Immunotherapy for hematologic malignancies

Presenter: Craig Speziali MD MSc FRCPC

Date: May 10, 2019

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

- **Faculty / Speaker's name: Craig Speziali MD MSc FRCPC**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** Celgene
  - **Other:** None

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Mitigating Potential Bias

- Consulting fees received from Celgene in relation to its CAR-T products. I will not be discussing these products during my presentation.

CancerCare Manitoba
Community Oncology Program

Objectives

- By the end of this presentation, participants should be able to:
  - Describe the role of immunotherapies in hematologic malignancies
  - Appreciate unique toxicities of immunotherapies used to treat hematologic malignancies

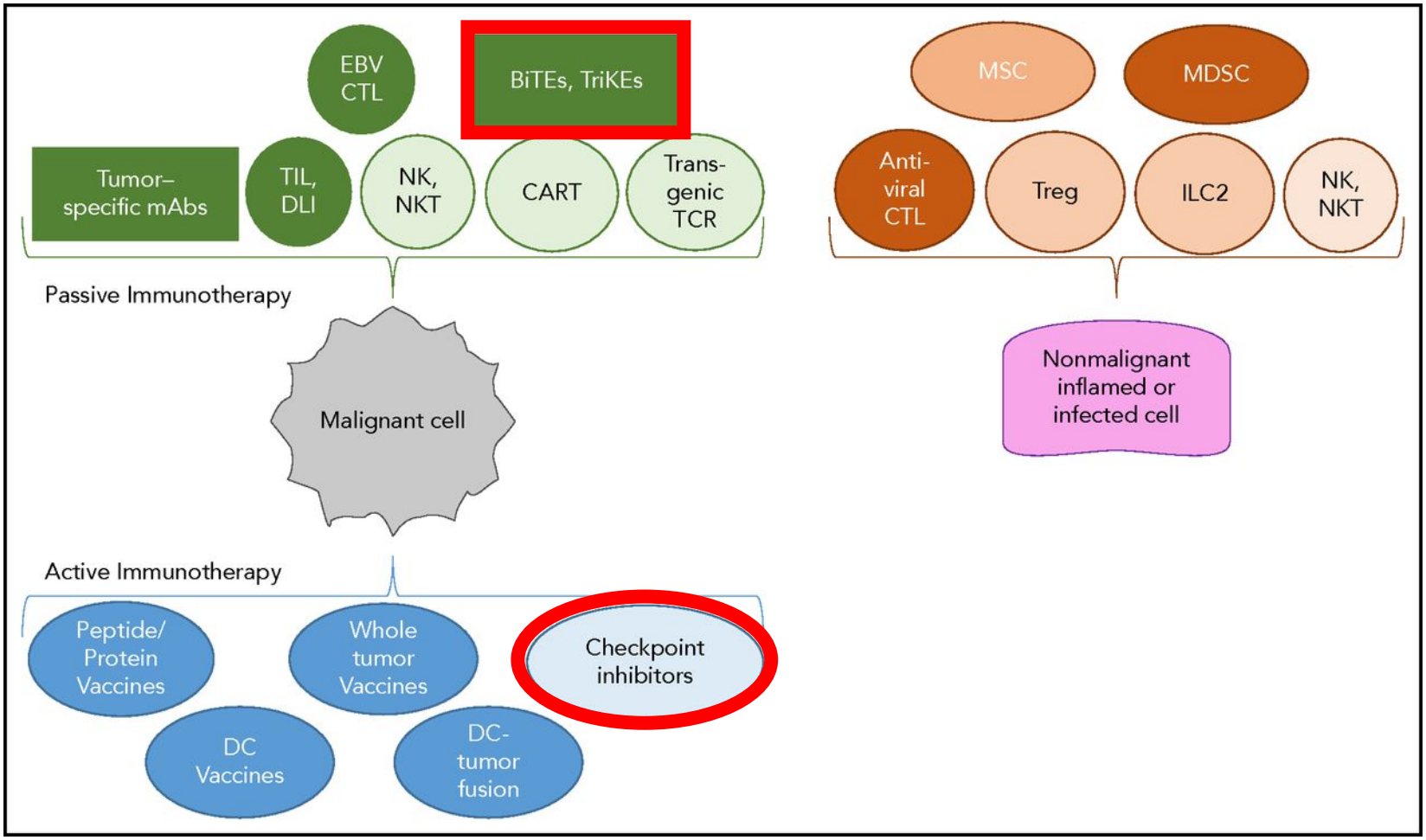
Principles of immunotherapy

- Immunotherapies use the patient's own immune cells to target and kill cancer cells in a specific fashion
- In general, the goal is to target a cytotoxic T-cell to kill defective cells (cancerous, infected, etc.) while limiting damage to normal tissues
- This is in contrast to conventional cytotoxic therapies that act by killing fast-growing cells, including cancer cells
  - But also skin, gut, hair, and hematopoietic stem cells, sperm, eggs, etc.

Immunotherapy in hematologic malignancies

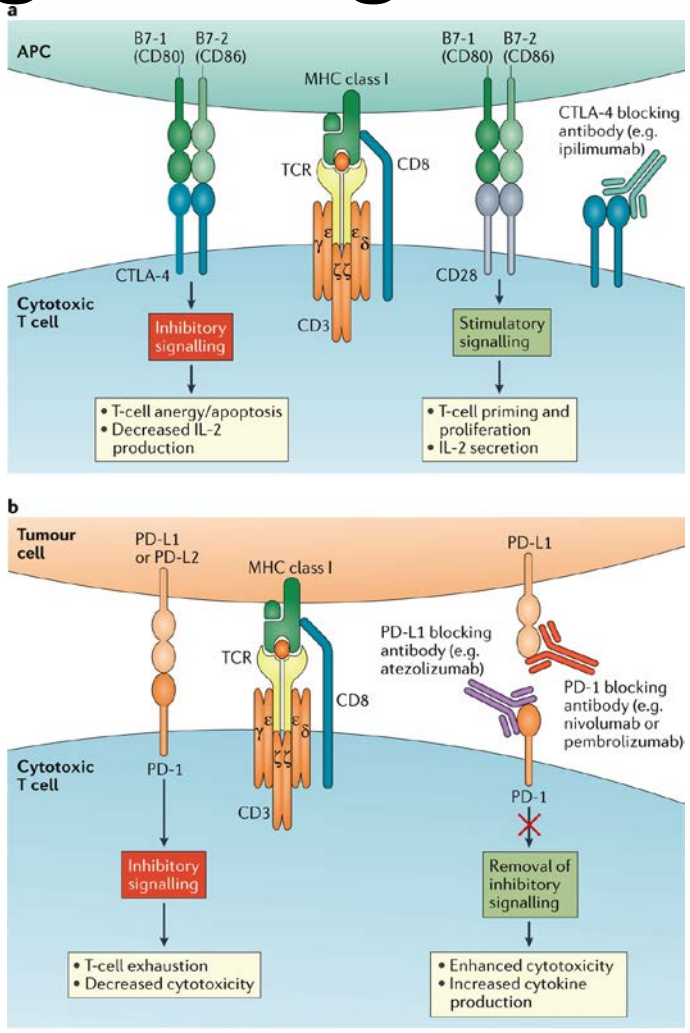
- There is a long tradition of immunotherapy in hematologic malignancies through the use of allogeneic stem cell transplantation
  - Harnesses “graft vs. tumor” effect to cure hematologic malignancies that respond poorly to chemotherapy
- More recently, there is an evolving armamentarium of immune and cellular therapies being used to treat blood cancers and benign blood disorders

Panoply of immunotherapies for malignant and nonmalignant hematological diseases.



Sophie Paczesny et al. Blood 2018;131:2617-2620

Immune checkpoint inhibitors in hematologic malignancies



Nature Reviews | Clinical Oncology

Goodman, A. *et al. Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.168

Checkpoint inhibitors in hematologic malignancies

PD-L1 expression in B-cell malignancies

Diagnosis	Rate of PD-L1 expression	Comment
Classical Hodgkin lymphoma	87-100%	9p24.1 copy number variants are commonly seen
Primary mediastinal B cell lymphoma	36-100%	9p24.1 copy number variants are commonly seen
Diffuse large B cell lymphoma	11-31%	High level PD-L1 expression correlates with inferior OS
Primary CNS lymphoma	10-50%	9p24.1 copy number variants are commonly seen
Follicular lymphoma	Not usually detected on FL cells	PD-L1 expression often seen on T-cells surrounding/infiltrating tumor
EBV+ DLBCL	65-100%	EBV drives PD-L1 expression
EBV+ PTLD	73%	EBV drives PD-L1 expression
Burkitt Lymphoma	0%	
Multiple myeloma	Upregulated on MM cells compared with normal plasma cells	

Adapted from Goodman *et al.* (2016) PD-1–PD-L1 immune-checkpoint blockade in B-cell lymphomas *Nat. Rev. Clin. Oncol. d*oi:10.1038/nrclinonc.2016.168

The Good – Hodgkin lymphoma

- Classical Hodgkin lymphoma is highly curable with combination chemotherapy
- However, patients who are refractory to, or relapse after, standard treatment have a poor outcome
  - Standard approach is salvage chemotherapy + autoHCT
    - Long time survival up to 50% with this approach
  - Few alternatives for those ineligible for transplant or who relapse after transplant
- Reed-Sternberg cells known to overexpress PD-L1 due to alterations of chromosome 9p24.1
  - Provides rationale for trial of PD1/PD-L1 blockade

