THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

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

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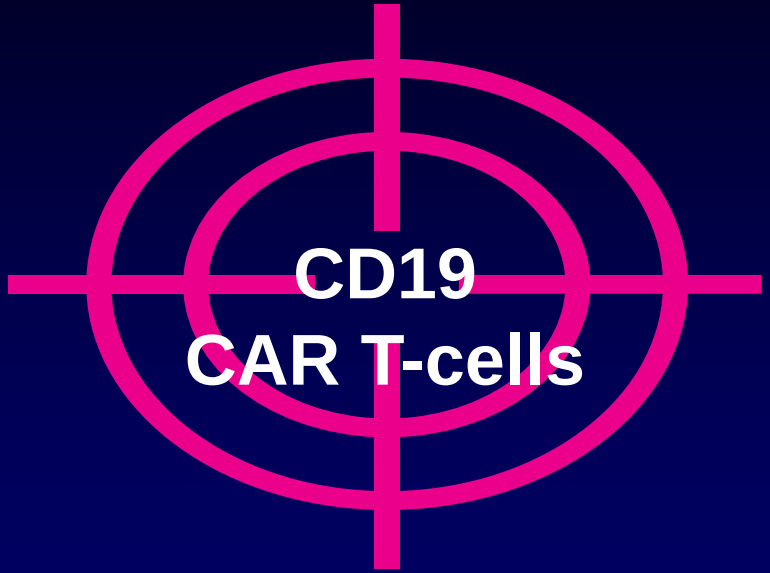
Targeted Therapy

Targeted Therapy for Lymphomas

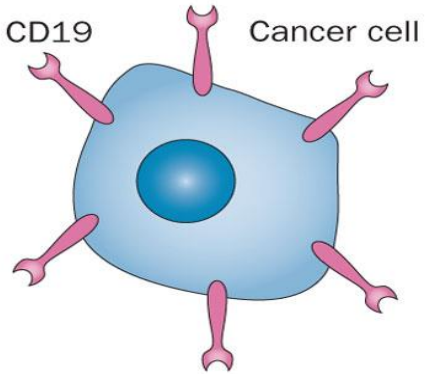
- **Antigenic (surface) targets**
  - **CD19: CAR T-cells, MOR 208 Ab, Lonca-T ADC**
  - **CD30: Brentuximab Vedotin**

