14 November 2019
EMA/CHMP/693880/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revlimid

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/000717/II/0107

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

AE	Adverse event
AESI	Adverse event of special interest
ANSM	Agence nationale de sécurité du médicament (French Agency)
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRu	Complete response unconfirmed
CSR	Clinical study report
DLBCL	Diffuse large B-cell lymphoma
DMC	Data Monitoring Committee
DOR	Duration of response
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EMZL	Extranodal marginal zone lymphoma
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe d'Etude des Lymphomes Folliculaires
HLT	High-level term
HR	Hazard ratio
HRQOL	Health-related quality of life
iNHL	Indolent non-Hodgkin lymphoma
IL-6	Interleukin-6
IRC	Independent Response Committee or Independent Review Committee
ITT	Intent-to-treat
IWG	International Working Group
IWGRC	International Working Group Response Criteria
LDH	Lactate dehydrogenase
LYSARC	Lymphoma Academic Research Organization
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Product Agency (Swedish Agency)
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NMZL	Nodal marginal zone lymphoma
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
R2	Lenalidomide in combination with rituximab
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SCT	Stem-cell transplant
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SMZL	Splenic marginal zone lymphoma
SPM	Second primary malignancy
TEAE	Treatment-emergent adverse event
tFL	Transformed follicular lymphoma

TNF-α	Tumour necrosis factor alpha
TTNLT	Time to next antilymphoma treatment
TTP	Time to progression
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, Celgene Europe BV submitted to the European Medicines Agency on 21 January 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; the PL is updated in accordance. An updated EU RMP (version 36.2) has also been submitted.

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

Revlimid was designated as an orphan medicinal product EU/3/03/177 on 19 June 2007 in the following indication: treatment of multiple myeloma; EU/3/04/192 on 17 June 2013 in the following indication: treatment of myelodysplastic syndromes; and EU/3/11/924 on 12 July 2016 in the following indication: treatment of mantle cell lymphoma.

The new indications, which are the subject of this application, fall within the separate orphan designations: EU/3/12/1097 on 24.01.2013 in the following indication: treatment of follicular lymphoma; and EU/3/15/1473 on 24.04.2015 in the following indication: treatment of marginal zone lymphoma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0279/2017 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.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	21 January 2019
Start of procedure:	1 March 2019
CHMP Rapporteur Assessment Report	30 April 2019
CHMP Co-Rapporteur Assessment Report	30 April 2019
PRAC Rapporteur Assessment Report	30 April 2019
PRAC members comments	7 May 2019
PRAC Outcome	16 May 2019
CHMP members comments	20 May 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2019
Request for supplementary information (RSI)	29 May 2019
CHMP Rapporteur Assessment Report	26 August 2019
PRAC Rapporteur Assessment Report	26 August 2019
PRAC members comments	28 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur Assessment Report	13 September 2019
2nd Request for supplementary information (RSI)	19 September 2019
PRAC and CHMP Rapporteur Assessment Report	30 October 2019
PRAC members comments	31 October 2019
PRAC Outcome	31 October 2019
CHMP members comments	4 November 2019
Updated CHMP Rapporteur Assessment Report	8 November 2019
Opinion	14 November 2019

2. Scientific discussion

2.1. Introduction

Lenalidomide (Revlimid) is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties (Revlimid Summary of Product Characteristics [SmPC], 2017). Cellular activities of lenalidomide are mediated by binding to its target cereblon, a component of a cullinring E3 ubiquitin ligase enzyme complex. In vitro, in the presence of drug, substrate proteins (including Aiolos, Ikaros, and CK1α) are recruited to cereblon and targeted for ubiquitination and subsequent proteosomal degradation leading to direct cytotoxic and immunomodulatory effects. In vitro, lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumour cells including multiple myeloma, mantle cell lymphoma (MCL), and del (5q) myelodysplastic syndromes, FL, and MZL.
Immunomodulatory properties of lenalidomide include increased number and activation of T and natural killer (NK) cells leading to direct and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via increased secretion of interleukin-2 and interferon-gamma, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., tumour necrosis factor alpha [TNF-α] and interleukin-6 [IL-6]) by monocytes.

A marketing authorisation has been granted for Revlimid in the following indications:

- Multiple myeloma

  Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

  Revlimid as combination therapy (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

  Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

- Myelodysplastic syndromes

  Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5qcytogenetic abnormality when other therapeutic options are insufficient or inadequate.

- Mantle cell lymphoma

  Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma

Problem statement

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment that vary from indolent (iNHL) to aggressive malignancies.

Follicular lymphoma and MZL are 2 major types of iNHLs; FL is the most common subtype of iNHL, constituting approximately 70% of iNHLs and approximately 20% to 25% of all NHLs (Bello, 2012; Sousou, 2010), followed by MZL (approximately 5% to 17% of all NHLs)

Follicular lymphoma originates from germinal center (GC) B cells and is characterized by a nodular growth pattern (Kahl, 2016; Smith, 2013). The FL cells consist of a mixture of centrocytes (small to medium sized cells) and centroblasts (large cells). A higher proportion of centroblasts correlates with the grade of the disease (Kahl, 2016). The WHO adopted grading from 1 to 3 based on the number of centroblasts counted per high power field (DeVita, 2014; Kahl, 2016; Smith, 2013). Grade 3 is often further subdivided into Grades 3a and 3b. Grade 3a is typically treated similarly to Grade 1 or 2 FL, while Grade 3b is treated as an aggressive lymphoma (Kahl, 2016; Smith, 2013).

In Europe, an incidence of approximately 5 per 100,000 person years for FL was reported during the period from 1996 to 2004. An incidence rate in Europe for MZL of 0.42 per 100,000 persons was estimated.

Follicular lymphoma is clinically characterized by disseminated disease at diagnosis, a generally indolent clinical course, and recurrent, increasingly treatment-resistant relapses. Most patients experience multiple relapses requiring multiple lines of treatment until eventually patients exhaust treatment options and develop fatal disease resistant to available therapy. The response rate, quality of response (CR *versus* partial response [PR], DOR), progression-free survival (PFS), and overall survival (OS) progressively decrease with each successive treatment.

The main goal of treatment in the previously treated disease setting is to achieve deep durable remissions with prolonged PFS in order to prevent disease related complications, without incurring significant treatment related toxicities. Despite recent improvement in treatment options an unmet need remains.

Rationale for the proposed change:

In follicular lymphoma (FL), lenalidomide has been shown to restore defective immunological synapse formation and increase NK cells and subsets of T cells in the blood.
In marginal zone lymphoma (MZL), lenalidomide stimulated immune mediated killing with a concomitant increase ingranzyme B secretion implicating activation of NK cells.

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and ADCC.
In FL and MZL, the combination of lenalidomide and rituximab (R^2) acts by complementary mechanisms including activation of NK and T cells and immune synapse formation resulting in increased ADCC and direct tumour apoptosis *in vitro*.
The activity demonstrated by R^2 in previously treated indolent non-Hodgkin lymphoma (iNHL), particularly the CR rates (35% to 41%), compared favourably with single-agent lenalidomide (CR: 9% to 20%) (Leonard, 2015; Witzig, 2009) and single-agent rituximab (CR: approximately 3% to 20%).

The proposed indication was applied as follows:

- REVLIMID in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma.

Following the evaluation of this application the indication was revised as follows:

Follicular lymphoma

Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

2.2. Non-clinical aspects

Non-clinical data were previously provided for Lenalidomide regarding pharmacology, pharmacokinetics and toxicology. For this application, pharmacology studies were provided to support lenalidomide in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma or marginal zone lymphoma.

2.2.1. Introduction

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.

Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.

The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells.

The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

2.2.2. Pharmacology

Primary pharmacodynamic studies

Table 1: *Summary of in vitro activity of lenalidomide*

Type of Study Study reference	Purpose	Test system	Main findings
Natural Killer (NK) Cell–Mediated Cytotoxicity in Mantle Cell Lymphoma (MCL) Preclinical Models ref 7879-025	to evaluate -the antiproliferative activity of lenalidomide and ibrutinib in MCL cell lines -the immunomodulatory activity of lenalidomide and ibrutinib against multiple MCL cell lines -the effect of lenalidomide on Aiolos and Ikaros in MCL cell lines and NK cells.	Mantle cell lymphomas cell lines proliferation assay flow cytometry	Lenalidomide treatment results in degradation of Aiolos and Ikaros in both MCL cell lines and CD56+ NK cells. Lenalidomide exerts antitumour activity against MCL cell lines mainly through a modulation of NK cell–mediated cytotoxicity. Immune co-cultures treated with lenalidomide are active against MCL cell lines with differing sensitivity to ibrutinib, including cell lines that are resistant to clinically relevant concentrations of ibrutinib (180 nM). Ibrutinib inhibits NK cell–mediated cytotoxicity against MCL cell lines.
Effects on Paediatric Diffuse Large B-cell Lymphoma (DLBCL) Cell Lines	to characterize the cell autonomous effects of lenalidomide against cell lines derived from	DLBCL cell lines: U698M, U2940, and SUDHL-5	Lenalidomide reduced proliferation by 42% in U2940 and by 9% in SUDHL-5 at 10 µM. Lenalidomide treatment did not result in decreased proliferation of U698M.

ref 8146-017	pediatric patients with DLBCL.		Lenalidomide did not increase apoptosis in U698M or U2940 cells. Lenalidomide demonstrates anti-proliferative activity in 1/3 juvenile DLBCL cell lines. No apoptotic activity by lenalidomide was observed in any cell line tested. The immune mediated effects of lenalidomide against pediatric DLBCL cell lines were not examined.
Effect of Lenalidomide Treatment as Single Agent or in Combination with Rituximab in a Preclinical Model of Splenic marginal zone lymphoma ref 8195-008	to assess antiproliferative and pro-apoptotic effects of lenalidomide alone and in combination with Rtx	SMZL cell line: SLVL ^{3}H-thymidine incorporation and Annexin-V/To-Pro-3 staining	Lenalidomide displayed dose-dependent antiproliferative and pro-apoptotic activity in the human SMZL model. Lenalidomide also induced anti-CD3 stimulated PBMCs to kill SMZL cells in a dose-dependent manner that correlated with Granzyme B release. In combination with Rtx, lenalidomide displays an additive, effect on proliferation, apoptosis, and PBMC mediated killing of SMZL cells when compared to single agent activity alone.
Effect as Single Agent and in Combination with Rtx in FL and of Splenic Marginal Zone Lymphoma (SMZL) ref 8195-014	to determine: - the effect of Len on proliferation and activation of T, NK and NK T subsets in PBMCs from healthy donors and FL patients ex vivo - the effect of R2 on PBMC mediated ADCC and cell autonomous apoptosis against FL cell lines - compare the effect of R2 with other chemo- and novel agents in combination with Rtx on PBMC mediated ADCC and cell autonomous apoptosis against FL cell lines - the effect of R2 on PBMC mediated ADCC and cell autonomous apoptosis against MZL cell lines	FL cell lines: DOHH2 and RL; SMZL cell line: SLVL. 10 to 10000 nM 3 to 5 days	Lenalidomide enhanced proliferation and activation of T, NK, and NK T subsets in FL PBMCs in a concentration-dependent manner. Lenalidomide did not negatively affect PBMC viability. The R2 combination (lenalidomide + rituximab) enhanced FL patient PBMC mediated antibody-dependent cellular cytotoxicity (ADCC) against parental and chemoresistant FL cell lines. The R2 combination was more potent at inducing PBMC-mediated ADCC than Rtx combined with chemotherapeutic/novel agents tested. The R2 combination additively or synergistically enhanced the autonomous cytotoxicity in FL cell lines as compared to the combination of Rtx with other chemotherapeutic/novel agents. The R2 combination enhances MZL patient PBMC mediated ADCC against MZL cell line. Lenalidomide enhanced autonomous cytotoxicity in the MZL cell line.
Effect as Single Agent and in Combination with Rituximab (Rtx) on T and NK Cell Lytic Immune Synapses in Follicular Lymphoma (FL) Ex Vivo refcc5013-10202017ar	to determine the effect of: - lenalidomide, rituximab and the combination on T and NK lytic immune synapse *ex vivo* from NK and T cells from PB and LN biopsies in treatment naïve FL patients	Lymph node (LN) single cell suspension and peripheral blood (PB) from patients with FL; NK cells from patient PBMC 1 µM	Lenalidomide alone enhanced immune synapse formation between CD4+T or CD8+T with FL B cells with an increase in F-actin polymerization. There was an associated increase P-Tyr expression at the CD4+T and Granzyme B at CD8+T immune synapse. Lenalidomide alone enhanced the immune synapse formation between NK cells from PB and B cells with an

	-lenalidomide, rituximab and the combination on T and NK autologous cytotoxicity assay	1 to 48 hours	increase in F-actin polymerization and increased Granzyme B expression at the immune synapse. Treatment of tumour-infiltrating CD8+ T and NK cells from PB of FL patients with lenalidomide enhanced the autologous FL tumour cell death.
Selective Growth Inhibitory Effects on Adult T-Cell Lymphoma/Leukemia (ATL) Cell Lines and Potential Mechanism of Action ref OU22122015HI	to examine direct anti-ATL cell effects of lenalidomide in vitro with 4 different ATL cell lines and 1 non-ATL type PTCL cell line	ATL cell lines: Hut102, ED40515, Su9T1, S1T, OATL4, OATL9, ST1, KOB, KK1, SO4; HTLV-1 transformed cell lines: MT-2, MT-4 and C8166 Peripheral T-cell lymphoma cell line: Hut78 T-cell lines: Jurkat, MOLT4, HL60; Monocyte cell lines: K562; Multiple myeloma cell lines: NCI-H929 and RPMI-8226. 0.1, 1, 10, and 100 µM 3 days	All but one of the ATL and non-ATL cell lines showed no or very poor responses to lenalidomide treatment (10 µM for three days). The Hut102 cell line exhibited highly sensitive behavior to lenalidomide, i.e., cell viability decreased to less than 20% at 1 µM lenalidomide. The mRNA expression levels of cereblon was highest in the HuT102 cell line compared with other ATL cell lines, and low for the expression of Ikaros family zinc finger 1 (IKZF1) to IKZF3.

Table 2 Summary of in vivo activity of lenalidomide

Type of Study Study reference	Purpose	Test system	Main findings
Evaluation on Xenografted Severe Combined Immunodeficient (SCID) Mouse Model Using Human ATL Cell Line HUT102 ref UM13102015KM	to evaluate the efficacy of lenalidomide against ATL using the tumour bearing SCID mouse model.	Female CB.17 SCID mice subcutaneously implanted with HUT102 cells (5.0 x 106 cells/mL). 5 to 6 females per group 10, 50, and 100 mg/kg/day PO 28 days	Lenalidomide suppressed HUT102 growth when started at the day of implantation and when administration was started after the growth of HUT102 cells in the SCID mice, i.e., therapeutically.

Secondary pharmacodynamic studies

Effects of lenalidomide (10 µM, during 19 days or 12 days with 7 days washout) on neutrophil maturation were evaluated using flow cytometry starting with bone marrow CD34+ cells from healthy volunteers. Cell numbers, differentiation, and apoptosis were measured twice a week during the experiment. Results showed that late-stage neutrophil maturation was blocked by lenalidomide, whereas cell viability was not affected. In case of wash out period during the experiment, 50% recovery of normal maturation was observed following the 3-day washout period, and control values were reached after one week.

2.2.3. Pharmacokinetics

Additional pharmacokinetic studies were not submitted.

2.2.4. Toxicology

Additional toxicology studies were not submitted.

2.2.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for the Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL) indication requested in this variation dossier was addressed in the updated ERA submitted recently with the EMA/H/C/000717/II/102G procedure. Based on the performed Phase I ERA, the intended medicinal use of lenalidomide are considered to be of negligible risk to the environment. As the updated ERA covering FL and MZL indications has already been submitted through the procedure II/102G, the ERA is not provided as part of this submission.

2.2.6. Discussion on non-clinical aspects

Complementary pharmacologic studies were provided for lenalidomide to support the proposed indication (Lenalidomide in combination with rituximab in FL and MZL) in different cell lines *in vitro* and in ATL *in vivo*.

Several in vitro studies were provided on mantle cell lymphoma cell lines, DLBCL, marginal zone lymphoma, follicular lymphoma and adult T-Cell Lymphoma/Leukaemia with lenalidomide as single agent or in combination with Rituximab. Lenalidomide exerts anti-tumour activity against MCL cell lines mainly through a modulation of NK cell–mediated cytotoxicity and is active against MCL cell lines resistant to ibrutinib. In paediatric DLBCL, lenalidomide demonstrates anti-proliferative activity in some (not all, 1/3) juvenile DLBCL cell lines with no associated apoptotic activity in any cell line tested. Concerning human SMZL model, lenalidomide displayed dose-dependent anti-proliferative and pro-apoptotic activity. In combination with Rituximab, effects on proliferation, apoptosis, and PBMC mediated killing of SMZL cells were additive. Lenalidomide expands and activates effector T, NK, and NKT subsets and increases cytokine production in both healthy and FL patient PBMC ex vivo and the combination with Rituximab demonstrated an enhanced effect on immune-mediated and direct cytotoxicity against FL and MZL cell lines. The growth inhibitory effects of lenalidomide was examined on 13 ATL related cell lines and 5 non-ATL type T-cell lymphoma, most of ATL or non-ATL cell lines showed no or very poor responses to lenalidomide treatment.

The effects of lenalidomide, as a single agent or in combination with rituximab demonstrated direct antiproliferative activity and apoptosis induction that was enhanced with the drug combination. The data provided support the proposed indication by demonstrating activity of the Lenalidomide Rituximab combination in NHL in vitro with FL and MZL patient cells. Moreover Lenalidomide was demonstrated to suppress the growth of adult T-cell lymphoma/leukaemia (ATL) on xenografted severe combined

immunodeficient (SCID) mouse model.
Furthermore, lenalidomide was found to be effective when administration was started after the growth of HUT102 cells. Cell viability and proliferation of CD34+ derived cells on myeloid cultures exposed to lenalidomide 10 µM was not affected under all treatment conditions. Washout for at least two days favors cell maturation, but it was not enough to recover a normal differentiation rate in vitro. Up to five or seven days were needed to recover control values.

2.2.7. Conclusion on the non-clinical aspects

The data provided demonstrate an anti-tumour activity in B-cell lymphomas, of which SMZL and FL are subtypes and supports the development of Lenalidomide and Rituximab as a therapeutic in the treatment of SMZL and FL.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3 Tabular overview of clinical studies

Clinical Studies in Previously Treated Follicular Lymphoma and Marginal Zone Lymphoma	
AUGMENT (CC-5013-NHL-007) (Registration Study)	A Phase 3, Double-blind Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) versus Rituximab Plus Placebo in Subjects with Relapsed/Refractory Indolent Lymphoma
MAGNIFY[a] (CC-5013-NHL-008) (Supportive Study)	A Phase 3b Randomized Study of Lenalidomide (CC-5013) Plus Rituximab Maintenance Therapy Followed by Lenalidomide Single-agent Maintenance versus Rituximab Maintenance in Subjects with Relapsed/Refractory Follicular, Marginal Zone, or Mantle Cell Lymphoma
Clinical Study in Indolent Non-Hodgkin Lymphoma	
CC-5013-NHL-001 (Additional Study)	A Phase 2, Multicenter, Single-arm, Open-label Study to Evaluate the Safety and Efficacy of Single-agent Lenalidomide (Revlimid®, CC-5013) in Subjects with Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma

CC-5013 = lenalidomide; FL = follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; R^2 = lenalidomide in combination with rituximab; SCE = Summary of Clinical Efficacy; tFL = transformed follicular lymphoma.
Note: Refer to Table 2 and Table 3 for more details of the studies.
[a] All enrolled subjects received 12 cycles of R^2 treatment (Initial Treatment Period) before randomization, and the efficacy data from the Initial Treatment Period is included in this SCE for subjects with FL Grades 1 to 3a and MZL. The efficacy data for subjects with MCL, tFL, and FL Grade 3b are included in CSR NHL-008.

Ongoing Clinical study – SPM data presented under Clinical Safety

Study RELEVANCE (ongoing)	phase 3, randomized, active-controlled, open-label study of R2for 18 4 week cycles followed by R for 6 8-week cycles *vs* R- CHEMO for 6 to 8 cycles followed by rituximab for up to twelve 8-week cycles in subjects with previously untreated FL (Grades 1 to 3a) requiring systemic treatment according to "Groupe d'Etude des Lymphomes folliculaires" (GELF) criteria.

2.3.2. Pharmacokinetics

No new information regarding clinical pharmacology was submitted.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

In Pivotal study AUGMENT (CC-5013-NHL-007) the starting dose of lenalidomide is 20 mg administered daily for 21 consecutive days in each 28-day cycle for up to 12 cycles.

Table 4 *Activity of lenalidomide in combination with rituximab in Phase 2 trials that enrolled previously treated Follicular Lymphoma patients*

References	Dose Regimen/Treatment Duration for Len + Rit Arm	Study Population	N	ORR[a] (FL)	CR[a] (FL)
Tuscano, 2014	**C1 and C2**: **Len:** 20 mg/d on D1 to D21 Q28d **Rit:** 375 mg/m^2, 4 weekly infusions starting on C1D15 4 additional doses may be given if < CR at the end of C2 **Maintenance**: Len mono until PD or toxicity	Previously Treated iNHL, ≥ 1 prior treatment, SCT experienced or ineligible	30 FL = 22	77%	41%
Chong, 2015	**Week 1 through 21** **Len:** 10 mg on D1 to D28 Q28d, for 2 cycles **Rit:** then add 4 weekly infusions at 375 mg/m^2 (Len continues during and after Rit) **Maintenance**: if SD or response after 5 cycles, patients are allowed to continue receiving Len monotherapy	iNHL (refractory to Rit)	50 FL: 26	C2: 19%[b] (FL: 5/26) C5: 65% (FL: 17/26)	35%
Leonard, 2015	**Len:** 15 mg/d, escalation per cycle to 20 mg/d, then 25 mg/d if tolerated on D1 to D21 Q28d, for 12 cycles **Rit:** 4 weekly infusions at 375 mg/m^2	Previously treated FL (nonrefractory to Rit)	FL: 46	76%	39%

C = cycle; CR = complete response; d = day; D = days; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; Len = lenalidomide; ORR = overall response rate; PD =progressive disease: PFS = median progression-free survival; Q28d = every 28 days; Rit = rituximab; SD = stable disease; SCT = stem-cell transplantation.

[a] Based on efficacy-evaluable patients unless otherwise indicated.

[b] The ORR reported at 8 weeks (ie, end of C2) is for lenalidomide monotherapy.

Source: CSR NHL-007 Table 3

In the randomized Phase 2 Cancer and Leukemia Group B (CALGB) 50401 trial (previously treated FL n = 46), the administration of 12 cycles of R^2 (lenalidomide in Cycles 1 to 12 and rituximab given in 4 weekly infusions in Cycle 1) *versus* lenalidomide monotherapy resulted in high response rates (ORR = 76% and CR = 39%) (Leonard, 2015).

The number of cycles for R^2 in AUGMENT was calculated based on lenalidomide schedule (i.e., up to 12 cycles of lenalidomide).

In previously treated FL/MZL the proposed duration of R^2 treatment is 12 cycles (lenalidomide:Cycles 1 to 12; rituximab: 4 weekly infusions in Cycle 1, and Day 1 of Cycles 2 to 5 for a total of 8 doses) as studied in AUGMENT. The choice of 12 cycles of R^2 in previously treated FL/MZL is supported by the published studies in relapsed or refractory FL/MZL (Table above).

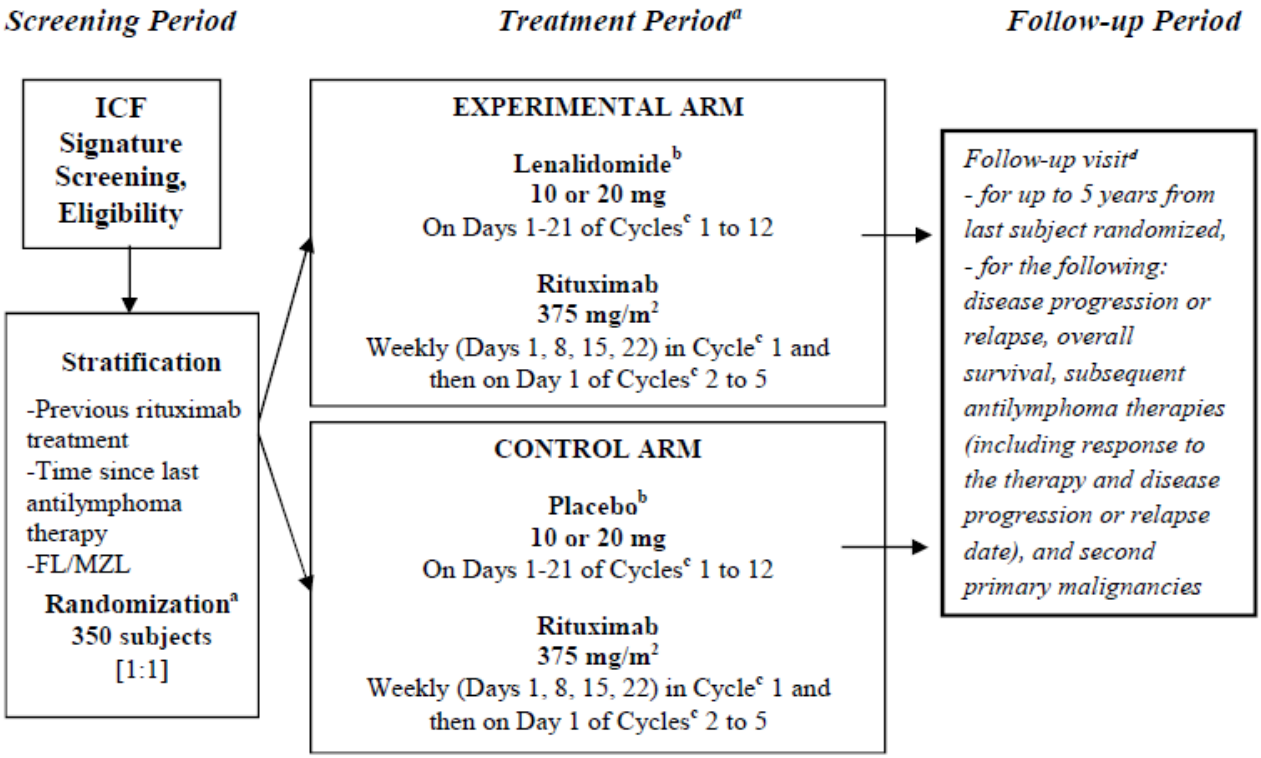
2.4.2. Main study(ies)

AUGMENT (Study CC-5013-NHL-007)

A Phase 3, Double-blind Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) *versus* Rituximab Plus Placebo in Subjects with Relapsed/Refractory Indolent Lymphoma.

Methods

Figure 1 Overall study design



CrCl = creatinine clearance; FL = follicular lymphoma; ICF = informed consent form; MZL = marginal zone lymphoma.

[a] Treatment had to begin as soon as possible after randomization but no later than 1 week after randomization.

[b] 10 mg if CrCl ≥ 30 mL/min but < 60 mL/min; 20 mg if CrCl ≥ 60 mL/min.

[c] Cycle defined as lenalidomide or placebo Cycle of 28 days (21-day treatment and 7-day rest period).

[d] All randomized subjects were followed for disease progression and overall survival using the same schedule described in Table 7. This included patients who discontinued the protocol-specified treatment or the study early for any reason without documented evidence of disease progression or relapse.

Study participants

Diagnosis and main criteria for inclusion

1. Males and females ≥ 18 years of age who signed an informed consent form.

2. Histologically confirmed MZL or Grade 1, 2, or 3a FL (CD20+ by flow cytometry or histochemistry) as assessed by investigator or local pathologist.

3. Previously treated with at least one prior systemic chemotherapy, immunotherapy or rituximab plus chemotherapy and had received at least 2 previous doses of rituximab (no antibody agents within 8 weeks prior to Cycle1 Day 1 and no radio-immunotherapy within 6months prior to Cycle1 Day 1).prior to Protocol Amendment 3, rituximab-naïve patients were allowed in the study] Modified Inclusion Criterion 4 to no longer allow rituximab-naïve subjects in the study. This modification was made based on the advice of some regulatory agencies who had suggested limiting the number of rituximab-naïve subjects enrolled in order to limit bias in the final analysis. The recommendation was to keep the number of rituximab-naïve subject's under 25%.

4. Had documented relapsed, refractory, or PD after treatment with systemic therapy and was not rituximab-refractory.

5. Bi-dimensionally measurable disease with at least one nodal lesion > 1.5 cm in diameter or at least one extranodal lesion > 1.0 cm in both long and short diameters.

6. Must have been in need of treatment as assessed by the investigator.

7. Performance status≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale.

8. Adequate bone marrow, liver, and renal function.

Main exclusion criteria

The presence of any of the following excluded a subject from enrollment:

1. Histology other than FL and MZL or clinical evidence of transformed lymphoma by investigator assessment.

2. Grade 3b FL.

3. Subjects taking corticosteroids during the last one week prior to Cycle 1 Day 1, unless administered at a dose equivalent to ≤ 20 mg/day prednisone or prednisolone (over this week).

4. Major surgery (excluding lymph node or BMB) within 28 days prior to signing informed consent.

5. Systemic therapy within 28 days prior to Cycle 1 Day 1 dosing or use of the following:

a. Antibody agents within 8 weeks prior to Cycle 1 Day 1 dosing

b. Radio immunotherapy within 6 months prior to Cycle 1 Day 1 dosing

6. Seropositive for or active viral infection with hepatitis B virus (HBV):

- Hepatitis B surface antigen (HBsAg) positive
- Hepatitis B surface antibody (anti-HBs) positive and/or hepatitis B core antibody

(anti-HBc) positive, and HBsAg negative and detectable viral DNA

Notes: Subjects who were anti-HBs positive and/or anti-HBc positive, and HBs Ag negative but viral DNA negative were eligible; Subjects who were seropositive because of HBV vaccination were eligible (anti-HBs positive, anti-HBc negative, and HBsAg negative)

7. Hepatitis C virus (HCV) positive subjects with chronic HCV hepatitis or subjects with an active HCV infection requiring antiviral medication (at time of randomization).

8. Known seropositive for or active viral infection with human immunodeficiency virus (HIV).

9. Life expectancy < 6 months.

10. Known sensitivity or allergy to murine products.

11. Prior history of malignancies, other than FL or MZL, unless the subject had been free of the disease for ≥ 5 years. Exceptions included a history of previously treated: a. Basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and related localized non-melanoma skin cancer. Carcinoma in situ of the cervix

12. Prior use of lenalidomide.

13. Known allergy to thalidomide.

14. Neuropathy > Grade 1.

15. Presence or history of central nervous system (CNS) involvement by lymphoma.

16. Subjects who were at a risk for a thromboembolic event and were not willing to take venous thromboembolism (VTE) prophylaxis.

17. Uncontrolled inter current illness.

18. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the ICF.

19. Pregnant or lactating females.

20. Any condition, including, for example, coronary artery disease, congestive heart failure, pulmonary disease, active, severe infections, chronic renal or immunological disease, or the presence of laboratory abnormalities that places the subject at unacceptable risk if he/she were to participate in the study or that could have confounded the ability to interpret data from the study.

Treatments

Eligible subjects entering the Treatment Phase were randomized in a 1:1 ratio using an interactive voice response system (IVRS) into one of the 2 arms (experimental or control).

- Experimental Arm (R^2):
    - Rituximab 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, 22) and on Day 1 of every 28-day Cycle from Cycles 2 through 5

      plus

    - Lenalidomide once daily on Days 1 to 21 of every 28-day Cycle up to 12 cycles
- Control Arm:
    - Rituximab 375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15, 22) and on Day 1 of every 28-day Cycle from Cycles 2 through 5

      plus

    - Placebo (identical matched capsule) once daily on Days 1 to 21 of every 28-day Cycle up to 12 cycles

Co-administration (i.e., lenalidomide intake during the rituximab infusion) was to be avoided. Due to the duration of the rituximab infusion and potential infusion-related reactions to rituximab, administration of lenalidomide before rituximab was to be considered.

Celgene supplied lenalidomide 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg capsules and the respective matching placebo capsules for oral administration.

Objectives

Primary

- To compare the efficacy of lenalidomide in combination with rituximab (R^2) to rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma. Efficacy determination was based upon progression-free survival (PFS) as the primary endpoint, as assessed by the Independent Review Committee (IRC) using the 2007 International Working Group Response Criteria (IWGRC) without positron emission tomography (PET).

Secondary

- To compare the safety of R^2 *versus* rituximab plus placebo
- To compare the efficacy of R^2 *versus* rituximab plus placebo using other parameters of efficacy:
    - Durable complete response rate (DCRR), overall response rate (ORR), complete response (CR) rate, duration of response(DOR), and duration of complete response (DOCR) by the 2007IWGRC without PET
    - Overall survival (OS), event-free survival (EFS), and time to next anti-lymphoma treatment (TTNLT)

Exploratory

- To compare the effects of R^2 *versus* rituximab plus placebo on:
    - TTF, time to next chemotherapy treatment (TTNCT), and response rate to next anti-lymphoma treatment (RTNLT)
    - CR/CRu rate in subjects with FL based on the 1999 IWGRC (Cheson, 1999)
    - PFS on next anti-lymphoma treatment (PFS 2)
    - time to histological transformation
- Health-related quality of life (QOL) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30(QLQ-C30) and Euro-Qol Group's questionnaire 5 dimensions (EQ-5D)

Outcomes/endpoints

Primary endpoint:

Progression Free Survival defined as the time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurred first.

Secondary/exploratory endpoints:

ORR, CR rate, DOCR, DOR, OS, EFS, TTNLT, TTNCT, PFS2, time to histological transformation.

Sample size

To fulfil the primary objective of the study, it had to be shown that the experimental arm was superior to the control arm on the primary endpoint at one-sided α-level of 0.025. It was hypothesized that the median PFS was 17.6 months in the experimental arm and 11 months in the control arm (corresponding HR of 0.625, assuming that FL and MZL subjects had the same median PFS). For 90% power to detect this difference with one-sided α-level of 0.025, a total of 193 PFS events was required.

Based on the rate of accrual anticipated in this study and annual dropout rate of 5%, it was planned to randomize a total of approximately 350 subjects in a 1:1 ratio to the 2 treatment arms and the time to reach the PFS events was expected to be 43 months.

Randomisation

The randomization is stratified as follows:

- previous rituximab treatment (yes, no)
- time since last anti-lymphoma therapy (≤ 2, > 2 years),
- disease histology (FL, MZL)

Blinding (masking)

For this trial, study subjects, investigators, staff, and Celgene clinical and medical representatives were all blinded to the treatment assignments. Both lenalidomide and placebo capsules were identical in appearance.

Statistical methods

Analysis population

ITT population: all subjects who were randomized into the trial, regardless of whether they received study treatment or not.

The ITT Population was used for the primary efficacy analysis. Subjects were analysed according to the treatment arm to which they were initially assigned.

mITT population: all randomized subjects who received at least one dose of study medication, had a confirmed diagnosis of relapsed/refractory FL or MZL by central pathology review, except SMZL which was based on local pathology assessment, and had baseline (Screening) and at least one post-baseline tumour assessment for efficacy.

The efficacy analysis was also performed on the mITT Population as supportive evidence and/or sensitivity analysis. Subjects were analyzed according to the treatment arm to which they were initially assigned.

Safety population: all subjects who received at least one dose of study medication.

The Safety Population was used for all safety analyses. Subjects were analyzed according to the treatment which they actually received.

In addition to analyses that include the ITT Population, certain efficacy analyses were performed for subgroups to compare treatments within stratification factors: previous rituximab treatment (yes, no), time since last anti-lymphoma therapy (≤ 2, > 2 years), and histology (FL, MZL).

Time to event endpoints: Kaplan-Meier (KM) survival analyses were performed (unadjusted for the stratification variables) for time-to-event data. The number and percent of subjects censored were provided. Kaplan-Meier product limit method was used to estimate the survivorship function for all time-to-event endpoints (e.g., PFS, OS, EFS). Event rates at specific time points were estimated from KM curves. Medians together with two-sided 95% confidence intervals (CIs), plus standard deviation (StD), minimum, and maximum were provided. The CI was constructed using log-log transformation.

The resulting survival estimates were presented graphically for selected endpoints.

Subjects were stratified according to previous rituximab treatment, time since last anti-lymphoma therapy, and histology. The stratified Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and associated 95% CIs for the HRs.

Categorical endpoints: The Cochran-Mantel-Haenszel (CMH) test with the stratification factors as strata was used for categorical data. The p-values were presented. The probability of rates was estimated using the proportion of subjects with responses with exact two-sided 95% CIs.

Quality of life endpoints: The analyses of the EORTC QLQ-C30 and the EQ-5D were based on all randomized subjects who completed the baseline assessment (at Screening) and had at least one follow-up assessment with the EORTC QLQ-C30 and EQ-5D, respectively. The observed case method and the describable statistics

were used to summarize the observed scores and the change from baseline score by visit and the treatment group for each domain of the QOL assessments.

Health-related quality of life (HRQOL) was assessed using the EORTC QLQ-C30 (Version 3) and the EQ-5D-3L (3 level version) questionnaire at Screening (i.e., baseline), after every 3 cycles during treatment (i.e., Day 1 Cycle 4; Day 1 Cycle 7; Day1 Cycle 10), and at the end of treatment, regardless of the causes. The assessments were completed every 6 months until PD after completion of treatment or discontinuation of treatment for reasons other than PD or relapse.

Analyses of the HRQOL data was detailed in a separate SAP for evaluating patient-reported outcomes in AUGMENT. The objective of the HRQOL analyses was to assess the effect of lenalidomide in combination with rituximab (the R^2 Arm) *versus* rituximab plus placebo (the Control Arm) on HRQOL over time. The global health status/QOL of the EORTC QLQ-C30 was the pre-specified primary domain of interest. The remaining domains and the EQ-5D health utility and visual analog scale (VAS) were assessed as exploratory outcomes.

Missing data

For the analysis of PFS, missing assessments or discontinuations due to reasons other than PD were handled by the censoring rules.

Table 5 Censoring rules used for the Primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
Death before first PD assessment while on study	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Progression documented	Date of earliest assessment which revealed progression determined by IRC	Event
Death or progression after more than 1 missed scheduled visit	Date of last adequate assessment which revealed no progression	Censored
No baseline assessment	Randomization	Censored
No progression, nor death	Date of last adequate assessment with evidence of no progression by IRC	Censored
Study discontinuation for any reason other than death or disease progression	Date of last adequate assessment with evidence of no progression by IRC	Censored
Non-protocol new antilymphoma treatment started prior to progression/death	Date of last adequate assessment with evidence of no progression by IRC before the start of new antilymphoma treatment	Censored

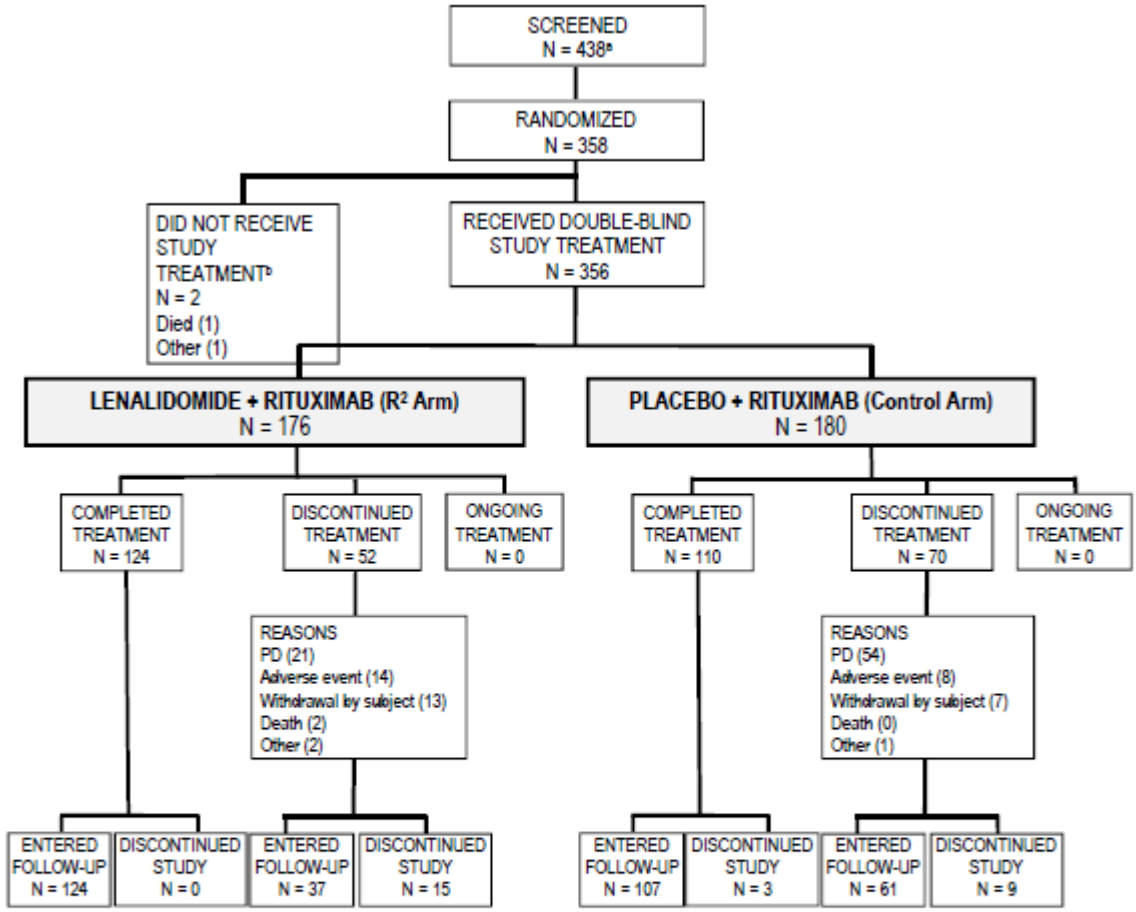
IRC = Independent Review Committee; PD = progressive disease.
Source: FDA, 2007.

In addition, various sensitivity analyses were performed to explore different ways of censoring to confirm the robustness of the planned primary analysis.

Results

Participant flow

Figure 2 Participant flow



FL = follicular lymphoma; MZL = marginal zone lymphoma; PD = progressive disease.

[a] In total, 438 subjects were screened for study participation, of which 18 subjects (4.1%) were screened twice. Of the total 456 screens, 98 were screen failures primarily due to failure of inclusion/exclusion criteria (96.9%). Screen failures either did not meet inclusion criteria (n = 70) and/or met at least one exclusion criterion (n = 28).

[b] Two subjects randomized to the R^2 Arm did not receive study medication: one subject with MZL died due to septic shock after randomization but prior to receiving the first dose of study treatment (Listing 16.2.7.6.2) and one subject with FL discontinued due to Grade 2 dyspnea on Cycle 1 Day 1, prior to administration of the first dose of study drug (Listing 16.2.1.2.1.3).

Table 6 Subject disposition – ITT population

Parameter	FL		MZL		Overall		Overall (N=358)
	Len+Rit (N=147)	Pbo+Rit (N=148)	Len+Rit (N=31)	Pbo+Rit (N=32)	Len+Rit (N=178)	Pbo+Rit (N=180)	
Number of Subjects Treated	**146**	**148**	**30**	**32**	**176**	**180**	**356**
Treatment Disposition[a],n(%)							
Completed treatment	105(71.9)	88(59.5)	19(63.3)	22(68.8)	124(70.5)	110(61.1)	234(65.7)
Entered follow-up	105(71.9)	86(58.1)	19(63.3)	21(65.6)	124(70.5)	107(59.4)	231(64.9)
Discontinued study	0(0.0)	2(1.4)	0(0.0)	1(3.1)	0(0.0)	3(1.7)	3(0.8)
Discontinued treatment	41(28.1)	60(40.5)	11(36.7)	10(31.3)	52(29.5)	70(38.9)	122(34.3)
Entered follow-up	31(21.2)	52(35.1)	6(20.0)	9(28.1)	37(21.0)	61(33.9)	98(27.5)

Discontinued treatment and	10(6.8)	8(5.4)	5(16.7)	1(3.1)	15(8.5)	9(5.0)	24(6.7)
Subjects discontinued lenalidomide/placebo[a], n(%)	**41(28.1)**	**60(40.5)**	**11(36.7)**	**10(31.3)**	**52(29.5)**	**70(38.9)**	**122(34.3)**
Death	1(0.7)	0(0.0)	1(3.3)	0(0.0)	2(1.1)	0(0.0)	2(0.6)
Adverse event	12(8.2)	6(4.1)	2(6.7)	2(6.3)	14(8.0)	8(4.4)	22(6.2)
Progressive disease	17(11.6)	46(31.1)	4(13.3)	8(25.0)	21(11.9)	54(30.0)	75(21.1)
Withdrawal by subject	11(7.5)	7(4.7)	2(6.7)	0(0.0)	13(7.4)	7(3.9)	20(5.6)
Lost to follow up	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Protocol violation	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other	0(0.0)	1(0.7)	2(6.7)	0(0.0)	2(1.1)	1(0.6)	3(0.8)
Subjects discontinued rituximab[a],n(%)	**11(7.5)**	**14(9.5)**	**8(26.7)**	**4(12.5)**	**19(10.8)**	**18(10.0)**	**37(10.4)**
Death	0(0.0)	0(0.0)	1(3.3)	0(0.0)	1(0.6)	0(0.0)	1(0.3)
Adverse event	4(2.7)	1(0.7)	2(6.7)	1(3.1)	6(3.4)	2(1.1)	8(2.2)
Progressive disease	4(2.7)	12(8.1)	2(6.7)	3(9.4)	6(3.4)	15(8.3)	21(5.9)
Withdrawal by subject	3(2.1)	1(0.7)	2(6.7)	0(0.0)	5(2.8)	1(0.6)	6(1.7)
Lost to follow-up	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Protocol violation	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other	0(0.0)	0(0.0)	1(3.3)	0(0.0)	1(0.6)	0(0.0)	1(0.3)
Study Disposition[b],n(%)							
On-going	114(77.6)	107(72.3)	21(67.7)	26(81.3)	135(75.8)	133(73.9)	268(74.9)
Discontinued study	33(22.4)	41(27.7)	10(32.3)	6(18.8)	43(24.2)	47(26.1)	90(25.1)
Subjects discontinued from study[b],n(%)	**33(22.4)**	**41(27.7)**	**10(32.3)**	**6(18.8)**	**43(24.2)**	**47(26.1)**	**90(25.1)**
Death	11(7.5)	24(16.2)	5(16.1)	2(6.3)	16(9.0)	26(14.4)	42(11.7)
Adverse Event	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Withdrew Consent	21(14.3)	13(8.8)	4(12.9)	4(12.5)	25(14.0)	17(9.4)	42(11.7)
Lost to follow-up	1(0.7)	3(2.0)	0(0.0)	0(0.0)	1(0.6)	3(1.7)	4(1.1)
Protocol Violation	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other[c]	0(0.0)	1(0.7)	1(3.2)	0(0.0)	1(0.6)	1(0.6)	2(0.6)
Duration of follow-up[d](months)							
N	147	148	31	32	178	180	358
Mean	28.18	27.64	23.24	28.08	27.32	27.72	27.52
StD	11.043	10.416	13.190	10.089	11.558	10.332	10.945
Median	29.24	27.94	25.23	28.93	28.50	28.21	28.30
Min, Max	0.5,50.9	0.6,50.9	0.1,47.3	2.3,51.3	0.1,50.9	0.6,51.3	0.1,51.3

FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R2 Arm); Max = maximum; Min = minimum; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm);StD = standard deviation.

a Percentages are calculated using the Safety Population.

b Percentages are calculated using the ITT Population.

c "Other" reasons include one subject was noncompliant (R^2 Arm) and one subject was moving (Control Arm).

d Duration from date of randomization to date of death or last date known alive.

Data cutoff: 22 Jun 2018.

