

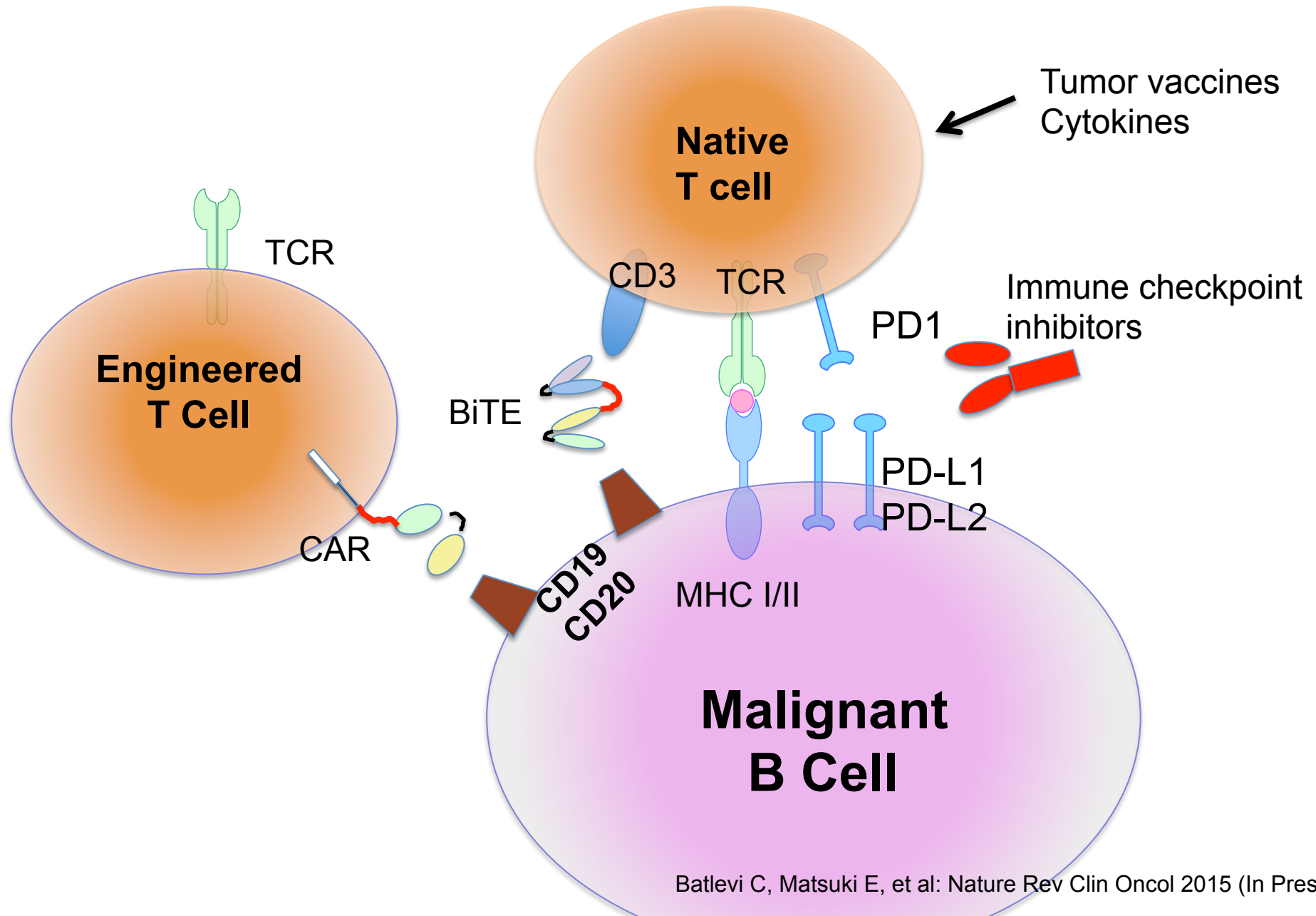
Novel approaches of active immune therapy in lymphoma

Anas Younes, M.D.

Chief, Lymphoma Service

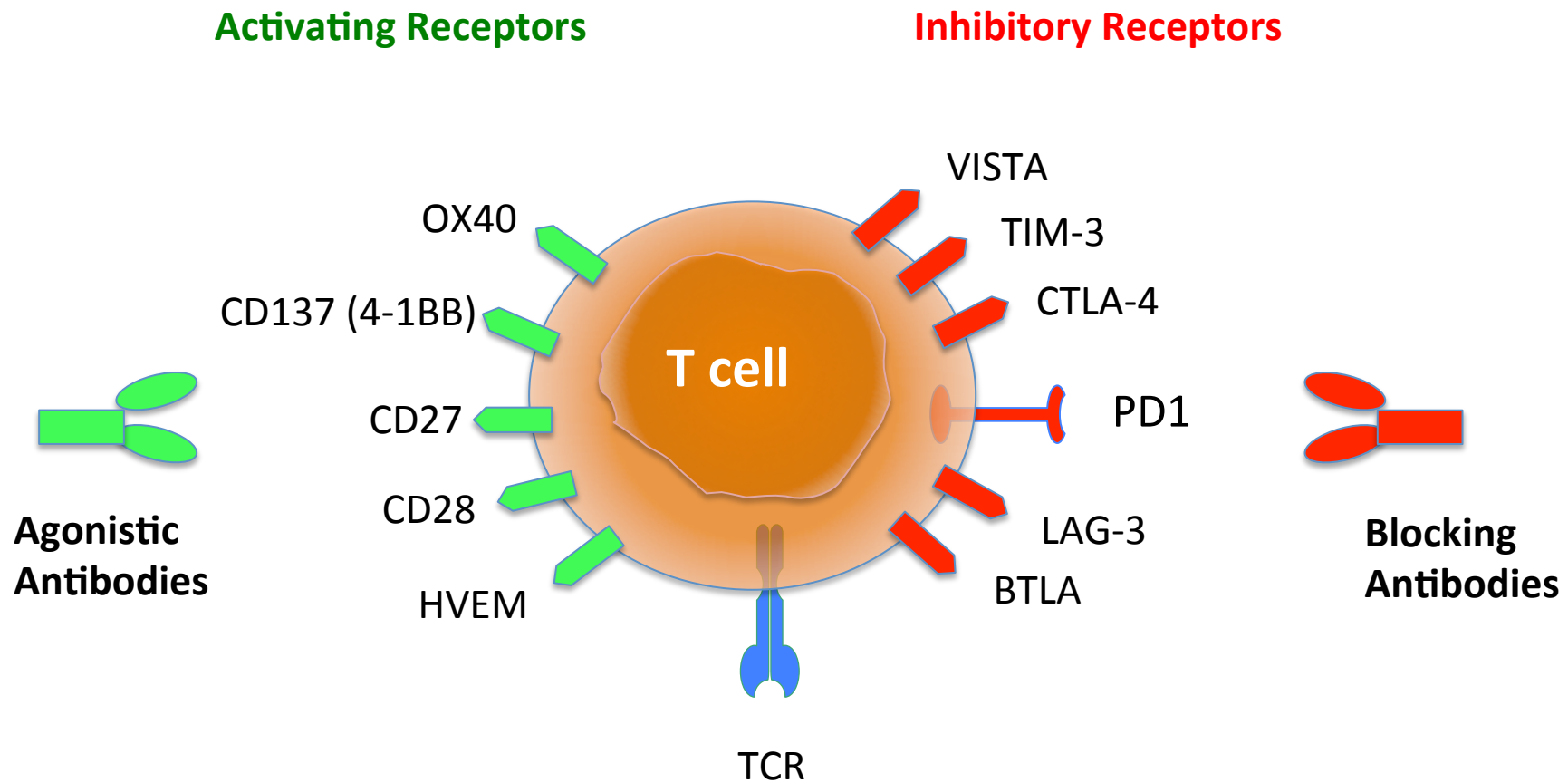
Memorial Sloan-Kettering Cancer Center

Therapeutic strategies to overcome immune tolerance to cancer

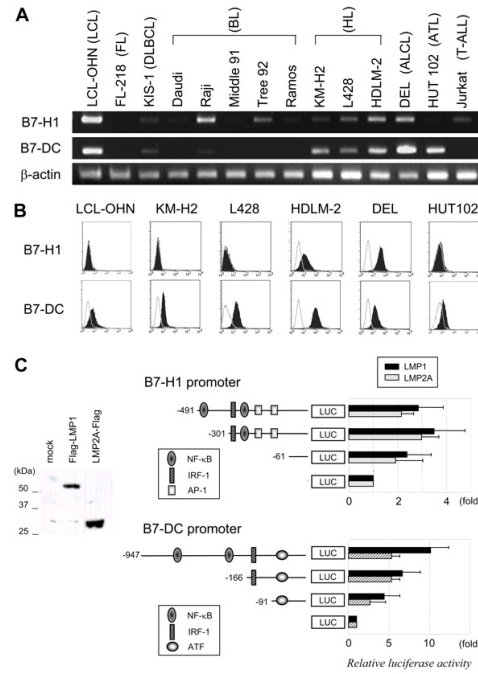


Therapeutic Activation of Autologous T Cells

Immune checkpoint inhibitors

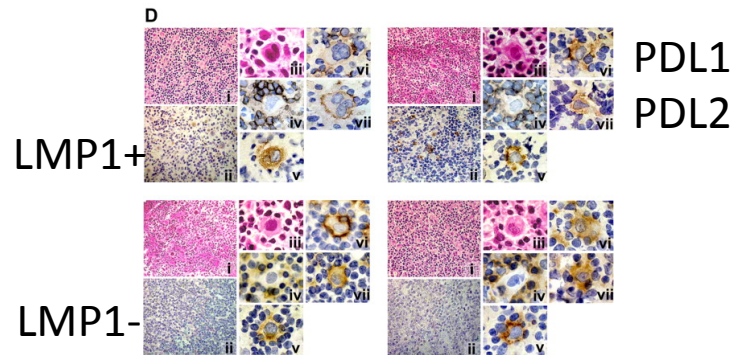


Expression and gene regulation of PDL-1 (CD273) and PDL-2 (CD274) in Hodgkin Lymphoma



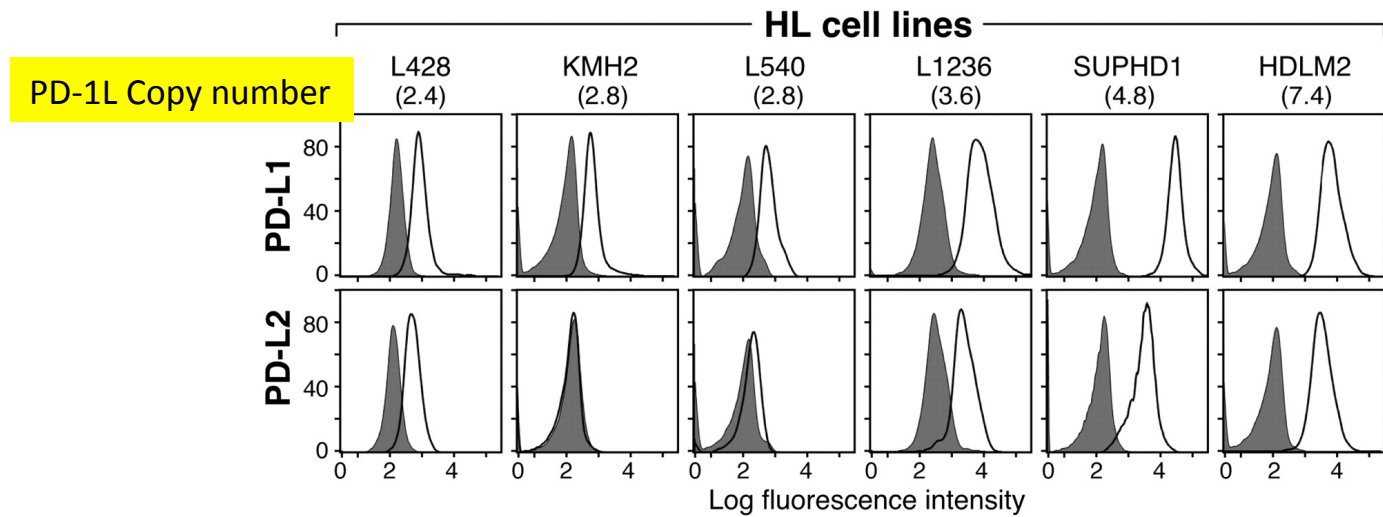
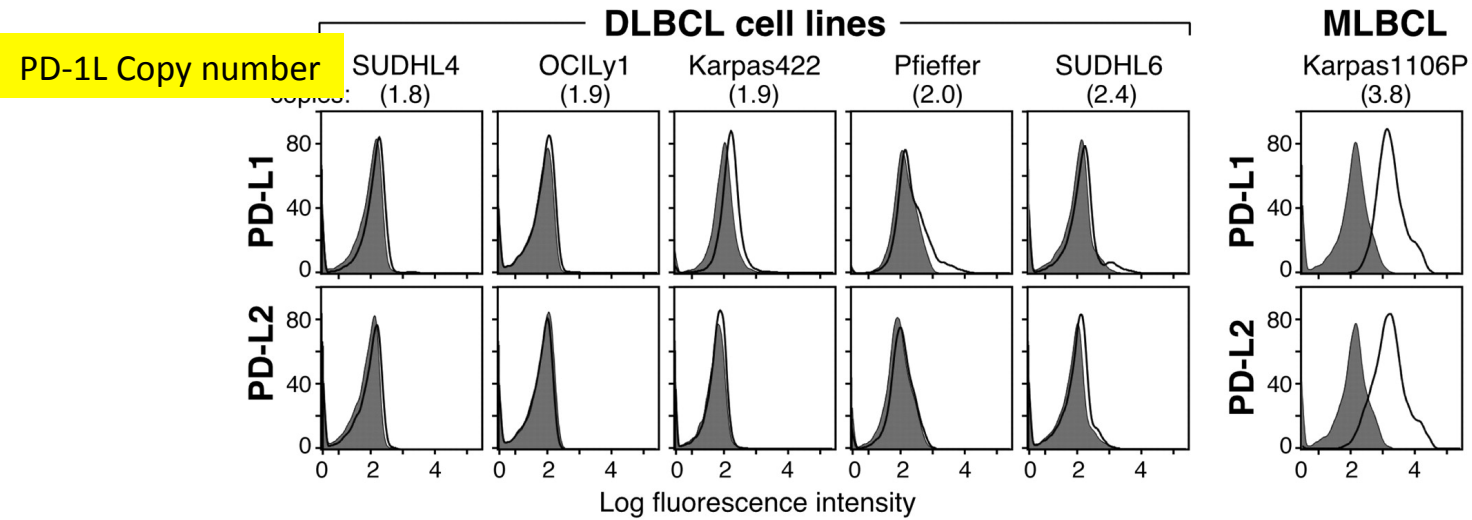
Expression of PDL1/PDL2 in HL cell lines

LMP1 and LMP2A enhanced the transcriptional activity of PDL1/PDL2



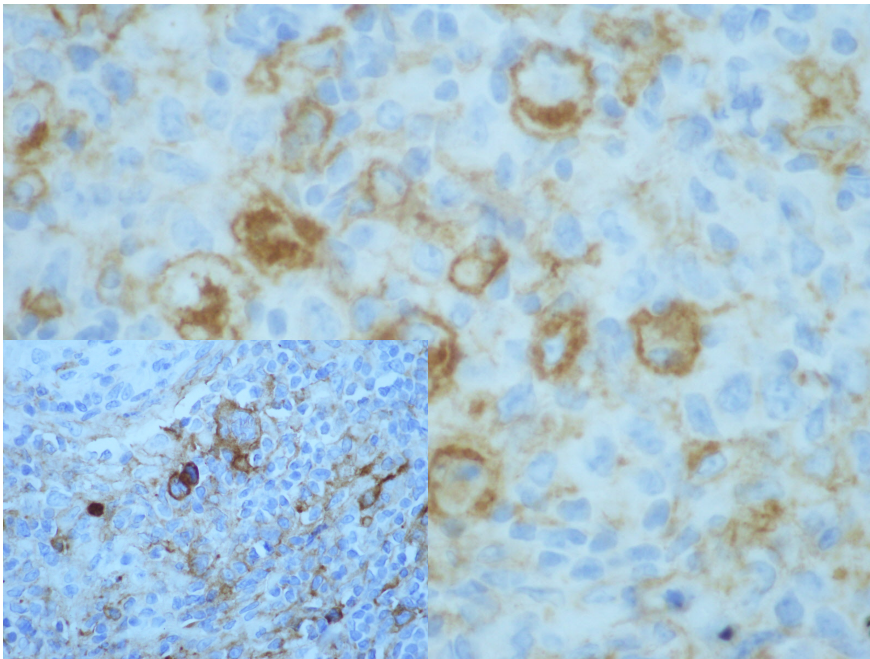
PDL1/PDL2 Expression in EBV+ and EBV- cHL

9p24.1 amplification and PD-1L cell-surface expression in HL and MLBCL cell lines.

