State of the Science
Aggressive Lymphomas 2017

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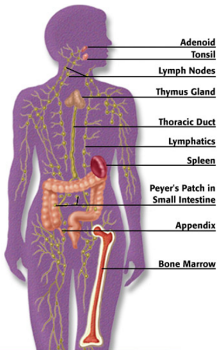
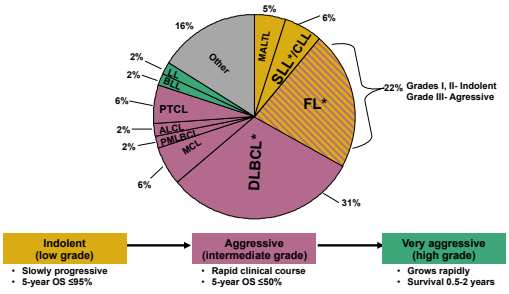
The Lymphatic System

- Lymphocytes
- Lymphoid organs
  - Bone marrow
  - Thymus
  - Lymph nodes
  - Spleen
- Lymphocyte circulation



Clinical Course and WHO Classification



Armitage JO, Weisenburger DD. *J Clin Oncol.* 1998;16:2780-2795; Harris NL et al. *Ann Oncol.* 1999;10:1419-1432; Hiddemann W et al. *Blood.* 1996;88:4085-4089; Horning SJ. *Blood.* 1994;83:881-884; Liu Q et al. *J Clin Oncol.* 2006;24:1582-1589; Fisher RI et al. *N Engl J Med.* 1993;328:1002-1006; Skarin AT, Dorfman DM. *CA Cancer J Clin.* 1997;47:351-372.

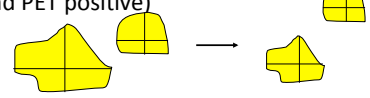
Aggressive Lymphomas

- "Aggression" determined clinically
- Goal is cure!
  - *Diffuse Large B-Cell Lymphoma*
  - *Burkitt Lymphoma*
  - *Peripheral T-Cell Lymphomas**
  - *Hodgkin Lymphoma*
- Goal is disease control and survival!
  - *Mantle Cell Lymphoma*
  - *Cutaneous T-Cell Lymphomas*

How to talk like an Oncologist…
or
"It's all Greek to me"

Definitions of "Response"

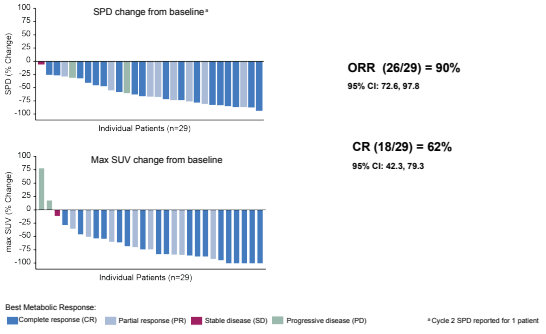
Partial (PR): reduction by at least 50% in the sum of products of cross-sectional diameters (and PET positive)



Complete (CR): resolution of nodes by CT and PET negative

Overall Response rate (ORR)= PR + CR

Tumor Response per Investigator



ORR (26/29) = 90%
95% CI: 72.6, 97.8

CR (18/29) = 62%
95% CI: 42.3, 79.3

Definition of "Survival"

Progression-Free Survival (PFS)

Time from start of therapy to disease progression

Event-free Survival (EFS)

Time from start of therapy to an event: I.e. serious toxicity or disease progression

Time to Next Treatment (DOR)

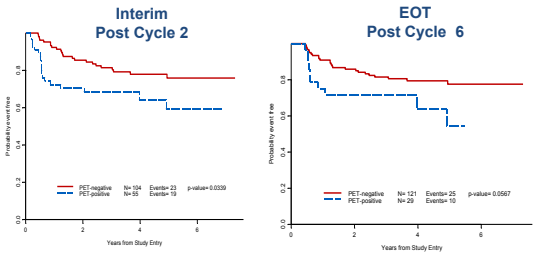
Time from response to disease progression

Overall Survival (OS)

PET and Survival in C5303

EFS by Interim and EOT PET

PET neg = Deauville 1-3



Schoder, H,
Menton, France 2016

Conclusions

- Response is easier to measure but offers the least tangible benefit for patients
  - Serves as a comparator of effectiveness of treatments but is not a guarantee for each individual patient
- Survival-based endpoints are harder to measure but ultimately more meaningful
  - Serves as a comparator of long-term benefit from treatment and is more realistic for patients

Lymphoma Treatment Overview

- **Chemotherapy**
- **Immunologic Therapy**
- **Biologic (Targeted) Agents**

What's New?

