ANCO Update in Lymphomas 2017

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Outline

- DLBCL
  - Incorporating biomarkers in treatment choice
  - CART19 therapy is here
- Mantle Cell Lymphoma:
  - Induction regimens
  - Maintenance rituximab again
- Follicular Lymphoma
  - Evolving standards in the front line setting
  - Bcl2 inhibition comes of age
- Hodgkin Lymphoma
  - CD30 meets PD1

DLBCL

- Initial Therapy
- Relapse Considerations
- Emerging Options

DLBCL

- Initial Therapy
  - To CHOP or not to CHOP?

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

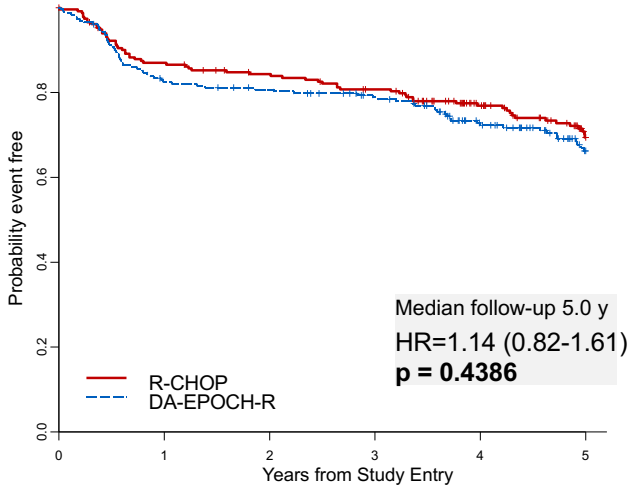
*** Treatment related deaths (10 total, 5 in each arm)**

- **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)

What about biomarkers?

- Cell of Origin Subtype
  - GCB vs. ABC (nonGCB)
- Double Hit/Double Protein
  - FISH: myc/bcl2/bcl6
  - IHC: MYC/BCL2
- Interim PET

R-CHOP in ABC/Non-GCB

Abstract 812: Prospective randomized trial of targeted therapy for DLBCL based on real-time GEP: Remodl-B trial of UK and SAKK lymphoma groups Davies, et al.

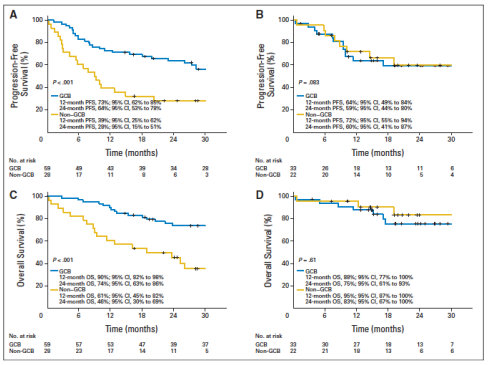
- RCHOP x 1 → central GEP on FFPE LN → randomization to RCHOP + bortezomib 1.6 mg/m^2 days 1 & 8 or RCHOP x 5
- N= 1132 patients (246 ABC (27%), 476 GCB (52%), 199 unclassifiable)

Subtype	ORR	CR
ABC	90%	66%
GCB	87%	63%

- No difference in ORR in ABC patients with RCHOP or BR-CHOP
- No difference in ORR in GCB patients with RCHOP or BR-CHOP
- No differences in PFS of ABC and GCB patients, 2-year PFS 71%
- Still awaiting 30 months of f/up which was primary endpoint

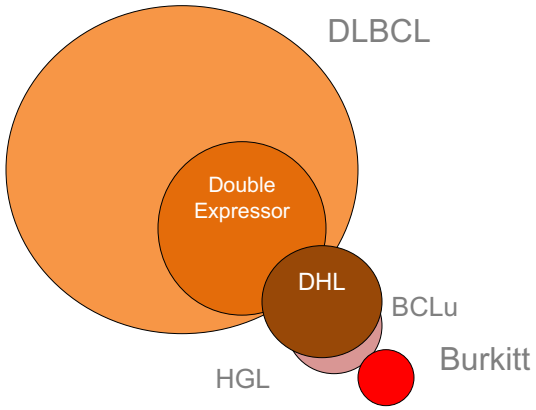
R2-CHOP

- 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

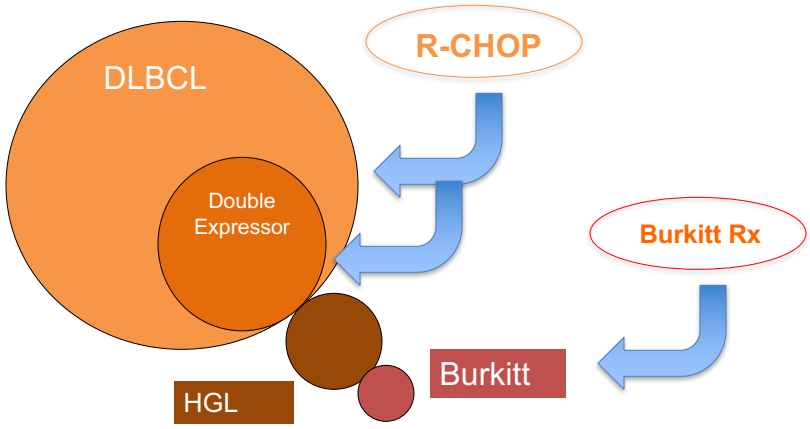


Nowakowski et al, JCO 2014

Double Hit/Double Protein Taxonomy



Double Hit/Double Protein Treatment

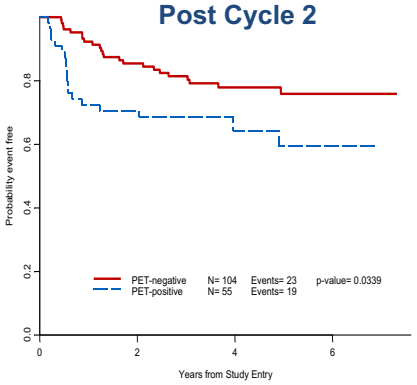


Alliance 50303 PET sub-study (n=171)