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

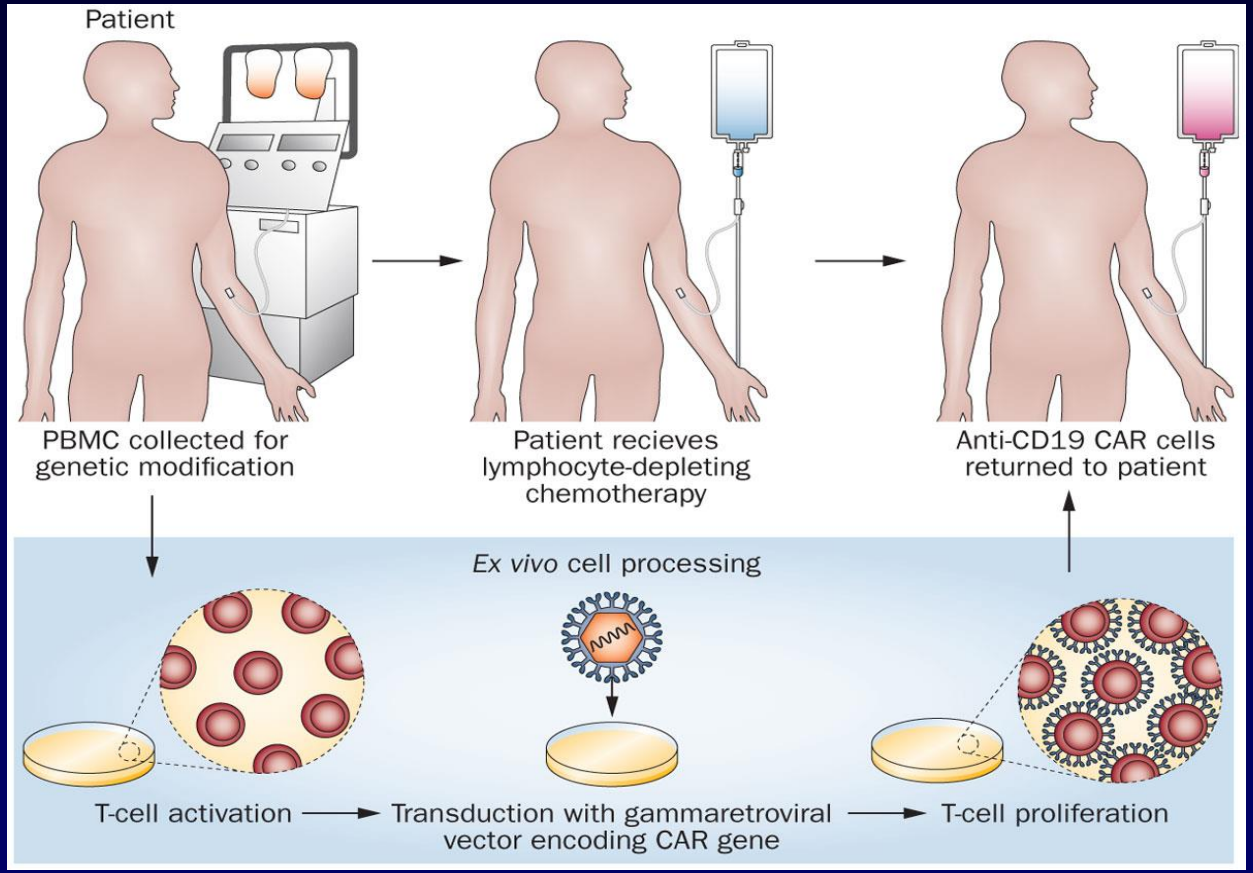
Targeted Therapy



Chimeric Antigen Receptor (CAR) T-cells



CAR T-cell Therapy



2-4 week process

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

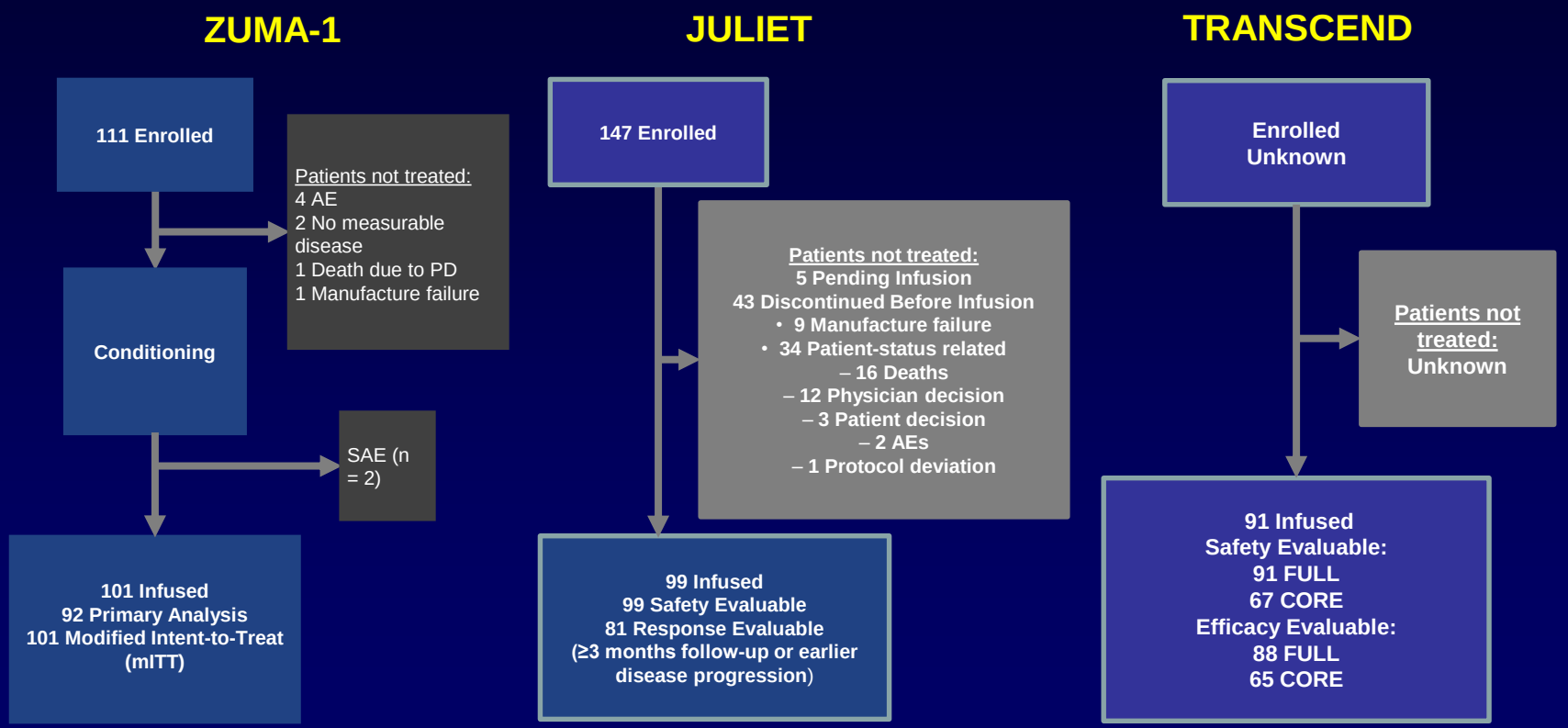
ASH 2017:
Results from three anti-CD19 CAR T-cell Platforms

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 Yescarta™ (FDA Approved)	JULIET Kymriah™	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

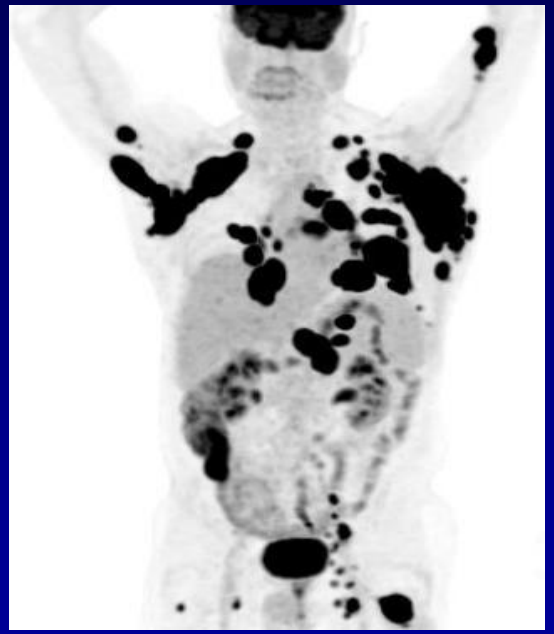
Efficacy	mITT = 108
	•Median follow-up 15.4 mo
	•ORR: 82%; 58% CR
	•Ongoing response: 42%, 40% CR
	•Median DOR: 11.1 mo
	
	ITT = 111
	•Median follow-up 8.7 mo
	•ORR: 77%; 51% CR
		• Minimum efficacy f/u: 3 mo
		• ORR: 53%; 40% CR
		  • 6-mo Rate: 37%; 30% CR
		  • Median DOR and OR NR
		  • 74% relapse-free 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%