Recruitment

First subject first visit: 01 Nov 2013

First subject randomized: 13 Feb 2014

Last subject randomized: 26 Jan 2017

Data cut-off (primary analysis): 22 Jun 2018

Conduct of the study

Protocol amendments

- *Protocol Amendment 1 (dated 17 Jul 2013)*

Amendment 1 changed the criteria to assess response from the 1999 IWGRC to the 2007 IWGRC (without PET). The change enabled the inclusion and appropriate assessments of FL and MZL subjects in the study, as these 2007 IWGRC for malignant lymphoma allowed the inclusion of extranodal disease as measurable disease. Overall, 30 subjects were enrolled under Amendment 1 of the protocol.

- *Protocol Amendment 2 (dated 22 May 2014)*

- Amended Exclusion Criteria to exclude severe infections ; Amended Inclusion Criteria to ensure that the female study subjects to be also informed about the pregnancy prevention guidelines provided in the Rituximab/Mabthera SmPC (as long as the infertility was not definitely confirmed); Revised the CT/MRI scan timing requirement after Year 5 to one per year. Amendment of Inclusion Criterion thus allowing subjects with only extranodal lesions to be eligible. Amended Exclusion Criterion allowing subjects with a history of HCV, and who received antiviral treatment and who had no detectable HCV RNA levels for at least 12 months. Amended Inclusion Criterion to require BMB at Screening only in case of abnormal blood counts (and not in all cases). Bone marrow biopsies were needed to confirm a CR and, since a large proportion of subjects were not anticipated to achieve a CR, limiting the BMB at Screening was to spare many subjects an invasive procedure.
- Revised the exclusionary time period from ≥ 10 to ≥ 5 years for prior malignancies and addition of precision on the exceptions of localized non-melanoma skin cancer. Basal cell carcinoma of the skin and squamous cell carcinoma of the skin were additional exceptions.
- Clarified management of subjects at risk for HBV reactivation; Clarified study treatment continuation rules in case of lenalidomide or rituximab intolerance/hypersensitivity.

Overall, 245 subjects were enrolled under Amendment 2 of the protocol.

- *Protocol Amendment 3 (dated 21 Oct 2015)*

Amendment 3 modified Inclusion Criterion 4 to no longer allow rituximab-naïve subjects in the study; to confirm that subjects had to have documented relapsed, refractory, or PD after treatment with systemic therapy, and must not be rituximab-refractory; defined refractory lymphoma as a subject who received a non-rituximab containing systemic therapy and who experienced the best response of PD to this therapy was considered to have refractory lymphoma. This amendment revised exclusion Criteria for HCV positive subjects who did not have an active hepatitis C infection and who were otherwise acceptable candidates for this study. The requirement for a diagnosis of SMZL for subjects who did not have a spleen specimen available during the Screening Period was defined. It was also clarified that all subjects had to receive tumour lysis prophylaxis.

Overall, 83 subjects were enrolled under Amendment 3 of the protocol.

Changes from final protocol to Final SAP: Due to the small number of histology transformations, exploratory endpoint time to histology transformation was changed to histology transformation rate. No changes were made to the final SAP before the study was un-blinded.

Changes to final statistical analysis plan after study unblinding: For FL/MZL subpopulation analyses, stratified analyses were replaced by un-stratified analyses to be consistent with subgroup analyses.

For DOR and DOCR, un-stratified analyses were conducted due to the small number of complete responses in the Control Arm.

Protocol deviations

Protocol deviations were defined as any unplanned diversions from the approved protocol.

Protocol violations were defined as any departures from the approved protocol that impacted the safety, rights, and/or welfare of the subject, negatively impacted the quality or completeness of the data, or made the informed consent process inaccurate.

A total of 326 subjects (166 subjects [93.3%] in the R^2 Arm and 160 subjects [88.9%] in the Control Arm) had at least one protocol deviation.

Table 7 Summary of Protocol Violations – ITT Population

Event Category Event Subcategory, n(%)	FL		MZL		Overall		Overall (N=358)
	Len+Rit (N=147)	Pbo+Rit (N=148)	Len+Rit(N=31)	Pbo+Rit (N=32)	Len+Rit (N=178)	Pbo+Rit (N=180)	
Number of subjects with							
Atleast1PV	10(6.8)	10(6.8)	3(9.7)	5(15.6)	13(7.3)	15(8.3)	28(7.8)
1violation	7(4.8)	8(5.4)	2(6.5)	5(15.6)	9(5.1)	13(7.2)	22(6.1)
2violations	3(2.0)	1(0.7)	1(3.2)	0(0.0)	4(2.2)	1(0.6)	5(1.4)
>2violations	0(0.0)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	1(0.3)
PV1: Safety related	**7(4.8)**	**3(2.0)**	**1(3.2)**	**5(15.6)**	**8(4.5)**	**8(4.4)**	**16(4.5)**
Failure to provide protocol specified pregnancy counseling	0(0.0)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	1(0.3)
SAEnotreportedtoSponsorand/orIRBwithin24hoursofnotice(ifapplicable)	6(4.1)	2(1.4)	1(3.2)	4(12.5)	7(3.9)	6(3.3)	13(3.6)
Subject administered expired drug or drug subject excursion and not approved for use by Sponsor subject	1(0.7)	0(0.0)	0(0.0)	1(3.1)	1(0.6)	1(0.6)	2(0.6)
PV2: Quality of data	**3(2.0)**	**8(5.4)**	**2(6.5)**	**0**	**5(2.8)**	**8(4.4)**	**13(3.6)**
History of prior malignancies other than FL, MZL unless disease free for more than	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.3)
Lymphoma biopsy not collected or available at	1(0.7)	2(1.4)	0(0.0)	0(0.0)	1(0.6)	2(1.1)	3(0.8)

Subject does not have documented relapsed, refractory or PD after treatment with systemic therapy; and/or is rituximab refractory	2(1.4)	6(4.1)	0(0.0)	0(0.0)	2(1.1)	6(3.3)	8(2.2)
Subject received wrong study medication	0(0.0)	0(0.0)	2(6.5)	0(0.0)	2(1.1)[a]	0(0.0)	2(0.6)

FL = follicular lymphoma; IP = investigational product; IRB = Institutional Review Board; ITT = intent-to-treat; IVRS = Interactive Voice Response System; Len + Rit = lenalidomide in combination with rituximab (R2 Arm);MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); PD = progressive disease; PV = protocol violation; SAE = serious adverse event.
a One subject received 21 doses of the incorrect IP. One subject received 6 doses of the incorrect IP
Note: A PV was defined as any departure from the approved protocol that: 1) impacted the safety, rights, and/or welfare of the subject; or 2) negatively impacted the quality or completeness of the data.
Data cutoff: 22 Jun 2018.

Baseline data

Table 8 Demographic characteristics–ITT Population

Demographic Characteristics	FL		MZL		Overall		Overall (N=358)
	Len + Rit (N=147)	Pbo+ Rit (N=148)	Len + Rit (N=31)	Pbo+ Rit (N=32)	Len + Rit (N=178)	Pbo+ Rit (N=180)	
Age (years)							
n	147	148	31	32	178	180	358
Mean	61.63	60.72	65.52	64.97	62.30	61.48	61.89
St D	11.310	11.078	10.405	11.041	11.227	11.160	11.186
Median	62.00	61.00	68.00	66.00	64.00	62.00	62.50
Min, Max	26.0, 86.0	35.0, 88.0	37.0, 80.0	36.0, 82.0	26.0, 86.0	35.0, 88.0	26.0, 88.0
Age distribution, n (%)							
<65	86 (58.5)	94 (63.5)	10 (32.3)	13 (40.6)	96(53.9)	107 (59.4)	203 (56.7)
≥65	61 (41.5)	54 (36.5)	21 (67.7)	19 (59.4)	82 (46.1)	73 (40.6)	155 (43.3)
≥70	34 (23.1)	32 (21.6)	13 (41.9)	12 (37.5)	47 (26.4)	44 (24.4)	91 (25.4)
Sex,n (%)							
Male	61 (41.5)	80 (54.1)	14 (45.2)	17 (53.1)	75 (42.1)	97(53.9)	172 (48.0)
Female	86 (58.5)	68 (45.9)	17 (54.8)	15 (46.9)	103 (57.9)	83 (46.1)	186 (52.0)
Region,n (%)							
US	19 (12.9)	15 (10.1)	4 (12.9)	2 (6.3)	23 (12.9)	17 (9.4)	40 (11.2)
EU	57 (38.8)	68 (45.9)	24 (77.4)	16 (50.0)	81 (45.5)	84 (46.7)	165 (46.1)
APAC and Brazil	71 (48.3)	65 (43.9)	3 (9.7)	14 (43.8)	74 (41.6)	79 (43.9)	153 (42.7)
Race,n (%)							

White	91 (61.9)	92 (62.2)	27 (87.1)	23 (71.9)	118 (66.3)	115 (63.9)	233 (65.1)
Other races	52 (35.4)	55 (37.2)	2 (6.5)	9 (28.1)	54(30.3)	64 (35.6)	118 (33.0)
Not collected or reported	4 (2.7)	1 (0.7)	2 (6.5)	0 (0.0)	6 (3.4)	1 (0.6)	7 (2.0)
BSA(m^2)[a]							
n	147	148	31	32	178	180	358
Mean	1.86	1.86	1.81	1.79	1.85	1.85	1.85
StD	0.246	0.257	0.174	0.180	0.236	0.246	0.241
Median	1.84	1.84	1.77	1.79	1.83	1.83	1.83
Min, Max	1.4, 3.1	1.3, 2.7	1.5, 2.3	1.5, 2.1	1.4, 3.1	1.3, 2.7	1.3, 3.1

APAC = Asia-Pacific region; BSA = body surface area; EU = European Union; FL = follicular lymphoma; ITT = intent-to-treat; Max = maximum; Min = minimum; MZL = marginal zone lymphoma;Len + Rit = lenalidomide in combination with rituximab (R2 Arm); Pbo + Rit = placebo plus rituximab(Control Arm); StD = standard deviation; US = United States.
a Weight and height were imputed for 2 subjects in the Control Arm due to missing baseline values.
Data cutoff: 22 Jun 2018.

Table 9 Baseline disease characteristics – ITT Population

Baseline Disease Characteristics ,n(%)	**FL**		**MZL**		**Overall**		**Overall (N=35**
	Len+Rit (N=147)	**Pbo+Rit (N=148)**	**Len+Rit (N=31)**	**Pbo+Rit (N=32)**	**Len+Rit (N=178)**	**Pbo+Rit (N=180)**	
Histology (Investigator Review)							
FL	147(100.0)	148(100.0)	-	-	147(82.6)	148(82.2)	295(82.4)
Grade1	50(34.0)	62(41.9)	-	-	50(28.1)	62(34.4)	112(31.3)
Grade2	75(51.0)	61(41.2)	-	-	75(42.1)	61(33.9)	136(38.0)
Grade3a	22(15.0)	25(16.9)	-	-	22(12.4)	25(13.9)	47(13.1)
MZL	-	-	31(100.0)	32(100.0)	31(17.4)	32(17.8)	63(17.6)
MALT	-	-	14(45.2)	16(50.0)	14(7.9)	16(8.9)	30(8.4)
Nodal	-	-	8(25.8)	10(31.3)	8(4.5)	10(5.6)	18(5.0)
Splenic	-	-	9(29.0)	6(18.8)	9(5.1)	6(3.3)	15(4.2)
Ann Arbor Stage at enrollment							
I	13(8.8)	13(8.8)	2(6.5)	5(15.6)	15(8.4)	18(10.0)	33(9.2)
II	21(14.3)	29(19.6)	5(16.1)	9(28.1)	26(14.6)	38(21.1)	64(17.9)
III	69(46.9)	60(40.5)	4(12.9)	5(15.6)	73(41.0)	65(36.1)	138(38.5)
IV	44(29.9)	46(31.1)	20(64.5)	13(40.6)	64(36.0)	59(32.8)	123(34.4)
Ann Arbor Stage at enrollment (categorized)							
I-II	34(23.1)	42(28.4)	7(22.6)	14(43.8)	41(23.0)	56(31.1)	97(27.1)
III-IV	113(76.9)	106(71.6)	24(77.4)	18(56.3)	137(77.0)	124(68.9)	261(72.9)
FLIPI category (derived)							
Low (0,1)	45(30.6)	53(35.8)	7(22.6)	14(43.8)	52(29.2)	67(37.2)	119(33.2)
Intermediate (2)	46(31.3)	48(32.4)	9(29.0)	10(31.3)	55(30.9)	58(32.2)	113(31.6)
High (≥3)	54(36.7)	46(31.1)	15(48.4)	8(25.0)	69(38.8)	54(30.0)	123(34.4)
Missing	2(1.4)	1(0.7)	0(0.0)	0(0.0)	2(1.1)	1(0.6)	3(0.8)

Baseline ECOG score							
0	99(67.3)	105(70.9)	17(54.8)	23(71.9)	116(65.2)	128(71.1)	244(68.2)
1	47(32.0)	42(28.4)	13(41.9)	8(25.0)	60(33.7)	50(27.8)	110(30.7)
2	1(0.7)	1(0.7)	1(3.2)	1(3.1)	2(1.1)	2(1.1)	4(1.1)
Baseline B symptom present							
Yes	12(8.2)	11(7.4)	4(12.9)	1(3.1)	16(9.0)	12(6.7)	28(7.8)
No	135(91.8)	137(92.6)	27(87.1)	31(96.9)	162(91.0)	168(93.3)	330(92.2)
Bone marrow biopsy performed							
Yes	83(56.5)	89(60.1)	23(74.2)	22(68.8)	106(59.6)	111(61.7)	217(60.6)
Involved	20(24.1)	22(24.7)	13(56.5)	9(40.9)	33(31.1)	31(27.9)	64(29.5)
Indeterminate	1(1.2)	3(3.4)	0(0.0)	2(9.1)	1(0.9)	5(4.5)	6(2.8)
Notinvolved	62(74.7)	64(71.9)	10(43.5)	11(50.0)	72(67.9)	75(67.6)	147(67.7)
No	64(43.5)	59(39.9)	8(25.8)	10(31.3)	72(40.4)	69(38.3)	141(39.4)
LDH elevated[a]							
Yes	34(23.1)	33(22.3)	9(29.0)	6(18.8)	43(24.2)	39(21.7)	82(22.9)
No	112(76.2)	114(77.0)	22(71.0)	26(81.3)	134(75.3)	140(77.8)	274(76.5)
Missing	1(0.7)	1(0.7)	0(0.0)	0(0.0)	1(0.6)	1(0.6)	2(0.6)
Bulky disease[b]							
Yes	39(26.5)	43(29.1)	6(19.4)	6(18.8)	45(25.3)	49(27.2)	94(26.3)
No	107(72.8)	105(70.9)	25(80.6)	26(81.3)	132(74.2)	131(72.8)	263(73.5)
Missing	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.3)
Baseline créatinine clearance							
≥30ml/min but <60ml/min	20(13.6)	16(10.8)	4(12.9)	8(25.0)	24(13.5)	24(13.3)	48(13.4)
≥60ml/min	127(86.4)	132(89.2)	27(87.1)	24(75.0)	154(86.5)	156(86.7)	310(86.6)
Prior antilymphoma regimens							
1	78(53.1)	79(53.4)	24(77.4)	18(56.3)	102(57.3)	97(53.9)	199(55.6)
>1	69(46.9)	69(46.6)	7(22.6)	14(43.8)	76(42.7)	83(46.1)	159(44.4)
Relapse/progression documented within 2years of initial diagnosis							
Yes	49(33.3)	50(33.8)	7(22.6)	11(34.4)	56(31.5)	61(33.9)	117(32.7)
No	98(66.7)	98(66.2)	24(77.4)	20(62.5)	122(68.5)	118(65.6)	240(67.0)
Missing	0(0.0)	0(0.0)	0(0.0)	1(3.1)	0(0.0)	1(0.6)	1(0.3)
Time since last anti lymphoma therapy							
≤2years	77(52.4)	78(52.7)	12(38.7)	14(43.8)	89(50.0)	92(51.1)	181(50.6)
>2years	70(47.6)	70(47.3)	19(61.3)	18(56.3)	89(50.0)	88(48.9)	177(49.4)
Previous rituximab treatment							
Yes	125(85.0)	124(83.8)	27(87.1)	26(81.3)	152(85.4)	150(83.3)	302(84.4)
No	22(15.0)	24(16.2)	4(12.9)	6(18.8)	26(14.6)	30(16.7)	56(15.6)
Prior rituximab-containing chemotherapy regimen							
Yes	108(73.5)	108(73.0)	22(71.0)	21(65.6)	130(73.0)	129(71.7)	259(72.3)

No	39(26.5)	40(27.0)	9(29.0)	11(34.4)	48(27.0)	51(28.3)	99(27.7)
Refractory to last prior regimen							
Yes	26(17.7)	25(16.9)	4(12.9)	1(3.1)	30(16.9)	26(14.4)	56(15.6)
No	121(82.3)	123(83.1)	27(87.1)	31(96.9)	148(83.1)	154(85.6)	302(84.4)
High tumour **burden(GELF criteria)**							
Yes	77(52.4)	68(45.9)	20(64.5)	18(56.3)	97(54.5)	86(47.8)	183(51.1)
No	70(47.6)	80(54.1)	11(35.5)	14(43.8)	81(45.5)	94(52.2)	175(48.9)
Chemo-resistant status[c]							
Yes	22(15.0)	24(16.2)	3(9.7)	2(6.3)	25(14.0)	26(14.4)	51(14.2)
No	125(85.0)	124(83.8)	28(90.3)	30(93.8)	153(86.0)	154(85.6)	307(85.8)
Chemotherapy eligible[d]							
Yes	83(56.5)	82(55.4)	21(67.7)	21(65.6)	104(58.4)	103(57.2)	207(57.8)
No	59(40.1)	64(43.2)	9(29.0)	11(34.4)	68(38.2)	75(41.7)	143(39.9)
Missing	5(3.4)	2(1.4)	1(3.2)	0(0.0)	6(3.4)	2(1.1)	8(2.2)
Unfit for chemotherapy[e]							
Yes	39(26.5)	35(23.6)	15(48.4)	14(43.8)	54(30.3)	49(27.2)	103(28.8)
No	108(73.5)	113(76.4)	16(51.6)	18(56.3)	124(69.7)	131(72.8)	255(71.2)

CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; GELF = Groupe d'Etude des Lymphomes Folliculaires; ITT = intent-to-treat; LDH = lactate dehydrogenase; Len + Rit = lenalidomide in combination with rituximab (R2 Arm); MALT = mucosa-associated lymphatic tissue; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); PR = partial response; PD = progressive disease; ULN = upper limit of normal.

a Lactate dehydrogenase elevated is defined as LDH > ULN.
b Bulky disease is defined as at least one lesion that is ≥ 7 cm or at least 3 lesions with 3 cm or larger in the longest diameter by investigator review.
c Chemo-resistant was defined as PR or PD ≤ 6 months from last chemotherapy (yes, no).
d Chemotherapy eligible was defined as chemo-naïve, or received prior chemotherapy and had progression > 2 years from last chemotherapy treatment.
e Unfit for chemotherapy was defined as age ≥ 70 years, or if 60 to 69 years old and CrCl < 60 mL/min or ECOG Performance Status ≥ 2 (yes, no).
Data cutoff: 22 Jun 2018.

Table 10 Demographic characteristics–ITT Population

Demographic Characteristics	**FL**		**MZL**		**Overall**		**Overall (N=358)**
	Len + Rit (N=147)	**Pbo+ Rit (N=148)**	**Len + Rit (N=31)**	**Pbo+ Rit (N=32)**	**Len + Rit (N=178)**	**Pbo+ Rit (N=180)**	
Age (years)							
n	147	148	31	32	178	180	358
Mean	61.63	60.72	65.52	64.97	62.30	61.48	61.89
St D	11.310	11.078	10.405	11.041	11.227	11.160	11.186
Median	62.00	61.00	68.00	66.00	64.00	62.00	62.50
Min, Max	26.0, 86.0	35.0, 88.0	37.0, 80.0	36.0, 82.0	26.0, 86.0	35.0, 88.0	26.0, 88.0
Age distribution, n (%)							
<65	86 (58.5)	94 (63.5)	10 (32.3)	13 (40.6)	96(53.9)	107 (59.4)	203 (56.7)

≥65	61 (41.5)	54 (36.5)	21 (67.7)	19 (59.4)	82 (46.1)	73 (40.6)	155 (43.3)
≥70	34 (23.1)	32 (21.6)	13 (41.9)	12 (37.5)	47 (26.4)	44 (24.4)	91 (25.4)
Sex,n (%)							
Male	61 (41.5)	80 (54.1)	14 (45.2)	17 (53.1)	75 (42.1)	97(53.9)	172 (48.0)
Female	86 (58.5)	68 (45.9)	17 (54.8)	15 (46.9)	103 (57.9)	83 (46.1)	186 (52.0)
Region,n (%)							
US	19 (12.9)	15 (10.1)	4 (12.9)	2 (6.3)	23 (12.9)	17 (9.4)	40 (11.2)
EU	57 (38.8)	68 (45.9)	24 (77.4)	16 (50.0)	81 (45.5)	84 (46.7)	165 (46.1)
APAC and Brazil	71 (48.3)	65 (43.9)	3 (9.7)	14 (43.8)	74 (41.6)	79 (43.9)	153 (42.7)
Race,n (%)							
White	91 (61.9)	92 (62.2)	27 (87.1)	23 (71.9)	118 (66.3)	115 (63.9)	233 (65.1)
Other races	52 (35.4)	55 (37.2)	2 (6.5)	9 (28.1)	54(30.3)	64 (35.6)	118 (33.0)
Not collected or reported	4 (2.7)	1 (0.7)	2 (6.5)	0 (0.0)	6 (3.4)	1 (0.6)	7 (2.0)
BSA(m^2)[a]							
n	147	148	31	32	178	180	358
Mean	1.86	1.86	1.81	1.79	1.85	1.85	1.85
StD	0.246	0.257	0.174	0.180	0.236	0.246	0.241
Median	1.84	1.84	1.77	1.79	1.83	1.83	1.83
Min, Max	1.4, 3.1	1.3, 2.7	1.5, 2.3	1.5, 2.1	1.4, 3.1	1.3, 2.7	1.3, 3.1

APAC = Asia-Pacific region; BSA = body surface area; EU = European Union; FL = follicular lymphoma; ITT = intent-to-treat; Max = maximum; Min = minimum; MZL = marginal zone lymphoma;Len + Rit = lenalidomide in combination with rituximab (R2 Arm); Pbo + Rit = placebo plus rituximab(Control Arm); StD = standard deviation; US = United States.
a Weight and height were imputed for 2 subjects in the Control Arm due to missing baseline values.
Data cutoff: 22 Jun 2018.

Table 11 Baseline disease characteristics – ITT Population

Baseline Disease Characteristics ,n(%)	**FL**		**MZL**		**Overall**		**Overall (N=35**
	Len+Rit (N=147)	**Pbo+Rit (N=148)**	**Len+Rit (N=31)**	**Pbo+Rit (N=32)**	**Len+Rit (N=178)**	**Pbo+Rit (N=180)**	
Histology (Investigator Review)							
FL	147(100.0)	148(100.0)	-	-	147(82.6)	148(82.2)	295(82.4)
Grade1	50(34.0)	62(41.9)	-	-	50(28.1)	62(34.4)	112(31.3)
Grade2	75(51.0)	61(41.2)	-	-	75(42.1)	61(33.9)	136(38.0)
Grade3a	22(15.0)	25(16.9)	-	-	22(12.4)	25(13.9)	47(13.1)
MZL	-	-	31(100.0)	32(100.0)	31(17.4)	32(17.8)	63(17.6)
MALT	-	-	14(45.2)	16(50.0)	14(7.9)	16(8.9)	30(8.4)
Nodal	-	-	8(25.8)	10(31.3)	8(4.5)	10(5.6)	18(5.0)

Splenic	-	-	9(29.0)	6(18.8)	9(5.1)	6(3.3)	15(4.2)
Ann Arbor Stage at enrollment							
I	13(8.8)	13(8.8)	2(6.5)	5(15.6)	15(8.4)	18(10.0)	33(9.2)
II	21(14.3)	29(19.6)	5(16.1)	9(28.1)	26(14.6)	38(21.1)	64(17.9)
III	69(46.9)	60(40.5)	4(12.9)	5(15.6)	73(41.0)	65(36.1)	138(38.5)
IV	44(29.9)	46(31.1)	20(64.5)	13(40.6)	64(36.0)	59(32.8)	123(34.4)
Ann Arbor Stage at enrollment (categorized)							
I-II	34(23.1)	42(28.4)	7(22.6)	14(43.8)	41(23.0)	56(31.1)	97(27.1)
III-IV	113(76.9)	106(71.6)	24(77.4)	18(56.3)	137(77.0)	124(68.9)	261(72.9)
FLIPI category (derived)							
Low (0,1)	45(30.6)	53(35.8)	7(22.6)	14(43.8)	52(29.2)	67(37.2)	119(33.2)
Intermediate (2)	46(31.3)	48(32.4)	9(29.0)	10(31.3)	55(30.9)	58(32.2)	113(31.6)
High (≥3)	54(36.7)	46(31.1)	15(48.4)	8(25.0)	69(38.8)	54(30.0)	123(34.4)
Missing	2(1.4)	1(0.7)	0(0.0)	0(0.0)	2(1.1)	1(0.6)	3(0.8)
Baseline ECOG score							
0	99(67.3)	105(70.9)	17(54.8)	23(71.9)	116(65.2)	128(71.1)	244(68.2)
1	47(32.0)	42(28.4)	13(41.9)	8(25.0)	60(33.7)	50(27.8)	110(30.7)
2	1(0.7)	1(0.7)	1(3.2)	1(3.1)	2(1.1)	2(1.1)	4(1.1)
Baseline B symptom present							
Yes	12(8.2)	11(7.4)	4(12.9)	1(3.1)	16(9.0)	12(6.7)	28(7.8)
No	135(91.8)	137(92.6)	27(87.1)	31(96.9)	162(91.0)	168(93.3)	330(92.2)
Bone marrow biopsy performed							
Yes	83(56.5)	89(60.1)	23(74.2)	22(68.8)	106(59.6)	111(61.7)	217(60.6)
Involved	20(24.1)	22(24.7)	13(56.5)	9(40.9)	33(31.1)	31(27.9)	64(29.5)
Indeterminate	1(1.2)	3(3.4)	0(0.0)	2(9.1)	1(0.9)	5(4.5)	6(2.8)
Not involved	62(74.7)	64(71.9)	10(43.5)	11(50.0)	72(67.9)	75(67.6)	147(67.7)
No	64(43.5)	59(39.9)	8(25.8)	10(31.3)	72(40.4)	69(38.3)	141(39.4)
LDH elevated[a]							
Yes	34(23.1)	33(22.3)	9(29.0)	6(18.8)	43(24.2)	39(21.7)	82(22.9)
No	112(76.2)	114(77.0)	22(71.0)	26(81.3)	134(75.3)	140(77.8)	274(76.5)
Missing	1(0.7)	1(0.7)	0(0.0)	0(0.0)	1(0.6)	1(0.6)	2(0.6)
Bulky disease[b]							
Yes	39(26.5)	43(29.1)	6(19.4)	6(18.8)	45(25.3)	49(27.2)	94(26.3)
No	107(72.8)	105(70.9)	25(80.6)	26(81.3)	132(74.2)	131(72.8)	263(73.5)
Missing	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.3)
Baseline créatinine clearance							
≥30ml/min but <60ml/min	20(13.6)	16(10.8)	4(12.9)	8(25.0)	24(13.5)	24(13.3)	48(13.4)
≥60ml/min	127(86.4)	132(89.2)	27(87.1)	24(75.0)	154(86.5)	156(86.7)	310(86.6)
Prior antilymphoma regimens							

1	78(53.1)	79(53.4)	24(77.4)	18(56.3)	102(57.3)	97(53.9)	199(55.6)
>1	69(46.9)	69(46.6)	7(22.6)	14(43.8)	76(42.7)	83(46.1)	159(44.4)
Relapse/progression documented within 2years of initial diagnosis							
Yes	49(33.3)	50(33.8)	7(22.6)	11(34.4)	56(31.5)	61(33.9)	117(32.7)
No	98(66.7)	98(66.2)	24(77.4)	20(62.5)	122(68.5)	118(65.6)	240(67.0)
Missing	0(0.0)	0(0.0)	0(0.0)	1(3.1)	0(0.0)	1(0.6)	1(0.3)
Time since last anti lymphoma therapy							
≤2years	77(52.4)	78(52.7)	12(38.7)	14(43.8)	89(50.0)	92(51.1)	181(50.6)
>2years	70(47.6)	70(47.3)	19(61.3)	18(56.3)	89(50.0)	88(48.9)	177(49.4)
Previous rituximab treatment							
Yes	125(85.0)	124(83.8)	27(87.1)	26(81.3)	152(85.4)	150(83.3)	302(84.4)
No	22(15.0)	24(16.2)	4(12.9)	6(18.8)	26(14.6)	30(16.7)	56(15.6)
Prior rituximab-containing chemotherapy regimen							
Yes	108(73.5)	108(73.0)	22(71.0)	21(65.6)	130(73.0)	129(71.7)	259(72.3)
No	39(26.5)	40(27.0)	9(29.0)	11(34.4)	48(27.0)	51(28.3)	99(27.7)
Refractory to last prior regimen							
Yes	26(17.7)	25(16.9)	4(12.9)	1(3.1)	30(16.9)	26(14.4)	56(15.6)
No	121(82.3)	123(83.1)	27(87.1)	31(96.9)	148(83.1)	154(85.6)	302(84.4)
High tumour **burden(GELF criteria)**							
Yes	77(52.4)	68(45.9)	20(64.5)	18(56.3)	97(54.5)	86(47.8)	183(51.1)
No	70(47.6)	80(54.1)	11(35.5)	14(43.8)	81(45.5)	94(52.2)	175(48.9)
Chemo-resistant status[c]							
Yes	22(15.0)	24(16.2)	3(9.7)	2(6.3)	25(14.0)	26(14.4)	51(14.2)
No	125(85.0)	124(83.8)	28(90.3)	30(93.8)	153(86.0)	154(85.6)	307(85.8)
Chemotherapy eligible[d]							
Yes	83(56.5)	82(55.4)	21(67.7)	21(65.6)	104(58.4)	103(57.2)	207(57.8)
No	59(40.1)	64(43.2)	9(29.0)	11(34.4)	68(38.2)	75(41.7)	143(39.9)
Missing	5(3.4)	2(1.4)	1(3.2)	0(0.0)	6(3.4)	2(1.1)	8(2.2)
Unfit for chemotherapy[e]							
Yes	39(26.5)	35(23.6)	15(48.4)	14(43.8)	54(30.3)	49(27.2)	103(28.8)
No	108(73.5)	113(76.4)	16(51.6)	18(56.3)	124(69.7)	131(72.8)	255(71.2)

CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; GELF = Groupe d'Etude des Lymphomes Folliculaires; ITT = intent-to-treat; LDH = lactate dehydrogenase; Len + Rit = lenalidomide in combination with rituximab (R2 Arm); MALT = mucosa-associated lymphatic tissue; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); PR = partial response; PD = progressive disease; ULN = upper limit of normal.

a Lactate dehydrogenase elevated is defined as LDH > ULN.

b Bulky disease is defined as at least one lesion that is ≥ 7 cm or at least 3 lesions with 3 cm or larger in the longest diameter by investigator review.

c Chemo-resistant was defined as PR or PD ≤ 6 months from last chemotherapy (yes, no).

d Chemotherapy eligible was defined as chemo-naïve, or received prior chemotherapy and had progression > 2 years from last chemotherapy treatment.

e Unfit for chemotherapy was defined as age ≥ 70 years, or if 60 to 69 years old and CrCl < 60 mL/min or ECOG Performance Status ≥ 2 (yes, no).

Data cutoff: 22 Jun 2018.

Numbers analysed

The ITT Population was comprised of 358 subjects. The mITT Population included a total of 312 subjects (87.2% of the ITT Population). The Safety Population was comprised of 356 subjects (99.4% of the ITT Population) including 176 subjects (98.9%) in the R^2 Arm and 180 subjects (100.0%) in the Control Arm.

Table 12 Analysis Population – ITT Population

Analysis Populations, n(%)	FL		MZL		Overall		Overall
	Len+Rit (N=147	Pbo+Rit (N=148)	Len+Rit (N=31)	Pbo+Rit (N=32)	Len+Rit (N=178	Pbo+Rit (N=180)	(N=35
Intent-to-treat[a]	147 (100.0)	148(100.0)	31(100.0)	32(100.0)	178(100.0)	180(100.0)	358(100.0)
Modified intent-to-	128(87.1)	135(91.2)	24(77.4)	25(78.1)	152(85.4)	160(88.9)	312(87.2)
Safety[c]	146(99.3)	148(100.0)	30(96.8)	32(100.0)	176(98.9)	180(100.0)	356(99.4)

FL = follicular lymphoma; ITT = intent-to-treat; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm);
MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); SMZL = splenic marginal zone lymphoma.
a Intent-to-treat Population includes all randomized subjects. Summarized by planned treatment.
b The mITT Population includes all randomized subjects who have received at least 1 dose of study medication, had a confirmed diagnosis of relapsed/refractory FL or MZL by central pathology review except SMZL which was based on local pathology assessment, and had baseline (Screening) and at least 1 postbaseline tumour assessment for efficacy. Summarized by planned treatment.
c Safety Population included all subjects who received at least 1 dose of study treatment. Summarized by actual treatment.
Data cutoff: 22 Jun 2018.

Outcomes and estimation

The ITT Population was used for the primary efficacy analysis. The primary efficacy analyses were based on data from the IRC review, using the modified 2007 IWGRC. Data from the investigator's assessments were used in a supportive analysis for the primary and key secondary efficacy endpoints.

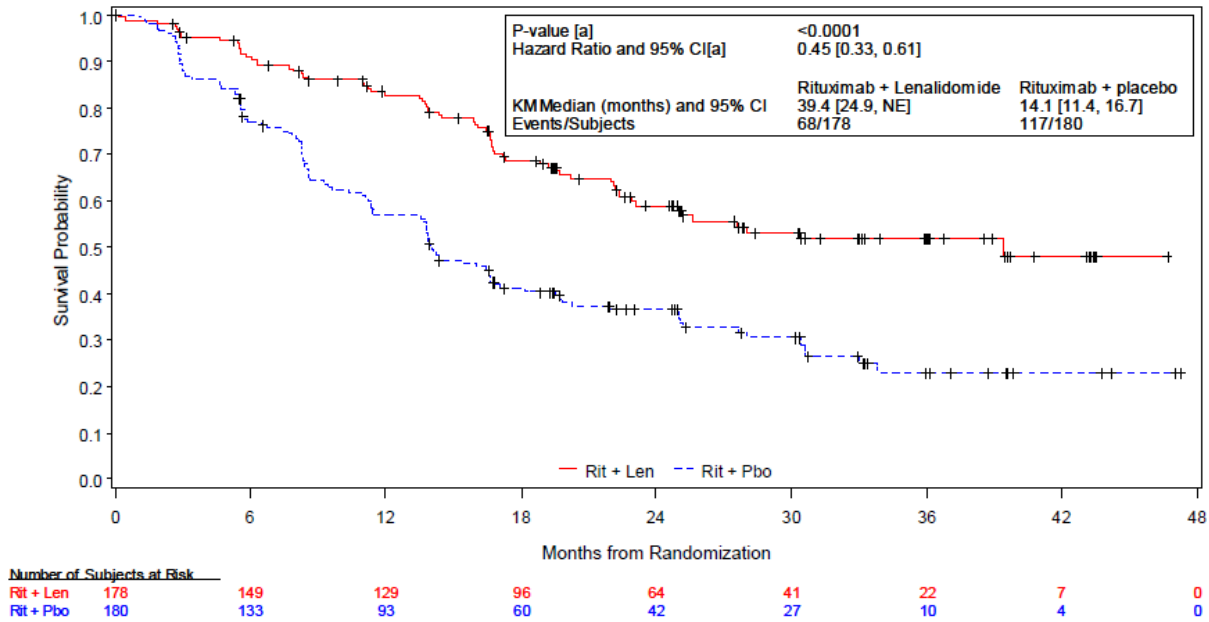
- *Primary endpoint (PFS)*

Table 13 *Progression-free Survival by IRC Assessment per 2007 IWGRC with Censoring Rules Based on EMA Guidance – ITT Population*

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Number of subjects, n (%)						
With event	56 (38.1)	101 (68.2)	12 (38.7)	16 (50.0)	68 (38.2)	117 (65.0)
Censored	91 (61.9)	47 (31.8)	19 (61.3)	16 (50.0)	110 (61.8)	63 (35.0)
Median PFS (95% CI) (months)[a]	39.4 (25.1, NE)	13.8 (11.2, 16.0)	24.9 (16.7, NE)	25.2 (11.1, NE)	39.4 (24.9, NE)	14.1 (11.4, 16.7)
PFS rate at 6 months (95% CI)	92.2% (86.3%, 95.6%)	76.7% (68.9%, 82.7%)	84.8% (64.3%, 94.0%)	78.0% (59.3%, 88.9%)	91.0% (85.5%, 94.5%)	76.9% (70.0%, 82.4%)
PFS rate at 1 year (95% CI)	82.6% (75.1%, 88.0%)	54.4% (45.8%, 62.2%)	84.8% (64.3%, 94.0%)	68.3% (49.0%, 81.5%)	82.9% (76.2%, 87.9%)	56.8% (49.1%, 63.8%)
PFS rate at 2 years (95% CI)	60.1% (50.7%, 68.3%)	31.8% (24.0%, 39.9%)	51.7% (29.1%, 70.2%)	60.0% (40.0%, 75.3%)	58.8% (50.2%, 66.5%)	36.6% (29.1%, 44.0%)
p-value	< 0.0001[b]		0.7068[b]		< 0.0001[c]	
Hazard ratio (95% CI)	0.40 (0.29, 0.55)[d]		0.87 (0.41, 1.83)[d]		0.45 (0.33, 0.61)e	

CI = confidence interval; EMA = European Medicines Agency; FL = follicular lymphoma; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; NE = not estimable; Pbo + Rit = placebo plus rituximab (Control Arm); PFS = progression-free survival.
[a] Median estimate is from Kaplan-Meier analysis.
[b] P-value from log-rank test.
[c] For overall, p-value from log-rank test stratified by 3 factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).
[d] From Cox proportional hazard model.
[e] For overall, hazard ratio and its CI were estimated from Cox proportional hazard model adjusting for the stratification factors noted above.
Data cutoff: 22 Jun 2018.

Figure 3 *Kaplan-Meier Curve of Progression-free Survival in AUGMENT by IRC assessment per 2007 IWGRC with Censoring Rules Based on EMA Guidance – ITT Population*



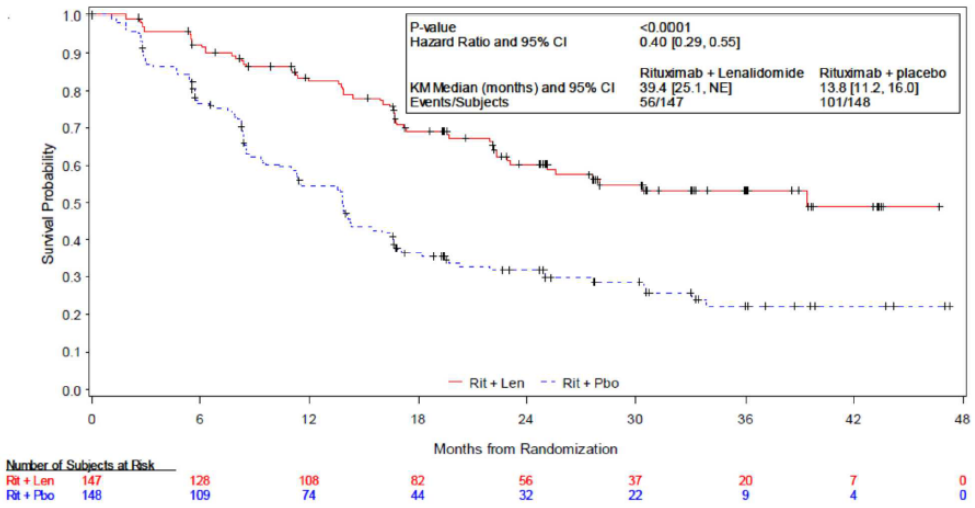
CI = confidence interval; EMA = European Medicines Agency; FL = follicular lymphoma; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; KM = Kaplan-Meier; MZL = marginal zone lymphoma; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).

[a] P-value from stratified log-rank test. Stratification factors include the following: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL). Hazard ratio and its CI were estimated from Cox proportional hazard model adjusting for the stratification factors.

Previously treated FL

For the primary endpoint PFS, when applying EMA censoring rules, there was a 60% reduction in the risk of progression or death for the R^2 Arm compared to the Control Arm (HR = 0.40; 95% CI: 0.29, 0.55; p < 0.0001).

Figure 4 *Kaplan-Meier Curve of Progression-free Survival in AUGMENT by IRC Assessment with Censoring Rules Based on EMA Guidance in Subjects with FL– ITT Population*



CI = confidence interval; EMA = European Medicines Agency; FL = follicular lymphoma; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; KM = Kaplan-Meier; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).
Data cutoff: 22 Jun 2018.

Previously treated MZL

The PFS results in subjects with MZL were inconsistent with that of the overall population. In the MZL subgroup, PFS results were numerically similar between the R^2 Arm and the Control Arm with an unstratified HR of 0.87 (95% CI: 0.41, 1.83) (EMA censoring rules). Univariate and multivariate analyses suggested that the PFS results in the MZL subgroup were likely explained by the small sample size and the imbalance in baseline prognostic factors (e.g., age, Ann Arbor Stage, FLIPI score, ECOG performance status score, B symptoms, and LDH) in favour of the Control Arm. Adjusting for the imbalance between arms in identified, statistically significant prognostic factors (Ann Arbor Stage and LDH) in the MZL subgroup resulted in a PFS HR of 0.460 (95% CI: 0.192, 1.101) in favour of the R^2 Arm; this HR was similar to in the overall ITT Population.

Univariate and multivariate analysis of PFS

Univariate analyses using Cox regression model revealed that several baseline factors were prognostic in the MZL subgroup. Specifically, Ann Arbor Stage IV, elevated LDH, and "unfit for chemotherapy" were identified as significant prognostic factors based on significance level of $p < 0.05$.
Multivariate analyses adjusting for the imbalance in these 3 significant prognostic factors in the MZL subgroup showed an adjusted PFS HR of 0.51 (95% CI: 0.20, 1.28) in favour of the R^2 Arm;

Table 14 Cox Proportional Hazard Model for Progression-free Survival Based on IRC

	Univariate Model[a]			Final Multivariate Model[b]		
Variable	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Treatment (R^2 Arm vs Control Arm)[c]	1.001	(0.471, 2.125)	0.998	0.509	(0.202, 1.284)	0.153
Age (≥ 70 vs < 70 yrs)	2.083	(0.936, 4.634)	0.072			
Sex (male vs female)	1.990	(0.939, 4.216)	0.072			
Ann Arbor Stage (IV vs I/II/III)	2.746	(1.205, 6.258)	0.016	2.436	(0.998, 5.947)	0.051
FLIPI (high vs low/medium)	1.775	(0.841, 3.745)	0.132			
ECOG (1-2 vs 0)	1.228	(0.562, 2.685)	0.607			
LDH (elevated vs not elevated)	2.348	(1.096, 5.031)	0.028	2.792	(1.131, 6.897)	0.026
B symptom (yes vs no)	0.931	(0.220, 3.941)	0.923			
High tumor burden (yes vs no)	1.465	(0.662, 3.244)	0.346			
Chemoresistant (yes vs no)	0.493	(0.067, 3.644)	0.488			
Unfit for chemotherapy (yes vs no)	2.377	(1.043, 5.416)	0.039	2.086	(0.892, 4.876)	0.090

ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; FLIPI = Follicular Lymphoma International Prognostic Index; IRC = Independent Review Committee; ITT = intent-to-treat; LDH = lactate dehydrogenase; MZL = marginal zone lymphoma; yrs = years.

[a] Model includes one risk factor.

[b] Model includes treatment arm and significant risk factors (p-value < 0.05) from univariate analyses.

[c] R^2 Arm = lenalidomide in combination with rituximab. Control Arm = placebo plus rituximab.

Data cutoff: 22 Jun 2018.

Investigator's assessment

The results of investigator-assessed PFS with censoring based on EMA Guidance are presented below for overall ITT population, FL subjects and MZL subject.

Table 15 Progression free survival by investigators assessment based on EMA guidance on ITT population- Overall Population

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Table 14.2.1.2.3
Progression-free Survival (PFS) by Investigator Assessment with Censoring Rules Based on EMA Guidance
ITT Population

Statistics	Rituximab + Lenalidomide (N=178)	Rituximab + Placebo (N=180)
Number of Subjects		
# of Subjects with event n(%)	80 (44.9)	120 (66.7)
# of Subjects censored n(%)	98 (55.1)	60 (33.3)
Median PFS (95% CI) (months) [a]	27.6 (22.1, NE)	14.3 (12.4, 17.7)
PFS Rate at 6 months (95% CI)	91.7% (86.4%, 95.0%)	81.4% (74.9%, 86.4%)
PFS Rate at 1 year (95% CI)	82.0% (75.2%, 87.0%)	58.9% (51.2%, 65.7%)
PFS Rate at 2 years (95% CI)	54.6% (46.4%, 62.1%)	34.4% (27.2%, 41.7%)
P-value [b]	<0.0001	
Hazard ratio (HR) estimate [c]	0.50	
95% CI for HR	(0.38, 0.67)	

Table 16 *Progression free survival by investigators assessment based on EMA guidance on ITT population-FL Population*

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Table 14.2.1.2.3a
Progression-free Survival (PFS) by Investigator Assessment with Censoring Rules Based on EMA Guidance
FL Subjects in ITT Population

Statistics	Rituximab + Lenalidomide (N=147)	Rituximab + Placebo (N=148)
Number of Subjects		
# of Subjects with event n(%)	63 (42.9)	101 (68.2)
# of Subjects censored n(%)	84 (57.1)	47 (31.8)
Median PFS (95% CI) (months) [a]	30.4 (22.1, NE)	14.1 (11.4, 16.8)
PFS Rate at 6 months (95% CI)	94.3% (88.9%, 97.1%)	80.7% (73.3%, 86.3%)
PFS Rate at 1 year (95% CI)	83.3% (76.0%, 88.6%)	57.4% (48.8%, 65.0%)
PFS Rate at 2 years (95% CI)	56.6% (47.4%, 64.7%)	33.4% (25.6%, 41.4%)
P-value [b]	<0.0001	
Hazard ratio (HR) estimate [c]	0.46	
95% CI for HR	(0.33, 0.63)	

Table 17 *Progression free survival by investigators assessment based on EMA guidance on ITT population-MZL Population*

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Protocol: CC-5013-NHL-007 — Database Cutoff Date: 22JUN2018

Table 14.2.1.2.3b
Progression-free Survival (PFS) by Investigator Assessment with Censoring Rules Based on EMA Guidance
MZL Subjects in ITT Population

Statistics	Rituximab + Lenalidomide (N=31)	Rituximab + Placebo (N=32)
Number of Subjects		
# of Subjects with event n(%)	17 (54.8)	19 (59.4)
# of Subjects censored n(%)	14 (45.2)	13 (40.6)
Median PFS (95% CI) (months) [a]	19.2 (16.0, NE)	22.1 (8.7, NE)
PFS Rate at 6 months (95% CI)	79.0% (59.1%, 90.0%)	84.4% (66.5%, 93.2%)
PFS Rate at 1 year (95% CI)	75.4% (55.2%, 87.5%)	65.3% (46.1%, 79.1%)
PFS Rate at 2 years (95% CI)	45.5% (26.4%, 62.8%)	39.2% (21.6%, 56.4%)
P-value [b]	0.8429	
Hazard ratio (HR) estimate [c]	0.93	
95% CI for HR	(0.48, 1.80)	

Further analysis revealed the PFS by investigator assessment results based on EMA Guidance on the mITT Population were also similar to those of the ITT Population with HR (95% CI):0.48 (0.35, 0.65); p-value < 0.0001.

