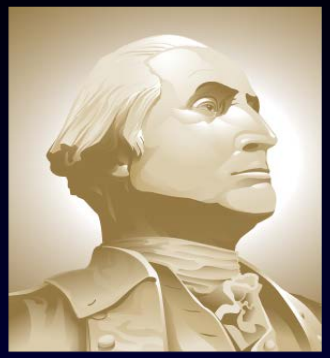

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

Targeted Therapy for B- and T-cell Non-Hodgkin's Lymphomas

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GW Cancer Center

Eduardo M. Sotomayor, MD

Targeted Therapy for B- and T-cell Non Hodgkin's Lymphomas

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Seattle Genetics, Genentech, Celgene, Pharmacyclics, Johnson, Teva

Speaker's Bureau: Seattle Genetics , Celgene

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

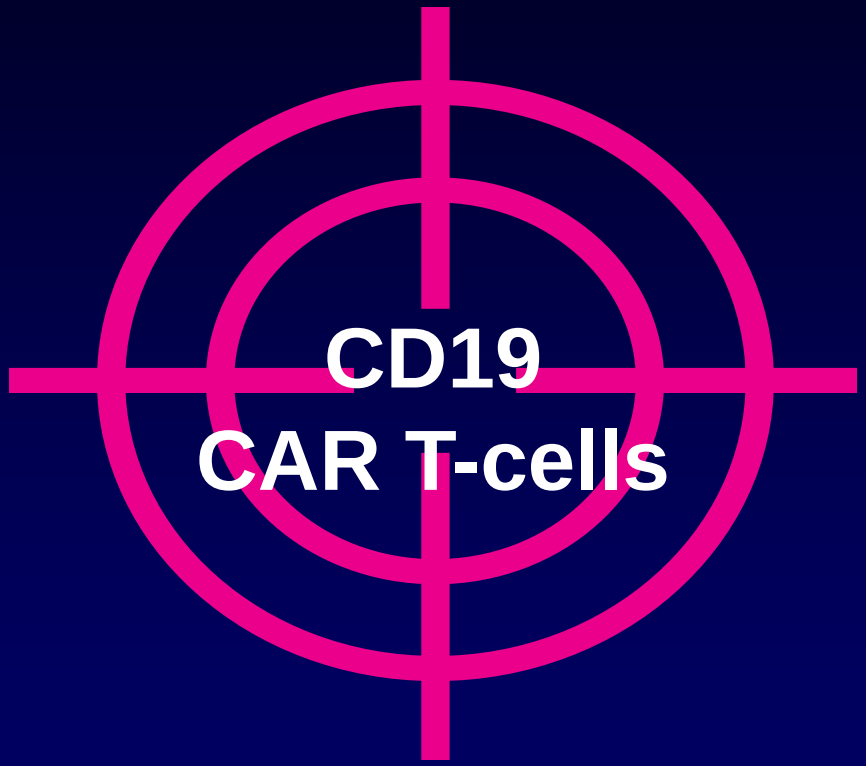
Targeted Therapy

Targeted Therapy for Lymphomas

- **Antigenic (surface) targets**
  - **CD19: CAR T-cells**
  - **CD30: Brentuximab Vedotin**

- **Intracellular targets**
  - **BTK**
  - **PI3K**
  - ***bcl2***
  - **Epigenetic Targets**

Targeted Therapy



Chimeric Antigen Receptor (CAR) T-cells

- Emerged from the groundwork set by the clinical successes of monoclonal antibody technology…

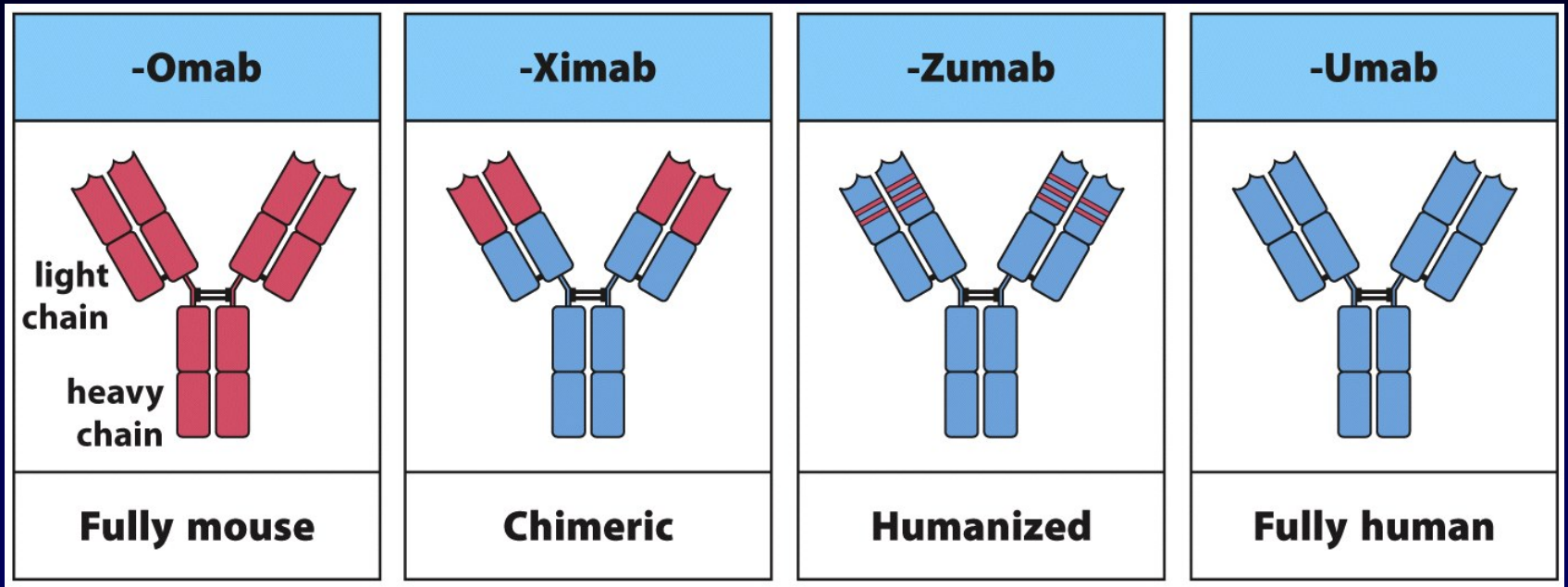
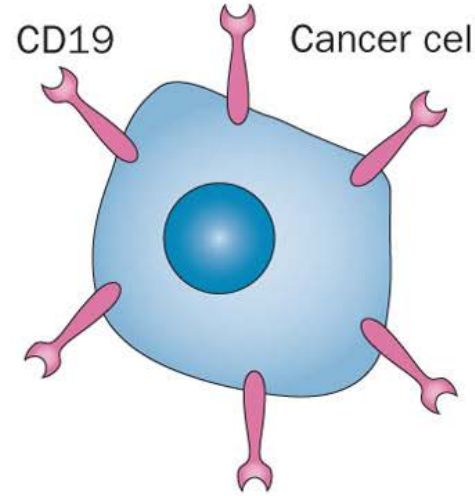


Figure 16.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

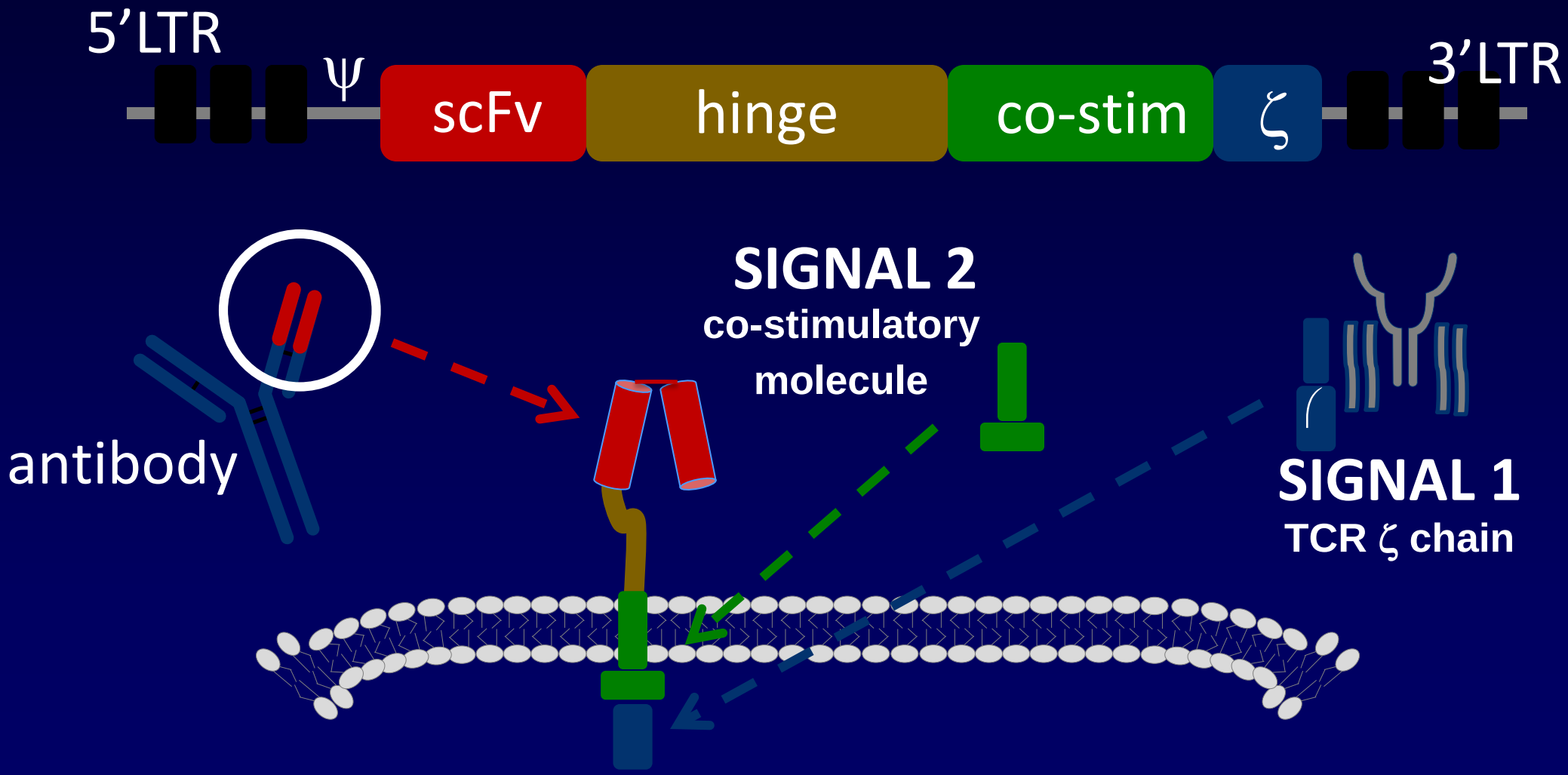
- Antibodies against CD19 have been generated and are highly specific…. Can this specificity be "introduced" into T-cells? How?

