AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
Michelle A Fanale, MD
Christopher Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

Research To Practice®

Disclosures for Moderator Neil Love, MD

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Agenda

Module 1: *Newly Diagnosed and Relapsed/Refractory (R/R) Multiple Myeloma (MM) — Drs Raje and Rajkumar*

Module 2: *Chronic Lymphocytic Leukemia (CLL)/Follicular Lymphoma (FL)/Mantle Cell Lymphoma (MCL) — Drs Flowers and Friedberg*

Module 3: *Hodgkin Lymphoma (HL)/Diffuse Large B-Cell Lymphoma (DLBCL)/T-Cell Lymphoma (TCL) — Drs Ansell and Fanale*

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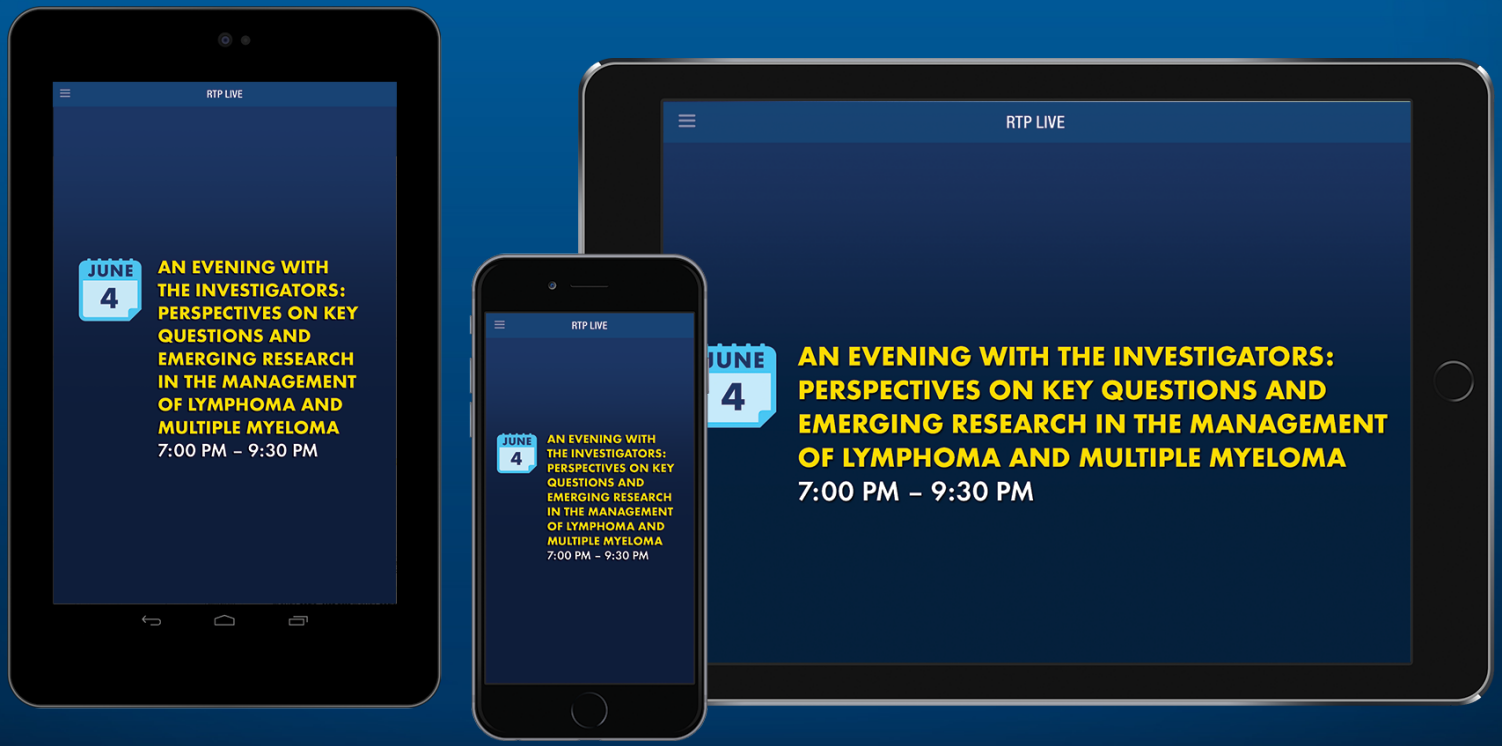

Beyond the Guidelines

Investigator Perspectives on Current Clinical Issues and Ongoing Research in the Management of Early and Advanced Breast Cancer

Monday, June 5, 2017
7:00 PM – 9:15 PM
Chicago, Illinois

Faculty

Kimberly L Blackwell, MD
Julie R Gralow, MD
Rita Nanda, MD
Mark D Pegram, MD
Hope S Rugo, MD
Eric P Winer, MD

Moderator

Neil Love, MD

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Multiple Myeloma

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Case #1 (Dr Raje)

- 78 yo woman with Kappa Light chain Stage III MM
  - RVD-lite x 9 cycles, achieved CR
  - Dose reduction of both bortezomib and lenalidomide
- Continued lenalidomide at 10 mgs x 2 months
  - Discontinued due to fatigue and diarrhea
- 13 months later: Increasing kappa light chains with associated renal insufficiency (creatinine of 1.9)
- Lenalidomide / dexamethasone / elotuzumab, achieved PR, remained on therapy for 14 months
  - Lenalidomide: 10 mgs adjusted for creatinine clearance
  - Treatment complicated by diarrhea which responded to diet modification, colestipol and intermittent immodium

Case #2 (Dr Rajkumar)

- Early 2012: A 64 yo male surgeon was diagnosed with t(11;14) MM
  - Rd x 6 cycles then stem cell transplant in Dec 2012
  - Lenalidomide maintenance
- 2016: Rising M-spike from 0.0 gm/dL to 1.0 gm/dL while on lenalidomide maintenance at 10 mg per day
  - Lenalidomide dose increased to 25 mg, and dexamethasone 40 mg once weekly was added
  - No significant response in M protein levels
- Daratumumab / bortezomib / dexamethasone

JAMA Oncology | Original Investigation

Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma
A Meta-analysis

Nikhil C. Munshi, MD; Herve Avet-Loiseau, PhD; Andy C. Rawstron, PhD; Roger G. Owen, MD; J. Anthony Child, MD; Anjan Thakurta, PhD; Paul Sherrington, PhD; Mehmet Kemal Samur, PhD; Anna Georgieva, MD, PhD; Kenneth C. Anderson, MD; Walter M. Gregory, PhD

Munshi N et al. *JAMA Oncol* 2017;3(1):28-35.

Association of MRD with Survival

- Effect of MRD status on survival was evaluated in 14 studies for PFS and 12 studies for OS
  - For those achieving a CR, data pooled from 5 studies for PFS and 6 for OS

Outcome	MRD-neg.	MRD-pos.	HR, *p*-value
All patients			
PFS (n = 660, 613)	54 mo	26 mo	0.41, <0.001
OS (n = 599, 501)	98 mo	82 mo	0.57, <0.001
Patients achieving CR			
PFS (n = 396, 178)	56 mo	34 mo	0.44, <0.001
OS (n = 430, 186)	112 mo	82 mo	0.47, <0.001

Munshi N et al. *JAMA Oncol* 2017;3(1):28-35.

Phase 3 Study (CLARION) of Carfilzomib, Melphalan, Prednisone (KMP) v Bortezomib, Melphalan, Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM)

Facon T et al
Proc IMW 2017;Abstract 373.

CLARION: KMP versus VMP

Efficacy	KMP (n = 478)	VMP (n = 477)	HR, *p*-value
Median PFS	22.3 mo	22.1 mo	0.9, 0.159
Overall response rate Complete response	84.3% 25.9%	78.8% 23.1%	1.4* 1.18*
Select adverse events (Grade ≥3)	**KMP (n = 478)**	**VMP (n = 477)**	
Acute renal failure	7.4%	2.1%	
Cardiac failure	8.2%	2.8%	
Dyspnea	3.6%	0.6%	

* Odds ratio

- OS data were immature (events: KMP: 20.7%, VMP:16.4%, HR 1.211)

Facon T et al. *Proc IMW* 2017;Abstract 373.

Frontline Therapy with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Induction Followed by Autologous Stem Cell Transplantation, KRd Consolidation and Lenalidomide Maintenance in Newly Diagnosed Multiple Myeloma Patients: Primary Results of the Intergroupe Francophone Du Myélome (IFM) KRd Phase II Study

Roussel M et al
Proc ASH 2016;Abstract 1142.

KRd in Newly Diagnosed MM

Outcome	Post induction	Post ASCT	Post consolidation
ORR (n = 46, 42, 42)	97.5%	97.5%	97.5%
CR + sCR	25.5%	45%	69%
VGPR	58%	43%	23.5%
MRD negativity (n = 30, 31, 36)	63%	81%	89%

- Median PFS: not reached
- No peripheral neuropathy but cardiovascular toxicity a concern

Roussel M et al. *Proc ASH* 2016;Abstract 1142.

Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) with Newly Diagnosed Multiple Myeloma (MMY1001): An Open-Label, Phase 1b Study

Jakubowiak AJ et al
Proc ASCO 2017;Abstract 8000.

MMY1001: Efficacy and Safety

DARA-KRd (N = 21)				
ORR	**CR**	**≥VGPR**	**PR**	**6-mo PFS**
100%	5%	86%	14%	100%

Serious AEs: 46% (14% possibly related to daratumumab)

Grade 3/4 Treatment-Emergent AEs: 18/22 (82%)

Most common Grade 3/4 TEAEs

- Lymphopenia: 50%
- Neutropenia: 23%

Jakubowiak AJ et al. *Proc ASCO* 2017;Abstract 8000. (Abstract only)

An Open-Label, Single Arm, Phase IIa Study of Bortezomib, Lenalidomide, Dexamethasone, and Elotuzumab in Newly Diagnosed Multiple Myeloma

Laubach J et al
Proc ASCO 2017;Abstract 8002.

Elotuzumab with Len/Dex/Bort for NDMM

Efficacy	**(n = 29)**
Overall response rate	100%
Complete response	24%
Very good partial response	47%
Partial response	29%
Adverse events (Grade ≥3)	
Thrombocytopenia	15%
Hypophosphatemia	12%
Peripheral neuropathy	2%

- 2 patients died on study: septicemia (n = 1), respiratory failure (n = 1)

Laubach J et al. *Proc ASCO* 2017;Abstract 8002.

Phase 1 Study of Elotuzumab in Combination with Autologous Stem Cell Transplantation and Lenalidomide Maintenance for Multiple Myeloma

Osman K et al
Proc ASH 2016;Abstract 3448.

Ongoing Phase Ib Study of Elo/ASCT

- 14 of 15 subjects have been enrolled
  - 9 of 14 have completed at least 4 of the first 5 planned elo. infusions and are evaluable.
- No delays in hematopoietic reconstitution observed
- Majority of adverse events Grade ≤2, including infusion reactions due to elo.
  - 1 episode of Grade 3 hypertension due to elo. resolved with supportive care
- Grade ≥3 AEs (including anemia, neutropenia, lymphopenia, thrombocytopenia, nausea, vomiting and dehydration) were attributable to the ASCT

Osman K et al. *Proc ASH* 2016;Abstract 3448.

Lenalidomide (LEN) Maintenance Following High-Dose Melphalan and Autologous Stem Cell Transplant (ASCT) in Patients (Pts) with Newly Diagnosed Multiple Myeloma (MM): A Meta-Analysis of Overall Survival (OS).

McCarthy P et al
Proc IMW 2017;Abstract 187.

Meta-Analysis of OS with LEN Maintenance

- Pooled data from 1,208 patients with newly diagnosed MM in 3 Phase III trials (CALGB 100104, IFM 2005-02 and GIMEMA-RV-209)
- Median follow-up: 6.6 y

Efficacy	LEN (n = 605)	Control (n = 603)
Overall survival* Median OS OS rate (7 y)	 Not reached 62%	 86 mo 50%
Adverse events		
Second primary malignancies Hematologic Solid tumors	6.1% 7.3%	2.8% 4.2%

* HR 0.75, $p = 0.001$

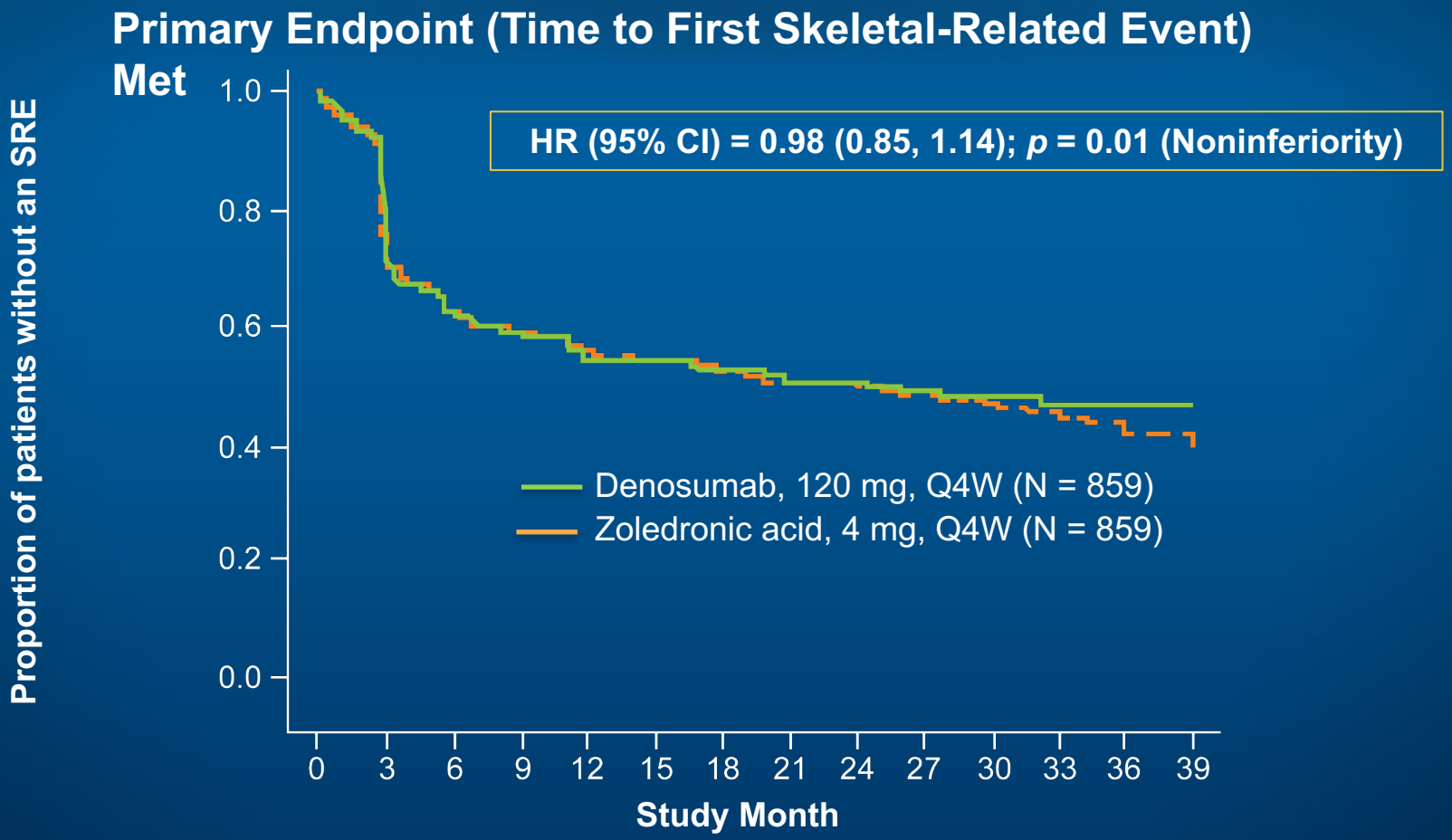
- Greatest OS benefit seen in patients who achieved deep responses

McCarthy M et al. *Proc IMW* 2017;Abstract 187.

An International, Randomized, Double Blind Trial Comparing Denosumab with Zoledronic Acid for the Treatment of Bone Disease in Patients with Newly Diagnosed Multiple Myeloma

Raje N et al
Proc IMW 2017;Abstract 546.

Phase III Trial of Denosumab versus Zoledronic Acid



- OS similar between arms (HR 0.9, $p = 0.41$)
- PFS numerically longer (HR 0.82, descriptive $p = 0.036$)

Raje N et al. *Proc IMW* 2017;Abstract 546.

Overall Survival of Patients with Relapsed or Refractory Multiple Myeloma Treated with Carfilzomib and Dexamethasone versus Bortezomib and Dexamethasone in the Randomized Phase 3 ENDEAVOR Trial

Dimopoulos MA et al
Proc IMW 2017;Abstract 374.

Phase III ENDEAVOR Trial Results

Efficacy	Kd (n = 464)	Vd (n = 465)	HR, *p*-value
Median OS	47.6 mo	40.0 mo	0.79, 0.0100
Select adverse events	**Kd**	**Vd**	
Anemia	42.5%	28.3%	
Dyspnea	32.2%	13.6%	
Hypertension	32.2%	9.9%	

- OS benefit was consistent regardless of prior bortezomib therapy, age group or number of prior lines of therapy
- Incidence of Grade ≥3 adverse events: Kd (81.4%); Vd (71.1%)

Dimopoulos MA et al. *Proc IMW* 2017;Abstract 374.

Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials

David S. Siegel, Katja C. Weisel, Meletios A. Dimopoulos, Rachid Baz, Paul Richardson, Michel Delforge, Kevin W. Song, Jesus F. San Miguel, Philippe Moreau, Hartmut Goldschmidt, Michele Cavo, Sundar Jagannath, Xin Yu, Kevin Hong, Lars Sternas, Mohamed Zaki & Antonio Palumbo

Siegel DS et al. *Leuk Lymphoma* 2016;57(12):2833-8.

POM + LoDEX in Patients with R/R MM and Moderate Renal Impairment (RI)

- Pooled safety and efficacy analysis of 3 trials (MM-002, MM-003 and MM-010) of POM/LoDEX in pts with and without moderate RI.

Efficacy	With RI (n = 355)	Without RI (n = 713)	*p*-value
Overall response rate	30.4%	33.8%	0.299
Median PFS	3.8 mo	4.6 mo	0.07
Median OS	10.5 mo	14.0 mo	0.004
Select Grade 3/4 AEs	**(n = 351)**	**(n = 709)**	
Neutropenia	46.7%	49.6%	NR
Anemia	36.5%	29.1%	NR
Infections	32.2%	34.4%	NR

NR = not reported

Siegel DS et al. *Leuk Lymphoma* 2016;57(12):2833-8.

Open-Phase 3 ELOQUENT-2 Study: Extended Four Year Follow-Up (FU) of Elotuzumab plus Lenalidomide/Dexamethasone (ELd) vs Ld in Relapsed/Refractory Multiple Myeloma (RRMM)

Lonial S et al.
Proc ASCO 2017;Abstract 8028.

ELOQUENT-2: Four Year Follow-up

Response	ELd (n = 321)	Ld (n = 325)
Overall response rate	79%	66%
≥VGPR*	35%	29%

VGPR = very good partial response

- ELd had 29% reduction in risk of progression/death vs Ld (HR 0.71) and relative improvement of 50% in PFS (21 vs 14%).
- Grade 3–4 adverse events in ≥5% of patients included:
  - Second primary malignancies (9% vs 6%), vascular diseases (10% vs 8%), cardiac disorders (5% vs 8%) and infections (33 vs 26%).

* Pts with ≥VGPR had greatest reduction in risk of progression/death (HR 0.65)

Lonial S et al. *Proc ASCO* 2017;Abstract 8028.

The NEW ENGLAND JOURNAL of MEDICINE

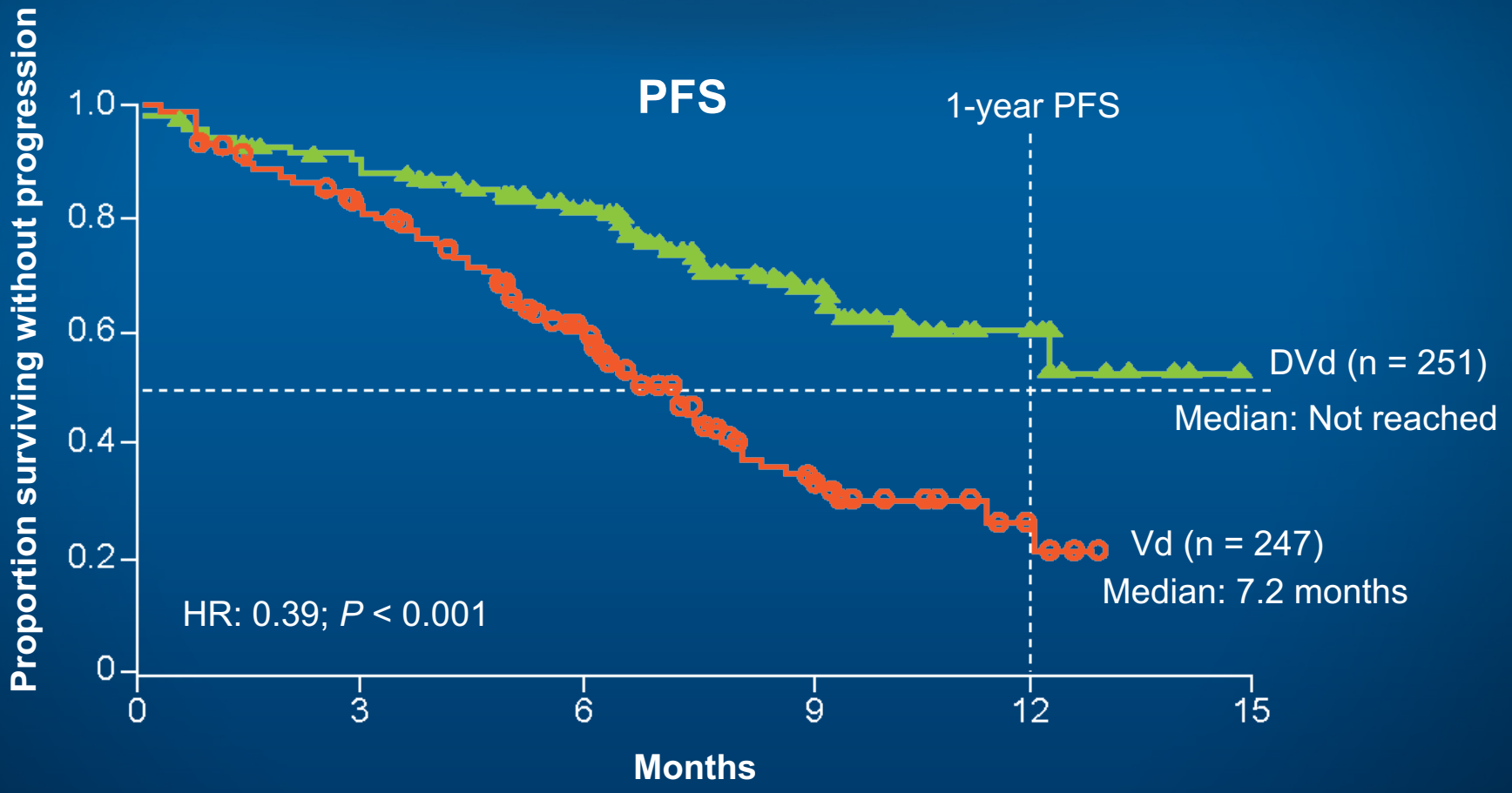
ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

Palumbo A et al. *N Engl J Med* 2016;375(8):754-66.