Aggressive Lymphoma Treatment Paradigm

DLBCL

- DLBCL is the most common NHL in adults, comprising ~40% of cases in US
- Aggressive malignancy with over 50% cure rate with modern front-line therapy
- Curable in the relapsed/refractory setting with high dose chemotherapy/ AutoHCT

Aggressive Lymphoma Treatment Paradigm

Phase III Randomized Study of R-CHOP vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/Alliance 50303

Wyndham H. Wilson, Sin-Ho Jung, Brandelyn N. Pitcher, Eric D.Hsi, Jonathan Friedberg, Bruce Cheson, Nancy L. Bartlett, Scott Smith, Nina Wagner-Johnston, Brad S. Kahl, Louis M. Staudt, Kristie A. Blum, Jeremy Abramson, Oliver W. Press, Richard I. Fisher, Kristy L. Richards, Heiko Schoder, Julie E. Chang, Andrew D. Zelenetz, John P. Leonard

Abstract 469, American Society of Hematology, Dec 4, 2016

50303 Enrollment

- Activated 05-02-2005
- Closed to Enrollment 05-08-2013
- Data cutoff for analysis 11-11-2016

	R-CHOP	DA-EPOCH-R
Enrolled (N=524)	**262**	**262**
Withdrew before treatment	4	7
Ineligible / elig. pending	9/16	9/14
Efficacy Analysis (n= 465)	**233**	**232**

50303 Grade 3-5 Toxicities

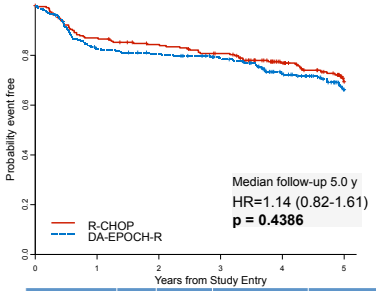
Event	R-CHOP	DA-EPOCH-R	P-value
Treatment related deaths*	2%	2%	0.975
ALL Gr 3-4	76.3%	96.5%	<0.001
Hematologic	73.1%	97.7%	<0.001
Non-Hematologic	41.3%	70.9%	<0.001
ANC	68%	96%	<0.001
Platelets	11%	65%	<0.001
Febrile neutropenia	17%	35%	<0.001
Infection	**11%**	**14%**	**0.169**
Mucositis	2%	6%	0.011
Neuropathy - sensory	2%	14%	<0.001
Neuropathy - motor	1%	8%	<0.001

*** Treatment related deaths (10 total, 5 in each arm)**
- **R-CHOP – CHF (1), CNS bleed (1), infection (1), F/N (1), unknown (1)**
- **DA-EPOCH R – infection (2), MI (1), unknown (2)**

50303 Response

	R-CHOP	DA-EPOCH-R	P-value
ORR	89.3%	88.8%	0.983
CR/CRu	62.3%	61.1%	
PR	27%	27.2%	
SD	2.6%	3.5%	
PD	1.7%	<1%	
Missing	6.4%	6.9%	

50303 Event Free Survival

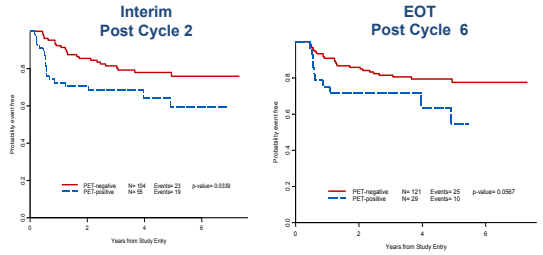


Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

50303 PET sub-study (n=171)

EFS by Interim and EOT PET

PET neg = Deauville 1-3



- **Treatment arms combined for analysis**
- **3 yr EFS by Interim PET 81% (-) vs 69% (+), P= 0.034**
- **3 yr EFS by EOT PET 80% (-) vs 72% (+), P= 0.057**

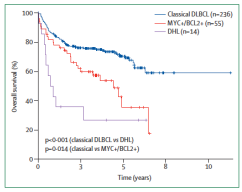
Schoder, H, Menton, France 2016

Conclusions

- No difference in 3-yr EFS or 3-yr OS
- No clinical subgroup identified based on age or IPI that appears to benefit from DA-EPOCH-R
  - Inadequate numbers to comment on PMBCL (n=28)
  - Double expressor, double hit analysis pending
- DA-EPOCH-R associated with modest increase in Gr-3-4 toxicities (cytopenias, F/N, neuropathy)

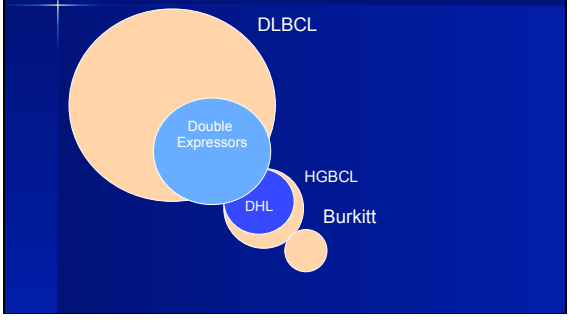
Double Protein Expression

- **25 to 30% of patients**
- **IHC cutoffs not uniformly defined**
- **Inferior PFS and OS across studies**

