

15–ICML

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

# Conflict of Interest Disclosure - Umberto Vitolo

| | |
|---|---|
| - Employment or leadership position: | N/A |
| - Consultant or advisory role: | Celgene, Janssen, Roche |
| - Stock ownership: | N/A |
| - Honoraria: | N/A |
| - Research funding: | Celgene, Roche |
| - Speaker's bureau: | Celgene, Gilead, Janssen, Roche, Sandoz, Takeda |

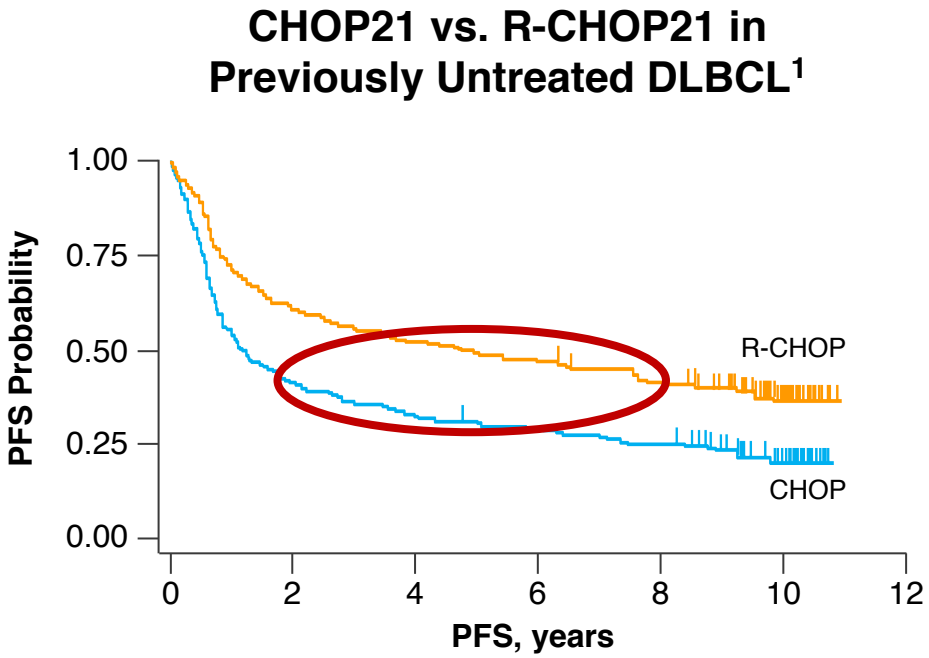


# ROBUST: First Report of Phase III Randomized Study of Lenalidomide/R-CHOP ($R^2$-CHOP) vs Placebo/R-CHOP in Previously Untreated ABC-type Diffuse Large B-cell Lymphoma

Umberto Vitolo, MD;[1] Thomas E. Witzig, MD;[2] Randy D. Gascoyne, MD;[3] David W Scott, MBChB, PhD;[3] Qingyuan Zhang, MD;[4] Wojciech Jurczak, MD, PhD;[5] Muhit Özcan, Prof Dr;[6] Xiaonan Hong, MD;[7] Jun Zhu, MD;[8] Jie Jin, MD;[9] David Belada, MD;[10] Juan Miguel Bergua, MD;[11] Francesco Piazza, MD;[12] Heidi Mócikova, MD;[13] Anna Lia Molinari, MD;[14] Dok Hyun Yoon;[15] Federica Cavallo, MD;[16] Monica Tani, MD;[17] Koji Izutsu, MD;[18] Koji Kato, MD;[19] Myron Czuczman, MD;[20] Sarah Hersey;[20] Adrian Kilcoyne, MD;[20] Jacqueline Russo;[20] Krista Hudak, PharmD;[20] Jingshan Zhang, PhD;[20] Annalisa Chiappella, MD;[1] and Grzegorz S. Nowakowski, MD;[2] on behalf of the ROBUST study investigators

*[1]Division of Hematology, A.O.U. Città della Salute e della Scienza Hospital and University, Torino, Italy; [2]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [3]Centre for Lymphoid Cancer, British Columbia Cancer, Vancouver, BC; [4]Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, China; [5]Department of Hematology, Jagiellonian University, Krakow, Poland; [6]Department of Hematology, Ankara University, Ankara, Turkey; [7]Cancer Hospital, Fudan University, Shanghai, China; [8]Beijing Cancer Hospital, Beijing, China; [9]The First Affiliated Hospital of Medical School of Zhejiang University, First Hospital of Zhejiang Province, Hangzhou, Zhejiang, China; [10]Fourth Department of Internal Medicine-Hematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [11]Servicio de Hematologia, Hospital Universitario San Pedro de Alcántara, Cáceres, Spain; [12]Division of Hematology, Department of Medicine, University of Padova and Azienda Ospedaliera di Padova, Padova, Italy; [13]Department of Internal Medicine and Haematology, Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic; [14]UO Ematologia, Ospedale Degli Infermi, Rimini, Italy; [15]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (Republic of Korea); [16]AOU Città della Salute e della Scienza di Torino, Turin, Italy; [17]U.O. Ematologia, Dipartimento Oncologia e Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy; [18]National Cancer Center Hospital, Tokyo, Japan; [19]Department of Medicine and Biosystemic Science, Kyushu University Faculty of Medicine, Fukuoka City, Japan*; and *[20]Clinical Research & Development and Precision Medicine/CDx, Celgene Corporation, Summit, NJ, USA*

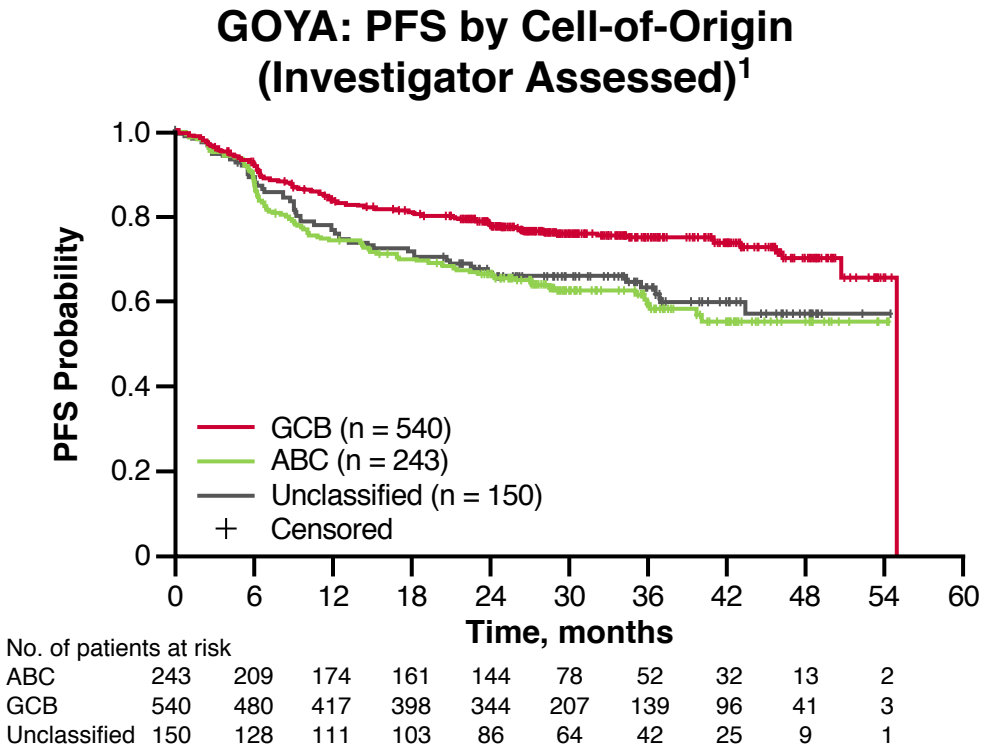
# Evolving Induction Treatment With R-CHOP + Novel Drugs




| Target | Randomized Phase II/III Studies | n | R-CHOP ± | Primary Endpoint Outcome |
|---|---|---|---|---|
| NF-κB | PYRAMID[2] | 399 | Bortezomib | No PFS improvement in non-GCB DLBCL |
| NF-κB | REMoDL-B[3] | 201 | Bortezomib | No PFS improvement in GCB/ABC DLBCL |
| CD20 | GOYA[4] | 1418 | GA101-CHOP vs R-CHOP | No PFS improvement |
| BTK | PHOENIX[5] | 838 | Ibrutinib | No EFS improvement in non-GCB DLBCL |
| *Cereblon* | *ROBUST* | *570* | *Lenalidomide* | *Current study* |

1. Coiffier et al, *Blood.* 2010;116:2040-2045. 2. Leonard et al. *J Clin Oncol.* 2017;35:3538-3546. 3. Davies et al. *Lancet Oncol* 2019;20:649-662.
4. Vitolo et al. *J Clin Oncol.* 2017;35:3529-3537. 5. Younes et al. *J Clin Oncol.* 2019;37:1285-1295.

