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Immune Based Treatment Options in Lymphoma: CAR-t cells

Leo I. Gordon, MD, FACP

Summary

- We are entering a new era in treatment for lymphomas
- CAR T-cell therapy may represent one of the more effective immunotherapeutic options
- Challenges
  - Time to manufacture
  - Patient selection and toxicity management
  - integration with or replacement of existing modalities (chemotherapy, small molecule inhibitors, autologous vs allogeneic stem transplant)
  - cost
- CAR T-cell therapy likely to alter how we treat DLBCL

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Coley's toxin

Sometimes referred as MBV for mixed bacterial vaccine, Coley's toxin was the first attempt to use immunotherapy and hyperthermia against cancer. William B. Coley MD, a bone surgeon at MSK from 1891 to 1936 developed interest when his first patient, a young girl died from metastatic sarcoma.

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

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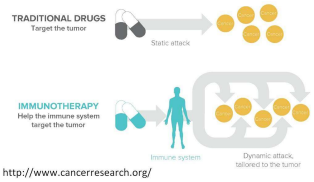
The Case for Cancer Cellular Therapy

- Immunotherapy is a "living drug"
- Immune system can evolve to treat the tumor
- Immunotherapy can cure some cancers



http://www.cancerresearch.org/

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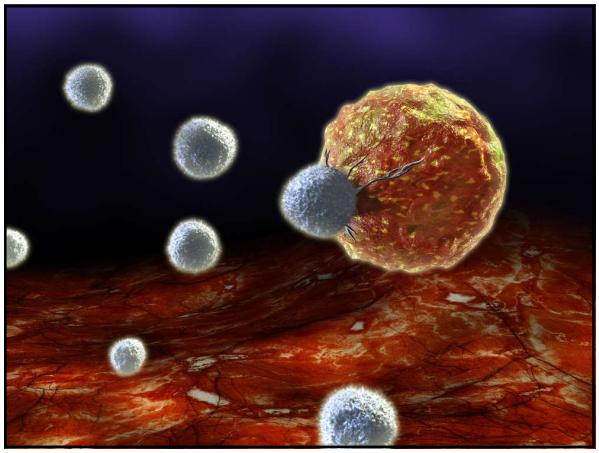
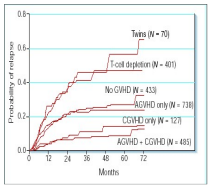
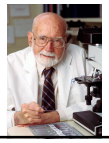
Presented By Carl June at 2016 ASCO Annual Meeting

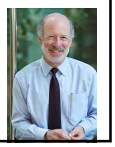


Graft vs. Leukemia/Lymphoma: The case for allogeneic transplant



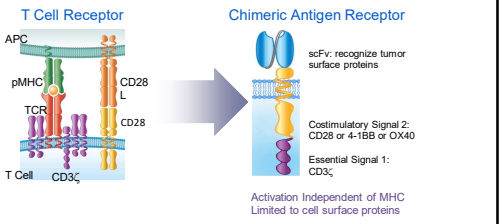
- **Presence of GvHD reduces the likelihood of recurrence in leukemia patients who had an allogeneic transplant.**
- **Provided rationale for "mini" transplants to take advantage of GvL effect without high dose chemotherapy**





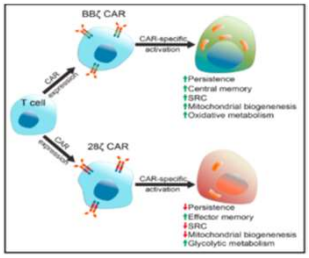
CAR Design: Critical Elements

CAR T cells are genetically altered to express CAR on the cell surface.



Activation Independent of MHC
Limited to cell surface proteins

CAR Construct: CD28 vs 4-1BB



Kalawekar at el, 2016

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CAR Construct: Antigen Selection

- CD19 expression is generally restricted to B cells and B cell precursors[1]
  - CD19 is not expressed on hematopoietic stem cells or other tissue
- CD19 is expressed by most B-cell malignancies
  - CLL, B-ALL, DLBCL, FL, MCL

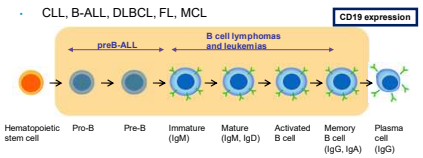

Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

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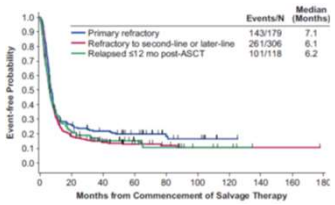
SCHOLAR-1 – Poor outcomes in R/R DLBCL

Refractory DLBCL, n=636; ORR 26%, CR 7%; median OS 6.3 months



Crump et al., Blood 2017

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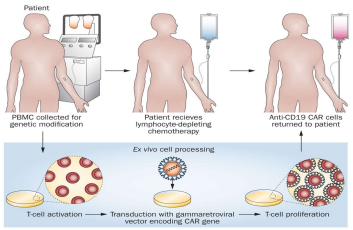
CAR T manufacturing and administration



*large range on timing for processing

Kochenderfer, J. N. & Rosenberg, S. A. (2013) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.46

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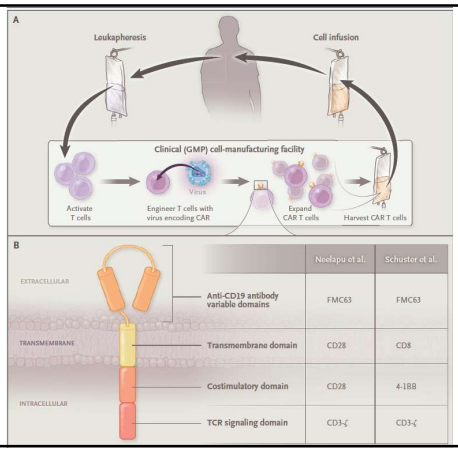
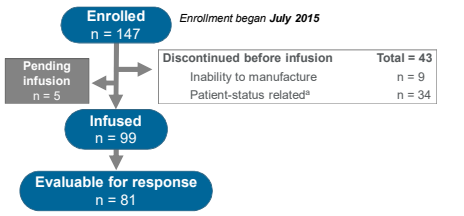


JULIET: Study Status (Data cut March 2017)



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[a] Death (n = 16); physician decision (n = 12); subject decision (n = 3); adverse event (n = 2); protocol deviation (n = 1).
Schuster SJ, et al. *Blood.* 2017; 130(23):[abstract 577].