CASTOR: Results



61% reduction in the risk of disease progression or death for DVd vs Vd

- ORR: 82.9% (DVd) vs 63.2% (Vd); $p < 0.001$

Palumbo A et al. *N Engl J Med* 2016;375(8):754-66; *Proc ASCO* 2016;Abstract LBA4.

The NEW ENGLAND JOURNAL of MEDICINE

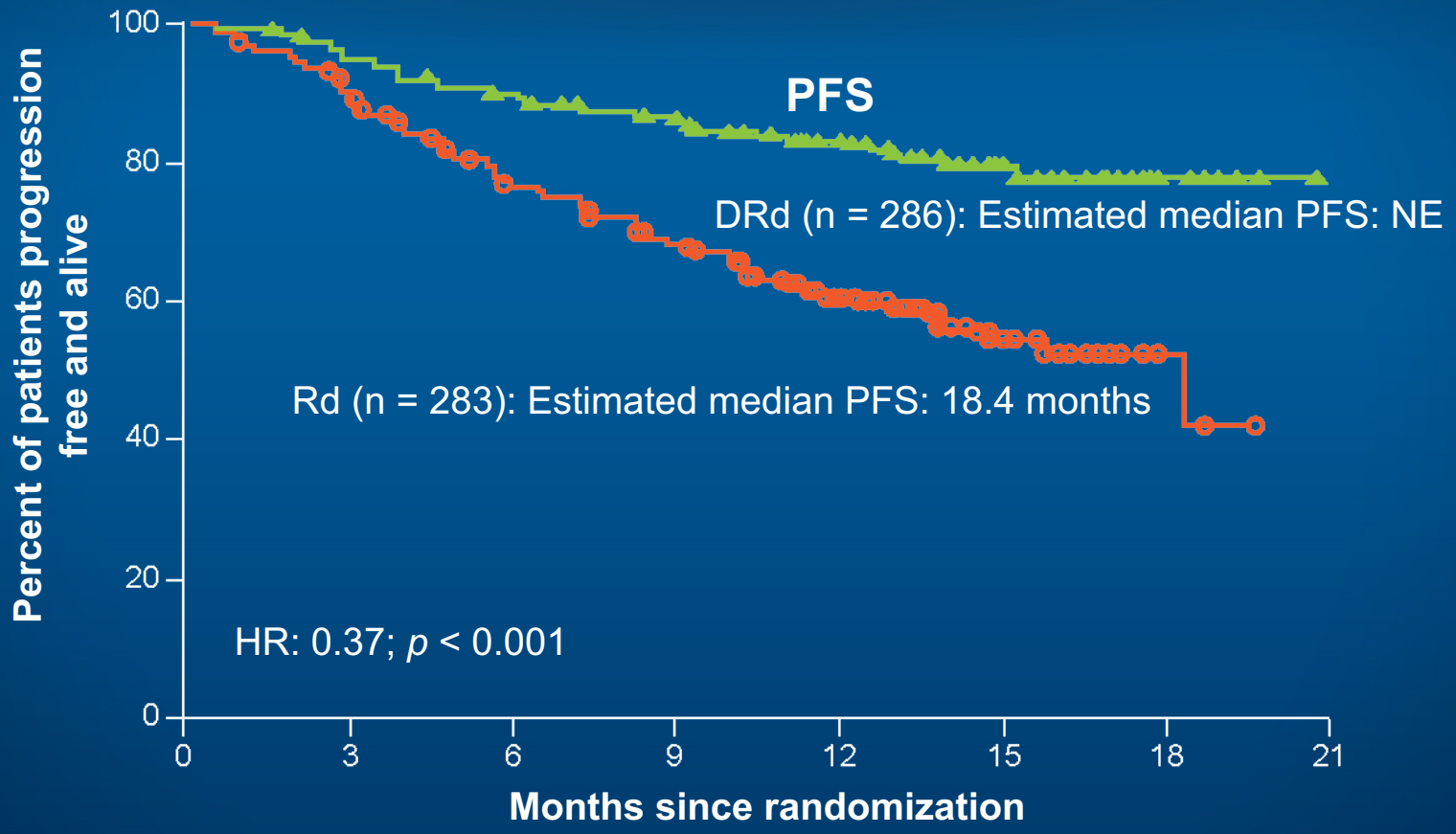
ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Dimopoulos MA et al. *N Engl J Med* 2016;375(14):1319-31.

POLLUX: Results at Interim Analysis



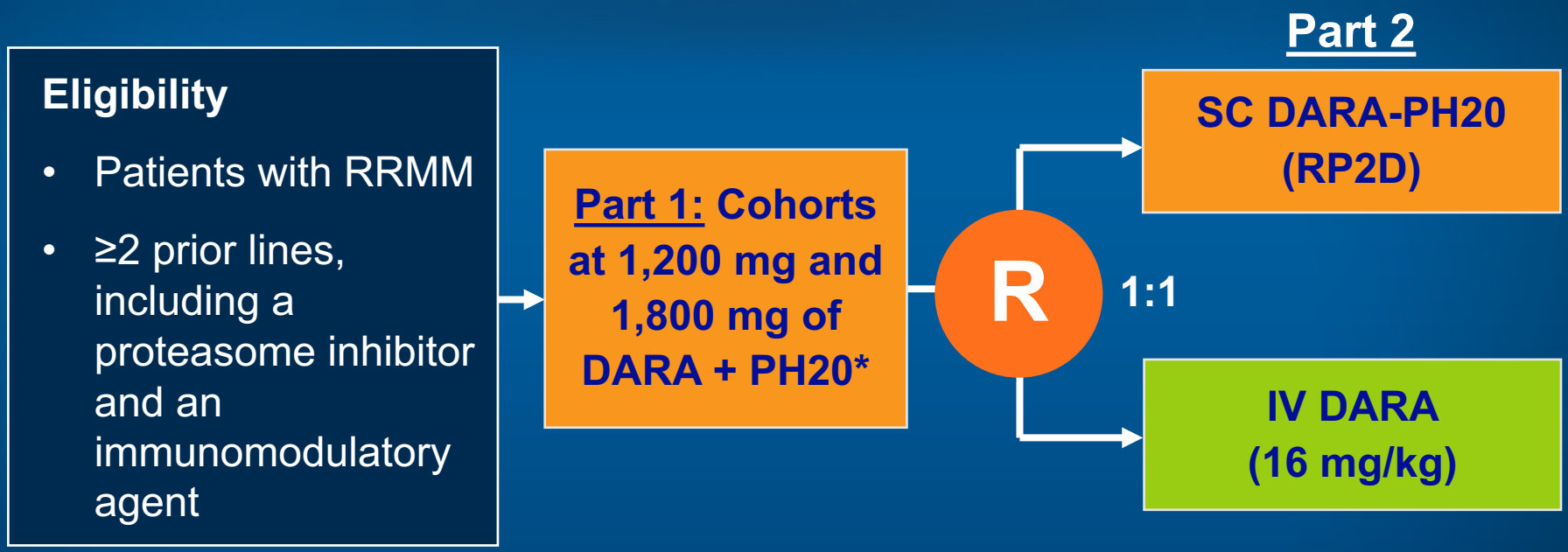
- ORR: 93% (dara/len/dex) vs 76% (len/dex); $p < 0.001$

Dimopoulos MA et al. *N Engl J Med* 2016;375(14):1319-31; *Proc EHA* 2016;Abstract LB2238.

Open-Label, Multicenter, Dose Escalation Phase 1b Study to Assess the Subcutaneous Delivery of Daratumumab in Patients (pts) with Relapsed or Refractory Multiple Myeloma (PAVO)

Usmani SZ et al.
Proc ASH 2016;Abstract 1149.

PAVO: Phase I Trial Design



* To determine the recommended SC dose of DARA (RP2D); DARA-PH20 administered in 4-week cycles: q1wk for 8 weeks, q2wk for 16 weeks and q4wk thereafter

- **Primary endpoint:** C_{trough} of DARA up to Cycle 3 Day 1 and safety
- Secondary endpoints include: Overall response rate (ORR)

Usmani SZ et al. *Proc ASH* 2016;Abstract 1149.

PAVO Part 1: Response and Infusion-Related Reactions (IRRs)

Response	DARA at 1,200 mg (n = 8)	DARA at 1,800 mg (n = 17)
ORR	2 (25%)	7 (41%)
VGPR	0	3 (17.6%)
PR	2 (25%)	4 (23.5%)
Median time to response	14 weeks	4 weeks

PR = partial response; VGPR = very good PR

- IRRs were reported in 9/41 pts (22%) and were mostly Grade 1/2 in severity including chills, fever, rigors, vomiting, itching, edema of the tongue, noncardiac chest pain and wheezing.
- All IRRs developed within 6 h of the first SC infusion and were controlled with antihistamines, corticosteroids, antiemetics or a bronchodilator.

Usmani SZ et al. *Proc ASH* 2016;Abstract 1149.

Case #3 (Dr Raje)

- A 55 yo patient with IgG Lambda MM presented with cord compression
  - RVD followed by stem cell transplant, no maintenance therapy
- Relapsed 4 years later
- Clinical trial with lenalidomide / dexamethasone and an HDAC inhibitor x 2 years
- BRAF V600E mutation identified
- Vemurafenib on a clinical trial
  - Progressed after 20 months
- Clinical trial with pomalidomide and ixazomib
  - Currently tolerating therapy and doing well

Case #4 (Dr Rajkumar)

- 2007: 46 yo man diagnosed with MM and treated with the following regimens
  - 10/2008 – 6/2010: Lenalidomide / dexamethasone
  - 6/2010: ASCT
  - 7/2011 – 5/2012: Pomalidomide / dexamethasone
  - 5/2012 – 4/2014: Bortezomib / cyclophosphamide / dexamethasone
  - 4/2014 – 9/2015: Bortezomib / lenalidomide / dexamethasone
  - 9/2015 – 6/2016: Carfilzomib / lenalidomide / dexamethasone
  - 6/2016 – 12/2016: Daratumumab
  - 12/2016 – 3/2017: Daratumumab / bortezomib / dexamethasone
- May 2017: 55 yo with relapsed/refractory MM treated with CAR-T

Venetoclax as Targeted Therapy for Relapsed/Refractory Multiple Myeloma

Kumar S et al
Proc IMW 2017;Abstract 129.

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Venetoclax for Relapsed/Refractory MM

Efficacy	All pts (n = 66)	t(11;14)	No t(11;14)
Overall response rate ≥VGPR	21% 15%	40% 27%	6% 6%
Median time to progression	2.6 mo	6.6 mo	1.9 mo

- Common AEs: nausea (47%), diarrhea (36%), vomiting (21%)
- Grade 3/4 hematologic AEs: thrombocytopenia (32%), neutropenia (27%), anemia (23%), leukopenia (23%)
- No TLS events reported

Kumar S et al. *Proc IMW* 2017;Abstract 129.

blood®

Prepublished online May 1, 2017;
doi:10.1182/blood-2017-03-775122

Pembrolizumab, pomalidomide and low dose dexamethasone for relapsed/refractory multiple myeloma

Ashraf Badros, Elizabeth Hyjek, Ning Ma, Alexander Lesokhin, Ahmet Dogan, Aaron P. Rapoport, Mehmet Kocoglu, Emily Lederer, Sunita Philip, Todd Milliron, Cameron Dell, Olga Goloubeva and Zeba Singh

Badros A et al. *Blood* 2017;[Epub ahead of print].

Pembrolizumab, POM, LoDEX for R/R MM

Efficacy	All pts (n = 48)	Double refractory (n = 32)	High risk (n = 27)
Overall response rate ≥VGPR	60% 19%	68% 24%	56% 15%
Median PFS	17.4 mo	Not reported	15.1 mo

- Responses ≥VGPR: more frequent in PD-L1-positive pts
- Median OS: not reached
- Toxicities were identical to those previously reported with POM and dexamethasone except for the autoimmune effects.
- Immune-related AEs included: pneumonitis (n = 6), hypothyroidism (n = 5), adrenal insufficiency (n = 2)

Badros AZ et al. *Blood* 2017;[Epub ahead of print].

B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM): Initial Safety and Efficacy from a Phase I Study

Cohen A et al
Proc ASH 2016;Abstract 1147.

CART-BCMA Therapy for Relapsed/Refractory MM

- Ongoing study of pts with relapsed/refractory MM
  - 3 cohorts planned: 1) 1-5 x 10^8 CART cells
    2) Cyclophosphamide (CTX) + 1-5 x 10^7 CART cells
    3) CTX + 1-5 x 10^8 CART cells
- This study evaluated 9 pts treated in cohort 1
- Best heme response: sCR (n = 1); VGPR (n = 2), unconfirmed partial response (n = 1), minimal response (n = 2), stable disease (n = 1), progressive disease (n = 2)
- Clinical activity correlated with degree of CART-BCMA expansion and cytokine release syndrome (CRS)
- CRS occurred in 8/9 pts (2 Grade 3) and 1 DLT reported (Grade 4 posterior reversible encephalopathy syndrome).
- Other Grade 3-4 adverse events included: hypophosphatemia, anemia, neutropenia, thrombocytopenia and hypertension.

Cohen A et al. *Proc ASH* 2016;Abstract 1147.

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
Michelle A Fanale, MD
Christopher Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

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Chronic Lymphocytic Leukemia

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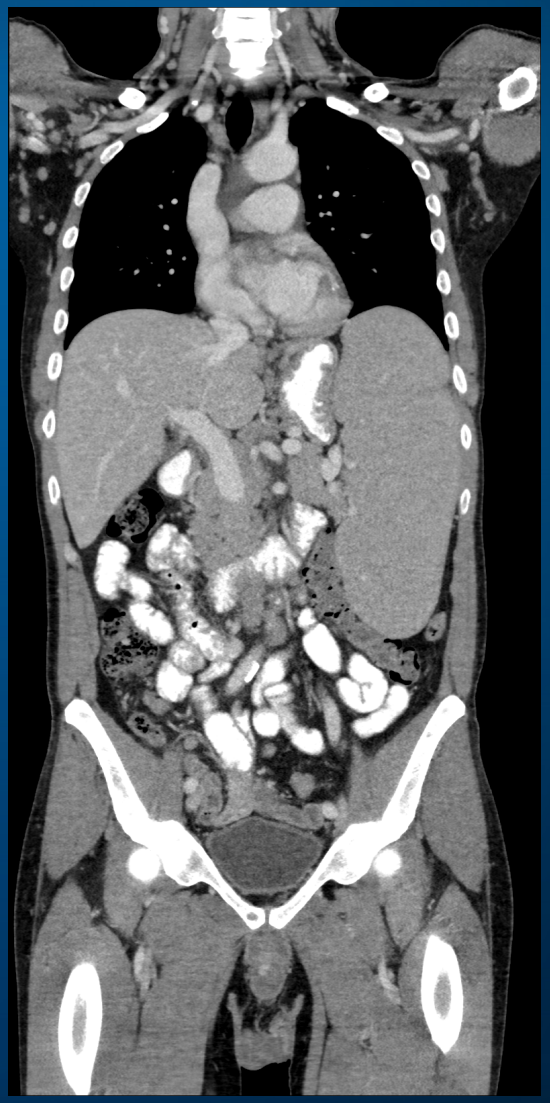
Case #5 (Dr Friedberg)

- 2011: A 62 yo engineer with CLL (Del 13q)
- Followed for two years, with progressive leukocytosis
  - 2012: WBC 70, HCT 29, PLT 143
  - No lymphadenopathy or symptoms noted
  - 2014: WBC 91, HCT 29, PLT 107
- Bone marrow aspirate:
  - Subtotal replacement by CLL
  - Typical immunophenotype; CD38 negative
  - No evidence of transformation



Case #5 (Dr Friedberg - Continued)

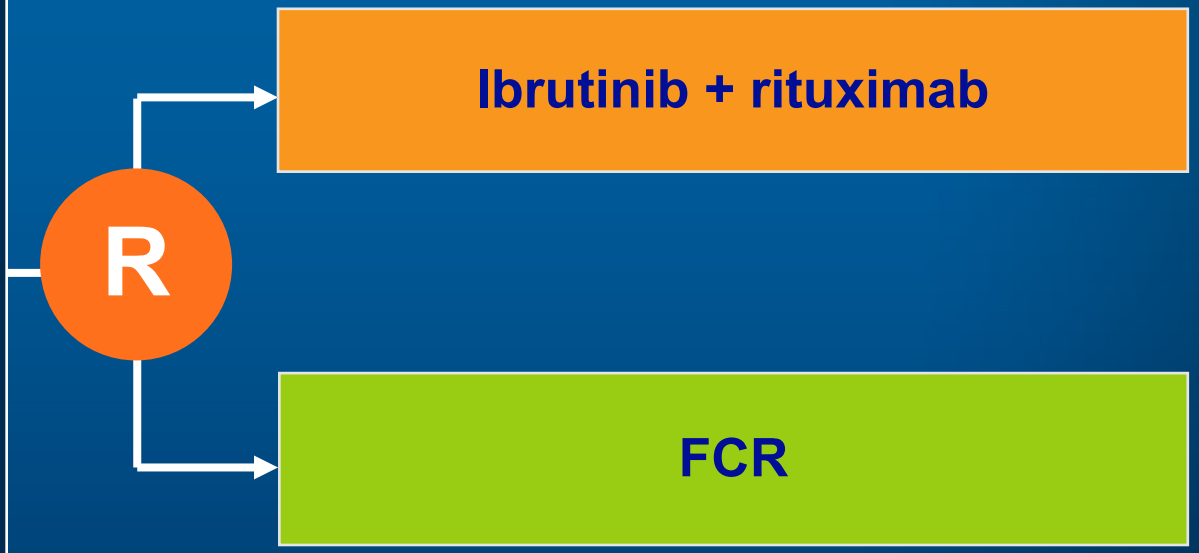
- 6/14: Enrolled in ECOG-E1912
  - Randomized to ibrutinib and rituximab
- 5/15: Clinical response
  - Normalization of CBC
  - Marrow showed 40% involvement by CLL
  - Spleen normalized on CT
- 3/17: Continues on ibrutinib
  - Mild hypertension
  - No other significant toxicities

ECOG-E1912 Phase III Schema

Target Accrual: 519

Eligibility

- Newly diagnosed CLL/SLL
- ECOG PS 0-2
- No prior chemotherapy, BTK inhibitor therapy, or monoclonal antibody therapy

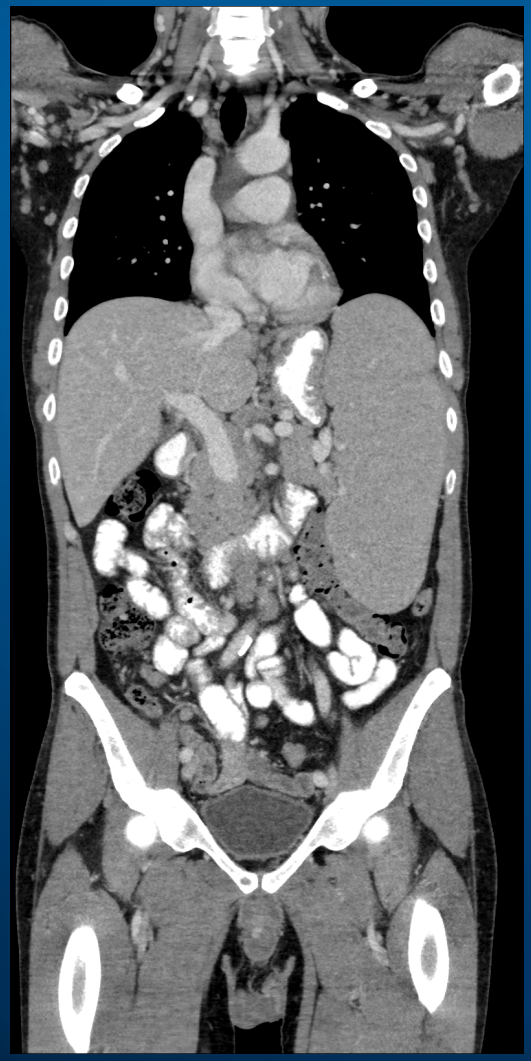


Primary Endpoints: Change in QoL, progression-free survival

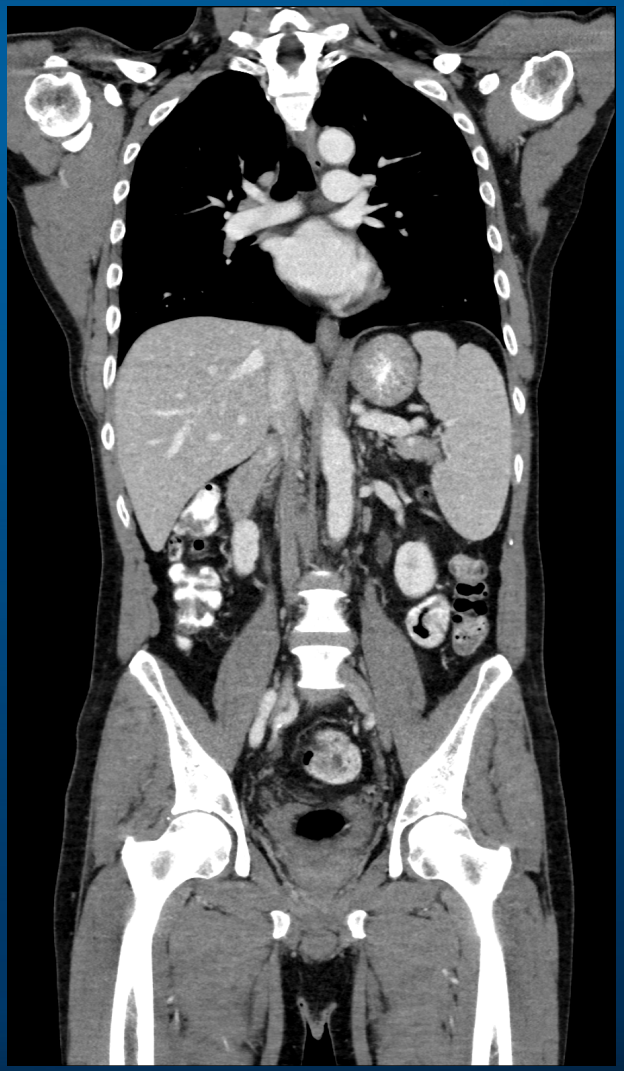
www.clinicaltrials.gov, Accessed June 4, 2017 (NCT02048813)