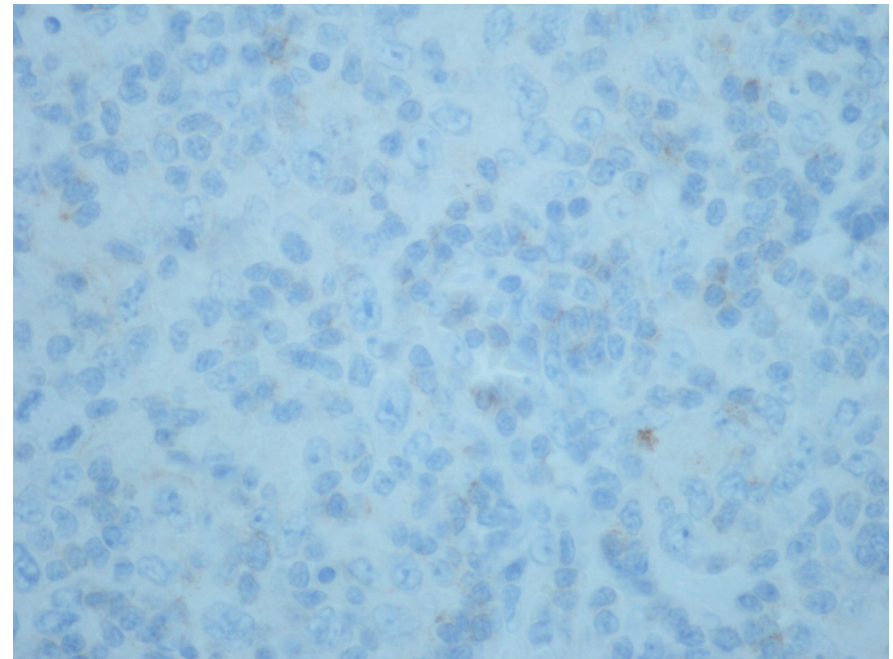


PD-1/PDL-1 expression in cHL Case# 2

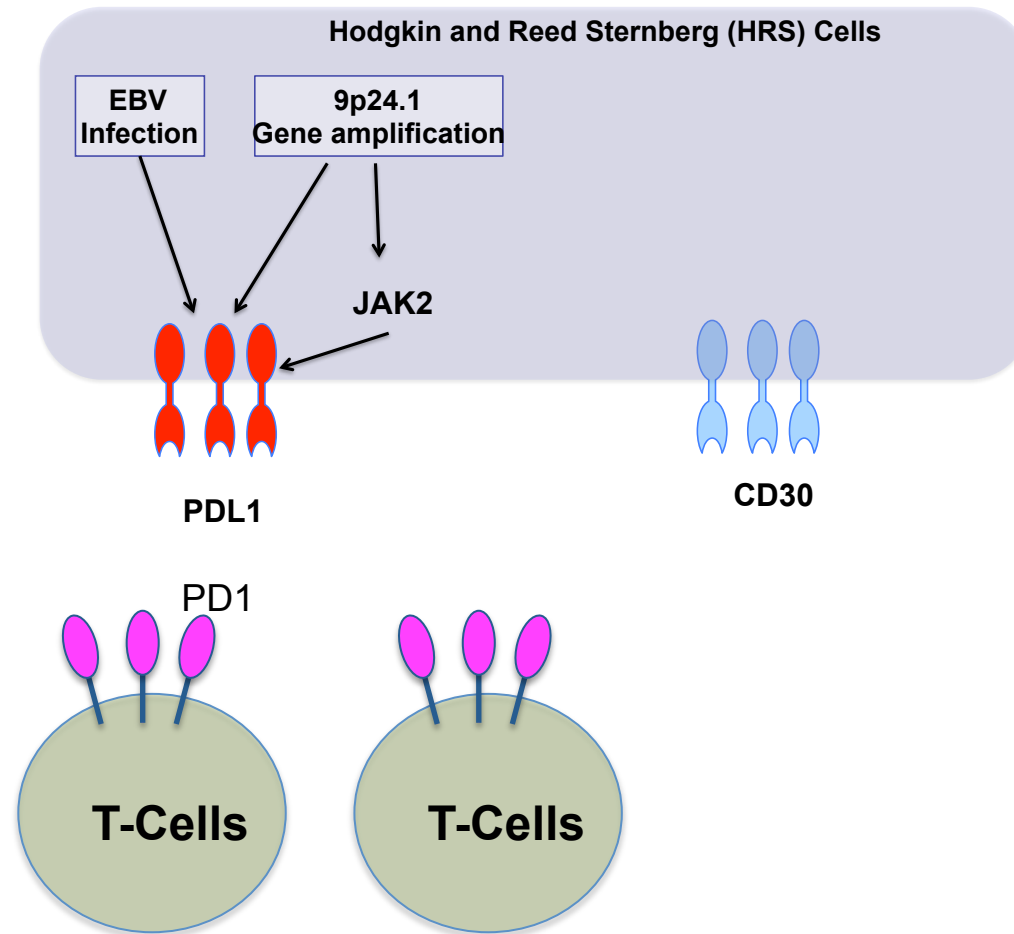
PDL-1



PD-1



HRS Cells Express High Levels of PDL-1

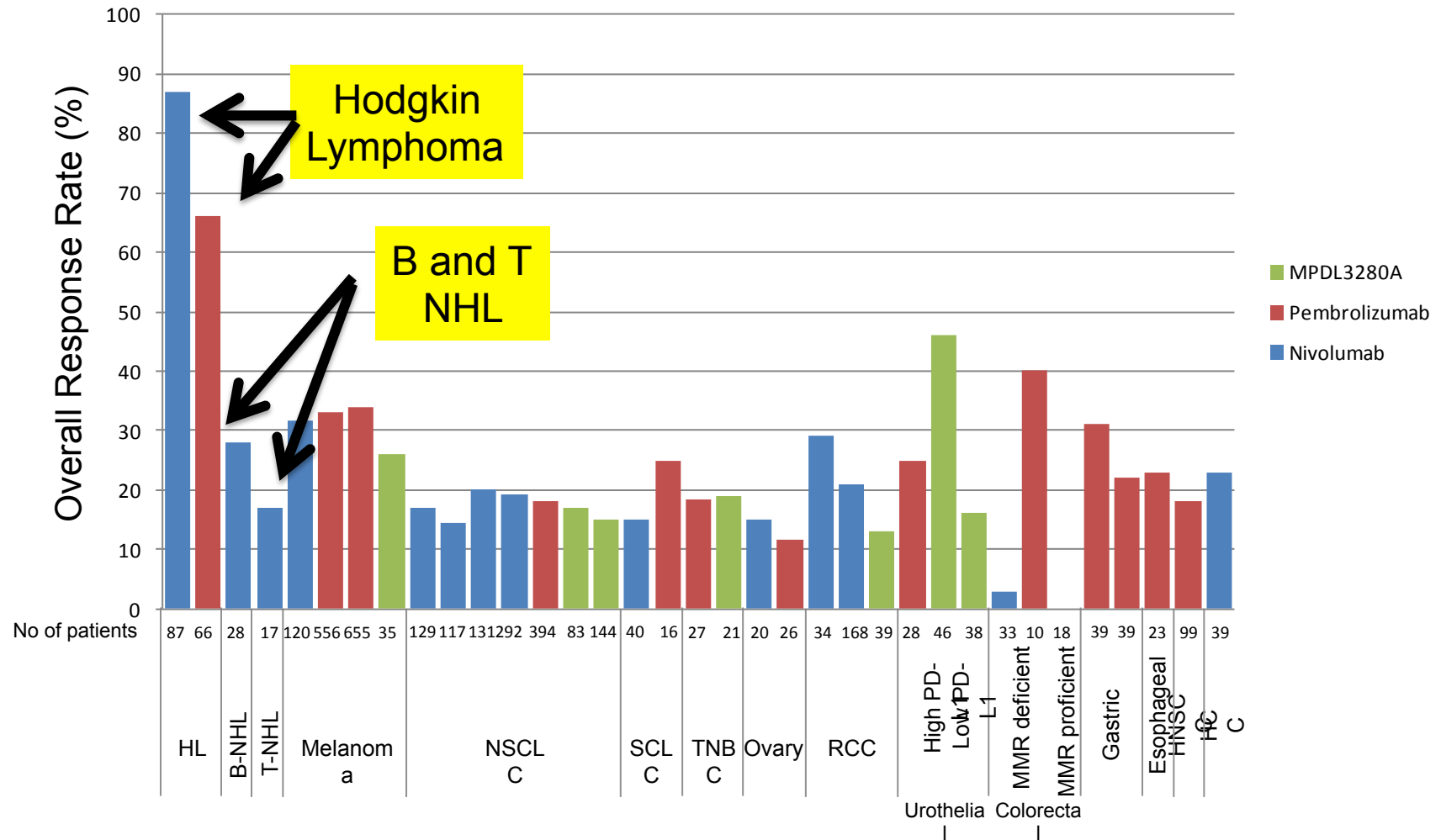


Adapted from Stathis & Younes: Ann Oncology 2015
And Younes A & Ansell S : Seminars in Hematology, 2016, 186–189

Results of PD1 Blocking Antibodies in Relapsed HL Phase-I Studies

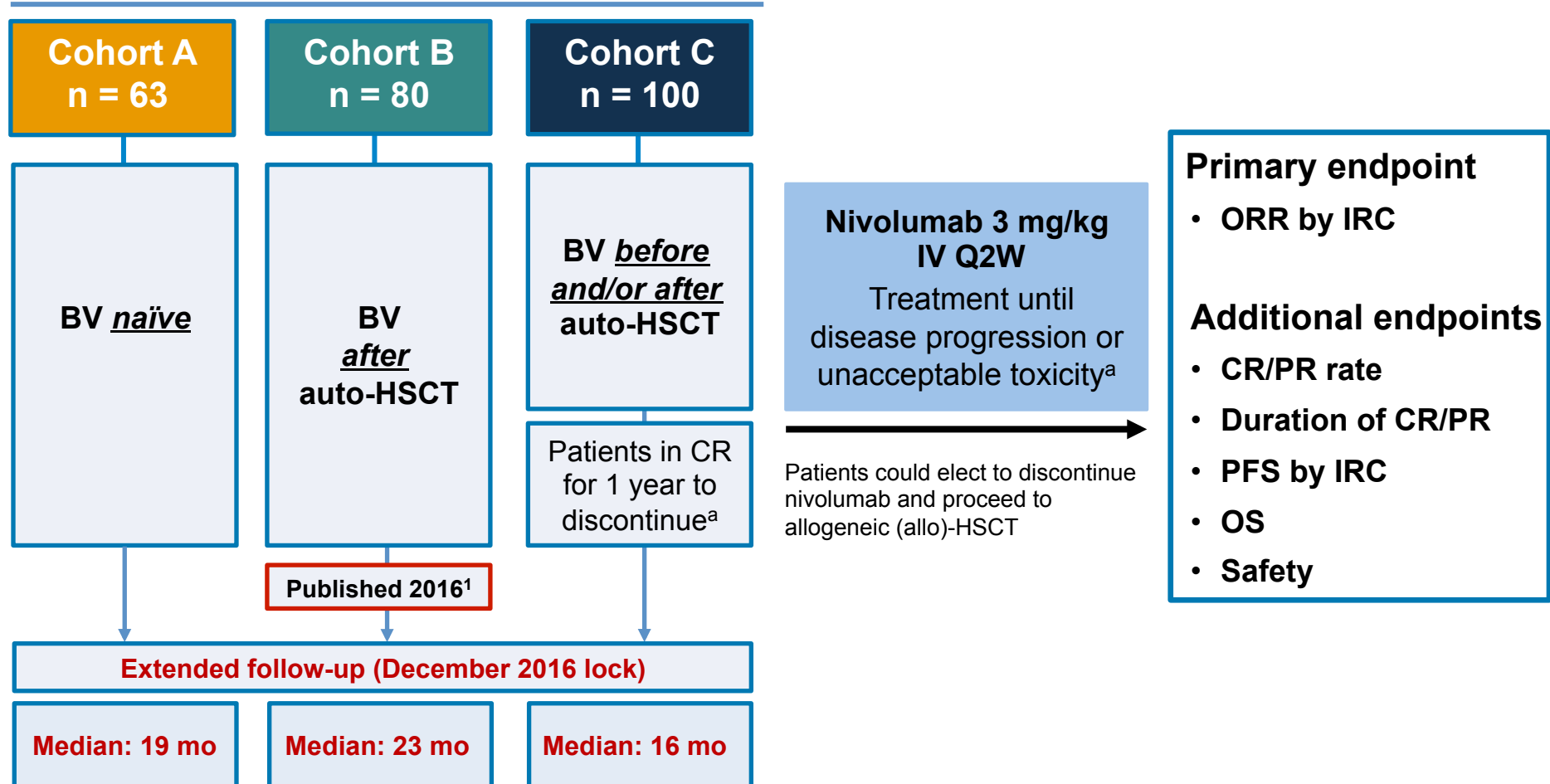
Drug	Dose/ Schedule	N	% ORR	% CR	ORR in BV treated HL	1 st Author
Pembrolizumab (humanized IgG4)	10 mg/kg IV Q 2wks	29	66%	21%	66% (n=19)	Armand P, JCO 2016
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2wks	23	87%	17%	70% (n=16)	Ansell S NEJM 2015

Single agent activity of PD-1/PD-L1 axis blockade in relapsed/refractory Cancer

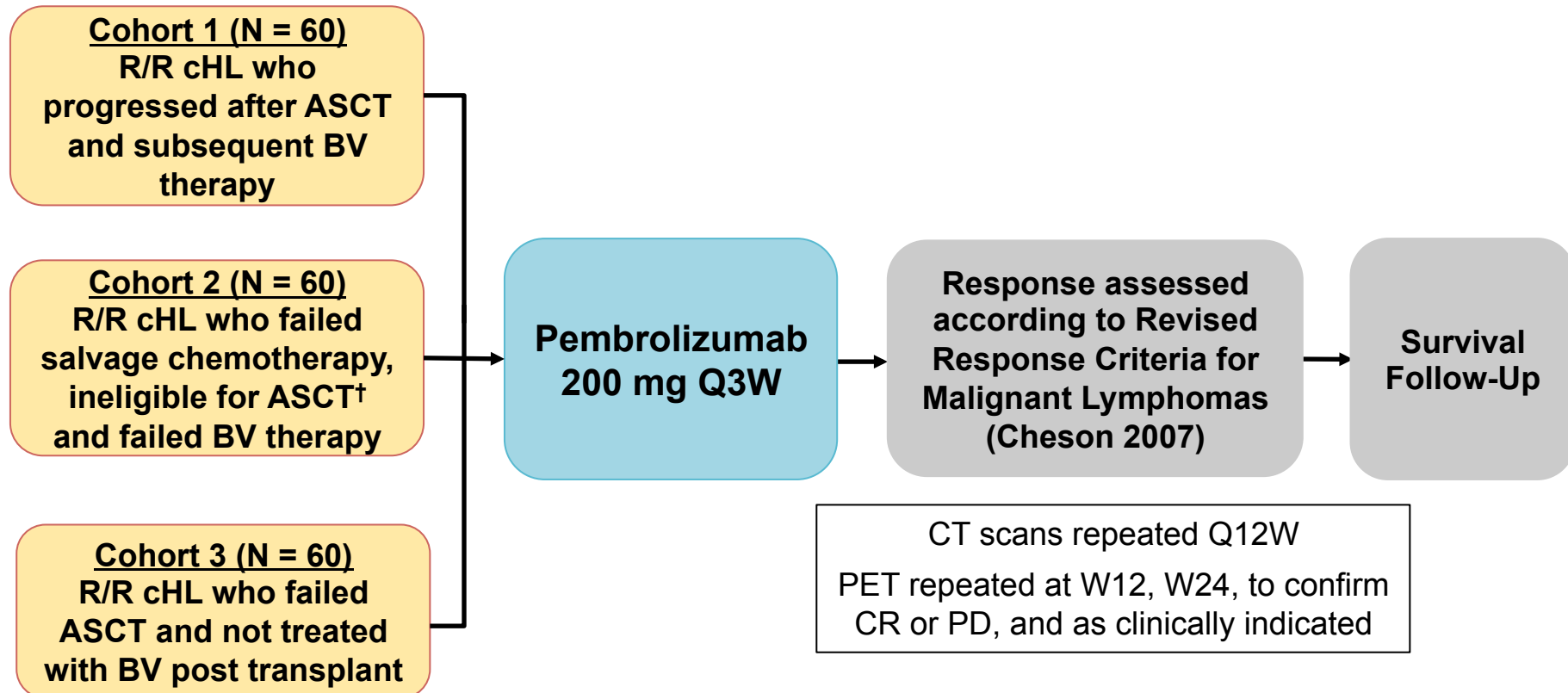


Phase 2 CheckMate 205 Study Design

Relapsed/refractory cHL after autologous (auto)-HSCT
Nivolumab monotherapy



Pembrolizumab : KEYNOTE-087 Study Design



- **Primary end point:** ORR (central review)
- **Secondary end points:** ORR (investigator review), PFS, OS
- Prespecified interim analysis, based on investigator-assessed response, performed after 30 patients in all 3 cohorts reached first response assessment

†Unable to achieve a CR or PR to salvage chemotherapy

Results of PD1 Blocking Antibodies in Relapsed HL

Results of Phase-II Studies

Post ASCT and Brentuximab Vedotin

Drug	Dose/Schedule	N	% ORR	% CR	1 st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3wks	69	72%	21%	Moskowitz, C/ ASH 2016
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	80	66%	9%	Younes, A/Lancet Oncology 2016

Results of PD1 Blocking Antibodies in Relapsed HL

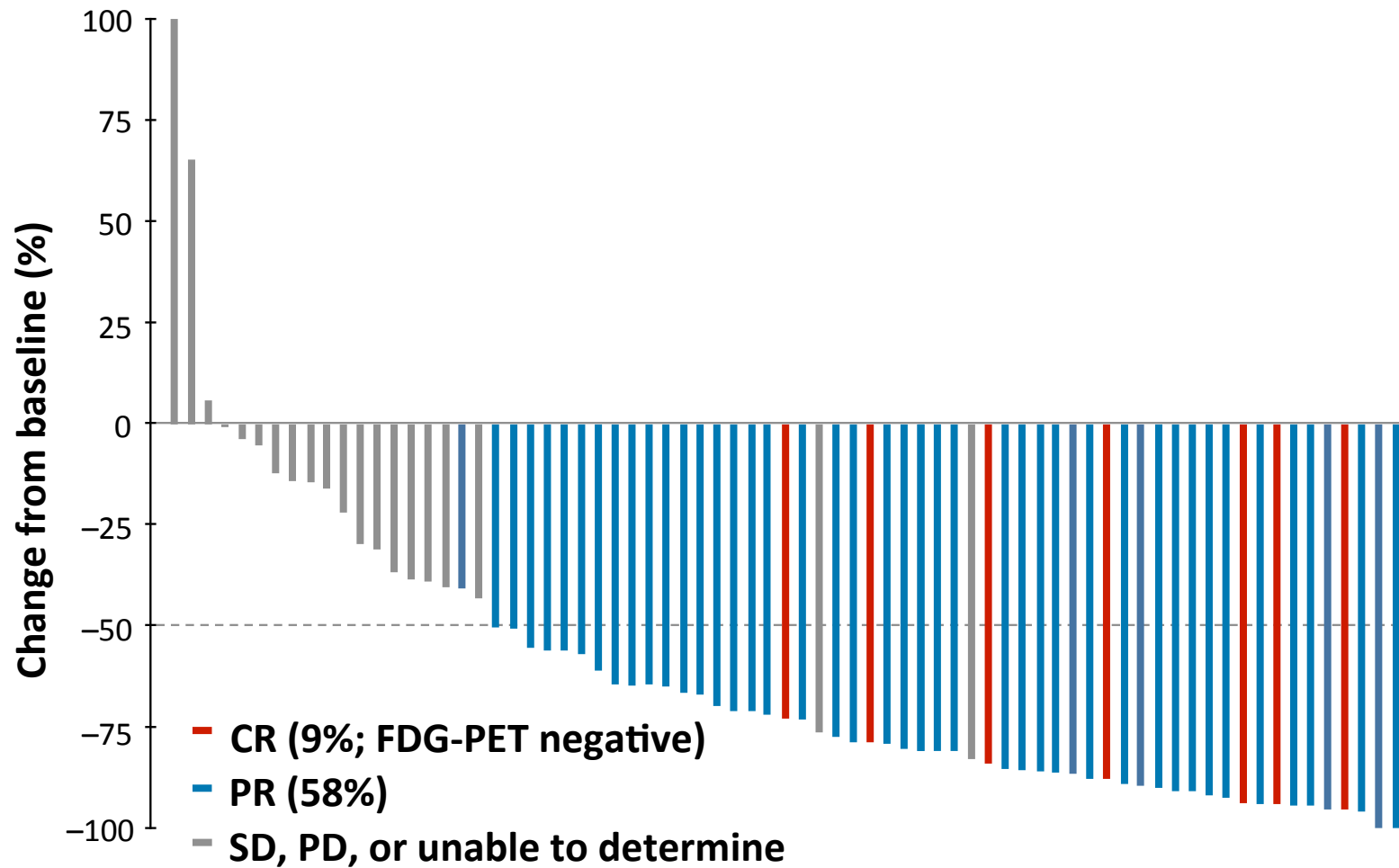
Results of Phase-II Studies

Post ASCT but No PRIOR Brentuximab Vedotin

Drug	Dose/Schedule	N	% ORR	% CR	1 st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3wks	60	67%	21%	Moskowitz, C/ ASH 2016
Nivolumab (Fully human IgG4)	3 mg/kg IV Q 2 wks	63	68%	22%	Timmerman, J/ ASH 2016

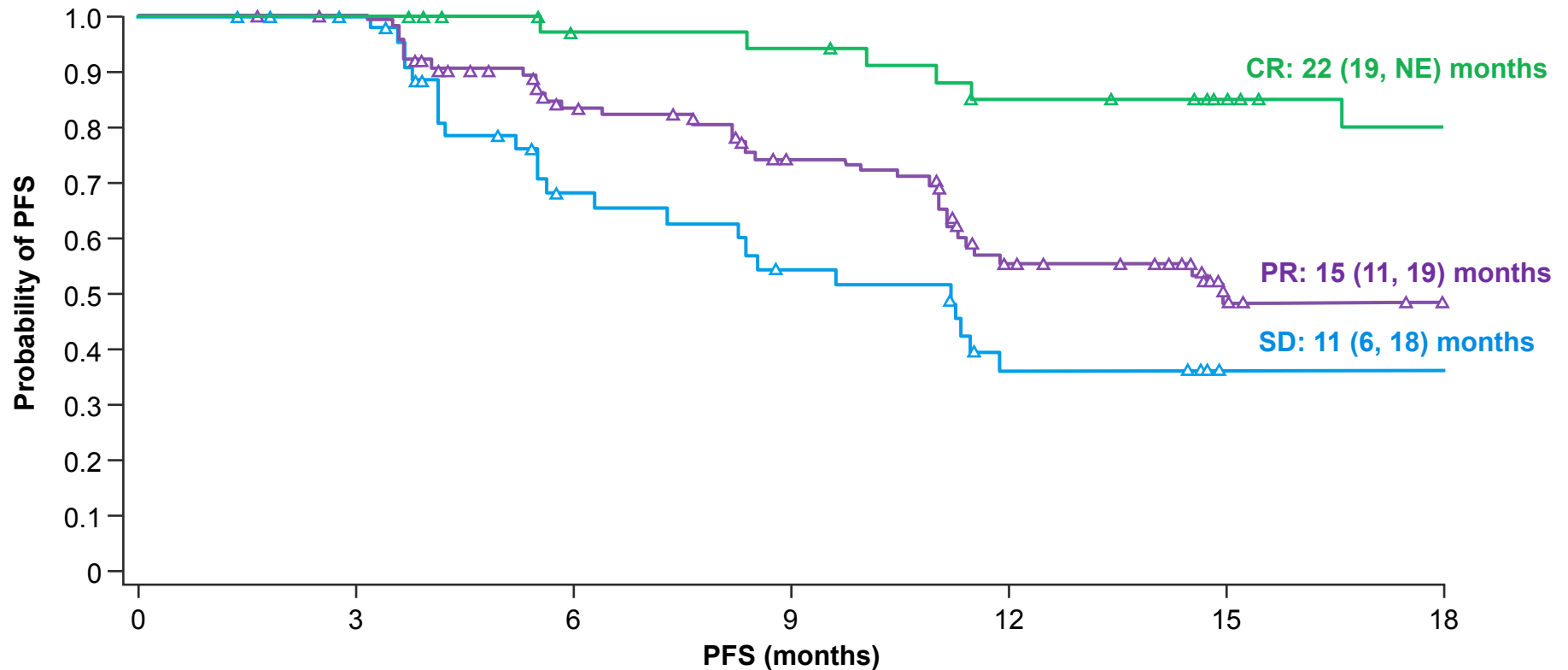
Tumor Burden Change From Baseline (all response-evaluable patients)

