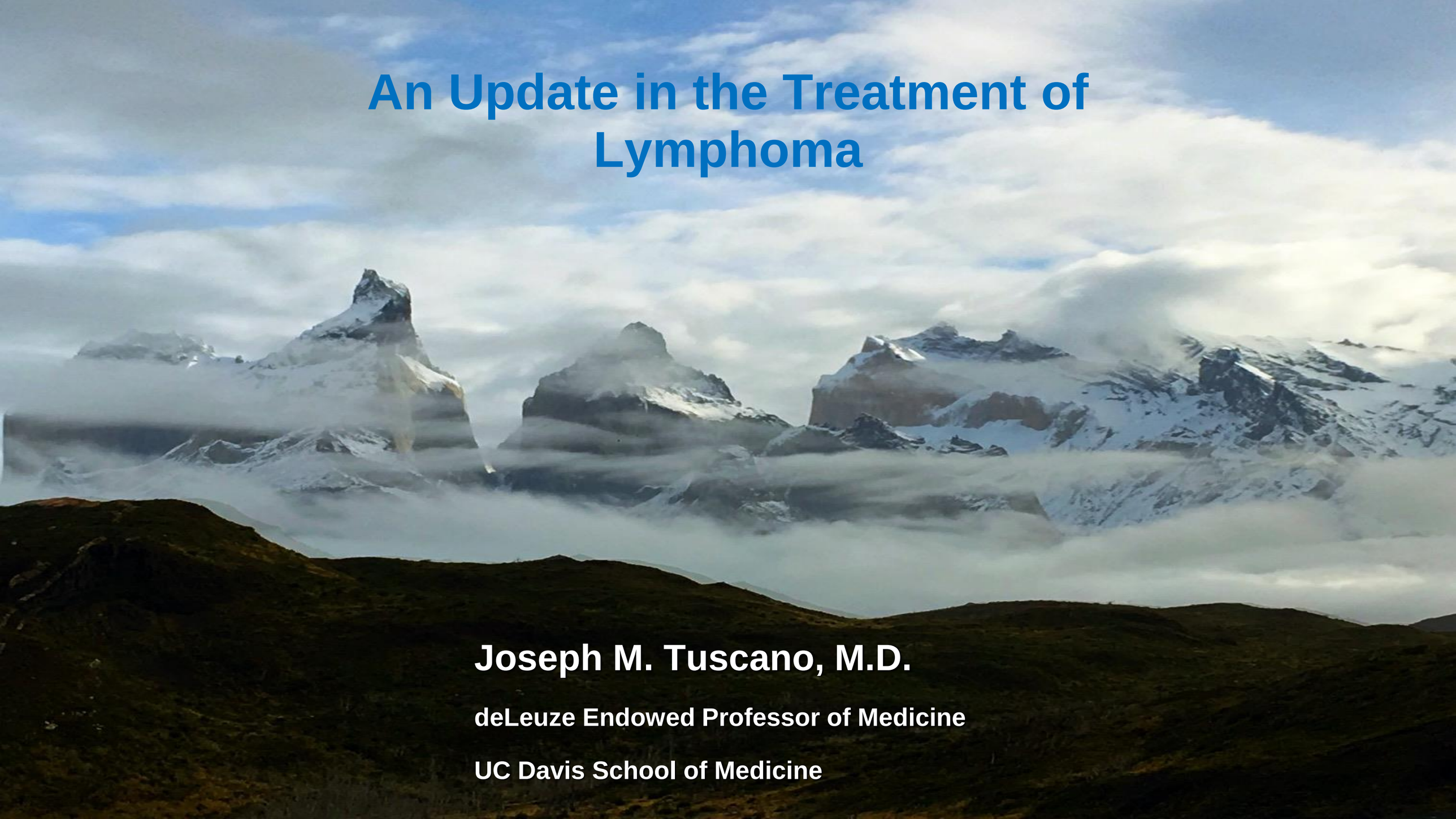

An Update in the Treatment of Lymphoma

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UC Davis School of Medicine

DLBCL

Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma

Frederick Lundry Locke, Armin Ghobadi, Caron A. Jacobson, Eric D. Jacobsen, David Bernard Miklos, Lazaros J. Lekakis, Ira Braunschweig, Olalekan O. Oluwole, Yi Lin, Tanya Siddiqi, Abhinav Deol, Patrick Michael Reagan, Umar Farooq, Adrian Bot, Yizhou Jiang, John M. Rossi, Allen Xue, William Y. Go, Sattva Swarup Neelapu

ASCO 2018

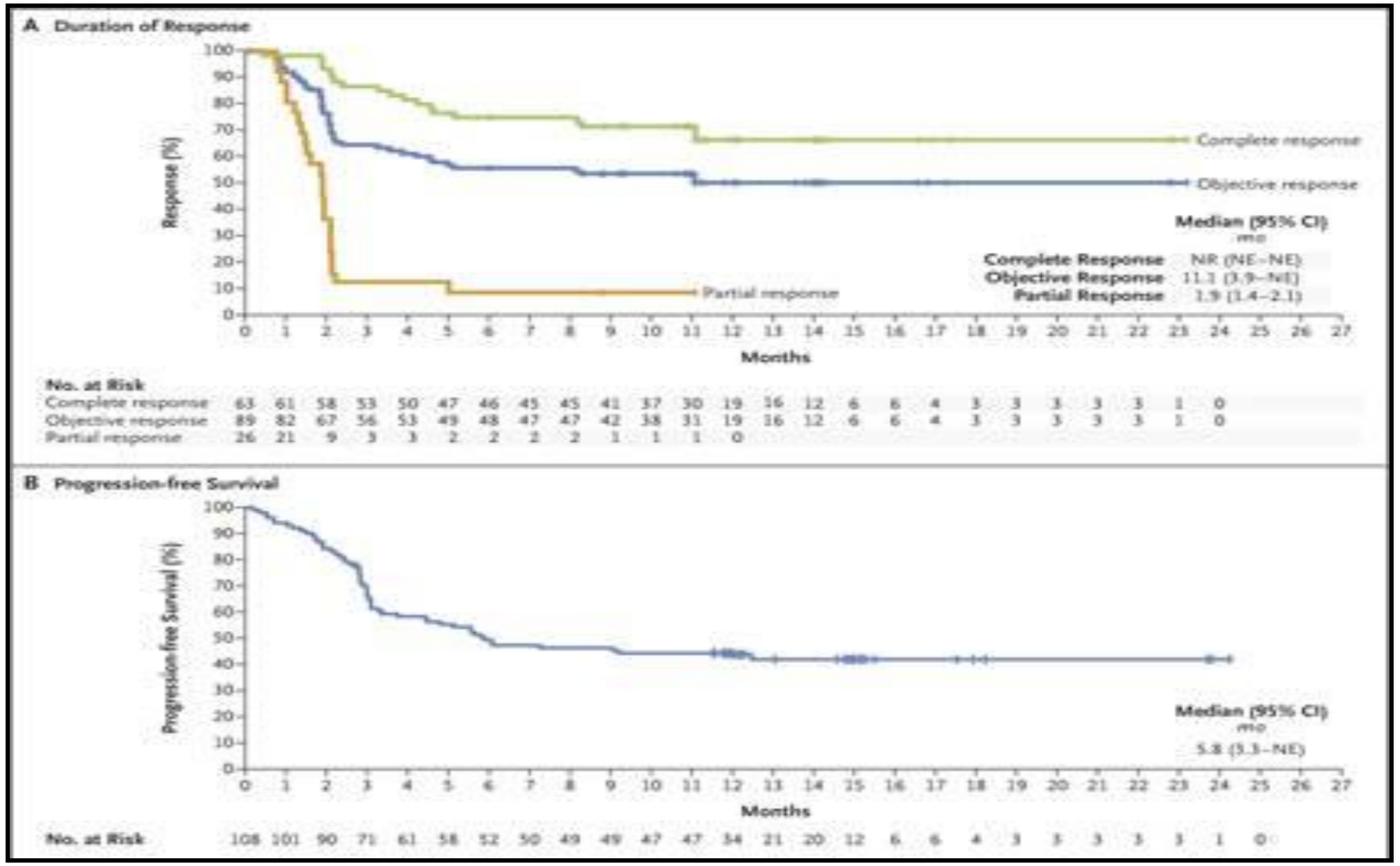
Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma

- **Pts with refractory large B cell lymphoma received 2 × 10^6 CAR T cells/kg after low-dose conditioning (Neelapu & Locke et al. *NEJM.* 2017).**
- **Best objective response rates (BOR) were analyzed locally by investigators (local) and centrally by independent review committee**
- **101 patients, median f/u 15.1 mo**

Data-cut; median f/u, mos N = 101	BOR, n (%)				ORR Concordance, %
	Local		IRC		
	ORR	CR	ORR	CR	
PA; 8.7	83 (82)	55 (54)	72 (71)	52 (51)	77
YESCARTA USPI; 11.6	84 (83)	55 (54)	73 (72)	52 (51)	79
LTFU; 15.1	84 (83)	59 (58)	73 (72)	52 (51)	79

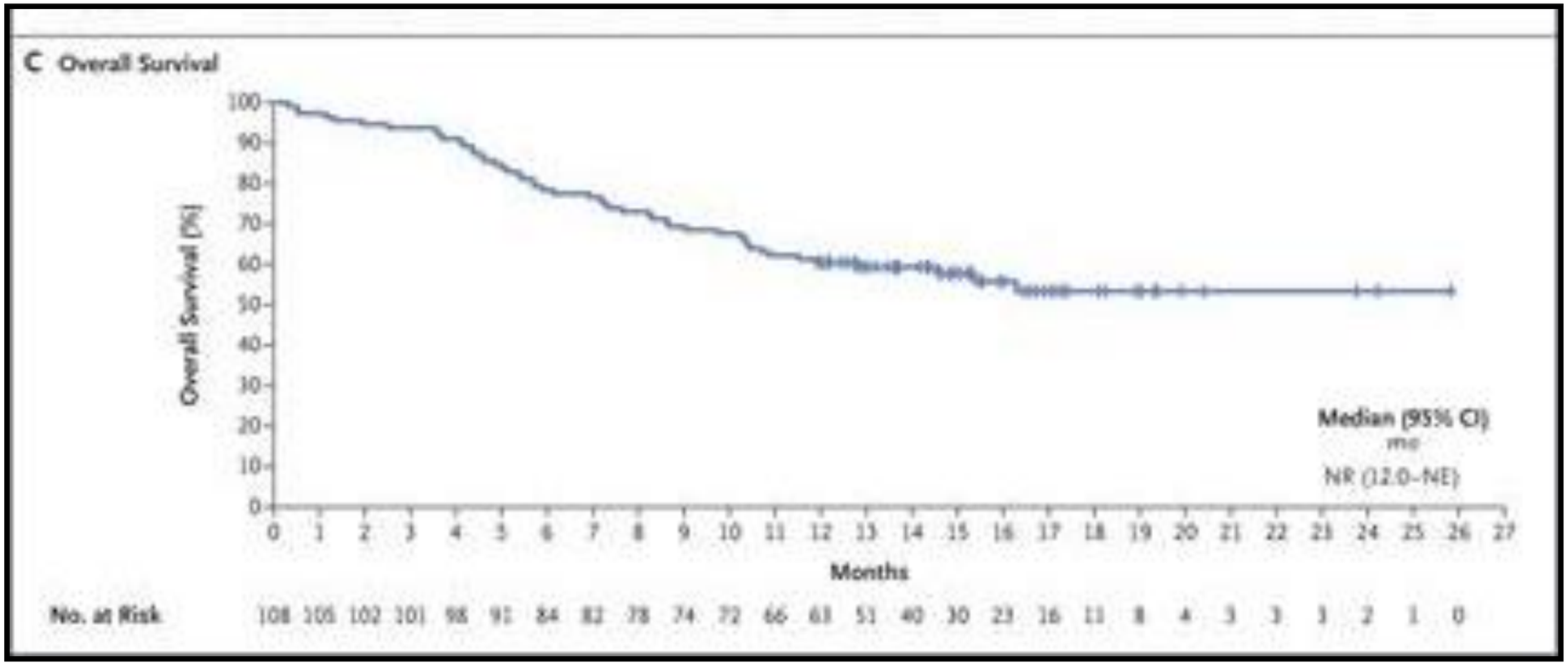
Lundry et al ASCO 2018

Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma



Lundry et al ASCO 2018

Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma



Lundry et al ASCO 2018

Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma

Conclusions:

- Treatment with axi-cel induces high response rates in pts with refractory large B cell lymphoma.
- CR rates increased through the LTFU, suggesting that responses deepen over time
- Patients with PR can eventually achieve CR as late as a year post-infusion.
- ORR at 3 mo may be prognostic for prolonged PFS

Lundry et al ASCO 2018

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

Jeremy S. Abramson,[1] Leo I. Gordon,[2] M. Lia Palomba,[3] Matthew Lunning,[4] Jon Arnason,[5] Andres Forero-Torres,[6] Michael Wang,[7] David Maloney,[8] Alison Sehgal,[9] Charalambos Andreadis,[10] Enkhtsetseg Purev,[11] Scott Solomon,[12] Nilanjan Ghosh,[13] Tina Albertson,[14] Benhuai Xie,[14] Jacob Garcia,[14] Tanya Siddiqi[15]

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PRESENTED BY: Jeremy S. Abramson

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Relapsed and Refractory Aggressive B-NHL Associated with High Unmet Need and Poor Outcomes

- Relapsed and refractory aggressive B-cell non-Hodgkin lymphoma (B-NHL) has a very poor prognosis
  - ORR < 40% and CR rate < 20% to historically available therapies[1]
  - High-risk DLBCL features predicting poor overall survival include: never achieved a CR, never received ASCT, refractory to ≥ second-line therapy, primary refractory disease, ECOG PS 2[2]
- Lisocabtagene maraleucel (liso-cel; JCAR017) is a CD19-directed CAR T cell product comprising individually formulated $CD4^+$ and $CD8^+$ CAR T cell suspensions that are administered in a precise, flat dose of $CD4^+$ and $CD8^+$ CAR T cells
  - Liso-cel manufacturing controls contribute to the low variability in administered cell dose and in cell function[3]
  - 4-1BB costimulatory signaling domain provides predictable CAR T cell expansion[4]

ASCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate.

1. Crump et al. *Blood*, 2017.
2. Sommermeyer et al. *Leukemia*, 2016.
3. Ramsborg et al. ASH 2017 [abstr 4471].
4. Van de Neste et al. *Bone Marrow Transplant*, 2016.

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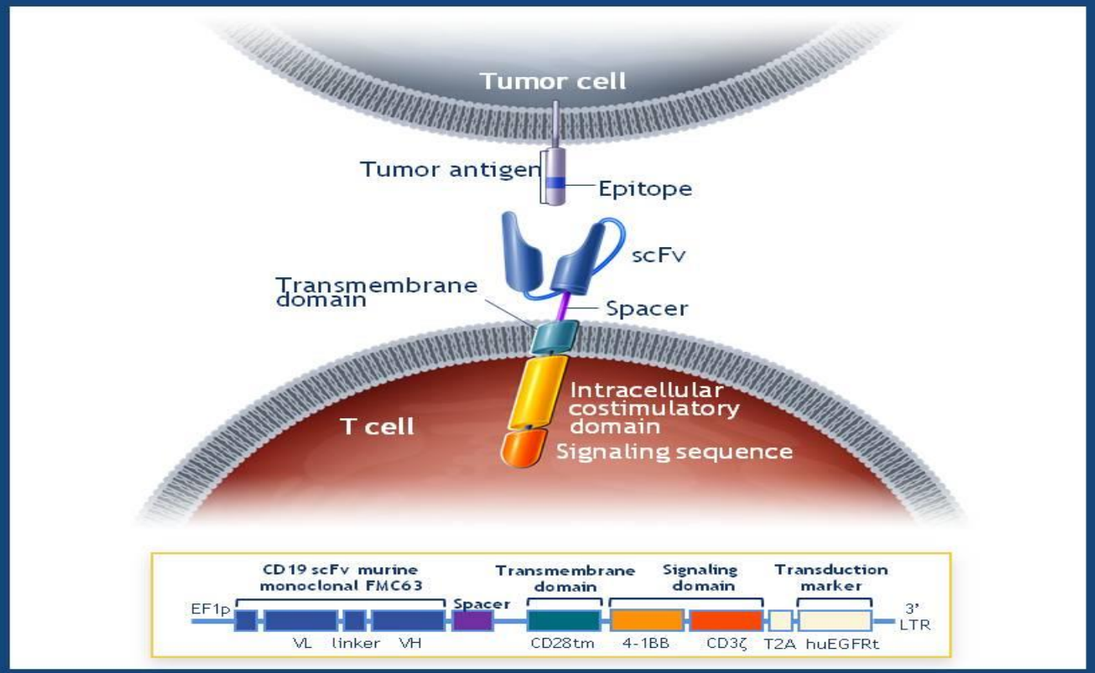
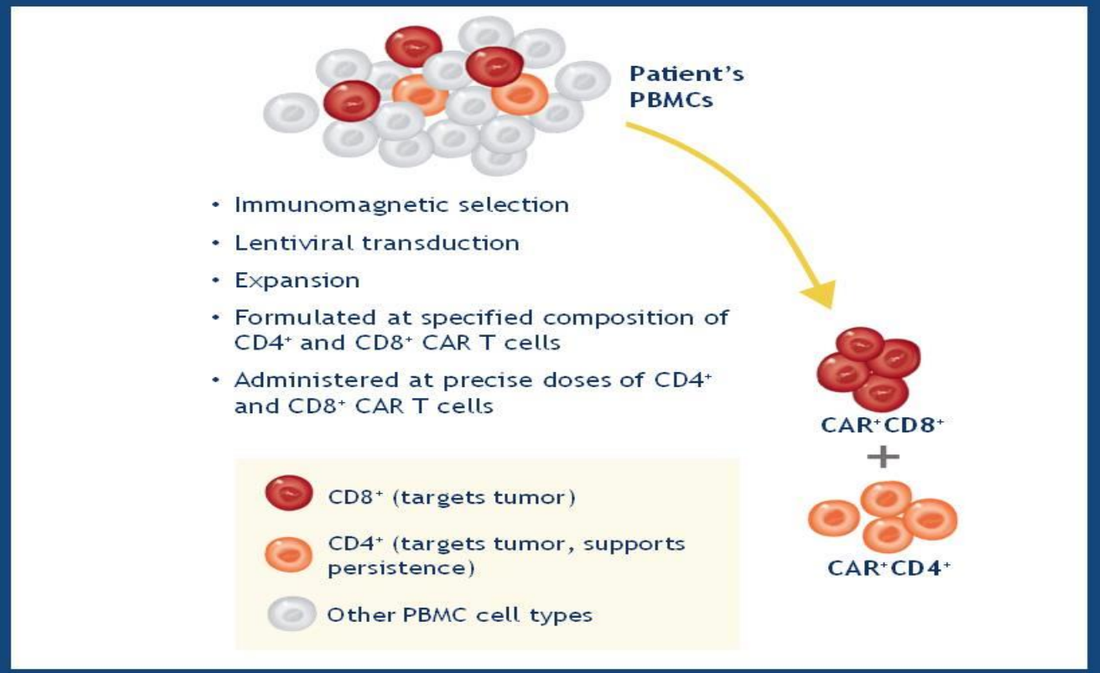
Lisocabtagene Maraleucel (liso-cel; JCAR017)
CD19-Directed Defined Cell Product





PBMC, peripheral blood mononuclear cell; scFv, single-chain variable fragment.

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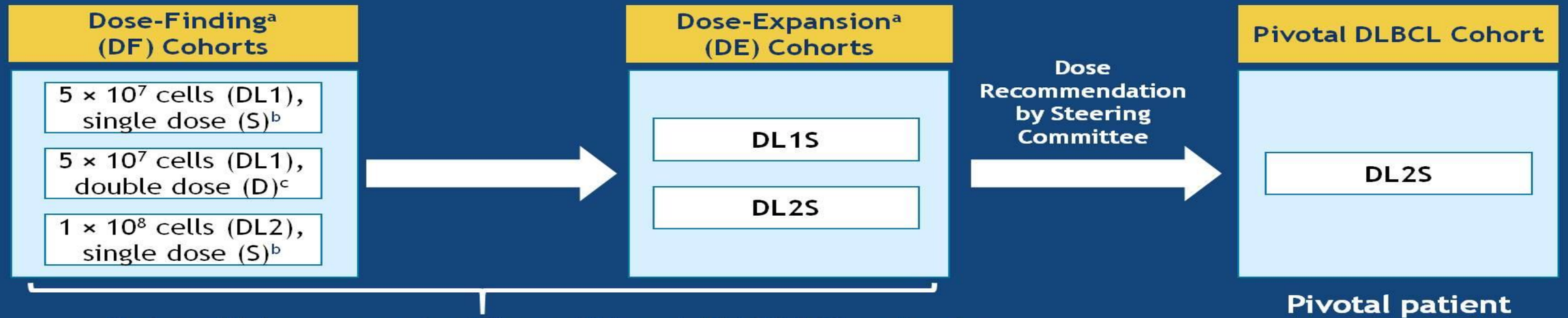
Multicenter, Seamless Design Pivotal Trial
(TRANSCEND NHL 001; NCT02631044)



- Data will be presented from DF and DE DLBCL cohorts
  - 102 patients treated (**FULL**)[d]
  - 73 patients treated in analysis set matching pivotal patient population (**CORE**)[e]

[a] Disease-specific dose-finding and dose-expansion cohorts enrolled (DLBCL and MCL).
[b] Administered on day 1.
[c] Administered on day 1 and day 14.
[d] DLBCL FULL cohort: DLBCL, NOS de novo and transformed from any indolent lymphoma, ECOG PS 0-2.
[e] DLBCL CORE cohort: DLBCL, NOS de novo and transformed from FL, ECOG PS 0-1, high-grade B-cell lymphoma.

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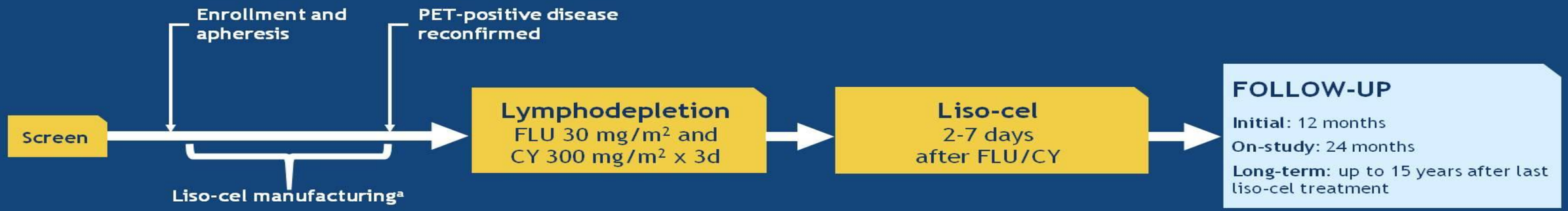
TRANSCEND NHL 001 (NCT02631044)



ENROLLMENT COHORTS

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

CORE
FULL

PATIENT ELIGIBILITY

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

CLL, chronic lymphocytic lymphoma; CNS, central nervous system; CY, cyclophosphamide; FLU, fludarabine; MZL, marginal zone lymphoma; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma.
[a] Therapy for disease control allowed.
[b] ECOG 2 and prior allogeneic HSCT excluded from pivotal cohort.

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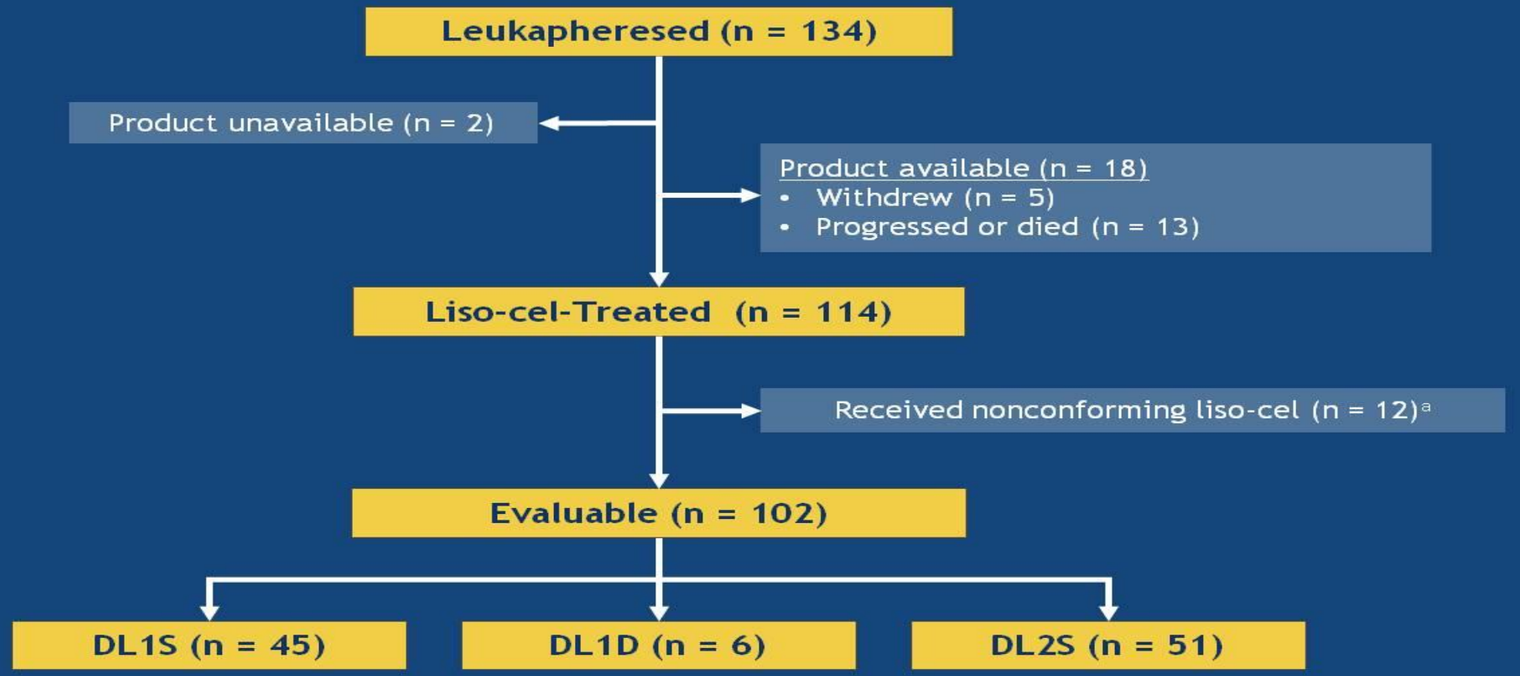
CONSORT Diagram: DLBCL Cohort



- Product available for 99% (132/134) of patients apheresed in DLBCL cohort
- Seven patients with MCL treated thus far with liso-cel at DL1S
- Eight patients in DF and DE cohorts treated in outpatient setting

[a] Nonconforming product has failed to meet specifications but is deemed safe to administer based on agreement among sponsor, FDA, principal investigator, and institutional review board.

Patient Characteristics: DLBCL Cohort

High-Risk Patient Population Enrolled

Characteristic	FULL (n = 102)	CORE (n = 73)
Median age (range), years	61 (20-82)	60 (20-82)
≥ 65 years, n (%)	37 (36)	24 (33)
B-NHL Subtype, n (%)		
DLBCL, NOS de novo	63 (62)	53 (73)
Transformed from FL (tFL)	23 (23)	20 (27)
Transformed from MZL (tMZL) /CLL (tCLL)	6 (6)/6 (6)	0
Follicular, grade 3B/PMBCL	1 (1)/3 (3)	0
Molecular Subtype, n (%)		
Double/triple hit[a]	19 (19)	16 (22)
Patient Characteristics, n (%)		
ECOG PS 0-1	93 (91)	73 (100)
IPI 3-5	43 (42)	26 (36)
CNS involvement	2 (2)	1 (1)
Chemorefractory[b]	71 (70)	49 (67)
Prior lines of therapy, median (range)	3 (1-8)	3 (2-8)
Never achieved CR	49 (48)	36 (49)
Any HSCT	41 (40)	28 (38)
Prior autologous	38 (37)	28 (38)
Prior allogeneic	5 (5)	0

HSCT, hematopoietic stem cell transplant; IPI, International Prognostic Index; SD, stable disease; WHO, World Health Organization.
[a] At trial initiation, included in DLBCL, NOS histology; based on most recent WHO criteria,[3] are now considered high-grade B-cell lymphoma, with *myc* and *bcl2* and/or *bcl6* rearrangements with DLBCL histology (double/triple hit).
[b] SD or PD to last chemo-containing regimen or relapse < 12 months after autologous SCT.

