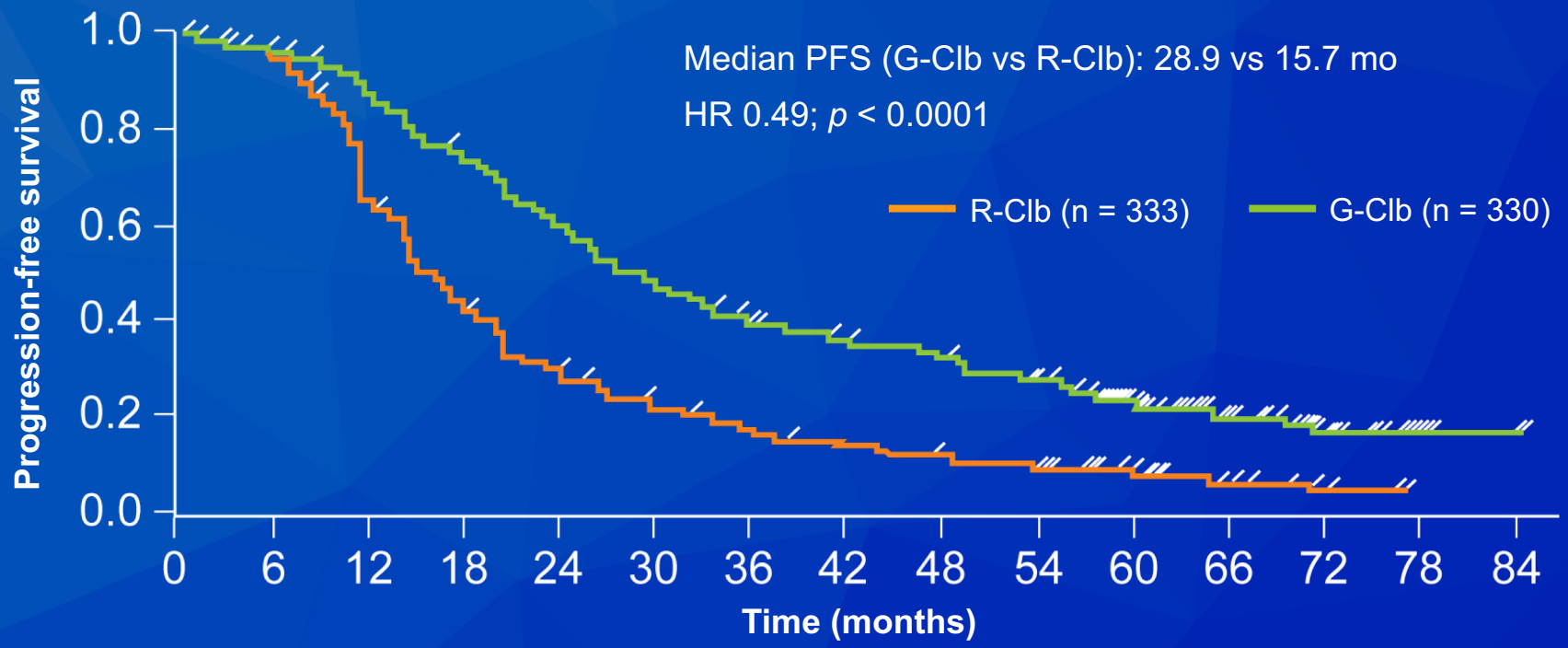
Overall Survival Benefit of Obinutuzumab Over Rituximab when Combined with Chlorambucil in Patients with Chronic Lymphocytic Leukemia and Comorbidities: Final Survival Analysis of the CLL11 Study

Goede V et al.
Proc EHA 2018;Abstract S151.

CLL11: Final Data Analysis

- After median follow-up time of 59.4 months, G-Clb demonstrated a significant improvement in PFS compared to R-Clb



- G-Clb also demonstrated a clinically meaningful improvement in OS compared to R-Clb (median OS: not reached vs 73.1 mo, $p = 0.0245$)
- After median follow-up of 62.5 months, G-Clb demonstrated improvements in PFS and OS compared to Clb alone
- No new safety signals were identified

Goede V et al. *Proc EHA* 2018;Abstract S151.

Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results from the Phase 1/2 ACE-CL-001 Study

Byrd JC et al.
Proc ASH 2017;Abstract 498.

ACE-CL-001: Efficacy of Acalabrutinib in R/R CLL/SLL

	Acalabrutinib (n = 134)
Overall response rate	85%
CR	2%
PR	83%
18-month duration of response rate	85%
18-month PFS	88%

ORR including PR-L = 93%

Byrd JC et al. *Proc ASH* 2017;Abstract 498.

ACE-CL-001: Tolerability of Acalabrutinib in R/R CLL/SLL

Adverse event, any grade	Acalabrutinib (n = 134)
Headache	46%
Diarrhea	43%
Upper respiratory tract infection	28%
Fatigue	27%
Nausea	27%
Arthralgia	23%
Pyrexia	23%
Contusion	22%
Hypertension	11%
Atrial fibrillation	3%

Byrd JC et al. *Proc ASH* 2017;Abstract 498.

blood

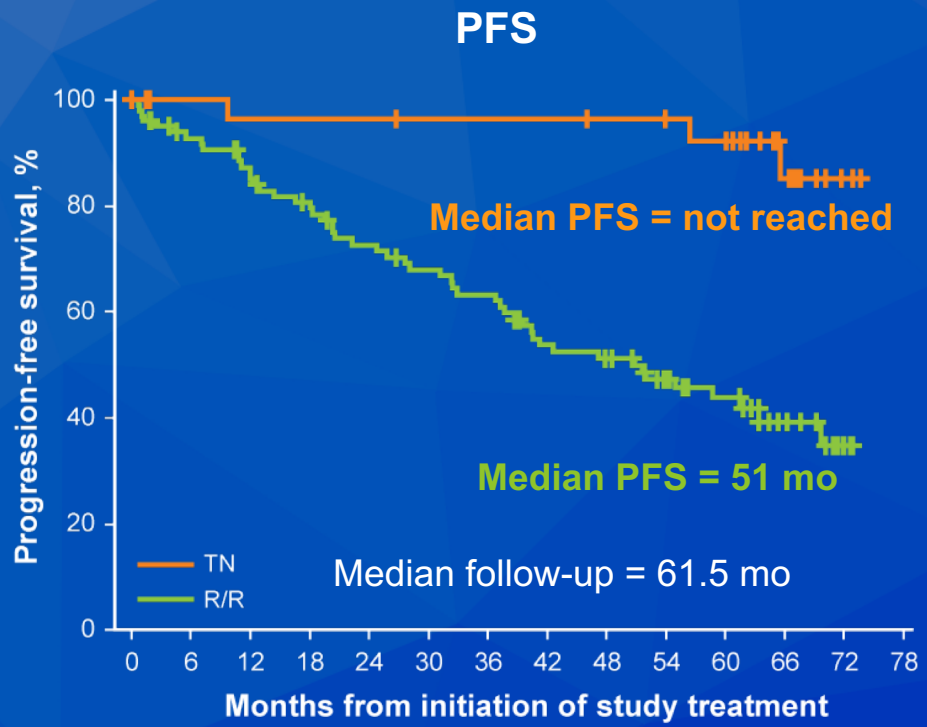
CLINICAL TRIALS AND OBSERVATIONS

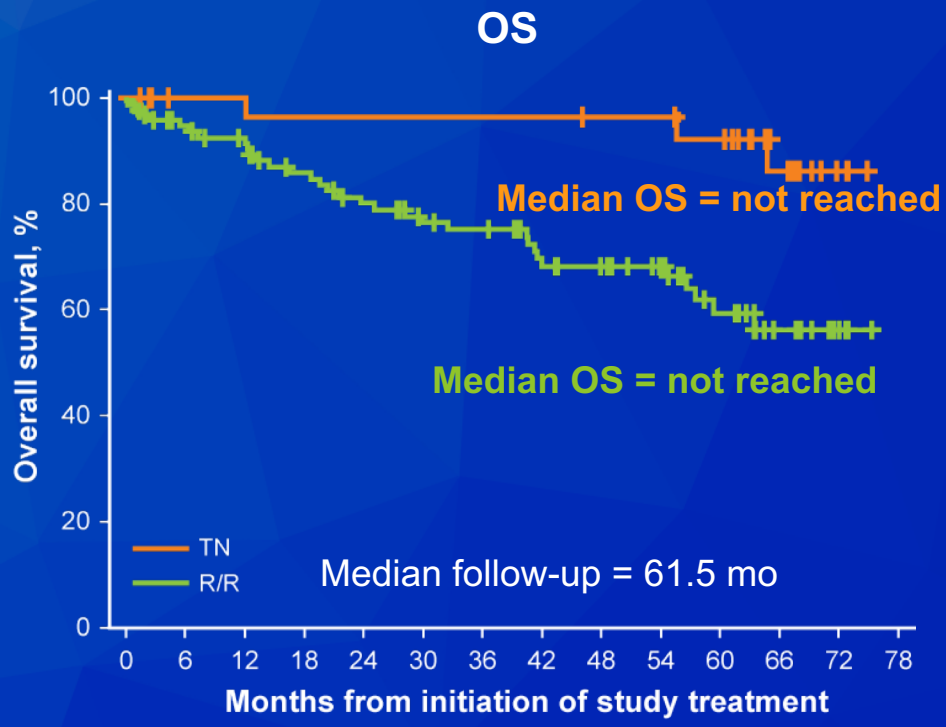
Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience

Susan O'Brien,[1,2] Richard R. Furman,[3] Steven Coutre,[4] Ian W. Flinn,[5] Jan A. Burger,[1] Kristie Blum,[6] Jeff Sharman,[7] William Wierda,[1] Jeffrey Jones,[6] Weiqiang Zhao,[6] Nyla A. Heerema,[6] Amy J. Johnson,[6] Ying Luan,[8] Danelle F. James,[8] Alvina D. Chu,[8] and John C. Byrd[6]

Blood 2018;131(17):1910-19.

Single-Agent Ibrutinib for Treatment-Naïve (TN) and R/R CLL – PFS and OS

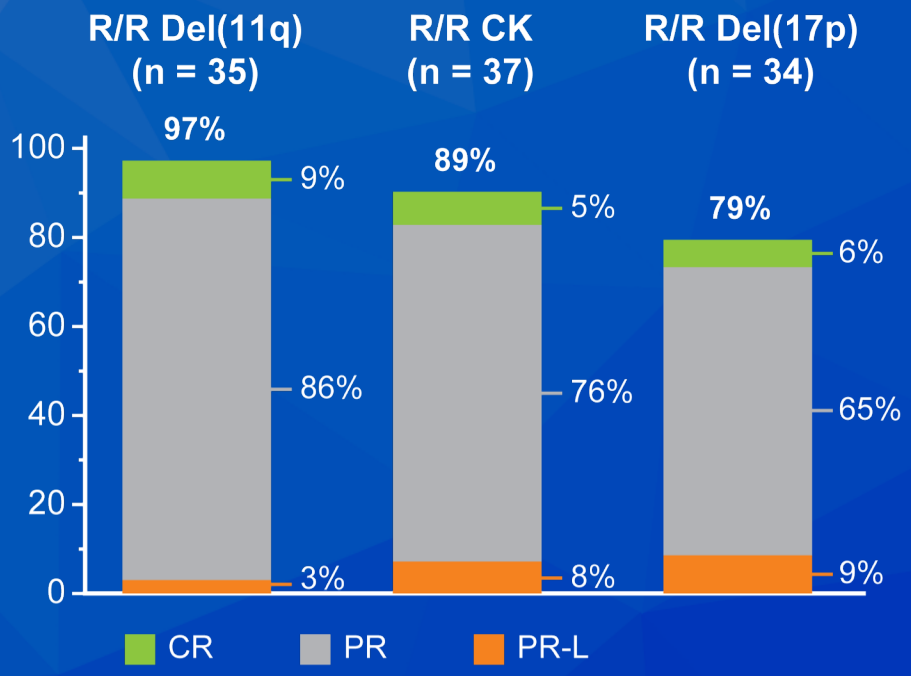


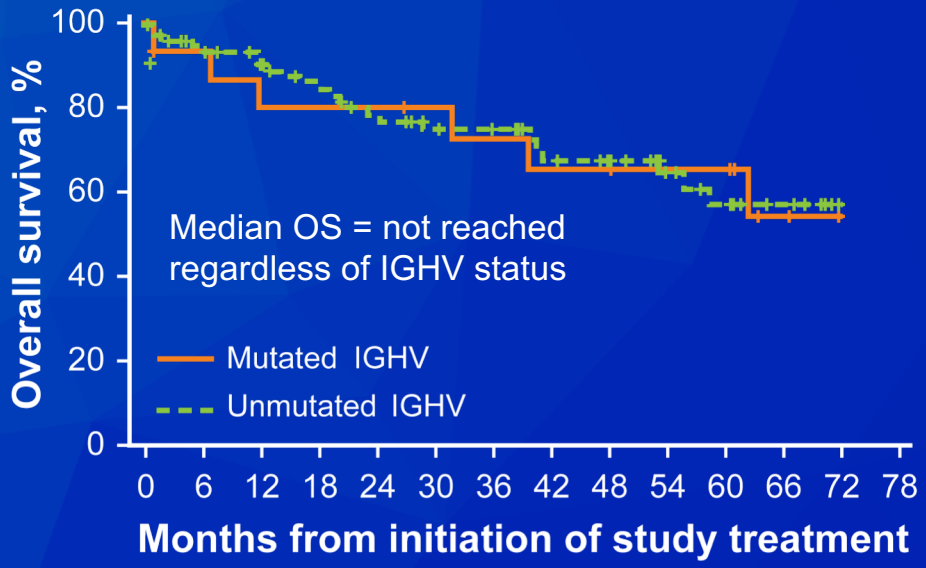


	TN (n = 31)	R/R (n = 101)
5-year PFS	92%	44%
5-year OS	92%	60%

O'Brien S et al. *Blood* 2018;131(17):1910-19.

Single-Agent Ibrutinib for R/R and Untreated CLL – Efficacy in High-Risk Subgroups





PR-L = PR with lymphocytosis; CK = complex karyotype

O'Brien S et al. *Blood* 2018;131(17):1910-19.

Phase II, Multicenter Trial Exploring "Chemo-Sparing" Strategy Associating Obinutuzumab + Ibrutinib Followed by a MRD Driven Strategy, in Previously Untreated Symptomatic Medically Fit Chronic Lymphocytic Leukemia Patients (CLL): Preliminary Results of the Induction Phase of the Icll-07 Filo Study

Michallet AS et al.
Proc ASH 2017;Abstract 497.

Obinutuzumab in Combination with Ibrutinib for Newly Diagnosed CLL: Response at 9 Months

	Obinutuzumab/ ibrutinib (n = 73)
Overall response rate	100%
CR	37%
PR	63%
MRD-positive in bone marrow	86%

- Of the 63 patients with MRD-positive disease in the bone marrow, 22 were in CR and 41 were in PR

Michallet AS et al. *Proc ASH* 2017;Abstract 497.

Obinutuzumab in Combination with Ibrutinib for Newly Diagnosed CLL: Tolerability

Select adverse events	Obinutuzumab/ ibrutinib (n = 135)
Infusion-related reactions	69.5%
Digestive toxicity	33.6%
Thrombocytopenia	30.8%
Anemia	6%

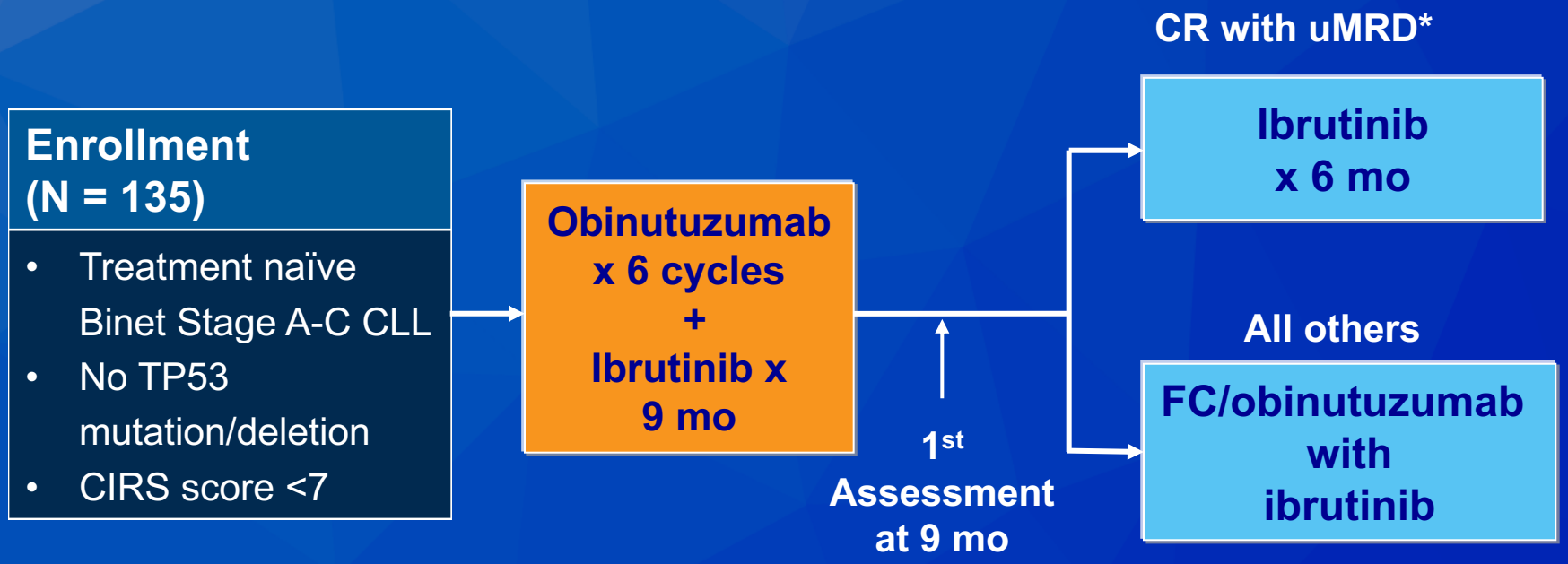
- Serious treatment-related AEs (n = 24) included
  - Tumor lysis syndrome (n = 3)
  - Hypertension (n = 1)
  - Atrial fibrillation (n = 2)
  - Atrial flutter (n = 2)
  - Neutropenia (n = 2)
  - Febrile neutropenia (n = 3)

Michallet AS et al. *Proc ASH* 2017;Abstract 497.

High Rate of Complete Response but Minimal Residual Disease Still Detectable After First-Line Treatment Combining Obinutuzumab and Ibrutinib in Chronic Lymphocytic Leukemia (CLL): ICLL07 FILO Trial

Michallet AS et al.
Proc EHA 2018;Abstract S804.

ICLL07 FILO: Phase II Study of First-Line Obinutuzumab with Ibrutinib in CLL



F/C = Fludarabine/cyclophosphamide

*uMRD = $<10^{-4}$ by 8-color cytometry

Primary objective: To obtain 30% CR (by IWCLL 2008 guidelines) with uMRD in the bone marrow at month 16

Michallet AS et al. *Proc EHA* 2018;Abstract S804.

ICLL07 FILO: Results Summary

- At month 9, 92% of patients had received the 8 planned obinutuzumab infusions

Response evaluation at month 9	Obinutuzumab + ibrutinib (N = 123)
ORR	100%
CR	41%
uMRD in peripheral blood and bone marrow*	12.5%

* Includes 9 patients in CR and 7 in PR

- Infusion-related reactions occurred only on cycle 1, day 1, in 69.5% of patients (8% Grade 3)
- Digestive toxicity (nausea, vomiting and diarrhea) occurred in 35% of patients (Grades 1 and 2), but only during cycle 1

Michallet AS et al. *Proc EHA* 2018;Abstract S804.

Phase III iLLUMINATE Trial of Ibrutinib and Obinutuzumab as First-Line Therapy for Patients with CLL
Press Release: May 24, 2018

The Phase 3 iLLUMINATE (PCYC-1130) trial met its primary endpoint of improvement in PFS. The study evaluated ibrutinib in combination with obinutuzumab for previously untreated CLL or small lymphocytic lymphoma (SLL), the most common adult leukemia types. Specifically, the study met its primary endpoint for a clinically and statistically significant difference in PFS for patients who received ibrutinib and obinutuzumab versus those who received chlorambucil and obinutuzumab.

https://www.prnewswire.com/news-releases/imbruvica-ibrutinib-plus-gazyva-obinutuzumab-phase-3-illuminate-trial-for-first-line-therapy-of-chronic-lymphocytic-leukemia-cll-patients-met-primary-endpoint-300654339.html

A Multicenter, Phase II Study of Ibrutinib plus FCR (iFCR) as Frontline Therapy for Younger CLL Patients

Davids MS et al.
Proc ASH 2017;Abstract 496.

Ibrutinib in Combination with FCR for Newly Diagnosed CLL: Efficacy

	Ibrutinib + FCR (n = 35)
Overall response rate	100%
CR/CRi	63%
PR	37%
Patients with MRD negativity in bone marrow 2 months after completing FCR	37%
Patients with MRD negativity in bone marrow during ibrutinib maintenance	57%

CRi = complete response with incomplete hematologic recovery.

Davids MS et al. *Proc ASH* 2017;Abstract 496.

Ibrutinib in Combination with FCR for Newly Diagnosed CLL: Tolerability

All-grade nonhematologic AEs	Ibrutinib + FCR (n = 35)
Nausea	71%
Bruising	43%
Rash	43%
Fatigue	37%
Diarrhea	26%
Grade 3/4 hematologic AEs	
Neutropenia	29%
Thrombocytopenia	26%
Anemia	6%

Davids MS et al. *Proc ASH* 2017;Abstract 496.