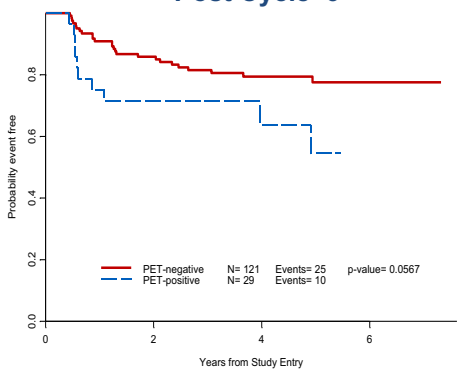
EFS by Interim and EOT PET

PET neg = Deauville 1-3

Interim
Post Cycle 2



EOT
Post Cycle 6



- **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**

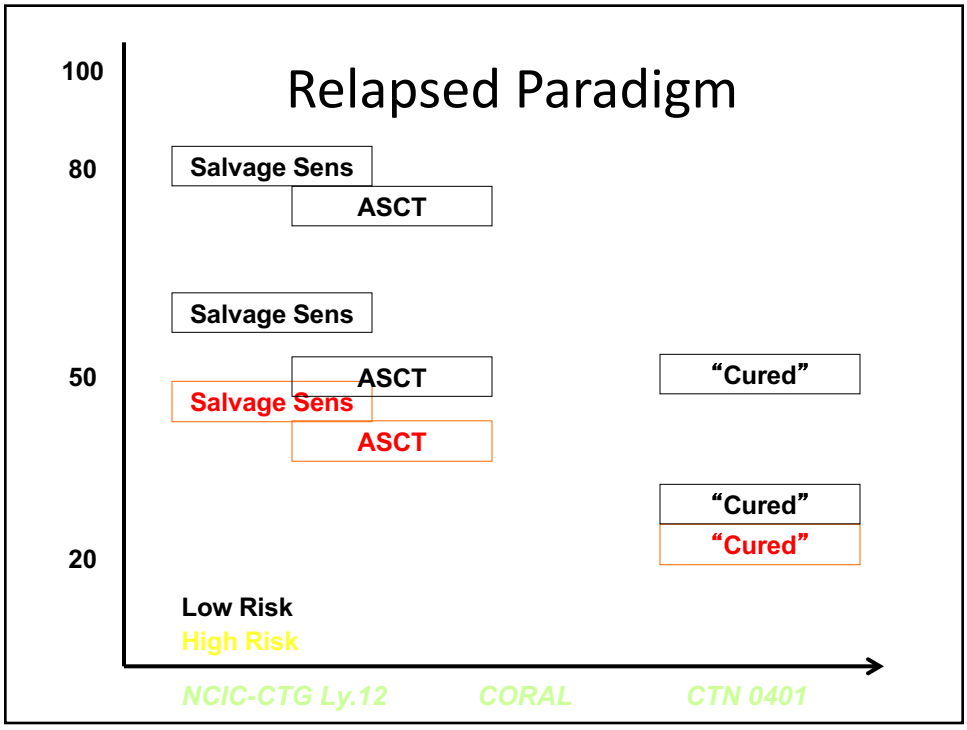
Schoder, H, Menton, France 2016

What about biomarkers?

- Cell of Origin Subtype
  - GCB vs. ABC (nonGCB): Awaiting trial results R2-CHOP vs. R-CHOP
- Double Hit/Double Protein
  - FISH: myc/bcl2/bcl6: Aggressive regimen needed
  - IHC: MYC/BCL2: R-CHOP
- Interim PET
  - Use with caution

DLBCL

- Initial Therapy
- Relapse Considerations
- Emerging Options

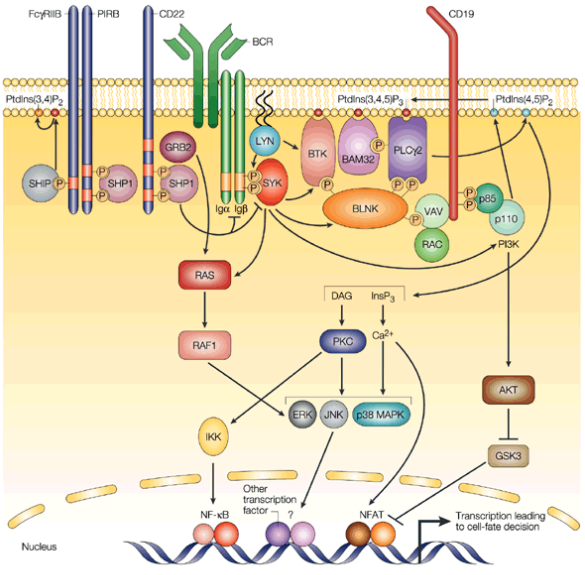


ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

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

Babis Andreadis PI

Target B-Cell Receptor Signaling in ABC-DLBCL



Nat Rev Immunol 2:945; 2009

Study Objectives

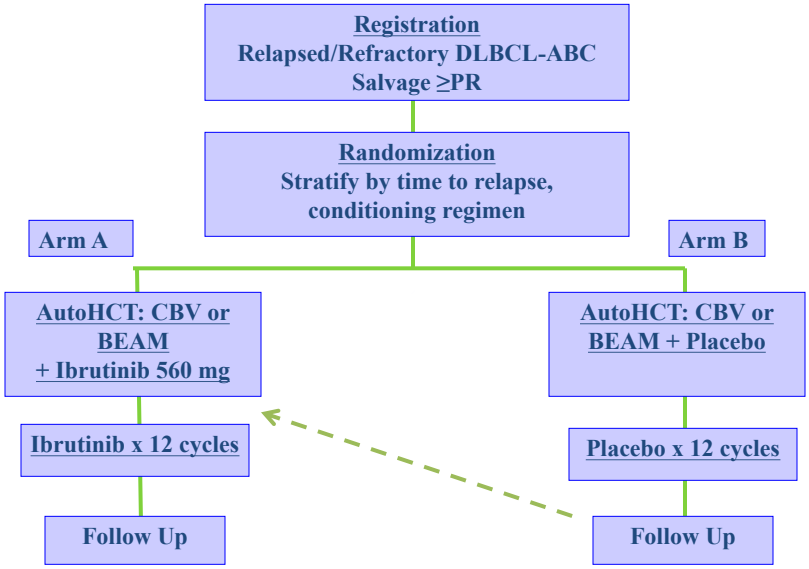
Primary objective

- Improve PFS at 24 months with ibrutinib vs. placebo

Secondary objective(s)

- Overall Survival
- Progression-Free Survival
- Post-Auto Response Rates
- Hematopoietic Recovery
- Safety/tolerability of Ibrutinib
- Secondary Malignancies
- Immune Reconstitution

Study Schema



DLBCL

- Initial Therapy
- Relapse Considerations
- Emerging Options

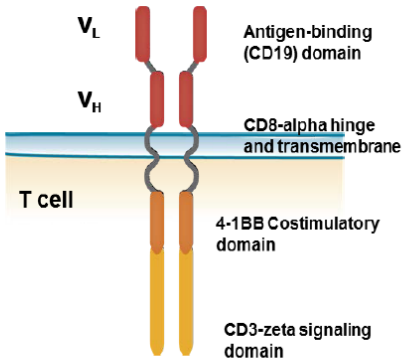
Global Trial of the Efficacy and Safety of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma: An Interim Analysis of the JULIET Study

Stephen J. Schuster, Michael R. Bishop, Constantine Tam, Edmund K. Waller, Peter Borchmann, Joseph McGuirk, Ulrich Jäger, Samantha Jaglowski, Charalambos Andreadis, Jason Westin, Isabelle Fleury, Veronika Bachanova, Stephen Ronan Foley, P. Joy Ho, Stephan Mielke, Harald Holte, Oezlem Anak, Lida Pacaud, Rakesh Awasthi, Feng Tai, Gilles Salles, Richard T. Maziarz

On behalf of the JULIET study investigators

CTL019: Genetically Engineered T Cells Directed Against CD19

- CTL019 is a chimeric antigen receptor (CAR) modified T-cell therapy currently under investigation for the treatment of r/r B-cell malignancies[1-3]

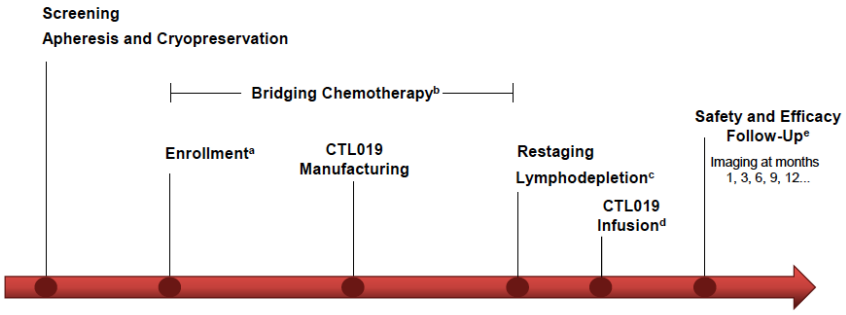


1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464.
2. Zhang H, et al. *J Immunol*. 2007;179:4910-4918.
3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73.