Case #5 (Dr Friedberg - Continued)

PRE



POST



Case #6 (Dr Flowers)

- 2002: A 65 yo African-American man diagnosed with CLL/SLL undergoes watchful waiting
- 2006-2007: Fludarabine + rituximab x 6 cycles
- 1/2010: Rising WBC, ↓ plts; Bone marrow biopsy and aspiration, 80% CLL; ZAP-70 expression, unmutated IGH gene and loss of 17P
- FCR x 6 cycles
  - Repeat EOT bone marrow biopsy: Normal cellular marrow
  - Flow: 3% CLL. FISH: Trisomy 12 was in 5% of the cells and 17P was in 8% of cells
- 01/2012: Repeat bone marrow biopsy. FISH: 17p in 68% of cells, decreased platelets
- 2013: Ofatumumab, with PD < 6 months

Case #6 (Dr Flowers - Continued)

- Clinical trial bendamustine / rituximab + Ibrutinib (or Placebo)
  - PD noted on restaging scans (on monotherapy)
  - Trial unblinded and patient was continued to open label Ibrutinib in 2014
- 3/2017: Progression on Ibrutinib with a large frontal sinus mass
  - Palliative XRT
- Started venetoclax 400 mg
  - No signs or symptoms of TLS

Day 0

Day 2

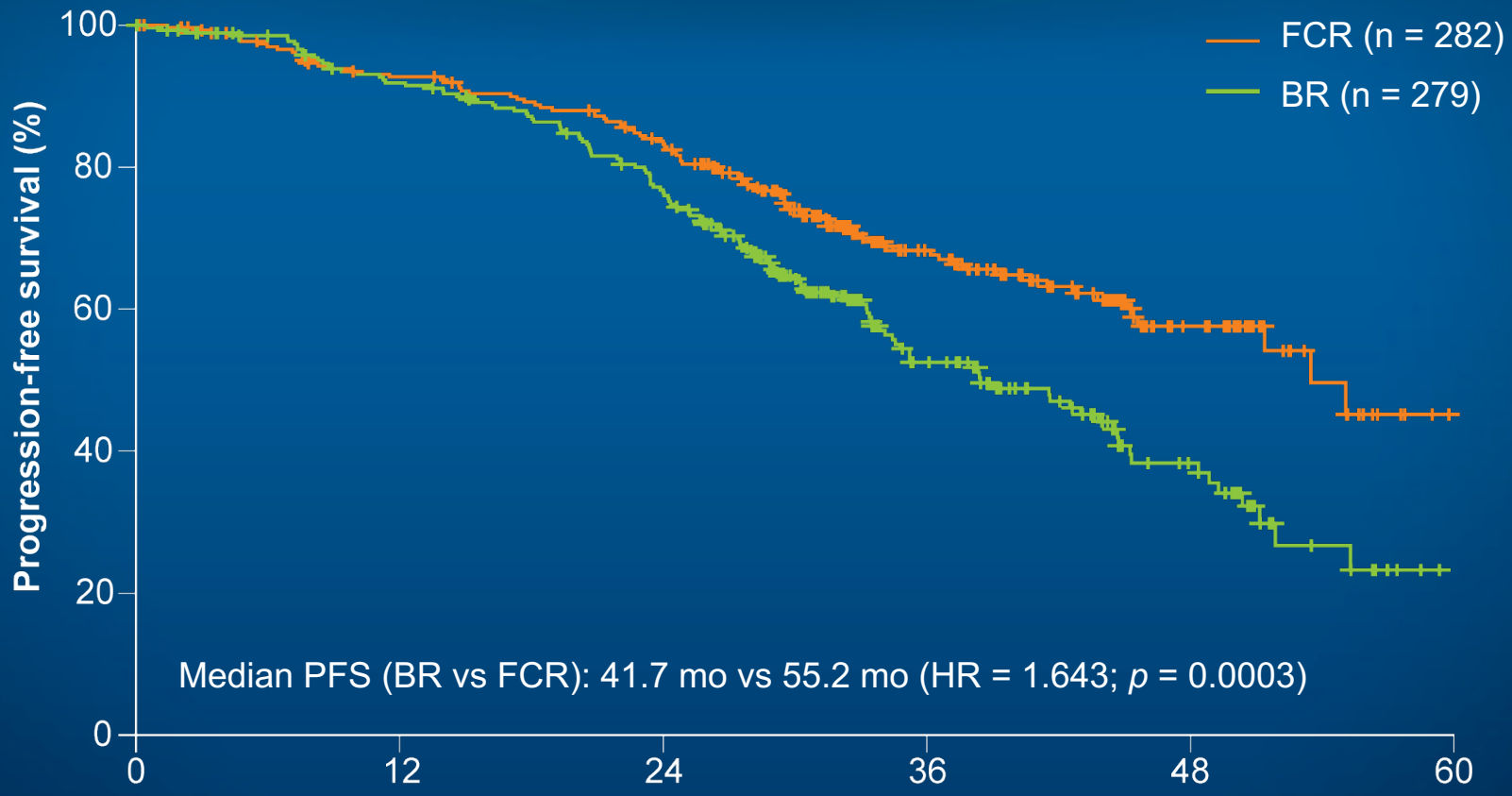
Day 7

First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

Barbara Eichhorst, Anna-Maria Fink, Jasmin Bahlo, Raymonde Busch, Gabor Kovacs, Christian Maurer, Elisabeth Lange, Hubert Köppler, Michael Kiehl, Martin Sökler, Rudolf Schlag, Ursula Vehling-Kaiser, Georg Köchling, Christoph Plöger, Michael Gregor, Torben Plesner, Marek Trneny, Kirsten Fischer, Harmut Döhner, Michael Kneba, Clemens-Martin Wendtner, Wolfram Klapper, Karl-Anton Kreuzer, Stephan Stilgenbauer, Sebastian Böttcher, Michael Hallek, on behalf of an international group of investigators and the German CLL Study Group (GCLLSG)

Lancet Oncol 2016; 17: 928–42

CLL10: A Phase III Trial of FCR versus BR in Advanced CLL



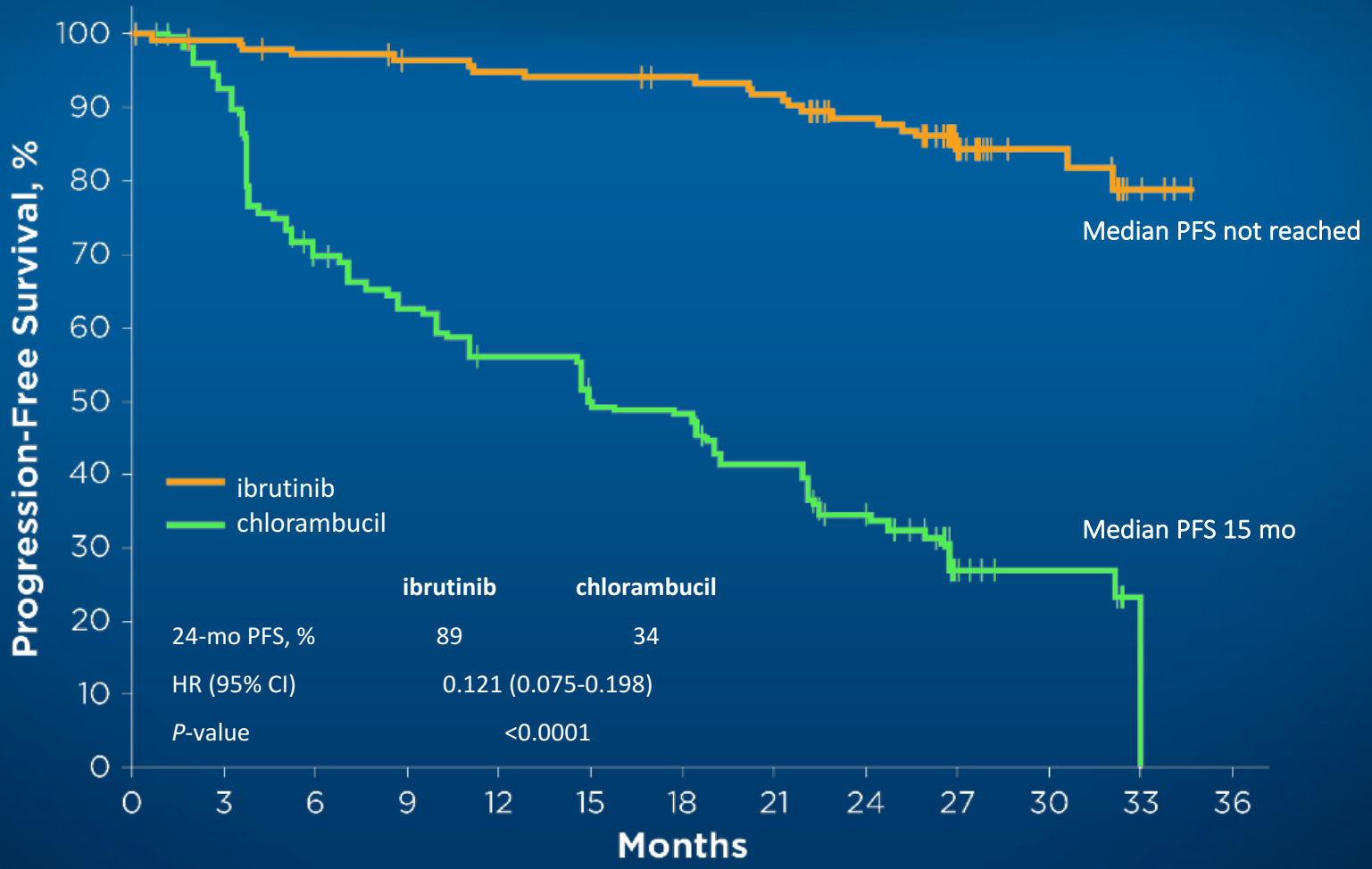
- Median PFS in younger patients (≤65 yrs) was significantly longer with FCR than with BR
- In elderly patients (>65 yrs) there was no significant difference in median PFS between FCR and BR

Eichhorst B et al. *Lancet Oncol* 2016;17(7):928-42.

Updated Efficacy and Safety from the Phase 3 RESONATE-2™ Study: Ibrutinib as First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Barr P et al
Proc ASH 2016;Abstract 234.

RESONATE-2: Updated PFS
(Median time on study: 29 months)



- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all subgroups

Barr P et al. *Proc ASH* 2016;Abstract 234.

Lenalidomide Maintenance After Front Line Therapy Substantially Prolongs Progression Free Survival in High Risk CLL: Interim Results of a Phase 3 Study (CLL M1 Study of the German CLL Study Group)

Fink AM et al.
Proc ASH 2016;Abstract 229.

CLLM1: Progression-Free Survival

- Patients with CLL achieving ≥PR after receiving ≥4 cycles of front-line chemoimmunotherapy (CIT) and either
  - MRD $\geq 10^{-2}$ or
  - MRD $\geq 10^{-4}$ to $< 10^{-2}$ plus ≥1 of the following:
    - Unmutated IGHV, del(17p) or TP53 after 1st-line CIT
- Median follow-up = 17.7 mo

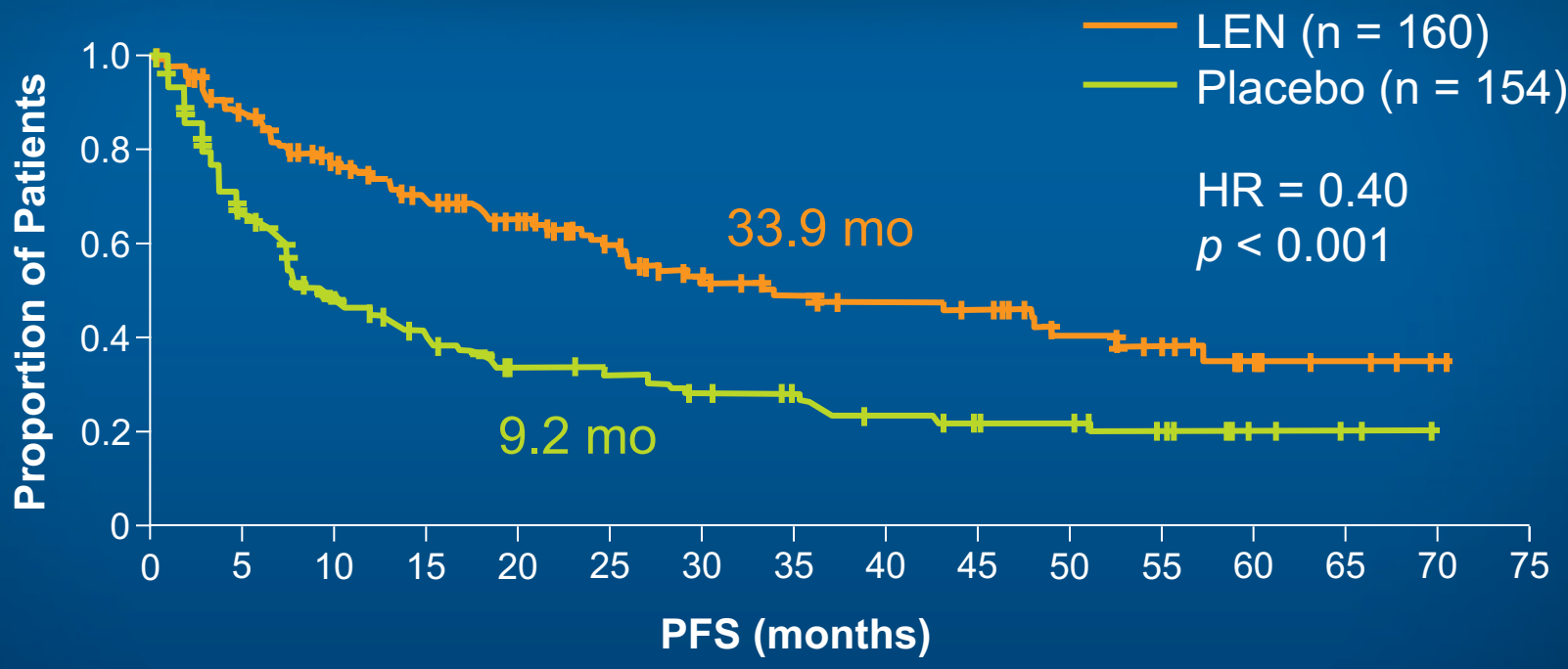
Outcome	LEN (n = 60)	Placebo (n = 29)	HR	*p*-value
Median PFS	Not reached	14.6 mo	0.198	0.000059

Fink AM et al. *Proc ASH* 2016;Abstract 229.

Results of the Phase 3 Study of Lenalidomide Versus Placebo As Maintenance Therapy Following Second-Line Treatment for Patients with Chronic Lymphocytic Leukemia (the CONTINUUM Trial)

Foa R et al.
Proc ASH 2016;Abstract 230.

CONTINUUM: PFS (Co-primary Endpoint with OS)



Median follow-up = 31.5 mo

- OS hazard ratio = 0.96, $p = 0.856$

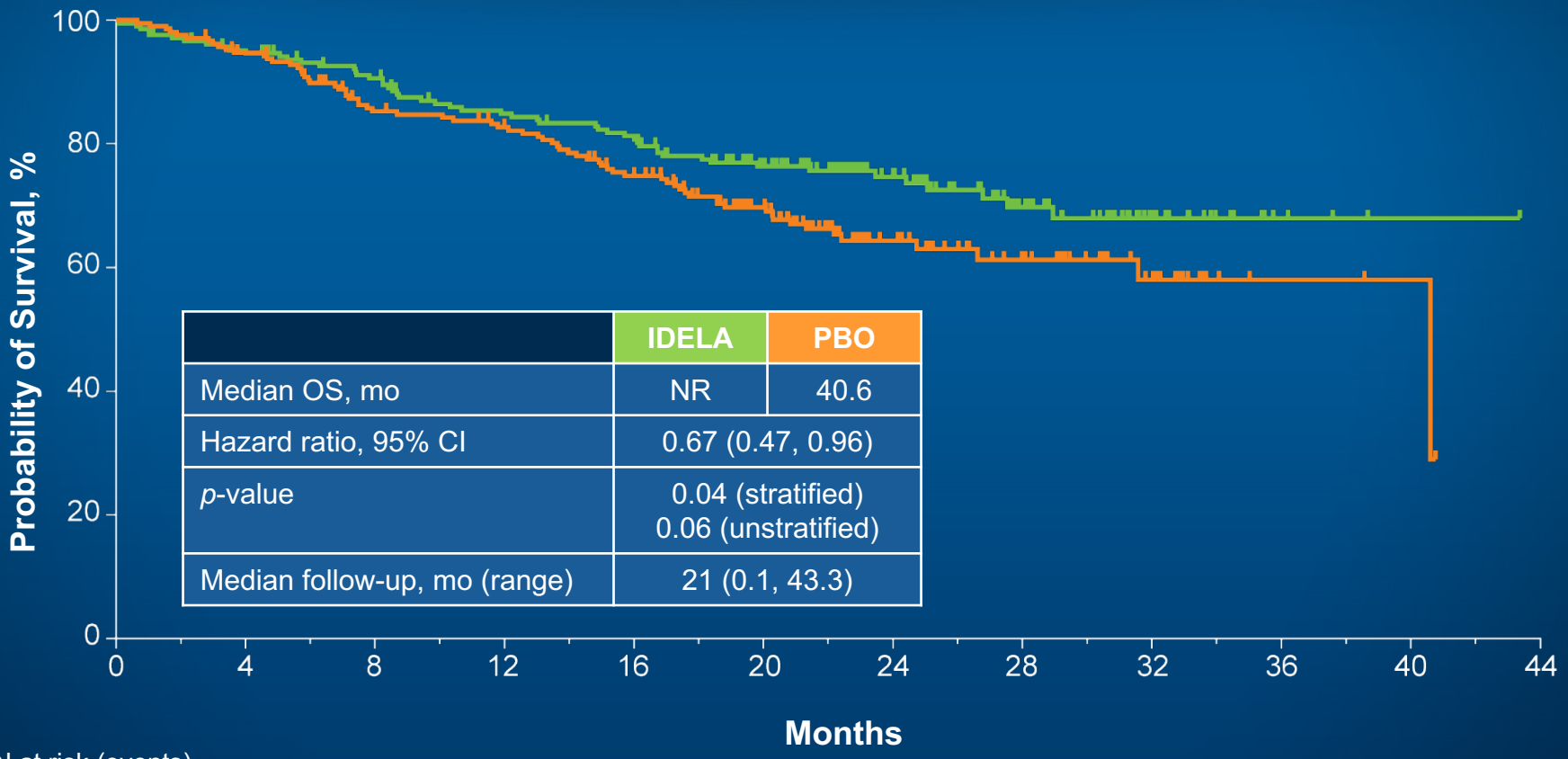
Foa R et al. *Proc ASH* 2016;Abstract 230.

Updated Analysis of Overall Survival in Randomized Phase III Study of Idelalisib in Combination with Bendamustine and Rituximab in Patients with Relapsed/Refractory CLL

Zelenetz AD et al.
Proc ASH 2016;Abstract 231.

