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DIFFUSE LARGE B-CELL LYMPHOMA AND T-CELL LYMPHOMA

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Research To Practice
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Atlanta, GA

COLUMBIA UNIVERSITY MEDICAL CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Disclosures

Consulting Agreements	Celgene Corporation, Mundipharma International Limited
Contracted Research	Celgene Corporation, Spectrum Pharmaceuticals Inc, Mundipharma International Limited

Case presentation 11: Dr Nadeem

71-year-old woman

- January 2017: Presented with B symptoms and adenopathy above and below diaphragm
  - Biopsy: DLBCL
  - GCB phenotype with MYC/Bcl-2 double expression with Bcl-6/Bcl-2 rearrangements but no MYC rearrangement
- February 2017: Initiated R-CHOP
  - Response after 2 cycles, slightly better after 4 cycles
  - 5-cm area in abdomen still PET-positive after 6 cycles; biopsy revealed persistent DLBCL
- June 2017: Initiated R-GDP
  - Good response after 2 cycles, PD after 4 cycles
  - Currently being evaluated for CAR-T therapy

PET scan after R-CHOP

Case presentation 12: Dr Chen

70-year-old woman

- 2015: Presented with cough and shortness of breath
  - Imaging: Pleural effusion
  - Cytology, flow cytometry from pleural fluid negative for malignancy
  - Axillary lymph node biopsy: Angioimmunoblastic T cell lymphoma
  - Bone marrow biopsy: Negative
  - PET/CT: Lymph nodes in chest, abdomen
  - Extranodal involvement: Pleural effusion
- CHOP x 6 (CR) → ASCT (CR)
- Currently under observation

Diffuse Large B-Cell Lymphoma and T-Cell Lymphoma

- Improving on R-CHOP in DLBCL
  - Lenalidomide plus
  - Ibrutinib plus
- CAR-T in DLBCL
- Broadening the Application of Brentuximab Vedotin to CTCL: The ALCANZA Study
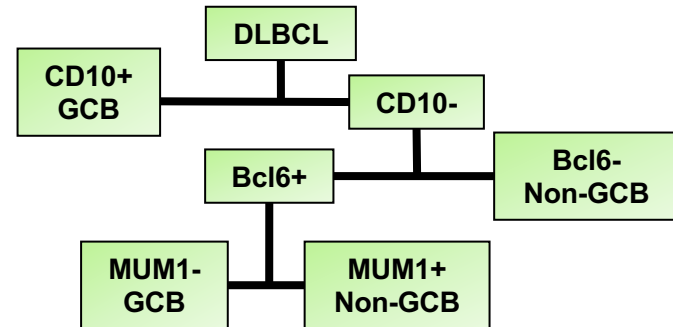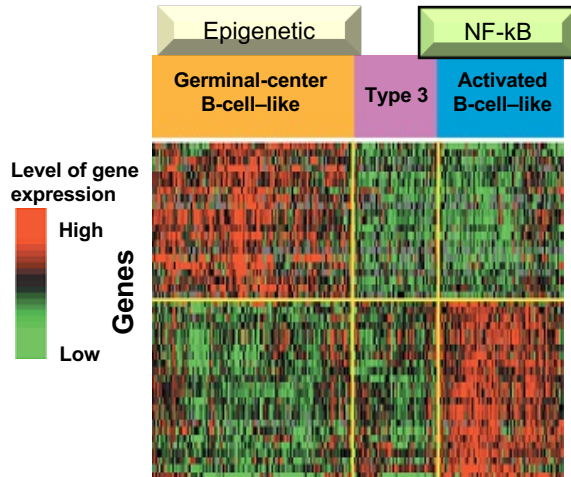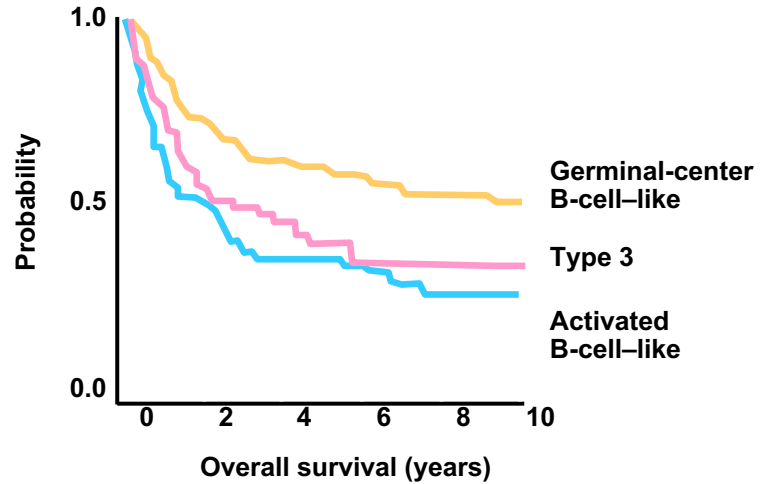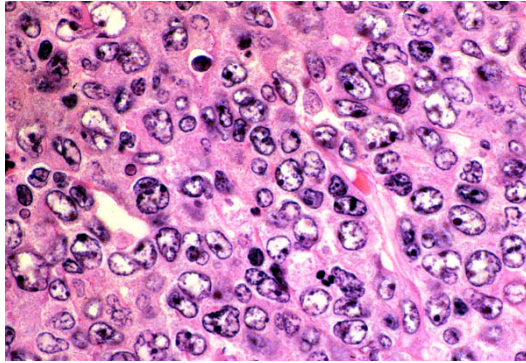
DIFFUSE LARGE B-CELL LYMPHOMA: IS NOT ONE DISEASE