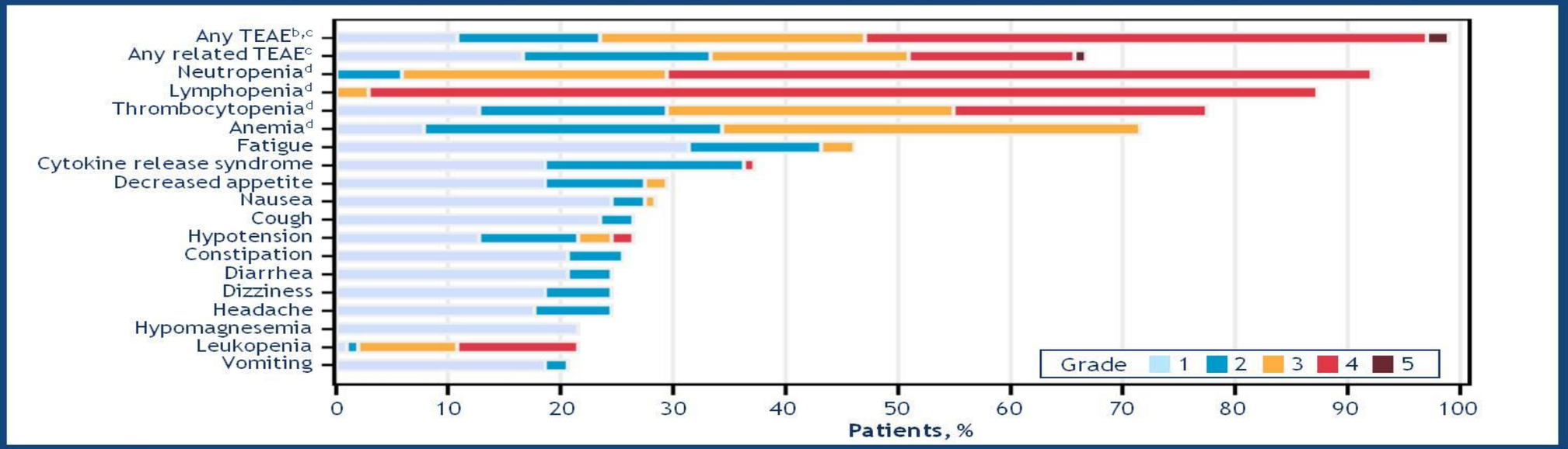
≈ 90% of treated patients (CORE or FULL) have at least 1 poor-risk disease feature predictive of short median OS (3-6 months)[1,2]

- Double/triple hit
- Primary refractory disease
- Refractory to ≥ second-line therapy
- Never in CR
- Never undergone ASCT
- ECOG PS 2

1 Crump et al. *Blood*, 2017.
2. Van de Neste et al. *Bone Marrow Transplant*, 2016.
3. Swerdlow et al. *Blood*, 2016.

TEAEs and Lab Abnormalities in DLBCL Cohort (FULL, N=102)

TEAEs and Laboratory Abnormalities Occurring in ≥ 20% of Patients[a]



TEAE, treatment-emergent adverse event.
[a] Data for 6 patients with MCL treated with conforming product at DL1 with at least 28 days of follow-up are not reported.
[b] One grade 5 AE of septic shock, unrelated to liso-cel, occurred in the setting of disease progression.
[c] One grade 5 AE of diffuse alveolar damage, investigator assessed as related to fludarabine, cyclophosphamide, and JCAR017, occurred on day 23 in a patient who refused mechanical ventilation for progressive respiratory failure while neutropenic on growth factors and broad-spectrum antibiotics and antifungals.
[d] Laboratory abnormalities.

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In CORE DLBCL Population, No Increase in CRS or NT at DL2

	FULL	CORE		
	All Dose Levels N = 102	All Dose Levels[a] n = 73	DL1S n = 33	DL2S n = 37
CRS[b], n (%)				
Any grade	38 (37)	27 (37)	14 (42)	11 (30)
Grade 1/2	37 (36)	26 (36)	13 (39)	11 (30)
Grade 3/4 (sCRS)	1 (1)	1 (1)	1 (3)	0
Neurotoxicity[c], n (%)				
Any grade	23 (23)	18 (25)	8 (24)	9 (24)
Grade 1/2	10 (10)	7 (10)	1 (3)	6 (16)
Grade 3/4 (sNT)	13 (13)	11 (15)	7 (21)	3 (8)
Any, n (%)				
CRS or NT	44 (43)	32 (44)	15 (45)	15 (41)
sCRS or sNT	13 (13)	11 (15)	7 (21)	3 (8)

- No deaths from CRS or NT
- In FULL, median time to onset of CRS was 5 days (range, 2-12 days) and NT was 10 days (range, 3-23 days)
- In FULL, 17% (n = 17) received tocilizumab and 21% (n = 21) received corticosteroids

CRS, cytokine release syndrome; NT, neurotoxicity; sCRS, serious CRS; sNT, serious NT.
[a] Three patients treated on DL1D had similar outcomes.
[b] Graded per Lee, et al. *Blood*, 2014.
[c] Graded per Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

High Response Rates in R/R DLBCL

Potential Dose Response Relationship in CORE Patient Population; DL2 Chosen for Pivotal Cohort

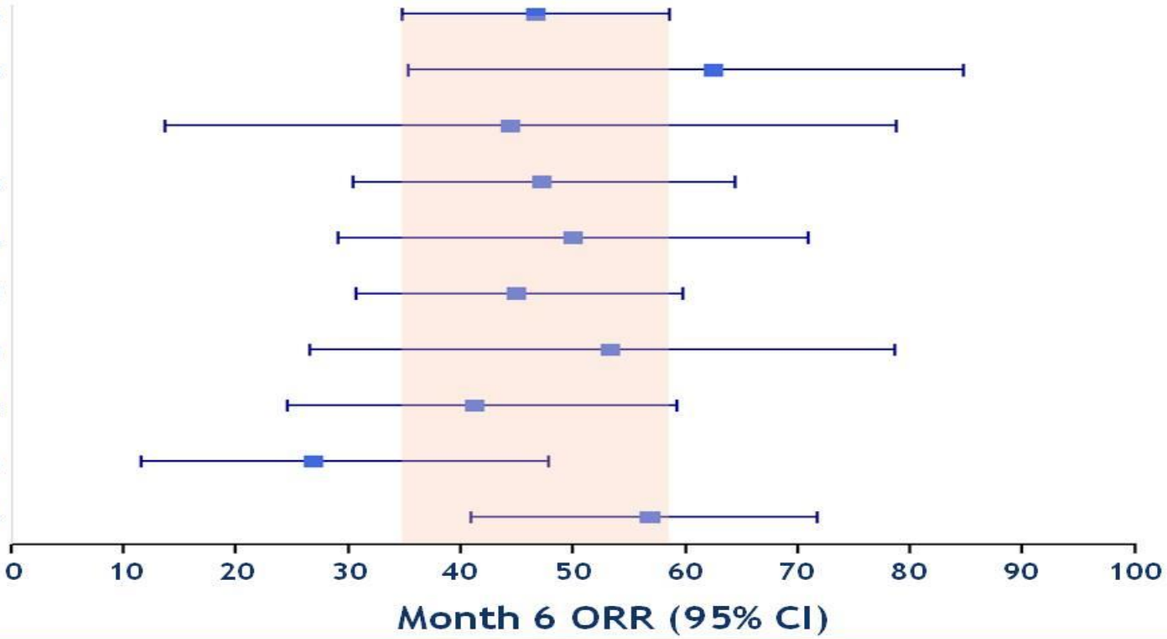
	FULL	CORE		
	All Dose Levels (n=102)	All Dose Levels[a] (n=73)	DL1S (n=33)	DL2S (n=37)
ORR (95% CI), %	75 (65-83)	80 (68-88)	79 (61-91)	78 (62-90)
CR (95% CI), %	55 (45-65)	59 (47-70)	55 (36-72)	62 (45-78)
3-mo ORR (95% CI), %	51 (41-61)	59 (47-70)	52 (34-69)	65 (48-80)
3-mo CR (95% CI), %	38 (29-48)	45 (34-57)	36 (20-55)	51 (34-68)
6-mo ORR (95% CI), %	40 (31-50)	47 (35-59)	42 (26-61)	49 (32-66)
6-mo CR (95% CI), %	34 (25-44)	41 (30-53)	33 (18-52)	46 (30-63)

Baseline high tumor burden well balanced between DL1 and DL2 (≈ 1/3)[b]

[a] Three patients treated on DL1D had similar outcomes.
[b] Defined as sum of the products of diameters (SPD) > 50 cm^2.

High Durable ORR in Poor-Risk DLBCL Subgroups

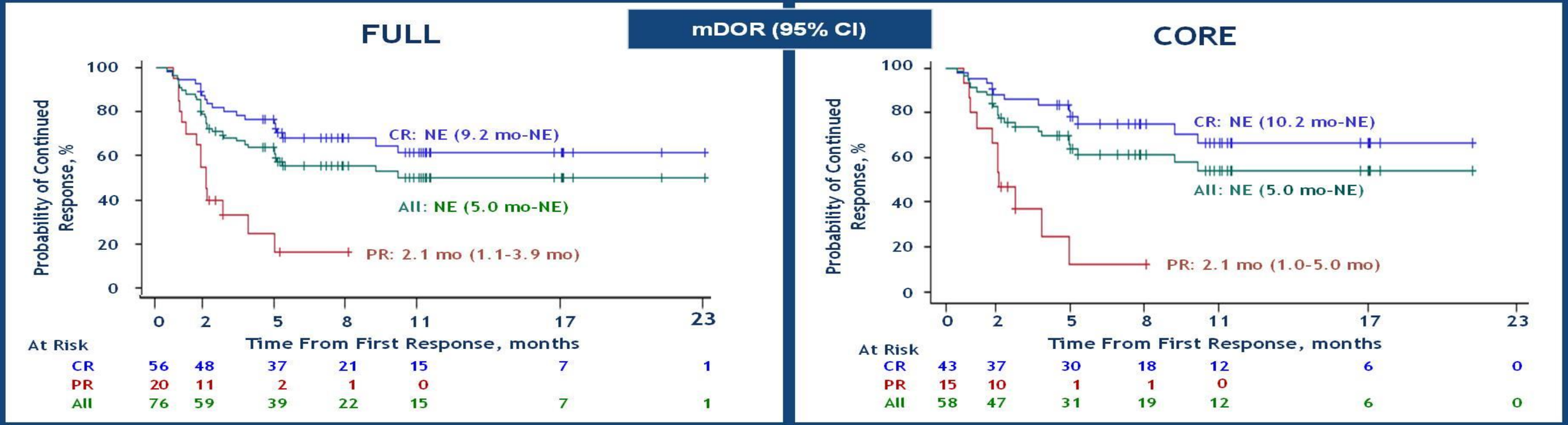
Population	ORR (95% CI)	n
CORE patient population[a]	46.6 (34.8-58.6)	73
Double/triple hit	62.5 (35.4-84.8)	16
Double expressor	44.4 (13.7-78.8)	9
Never in CR	47.2 (30.4-64.5)	36
Chemosensitive	50 (29.1-70.9)	24
Chemorefractory	44.9 (30.7-59.8)	49
Relapse < 12 mo from ASCT	53.3 (26.6-78.7)	15
SD/PD to last chemotherapy	41.2 (24.6-59.3)	34
IPI 3-5	26.9 (11.6-47.8)	26
IPI 0-2	56.8 (41-71.7)	44



[a] Includes all DLBCL patients treated at all dose levels in CORE.

Durability of Response (DOR)

DOR Encouraging in High-Risk DLBCL Patient Population (Median Follow-up 8 Months)



In CORE population, 88% of patients with CR at 3 months stayed in CR at 6 months; 93% of patients in CR at 6 months had ongoing response

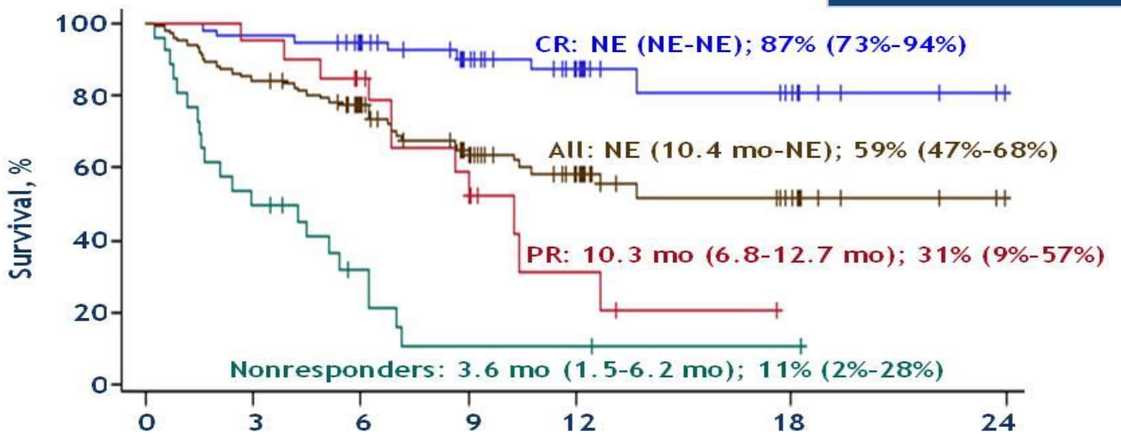
NE, not estimable.

Overall Survival (OS)

Early OS Encouraging in High-Risk DLBCL Patient Population (Median Follow-up 12 Months)

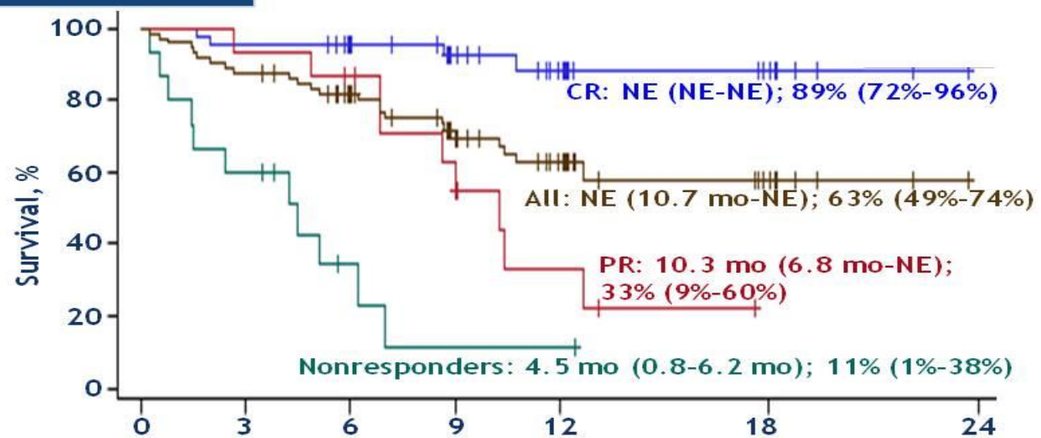
mOS (95% CI); 12 mo OS (95% CI)

FULL



At Risk							
All	102	86	68	48	28	11	0
CR	56	54	47	37	23	10	0
PR	20	19	15	9	3	0	
Non-responder	26	13	6	2	2	1	0

CORE



At Risk							
All	73	64	50	37	22	8	0
CR	43	41	35	28	18	8	0
PR	15	14	12	8	3	0	
Non-responder	15	9	3	1	1	0	

NE, not estimable.

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Conclusions

- Lisocabtagene maraleucel (liso-cel; JCAR017), a CD19-directed CAR T cell product with defined composition, induced durable responses in poor-prognosis patients with R/R aggressive NHL
- Encouraging durable response rates in the CORE patient population
  - 49% ORR and 46% CR rate at 6 months
  - Across dose levels, 93% of patients in CR at 6 months remained in response at data cutoff
- Liso-cel toxicities have been manageable at all dose levels tested
  - Low rates of severe CRS (1%) and NT (13%)
  - Liso-cel continues to be administered safely in the outpatient setting
- Pivotal cohort is fully enrolled

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Patients, Families, and Caregivers

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- University of Nebraska Medical Center, Omaha, NE
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- The University of Texas MD Anderson Cancer Center, Houston, TX
- University of Alabama at Birmingham, Birmingham, AL
- Fred Hutchinson Cancer Research Center, Seattle, WA
- UPMC Hillman Cancer Center, Pittsburgh, PA
- University of California San Francisco, San Francisco, CA
- University of Colorado School of Medicine, Aurora, CO
- Blood and Marrow Transplant Group of Georgia, Atlanta, GA
- Levine Cancer Institute, Charlotte, NC
- City of Hope National Medical Center, Duarte, CA

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CAR T-Cell Therapy JCAR017 in R/R DLBCL From TRANSCEND NHL 001: Correlation Between Patient Characteristics and Clinical Outcomes

1. Nandagopal L, et al. Expert Rev Hematol. 2017;10:259-273. 2. Siddiqi T, et al. ASH 2017. Abstract 193. 3. Abramson JS, et al. ASCO 2017. Abstract 7513.

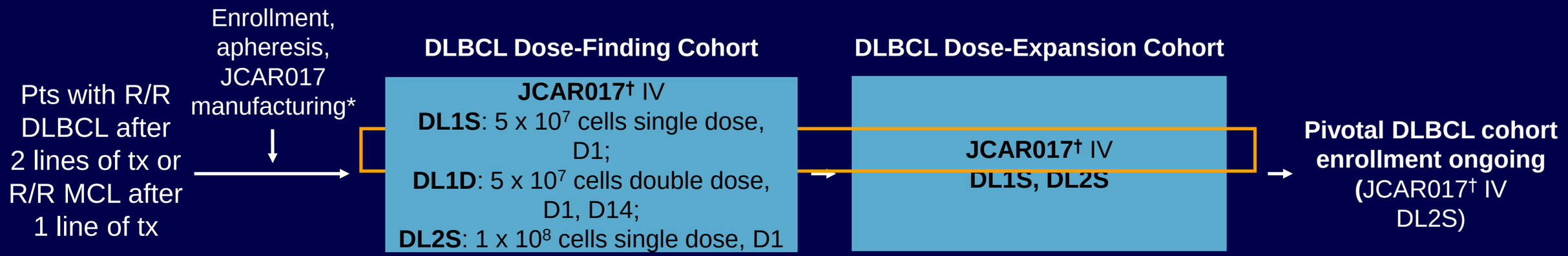
CAR T-Cell Therapy JCAR017 in R/R DLBCL: Background

- Relapsed/refractory, aggressive DLBCL remains difficult to treat[1]
- JCAR017 (lisocabtagene maraleucel): investigational CD19-directed CAR T-cell product with 4-1BB/CD3ζ signaling domain[2,3]
  - Formulated at a defined composition of CD4+ and CD8+ CAR T-cells
- Current exploratory analysis evaluated potential associations between pt baseline characteristics, CAR T-cell expansion, and clinical outcomes in DLBCL pts enrolled in phase I TRANSCEND NHL 001[2]
  - Preliminary report of TRANSCEND NHL 001 showed promising response rates (ORR: 76%; CR: 52%) with manageable toxicity and low rates of CRS and neurotoxicity[3]

1. Nandagopal L, et al. Expert Rev Hematol. 2017;10:259-273. 2. Siddiqi T, et al. ASH 2017. Abstract 193. 3. Abramson JS, et al. ASCO 2017. Abstract 7513.

TRANSCEND NHL 001: Study Design

- Multicenter, multicohort, open-label phase I trial
  - DLBCL CORE (n = 67): high-grade B-cell lymphoma (double/triple hit), DLBCL NOS de novo or transformed from FL
  - DLBCL FULL (n = 91): CORE + pts with DLBCL transformed from CLL/MZL, PMBCL, or FL3B



*Pts could receive low-dose CT for disease control during JCAR017 manufacturing. †Pts received ≥ 1 cycle of JACR017 tx, with each cycle preceded by lymphodepletion (fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 x 3 days). Follow-up: PK, scans Q3M for 1 yr; safety, viral vector for 15 yrs.

- Endpoints: response, laboratory values, cytokines, CAR T-cell expansion, safety

Siddiqi T, et al. ASH 2017. Abstract 193. ClinicalTrials.gov. NCT02631044.

Slide credit: clinicaloptions.com

TRANSCEND NHL 001 Exploratory Analysis: Response*

Response,* n (%)	FULL	CORE		
	All Dose Levels	All Dose Levels	DL1S	DL2S
Best overall response	n = 68	n = 49		
▪ ORR	51 (75)	41 (84)	--	--
▪ CR	38 (56)	30 (61)		
Pts with ≥ 3-mo f/u	n = 55	n = 40	n = 21	n = 15
▪ 3-mo ORR	27 (49)	26 (65)	11 (52)	12 (80)
▪ 3-mo CR	22 (40)	21 (53)	7 (33)	11 (73)

*Data cutoff: July 7, 2017.

- In CORE population, pts with durable responses (CR/PR) at 3 mos had generally lower baseline tumor burden, inflammation markers, and inflammatory cytokines

Siddiqi T, et al. ASH 2017. Abstract 193.

Slide credit: clinicaloptions.com

TRANSCEND NHL 001 Exploratory Analysis: Safety*

- No differences observed in rates of CRS or neurotoxicity by dose level or dose schedule
- No grade 5 CRS or neurotoxicity events observed
- 1 serious CRS event observed (grade 4)

Event, n (%)	Safety Population† (n = 69)
Any-grade CRS	21 (30)
▪ Grade 3/4	1 (1)
Any-grade neurotoxicity	14 (20)
▪ Grade 3/4	10 (14)

*Data cutoff, July 7, 2017. †Included all pts treated with ≥ 1 dose of conforming JCAR017 tx 28 days before data snapshot cutoff or died.

Siddiqi T, et al. ASH 2017. Abstract 193.

Slide credit: clinicaloptions.com

TRANSCEND NHL 001 Exploratory Analysis: BL Factors Correlating With CRS, NT (CORE)

- Any-grade CRS and neurotoxicity associated with higher BL levels of:
  - Tumor burden (CRS: $P < .001$; NT, $P = .006$)
  - LDH (CRS: $P < .001$; NT: $P = .018$)
  - Inflammatory cytokines/Inflammation markers
    - CRS: IL-10, IL-15, IL-16, TNFα, MIP-1β ($P < .05$)
    - Neurotoxicity: ferritin, CRP, D-dimer, IL-6, IL-15, TNFα, MIP-1 α ($P < .05$)
- Odds ratio for CRS or neurotoxicity ~ 8-fold higher with high BL levels of LDH (≥ 500 U/L) and/or tumor burden (SPD ≥ 50 cm^2) = preliminary risk boundaries
- In univariate analysis, CRS and neurotoxicity also associated with shorter time since diagnosis, but not with prior no. therapies, pt weight, disease stage (0-2 vs 3-4), ECOG PS (0-1 vs 2)

Siddiqi T, et al. ASH 2017. Abstract 193.

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TRANSCEND NHL 001 Exploratory Analysis: BL Factors Correlating With CAR T-Cell Expansion

- CAR T-cell expansion positively correlated with BL tumor burden (Spearman correlation coefficient ρ = 0.22; *P* = .010)
  - BL inflammatory cytokine levels also higher among pts with greater CAR T-cell expansion
    - IL-7, IL-15, MIP-1α, TNFα
- Logistic modeling suggested a potential therapeutic window for JCAR017 CAR T-cell expansion balancing toxicity vs efficacy
  - Target expansion associated with higher probabilities of ORR and response at 3 mos vs low expansion
  - Target expansion associated with lower probabilities of any CRS, any neurotoxicity, and grade 3/4 neurotoxicity vs high expansion

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TRANSCEND NHL 001 Exploratory Analysis: Conclusions

- Among R/R DLBCL pts treated with JCAR017, preliminary analyses suggest that high BL tumor burden, inflammatory biomarkers are associated with high CAR T-cell expansion but increased rates of CRS and neurotoxicity
- Lower BL tumor burden and markers of inflammation, inflammatory cytokines may be associated with durability of response
- Preliminary modeling data identified a therapeutic window of JCAR017 CAR T-cell expansion that appears to offer limited toxicity while optimizing efficacy
- Investigators conclude that clinical outcomes with JCAR017 may be improved by identifying pts at risk for low or high CAR T-cell expansion and finding strategies to drive them into the ideal therapeutic window

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ABSTRACT 192

A Phase I, Open–Label, Multicenter Trial of Oral Azacitidine (CC-486) Plus R-CHOP in Patients With High-Risk, Previously Untreated DLBCL, Grade 3B FL, or Transformed Lymphoma

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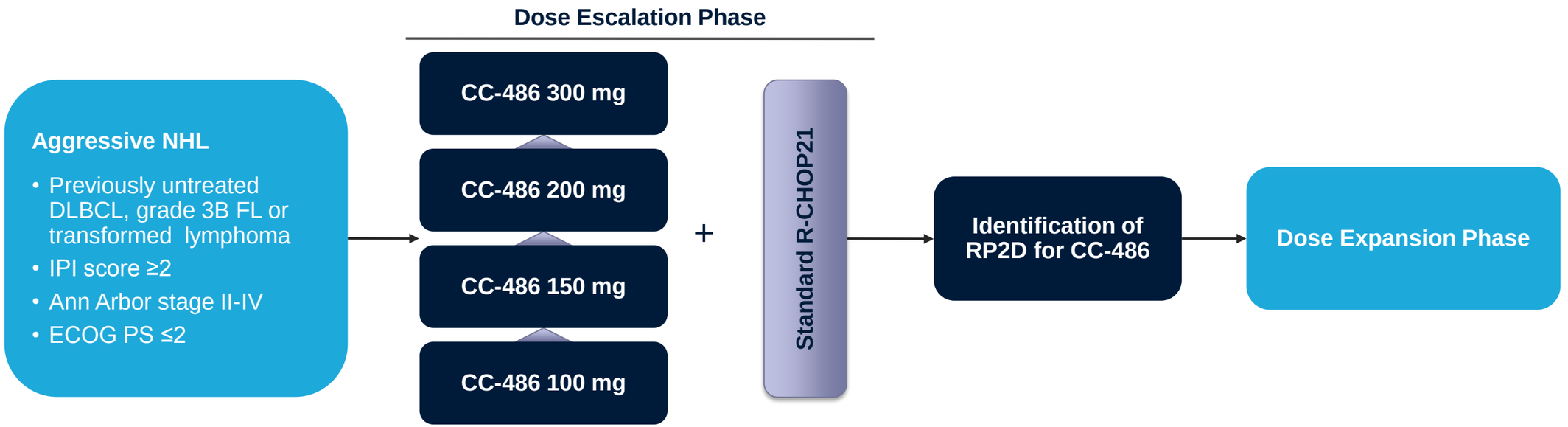
BACKGROUND AND RATIONALE

- Approximately 30% of patients with DLBCL are not cured with R-CHOP[1,2]
- A proposed mechanism of chemoresistance is aberrant DNA methylation[3,4]
- Preclinical data show low doses of DNA methyltransferase inhibitors, such as azacitidine, enhance chemosensitivity while causing minimal DNA damage[5]
- Phase I study of subcutaneous azacitidine + R-CHOP showed 11 of 12 CRs in DLBCL patients with a ≥2 international prognostic index (IPI) score[5]
- The recent development of oral azacitidine (CC-486) facilitates chronic, low-dose exposure required to maximize tumor hypomethylation

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine; prednisone.

1. Vitolo et al. *J Clin Oncol.* 2017;35:3529-3537. 2. Coiffier et al. *Blood.* 2010;116:2040-2045. 3. Martinez-Delgado et al*. Leukemia.* 1997;11:425-428.
4. Pinyol et al. *Blood*. 1998;91:2977-2984. 5. Clozel et al. *Cancer Discovery*. 2013;3:1002-1019. 6. Martin et al. A Phase I, Open–Label, Multicenter Trial of Oral Azacitidine (CC-486) Plus R-CHOP in Patients With High-Risk, Previously Untreated DLBCL, Grade 3B FL, or Transformed Lymphoma. *Oral presentation at: Annual Meeting of the American Society of Hematology* 2017; Dec 9-12; Atlanta, GA. Abstract 192.