Results: Overall Survival (ITT Population)

Secondary Endpoint



	IDELA	PBO
Median OS, mo	NR	40.6
Hazard ratio, 95% CI	0.67 (0.47, 0.96)	
p-value	0.04 (stratified) 0.06 (unstratified)	
Median follow-up, mo (range)	21 (0.1, 43.3)	

N at risk (events)

IDELA + BR	207 (0)	199 (6)	193 (10)	184 (14)	178 (19)	166 (27)	163 (30)	159 (33)	154 (38)	143 (43)	126 (46)	106 (47)	76 (48)	56 (50)	45 (52)	34 (53)	21 (53)	9 (53)	4 (53)	2 (53)	1 (53)	1 (53)	0 (53)
PBO + BR	209 (0)	204 (5)	195 (11)	182 (21)	168 (30)	166 (31)	159 (35)	151 (43)	140 (50)	123 (56)	107 (59)	78 (64)	52 (66)	42 (67)	31 (68)	24 (68)	17 (69)	5 (69)	3 (69)	2 (69)	2 (69)	0 (70)	0 (70)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2016 VOL. 374 NO. 4

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

N Engl J Med 2016;374:311-22

Response Rates in Phase I Dose-Escalation Study of Venetoclax in Relapsed CLL or SLL

- Dose-escalation cohort: 8 dosing groups (150 mg-1,200 mg)
- Expansion cohort: 400 mg venetoclax

Clinical variable	All patients (N = 116)	Dose-escalation cohort (n = 56)	Expansion cohort (n = 60)
Overall response rate (ORR)	79%	77%	82%
Complete response rate*	20%	30%	10%

* Includes complete remission with incomplete bone marrow recovery

- ORR did not vary according to age, number of previous therapies or risk factors for poor outcome

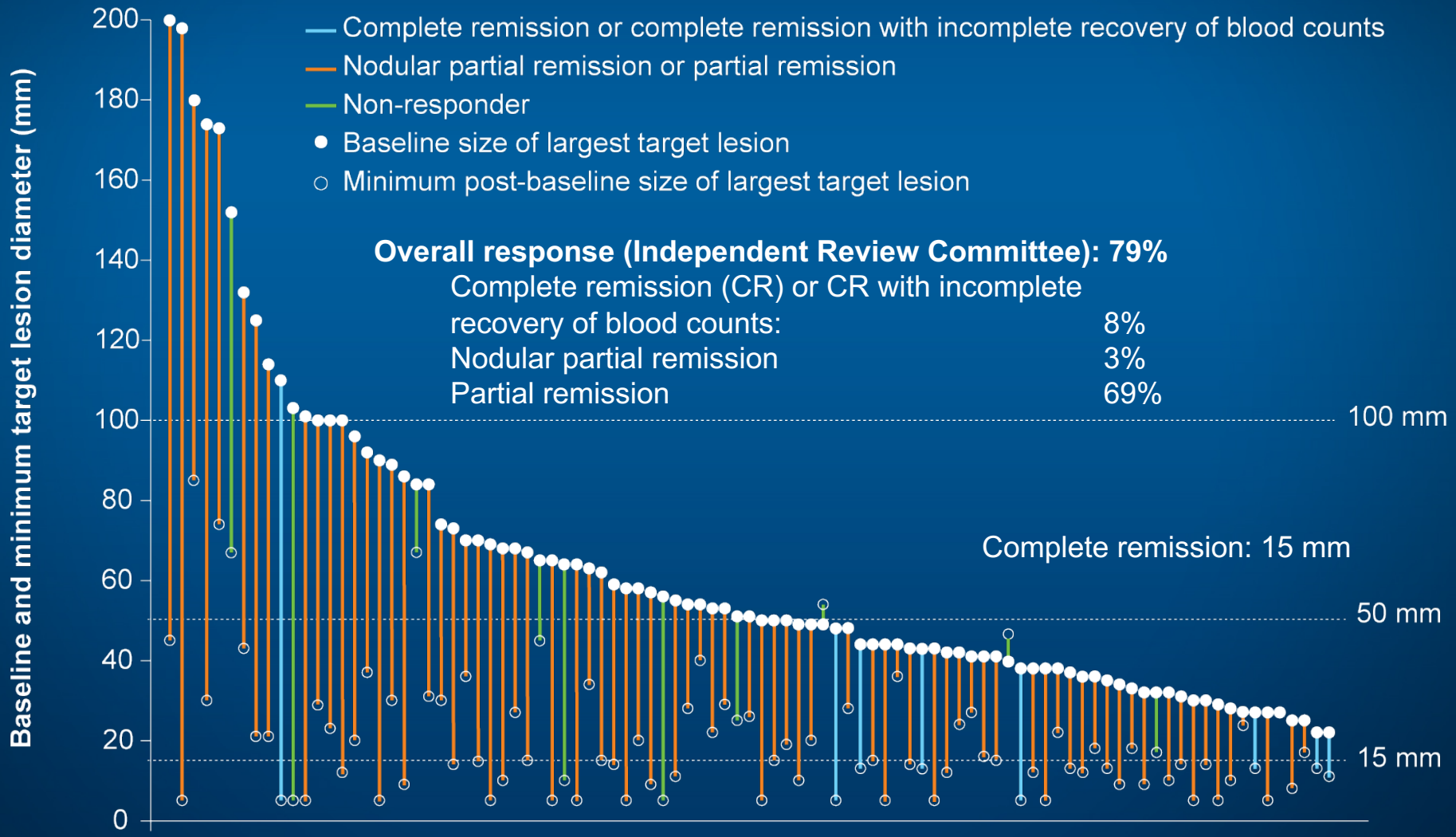
Roberts AW et al. *N Engl J Med* 2016;374(4):311-22.

Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study

Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schetelig, Steven Coutre, John F Seymour, Talha Munir, Soham D Puvvada, Clemens-Martin Wendtner, Andrew W Roberts, Wojciech Jurczak, Stephen P Mulligan, Sebastian Böttcher, Mehrdad Mobasher, Ming Zhu, Monali Desai, Brenda Chyla, Maria Verdugo, Sari Heitner Enschede, Elisa Cerri, Rod Humerickhouse, Gary Gordon, Michael Hallek, William G Wierda

Lancet Oncol 2016; 17: 768–78

Overall Response and Best Response in Nodal Diameter



Stilgenbauer S et al. *Lancet Oncol* 2016;17:768-78.

Recommended TLS Prophylaxis and Monitoring During Venetoclax Therapy

Tumor burden		Prophylaxis		Blood chemistry monitoring
		Hydration	Anti-hyperuricemics	
Low	All LN <5 cm *AND* ALC <25 x 10^9/L	Oral (1.5-2 L)	Allopurinol	*Outpatient* • Pre-dose, 6-8 hrs, 24 hrs at 1st dose of 20 mg and 50 mg • Pre-dose at ramp-up doses
Medium	Any LN 5 cm to <10 cm *OR* ALC ≥25 x 10^9/L	Oral (1.5-2 L); consider additional IV	Allopurinol	*Outpatient* • Same as above • Consider hospitalization if CrCl <80 mL/min at 1st dose of 20 mg and 50 mg
High	Any LN ≥10 cm *OR* ALC ≥25 x 10^9/L *AND* Any LN ≥5 cm	Oral (1.5-2 L) and IV (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid elevated	*In hospital at 1st dose of 20 mg and 50 mg* • Pre-dose, 4, 8, 12 and 24 hrs *Outpatient at ramp-up doses* • Pre-dose, 6-8 hrs, 24 hrs

http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

The NEW ENGLAND JOURNAL of MEDICINE

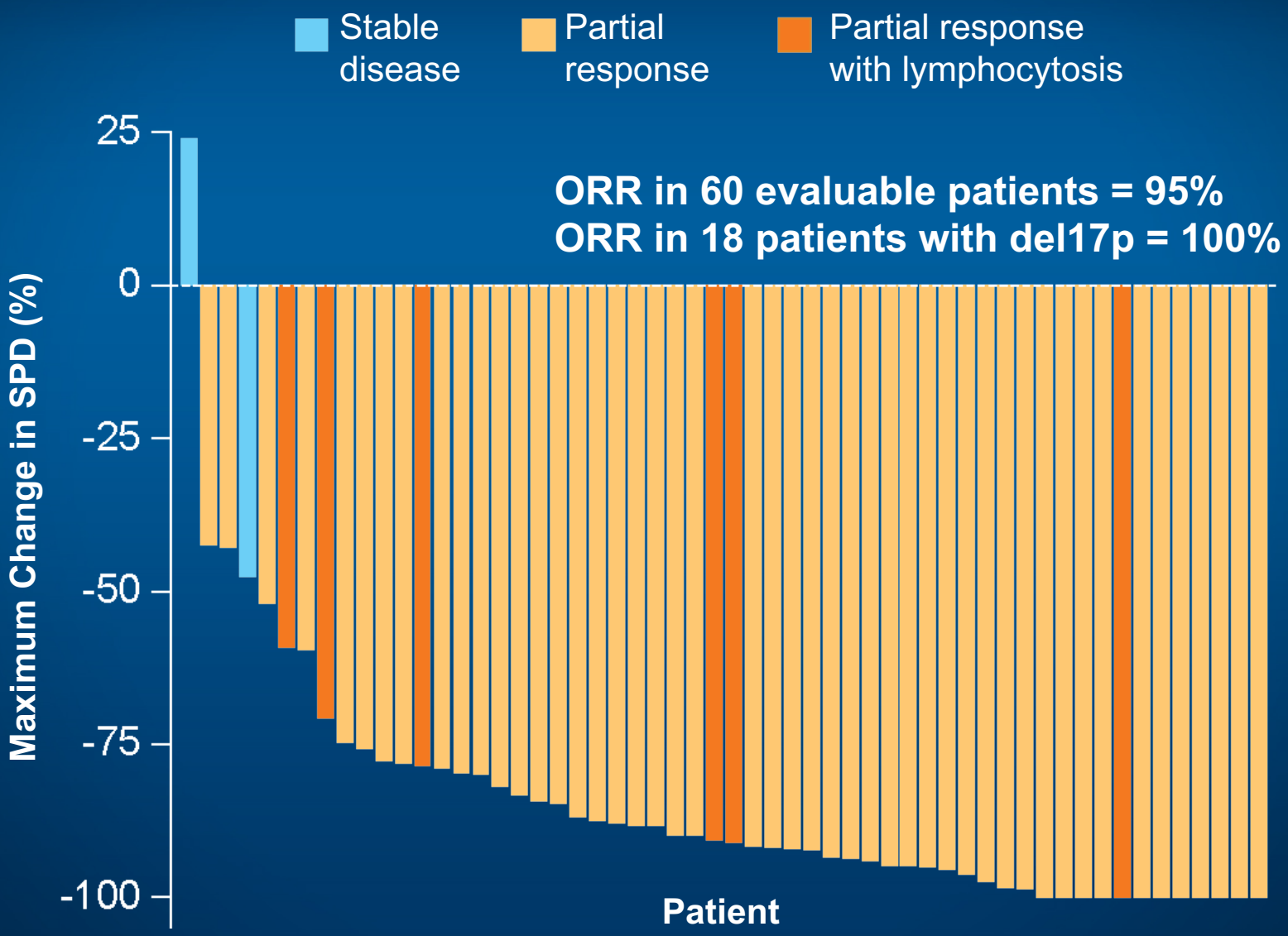
ORIGINAL ARTICLE

Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Bonnie Harrington, D.V.M., Susan O'Brien, M.D., Jeffrey A. Jones, M.D., M.P.H., Anna Schuh, M.D., Ph.D., Steve Devereux, M.D., Jorge Chaves, M.D., William G. Wierda, M.D., Ph.D., Farrukh T. Awan, M.D., Jennifer R. Brown, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Deborah M. Stephens, D.O., Paolo Ghia, M.D., Jacqueline C. Barrientos, M.D., John M. Pagel, M.D., Ph.D., Jennifer Woyach, M.D., Dave Johnson, B.S., Jane Huang, M.D., Xiaolin Wang, Sc.D., Allard Kaptein, Ph.D., Brian J. Lannutti, Ph.D., Todd Covey, B.A., Maria Fardis, Ph.D., Jesse McGreivy, M.D., Ahmed Hamdy, M.B., B.Ch., Wayne Rothbaum, M.A., Raquel Izumi, Ph.D., Thomas G. Diacovo, M.D., Amy J. Johnson, Ph.D., and Richard R. Furman, M.D.

N Engl J Med 2016;374:323-32

Response to Acalabrutinib



Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

Adverse Events Associated with Acalabrutinib

Adverse event (N = 61)	Any grade	Grade 3/4
Headache	43%	0%
Diarrhea	39%	2%
Increased weight	26%	2%
Pyrexia	23%	3%
Upper respiratory tract infection	23%	0%

- Major hemorrhage or atrial fibrillation: 0 cases
- No clinically significant changes in the numbers of T cells, NK cells and monocytes over time

Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
Michelle A Fanale, MD
Christopher Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

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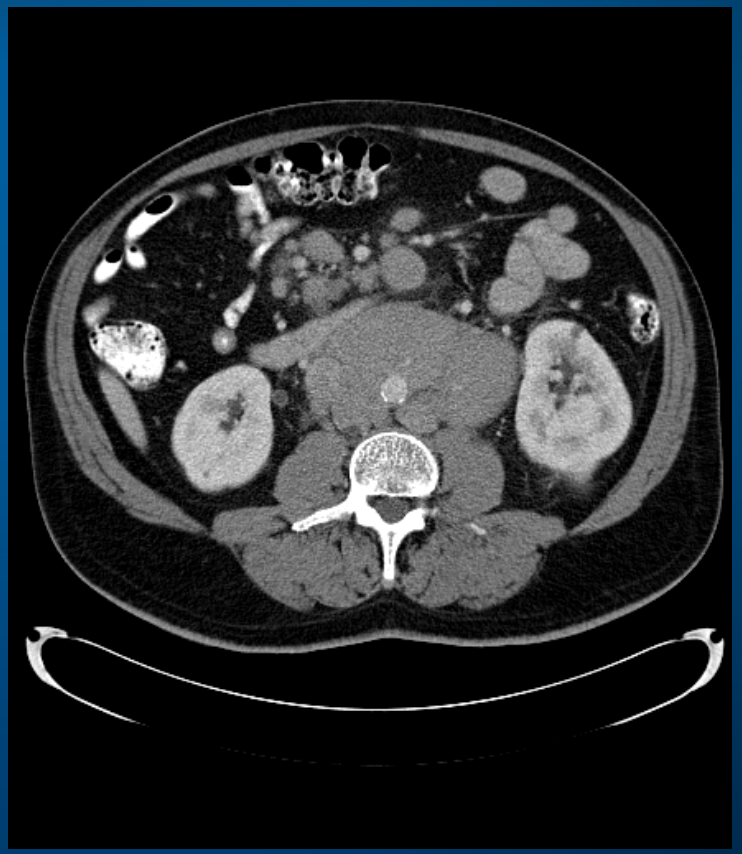
Follicular Lymphoma

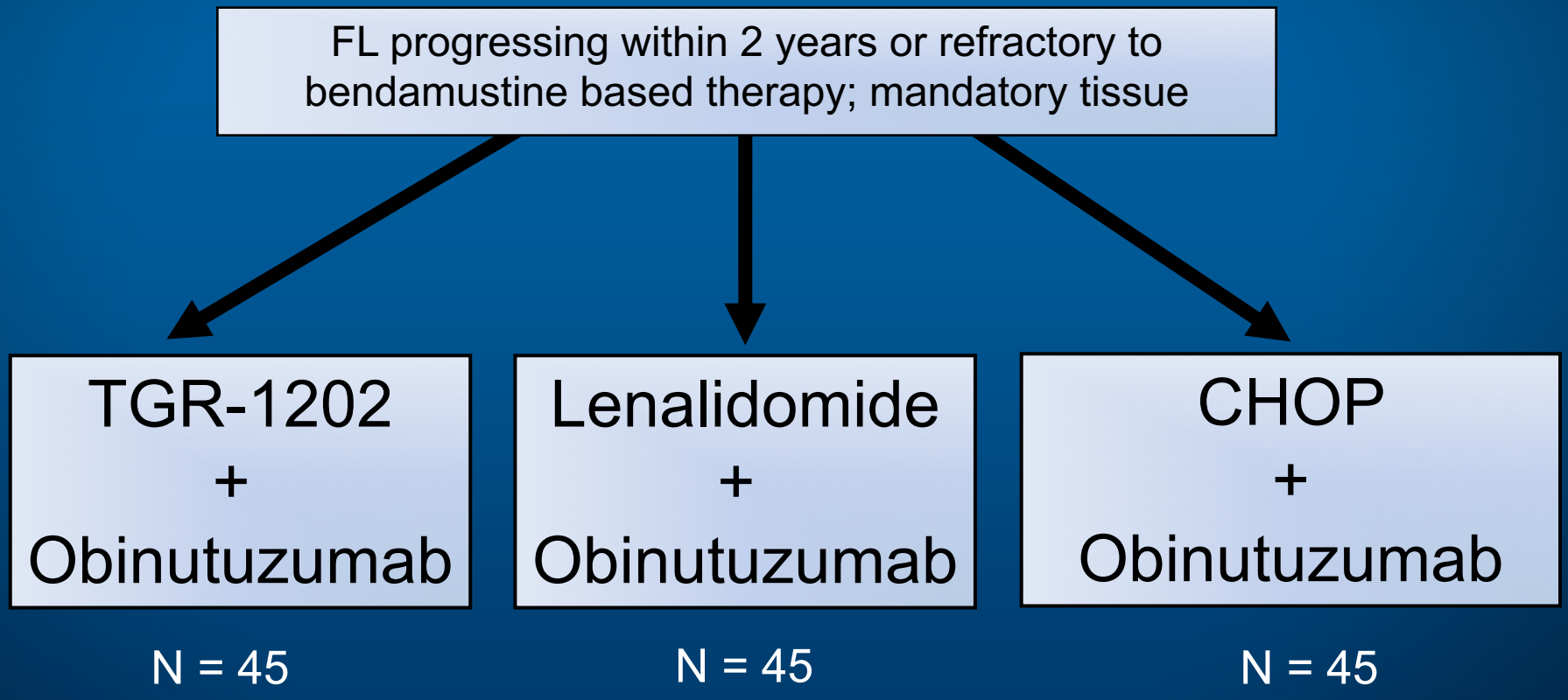
Research
To Practice®

Case #7 (Dr Friedberg)

- Aug 2016: 56 yo patient presents with shoulder pain and diffuse adenopathy
- Biopsy: Low-grade FL
- Marrow extensively involved with FL
- Bendamustine / rituximab x 6
  - Excellent response, but on PET restaging, new 2-cm retrocaval node seen with SUV 12
  - Biopsy: low grade FL, with increased proliferation index (Ki-67 50-60%)



SWOG-S1608: Randomized phase II trial in early progressing or refractory FL



ASCT allowed as consolidation per investigator choice

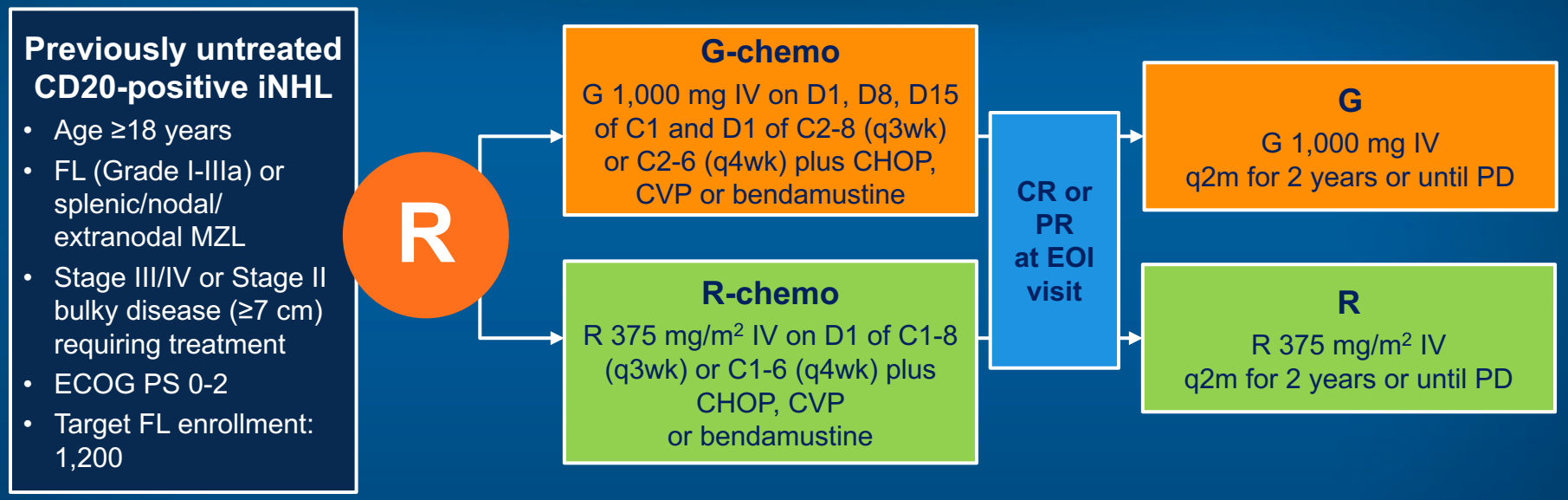
Primary clinical objective: CR by PET/CT

Primary translational objective: Validation of m7-FLIPI

Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study

Marcus RE et al.
Proc ASH 2016;Abstract 6.

GALLIUM: A Phase III Trial of Obinutuzumab-Based Induction and Maintenance in Newly Diagnosed FL



	G-chemo (n = 601)	R-chemo (n = 601)	HR (*p*-value)
3-year PFS rate	80.0%	73.3%	0.66 (0.0012)
3-year OS rate	94.0%	92.1%	0.75 (0.21)
ORR	88.5%	86.9%	—

Marcus R et al. *Proc ASH* 2016;Abstract 6.

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	37.9%	43.9%
Leucopenia	8.4%	8.6%
Febrile neutropenia	4.9%	6.9%
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. *Proc ASH* 2016;Abstract 6.

March 29, 2017 Press Release

FDA Advisory Committee Unanimously Recommends Approval of Subcutaneous Rituximab

- The proposed indications for the treatment include previously untreated follicular lymphoma (FL), previously untreated diffuse large B-cell lymphoma (DLBCL), relapsed or refractory low-grade or follicular lymphoma and previously untreated and relapsed or refractory chronic lymphocytic leukemia (CLL)
- Subcutaneous rituximab can be administered in 5-7 minutes compared to 1.5 hours or more for intravenous rituximab
- A final approval decision is expected from the FDA by June 26, 2017

https://www.gene.com/media/press-releases/14658/2017-03-29/fda-advisory-committee-unanimously-recom

Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial

Andrew Davies, Francesco Merli, Biljana Mihaljević, Santiago Mercadal, Noppadol Siritanaratkul, Philippe Solal-Céligny, Axel Boehnke, Claude Berge, Magali Genevray, Artem Zharkov, Mark Dixon, Michael Brewster, Martin Barrett, David MacDonald

Lancet Haematol 2017;[Epub ahead of print].

Previously untreated, CD20-positive Grade 1, 2 or 3a FL randomly assigned (1:1):

- IV rituximab 375 mg/m^2 + CHOP or CVP
- SubQ rituximab 1,400 mg + CHOP or CVP
- Followed by maintenance rituximab

SABRINA: Efficacy and Adverse Events

	IV rituximab (n = 205)	SubQ rituximab (n = 205)
Overall response	84.9%	84.4%
Complete response	32.2%	32.2%
PFS*	HR = 0.84	
EFS*	HR = 0.91	
OS*	HR = 0.81	

* At a median follow-up of 37 months, no significant difference between groups

	IV rituximab (n = 210)	SubQ rituximab (n = 197)
Serious AEs	95%	96%
Grade ≥3 AEs	55%	56%
Administration-related reaction	35%	48%

Davies A et al. *Lancet Haematol* 2017;[Epub ahead of print].

Phase IIIb Randomized Study of Lenalidomide plus Rituximab (R^2) Followed by Maintenance in Relapsed/Refractory NHL: Analysis of Patients with Double-Refractory or Early Relapsed Follicular Lymphoma (FL)

Andorsky DJ et al.
Proc ASCO 2017;Abstract 7502.