The NEW ENGLAND JOURNAL of MEDICINE

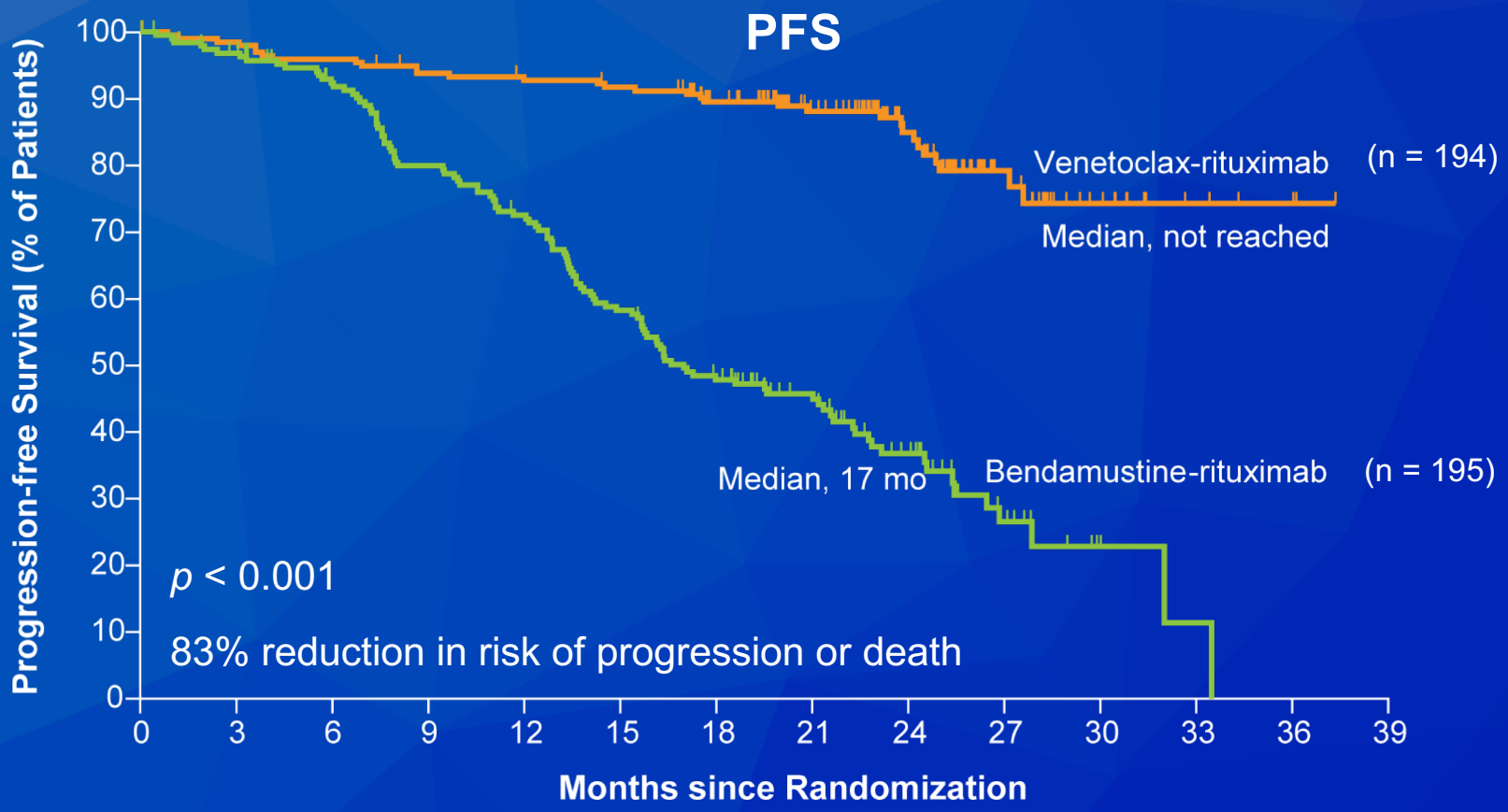
ORIGINAL ARTICLE

Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

J.F. Seymour, T.J. Kipps, B. Eichhorst, P. Hillmen, J. D'Rozario, S. Assouline, C. Owen, J. Gerecitano, T. Robak, J. De la Serna, U. Jaeger, G. Cartron, M. Montillo, R. Humerickhouse, E.A. Punnoose, Y. Li, M. Boyer, K. Humphrey, M. Mobasher, and A.P. Kater

N Engl J Med 2018;378(12):1107-20.

MURANO Trial: PFS and Response Results



Response by investigator assessment	Venetoclax/ rituximab (n = 194)	Bendamustine/ rituximab (n = 195)
Overall response rate	93.3%	67.7%
CR/CRi	26.8%	8.2%

Seymour JF et al. *N Engl J Med* 2018;378(12):1107-20.

MURANO: Subgroup Analysis of PFS by Investigator Assessment

Subgroup	Total No.	Venetoclax-Rituximab Group		Bendamustine-Rituximab Group		Hazard Ratio
		no.	median (mo)	no.	median (mo)	
All patients	389	194	NR	195	17.0	0.17
Age						
<65 yr	186	97	NR	89	15.4	0.11
≥65 yr	203	97	NR	106	21.7	0.24
CLL risk status						
Low	178	90	NR	88	21.6	0.14
High	211	104	NR	107	15.4	0.19
No. of previous therapies						
1	228	111	NR	117	16.6	0.14
2	100	57	NR	43	21.2	0.24
≥3	61	26	NR	35	10.5	0.24
Effect of most recent therapy						
CLL refractory to therapy	59	30	NR	29	13.6	0.32
Relapse of CLL	330	164	NR	166	18.6	0.14
Chromosome 17p deletion status						
Absent	250	127	NR	123	21.4	0.19
Present	92	46	NR	46	15.4	0.13
TP53 mutation status						
Unmutated	277	144	NR	133	21.2	0.15
Mutated	99	48	NR	51	12.9	0.19
Baseline IGHV mutation status						
Unmutated	246	123	NR	123	15.7	0.16
Mutated	104	53	NR	51	22.9	0.11

NR = not reached

Seymour JF et al. *N Engl J Med* 2018;378(12):1107-20.

MURANO: Tolerability

	Venetoclax/ rituximab (n = 194)	Bendamustine/ rituximab (n = 188)
Grade 3/4 AE	82%	70.2%
Neutropenia	57.7%	38.8%
Infections and infestations	17.5%	21.8%
Anemia	10.8%	13.8%
Thrombocytopenia	5.7%	10.1%
Febrile neutropenia	3.6%	9.6%
Pneumonia	5.2%	8.0%
Infusion-related reaction	1.5%	5.3%
Tumor lysis syndrome	3.1%	1.1%

Seymour JF et al. *N Engl J Med* 2018;378(12):1107-20.

JOURNAL OF CLINICAL ONCOLOGY

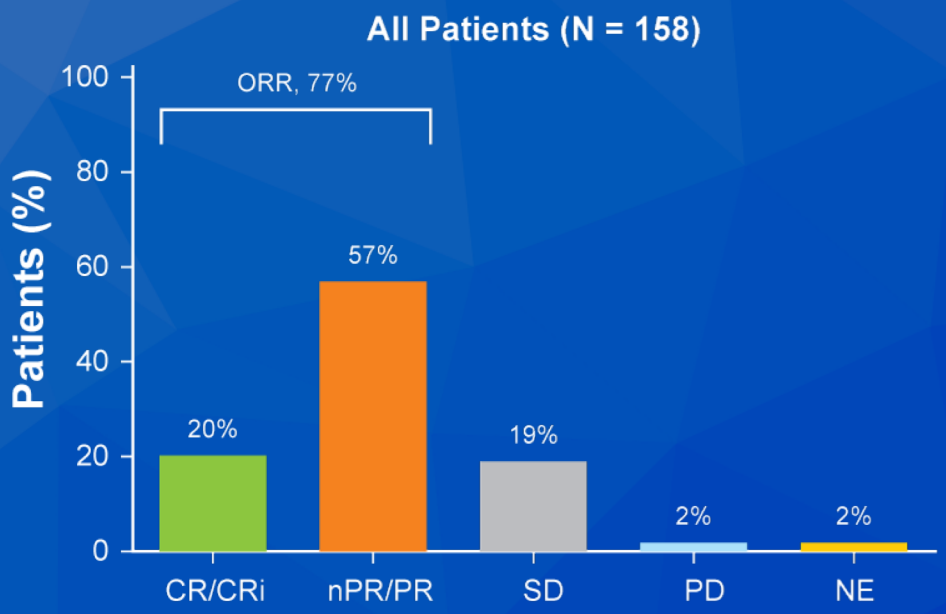
ORIGINAL REPORT

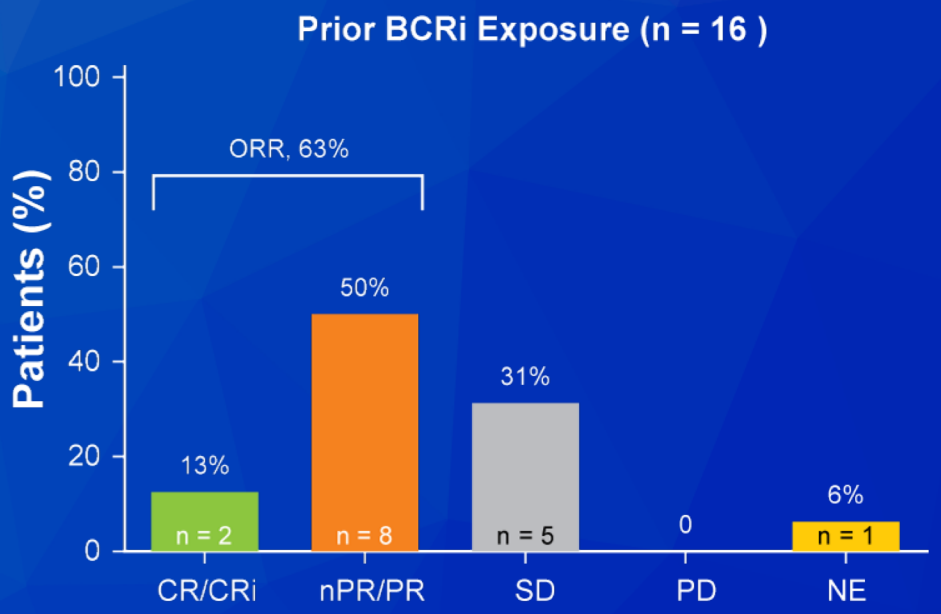
Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial

Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Peter Hillmen, John F. Seymour, Steven Coutre, Wojciech Jurczak, Stephen P. Mulligan, Anna Schuh, Sarit Assouline, Clemens-Martin Wendtner, Andrew W. Roberts, Matthew S. Davids, Johannes Bloehdorn, Talha Munir, Sebastian Böttcher, Lang Zhou, Ahmed Hamed Salem, Monali Desai, Brenda Chyla, Jennifer Arzt, Su Young Kim, Maria Verdugo, Gary Gordon, Michael Hallek, and William G. Wierda

J Clin Oncol 2018;36(19):1973-80.

Venetoclax for CLL with Del(17p) – Efficacy





BCRi = B-cell receptor inhibitor; nPR = nodular PR; PD = disease progression; NE = not evaluated for response

	Venetoclax (n = 158)
2-year PFS	54%
2-year OS	73%

Stilgenbauer S et al. *J Clin Oncol* 2018;36(19):1973-80.

Venetoclax for CLL with Del(17p) – Tolerability

Adverse event	All patients (N = 158)
Any grade AE	98%
Neutropenia	42%
Diarrhea	39%
Nausea	37%
Anemia	25%
Fatigue	23%
Thrombocytopenia	20%
Grade 3 or 4 AE	75%
Neutropenia	40%
Thrombocytopenia	15%
Anemia	15%

Stilgenbauer S et al. *J Clin Oncol* 2018;36(19):1973-80.

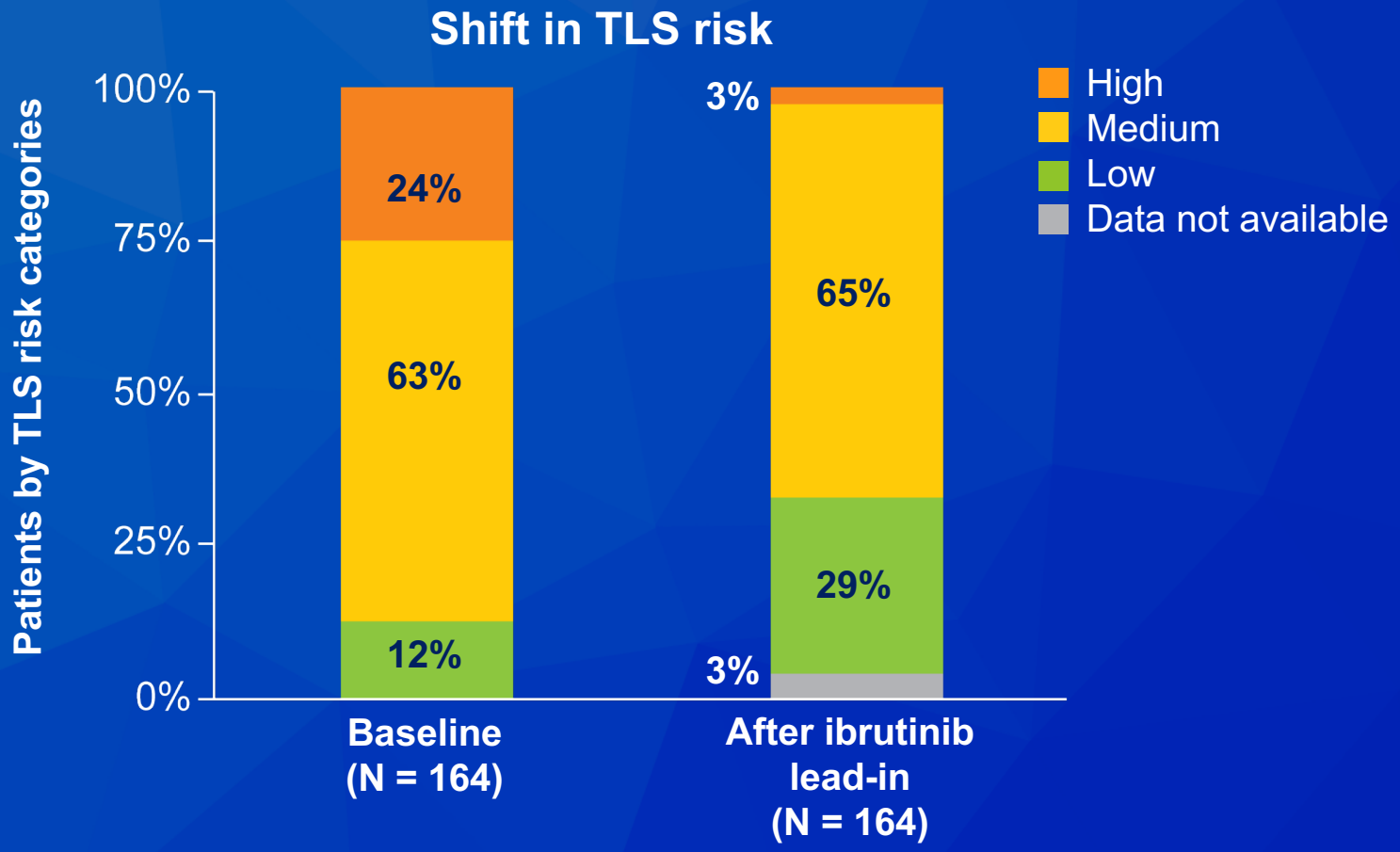
Phase 2 CAPTIVATE Results of Ibrutinib (Ibr) plus Venetoclax (Ven) in First-Line Chronic Lymphocytic Leukemia (CLL)

Combined Venetoclax and Ibrutinib for Patients with Previously Untreated High-Risk CLL, and Relapsed/Refractory CLL: A Phase II Trial

Wierda WG et al.
Proc ASCO 2018;Abstract 7502.

Jain N et al.
Proc ASH 2017;Abstract 429.

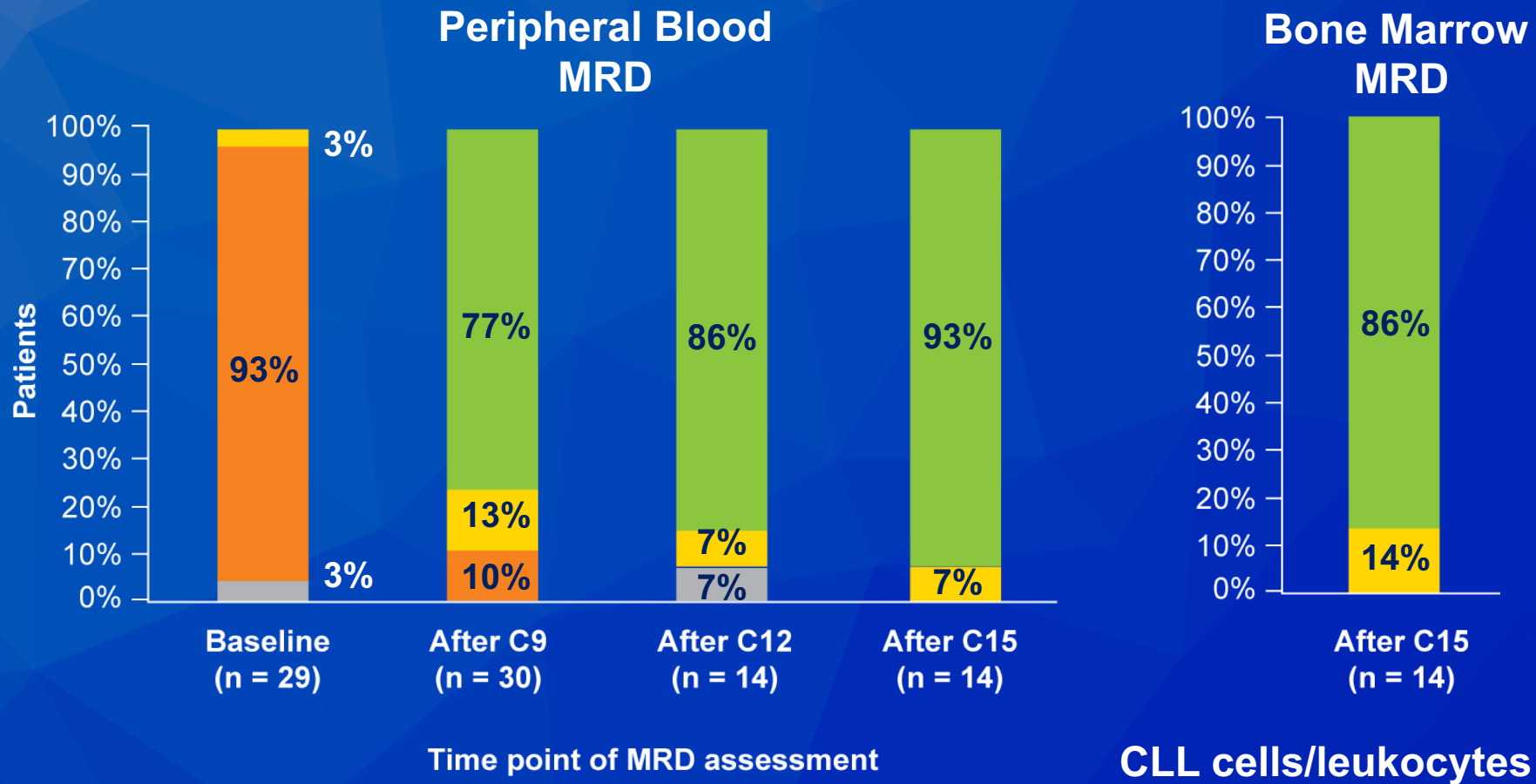
CAPTIVATE: Ibrutinib/Venetoclax – Reduction in Tumor Lysis Syndrome (TLS) Risk



- Patients received 3 cycles of ibrutinib 420 mg/day lead-in before beginning venetoclax ramp-up to 400 mg/day

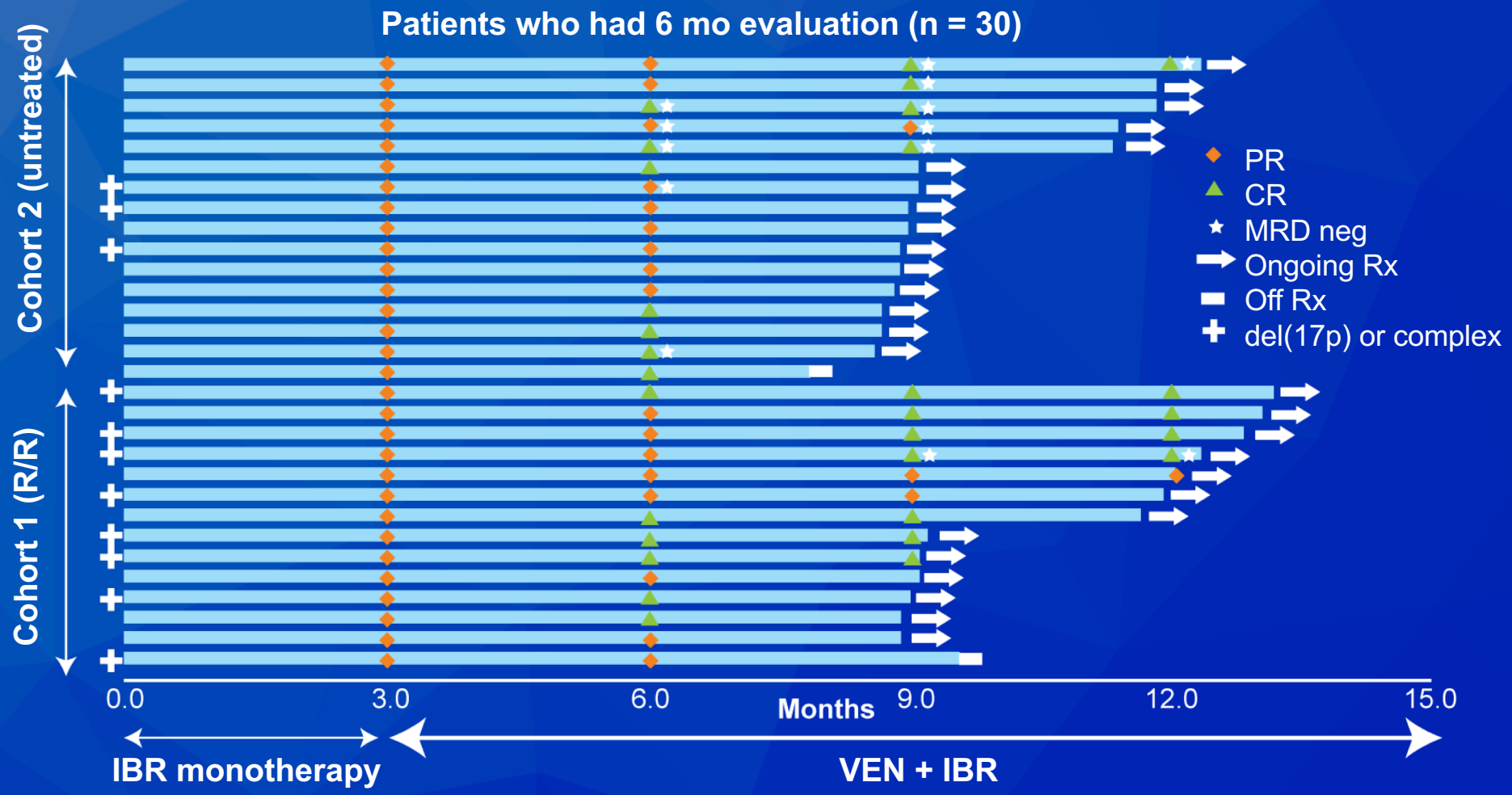
Wierda WG et al. *Proc ASCO* 2018;Abstract 7502.