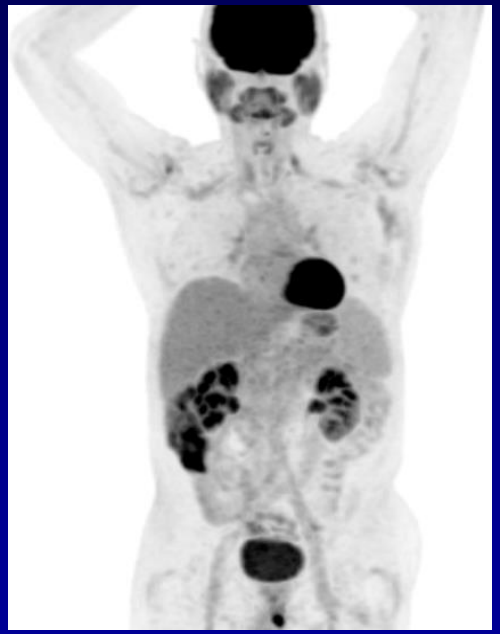
Patient Case: Ongoing 9+ mo Durable CR in Refractory DLBCL

- 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

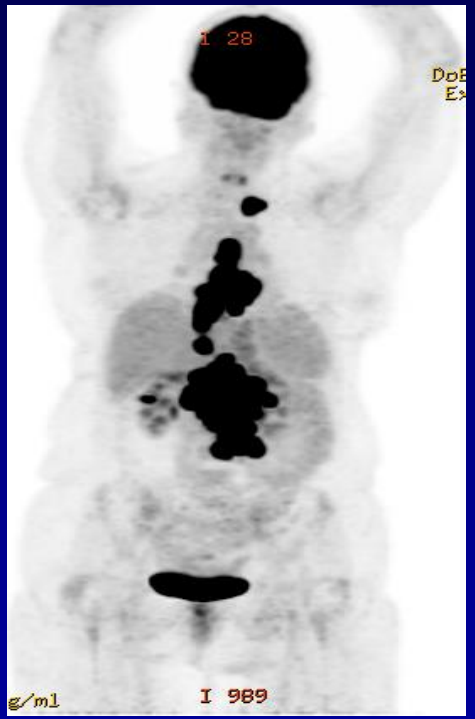
KTE-C19 Induces Ongoing Complete Remission in TFL to Refractory DLBCL

66 y/o female

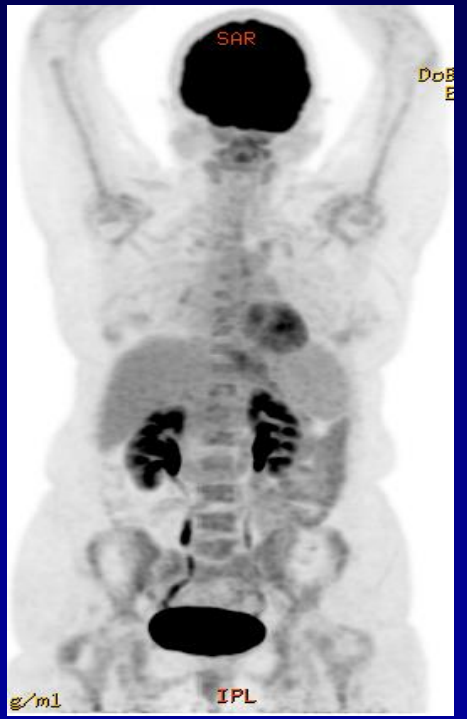
Prior therapies:

- R-CHOP
- R-ICE

Baseline



3 months (CR)



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

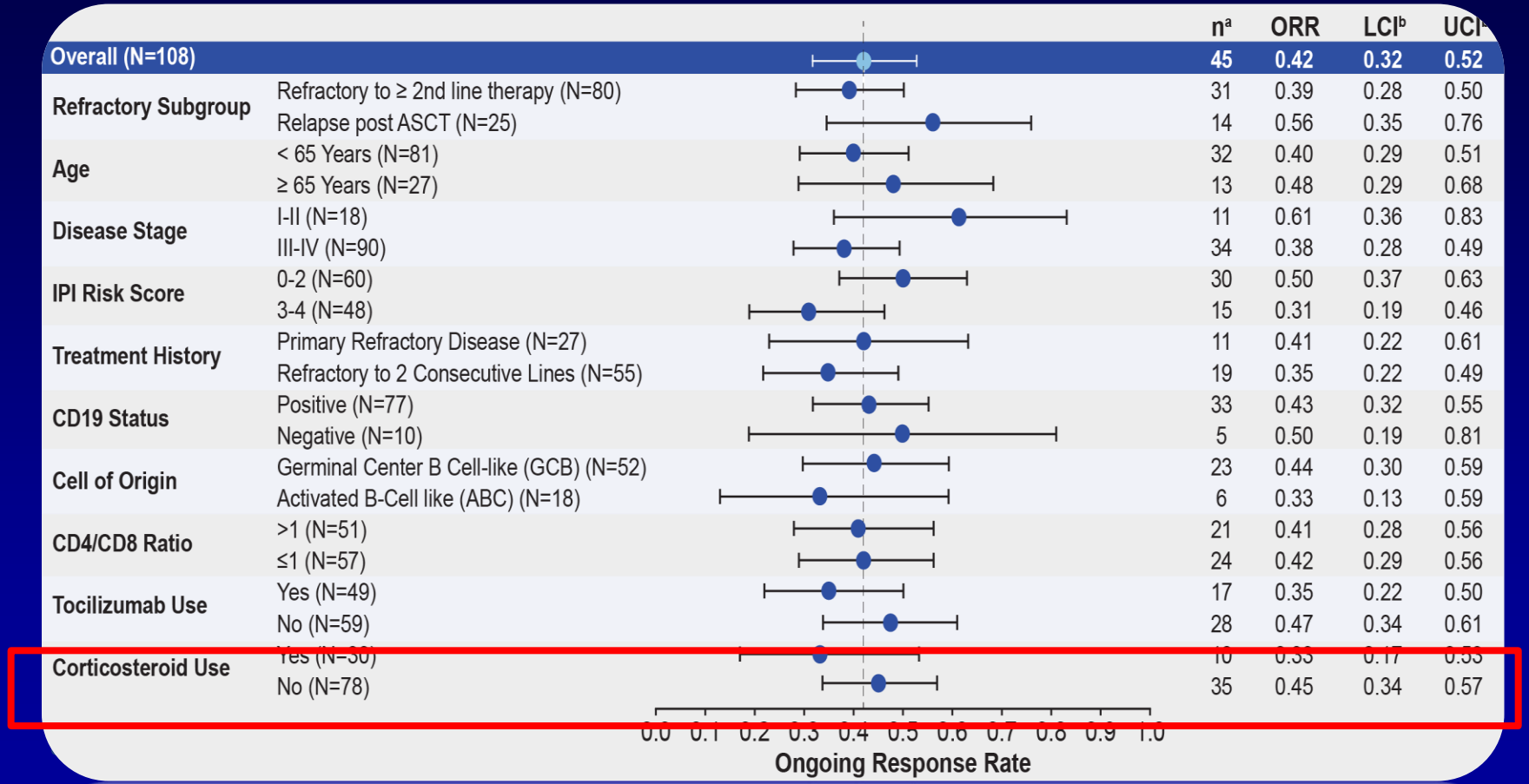
ZUMA-1: Long Term Follow-up
Best Objective Response