- CD19-CARs are antibody-derived receptors (anti-CD19) genetically "introduced" into T cells to allowed them to better recognize and destroy tumor cells expressing CD19……

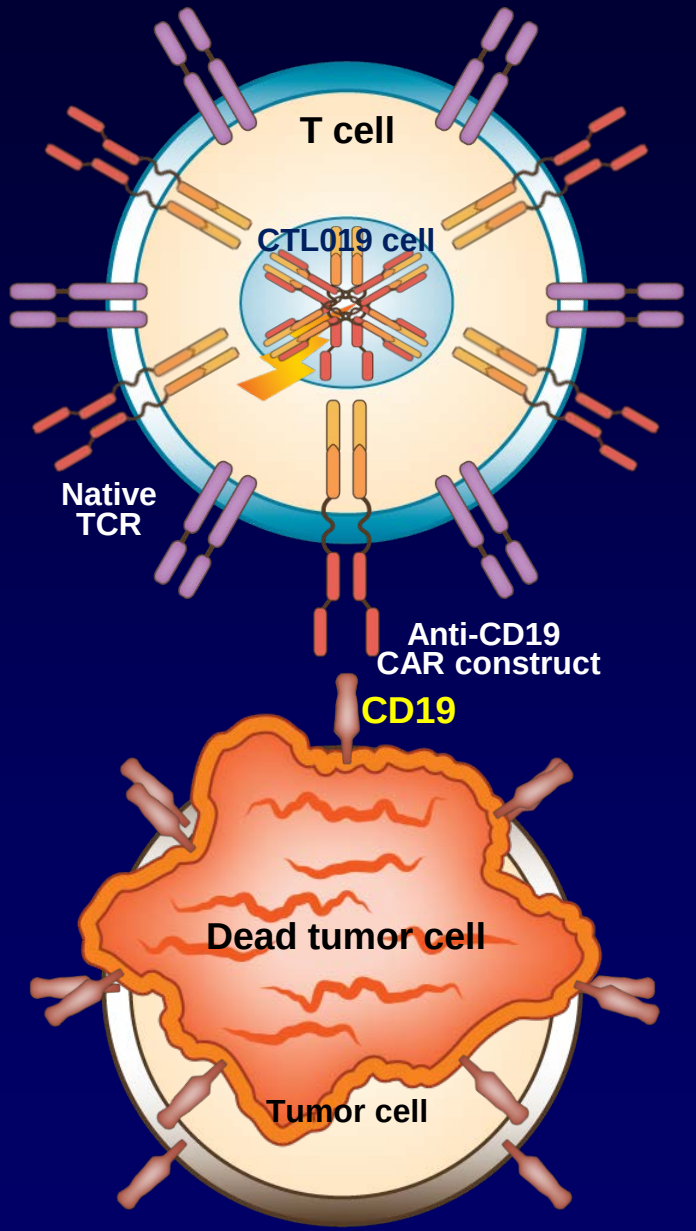
Chimeric Antigen Receptor (CAR) T-cells



Designing a Chimeric Antigen Receptor



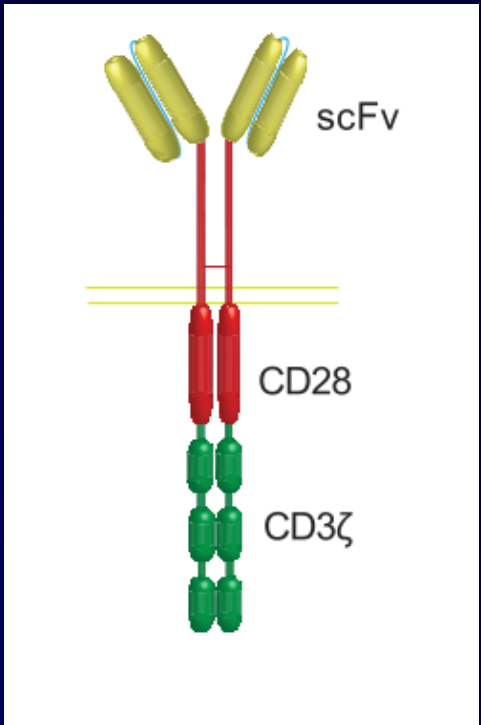
Redirecting the Specificity of T Cells



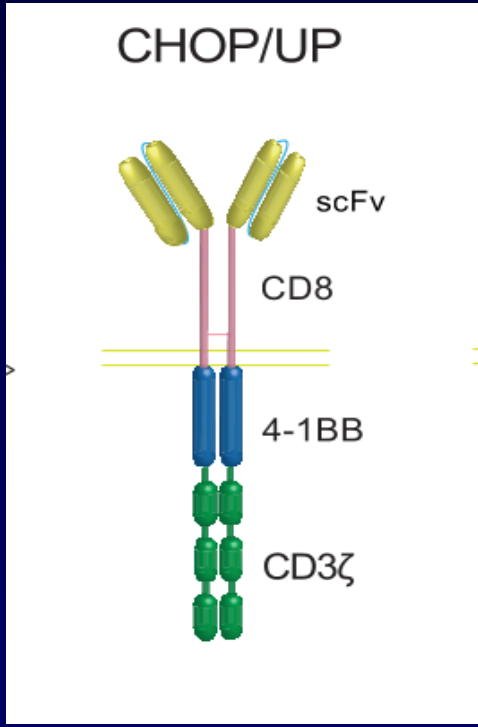
Courtesy of David Porter- U Penn

CD19 CARS in clinical trials

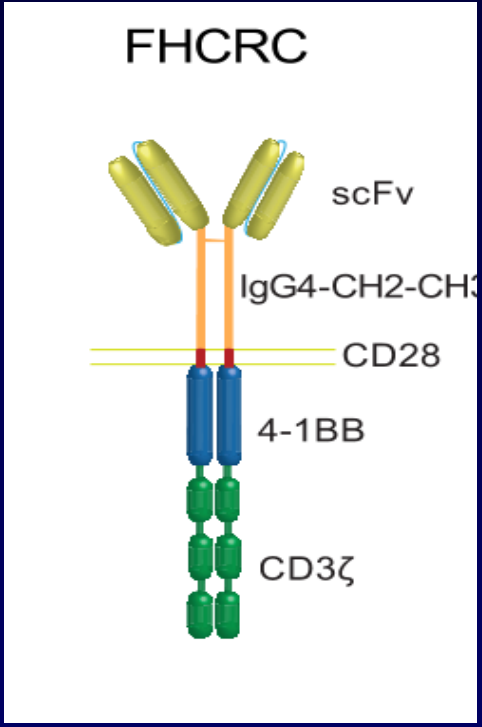
NCI



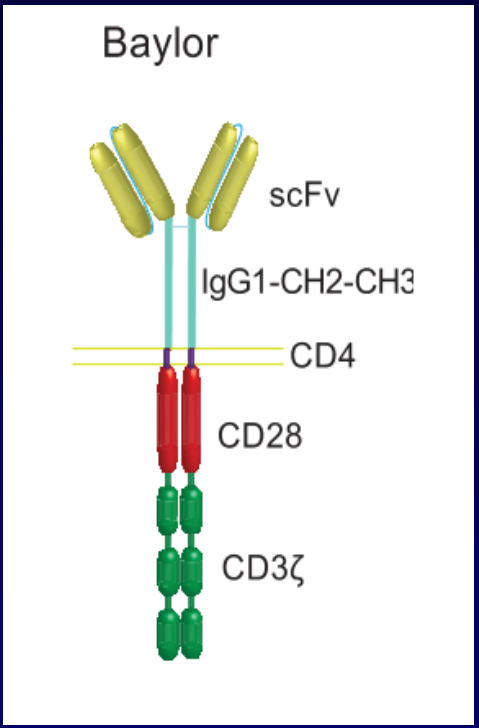
CHOP/U. Penn



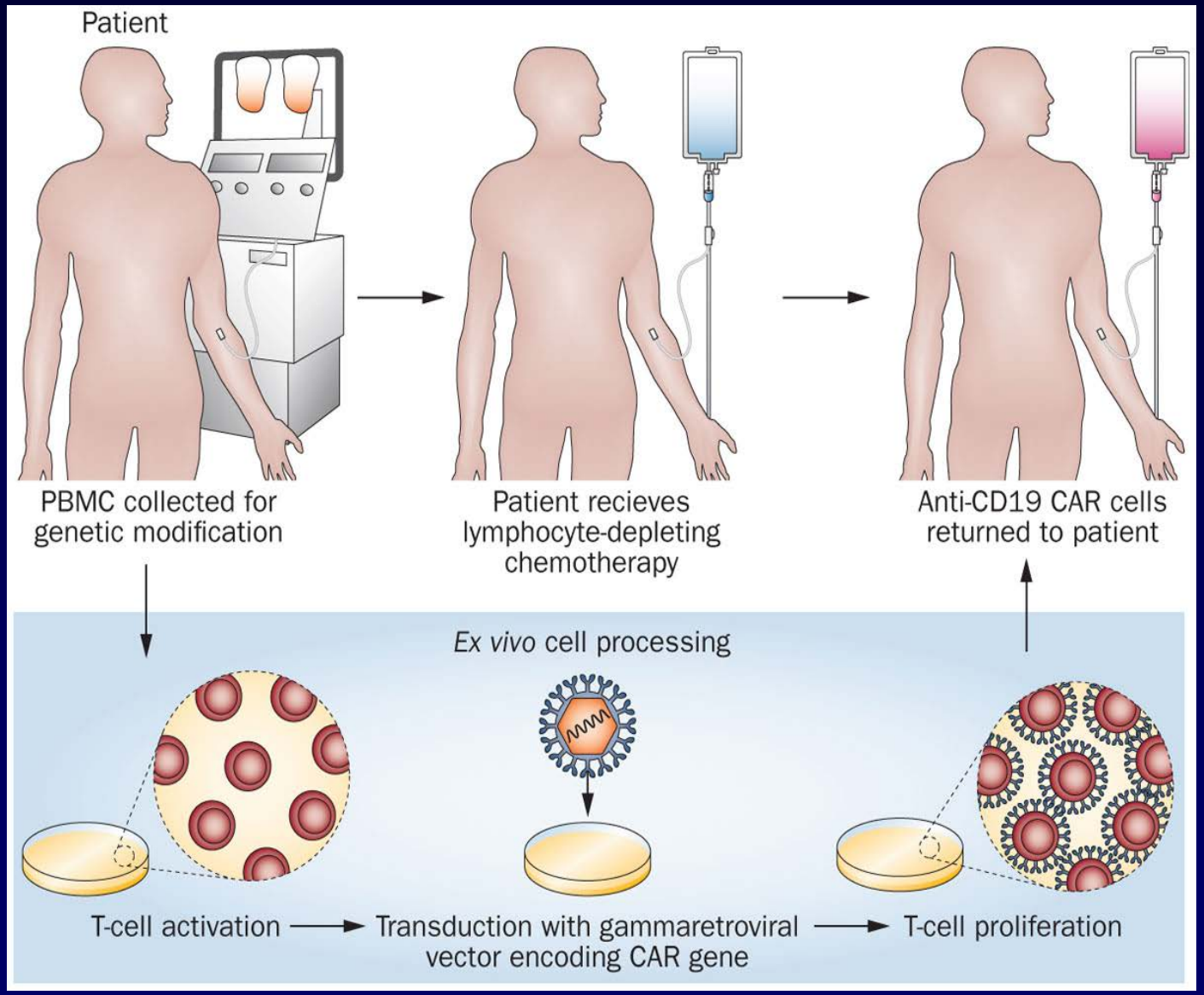
FHCC



Baylor



CAR T-cell Therapy



2-4 week process

Kochenderfer JN & Rosenberg SA. Nat Rev Clin Oncol 10, 267-176, 2013

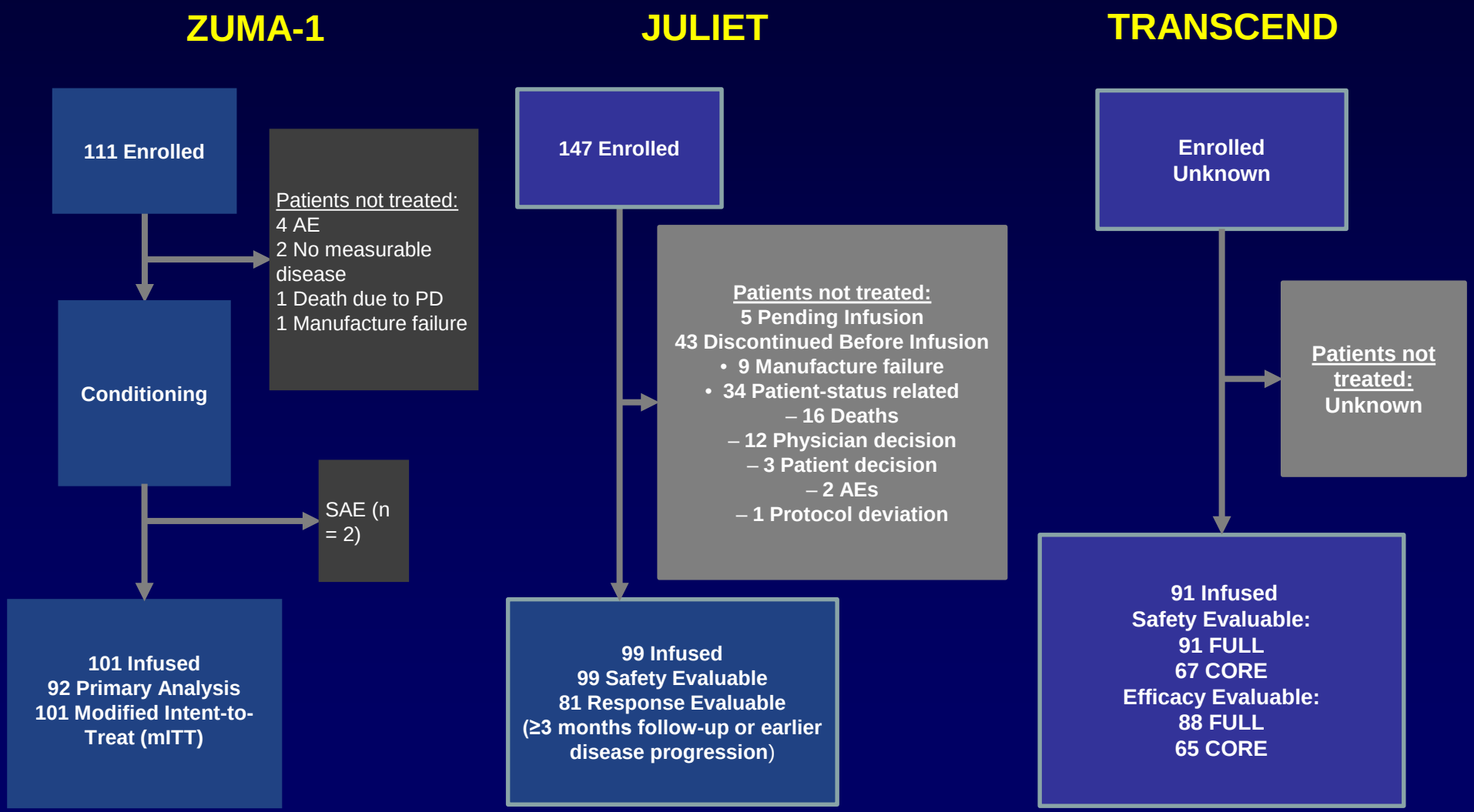
ASH 2017:
Results from three anti-CD19 CAR T-cell Platforms

Long-Term Follow-up ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)
Sattva S. Neelapu, MD; Frederick L. Locke, MD at al

Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma
Stephen J. Schuster, MD, Michael R. Bishop, MD et al

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

Anti-CD19 CAR T-cell Platforms
Patient Flow Diagrams



CAR T-cell studies in B-cell NHL

	ZUMA-1 (FDA Approved)	JULIET	TRANSCEND JCAR017