CAPTIVATE: Ibrutinib/Venetoclax – MRD Response Over Time



Wierda WG et al. *Proc ASCO* 2018;Abstract 7502.

Ibrutinib/Venetoclax in R/R or Untreated CLL: Duration of Response and Safety



- The most common reason for dose reduction was neutropenia
- 8 pts developed atrial fibrillation; no pt experienced clinical TLS

Jain N et al. *Proc ASH* 2017;Abstract 429.

Safety, Efficacy and MRD Negativity of a Combination of Venetoclax and Obinutuzumab in Patients with Previously Untreated Chronic Lymphocytic Leukemia — Results from a Phase 1b Study (GP28331)

Flinn IW et al.
Proc ASH 2017;Abstract 430.

First-Line Venetoclax in Combination with Obinutuzumab in CLL: Efficacy

	Venetoclax/ obinutuzumab (n = 32)
Overall response rate	100%
CR/CRi	56.3%
PR	43.8%
Patients with MRD negativity in peripheral blood	100%
Patients with MRD negativity in bone marrow	62.5%

Flinn IW et al. *Proc ASH* 2017;Abstract 430.

First-Line Venetoclax in Combination with Obinutuzumab in CLL: Tolerability

Grade 3-4 AEs	Venetoclax/ obinutuzumab (n = 32)
Neutropenia	40.6%
Febrile neutropenia	12.5%
Thrombocytopenia	12.5%
Anemia	9.4%

Flinn IW et al. *Proc ASH* 2017;Abstract 430.

Initial Results of the Phase 2 Treatment Naive Cohort in a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in Chronic Lymphocytic Leukemia

Rogers KA et al.
Proc ASH 2017;Abstract 431.

First-Line Venetoclax in Combination with Obinutuzumab and Ibrutinib: Efficacy

Response after cycle 8	Venetoclax/ obinutuzumab/ ibrutinib (n = 24)
Overall response rate	96%
CR/CRi	50%
PR	46%
Patients with MRD-negative disease in blood and bone marrow	58%

Rogers KA et al. *Proc ASH* 2017;Abstract 431.

First-Line Venetoclax in Combination with Obinutuzumab and Ibrutinib: Tolerability

Grade 3/4 adverse events	(n = 25)
Thrombocytopenia	36%
Neutropenia	44%
Leukopenia	36%
Lymphopenia	32%
Hypertension	20%
Hyperuricemia	4%
Arthralgia	4%
AST increase	4%

Rogers KA et al. *Proc ASH* 2017;Abstract 431.

VOLUME 35 · NUMBER 26 · SEPTEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

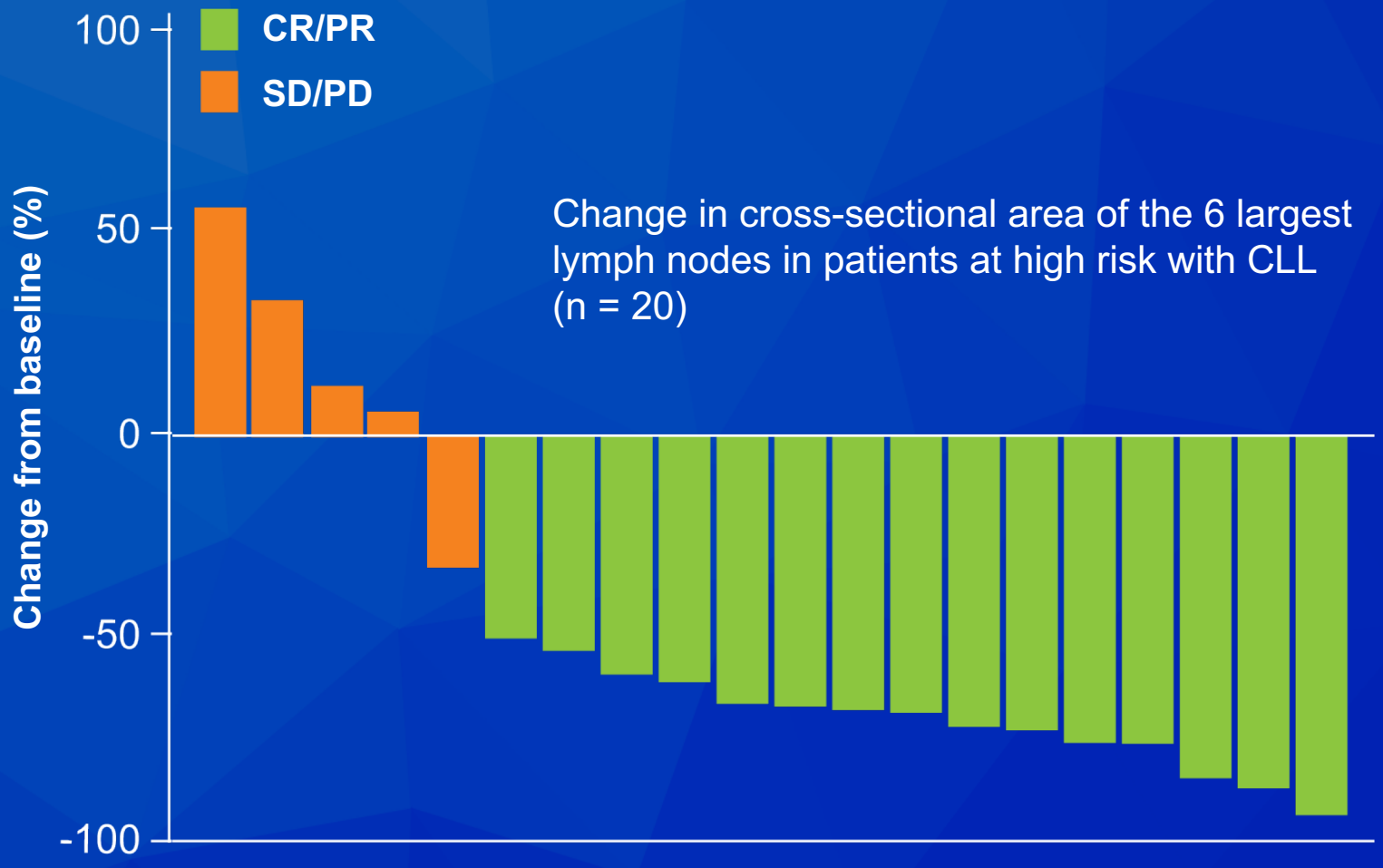
ORIGINAL REPORT

Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib

Cameron J. Turtle, Kevin A. Hay, Laïla-Aïcha Hanafi, Daniel Li, Sindhu Cherian, Xueyan Chen, Brent Wood, Arletta Lozanski, John C. Byrd, Shelly Heimfeld, Stanley R. Riddell, and David G. Maloney

J Clin Oncol 2017;35(26):3010-20.

Anti-CD19 CAR T-Cell Therapy After Ibrutinib Failure



Turtle CJ et al. *J Clin Oncol* 2017;35(26):3010-20.

Anti-CD19 CAR T-Cell Therapy After Ibrutinib – Toxicity

- 20/24 patients developed cytokine release syndrome (CRS)
  - Grade 1/2 (n = 18)
  - Grade 4 (n = 1)
  - Grade 5 (n = 1)
- 8/24 patients developed neurotoxicity
  - Grade 1/2 (n = 2)
  - Grade 3 (n = 5)
  - Grade 5 (n = 1)
- All patients who developed neurotoxicity also experienced CRS

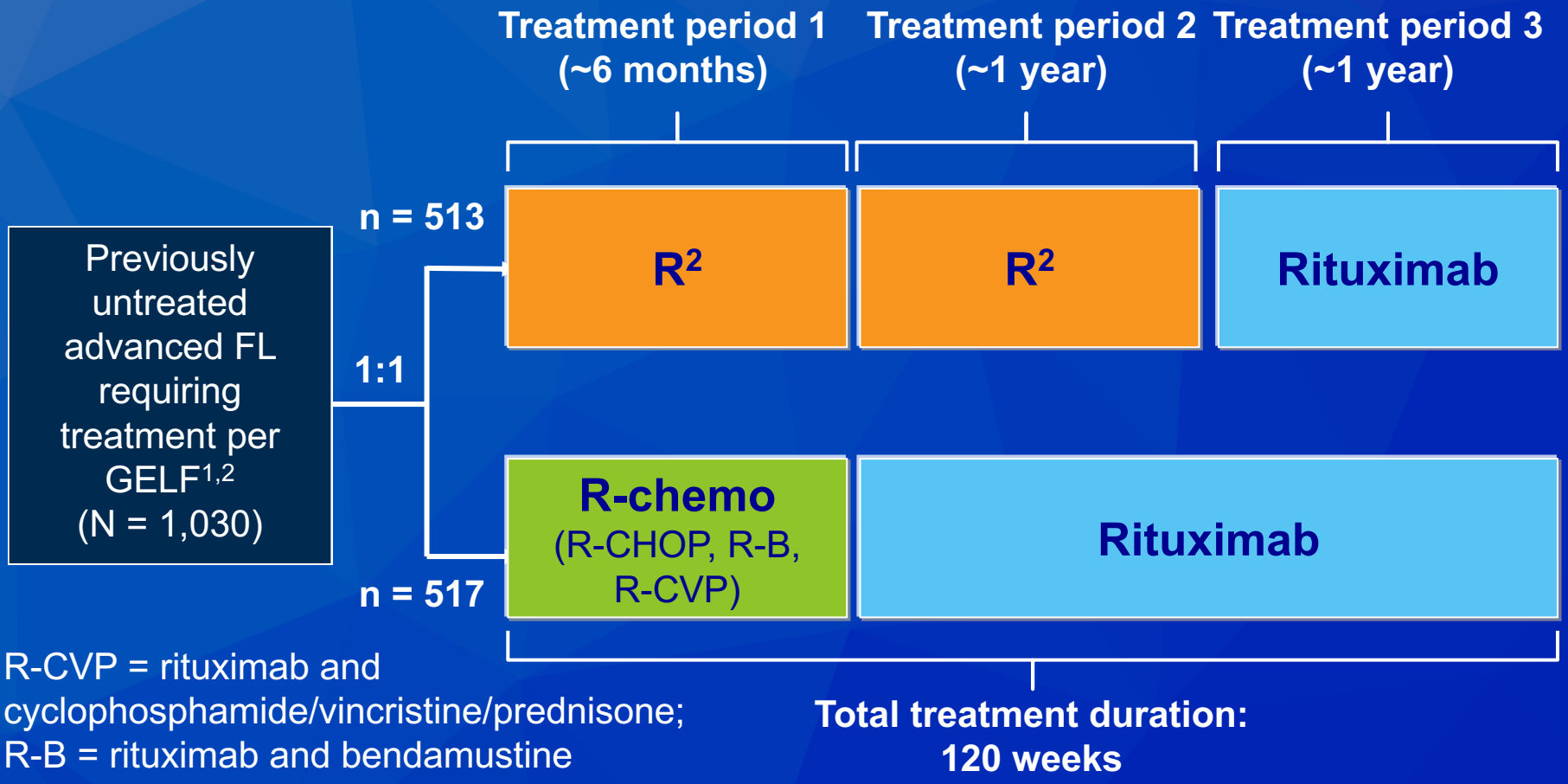
Turtle CJ et al. *J Clin Oncol* 2017;35(26):3010-20.

RELEVANCE: Phase III Randomized Study of Lenalidomide plus Rituximab (R^2) versus Chemotherapy plus Rituximab, followed by Rituximab Maintenance, in Patients with Previously Untreated Follicular Lymphoma

Fowler NH et al.

Proc ASCO 2018;Abstract 7500.

RELEVANCE: Phase III Trial Design



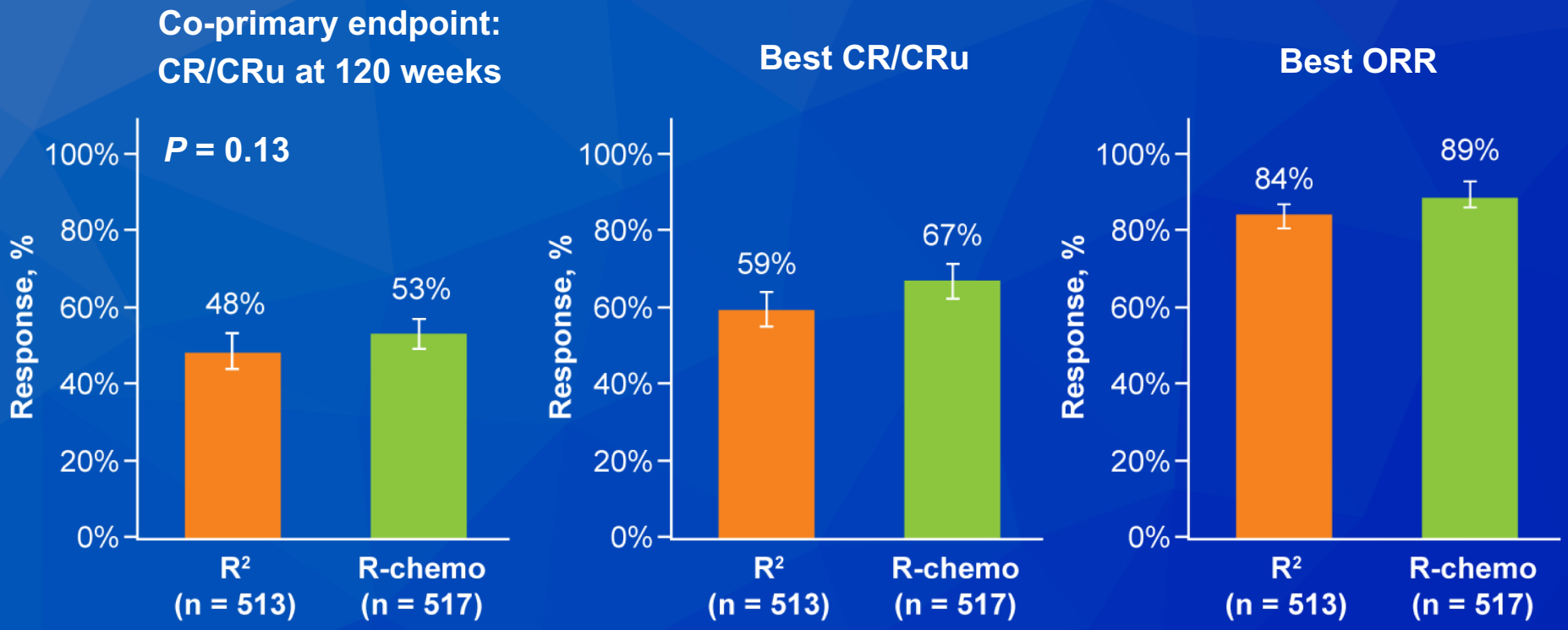
R-CVP = rituximab and cyclophosphamide/vincristine/prednisone;
R-B = rituximab and bendamustine

- **Primary endpoints: CR/CRu at 120 weeks and PFS**

[1] Salles et al. *Lancet* 2011;377:42-51;
[2] Brice et al. *J Clin Oncol* 1997;15:1110-7.

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

RELEVANCE: Survival and Response



- 3-y duration of response = 77% (R^2) vs 74% (R-Chemo)

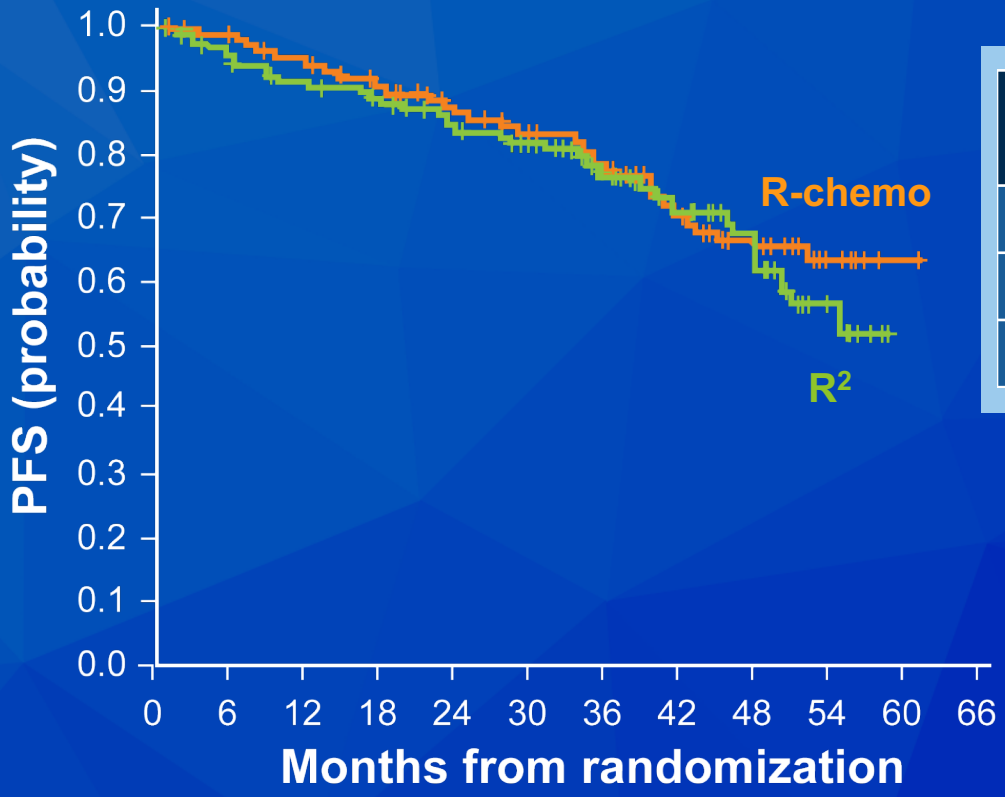
Co-primary endpoint (PFS): 3-year PFS	R^2 (n = 513)	R-Chemo (n = 517)	HR	*p*-value
By INV	77%	78%	0.94	0.63
By IRC	77%	78%	1.10	0.48

- 3-y OS (Immature in ITT) = 94% (R^2) vs 94% (R-Chemo); HR = 1.16

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

RELEVANCE: Interim PFS by Independent Review Committee

Co-primary endpoint: Interim PFS (~50% events)

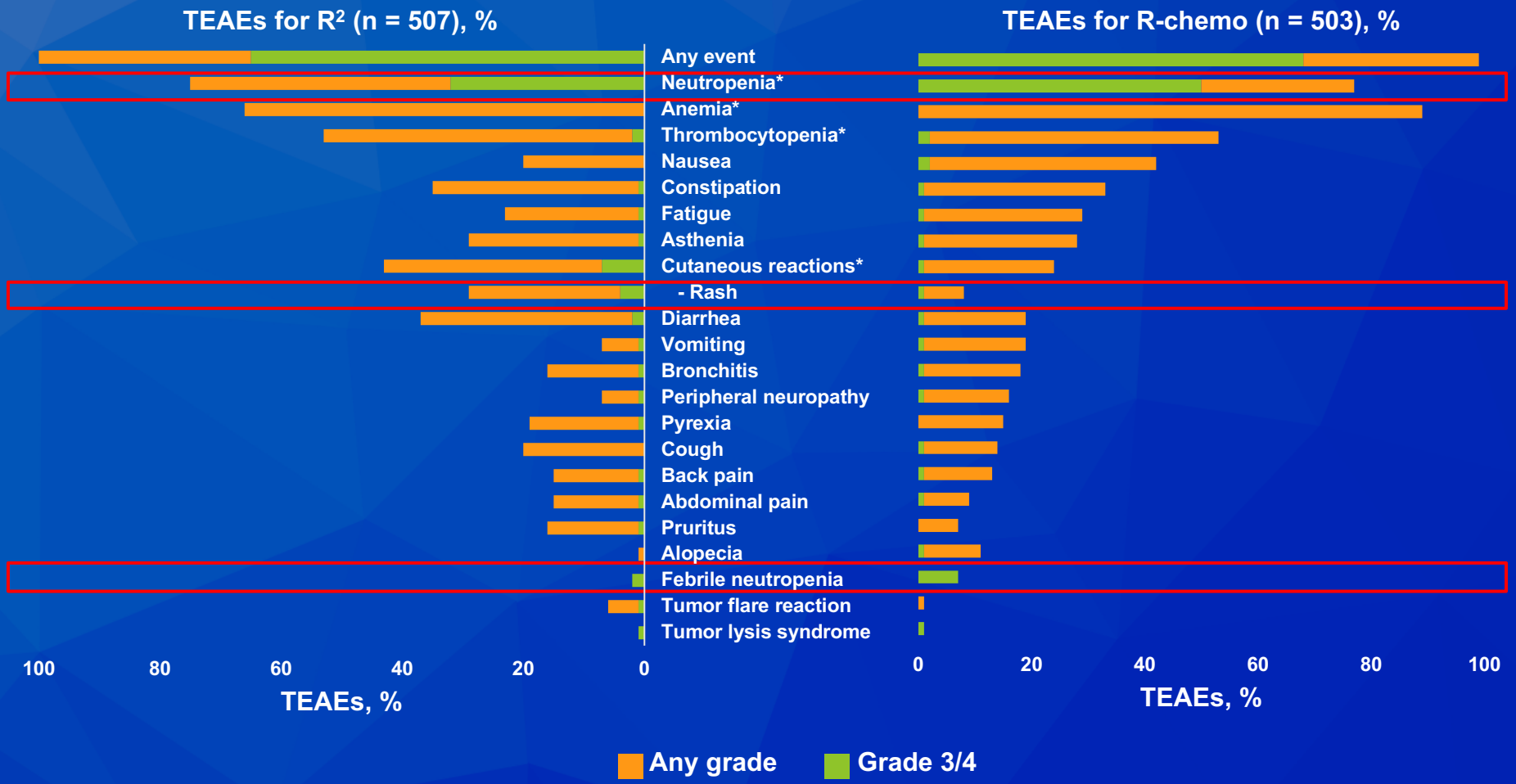


	R² (n = 513)	R-chemo (n = 517)
3-year PFS	77%	78%
HR	1.10	
p-value	0.48	

- At median follow-up of 37.9 mo, interim PFS was similar in both arms

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

RELEVANCE: Select Treatment-Emergent AEs (TEAEs)



* Hematologic AEs were based on laboratory tests; anemia AEs were Grade 1. Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders

Fowler NH et al. *Proc ASCO* 2018;Abstract 7500.