Secondary endpoints

Best response and Objective response

IRC assessment

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Best response, n (%)						
Complete response	51 (34.7)	29 (19.6)	9 (29.0)	4 (12.5)	60 (33.7)	33 (18.3)
Partial response	67 (45.6)	53 (35.8)	11 (35.5)	10 (31.3)	78 (43.8)	63 (35.0)
Stable disease	14 (9.5)	44 (29.7)	6 (19.4)	11 (34.4)	20 (11.2)	55 (30.6)
Progressive disease/ Death	7 (4.8)	19 (12.8)	0 (0.0)	4 (12.5)	7 (3.9)	23 (12.8)
No evidence of disease	3 (2.0)	2 (1.4)	0 (0.0)	2 (6.3)	3 (1.7)	4 (2.2)
Unknown/ND/Missing	5 (3.4)	1 (0.7)	5 (16.1)	1 (3.1)	10 (5.6)	2 (1.1)
Objective response (CR+PR), n (%)	118 (80.3)	82 (55.4)	20 (64.5)	14 (43.8)	138 (77.5)	96 (53.3)
95% CI[a]	(72.9, 86.4)	(47.0, 63.6)	(45.4, 80.8)	(26.4, 62.3)	(70.7, 83.4)	(45.8, 60.8)
p-value	< 0.0001[b]		0.1313[b]		< 0.0001[c]	
Complete response, n (%)	51 (34.7)	29 (19.6)	9 (29.0)	4 (12.5)	60 (33.7)	33 (18.3)
95% CI[a]	(27.0, 43.0)	(13.5, 26.9)	(14.2, 48.0)	(3.5, 29.0)	(26.8, 41.2)	(13.0, 24.8)
p-value	0.0040[b]		0.1289[b]		0.0010[c]	

CI = confidence interval; CR = complete response; FL = follicular lymphoma; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; ND = not determined; Pbo + Rit = placebo plus rituximab (Control Arm); PR = partial response.

[a] Exact confidence interval for binomial distribution.

[b] P-value obtained from Fisher-Exact test.

[c] P-value obtained from Cochran–Mantel–Haenszel test adjusting for stratification factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

NOTE: Percentage is based on the total number of subjects in each treatment arm.

Data cutoff: 22 Jun 2018

Table 18 Best Response by IRC Assessment per 2007 IWGRC – ITT Population

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Best response, n (%)						
Complete response	51 (34.7)	29 (19.6)	9 (29.0)	4 (12.5)	60 (33.7)	33 (18.3)
Partial response	67 (45.6)	53 (35.8)	11 (35.5)	10 (31.3)	78 (43.8)	63 (35.0)
Stable disease	14 (9.5)	44 (29.7)	6 (19.4)	11 (34.4)	20 (11.2)	55 (30.6)
Progressive disease/ Death	7 (4.8)	19 (12.8)	0 (0.0)	4 (12.5)	7 (3.9)	23 (12.8)
No evidence of disease	3 (2.0)	2 (1.4)	0 (0.0)	2 (6.3)	3 (1.7)	4 (2.2)
Unknown/ND/Missing	5 (3.4)	1 (0.7)	5 (16.1)	1 (3.1)	10 (5.6)	2 (1.1)
Objective response (CR+PR), n (%)	118 (80.3)	82 (55.4)	20 (64.5)	14 (43.8)	138 (77.5)	96 (53.3)
95% CI[a]	(72.9, 86.4)	(47.0, 63.6)	(45.4, 80.8)	(26.4, 62.3)	(70.7, 83.4)	(45.8, 60.8)
p-value	< 0.0001[b]		0.1313[b]		< 0.0001[c]	
Complete response, n (%)	51 (34.7)	29 (19.6)	9 (29.0)	4 (12.5)	60 (33.7)	33 (18.3)
95% CI[a]	(27.0, 43.0)	(13.5, 26.9)	(14.2, 48.0)	(3.5, 29.0)	(26.8, 41.2)	(13.0, 24.8)
p-value	0.0040[b]		0.1289[b]		0.0010[c]	

CI = confidence interval; CR = complete response; FL = follicular lymphoma; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; ND = not determined; Pbo + Rit = placebo plus rituximab (Control Arm); PR = partial response.

[a] Exact confidence interval for binomial distribution.

[b] P-value obtained from Fisher-Exact test.

[c] P-value obtained from Cochran–Mantel–Haenszel test adjusting for stratification factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

NOTE: Percentage is based on the total number of subjects in each treatment arm.

Data cutoff: 22 Jun 2018

Investigator's assessment

Table 19 Best response assessment by investigator

Celgene Corporation
Protocol: CC-5013-NHL-007

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Table 14.2.2.2.2.1
Best Response Assessment by Investigator per 2007 IWGRC
ITT Population

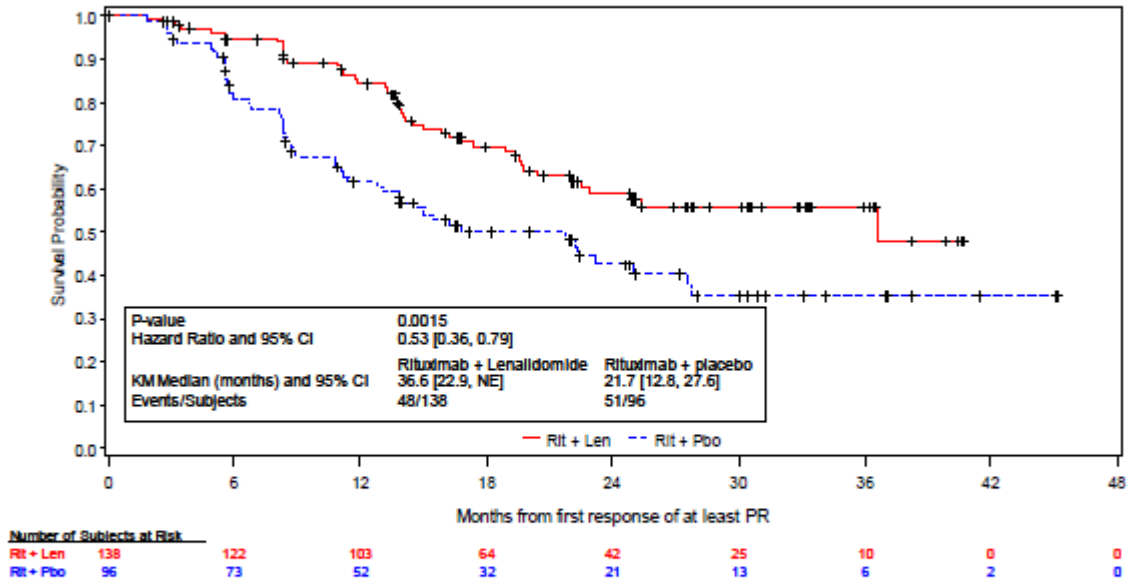
	Rituximab + Lenalidomide (N=178)	Rituximab + Placebo (N=180)
Best Response		
Complete Response (CR) - n (%)	57 (32.0)	37 (20.6)
Partial Response (PR) - n (%)	84 (47.2)	70 (38.9)
Stable Disease (SD) - n (%)	22 (12.4)	56 (31.1)
Progressive Disease (PD)/Death - n (%)	6 (3.4)	15 (8.3)
UNK/Not Done/Missing - n (%)	9 (5.1)	2 (1.1)
Objective Response (CR+PR) - n (%)	141 (79.2)	107 (59.4)
95% CI [a]	(72.5, 84.9)	(51.9, 66.7)
P-value [b]	<0.0001	
Complete Response (CR) - n (%)	57 (32.0)	37 (20.6)
95% CI [a]	(25.2, 39.4)	(14.9, 27.2)
P-value [b]	0.0119	

Percentage is based on the total number of subjects in each treatment arm.
[a] Exact confidence interval for binomial distribution.
[b] P-value obtained from CMH test adjusting for stratification factors: previous rituximab treatment (yes; no), time since last antilymphoma therapy (<= 2; > 2 year), and disease histology (FL; MZL).
Program Source: \\wilbtib\wilbtib05\Celgene CGNCC5013NHL007\Trunk\TLF\T140202020201.sas Version: Final
Data Source: ADRESP Data Extraction Date: 17JUL2018 Run date: 13SEP2018

Duration of response (DOR)

Overall, the median DOR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 36.6 months (22.9, not estimable [NE]) in the R^2 Arm and 21.7 months (12.8, 27.6) in the Control Arm.

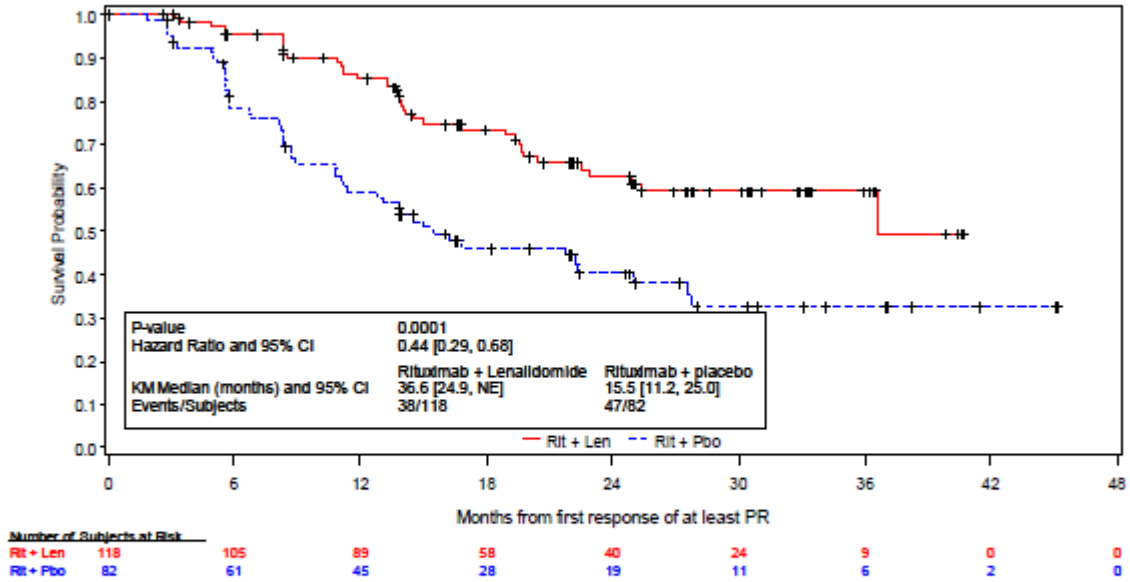
Figure 8: Kaplan-Meier Curve of Duration of Response by IRC Assessment per IWGRC 2007 – ITT Population



CI = confidence interval; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; KM = Kaplan-Meier; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).
Applicable to subjects who have achieved a complete response or partial response postbaseline.
Note: P-value from log-rank text. Hazard ratio and its CI were estimated from Cox proportional hazard method.
Data cutoff: 22 Jun 2018.

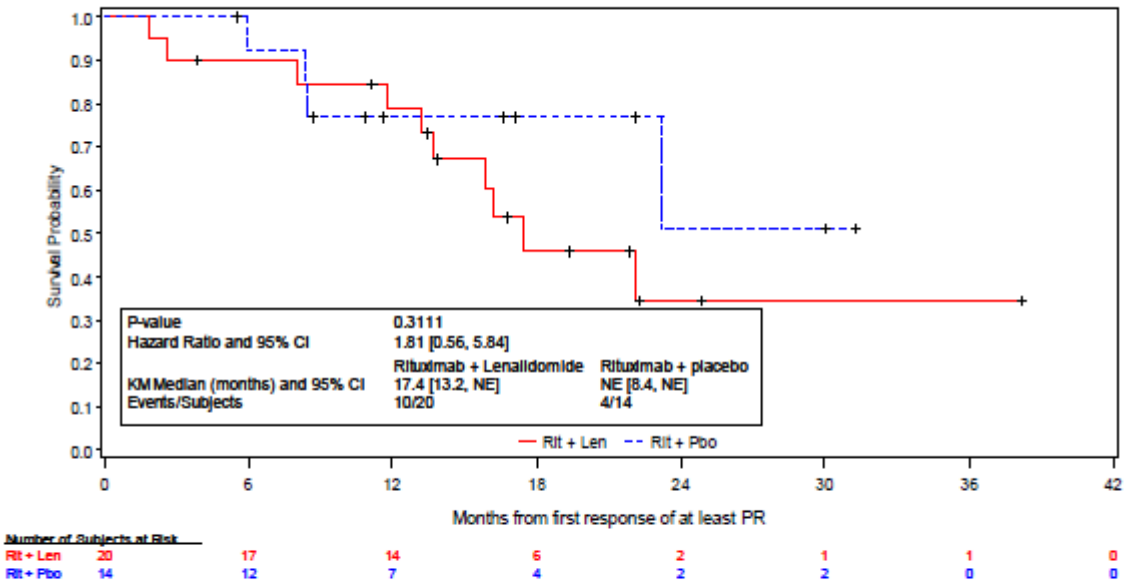
Similar results were noted in subjects with FL. In subjects with MZL, the median DOR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 17.4 months (13.2, NE) in the R^2 Arm and not estimable in in the Control Arm.

Figure 9: Kaplan-Meier Curve of Duration of Response by IRC Assessment per IWGRC 2007 in Subjects with FL – ITT Population



CI = confidence interval; FL = follicular lymphoma; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; KM = Kaplan-Meier; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).
Applicable to subjects who have achieved a complete response or partial response postbaseline.
Note: P-value from log-rank text. Hazard ratio and its CI were estimated from Cox proportional hazard method.
Data cutoff: 22 Jun 2018.

Figure 10: Kaplan-Meier Curve of Duration of Response by IRC Assessment per IWGRC 2007 in Subjects with MZL – ITT Population



CI = confidence interval; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; KM = Kaplan-Meier; MZL = marginal zone lymphoma; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).
Applicable to subjects who have achieved a complete response or partial response postbaseline.
Note: P-value from log-rank text. Hazard ratio and its CI were estimated from Cox proportional hazard method.
Data cutoff: 22 Jun 2018.

Duration of Complete Response (DOCR)

Overall, the median DOCR (95% CI) by IRC assessment per the 2007 IWGRC among responders was not estimable in either treatment arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 12 months was 84.2% (71.8%, 91.5%) *versus* 77.0% (57.6%, 88.3%) in the Control Arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 24 months was 67.4% (50.8%, 79.5%) *versus* 61.7% (41.2%, 76.8%) in the Control Arm. Similar results were shown in subjects with FL.

In subjects with MZL, the median DOCR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 22.1 months in the R^2 Arm and not estimable in the Control Arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 12 months was 88.9% (43.3%, 98.4%) *versus* 100.0% (100.0%, 100.0%) in the Control Arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 24 months was 44.4% (1.0%, 86.6%) *versus* 100.0% (100.0%, 100.0%) in the Control Arm.

Durable Complete Response Rate (DCRR)

Overall, 45 subjects (25.3%) in the R^2 Arm and 20 subjects (11.1%) in the Control Arm had a DCRR (p = 0.0006). Furthermore, of the subjects with ongoing CR, 6 subjects (10.0%) in theR^2 Arm and 3 subjects (9.1%) in the Control Arm achieved CR for < 1 year. Of subjects who had CR but were no longer in CR, 9 subjects (15.0%) in the R^2 Arm and 10 subjects (30.3%) in the Control Arm achieved CR for < 1 year. Similar results were noted in subjects with FL.

A similar trend was observed in subjects with MZL: DCRR was achieved by 7 subjects (22.6%)in the R^2 Arm *versus* 2 subjects (6.3%) in the Control Arm (p = 0.0816).

Overall survival (OS)

With a median follow up of 28.30 months, there were 16 deaths in the R^2 Arm *versus* 26 deaths in the Control Arm reported (HR [95% CI]: 0.61 [0.33, 1.13]); the medians OS for both arms have not been reached, see table below. Kaplan-Meier curves overlapped until 1 year with separation shown after 1 year, see figure below.

Table 20 Summary of Overall Survival – ITT Population

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Number of subjects, n (%)						
Number of subjects with event	11 (7.5)	24 (16.2)	5 (16.1)	2 (6.3)	16 (9.0)	26 (14.4)
Number of subjects censored	136 (92.5)	124 (83.8)	26 (83.9)	30 (93.8)	162 (91.0)	154 (85.6)
Median OS time (95% CI) (months)[a]	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
OS rate at 1 year (95% CI)	96.3% (91.4%, 98.5%)	95.9% (91.0%, 98.1%)	93.5% (76.6%, 98.3%)	96.9% (79.8%, 99.6%)	95.8% (91.4%, 98.0%)	96.0% (91.9%, 98.1%)
OS rate at 2 years (95% CI)	94.8% (89.5%, 97.5%)	85.8% (78.5%, 90.7%)	81.8% (61.3%, 92.1%)	93.6% (76.9%, 98.4%)	92.6% (87.3%, 95.7%)	87.2% (81.0%, 91.5%)
Hazard ratio	0.45[b]		2.89[b]		0.61[c]	
95% CI for hazard ratio	(0.22, 0.92)[b]		(0.56, 14.92)[b]		(0.33, 1.13)[c]	

CI = confidence interval; FL = follicular lymphoma; ITT = intent-to-treat; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; NE = not estimable; OS = overall survival; Pbo + Rit = placebo plus rituximab (Control Arm).

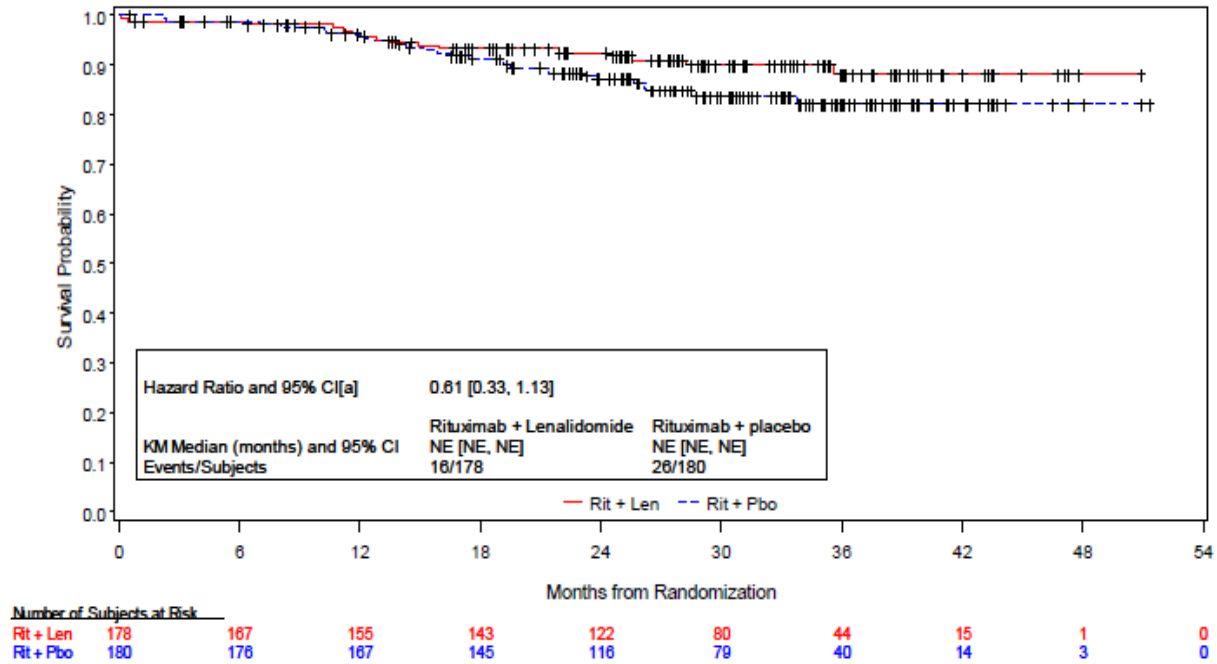
[a] Median estimate is from Kaplan-Meier analysis.

[b] From Cox proportional hazard model.

[c] For overall, hazard ratio and its CI were estimated Cox model adjusting for the stratification factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

Data cutoff: 22 Jun 2018

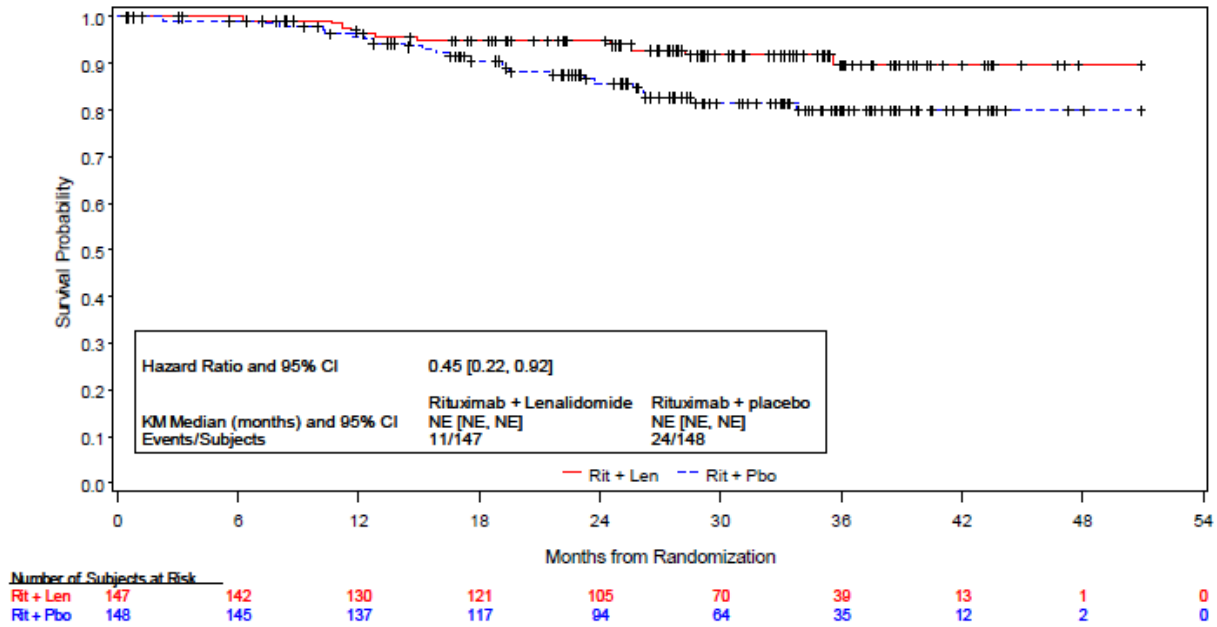
Figure 5 Kaplan-Meier Curve of Overall Survival in AUGMENT – ITT Population



CI = confidence interval; FL = follicular lymphoma; ITT = intent-to-treat; KM = Kaplan-Meier; MZL = marginal zone lymphoma; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).

[a] Hazard ratio and its confidence interval were estimated from Cox model adjusting for the stratification factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

Figure 6 Kaplan-Meier Curve of Overall Survival in Subjects with FL – ITT Population



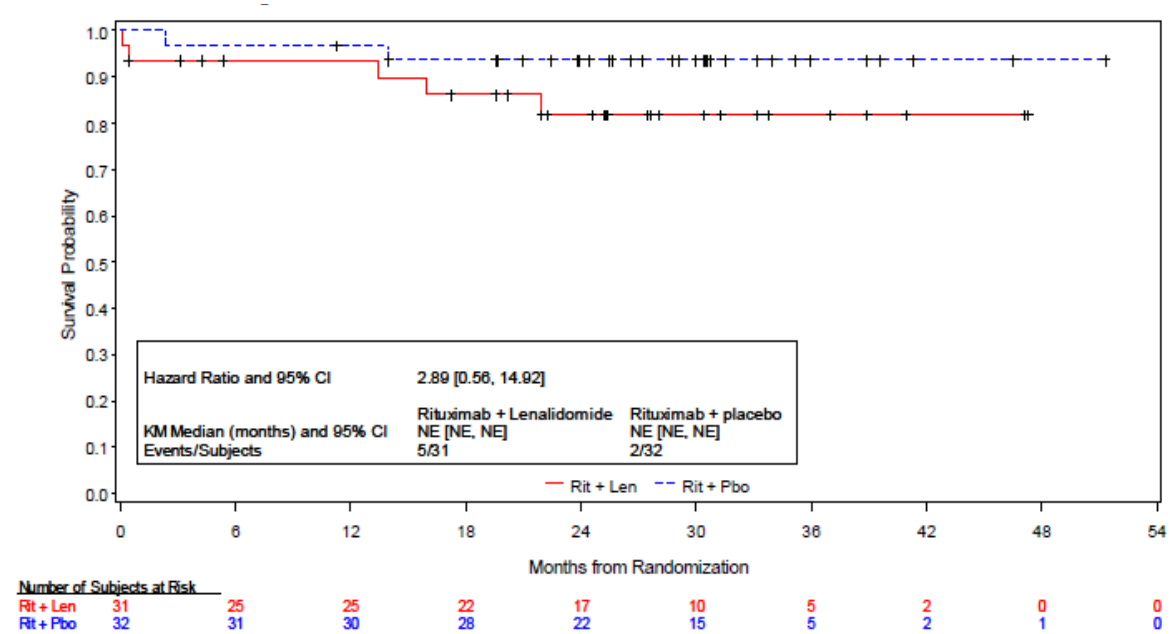
CI = confidence interval; FL = follicular lymphoma; KM = Kaplan-Meier; ITT = intent-to-treat;

Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); NE = not estimable; OS = overall survival; Pbo + Rit = placebo plus rituximab (Control Arm).

Median estimate is from Kaplan-Meier analysis. Hazard ratio and its CI were estimated from Cox proportional hazard method.

Data cutoff: 22 Jun 2018.

Figure 7 Kaplan-Meier Curve of Overall Survival in Subjects with MZL – ITT Population



CI = confidence interval; KM = Kaplan-Meier; ITT = intent-to-treat; MZL = marginal zone lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); NE = not estimable; OS = overall survival; Pbo + Rit = placebo plus rituximab (Control Arm).

Median estimate is from Kaplan-Meier analysis. Hazard ratio and its CI were estimated from Cox proportional hazard method.

Time to next antilymphoma treatment (TTNLT) and Time to next antilymphoma chemotherapy (TTNCT)

Table 21– *ITT Population*

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Time to next antilymphoma treatment						
# of subjects with events, n (%)	37 (25.2)	70 (47.3)	12 (38.7)	10 (31.3)	49 (27.5)	80 (44.4)
Hazard ratio estimate (95% CI)	0.43 (0.29, 0.65)[a]		1.58 (0.68, 3.67)[a]		0.54 (0.38, 0.78)[b]	
p-value	p < 0.0001[c]		p = 0.2833[c]		p = 0.0007[d]	
Time to next antilymphoma chemotherapy						
# of subjects with events, n(%)	24 (16.3)	48 (32.4)	6 (19.4)	9 (28.1)	30 (16.9)	57 (31.7)
Hazard ratio estimate (95% CI)	0.44 (0.27, 0.72)[a]		0.82 (0.29, 2.30)[a]		0.50 (0.32, 0.78)[b]	
p-value	p = 0.0007[c]		p = 0.7001[c]		p < 0.0017[d]	

CI = confidence interval; FL = follicular lymphoma; ITT = intent-to-treat; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm).

[a] From Cox proportional hazard model.

[b] From Cox proportional hazard model adjusting for the stratification factors noted below in footnote "d".

[c] P-value from log-rank test.

[d] P-value from log-rank test stratified by 3 factors: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

Data cutoff: 22 Jun 2018.

Table 22 Summary of Response Rate to Next Antilymphoma Chemotherapy – ITT Population

	Subjects with Next Antilymphoma Treatment	
	Len + Rit (N = 49)	Pbo + Rit (N = 80)
Objective Response (CR+PR) – n (%)	28 (57.1)	29 (36.3)
95% CI[a]	(42.2, 71.2)	(25.8, 47.8)
p-value[b]	0.0282	
Complete Response (CR) – n (%)	15 (30.6)	13 (16.3)
95% CI[a]	(18.3, 45.4)	(8.9, 26.2)
p-value[b]	0.0775	

CI = confidence interval; CR = complete response; ITT = intent-to-treat; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Pbo + Rit = placebo plus rituximab (Control Arm); PR = partial response.

[a] Exact confidence interval for binomial distributions.

[b] P-value obtained from Fisher-Exact test.

Note: Response rate to next antilymphoma treatment is defined as the proportion of subjects with best response of at least PR during the next antilymphoma therapy among subjects who have taken it.

Data cutoff: 22 Jun 2018.

Event-free Survival (EFS)

The EFS HR (95% CI) was 0.51 (0.38, 0.67); p-value < 0.0001. The EFS rate (95% CI) as assessed by the IRC at one year was 80.5% (73.7%, 85.7%) for the R^2 Arm and 56.2% (48.6%, 63.1%) for the Control Arm. Similar results were seen in subjects with FL.

In subjects with MZL, the median EFS (95% CI) was 20.2 months (14.5, NE) in the R^2 Arm and 25.1 months (9.2, NE) in the Control Arm. The EFS HR (95% CI) was 1.18 (0.60, 2.29); p-value = 0.6324. The EFS rate (95% CI) as assessed by the IRC at 1 year was 75.5% (55.2%, 85.7%) for the R^2 Arm and 65.6% (46.6%, 79.3%) for the Control Arm.

Exploratory endpoints

Response rate by IRC per the 1999 IWRC

Best Response by IRC Assessment per 1999 IWGRC – ITT Population

Results by IRC assessment per the 1999 IWGRC criteria (overall and in subjects with FL and subjects with MZL) were consistent with the results using the 2007 IWGRC criteria. The response rates were very similar to the 2007 IWGRC results, but differences were noted due to combined CR/CRu.

Table 23 Best Response by IRC Assessment per 1999 IWGRC – ITT Population

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Best response, n (%)						
Complete response	51 (34.7)	28 (18.9)	9 (29.0)	4 (12.5)	60 (33.7)	32 (17.8)
Complete response unconfirmed	12 (8.2)	7 (4.7)	1 (3.2)	1 (3.1)	13 (7.3)	8 (4.4)
Partial response	55 (37.4)	47 (31.8)	10 (32.3)	9 (28.1)	65 (36.5)	56 (31.1)
Stable disease	14 (9.5)	44 (29.7)	6 (19.4)	11 (34.4)	20 (11.2)	55 (30.6)
Progressive disease/Death	7 (4.8)	19 (12.8)	0 (0.0)	4 (12.5)	7 (3.9)	23 (12.8)
No evidence of disease	3 (2.0)	2 (1.4)	0 (0.0)	2 (6.3)	3 (1.7)	4 (2.2)
Unknown/ND/Missing	5 (3.4)	1 (0.7)	5 (16.1)	1 (3.1)	10 (5.6)	2 (1.1)
Objective response (CR/CRu + PR), n (%)	118 (80.3)	82 (55.4)	20 (64.5)	14 (43.8)	138 (77.5)	96 (53.3)
95% CI[a]	(72.9, 86.4)	(47.0, 63.6)	(45.4, 80.8)	(26.4, 62.3)	(70.7, 83.4)	(45.8, 60.8)
p-value	< 0.0001[b]		0.1313[b]		<0.0001[c]	
Complete response, n (%) (95% CI)	63 (42.9)	35 (23.6)	10 (32.3)	5 (15.6)	73 (41.0)	40 (22.2)
95% CI[a]	(34.7, 51.3)	(17.1, 31.3)	(16.7, 51.4)	(5.3, 32.8)	(33.7, 48.6)	(16.4, 29.0)
p-value	0.0005[b]		0.1477[b]		0.0002[c]	

Histological transformation

Table 24 Summary of Histological Transformation – ITT Population

	FL		MZL		Overall	
	Len + Rit (N = 147)	Pbo + Rit (N = 148)	Len + Rit (N = 31)	Pbo + Rit (N = 32)	Len + Rit (N = 178)	Pbo + Rit (N = 180)
Number of subjects with histological transformation, n (%)	2 (1.4)	9 (6.1)	0 (0.0)	1 (3.1)	2 (1.1)	10 (5.6)
95% CI[a]	(0.2, 4.8)	(2.8, 11.2)	(0.0, 11.2)	(0.1, 16.2)	(0.1, 4.0)	(2.7, 10.0)

CI = confidence interval; FL = follicular lymphoma; ITT = intent-to-treat; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm).

[a] 95% CI is based on the Clopper-Pearson exact method.

Data cutoff: 22 Jun 2018.

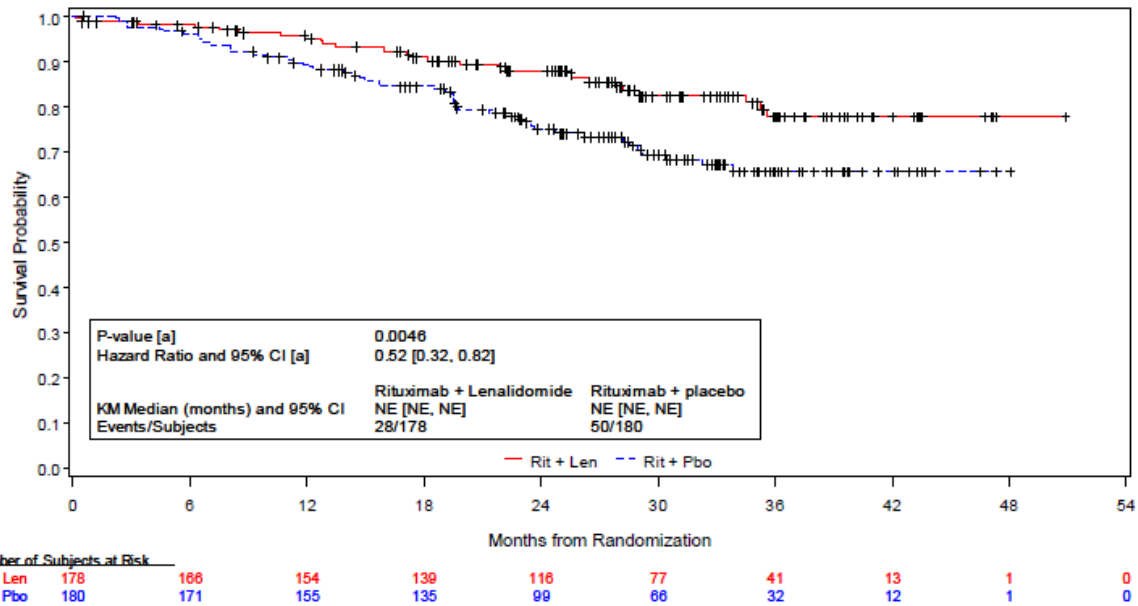
PFS2

Progression-free survival on next antilymphoma treatment (PFS2) was defined as time from randomization to the first observation of disease progression or death due to any cause after next antilymphoma treatment, or start of a third antilymphoma treatment since randomization in the study, whichever occurs first.

In the ITT Population, PFS2 was improved in the R2 Arm compared with the Control Arm with an HR (95% CI) of 0.52 (0.32, 0.82); p = 0.0046. Median PFS2was not estimable. Similar results were seen in subjects with FL.

In subjects with MZL, the PFS2 HR (95% CI) was 1.02 (0.39, 2.65); p = 0.9643.

Figure 8 *Kaplan-Meier Curve of Progression-free Survival on Next Antilymphoma Treatment – ITT Population*



CI = confidence interval; FL = follicular lymphoma; ITT = intent-to-treat; KM = Kaplan-Meier; MZL = marginal zone lymphoma; NE = not estimable; Rit + Len = rituximab plus lenalidomide (R^2 Arm); Rit + Pbo = rituximab plus placebo (Control Arm).

[a] P-value from stratified log-rank test. Stratification factors include the following: previous rituximab treatment (yes, no), time since last antilymphoma therapy (≤ 2, > 2 years), and disease histology (FL, MZL).

Note: Hazard ratio and its CI were obtained from Cox proportional hazard model adjusting for the stratification factors.

Data cutoff: 22 Jun 2018.

Evaluation of Quality of life

Health-related quality of life (HRQOL) were measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and EuroQol Group's questionnaire 5 dimensions (EQ-5D).

A minimal important difference (MID) of a ≥ 10-point change from baseline at the individual subject level was used to define the proportion of subjects reporting a meaningful difference in QOL for any given domain of the EORTC QLQ-C30 (Osoba, 1998). For the EQ-5D health utility, the MID was defined as a change from baseline of ≥ 0.08 for improvement and ≥ 0.10 for deterioration (Kvam, 2011). For the EQ-5D VAS, a MID of 7 was used (Pickard, 2007).

The HRQOL compliance rates, based on the number of expected subjects at a given visit as the denominator, were ≥ 89% across all assessment visits during the treatment phase, regardless of treatment group

Table 25 Compliance quotient EORCT-C30 global health status questionnaire – ITT population

Table 14.2.5.1.2
Compliance Quotient EORCT-QLQ-C30 Global Health Status Questionnaire
(Intent-to-Treat Population)

Visit	Rituximab + Lenalidomide (N=178)	Rituximab + Placebo (N=180)	Overall (N=358)
Screening	174/178 (97.8%)	177/180 (98.3%)	351/358 (98.0%)
p-value [a]	0.723		
CYCLE 4 DAY 1	158/163 (96.9%)	165/169 (97.6%)	323/332 (97.3%)
p-value [a]	0.747		
CYCLE 7 DAY 1	140/148 (94.6%)	140/148 (94.6%)	280/296 (94.6%)
p-value [a]	1.000		
CYCLE 10 DAY 1	121/131 (92.4%)	106/119 (89.1%)	227/250 (90.8%)
p-value [a]	0.390		
Cycle 12	113/119 (95.0%)	86/92 (93.5%)	199/211 (94.3%)
p-value [a]	0.767		

Note: A subject is considered compliant at a visit if the Global Health Status/QoL domain of the QLQ-C30 is not missing. The denominator is estimated based on the number of subjects who are alive and eligible for assessment at a given time point.
[a]: The p-values are calculated based on the Fisher exact test comparing Rituximab + Lenalidomide vs. Rituximab + Placebo.

The primary HRQOL analyses were performed based on the HRQOL-evaluable population, which included subjects in the ITT Population who had a global health status/QOL domain score at the Screening (ie, baseline) visit and at least 1 post baseline assessment. Of the ITT Population (n = 358), 94.4% (n = 338) met the inclusion criteria for the HRQOL-evaluable population at Screening (165 [92.7%] subjects in the R^2 Arm and 173 [96.1%] subjects in the Control Arm).

Table 26 *Summary of EORTC QLQ-C30 scale (global health status) and change from baseline – ITT population*

Table 14.2.4.1
Summary of EORTC QLQ-C30 Scale and Change from Baseline
ITT Population

			Rituximab + Lenalidomide (N=178)			Rituximab + Placebo (N=180)		
Scales	Visit	Stat	Baseline	Post Baseline	Change	Baseline	Post Baseline	Change
Global Health Status/QOL	Baseline	n	173			177		
		Mean	71.8			71.1		
		SD	20.16			18.59		
		Median	75.0			66.7		
		Min	0			17		
		Max	100			100		
	Cycle 4 Day 1	n	155	155	155	162	162	162
		Mean	72.5	72.5	0.0	71.9	75.0	3.1
		SD	20.24	17.65	18.78	18.27	16.03	18.01
		Median	75.0	75.0	0.0	75.0	83.3	0.0
		Min	0	17	-58	17	33	-50
		Max	100	100	58	100	100	67
	Cycle 7 Day 1	n	137	137	137	138	138	138
		Mean	73.5	73.5	-0.1	73.2	73.8	0.5
		SD	19.12	16.92	20.57	18.11	17.86	16.91
		Median	75.0	75.0	0.0	75.0	79.2	0.0
		Min	0	17	-42	17	33	-67
		Max	100	100	100	100	100	67
	Cycle 10 Day 1	n	119	119	119	105	105	105
		Mean	72.2	70.4	-1.8	73.6	75.2	1.7
		SD	19.57	19.49	20.98	18.29	17.58	19.14
		Median	75.0	75.0	0.0	75.0	83.3	0.0
		Min	0	0	-75	33	17	-50
		Max	100	100	50	100	100	50

			Rituximab + Lenalidomide (N=178)			Rituximab + Placebo (N=180)		
Scales	Visit	Stat	Baseline	Post Baseline	Change	Baseline	Post Baseline	Change
Global Health Status/QOL	End of Treatment	n	151	151	151	158	158	158
		Mean	73.2	68.6	-4.6	72.2	71.2	-0.9
		SD	20.14	20.10	20.77	18.50	19.92	21.01
		Median	75.0	66.7	0.0	75.0	70.8	0.0
		Min	0	0	-75	17	0	-100
		Max	100	100	50	100	100	67

At a group level, there was no change from baseline through the end of treatment exceeding the threshold of MID in the global health status/QOL domain of the EORTC QLQ-C30, regardless of treatment group.

Table 27 *Summary of change from baseline in HRQOL by visit (global QOL) – HRQOL-evaluable population*

Table 14.2.5.3.1 Appendix
Summary of Change from Baseline in HRQoL by Visit
(HRQoL Evaluable Population)

		Cycle 4		Cycle 7		Cycle 10		Cycle 12 TC		FU 1		FU 2		FU 3	
Domain	Treatment	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Global QoL	Rituximab + Lenalidomide	155	0.0	137	-0.1	119	-1.8	111	-1.4	119	3.5	102	2.8	83	2.5*
	Rituximab + Placebo	162	3.1	138	0.5	105	1.7	85	1.3	88	1.7	69	-0.2	45	-2.8*

Note: "HRQoL evaluable population" are subjects with an evaluable QLQ-C30 questionnaire at screening visit and at least one post-baseline visit. A QLQ-C30 is considered evaluable if the Global Health Status/QoL scale of the QLQ-C30 is not missing. FU = follow-up. The "*" sign will be used to indicate a significant difference ($p < 0.05$) in the change from baseline between treatment groups at a given assessment visit based on ANCOVA tests

Comparison of the proportion of subjects in each treatment group who experienced a clinically meaningful worsening across each post baseline visit showed that there was no significant difference in the worsening of the global health status/QOL domain between treatment groups across all post baseline assessment visits, except for the Cycle 4 Day 1 visit, when the R^2 Arm showed a significant greater percentage of worsening ($p = 0.049$).

The difference in the time to first clinically meaningful worsening in the global health status/QOL domain between treatment groups was not statistically significant (HR = 1.22; p = 0.1594).

Table 28 Summary of Time to First Clinically Meaningful Deterioration (HRQoL Evaluable Population)

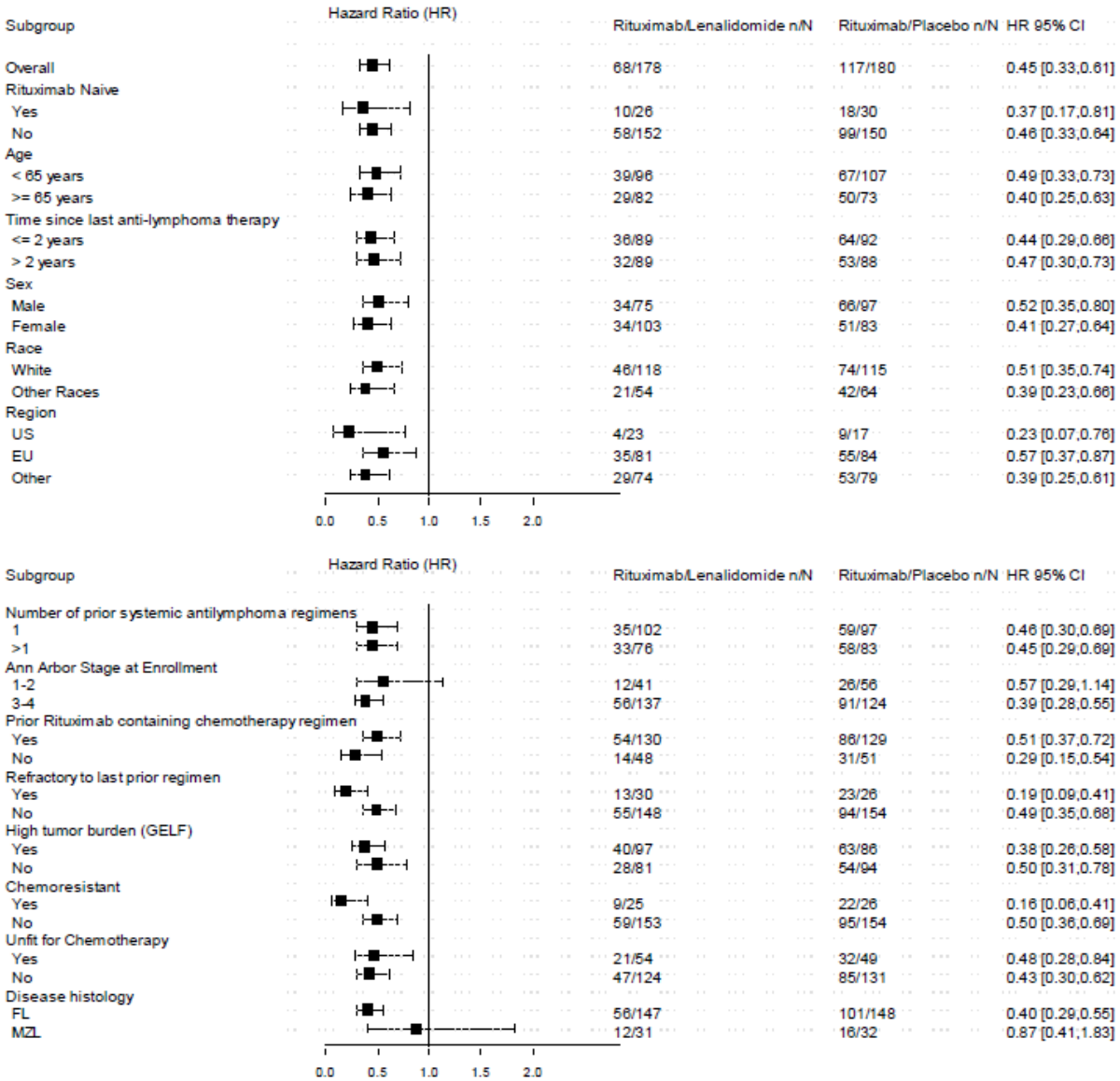
Table 14.2.5.7.2
Summary of Time to First Clinically Meaningful Deterioration
(HRQoL Evaluable Population)

Domain	Arm	Median (95% CI) (Months)			HR[a]	95% CI		p-value
Global QoL[b]	Rituximab + Lenalidomide (N=165)	11.4	(6.2	19.5)	1.2685	0.9500	1.6937	0.1069
	Rituximab + Placebo (N=173)	23.6	(14.2	28.5)				
Global QoL[c]	Rituximab + Lenalidomide (N=165)	11.4	(6.3	17.0)	1.2201	0.9248	1.6097	0.1594
	Rituximab + Placebo (N=173)	19.5	(12.8	26.1)				

There were, however, a few domains where the R^2 Arm had a significantly greater percentage of worsening than the Control Arm for at least 2 consecutive assessment visits during the treatment period, including fatigue, appetite loss, constipation, and diarrhoea.

Subgroup analyses

Figure 9 *Forest Plot for Subgroup Analyses for Progression-free Survival by IRC Assessment per 2007 IWGRC with Censoring Rules Based on EMA Guidance – ITT Population – AUGMENT Study*



CI = confidence interval; EMA = European Medicines Agency; EU = European Union; FL = follicular lymphoma; GELF = Groupe d'Etude des Lymphomes Folliculaires; HR = hazard ratio; IRC = Independent Review Committee; ITT = intent-to-treat; IWGRC = International Working Group Response Criteria; MZL = marginal zone lymphoma; US = United States.

Hazard ratio and its CI were estimated from unstratified Cox model except overall ITT Population, for which HR and its CI were estimated using Cox model adjusted by the 3 stratification factors.

Source: CSR NHL-007 Figure 18.