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

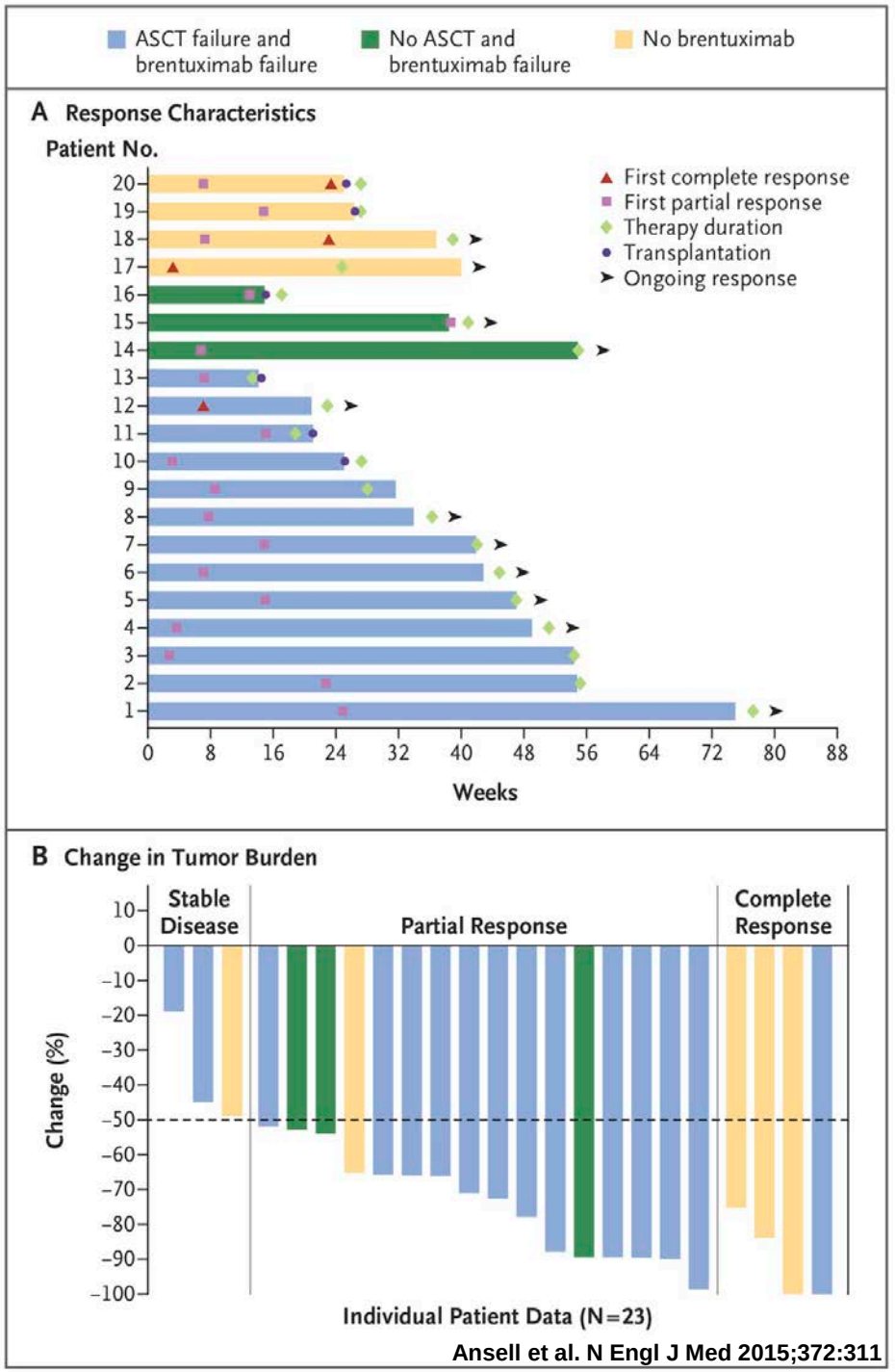
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

- Phase 1 study enrolling 23 patients with heavily pretreated classical Hodgkin lymphoma
- Treatment with nivolumab 3 mg/kg q14 days until disease progression, complete response, or for a maximum of 2 years

Table 1. Characteristics of the 23 Patients at Baseline.

Characteristic	Value
Age — yr	
Median	35
Range	20–54
Male sex — no. (%)	12 (52)
Race — no. (%)*	
White	20 (87)
Black	2 (9)
Other	1 (4)
ECOG performance-status score — no. (%)†	
0	6 (26)
1	17 (74)
Histologic findings — no. (%)	
Nodular sclerosis	22 (96)
Mixed cellularity	1 (4)
No. of previous systemic therapies — no. (%)	
2 or 3	8 (35)
4 or 5	7 (30)
≥6	8 (35)
Previous treatment — no. (%)	
Brentuximab vedotin	18 (78)
Autologous stem-cell transplantation	18 (78)
Radiotherapy	19 (83)
Extranodal involvement — no. (%)‡	4 (17)

- Overall response rate 87%
- CR rate 17%
- 24 week PFS of 84%
- Median OS not reached, albeit with limited follow up



Ansell et al. N Engl J Med 2015;372:311

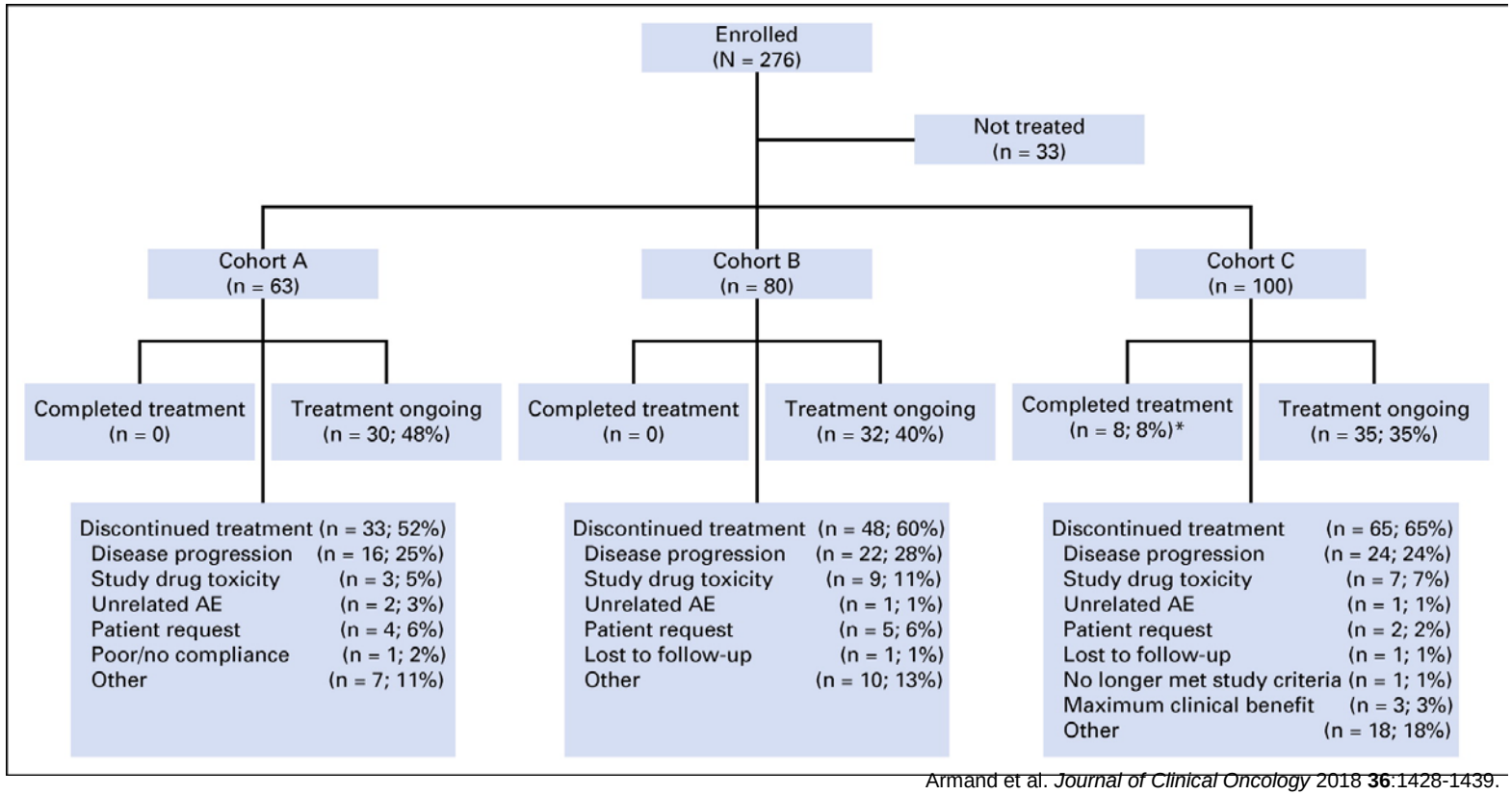
Table 2. Drug-Related Adverse Events in the 23 Patients.*

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

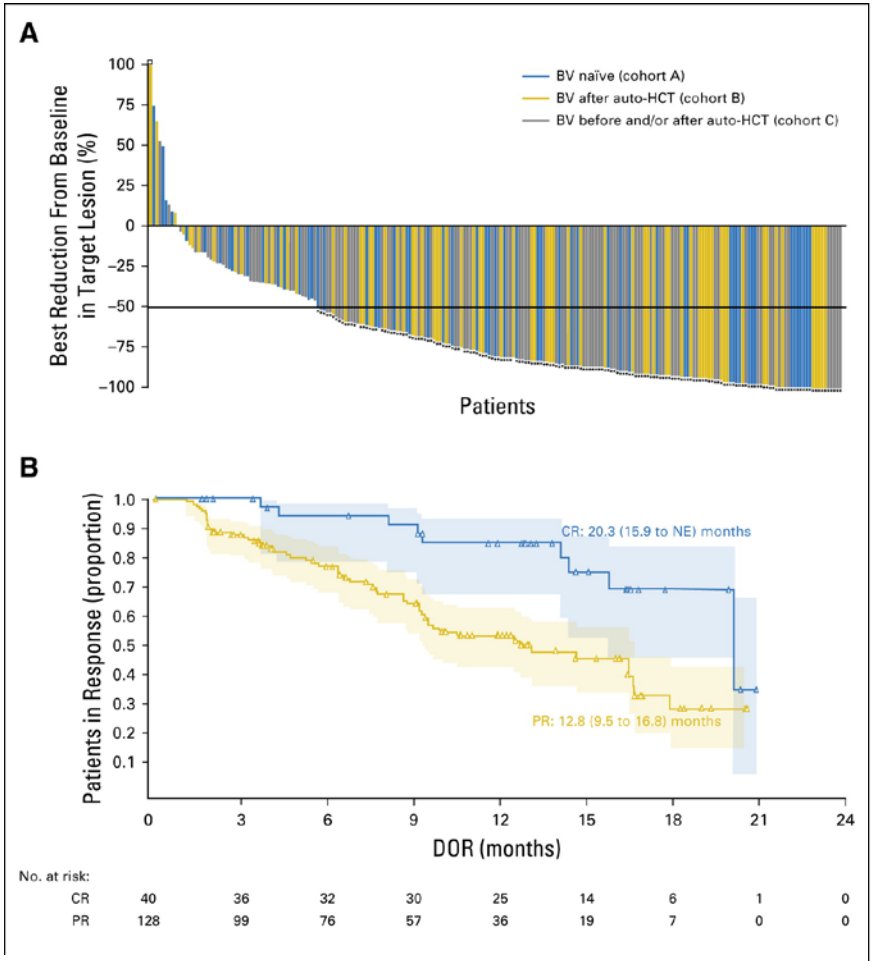
* No grade 4 or grade 5 drug-related adverse events were reported. Decisions about whether the adverse event was related to the study drug were made by the investigators. A more detailed list of adverse events is provided in Table S1 in the Supplementary Appendix.