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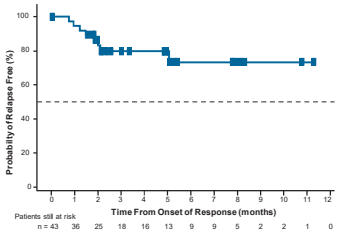
Duration of Response, 74% Relapse-free at 6 Months



- **Median DOR and OS not reached**
- Most patients achieving CR at month 3 have remained in CR
- No patients proceeded to transplant while in response

Response Rate	
Best overall response (CR + PR)	59%
CR[1]	43%
PR[1]	16%
SD[1]	12%
PD[1]	24%
Overall response rate (CR + PR) at 3 months	45%
CR[1]	37%
PR[1]	8%

CR, complete response; DOR, duration of response; OS, overall response.
Efficacy analysis set = All patients who received a tisagenlecleucel infusion at least 3 months prior to data-cut date.
Schuster SJ, et al. *Blood.* 2017; 130(23):[abstract 577].

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JULIET: Adverse Events of Special Interest

	(N = 99)		
AESI[a]	All grade, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	58	15	8
Neurological events	21	8	4
Prolonged cytopenia[c]	36	15	12
Infections	34	18	2
Febrile neutropenia	13	11	2

- **No deaths attributed to tisagenlecleucel, CRS or cerebral edema**
- 26 (26%) patients were infused as outpatients
- 20/26 (77%) patients remained outpatient for ≥ 3 days after infusion

[a] Occurring within 8 weeks of tisagenlecleucel infusion. [b] Cytokine release syndrome was graded using the Penn scale. [c] At day 28.
AESI, adverse events of special interest.
Schuster SJ, et al. *Blood.* 2017; 130(23):[abstract 577].

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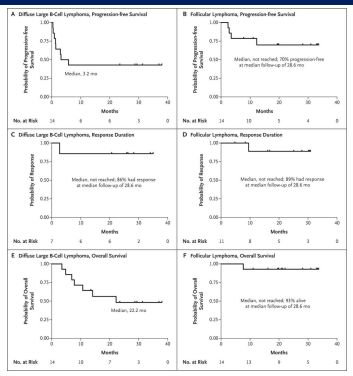
Progression-free Survival, Response Duration, and Overall Survival.



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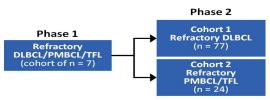
Schuster SJ et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1708566

ZUMA-1 Study Design Summary and Outcomes



Of 101 patients with refractory aggressive NHL treated with axi-cel in the Phase 2 multicenter ZUMA-1 study:

- ORR: 82%; CR, 54%
  - 44% in ongoing response
  - 39% in ongoing CR
- Grade ≥3 CRS: 13%
- Grade ≥3 NE: 28%
- Grade ≥3 AEs resulting in death (n=3)

AE, adverse events; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; NE, neurologic event; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma

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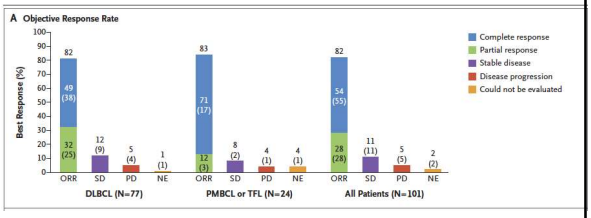
Objective Response Rate among the 101 Treated Patients.



Neelapu SS et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1707447

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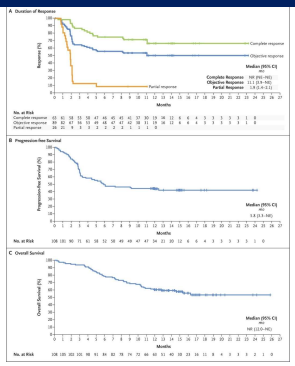
Kaplan–Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.



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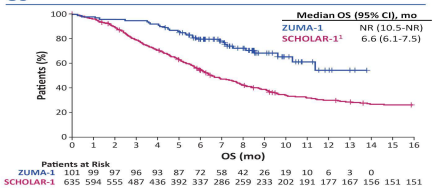
Neelapu SS et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1707447

Results

OS



- Median OS for ZUMA-1 was not reached
- 6-month OS in ZUMA-1 was 80% vs. 55% in SCHOLAR-1

Locke & Neelapu et al ASCO 2017 8

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Conclusions

- ZUMA-1 is the first pivotal trial of anti-CD19 CAR T cells in refractory aggressive NHL and has demonstrated significant clinical benefit for patients lacking curative options
- Axi-cel significantly improved ORR ($P < .0001$)
  - CR rate of 54% is ~7-fold higher than the historic control rate of 8%[1]
  - 44% have an ongoing response with a median DOR of 8.2 months
- Axi-cel showed durable and high ORR rates even in disease with poor prognostic indicators, such as ABC DLBCL and presence of bulky or extranodal disease
- CRS and NEs were generally reversible and rates decreased over course of study
- Clinical response rates were comparable across CD19 expression levels and between patients who did or did not receive tocilizumab and/or steroids

Locke & Neelapu et al ASCO 2017 13

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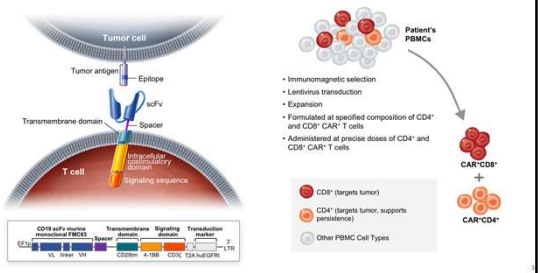
High Durable CR Rates in R/R Aggressive B-NHL Treated with JCAR017 (lisocabtagene maraleucel; liso-cel) (TRANSCEND NHL 001): Defined Composition CD19-Directed CAR T Cell Product Allows for Dose Finding and Definition of Pivotal Cohort