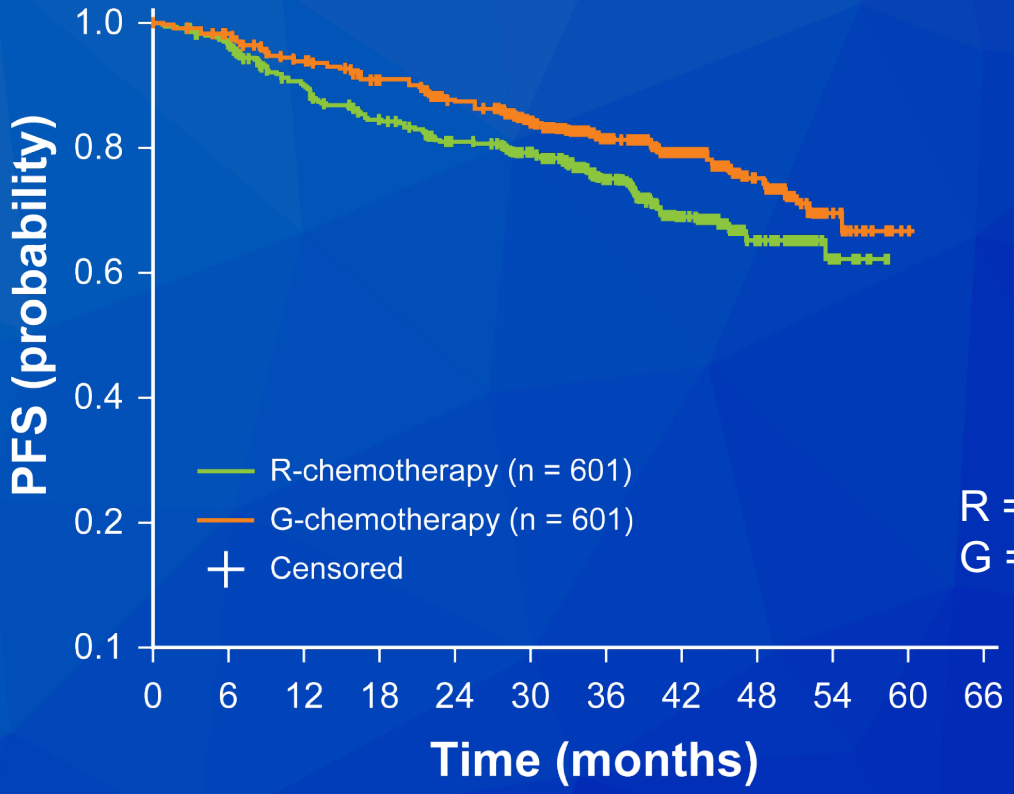
Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

Immunochemotherapy with Obinutuzumab or Rituximab for Previously Untreated Follicular Lymphoma in the GALLIUM Study: Influence of Chemotherapy on Efficacy and Safety

Marcus R et al.
N Engl J Med 2017;377(14):1331-44.

Hiddemann W et al.
J Clin Oncol 2018;36(23):2395-404.

GALLIUM: PFS (Investigator Assessed)



R = Rituximab
G = Obinutuzumab

Estimated 3-year PFS (median follow-up: 41.1 months)			
	G-chemo	R-chemo	HR, *p*-value
All patients (n = 601, 601)	82%	75%	0.68, *p* = 0.0016
CHOP (n = 196, 203)	81%	76%	0.72, *p* = 0.13
CVP (n = 60, 57)	71%	64%	0.79, *p* = 0.46
Bendamustine (n = 345, 341)	84%	76%	0.63, *p* = 0.0062

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

GALLIUM: Adverse Events (AEs) Summary

	G-chemo (n = 595)	R-chemo (n = 597)
Any AE	100%	98%
Grade 3-5 AEs	75%	69%
Neutropenia	45%	38%
Thrombocytopenia	6%	3%
Grade 3-5 AEs of special interest		
Infections	20%	16%
Second neoplasms	5%	4%

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

GALLIUM: Adverse Events by Chemotherapy Regimen

	Bendamustine (B)		CHOP		CVP	
	G + B (n = 338)	R + B (n = 338)	G + CHOP (n = 193)	R + CHOP (n = 203)	G + CVP (n = 61)	R + CVP (n = 56)
Grade 3-5 AEs	69%	67%	89%	74%	69%	54%
Neutropenia	30%	30%	71%	55%	46%	23%
Leukopenia	3%	4%	20%	17%	2%	2%
Febrile neutropenia	5%	4%	11%	7%	3%	4%
Infections	26%	20%	12%	12%	13%	13%
Deaths	8%	11%	6%	4%	5%	11%
Second neoplasms	6%	4%	4%	3%	2%	4%
Infusion-related reaction	5%	3%	9%	4%	3%	5%

Hiddemann W et al. *J Clin Oncol* 2018;36(23):2395-404.

FDA Approval of Obinutuzumab for Previously Untreated Advanced Follicular Lymphoma

Press Release: November 16, 2017

"The US Food and Drug Administration approved obinutuzumab in combination with chemotherapy, followed by obinutuzumab alone in those who responded, for people with previously untreated advanced follicular lymphoma (stage II bulky, III or IV). The approval is based on results from the Phase III GALLIUM study, which showed superior progression-free survival (PFS) for patients who received this obinutuzumab-based regimen compared with those who received a rituximab-based regimen as an initial (first-line) therapy."

http://www.businesswire.com/news/home/20171116006149/en/FDA-Approves-Genentech%E2%80%99s-Gazyva-Previously-Untreated-Advanced

CLINICAL TRIALS AND OBSERVATIONS

Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial

Nancy L. Bartlett,[1] Brian A. Costello,[2] Betsy R. LaPlant,[2] Stephen M. Ansell,[2] John G. Kuruvilla,[3] Craig B. Reeder,[4] Lim S. Thye,[5,6] Daniel M. Anderson,[7] Kilannin Krysiak,[1,8] Cody Ramirez,[1,8] Jing Qi,[9] Barry A. Siegel,[9] Malachi Griffith,[1,8] Obi L. Griffith,[1,8] Felicia Gomez,[1,8,*] and Todd A. Fehniger[1,*]

[1]Division of Oncology and Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; [2]Mayo Clinic, Rochester, MN; [3]University of Toronto, Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Mayo Clinic Arizona, Phoenix, AZ; [5]National Cancer Center Singapore, Singapore; [6]Office of Education, Duke-National University of Singapore Graduate Medical School, Singapore; [7]Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, MN; [8]McDonnell Genome Institute, Washington University School of Medicine, St. Louis, MO; and [9]Division of Nuclear Medicine and Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

Blood 2018;131(2):182-90.

Phase II Study of Ibrutinib for Relapsed/Refractory FL

- ORR (n = 25): 37.5%, CR: 12.5%
- Response rates were significantly higher for patients with rituximab-sensitive disease (52.6%) than for those with rituximab-refractory FL (16.7%)
- CARD11 mutations were predictive of ibrutinib resistance: Only patients with CARD11 wild-type disease responded to ibrutinib
- Ibrutinib was well tolerated, with a toxicity profile similar to label descriptions

Bartlett N et al. *Blood* 2018;131(2):182-90.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Ibrutinib as Treatment for Patients With Relapsed/Refractory Follicular Lymphoma: Results From the Open-Label, Multicenter, Phase II DAWN Study

Ajay K. Gopal, Stephen J. Schuster, Nathan H. Fowler, Judith Trotman, Georg Hess, Jing-Zhou Hou, Abdulraheem Yacoub, Michael Lill, Peter Martin, Umberto Vitolo, Andrew Spencer, John Radford, Wojciech Jurczak, James Morton, Dolores Caballero, Sanjay Deshpande, Gary J. Gartenberg, Shean-Sheng Wang, Rajendra N. Damle, Michael Schaffer, Sriram Balasubramanian, Jessica Vermeulen, Bruce D. Cheson, and Gilles Salles

J Clin Oncol 2018;36(23):2405-12.

Phase II DAWN Study of Ibrutinib for Relapsed/Refractory FL

- ORR (n = 110): 20.9% at a median follow-up of 27.7 mo
  - This did not meet the primary efficacy endpoint
- Median duration of response: 19.4 mo
- Median PFS: 4.6 mo
- Although ibrutinib failed to meet its primary endpoint, responses were durable and associated with reduction in regulatory T cells and increase in proinflammatory cytokines

Gopal A et al. *J Clin Oncol* 2018;36(23):2405-12.

JOURNAL OF CLINICAL ONCOLOGY

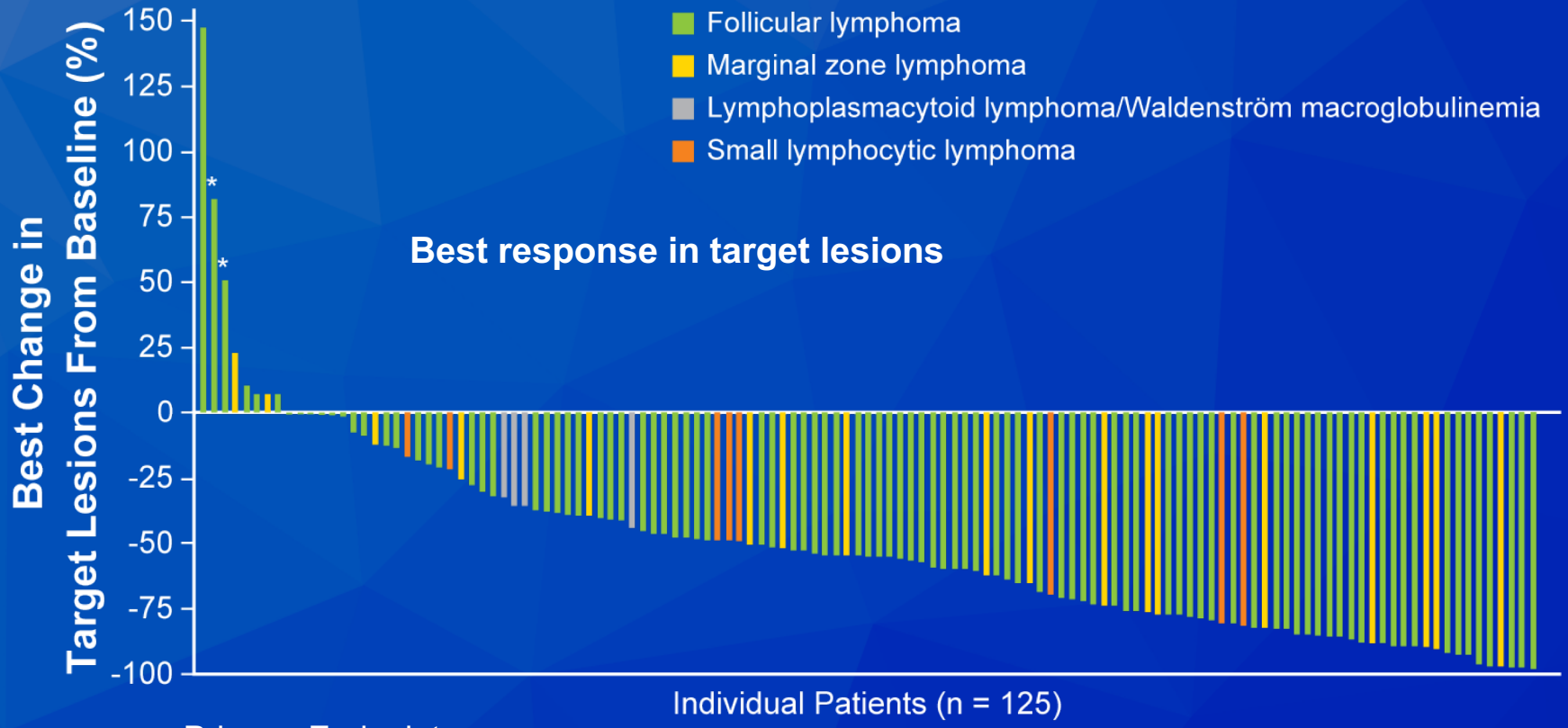
ORIGINAL REPORT

Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma

Martin Dreyling, Armando Santoro, Luigina Mollica, Sirpa Leppä, George A. Follows, Georg Lenz, Won Seog Kim, Arnon Nagler, Panayiotis Panayiotidis, Judit Demeter, Muhit Özcan, Marina Kosinova, Krimo Bouabdallah, Franck Morschhauser, Don A. Stevens, David Trevarthen, Marius Giurescu, Lisa Cupit, Li Liu, Karl Köchert, Henrik Seidel, Carol Peña, Shuxin Yin, Florian Hiemeyer, Jose Garcia-Vargas, Barrett H. Childs, and Pier Luigi Zinzani

J Clin Oncol 2017;35(35):3898-905.

CHRONOS-1: A Pivotal Phase II Trial of Copanlisib for Relapsed/Refractory Indolent NHL



- Primary Endpoint:
  - ORR (FL) = 61/104 (59%)
  - ORR (all patients) = 84/142 (59%)
- Select Secondary Endpoints (All Patients):
  - Median PFS = 11.2 mo
  - Median OS not reached

Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905.

CHRONOS-1: Select Adverse Events with Copanlisib

(N = 142)	All grades	Grade ≥3
Any treatment-related AE	99%	84%
Hyperglycemia	50%	41%
Hypertension	30%	24%
Neutropenia	30%	24%
Diarrhea	34%	5%
Lung infection	21%	16%
Fatigue	30%	2%
Laboratory toxicities		
Increased aspartate aminotransferase	28%	1%
Increased alanine aminotransferase	23%	1%
Treatment-related AEs of special interest		
Pneumonitis (noninfectious)	8%	1%
Colitis	1%	1%

Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905.

High Complete Response Rates with Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study

Safety and Efficacy of Atezolizumab in Combination with Obinutuzumab and Bendamustine in Patients with Previously Untreated Follicular Lymphoma: An Interim Analysis

Nastoupil L et al.
Proc ASH 2017;Abstract 414.

Younes A et al.
Proc ASH 2017;Abstract 481.

Pembrolizumab with Rituximab for Relapsed FL

- ORR (n = 25): 64%, CR: 48%
- Adverse events: Mostly Grade 1-2
- Grade 3 AEs included nausea (n = 2), infusion reaction (n = 2), hypertension (n = 1), aseptic meningitis (n = 1), pneumonia (n = 1)
- Immune-related AEs included Grade 1/2 diarrhea (n = 10), rash (n = 4), transaminitis (n = 4), pneumonitis (n = 1), pancreatitis (n = 1), hypothyroidism (n = 1)

Nastoupil L et al. *Proc ASH* 2017;Abstract 414.

Atezolizumab with Obinutuzumab and Bendamustine for Untreated FL

- CR: 67%
- Adverse events: All patients had ≥1 AE:
  Grade 3 or 4 AEs were reported in 48% of patients
- Most common Grade 3 and 4 AEs: Neutropenia (14%), thrombocytopenia (5%)
- 1 treatment-related fatal AE: Atezolizumab-related cardiac arrest

Younes A et al. *Proc ASH* 2017;Abstract 481.

The NEW ENGLAND JOURNAL of MEDICINE

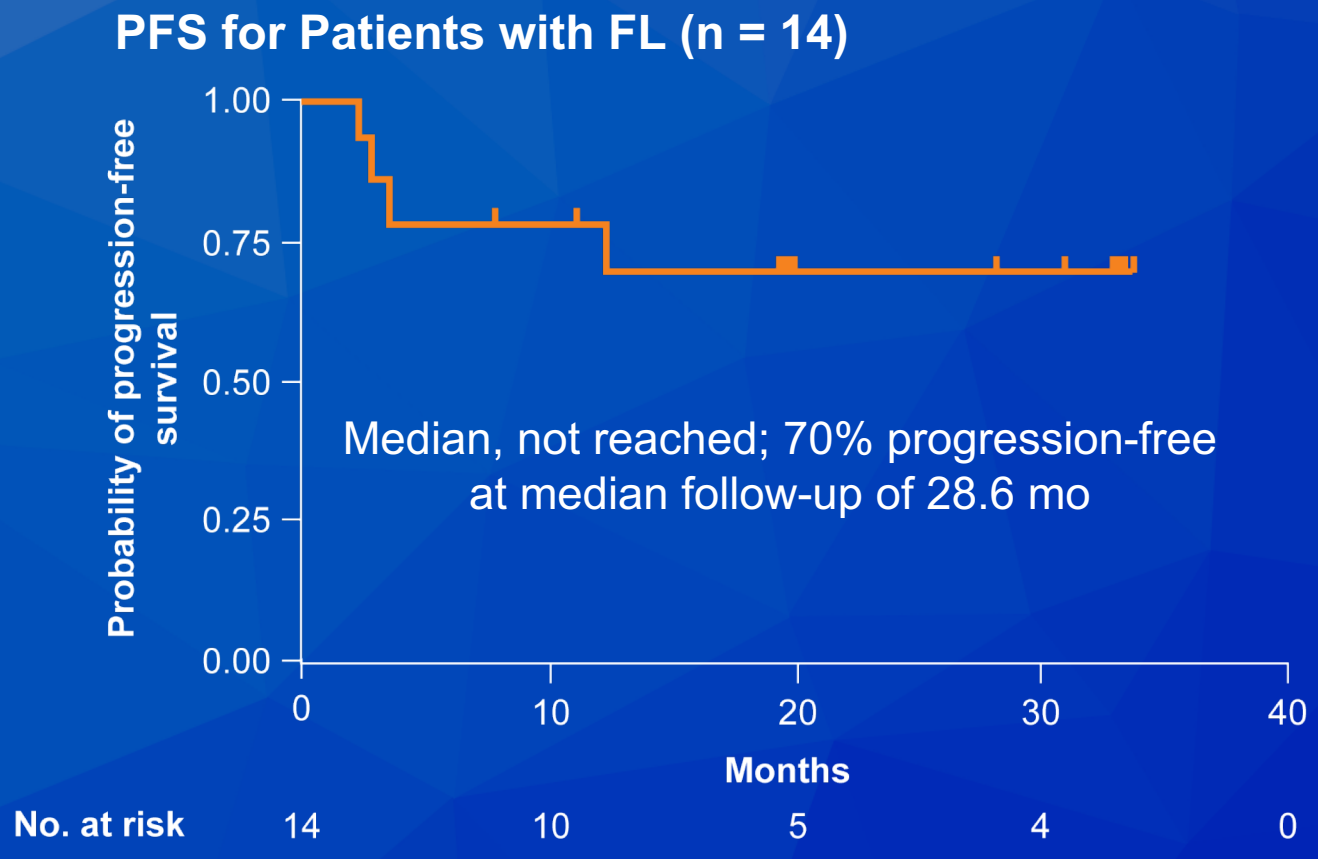
ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D., Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D., Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D., Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D., Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D., David L. Porter, M.D., and Carl H. June, M.D.

N Engl J Med 2017;377(26):2545-54.

Chimeric Antigen Receptor (CAR) T Cells in FL



- 28 patients with B-cell lymphoma received CTL019 cells: 14 patients with FL (18 of 28) experienced a response.
- CR rate = 71% (10 of 14 patients with FL).
- 89% of patients with FL who experienced a response maintained the response at a median follow-up of 28.6 months.

Schuster SJ et al. *N Engl J Med* 2017;377(26):2545-54.

CTL019 CAR-T Therapy: Select Adverse Events

Event (n = 28)	Any grade	Grade 3 or higher
Cytokine release syndrome	16 (57%)	5 (18%)
Neurotoxicity	11 (39%)	3 (11%)
Encephalopathy	3 (27%)	—
Delirium	2 (18%)	—
Tremor	2 (18%)	—
Cognitive disturbance	1 (5%)	—
Confusion	1 (5%)	—
Involuntary movement	1 (5%)	—
Memory impairment	1 (5%)	—

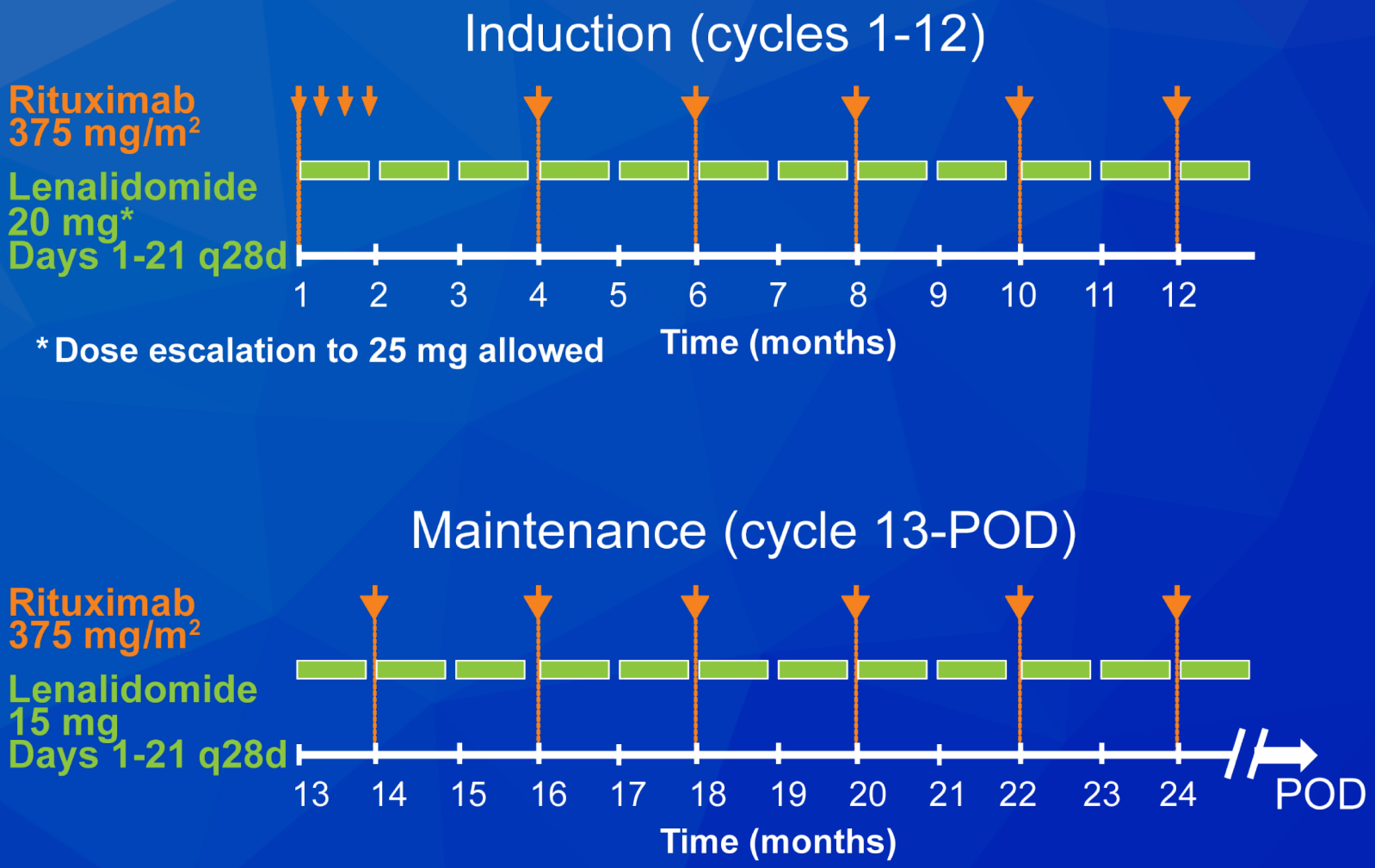
Schuster SJ et al. *N Engl J Med* 2017;377(26):2545-54.

