines per participant** | | | |
| Mean (STD) | 1.8 (1.13) | 1.8 (1.16) | 1.8 (1.15) |
| Median (min, max) | 1.0 (1, 7) | 1.0 (1, 10) | 1.0 (1, 10) |
| **Number of prior systemic anticancer therapy lines, n (%)** | | | |
| 1 | 147 (53.8) | 153 (55.6) | 300 (54.7) |
| 2 | 66 (24.2) | 71 (25.8) | 137 (25.0) |
| 3 | 39 (14.3) | 30 (10.9) | 69 (12.6) |
| 4 | 12 (4.4) | 11 (4.0) | 23 (4.2) |
| > 4 | 9 (3.3) | 10 (3.6) | 19 (3.5) |
| **Time between last prior regimen end date and randomization date, n (%)** | | | |
| 0 to ≤ 2 years | 147 (53.8) | 157 (57.1) | 304 (55.5) |
| > 2 to ≤ 5 years | 87 (31.9) | 66 (24.0) | 153 (27.9) |
| > 5 to ≤ 10 years | 32 (11.7) | 34 (12.4) | 66 (12.0) |
| > 10 years | 7 (2.6) | 18 (6.5) | 25 (4.6) |
| **Number of anti-CD20–containing prior therapy lines per participant** | | | |
| Mean (STD) | 1.6 (0.87) | 1.6 (0.91) | 1.6 (0.89) |
| Median (min, max) | 1.0 (1, 5) | 1.0 (1, 6) | 1.0 (1, 6) |
| **Number of anti-CD20–containing prior therapy lines, n (%)** | | | |
| 1 | 168 (61.5) | 168 (61.1) | 336 (61.3) |
| 2 | 66 (24.2) | 70 (25.5) | 136 (24.8) |
| 3 | 30 (11.0) | 25 (9.1) | 55 (10.0) |
| 4 | 5 (1.8) | 7 (2.5) | 12 (2.2) |
| > 4 | 4 (1.5) | 5 (1.8) | 9 (1.6) |
| **Participants with rituximab-refractory disease[a], n (%)** | | | |
| Yes | 112 (41.0) | 103 (37.5) | 215 (39.2) |
| No | 143 (52.4) | 155 (56.4) | 298 (54.4) |

| | | | |
|---|---|---|---|
| Indeterminate[b] | 7 (2.6) | 4 (1.5) | 11 (2.0) |
| Not applicable[c] | 11 (4.0) | 13 (4.7) | 24 (4.4) |
| Participants with prior radiation therapy for FL, n (%) | 52 (19.0) | 46 (16.7) | 98 (17.9) |
| Participants with prior surgery or surgical procedure for FL[d], n (%) | 88 (32.2) | 71 (25.8) | 159 (29.0) |
| Participants with prior ASCT for FL, n (%) | 13 (4.8) | 15 (5.5) | 28 (5.1) |
| Participants with prior anti-CD19-containing therapy | 0 (0.0) | 2 (0.7) | 2 (0.4) |
| CAR-T NOS | 0 (0.0) | 1 (0.4) | 1 (0.2) |
| Blinatumomab | 0 (0.0) | 1 (0.4) | 1 (0.2) |

[a] Rituximab-refractory is defined as PD within 6 months from last dose of rituximab or a best overall response of SD following the last prior rituximab-containing regimen.
[b] Indeterminate includes participants whose best overall response to the prior rituximab-containing regimen of therapy was unknown
[c] Not applicable includes participants who did not have a prior rituximab-containing regimen.
[d] Prior surgery or surgical procedures may include bone marrow aspirations and biopsies among other surgeries (refer to Listing 2.4.5.1).
.

***Numbers analysed***

**Table 15 Summary of Analysis populations (All screened)**

| Participant Population Analysis Population, n (%) | Tafasitamab+R$^2$ | Placebo+R$^2$ | Total |
|---|---|---|---|
| **FL Population (N = 548)** | | | |
| FAS | 273 (100.0) | 275 (100.0) | 548 (100.0) |
| PPS | 254 (93.0) | 267 (97.1) | 521 (95.1) |
| Safety Population | 274 (100.4)[a] | 272 (98.9)[a,b] | 546 (99.6) |
| MRD Blood-Evaluable Set | 57 (20.9) | 66 (24.0) | 123 (22.4) |
| MRD Bone Marrow–Evaluable Set | 78 (28.6) | 92 (33.5) | 170 (31.0) |
| FDG-Avid Set | 251 (91.9) | 254 (92.4) | 505 (92.2) |
| **Overall Population (N = 654)** | | | |
| FAS | 326 (100.0) | 328 (100.0) | 654 (100.0) |
| PPS | 304 (93.3) | 315 (96.0) | 619 (94.6) |
| Safety Population | 327 (100.3)[a] | 325 (99.1)[a,b] | 652 (99.7) |
| MRD Blood-Evaluable Set | 74 (22.7) | 86 (26.2) | 160 (24.5) |
| MRD Bone Marrow–Evaluable Set | 104 (31.9) | 118 (36.0) | 222 (33.9) |
| FDG-Avid Set | 290 (89.0) | 293 (89.3) | 583 (89.1) |
| **MZL Population (N = 106)** | | | |
| FAS | 53 (100.0) | 53 (100.0) | 106 (100.0) |
| PPS | 50 (94.3) | 48 (90.6) | 98 (92.5) |
| Safety Population | 53 (100.0) | 53 (100.0) | 106 (100.0) |
| MRD Blood-Evaluable Set | 17 (32.1) | 20 (37.7) | 37 (34.9) |
| MRD Bone Marrow–Evaluable Set | 26 (49.1) | 26 (49.1) | 52 (49.1) |
| FDG-Avid Set | 39 (73.6) | 39 (73.6) | 78 (73.6) |

Note: Analysis populations are defined in Section 5.1.

[a] One participant randomized to the placebo+R$^2$ group was included in the tafasitamab+R$^2$ Safety Population because the participant erroneously received tafasitamab (refer to Listings 2.2.1.1, 2.3.1.1, and 2.5.2.1).

[b] Two participants randomized to the placebo+R$^2$ group were not included in the Safety Population because they did not receive study treatment due to confirmation of rituximab hypersensitivity and withdrawal by participant, respectively (refer to Listing 2.1.1.1).

***Outcomes and estimation***

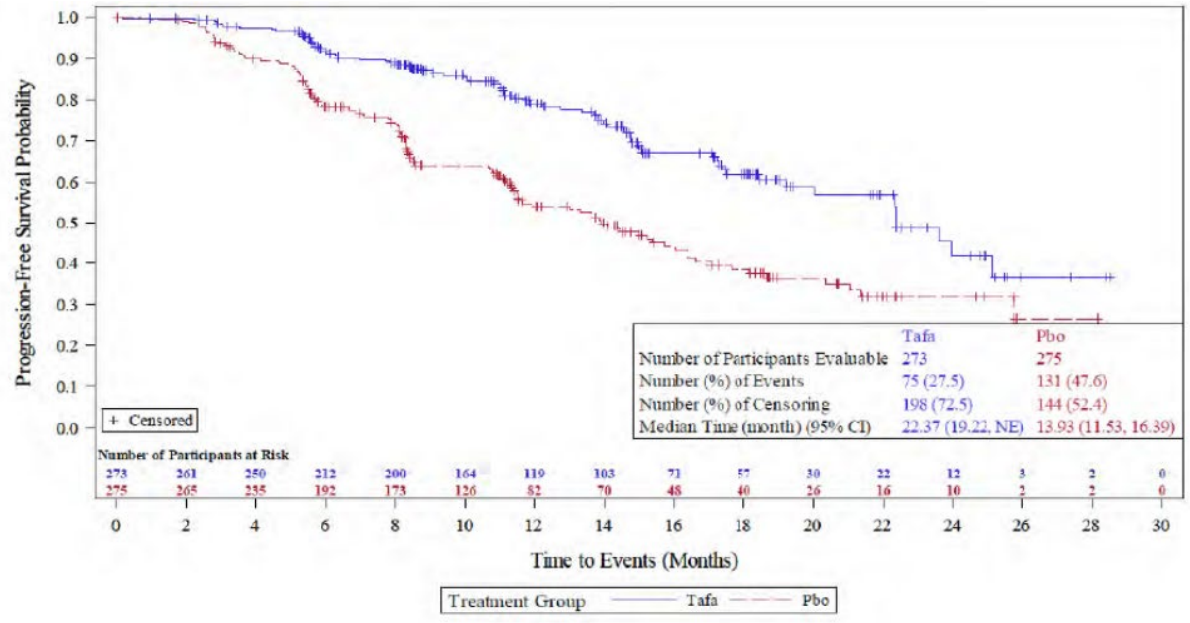
***Primary endpoint: PFS by investigator assessment in the FL Population.***

**Table 16 PFS by Investigator assessment (FL FAS)**

| Variable | Tafasitamab+R$^2$ (N = 273) | Placebo+R$^2$ (N = 275) |
|---|---|---|
| Participants with events, n (%) | 75 (27.5) | 131 (47.6) |
| Disease progression | 67 (24.5) | 124 (45.1) |
| Death | 8 (2.9) | 7 (2.5) |
| Censored participants, n (%) | 198 (72.5) | 144 (52.4) |
| No postbaseline assessment | 6 (2.2) | 6 (2.2) |
| Ongoing | 174 (63.7) | 121 (44.0) |
| Study discontinuation | 5 (1.8) | 3 (1.1) |
| Start of new antilymphoma treatment | 13 (4.8) | 13 (4.7) |
| Death or PD after 2 or more missed assessments | 0 (0.0) | 1 (0.4) |
| Median PFS, months (95% CI)[a] | 22.37 (19.22, NE) | 13.93 (11.53, 16.39) |
| Kaplan-Meier estimates (95% CI) of PFS rate | | |
| 6 months | 92.4 (88.3, 95.1) | 78.2 (72.7, 82.7) |
| 12 months | 79.0 (72.8, 84.0) | 54.0 (47.1, 60.5) |
| 18 months | 61.9 (53.4, 69.3) | 38.5 (30.8, 46.1) |
| 2 years | 41.7 (28.4, 54.6) | 31.8 (23.6, 40.2) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[b] | 0.434 (0.324, 0.580) | |

[a] Median survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the tafasitamab+R$^2$ group and the placebo+R$^2$ group was estimated using a stratified Cox proportional hazards model.
Source: Table 2.1.1.1.

**Figure 11 Kaplan – Meier Estimates of progression-free survival by Investigator (FL FAS)**




Tafa = tafasitamab+R$^2$; Pbo = placebo+R$^2$.

**Table 17 Summary of sensitivity analysis of PFS by Investigator assessment with alternative censoring rules (FL FAS)**

| Variable | Median PFS[a] (95% CI) Tafasitamab+R² | Median PFS[a] (95% CI) Placebo+R² | HR[b] (95% CI) |
|---|---|---|---|
| Treating PD or death after 2 or more assessments as a PFS event instead of censoring | 22.37 (19.22, NE) | 13.93 (11.53, 16.39) | 0.432 (0.323, 0.577) |
| Using Protocol-scheduled visit as the date of progression if progression is documented between scheduled response assessments | 22.37 (19.22, NE) | 13.86 (11.53, 16.39) | 0.433 (0.324, 0.579) |
| Treating new antilymphoma treatment as an event | 22.37 (17.51, 25.13) | 13.40 (11.37, 15.21) | 0.465 (0.355, 0.610) |
| Treating PD/death as an event regardless of initiation of new antilymphoma treatment | 22.37 (20.04, 25.76) | 13.93 (11.53, 16.39) | 0.445 (0.335, 0.592) |

[a] Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the tafasitamab+R² group and the placebo+R² group was estimated using a stratified Cox proportional hazards model.

**Table 18: Summary of PFS by Investigator Assessment Limited to Participants Fulfilling at Least One of the GELF Criterion (FL FAS)**

| | Tafasitamab + R² (N=222) | Placebo + R² (N=232) |
|---|---|---|
| Number (%) of participants with disease progression or death | | |
| Observed Events | 68 (30.6) | 114 (49.1) |
| Disease Progression | 60 (27.0) | 108 (46.6) |
| Death | 8 (3.6) | 6 (2.6) |
| Censored | 154 (69.4) | 118 (50.9) |
| No baseline tumor assessments | 0 (0.0) | 0 (0.0) |
| No postbaseline assessment | 4 (1.8) | 3 (1.3) |
| Ongoing | 136 (61.3) | 100 (43.1) |
| Study discontinuation | 5 (2.3) | 3 (1.3) |
| Start of new antilymphoma treatment | 9 (4.1) | 11 (4.7) |
| Death or PD after two or more missed assessments | 0 (0.0) | 1 (0.4) |
| Median PFS (months and 95% CI) | 22.37 (17.51, NE) | 13.63 (11.50, 16.39) |
| HR (95% CI) | 0.463 (0.341, 0.629) | |

**Table 19: Summary of PFS by Investigator Assessment for Participants Not Meeting at Least 1 GELF Criterion or Missing GELF information (FL FAS)**

| | Tafasitamab + R² (N=51) | Placebo + R² (N=43) |
|---|---|---|
| Number (%) of participants with disease progression or death | | |
| Observed Events | 7 (13.7) | 17 (39.5) |
| Disease Progression | 7 (13.7) | 16 (37.2) |

| | | |
|---|---|---|
| Death | 0 (0.0) | 1 (2.3) |
| Censored | 44 (86.3) | 26 (60.5) |
| No baseline tumor assessments | 0 (0.0) | 0 (0.0) |
| No postbaseline assessment | 2 (3.9) | 3 (7.0) |
| Ongoing | 38 (74.5) | 21 (48.8) |
| Study discontinuation | 0 (0.0) | 0 (0.0) |
| Start of new antilymphoma treatment | 4 (7.8) | 2 (4.7) |
| Death or PD after two or more missed assessments | 0 (0.0) | 0 (0.0) |
| Median PFS (months and 95% CI) | 22.37 (19.22, NE) | 15.01 (8.31, NE) |
| HR (95% CI) | 0.197 (0.065, 0.594) | |

**Key secondary endpoints**

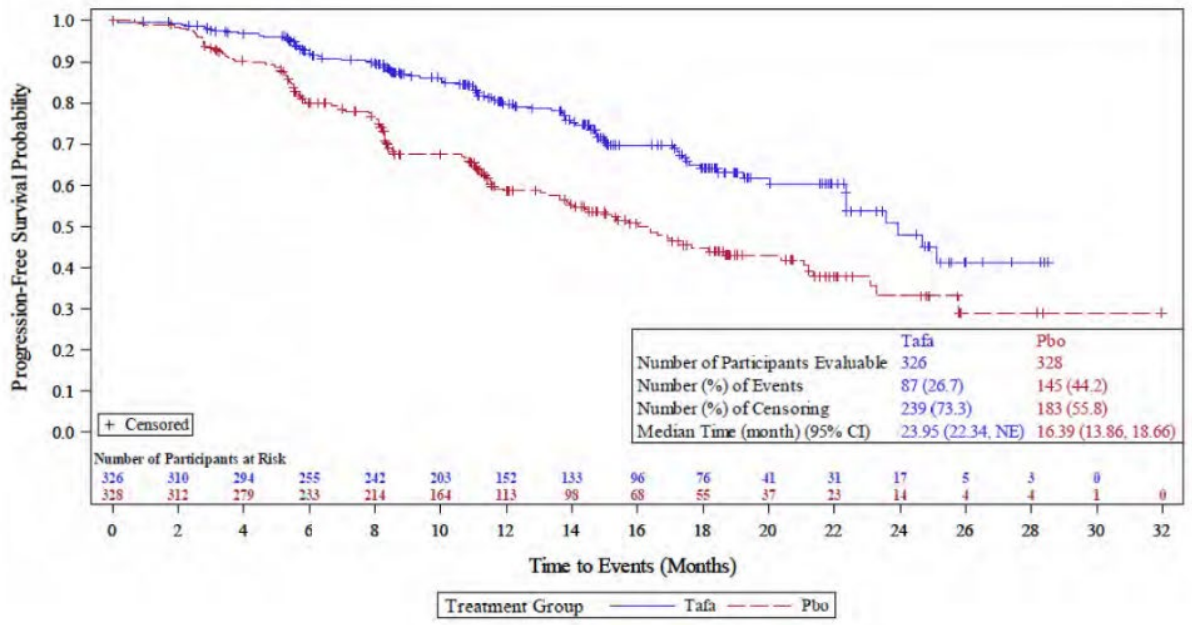
**Table 20 PFS by investigator assessment (Overall FAS)**

| Variable | Tafasitamab+R² (N = 326) | Placebo+R² (N = 328) |
|---|---|---|
| Participants with events, n (%) | 87 (26.7) | 145 (44.2) |
| Disease progression | 76 (23.3) | 137 (41.8) |
| Death | 11 (3.4) | 8 (2.4) |
| Censored participants, n (%) | 239 (73.3) | 183 (55.8) |
| No postbaseline assessment | 9 (2.8) | 9 (2.7) |
| Ongoing | 206 (63.2) | 155 (47.3) |
| Study discontinuation | 9 (2.8) | 4 (1.2) |
| Start of new antilymphoma treatment | 15 (4.6) | 14 (4.3) |
| Death or PD after 2 or more missed assessments | 0 (0.0) | 1 (0.3) |
| Median PFS, months (95% CI)[a] | 23.95 (22.34, NE) | 16.39 (13.86, 18.66) |
| Kaplan-Meier estimates (95% CI) of PFS rate | | |
| 6 months | 92.7 (89.0, 95.1) | 80.0 (75.0, 84.0) |
| 12 months | 79.7 (74.1, 84.2) | 58.7 (52.4, 64.4) |
| 18 months | 64.1 (56.7, 70.6) | 44.7 (37.6, 51.5) |
| 2 years | 48.0 (36.1, 59.0) | 33.1 (24.1, 42.3) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[b] | 0.500 (0.383, 0.653) | |

[a] Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.

[b] The HR between the tafasitamab+R² group and the placebo+R² group was estimated using a stratified Cox proportional hazards model.

**Figure 12 Kaplan Meier Estimates of PFS by investigator assessment (Overall FAS)**




Tafa = tafasitamab+R$^2$; Pbo = placebo+R$^2$.

**Table 21 Summary of sensitivity analysis of PFS by Investigator assessment with alternative censoring rules (Overall FAS)**

| Variable | Median PFS[a] (95% CI) Tafasitamab+R$^2$ | Median PFS[a] (95% CI) Placebo+R$^2$ | HR[b] (95% CI) |
|---|---|---|---|
| Treating PD or death after 2 or more assessments as a PFS event instead of censoring | 23.95 (22.34, NE) | 16.03 (13.63, 18.66) | 0.498 (0.381, 0.650) |
| Using Protocol-scheduled visit as the date of progression if progression is documented between scheduled response assessments | 23.95 (22.34, NE) | 16.39 (13.63, 19.45) | 0.502 (0.384, 0.655) |
| Treating new antilymphoma treatment as an event | 23.59 (19.22, NE) | 15.01 (13.04, 16.92) | 0.535 (0.417, 0.687) |
| Treating PD/death as an event regardless of initiation of new antilymphoma treatment | 23.95 (22.34, NE) | 16.03 (13.80, 18.66) | 0.506 (0.389, 0.658) |

[a] Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.

[b] The HR between the tafasitamab+R$^2$ group and the placebo+R$^2$ group was estimated using a stratified Cox proportional hazards model.