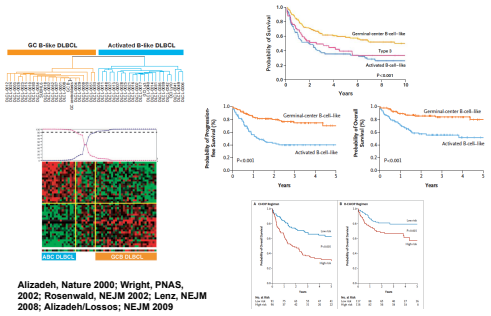


Sarkozy et al, Lancet Onc 2015; Johnson et al, JCO 2012

c-Myc/Bcl-2 Taxonomy



DLBCL- Cell of Origin



Alizadeh, Nature 2000; Wright, PNAS, 2002; Rosenwald, NEJM 2002; Lenz, NEJM 2008; Alizadeh/Lossos; NEJM 2009

Agents hypothesized to target ABC - DLBCL

- Lenalidomide (IRF4, CRBN)
- Bortezomib (NF-kB Signaling)
- Ibrutinib, Fostamatinib, Enzastaurin (BCR Signaling)
- Venetoclax? (Bcl2)

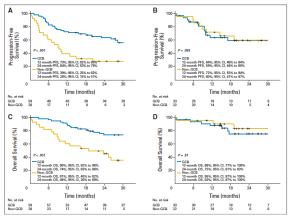
Lenalidomide

- Early data of single agent activity in relapsed ABC-DLBCL
- PII/III versus IC showed activity in both subtypes at relapse.
  - Non-GCB vs. GCB similar ORR but longer PFS in the non-GCB group
  - ABC vs. GCB trends in ORR, PFS, OS
- R2-CHOP upfront phase 2
  - High ORR/CR (98%/80%)
  - 60% PFS2

Czuczman et al ASH 2014; Nowakowski, JCO 2014

R2-CHOP

- Newly diagnosed DLBCL – GCB vs non-GCB by IHC
- 60 pts treated (compared to control 87 RCHOP treated DLBCL pts)
- RCHOP-21+ lenalidomide 25mg PO days 1-10 x 6 cycles



Nowakowski et al, JCO 2014

Ibrutinib

- A Bruton's Tyrosine Kinase (Btk) inhibitor that interferes with B-Cell receptor signaling.
- Activity against ABC-type DLBCL cell lines [1]
- Phase I and II data in heavily pretreated patients with DLBCL showed 40% RR in ABC subtype (8% CR, 32% PR, N=25), only 5% in GCB. [2, 3]
- Well tolerated with 13% ≥ gr 3 AEs. [2, 3]
  - Most common related gr 3: hyponatremia, fatigue, GI
  - Heme: <8% gr3,4 neutropenia, anemia, or thrombocytopenia

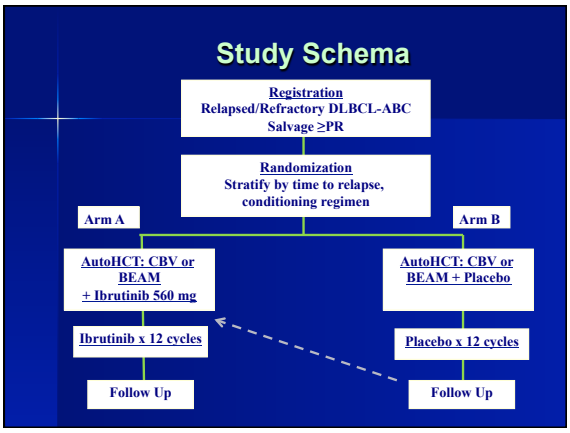
1: Davis et al, Nature 2010 2: Advani et al, JCO 2012 3: Wilson et al, ASH 2012

Aggressive Lymphoma Treatment Paradigm

Alliance A051301

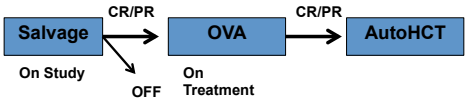
A randomized phase III study of Ibrutinib during and following autologous stem cell transplantation versus placebo in patients with relapsed or refractory Diffuse Large B-Cell Lymphoma of the Activated-B-Cell Subtype

- Study Chair: C. Babis Andreadis, MD, MSCE
- BMT-CTN Chair: Timothy Fenske, MD
- Transplant Committee Chair: Steven Devine, MD
- Lymphoma Committee Chair: John Leonard, MD
- Imaging Committee Chair: Lawrence Schwartz, MD
- PPP Committee Chair: Mark Ratain, MD
- Pathology Committee Chair: Eric Hsi, MD
- Faculty Statistician: Sin-Ho Jung, PhD



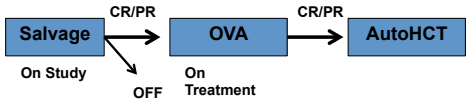
OVA: Intensive Consolidation

- Retrospective data suggest improvement in outcomes by addition of an intensive chemotherapy step (etoposide/Ara-C) between "salvage" and AutoHCT
- Hypothesis: Incorporation of Ofatumumab to this step during stem cell collection would address MRD in the patient and the graft