Source	Phase 2 Primary Analysis NEJM 2017 (DCO 11Aug17)	Phase 2 Primary Analysis ASH 2017 (DC0 8Mar17)	Phase 1/2 Interim Analysis Dose Finding ASH 2017
Manufacturing	• 17 days; 99% successful	• 22 days	< 21 days
Enrollment	111 enrolled; 101 dosed and evaluable No bridging chemotherapy	147 enrolled; 99 dosed, 81 evaluable 90% Bridging chemotherapy	Enrollment not reported, 91 dosed (FULL); 67 in CORE
Dose	2.0 x10^6 CAR T cells/kg >100 kg 2.0 x 10^8 fixed	Median, 3.1 × 10^8 Range, 0.1-6.0 × 10^8 cells	DL1 5.0 x 10^7 CAR T cells (N=34) DL2 1.0 x10^8 CAR T cells (N=29)
Population	• 76% DLBCL; 16% TFL; 8% PMBCL • 79% refractory • 21% relapsed post-ASCT • ECOG 0 / 1: 42% / 58%	• 80% DLBCL; 19% FL • 48% relapsed; 52% refractory • 47% post ASCT • ECOG 0/1: 55% / 45%	(CORE; N = 67) • 76% de novo DLBCL; 24% TFL • 66% chemorefractory • 100% ECOG 0-1
Efficacy	mITT = 108 • Median follow-up 15.4 mo • ORR: 82%; 58% CR • Ongoing response: 42%, 40% CR • Median DOR: 11.1 mo ITT = 111 • Median follow-up 8.7 mo • ORR: 77%; 51% CR	• Minimum efficacy f/u: 3 mo • ORR: 53%; 40% CR • 6-mo Rate: 37%; 30% CR • Median DOR and OR NR • 74% relapse-free at 6-mo • Median follow-up: 5.6 mo	(CORE; N = 65) • ORR: 80%; 55% CR • Median OS NR; 6-mo: 86% • Median DOR: 9.2 mo (NR for CR) • Median follow-up: 6.3 mo
Safety	• Gr ≥ 3 CRS 13% • Gr ≥ 3 NE 28% • Gr 5 AE 3%	• Gr ≥ 3 CRS 23% • Gr ≥ 3 NE 12% • Gr 5 AE 3%	• Gr ≥ 3 CRS 1% • Gr ≥ 3 NE 15% • Gr 5 AE 2%