- All but 1 responder had a reduction of $\geq 50\%$ from baseline in tumor burden



Nivolumab for Relapsed cHL

Progression-Free Survival by Best Overall Response



Number of patients at risk

CR	40	40	33	32	27	20	16
PR	128	126	89	71	46	25	21
SD	47	44	25	19	11	8	8

International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)

A Younes P Hilden B Coiffier A Hagenbeek G Salles W Wilson J.F. Seymour K Kelly J
Gribben M Pfreunschuh F Morschhauser H Schoder A.D. Zelenetz J Rademaker R
Advani N Valente C Fortpied T.E. Witzig L.H. Sehn A. Engert R.I. Fisher P-L Zinzani
M. Federico M. Hutchings C. Bollard M. Trneny Y.A. Elsayed K Tobinai J.S.
Abramson N Fowler A Goy M Smith S Ansell J Kuruvilla M Dreyling C Thieblemont
R.F. Little I Aurer M.H. J. Van Oers K Takeshita A Gopal S Rule S de Vos I Kloos M.S.
Kaminski M Meignan L.H. Schwartz J.P. Leonard S.J. Schuster V.E. Seshan

50 co-authors

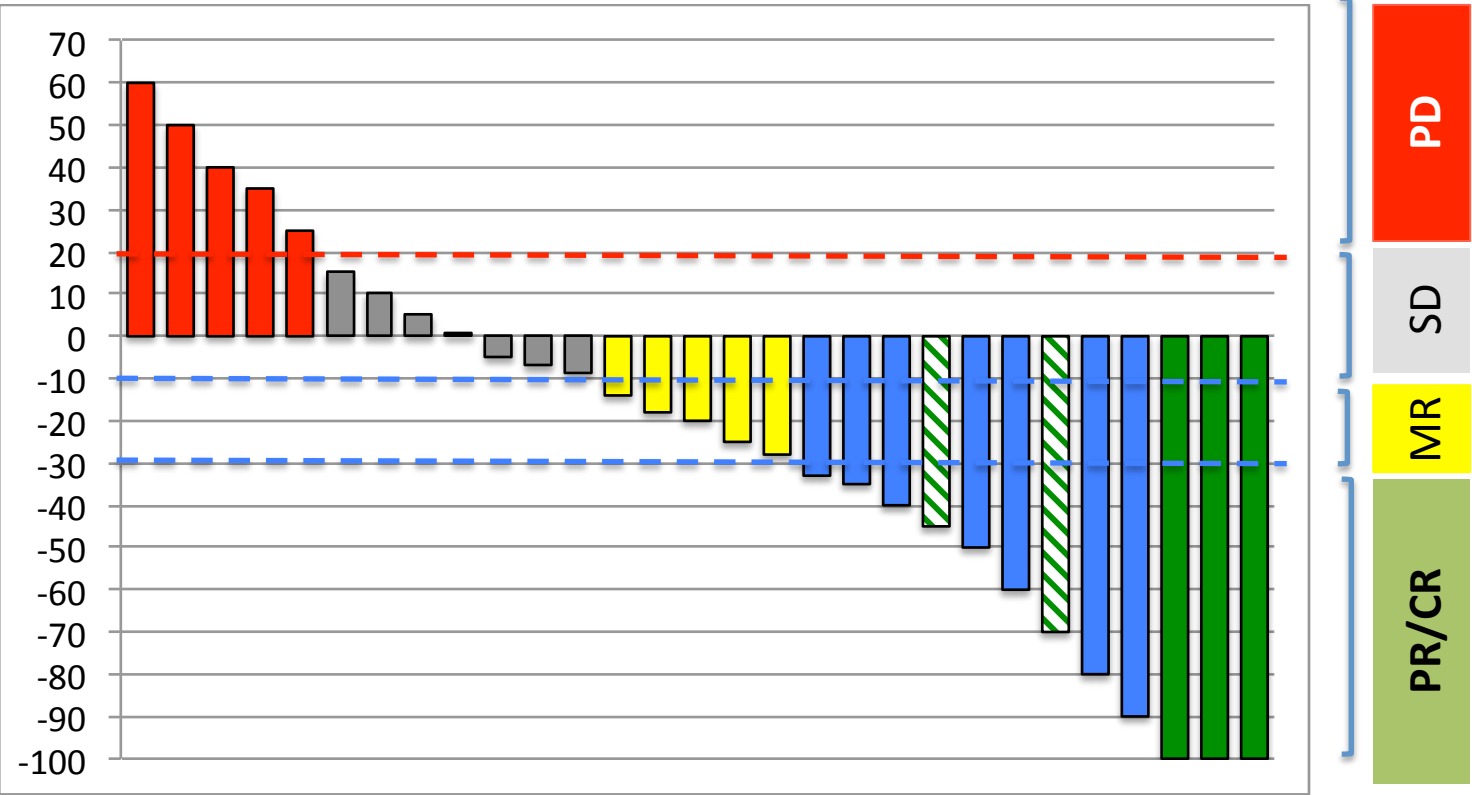
38 Academic centers

4 Pharmaceutical companies

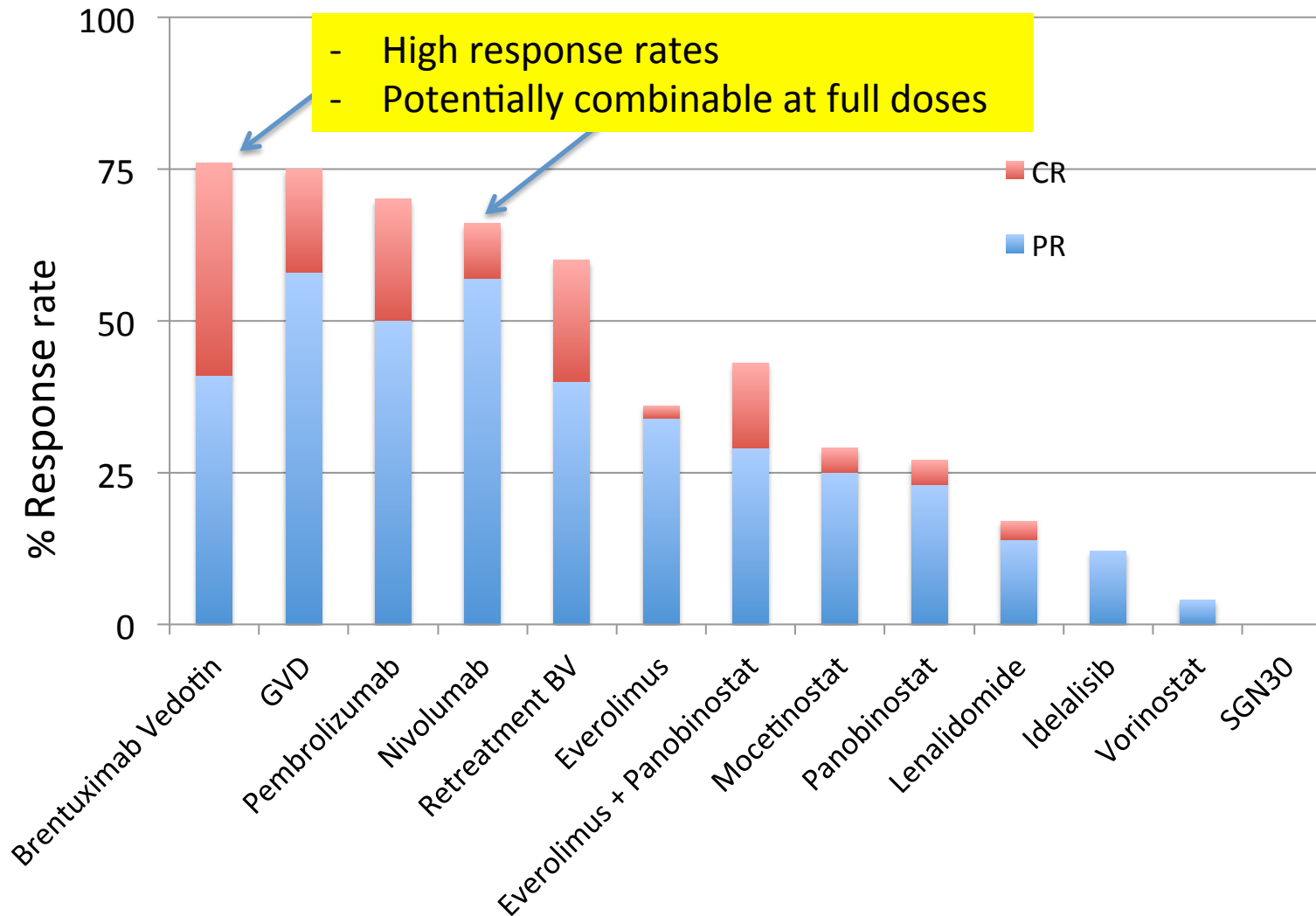
4 Imaging experts

3 statisticians

RECIL 2017



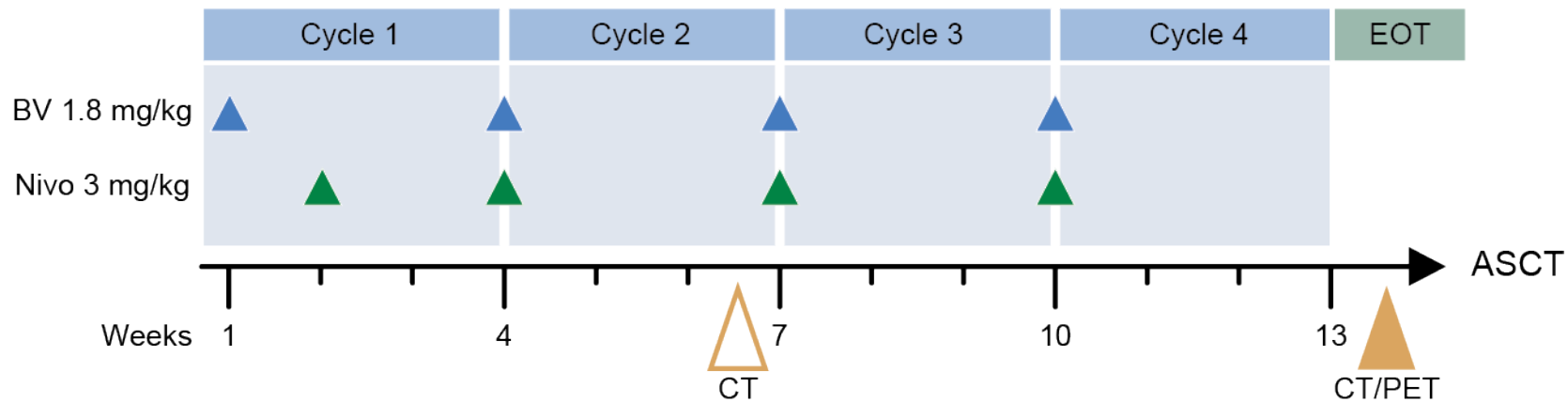
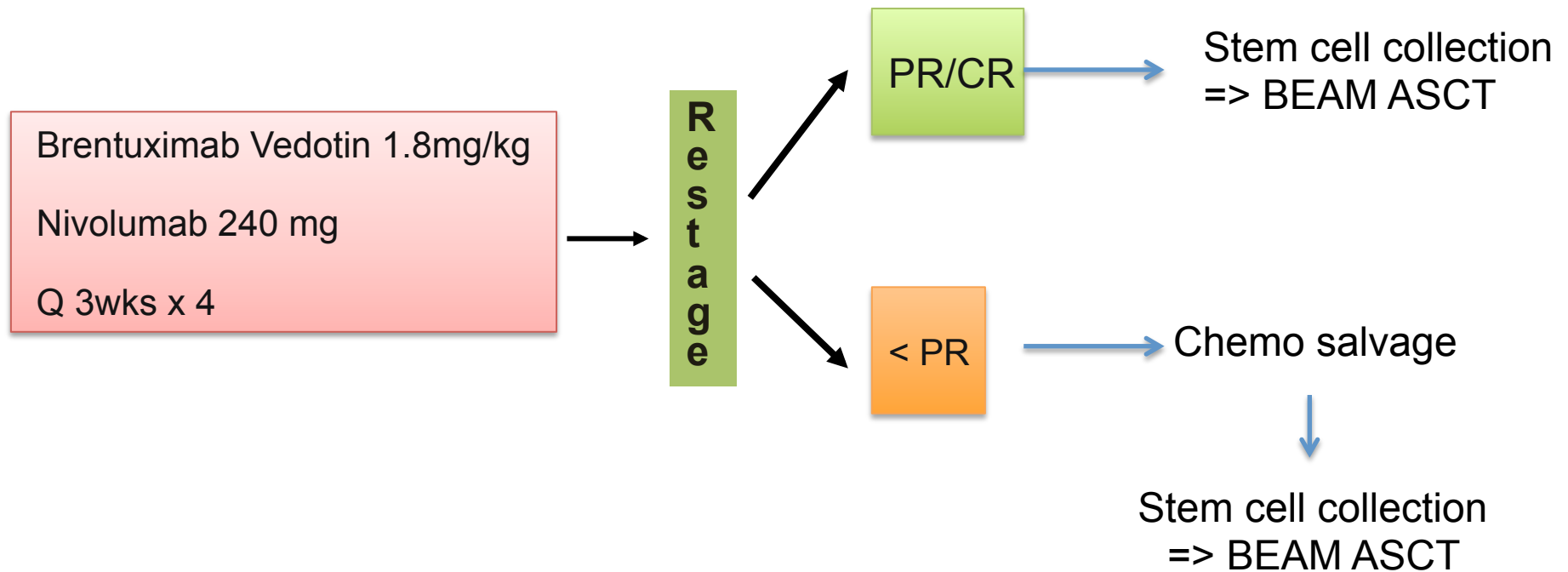
Single agent activity of novel agents in relapsed cHL



1105 Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

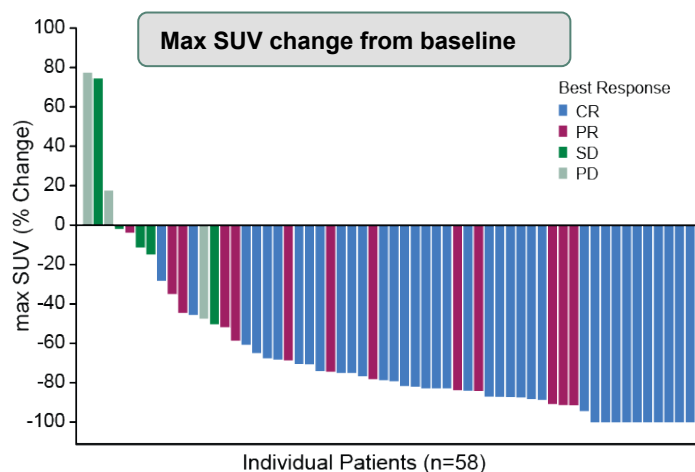
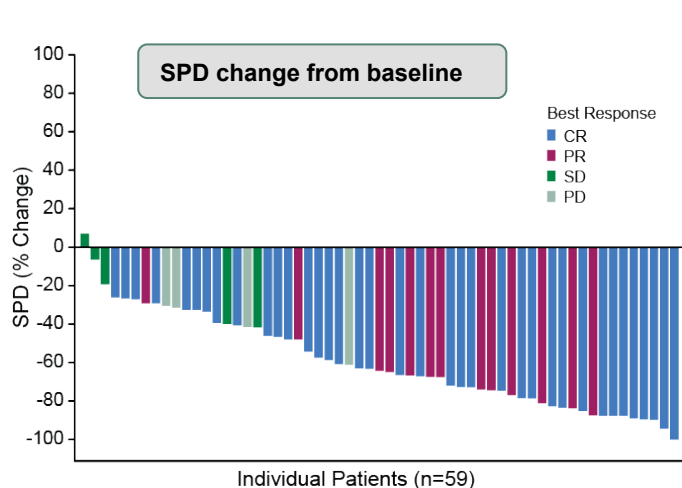
Alex F Herrera, MD¹, Nancy L Bartlett, MD², Radhakrishnan Ramchandren, MD^{3*}, Julie M Vose, MD⁴, Alison J Moskowitz, MD⁵, Tatyana A Feldman, MD⁶, Ann S LaCasce, MD⁷, Stephen M Ansell, MD, PhD^{8*}, Craig H. Moskowitz, MD⁵, Keenan Fenton^{9*}, Kazunobu Kato, MD¹⁰, Abraham Fong, MD, PhD⁹ and Ranjana H Advani, MD¹¹

Nivolumab + Brentuximab Salvage Therapy for HL



Tumor Response (N=59)

85% objective response rate with 63% complete responses

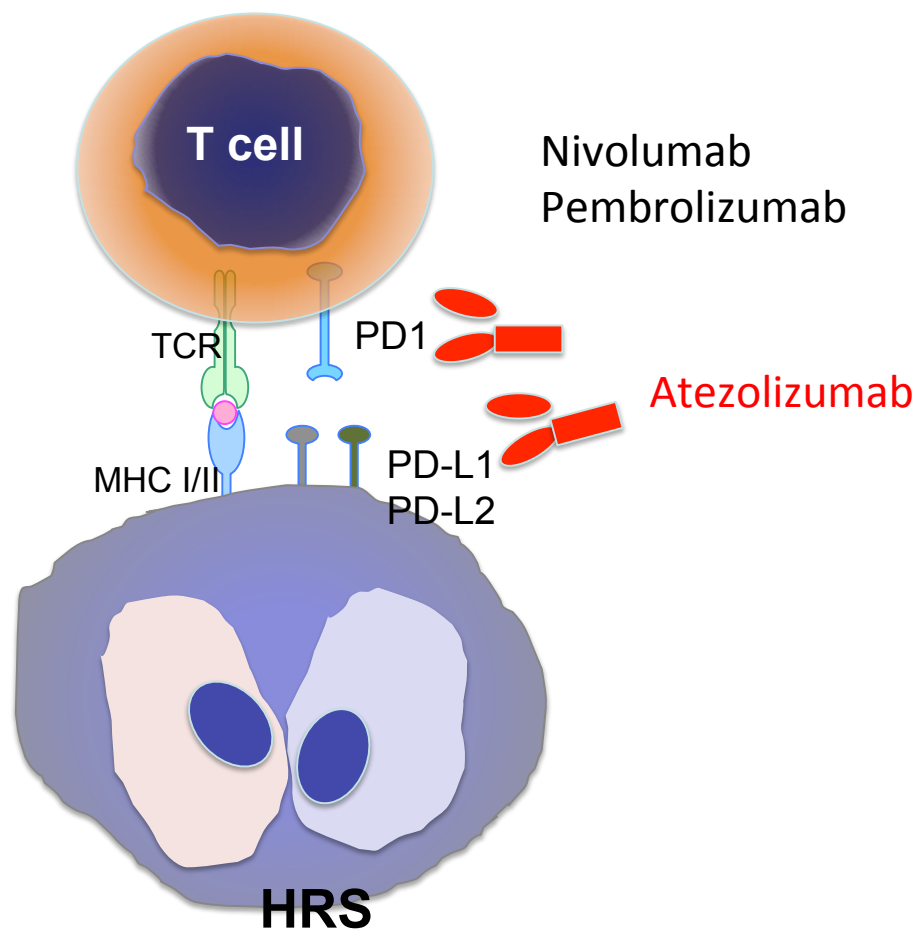


	N = 59 n (%)
Complete response (CR)	37 (63)
Deauville ≤ 2	29 (49)
Deauville 3	7 (12)
Deauville 5 ^a	1 (2)
Partial response (PR)	13 (22)
Deauville 4	7 (12)
Deauville 5	6 (10)
No metabolic response (SD)	5 (8)
Deauville 5	5 (8)
Progressive disease (PD)	3 (5)
Deauville 5	2 (3)
Missing	1 (2)
Clinical Progression (CP)	1 (2)

a. 1 pt had uptake in lymph node, but no evidence of disease was found on biopsy

SPD, sum of the product of the diameters; SUV, standard uptake value

Is there a role of targeting PDL-1 in HL?