	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

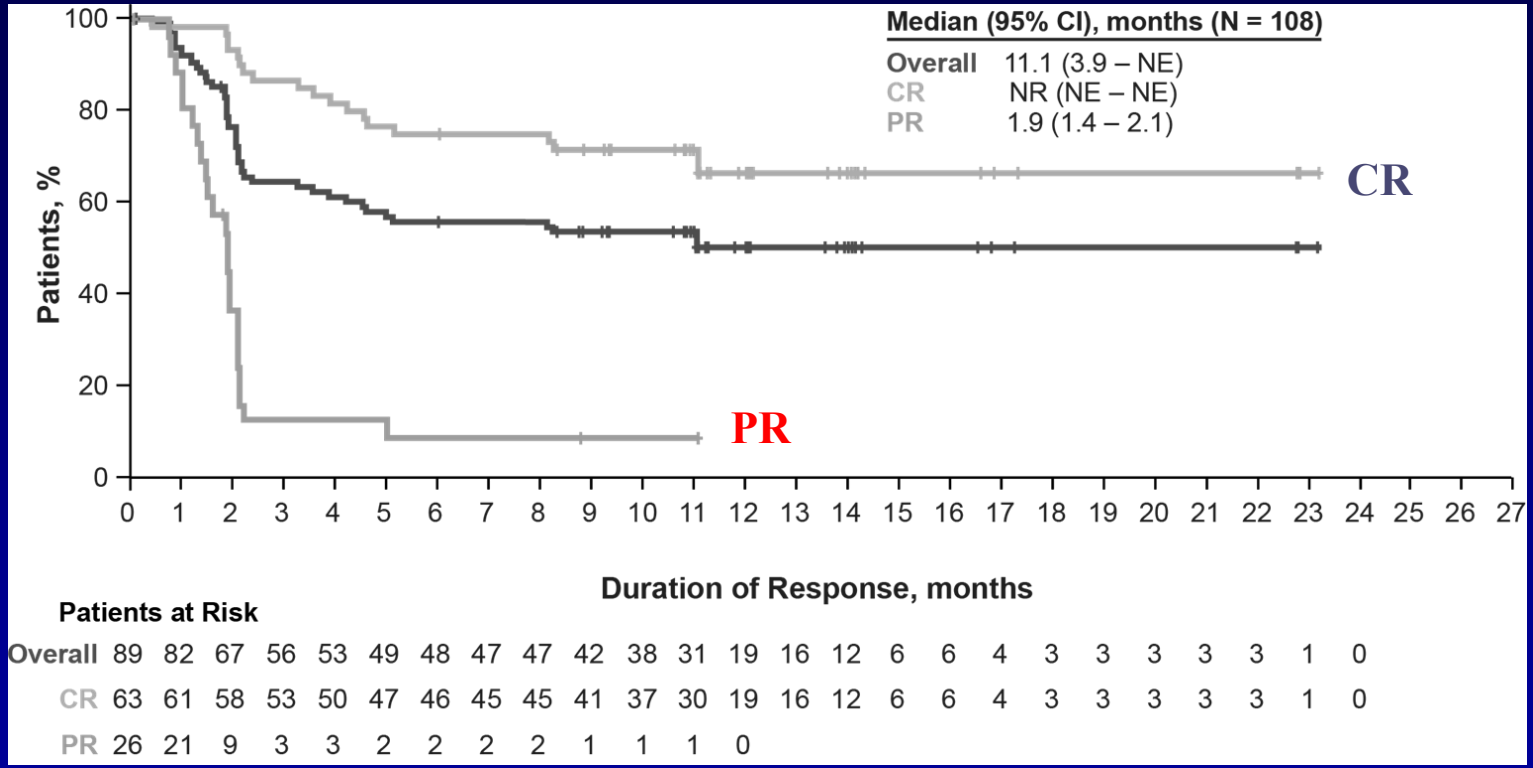
- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 month post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from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

ZUMA-1

Ongoing Responses (> 1 year) Across Key Covariates



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

Future Directions in CAR T-cell Therapy….