Jeremy S. Abramson,[1] M. Lia Palomba,[2] Leo I. Gordon,[3] Matthew Lunning,[4] Jon Arnason,[5] Michael Wang,[6] Andres Forero-Torres,[7] David Maloney,[8] Tina Albertson,[9] Jacob Garcia,[9] Daniel Li,[9] Benhuai Xie,[9] Tanya Siddiqi[10]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; [4]University of Nebraska Medical Center, Omaha, NE; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]University of Texas MD Anderson Cancer Center, Houston, TX; [7]University of Alabama at Birmingham, Birmingham, AL; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]Juno Therapeutics, Seattle, WA; [10]City of Hope National Medical Center, Duarte, CA

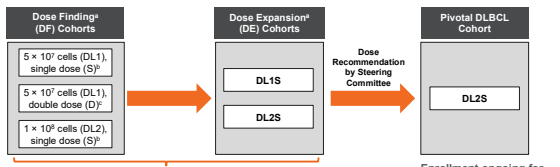
JCAR017 (lisocabtagene maraleucel; liso-cel)

CD19-Directed Defined Cell Product



Multicenter, Seamless Design Pivotal Trial

(TRANSCEND NHL 001; NCT02631044)



Enrollment ongoing for pivotal patient population

Data will be presented from DF and DE DLBCL cohorts

- 91 patients treated (**FULL**)[d]
- 67 patients treated in identified pivotal patient population (**CORE**)[e]

[a] Disease-specific Dose Finding and Dose Expansion cohorts enrolled (DLBCL and MCL).
[b] Administered on Day 1.
[c] Administered on Day 1 and Day 14.
[d] DLBCL FULL cohort: DLBCL NOS de novo and transformed from any indolent lymphoma, ECOG 0-2.
[e] DLBCL CORE cohort: DLBCL NOS de novo and transformed from FL, ECOG 0-1, high grade B-cell lymphoma.

TRANSCEND NHL 001 (NCT02631044)

FOLLOW-UP
Initial: 12 months
On-study: 24 months
Long-term: up to 15 years after last JCAR017 treatment

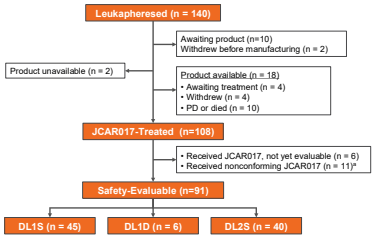
ENROLLMENT COHORTS
- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed FL)
  - High grade B-cell lymphoma (double/triple hit)
  - DLBCL transformed from CLL or MZL
  - PMBCL
  - FL3B
- MCL after 1 line of therapy

Pivotal population (CORE)
All enrolled DLBCL population (FULL)

PATIENT ELIGIBILITY
- Prior SCT allowed[b]
- Secondary CNS involvement allowed
- ECOG 0-2[b]
- No minimum absolute lymphocyte count requirement for apheresis

FLU, fludarabine; CY, cyclophosphamide.
[a] Therapy for disease control allowed.
[b] ECOG 2 and prior allogeneic HSCT excluded from pivotal cohort.

CONSORT Diagram: DLBCL Cohort

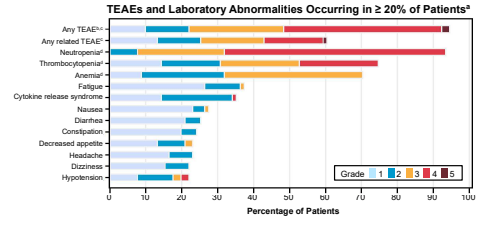


- **Product available for 98% (126/128) of patients apheresed in DLBCL cohort**
- **Six MCL subjects treated thus far with JCAR017 at DL1S**
- **Five patients treated in outpatient setting as of October 9 data snapshot[a]**

[a] For further details, see Maloney et al (abstract 1552).

Data as of October 9, 2017

TEAEs and Lab Abnormalities in DLBCL Cohort (FULL, N=91)



TEAE, treatment-emergent adverse event.
[a] Data for 5 patients with MCL treated with conforming product at DL1 with at least 28 days of follow-up are not reported.
[b] One grade 5 AE of septic shock, unrelated to JCAR017, occurred in the setting of disease progression.
[c] One grade 5 AE of diffuse alveolar damage, investigator assessed as related to fludarabine, cyclophosphamide, and JCAR017, occurred on day 23 in a patient who refused mechanical ventilation for progressive respiratory failure while neutropenic on growth factors and broad-spectrum antibiotics and antifungals.
[d] Laboratory abnormalities.

Data as of October 9, 2017

High Rates of Response in FULL DLBCL Population

Homogeneous Patient Population Moving Forward in Pivotal Cohort

	FULL	By B-NHL Subtype			
		DLBCL, NOS	tFL	tCLL/MZL	FL3B/PMBCL
BOR, n[a]	88	57	19	10	2
ORR, % (95% CI)	74 (63, 83)	74 (60, 85)	84 (60, 97)	50 (19, 81)	100 (16, 100)
CR, % (95% CI)	52 (41, 63)	51 (37, 64)	63 (38, 84)	30 (7, 65)	100 (16, 100)
≥ 3-mo f/u, n[b]	72	46	15	9	2
3-mo ORR, % (95% CI)	53 (41, 65)	54 (39, 69)	67 (38, 88)	22 (3, 60)	50 (1, 99)
3-mo CR, % (95% CI)	44 (33, 57)	43 (29, 59)	60 (32, 84)	22 (3, 60)	50 (1, 99)
≥ 6-mo f/u, n[c]	54	37	10	6	2
6-mo ORR, % (95% CI)	35 (23, 49)	35 (20, 53)	50 (19, 81)	0 (0, 46)	50 (1, 99)
6-mo CR, % (95% CI)	31 (20, 46)	32 (18, 50)	40 (12, 74)	0 (0, 46)	50 (1, 99)

BOR, best overall response; NOS, not otherwise specified.

Homogeneous CORE patient population identified and will move forward in pivotal trial

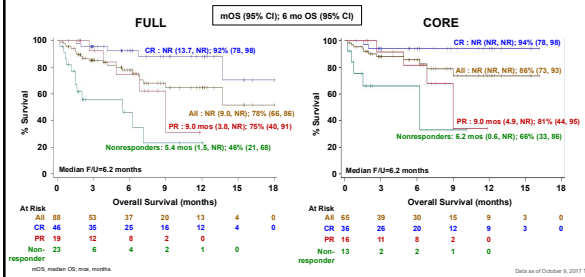
[a] Includes patients with event of PD, death, or 28-day restaging scans. Two patients did not have restaging scans available.
[b] The denominator is number of patients who received JCAR017 ≥ 3 months ago, prior to data snapshot date, with an efficacy assessment at month 3 or prior assessment of PD or death.
[c] The denominator is number of patients who received JCAR017 ≥ 6 months ago, prior to data snapshot date, with an efficacy assessment at month 6 or prior assessment of PD or death.

