Subgroup Analyses of Elderly Patients Aged ≥ 70 Years in AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab Plus Placebo (R-Placebo) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)

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Background:

The combination of lenalidomide+rituximab (R^2) recently showed superior efficacy vs R-placebo in patients (pts) with R/R iNHL (Leonard et al. *J Clin Oncol* 2019). Based on these AUGMENT study results, R^2 was approved by the US FDA for treatment of adult pts with previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL). Advanced age at diagnosis is a risk factor in pts with iNHL. We performed post-hoc subgroup analyses by age from AUGMENT and data here focus on pts age ≥ 70 y.

Methods:

AUGMENT (NCT01938001) is a multicenter, double-blind, randomized phase III study of R^2 vs R-placebo in pts with FL grade 1-3a or MZL previously treated with ≥ 1 systemic therapy with R/R disease but not refractory to rituximab. Pts were randomized 1:1 to R^2 or R-placebo. R^2 was oral lenalidomide 20 mg/d, d1-21/28 for 12c plus rituximab IV 375 mg/m^2 weekly in c1 and d1 of c2-5. R-placebo was rituximab+placebo on the same schedule. The primary endpoint was

progression-free survival (PFS) per 2007 IWG response criteria (without PET) as assessed by IRC (central review). Secondary endpoints included overall response rate (ORR), complete response (CR), time to next anti-lymphoma treatment (TTNLT) and safety. Post-hoc analyses were performed by dividing pts into age < 70 y and ≥ 70 y subgroups, the latter group considered unfit for chemotherapy.

Results:

Of 358 pts randomized (R^2, n = 178; R-placebo, n = 180), 267 pts were age < 70 y (R^2, n = 131; R-placebo, n = 136), and 91 pts were age ≥ 70 y (R^2, n = 47; R-placebo, n = 44). Baseline characteristics including histology, disease status, and prior treatments are shown in the table and were similar across treatment arms in pts ≥ 70 y. At a median follow-up of 28.3 mo, the study met its primary endpoint of PFS, with a hazard ratio (HR) of 0.46 (95% CI, 0.34-0.62; $P <$ 0.0001) in the overall population. R^2 had superior PFS vs R-placebo in both < 70 and ≥ 70 y subgroups, with HR of 0.41 (95% CI, 0.29-0.59) and HR of 0.66 (95% CI, 0.37-1.18), respectively. In pts ≥ 70 y, median PFS with R^2 vs R-placebo was 24.9 vs 14.3 mo; ORR/CR was 81%/26% vs 59%/16%; and TTNLT was not reached in either arm. Efficacy results for all pts and those < 70 y are reported in the table; notably in pts receiving R^2, mPFS was longer in pts < 70 y vs ≥ 70 y (39.4 mo [95% CI, 22.9-NE] vs 24.9 mo [95% CI, 16.4-NE]). In pts ≥ 70 y, any-grade adverse events (AEs) with a ≥ 10 % difference between R^2 vs R-placebo included neutropenia (63% vs 11%), constipation (33% vs 16%), cough (33% vs 16%), leukopenia (26% vs 2%), anemia (24% vs 9%), pyrexia (24% vs 9%), pruritus/pruritus generalized (24% vs 2%), muscle spasms (22% vs 11%), rash/rash maculopapular (22% vs 5%), headache (20% vs 9%), thrombocytopenia (17% vs 2%), dyspepsia (13% vs 2%), influenza (13% vs 2%), back pain (7% vs 18%), and nasopharyngitis (4% vs 16%). Also, tumor flare was reported in 9% vs 0% of pts, respectively. In pts ≥ 70 y, 75% of R^2 pts vs 36% of R-placebo pts had ≥ 1 grade 3/4 AE, mainly due to neutropenia (50% vs 7%). All other grade 3/4 AEs occurred in < 10% of pts ≥ 70 y in both treatment arms. One grade 5 AE occurred in pts ≥ 70 y (R-placebo arm). In the R^2 arm, the median number of treatment cycles was 12 for both the < 70 y vs ≥ 70 y subgroups; however, fewer older pts completed 12 cycles of lenalidomide (76% vs 57%), and more started lenalidomide at the lower dose of 10 mg (6% vs 35%) because of low creatinine clearance, respectively. In the R^2 < 70 y and ≥ 70 y subgroups, the average daily dose of lenalidomide was 17.9 mg/d (range, 5.6-20.0) and 14.4 mg/d (range 4.2-20.0), and median relative dose intensity was 95% and 86%, respectively.

Conclusions:

Similar to the results in the original population, R^2 showed superior efficacy vs rituximab monotherapy (plus placebo) as measured by the primary end point of PFS and secondary end points of ORR and CR in pts with R/R FL grade 1-3a and MZL irrespective of age. The efficacy and safety profiles of R^2 and R-placebo in pts ≥ 70 y were similar to those reported in the overall

population. Older pts treated with R^2 vs R-placebo had superior mPFS (24.9 vs 14.3 mo). They were more likely to start lenalidomide at a lower dose and had lower median dose intensity which may have contributed to their shorter mPFS vs younger pts receiving R^2. These data show that R^2 maintained efficacy improvements vs R-placebo in pts ≥ 70 y, despite higher unfit status and lower overall lenalidomide treatment/exposure. Thus, R^2 is an effective and available treatment option for pts with iNHL, including those with advanced age.

