Abstract OT10

Efficacy and Safety of Lenalidomide and Rituximab vs Placebo and Rituximab in a Phase 3 Trial in Relapsed/Refractory Non-Hodgkin Lymphoma

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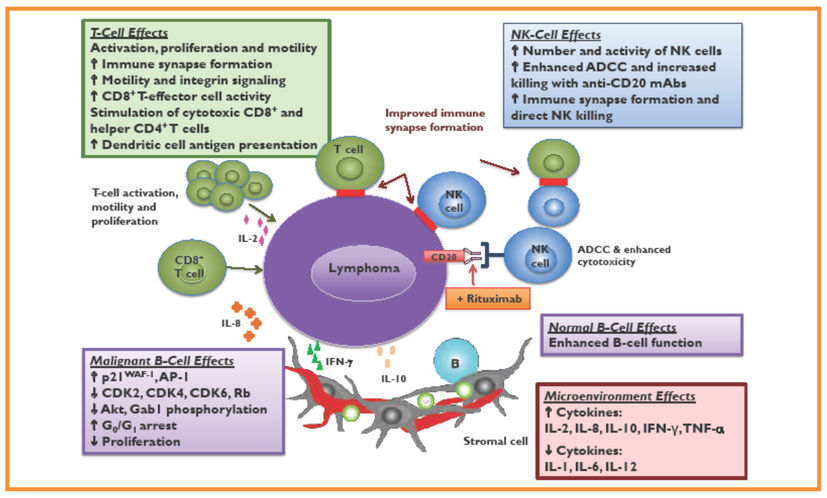
Background

- Single-agent rituximab has yielded objective response rates (ORRs) between 40% and 69% in patients with relapsed/refractory (R/R) indolent NHL (iNHL)[1-3]
- Although combining rituximab with chemotherapies increased ORR in patients with iNHL,[4] the associated toxicity has led to exploration of other treatment approaches (ie, biologic doublets) in patients with iNHL[5]
- Combining lenalidomide, an immunomodulatory agent with antitumor activity,[6-9] with rituximab (R^2) could potentially improve response by enhancing the proapoptotic and antibody-dependent cell-mediated cytotoxicity (ADCC) activities of rituximab[8,10]
- The R^2 regimen has demonstrated activity in a number of phase 2 studies in untreated and R/R iNHL (**Table 1**)

Figure 1. Proposed mechanism of action of lenalidomide in combination with rituximab.



Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; IFN-γ, interferon gamma; IL, interleukin; mAb, monoclonal antibody; NK, natural killer; TNF-α, tumor necrosis factor alfa.

Table 1. Lenalidomide + Rituximab in iNHL

Type of Study	Population, N		Treatment	Key Results
Phase 2, single arm (CALGB 50803/ ALLIANCE)[11]	Untreated FL N = 66		20 mg LEN d1-d21 of 28d cycle ×12 cycles 375 mg/m² RIT weekly Cycle 1, then d1 Cycles 4, 6, 8, 10	**FL (n = 54):** ORR, 93% (72% CR), PFS not reached
Phase 2, single arm[12]	Advanced, untreated iNHL N = 110		20 mg LEN d1-d21 375 mg/m² RIT d1 28d cycle ×6	**FL (n = 46):** ORR, 98% (87% CR/CRu); 3-yr PFS 79% **MZL (n = 27):** ORR, 89% (67% CR); 3-yr PFS 87% **SLL (n = 30):** ORR, 80% (23% CR); 3-yr PFS 62%
Phase 2, randomized, open label (CALGB 50401)[13]	Relapsed FL, previous RIT, not RIT-refractory LEN + RIT, n = 44 LEN, n = 45		15-20 mg LEN d1-d21 of 28d cycle ×12 cycles 375 mg/m² RIT weekly ×4	**FL, LEN + RIT:** ORR, 73% (36% CR); EFS, 2.0 yr **FL, LEN:** ORR, 51% (13% CR); EFS, 1.2 yr
Phase 2, single arm[14]	R/R iNHL N = 30		25 mg LEN d1-d21 of 28d cycle 375 mg/m² RIT d15 of Cycle 1, then weekly ×4	**Overall (n = 27):** ORR, 74% (44% CR); PFS, 12.4 mo **FL (n = 22):** ORR, 77% (41% CR/CRu)
Phase 2, single arm[15]	R/R, RIT-resistant indolent B-cell lymphoma or MCL N = 27		10 mg LEN d1-d28 8 mg DEX weekly for two 28d cycles, then LEN + DEX + 375 mg/m² RIT weekly ×4 during Cycle 3	**Overall (n = 24):** ORR, 58% (33% CR); PFS 23.7 mo **FL (n = 15):** ORR, 53%
Phase 2, single arm[16]	R/R MZL N = 46		20 mg LEN d1-d21 (28d cycle) + 375 mg/mg² RIT d1	**Overall (n = 40)** ORR, 80% (55% CR)

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DEX, dexamethasone; EFS, event-free survival; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; LEN, lenalidomide; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; PFS, progression-free survival; RIT, rituximab; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Key: ● FL ● MZL ● SLL/CLL ● MCL/Other