STUDY DESIGN: MARTIN (CC-486+R-CHOP PHASE I DOSE ESCALATION STUDY IN HIGH-RISK TN DLBCL) (NCT02343536)



- **Study objectives***
  - Primary endpoints: safety, DLT, and maximal administered dose of CC-486
  - Secondary endpoints: preliminary efficacy (ORR, CR) and PK
  - Correlative analyses: cytokines, gene expression, methylation status
- Sequential enrollment in a time-to-event continual reassessment method (TiTE-CRM) design

CR, complete response; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PK, pharmacokinetics; RP2D, recommended phase II dose; TN, treatment naive.

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PATIENT CHARACTERISTICS: MARTIN (CC-486+R-CHOP IN HIGH-RISK TN DLBCL)

CC-486 Dose	Overall	100 mg	150 mg	200 mg	300 mg
	(N = 33)	(n = 1)	(n = 4)	(n = 14)	(n = 14)
NHL type, n (%)					
DLBCL	28 (85)	1 (100)	3 (75)	13 (93)	11 (79)
DLBCL transformed from FL	5 (15)	0	1 (25)	1 (7)	3 (21)
Median age, y (range)	65 (25-80)	70 (70-70)	64 (62-72)	65 (25-77)	61.5 (30-80)
>60 years, n (%)	22 (67)	1 (100)	4 (100)	9 (64)	8 (57)
Males, n (%)	18 (55)	0	2 (50)	8 (57)	8 (57)
Ann Arbor stage, n (%)					
II	3 (9)	0	1 (25)	1 (7)	1 (7)
III	10 (30)	0	1 (25)	4 (29)	5 (36)
IV	20 (61)	1 (100)	2 (50)	9 (64)	8 (57)
IPI score, n (%)					
Low/intermed. (2)	14 (42)	0	2 (50)	3 (21)	9 (64)
High-intermed./high (≥3)	19 (58)	1 (100)	2 (50)	11 (79)	5 (36)
Bulky disease (>10 cm), n (%)	5 (15)	0	0	4 (29)	1 (7)

- Median age of patients was 65 years; 67% were over the age of 60 years
- Over half of all patients had a high-intermediate to high IPI score (ie, high risk)

FL, follicular lymphoma

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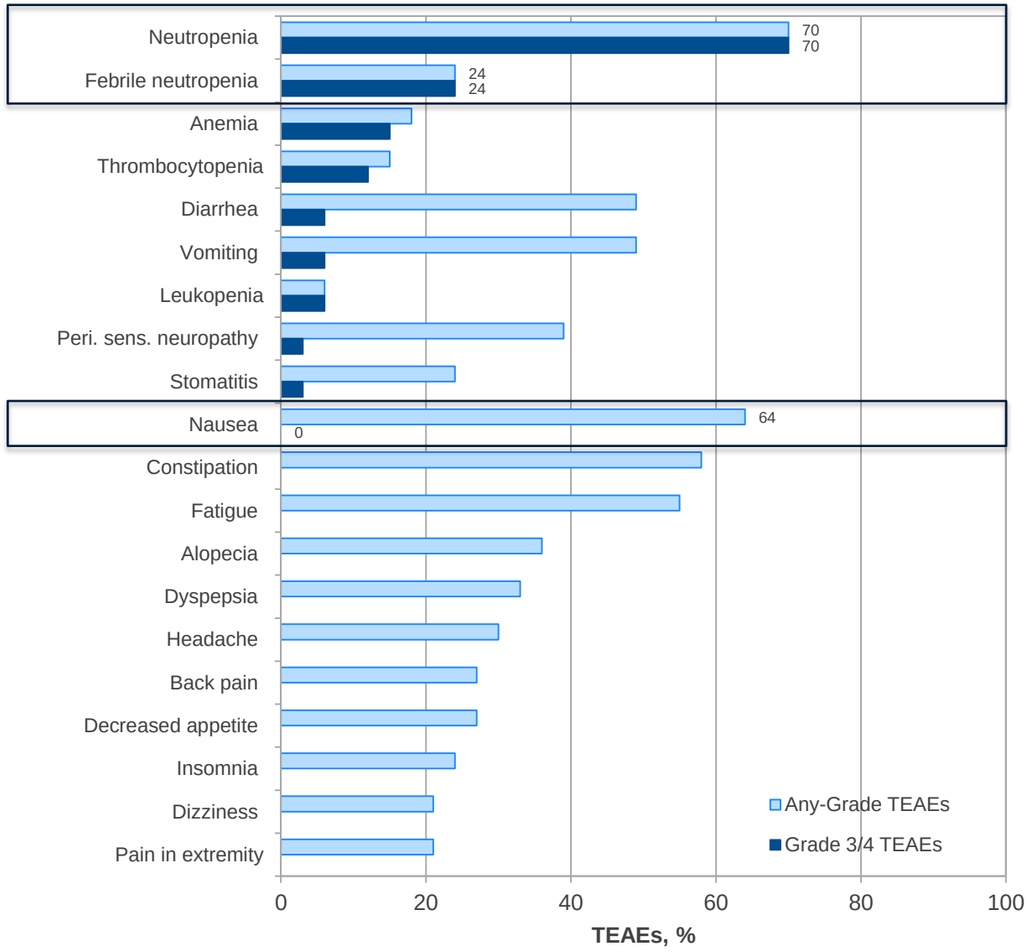
SAFETY: MARTIN (CC-486+R-CHOP IN HIGH-RISK TN DLBCL)

- 91% of patients completed all 6 cycles of CC-486+R-CHOP
  - CC-486 (150 mg) was discontinued in only 1 patient due to febrile neutropenia
- DLTs were observed in 2 patients
  - 1 grade 4 febrile neutropenia (200 mg cohort)
  - 1 grade 4 neutropenia with >7 day delay in cycle 2 start of R-CHOP (300 mg cohort)
- Serious adverse events (SAEs) occurred in 13 (39%) patients; febrile neutropenia was the only SAE occurring in >1 patient (24%)
  - Febrile neutropenia mainly occurred within the first 2 cycles (n = 4 cycle 1, n = 3 cycle 2, and n = 1 cycle 6)
- No deaths occurred



TEAEs, treatment-emergent adverse events.

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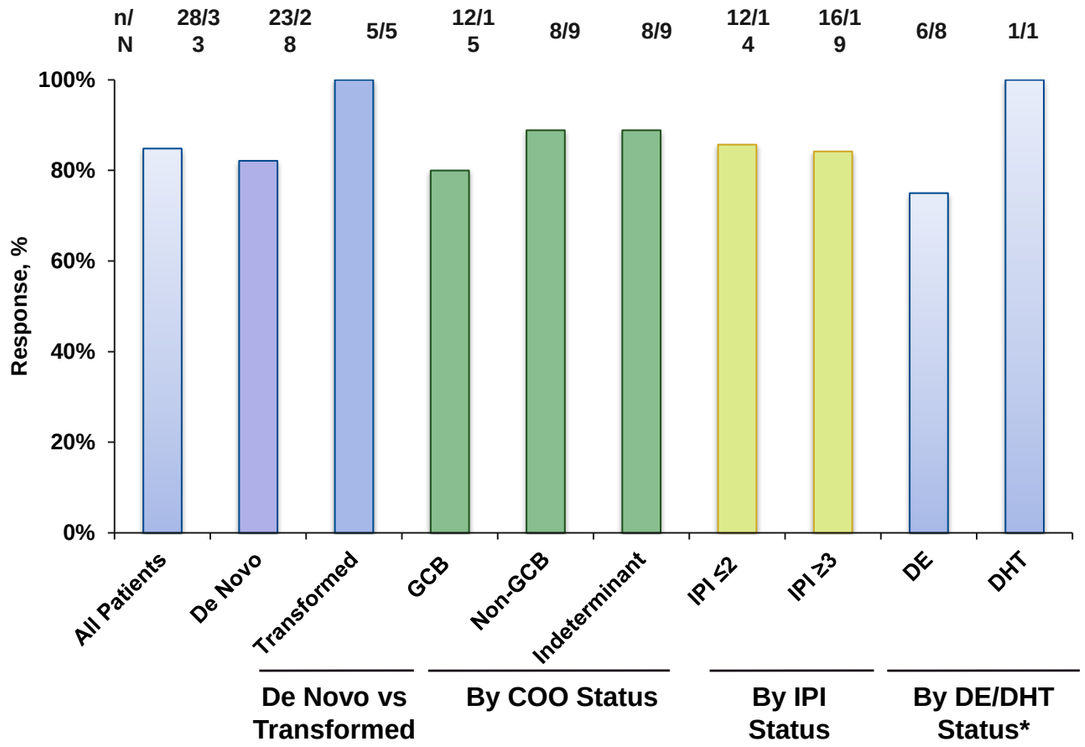
EFFICACY: MARTIN (CC-486+R-CHOP IN HIGH-RISK TN DLBCL)

CC-486 Dose	Overall	100 mg	150 mg	200 mg	300 mg
Response Status, n (%)	**(N = 33)**	**(n = 1)**	**(n = 4)**	**(n = 14)**	**(n = 14)**
ORR	**32 (97)**	**1 (100)**	**4 (100)**	**13 (93)**	**14 (100)**
CR	28 (85)	1 (100)	4 (100)	10 (71)	13 (93)
PR	4 (12)	0	0	3 (21)	1 (7)
SD	1 (3)	0	0	1 (7)	0
PD	0	0	0	0	0



- Patients had a 97% ORR, with 28 (85%) achieving PET− CR
- At a median follow-up of 10.6 months, only 1 patient had progressed

- High CR rates were observed in all DLBCL subtypes

COO, cell of origin; DE, double expressor; DHT, double-hit; IPI, International Prognostic Index; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

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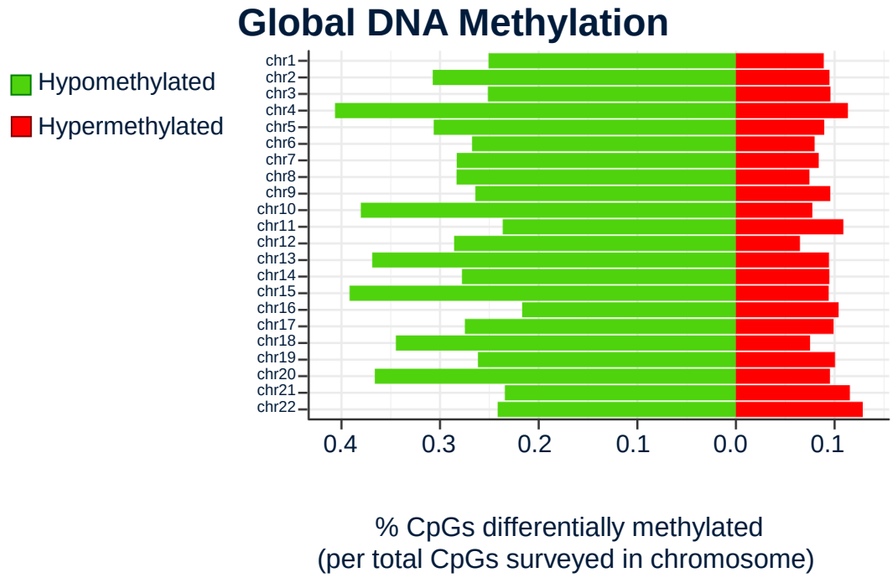
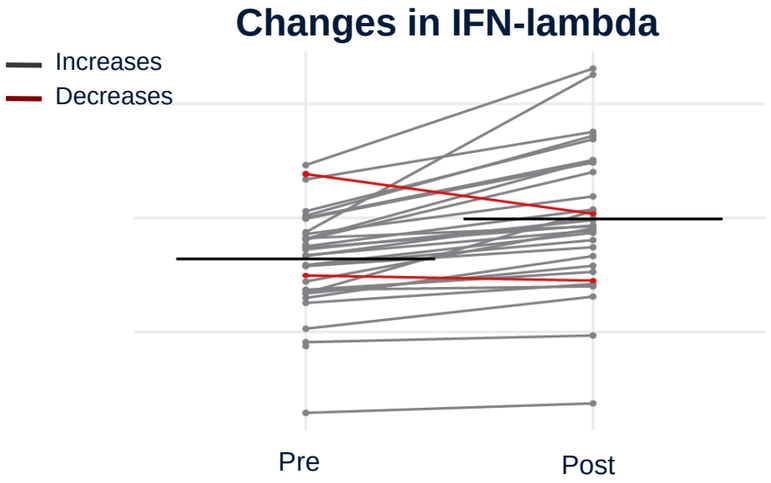
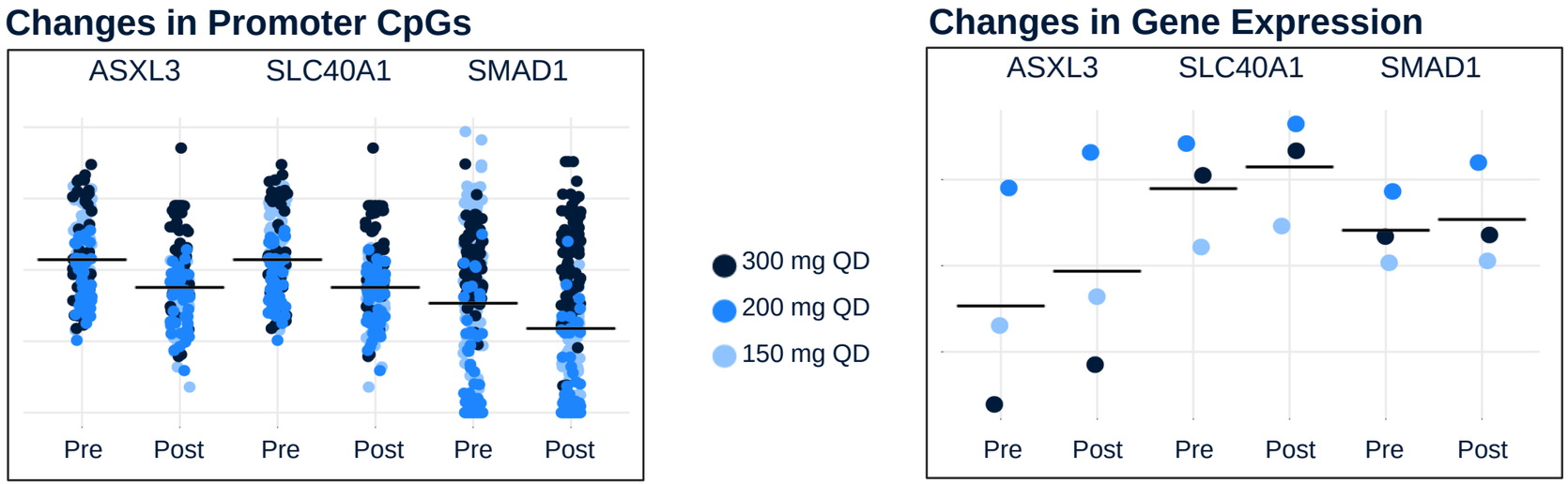
CORRELATIVES: MARTIN (CC-486+R-CHOP IN HIGH-RISK TN DLBCL)





- Correlative changes in hypomethylation and immune-related responses supported the hypothesized mechanisms of CC-486



IFN, interferon.

Martin et al. A Phase I, Open–Label, Multicenter Trial of Oral Azacitidine (CC-486) Plus R-CHOP in Patients With High-Risk, Previously Untreated DLBCL, Grade 3B FL, or Transformed Lymphoma. *Oral presentation at: Annual Meeting of the American Society of Hematology* 2017; Dec 9-12; Atlanta, GA. Abstract 192.

AUTHORS' CONCLUSIONS: MARTIN (CC-486+R-CHOP IN HIGH-RISK TN DLBCL)

- Adverse events were generally consistent with the known safety profile of azacitidine and toxicities associated with R-CHOP
  - Most common grade 3/4 AEs were 70% neutropenia and 24% febrile neutropenia
  - There was no association between dose level tested and grade 3/4 AEs
- CC-486 treatment showed significant correlative changes in gene expression for IFN-related immune responses and DNA hypomethylation
- CC-486 combined with R-CHOP showed promising preliminary efficacy in patients with high-risk, previously untreated DLBCL
  - 97% ORR and 85% PET− CR
  - 13 of 14 patients at the 300 mg CC-486 dose achieved a CR
- RP2D of 300 mg CC-486 (+ R-CHOP) was identified for future DLBCL studies

Martin et al. A Phase I, Open–Label, Multicenter Trial of Oral Azacitidine (CC-486) Plus R-CHOP in Patients With High-Risk, Previously Untreated DLBCL, Grade 3B FL, or Transformed Lymphoma. *Oral presentation at: Annual Meeting of the American Society of Hematology* 2017; Dec 9-12; Atlanta, GA. Abstract 192.

MCL

Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma: 3.5-Year Follow-up of a Pooled Analysis of 3 Clinical Trials

Rule S, et al. ASH 2017. Abstract 151..

Pooled Analysis of Ibrutinib in R/R MCL: Background

- MCL is an uncommon B-cell non-Hodgkin lymphoma with a poor prognosis[1,2]
  - Majority of pts relapse after initial therapy, with time to next therapy decreasing with each new line of therapy
- Ibrutinib: irreversible BTK inhibitor with once-daily dosing[3]
  - In a 3-yr follow-up of the phase III RAY study, ibrutinib significantly improved median PFS vs temsirolimus in pts with R/R MCL (15.6 vs 6.2 mos; HR: 0.45; *P* < .0001)[4]
  - Common AEs include atrial fibrillation, bleeding, and neutropenia[3]
- Previous analysis of pooled data from 370 pts with R/R MCL who received ibrutinib through 3 clinical trials demonstrated a median PFS of 12.8 mos after median follow-up of 2 yrs[5]
- Current pooled analysis evaluated ibrutinib outcomes across 3 clinical trials after median follow-up of 3.5 yrs[6]

References in slidenotes

Pooled Analysis of Ibrutinib in R/R MCL: Study Design

- Mature follow-up of pooled analysis of ibrutinib-treated pts with R/R MCL from 3 clinical trials (N = 370)[1]
  - Single-arm phase II SPARK (n = 120): MCL pts previously treated with ≥ 1 rituximab-based regimen and who progressed following bortezomib tx[2]
  - Randomized, controlled phase III RAY (ibrutinib arm, n = 139): pts with R/R MCL previously treated with ≥ 1 rituximab-containing regimen[2]
  - Single-arm phase II PCYC-1104 (n = 111): pts with R/R MCL[2]
- Pts with continued benefit from ibrutinib enrolled in phase III CAN3001 (n = 87)[1]
- All pts received ibrutinib 560 mg PO QD until PD, unacceptable toxicity[1,2]
- Outcomes analyzed[1]
  - Investigator-assessed response per IWG 2007 criteria*
  - PFS
  - OS
  - Safety, including CV events
- Evaluated relationships between BL pt characteristics and PFS, OS with multivariate analyses[1]

*CR confirmed with PET and, if positive at BL, BM biopsy and/or endoscopy.

1. Rule S, et al. ASH 2017. Abstract 151. 2. Rule S, et al. Br J Haematol. 2017;179:430-438.

Pooled Analysis of Ibrutinib in R/R MCL: Baseline Pt Characteristics

Characteristic	Pooled Analysis (N = 370)
Median age, yrs (range) ▪ ≥ 70 yrs of age, n (%)	67.5 (35-85) 160 (43.2)
Male, n (%)	289 (78.1)
ECOG PS, n (%) ▪ 0-1 ▪ ≥ 2	 346 (93.5) 24 (6.4)
Simplified MIPI, n (%) ▪ Low risk (1-3) ▪ Intermediate risk (4-5) ▪ High risk (6-11)	 87 (23.6) 164 (44.6) 117 (31.8)

Characteristic	Pooled Analysis (N = 370)
Bulky disease ≥ 5 cm, n (%)	180 (48.9)
Median prior tx, n (range) ▪ 1 tx, n (%) ▪ > 1 tx, n (%)	2.0 (1-9) 99 (26.8) 271 (73.2)
Extranodal disease, n (%)	215 (58.1)
Blastoid, n (%)	44 (11.9)
Prior transplant, n (%)	85 (23.0)

Rule S, et al. ASH 2017. Abstract 151.

Pooled Analysis of Ibrutinib in R/R MCL: Response

- Median follow-up: 41.1 mos (range: 0.2-72.1)
- 36% CR with ibrutinib in pts receiving only 1 prior therapy
- For pts achieving CR, DoR was ~ 4.5 yrs
- DoR almost double for pts previously treated with 1 vs > 1 prior therapy

Response, %	ITT (N = 370)	No. Prior Lines Tx	
		1 (n = 99)	> 1 (n = 271)
ORR	69.7	77.8	66.8
▪ CR	26.5	36.4	22.9
▪ PR	43.2	41.4	43.9

Median, mos (95% CI)	Overall (n = 258)	No. Prior Lines Tx	
		1 (n = 77)	> 1 (n = 181)
DoR	22.2 (16.5-28.8)	34.4 (23.1-NE)	16.0 (12.9-23.5)
▪ CR	55.7 (55.7-NE)	55.7 (33.1-NE)	NE (40.7-NE)
▪ PR	10.4 (7.7-14.9)	22.1 (10.6-34.4)	8.5 (6.2-12.1)

Rule S, et al. ASH 2017. Abstract 151.

Pooled Analysis of Ibrutinib in R/R MCL: Survival

Median, Mos (95% CI)	Overall (N = 370)	No. Prior Lines Tx		Best Response	
		1 (n = 99)	> 1 (n = 271)	CR (n = 98)	PR (n = 160)
PFS	13.0 (8.4-16.8)	33.6 (19.4-42.1)	8.4 (7.1-12.8)	46.2 (42.1-NE)	14.3 (10.4-17.5)
OS	26.7 (22.5-38.4)	NR (36.0-NE)	22.5 (16.2-26.7)	NE (59.9-NE)	26.2 (21.6-34.7)

- For pts achieving CR with ibrutinib, PFS was nearly 4 yrs
- 58.9% of pts discontinued ibrutinib due to PD and 5.1% died
- Per multivariate analyses for independent predictors of ibrutinib outcomes
  - Significantly higher risk of progression (all *P* < .05): ECOG PS ≥ 2 vs 0-1, high- or intermediate- vs low-risk sMIPI score, > 1 vs 1 prior treatment lines, bulky disease ≥ 5 cm, blastoid history
  - Significantly higher risk of death (all *P* < .05): ECOG PS ≥ 2 vs 0-1, high- or intermediate- vs low-risk sMIPI score, bone marrow involvement, bulky disease ≥ 5 cm, blastoid history

Rule S, et al. ASH 2017. Abstract 151.

Pooled Analysis of Ibrutinib in R/R MCL: Grade ≥ 3 Treatment-Emergent AEs

- New onset of grade ≥ 3 treatment-emergent AEs
  - Decreased after first yr of therapy
  - Appear to be lower in pts previously treated with 1 vs > 1 prior therapy

Grade ≥ 3 Treatment-Emergent AE, %	ITT (N = 370)	No. Prior Lines Tx	
		1 (n = 99)	> 1 (n = 271)
Overall	79.7	68.7	83.8
▪ At Yr 1	67.8	55.6	72.3
▪ At Yr 2	47.8	34.4	54.6
▪ At Yr > 4	20.0	7.1	26.9
Neutropenia	17.0	7.1	20.7
Thrombocytopenia	12.2	7.1	14.0
Pneumonia	11.9	7.1	13.7
Anemia	9.5	5.1	11.1
Atrial fibrillation	5.9	5.1	6.3
Hypertension	5.1	6.1	4.8
Secondary malignancies*	9.7	--	--

*Including nonmelanoma skin cancers.

Rule S, et al. ASH 2017. Abstract 151.

Pooled Analysis of Ibrutinib in R/R MCL: Cardiovascular AEs

- Pooled trials enrolled pts with baseline cardiac risk factors
  - Prevalence ≥ 10% in pooled population: HTN (47.6%), hyperlipidemia (16.2%), AF/arrhythmia (14.3%), diabetes (13.0%)
- Of 53 pts with history of AF/arrhythmia, no recurrence in 37/53 pts (70%)
- Ibrutinib discontinuation or dose reduction due to grade ≥ 3 bleeding or AF required in < 2% of pts

Safety Population, n (%)	Pooled Analysis (N = 370)
Grade ≥ 3 bleeding	21 (5.7)
▪ Dose reduction	1 (0.3)
▪ Discontinuation	3 (0.8)
Grade ≥ 3 AF	22 (5.9)
▪ Dose reduction	2 (0.5)
▪ Discontinuation	0

Rule S, et al. ASH 2017. Abstract 151.

Pooled Analysis of Ibrutinib in R/R MCL: Conclusions

- In pooled analysis of mature data from R/R MCL pts in 3 clinical trials, ibrutinib treatment was associated with an ORR of 69.7% and a median PFS of 13.0 mos
  - Outcomes improved in pts achieving CR vs PR or with 1 vs > 1 prior line of tx
    - Median PFS ~ 4 yrs and DoR ~ 4.5 yrs in pts achieving CR
    - Median PFS ~ 3 yrs in pts with 1 earlier line of therapy
  - Pts at higher risk of progression and/or death with increasing number of prior tx lines, ECOG PS ≥ 2, BM involvement, bulky disease, blastoid history, higher sMIPI risk score
- Overall rate of grade ≥ 3 TEAEs highest in Yr 1 (67.8%), declining through Yr > 4 (20.0%), and appears to be lower in pts previously treated with 1 vs > 1 therapy
  - Majority of pts (70%) with history of AF did not experience a recurrence
  - Ibrutinib d/c, dose reduction due to grade ≥ 3 bleeding or AF required in < 2% of pts

Rule S, et al. ASH 2017. Abstract 151.

ACE-LY-004: Phase II Trial of BTK Inhibitor Acalabrutinib in Patients With Relapsed/ Refractory Mantle Cell Lymphoma

Wang M, et al. ASH 2017. Abstract 155.

Acalabrutinib in R/R MCL (ACE-LY-004): Background

- MCL is a rare form of non-Hodgkin lymphoma with poor prognosis[1]
- Treatment of R/R MCL with the BTK inhibitor ibrutinib effective, but associated with atrial fibrillation, bleeding, and infection[2,3]
  - Ibrutinib-associated AEs may be due to off-target kinase inhibition[1]
- Acalabrutinib: selective, covalent BTK inhibitor[4,5]
  - Associated with limited off-target effects in preclinical studies
- Current analysis evaluated efficacy and safety of acalabrutinib monotherapy in pts with R/R MCL[6]

References in slidenotes

ACE-LY-004: Study Design

- International, multicenter, open-label phase II trial[1]

Adult MCL pts with translocation t(11;14)(q13;q32) and/or cyclin D1 overexpression; relapsed/refractory to 1-5 prior tx; measurable nodal disease (≥ 1 LN with longest diameter ≥ 2 cm); ECOG PS 0-2; no notable CVD*; no concurrent use of warfarin/equivalent vitamin K antagonists, no prior BTK inhibitors
(N = 124)

→ **Acalabrutinib** 100 mg PO BID in 28-day cycles → ***Until PD***

*Includes: class 3/4 cardiac disease per NYHA Functional Classification; CHF or MI within 6 mos of screening;
QTc > 480 ms; uncontrolled/symptomatic arrhythmias.

- Primary endpoint: investigator-assessed ORR per 2014 Lugano Classification[1,2]
- Secondary endpoints: IRC-assessed ORR, DoR, PFS, OS, PK/PD, safety[1]
- Exploratory endpoints: TTR, IRC-assessed ORR per 2007 IHP criteria[1,3]

1. Wang M, et al. ASH 2017. Abstract 155. 2. Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068. 3. Cheson BD, et al. J Clin Oncol. 2007;25:579-586.

ACE-LY-004: Baseline Characteristics

Characteristic	Pts (N = 124)
Median age, yrs (range)	68 (42-90)
Male, n (%)	99 (80)
ECOG PS 0-1, n (%)	115 (93)
Simplified MIPI score,* n (%)	
▪ Low risk (0-3)	48 (39)
▪ Intermediate risk (4-5)	54 (44)
▪ High risk (6-11)	21 (17)
Ann Arbor Stage IV disease, n (%)	93 (75)
Tumor bulk, n (%)	
▪ ≥ 5 cm	46 (37)
▪ ≥ 10 cm	10 (8)
Extranodal disease, n (%)	90 (73)
▪ BM	63 (51)
▪ GI	13 (10)
▪ Lung	12 (10)

Characteristic	Pts (N = 124)
Median prior therapies, n (range)	2 (1-5)
Refractory disease, n (%)	30 (24)
Prior therapy, n (%)	
▪ Rituximab monotherapy or in combination	118 (95)
▪ CHOP-based	64 (52)
▪ Bendamustine ± rituximab	27 (22)
▪ Hyper-CVAD	26 (21)
▪ Bortezomib/carfilzomib	24 (19)
▪ SCT	22 (18)
▪ Lenalidomide	9 (7)

*Data missing for 1 pt.