Adapted from Stathis & Younes: Ann Oncology 2015
And Younes A & Ansell S : Seminars in Hematology, 2016, 186–189

Blockade of the PD-1 checkpoint with anti-PD-L1 avelumab is sufficient for clinical activity in relapsed/refractory classical Hodgkin lymphoma (cHL)

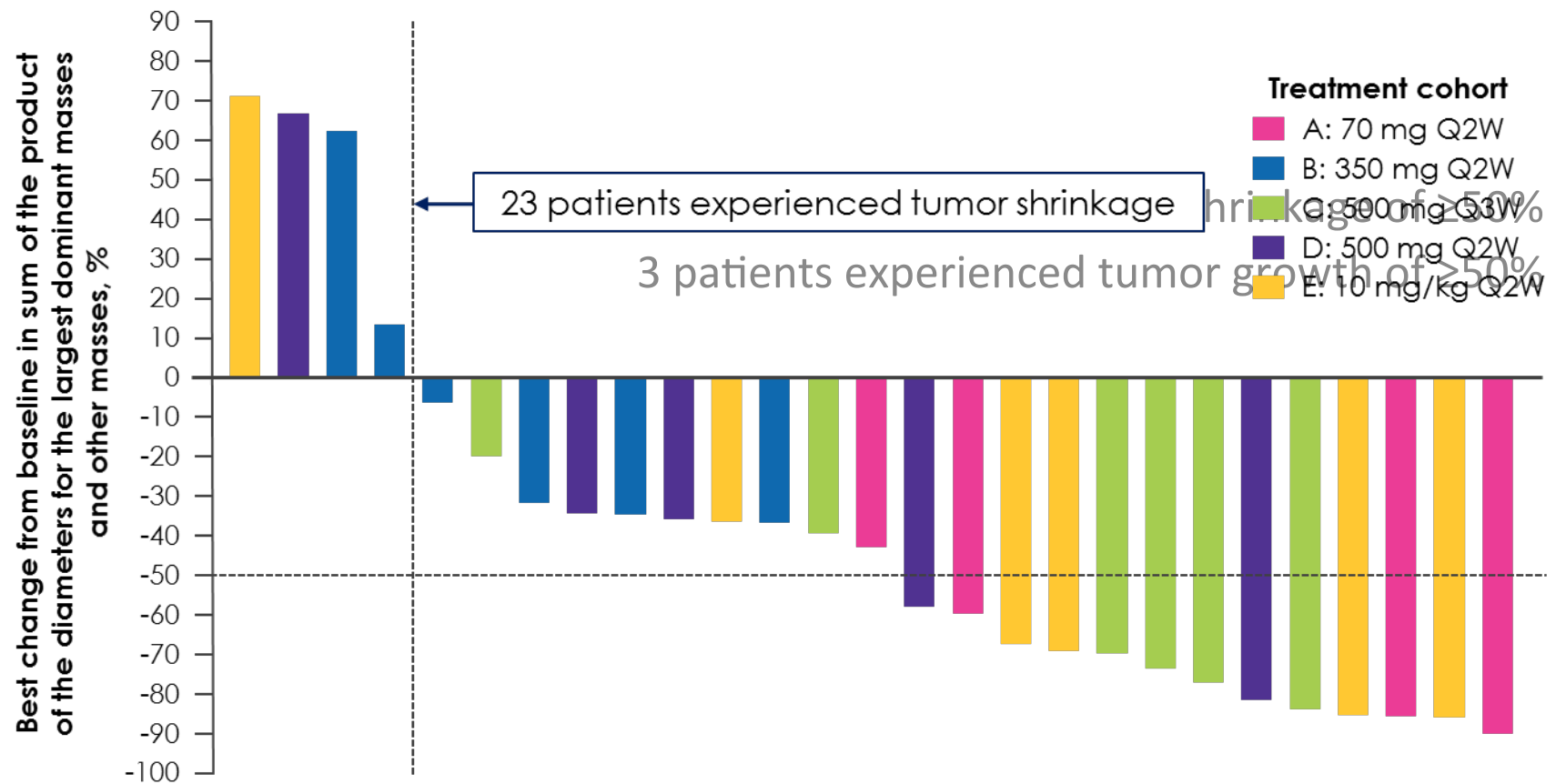
Robert Chen¹, Adam Gibb², Graham P. Collins³, Rakesh Popat⁴,
Dima El-Sharkawi⁴, Cathy Burton⁵, David Lewis⁶, Fiona Miall⁷,
Alison Forgie⁸, Anna Compagnoni⁹, Giovanna Andreola⁹, Satjit Brar¹⁰, Aron
Thall¹⁰, Adrian Woolfson¹¹, and John Radford²

¹City of Hope Medical Center, Duarte, California, USA; ²The Christie NHS Foundation Trust, Manchester, United Kingdom; ³Churchill Hospital, Cancer and Haematology Centre, Oxford, United Kingdom; ⁴University College London Hospitals NHS Foundation Trust, London, United Kingdom; ⁵St. James's University Hospital, Leeds, United Kingdom; ⁶Plymouth Hospital NHS Trust, Plymouth, United Kingdom; ⁷University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; ⁸Pfizer Oncology Research and Development, San Francisco, California, USA; ⁹Pfizer Oncology, Milano, Italy; ¹⁰Pfizer Oncology, La Jolla, California, USA; ¹¹Pfizer Oncology, New York, New York, USA

Oral Presentation at the 14th International Conference on Malignant Lymphoma; June 14-17, 2017; Lugano, Switzerland

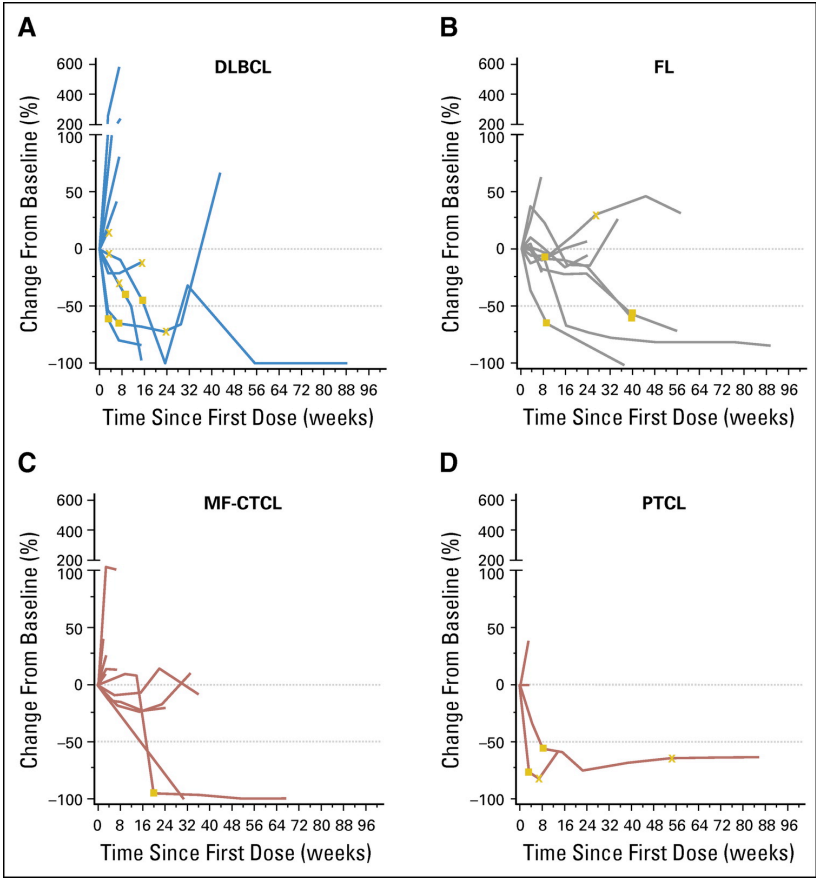
Abstract No. 055

Best percent change in tumor burden from baseline (n=27*)

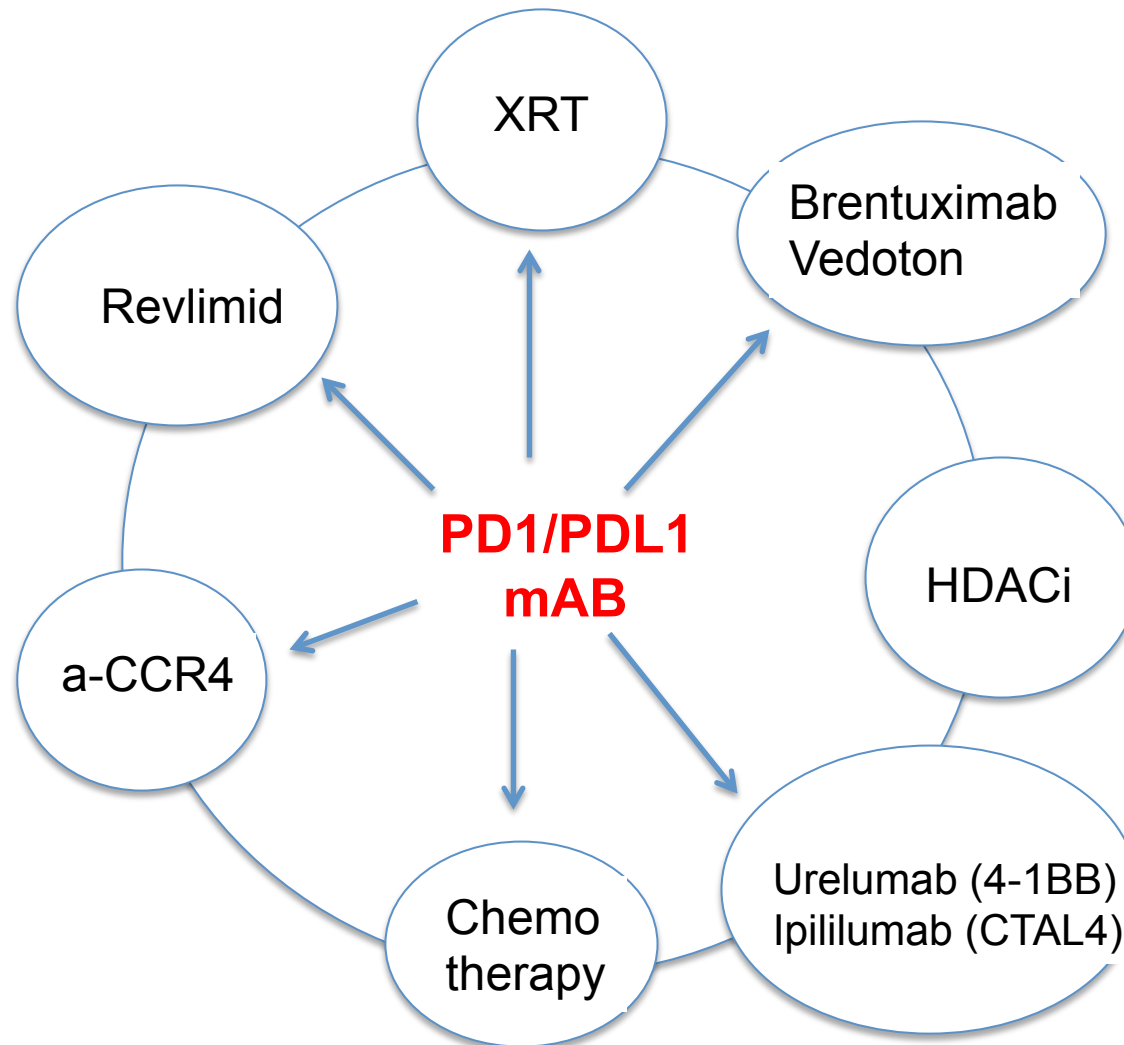


* Only patients with baseline and ≥ 1 post-baseline largest dominant mass or other mass based on investigator assessment per Response Criteria for Malignant Lymphoma are included.

Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study



Development of Anti-PD1/PDL1-Based Therapy

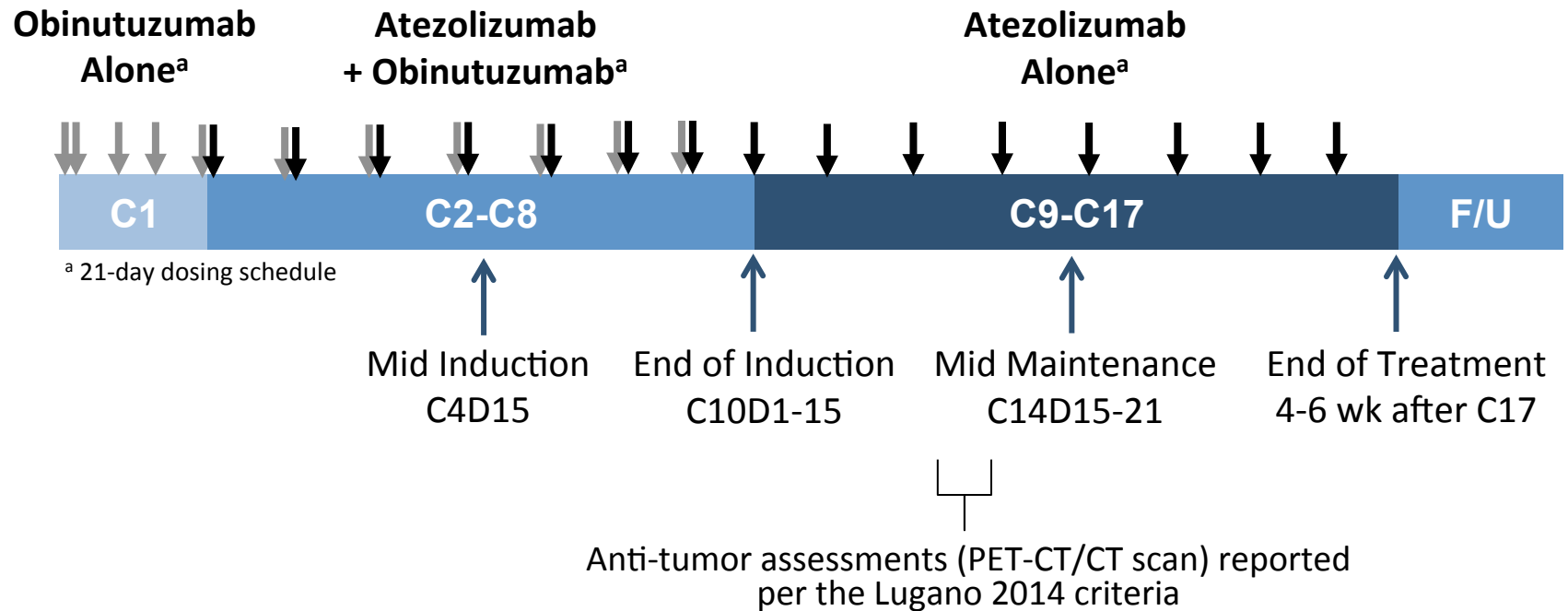


A Phase Ib Study Evaluating the Safety and Clinical Activity of Atezolizumab Combined With Obinutuzumab in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

M. Lia Palomba,¹ Brian G. Till,² Steven I. Park,³ Franck Morschhauser,⁴
Guillaume Cartron,⁵ Reinhard Marks,⁶ Elicia Penuel,⁷ Surya Chitra,⁷
Melissa Kuhn,⁷ Leslie Popplewell⁸

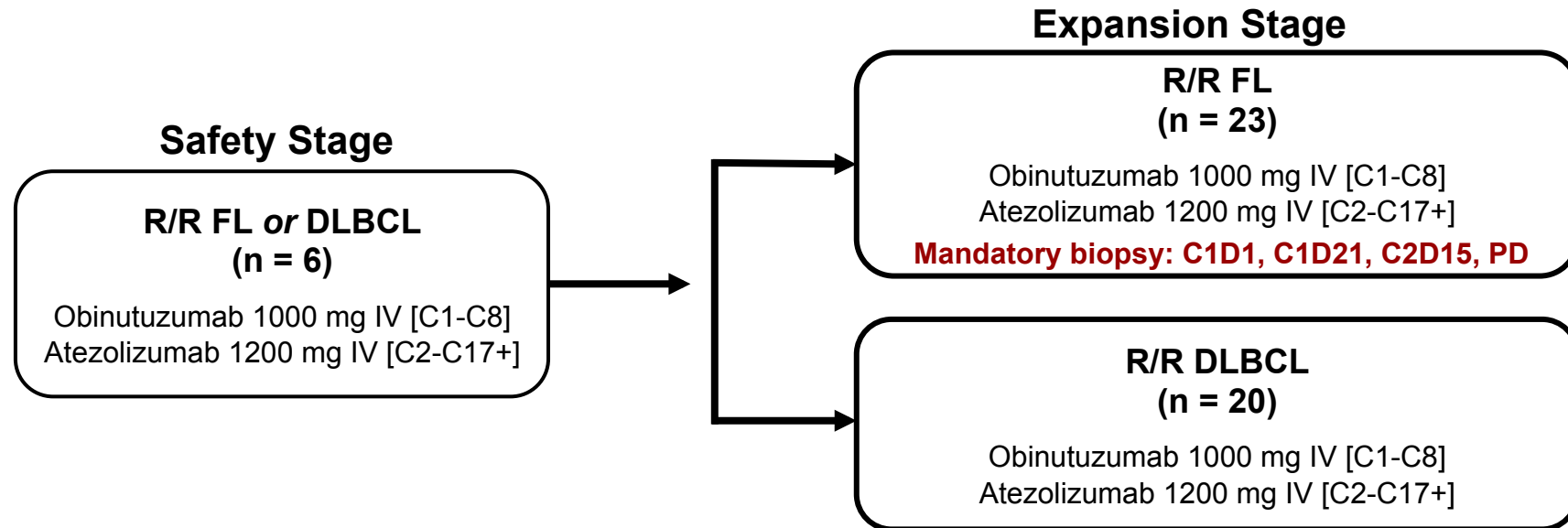
¹Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ³Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; ⁴Department of Clinical Hematology, Lille University Hospital Center, Lille Cedex, France; ⁵Department of Clinical Hematology, University Hospital Center of Montpellier, Montpellier, France; ⁶Department of Hematology, Oncology and Stem Cell Transplantation, Universitätsklinikum Freiburg, Freiburg, Germany; ⁷Product Development Oncology, Genentech, Inc., South San Francisco, CA, USA; ⁸Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, USA

Phase I Study of Atezolizumab + Obinutuzumab in NHL (FL or DLBCL)



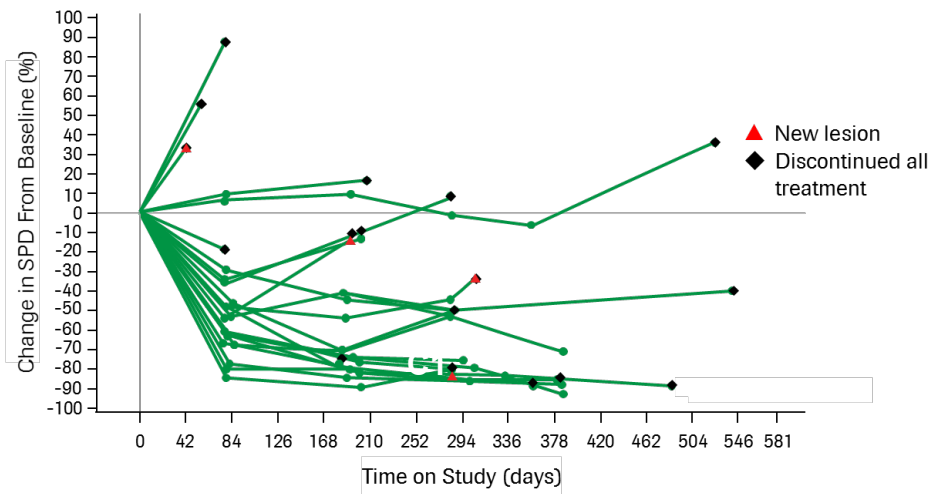
↓ Obinutuzumab 1000 mg IV q3w
↓ Atezolizumab 1200 mg IV q3w

Phase I Study of Atezolizumab + Obinutuzumab in NHL (FL or DLBCL)