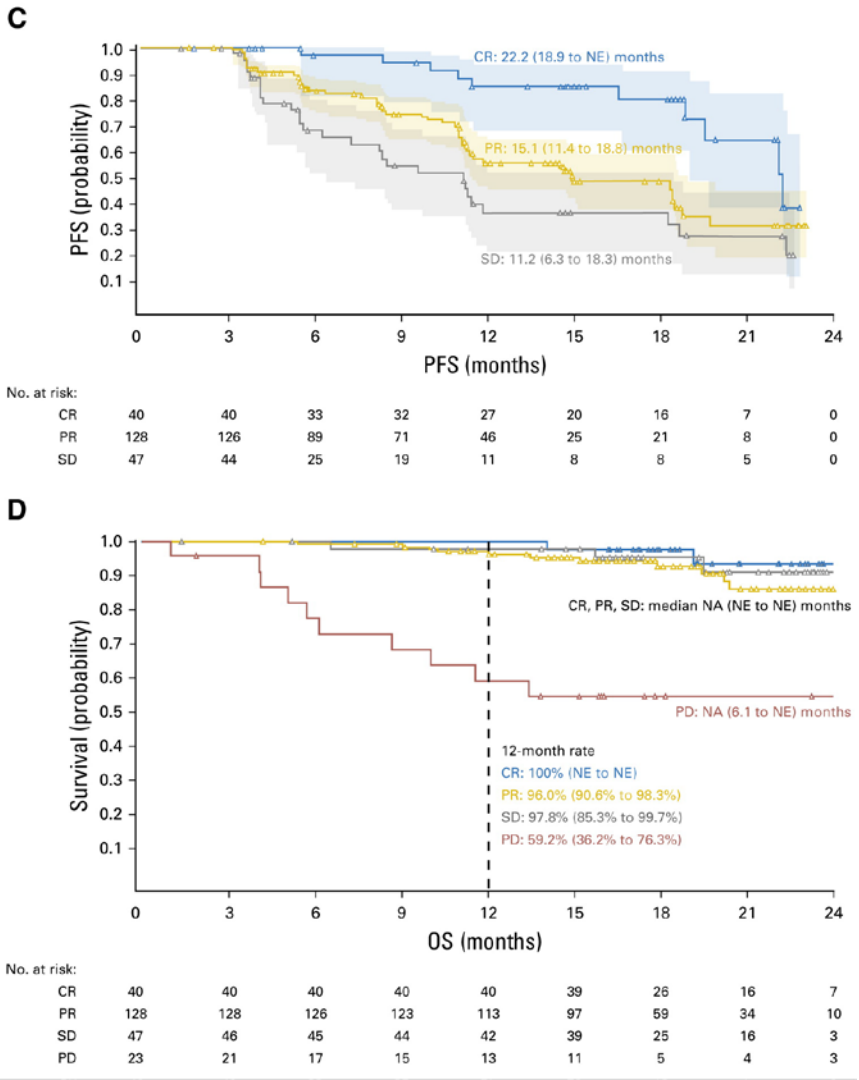
Nivolumab for Hodgkins

- Phase II CheckMate 205 study enrolled 276 patients with relapsed/refractory Hodgkin lymphoma post autoHCT
- Nivolumab 3 mg/kg q14d until disease progression or unacceptable toxicity



Armand et al. *Journal of Clinical Oncology* 2018 **36**:1428-1439.





ORR 69%(95% CI 63 to 75%)

Median PFS 14.7 months (95% CI 11.3 to 18.5 months)

Armand et al. *Journal of Clinical Oncology* 2018 **36**:1428-1439.

CheckMate 205 – Adverse events

Table 3. Adverse Events

Adverse Event	All-Cause Adverse Events (n = 243)		Drug-Related Adverse Events (n = 243)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Diarrhea	86 (35)	2 (< 1)	37 (15)	2 (< 1)
Fatigue	85 (35)	3 (1)	56 (23)	2 (< 1)
Cough	83 (34)	0	15 (6)	0
Pyrexia	72 (30)	1 (< 1)	22 (9)	0
Upper respiratory tract infection	53 (22)	2 (< 1)	7 (3)	0
Nausea	52 (21)	0	25 (10)	0
Vomiting	48 (20)	2 (< 1)	21 (9)	1 (< 1)
Nasopharyngitis	48 (20)	0	2 (< 1)	0
Pruritus	47 (19)	0	25 (10)	0
Rash	46 (19)	3 (1)	29 (12)	2 (< 1)
Headache	46 (19)	1 (< 1)	16 (7)	0
Arthralgia	44 (18)	1 (< 1)	20 (8)	0
Abdominal pain	35 (14)	2 (< 1)	18 (7)	2 (< 1)
Constipation	35 (14)	1 (< 1)	11 (5)	0
Infusion-related reaction	35 (14)	1 (< 1)	34 (14)	1 (< 1)
Dyspnea	34 (14)	3 (1)	10 (4)	1 (< 1)
Anemia	32 (13)	6 (2)	8 (3)	1 (< 1)
Back pain	30 (12)	1 (< 1)	6 (2)	0
Oropharyngeal pain	29 (12)	0	5 (2)	0
Pneumonia	27 (11)	6 (2)	5 (2)	3 (1)
Nasal congestion	27 (11)	0	2 (< 1)	0
Myalgia	26 (11)	0	12 (5)	0
Lipase increased	22 (9)	14 (6)	17 (7)	11 (5)
Neutropenia	20 (8)	9 (4)	15 (6)	8 (3)
ALT increased	19 (8)	8 (3)	18 (7)	8 (3)
AST increased	18 (7)	6 (2)	17 (7)	5 (2)
Blood alkaline phosphatase increased	14 (6)	4 (2)	6 (2)	1 (< 1)
Amylase increased	13 (5)	5 (2)	11 (5)	5 (2)
Lymphocyte count decreased	10 (4)	5 (2)	3 (1)	2 (< 1)
Malignant neoplasm progression	5 (2)*	4 (2)	0	0

NOTE. Data presented as No. (%). Adverse events in this table are events reported in ≥ 10% of patients and grade 3 or 4 events reported in ≥ 2% of patients, occurring between first dose and 30 days after the last dose of nivolumab.

*Includes one grade 5 event. Three patients were reported as having grade 5 adverse events (multiple organ dysfunction and peripheral T-cell lymphoma in one patient, malignant neoplasm progression in one patient, and cardiac arrest in one patient); all were considered unrelated to treatment.

Armand et al. *Journal of Clinical Oncology* 2018 **36**:1428-1439.

VOLUME 35 · NUMBER 19 · JULY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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

- Phase II Keynote-087 enrolled 210 patients with relapsed/refractory Hodgkin lymphoma
- Pembrolizumab 200 mg q3 weeks until CR, progresion, toxicity, or maximum 24 months
- ORR 69%, estimated 9-month OS 97% and PFS 63%
- No new safety signals

Primary mediastinal B cell lymphoma

- A subtype of DLBCL that occurs predominantly in young women
- Most cured with frontline therapy, but poor prognosis for those with relapsed/refractory disease
  - Response to salvage and long term survival are half of those seen for “standard” DLBCL
  - No defined standard of care for relapsed/refractory PMBCL
- Genome expression profiling of PMBCL identifies significant overlap with Hodgkin lymphoma, including changes in 9p24.1
  - Again, this results in the overexpression of PD-1 ligands

Brief Report

blood

CLINICAL TRIALS AND OBSERVATIONS

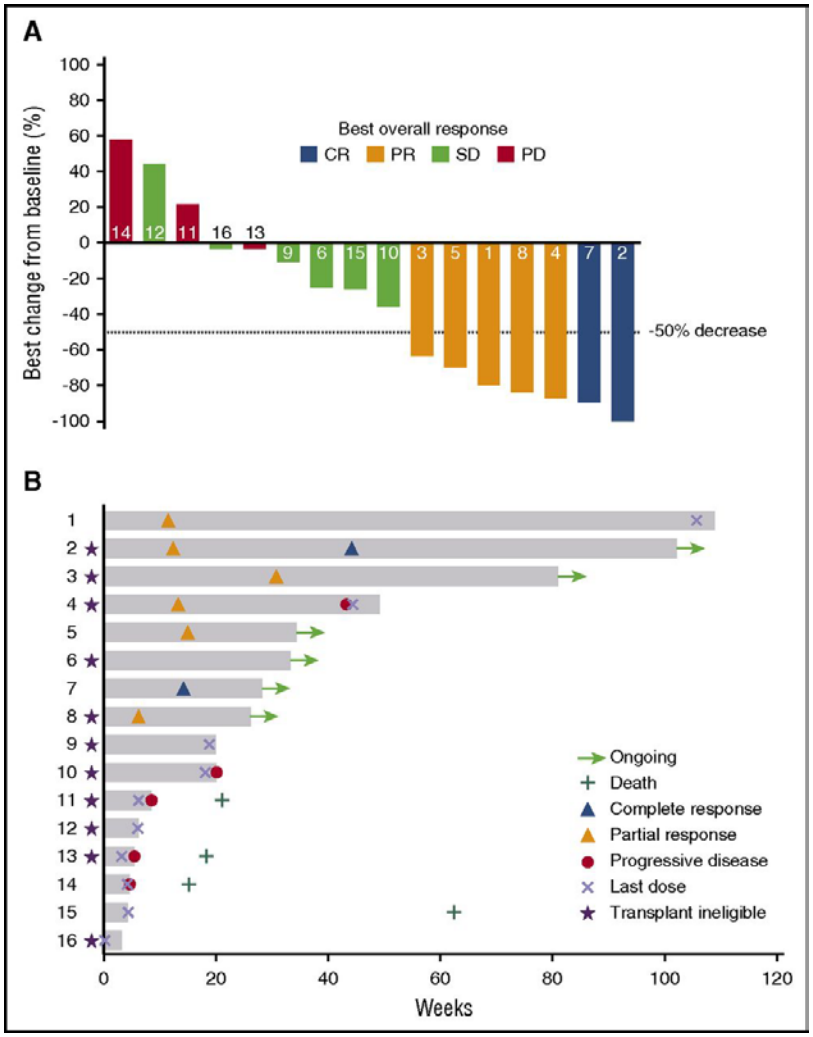
Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma

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

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

- KEYNOTE-013 enrolled 19 women with relapsed/refractory PMBCL who were ineligible for autoHCT or relapsed after autoHCT
  - Median 4 prior lines of treatment
- Pembrolizumab q3 weeks until progression, toxicity, or 24 months

Treatment response in the 16 pembrolizumab-treated patients with rrPMBCL who were evaluable (by imaging) for efficacy at the time of data cutoff.

