Year in Review

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

Saturday, February 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Disclosures

Consulting Agreements	Abbott Laboratories, Bayer HealthCare Pharmaceuticals, Genentech BioOncology

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Disclosures

Advisory Committee and Consulting Agreements	Celgene Corporation, Gilead Sciences Inc, Takeda Oncology, TG Therapeutics Inc
Contracted Research	Allos Therapeutics, Celgene Corporation, Gilead Sciences Inc, Novartis, TG Therapeutics Inc

Select Recently Approved Agents in CLL/Lymphomas

Agent	Approval date	Indication
Obinutuzumab	11/16/17	**FL** – previously untreated, advanced (Stage II bulky, III or IV)
Brentuximab vedotin	11/9/17	Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides – received prior systemic therapy
Acalabrutinib	10/31/17	**MCL** – received at least 1 prior therapy
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

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

Select Recently Approved Agents in CLL/Lymphomas

Agent	Approval date	Indication
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 Kahl and Williams

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

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.

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.

Tisagenlecleucel (CTL019) in Refractory B-Cell Lymphomas

- Patients with B-cell lymphomas on study (n = 28)
  - DLBCL (n = 14)
  - FL (n = 14)
- All patients received CTL019 cells
- Overall response rate = 18/28 (64%)
  - CR in patients with DLBCL = 6/14 (43%)
  - CR in patients with FL = 10/14 (71%)
- CTL019 cells proliferated in vivo and were detectable in the blood and bone marrow of patients who had a response and patients who did not have a response.

Survival at median follow-up of 28.6 mo	DLBCL	FL
Median PFS (n = 14, 14)	3.2 mo	Not reached
Median OS (n = 14, 14)	22.2 mo	Not reached
Response rate (n = 7, 11)	86%	89%
Median duration of response (n = 7, 11)	Not reached	Not reached

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

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.

A Comparison of One Year Outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in Patients with Refractory, Aggressive Non-Hodgkin Lymphoma (NHL)

Neelapu SS et al.
Proc ASH 2017;Abstract 579.

ZUMA-1 and SCHOLAR-1: Comparison of Outcomes

- **ZUMA-1**: Prospective trial of axicabtagene ciloleucel in refractory large B-cell lymphoma (median follow-up 15.1 mo)
- **SCHOLAR-1**: Retrospective study and largest reported analysis of outcomes in patients with refractory large B-cell lymphoma (median follow-up 7.6-14.8 years across institutions)
- Propensity score methods were used to allow comparison between the 2 studies by creating balance between a broad set of prognostic covariates (eg, age, sex, prior therapy, SCT after treatment for refractory disease).

Outcome	Propensity Score Analysis (n = 523)	
	CAR T	Non-CAR T
ORR (CR)	83% (57%)	33% (12%)
Median OS	16.4 mo	5.4 mo
HR	0.28	

Neelapu SS et al. *Proc ASH* 2017;Abstract 579.

High Durable CR Rates in Relapsed/Refractory (R/R) Aggressive B-NHL Treated with the CD19-Directed CAR T Cell Product JCAR017 (TRANSCEND NHL 001): Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort

Abramson JS et al.
Proc ASH 2017;Abstract 581.

Response Rates in R/R DLBCL

Core Patient Population (Dose Level 2 [DL2]) Chosen for Pivotal Cohort

Endpoint	DL2 single dose
Best observed response (n = 27)	
ORR	81%
CR	63%
≥ 3-mo follow-up (n = 19)	
3-mo ORR	74%
3-mo CR	68%
≥ 6-mo follow-up (n = 14)	
6-mo ORR	50%
6-mo CR	50%

- 80% (16/20) of pts with CR at 3 mo stay in CR at 6 mo
- 92% (11/12) of pts in response at 6 mo stay in response for a longer term

Abramson JS et al. *Proc ASH* 2017;Abstract 581.

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

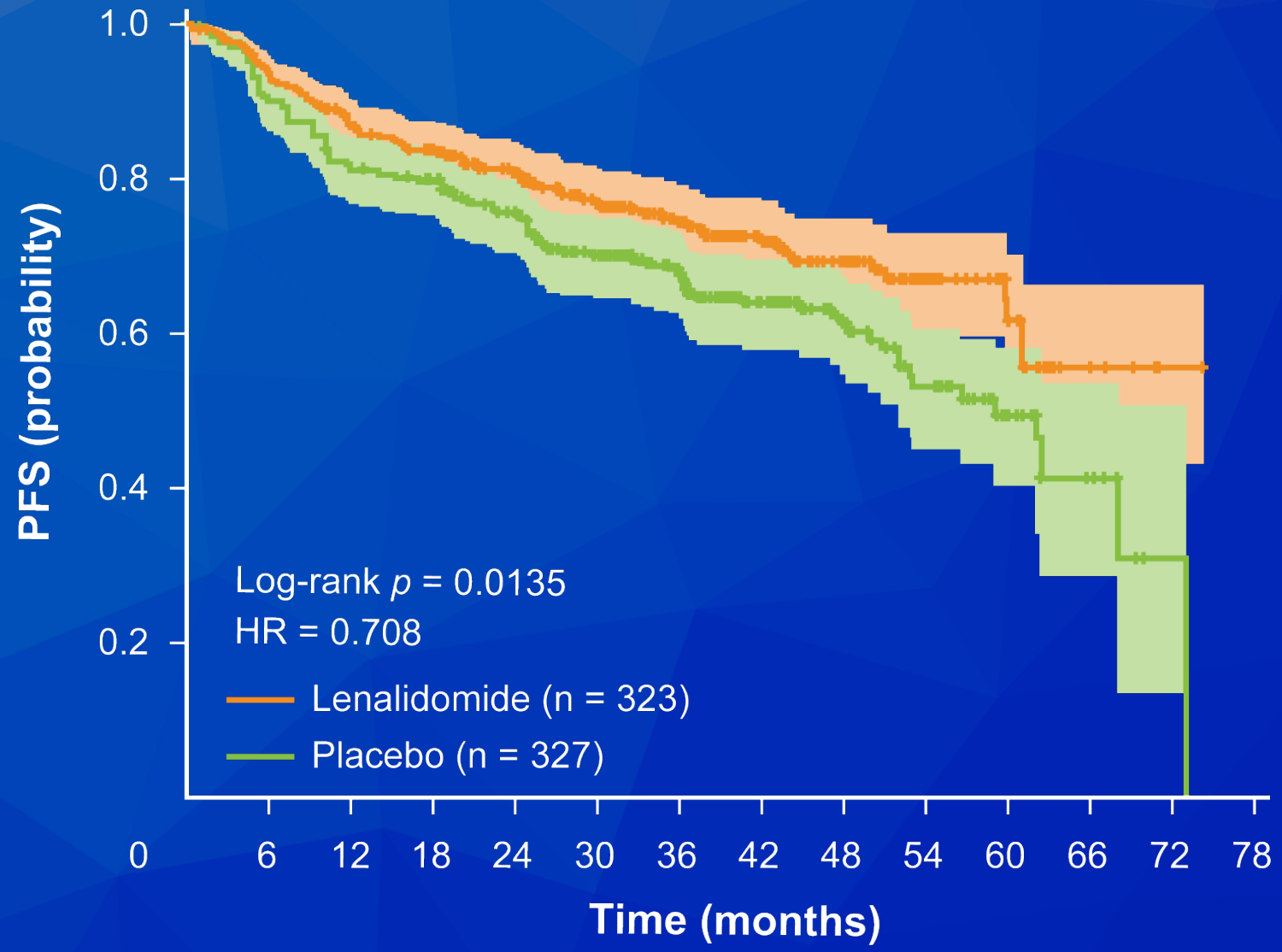
ORIGINAL REPORT

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

Thieblemont C et al. *J Clin Oncol* 2017;5(22):2473-81.

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

Lugtenburg P et al. *Haematologica* 2017;102(11):1913-22.

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;102(11):1913-22.

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)

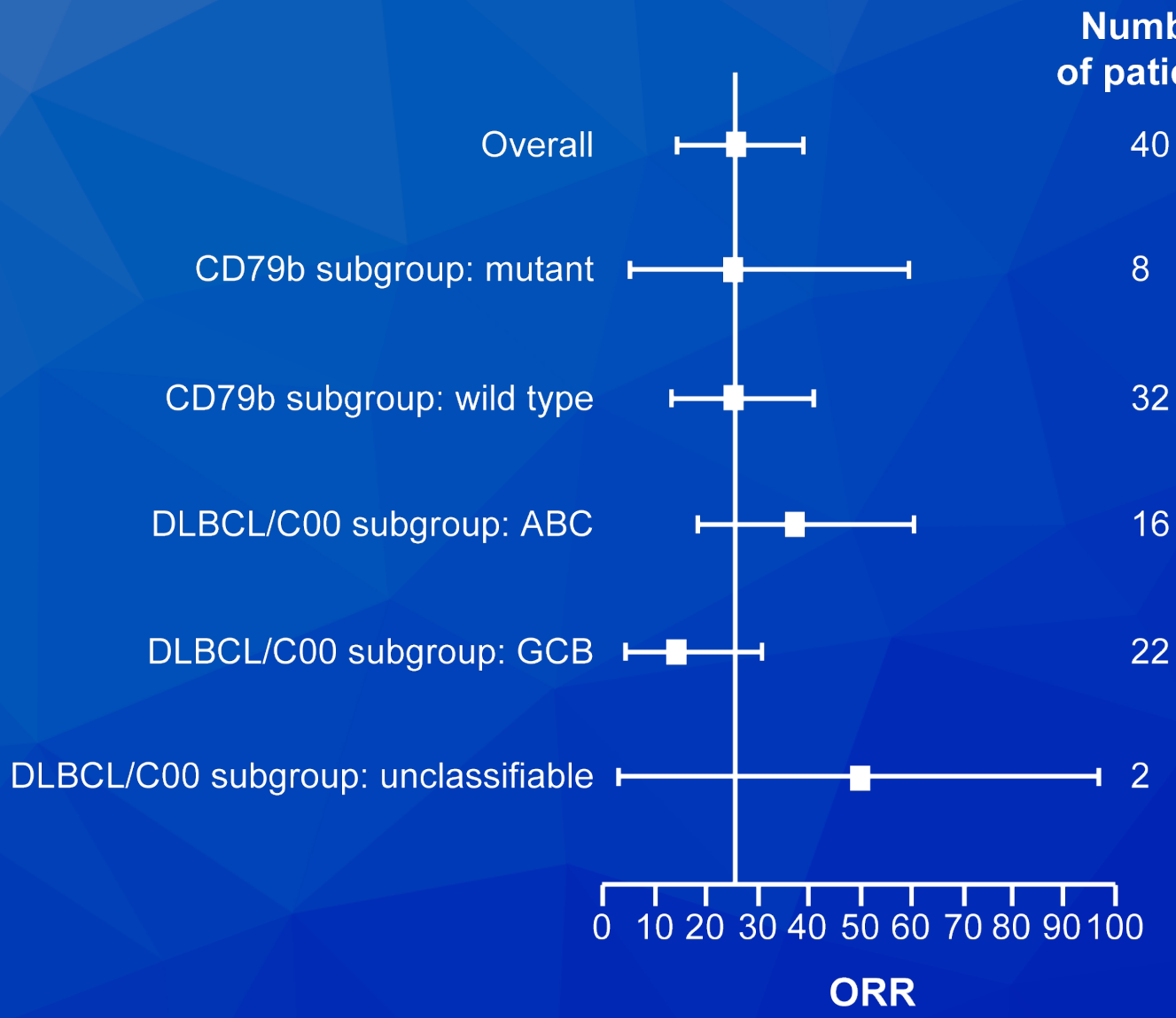
The SC formulation allowed much quicker delivery with a median time of administration of 6 minutes compared to 2.6-3.0 hours with the IV route. On questionnaires, 91% of subjects preferred SC over IV rituximab.

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.