3

Study Schema

- JULIET is a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in adult patients with r/r DLBCL (NCT02445248)



[a] Eligibility criteria confirmed.
[b] To prevent rapid disease progression during CTL019 manufacturing.
[c] To be completed 2 to 14 days prior to CTL019 infusion.
[d] Infusion conducted in- or out-patient at investigator discretion.
[e] Long-term follow-up for 15 years (NCT02445222).

DLBCL, diffuse large B-cell lymphoma, r/r, relapsed/refractory; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

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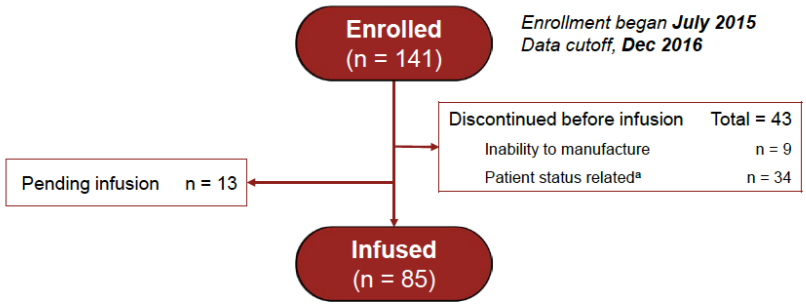
Patient Disposition



- 85 patients evaluated for safety
- 51 patients evaluated for response (completed ≥3 months follow-up or discontinued earlier)
  - Median time of 3.7 months from infusion to data cutoff (20 Dec 2016)
- CTL019 cell dose[b]:
  - Median (range), 3.1 x 10^8 (0.1-6.0 x 10^8) cells

[a] Progressive disease (n = 28; including 16 deaths); adverse event (n = 2), investigator decision (n = 2), withdrawal (n = 1), protocol deviation (n = 1).
[b] 1 patient received < and 3 patients received > the target dose range.

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Primary Endpoint Was Met

Response Rate	Patients (N = 51)[a]	
Best overall response (CR + PR)	**59%**	*P* < .0001[b] (95% CI, 44-72)
CR	**43%**	
PR	16%	
SD	12%	
PD	24%	
Overall response rate (CR + PR) at 3 months	**45%**	
CR	**37%**	
PR	8%	

[a] The interim analysis was preplanned to include the first 51 patients treated with CTL019 and followed for at least 3 months or discontinued early.
[b] Null hypothesis of ORR ≤20%; the one-sided p-value threshold to reject the null hypothesis is 0.0047 (O'Brien-Fleming boundary) at the interim analysis and 0.0235 at the primary analysis.

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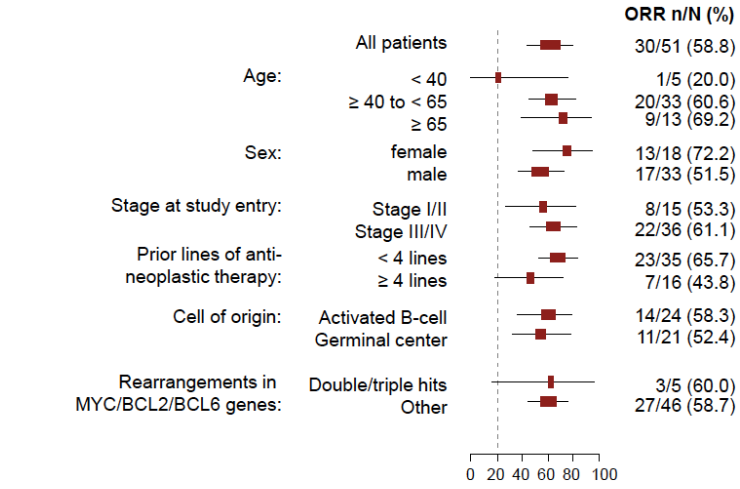
CI, confidence interval; CR, complete remission; ORR, overall remission rate; PD, progressive disease; PR, partial remission; SD, stable disease.

ORR by Subgroup



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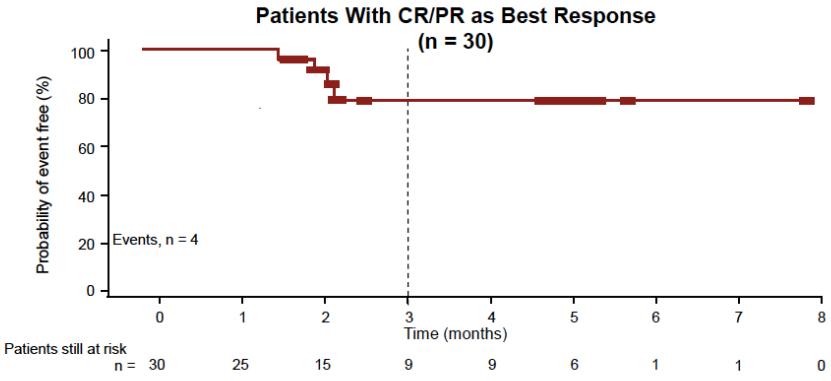
Duration of Response: 79% Relapse-free at 6 Months



- All responses at 3 months were ongoing at the time of cut-off
  - No responding patients went on to SCT
- Median DOR and OS not reached

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DOR, duration of response; OS, overall survival; SCT, stem cell transplant.

Adverse Events of Special Interest

	Patients (N = 85)		
AESI[a]	All grade %	Grade 3 %	Grade 4 %
Cytokine release syndrome[b]	57	17	9
Infections	27	12	1
Cytopenias not resolved by day 28	26	13	8
Neurologic events	21	9	4
Febrile neutropenia	14	13	1
Tumor lysis syndrome	1	1	0

[a] Occurring within 8 weeks of CTL019 infusion.
[b] Cytokine release syndrome was graded using the Penn scale and managed by a protocol-specific algorithm.

- No cases of cerebral edema
- No deaths attributable to CTL019

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AESI, adverse events of special interest.

Cytokine Release Syndrome

	Patients (n = 85)
Time to onset, median (range), days[a]	3.0 (1-8)
Duration, median (range), days[a]	7.0 (3-34)
Admitted to intensive care unit	24%
Hypotension that required intervention	29%
High dose vasopressors	7%
Intubated	8%
Anti-cytokine therapy[b]	18%
Tocilizumab	16%
Corticosteroids	11%

[a] Calculated based only on patients who had cytokine release syndrome (n = 48).
[b] 8 patients received both tocilizumab and corticosteroids.

CRS was graded using the Penn scale and managed by a protocol-specific algorithm.

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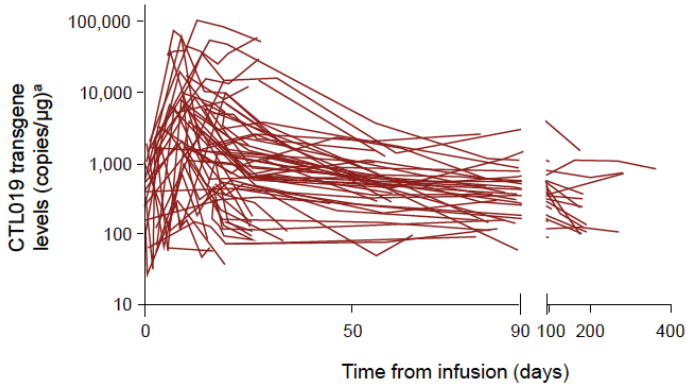
Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.