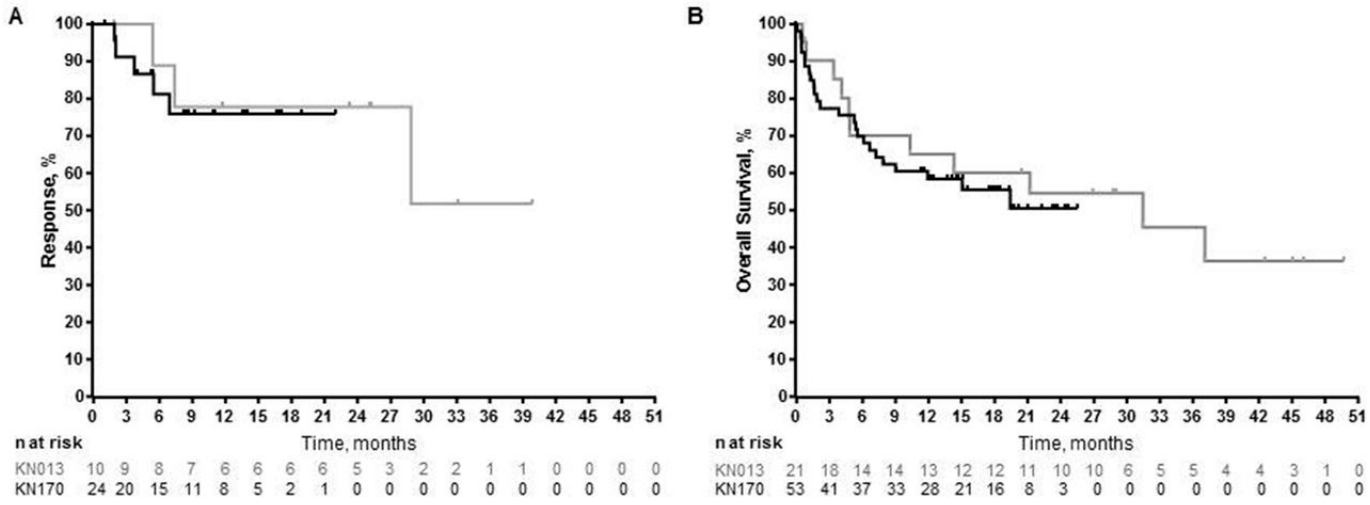


Pier Luigi Zinzani et al. Blood 2017;130:267-270

Keynote-170

- Expanded Phase II trial of pembrolizumab in rrPBMCL, presented in abstract at ASH 2018, n=53
- ORR 45%, including CR in 13%
- Median duration of response not reached after median of 12.5 months follow up.

Figure. Duration of response and overall survival in patients with rrPMBCL treated with pembrolizumab



Armand et al. Blood 2018 vol. 132 no. Suppl. 1 228

Checkpoint inhibitors – The Good

- Convincing evidence of activity in relapsed/refractory classical Hodgkin lymphoma and PMBCL
  - Nivolumab and pembrolizumab granted conditional Health Canada approval for relapsed/refractory Hodgkins lymphoma
    - Available through special access programs while funding negotiated
  - Pemroblizumab granted conditional Health Canada approval from relapsed/refractory PMBCL

Checkpoint inhibitors – The Bad (or at least the ineffective…)

- Clinical responses outside of classical Hodgkin lymphoma and PMBCL have been disappointing
- Reasons for lack of response amongst different lymphoproliferative disease are not well understood
- Still waiting for an effective immunotherapy that targets myeloid malignancies (e.g. AML, MDS)

Ipilimumab – anti-CTLA mAb

Cancer Therapy: Clinical Clin Cancer Res 2009;15(20) October 15, 2009

Phase I Study of Ipilimumab, an Anti–CTLA-4 Monoclonal Antibody, in Patients with Relapsed and Refractory B-Cell Non–Hodgkin Lymphoma

Stephen M. Ansell,[1] Sara A. Hurvitz,[3] Patricia A. Koenig,[1] Betsy R. LaPlant,[1] Brian F. Kabat,[1] Donna Fernando,[3] Thomas M. Habermann,[1] David J. Inwards,[1] Meena Verma,[3] Reiko Yamada,[3] Charles Erlichman,[2] Israel Lowy,[4] and John M. Timmerman[3]

- Objective responses in just 2/18 patients (11%)
- Grade 3 diarrhea in 5/18 patients

Table 1. Patient characteristics

	n = 18
Gender	
Male	12
Female	6
Performance status	
0	11
1	7
Age (y), median (range)	56 (37-79)
Disease histology	
Follicular grade 1 lymphoma	9
Follicular grade 2 lymphoma	5
Diffuse large B-cell lymphoma	3
Mantle cell lymphoma	1
Stage of disease-	
I/II	2
III/IV	16
No. of prior treatments, median (range)	2 (1-4)
Prior therapy	
Idiotype vaccine	6
Rituximab	7
Radioimmunotherapy	4
Chemotherapy	15
Dose level	
3 mg/kg first dose, then 1 mg/kg monthly × 3 doses	12
3 mg/kg monthly × 4 doses	6

Nivolumab in non-Hodgkin lymphoma

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Alexander M. Lesokhin, Stephen M. Ansell, Philippe Armand, Emma C. Scott, Ahmad Halwani, Martin Gutierrez, Michael M. Millenson, Adam D. Cohen, Stephen J. Schuster, Daniel Lebovic, Madhav Dhodapkar, David Avigan, Bjoern Chapuy, Azra H. Ligon, Gordon J. Freeman, Scott J. Rodig, Deepika Cattry, Lili Zhu, Joseph F. Grosso, M. Brigid Bradley Garelik, Margaret A. Shipp, Ivan Borrello, and John Timmerman

- Enrolled 81 patients with relapsed/refractory nHL
- Nivolumab 1-3 mg/kg q2 weeks until CR, progression, toxicity, or 24 months

Table 1. Baseline Characteristics

Characteristic	B-Cell Lymphoma, No. (%)	T-Cell Lymphoma, No. (%)	Multiple Myeloma, No. (%)
No. of patients	31	23	27
Age, years			
Median	65	61	63
Range	23-74	30-81	32-81
Sex			
Female	11 (35)	8 (35)	15 (56)
Male	20 (65)	15 (65)	12 (44)
Race			
White	29 (94)	17 (74)	22 (81)
Black	1 (3)	3 (13)	5 (19)
Asian	1 (3)	1 (4)	0
Other	0	2 (9)	0
ECOG performance status			
0	16 (52)	4 (17)	13 (48)
1	12 (39)	18 (78)	13 (48)
2	0	0	1 (4)
Not reported	3 (10)	1 (4)	0
Extranodal involvement	8 (26)	4 (17)	NA
Prior systemic therapies			
2-3	15 (48)	6 (26)	12 (44)
4-5	7 (23)	9 (39)	8 (30)
≥ 6	5 (16)	5 (22)	6 (22)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

J Clin Oncol 34:2698-2704.

- Grade 3 or higher AEs in 18/81 (22%)
- Pneumonitis, rash and hematologic toxicities most common

Table 2. Drug-Related AEs

AEs	Any Grade, No. (%)	Grade ≥ 3, No. (%)
Summary of AEs by tumor type		
B-cell NHL* (n = 31)	22 (71)	8 (26)
T-cell NHL (n = 23)	17 (74)	5 (22)
Multiple myeloma (n = 27)	14 (52)	5 (19)
Chronic myelogenous leukemia (n = 1)	0	0
Any grade AE in ≥ 5% of patients and all grade ≥ 3 AEs		
Nonhematologic		
Fatigue	14 (17)	0
Pneumonitis	9 (11)	3 (4)
Decreased appetite	7 (9)	0
Pruritus	7 (9)	0
Rash	7 (9)	1 (1)
Diarrhea	6 (7)	0
Pyrexia	6 (7)	0
Hypocalcemia	5 (6)	0
Blood creatine phosphokinase increased	3 (4)	1 (1)
Lipase increased	3 (4)	1 (1)
Mucosal inflammation	3 (4)	1 (1)
Stomatitis	2 (2)	1 (1)
Diplopia	1 (1)	1 (1)
Pneumonia	1 (1)	1 (1)
Pulmonary embolism	1 (1)	1 (1)
Rash pustular	1 (1)	1 (1)
Sepsis	1 (1)	1 (1)
ARDS†	1 (1)	1 (1)
Hematologic		
Anemia	5 (6)	3 (4)
Leukopenia	4 (5)	3 (4)
Lymphopenia	3 (4)	1 (1)
Neutropenia	3 (4)	1 (1)
Eosinophilia	1 (1)	1 (1)
Lymphocyte decrease	1 (1)	1 (1)
Select AEs‡		
Skin (pruritus, rash)	15 (18)	1 (1)
Pulmonary (pneumonitis)	9 (11)	3 (4)
Gastrointestinal (diarrhea, enteritis)	6 (7)	0
Hypersensitivity (hypersensitivity, infusion reactions)	3 (4)	0
Hepatic (ALT increased, AST increased)	2 (2)	0
Renal (blood creatinine increased)	2 (2)	0

Abbreviations: AE, adverse event; ARDS, acute respiratory distress syndrome; NHL, non-Hodgkin lymphoma.

*One grade 5 event was observed (pneumonitis/ARDS).

†Event was grade 5.

‡Select AEs have potential immunologic etiology that require frequent monitoring and intervention.

J Clin Oncol 34:2698-2704.

Nivolumab in non-Hodgkin lymphoma

Table 3. Efficacy Results

Tumor	OR, No. (%)	CR, No. (%)	PR, No. (%)	SD, No. (%)	Median PFS, Weeks (95% CI)
B-cell lymphoma (n = 31)	8 (26)	3 (10)	5 (16)	16 (52)	23 (7 to 44)
DLBCL (n = 11)	4 (36)	2 (18)	2 (18)	3 (27)	7 (6 to 29)
FL (n = 10)	4 (40)	1 (10)	3 (30)	6 (60)	NR (7 to NR)
Other B-cell lymphoma (n = 10)	0	0	0	7 (70)	11 (3 to 39)
T-cell lymphoma (n = 23)	4 (17)	0	4 (17)	10 (43)	10 (7 to 33)
MF (n = 13)	2 (15)	0	2 (15)	9 (69)	10 (7 to 35)
PTCL (n = 5)	2 (40)	0	2 (40)	0	14 (3 to NR)
Other CTCL (n = 3)	0	0	0	0	7 (6 to NR)
Other non-CTCL (n = 2)	0	0	0	1 (50)	10 (2 to 18)
Multiple myeloma (n = 27)	1 (4)	1 (4)*	0	17 (63)	10 (5 to 15)

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; NR, not reported; OR, objective response; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease.
*CR was obtained after radiotherapy. SD was the best response to nivolumab.

- Modest response rates to single agent nivolumab
- Responses generally short lived, particularly for DLBCL
- Other B-cell lymphomas included mantle cell (4), CLL/SLL (2), PMBCL (2), marginal zone (1), and B-cell nHL NOS (1)
- The one responding myeloma patient received concurrent radiation

Pembrolizumab in CLL

Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL

Wei Ding,[1] Betsy R. LaPlant,[2] Timothy G. Call,[1] Sameer A. Parikh,[1] Jose F. Leis,[3] Rong He,[4] Tait D. Shanafelt,[1] Sutapa Sinha,[1] Jennifer Le-Rademacher,[2] Andrew L. Feldman,[4] Thomas M. Habermann,[1] Thomas E. Witzig,[1] Gregory A. Wiseman,[5] Yi Lin,[1] Erik Asmus,[2] Grzegorz S. Nowakowski,[1] Michael J. Conte,[1] Deborah A. Bowen,[1] Casey N. Aitken,[1] Daniel L. Van Dyke,[6] Patricia T. Greipp,[6] Xin Liu,[7] Xiaosheng Wu,[1] Henan Zhang,[1] Charla R. Secreto,[1] Shulan Tian,[2] Esteban Braggio,[3] Linda E. Wellik,[1] Ivana Micallef,[1] David S. Viswanatha,[4] Huihuang Yan,[2] Asher A. Chanan-Khan,[8] Neil E. Kay,[1] Haidong Dong,[7] and Stephen M. Ansell[1]

BLOOD, 29 JUNE 2017 • VOLUME 129, NUMBER 26

- Objective responses in 0/16 patients with relapsed/refractory CLL
- Interestingly, 4/9 patients with Richter transformation had an objective response
  - All had ibrutinib as most recent therapy prior to pembrolizumab
  - Ongoing phase II trial of pembrolizumab + ibrutinib in r/r CLL with or without Richter transformation

What about combinations of checkpoint inhibitors?