Supportive analyses on mITT population

The mITT Population was supportive to evaluate robustness of efficacy findings

Ancillary analyses

PFS

Table 29 PFS by IRC assessment per 2007 IWGRC with censoring rules based on EMA Guidance

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Table 14.2.1.1.4
Progression-free Survival (PFS) by IRC Assessment per 2007 IWGRC with Censoring Rules Based on EMA Guidance
mITT Population

Statistics	Rituximab + Lenalidomide (N=152)	Rituximab + Placebo (N=160)
Number of Subjects		
# of Subjects with event n(%)	57 (37.5)	104 (65.0)
# of Subjects censored n(%)	95 (62.5)	56 (35.0)
Median PFS (95% CI) (months) [a]	NE (25.1, NE)	14.0 (11.4, 16.7)
PFS Rate at 6 months (95% CI)	91.2% (85.4%, 94.8%)	77.3% (70.0%, 83.1%)
PFS Rate at 1 year (95% CI)	82.1% (74.8%, 87.4%)	56.9% (48.7%, 64.3%)
PFS Rate at 2 years (95% CI)	61.0% (51.9%, 68.8%)	37.3% (29.4%, 45.1%)
P-value [b]	<0.0001	
Hazard ratio (HR) estimate [c]	0.43	
95% CI for HR	(0.31, 0.60)	

[a] Median estimate is from Kaplan-Meier analysis.
[b] P-value from log-rank test stratified by previous rituximab treatment (yes; no), time since last antilymphoma therapy (<= 2; > 2 year), and disease histology (FL; MZL).
[c] From Cox proportional hazard model adjusting for the stratification factors mentioned above.
Program Source: \\wilbtib\wilbtib05\Celgene CGNCC5013NHL007\Trunk\TLF\T1402010104.sas Version: Final
Data Source: ADTTEIRC Data Extraction Date: 17JUL2018 Run date: 12SEP2018

Overall Survival

Table 30 OS, 2007 IWGRC with censoring rules

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Table 14.2.2.1.2
Summary of Overall Survival
mITT Population

Statistics	Rituximab + Lenalidomide (N=152)	Rituximab + Placebo (N=160)
Number of Subjects		
# of Subjects with event n(%)	12 (7.9)	22 (13.8)
# of Subjects Censored n(%)	140 (92.1)	138 (86.3)
Median OS (95% CI) (months) [a]	NE (NE, NE)	NE (NE, NE)
OS Rate at 1 year (95% CI)	96.5% (91.9%, 98.5%)	96.2% (91.7%, 98.3%)
OS Rate at 2 years (95% CI)	93.6% (88.0%, 96.6%)	87.8% (81.2%, 92.1%)
Hazard ratio (HR) estimate [b]	0.54	
95% CI for HR	(0.27, 1.10)	

[a] Median estimate is from Kaplan-Meier analysis.
[b] From Cox proportional hazard model adjusting for the three stratification factors: previous rituximab treatment (yes; no), time since last antilymphoma therapy (<= 2; > 2 year), and disease histology (FL; MZL).
Program Source: \\wilbtib\wilbtib05\Celgene CGNCC5013NHL007\Trunk\TLF\T1402020102.sas Version: Final
Data Source: ADTTE Data Extraction Date: 17JUL2018 Run date: 12SEP2018

Duration of response

Table 31 Duration of response by IRC assessment per 2007 IWGRC with censoring rules

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Table 14.2.2.4.2
Summary of Duration of Response by IRC Assessment per 2007 IWGRC
Subjects Achieved Response in mITT Population

Statistics	Rituximab + Lenalidomide (N=123)	Rituximab + Placebo (N=88)
Number of Subjects with Response (CR/PR)	123	88
# of Subjects with events (progressed/died after CR/PR) - n (%)	39 (31.7)	46 (52.3)
# of Subjects censored (not progressed/died after CR/PR) - n (%)	84 (68.3)	42 (47.7)
Median duration of response (95% CI) (months) [a]	NE (25.3, NE)	21.7 (11.3, 27.8)
Probability of duration of response >= 6 months (95% CI) [a]	94.1% (88.1%, 97.2%)	82.4% (72.4%, 89.0%)
Probability of duration of response >= 12 months (95% CI) [a]	83.2% (74.9%, 88.9%)	61.4% (50.0%, 70.9%)
Probability of duration of response >= 18 months (95% CI) [a]	70.7% (60.9%, 78.5%)	51.6% (40.0%, 62.0%)
Probability of duration of response >= 24 months (95% CI) [a]	63.8% (53.2%, 72.7%)	43.4% (31.4%, 54.9%)
P-value [b]	0.0013	
Hazard ratio (HR) estimate [c]	0.50	
95% CI for HR	(0.33, 0.77)	

Best response and Objective response

Table 32 Best Response by IRC assessment per 2007 IWGRC with censoring rules

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Table 14.2.2.2.1.2
Best Response Assessment by IRC per 2007 IWGRC
mITT Population

	Rituximab + Lenalidomide (N=152)	Rituximab + Placebo (N=160)
Best Response		
Complete Response (CR) - n (%)	54 (35.5)	31 (19.4)
Partial Response (PR) - n (%)	69 (45.4)	57 (35.6)
Stable Disease (SD) - n (%)	18 (11.8)	49 (30.6)
Progressive Disease (PD)/Death - n (%)	7 (4.6)	21 (13.1)
No Evidence of Disease (NED) at baseline - n (%)	3 (2.0)	2 (1.3)
UNK/Not Done/Missing - n (%)	1 (0.7)	0
Objective Response (CR+PR) - n (%)	123 (80.9)	88 (55.0)
95% CI [a]	(73.8, 86.8)	(46.9, 62.9)
P-value [b]	<0.0001	
Complete Response (CR) - n (%)	54 (35.5)	31 (19.4)
95% CI [a]	(27.9, 43.7)	(13.6, 26.4)
P-value [b]	0.0019	

Duration of complete response

Table 33 *Duration of CR by IRC assessment per 2007 IWGRC with censoring rules*

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Table 14.2.2.5.2
Summary of Duration of Complete Response by IRC Assessment per 2007 IWGRC
Subjects Achieved Complete Response in mITT Population

Statistics	Rituximab + Lenalidomide (N=54)	Rituximab + Placebo (N=31)
Number of Subjects with CR	54	31
# of Subjects with event (progressed/died after CR) - n (%)	14 (25.9)	10 (32.3)
# of Subjects censored (not progressed/died after CR) - n (%)	40 (74.1)	21 (67.7)
Median duration of CR (95% CI) (months) [a]	NE (25.3, NE)	NE (15.0, NE)
Probability of duration of CR >= 6 months (95% CI) [a]	90.5% (78.7%, 95.9%)	90.0% (72.0%, 96.7%)
Probability of duration of CR >= 12 months (95% CI) [a]	84.4% (71.2%, 91.9%)	78.7% (58.5%, 89.9%)
Probability of duration of CR >= 18 months (95% CI) [a]	79.2% (64.4%, 88.3%)	66.2% (44.8%, 81.0%)
Probability of duration of CR >= 24 months (95% CI) [a]	69.7% (52.8%, 81.6%)	66.2% (44.8%, 81.0%)
P-value [b]	0.5208	
Hazard ratio (HR) estimate [c]	0.77	
95% CI for HR	(0.34, 1.73)	

EFS

Table 34 EFS by IRC assessment per 2007 IWGRC with censoring rules

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Table 14.2.2.6.2
Event-free Survival (EFS) by IRC Assessment per 2007 IWGRC
mITT Population

Statistics	Rituximab + Lenalidomide (N=152)	Rituximab + Placebo (N=160)
Number of Subjects		
# of Subjects with events n(%)	69 (45.4)	113 (70.6)
# of Subjects censored n(%)	83 (54.6)	47 (29.4)
Median EFS (95% CI) (months) [a]	39.4 (22.3, NE)	13.9 (11.4, 16.7)
EFS Rate at 6 months (95% CI)	90.7% (84.8%, 94.4%)	76.9% (69.5%, 82.6%)
EFS Rate at 1 year (95% CI)	79.8% (72.3%, 85.4%)	56.6% (48.5%, 63.9%)
EFS Rate at 2 years (95% CI)	55.3% (46.6%, 63.2%)	34.7% (27.2%, 42.2%)
P-value [b]	<0.0001	
Hazard ratio (HR) estimate [c]	0.49	
95% CI for HR	(0.36, 0.66)	

TTNLT

Table 35 TTNLT by IRC assessment per 2007 IWGRC with censoring rules based on EMA Guidance

Celgene Corporation
Protocol: CC-5013-NHL-007

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Database Cutoff Date: 22JUN2018

Table 14.2.2.7.2
Time to Next Antilymphoma Treatment (TTNLT)
mITT Population

Statistics	Rituximab + Lenalidomide (N=152)	Rituximab + Placebo (N=160)
Number of Subjects		
# of Subjects with events n(%)	44 (28.9)	72 (45.0)
# of Subjects censored n(%)	108 (71.1)	88 (55.0)
Median TTNLT (95% CI) (months) [a]	NE (NE, NE)	32.2 (22.0, NE)
TTNLT Rate at 6 months (95% CI)	96.7% (92.2%, 98.6%)	91.8% (86.3%, 95.2%)
TTNLT Rate at 1 year (95% CI)	89.7% (83.5%, 93.7%)	79.7% (72.5%, 85.2%)
TTNLT Rate at 2 years (95% CI)	74.3% (65.9%, 81.0%)	57.0% (48.5%, 64.6%)
P-value [b]	0.0012	
Hazard ratio (HR) estimate [c]	0.54	
95% CI for HR	(0.37, 0.79)	

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36 Summary of Efficacy for trial AUGMENT

Title: A PHASE 3, DOUBLE-BLIND RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF RITUXIMAB PLUS LENALIDOMIDE *VERSUS* RITUXIMAB PLUS PLACEBO IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENTLYMPHOMA	
Study identifier	AUGMENT (Study CC-5013-NHL-007)
Design	Phase 3, double-blind, randomized at 1:1 ratio, placebo-controlled, multicenter study

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Experimental arm		Lenalidomide 10 or 20 mg (on Days 1-21 of Cycles 1 to 12) + Rituximab 375 mg/m2 (weekly in Cycle 1 and then on D1 of Cycles 2 to 5),<duration>, N=178
	Control arm		Placebo 10 or 20 mg (on Days 1-21 of Cycles 1 to 12) + Rituximab 375 mg/m2 (weekly in Cycle 1 and then on D1 of Cycles 2 to 5), <duration>, N=180
Endpoints and definitions	Primary endpoint	PFS	Progression-free survival: Time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurred first
	Secondary endpoints	Response rate (ORR and CRR)	Overall response rate: Proportion of subjects with best response of at least PR during the trial without administration of new antilymphoma therapy. The number and percent of subjects with CR/PR were tabulated by treatment arm. Complete response rate: Proportion of subjects with best response of CR during the study without administration of new antilymphoma therapy. The number and percent of subjects with CR were tabulated by treatment arm.
		DOR	Duration of response: Time from initial response (at least PR) until documented PD or death. Subjects who did not progress at the time of analysis were censored at the last assessment date that the subject was known to be progression free. Subjects who received a new treatment without documented progression were censored at the last assessment date that the subject was known to be progression free.
		DOCR	Duration of complete response: Time of initial CR until documented disease progression or death. Subjects who did not progress at the time of analysis were censored at the last assessment date that the subject was known to be progression free

		DCRR	Durable complete response rate: Proportion of subjects with a best response of CR that lasted no less than one year (⩾ 48 weeks) during the study prior to administration of new antilymphoma therapy
		EFS	Event-free survival: Time from the date of randomization to the date of first documented disease progression, initiation of a new antilymphoma treatment, or death by any cause before documented progression
		OS	Overall survival: Time from randomization to death from any cause
		TTNLT	Time to next antilymphoma treatment: Time from date of randomization to date of first documented administration of a new antilymphoma treatment (including chemotherapy, radiotherapy, radio-immunotherapy, or immunotherapy).
		TTNCT	Time to next anti-lymphoma chemotherapy: Time from date of randomization to date of first documented administration of a new antilymphoma chemotherapy
		PFS2	Progression-free survival on next antilymphoma treatment: Time from randomization to the first observation of disease progression or death due to any cause after next antilymphoma treatment, or start of a third antilymphoma treatment since randomization in the study, whichever occurs first. For subjects without baseline assessment, PFS2 was censored at randomization date.
		Histological transformation	Based on documentation of histological transformation as assessed by the investigator
Database lock	22 Jun 2018		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat (ITT):**all subjects who were randomized into the trial, regardless of whether they received study treatment or not		
Descriptive statistics and estimate variability	Treatment group	**Len + Rit**	**Pbo + Rit**
	Number of subject	N = 178	N = 180
	Median PFS, months	39.4	14.1
	95% CI	24.9, NE	11.4, 16.7

	Objective response (CR+PR), n (%)	138 (77.5)	96 (53.3)
	95% CI	70.7, 83.4	45.8, 60.8
	DCRR, n (%)	45 (25.3)	20 (11.1)
	95% CI	19.1, 32.3	6.9, 16.6
	Median DOR, months	36.6	21.7
	95% CI	22.9, NE	12.8, 27.6
	OS, number (%) of deaths	16 (9.0)	26 (14.4)
	Variability statistic	N/A	N/A
	Median EFS, months	27.6	13.9
	95% CI	22.1, NE	11.4, 16.7
	TTNLT, number of subjects with events (%)	49 (27.5)	80 (44.4)
	Variability statistic	N/A	N/A
	TTNCT, n (%)	30 (16.9)	57 (31.7)
	Variability statistic	N/A	N/A
	PFS2, n (%)	28 (15.7)	50 (27.8)
	Variability statistic	N/A	N/A
	Histological trans, n (%)	2 (1.1)	10 (5.6)
	95% CI	0.1, 4.0	2.7, 10.0
Effect estimate per comparison	Primary endpoint (PFS) ITT population	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.45
		95% CI	0.33, 0.61
		P-value	< 0.0001
	PFS follicular lymphoma patients	Comparison groups	Len+ Ritux, Pbo + Rit
		Hazard ratio	0.40
		95% CI	0.29; 0.55
		P-value	< 0.0001
	PFS Marginal Zone Lymphoma patients	Comparison groups	Len+ Ritux, Pbo + Rit
		Hazard ratio	0.87
		95% CI	0.41; 1.83
		P-value	0.7068
	Secondary endpoint (DOR)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.53
		95% CI	0.36, 0.79
		P-value	0.0015
	Secondary endpoint (OS)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.61

		95% CI	0.33, 1.13
		P-value	N/A
	Secondary endpoint (EFS)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.51
		95% CI	0.38, 0.67
		P-value	<0.0001
	Secondary endpoint (TTNLT)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.54
		95% CI	0.38, 0.78
		P-value	0.0007
	Secondary endpoint (TTNCT)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.50
		95% CI	0.32, 0.78
		P-value	<0.0017
	Secondary endpoint (PFS2)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.52
		95% CI	0.32, 0.82
		P-value	0.0046
Notes	<free text>		
Analysis description	**Secondary analysis**		
Analysis population and time point description	**Modified Intended to treat (mITT):**all randomized subjects who received at least one dose of study medication, had a confirmed diagnosis of relapsed/refractory FL or MZL by central pathology review, except SMZL which was based on local pathology assessment, and had baseline (Screening) and at least one post baseline tumour assessment for efficacy		
Descriptive statistics and estimate variability	Treatment group	**Len + Rit**	**Pbo + Rit**
	Number of subject	N = 152	N = 160
	Median PFS, months	NE	14.0
	95% CI	25.1, NE	11.4, 16.7
	Objective response (CR+PR), n (%)	126 (82.9)	97 (60.6)
	95% CI	76.0, 88.5	52.6, 68.2
	DCRR, n (%)	40 (26.3)	20 (12.5)
	95% CI	19.5, 34.1	7.8, 18.6
	Median DOR, months	NE	21.7
	95% CI	25.3, NE	11.3, 27.8
	OS, number (%) of deaths	12 (7.9)	22 (13.8)
	Variability statistic	N/A	N/A

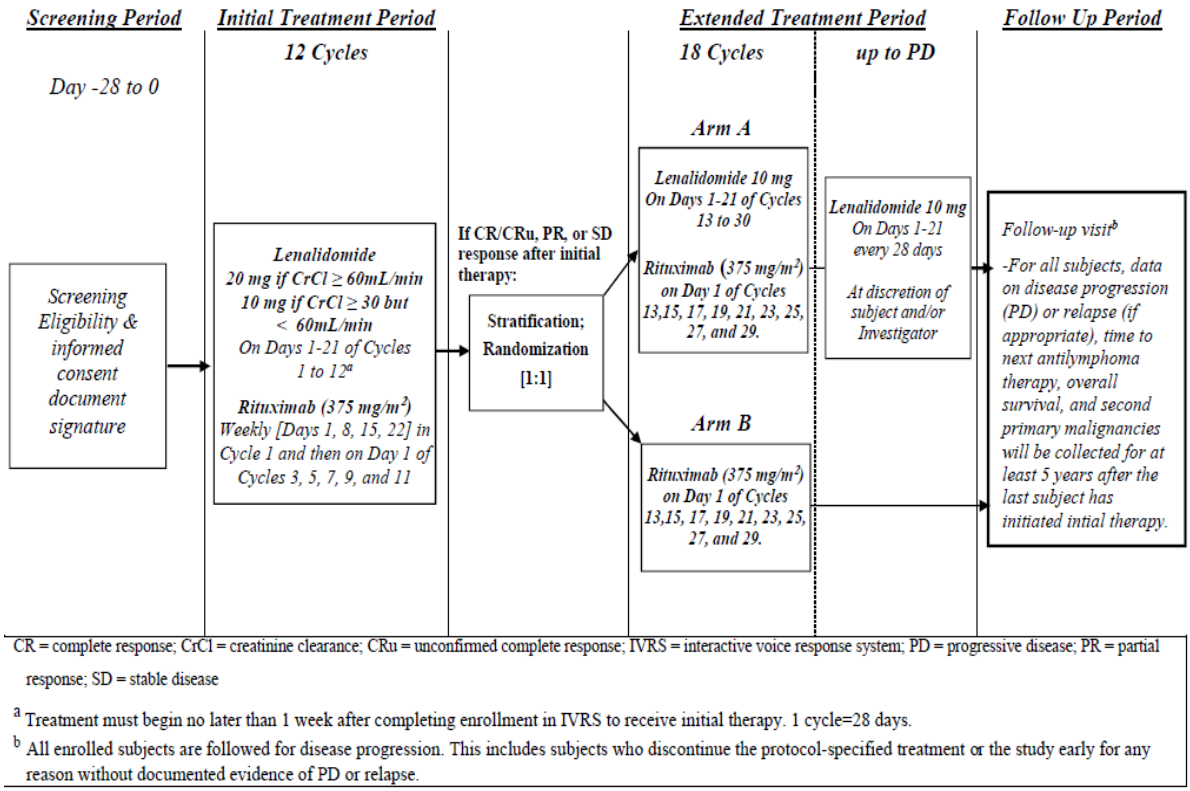
	Median EFS, months	39.4	13.9
	95% CI	22.3, NE	11.4, 16.7
	TTNLT, number of subjects with events (%)	44 (28.9)	72 (45.0)
	Variability statistic	N/A	N/A
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.43
		95% CI	0.31, 0.60
		P-value	<0.0001
	Secondary endpoint (DOR)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.50
		95% CI	0.33, 0.77
		P-value	0.0013
	Secondary endpoint (OS)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.54
		95% CI	0.27, 1.10
		P-value	N/A
	Secondary endpoint (EFS)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.49
		95% CI	0.36, 0.66
		P-value	<0.0001
	Secondary endpoint (TTNLT)	Comparison groups	Len + Rit, Pbo + Rit
		Hazard ratio	0.54
		95% CI	0.37, 0.79
		P-value	0.0012
Notes	<free text>		

Supportive study

➢ MAGNIFY (Study CC-5013-NHL-008)

This is a multicenter, 2-part Phase 3b study with an open-label, single-arm Initial Treatment Period with R^2 followed by a 2-arm, randomized Extended Treatment Period in subjects with previously treated FL Grades 1 to 3b, tFL, MZL, or MCL. The study design is presented below.

Figure 10 Overall study design of MAGNIFY



CR = complete response; CrCl = creatinine clearance; CRu = unconfirmed complete response; IVRS = interactive voice response system; PD = progressive disease; PR = partial response; SD = stable disease

[a] Treatment must begin no later than 1 week after completing enrollment in IVRS to receive initial therapy. 1 cycle=28 days.

[b] All enrolled subjects are followed for disease progression. This includes subjects who discontinue the protocol-specified treatment or the study early for any reason without documented evidence of PD or relapse.

This study is ongoing, and enrolment is ongoing (295 subjects enrolled as of 01 May 2017). The interim clinical study report submitted for this study presents safety and efficacy data from the Initial Treatment Period only based on a data cut-off date of 01 May 2017.

Eligible subjects were 18 years or older with histologically confirmed FL Grade 1, 2, or 3; tFL; MZL; or MCL and were previously treated with at least one prior lymphoma treatment and have documented relapsed, refractory, or progressive disease (PD) (subjects could be refractory or non-refractory to rituximab). Following the Screening Period, all eligible subjects entered a 12-cycle Initial Treatment Period during which they received 12 cycles of R^2.

The primary endpoint for the final analysis is PFS of the extended treatment period post-randomization whereas the primary efficacy endpoint for the interim analysis is ORR of the Initial Treatment Period, defined as proportion of subjects with a best overall response of at least PR (including CR, CRu and PR) before any Extended Treatment Period treatment and prior to any subsequent anti-lymphoma therapy using 1999 IWGRC with a modification to allow inclusion of extranodal disease as measurable disease.

Secondary efficacy endpoints include CR (CR and CRu) rate, DOR, DOCR, TTR, and ORR. Transformation and PFS are exploratory efficacy endpoints.

The analysis population is defined as follows:

Induction intent-to-treat (IITT) population: all enrolled subjects with FL Grade 1 to 3a or MZL who met all the eligibility criteria for the study.

Induction efficacy evaluable (IEE) population: all subjects in the IITT population who have received at least 1 dose of initial therapy, who have baseline and at least one post-baseline efficacy assessment, including subjects who died or progressed before first on-study assessment. The IEE population will be used as the primary analysis population to evaluate the response rate of the initial treatment period.

Induction Safety Population: subjects with FL Grade 1 to 3a or MZL who had received at least 1 dose of initial therapy, either lenalidomide or rituximab. Safety analyses of the Induction Period are based on the induction safety population.

Second primary malignancy (SPM) safety population: all subjects with FL Grade 1 to 3b, tFL, MZL and MCL who have received at least 1 dose of initial therapy, either lenalidomide or rituximab. SPM safety population will be used for the SPM analyses.

The number of subjects in each analysis population is summarized below.

Table 37 *Number of Subjects Included in the Data Sets Analyzed (Initial Treatment Period)*

Parameter	FL Subjects	MZL Subjects	Total
Induction Efficacy Evaluable Population[a]	148	39	187
Induction Safety Population[b]	177	45	222
Induction Intent-to-Treat Population[c]	186	46	232
Second Primary Malignancy Safety Population[d]	177	45	283

FL = Follicular lymphoma; IEE = induction efficacy evaluable; IITT = induction intent-to-treat; MZL = marginal zone lymphoma; tFL = transformed follicular lymphoma

a The IEE Population is defined as all subjects in the IITT Population who have received at least 1 dose of initial therapy, who have at least 1 post-baseline efficacy assessment including subjects who died or progressed before first on-study assessment.

b The Induction Safety Population is defined as subjects with FL Grade 1 to 3a or MZL who have received at least 1 dose of initial therapy, either lenalidomide or rituximab.

c The IITT Population is defined as all enrolled subjects with FL Grade 1 to 3a or MZL who met all criteria for eligibility into the study.

d Second Primary Malignancy Safety Population is defined as all subjects with FL Grade 1 to 3b, tFL, MZL and MCL who have received at least 1 dose of initial therapy, either lenalidomide or rituximab.

Data Cutoff: 01 May 2017

The results are summarized in the table below.

Table 38 Summary of MAGNIFY

Study Design: Phase 3b, multicenter study of initial treatment with 12 cycles of R^2 followed by randomized comparison of extended treatment with R^2 *versus* rituximab			
Key Baseline Characteristics for ITT Population: median age 66.0years, males 54.3%, white 93.1%. FL: 186(80.2 %) subjects; MZL:46(19.8%) subjects. Most subjects had an ECOG performance score of0/1 (45.7%/50.4%) and Ann Arbor stage III/IV (24.6%/64.2%); 12.5% had B symptoms, 40.5% were refractory to rituximab, 23.3%were refractory to both rituximab and chemotherapy, 66.4% had high tumour burden disease, and 35.3% had early relapsed disease.			
Primary Endpoint for the interim CSR: ORR			
Other Endpoints: CR rate, DOR, DOCR, TTR, transformation, 1-year PFS rate			
Conclusions: • R^2 demonstrated high antitumour activity in both FL and MZL with overall response observed in 67.9% of total subjects, 70.3% of subjects with FL, and 59.0% of subjects with MZL. • R^2 resulted in high quality responses in both FL and MZL with complete response in 42.2%of total subjects, 41.9% of subjects with FL, and 43.6% of subjects with MZL. • The responses with R^2 are durable with74.7% of responses ongoing at2-year follow up. • Clinically meaningful responses were observed in subjects who were refractory to rituximab or refractory to both rituximab and chemotherapy (double-refractory) in both FL and MZL.			
	R^2		
	FL (N=148)	**MZL (N=39)**	**Total (N=187)**
Overall response (CR, CRu, PR), n(%), (95%CI)[a]	104 (70.3) (62.2%, 77.5%)	23 (59.0) (42.1, 74.4)	127 (67.9) (60.7%, 74.5%)
ORR in rituximab-refractory[b],% (95%CI)	58.3 (44.9%, 70.9%)	58.8 (32.9, 81.6)	58.4 (46.6%, 69.6%)
ORR in double-refractory[c],% (95%CI)	44.4 (27.9%, 61.9%)	55.6 (21.2, 86.3)	46.7 (31.7, 62.1%)
CR (CR+CRu),n(%), (95%CI)[a]	62 (41.9) (33.8%, 50.3%)	17 (43.6) (27.8%, 60.4%)	79 (42.2) (35.1%, 49.7%)
CR rate in rituximab- (95%CI)	33.3 (21.7%, 46.7%)	41.2 (18.4, 67.1)	35.1 (24.5%, 46.8%)
CRrate in double-refractory[c],% (95%CI)	19.4 (8.2%, 36.0%)	33.3% (7.5, 70.1)	22.2 (11.2%, 37.1%)
DOR			
1-yearDORrate,%(95%CI)[d]	79.5 (65.5%, 88.3%)	76.7 (49.2%, 90.6%) 70.0% (rituximab-refractory)	79.1 (67.4%, 87.0%)
2-year DOR rate,%(95%CI)[d]	73.9 (58.5%, 84.3%)	76.7 (49.2%, 90.6%) 70.0% (rituximab-refractory)	74.7 (61.8%, 83.8%)

1-year DOCR rate,%(95%CI)[e]	80.7 (61.4%, 91.0%)	81.8 (44.7%, 95.1%)	81.2 (65.5%, 90.3%)
Median TTR (Min, Max), months	2.8 (1.7, 12.0)	2.8 (2.4, 11.1)	2.8 (1.7, 12.0)
1-year PFS rate,%(95%CI)	68.5 (57.4%, 77.3%)	69.8 (49.5%, 83.2%)	68.9 (59.5%, 76.5%)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOCR = duration of complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; IITT = induction intent-to-treat; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; NC = not calculated; NE = not estimable; ORR = overall response rate; PFS = progression-free survival; PR = partial response; R2 = lenalidomide in combination with rituximab; TTR = time to response.
a 95% CI is based on the Clopper-Pearson exact method.
b A total of 60, 17, and 77 subjects in the FL, MZL, and Induction Efficacy Evaluable Populations, respectively, were rituximab-refractory.
c A total of 36, 9, and 45 subjects in the FL, MZL, and Induction Efficacy Evaluable Populations, respectively, were double-refractory.
d Number of responders was 104, 23, and 127 for FL, MZL, and total, respectively. Statistics obtained from Kaplan-Meier method. Standard error is based on Greenwood formula.
e Number of complete responders was 62, 17, and 79 for FL, MZL, and total, respectively. Statistics obtained from Kaplan-Meier method. Standard error is based on Greenwood formula.
Data cutoff: 01 May 2017.

Study NHL-001

Study NHL-001 was a Phase 2, multicenter, single-arm, open-label study of lenalidomide monotherapy in subjects with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL).

Subjects entered the treatment phase and received single-agent lenalidomide 25 mg QD on Days 1 to 21 of every 28-day cycle. Subjects continued in the treatment phase for up to 52 weeks or until disease progression developed or lenalidomide treatment was discontinued for any reason. All subjects who discontinued the treatment phase for any reason as well as all subjects who completed the treatment phase were followed until disease progression or until the next lymphoma treatment was given, whichever came first. A subject who achieved a CR at any time during the 52-week treatment period received 2 additional cycles of treatment prior to discontinuing the treatment phase and entering the follow-up phase.

Table 39 Summary of Study NHL-001: Subjects with Previously Treated iNHL

Study Design: Phase 2, single-arm, open-label, multicenter study		
Key Baseline Characteristics: median age 63 years, males 60.5%. FL: 22 (51.2%) subjects; SLL: 18 (41.9%) subjects; MZL: 3 (7.0%) subjects. Most subjects were white (86.0%). Most subjects had an ECOG performance score of 0 (62.8%) or 1 (27.9%). High risk IPI was 18.6%. Median number of prior systemic regimens was 3. NHL staging at baseline was 2.3% Stage I, 25.6% Stage II, 14.0% Stage III, and 58.1% Stage IV.		
Primary Endpoint: Tumor response (CR, CRu, PR) (overall response)		
Other Endpoints: Tumor control rate (CR, CRu, PR, SD), DOR, PFS		
Conclusions: • Lenalidomide monotherapy produced an ORR of 23.3% in ITT Population. o ORR was 27.3% in subjects with FL. o The 2 subjects with MZL who had responses assessed achieved best response of SD. • Median PFS for lenalidomide monotherapy was 4.4 months.		
	Lenalidomide Monotherapy	
	Total (N = 43[a])	**FL (N =22)**
ORR, n (%) (95% CI)	10 (23.3), (11.8, 38.6)	6 (27.3), (10.7, 50.2)
Median time to response (Min, Max), months	3.6 (1.7, 4.2)	–
CR rate, n (%)	2 (4.7)	2 (9.1)
Median DOR (CR, CRu, PR) (95% CI), months	NR (15.5, NE)	NR (14.2, NE)
Median PFS (95% CI), months	4.4 (2.5, 10.4)	4.4 (2.5, 10.4)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; iNHL = indolent non-Hodgkin lymphoma; IPI = International Prognostic Index; ITT = intent-to-treat; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; NE = not estimable; NHL = non-Hodgkin lymphoma; NR = not reached; ORR = overall response rate; PFS = progression-free survival; PR = partial response; SD = stable disease; SLL = small lymphocytic lymphoma.

[a] Includes n = 22 subjects with FL, n = 18 subjects with SLL, and n = 3 subjects with MZL.

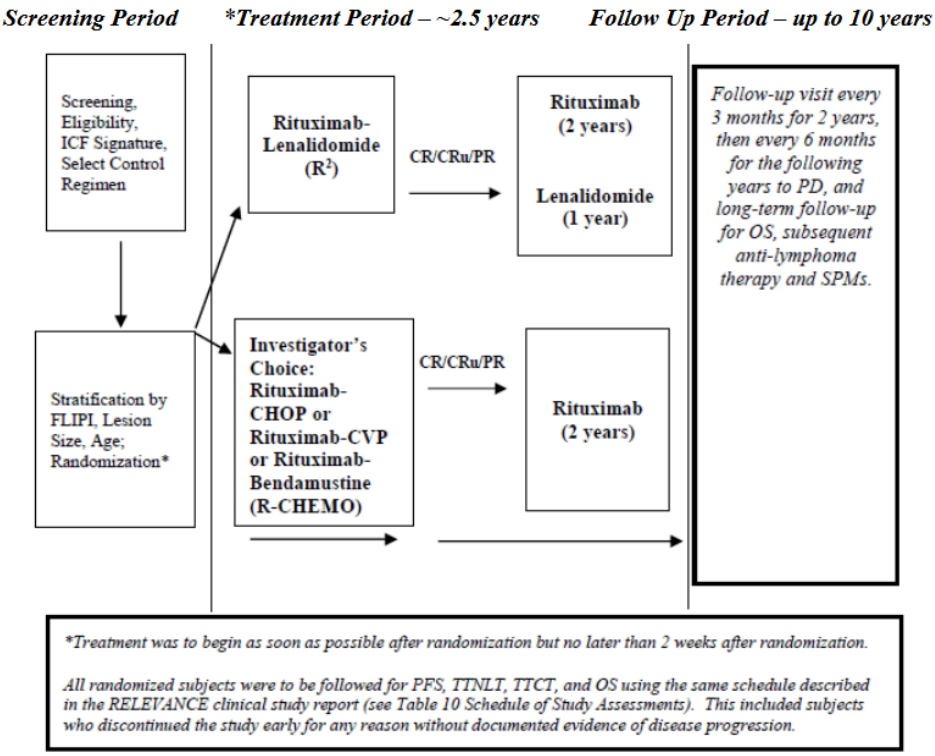
Data cutoff date: 18 Apr 2008.

Data from the RELEVANCE STUDY

RELEVANCE is an ongoing, phase 3, randomized, active-controlled, open-label study of R2for eighteen 4 week cycles followed by rituximab monotherapy for another six 8-week cycles (total duration of ~30 months) *versus* R- CHEMO for 6 to 8 cycles followed by rituximab for up to twelve 8-week cycles (total duration of 30 months), subjects with previously untreated FL (Grades 1 to 3a) requiring systemic treatment according to "Groupe d'Etude des Lymphomes folliculaires" (GELF) criteria. Second primary malignancy data and analyses presented for the RELEVANCE study are based on the safety population defined as all subjects who received at least 1 dose of study medication.

A total of 1010 subjects received at least 1 dose of study medication with either R2 (507subjects) or R-CHEMO (503subjects). In the R-CHEMO Arm, 365 subjects received R-CHOP, 26 subjects received R-CVP, and 112subjects received R-Benda. The overall median follow- up time for surviving subjects in the safety population was 39.1months (range: 0.9 to 61.3months) as of the data cutoff date of 31May2017

Figure 14: Study Design for RELEVANCE



Findings from this study with regards to second primary malignancies are discussed under Clinical Safety.

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

Integrated efficacy analysis was done by pooling subjects in the R2 Arm from the AUGMENT study together with the R^2 Initial Treatment Period from the MAGNIFY study to increase the sample size of data in subgroups. Efficacy data were analyzed based on response (eg, ORR, CR, DOR) and PFS (median PFS, 1-year PFS rate) for the entire pooled data set and by histology (ie, FL and MZL). Subpopulation analyses were performed for the Full Analysis Set (FAS) and FL FAS populations. In addition, efficacy analyses were performed by MZL subtype (MALT, SMZL, and NMZL).

The inclusion of data from the Initial Treatment Period of the MAGNIFY study was based on the following considerations:

- MAGNIFY enrolled previously treated FL and MZL patients regardless of rituximab refractory status, which allows assessment of efficacy for R2 in broader subgroups of subjects with previously treated Fl or MZL.
- Dose and schedule of R^2 in MAGNIFY Initial Treatment Period are similar to those of AUGMENT. The subtle difference in the schedule of rituximab between AUGMENT (4 weekly infusions followed by 4 additional doses on Day 1 of Cycles 2, 3, 4, and 5) and MAGNIFY (4 weekly infusions of rituximab followed by 5 additional doses on Day 1 of Cycles 3, 5, 7, 9, and 11) is not expected to have a meaningful impact on therapeutic benefit of R2 based on a number of considerations. The widely accepted standard dosing schedule of rituximab in previously treated iNHL is 4 weekly infusions of rituximab, which is identical between AUGMENT and MAGNIFY. The totality of published studies showed that extended dosing (i.e., additional doses of rituximab beyond standard 4 weekly infusions) further improves benefit in a manner that is independent of the number or schedule of extended rituximab dosing (i.e., 4 or more doses; every 1, 2, 3, or 6 months) (Hainsworth, 2002; Ardeshna, 2014; Taverna, 2016; Ghielmini, 2004; Coiffier, 2011).
- Objective response rate as assessed per 1999 IWGRC, an established efficacy endpoint for indolent lymphoma, is used in both AUGMENT and MAGNIFY to assess the antitumour activity of R^2.

The following populations were analyzed:

- Full Analysis Set: includes all enrolled subjects with FL Grades 1 to 3a or MZL who met all criteria for eligibility and had baseline and at least one post-baseline efficacy assessment from the MAGNIFY study (ie, induction efficacy evaluable population) and all randomized subjects from the AUGMENT study (ie, ITT population).
- Safety: includes all enrolled subjects with FL Grades 1 to 3a or MZL who received at least 1 dose of study medication (including placebo) in the AUGMENT and MAGNIFY studies. The Safety Population was used to assess the treatment duration and other safety data.

Integrated efficacy data were analyzed in subjects with previously treated FL or MZL for the entire data set. Additionally, efficacy data were analyzed by histology:

- Follicular lymphoma (Grades 1 to 3a) histology subgroup: includes all previously treated FL subjects (Grades 1 to 3a) from the AUGMENT and MAGNIFY studies analyzed and presented as data from the whole population.
- Marginal zone lymphoma histology subgroup: includes all previously treated MZL subjects from the AUGMENT and MAGNIFY studies analyzed and presented as data from the whole population.

Table 40 Subject disposition, FAS population

	Previously Treated FL/MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter, n (%)	Pbo + Rit (N = 180)	Len + Rit (N = 178)	Len + Rit (N = 187)	Len + Rit (N = 365)
Full Analysis Set[a]	180 (100.0)	178 (100.0)	187 (100.0)	365 (100.0)
Subjects who discontinued study treatment early	70 (38.9)	52 (29.2)	74 (39.6)	126 (34.5)
Progressive disease	54 (30.0)	21 (11.8)	31 (16.6)	52 (14.2)
Adverse event	8 (4.4)	14 (7.9)	26 (13.9)	40 (11.0)
Death	0 (0.0)	2 (1.1)	4 (2.1)	6 (1.6)
Withdrew consent	7 (3.9)	13 (7.3)	7 (3.7)	20 (5.5)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.6)	2 (1.1)	6 (3.2)	8 (2.2)

FAS = Full Analysis Set; FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm).

[a] The FAS included all randomized subjects from AUGMENT and induction efficacy evaluable subjects from MAGNIFY.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

Table 41 Subject disposition, FL FAS population

Parameter, n (%)	Previously Treated FL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	Pbo + Rit (N = 148)	Len + Rit (N = 147)	Len + Rit (N = 148)	Len + Rit (N = 295)
FL FAS[a]	148 (100.0)	147 (100.0)	148 (100.0)	295 (100.0)
Subjects who discontinued study treatment early	60 (40.5)	41 (27.9)	59 (39.9)	100 (33.9)
Progressive disease	46 (31.1)	17 (11.6)	26 (17.6)	43 (14.6)
Adverse event	6 (4.1)	12 (8.2)	20 (13.5)	32 (10.8)
Death	0 (0.0)	1 (0.7)	3 (2.0)	4 (1.4)
Withdrew consent	7 (4.7)	11 (7.5)	7 (4.7)	18 (6.1)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.7)	0 (0.0)	3 (2.0)	3 (1.0)

FAS = Full Analysis Set; FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Pbo + Rit = placebo plus rituximab (Control Arm).

[a] The FL FAS included all randomized FL 1-3a subjects from AUGMENT and induction efficacy evaluable FL 1-3a subjects from MAGNIFY.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

Source: SCE/ISE Table 1.1.2

Table 42 Subject disposition, MZL FAS population

Parameter, n (%)	Previously Treated MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	Pbo + Rit (N = 32)	Len + Rit (N = 31)	Len + Rit (N = 39)	Len + Rit (N = 70)
MZL FAS[a]	32 (100.0)	31 (100.0)	39 (100.0)	70 (100.0)
Subjects who discontinued study treatment early	10 (31.3)	11 (35.5)	15 (38.5)	26 (37.1)
Progressive disease	8 (25.0)	4 (12.9)	5 (12.8)	9 (12.9)
Adverse event	2 (6.3)	2 (6.5)	6 (15.4)	8 (11.4)
Death	0 (0.0)	1 (3.2)	1 (2.6)	2 (2.9)
Withdrew consent	0 (0.0)	2 (6.5)	0 (0.0)	2 (2.9)
Other	0 (0.0)	2 (6.5)	3 (7.7)	5 (7.1)

FAS = Full Analysis Set; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm).

[a] The MZL FAS included all randomized MZL subjects from AUGMENT and induction efficacy evaluable MZL subjects from MAGNIFY.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

Source: SCE/ISE Table 1.1.3

In the pooled R^2 data from AUGMENT and MAGNIFY, median treatment duration was 11 months (range: 0.1 to 15.0 months) for the total safety population. Overall, 48.5% of the pooled subjects received or completed all 12 cycles of planned study treatment. The median duration of treatment among subjects with FL Safety Population and subjects with MZL safety population was similar to that in the total Safety Population (FL and MZL).

Demographic and baseline disease characteristics for FAS population are presented below.

Table 43 Subject Demographics for FAS Population

	Previously Treated FL/MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter, n (%)	Pbo + Rit (N = 180)	Len + Rit (N = 178)	Len + Rit (N = 187)	Len + Rit (N = 365)
Age (years)				
Mean (StD)	61.5 (11.16)	62.3 (11.23)	64.8 (10.93)	63.6 (11.13)
Median	62.0	64.0	65.0	64.0
Min, Max	35.0, 88.0	26.0, 86.0	35.0, 91.0	26.0, 91.0
Age categories (years), n (%)				
< 65	107 (59.4)	96 (53.9)	88 (47.1)	184 (50.4)
≥ 65	73 (40.6)	82 (46.1)	99 (52.9)	181 (49.6)
Sex, n (%)				
Male	97 (53.9)	75 (42.1)	107 (57.2)	182 (49.9)
Female	83 (46.1)	103 (57.9)	80 (42.8)	183 (50.1)
Ethnicity, n (%)				
Hispanic	20 (11.1)	24 (13.5)	12 (6.4)	36 (9.9)
Non-Hispanic	158 (87.8)	147 (82.6)	172 (92.0)	319 (87.4)
Missing	2 (1.1)	7 (3.9)	3 (1.6)	10 (2.7)
Region, n (%)				
US	17 (9.4)	23 (12.9)	187 (100.0)	210 (57.5)
EU	84 (46.7)	81 (45.5)	0 (0.0)	81 (22.2)
Other	79 (43.9)	74 (41.6)	0 (0.0)	74 (20.3)

EU = European Union; FAS = Full Analysis Set; FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Max = maximum; Min = minimum; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); StD = standard deviation; US = United States.
Notes: FAS included all randomized subjects from AUGMENT and induction efficacy evaluable subjects from MAGNIFY. Percentages were based on the number of subjects in each treatment group.
Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.
Source: SCE/ISE Table 1.2.1

Table 44 Subject Baseline Disease Characteristics for FAS Population

Parameter,n (%)	Previously Treated FL/MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	Pbo+ Rit (N=180)	Len + Rit (N=178)	Len + Rit (N=187)	Len+Rit (N=365)
Histological diagnosis				
FL	148 (82.2)	147 (82.6)	148 (79.1)	295 (80.8)
MZL	32 (17.8)	31 (17.4)	39 (20.9)	70 (19.2)
Stage at enrollment				
I	18 (10.0)	15 (8.4)	4 (2.1)	19 (5.2)
II	38 (21.1)	26 (14.6)	14 (7.5)	40 (11.0)
III	65 (36.1)	73 (41.0)	49 (26.2)	122 (33.4)
IV	59 (32.8)	64 (36.0)	120 (64.2)	184 (50.4)
FLIPI score				
0-1	67 (37.2)	52 (29.2)	–	–
2	58 (32.2)	55 (30.9)	–	–
3-5	54 (30.0)	69 (38.8)	–	–
Missing	1 (0.6)	2 (1.1)	–	–
LDH elevated at baseline[a]				
Yes	39 (21.7)	43 (24.2)	48 (25.7)	91 (24.9)
No	140 (77.8)	134 (75.3)	138 (73.8)	272 (74.5)
Missing	1 (0.6)	1 (0.6)	1 (0.5)	2 (0.5)
B symptoms				
Yes	12 (6.7)	16 (9.0)	26 (13.9)	42 (11.5)
No	168 (93.3)	162 (91.0)	161 (86.1)	323 (88.5)
Bulky disease[b]				
Yes	49 (27.2)	45 (25.3)	84 (44.9)	129 (35.3)
No	131(72.8)	132 (74.2)	101 (54.0)	233 (63.8)
Missing	0 (0.0)	1 (0.6)	2 (1.1)	3 (0.8)
High tumour burden per GELF criteria				
Yes	86 (47.8)	97 (54.5)	126 (67.4)	223 (61.1)
No	94 (52.2)	81 (45.5)	61 (32.6)	142 (38.9)
Early relapses (within 2years of initial diagnosis)				
Yes	61 (33.9)	56 (31.5)	69 (36.9)	125 (34.2)
No	118 (65.6)	122 (68.5)	118 (63.1)	240 (65.8)
Missing	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

ECOG score at baseline				
0	128 (71.1)	116 (65.2)	89 (47.6)	205 (56.2)
1	50 (27.8)	60 (33.7)	93(49.7)	153 (41.9)
2	2 (1.1)	2 (1.1)	5 (2.7)	7 (1.9)
≥3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unfit for chemotherapy[c]				
Yes	49 (27.2)	54 (30.3)	77 (41.2)	131 (35.9)
No	131 (72.8)	124 (69.7)	110 (58.8)	234 (64.1)

ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; FL = follicular lymphoma;

FLIPI = Follicular Lymphoma International Prognostic Index; GELF = Groupe d'Etude des Lymphomes Folliculaires; LDH = lactate dehydrogenase; Len + Rit = lenalidomide in combination with rituximab (R2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm).

a Defined as LDH > upper limit of normal.

b Bulky disease was defined as a nodal or extranodal (except spleen) mass > 7 cm in its greatest diameter or involvement of at least 3 nodal or extranodal sites (each with a diameter > 3 cm).

c Unfit for chemotherapy defined by age ⩾ 70 years or (age ⩾ 60 years and < 70 years, with at least one of the following: CrCL is ⩾ 30 mL/min AND < 60 mL/min or ECOG = 2).

Notes: FAS included all randomized subjects from AUGMENT and induction efficacy evaluable subjects from MAGNIFY. Percentages were based on the number of subjects in each treatment group.
Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.
Source: SCE/ISE Table 1.3.1

Efficacy across clinical trials was based on ORR, CR rate, DOR, and the 1-year PFS rate. Efficacy for the FAS Population, FL FAS Population, and the MZL FAS Population per the 1999 IWGRC is summarized below.

Table 45 Summary of efficacy per 1999 IWGRC

Parameter	Previously Treated FL/MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	Pbo + Rit (N = 180)	Len + Rit (N = 178)	Len + Rit (N = 187)	Len + Rit (N = 365)
Objective response (CR+CRu+PR), n (%) (95% CI)	96 (53.3) (45.8, 60.8)	138 (77.5) (70.7, 83.4)	127 (67.9) (60.7, 74.5)	265 (72.6) (67.7, 77.1)
Complete response (CR+CRu), n (%) (95% CI)	40 (22.2) (16.4, 29.0)	73 (41.0) (33.7, 48.6)	79 (42.2) (35.1, 49.7)	152 (41.6) (36.5, 46.9)
DOR				
Number of subjects with event, n (%)	51 (53.1)	48 (34.8)	17 (13.4)	65 (24.5)
Number of subjects censored, n (%)	45 (46.9)	90 (65.2)	110 (86.6)	200 (75.5)
Median DOR (95% CI), months	21.7 (12.8, 27.6)	36.6 (22.9, NE)	NE (NE, NE)	36.6 (25.3, NE)
≥ 12 months (95% CI), %	61.6 (50.7, 70.7)	84.4 (76.8, 89.6)	79.1 (67.4, 87.0)	82.3 (76.2, 87.0)
≥ 24 months (95% CI), %	42.5 (31.1, 53.5)	59.0 (48.7, 67.9)	74.7 (61.8, 83.8)	61.0 (52.2, 68.7)
1-year PFS rate[a] (95% CI), %	57.1 (49.3, 64.1)	82.7 (75.9, 87.7)	68.9 (59.5, 76.5)	76.8 (71.4, 81.3)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; FAS = Full Analysis Set; FDA = Food and Drug Administration; FL = follicular lymphoma; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); PFS = progression-free survival; PR = partial response.