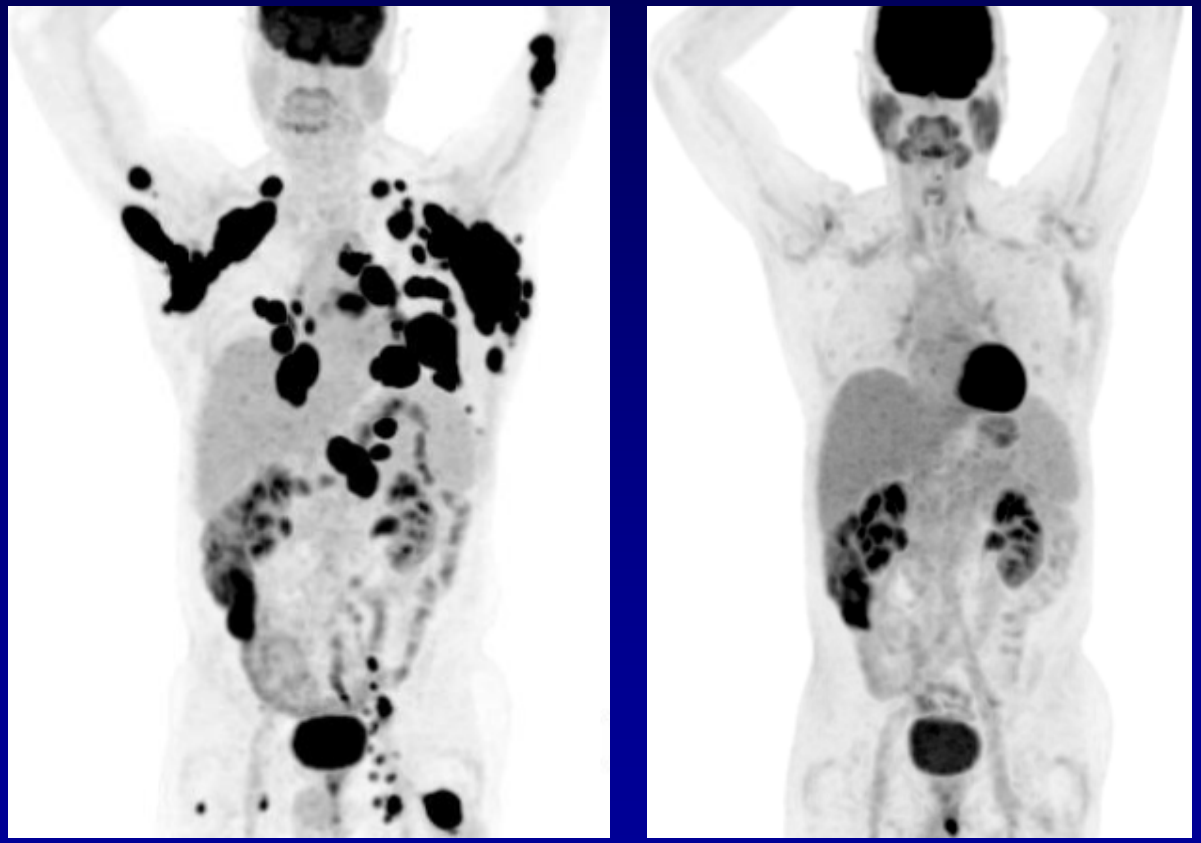
Adverse Events

- Cytokine release syndrome (CRS)
- CAR-related encephalopathy syndrome (CRES)
- Hemophagocytic lymphohistiocytosis (HLH)
- B-cell aplasia

Patient Case: Ongoing 9+ mo Durable CR in Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-Lenalidomide
- No response to last 3 lines of therapy

Baseline **3 months**



Neelapu & Locke et al ASH 2016, #LBA-6

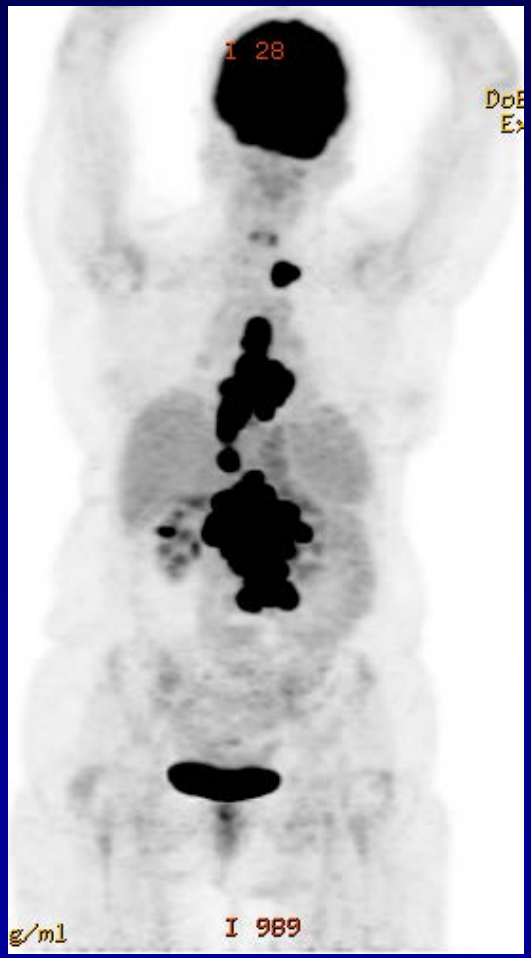
KTE-C19 Induces Ongoing Complete Remission in TFL to Refractory DLBCL

66 y/o female

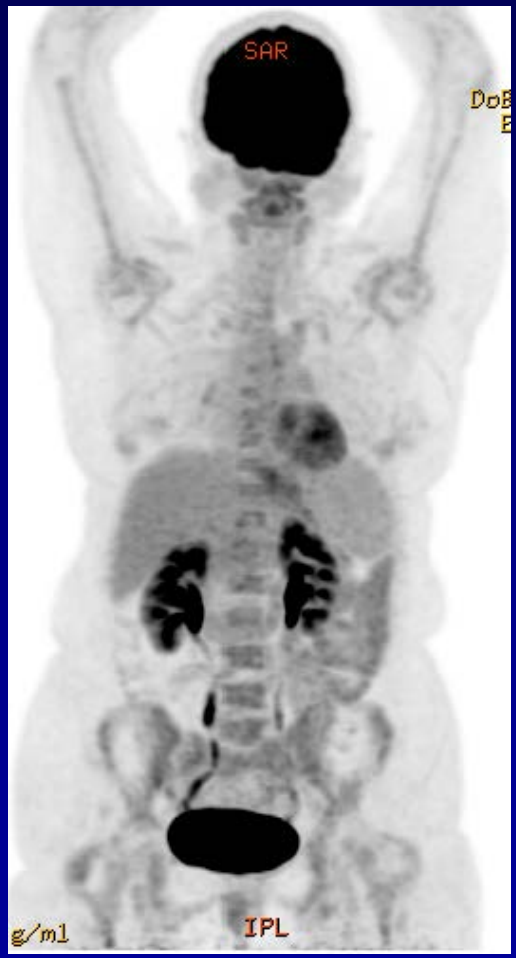
Prior therapies:

- R-CHOP
- R-ICE

Baseline



3 months (CR)