Table. Efficacy in patients treated with nivo+ipi (investigator-assessed)

	Hodgkin lymphoma (n=31)	B-cell NHL (n=15)	T-cell NHL (n=11)	Multiple myeloma (n=7)
Histology	NSHL: 22 MCHL: 4 LPHL: 1 Other HL: 4	FL: 5 DLBCL: 10	CTCL: 7 PTCL: 4	–
ORR, n (%)	23 (74)	3 (20)	1 (9)	0
CR, n (%)	6 (19)	0	0	0
PR, n (%)	17 (55)	3 (20)	1 (9)	0
SD, n (%)	3 (10)	1 (7)	4 (36)	1 (14)
Median DOR, months (range)	NR (0, 13.4)	NR (11.0, 12.7)	NR (3.9, 3.9)	–
Median time to response, months (range)	2.7 (1.1, 6.5)	2.8 (1.3, 2.8)	1.4 (1.4, 1.4)	–
Median PFS, months (95% CI)	NR (7.2, NR)	1.5 (0.5, 4.5)	2.0 (1.2, 12.5)	2.2 (0.6, NR)
Median OS, months (95% CI)	NR (NR, NR)	2.9 (1.2, 7.1)	13.2 (2.0, NR)	7.6 (0.6, NR)

CR, complete response; LPHL, lymphocyte-predominant HL; MCHL, mixed cellularity HL; NR, not reached; NSHL, nodular sclerosing HL; OS, overall survival; PR, partial response; SD, stable disease.

Stephen Ansell et al. Blood 2016;128:183

- No improvement in responses compared with nivolumab alone
- 29% had a grade 3 or higher adverse event
- No deaths due to adverse events

Checkpoint inhibitors in myeloid malignancies

Table 1 Selected completed trials of immune checkpoint inhibitor–based monotherapies and combination therapies

Author/year of reference	Phase	Intervention	Patient population	*N*	Outcomes
Monotherapy					
Berger et al. Clin Cancer Res 2008 [25]	I	CT-011	Advanced hematological malignancies	17 AML:8	1/8 patients with a minimal response (reduction of peripheral blasts from 50%v to 5%)
Davids et al. NEJM 2016 [22••]	I	Ipilimumab	Hematologic malignancies with relapse after alloSCT	28 AML:12	No response with 3 mg/kg but responses observed with 10 mg/kg CR in 4 pts. with extramedullary AML and 1 pt. with AML secondary to MDS
Combination with chemotherapy					
Ravandi et al. ASH 2017 [26]	II	Nivolumab + cytarabine/-idarubicin	AML/high-risk MDS upfront therapy	32 AML:30	CR/CRi 72% CR 59% CRi 13% 28% with subsequent alloSCT Median RFS and OS not reached (at median follow-up of 8.3 months)
Zeidner et al. ASH 2017 [27]	II	High-dose cytarabine followed by pembrolizumab (including maintenance pembrolizumab in case of response)	RR-AML	13	CR/CRi 40% CR 39% 15% with subsequent alloSCT
Combination with hypomethylating agents					
Daver et al. Cancer Discovery 2018 [28••]	II	Nivolumab + azacitidine	Relapsed AML	70	ORR 33% CR/CRi 22% HI 10% Median OS 6.3 months

CR complete response, *CRi* complete response with incomplete count recovery, *RFS* relapse-free survival, *OS* overall survival, *HI* hematologic improvement, *ORR* overall response rate = CR + CRi + PR + HI

The Ugly - A cautionary tale…

- Adult T-cell leukemia/lymphoma is a rare and aggressive T-cell cancer cause by the HTLV-I virus

- Poor response to traditional treatments
  - Found to overexpress PD-L1
  - Lead to an investigator initiated phase II trial of nivolumab in ATLL

A cautionary tale

- The first 3 patients enrolled on the trial of nivolumab for ATLL all experienced rapid disease progression after the first dose

Table 1. Laboratory Data.*

Variable	Baseline Value	Peak Value after Nivolumab Treatment†		
	All Patients	Patient 1, Chronic ATLL‡	Patient 2, Smoldering ATLL§	Patient 3, Acute ATLL¶
PD-L1 expression on ATLL cells (%)‖		<1	<1	5
Creatinine (mg/dl)	<1.1	1.4	2.5	1.7
Calcium (mg/dl)	<10.0	12.2	13.3	11.8
Lactate dehydrogenase (U/liter)	<320	1335	351	3520
White-cell count (per mm^3)	<12.0	40.6	17.0	41.2
Factor increase in absolute lymphocyte count		11.7	1.5	10.6
Atypical lymphocytes (%)	≤5	24	NA	30
Bilirubin (mg/dl)	<1.0	2.5	0.6	21.7
Factor increase in HTLV-1 DNA**		63.0	NA	2.4

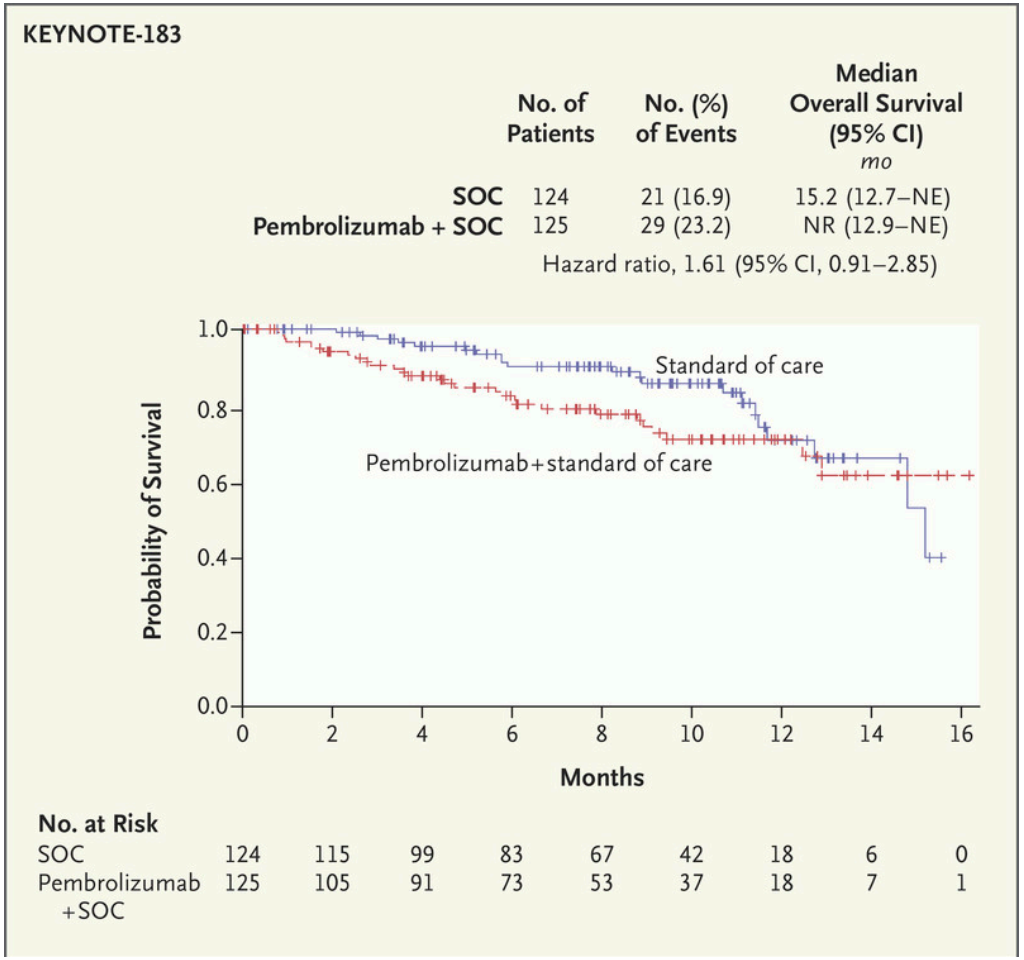
L Ratner et al. N Engl J Med 2018;378:1947-1948.

Myeloma, another cautionary tale

- Plasma cells in multiple myeloma have been demonstrated to overexpress PD-L1
- Early studies of single agent checkpoint inhibitors for the treatment of multiple myeloma demonstrated minimal activity (ORR < 5%)
- Despite lack of single agent activity, numerous trials launched to investigate checkpoint inhibitors in combination with active agents commonly used to treat myeloma