Rosenwald A et al. *N Engl J Med*. 2002;346:1937-1947

Hans 2002

ASSIGNING COO IN CLINICAL PRACTICE
NANOSTRING TECHNOLOGY
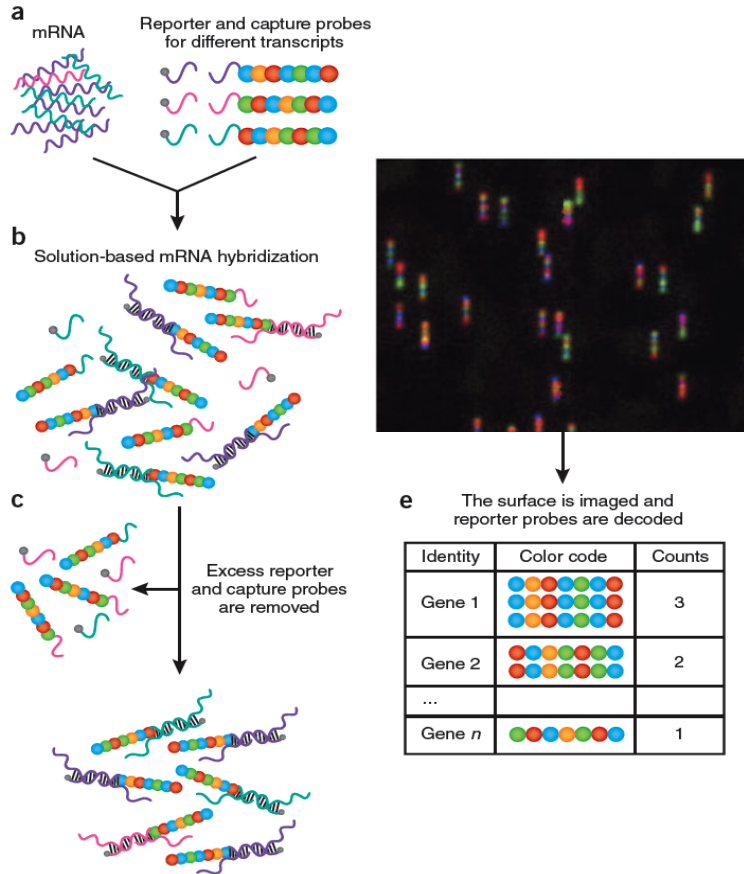
- Gene expression assay can utilize **total RNA isolated from Formalin Fixed Paraffin Embedded (FFPE) samples**

- **Powerful tool for validating biomarkers** from large numbers of samples

- Uses **digital gene expression and color-coded molecular barcodes** allowing the analysis of the expression levels of up to 800 genes simultaneously

- The Barcode is made up of an **unique string of colored fluorophores. Identification gene depends on the order of fluors on the string**.

- **Its speed and ability to be performed on FFPE make it an ideal clinical based assay for determining COO**

ADDITION OF LENALIDOMIDE TO R-CHOP IN UNTREATED DLBCL IMPROVES NON-GCB OUTCOMES

	Mayo Clinic MC078E*		FIL REAL07**
	R^2-CHOP	R-CHOP	R^2-CHOP
N	55 (51 evaluable)	87 (83 evaluable)	49
Regimen	R-CHOP21 + lenalidomide 25mg days 1-10	R-CHOP21	R-CHOP21 + lenalidomide 15mg days 1-14
ORR	51 (100%)	68 (83%)	45 (92%)
CR	37 (73%)	56 (67%)	42 (86%)
PFS at 24 mo	59%	52%	80%

	GCB n = 31	Non-GCB n = 20	GCB n = 57	Non-GCB n = 26	GCB n = 16	Non-GCB n = 16
ORR	31 (100%)	20 (100%)	50 (88%)	18 (69%)	14 (88%)	14 (88%)
CR	23 (74%)	16 (80%)	43 (75%)	13 (50%)	13 (81%)	14 (88%)
PFS at 24 mo	59%	**60%**	64%	**28%**	71%	**81%**
OS at 24 mo	75%	**83%**	74%	**46%**	88%	**94%**

Two independent studies generate similar results

*Nowakowski *et al*. ASCO 2014 Oral Session
**Vitolo, et al. Lancet Oncol 2014;15:730-37

PFS and OS in GCB and Non-GCB DLBCL For Patients Treated With R-CHOP and R²-CHOP[1,2]