OVA Results

- 24 patients enrolled to date
- 18 On-treatment/ 16 evaluable
  - 6 off study due to suboptimal response
    1 GCB/DPE, 1 GCB/DHL, 3 GCB/neg, 1 unk
- 11/16 primary refractory to R-CHOP/R-EPOCH
- 15/16 refractory or relapsed within 12 mos
- Median 2 prior regimens (range: 2-3)

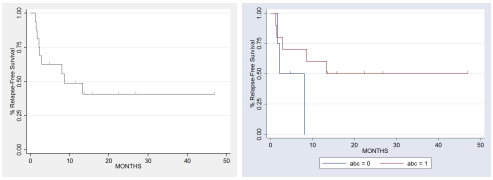


OVA Response and PFS

- Overall CMR: 56%% and ORR: 56%

Non-GCB	7/10	8/10
GCB	1/4	2/4

Progression Free Survival

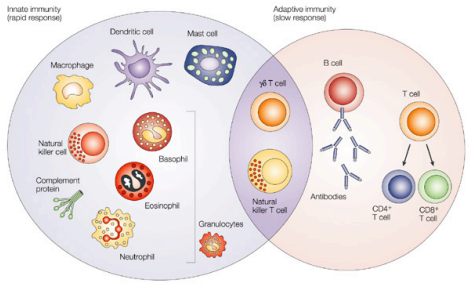


Immunotherapy

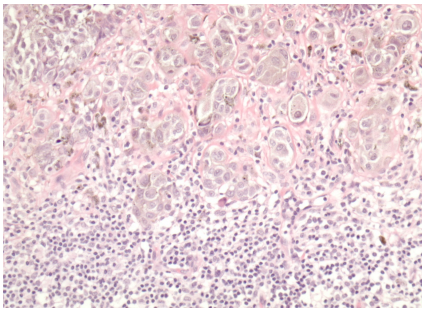
- Antibody Therapies
  - "naked" antibodies
  - Antibodies with payload
  - Bispecific antibodies
- Cell-based Therapies
  - Allogeneic Stem cell Transplantation
  - CART Cells
  - Checkpoint Inhibitors
- Vaccines

Aggressive Lymphoma Treatment Paradigm

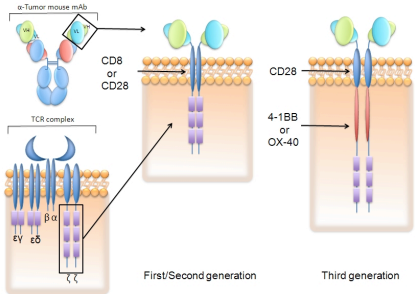
The Immune System



Tumor-Infiltrating Lymphocytes



Chimeric Antigen Receptor T-cells



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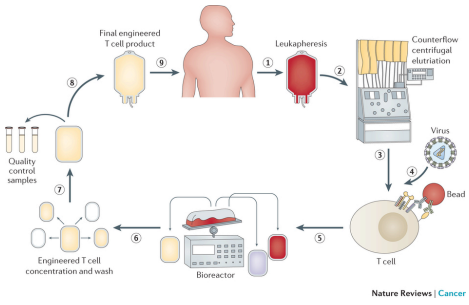
CART Processing



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Abstract LBA-6

KTE-C19 Induces Complete Remissions in Patients with Refractory Diffuse Large B Cell Lymphoma: Interim Results from the Pivotal Phase 2 ZUMA-1

Sattva S. Neelapu[1*], Frederick L. Locke[2*], Nancy L. Bartlett[3], Lazaros J. Lekakis[4], David Miklos[5], Caron A. Jacobson[6], Ira Braunschweig[7], Olalekan Oluwole[8], Tanya Siddiqi[9], Yi Lin[10], John Timmerman[11], Patrick J. Stiff[12], Jonathan W. Friedberg[13], Ian Flinn[14], Andre Goy[15], Mitchell Smith[16], Abhinav Deol[17], Umar Farooq[18], Peter McSweeney[14], Javier Munoz[19], Irit Avivi[20], Januario E. Castro[21], Jason R. Westin[1], Julio C. Chavez[2], Armin Ghobadi[3], Krishna V. Komanduri[4], Ronald Levy[5], Eric D. Jacobsen[6], Patrick Reagan[13], Adrian Bot[22], John Rossi[22], Lynn Navale[22], Yizhou Jiang[22], Jeff Aycock[22], Meg Elias[22], Jeff Wiezorek[22], and William Y. Go[22]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Washington University, St. Louis, MO, USA; [4]University of Miami, Miami, FL, USA; [5]Stanford University, Stanford, CA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Montefiore Medical Center, Bronx, NY, USA; [8]Vanderbilt University Medical Center, Nashville, TN, USA; [9]City of Hope, Duarte, CA, USA; [10]Mayo Clinic, Rochester, MN, USA; [11]University of California at Los Angeles, Los Angeles, CA, USA; [12]Loyola University Medical Center, Maywood, IL, USA; [13]University of Rochester School of Medicine, Rochester, NY, USA; [14]Sarah Cannon Research Institute, Nashville, TN, USA; [15]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [16]Cleveland Clinic, Cleveland, OH,