Data as of October 9, 2017

Overall Survival (OS)

Early OS Encouraging in High-Risk DLBCL Patient Population

mOS (95% CI); 6 mo OS (95% CI)



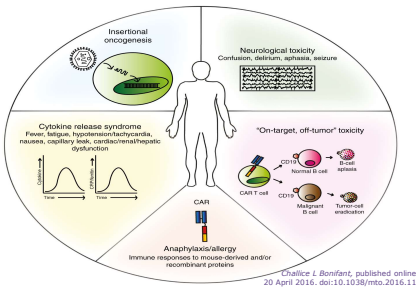
mOS, median OS; mos, months.

Data as of October 9, 2017

TRANSCEND NHL 001: Conclusions

- JCAR017 (lisocabtagene maraleucel; liso-cel), a CD19-directed CAR T cell product with defined composition, shows potent and durable responses in poor-prognosis patients with R/R aggressive NHL
- The pivotal cohort has begun enrollment in the CORE population based on encouraging durable response rate at dose level 2
  - 74% ORR and 68% CR rate at 3 months and 50% CR at 6 months
  - Across dose levels, 80% of patients in CR at 3 months remain in response at month 6 and 92% of patients in CR at 6 months remain in response
- Liso-cel toxicities have been manageable at all dose levels tested with a favorable safety profile that may enable outpatient administration
  - Low rates of severe CRS (1%) and NT (12%)
  - Evaluation of outpatient administration is ongoing in pivotal cohort (Maloney et al, abstract 1552)
- Optimized, commercial-ready liso-cel defined cell product being utilized for pivotal cohort with expected apheresis to product release < 21 days

CAR T Toxicities



Challice L Bonifant, published online 20 April 2016. doi:10.1038/mto.2016.11

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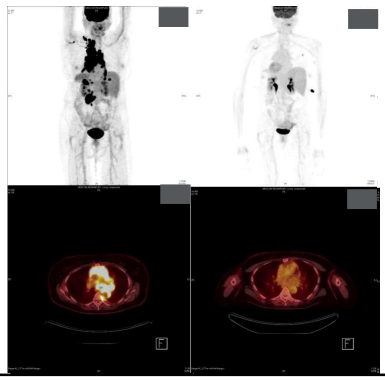
DLBCL AFTER CAR-T THERAPY

BASELINE Day +30



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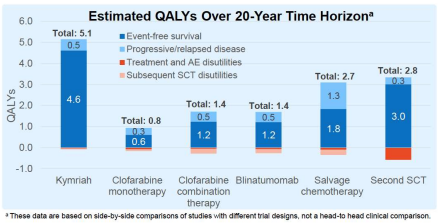
Kymriah™ Offers Value Benefit Based on Economic Model

- Over a 20-year time horizon, Kymriah™ was associated with 2.1-4.6 increase in LYs, and 2.3-4.3 increase in QALYs compared with other treatments



[a] These data are based on side-by-side comparisons of studies with different trial designs, not a head-to head clinical comparison.

Hao V, et al. *Blood*. 2017;130(23):[abstract 609].

Novartis Oncology

NOVARTIS

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Kymriah™ is Cost-Effective at the Current List Price in the US

- Based on the current list price of $475,000, Kymriah is cost-effective compared to other treatments, with incremental costs per QALY gained ranging from $18,212 to $95,489

	Kymriah™	Clofarabine monotherapy	Clofarabine combination	Blinatumomab	Salvage chemotherapy	Second SCT
Total Costs (2016 $)	$651,496	$253,233	$369,799	$303,440	$433,328	$609,418
Effectiveness: QALYs	5.07	0.77	1.43	1.42	2.75	2.76
Incremental costs per QALY gained (Kymriah™ vs. comparator)	-	$92,778	$77,424	$95,489	$94,185	$18,212

***Base-case scenario**: $475,000 price for Kymriah; 20-year time horizon; 3% discount rate; Kymriah™ efficacy based on pooled three trial data (B2202, B2101J, and B2205J); efficacy benefit, cost and disabilities associated with subsequent SCT is considered*

Hao V, et al. *Blood*. 2017;130(23):[abstract 609].

Novartis Oncology

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NOVARTIS

Approved date 12/2017 M-CTL-179339

Summary

- **We are entering a new era in treatment for lymphomas**
- **CAR T-cell therapy may represent one of the more effective immunotherapeutic options**
- **Challenges**
  - Time to manufacture
  - Patient selection and toxicity management
  - integration with or replacement of existing modalities (chemotherapy, small molecule inhibitors, autologous vs allogeneic stem transplant)
  - cost
- **CAR T-cell therapy likely to alter how we treat DLBCL**

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Treatment of Newly Diagnosed DLBCL in 2018

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WHO Classification of Aggressive B- Cell Lymphoid Neoplasms 2008 v 2016

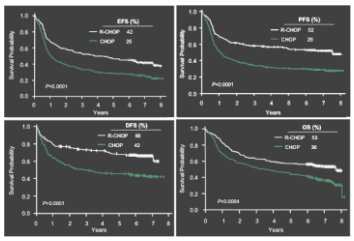
2008	2016
Diffuse large B-cell lymphoma (DLBCL), NOS	Diffuse large B-cell lymphoma (DLBCL), NOS
– OPTIONAL Germinal Center/Activated B cell	– REQUIRED Germinal Center DLBLC
	– REQUIRED ABC DLBCL
– T cell/histiocyte-rich large B-cell lymphoma	– T cell/histiocyte-rich large B-cell lymphoma
– Primary DLBCL of the CNS	– Primary DLBCL of the CNS
– Primary cutaneous DLBCL, leg type	– Primary cutaneous DLBCL, leg type
– EBV positive DLBCL, NOS	– EBV positive DLBCL, NOS
– EBV+ Mucocutaneous ulcer	– EBV+ Mucocutaneous ulcer
DLBCL associated with chronic inflammation	DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma	Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
ALK positive large B-cell lymphoma	ALK positive large B-cell lymphoma
Plasmablastic lymphoma	Plasmablastic lymphoma
Primary effusion lymphoma	Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman Dis	HHV8 positive DLBCL, NOS
	High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High grade B-cell lymphoma, NOS	High grade B-cell lymphoma, NOS
	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Swerdlow et al. Blood (2016) http://dx.doi.org/10.1182/blood-2016-01-643569 *Excluding Precursor Neoplasms

International Standard of Care: R-CHOP

Rituximab 375 mg/m2 day 1
Cyclophosphamide 750 mg/m2 day 1
Doxorubicin 50 mg/m2 day 1
Vincristine 1.4 mg/m2 day 1 (2 mg max)
Prednisone 40 mg/m2 (or 100 mg) daily x 5

Age > 60 Pegfilgrastim 6 mg subcut day 2
Original Gela LNH 98-5 confirmed in multiple studies



Coiffier et al. ASCO 2007. Abstract 8009.