Cellular Kinetics

- CTL019 transgene levels were observed to undergo significant expansion and demonstrated measurable persistence in vivo for up to 355 days



Mantle Cell Lymphoma

- Initial Therapy
- Relapse Considerations

Mantle Cell Lymphoma

- Initial Therapy
  - Does transplant Fitness make a difference?
  - Goal is deep response
  - Maintenance Approaches
- Relapse Considerations

Mantle Cell Lymphoma
Step 1

- Induction Therapy for non-indolent (95%)
  - High Dose Ara-C +/- R-CHOP-like
    - e.g. “Nordic”, “Lyma”, “UCSF/Alliance”, real hCVAD,
  - R-Bendamustine-based
    - R-Bendamustine or R-Benda-Ara-C (R-BAC)
  - R-CHP/Velcade
  - R-CHOP

Mantle Cell Lymphoma
Step 2

- Autologous Transplant in CR1
  - High Dose Ara-C +/- R-CHOP-like
  - R-Bendamustine
  - R-CHP/Velcade
  - R-CHOP

Mantle Cell Lymphoma
Step 3

- Maintenance therapy with Rituximab
  - High Dose Ara-C +/- R-CHOP-like + Auto ?
    - No Auto? Shouldn't be doing this regimen
  - R-Bendamustine + Auto ?
    - No Auto, NO
  - R-CHP/Velcade + Auto ?
    - No Auto: yes?
  - R-CHOP + Auto ?
    - No Auto, FOR SURE

B-R + Watch & Wait vs. B-R + 2 years Rituximab

StiL NHL 7-2008 - MAINTAIN

MCL → B-R → ≥ PR → R

Any age
No ASCT

up to
6 cycles

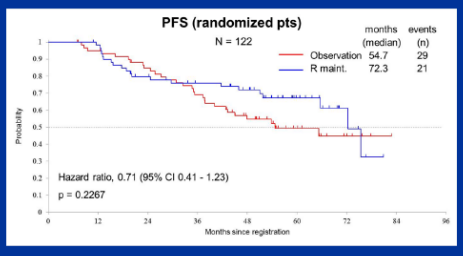
SD, PD
off study

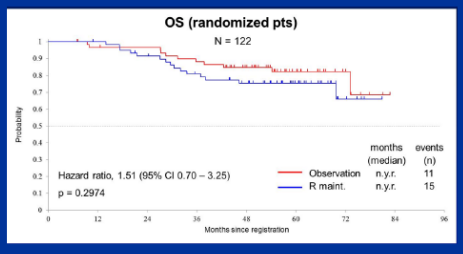
n = 122

Observation
(n = 62)

Rituximab
2 yrs, q 2 mo
(n = 60)

Results: Rituximab maintenance does not improve PFS or OS after Bendamustine





CONCLUSION: For older patients with mantle cell lymphoma, Rituximab maintenance after initial treatment with R-Bendamustine is not needed.

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

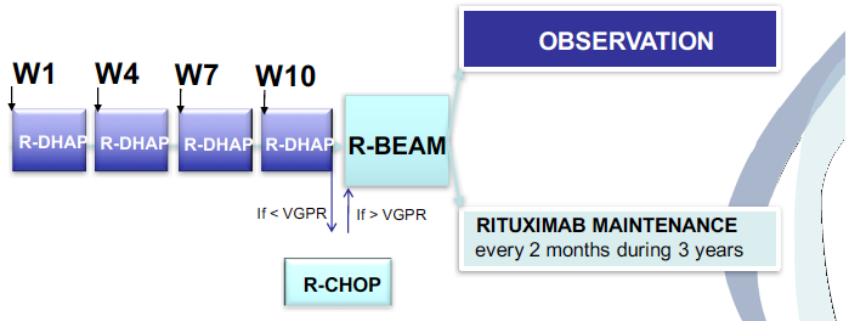
Steven Le Gouill, MD, PhD, Catherine Thieblemont, MD, PhD, Anne Moreau, MD, Lucie Oberic, MD, Krimo Bouabdallah, MD, Emmanuel Gyan, MD, PhD, Gandhi Damaj, MD, PhD, Vincent Ribrag, MD, PhD, Pierre Feugier, MD, PhD, Olivier Casasnovas, MD, Hacène Zerazhi, MD, Corinne Haioun, MD, PhD, Hervé Maisonneuve, 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, Danielle 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

Lysa
THE LYMPHOMA STUDY ASSOCIATION

Abstract # 145 ASH 2016

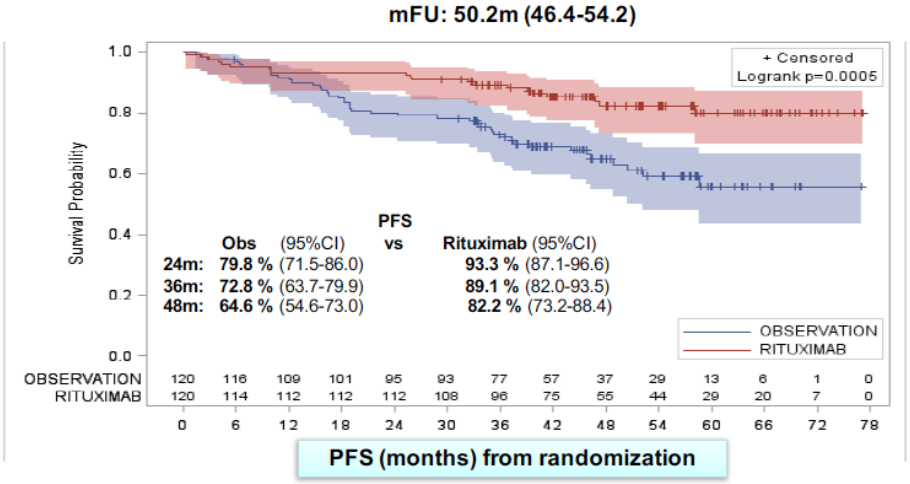
LyMa trial



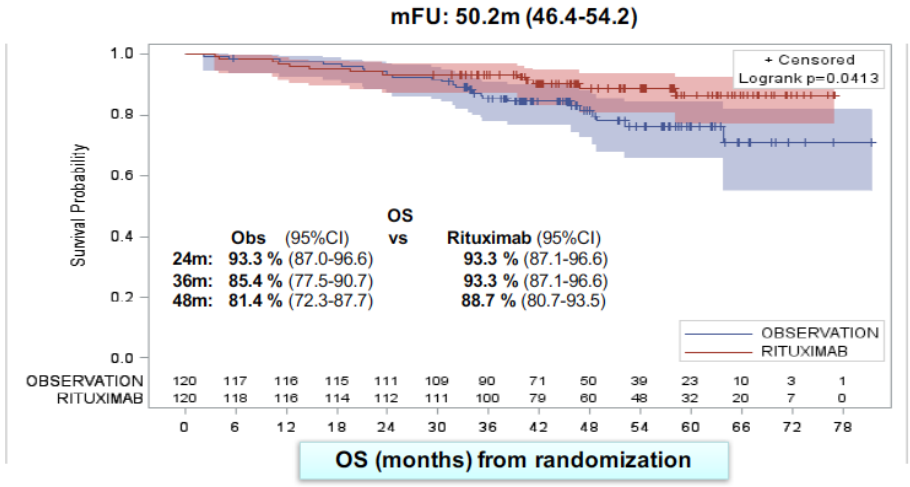
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

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



Mantle Cell Lymphoma
Step 3

- Maintenance therapy with Rituximab
  - High Dose Ara-C +/- R-CHOP-like + Auto Yes
    - No Auto? Shouldn't be doing this regimen
  - R-Bendamustine + Auto ?
    - No Auto, NO
  - R-CHP/Velcade + Auto Yes?
    - No Auto: yes?
  - R-CHOP + Auto Yes
    - No Auto, FOR SURE