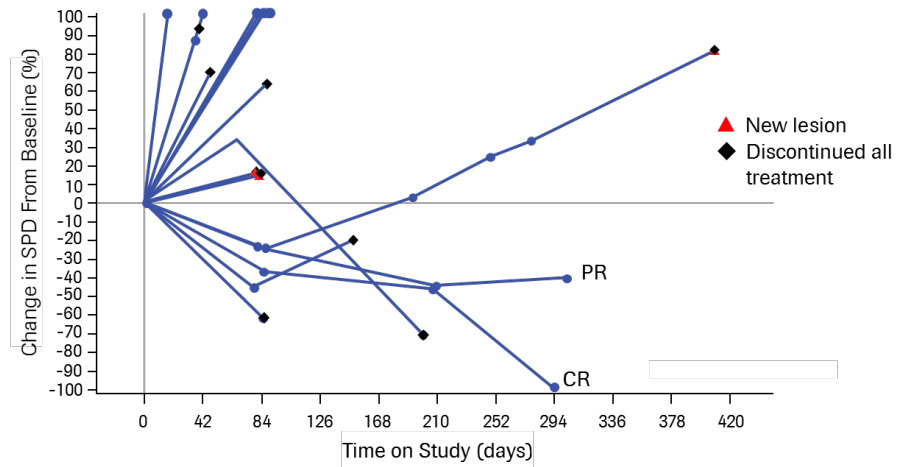
Phase I Study of Atezolizumab + Obinutuzumab in NHL (FL or DLBCL)

FL



- **14/23 patients (61%)**

DLBCL



- **5/20 patients (25%)**

Pembrolizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma:

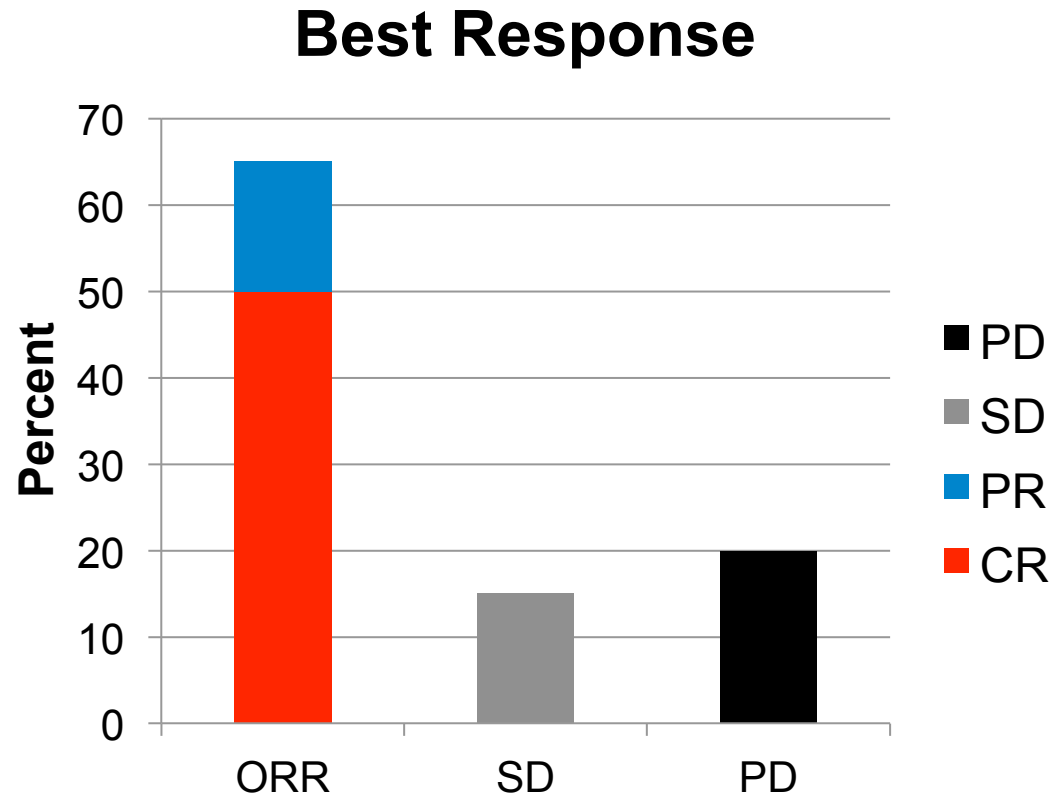
Loretta J. Nastoupil, Jason Westin, Nathan Fowler, Michelle Fanale, Felipe Samaniego, Yasohiro Oki, Chizobam Obi, JingJing Cao, Xiaoyun Cheng, Man Chun John Ma, Zhiqiang Wang, Fuliang Chu, Lei Feng, Shouhao Zhou, R. Eric Davis, and Sattva S. Neelapu

THE UNIVERSITY OF TEXAS
MD Anderson
~~Cancer Center~~

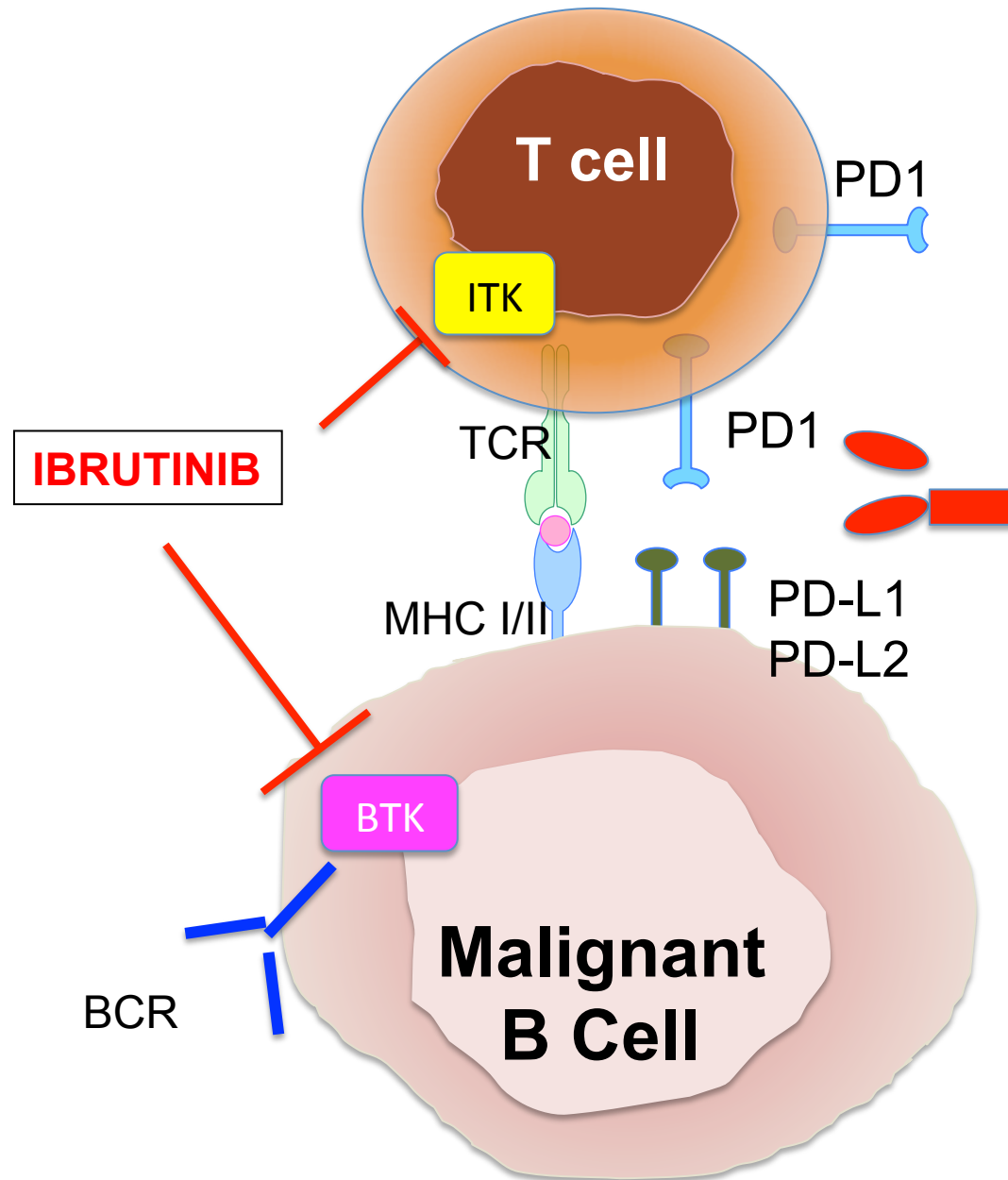
Making Cancer History®

Pembrolizumab + Rituximab in Relapsed FL

- 20 evaluable for response
- **ORR was 65%**
(CR N=10/PR N=3)
- **CR rate was 50%**
- 3 patients with stable disease and 4 with progressive disease as best response

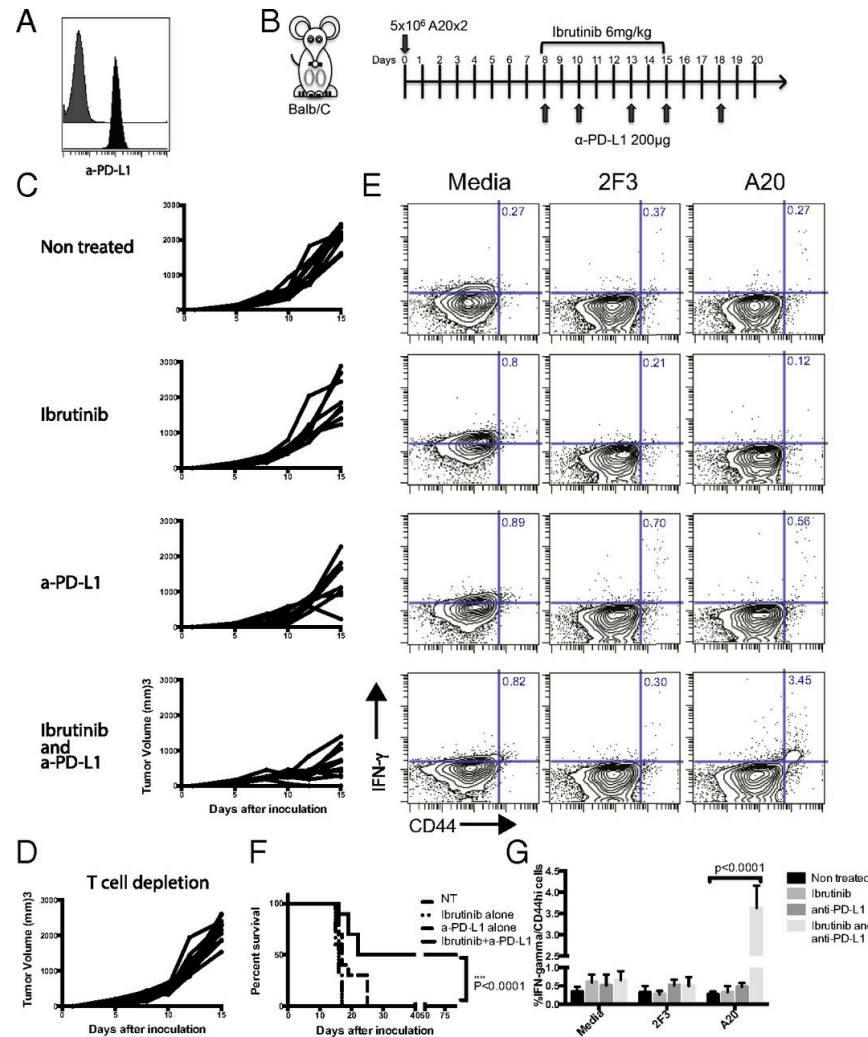


Rationale for combining Ibrutinib with PD1/PDL1 antibodies



Ibrutinib in combination with anti-PD-L1 induces an antitumor immune response

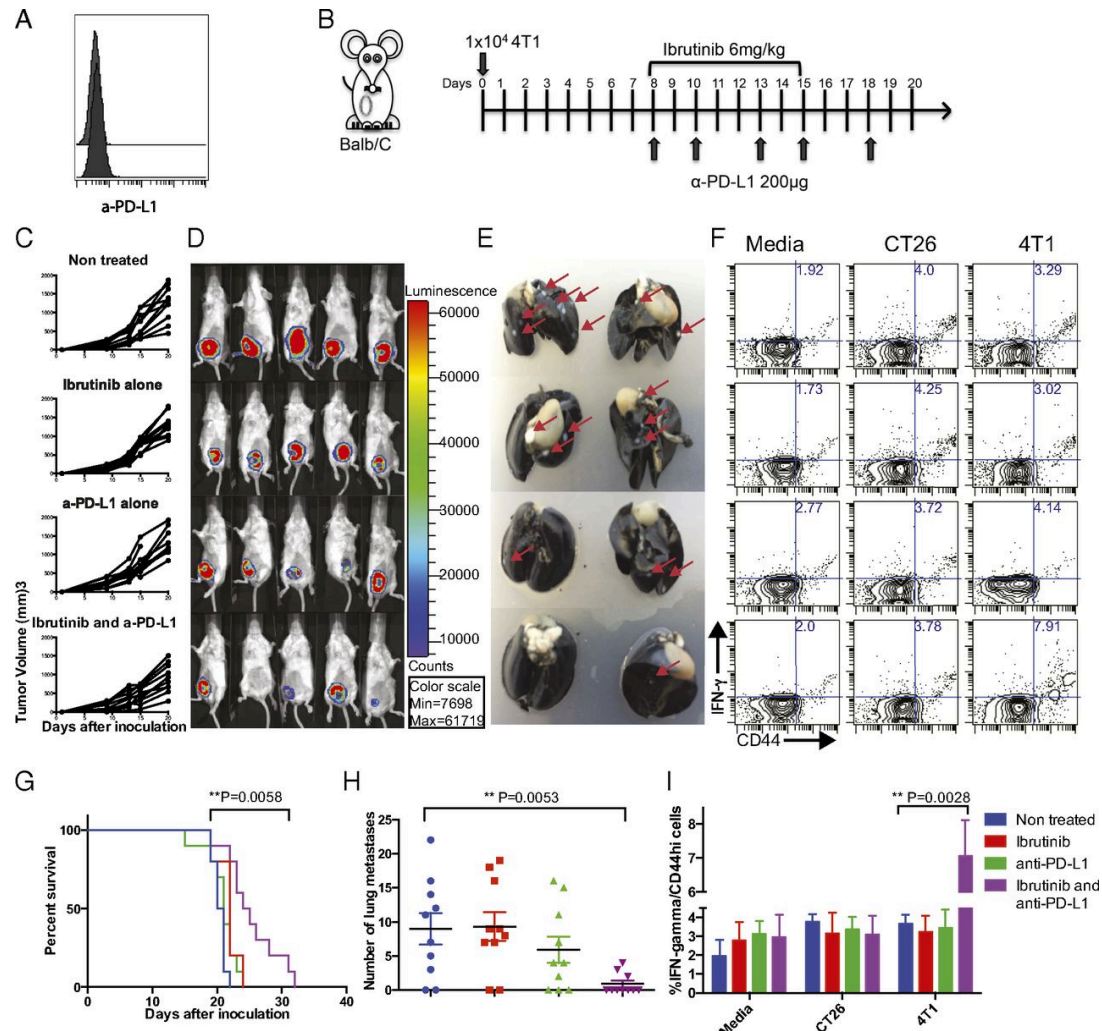
A20 mouse B cell lymphoma model



Idit Sagiv-Barfi et al. PNAS 2015;112:E966-E972

PNAS

The combination of ibrutinib with anti-PD-L1 reduces tumor burden in 4T1 (Mouse Tripple Negative Breast Carcinoma) tumor-bearing mice.



Idit Sagiv-Barfi et al. PNAS 2015;112:E966-E972

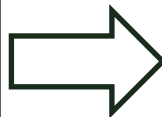
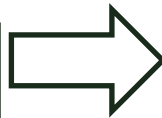
PCI32765-LYM-1002: Study Design

Nivolumab + Ibrutinib in relapsed B-cell malignancies

Part A n=18
(Dose Optimization)

A-1
I: 420 mg, po, qd
N: 3mg/kg, i.v., q14d

A-2
I: 560 mg, p.o., qd
N: 3 mg/kg, i.v., q14d



Part B (n=30 in each cohort)
(Expansion Cohort: Two-stage design)

B 1: I: 420 mg/qd PO + N: 3 mg/kg/q14d

B1: CLL (del 17p or del 11q)

B 2 and B 3: I: 560 mg/qd PO + N: 3 mg/kg/q14d

B2: Follicular Lymphoma

B3: DLBCL

Safety and Efficacy of the Combination of Ibrutinib and Nivolumab in Patients With Relapsed Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia

Anas Younes,¹ Joshua Brody,² Cecilia Carpio,³ Armando López-Guillermo,⁴ Dina Ben-Yehuda,⁵ Burhan Ferhanoglu,⁶ Arnon Nagler,⁷ Muhit Ozcan,⁸ Irit Avivi,⁹ Francesc Bosch,³ Maria Dolores Caballero Barrigon,¹⁰ Daniela Buglio,¹¹ Michael Streit,¹² John Alvarez,¹² Rob Ceulemans,¹³ Behzad Kharabi Masouleh,¹³ Sriram Balasubramanian,¹² Michael Schaffer,¹² Shean-Sheng Wang,¹⁴ Nele Fourneau,¹³ Wojciech Jurczak¹⁵

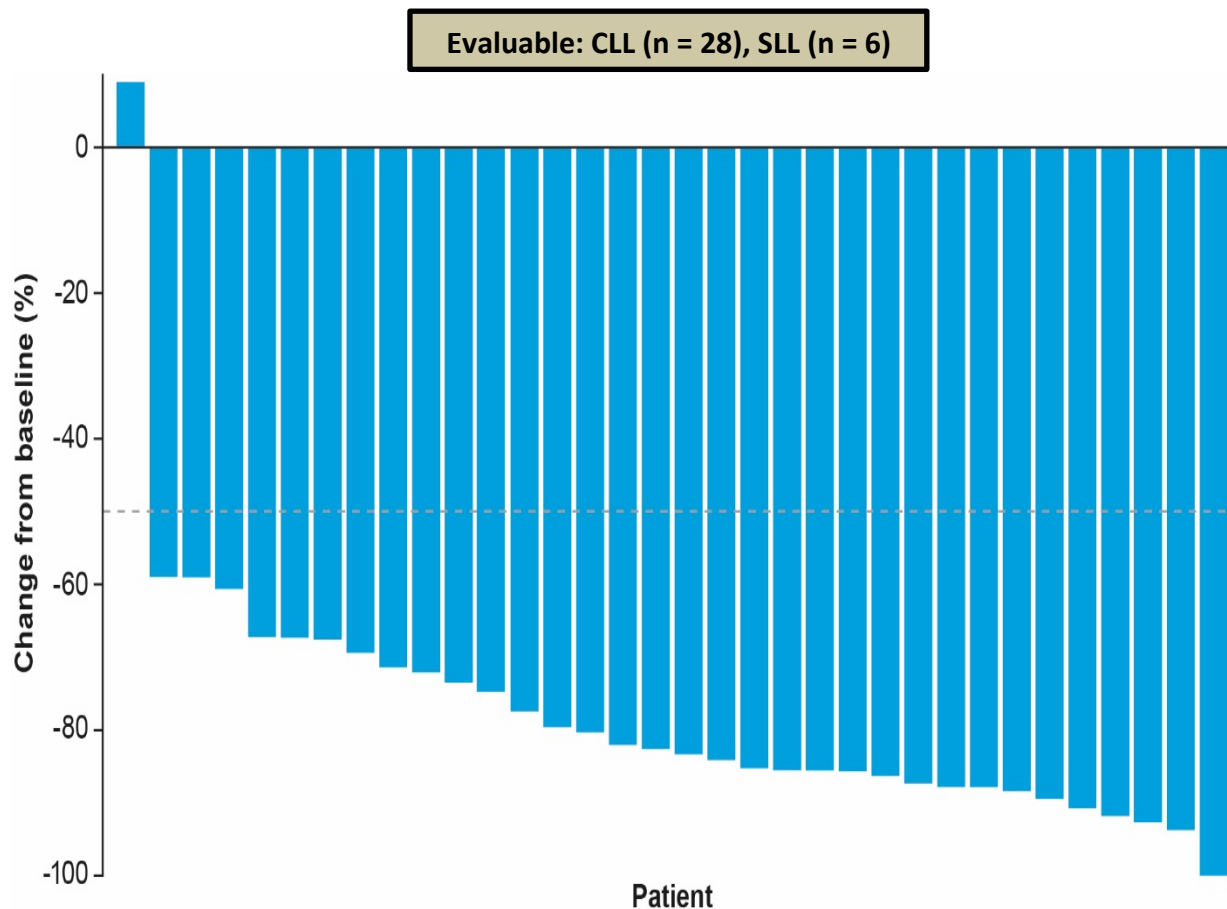
¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³University Hospital Vall d'Hebron, Barcelona, Spain; ⁴University of Barcelona, Barcelona, Spain; ⁵Hadassah-Hebrew University Medical Center, Jerusalem, Israel; ⁶Koc University, Istanbul, Turkey; ⁷Chaim Sheba Medical Center, Tel-Hashomer, Israel; ⁸Ankara University School of Medicine, Ankara, Turkey; ⁹Tel Aviv Medical Center, Tel Aviv, Israel; ¹⁰Hospital Clínico Universitario de Salamanca, Salamanca, Spain; ¹¹Bristol-Myers Squibb, Lawrenceville, NJ, USA; ¹²Janssen R&D, Spring House, PA, USA; ¹³Janssen R&D, Beerse, Belgium; ¹⁴Janssen R&D, Raritan, NJ, USA; ¹⁵Jagiellonian University, Krakow, Poland