Historical R-CHOP
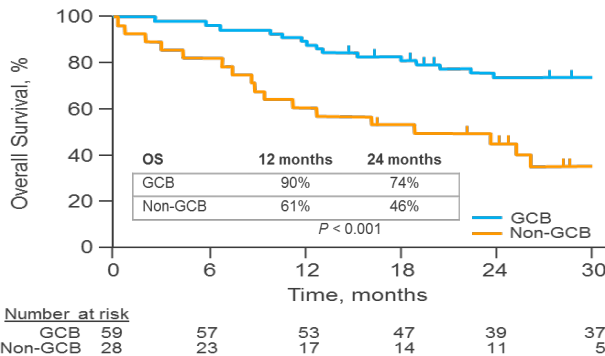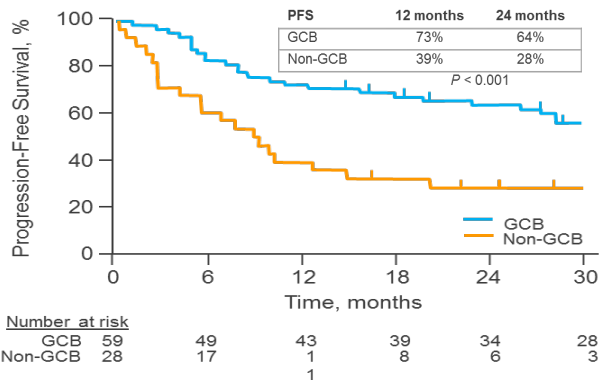
R²-CHOP
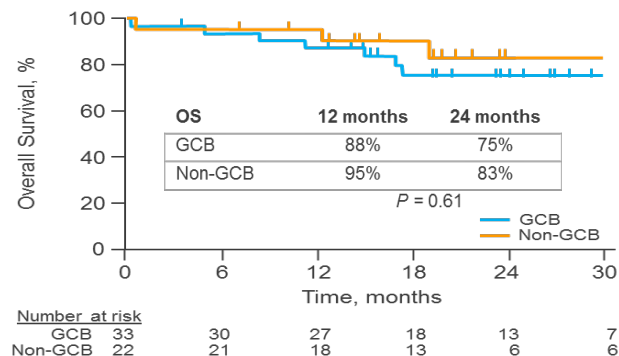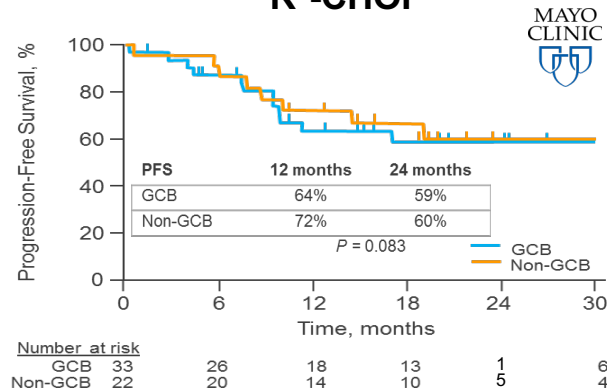
Non-GCB subtype was defined by Hans algorithm.

1.Nowakowski et al. *J Clin Oncol*. 2015;33:251-257. 2. Hans et al. *Blood*. 2004;103:275-282.

ROBUST CLINICAL STUDY SCHEMA
RESULTS EXPECTED LATE 2018
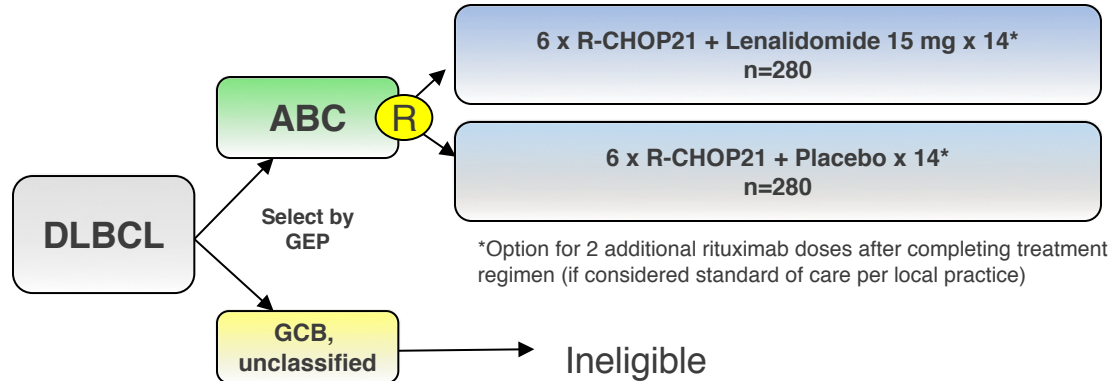
- Newly diagnosed DLBCL of ABC type ONLY
- IPI ≥ 2; ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = PFS
- N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 mo)

Phase 2 Study: Ibrutinib for Relapsed/Refractory DLBCL: Superiority in ABC……??