ZUMA-1: Patient Characteristics

Characteristic	DLBCL (n=73)	TFL/PMBCL (n=20)	All Patients (n=93)
Median age (range), years Age ≥60 years, n (%)	59 (25-76) 36 (49)	58 (28-76) 9 (45)	59 (25-76) 45 (48)
Male, n (%)	47 (64)	15 (75)	62 (67)
ECOG performance status 1, n (%)	48 (66)	8 (40)	56 (60)
Median number of prior therapies (#)	3 (1-7)	4 (2-12)	3 (1-12)
IPI 3-4, n (%)	32 (44)	9 (45)	41 (44)
Disease stage III/IV, n (%)	64 (88)	15 (75)	79 (85)
Refractory subgroup, n (%)* Refractory to 2nd or later-line therapy Relapse post-ASCT	 56 (77) 15 (21)	 16 (80) 4 (20)	 72 (77) 19 (20)

Summary of Adverse Events

Adverse Event, n (%)	Cohort 1 (n=73)	Cohort 2 (n=20)	Total (N=93)
Grade ≥3 adverse event	68 (93)	18 (90)	86 (92)
Grade ≥3 cytokine release syndrome	10 (14)	2 (10)	12 (13)
Grade ≥3 neurologic events (NE)	18 (25)	9 (45)	27 (29)
Fatal events excluding PD 2 of 3 KTE-C19-related	1 (1)	2 (10)	3 (3)

- CRS and NE were generally reversible
  - All CRS events resolved except 1 cardiac arrest (Cohort 2)
  - 3 NEs ongoing at data-cut (Gr 1 memory impairment, Gr 1 tremor, Gr 2 tremor)
  - 1 patient died due to PD with NE ongoing
  - 38% received tocilizumab, 17% received corticosteroids, 17% received both
- No cases of cerebral edema
- Grade 5 events occurred in 3 patients (3%)
  - KTE-C19-related: HLH (Cohort 1) and cardiac arrest (Cohort 2) in the setting of CRS
  - KTE-C19-unrelated: pulmonary embolism (Cohort 2)

ZUMA-1 Pivotal Trial Met Primary Endpoint of ORR At the Interim Analysis (P<0.0001)*

Best Overall Response in Patients with ≥3 Month Follow-up

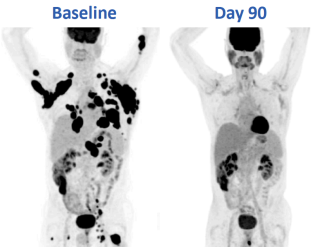
Subgroup	n	ORR	CR
DLBCL	51	76%*	47%
TFL / PMBCL	11	91%	73%
Total	**62**	**79%**	**52%**

*P<0.0001 (exact binomial test comparing observed ORR to a historical control assumption of 20%)

- At month 3 assessment the CR rate was 39%
- 7 patients with SD/PR at 1 mo converted to CR at 3 mo
- Complete Response in key subgroups:
  - 75% (n=9/12) CR relapsed post-ASCT
  - 47% (n=23/49) CR refractory to ≥2nd line

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



KTE-C19 Therapy Induces Rapid Response:
Most Responses Were Evident at First Tumor Assessment

Patient Response at the 1 Month Follow-up

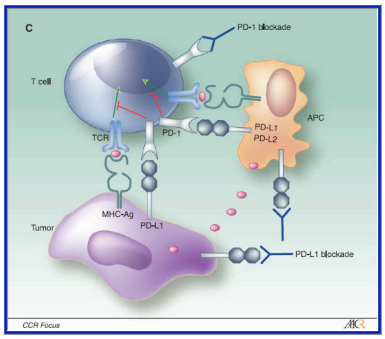
Subgroup	n	ORR	CR
DLBCL	73	68%	33%
PMBCL/TFL	20	80%	55%
Total	**93**	**71%**	**38%**

- Follow up ongoing
- Does not include responses after 1 month

ZUMA-1: Conclusions

- ZUMA-1 met primary endpoint with 76% ORR and 47% CR (p<0.0001) at this pre-specified interim analysis
  - 6-fold higher CR rate compared with historical outcomes, with 39% durable CR at 3 months
- First pivotal, multicenter study of anti-CD19 CAR T cells in refractory aggressive NHL
  - 99% manufacturing success rate with 17-day turnaround time
- AE management effectively implemented across 22 sites, most with no prior CAR T therapy experience
  - Grade 5 adverse event rate was 3%
  - Grade ≥3 CRS (13%) and neurologic events (29%)