Mantle Cell Lymphoma

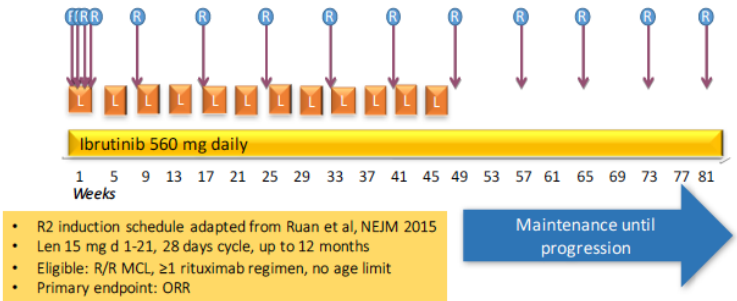
- Initial Therapy
- Relapse Considerations
  - Alternate induction regimens
  - Ibrutinib
  - Lenalidomide
  - velcade

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



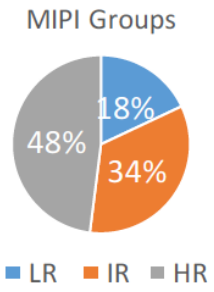
- R2 induction schedule adapted from Ruan et al, NEJM 2015
- Len 15 mg d 1-21, 28 days cycle, up to 12 months
- Eligible: R/R MCL, ≥1 rituximab regimen, no age limit
- Primary endpoint: ORR
- Aim: to improve ORR in R/R MCL, compared to single agent ibrutinib

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

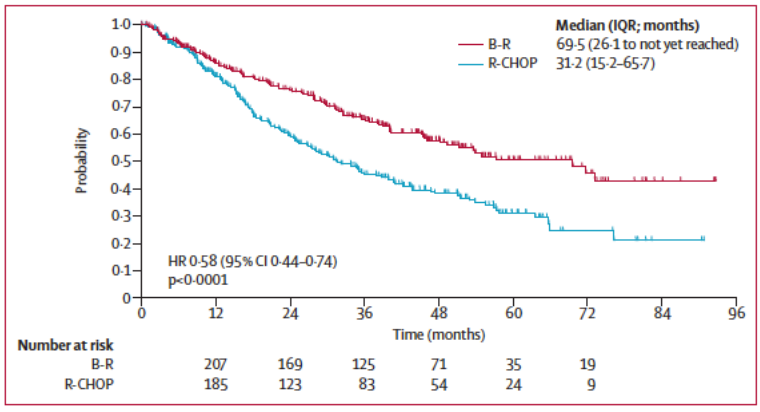
Follicular Lymphoma

- Choosing initial therapy
- Role for maintenance
- Relapse Considerations

Follicular Lymphoma

- Choosing initial therapy
  - Is Bendamustine StiL the standard?
  - Is Rituxan still the standard?
- Role for maintenance
- Relapse Considerations

StiL NHL1: PFS with R-Bendamustine superior to R-CHOP

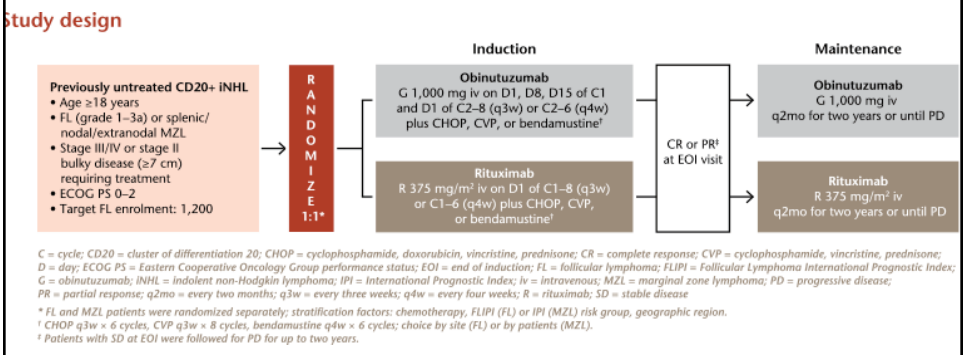


Rummel et al 2013, Lancet

Gallium Study: Obinutuzumab+chemo vs. Rituximab+chemo 1st Line

- International, open- label, randomized phase III trial
- Previously untreated, CD20-positive FL or splenic/nodal/extranodal marginal zone lymphoma (MZL) were included
- Patients received obinutuzumab or rituximab plus:
  - Bendamustine (n = 827)
  - Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (n = 433)
  - Cyclophosphamide, vincristine, prednisone (CVP) (n = 141)
- Primary endpoint was investigator-assessed PFS in patients with FL.
- The study was unblinded per IDMC recommendation because of superiority in the FL arm.

Gallium Design



Gallium Results

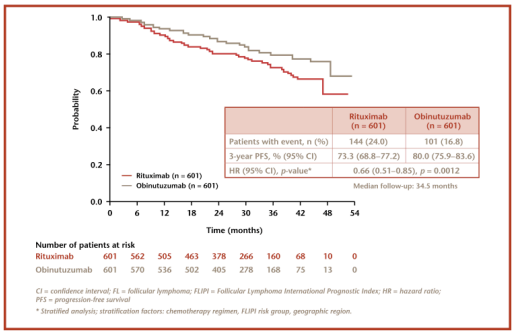
- 1,202 patients with FL were enrolled and randomized to treatment (intent to treat population).
- Median follow-up was 41.1 months
- Baseline patient and disease characteristics were similar between the obinutuzumab and rituximab arms.
- A large number of patients had a FLIPI score ≥3 (42.1% in the rituximab arm and 41.4% in the obinutuzumab arm) and bulky disease (45.2% in the rituximab arm and 42.5% in the obinutuzumab arm).

Gallium Efficacy

- ORR was 86.9% in the rituximab arm and 88.5% in the obinutuzumab arm.
  - CR: 23.8% in the rituximab arm and 19.5% in the obinutuzumab arm
- The three-year investigator-assessed PFS was 80.0% in the obinutuzumab arm and 73.3% in the rituximab arm (HR = 0.66; 95% CI: 0.51–0.85; $p = 0.0012$).
  - IRC-assessed PFS was 81.9% and 77.9% respectively (HR = 0.71; 95% CI: 0.54–0.93; $p = 0.0138$).
- Three-year TTNT was 87.1% in the obinutuzumab arm and 81.2% in the rituximab arm (HR = 0.68; 95% CI: 0.51–0.91; $p = 0.0094$).
- Three-year OS was 94.0% in the obinutuzumab arm and 92.1% in the rituximab arm (HR = 0.75; 95% CI: 0.49–1.17; $p = 0.21$)

Gallium: PFS in FL

Figure 1. Investigator-assessed progression-free survival (FL population)



	Rituximab (n = 601)	Obinutuzumab (n = 601)
Patients with event, n (%)	144 (24.0)	101 (16.8)
3-year PFS, % (95% CI)	73.3 (68.8–77.2)	80.0 (75.9–83.6)
HR (95% CI), *p*-value*	0.66 (0.51–0.85), *p* = 0.0012	

CI = confidence interval; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; HR = hazard ratio; PFS = progression-free survival

** Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region.*

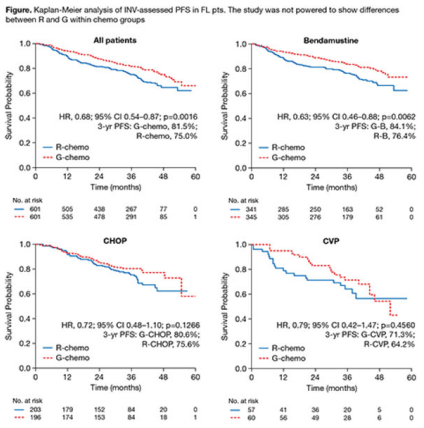


Figure. Kaplan-Meier analysis of INV-assessed PFS in FL pts. The study was not powered to show differences between R and G within chemo groups

Gallium Toxicity

TABLE 1 Safety summary (number [%] of FL pts* with ≥1 AE).