GOYA R-CHOP v G-CHOP for DLBCL: Study design

Previously untreated DLBCL
Age ≥18 years
IPI ≥2 or IPI 1 (not age) or IPI 0 with bulky disease ≥7.5cm
ECOG PS ≤2

Target enrolment: 1400

Randomized 1:1

G-CHOP (N=706)
G 1000mg C1 D1/8/15 and C2–8 D1
CHOP‡ 21 cycles every 21 days

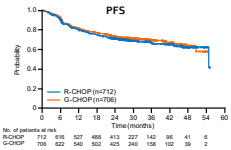
R-CHOP (N=712)
R 375mg/m² C1–8 D1
CHOP‡ 21 cycles every 21 days

Primary endpoint	Secondary and other endpoints	
• PFS (INV-assessed)	• PFS (IRC-assessed)[1] • OS, EFS, DFS, DoR, TTNT	• CR/ORR at EOI (+/- FDG-PET) • Safety

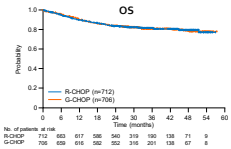
- Statistical assumption for primary endpoint: G-CHOP v R-CHOP HR = 0.75
- Number of CHOP cycles pre-planned in advance for all pts at each site
- Stratification factors: number of CHOP cycles, IPI, geographic region
- [1]Confirmatory endpoint
- Exploratory endpoint: PFS by cell of origin

Vitolo U, et al. ASH 2016 Abstract 470

GOYA: Investigator-assessed PFS and OS



	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	



	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	126 (17.7)	126 (17.8)
1-yr OS, %	89.9	90.7
2-yr OS, %	83.7	83.9
3-yr OS, %	81.4	81.2
HR (95% CI), p-value*	1.00 (0.78, 1.28), p=0.9982	

Vitolo U, et al. ASH 2016 Abstract 470

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles. *Median follow-up: 29 months*

Dose-Adjusted (DA)-EPOCH-R

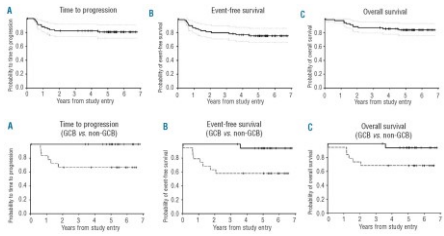
Drug	Dose
Rituximab	375 mg/m² day 1 IVPB
Doxorubicin	10 mg/m²/day x 4 by CI
Vincristine	0.4 mg/m²/day x 4 by CI
Etoposide	50 mg/m²/day x 4 by CI
Cyclophosphamide	750 mg/m² day 5 IVBP
Prednisone	60 mg/m² BID days 1-5 oral
Filgrastim*	Weight-adjusted dose starting day 5 until ANC > 5000/μL

*Data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim

- Dosed every 21 days if ANC > 1/μL and PLTS > 100K μL
- Dose-adjusted based on ANC nadir:
  - >500/μL, increase cytotoxic drugs by 20%
  - <500/μL for 1-3 days, no change
  - <500/μL for >3 days or FN, decrease cytotoxic drugs by 20%

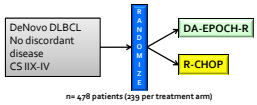
Wilson, J Clin Oncol 2008 26: 2717-2724; Lunning et al. SHO, abstract

CALGB 59910: Multi-Center DA-EPOCH-R, Outcomes



Wilson W H et al. Haematologica 2012;97:758-765

CALGB 50303: DA-EPOCH-R vs RCHOP21

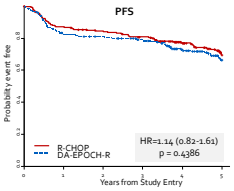


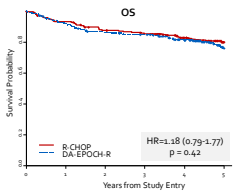
n= 478 patients (239 per treatment arm)

- **OBJECTIVES:**
  - *Primary*
    - EFS untreated de novo DLBCL treated with RCHOP vs DA-R-EPOCH
    - Determine molecular predictors of outcome (using molecular profiling) in patients treated with these regimens.
  - *Secondary*
    - Compare ORR and OS
    - Compare the toxicity of these regimens in these patients.
    - Correlate the clinical parameters (i.e., toxicity, response, survival outcomes, and laboratory results) with molecular profiling in patients treated with these regimens.
    - Determine the use of molecular profiling for pathological diagnosis
    - PET/CT parameters as potential biomarker, predictive value of interim PET, reproducibility and standardization of PET/CT

Wilson et al. ASH 2016, Abstract 489

CALGB 50303: Event-Free and Overall Survival





Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

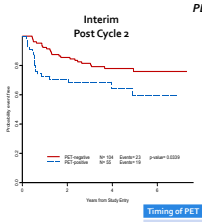
Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	44	0.85 (0.80-0.89)	0.80 (0.74-0.85)
DA-EPOCH-R	232	50	0.85 (0.79-0.89)	0.76 (0.70-0.71)

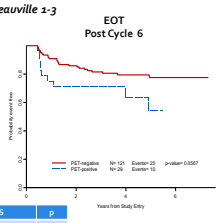
Additional analyses pending including outcome by COO, DH and DE

Wilson et al. ASH 2016, Abstract 489

CALG 50303: PET Sub-study n=171

PET neg = Deauville 1-3





Timing of PET	3 year EFS	p
Interim	81% (-) vs 69% (+)	0.034
End of treatment	80% (-) vs 72% (+)	0.057