Immune Checkpoint Inhibition



Hodgkin Lymphoma

- Highly curable lymphoma with initial therapy in 60 to 90% of patients
- At relapse, AutoHCT is the standard
- Newer agents making a difference
  - Brentuximab Vedotin
  - Checkpoint Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

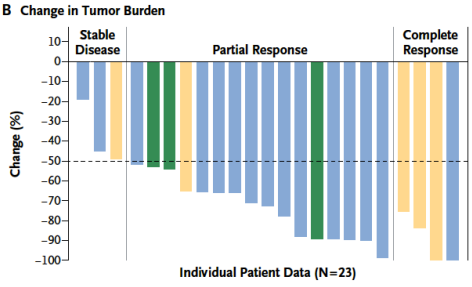
ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

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

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

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

Response On Study



Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F. Herrera[1], Nancy L. Bartlett[2], Radhakrishnan Ramchandren[3], Julie M. Vose[4], Alison J. Moskowitz[5], Tatyana A. Feldman[6], Ann S. LaCasce[7], Stephen M. Ansell[8], Craig H. Moskowitz[5], Keenan Fenton[9], Kazunobu Kato[10], Abraham Fong[9], Ranjana H. Advani[11]

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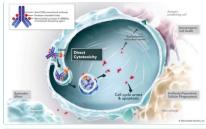
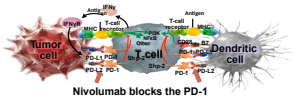
American Society of Hematology, San Diego, California, December 3–6, 2016, Abstract No. 1105

Rationale



Brentuximab vedotin disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress[a]

Nivolumab targets the programmed death-1 (PD-1) immune checkpoint pathway and restores antitumor immune responses



Nivolumab blocks the PD-1 receptor

- Both agents are well tolerated with high single-agent response rates in patients with R/R HL (BV=72% ORR, 33% CR[b]; Nivo=73% ORR, 28% CR[c])*
- Together, they could yield improved CR rates and improved durability of responses, and potentially lead to better long-term outcomes

*per investigator

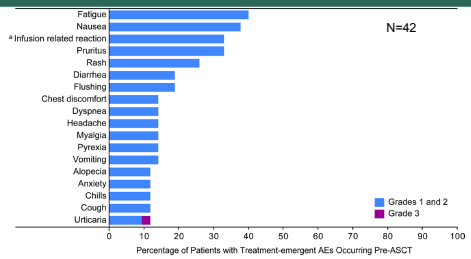
[a] Gardai et al., Cancer Res 75: Abstract 2469; 2015
[b] Gopal et al., Blood 2015;125(8):1236-43
[c] Younes et al., Lancet Oncol 2016; 17(9):1283-94

Demographics and Disease Characteristics

42 patients (52% F, 48% M) with a median age of 37 years have been enrolled

	n (%)
Disease status at study entry	
Primary Refractory	17 (40)
Relapsed, remission duration ≤ 1 year	14 (33)
Relapsed, remission duration > 1 year	11 (26)
Extranodal disease	11 (26)
Bulky disease	4 (10)
Prior chemotherapy regimens	
ABVD	37 (88)
ABVE-PC	2 (5)
BEACOPP	1 (2)
BEACOPP after ABVD discontinuation	1 (2)
Stanford V	1 (2)
Prior radiation	5 (12)

Adverse Events



- **Pre-ASCT** adverse events (AEs) occurring in ≥10% of patients were Grade 1 or 2, with the exception of one Grade 3 urticaria event
- 3 patients (7%) experienced peripheral sensory neuropathy, all Grade 1
- One patient with treatment-related **serious adverse event** after Cycle 1 BV: dehydration (G3), asthenia (G1), hypercalcemia (G2), malaise (G2), nausea (G1)

[a] One PT of IRR not reported as associated with infusion

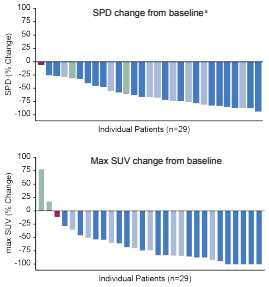
Potential Immune-Related Adverse Events

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3/4 n (%)	N=42 Total n (%)
Hypothyroidism	0	2 (5)	0	2 (5)
Transaminase elevation	3 (7)	0	1 (2)	4 (10)
Diarrhea	8 (19)	3 (7)	0	11 (26)
Rash	8 (19)	4 (10)	0	12 (29)
Infusion related reaction (IRR)[b, c]	6 (14)	9 (21)	0	15 (36)

[a] Select AEs identified as potentially immune-related [b] One PT of IRR not reported as associated with infusion; [c] Includes hypersensitivity

- There were no occurrences of pneumonitis or colitis
- 4 patients received topical steroids for rash and IRR
- 10 patients received systemic steroid treatment for: IRR (5 patients), urticaria, rash, pruritus, ear itching, and elevated AST