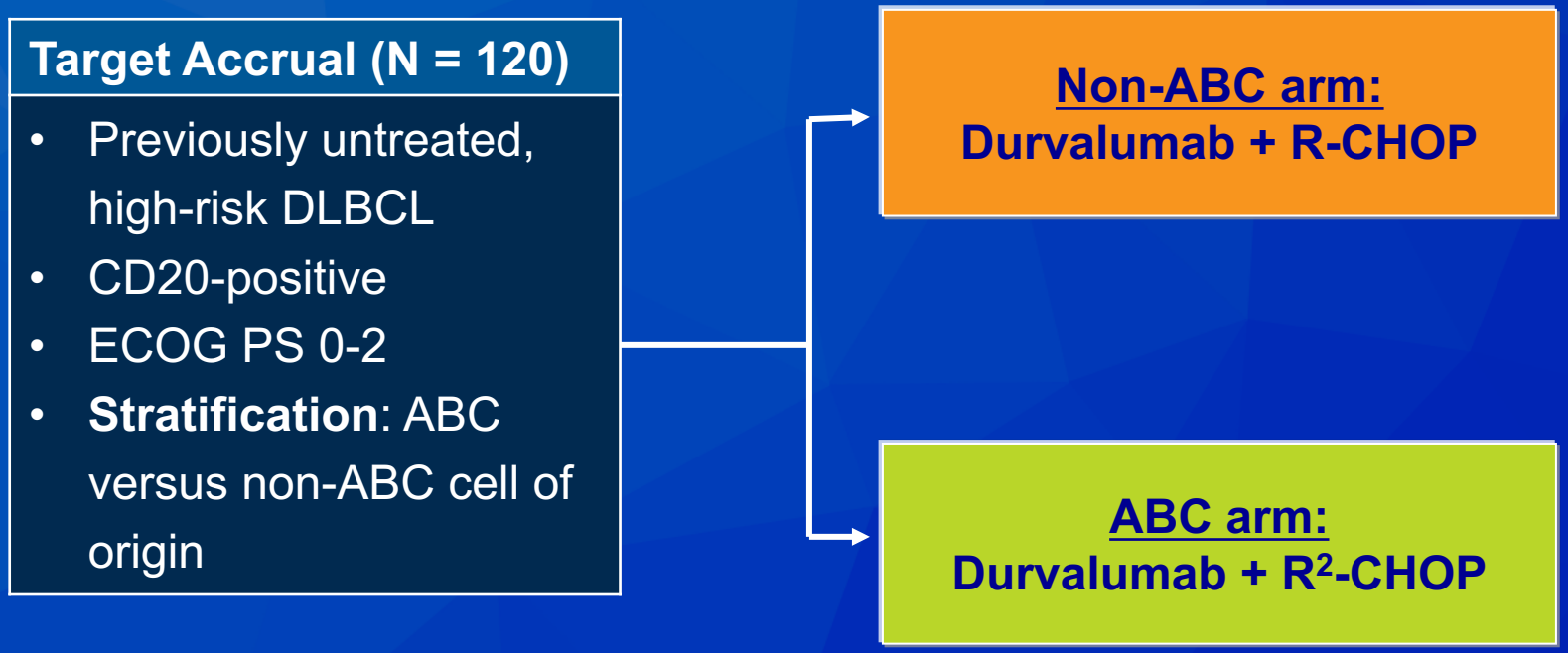
Editorial — Dr Abramson (continued)

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

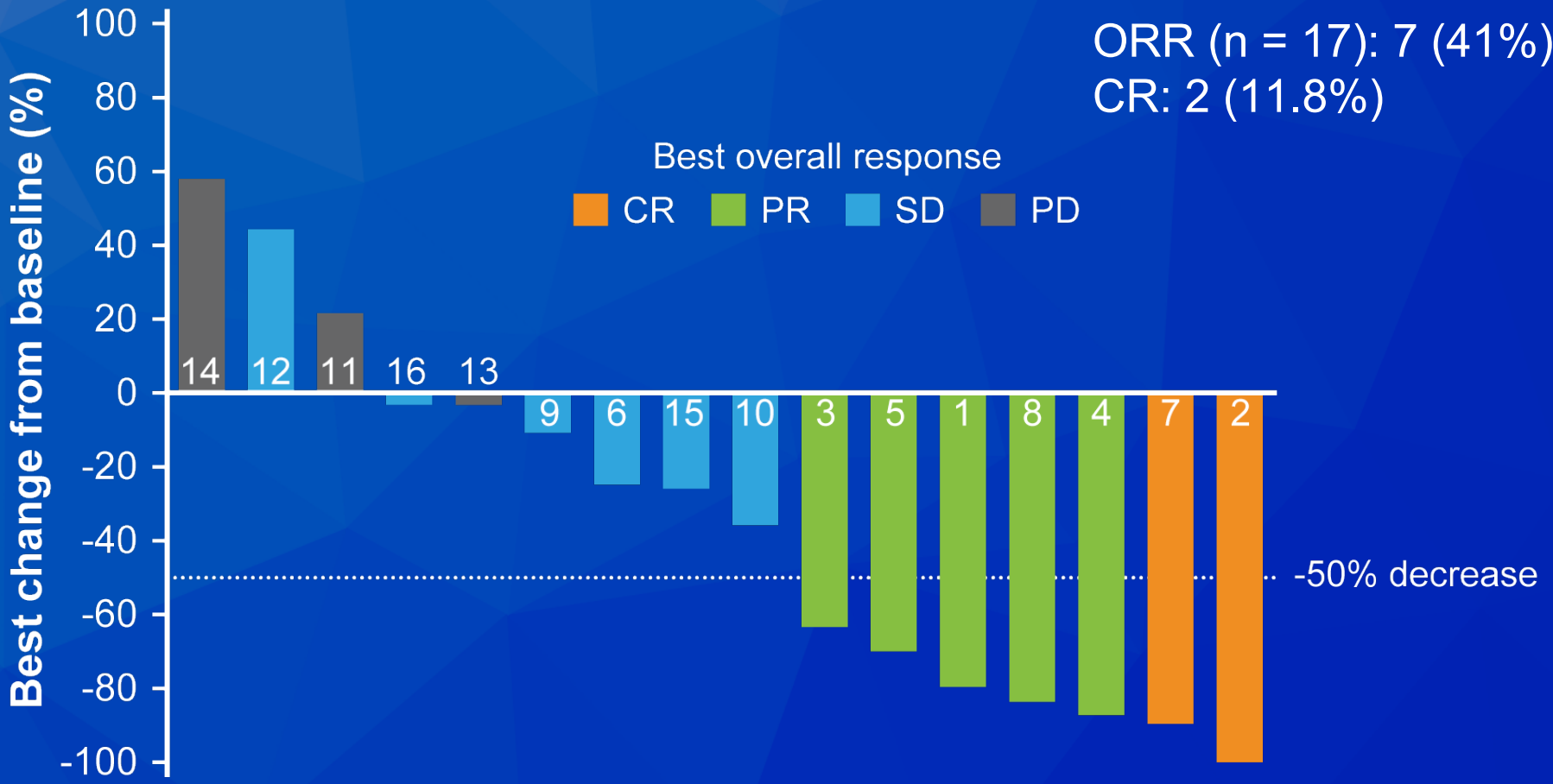
Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma

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 Nastoupil

Relapsed/refractory primary mediastinal B-cell lymphoma (PMBCL) has a very poor prognosis and is often chemo-refractory. Similar to classical Hodgkin lymphoma, PMBCL frequently exhibits 9p24.1/PD-L1/PD-L2 copy-number alterations and rearrangements with associated PD-L1 and/or PD-L2 overexpression facilitating immune evasion. Therefore, PMBCL may be particularly susceptible to PD-1 blockade. Pembrolizumab is an anti-PD-1 monoclonal antibody with efficacy in Hodgkin lymphoma. Zinzani et al report the efficacy and safety of pembrolizumab in a cohort of R/R PMBCL patients in an ongoing multicenter, international phase I trial (KEYNOTE-013) in hematologic malignancies.

Editorial — Dr Nastoupil (continued)

19 patients with R/R PMBCL were enrolled in KEYNOTE-013; 18 had received ≥1 dose by the analysis cut-off date (17 were evaluable for response). The first 11 patients were treated with 10 mg/kg of pembrolizumab every 2 weeks for the trial's duration; the subsequent 8 were enrolled after a study amendment and received a fixed dose of 200 mg every 3 weeks up to 2 years, or until disease progression or unacceptable toxicity. Primary endpoints were ORR and safety. The most common treatment related AEs were hypothyroidism, diarrhea, nausea, fatigue, pyrexia, and decreased appetite (2 patients each). The only grade 3 AE was neutropenia in 1 patient. Immune-related AEs were grade 2 diarrhea and grade 2 pneumonitis (1 patient each).

Editorial — Dr Nastoupil (continued)

No patient discontinued treatment due to AEs. There were no treatment-related deaths.

The ORR was 41% (12% CR; 29% PR) with an additional 35% with stable disease. With a median follow-up of 11.3 months, the median duration of response was not reached. 2 patients with an objective response (CR or PR) reached the 2 years of treatment and remain in remission.

PMBCL is a rare subtype of DLBCL. With outcomes following front-line chemoimmunotherapy being very favorable, it is difficult to conduct prospective trials for patients with R/R PMBCL. In addition, these patients can be very sick with rapidly progressive disease and cannot wait to initiate therapy to allow ample time for screening tests or washout periods.

Editorial — Dr Nastoupil (continued)

Therefore, despite the small number of patients in this phase I study, these results are impactful as they demonstrate pembrolizumab to be a safe and effective strategy for patients with R/R PMBCL.

Lymphomas — Drs Kahl and Williams

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

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 Zelenetz

Acalabrutinib (ACP-196) is a second-generation BTK inhibitor that has a more restricted kinome than ibrutinib. A phase 1 study, published by Byrd et al in the *NEJM,* demonstrated that the drug was highly efficacious in relapsed/refractory CLL. Long-term administration has not been associated with cumulative high-grade toxicity. However, there was frequent grade 1-2 headache (43%) as well as grade 1-2 diarrhea (39%, grade 3-4 in 2%). Hypertension grade 1-2 was seen in 13% of patients and grade 3-4 in 7% of patients. The frequency of bleeding, bruising and atrial fibrillation appear to be lower than expected with ibrutinib. This led to the conduct of a trial of acalabrutinib in patients with relapsed/refractory CLL intolerant of ibrutinib.

Editorial — Dr Zelenetz (continued)

Thirty-three patients were included in this analysis presented by Awan for his colleagues at ASH in 12/2016. The primary reasons for ibrutinib intolerance were rash, arthralgia/myalgia, diarrhea, fatigue and hemorrhage.

At the time of the presentation, 24 of the 33 patients treated with acalabrutinib were remaining on study. The safety profile was similar to what was seen in the ibrutinib-naïve cohort with frequent grade 1-2 diarrhea and headache. Twelve patients experienced recurrent adverse events, most of which were decreased or of similar severity. These results suggest that acalabrutinib has similar high efficacy to ibrutinib and may be better tolerated. However, this will be definitively answered in the ongoing head-to-head comparison of ibrutinib versus acalabrutinib.

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 Zelenetz

Idelalisib is a phosphoinositide 3-kinase delta isoform (PI3k delta) inhibitor approved for the treatment of relapsed/refractory CLL in combination with rituximab. Prior to the approval of idelalisib and ibrutinib for treatment of relapsed/refractory CLL, bendamustine and rituximab (BR) was a standard of care for the treatment of these patients. In the Gilead 115 study, we investigated adding idelalisib to the backbone of BR. Four hundred and sixteen patients were randomly assigned to treatment with BR + idelalisib (207) versus BR + placebo (209). A planned interim analysis led the DSMC to recommend discontinuation of the study because the primary endpoint of improvement in PFS had been met, 23 months for BR + idelalisib versus 11 months for BR + placebo. These results have been published.

Editorial — Dr Zelenetz (continued)

A subsequent analysis with a median follow-up of 21 months confirmed the preliminary finding of an OS benefit for the addition of idelalisib to BR with a hazard ratio of 0.67 (p=0.04, stratified). There was significant infectious toxicity in this study, but overall the toxicity was manageable. A frequent critique of this study is that it does not evaluate the impact of bendamustine in the combination. While a valid criticism, the study design was based on the fact that BR was commonly used in the setting of relapsed or refractory CLL. Some have pointed to the cross-trial comparison of Gilead 116 (R + placebo vs R + idelalisib), which demonstrated a 20-month PFS for the R + idelalisib arm. However, the same cross-trial comparison demonstrates an approximately 10% difference in OS at 36 months in favor of BR + idelalisib over R + idelalisib.

Editorial — Dr Zelenetz (continued)

The direct comparison of BR + idelalisib vs R + idelalisib will likely never be done. This combination is most appropriate in a situation where the treating physician plans on giving BR. In that case, there is a PFS and OS benefit of adding idelalisib.

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 Zelenetz

Ibrutinib is the first in class Bruton tyrosine kinase inhibitor (BTKi) and is approved for use in relapsed/refractory CLL (based on the RESONATE study) and first line in patients with del(17p) based on RESONATE-17. In the relapsed setting, it is also approved in combination with BR based on the HELIOS trial. It is also approved for all first-line use based on the results of the RESONATE-2 trial comparing ibrutinib to chlorambucil. This approval was extended substantially beyond the trial eligibility and remains controversial among CLL experts. There are a number of other BTKis in development, including acalabrutinib, which is the only other marketed BTKi (approved for use in MCL, not CLL). Kipps et al analyzed the results of RESONATE, HELIOS and RESONATE-2 to identify prognostic risk factors other than del(17p).

Editorial — Dr Zelenetz (continued)

In a multivariate analysis for patients treated with ibrutinib, no clear associations were found for unmutated IGHV, del(11q), trisomy 12, or complex karyotype. Among the patients not treated with ibrutinib, unmutated IGHV, del(11q) and complex karyotype were associated with shorter PFS, OS and ORR. The authors conclude that patients with these adverse risk factors should be treated with ibrutinib. However, the combination of two studies in the R/R setting with the front-line trial (RESONATE-2) complicates this analysis. It would be essential to determine that there was no interaction between these variables and the line of therapy. It is premature to use this model to choose first-line therapy until it can be independently validated or the appropriate sensitivity analyses are performed.

Initial Results of Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL (Bloodwise TAP CLARITY Study): High Rates of Overall Response, Complete Remission and MRD Eradication After 6 Months of Combination Therapy

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

Hillmen P et al.
Proc ASH 2017;Abstract 428.