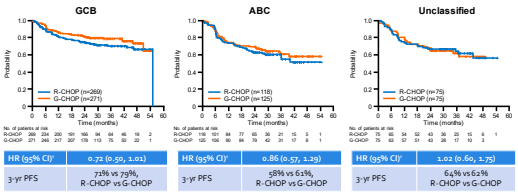
Treatment arms combined for analysis

Schoder, H, Menton, France 2016; Wilson et al. ASH 2016, Abstract 489

Methods for determination of COO

- **Gene Expression Profiling on fresh tissue**
  - 'The gold standard'
  - Not practically applicable in clinical practice
- **Immunohistochemistry**
  - Widely available
  - Reproducibility may be difficult
  - Many assays (Hans, Choi, Muris, Natkurman, Tally)
  - Lack of correlation with GEP in many studies
- **GEP of formalin-fixed paraffin-embedded (FFPE) tissue**
  - Multiple platforms
  - Hybrid capture/fluorescent reporter emerging as a widely validated assay

GOYA: COO is prognostic



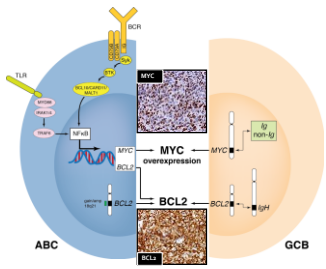
	GCB	ABC	Unclassified
HR (95% CI)*	0.72 (0.59, 1.01)	0.86 (0.57, 1.29)	1.02 (0.60, 1.75)
3-yr PFS	73% vs 79%, R-CHOP vs G-CHOP	58% vs 63%, R-CHOP vs G-CHOP	64% vs 62% R-CHOP vs G-CHOP

*Exploratory analysis; COO classification available in 933 pts; missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.81 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification
†Unstratified analysis

Vitolo U, et al. ASH 2016 Abstract 470

Double-Hit B-cell Lymphomas

Expression of MYC and BCL2 is a consequence of the biology of ABC DLBCL

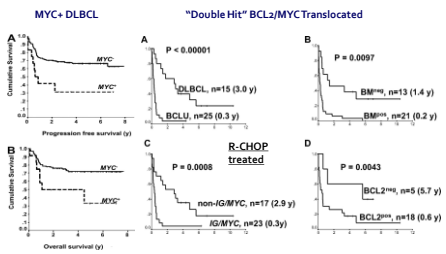


Translocation of BCL2 and/or BCL6 is seen in a subset of GC DLBCL; simultaneous translocation of MYC is seen in ~6% of cases of GC DLBCL.

Reclassified in WHO as HGBCL with rearrangement of MYC and BCL2 and/or BCL6

Mottock & Gascoyne, CCR 2014

MYC Translocation in DLBCL Associated with Poor Outcomes with CHOP-based Therapy

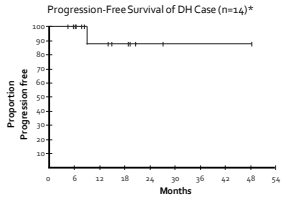


Savage KJ et al. Blood 2009; Johnson NA et al. Blood 2009

DA-EPOCH-R for DLBCL with translocation of MYC and BCL2 and/or BCL6

Characteristic	
Number	52
Median age	61 y (29-80)
IPI Score 0-2 3-5	 35% 65%
Histology DLBCL BCL-U	 86% 14%
BCL2 translocated by FISH	14/31*

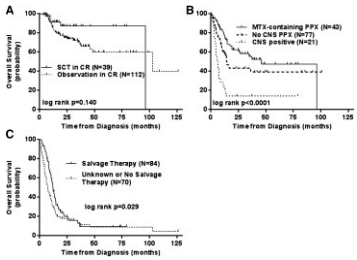
*31 of 52 tested



*Cases were censored if they were transplanted; number censored for transplant NOT REPORTED

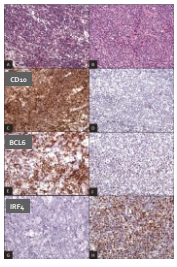
Dunleavy, ASH 2015

Impact of induction regimen and SCT on outcomes in DH lymphoma: a multicenter retrospective analysis

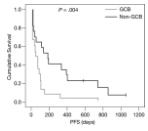


Adam M. Petrich et al. Blood 2014;124:2354-2361

Lenalidomide for DLBCL: Impact of Cell of Origin



	All	GCB	Non-GCB
Lenalidomide cycles			
Median (Range)	2 (1-35)	2 (1-21)	4 (1-35)
Response			
CR	6 (15.0)	1 (4.3)	5 (29.4)
PR	5 (12.5)	1 (4.3)	4 (23.5)
SD	7 (17.5)	7 (30.4)	0
PD	21 (52.5)	14 (60.9)	7 (41.2)
Unknown	1 (2.5)	0	1 (5.9)
ORR (CR + PR)	11 (27.5)	2 (8.7)	9 (52.9)
PFS, mo			
Median	2.6	1.7	6.2
95% CI	0.9-4.2	0.3-3.1	2.9-9.6

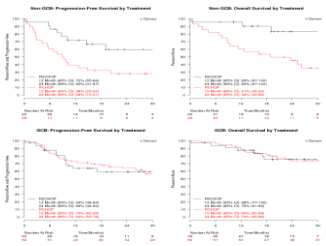


Hernandez-Ilizaliturri et al, Cancer 2011 117:5098

Mayo Series: Outcomes for RL-CHOP v R-CHOP Case Match Control by Cell of Origin

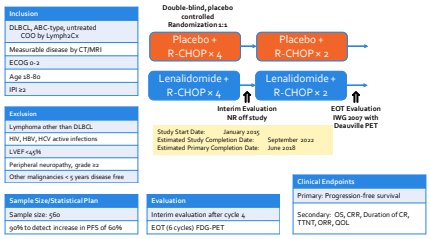
Non-GC DLBCL

GC DLBCL



Nowakowski et al. ASH 2012, ASCO 2014

ROBUST (NCT02285062): Lenalidomide Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Subjects With Untreated ABC-DLBCL, Phase 3, double-blind, placebo-controlled