…combination with checkpoint blockade antibodies

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

Pembro After Anti-CD19 CAR T Cell Therapy for R/R DLBCL

Study Design

- Patients with progressive NHL received 200 mg IV pembrolizumab every 3 weeks for 18 doses until PD or toxicity after CTL019 (murine) or CTL119 (human) anti-CD19 CAR T cell therapy
- Primary objective: Safety
- Secondary objectives: 3-month ORR, PRS, RD, OS

Patients

- Median PFS after CTL019/119 was 2.2 months (range 0.4-3.2)
- Median time to first pembro dose was 2.5 mos (range, 3 – 7)

Efficacy

- **ORR: 25%**
  - 1 CR, 1 PR, 6 PD
  - CR ongoing at 280 days

Biomarkers

- CD4 and CD8 T cell increases were observed post-pembro in all patients
- Responders Have multiple CAR Peaks vs Nonresponders With 1 Peak
- 4/5 patients assessed had PD-1 expression in the tumor microenvironment: 2 on macrophages and 2 on tumor cells
- Median 1.6-fold (range, 1.2-2.0) increase in peak CAR transgene copy a median 2.5 (range, 2-13) days after first pembro dose

Chong EA, et al. ASH 2017. Abstract #4121.

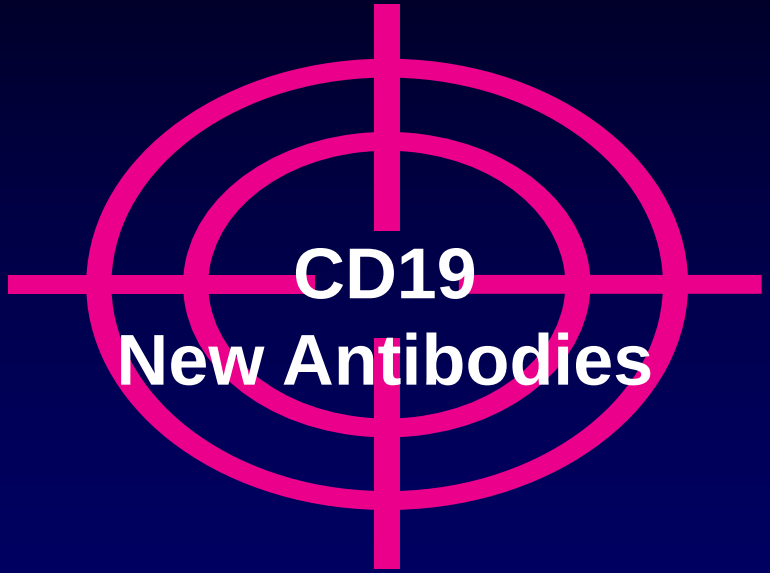
ASH 2017: Anti-PD1/PDL1 in NHL

- Initial studies demonstrated activity across multiple NHL subtypes:
  - ORRs of 40% in FL and 36% in DLBCL
  - ORRs of 15% in MF and 40% in PTCL

- Unlike the dramatic responses observed in Hodgkin's lymphomas, the efficacy of anti PD1/PL1 antibodies as single agents in follicular and large cell lymphoma has been disappointed so far.

- Likely to find a "niche" in selected subtypes of NHL (ie, viral-related lymphomas) or in combination with other agents

Targeted Therapy



Encouraging Early Results from the First in-Human Clinical Trial of Adct-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody Drug Conjugate, in Relapsed/Refractory B-Cell NHL

Study Design

- Adct-402 (loncastuximab tesirine; Lonca-T) is an antibody-drug conjugate of a humanized anti-CD19 antibody conjugated to pyrrolobenzodiazepine (PBD) dimer toxin
- Patients received doses of Lonca-T from 15 to 200 µg/kg

Patients

- 138 patients enrolled
- Median age 63.5 years, median 3 prior therapies, with DLBCL (n=95), MCL, (n=12), FL (n=12), MZL (n=5), CLL (n=4), or other (n=10)

Efficacy

- ORR in DLBCL: 55% (CR: 37%)
- Median PFS in DLBCL: 3.5 months
- Median DOR in DLBCL: 4.9months

Safety

- TEAEs reported in 98%; Grade ≥ 3 in 64%
- Most common Grade ≥ 3 TEAEs:
  - Nonhematologic: increased gamma-glutamyltransferase 14%, fatigue 5%, increased alkaline phosphatase 5%
  - Hematologic: neutropenia 15%, anemia 12%, thrombocytopenia 12%
- 1 DLT reported (worsening of thrombocytopenia at 200 µg/kg) and MTD was not reached

Brad S. Kahl et al. Abstract # 187

Single-Arm Phase II Study of MOR208 Combined With Lenalidomide in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma: L-Mind

Study Design

- Multicenter, phase 2 study of the efficacy and safety of MOR208 (humanized monoclonal anti-CD19 antibody) plus LEN in R/R DLBCL
- Eligibility criteria: adults with ECOP PS 0-1, adequate organ function, R/R to ≥1 and ≤3 prior therapies including anti-CD20 therapy, ineligible for high-dose chemotherapy or ASCT

Patients

- 51 patients enrolled, 44 response evaluable (median follow-up 5.5 months)
- Median age 73.5 years, 47% ≥2 prior lines therapy, 47% IPI score 3-5

Efficacy

- ORR: 52% (CR 32%; PR 20%)
  - 83% (19/23) in remission
- Stable disease: 14%
- Median time to response: 1.8 mo; median time to CR: 2.3 mo
- Median PFS: 11.3 mo (95% CI, 5.4-NR)