# Evolving Induction Treatment With R-CHOP + Novel Drugs

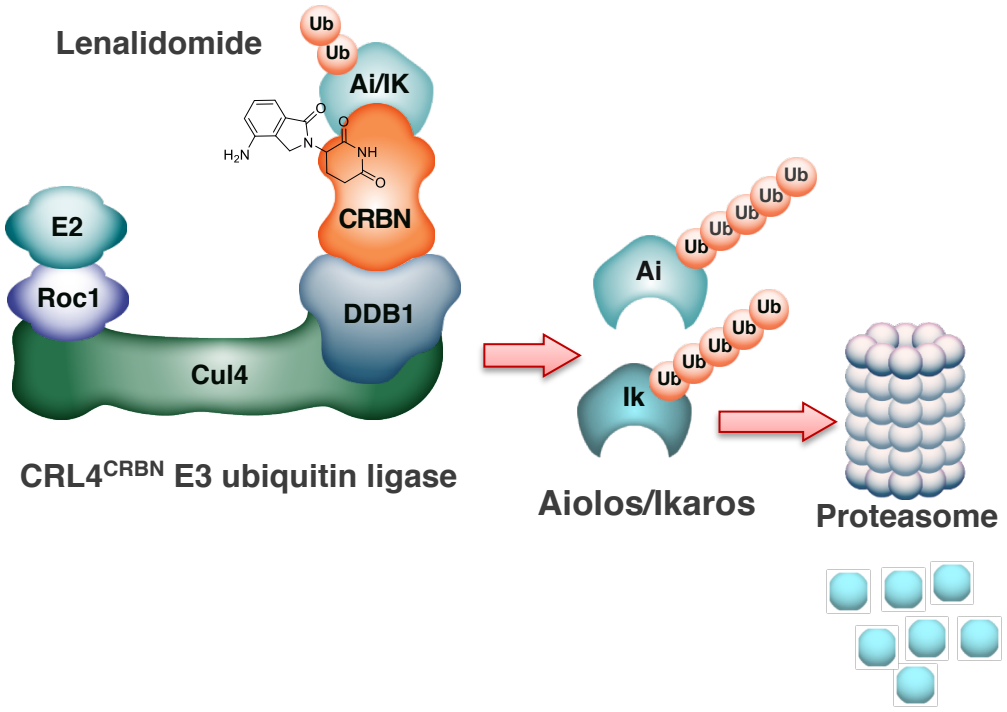



| Target | Randomized Phase II/III Studies | n | R-CHOP ± | Primary Endpoint Outcome |
|---|---|---|---|---|
| NF-κB | PYRAMID[2] | 399 | Bortezomib | No PFS improvement in non-GCB DLBCL |
| NF-κB | REMoDL-B[3] | 201 | Bortezomib | No PFS improvement in GCB/ABC DLBCL |
| **CD20** | **GOYA[1]** | **1418** | **GA101-CHOP vs R-CHOP** | **No PFS improvement** |
| BTK | PHOENIX[4] | 838 | Ibrutinib | No EFS improvement in non-GCB DLBCL |
| *Cereblon* | *ROBUST* | *570* | *Lenalidomide* | *Current study* |

- ABC (vs GCB) subtype of DLBCL has inferior survival following R-CHOP or G-CHOP[4]

1. Vitolo et al. *J Clin Oncol.* 2017;35:3529-3537. 2. Leonard et al. *J Clin Oncol.* 2017;35:3538-3546. 3. Davies et al. *Lancet Oncol* 2019;20:649-662. 4. Younes et al. *J Clin Oncol.* 2019;37:1285-1295.

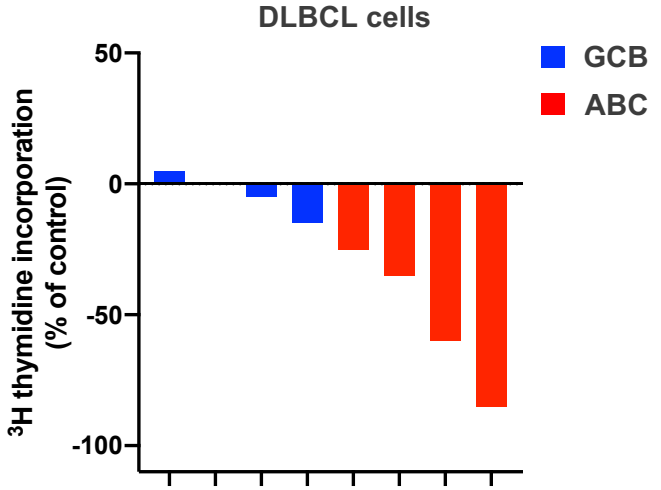
# Mechanism-Based Rationale for Lenalidomide in DLBCL




CRL4$^{CRBN}$ E3 ubiquitin ligase

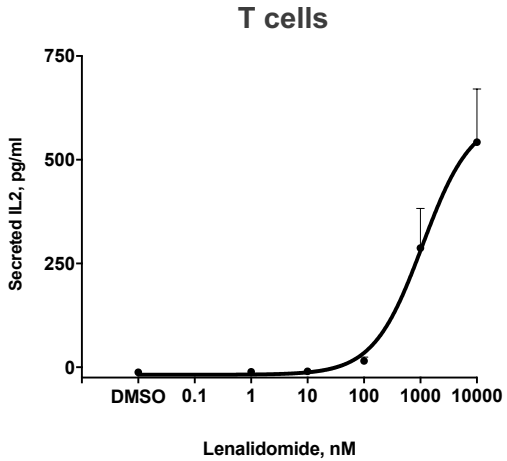
**Anti-proliferative activity In ABC-DLBCL**

**Interferon stimulated gene transcription (IRF7, DDX58, etc.)**



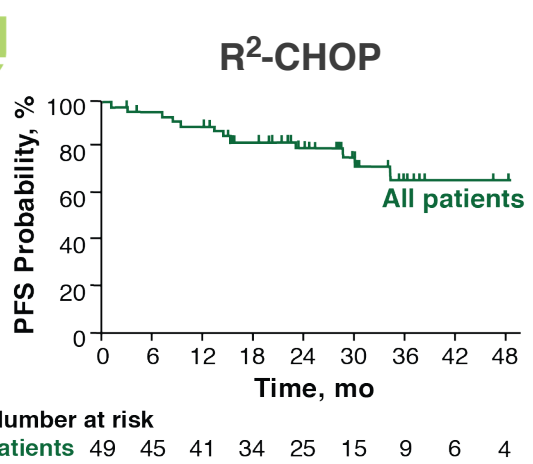

**Immunomodulatory activity**

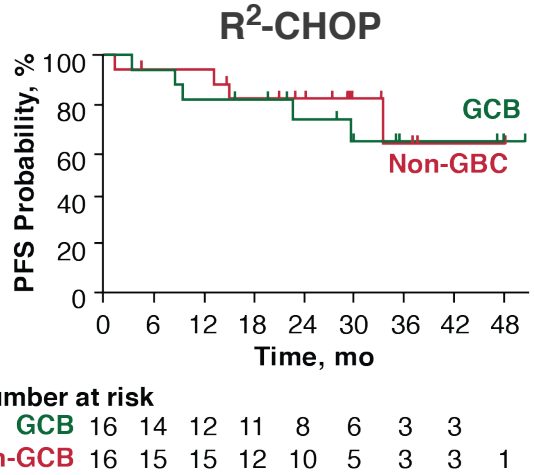
**Interferon cytokine production (IL-2, IFNγ, etc)**