Wang M, et al. ASH 2017. Abstract 155.

ACE-LY-004: Investigator-Assessed ORR (Primary Endpoint)

Response,* n (%)	Investigator Assessed	IRC Assessed
ORR (CR + PR)	100 (81)	99 (80)
Best response		
▪ CR	49 (40)	49 (40)
▪ PR	51 (41)	50 (40)
▪ SD	11 (9)	9 (7)
▪ PD	10 (8)	11 (9)
▪ Not evaluable	3 (2)	5 (4)

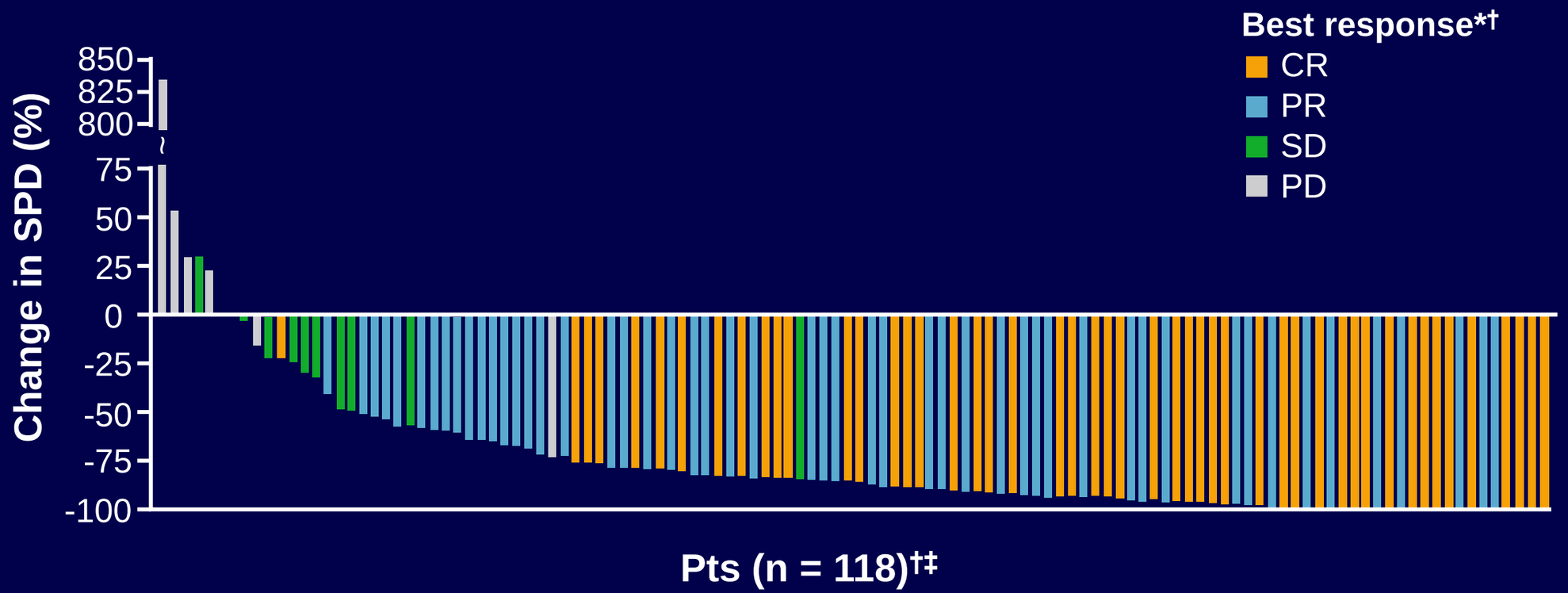
(range: 0.3-23.7).

- Investigator-assessed ORR concordant with IRC-assessed ORR (91%) and CR (94%)
- ORR consistent across prespecified subgroups
- Median TTR: 1.9 mos (range: 1.5-4.4)
- Median DoR: NR (12-mo DoR rate: 72%)

Wang M, et al. ASH 2017. Abstract 155.

ACE-LY-004: Change in Tumor Burden per Best Response Status

- 94% of pts with reduced lymphadenopathy

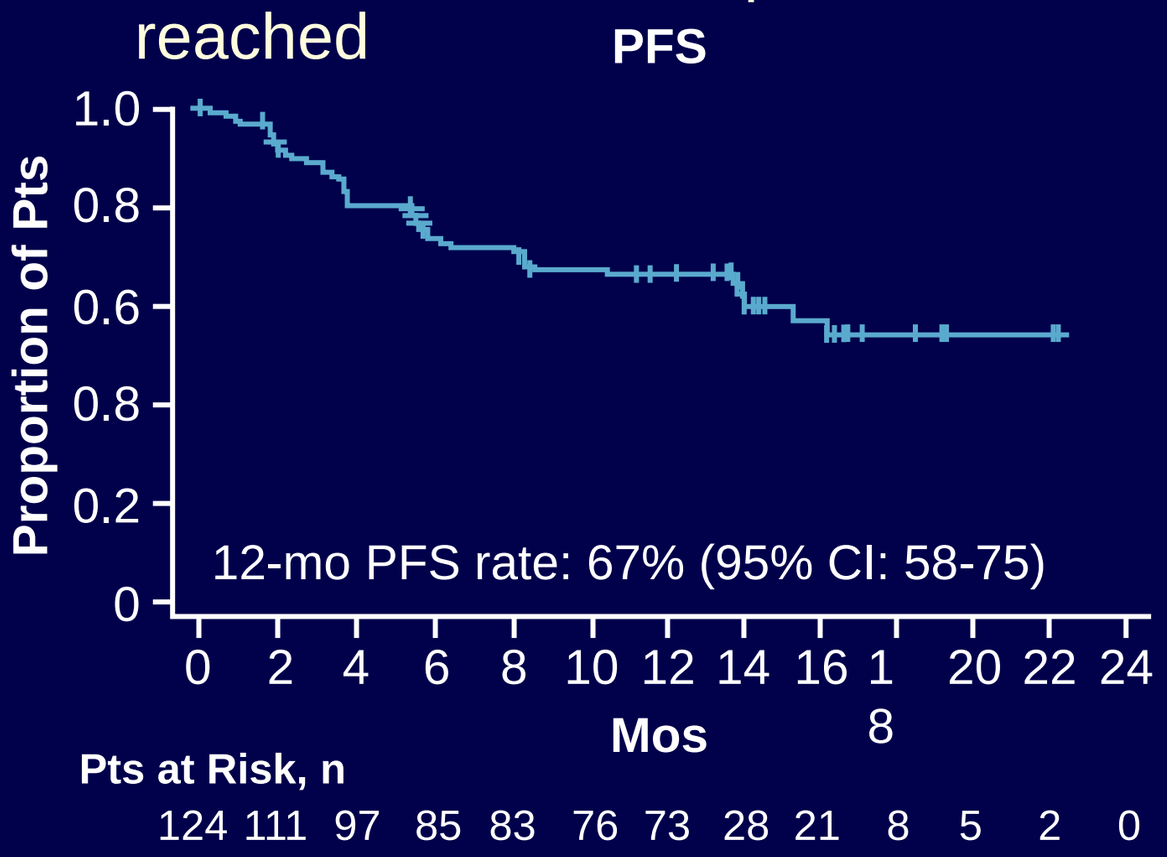


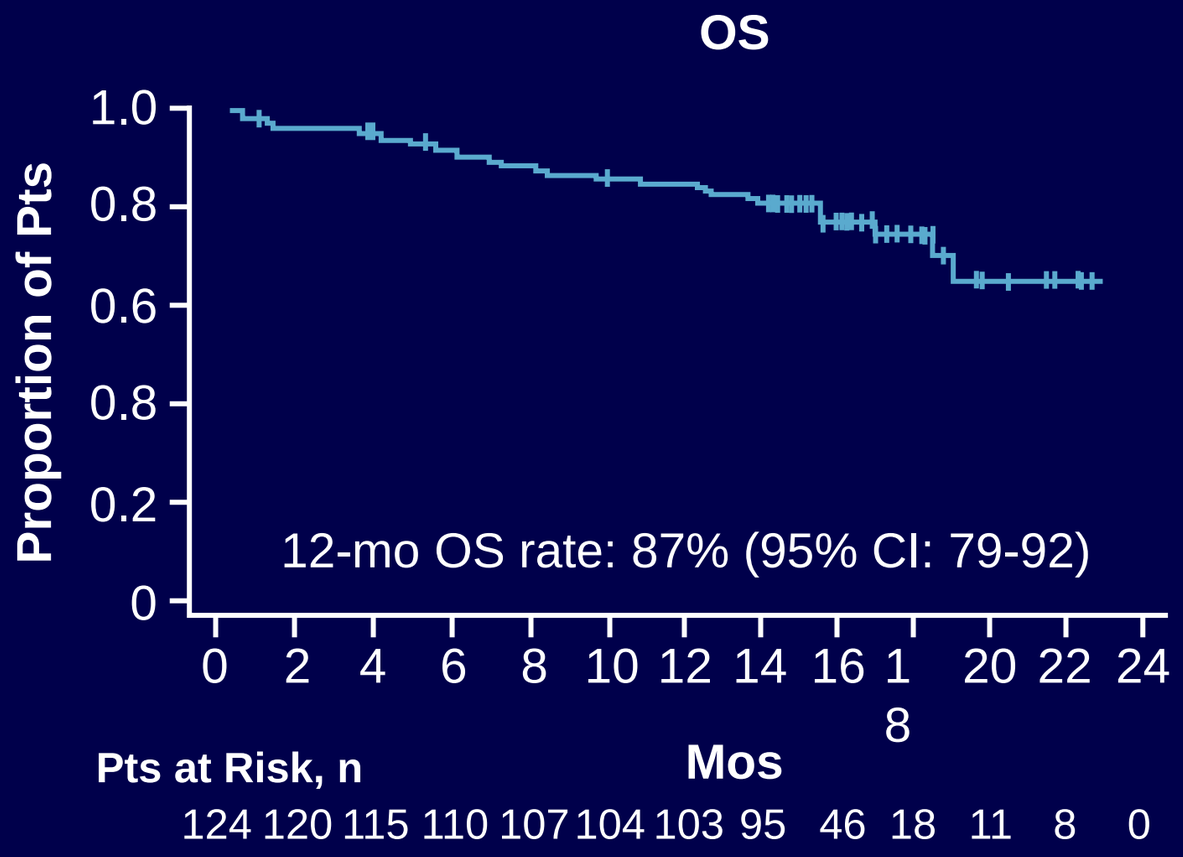
*Per 2014 Lugano Classification. †Best response NE in 3 pts (2%). ‡All treated pts with lesion measurements at BL and ≥ 1 post BL; 6 pts excluded (n = 4, early PD by evidence other than CT; n = 1, began subsequent anticancer treatment; n = 1, death).

Wang M, et al. ASH 2017. Abstract 155. Reprinted with permission.

ACE-LY-004: Survival

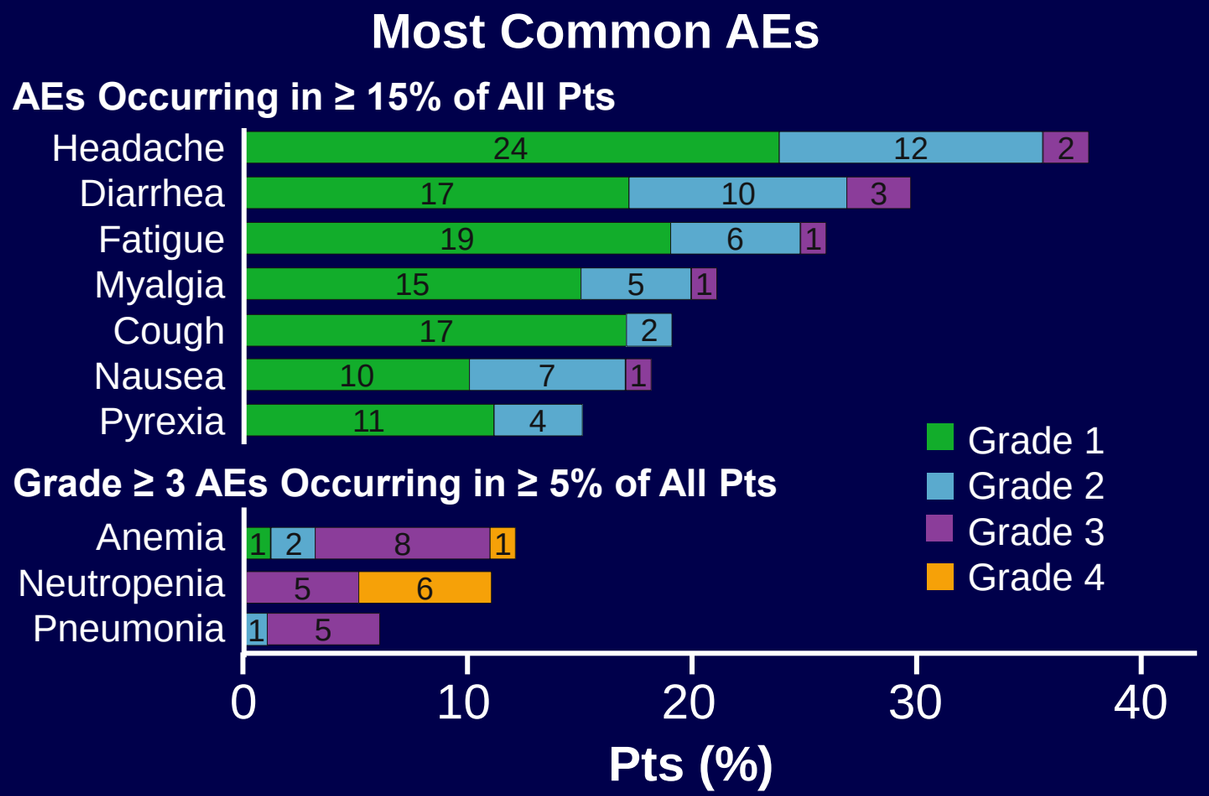
- After median follow-up of 15.2 mos, neither median PFS or median OS reached





Wang M, et al. ASH 2017. Abstract 155. Reprinted with permission.

ACE-LY-004: Safety



Event, n (%)	Pts (N = 124)
Serious AEs	48 (39)
Serious AEs in ≥ 2 pts*	
▪ Pneumonia	5 (4)
▪ Anemia	4 (3)
▪ General physical health deterioration	3 (2)
▪ Sepsis	2 (2)
▪ Tumor lysis syndrome	2 (2)
▪ Vomiting	2 (2)
AE-related discontinuation†	7 (6)

*Other serious AEs: n = 1, grade 3 GI hemorrhage in pt with history of GI ulcer; n = 1, grade 5 aortic stenosis in pt with history of nontreatment-related aortic stenosis.

†n = 1 each: aortic stenosis, DLBCL, blood blister and petechiae (both in same pt on clopidogrel for grade 3 acute coronary syndrome), dyspnea and leukostasis syndrome, noncardiac chest pain, pulmonary fibrosis, and thrombocytopenia.

Wang M, et al. ASH 2017. Abstract 155. Reprinted with permission.

ACE-LY-004: AEs of Clinical Interest

- Grade 3/4 cardiac AEs occurred in 3 pts
- No atrial fibrillation
- 31% of pts with bleeding events
  - All grade 1/2, except for 1 grade 3 GI hemorrhage in pt with history of GI ulcer
- 53% of pts with any grade infection, 13% grade 3/4

Pt With Grade 3/4 Cardiac AE	Cardiac AE	Relationship to Treatment
Pt 1	Grade 3 acute coronary syndrome	Related
Pt 2	Grade 3 acute MI	Not related
Pt 3	Grade 4 cardiorespiratory arrest	Not related

Wang M, et al. ASH 2017. Abstract 155.

ACE-LY-004: Conclusions

- In pts with R/R MCL, acalabrutinib monotherapy associated with ORR of 81%, CR of 40%
  - Responses durable with a 12-mo DoR rate of 72%
- Safety profile of acalabrutinib was favorable, with mostly low grade AEs, low rate of AE-related discontinuation (6%), no cases of atrial fibrillation, and low rate of grade ≥ 3 hemorrhage (1%)
- Investigators conclude that acalabrutinib 100 mg BID is an effective therapeutic option with a differentiated safety profile from ibrutinib in pts with R/R MCL
  - Acalabrutinib 100 mg BID approved by FDA in October 2017 for adult pts with MCL who received ≥ 1 prior therapy

Wang M, et al. ASH 2017. Abstract 155. Acalabrutinib [package insert]. 2017.

Extended Follow-up of Mantle Cell Lymphoma Patients Treated With First-line Lenalidomide + Rituximab

Ruan J, et al. ASH 2017. Abstract 154. ClinicalTrials.gov. NCT01472562.

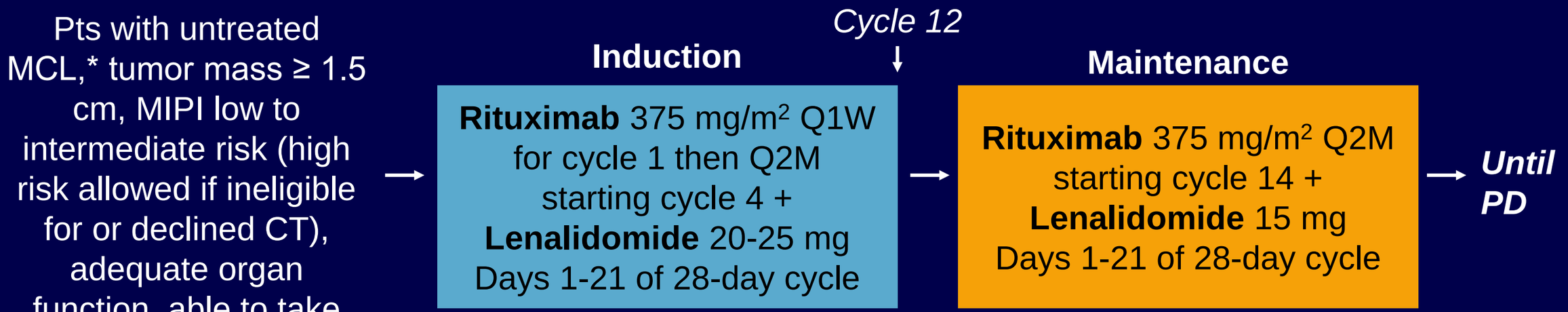
First-line Lenalidomide + Rituximab in MCL 5-Yr Follow-up: Background

- MCL is a rare non-Hodgkin lymphoma without a standardized first-line treatment[1,2]
  - Majority of MCL pts relapse following initial treatment[3]
- Lenalidomide: thalidomide analogue with antiangiogenic, antineoplastic, and immunomodulatory effects against hematopoietic tumor cells[4]
  - In R/R MCL, 40% ORR (5% CR) with single-agent lenalidomide,[5] 57% ORR (36% CR) with combination lenalidomide + rituximab[6]
- Rituximab: CD20-directed cytolytic antibody[7]
  - In first-line setting for MCL, rituximab maintenance for pts in remission following R-CHOP induction[8,9] or autoHSCT associated with improved survival[10]
- Current analysis assessed long-term efficacy, safety in MCL pts initially treated with induction and maintenance regimens of lenalidomide + rituximab in phase II trial[9]

References in slidenotes

First-line Lenalidomide + Rituximab in MCL 5-Yr Follow-up: Study Design

- 5-yr follow-up of open-label, single-group, multicenter phase II trial



*With disease that is CD20+, CD5+, CD23-, and cyclin D1+. Response assessed every 3 mos for first 2 yrs, then every 6 mos during Yr 3+.

- Primary endpoint: ORR per IWG 2007 criteria
- Secondary endpoints: survival, QoL, safety

Ruan J, et al. ASH 2017. Abstract 154. ClinicalTrials.gov. NCT01472562.

First-line Lenalidomide + Rituximab in MCL 5-Yr Follow-up: Baseline Pt Characteristics

Characteristic	Pts (N = 38)
Median age, yrs (range)	65 (42-86)
Male, n (%)	27 (71)
ECOG PS 0-1/> 1, n (%)	37 (97)/1 (3)
Stage III-IV MCL, n (%)	38 (100)
Elevated LDH, n (%)	14 (37)
Bone marrow involvement, n (%)	34 (89)
MIPI risk, n (%) ▪ Low (score < 5.7) ▪ Intermediate (score ≥ 5.7 to < 6.2) ▪ High (score ≥ 6.2)	 13 (34) 13 (34) 12 (32)
Ki67 < 30%/≥ 30%, n (%)	26 (68)/8 (21)

Ruan J, et al. ASH 2017. Abstract 154.

First-line Lenalidomide + Rituximab in MCL 5-Yr Follow-up: ORR

Outcome	ITT (N = 38)	Evaluable (n = 36)
ORR,* %	87	92
▪ CR	61	64
▪ PR	26	28
▪ SD	3	3
▪ PD	5	6
Median time, mos (range)		
▪ To PR	3 (3-13)	
▪ To CR	11 (3-22)	

*Treatment discontinued due to tumor flare without PD before tumor response evaluated: n = 2.

- 22 of 33 pts in maintenance phase have ongoing response
  - n = 3 in CR completed 3 yrs of therapy
  - n = 19 in treatment beyond 3 yrs
    - n = 1, lenalidomide; n = 14, lenalidomide + rituximab; n = 4, rituximab
  - n = 8 with PD, 6 whom have died
- 8 of 9 pts (89%) with CR who completed ≥ 35 mos of study therapy achieved MRD-negative PB

Ruan J, et al. ASH 2017. Abstract 154. Reprinted with permission.

First-line Lenalidomide + Rituximab in MCL 5-Yr Follow-up: Other Efficacy Results

Efficacy Endpoint, % (95% CI)	36 Mos	48 Mos
PFS rate	80.3 (63.0-90.1)	70.6 (52.0-83.1)
OS rate	91.9 (76.9-93.7)	83.0 (65.9-92.0)

- Median follow-up: 61 mos (range: 21-74)
- Differences in survival outcomes between low/intermediate-risk and high-risk MIPI subgroups:
  - Not significantly different for PFS (log-rank *P* = .68)
  - Significantly different for OS (log-rank *P* = .02)
    - 4-yr OS rate: 91.4% vs 65.6%

Ruan J, et al. ASH 2017. Abstract 154.

First-line Lenalidomide + Rituximab in MCL Follow-up: Safety

AE, %	Induction		Maintenance	
	Any	Gr ≥ 3	Any	Gr ≥ 3
Hematologic				
▪ Neutropenia	68	42	66	42
▪ Anemia	47	8	32	3
▪ Thrombocytopenia	29	11	37	5
▪ Febrile neutropenia	3	3	5	5
Infections				
▪ URI	24	0	45	0
▪ UTI	11	0	21	5
▪ Sinusitis	5	0	13	0
▪ Cellulitis	5	0	11	3
▪ Pneumonia	3	3	8	8

Incidence of Secondary Malignancies

Pt Age, Sex	Tx Phase	Secondary Malignancy	Status
74, M	Induct	Squamous cell CA	Alive, CR
	Maint	Squamous cell CA	
60, M	Maint	Squamous cell CA	Alive, CR
	Maint	Basal cell CA	
58, M	Maint	Basal cell CA	Alive, CR
86, M	Maint	Melanoma in situ	Deceased
	Maint	Merkel cell CA	
68, M	Maint	Pancreatic CA	Deceased
66, M	Induct	Melanoma in situ	Alive, PR

Ruan J, et al. ASH 2017. Abstract 154.

First-line Lenalidomide + Rituximab in MCL Follow-up: Conclusions

- After a median follow-up of 61 mos in MCL pts initially treated with lenalidomide + rituximab, the ORR was 87% (CR rate: 61%)
  - 4-yr PFS: 70.6%; no difference between MIPI risk groups
  - 4-yr OS: 83.0%; rate significantly higher with low/intermediate-risk vs high-risk MIPI score (91.4% vs 65.6%; log-rank *P* = .02)
  - Of pts with CR who were tested, 89% were MRD negative
- Continued treatment was not associated with notable cumulative toxicity
- Investigators conclude that outpatient treatment with lenalidomide + rituximab is an active, feasible, safe option for initial and maintenance therapy in pts with previously untreated MCL
  - Further investigation of regimen in first-line setting warranted in larger RCTs

Ruan J, et al. ASH 2017. Abstract 154.

Indolent Lymphoma

Phase III MAINTAIN: Extended Rituximab Maintenance in Follicular Lymphoma After First-line Bendamustine + Rituximab

Rummel MJ, et al. ASH 2017. Abstract 483. ClinicalTrials.gov. NCT00877214.

Rituximab Maintenance in FL (StiL NHL7-2008 MAINTAIN): Background

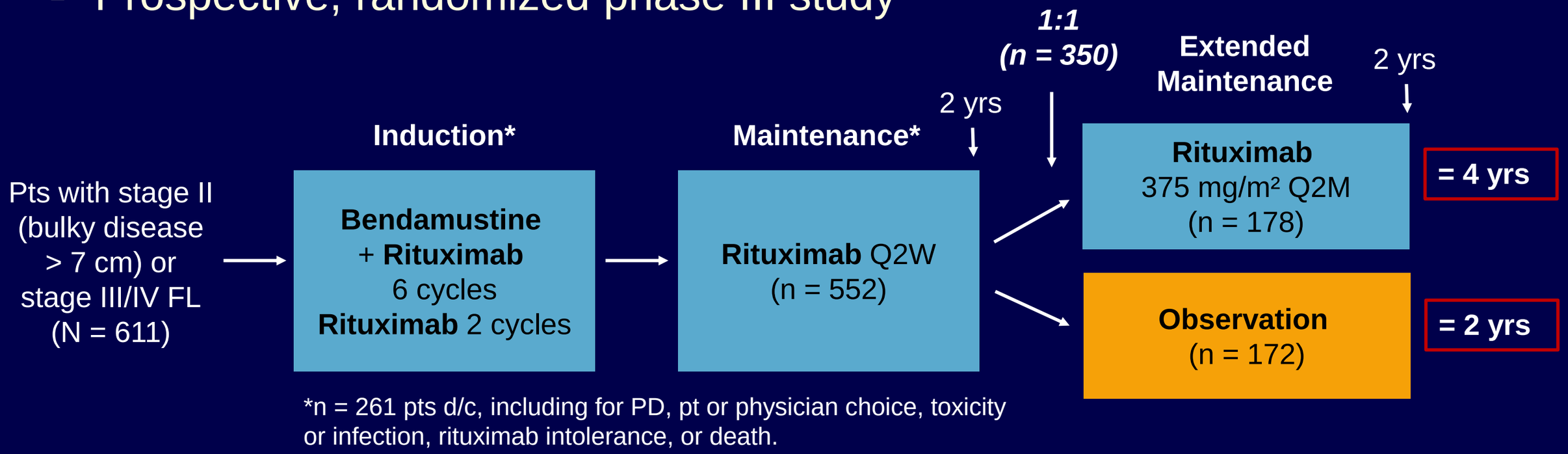
- Bendamustine + rituximab accepted frontline therapy for previously untreated FL[1]
- Rituximab maintenance therapy for 2 yrs established consolidation in FL after first-line induction therapy[1]
  - Commonly used after first-line R-CHOP, R-CVP based on randomized phase III trials showing improved PFS vs observation[2,3]
  - Also used after BR despite lack of evidence from randomized trials[4]
    - BR followed by maintenance rituximab even used as standard comparator in the phase III GALLIUM trial of obinutuzumab-based chemotherapy followed by obinutuzumab maintenance[5]
- Current study evaluated safety, efficacy of 2 yrs vs 4 yrs of rituximab maintenance following frontline BR treatment for FL[6]

1. Kahl BS, et al. Blood. 2016;127:2055-2063. , 2. Schneider T, et al. Pathol Oncol Res. 2017;[Epub ahead of print]. 3. Salles G, et al. Lancet. 2011;377:42-51. 4. Tees MT, et al. 2017. Curr Treat Options Oncol. 2017;18:16. 5. Marcus R, et al. N Engl J Med. 2017;377:1331-1344.