Tumor Response per Investigator



ORR (26/29) = 90%
95% CI: 72.6, 97.8

CR (18/29) = 62%
95% CI: 42.3, 79.3

Deauville score (N=29)

5-Point Score	Best Metabolic Response	n (%)	Total n (%)
1	CR	8 (28)	18 (62)
2		6 (21)	
3		3 (10)	
Missing		1 (3)	
4	PR	6 (21)	8 (28)
5		2 (7)	
5	SD	1 (3)	1 (3)
5	PD	2 (7)	2 (7)

Best Metabolic Response:
Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD)

[a] Cycle 2 SPD reported for 1 patient

Conclusions

- Early data suggest the combination of BV and Nivo is an active and well-tolerated outpatient regimen
  - 90% ORR and 62% CR
  - 38% of patients have experienced IRRs, however the overall safety profile is manageable with no dose reductions or discontinuations due to AEs
  - The incidence of immune-related adverse events is low
- Preliminary biomarker results indicate
  - No antagonism between BV and Nivo
  - Decrease in Treg cells with BV
- The promising activity of the BV and Nivo combination supports further exploration of this chemotherapy-free regimen for R/R HL patients

Mantle Cell Lymphoma

- Presents as indolent, slow-growing disease
- High response rates to initial therapy
- Behaves very aggressively at relapse
- Standard of care is AutoHCT in first remission
- Maintenance therapy may play a role

Aggressive Lymphoma Treatment Paradigm

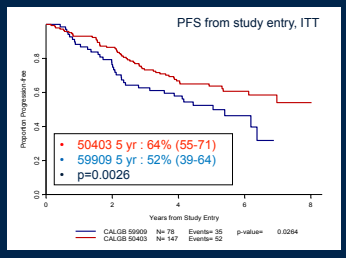
Mantle Cell Lymphoma Step 1

- Induction Therapy
  - R-Lenalidomide
  - R-Bendamustine
  - R-CHOP +/- Ara-C
  - R-CHP/Velcade

Mantle Cell Lymphoma Steps 2 and 3

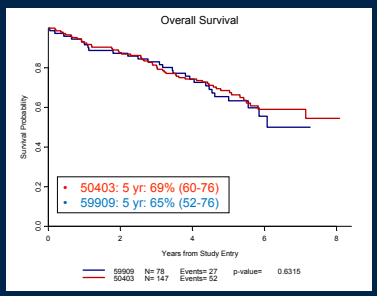
- Autologous Stem cell Transplantation in remission prolongs Progression-free Survival
- Subsequent therapy may also prolong PFS
  - Bortezomib
  - Rituximab
  - others

Progression-Free survival from Study Entry: All Patients CALGB 50403 vs 59909



MIPI Score	50403 (n=147)	59909 (n=78)
Low	77 (52.4%)	41 (53.2%)
Intermediate	45 (30.6%)	24 (31.2%)
High	25 (17.1%)	12 (15.6%)

Overall Survival from Study Entry: 59909 vs 50403



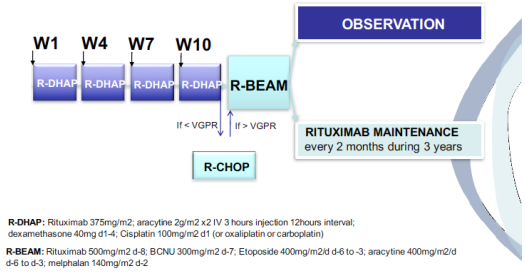
Rituximab maintenance after autologous stem cell transplantation prolongs survival in patients with mantle cell lymphoma (final result of the LyMa trial)

Steven Le Gouill, MD, PhD, Catherine Thieblemont, MD, PhD, Anne Moreau, MD, Lucie Oberic, MD, Krimo Bouabdallah, MD, Emmanuel Gyan, MD, PhD, Gandhi Damaj, MD, PhD, Vincent Ribrag, MD, PhD, Pierre Feugier, MD, PhD, Olivier Casasnovas, MD, Hacène Zerazhi, MD Corinne Haioun, MD, PhD, Hervé Maisonneuve, MD, Eric Van Den Neste, MD, PhD, Olivier Tournilhac, MD, PhD, Katell Ledu, MD, Franck Morschhauser, MD, PhD, Bernard Christian, MD, Guillaume Cartron, MD, PhD, Luc Fornecker, MD, PhD, Daniele Canioni, MD, PhD, Marie-Christine Béné, MD, PhD, Gilles Salles, MD, PhD, Hervé Tilly, MD, PhD, Thierry Lamy, MD, PhD, Remi Gressin, MD, Olivier Hermine, MD, PhD, on behalf of the LYSA group