Best Response for Evaluable Patients in Induction and Maintenance

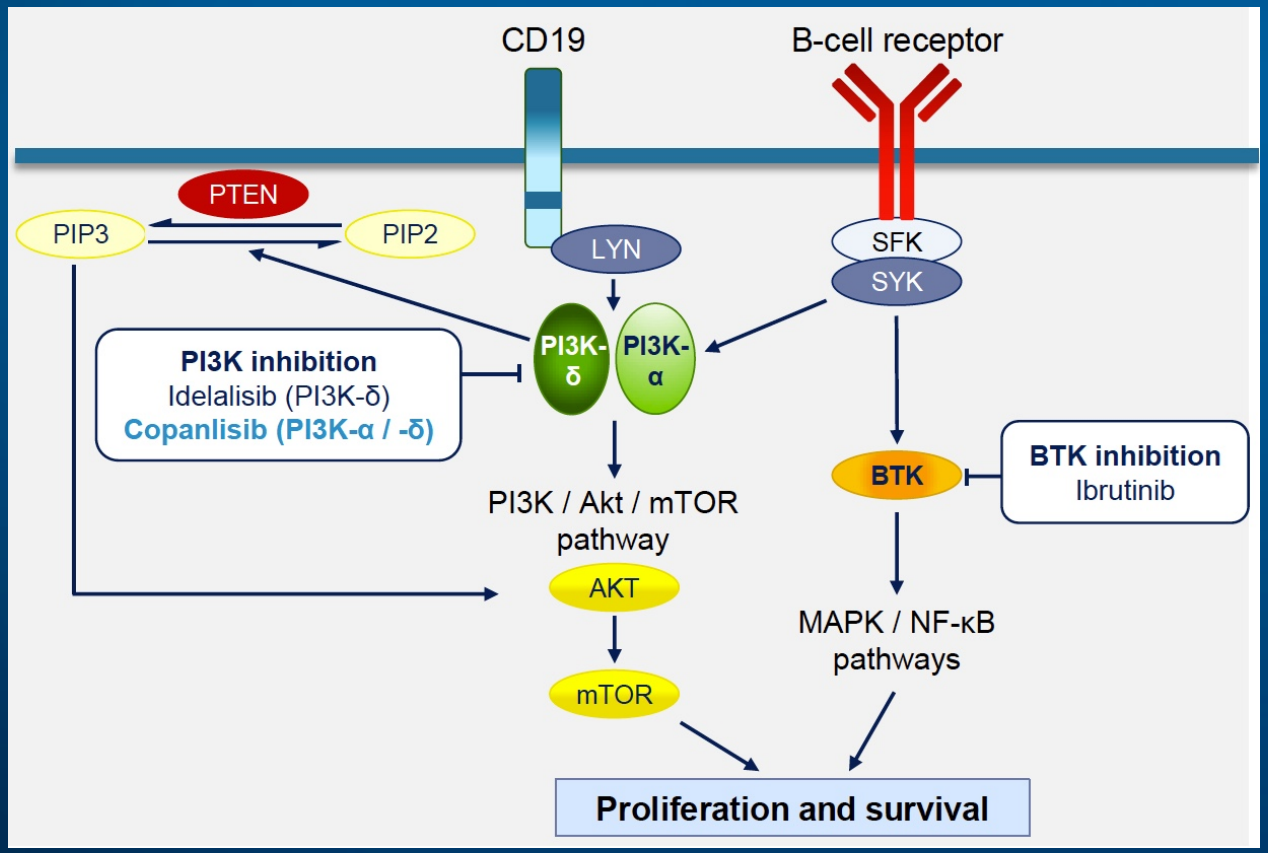
Response	Double refractory (n = 28)	Early relapse (n = 33)	All patients (N = 91)
ORR	13 (46%)	16 (48%)	61 (67%)
CR/CRu	6 (21%)	4 (12%)	33 (36%)
PR	7 (25%)	12 (36%)	28 (31%)
SD	10 (36%)	13 (39%)	21 (23%)
PD	5 (18%)	4 (12%)	9 (10%)

Andorsky DJ et al. *Proc ASCO* 2017;Abstract 7502.

Copanlisib in Patients with Relapsed or Refractory Indolent B-Cell Lymphoma: Primary Results of the Pivotal CHRONOS-1 Study

Dreyling M et al.
Proc AACR 2017;Abstract CT149.

Key Signaling Pathways in B-Cell Lymphoma



- The B-cell receptor (BCR) and phosphoinositide 3-kinase (PI3K) signaling pathways play a key role in the proliferation and survival of indolent B-cell lymphomas
- Targeted inhibition of BCR/PI3K signaling has emerged as a therapeutic strategy for relapsed/refractory indolent B-cell lymphoma
- Copanlisib is an intravenous pan-class I PI3K inhibitor with predominant and potent activity against the PI3K-α and PI3K-δ isoforms

Dreyling M et al. *Proc AACR* 2017;Abstract CT149.

CHRONOS-1: Phase II Study Schema

Assigned to Treatment: 142

- Indolent B-cell lymphoma (FL Gr1-3a), MZL, SLL, LPL/WM
- Failed at least 2 lines of prior therapy

→

Copanlisib 60 mg IV
D 1, 8, 15 of 28-day cycle
until disease progression or unacceptable toxicity

Primary study outcome: ORR by central review
Select secondary outcomes: PFS, DoR, OS, Safety, QoL

Dreyling M et al. *Proc AACR* 2017;Abstract CT149.

CHRONOS-1: Efficacy Data in FL

Endpoint	FL (n = 104)
ORR	58.7%
Complete response	14.4%
Partial response	44.2%
Stable disease	33.7%
Median DoR	12.2 mo
Median PFS	11.2 mo
Median OS	Not yet reached

Safety in All Patients (N = 141)

- 3 deaths due to drug-related AEs (respiratory failure, lung infection, thromboembolic event)
- Grade 3/4 hyperglycemia: 40.1%
- Grade 3 hypertension: 22.5%
- Grade 3/4 neutropenia: 19%
- Grade 3 lung infection: 9.2%

Dreyling M et al. *Proc AACR* 2017;Abstract CT149.

CHRONOS-1: Safety Profile

Common treatment-related AEs	Total (N = 142)		
	All grades	Grade 3	Grade 4
Hyperglycemia	48.6%	33.1%	7.0%
Hypertension	28.9%	22.5%	0
Neutropenia	24.6%	6.3%	12.7%
Lung infection	14.1%	9.2%	1.4%
Pneumonitis (noninfectious)	7.0%	1.4%	0
Colitis	0.7%	0	0.7%

Dreyling M et al. *Proc AACR* 2017;Abstract CT149.

FDA Priority Review for Copanlisib in Relapsed/Refractory Follicular Lymphoma

- On May 17, 2017, the U.S. Food and Drug Administration (FDA) granted Priority Review designation for the New Drug Application (NDA) for copanlisib for the treatment of relapsed or refractory follicular lymphoma (FL) patients who have received at least 2 prior therapies.
- Results of the Phase II CHRONOS-1 trial (NCT01660451) form the basis of this Priority Review.

https://lymphomanewstoday.com/2017/05/18/fda-copanlisib-priority-review-follicular-lymphoma/

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
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Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

Research To Practice®

Mantle Cell Lymphoma

Research
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Case #8 (Dr Flowers)

- 12/2008: A 51 yo man with acute onset of weight loss and weakness
  - Noted to have an intussusception and underwent surgery
  - Biopsy of his cecum and colon: MCL
    - FISH: t(11;14)
    - Sample positive for Cyclin D1 with KI67 40%
  - Peripheral blood flow cytometry: CD20 positive, CD38 positive, CD5 positive population with lambda expression
- 2009: R-HCVAD x 4 followed by ASCT
- 2013: Relapsed disease within the sinus
- Bortezomib x 4 cycles, with PD
- Lenalidomide x 6 cycles, with PD
- 2014: Ibrutinib

VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

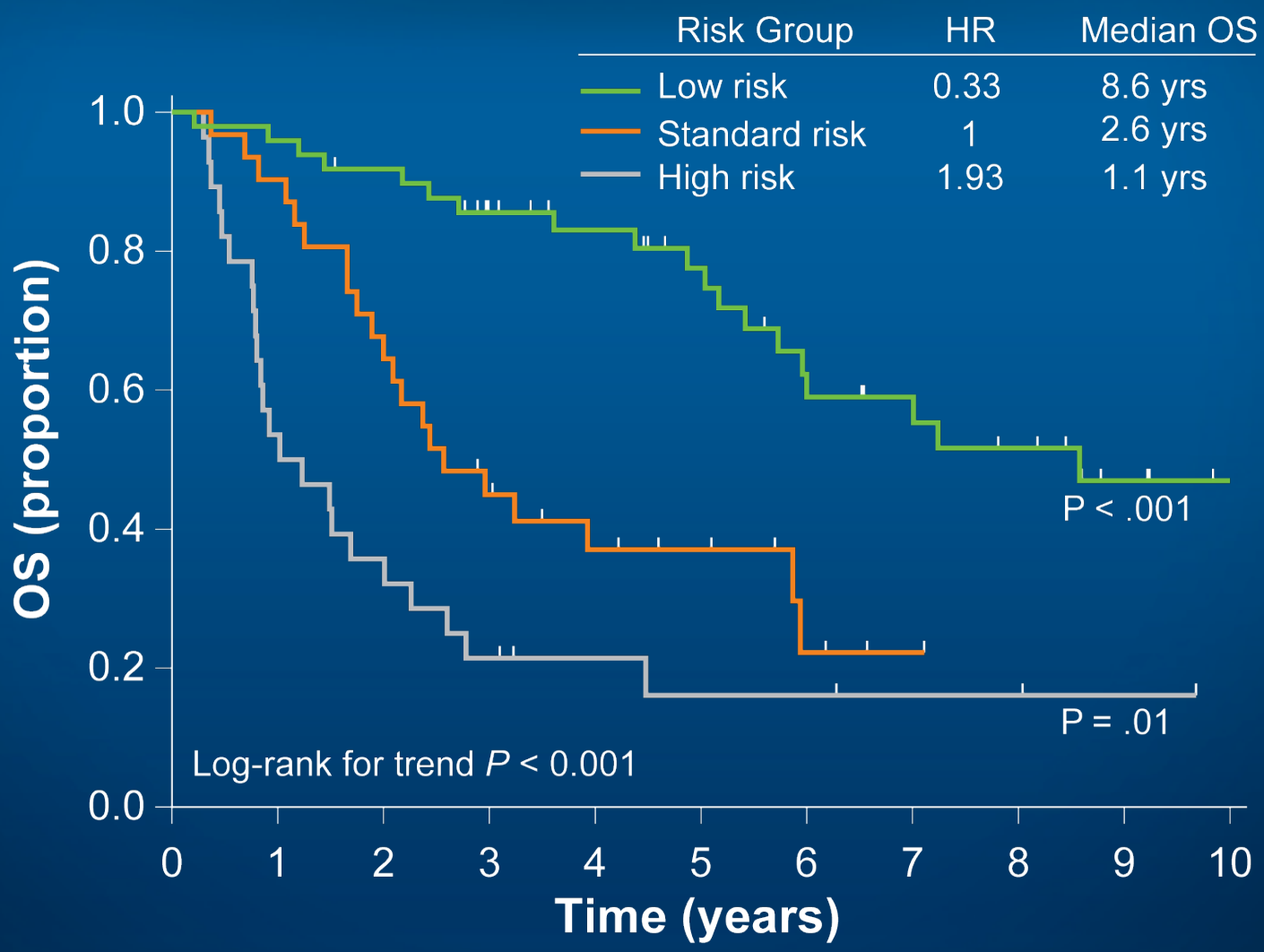
New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies

David W. Scott, Pau Abrisqueta, George W. Wright, Graham W. Slack, Anja Mottok, Diego Villa, Pedro Jares, Hilka Rauert-Wunderlich, Cristina Royo, Guillem Clot, Magda Pinyol, Merrill Boyle, Fong Chun Chan, Rita M. Braziel, Wing C. Chan, Dennis D. Weisenburger, James R. Cook, Timothy C. Greiner, Kai Fu, German Ott, Jan Delabie, Erlend B. Smeland, Harald Holte, Elaine S. Jaffe, Christian Steidl, Joseph M. Connors, Randy D. Gascoyne, Andreas Rosenwald, Louis M. Staudt, Elias Campo, and Lisa M. Rimsza, for the Lymphoma/Leukemia Molecular Profiling Project

Scott DW et al. *J Clin Oncol* 2017;35:1668-77.

Survival Outcomes Based on MCL35 Assay Risk Subgroups

(N = 110 patients with MCL treated with R-CHOP)

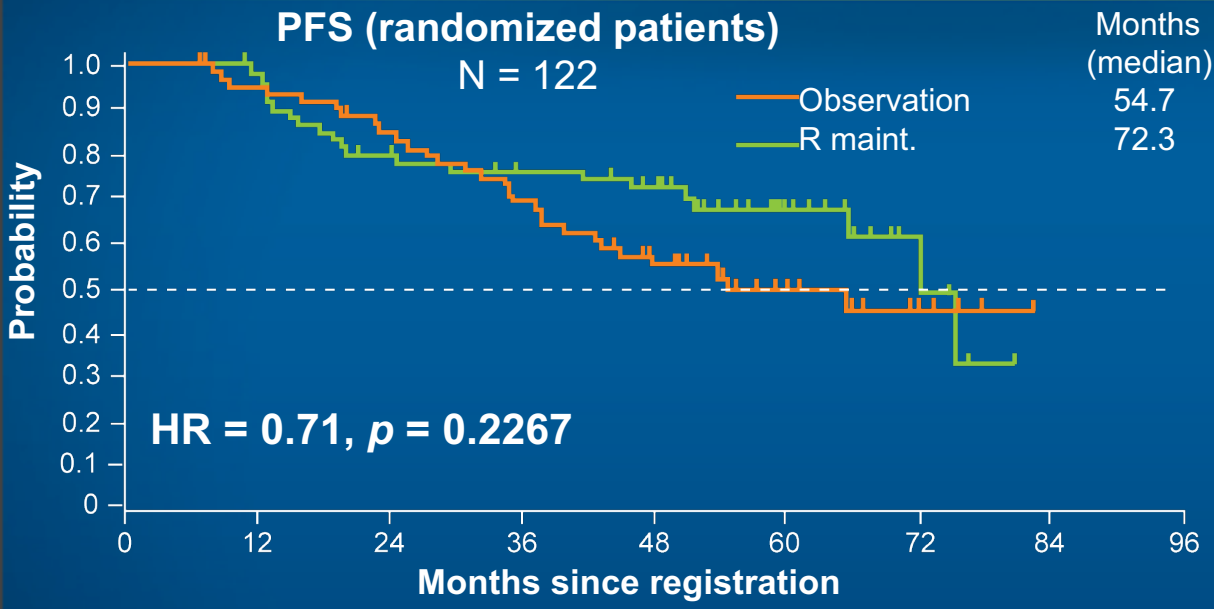


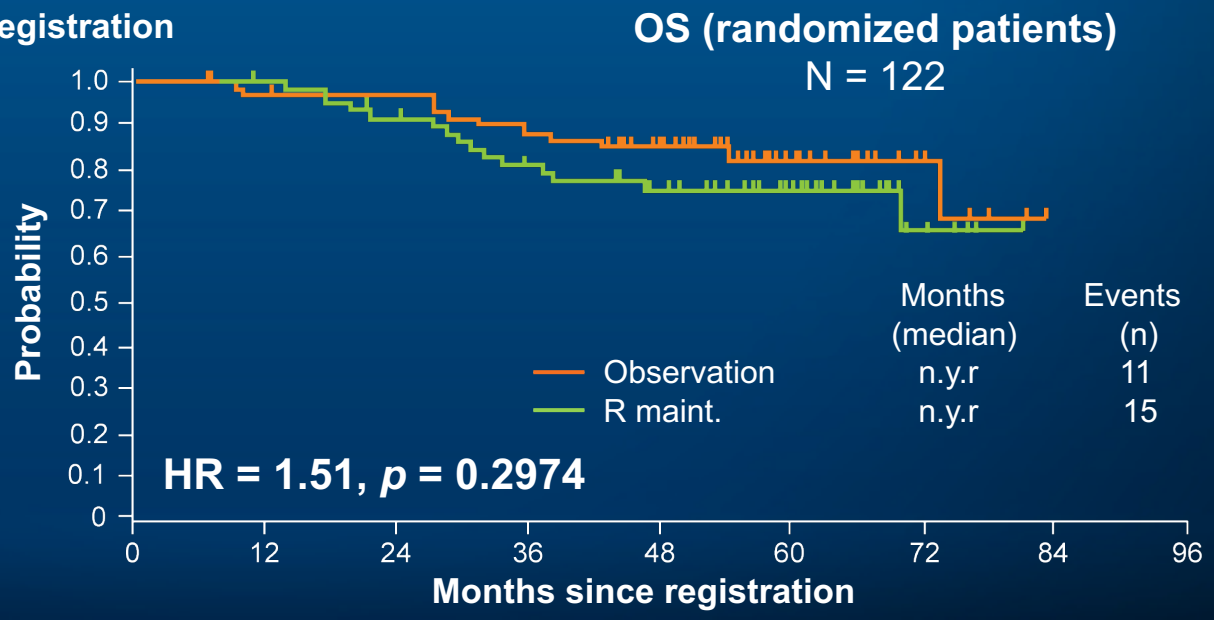
Scott DW et al. *J Clin Oncol* 2017;35:1668-77.

Two Years Rituximab Maintenance vs Observation After First-Line Treatment with Bendamustine plus Rituximab (B-R) in Patients with Mantle Cell Lymphoma: First Results of a Prospective, Randomized, Multicenter Phase II Study (A Subgroup Study of the StiL NHL7-2008 MAINTAIN Trial)

Rummel MJ et al.
Proc ASCO 2016;Abstract 7503.

MAINTAIN: Survival Analysis





Rituximab Maintenance After Autologous Stem Cell Transplantation Prolongs Survival in Younger Patients with Mantle Cell Lymphoma: Final Results of the Randomized Phase 3 LyMa Trial of the Lysa/Goelams Group

Le Gouill S et al.
Proc ASH 2016;Abstract 145.

Efficacy of Post-ASCT Maintenance Rituximab vs Observation

Endpoint	Rituximab (n = 120)	Observation (n = 120)	Hazard ratio	*p*-value
Median event-free survival	Not reached	Not reached	0.457	0.0016
4-yr EFS	78.9%	61.4%	—	0.0012
Median progression-free survival	Not reached	Not reached	0.40	0.0007
4-yr PFS	82.2%	64.6%	—	0.0005
Median overall survival	Not reached	Not reached	0.50	0.0454
4-yr OS	88.7%	81.4%	—	0.0413

Le Gouill S et al. *Proc ASH* 2016;Abstract 145.

