Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

October 28, 2017, 8:00 AM – 4:00 PM
Orlando, Florida

Faculty

Jeremy Abramson, MD
Deborah K Armstrong, MD
Jordan D Berlin, MD
Michael Birrer, MD, PhD
Harry P Erba, MD, PhD
Axel Grothey, MD
Hagop M Kantarjian, MD
Ann S LaCasce, MD, MMSc
William K Oh, MD
Joyce O'Shaughnessy, MD
Daniel P Petrylak, MD
Gregory J Riely, MD, PhD
Hope S Rugo, MD
Sonali M Smith, MD
David R Spigel, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

Research To Practice®

Jeremy Abramson, MD
Director of the Lymphoma Program
Jon and Jo Ann Hagler Chair in Lymphoma
Massachusetts General Hospital Cancer Center
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Disclosures

Consulting Agreements	Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc

Ann S LaCasce, MD, MMSc
Program Director, Fellowship in Hematology/Oncology
Associate Professor of Medicine
Harvard Medical School
Lymphoma Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Disclosures

Advisory Committee	Bristol-Myers Squibb Company, Forty Seven Inc
Consulting Agreement	Seattle Genetics

Sonali M Smith, MD
Associate Professor
Section of Hematology/Oncology
Director, Lymphoma Program
The University of Chicago
Chicago, Illinois

Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Juno Therapeutics, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics Inc

Select Recently Approved Agents in CLL/Lymphomas

Agent	Approval date	Indication
Axicabtagene ciloleucel (CAR T-cell therapy)	10/18/17	DLBCL/PMBCL/high-grade BCL/DLBCL arising from FL - relapsed after ≥2 prior therapies
Copanlisib	9/14/17	**FL** - relapsed after ≥2 prior systemic therapies
Rituximab and hyaluronidase human (subQ)	6/22/17	**FL** - relapsed/refractory or nonprogressing - untreated, in combination with chemo and as single-agent maintenance for those with a CR/PR to rituximab/chemo **DLBCL** - untreated, in combination with CHOP or anthracycline-based regimens **CLL** - previously untreated or treated in combination with FC
Pembrolizumab	3/15/17	**cHL** - refractory or relapsed after ≥3 prior lines of therapy
Nivolumab	5/17/16	cHL that has relapsed or progressed after autologous HSCT and post-transplantation brentuximab vedotin

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

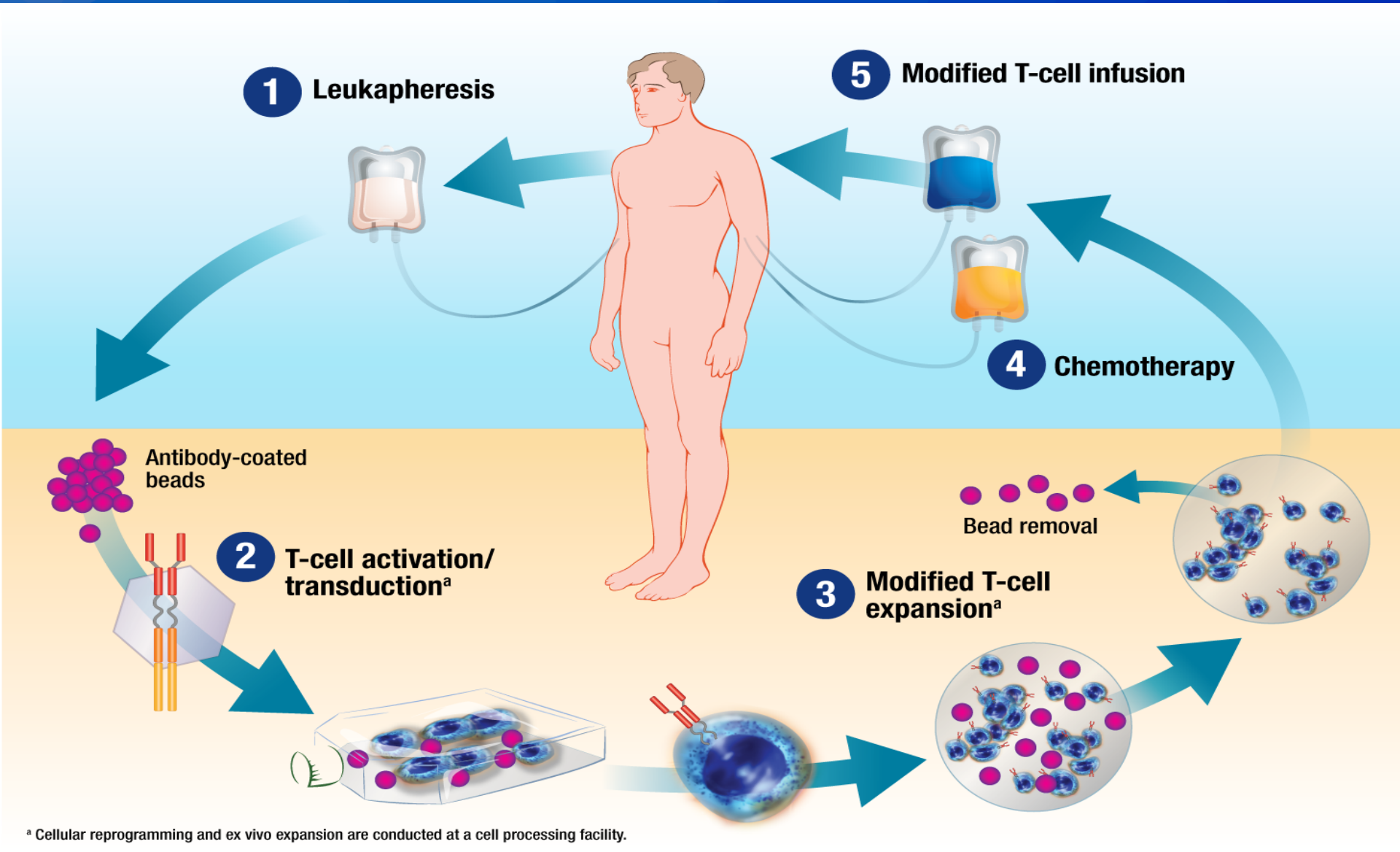
Mantle Cell Lymphoma

T-Cell Lymphoma

Approved Treatment Centers Offering CAR T-Cell Therapy for DLBCL

Approved Treatment Centers Offering CAR T-Cell Therapy for ALL

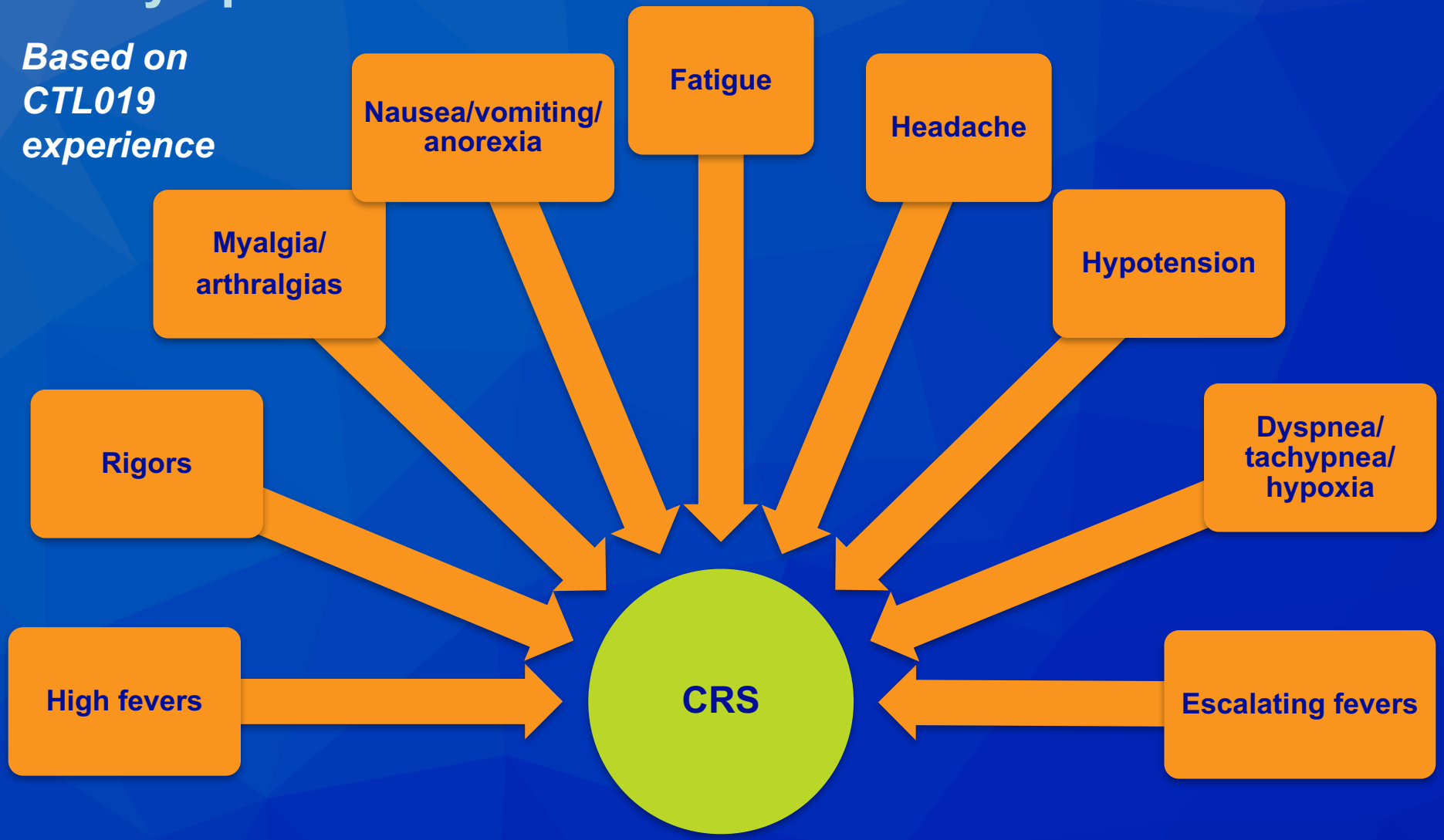
Overview of CTL019 Therapy



[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

Cytokine Release Syndrome (CRS): Common Symptoms

Based on CTL019 experience



Diagnosis based on clinical symptoms and events

Axicabtagene Ciloleucel (AXI-CEL; KTE-C19) in Patients with Refractory Aggressive Non-Hodgkin Lymphomas (NHL): Primary Results of the Pivotal Trial ZUMA-1

Neelapu SS et al.
Proc ICML 2017;Abstract 008.

ZUMA-1: Primary Endpoint — ORR

	ZUMA-1 Phase II					
Best response	DLBCL (n = 77)		TFL/PMBCL (n = 24)		Combined (n = 101)	
	ORR	CR	ORR	CR	ORR	CR
mITT	82%	49%	83%	71%	82%	54%

TFL = transformed follicular lymphoma; PMBCL = primary mediastinal B-cell lymphoma; ORR = objective response rate; CR = complete response; mITT = modified intention to treat

Neelapu SS et al. *Proc ICML* 2017;Abstract 008.

ZUMA-1: Select AEs

Grade ≥ 3 AE	N = 101
Anemia	43%
Neutropenia	39%
Neutrophil count decreased	32%
Febrile neutropenia	31%
White blood cell count decreased	29%
Neurologic events	28%
Thrombocytopenia	24%
Encephalopathy	21%
Lymphocyte count decreased	20%
Cytokine release syndrome	13%

Cytokine release syndrome and neurologic events were mostly reversible.

Neelapu SS et al. *Proc ICML* 2017;Abstract 008.

Press Release — October 18, 2017
FDA Approval of Axicabtagene Ciloleucel

The US Food and Drug Administration today approved axicabtagene ciloleucel, a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma after at least two other kinds of treatment failed, including DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Axicabtagene ciloleucel, a chimeric antigen receptor (CAR) T-cell therapy, is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin lymphoma.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm

Editorial — Dr Abramson

ZUMA-1 is a pivotal phase 2 trial of axicabtagene ciloleucel (axi-cel), an anti-CD19 CAR T cell with a CD28 costimulatory domain. Patients were enrolled with DLBCL, PMBCL, and transformed follicular lymphoma (tFL). All patients underwent enrollment and apheresis and then received lymphodepleting chemotherapy with fludarabine and cyclophosphamide, prior to CAR T-cell infusion. No bridging chemotherapy was allowed between apheresis and lymphodepleting therapy. Patients had to have disease refractory to their prior chemotherapy regimen, or relapse less than one year after autologous stem cell transplant. 111 patients were enrolled, 101 of whom received axi-cel. 77% of subjects were refractory to 2nd line therapy, and 21% relapsed ≤1 year of ASCT.

Editorial — Dr Abramson (continued)

The average time from apheresis to delivery back to the clinical site was 17 days.

Among 101 treated patients, the ORR was 82%, with 54% of patients achieving CR. At a median follow-up of 9 months, 44% and 39% of subjects remained in overall and complete response, respectively. Overall survival at 6 months was 80%. Any CRS (graded with the Lee scale) was observed in 93% of subjects, with 13% of subjects having grade 3-4 CRS. Severe neurologic events occurred in 28% of subjects, and nearly all CRS and neurotoxicity were entirely reversible.

Editorial — Dr Abramson (continued)

These remarkable data demonstrate high overall and complete response rates in a population of patients with chemotherapy-refractory aggressive B-cell lymphoma, and are far superior to historical data in this population. This treatment can now be considered the standard of care for patients with chemorefractory DLBCL, PMBCL and tFL who have relapsed after at least 2 prior regimens, but patients must also have a sufficient performance status and organ and marrow function to allow for safe tolerance of CAR T-cell therapy given the toxicity profile. Further investigation will optimize efficacy of this product alone and in combinations and will also identify biomarkers and clinical predictors of toxicity, which may help guide prophylactic or early intervention strategies which optimize safe administration of this exciting cellular immunotherapy.

Global Pivotal Phase 2 Trial of the CE19-Targeted Therapy CTL019 in Adult Patients with Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) — an Interim Analysis

Schuster SJ et al.
Proc ICML 2017;Abstract 007.

JULIET: Primary Endpoint — Best ORR

Response rate	Patients (n = 51)*	
Best overall response (CR + PR)	**59%**	$p < 0.0001$
CR	**43%**	
PR	16%	
SD	12%	
PD	24%	
Overall response rate (CR + PR) at 3 months	**45%**	
CR	**37%**	
PR	8%	

* Interim analysis was preplanned to include the first 51 patients treated with CTL019 and followed for at least 3 months or discontinued early

Schuster SJ et al. *Proc ICML* 2017;Abstract 007.

JULIET: Select AEs

AE of special interest (n = 85)	All grade	Grade 3	Grade 4
Cytokine release syndrome	57%	17%	9%
Infections	27%	12%	1%
Cytopenias not resolved by day 28	26%	13%	8%
Neurologic events	21%	9%	4%
Febrile neutopenia	14%	13%	1%
Tumor lysis syndrome	1%	1%	0%

- AEs were reversible and effectively managed by appropriately trained study site personnel
  - No CTL019-related deaths or cerebral edema events were reported

Schuster SJ et al. *Proc ICML* 2017;Abstract 007.

Editorial — Dr Abramson

This multicenter global phase 2 pivotal trial evaluated CTL019 for treatment of adults with relapsed/refractory DLBCL. CTL019 is an autologous T-cell product genetically modified to express an anti-CD19 chimeric antigen receptor (CAR) and includes a 4-1BB costimulatory domain. Patients had to have had at least 2 prior lines of therapy and have relapsed after or been ineligible for autologous stem cell transplant. 141 subjects were enrolled and 85 ultimately treated with CTL019, which is administered as a single dose following lymphodepleting chemotherapy. The majority of patients required bridging chemotherapy between the time of enrollment and lymphodepleting therapy. The median number of prior treatments was 3, and half of patients had undergone prior autologous stem cell transplant.

Editorial — Dr Abramson (continued)

Among 51 subjects with a minimum of 3 months follow-up included in the interim analysis, the ORR was 59% and CRR 43%. Median duration of response had not been reached at last follow-up. Cytokine release syndrome (CRS) occurred in 57% of patients and was grade 3-4 in 24% (graded using the University of Pennsylvania scale). Tocilizumab was used in 16% of patients and there were no deaths from CRS. Severe neurologic toxicity occurred in 13%. There were no treatment-related deaths.

These data show remarkable activity of anti-CD19 CAR T-cell therapy producing durable responses in a significant proportion of patients with chemotherapy refractory DLBCL for whom no appealing standard therapy exists.

Editorial — Dr Abramson (continued)

Toxicities include those related to the CAR T-cell activation, most notably including CRS and neurologic toxicities, though these are almost always treatable and reversible. Ongoing investigation is warranted to further optimize the CAR T-cell product itself, to identify and overcome mechanisms of resistance, and to identify biomarkers for both efficacy and toxicity.