6. Rummel MJ, et al. ASH 2017. Abstract 483.

MAINTAIN: Study Design

- Prospective, randomized phase III study



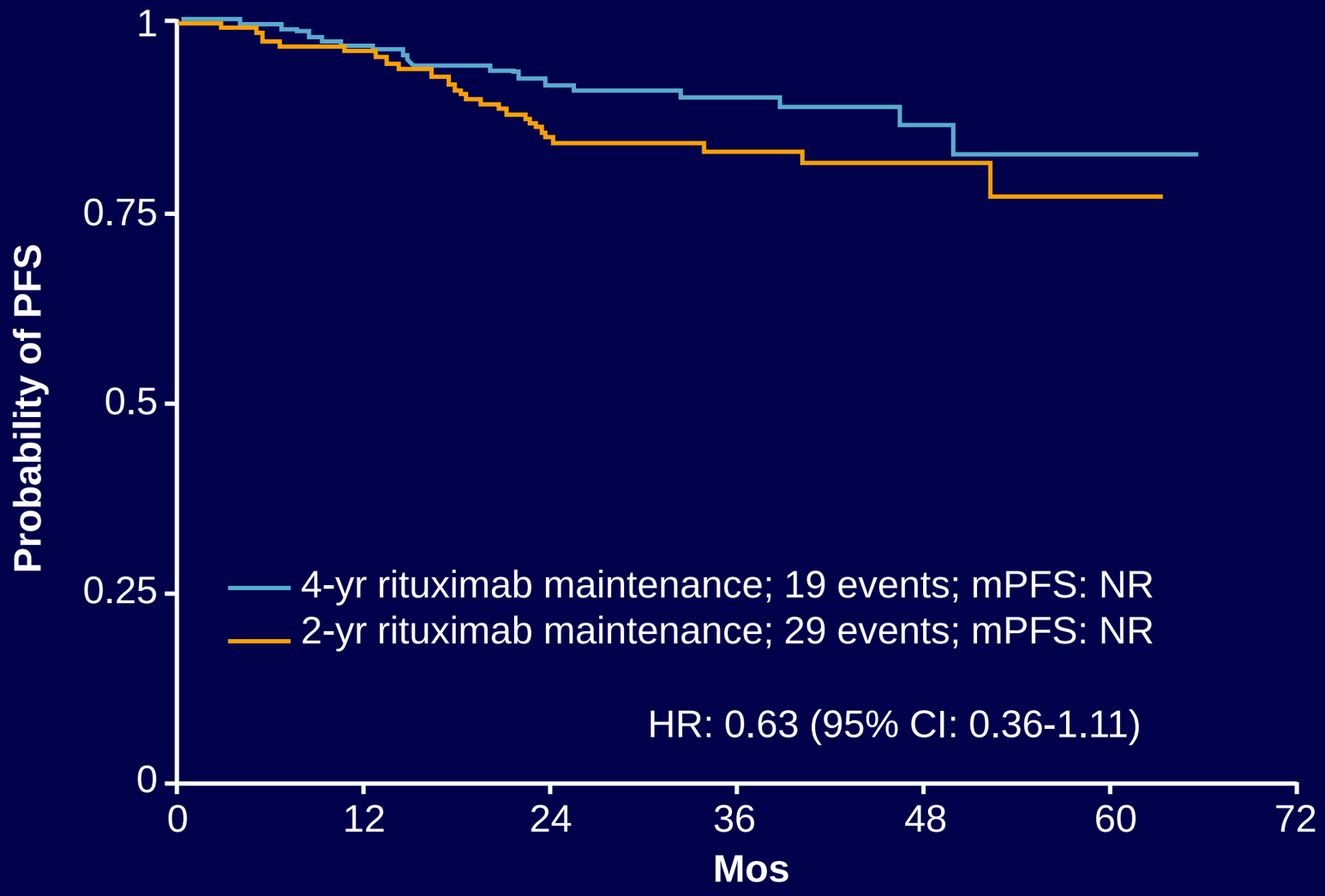
*n = 261 pts d/c, including for PD, pt or physician choice, toxicity or infection, rituximab intolerance, or death.

- Primary endpoint: PFS
- Secondary endpoints: response rates, OS, toxicity

Rummel MJ, et al. ASH 2017. Abstract 483. ClinicalTrials.gov. NCT00877214.

MAINTAIN: PFS (Primary Endpoint)

- 4 yrs vs 2 yrs rituximab maintenance appeared to prolong mPFS in pts treated with BR induction
  - Not statistically significant
- OS similar between arms



Rummel MJ, et al. ASH 2017. Abstract 483.

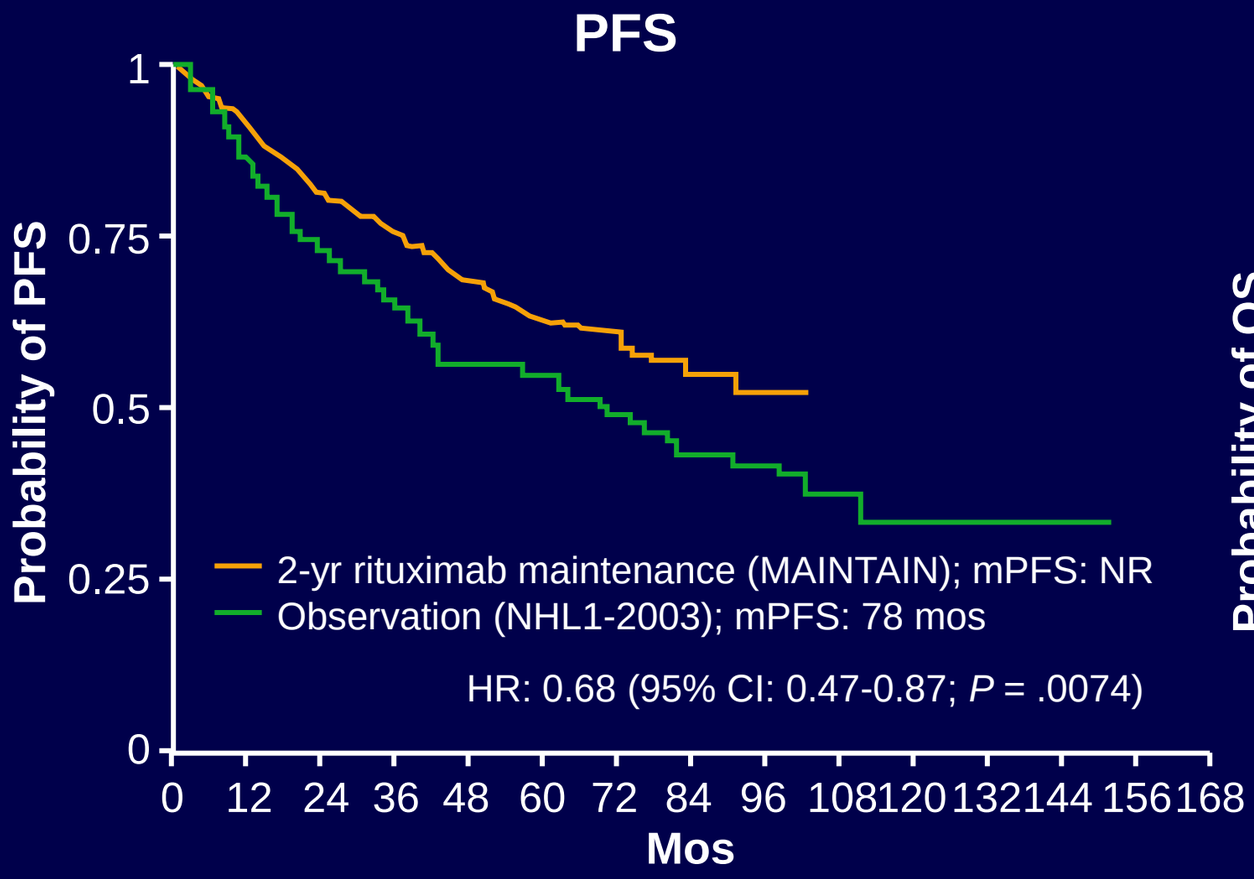
MAINTAIN: BL Pt Characteristics for Current vs Historical Cross-Study Comparison

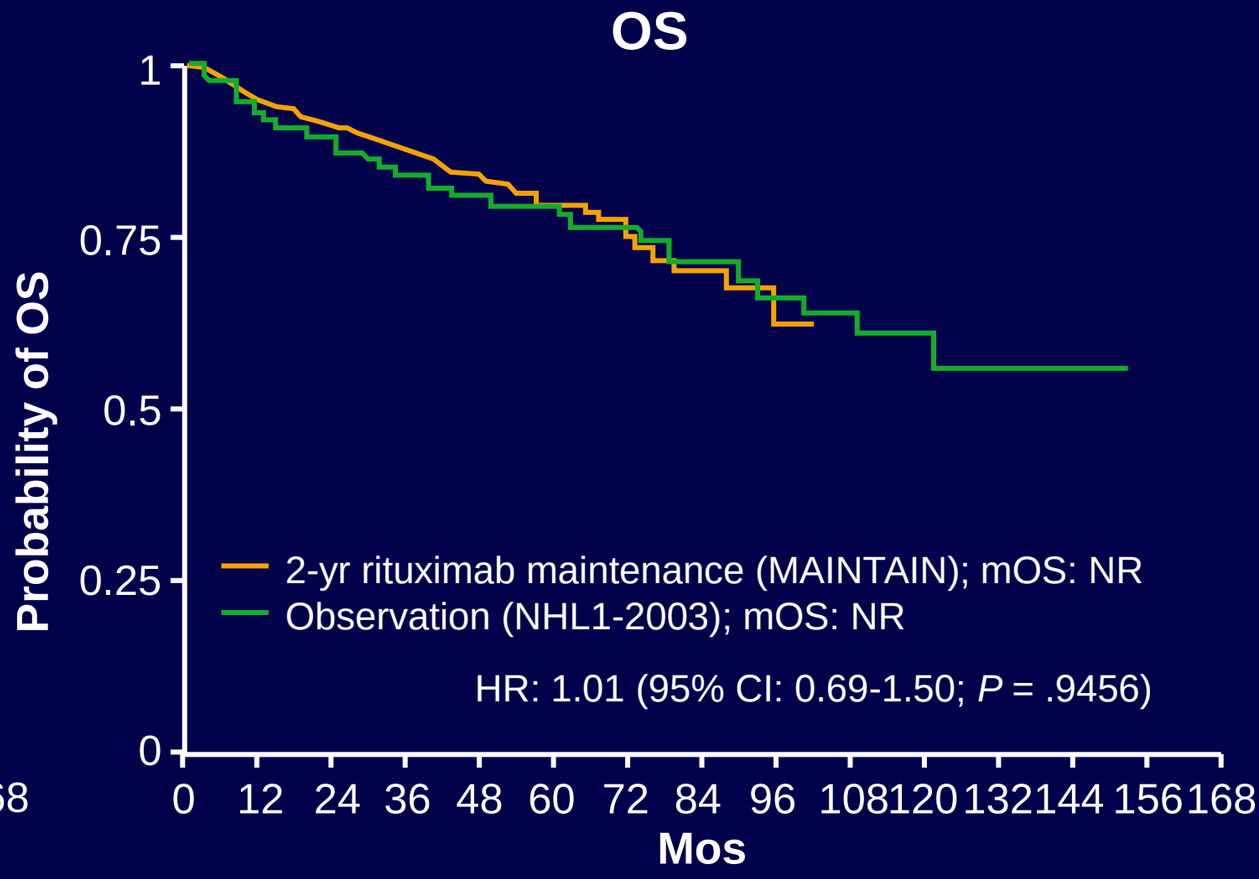
Characteristic	MAINTAIN[1] (n = 595)	NHL1-2003[2] (n = 139)
Median age, yrs (range)	61	60
Male, %	49	45
Stage, %		
▪ III	29	26
▪ IV	59	69
B-symptoms	36	38
Bone marrow involved	54	60
LDH > 240	36	41
FLIPI		
▪ Good	17	12
▪ Intermediate	32	51
▪ Poor	50	45

- MAINTAIN: pts with BR induction + 2-yr rituximab maintenance[1]
  - Pts with 4-yr rituximab maintenance censored
- StiL NHL1-2003: FL pts with BR induction followed by observation[2]
  - Did not include pts from study who received R-CHOP

1. [illegible] 03-1210.

MAINTAIN: PFS of 2-Yr Rituximab Maintenance vs Observation Post BR (Cross-Study Comparison)





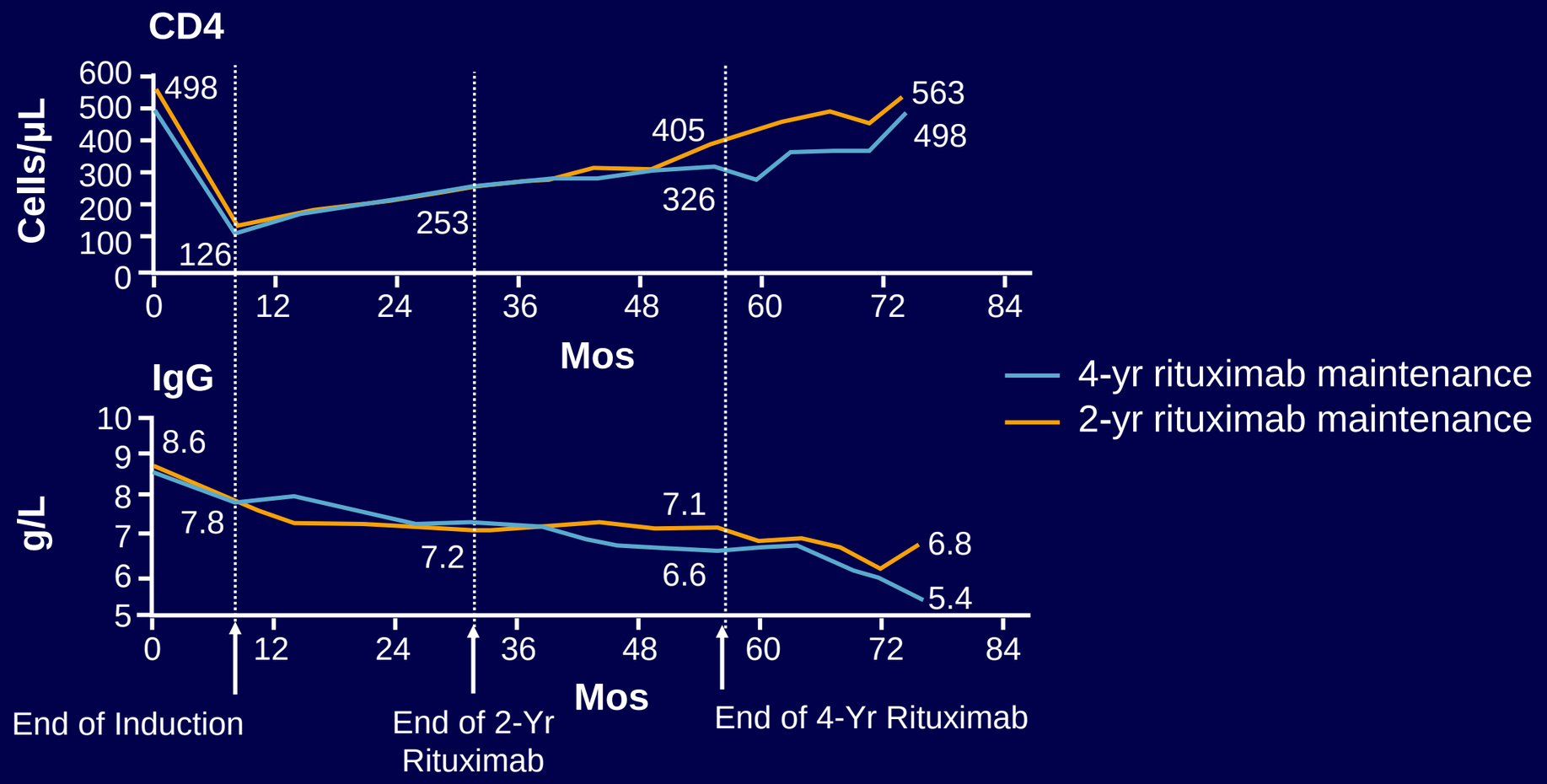
- In nonrandomized, cross-study comparison, 2-yr rituximab maintenance significantly increased PFS but not OS vs observation following BR

Rummel MJ, et al. ASH 2017. Abstract 483.

MAINTAIN: Second Primary Malignancy

Second Primary Malignancies	4-Yr Rituximab Maintenance (n = 178)	2-Yr Rituximab Maintenance (n = 172)	Not Randomized (n = 261)
Pts with second primary malignancy (n = 64), n (%)	15 (8)	18 (10)	31 (12)
Secondary malignancies (n = 73), n			
▪ Prostate	21	18	34
▪ Colon/gastric	2	3	0
▪ Lung	2	1	7
▪ Kidney/urothelial	1	0	8
▪ Pancreatic	0	2	1
▪ Breast	0	0	1
▪ Other, including nonmelanoma skin cancer	1	2	2
▪ Myelodysplastic syndromes	14	9	12
▪ Acute myeloid leukemia	0	0	2
▪ Chronic myeloproliferative neoplasia	0	1	1

MAINTAIN: CD4+ Cell Count and IgG Over Time



- CD4+ cell count and IgG levels similar over course of study for pts receiving 4 yrs or 2 yrs of rituximab maintenance following BR induction

Rummel MJ, et al. ASH 2017. Abstract 483.

MAINTAIN: Conclusions

- In pts with FL treated with BR, 4 yrs vs 2 yrs of rituximab maintenance appears to prolong median PFS
  - Difference not statistically significant
  - Investigators suggest that pts in analysis may not be suitable candidates for rituximab maintenance due to stringent exclusion requirements
    - Fewer PFS events than expected
- In a nonrandomized comparison to earlier study, PFS but not OS was improved with 2-yr rituximab maintenance following BR therapy for FL vs observation

Rummel MJ, et al. ASH 2017. Abstract 483.

RELEVANCE: PHASE III RANDOMIZED STUDY OF LENALIDOMIDE PLUS RITUXIMAB (R^2) VERSUS CHEMOTHERAPY PLUS RITUXIMAB, FOLLOWED BY RITUXIMAB MAINTENANCE, IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA (FL)

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on behalf of the RELEVANCE Trial Investigators

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Lille, CHU Lille, Lille, France; [3]Centre Hospitalier Universitaire Régional de Nancy, Service d'Hématologie, Vandoeuvre les Nancy, France; [4]Institut Paoli Calmettes, Marseille, France; [5]Centre Henri Becquerel, Rouen, France; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]Institut d'Hématologie de Basse Normandie, Caen, France; [8]University of Washington, Seattle, WA; [9]CHU Le Bocage Service d'Hématologie Clinique, Dijon, France; [10]Instituto Português de Oncologia Lisboa Francisco Gentil (IPOLFG) Departamento de Hematologia, Lisboa, Portugal; [11]Grand Hôpital de Charleroi, Charleroi, Belgium; [12]ZNA Stuivenberg, Antwer, Belgium; [13]Hospital Universitario de Salamanca and IBSAL, CIBERONC, Salamanca, Spain; [14]Hospital Clinic de Barcelona, Barcelona, Spain; [15]CHU de Québec, Hôpital de l'Enfant-Jésus, Québec, Canada; [16]Tokai University Hospital, Kanagawa, Japan; [17]Celgene Corporation, Summit, NJ; [18]Departement de Bio-pathologie, Institut Paoli-Calmettes, Marseilles, France; [19]Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, University of Lyon, Pierre-Benite, France

Presented By Nathan Fowler at 2018 ASCO Annual Meeting

BACKGROUND AND RATIONALE

- **Current standard of care is rituximab + chemotherapy (R-chemo) with rituximab (R) maintenance in advanced-stage, previously untreated FL[1,2]**
  - **3-year PFS was 73%-78% for PRIMA and GALLIUM studies**
  - **Repeated relapses are common and usually shorter with each line of therapy**
- **Lenalidomide is an immunomodulatory agent activating NK and T cells and results in apoptosis of neoplastic B cells; has complementary mechanisms with rituximab[3]**
- **Phase II results for combined immunotherapy with lenalidomide and rituximab (R^2) demonstrated 3-year PFS of 79%-81% in previously untreated FL[4,5]**

RELEVANCE is the first multicenter, international, open-label, randomized phase III trial of R^2 versus R-chemo followed by rituximab maintenance in previously untreated, advanced FL requiring systemic treatment (LYSA/Celgene collaboration)

1. Salles et al. *Lancet*. 2011;377:42-51. 2. Marcus et al. *N Engl J Med* 2017;377:1331-1344. 3. Gribben et al. *J Clin Oncol*. 2015;33:2803-2811.
4. Fowler et al. *Lancet Oncol*. 2014;15:1311-1318. 5. Martin et al. *Ann Oncol*. 2017;28:2806-2812.

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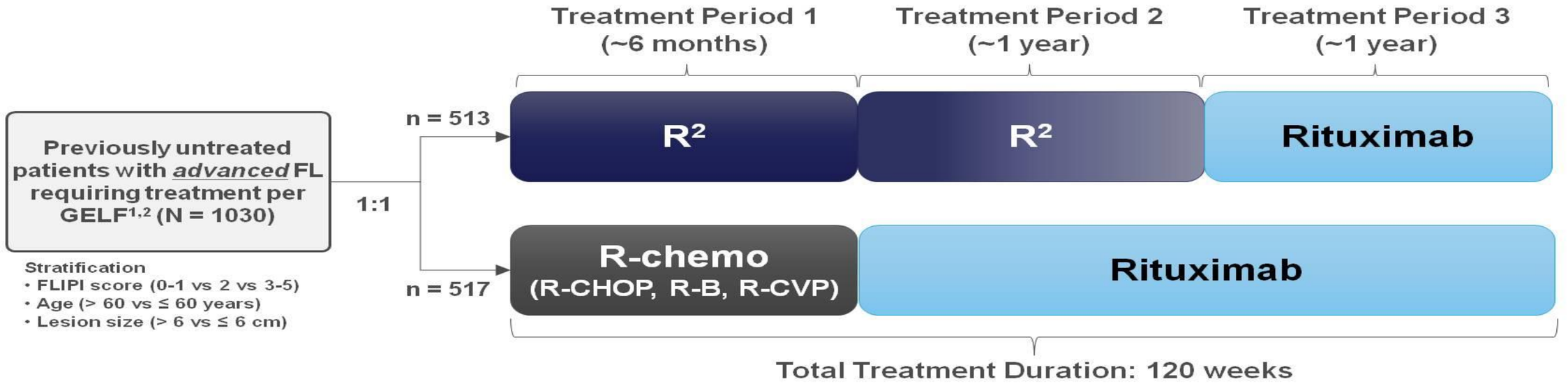
RELEVANCE: STUDY DESIGN



Co-primary endpoints (superiority)*

- CR/CRu at 120 weeks
- PFS

NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.
1. Salles et al. *Lancet*. 2011;377:42-51. 2. Brice et al. *J Clin Oncol*. 1997;15:1110-1117.

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RELEVANCE: DOSING SCHEDULE

Treatment Period	R^2 Arm	R-Chemo Arm
1 (~6 months)	• Lenalidomide: 20 mg/d, d2-22/28 • Rituximab: 375 mg/m^2	Investigator/Patient choice prior to randomization • R-CHOP (72%) • R-B (23%) • R-CVP (5%)
2 (~1 year)	• Lenalidomide: 20 or 10 mg/d per response at 6, 9 or 12 cycles • Rituximab: 375 mg/m^2	• Rituximab: 375 mg/m^2
3 (~1 year)	• Rituximab: 375 mg/m^2	• Rituximab: 375 mg/m^2

- **R^2:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles)
  Rituximab (R) 375 mg/m^2/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-CHOP**: R 375 mg/m^2 IV d1, cyclophosphamide 750 mg/m^2 IV d1, doxorubicin 50 mg/m^2 IV d1, vincristine 1.4 mg/m^2 IV d1, prednisone 100 mg/d PO d1-5; q21d X6 and two 21-day cycles R 375 mg/m^2 IV d1
- **R-B**: R 375 mg/m^2 IV d1 and bendamustine 90 mg/m^2 IV d1-2; q28d X6
- **R-CVP**: R 375 mg/m^2 IV d1, cyclophosphamide 750 mg/m^2 IV d1, vincristine 1.4 mg/m^2 IV d1, prednisone 40 mg/d PO d1–5; q21d X8
- **R maintenance**: In responders, 375 mg/m^2 IV d1 of each cycle q8wk

RELEVANCE

RELEVANCE: BASELINE CHARACTERISTICS (ITT)

Characteristics, n (%)		R^2 (n = 513)	R-chemo (n = 517)
Median age, years (range)		59 (30-89)	59 (23-83)
Age > 70 years		80 (16)	78 (15)
Male		251 (49)	251 (49)
ECOG PS	0	341 (66)	345 (67)
	1	157 (31)	157 (30)
	2	13 (3)	14 (3)
	Not evaluated	2 (< 1)	1 (< 1)
Ann Arbor stage	I/II	30 (6)	40 (8)
	III/IV	483 (94)	477 (92)
Bulky disease (> 7 cm)		218 (42)	199 (38)
FL grade*	1 or 2	437 (85)	443 (86)
	3a	65 (13)	63 (12)
FLIPI score	Low risk (0-1)	77 (15)	76 (15)
	Intermediate risk (2)	183 (36)	191 (37)
	High risk (3-5)	253 (49)	250 (48)
Lactate dehydrogenase (> ULN)		156 (30)	137 (26)
B-symptoms - yes		141 (27)	134 (26)

Data cut-off 31May2017. *FL grade was unspecified or not FL grade 1-3a for 11 patients in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, FL International Prognostic Index; ULN, upper limit of normal.

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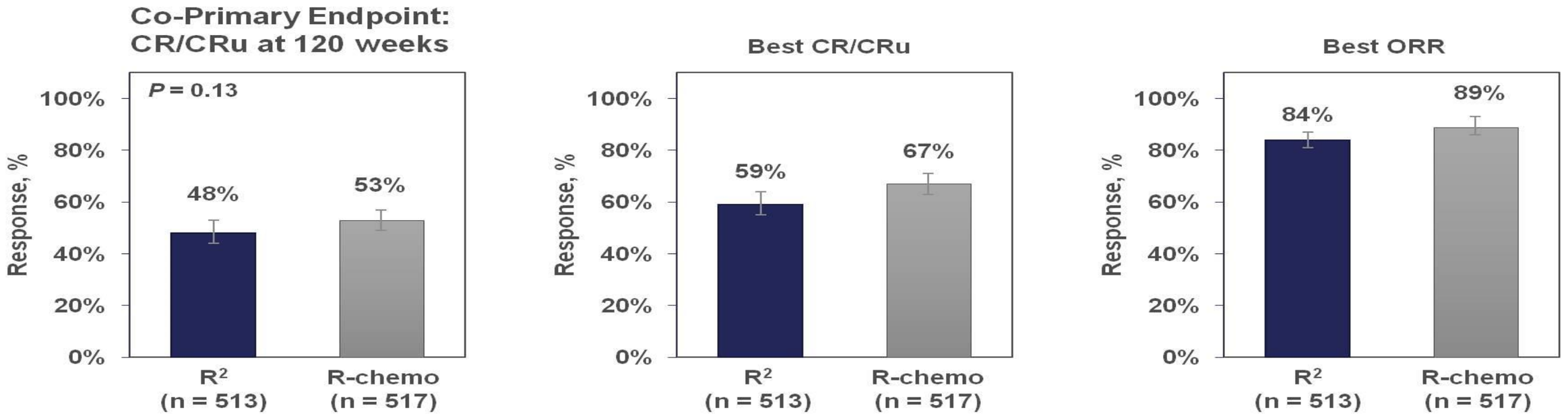
RITUXIMAB LENALIDOMIDE VERSUS ANY CHEMOTHERAPY

RELEVANCE: RESPONSE BY IRC (ITT)



- 3-year DOR was 77% for R^2 vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

Data cut-off 31May2017.