- Grade 3/4 toxicities reported in previous studies of lenalidomide and rituximab in R/R indolent NHL were similar and included
  - Hematologic toxicities such as neutropenia (6% to 55%, grade 3-4),[13-16] lymphopenia (up to 45%, grade 3-4),[14] thrombocytopenia (up to 7%, grade 3-4),[15] and leukopenia (up to 15%, grade 3-4)[15]
  - Nonhematologic toxicities such as thrombosis (4%, grade 3-4),[13] fatigue (4% to 23%, grade 3-4),[13-15] and rash (4% to 8%, grade 3-4)[15-16]
- The phase 2 ALLIANCE/CALGB-50803 study showed that the R^2 regimen is highly active in patients with previously untreated follicular lymphoma and low- or intermediate-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores[11]
  - ORR of 93 % (72% with complete response [CR], 21% with partial response, 4% with stable disease)
  - Median progression-free survival (PFS) had not been reached
- The phase 2 CALGB-50401 study also demonstrated significant activity of both single-agent lenalidomide as well as R^2 in patients with recurrent follicular lymphoma[13]
  - Lenalidomide monotherapy: ORR of 51%, event-free survival of 1.2 years
  - R^2: ORR of 73%, event-free survival of 2.0 years

Objective

The objective of the AUGMENT trial is to compare the efficacy and safety of rituximab plus lenalidomide versus rituximab plus placebo in patients with R/R follicular lymphoma or marginal zone lymphoma

Methods

AUGMENT (NCT01938001) is a phase 3, double-blind, randomized study of rituximab plus lenalidomide versus rituximab monotherapy in patients with R/R iNHL (follicular or marginal zone lymphoma **Table 2** and **Figure 2**)

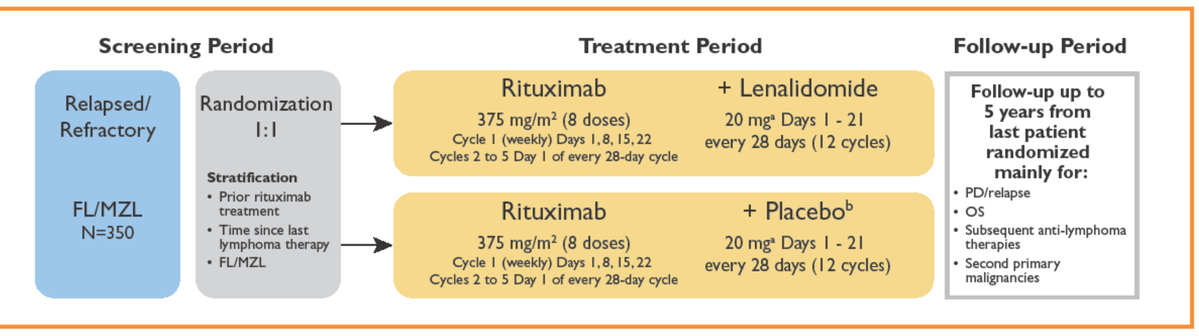
Table 2. Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed MZL or grade 1, 2, or 3a FL, CD20+ by flow cytometry or histochemistry • Previous treatment with at least 1 prior line of systemic chemotherapy, immunotherapy, or chemoimmunotherapy • Documented relapsed, refractory, or progressive disease post-systemic therapy • Rituximab-sensitive if had previously received rituximab-based therapy • Investigator considers, based on his or her professional opinion and guidance from study resource documents, that rituximab monotherapy is appropriate • At least one bi-dimensionally measurable lesion • ECOG performance status ≤ 2 • Adequate hematologic function	• Grade 3b FL • Clinical evidence of transformed lymphoma • CNS involvement • Condition requiring chronic steroid use • Seropositive for or active viral infection with HBV, HCV, or HIV • History of other malignancies within the preceding 10 years, except for localized non-melanoma skin cancer or carcinoma in situ of the cervix • Prior lenalidomide • Risk for a thromboembolic event and unwilling to take VTE prophylaxis

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MZL, marginal zone lymphoma; VTE, venous thromboembolism.

Methods (continued)

Figure 2. AUGMENT study design.



Abbreviations: CrCl, creatinine clearance; FL, follicular lymphoma; MZL, marginal cell lymphoma; OS, overall survival; PD, progressive disease.
[a] 10 mg if CrCl ≥ 30 mL/min but < 60 mL/min; 20 mg if CrCl ≥ 60 mL/min.
[b] Identically matched capsule.

Study Endpoints

- The primary endpoint is progression-free survival (PFS)
- Key secondary endpoints include
  - Durable CR
  - Overall survival
  - ORR
  - Safety
  - Time to next anti-lymphoma treatment

Efficacy Assessments

- Primary and all other secondary efficacy endpoints will be assessed using the 2007 International Working Group (IWG) criteria[17] (without positron emission tomography [PET] scan) by the Independent Response Committee (IRC)
- Patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma will also undergo endoscopy as part of the response assessment, according to Groupe d'Etude des Lymphomes de l'Adult (GELA) criteria[18,19]

Safety Assessments

- Adverse events
  - Assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03[20] (version 3.0[21] for tumor flare reaction)
- Tumor lysis syndrome
- Hematology and serum chemistry laboratory tests
- B symptoms
  - Fever (>38°C), night sweats, and weight loss greater than 10% within the prior 6 months

Statistical Analyses

- A total of 193 PFS events required to have 90% power to detect a hazard ratio of 0.625 using a 1-sided log-rank test at a significance level of 0.025
- Interim analysis planned at approximately 50% information (96 PFS events) for futility only

Enrollment

- Approximately 350 patients worldwide are planned to be randomized
- Patient enrollment began in November 2013
- This trial is open for enrollment; as of May 12, 2015, there are 109 patients enrolled
- For more information on recruitment to the study, contact:
  - Emmanuel Ryembault, MS (eryembault@celgene.com)
  - Barbara Amoroso, MD PhD (bamoroso@celgene.com)
  - http://clinicaltrials.gov/show/NCT01938001

AUGMENT Trial Investigators

This poster is presented on behalf of all the AUGMENT trial investigators at the following sites

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