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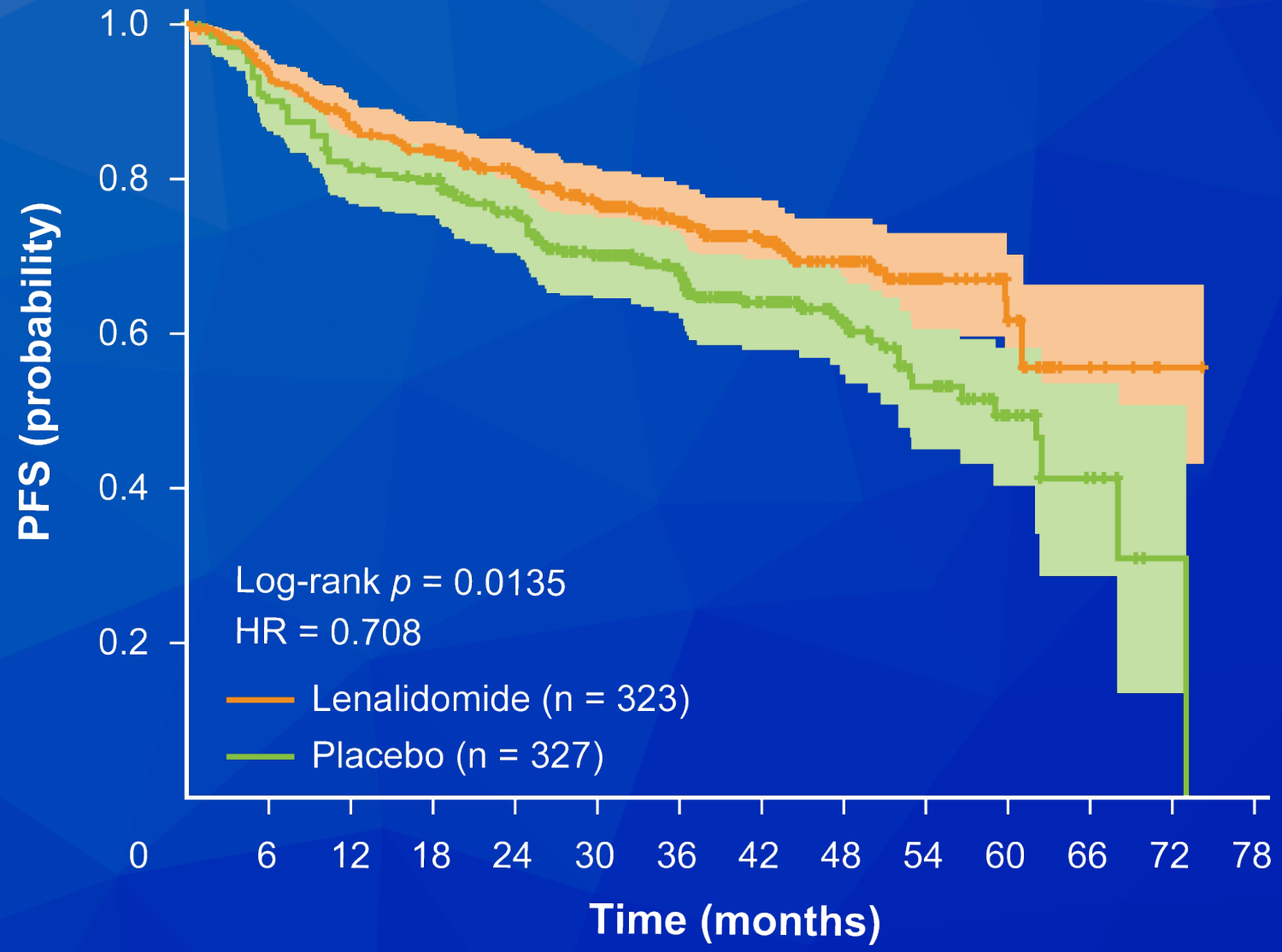
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

Catherine Thieblemont, Hervé Tilly, Maria Gomes da Silva, Rene-Olivier Casasnovas, Christophe Fruchart, Franck Morschhauser, Corinne Haioun, Julien Lazarovici, Anida Grosicka, Aurore Perrot, Judith Trotman, Catherine Sebban, Dolores Caballero, Richard Greil, Koen van Eygen, Amos M. Cohen, Hugo Gonzalez, Reda Bouabdallah, Lucie Oberic, Bernadette Corront, Bachra Choufi, Armando Lopez-Guillermo, John Catalano, Achiel Van Hoof, Josette Briere, Jose Cabeçadas, Gilles Salles, Philippe Gaulard, Andre Bosly, and Bertrand Coiffier

REMARC: Primary Endpoint – PFS



Thieblemont C et al. *J Clin Oncol* 2017;35(22):2473-81.

REMARC: Select Grade 3 or 4 TEAEs

Adverse events	Lenalidomide (n = 322)	Placebo (n = 323)
Neutropenia	181 (56)	72 (22)
Infection	25 (8)	18 (6)
Cardiac disorders	18 (6)	11 (3)
Cutaneous reaction	16 (5)	4 (1)
Thrombocytopenia	8 (3)	2 (1)
Venous thromboembolic event	6 (1)	1 (0.3)
Diarrhea and constipation	5 (2)	2 (1)
Hepatic disorder	4 (1)	6 (2)
Peripheral neuropathy	2 (1)	6 (2)
SPMs observed during and after maintenance		
Patients with ≥1 SPM	32 (10)	41 (13)
≥1 hematologic SPM	7 (2)	5 (2)
≥1 solid tumor	12 (4)	18 (6)
≥1 solid tumor, including nonmelanoma skin cancer	27 (8)	37 (11)
Deaths associated with SPMs	9 (3)	9 (3)

SPM = second primary malignancy

Thieblemont C et al. *J Clin Oncol* 2017;35(22):2473-81.

Editorial — Dr Abramson

The REMARC trial asked whether maintenance lenalidomide improved outcome compared to placebo in DLBCL patients aged 60-80 who achieved a complete or partial response to initial R-CHOP. 796 patients were enrolled, of whom 650 responded to R-CHOP and were randomized to lenalidomide at a dose of 25 mg daily on days 1-21 of the 28-day cycle, or placebo. Both groups were treated for up to 2 years.

The study met its primary endpoint with an improved PFS in the lenalidomide arm. At 2 years, the PFS for lenalidomide was 80%, compared to 75% with placebo. Overall survival was no different, with 87% of lenalidomide patients remaining alive at 2 years and 89% in the placebo arm.

Editorial — Dr Abramson (continued)

On subset analysis, the PFS benefit appeared limited to the GCB subset (defined by immunohistochemistry), in whom the median PFS was 61 months compared to 53 months.

Two thirds of patients on the lenalidomide required dose reductions due to adverse events, and 36% stopped treatment due to toxicity. The most common grade 3-4 toxicity was neutropenia, occurring in 56% of lenalidomide subjects compared to 22% with placebo. Grade 3-4 rash also occurred more frequently with lenalidomide (5% vs 1%).

Editorial — Dr Abramson (continued)

Notably, this is the first randomized trial to show a PFS benefit for a maintenance therapy in DLBCL, but the magnitude of benefit was modest, and given the associated toxicity and the absence of an OS benefit, this does not appear to establish a new standard of care for most patients with DLBCL. The presence of a 5% improvement in 2-year PFS with identical OS likely reflects availability of effective 2nd line therapy in a proportion of relapsing subjects on the placebo arm, including autologous stem cell transplantation. It is interesting that the PFS benefit applied exclusively to GCB patients, while lenalidomide monotherapy for relapsed disease appears to be preferentially beneficial in ABC-like disease.

Editorial — Dr Abramson (continued)

This may reflect that the relevant mechanism of action as maintenance therapy in patients who have already achieved remission is in enhancing NK and T-cell activity post induction therapy, thus improving anti-tumor immune surveillance in the host. It is not readily clear, however, why this benefit would apply exclusively to GCB subjects as opposed to being agnostic in terms of cell of origin. Further investigation is warranted regarding clinical and biologic subsets who may benefit the most from this approach.

Efficacy And Safety Of Subcutaneous And Intravenous Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, And Prednisone In First-Line Diffuse Large B-Cell Lymphoma: The Randomized MabEase Study

Pieternella Lugtenburg, Irit Avivi, Henriette Berenschot, Osman Ilhan, Jean Pierre Marolleau, Arnon Nagler, Antonio Rueda, Monica Tani, Mehmet Turgut, Stuart Osborne, Rodney Smith, Michael Pfreundschuh

Haematologica 2017;[Epub ahead of print].

MabEase: Efficacy, Tolerability and QoL

End of induction therapy	Rituximab SC plus CHOP (n = 342)	Rituximab IV plus CHOP (n = 177)	*p*-value
CR/CRu	50.6%	42.4%	0.076
ORR	82.2%	78.0%	
35 months follow-up			**HR (*p*-value)**
PFS	72.2%	78.5%	1.30 (0.175)
EFS	66.1%	71.2%	1.18 (0.314)

- Grade ≥3 adverse events and administration-related reactions were similar
- Febrile neutropenia occurred more often in the SC arm (12.5% vs 6.9%, $p = 0.06$)
- RASQ scores for 'impact on activities of daily living,' 'convenience' and 'satisfaction' were improved with SC vs IV
    - Treatment preference: 90.8% preference for SC over IV

RASQ = Rituximab Administration Satisfaction Questionnaire

Lugtenburg P et al. *Haematologica* 2017;[Epub ahead of print].

Editorial — Dr Abramson

The MabEase trial evaluated a subcutaneous (SC) formulation of rituximab in combination with CHOP for front-line DLBCL therapy, compared to the standard IV formulation. 576 patients were randomized 2:1 to rituximab SC or IV. Patients in the SC group still received the first dose IV at the standard dose of 375 mg/m^2, and all remaining doses at a flat dose of 1,400 mg. The IV arm received standard IV rituximab dosing.

In terms of clinical endpoints, no differences were observed in terms of ORR, CRR, PFS, EFS or OS. Rates of adverse events were also similar between arms, though local infusion site reactions and febrile neutropenia were both increased in the SC arm.

Editorial — Dr Abramson (continued)

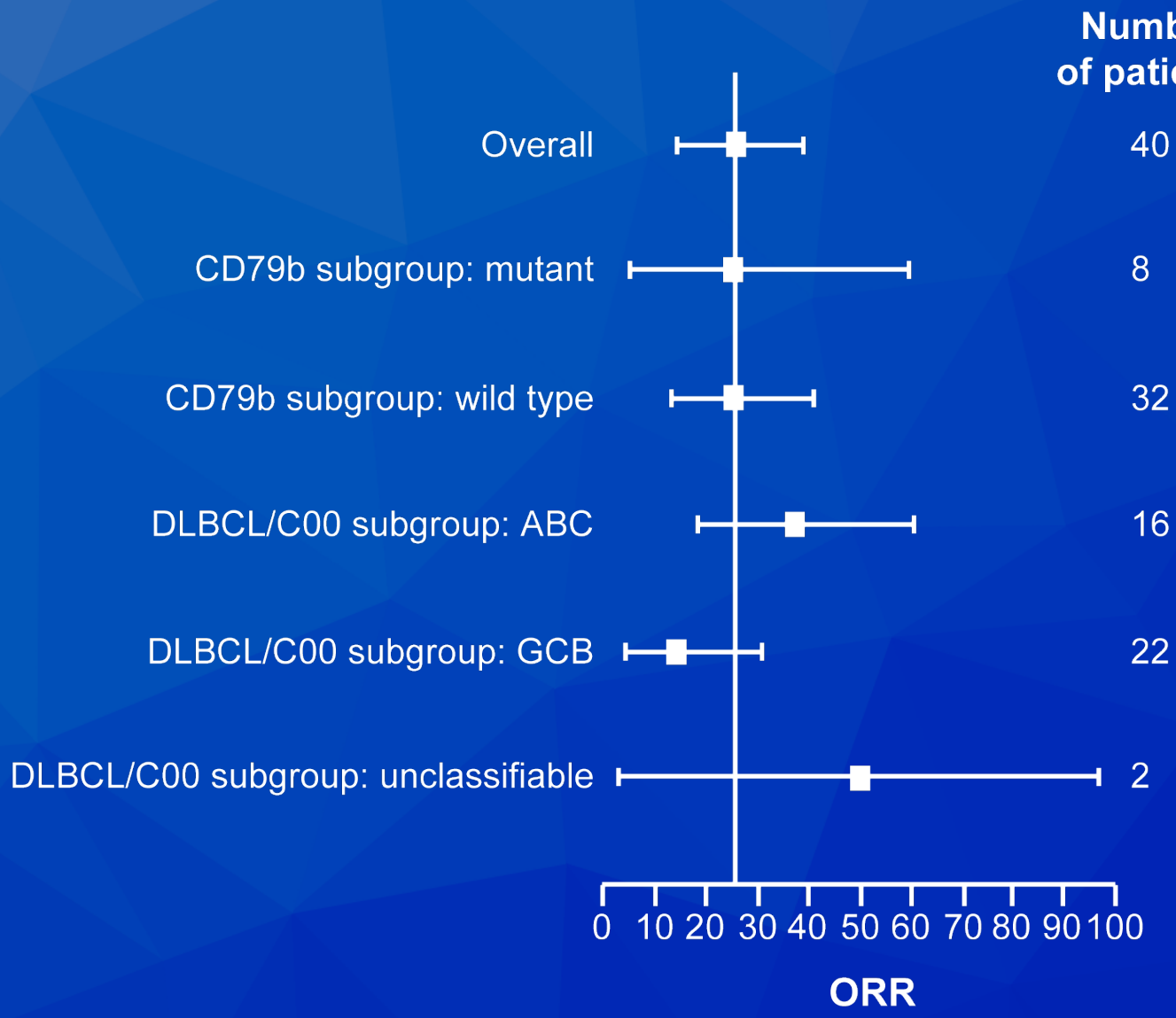
The SC formulation allowed much quicker delivery with a median time of administration of 6 minutes compared to 2.6-3.0 hours with the IV route. On questionnaires, 91% of subjects preferred SC over IV rituximab.

These data establish SC rituximab as an appropriate alternative to IV rituximab when combined with CHOP for initial therapy of DLBCL. Cure rates appear identical, and SC administration is preferred by the vast majority of subjects, likely reflecting the ease of delivery and marked reduction in time required. Centers may prefer this option as well as it will allow a greater number of patients to be treated in a given infusion chair. Cost will require some consideration as the SC formulation will be more expensive than IV rituximab, which will likely be available as biosimilars in the not too distant future.

Clinical Outcomes and Molecular Characterization from a Phase II Study of Copanlisib in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Lenz G et al.
Proc ICML 2017;Abstract 57.

Phase II Study of Copanlisib for R/R DLBCL



Most common AEs (all grade):

- Diarrhea (36%)
- Nausea (31%)
- Fatigue (31%)
- Fever (21%)
- Transient hypertension (40%)
- Hyperglycemia (34%)

Lenz G et al. *Proc ICML* 2017;Abstract 57.

Editorial — Dr Abramson

This phase II study evaluated the PI3K alpha/delta inhibitor copanlisib in patients with relapsed or refractory DLBCL. Copanlisib is administered at a flat dose of 60 mg IV on days 1, 8 and 15 of a 28-day cycle, and was administered until disease progression. Among 67 enrolled subjects, the ORR was 19%; however, in a per protocol analysis, 10 of 40 (25%) of subjects responded, including 5 complete remissions. On preplanned subset analysis, responses appeared likelier in ABC-like DLBCL (37.5%) than in GCB-like DLBCL (13.6%). Toxicities included diarrhea, nausea, fatigue, hypertension, and hyperglycemia and were predominately grade 1-2, though grade 3-4 hyperglycemia and hypertension were seen in 1/3 of patients.

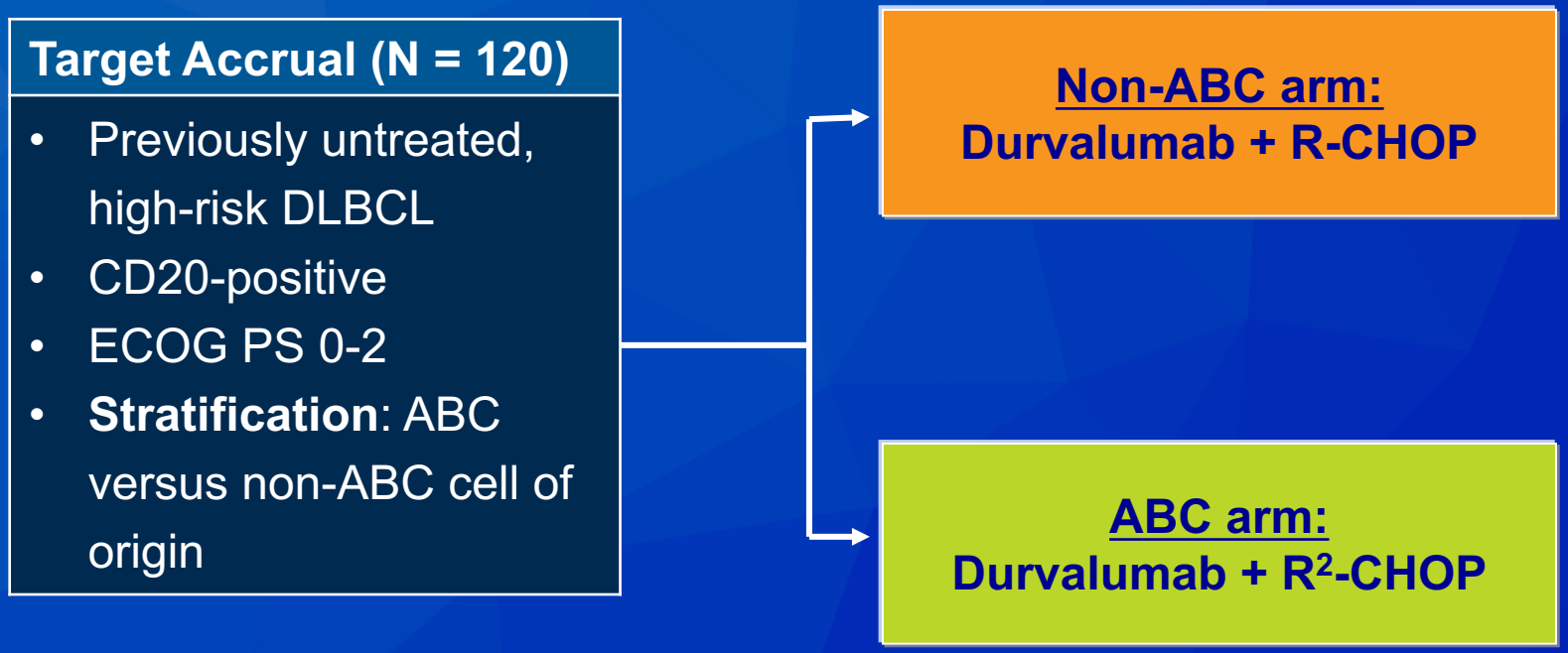
Editorial — Dr Abramson (continued)

The ORR and CRR in this small study are encouraging, particularly in ABC-DLBCL. Broader mutational analysis will be important to identify likely responders from resistant patients, even in a biologically enriched subgroup, and combination studies with other active agents in ABC-DLBCL, such as BTK inhibitors and lenalidomide, warrant exploration.