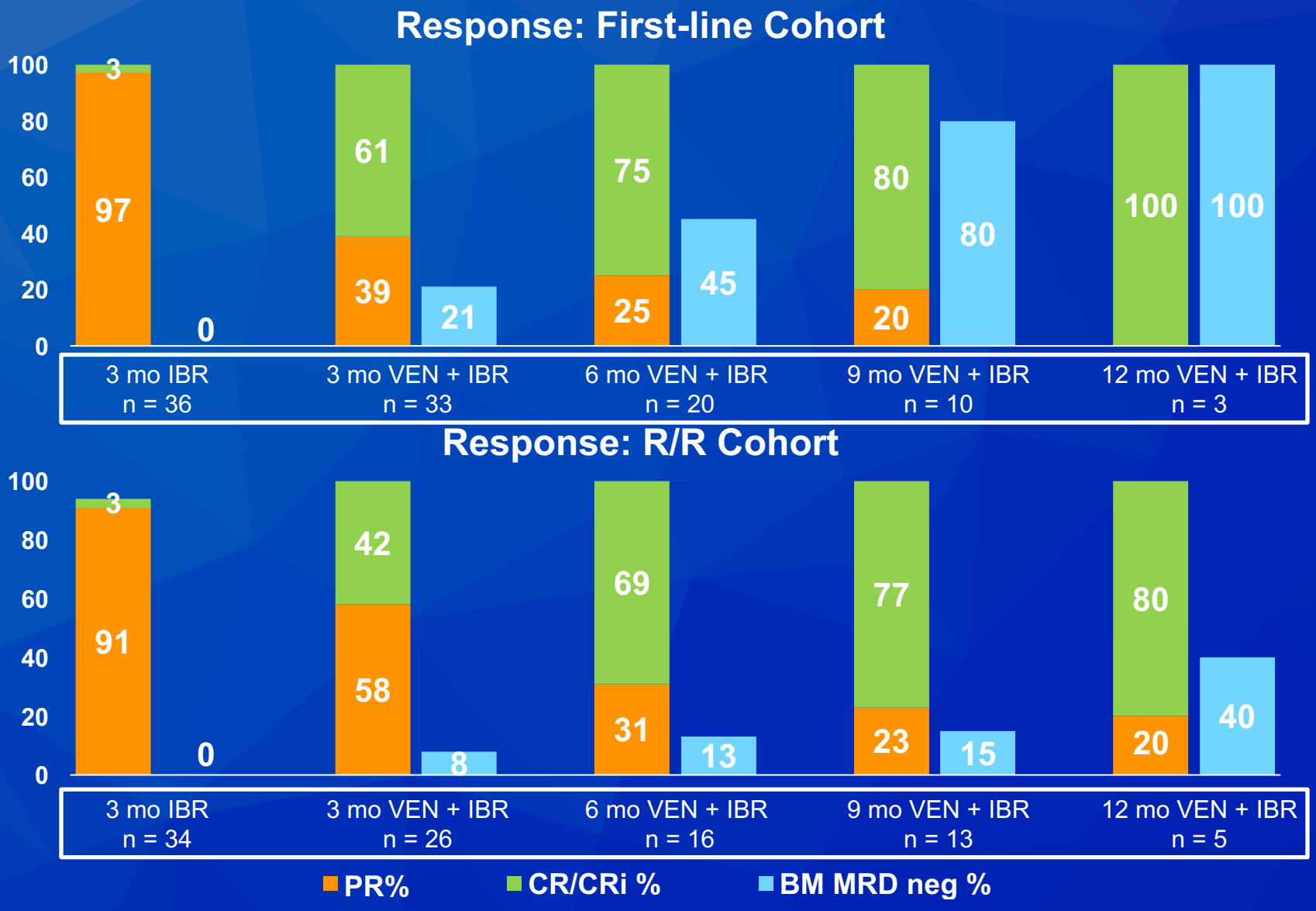
Jain N et al.
Proc ASH 2017;Abstract 429.

Bloodwise TAP CLARITY: Study Outcomes

- Patients with CLL requiring therapy who had either relapsed within 3 years of FCR or BR or had del(17p) and failed ≥1 prior therapy (n = 50)
- After 8 weeks of ibrutinib monotherapy (420 mg/day), venetoclax was added with weekly dose escalations
- Biochemical tumor lysis syndrome (TLS) (n = 2), resolved
- Evaluable patients (n = 25)
  - Overall response rate = 100%
    - CR/CRi = 60%
  - After 6 mo of follow-up (n = 25)
    - No morphological evidence of CLL in marrow biopsy: 84%
    - <1% CLL cells in the marrow: 76%
    - MRD-negative remission ($<10^{-4}$): 28%
- All patients will continue therapy until ≥14 mo assessment

Hillmen P et al. *Proc ASH* 2017;Abstract 428.

Phase II Trial of Ibrutinib/Venotoclax: Response

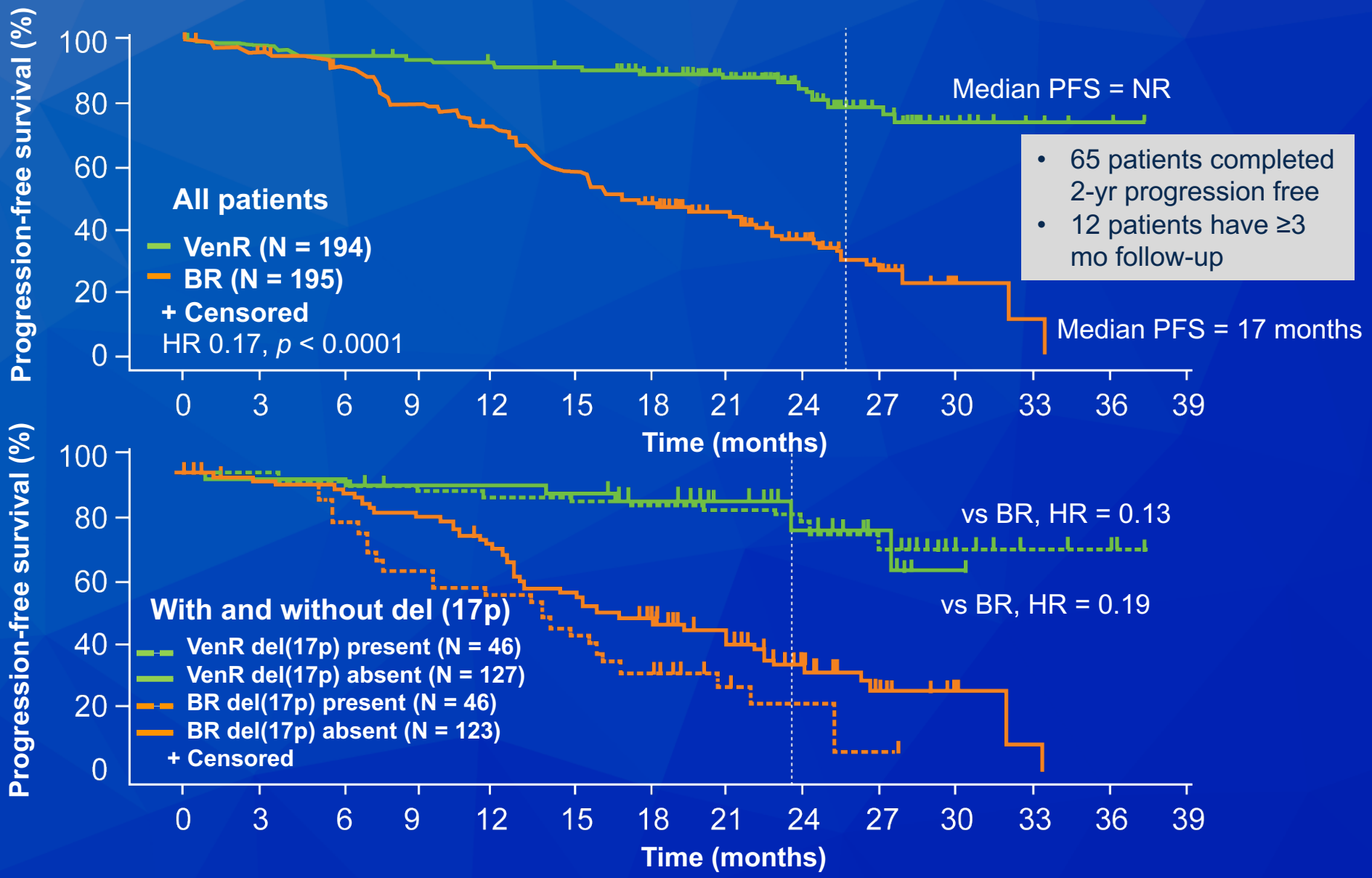


Jain N et al. *Proc ASH* 2017;Abstract 429.

Venetoclax Plus Rituximab Is Superior to Bendamustine Plus Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia — Results from Pre-Planned Interim Analysis of the Randomized Phase 3 Murano Study

Seymour JF et al.
Proc ASH 2017;Abstract LBA-2.

MURANO: INV-Assessed PFS



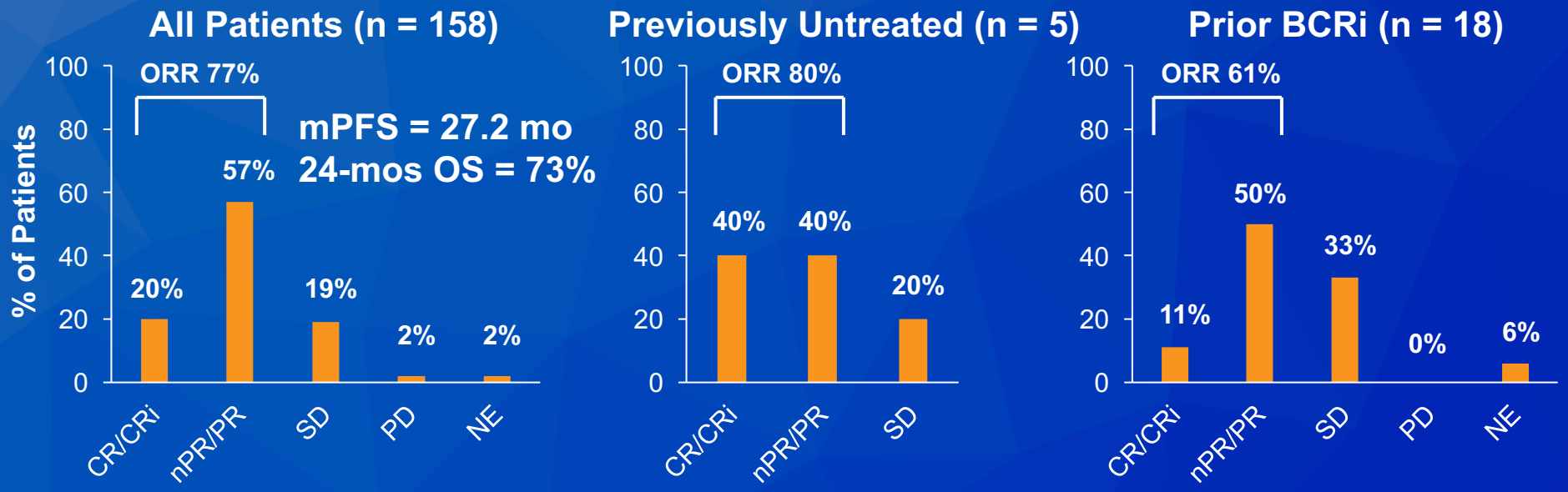
- 65 patients completed 2-yr progression free
- 12 patients have ≥3 mo follow-up

Seymour JF et al. *Proc ASH* 2017;Abstract LBA-2.

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 Zelenetz

Venetoclax is a Bcl-2 specific, BH3 mimetic which promotes apoptosis by displacing pro-apoptotic BH3-only proteins from Bcl-2 so they can bind with BAX and BAK and promote apoptosis. In the early development of this drug, substantial clinical activity was seen in patients with CLL. However, a dose-limiting toxicity of the drug was fatal tumor lysis. After a clinical hold, the dosing was modified to include a weekly dose escalation (20 mg, 50 mg, 100 mg, 200 mg, target dose 400 mg) combined with hospitalization for patients at high risk (any LN ≥10 cm or ALC ≥25 x 10^9/L AND any LN ≥5 cm) and intermediate (any LN 5 cm to <10 cm OR ALC ≥25 x 10^9/L) with CrCl <80 mL/min, which eliminated significant clinical tumor lysis.

Editorial — Dr Zelenetz (continued)

A phase 2 study of venetoclax for patients with relapsed/refractory CLL with del(17p) was presented by Dr Stephan Stilgenbauer at ASH 2015 and subsequently published in *The Lancet Oncology*. That study demonstrated an ORR (IRC) of 79.4% with a CRR of 7.5%. The responses were very rapid with a median time to response of 0.8 months. However, the MRD-negativity rate continued to increase through the 18 months of available follow-up. At EHA 2017, these results were updated. The CR rate increased to 18%, and 24-month estimates of PFS and OS were 52% and 72%, respectively. Most common AEs included neutropenia (42%, grade 3-4, 39%), nausea (37%), diarrhea (37%), anemia (24%, grade 3-4, 14%), fatigue (22%), and thrombocytopenia (grade 3-4, 15%).

Editorial — Dr Zelenetz (continued)

The rate of laboratory tumor lysis syndrome (TLS) was 5%, with no cases of clinical TLS. From the full trial cohort of 158 pts, 42 (27%) demonstrated blood MRD negativity at 10^{-4} by flow cytometry. Of 28 who had a contemporaneous NGS sample, MRD was confirmed in 20 pts (71%). Patients who achieved blood MRD-negative CR by flow cytometry (n=19) had a 24-month PFS estimate of 100%, compared with 78.5% pts who had blood MRD-negative PR (n=23).

These results confirm the substantial single-agent activity of venetoclax. However, also published in 2017 was the preliminary data with rituximab in combination with venetoclax with a higher MRD rate, 50% in bone marrow at 7 months. In that study, patients had an option to come off the drug.

Editorial — Dr Zelenetz (continued)

Eleven patients who were MRD negative (10 iwCLL CR, 1 PR) opted to discontinue therapy; at the time of the publication, none had relapsed with follow-up ranging 4-32 months. The ability to generate durable MRD makes this agent unique among the novel targeted therapies in CLL.