Wilson, et al 2012
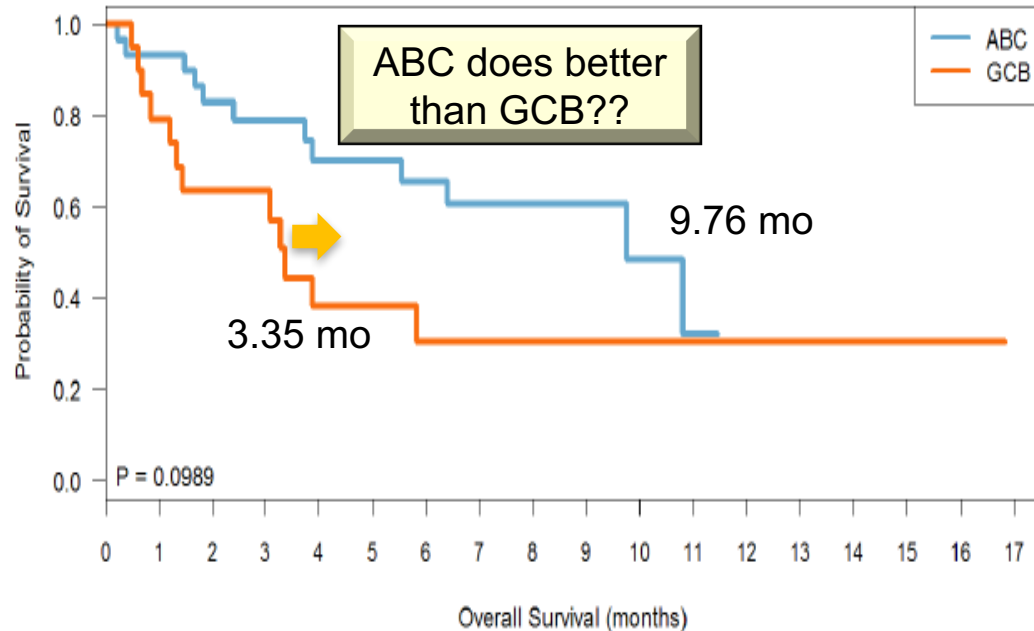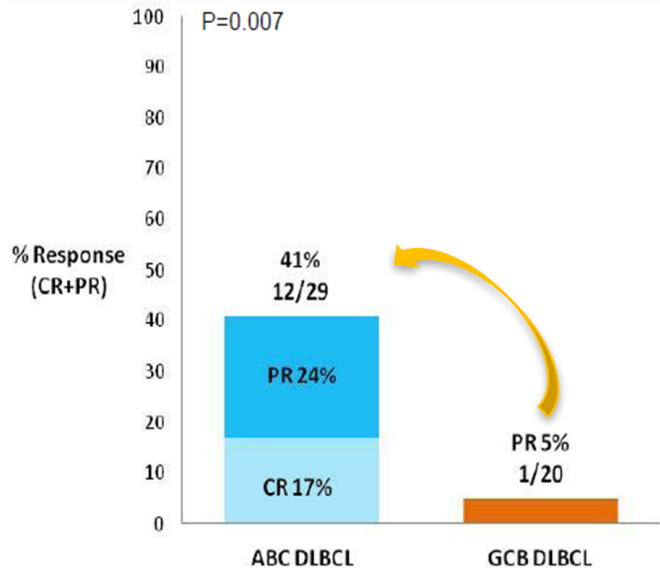
IBRUTINIB + R-CHOP:
WELL TOLERATED & ACTIVE COMBINATION

Assigned Ibrutinib dose	Part 1		
	280 mg N = 7	420 mg N = 4	560 mg N = 6
Pts with ≥ 1 AE G ≥ 3, n (%)	6 (85.7)	4 (100.0)	3 (50.0)
Neutropenia, n (%)	6 (85.7)	4 (100.0)	5 (83.3)
Thrombocytopenia, n (%)	4 (57.1)	1 (25.0)	2 (33.3)
Anemia, n (%)	4 (57.1)	0 (0.0)	1 (16.7)
Febrile neutropenia, n (%)	2 (28.6)	0 (0.0)	0 (0.0)
Syncope, n (%)	1 (14.3)	1 (25.0)	1 (16.7)

	280 mg (n=7)	420 mg (n=4)	560 mg (n=21)	Combined (n=32)	All (n=33)
Overall response	6 (86%)	4 (100%)	20 (95%)	30 (94%)	30 (91%)
Complete response	5 (71%)	3 (75%)	15 (71%)	23 (72%)	23 (70%)
Partial response	1 (14%)	1 (25%)	5 (24%)	7 (22%)	7 (21%)
Stable disease	0	0	0	0	0
Progressive disease	0	0	0	0	0
Not evaluable	1 (14%)	0	1 (5%)	2 (6%)	3 (9%)