Phase II Study of Durvalumab (Anti–PD-L1) Combined with Either R-CHOP or Lenalidomide and R-CHOP in Previously Untreated, High-Risk Diffuse Large B-Cell Lymphoma

Jaeger U et al.
Proc ICML 2017;Abstract OT02.

MEDI4736-DLBCL-001: A Phase II Study of Durvalumab with Chemotherapy for Previously Untreated DLBCL



Primary Endpoint: 2-year progression-free survival

Jaeger U et al. *Proc ICML* 2017;Abstract OT02; www.clinicaltrials.gov (NCT03003520).

Editorial — Dr Abramson

This planned phase II trial will be evaluating the PD-L1 inhibitor durvalumab in combination with either R-CHOP or R-CHOP-lenalidomide in previously untreated GCB-like or ABC-like DLBCL, respectively, as defined by gene expression profiling. All patients enrolled in the study will be considered high-risk, as defined by bulky stage II or stage III-V disease, along with IPI ≥3 or NCCN IPI ≥4. Responding patients will continue consolidation durvalumab once monthly for up to 1 year from beginning of treatment. The primary endpoint is 2-year PFS, and the planned enrollment goal is 120 subjects.

Results of this study will be of great interest given the emerging role of immune checkpoint inhibitors across the oncologic spectrum.

Editorial — Dr Abramson (continued)

Notably, however, rates of PD-L1 expression are overall quite low in DLBCL, though they may be higher in ABC- compared to GCB-DLBCL, and are substantially increased in selected DLBCL subsets, including primary mediastinal B-cell lymphoma (PMBCL), primary CNS DLBCL (PCNSL), primary testicular DLBCL (PTL), EBV+ DLBCL, and T-cell histiocyte-rich B-cell lymphoma. Notably, response rates to single-agent immune checkpoint inhibitors have been quite low in unselected DLBCL populations, while increased single-agent activity has been seen in select aforementioned subsets with known amplifications of PD-L1 (PMBCL, PCNSL, PTL).

Editorial — Dr Abramson (continued)

Results of this study, once available, will certainly be of great interest, particularly in regard to outcome by cell of origin, but further evaluation in DLBCL subsets likelier to garner benefit from immune checkpoint inhibition is also needed.

Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

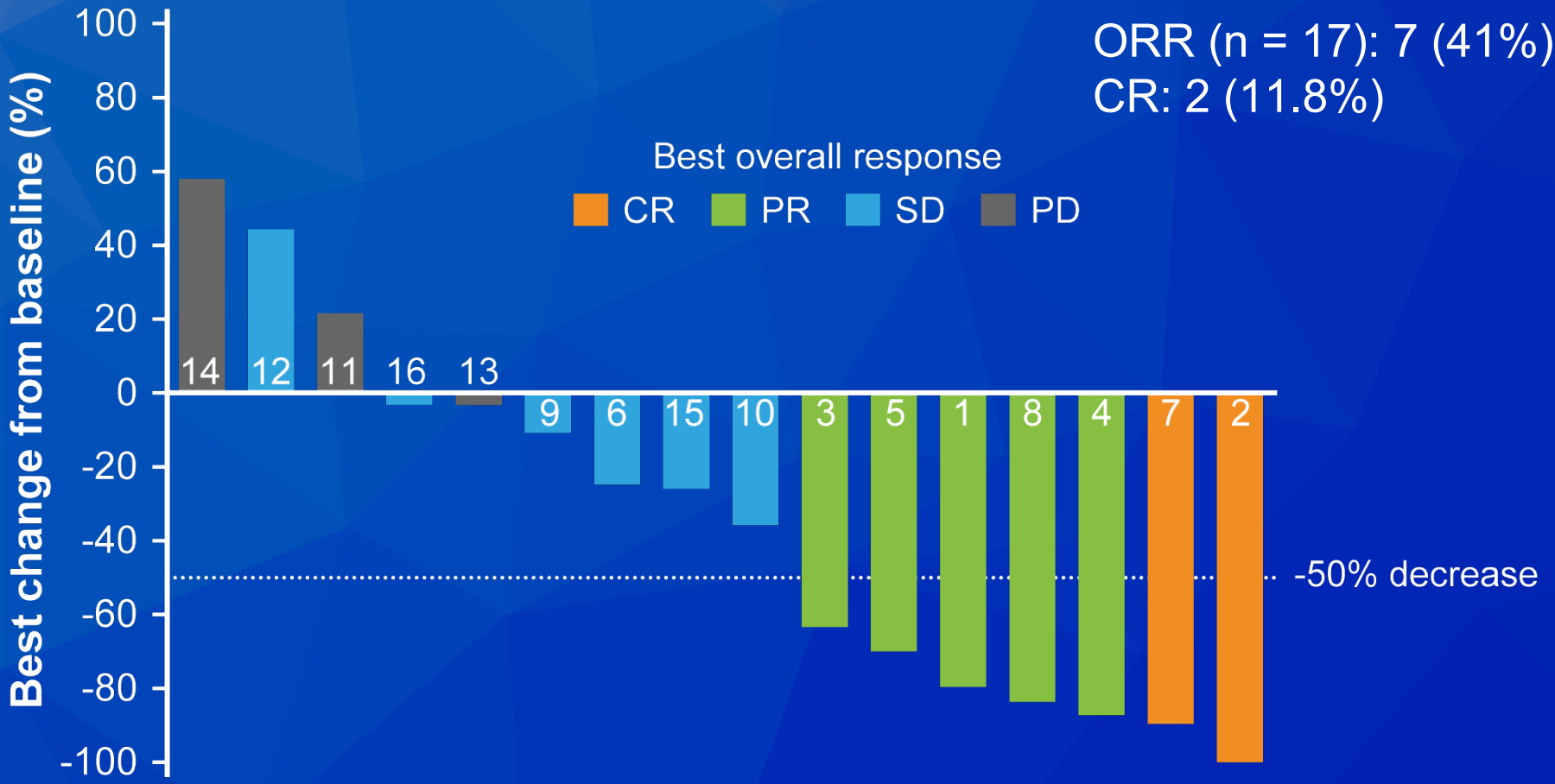
Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma

Pier Luigi Zinzani,[1] Vincent Ribrag,[2] Craig H. Moskowitz,[3] Jean-Marie Michot,[2] John Kuruvilla,[4] Arun Balakumaran,[5] Yayan Zhang,[5] Sabine Chlosta,[5] Margaret A. Shipp,[6] and Philippe Armand[6]

[1]Institute of Hematology "L. e A. Seràgnoli," University of Bologna, Bologna, Italy; [2]Gustave Roussy, Université Paris-Saclay, Département d'hématologie, INSERM U1170, Villejuif, France; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada; [5]Merck & Co., Inc., Kenilworth, NJ; and [6]Dana-Farber Cancer Institute, Boston, MA

Blood 2017;130(3):267-70.

KEYNOTE-013: Pembrolizumab for Primary Mediastinal Large B-Cell Lymphoma



- Median OS: not reached
- 61% patients had AEs, mostly Grade 1/2

Zinzani PL et al. *Blood* 2017;130(3):267-70.

Editorial — Dr Smith

Cancer cells, including malignant lymphoma cells, circumvent the immune system in many ways. One mechanism is upregulation of the “checkpoint” PD-L1 on malignant cells, which engages with PD-1 on T cells, thus inducing T-cell anergy and exhaustion. Inhibiting the PD-1/PD-L1 axis has been highly successful in Hodgkin lymphoma, where amplification of 9p24.1 is a near universal finding. 9p24.1 is the locus for PD-L1, PD-L2, and JAK genes.

Primary mediastinal B-cell lymphoma is a relatively rare subtype of diffuse large B-cell lymphoma occurring in younger patients with a female predominance; initial therapy is associated with improved survival, but relapses are often fulminant and characterized by chemoresistance.

Editorial — Dr Smith (continued)

Primary mediastinal B-cell lymphoma (PMBL) shares many biologic features with classical Hodgkin lymphoma, including similar gene expression profiles, a younger patient population, and presenting with a mediastinal mass. The majority of patients also have 9p24.1 amplification, offering a rational reason to target the PD-1/PD-L1 checkpoint.

The KEYNOTE-013 trial tests pembrolizumab monotherapy in patients with relapsed and refractory PMBL. Among 16 evaluable patients, the median age was 30.5 years, 72% were female, 61% had more than 2 lines of prior therapy, 33% had a prior autologous stem cell transplant and 61% had prior radiation.

Editorial — Dr Smith (continued)

The overall response rate was 41% with 2 patients achieving a PET-negative CR. Treatment-related adverse events occurred in 11 (61%) of patients, but were mainly grade 1-2 in severity. One patient proceeding to allogeneic stem cell transplant had grade 4 veno-occlusive disease.

Overall, these data are encouraging in a disease where relapse is often fatal and difficult to manage. The response rates are not as high as in Hodgkin lymphoma despite the increased 9p24.1 amplification, and much remains to be learned about mechanisms of intrinsic and acquired resistance to checkpoint blockade across lymphomas. Nevertheless, these promising data have prompted a global phase II trial of pembrolizumab in relapsed/refractory PMBL.

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

Integrated Analysis: Outcomes of Ibrutinib-Treated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL) with High-Risk Prognostic Factors

Kipps TJ et al.
Proc ICML 2017;Abstract 100.

Survival Outcomes in Ibrutinib- and Comparator-Treated Patients by Genomic Prognostic Factors

- Data from 3 studies (N = 1,238) were pooled to analyze outcomes with/without genomic risk factors
- Comparators: Ofatumumab, chlorambucil and bendamustine/rituximab

		Ibrutinib treated		Comparators	
		Present	Absent	Present	Absent
24-mo PFS	Unmutated IGHV	78%	81%	10%	32%
	Del 11q	82%	75%	9%	19%
	Trisomy 12	77%	80%	16%	18%
	Complex karyotype	76%	79%	NE	20%
30-mo OS	Unmutated IGHV	88%	89%	76%	87%
	Del 11q	93%	86%	76%	78%
	Trisomy 12	89%	89%	79%	79%
	Unmutated IGHV	84%	90%	69%	81%

NE = Not evaluable

Kipps TJ et al. *Proc ICML* 2017;Abstract 100.

Editorial — Dr LaCasce

This analysis examined the outcome of 1,238 CLL patients without deletion 17p treated with ibrutinib on 3 clinical trials (ofatumumab versus ibrutinib in relapsed/refractory CLL, ibrutinib versus chlorambucil in treatment naïve patients and bendamustine/rituximab with or without ibrutinib in previously untreated disease) with regard to IGHV, deletion 11q, trisomy 12 and/or complex karyotype. In addition, age, sex, performance status, cytopenias, LDH, bulky disease and number of prior therapies were assessed. With median follow-up of 21 months, PFS (76%-82% vs 9%-16%) and OS (84%-93% vs 69%-76%) were superior in the ibrutinib containing arms regardless of risk factors.

Editorial — Dr LaCasce (continued)

In multivariate analysis in the ibrutinib arms, only one or more prior therapies was associated with shorter PFS and OS. Age ≥65 and elevated LDH were associated with shorter OS. In contrast, for the non-ibrutinib arms, >1 prior therapy, unmutated IGHV, deletion 11q, complex cytogenetics, male sex and bulky disease (≥5 cm) were associated with shorter PFS, and complex cytogenetics, male sex, bulky disease, ECOG PS ≥1 and elevated LDH were associated with inferior OS.

In the absence of 17p deletion, traditional adverse molecular prognostic indicators, including complex karyotype and unmutated IGHV, do not predict outcome in ibrutinib treated patients.

Editorial — Dr LaCasce (continued)

Prior lines of therapy, older age and elevated LDH, reflecting disease burden and possibly occult transformation, were associated with inferior overall survival. This data suggests that patients may derive the greatest benefit from ibrutinib when it’s given in the first or second line as opposed to following multiple chemoimmunotherapy regimens.

Acalabrutinib Monotherapy in Patients with Ibrutinib Intolerance: Results from the Phase 1/2 ACE-CL-001 Clinical Study

Awan FT et al.
Proc ASH 2016;Abstract 638.

Safety and Efficacy of Acalabrutinib in Patients wit CLL Intolerant to Ibrutinib

- N = 33 patients intolerant to ibrutinib
- Median duration of ibrutinib treatment: 10.5 months
  - Range 1-62.3 mo
- ORR (CR + PR + PRL): 23/29 (79%)
- 81% of responding pts have a DoR of ≥12 mo (PFS not reached)
- Most AEs were Grade 1/2 (58%); Most common AEs (all grades):
  - Diarrhea (52%)
  - Cough (24%)
  - Nausea (21%)
  - Headache (39%)
  - Increased weight (24%)
- Grade 3 AEs in ≥2 pts
  - Thrombocytopenia (9%)
  - Anemia, neutropenia, pneumonia, hypertension, parasthesia (6%, each)
- 2 atrial fibrillation events were reported (1 Gr 2, 1 Gr 3)
- Treatment discontinuation due to AEs: 3/33 (9%)

Awan FT et al. *Proc ASH* 2016;Abstract 638.

Editorial — Dr LaCasce

Acalabrutinib is a second generation, potent, highly selective BTK inhibitor. Compared with ibrutinib, the drug is likely to have fewer off target effects, including atrial fibrillation and bleeding. In this phase 1/2 study of acalabrutinib, 33 patients intolerant of ibrutinib, 30% of whom harbored deletion 17p, were treated at 100 mg BID (n = 30) or 200 mg daily (n = 3). The drug was well tolerated with pneumonia as the only serious adverse event occurring in 2 patients. There were 2 cases of atrial fibrillation, one of which occurred in a patient with a history of paroxysmal atrial fibrillation, and no cases of major hemorrhage. With median follow-up of 9.5 months, the overall response rate was 76% (1 CR, 14 PR and 7 PR with lymphocytosis) with a median duration of response of 13 months.

Editorial — Dr LaCasce (continued)

Median PFS was not reached, and acalabrutinib appears to offer a significant advantage over ibrutinib in terms of its side effect profile, particularly with respect to atrial fibrillation and risk of bleeding, which can be problematic in CLL patients, who are often elderly with multiple co-morbidities. Longer follow-up to assess for the later occurrence of atrial fibrillation and to determine longer-term efficacy is forthcoming.

Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial

Andrew D Zelenetz, Jacqueline C Barrientos, Jennifer R Brown, Bertrand Coiffier, Julio Delgado, Miklós Egyed, Paolo Ghia, Árpád Illés, Wojciech Jurczak, Paula Marlton, Marco Montillo, Franck Morschhauser, Alexander S Pristupa, Tadeusz Robak, Jeff P Sharman, David Simpson, Lukáš Smolej, Eugen Tausch, Adeboye H Adewoye, Lyndah K Dreiling, Yeonhee Kim, Stephan Stilgenbauer, Peter Hillmen

Lancet Oncol **2017; 18: 297–311**

Response and Survival Analyses

Endpoint	N	Idelalisib + BR	Placebo + BR	HR	*P*
Median PFS	207, 209	20.8 mo	11.1 mo	0.33	<0.0001
Either del(17p) or TP53 mutant	69, 68	11.3 mo	8.3 mo	0.47	<0.0001
Median OS	207, 209	Not reached	31.6 mo	0.62	0.031
ORR	207, 209	70%	45%	—	—
With del(17p)	38, 40	58%	23%	—	—
With unmutated IGHV	173, 173	71%	43%	—	—

- ≥Grade 3 neutropenia: 60% vs 47%
- ≥Grade 3 febrile neutropenia: 23% vs 6%
- ≥Grade 3 infections and infestations: 39% vs 25%

Zelenetz AD et al. *Lancet Oncol* 2017;18(3):297-311; *Proc ASH* 2016;Abstract 231.