[a] Based on FDA censoring rules.

Note: The FAS included all randomized subjects from AUGMENT and induction efficacy evaluable subjects from MAGNIFY. Central review of IWGRC 1999 was used in the AUGMENT study; investigator assessments of IWGRC 1999 were used in the MAGNIFY study.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

Source: SCE/ISE Table 2.1.1

Table 46 Summary of Efficacy for FL FAS Population per 1999 IWGRC

Parameter	Previously Treated FL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	Pbo + Rit (N = 148)	Len + Rit (N = 147)	Len + Rit (N = 148)	Len + Rit (N = 295)
Objective response (CR+CRu+PR), n (%) (95% CI)	82 (55.4) (47.0, 63.6)	118 (80.3) (72.9, 86.4)	104 (70.3) (62.2, 77.5)	222 (75.3) (69.9, 80.1)
Complete response (CR+CRu), n (%) (95% CI)	35 (23.6) (17.1, 31.3)	63 (42.9) (34.7, 51.3)	62 (41.9) (33.8, 50.3)	125 (42.4) (36.7, 48.2)
DOR				
Number of subjects with event, n (%)	47 (57.3)	38 (32.2)	13 (12.5)	51 (23.0)
Number of subjects censored, n (%)	35 (42.7)	80 (67.8)	91 (87.5)	171 (77.0)
Median DOR (95% CI), months	15.5 (11.2, 25.0)	36.6 (24.9, NE)	NE (NE, NE)	36.6 (25.3, NE)
≥ 12 months (95% CI), %	59.1 (47.4, 69.1)	85.3 (77.1, 90.7)	79.5 (65.5, 88.3)	83.2 (76.4, 88.2)
≥ 24 months (95% CI), %	40.5 (28.8, 51.8)	62.7 (51.6, 71.9)	73.9 (58.5, 84.3)	63.4 (53.7, 71.5)
1-year PFS rate[a] (95% CI), %	54.7 (46.0, 62.5)	82.5 (75.0, 87.9)	68.5 (57.4, 77.3)	76.8 (70.8, 81.7)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; FAS = Full Analysis Set; FDA = Food and Drug Administration; FL = follicular lymphoma; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); NE = not estimable; Pbo + Rit = placebo plus rituximab (Control Arm); PFS = progression-free survival; PR = partial response.

[a] Based on FDA censoring rules.

Note: The FL FAS included all randomized FL 1-3a subjects from AUGMENT and induction efficacy evaluable FL 1-3a subjects from MAGNIFY. Central Review of 1999 IWGRC was used in the AUGMENT study; investigator assessments of 1999 IWGRC were used in the MAGNIFY study.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

Source: SCE/ISE Table 2.2.1

Table 47 Summary of Efficacy for MZL FAS Population per 1999 IWGRC

Parameter	Previously Treated MZL			
	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	Pbo + Rit (N = 32)	Len + Rit (N = 31)	Len + Rit (N = 39)	Len + Rit (N = 70)
Objective response (CR+CRu+PR), n (%) (95% CI)	14 (43.8) (26.4, 62.3)	20 (64.5) (45.4, 80.8)	23 (59.0) (42.1, 74.4)	43 (61.4) (49.0, 72.8)
Complete response (CR+CRu), n (%) (95% CI)	5 (15.6) (5.3, 32.8)	10 (32.3) (16.7, 51.4)	17 (43.6) (27.8, 60.4)	27 (38.6) (27.2, 51.0)
DOR				
Number of subjects with event, n (%)	4 (28.6)	10 (50.0)	4 (17.4)	14 (32.6)
Number of subjects censored, n (%)	10 (71.4)	10 (50.0)	19 (82.6)	29 (67.4)
Median DOR (95% CI), months	NE (8.4, NE)	17.4 (13.2, NE)	NE (7.1, NE)	22.1 (15.9, NE)
≥ 12 months (95% CI), %	76.9 (44.2, 91.9)	79.1 (53.2, 91.6)	76.7 (49.2, 90.6)	77.6 (59.9, 88.2)
≥ 24 months (95% CI), %	51.3 (9.1, 83.0)	34.6 (10.9, 60.2)	76.7 (49.2, 90.6)	49.6 (27.7, 68.1)
1-year PFS rate[a] (95% CI), %	68.3 (49.0, 81.5)	84.4 (63.4, 93.9)	69.8 (49.5, 83.2)	76.8 (63.1, 85.9)

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; FAS = Full Analysis Set; FDA = Food and Drug Administration; IWGRC = International Working Group Response Criteria; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; NE = not estimable; Pbo + Rit = placebo plus rituximab (Control Arm); PFS = progression-free survival; PR = partial response.

[a] Based on FDA censoring rules.

Note: The MZL FAS included all randomized MZL subjects from AUGMENT and induction efficacy evaluable MZL subjects from MAGNIFY. Central review of 1999 IWGRC was used in the-AUGMENT study; investigator assessments of 1999 IWGRC were used in the MAGNIFY study.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY

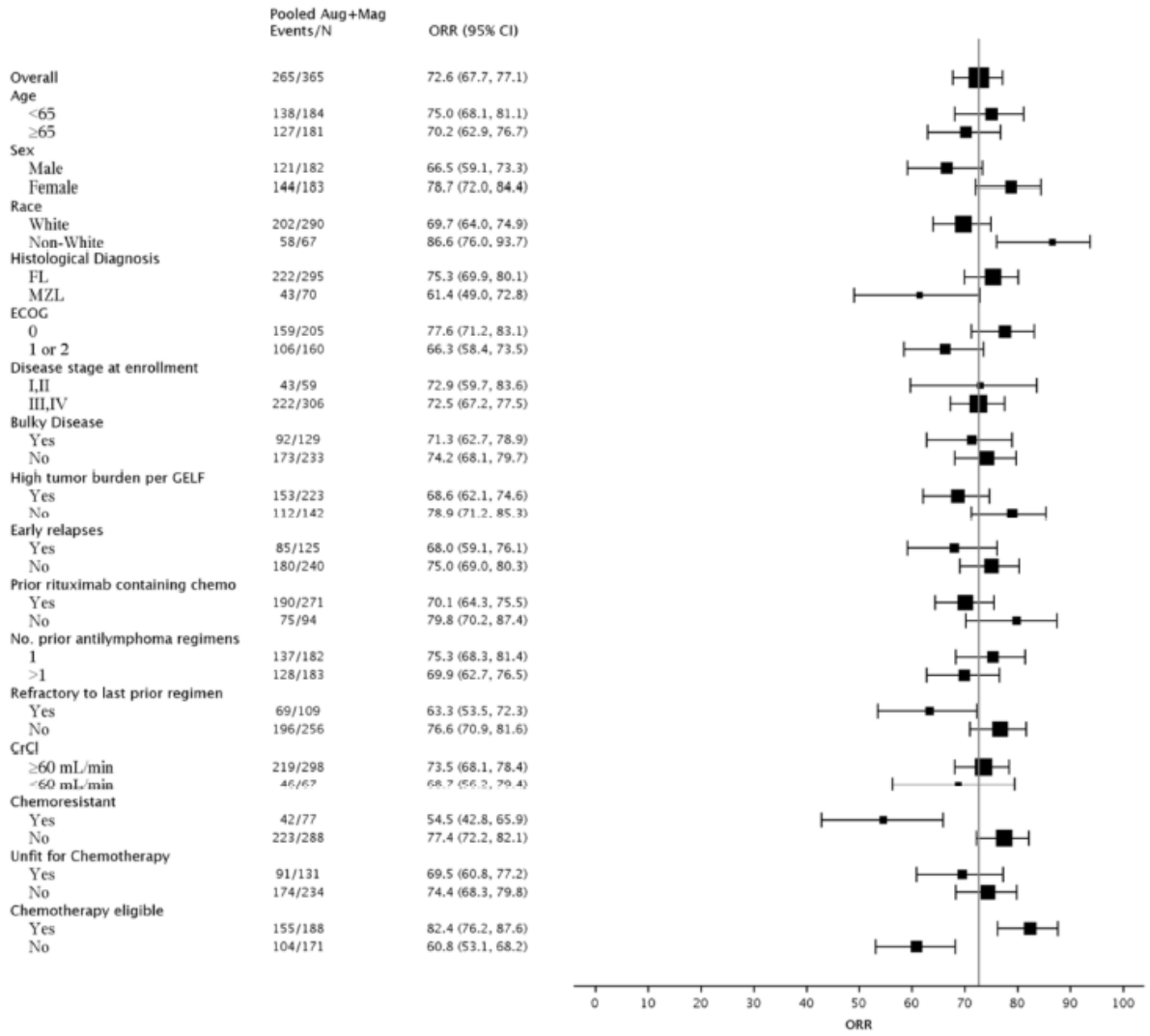
Table 48 *Summary of Efficacy in Subtypes of MZL per 1999 IWGRC (MZL FAS Population)*

	MALT MZL				Splenic MZL				Nodal MZL			
	AUG		MAG	Pooled AUG+ MAG	AUG		MAG	Pooled AUG+ MAG	AUG		MAG	Pooled AUG+ MAG
Endpoint	Pbo+Rit (N=16)	Len+Rit (N=14)	Len+Rit (N=10)	Len+Rit (N=24)	Pbo+Rit (N=6)	Len+Rit (N=9)	Len+Rit (N=9)	Len+Rit (N=18)	Pbo+Rit (N=10)	Len+Rit (N=8)	Len+Rit (N=20)	Len+Rit (N=28)
Objective response (CR+CRu+PR), n (%) (95% CI)	10 (62.5) (35.4, 84.8)	9 (64.3) (35.1, 87.2)	9 (90.0) (55.5, 99.7)	18 (75.0) (53.3, 90.2)	1 (16.7) (0.4, 64.1)	6 (66.7) (29.9, 92.5)	4 (44.4) (13.7, 78.8)	10 (55.6) (30.8, 78.5)	3 (30.0) (6.7, 65.2)	5 (62.5) (24.5, 91.5)	10 (50.0) (27.2, 72.8)	15 (53.6) (33.9, 72.5)
Complete response (CR+CRu), n (%) (95% CI)	4 (25.0) (7.3, 52.4)	7 (50.0) (23.0, 77.0)	6 (60.0) (26.2, 87.8)	13 (54.2) (32.8, 74.4)	0 (0.0) (0.0, 45.9)	1 (11.1) (0.3, 48.2)	1 (11.1) (0.3, 48.2)	2 (11.1) (1.4, 34.7)	1 (10.0) (0.3, 44.5)	2 (25.0) (3.2, 65.1)	10 (50.0) (27.2, 72.8)	12 (42.9) (24.5, 62.8)
DOR												
No. of subjects with event, n (%)	2 (20.0)	3 (33.3)	1 (11.1)	4 (22.2)	1 (100.0)	6 (100.0)	1 (25.0)	7 (70.0)	1 (33.3)	1 (20.0)	2 (20.0)	3 (20.0)
No. of subjects censored, n (%)	8 (80.0)	6 (66.7)	8 (88.9)	14 (77.8)	0 (0.0)	0 (0.0)	3 (75.0)	3 (30.0)	2 (66.7)	4 (80.0)	8 (80.0)	12 (80.0)
≥ 12 months (95% CI), %	80.0 (40.9, 94.6)	77.8 (36.5, 93.9)	85.7% (33.4, 97.9)	82.5 (54.9, 94.0)	100.0 (NE, NE)	83.3 (27.3, 97.5)	75.0 (12.8, 96.1)	78.8 (38.1, 94.3)	NE (NE, NE)	75.0 (12.8, 96.1)	71.4 (25.8, 92.0)	72.7 (37.1, 90.3)
≥ 24 months (95% CI), %	80.0 (40.9, 94.6)	51.9 (8.4, 84.0)	85.7 (33.4, 97.9)	61.9 (18.3, 87.3)	0.0 (NE, NE)	0.0 (NE, NE)	75.0 (12.8, 96.1)	13.5 (0.7, 44.4)	NE (NE, NE)	NE (NE, NE)	71.4 (25.8, 92.0)	72.7 (37.1, 90.3)
1-year PFS rate[a] (95% CI), %	75.0 (46.3, 89.8)	67.7 (34.9, 86.5)	87.5 (38.7, 98.1)	76.8 (52.8, 89.7)	83.3 (27.3, 97.5)	100.0 (NE, NE)	59.3 (18.6, 85.0)	78.1 (46.0, 92.5)	46.7 (15.0, 73.7)	100.0 (NE, NE)	65.7 (35.3, 84.4)	75.2 (49.7, 89.1)

AUG = AUGMENT; CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DOR = duration of response; FAS = Full Analysis Set; FDA = Food and Drug Administration; IWGRC = International Working Group Response Criteria; Len+Rit = lenalidomide in combination with

Subgroup analyses for overall response rate for the pooled R^2 data set for the FAS Population are presented in the figure below. In the pooled data set for R^2 in the FAS Population, Complete response rates of least 19% (range: 19.5% to 52.7%) were observed in all subgroups analyzed.

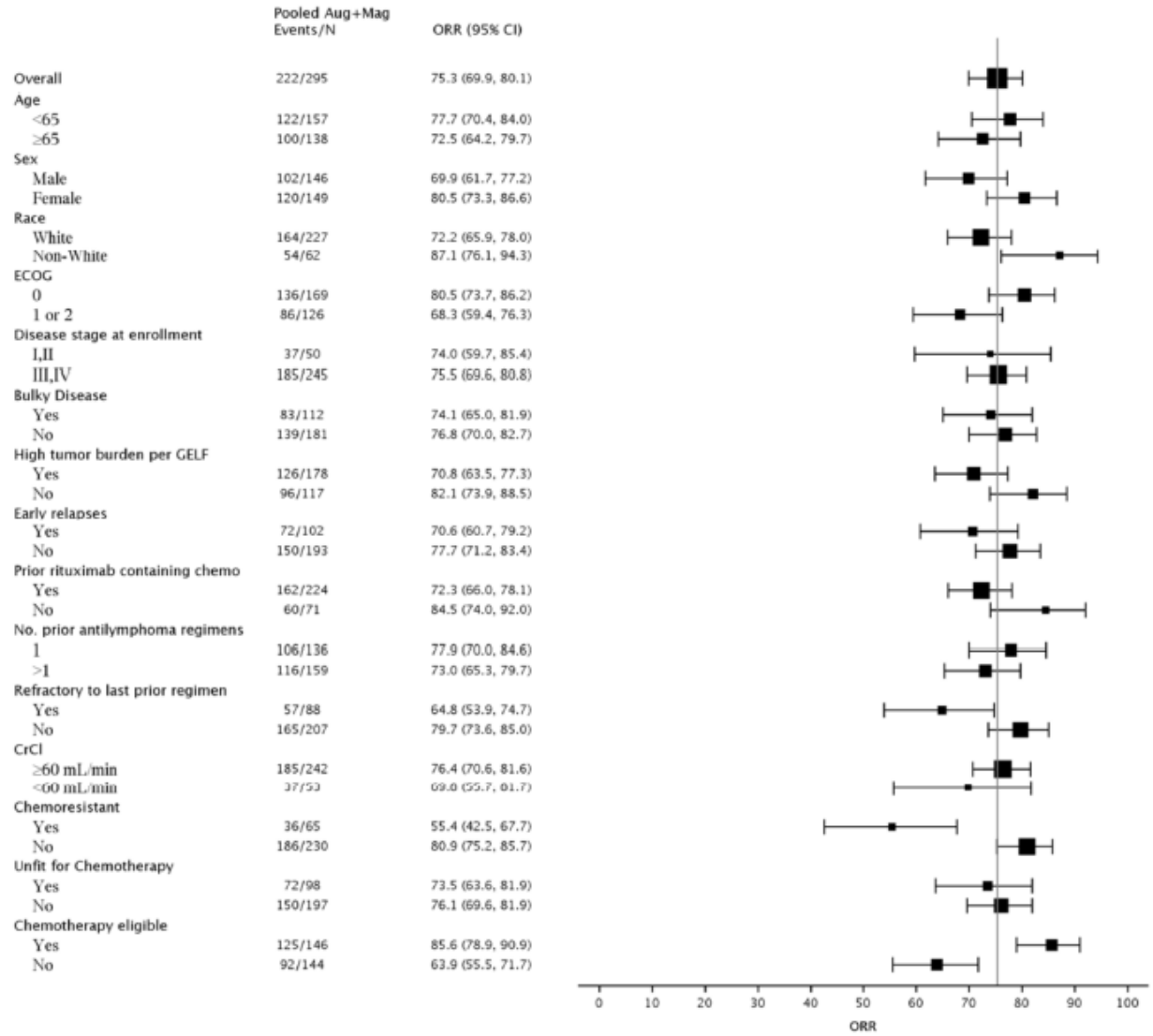
Figure 11 *Subgroup Analyses for Overall Response Rate for FAS Population (Pooled R2 Data)*



Aug = AUGMENT study; CI = confidence interval; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; FL = follicular lymphoma; GELF = Groupe d'Etude des Lymphomes Folliculaires; Mag = MAGNIFY study; MZL = marginal zone lymphoma; ORR = overall response rate; R^2 = lenalidomide in combination with rituximab.
Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.
Source: SCE/ISE Graph 2.1

In the pooled data set for R^2 in the FL FAS Population, response rates of at least 55%(range: 55.4% to 87.1%) were observed in all subgroups analyzed, including subjects who were refractory to last prior regimen, were chemoresistant, had bulky disease, or had a high tumour burden.

Figure 12 *Subgroup Analyses for Overall Response Rate for FL FAS Population (Pooled R2 Data)*



Aug = AUGMENT study; CI = confidence interval; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; FL = follicular lymphoma; GELF = Groupe d'Etude des Lymphomes Folliculaires; Mag = MAGNIFY study; ORR = overall response rate; R^2 = lenalidomide in combination with rituximab.
Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.
Source: SCE/ISE Graph 2.3

Among subjects who received R^2 (pooled R^2 data):

- FAS population: CR rates of least 19% (range: 19.5% to 52.7%) were observed in all subgroups analyzed.CR rates were lower among subjects who were male (33.5% *versus* 49.7% for female), chemoresistant (19.5% *versus* 47.6% for not chemoresistant), or ineligible for chemotherapy (29.8% *versus* 52.7% for eligible for chemotherapy)
- FL FAS population: CR rates of least 15% (range: 16.9% to 55.5%) were observed in all subgroups analyzed. CR rates were lower among subjects who had early relapses (30.4% *versus* 48.7% for no early relapses), were chemo resistant (16.9% *versus* 49.6% for not chemo resistant), or were ineligible for chemotherapy (29.2% *versus* 55.5% for eligible for chemotherapy).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Results are mainly coming from a phase 3, double-blind randomized study designed to compare the efficacy and safety of rituximab plus lenalidomide *versus* rituximab plus placebo in subjects with relapsed/refractory follicular lymphoma or relapsed/refractory marginal zone lymphoma (AUGMENT). Data are also supported by one phase 3b supportive study (MAGNIFY).

Patients were randomized in a 1:1 ratio to receive rituximab 375 mg/m^2 every week in Cycle 1 and on Day 1 of every 28-day cycle from cycles 2 through 5 plus lenalidomide once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles (experimental arm R^2) or rituximab plus placebo (control arm).

Efficacy determination was based upon PFS as primary endpoint, assessed by the Independent Review Committee (IRC). Secondary/exploratory endpoints were ORR, CR rate, DOCR, DOR, OS, EFS, TTNLT, TTNCT, PFS2, and time to histological transformation.
The overall analysis included 358 patients (178 R^2 and 180 R). The Follicular lymphoma population was comprised of 295 patients (147 R^2 and 148 R), and the MZL population was comprised of 63 patients (31 R^2 and 32 R alone).

Efficacy data and additional analyses

In the overall population, PFS by IRC assessment was significantly higher in the experimental arm than in the control arm. (HR: 0.45 p<0.0001 95% CI = 0.33, 0.61). Results were comparable to those observed for the overall population in the FL subgroup (HR= 0.4; p<0.0001; 95% CI = 0.29, 0.55): When applying EMA censoring rules, there was a 60% reduction in the risk of progression or death for the R^2 Arm compared to the Control Arm.

Objective response rate by IRC assessment (CR+PR; %) are significantly in favour of the R^2 arm in the overall population (77.5% 95% CI = 70.7; 83.4 *versus* 53.3% 95% CI= 45.8; 60.8) p<0.0001). Similar trend could be observed in the follicular lymphoma subgroup (80.3 IC95=72.9; 86.4) *versus* 55.4% IC= 47.0; 63.6) p<0.0001).

Overall, the median DOR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 36.6 months (22.9, not estimable [NE]) in the R^2 Arm and 21.7 months (12.8, 27.6) in the Control Arm. Similar results were noted in subjects with FL.

Finally, in subjects with FL, there were 11 deaths in the R^2 arm *versus* 24 deaths in the control arm reported (HR [95% CI]: 0.45 [0.22, 0.92]).
AUGMENT study Efficacy results, although globally in favour of R^2 *versus* R, have to be interpreted with serious caution, mostly in the MZL setting:

Based on the results obtained from the AUGMENT study, the clinical benefit of the Lenalidomide plus Rituximab combination is uncertain for MZL patients (PFS HR [95% CI]: 0.87 [0.41, 1.83] p =0.7068). This is not only a matter of statistical power but could correspond to an inferior benefit (overall population, R^2 *versus* R PFS HR: 0.45 p<0.0001 95% CI = 0.33, 0.61).

ORR and CR rate were higher in the R^2 Arm than in the control arm in subjects with MZL; however, due to the small sample size, results were not significant (64.5% 95% CI = 45.4, 80.8 *versus* 43.8% 95% CI= 26.4; 63.3) p=0.1313).
In subjects with MZL, the median DOR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 17.4 months (13.2, NE) in the R^2 Arm and not estimable in in the Control Arm.

Overall, the median DOCR (95% CI) by IRC assessment per the 2007 IWGRC among responders was not estimable in either treatment arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 12 months was 84.2% (71.8%, 91.5%) *versus* 77.0% (57.6%, 88.3%) in the control arm. In the R^2 Arm, the probability

of DOCR (95% CI) at ≥ 24 months was 67.4% (50.8%, 79.5%) *versus* 61.7% (41.2%, 76.8%) in the control arm. Similar results were shown in subjects with FL.

In subjects with MZL, the median DOCR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 22.1 months in the R^2 Arm and not estimable in the control arm. In the R^2 arm, the probability of DOCR (95% CI) at ≥ 12 months was 88.9% (43.3%, 98.4%) *versus* 100.0% (100.0%, 100.0%) in the control arm. In the R^2 Arm, the probability of DOCR (95% CI) at ≥ 24 months was 44.4% (1.0%, 86.6%) *versus* 100.0% (100.0%, 100.0%) in the rituximab alone arm.

Finally, with a median follow up of 28.30 months, there were 16 deaths in the R^2 Arm *versus* 26 deaths in the control arm reported (HR [95% CI]: 0.61 [0.33, 1.13]); the medians for both arms have not been reached. Kaplan-Meier curves overlapped until 1 year with separation shown after 1 year. The 2-year OS rate was 92.6% in the R^2 Arm and 87.2% in the control arm.
In subjects with MZL, there were 5 deaths in the R^2 Arm *versus* 2 deaths in the Control Arm reported (HR [95% CI]: 2.89 [0.56, 14.92]); the medians for both arms have not been reached.

Relapse / refractory indolent lymphoma remains an incurable disease. In previously treated iNHL patients, rituximab monotherapy is associated with ORR of approximately 38% to 59%. Over time many patients become refractory to Rituximab.

Association of Lenalidomide to Rituximab *versus* Rituximab alone improves significantly the median PFS in patients with follicular lymphoma disease. ORR, OS and PFS 2 are also improved by adjunction of Lenalidomide to Rituximab. However, rituximab monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. AUGMENT study participants were however patients with mostly Grade 1 and 2 FL (more than 70% of the included population).

In the r/r FL setting, selection of salvage treatment usually depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or *vice versa*). Other options, including fludarabine-based, platinum salts based or alkylating agents-based regimens, could also be useful. Rituximab should be proposed to patients if the previous antibody-containing scheme achieved >6- to 12-month duration of remission.

R^2 treatment not only delays progression but also improves overall response rate. However, in patients with marginal zone Lymphoma, the combination of Lenalidomide with Rituximab has no impact on the progression free survival and on objectives responses rates. More worrying, there were 5 deaths in the R^2 Arm *versus* 2 deaths in the control arm in subjects with MZL (HR [95% CI]: 2.89 [0.56, 14.92]); these results should however be interpreted with caution due to the low number of r/r MZL patients.

Overall, the approvability of the MZL indication was contingent on the assumption of homogeneity of response between FL and MZL, which could not be demonstrated based on AUGMENT and MAGNIFY data; following these uncertainties, the MAH has withdrawn the proposed MZL indication.

In order to adequately reflect the studied population, the following indication wording was proposed for section 4.1 of the SmPC: "Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a)".

Further, some characteristics of the patient population were specified (appropriateness to rituximab monotherapy and life expectancy < 6 months) in section 5.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

The combination of Lenalidomide to Rituximab improves significantly the median PFS in patients with follicular lymphoma disease *versus* Rituximab alone; secondary endpoints ORR, OS and PFS 2 were also improved. Therefore the efficacy of the combination in the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a) has been adequately demonstrated.

2.5. Clinical safety

Introduction

The safety experience for lenalidomide in combination with rituximab (Len + Rit or R2) is primarily based on data from one registrational Phase 3 study (Study CC-5013-NHL-007, AUGMENT), and one supportive Phase 3b study (Study CC-5013-NHL-008, MAGNIFY). The safety data from the R2 Arm in AUGMENT was pooled with the safety data from the R2 Arm in the Initial Treatment Period of MAGNIFY to increase the safety database in previously treated FL/MZL.

The inclusion of safety data from only the Initial Treatment Period of MAGNIFY and not the extended treatment period is based on the following considerations:

-Dose and schedule of lenalidomide in the MAGNIFY Initial Treatment Period are identical to those in AUGMENT. Depending on baseline renal function, (Cl Creat > 60 ml/min or >30 ml/min but < 60 ml/min) the starting dose of Lenalidomide or placebo was either 20 mg or 10 mg respectively.

-Dose of rituximab in the MAGNIFY Initial Treatment Period is identical to AUGMENT, and the treatment schedule is similar to that in AUGMENT. The subtle difference in the schedule of rituximab between AUGMENT (4 weekly infusions followed by 4 additional doses on Day 1 of Cycles 2, 3, 4, and 5) and MAGNIFY (4 weekly infusions of rituximab followed by5 additional doses on Day 1 of Cycles 3, 5, 7, 9, and 11) is not expected to have a meaningful impact on therapeutic benefit or safety profile of R2 based on several considerations. The widely accepted standard dosing schedule of rituximab in previously treated iNHL is 4 weekly infusions of rituximab, which is identical between AUGMENT and MAGNIFY. The totality of published studies showed that extended dosing (ie, additional doses of rituximab beyond standard 4 weekly infusions) further improves benefit (limited added toxicities) in a manner that is independent of the number or schedule of extended rituximab dosing (eg, 4 or more doses every 1, 2, 3, or 6 months).

For the Phase 2 clinical trial using lenalidomide monotherapy in iNHL (ie, Study NHL-001), the safety results are briefly summarized.

Patient exposure

The disposition of subjects in the Safety Population for each study (AUGMENT and MAGNIFY) and for the pooled AUGMENT + MAGNIFY R2 Arms is presented in the followed Table:

Table 49 Subject Disposition for Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter	**PBO + Rit (N = 180) n (%)**	**Len + Rit (N = 176) n (%)**	**Len + Rit (N = 222) n (%)**	**Len + Rit (N = 398) n (%)**
Subjects who discontinued study treatment early	70 (38.9)	52 (29.5)	84 (37.8)	136 (34.2)
Adverse event	8 (4.4)	14 (8.0)	29 (13.1)	43 (10.8)
Progressive disease	54 (30.0)	21 (11.9)	31 (14.0)	52 (13.1)
Death	0 (0.0)	2 (1.1)	4 (1.8)	6 (1.5)
Withdrew consent	7 (3.9)	13 (7.4)	11 (5.0)	24 (6.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.6)	2 (1.1)	9 (4.1)	11 (2.8)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); PBO = placebo; Rit = rituximab.
Source: SCS Table 1.1.1

FL Safety Population

The disposition of subjects in the FL Safety Population for each study (AUGMENT and MAGNIFY) and for the pooled AUGMENT + MAGNIFY R2 Arms is presented in the following table:

Table 50 Subject Disposition for FL Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter	PBO + Rit (N = 148) n (%)	Len + Rit (N = 146) n (%)	Len + Rit (N = 177) n (%)	Len + Rit (N = 323) n (%)
Subjects who discontinued study treatment early	60 (40.5)	41 (28.1)	67 (37.9)	108 (33.4)
Adverse event	6 (4.1)	12 (8.2)	23 (13.0)	35 (10.8)
Progressive disease	46 (31.1)	17 (11.6)	26 (14.7)	43 (13.3)
Death	0 (0.0)	1 (0.7)	3 (1.7)	4 (1.2)
Withdrew consent	7 (4.7)	11 (7.5)	10 (5.6)	21 (6.5)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.7)	0 (0.0)	5 (2.8)	5 (1.5)

FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); PBO = placebo; Rit = rituximab.
Source: SCS Table 1.1.2

MZL Safety Population

The disposition of previously treated subjects in the MZL Safety Population is presented in the following table:

Table 51 *Subject Disposition for MZL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Subjects who discontinued study treatment early	10 (31.3)	11 (36.7)	17 (37.8)	28 (37.3)
Adverse event	2 (6.3)	2 (6.7)	6 (13.3)	8 (10.7)
Progressive disease	8 (25.0)	4 (13.3)	5 (11.1)	9 (12.0)
Death	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Withdrew consent	0 (0.0)	2 (6.7)	1 (2.2)	3 (4.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (6.7)	4 (8.9)	6 (8.0)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab.
Source: SCS Table 1.1.3

Treatment Exposure

-Safety Population

The exposure to study treatment of subjects in the Safety Population for each study (AUGMENT and MAGNIFY) and for the pooled AUGMENT + MAGNIFY R2 Arms is presented in the following table:

Table 52 *Treatment Exposure for Rituximab + Lenalidomide/Control in Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N = 180)**	**Len + Rit (N = 176)**	**Len + Rit (N = 222)**	**Len + Rit (N = 398)**
Treatment duration (months) [a]				
Mean	9.4	9.8	7.5	8.5
SD	2.98	3.13	3.76	3.68
Median	11.0	11.2	7.5	11.0
Min, Max	0.9, 15.8	0.1, 15.0	1.0, 13.1	0.1, 15.0
Number of cycles				
Mean	9.9	10.2	7.3	8.6
SD	3.11	3.22	4.32	4.13
Median	12.0	12.0	7.5	11.0
Min, Max	1.0, 12.0	1.0, 12.0	0.0, 12.0	0.0, 12.0
Received all planned cycles[b] -n(%)	111 (61.7)	125 (71.0)	68 (30.6)	193 (48.5)
Relative Dose Intensity for Len/PBO[c]				
Mean	95.1	84.6	77.3	80.5
Standard Deviation	15.46	19.28	24.77	22.77
Median	98.5	93.8	83.1	88.1
Min, Max	4.8, 195.0	28.6, 139.9	4.8, 175.0	4.8, 175.0

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Max = maximum; Min = minimum; PBO = placebo; Rit = rituximab; SD = standard deviation.

[a] Treatment duration was defined as [(Last cycle end date of the study treatment minus the first dosing date of the study treatment) + 1] / 30.4375.

[b] In MAGNIFY, completed treatment cycles were counted, while in AUGMENT, started treatment cycles were counted. AUGMENT and MAGNIFY: 12 total planned cycles.

[c] Relative dose intensity is defined as dose intensity divided by planned dose intensity.

The exposure to study treatment for subjects in the FL Safety Population is presented in the following table:

Table 53 *Treatment Exposure for Rituximab +Lenalidomide/Control in FL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=148)**	**Len + Rit (N=146)**	**Len + Rit (N=177)**	**Len + Rit (N=323)**
Treatment duration (months)[a]				
Mean	9.3	10.0	7.3	8.5
SD	2.93	2.82	3.75	3.62
Median	11.0	11.2	7.4	11.0
Min, Max	0.9, 13.1	0.9, 15.0	1.2, 13.1	0.9, 15.0
Number of cycles				
Mean	9.9	10.4	7.1	8.6

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
SD	3.10	2.94	4.29	4.09
Median	12.0	12.0	7.0	11.0
Min, Max	1.0, 12.0	1.0, 12.0	0.0, 12.0	0.0, 12.0
Received all planned cycles [b], n (%)	89 (60.1)	106 (72.6)	52 (29.4)	158 (48.9)
Relative Dose Intensity for Len/PBO[c]	148	146	177	323
Mean	95.5	85.0	77.9	81.1
SD	15.21	18.57	23.96	21.94
Median	98.5	92.1	82.9	88.1
Min, Max	4.8, 195.0	39.0, 139.9	4.8, 175.0	4.8, 175.0

FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Max = maximum; Min = minimum; PBO = placebo; Rit = rituximab; SD = standard deviation.
[a] Treatment duration was defined as [(Last cycle end date of the study drug (minus the first dosing date of the study drug) + 1] / 30.4375.
[b] In MAGNIFY, completed treatment cycles are counted, while in AUGMENT, started treatment cycles are counted. AUGMENT and MAGNIFY: 12 total planned cycles.
[c] Relative dose intensity is defined as dose intensity divided by planned dose intensity.

The exposure to study treatment for previously treated subjects in the MZL Safety Population is presented in the following table:

Table 54 *Treatment Exposure for Rituximab + Lenalidomide/Control in MZL Safety Population*

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32)	Len + Rit (N = 30)	Len + Rit (N = 45)	Len + Rit (N = 75)
Treatment duration[a] (months)				
Mean	9.6	8.9	8.1	8.5
SD	3.22	4.28	3.73	3.95
Median	11.1	11.1	11.0	11.0
Min, Max	1.8, 15.8	0.1, 13.9	1.0, 12.0	0.1, 13.9
Number of Cycles				
Mean	10.1	9.2	8.1	8.5
SD	3.20	4.22	4.38	4.32
Median	12.0	12.0	11.0	11.0
Min, Max	2.0, 12.0	1.0, 12.0	0.0, 12.0	0.0, 12.0
Received all planned cycles [b], n(%)	22 (68.8)	19 (63.3)	16 (35.6)	35 (46.7)

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32)	Len + Rit (N = 30)	Len + Rit (N = 45)	Len + Rit (N = 75)
Relative Dose Intensity for Len/PBO[c]				
Mean	93.5	82.5	75.0	78.0
SD	16.72	22.67	27.91	26.04
Median	98.5	95.2	83.2	89.4
Min, Max	19.7, 125.0	28.6, 101.6	14.3, 132.9	14.3, 132.9

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; SD = standard deviation.
[a] Treatment duration was defined as [(last cycle end date of the study drug) - (the first dosing date of the study drug) + 1)] / 30.4375.
[b] In MAGNIFY, completed treatment cycles are counted, while in AUGMENT started treatment cycles are counted. AUGMENT and MAGNIFY: 12 total planned cycles.
[c] Relative dose intensity is defined as dose intensity divided by planned dose intensity.

The demographics of subjects in the Safety Population for each study (AUGMENT and MAGNIFY) and for the pooled AUGMENT + MAGNIFY R2 Arms is presented in the following table:

Table 55 *Demographics for Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=180)**	**Len + Rit (N=176)**	**Len + Rit (N=222)**	**Len + Rit (N=398)**
Age (years)				
Mean	61.5	62.2	65.0	63.8
SD	11.16	11.26	10.77	11.06
Median	62.0	64.0	65.0	64.5
Min, Max	35.0, 88.0	26.0, 86.0	35.0, 91.0	26.0, 91.0
Age Categories (years) - n (%)				
< 65	107 (59.4)	96 (54.5)	103 (46.4)	199 (50.0)
≥ 65	73 (40.6)	80 (45.5)	119 (53.6)	199 (50.0)
Sex - n (%)				
Male	97 (53.9)	74 (42.0)	122 (55.0)	196 (49.2)
Female	83 (46.1)	102 (58.0)	100 (45.0)	202 (50.8)
Ethnicity				
Hispanic	20 (11.1)	24 (13.6)	16 (7.2)	40 (10.1)
Non- Hispanic	158 (87.8)	145 (82.4)	203 (91.4)	348 (87.4)
Missing	2 (1.1)	7 (4.0)	3 (1.4)	10 (2.5)
Region				
US	17 (9.4)	22 (12.5)	222 (100.0)	244 (61.3)
EU	84 (46.7)	80 (45.5)	0 (0.0)	80 (20.1)
Other[a]	79 (43.9)	74 (42.0)	0 (0.0)	74 (18.6)

EU = European Union; Len = lenalidomide; Max = maximum; Min = minimum; PBO = placebo; Rit = rituximab; Len + Rit = lenalidomide in combination with rituximab; SD = standard deviation; US = United States.
Other = Asia-Pacific region and Brazil

Demographics are summarized for subjects in the FL Safety Population in the following table:

Table 56 *Demographics for FL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=148)**	**Len + Rit (N=146)**	**Len + Rit (N=177)**	**Len + Rit (N=323)**
Age (years)				
Mean	60.7	61.6	64.5	63.2
SD	11.08	11.34	10.70	11.07
Median	61.0	62.0	65.0	64.0
Min, Max	35.0, 88.0	26.0, 86.0	35.0, 91.0	26.0, 91.0
Age Categories (years) - n (%)				
< 65	94 (63.5)	86 (58.9)	84 (47.5)	170 (52.6)
≥ 65	54 (36.5)	60 (41.1)	93 (52.5)	153 (47.4)
Sex - n (%)				
Male	80 (54.1)	61 (41.8)	97 (54.8)	158 (48.9)
Female	68 (45.9)	85 (58.2)	80 (45.2)	165 (51.1)
Ethnicity				
Hispanic	13 (8.8)	19 (13.0)	10 (5.6)	29 (9.0)
Non-Hispanic	133 (89.9)	122 (83.6)	164 (92.7)	286 (88.5)
Missing	2 (1.4)	5 (3.4)	3 (1.7)	8 (2.5)

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=148)**	**Len + Rit (N=146)**	**Len + Rit (N=177)**	**Len + Rit (N=323)**
Region				
US	15 (10.1)	18 (12.3)	177 (100.0)	195 (60.4)
EU	68 (45.9)	57 (39.0)	0 (0.0)	57 (17.6)
Other[a]	65 (43.9)	71 (48.6)	0 (0.0)	71 (22.0)

EU = European Union; FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); Max = maximum; Min = minimum; PBO = placebo; Rit = rituximab; SD = standard deviation; US = United States.
[a]Other = Asia-Pacific region and Brazil.

The demographic profile for previously treated subjects in the MZL Safety Population is presented in the followed Table

Table 57 Demographics for MZL Safety Population

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32)	Len + Rit (N = 30)	Len + Rit (N = 45)	Len + Rit (N = 75)
Age (years)				
n	32	30	45	75
Mean	65.0	65.3	67.2	66.4
SD	11.04	10.51	10.90	10.72
Median	66.0	68.0	68.0	68.0
Min, Max	36.0, 82.0	37.0, 80.0	46.0, 86.0	37.0, 86.0
Age Categories (years), n (%)				
< 65	13 (40.6)	10 (33.3)	19 (42.2)	29 (38.7)
≥ 65	19 (59.4)	20 (66.7)	26 (57.8)	46 (61.3)
Sex, n (%)				
Male	17 (53.1)	13 (43.3)	25 (55.6)	38 (50.7)
Female	15 (46.9)	17 (56.7)	20 (44.4)	37 (49.3)
Ethnicity, n (%)				
Hispanic	7 (21.9)	5 (16.7)	6 (13.3)	11 (14.7)
Non-Hispanic	25 (78.1)	23 (76.7)	39 (86.7)	62 (82.7)
Missing	0 (0.0)	2 (6.7)	0 (0.0)	2 (2.7)

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32)	Len + Rit (N = 30)	Len + Rit (N = 45)	Len + Rit (N = 75)
Region, n (%)				
US	2 (6.3)	4 (13.3)	45 (100.0)	49 (65.3)
EU	16 (50.0)	23 (76.7)	0 (0.0)	23 (30.7)
Other [a]	14 (43.8)	3 (10.0)	0 (0.0)	3 (4.0)

EU = European Union; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; Max = maximum; Min = minimum; MZL = marginal zone lymphoma; Other = Asia-Pacific region and Brazil; PBO = placebo; SD = standard deviation; US = United States.
[a] Other = Asia-Pacific region and Brazil.

Baseline Disease Characteristics - Safety Population

The baseline disease characteristics of subjects in the Safety Population for each study (AUGMENT and MAGNIFY) and for the pooled AUGMENT + MAGNIFY R2 Arms is presented in the following table:

Table 58 Baseline Disease Characteristics for Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter, n (%)	**PBO + Rit (N=180)**	**Len + Rit (N=176)**	**Len + Rit (N=222)**	**Len + Rit (N=398)**
Histological diagnosis				
Follicular lymphoma				
Grade 1-2	123 (68.3)	124 (70.5)	149 (67.1)	273 (68.6)
Grade 3a	25 (13.9)	22 (12.5)	28 (12.6)	50 (12.6)
Marginal zone lymphoma				
MALT	16 (8.9)	13 (7.4)	10 (4.5)	23 (5.8)
SMZL	6 (3.3)	9 (5.1)	10 (4.5)	19 (4.8)
NMZL	10 (5.6)	8 (4.5)	25 (11.3)	33 (8.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter, n (%)	**PBO + Rit (N=180)**	**Len + Rit (N=176)**	**Len + Rit (N=222)**	**Len + Rit (N=398)**
Ann Arbor Stage at enrollment				
I	18 (10.0)	15 (8.5)	4 (1.8)	19 (4.8)
II	38 (21.1)	25 (14.2)	19 (8.6)	44 (11.1)
III	65 (36.1)	73 (41.5)	56 (25.2)	129 (32.4)
IV	59 (32.8)	63 (35.8)	143 (64.4)	206 (51.8)
FLIPI score				
0-1	67 (37.2)	52 (29.5)	NA	NA
2	58 (32.2)	54 (30.7)	NA	NA
3-5	54 (30.0)	69 (39.2)	NA	NA
Missing	1 (0.6)	1 (0.6)	NA	NA
LDH elevated at baseline - n (%)				
Yes	39 (21.7)	42 (23.9)	60 (27.0)	102 (25.6)
No	140 (77.8)	133 (75.6)	161 (72.5)	294 (73.9)
Missing	1 (0.6)	1 (0.6)	1 (0.5)	2 (0.5)
B symptoms				
Yes	12 (6.7)	16 (9.1)	29 (13.1)	45 (11.3)
No	168 (93.3)	160 (90.9)	193 (86.9)	353 (88.7)
Bulky disease[a]				
Yes	49 (27.2)	44 (25.0)	95 (42.8)	139 (34.9)
No	131 (72.8)	132 (75.0)	125 (56.3)	257 (64.6)
Missing	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)
High tumor burden per GELF				
Yes	86 (47.8)	95 (54.0)	148 (66.7)	243 (61.1)
No	94 (52.2)	81 (46.0)	74 (33.3)	155 (38.9)
ECOG score at baseline - n (%)				
0	128 (71.1)	115 (65.3)	102 (45.9)	217 (54.5)
1	50 (27.8)	59 (33.5)	113 (50.9)	172 (43.2)
2	2 (1.1)	2 (1.1)	7 (3.2)	9 (2.3)
≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter, n (%)	**PBO + Rit (N=180)**	**Len + Rit (N=176)**	**Len + Rit (N=222)**	**Len + Rit (N=398)**
BM biopsy performed (baseline)				
Yes	111 (61.7)	104 (59.1)	218 (98.2)	322 (80.9)
Involved	31 (27.9)	32 (30.8)	77 (35.3)	109 (33.9)
Indeterminate	5 (4.5)	1 (1.0)	2 (0.9)	3 (0.9)
Not involved	75 (67.6)	71 (68.3)	139 (63.8)	210 (65.2)
No	69 (38.3)	72 (40.9)	4 (1.8)	76 (19.1)
Creatinine clearance - n (%)				
≥ 60 mL/min	156 (86.7)	152 (86.4)	174 (78.4)	326 (81.9)
≥ 30 mL/min, < 60 mL/min	24 (13.3)	24 (13.6)	48 (21.6)	72 (18.1)
Chemo-resistant[b]				
Yes	26 (14.4)	24 (13.6)	62 (27.9)	86 (21.6)
No	154 (85.6)	152 (86.4)	160 (72.1)	312 (78.4)
Unfit for Chemotherapy[c]				
Yes	49 (27.2)	53 (30.1)	92 (41.4)	145 (36.4)
No	131 (72.8)	123 (69.9)	130 (58.6)	253 (63.6)
Chemotherapy eligible[d]				
Yes	103 (57.2)	103 (58.5)	101 (45.5)	204 (51.3)
No	75 (41.7)	67 (38.1)	121 (54.5)	188 (47.2)
Missing	2 (1.1)	6 (3.4)	0 (0.0)	6 (1.5)

BM = bone marrow; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FLIPI = Follicular Lymphoma International Prognostic Index; GELF = Groupe d'Etude des Lymphomes Folliculaires; LDH = lactate dehydrogenase; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab;

Adverse events

Table 59 Summary of Treatment-emergent Adverse Events for Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=180)**	**Len + Rit (N=176)**	**Len + Rit (N=222)**	**Len + Rit (N=398)**
Subjects with at least one TEAE	173 (96.1)	174 (98.9)	216 (97.3)	390 (98.0)
Subjects with at least one related TEAE	136 (75.6)	163 (92.6)	202 (91.0)	365 (91.7)
Subjects with at least one treatment-emergent SAE	25 (13.9)	45 (25.6)	65 (29.3)	110 (27.6)
Subjects with at least one related treatment-emergent SAE	8 (4.4)	27 (15.3)	35 (15.8)	62 (15.6)
Subjects with at least one NCI CTCAE Grade 3 or 4 TEAE	58 (32.2)	121 (68.8)	138 (62.2)	259 (65.1)
Subjects with at least one related NCI CTCAE Grade 3 or 4 TEAE	41 (22.8)	104 (59.1)	118 (53.2)	222 (55.8)
Subjects with at least one NCI CTCAE Grade 5 TEAE	2 (1.1)	2 (1.1)	4 (1.8)	6 (1.5)
Subjects with at least one TEAE leading to dose reduction [a]	6 (3.3)	46 (26.1)	96 (43.2)	142 (35.7)
Subjects with at least one TEAE leading to dose interruption of any study drug	68 (37.8)	122 (69.3)	130 (58.6)	252 (63.3)
Subjects with at least one TEAE leading to any study drug discontinuation	10 (5.6)	18 (10.2)	40 (18.0)	58 (14.6)

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; PBO = placebo; Rit = rituximab; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] All TEAES leading to dose reduction refer to lenalidomide/PBO, as dose reductions of rituximab were not allowed in the 2 studies per protocols.