	Benda		CHOP		CVP		All	All
	G-B (n=338)	R-B (n=338)	G-CHOP (n=193)	R-CHOP (n=203)	G-CVP (n=61)	R-CVP (n=56)	G-chemo (n=595)	R-chemo (n=597)
AEs	338 (100)	331 (97.9)	191 (99.0)	201 (99.0)	61 (100)	56 (100)	593 (99.7)	585 (98.0)
Grade 3–5 AEs	233 (68.9)	228 (67.5)	171 (88.6)	151 (74.4)	42 (68.9)	30 (53.6)	449 (75.5)	409 (68.5)
Neutropenia†	100 (29.6)	102 (30.2)	137 (71.0)	111 (54.7)	28 (45.9)	13 (23.2)	265 (44.5)	226 (37.9)
Leucopenia†	11 (3.3)	15 (4.4)	39 (20.2)	34 (16.7)	1 (1.6)	1 (1.8)	51 (8.6)	50 (8.4)
Febrile neutropenia†	18 (5.3)	13 (3.8)	22 (11.4)	14 (6.9)	2 (3.3)	2 (3.6)	42 (7.1)	29 (4.9)
AEs of special interest by category								
Grade 3–5 infections‡	89 (26.3)	66 (19.5)	23 (11.9)	24 (12.4)	8 (13.1)	7 (12.5)	121 (20.3)	98 (16.4)
Second neoplasms§	37 (10.9)	23 (6.8)	9 (4.7)	11 (5.4)	1 (1.6)	2 (3.6)	47 (7.9)	36 (6.0%)
SAEs	176 (52.1)	160 (47.3)	76 (39.4)	67 (33.0)	26 (42.6)	19 (33.9)	281 (47.2)	246 (41.2)
Fatal AEs	20 (5.9)	16 (4.7)	3 (1.6)	4 (2.0)	1 (1.6)	1 (1.8)	24 (4.0)	21 (3.5)
AEs causing treatment discontinuation	52 (15.4)	48 (14.2)	32 (16.6)	31 (15.3)	11 (18.0)	9 (16.1)	98 (16.5)	88 (14.7)

*Pts who received ≥1 dose of study drug. Three pts received G but no chemo. †Occurring in >10% of pts in any group.‡MedDRA System Organ Class 'Infections and Infestations.'§Malignant or unspecified tumours occurring >6 months after first study drug intake.

Follicular Lymphoma

- Choosing initial therapy
  - Is Bendamustine StiL the standard? YES
  - Is Rituxan still the standard? No?
- Role for maintenance
- Relapse Considerations

Alliance/CALGB 50803: A phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma

P Martin[1], SH Jung[2], BN Pitcher[2], NL Bartlett[3], KA Blum[4], T Shea[5], J Ruan[1], SE Smith[6], JP Leonard[1], BD Cheson[7]

[1]Weill Cornell Medical College, [2]Alliance Statistics and Data Center, [3]Washington University, [4]Ohio State University, [5]University of North Carolina, [6] Alliance Protocol Office, [7]Georgetown University

ICML Meeting, June 17, 2017

Objectives

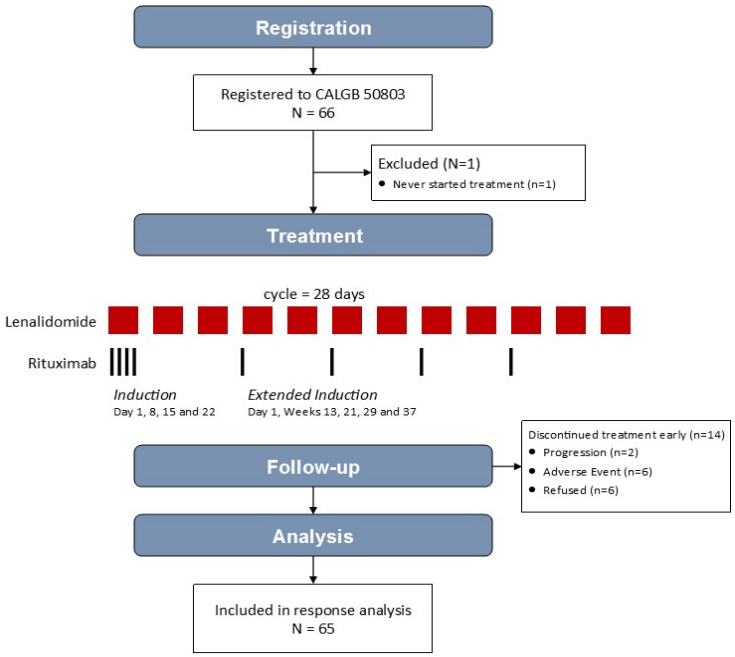
Aim: To assess the safety and efficacy of lenalidomide plus rituximab as upfront treatment for patients with follicular lymphoma in a multicenter setting.

- Primary objectives
  - Complete response
  - H_{A1} CR rate $\geq$ 85% for FLIPI 0-1
  - H_{A2} CR rate $\geq$ 67% for FLIPI 2
  - H_{null1} CR rate < 70% for FLIPI 0-1
  - H_{null2} CR rate < 47% for FLIPI 2
- Secondary objectives
  - Time to progression
  - Toxicity profile
- Correlative objectives
  - FcgR polymorphism
  - Angiogenic parameters

Subjects

- Untreated Follicular lymphoma
  - Grade 1-3a
  - Stage 2 bulky, 3, 4
  - FLIPI 0-2 risk factors
- No CNS involvement
- ANC $\geq$ 1,000/μL
- Plts $\geq$ 75,000/μL
- CrCl $\geq$ 30 mL/min
- T bili $\leq$ 2 x ULN
- No HBV, HCV

Characteristics	N = 66
Age	53 years (32-79)
Sex M vs. F	32 vs. 34
FLIPI 0-1 vs. 2 vs. 3	21 vs. 43 vs. 2
Grade 1 vs. 2. vs 3a	39 vs. 21 vs. 4
Non-bulky vs. bulky	50 vs. 15
FCGR3A 158F vs. 158F/V vs 158V	22 vs. 27 vs. 10
FCGR2A 131H vs. 131R/H vs 131R	18 vs. 28 vs. 13



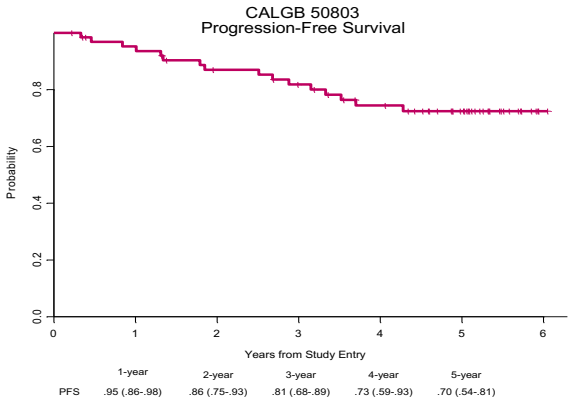
Adverse Events

Adverse Event	Grade 3	Grade 4
Neutrophil	15%	6%
Platelets	0%	2%
Infections	20%	0%
Rash	9%	0%
Fatigue	6%	0%
Hyperglycemia	6%	0%
Hypophosphatemia	6%	0%
Hypertension	6%	0%

Notable AEs include:
Thromboembolism: grade 1 (1), grade 2 (2)
Febrile neutropenia: grade 3 (1)
Tumor lysis syndrome: grade 3 (2)
No grade 4 non-hematologic AEs, second malignancies, tumor flare, or pregnancies reported.