**Table 22 Positron emission tomography – Complete Response Rate at End of treatment by Investigator Assessment (FL FDG-Avid set)**

| Variable | Tafasitamab+R² (N = 251) | Placebo+R² (N = 254) |
|---|---|---|
| Participants with postbaseline PET assessments, n (%)[a] | 201 (80.1) | 205 (80.7) |
| Best metabolic response based on PET, n (%) | | |
| CMR | 124 (49.4) | 101 (39.8) |
| PMR | 37 (14.7) | 39 (15.4) |
| No metabolic response/SD | 19 (7.6) | 12 (4.7) |
| Progressive metabolic disease | 19 (7.6) | 51 (20.1) |
| NE | 0 (0.0) | 0 (0.0) |
| PET scan performed after a confirmed PD or start of new antilymphoma treatment | 2 (0.8) | 2 (0.8) |
| Not assessed[b] | 50 (19.9) | 49 (19.3) |
| PET-CR rate (95% CI)[c,d] | 49.4 (43.06, 55.76) | 39.8 (33.70, 46.07) |
| OR by stratified CMH test (95% CI)[e] | 1.5 (1.04, 2.13) | |
| Stratified CMH test p-value | 0.0286 | |

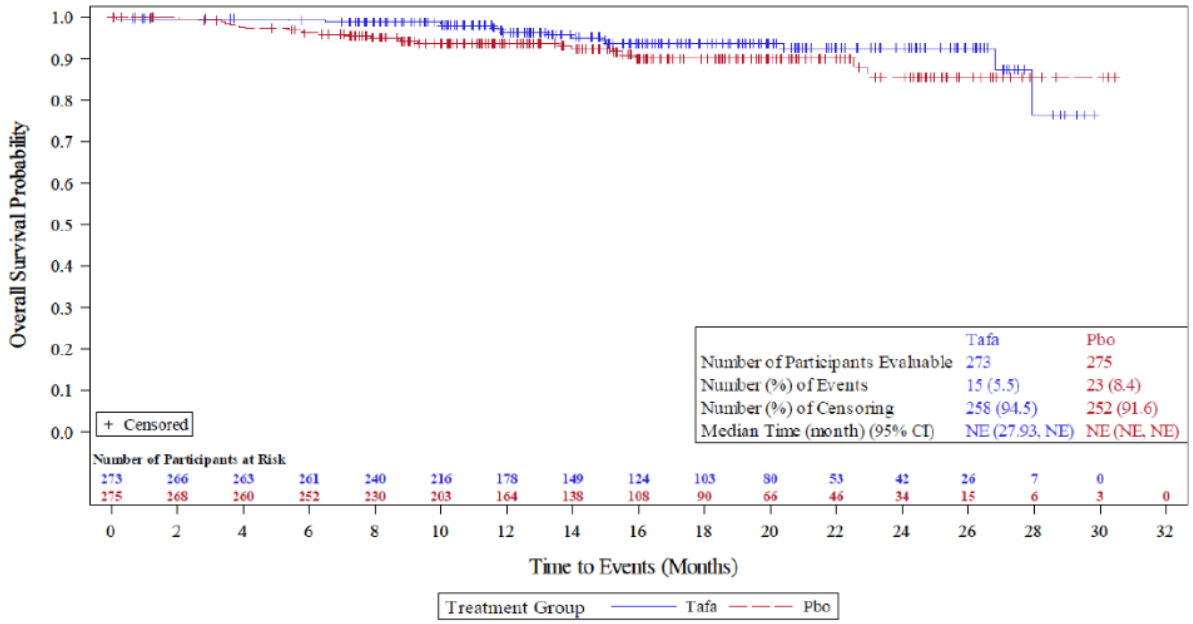
[a] Percentages were calculated based on participants with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline.
[b] Not assessed includes participants who did not have a postbaseline PET scan.
[c] The PET-CR rate was defined as the proportion of participants who achieved a CMR at any time after the start of treatment as per Lugano classification among the participants with a positive PET scan at baseline. Participants with no postbaseline assessment by PET or who did not achieve a CMR were classified as non-CR responders.
[d] The 95% CIs were calculated using the Clopper-Pearson method.
[e] The strata information was based on the data obtained from the IRT that was used for randomization.

**Table 23 Overall Survival (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with death, n (%) | 15 (5.5) | 23 (8.4) |
| Censored participants, n (%) | 258 (94.5) | 252 (91.6) |
| Last known alive | 244 (89.4) | 229 (83.3) |
| Study discontinuation | 14 (5.1) | 23 (8.4) |
| Median OS, months (95% CI)[a] | NE (27.93, NE) | NE (NE, NE) |
| Kaplan-Meier estimates (95% CI) of OS rate | | |
| 6 months | 99.3 (97.1, 99.8) | 96.2 (93.1, 98.0) |
| 12 months | 96.4 (92.8, 98.2) | 93.7 (90.0, 96.1) |
| 18 months | 93.8 (89.1, 96.5) | 90.1 (84.8, 93.6) |
| 2 years | 92.5 (87.0, 95.8) | 85.5 (76.2, 91.4) |
| Stratified log-rank test p-value | 0.1061 | |
| HR (95% CI)[b] | 0.587 (0.306, 1.128) | |

[a] Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the tafasitamab+R² group and the placebo+R² group was estimated using a stratified Cox proportional hazards model.

**Figure 13 Kaplan – Meier Estimates of Overall Survival (FL FAS)**




Tafa = tafasitamab+R$^2$; Pbo = placebo+R$^2$.

***Ancillary analyses***

The applicant has investigated a number of exploratory secondary endpoints. For the efficacy assessment, only those pertaining to indication sought (i.e. those performed in the FL FAS) will be presented here. Selected results from the MZL FAS will be briefly touched upon in the "Supportive studies" section as the safety population includes both FL and MZL populations.

**Table 24 Summary of Minimal Residual Disease-Negativity Rate in peripheral blood at End of Treatment in the Follicular Lymphoma Population (FL MRD Blood – evaluable set)**

| Variable | Tafasitamab+R[2] (N = 57) | Placebo+R[2] (N = 66) |
|---|---|---|
| Participants with peripheral blood MRD performed at EOT, n (%)[a] | 29 (50.9) | 33 (50.0) |
| Peripheral blood MRD status at EOT, n (%) | | |
| Negative[b] | 15 (26.3) | 12 (18.2) |
| Positive | 9 (15.8) | 20 (30.3) |
| NE | 5 (8.8) | 1 (1.5) |
| Not assessed | 28 (49.1) | 33 (50.0) |
| MRD-negativity rate at EOT (95% CI)[c,d] | 26.3 (15.54, 39.66) | 18.2 (9.76, 29.61) |
| OR by stratified CMH test (95% CI)[e] | 1.4 (0.61, 3.33) | |
| Stratified CMH test p-value | 0.4093 | |

[a] The percentage was calculated based on participants who received at least 1 dose of tafasitamab/placebo, lenalidomide, or rituximab with identifiable clonality in a peripheral blood sample at Cycle 1 Day 1.
[b] The threshold used to define MRD negativity was $\leq 10^{-5}$ cells.
[c] The MRD-negativity rate was defined as the proportion of participants who achieved a negative MRD result in peripheral blood at EOT among the MRD Blood-Evaluable Set. Participants with no postbaseline assessment or who did not achieve a negative MRD result were classified as non–MRD negative.
[d] The 95% CIs were calculated using the Clopper-Pearson method.
[e] The strata information was based on the data obtained from the IRT that was used for randomization.

**Table 25 Best Overall response and Overall Response Rate by Investigator Assessment (FL FAS)**

| Variable | Tafasitamab+R[2] (N = 273) | Placebo+R[2] (N = 275) |
|---|---|---|
| Best overall response based on Lugano classification, n (%) | | |
| CR | 142 (52.0) | 112 (40.7) |
| PR | 86 (31.5) | 87 (31.6) |
| SD | 28 (10.3) | 46 (16.7) |
| PD | 7 (2.6) | 20 (7.3) |
| NE | 2 (0.7) | 0 (0.0) |
| Not assessed | 8 (2.9) | 10 (3.6) |
| ORR (95% CI)[a,b] | 83.5 (78.57, 87.72) | 72.4 (66.67, 77.56) |
| OR by stratified CMH test (95% CI)[c] | 2.0 (1.30, 3.02) | |
| Stratified CMH test p-value | 0.0014 | |

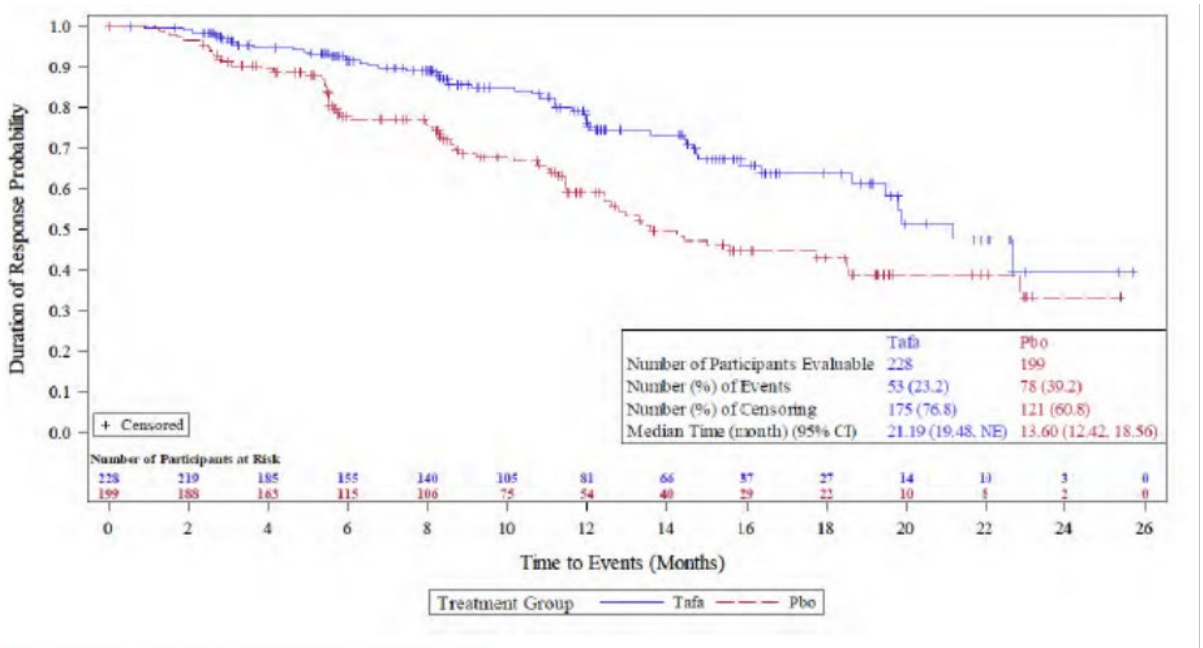
[a] Overall response rate was defined as the proportion of participants who achieved a CR or PR as determined per Lugano classification at any time during the study but before the first PD and before/at the start of a new antilymphoma treatment.
[b] The 95% CIs were calculated using the Clopper-Pearson method.
[c] The strata information was based on the data obtained from the IRT that was used for randomization.

**Table 26 Summary of Duration of Response by Investigator Assessment (FL FAS)**

| Variable | Tafasitamab+R$^2$ (N = 273) | Placebo+R$^2$ (N = 275) |
|---|---|---|
| Responders, n (%)[a] | 228 (83.5) | 199 (72.4) |
| Responders with events, n (%)[b] | 53 (23.2) | 78 (39.2) |
| Disease progression | 48 (21.1) | 76 (38.2) |
| Death | 5 (2.2) | 2 (1.0) |
| Responders censored, n (%) | 175 (76.8) | 121 (60.8) |
| Ongoing | 166 (72.8) | 111 (55.8) |
| Study discontinuation | 4 (1.8) | 3 (1.5) |
| Start of new antilymphoma treatment | 5 (2.2) | 6 (3.0) |
| Death or PD after 2 or more missed assessments | 0 (0.0) | 1 (0.5) |
| Median DoR, months (95% CI)[c] | 21.19 (19.48, NE) | 13.60 (12.42, 18.56) |
| Kaplan-Meier estimates (95% CI) of DoR | | |
| 6 months | 91.5 (86.6, 94.6) | 77.8 (70.9, 83.2) |
| 12 months | 76.3 (68.4, 82.4) | 59.1 (50.3, 66.9) |
| 18 months | 63.7 (53.4, 72.2) | 42.9 (33.1, 52.4) |
| 2 years | 39.5 (21.4, 57.1) | 33.3 (20.5, 46.6) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[d] | 0.473 (0.330, 0.678) | |

[a] Participants with a response of CR or PR per Lugano classification.
[b] Percentages were calculated using the number of responders as the denominator.
[c] Duration of response was defined as the time from first tumor response (CR or PR as per the Lugano classification) until the time of first documented disease progression or death from any cause, whichever is earlier, among participants who achieve an objective response. Median DoR was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[d] The HR between the tafasitamab+R$^2$ group and the placebo+R$^2$ group was estimated using a stratified Cox proportional hazards model.

**Figure 14 Kaplan- Meier Estimates of Duration of response by Investigator Assessment (FL FAS)**




Note: Tafa = tafasitamab+R$^2$, Pbo=placebo+R$^2$.

**Table 27 Progression-Free Survival by IRC (FL FAS)**

| Variable | Tafasitamab+R[2] (N = 273) | Placebo+R[2] (N = 275) |
|---|---|---|
| Participants with events, n (%) | 59 (21.6) | 111 (40.4) |
| Disease progression | 51 (18.7) | 103 (37.5) |
| Death | 8 (2.9) | 8 (2.9) |
| Censored participants, n (%) | 214 (78.4) | 164 (59.6) |
| No postbaseline assessment | 7 (2.6) | 8 (2.9) |
| Ongoing | 179 (65.6) | 125 (45.5) |
| Study discontinuation | 6 (2.2) | 5 (1.8) |
| Start of new antilymphoma treatment | 21 (7.7) | 24 (8.7) |
| Death or PD after 2 or more missed assessments | 1 (0.4) | 2 (0.7) |
| Median PFS, months (95% CI)[a] | NE (19.29, NE) | 16.00 (13.86, 21.06) |
| Kaplan-Meier estimates (95% CI) of PFS rate | | |
| 6 months | 94.0 (90.2, 96.3) | 80.3 (74.9, 84.7) |
| 12 months | 83.1 (77.1, 87.7) | 59.8 (52.9, 66.1) |
| 18 months | 67.5 (58.8, 74.8) | 45.8 (37.3, 53.8) |
| 2 years | 53.9 (41.9, 64.4) | 35.0 (24.7, 45.6) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[b] | 0.407 (0.294, 0.563) | |

[a] Median survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the 2 groups was estimated using a stratified Cox proportional hazards model.
Source: Table 2.1.2.1.

**Table 28 Best Overall response and Overall Response Rate by Independent Review committee (FL FAS)**

| Variable | Tafasitamab+R[2] (N = 273) | Placebo+R[2] (N = 275) |
|---|---|---|
| Best overall response based on Lugano classification, n (%) | | |
| CR | 143 (52.4) | 120 (43.6) |
| PR | 91 (33.3) | 82 (29.8) |
| SD | 24 (8.8) | 41 (14.9) |
| PD | 5 (1.8) | 18 (6.5) |
| NE | 2 (0.7) | 0 (0.0) |
| Not assessed | 8 (2.9) | 14 (5.1) |
| ORR (95% CI)[a,b] | 85.7 (80.99, 89.64) | 73.5 (67.82, 78.58) |
| OR by stratified CMH test (95% CI)[c] | 2.2 (1.43, 3.43) | |
| Stratified CMH test p-value | 0.0003 | |

[a] The ORR was defined as the proportion of participants who achieved a CR or PR as determined per Lugano classification at any time during the study but before the first PD and before/at the start of a new antilymphoma treatment.
[b] The 95% CIs were calculated using the Clopper-Pearson method.
[c] The strata information was based on the data obtained from the IRT that was used for randomization.

**Table 29 Summary of Concordance rates between INV and IRC for ORR (FL FAS)**

| | IRC Assessment | | | | | | |
|---|---|---|---|---|---|---|---|
| INV Assessment | CR (N=263) | PR (N=173) | SD (N=65) | PD (N=23) | NE (N=2) | Not Done (N=22) | Total (N=548) |
| Complete Response (CR) (N=254) | 226 ( 85.9) | 25 ( 14.5) | 1 ( 1.5) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 9.1) | 254 ( 46.4) |
| Partial Response (PR) (N=173) | 34 ( 12.9) | 129 ( 74.6) | 6 ( 9.2) | 3 ( 13.0) | 1 ( 50.0) | 0 ( 0.0) | 173 ( 31.6) |
| Stable Disease (SD) (N=74) | 2 ( 0.8) | 18 ( 10.4) | 48 ( 73.8) | 5 ( 21.7) | 0 ( 0.0) | 1 ( 4.5) | 74 ( 13.5) |
| Progressive Disease (PD) (N=27) | 1 ( 0.4) | 1 ( 0.6) | 10 ( 15.4) | 14 ( 60.9) | 0 ( 0.0) | 1 ( 4.5) | 27 ( 4.9) |
| Not Evaluable (NE) (N=2) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.3) | 1 ( 50.0) | 0 ( 0.0) | 2 ( 0.4) |
| Not Done (N=18) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 18 ( 81.8) | 18 ( 3.3) |
| Total (N=548) | 263 (100.0) | 173 (100.0) | 65 (100.0) | 23 (100.0) | 2 (100.0) | 22 (100.0) | 548 (100.0) |
| Concordance rate (%) (i) | | | | | | | 79.5 |
| Concordance rate (%) (ii) | | | | | | | 79.6 |

**Table 30 Summary of Duration of Response by IRC (FL FAS)**

| Variable | Tafasitamab+R[2] (N = 273) | Placebo+R[2] (N = 275) |
|---|---|---|
| Responders, n (%)[a] | 234 (85.7) | 202 (73.5) |
| Responders with events, n (%)[b] | 44 (18.8) | 68 (33.7) |
| Disease progression | 37 (15.8) | 66 (32.7) |
| Death | 7 (3.0) | 2 (1.0) |
| Responders censored, n (%) | 190 (81.2) | 134 (66.3) |
| Ongoing | 176 (75.2) | 117 (57.9) |
| Study discontinuation | 3 (1.3) | 3 (1.5) |
| Start of new antilymphoma treatment | 11 (4.7) | 14 (6.9) |
| Median DoR, months (95% CI)[c] | NE (19.02, NE) | 18.23 (12.94, NE) |
| Kaplan-Meier estimates (95% CI) of DoR | | |
| 6 months | 92.4 (87.6, 95.3) | 78.7 (71.8, 84.0) |
| 12 months | 78.8 (70.9, 84.8) | 61.4 (52.4, 69.3) |
| 18 months | 64.3 (53.1, 73.5) | 52.2 (41.7, 61.7) |
| 2 years | 58.2 (44.9, 69.4) | 35.5 (21.3, 50.0) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[d] | 0.461 (0.312, 0.681) | |

[a] Participants with a response of CR or PR per Lugano classification.
[b] Percentages were calculated using the number of responders as the denominator.
[c] Duration of response was defined as the time from first tumor response (CR or PR as per the Lugano classification) until the time of first documented disease progression or death from any cause, whichever is earlier, among participants who achieve an objective response. Median DoR was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[d] The HR between the 2 treatment groups was estimated using a stratified Cox proportional hazards model.