Conclusions

- DLBCL should always be approached with curative intent
  - The majority of patients will be cured with R-CHOP
  - R-CHOP remains the standard of care for de novo DLBCL in most situations
  - DA-R-EPOCH is a reasonable alternative with OS ~80% at 5 years
    - No difference in EFS and OS
  - G-CHOP does not appear to be better than R-CHOP for newly diagnosed DLBCL
- Not all DLBCL are created equally
  - GCB versus non-GCB
    - Data is limited for GCB versus non-GCB
- MYC alteration and Double Hit DLBCL remain challenging
- Many novel agents and approaches are in development and warrant further investigation

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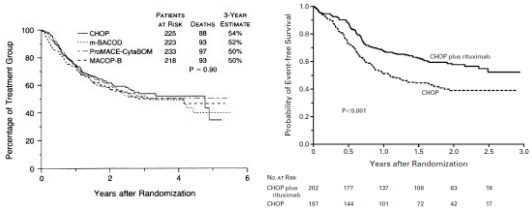
City of Hope

Jasmine Zain, M.D.
Director, T-Cell Lymphoma Program
City of Hope National Medical Center

NOVEL TREATMENTS OF DIFFUSE LARGE B-CELL LYMPHOMA

NO NEW FDA-APPROVED AGENTS SINCE RITUXIMAB!



Fisher RI et al. N Engl J Med 1993;328:1002-1006.

Coiffier B, et al. NEJM. 2002.

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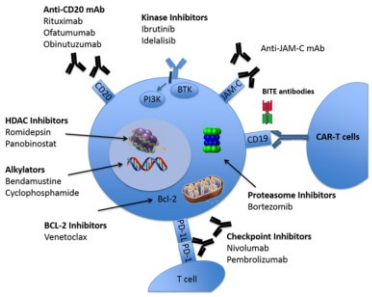
POTENTIAL TARGETS FOR TREATING B-CELL MALIGNANCIES



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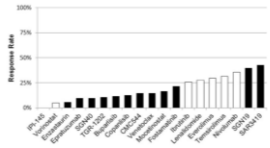
BROAD CATEGORIES FOR TARGETED AGENTS FOR DLBCL

- Immune modifiers - Lenalidomide
- Molecualar targets- Ibrutinib, Venetoclax, Idelalisib
- Antibodies and antibody drug conjugates – anti CD37
- Blinotumumab and other bispecific antibodies
- Immune-check point inhibitors
- Microenvoirnment targets- Anti CD47
- Epigenetic agents



Single agent activity of agents in relapsed DLBCL gathered from published phase 1 and 2 studies.

Staudacher et al. Hem Clinics of North America Dec 2016

IMPROVE ON R-CHOP?

- HDAC inhibitors = no
- Bortezomib = no
- Next up:
  - Lenalidomide (immunomodulator)
  - Polatuzumab vedotin (anti-CD79b ADC)
  - Venetoclax (BCL2 inhibitor)
  - SGN-CD19A (anti-CD19 ADC)

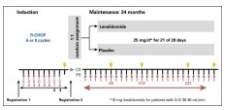
LENALIDOMIDE

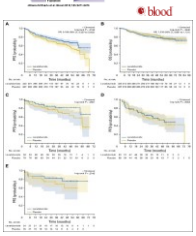
Lenalidomide has an ORR of 19% and 28% in RR. Witzig, et al. Zinzani, et al. 2008.

More effective in non-GCB subtype- ORR 53% vs 9%. Hernandez, et al. Cancer. 2011.

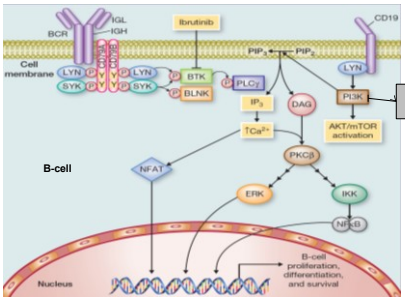
Tested in combination with Rituximab, RICE and as maintenance post transplant. Feldman, et al. 2014.

Lenalidomide maintenance vs placebo in elderly patients after RCHOP. PFS was not reached in the Len arm vs 58.9 months in the placebo arm. Diff was notable in the GCB subtype. Thieblemont, et al. Blood. 2017.





TARGETED TERAPIES – PI3K INHIBITORS

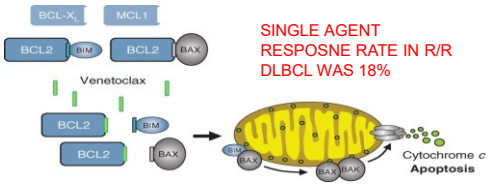


Herrera AF and Jacobsen EJ. CCR. 2014.

IBRUTINIB

- Selective and irreversible inhibitor of BTK
- Modest clinical activity in DLBCL as a single agent - 23% seen mostly in the ABC-subtype.
- Phase 1b/2 study of Ibrutinib plus lenalidomide and Rituximab is underway. Preliminary results show a RR of 44%.
- RCHOP vs RCHOP+ibrutinib for non-GCB subtype of DLBCL.
- Most common side effects are rash and diarrhea.

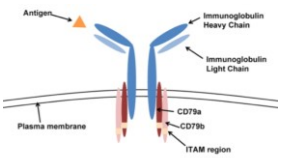
BCL-2 INHIBITION - VENETOCLAX

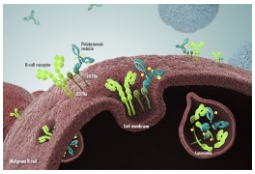


SINGLE AGENT RESPOSNE RATE IN R/R DLBCL WAS 18%

Konopleva M, et al. Cancer Discovery. 2016.

POLATUZUMAB VEDOTIN- ADC TARGETS CD79B CONJUGATED TO MMAE





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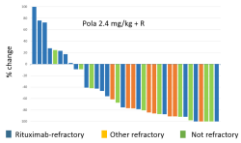
POLATUZUMAB VEDOTIN IN R/R DLBCL

Treatment Regimen	Best Overall Response
Pola 1.8–2.4 mg/kg	51%[1]
Pola 1.8–2.4 mg/kg + rituximab	56%[2]

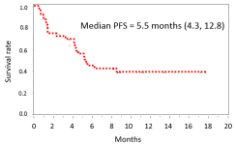
R/R DLBCL from the ROMULUS trial: pola + rituximab:

Best SPD Change from Baseline



Palanca-Wessels MCA, et al. Lancet Oncol 2015; 16: 704-15.

Progression-Free Survival



Morschhauser F, et al. Blood 2014; 124:4457.