PLACEBO-CONTROLLED PHASE 3 STUDY OF IBRUTINIB IN COMBINATION WITH R-CHOP IN PATIENTS WITH NEWLY DIAGNOSED NON-GCB DLBCL

- **Disease:** Newly diagnosed DLBCL non-GCB (by Hans, not nanostring)
- **Schema (N=800):**
- **Stratification**
  – Stratify by R-IPI (1-2 vs. 3-5), region, and number of pre-specified treatment cycles (6 vs. 8)
- **Primary Objective:**
  – Event-free survival
- **Key Secondary Objectives:**
  – Progression-free survival
  – Overall survival
  – Complete response rate
  – Safety

This study completed accrual

Randomize

1:1

ARM A
R-CHOP + placebo PO

ARM B
R-CHOP + ibrutinib 560 mg PO until disease progression
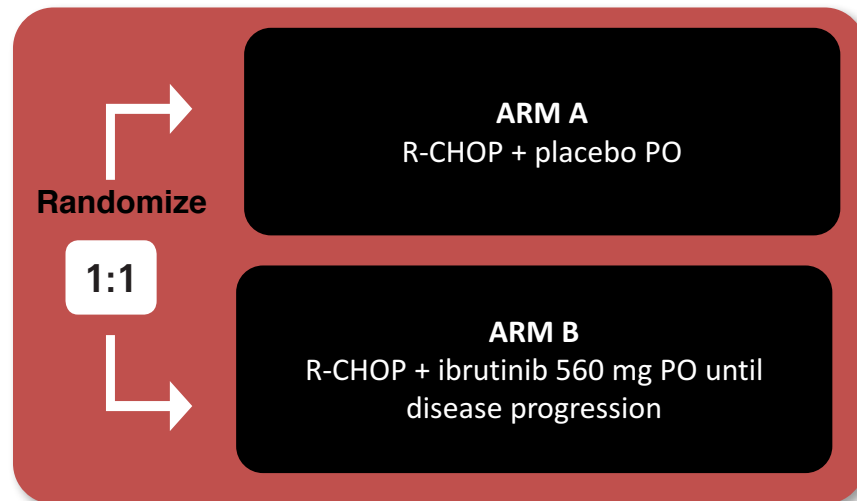
Abbreviations: DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; PO, orally; R-IPI, revised International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

HOW CAR-T THERAPY WORKS
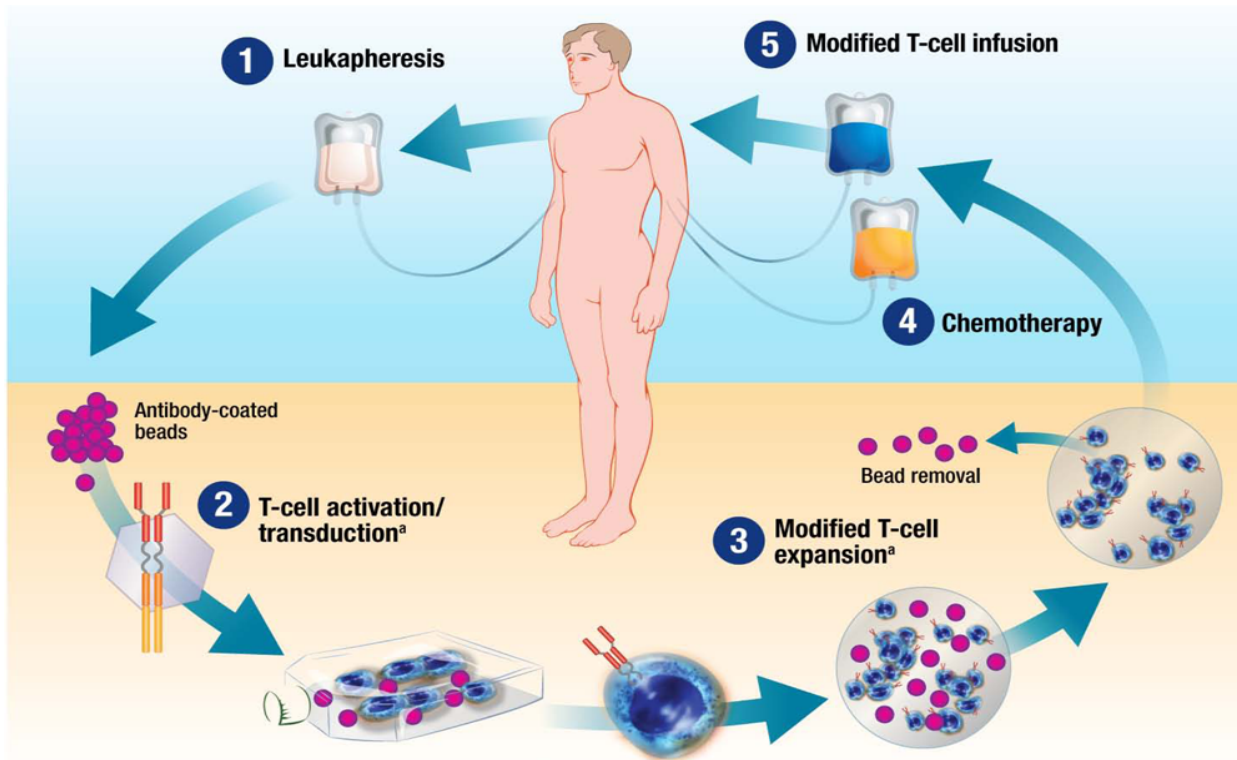
T cells transduced ex vivo with a lentivirus encoding anti-CD19
scFv linked to 4-1BB and CD3-ζ signaling domains