Table. AUGMENT: Baseline Characteristics and Efficacy by Age Group

	≥ 70 y		< 70 y		Total	
	R^2 (n = 47)	R-Placebo (n = 44)	R^2 (n = 131)	R-Placebo (n = 136)	R^2 (n = 178)	R-Placebo (n = 180)
Baseline characteristics, n (%)						
FL	34 (72)	32 (73)	113 (86)	116 (85)	147 (83)	148 (82)
MZL	13 (28)	12 (27)	18 (14)	20 (15)	31 (17)	32 (18)
Ann Arbor stage III-IV	32 (68)	28 (63)	105 (80)	96 (71)	137 (77)	124 (69)
FLIPI score ≥ 3	24 (51)	21 (48)	45 (34)	33 (24)	69 (39)	54 (30)
ECOG PS 0-1	46 (99)	43 (98)	130 (99)	135 (99)	176 (99)	178 (99)
Bulky disease	13 (28)	9 (20)	32 (24)	40 (29)	45 (25)	49 (27)
> 1 Prior systemic antilymphoma regimen	25 (53)	17 (39)	51 (39)	66 (49)	76 (43)	83 (46)
Unfit for chemotherapy*	47 (100)	44 (100)	7 (5)	5 (4)	54 (30)	49 (27)
Efficacy						
mPFS, mo (95% CI)	24.9 (16.4-NE)	14.3 (11.3-27.7)	39.4 (22.9-NE)	13.9 (9.6-16.7)	39.4 (22.9-NE)	14.1 (11.4-16.7)
ORR, n (%)	38 (81)	26 (59)	100 (76)	70 (51)	138 (78)	96 (53)
CR, n (%)	12 (26)	7 (16)	48 (37)	26 (19)	60 (34)	33 (18)
mTTNLT, mo (95% CI)	NE (22.9-NE)	NE (20.8-NE)	NE (NE-NE)	28.2 (21.5-NE)	NE (NE-NE)	32.2 (23.2-NE)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, FL International Prognostic Index; mPFS, median progression-free survival; mTTNLT, median time to next antilymphoma treatment; MZL, marginal zone lymphoma; NE, not evaluable; ORR, overall response rate.

*Defined as age ≥ 70 y, or age 60-69 y with creatinine clearance < 60 mL/min or ECOG PS ≥ 2.

Results of a Phase II Study of Obinutuzumab in Combination with Lenalidomide in Previously Untreated, High Tumor Burden Follicular Lymphoma (FL)

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Introduction: FL, the most common indolent non-Hodgkin lymphoma, is characterized by a defective immune microenvironment that suppresses normal T-cell and natural-killer (NK)-cell activity. The clinical course is often depicted by high initial response rates coupled with a prolonged natural history and repeated relapses with most patients (pts) succumbing to their disease. Effective, well tolerated therapies are desirable. Obinutuzumab (O) is a humanized, type II anti-CD20 monoclonal antibody glycoengineered for enhanced antibody-dependent cellular cytotoxicity (ADCC). Lenalidomide (len) is an immunomodulatory agent that binds the cereblon E3 ubiquitin ligase complex resulting in recruitment, ubiquitination, and degradation of transcription factors Aiolos and Ikaros resulting in T-cell and NK-cell activation. Therefore, combining O with len is anticipated to be synergistic in augmenting the innate and adaptive immune response in FL. The combination has been shown to be well tolerated and effective in relapsed FL (Fowler ICML 2017). Therefore, we sought to explore the efficacy and safety of O-len in previously untreated, high tumor burden FL.

Methods:We conducted as single-center, phase 2 study in previously untreated, stage II, III, or IV, high tumor burden (defined by GELF) FL (grade 1, 2 or 3A). Pts received 1000mg of O on days 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and day 1 of even numbered cycles, cycle 8-30. Cycle length was 28 days. Len was administered as 20mg on days 1-21 of cycles 1-6. Pts in a complete

response (CR) after 6 cycles received reduced dose len (10mg on days 1-21) for cycles 7-18. Among pts in a partial response (PR) after 6 cycles, len was continued at 20mg for the next 3-6 cycles or until CR, whichever occurred first, len was then dose reduced to 10mg on days 1-21 for the remainder of 18 cycles. The primary endpoint was progression-free survival (PFS) at 2 years (according to Lugano 2014 criteria). Secondary endpoints included: safety, CR, PR, overall response (ORR), and overall survival (OS).

Results: 90 pts with high tumor burden FL were enrolled. Median age was 58 years (range 33-84), 52% (N=47) were male, 67 (74%) had an ECOG performance status of 0, 9 (10%) had stage II, 23 (26%) stage III, and 58 (64%) had stage IV disease. The majority had grade 1/2 FL (80%). Twenty-one percent had low risk FLIPI scores, 37% intermediate risk, and 42% were high risk. With a median follow-up of 22 months (range 1-30 months), the 2-year PFS estimate is 96% (95% CI 92-100%) with only 2 pts experiencing progression to date. The ORR is 98% (85 CR, 1 PR), 92% achieved a CR at the first response assessment (cycle 4, day 1). Correlative studies are underway including serial circulating tumor DNA measurements.

No deaths have been observed to date. Eleven pts (12%) discontinued therapy as a result of an adverse event (AE), upper respiratory infection was the most common reason (N=5). Other reasons included bradycardia with sick sinus syndrome, urinary tract infection, constipation, abdominal pain, fatigue, foot neuroma (N=1 for each instance). The most common grade 3 or higher AEs include neutropenia (16%, grade 3 N=5, grade 4 N= 9), rash (10%), lung infection (4%), neutropenic fever (1%).

Conclusions: O-Len was associated with very high CR rates and 2-year PFS estimates in untreated, high tumor burden FL. The toxicity profile was manageable. Further study of this effective, immune therapy approach in untreated FL is warranted.