## Quality of Life in the Follicular Lymphoma Population

**Figure 15: Mean (+/- SD) for Global Health Status QoL QLQ -C30 FL FAS**

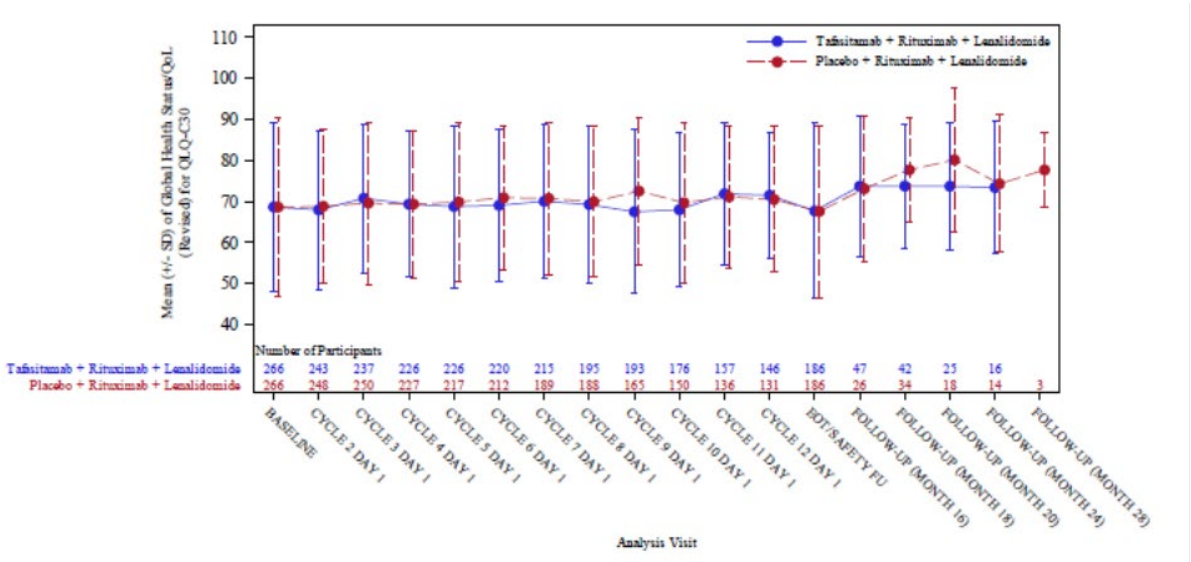
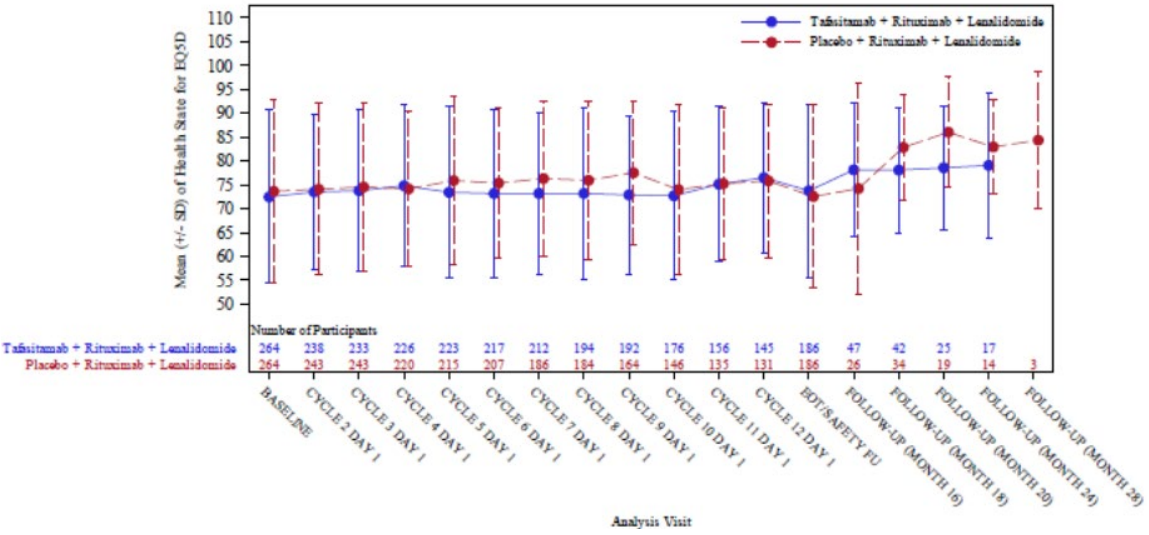



**Figure 16 Mean (+/- SD) for Health State QoL EQ5D FL FAS**




**Time to Next Treatment by Investigator Assessment in the Follicular Lymphoma**

**Table 31 Summary of Time to Next Treatment (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with events, n (%) | 47 (17.2) | 89 (32.4) |
| Start of new antilymphoma treatment | 36 (13.2) | 78 (28.4) |
| Death | 11 (4.0) | 11 (4.0) |
| Censored participants, n (%) | 226 (82.8) | 186 (67.6) |
| No start of new antilymphoma treatment | 226 (82.8) | 186 (67.6) |
| Median TTNT, months (95% CI)[a] | NE (NE, NE) | 28.81 (20.73, NE) |
| Stratified log-rank test p-value | < 0.0001 | |
| HR (95% CI)[b] | 0.447 (0.314, 0.638) | |

[a] Median survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the tafasitamab+R² group and the placebo+R² group was estimated using a stratified Cox proportional hazards model.

**Post-treatment systemic antilymphoma treatments**

Table 32 Summary of Post-treatment systemic antilymphoma treatments (FL FAS)

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with post-treatment systemic antilymphoma therapies, n (%) | 36 (13.2) | 78 (28.4) |
| Number of post-treatment systemic antilymphoma therapies per participant | | |
| Mean (STD) | 0.2 (0.63) | 0.4 (0.64) |
| Median (min, max) | 0.0 (0, 6) | 0.0 (0, 3) |
| Participants with post-treatment systemic antilymphoma therapies, n (%) | | |
| 0 | 237 (86.8) | 197 (71.6) |
| 1 | 27 (9.9) | 59 (21.5) |
| 2 | 5 (1.8) | 16 (5.8) |
| 3 | 2 (0.7) | 3 (1.1) |
| > 3 | 2 (0.7) | 0 (0.0) |

| Variable | Treatment Group: Tafasitamab + Rituximab + Lenalidomide (N=273) | Treatment Group: Placebo + Rituximab + Lenalidomide (N=275) | Total (N=548) |
|---|---|---|---|
| Number (%) of participants with post-treatment systemic antilymphoma therapies | 36 ( 13.2) | 78 ( 28.4) | 114 ( 20.8) |
| Number of post-treatment systemic antilymphoma therapies per participant | | | |
| n | 273 | 275 | 548 |
| Mean | 0.2 | 0.4 | 0.3 |
| STD | 0.63 | 0.64 | 0.64 |
| Min | 0 | 0 | 0 |
| Median | 0.0 | 0.0 | 0.0 |
| Max | 6 | 3 | 6 |
| Number (%) of participants with post-treatment systemic antilymphoma therapies | | | |
| 0 | 237 ( 86.8) | 197 ( 71.6) | 434 ( 79.2) |
| 1 | 27 ( 9.9) | 59 ( 21.5) | 86 ( 15.7) |
| 2 | 5 ( 1.8) | 16 ( 5.8) | 21 ( 3.8) |
| 3 | 2 ( 0.7) | 3 ( 1.1) | 5 ( 0.9) |
| >3 | 2 ( 0.7) | 0 ( 0.0) | 2 ( 0.4) |

**Table 33: Best Overall Response Rates by Investigator After the Start of CD19–Directed Next Anti-lymphoma Therapy Treatment (FL Population)**

| | Tafasitamab + R² (N=9) | Placebo + R² (N=10) |
|---|---|---|
| **Best Overall Response CRF Data on Form: Next Anti-lymphoma Treatments** | | |
| Complete Response (CR) | 4 (44.4) | 5 (50.0) |
| Partial Response (PR) | 2 (22.2) | 0 (0.0) |
| Stable Disease (SD) | 0 (0.0) | 1 (10.0) |
| Progressive Disease (PD) | 0 (0.0) | 0 (0.0) |
| Not Evaluable (NE) | 0 (0.0) | 0 (0.0) |
| Unknown [1] | 3 (33.3) | 4 (40.0) |
| ORR (95% CI) | 66.7 (29.93, 92.51) | 50.0 (18.71, 81.29) |
| Odds ratio by stratified CMH test (95% CI) | 2.7 (0.34, 20.75) | |
| [1] Unknown includes missing values for best response in the CRF. | | |

**Table 34: Progression-Free Survival on CD19-directed Next Anti-lymphoma Treatment (FL Population)**

| | Tafasitamab + R² (N=273) | Placebo + R² (N=275) |
|---|---|---|
| Participants with events, n (%) | 5 (1.8) | 7 (2.5) |
| Disease progression on CD19-directed next antilymphoma treatment | 4 (1.5) | 1 (0.4) |
| Start of a subsequent antilymphoma treatment | 1 (0.4) | 6 (2.2) |
| Death | 0 (0.0) | 0 (0.0) |
| Censored participants, n (%) | 268 (98.2) | 268 (97.5) |
| Alive with no PD after CD19directed next antilymphoma treatment | 4 (1.5) | 3 (1.1) |
| Alive with no CD19-directed next antilymphoma treatment | 264 (96.7) | 265 (96.4) |
| Median PFS2, months (95% CI)[a] | NE (NE, NE) | NE (NE, NE) |
| Kaplan-Meier estimates (95% CI) of PFS rate on CD19-directed next anti-lymphoma treatment | | |
| 6 months | 99.2 (97.0, 99.8) | 100.0 (100.0, 100.0) |
| 12 months | 97.9 (94.9, 99.1) | 98.1 (94.8, 99.3) |
| 18 months | 97.9 (94.9, 99.1) | 97.4 (93.8, 98.9) |
| 2 years | 97.9 (94.9, 99.1) | 93.6 (84.6, 97.4) |
| 3 years | NE (NE, NE) | NE (NE, NE) |
| 4 years | NE (NE, NE) | NE (NE, NE) |
| Note: Progression-free survival on next treatment was defined as the time from randomization to the time of second objective disease progression or death from any cause, whichever occurs first. The start of a subsequent therapy after next line was considered as an event. Participants who were alive and for whom tumor progression after the next anti-lymphoma treatment had not been observed were censored at the last time known to be alive. | | |

a Median PFS on next treatment survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the Brookmeyer and Crowley (1982) method with log-log transformation.

### Progression-Free Survival on Next Treatment by Investigator Assessment in the FL Population

**Table 35 Progression-Free Survival on Next Antilymphoma Treatment (FL FAS)**

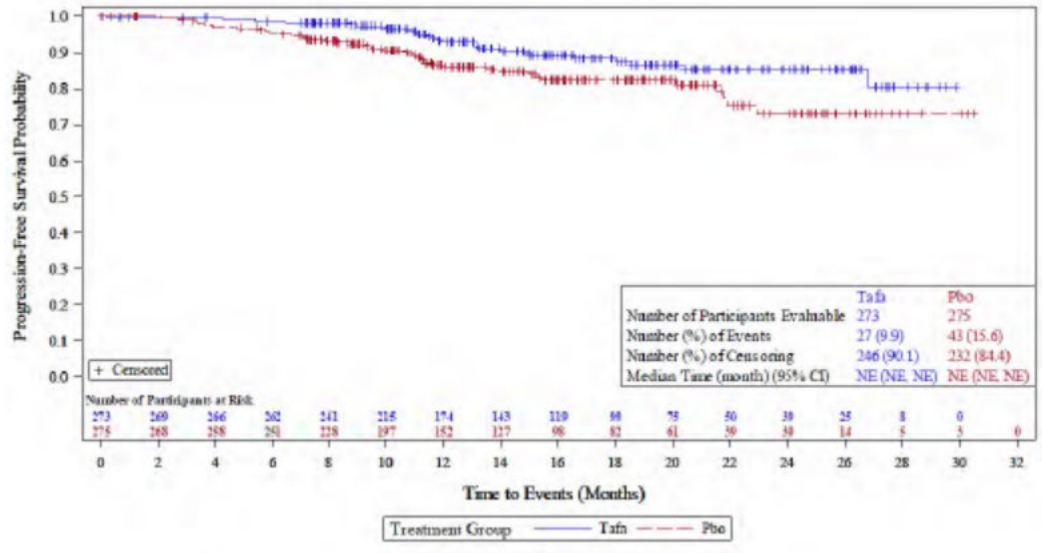
| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with events, n (%) | 27 (9.9) | 43 (15.6) |
| Disease progression on next antilymphoma treatment | 10 (3.7) | 15 (5.5) |
| Start of subsequent antilymphoma treatment | 3 (1.1) | 13 (4.7) |
| Death | 14 (5.1) | 15 (5.5) |
| Censored participants, n (%) | 246 (90.1) | 232 (84.4) |
| Alive with no PD after next antilymphoma treatment | 20 (7.3) | 46 (16.7) |
| Alive with no next antilymphoma treatment | 226 (82.8) | 186 (67.6) |
| Median PFS, months (95% CI)[a] | NE (NE, NE) | NE (NE, NE) |
| Kaplan-Meier estimates (95% CI) of PFS rate on next antilymphoma treatment | | |
| 6 months | 98.5 (96.1, 99.4) | 95.5 (92.2, 97.4) |
| 12 months | 92.8 (88.5, 95.6) | 86.5 (81.4, 90.3) |
| 18 months | 87.4 (81.5, 91.5) | 82.3 (76.2, 87.0) |
| 2 years | 85.3 (78.6, 90.0) | 72.9 (62.5, 80.9) |
| Stratified log-rank test p-value | 0.0158 | |
| HR (95% CI)[b] | 0.556 (0.343, 0.902) | |

Note: Progression-free survival on next treatment was defined as the time from randomization to the time of second objective disease progression or death from any cause, whichever occurs first. The start of a subsequent therapy after next line was considered as an event. Participants who were alive and for whom tumor progression after the next antilymphoma treatment had not been observed were censored at the last time known to be alive.

[a] Median PFS on next treatment survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the Brookmeyer and Crowley (1982) method with log-log transformation.

[b] The HR between the 2 groups was estimated using a stratified Cox proportional hazards model.

**Figure 17 Kaplan Meier estimates on Progression-Free Survival on Next Treatment (FL FAS)**




Tafa = tafasitamab+R²; Pbo = placebo+R².

**Rate of Histological Transformation and Time to Histological Transformation in the Follicular Lymphoma Population**

**Table 36 Summary of histological transformation and time to Histological Transformation of follicular lymphoma to a more aggressive state (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with transformation into more aggressive histology, n (%)[a] | 0 (0.0) | 9 (3.3) |
| Rate of histological transformation into more aggressive histology (95% CI)[b] | 0.0 (0.00, 1.34) | 3.3 (1.51, 6.12) |
| OR by stratified CMH test (95% CI)[c] | 0.0 (NE, NE) | |
| Stratified CMH test p-value | 0.0026 | |
| Median time to transformation into more aggressive histology, months (95% CI)[d] | NE (NE, NE) | NE (NE, NE) |

[a] Transformation of FL into more aggressive histology (eg, DLBCL) was defined as the appearance of diffuse areas of large-cell lymphoma cells within a lymphoma site as proven by a histological examination of a tumor biopsy at the time of disease progression.
[b] The 95% CIs were calculated using the Clopper-Pearson method.
[c] The strata information was based on the data obtained from the IRT that was used for randomization.
[d] Median time to transformation was estimated using the KM method.

**Time to First Objective Response in the Follicular Lymphoma Population**

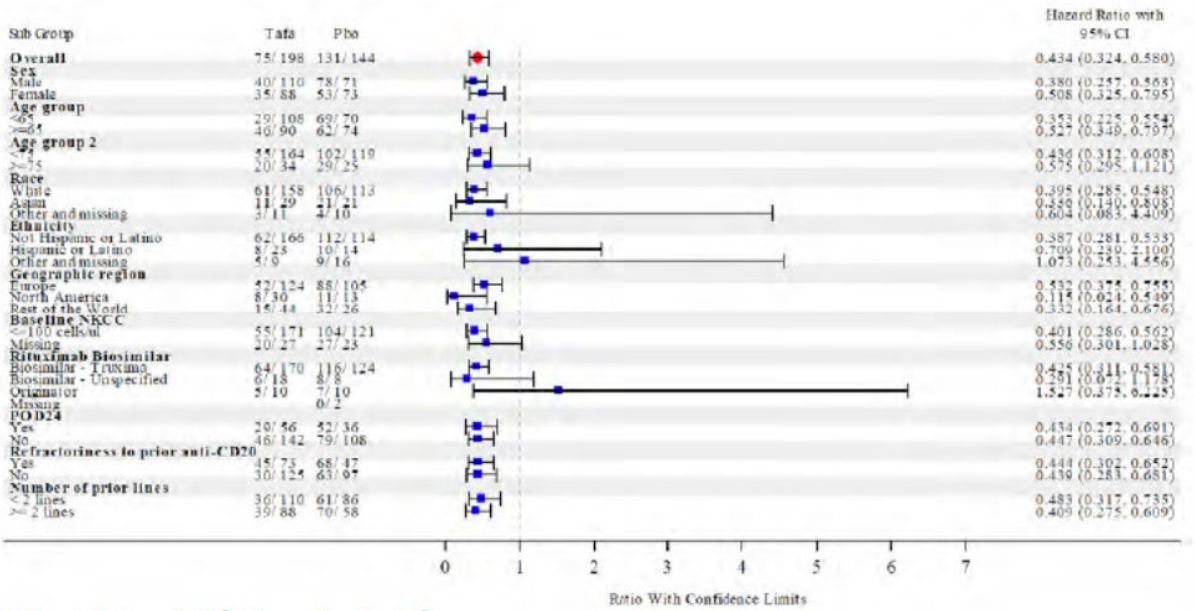
**Table 37 Summary of time to objective response (FL FAS)**

| Variable | Tafasitamab+R² (N = 273) | Placebo+R² (N = 275) |
|---|---|---|
| Participants with objective response, n (%)[a] | 228 | 199 |
| Median time to first objective response, months (95% CI) | 2.83 (1.0, 10.9) | 2.83 (1.9, 11.4) |

[a] Time to objective response was defined as the time from the randomization date to the date of first objective response (CR or PR).

**Subgroup Analyses**

**Figure 18 Forest plot of hazard ratio for PFS by investigator assessment (FL FAS)**




Tafa = tafasitamab+R²; Pbo = placebo+R².
Note 1: The numbers below each treatment group represent the number of participants in each subgroup who had events / who were censored.
Note 2: The strata information for POD24, refractoriness to prior anti-CD20 therapy, and number of prior lines of therapy was based on the data obtained from the eCRF.