An overview summary of AEs for the FL Safety Population is presented in the following table:

Table 60 *Summary of Treatment-emergent Adverse Events for FL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
Parameter	**PBO + Rit (N=148)**	**Len + Rit (N=146)**	**Len + Rit (N=177)**	**Len + Rit (N=323)**
Subjects with at least one TEAE	141 (95.3)	144 (98.6)	171 (96.6)	315 (97.5)
Subjects with at least one related TEAE	108 (73.0)	137 (93.8)	163 (92.1)	300 (92.9)
Subjects with at least one treatment-emergent SAE	19 (12.8)	34 (23.3)	50 (28.2)	84 (26.0)
Subjects with at least one related treatment-emergent SAE	5 (3.4)	20 (13.7)	28 (15.8)	48 (14.9)
Subjects with at least one NCI CTCAE Grade 3/4 TEAE	48 (32.4)	98 (67.1)	105 (59.3)	203 (62.8)
Subjects with at least one related NCI CTCAE Grade 3/4 TEAE	32 (21.6)	85 (58.2)	92 (52.0)	177 (54.8)
Subjects with at least one NCI CTCAE Grade 5 TEAE	1 (0.7)	1 (0.7)	3 (1.7)	4 (1.2)
Subjects with at least one TEAE leading to dose reduction [a]	4 (2.7)	40 (27.4)	74 (41.8)	114 (35.3)
Subjects with at least one TEAE leading to dose interruption of any study drug	54 (36.5)	100 (68.5)	103 (58.2)	203 (62.8)
Subjects with at least one TEAE leading to any study drug discontinuation	8 (5.4)	13 (8.9)	29 (16.4)	42 (13.0)

CTCAE = Common Terminology Criteria for Adverse Events; FL = follicular lymphoma; Len = lenalidomide; NCI = National Cancer Institute; PBO = placebo; Rit = rituximab; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] All TEAES leading to dose reduction refer to lenalidomide/placebo, as dose reductions of rituximab were not allowed in the 2 studies per protocols.

Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose.

An overview summary of AEs for the MZL Safety Population is presented in the following table:

Table 61 *Summary of Treatment-emergent Adverse Events for MZL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Parameter	**PBO + Rit (N = 32)**	**Len + Rit (N = 30)**	**Len + Rit (N = 45)**	**Len + Rit (N = 75)**
Subjects with at least one TEAE	32 (100.0)	30 (100.0)	45 (100.0)	75 (100.0)
Subjects with at least one related TEAE	28 (87.5)	26 (86.7)	39 (86.7)	65 (86.7)
Subjects with at least one treatment-emergent SAE	6 (18.8)	11 (36.7)	15 (33.3)	26 (34.7)
Subjects with at least one related treatment-emergent SAE	3 (9.4)	7 (23.3)	7 (15.6)	14 (18.7)

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32)	Len + Rit (N = 30)	Len + Rit (N = 45)	Len + Rit (N = 75)
Subjects with at least one NCI CTCAE Grade 3 or 4 TEAE	10 (31.3)	23 (76.7)	33 (73.3)	56 (74.7)
Subjects with at least one related NCI CTCAE Grade 3 or 4 TEAE	9 (28.1)	19 (63.3)	26 (57.8)	45 (60.0)
Subjects with at Least One NCI CTCAE Grade 5 TEAE	1 (3.1)	1 (3.3)	1 (2.2)	2 (2.7)
Subjects with at Least One TEAE Leading to Dose Reduction[a]	2 (6.3)	6 (20.0)	22 (48.9)	28 (37.3)
Subjects with at Least One TEAE Leading to Dose Interruption of any study drug	14 (43.8)	22 (73.3)	27 (60.0)	49 (65.3)
Subjects with at Least One TEAE Leading to Study Drug Discontinuation	2 (6.3)	5 (16.7)	11 (24.4)	16 (21.3)

CTCAE = Common Terminology Criteria for Adverse Events; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MZL = marginal zone lymphoma; NCI = National Cancer Institute; PBO = placebo; Rit = rituximab; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a All TEAEs leading to dose reduction refer to lenalidomide/placebo, as dose reductions of rituximab were not allowed in the 2 studies per protocols.
Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. Percentages are based on the number of subjects in each treatment group.

Common Treatment-emergent Adverse Events

Safety Population

The most common TEAEs (i.e., ≥ 10% frequency in any treatment arm) in the Safety Population are summarized in the following table:

Table 62 *Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in Any Treatment Arm -Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Subjects With at Least One TEAE	**173 (96.1)**	**174 (98.9)**	**216 (97.3)**	**390 (98.0)**
Gastrointestinal Disorders	**88 (48.9)**	**115 (65.3)**	**154 (69.4)**	**269 (67.6)**
Diarrhoea	41 (22.8)	55 (31.3)	74 (33.3)	129 (32.4)
Constipation	25 (13.9)	46 (26.1)	62 (27.9)	108 (27.1)
Nausea	23 (12.8)	20 (11.4)	64 (28.8)	84 (21.1)
Abdominal pain	16 (8.9)	22 (12.5)	32 (14.4)	54 (13.6)
Vomiting	13 (7.2)	17 (9.7)	23 (10.4)	40 (10.1)

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
General Disorders and Administration Site Conditions	**89 (49.4)**	**98 (55.7)**	**139 (62.6)**	**237 (59.5)**
Fatigue	33 (18.3)	38 (21.6)	109 (49.1)	147 (36.9)
Oedema peripheral	16 (8.9)	23 (13.1)	41 (18.5)	64 (16.1)
Pyrexia	27 (15.0)	37 (21.0)	21 (9.5)	58 (14.6)
Asthenia	19 (10.6)	24 (13.6)	11 (5.0)	35 (8.8)
Blood and Lymphatic System Disorders	**58 (32.2)**	**118 (67.0)**	**118 (53.2)**	**236 (59.3)**
Neutropenia	40 (22.2)	102 (58.0)	87 (39.2)	189 (47.5)
Anaemia	8 (4.4)	28 (15.9)	46 (20.7)	74 (18.6)
Thrombocytopenia	8 (4.4)	26 (14.8)	45 (20.3)	71 (17.8)
Leukopenia	17 (9.4)	36 (20.5)	19 (8.6)	55 (13.8)
Skin And Subcutaneous Tissue Disorders	**43 (23.9)**	**89 (50.6)**	**134 (60.4)**	**223 (56.0)**
Pruritus	7 (3.9)	21 (11.9)	42 (18.9)	63 (15.8)
Rash	7 (3.9)	19 (10.8)	36 (16.2)	55 (13.8)
Rash Maculo-Papular	4 (2.2)	14 (8.0)	27 (12.2)	41 (10.3)
Infections and Infestations	**88 (48.9)**	**110 (62.5)**	**109 (49.1)**	**219 (55.0)**
Upper Respiratory Tract Infection	23 (12.8)	32 (18.2)	29 (13.1)	61 (15.3)
Nasopharyngitis	18 (10.0)	13 (7.4)	4 (1.8)	17 (4.3)
Musculoskeletal and Connective Tissue Disorders	**58 (32.2)**	**73 (41.5)**	**108 (48.6)**	**181 (45.5)**
Muscle Spasms	9 (5.0)	23 (13.1)	23 (10.4)	46 (11.6)
Arthralgia	14 (7.8)	15 (8.5)	27 (12.2)	42 (10.6)
Back Pain	18 (10.0)	14 (8.0)	25 (11.3)	39 (9.8)

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Respiratory, Thoracic and Mediastinal Disorders	**65 (36.1)**	**73 (41.5)**	**105 (47.3)**	**178 (44.7)**
Cough	31 (17.2)	40 (22.7)	40 (18.0)	80 (20.1)
Dyspnoea	8 (4.4)	19 (10.8)	32 (14.4)	51 (12.8)
Nervous System Disorders	**39 (21.7)**	**58 (33.0)**	**96 (43.2)**	**154 (38.7)**
Headache	17 (9.4)	26 (14.8)	34 (15.3)	60 (15.1)
Dizziness	9 (5.0)	15 (8.5)	27 (12.2)	42 (10.6)
Metabolism and Nutrition Disorders	**40 (22.2)**	**58 (33.0)**	**87 (39.2)**	**145 (36.4)**
Decreased Appetite	11 (6.1)	23 (13.1)	31 (14.0)	54 (13.6)
Hypokalaemia	5 (2.8)	14 (8.0)	27 (12.2)	41 (10.3)
Investigations	**50 (27.8)**	**60 (34.1)**	**70 (31.5)**	**130 (32.7)**
Alanine Aminotransferase Increased	15 (8.3)	18 (10.2)	11 (5.0)	29 (7.3)
Injury, Poisoning and Procedural Complications	**40 (22.2)**	**42 (23.9)**	**50 (22.5)**	**92 (23.1)**
Infusion Related Reaction	24 (13.3)	26 (14.8)	30 (13.5)	56 (14.1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	**9 (5.0)**	**26 (14.8)**	**20 (9.0)**	**46 (11.6)**
Tumour Flare	1 (0.6)	19 (10.8)	9 (4.1)	28 (7.0)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events with Preferred Term/System Organ Class.

FL Safety Population

The most common TEAEs (i.e., ≥ 10% frequency in any treatment arm) in the FL Safety Population are summarized in the following table:

Table 63 *Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in Any Treatment Arm – FL Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
Subjects With at Least One TEAE	**141 (95.3)**	**144 (98.6)**	**171 (96.6)**	**315 (97.5)**
Gastrointestinal Disorders	**70 (47.3)**	**94 (64.4)**	**126 (71.2)**	**220 (68.1)**
Diarrhoea	33 (22.3)	45 (30.8)	60 (33.9)	105 (32.5)
Constipation	18 (12.2)	32 (21.9)	51 (28.8)	83 (25.7)
Nausea	18 (12.2)	16 (11.0)	56 (31.6)	72 (22.3)
Abdominal pain	14 (9.5)	19 (13.0)	26 (14.7)	45 (13.9)
Vomiting	10 (6.8)	14 (9.6)	20 (11.3)	34 (10.5)
Dyspepsia	3 (2.0)	15 (10.3)	14 (7.9)	29 (9.0)
General Disorders and Administration Site Conditions	**69 (46.6)**	**77 (52.7)**	**113 (63.8)**	**190 (58.8)**
Fatigue	29 (19.6)	32 (21.9)	89 (50.3)	121 (37.5)
Oedema peripheral	14 (9.5)	19 (13.0)	37 (20.9)	56 (17.3)
Pyrexia	21 (14.2)	28 (19.2)	16 (9.0)	44 (13.6)
Asthenia	14 (9.5)	18 (12.3)	9 (5.1)	27 (8.4)
Blood and Lymphatic System Disorders	**47 (31.8)**	**99 (67.8)**	**86 (48.6)**	**185 (57.3)**
Neutropenia	32 (21.6)	85 (58.2)	63 (35.6)	148 (45.8)
Anaemia	6 (4.1)	22 (15.1)	35 (19.8)	57 (17.6)
Thrombocytopenia	4 (2.7)	23 (15.8)	32 (18.1)	55 (17.0)
Leukopenia	15 (10.1)	28 (19.2)	14 (7.9)	42 (13.0)
Infections and Infestations	**68 (45.9)**	**92 (63.0)**	**90 (50.8)**	**182 (56.3)**
Upper respiratory tract infection	19 (12.8)	24 (16.4)	24 (13.6)	48 (14.9)
Nasopharyngitis	15 (10.1)	11 (7.5)	3 (1.7)	14 (4.3)
Skin and Subcutaneous Tissue Disorders	**33 (22.3)**	**73 (50.0)**	**108 (61.0)**	**181 (56.0)**
Pruritus	5 (3.4)	20 (13.7)	36 (20.3)	56 (17.3)

System Organ Class Preferred Term	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
Rash	5 (3.4)	17 (11.6)	27 (15.3)	44 (13.6)
Rash maculo-papular	4 (2.7)	13 (8.9)	25 (14.1)	38 (11.8)
Musculoskeletal and Connective Tissue Disorders	**47 (31.8)**	**59 (40.4)**	**90 (50.8)**	**149 (46.1)**
Muscle spasms	8 (5.4)	18 (12.3)	19 (10.7)	37 (11.5)
Arthralgia	11 (7.4)	11 (7.5)	22 (12.4)	33 (10.2)
Back pain	14 (9.5)	11 (7.5)	21 (11.9)	32 (9.9)
Respiratory, Thoracic and Mediastinal Disorders	**52 (35.1)**	**59 (40.4)**	**85 (48.0)**	**144 (44.6)**
Cough	26 (17.6)	32 (21.9)	34 (19.2)	66 (20.4)
Dyspnoea	5 (3.4)	13 (8.9)	25 (14.1)	38 (11.8)
Nervous System Disorders	**34 (23.0)**	**48 (32.9)**	**76 (42.9)**	**124 (38.4)**
Headache	14 (9.5)	21 (14.4)	26 (14.7)	47 (14.6)
Dizziness	8 (5.4)	12 (8.2)	21 (11.9)	33 (10.2)
Metabolism and Nutrition Disorders	**34 (23.0)**	**46 (31.5)**	**75 (42.4)**	**121 (37.5)**
Decreased appetite	9 (6.1)	17 (11.6)	26 (14.7)	43 (13.3)
Hypokalaemia	4 (2.7)	12 (8.2)	23 (13.0)	35 (10.8)
Investigations	**42 (28.4)**	**52 (35.6)**	**58 (32.8)**	**110 (34.1)**
White blood cell count decreased	12 (8.1)	16 (11.0)	12 (6.8)	28 (8.7)
Alanine aminotransferase increased	13 (8.8)	16 (11.0)	8 (4.5)	24 (7.4)
Injury, Poisoning and Procedural Complications	**32 (21.6)**	**35 (24.0)**	**42 (23.7)**	**77 (23.8)**
Infusion related reaction	21 (14.2)	22 (15.1)	24 (13.6)	46 (14.2)

System Organ Class Preferred Term	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**9 (6.1)**	**25 (17.1)**	**16 (9.0)**	**41 (12.7)**
Tumour flare	1 (0.7)	19 (13.0)	7 (4.0)	26 (8.0)

FL = follicular lymphoma; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events with Preferred Term/System Organ Class.
Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column.

MZL Safety Population

The most common TEAEs (i.e., ≥ 10% frequency in any treatment arm) in previously treated subjects in the MZL Safety Population are summarized in table

Table 64 *Treatment-emergent Adverse Events Reported in at Least 10% of Subjects in Any Treatment Arm – MZL Safety Population*

System Organ Class Preferred Term[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Subjects with at least one TEAE	**32 (100.0)**	**30 (100.0)**	**45 (100.0)**	**75 (100.0)**
Blood and Lymphatic System Disorders	**11 (34.4)**	**19 (63.3)**	**32 (71.1)**	**51 (68.0)**
Neutropenia	8 (25.0)	17 (56.7)	24 (53.3)	41 (54.7)
Anaemia	2 (6.3)	6 (20.0)	11 (24.4)	17 (22.7)
Thrombocytopenia	4 (12.5)	3 (10.0)	13 (28.9)	16 (21.3)
Leukopenia	2 (6.3)	8 (26.7)	5 (11.1)	13 (17.3)
Gastrointestinal Disorders	**18 (56.3)**	**21 (70.0)**	**28 (62.2)**	**49 (65.3)**
Constipation	7 (21.9)	14 (46.7)	11 (24.4)	25 (33.3)
Diarrhoea	8 (25.0)	10 (33.3)	14 (31.1)	24 (32.0)
Nausea	5 (15.6)	4 (13.3)	8 (17.8)	12 (16.0)
Abdominal pain	2 (6.3)	3 (10.0)	6 (13.3)	9 (12.0)
Dyspepsia	2 (6.3)	1 (3.3)	6 (13.3)	7 (9.3)
Abdominal pain upper	1 (3.1)	3 (10.0)	3 (6.7)	6 (8.0)
Vomiting	3 (9.4)	3 (10.0)	3 (6.7)	6 (8.0)
Abdominal discomfort	0 (0.0)	3 (10.0)	0 (0.0)	3 (4.0)
General Disorders and Administration Site Conditions	**20 (62.5)**	**21 (70.0)**	**26 (57.8)**	**47 (62.7)**
Fatigue	4 (12.5)	6 (20.0)	20 (44.4)	26 (34.7)
Pyrexia	6 (18.8)	9 (30.0)	5 (11.1)	14 (18.7)
Asthenia	5 (15.6)	6 (20.0)	2 (4.4)	8 (10.7)
Oedema peripheral	2 (6.3)	4 (13.3)	4 (8.9)	8 (10.7)

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Chills	3 (9.4)	4 (13.3)	3 (6.7)	7 (9.3)
Skin and Subcutaneous Tissue Disorders	**10 (31.3)**	**16 (53.3)**	**26 (57.8)**	**42 (56.0)**
Rash	2 (6.3)	2 (6.7)	9 (20.0)	11 (14.7)
Pruritus	2 (6.3)	1 (3.3)	6 (13.3)	7 (9.3)
Pruritus generalized	0 (0.0)	5 (16.7)	1 (2.2)	6 (8.0)
Infections and Infestations	**20 (62.5)**	**18 (60.0)**	**19 (42.2)**	**37 (49.3)**
Upper respiratory tract infection	4 (12.5)	8 (26.7)	5 (11.1)	13 (17.3)
Influenza	1 (3.1)	3 (10.0)	2 (4.4)	5 (6.7)
Pneumonia	4 (12.5)	1 (3.3)	2 (4.4)	3 (4.0)
Respiratory, Thoracic and Mediastinal Disorders	**13 (40.6)**	**14 (46.7)**	**20 (44.4)**	**34 (45.3)**
Cough	5 (15.6)	8 (26.7)	6 (13.3)	14 (18.7)
Dyspnoea	3 (9.4)	6 (20.0)	7 (15.6)	13 (17.3)
Productive cough	4 (12.5)	3 (10.0)	4 (8.9)	7 (9.3)
Musculoskeletal and Connective Tissue Disorders	**11 (34.4)**	**14 (46.7)**	**18 (40.0)**	**32 (42.7)**
Arthralgia	3 (9.4)	4 (13.3)	5 (11.1)	9 (12.0)
Muscle spasms	1 (3.1)	5 (16.7)	4 (8.9)	9 (12.0)
Back pain	4 (12.5)	3 (10.0)	4 (8.9)	7 (9.3)
Pain in extremity	1 (3.1)	3 (10.0)	4 (8.9)	7 (9.3)
Myalgia	4 (12.5)	2 (6.7)	1 (2.2)	3 (4.0)
Nervous System Disorders	**5 (15.6)**	**10 (33.3)**	**20 (44.4)**	**30 (40.0)**
Headache	3 (9.4)	5 (16.7)	8 (17.8)	13 (17.3)
Dizziness	1 (3.1)	3 (10.0)	6 (13.3)	9 (12.0)
Metabolism and Nutrition Disorders	**6 (18.8)**	**12 (40.0)**	**12 (26.7)**	**24 (32.0)**
Decreased appetite	2 (6.3)	6 (20.0)	5 (11.1)	11 (14.7)

Parameter	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Injury, Poisoning and Procedural Complications	**8 (25.0)**	**7 (23.3)**	**8 (17.8)**	**15 (20.0)**
Infusion related reaction	3 (9.4)	4 (13.3)	6 (13.3)	10 (13.3)
Psychiatric Disorders	**6 (18.8)**	**4 (13.3)**	**10 (22.2)**	**14 (18.7)**
Insomnia	2 (6.3)	3 (10.0)	6 (13.3)	9 (12.0)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] A subject is counted only once for multiple events within Preferred Term/System Organ Class. Coded using MedDRA version 21.0.

Grade 3 or 4 Treatment-emergent Adverse Events

-Safety Population

The Grade 3 or 4 TEAEs reported in ≥ 5% of subjects in any treatment arm in the Safety Population are summarized in Table

Table 65 *Grade 3 or 4 Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Any Treatment Arm -Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Subjects With at Least One Grade 3/4 TEAE	**58 (32.2)**	**121 (68.8)**	**138 (62.2)**	**259 (65.1)**
Blood and Lymphatic System Disorders	**25 (13.9)**	**91 (51.7)**	**82 (36.9)**	**173 (43.5)**
Neutropenia	23 (12.8)	88 (50.0)	74 (33.3)	162 (40.7)
Leukopenia	3 (1.7)	12 (6.8)	13 (5.9)	25 (6.3)
Thrombocytopenia	2 (1.1)	4 (2.3)	17 (7.7)	21 (5.3)

Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within Preferred Term/System Organ Class.

-FL Safety Population

The Grade 3 or 4 TEAEs reported in ≥ 5% of subjects in any treatment arm in the FL Safety Population are summarized in Table.

Table 66 *Grade 3 or 4 Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Any Treatment Arm – FL Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
Subjects With at Least One Grade 3/4 TEAE	**48 (32.4)**	**98 (67.1)**	**105 (59.3)**	**203 (62.8)**
Blood and Lymphatic System Disorders	**20 (13.5)**	**77 (52.7)**	**60 (33.9)**	**137 (42.4)**
Neutropenia	18 (12.2)	74 (50.7)	56 (31.6)	130 (40.2)
Leukopenia	3 (2.0)	9 (6.2)	9 (5.1)	18 (5.6)
Thrombocytopenia	0 (0.0)	2 (1.4)	9 (5.1)	11 (3.4)

FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within preferred term/system organ class.

-MZL Safety Population

The Grade 3 or 4 TEAEs reported in ≥ 5% of previously treated subjects in any treatment arm in the MZL Safety Population are summarized in the following table:

Table 67 *Grade 3 or 4 Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Any Treatment Arm – MZL Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Subjects with at least one Grade 3 or 4 TEAE	**10 (31.3)**	**23 (76.7)**	**33 (73.3)**	**56 (74.7)**
Blood and Lymphatic System Disorders	**5 (15.6)**	**14 (46.7)**	**22 (48.9)**	**36 (48.0)**
Neutropenia	5 (15.6)	14 (46.7)	18 (40.0)	32 (42.7)
Thrombocytopenia	2 (6.3)	2 (6.7)	8 (17.8)	10 (13.3)
Leukopenia	0 (0.0)	3 (10.0)	4 (8.9)	7 (9.3)
Anaemia	0 (0.0)	2 (6.7)	3 (6.7)	5 (6.7)
Infections and Infestations	**5 (15.6)**	**4 (13.3)**	**4 (8.9)**	**8 (10.7)**
Pneumonia	4 (12.5)	1 (3.3)	0 (0.0)	1 (1.3)
Injury, Poisoning and Procedural Complications	**0 (0.0)**	**5 (16.7)**	**0 (0.0)**	**5 (6.7)**
Infusion related reaction	0 (0.0)	3 (10.0)	0 (0.0)	3 (4.0)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0)**	**2 (6.7)**	**1 (2.2)**	**3 (4.0)**
Pain in extremity	0 (0.0)	2 (6.7)	1 (2.2)	3 (4.0)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within preferred term/system organ class.

Grade 5 Treatment-emergent Adverse Events

-Safety Population

The Grade 5 TEAEs reported in subjects in any treatment arm in the Safety Population are summarized in the following table:

Table 68 *Grade 5 Treatment-emergent Adverse Events Reported in Subjects in Any Treatment Arm - Safety Population*

System Organ Class Preferred Term [a]	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
	PBO + Rit (N=180) n (%)	Len + Rit (N=176) n (%)	Len + Rit (N=222) n (%)	Len + Rit (N=398) n (%)
Subjects With at Least One Grade 5 TEAE	**2 (1.1)**	**2 (1.1)**	**4 (1.8)**	**6 (1.5)**
Cardiac Disorders	**0 (0.0)**	**2 (1.1)**	**1 (0.5)**	**3 (0.8)**
Arrhythmia	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Cardiopulmonary failure	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
General Disorders and Administration Site Conditions	**1 (0.6)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
General physical health deterioration	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and Infestations	**1 (0.6)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**
Sepsis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Pneumonia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and Urinary Disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**
Acute kidney injury	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within Preferred Term/System Organ Class.
Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. Percentages are based on the number of subjects in each treatment group. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column.
Source: SCS Table 1.5.8.1

In AUGMENT study, two subjects (1.1%) in each treatment arm had a Grade 5 TEAE. In the R2 Arm, Grade 5 TEAEs included the following (in one subject each):

• Arrhythmia occurring on Study Day 192 in a subject with FL. The investigator suspected a relationship of this TEAE to lenalidomide but not to rituximab.

• Cardiopulmonary failure on Study Day 3 in a subject with MZL. The investigator did not suspect a relationship to lenalidomide or rituximab.

In the Control Arm, Grade 5 TEAEs included the following (in one subject each):

• General physical health deterioration on Study Day 214 in a subject with FL. The investigator did not suspect a relationship to placebo or rituximab.

• Pneumonia on Study Day 70 in a subject with MZL. The investigator suspected a relationship to placebo and to rituximab.

In MAGNIFY study, Grade 5 TEAEs were reported for 4 (1.8%) subjects (one subject for each TEAE): multiple organ dysfunction syndrome, sepsis, acute kidney injury, and cardio-respiratory arrest.

In the Pooled AUGMENT and MAGNIFY Len + Rit Treatment Arm; Grade 5 TEAEs were reported for 6 (1.5%) subjects (one subject for each TEAE): arrhythmia, cardiorespiratory arrest, cardiopulmonary failure, multiple organ dysfunction syndrome, sepsis, and acute kidney injury.

Treatment-emergent Adverse Events of Special Interest

-Safety Population

All TEAEs by AESI category are summarized for the Safety Population in the following table:

Table 69 Treatment-emergent Adverse Events of Special Interest -- Safety Population

AESI Category[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Infection	88 (48.9)	110 (62.5)	109 (49.1)	219 (55.0)
Neutropenia	41 (22.8)	102 (58.0)	84 (37.8)	186 (46.7)
Cutaneous reaction	21 (11.7)	57 (32.4)	79 (35.6)	136 (34.2)
Diarrhea	41 (22.8)	55 (31.3)	74 (33.3)	129 (32.4)
Constipation	25 (13.9)	46 (26.1)	62 (27.9)	108 (27.1)
Hepatic disorder	20 (11.1)	36 (20.5)	27 (12.2)	63 (15.8)
Thrombocytopenia	8 (4.4)	26 (14.8)	32 (14.4)	58 (14.6)
Bleeding	20 (11.1)	16 (9.1)	25 (11.3)	41 (10.3)
Cardiac arrhythmias	15 (8.3)	18 (10.2)	18 (8.1)	36 (9.0)
Peripheral neuropathy	7 (3.9)	13 (7.4)	23 (10.4)	36 (9.0)
Renal failure	7 (3.9)	12 (6.8)	19 (8.6)	31 (7.8)
Tumour flare reaction	1 (0.6)	19 (10.8)	9 (4.1)	28 (7.0)
Hypersensitivity	4 (2.2)	4 (2.3)	12 (5.4)	16 (4.0)
Venous thromboembolic event	3 (1.7)	6 (3.4)	5 (2.3)	11 (2.8)
Angioedema	3 (1.7)	4 (2.3)	6 (2.7)	10 (2.5)
Ischaemic heart disease (including myocardial infarction)	2 (1.1)	1 (0.6)	7 (3.2)	8 (2.0)
Mixed thromboembolism	1 (0.6)	3 (1.7)	2 (0.9)	5 (1.3)
Arterial thromboembolic event	4 (2.2)	1 (0.6)	3 (1.4)	4 (1.0)
Tumour lysis syndrome	0 (0.0)	2 (1.1)	1 (0.5)	3 (0.8)
Cardiac failure	2 (1.1)	1 (0.6)	1 (0.5)	2 (0.5)
Interstitial lung disease/pneumonitis	1 (0.6)	0 (0.0)	1 (0.5)	1 (0.3)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximabSMQ = standardized MedDRA query; SOC = System Organ Class.

[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms. A subject is counted only once for multiple events within each AESI category.

Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for AESI category in the Pooled AUGMENT + MAGNIFY column.

-FL Safety Population

All TEAEs by AESI category are summarized for the FL Safety Population in the following table.

Table 70 Treatment-emergent Adverse Events of Special Interest –FL Safety Population

AESI Category[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 148) n (%)	Len + Rit (N = 146) n (%)	Len + Rit (N = 177) n (%)	Len + Rit (N = 323) n (%)
Infection	68 (45.9)	92 (63.0)	90 (50.8)	182 (56.3)
Neutropenia	33 (22.3)	85 (58.2)	60 (33.9)	145 (44.9)
Cutaneous reaction	17 (11.5)	50 (34.2)	63 (35.6)	113 (35.0)
Diarrhea	33 (22.3)	45 (30.8)	60 (33.9)	105 (32.5)
Constipation	18 (12.2)	32 (21.9)	51 (28.8)	83 (25.7)
Hepatic disorder	17 (11.5)	32 (21.9)	20 (11.3)	52 (16.1)
Thrombocytopenia	4 (2.7)	23 (15.8)	21 (11.9)	44 (13.6)

AESI Category[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 148) n (%)	Len + Rit (N = 146) n (%)	Len + Rit (N = 177) n (%)	Len + Rit (N = 323) n (%)
Bleeding	15 (10.1)	14 (9.6)	23 (13.0)	37 (11.5)
Cardiac arrhythmia	13 (8.8)	17 (11.6)	12 (6.8)	29 (9.0)
Peripheral neuropathy	6 (4.1)	12 (8.2)	17 (9.6)	29 (9.0)
Renal failure	4 (2.7)	10 (6.8)	17 (9.6)	27 (8.4)
Tumour flare reaction	1 (0.7)	19 (13.0)	7 (4.0)	26 (8.0)
Hypersensitivity	3 (2.0)	1 (0.7)	10 (5.6)	11 (3.4)
Venous thromboembolic event	3 (2.0)	6 (4.1)	4 (2.3)	10 (3.1)
Angioedema	2 (1.4)	3 (2.1)	5 (2.8)	8 (2.5)
Ischaemic heart disease (including myocardial infarction)	2 (1.4)	1 (0.7)	7 (4.0)	8 (2.5)
Mixed thromboembolism	1 (0.7)	3 (2.1)	2 (1.1)	5 (1.5)
Arterial thromboembolic event	4 (2.7)	1 (0.7)	3 (1.7)	4 (1.2)
Tumour lysis syndrome	0 (0.0)	2 (1.4)	1 (0.6)	3 (0.9)
Cardiac failure	2 (1.4)	0 (0.0)	1 (0.6)	1 (0.3)
Interstitial lung disease/pneumonitis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; FL = follicular lymphoma; HLT = Higher-Level Term; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.

-MZL Safety Population

All TEAEs by AESI category are summarized for the MZL Safety Population in the following table:

Table 71 Treatment-emergent Adverse Events of Special Interest –MZL Safety Population

AESI Category[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Neutropenia	8 (25.0)	17 (56.7)	24 (53.3)	41 (54.7)
Infection	20 (62.5)	18 (60.0)	19 (42.2)	37 (49.3)
Constipation	7 (21.9)	14 (46.7)	11 (24.4)	25 (33.3)
Diarrhea	8 (25.0)	10 (33.3)	14 (31.1)	24 (32.0)
Cutaneous reaction	4 (12.5)	7 (23.3)	16 (35.6)	23 (30.7)
Thrombocytopenia	4 (12.5)	3 (10.0)	11 (24.4)	14 (18.7)
Hepatic disorder	3 (9.4)	4 (13.3)	7 (15.6)	11 (14.7)
Cardiac arrhythmia	2 (6.3)	1 (3.3)	6 (13.3)	7 (9.3)
Peripheral neuropathy	1 (3.1)	1 (3.3)	6 (13.3)	7 (9.3)
Hypersensitivity	1 (3.1)	3 (10.0)	2 (4.4)	5 (6.7)
Bleeding	5 (15.6)	2 (6.7)	2 (4.4)	4 (5.3)
Renal failure	3 (9.4)	2 (6.7)	2 (4.4)	4 (5.3)
Angioedema	1 (3.1)	1 (3.3)	1 (2.2)	2 (2.7)
Tumour flare reaction	0 (0.0)	0 (0.0)	2 (4.4)	2 (2.7)
Cardiac failure	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Venous thromboembolic event	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Arterial thromboembolic event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease/pneumonitis	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic heart disease (including myocardial infarction)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.
[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms.

Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest

-Safety Population

Grade 3 or 4 TEAEs by AESI category are summarized for the Safety Population in the following table:

Table 72 Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest -- Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
AESI Category[a]	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Neutropenia	24 (13.3)	88 (50.0)	71 (32.0)	159 (39.9)
Infection	12 (6.7)	26 (14.8)	27 (12.2)	53 (13.3)
Thrombocytopenia	2 (1.1)	4 (2.3)	13 (5.9)	17 (4.3)
Cutaneous Reaction	2 (1.1)	5 (2.8)	8 (3.6)	13 (3.3)
Diarrhea	0 (0.0)	5 (2.8)	7 (3.2)	12 (3.0)
Renal Failure	2 (1.1)	2 (1.1)	10 (4.5)	12 (3.0)
Cardiac Arrhythmia	2 (1.1)	4 (2.3)	6 (2.7)	10 (2.5)
Hepatic Disorder	1 (0.6)	5 (2.8)	4 (1.8)	9 (2.3)
Venous thromboembolic event	1 (0.6)	4 (2.3)	2 (0.9)	6 (1.5)
Ischaemic Heart Disease (including Myocardial Infarction)	1 (0.6)	1 (0.6)	3 (1.4)	4 (1.0)
Peripheral neuropathy	0 (0.0)	1 (0.6)	3 (1.4)	4 (1.0)
Constipation	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.8)
Hypersensitivity	1 (0.6)	1 (0.6)	2 (0.9)	3 (0.8)
Angioedema	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)
Arterial thromboembolic event	3 (1.7)	0 (0.0)	1 (0.5)	1 (0.3)
Bleeding	3 (1.7)	0 (0.0)	1 (0.5)	1 (0.3)
Mixed Thromboembolism	1 (0.6)	0 (0.0)	1 (0.5)	1 (0.3)
Tumour Flare Reaction	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Tumour Lysis Syndrome	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Cardiac Failure	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial Lung Disease/Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.

[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms. A subject is counted only once for multiple events within each AESI category.

Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for AESI category in the Pooled AUGMENT + MAGNIFY column.

-FL Safety Population

Grade 3 or 4 TEAEs by AESI category are summarized for the FL Safety Population in the following table:

Table 73 *Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest – FL Safety Population*

AESI Category[a]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 148) n (%)	Len + Rit (N = 146) n (%)	Len + Rit (N = 177) n (%)	Len + Rit (N = 323) n (%)
Neutropenia	19 (12.8)	74 (50.7)	53 (29.9)	127 (39.3)
Infection	7 (4.7)	22 (15.1)	23 (13.0)	45 (13.9)
Diarrhea	0 (0.0)	5 (3.4)	6 (3.4)	11 (3.4)
Renal Failure	1 (0.7)	2 (1.4)	9 (5.1)	11 (3.4)
Cutaneous Reaction	2 (1.4)	4 (2.7)	6 (3.4)	10 (3.1)
Thrombocytopenia	0 (0.0)	2 (1.4)	6 (3.4)	8 (2.5)
Cardiac Arrhythmia	2 (1.4)	4 (2.7)	3 (1.7)	7 (2.2)
Venous thromboembolic event	1 (0.7)	4 (2.7)	1 (0.6)	5 (1.5)
Hepatic Disorder	1 (0.7)	3 (2.1)	1 (0.6)	4 (1.2)
Ischaemic Heart Disease (including Myocardial Infarction)	1 (0.7)	1 (0.7)	3 (1.7)	4 (1.2)
Constipation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.6)
Peripheral neuropathy	0 (0.0)	1 (0.7)	1 (0.6)	2 (0.6)
Angioedema	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Arterial thromboembolic event	3 (2.0)	0 (0.0)	1 (0.6)	1 (0.3)
Bleeding	3 (2.0)	0 (0.0)	1 (0.6)	1 (0.3)
Hypersensitivity	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.3)
Mixed thromboembolism	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.3)
Tumour flare reaction	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Cardiac Failure	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial Lung Disease/Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; FL = follicular lymphoma; HLT = Higher-Level Term; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.

[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms. A subject is counted only once for multiple events within each AESI category.

Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for AESI category in the Pooled AUGMENT + MAGNIFY column.

-MZL Safety Population

Grade 3 or 4 TEAEs by AESI category are summarized for the MZL Safety Population in the following table:

Table 74 Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest –MZL Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
AESI Category[a]	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Neutropenia	5 (15.6)	14 (46.7)	18 (40.0)	32 (42.7)
Thrombocytopenia	2 (6.3)	2 (6.7)	7 (15.6)	9 (12.0)
Infection	5 (15.6)	4 (13.3)	4 (8.9)	8 (10.7)
Hepatic Disorder	0 (0.0)	2 (6.7)	3 (6.7)	5 (6.7)
Cardiac Arrhythmias	0 (0.0)	0 (0.0)	3 (6.7)	3 (4.0)
Cutaneous Reaction	0 (0.0)	1 (3.3)	2 (4.4)	3 (4.0)
Hypersensitivity	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Peripheral Neuropathy	0 (0.0)	0 (0.0)	2 (4.4)	2 (2.7)
Angioedema	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Constipation	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Diarrhea	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Renal Failure	1 (3.1)	0 (0.0)	1 (2.2)	1 (1.3)
Venous thromboembolic event	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Arterial thromboembolic event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial Lung Disease/Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic Heart Disease (including Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed Thromboembolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratogenicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumour Flare Reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumour Lysis Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class

Adverse Events of Special Interest by AESI Category

-Neutropenia

In the Safety Population, TEAEs in the AESI category of neutropenia were reported in 58.0% of subjects in the AUGMENT R2 Arm *versus* 22.8% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of neutropenia events was 37.8%. Nearly all of the reported TEAEs in the AESI category of neutropenia were the PT of neutropenia. A small percentage of subjects in the pooled dataset (3%) had febrile neutropenia. Grade 3 or 4 neutropenia events were reported in 50.0% of subjects in the AUGMENT R2 Arm *versus* 13.3% in the Control Arm.

In the AUGMENT study, less than one third of subjects in the R2 Arm with Grade ≥ 3 neutropenia had a concurrent infection (28/88 [31.8%]) and 9.1% (8/88) had a concurrent Grade 3 or 4 infection. Only 5 subjects (2.8%) in the R2 Arm discontinued study treatment due to neutropenia. The median time to onset of Grade 3 or 4 neutropenia was approximately 14 weeks in the R2 Arm and 12 weeks in the Control Arm while the median time to improvement and resolution of the event was 9 days in both arms. Events of neutropenia were managed by dose modifications including dose reductions, dose interruptions, and/or growth factor support. In general, similar frequencies of TEAEs and Grade 3 or 4 TEAEs in the

AESI category of neutropenia were seen in subjects with FL and subjects with MZL compared with the Safety Population.

Table 75 *Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest -Neutropenia -- Safety Population*

AESI Category[a] Preferred Term[b]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Subjects with at Least One Grade 3 or 4 TEAE of Neutropenia	**24 (13.3)**	**88 (50.0)**	**71 (32.0)**	**159 (39.9)**
Neutropenia	23 (12.8)	88 (50.0)	69 (31.1)	157 (39.4)
Febrile neutropenia	1 (0.6)	5 (2.8)	7 (3.2)	12 (3.0)
Neutropenic colitis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Neutrophil percentage decreased	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.

Infections

Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of infection events of 55.0%. The most frequently reported events of infection in the pooled dataset were upper respiratory tract infection (15.3%), sinusitis (8.3%), urinary tract infection (7.5%), pneumonia (6.8%), bronchitis (5.0%), and influenza (5.0%). All other events occurred at frequencies less than 5%.

In the Safety Population, Grade 3 or 4 TEAEs of infection are presented in the following table:

Table 76 *Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest -Infection in at Least 1% of Subjects in Pooled AUGMENT and MAGNIFY-- Safety Population*

AESI Category[a] Preferred Term[b]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Subjects with at Least One Grade 3 or 4 TEAE of infection	**12 (6.7)**	**26 (14.8)**	**27 (12.2)**	**53 (13.3)**
Pneumonia	4 (2.2)	6 (3.4)	4 (1.8)	10 (2.5)
Sepsis	2 (1.1)	3 (1.7)	3 (1.4)	6 (1.5)
Lung infection	3 (1.7)	2 (1.1)	2 (0.9)	4 (1.0)
Urinary tract infection	1 (0.6)	1 (0.6)	3 (1.4)	4 (1.0)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.
[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms. A subject is counted only once for multiple events within each AESI category.
[b] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within the Preferred Term.
Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column.

Cutaneous Reactions

Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of events of cutaneous reaction of 34.2%. The most frequently reported events of cutaneous reaction in the pooled dataset were rash (13.8%), maculo-papular rash (10.3%), and stomatitis (6.5%).

In the AUGMENT study, the median time to onset of Grade 2 to 4 cutaneous reaction was less than 3 weeks in each arm while the median time to resolution of the event was 16 days in the R2 Arm and 6.5 days in the Control Arm. Among the subjects with cutaneous reaction, medications were used for

management by approximately 61% of subjects in each arm. Grade 3 or 4 cutaneous reaction events were reported in 2.8% of subjects in the AUGMENT R2 Arm versus 1.1% in the Control Arm.

Table 77 *Grade 3 or 4 Treatment-emergent Adverse Events of Special Interest - Cutaneous Reaction -- Safety Population*

AESI Category[a] Preferred Term[b]	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Subjects with at Least One Grade 3 or 4 TEAE of cutaneous reaction	2 (1.1)	5 (2.8)	8 (3.6)	13 (3.3)
Rash	1 (0.6)	2 (1.1)	1 (0.5)	3 (0.8)
Rash maculo-papular	1 (0.6)	1 (0.6)	2 (0.9)	3 (0.8)
Rash generalised	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)
Rash erythematous	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Rash macular	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Stomatitis	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.8)

AESI = adverse event of special interest; HLT = Higher-Level Term; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SMQ = standardized MedDRA query; SOC = System Organ Class.
[a] AESI categories used either MedDRA version 21.0 SMQ or sub-SMQ or SOC or HLT or list of Preferred Terms. A subject is counted only once for multiple events within each AESI category.
[b] Coded using MedDRA version 21.0. A subject is counted only once for multiple events within the Preferred Term.

Diarrhea

In the Safety Population, diarrhea was reported in 31.3% of subjects in the AUGMENT R2 Arm versus 22.8% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of diarrhea was 33.3%.

Grade 3 or 4 TEAEs of diarrhea were reported in 2.8% of subjects in the AUGMENT R2 Arm versus 0% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of diarrhea was 3.2%. Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of 3.0%.

Hepatic Disorder

In the Safety Population, TEAEs in the AESI category of hepatic disorder were reported in 20.5% of subjects in the AUGMENT R2 Arm versus 11.1% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of hepatic disorder events was 12.2%. Nearly all of the reported hepatic disorder events were laboratory abnormalities. The most frequently reported events in the pooled dataset were alanine aminotransferase increased (7.3%), aspartate aminotransferase increased (4.3%), blood bilirubin increased (3.8%), and blood alkaline phosphatase increased (3.3%).

Grade 3 or 4 hepatic disorder events were reported in 2.8% of subjects in the AUGMENT R2 Arm versus 0.6% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of hepatic disorder events was 1.8%. The only PT within the AESI category reported in the pooled dataset at greater than 1% was alanine aminotransferase increased (1.5%).

Thrombocytopenia

In the Safety Population, thrombocytopenia was reported in 14.8% of subjects in the AUGMENT R2 Arm versus 4.4% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of thrombocytopenia was 14.4%.

Grade 3 or 4 thrombocytopenia was reported in 2.3% of subjects in the AUGMENT R2 Arm versus 1.1% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of thrombocytopenia was 5.9%.

In the FL Safety Population, observations were similar to the overall Safety Population while in the MZL Safety Population, higher frequencies of thrombocytopenia were observed compared with the Safety Population for MAGNIFY.

Bleeding

Antithrombotic prophylaxis, which is associated with side effects of bleeding, was recommended per protocol for subjects at high risk of thromboembolic events in the AUGMENT and MAGNIFY, (only recommended for R2 Arm) studies.

In the Safety Population, TEAEs in the AESI category of bleeding were reported in 9.1% of subjects in the AUGMENT R2 Arm versus 11.1% in the Control Arm (approximately 70% of subjects in both arms used antiplatelet and/or anticoagulant medication concomitantly). During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of bleeding events was 11.3%. Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of 10.3%. The most commonly reported bleeding event in the pooled dataset was epistaxis (2.0%).

There were no Grade 3 or 4 events of bleeding reported in the AUGMENT R2 Arm and only 1 subject (0.5%) in the MAGNIFY study reported Grade 3 or 4 bleeding during the Initial Treatment Period while on R2 treatment.

Cardiac Arrhythmias

In the Safety Population, TEAEs in the AESI category of cardiac arrhythmia were reported in 10.2% of subjects in the AUGMENT R2 Arm versus 8.3% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of cardiac arrhythmia events was 8.1%. The most frequently reported event in the pooled dataset was palpitations (2.5%).

Grade 3 or 4 cardiac arrhythmia events were reported in 2.3% of subjects in the AUGMENT R2 Arm versus 1.1% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of events was 2.7%.The only PT within the AESI category reported in the pooled dataset at greater than 1% was syncope (1.3%).

Peripheral Neuropathy

In the Safety Population, TEAEs in the AESI category of peripheral neuropathy were reported in 7.4% of subjects in the AUGMENT R2 Arm versus 3.9% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of events was 10.4%.Only 1 subject (0.6%) in the AUGMENT R2 Arm and no subjects in the Control Arm had Grade 3 or 4 events of peripheral neuropathy. Only 3 subjects (1.4%) had Grade 3 or 4 peripheral neuropathy events in the MAGNIFY study during the Initial Treatment Period while on R2 treatment.

Renal Failure

In the Safety Population, TEAEs in the AESI category of renal failure were reported in 6.8% of subjects in the AUGMENT R2 Arm versus 3.9% in the Control Arm.

During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of renal failure events was 8.6%. Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of 7.8%. The most frequently reported events in the pooled dataset were blood creatinine increased (4.8%), followed by acute kidney injury (3.3%).

Grade 3 or 4 renal failure events were reported in 1.1% of subjects in each of the AUGMENT treatment arms. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of renal failure events was 4.5%. Pooling the AUGMENT and MAGNIFY R2 arms resulted in a frequency of 3.0%.

Tumour Flare Reaction

In the Safety Population, tumour flare reaction was reported in 10.8% of subjects in the AUGMENT R2 Arm versus 0.6% (1 subject) in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of tumour flare reaction was 4.1%.

Only 1 (0.6%) subject in the AUGMENT R2 Arm had Grade 3 or 4 tumour flare reaction. No subjects had Grade 3 or 4 events in the AUGMENT Control Arm or in the MAGNIFY study during the Initial Treatment Period while on R2 treatment.

In the AUGMENT study, all events of tumour flare reaction were in subjects with FL; in the MAGNIFY study, the frequencies of tumour flare reaction were similar across the FL, MZL, and Safety populations.

Hypersensitivity and Angioedema

In the Safety Population, hypersensitivity was reported in 2.3% of subjects in the AUGMENT R2 Arm versus 2.2% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of hypersensitivity was 5.4%. Only 1 (0.6%) subject in each the AUGMENT R2 Arm and Control Arm had Grade 3 or 4 hypersensitivity. Only 2 subjects had Grade 3 or 4 events in the MAGNIFY study during the Initial Treatment Period while on R2 treatment.

Angioedema occurred at frequencies of less than 5% across all arms in the AUGMENT and MAGNIFY studies. Only 2 subjects (0.9%) in the MAGNIFY R2 Arm had Grade 3 or 4 events.

Venous Thromboembolic Event

Antithrombotic prophylaxis was recommended for high-risk subjects in the AUGMENT and MAGNIFY (R2 Arm only) studies. In the Safety Population, TEAEs in the AESI category of VTE were reported in less than 5% of subjects across all arms in the AUGMENT and MAGNIFY studies.

Grade 3 or 4 VTE events were reported in 2.3% of subjects in the AUGMENT R2 Arm versus 0.6% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of events was 0.9%.

Ischemic Heart Disease (including Myocardial Infarction)

In the Safety Population, TEAEs in the AESI category of ischemic heart disease (including MI) were reported in less than 5% of subjects across all arms in the AUGMENT and MAGNIFY studies. All of these events occurred in subjects with FL; none of the events occurred in subjects with MZL.

One subject (0.6%) in each of the AUGMENT treatment arms and 3 subjects (1.4%) in the MAGNIFY study during the Initial Treatment Period had Grade 3 or 4 ischemic heart disease (IHD) events.