Initial Treatment with Lenalidomide plus Rituximab for Mantle Cell Lymphoma: 5-Year Follow-up and Correlative Analysis from a Multi-Center Phase II Study

Ruan J et al.

Proc ASH 2017;Abstract 154.

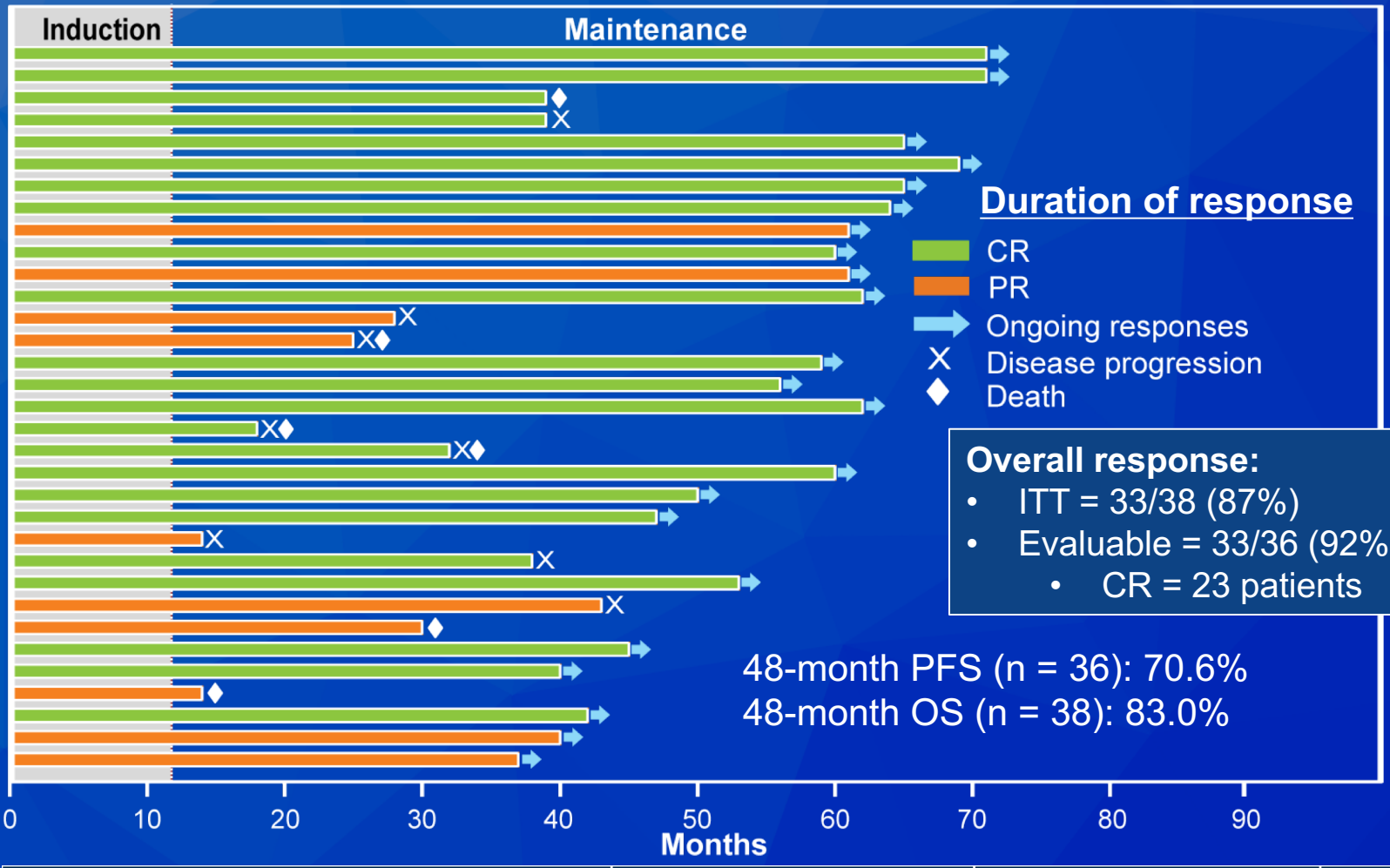
Phase II Trial Design



- **Primary endpoint: Overall response rate**
  - Scan frequency: Every 3 mo (year 1 to 2), every 6 mo (year ≥3)

Ruan J et al. *Proc ASH* 2017;Abstract 154.

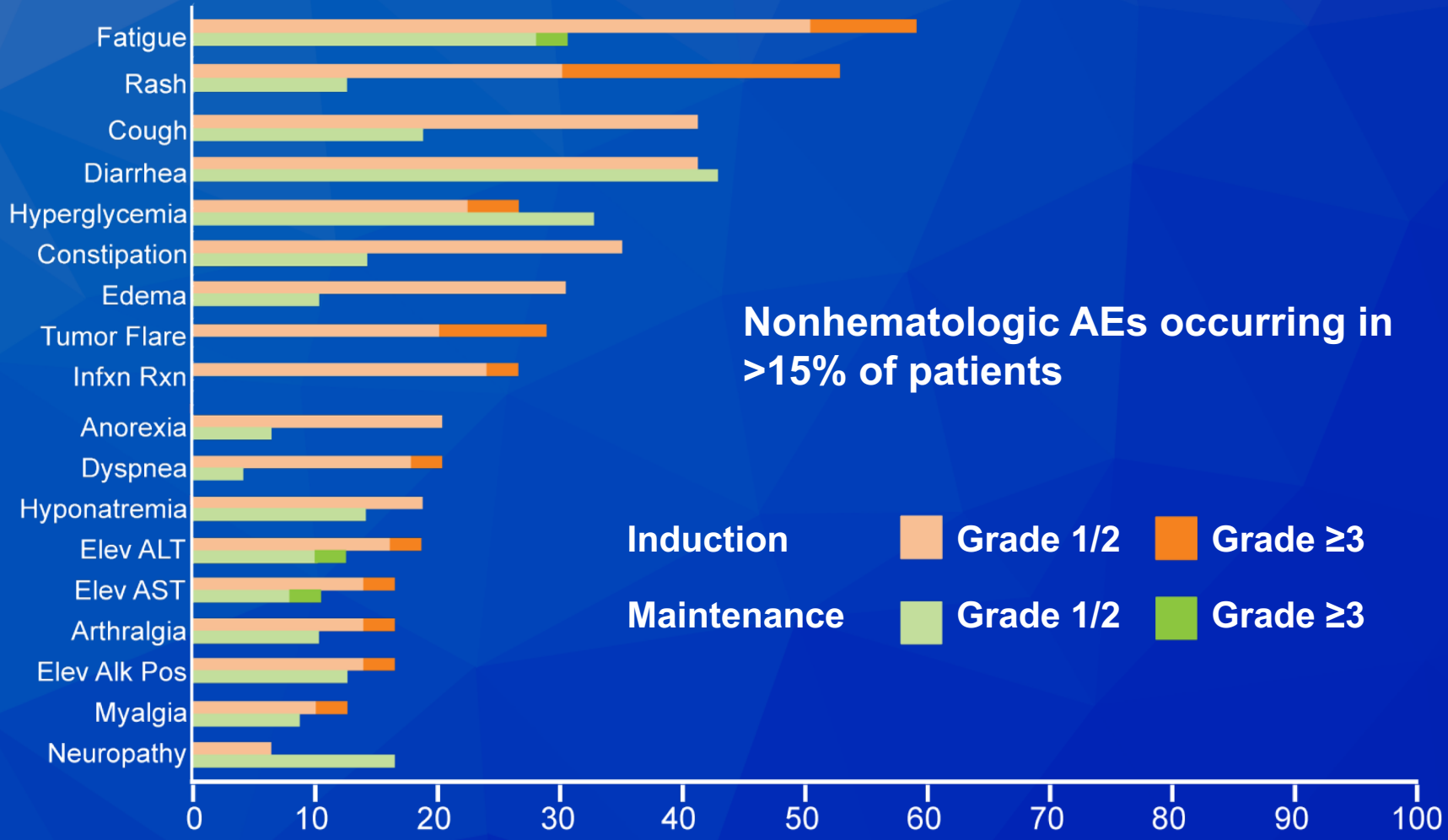
Study Outcomes (Median Follow-Up of 61 Months)



OS by MIPI score	Low/Int	High	*p*-value
4-year OS (n = 26, 12)	91.4%	65.6%	0.02

Ruan J et al. *Proc ASH* 2017;Abstract 154.

Select AEs with Lenalidomide/Rituximab



- The most frequently occurring hematologic AE was neutropenia
  - Grade ≥3: 42% (induction) and 42% (maintenance)
- The accumulative nature of toxicity was not significantly affected by continuous treatment

Ruan J et al. *Proc ASH* 2017;Abstract 154.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

Constantine S. Tam, M.B., B.S., M.D., Mary Ann Anderson, M.B., B.S., Ph.D., Christiane Pott, M.D., Ph.D., Rishu Agarwal, M.B., B.S., Sasanka Handunnetti, M.B., B.S., Rodney J. Hicks, M.B., B.S., Kate Burbury, M.B., B.S., Gillian Turner, B.N., M.I.P.H., Juliana Di Iulio, Ph.D., Mathias Bressel, M.Sc., David Westerman, M.B., B.S., Stephen Lade, M.B., B.S., Martin Dreyling, M.D., Sarah-Jane Dawson, M.B., B.S., Ph.D., Mark A. Dawson, M.B., B.S., Ph.D., John F. Seymour, M.B., B.S., Ph.D., and Andrew W. Roberts, M.B., B.S., Ph.D.

N Engl J Med 2018;378(13):1211-23.

Response to Ibrutinib/Venetoclax

Best response	Without PET (n = 24)	With PET (n = 24)
Complete response	16 (67%)	17 (71%)
Partial response	1 (4%)	0
MRD status		
MRD negative	16 (67%)	9 (38%)
MRD not negative	8 (33%)	15 (62%)

Complete response at week 16: without PET 42%, with PET 62%
Median PFS: not reached
Overall survival rate: 79% at 12 months, 74% at 18 months

Tam CS et al. *N Engl J Med* 2018;378(13):1211-23.

Select Adverse Events with Ibrutinib/Venetoclax

Events (n = 24)	Any grade	Grade ≥3
Diarrhea	83%	12%
Nausea or vomiting	71%	0
Bleeding or bruising	54%	4%
Neutropenia	33%	33%
Anemia	29%	12%
Peripheral sensory neuropathy	21%	0
Tumor lysis syndrome	8%	8%
Atrial fibrillation	8%	8%

Tam CS et al. *N Engl J Med* 2018;378(13):1211-23.

Efficacy of Venetoclax Monotherapy in Patients with Relapsed, Refractory Mantle Cell Lymphoma Post BTK Inhibition Therapy

Eyre T et al.
Proc EHA 2018;Abstract S855.

Venetoclax Monotherapy in BTK Inhibitor-Resistant MCL: Results Summary

- N = 20 patients with relapsed/refractory MCL whose disease progressed on previous BTK inhibitor (BTKi) therapy

Clinical endpoint	Venetoclax (N = 20)
Overall response rate (ORR) Complete response rate	60% 20%
Median duration of response	Not reached
Median PFS	2.6 mo
Median OS	4.3 mo

- ORR among patients with responses to prior BTKi (n = 11) was higher than that among patients with primary resistance to BTKi (n = 9): 72.7% vs 44.4%
- No cases of clinical TLS were observed

Eyre T et al. *Proc EHA* 2018;Abstract S855.

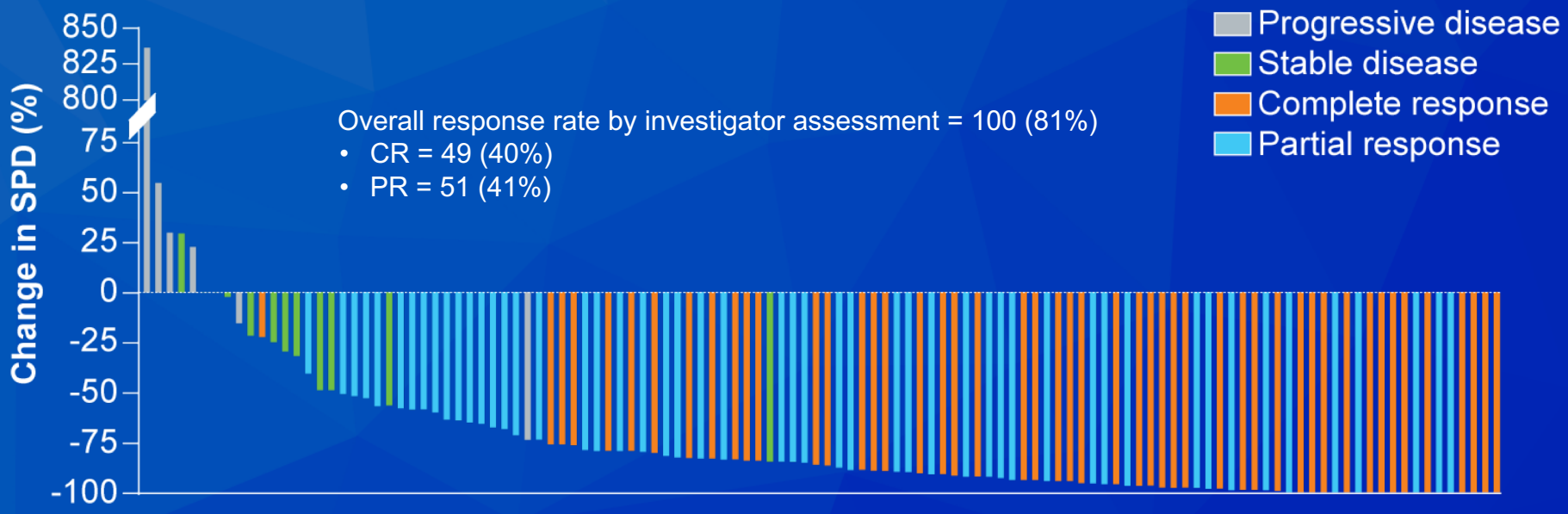
Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D Smith, Gandhi Damaj, Jeanette Doorduijn, Thierry Lamy, Franck Morschhauser, Carlos Panizo, Bijal Shah, Andrew Davies, Richard Eek, Jehan Dupuis, Eric Jacobsen, Arnon P Kater, Steven Le Gouill, Lucie Oberic, Tadeusz Robak, Todd Covey, Richa Dua, Ahmed Hamdy, Xin Huang, Raquel Izumi, Priti Patel, Wayne Rothbaum, J Greg Slatter, Wojciech Jurczak

Lancet 2018;391(10121):659-67.

ACE-LY-004 Phase II Trial of Acalabrutinib: Response

Maximum change from baseline in the SPD of target lesions for all patients (n = 118)



- Median time to best response = 1.9 mo
- Median time to CR = 3.4 mo
- Median duration of response = not reached
- Median PFS and median OS = not reached

Wang M et al. *Lancet* 2018;391(10121):659-67.

Select Adverse Events with Acalabrutinib

Event (n = 124)	Any grade	Grade ≥3
Diarrhea	31%	3%
Myalgia	21%	1%
Anemia	12%	9%
Neutropenia	10%	11%
Pneumonia	6%	5%

Wang M et al. *Lancet* 2018;391(10121):659-67.

Updated Safety and Long Term Clinical Outcomes in TRANSCEND NHL 001, Pivotal Trial of Lisocabtagene Maraleucel (JCAR017) in R/R Aggressive NHL

Abramson JS et al.
Proc ASCO 2018;Abstract 7505.

TRANSCEND NHL 001: Phase I Trial Design

ENROLLMENT COHORTS

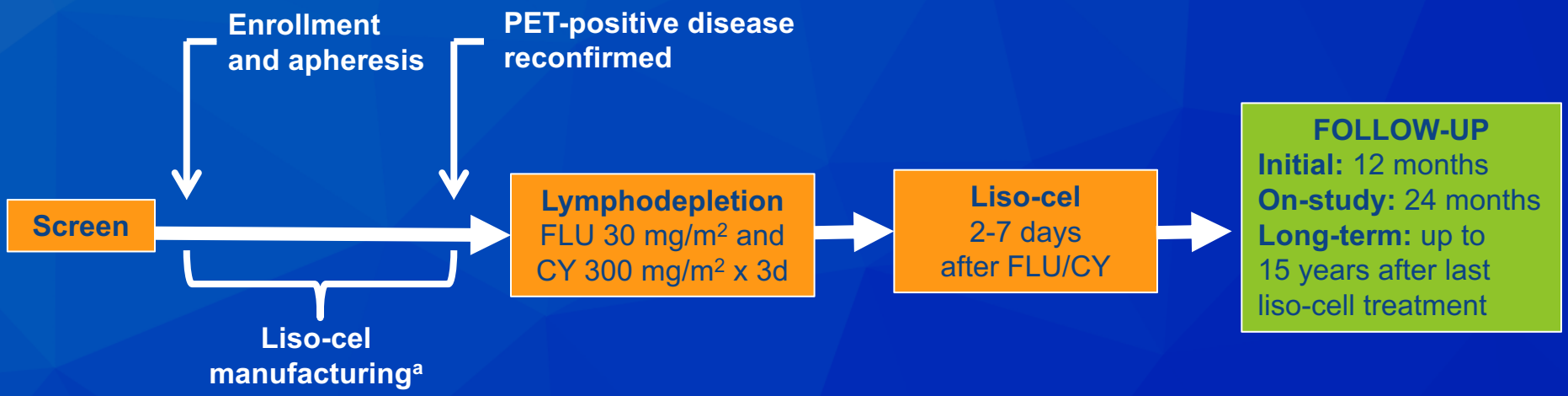
- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed FL)
  - High grade B-cell lymphoma (double/triple hit)
  - DLBCL transformed from CLL or MZL
  - PMBCL
  - FL3B
- MCL after 1 line of therapy

CORE

FULL

PATIENT ELIGIBILITY

- Prior SCT allowed[b]
- Secondary CNS involvement allowed
- ECOG PS 0-2[b]
- No minimum absolute lymphocyte count requirement for apheresis



[a] Therapy for disease control allowed; [b] ECOG PS 2 and prior allogeneic HSCT excluded from pivotal cohort

- **Primary endpoints: Safety, dose-limiting toxicities and objective response rate**

Abramson JS et al. *Proc ASCO* 2018;Abstract 7505.

TRANSCEND NHL 001: Efficacy

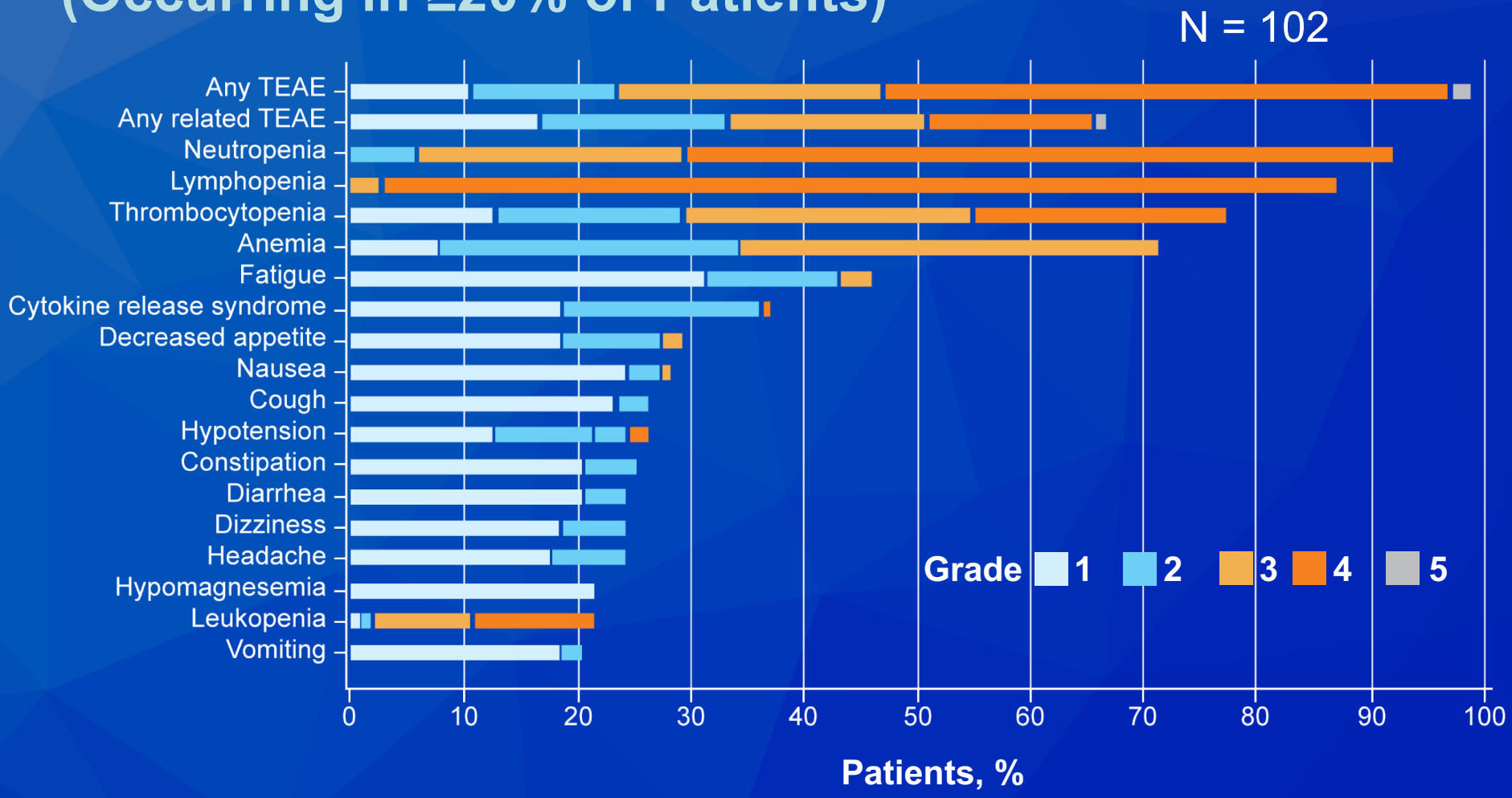
Response	FULL	CORE		
	All DLs (n = 102)	All DLs (n = 73)	DL1S (n = 33)	DL2S (n = 37)
Objective response	75%	80%	79%	78%
CR	55%	59%	55%	62%
6-mo objective response	40%	47%	42%	49%
6-mo CR	34%	41%	33%	46%

DLs = dose levels; FULL data set includes all patients in the DLBCL cohort treated with liso-cel at all DLs; CORE data set includes only patients meeting the inclusion criteria for the pivotal cohort, including DLBCL NOS (de novo or transformed from FL) and high-grade lymphoma

- High response rates observed in R/R DLBCL
- High durable objective response rates observed in pts with poor-risk DLBCL
- Durability of response was encouraging in pts with high-risk DLBCL
- Early OS results were encouraging in pts with high-risk DLBCL

Abramson JS et al. *Proc ASCO* 2018;Abstract 7505.