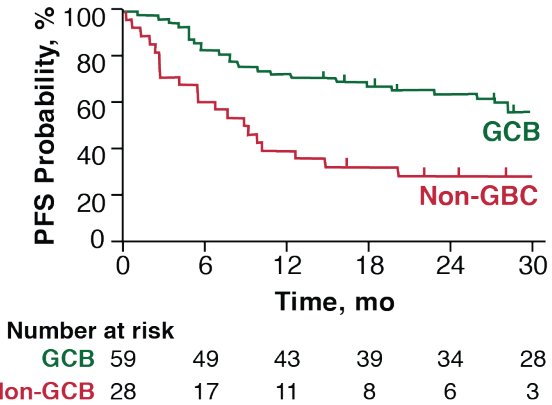


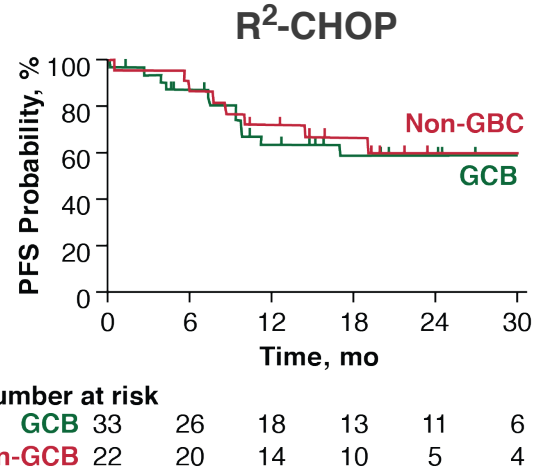

1. Zhang et al. *Br J Haematol.* 2013;160:487-502. 2. Chamberlain et al. *Nat Struct Mol Biol.* 2014;21:803-809. 3. Hagner et al. *Blood.* 2015;126:779-789.
4. REVLIMID (lenalidomide) PI. May 2019. Celgene Corporation, Summit, NJ.

# Rationale for Lenalidomide + R-CHOP ($R^2$-CHOP) in DLBCL



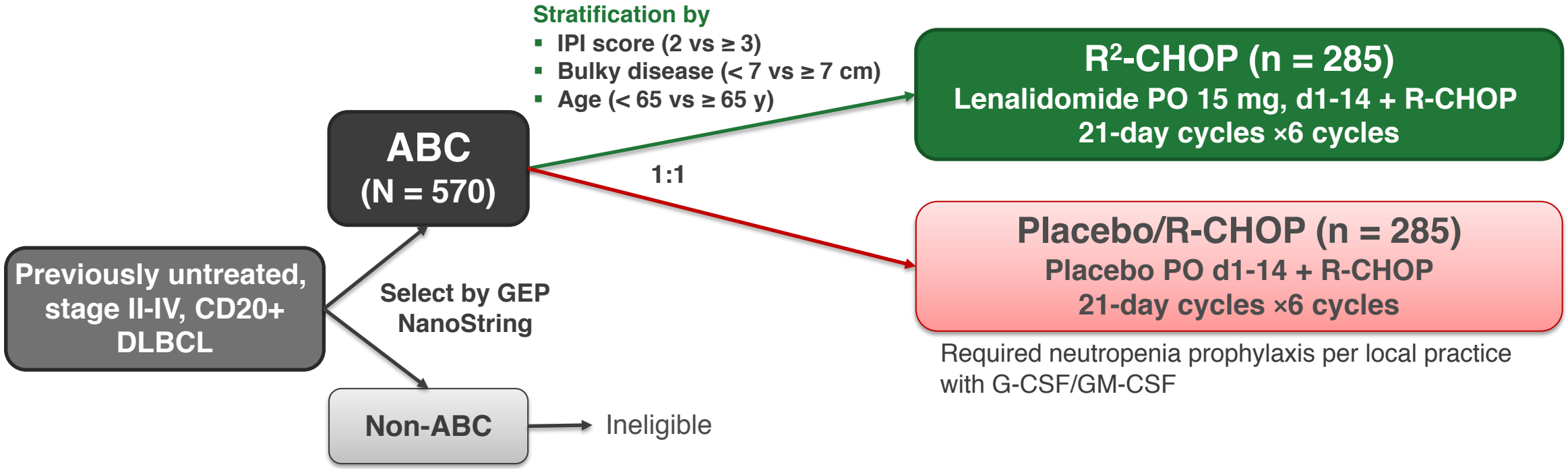

- Single-agent lenalidomide was clinically active in patients with R/R DLBCL, especially non-GCB type[1,2]
- Lenalidomide + R-CHOP ($R^2$-CHOP) proof of concept studies in previously untreated DLBCL (FIL REAL07 and Mayo Clinic MC078E)[3,4]
  - Cell-of-origin was evaluated by IHC
- Lenalidomide dosing differences
  - REAL07: 15 mg/d, d1-14 + R-CHOP21
  - MC078E: 25 mg/d, d1-10 + R-CHOP21

**Lenalidomide 15 mg/d, d1-14 dose was selected for ROBUST based on benefit:risk considerations**


1. Hernandez-Ilizaliturri et al. *Cancer*. 2011;117:5058-5066. 2. Czuczman et al. *Clin Cancer Res*. 2017;23:4127-4137.
3. Nowakowski et al. *J Clin Oncol*. 2015;33:251-257. 4. Vitolo et al. *Lancet Oncol*. 2014;15:730-737.

# ROBUST (DLC-002) Phase III Study Design

- Multicenter, international, randomized, double-blind, placebo-controlled, phase III study in 257 global sites
- Primary endpoint: PFS by central review (per 2014 IWG)[1]
  - PFS improvement from 24 mo with R-CHOP to 38 mo with $R^2$-CHOP (192 events with 90% power; HR = 0.625)
- Secondary endpoints: EFS (key secondary), OS, ORR, CR rate, DOR, and safety




NCT02285062; EudraCT 2013-004054-21. 1. Cheson et al. *J Clin Oncol.* 2014;32:3059-3068.