Neelapu & Locke et al ASH 2016, #LBA-6

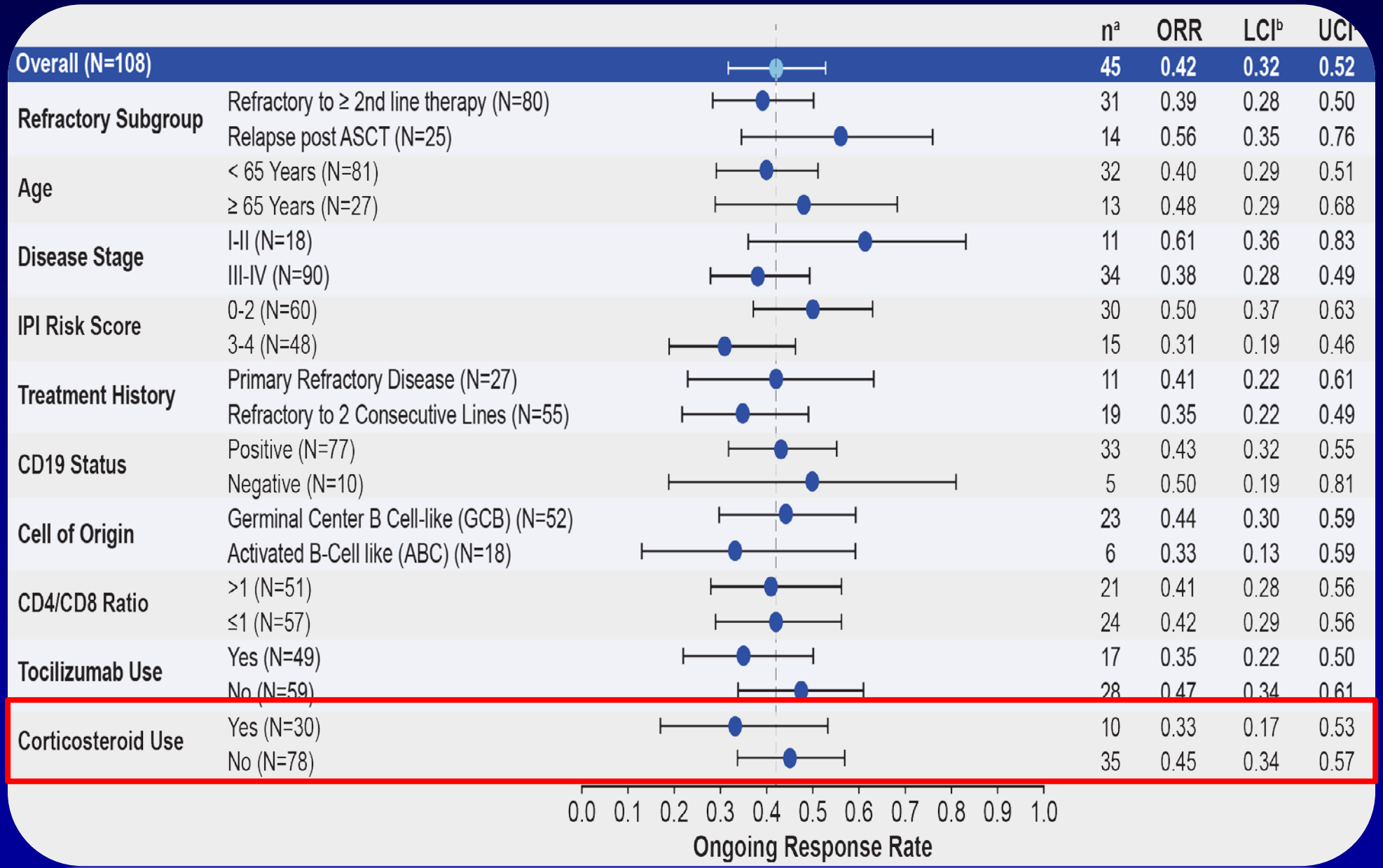
ZUMA-1: Long Term Follow-up
Best Objective Response

	Phase 2 Primary Analysis (n = 101)		Phase 1 and 2 Updated Analysis (N = 108)	
Median follow-up, mo	8.7		15.4	
	ORR	CR	ORR	CR
Best response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 month post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days

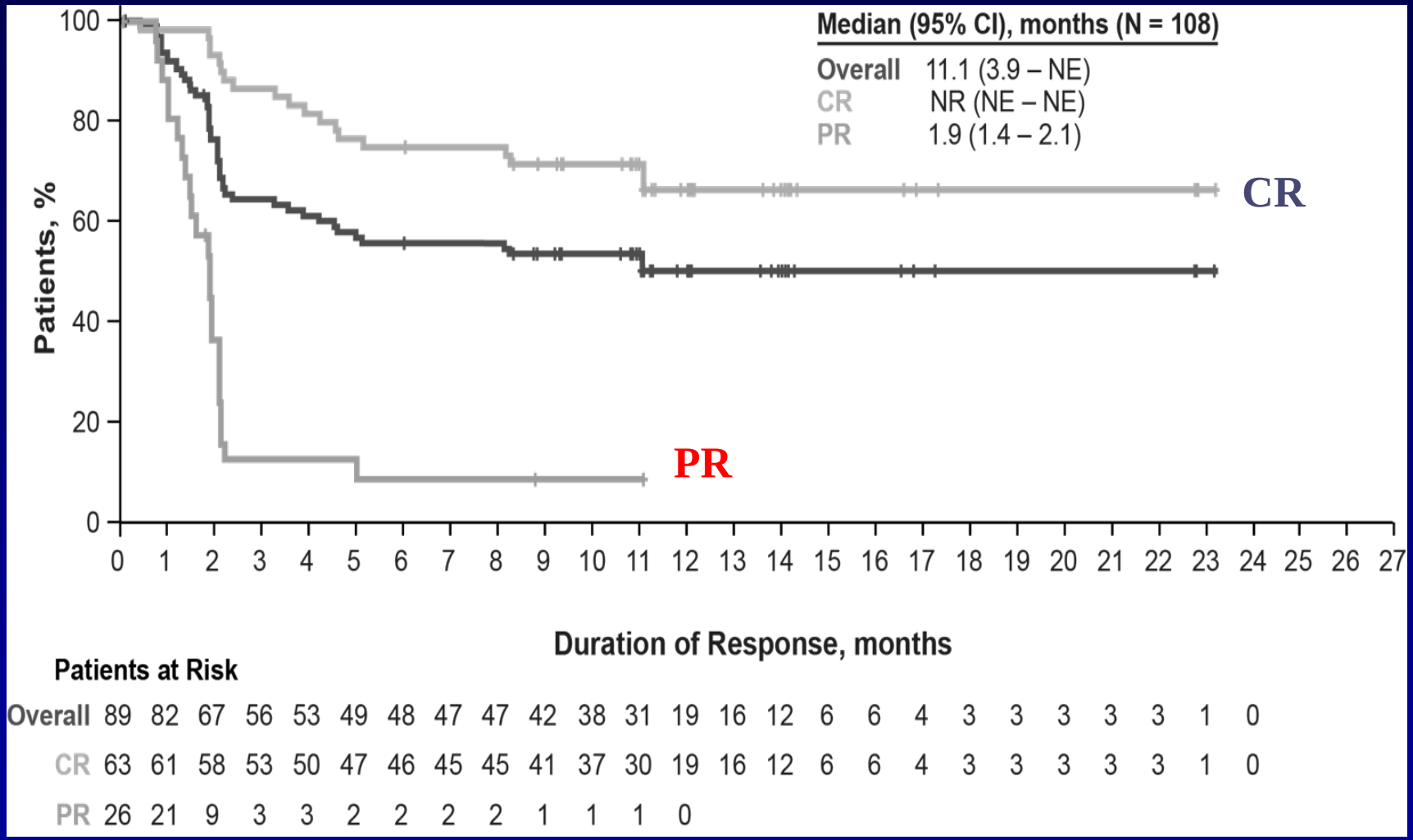
ZUMA-1

Ongoing Responses (> 1 year) Across Key Covariates



		n[a]	ORR	LCI[b]	UCI
Overall (N=108)		45	0.42	0.32	0.52
Refractory Subgroup	Refractory to ≥ 2nd line therapy (N=80)	31	0.39	0.28	0.50
	Relapse post ASCT (N=25)	14	0.56	0.35	0.76
Age	< 65 Years (N=81)	32	0.40	0.29	0.51
	≥ 65 Years (N=27)	13	0.48	0.29	0.68
Disease Stage	I-II (N=18)	11	0.61	0.36	0.83
	III-IV (N=90)	34	0.38	0.28	0.49
IPI Risk Score	0-2 (N=60)	30	0.50	0.37	0.63
	3-4 (N=48)	15	0.31	0.19	0.46
Treatment History	Primary Refractory Disease (N=27)	11	0.41	0.22	0.61
	Refractory to 2 Consecutive Lines (N=55)	19	0.35	0.22	0.49
CD19 Status	Positive (N=77)	33	0.43	0.32	0.55
	Negative (N=10)	5	0.50	0.19	0.81
Cell of Origin	Germinal Center B Cell-like (GCB) (N=52)	23	0.44	0.30	0.59
	Activated B-Cell like (ABC) (N=18)	6	0.33	0.13	0.59
CD4/CD8 Ratio	>1 (N=51)	21	0.41	0.28	0.56
	≤1 (N=57)	24	0.42	0.29	0.56
Tocilizumab Use	Yes (N=49)	17	0.35	0.22	0.50
	No (N=59)	28	0.47	0.34	0.61
Corticosteroid Use	Yes (N=30)	10	0.33	0.17	0.53
	No (N=78)	35	0.45	0.34	0.57

ZUMA-1: Duration of Response by Best Objective Response



- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients having ongoing CR at 24 months

ASH 2017:
Combinations of CAR T cell and checkpoint blockade

Phase 1 Results from ZUMA-6: Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Combination with Atezolizumab for the Treatment of Patients with Refractory Diffuse Large B Cell Lymphoma (DLBCL)

Frederick L. Locke, MD at al.

Marked Re-Expansion of Chimeric Antigen Receptor (CAR) T Cells and Tumor Regression Following Nivolumab Treatment in a Patient Treated with Axicabtagene Ciloleucel (axi-cel; KTE-C19) for Refractory Diffuse Large B Cell Lymphoma (DLBCL)

Brian T. Hill, MD, PhD; Zachary J. Roberts, MD, PhD; John M. Rossi, MS; Mitchell R. Smith, MD, PhD

Phase I/II Study of Pembrolizumab for Progressive Diffuse Large B Cell Lymphoma after Anti-CD19 Directed Chimeric Antigen Receptor Modified T Cell Therapy

Elise A. Chong, Stephen J. Schuster et al.