KEYNOTE-183

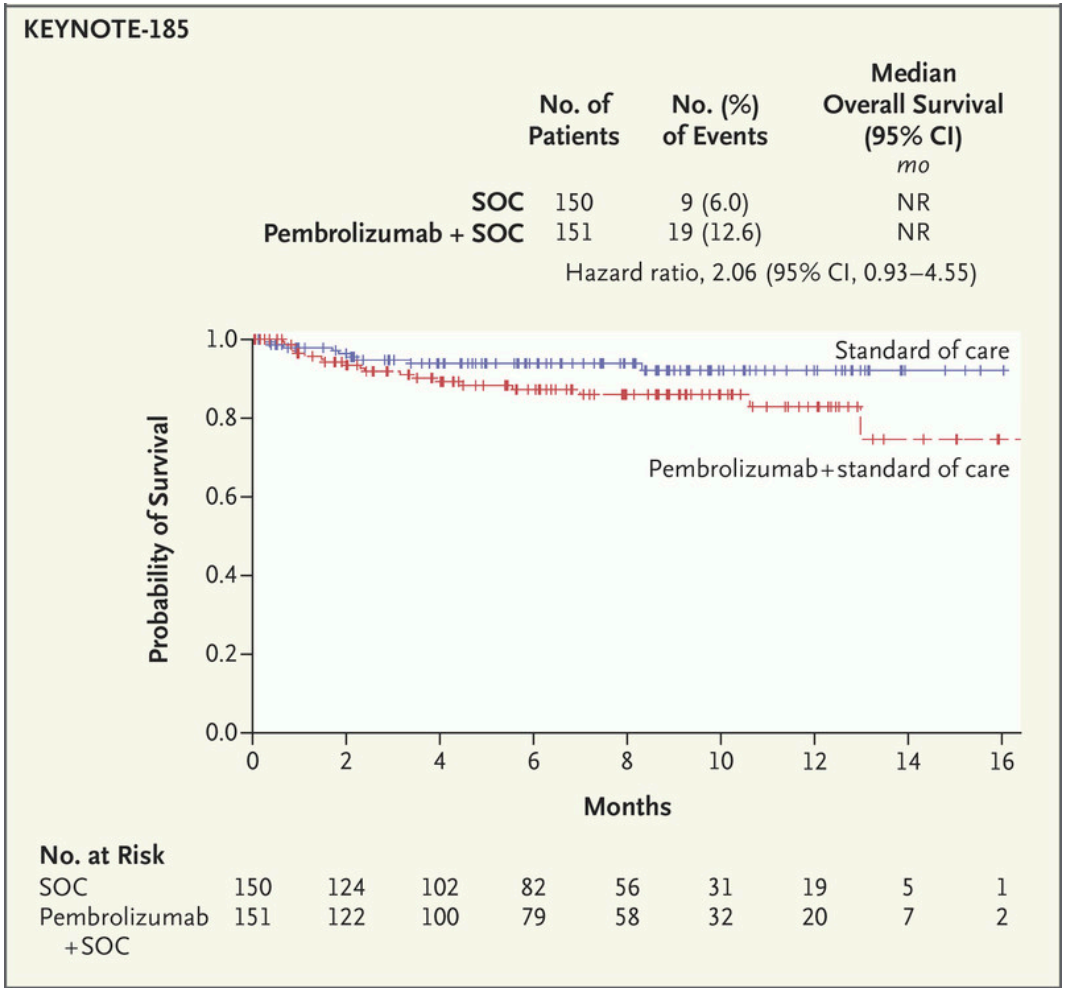
- Phase III RCT pomalidomide and dexamethasone +/- pembrolizumab in relapsed multiple myeloma
- No difference in objective response rate
- More serious adverse events in the pembrolizumab arm
- Trend toward increased risk of death in the pembrolizumab arm



NJ Gormley, R Pazdur. N Engl J Med 2018;379:1791-1795.

KEYNOTE-185

- Phase III RCT lenalidomide and dexamethasone +/- pembrolizumab in newly diagnosed multiple myeloma not eligible for stem cell transplant
- No difference in objective response rate
- More serious adverse events in the pembrolizumab arm
- Trend toward increased risk of death in the pembrolizumab arm



NJ Gormley, R Pazdur. N Engl J Med 2018;379:1791-1795.

Checkpoint inhibitors in multiple myeloma

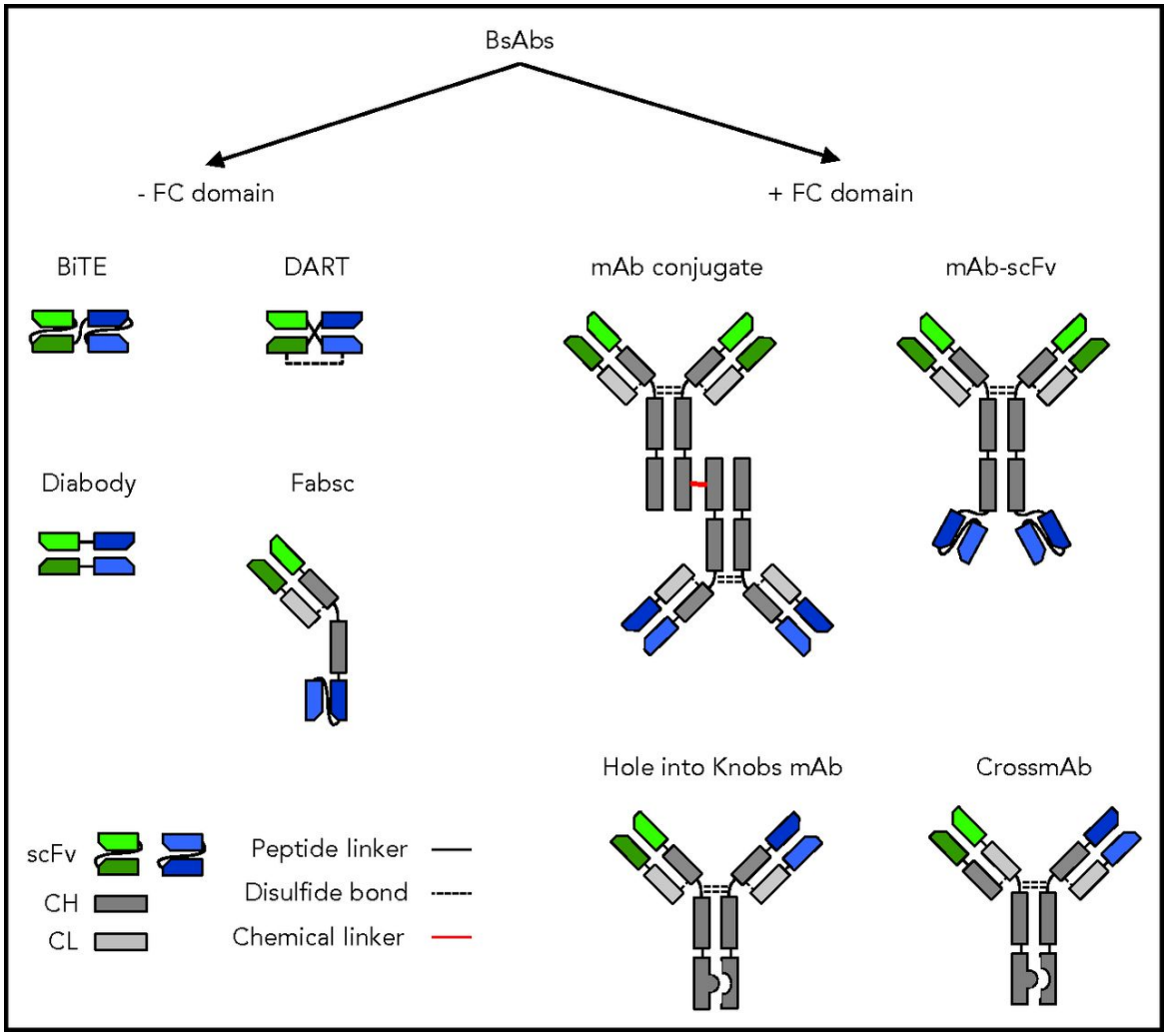
- No improvement in response rate when combined with existing agents
- Increased risk of serious adverse events
- Increased risk of death
  - No unifying cause of death or unique toxicity identified
- Results led to partial or full holds on more than 30 trials of checkpoint inhibitors in multiple myeloma in July 2017

Bispecific antibodies

- The concept of an engineered bispecific antibody that can direct immune responses was first proposed more than 50 years ago

- These constructs allow for MHC-independent targeting of cytotoxic T cells toward antigens of interest

Selected BsAb formats.

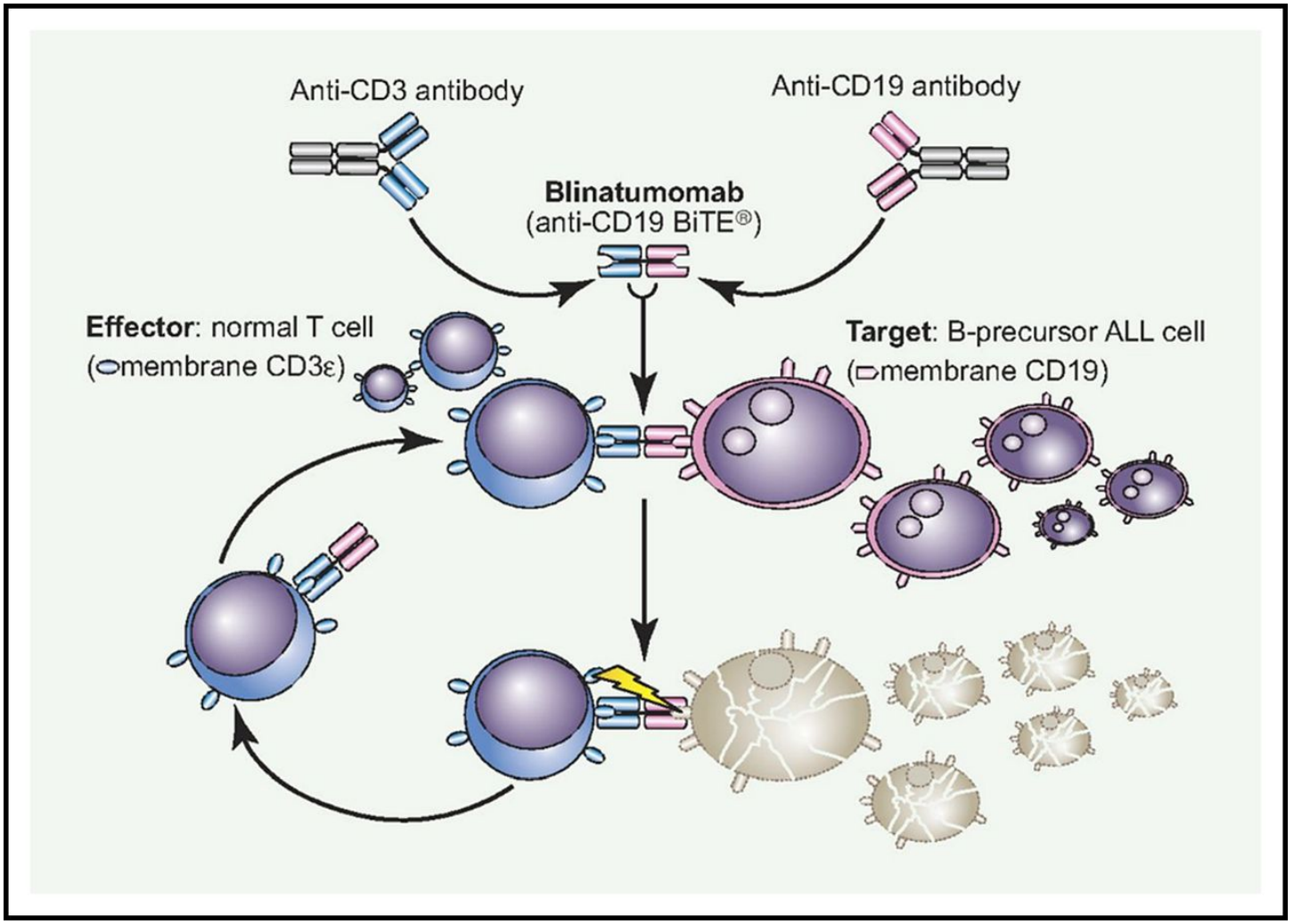


Mireya Paulina Velasquez et al. Blood 2018;131:30-38

Blinatumomab

- First in class bispecific T cell engaget (BiTE) approved for treatment of relapsed/refractory B-cell acute lymphoblastic leukemia