Demographics and Characteristics

	CLL/SLL (n = 36)	FL (n = 40)	DLBCL (n = 45)	Richter (n = 20)	Total (N = 141)
Age, years					
Median (range)	65 (41-79)	63 (42-83)	64 (20-89)	68 (41-83)	65 (20-89)
Sex, n (%)					
Male	27 (75)	23 (58)	29 (64)	8 (40)	87 (62)
Female	9 (25)	17 (42)	16 (36)	12 (60)	54 (38)
ECOG, n (%)					
0	17 (47)	30 (75)	19 (42)	4 (20)	70 (50)
1	18 (50)	8 (20)	21 (47)	13 (65)	60 (43)
2	1 (3)	2 (5)	5 (11)	3 (15)	11 (8)
Prior lines of therapy, n					
Median (range)	2.0 (1-6)	3.0 (2-12)	3.0 (1-9)	2.0 (1-5)	3.0 (1-12)
Bulky disease (≥ 5 cm), n (%)	26 (72)	15 (38)	17 (38)	10 (50)	68 (48)

Efficacy: CLL/SLL

Maximum Decrease in Target Lesions



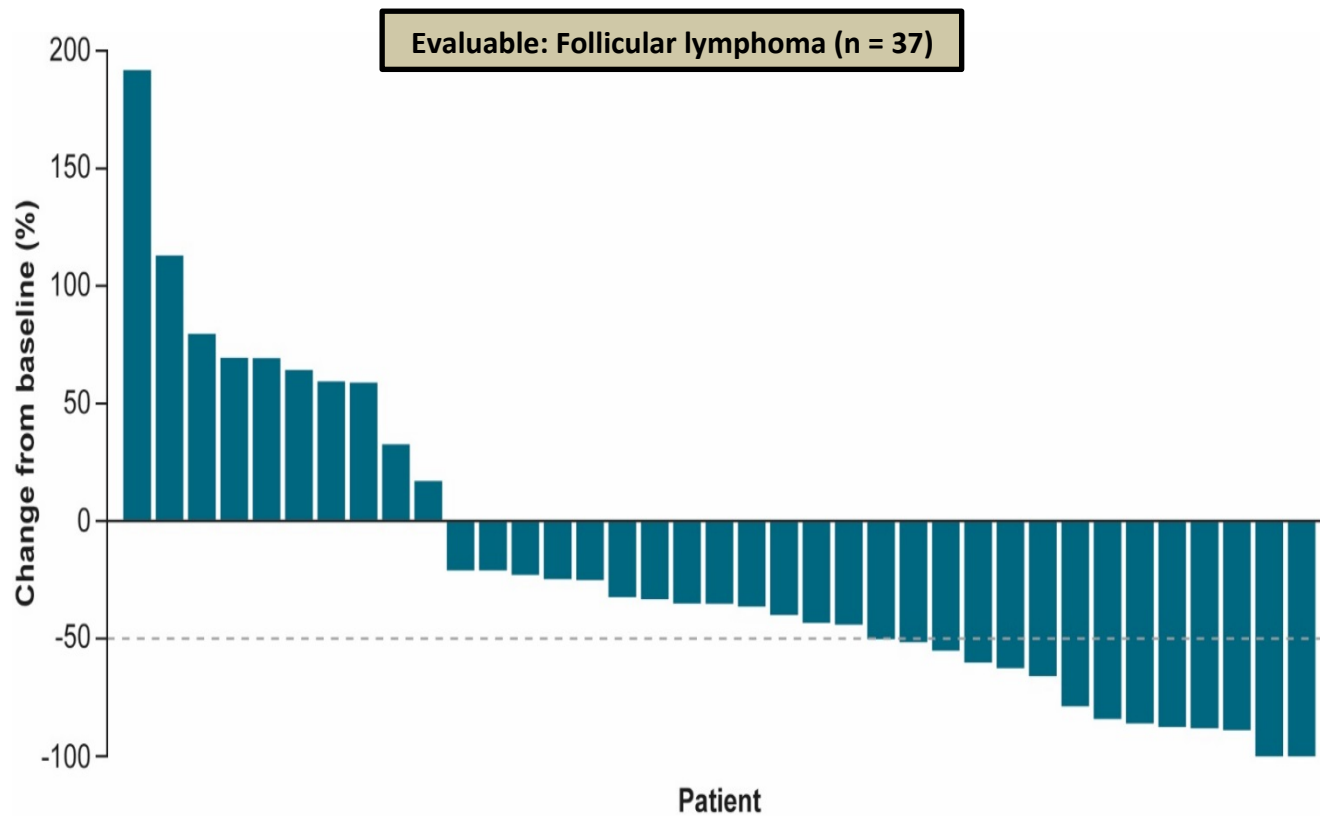
n (%)	CLL/SLL (n = 36)
ORR^{a,b}	27 (75)
Complete response (CR)	0
Partial response (PR)	22 (61)
PR with lymphocytosis (PRL)	5 (14)
Stable disease (SD)	5 (14)
Progressive disease (PD)	1 (3)
Treatment-related lymphocytosis	1 (3)
Missing	2 (6)

^aORR includes CR, PR, and PRL.

^biwCLL criteria (CLL); Lugano classification (SLL).

Efficacy: Follicular Lymphoma

Maximum Decrease in Target Lesions



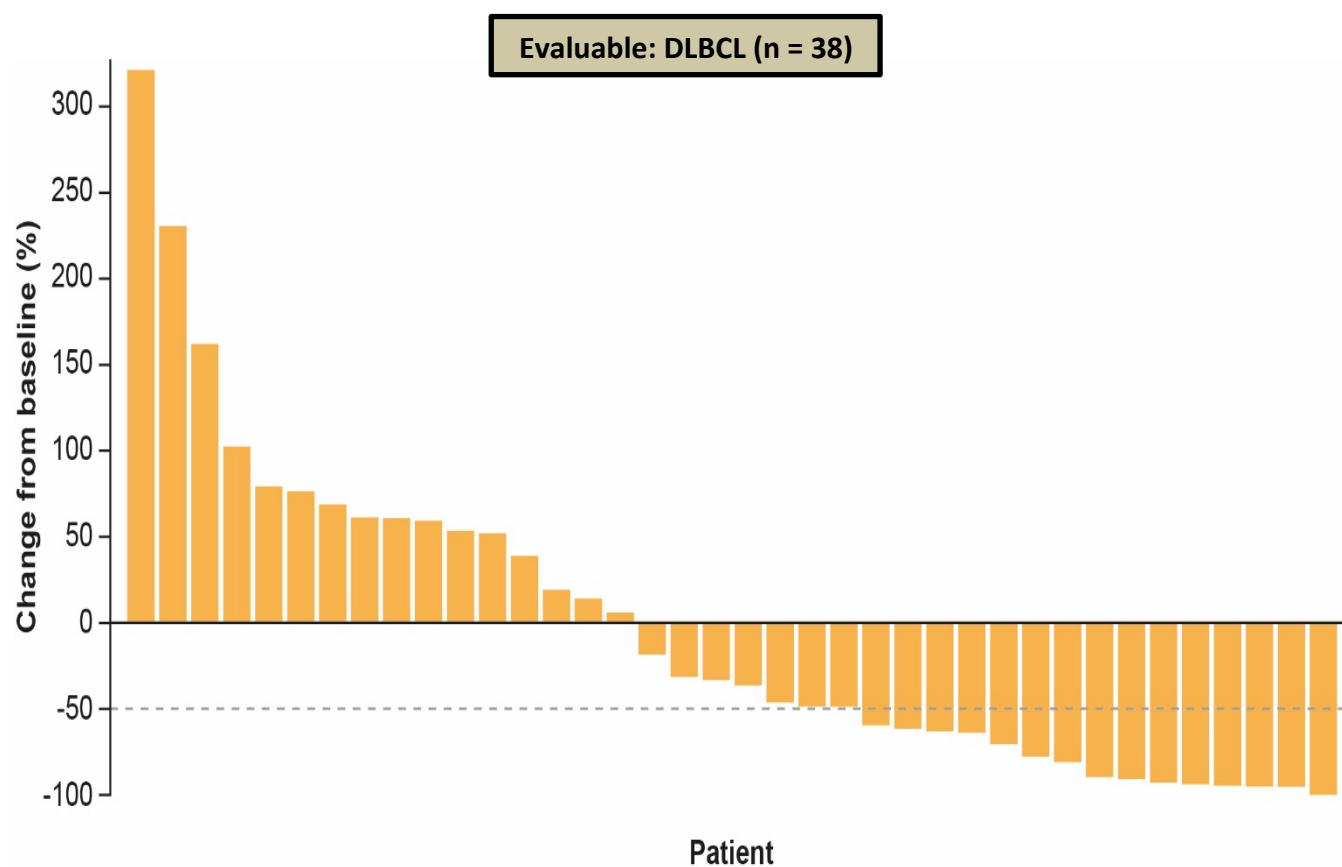
n (%)	FL (n = 40)
ORR, ^{a,b}	13 (32)
CR	4 (10)
PR	9 (22)
SD	13 (32)
PD	11 (28)
Missing	3 (8)

^aORR includes CR and PR.

^bLugano classification.

Efficacy: Diffuse Large B-Cell Lymphoma

Maximum Decrease in Target Lesions



n (%)	DLBCL (n = 45)
ORR,^{a,b}	16 (36)
CR	7 (16)
PR	9 (20)
SD	6 (13)
PD^c	19 (42)
Missing	4 (9)

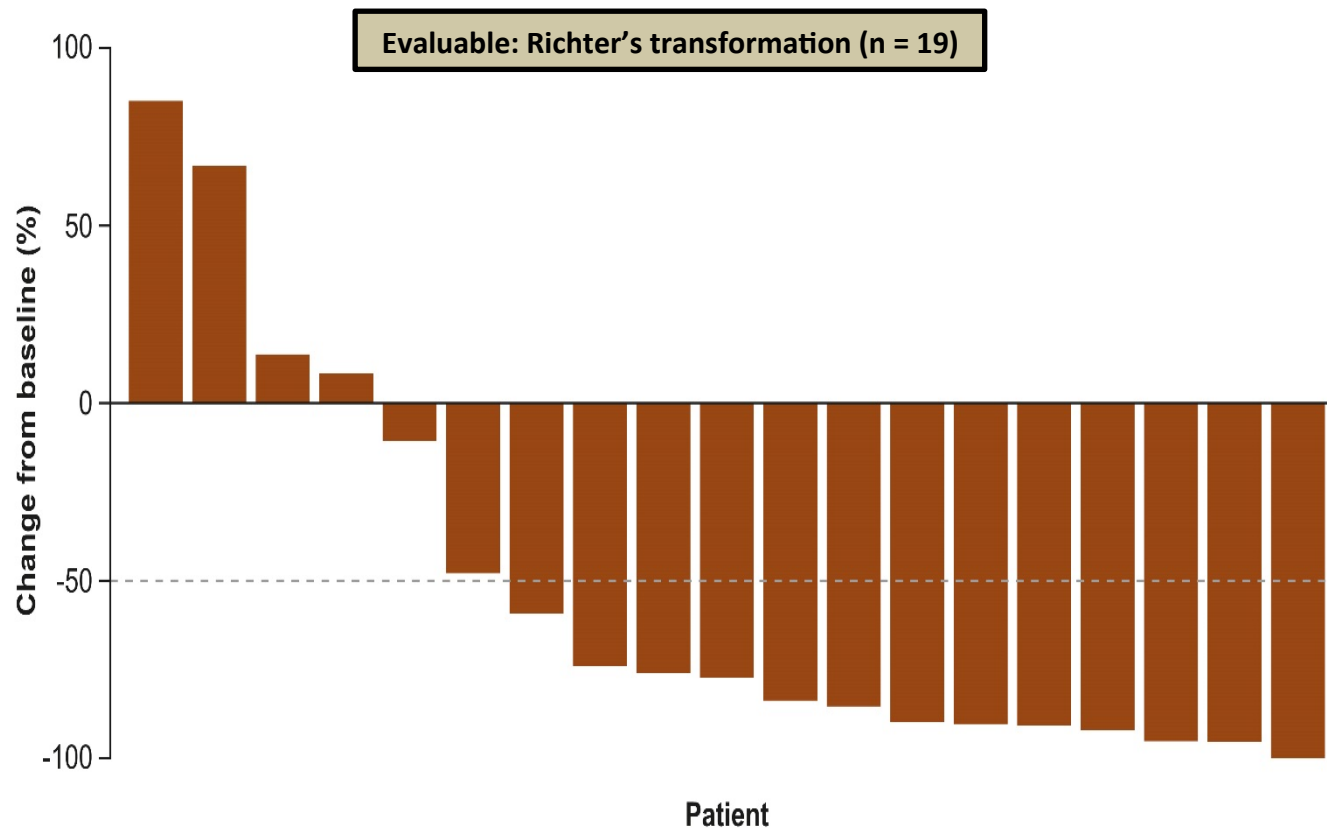
^aORR includes CR and PR.

^bLugano classification.

^cData not available for 3 patients (PD based on clinical progression).

Efficacy: Richter's Transformation

Maximum Decrease in Target Lesions



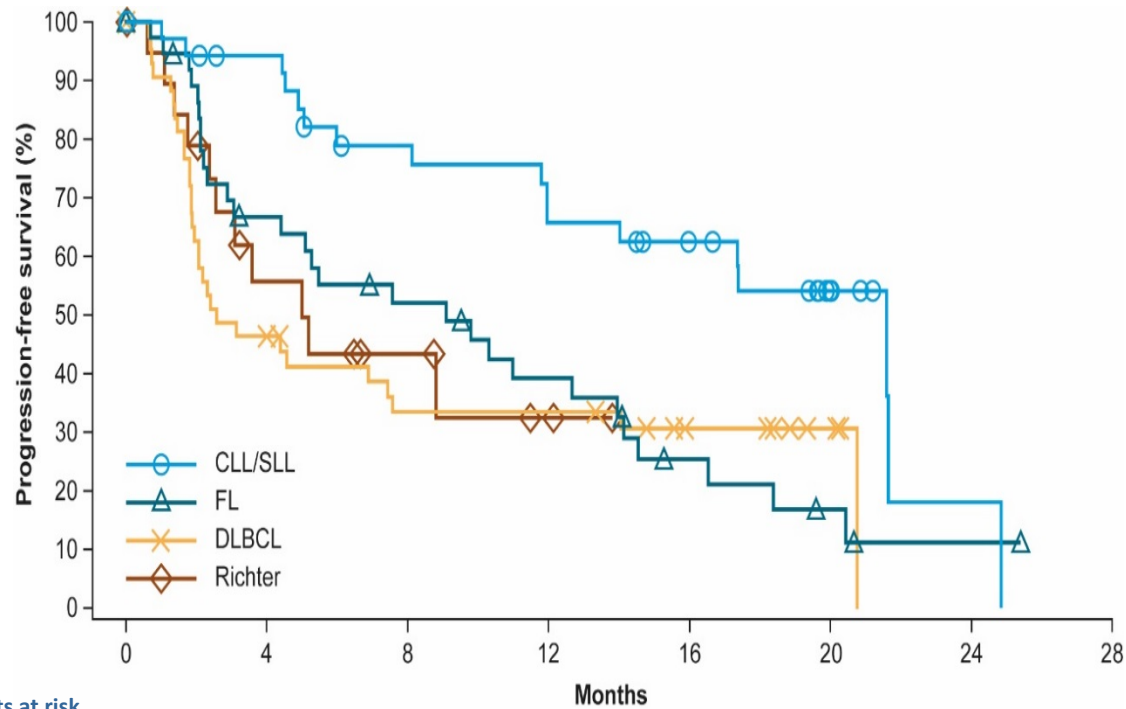
n (%)	Richter (n = 20)
ORR,^{a,b}	13 (65)
CR	2 (10)
PR	11 (55)
SD	1 (5)
PD	5 (25)
Missing	1 (5)

^aORR includes CR and PR.

^bLugano classification.

Nivolumab + Ibrutinib

Progression-Free Survival



Patients at risk

	0	4	8	12	16	20	24	28
CLL/SLL	36	31	24	20	16	8	1	0
FL	40	23	17	12	6	3	1	0
DLBCL	45	20	13	13	8	3	0	0
Richter	20	9	5	2	0	0	0	0

	CLL/SLL (n = 36)	FL (n = 40)	DLBCL (n = 45)	Richter (n = 20)
Median PFS, months (95% CI)	NE	9 (3-14)	3 (2-8)	5 (2-NE)
Median follow-up, months (95% CI)	20 (16-20)	20 (14-25)	18 (15-19)	9 (6-12)