TRANSCEND NHL 001: TEAEs in the DLBCL Cohort (Occurring in ≥20% of Patients)



- Liso-cel toxicities were manageable at all dose levels tested
- Low rates of severe CRS (1%) and neurotoxicity (13%) observed

Abramson JS et al. *Proc ASCO* 2018;Abstract 7505.

Durability of Response in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma

Locke FL et al.
Proc ASCO 2018;Abstract 3003.

ZUMA-1: Pivotal Phase I/II Trial Design

Eligibility (N = 108)

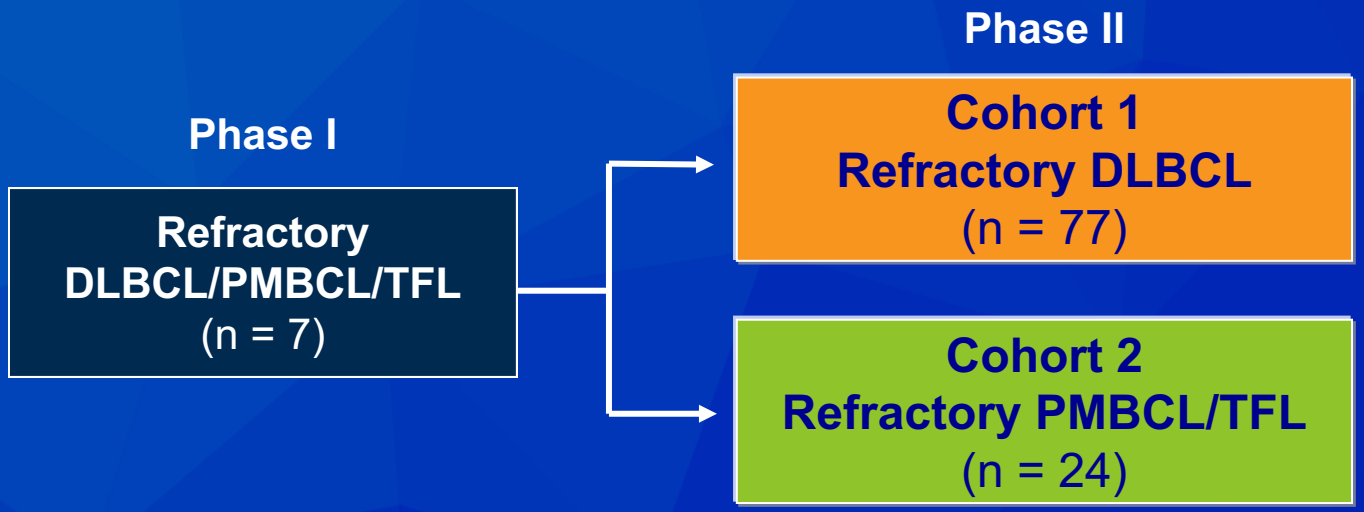
- No response to last chemotherapy, or relapse ≤12 mo after ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Conditioning regimen

- Cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 for 3 days

Axi-cel: 2 x 106 CAR+ cells/kg

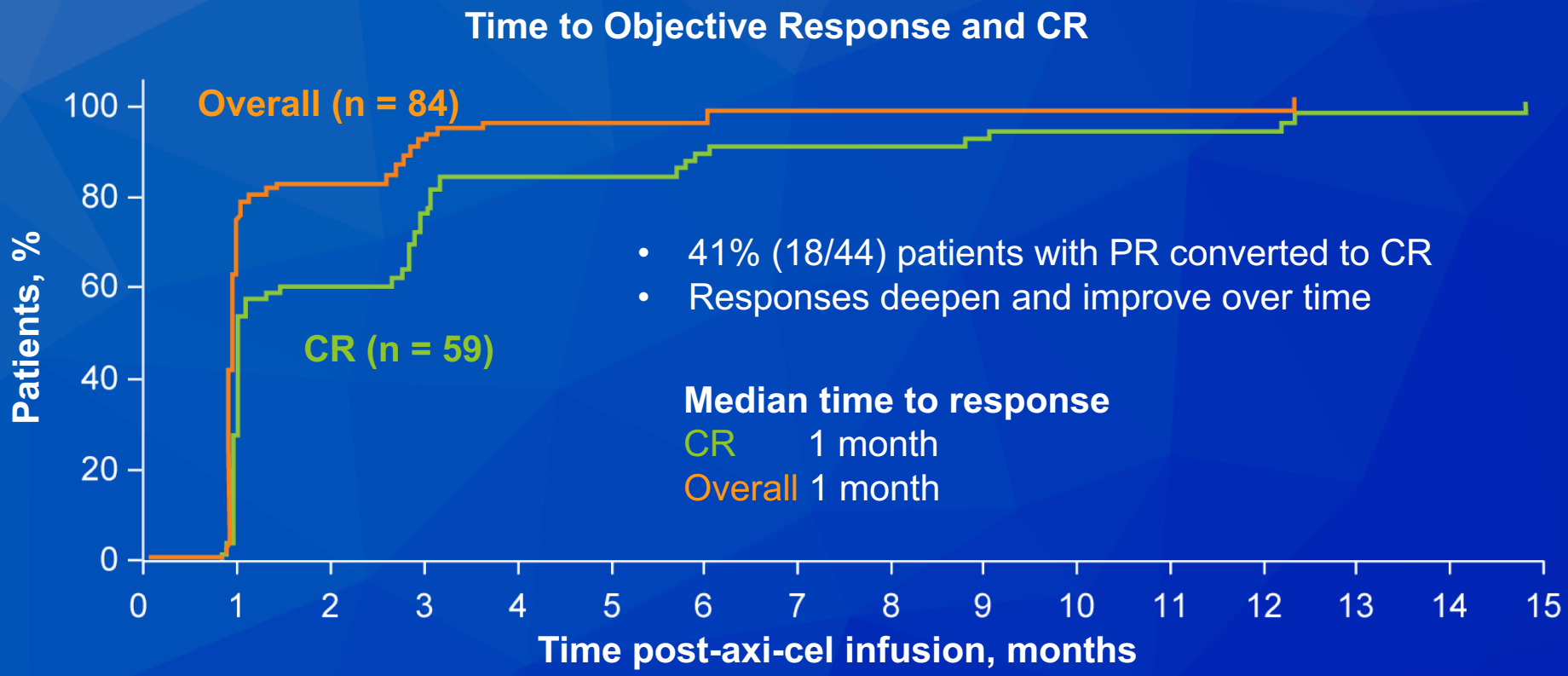
- 99% enrolled, successful manufacture
- 91% enrolled, dose administered



- **Objectives: Evaluate time to response for patients with both an objective response and a CR; assess PR and CR at month 3 as a prognostic factor for PFS**

Locke FL et al. *Proc ASCO* 2018;Abstract 3003.

ZUMA-1: Response



Patients with response at month 3	PR (n = 9)	CR (n = 42)
6-month PFS	78%	88%
9-month PFS	78%	83%
12-month PFS	78%	79%

Locke FL et al. *Proc ASCO* 2018;Abstract 3003.

ZUMA-1: Safety

Adverse events	Overall (n = 101)	Response at month 3	
		PR (n = 9)	CR (n = 42)
All AEs	101 (100%)	9 (100%)	42 (100%)
Grade ≥3	98 (97%)	9 (100%)	39 (93%)
CRS	94 (93%)	9 (100%)	39 (93%)
Grade ≥3	12 (12%)	0	5 (12%)
Neurologic events	65 (64%)	7 (78%)	28 (67%)
Grade ≥3	29 (29%)	3 (33%)	15 (36%)

CRS = cytokine release syndrome

Similar rates of CRS and neurologic events were observed across all response groups.

Locke FL et al. *Proc ASCO* 2018;Abstract 3003.

Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Schuster SJ et al.
Proc ASH 2017;Abstract 577.

JULIET: Study Methods

Eligibility (N = 147)

- Patients with R/R DLBCL with disease progression after receiving 2 or more lines of chemotherapy
- Patients ineligible for or after failure of autologous stem cell transplant (ASCT)

Methods

- Centrally manufactured CAR T cells were provided to patients at 27 study centers in 10 countries on 4 continents using cryopreserved apheresis, central production facilities and a global supply chain.
- CTL019 was manufactured at 2 sites (United States and Germany).
- Genetically modified autologous T cells were infused in 99 patients.

Primary endpoint

- Best overall response rate (CR + PR) by independent review committee

Schuster SJ et al. *Proc ASH* 2017;Abstract 577.

JULIET: Primary Analysis of Efficacy

Response (pts in the US)	Infused pts (overall) with ≥3 month follow-up (n = 81)	At month 3 (n = 81)	At month 6 (n = 46)
Best overall response	53.1%	38%	37%
CR	39.5%	32%	30%
PR	13.6%	6%	7%

- Response rates were consistent across prognostic subgroups (including patients who received prior ASCT and those with double-hit lymphoma).
  - Median duration of response was not reached
- 6-month probability of being relapse free: 73.5%
- Median OS was not reached
  - 6-month probability of OS: 64.5%
- No patient who achieved CR or PR proceeded to allogeneic or autologous SCT
- CTL019 was detected in the peripheral blood by quantitative PCR for up to 367 days in responders

Schuster SJ et al. *Proc ASH* 2017;Abstract 577.

JULIET: Safety

- Overall, 86% of patients experienced Grade 3 or 4 AEs
- CRS occurred in 58% of infused patients:
  - 15% Grade 3 and 8% Grade 4 using the Penn grading scale and managed by a protocol-specific algorithm
  - 15% of patients received tocilizumab for CRS management, with good response
  - 11% of patients received corticosteroids
- Other Grade 3 or 4 AEs of special interest included neurologic AEs (12%), cytopenias lasting more than 28 days (27%), infections (20%) and febrile neutropenia (13%)
- Three patients died within 30 days of infusion, with all 3 deaths attributed to disease progression
- No deaths were attributed to CTL019
- No deaths were attributed to CRS or neurologic events

Schuster SJ et al. *Proc ASH* 2017;Abstract 577.

An Updated Analysis of JULIET, a Global Pivotal Phase 2 Trial of Tisagenlecleucel in Adult Patients with Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)

Borchmann P et al.
Proc EHA 2018;Abstract S799.

JULIET: Updated Efficacy Data

- 111 patients received an infusion: 95 received US-manufactured tisagenlecleucel (main cohort) and 16 received EU-manufactured tisagenlecleucel (cohort A)
- Efficacy results reported for patients in main cohort with ≥3 mo follow-up or earlier discontinuation

Clinical endpoint	N = 93
Best ORR	52%
CR	40%
PR	12%
Median duration of response	Not reached
12-mo relapse-free probability	65%

- Response rates were consistent across prognostic subgroups
- Median OS among all infused patients was 11.7 mo
  - 12-mo OS = 49%

Borchmann P et al. *Proc EHA* 2018;Abstract S799.

JULIET: Updated Safety Data

- Safety is reported for all infused patients

Grade 3/4 AEs of special interest	
Cytopenias lasting >28 days	32%
Cytokine release syndrome (CRS)*	22%
Infections	20%
Febrile neutropenia	14%
Neurologic AEs	12%

* 14% Grade 3 and 8% Grade 4 by Penn grading scale

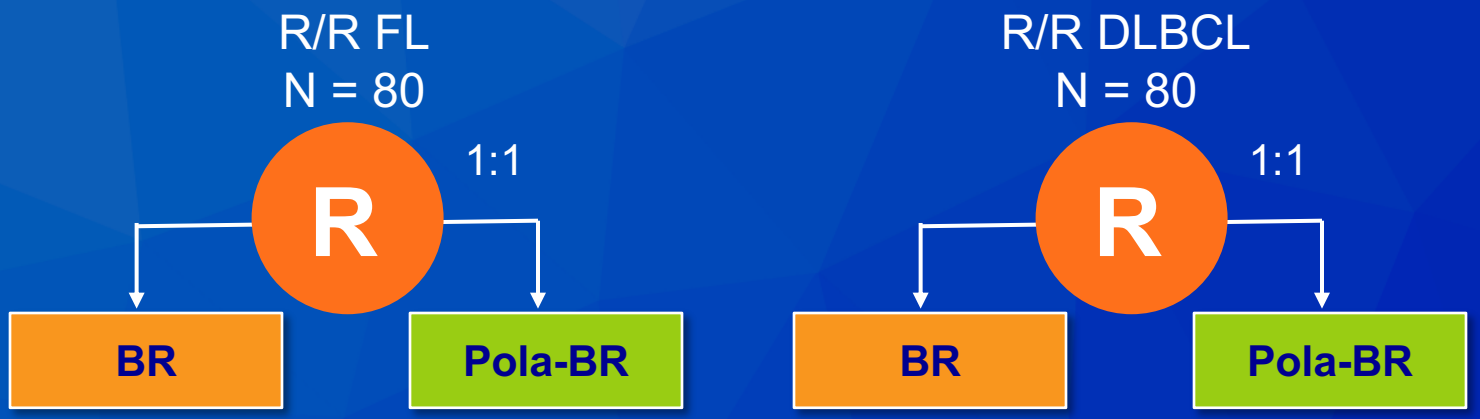
- 15% of patients received tocilizumab for management of CRS
- No deaths were attributed to tisagenlecleucel or CRS

Borchmann P et al. *Proc EHA* 2018;Abstract S799.

Randomized Phase 2 Trial of Polatuzumab Vedotin (Pola) with Bendamustine and Rituximab (BR) in Relapsed/Refractory (R/R) FL and DLBCL

Sehn LH et al.
Proc ASCO 2018;Abstract 7507.

GO29365: Phase I/II Trial Design



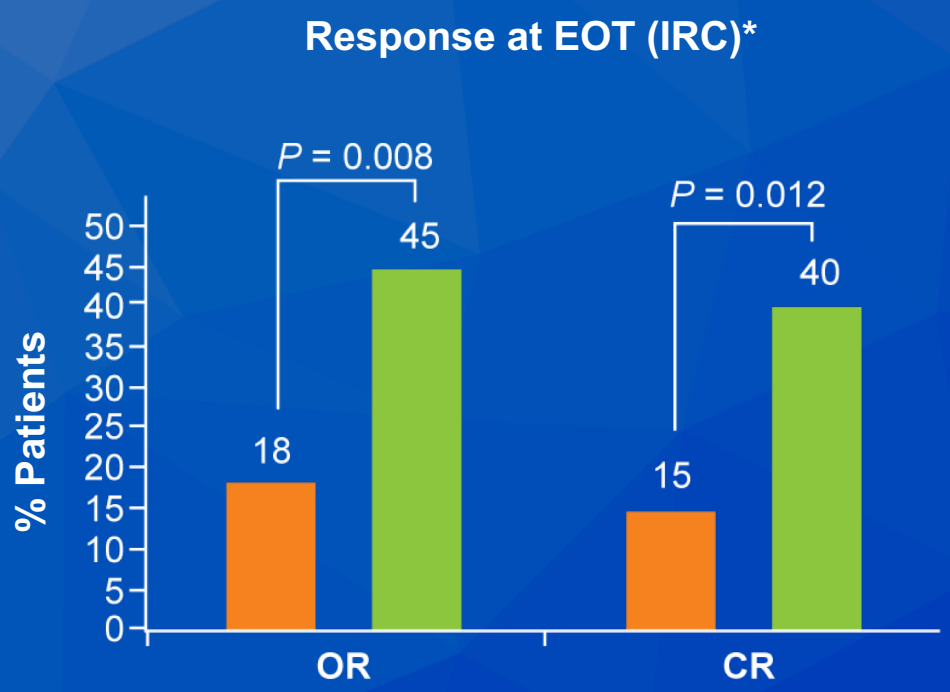
Stratification	DOR ≤12 mo vs >12 mo High vs low disease burden	DOR ≤12 mo vs >12 mo
Schedule	FL: 28-day cycles x 6	DLBCL: 21-day cycles x 6

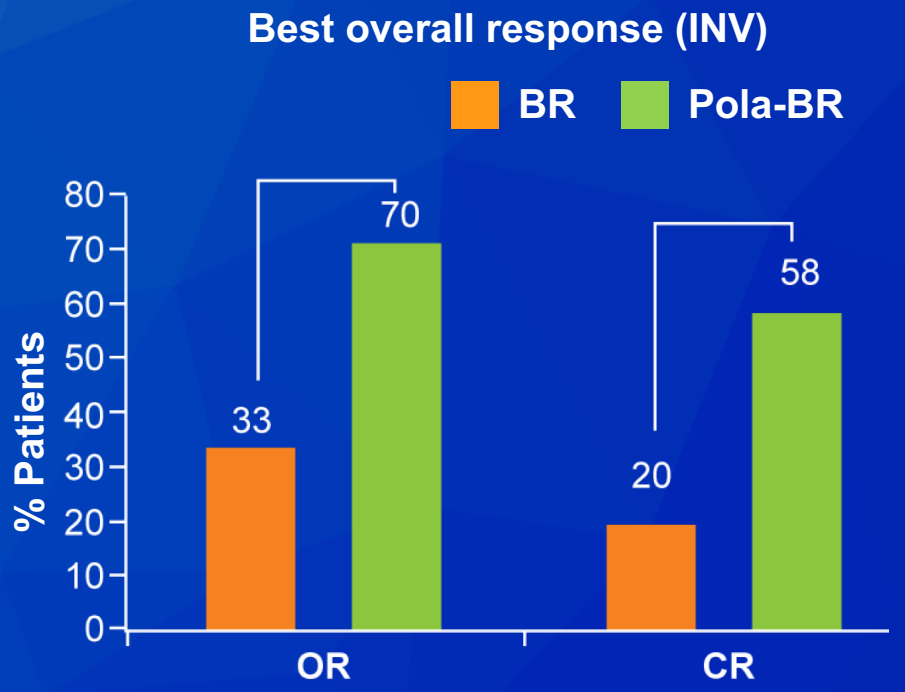
Polatuzumab vedotin (1.8 mg/kg IV x 1 day); bendamustine (90 mg/m^2 IV x 2 days); rituximab (375 mg/m^2 IV x 1 day)

- **Primary endpoint: PET-CR by IRC, 6-8 weeks after end of treatment (EOT)**
  - PET-CR measurements by modified Lugano 2014 criteria

Sehn LH et al. *Proc ASCO* 2018;Abstract 7507.

GO29365: PET-CR and Survival for Patients with DLBCL

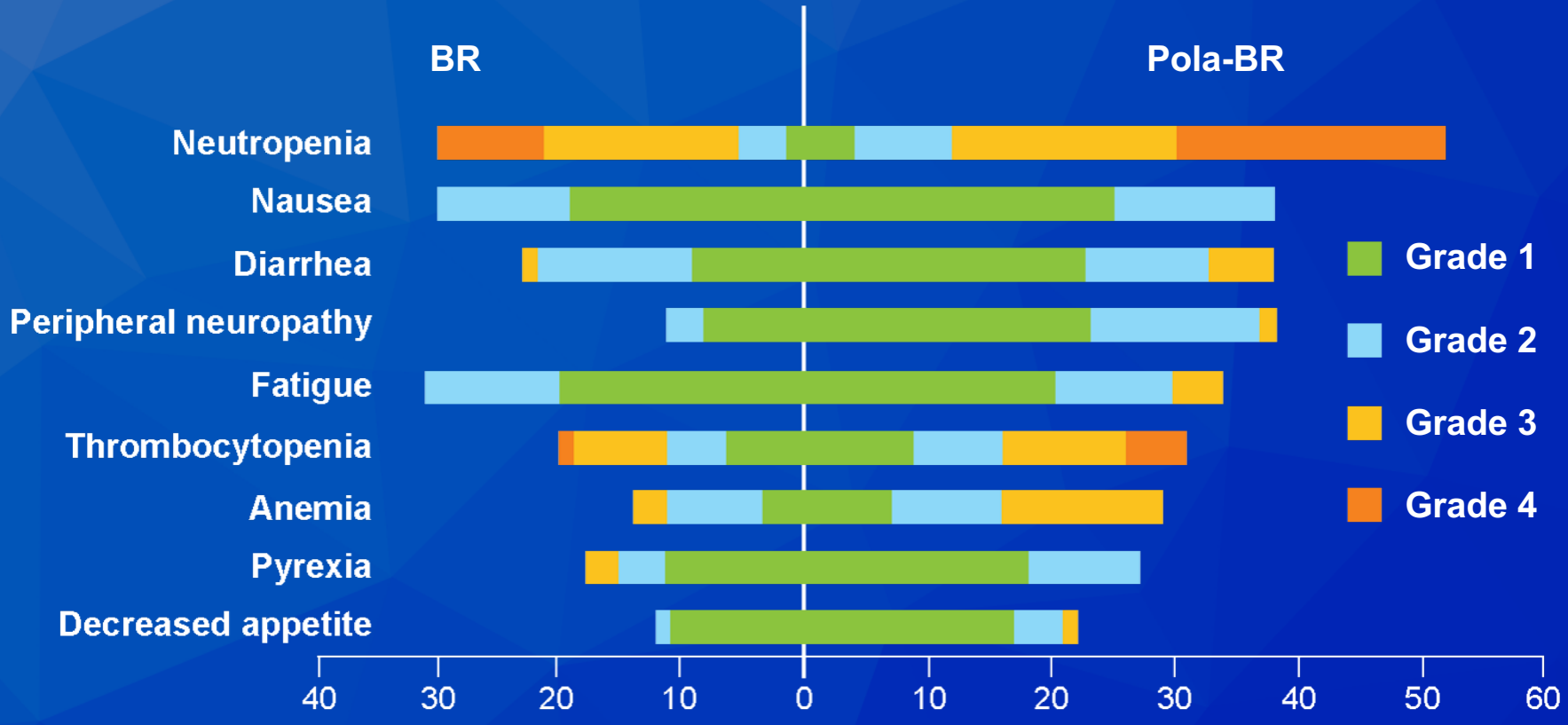




Survival	BR (n = 40)	Pola-BR (n = 40)	HR	*p*-value
Median PFS	2.0 mo	6.7 mo	0.31	<0.0001
Median OS	4.7 mo	11.8 mo	0.35	0.0008

Sehn LH et al. *Proc ASCO* 2018;Abstract 7507.