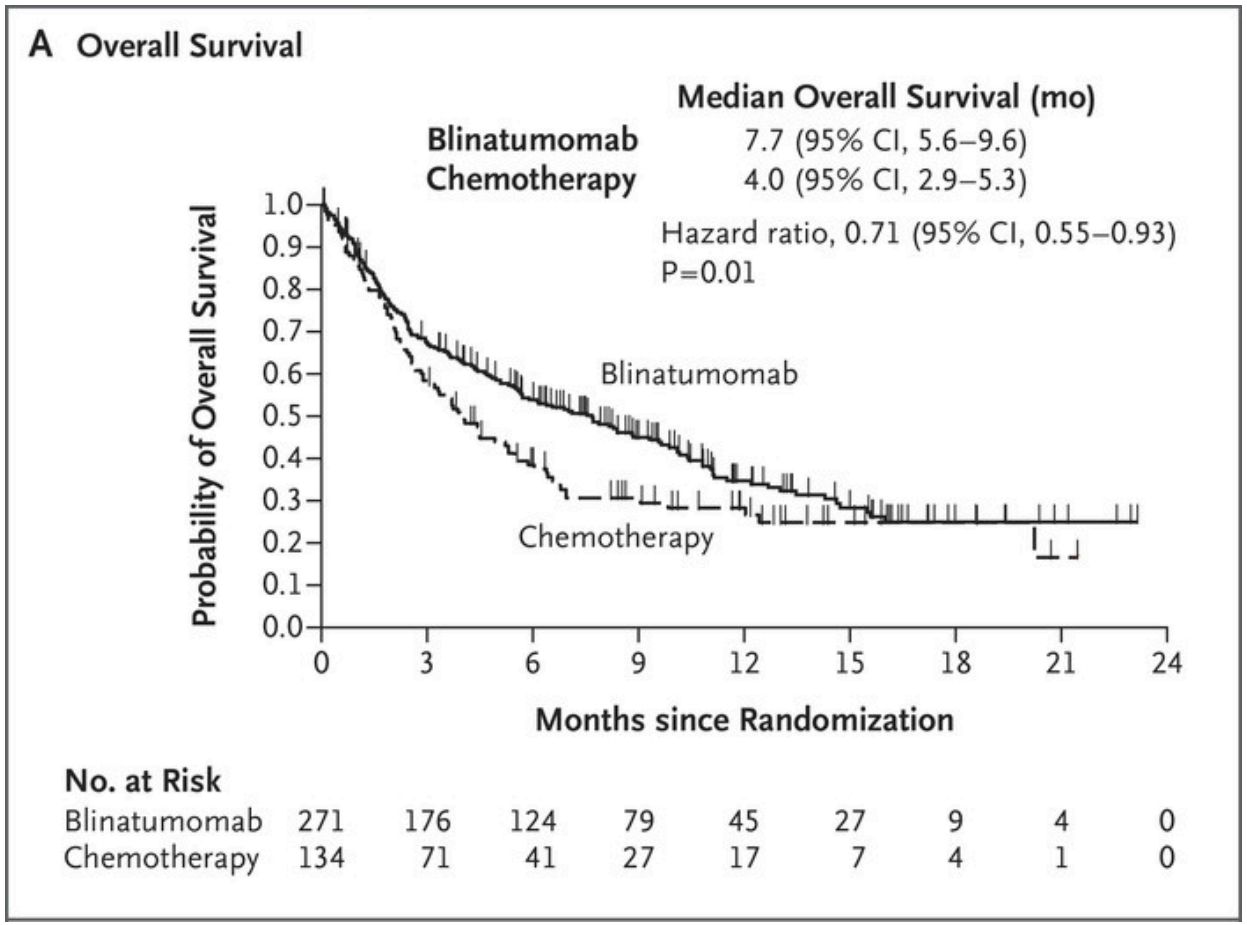
- Modified “antibody” with two Fab regions recognizing CD19 on leukemic blasts and CD3 on T cells



Patrick Brown Blood 2018;131:1497-1498

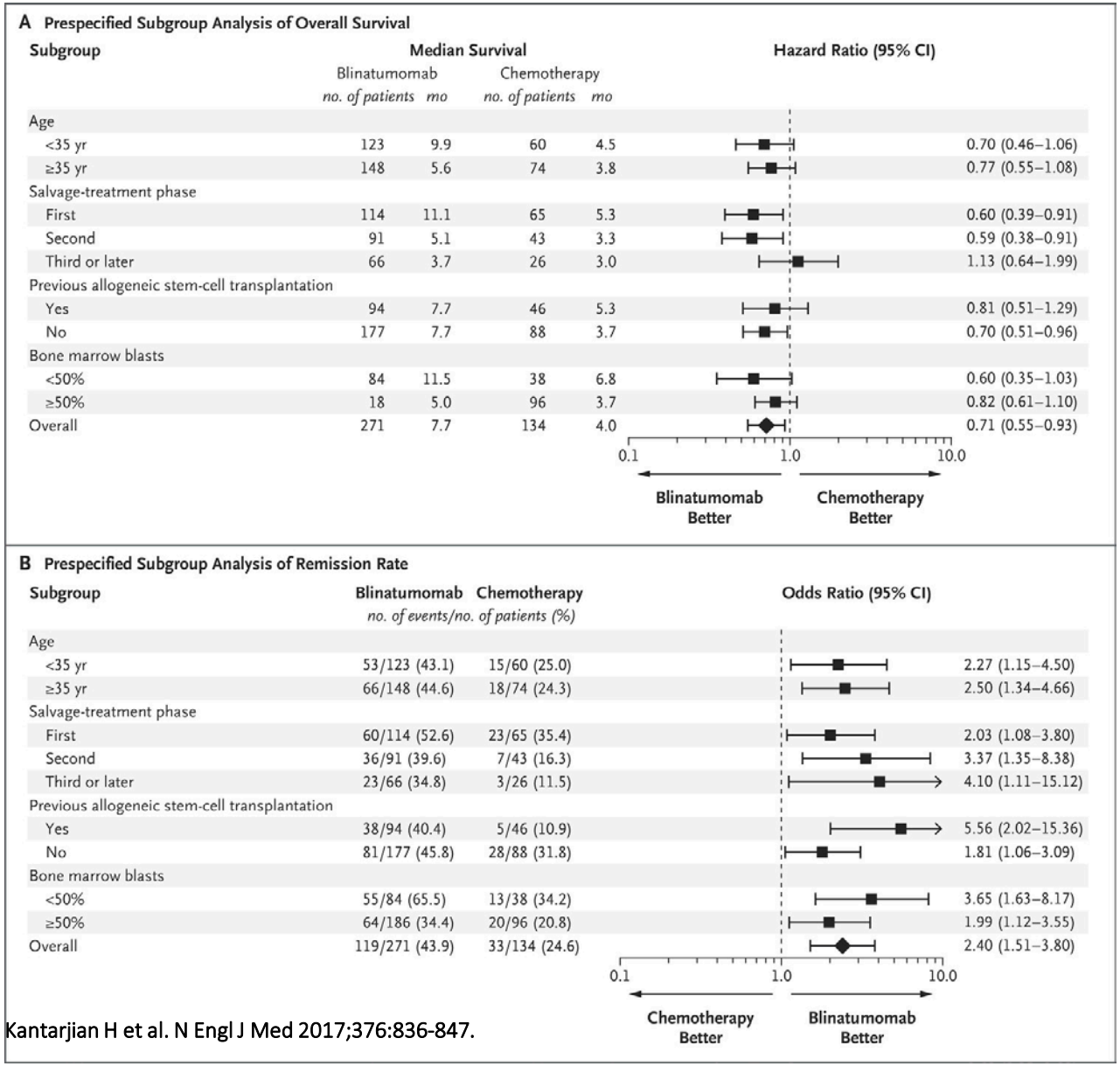
TOWER Study - Results

- Complete remission rate of 44% with blinatumomab vs. 25% for standard of care (p<0.001)



Kantarjian H et al. N Engl J Med 2017;376:836-847.

TOWER Study – subgroup analysis



Kantarjian H et al. N Engl J Med 2017;376:836-847.

TOWER Study – Adverse events

Table 3. Adverse Events.*

Event	Blinatumomab Group (N=267)	Chemotherapy Group (N=109)
	no. of patients (%)	
Any adverse event	263 (98.5)	108 (99.1)
Event leading to premature discontinuation of trial treatment	33 (12.4)	9 (8.3)
Serious adverse event	165 (61.8)	49 (45.0)
Fatal serious adverse event	51 (19.1)	19 (17.4)
Any adverse event of grade ≥3	231 (86.5)	100 (91.7)
Grade ≥3 adverse event of interest reported in at least 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
★ Neurologic event	25 (9.4)	9 (8.3)
★ Cytokine release syndrome	13 (4.9)	0
Infusion reaction	9 (3.4)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelet count	17 (6.4)	13 (11.9)
Any decrease in white-cell count	14 (5.2)	6 (5.5)

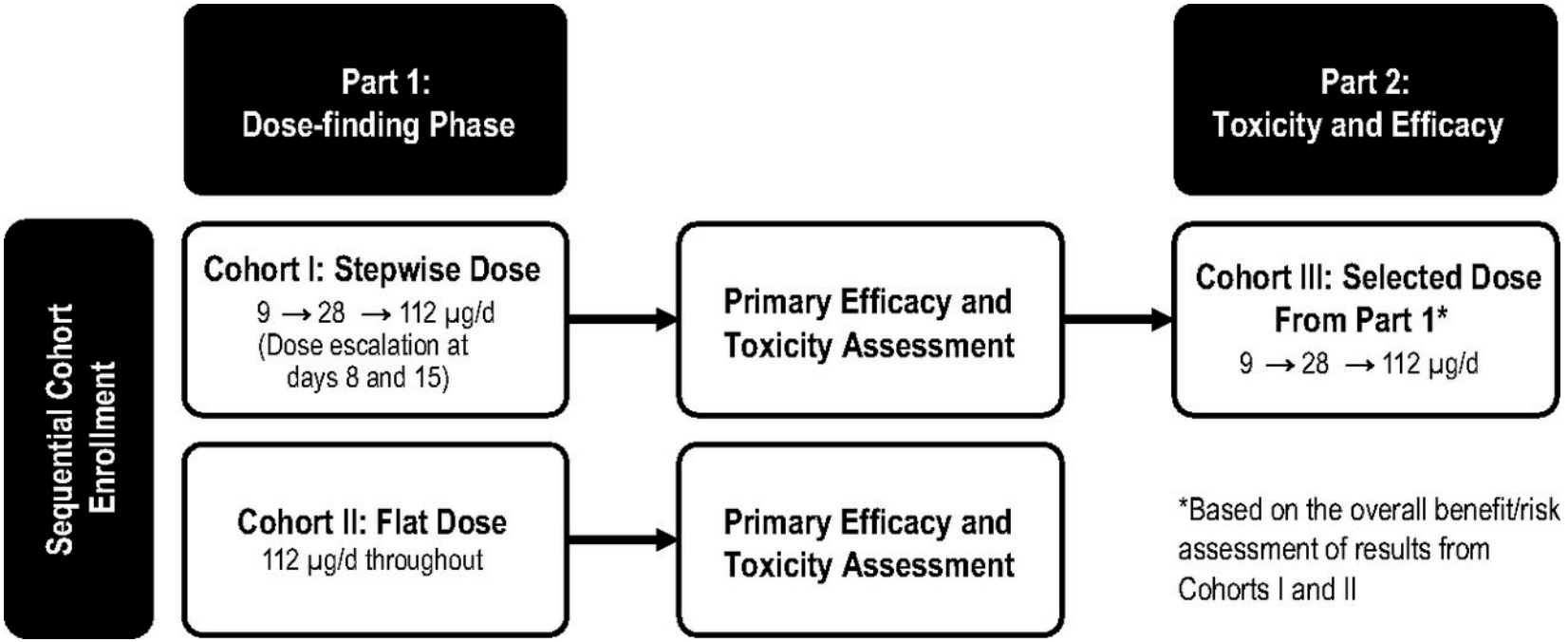
* Data are summarized for all patients who received at least one dose of trial treatment.