Pt with relapsed FL
1st dose of Nivo 2/15/2016 at 10 a.m

2/15 2 PM



2/15 10 PM



Pt with relapsed FL
1st dose of Nivo 2/15/2016 at 10 a.m

Day 2



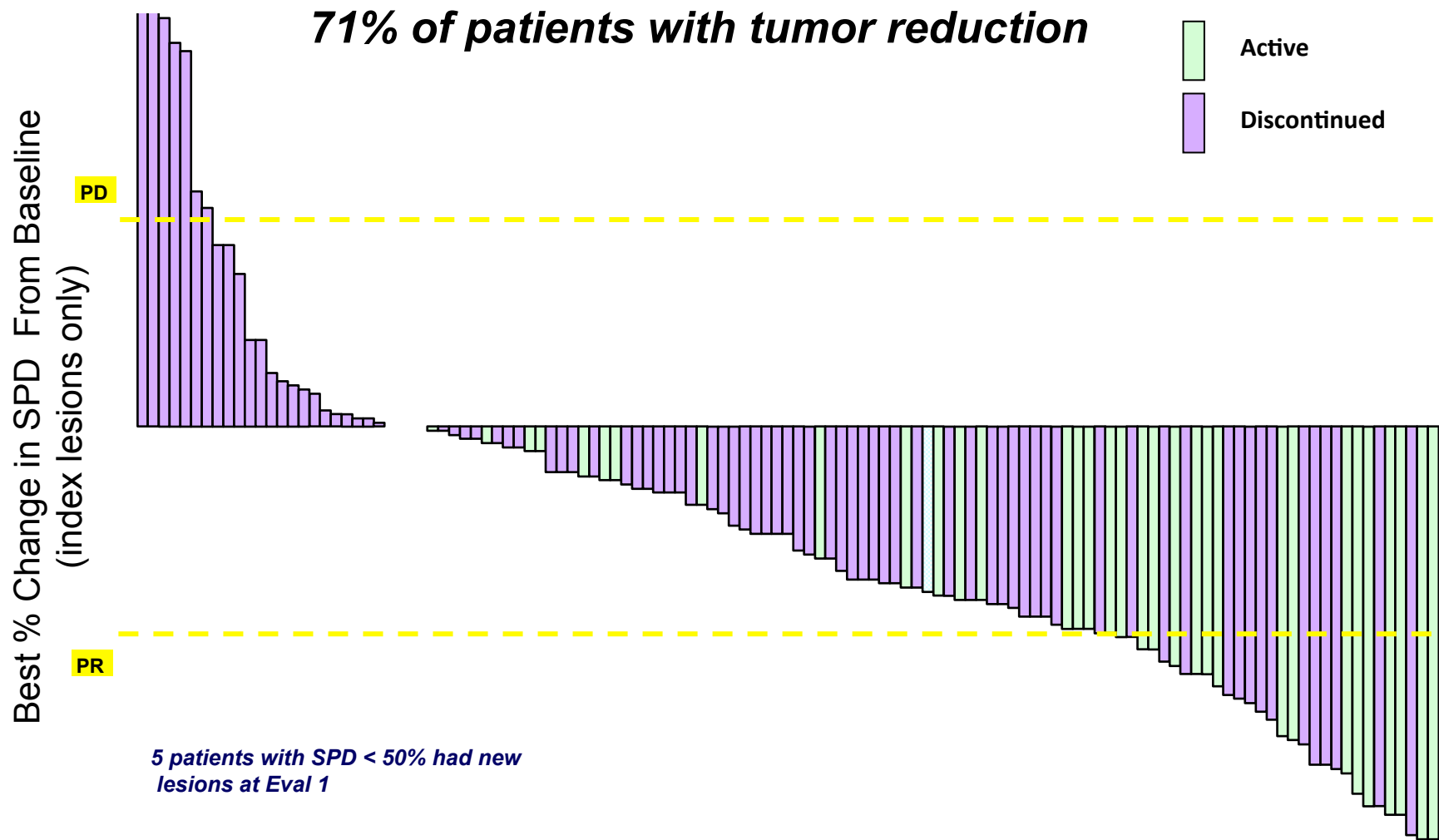
Day 4



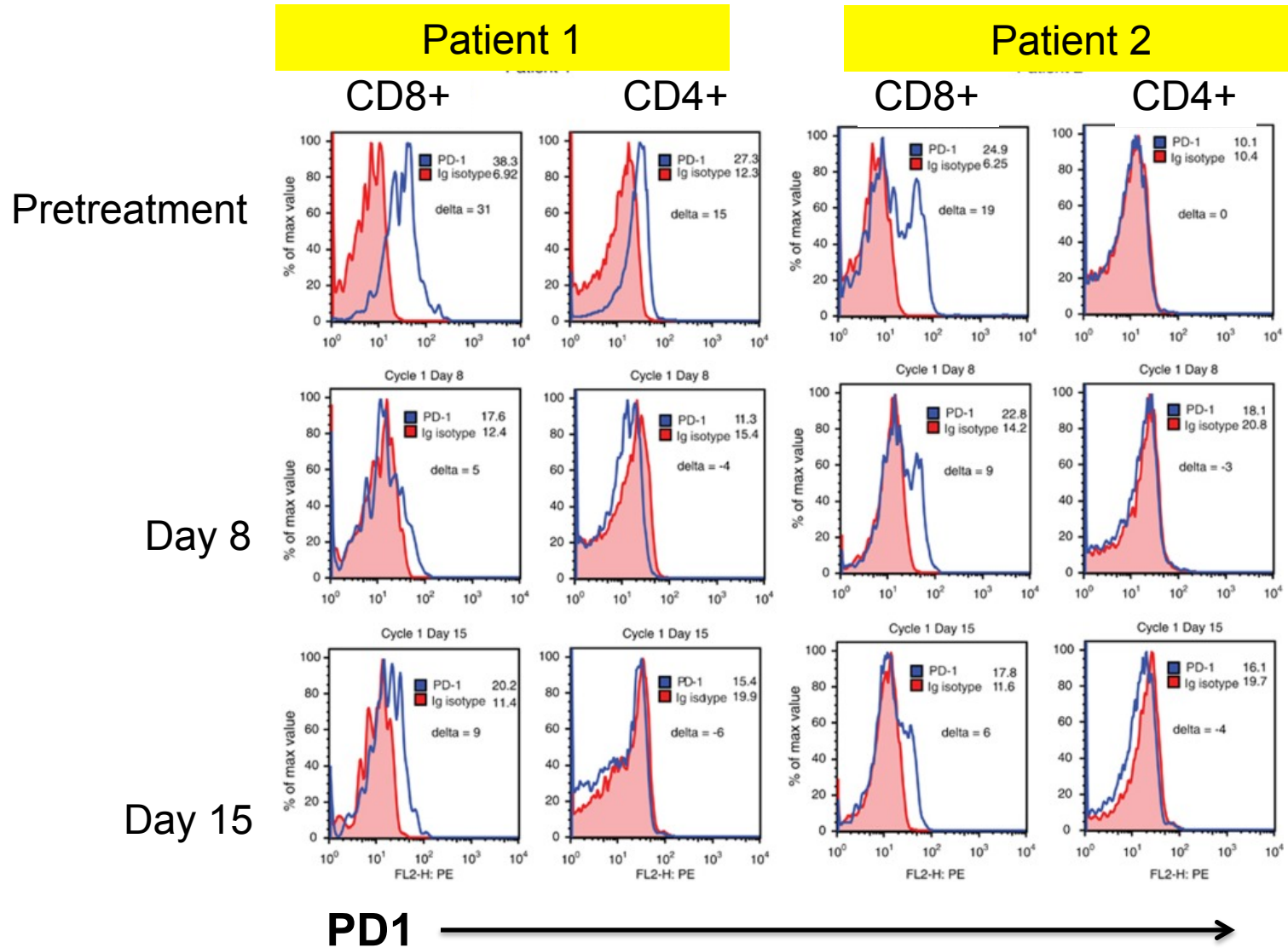
Day 10



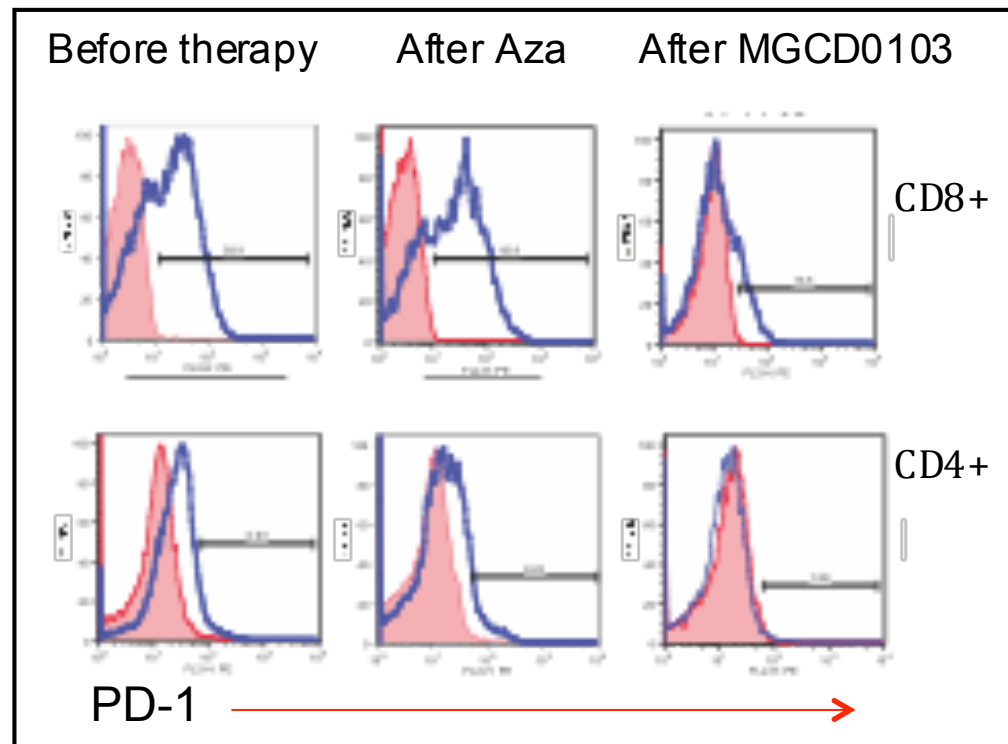
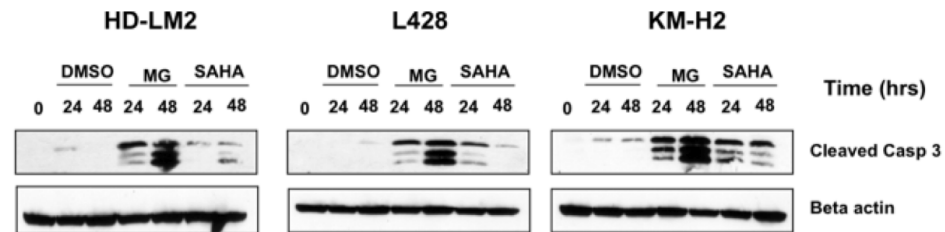
Panobinostat Phase II Study in Relapsed HL