GO29365: AEs in ≥20% of All Patients (FL and DLBCL)



- In the Pola-BR arm, peripheral neuropathy was mostly Grade 1 (25%) and 2 (13%) and mostly reversible
- Grade 3-5 infections (system organ class): 16% (BR) vs 19% (Pola-BR)
- Rate of Grade 5 AEs was similar between arms: 11% (BR) vs 12% (Pola-BR)

Sehn LH et al. *Proc ASCO* 2018;Abstract 7507.

Activity and Tolerability of the First-in-Class Anti-CD47 Antibody Hu5F9-G4 with Rituximab Tolerated in Relapsed/Refractory Non-Hodgkin Lymphoma: Initial Phase 1b/2 Results

Advani RH et al.
Proc ASCO 2018;Abstract 7504.

5F9003: Phase Ib/II Trial Design

Estimated enrollment (N = 72)

Eligibility

- Relapsed/refractory B-cell NHL
- Disease progression on or after standard approved therapies

Standard 3 + 3 design

Phase Ib Dose escalation

Level 1: 1, 10 mg/kg 5F9 weekly + 375 mg/m^2 rituximab

Level 2: 1, 20 mg/kg 5F9 weekly + 375 mg/m^2 rituximab

Level 3: 1, 30 mg/kg 5F9 + 375 mg/m^2 rituximab

RP2D

Phase II Expansion

DLBCL

RP2D of 5F9 + 375 mg/m^2 rituximab

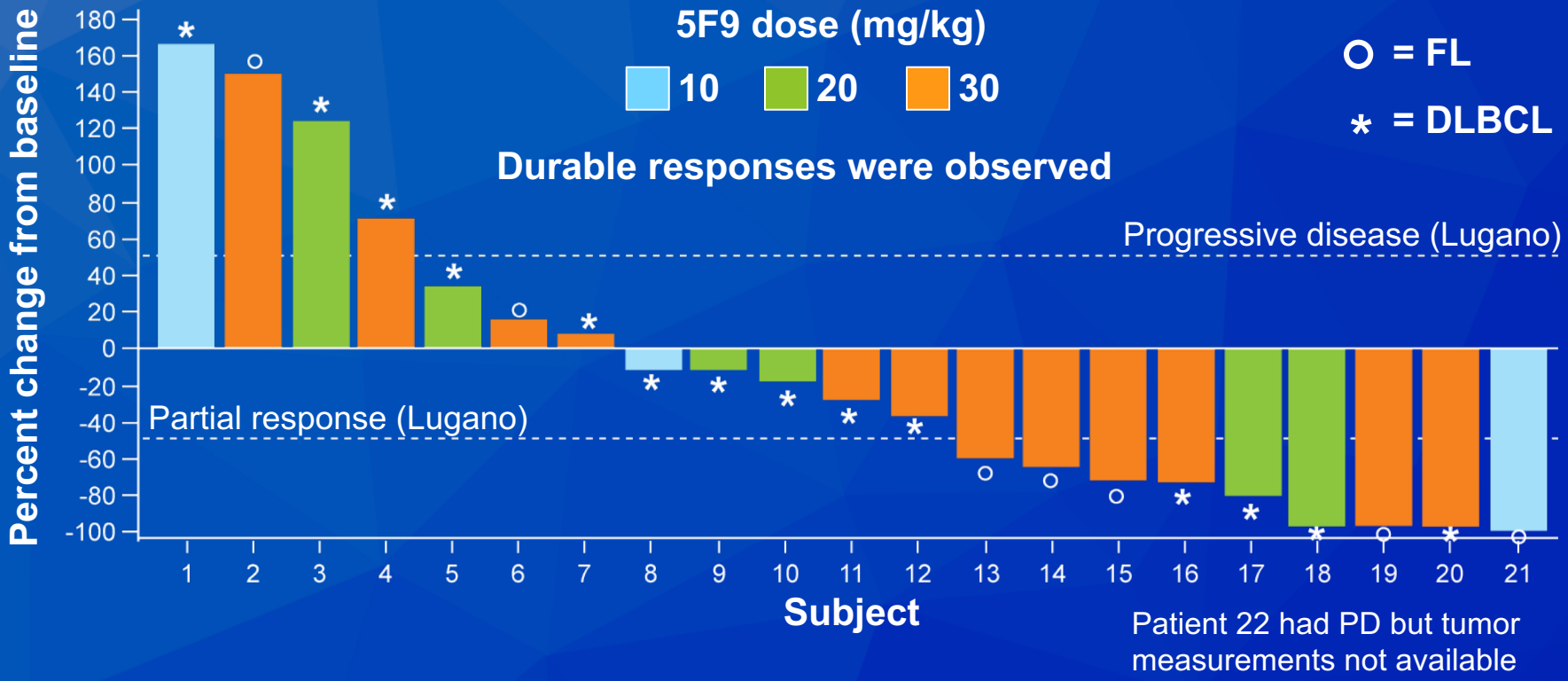
Indolent lymphoma

RP2D of 5F9 + 375 mg/m^2 rituximab

- **Primary endpoints: Safety, tolerability and recommended Phase II dose (RP2D) of the combination of 5F9 and rituximab**
  - Initial analysis of the results from 22 patients

Advani RH et al. *Proc ASCO* 2018;Abstract 7504; www.clinicaltrials.gov (NCT02953509).

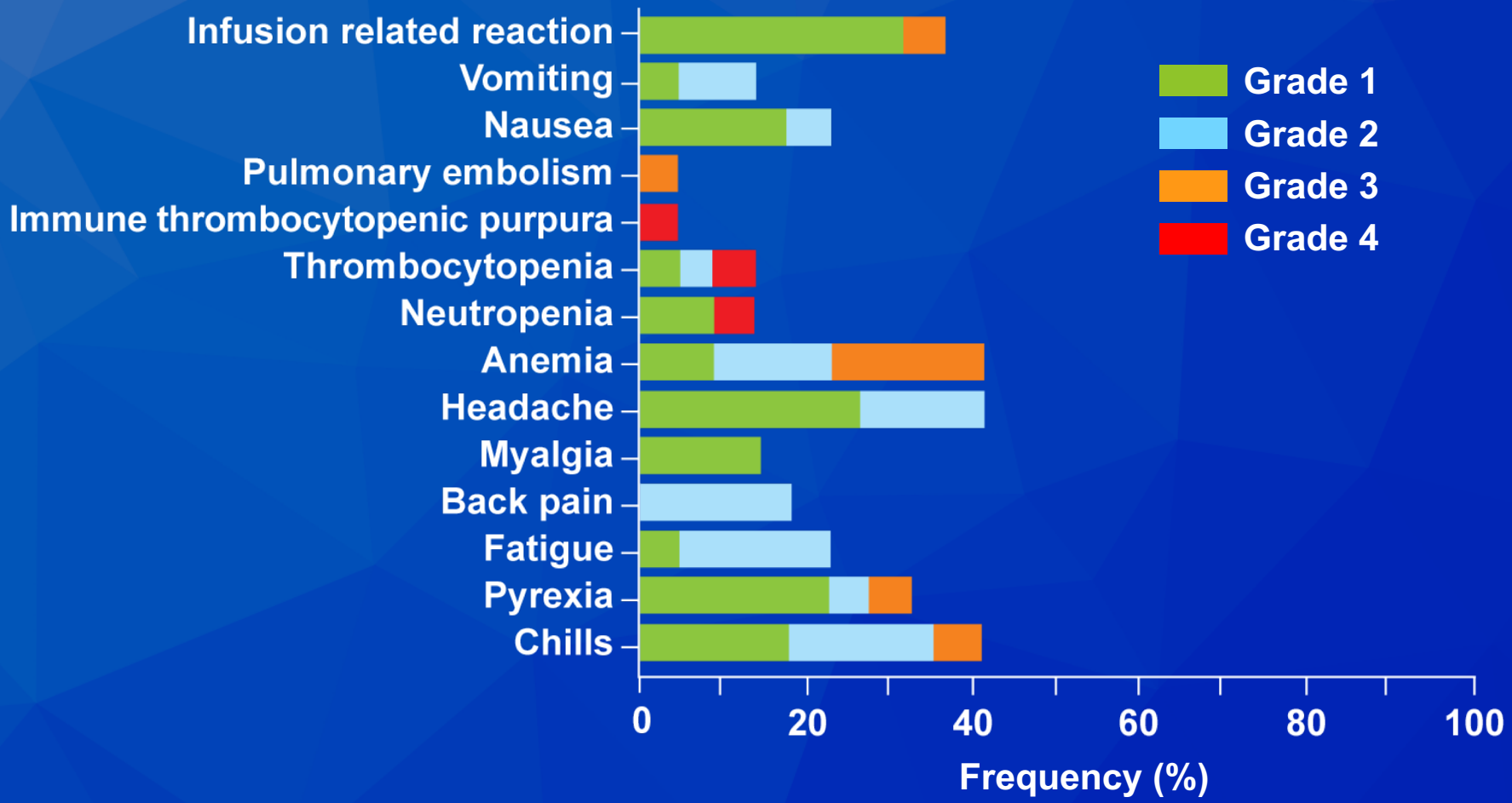
5F9003: Antitumor Activity in FL and DLBCL (Phase Ib)



Response	All pts (n = 22)	DLBCL (n = 15)	FL (n = 7)
Objective response rate	11 (50%)	6 (40%)	5 (71%)
Disease control rate	14 (64%)	9 (60%)	5 (71%)
CR	8 (36%)	5 (33%)	3 (43%)

Advani RH et al. *Proc ASCO* 2018;Abstract 7504.

5F9003: Treatment-Related AEs (>10% Frequency)



- Most common AEs were Grade 1/2
- No autoimmune AEs observed
- Patients received long-term treatment (up to 18+ months) without any significant late safety signals

Advani RH et al. *Proc ASCO* 2018;Abstract 7504;www.clinicaltrials.gov.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

J.M. Connors, W. Jurczak, D.J. Straus, S.M. Ansell, W.S. Kim, A. Gallamini, A. Younes, S. Alekseev, Á. Illés, M. Picardi, E. Lech-Maranda, Y. Oki, T. Feldman, P. Smolewski, K.J. Savage, N.L. Bartlett, J. Walewski, R. Chen, R. Ramchandren, P.L. Zinzani, D. Cunningham, A. Rosta, N.C. Josephson, E. Song, J. Sachs, R. Liu, H.A. Jolin, D. Huebner, and J. Radford, for the ECHELON-1 Study Group*

N Engl J Med 2018;378(4):331-44.

ECHELON-1: Phase III Study Schema

Accrual: 1,334 patients

Eligibility

- Advanced classical Hodgkin lymphoma
- Treatment naïve
- No sensory or motor peripheral neuropathy

(1:1)

R

Brentuximab vedotin (BV) + AVD

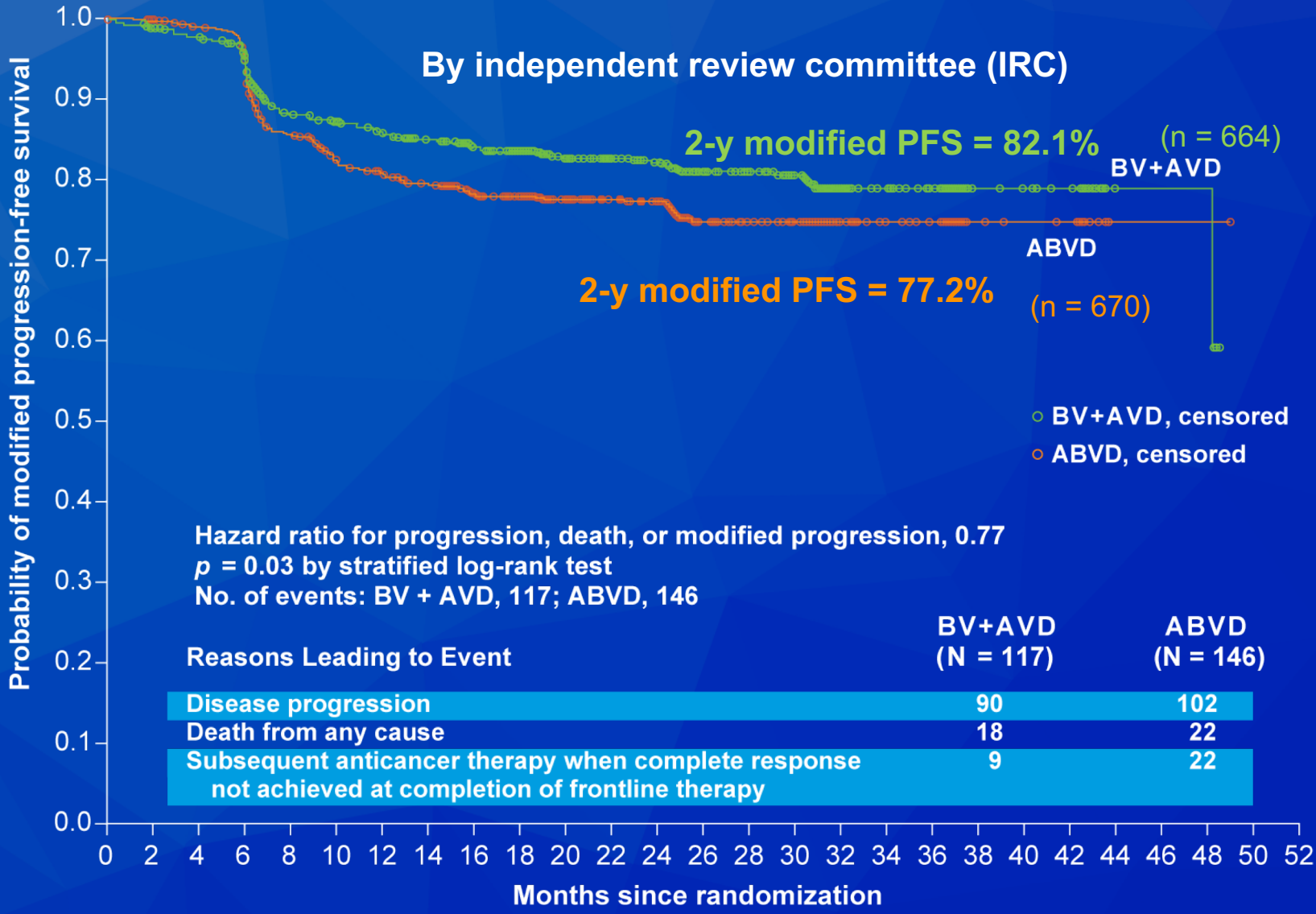
BV 1.2 mg/kg,
doxorubicin 25 mg/m^2,
vinblastine 6 mg/m^2,
dacarbazine 375 mg/m^2

ABVD

Doxorubicin 25 mg/m^2,
bleomycin 10 units/m^2,
vinblastine 6 mg/m^2,
dacarbazine 375 mg/m^2

www.clinicaltrials.gov; NCT01712490.

ECHELON-1: Modified PFS



Hazard ratio for progression, death, or modified progression, 0.77
p = 0.03 by stratified log-rank test
No. of events: BV + AVD, 117; ABVD, 146

Reasons Leading to Event	BV+AVD (N = 117)	ABVD (N = 146)
Disease progression	90	102
Death from any cause	18	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	9	22

Connors JM et al. *N Engl J Med* 2018;378(4):331-44.

ECHELON-1: Select Adverse Events

	BV + AVD (n = 662)		ABVD (n = 659)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Neutropenia	58%	54%	45%	39%
Febrile neutropenia	19%	NR	8%	NR
Peripheral sensory neuropathy	29%	5%	17%	<1%
Infections	55%	18%	50%	10%

NR = Not reported

In the BV + AVD group, the incidence of febrile neutropenia was lower among the patients who received primary prophylaxis with G-CSF than among those who did not.

Connors JM et al. *N Engl J Med* 2018;378(4):331-44.

Regular Article

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CLINICAL TRIALS AND OBSERVATIONS

Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL

Jonathan W. Friedberg,[1] Andres Forero-Torres,[2] Rodolfo E. Bordoni,[3] Vivian J. M. Cline,[4] Dipti Patel Donnelly,[5] Patrick J. Flynn,[6] Gregg Olsen,[7] Robert Chen,[8] Abraham Fong,[9] Yinghui Wang,[9] and Christopher A. Yasenchak[10]

[1]Wilmot Cancer Institute, University of Rochester, Rochester, NY; [2]Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL; [3]Georgia Cancer Specialists, Marietta, GA; [4]Texas Oncology-Round Rock Seton Williamson, Round Rock, TX; [5]Virginia Cancer Specialists, Fairfax, VA; [6]Minnesota Oncology, Woodbury, MN; [7]Providence Saint Joseph Medical Center, Burbank, CA; [8]City of Hope Medical Center, Duarte, CA; [9]Seattle Genetics, Inc., Bothell, WA; and [10]Willamette Valley Cancer Institute and Research Center/US Oncology Research, Eugene, OR

Blood 2017;130(26):2829-37.

Efficacy of Brentuximab Vedotin with DTIC or Bendamustine

Response	BV + DTIC (n = 21)	BV + bendamustine* (n = 17)
Objective response rate	100%	100%
Complete response rate	62%	88%
Survival		
Median PFS	17.9 mo	Not reached
Median overall survival	Not reached	Not reached

* BV + bendamustine treatment stopped early due to high rate of SAEs and deaths

Friedberg JW et al. *Blood* 2017;130(26):2829-37.

Adverse Events (AEs) with Brentuximab Vedotin and DTIC or Bendamustine

Treatment-emergent AEs	BV + DTIC (n = 22)	BV + bendamustine (n = 20)
Any AE	100%	100%
Grade ≥3 AEs	45%	90%
Serious AEs	18%	65%
Deaths within 30 d of last dose	0	2 (10%)

Despite activity, BV with bendamustine is not a tolerable regimen in elderly patients.

Friedberg JW et al. *Blood* 2017;130(26):2829-37.

CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma

Ann S. LaCasce,[1] R. Gregory Bociek,[2] Ahmed Sawas,[3] Paolo Caimi,[4] Edward Agura,[5] Jeffrey Matous,[6] Stephen M. Ansell,[7] Howland E. Crosswell,[8] Miguel Islas-Ohlmayer,[9] Caroline Behler,[10] Eric Cheung,[11] Andres Forero-Torres,[12] Julie Vose,[2] Owen A. O'Connor,[3] Neil Josephson,[13] Yinghui Wang,[13] and Ranjana Advani[14]

Blood 2018;132(1):40-8.

Efficacy of Brentuximab Vedotin/Bendamustine

Response	BV + bendamustine (n = 53)
Objective response rate	92.5%
Complete response rate	73.6%
Survival	
PFS (2 y)	62.6%
OS (2 y)	94.2%

Patients who underwent ASCT (n = 40): objective response rate 95.0%, complete response rate 85.0%

LaCasce AS et al. *Blood* 2018;132(1):40-8.

Select Adverse Events with Brentuximab Vedotin/Bendamustine

	(n = 55)
Grade 3/4 AEs	47.3%
AEs leading to discontinuation	23.6%
Infusion-related reactions	56.4%
Peripheral neuropathy	23.6%

Grade 3 or 4 AEs included lymphopenia, rash and hypotension.

LaCasce AS et al. *Blood* 2018;132(1):40-8.

Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial

Owen A O'Connor, Jennifer K Lue, Ahmed Sawas, Jennifer E Amengual, Changchun Deng, Matko Kalac, Lorenzo Falchi, Enrica Marchi, Ithamar Turenne, Renee Lichtenstein, Celeste Rojas, Mark Francescone, Lawrence Schwartz, Bin Cheng, Kerry J Savage, Diego Villa, Michael Crump, Anca Prica, Vishal Kukreti, Serge Cremers, Joseph M Connors, John Kuruvilla

Lancet Oncol 2018;19(2):257-66.