ZUMA-6: Axi-cel + Atezo in Refractory DLBCL Results

Patients

- Median age: 57 y (range, 29 – 66)
- Disease stage: 33% stage II, 33 % stage III, 44% stage IV
- Median 3 prior therapies (range, 2 – 4)
- 22% B symptoms
- 33% bulky disease
- All patients assessed (6/9) had baseline PD-L1 expression on tumor cells and/or immune cell infiltrate

Efficacy

- **CR rate: 56%; ORR: 89%**
- 2/9 patients experienced PR to CR conversions at 6 and 9 months after axi-cel treatment
- 3/9 patients had PD following response

Safety

Patients With Adverse Event[a], n (%)	Overall (N = 9)		
	Any Grade	Worst Grade 3	Worst Grade 4
Any AE	9 (100)	1 (11)	7 (78)
Axi-cel–related AE	9 (100)	3 (33)	4 (44)
Atezo-related AE	4 (44)	0	1 (11)

- There were no Grade 5 events
- Combination of atezo after axi-cel did not lead to increased use of tocilizumab or steroids
- One DLT of cytopenias (Grade 3 anemia, Grade 4 thrombocytopenia, and Grade 4 neutropenia)
- Generally, atezo-related AEs were infrequent and did not require specific intervention

Locke FL, et al. ASH 2017. Abstract #2826

CAR T-cells: Efficacy

•**August 30, 2017: FDA Approves tisagenlecleucel (Kymriah, formerly CTL019) for the treatment of children and young adults (up to 25 years of age) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.**

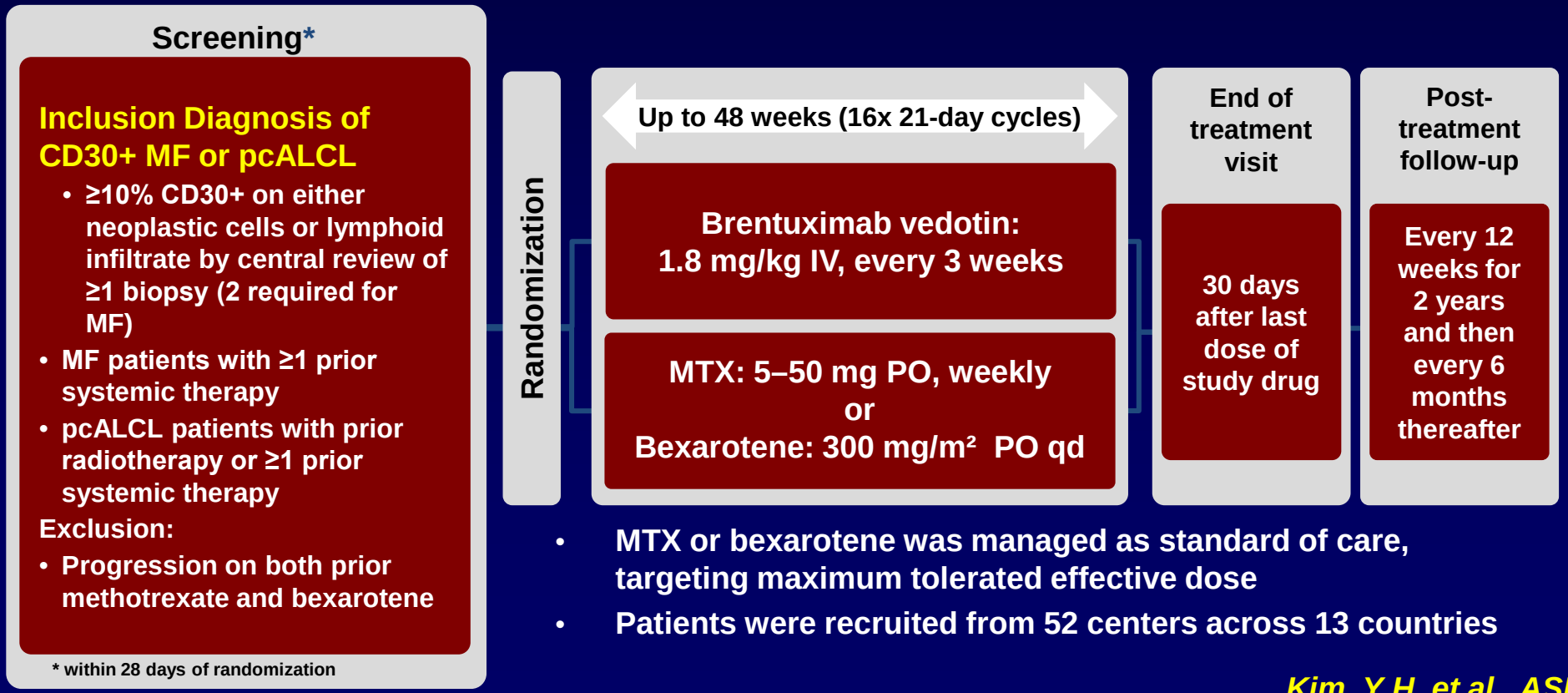
October 19, 2017: FDA Approves axicabtagene ciloleucel (Yescarta), formerly KTE-C19) for the treatment of adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment

November 16, 2017: FDA gives "breakthrough" designation to anti-BCMA CAR T-Cell therapy for patients with Multiple Myeloma

Targeted Therapy

Phase 3 ALCANZA Trial: Brentuximab vs investigator's choice

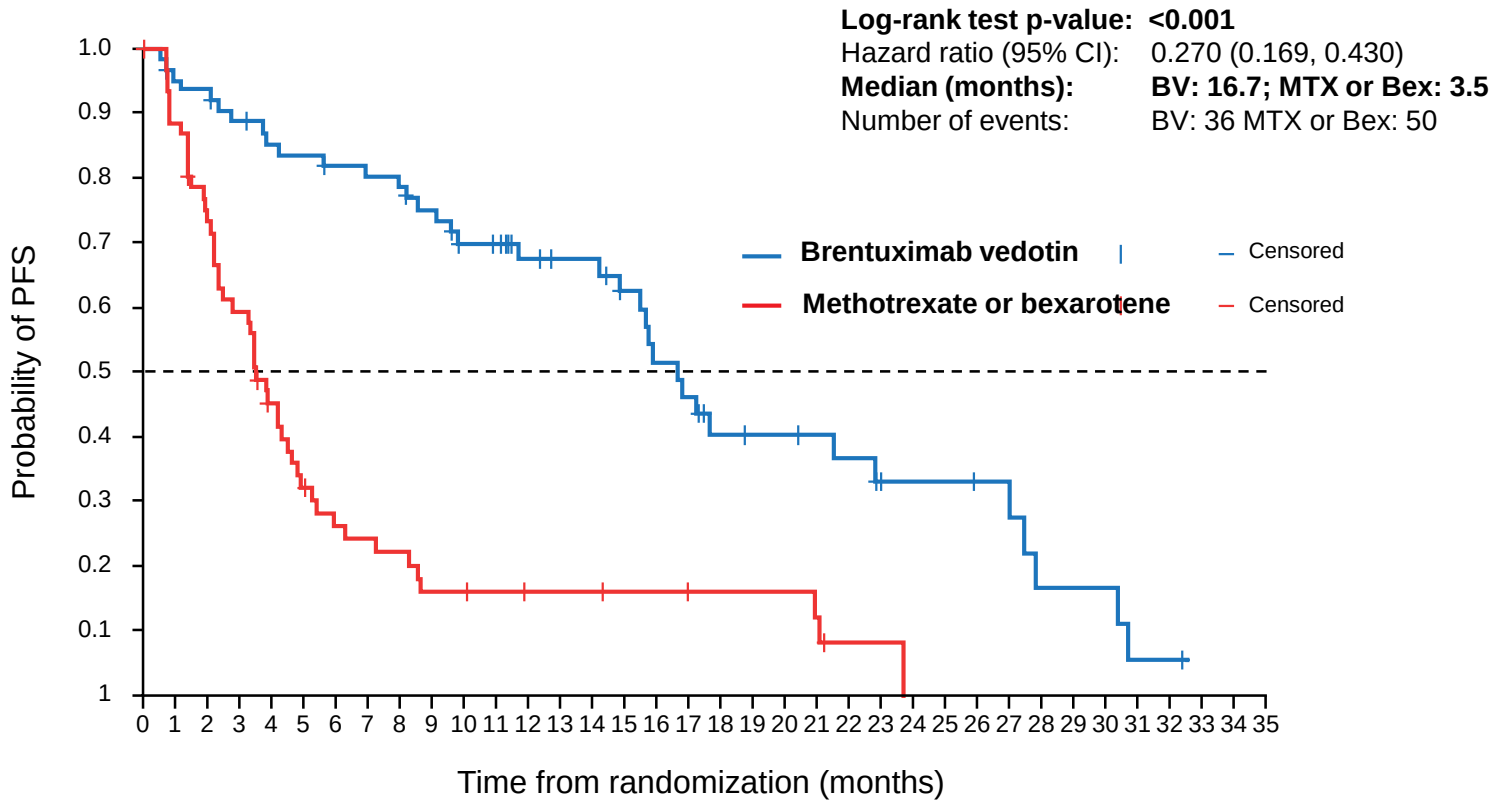
- 131 patients with CD30+ CTCL who received prior systemic or radiation therapy
  - **Primary cutaneous ALCL**: At least one prior systemic or radiation therapy
  - **Mycosis Fungoides**: At least one prior systemic therapy



- MTX or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centers across 13 countries

Kim, Y.H. et al , ASH 2016

Progression-free survival (ITT population)



Number of patients at risk:

Brentuximab vedotin	64	59	58	54	51	50	48	47	46	43	38	38	29	27	27	23	19	17	13	12	12	11	10	8	7	7	7	6	3	3	3	1	1
Methotrexate or bexarotene	64	54	42	34	24	17	13	12	11	8	8	7	7	6	6	5	5	5	4	4	4	3	1	1									