CAR-T Path to Approval

NOVARTIS

BLA – March 2017

Breakthrough – April 2017

ODAC – July 2017

Approval –*for ALL up to age 25*

Kite Pharma

Breakthrough – Dec. 2015

BLA – March 2017

ODAC – *Aug-Sept 2017*

Approval – *Recent for aggressive non-Hodgkin lymphoma*

JUNO THERAPEUTICS

Breakthrough JCAR015 – Nov. 2014

Breakthrough JCAR017 – Dec. 2016

JCAR015 discontinued – March 2017

Other cell therapy companies:
Bluebird Bio, Atara, Kiadis, Celgene, Cellenkos, Cellectis, Bellicum, Magenta, Viracyte…

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A Comprehensive Cancer Center Designated by the National Cancer Institute

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

CAR-T Cells – Efficacy and Toxicity in Acute Lymphoblastic Leukemia (ALL)

Product	Disease	N	ORR / CR	Durability	Toxicity
CTL019	Pediatric ALL	50	82% CR/CRi 82% MRD(-)	60% relapse-free at 6 mo. 89% 6-mo. survival	Gr≥3 CRS 48% Gr≥3 Neuro 15%
KTE-C19	ALL >25% blasts	5	80% CR/CRp 20% MRD(-)	Not reported	No severe CRS Gr≥3 Neuro 60%
JCAR015	Ped. ALL	30	87% CR	Too early	Gr≥3 CRS 13% Neuro 30%

MAJOR TOXICITIES: (1) Cytokine Release Syndrome (CRS) – fever, hypotension, hypoxia, hemodynamic instability, transaminitis vent support [immediate to D7]
(2) Neurologic – difficulty writing a sentence, confusion, tremors, aphasia, encephalopathy (correlates with high CAR-T and/or cytokines [D5-14]

CAR-T Cells – Efficacy and Toxicity
Diffuse Large B-Cell Lymphoma

Product	Disease	N	ORR / CR	Durability	Toxicity
KTE-C19	DLBCL, TFL, PMBCL	101	82% / 54%	44% response (39% CR) at 8.7 mo.	Gr≥3 CRS 13% Gr≥3 Neuro 28% Fatal 3%
JCAR017	DLBCL, TFL	20	80% / 60%	42% response at 3 mo.	No severe CRS Neurotox 14%
CTL019	FL	14	79% / 50%	77% progression-free at 1 yr	Gr≥3 CRS 14% 1 Fatal Neurotox
CTL019	DLBCL	13	52% / 38%	CRs durable	Gr≥3 CRS 8% Gr≥3 Neuro 8%

Reproducible Clinical Activity Across the CAR T in Study

Axicabtagene Ciloleucel: CD19 CAR-T IN DLBCL

	Recipients of Axicabtagene Ciloleucel (N=101)
Objective Response Rate (95% CI)	73 (72%) (62, 81)
Complete Remission Rate (95% CI)	52 (51%) (41, 62)
Partial Remission Rate (95% CI)	21 (21%) (13, 30)

TIME TO EVENT METRICS

DOR (Months) Median (95% CI) Range	9.2 (5.4, NE) 0.03, 14.4+
DOR if best response is CR (mo) Median 95% CI Range	NE (8.1, NE) 0.4, 14.4+
DOR if Best Response is PR (mo) Median 95% CI Range	2.1 (1.3, 5.3) 0.03+, 8.4+
Median Follow-up for DOR (Months)	7.9

ALCANZA: First Reported Phase 3 Trial of Brentuximab vedotin vs Standard Therapy in CTCL

Randomised, open-label, phase 3 trial of brentuximab vedotin vs physician's choice (methotrexate or bexarotene) in patients with CD30+ CTCL

Screening

Inclusion:
- Adults with diagnosis of CD30+ MF or pcALCL
  - ≥10% CD30+ on either neoplastic cells or lymphoid infiltrate by central review of ≥1 biopsy (2 required for MF)
- MF patients with ≥1 prior systemic therapy
- Patients with pcALCL with prior radiotherapy or ≥1 prior systemic therapy

Exclusion:
- Progression on both prior methotrexate and bexarotene

**Within 28 days of randomization*

Randomisation

Up to 48 weeks (16x 21-day cycles)

Brentuximab vedotin:
1.8 mg/kg IV, every 3 weeks

Methotrexate: 5–50 mg PO, weekly
OR
Bexarotene: 300 mg/m² (target dose) PO, daily

End of treatment visit

30 days after last dose of study drug

Post-treatment follow-up

Every 12 weeks for 2 years and then every 6 months thereafter

- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose

- Patients were recruited from 52 centers across 13 countries

CD30, cluster of differentiation 30; CTCL, cutaneous T-cell lymphoma; IV, intravenously; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma; PO, orally

Kim YH, et al. J Invest Dermatol 2017;137(suppl 1):S45, abstract 262, oral presentation at SID 2017.