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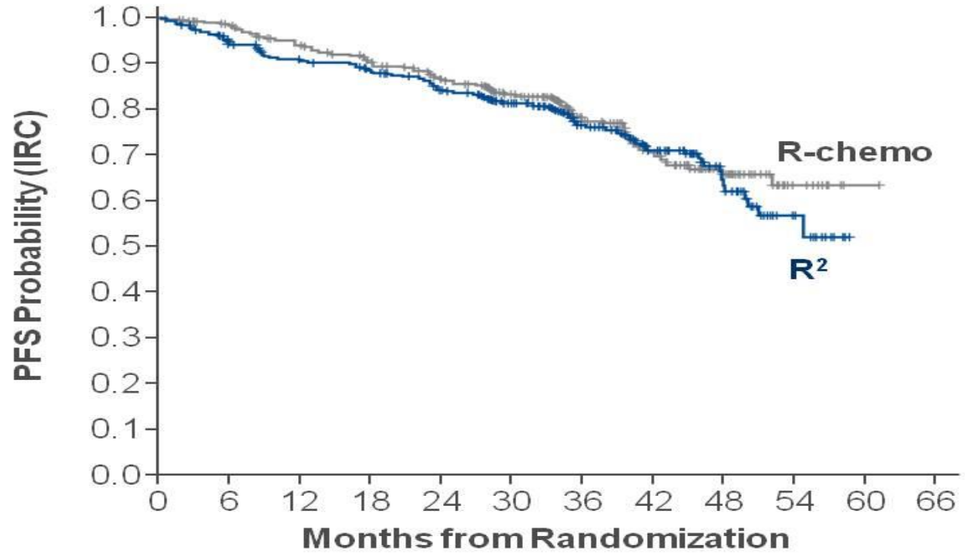
RELEVANCE: INTERIM PFS BY IRC

Co-Primary Endpoint: Interim PFS (~50% events)



Number of Patients at Risk

R²	513	435	409	393	364	282	174	107	49	13	0	
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

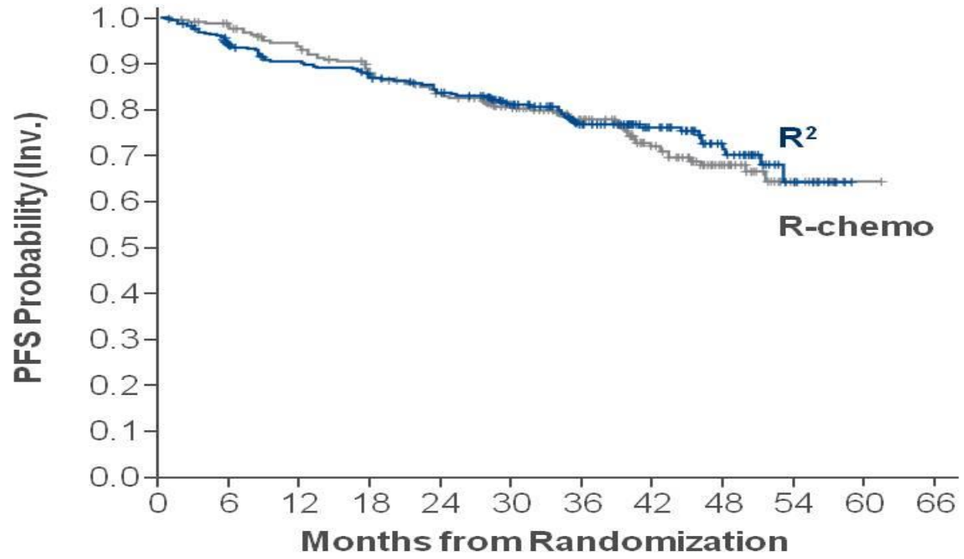
	R² (n = 513)	R-chemo (n = 517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI)	1.10 (0.85-1.43)	
P value	0.48	

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

Data cut-off 31May2017.

RELEVANCE™
RITUXIMAB LENALIDOMIDE VERSUS ANY CHEMOTHERAPY

RELEVANCE: INTERIM PFS BY INVESTIGATOR REVIEW



Number of Patients at Risk

R²	513	443	423	404	385	306	184	114	56	13	0	
R-chemo	517	480	451	418	392	297	188	119	57	15	1	0

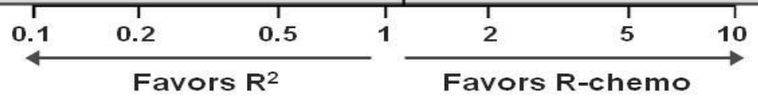
	R² (n = 513)	R-chemo (n = 517)
Events, n (%)	111 (22)	121 (23)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-81%)
HR (95% CI)	0.94 (0.73-1.22)	
P value	0.63	

Data cut-off 31May2017.

RELEVANCE™
RITUXIMAB LENALIDOMIDE VERSUS ANY CHEMOTHERAPY

RELEVANCE: PRESPECIFIED SUBGROUP ANALYSIS OF INTERIM PFS (IRC)

	R², n/N	R-chemo, n/N	HR (95% CI)
Overall	119/513	115/517	1.10 (0.85-1.43)
Age			
≤ 60	58/281	55/282	1.15 (0.79-1.66)
> 60	61/232	56/235	1.06 (0.74-1.53)
Sex			
Male	61/251	59/251	1.02 (0.71-1.46)
Female	58/262	52/266	1.23 (0.85-1.79)
Disease stage			
I/II	6/30	5/40	2.23 (0.66-7.55)
III/IV	113/483	106/477	1.06 (0.82-1.39)
Longest diameter of the longest node			
≤ 6 cm	62/253	58/271	1.19 (0.83-1.71)
> 6 cm	57/260	53/246	1.04 (0.71-1.51)
FLIPI score			
0-1	14/77	9/76	2.06 (0.88-4.80)
2	37/183	35/191	1.12 (0.70-1.78)
3-5	68/253	67/250	1.00 (0.72-1.41)
Country			
Ex-North America	93/384	92/379	1.03 (0.77-1.38)
North America	26/129	19/138	1.53 (0.84-2.76)



- Post-hoc analysis showed no differences between R² and the three R-chemo regimens

Data cut-off 31May2017.

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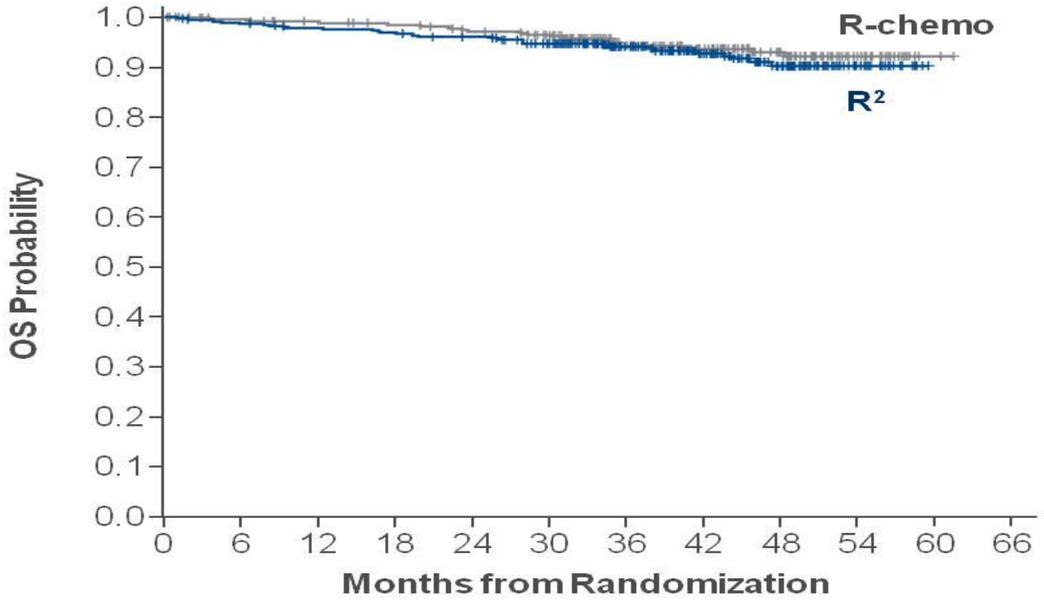
RELEVANCE: OVERALL SURVIVAL (IMMATURE; ITT)



Number of Patients at Risk

R²	513	499	491	486	479	459	312	194	105	24	0	
R-chemo	517	496	487	481	470	453	298	193	115	32	2	0

	R² (n = 513)	R-chemo (n= 517)
Events, n (%)	38 (7)	31 (6)
3-year OS (95% CI)	94% (91%-96%)	94% (91%-96%)
HR (95% CI)	1.16 (0.72-1.86)	

Data cut-off 31May2017.

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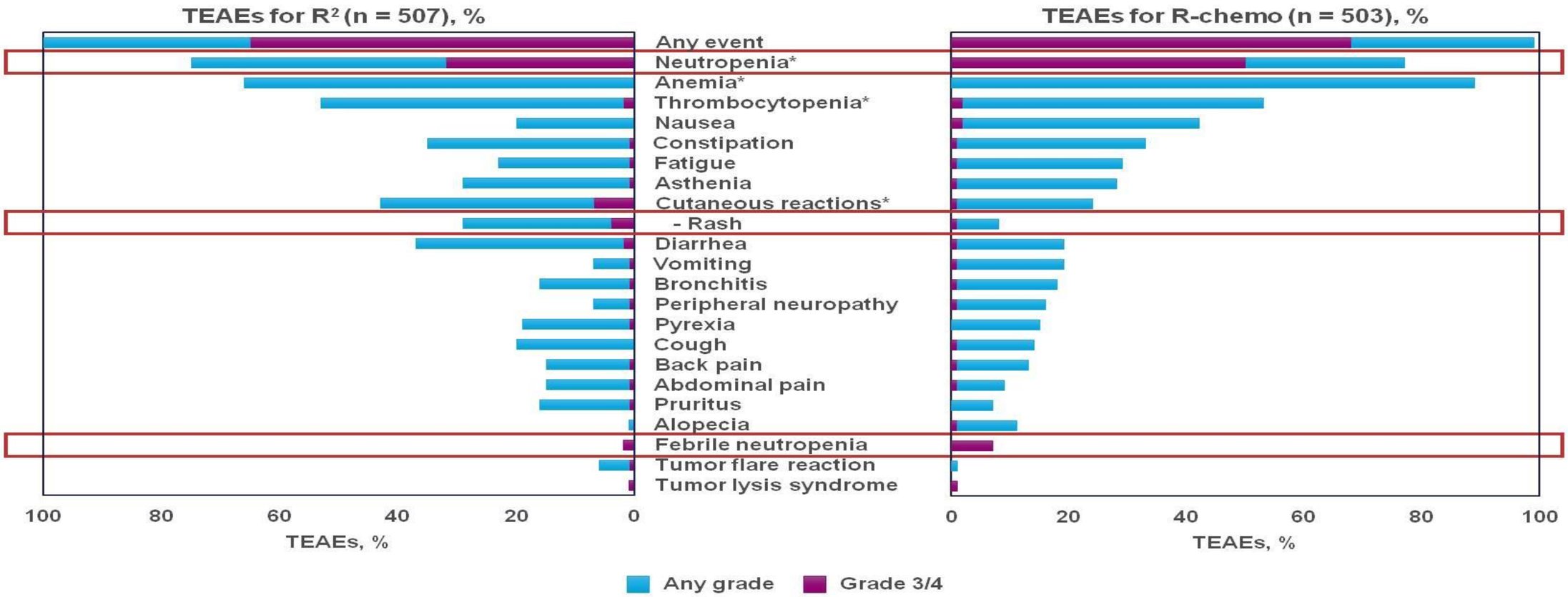
RELEVANCE: TREATMENT-EMERGENT ADVERSE EVENTS



Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

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RELEVANCE: NEUTROPENIA AND NEUTROPENIC COMPLICATIONS (ENTIRE TREATMENT PERIOD)

Patients, n (%)	R^2 (n = 507)	R-chemo (n = 503)
Grade 3/4 neutropenia*	160 (32)	252 (50)
Grade 4 neutropenia	41 (8)	154 (31)
Nadir ANC < 100/μL	5 (1)	32 (6)
Median time to onset of first grade 3/4 lab neutropenia	3.7 months	0.6 months
Grade 3/4 infections associated with grade 3/4 neutropenia	10 (2)	20 (4)
Febrile neutropenia*	11 (2)	34 (7)
Febrile neutropenia requiring hospitalization	8 (2)	26 (5)
Infections requiring hospitalization	46 (9)	60 (12)
Received growth factors	117 (23)	340 (68)

- Per protocol, patients in the R^2 arm had more frequent laboratory assessments than the R-chemo arm

*Including 4 cases of febrile bone marrow aplasia (all in R-chemo arm).

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RELEVANCE: TREATMENT DISCONTINUATIONS (SAFETY)

- 69% R^2 and 71% R-chemo patients completed treatment

Reasons for Discontinuation, n (%)	R^2 (n = 507)	R-chemo (n = 503)
All discontinuations	157 (31)	146 (29)
Progression	64 (13)	71 (14)
Toxicity	43 (8)	16 (3)
Insufficient response*	15 (3)	3 (1)
Concurrent illness	12 (2)	9 (2)
Voluntary discontinuation/ consent withdrawal	11 (2)	18 (4)
Major protocol violation	1 (< 1)	6 (1)
Death	0	1 (< 1)
Other†	11 (2)	22 (4)

Data cut-off 31May2017.
*Per protocol design.
†Most common other reasons for discontinuation were second primary malignancy (SPM), investigator decision, and lost to follow-up.

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RELEVANCE: OTHER SAFETY RESULTS

- Second primary malignancies (SPMs) were similar between arms
  - All SPMs
    - R^2: 38 (7%)
    - R-chemo: 48 (10%)
  - Invasive SPMs
    - R^2: 25 (5%)
    - R-chemo: 27 (5%)
- Grade 5 TEAEs: 4 (1%) R^2 and 5 (1%) R-chemo patients
- Deaths related to study treatment occurred in 2 patients (1 per arm)

Data cut-off 31May2017.

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RELEVANCE: CONCLUSIONS

- R^2 was not superior to R-chemo based on mature CR/CRu at 120 weeks and interim PFS
  - R^2 and R-chemo showed similar efficacy results
  - Treatment effects on PFS were consistent across prespecified subgroups
  - Continued follow-up for more mature PFS and OS results is ongoing
- Important differences in safety profiles were observed between arms
  - R-chemo: More frequent neutropenia (grade 3/4), febrile neutropenia, growth factor usage, nausea, vomiting, neuropathy, and alopecia
  - R^2: More frequent cutaneous reactions, tumor flare, and diarrhea
- These results show that R^2, a novel immunomodulatory approach, is a potential first-line option for patients with FL requiring treatment

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THANK YOU

- All our patients, families, caregivers, and investigators who participated in the RELEVANCE clinical study, and to the numerous research and study groups (ALLG, GELTAMO, GLSG, LYSA, NCIC CTG) for including patients on the study
- Study sponsors Celgene Corporation and LYSARC
- Roche for providing rituximab
- LYSARC team: Nadine Vailhen (Central Pathology), Romain Ricci (Central Imaging), Loic Chartier (Statistics), and the international board of expert pathologists providing histopathology review at the LYSA Pathology Institute (LYSA-P), Hôpital Henri Mondor, Créteil, France: Luc Xerri, Camille Laurent, Danielle Canioni, Catherine Chassagne-Clement, Peggy Dartigues, and Bettina Fabiani
- Professor Christian Gisselbrecht and Andre Bosly for validating response data as independent expert hematologists for clinical assessment and imaging review
- John Leonard, MD for his initial input on the study design and participation in the steering committee
- Data monitoring committee (DMC):
  - Dirk Hasenclever, PhD (statistician, DMC chairman)
  - John Gribben, MD (medical advisor)
  - Brad Kahl, MD (medical advisor)
  - Jean-Philippe Jais, PhD (independent statistician for DMC meetings)

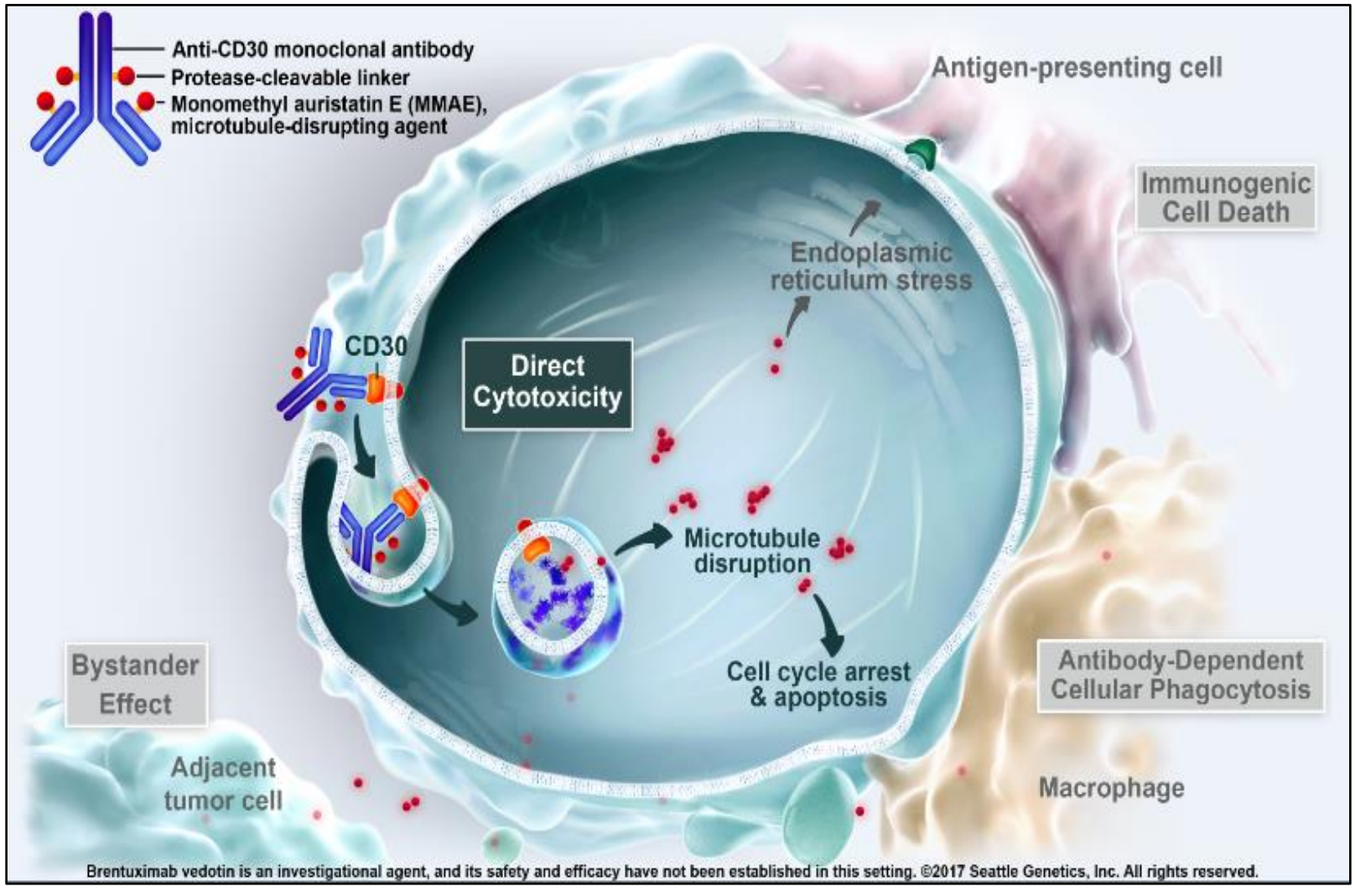
Hodgkin's Lymphoma

Brentuximab Vedotin Plus Doxorubicin, Vinblastine, Dacarbazine (A+AVD) as Frontline Therapy Demonstrates Significantly Improved Modified Progression-Free Survival versus ABVD in Patients with Previously Untreated Stage III or IV Hodgkin Lymphoma: The Phase 3 ECHELON-1 Study

Joseph M. Connors, Wojciech Jurczak, David J. Straus, Stephen M. Ansell, Won Seog Kim, Andrea Gallamini, Anas Younes, Sergey Alekseev, Árpád Illés, Marco Picardi, Ewa Lech-Maranda, Yasuhiro Oki, Tatyana Feldman, Piotr Smolewski, Kerry J. Savage, Nancy L. Bartlett, Jan Walewski, Robert Chen, Radhakrishnan Ramchandren, Pier Luigi Zinzani, David Cunningham, Andras Rosta, Neil C. Josephson, Eric Song, Jessica Sachs, Rachael Liu, Hina A. Jolin, Dirk Huebner, John Radford

Background and rationale

- HL[1,2]
  - Worldwide annual incidence 65,950
  - Stage III/IV 40%
- Standard chemotherapy[3,4]
  - ABVD, originally described in the 1970s
  - Major toxicity
    - Myelosuppression
    - Pulmonary (bleomycin)
- Relapse/refractory disease[5,6]
  - 25–30%
  - Standard treatment = high-dose chemotherapy + ASCT
- Brentuximab vedotin[7–10]
  - Anti-CD30 antibody, covalently attached via a cleavable linker to MMAE, a microtubule-disrupting agent
- Phase 1 experience with brentuximab vedotin + AVD (A+AVD) (N=26)[11,12]
  - Well tolerated
  - CR rate 96%
  - 5-year FFS 92%
  - 5-year OS 100%



A(B)VD, doxorubicin, (bleomycin), vinblastine, dacarbazine; CR, complete response; FFS, failure-free survival; HL, Hodgkin lymphoma; MMAE, monomethyl auristatin E; OS, overall survival

1. Ferlay J, et al. GLOBOCAN 2012 v1.0. Cancer Incidence and Mortality Worldwide. Accessed Nov 2017
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3. Vakkalanka B and Link BK. Adv Hematol 2011;doi 10.1155/2011/656013; 4. Martin WG, et al. J Clin Oncol 2005;23:7614–20
5. Carde P, et al. J Clin Oncol 2016;34:2028–36; 6. Ansell SM, Am J Hematol 2016;91:434–42
7. Wahl AF, et al. Cancer Res 2002;62:3736–42; 8. Francisco JA, et al. Blood 2003;102:1458–65
9. Doronina SO, et al. Nat Biotechnol 2003;21:778–84; 10. Okeley NM, et al. Clin Cancer Res 2010;16:888–97
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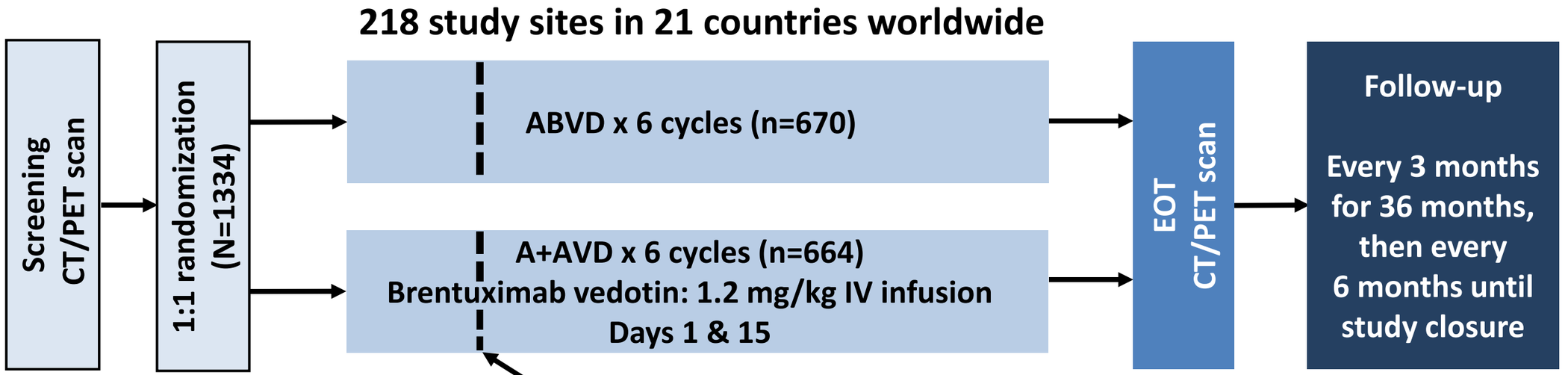
ECHELON-1: Open-label, global, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL



- **Inclusion criteria**
  - cHL stage — III or IV
  - ECOG PS — 0, 1 or 2
  - Age — ≥18 years
  - Measurable disease
  - Adequate liver and renal function

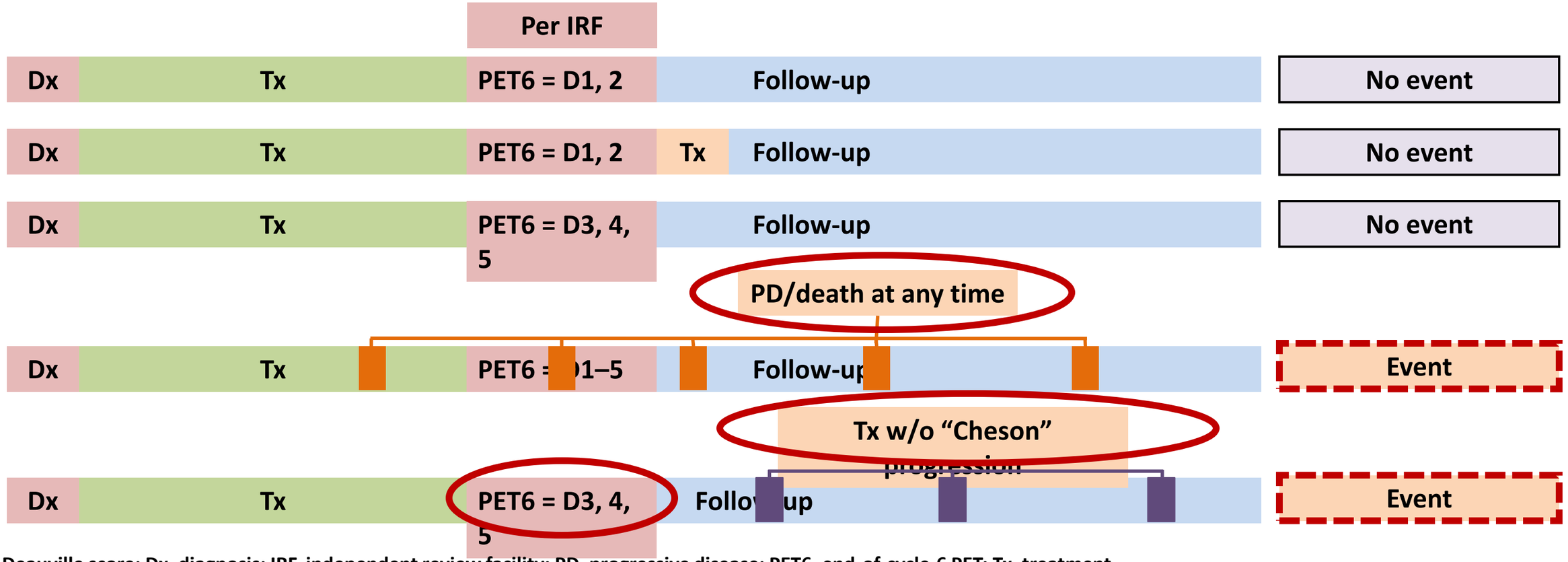
End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

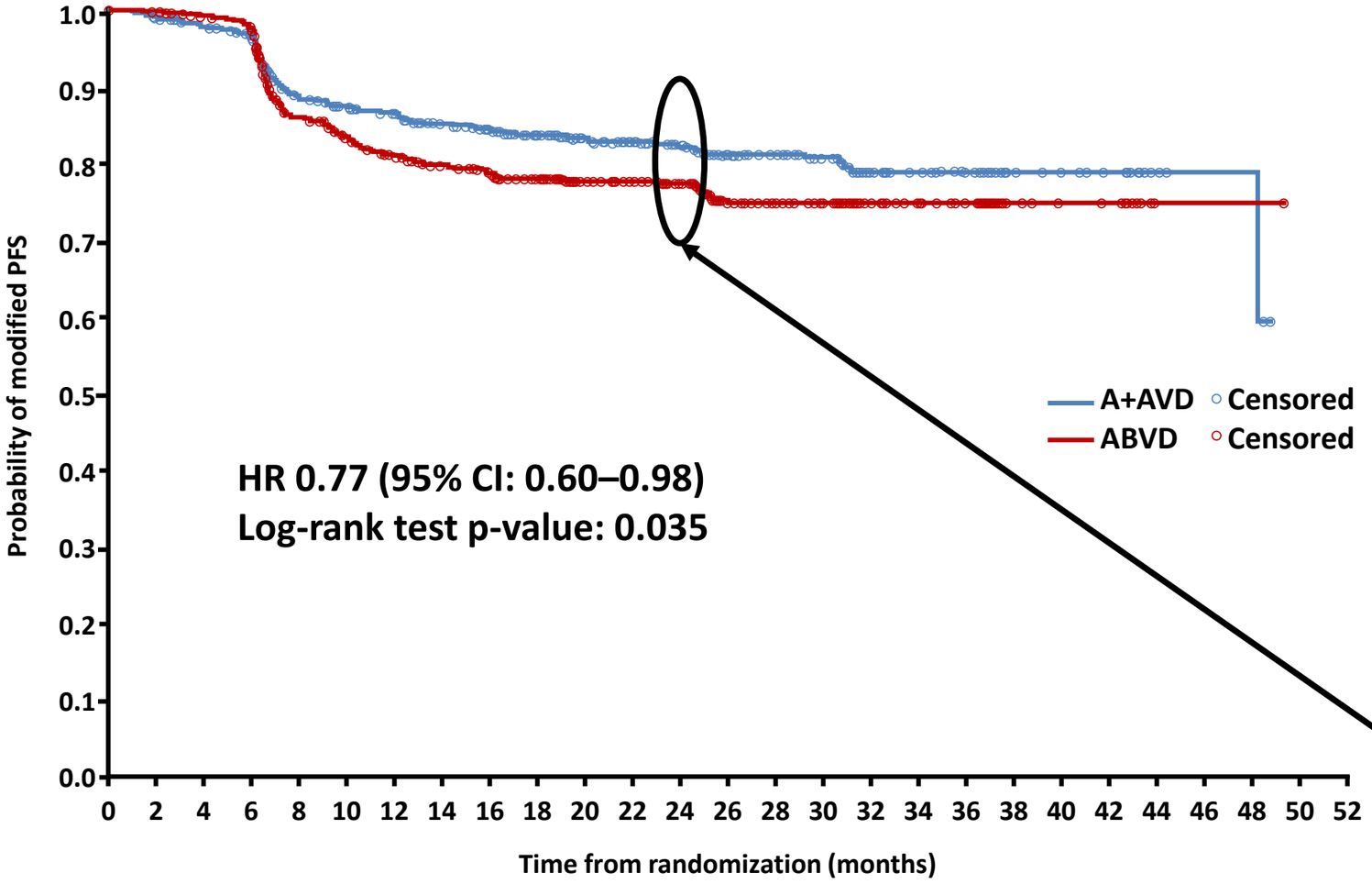
ECHELON-1: Primary endpoint definition

- Primary endpoint: modified PFS per IRF
  - A modified PFS event was defined as the first of:
    - Progression
    - Death from any cause
    - PET6 = D3, 4, 5 after completion of frontline therapy followed by subsequent anticancer therapy