# Eligibility Criteria

## Key Inclusion Criteria

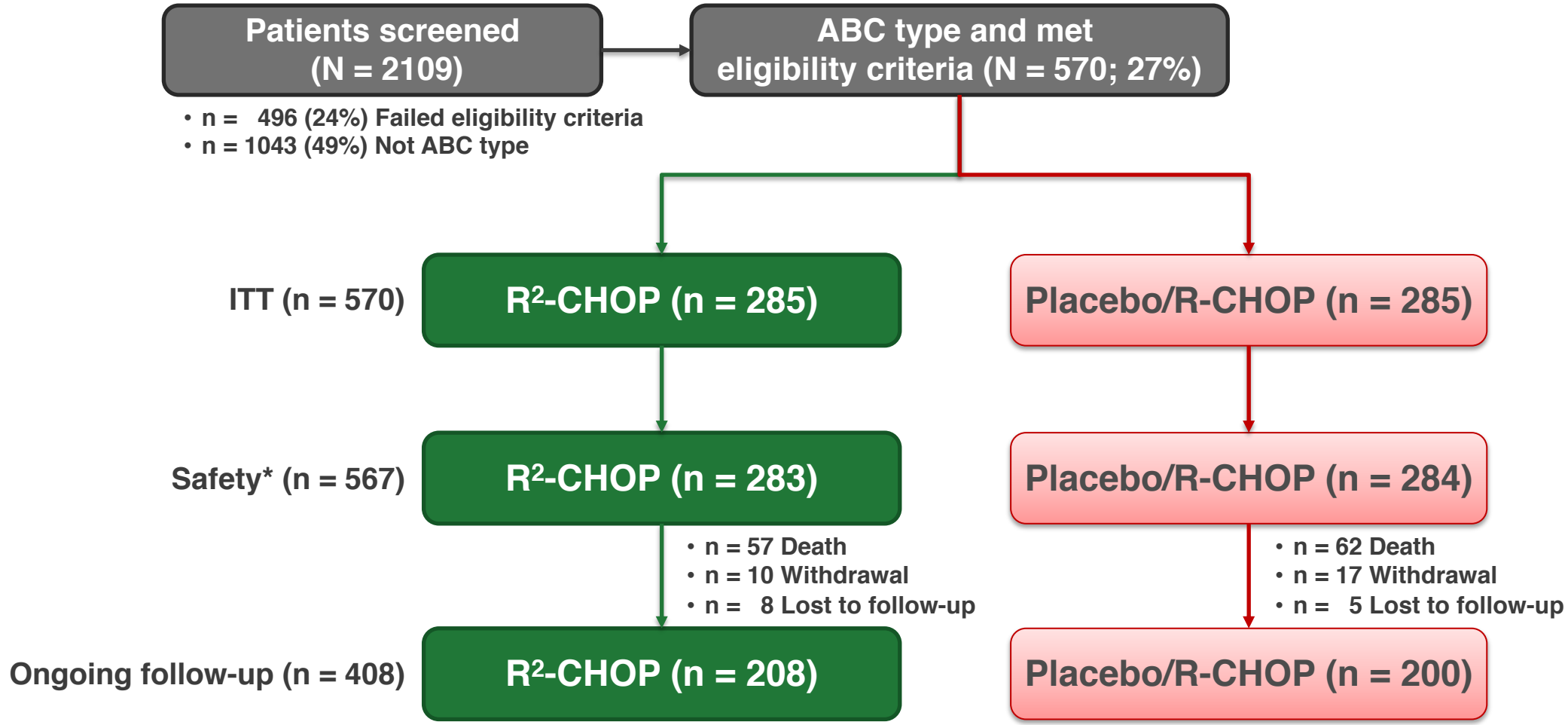
- Previously untreated, histologically-confirmed (by central review) CD20+ DLBCL
- **ABC subtype confirmed by GEP NanoString**
- **IPI score ≥ 2**
- **Ann Arbor stage II-IV disease**
- Measurable disease ≥ 1.5 cm in longest diameter and in 2 perpendicular directions by CT/MRI
- Age 18-80 years*
- ECOG PS ≤ 2
- Absolute neutrophil count ≥ $1.5 \times 10^9$/L
- Platelet count ≥ $75 \times 10^9$/L
- Creatinine clearance ≥ 30 mL/min
- Contraception as appropriate

## Key Exclusion Criteria

- **GCB or unclassified type DLBCL**
- **Evidence of transformed NHL or composite DLBCL/FL**
- History of other malignancies, unless disease free for ≥ 5 years
- Left ventricular ejection fraction < 45%
- Grade ≥ 2 peripheral neuropathy
- Unwilling to take venous thromboembolic prophylaxis
- Prior use of lenalidomide

*Patients > 80 y could be enrolled per investigator discretion if they met certain prespecified criteria, including ECOG ≤ 1, Cumulative Illness Rating scale for each organ system ≤ 2, and eligibility to receive full dose R-CHOP per local practice.

# Patient Disposition




*2 $R^2$-CHOP and 1 Placebo/R-CHOP patients were randomized but never received lenalidomide/placebo or R-CHOP.

*Note: Possible inclusion of geographic distribution in the table*

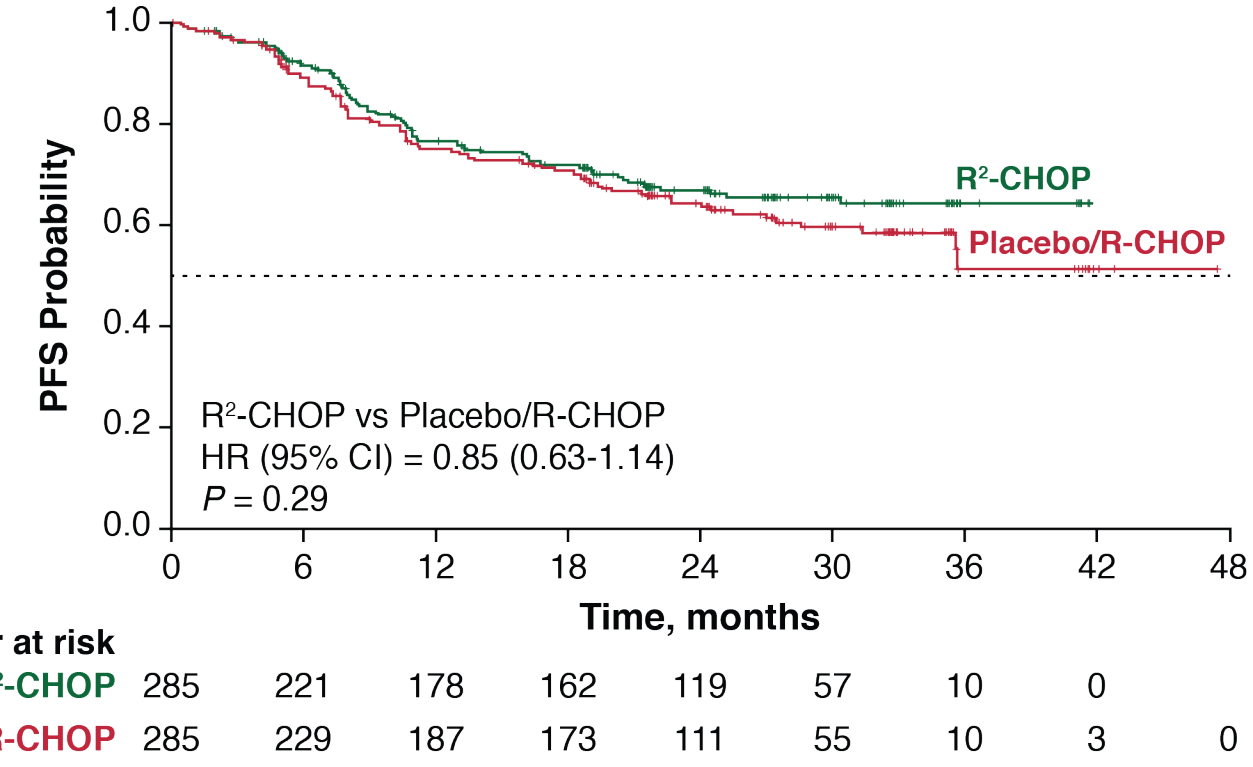
# Patient Demographics and Baseline Characteristics (ITT)

| n (%) | | $R^2$-CHOP (n = 285) | Placebo/R-CHOP (n = 285) |
|---|---|---|---|
| IPI score* | 2 | 121 (42) | 120 (42) |
| | ≥ 3 | 164 (58) | 165 (58) |
| Bulky disease (≥ 7 cm)* | | 97 (34) | 99 (35) |
| Median age, y (range) | | 65 (21-82) | 65 (28-83) |
| ≥ 65 y* | | 147 (52) | 148 (52) |
| Male/female | | 164 (58)/121 (42) | 143 (50)/142 (50) |
| ECOG PS | 0 | 129 (45) | 111 (39) |
| | 1 | 104 (36) | 118 (41) |
| | 2 | 52 (18) | 56 (20) |
| Ann Arbor disease stage | II | 37 (13) | 33 (12)† |
| | III | 80 (28) | 98 (34) |
| | IV | 168 (59) | 154 (54) |
| Elevated LDH (> 234 U/L) | | 177 (62) | 176 (62) |

- Baseline demographics were similar between arms
- Stratification factors were balanced
  - 42% IPI score of 2
  - 34% bulky disease
  - Median age overall was 65 y (52% ≥ 65 y; 2% ≥ 80 y)
- 88% had stage III/IV disease

Data cut-off 15Mar2019.
*Stratification factors. †Includes 1 patient with ineligible stage I disease.