Safety

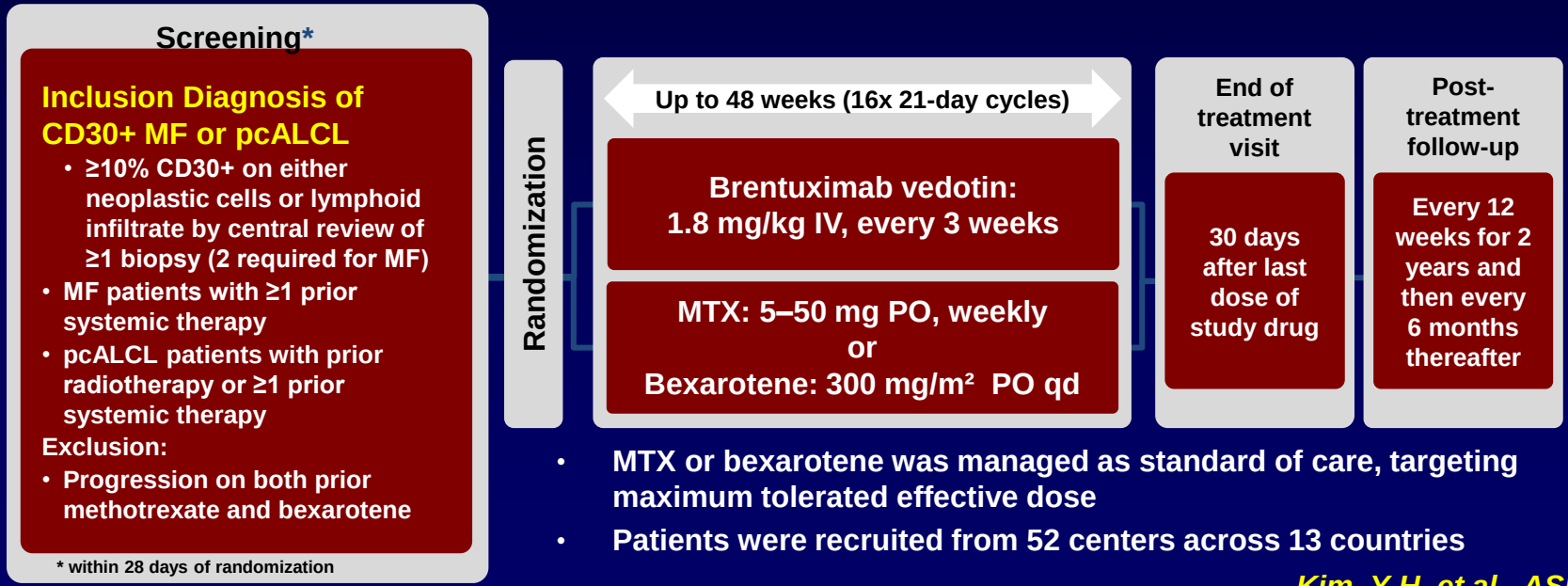
- Most common TEAEs grade ≥3 were neutropenia 36%, thrombocytopenia 10%; pneumonia 10%; leukopenia 8%, hypokalemia 8%
- Serious TEAEs in 8 patients: pneumonia, febrile neutropenia, agranulocytosis, bronchitis, tumor flare, pyrexia, asthenia, pulmonary embolism, arthritis
- 23/51 (45%) patients required LEN dose reduction

Gilles Andre Salles, Abstract # 4123

Targeted Therapy

Phase 3 ALCANZA Trial: Brentuximab vs investigator's choice

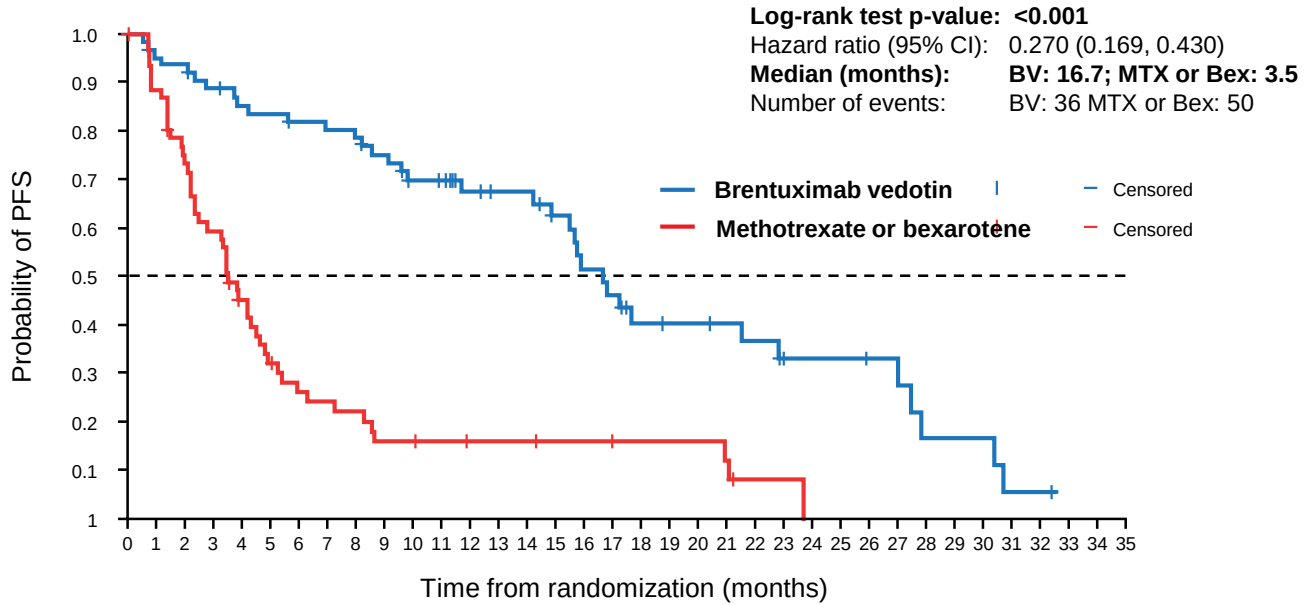
- 131 patients with CD30+ CTCL who received prior systemic or radiation therapy
  - **Primary cutaneous ALCL**: At least one prior systemic or radiation therapy
  - **Mycosis Fungoides**: At least one prior systemic therapy