Assessed by independent review

Bex, bexarotene; MTX, methotrexate

Kim, Y.H. et al , ASH 2016

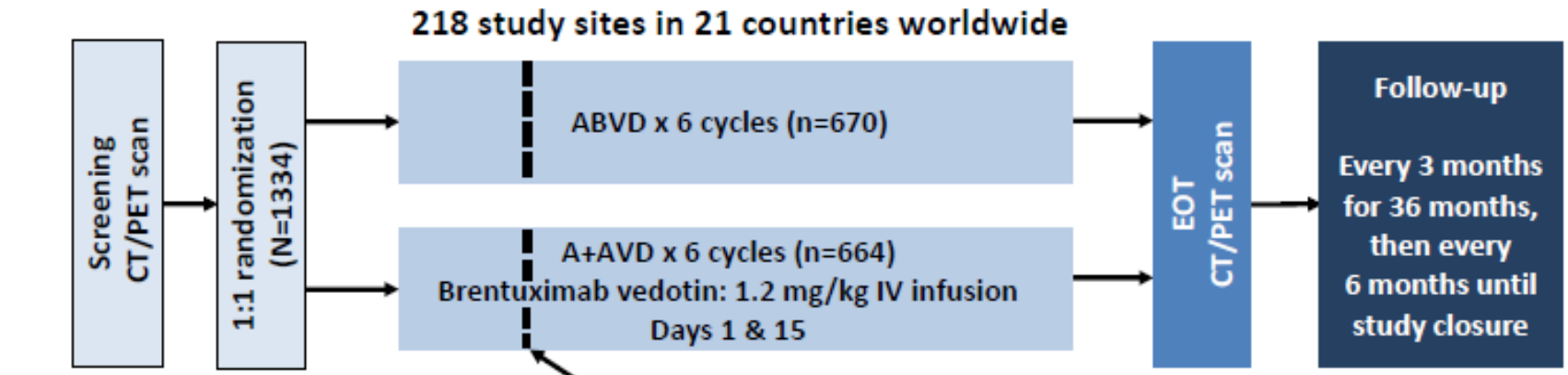
Brentuximab Vedotin in Frontline Hodgkins
(ASH 2017-Plenary presentation)

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

Brentuximab Vedotin in Frontline Hodgkins
(ASH 2017-Plenary presentation)

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

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

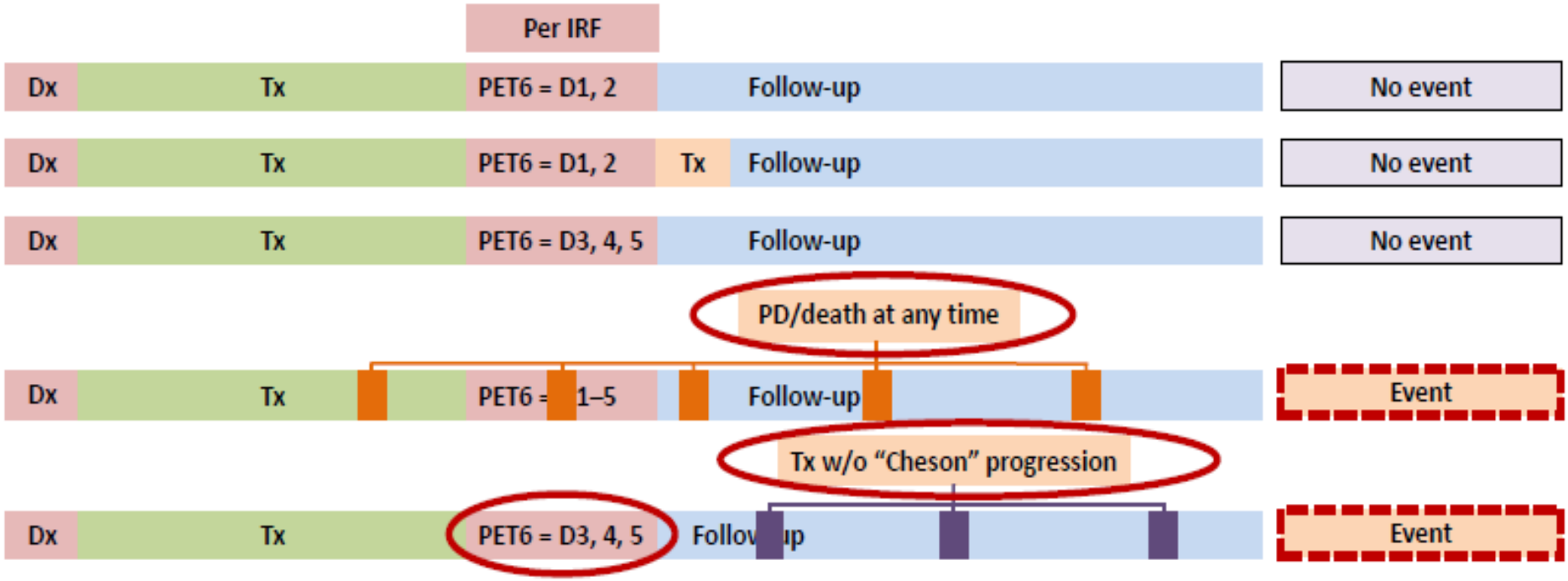
JM Connors et al. NEJM . December 2017

Brentuximab Vedotin in Frontline Hodgkins

(ASH 2017-Plenary presentation)

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

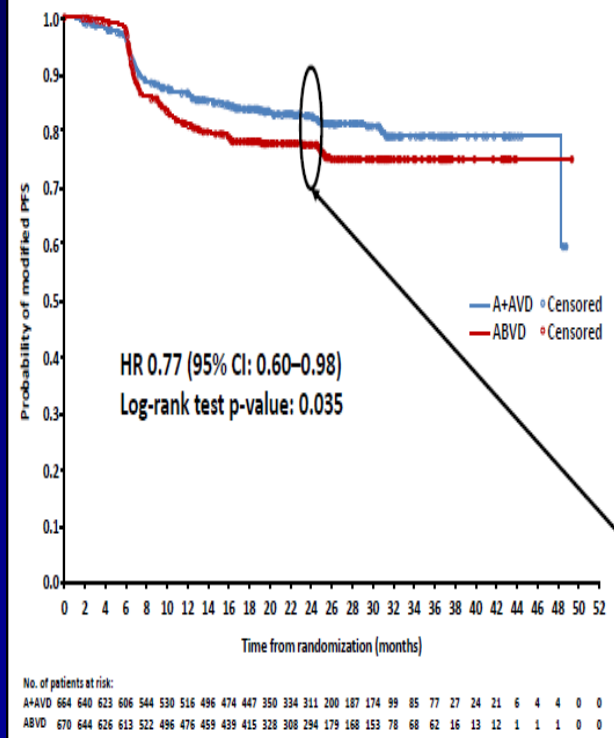


D, Deauville score; Dx, diagnosis; IRF, independent review facility; PD, progressive disease; PET6, end-of-cycle-6 PET; Tx, treatment

Brentuximab Vedotin in Frontline Hodgkins

(ASH 2017-Plenary presentation)

Modified PFS per independent review



Number of events

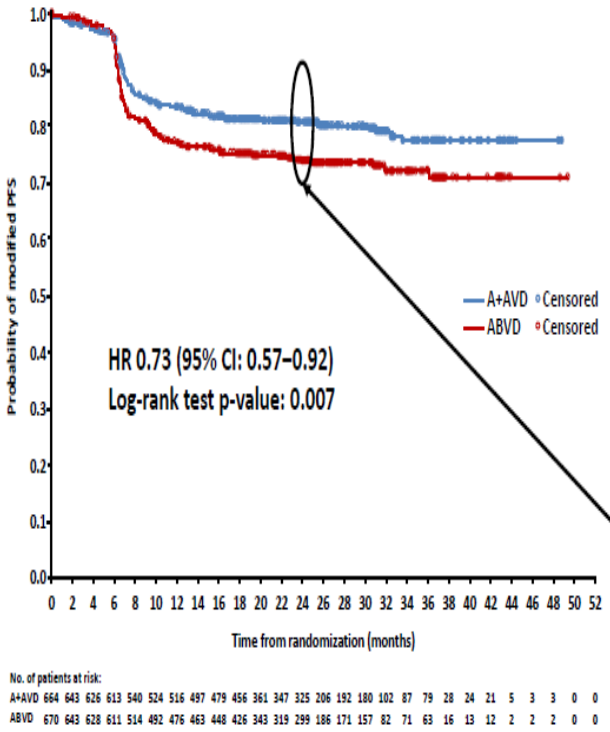
Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

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



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)

JM Connors et al. NEJM . December 2017

Brentuximab Vedotin in Frontline Hodgkins
(ASH 2017-Plenary presentation)