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

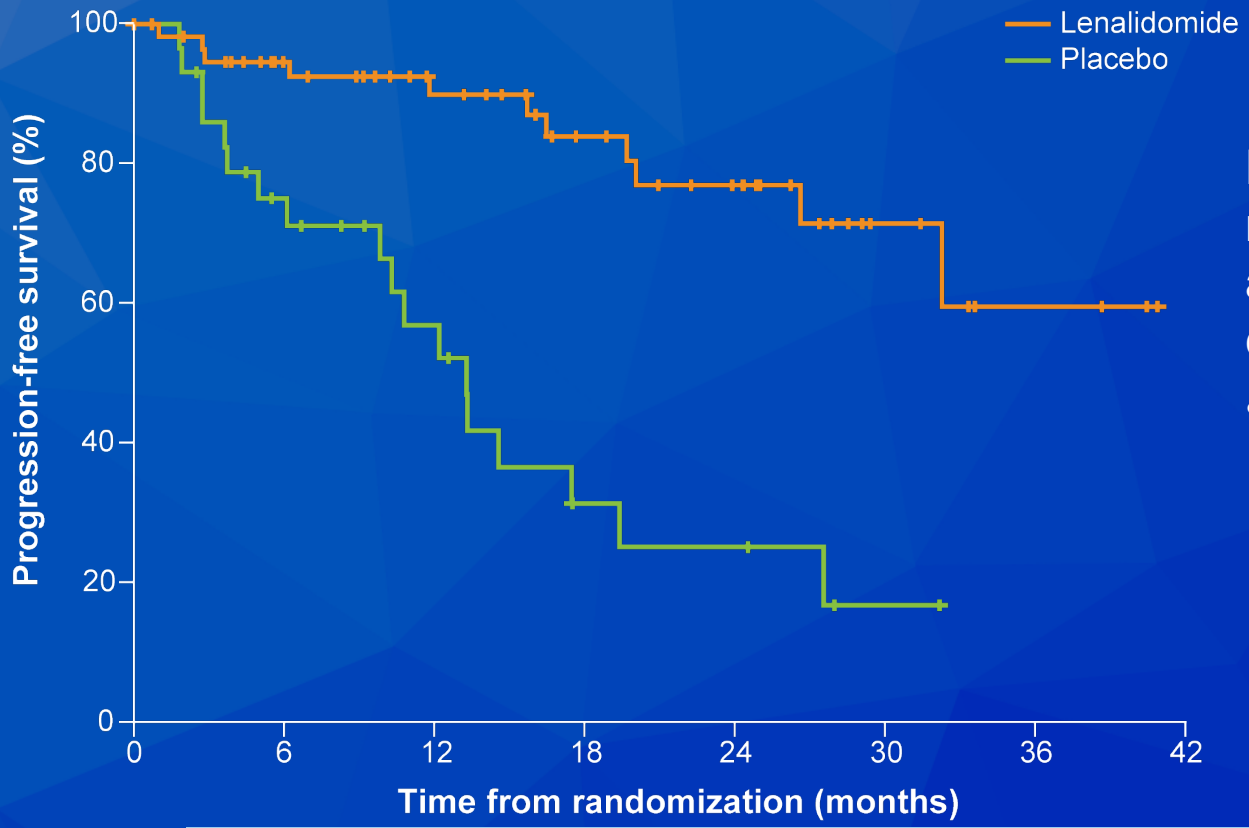
Lancet Haematol 2017;4(10):e475-86.

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;4(11):e534-43.

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



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

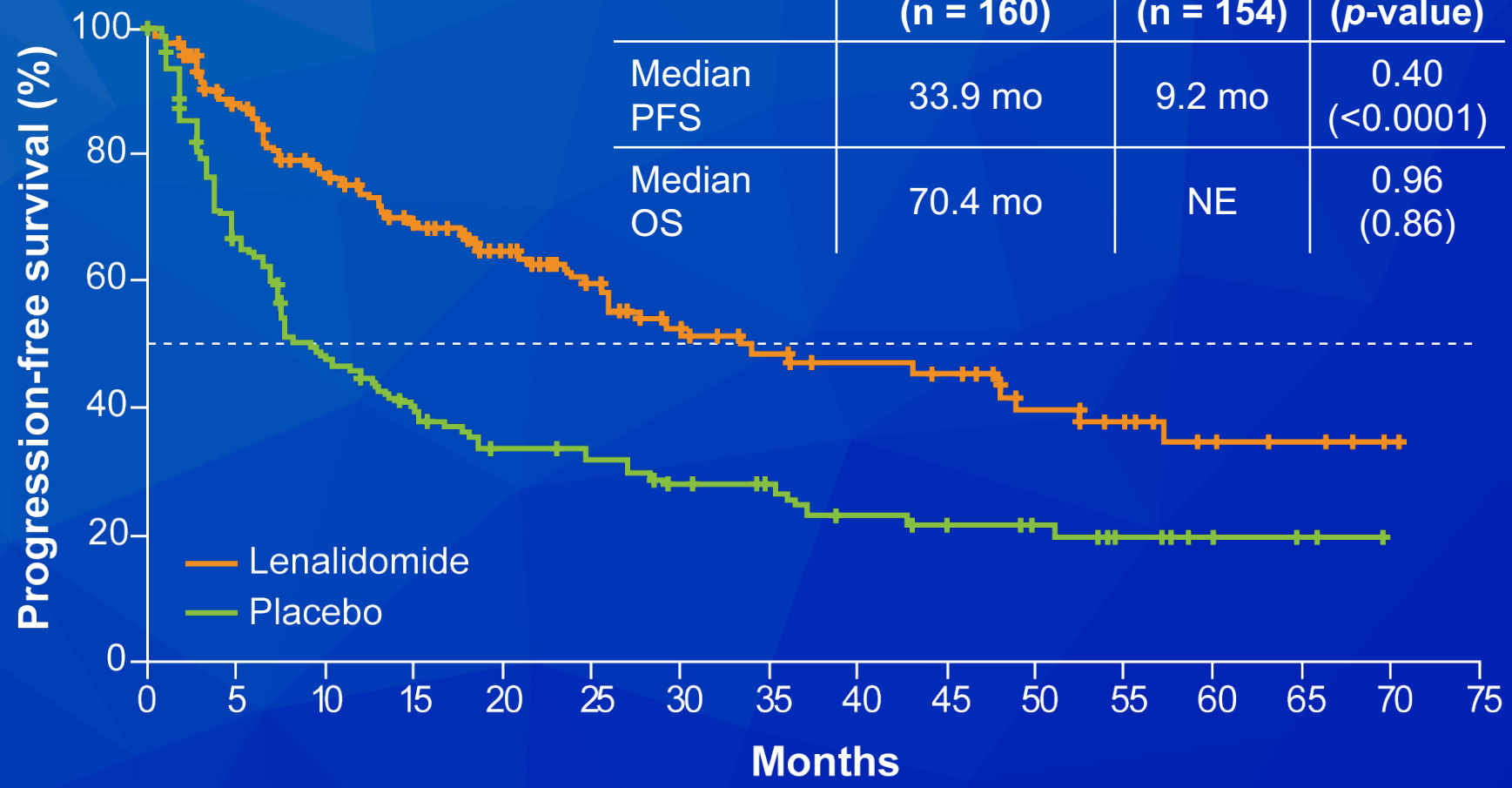
- High MRD levels or intermediate MRD levels combined with unmutated IGHV gene status or TP53 alterations

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;4(11):e534-43.

Editorial — Dr Zelenetz

Lenalidomide targets the cereblon component of E3-ubiquitin ligase, accelerating the degradation of IZF 1 and 3. This has wide-ranging effects targeting the tumor, the tumor micro-environment as well as T-cell and NK-cell activity. The relative contribution of these various targets depends on the tumor type. Single agent activity of lenalidomide in CLL has been demonstrated in a number of studies. In the past year, two studies examined the role of lenalidomide as maintenance. The CLLM1 study from the German CLL Study Group was published by Fink et al in *The Lancet Haematology* in 2017. This study examined the role of maintenance lenalidomide in patents with “high risk disease” at the end of induction chemo-immunotherapy (BR, FCR, FR) or chemotherapy (FC).

Editorial — Dr Zelenetz (continued)

High-risk patients were defined as those with MRD $\geq 10^{-2}$, MRD $\geq 10^{-4}$ to $<10^{-2}$ plus (unmutated IGHV or del(17p) or TP53 mutation at baseline). Part of this definition would not apply to current practice. Patients with del(17p) and/or TP53 mutation would be treated with ibrutinib at first line and not receive chemo-immunotherapy. This population represented approximately 20% of the patients who received maintenance or placebo. Patients were randomized 2:1 to lenalidomide maintenance versus placebo.

One of the key findings is that this was not a common population. Of 468 patients, 379 were excluded, 347 because they were low risk. Only 89 “high risk” patients were identified.

Editorial — Dr Zelenetz (continued)

There was a substantial improvement in PFS for patients randomized to maintenance lenalidomide (median PFS 12 months for placebo versus NR for the lenalidomide maintenance). However, there was no difference in OS. This improvement was associated with substantial Grade 3-4 toxicity, especially hematologic toxicity. I agree with the assessment of Dr Rossi who wrote in an editorial accompanying the publication that the lack of a survival benefit dampens enthusiasm for this approach. There are alternative approaches that could be evaluated in this setting. I do not see a role for maintenance lenalidomide following first-line therapy of CLL.

Another approach is to use lenalidomide maintenance after second-line therapy.

Editorial — Dr Zelenetz (continued)

Dr Chanan-Khan published the CONTINUUM study in *The Lancet Haematology* in 2017, which evaluated lenalidomide maintenance in patients achieving at least a PR to second-line therapy among patients who had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment. Three hundred and fourteen patients with CLL were enrolled to lenalidomide (n=160) or placebo (n=154). With a median follow-up of 31.5 months (IQR 18.9–50.8), there was no significant difference in overall survival between the lenalidomide and the placebo groups. PFS was significantly longer in the lenalidomide group (median 33.9 months) than the placebo group (9.2 months).

Editorial — Dr Zelenetz (continued)

Again, in the absence of an OS benefit, this is not a compelling option. In the US, these patients would be receiving ibrutinib rather than chemo-immunotherapy for R/R CLL. Thus, the results of the CONTINUUM trial are not very relevant in the US.

Lymphomas — Drs Kahl and Williams

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

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

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

(1:1)

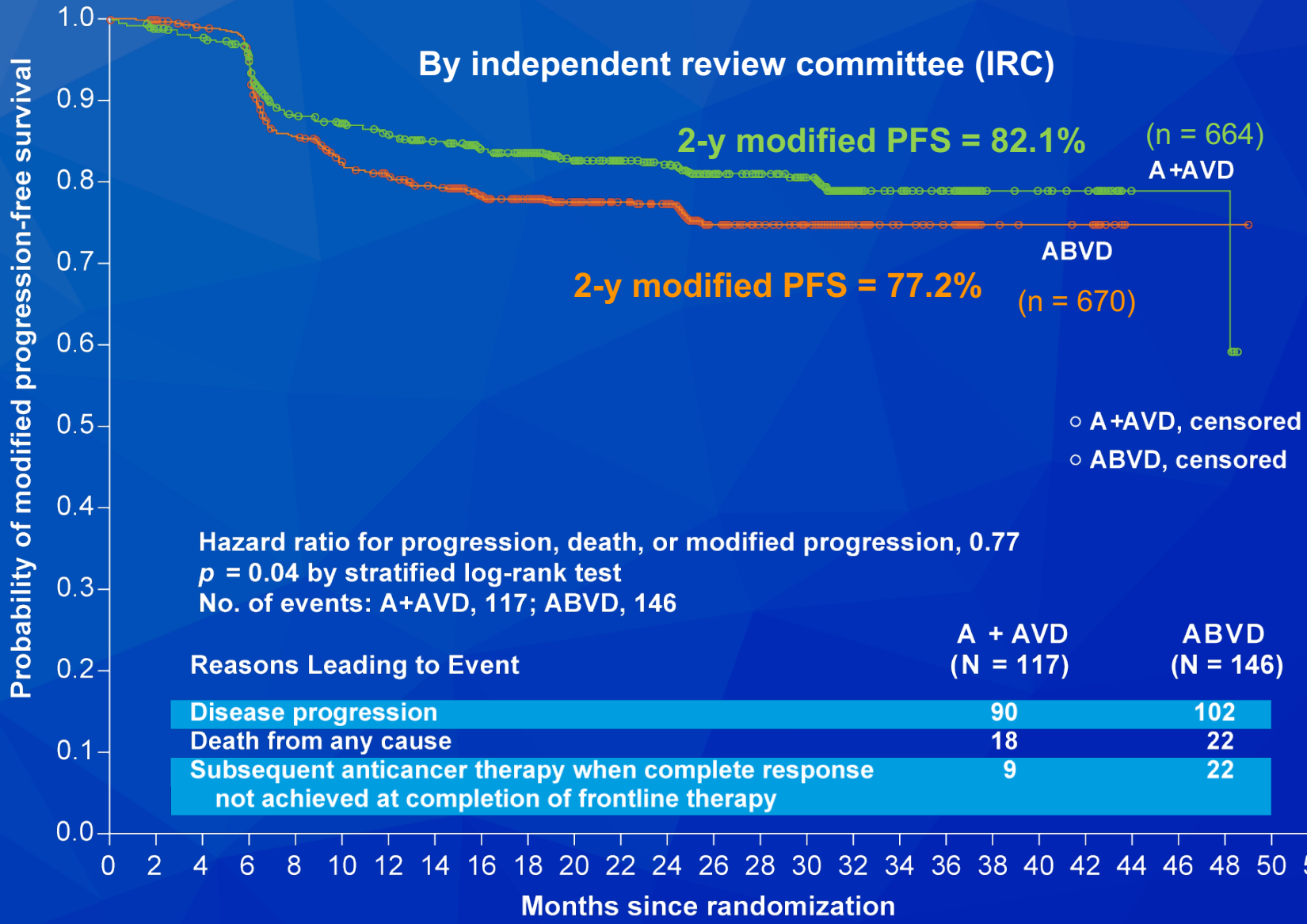
R

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

ECHELON-1: Modified PFS



Hazard ratio for progression, death, or modified progression, 0.77
p = 0.04 by stratified log-rank test
No. of events: A+AVD, 117; ABVD, 146

Reasons Leading to Event	A + 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.

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.

Interim Results 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.
Blood 2017;[Epub ahead of print].