Editorial — Dr LaCasce

In this phase 3 study, 416 patients with relapsed/refractory CLL who were within 36 months of their most recent therapy were randomized to receive bendamustine/rituximab for 6 cycles with idelalisib versus placebo until progression. With 14 months of median follow-up, the median PFS was 20.8 months in the idelalisib arm versus 11.1 months in the control arm. With longer term median follow-up of 21 months, the overall survival was not met in the idelalisib arm compared with 41 months in the placebo arm. Serious adverse events occurred in 71% and 5% in the idelalisib and placebo arms respectively.

Editorial — Dr LaCasce (continued)

Pneumocystis jirovecii pneumonia was seen in 13 versus 5 patients, and 3 patients receiving idelalisib developed CMV reactivation. Treatment associated deaths were also more common in the idelalisib arm, with 23 compared to 15 patients in the placebo arm.

This data and the recent preliminary report of the bendamustine plus obinutuzumab versus rituximab highlight the increased risk of serious infections and treatment related mortality seen in patients treated with bendamustine. In addition, idelalisib is associated with opportunistic infections and risk of CMV reactivation, as well as pneumonitis and the development of colitis, particularly after longer term administration of the drug.

Editorial — Dr LaCasce (continued)

With the emergence of additional novel agents in CLL, including venetoclax and second generation BTK inhibitors, the future role of bendamustine/rituximab plus idelalisib is unclear.

Phase 3 MURANO Study with Venetoclax/Rituximab in CLL Meets Primary Endpoint

Press Release: September 18, 2017

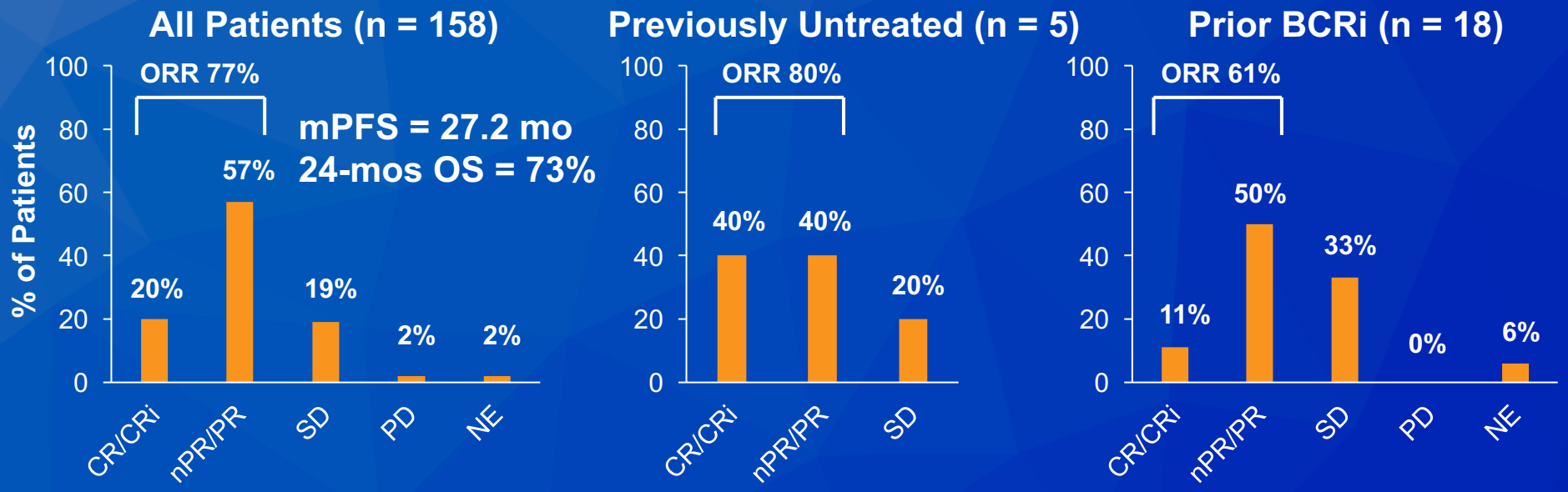
"Results showed that venetoclax in combination with Rituxan prolonged progression-free survival (PFS) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) compared with bendamustine combined with Rituxan. An independent data monitoring committee reviewed this study and made the recommendation to unblind the trial based on the positive results."

https://news.abbvie.com/news/abbvie-announces-positive-topline-results-from-phase-3-trial-evaluating-venclextavenclyxto-venetoclax-tablets-in-combination-with-rituxan-rituximab-for-treatment-patients-with-relapsedrefractory-chronic-lymphocytic-leukemia.htm

Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) with 17p Deletion: Outcome and Minimal Residual Disease from the Full Population of the Pivotal M13-982 Trial

Stilgenbauer S et al.
Proc EHA 2017;Abstract S771.

M13-982: Response, Survival and MRD Status with Venetoclax in CLL with Del(17p)



Best MRD Status by Flow Cytometry and/or NGS			
n	CR/CRi	nPR	PR
Total peripheral blood negative (-)	20	1	19
Peripheral blood (-) and bone marrow (-)	14	0	4
Peripheral blood (-) but bone marrow (+)	3	0	4
Peripheral blood (-) but bone marrow not assessed	3	1	11

Stilgenbauer S et al. *Proc EHA* 2017;Abstract S771.

Editorial — Dr LaCasce

In this phase 2 study, 158 patients with relapsed/refractory CLL received 400 mg of venetoclax daily until progression, after the standard initial dose escalation phase to mitigate the risk of tumor lysis syndrome. The overall and complete remission rates for all patients were 77% and 18% respectively, and at 2 years the PFS was 52% and OS 72%. For the 18 patients previously treated with B-cell receptor signaling inhibitors, the ORR was 61% and CR 11%, with similar PFS and OS to the overall cohort. Of 5 previously untreated patients with deletion 17p, the ORR and CR rates were 80% and 40% respectively, and all patients were progression free at one year.

Editorial — Dr LaCasce (continued)

Grade 3/4 adverse events included neutropenia (39%), thrombocytopenia (15%), anemia (14%) and infection (22%). Of 101 patients with specimens analyzed for MRD status by flow cytometry, 42 (27%) were MRD negative. Of these 42 patients, 28 had concurrent next generation sequencing (NGS) analysis performed, of whom 20 (71%) were negative. For patients who achieved MRD-negative CR by flow cytometry in blood, 24 month PFS was 100% compared with 78.5% for those with MRD-negative PR. Results using NGS were similar.

This study confirmed the activity of venetoclax in this high risk group of patients with CLL, with nearly 30% of patients achieving MRD negativity by flow cytometry.

Editorial — Dr LaCasce (continued)

With its favorable toxicity profile, consisting predominantly of manageable cytopenias, combination studies with monoclonal antibodies, chemotherapy and/or other novel agents are highly promising.

Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study

Anna Maria Fink, Jasmin Bahlo, Sandra Robrecht, Othman Al-Sawaf, Ali Aldaoud, Holger Hebart, Kathleen Jentsch-Ullrich, Steffen Dörfel, Kirsten Fischer, Clemens-Martin Wendtner, Thomas Nösslinger, Paolo Ghia, Francesc Bosch, Arnon P Kater, Hartmut Döhner, Michael Kneba, Karl-Anton Kreuzer, Eugen Tausch, Stephan Stilgenbauer, Matthias Ritgen, Sebastian Böttcher, Barbara Eichhorst, Michael Hallek

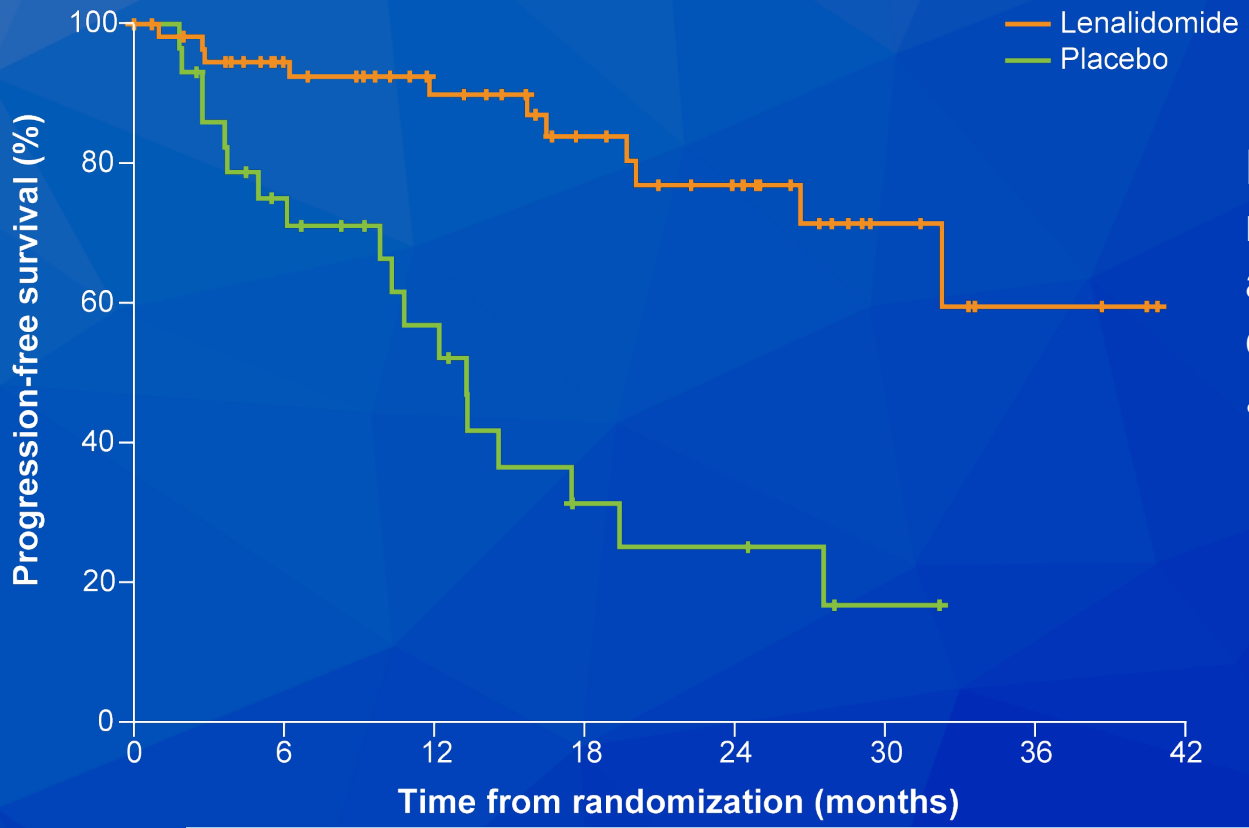
Lancet Haematol 2017;4(10):e475-86.

Lenalidomide maintenance therapy in previously treated chronic lymphocytic leukaemia (CONTINUUM): a randomised, double-blind, placebo-controlled, phase 3 trial

Asher A Chanan-Khan, Andrey Zaritskey, Miklos Egyed, Samuel Vokurka, Sergey Semochkin, Anna Schuh, Jeannine Kassis, David Simpson, Jennie Zhang, Brendan Purse, Robin Foà

Lancet Haematol 2017;[Epub ahead of print].

CLLM1: Progression-Free Survival (BICR) to Maintenance Lenalidomide



Patients with CLL at high risk of early recurrence after 1st-line chemoimmunotherapy

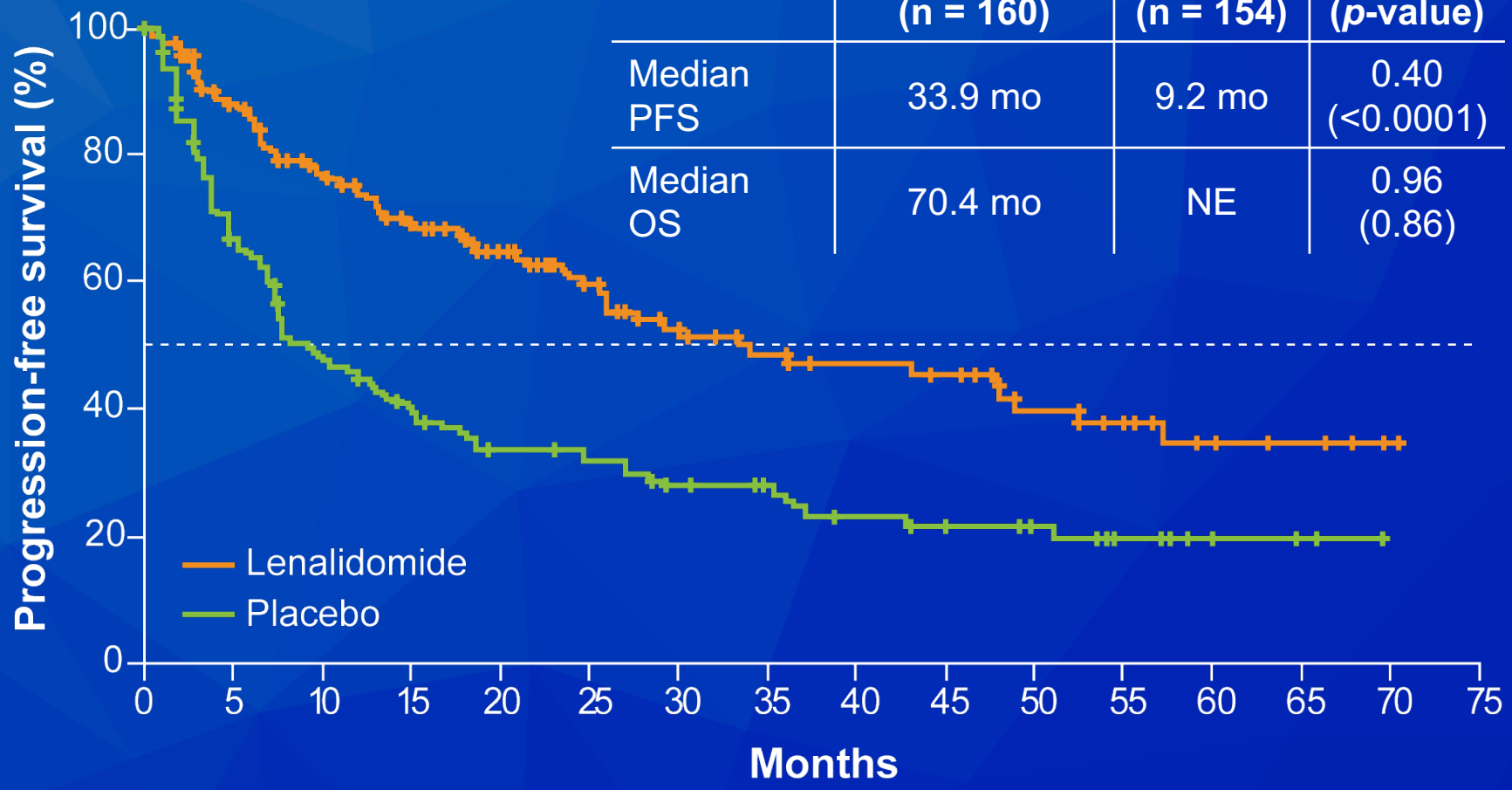
- High MRD levels or intermediate MRD levels combined with unmutated IGHV gene status or TP53 alterations

Endpoint	Lenalidomide (n = 60)	Placebo (n = 29)	HR	*p*
Median PFS	Not reached	13.3 mo	0.168	<0.0001
24-month PFS	76.5%	24.8%	—	—

Fink AM et al. *Lancet Haematol* 2017;4(10):e475-86.

CONTINUUM: Progression-Free Survival (ITT) to Maintenance Lenalidomide in Patients Treated with 2 Prior Lines of Therapy

	Lenalidomide (n = 160)	Placebo (n = 154)	HR (*p*-value)
Median PFS	33.9 mo	9.2 mo	0.40 (<0.0001)
Median OS	70.4 mo	NE	0.96 (0.86)



Chanan-Khan AA et al. *Lancet Haematol* 2017;[Epub ahead of print].

Editorial — Dr LaCasce

The CLLM1 study enrolled previously untreated patients achieving at least a PR after chemoimmunotherapy who had high risk MRD levels or intermediate levels in conjunction with unmutated IGVH or TP53 alterations. Patients were randomized in a 2:1 fashion to 5 mg of lenalidomide (escalated to 15 mg) or placebo and continued to progression, if tolerating the treatment. Given low eligibility rates, the study was closed early for poor accrual following randomization of 89 of 200 planned patients. Overall, 56 patients received lenalidomide (LEN) and 29 placebo (PBO). With median follow-up of 17.9 months, median PFS was not reached (LEN) versus 13.1 months (PBO).

Editorial — Dr LaCasce (continued)

The most common adverse events associated with lenalidomide were gastrointestinal disorders and hematologic toxicity, and infections were comparable in both arms. One patient on lenalidomide developed fatal acute lymphoblastic leukemia, and there was one death in each arm.

In the CONTINUUM trial, 214 patients achieving at least a PR to second line therapy were randomized 1:1 to 2.5 mg of lenalidomide (escalated to 10 mg) or placebo. With a median follow-up of 31.5 months, median PFS was 33.9 compared to 9.2 months in the lenalidomide versus placebo arms respectively, without difference in OS. The most common grade 3/4 adverse events were neutropenia, thrombocytopenia and diarrhea. Infections and second malignancies were similar between arms.