- 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

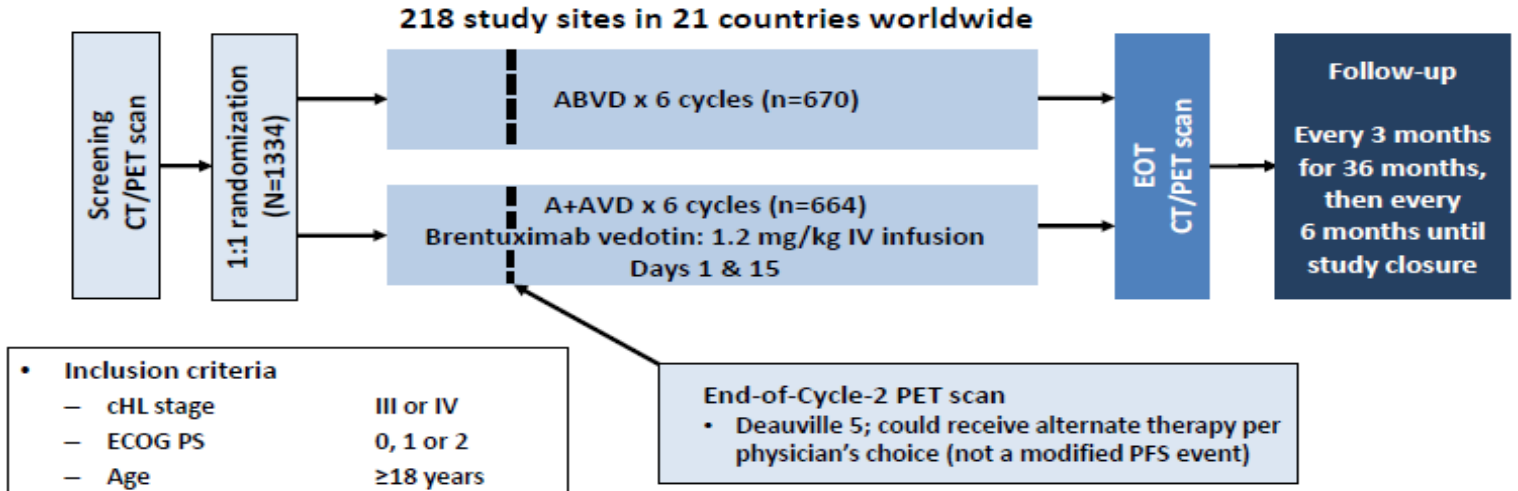
Joseph M. Connors, Wojciech Jurczak, David J. Straus, Stephen M. Ansell, Won Seog Kim, Andrea Gallamini, Anas Younes, Sergey Alekseev, Árpád Illés, Marco Picardi, Ewa Lech-Maranda, Yasuhiro Oki, Tatyana Feldman, Piotr Smolewski, Kerry J. Savage, Nancy L. Bartlett, Jan Walewski, Robert Chen, Radhakrishnan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

JM Connors et al. NEJM . December 2017

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



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

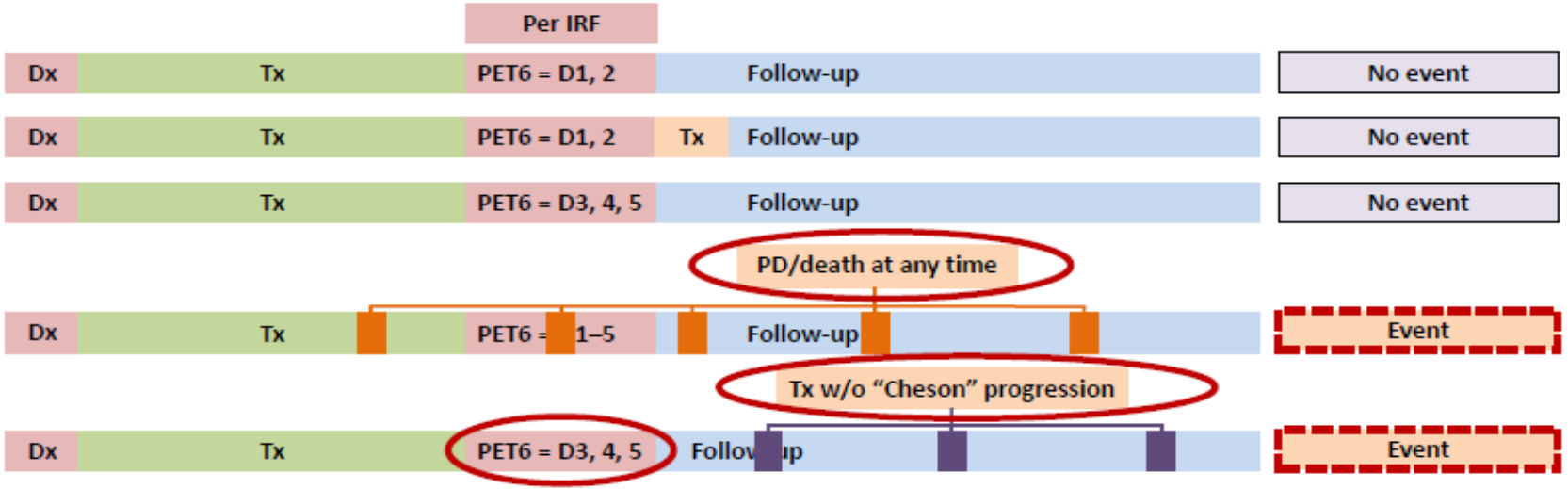
JM Connors et al. NEJM . December 2017

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

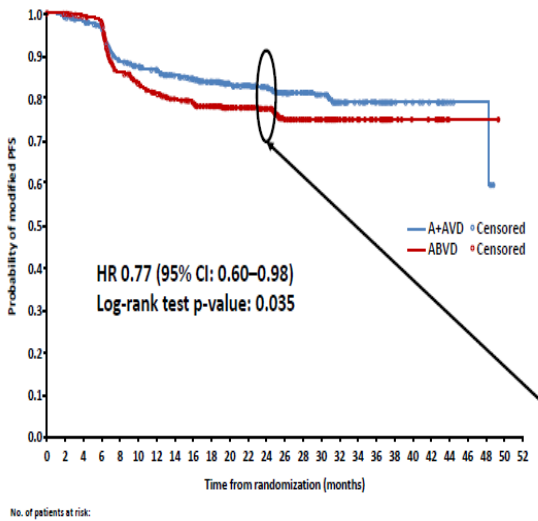


D, Deauville score; Dx, diagnosis; IRF, independent review facility; PD, progressive disease; PET6, end-of-cycle-6 PET; Tx, treatment