Mixed Thromboembolism

In the Safety Population, TEAEs in the AESI category of mixed thromboembolism were reported in less than 2% of subjects across all arms in the AUGMENT and MAGNIFY studies. All of these events occurred in subjects with FL; none of the events occurred in subjects with MZL. 1 subject in the MAGNIFY study during the Initial Treatment Period had Grade 3 or 4 mixed thromboembolism events.

Arterial Thromboembolic Event

In the Safety Population, TEAEs in the AESI category of arterial thromboembolic event (ATE) were reported in less than 5% of subjects across all arms in the AUGMENT and MAGNIFY studies. Results were similar in the FL Safety Population and no events of ATE were reported in the MZL Safety Population. Only 1 subject had Grade 3 or 4 ATE events in the MAGNIFY study during the Initial Treatment Period.

Tumour Lysis Syndrome

Subjects were required to receive tumour lysis prophylaxis in the AUGMENT and MAGNIFY (R2 Arm only) studies. In the Safety Population, TLS was reported in less than 2% of subjects across all arms in the AUGMENT and MAGNIFY studies. All of these events occurred in subjects with FL; none of the events occurred in subjects with MZL. Only 1 subject (0.5%) in the MAGNIFY study during the Initial Treatment Period had Grade 3 or 4 TLS.

Cardiac Failure

In the Safety Population, TEAEs in the AESI category of cardiac failure were reported in less than 2% of subjects across all arms in the AUGMENT and MAGNIFY studies. Cardiac failure events were reported for 1 subject with FL in the MAGNIFY study and 1 subject with MZL in the AUGMENT R2 Arm.

Interstitial Lung Disease (Interstitial Pneumonitis)

In the Safety Population, TEAEs in the AESI category of interstitial lung disease (ILD) were reported for no subjects in the R2 Arm and 1 subject (0.6%) in the Control Arm. In the MAGNIFY study, 1 subject (0.5%) had an ILD event during the initial treatment period.

Serious adverse event/deaths/other significant events

Deaths

Deaths in the Safety Population are summarized by primary cause of death.

Table 78 *Summary of Cause of Death in the Safety Population*

Primary Cause	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 180) n (%)	Len + Rit (N = 176) n (%)	Len + Rit (N = 222) n (%)	Len + Rit (N = 398) n (%)
Overall Number of Deaths	**26 (14.4)**	**15 (8.5)**	**21 (9.5)**	**36 (9.0)**
Death from adverse event	1 (0.6)	3 (1.7)	4 (1.8)	7 (1.8)
Death from malignant disease under study, or complication due to malignant disease under study	18 (10.0)	5 (2.8)	12 (5.4)	17 (4.3)
Death from other cause	4 (2.2)	6 (3.4)	3 (1.4)	9 (2.3)
Death from other primary malignancy, or complication due to other primary malignancy	2 (1.1)	0 (0.0)	1 (0.5)	1 (0.3)
Death from unknown cause (not assessable or insufficient data)	1 (0.6)	1 (0.6)	1 (0.5)	2 (0.5)
Death on Treatment[a]	**2 (1.1)**	**2 (1.1)**	**8 (3.6)**	**10 (2.5)**
Death from adverse event	1 (0.6)	1 (0.6)	4 (1.8)	5 (1.3)
Death from malignant disease under study, or complication due to malignant disease under study	1 (0.6)	0 (0.0)	3 (1.4)	3 (0.8)
Death from other cause	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)
Death from other primary malignancy, or complication due to other primary malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death from unknown cause (not assessable or insufficient data)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)
Death During Post-Treatment[b]	**24 (13.3)**	**13 (7.4)**	**13 (5.9)**	**26 (6.5)**
Death from adverse event	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)
Death from malignant disease under study, or complication due to malignant disease under study	17 (9.4)	5 (2.8)	9 (4.1)	14 (3.5)
Death from other cause	4 (2.2)	5 (2.8)	3 (1.4)	8 (2.0)
Death from other primary malignancy, or complication due to other primary malignancy	2 (1.1)	0 (0.0)	1 (0.5)	1 (0.3)
Death from unknown cause (not assessable or insufficient data)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.3)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; PBO = placebo; Rit = rituximab.
[a] Deaths within 28 days from the last dose of study medication(s).
[b] Deaths occurring after 28 days from the last dose date of study medication(s).
Source: SCS Table 1.6.1

Of note, Of the 5 subjects who died from TEAEs while on treatment in the pooled R2-treated subjects from AUGMENT and MAGNIFY, the causes of death were arrhythmia, sepsis, multiple organ system failure, cardiorespiratory arrest, and acute kidney injury secondary to lymphoma.

Table 79 Summary of Cause of Death in the FL Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
Primary Cause	**PBO + Rit (N=148)**	**Len + Rit (N=146)**	**Len + Rit (N=177)**	**Len + Rit (N=323)**
Overall Number of Deaths	**24 (16.2)**	**11 (7.5)**	**17 (9.6)**	**28 (8.7)**
Death from adverse event	0 (0.0)	3 (2.1)	3 (1.7)	6 (1.9)
Death from malignant disease under study, or complication due to malignant disease under study	18 (12.2)	4 (2.7)	11 (6.2)	15 (4.6)
Death from other cause	4 (2.7)	4 (2.7)	2 (1.1)	6 (1.9)
Death from other primary malignancy, or complication due to other primary malignancy	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Death from unknown cause (not assessable or insufficient data)	1 (0.7)	0 (0.0)	1 (0.6)	1 (0.3)
Death On Treatment[a]	**1 (0.7)**	**1 (0.7)**	**6 (3.4)**	**7 (2.2)**
Death from adverse event	0 (0.0)	1 (0.7)	3 (1.7)	4 (1.2)
Death from malignant disease under study, or complication due to malignant disease under study	1 (0.7)	0 (0.0)	2 (1.1)	2 (0.6)
Death from other cause	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death from other primary malignancy, or complication due to other primary malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death from unknown cause (not assessable or insufficient data)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Post Treatment[b]	**23 (15.5)**	**10 (6.8)**	**11 (6.2)**	**21 (6.5)**
Death from adverse event	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.6)
Death from malignant disease under study, or complication due to malignant disease under study	17 (11.5)	4 (2.7)	9 (5.1)	13 (4.0)
Death from other cause	4 (2.7)	4 (2.7)	2 (1.1)	6 (1.9)
Death from other primary malignancy, or complication due to other primary malignancy	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Death from unknown cause (not assessable or insufficient data)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; PBO = placebo; Rit = rituximab.

[a] Deaths within 28 days from the last dose of study medication(s).

[b] Deaths occurring after 28 days from the last dose date of study medication(s).

Deaths in the MZL Safety Population are summarized by primary cause of death in the following table:

Table 80 Summary of Cause of Death in the MZL Safety Population

Primary Cause	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Overall Number of Deaths	**2 (6.3)**	**4 (13.3)**	**4 (8.9)**	**8 (10.7)**
Death from AE	1 (3.1)	0 (0.0)	1 (2.2)	1 (1.3)
Death from malignant disease under study, or complication due to malignant disease under study	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Death from other cause	0 (0.0)	2 (6.7)	1 (2.2)	3 (4.0)
Death from other primary malignancy, or complication due to other primary malignancy	1 (3.1)	0 (0.0)	1 (2.2)	1 (1.3)
Death from unknown cause (not assessable or insufficient data)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Death on Treatment[a]	**1 (3.1)**	**1 (3.3)**	**2 (4.4)**	**3 (4.0)**
Death from AE	1 (3.1)	0 (0.0)	1 (2.2)	1 (1.3)
Death from malignant disease under study, or complication due to malignant disease under study	0 (0.0)	0 (0.0)	1 (2.2)	1 (1.3)
Death from other cause	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Death from other primary malignancy, or complication due to other primary malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death from unknown cause (not assessable or insufficient data)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death During Post-Treatment[b]	**1 (3.1)**	**3 (10.0)**	**2 (4.4)**	**5 (6.7)**
Death from AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death from malignant disease under study, or complication due to malignant disease under study	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)
Death from other cause	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Death from other primary malignancy, or complication due to other primary malignancy	1 (3.1)	0 (0.0)	1 (2.2)	1 (1.3)
Death from unknown cause (not assessable or insufficient data)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.3)

AE = adverse event; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab.

[a] Deaths within 28 days from the last dose of study medication(s).

Other Serious Adverse Events

Table 81 *Treatment-emergent Serious Adverse Events Reported in at Least 2% of Subjects in any Treatment Arm —Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
System Organ Class Preferred Term	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Subjects with at least one treatment-emergent SAE	**25 (13.9)**	**45 (25.6)**	**65 (29.3)**	**110 (27.6)**
Infections and infestations	**10 (5.6)**	**17 (9.7)**	**24 (10.8)**	**41 (10.3)**
Pneumonia	5 (2.8)	5 (2.8)	4 (1.8)	9 (2.3)
Blood and lymphatic system disorders	**0 (0.0)**	**9 (5.1)**	**15 (6.8)**	**24 (6.0)**
Febrile neutropenia	0 (0.0)	5 (2.8)	7 (3.2)	12 (3.0)
Neutropenia	0 (0.0)	3 (1.7)	5 (2.3)	8 (2.0)
Respiratory, thoracic and mediastinal disorders	**5 (2.8)**	**10 (5.7)**	**8 (3.6)**	**18 (4.5)**
Pulmonary embolism	1 (0.6)	4 (2.3)	1 (0.5)	5 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.7)**	**3 (1.7)**	**13 (5.9)**	**16 (4.0)**
Basal cell carcinoma	1 (0.6)	0 (0.0)	5 (2.3)	5 (1.3)
Renal and urinary disorders	**1 (0.6)**	**2 (1.1)**	**9 (4.1)**	**11 (2.8)**
Acute kidney injury	0 (0.0)	2 (1.1)	7 (3.2)	9 (2.3)
Metabolism and nutrition disorders	**1 (0.6)**	**0 (0.0)**	**8 (3.6)**	**8 (2.0)**
Dehydration	1 (0.6)	0 (0.0)	5 (2.3)	5 (1.3)
Hypercalcaemia	0 (0.0)	0 (0.0)	5 (2.3)	5 (1.3)

Table 82 *Treatment-emergent Serious Adverse Events Reported in at Least 2% of Subjects in Any Treatment Arm —FL Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
System Organ Class Preferred Term	PBO + Rit (N=148)	Len + Rit (N=146)	Len + Rit (N=177)	Len + Rit (N=323)
Subjects with at least one treatment-emergent SAE	**19 (12.8)**	**34 (23.3)**	**50 (28.2)**	**84 (26.0)**
Infections and infestations	**5 (3.4)**	**14 (9.6)**	**20 (11.3)**	**34 (10.5)**
Pneumonia	1 (0.7)	4 (2.7)	4 (2.3)	8 (2.5)
Sepsis	1 (0.7)	3 (2.1)	3 (1.7)	6 (1.9)
Blood and lymphatic system disorders	**0 (0.0)**	**7 (4.8)**	**11 (6.2)**	**18 (5.6)**
Febrile neutropenia	0 (0.0)	4 (2.7)	6 (3.4)	10 (3.1)
Neutropenia	0 (0.0)	2 (1.4)	4 (2.3)	6 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (2.0)**	**3 (2.1)**	**11 (6.2)**	**14 (4.3)**
Squamous cell carcinoma of skin	0 (0.0)	2 (1.4)	4 (2.3)	6 (1.9)
Basal cell carcinoma	1 (0.7)	0 (0.0)	5 (2.8)	5 (1.5)
Respiratory, thoracic and mediastinal disorders	**3 (2.0)**	**8 (5.5)**	**6 (3.4)**	**14 (4.3)**
Pulmonary embolism	1 (0.7)	4 (2.7)	0 (0.0)	4 (1.2)
Renal and urinary disorders	**1 (0.7)**	**2 (1.4)**	**8 (4.5)**	**10 (3.1)**
Acute kidney injury	0 (0.0)	2 (1.4)	6 (3.4)	8 (2.5)
Metabolism and nutrition disorders	**1 (0.7)**	**0 (0.0)**	**8 (4.5)**	**8 (2.5)**
Dehydration	1 (0.7)	0 (0.0)	5 (2.8)	5 (1.5)
Hypercalcaemia	0 (0.0)	0 (0.0)	5 (2.8)	5 (1.5)

AE = adverse event; FL = follicular lymphoma; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; SAE = serious adverse event.
Notes: TEAEs include AEs that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column. A subject is counted only once for multiple events within Preferred Term/System Organ Class. Coded using MedDRA version 21.0.

Table 83 *Treatment-emergent Serious Adverse Events Reported in at Least 2 Subjects in Any Treatment Arm—MZL Safety Population (Previously Treated)*

System Organ Class Preferred Term	AUGMENT		MAGNIFY	Pooled AUGMENT + MAGNIFY
	PBO + Rit (N = 32) n (%)	Len + Rit (N = 30) n (%)	Len + Rit (N = 45) n (%)	Len + Rit (N = 75) n (%)
Subjects with at least one treatment-emergent SAE	**6 (18.8)**	**11 (36.7)**	**15 (33.3)**	**26 (34.7)**
Infections and infestations	**5 (15.6)**	**3 (10.0)**	**4 (8.9)**	**7 (9.3)**
Pneumonia	4 (12.5)	1 (3.3)	0 (0.0)	1 (1.3)
Blood and lymphatic system disorders	**0 (0.0)**	**2 (6.7)**	**4 (8.9)**	**6 (8.0)**
Thrombocytopenia	0 (0.0)	0 (0.0)	3 (6.7)	3 (4.0)
Anaemia	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Febrile neutropenia	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Neutropenia	0 (0.0)	1 (3.3)	1 (2.2)	2 (2.7)
Injury, poisoning and procedural complications	**0 (0.0)**	**4 (13.3)**	**0 (0.0)**	**4 (5.3)**
Infusion related reaction	0 (0.0)	2 (6.7)	0 (0.0)	2 (2.7)
Respiratory, thoracic and mediastinal disorders	**2 (6.3)**	**2 (6.7)**	**2 (4.4)**	**4 (5.3)**
Cardiac disorders	**0 (0.0)**	**1 (3.3)**	**2 (4.4)**	**3 (4.0)**
Atrial fibrillation	0 (0.0)	0 (0.0)	2 (4.4)	2 (2.7)
General disorders and administration site conditions	**0 (0.0)**	**2 (6.7)**	**1 (2.2)**	**3 (4.0)**
Pyrexia	0 (0.0)	2 (6.7)	0 (0.0)	2 (2.7)

AE = adverse event; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; MZL = marginal zone lymphoma; PBO = placebo; Rit = rituximab; SAE = serious adverse event.
Notes: TEAEs include AEs that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column. A subject is counted only once for multiple events within Preferred Term/System Organ Class. Coded using MedDRA version 21.0.

Second primary malignancies

Analyses of SPMs were performed by pooling the R2Armsfrom AUGMENT and MAGNIFY studies for a median follow up of 29.83 months for AUGMENT Study and 10.25 months for MAGNIFY study.

Table 84 Patients with second primary malignancies- pooled data for the AUGMENT and MAGNIFY Studies (Safety population)- as of the data cutoff dates of 22.06.2018 (AUGMENT) and 01.05.2017 (MAGNIFY)

SPM Category	AUGMENT Len + Rit (N = 176) n (%)	MAGNIFY Len + Rit (N = 283) n (%)	Pooled AUGMENT and MAGNIFY Len + Rit (N = 459) n (%)	AUGMENT Pbo + Rit (N = 180) n (%)
Hematologic Malignancies	1 (0.6)	2 (0.7)	3 (0.7)	2 (1.1)
AML	1 (0.6)	0 (0.0)	1 (0.2)	2 (1.1)
MDS to AML	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MDS	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
B-cell malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[a]	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Solid Tumors	2 (1.1)	4 (1.4)	6 (1.3)	6 (3.3)
Invasive SPMs	**3 (1.7)**	**6 (2.1)**	**9 (2.0)**	**8 (4.4)**
Non-invasive SPMs (Non-melanoma skin cancers)	3 (1.7)	12 (4.2)	15 (3.3)	3 (1.7)
TOTAL SPMs	**6 (3.4)**	**18 (6.4)**	**24 (5.2)**	**10 (5.6)[b]**

AML = acute myeloid leukemia; FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); SPM = second primary malignancy; tFL = transformed follicular lymphoma.

[a] Other hematologic malignancies included 1 case of large granular lymphocytosis in Len + Rit (R^2 Arm) in the MAGNIFY study.

Table 85Incidence rates for SPM- Pooled data for AUGMENT and MAGNIFY – Safety population

SPM Category	AUGMENT Len + Rit (N = 176) IR/100 PY[a] (95% CI)	MAGNIFY Len + Rit (N = 283) IR/100 PY[a] (95% CI)	Pooled AUGMENT and MAGNIFY Len + Rit (N = 459) IR/100 PY[a] (95% CI)	AUGMENT Pbo + Rit (N = 180) IR/100 PY[a] (95% CI)
Hematologic Malignancies	0.25 (0.03 – 1.75)	0.73 (0.18 – 2.90)	0.44 (0.14 – 1.37)	0.48 (0.12 – 1.93)
Solid Tumors	0.50 (0.12 – 1.98)	1.46 (0.55 – 3.89)	0.88 (0.40 – 1.97)	1.47 (0.66 – 3.27)
Invasive SPMs	**0.74 (0.24 – 2.30)**	**2.19 (0.99 – 4.88)**	**1.33 (0.69 – 2.55)**	**1.97 (0.98 – 3.93)**
Non-invasive SPMs (Non-melanoma skin cancers)	0.75 (0.24 – 2.33)	4.50 (2.56 – 7.92)	2.25 (1.36 – 3.74)	0.73 (0.23 – 2.25)
TOTAL SPMs	**1.50 (0.68 – 3.35)**	**6.82 (4.29 – 10.82)**	**3.62 (2.43 – 5.40)**	**2.47 (1.33 – 2.49)**

CI = confidence interval; FL = follicular lymphoma; IR = incidence rate; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MCL = mantle cell lymphoma; MDS = myelodysplastic syndrome; MZL = marginal zone lymphoma; Pbo + Rit = placebo plus rituximab (Control Arm); PY = person-years; SPM = second primary malignancy; tFL = transformed follicular lymphoma.

[a] Person-years are the time in years from the first dose date to the onset date of the first SPM for subjects with an SPM or the first dose date to the date of the last follow up or death for subjects without an SPM.

Note: For the MAGNIFY study, the SPM safety population is defined as all subjects with FL Grade 1 to 3b, tFL, MZL, and MCL who have received at least 1 dose of initial therapy with either lenalidomide or rituximab.

Data cutoff dates: 22 Jun 2018 for AUGMENT and 01 May 2017 for MAGNIFY.

SPMs in the RELEVANCE STUDY

Table 86: Number and percentage of subjects with SPMs in the RELEVANCE study (safety population)

SPM Category	Len + Rit (N = 507) n (%)	R-CHEMO (N = 503) n (%)	R-CHOP (N = 365) n (%)	R-CVP (N = 26) n (%)	R-Benda (N = 112) n (%)
Hematologic malignancies	4 (0.8)	2 (0.4)	1 (0.3)	0 (0.0)	1 (0.9)
AML	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MDS to AML	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MDS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
B-cell malignancies[a]	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[b]	0 (0.0)	2 (0.4)	1 (0.3)	0 (0.0)	1 (0.9)
Solid tumors	21 (4.1)[c]	26 (5.2)[d,e,f]	19 (5.2)[d,e]	0 (0.0)	7 (6.3)[f]
Invasive SPMs	**25 (4.9)**	**27 (5.4)[f]**	**20 (5.5)**	0 (0.0)	**7 (6.3)[f]**
Non-invasive SPMs (Non-melanoma skin cancer)	13 (2.6)	21 (4.2)	9 (2.5)	3 (11.5)	9 (8.0)
TOTAL SPMs	**38 (7.5)**	**48 (9.5)**	**29 (7.9)**	**3 (11.5)**	**16 (14.3)**

AML = acute myeloid leukemia; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MDS = myelodysplastic syndromes; R-Benda = rituximab plus bendamustine; R-CHEMO = rituximab plus chemotherapy; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab plus cyclophosphamide, vincristine, and prednisone; SPM = second primary malignancy.
[a] B-cell malignancies include 3 cases of Hodgkin's disease and 1 case of acute lymphocytic leukemia in the Len + Rit Arm.
[b] Other hematologic malignancies include 1 case of lymphoproliferative disorder in the R-CHEMO Arm (R-CHOP) and 1 case of chronic myeloid leukemia in the R-CHEMO Arm (R-Benda).

Table 87 Incidence rates of SPMs for the RELEVANCE study (safety population)

SPM Category	Incidence Rate per 100 person-years[a] (95% Confidence Intervals)				
	Len + Rit (N = 507)	R-CHEMO (N = 503)	R-CHOP (N = 365)	R-CVP (N = 26)	R-Benda (N = 112)
Hematologic malignancies	0.25 (0.09 – 0.65)	0.12 (0.03 – 0.50)	0.08 (0.01 – 0.60)	--	0.30 (0.04 – 2.14)
Solid tumors	1.31 (0.86 – 2.02)	1.64 (1.12 – 2.41)	1.63 (1.04 – 2.55)	--	2.16 (1.03 – 4.52)
Invasive SPMs	**1.57 (1.06 –2.32)**	**1.71 (1.17 – 2.49)**	**1.72 (1.11 – 2.66)**	--	**2.16 (1.03 – 4.52)**
Non-invasive SPMs (Non-melanoma skin cancer)	0.81 (0.47 – 1.39)	1.34 (0.87 – 2.05)	0.77 (0.40 – 1.48)	3.49 (1.13 – 10.82)	2.86 (1.49 – 5.49)
TOTAL SPMs	**2.42 (1.76 –3.32)**	**3.13 (2.36 – 4.15)**	**2.54 (1.76 – 3.65)**	**3.49 (1.13 – 10.82)**	**5.22 (3.20 – 8.51)**

Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); R-Benda = rituximab plus bendamustine; R-CHEMO = rituximab plus chemotherapy; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab plus cyclophosphamide, vincristine, and prednisone; SPM = second primary malignancy.
[a] Person-years are defined as the time from the date of first dose of study treatment to the onset date of the first SPM for subjects with SPMs and to the date of last follow-up for subjects without SPMs.
Notes: 1) "--" denotes that incidence rates were not calculated for these SPM categories.
2) R-CHEMO = total of the R-CHOP, R-CVP, and R-Benda combined.
Data cutoff date: 31 May 2017.

The HR of the difference between the R2and R-CHEMO KM cumulative incidence curves for hematologic SPMs is greater than 1.0, suggestive of a trend towards an increased risk of hematologic SPMs for the R2Arm *versus* the R-CHEMO Arm.

Laboratory findings

In AUGMENT study;

For most parameters, the percentages of subjects with post baseline Grade 3 or 4 abnormal values were relatively low (Table 71).

Table 88 *Maximum NCI CTC Grades in Selected Hematology Parameters by Treatment – Safety Population*

Postbaseline[a] Parameter	Worst CTCAE Grade	FL		MZL		Overall	
		Len + Rit (N = 146)	Pbo = Rit (N = 148)	Len + Rit (N = 30)	Pbo = Rit (N = 32)	Len + Rit (N = 176)	Pbo = Rit (N = 180)
Hemoglobin	0	82 (56.2)	104 (70.7)	12 (42.9)	13 (40.6)	94 (54.0)	117 (65.4)
	1	46 (31.5)	36 (24.5)	10 (35.7)	17 (53.1)	56 (32.2)	53 (29.6)
	2	15 (10.3)	6 (4.1)	5 (17.9)	2 (6.3)	20 (11.5)	8 (4.5)
	3	3 (2.1)	0 (0.0)	1 (3.6)	0 (0.0)	4 (2.3)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3-4	3 (2.1)	0 (0.0)	1 (3.6)	0 (0.0)	4 (2.3)	0 (0.0)
Neutrophils	0	17 (11.6)	83 (56.5)	5 (17.9)	14 (43.8)	22 (12.6)	97 (54.2)
	1	24 (16.4)	26 (17.7)	5 (17.9)	8 (25.0)	29 (16.7)	34 (19.0)
	2	37 (25.3)	21 (14.3)	6 (21.4)	5 (15.6)	43 (24.7)	26 (14.5)
	3	43 (29.5)	14 (9.5)	7 (25.0)	3 (9.4)	50 (28.7)	17 (9.5)
	4	24 (16.4)	2 (1.4)	5 (17.9)	2 (6.3)	29 (16.7)	4 (2.2)
	3-4	67 (45.9)	16 (10.9)	12 (42.9)	5 (15.6)	79 (45.4)	21 (11.7)
Lymphocytes	0	67 (45.9)	72 (49.0)	10 (35.7)	15 (46.9)	77 (44.3)	87 (48.6)
	1	2 (1.4)	9 (6.1)	1 (3.6)	0 (0.0)	3 (1.7)	9 (5.0)
	2	60 (41.1)	44 (29.9)	7 (25.0)	11 (34.4)	67 (38.5)	55 (30.7)
	3	17 (11.6)	20 (13.6)	10 (35.7)	6 (18.8)	27 (15.5)	26 (14.5)
	4	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
	3-4	17 (11.6)	21 (14.3)	10 (35.7)	6 (18.8)	27 (15.5)	27 (15.1)
Platelets	0	70 (47.9)	111 (75.5)	14 (50.0)	24 (75.0)	84 (48.3)	135 (75.4)
	1	60 (41.1)	31 (21.1)	11 (39.3)	4 (12.5)	71 (40.8)	35 (19.6)
	2	14 (9.6)	3 (2.0)	1 (3.6)	2 (6.3)	15 (8.6)	5 (2.8)
	3	2 (1.4)	1 (0.7)	2 (7.1)	1 (3.1)	4 (2.3)	2 (1.1)
	4	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.6)
	3-4	2 (1.4)	1 (0.7)	2 (7.1)	2 (6.3)	4 (2.3)	3 (1.7)

FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03); Pbo + Rit = placebo plus rituximab (Control Arm).

The denominator for a period is the number of subjects who are still under the treatment exposure in that period. The treatment exposure is defined as the duration from the first dose of study drug through the earlier of the last dose of study drug plus 28 days and the death date. The denominator for Cycles 1-2 is the number of all treated subjects.

[a] Baseline value is the latest central lab value by the first dose date. If there is no central lab value available, local lab value will be used. Worst postbaseline value is the worst central lab value throughout the study after first dose date.

Data cutoff: 22 Jun 2018.

Selected serum chemistry parameters with a worst post-baseline Grade of 3 or 4 are shown in the following table:

Table 89 *Maximum NCI CTC Grades in Selected Chemistry Parameters by Treatment – Safety Population*

Postbaseline[a] Parameter	Worst CTCAE Grade	FL		MZL		Overall (Safety)	
		Len + Rit (N = 146)	Pbo = Rit (N = 148)	Len + Rit (N = 30)	Pbo = Rit (N = 32)	Len + Rit (N = 176)	Pbo = Rit (N = 180)
ALT	0	61 (41.8)	101 (68.7)	18 (64.3)	27 (84.4)	79 (45.4)	128 (71.5)
	1	76 (52.1)	43 (29.3)	9 (32.1)	5 (15.6)	85 (48.9)	48 (26.8)
	2	8 (5.5)	1 (0.7)	1 (3.6)	0 (0.0)	9 (5.2)	1 (0.6)
	3	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3-4	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
AST	0	87 (59.6)	112 (76.2)	23 (82.1)	30 (93.8)	110 (63.2)	142 (79.3)
	1	56 (38.4)	33 (22.4)	4 (14.3)	2 (6.3)	60 (34.5)	35 (19.6)
	2	3 (2.1)	1 (0.7)	1 (3.6)	0 (0.0)	4 (2.3)	1 (0.6)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Bilirubin	0	117 (80.1)	129 (87.8)	23 (82.1)	30 (93.8)	140 (80.5)	159 (88.8)
	1	21 (14.4)	14 (9.5)	5 (17.9)	1 (3.1)	26 (14.9)	15 (8.4)
	2	7 (4.8)	3 (2.0)	0 (0.0)	1 (3.1)	7 (4.0)	4 (2.2)
	3	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3-4	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Serum Creatinine	0	120 (82.2)	125 (85.0)	25 (89.3)	24 (75.0)	145 (83.3)	149 (83.2)
	1	16 (11.0)	16 (10.9)	2 (7.1)	5 (15.6)	18 (10.3)	21 (11.7)
	2	8 (5.5)	5 (3.4)	1 (3.6)	3 (9.4)	9 (5.2)	8 (4.5)
	3	2 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3-4	2 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FL = follicular lymphoma; Len + Rit = lenalidomide in combination with rituximab (R^2 Arm); MZL = marginal zone lymphoma; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Pbo + Rit = placebo plus rituximab (Control Arm).
The denominator for a period is the number of subjects who are still under the treatment exposure in that period. The treatment exposure is defined as the duration from the first dose of study drug through the earlier of the last dose of study drug plus 28 days and the death date. The denominator for Cycles 1-2 is the number of all treated subjects.
[a] Baseline value is the latest central lab value by the first dose date. If there is no central lab value available, local lab value will be used. Worst postbaseline value is the worst central lab value throughout the study after first dose date.

Hematology

The majority of parameters at baseline were Grade 1 or 2 in intensity. The percentages of subjects with post-baseline Grade 3/4 values ranged from 4.5% of subjects with Grade 3/4 anemia to 33.3% of subjects with Grade 3/4 neutropenia. Post-baseline, Grade 3/4 leukopenia was reported for 18.5% of subjects, Grade 3/4 thrombocytopenia was reported for 9.0% of subjects, and Grade 3/4 lymphopenia was reported for 24.3% of subjects. The changes observed in post-baseline hematology parameters were consistent with TEAEs of neutropenia, anemia, and thrombocytopenia.

Clinical Chemistry

For most parameters, the percentages of subjects with Grade 3 or 4 values were relatively low. The largest change in baseline grade was in hypokalemia (0% subjects with Grade 3/4 at baseline and 5.0% of subjects post-baseline). Changes from baseline to maximum grade in clinical chemistry parameters were similar between FL subjects and MZL subjects.

Safety in special populations

-Age

All Treatment-emergent Adverse Events by Age

In the Safety Population (pooled analysis), the incidence of R2-treated subjects with at least one TEAE was the same between those < 65 years old and those ≥ 65 years old (98.0%). The following TEAEs

differed in frequency ≥ 10% in subjects < 65 years old and subjects ≥ 65 years old, respectively: anemia (13.1% *versus* 24.1%), thrombocytopenia (12.6% *versus* 23.1%), and asthenia (3.5% *versus* 14.1%). Results were similar in the FL Safety Population.

Grade 3 or 4 Treatment-emergent Adverse Events by Age

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was higher (≥ 5% difference) in subjects ≥ 65 years old than in subjects < 65 years old, (70.9% *versus* 59.3%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between subjects < 65 years old and ≥ 65 years old, respectively: neutropenia (38.2%*versus* 43.2%), fatigue (2.0% *versus* 4.0%), thrombocytopenia (3.0% *versus* 7.5%), pneumonia (1.5% *versus* 3.5%), dehydration (1.0% *versus* 3.5%), sepsis (0.5% *versus* 2.5%), and infusion related reaction (0% *versus* 2.5%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Age

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2- treated subjects was higher (> 5% difference) in subjects ≥ 65 years old than in subjects < 65 years old (37.2% *versus* 18.1%, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between subjects < 65 years old and ≥ 65 years old, respectively: pneumonia and acute kidney injury (1.0% *versus* 3.5%), sepsis (0.5% *versus* 3.0%), squamous cell carcinoma of skin (0.5% *versus* 2.5%), and dyspnea (0% *versus* 2.0%). Results were similar in the FL Safety Population.

-Sex

All Treatment-emergent Adverse Events by Sex

In the Safety Population (pooled analysis), the incidence of TEAEs for R2-treated subjects with at least one TEAE was the same between male and female subjects (98.0%). The only TEAE that differed in frequency by ≥ 10% between male and female subjects, respectively was diarrhea (25.5% *versus* 39.1%).

Grade 3 or 4 Treatment-emergent Adverse Events by Sex

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was higher (≥ 5% difference) in female subjects than in male subjects (67.8% *versus* 62.2%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between male and female subjects, respectively: neutropenia (39.3% *versus* 42.1%), leukopenia (8.2% *versus* 4.5%), thrombocytopenia (7.7% *versus* 3.0%), dyspnea (2.6% *versus* 0.5%), diarrhea (0.5% *versus* 5.4%), hypokalemia (1.0% *versus* 4.0%), and dehydration (1.0% *versus* 3.5%).

Treatment-emergent Serious Adverse Events by Sex

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2-treated subjects was higher (≥ 5% difference) in male subjects than in female subjects (30.6% *versus* 24.8%, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between male and female subjects, respectively: neutropenia (3.1% *versus* 1.0%), squamous cell carcinoma of skin (3.1% *versus* 0%), and dyspnea (2.0% *versus* 0%). Results were similar in the FL Safety Population.

-Race

All Treatment-emergent Adverse Events by Race

In the Safety Population (pooled analysis), the incidence of R2-treated subjects with at least one TEAE was similar (< 10% difference) between those who were White and those of other races (97.8% and 98.5%, respectively). The following TEAEs differed in frequency by ≥ 10% in subjects who were White and subjects of Other races, respectively: neutropenia (43.5% *versus* 67.6%), fatigue (40.4% *versus* 17.6%), nausea (23.6% *versus* 8.8%), cough (22.4% *versus* 10.3%), edema peripheral (17.7% *versus* 5.9%), dyspnea (15.5% *versus* 0%), abdominal pain (14.6% *versus* 4.4%), leukopenia (10.2% *versus*

30.9%), alanine aminotransferase increased (5.0% *versus* 19.1%), white blood cell count decreased (4.7% *versus* 23.5%), and lymphocyte count decreased (3.7% *versus* 16.2%). Results were similar in the FL Safety Population.

Grade 3 or 4 Treatment-emergent Adverse Events by Race

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was similar (< 5% difference) in subjects who were White than in subjects of other races (64.6% and 67.6%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between subjects who were White and subjects of Other races, respectively: neutropenia (37.0% *versus* 58.8%), leukopenia (5.0% *versus* 11.8%), white blood cell count decreased (2.5% *versus* 5.9%), lymphopenia (2.2% *versus* 5.9%), lung infection (0.6% *versus* 2.9%), lymphocyte count decreased (2.2% *versus* 5.9%), anemia (5.3% *versus* 0%), thrombocytopenia (5.9% *versus* 2.9%), and diarrhea and fatigue (each 3.7% *versus* 0%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Race

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2- treated subjects was higher (≥ 5% difference) in subjects who were White than in subject of Other races (29.2% *versus* 20.6%, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between White subjects and subjects of other races, respectively: pneumonia (2.8% *versus* 0%) and sepsis (2.2% *versus* 0%). Results were similar in the FL Safety Population.

-Ann Arbor Stage at Enrollment

Analyses by Ann Arbor Stage at enrollment (Stage I or II: n = 63; and Stage III or IV: n = 335).

All Treatment-emergent Adverse Events by Ann Arbor Stage at Enrollment

In the Safety Population (pooled analysis), the incidence of R2-treated subjects with at least one TEAE was similar (< 10% difference) between the Ann Arbor Stage I or II group and the Ann Arbor Stage III or IV group (100% *versus* 97.6%, respectively). The following TEAEs differed in frequency by ≥ 10% between the Ann Arbor Stage I or II group and the Ann Arbor Stage III or IV group, respectively: fatigue (27.0% *versus* 38.8%), anemia (7.9% *versus* 20.6%), asthenia (17.5% *versus* 7.2%), and cough (28.6% *versus* 18.5%). Results were similar in the FL Safety Population.

Grade 3 or 4 Treatment-emergent Adverse Events by Ann Arbor Stage at Enrollment

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was similar (< 5% difference) in the Ann Arbor Stage I or II group than the Ann Arbor Stage III or IV group (68.3% and 64.5%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between the Ann Arbor Stage I or II group and the Ann Arbor Stage III or IV group, respectively: neutropenia (36.5% versus 41.5%); lymphocyte count decreased (7.9% versus 1.8%); leukopenia (1.6% versus 7.2%); thrombocytopenia (0% versus 6.3%); anemia (1.6% versus 5.1%); diarrhea (4.8% versus 2.7%); dehydration (4.8% versus 1.8%); febrile neutropenia (0% versus 3.6%); sepsis, dyspnea, and pulmonary embolism (3.2% versus 1.2%); syncope (3.2% versus 0.9%); rash maculo-papular (3.2% versus 0.3%); respiratory failure and supraventricular tachycardia (3.2% versus 0%); hypokalemia (0% versus 3.0%); and acute kidney injury (0% versus 2.4%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Ann Arbor Stage at Enrollment

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2- treated subjects was similar (< 5% difference) in the Ann Arbor Stage I and II group than the Ann Arbor Stage III or IV group (25.4% and 28.1%, respectively). The following treatment emergent SAEs differed in frequency by ≥ 2% between subjects in the Ann Arbor Stage I or II group and the Ann Arbor Stage III or IV group, respectively: pulmonary embolism (3.2% *versus* 0.9%), febrile neutropenia (0% *versus* 3.6%), respiratory failure and supraventricular tachycardia (3.2% *versus* 0%), and acute kidney injury (0% *versus* 2.7%). Results were similar in the FL Safety Population.

-Baseline Creatinine Clearance

Analyses by baseline creatinine clearance (30 to < 60 mL/min: n = 72; and ≥ 60 mL/min: n = 326) for R2-treated subjects.

All Treatment-emergent Adverse Events by Baseline Creatinine Clearance

In the Safety Population (pooled analysis), the incidence of R2-treated subjects with at least one TEAE was similar (< 10% difference) between those with a baseline creatinine clearance < 60 mL/min and those with one ≥ 60 mL/min (98.6% *versus* 97.9 %, respectively). The following TEAEs differed in frequency by ≥ 10% in subjects with a baseline creatinine clearance < 60 mL/min and ≥ 60 mL/min, respectively: anemia (27.8% *versus* 16.6%), decreased appetite (23.6% *versus* 11.3%), dyspnea (22.2% *versus* 10.7%), and urinary tract infection (16.7% *versus* 5.5%). Results were similar in the FL Safety Population.

Grade 3 or 4 Treatment-emergent Adverse Events by Baseline Creatinine Clearance

In the Safety Population, (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was higher (≥ 5% difference) in subjects with a baseline creatinine clearance < 60 mL/min than in subjects with a baseline creatinine clearance ≥ 60 mL/min (73.6% *versus* 63.2%, respectively). Grade 3 or 4 TEAEs were similar by baseline CrCl in AUGMENT (70.8% *versus* 68.4%, < 60 mL/min *versus* ≥ 60 mL/min respectively), but a difference was observed in MAGNIFY (75.0% *versus* 58.6%, < 60 mL/min *versus* ≥ 60 mL/min, respectively). In the pooled analysis, the following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between subjects with a baseline creatinine clearance < 60 mL/min and ≥ 60 mL/min, respectively: neutropenia (43.1% *versus* 40.2%); fatigue and diarrhea (5.6% *versus* 2.5%); pneumonia (5.6% *versus* 1.8%); dehydration (4.2% *versus* 1.8%); acute kidney injury (4.2% *versus* 1.5%);constipation (4.2% *versus* 0%); urinary tract infection, chronic obstructive pulmonary disease, and atrial fibrillation (2.8% *versus* 0.6%); chronic kidney disease and decreased appetite (2.8% *versus* 0.3%); and rash generalized and muscular weakness (2.8% *versus* 0%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Baseline Creatinine Clearance

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2-treated subjects was higher (≥ 5% difference) in subjects with a baseline creatinine clearance < 60 mL/min than in subjects with a baseline creatinine clearance ≥ 60 mL/min (43.1% versus 24.2%, respectively). Treatment-emergent SAEs for R2-treated subjects were similar by baseline CrCl in AUGMENT (29.2% versus 25.0%, < 60 mL/min versus ≥ 60 mL/min respectively), but a difference was observed in MAGNIFY (50.0% versus 23.6%, < 60 mL/min versus ≥60 mL/min, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between subjects with a baseline creatinine clearance < 60 mL/min and ≥ 60 mL/min, respectively: acute kidney injury (6.9% versus 1.2%); pneumonia (5.6% versus 1.5%); sepsis (4.2% versus 1.2%); basal cell carcinoma (4.2% versus 0.6%); dyspnea (4.2% versus 0.3%); thrombocytopenia and atrial fibrillation (each 2.8% versus 0.6%); urinary tract infection, diarrhea, and chronic obstructive pulmonary disease (each 2.8% versus 0.3%); and asthenia (2.8% versus 0%). Results were similar in the FL Safety Population.

-Number of Prior Anti-lymphoma Regimens

All Treatment-emergent Adverse Events by Number of Prior Anti-lymphoma Regimens

In the Safety Population (pooled analysis), the incidence of R2-treated subjects with at least one TEAE was similar (< 10% difference) between subjects with 1 line of prior anti-lymphoma regimen and those with > 1 line of prior anti-lymphoma regimen (99.0% *versus* 97%, respectively). There were no TEAEs for R2-treated subjects that differed by ≥ 10% between the 1-line or > 1-line prior anti-lymphoma regimen groups in the Safety Population and in the FL Safety Population.

Grade 3 or 4 Treatment-emergent Adverse Events by Number of Prior Antilymphoma Regimens

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treatedsubjects was higher (≥ 5% difference) in subjects with > 1 line of prior anti-lymphoma regimens than those with 1 line of prior anti-lymphoma regimen (68.8% *versus* 61.2%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between the 1-line or > 1-line prior anti-lymphoma regimen groups, respectively: neutropenia (35.2% *versus* 46.0%), leukopenia (3.6% *versus* 8.9%), pneumonia (1.5% *versus* 3.5%), diarrhea (1.0% *versus* 5.0%), dehydration (1.0% *versus* 3.5%), acute kidney injury (0.5% *versus* 3.5%), febrile neutropenia (2.0% *versus* 4.0%), and hypertension (2.0% *versus* 0%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Number of Prior Antilymphoma Regimens

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2- treated subjects was similar (≥ 5% difference) in subjects with 1 line or > 1 line of prior anti-lymphoma regimens (27.6% *versus* 27.7%, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between the 1-line or > 1-line prior anti-lymphoma regimen groups, respectively: febrile neutropenia (2.0% *versus* 4.0%), acute kidney injury (0.5% *versus* 4.0%) and thrombocytopenia (2.0% *versus* 0.0%). Results were similar in the FL Safety Population.

-Region

AUGMENT was conducted at study sites in the US, the EU, and Other regions; MAGNIFY in the US.

All Treatment-emergent Adverse Events by Region

In the Safety Population (pooled analysis), the incidence of TEAEs for R2-treated subjects was similar (< 10% difference) between subjects in the US, EU, and Other regions (97.5%, 97.5%, and 100%, respectively). The following TEAEs differed in frequency by ≥ 10% between the US, EU, or Other regions: neutropenia (39.3%, 48.8%, 73.0%), fatigue (50.8%, 20.0%, 9.5%), leukopenia (9.0%, 12.5%, 31.1%), nausea (28.7%, 12.5%, 5.4%), thrombocytopenia (19.3%,5.0%, 27.0%), pyrexia (11.5%, 25.0%, and 13.5%), infusion related reaction (13.1%, 7.5%, 24.3%), asthenia (5.3%, 22.5%, 5.4%), anemia (21.7%, 11.3%, 16.2%), white blood cell count.

Grade 3 or 4 Treatment-emergent Adverse Events by Region

In the Safety Population (pooled analysis), the incidence of Grade 3 or 4 TEAEs for R2-treated subjects was higher (≥ 5% difference) in the Other regions than in the US and EU, (70.3% *versus* 63.9% and 63.8%, respectively). The following Grade 3 or 4 TEAEs differed in frequency by ≥ 2% between the US, EU, or Other regions, respectively: neutropenia (33.2%, 45.0%, 60.8%), leukopenia (5.7%, 5.0%, 9.5%), thrombocytopenia (7.4%, 2.5%, 1.4%), white blood cell count decreased (3.3%, 0%, 5.4%), lymphopenia (2.9%, 0%, 5.4%), lymphocyte count decreased(3.3%, 0%, 4.1%), fatigue (4.1%, 1.3%, 1.4%), pneumonia (2.9%, 0%, 4.1%), hypokalemia(3.3%, 0%, 2.7%), dehydration (3.3%, 0%, 1.4%), rash (0.4%, 0%, 2.7%), infusion related reaction (0.4%, 2.5%, 2.7%), syncope (1.2%, 0%, 2.7%), lung infection (0.8%, 0%, 2.7%), general physical health deterioration (0%, 0%, 2.7%), hypertension and chronic obstructive pulmonary disease (0.8%, 2.5%, 0%), asthenia (1.2%, 2.5%, 0%), dyspnea (2.5%, 0%, 0%), rash generalized and upper respiratory tract infection (0%, 2.5%, 0%), sepsis (2.0%, 1.3%, 0%), and hypercalcemia and neck pain (2.0%, 0%, 0%). Results were similar in the FL Safety Population.

Treatment-emergent Serious Adverse Events by Region

In the Safety Population (pooled analysis), the incidence of treatment-emergent SAEs for R2-treated subjects was higher (≥ 5% difference) in the US than in the EU or Other regions (31.1% *versus* 21.3% and 23.0%, respectively). The following treatment-emergent SAEs differed in frequency by ≥ 2% between the US, EU, or Other regions, respectively: pneumonia (2.9%, 0%, 2.7%); general physical health deterioration (0%, 0%, 2.7%); sepsis (2.5%, 1.3%, 0%); anemia and squamous cell carcinoma of skin (2.0%, 1.3%, 0%); and basal cell carcinoma, dehydration, and hypercalcemia (2.0%, 0%, 0%). Results were similar in the FL Safety Population.

Safety in special populations

Sex and race have no influence on the safety profile.

Safety related to drug-drug interactions and other interactions

No new data available.