Editorial — Dr LaCasce (continued)

In both trials, lenalidomide maintenance was associated with improved PFS without difference in OS. The inclusion criteria were different, with the first study examining front line maintenance in high risk patients whereas the second study included relapsed patients achieving at least a PR. Therapy was well tolerated with low rates of secondary cancers, though follow-up in the first study was short. For patients receiving chemoimmunotherapy, maintenance lenalidomide represents a reasonable option, though longer follow-up is required to fully assess late toxicities as well as response to subsequent therapy.

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

ECHELON-1 Phase III Study Schema

Accrual: 1,334 patients

Eligibility

- Classical Hodgkin lymphoma
- Treatment naïve
- No sensory or motor peripheral neuropathy

(1:1)

R

Brentuximab vedotin + AVD
Brentuximab vedotin 1.2 mg/kg, doxorubicin 25 mg/kg, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2

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

www.clinicaltrials.gov; NCT01712490

Press Release: June 26, 2017

Positive Results from the Phase III ECHELON-1 Clinical Trial

"ECHELON-1 is a randomized, multicenter trial evaluating brentuximab vedotin as part of a frontline combination chemotherapy regimen in 1,334 patients with previously untreated advanced classical Hodgkin lymphoma.

"The results of the ECHELON-1 trial demonstrated that combination treatment with brentuximab vedotin resulted in a statistically significant improvement in modified PFS versus the control arm as assessed by an Independent Review Facility (hazard ratio = 0.770; *p*-value = 0.035). The two-year modified PFS rate for patients in the brentuximab vedotin arm was 82.1 percent compared to 77.2 percent in the control arm."

investor.seattlegenetics.com/phoenix.zhtml?c=124860&p=RssLanding&cat=news&id=2282975

Results of a Phase II Study of Brentuximab Vedotin in the First Line Treatment of Hodgkin Lymphoma Patients Considered Unsuitable for Standard Chemotherapy (BREVITY)

Gibb A et al.
Proc ICML 2017;Abstract 69.

BREVITY: Response Adaptive Phase II Study of Brentuximab Vedotin (BV)

- BV monotherapy in previously untreated patients with HL unfit for standard treatment due to age, frailty or co-morbidity
- Primary outcome: Complete metabolic response (CMR, Deauville Score 1-3) by centrally reviewed PET-CT after 4 cycles of BV
- N = 35 evaluable for toxicity, 31 evaluable for response
- 88% of AEs were Grade 1-2, 77% of patients had at least one Grade 3 or greater AE
- Most common ≥Grade 3 AEs
  - Infection — Myelosuppression — Neuropathy
- CMR: 26%
- ORR: 84%
- Median PFS: 7.4 months

Gibb A et al. *Proc ICML* 2017;Abstract 69.

Editorial — Dr LaCasce

In this phase 2 study, 38 patients with stage II classical Hodgkin lymphoma with B symptoms and/or mediastinal bulk to stage IV classical Hodgkin lymphoma with cardiac or respiratory compromise or age ≥60 with PS ≤3 and considered unfit for standard chemotherapy were treated with single agent brentuximab vedotin at the standard dose of 1.8 mg/kg every 3 weeks. Patients responding at cycle 4 could receive up to 16 cycles. Of 35 patients evaluable for toxicity, 14 patients required dose reduction in 28 cycles of treatment and 11 patients stopped brentuximab due to adverse events. 77% of patients had at least one grade 3 or higher adverse event, most commonly myelosuppression or peripheral neuropathy.

Editorial — Dr LaCasce (continued)

The overall response rate was 84%, but only 26% of patients were PET negative after cycle 4. The median progression free survival was 7.4 months, and 28 of 31 evaluable patients have progressed thus far.

The results of this study demonstrate disappointingly low complete metabolic responses, short PFS and high toxicity rates in patients not eligible for standard chemotherapy treated with single agent brentuximab. Combination strategies with lower dose brentuximab or other novel agents, including checkpoint inhibitors, may represent better therapeutic options in these patient populations.

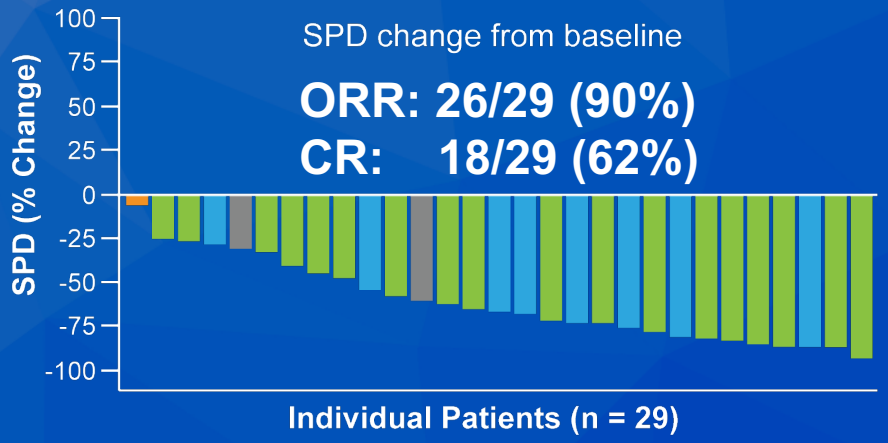
Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

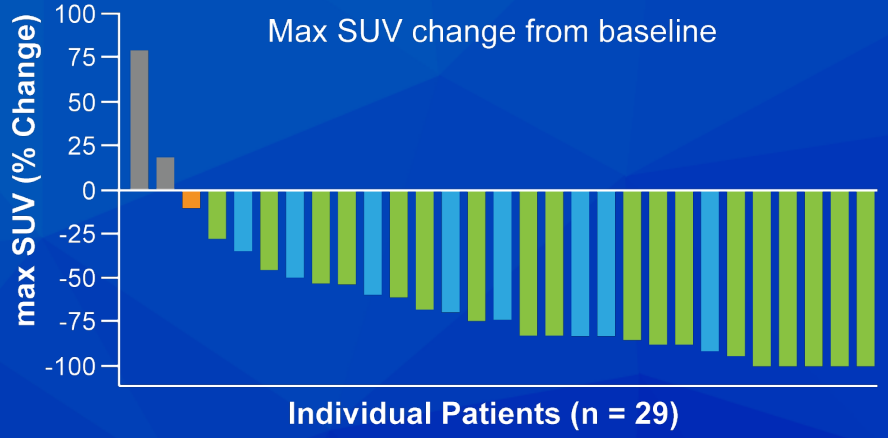
A Phase I Study with an Expansion Cohort of the Combination of Ipilimumab and Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E)

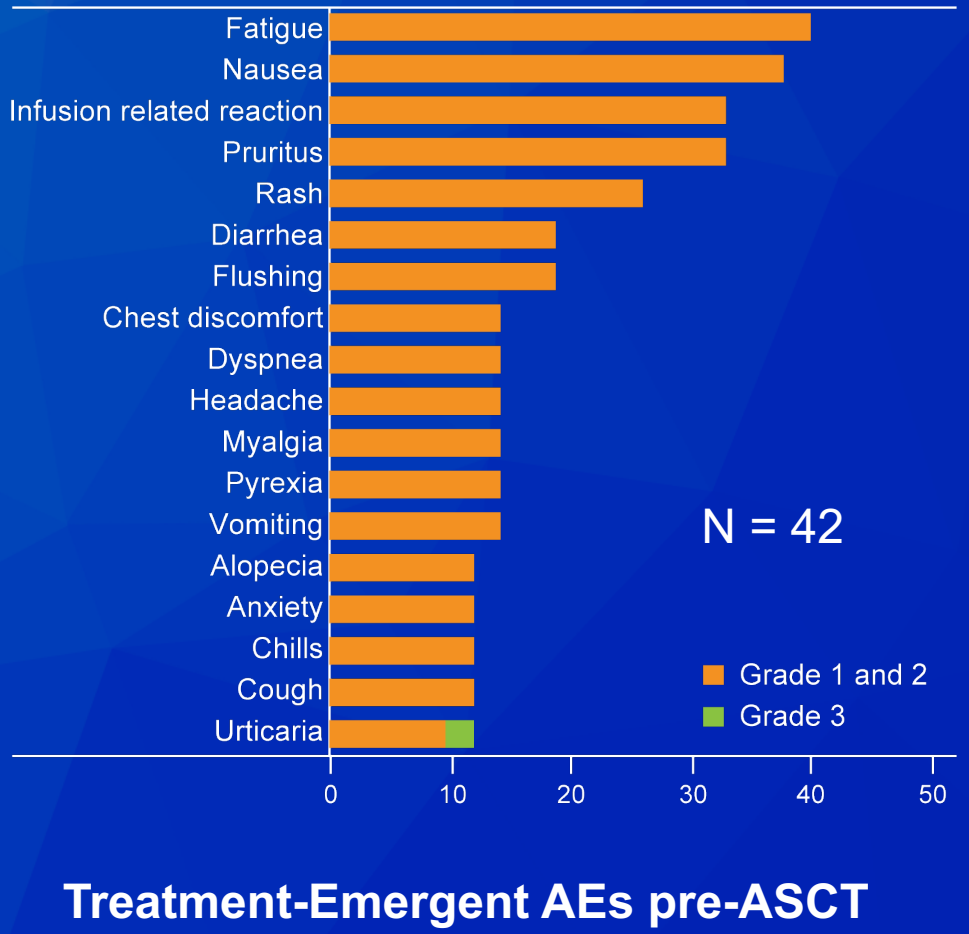
Herrera AF et al.
Proc ASH 2016;Abstract 1105.

Diefenbach CS et al.
Proc ASH 2016;Abstract 1106.

Response and Adverse Events to Brentuximab Vedotin with Nivolumab



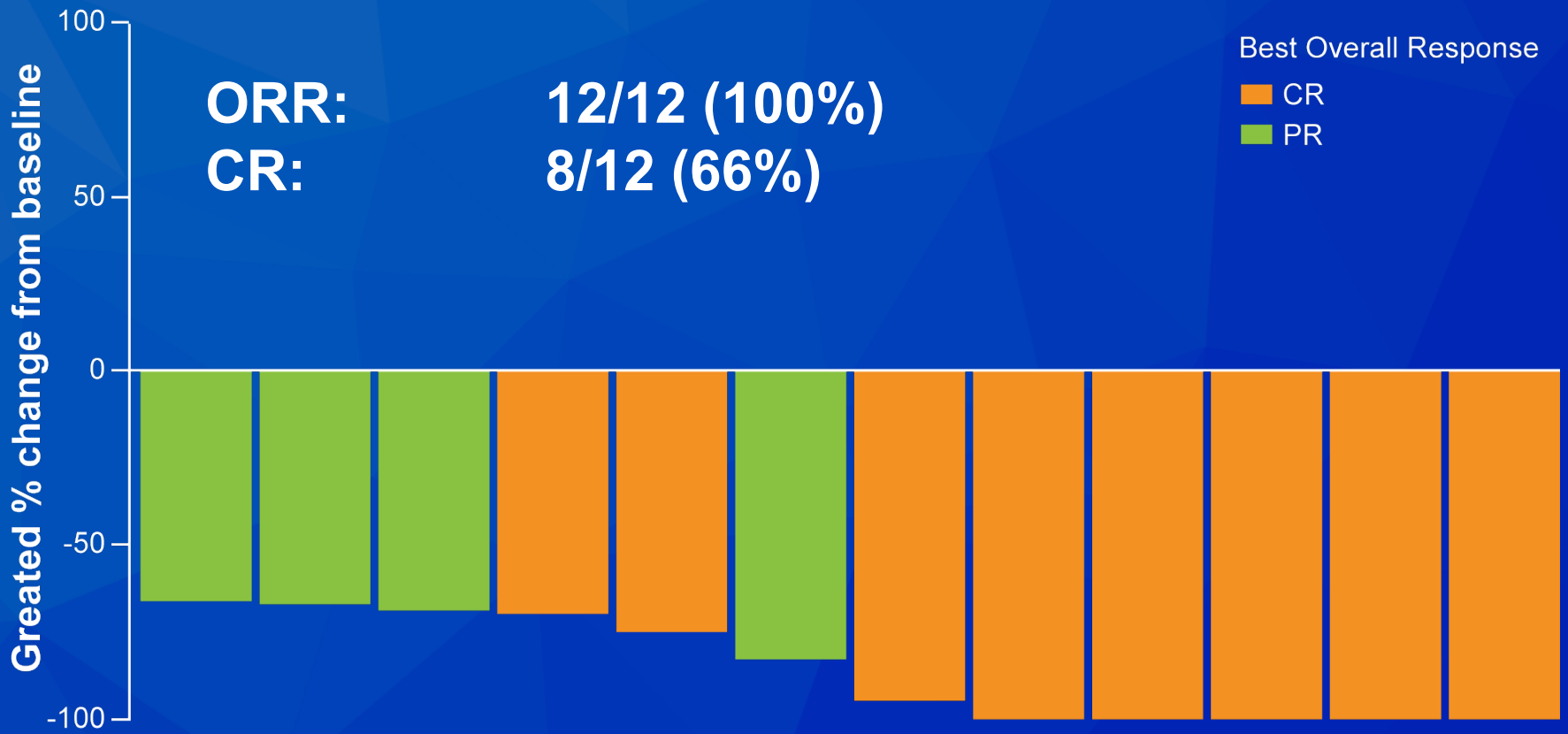




Treatment-Emergent AEs pre-ASCT

Herrera AF et al. *Proc ASH* 2016;Abstract 1105.

ECOG-E4412: Activity of Brentuximab Vedotion with Nivolumab in a Phase I Study



Diefenbach CS et al. *Proc ASH* 2016;Abstract 1106.

Editorial — Dr LaCasce

In this phase 1/2 study, patients with primary refractory or first relapse of classical Hodgkin lymphoma were treated with brentuximab vedotin (BV) and nivolumab for 4 cycles prior to autologous stem cell transplant. In this report of the first 42 patients treated, the overall and complete response rates were 90% and 62% respectively. Infusion related reactions were common at 38% but were predominantly grade 1/2, and immune related events were also low grade with only one grade 3/4 toxicity (hepatitis). Preliminary biomarker data showed no antagonism between BV and nivolumab.

Editorial — Dr LaCasce (continued)

The phase I ECOG study examined the same combination in the relapsed/refractory setting with BV and nivolumab given every 3 weeks for up to 16 cycles with up to an additional year of nivolumab. 10 patients were presented and the overall and complete remission rates were remarkably similar to the first study at 100% and 62.5% respectively. One patient in dose escalation who had undergone prior autologous stem cell transplantation experienced a DLT of grade 3 pneumonitis and typhlitis. No grade 4 toxicities were reported.

The combination of BV and nivolumab is well tolerated and active in relapsed/refractory Hodgkin lymphoma. With nearly all patients responding, the complete remission rates were significantly higher than what is seen with the single agents.

Editorial — Dr LaCasce (continued)

As a salvage regimen prior to transplant, however, the CR rates are comparable to standard chemotherapy, and longer-term outcome post-ASCT is necessary to fully assess the regimen in terms of both efficacy and toxicity.

VOLUME 35 · NUMBER 19 · JULY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma

Robert Chen, Pier Luigi Zinzani, Michelle A. Fanale, Philippe Armand, Nathalie A. Johnson, Pauline Brice, John Radford, Vincent Ribrag, Daniel Molin, Theodoros P. Vassilakopoulos, Akihiro Tomita, Bastian von Tresckow, Margaret A. Shipp, Yinghua Zhang, Alejandro D. Ricart, Arun Balakumaran, Craig H. Moskowitz, for the KEYNOTE-087 Investigators

Pembrolizumab Monotherapy in Patients with Primary Refractory Classical Hodgkin Lymphoma: Subgroup Analysis of the Phase 2 KEYNOTE-087 Study

Zinzani PL et al. *Proc ICML* 2017;Abstract 126.

KEYNOTE-087: Response and Survival to Pembrolizumab in Classical Hodgkin Lymphoma

	All pts (N = 210)[1]	Cohort 1 After ASCT/BV (n = 69)[1]	Cohort 2 Ineligible for ASCT, failed BV (n = 81)[1]	Cohort 3 No BV after ASCT (n = 60)[1]	* Primary refractory (n = 73)[2]
ORR	69%	73.9%	64.2%	70.0%	79.5%
CR	22.4%	21.7%	24.7%	20.0%	23.3%
6-mo PFS	72.4%	—	—	—	79.6%
6-mo OS	99.5%	—	—	—	100%

*** Primary refractory subgroup analysis[2]**

- Median number prior lines of therapy: 3 (range: 1-12)
- Received prior BV: 86.3%

[1] Chen R et al. *J Clin Oncol* 2017;35(19):2125-32; [2] Zinzani PL et al. *Proc ICML* 2017; Abstract 126.

Nivolumab for Relapsed/Refractory Classical Hodgkin Lymphoma After Autologous Transplant: Full Results After Extended Follow-Up of the Phase 2 CheckMate 205 Trial

Fanale M et al.
Proc ICML 2017;Abstract 125.

CheckMate 205: Nivolumab for R/R Classical Hodgkin Lymphoma — Response and PFS with Extended Follow-Up

	Cohort A BV-naive (n = 63)	Cohort B BV after ASCT (n = 80)	Cohort C BV before and/or after ASCT (n = 100)
Median follow-up	19 mo	23 mo	16 mo
ORR	65%	68%	73%
Median DoR	20 mo	16 mo	15 mo
Median PFS	18.3 mo	14.7 mo	11.9 mo

PFS observed in all 3 cohorts for pts with:

- CR: ≥17 mo
- PR: ≥15 mo
- Stable disease: ≥9 mo

Fanale M et al. *Proc ICML* 2017;Abstract 125.