Kantarjian H et al. N Engl J Med 2017;376:836-847.

Blinatumomab for non-Hodgkin lymphoma

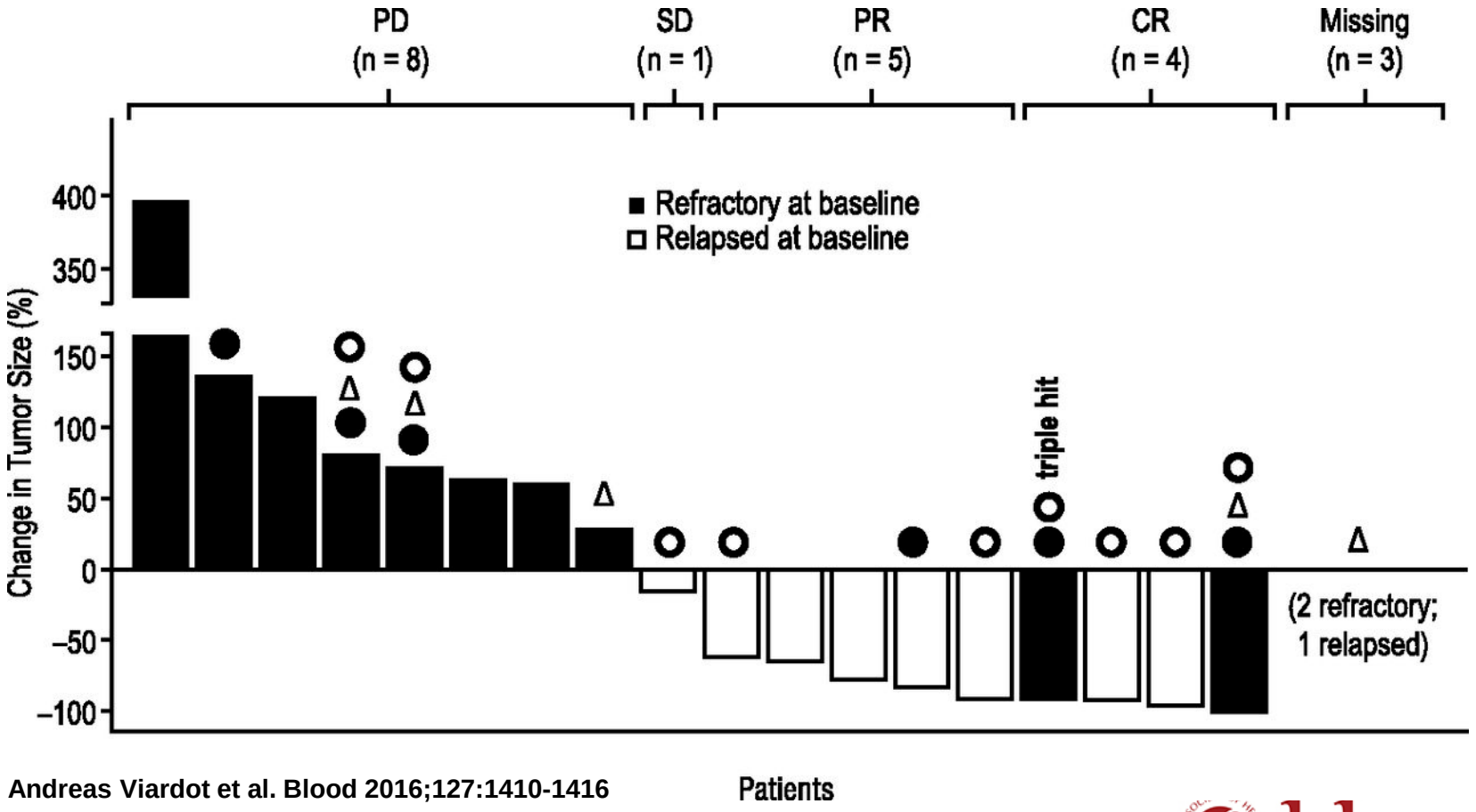
- Early studies of blinatumomab also included patients with relapsed/refractory CD19+ non-Hodgkins lymphoma, primarily diffuse large B-cell lymphoma

Simon 2-stage study design.



Andreas Viardot et al. Blood 2016;127:1410-1416

- Overall response rate 41%, including 19% CR
- Median PFS just 3.7 months



Andreas Viardot et al. Blood 2016;127:1410-1416

- Toxicities generally greater compared with B-ALL cohorts
- Excessive neurologic toxicity lead to early closure of flat dose arm

Table 3. Treatment-emergent adverse events with stepwise dosing

	Cohorts I + III (n = 23)	
Adverse events, n (%)	**Any grade**	**Grade ≥3**
Any adverse event	23 (100.0)	22 (95.7)
Events reported for >15% of patients (any grade)		
Tremor	11 (47.8)	1 (4.3)
Pyrexia	10 (43.5)	1 (4.3)
Fatigue	6 (26.1)	0 (0.0)
Edema	6 (26.1)	0 (0.0)
Thrombocytopenia	5 (21.7)	4 (17.4)
Device-related infection	5 (21.7)	3 (13.0)
Pneumonia	5 (21.7)	3 (13.0)
Diarrhea	5 (21.7)	0 (0.0)
Leukopenia	4 (17.4)	4 (17.4)
C-reactive protein increased	4 (17.4)	3 (13.0)
Hyperglycemia	4 (17.4)	2 (8.7)
Blood glucose increased	4 (17.4)	2 (8.7)
Speech disorder	4 (17.4)	1 (4.3)
Cough	4 (17.4)	0 (0.0)
Back pain	4 (17.4)	0 (0.0)
Hypokalemia	4 (17.4)	0 (0.0)
Any neurologic event reported for >1 patient (any grade)*	16 (69.6)	5 (21.7)
Tremor	11 (47.8)	1 (4.3)
Speech disorder	4 (17.4)	1 (4.3)
Dizziness	3 (13.0)	1 (4.3)
Encephalopathy	3 (13.0)	2 (8.7)
Aphasia	2 (8.7)	2 (8.7)
Somnolence	2 (8.7)	1 (4.3)
Disorientation	2 (8.7)	1 (4.3)
Confusional state	2 (8.7)	0 (0.0)
Paresthesia	2 (8.7)	0 (0.0)

Blinatumomab for nHL

- Although a few CRs were identified, response rates were generally disappointing
- Responses were short lived
- Toxicities, particularly neurotoxicity, were more common than in B-ALL cohorts
- Logistics of treatment difficult
  - 8 week continuous infusion protocol for DLBCL
- As a result, limited ongoing development of blinatumomab for non-Hodgkin lymphoma

Cytokine release syndrome

- A systemic inflammatory response resulting from antigen driven activation of cytotoxic T cells
- Exact mechanisms remain unclear, but inflammatory cytokines such as IL-6, IL-10, IFN-γ are implicated

CRS – Risk factors

- High disease burden
  - Bone marrow blasts >50% or circulating blast count above $15x10^9/L$
- Extramedullary disease
- Cycle 1 of treatment
- Those with “good response”
  - E.g. early and/or rapid decline in circulating blasts

Grade	Criteria*	Management†
Grade 1	Fever ± constitutional symptoms	Symptom management without interruption of therapy
Grade 2	Hypotension not requiring pressors, responding to fluids Hypoxia responsive to <40% O_2	Symptomatic treatment with intravenous fluids, respiratory support, anti-inflammatory, narcotics; interrupting blinatumomab can be considered
Grade 3	Hypotension managed with one pressor Hypoxia requiring ≥40% O_2	Discontinue blinatumomab until resolution; resume at 9 μg/d and then escalate to 28 μg/d if recurrence of CRS after 7 d
Grade 4	Life-threatening complications Urgent intervention indicated	Discontinue blinatumomab permanently; if refractory to corticosteroids, tocilizumab may be considered
Grade 5	Death	—

*Adapted from Common Terminology Criteria for Adverse Events, Version 5.0, November 2017, National Institutes of Health.
†Adapted from blinatumomab (BLINCYTO) packaging insert.

CRS – Management

- Dexamethasone prophylaxis on day 1 of each cycle
- Step-up dosing during cycle 1 (dose increase on day 8 of 28 day cycle)
- Grade 1-2 CRS: supportive care, IV fluids
- Grade 3-4 CRS:
  - Stop blinatumomab infusion ($T_{1/2}$ = 75 minutes)
  - Dexamethasone up to 8 mg tid
  - For refractory cases, consider tocilizumab (anti IL-6 mAb)

Blinatumomab - neurotoxicity

- Range of presentations from headache to confusion, somnolence, seizure, and stupor
- Mechanism remains uncertain, as do risk factors
- Up to half of patients in clinical trials experienced any neuruologic toxicity, mostly Grade I-II
  - 6% of patients in phase III RCT discontinued treatment due to neurotoxicity
- Median onset of neurologic symptoms around d7, but can be later in course

Blinatumomab - neurotoxicity

- Management consists of monitoring for early signs of toxicity
  - Tremor, disorientation, word finding difficulties
- No role for anti-seizure prophylaxis
- Interruption of drug appropriate for those with prolonged low
  - Restart at lower dose once symptoms improve
- Permanent discontinuation for those with seizure or other serious complications

Conclusions

- The role of checkpoint inhibitors in the treatment of hematologic malignancies remains uncertain
  - Apparent benefit in Hodgkins and PMBCL
  - Otherwise, limited activity in non-Hodgkin lymphoma
  - Ongoing trials of checkpoint inhibitors in combination with more traditional chemoimmunotherapy may define a role
- Bispecific antibodies can affect antigen directed cytotoxic responses
  - Unique toxicities associated with T-cell activation including cytokine release syndrome and neurotoxicity

Thank you

- Any questions?