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

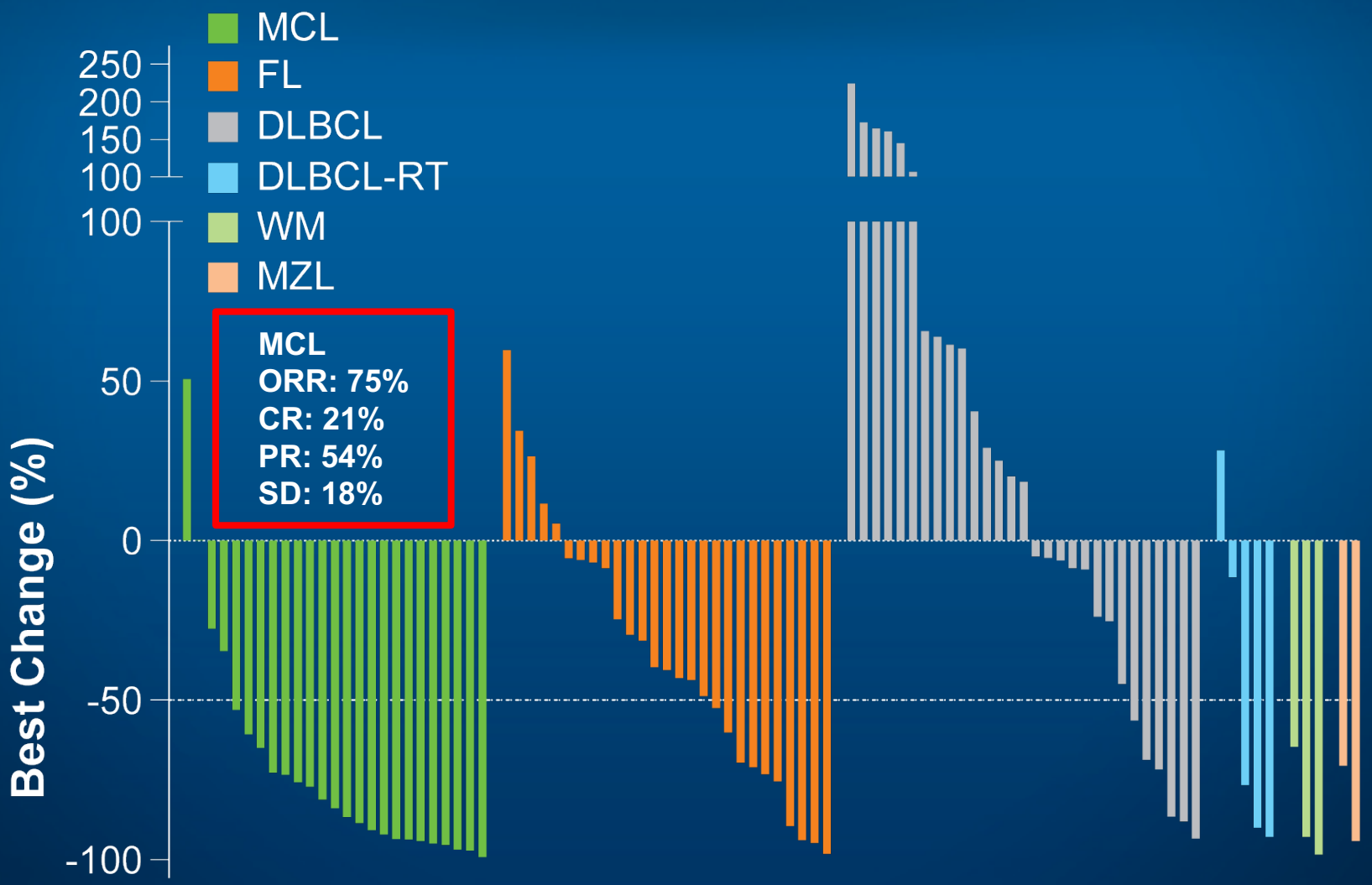
ORIGINAL REPORT

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

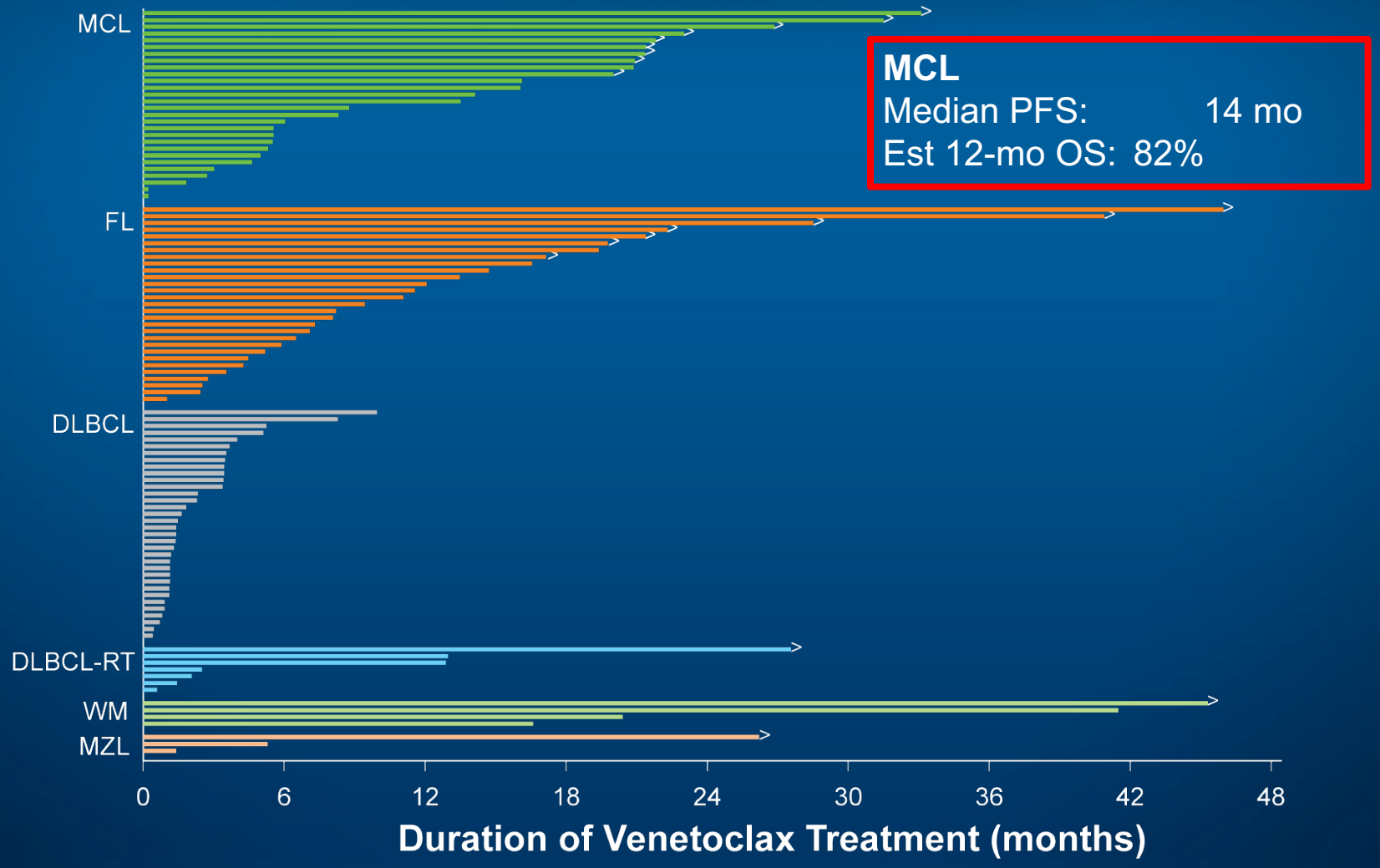
Davids MS et al. *J Clin Oncol* 2017;35(8):826-33.

Best Response



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

Duration of Response and Survival



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

A Phase I Trial of Ibrutinib Plus Palbociclib in Patients with Previously Treated Mantle Cell Lymphoma

Martin P et al.
Proc ASH 2016;Abstract 150.

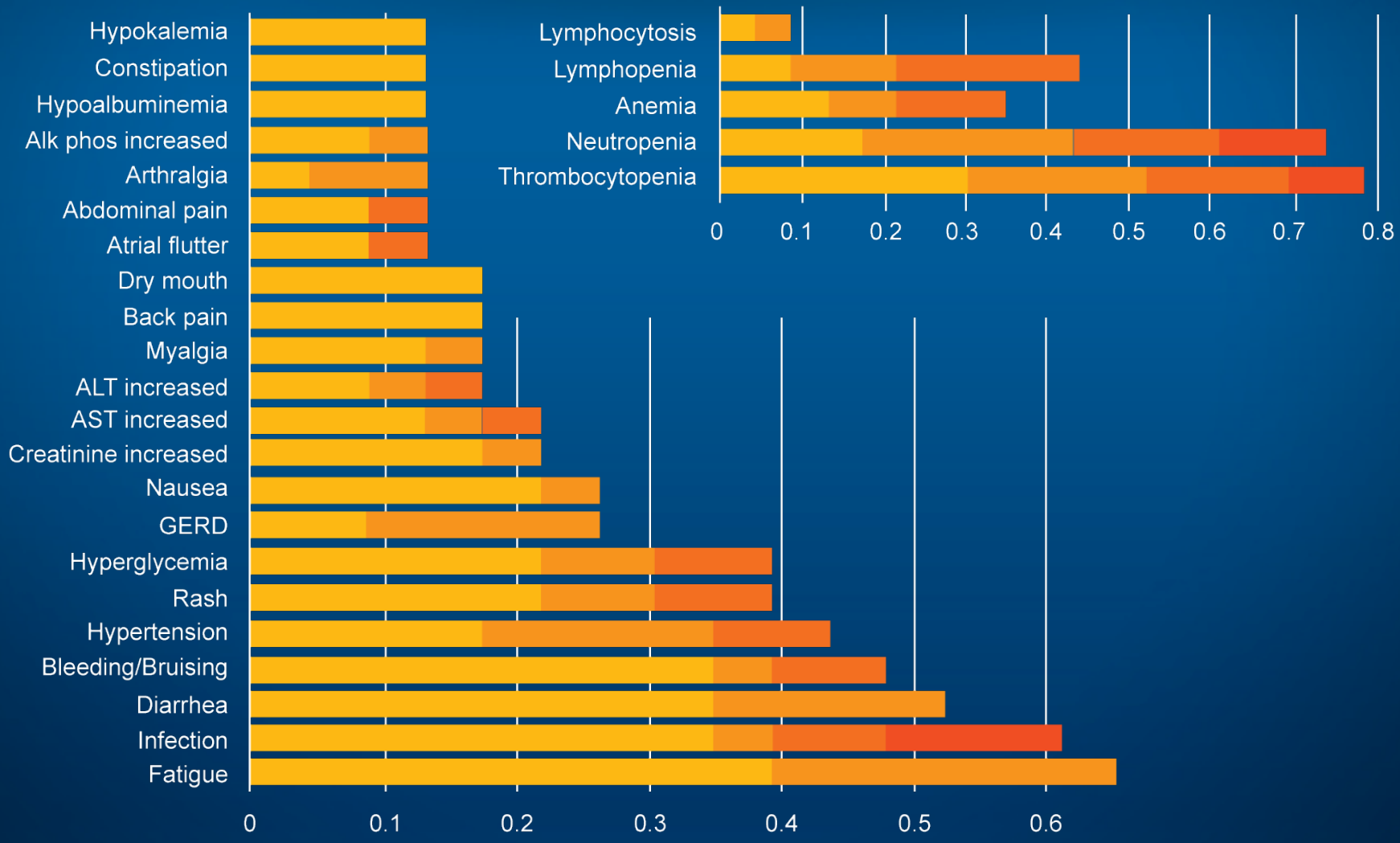
Best Response – Intent-to-Treat

Response	Total n = 21	DL 1 n = 3	DL 2 n = 3	DL 3 n = 6	DL 4 n = 4	DL 5 n = 5
ORR	13 (64%)	3	2	4	1	3
CR	9 (43%)	3	1	2		3
PR	4 (21%)		1	2	1	
SD	1 (5%)		1			
PD	5 (24%)			1	2	2
NE	2 (20%)			1	1	

Dose level	Ibrutinib	Palbociclib
1	280 mg	75 mg x 21 days
2	420 mg	75 mg x 21 days
3	420 mg	100 mg x 21 days
4	560 mg	100 mg x 21 days — MTD
5	560 mg	125 mg x 21 days

Martin P et al. *Proc ASH* 2016;Abstract 150.

Adverse Events Occurring in >10%



Martin P et al. *Proc ASH* 2016;Abstract 150.

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
Michelle A Fanale, MD
Christopher Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

Research To Practice®

Hodgkin Lymphoma

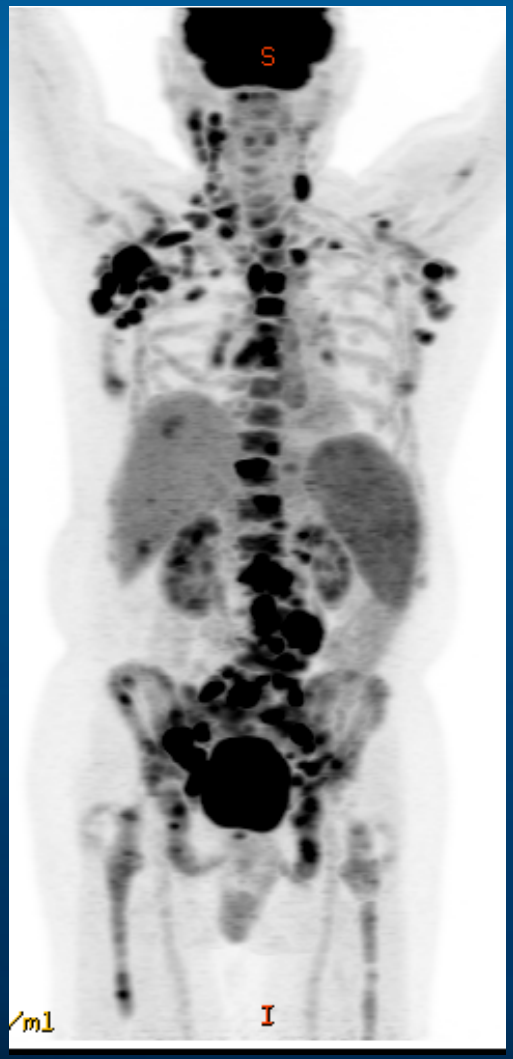
Research
To Practice®

Case #9 (Dr Ansell)

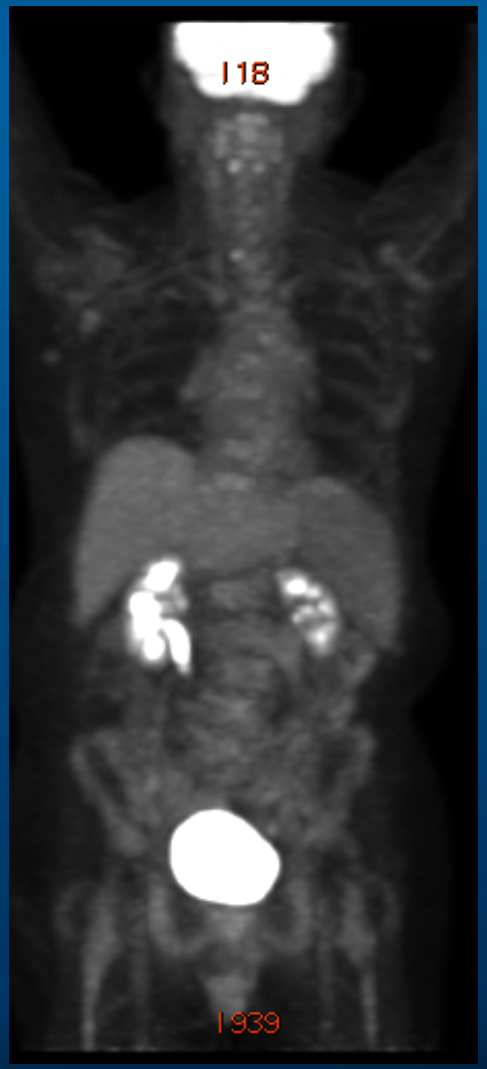
- A 74 yo man with fevers and sweats since Sept 2016
- PET scan showed extensive adenopathy
- Biopsy: Classical Hodgkin lymphoma
- Previous CAD with prior MI
  - Ejection fraction: -34%
- Brentuximab vedotin plus nivolumab

Case #9 (Dr Ansell - Continued)

Baseline



2 months of treatment



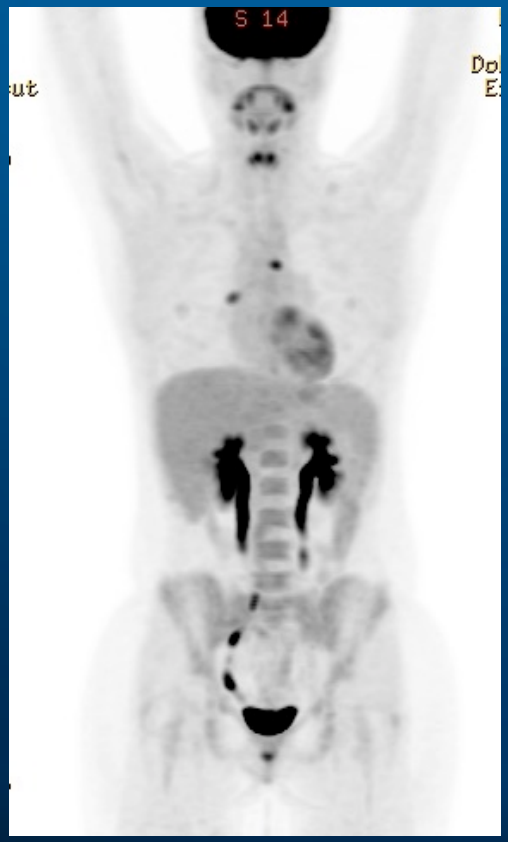
Case #10 (Dr Fanale)

- 7/30/2014: A 23 yo woman is diagnosed with Stage IIB classical Hodgkin lymphoma
- ABVD x 2 cycles. Refractory disease
- IGEV x 3 cycles. Refractory disease
- Brentuximab vedotin x 4 cycles
- 3/17/2015: Autologous stem cell transplant with BEAM
- 04/14-04/27/2015: Radiation therapy (21Gy total dose)
- 8/31/2015: Rresented to MDACC as new patient
- 9/23/2015: Pembrolizumab on protocol 2015-0082
  - Complete remission
- 5/24/2017: Currently status post cycle 30

Case #10 (Dr Fanale - Continued)

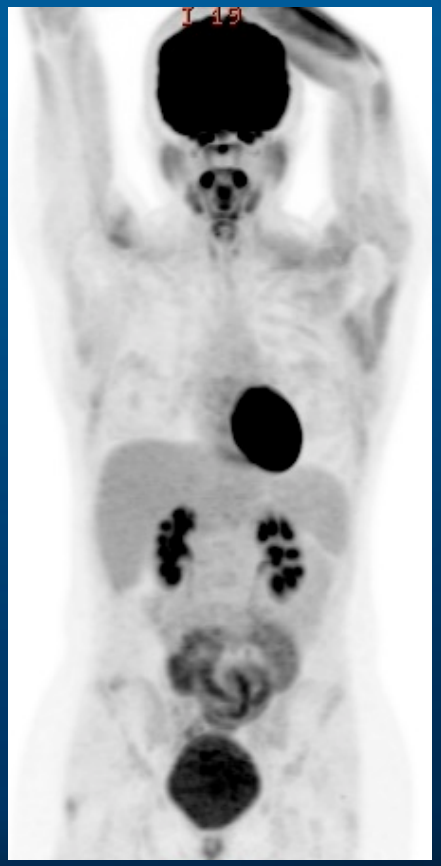
Baseline *PET/CT on 09/02/15*

Two new foci of FDG-avidity within the residual anterior mediastinal lymphadenopathy, most compatible with recurrent active lymphoma. No additional sites of concern for FDG-avid disease are identified



PET/CT on 05/02/17

After C28 of therapy showed continued complete remission with Five Point Lymphoma Score of 1



A Phase 1/2 Clinical Trial of Brentuximab-Vedotin and Bendamustine in Elderly Patients with Previously Untreated Advanced Hodgkin Lymphoma (HALO Study. NCT Identifier: 02467946): Preliminary Report

Gallamini A et al.
Proc ASH 2016;Abstract 4154.

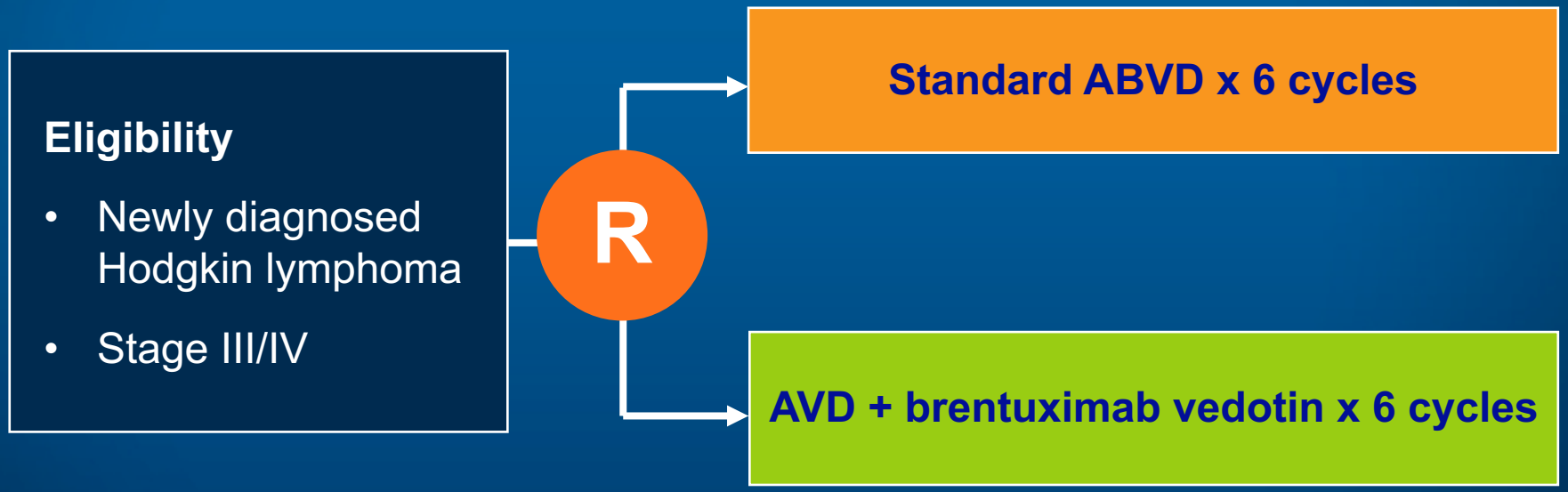
Preliminary Results

- Objective: Assess an attenuated combination schedule of brentuximab vedotin (BV) and bendamustine in elderly patients with advanced-stage (IIB-IVB) HL
  - BV: 1.2 mg/kg D1 q3wk x 6
  - Bendamustine: 90 mg/m^2 D1 and D2 q3wk x 6
- N = 14
- Grade 3/4 AEs: Lymphopenia, neutropenia, thrombocytopenia, pulmonary embolism, CMV reactivation, fever, allergic reaction and rash
- CR in 9/9 evaluable patients
  - No data yet on 5 remaining patients

Gallamini A et al. *Proc ASH* 2016;Abstract 4154.