Discontinuation due to adverse events

Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug

Treatment-emergent AEs leading to discontinuation of any study drug in the Safety Population are summarized in the following table:

Table 90 *Treatment-emergent AEs leading to discontinuation of any study drug in the Safety Population*

Table 1.5.9.8.1
Treatment-emergent Adverse Events Leading to Discontinuation of any study medication by Treatment, System Organ Class and Preferred Term
Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY	RELEVANCE		Pooled ALL 3 STUDIES
System Organ Class Preferred Term [a]	PBO+Rit (N=180)	Len+Rit (N=176)	Len+Rit (N=222)	Len+Rit (N=398)	Len+Rit (N=507)	R-Chemo (N=503)	Len+Rit (N=905)
Subjects With at Least One TEAE Leading to Dose Discontinuation	10 (5.6)	18 (10.2)	40 (18.0)	58 (14.6)	58 (11.4)	16 (3.2)	116 (12.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1.1)	6 (3.4)	15 (6.8)	21 (5.3)	5 (1.0)	2 (0.4)	26 (2.9)
NEUTROPENIA	1 (0.6)	5 (2.8)	14 (6.3)	19 (4.8)	5 (1.0)	1 (0.2)	24 (2.7)
THROMBOCYTOPENIA	1 (0.6)	1 (0.6)	2 (0.9)	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.3)
LEUKOPENIA	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
FEBRILE NEUTROPENIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
LYMPHADENOPATHY	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	1 (0.6)	1 (0.6)	6 (2.7)	7 (1.8)	6 (1.2)	1 (0.2)	13 (1.4)
PNEUMONIA	1 (0.6)	1 (0.6)	2 (0.9)	3 (0.8)	1 (0.2)	0 (0.0)	4 (0.4)
SEPSIS	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)	1 (0.2)	0 (0.0)	3 (0.3)
PSEUDOMONAS INFECTION	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
VARICELLA ZOSTER VIRUS INFECTION	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
ESCHERICHIA SEPSIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
FUSOBACTERIUM INFECTION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
HEPATITIS E	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
NAIL INFECTION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
PERITONITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
SEPTIC SHOCK	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	3 (1.7)	3 (1.4)	6 (1.5)	4 (0.8)	1 (0.2)	10 (1.1)
PULMONARY EMBOLISM	0 (0.0)	1 (0.6)	1 (0.5)	2 (0.5)	1 (0.2)	0 (0.0)	3 (0.3)

Table 1.5.9.8.1
Treatment-emergent Adverse Events Leading to Discontinuation of any study medication by Treatment, System Organ Class and Preferred Term
Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY	RELEVANCE		Pooled ALL 3 STUDIES
System Organ Class Preferred Term [a]	PBO+Rit (N=180)	Len+Rit (N=176)	Len+Rit (N=222)	Len+Rit (N=398)	Len+Rit (N=507)	R-Chemo (N=503)	Len+Rit (N=905)
DIARRHOEA	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)	1 (0.2)	0 (0.0)	3 (0.3)
GASTROINTESTINAL HAEMORRHAGE	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
VOLVULUS	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
ABDOMINAL PAIN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
ABDOMINAL PAIN UPPER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
CONSTIPATION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
SMALL INTESTINAL OBSTRUCTION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	4 (1.8)	4 (1.0)	5 (1.0)	1 (0.2)	9 (1.0)
ASTHENIA	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
FATIGUE	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
GENERALISED OEDEMA	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
MULTIPLE ORGAN DYSFUNCTION SYNDROME	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
CARDIAC DEATH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
DRUG INTOLERANCE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
GENERAL PHYSICAL HEALTH DETERIORATION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
OEDEMA PERIPHERAL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
IMMUNE SYSTEM DISORDERS	1 (0.6)	1 (0.6)	2 (0.9)	3 (0.8)	3 (0.6)	0 (0.0)	6 (0.7)
ANAPHYLACTIC SHOCK	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
DRUG HYPERSENSITIVITY	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
HYPERSENSITIVITY	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
ANAPHYLACTIC REACTION	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1.5.9.8.1
Treatment-emergent Adverse Events Leading to Discontinuation of any study medication by Treatment, System Organ Class and Preferred Term
Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY	RELEVANCE		Pooled ALL 3 STUDIES
System Organ Class Preferred Term [a]	PBO+Rit (N=180)	Len+Rit (N=176)	Len+Rit (N=222)	Len+Rit (N=398)	Len+Rit (N=507)	R-Chemo (N=503)	Len+Rit (N=905)
ACUTE LUNG INJURY	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
ACUTE RESPIRATORY FAILURE	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
DYSPNOEA	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
PLEURAL EFFUSION	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	1 (0.1)
BRONCHOSPASM	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.6)	2 (1.1)	4 (1.8)	6 (1.5)	11 (2.2)	0 (0.0)	17 (1.9)
ANGIOEDEMA	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
PRURITUS GENERALISED	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
RASH MACULO-PAPULAR	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.2)
RASH PRURITIC	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
SKIN EXFOLIATION	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
HYPERSENSITIVITY VASCULITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
PETECHIAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
PRURITUS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
PSORIASIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
RASH	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)
RASH PAPULAR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
SKIN TOXICITY	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
STEVENS-JOHNSON SYNDROME	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
VASCULAR PURPURA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
GASTROINTESTINAL DISORDERS	0 (0.0)	1 (0.6)	3 (1.4)	4 (1.0)	4 (0.8)	1 (0.2)	8 (0.9)

Treatment-emergent AEs leading to discontinuation of lenalidomide/placebo reported in at least 1% of subjects and at least 2 subjects in the Safety Population are summarized in the following table:

Table 91 *Treatment-emergent Adverse Events Leading to Discontinuation of Lenalidomide/Placebo Reported in at Least 1% of Subjects and at Least 2 Subjects - Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
System Organ Class Preferred Term	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Subjects With At Least One TEAE Leading to Dose Discontinuation of Lenalidomide/Placebo	**9 (5.0)**	**15 (8.5)**	**40 (18.0)**	**55 (13.8)**
Blood and Lymphatic System Disorders	**2 (1.1)**	**6 (3.4)**	**15 (6.8)**	**21 (5.3)**
Neutropenia	1 (0.6)	5 (2.8)	14 (6.3)	19 (4.8)

AE = adverse event; Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
Notes: TEAEs include AEs that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the Pooled AUGMENT + MAGNIFY column. A subject is counted only once for multiple events within System Organ Class/Preferred Term. Coded using MedDRA version 21.0.

AUGMENT

The only TEAE reported in at least 1% of subjects and at least 2 subjects was neutropenia (2.8% in the R2 Arm (all of which were from the FL Safety Population) and 0.6% in the Control Arm (all of which were from the MZL Safety Population).

MAGNIFY

The only TEAE reported in at least 1% of subjects and at least 2 subjects was neutropenia (6.3%), which is comparable to what was reported in the FL Safety Population (5.6%) and lower than the MZL Safety Population (8.9%). In the FL Safety Population, pneumonia was additionally reported as a TEAE leading to discontinuation of lenalidomide (1.1%).

Pooled AUGMENT and MAGNIFY Len + Rit Treatment Arms

In the pooled R2 Arms, the only TEAE reported in at least 1% of subjects and at least 2 subjects leading to discontinuation of lenalidomide/placebo was neutropenia (4.8%). In the pooled R2 Arms in the MZL Safety Population, thrombocytopenia was additionally reported as a TEAE leading to discontinuation in 2 subjects, 1 in MAGNIFY and 1 in AUGMENT.

Treatment-emergent Adverse Events Leading to Dose Reduction of Study Drug

Treatment-emergent AEs leading to dose reduction were collected for lenalidomide and placebo in AUGMENT and for lenalidomide in MAGNIFY (ie, dose reductions of rituximab were not allowed in these 2 study protocols).

Treatment-emergent Adverse Events Leading to Dose Reduction Reported in at Least 1% of Subjects and at Least 2 Subjects -- Safety Population

Table 92 *Treatment-emergent Adverse Events Leading to Dose Reduction Reported in at Least 1% of Subjects and at Least 2 Subjects -- Safety Population*

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
System Organ Class Preferred Term	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Subjects with at least one TEAE leading to dose reduction	**6 (3.3)**	**46 (26.1)**	**96 (43.2)**	**142 (35.7)**
Blood and lymphatic system disorders	**6 (3.3)**	**35 (19.9)**	**58 (26.1)**	**93 (23.4)**
Neutropenia	4 (2.2)	32 (18.2)	48 (21.6)	80 (20.1)
Thrombocytopenia	1 (0.6)	3 (1.7)	10 (4.5)	13 (3.3)
Anaemia	0 (0.0)	0 (0.0)	4 (1.8)	4 (1.0)
Leukopenia	0 (0.0)	2 (1.1)	1 (0.5)	3 (0.8)
	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY
System Organ Class Preferred Term	PBO + Rit (N=180)	Len + Rit (N=176)	Len + Rit (N=222)	Len + Rit (N=398)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**4 (2.3)**	**12 (5.4)**	**16 (4.0)**
Rash maculo-papular	0 (0.0)	1 (0.6)	4 (1.8)	5 (1.3)
Rash pruritic	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.8)
Investigations	**0 (0.0)**	**6 (3.4)**	**5 (2.3)**	**11 (2.8)**
Weight decreased	0 (0.0)	3 (1.7)	0 (0.0)	3 (0.8)
General disorders and administration site conditions	**0 (0.0)**	**2 (1.1)**	**8 (3.6)**	**10 (2.5)**
Fatigue	0 (0.0)	1 (0.6)	7 (3.2)	8 (2.0)
Gastrointestinal Disorders	**0 (0.0)**	**2 (1.1)**	**6 (2.7)**	**8 (2.0)**
Diarrhoea	0 (0.0)	1 (0.6)	3 (1.4)	4 (1.0)

Len = lenalidomide; Len + Rit = lenalidomide in combination with rituximab; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; Rit = rituximab; TEAE = treatment-emergent adverse event.
[a] All TEAES leading to dose reduction refer to lenalidomide/placebo, as dose reductions of rituximab were not allowed in the 2 studies per protocol.
Notes: TEAEs include adverse events that started between the date of first dose and 28 days after the date of last dose. The table is presented in descending order of frequency for System Organ Class and Preferred Term in the pooled AUGMENT + MAGNIFY column. A subject is counted only once for multiple events within System Organ Class/Preferred Term. Coded using MedDRA version 21.0.
Source: SCS Table 1.5.9.2.1

AUGMENT

The most frequently reported TEAE in at least 1% of subjects and at least 2 subjects was neutropenia (18.2% in the R2 Arm and 2.2% in the Control Arm), which was consistent with that seen in the FL and MZL Safety Populations. The incidence of thrombocytopenia in the R2 Arm was higher in the MZL Safety Population (6.7%) than in the overall Safety Population (1.7%) and the FL Safety Population (0.7%)

MAGNIFY

The most frequently reported TEAE in at least 1% of subjects and at least 2 subjects was neutropenia (21.6%), which was consistent with frequencies reported in the FL and MZL Safety Populations.

The incidence of thrombocytopenia was higher in the MZL Safety Population (8.9%) than in the overall Safety Population (4.5%) and the FL Safety Population (3.4%). Additional TEAEs leading to dose reduction of lenalidomide that were reported in at least 1% of subjects and at least 2 subjects included febrile neutropenia, pruritis, anemia, maculopapular rash, fatigue, hypersensitivity, pruritic rash, diarrhea, and nausea (1.1%) in the FL Safety Population, and neuropathy peripheral (4.4%) in the MZL Safety Population.

Pooled AUGMENT and MAGNIFY Len + Rit Treatment Arms

In the pooled R2 Arms, the most frequently reported TEAE in at least 1% of subjects and at least 2 subjects leading to dose reduction of lenalidomide was neutropenia (20.1%). Additional TEAEs leading to dose reduction of lenalidomide in at least 1% of subjects and at least 2 subjects that were reported in the pooled R2 Arms in the MZL Safety Population included neuropathy peripheral (2.7%).

Table 93 Treatment-emergent Adverse Events Leading to Dose Interruption of Study Drug

Table 1.5.9.6.1
Treatment-emergent Adverse Events Leading to Dose Interruption of Lenalidomide/Placebo by Treatment, System Organ Class and Preferred Term in greater than 1% and at least 2 subjects
Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY	RELEVANCE		Pooled ALL 3 STUDIES
System Organ Class Preferred Term [a]	PBO+Rit (N=180)	Len+Rit (N=176)	Len+Rit (N=222)	Len+Rit (N=398)	Len+Rit (N=507)	R-Chemo (N=503)	Len+Rit (N=905)
Subjects With at Least One TEAE Leading to Dose Interruption of Lenalidomide/Placebo	47 (26.1)	112 (63.6)	108 (48.6)	220 (55.3)	301 (59.4)	174 (34.6)	521 (57.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18 (10.0)	71 (40.3)	49 (22.1)	120 (30.2)	171 (33.7)	70 (13.9)	291 (32.2)
NEUTROPENIA	18 (10.0)	69 (39.2)	42 (18.9)	111 (27.9)	160 (31.6)	61 (12.1)	271 (29.9)
THROMBOCYTOPENIA	1 (0.6)	8 (4.5)	10 (4.5)	18 (4.5)	7 (1.4)	5 (1.0)	25 (2.8)
LEUKOPENIA	3 (1.7)	11 (6.3)	2 (0.9)	13 (3.3)	5 (1.0)	8 (1.6)	18 (2.0)
ANAEMIA	0 (0.0)	6 (3.4)	4 (1.8)	10 (2.5)	1 (0.2)	2 (0.4)	11 (1.2)
FEBRILE NEUTROPENIA	0 (0.0)	3 (1.7)	4 (1.8)	7 (1.8)	7 (1.4)	5 (1.0)	14 (1.5)
INFECTIONS AND INFESTATIONS	17 (9.4)	29 (16.5)	31 (14.0)	60 (15.1)	78 (15.4)	56 (11.1)	138 (15.2)
PNEUMONIA	3 (1.7)	5 (2.8)	6 (2.7)	11 (2.8)	7 (1.4)	0 (0.0)	18 (2.0)
UPPER RESPIRATORY TRACT INFECTION	5 (2.8)	6 (3.4)	4 (1.8)	10 (2.5)	8 (1.6)	7 (1.4)	18 (2.0)
URINARY TRACT INFECTION	0 (0.0)	3 (1.7)	3 (1.4)	6 (1.5)	4 (0.8)	4 (0.8)	10 (1.1)
INFLUENZA	1 (0.6)	3 (1.7)	2 (0.9)	5 (1.3)	6 (1.2)	0 (0.0)	11 (1.2)
BRONCHITIS	2 (1.1)	1 (0.6)	2 (0.9)	3 (0.8)	12 (2.4)	14 (2.8)	15 (1.7)
LUNG INFECTION	2 (1.1)	1 (0.6)	2 (0.9)	3 (0.8)	7 (1.4)	4 (0.8)	10 (1.1)
SINUSITIS	0 (0.0)	2 (1.1)	1 (0.5)	3 (0.8)	4 (0.8)	1 (0.2)	7 (0.8)
NASOPHARYNGITIS	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.3)	6 (1.2)	6 (1.2)	7 (0.8)
PHARYNGITIS	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)
GASTROINTESTINAL DISORDERS	1 (0.6)	15 (8.5)	16 (7.2)	31 (7.8)	26 (5.1)	9 (1.8)	57 (6.3)
DIARRHOEA	0 (0.0)	6 (3.4)	5 (2.3)	11 (2.8)	10 (2.0)	3 (0.6)	21 (2.3)

Table 1.5.9.6.1
Treatment-emergent Adverse Events Leading to Dose Interruption of Lenalidomide/Placebo by Treatment, System Organ Class and Preferred Term in greater than 1% and at least 2 subjects
Safety Population

	AUGMENT		MAGNIFY	Pooled AUGMENT+ MAGNIFY	RELEVANCE		Pooled ALL 3 STUDIES
System Organ Class Preferred Term [a]	PBO+Rit (N=180)	Len+Rit (N=176)	Len+Rit (N=222)	Len+Rit (N=398)	Len+Rit (N=507)	R-Chemo (N=503)	Len+Rit (N=905)
NAUSEA	0 (0.0)	4 (2.3)	2 (0.9)	6 (1.5)	2 (0.4)	1 (0.2)	8 (0.9)
VOMITING	0 (0.0)	5 (2.8)	1 (0.5)	6 (1.5)	4 (0.8)	1 (0.2)	10 (1.1)
ABDOMINAL PAIN	1 (0.6)	1 (0.6)	3 (1.4)	4 (1.0)	1 (0.2)	1 (0.2)	5 (0.6)
DYSPEPSIA	0 (0.0)	3 (1.7)	1 (0.5)	4 (1.0)	0 (0.0)	0 (0.0)	4 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (3.9)	12 (6.8)	14 (6.3)	26 (6.5)	38 (7.5)	11 (2.2)	64 (7.1)
FATIGUE	2 (1.1)	2 (1.1)	6 (2.7)	8 (2.0)	2 (0.4)	2 (0.4)	10 (1.1)
PYREXIA	3 (1.7)	4 (2.3)	2 (0.9)	6 (1.5)	12 (2.4)	6 (1.2)	18 (2.0)
ASTHENIA	1 (0.6)	1 (0.6)	3 (1.4)	4 (1.0)	4 (0.8)	2 (0.4)	8 (0.9)
MALAISE	0 (0.0)	3 (1.7)	1 (0.5)	4 (1.0)	1 (0.2)	1 (0.2)	5 (0.6)
OEDEMA PERIPHERAL	0 (0.0)	2 (1.1)	2 (0.9)	4 (1.0)	1 (0.2)	1 (0.2)	5 (0.6)
INFLUENZA LIKE ILLNESS	2 (1.1)	2 (1.1)	0 (0.0)	2 (0.5)	5 (1.0)	1 (0.2)	7 (0.8)
INVESTIGATIONS	1 (0.6)	13 (7.4)	10 (4.5)	23 (5.8)	21 (4.1)	10 (2.0)	44 (4.9)
WHITE BLOOD CELL COUNT DECREASED	0 (0.0)	6 (3.4)	3 (1.4)	9 (2.3)	7 (1.4)	5 (1.0)	16 (1.8)
ALANINE AMINOTRANSFERASE INCREASED	1 (0.6)	2 (1.1)	2 (0.9)	4 (1.0)	5 (1.0)	2 (0.4)	9 (1.0)
BLOOD CREATININE INCREASED	0 (0.0)	2 (1.1)	2 (0.9)	4 (1.0)	4 (0.8)	0 (0.0)	8 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (3.3)	15 (8.5)	6 (2.7)	21 (5.3)	21 (4.1)	13 (2.6)	42 (4.6)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0 (0.0)	3 (1.7)	1 (0.5)	4 (1.0)	1 (0.2)	2 (0.4)	5 (0.6)
COUGH	2 (1.1)	1 (0.6)	3 (1.4)	4 (1.0)	3 (0.6)	0 (0.0)	7 (0.8)

Post marketing experience

Not submitted with this application. For post-marketing data regarding lenalidomide, refer to the PSUR for the most recent reporting period (27 Dec 2016 through 26 Dec 2017) submitted on 02 Mar 2018.

2.5.1. Discussion on clinical safety

The safety experience for lenalidomide in combination with rituximab (Len + Rit or R2) is primarily based on data from one registrational Phase 3 study (Study CC-5013-NHL-007, AUGMENT), and one supportive Phase 3b study (Study CC-5013-NHL-008, MAGNIFY). The safety data from the R2 Arm in AUGMENT was pooled with the safety data from the R2 Arm in the Initial Treatment Period of MAGNIFY to increase the safety database in previously treated FL/MZL.

In general, severity conditions criteria are higher in the arm R2 of the pooled results R2 than in the placebo arm: Grade IV Ann arbor stage disease is more frequent in the pooled R2 arm than in the placebo arm. (51.8 *versus* 31.8% respectively), proportion of patients with LDH elevated at baseline (25.6% *versus* 21.7% respectively), with bulky disease (34.9% *versus* 27.2% respectively), unfit for chemotherapy (36.4% *versus* 27.2% respectively).

Common (>10%) Treatment Emergent Adverse Event (TEAE) are reported in the safety population and, in general, are more frequent in the R2 arm than in the placebo group: gastro-intestinal disorders (68.1 *versus* 47.3%), general disorders (58.8 *versus* 46.6%), blood and lymphatic disorders (57.3 *versus* 31.8%), infections and infestations (56.3 *versus* 45.9%), skin and subcutaneous tissue disorders (56 *versus* 22.3%), musculoskeletal and connective tissue disorders (46.1 *versus* 31.8%), respiratory thoracic and mediastinal disorders (44.6 *versus*35.1%), nervous system disorders (38.4 *versus* 23%), metabolism and nutrition disorders (37.5 *versus* 23%), investigations (34.1 *versus* 28.4 %), infusion related reaction (14.2% both), tumour flare (8 *versus* 0.7%) respectively. This is comprehensible.

It follows the same trend for FL and MZL subgroups of patients, except that for MZL subgroups of patients, Psychiatric disorders are new common TEAE (18% in both arm).

Furthermore, among common TEAE (>10%) causal relationship with Lenalidomide is not established. The applicant is asked to provide the adverse drug reaction (OC)

In the safety population, a higher proportion of patients with at least one NCI CTCAE grade 3 or 4 TEAE are twice as high (65.1% in the pooled R2 arm *versus* 32.2% for R + placebo group). Proportion of patients with at least one related NCI CTCAE grade 3 or 4 TEAE are twice as high (55.8% in the pooled R2 *versus* 22.8% for rituximab and placebo group).

Proportion of patients with at least one TEAE leading to dose reduction in the R2 arm is ten times the amount of those in the placebo group (35.7% in the pooled R^2 *versus* 3.3% for Rituximab and placebo group). Proportion of patients with at least one TEAE leading to any study drug interruption in the R2 pooled arm is twice the amount of those in the placebo group (14.6% in the pooled R^2 *versus* 5.6% for Rituximab and placebo group).

Grade 3-4 TEAE reported in at least 5% of safety population are exclusively haematologic disorders, that it is concordant with the known safety profile of Lenalidomide and Rituximab. The proportion of patients with a grade 3-4 TEAE reported in at least 5% is twice in the R^2 arm. Haematologic disorders are a synergic effect of the combination of rituximab associated with Lenalidomide. The trend is the same for FL patients. Grade 3-4 TEAE reported in at least 5% of MZL population is slightly different with haematologic disorders, infections and infestations, infusion related reaction and Musculoskeletal and connective tissue disorders.

As a conclusion across the two studies, in the safety population, association of Rituximab + Lenalidomide leads to more frequent grade 3 or 4 TEAES, more frequent dose reduction or treatment discontinuation

A similar trend is observed in the FL and MZL population.

Grade 5 TEAE had a fatal outcome and are involved in 4 System Organ Class: cardiac disorders, general condition, infections, renal and urinary disorders. . Grade 5 are equivalent between placebo arm and pooled R2 arm (1.1 *versus* 1.5% respectively). In this context, conclusion on the imputability of the disease condition or of the treatment arm is challenging and not clear.

In general, Grade 3 or 4 AESI are more frequent in the pooled R2 arm than in the control arm, except for arterial thromboembolism (1.7% in the control group *versus* 0.3% in the experimental arm), bleeding (1.7% *versus* 0.3%), mixed thromboembolism (0.6% *versus* 0.3%), cardiac failure (0.6% *versus* 0% in the control *versus* experimental respectively). The trend is the same for FL and MZL subgroups of subjects.

Neutropenia is the more frequent grade 3 or 4 AESI in any treatment arm and is three times higher in the experimental arm. (39.3% in the pooled R^2 arm and 12.8% in the placebo group). Consequently, infections are more frequent also (13.3% *versus* 6.7%). Association of Rituximab and Lenalidomide have a synergic effect on hematologic disorders especially on Neutropenia.

Tumour flare reaction (TFR) is a very common adverse event in the experimental arm of the AUGMENT study (19/176=10.8%) and reported in the MAGNIFY R^2 arm (9/222=4.1%). TFR are a well-known adverse event already reported in the safety profile of Lenalidomide when used for mantle cell lymphoma with the same frequency (10%). Only 1 subject in the AUGMENT R^2 arm (0.6%) had grade 3 or 4 TFR and no patient had to discontinue lenalidomide/Rituximab therapy due to TFR. Association of Lenalidomide and Rituximab didn't increase the risk and the grade of TFR, which remain, with a TFR prophylaxis, a manageable adverse event. This is acceptable. In the SmPC section 4.4 Careful monitoring and evaluation for TFR is recommended. Tumour flare may mimic PD. Patients who experienced Grade 1 and 2 TFR were treated with corticosteroids, NSAIDs and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (see sections 4.2 and 4.8).

Careful monitoring and evaluation for TLS is recommended (see SmPC section 4.4). Patients should be well hydrated and receive TLS prophylaxis, in addition to weekly chemistry panels during the first cycle or longer, as clinically indicated (see sections 4.2 and 4.8).

Subjects with at least one grade 3 or 4 TEAE of cutaneous reaction are three time as much in the group treated by R^2 than in the placebo + Rituximab group (3.3% *versus* 1.1% respectively). Cutaneous reaction are well known adverse events in the safety profile of Lenalidomide and Rituximab. Potentialisation of the two drugs cannot be excluded.

In the experimental arm, deaths during the treatment period are more frequent (10/398=2.5%) than in the placebo arm (2/180=1.1%). Death from adverse events are twice as high in the experimental arm than in the placebo group (1.3% *versus* 0.6%). Detail of grade 5 events and correlation with the treatment has been asked in the dedicated section (see previous section TEAE grade 5).

Neoplasm benign, malignant and unspecified are higher in the pooled arm (16/398=4%) *versus* in the control arm (3/180=1.7%). Basal cell carcinoma are related in 5 subjects (1.3%) of the experimental arm. Squamous cell carcinoma are related in 6 patients of the experimental arm (*versus* 0 subject in the control arm) of the subgroups of follicular lymphoma patients.

With regards to second primary malignancies, pooled data of the two studies AUGMENT (pivotal study) and Magnify study (supportive study) were provided with a median follow-up of 29.83 months and 10.25 months respectively. Furthermore, data from RELEVANCE study, an ongoing phase 3 study randomized, active-controlled, open-label study of R2 for eighteen 4 week cycles followed by rituximab monotherapy for another six 8-week cycles (total duration of ~30 months) *versus* R- CHEMO for 6 to 8 cycles followed by rituximab for up to twelve 8-week cycles (total duration of 30 months), subjects with previously untreated FL (Grades 1 to 3a) was also provided with a median follow up of 39.1 months. Median follow up for the three studies are acceptable and judged sufficient to evaluate the risk.

Data of study NHL-001 wasn't reported because Lenalidomide was used in monotherapy and the median follow-up at the time of cut of date was 3.6 months. It was judged non contributive.

The frequency of subjects with invasive SPMs (hematologic and solid tumour SPMs) was lower for the pooled R2 Arm (AUGMENT and MAGNIFY) compared with the Control Arm (AUGMENT) (9 [2.0%] *versus* 8 [4.4%], respectively) (Table 8), with the incidence rates being lower (1.33 *versus* 1.97 per 100 person-years, respectively) (Table 9).

The frequency of subjects with invasive SPMs (hematologic and solid tumour SPMs) was lower for the pooled R2 Arm (AUGMENT and MAGNIFY) compared with the Control Arm (AUGMENT) (9 [2.0%] *versus* 8 [4.4%], respectively) (Table 8), with the incidence rates being lower (1.33 *versus* 1.97 per 100 person-years, respectively) (Table 9). However, the incidence of non-melanoma skin cancer in higher in the pooled R2 arm (2.25 per 100 person years (1.36-3.74) than in the control arm (0.73 per 100 person year (0.23-2.25). This is concordant with the previous results of serious adverse event reported in >2% of the pooled safety population where Neoplasm benign, malignant and unspecified are higher in the pooled R2 arm (16/398=4%) *versus* in the control arm (3/180=1.7%).

Data from the RELEVANCE study suggest an higher incidence rate of haematologic malignancies development with an incidence rates of 0.25 per 100 person-years in the R2 arm *versus* 0.12, 0.08 of R-chemo, R-CHOP. Incidence rates in the arm R-Benda is higher (0.3 per 100 person-year).

The HR of the difference between the R2 and R-aCHEMO KM cumulative incidence curves for hematologic SPMs is greater than 1.0, suggestive of a trend towards an increased risk of hematologic SPMs for the R2 Arm *versus* the R-CHEMO Arm.

In overall, in the RELEVANCE study the frequencies of subjects with invasive SPMs (hematologic and solid tumour SPMs) were similar for the R2and R-CHEMO Arms (25[4.9%] and 27[5.4%], respectively) with the incidence rates being similar (1.57 and 1.71per 100person-years, respectively).

Grade 3 or 4 cardiac arrhythmia events were reported in 2.3% of subjects in the AUGMENT R2 Arm *versus* 1.1% in the Control Arm. During the Initial Treatment Period in the MAGNIFY study while on R2 treatment, the frequency of events was 2.7%. The only PT within the AESI category reported in the pooled dataset at greater than 1% was syncope (1.3%). Arrhythmia was included in section 4.8 of the SmPC with an "uncommon" frequency.

2.5.2. Conclusions on clinical safety

No unexpected safety signal was identified from the provided safety results.

Association of Lenalidomide with Rituximab tends to potentiate adverse events especially haematologic disorders, tumour lysis syndrome and tumour flare syndrome. However, among common TEAE, adverse drug reaction are not established. Causal relationship between treatment by Lenalidomide + Rituximab and the development of non-melanoma skin cancer and haematologic malignancies is currently under further investigation.

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 CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 37.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 37.0 with the following content:

Safety concerns

Important Identified Risks	– Teratogenicity – Serious infection due to neutropenia – SPM <u>Important Identified Risk Related to Indication/Target Population</u> – For MCL and FL: TFR
Important Potential Risks	– Cardiac failure – Cardiac arrhythmias – Ischaemic heart disease (including myocardial infarction) – Off-label use

Missing Information	None

Pharmacovigilance plan

Study/Activity Type, Title and Category (1 to 3)	**Objectives**	**Safety Concerns Addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
MDS PASSes *Non-interventional: observational Category 1*	To gather safety data on the use of lenalidomide in MDS patients and monitor off-label use (prospective disease registry in transfusion-dependent low- and INT-1-risk MDS with an isolated del 5q [MDS-010] and a retrospective drug utilisation study of Revlimid in MDS [MDS-012]).	AML and survival. Safety profile in a 'real world' setting.	Ongoing	Safety updates will be submitted with future PSURs. The final study report for MDS-010 is expected Q1 2023. The final study report for MDS-012 is expected Q3 2023.
Revlimid TNE NDMM Registry *Non-interventional: Category 1*	The primary objectives are to compare the incidence of cardiovascular events between TNE NDMM patients treated with a first-line lenalidomide-containing regimen and those treated with a first-line non lenalidomide-containing regimen; and to identify, quantify, and characterise risk factors for cardiovascular events in this population of TNE NDMM patients.	Cardiac events (cardiac failure, cardiac arrhythmias, IHD [including MI]).	Ongoing.	An interim study report is expected 30 Jun 2024. The final study report is expected 01 Dec 2025. Safety updates will be submitted with future PSURs.
Monitoring of Pregnancy Prevention Programme implementation *Category 3*	Monitoring of implementation of PPP.	Monitoring of pregnancy prevention.	Ongoing	Safety updates will be submitted with future PSURs.
Connect® MM Registry. Category 3	The primary objectives of the registry are to describe practice patterns of common first-line and subsequent treatment regimens (including lenalidomide based) in patients with previously untreated MM, whether or not eligible for transplant, as well as diagnostic patterns and occurrence of SPM in a 'real world' population.	SPM (AML and B-cell malignancies, NMSC and other SPM), cardiac events (cardiac failure, cardiac arrhythmias, IHD [including	Ongoing	Safety updates will be submitted with future PSURs.

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
		MI]), Serious Infection due to Neutropenia.		
Connect® MDS/AML Disease Registry Non-interventional: observational Category 3	The objectives of the registry are: to describe patterns for diagnosis, prognosis, treatment, clinical monitoring and outcome measures in patients with MDS, ICUS and AML; to compare routine clinical practice patterns with existing management guidelines (eg, National Comprehensive Cancer Network); to describe treatment patterns and outcomes in del(5q) patients with or without additional cytogenetic abnormalities; and in non-del(5q) patients; and to summarise patient-reported outcomes (eg, HRQoL) and economic outcomes, and their association with patient characteristics, treatment regimens, and clinical outcomes. Exploratory objectives are: to evaluate molecular and/or cellular markers in the blood/bone marrow tissues and oral epithelial cells that may provide further prognostic classification of MDS and AML subtypes and/or may provide information on drug mechanism of action and on-therapy markers predictive of clinical outcomes and potentially impact clinical outcomes with therapy; to summarise the clinical status (eg, OS, PFS, response rate) of patients with or without mutations by treatment regimen, and to analyse the correlation between mutation detection/allele burden in bone marrow and peripheral blood samples. Data regarding SPM are also being collected.	SPM	Ongoing	Safety updates will be submitted with future PSURs.
RRMCL PASS Category 3	The study is designed as a retrospective non-interventional study of patients with RRMCL with the objective to quantify and characterise the event of TFR by tumour burden and the proportion of early deaths by tumour burden in patients treated with lenalidomide in a 'real world' setting.	TFR/high tumour burden and early deaths	Ongoing	Version 3 of the protocol was submitted on 14 Aug 2017, approved by PRAC on 26 Oct 2017 and endorsed by CHMP on 09 Nov 2017. The final study report could be available in Q4 2027.

Study/Activity Type, Title and Category (1 to 3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
				Safety updates will be submitted with future PSURs.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Important Identified Risks	
Teratogenicity	**Routine risk minimisation activities**: Section 4.3 of SmPC: contraindicated in pregnant women and in FCBP unless all the conditions of the Celgene PPP are met. Section 4.4 of SmPC: warnings and precautions for use – Criteria for women of non-childbearing potential – Counselling – Contraception – Pregnancy testing – Precautions for men – Additional precautions – Reference to educational materials, prescribing and dispensing restrictions. Section 4.6 of SmPC: fertility, pregnancy and lactation. Sections 4.8 and 5.3 of SmPC: the potential teratogenic effects of lenalidomide are highlighted. **Pack size:** The pack is based on a maximum 4-week supply of capsules to ensure that FCBP are required to obtain a new monthly prescription with a medically supervised pregnancy test. **Legal status:** Lenalidomide is subject to restricted medical prescription. **Additional risk minimisation measures** – Celgene PPP – Educational Programme o Direct HCP communication prior to launch o Direct HCP communication with findings from CC-501-TOX-004 o HCP kit to include booklet o Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists. – Therapy management o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP o Advice in SmPC, Dear HCP letter and educational materials – System to ensure appropriate measures have been completed. – Patient card to document childbearing status, counselling and pregnancy testing.

Safety Concern	Risk Minimisation Measures
Serious Infection due to Neutropenia	**Routine risk minimisation activities:** – Section 4.2 of SmPC: dose reduction advice for neutropenia. – Section 4.4 of SmPC: warning of neutropenia, and infection with or without neutropenia, and advice for monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episodes promptly. Advice regarding establishing HBV status before treatment, use in patients previously infected with HBV and monitoring for signs and symptoms of active HBV infection throughout therapy. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients in PL, including that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting lenalidomide treatment. **Additional risk minimisation measures:** None.
SPM	**Routine risk minimisation activities**: – Section 4.4 of SmPC warning of SPM and advice for cancer screening. – Listed as ADRs in Section 4.8 of SmPC. – Advice to patients provided in PL. **Additional risk minimisation measures:** – Dear HCP letter. – HCP Kit: HCP Guide.
Tumour Flare Reaction (MCL and FL Indications)	**Routine risk minimisation activities**: – Section 4.2 of SmPC: dose interruption advice for TFR. – Section 4.4 of SmPC warning. – Listed as an ADR in Section 4.8 of SmPC. **Additional risk minimisation measures:** – HCP Kit: HCP Guide.
Important Potential Risks	
Cardiac Failure and Cardiac Arrhythmias	**Routine risk minimisation activities**: – Listed as ADRs in Section 4.8 of SmPC. – Listed in PL. **Additional risk minimisation measures:** None.
Ischaemic Heart Disease (including myocardial infarction)	**Routine risk minimisation activities:** – The association between ischaemic heart disease and lenalidomide is unknown. Close monitoring will continue. – Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None.
Off-label Use	**Routine risk minimisation activities:** – Collection of off-label use data detailed in Section 4.4 of SmPC. **Additional risk minimisation measures:** None.

2.7. Update of the Product information

As a consequence of this new indication, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. Particularly, a new warning with regards to second primary malignancies in FL and a warning regarding tumour flare reaction in FL have 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 and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Revlimid in combination with rituximab is proposed for the treatment of adult patients with previously treated follicular lymphoma (Grade 1- 3a).

Follicular lymphomas (FLs) are the second most frequent subtype of nodal lymphoid malignancies. Treatment of FL is driven by the impact of disease symptoms and tumour burden on the patient, with the intent to improve and extend life, as options for curative treatment are lacking.

3.1.2. Available therapies and unmet medical need

At relapse of FL, selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa). Other options, including fludarabine-based, platinum- salts based or alkylating agents-based regimens, could also be useful. Rituximab should be added if the previous CD20 antibody-containing scheme achieved >6- to 12-month duration of remission. In symptomatic cases with low tumour burden, rituximab monotherapy can be proposed.

Relapse and refractory indolent lymphoma (such as FL) remains an incurable disease. In previously treated iNHL follicular lymphoma patients, rituximab monotherapy is associated with ORR of approximately 38% to 59%. Over time many patients become refractory to rituximab.

Obinutuzumab, another anti-CD 20 monoclonal antibody, has also been approved in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, in whom it was associated with an ORR of approximately 80%.

Radioimmunotherapy (90Yyttrium– labelled ibritumomab– tiuxetan) is also authorised for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B lymphoma; this could also represent an effective therapeutic approach in elderly patients with comorbidities not appropriate for chemotherapy as per Dreyling et al. ESMO 2016.

Finally, idelalisib is indicated as monotherapy for the treatment of adult patients with a FL that is refractory to two prior lines of treatment.

Given the incurable nature of previously treated FL, the efficacy and safety limitations of current treatment options, and the fact that patients are typically older and with comorbidities, a high medical need exists for the development of novel treatment options associated with a more tolerable safety profile.

3.1.3. Main clinical studies

Results are mainly coming from a phase 3, double-blind randomized study designed to compare the efficacy and safety of rituximab plus lenalidomide *versus* rituximab plus placebo in subjects with relapsed/refractory follicular lymphoma or relapsed/refractory marginal zone lymphoma (AUGMENT, N = 358, including 295 with a FL). Supportive data from one phase 3b supportive study (MAGNIFY) were submitted.

In the AUGMENT trial, Patients were randomized in a 1:1 ratio to receive rituximab 375 mg/m^2 every week in Cycle 1 and on Day 1 of every 28-day cycle from cycles 2 through 5 plus lenalidomide once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles (experimental arm R^2) or rituximab plus placebo (control arm). The ITT Population was comprised of 358 subjects.

Efficacy determination was based upon PFS as primary endpoint, assessed by the Independent Review Committee (IRC). Secondary/exploratory endpoints were ORR, CR rate, DOCR, DOR, OS, EFS, TTNLT, TTNCT, PFS2, and time to histological transformation.

3.2. Favourable effects

In the overall population in the AUGMENT trial, PFS by IRC assessment was significantly higher in the experimental arm than in the control arm (HR: 0.45 p<0.0001 95% CI = 0.33, 0.61). Results observed for the overall population were comparable to those in the FL subgroup (HR= 0.4; p<0.0001; 95% CI = 0.29, 0.55), for which a 60% reduction in the risk of progression or death was found for the R^2 Arm compared to the Control Arm.

The objective response rate (CR+PR; %) by IRC assessment was significantly higher in the R^2 arm in the overall population (77.5% 95% CI = 70.7; 83.4 *versus* 53.3% 95% CI= 45.8; 60.8) p<0.0001) and in the follicular lymphoma subgroup (80.3 % 95% CI =72.9; 86.4) *versus* 55.4% 95% CI = 47.0; 63.6) p<0.0001).

Overall, the median DOR (95% CI) by IRC assessment per the 2007 IWGRC among responders was 36.6 months (95% CI 22.9, not estimable [NE]) in the R^2 Arm and 21.7 months (95% CI 12.8, 27.6) in the Control Arm. Similar results were noted in subjects with FL.

Finally, in subjects with FL, there were 11 deaths in the R^2 arm *versus* 24 deaths in the control arm reported (HR [95% CI]: 0.45 [0.22, 0.92]).

3.3. Uncertainties and limitations about favourable effects

In patients with marginal zone Lymphoma, the combination of Lenalidomide with Rituximab did not appear to have any impact on the progression free survival and on objectives responses rates. More worrying, there were 5 deaths in the R^2 Arm *versus* 2 deaths in the control arm in subjects with MZL (HR [95% CI]: 2.89 [0.56, 14.92]); these results should however be interpreted with caution due to the low number of r/r MZL patients. The approvability of the MZL indication was contingent on the assumption of

homogeneity of response between FL and MZL, which could not be demonstrated based on AUGMENT and MAGNIFY data; following these uncertainties, the MAH has withdrawn the proposed MZL indication.

3.4. Unfavourable effects

The safety data from the R^2 Arm in AUGMENT was pooled with the safety data from the R^2 Arm in the Initial Treatment Period of MAGNIFY to increase the safety database in previously treated FL/MZL. Common (>10%) Treatment Emergent Adverse Event (TEAE) are reported in the safety population and, in general, are more frequent in the R^2 arm than in the placebo group: gastro-intestinal disorders (68.1 *versus* 47.3%), general disorders (58.8 *versus* 46.6%), blood and lymphatic disorders (57.3 *versus* 31.8%), infections and infestations (56.3 *versus* 45.9%), skin and subcutaneous tissue disorders (56 *versus* 22.3%), musculoskeletal and connective tissue disorders (46.1 *versus* 31.8%), respiratory thoracic and mediastinal disorders (44.6 *versus* 35.1%), nervous system disorders (38.4 *versus* 23%), metabolism and nutrition disorders (37.5 *versus* 23%), investigations (34.1 *versus* 28.4 %), infusion related reaction (14.2% both), tumour flare (8 *versus* 0.7%) respectively. In the safety population, a higher proportion of patients with at least one NCI CTCAE grade 3 or 4 TEAE are twice as high (65.1% in the pooled R^2 arm *versus* 32.2% for R + placebo group). Proportion of patients with at least one related NCI CTCAE grade 3 or 4 TEAE are twice as high (55.8% in the pooled R2 *versus* 22.8% for Rituximab and placebo group).

Grade 3-4 TEAE reported in at least 5% of safety population are exclusively haematologic disorders. This is concordant with the known safety profile of Lenalidomide and Rituximab. The proportion of patients with a grade 3-4 TEAE reported in at least 5% is twice in the R^2 arm. Haematologic disorders are a synergic effect of the combination of Rituximab associated with Lenalidomide. The trend is the same for FL patients. Grade 3-4 TEAE reported in at least 5% of MZL population is slightly different with haematologic disorders, infections and infestations, infusion related reaction and Musculoskeletal and connective tissue disorders.

Concerning grade 3 or 4 Adverse events of specific interest (AESI): In general, Grade 3 or 4 AESI are more frequent in the pooled R2 arm than in the control arm, except for arterial thromboembolism (1.7% in the control group *versus* 0.3% in the experimental arm), bleeding (1.7% *versus* 0.3%), mixed thromboembolism (0.6% *versus* 0.3%), cardiac failure (0.6% *versus* 0% in the control *versus* experimental respectively). Neutropenia is the more frequent grade 3 or 4 AESI in any treatment arm and is three times higher in the experimental arm. (39.3% in the pooled R2 arm and 12.8% in the placebo group). Consequently, infections are more frequent also (13.3% *versus* 6.7%). Association of Rituximab and Lenalidomide have a synergic effect on hematologic disorders especially on Neutropenia.

Tumour flare reaction (TFR) is a very common adverse event in the experimental arm of the AUGMENT study (19/176=10.8%) and reported in the MAGNIFY R2 arm (9/222=4.1%). TFR are a well-known adverse event already reported in the safety profile of Lenalidomide when used for mantle cell lymphoma with the same frequency (10%)

Concerning serious adverse event and deaths: In the experimental arm, deaths during the treatment period are more frequent (10/398=2.5%) than in the placebo arm (2/180=1.1%). Death from adverse events are twice as high in the experimental arm than in the placebo group (1.3% *versus* 0.6%).

Concerning serious TEAE: Neoplasm benign, malignant and unspecified are higher in the pooled arm (16/398=4%) *versus* in the control arm (3/180=1.7%). Basal cell carcinoma are related in 5 subjects (1.3%) of the experimental arm. Squamous cell carcinoma are related in 6 patients of the experimental arm (*versus* 0 subject in the control arm) of the subgroups of follicular lymphoma patients.

The frequency of subjects with invasive SPMs (hematologic and solid tumour SPMs) was lower for the pooled R^2 arm (AUGMENT and MAGNIFY) compared with the Control Arm (AUGMENT) (9 [2.0%] *versus* 8

[4.4%], respectively), with the incidence rates being lower (1.33 *versus* 1.97 per 100 person-years, respectively). However, the incidence of non-melanoma skin cancer is higher in the pooled R2 arm (2.25 per 100 person years (1.36-3.74) than in the control arm (0.73 per 100 person year (0.23-2.25).This is concordant with the previous results of serious adverse event reported in >2% of the pooled safety population where Neoplasm benign, malignant and unspecified are higher in the pooled R^2 arm (16/398=4%) *versus* in the control arm (3/180=1.7%). Data from the RELEVANCE study suggest an higher incidence rate of haematologic malignancies development with an incidence rates of 0.25 per 100 person-years in the R2 arm *versus* 0.12, 0.08 of R-chemo, R-CHOP. Incidence rates in the arm R-Benda is higher (0.3 per 100 person-year).

The HR of the difference between the R^2 and R-CHEMO KM cumulative incidence curves for hematologic SPMs is greater than 1.0, suggestive of a trend towards an increased risk of hematologic SPMs for the R^2 Arm *versus* the R-CHEMO Arm. Consistent results were found from the supportive MAGNIFY study.

3.5. Uncertainties and limitations about unfavourable effects

As it is a known concern in the safety profile of Lenalidomide, the causal relationship of the higher proportion of non-melanoma skin cancer in the pooled R2 arm versus the Placebo + rituximab from the two main studies and the higher incidence rates of haematologic malignancies on the R2 arm from the RELEVANCE study has been discussed by the MAH. SPM is an important identified risk in the RMP, data from ongoing studies are awaited.

3.6. Effects Table

Table 94 Effects Table for Revlimid in combination with Rituximab for the treatment of patients with previously treated follicular lymphoma (data cut-off: 22 Jun 2018))

Effect	Short description	Unit	Treatment (R2)	Control (Rituximab+ placebo)	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS FL population	Median time from randomization to progression disease or death	months	39.4 (25.1;NE)	13.8 (11.2;16.0)	Superiority HR = 0.4 (0.29;0.55) p< 0.0001	AUGMENT study
Overall response rate	Proportion of patients with best response of at least partial response (CR+PR)	%	80.3 (72.9, 86.4)	55.4 (47.0, 63.6)	Superiority P<0.0001 Fisher exact test	AUGMENT Study
Duration of response	(median) 95% CI	Months	36.6 (24.9, NE)	15.5 (11.2, 25.0)		
Unfavourable Effects						
Neutropenia	Proportion of patients with grade 3 or 4	%	39.9	13.3		Pooled AUGMENT + MAGNIFY

Effect	Short description	Unit	Treatment (R2)	Control (Rituximab+ placebo)	Uncertainties / Strength of evidence	References
Infection	Proportion of patients with grade 3 or 4	%	13.3	6.7		Pooled AUGMENT + MAGNIFY
Tumour Flare syndrome	Proportion of patients	%	7	0.6		Pooled AUGMENT + MAGNIFY
Non melanoma skin cancer	Incidence rate	Per 100 person year	2.25	0.73		Pooled AUGMENT + MAGNIFY
SPM						

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main goal of treatment in previously treated patients with follicular lymphoma (FL) is to achieve deep durable remissions, with prolonged progression-free survival (PFS), in order to prevent disease-related complications without incurring significant treatment-related toxicities. In these patients, the treatment choice is based on duration of response (DoR) to prior therapies, types of prior therapies, and patient comorbidities (Johnson, 1995; Smith, 2013), as well as physician and patient preferences.

The combination of Lenalidomide to Rituximab *versus* Rituximab alone improves significantly the median PFS in patients with follicular lymphoma disease. ORR, OS and PFS 2 are also improved by the combination of Lenalidomide and Rituximab. AUGMENT study participants were patients with Grade 1 to 3a FL; the indication, adequately reflects the concerned population. The wording in the Summary of Product Characteristics (SmPC) Section 5.1 was modified to adequately describe the study population included based on the AUGMENT protocol requirements.

Considering the safety profile and as expected, the association of Lenalidomide + Rituximab increases the proportion of treatment emergent adverse events, leads to more frequent grade 3 or 4 TEAE, more frequent dose reduction or treatment discontinuation. Second primary malignancies are listed as "identified risk" in the RMP, relevant warnings in line with the other indications are included in the SmPC.

3.7.2. Balance of benefits and risks

Data from the Phase 3, multicenter, randomized, double-blind controlled study CC-5013-NHL-007 (AUGMENT) show that patients with previously treated FL who can tolerate lenalidomide in combination with rituximab (R2) demonstrated a highly statistically significant and clinically meaningful PFS benefit over rituximab plus placebo and a significant improvement in secondary efficacy parameters.

The combination remains manageable despite unfavourable effects especially in the context of an incurable disease for which potential therapeutic alternatives are limited.

3.7.3. Additional considerations on the benefit-risk balance

In patients with marginal zone lymphoma, no impact on the PFS of the association R^2 has been shown. The MAH has withdrawn this indication from this application.

3.8. Conclusions

The overall B/R of Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a) is positive.

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 accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include Revlimid in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a); as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated; the PL is updated in accordance. The RMP version 37.0 has also been agreed.

Amendments to the marketing authorisation

In view of the date submitted with the variation, amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP) are recommended.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Revlimid is not similar to Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific discussion Revlimid-H-C-717-II-0107.