ALCANZA: Primary and Key Secondary Endpoint Analyses (ITT)

Endpoint	Brentuximab vedotin (n=64)	Methotrexate or bexarotene (n=64)	Difference between arms (95% CI)	p-value
Primary				
ORR4, n (%)	36 (56.3)	8 (12.5)	43.8 (29.1, 58.4)	<0.0001
Key secondary endpoints				
CR, n (%)	10 (15.6)	1 (1.6)	14.1 (-4.0, 31.5)	0.0046 [adj]
Median PFS, months	16.7	3.5		0.0001 [adj] (HR 0.270; 95% CI: 0.169, 0.430)
Mean maximum reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9 (-26.6, -11.2)	<0.0001 [adj]

Adj, adjusted p-value calculated from a weighted Holm's procedure
CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent to treat;
ORR4, overall response rate lasting ≥4 months; PFS, progression-free survival

ALCANZA:
ORR4 Favors Bv Across Key Subgroups

Favors brentuximab vedotin

Response/ N (%)

Subgroup	Brentuximab vedotin	Methotrexate or bexarotene	Difference in rates (95% CI)
Overall	36/64 (56.3)	8/64 (12.5)	43.8 (29.1, 58.4)
MF	24/48 (50.0)	5/49 (10.2)	39.8 (19.9, 56.2)
pcALCL	12/16 (75.0)	3/15 (20.0)	55.0 (19.7, 80.4)
Baseline ECOG PS 0	29/43 (67.4)	6/46 (13.0)	54.4 (37.3, 71.5)
Baseline ECOG PS ≥1	7/21 (33.3)	2/18 (11.1)	22.2 (-10.2, 51.2)
Male	19/33 (57.6)	5/37 (13.5)	44.1 (21.3, 63.3)
Female	17/31 (54.8)	3/27 (11.1)	43.7 (18.5, 64.7)
Age <65 years	20/36 (55.6)	2/40 (5.0)	50.6 (29.3, 68.3)
Age ≥65 years	16/28 (57.1)	6/24 (25.0)	32.1 (6.9, 57.4)
Europe	23/37 (62.2)	3/35 (8.6)	53.6 (32.7, 71.3)
Non-Europe	13/27 (48.1)	5/29 (17.2)	30.9 (4.2, 53.5)
Bexarotene	36/64 (56.3)	6/38 (15.8)	40.5 (23.7, 57.3)
Methotrexate	36/64 (56.3)	2/26 (7.7)	48.6 (26.7, 67.7)
Skin only	21/31 (67.7)	5/30 (16.7)	51.1 (27.3, 71.0)
Skin and other involvement	15/33 (45.5)	3/34 (8.8)	36.6 (12.3, 56.3)
Baseline skin tumor score >0	26/41 (63.4)	2/38 (5.3)	58.2 (38.1, 74.1)
Baseline skin tumor score 0	10/23 (43.5)	6/26 (23.1)	20.4 (-5.5, 46.3)

−25   0   25   50   75   100

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MF, mycosis fungoides; ORR4, overall response rate lasting ≥4 months; pcALCL, primary cutaneous anaplastic large cell lymphoma