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

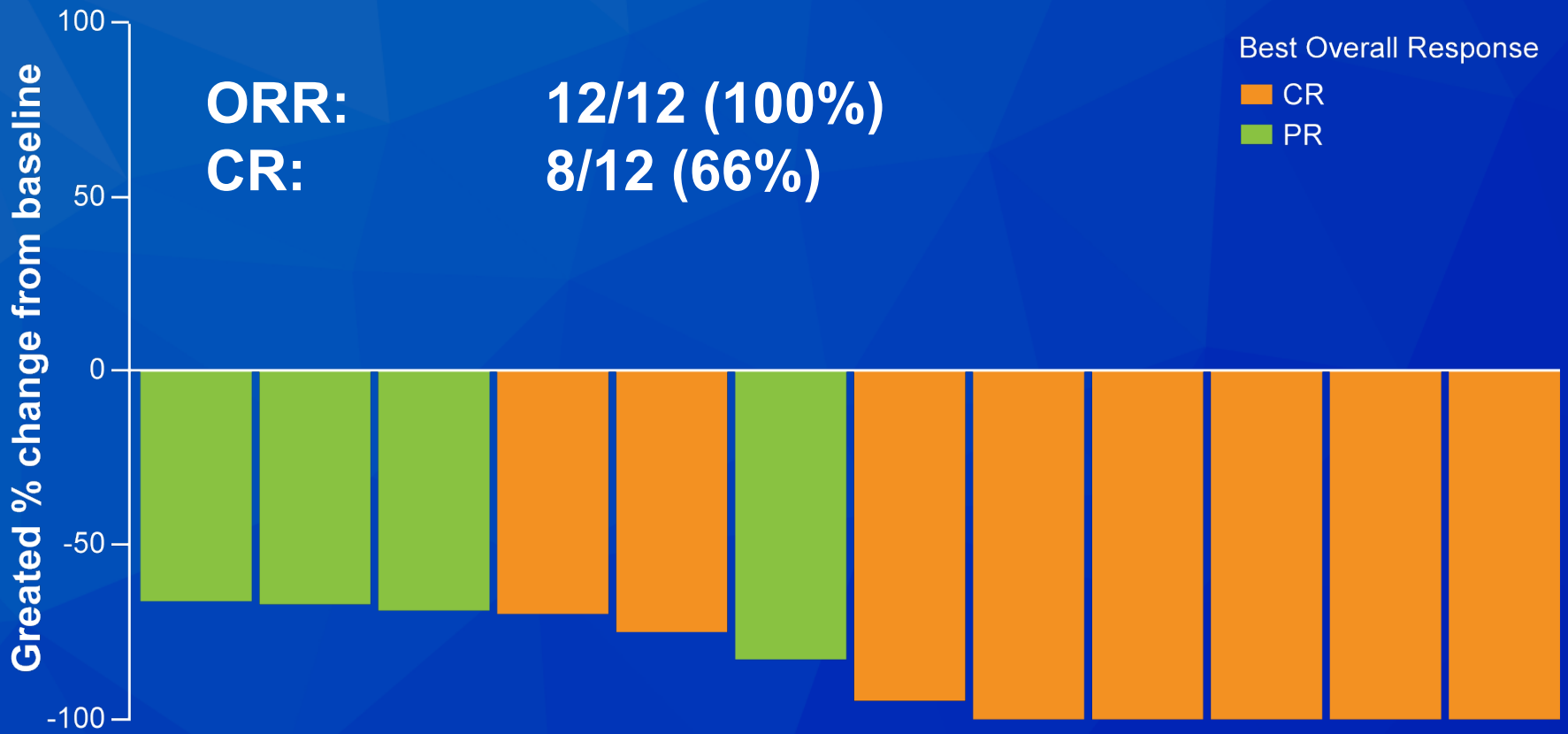
Response and Adverse Events with Brentuximab Vedotin/Nivolumab

	Efficacy evaluable patients (N = 55)
Objective response rate	85%
Complete response rate	64%
Treatment-emergent AEs before ASCT	**N = 61**
Any AE Grade 2 Grade 3 Grade 4	98% 66% 28% 5%
Infusion-related reactions (IRRs), any grade	41%*
Immune-related reactions other than IRRs, any grade	72%

* Grade 3 IRRs: <5%

Herrera AF et al. *Blood* 2017;[Epub ahead of print]; *Proc ICML* 2017;Abstract 74.

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



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

Editorial — Dr Zelenetz

The PD-1 blocking antibodies nivolumab and pembrolizumab have potent activity in relapsed/refractory cHL with high response rates and good PFS as single agents. However, optimization of the use of the checkpoint inhibitors remains to be determined. Two studies presented this year may provide some glimpse of the future.

The first study, presented by Dr Herrera at ICML in 6/2017, combined nivolumab with brentuximab vedotin (BV). BV is an antibody-drug conjugate directed against CD30 and has shown substantial activity in relapsed/refractory cHL. It is approved for disease progression after HDT/ASCR as well as maintenance post HDT/ASCR based on the AETHERA study.

Editorial — Dr Zelenetz (continued)

The study combined nivolumab and BV in patients with relapsed/refractory cHL. Sixty-two patients were enrolled who had not undergone HDT/ASCR for relapsed/refractory cHL. Among the 55 patients evaluable for efficacy, the ORR was 85% and CRR was 64%. At the time of this analysis, 29 patients had initiated HDT/ASCR. The combination appears promising and further studies are warranted.

The other combination study addressed the question of combining nivolumab, ipilimumab (IPI) and BV for patients with relapsed/refractory cHL. The plan was to conduct sequential cohorts of IPI and BV, followed by nivolumab and BV and finally the triple combination. Dr Diefenbach presented the preliminary results of the IPI + BV cohort at ASH in 2015.

Editorial — Dr Zelenetz (continued)

For the 12 evaluable patients, the overall response (ORR) for the combination of BV + IPI was 67% with a complete response (CR) rate of 42% (5 of 12 patients). At ICML-14 in 2017, Dr Diefenbach presented the second cohort of BV + nivolumab. The ORR was 89% with 61% CR. The combination was well tolerated. In the IPI and nivolumab cohort, follow-up is too short to accurately determine PFS. The goal is to continue with the triple combination portion of this ongoing phase I study.

The CR rates seems to be higher with the BV + nivolumab combinations, but this is based on cross-trial comparisons in different patient populations.

Editorial — Dr Zelenetz (continued)

As with all combination studies, it is important to ultimately determine the relative contribution of different elements to the outcome. Randomized phase II trials may help determine the contribution of the checkpoint inhibitor to the BV.

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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 Zelenetz

Nivolumab and pembrolizumab are highly selective, humanized monoclonal antibodies that block the interaction between PD-1 and its ligands. These checkpoint inhibitors have shown robust antitumor activity and a favorable safety profile in multiple tumors. However, in phase I studies of patients with hematologic malignancies, the highest antitumor activity seen in ANY malignancy was observed in patients with relapsed/refractory Hodgkin lymphoma. Rationale for this response is found in the observation that in classical Hodgkin lymphoma chromosomal abnormalities at 9p24 are common. These chromosomal abnormalities result in the overexpression of PD-L1 and PD-L2, which are the ligands for nivolumab and pembrolizumab.

Editorial — Dr Zelenetz (continued)

KEYNOTE-087 (pembrolizumab) and CheckMate 205 (nivolumab) are phase II studies that sought to confirm the phase I findings. KEYNOTE-087 had three cohorts of patients with relapsed/refractory cHL: disease progression after high-dose therapy with autologous stem cell rescue (HDT/ASCR) and subsequent brentuximab vedotin (BV); salvage chemotherapy and BV, and thus, ineligible for HDT/ASCR because of chemoresistant disease; and ASCT, but without BV after transplantation. A total of 210 patients were enrolled and treated (69 in cohort 1, 81 in cohort 2, and 60 in cohort 3). At the time of analysis, patients received a median of 13 treatment cycles. The ORR and CRR were 69.0% and 22.4%, respectively.

Editorial — Dr Zelenetz (continued)

There were no major differences in ORR by cohort: cohort 1, 73.9%; cohort 2, 64.2%; and cohort 3, 70.0%. At 6 months, the PFS and OS rates were 79.6% and 100%, respectively.

Similar results were seen in the CheckMate 205 trial, which enrolled patients with relapsed/refractory cHL after HDT/ASCR into one of three cohorts: BV naïve; BV after HDT/ASCR; BV before and/or after HDT/ASCR. Two hundred and forty-three patients were enrolled: BV naïve 63; BV post HDT/ASCR 80; BV before (n = 33), after (n = 58), or before and after (n = 9) ASCT. At the median follow-up of 19, 23, and 16 months for the three cohorts, the ORR was BV naïve 65%; BV post HDT/ASCR 68%, and BV before and/or after HDT/ASCR 73%.

Editorial — Dr Zelenetz (continued)

Median PFS by cohort: 18.3, 14.7, and 11.8; however, the KM curves are overlapping.

Checkpoint inhibition targeted at PD-1 is highly effective in relapsed/refractory cHL. Further work needs to be done to determine where this therapy best fits in the treatment of cHL.

Lymphomas — Drs Kahl and Williams

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

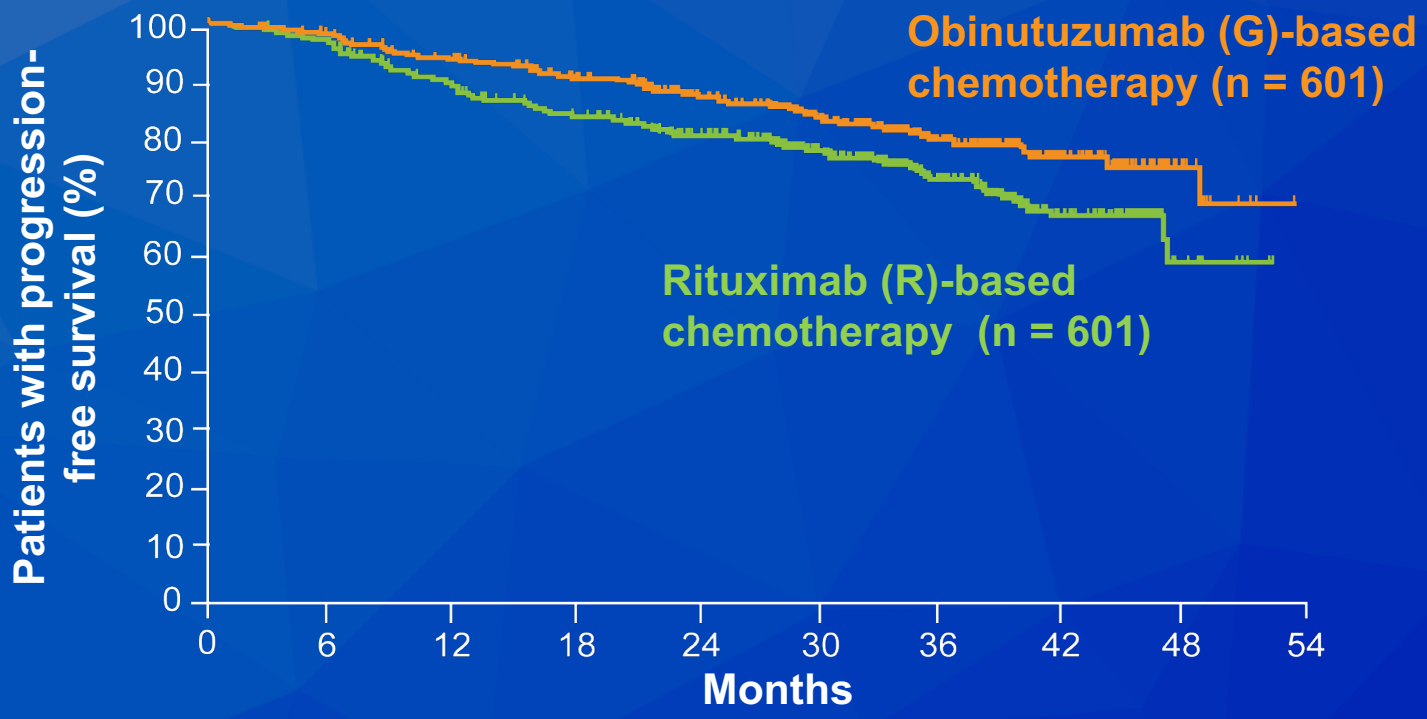
Mantle Cell Lymphoma

T-Cell Lymphoma

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.

GALLIUM: Safety Summary

	R-Chemo (n = 597)	G-Chemo (n = 595)
Any AE	98.3%	99.5%
Grade ≥3 AEs (≥5% in either arm)	67.8%	74.6%
Neutropenia	39.5%	45.9%
Thrombocytopenia	2.7%	6.1%
Grade ≥3 AEs of special interest		
Infections	15.6%	20.0%
IRRs	6.7%	12.4%
Second neoplasms	2.7%	4.7%
Grade 5 AEs	3.4%	4.0%

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

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

Editorial — Dr Nastoupil

Marcus et al report the results of the randomized phase III trial investigating the preferred anti-CD20 monoclonal antibody, rituximab (R) versus obinutuzumab (O), in combination with chemotherapy in previously untreated follicular lymphoma. Patients were randomized in a 1:1 ratio to either R (375 mg/m^2 on day 1 of each cycle) or O (1,000 mg on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles) in combination with bendamustine; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); or CVP.

Editorial — Dr Nastoupil (continued)

Doses of chemotherapy were as follows: CHOP — cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) on day 1 plus prednisone 100 mg orally per day on days 1 to 5 of six 21-day cycles; CVP — same doses (for C, V, and P) as in CHOP for eight 21-day cycles; bendamustine — 90 mg/m^2 on days 1 and 2 of six 28-day cycles. The chemotherapy regimen was determined by each site; therefore, all patients at each site received the same regimen. Patients who achieved a response at the end of induction were continued on maintenance therapy with the same antibody every 2 months for 2 years or until disease progression or withdrawal.