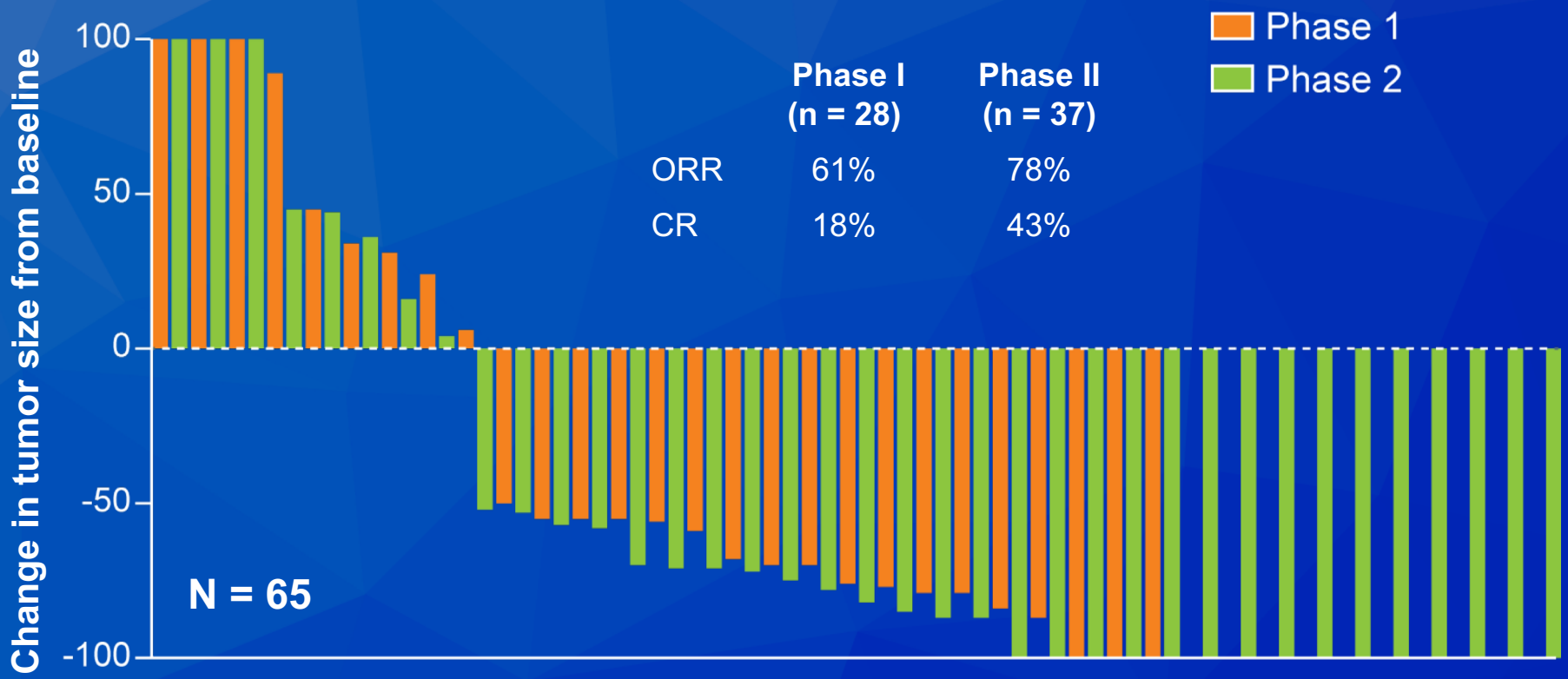
Select Adverse Events with Brentuximab Vedotin/Bendamustine

	Phase I (n = 28)		Phase II (n = 37)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Anemia	18%	18%	5%	0
Infusion-related reactions	11%	7%	11%	0
Neutropenia	11%	11%	35%	35%
Peripheral sensory neuropathy	32%	0	5%	0

- In Phase I, the MTD was not reached
- Dose limiting toxicities in 3 patients (11%) included neutropenia and rash

O'Connor OA et al. *Lancet Oncol* 2018;19(2):257-66.

Response to Brentuximab Vedotin/Bendamustine



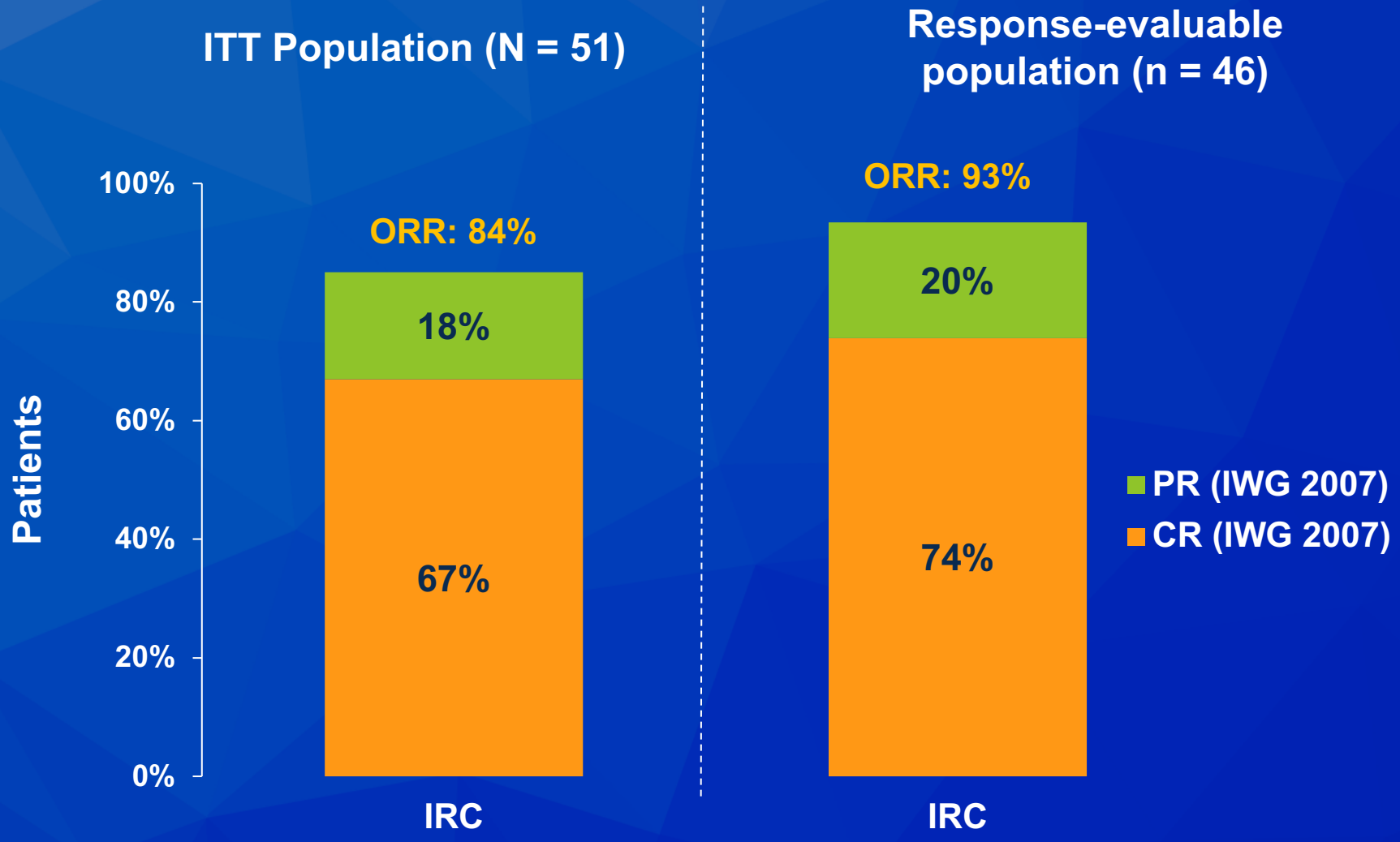
- Median PFS: Phase I, 7.5 mo; Phase II, not reached
- Median OS: Phase I, 43.3 mo; Phase II, not reached

O'Connor OA et al. *Lancet Oncol* 2018;19(2):257-66.

Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma (cHL): Results from the Phase 2 CheckMate 205 Study

Ramchandren R et al.
Proc ASH 2017;Abstract 651.

CheckMate 205: Response at End of Therapy



IRC = Independent review committee

Ramchandren R et al. *Proc ASH* 2017;Abstract 651.

CheckMate 205: Select Adverse Events

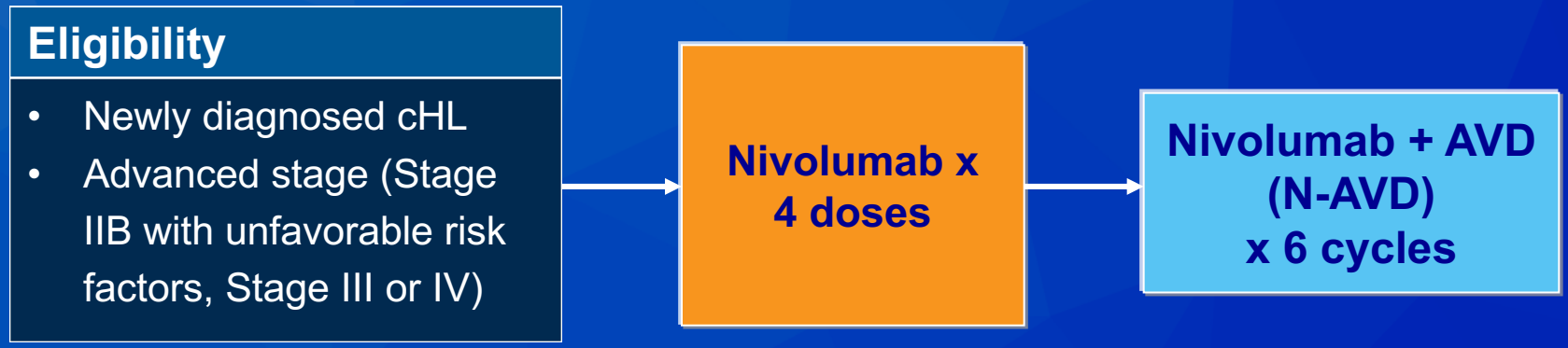
Event (n = 51)	Any grade	Grade 3/4
Neutropenia	55%	49%
Febrile neutropenia	10%	10%
Alanine aminotransferase increase	8%	4%
Hypothyroidism	14%	0
Infusion-related reaction	31%	0

Ramchandren R et al. *Proc ASH* 2017;Abstract 651.

CHECKMATE 205 Cohort D: A Phase 2 Trial of Nivolumab for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma

Ramchandren R et al.
Proc EHA 2018;Abstract S114.

CheckMate 205 Cohort D: Phase II Study of Nivolumab in Newly Diagnosed cHL



AVD = Doxorubicin + vinblastine + dacarbazine

Primary endpoint: Proportion of patients with Grade ≥3 treatment-related adverse events (TRAEs) within 30 days or less after last dose

Ramchandren R et al. *Proc EHA* 2018;Abstract S114.

CheckMate 205 Cohort D: Results Summary

- At database lock, 51 patients had been treated, with 49/51 (96%) completing monotherapy and 45/50 (90%) completing combination therapy

Grade 3/4 TRAEs	All treated patients (N = 51)
Neutropenia	49%
Febrile neutropenia	10%
Hepatitis	4%
Pneumonitis	0

- No Grade 5 TRAEs occurred ≤30 days from last dose
- Objective response rate in the ITT population was 84% (67% CR) by independent review committee
- Nearly all response-evaluable patients showed a >50% reduction in tumor burden

Ramchandren R et al. *Proc EHA* 2018;Abstract S114.

VOLUME 36 · NUMBER 14 · MAY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

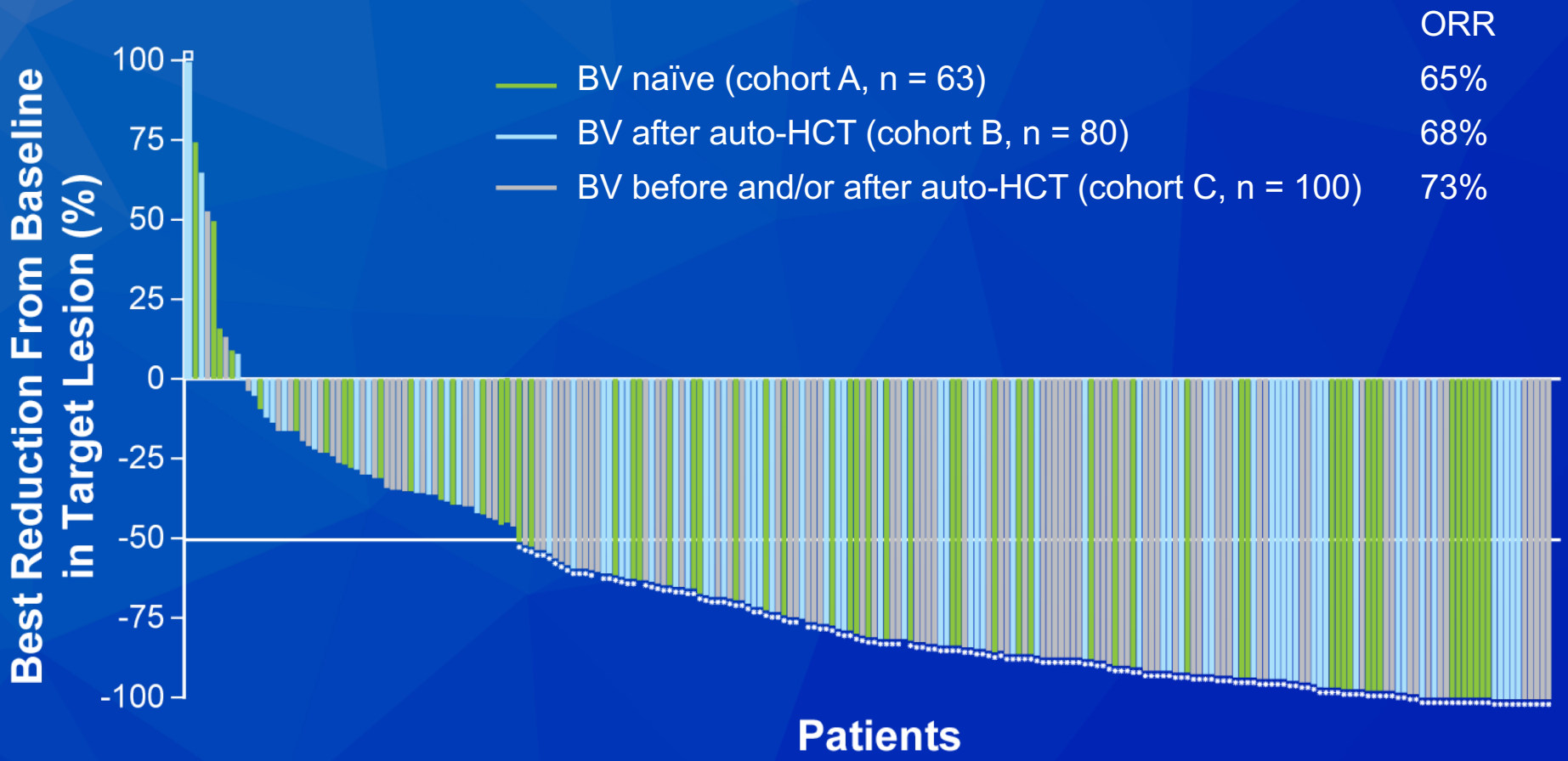
ORIGINAL REPORT

Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

Philippe Armand, Andreas Engert, Anas Younes, Michelle Fanale, Armando Santoro, Pier Luigi Zinzani, John M. Timmerman, Graham P. Collins, Radhakrishnan Ramchandren, Jonathon B. Cohen, Jan Paul De Boer, John Kuruvilla, Kerry J. Savage, Marek Trneny, Margaret A. Shipp, Kazunobu Kato, Anne Sumbul, Benedetto Farsaci, and Stephen M. Ansell

J Clin Oncol 2018;36(14):1428-39.

CheckMate 205 Trial: Response to Nivolumab



BV = brentuximab vedotin

Armand P et al. *J Clin Oncol* 2018;36(14):1428-39.

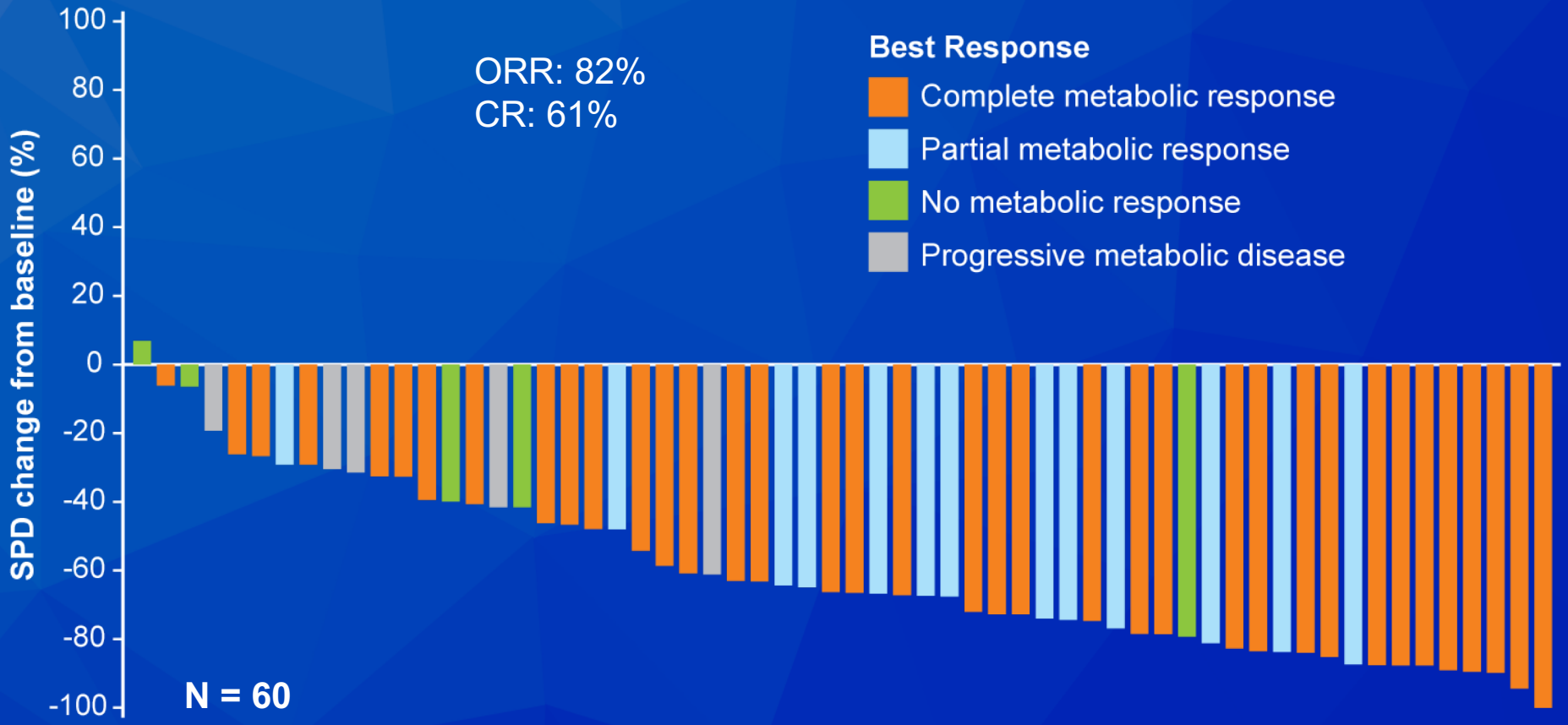
CLINICAL TRIALS AND OBSERVATIONS

Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

Alex F. Herrera,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Stephen M. Ansell,[8] Craig H. Moskowitz,[2] Keenan Fenton,[9] Carol Anne Ogden,[9] David Taft,[9] Qu Zhang,[9] Kazunobu Kato,[10] Mary Campbell,[9] and Ranjana H. Advani[11]

Blood 2018;131:1183-94.

Response with Brentuximab Vedotin/Nivolumab



Herrera AF et al. *Blood* 2018;131(11):1183-94.

Brentuximab Vedotin/Nivolumab: Adverse Events

Events before ASCT (n = 61)	Any grade	Grade ≥3
Nausea	49%	0
Infusion-related reactions	44%	3%
Peripheral sensory neuropathy	15%	0
Diarrhea	26%	2%

Herrera AF et al. *Blood* 2018;131(11):1183-94.

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Special Report

Recommendations for managing PD-1 blockade in the context of allogeneic HCT in Hodgkin lymphoma: taming a necessary evil

Charles Herbaux,[1,*] Reid Merryman,[2,*] Steven Devine,[3] Philippe Armand,[2] Roch Houot,[4] Franck Morschhauser,[1,†] and Bradley Haverkos[5,†]

Blood 2018;132(1):9-16

Recommendations for Patients Receiving PD-1 Blockade

Patient selection

Early referral to transplant center for all patients who may be allo-HCT candidates*

Consider allo-HCT for patients in remission (PR or CR) after PD-1 blockade with very limited post–PD-1 salvage options (ie, low chance to reach a new objective response)*

Consider allo-HCT for any patient after failure of auto-HCT and PD-1 blockade who achieves subsequent remission

Transplant strategy

Hold PD-1 therapy for at least 6 wk before allo-HCT

Use veno-occlusive disease (VOD) prophylaxis (ie, ursodiol) and monitor closely for VOD*

Reduce the risk of GVHD by favoring:

- Bone marrow source
- Reduced-intensity conditioning
- PtCy-based GVHD prophylactic regimen (eg, PtCy/tacrolimus/MMF)*

Perform close monitoring of early transplant complications (eg, noninfectious febrile syndrome)

Management of transplant complications

In the case of noninfectious febrile syndrome:

- Consider rapid initiation of IV methylprednisolone at 1 mg/kg per day*

In the case of GVHD:

- Rapid initiation of IV methylprednisolone at 2 mg/kg per day
- Early intervention with second-line immunosuppression if the patient does not respond rapidly to steroids: consider ATG for second line* or, alternatively, calcineurin inhibitor + ECP*

MMF = mycophenolate mofetil; ATG = anti-thymocyte globulin; ECP = extracorporeal photopheresis

* Recommendation based on expert opinion and experience. The other recommendations are based on published data.

Herbaux C et al. *Blood* 2018;132(1):9-16.

Recommendations for PD-1 Blockade After Allo-HCT

Patient specific

Consideration of the following characteristics:

- History of GVHD: clinical data suggest higher risk in patients with history of GVHD
- Timing of relapse after transplant: safety profile seems better for relapse occurring >180 d; murine and clinical data suggest higher risk when given earlier posttransplant
- Weighing the risks/benefits of checkpoint blockade in light of other therapeutic options*

PD-1 blockade strategy

Start anti-PD-1 at a low dose (eg, nivolumab 0.5 mg/kg) and consider escalation if no response and no toxicity

Perform close monitoring of treatment-emergent GVHD

Management of treatment-emergent GVHD

Stop anti-PD-1 therapy immediately

Rapid initiation of IV methylprednisolone at 2 mg/kg per day

- Early intervention with second-line immunosuppression if the patient does not respond rapidly to steroids: consider ATG for second line* or, alternatively, calcineurin inhibitor + ECP*

* Recommendation based on expert opinion and experience. The other recommendations are based on published data.

Herbaux C et al. *Blood* 2018;132(1):9-16.