D, Deauville score; Dx, diagnosis; IRF, independent review facility; PD, progressive disease; PET6, end-of-cycle-6 PET; Tx, treatment

Modified PFS per independent review



No. of patients at risk:

A+AVD	664	640	623	606	544	530	516	496	474	447	350	334	311	200	187	174	99	85	77	27	24	21	6	4	4	0	0
ABVD	670	644	626	613	522	496	476	459	439	415	328	308	294	179	168	153	78	68	62	16	13	12	1	1	1	0	0

Number of events

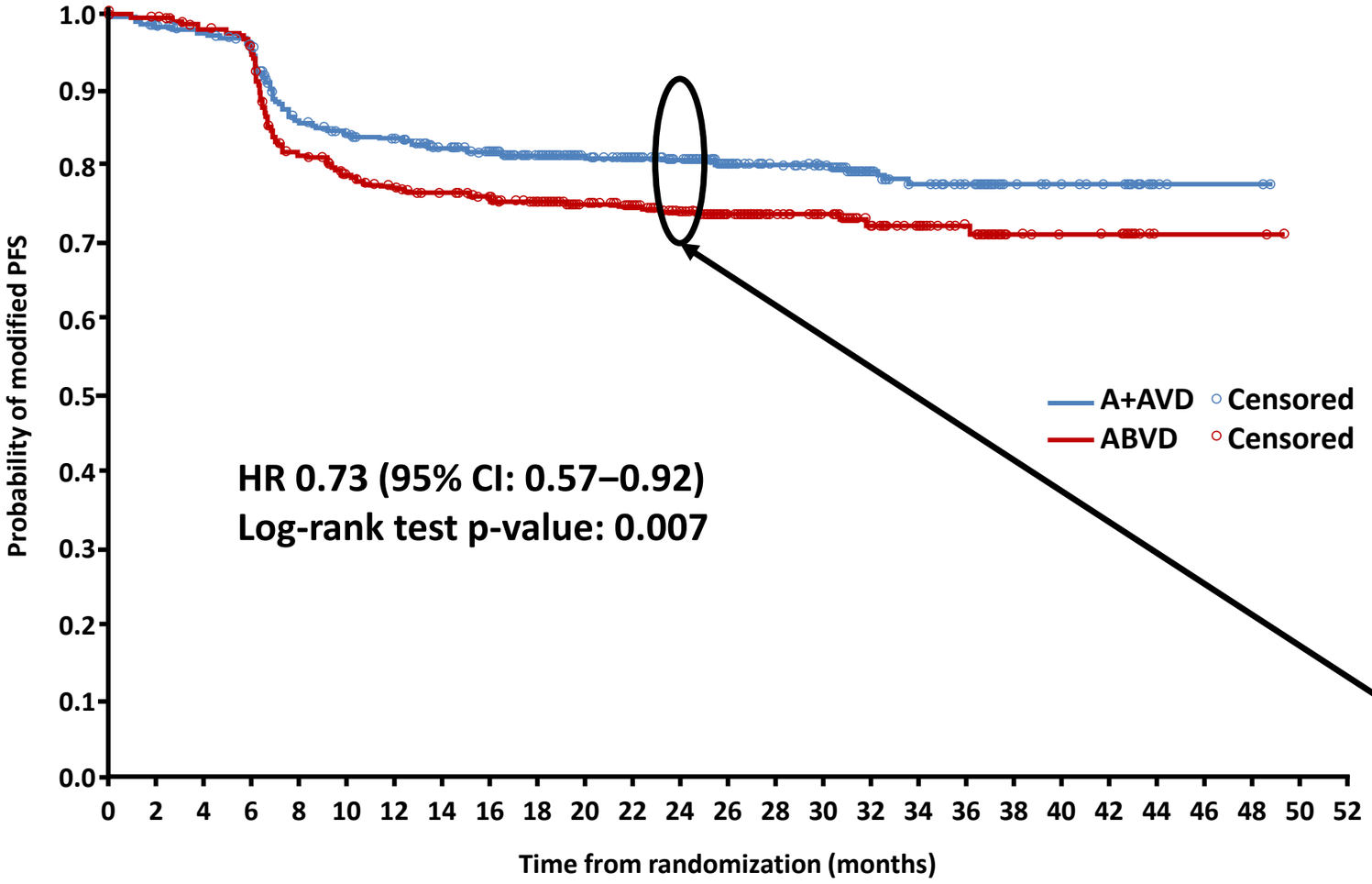
Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

Modified PFS per investigator



No. of patients at risk:

A+AVD	664	643	626	613	540	524	516	497	479	456	361	347	325	206	192	180	102	87	79	28	24	21	5	3	3	0	0
ABVD	670	643	628	611	514	492	476	463	448	426	343	319	299	186	171	157	82	71	63	16	13	12	2	2	2	0	0

Number of events

Category	A+AVD N=123	ABVD N=164
Progression	73	103
Death	15	22
Modified progression	35	39

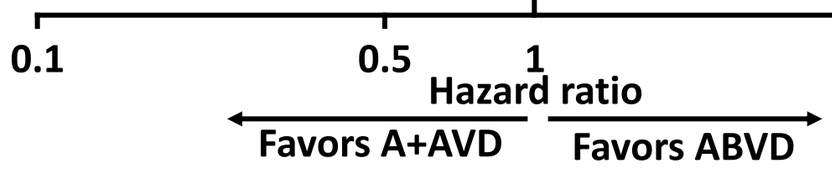
Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	81.0 (77.6–83.9)	74.4 (70.7–77.7)

Median follow-up (range): 25.0 months (0.0–49.3)

Forest plot of modified PFS per IRF: subgroup analysis

Subgroup	Event / N (%) A+AVD		Event / N (%) ABVD		Hazard ratio (95% CI)
Overall	**117/664**	**(17.6)**	**146/670**	**(21.8)**	**0.77 (0.60–0.98)**
Age <60 years	93/580	(16.0)	117/568	(20.6)	0.73 (0.56–0.96)
Age ≥60 years	24/84	(28.6)	29/102	(28.4)	1.01 (0.59–1.73)
Age <45 years	70/451	(15.5)	83/423	(19.6)	0.73 (0.53–1.01)
Age ≥45 years	47/213	(22.1)	63/247	(25.5)	0.86 (0.59–1.26)
Region: Americas	41/261	(15.7)	58/262	(22.1)	0.65 (0.44–0.97)
Region: North America	38/250	(15.2)	57/247	(23.1)	0.60 (0.39–0.90)
Region: Europe	62/333	(18.6)	74/336	(22.0)	0.83 (0.59–1.17)
Region: Asia	14/70	(20.0)	14/72	(19.4)	0.91 (0.43–1.93)
IPS: 0–1	22/141	(15.6)	25/141	(17.7)	0.83 (0.47–1.48)
IPS: 2–3	57/354	(16.1)	68/351	(19.4)	0.79 (0.56–1.13)
IPS: 4–7	38/169	(22.5)	53/178	(29.8)	0.70 (0.46–1.07)
Stage III	40/237	(16.9)	43/246	(17.5)	0.92 (0.60–1.42)
Stage IV	77/425	(18.1)	102/421	(24.2)	0.71 (0.53–0.96)
B symptoms: Present	77/399	(19.3)	94/381	(24.7)	0.74 (0.55–1.01)
B symptoms: Absent	40/265	(15.1)	52/289	(18.0)	0.79 (0.52–1.20)
Extranodal sites: 0	40/217	(18.4)	39/228	(17.1)	1.04 (0.67–1.62)
Extranodal sites: 1	36/217	(16.6)	45/223	(20.2)	0.75 (0.48–1.16)
Extranodal sites: >1	39/194	(20.1)	57/193	(29.5)	0.67 (0.44–1.00)
Gender: Male	64/378	(16.9)	90/398	(22.6)	0.71 (0.51–0.97)
Gender: Female	53/286	(18.5)	56/272	(20.6)	0.86 (0.59–1.26)



Summary of secondary efficacy endpoints

OS, CR, ORR, and PET negativity by IRF

- Key secondary endpoint - Interim OS: HR 0.72 (95% CI: 0.44–1.17; p=0.19) in favor of A+AVD versus ABVD
  - Interim OS analysis based on 67 deaths
  - Final OS analysis planned after 112 deaths
- All secondary efficacy endpoints trended in favor of A+AVD

Patients with event, n (%)	A+AVD N=664	ABVD N=670	p-value†
CR rate* at end of randomized regimen	488 (73)	472 (70)	0.22
ORR* at end of randomized regimen	569 (86)	553 (83)	0.12
PET Deauville score 1 or 2 after completion of frontline therapy	563 (85)	537 (80)	0.03
PET Deauville score 1, 2, or 3 after cycle 2	588 (89)	577 (86)	0.18
PET Deauville score 4, or 5 after cycle 2			
4	26 (4)	28 (4)	
5	21 (3)	30 (4)	
Unavailable	29 (4)	35 (5)	

*Per Cheson 2007; †Cochran-Mantel-Haenszel, chi-square test; ORR, overall response rate

Summary of subsequent therapy

Type of subsequent therapy, n (%)	A+AVD N=662	ABVD N=659
Patients with ≥1 subsequent anticancer therapy	**121 (18)**	**144 (22)**
Patients receiving systemic therapy and radiation		
Systemic Total*	80	111
Radiation Total*	52	52
Types of systemic treatment (+/- radiation)*		
Chemotherapy	66	99
High-dose chemotherapy + transplant	36	54
Immunotherapy	10	16
Radiation only*	41	33

- 33% fewer A+AVD patients received subsequent chemotherapy
- 33% fewer A+AVD patients received subsequent high-dose chemotherapy + transplant

*Sums of subsets exceed totals because some patients received more than one systemic treatment or systemic + radiation treatment

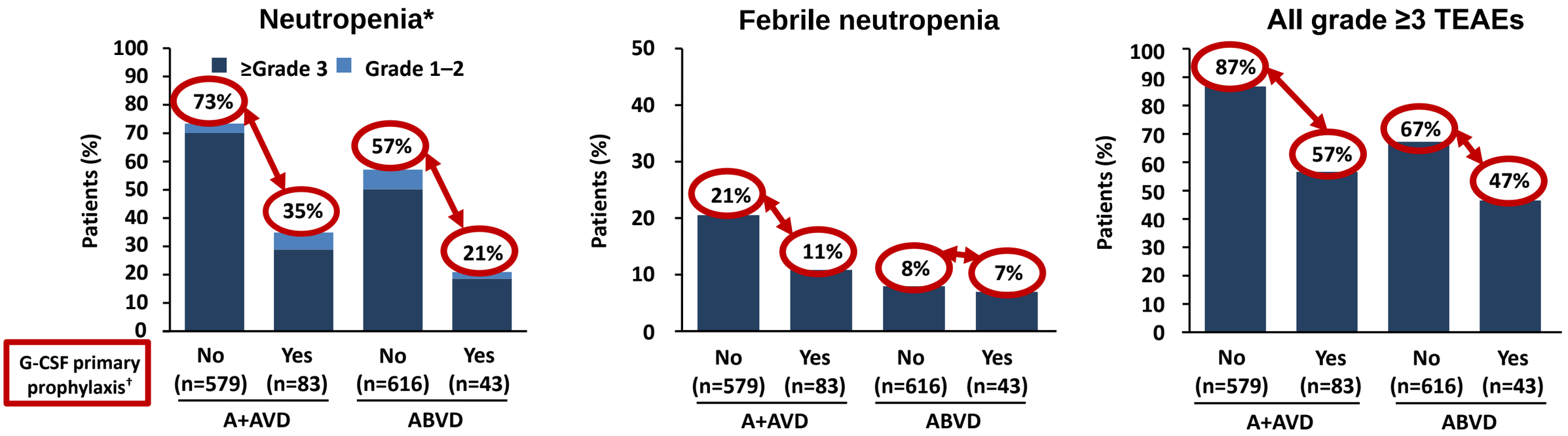
Most clinically important treatment-emergent adverse events

Incidence (any grade) ≥20% + febrile neutropenia

	A+AVD (N=662)		ABVD (N=659)	
Common adverse events, %*	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	58	54	45	39
Constipation	42	2	37	<1
Vomiting	33	3	28	1
Fatigue	32	3	32	1
Peripheral sensory neuropathy	29	5	17	<1
Diarrhea	27	3	18	<1
Pyrexia	27	3	22	2
Peripheral neuropathy	26	4	13	<1
Abdominal pain	21	3	10	<1
Stomatitis	21	2	16	<1
Febrile neutropenia	19	19	8	8

*Partial list focusing on the most clinically important adverse events. Adverse events (≥20% any grade in either arm) excluded from the table include nausea, alopecia, weight decreased, and anemia

Summary of treatment-emergent febrile neutropenia and adverse events by primary prophylaxis with G-CSF

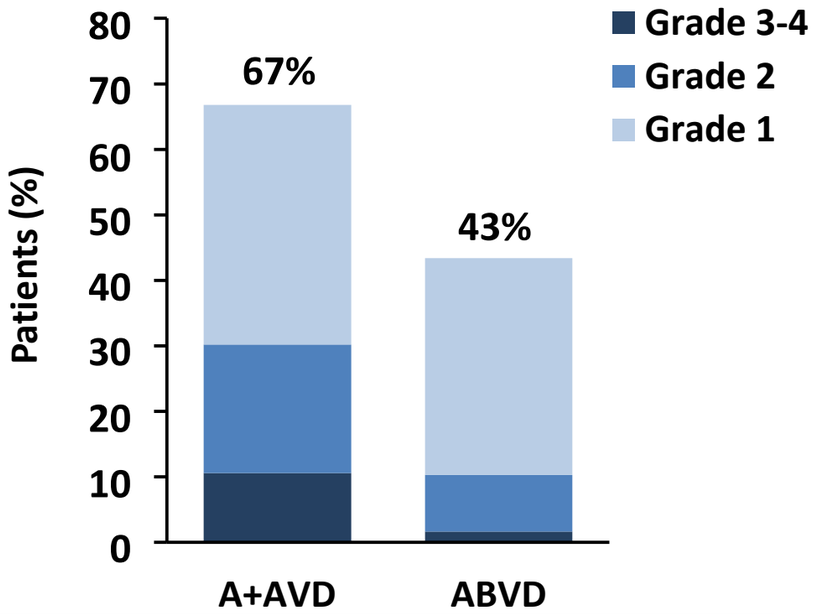


- G-CSF primary prophylaxis for A+AVD resulted in an overall safety profile comparable to ABVD
- G-CSF primary prophylaxis is recommended for all A+AVD patients

*Includes preferred terms of 'neutropenia' and 'neutrophil count decreased'; †Defined as G-CSF use by Day 5 of study treatment; TEAEs, treatment-emergent adverse events

Peripheral neuropathy and pulmonary events

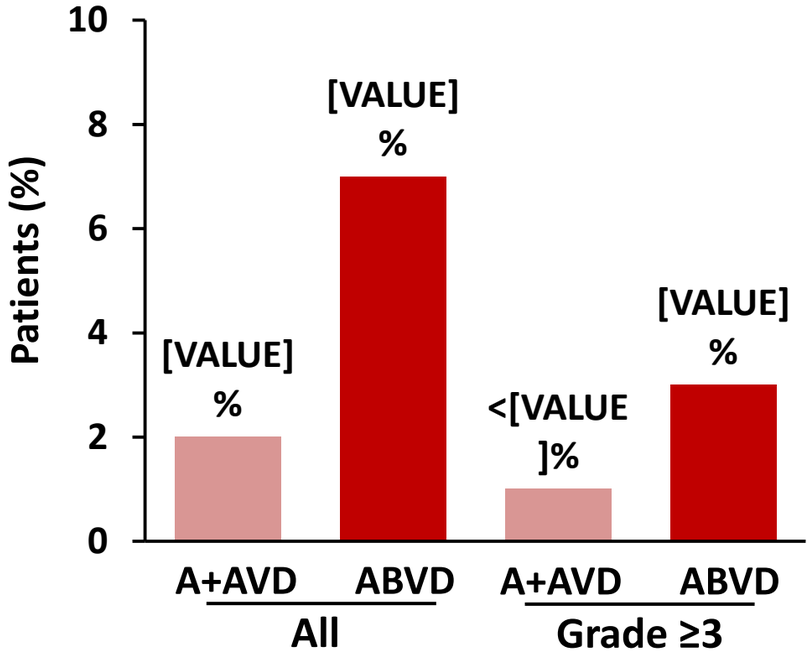
Treatment-emergent PN*



- 67% of pts with PN in the A+AVD arm had resolution or improvement by ≥1 grade at last follow-up
- Of those with ongoing PN at last follow-up:
  - Grade 1 64%
  - Grade 2 29%
  - Grade 3 7%

- Drug discontinuations due to PN:
  - A+AVD 7%
  - ABVD 2%

Interstitial lung disease†

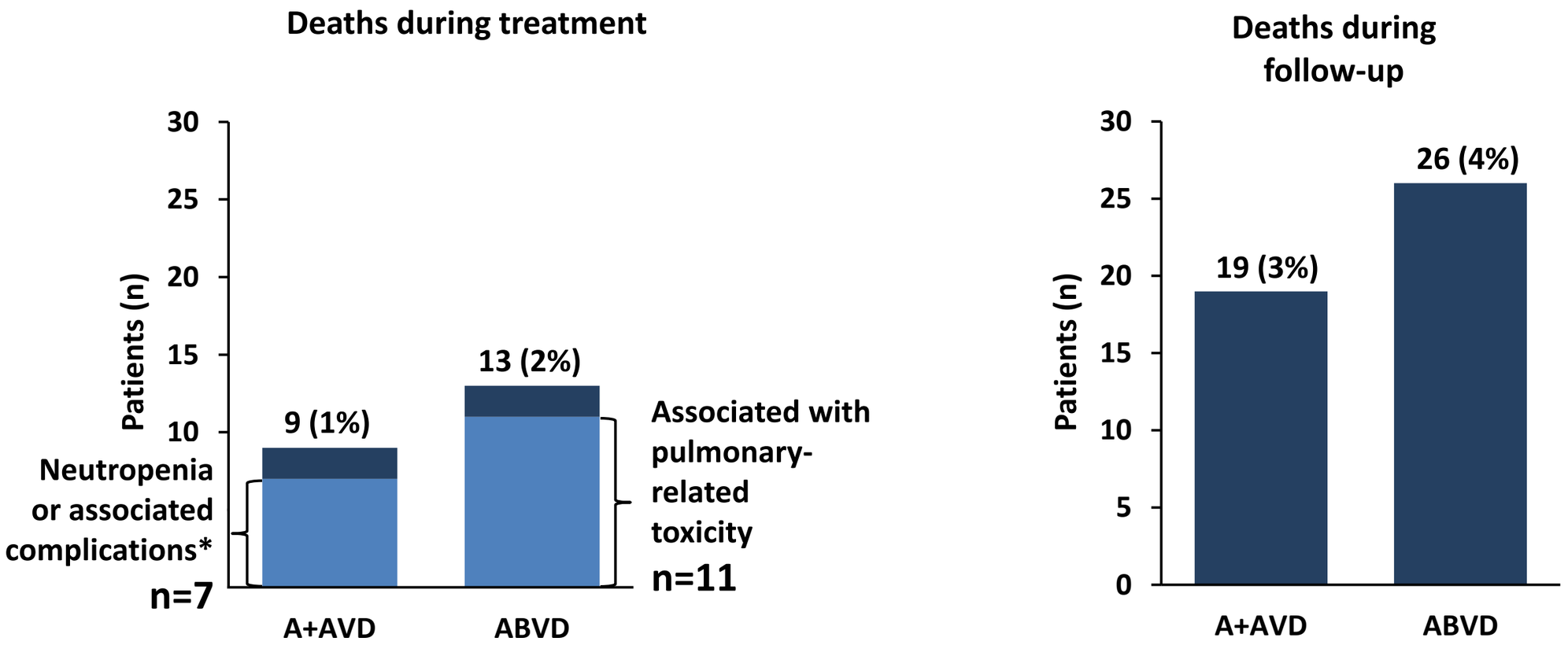


Interstitial lung disease was more frequent and more severe in ABVD arm

*Includes the preferred terms peripheral sensory neuropathy, PN, hypoesthesia, polyneuropathy, paraesthesia, muscular weakness, peripheral motor neuropathy, peroneal nerve palsy, muscle atrophy, hypotonia, autonomic neuropathy, neuralgia, burning sensation, dysesthesia, gait disturbance, toxic neuropathy, neurotoxicity, and sensory disturbance; PN, peripheral neuropathy

†Includes the preferred terms lung infiltration, pneumonitis, interstitial lung disease, acute respiratory distress syndrome, organizing pneumonia, pulmonary fibrosis, and pulmonary toxicity

Summary of deaths during treatment and during follow-up



Total deaths during treatment plus deaths during follow-up:
A+AVD: n=28; ABVD: n=39

*All neutropenia-associated deaths occurred in patients who had not received G-CSF primary prophylaxis before the onset of neutropenia with the exception of 1 patient who entered the trial with pre-existing neutropenia

Summary and conclusions

- **ECHELON-1 results**
  - **Significantly superior modified PFS with brentuximab vedotin in combination with AVD compared to ABVD**
  - **Independent review 23% reduction in risk of progression, death or need for additional anticancer therapy**
    - **2-year modified PFS 82% vs 77%**
  - **Investigator review 27% reduction in risk of progression, death or need for additional anticancer therapy**
    - **2-year modified PFS 81% vs 74%**

- **Brentuximab vedotin in combination with AVD**
  - **More effective than ABVD for the frontline treatment of advanced-stage cHL**
  - **Manageable toxicity profile**
    - **Bleomycin can be omitted**
    - **G-CSF primary prophylaxis is recommended for all patients**
    - **67% of pts with PN had resolution or improvement by ≥1 grade at last follow-up**

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

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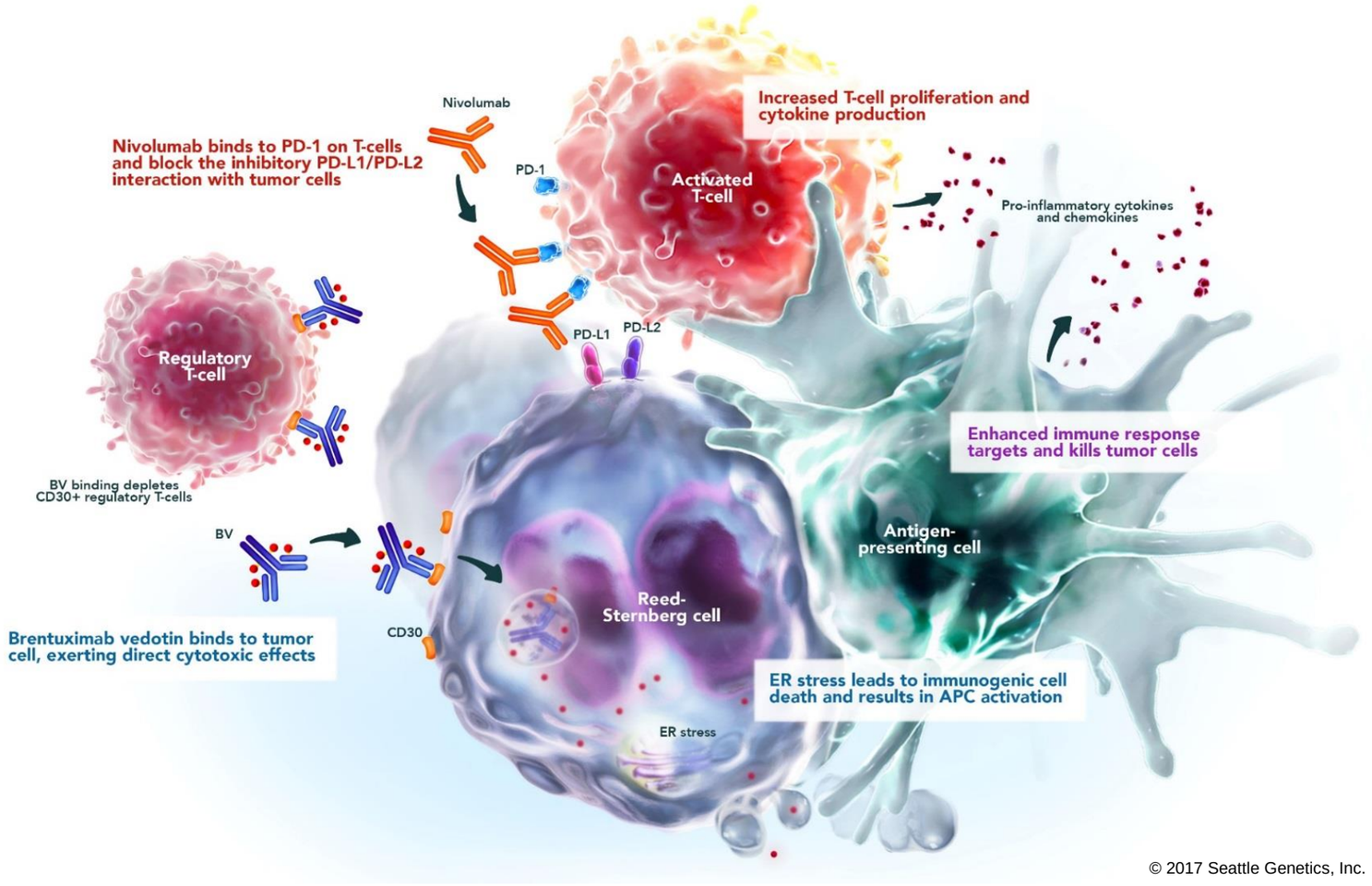
Study Rationale

Proposed Mechanism of Action



Brentuximab vedotin plus nivolumab is an investigational drug combination; the safety and efficacy of this combination has not been established.