ClinicalTrials.gov, NCT00921414

Abstract # 145 ASH 2016

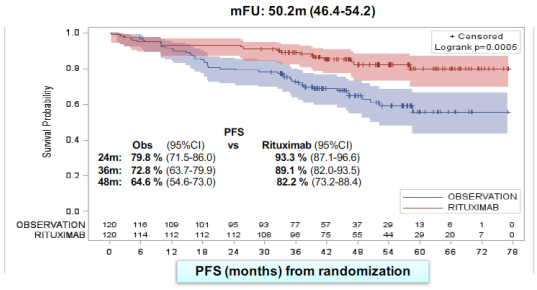
LyMa trial



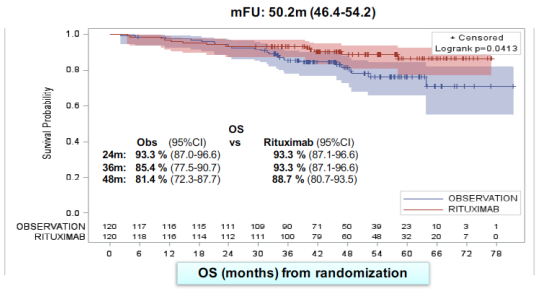
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

PFS from Randomization



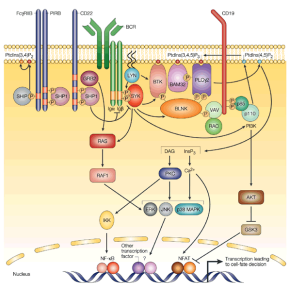
OS from Randomization



Biologic Combinations

Aggressive Lymphoma Treatment Paradigm

Targeting of B-Cell Receptor Signaling



- BCR-associated kinases are targets of new drugs in preclinical and clinical development
- Btk (Bruton's tyrosine kinase) inhibitors: **Ibrutinib**, CC-292, ACP-196
- PI3 kinase inhibitors: Isoform-Selective Inhibitor of PI3-Kinases[1], **Idelalisib**, IPI-145, TGR-1202
- Syk (spleen tyrosine kinase) inhibitors: GS-9973, Fostamatinib, PRT-2070[2]

From: Nat Rev Immunol 2:945

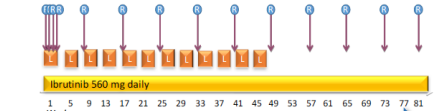
[1] Niedermeier M, et al. Blood 113(22):5549-57, 5/2009
[2] Quiroga MP, et al. Blood 114(5):1029-37, 07/2009

Ibrutinib-Lenalidomide-Rituximab in Patients with Relapsed/Refractory Mantle Cell Lymphoma: First Results from the Nordic Lymphoma Group MCL6 (PHILEMON) Phase II Trial

Mats Jerkeman, Martin Hutchings, Riikka Räty, Karin Fahl Wader, Anna Laurell, Hanne Kuitunen, Helle Toldbod, Lone Bredo Pedersen, Christian Winther Eskelund, Kirsten Grønbæk, Carsten Utoft Niemann, Christian H Geisler and Arne Kolstad

Nordic Lymphoma Group

Treatment schedule



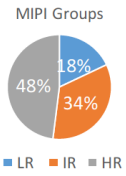
- R2 induction schedule adapted from Ruan et al, NEJM 2015
- Len 15 mg d 1-21, 28 days cycle, up to 12 months
- Eligible: R/R MCL, ≥1 rituximab regimen, no age limit
- Primary endpoint: ORR
- Aim: to improve ORR in R/R MCL, compared to single agent ibrutinib

Maintenance until progression

Patient characteristics

50 patients included in 12 months at 10 centres in Sweden, Norway, Denmark and Finland
Median follow-up 8 months

Median age (years)	70	46-85
Male gender	36	72%
Median lines of therapy	1.5	(1-7)
Previous autologous SCT	21	42%
Previous allogeneic SCT	3	6%
Previous ibrutinib	4	8%
Previous lenalidomide	1	2%



Response

	All patients		No previous ibrutinib		Previous ibrutinib		Single ibrutinib Wang NEJM 2013
	N=42	%	N=39	%	N=3	%	N=111
ORR	***37***	***88***	***35***	***90***	***2***	***67***	***68***
CR	27	64	27	69	0	0	21
PR	10	24	8	21	2	67	47
No response	5	12	4	10	1	33	20

- PET-CT performed to confirm a CR, or at the time of maximal tumor reduction.
- 8 patients not evaluable

Conclusions

- Combination tolerable in R/R MCL– less severe rash than in 1st line FL
  - *Ujjani et al, Blood 2016* – Grade 3 rash 36% (here 13%)
- ORR and CR rates higher than with single agent ibrutinib
- Molecular remission in half of patients
- Some activity in ibrutinib-exposed MCL
- Active regimen also in *TP53* mutated MCL

General Conclusions

- Better understanding of molecular pathways is getting translated to targeted biologic agents
- Biologic combinations are challenging chemo regimens as safer options
- Biologic agents can hopefully improve chemotherapy effectiveness without adding toxicity

General Conclusions

- Immunotherapy is making great strides for patients with hematologic malignancies and especially lymphomas.
- Effective in every phase of therapy
- Moving from the research realm to the real world and coming soon to a center near you

Questions?