Brentuximab Vedotin in Frontline Hodgkins

(ASH 2017-Plenary presentation)

Modified PFS per independent review



Number of events

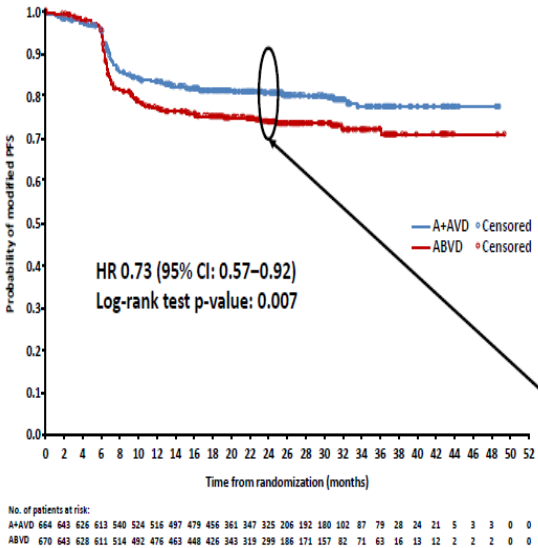
Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

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

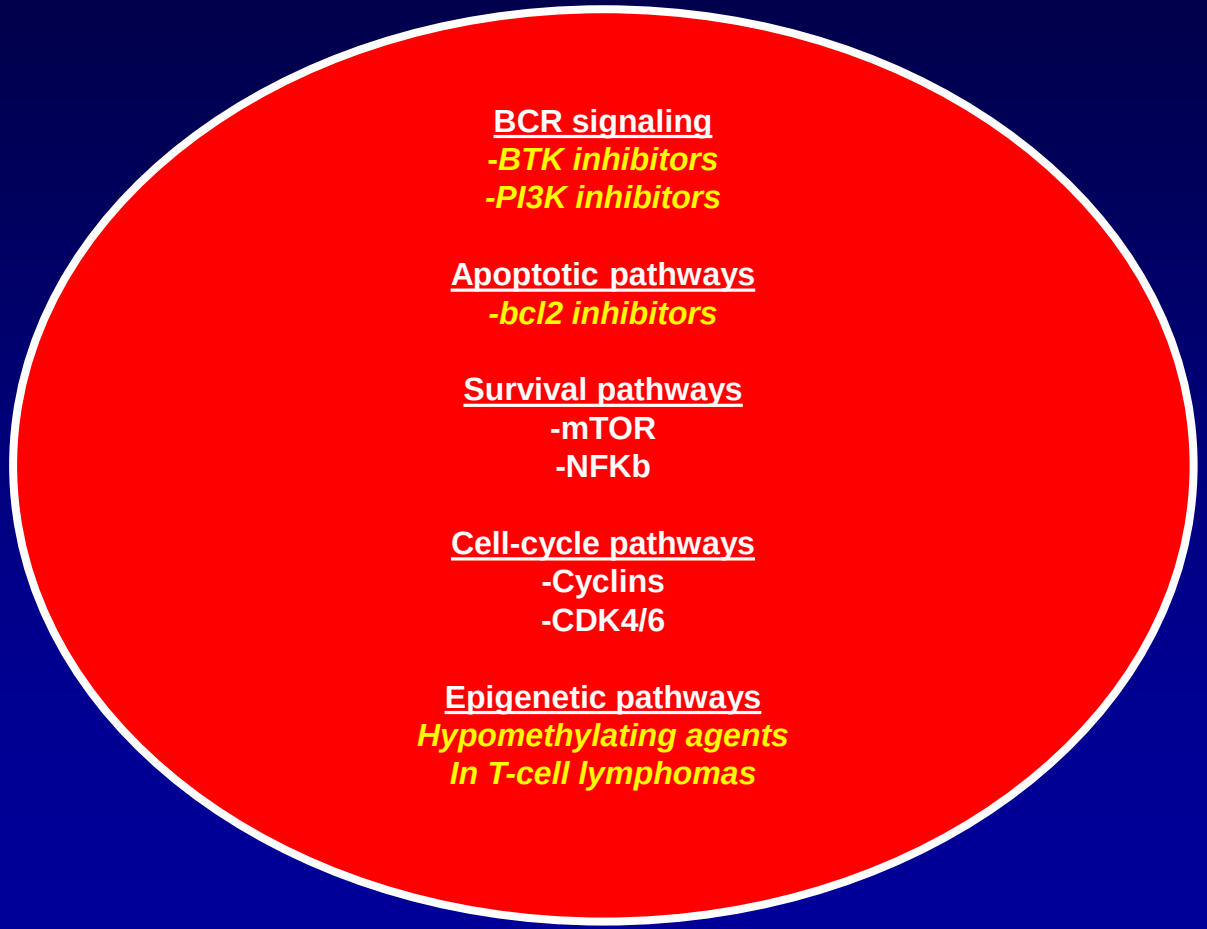
Brentuximab Vedotin in Frontline Hodgkins (ASH 2017-Plenary presentation)

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

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 MCL

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
  - Venetoclax
  - 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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