Editorial — Dr Nastoupil (continued)

1,202 adult (≥18 years of age) patients with follicular lymphoma (grade 1-3a) in need of therapy as defined by GELF criteria were enrolled between 7/6/11 and 2/4/14. The median age was 59 years. Slight majority were female (53%). Baseline characteristics were balanced between the 2 arms. 41%-42% had high-risk FLIPI scores. 57% received bendamustine, approximately a third received CHOP and the remaining 10% received CVP in combination with a CD20 antibody.

The primary endpoint was progression-free survival (PFS) as assessed by the investigator. PFS was also assessed by an independent review committee. The study was powered to detect a difference in PFS that corresponded to a 26% lower risk of progression or death.

Editorial — Dr Nastoupil (continued)

With a median follow-up of 34.5 months, the primary endpoint was met at the preplanned interim analysis with 80% and 73% 3-year PFS estimates for O-chemo vs R-chemo and HR of 0.66 with a 34% reduction in risk of progression or death with O-chemo vs R-chemo. Responses at the end of induction and overall survival were similar.

Infusion-related adverse events were more frequent in the O-chemo arm (59% vs 49%, P<.001) and typically occurred during the first infusion. Higher rates of infection, cardiac events, second neoplasms, neutropenia and thrombocytopenia were also seen among those receiving O.

Editorial — Dr Nastoupil (continued)

Bendamustine was associated with higher rates of grade 3-5 infection and second neoplasm during the maintenance and follow-up phase with CHOP being associated with higher grade 3-5 neutropenia during the induction phase.

The GALLIUM trial demonstrated an improvement in PFS was achieved with O-chemo vs R-chemo in previously untreated, high tumor burden follicular lymphoma patients. This was achieved with a higher cumulative dose of monoclonal antibody and higher rates of grade 3-5 adverse events.

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 Nastoupil

Morschhauser reports the efficacy and safety of lenalidomide in combination with obinutuzumab (O) in relapsed/refractory follicular lymphoma. O was glycoengineered to have superior ADCC (antibody-dependent cell-mediated cytotoxicity) compared to rituximab. Lenalidomide and rituximab (R) have demonstrated promising efficacy through targeting the microenvironment in follicular lymphoma, suggesting the replacement of R with O may be more effective, the question is whether safety will be impacted with the modern regimen.

Editorial — Dr Nastoupil (continued)

Induction consisted of 20 mg of lenalidomide on days 1-21 of a 28-day cycle for the first cycle and days 2-22 of a 28-day cycle from cycles 2-6. O (1,000 mg) was given on days 8, 15, and 22 of cycle 1 and day 1 of cycles 2-6. Patients who responded to induction then received maintenance with 12 cycles of lenalidomide (10 mg) on days 2-22 of every 28 days and O (1,000 mg) every 8 weeks. The primary endpoint was ORR.

89 patients were enrolled. Median age was 64 years. Thirty-five percent had bulky disease (≥5 cm). Median number of prior regimens was 2 (range 1-7). Twenty-seven percent were refractory to R-containing therapy or the last prior therapy.

Editorial — Dr Nastoupil (continued)

With a median follow-up of 18 months, ORR was 80% (CR 40%). Most common grade ≥3 adverse events were neutropenia (28%), infections (7%), with neutropenic fever 3.4%.

The combination of O + lenalidomide in relapsed/refractory follicular lymphoma is associated with promising efficacy and a manageable safety profile.

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 Nastoupil

We reported the pre-planned interim analysis of pembrolizumab in combination with rituximab in relapsed follicular lymphoma patients. Patients were eligible if they had disease progression following at least 1 prior therapy and had rituximab sensitive disease defined as a complete or partial response lasting at least 6 months following the most recent rituximab containing therapy. Among the first 27 patients enrolled, the median age was 65 years, the majority were of high tumor burden (as defined by GELF criteria), and less than 24% were of low risk FLIPI score. The median number of prior therapies was 1 (range 1-4). The primary endpoint was ORR. Patients received 4 weekly doses of rituximab (375 mg/m^2) starting on day 1.

Editorial — Dr Nastoupil (continued)

Pembrolizumab (200 mg) was started on day 2 and continued every 3 weeks for a total of 16 doses.

Among the first 15 subjects enrolled, ORR was 80% (CR 60%). Adverse events were mostly grade 1/2 with no grade 4 or 5 adverse events observed with a median follow-up of 7 months. Grade 2 immune-mediated adverse events leading to treatment discontinuation included diarrhea (N=2), pneumonitis (N=1), and rash (N=1). PD-L1 expression was tested in 8 baseline tumor samples and was detected in histiocytes in all 8 tumors, present in only 1%-8% of tumor cells in 5 tumors.

This is a single-arm, single-center phase II study with a relatively low risk population (sensitive to rituximab, not heavily treated).

Editorial — Dr Nastoupil (continued)

The complete response rate is high and the adverse event profile is favorable, suggesting this may be a promising combination for relapsed follicular lymphoma.

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

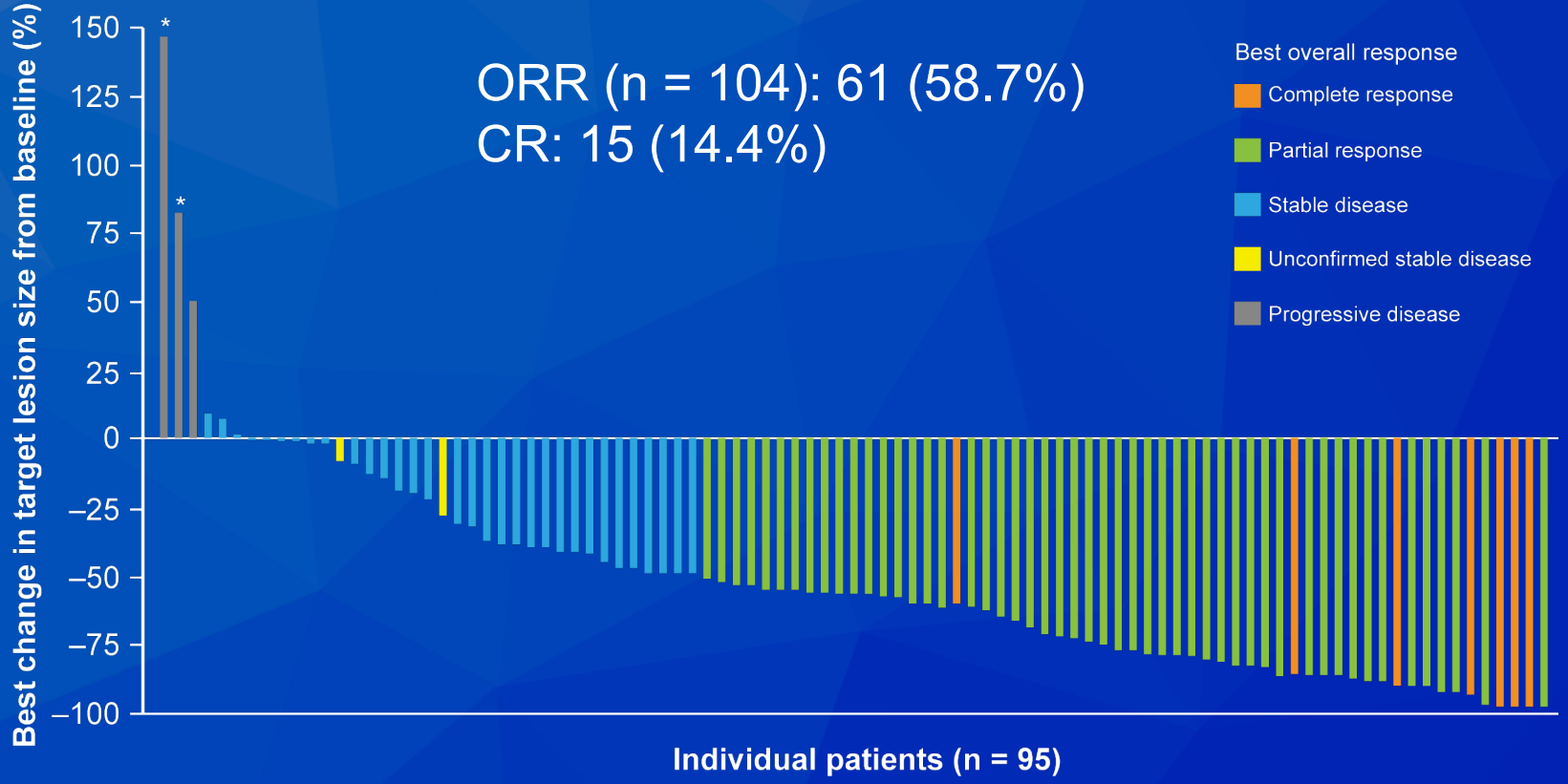
	FL (n = 104)	MZL (n = 23)	SLL (n = 8)	LPL/WM (n = 6)	All patients (n = 142)
ORR	61 (59%)	16 (70%)	6 (75%)	1 (17%)	84 (59%)
CR	15 (14%)	2 (9%)	0	0	17 (12%)
PR	46 (44%)	14 (61%)	6 (75%)	1 (17%)	67 (47%)
Median duration of response	12.2 mo	—	—	—	22.6 mo

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 Nastoupil

Copanlisib is a pan-class I PI3K inhibitor with predominant activity against α and δ isoforms. It is an IV formulation, which is another distinguishing feature from other PI3K inhibitors. Zinzani et al report the results of a phase II study of copanlisib in indolent non-Hodgkin lymphoma (iNHL), which led to accelerated FDA approval for patients with relapsed follicular lymphoma (FL) who have received at least 2 prior systemic therapies. The study enrolled patients with iNHL with relapsed/refractory disease following ≥2 prior lines of therapy.

A total of 141 patients (104 FL) were treated with 60 mg IV infusion of copanlisib administered on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Editorial — Dr Nastoupil (continued)

The primary endpoint was overall response rate (ORR) as assessed by an independent radiology review. The ORR was 59% with 14% complete response and 44% partial response. The most common treatment-emergent AEs included diarrhea (34%), neutropenia (30%/grade 3, 24%), fatigue (30%), and fever (25%). Setting this drug apart from PI3Kδ inhibitors were hyperglycemia (50%/grade 3, 41%) and hypertension (30%/grade 3, 24%) which were transient, and low rates of pneumonitis (8%), hepatic transaminitis (AST 28%; ALT 23%), opportunistic infection (1.4%), and colitis (0.7%).

Editorial — Dr Nastoupil (continued)

Copanlisib is now approved for patients with relapsed/refractory FL who have had at least 2 prior systemic therapies. Confirmatory phase III studies are under way. The IV formulation and AE profile differentiate this pan-PI3K inhibitor from others.

Lymphomas — Drs Kahl and Williams

Diffuse Large B-Cell Lymphoma

Chronic Lymphocytic Leukemia

Hodgkin Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

T-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

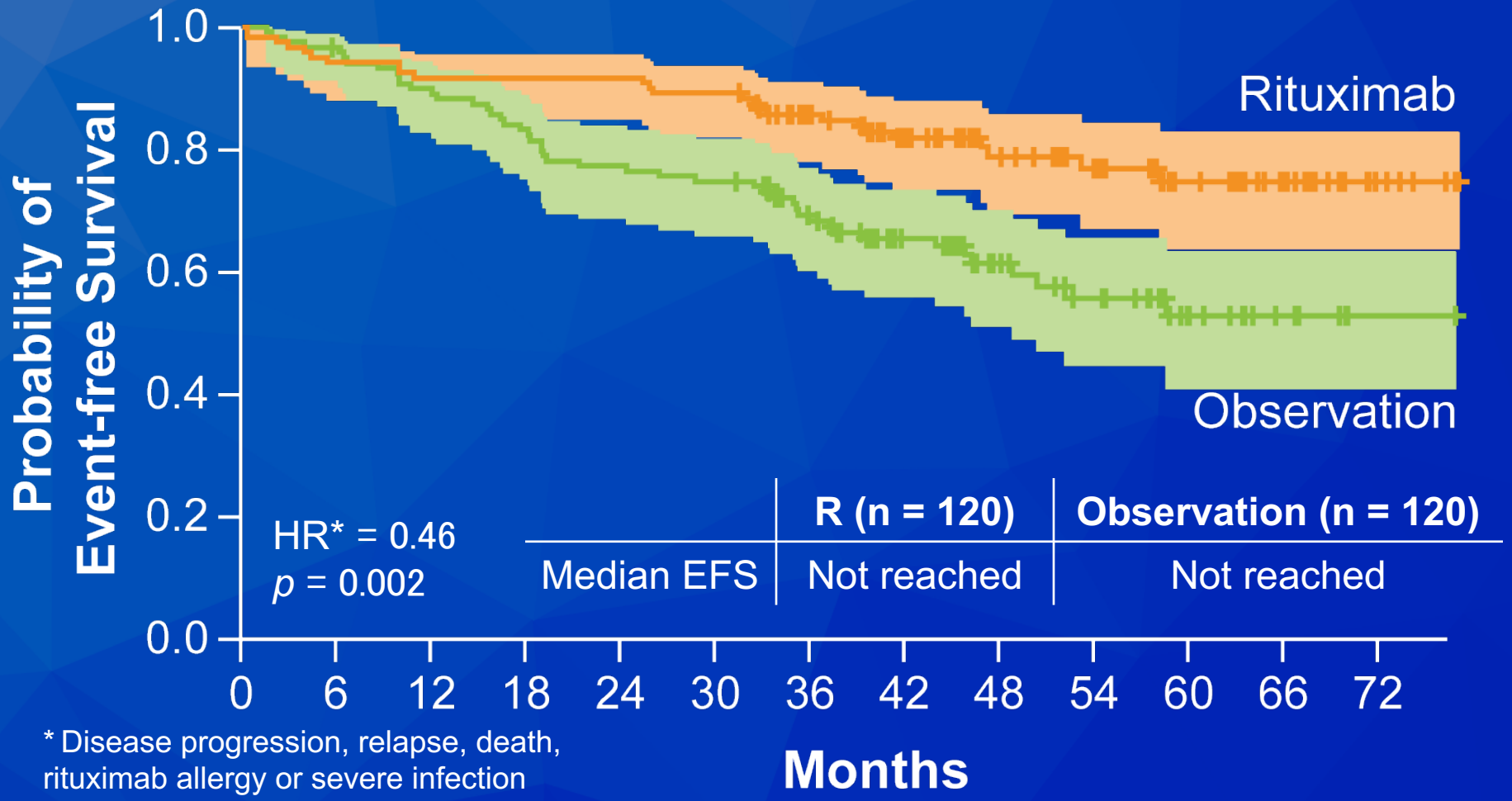
ORIGINAL ARTICLE

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



* Disease progression, relapse, death, rituximab allergy or severe infection

- 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 Nastoupil

There is no agreed upon standard of care for mantle cell lymphoma. Outside of a clinical trial, young, fit patients deemed appropriate for intensive therapy are often treated with chemoimmunotherapy followed by high dose therapy/autologous stem cell transplant (HDT/ASCT). Older, less fit patients are commonly managed with chemoimmunotherapy followed by rituximab maintenance. Le Gouill et al report the results of a randomized, phase III study investigating the role of rituximab maintenance therapy in patients younger than 66 years of age with mantle cell lymphoma who had undergone R-DHAP (4 cycles) followed by R-BEAM/ASCT.