Efficacy

Best Response	FLIPI 0-1, N=21	FLIPI 2-3, N=44*	Overall (N=65)
ORR	94%	96%	95%
CR	15 (71%)	32 (73%)	47 (72%)
PR	5 (23%)	10 (23%)	15 (23%)
Stable	0	1 (2%)	1 (2 %)
Not evaluated – AE	1 (5%)	1 (2%)	1 (2%)



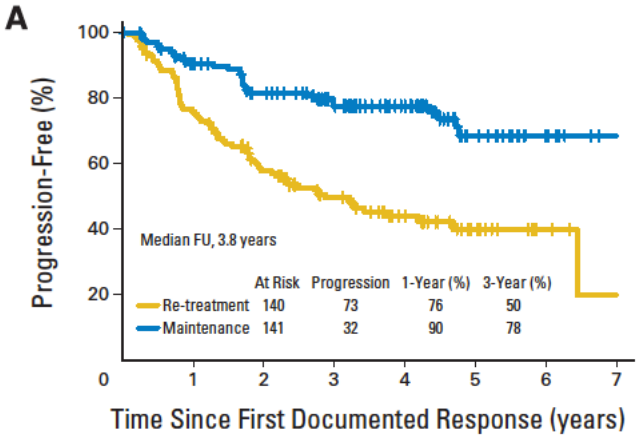
Conclusion

- Lenalidomide plus rituximab is highly active as front-line therapy in patients with low and intermediate-risk FLIPI scores.
  - ORR 95%, CR 72%. No association between FLIPI and CR.
  - 5-year PFS is 70%
- The regimen was well tolerated
  - Grade 3-4 adverse events were rare
- There was no association between FcR polymorphism or change in angiogenic markers and CR/PFS.

Follicular Lymphoma

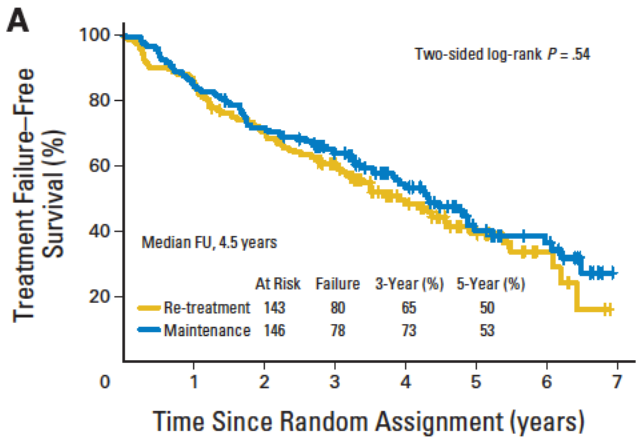
- Choosing initial therapy
- Role for maintenance
- Relapse Considerations

Maintenance vs Retreatment RESORT Trial



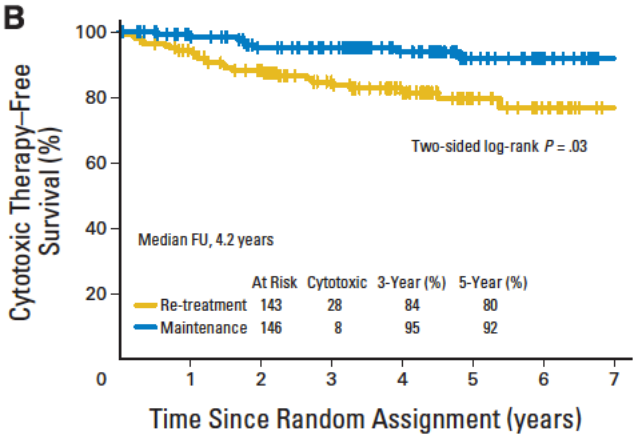
Kahl et al, JCO 2014

Maintenance vs Retreatment RESORT Trial



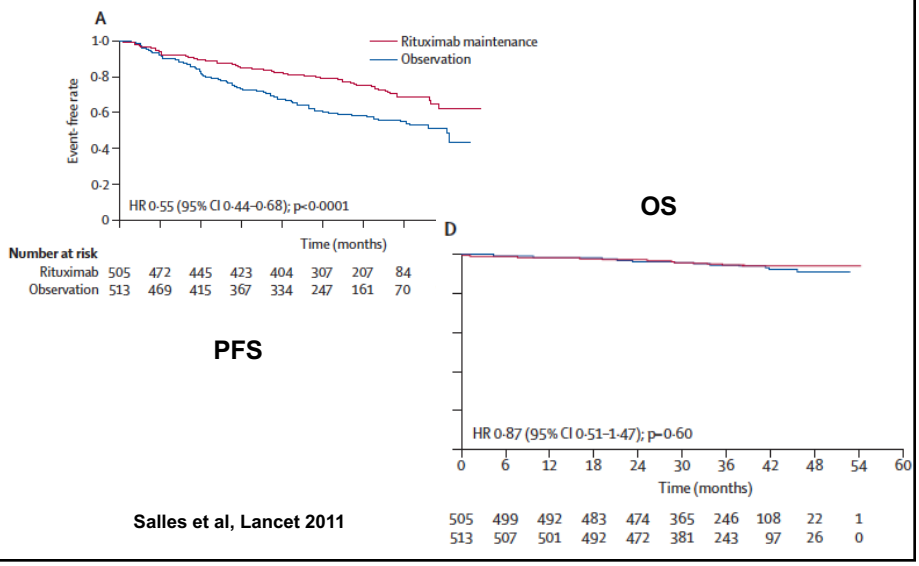
Kahl et al, JCO 2014

Maintenance vs Retreatment RESORT Trial



Kahl et al, JCO 2014

PRIMA: PFS and OS analyses



Salles et al, Lancet 2011

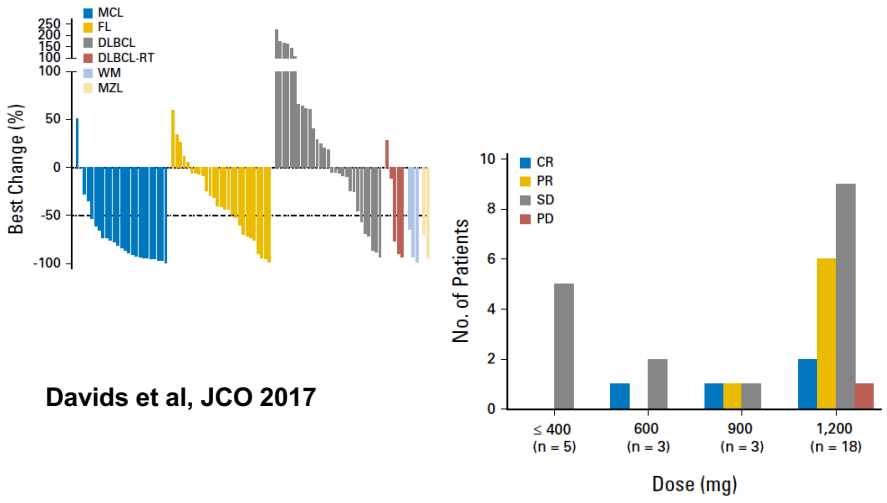
Follicular Lymphoma

- Choosing initial therapy
- Role for maintenance Unclear
- Relapse Considerations