**Table 38: Summary of Concordance Rate Between Investigator Based *and IRC Based PFS Indicator (FL FAS)***

| | IRC Assessment | | |
|---|---|---|---|
| **INV Assessment** | **Event N= 170** | **Censored (N=378)** | **Total (N=548)** |
| **Event (N=206)** | 157 (92.4) | 49 (13.0) | 206 (37.6) |
| **Censored (N=342)** | 13 (7.6) | 329 (87.0) | 342 (62.4) |
| **Total (N=548)** | 170 (100.0) | 378 (100.0) | 548 (100.0) |
| **Concordance rate* (%)** | | | 88.7 |

* The concordance rate is defined as proportion of concordant participants between Investigator and IRC (events and censored) divided by the total number of participants assessed. Here 157 (concordant events) +329 (concordant censored)/548 (total number of FAS participants)*100

## Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 10: Summary of Efficacy for Study INCMOR 0208-301 (inMIND)**

| **Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients With Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma** | | |
|---|---|---|
| Study identifier | INCMOR 0208-301 | |
| Design | Randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study | |
| | Duration of main phase:<br><br><br>Duration of Run-in phase:<br>Duration of Extension phase: | First participant dosed on 16 APR 2021 and study is currently ongoing.<br>Not applicable<br>Not applicable |
| Hypothesis | Superiority<br><br>The primary hypothesis is that tafasitamab in combination with lenalidomide and rituximab improves PFS compared with lenalidomide and rituximab alone in participants with R/R FL. Assume $S_1(t)$ is the survival function of tafasitamab in combination with lenalidomide and rituximab, and $S_2(t)$ is the survival function of lenalidomide and rituximab alone. The hypotheses of the study are as follows:<br><br>• $H_0$ (null hypothesis): $S_1(t) = S_2(t)$<br>• $H_A$ (alternative hypothesis): $S_1(t) \neq S_2(t)$<br><br>A hierarchical testing procedure is implemented for the key secondary endpoints, with the primary endpoint PFS serving as a gatekeeper. This hierarchical testing procedure maintains the study-wise Type I error rate at 2-sided 5%. If the primary null hypothesis is rejected, the key secondary | |

| | | | |
|---|---|---|---|
| | endpoints can be tested in the following fixed order: (1) PFS by INV in the overall population (FL and MZL); (2) PET-CR rate by INV in the FDG-avid FL population; (3) OS in the FL population. | | |
| Treatments groups | tafasitamab+R[2] | | Study treatment administered:<br><br>Tafasitamab 12 mg/kg IV on Days 1, 8, 15, and 22 of Cycles 13 and on Days 1 and 15 of Cycles 412<br>Rituximab 375 mg/m2 IV on Days 1, 8, 15, and 22 in Cycle 1 and on Day 1 of Cycles 25<br>Lenalidomide 20 mg PO QD on Days 121 of Cycles 112<br><br>Duration: Up to twelve 28-day cycles<br>Number randomized: 326 participants (273 in the FL Population and 53 in the MZL Population) |
| | Placebo+R[2] | | Study treatment administered:<br><br>Tafasitamab placebo (saline solution 0.9%) IV on Days 1, 8, 15, and 22 of Cycles 1-3 and on Days 1 and 15 of Cycles 4-12<br><br>Rituximab 375 mg/m2 IV on Days 1, 8, 15, and 22 in Cycle 1 and on Day 1 of Cycles 25<br><br>Lenalidomide 20 mg PO QD on Days 121 of Cycles 112<br><br>Duration: Up to twelve 28-day cycles<br><br>Number randomized: 328 participants (275 in the FL Population and 53 in the MZL Population) |
| Endpoints and definitions | Primary endpoint | PFS by INV assessment in the FL Population | Defined as the time from the date of randomization to the date of first documented disease progression, as determined by disease assessment per the 2014 Lugano classification or death due to any cause, whichever occurs earlier |
| | Key Secondary | PFS by INV assessment in the Overall Population | Compared and analyzed in the same manner as the PFS in the FL Population described above |

| | | | |
|---|---|---|---|
| | | (FL and MZL populations) | |
| | Key Secondary | PET-CR rate at EOT by INV assessment in the FL Population | Defined as the proportion of FDG-avid participants who achieved a CR as per 2014 Lugano classification, with a PET-negative result defined as a complete metabolic response (CMR) at any time after start of treatment over the FDG-avid FL population at baseline |
| | Key Secondary | OS in the FL Population | Defined as the time from randomization until death from any cause. All participants should be followed until death or until the end of study, whichever comes first |
| Database lock | 22 JUL 2024 (with DCO on 23 FEB 2024) | | |
| **Results and Analysis (data cutoff date: 23 FEB 2024)** | | | |
| **Analysis description** | **Primary Analysis** | | |
| **Analysis population and time point description** | Full Analysis Set (FAS) of the FL Population.<br>The FAS included all participants randomized to the tafasitamab+$R^2$ group (n = 273) or the placebo+$R^2$ group (n = 275).<br>The primary analysis was to be performed after approximately 174 investigator-assessed PFS events (including a 5% margin to account for loss of events due to censoring of new anti-lymphoma treatment) were observed in the FL FAS. The primary analysis was independent of the number of enrolled participants with MZL. | | |
| Descriptive statistics and estimate of variability | Treatment group | FL FAS; tafasitamab+$R^2$ | FL FAS; placebo+$R^2$ |
| | Number of participants | 273 | 275 |
| | Median PFS (months) | 22.37 | 13.93 |
| | 95% CI | 19.22, NE | 11.53, 16.39 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | tafasitamab+$R^2$ vs placebo+$R^2$ |
| | | HR | 0.434 |
| | | 95% CI | 0.324, 0.580 |
| | | Stratified log-rank test pvalue | < 0.0001 |
| Notes | Median survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation. The HR between the tafasitamab+$R^2$ group and the placebo+$R^2$ group was estimated using a stratified Cox proportional hazards model. | | |
| | **Key Secondary Endpoints** | | |

| | | | |
|---|---|---|---|
| **Analysis population and time point description** | Overall (FL + MZL) FAS Population<br>PFS by INV assessment | | |
| Descriptive statistics and estimate variability | Treatment group | tafasitamab+$R^2$ | placebo+$R^2$ |
| | Number of participants | 326 | 328 |
| | median PFS<br><br>(months) | 23.95 | 16.39 |
| | 95% CI | 22.34, NE | 13.86, 18.66 |
| Effect estimate per comparison | Key secondary endpoint | Comparison groups | tafasitamab+$R^2$ vs placebo+$R^2$ |
| | | HR | 0.500 |
| | | 95% CI | 0.383, 0.653 |
| | | Stratified log-rank test pvalue | < 0.0001 |
| Notes | Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation. The HR between the tafasitamab+$R^2$ group and the placebo+$R^2$ group was estimated using a stratified Cox proportional hazards model. | | |
| **Analysis population and time point description** | FL Population (FDG-avid at baseline)<br><br>PET-CR rate at EOT by INV assessment | | |
| Descriptive statistics and estimate variability | Treatment group | tafasitamab+$R^2$ | placebo+$R^2$ |
| | Number of participants | 251 | 254 |
| | PET-CR rate (%) | 49.4 | 39.8 |
| | 95% CI | 43.06, 55.76 | 33.70, 46.07 |
| Effect estimate per comparison | Key secondary endpoint | Comparison groups | tafasitamab+$R^2$ vs placebo+$R^2$ |
| | | OR by stratified CMH test | 1.5 |
| | | 95% CI | 1.04, 2.13 |
| | | Stratified CMH test pvalue | 0.0286 |
| Notes | Metabolic response based on PET was calculated based on participants with a positive PET scan at baseline, defined as having a Deauville score of 4 or 5 at baseline, and not assessed included participants who did not have a postbaseline PET scan. Participants with no postbaseline assessment by PET or who did not achieve a CMR were classified as non-CR responders.<br>The PET-CR rate 95% CIs were calculated using the Clopper-Pearson method.<br>The strata information for the p-value was based on the data obtained from the IRT that was used for randomization. | | |
| **Analysis population and time point description** | FL FAS Population<br><br>OS | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | tafasitamab+$R^2$ | placebo+$R^2$ |
| | Median OS<br><br>(months) | NE | NE |
| | 95% CI | 27.93, NE | NE, NE |
| | OS rate (%) | at 6 months: 99.3<br>at 12 months: 96.4<br>at 18 months: 93.8<br>at 24 months: 92.5 | at 6 months: 96.2<br>at 12 months: 93.7<br>at 18 months: 90.1<br>at 24 months: 85.5 |
| | 95% CI | at 6 months: 97.1, 99.8<br>at 12 months: 92.8, 98.2<br>at 18 months: 89.1, 96.5<br>at 24 months: 87.0, 95.8 | at 6 months: 93.1, 98.0<br>at 12 months: 90.0, 96.1<br>at 18 months: 84.8, 93.6<br>at 24 months: 76.2, 91.4 |
| Effect estimate per comparison | Key secondary endpoint | Comparison groups | tafasitamab+$R^2$ vs placebo+$R^2$ |
| | | HR | 0.587 |
| | | 95% CI | 0.306, 1.128 |
| | | Stratified log-rank test pvalue | 0.1061 |
| Notes | Median survival time was estimated using the KM method, and the 2–sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation. The HR between the tafasitamab+$R^2$ group and the placebo+$R^2$ group was estimated using a stratified Cox proportional hazards model.<br><br>Hierarchical inferential statistical testing of OS will be performed at the time of final analysis after the end of the study, which is expected when the last participant has completed a minimum of 5 years of post-treatment follow-up. | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

The MAH has provided pooled results for the combined FL and MZL populations in the inMIND study, however these were not considered of relevance to the sought indication and are not presented here. Selected efficacy results for the MZL population are presented below in the "Supportive studies" section as the safety population for the present indication includes both FL and MZL patients.

## Supportive study

**INCMOR 0208-301 (inMIND) MZL Population:**

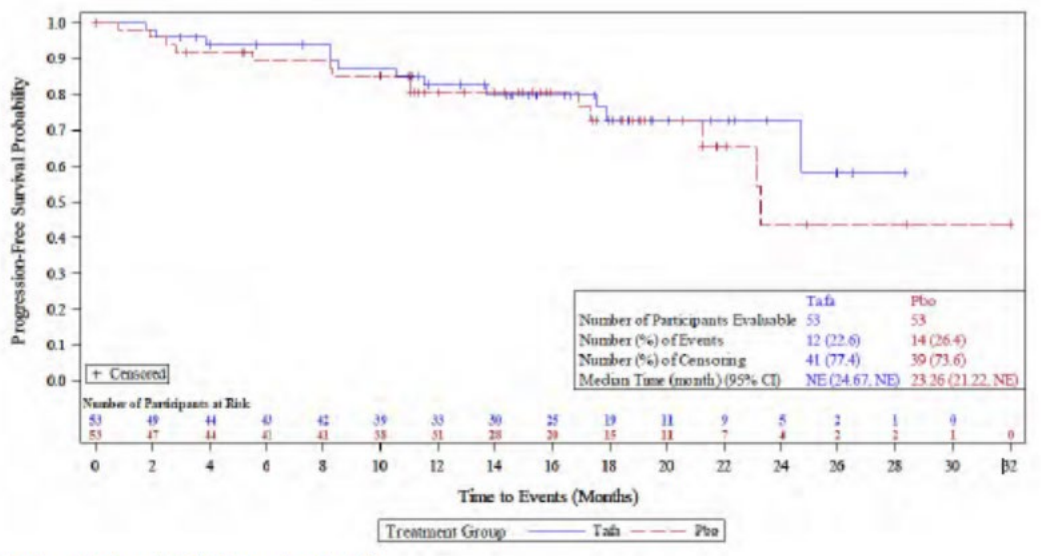
**Table 39 PFS by investigator (MZL)**

| Variable | Tafasitamab+R² (N = 53) | Placebo+R² (N = 53) |
|---|---|---|
| Participants with events, n (%) | 12 (22.6) | 14 (26.4) |
| Disease progression | 9 (17.0) | 13 (24.5) |
| Death | 3 (5.7) | 1 (1.9) |
| Censored participants, n (%) | 41 (77.4) | 39 (73.6) |
| No postbaseline assessment | 3 (5.7) | 3 (5.7) |
| Ongoing | 32 (60.4) | 34 (64.2) |
| Study discontinuation | 4 (7.5) | 1 (1.9) |
| Start of new antilymphoma treatment | 2 (3.8) | 1 (1.9) |
| Median PFS, months (95% CI)[a] | NE (24.67, NE) | 23.26 (21.22, NE) |
| Kaplan-Meier estimates (95% CI) of PFS rate | | |
| 6 months | 93.9 (82.3, 98.0) | 89.7 (76.9, 95.6) |
| 12 months | 82.5 (68.0, 90.9) | 80.7 (66.1, 89.5) |
| 18 months | 72.6 (55.1, 84.2) | 72.6 (54.7, 84.4) |
| 2 years | 72.6 (55.1, 84.2) | 43.6 (16.8, 67.9) |
| Stratified log-rank test p-value | 0.4894 | |
| HR (95% CI)[b] | 0.760 (0.348, 1.659) | |

[a] Median survival time was estimated using the KM method. The 2-sided 95% CIs were calculated using the Brookmeyer and Crowley (1982) method with log-log transformation.
[b] The HR between the 2 groups was estimated using a stratified Cox proportional hazards model.
Source: Table 2.1.1.2.

**Overall Survival in MZL Population**

**Figure 19 Kaplan -Meier estimates of PFS by investigator assessment (MZL FAS)**



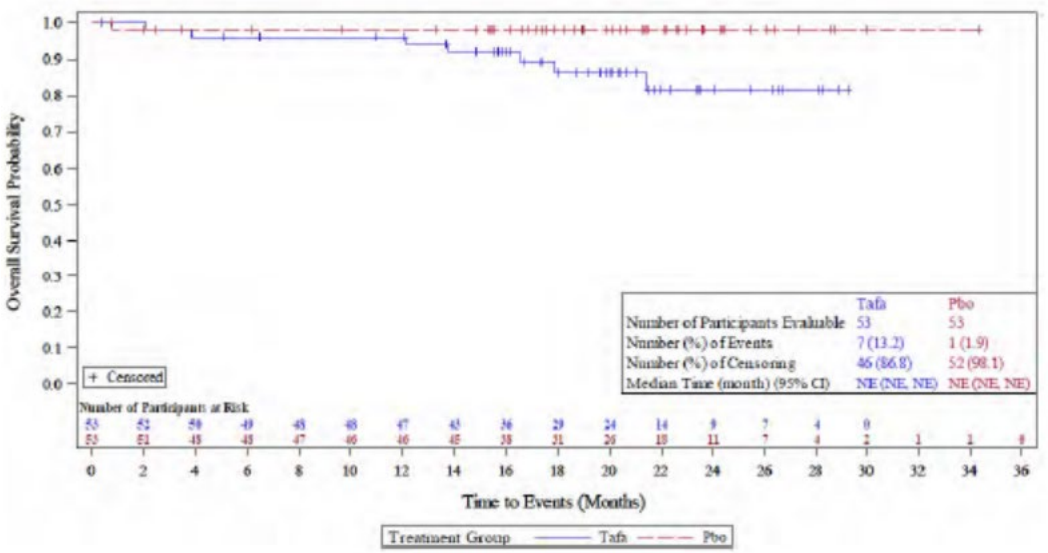

Tafa = tafasitamab+R²; Pbo = placebo+R².

**Table 40 Overall Survival (MZL FAS)**

| Variable | Tafasitamab+R$^2$ (N = 53) | Placebo+R$^2$ (N = 53) |
|---|---|---|
| Participants with death, n (%) | 7 (13.2) | 1 (1.9) |
| Censored participants, n (%) | 46 (86.8) | 52 (98.1) |
| Last known alive | 39 (73.6) | 46 (86.8) |
| Study discontinuation | 7 (13.2) | 6 (11.3) |
| Median OS, months (95% CI)[a] | NE (NE, NE) | NE (NE, NE) |
| Kaplan-Meier estimates (95% CI) of OS rate | | |
| 6 months | 96.2 (85.5, 99.0) | 98.1 (87.1, 99.7) |
| 12 months | 96.2 (85.5, 99.0) | 98.1 (87.1, 99.7) |
| 18 months | 86.2 (71.5, 93.7) | 98.1 (87.1, 99.7) |
| 2 years | 81.5 (63.2, 91.2) | 98.1 (87.1, 99.7) |
| Stratified log-rank test p-value | 0.0316 | |
| HR (95% CI)[b] | 7.162 (0.880, 58.317) | |

[a] Median survival time was estimated using the KM method, and the 2-sided 95% CIs were calculated using the method of Brookmeyer and Crowley (1982) with log-log transformation.
[b] The HR between the tafasitamab+R$^2$ group and the placebo+R$^2$ group was estimated using a stratified Cox proportional hazards model.

**Figure 20 Kaplan Meier Estimates of Overall Survival (MZL FAS)**




Tafa = tafasitamab+R$^2$; Pbo = placebo+R$^2$.

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

The pivotal INCMOR 0208-301 (inMIND) study is a randomized, double-blind, placebo-controlled, multicentre study to investigate the addition of tafasitamab to an already-approved standard regimen, rituximab-lenalidomide (R$^2$). Inclusion of an IV placebo to tafasitamab is particularly endorsed.

The study included separate randomizations for both an R/R FL and an R/R MZL population but was only powered to assess the effect of tafasitamab addition in the FL population. Hence, the MZL

population will only briefly be discussed as part of this report. After confirmation of the eligibility criteria, participants were randomized at a 1:1 ratio to either tafasitamab+$R^2$ or placebo+$R^2$. Participants with FL were randomized using stratification factors (ie, number of prior lines of therapy, POD24, refractoriness to prior anti-CD20 therapy for FL).

Only patients in need of treatment were eligible and treatment need was assessed by GELF criteria, however not all patients fulfilled, or some lacked information on the GELF criteria. All patients must have received prior CD20-targeted therapy. Of note, rituximab refractory patients were also included, although these patients could have received obinutuzumab, it is endorsed that patient who develop rituximab refractoriness may still receive rituximab containing regimens in clinical practice. All included patients should have confirmed both CD19+CD20 expression and have Grade 1-3a FL. CD19 and CD20 expression is considered of importance as all patients must have been exposed to prior CD20-targeted therapy and prior CD19-targeted therapy was allowed. The inclusion of FL grade in the indication will serve to align the sought indication to the approved indication of lenalidomide in combination with rituximab (the therapy backbone upon which tafasitamab is added) and reflect the population that was included. Slightly more patients with refractory disease were noted in the experimental arm, however, this would, if anything, place the experimental arm at a disadvantage and is therefore of less concern. Treatment in the comparator arm was administered according to the approved posology for $R^2$ in R/R FL (as per the Lenalidomide SmPC).

The primary objective of the study is to compare the efficacy of tafasitamab versus placebo, each administered in combination with lenalidomide and rituximab, based on investigator-assessed PFS in patients with R/R FL. The key secondary objectives are to assess PFS in the overall study population (including FL and MZL), PET-CR in the FDG-avid FL population, and OS in the FL population. Additional secondary objectives include evaluation of safety, quality of life, and other efficacy measures such as ORR, DOR, TTNT and PFS2. The objectives are considered clinically relevant but not all pertain directly to the indication sought as part of the present procedure. With respect to this, it might be noted that the first key secondary endpoint (PFS in the overall population; FL & MZL) is not directly relevant to the present application but had to succeed in order to allow hierarchical testing of the remaining key secondary endpoints. In addition, formal testing of the key secondary endpoint OS in the FL population will not be done until the end of the study.

For the primary analysis of PFS, data were planned to be censored at the date of the last adequate tumour assessment prior to the data cut-off or prior to the initiation of new anti-lymphoma therapy, in accordance with FDA guidance. In the FL FAS population, the majority of censoring occurred because patients remained on study without documented progression at the time of the cut-off. Other censoring reasons, including study discontinuation, initiation of new anti-lymphoma therapy, or death or progression after missed assessments, were infrequent and occurred at comparable rates between the treatment groups. Multiple sensitivity analyses were conducted to evaluate the robustness of the primary analysis, including scenarios in which progression or death after missed assessments was treated as an event, progression dates were assigned to the next scheduled assessment, and post-treatment progression or death was considered as a PFS event. Across all these analyses, hazard ratios remained consistent and continued to demonstrate a statistically significant treatment benefit, thereby confirming the robustness of the primary PFS results.

Among the key secondary endpoints, PFS in the overall population (FL and MZL) was analysed using methods consistent with the primary endpoint and showed a statistically significant benefit, supported by consistent results across sensitivity analyses. PET-CR in the FDG-avid FL population

was defined as the proportion of participants who achieved a complete metabolic response on PET at any time after treatment initiation. Participants without postbaseline PET assessments or without a PET-CR were classified as non-responders. The PET-CR rate was significantly higher in the tafasitamab+R² group. Overall survival data are still maturing, with most participants censored and the median OS not reached in either treatment group.

Approximately 528 participants with FL and 60 to 90 with MZL were planned to be randomized, with MZL enrolment capped based on expected proportions. In the FL population, 174 PFS events were required to detect a hazard ratio of 0.65 with 80% power using a two-sided log-rank test at the 5% significance level. This calculation assumed median PFS values of 42.8 months in the tafasitamab arm and 27.8 months in the control arm, with 21 months of accrual, 12 months of follow-up, and a 15% dropout rate. 548 participants were randomized in the FL population, and 206 PFS events were observed in the FL population at time of analysis. Although the observed median PFS in both arms was much shorter than initially assumed, the relative treatment effect was consistent, and the study retained adequate power to assess the primary endpoint.

