Supplemental Methods

Recommended Phase 2 Dose

Per protocol, if the dose level of 20 mg lenalidomide was determined to be safe and tolerated in the phase 1b, this dose would be considered the recommended phase 2 dose (RP2D) and a phase 2 cohort initiated with 20 mg lenalidomide. This decision was made due to delays in the study with 2 additional cohorts that had not been planned originally (10 mg lenalidomide and repeat 15 mg lenalidomide cohorts). To be able to push the dose to the maximum of 25 mg lenalidomide[1], which is the approved dose for multiple myeloma, concurrent with the phase 2 at 20 mg lenalidomide, a phase 1b cohort with 25 mg lenalidomide was initiated. An interim analysis was planned to be performed including approximately 28 evaluable patients with adequate tumor response assessments. At the interim analysis, the review committee recommended continuation of the study with 20 mg lenalidomide and addition of a cohort within the phase 2 portion of the study assessing 25 mg lenalidomide, based on the fact that there were no DLTs in the phase 1b for this dose. This phase 2 cohort included approximately 28 evaluable patients with adequate tumor response assessment followed by an interim analysis.

Protocol Amendment to DLT Criteria

The protocol DLT criteria were relaxed as described in the manuscript during the study to focus on severe events resulting in complications, requiring supportive care, or unresponsive to management, to accommodate the risk/benefit of treatment. After protocol amendments, rash was only considered a DLT if it did not resolve with a dose hold and concomitant corticosteroids and/or antihistamines within 10 days. Similarly,

after protocol amendments, only grade 4 neutropenia was considered a DLT, rather than grade 3 neutropenia lasting >7 days. Additionally, patients with a DLT were allowed to continue treatment if considered beneficial.

Supplemental References

1. REVLIMID® (lenalidomide) [package insert]. Summit, NJ: Celgene Corporation; February 2017; 2017.

Supplemental Table 1. Dose reductions, delays, modifications, and discontinuations due to febrile neutropenia and atrial fibrillation.

	560 mg/day ibrutinib + 375 mg/m^2 IV rituximab combined with:						
	Dose level −1 10 mg LEN (n=7)	**Dose level 1 15 mg LEN (n=12)**	**Dose level 1+ 15 mg LEN (n=9)**	**Dose level 2 20 mg LEN (n=9)**	**Dose level 3 25 mg LEN (n=8)**	**Dose level 1 combined (n=21)**	**All dose levels (N=45)**
Febrile neutropenia							
Dose modification	0	0	1 (11)	0	1 (13)	1 (5)	2 (4)
Dose reduction	0	0	1 (11)	0	1 (13)	1 (5)	2 (4)
Dose delay	0	0	1 (11)	0	1 (13)	1 (5)	2 (4)
Discontinuation	0	0	0	0	0	0	0
Atrial fibrillation							
Dose modification	0	0	0	1 (11)	1 (13)	0	2 (4)
Dose reduction	0	0	0	1 (11)	1 (13)	0	2 (4)
Dose delay	0	0	0	1 (11)	1 (13)	0	2 (4)
Discontinuation	0	0	0	0	0	0	0

IV, intravenous; LEN, lenalidomide.
Dose modifications include dose reductions and dose delays.

Supplemental Table 2. Overall response rate in overall population and response-evaluable population

	Overall population	Response-evaluable population
All DLBCL, % (n/N)	38 (17/45)	44 (17/39)
Non-GCB DLBCL, % (n/N)	48 (11/23)	65 (11/17)