Editorial — Dr LaCasce

In the KEYNOTE-87 study of 210 patients with relapsed/refractory classical Hodgkin lymphoma treated with pembrolizumab, the ORR was 69% with a CR rate of 22%. For the subset who progressed after autologous transplant (ASCT) and brentuximab vedotin (BV), the ORR/CR rates were 74%/15%. In patients not eligible for ASCT who had received prior BV, the ORR/CR was 64%/25% and 70%/20% for those s/p ASCT but BV naïve. Therapy was well tolerated with no grade 4 adverse events, and the most common grade 3 adverse event was hypothyroidism in 5 patients. In a recent report of the subset of 73 patients with primary refractory HL treated on the study, 86% of whom had received prior BV, the ORR and CR rates were 80% and 23% respectively.

Editorial — Dr LaCasce (continued)

At 6 months, the PFS was 80%. 4 patients experienced treatment related SAEs and 3 patients discontinued therapy as a result of myocarditis, cytokine release syndrome and pneumonitis. In the CheckMate 205 trial, 243 patients with relapsed HL s/p ASCT were treated with nivolumab. The ORR and CR rates were 65% and 29% for BV naïve patients, 68% and 13% for those who received BV after ASCT, and 73% and 12% in patients who had received BV before and after ASCT. Median PFS in the 3 cohorts was 18, 15 and 12 months respectively. The most common serious drug related adverse events were infusion reactions in 2% and pneumonitis in 1%.

Editorial — Dr LaCasce (continued)

Overall, these studies demonstrate significant and comparable activity of pembrolizumab and nivolumab in the relapsed/refractory setting across all groups of patients treated. Overall response rates are in the 65%-80% range with complete remissions seen in 12%-30% of patients. Toxicity has been similar to that seen in other diseases. Future studies are needed to identify the appropriate duration of therapy, predictive biomarkers and the role of these agents in combination regimens, including earlier in the disease course.

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

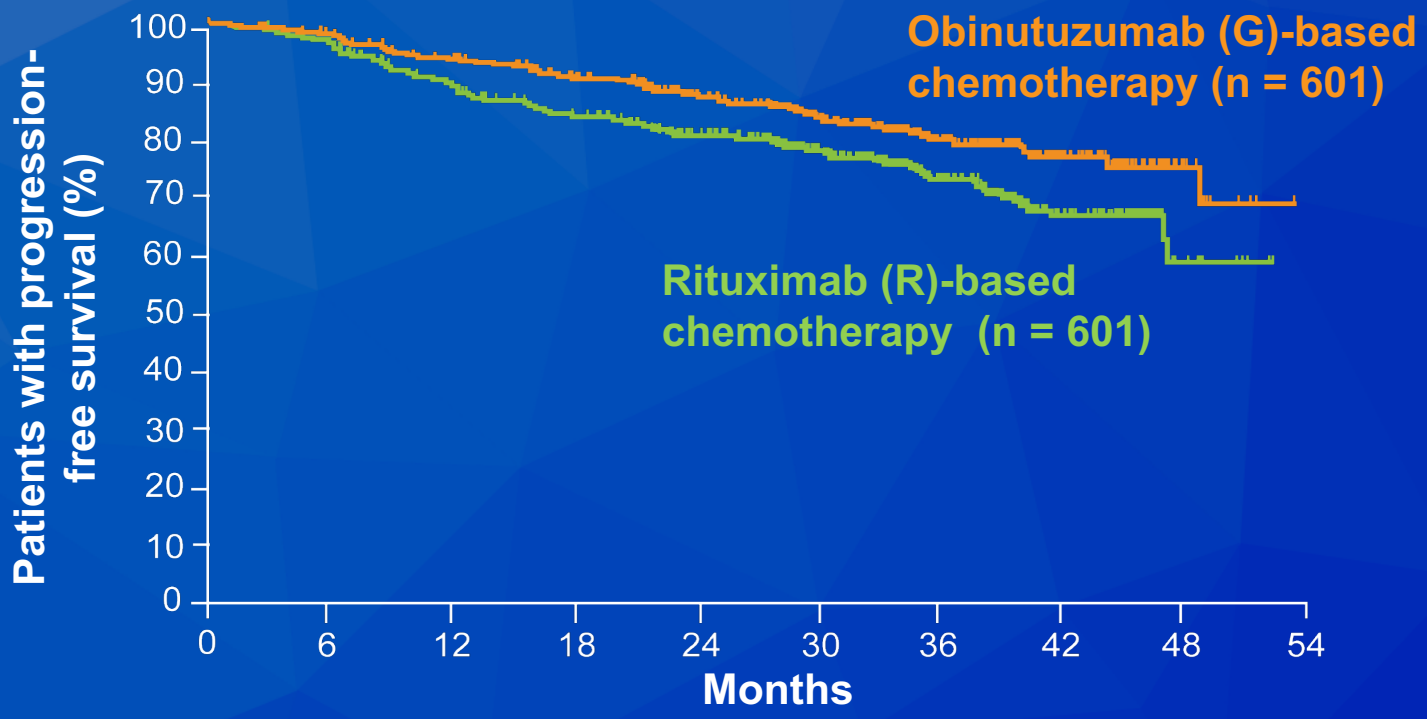
An 80 year-old patient with asymptomatic, moderately bulky Stage IIA FL wishes to receive short-term treatment with an anti-CD20 antibody without chemotherapy. What would you recommend?

a. Rituximab
b. Obinutuzumab
c. Either rituximab or obinutuzumab — coin flip

Obinutuzumab for the First-Line Treatment of Follicular Lymphoma

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

GALLIUM: PFS (Investigator Assessed)



One-year PFS			
	R-chemo	G-chemo	HR, *p*-value
All patients (n = 601, 601)	89.74%	93.94%	0.66, *p* = 0.001
CHOP (n = 203, 195)	93.84%	93.64%	0.77, not reported
CVP (n = 57, 61)	78.96%	95.00%	0.63, not reported
Bendamustine (n = 341, 345)	89.02%	93.93%	0.61, not reported

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

Editorial — Dr Smith

The introduction of rituximab, now 20 years ago, improved nearly every meaningful aspect of follicular lymphoma outcomes including progression-free survival, duration of response, and overall survival. Obinutuzumab is a type II glycoengineered anti-CD20 monoclonal antibody designed to optimize rituximab effects by enhancing ADCC and direct cell kill with diminished CDC. The GALLIUM trial is an international randomized phase 3 trial directly comparing obinutuzumab-chemotherapy versus rituximab-chemotherapy in treatment-naïve follicular lymphoma with the primary endpoint of investigator-determined progression-free survival.

Editorial — Dr Smith (continued)

The trial enrolled 1,202 patients with advanced stage grade 1-3a follicular lymphoma patients meeting GELF criteria for treatment. The chemotherapy backbone was per each site's choice, but limited to either bendamustine, CHOP, or CVP. Treatment was R-chemo versus O-chemo for 6-8 cycles followed by maintenance with the same monoclonal antibody as used in induction every 8 weeks up to two years. Patients were stratified by their FLIPI score and by geographic region. The median age was 59 years, with 53% female. Approximately 80% of patients had an intermediate- or high-risk FLIPI. Bendamustine was the most common chemotherapy backbone selected, constituting 57% of patients, compared to only 33% CHOP and 10% CVP.

Editorial — Dr Smith (continued)

With a median follow-up of 34.5 months, the results of the study favor the obinutuzumab arm in terms of progression-free survival (HR 0.66, *p* = 0.001). The median PFS has not been reached in either arm, but estimated 3-year PFS favors the obinutuzumab arm over rituximab (80% vs 73%). There is no difference in terms of overall survival (HR 0.75, *p* = 0.21), and approximately 92%-94% of patients are still alive at 3 years. There were more grade 3-5 adverse events in the obinutuzumab arm, although toxicity was also higher in patients receiving bendamustine with either antibody. It is important to note that there were toxic deaths in this study on both arms, with 4% on the obinutuzumab arm and 3.4% on the rituximab arm.

Editorial — Dr Smith (continued)

Again, this seems partly driven by bendamustine where O-benda had 5.6% toxic deaths compared to 1.6% for O-CHOP, and R-benda had 4.4% toxic deaths versus 2% for R-CHOP.

Overall, the improved PFS but not OS is a recurring theme in follicular lymphoma, and the main question here is whether or not the improved PFS justifies a change in practice. For now, there is also a difference in cost, and the advent of a subcutaneous formulation of rituximab further challenges the appeal of obinutuzumab, which has a longer infusion time and increased infusion-related toxicities compared to rituximab.

Editorial — Dr Smith (continued)

However, the follow-up is relatively short for follicular lymphoma, and longer follow-up will be critical, particularly if the PFS curves continue to separate. Although the trial was not designed to compare chemotherapy backbones, increased neutropenia and toxic deaths in both bendamustine arms compared to standard CHOP reinvigorate the question of the optimal chemotherapy regimen in follicular lymphoma. Finally, while there is increased toxicity in the obinutuzumab-chemotherapy arm, it is sobering that even rituximab-chemotherapy has a toxic death rate in an indolent lymphoma, and it underscores the importance of trying to move away from chemotherapy altogether in this disease.

A Phase II LYSA Study of Obinutuzumab Combined with Lenalidomide for Relapsed or Refractory Follicular B-Cell Lymphoma

Morschhauser F et al.
Proc ICML 2017;Abstract 37.

Efficacy with Obinutuzumab (GA) and Lenalidomide (LEN)

Outcome	All patients (n = 86)	Early relapse (n = 24)	Refractory patients (n = 23)
Overall response rate	74.4%	66.7%	56.5%
Complete response	44.2%	54.2%	30.4%
PFS (1 y)	75.5%	74.8%	65.2%
OS (1 y)	88.8%	86.9%	71.5%

- No unexpected toxicity reported with the combination of GA + LEN

Morschhauser F et al. *Proc ICML* 2017;Abstract 37.

Editorial — Dr Smith

At the time of relapse, there is no consensus on the optimal management of patients with follicular lymphoma. Options range widely from rituximab monotherapy, chemoimmunotherapy, radioimmunotherapy, hematopoietic stem cell transplant and signaling pathway inhibitors. Lenalidomide is an oral immunomodulatory agent with pleiotropic effects on both malignant and non-malignant stromal cells that is approved for use in several lymphomas. Surprisingly, lenalidomide plus rituximab has clinical synergy compared to lenalidomide monotherapy (CALGB-50401), and the combination yields high response rates and durable remissions in both relapsed and treatment-naïve follicular lymphoma.

Editorial — Dr Smith (continued)

The success of lenalidomide plus rituximab has prompted an international phase III trial comparing lenalidomide-rituximab versus chemoimmunotherapy (RELEVANCE).

Obinutuzumab, a type II glycoengineered monoclonal antibody against CD20, was designed to enhance rituximab's antineoplastic effects by increasing ADCC and direct induction of apoptosis. This phase II open label trial tested the efficacy and safety of obinutuzumab plus rituximab in 88 patients with relapsed or refractory follicular lymphoma; the primary endpoint was overall response rate by CT criteria (IWG 1999).

Editorial — Dr Smith (continued)

The treatment plan was lenalidomide 20 mg for 21 of 28 days each cycle plus obinutuzumab 1,000 mg weekly for four weeks followed by monthly administration through the sixth month. Patients with a complete or partial response at six months proceeded to maintenance obinutuzumab plus lenalidomide for 12 additional cycles.

Key patient characteristics include a median age of 64 years, 35% with bulky disease, 28% of patients with disease progression within 2 years of initial treatment, and 27% with disease refractory to rituximab or their last prior therapy. The primary endpoint was overall response rate; among 86 evaluable patients, the ORR was 80% and CR/CRu rate was 39.5%. With a median follow-up of 18 months, the 1-year PFS and OS are 75.5% and 88.8%, respectively.

Editorial — Dr Smith (continued)

The most common grade 3 and 4 toxicity was neutropenia (28%), although febrile neutropenia occurred in only 3.4% of patients. Infections occurred in 63% of patients, but only 6.8% were grade 3 or higher. There were no cases of grade 3 or 4 venous thrombosis.

It is difficult to assess the significance of this trial compared to rituximab and lenalidomide. Overall response rates and even complete response rates are quite similar, and even toxicity is comparable. The most interesting and intriguing aspect is the high overall and complete response rate (61% and 35%, respectively) in patients with refractory disease. Short of a head-to-head comparison, these data are promising but essentially constitute a preliminary data set for future investigations.

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

Nastoupil LJ et al.
Proc ICML 2017;Abstract 109.

Pembrolizumab with Rituximab for Relapsed FL

- ORR (n = 15): 80%, CR: 60%
- Median PFS, OS: not reached
- Adverse events: mostly Grade 1-2
- Grade 3 AEs included: nausea (n = 2), infusion reaction (n = 2), aseptic meningitis (n = 1), pneumonia (n = 1)
- Immune-related AEs included Grade 2 diarrhea (n = 2), pneumonitis (n = 1), skin rash (n= 1)

Nastoupil LJ et al. *Proc ICML* 2017;Abstract 109.

Editorial — Dr Smith

The microenvironment in follicular lymphoma has a critical impact on outcome, elegantly supported by gene expression profiling work done more than a decade ago showing that T cells, macrophages, and dendritic cell populations affect survival. However, understanding the role of individual cellular components has been more complex. One emerging concept across malignancies is the “checkpoint” between tumor cells and T cells that evolutionarily protects humans from T-cell activation and autoimmunity but in malignances serves to promote tumor cell survival. One such checkpoint is the interface between PD-L1 on tumor cells and PD-1 on T cells. Disrupting this interaction has been highly successful in Hodgkin lymphoma, as well as solid tumors.

Editorial — Dr Smith (continued)

While the role of PD-1/PD-L1 in follicular lymphoma is unknown, it is reasonable to target T cells in the follicular lymphoma microenvironment.

This is a single institution phase II trial of the PD-1 inhibitor pembrolizumab plus rituximab in 27 patients with relapsed or refractory follicular lymphoma. Patient characteristics include a median age of 65 years, 76% with intermediate- or high-risk FLIPI, and 56% with high tumor burden and in need of treatment as per GELF criteria. Among 15 evaluable patients, the overall response rate was 80% and the complete response rate was 60%. The median follow-up is quite short at 7 months. Immune-related toxicities included diarrhea, pneumonitis, and rash, but none were greater than grade 2 in severity.

Editorial — Dr Smith (continued)

An exploratory analysis of PD-L1 expression showed high expression in histiocytes but only 1%-8% of malignant cells.

This small trial is preliminary but intriguing. Other studies have not shown the same degree of activity with checkpoint inhibitors in NHL as compared to Hodgkin lymphoma where the rationale for PD-1 inhibition is the strongest. Further information (and a larger sample size) is needed before this trial can be appropriately interpreted. For example, the abstract does not state how many patients had rituximab-refractory disease. Overall, this is an exciting target in cancer, and we await more mature results.

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

Efficacy and Safety of Copanlisib in Patients with Relapsed/Refractory Follicular Lymphoma: A Subset Analysis of the CHRONOS-1 Study

Dreyling M et al.
J Clin Oncol 2017;[Epub ahead of print].

Zinzani PL et al.
Proc EHA 2017;Abstract S776.