Randomization was stratified separately for the FL and MZL populations using population-specific factors. Participants with FL were stratified by POD24 status, refractoriness to prior anti-CD20 therapy, and number of prior lines of therapy. Participants with MZL were stratified only by number of prior lines of therapy. For the analysis of progression-free survival in the overall population, a stratified Cox proportional hazards model was used that included only the common stratification factor, which was number of prior lines of therapy. While it is unclear whether blocked randomization was applied, the treatment groups are balanced with respect to the stratification factors, and randomization was centrally managed. Therefore, the absence of information on block structure does not raise concerns.

The survival distribution of the treatment and placebo groups for PFS in the FL FAS population was compared using a stratified log-rank test. The hazard ratio between treatment groups was estimated using a stratified Cox proportional hazards model. The null-hypothesis of no treatment difference was rejected at a 2-sided 5% significance level. The estimated hazard ratio was 0.434 (95% CI: 0.324, 0.580) with a p-value < 0.0001, favoring the treatment group. The median PFS was 22.37 months (95% CI: 19.22, NE) in the tafasitamab arm compared with 13.93 months (95% CI: 11.53, 16.39) in the placebo arm. The upper bound of the 95% CI for median PFS in the tafasitamab arm was not estimable, reflecting ongoing follow-up and a lower event rate at the time of analysis. The KM curves began to separate early and remained consistently apart throughout follow-up, with higher PFS rates maintained in the tafasitamab arm. Sensitivity analyses confirmed the robustness of the primary results, including a restricted mean survival time (RMST) analysis, an unstratified Cox model, an eCRF-based stratification model, and PFS using PPS analysis set.

The key secondary endpoints included PFS in the overall population, PET-CR rate in the FDG-avid FL population, and OS in the FL population. PFS in the overall population was analyzed using the same stratified methods as the primary analysis, including all planned sensitivity analyses. Results demonstrated a consistent treatment benefit, supporting the robustness of the effect across populations. The PET-CR rate was significantly higher in the tafasitamab+R² group, with an odds ratio of 1.5 (95% CI: 1.04, 2.13) and a p-value of 0.0286. Sensitivity analyses using eCRF-based stratification, Fisher's exact test, and the per-protocol population yielded consistent findings. OS data are still maturing; the median OS was not reached in either group, and most participants remained censored at the time of analysis. The OS KM curves overlapped initially and crossed around 28 months, suggesting a potential violation of the PH assumption. This was supported by

formal diagnostics, the goodness-of-fit test (p = 0.0892) and the weighted log-rank test (p = 0.0851) indicated moderate deviation from proportionality. An RMST analysis showed a numerical difference of 0.89 months in favor of treatment arm (p = 0.0609), though not statistically significant. These results indicate no evidence of a potential survival benefit. The MAH has confirmed that an RMST analysis will be performed at the final OS analysis, in addition to the pre-planned Cox model and log-rank test. PH will be tested using Schoenfeld residuals, and if non-proportional hazards are detected, a weighted log-rank and RMST will be presented. The RMST truncation time will be clinically justified, common to both arms, and chosen to ensure at least 30 participants at risk per arm.

Subgroup analyses of PFS were exploratory and not controlled for multiplicity. A generally consistent treatment benefit of tafasitamab+R² was observed across most subgroups, including high-risk groups such as POD24-positive and anti-CD20-refractory participants. It is worth noting that non-GELF patients i.e having lower tumor volume still have benefit from the treatment. No multiplicity control was implemented for subgroup analyses or exploratory endpoints.

Interim analyses for futility were pre-specified for both PFS and OS. The PFS interim analysis was planned after approximately 35 investigator-assessed events in the FL population, using a nonbinding futility boundary of HR ≥ 1.05. This analysis was performed after 34 PFS events, and the IDMC recommended continuation of study as planned. For OS, a nonbinding interim futility analysis was planned using an O'Brien and Fleming beta spending function, with a futility boundary defined as HR > 1.24. This analysis was conducted at the time of PFS maturation, and the futility boundary was not reached (HR: 0.587; 95% CI: 0.306, 1.128), indicating, according to the applicant, no evidence of detriment. A fixed-sequence hierarchical testing procedure to control study-wise Type I error was predefined and followed. The primary endpoint, PFS by investigator assessment in the FL population, served as the gatekeeper. Upon rejection of the primary null hypothesis, key secondary endpoints were tested in the following fixed order: PFS in the overall population, PET-CR rate in the FDG-avid FL population, and OS in the FL population. Both PFS in the overall population and PET-CR rate met statistical significance, allowing hierarchical testing to proceed to OS. However, hierarchical inferential testing of OS will be formally performed at the time of final analysis after study completion. At the time of the interim OS analysis, the RMST comparison did not reach statistical significance.

Demographics and clinical characteristics of patients at baseline were generally balanced in the two groups and reflect a rather fit patient population with RR FL. Most participants had ECOG performance status of 0 (66.4%). At baseline, the median age was 66.0 years (range: 29-88 years). Most participants (53.6%) had Grade 2 FL, high-risk disease according to FLIPI score (52.4%), and an Ann Arbor Stage of IV (56.8%) at baseline. All participants in the FL Population had received prior anti-CD20 therapy; most participants had received 1 (61.3%) or 2 (24.8%) anti–CD20 therapies with 43% being refractory to prior anti-CD20 but still expressing CD20. Median number of prior treatment lines was 1 (range, 1-10) with 45% having ≥2 prior lines and 32% disease progression within 24 months (POD24).

## Efficacy data and additional analyses

Overall, 548 participants were randomized, including 273 participants in the tafasitamab+$R^2$ group and 275 participants in the placebo+$R^2$ group. A total of 546 participants (99.6%) were treated, including 273 participants (100.0%) in the tafasitamab+$R^2$ group and 273 participants (99.3%) in the placebo+$R^2$ group. As of the data cutoff date (23/02/2024), 51 participants (18.7%) in the tafasitamab+$R^2$ group and 42 participants (15.3%) in the $R^2$ group were still receiving treatment,

53.5% of participants in the tafasitamab+$R^2$ treatment group completed 12 cycles of treatment compared with 42.9% of participants in the $R^2$ treatment group. A lower proportion of participants in the tafasitamab+$R^2$ treatment group discontinued treatment due to progressive disease (11.0% vs 30.5%) and death was the most common reason for study withdrawal in both treatment groups (5.5% and 8.0%, respectively).

The estimated median PFS was 22.37 months (95% CI: 19.22, NE) in the tafasitamab+$R^2$ group compared with 13.93 months (95% CI: 11.53, 16.39) in the placebo+$R^2$ group, with an HR of 0.434 (95% CI: 0.324, 0.580) and a p-value of < 0.0001. The result is statistically significant and is considered a clinically meaningful improvement in PFS.2. Key secondary endpoint – PFS by INV in overall population: The overall population consists of 83.8% of participants with FL and 16.2% of participants with MZL. The main analysis demonstrated an estimated HR of 0.500 (95% CI: 0.383, 0.653) and a p-value of < 0.0001. The estimated median PFS was 23.95 months (95% CI: 22.34, NE) in the tafasitamab+R2 group compared with 16.39 months (95% CI: 13.86, 18.66) in the placebo+R2 group. As mentioned elsewhere, this key secondary endpoint is not directly relevant to the sought indication (FL only) as it includes both FL and MZL patients.

With regard to the key secondary endpoint – PET-CR rate at EoT by INV (only measured in the FDG-avid FL population), the PET-CR rate was 49.4% (95% CI: 43.06, 55.76) among 201 participants (80.1%) in the tafasitamab+$R^2$ group compared with 39.8% (95% CI: 33.70, 46.07) among 205 participants (80.7%) in the placebo+$R^2$ group. For comparison, the CR rates for the entire FL FAS (assessed by CT or MRI) were: 52% in the tafa-R2 arm vs 40.7% in the R2 arm.

Key secondary endpoint: OS in the FL population was not formally tested under the study hierarchy at the time of the present application. Instead, this will be done at the time of final analysis after the end of the study, which is expected when the last participant has completed a minimum of 5 years of post-treatment follow-up. Results of this final OS analysis will be provided by the MAH as per a CHMP recommendation.

The MAH has performed an interim futility analysis (prespecified but introduced with an amendment to the SAP) that demonstrates that the OS HR estimate was lower than the predefined futility boundary of 1.24. The estimated HR for OS was 0.587 (95% CI: 0.306, 1.128). Based on the point estimate, no detriment to OS is currently suspected.

A number of ancillary analyses have been provided to support the results of the primary endpoint and further contextualize the efficacy of tafasitamab+$R^2$ in R/R FL.

Minimal Residual Disease-negativity rate (using a threshold of ≤ 10−5 cells to define MRD negativity) at end of treatment showed higher rate of MRD negativity in the tafasitamab+$R^2$ group compared to the $R^2$ group, 15 (26.3%) VS 12 (18.2%) respectively, favouring tafasitamab+$R^2$. At the end of treatment, MRD negativity rate was 26.3% (95% CI: 15.54, 39.66) in the tafasitamab+$R^2$ group and 18.2% (95% CI: 9.76, 29.61) in the $R^2$ group. Of note, MRD analysis in peripheral blood at EOT was only performed in 29 participants (50.9%) in the tafasitamab+$R^2$ group and 33 participants (50.0%) in the $R^2$ group.

Overall Response Rate by investigator also favoured Tafasitamab+$R^2$ compared to $R^2$ alone, with 83.5% (95% CI: 78.57, 87.72) and 72.4% (95% CI: 66.67, 77.56), respectively, with an odds ratio of 2.0 (95% CI: 1.30, 3.02). IRC assessment was consistent with investigator assessment.

Duration of Response by investigator assessment also favoured tafasitamab+R² over R² and was 21.19 months (95% CI: 19.48, NE) among 228 responders in the tafasitamab+R² group and 13.60 months (95% CI: 12.42, 18.56) among 199 responders in the R² group, with an HR of 0.473 (95% CI: 0.330, 0.678) demonstrating deep and durable responses.

Multiple QoL testing were performed, namely EQ-5D-5L, EORTC QLQ-C30, and FACT-Lym. The outcomes were generally similar between treatment groups, presuming no detrimental effect of the addition of tafasitamab to the R² backbone. Moreover, these data are considered relevant due to the double-blind design.

Fewer patients in the tafasitamab+$R^2$ arm started NALT compared to those treated with placebo+$R^2$. TTNT was longer in the experimental arm compared to the control arm. Anti-CD19-targeting therapies were frequently employed as NALT, also in patients from the experimental arm (who, by definition, had just failed an anti-CD19-targeting therapy). PFS2 in the tafasitamab+$R^2$ arm was longer than in the control arm. Based on limited data, response to subsequent CD19-directed therapy does not appear to be altered by prior tafasitamab treatment.

Subgroup analyses: Subgroup analyses of the primary endpoint (PFS in FL) corroborated the results of the main analysis. Only subgroups with very few patients deviated from this. Notably, treatment benefit was maintained in the difficult-to-treat subgroups of POD24 and CD20 refractory (but CD20 expressing) FL.

Supportive study inMIND included a randomization of R/R MZL patients to the same treatments as in the FL population. Here efficacy results were considerably less impressive with no apparent gains observed but with alarming OS data: A higher proportion of participants in the tafasitamab+R2 group had died (13.2%) compared with the placebo+R2 group (1.9%). The estimated median OS was not reached (95% CI: NE, NE) in either the tafasitamab+R2 group or the placebo+R2 group, with an HR of 7.162 (95% CI: 0.880, 58.317) due to an imbalance in deaths. Most participants were censored as ongoing at the data cut-off date (73.6% and 86.8%, respectively).

This, while not directly relevant to the indication sought (from an efficacy perspective), is still considered of importance since the safety population of the present application also includes the patients with MZL.

As per study inMIND inclusion criterion, participants were eligible in the study if they had documented expression of CD19 and CD20 on lymphoma cells, prior to randomization. Documentation of positive CD19 and CD20 expression for inclusion purposes was based on results reported locally and pathologic review of representative biopsies obtained before or during screening. In addition, the applicant also conducted central assessment of CD19 and CD20 expression on available tumor biopsies. Tissue samples with sufficient tumour content were submitted approximately 30 days after randomization. Centrally, CD19 and CD20 expression was assessed by IHC.

Based on central assessment, 7 participants with R/R FL were found to be CD20-negative, of which 4 were in the tafasitamab arm and 3 were in the placebo arm. Among the 4 CD20-negative participants in the tafasitamab arm, 3 had best overall response of a CR and 1 had PR; among the 3 CD20-negative participants in the placebo arm, there was 1 CR, 1 PR, and 1 PD; In addition, 3 participants were found to be CD19-negative. However, only 1 participant out of the 3 had FL (the other 2 had MZL). All 3 of the CD19 negative participants were in the placebo group. The CD19-negative FL participant on the placebo arm had a best overall response of CR. However, In this

context the numbers are small, a special warning considering the lack of data and potential detrimental effect for CD19- and/or CD20- patients was added in section 4.4.

Given that the FL grade being 1-3a was an inclusion criterion of the trial and to align with the approved indication of lenalidomide in combination with rituximab (to which the presently sought indication is an add-on), the Applicant was requested to include "Grade 1-3a" in the indication wording. The final indication reads: *"MINJUVI is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL)* ***(Grade 1-3a)*** *after at least one line of systemic therapy."*

### Additional expert consultation

Not applicable

### Assessment of paediatric data on clinical efficacy

Not applicable

## 2.4.4. Conclusions on the clinical efficacy

The inMIND pivotal trial met its primary endpoint, PFS by INV in the R/R FL population, demonstrating a statistically significant and clinically meaningful PFS gain with addition of tafasitamab to lenalidomide in combination with rituximab. This result was supported by a number of other investigations including an OS futility analysis that did not give rise to any suspicion of OS detriment.

The MAH agreed to the following recommendations by the CHMP:

- The MAH will be using a RMST approach for final OS analysis of study INCMOR 0208-301 (inMIND), in addition to the Cox PH model.
- The MAH will provide final efficacy and safety analysis for study INCMOR 0208-301 (inMIND). These analyses will be performed at the end of the study, after the last participant has completed a minimum of 5 years of post-treatment follow-up.

# *2.5. Clinical safety*

## *Introduction*

Tafasitamab in the approved indication in combination with up to 12 cycles of lenalidomide and subsequently as monotherapy in patients with R/R DLBCL, presents with the following ADRs listed as very common: Infections, cytopenia, GI disorders, rash (grouped term), headache, back pain & muscle spasms, and asthenia (grouped term). The **overall safety population** treated with tafasitamab+$R^2$ (N=327) in the ongoing, randomised, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study study INCMOR 0208-301 (also named InMind-301), includes patients with R/R FL (N=274) and R/R MZL (N=53). In the comparator arm 325 R/R FL+R/R MZL patients were treated with placebo + $R^2$.

**Patient exposure**

**Table 41:** ***Summary of Exposure in the Overall Safety Population (Primary Analysis)***

| **Variable** | **Tafasitamab+R²** **(N = 327)** | | | | **Placebo+R²** **(N = 325)** | | | |
|---|---|---|---|---|---|---|---|---|
| | | LEN (mg) | | | | LEN (mg) | | |
| | Tafasitamab (mg/kg) | Baseline CrCl < 60 ml/min (N=60) | Baseline CrCl ≥ 60 ml/min (N=265) | Rituximab (mg/m²) | Placebo | Baseline CrCl < 60 ml/min (N=70) | Baseline CrCl ≥ 60 ml/min (N=252) | Rituximab (mg/m²) |
| **Total number of cycles*** | | | | | | | | |
| Mean (STD) | 9.9 (3.24) | – | – | 4.6 (0.99) | 9.4 (3.41) | – | – | 4.6 (0.98) |
| Median (min, max) | 12.0 (1, 12) | – | – | 5.0 (1, 5) | 12.0 (1, 12) | – | – | 5.0 (1, 5) |
| **Duration of treatment (days)** | | | | | | | | |
| Mean (STD) | 263.1 (93.37) | 246.0 (101.36) | 266.5 (96.65) | 103.9 (28.35) | 248.7 (97.65) | 225.0 (112.03) | 258.0 (95.63) | 102.6 (27.29) |
| Median (min, max) | 322.0 (1, 359) | 273.0 (6, 343) | 328.0 (1, 366) | 113.0 (1, 225) | 313.0 (1, 381) | 260.0 (4, 352) | 325.0 (1, 384) | 113.0 (1, 161) |
| **Participants in each duration category, n (%)** | | | | | | | | |
| < 1 month | 15 (4.6) | 3 (5.0) | 11 (4.2) | 19 (5.8) | 10 (3.1) | 5 (7.1) | 5(2.0) | 20 (6.2) |
| 1 to < 3 months | 18 (5.5) | 6 (10.0) | 14 (5.3) | 37 (11.3) | 27 (8.3) | 8 (11.4) | 19(7.5) | 41 (12.6) |
| 3 to < 6 months | 24 (7.3) | 5 (8.3) | 24 (9.1) | 268 (82.0) | 46 (14.2) | 11 (15.7) | 36(14.3) | 264 (81.2) |
| 6 to < 9 months | 60 (18.3) | 16 (26.7) | 43 (16.2) | 2 (0.6) | 63 (19.4) | 16 (22.9) | 48(19.0) | 0 (0.0) |
| 9 to ≤ 12 months | 210 (64.2) | 29 (48.3) | 172 (64.9) | 0 (0.0) | 178 (54.8) | 30 (42.9) | 143(56.7) | 0 (0.0) |
| >12 months | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Missing | – | 1 (1.7) | 0 (0.0) | 1 (0.3) | – | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| *Number of cycles for lenalidomide were not included in the TLFs | | | | | | | | |

**Table 42: Summary of Exposure in the Overall Safety Population (Cont)**

| **Variable** | **Tafasitamab+R²** **(N = 327)** | | | **Placebo+R²** **(N = 325)** | | |
|---|---|---|---|---|---|---|
| | | LEN (mg) | | Placebo | LEN (mg) | |

| | Tafasitamab (mg/kg) | Baseline CrCl < 60 ml/min (N=60) | Baseline CrCl ≥ 60 ml/min (N=265) | Rituximab (mg/m$^2$) | | Baseline CrCl < 60 ml/min (N=70) | Baseline CrCl ≥ 60 ml/min (N=252) | Rituximab (mg/m$^2$) |
|---|---|---|---|---|---|---|---|---|
| **Actual dose intensity** | | | | | | | | |
| n | 326 | 59 | 265 | 326 | N/A | 70 | 252 | 325 |
| Mean (STD) | 275.9 (88.20) | 1808.0 mg (1105.72) | 3308.7 mg (1446.77) | 2631.1 mg/m$^2$ (591.38) | N/A | 1661.2 mg (1104.35) | 3279.1 mg (1405.08) | 2645.7 mg/m$^2$ (564.01) |
| Median (min, max) | 300.0 mg/kg (1, 360) | 1730.0 (60, 5040) | 3675.0 (20, 5040) | 3000.0 mg/m$^2$ (375; 3375) | N/A | 1627.5 (40, 4800) | 3490.0 (0, 5040) | 3000.0 mg/m$^2$ (0; 3375) |
| **Relative dose intensity (%)** | | | | | | | | |
| n | 326 | 59 | 265 | 326 | N/A | 70 | 252 | 325 |
| Mean (STD) | 87.10 (14.665) | 81.44 (31.191) | 77.69 (21.385) | 90.56 (15.738) | N/A | 81.30 (31.120) | 80.96 (20.306) | 91.76 (15.810) |
| Median (min, max) | 92.59 (2.2, 100.0) | 86.19 (28.6, 200.0) | 84.29 (4.8, 100.0) | 100.00 (14.3, 150.0) | N/A | 82.44 (9.5, 182.9) | 86.81 (0.0, 104.2) | 100 (0, 200) |
| | | | | | | | | |