Editorial — Dr Nastoupil (continued)

The protocol allowed for 4 additional cycles of R-CHOP prior to HDT/ASCT for those who had achieved a partial response (PR) with less than 75% reduction in tumor mass. Only patients with a complete response or PR ≥75% reduction in tumor volume were eligible for HDT/ASCT. After transplant, patients were randomized to rituximab maintenance (375 mg/m^2) every 2 months for 3 years versus observation. The primary endpoint was event-free survival (EFS). Events were defined as disease progression, relapse, death, severe infection, or allergy to rituximab that led to the discontinuation of treatment after randomization.

Editorial — Dr Nastoupil (continued)

Between 9/2008 and 8/2012, 299 patients were enrolled. The ORR after induction was 94% (CR 41%/unconfirmed CR 36%). 20 patients received R-CHOP due to an insufficient response to R-DHAP, and 10 of these proceeded to transplant, for a total of 257 patients undergoing transplant (86%) and 240 undergoing randomization post-transplant (80%). With a median follow-up of 54 months (50 months from randomization), the median EFS was not reached in either group. The 4-year EFS rate was 79% (95% CI, 70 to 86) in the rituximab group, as compared with 61% (95% CI, 51 to 70) in the observation group (P = 0.001), with a HR of 0.46 (95% CI, 0.28-0.74; P = 0.002).

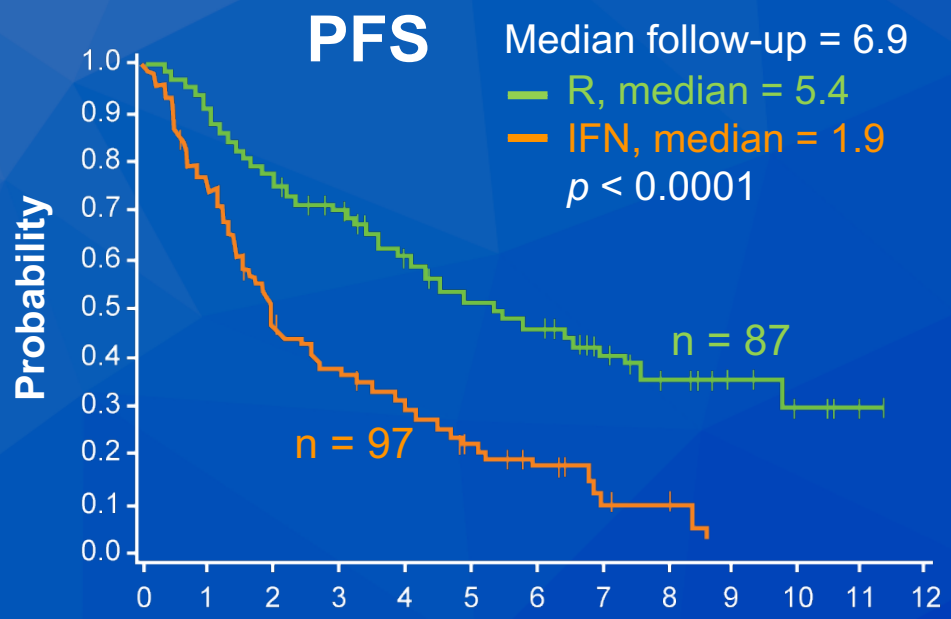
Editorial — Dr Nastoupil (continued)

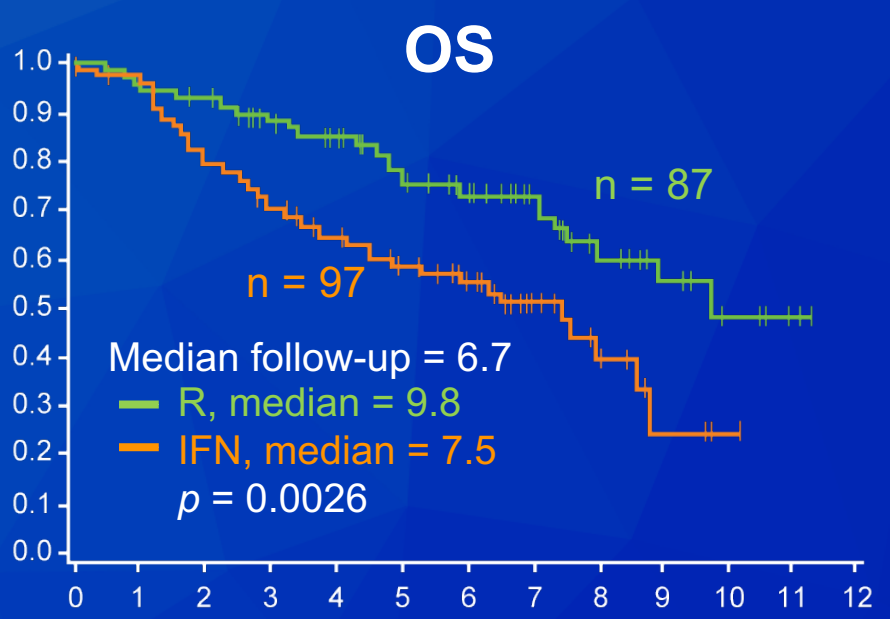
Rituximab maintenance therapy administered every other month for 3 years after HDT/ASCT prolonged EFS, PFS, and OS in patients with mantle cell lymphoma who were younger than 66 years of age.

Rituximab Maintenance after First-Line Immunochemotherapy in Mantle Cell Lymphoma: Long-Term Follow-up of the Randomized European MCL Elderly Trial

Hoster E et al.
Proc ASH 2017;Abstract 153.

Long-Term Follow-Up: Survival after R-CHOP Stratified by Maintenance R or Interferon-alpha (IFN)





5-year PFS	R	IFN	*p*-value	Interaction *p*
After response to R-CHOP	51%	22%	<0.0001	0.19
After response to R-FC	52%	32%	0.032	
5-year OS	**R**	**IFN**	***p*-value**	**Interaction *p***
After response to R-CHOP	79%	59%	0.0026	0.096
After response to R-FC	57%	54%	0.60	

Hoster E et al. *Proc ASH* 2017;Abstract 153.

Press Release — October 31, 2017
FDA Approval of Acalabrutinib for Mantle Cell Lymphoma

"The Food and Drug Administration granted accelerated approval to acalabrutinib for treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Approval was based on Study LY-004, an open-label, phase 2 trial (NCT02213926) enrolling 124 patients with MCL who received at least one prior therapy. Patients received acalabrutinib, 100 mg orally twice daily, until disease progression or unacceptable toxicity."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm583106.htm

Acalabrutinib in Relapsed or Refractory Mantle Cell Lymphoma (ACE-LY-004): A Single-Arm, Multicentre, Phase 2 Trial

Efficacy and Safety of Acalabrutinib Monotherapy in Patients with Relapsed/ Refractory Mantle Cell Lymphoma in the Phase 2 ACE-LY-004 Study

Wang M et al.
Lancet 2017;[Epub ahead of print].

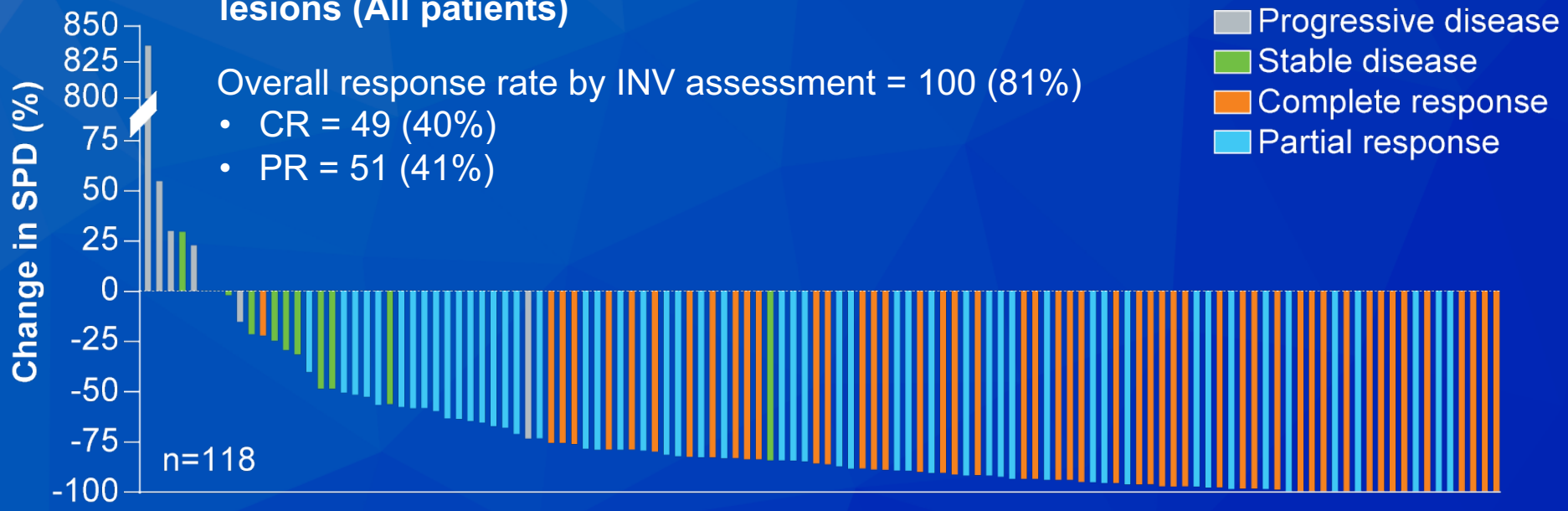
Wang M et al.
Proc ASH 2017;Abstract 155.

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

Maximum change from baseline in the SPD of target lesions (All patients)

Overall response rate by INV assessment = 100 (81%)

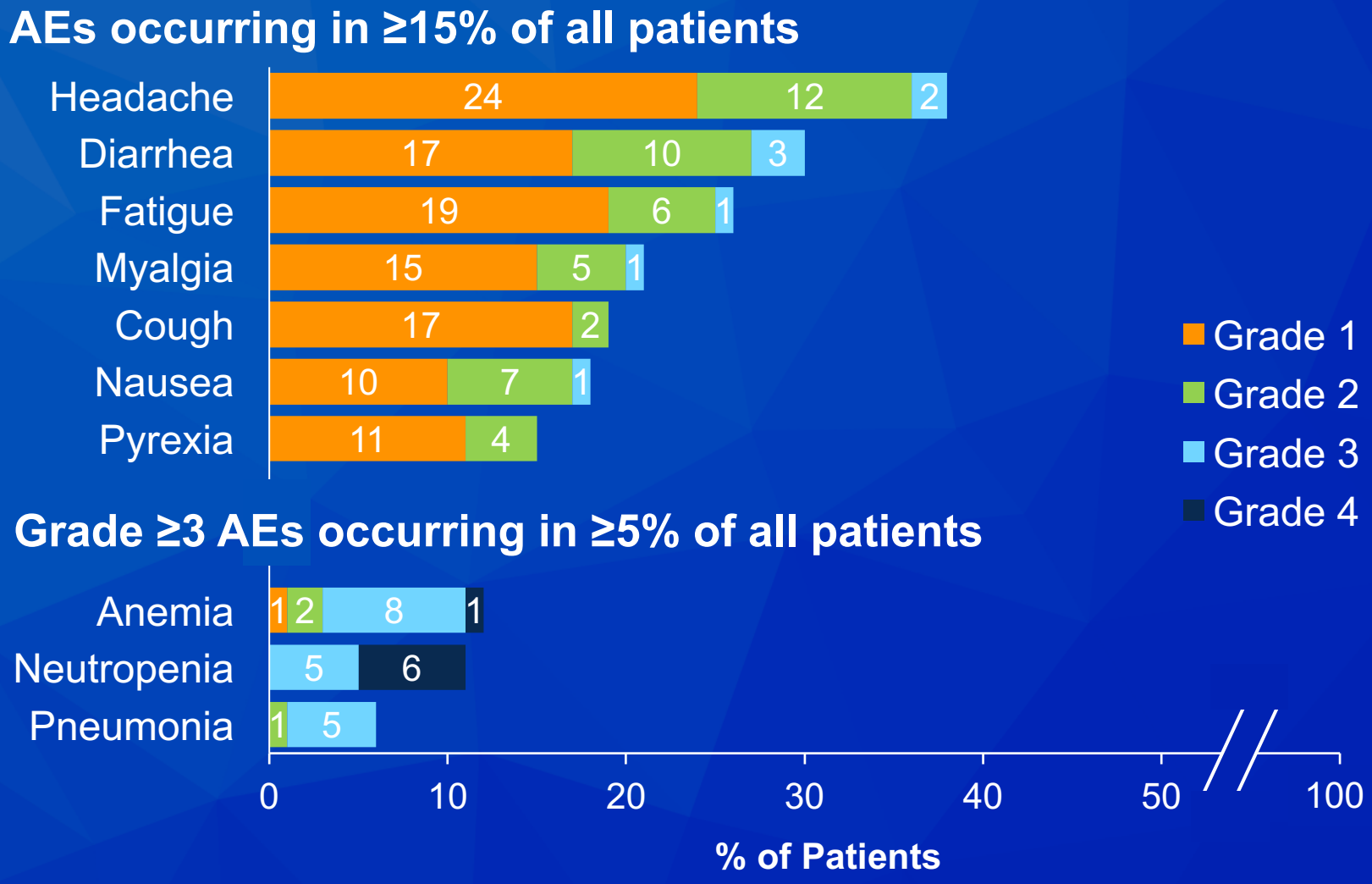
- CR = 49 (40%)
- PR = 51 (41%)



- 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* 2017;[Epub ahead of print].