Panobinostat Downregulates PD-1 on T cells of Patients with Relapsed HL in Vivo

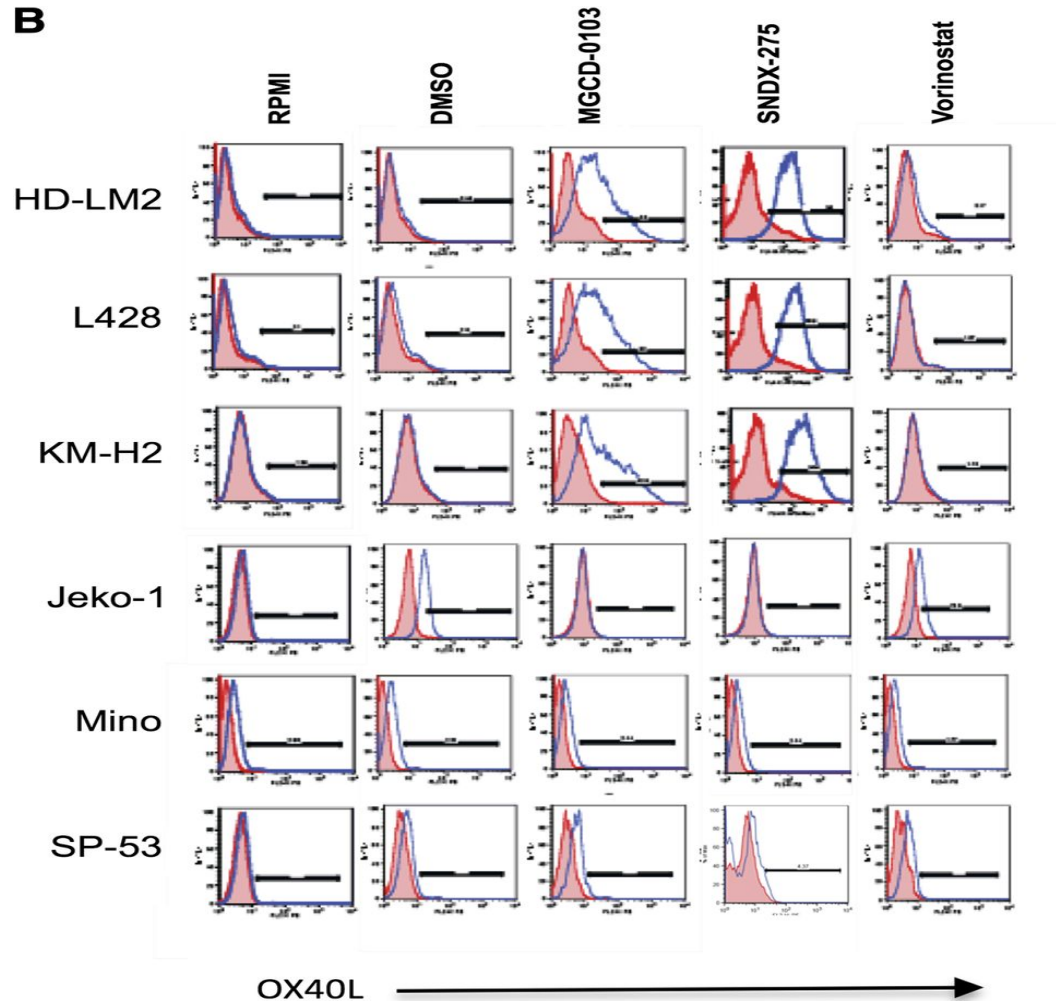


HDAC Inhibitors in HL: Regulation of Cell Survival and Immunity

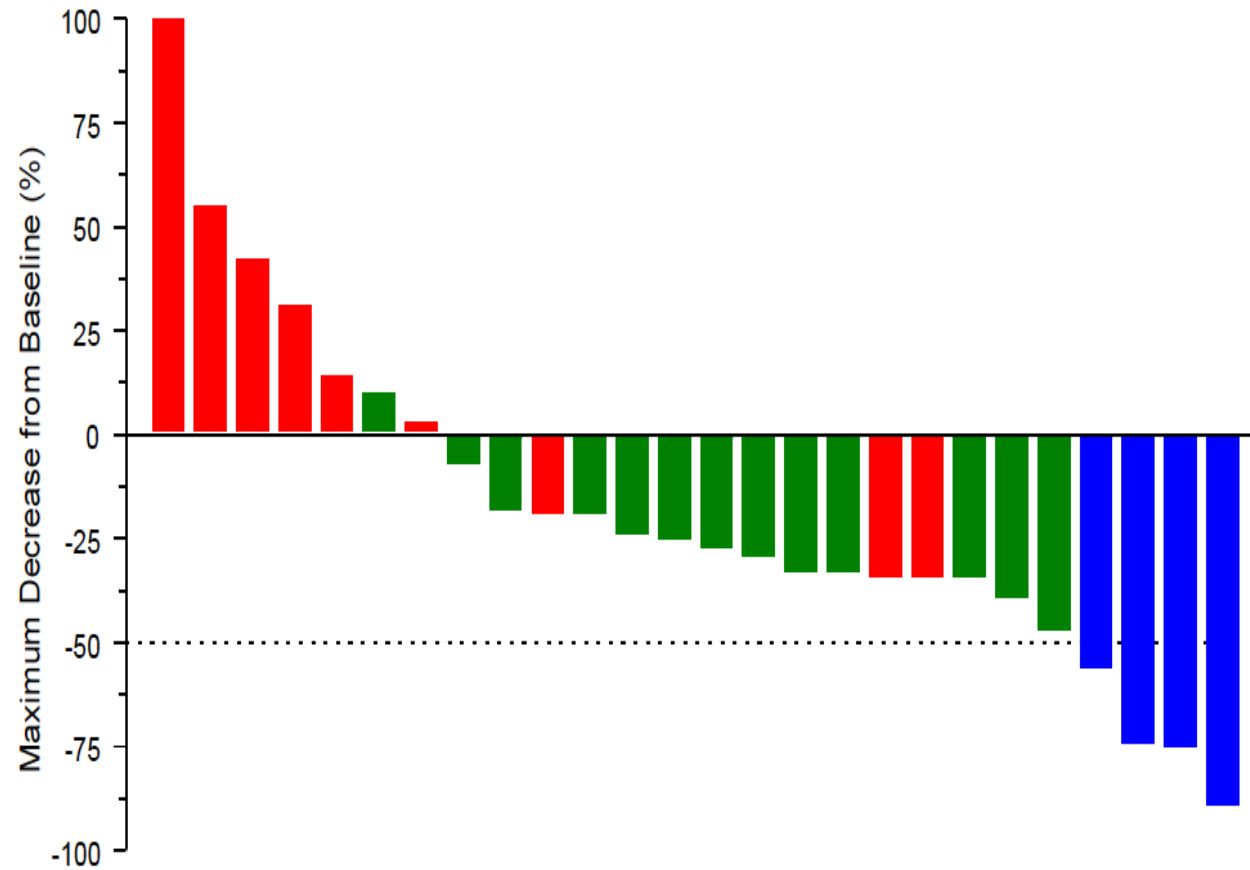


HDACi Upregulate OX40L on HRS Cells

Inhibition of T-reg function

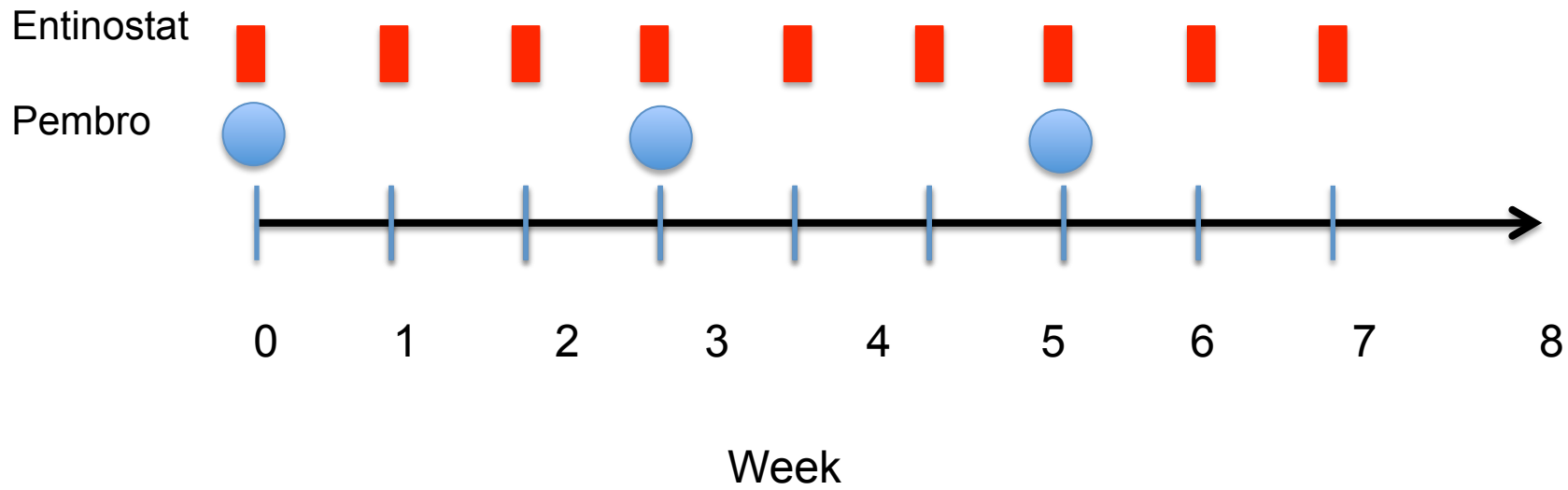


Entinostat in Relapsed HL

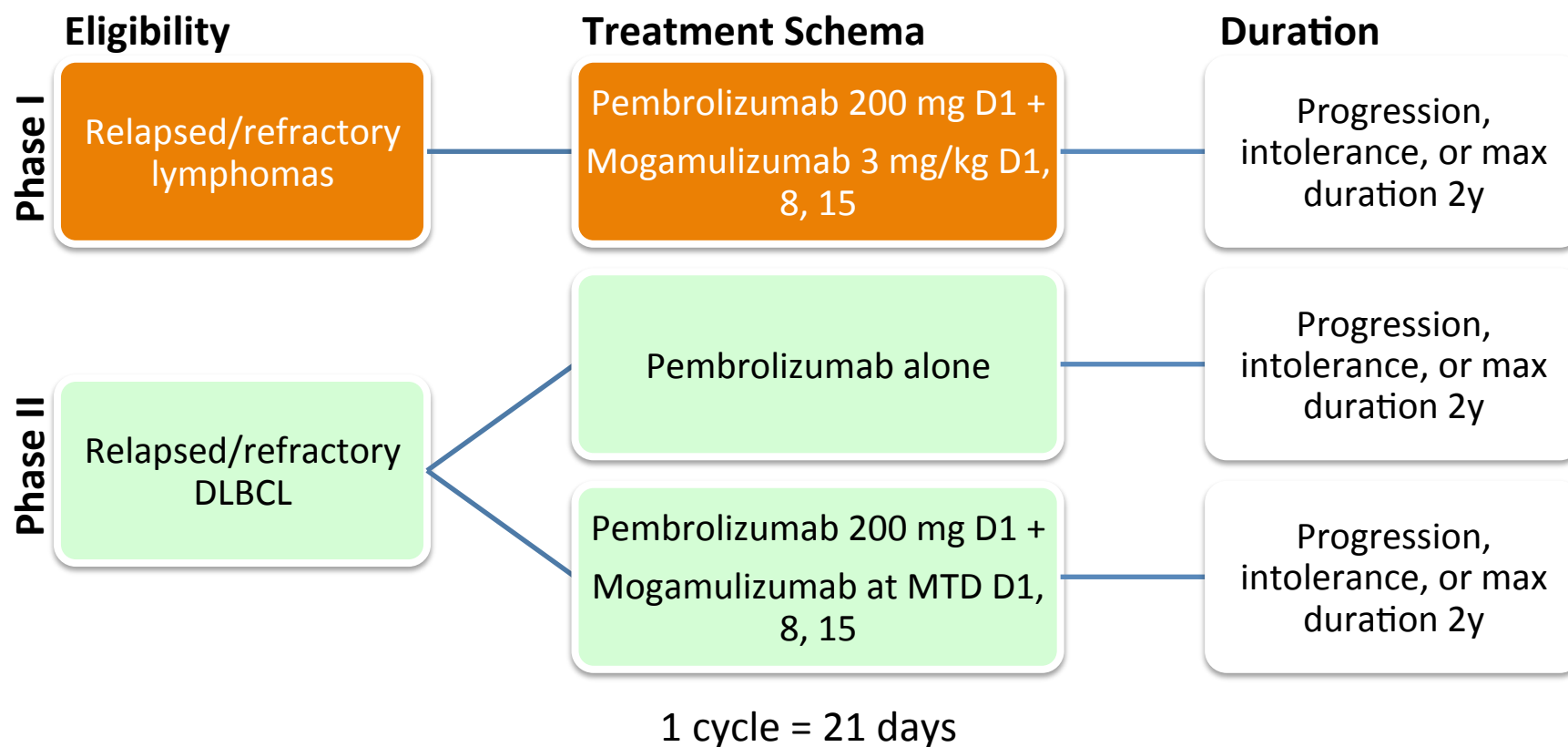


Best Overall Response: ● Partial response
● Stable disease
● Progressive disease

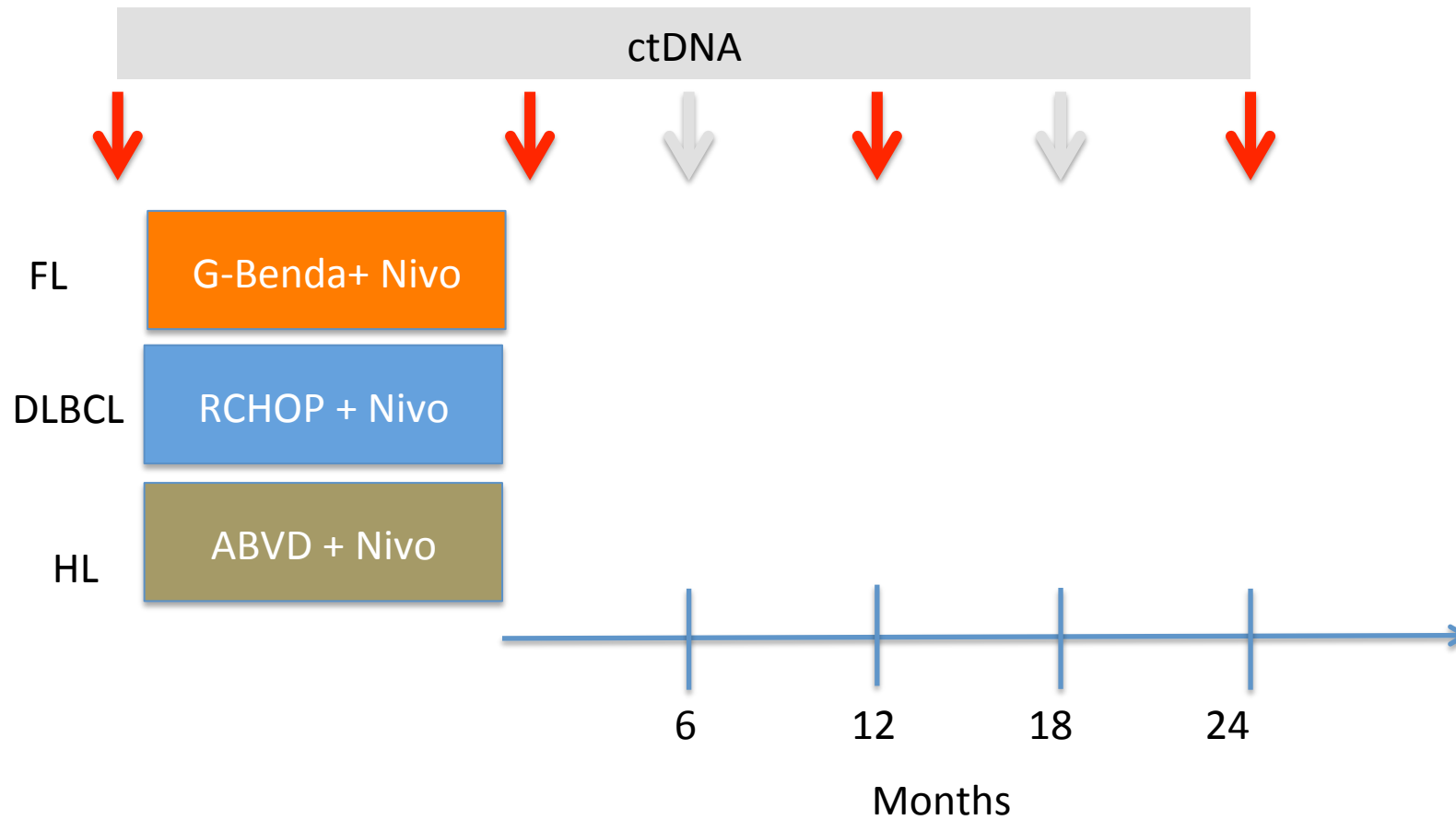
Phase I/II Study of Entinostat (HDACi) + Pembrolizumab (anti-PD1)



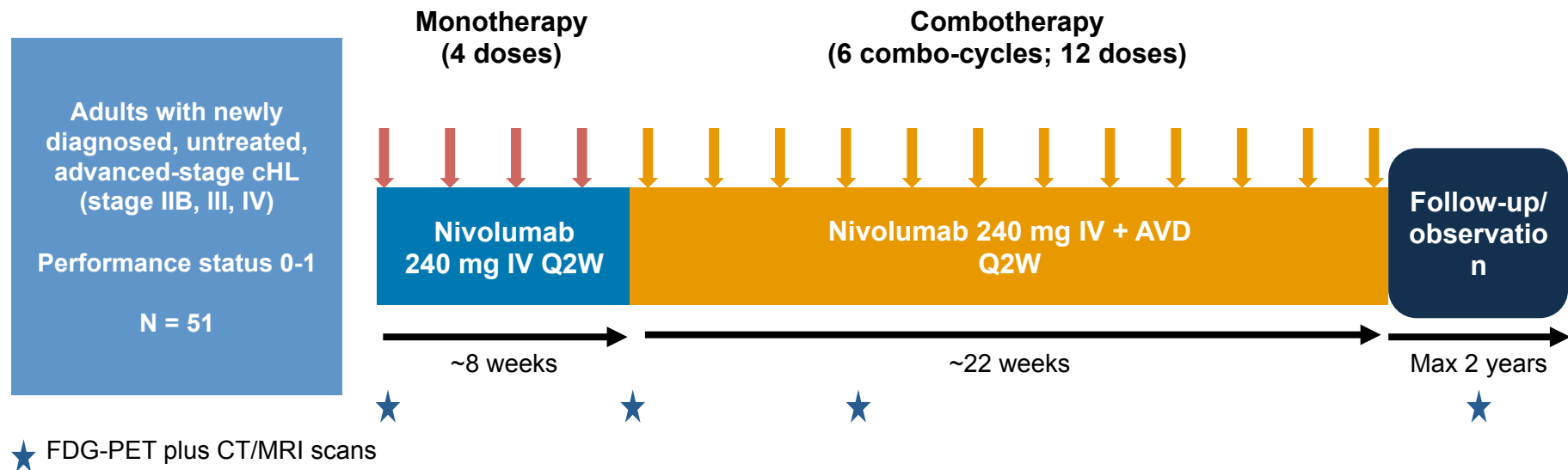
A phase I/II of mogamulizumab (anti CCR4 antibody) and pembrolizumab in relapsed/refractory DLBCL



Evaluating ctDNA in Curable Lymphomas (HL and DLBCL)



Phase 2 CheckMate 205 Study Design: Nivolumab in Newly Diagnosed cHL¹



Primary Endpoint

- Safety and tolerability (Grade 3-5 TRAEs)

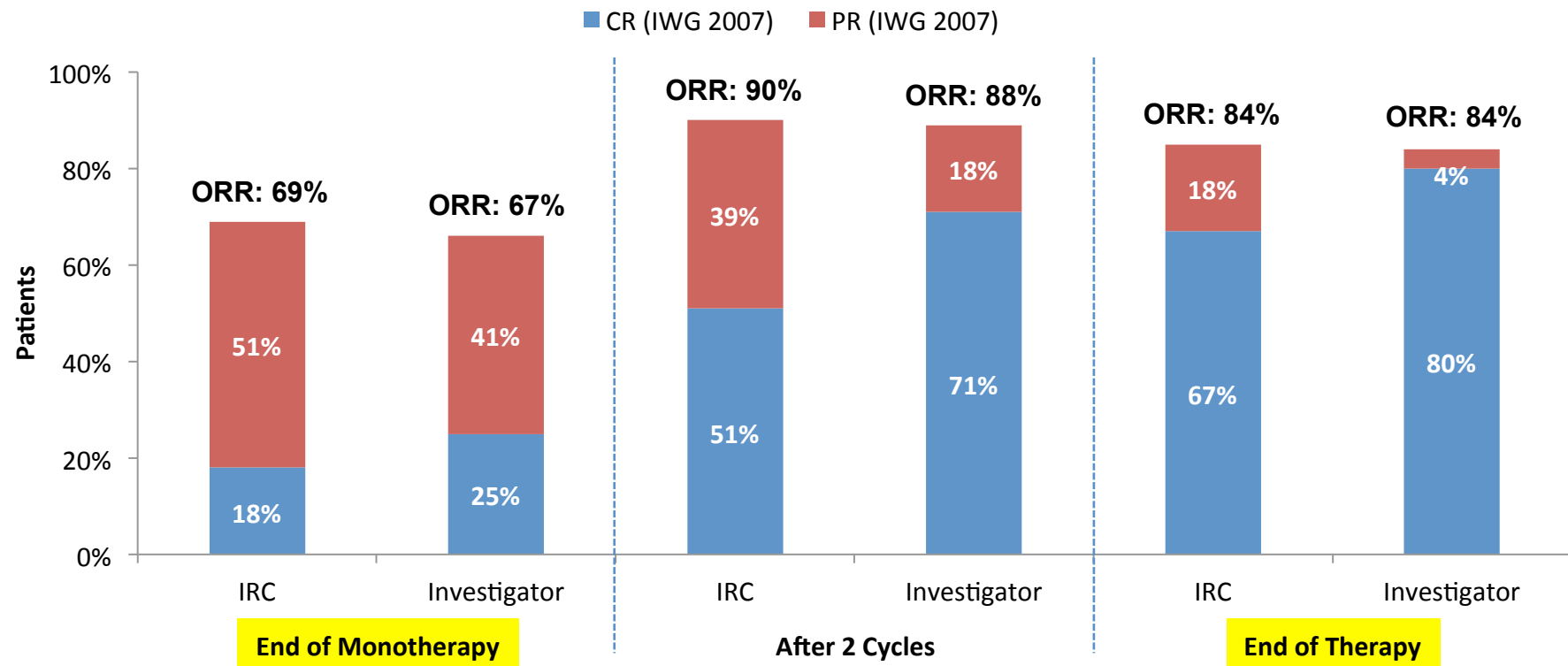
Additional Endpoints

- Discontinuation rate
- CR and ORR by IRC
- CR and ORR by investigator
- mPFS
- OS

Responses were assessed using the IWG 2007 criteria.
At database lock (October 2017), median duration of follow-up was 11.1 months.
Bleomycin excluded due to potential overlapping pulmonary toxicity.

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

Response per IRC and Investigator: ITT Population¹

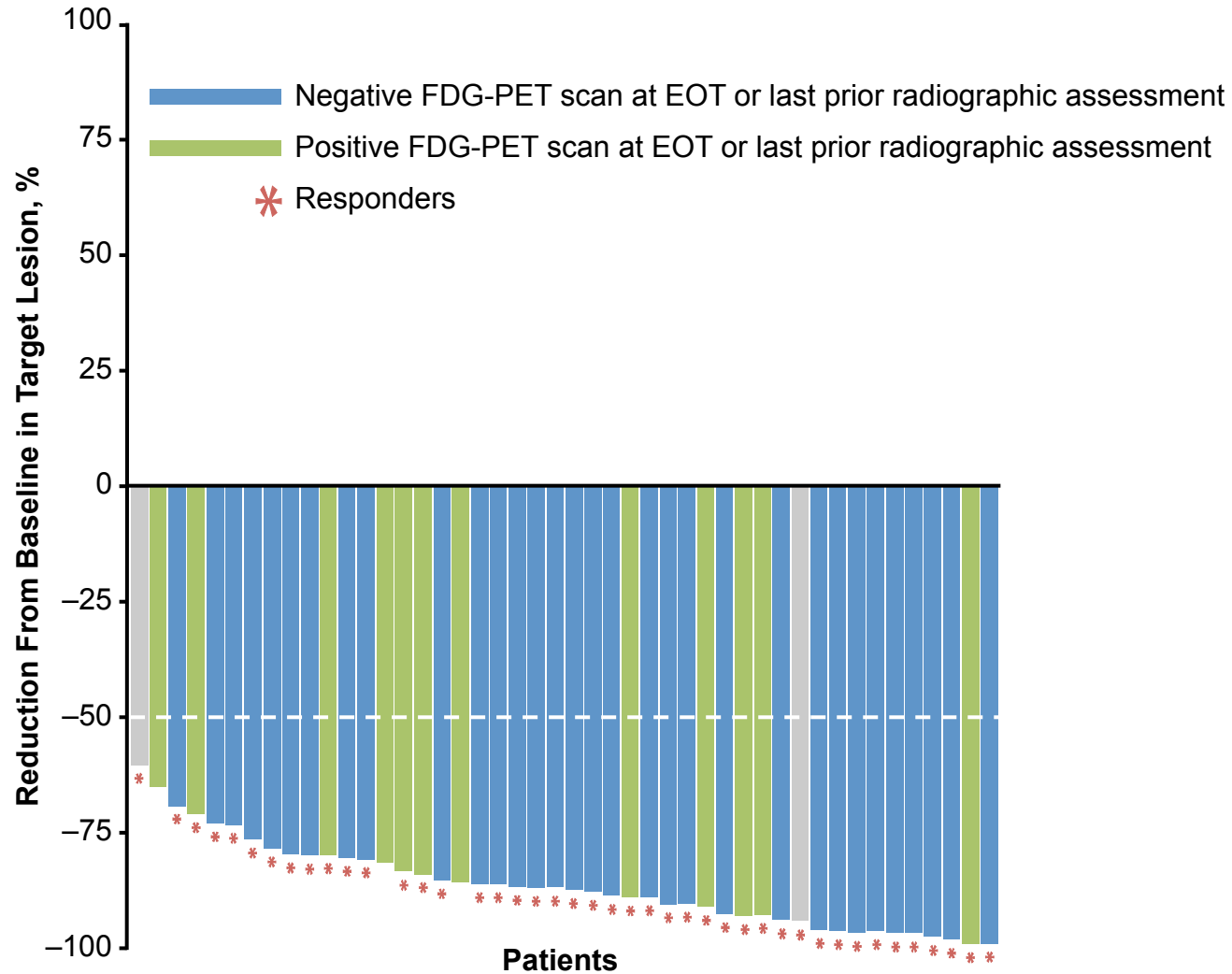


- At end of therapy, ORR per investigator for the ITT population was 84%, with 80% of patients achieving CR
- Five patients were nonevaluable at end of therapy^a

^a No evaluable scan in at least one on-study time point.
Biopsies were not required for patients to be considered to have progressive disease.
Values may not add together due to rounding.

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

Best Change in Target Lesion Per IRC at End of Chemoimmunotherapy¹



46/51 patients had available response data.

1. Ramchandren R et al. *Blood*. 2017;130:Abstract 651.

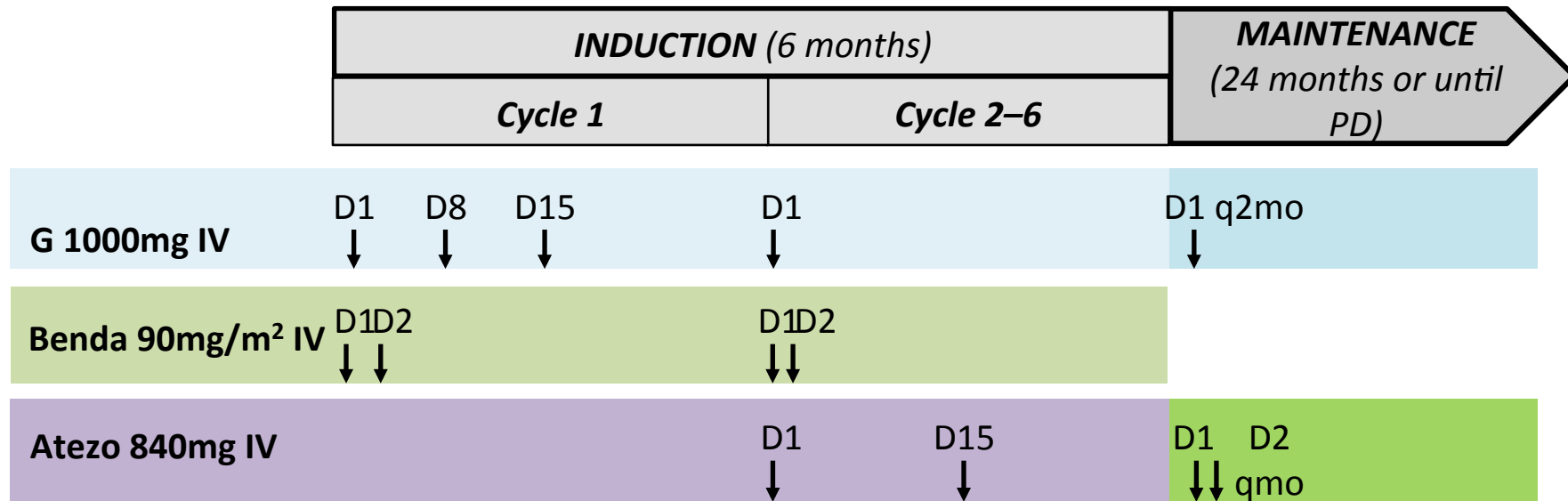
Safety and efficacy of atezolizumab in combination with obinutuzumab and bendamustine in patients with previously untreated follicular lymphoma (FL): primary analysis

Anas Younes,¹ John M Burke,² Catherine Diefenbach,³ Silvia Ferrari,⁴ Cyrus Khan,⁵ Jeff Sharman,⁶ Monica Tani,⁷ Chaitra Ujjani,⁸ Umberto Vitolo,⁹ Sam Yuen,¹⁰ Melissa Kuhn,¹¹ Mikkel Z Oestergaard,¹² Kirsten Mundt,¹² Günter Fingerle-Rowson,¹² Surya Chitra,¹² Gila Sellam,¹² Rodica Morariu-Zamfir,¹² Michael Gilbertson¹³

¹Memorial Sloan Kettering Cancer Center, New York City, NY, USA; ²US Oncology Research, The Woodlands, TX, USA; ³NYU Langone Medical Center, New York City, NY, USA; ⁴Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; ⁵Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA; ⁶Willamette Valley Cancer Institute, Eugene, OR, USA; ⁷Ospedale Santa Maria delle Croci, Ravenna, Italy; ⁸Georgetown University Medical Center, Washington, DC, USA; ⁹Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; ¹⁰Calvary Mater Newcastle Hospital, Newcastle, NSW, Australia; ¹¹Genentech Inc, South San Francisco, CA, USA; ¹²F. Hoffmann-La Roche Ltd, Basel, Switzerland; ¹³Monash Health, Melbourne, VIC, Australia

Atezolizumab + obinutuzumab + bendamustine in previously untreated FL

Study design



End-of-induction (EOI) response rates in 1L FL (N=40)

*Early

<i>n (%)</i>	<i>Modified Lugano 2014¹</i>		<i>Cheson 2007²</i>	
	<i>IRC</i>	<i>INV</i>	<i>IRC</i>	<i>INV</i>
ORR	34 (85)	38 (95)	36 (90)	38 (95)
CR	30 (75)	34 (85)	30 (75)	32 (80)
PR	4 (10)	4 (10)	6 (15)	6 (15)
SD	4 (10)	0	2 (5)	0
PD	0	0	0	0
Not evaluable*	2 (5)	2 (5)	2 (5)	2 (5)

Modified Lugano 2014

- The designation of a PR requires PR criteria by PET and CR or PR by CT scan
- If BM involvement at baseline, CR must be confirmed with a negative BM at EOI

1. Cheson D, et al. J Clin Oncol 2014;32:3059–
2. Cheson D, et al. J Clin Oncol 2007;5:579–8

Conclusions

- Antibodies targeting PD1 demonstrated significant clinical activity in HL, leading to regulatory approval
- Anti PD1/PDL1 antibodies have modest single agent activity in NHL => Combination strategies
- The role of immune checkpoint inhibitors in eradicating MRD/ctDNA in HL and NHL is being investigated