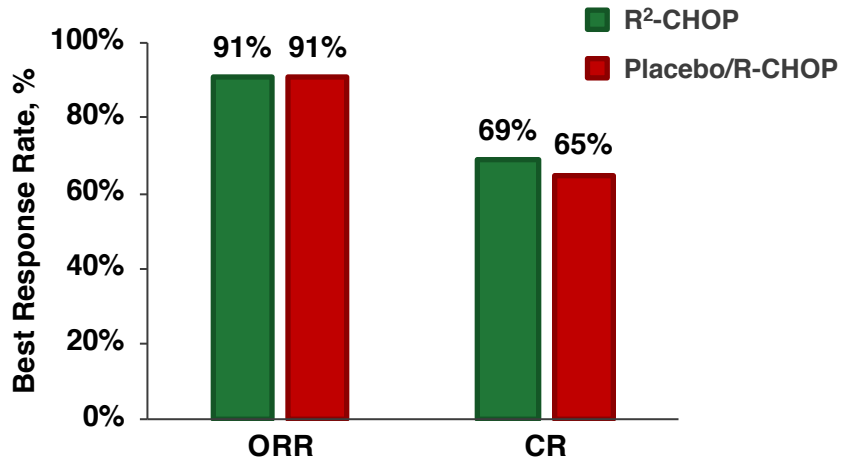
# Primary Endpoint: Progression-Free Survival (ITT, IRAC)




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R²-CHOP | 285 | 221 | 178 | 162 | 119 | 57 | 10 | 0 | |
| Placebo/R-CHOP | 285 | 229 | 187 | 173 | 111 | 55 | 10 | 3 | 0 |

| PFS Rates | R²-CHOP (n = 285) | Placebo/R-CHOP (n = 285) |
|---|---|---|
| 1-y | 77% | 75% |
| 2-y | 67% | 64% |

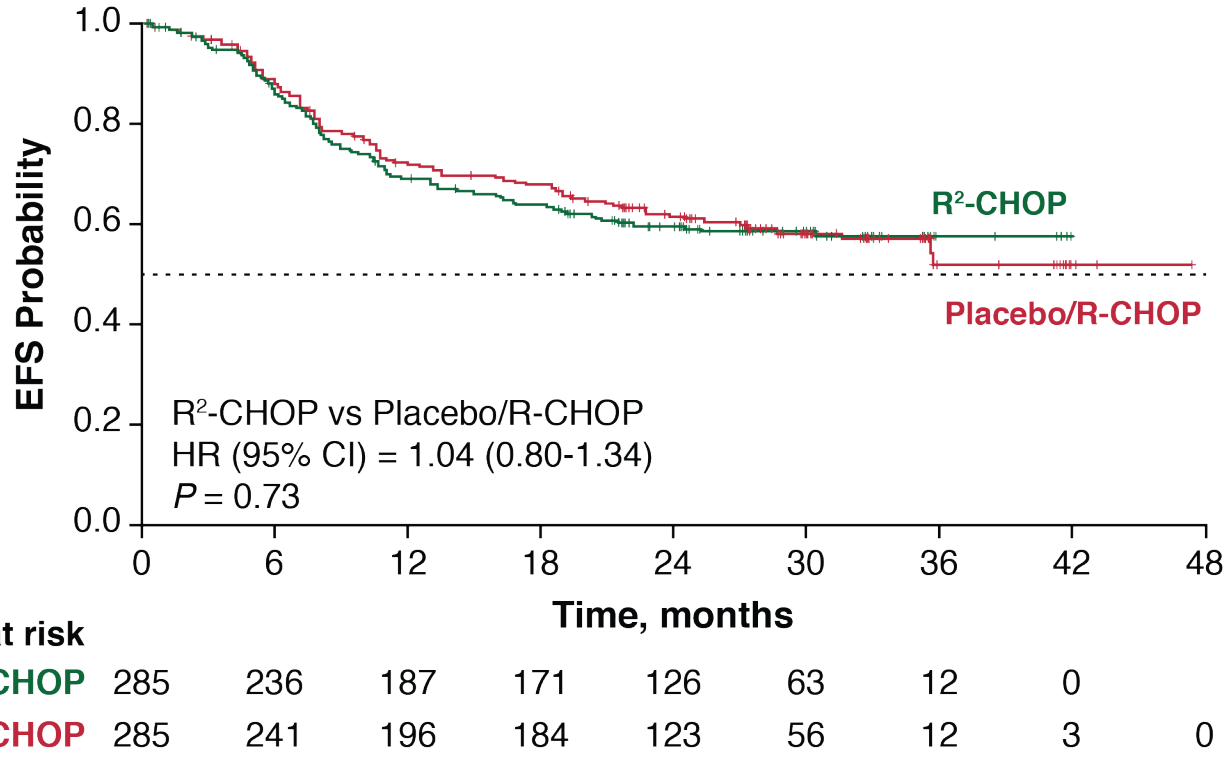



- At a median follow-up of 27.1 mo (range, 0-47), the primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- Median time from diagnosis to treatment was 31 days for each arm

Data cut-off 15Mar2019. IRAC, Independent Radiology Adjudication Committee; ITT, intention-to-treat; ORR, overall response rate; PFS, progression-free survival.
Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson et al. *J Clin Oncol.* 2014;32:3059-3068).

*Note: Possible inclusion of PET+ PR patient n values and receipt of additional therapy*

# Key Secondary Endpoint: Event-Free Survival (ITT, IRAC)



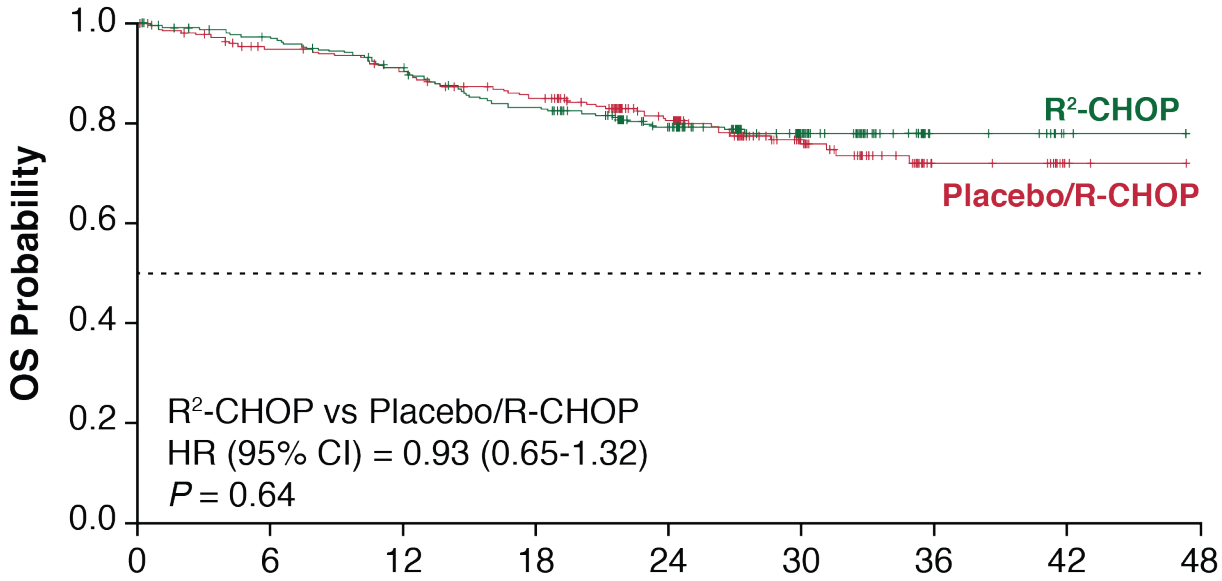

| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R²-CHOP | 285 | 236 | 187 | 171 | 126 | 63 | 12 | 0 | |
| Placebo/R-CHOP | 285 | 241 | 196 | 184 | 123 | 56 | 12 | 3 | 0 |

| EFS Rate | R²-CHOP (n = 285) | Placebo/R-CHOP (n = 285) |
|---|---|---|
| 1-y | 68% | 71% |
| 2-y | 59% | 61% |

- Median EFS was not reached for either arm

Data cut-off 15Mar2019. Note: EFS included the first occurrence of PD, death, relapse from CR, or initiation of subsequent antilymphoma therapy.
IRAC, Independent Radiology Adjudication Committee; ITT, intention-to-treat.