CHRONOS-1: Copanlisib for Relapsed/Refractory Indolent Lymphoma

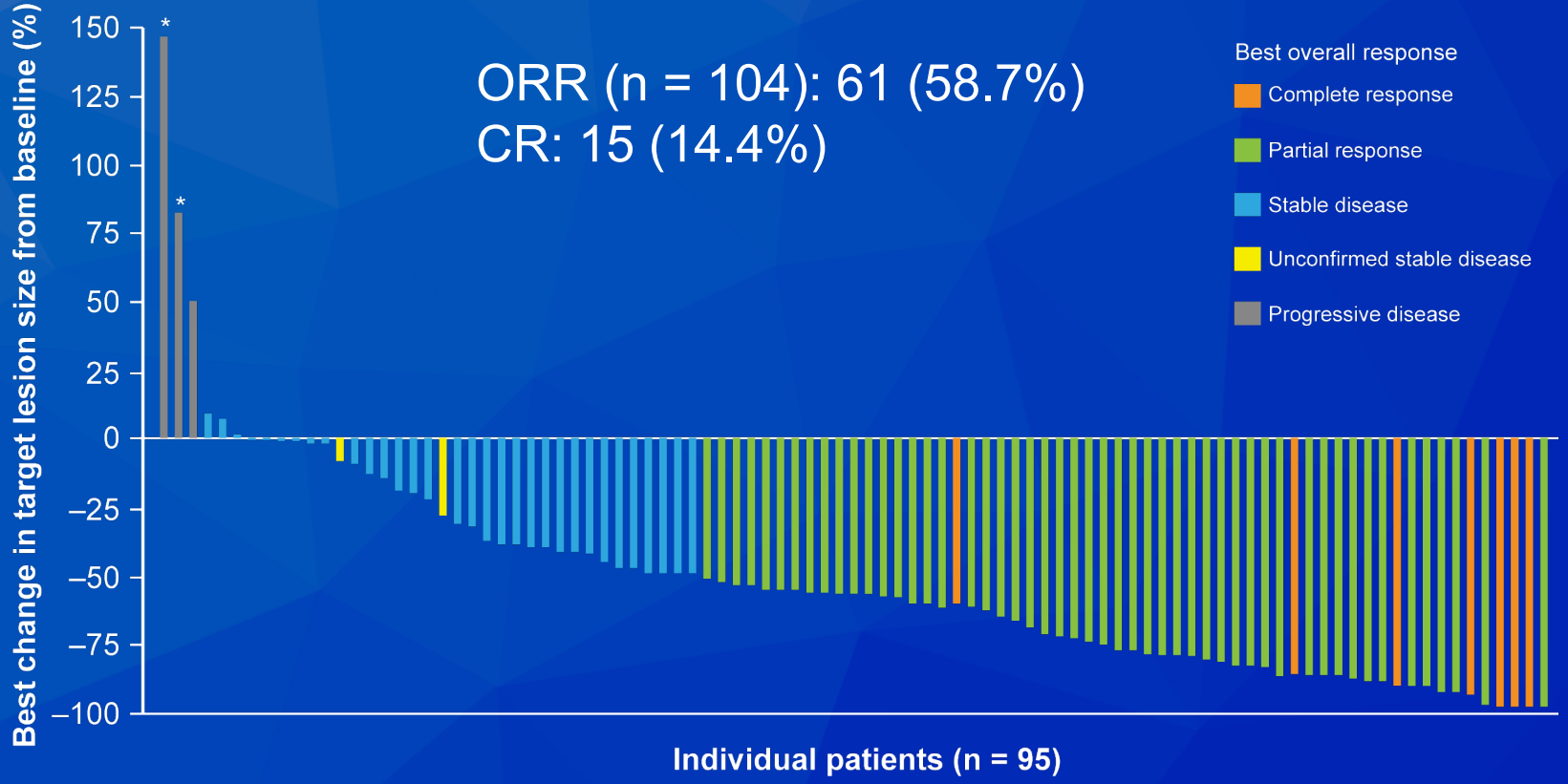
	FL (n = 104)	MZL (n = 23)	SLL (n = 8)	LPL/WM (n = 6)	All patients (n = 142)
ORR	61 (59%)	16 (70%)	6 (75%)	1 (17%)	84 (59%)
CR	15 (14%)	2 (9%)	0	0	17 (12%)
PR	46 (44%)	14 (61%)	6 (75%)	1 (17%)	67 (47%)
Median duration of response	12.2 mo	—	—	—	22.6 mo

FL = follicular lymphoma; MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma; LPL/WM = lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia

- Median PFS (all patients): 11.2 months
- Median OS has not been reached

Dreyling M et al. *J Clin Oncol* 2017;[Epub ahead of print].

CHRONOS-1: Copanlisib for Relapsed/ Refractory FL



- Toxicities were manageable, with a low incidence of severe AEs associated with other PI3K inhibitors
- Grade 3/4 AEs included hyperglycemia (41%), hypertension (24%), neutropenia (24%), pneumonitis (1.4%), opportunistic infections (1.4%), colitis (0.7%)

Zinzani PL et al. *Proc EHA* 2017;Abstract S776.

Editorial — Dr Smith

PI3K is a ubiquitous and evolutionarily conserved family of serine/threonine kinases with four isoforms: alpha, beta, delta and gamma. In leukocytes, the delta isoform appears critical in mediating BCR signaling and in controlling other PI3K targets that mediate growth and cell survival. Inhibition of the delta isoform with agents such as idelalisib, a highly selective inhibitor of PI3K delta, is effective as monotherapy in heavily pretreated patients with indolent lymphoma, leading to FDA approval in third-line management. However, there are several challenges with idelalisib, including an increased risk of infections possibly associated with on-target inhibition of PI3K delta in T cells and resistance mediated by upregulation of isoforms other than delta.

Editorial — Dr Smith (continued)

Copanlisib is an intravenous formulation of a dual PI3K alpha and delta isoform inhibitor. The study is an open label phase II international trial of copanlisib in relapsed and refractory indolent lymphomas, although this abstract focuses on the follicular lymphoma cohort. The treatment schedule was copanlisib 60 mg IV weekly for three consecutive weeks, repeated every 28 days until progression or toxicity. The primary endpoint was overall response rate.

Patients in this study had very high-risk features. Among 104 patients with FL, the median age was 62 years, 63% refractory to the most recent treatment, and median time from most recent progression was 8 weeks.

Editorial — Dr Smith (continued)

The median number of prior therapies was 3. Among this poor-risk group of patients, the ORR was 59% with 14% complete and 44% partial responses.

The spectrum of grade 3 or 4 adverse events is similar to other inhibitors of the PI3K/Akt/mTOR axis, with hyperglycemia (41%) and hypertension (24%) as early events. However, transaminase elevation (1.4%), opportunistic infections (1.4%) and colitis (0.7%) were uncommon. Based on the balance of efficacy and toxicity, copanlisib received FDA approval for relapsed/refractory indolent lymphomas in September 2017.

There are several questions regarding clinical use of copanlisib as the second PI3K inhibitor approved in relapsed/refractory indolent lymphomas.

Editorial — Dr Smith (continued)

The route of administration may affect patient preference; some patients will prefer an oral agent such as idelalisib whereas compliance, adherence and patient co-pays may lead to a preference for an intravenous agent. The safety profile for copanlisib is promising in that there is minimal hepatotoxicity, colitis, and pneumonitis. Although the risk of opportunistic infections is low, it is worth recalling that severe infections with idelalisib occurred mainly when used in less heavily pretreated, and presumably more immune competent, patients. Overall, copanlisib offers an excellent option for relapsed/refractory follicular lymphoma.

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

A 75-year-old patient with MCL receives 6 cycles of BR and has a clinical complete response. Would you recommend rituximab maintenance?

a. Yes, for 2 years
b. Yes, until toxicity or disease progression
c. No

The NEW ENGLAND JOURNAL of MEDICINE

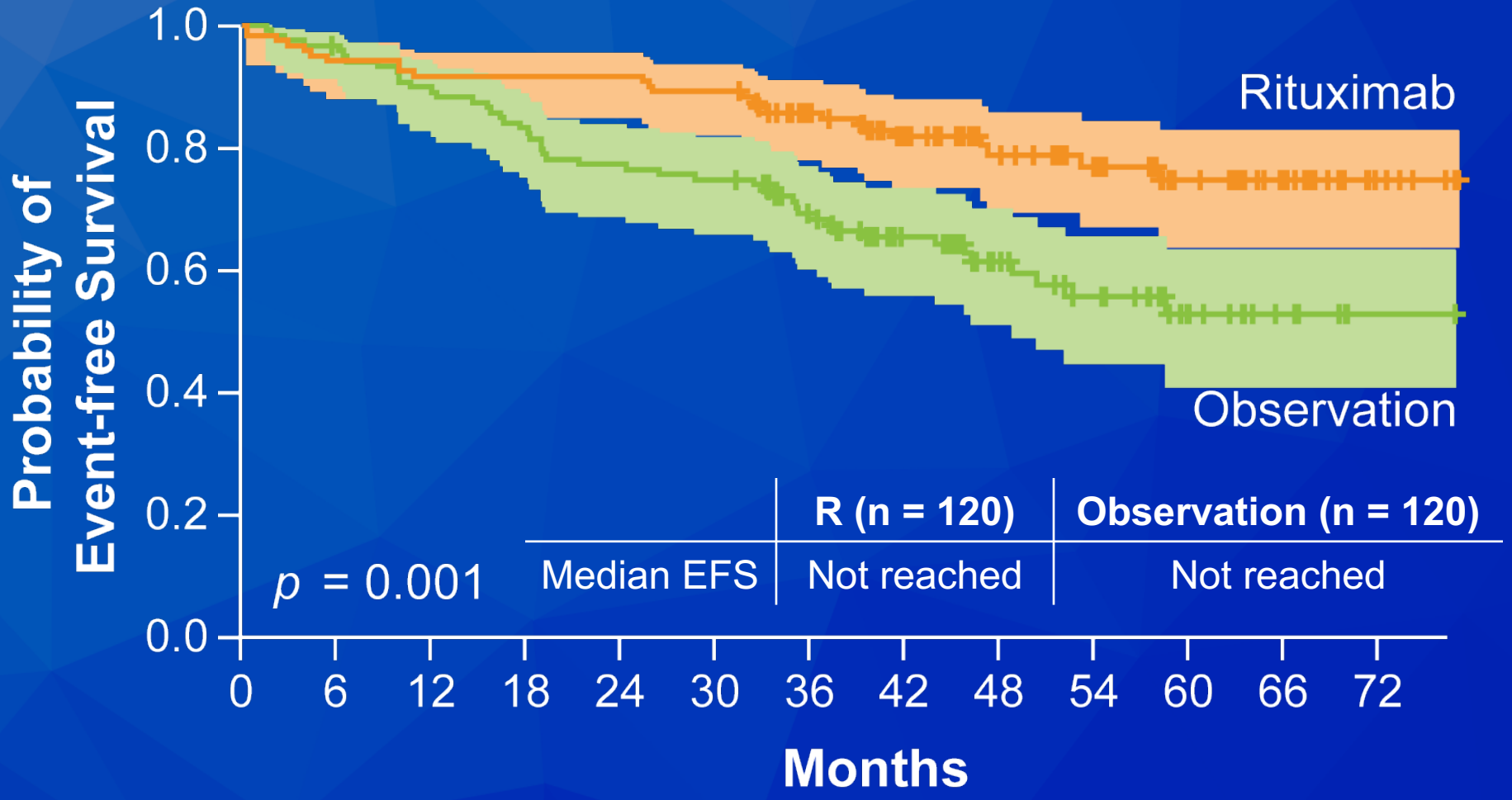
ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, G. Damaj, T. Gastinne, V. Ribrag, P. Feugier, O. Casasnovas, H. Zerazhi, C. Haioun, H. Maisonneuve, R. Houot, F. Jardin, E. Van Den Neste, O. Tournilhac, K. Le Dû, F. Morschhauser, G. Cartron, L.-M. Fornecker, D. Canioni, M. Callanan, M.C. Béné, G. Salles, H. Tilly, T. Lamy, R. Gressin, and O. Hermine, for the LYSA Group*

N Engl J Med 2017;377:1250-60.

LyMa: Event-Free Survival



- PFS (4-y): R, 83%; observation, 64% (p <0.001)
- OS (4-y): R, 89%; observation, 80% (p = 0.04)

Le Gouill S et al. *N Engl J Med* 2017;377(13):1250-60.

Editorial — Dr Smith

The treatment of younger patients with MCL consists of intensive induction, often cytarabine-based, followed by consolidative high-dose chemotherapy plus autologous hematopoietic stem cell transplant in first remission. This strategy leads to impressive response durations of 5-7 years, but does not offer cure. Nevertheless, the long response duration makes this a very reasonable and appropriate option for younger patients.

The current study treated all patients with four cycles of R-DHAP. Responding patients underwent transplantation and then were randomized to either maintenance rituximab with one dose every 8 weeks for three years or observation.

Editorial — Dr Smith (continued)

Among 299 enrolled patients, 257 (86%) underwent transplant and 240 were randomized. Patient characteristics were balanced, and reflected a typical younger MCL population: median age 57 years, 79% male, 94% advanced stage disease. The response rate to induction therapy was 89% with 77% complete responders. Among patients undergoing randomization (n = 240), the 4-year EFS (79% vs 61%, $p = 0.001$), PFS (83% vs 64%, $p < 0.001$), and OS (89% vs 80%, $p = 0.04$) favored the maintenance arm.

There are several practical aspects to consider when interpreting this data. First, the induction regimen for MCL is not uniform, and it's unclear how the initial treatment might affect outcomes.

Editorial — Dr Smith (continued)

In general, cytarabine-based regimens are associated with a higher rate of MRD negativity, but MRD was not assessed in this study. The second issue is that the duration of maintenance was not tested, and it's unknown if all three years of maintenance are needed. The authors did not collect information on hypogammaglobulinemia or the need for IVIG replacement.

However, the ability to show a survival difference with maintenance therapy is impressive. The vast majority of maintenance rituximab after initial chemoimmunotherapy trials in lymphoma consistently show a PFS without an OS advantage. An exception is the benefit of maintenance rituximab following R-CHOP in MCL which was done in elderly patients.

Editorial — Dr Smith (continued)

This study is practice changing and supports the routine use of maintenance rituximab after autologous stem cell transplant in front-line treatment of MCL. Future studies should help determine if 3 years are truly needed and if other agents (ie, ibrutinib, lenalidomide) might have a role in this setting.

Combination Ibrutinib (Ibr) and Venetoclax (Ven) for the Treatment of Mantle Cell Lymphoma (MCL): Primary Endpoint Assessment of the Phase 2 AIM Study[1]

Phase 3 Study of Ibrutinib in Combination with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma (MCL)[2]

[1] Tam CS et al.
Proc ICML 2017;Abstract 135.

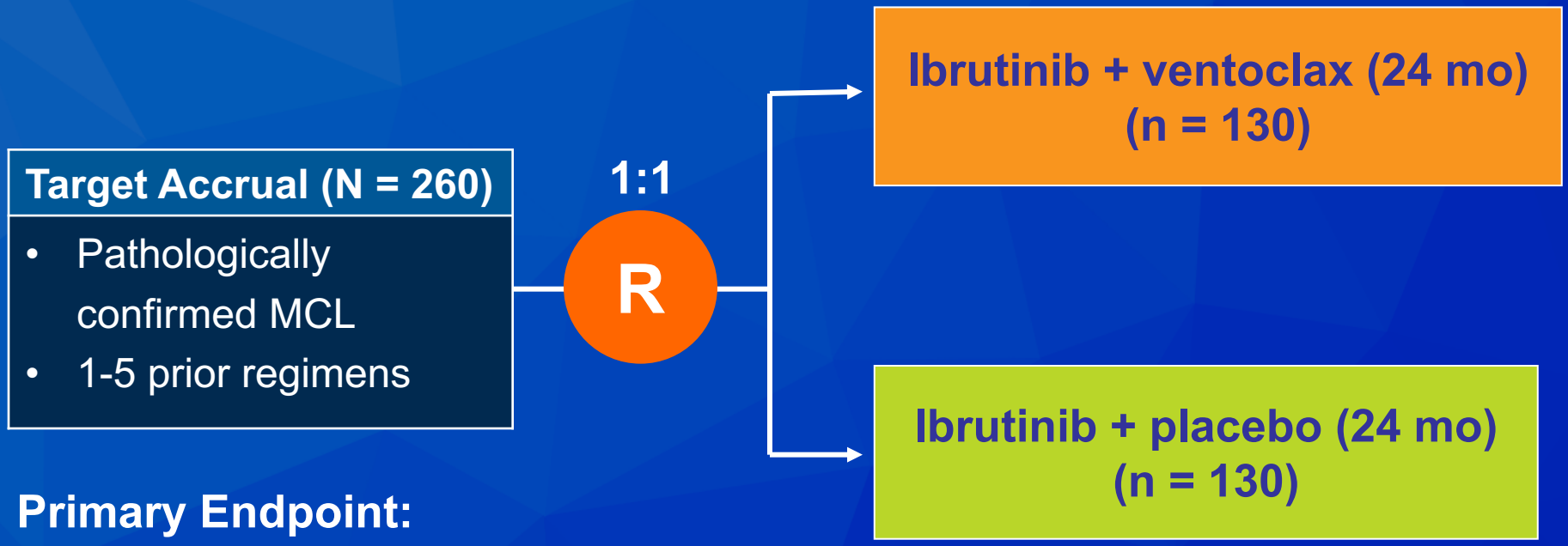
[2] Tam CS et al.
Proc ICML 2017;Abstract OT05.

AIM: Ibrutinib with Venetoclax for MCL

- ORR (n = 24): 71%, CR: 63%
- PFS (8 mo): 74%; OS (8 mo): 81%
- Adverse events: mostly Grade 1-2, except neutropenia (Grade 3/4 25%)
- Tumor lysis syndrome (TLS): 2 patients with high tumor burden
- Other AEs included: fatigue (71%), diarrhea (67%), URTI (38%), neutropenia (33%), bruising (21%)

Tam CS et al. *Proc ICML* 2017;Abstract 135.

PCYC-1143: A Phase III Study of Ibrutinib with Venetoclax for Relapsed/Refractory MCL



Primary Endpoint:
PFS, occurrence of TLS and dose-limiting toxicities

After 24 mo, ibrutinib only will be continued in both groups until progression/ unacceptable toxicity

Tam CS et al. *Proc ICML* 2017;Abstract OT05. (NCT03112174)

Editorial — Dr Smith

Although there have been several agents approved for use in relapsed MCL, this remains an incurable disease. Most patients are older, and aggressive treatment with cytarabine-based induction and consolidative stem cell transplant is mainly limited to front-line settings and in younger patients. The most active single agent in relapsed disease is ibrutinib, but the vast majority of patients have disease progression within 18 months. Furthermore, progression following ibrutinib can have a fulminant course with rapid progression and almost no effective agents. Venetoclax, an oral BH3 mimetic which blocks BCL2 anti-apoptotic effects, holds promise in patients with progression after ibrutinib, and a combination approach is rational and promising.