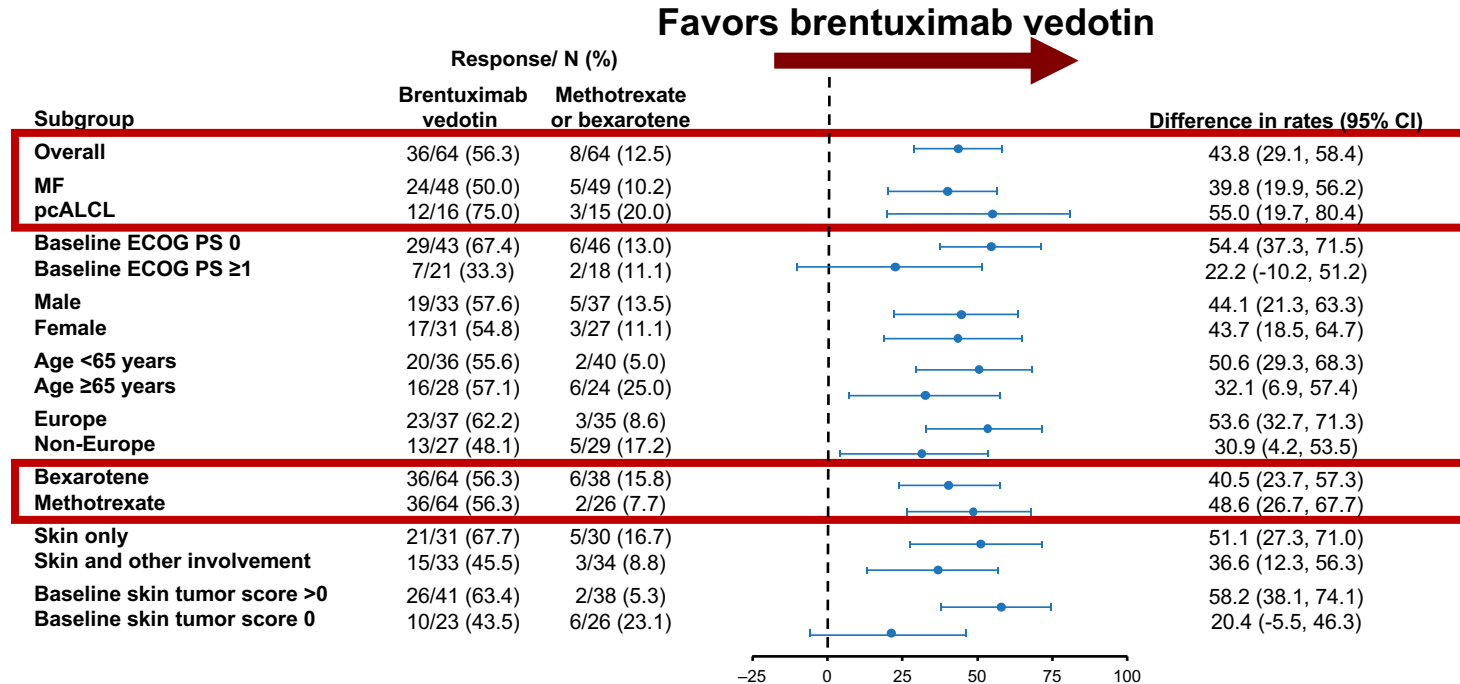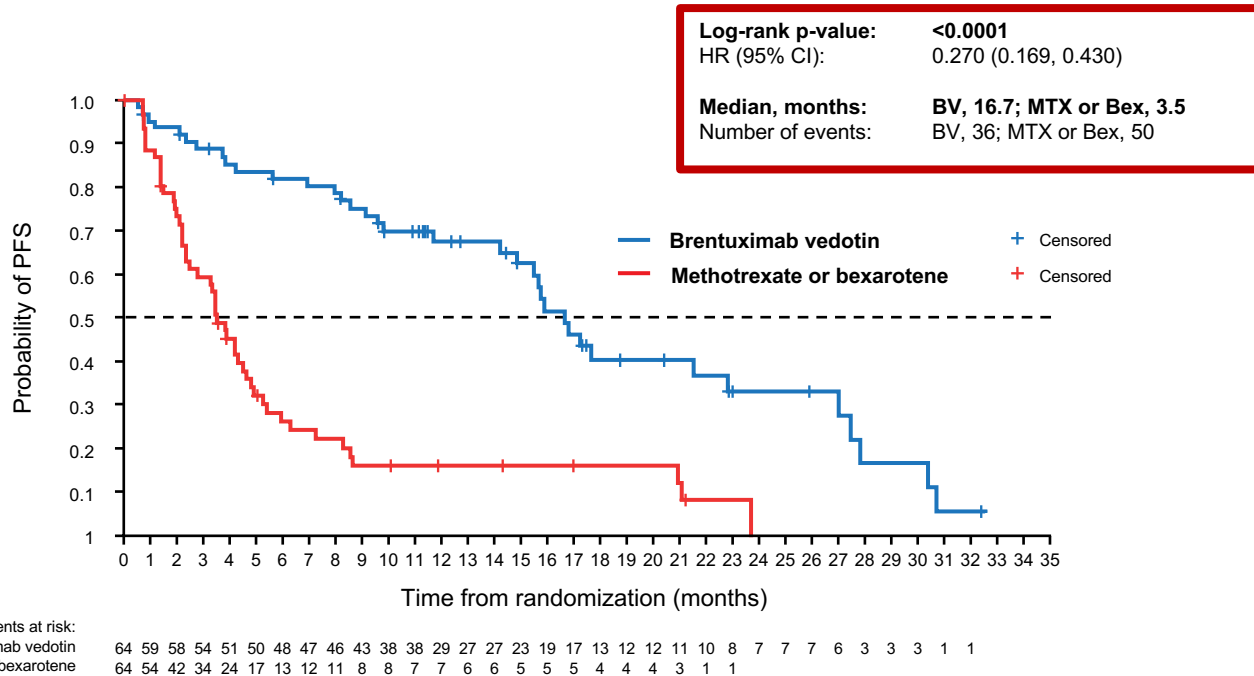Kim YH, et al. J Invest Dermatol 2017;137(suppl 1):S45, abstract 262, oral presentation at SID 2017.

ALCANZA
PROGRESSION-FREE SURVIVAL (ITT)

Assessed by independent review
Bex, bexarotene; BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; MTX, methotrexate; PFS, progression-free survival

Kim YH, et al. J Invest Dermatol 2017;137(suppl 1):S45, abstract 262, oral presentation at SID 2017.