Follicular Lymphoma

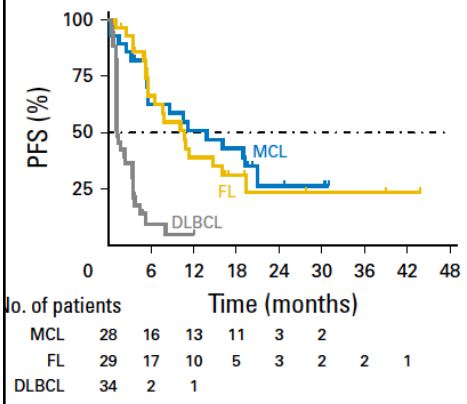
- Choosing initial therapy
- Role for maintenance
- Relapse Considerations
  - Bendamustine + Obinutuzumab
    - Not if benda given previously!
  - Venetoclax

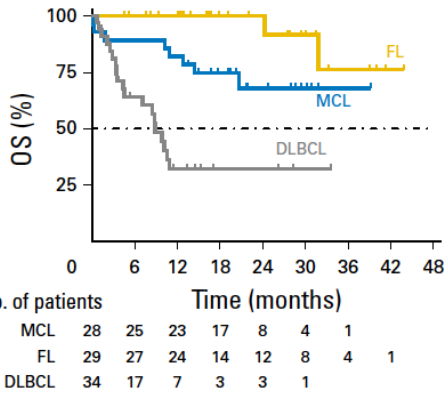
Venetoclax Monotherapy



Davids et al, JCO 2017

Venetoclax PFS and OS in NHLs





Venetoclax AEs

Adverse Event	All grades: All Doses (N = 106)	Grade 3/4: All Doses (N = 106)
Emergent*		
Any event	103 (97)	59 (56)
Nausea	51 (48)	0
Diarrhea	48 (45)	3 (3)
Fatigue	44 (42)	7 (7)
Decreased appetite	23 (22)	1 (1)
Vomiting	23 (22)	0
Constipation	22 (21)	2 (2)
Headache	19 (18)	0
Anemia	18 (17)	16 (15)
Cough	18 (17)	1 (1)
Neutropenia	18 (17)	12 (11)
Back pain	17 (16)	1 (1)
Upper RTI	17 (16)	1 (1)

Questions?

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

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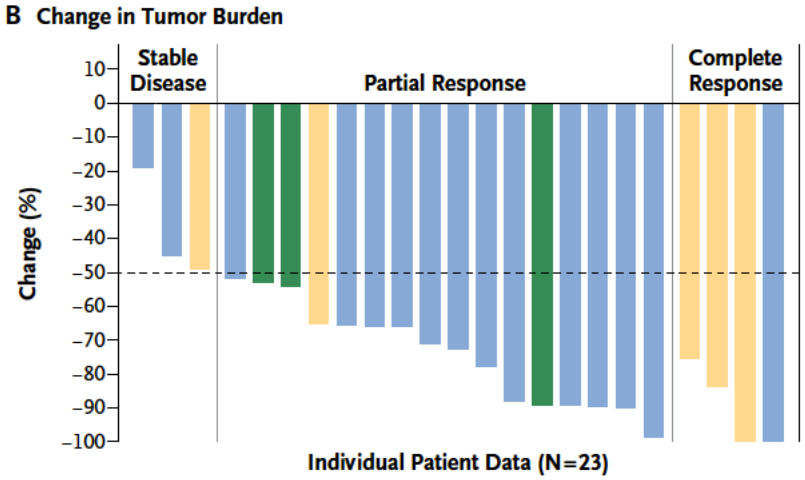
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

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



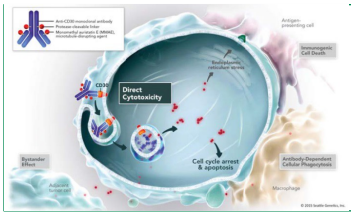
•Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

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]

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Karmanos Cancer Institute, Detroit, MI, USA; [4]University of Nebraska Medical Center, Omaha, NE, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Hackensack University Medical Center, Hackensack, NJ, USA; [7]Dana Farber Cancer Institute, Boston, MA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]Seattle Genetics, Inc., Bothell, WA, USA; [10]Bristol-Myers Squibb, Princeton, NJ, USA; [11]Stanford University Medical Center, Palo Alto, CA, USA

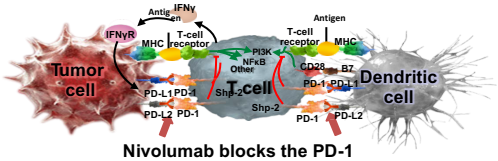
American Society of Hematology, San Diego, California, December 3–6, 2016, Abstract No. 1105

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

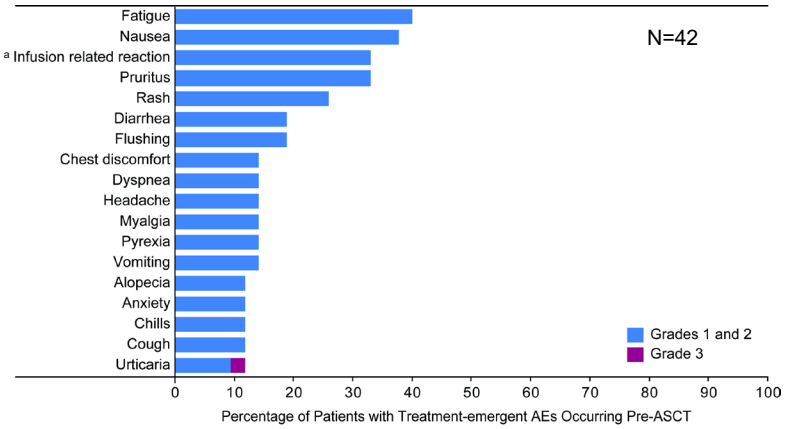
[a] Gardai et al., Cancer Res 75: Abstract 2469; 2015
[b] Gopal et al., Blood 2015;125(8):1236-43
[c] Younes et al., Lancet Oncol 2016; 17(9):1283-94

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

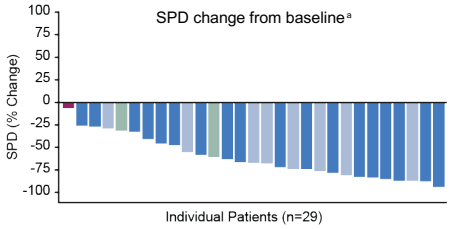
N=42

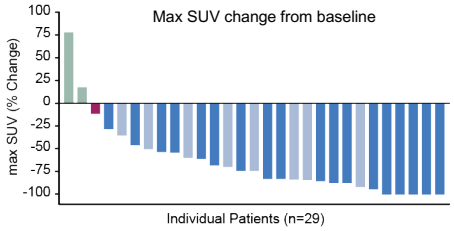
Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3/4 n (%)	Total n (%)
Hypothyroidism	0	2 (5)	0	2 (5)
Transaminase elevation	3 (7)	0	1 (2)	4 (10)
Diarrhea	8 (19)	3 (7)	0	11 (26)
Rash	8 (19)	4 (10)	0	12 (29)
Infusion related reaction (IRR)[b, c]	6 (14)	9 (21)	0	15 (36)

[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