Editorial — Dr Smith (continued)

This was an open label phase II trial of ibrutinib 560 mg/d for four weeks followed by venetoclax “ramped up” to 400 mg/d. Twenty-four patients were enrolled, with only one treatment-naïve patient. Patients had a median age of 68 years with 48% refractory to last treatment and 30% failing a prior autologous stem cell transplant. The ORR was 71% with a CR rate of 63%. Of note, 80% of patients with a CR had negative MRD via flow cytometry. Follow-up is 8.3 months.

The only grade 3 or 4 toxicity was neutropenia, but fatigue, diarrhea, nausea, upper respiratory tract infections, gastro-esophageal reflux, cough and bruising occurred in at least 20% of patients at lower severities.

Editorial — Dr Smith (continued)

The most compelling aspect of this small study is the very high complete response rate and ability to achieve MRD negativity without the use of chemotherapy. Single agent studies with ibrutinib do not show this depth of response, and the combination may thus be suggestive of potent synergy. Further data, both in terms of increased sample size and longer follow up, will be highly informative. To this point, there is a planned randomized trial of ibrutinib/venetoclax versus ibrutinib/placebo (PCYC-1143) with progression-free survival as the primary endpoint.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Matthew S. Davids, Andrew W. Roberts, John F. Seymour, John M. Pagel, Brad S. Kahl, William G. Wierda, Soham Puvvada, Thomas J. Kipps, Mary Ann Anderson, Ahmed Hamed Salem, Martin Dunbar, Ming Zhu, Franklin Peale, Jeremy A. Ross, Lori Gressick, Monali Desai, Su Young Kim, Maria Verdugo, Rod A. Humerickhouse, Gary B. Gordon, and John F. Gerecitano

J Clin Oncol 2017;35(8):826-33.

Phase I Study of Venetoclax in R/R NHL

Outcome	All patients (n = 106)	MCL (n = 28)	FL (n = 29)	DLBCL (n = 34)
ORR	44%	75%	38%	18%
CR	13%	21%	14%	12%
Median PFS	6 mo	14 mo	11 mo	1 mo
OS (1 y)	70%	82%	100%	32%

- Venetoclax was well tolerated with mostly Grade 1/2 AEs
- Clinical TLS: not observed, laboratory TLS: n = 3
- Grade 3/4 AEs: 56%, mostly hematologic, including anemia (15%), neutropenia (11%) and thrombocytopenia (9%)

Davids MS et al. *J Clin Oncol* 2017;35(8):826-33.

Editorial — Dr Smith

Venetoclax is an oral BH3 mimetic that prevents BCL2 from exerting anti-apoptotic effects in cancer. Given the role of anti-apoptosis in drug resistance and cancer cell survival, this is a very promising agent and a rational target. Venetoclax is already approved in relapsed/refractory CLL, and this study presents the phase I data in other NHL.

This is a phase I trial with an expansion cohort totaling 104 patients with a variety of relapsed/refractory non-Hodgkin lymphomas, including mantle cell lymphoma (MCL) (n = 28), follicular lymphoma (FL) (n = 29), diffuse large B-cell lymphoma (n = 34), Richter's transformation (n = 7), Waldenström macroglobulinemia (WM) (n = 4) and marginal zone lymphoma (MZL) (n = 3).

Editorial — Dr Smith (continued)

Venetoclax was started at low dose on Day 1 (200 mg) with intrapatient dose escalation to a maximum of 1,200 mg daily if there was no evidence of tumor lysis syndrome (TLS). Laboratory monitoring for TLS was done at 8 and 24 hours after each dose increase.

Responses were seen in all subsets of patients, but varied by histology. There was significant activity in MCL (ORR 75%, CR 21%) followed by FL (ORR 38%, CR 14%). Numbers are small, but all 4 patients with WM and 2/3 patients with MZL had partial responses. In DLBCL, the ORR was 18% with 12% CR, and 3/7 patients with Richter's transformation had a partial response. Durability also varied by histology, with the best results in MCL and FL patients achieving CRs.

Editorial — Dr Smith (continued)

Of note, three patients with refractory aggressive lymphomas had durable remissions approximating two years.

Of note, clinical TLS was not seen in any patients, and laboratory TLS was only seen in three patients with bulky disease (maximal LN >10 cm) at 24 hours following the initial dose. Nonhematologic toxicities were overwhelmingly grade 1-2, and the most common grade 3-4 adverse events were neutropenia and anemia. The cytopenias prompted dose reduction in 15 patients and use of growth factor support in 17 patients.

This trial establishes an initial benchmark for single agent activity of venetoclax in NHL, and these data will likely be used in the design of future combination trials.

Editorial — Dr Smith (continued)

It is exciting to see activity with acceptable tolerability, especially in MCL and in some patients with DLBCL. Given the initial concerns about fatal TLS in CLL, this study is reassuring that venetoclax therapy can be safely initiated in the outpatient setting, a practical aspect that is important for providers. Monitoring for TLS is still advised, but inpatient admission does not seem necessary. The relatively modest activity in follicular lymphoma is surprising given the fundamental association with t(14;18), but supports that subsequent events (and not BCL2 rearrangement) are likely driving follicular lymphoma. The ability to achieve a complete response in some patients is also promising, and many combination trials are under way.

Lymphomas — Drs LaCasce, Smith and Abramson

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

H Miles Prince, Youn H Kim*, Steven M Horwitz, Reinhard Dummer, Julia Scarisbrick, Pietro Quaglino, Pier Luigi Zinzani, Pascal Wolter, Jose A Sanches, Pablo L Ortiz-Romero, Oleg E Akilov, Larisa Geskin, Judith Trotman, Kerry Taylor, Stephane Dalle, Michael Weichenthal, Jan Walewski, David Fisher, Brigitte Dréno, Rudolf Stadler, Tatyana Feldman, Timothy M Kuzel, Yinghui Wang, Maria Corinna Palanca-Wessels, Erin Zagadailov, William L Trepicchio, Wenwen Zhang, Hui-Min Lin, Yi Liu, Dirk Huebner, Meredith Little, Sean Whittaker†, Madeleine Duvic†, on behalf of the ALCANZA study group‡*

Lancet 2017; 390: 555–66

Brentuximab Vedotin vs Physician's Choice in CTCL Patients from the Phase 3 ALCANZA study: Analysis of Outcomes by CD30 Expression

Kim YH et al. *Proc ICML* 2017;Abstract 66.

ALCANZA: Response and PFS

Response	Brentuximab vedotin (n = 64)			Physician's choice* (n = 64)		
	ORR4	ORR	CR	ORR4	ORR	CR
ITT population	56%	67%	16%	13%	20%	2%
MF	50%	65%	10%	10%	16%	0%
pcALCL	75%	75%	31%	20%	33%	7%

Median PFS	Brentuximab vedotin	Physician's choice*	HR (*p*-value)
ITT population	16.7 mo	3.5 mo	0.270 (<0.0001)
MF	15.9 mo	3.5 mo	0.273 (NR)
pcALCL	27.5 mo	5.3 mo	0.252 (NR)

ITT = intent-to-treat; ORR4 = proportion of patients in ITT population achieving objective response lasting at least 4 months; ORR = objective response rate; CR = complete response; MF = mycosis fungoides; pcALCL = primary cutaneous anaplastic large cell lymphoma; NR = not reported

* Methotrexate or bexarotene

Prince HM et al. *Lancet* 2017;390(10094):555-66.

ALCANZA: Select TEAEs

	Brentuximab vedotin (n = 66)		Methotrexate (n = 25)		Bexarotene (n = 37)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Peripheral sensory neuropathy	45%	5%	4%	0%	0%	0%
Nausea	36%	2%	16%	0%	11%	0%
Diarrhea	29%	3%	4%	0%	8%	0%
Fatigue	29%	5%	20%	4%	32%	0%
Alopecia	15%	0%	4%	0%	3%	0%
Pruritis	17%	2%	8%	0%	16%	5%
Pyrexia	17%	0%	28%	4%	11%	0%
Asthenia	11%	2%	12%	0%	5%	3%
Peripheral edema	11%	0%	16%	0%	5%	0%
Anemia	5%	0%	0%	0%	16%	8%
Skin infection	3%	3%	12%	4%	11%	0%

Prince HM et al. *Lancet* 2017;390(10094):555-66.

ALCANZA: Outcomes by CD30 Expression

ORR4	Brentuximab vedotin	Physician's choice	Difference
$CD30_{min}$ < 10%	40.9%	9.5%	31.4%
$CD30_{min}$ ≥ 10%	57.1%	10.3%	46.8%

Median PFS	Brentuximab vedotin	Physician's choice	HR
$CD30_{min}$ < 10%	27.9 mo	2.3 mo	0.125
$CD30_{min}$ ≥ 10%	17.2 mo	3.5 mo	0.176

- Notable interpatient or interlesional variability in CD30 expression was observed in patients with MF
  - 44% (55/125) of CD30+ patients with MF had ≥1 biopsy with low (<10%) or undetectable CD30
- Brentuximab vedotin produced highly superior ORR4 and PFS endpoints compared to physician's choice regardless of $CD30_{min}$ expression level

Kim YH et al. *Proc ICML* 2017;Abstract 66.

Editorial — Dr Abramson

The ALCANZA study is a randomized trial of the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) versus physician's choice (PC) of either oral methotrexate or oral bexarotene for relapsed or refractory CD30+ mycosis fungoides or cutaneous anaplastic large cell lymphoma (ALCL). BV was administered at a dose of 1.8 mg/kg on a 21-day schedule, and both treatment arms continued therapy for up to 48 weeks. The primary endpoint was overall response lasting at least 4 months. 128 subjects were randomized 1:1 to BV or PC and included in the intent to treat analysis.

56.3% of subjects randomized to BV achieved the primary endpoint of overall response lasting at least 4 months, compared to 12.5% randomized to PC.

Editorial — Dr Abramson (continued)

Median PFS was also markedly improved in the experimental arm by both FDA and EMA criteria. Improvement of clinical endpoints was independent of the degree of CD30 positivity, with even expression in less than 10% of cells associated with improved outcome in the BV arm. Toxicity was consistent with previous studies of BV as monotherapy, with 2/3 of subjects reporting peripheral neuropathy, 82% of which had improved or resolved at last follow-up.

Editorial — Dr Abramson (continued)

Superiority of BV in this trial is demonstrated relative only to oral methotrexate and bexarotene, rather than single-agent IV chemotherapies such as gemcitabine or liposomal doxorubicin, but the efficacy with BV is excellent with a manageable safety profile, and so these data support BV as a treatment of choice in relapsed/refractory CD30+ mycosis fungoides and cutaneous ALCL, independent of the degree of CD30 positivity.

Peripheral sensory neuropathy is the most important toxicity signal, and so physicians must ask their patients about neurotoxicity at every visit, and feel comfortable dose reducing and discontinuing therapy if needed to prevent permanent neuropathy, which can significantly impair patients' long-term quality of life.

A Phase 1 Study of Pralatrexate Plus Romidepsin Reveals Marked Activity in Patients with Relapsed or Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL)

Amengual JE et al.
Proc ICML 2017;Abstract 76.

Pralatrexate (P) with Romidepsin (R) for R/R PTCL

- **Determination of MTD and DLT (primary endpoint):**
  - 3 + 3 dose-escalation design started with P 10 mg/m^2 and R 12 mg/m^2 with escalation to P 25 mg/m^2 and R 14 mg/m^2.
  - Patients were treated on 1 of 3 dosing schedules (D1, 8, 15 Q28D; D1, 8 Q21D and D1, 15 Q28D).
  - D1, 15 Q28D schedule had no mucositis and resulted in no DLTs at any dose level.

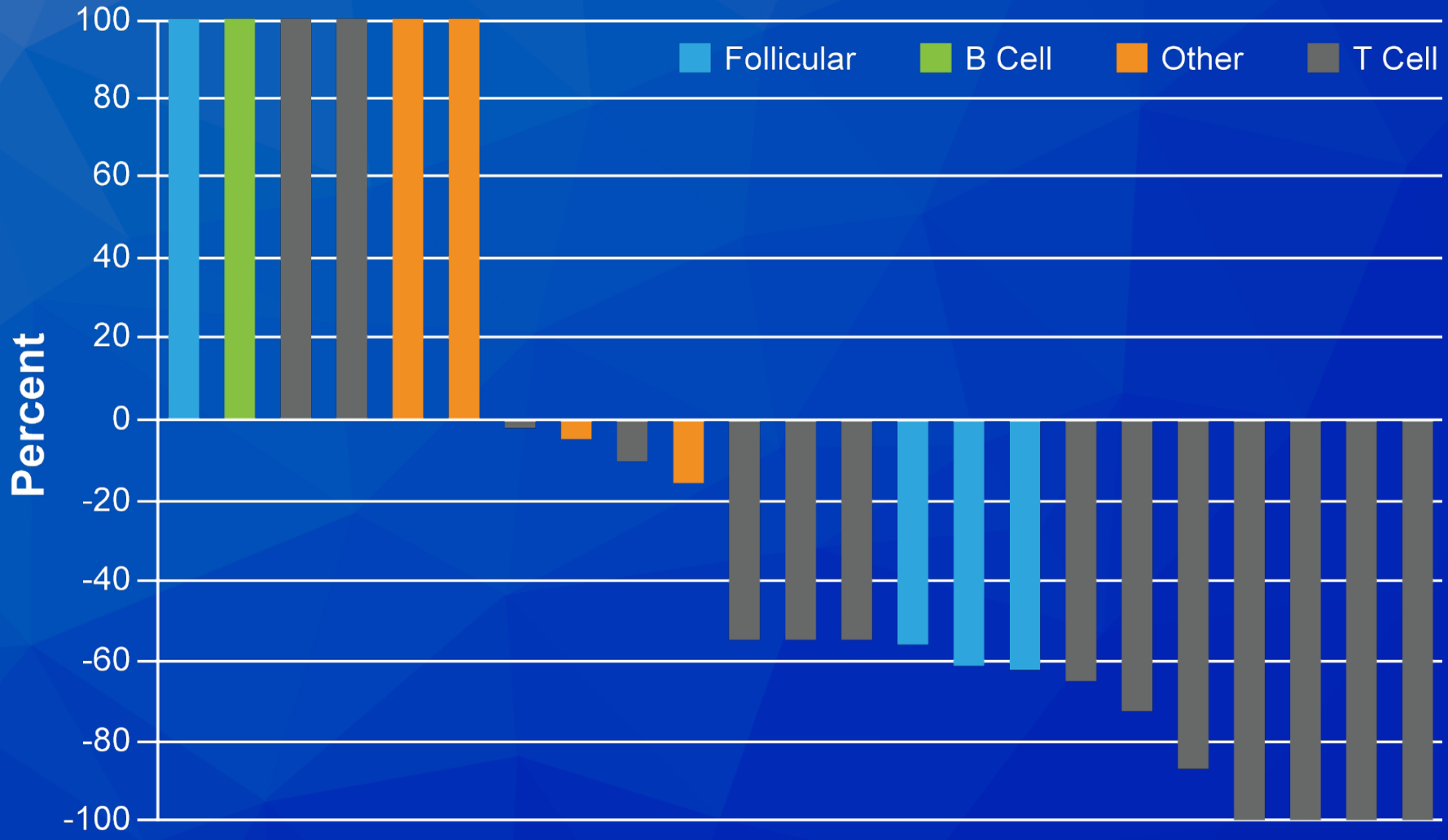
Key secondary endpoints	Overall	PTCL	Non-PTCL
ORR (CR + PR)	57%	71%	33%
PFS	3.7 mo	4.4 mo	NR
OS	13.8 mo	12.8 mo	NR
Mean duration of response	3.5 mo	NR	NR

NR = not reported

- Grade 3/4 toxicities reported in >5% of patients: anemia (29%), thrombocytopenia (28%), febrile neutropenia (14%), oral mucositis (14%), hyponatremia (7%), pneumonia (6%), neutropenia (6%) and sepsis (7%)

Amengual JE et al. *Proc ICML* 2017;Abstract 76.

Pralatrexate with Romidepsin: Reduction in Tumor Burden



Amengual JE et al. *Proc ICML* 2017;Abstract 76.

Editorial — Dr Abramson

Amengual and colleagues report a phase 1 study combining the HDAC inhibitor romidepsin with the antifolate chemotherapy pralatrexate in relapsed or refractory lymphoma. 29 subjects were enrolled in a standard 3+3 dose escalation design. 18 subjects had T-cell lymphoma, 7 had B-cell lymphoma, and 4 had Hodgkin lymphoma or other. Multiple schedules were explored, with the chosen schedule being days 1 and 15 of a 28-day schedule.

The most common grade 3-4 toxicities associated with this combination were anemia, thrombocytopenia, neutropenic fever, and oral mucositis. The ORR for the entire study was 57%, and 71% in PTCL, including a 29% rate of CR.

Editorial — Dr Abramson (continued)

The median PFS was 3.7 months in the overall population and 4.4 months in PTCL. The overall and complete response rates are quite high for the combination in PTCL, for which each agent is FDA approved, though each with relatively modest activity as single agents. Unfortunately, the median PFS remains brief, so responses may not be durable.

Further follow-up is needed of this study as well as larger numbers treated for PTCL to further clarify degree of activity in this difficult to treat population. Further attention should also be paid to activity within histologic subtypes of PTCL since the single agents show significant variability across subtypes such as PTCL NOS, angioimmunoblastic T-cell lymphoma, and others.

Editorial — Dr Abramson (continued)

Until such time as additional data are available, I would recommend continuing to use romidepsin and pralatrexate as single agents in PTCL, rather than in a doublet combination.