# Overall Survival (ITT)




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R²-CHOP | 285 | 269 | 248 | 224 | 165 | 83 | 18 | 2 | 0 |
| Placebo/R-CHOP | 285 | 260 | 245 | 226 | 162 | 77 | 15 | 3 | 0 |

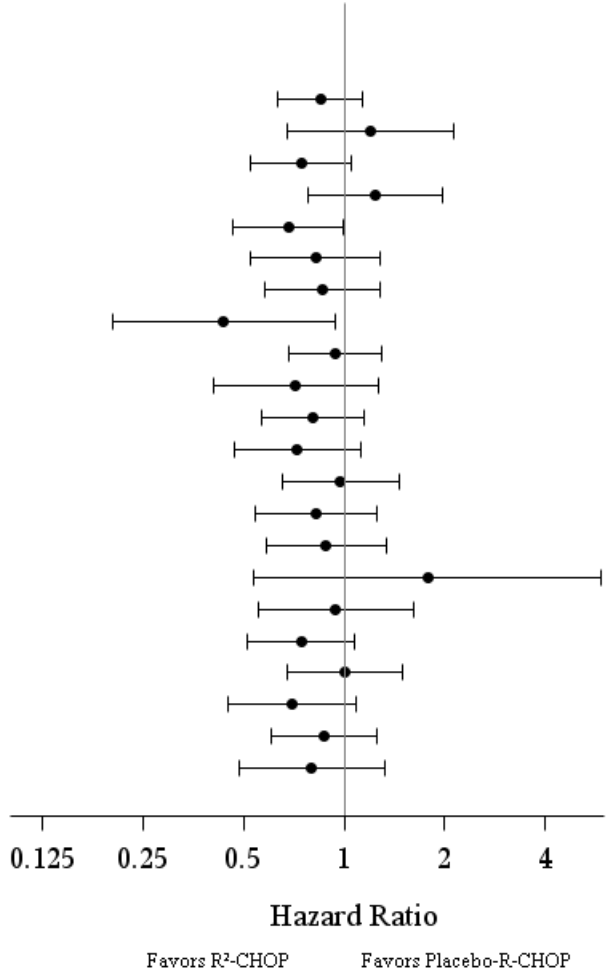
| | R²-CHOP (n = 283) | Placebo/R-CHOP (n = 284) |
|---|---|---|
| **No. of Patient Deaths (safety)** | | |
| | 57 | 62 |
| **OS Rates (ITT)** | (n = 285) | (n = 285) |
| 1-y | 91% | 90% |
| 2-y | 79% | 80% |

- Median OS was not reached for either arm
- Of 119 total patients who died, 93 (16%) were due to PD (< 2% from AEs or other causes)

Data cut-off 15Mar2019.

# Subgroup Analysis of PFS (ITT)

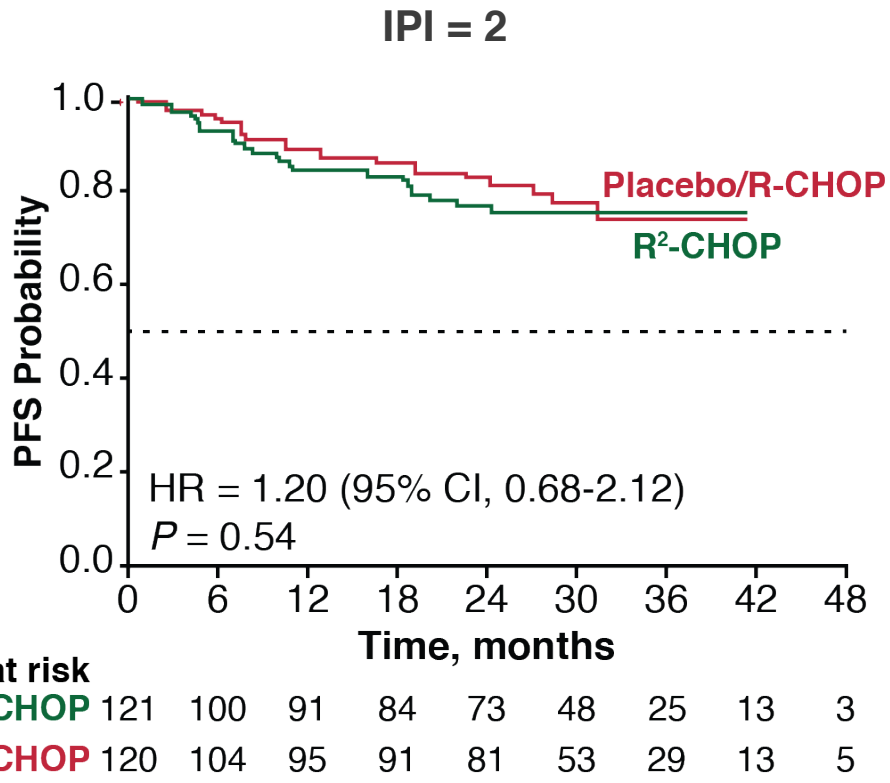
*Note: these data are currently being analyzed and the figure will be updated*