## *Adverse events*

**Common Treatment-Emergent Adverse Events**

**Table 43: Summary of Treatment-Emergent Adverse Events in ≥ 10% of Participants in Either Group by MedDRA Preferred Term (Overall Safety Population)**

| MedDRA SOC, PT, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Participants with any TEAE** | 325 (99.4) | 322 (99.1) | 647 (99.2) |
| **Gastrointestinal disorders** | 217 (66.4) | 202 (62.2) | 419 (64.3) |
| Diarrhoea | 123 (37.6) | 101 (31.1) | 224 (34.4) |
| Constipation | 90 (27.5) | 81 (24.9) | 171 (26.2) |
| Nausea | 59 (18.0) | 47 (14.5) | 106 (16.3) |
| Abdominal pain | 25 (7.6) | 33 (10.2) | 58 (8.9) |
| **Infections and infestations** | 222 (67.9) | 220 (67.7) | 442 (67.8) |
| COVID-19 | 104 (31.8) | 78 (24.0) | 182 (27.9) |
| Pneumonia | 38 (11.6) | 29 (8.9) | 67 (10.3) |
| **Upper respiratory tract infection** | 29 (8.9) | 36 (11.1) | 65 (10.0) |
| **Blood and lymphatic system disorders** | 197 (60.2) | 196 (60.3) | 393 (60.3) |
| Neutropenia | 164 (50.2) | 155 (47.7) | 319 (48.9) |
| Anaemia | 55 (16.8) | 47 (14.5) | 102 (15.6) |
| Thrombocytopenia | 49 (15.0) | 59 (18.2) | 108 (16.6) |
| **General disorders and administration site conditions** | 180 (55.0) | 177 (54.5) | 357 (54.8) |
| Fatigue | 68 (20.8) | 53 (16.3) | 121 (18.6) |
| Pyrexia | 62 (19.0) | 56 (17.2) | 118 (18.1) |
| Asthenia | 44 (13.5) | 35 (10.8) | 79 (12.1) |
| Oedema peripheral | 25 (7.6) | 44 (13.5) | 69 (10.6) |
| **Skin and subcutaneous tissue disorders** | 179 (54.7) | 154 (47.4) | 333 (51.1) |
| Rash | 72 (22.0) | 71 (21.8) | 143 (21.9) |
| Pruritus | 51 (15.6) | 38 (11.7) | 89 (13.7) |
| **Respiratory, thoracic and mediastinal disorders** | 133 (40.7) | 115 (35.4) | 248 (38.0) |
| Cough | 62 (19.0) | 55 (16.9) | 117 (17.9) |
| **Musculoskeletal and connective tissue disorders** | 126 (38.5) | 122 (37.5) | 248 (38.0) |
| Muscle spasms | 53 (16.2) | 57 (17.5) | 110 (16.9) |
| Back pain | 33 (10.1) | 18 (5.5) | 51 (7.8) |
| **Nervous system disorders** | 109 (33.3) | 104 (32.0) | 213 (32.7) |
| Headache | 34 (10.4) | 25 (7.7) | 59 (9.0) |
| **Injury, poisoning and procedural complications** | 96 (29.4) | 73 (22.5) | 169 (25.9) |
| Infusion related reaction | 52 (15.9) | 49 (15.1) | 101 (15.5) |
| **Metabolism and nutrition disorders** | 89 (27.2) | 100 (30.8) | 189 (29.0) |
| Decreased appetite | 36 (11.0) | 31 (9.5) | 67 (10.3) |
| Hypokalaemia | 27 (8.3) | 41 (12.6) | 68 (10.4) |

Note 1: Participants were counted once under each MedDRA PT.
Note 2: System organ classes and PTs within SOCs are listed in decreasing order of frequency by the tafasitamab+$R^2$ group.
Source: INCMOR 0208-301 CSR Tables 3.2.2.3 and 3.2.3.3.

**Grade 3 or 4 Treatment-Emergent Adverse Events**

**Table 44: Summary of Grade 3 or 4 Treatment-Emergent Adverse Events in ≥ 2% of Participants in Either Group by MedDRA Preferred Term (Overall Safety Population)**

| MedDRA SOC, PT, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|
| **Participants with any Grade 3 or 4 TEAE** | 238 (72.8) | 229 (70.5) | 467 (71.6) |
| **Blood and lymphatic system disorders** | 148 (45.3) | 148 (45.5) | 296 (45.4) |
| Neutropenia | 137 (41.9) | 129 (39.7) | 266 (40.8) |
| Anaemia | 21 (6.4) | 21 (6.5) | 42 (6.4) |
| Thrombocytopenia | 21 (6.4) | 29 (8.9) | 50 (7.7) |
| Febrile neutropenia | 14 (4.3) | 11 (3.4) | 25 (3.8) |
| **Infections and infestations** | 84 (25.7) | 56 (17.2) | 140 (21.5) |
| Pneumonia[a] | 27 (8.3) | 16 (4.9) | 43 (6.6) |
| COVID-19[b] | 20 (6.1) | 7 (2.2) | 27 (4.1) |
| COVID-19 pneumonia | 15 (4.6) | 4 (1.2) | 19 (2.9) |
| **Investigations** | 31 (9.5) | 35 (10.8) | 66 (10.1) |
| Neutrophil count decreased | 17 (5.2) | 21 (6.5) | 38 (5.8) |
| **General disorders and administration site conditions** | 17 (5.2) | 19 (5.8) | 36 (5.5) |
| Fatigue | 7 (2.1) | 0 (0.0) | 7 (1.1) |
| Pyrexia | 4 (1.2) | 10 (3.1) | 14 (2.1) |
| **Renal and urinary disorders** | 14 (4.3) | 13 (4.0) | 27 (4.1) |
| Acute kidney injury | 9 (2.8) | 8 (2.5) | 17 (2.6) |
| **Nervous system disorders** | 10 (3.1) | 9 (2.8) | 19 (2.9) |
| Syncope | 7 (2.1) | 2 (0.6) | 9 (1.4) |

Note 1: Participants were counted once under each MedDRA PT.
Note 2: System organ classes and PTs within SOCs are listed in decreasing order of frequency by the tafasitamab+R$^2$ group.
[a] The majority of the Grade 3 or 4 TEAEs of pneumonia were Grade 3: 26 participants (8.0%) in the tafasitamab+R$^2$ group and 15 participants (4.6%) in the placebo+R$^2$ group (refer to INCMOR 0208-301 CSR Table 3.2.4.3). One participant had both a Grade 3 (included in this table) and a Grade 5 TEAE of pneumonia (refer to INCMOR 0208-301 CSR Listing 2.7.1.1).
[b] All of the Grade 3 or 4 TEAEs of COVID-19 were Grade 3 (refer to INCMOR 0208-301 CSR Table 3.2.4.3).

Treatment-Related Treatment-Emergent Adverse Events

**Table 45: Summary of Tafasitamab/Placebo-Related Treatment-Emergent Adverse Events in ≥ 5% of Participants in Any Group by MedDRA Preferred Term (Overall Safety Population)**

| MedDRA SOC, PT, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|
| **Participants with any tafasitamab/placebo-related TEAE** | 249 (76.1) | 218 (67.1) | 467 (71.6) |

| | | | |
|---|---|---|---|
| **Blood and lymphatic system disorders** | 135 (41.3) | 125 (38.5) | 260 (39.9) |
| Neutropenia | 116 (35.5) | 102 (31.4) | 218 (33.4) |
| Thrombocytopenia | 35 (10.7) | 37 (11.4) | 72 (11.0) |
| Anaemia | 27 (8.3) | 25 (7.7) | 52 (8.0) |
| **General disorders and administration site conditions** | 83 (25.4) | 58 (17.8) | 141 (21.6) |
| Fatigue | 33 (10.1) | 15 (4.6) | 48 (7.4) |
| Pyrexia | 26 (8.0) | 19 (5.8) | 45 (6.9) |
| Gastrointestinal disorders | 70 (21.4) | 68 (20.9) | 138 (21.2) |
| Diarrhoea | 27 (8.3) | 27 (8.3) | 54 (8.3) |
| Constipation | 23 (7.0) | 19 (5.8) | 42 (6.4) |
| Nausea | 20 (6.1) | 16 (4.9) | 36 (5.5) |
| **Infections and infestations** | 69 (21.1) | 51 (15.7) | 120 (18.4) |
| Pneumonia | 20 (6.1) | 9 (2.8) | 29 (4.4) |
| **Skin and subcutaneous tissue disorders** | 50 (15.3) | 53 (16.3) | 103 (15.8) |
| Rash | 18 (5.5) | 19 (5.8) | 37 (5.7) |
| **Investigations** | 46 (14.1) | 42 (12.9) | 88 (13.5) |
| Neutrophil count decreased | 17 (5.2) | 12 (3.7) | 29 (4.4) |
| **Injury, poisoning and procedural complications** | 30 (9.2) | 12 (3.7) | 42 (6.4) |
| Infusion related reaction | 28 (8.6) | 10 (3.1) | 38 (5.8) |

Note 1: Participants were counted once under each MedDRA PT.
Note 2: System organ classes and PTs within SOCs are listed in decreasing order of frequency by the tafasitamab+$R^2$ group.

**Table 46: Treatment-Emergent Adverse Drug Reactions in Participants Treated with Tafasitamab/Placebo in Combination with Lenalidomide and Rituximab (Overall Safety Population)**

| ADR, n (%) | Tafasitamab+$R^2$ (N = 327) | | Placebo+$R^2$ (N = 325) | |
|---|---|---|---|---|
| | **All Grades** | **Grade 3-4** | **All Grades** | **Grade 3-4** |
| **Blood and lymphatic system disorders** | | | | |
| Neutropenia[a] | 186 (56.9) | 153 (46.8) | 176 (54.2) | 148 (45.5) |
| Anemia[b] | 56 (17.1) | 21 (6.4) | 47 (14.5) | 21 (6.5) |
| Thrombocytopenia[c] | 56 (17.1) | 21 (6.4) | 67 (20.6) | 32 (9.8) |
| Febrile neutropenia | 14 (4.3) | 14 (4.3) | 12 (3.7) | 11 (3.4) |
| Leukopenia | 7 (2.1) | 1 (0.3) | 8 (2.5) | 2 (0.6) |
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 123 (37.6) | 3 (0.9) | 101 (31.1) | 6 (1.8) |
| Constipation | 90 (27.5) | 2 (0.6) | 81 (24.9) | 0 (0.0) |
| Abdominal pain[d] | 39 (11.9) | 0 (0.0) | 53 (16.3) | 6 (1.8) |
| **General disorders and administration site conditions** | | | | |

| | | | | |
|---|---|---|---|---|
| Asthenia[e] | 114 (34.9) | 10 (3.1) | 86 (26.5) | 3 (0.9) |
| Pyrexia | 62 (19.0) | 4 (1.2) | 56 (17.2) | 10 (3.1) |
| Chills | 14 (4.3) | 0 (0.0) | 17 (5.2) | 0 (0.0) |
| **Infections and infestations** | | | | |
| Viral infections[f] | 135 (41.3) | 38 (11.6) | 104 (32.0) | 15 (4.6) |
| Bacterial infections[g] | 89 (27.2) | 25 (7.6) | 82 (25.2) | 25 (7.7) |
| Pneumonia | 38 (11.6) | 27 (8.3) | 29 (8.9) | 16 (4.9) |
| Bronchitis | 18 (5.5) | 0 (0.0) | 14 (4.3) | 0 (0.0) |
| Sepsis | 4 (1.2) | 3 (0.9) | 6 (1.8) | 4 (1.2) |
| **Injury, poisoning, and procedural complications** | | | | |
| IRR | 52 (15.9) | 3 (0.9) | 49 (15.1) | 1 (0.3) |
| **Investigations** | | | | |
| ALT increased | 19 (5.8) | 2 (0.6) | 23 (7.1) | 2 (0.6) |
| AST increased | 14 (4.3) | 1 (0.3) | 16 (4.9) | 0 (0.0) |
| **Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)** | | | | |
| Tumor lysis syndrome | 2 (0.6) | 1 (0.3) | 1 (0.3) | 1 (0.3) |
| **Nervous system disorders** | | | | |
| Headache | 34 (10.4) | 1 (0.3) | 25 (7.7) | 0 (0.0) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash[h] | 119 (36.4) | 9 (2.8) | 107 (32.9) | 5 (1.5) |
| Pruritus | 51 (15.6) | 1 (0.3) | 38 (11.7) | 0 (0.0) |

Note 1: Participants were counted once under each group term and PT.
Note 2: ADRs were identified using predefined PTs (refer to Listing 2.7.16.1) and coded using MedDRA v26.0.
[a] Neutropenia includes the PTs neutropenia and neutrophil count decreased.
[b] Anemia includes the PTs anemia, erythropenia, red blood cell count decreased, hemoglobin decreased, and hematocrit decreased.
[c] Thrombocytopenia includes the PTs thrombocytopenia and platelet count decreased.
[d] Abdominal pain includes the PTs abdominal pain, abdominal tenderness, abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.
[e] Asthenia includes the PTs asthenia, malaise, and fatigue.
[f] The PTs included in the FMQ viral infections are provided in Listing 2.7.16.1.
[g] The PTs included in the FMQ bacterial infections are provided in Listing 2.7.16.1.
[h] Rash includes the PTs rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, rash maculovesicular, exfoliative rash, rash vesicular, urticaria, urticarial dermatitis, vasculitic rash, and erythema.

## *Serious adverse event/deaths/other significant events*

**Serious adverse events**

**Table 47: Summary of Serious Treatment-Emergent Adverse Events in ≥ 1% of Participants in Either Group by MedDRA Preferred Term (Overall Safety Population)**

| MedDRA SOC, PT, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|
| **Participants with any serious TEAE** | 125 (38.2) | 110 (33.8) | 235 (36.0) |
| **Infections and infestations** | 86 (26.3) | 57 (17.5) | 143 (21.9) |
| Pneumonia | 25 (7.6) | 15 (4.6) | 40 (6.1) |
| COVID-19 | 21 (6.4) | 8 (2.5) | 29 (4.4) |
| COVID-19 pneumonia | 17 (5.2) | 7 (2.2) | 24 (3.7) |

| | | | |
|---|---|---|---|
| Sepsis | 4 (1.2) | 5 (1.5) | 9 (1.4) |
| **Blood and lymphatic system disorders** | 14 (4.3) | 15 (4.6) | 29 (4.4) |
| Febrile neutropenia | 9 (2.8) | 10 (3.1) | 19 (2.9) |
| **Renal and urinary disorders** | 10 (3.1) | 8 (2.5) | 18 (2.8) |
| Acute kidney injury | 9 (2.8) | 6 (1.8) | 15 (2.3) |
| **General disorders and administration site conditions** | 9 (2.8) | 17 (5.2) | 26 (4.0) |
| Pyrexia | 6 (1.8) | 11 (3.4) | 17 (2.6) |
| **Gastrointestinal disorders** | 4 (1.2) | 13 (4.0) | 17 (2.6) |
| Abdominal pain | 0 (0.0) | 5 (1.5) | 5 (0.8) |

Note 1: Participants were counted once under each MedDRA PT.
Note 2: System organ classes and PTs within SOCs are listed in decreasing order of frequency by the tafasitamab+$R^2$ group.

**Table 48 Summary of treatment – emergent adverse events with a fatal outcome by MedDRA system organ class and Preferred Term (Overall Safety population)**

| MedDRA SOC, n (%)<br>PT, n (%) | Tafasitamab+$R^2$<br>(N = 327) | Placebo+$R^2$<br>(N = 325) | Total<br>(N = 652) |
|---|---|---|---|
| Participants with any fatal TEAE | 8 (2.4) | 8 (2.5) | 16 (2.5) |
| Cardiac disorders | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Cardiac failure | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| General disorders and administration site conditions | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| Death | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Multiple organ dysfunction syndrome | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Infections and infestations | 3 (0.9) | 5 (1.5) | 8 (1.2) |
| Bronchopulmonary aspergillosis | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| COVID-19 | 2 (0.6) | 0 (0.0) | 2 (0.3) |
| COVID-19 pneumonia | 0 (0.0) | 2 (0.6) | 2 (0.3) |
| Pneumonia | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Sepsis | 1 (0.3) | 1 (0.3) | 2 (0.3) |

**Treatment-Emergent Adverse Events of Special Interest**

Adverse events of special interest were identified by 2 methods: programmatically (ie, based on a sponsor-defined prespecified list of PTs) and by investigator assessment (noted in the eCRF). For the purposes of this summary, the discussion that follows will focus on the AESIs identified programmatically, unless otherwise specified.

Adverse events of special interest for tafasitamab/placebo are CRS, hepatitis B reactivation, IRRs ≥ Grade 3, PML, SPM, and TLS, and the AESI for lenalidomide is SPM.

**Table 49 Summary of treatment – emergent adverse events of Special interest by MedDRA Preferred Term (Overall Safety Population)**

| AESI, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|
| Participants with any AESI | 26 (8.0) | 15 (4.6) | 41 (6.3) |
| CRS | 4 (1.2) | 4 (1.2) | 8 (1.2) |
| Hepatitis B reactivation | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| IRRs ≥ Grade 3 | 20 (6.1) | 9 (2.8) | 29 (4.4) |
| PML | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| SPM[a] | 11 (3.4) | 6 (1.8) | 17 (2.6) |
| TLS | 2 (0.6) | 1 (0.3) | 3 (0.5) |

Note: For PTs pertaining to the AESI categories, refer to INCMOR 0208-301 CSR Listing 2.7.13.

[a] Based on medical review, the SPM CMQ included the SMQs haematological malignant tumours and non-haematological malignant tumours as well as select PTs from the SMQ myelodysplastic syndrome.

Cytokine Release Syndrome (CSR)

In the Overall Safety Population, 4 participants (1.2%) in each group had AESIs of CRS.

- In the tafasitamab+R$^2$ group, the CRS AESIs were Grade 1 or Grade 2 (2 participants each). The median time to onset of CRS AESIs was 1.0 day (range: 1-13 days). The median longest duration of these events was 1.0 day (range: 1-2 days).
- In the placebo+R$^2$ group, the CRS AESIs were Grade 1 (3 participants) or Grade 2 (1 participant). The median time to onset of CRS AESIs was 2.5 days (range: 1-6 days). The median longest duration of these events was 5.0 days (range: 2-16 days).

Hepatitis B Reactivation

There were no participants in either treatment group with an AESI of hepatitis B reactivation in the FL Safety Population or the Overall Safety Population.

Infusion-Related Reactions Grade 3 or Higher

In the Overall Safety Population, 20 participants (6.1%) in the tafasitamab+R$^2$ group and 9 participants (2.8%) in the placebo+R$^2$ group had AESIs of IRRs.

- In the tafasitamab+R$^2$ group, the IRR AESIs were all Grade 3. The PTs identified in ≥ 2 participants included IRR, rash, and maculopapular rash (3 participants each) and hypersensitivity and erythematous rash (2 participants each). The median time to onset of IRR AESIs was 11.0 days (range: 1-311 days). The median longest duration of these events was 6.5 days (range: 1-22 days).
- In the placebo+R$^2$ group, the IRR AESIs were all Grade 3. The only PT identified in ≥ 2 participants was rash (2 participants). The median time to onset of IRR AESIs was 14.0 days (range: 1-142 days). The median longest duration of these events was 7.0 days (range: 1-40 days).

Progressive Multifocal Leukoencephalopathy (PML)

In the Overall Safety Population, 1 participant (0.2%) in the placebo+R$^2$ group had an AESI of PML identified programmatically.