ACE-LY-004: Most Common Adverse Events



Wang M et al. *Lancet* 2017;[Epub ahead of print]; *Proc ASH* 2017;Abstract 155.

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.

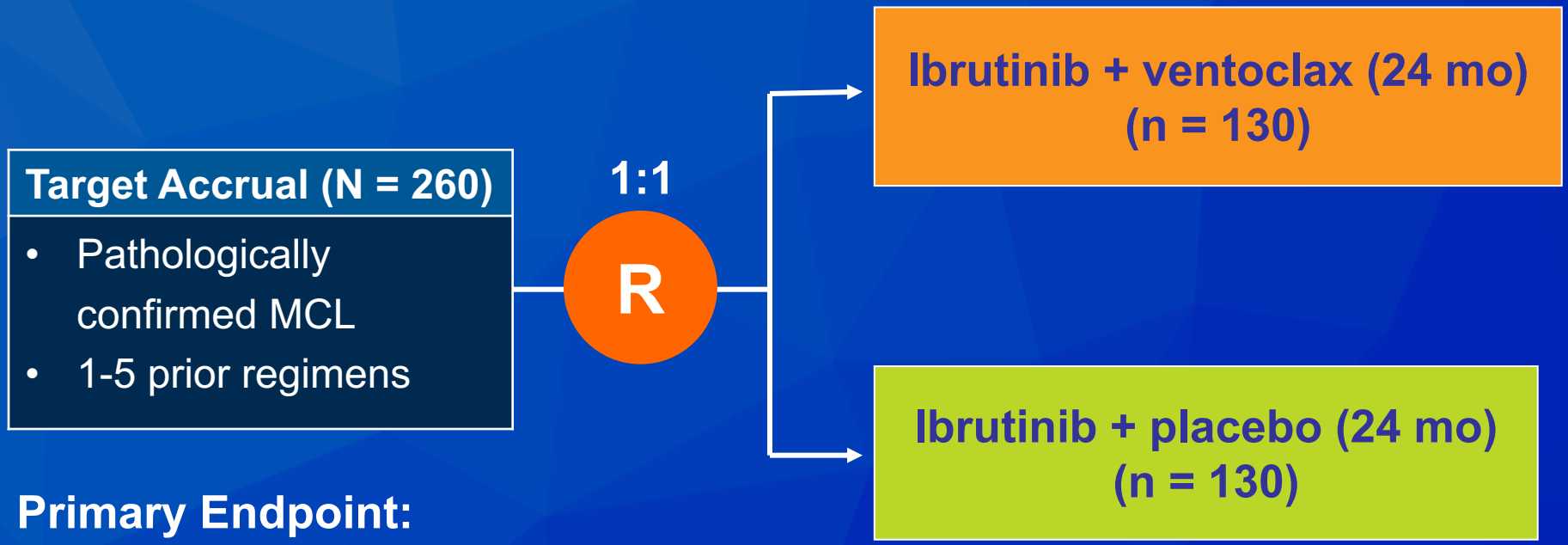
[2] Tam CS et al.
Proc ICML 2017;Abstract OT05.

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 Nastoupil

Ibrutinib (BTK inhibitor) is currently FDA approved for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Patients with relapsed/refractory MCL who experience disease progression on ibrutinib often have poor prognosis. Venetoclax (Bcl-2 inhibitor) has demonstrated activity in relapsed/refractory MCL in an early phase study. Tam et al report the findings of a phase II investigator-initiated study examining the efficacy of the combination of ibrutinib and venetoclax in MCL. 24 patients were enrolled (23 with relapsed/refractory and 1 untreated MCL) and received 4 weeks of ibrutinib (560 mg/day) followed by introduction of venetoclax with a weekly ramp-up to the target dose of 400 mg/day. The primary endpoint was CR rate at week 16.

Editorial — Dr Nastoupil (continued)

The ORR was 71% (63% CR) with 8-month estimates of PFS and OS 74% and 81%. The most common adverse events were fatigue (71%), diarrhea (67%), nausea (50%), upper respiratory tract infection (38%), gastro-esophageal reflux (33%), neutropenia (33%/25% grade 3-4), cough (25%), and bruising (21%). Tumor lysis syndrome occurred in 2 patients with high tumor burden.

The preliminary results of this phase II study examining ibrutinib in combination with venetoclax in MCL appear promising, with a CR rate of 63% at 16 weeks suggesting synergy. The durability of response and toxicity profile with longer follow-up will impact the future of this combination.

Editorial — Dr Nastoupil (continued)

The possibility of promising synergism with the combination of ibrutinib plus venetoclax in MCL has led to a randomized phase III study. The trial will start with an open-label safety run-in of ibrutinib (560 mg daily) and venetoclax (20 mg weekly ramp-up to a target dose of 400 mg daily) and then transition to a randomized, double blind design. Patients will be treated for 24 months with the combination, followed by single-agent ibrutinib until disease progression or unacceptable toxicity. This randomized study will provide the necessary information on efficacy and safety to inform practice patterns.

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 Nastoupil

Venetoclax is a potent, selective Bcl-2 inhibitor. Davids et al report the results of the phase I study of venetoclax in relapsed/refractory NHL. 106 patients were enrolled between 9/2011 and 11/2014. 70 patients were treated in dose-escalation cohorts with 36 subjects treated in the safety expansion cohort (1,200 mg). The mean duration of venetoclax treatment was 5.3 months.

The maximum tolerated dose was not reached. Clinical TLS was not observed in the NHL population. 3 patients with bulky disease (>10 cm) had laboratory changes meeting Cairo-Bishop criteria for laboratory TLS within 24 hours of initial dosing. All 3 patients received TLS treatment and continued venetoclax as scheduled without dose interruption.

Editorial — Dr Nastoupil (continued)

Grade 3 to 4 hematologic toxicities included anemia (15%), neutropenia (11%), and thrombocytopenia (9%). There was no cumulative toxicity apparent with prolonged dosing and no clear association of toxicity with venetoclax dose. Dose reductions were required in 15 patients (9 at the 1,200 mg dose); the most common reasons were nausea and diarrhea.

The ORR was 44%. The highest response rate was seen in mantle cell lymphoma (ORR 75% [CR 21%]). Similarly, high response rates were seen in those with marginal zone lymphoma (ORR 67% [no CR]) and Waldenström's macroglobulinemia (ORR 100% [no CR]). The ORR in DLBCL was 18% (CR 12%), and 43% in DLBCL-Richter transformation.

Editorial — Dr Nastoupil (continued)

In follicular lymphoma, the ORR was 38% (CR 14%). The median PFS was 6 months but varied by histology. Responses were more durable among those who achieved a CR vs PR.

In this phase I study, venetoclax demonstrated single-agent activity across NHL subtypes. The highest response rate was seen in MCL with a median PFS of 14 months. These results also provide information regarding dosing strategies that vary according to NHL subtype. A dosing strategy starting at 400 mg daily for 1 week followed by weekly ramp-up from 800 mg daily to 1,200 mg daily thereafter with outpatient monitoring for TLS may be appropriate for NHL subtypes other than MCL.

Editorial — Dr Nastoupil (continued)

Patients with high tumor burden, and those with MCL, may be best managed with a starting dose of 100 mg daily for 1 week, followed by weekly ramp-up to 200, 400, and 800 mg daily.

Lymphomas — Drs Kahl and Williams

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.

Press Release — November 9, 2017

FDA Approval of Brentuximab Vedotin for Primary Cutaneous Large Cell Lymphoma

"The Food and Drug Administration granted regular approval to brentuximab vedotin for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

Approval was based on a phase 3, randomized, open-label, multicenter clinical trial (ALCANZA) of brentuximab vedotin in patients with MF or pcALCL who had previously received one prior systemic therapy and required systemic treatment."

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm584543.htm

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 romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma

Jennifer E. Amengual, Renee Lichtensein, Jennifer Lue, Ahmed Sawas, Changchun Deng, Emily Lichtenstein, Karen Khan, Laine Atkins, Aishling Rada, Hyde A Kim, Codruta Chiuzan, Matko Kalac, Enrica Marchi, Lorenzo Falchi, Mark A. Francescone, Lawrence Schwartz, Serge Cremers, and Owen A. O'Connor

Amengual JE et al. *Blood* 2018;131(4):397-407.

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.

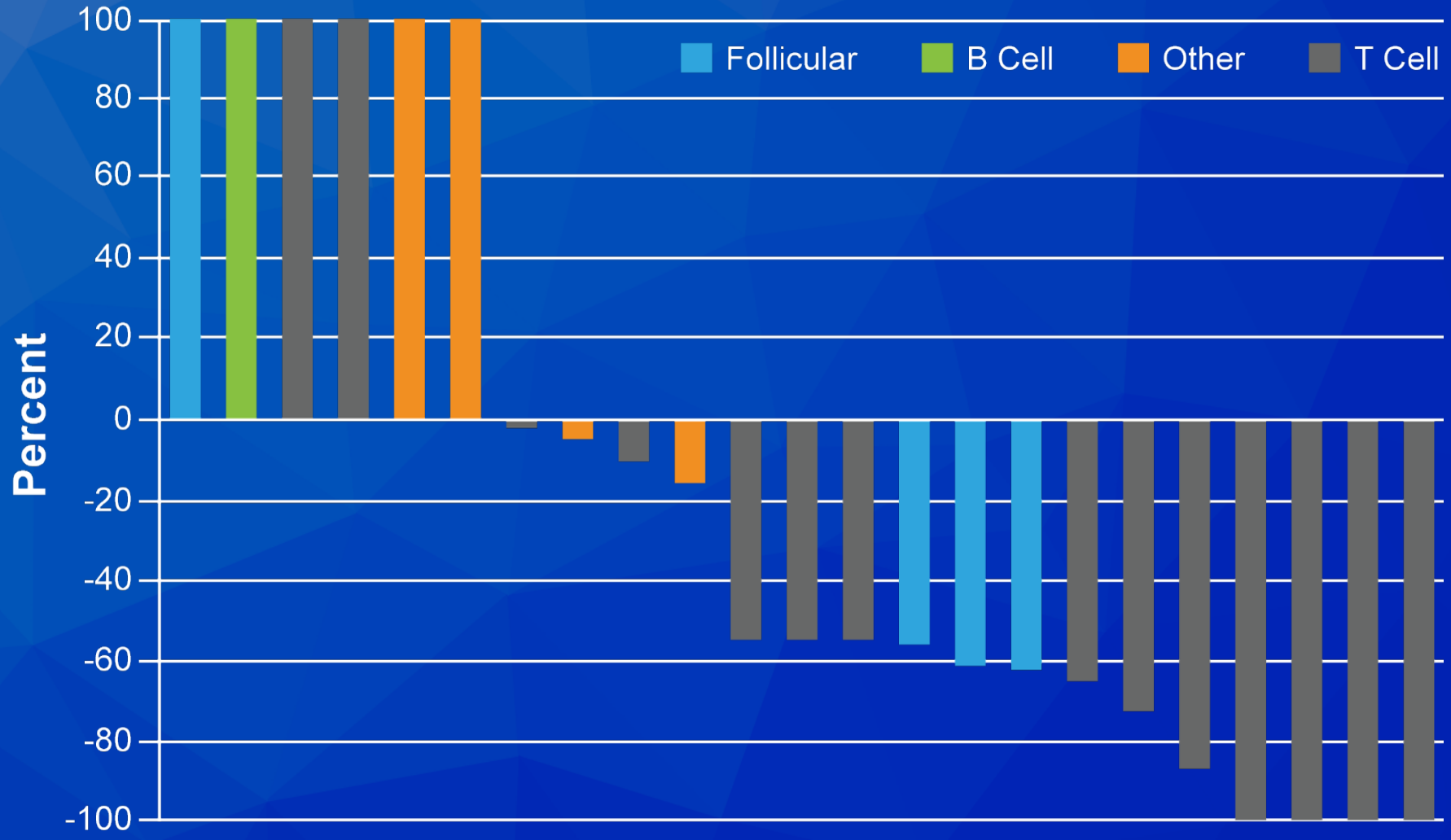
Key secondary endpoints	Overall	PTCL	Non-PTCL
ORR (CR + PR)	57%	71%	33%
PFS	3.7 mo	4.4 mo	NR
OS	13.8 mo	12.8 mo	NR
Mean duration of response	3.5 mo	NR	NR

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. *Blood* 2018;131(4):397-407; *Proc ICML* 2017;Abstract 76.

Pralatrexate with Romidepsin: Reduction in Tumor Burden



Amengual JE et al. *Blood* 2018;131(4):397-407; *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.