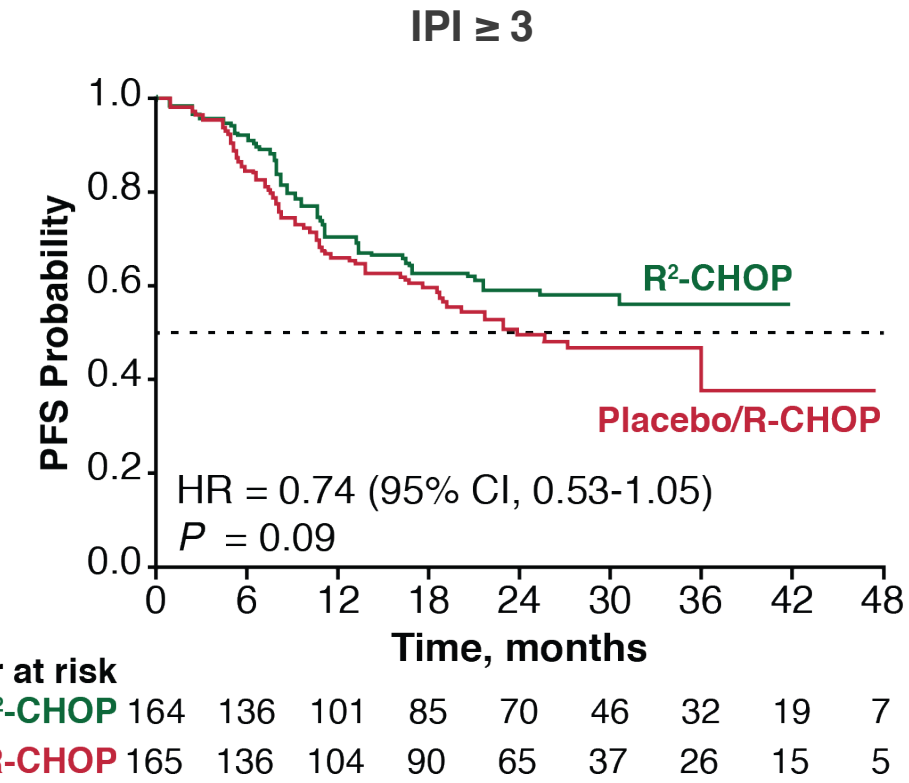

| | R2-CHOP | Placebo-R-CHOP | Hazard Ratio (95% CI) |
|---|---|---|---|
| Overall | 81/285 | 98/285 | 0.846 ( 0.631 - 1.136) |
| Baseline IPI Score: = 2 | 25/121 | 22/120 | 1.197 ( 0.675 - 2.124) |
| Baseline IPI Score: >= 3 | 56/164 | 76/165 | 0.743 ( 0.526 - 1.049) |
| Presence of Bulky Disease: Bulky (>=7.0cm) | 36/97 | 35/99 | 1.235 ( 0.775 - 1.967) |
| Presence of Bulky Disease: Non-bulky (<7.0cm) | 45/188 | 63/186 | 0.680 ( 0.464 - 0.997) |
| Age: <65 | 35/138 | 44/137 | 0.820 ( 0.526 - 1.278) |
| Age: >=65 | 46/147 | 54/148 | 0.859 ( 0.580 - 1.273) |
| Baseline CrCl: >= 30 to < 60 | 10/41 | 19/39 | 0.435 ( 0.202 - 0.937) |
| Baseline CrCl: >= 60 | 71/244 | 79/245 | 0.943 ( 0.684 - 1.299) |
| Total Lenalidomide/Placebo: < 75% Planned Dose | 27/82 | 21/49 | 0.716 ( 0.405 - 1.267) |
| Total Lenalidomide/Placebo: >= 75% Planned Dose | 53/200 | 77/234 | 0.806 ( 0.568 - 1.144) |
| Sex: Female | 33/121 | 52/142 | 0.724 ( 0.468 - 1.119) |
| Sex: Male | 48/164 | 46/143 | 0.976 ( 0.651 - 1.462) |
| Pre-phase Steroid: No | 40/156 | 48/152 | 0.821 ( 0.539 - 1.249) |
| Pre-phase Steroid: Yes | 41/129 | 50/132 | 0.881 ( 0.583 - 1.332) |
| DLBCL Stage at Diagnosis: II | 8/37 | 4/32 | 1.775 ( 0.534 - 5.897) |
| DLBCL Stage at Diagnosis: III | 24/80 | 31/98 | 0.944 ( 0.554 - 1.608) |
| DLBCL Stage at Diagnosis: IV | 49/168 | 63/154 | 0.742 ( 0.511 - 1.078) |
| Time from Diagnosis to Treatment: <= 31 days | 48/146 | 50/146 | 1.002 ( 0.675 - 1.490) |
| Time from Diagnosis to Treatment: > 31 days | 33/139 | 48/139 | 0.696 ( 0.447 - 1.084) |
| Asian: No | 52/184 | 66/196 | 0.866 ( 0.602 - 1.246) |
| Asian: Yes | 29/101 | 32/89 | 0.800 ( 0.484 - 1.322) |

Data cut-off 15Mar2019.

# PFS Based on International Prognostic Index Score (ITT)




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R²-CHOP | 121 | 100 | 91 | 84 | 73 | 48 | 25 | 13 | 3 |
| Placebo/R-CHOP | 120 | 104 | 95 | 91 | 81 | 53 | 29 | 13 | 5 |



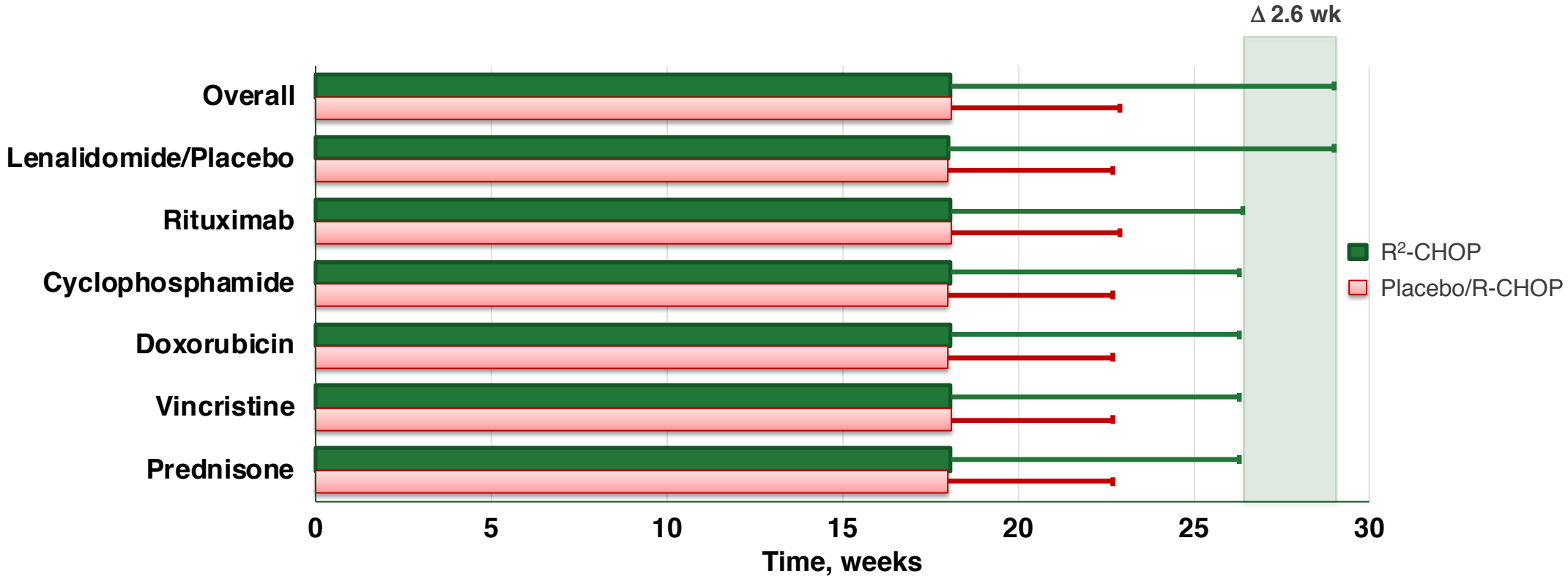

| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| R²-CHOP | 164 | 136 | 101 | 85 | 70 | 46 | 32 | 19 | 7 |
| Placebo/R-CHOP | 165 | 136 | 104 | 90 | 65 | 37 | 26 | 15 | 5 |

- Positive trends for PFS favoring R²-CHOP over placebo/R-CHOP were observed in patients with IPI score ≥ 3

Data cut-off 15Mar2019.