ECHELON-1 Phase III Schema

Target Accrual: 1,334



Primary Endpoint: Modified progression-free survival

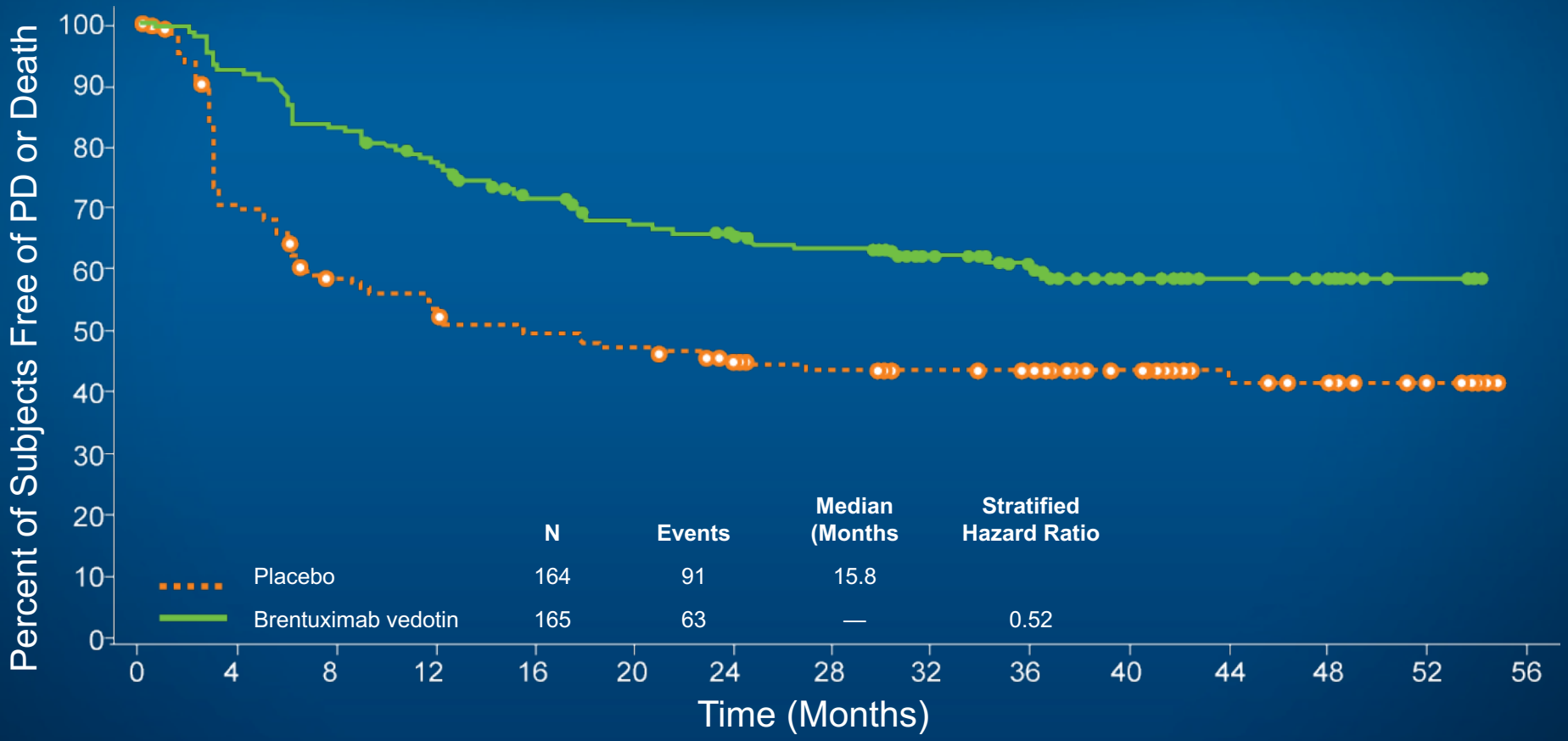
Clinicaltrials.gov, June 3, 2017 (NCT01712490)

Updated Efficacy and Safety Data from the AETHERA Trial of Consolidation with Brentuximab Vedotin After Autologous Stem Cell Transplant (ASCT) in Hodgkin Lymphoma Patients at High Risk of Relapse

Sweetenham JW et al

Biol Blood Marrow Transplant 2016:S23.

AETHERA: PFS per Investigator
(Approximately 3 years after the last randomization)



No additional secondary malignancies have been observed and most patients experienced resolution of peripheral neuropathy symptoms

Sweetenham JW et al. *Biol Blood Marrow Transplant* 2016:S23.

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PD-L1 and *PD-L2* Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome

Margaretha G.M. Roemer, Ranjana H. Advani, Azra H. Ligon, Yasodha Natkunam, Robert A. Redd, Heather Homer, Courtney F. Connelly, Heather H. Sun, Sarah E. Daadi, Gordon J. Freeman, Philippe Armand, Bjoern Chapuy, Daphne de Jong, Richard T. Hoppe, Donna S. Neuberg, Scott J. Rodig, and Margaret A. Shipp

Methods and Key Findings

- FISH was used to evaluate PD-L1 and PD-L2 alterations in 108 biopsy specimens from patients with newly diagnosed cHL who received the Stanford V regimen and had long-term follow-up
- 97% had concordant alterations of the PD-L1 and PD-L2 loci
  - Polysomy = 5%
  - Copy gain = 56%
  - Amplification = 36%
- There was an association between PD-L1 protein expression and relative genetic alterations
- The near-uniform alterations of PD-L1/PD-L2 loci likely explain the remarkable activity of PD-1 blockade in cHL
- PFS was significantly shorter for patients with 9p24.1 amplification
  - Increased incidence of 9p24.1 amplification in advanced-stage cH

Roemer MGM et al. *J Clin Oncol* 2016;34:2690-7.

Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial

Anas Younes, Armando Santoro, Margaret Shipp, Pier Luigi Zinzani, John M Timmerman, Stephen Ansell, Philippe Armand, Michelle Fanale, Voravit Ratanatharathorn, John Kuruvilla, Jonathon B Cohen, Graham Collins, Kerry J Savage, Marek Trneny, Kazunobu Kato, Benedetto Farsaci, Susan M Parker, Scott Rodig, Margaretha G M Roemer, Azra H Ligon, Andreas Engert

Lancet Oncol 2016;17:1283-94.

CheckMate 205: A Phase II Trial of Nivolumab in cHL

	Survival (by independent review)
Six-month PFS	76.9%
Six-month OS	98.7%

Younes A et al. *Lancet Oncol* 2016;17(9):1283-94.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

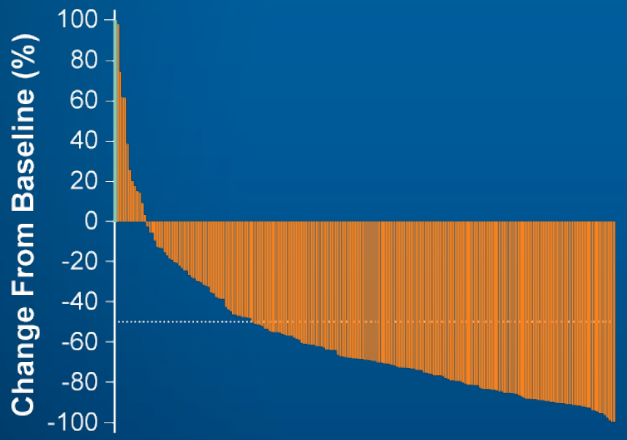
Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma

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

April 25, 2017;[Epub ahead of print]

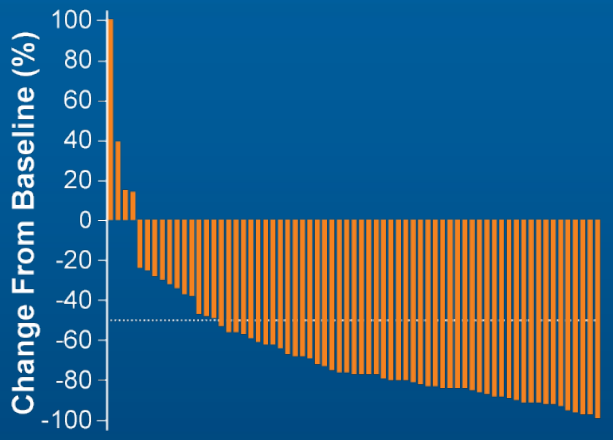
KEYNOTE-087: Decrease in Tumor Burden from Baseline and Response by Cohort

Cohort 1: Progression after ASCT and BV (n = 69)



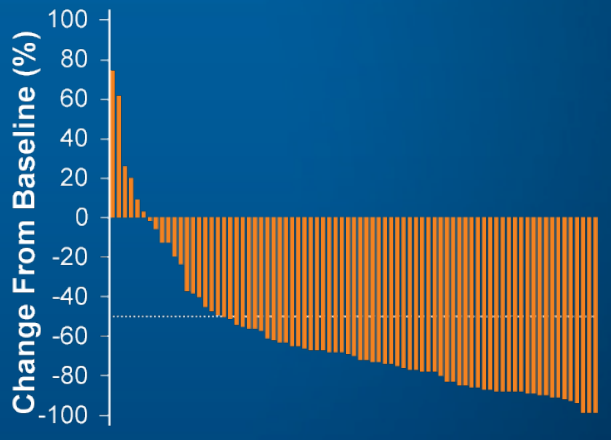
ORR = 74%
CR = 22%

Cohort 2: Progression after salvage chemo and BV (n = 81)



ORR = 64%
CR = 25%

Cohort 3: Progression after ASCT (n = 60)



ORR = 70%
CR = 20%

All cohorts: 6-mo OS = 99.5%, 6-mo PFS = 72.4%

Chen R et al. *J Clin Oncol* 2017;[Epub ahead of print].

Published Ahead of Print on June 27, 2016 as 10.1200/JCO.2016.67.3467
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.67.3467

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

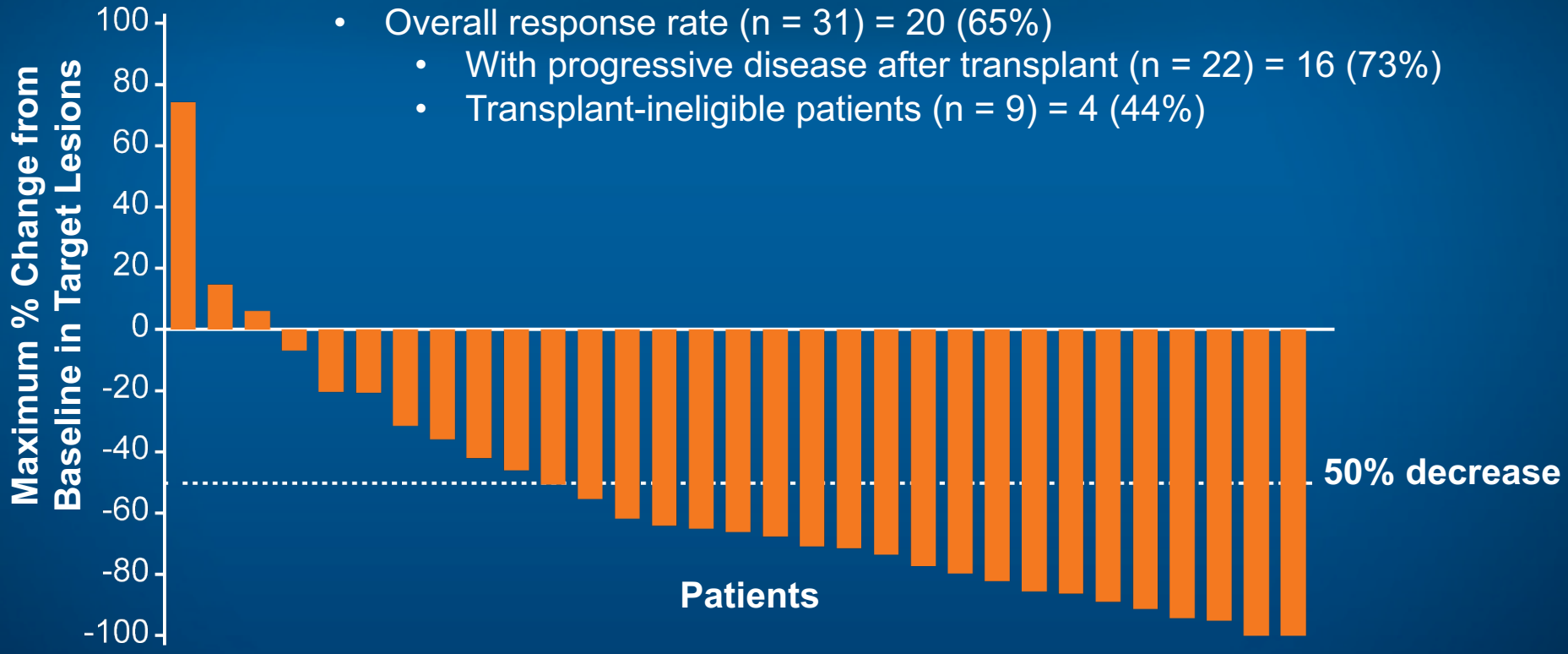
Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure

Philippe Armand, Margaret A. Shipp, Vincent Ribrag, Jean-Marie Michot, Pier Luigi Zinzani, John Kuruvilla, Ellen S. Snyder, Alejandro D. Ricart, Arun Balakumaran, Shelonitda Rose, and Craig H. Moskowitz

Armand P et al. *J Clin Oncol* 2016;[Epub ahead of print].

KEYNOTE-013: Efficacy of Pembrolizumab in Relapsed/Refractory cHL

- Overall response rate (n = 31) = 20 (65%)
  - With progressive disease after transplant (n = 22) = 16 (73%)
  - Transplant-ineligible patients (n = 9) = 4 (44%)



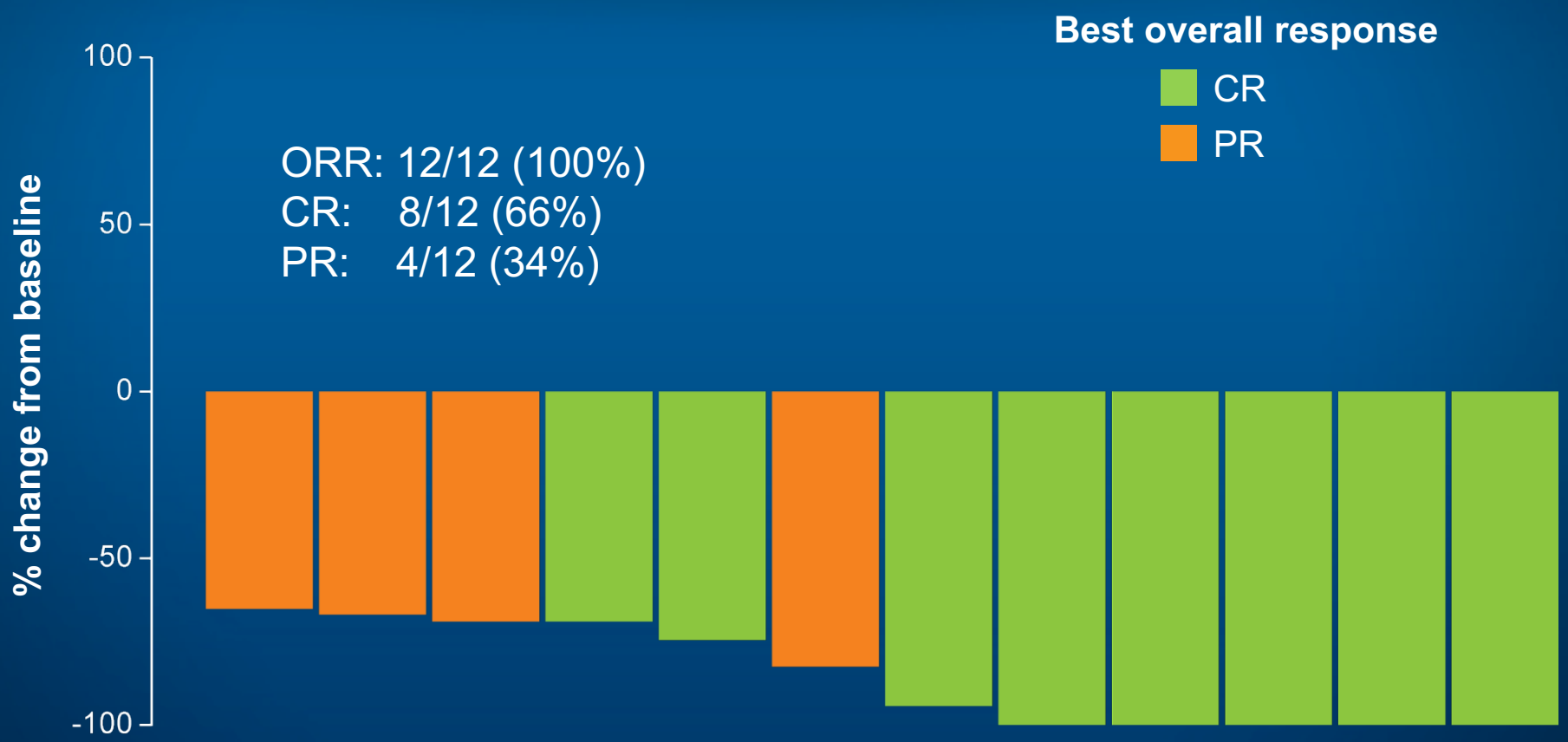
Survival (n = 31)	At 24 weeks	At 52 weeks
PFS	69%	46%
OS	100%	Not reported

Armand P et al. *J Clin Oncol* 2016;[Epub ahead of print].

Safety and Efficacy of the Combination of Brentuximab Vedotin and Nivolumab (Arms D-F) in Relapsed and Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412)

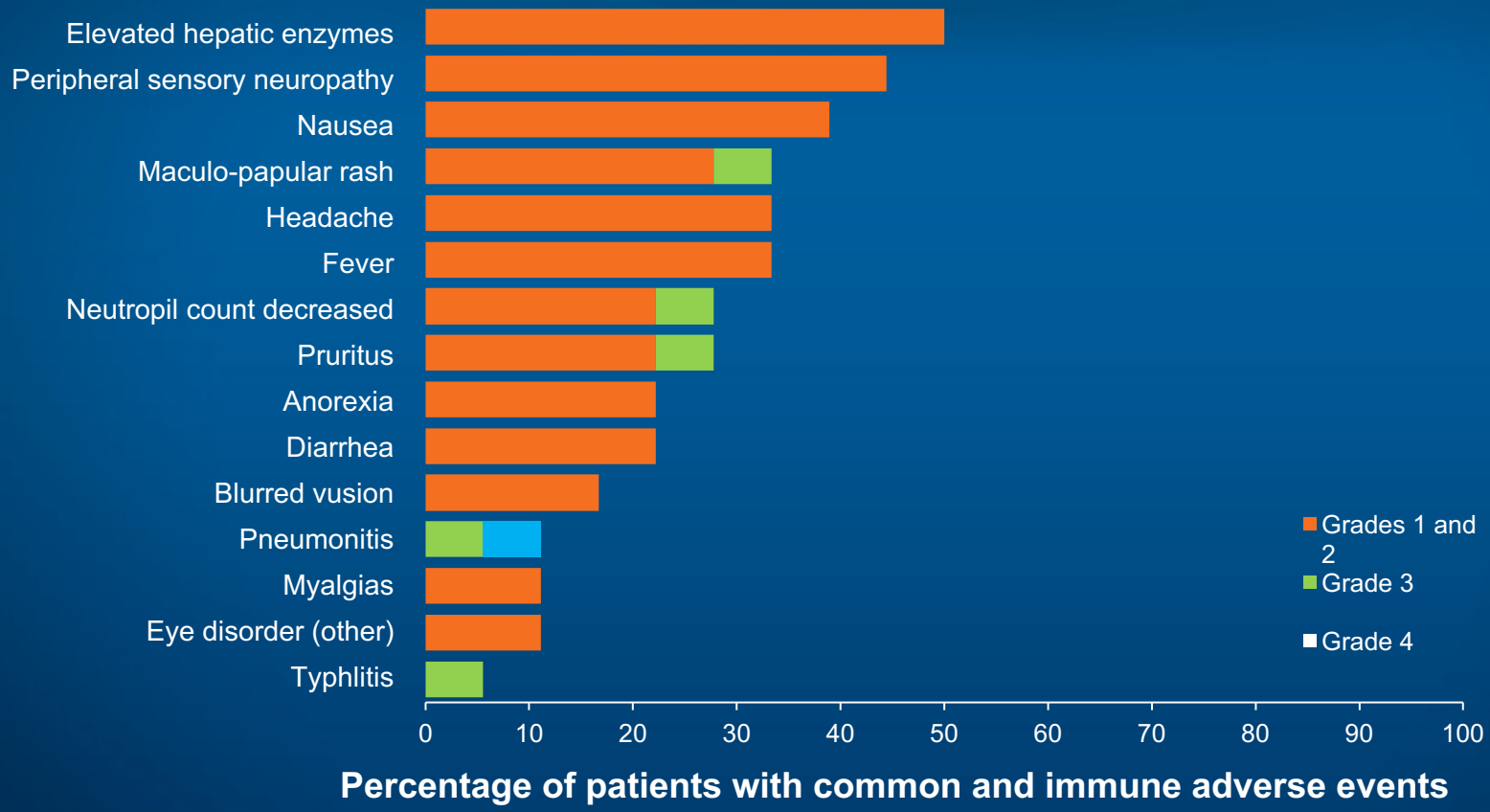
Diefenbach CS et al.
Proc ASH 2016;Abstract 1106.

Response and Tumor Reduction from Baseline



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

Common and Immune-Related Adverse Events



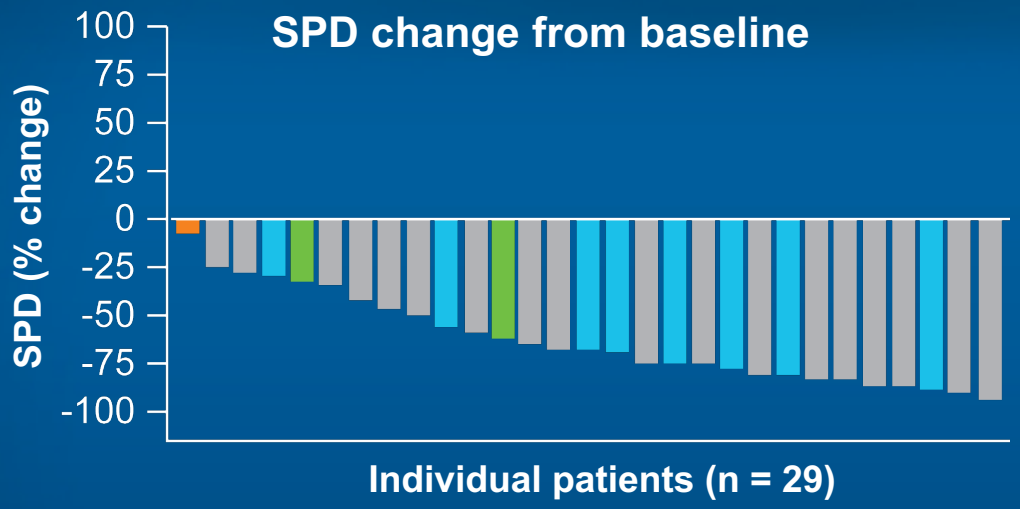
- Elevated hepatic enzymes most common: transient, primarily cycle 1, no impact on treatment
- Peripheral sensory neuropathy common in BV re-treatment patients
- 1 Grade 3 and 1 Grade 5 episode of pneumonitis

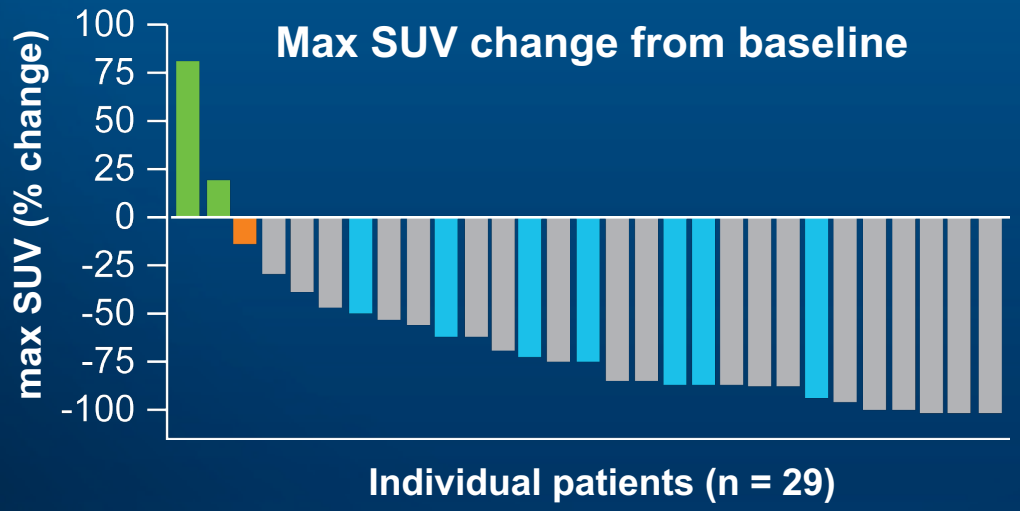
Diefenbach CS et al. *Proc ASH* 2016;Abstract 1106.