Second Primary Malignancies (SPM)

**Table 50 Summary of Second Primary Malignancies; treatment – emergent adverse events**

**Events Defined by Customized MedDRA Query by MedDRA Preferred Term (Overall Safety Population)**

| Variable, n (%) | Tafasitamab+R$^2$ (N = 327) | Placebo+R$^2$ (N = 325) | Total (N = 652) |
|---|---|---|---|
| Any SPM TEAE | 11 (3.4) | 6 (1.8) | 17 (2.6) |
| Adenocarcinoma gastric | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Basal cell carcinoma | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Carcinoid tumour in the large intestine | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Colon cancer | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Lung adenocarcinoma | 1 (0.3) | 0 (0.0) | 1 (0.2) |
| Lung neoplasm malignant | 1 (0.3) | 2 (0.6) | 3 (0.5) |
| Myelodysplastic syndrome | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Prostate cancer | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Squamous cell carcinoma | 3 (0.9) | 0 (0.0) | 3 (0.5) |
| Squamous cell carcinoma of skin | 2 (0.6) | 0 (0.0) | 2 (0.3) |
| Transitional cell carcinoma | 1 (0.3) | 1 (0.3) | 2 (0.3) |

Note: Based on medical review, the SPM CMQ consisted of the SMQs haematological malignant tumours and non-haematological malignant tumours as well as select PTs (myelodysplastic syndrome, myelodysplastic syndrome transformation, myelodysplastic syndrome unclassifiable, myelodysplastic syndrome with excess blasts, myelodysplastic syndrome with multilineage dysplasia, myelodysplastic syndrome with ringed sideroblasts, myelodysplastic syndrome with single lineage dysplasia, myelodysplastic syndrome/myeloproliferative neoplasm overlap syndrome, myeloid maturation arrest, and myeloid metaplasia) from the SMQ myelodysplastic syndrome.

Tumour Lysis Syndrome (TLS)

In the FL Safety Population, 2 participants (0.7%) in the tafasitamab+R$^2$ group and 1 participant (0.4%) in the placebo+R$^2$ group had AESIs of TLS.

- In the tafasitamab+R$^2$ group, the TLS AESIs were Grade 1 (1 participant) or Grade 3 (1 participant). The time to onset of TLS AESIs was 15 and 71 days, respectively. The duration was 1 and 8 days, respectively.
- In the placebo+R$^2$ group, the TLS AESI was Grade 3. The time to onset was 24 days, and the duration was 14 days.

In the Overall Safety Population, 3 participants (0.5%) had AESIs of TLS identified programmatically.

**Severe or Fatal Select haematological Treatment-Emergent Adverse Events**

Grade 3, Grade 4, and fatal select hematological TEAEs included neutropenia, febrile neutropenia, anemia, and thrombocytopenia, and they are summarized for the following PTs:

- For neutropenia: "neutropenia" and "neutrophil count decreased"
- For anemia: "anemia" and "red blood cell count decreased"
- For thrombocytopenia: "platelet count decreased" and "thrombocytopenia"
- For febrile neutropenia: "febrile neutropenia"

**Table 51 Summary of grade 3 or 4 selected heamatological treatment – emergent adverse events Overall Safety**

| MedDRA System Organ Class<br>Preferred Term<br>Maximum Grade | Treatment Group<br>Tafasitamab + Rituximab + Lenalidomide (N=327) | Placebo + Rituximab + Lenalidomide (N=325) | Total (N=652) |
|---|---|---|---|
| Number(%) of participants with any selected Hematological TEAE | | | |
| Grade 3 | 89 ( 27.2) | 79 ( 24.3) | 168 ( 25.8) |
| Grade 4 | 68 ( 20.8) | 78 ( 24.0) | 146 ( 22.4) |
| Blood and lymphatic system disorders | | | |
| Grade 3 | 79 ( 24.2) | 67 ( 20.6) | 146 ( 22.4) |
| Grade 4 | 62 ( 19.0) | 73 ( 22.5) | 135 ( 20.7) |
| Febrile neutropenia | | | |
| Grade 3 | 8 ( 2.4) | 8 ( 2.5) | 16 ( 2.5) |
| Grade 4 | 6 ( 1.8) | 3 ( 0.9) | 9 ( 1.4) |
| Neutropenia | | | |
| Grade 3 | 78 ( 23.9) | 63 ( 19.4) | 141 ( 21.6) |
| Grade 4 | 59 ( 18.0) | 66 ( 20.3) | 125 ( 19.2) |

| MedDRA System Organ Class<br>Preferred Term<br>Maximum Grade | Treatment Group<br>Tafasitamab + Rituximab + Lenalidomide (N=327) | Placebo + Rituximab + Lenalidomide (N=325) | Total (N=652) |
|---|---|---|---|
| Blood and lymphatic system disorders (cont.) | | | |
| Thrombocytopenia | | | |
| Grade 3 | 12 ( 3.7) | 19 ( 5.8) | 31 ( 4.8) |
| Grade 4 | 9 ( 2.8) | 10 ( 3.1) | 19 ( 2.9) |
| Investigations | | | |
| Grade 3 | 11 ( 3.4) | 16 ( 4.9) | 27 ( 4.1) |
| Grade 4 | 6 ( 1.8) | 5 ( 1.5) | 11 ( 1.7) |
| Neutrophil count decreased | | | |
| Grade 3 | 11 ( 3.4) | 16 ( 4.9) | 27 ( 4.1) |
| Grade 4 | 6 ( 1.8) | 5 ( 1.5) | 11 ( 1.7) |
| Platelet count decreased | | | |
| Grade 3 | 0 ( 0.0) | 2 ( 0.6) | 2 ( 0.3) |
| Grade 4 | 0 ( 0.0) | 1 ( 0.3) | 1 ( 0.2) |

Note 1: Treatment-Emergent Adverse Events (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study treatment until 90 days after the last dose of study treatment.
Note 2: Participants were counted once under the highest grade considered.
Severity vs CTCAE Grade: Severe = Grade 3, Life-Threatening = Grade 4.
Note 3: MedDRA Version: 26.0

***Laboratory findings***

**Table 52 Treatment – emergent laboratory abnormalities by maximum grade (overall safety population)**

| Laboratory Parameter | Tafasitamab+R² (N = 327) | | | | Placebo+R² (N = 325) | | | |
|---|---|---|---|---|---|---|---|---|
| | No. Evaluable[a] | All Grade, n (%) | Grade 3-4, n (%)[b] | Grade 4, n (%) | No. Evaluable[a] | All Grade, n (%) | Grade 3-4, n (%)[b] | Grade 4, n (%) |
| **Hematology** | | | | | | | | |
| Hemoglobin (g/L) | 184 | 184 (100.0) | 0 (0.0) | 0 (0.0) | 175 | 175 (100.0) | 0 (0.0) | 0 (0.0) |
| Hemoglobin (g/L) increased | 4 | 4 (100.0) | 0 (0.0) | 0 (0.0) | 2 | 2 (100.0) | 0 (0.0) | 0 (0.0) |
| Leukocytes (GI/L) | 232 | 232 (100.0) | 3 (1.3) | 9 (3.9) | 222 | 222 (100.0) | 1 (0.5) | 9 (4.1) |
| Leukocytes (GI/L) increased | 72 | 72 (100.0) | 0 (0.0) | 0 (0.0) | 67 | 67 (100.0) | 0 (0.0) | 0 (0.0) |
| Lymphocytes (GI/L) | 190 | 190 (100.0) | 2 (1.1) | 8 (4.2) | 167 | 167 (100.0) | 1 (0.6) | 6 (3.6) |
| Lymphocytes (GI/L) increased | 43 | 43 (100.0) | 0 (0.0) | 0 (0.0) | 31 | 31 (100.0) | 0 (0.0) | 0 (0.0) |
| Neutrophils (GI/L) | 241 | 241 (100.0) | 2 (0.8) | 68 (28.2) | 235 | 235 (100.0) | 0 (0.0) | 77 (32.8) |
| Platelets (GI/L) | 134 | 134 (100.0) | 2 (1.5) | 13 (9.7) | 140 | 140 (100.0) | 1 (0.7) | 12 (8.6) |
| **Chemistry** | | | | | | | | |
| ALT (IU/L) | 151 | 151 (100.0) | 0 (0.0) | 0 (0.0) | 132 | 132 (100.0) | 0 (0.0) | 0 (0.0) |
| Albumin (g/L) | 63 | 63 (100.0) | 0 (0.0) | 0 (0.0) | 66 | 66 (100.0) | 0 (0.0) | 0 (0.0) |
| ALP (IU/L) | 111 | 111 (100.0) | 0 (0.0) | 0 (0.0) | 97 | 97 (100.0) | 0 (0.0) | 0 (0.0) |
| AST (IU/L) | 95 | 95 (100.0) | 0 (0.0) | 0 (0.0) | 98 | 98 (100.0) | 0 (0.0) | 0 (0.0) |
| Bilirubin (µmol/L) | 43 | 43 (100.0) | 0 (0.0) | 0 (0.0) | 42 | 42 (100.0) | 0 (0.0) | 0 (0.0) |
| Creatinine (µmol/L) | 88 | 88 (100.0) | 0 (0.0) | 0 (0.0) | 100 | 100 (100.0) | 0 (0.0) | 1 (1.0) |
| Glucose (mmol/L) | 95 | 95 (100.0) | 0 (0.0) | 2 (2.1) | 91 | 91 (100.0) | 0 (0.0) | 3 (3.3) |
| LDH (IU/L) | 88 | 88 (100.0) | 0 (0.0) | 0 (0.0) | 90 | 90 (100.0) | 0 (0.0) | 0 (0.0) |
| Potassium (mmol/L) | 74 | 74 (100.0) | 0 (0.0) | 1 (1.4) | 82 | 82 (100.0) | 0 (0.0) | 2 (2.4) |
| Potassium (mmol/L) increased | 37 | 37 (100.0) | 0 (0.0) | 1 (2.7) | 22 | 22 (100.0) | 0 (0.0) | 2 (9.1) |

| Laboratory Parameter | Tafasitamab+R² (N = 327) | | | | Placebo+R² (N = 325) | | | |
|---|---|---|---|---|---|---|---|---|
| | No. Evaluable[a] | All Grade, n (%) | Grade 3-4, n (%)[b] | Grade 4, n (%) | No. Evaluable[a] | All Grade, n (%) | Grade 3-4, n (%)[b] | Grade 4, n (%) |
| **Chemistry (continued)** | | | | | | | | |
| Sodium (mmol/L) | 80 | 80 (100.0) | 0 (0.0) | 1 (1.3) | 71 | 71 (100.0) | 0 (0.0) | 0 (0.0) |
| Sodium (mmol/L) increased | 22 | 22 (100.0) | 0 (0.0) | 1 (4.5) | 26 | 26 (100.0) | 0 (0.0) | 0 (0.0) |
| **Coagulation** | | | | | | | | |
| Activated partial thromboplastin time (s) | 61 | 61 (100.0) | 0 (0.0) | 0 (0.0) | 75 | 75 (100.0) | 0 (0.0) | 0 (0.0) |
| Prothrombin international normalized ratio | 55 | 55 (100.0) | 0 (0.0) | 0 (0.0) | 47 | 47 (100.0) | 0 (0.0) | 0 (0.0) |

[a] Generally defined as the number of participants with a baseline and at least 1 postbaseline grade for the particular laboratory study.
[b] A shift from Grade 3 to Grade 4 would be included in this column.

**Table 53 Treatment – emergent worsening of laboratory abnormalities Chemistry – Overall Safety**

| Lab Test<br>Severity Grade | Treatment Group<br>Tafasitamab + Rituximab + Lenalidomide (N=327) | Placebo + Rituximab + Lenalidomide (N=325) | Total (N=652) |
|---|---|---|---|
| Alanine Aminotransferase (IU/L) | | | |
| Any Grade | 151 ( 46.2) | 132 ( 40.6) | 283 ( 43.4) |
| Grade 1 | 138 ( 42.2) | 118 ( 36.3) | 256 ( 39.3) |
| Grade 2 | 9 ( 2.8) | 10 ( 3.1) | 19 ( 2.9) |
| Grade 3 | 4 ( 1.2) | 4 ( 1.2) | 8 ( 1.2) |
| Grade 4 | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Missing | 3 ( 0.9) | 2 ( 0.6) | 5 ( 0.8) |

***Safety in special populations***

Age

Table 54 Overall Summary of Treatment – emergent adverse events by age group: <65 years and ≥65 years (Overall Safety population)

| Participants (n [%]) Who Had at Least 1 | Tafasitamab+R² (N = 327) | | Placebo+R² (N = 325) | | Total (N = 652) | |
|---|---|---|---|---|---|---|
| | < 65 Years (N = 150) | ≥ 65 Years (N = 177) | < 65 Years (N = 154) | ≥ 65 Years (N = 171) | < 65 Years (N = 304) | ≥ 65 Years (N = 348) |
| TEAE | 149 (99.3) | 176 (99.4) | 153 (99.4) | 169 (98.8) | 302 (99.3) | 345 (99.1) |
| Serious TEAE | 51 (34.0) | 74 (41.8) | 49 (31.8) | 61 (35.7) | 100 (32.9) | 135 (38.8) |
| Grade 3 or 4 TEAE | 100 (66.7) | 138 (78.0) | 102 (66.2) | 127 (74.3) | 202 (66.4) | 265 (76.1) |
| Fatal TEAE | 1 (0.7) | 7 (4.0) | 1 (0.6) | 7 (4.1) | 2 (0.7) | 14 (4.0) |

Sex

**Table 55 Overall Summary of Treatment – emergent adverse events by Sex (Overall Safety population)**

| Participants (n [%]) Who Had at Least 1 | Tafasitamab+R² (N = 327) | | Placebo+R² (N = 325) | | Total (N = 652) | |
|---|---|---|---|---|---|---|
| | Male (N = 177) | Female (N = 150) | Male (N = 174) | Female (N = 151) | Male (N = 351) | Female (N = 301) |
| TEAE | 175 (98.9) | 150 (100.0) | 171 (98.3) | 151 (100.0) | 346 (98.6) | 301 (100.0) |
| Serious TEAE | 64 (36.2) | 61 (40.7) | 61 (35.1) | 49 (32.5) | 125 (35.6) | 110 (36.5) |
| Grade 3 or 4 TEAE | 124 (70.1) | 114 (76.0) | 117 (67.2) | 112 (74.2) | 241 (68.7) | 226 (75.1) |
| Fatal TEAE | 2 (1.1) | 6 (4.0) | 6 (3.4) | 2 (1.3) | 8 (2.3) | 8 (2.7) |

Race

**Table 56 Overall Summary of Treatment – emergent adverse events by Race (Overall Safety population)**

| Participants (n [%]) Who Had at Least 1 | Tafasitamab+R² (N = 327) | | | Placebo+R² (N = 325) | | | Total (N = 652) | | |
|---|---|---|---|---|---|---|---|---|---|
| | White (N = 263) | Asian (N = 47) | Other[a] (N = 17) | White (N = 258) | Asian (N = 48) | Other[a] (N = 19) | White (N = 521) | Asian (N = 95) | Other[a] (N = 36) |
| TEAE | 261 (99.2) | 47 (100.0) | 17 (100.0) | 255 (98.8) | 48 (100.0) | 19 (100.0) | 516 (99.0) | 95 (100.0) | 36 (100.0) |
| Serious TEAE | 110 (41.8) | 9 (19.1) | 6 (35.3) | 93 (36.0) | 13 (27.1) | 4 (21.1) | 203 (39.0) | 22 (23.2) | 10 (27.8) |
| Grade 3 or 4 TEAE | 190 (72.2) | 36 (76.6) | 12 (70.6) | 180 (69.8) | 37 (77.1) | 12 (63.2) | 370 (71.0) | 73 (76.8) | 24 (66.7) |
| Fatal TEAE | 7 (2.7) | 0 (0.0) | 1 (5.9) | 8 (3.1) | 0 (0.0) | 0 (0.0) | 15 (2.9) | 0 (0.0) | 1 (2.8) |

[a] Other races include Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, not reported, and other.

Creatinine Clearance

Few patients had a creatinine clearance <60ml/min. There was a tendency towards a higher frequency of SAEs and Grade 3-4 AEs in this pool in both arms.

***Safety related to drug-drug interactions and other interactions***

No clinically meaningful differences in tafasitamab PK were observed when used concomitantly with lenalidomide. Drug interactions for the components of lenalidomide and rituximab are described in the respective SmPCs.

***Discontinuation due to adverse events***

**Table 57 Summary of Treatment – emergent adverse events leading to dose modification of tafasitamab / placebo in ≥2% of participants in any group by MedDRA SOC and PT (Overall Safety population)**

| MedDRA SOC, n (%)<br>PT, n (%) | Tafasitamab+R[2]<br>(N = 327) | Placebo+R[2]<br>(N = 325) | Total<br>(N = 652) |
|---|---|---|---|
| Participants with any TEAE leading to dose modification of tafasitamab/placebo | 245 (74.9) | 229 (70.5) | 474 (72.7) |
| Blood and lymphatic system disorders | 128 (39.1) | 114 (35.1) | 242 (37.1) |
| Anaemia | 10 (3.1) | 9 (2.8) | 19 (2.9) |
| Febrile neutropenia | 11 (3.4) | 7 (2.2) | 18 (2.8) |
| Neutropenia | 114 (34.9) | 99 (30.5) | 213 (32.7) |
| Thrombocytopenia | 15 (4.6) | 24 (7.4) | 39 (6.0) |
| Gastrointestinal disorders | 19 (5.8) | 14 (4.3) | 33 (5.1) |
| Diarrhoea | 9 (2.8) | 6 (1.8) | 15 (2.3) |
| General disorders and administration site conditions | 34 (10.4) | 28 (8.6) | 62 (9.5) |
| Fatigue | 9 (2.8) | 0 (0.0) | 9 (1.4) |
| Pyrexia | 16 (4.9) | 14 (4.3) | 30 (4.6) |
| Infections and infestations | 135 (41.3) | 111 (34.2) | 246 (37.7) |
| Bronchitis | 10 (3.1) | 3 (0.9) | 13 (2.0) |
| COVID-19 | 69 (21.1) | 53 (16.3) | 122 (18.7) |
| COVID-19 pneumonia | 12 (3.7) | 4 (1.2) | 16 (2.5) |
| Pneumonia | 28 (8.6) | 16 (4.9) | 44 (6.7) |
| Respiratory tract infection | 12 (3.7) | 9 (2.8) | 21 (3.2) |
| Upper respiratory tract infection | 9 (2.8) | 4 (1.2) | 13 (2.0) |
| Injury, poisoning and procedural complications | 31 (9.5) | 8 (2.5) | 39 (6.0) |
| Infusion related reaction | 24 (7.3) | 4 (1.2) | 28 (4.3) |
| Investigations | 21 (6.4) | 26 (8.0) | 47 (7.2) |
| Neutrophil count decreased | 14 (4.3) | 17 (5.2) | 31 (4.8) |
| Renal and urinary disorders | 10 (3.1) | 6 (1.8) | 16 (2.5) |
| Acute kidney injury | 7 (2.1) | 3 (0.9) | 10 (1.5) |
| Skin and subcutaneous tissue disorders | 15 (4.6) | 15 (4.6) | 30 (4.6) |
| Rash | 8 (2.4) | 4 (1.2) | 12 (1.8) |

Note 1: Participants were counted once under each MedDRA SOC and PT.
Note 2: For tafasitamab/placebo, dose modification included dose interruption, dose skipped, and dose delays. As per Protocol, dose reduction was not permitted for tafasitamab/placebo.

***Post marketing experience***

The cumulative postmarketing patient exposure to tafasitamab from approval until the IB data cutoff date (30 July 2024) is approximately 8376 patient-years (IB). Overall, review of the safety data issued to date does not reveal any new significant safety information or new safety concerns from spontaneous reports.

A review of reported events for MONJUVI (tafasitamab-cxix) in the US submitted via either PAER or PBRER covering the period from 31 JAN 2024 to 30 JUL 2024 did not reveal any new significant

safety information or identify any new safety concerns from spontaneous reports during this PAER/PBRER reporting period.

## 2.5.1. Discussion on clinical safety

The overall safety population treated with tafasitamab+$R^2$ (N=327) in study INCMOR 0208-301 (also named InMind-301), which includes patients with R/R FL (N=274) and R/R MZL (N=53), is considered the most comprehensive safety pool, and is the population presented in the SmPC. In the comparator arm 325 R/R FL+R/R MZL patients were treated with placebo + $R^2$.