*Note: ongoing analyses of additional dose intensity data*

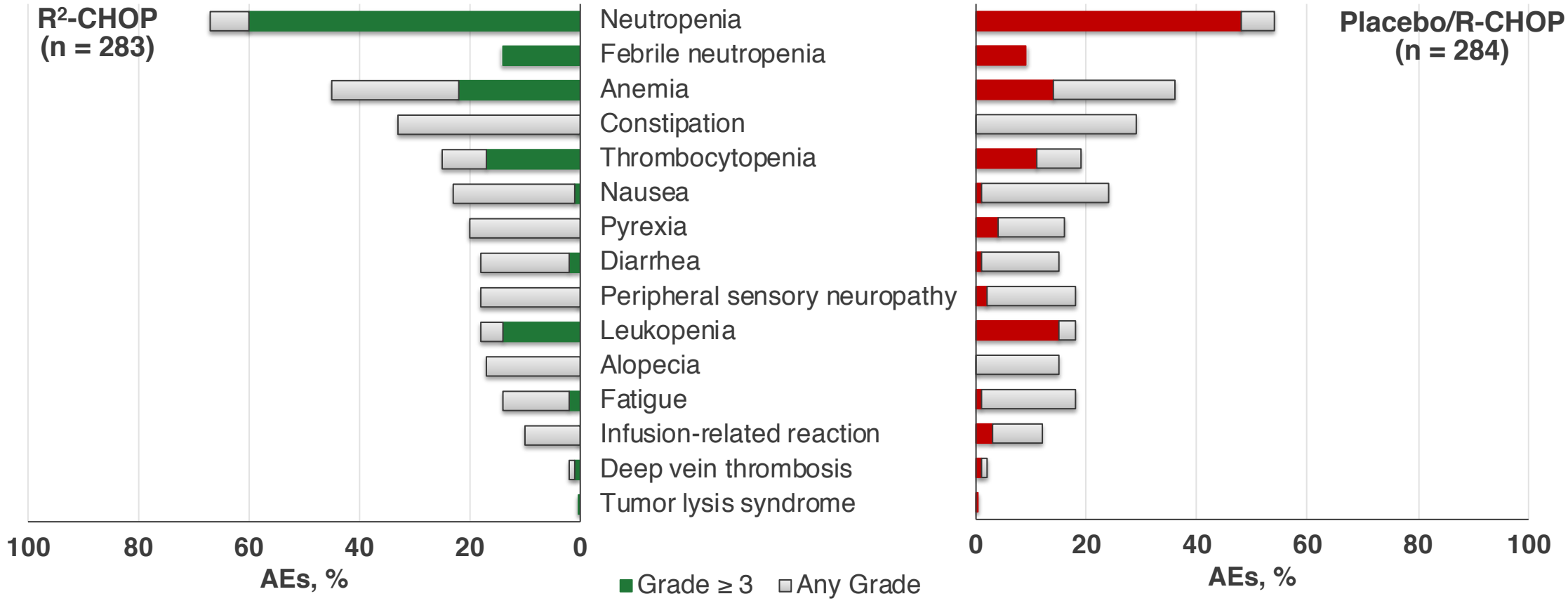
# Treatment Duration and Completion




- Overall, treatment in both arms was given for a median of 18.1 weeks (range, 0.3-29.0)
- The lenalidomide/placebo component added 2.6 wk to the overall treatment duration for R²-CHOP
- 74% R²-CHOP and 84% R-CHOP patients completed 6 cycles of both lenalidomide/placebo and R-CHOP
- > 80% of patients in both arms received a relative dose intensity of > 90% lenalidomide/placebo

Data cut-off 15Mar2019.

# Any Grade (≥ 15%) and Grade ≥ 3 TEAEs (Safety Population)



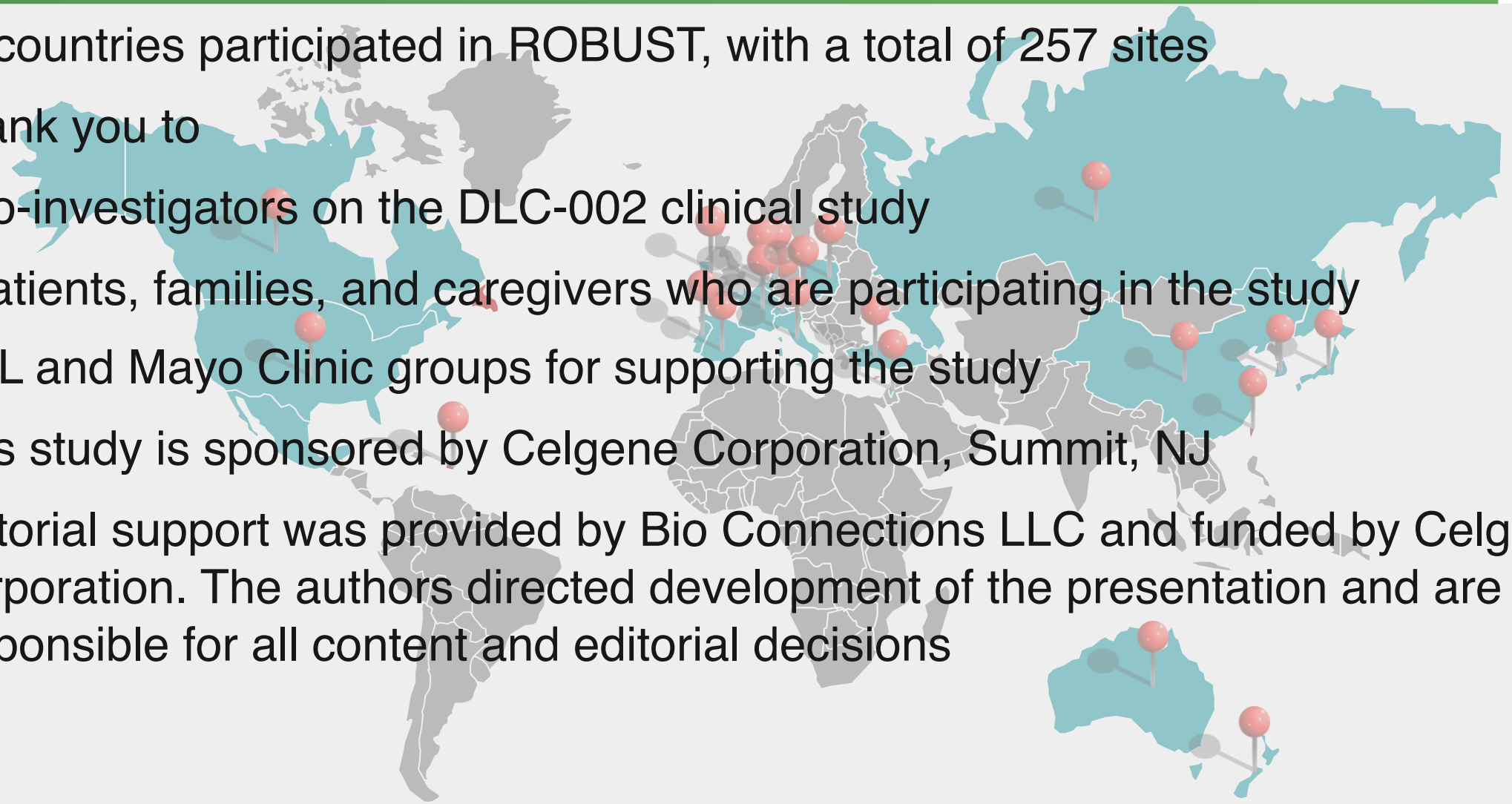

- 78% R²-CHOP and 71% Placebo/R-CHOP patients had at least one grade ≥ 3 AE; the most common were hematologic
- Compliance to prophylactic growth factor usage was > 89% through all 6 cycles
- SPMs were observed in 11 (4%) R²-CHOP and 9 (3%) Placebo/R-CHOP patients

Data cut-off 15Mar2019. Table includes AEs of interest IRR, deep vein thrombosis, and TLS; there were no incidences of TFR in either arm.

# Conclusions

- ROBUST did not meet the PFS primary or secondary endpoints for $R^2$-CHOP vs placebo/R-CHOP in previously untreated patients with ABC-DLBCL
- Positive trends for PFS favoring $R^2$-CHOP were observed in patients with higher risk IPI ≥ 3
- The safety profile of $R^2$-CHOP was consistent with those of the individual medicines, and no new safety signals were identified for lenalidomide or with the combination
- Preclinical data with next generation immunomodulatory agents (CELMoDs) suggest a positive mechanism-based outlook for improving therapies in first-line DLBCL
- Ongoing and future ROBUST analyses are underway, including evaluation of pharmacokinetics/dosing, molecular classification, and mutational status

# Thank You



- 21 countries participated in ROBUST, with a total of 257 sites
- Thank you to
  - Co-investigators on the DLC-002 clinical study
  - Patients, families, and caregivers who are participating in the study
  - FIL and Mayo Clinic groups for supporting the study
- This study is sponsored by Celgene Corporation, Summit, NJ
- Editorial support was provided by Bio Connections LLC and funded by Celgene Corporation. The authors directed development of the presentation and are fully responsible for all content and editorial decisions