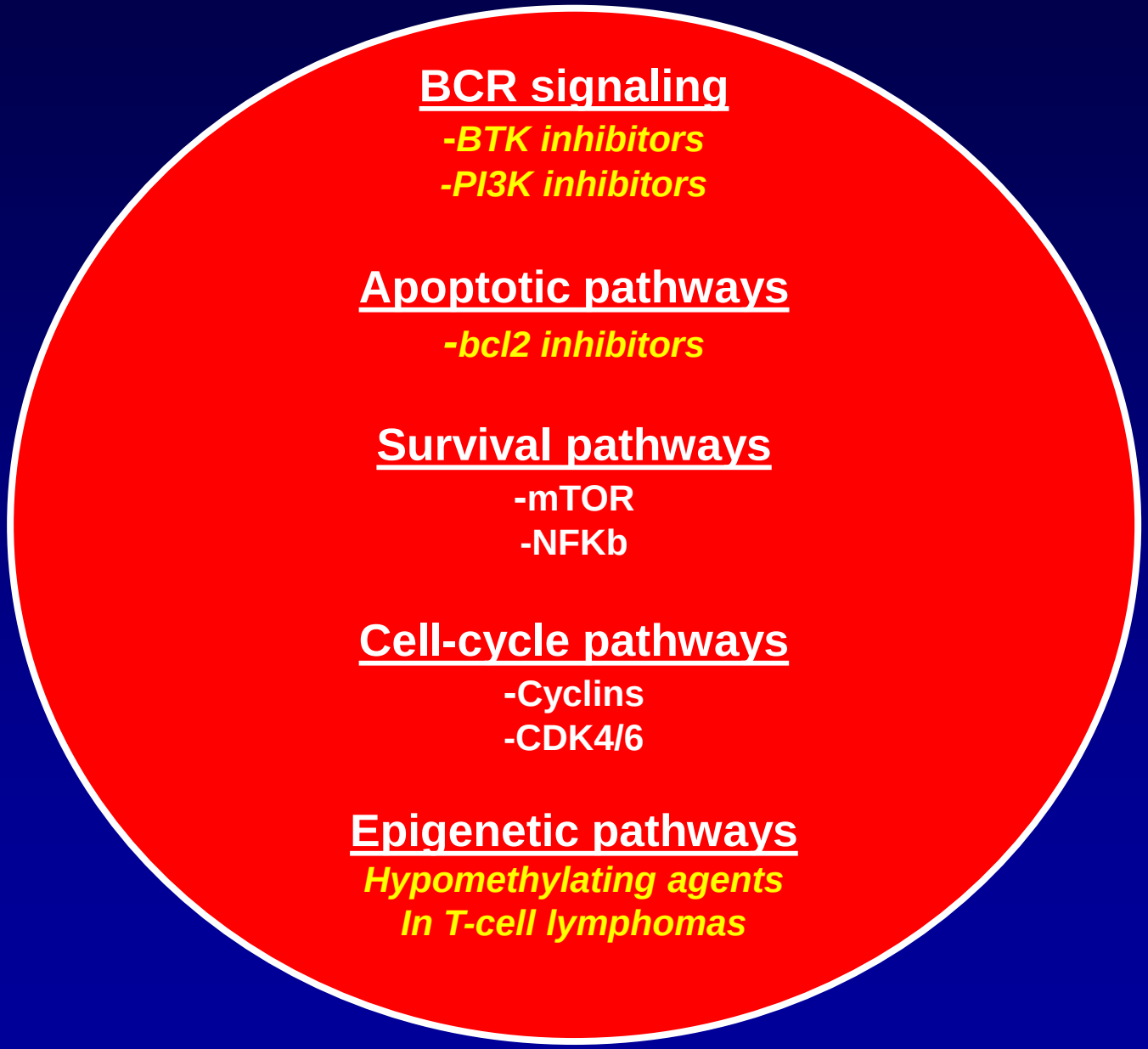
Summary and conclusions

- 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

FDA Approval: March 2018

Intracellular Targets



ASH 2017: BTK inhibitors in relapsed MCL

- **Ibrutinib, Acalabrutinib and Zanabrutinib (BGB311-BeiGene)**

- **Ibrutinib: (Rule et al)**
  - **3.5 years f/u: Better outcomes for patients with relapsed/refractory MCL that received ibrutinib after one line of treatment versus >1**
  - **Median PFS: Approx. 3 years in patients with 1 prior therapy and 4 y for those in CR**

– **Acalabrutinib Phase 2 ACE-LY-004 Study (Wang et al)**
  - **ORR: 81%, CR: 40%, PR:41%**
  - **High risk MIPI: Only 17%**
  - **Less AF and bleeding episodes**
  - **Most common AE: Headaches**

– **Zanabrutinib (Tam et al)**
  - **High plasma concentration and longer exposure (160 mg bid: 100% BTK in LN)**
  - **38 MCL patients. ORR: 88% CR: 25%**
  - **Responses in other subtypes (FL: ORR: 41%, CR; 18% ; LCL: ORR:31%, CR: 15%)**
  - **Durable responses seen**

PI3K inhibitors in B-cell malignancies

- **Idelalisib (δ) (FDA-approved)**
  - Treatment of Relapsed CLL in combination with rituximab
  - Treatment of Relapsed Follicular or SLL who have received 2 prior treatments

- **Copanlisib (α,δ) (FDA-approved)**
  - As a third-line treatment for patients with relapsed follicular lymphoma

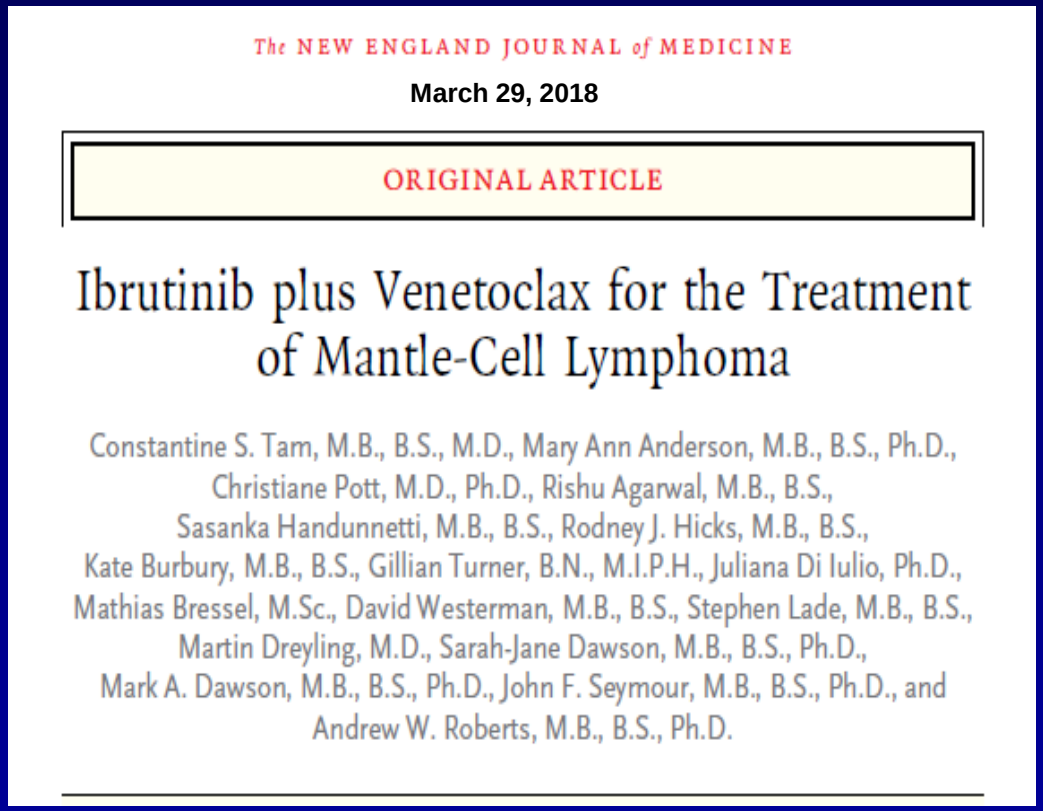
- **Umbralisib (δ) (TGR-1202)**
  - ASH 2017 (David et al): Integrated Safety Analysis in Patients with Relapsed/Refractory Lymphoid Malignancies

- **INCB050465 (highly selective δ)**
  - ASH 2017 (Forero-Torres et al): Results from a Phase 1/2 Study in Patients with Relapsed or Refractory B-Cell Malignancies(CITADEL-101)

Venetoclax (ABT-199): A selective oral *bcl2* inhibitor in B-cell Malignancies

- Venetoclax is FDA-approved for the treatment of patients with:
  - Chronic Lymphocytic Leukemia (CLL) with 17p deletion who have received at least one prior treatment
- As a single agent significant activity in relapsed/refractory MCL
- ASH 2017: Impressive results when used in combination with BTK inhibitor, Ibrutinib, in patients with relapsed/refractory B-cell malignancies

Venetoclax in combination with Ibrutinib: A promising combination for MCL



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ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

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- 23 pts with relapsed/refractory MCL
  - 50% have p53 aberrations
  - 75% have high risk prognostic score

– CR at 16 weeks by CT scan: 42% (9% with ibrutinib- historical controls)

– CR rate by PET: 62% at 16 weeks

– MRD clearance: 67% by flow and 38% by ASO-PCR

– Time-to-event analysis: 78% of patients with ongoing response at 15 months.

– Well tolerated

Azacitidine in Patients With Relapsed/Refractory PTCL: Efficacy

- Median follow-up: 84 days (19 –1236)
- ORR for the entire population was 53% (10/19), but was significantly higher in AITL patients than in patients with other PTCL entities
  - 9/12: 75% (AITL)
  - 1/7: 14% (other PTCL)
- • *TET2* was sequenced in 16 patients and was mutated in 11/12 (92%) AITL and 1/4 (25%) other PTCL
  - 9/9 (100%) AITL patients who experienced at least partial response after 5-AZA treatment were *TET2* mutated

Delarue et al. ASH 2016; Abstract 4164

Where Are We Going Next?.....

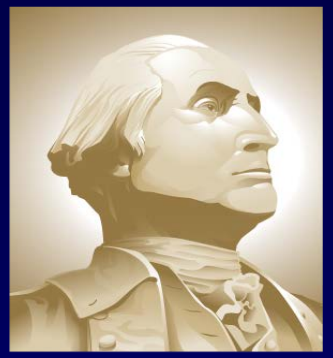
Combinations

Combinations

- **Of targeted agents… ie, BTK inhibitor plus:**
  - Lenalidomide or next generation IMIDs
  - Next generation MTOR inhibitors
  - Bortezomib or novel proteasome inhibitors
  - Epigenetic modifiers

- **Targeted agents plus immunotherapy:**
  - Targeted agent (s) + Novel monoclonal antibodies
  - Targeted agents + checkpoint blockade antibodies
  - Targeted agents (Ibrutinib) + CAR T-cells

- **Targeted agents plus conventional chemotherapy:**
  - BTK inhibitor plus BR
  - PI3K inhibitor plus BR



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THANKS

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