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

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

Tumor Response per Investigator





ORR: 26/29 (90%)

CR: 18/29 (62%)

SPD = sum of the product of the greatest diameters

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

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

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Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

Research To Practice®

Diffuse Large B-Cell Lymphoma

Research
To Practice®

Case #11 (Dr Ansell)

- A 55 yo man is diagnosed with ABC-type stage IIIA DLBCL
  - R-CHOP but progressed on therapy
- Repeat biopsy: Same histology
  - RICE x 2 but progressed
- Treated with CAR T-cells after fludarabine + cyclophosphamide conditioning
  - Cytokine release syndrome and neurotoxicity requiring tocilizumab and steroids as well as an ICU admission
  - Metabolic CR lasting 9 months

Obinutuzumab or Rituximab Plus CHOP in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma: Final Results from an Open-Label, Randomized Phase 3 Study (GOYA)

Vitolo U et al.
Proc ASH 2016;Abstract 470.

GOYA: Progression-Free Survival (PFS) (Investigator Assessed)

	R-CHOP (n = 712)	O-CHOP (n = 706)
1-year PFS	79.8%	81.6%
2-year PFS	71.3%	73.4%
3-year PFS	66.9%	69.6%
Hazard ratio (stratified *p*-value)	0.92 (0.3868)	

Median follow-up: 29 months

- In a prespecified subgroup analysis of investigator-assessed PFS, a stratified HR of 0.72 in favor of O-CHOP over R-CHOP was determined for patients with germinal center B-cell (GCB) DLBCL (3-year PFS: 79% vs. 70%).

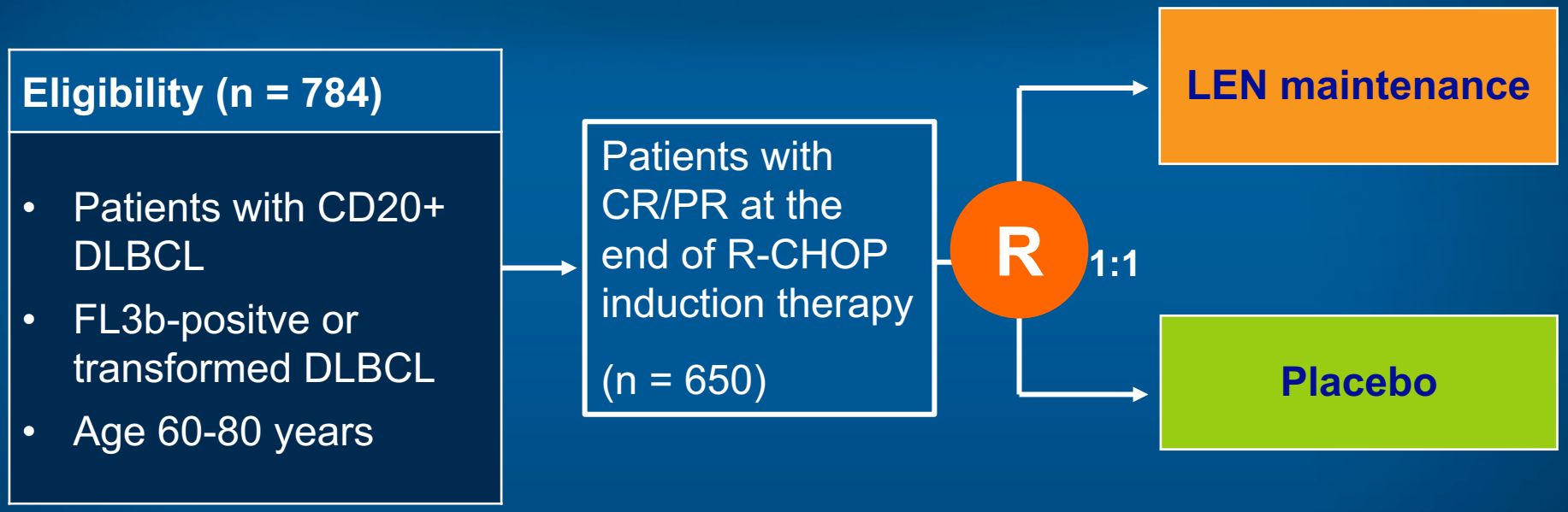
Vitolo U et al. *Proc ASH* 2016;Abstract 470.

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

J Clin Oncol 2017;[Epub ahead of print].

REMARC: Phase III Trial Design and Results



PFS	LEN (n = 323)	Placebo (n = 327)	HR	*p*-value
Median PFS	NR	58.9 mo	0.708	0.01
Conversion rate	**n = 69**	**n = 83**	**HR**	***p*-value**
PR → CR conversion	23 (33%)	24 (29%)	NR	0.56

Thieblemont C et al. *J Clin Oncol* 2017;[Epub ahead of print].

REMARC: Select Adverse Events (AEs)

Grade 3/4 AE	LEN (n = 322)	Placebo (n = 323)
Neutropenia	56%	22%
Infections	8%	6%
Cutaneous reaction	5%	1%
Thrombocytopenia	3%	1%

- Secondary primary malignancies occurred in 32 patients receiving LEN and in 41 patients on placebo

Thieblemont C et al. *J Clin Oncol* 2017;[Epub ahead of print].

ROBUST: A Phase III Trial of Lenalidomide or Placebo with R-CHOP for Previously Untreated Activated B-Cell (ABC)-Type DLBCL

Target accrual: 560

- Previously untreated DLBCL
- Activated B-cell type
- ECOG PS 0-2

R

R-CHOP + Lenalidomide

R-CHOP + Placebo

Primary study outcome: Progression-free survival
Select secondary outcomes: Overall survival, complete response rate, duration of response

www.clinicaltrials.gov. Accessed May 26, 2017. (NCT02285062)

Safety & 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]

Blood 2017;[Epub ahead of print].

KEYNOTE-013: Response

Response	Evaluable patients (n = 17)
ORR	7 (41%)
Complete response	2 (12%)
Partial response	5 (29%)
Stable disease	6 (35%)

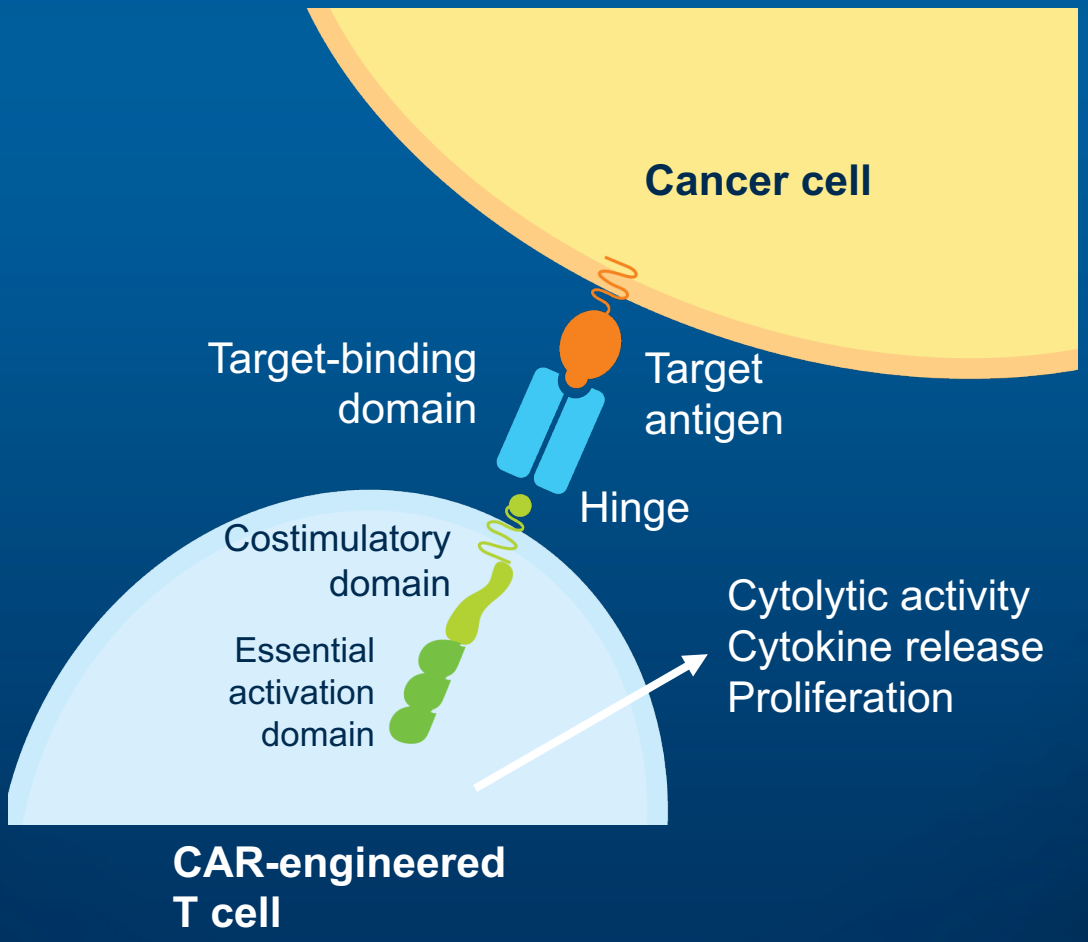
- Median follow-up = 11.3 mo
- Median DoR = not reached, but ranged from 2.4+ to 22.5+ mo
- Overall, 81% (13/16) of evaluable patients had target lesion reductions
- 2 patients received pembrolizumab for the maximum 2 y and remain in remission

Zinzani PL et al. *Blood* 2017;[Epub ahead of print].

Primary Results from ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-cel; KTE-C19) in Patients with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)

Locke FL et al
Proc AACR 2017;Abstract CT019.

Chimeric Antigen Receptor



http://kitepharma.com/technology/

ZUMA-1: Overall Response Rate (ORR) (Primary Endpoint)

	ZUMA-1 Phase II (modified ITT population)					
	DLBCL (n = 77)		TFL/PMBCL (n = 24)		Combined* (N = 101)	
	ORR	CR	ORR	CR	ORR	CR
Month 6	36%	31%	54%	50%	41%	36%
Ongoing†	36%	31%	67%	63%	44%	39%

*$p < 0.0001$ (exact binomial test comparing observed ORR to a historical control assumption of 20%)

† Median follow-up: 8.7 months

Six-month OS: 80%

Locke FL et al. *Proc AACR* 2017;Abstract CT019.

ZUMA-1: Most Frequent Grade ≥3 Treatment-Emergent AEs

Grade ≥3 adverse event	N = 101
Anemia	43%
Neutropenia	39%
Neutrophil count decrease	32%
Febrile neutropenia	31%
While blood cell count decrease	29%
Thrombocytopenia	24%
Encephalopathy	21%
Lymphocyte count decrease	20%

Locke FL et al. *Proc AACR* 2017;Abstract CT019.

FDA Priority Review for KTE-C19 in Relapsed/Refractory NHL

- On May 26, 2017, KTE-C19 (axicabtagene ciloleucel) was granted Priority Review by the US Food and Drug Administration (FDA) for the treatment of patients who are ineligible for transplant with R/R NHL.
- Results of the Phase II ZUMA-1 trial (NCT02348216) form the basis of this Priority Review.

http://www.lymphomahub.com/medical-information/the-fda-grants-kte-c19-priority-review-for-the-treatment-of-transplant-ineligible-relapsedrefractory-non-hodgkin-lymphoma

AN EVENING WITH THE INVESTIGATORS

Perspectives on Key Questions and Emerging Research in the Management of Lymphoma and Multiple Myeloma

Sunday, June 4, 2017
7:00 PM – 9:30 PM
Chicago, Illinois

Faculty

Stephen M Ansell, MD, PhD
Michelle A Fanale, MD
Christopher Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Noopur Raje, MD
S Vincent Rajkumar, MD

Moderator

Neil Love, MD

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T-Cell Lymphoma

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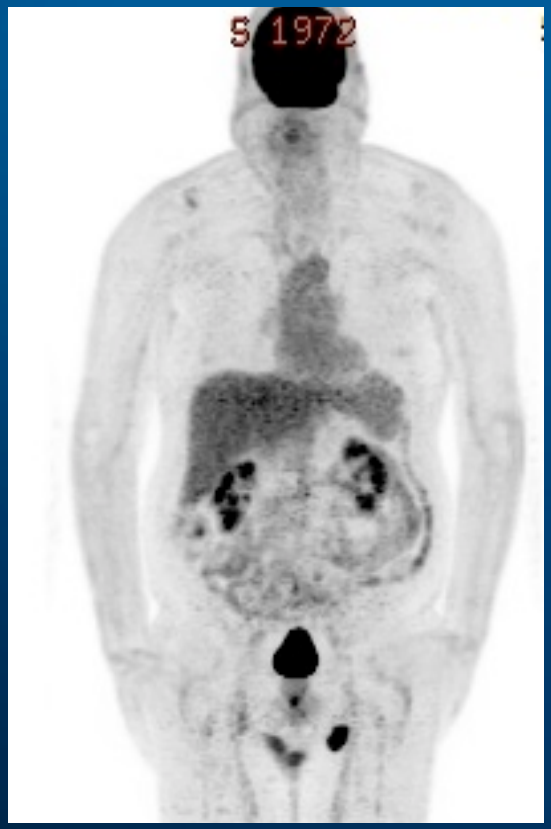
Case #12 (Dr Fanale)

- 9/26/2008: A 70 yo man is diagnosed with Stage IVA, CD30+ PTCL-NOS, with some features of angioimmunoblastic TCL
- R-CHOP x 6 cycles plus IT chemotherapy, complete remission
- 3/13/2009: ASCT with BEAM conditioning
- 2/25/2015: Biopsy proven relapse
- 3/19/15 – 3/20/2016: Brentuximab vedotin (induction followed by maintenance) x 16 cycles
- 5/13/2016: Resumed maintenance therapy again once per cycle and completed another 3 additional cycles on 07/20/16
- Observation
- 10/03/2016: PET/CT: Complete metabolic remission
- 04/21/2017: CT: Continued complete metabolic remission

Case #12 (Dr Fanale - Continued)

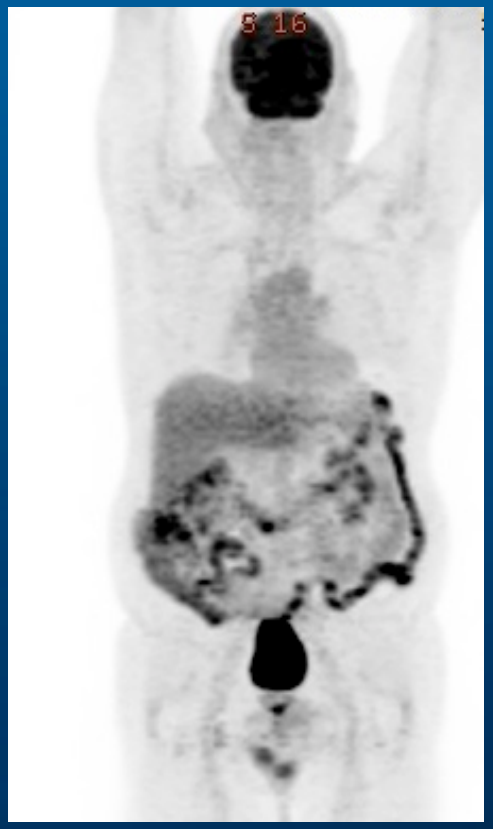
03/05/16 PET/CT

A 3.4 cm x 2.6 cm enlarged lymph node in the left groin is markedly FDG avid in keeping with lymphoma. There were no other sites of FDG avid disease



Repeat PET/CT on 6/05/16 after Cycle 3

Complete metabolic remission



Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients with CD30-Expressing Cutaneous T Cell Lymphoma versus Physician's Choice (Methotrexate or Bexarotene): The Phase 3 ALCANZA Study

Kim YH et al.
Proc ASH 2016;Abstract 182.

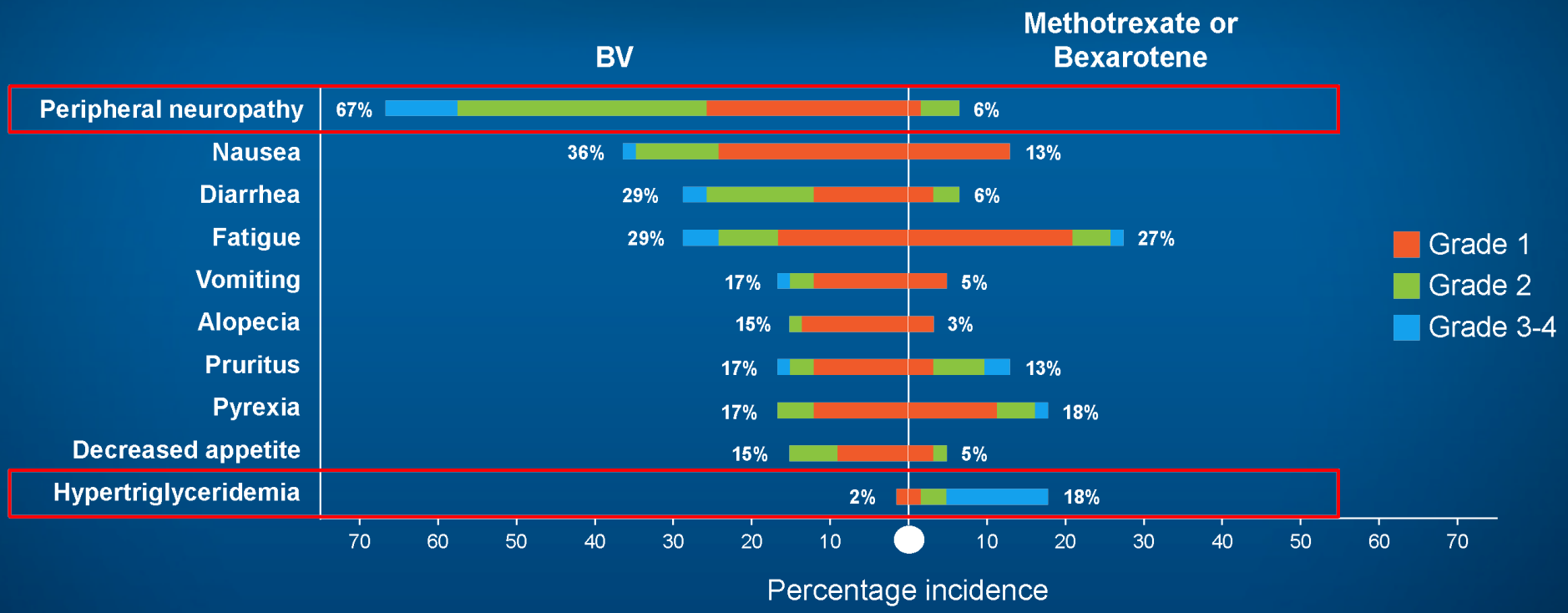
ALCANZA: Study Outcomes

Endpoint	Brentuximab vedotin N = 64	Physician's choice N = 64	Difference between arms	Statistical significance
Primary endpoint				
ORR4, n (%)	36 (56.3%)	8 (12.5%)	43.8%	$p < 0.0001$
Key secondary endpoints				
CR, n (%)	10 (15.6%)	1 (1.6%)	14.1%	$p = 0.0046^{adj}$
Median PFS, months	16.7	3.5	—	$p < 0.0001^{adj}$ HR = 0.270
Mean maximum reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9	$p < 0.0001^{adj}$

Adj = adjusted *p*-value; HR = hazard ratio

Kim YH et al. *Proc ASH* 2016;Abstract 182.

ALCANZA: Treatment-Emergent Adverse Events



No Grade 4 peripheral neuropathy was reported in the BV or physician's choice arm.

At last follow-up, 36/44 (82%) patients in the BV arm had experienced improvement or resolution of peripheral neuropathy.

With permission from Kim YH et al. *Proc ASH* 2016;Abstract 182.

The Pralatrexate – Romidepsin Doublet: A Well Tolerated and Highly Effective Combination for Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

Amengual JE et al.
Proc ASH 2016;Abstract 1824.

Primary and Secondary Study Objectives

Determination of maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) (Primary Study Objective):

- 3 DLTs recorded in cohort 4 (P 20 mg/m^2 & R 12 mg/m^2 given weekly x 2 Q21D) consisting of 2 Grade 3 oral mucositis and 1 Grade 4 sepsis.

- The QOW Q28D schedule had no mucositis at all dose levels.

- Patients dosed at the MTD (P 25 mg/m^2 & R 12 mg/m^2 QOW) did not experience any toxicities.

ORR (Secondary Study Objective)	
Parameter	**Number**
Total number of patients (evaluable)	29 (23)
ORR (all)	13/23 (57%)
ORR non-TCL	3/9 (33%)
ORR T-cell	**10/14 (71%)**
T-cell CR	**4/10 (40%)**
T-cell PR	**6/10 (60%)**

Amengual JE et al. *Proc ASH* 2016;Abstract 1824.

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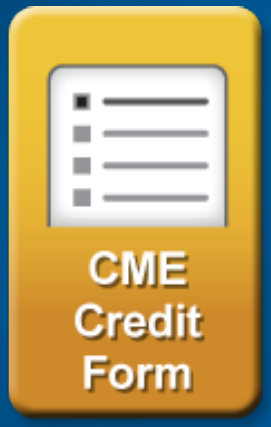

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