Exposure to tafasitamab/placebo in the Overall Safety Population showed a slightly longer median duration of treatment in the tafasitamab+$R^2$ group (322.0 days [range: 1-359 days]) compared to the placebo+$R^2$ group (313.0 days [range: 1-381 days]). Exposure to tafasitamab or placebo in the FL Safety Population was similar to that of the overall safety population. Exposure to lenalidomide was higher in the tafasitamab arm; 326.5 days compared to 310.0 days in the placebo arm. Due to impaired renal function 52 patients in the tafasitamab arm and 70 patients in the placebo arm received a start dose of 10 mg instead of 20 mg, as per dosing according to the lenalidomide SmPC. The median duration of treatment with rituximab was the same in both arms (113 days).

At the time of the data cut-off (23 February 2024), 93 participants with R/R FL (17.0% of the FL FAS and 14.2% of the Overall FAS) continued to receive study treatment. The MAH has conducted updated safety analysis for the study INCMOR 0208-301 with a data cut-off date of 31 Dec 2024 to explore whether new topics/signals arose.

In the overall safety population common adverse events that occurred more frequently in the tafasitamab+$R^2$ group were diarrhoea, COVID-19, oropharyngeal pain, pain in extremity, and increased blood ALP. In the placebo+$R^2$ group peripheral oedema was observed more frequently (13.5% vs 7.6%).

There were no differences ≥ 5% in the incidence of any Grade 3 or 4 AEs between treatment groups. The only SOC with a marked difference in Grade 3-4 AE frequencies was Infections and infestations (tafasitamab+$R^2$; 25.7% vs placebo+$R^2$; 17.2%) with the differences mainly caused by COVID-19 infections (10.7% cs 3.4%, respectively) and pneumonia (general term; 8.3% vs 4.9%, respectively).

SAEs that occurred more frequently (≥ 2% difference) in the tafasitamab+$R^2$ group versus the placebo+$R^2$ group, respectively, were also related to the SOC Infections and infestations and included pneumonia (7.6% vs 4.6%), COVID-19 (6.4% vs 2.5%), and COVID-19 pneumonia (5.2% vs 2.2%).

In the Overall safety population PTs in the SOC Infections were the most frequent cause of death with 3/8 deaths in the tafasitamab-group and 5/8 in the placebo group. Fatal haemorrhage (one case of cerebral and one case of pulmonary) occurred in the tafasitamab group (in MZL patients), whereas no SAE or fatal haemorrhage was seen in the placebo arm. According to the narratives of the case of cerebral haemorrhage in the tafasitamab group in a 74 years old female with MZL, the causality was reported as enoxaparine 60 mg twice daily. For the pulmonary haemorrhage, the causality was not estimated in the narrative. As a first step, the PRAC's proposal for a cumulative review of bleeding events in the next PSUR and a discussion on whether any update to the SmPC is warranted based on those findings is supported. Adding this safety concern as an important

potential risk to the RMP could be considered afterwards if relevant.

Adverse events of special interest (AESI):

Adverse events of special interest for tafasitamab/placebo are CRS, hepatitis B reactivation, IRRs ≥ Grade 3, PML, SPM, and TLS. The AESI for lenalidomide is SPM.

The frequency of CRS was low in both arms and were all Grade 1 or 2.

IRR ≥ Grade 3 were defined as an AESI and was observed with a frequency of 6.1% in the tafasitamab group and 2.8% in the placebo group and were all Grade 3. The frequency of IRR overall (all grades) was 15.9% and 15.1%, respectively.

Overall, the incidence of SPMs between treatment groups was 3.4% in the tafasitamab+$R^2$ group and 1.8% in the placebo+$R^2$ group. For lenalidomide SPM is an identified risk. The relatively small difference between the two groups precludes any conclusion on the risk for SPM related to tafasitamab. Long-term safety is listed as missing information in the RMP, which hopefully will help resolve this issue in the future.

The incidence of TLS was low, as is expected in indolent lymphomas.

Changes in haematological laboratory parameters were similar between the two treatment groups. However, the proportion of patients per treatment group receiving G-CSF or other antianaemic preparations like darbepoetin alfa, epoetin alfa, epoetin theta, epoetin zeta or erythropoietin needs to be clarified. The parameter with the largest difference in treatment-emergent worsening of chemistry parameters of any grade between groups was observed for increased ALT (46.2% in the tafasitamab+$R^2$ group vs 40.6% in the placebo+$R^2$ group) with four Grade 3 events in each group and no Grade 4 events. Generally, there were few patients who had worst-grade clinical chemistry values of Grade 3 or 4.

As could be expected, SAEs and Grade 3-4 AEs (overall) were observed with a higher frequency in the older population whether ≥65 years or ≥75 years, and with a higher frequency in the tafasitamab+$R^2$ group compared to the placebo+$R^2$ group. Anaemia and thrombocytopenia (PT) were observed more frequently in the older population in the tafasitamab+$R^2$ group, whereas COVID-19 was more frequent in the younger population. Cardiac disorders by SOC were more frequent in the older population without any PT standing out, which is to be expected.

Seven patients who were ≥65 years had a fatal adverse event versus one patient <65 years old in each of the tafasitamab+$R^2$ and placebo+$R^2$ groups. The one patient who was <65 years in the tafa group died due to COVID-19 and the patient <65 years in the and placebo group died of cardiac failure. Infections and SPM were the causes seen in more than one patient and were observed in both treatment groups.

There were some differences between the females and males, which are not considered clinically relevant. The main pool of patients was white and a small population was Asian, which makes any conclusion speculative.

Few patients had a creatinine clearance <60ml/min. There was a tendency towards a higher frequency of SAEs and Grade 3-4 AEs in this pool in both arms. In case of renal impairment, no

dose adjustment is needed for patients with mild or moderate renal impairment and there are no data in patients with severe renal impairment with regards to dosing recommendations.

The frequency of AEs leading to discontinuation was 11.6% in the tafasitamab+$R^2$ group and 6.2% in the placebo+$R^2$ group. The main differences were due to a higher frequency of infections (particularly COVID-19) and IRRs (including pyrexia) in the tafasitamab+$R^2$ group. The same pattern was also observed for dose modifications.

The clinical assessment of immunogenicity for tafasitamab was evaluated in 986 participants (overall) and 652 participants from Study INCMOR 0208-301. The overall number of participants that were ADA positive was 36 (3.7%) whereas in Study INCMOR 0208-301 17 (2.6%) participants were ADA positive. Based on INCMOR 0208-301, ADA-positive participants and samples were 2.6% and 0.9%, respectively, with no participants or samples testing positive for NAbs. Studies INCMOR 0208-102 (ongoing) and MOR0208C107 (complete), as well as those finalized studies that supported the initial application of tafasitamab for the indication of DLBCL, were compared to Study INCMOR 0208-301 to evaluate and underscore the inference that the overall incidence of ADA-positive participants and samples remains low (< 5%). The risk of clinically significant immunogenicity impacting the PK, safety, and efficacy of tafasitamab seems low and not different to the data from the initial application of tafasitamab.

At the time of the data cut-off (23 February 2024), 93 participants with R/R FL (17.0% of the FL FAS and 14.2% of the Overall FAS) continued to receive study treatment. The MAH was asked to provide updated safety data, in particular whether new topics/signals arose. The MAH has conducted updated safety analysis for the study INCMOR 0208-301 with a data cut-off date of 31 Dec 2024. Overall the additional safety data do not identify any new safety pattern and these did not have any impact on the benefit/risk ratio of tafasitamab in combination with R2. Furthermore, the MAH displayed in a table the number and rate of patients per treatment group receiving Granulocyte Colony-stimulating factors and Erythropoiesis-Stimulating Agents and these are well-balanced with no significant clinical trend for more administration of these preparations in the tafasitamab group.

### Additional expert consultations

Not applicable.

### Assessment of paediatric data on clinical safety.

Not applicable.

## 2.5.2. Conclusions on clinical safety

The safety profile in patients with R/R FL (84% of the study population) and R/R MZL (16% of the study population) was generally consistent with the known safety profile of tafasitamab in R/R DLBCL. Safety and tolerability were comparable with the addition of tafasitamab to lenalidomide in combination with rituximab, with an increase in severe neutropenias and severe infections such as COVID-19 and pneumonia, which most likely reflect the additional immunosuppressive effect from tafasitamab. Furthermore, there were no new safety signals compared to the known safety profile observed in DLBCL (tafasitamab+lenalidomide for 12 cycles followed by tafasitamab monotherapy). In conclusion, safety data from the InMind study demonstrate that tafasitamab in combination with

lenalidomide and rituximab is generally well tolerated in participants with R/R FL, with a manageable safety profile: The assessment of the additional data requested resolved the uncertainties regarding the safety profile of tafasitamab in the indication sought since no new safety pattern was identified.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version 3.2. with this application.

The CHMP endorsed the consolidated Risk Management Plan version 4.0 with the following content:

### *Safety concerns*

Summary of Safety Concerns

| Summary of safety concerns | |
|---|---|
| Important identified risks | None |
| Important potential risks | Progressive multifocal leukoencephalopathy |
| Missing information | Use in pregnancy and lactation<br>Use in patients with recent use of B-cell depleting drugs or chemotherapy<br>Long-term safety |

### *Pharmacovigilance plan*

Additional pharmacovigilance activities: none

### *Risk minimisation measures*

Additional Risk Minimisation measures: none

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to lack of data in relation to CD19, CD20 negativity has been added to the product information. The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH; this has been found acceptable as the changes and additions to the PL are in line with the original text of the PL in the initial MAA.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Minjuvi is indicated in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) **(Grade 1-3a)** after at least one line of systemic therapy.

The clinical history of Relapsed /Refractory FL is typically one of multiple relapses, with successive treatment regimens resulting in progressively shorter disease-control intervals, until fatal, resistant disease emerges or patients succumb to non-lymphoma causes of death. In addition to the morbidity and mortality associated with treatment resistance, cumulative treatment-related toxicity (especially immunosuppression, myelosuppression, and secondary leukaemia related to alkylator exposure) and transformation to diffuse large B-cell lymphoma (DLBCL) remain significant contributors to mortality in patients with FL.

### 3.1.2. Available therapies and unmet medical need

Patients with R/R FL do not necessarily require treatment at the time of lymphoma progression. When they do become in need of treatment as assessed by their treating physician, often using the GELF criteria, there are many treatment options available. For patients in 2L+, therapeutic options include: combinations of chemotherapy with anti-CD20-targeting monoclonal antibodies, rituximab-lenalidomide ($R^2$, the comparator of the present study) or rituximab monotherapy. For patients in 3L+, options include: bispecific CD20xCD3-targeting antibodies, CAR-T (CD19-targeting) treatment, PI3K inhibitors and the BTK inhibitor zanubrutinib in combination with obinutuzumab.

### 3.1.3. Main clinical studies

A single pivotal study, INC-MOR-0208-301 ("inMIND"), supports this application for extension of indication. inMIND was a Phase III, randomized, double-blind, multicentre study to investigate the effect of adding tafasitamab to rituximab+lenalidomide ($R^2$) in patients with R/R FL and R/R marginal zone lymphoma (MZL). Only patients in need of treatment according to GELF and whose lymphomas expressed both CD19 and CD20 were eligible. The primary endpoint was PFS by INV in the FL population with key secondary endpoints of PFS by INV in the overall population, PET-CR in the FL population (only patients whose lymphoma was FDG-avid) and OS in the FL population (to be assessed at 5 years follow up of all patients). The efficacy population (n=548 patients) included patients with FL while both FL and MZL patients were included in the safety population (n=652). Results are based on analyses with a data cut-off of 23.02.2024.

## *3.2. Favourable effects*

Primary endpoint – PFS by INV in FL population: The estimated median PFS was 22.37 months (95% CI: 19.22, NE) in the tafasitamab+R2 group compared with 13.93 months (95% CI: 11.53,

16.39) in the placebo+R2 group, with an HR of 0.434 (95% CI: 0.324, 0.580) and a p-value of < 0.0001. The estimated median PFS follow-up time was 14.32 months (95% CI: 11.83, 14.95) in the tafasitamab+R2 group and 14.13 months (95% CI: 11.53, 15.01) in the placebo+R2 group.

Key secondary endpoint – PFS by INV in the Overall population: The Overall Population consists of 83.8% of participants with FL and 16.2% of participants with MZL. The main analysis demonstrated an estimated HR of 0.500 (95% CI: 0.383, 0.653) and a p-value of < 0.0001. The estimated median PFS was 23.95 months (95% CI: 22.34, NE) in the tafasitamab+$R^2$ group compared with 16.39 months (95% CI: 13.86, 18.66) in the placebo+$R^2$ group. While this key secondary endpoint is not of direct relevance to the indication sought (FL only), it had to succeed in order for the Applicant to proceed with hierarchical testing.

Key secondary endpoint – PET-CR rate at EoT by INV (in the FDG-avid FL population): PET-CR rate was 49.4% (95% CI: 43.06, 55.76) among 201 participants (80.1%) in the tafasitamab+$R^2$ group compared with 39.8% (95% CI: 33.70, 46.07) among 205 participants (80.7%) in the placebo+$R^2$ group. For comparison, the CR rates for the full FL population were: 52% in the tafa-$R^2$ arm vs 40.7% in the $R^2$ arm.

Key secondary endpoint – OS in the FL population: was not formally tested under the study hierarchy at the time of the present application. Instead, this will be done at the time of final analysis after the end of the study, which is expected when the last participant has completed a minimum of 5 years of post-treatment follow-up. The Applicant has performed an interim futility analysis that demonstrates that the OS HR estimate was lower than the predefined futility boundary of 1.24. The estimated HR for OS was 0.587 (95% CI: 0.306, 1.128). Based on the point estimate, no detriment to OS is currently suspected.

Subgroup analyses corroborated the results of the main analysis of the primary endpoint, including in patients with difficult-to-treat disease characteristics such as POD24 and refractoriness to prior anti-CD20 treatment.

## *3.3. Uncertainties and limitations about favourable effects*

PFS2 seems to corroborate that including an anti-CD19 targeting antibody with R2 from 2L+ in R/R FL generally does not diminish the duration of PFS in those who progress and require new anti-lymphoma treatment (NALT). However, the NALT instituted upon progression in inMIND was very heterogeneous and considering the short follow up it is difficult to conclude on PFS2. Results from longer follow up are expected post authorisation.

OS data are still immature, but no detrimental effect is expected at this stage (HR [95% CI], 0.59 [0.31, 1.13]). Efficacy data after a longer follow up and final OS data will be submitted post-approval.

## *3.4. Unfavourable effects*

Safety and tolerability were comparable with the addition of tafasitamab to lenalidomide in combination with rituximab, with an increase in severe neutropenias and severe infections such as COVID-19 and pneumonia, which most likely reflect the additional immunosuppressive effect from tafasitamab. In the SOC Infections and infestations, the overall incidence of Grade 3 or 4 TEAEs was higher in the tafasitamab+$R^2$ group than in the placebo+$R^2$ group (25.7% vs 17.2%) with pneumonia (8.3% vs 4.9%), COVID-19 (6.1% vs 2.2%), and COVID-19 pneumonia (4.6% vs 1.2%) being the most frequent PTs.

Neutropenia was frequent and comparable between groups.

Infusion-related reactions ≥ grade 3 were few but occurred with a higher frequency in the tafasitamab group (6.1% vs 2.8%).

## 3.5. Uncertainties and limitations about unfavourable effects

Given the study design with tafasitamab as an add-on to lenalidomide and rituximab the safety results are considered reliable; no uncertainties are noted.

## 3.6. Effects Table

Table 58 Effects Table for tafasitamab in combination with lenalidomide and rituximab for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least one line of systemic therapy. (data cut-off: 23 FEB. 2024)

| Effect | Short description | Unit | Tafasitamab +R² | Placebo + R² | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | **N=273** | **N=275** | **(Efficacy population)** | |
| **PFS by INV (FL pop)** | Progression-Free Survival | Median, months (95 % CI) | 22.37 (19.22, NE) | 13.93 (11.53, 16.39) | | Study INCMOR 0208-301 |
| | | | | | | |
| **Unfavourable Effects population)** | | | **N=327** | **N=325** | **(Overall safety** | |
| Adverse events | All<br>Grade 3-4<br>Serious AE<br>Fatal AEs<br>Discont. | % | 99.4<br>72.8<br>38.2<br>2.4<br>11.6 | 99.1<br>70.5<br>38.8<br>2.5<br>6.2 | | |
| Infections and infestations (SOC) | All<br>Grade 3-4 | % | 67.9<br>25.7 | 67.7<br>17.2 | | |
| Blood and lymphatic system disorders (SOC) | All<br>Grade 3-4 | % | 60.2<br>45.3 | 60.3<br>45.5 | | |
| a. Neutropenia | Grade 3<br>Grade 4 | % | 23.9<br>18.0 | 19.4<br>20.3 | | Study INCMOR 0208-301 CSR |
| a. Febrile neutropenia | Grade 3<br>Grade 4 | % | 2.4<br>1.8 | 2.5<br>0.9 | | |
| b. Thrombocyto-penia | Grade 3<br>Grade 4 | % | 3.7<br>2.8 | 5.8<br>3.1 | | |
| Infusion-related reactions* | All<br>Grade 3 | % | 15.9<br>6.1 | 15.1<br>2.8 | No Grade 4 in either group. | |

Table 1. Abbreviations: CR= complete response; EoT= end of treatment; FDG= Fluorodeoxyglucose; INV= investigator; PET= positron emission tomography; R²: Rituximab+Revlimid (lenalidomide);

Table 1. Notes: *; grouped term,

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The improvement in median PFS of more than 8 months with addition of tafasitamab to lenalidomide and rituximab is statistically significant and clinically meaningful for patients with R/R FL grade 1-3a. These results are supported by secondary endpoints (ORR) and PET-CR rate and corroborated by several sensitivity analyses and a favourable trend on OS.

The safety profile was generally consistent with the known safety profile of tafasitamab in R/R LBCL and manageable. Safety and tolerability were comparable with the addition of tafasitamab to lenalidomide and rituximab, with an increased risk of severe neutropenia and severe infections.

### 3.7.2. Balance of benefits and risks

Addition of tafasitamab to rituximab and lenalidomide resulted in significant and clinically meaningful improvement in PFS and a trend towards a favourable OS, although immature. No new safety concerns were identified. The safety profile of tafasitamab in combination with rituximab and lenalidomide as reported in the pivotal study is overall consistent with the already known safety profile of tafasitamab. The benefit of the combination treatment is considered to outweigh the associated toxicities.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall B/R of Minjuvi in combination with lenalidomide and rituximab is positive for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) (Grade 1-3a) after at least one line of systemic therapy.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation requested** | | **Type** |
|---|---|---|
| C.I.6.a | C.I.6.a Addition of a new therapeutic indication or modification of an approved one | Variation type II |

Extension of indication to include in combination with lenalidomide and rituximab treatment of adult patients with relapsed or refractory follicular lymphoma (FL) Grade 1 to 3a after at least one line of systemic therapy for MINJUVI, based on interim results from study INCMOR 0208-301 (inMIND); this is a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of tafasitamab plus lenalidomide and rituximab vs lenalidomide

and rituximab in patients with relapsed/refractory (R/R) follicular lymphoma Grade 1 to 3a or R/R marginal zone lymphoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP and final version 4.0 have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor changes to the PI.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

### Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

These conditions do reflect the advice received from the PRAC.

### *Similarity with authorised orphan medicinal products*

The CHMP by consensus is of the opinion that Minjuvi is not similar to Yescarta, Lunsumio, Gazyvaro and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

### *Additional market protection*

The MAH withdrew the claim of one additional year of market protection in accordance with the Article 14(11) of Regulation (EC) No 726/2004, within the responses to the 2nd RSI and by letter to the CHMP dated 11 November 2025.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR- Procedural steps taken and scientific information after authorisation" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Minjuvi-H-C-II-EMA/VR/0000255975'