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POLATUZUMAB VEDOTIN PLUS OBINUTUZUMAB

	FL (N=35)	DLBCL (N=43)
Objective response, n (%)	24 (69)	17 (40)
Complete Response	11 (31)	9 (21)
[90% CI]	[19–47]	[11–34]
Partial Response	13 (37)	8 (19)
[90% CI]	[24–52]	[10–31]
Stable disease, n (%)	4 (11)	0
Progressive disease, n (%)	1 (3)	18 (42)
Unable to evaluate, n (%)	6 (17)[b]	8 (19)[c]

[a]Patients who received ≥1 dose of study treatment; assessment per Lugano Criteria (Cheson 2014)
[b]No Pola dose due to IRR from G, taken off-study (n=2); no PET assessment (n=2); taken off-study due to neutropenia before assessment (n=1); fatal pneumonia before assessment (n=1)
[c]Died before assessment (n=1); PD not by PET (n=4); not assessed due to hospitalization / taken off study (n=2); W/D consent / not dosed (n=1)

Data Cut-Off: 26 JUL 2016
Download this presentation: http://tago.ca/TPH6

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POLA + R/G-BENDAMUSTINE

Investigator-Assessed Response by PET/CT[a]	FL		DLBCL	
	Pola + BR (n=6)	Pola + BG (n=26)	Pola + BR (n=6)	Pola + BG (n=27)
Best Objective Response				
ORR, n (%)	6 (100)	23 (89)	3 (50)	16 (60)
CR	4 (67)	17 (65)	2 (33)	11 (41)
PR	2 (33)	6 (23)	1 (17)	5 (19)
SD	0	0	0	2 (7)
PD	0	1 (4)	2(33)	6 (22)
UE	0	2 (8)	1 (17)	3 (11)
Objective Response at End of Treatment				
ORR, n (%)	5 (83)	21 (81)	3 (50)	10 (37)
CR	4 (67)	17 (65)	2 (33)	9 (33)
PR	1 (17)	4 (15)	1 (17)	1 (4)
Median duration of response, mo (range)[b]	16.1 (3.8–16.3)	NR (15.2–20.6)	NR (0.03–14.5)	NR (0.03–15.7)
Median PFS, mo (range)[b]	18.4 (7.2–18.9)	NR (1.4–17.1)	NR (1.5–22.7)	5.4 (0.03–17.6)

[a]Modified Lugano 2014 response criteria; for CR, repeat bone marrow biopsy required to confirm clearance of bone marrow if involved at screening. [b]Kaplan-Meier method; range data are at clinical data cut-off.
CT, computed tomography; ORR, objective response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SD, stable disease; UE, unable to evaluate.

EZH2 - INHIBITORS

Enhancer of zeste homolog 2 (EZH2) results in methylation of the histone H3-associated with gene repression
EZH2 activating mutations and overexpression is seen in cancers, GCB type of DLBCL not ABC subtype
EZH2 inhibitor Tazemostat is in clinical trials- first in class inhibitor of mutated and wild type EZH2.

Initial trials showed promising activity in B-cell lymphomas.

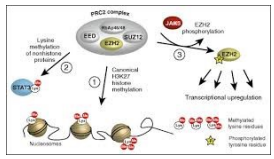
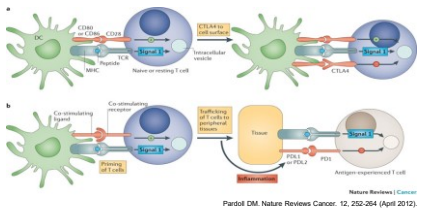


TABLE 1. Patient Outcomes From Treatment With Tazemetostat in Non-Hodgkin Lymphomas[a]

	FL, *EZH2*-mut (n = 13)	FL, *EZH2* WT (n = 54)	DLBCL, *EZH2*-mut (n = 17)	DLBCL, *EZH2* WT (n = 119)
Objective response rate, n (%)	12 (92%)	14 (26%)	5 (29%)	18 (15%)
Complete response, n (%)	1 (8%)	3 (6%)	0	10 (8%)
Partial response, n (%)	11 (85%)	11 (20%)	5 (29%)	8 (7%)
Stable disease, n (%)	1 (8%)	23 (43%)	6 (35%)	22 (18%)
Time to first response, median (range)	11.9 weeks (4.9-35.9)	15.2 weeks (8.1-32.1)	8.3 weeks (4.6-48.1)	8.1 weeks (5.3-24.7)

[a]DLBCL indicates diffuse large B-cell lymphoma; *EZH2*-mut, *EZH2*-mutant; FL, follicular lymphoma; WT, wild type.

CHECKPOINT INHIBITION: PD-1 PATHWAY



Pardoll DM. Nature Reviews Cancer. 12, 252-264 (April 2012).

Effects of PD-L1 binding:

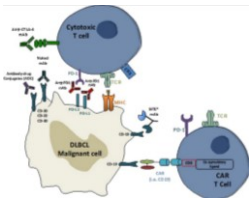
Inhibits T-cell activation

Inhibits cytokine production

Decreased cytolytic activity of CD4+ and CD8+ cells

CHECK POINT INHIBITORS IN DLBCL

- CTLA-4 AND PD-1 are being targeted.
- CT-011 (pidilizumab) in post ASCT- 16 mo PFS 72% including high risk patients. Armand, et al. 2013.
- Nivolumab- ORR 36% Lesokin, et al. 2016.
- Pembrolizumab- in trials – encouraging rates in PMBCL and CNS.
- Combinations with other therapies especially CAR-T.



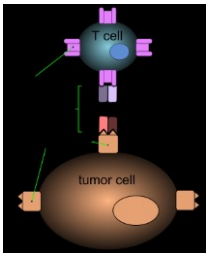
Juarez-Salcedo, et al. 2017.

BISPECIFIC ANTIBODIES

Phase II study of single agent bispecific engager (BiTE®) antibody Blinatumomab– ORR was 43% including 19% CRs. Viardot, et al. 2016.

Trials ongoing with lenalidmide and alternative strategies of administration (subcutaneous) using Blinatumomab, lenalidmide.

Other targets – CD 20 bispecific engager antibodies- encouraging RR and do not require CD19.



CONCLUSION

- Many promising strategies to treat RR DLBCL
- Combination therapies are likely to win
- Attempts to improve upon RCHOP continue especially for double hit and ABC subtypes