- Brentuximab vedotin (BV) and nivolumab (Nivo) are effective single-agent treatments for relapsed or refractory Hodgkin lymphoma (R/R HL)
- BV is an antibody-drug conjugate directed against CD30; a receptor expressed by Reed-Sternberg (RS) cells and subsets of activated T and B cells
- BV may activate the innate immune system and initiate an antitumor immune response through the induction of immunogenic cell death*
- Nivo targets the programmed death receptor, PD-1, blocking the interaction with its ligands that are overexpressed by RS cells, and restores an effective antitumor immune response
- BV + Nivo in combination may be an active salvage regimen for R/R HL, offering patients an alternative to traditional chemotherapy

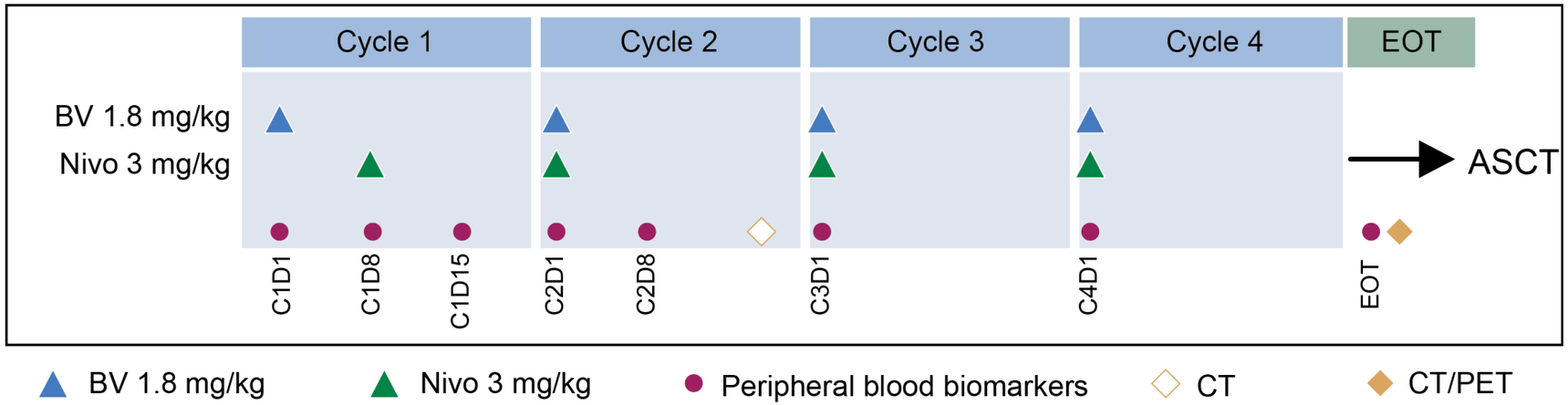
*Gardai et al., Cancer Res 75: Abstract 2469; 2015

Phase 1/2 Trial Design

- Phase 1/2, open label, multicenter trial of BV in combination with Nivo
- 62 adult patients with classical HL who had relapsed or were refractory to frontline chemotherapy were enrolled
- Patients were excluded if they previously received:
  - Prior salvage therapy, including salvage radiotherapy, for R/R HL
  - BV
  - Any immuno-oncology therapy affecting the PD-1, CTLA4, or CD137 pathways
  - Autologous or allogeneic stem cell transplant
- Primary endpoints –Safety; adverse event (AE) incidence and severity, and complete response (CR) rate* following the completion of study treatment
- Secondary and additional endpoints – Objective response rate (ORR), duration of response (DOR), progression-free survival (PFS) post-autologous stem cell transplant (ASCT), overall PFS, and biomarker analyses

*Responses were assessed using the 2014 Lugano classification

Methods



- Patients received treatment every 3 weeks (1 cycle) for up to 12 weeks (4 cycles)
  - Cycle 1: BV was given on Day 1 and Nivo on Day 8
  - Cycles 2–4: Both BV and Nivo were given on Day 1
- Samples for biomarker analyses were taken on Days 1, 8, and 15 of Cycle 1; Days 1 and 8 of Cycle 2; Day 1 of Cycles 3 and 4; and at EOT
- After completion of the EOT response assessment, patients were eligible to undergo ASCT
- AEs were recorded from the start of treatment through 100 days post last dose of Nivo including the ASCT period, as applicable

Patient Characteristics and Disposition

	n=62
Age (y), median (range)	36 (18 to 69)
Gender, n (%)	
Male	30 (48)
Female	32 (52)
Disease stage at initial diagnosis, n (%)	
I/II	37 (60)
III/IV	24 (39)
Unknown	1 (2)
Prior systemic therapy regimens, n (%)	
ABVD / ABVE-PC / R-ABVD	59 (95)
BEACOPP*	2 (3)
Stanford V	2 (3)
Disease status relative to frontline treatment, n (%)	
Primary refractory	28 (45)
Relapsed, remission duration ≤1 year	19 (31)
Relapsed, remission duration >1 year	15 (24)

*One patient received BEACOPP after discontinuing ABVD due to inadequate interim response

- 62 patients enrolled; 61 patients received at least one dose of study drug
- 58 patients completed all 4 cycles of BV + Nivo**
- 4 patients discontinued from the study early:
  - Patient decision, non-AE (n=2)
  - Investigator decision (n=1)
  - Adverse event (n=1, peripheral neuropathy)

**One patient discontinued prior to receiving study treatment; one patient withdrew consent after Cycle 1; one patient discontinued after Cycle 2 due to lack of response; one patient discontinued during Cycle 4 BV administration due to an AE

Adverse Events Occurring Prior to ASCT or Subsequent Salvage Therapy

- 60 patients (98%) experienced AEs
  (before undergoing ASCT or receiving salvage therapy after BV + Nivo)
- 40 patients (66%) experienced Grade 1 or 2 AEs
- 19 patients (31%) had AEs ≥ Grade 3
  - Grade 3: 17 patients (28%)
  - Grade 4: 2 patients (3%, thrombocytopenia and increased lipase enzymes)

Infusion-related reactions (IRRs):

- Experienced by 27 patients (44%) overall, with 25 patients (41%) experiencing an IRR during a BV infusion
- Occurred most frequently during the Cycle 2 BV infusion
- Pretreatment with low-dose steroid and antihistamine did not impact frequency or severity
- Caused an interruption of infusion in 16 patients (26%)
- No patients discontinued treatment due to an IRR

AEs occurring in >15% of patients (n=61)

	Grade 1 or 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	30 (49)	0	0
Fatigue	24 (39)	1 (2)	0
Infusion-related reaction	25 (41)	2 (3)	0
Pruritus	18 (30)	1 (2)	0
Diarrhea	15 (25)	1 (2)	0
Headache	15 (25)	0	0
Cough	13 (21)	0	0
Vomiting	13 (21)	0	0
Dyspnea	12 (20)	0	0
Nasal Congestion	12 (20)	0	0
Pyrexia	12 (20)	0	0
Rash	12 (20)	0	0
Anxiety	11 (18)	0	0
Rash Pruritic	11 (18)	0	0
Chills	10 (16)	0	0

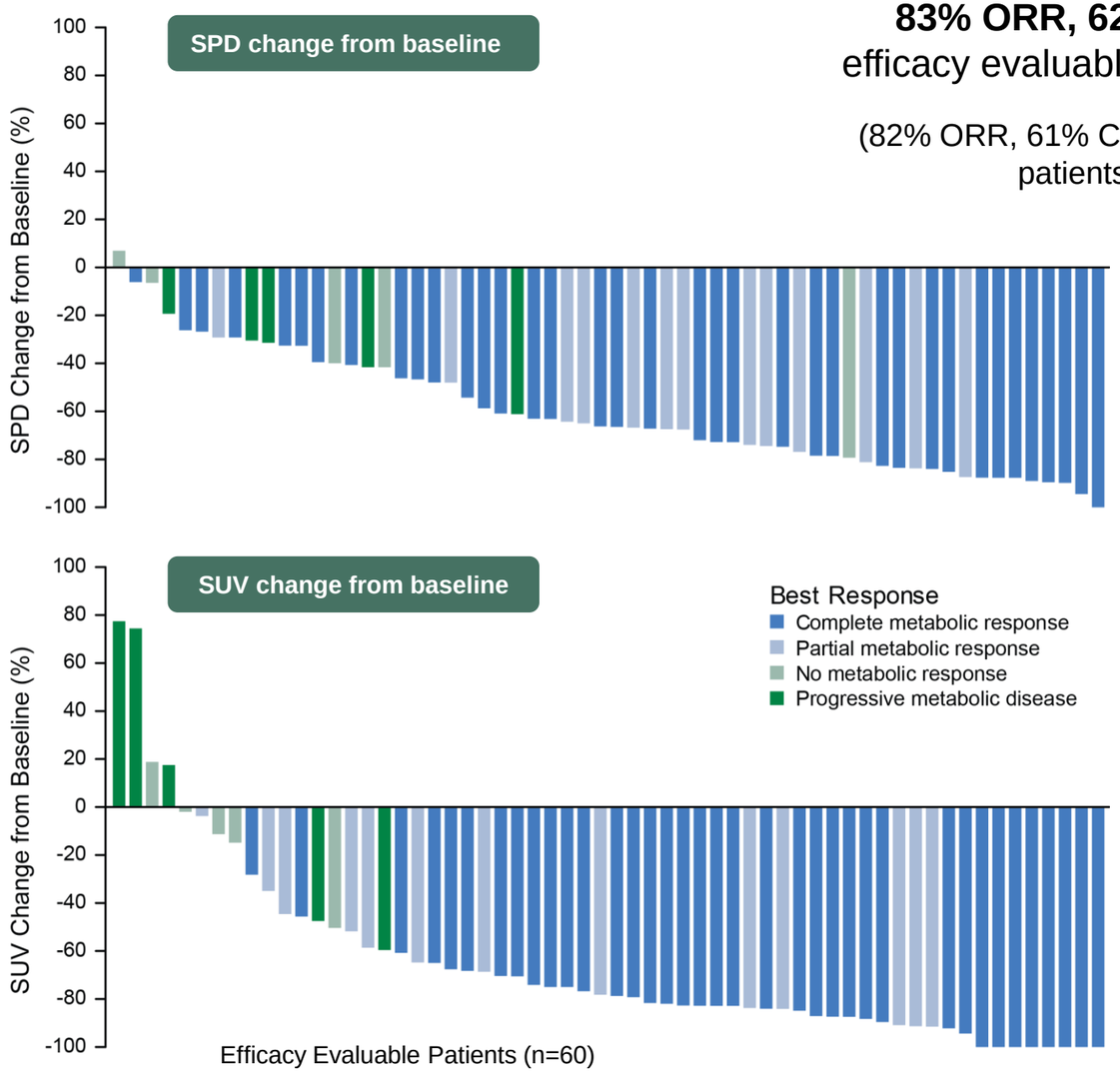
Immune-Related Adverse Events

- Potential immune-related adverse events (IrAEs, based on a pre-defined list of preferred terms) occurred in 50 patients (82%), excluding IRRs
- 5 patients received systemic steroids for treatment of an IrAE:
  - Grade 3 diarrhea and Grade 2 colitis
  - Grade 3 aspartate aminotransferase elevation
  - Grade 4 colitis and Grade 4 pneumonitis (both after receiving additional salvage therapy)
  - Grade 2 pneumonitis
  - Grade 4 pneumonitis (after BEAM, as part of the conditioning regimen)
- No patients discontinued treatment due to an IrAE

Tumor Response

	n (%)	95% CI
Objective response rate (CR + PR)	50 (83)	72, 92
Complete response	37 (62)	48, 74
Deauville score = 1	14 (23)	
Deauville score = 2	15 (25)	
Deauville score = 3	7 (12)	
Deauville score = 5*	1 (2)	
Partial response	13 (22)	12, 34
Deauville score = 4	7 (12)	
Deauville score = 5	6 (10)	
Stable disease	5 (8)	3, 18
Deauville score = 5	5 (8)	
Progressive disease	4 (7)	2, 16
Deauville score = 5	4 (7)	
Clinical progression	1 (2)	

*Residual area of FDG-avidity on PET was biopsied and was not consistent with residual Hodgkin lymphoma



83% ORR, 62% CR among efficacy evaluable patients (n=60)

(82% ORR, 61% CR among all treated patients,; n=61)

ASCT and Long-Term Follow-up

ASCT Summary

- Treatment with BV + Nivo did not appear to impact stem cell mobilization and collection yields or engraftment
- Patients did not appear to have increased toxicity during or after the transplant period

ASCT Mobilization and Engraftment

	n=44*
Median days of apheresis sessions (range)	2 (1 to 4)
Median number of CD34+ cells (10^6 cells/kg) harvested (range)	$4.7x10^6$ (3 to 60)
Median days to neutrophil engraftment (range)	11.5 (8 to 29)
Median days to platelet engraftment (range)	16 (7 to 63)

*Stem cell mobilization/engraftment data includes all 42 patients who underwent ASCT post-BV + Nivo and 2 patients who underwent ASCT post-subsequent salvage therapy

Follow-up

- 41 of 42 patients with ASCT post-BV + Nivo remain in follow-up
- 16 of 17 patients with salvage therapy post-BV + Nivo remain in follow-up
- Median follow-up time: 8 months
- Median DOR not reached
- 6 month PFS: 89% (95% CI: 75%, 95%)

Conclusions

- A high ORR was demonstrated with BV + Nivo (83%), with a 62% CR rate among efficacy evaluable patients
- BV + Nivo was well-tolerated in patients with classical R/R HL:
  - 44% of patients experienced IRRs, of whom, 41% had Gr 1 or 2 and 3% had Gr 3 – No patients discontinued treatment due to IRRs
  - <10% of patients had potential IrAEs requiring treatment with systemic steroids – No patients discontinued treatment due to an IrAE
- Treatment with BV + Nivo did not adversely impact mobilization and stem cell collection; patients were able to proceed to ASCT uneventfully
- BV + Nivo treatment appeared to result in:
  - Increased circulating T cell numbers, and increased innate and adaptive immune activating cytokines and chemokines
  - Increased ability of memory T cells to mount an immune response
- A high proportion of patients with classical R/R HL achieved a CR with this chemotherapy-free regimen. The encouraging activity of BV + Nivo will be further evaluated in multiple settings, including a pivotal phase 3 trial in patients with advanced HL who are ineligible for ASCT or after failure of ASCT (CheckMate 812, NCT03138499)

CLL

Phase II Trial of Venetoclax + Ibrutinib in Patients With Relapsed/Refractory or Untreated High-Risk CLL

Jain N, et al. ASH 2017. Abstract 429. ClinicalTrials.gov. NCT02756897.

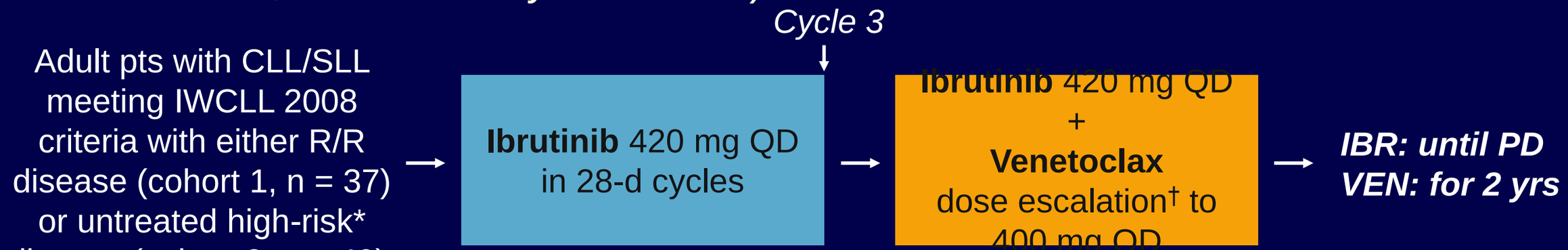
Venetoclax + Ibrutinib in CLL: Background

- Ibrutinib: irreversible BTK inhibitor approved for all pts with CLL[1]
  - ORR ~ 80% in previously untreated CLL, ~ 40% in R/R CLL; majority PR for both[2,3]
  - Common AEs: atrial fibrillation, neutropenia, bleeding[1]
- Venetoclax: BCL-2 inhibitor approved for R/R CLL pts with del(17p)[4]
  - ORR < 70% in pts with R/R CLL; ~ 20% CR[5,6]
  - Common AEs: TLS, neutropenia[4]
- Combination of ibrutinib + venetoclax reported to have synergistic activity in preclinical studies[7,8]
- Current interim analysis reported efficacy, safety of ibrutinib + venetoclax in pts with either R/R CLL (cohort 1) or previously untreated high-risk CLL (cohort 2)[9]

References in slidenotes

Venetoclax + Ibrutinib in CLL: Study Design

- Investigator-initiated, single-arm, multicohort phase II trial (all pts initiating tx: N = 116; current analysis: n = 77)



*≥ 1 of following high-risk characteristics: ≥ 65 yrs of age; del(11q); del(17p) or mutated *TP53*; unmutated *IGHV*.

†Venetoclax weekly dose escalation (all doses QD): 20 mg, 50 mg, 100 mg, 200 mg, 400 mg. Response assessment by blood, BM, CT every 3 mos during Yr 1, every 6 mos during Yr 2, then every 6-12 mos thereafter.

- Primary endpoint: CR/CRi per IWCLL 2008 criteria
- Other endpoints: OS, TLS risk categorization at BL vs post-IBR, safety

Jain N, et al. ASH 2017. Abstract 429. ClinicalTrials.gov. NCT02756897.

Venetoclax + Ibrutinib in CLL: Baseline Pt Characteristics

Characteristic	Cohort 1: R/R (n = 37)	Cohort 2: First Line (n = 40)
Median age, yrs (range)	59 (32-76)	64.5 (35-82)
Male, n (%)	30 (81)	30 (75)
Median prior tx, n (range)	1 (1-4)	--
FISH, n (%)		
▪ del(17p)	11 (30)	7 (18)
▪ del(11q)	14 (38)	10 (25)
▪ Trisomy 12	5 (14)	5 (12)
▪ Negative	2 (5)	5 (12)
▪ del(13q)	5 (14)	13 (33)
Unmutated *IGHV*, n/N (%)	27/31 (87)	30/37 (81)

Characteristic, n/N (%)	Cohort 1: R/R (n = 37)	Cohort 2 First Line (n = 40)
Cytogenetics		
▪ Complex	5/29 (17)	6/39 (15)
▪ Diploid	10/29 (34)	16/39 (41)
Mutations		
▪ *TP53*	10/32 (31)	7/40 (18)
▪ *NOTCH1*	3/32 (9)	14/40 (35)
▪ *SF3B1*	7/32 (22)	11/40 (28)
ZAP-70 (≥ 20% or IHC+)	21/27 (78)	33/40 (83)
CD38 ≥ 30%	22/36 (61)	23/40 (58)

- Unmutated *IGHV*, *TP53* aberration, or del(11q): 92% for R/R cohort 1, 93% for first-line cohort 2

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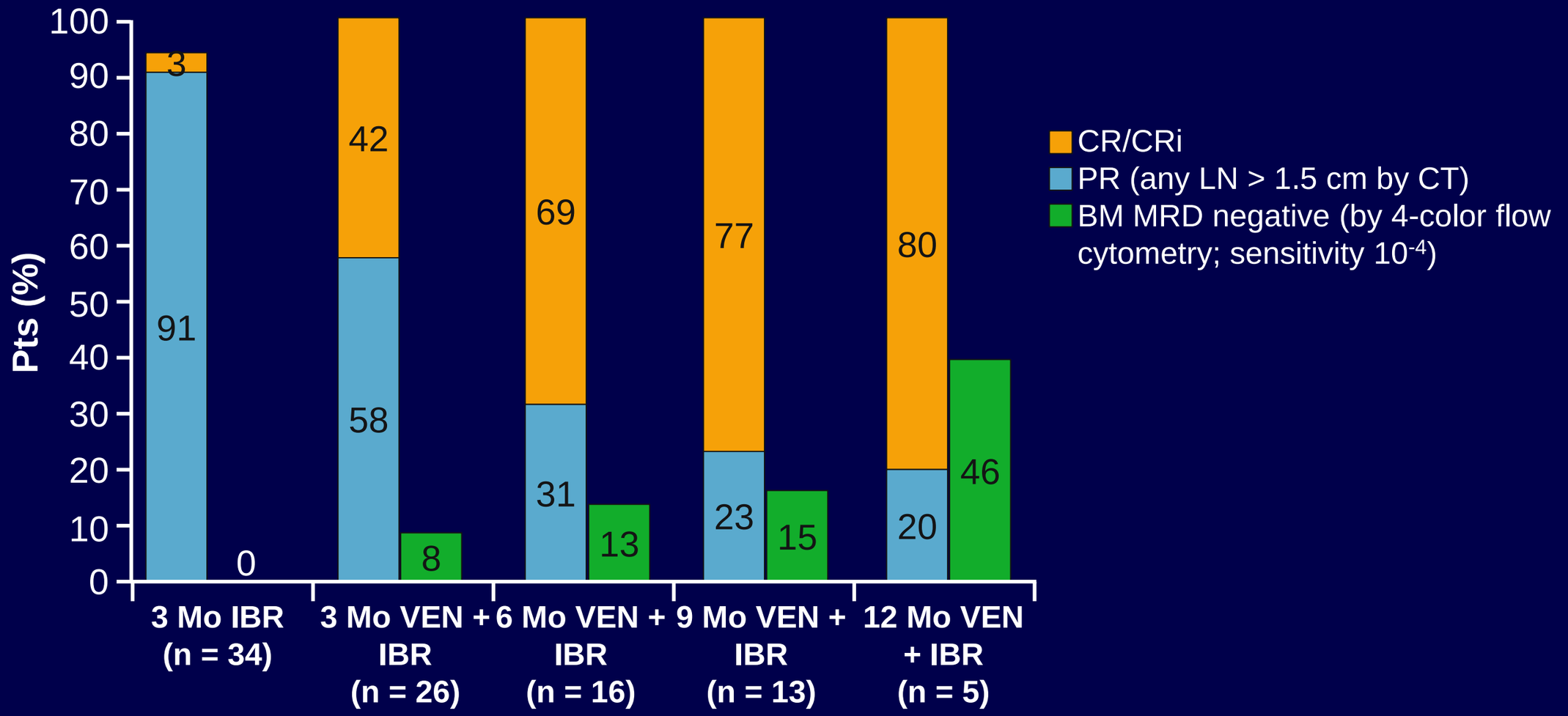
Venetoclax + Ibrutinib in CLL: Response in R/R Disease (Cohort 1)



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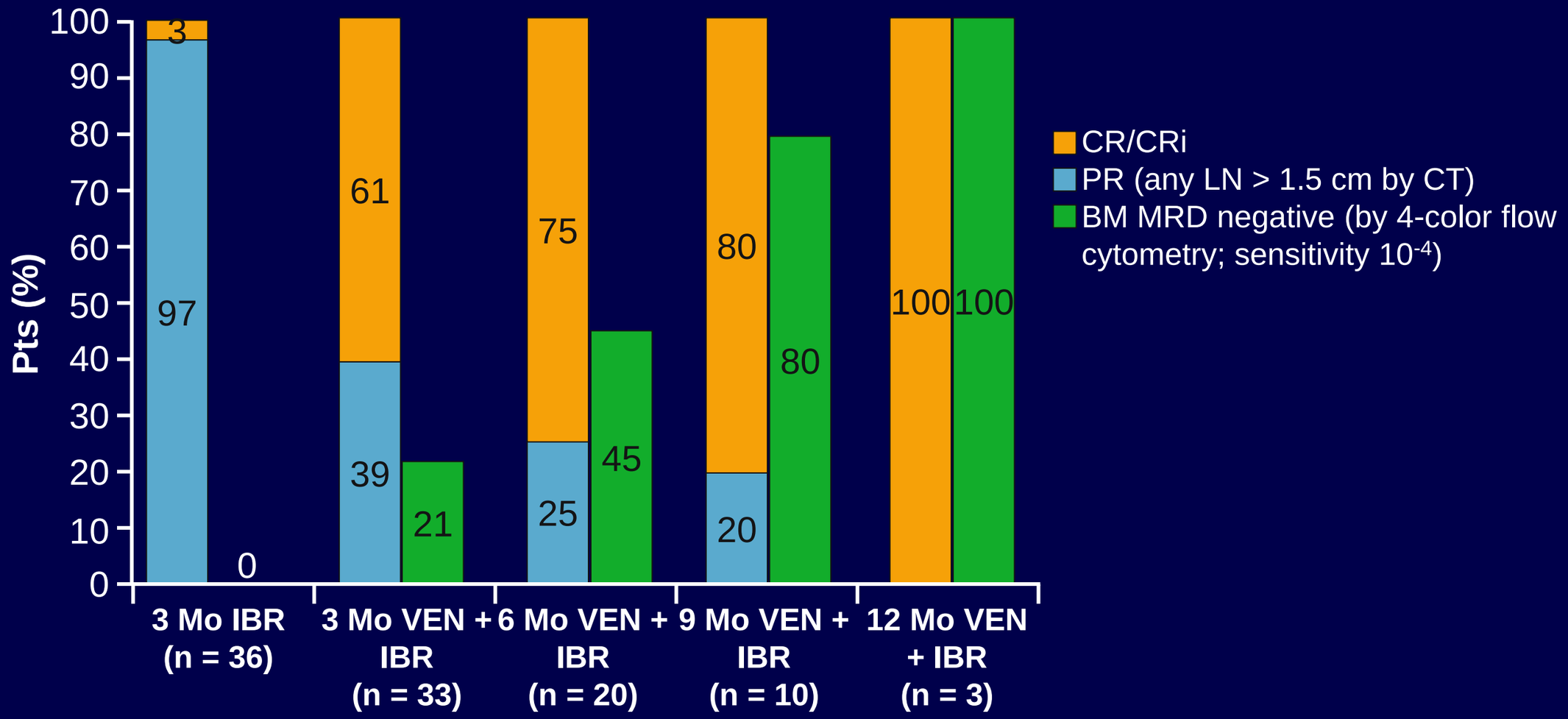
Venetoclax + Ibrutinib in CLL: Response in Untreated High-Risk Disease (Cohort 2)



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Venetoclax + Ibrutinib in CLL: Pt Disposition

- 15 pts discontinued study: 7 on ibrutinib, 8 after venetoclax added
- 70 pts started venetoclax: R/R cohort 1, n = 34; first-line cohort 2, n = 36
- Dose reductions: 36% ibrutinib, 26% venetoclax
- After median follow-up of 11.8 mos, only 1 death (in first-line cohort 2)
  - Death attributed to CNS Cryptococcus; pt had received 1 day of ibrutinib

Reason for D/c*	Cohort 1: R/R	Cohort 2: First Line
During IBR	Skin rash, insurance denial, consent withdrawal	Skin rash, dizziness/gait imbalance/HTN, infection, need for prohibited rx
During IBR + VEN	Hodgkin's transformation, pancytopenia, noncompliance, myalgia†	Recurrent neutropenia, alloSCT, fallopian tube CA

*n = 1 each (except recurrent neutropenia, n = 2).
†Deemed likely related to IBR.

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Venetoclax + Ibrutinib in CLL: Safety

- 2/3 of infections observed in ibrutinib monotherapy phase

AE	Pts (n = 77)
Grade 3/4 hematologic AE,* %	
▪ Neutropenia	44
▪ Thrombocytopenia	4
Atrial fibrillation, n (%)	10 (13)
Infections, n (%)	
▪ Neutropenic fever†	6 (8)
▪ Pneumonia	1 (2)
▪ Cellulitis	1 (2)
▪ Septic arthritis	1 (2)

*Most grade 3/4 hematologic AEs occurred during VEN + IBR (neutropenia, 70%; thrombocytopenia, 100%). †Associated with aspergillosis (n = 1), anaplasmosis (n = 1), Vibrio (n = 1), or culture negative (n = 3).

- No clinical TLS observed; laboratory TLS observed in 2 pts
- TLS risk categorization downgraded (BL vs post-IBR) in 54% of pts

TLS Risk Category,‡ n (%)	Baseline	Post-IBR
High	18 (26)	2 (3)
Medium	38 (54)	29 (41)
Low	14 (20)	39 (56)

‡Assessed in 70 pts.

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Venetoclax + Ibrutinib in CLL: Conclusions

- In an interim analysis of pts with either R/R or previously untreated high-risk CLL, combination venetoclax + ibrutinib associated with high response rate
  - Depth of response increased over time with BM MRD-negativity achieved by many pts
- Safety
  - Grade 3/4 neutropenia observed in 44% of pts, with most cases observed during combination therapy
  - Most infections observed during ibrutinib monotherapy
  - TLS risk categorizations downgraded in 54% of pts after completing 3 mos of ibrutinib monotherapy
- Investigators conclude that chemotherapy-free combination of venetoclax + ibrutinib safe, active in pts with CLL

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Conclusions

- Longer term f/u data for CAR T cells looks promising for R/R DLBCL
  -? When to use it? Earlier seems better?
- Methyl Transferase Inhibitors, not just for myeloid malignancies anymore?
- Ibrutinib can produce durable remissions in MCL w/ modest toxicity
- Acalabrutinib similar efficacy as ibrutinib w/ less toxicity ??
- R^2 can produce high ORR/CR and durable remissions in untreated MCL
- Does A-AVD represent a new SOC in previously untreated HD?
- R^2 may be a non-chemotherapeutic alternative for previously untreated FL
- Rituxan maintenance seems effective after BR induction in indolent lymphoma
- Venatoclax + ibrutinib produces dramatic responses in R/R and prev untreated CLL

Questions?