NHL: Update on Slow-Growing Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

Program will begin shortly

1

NHL: Update on Slow-Growing Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

Welcome & Introductions

2

NHL: Update on Slow-Growing Lymphomas

Owen A. O'Connor, MD, PhD
Professor of Medicine and Experimental Therapeutics
Director, Center for Lymphoid Malignancies
Department of Medicine
Columbia University Medical Center
New York Presbyterian Hospital
New York, NY

Disclosure

Owen A. O'Connor, MD, PhD
Consulting: Millennium Takeda, Spectrum Pharmaceuticals and Mundipharma

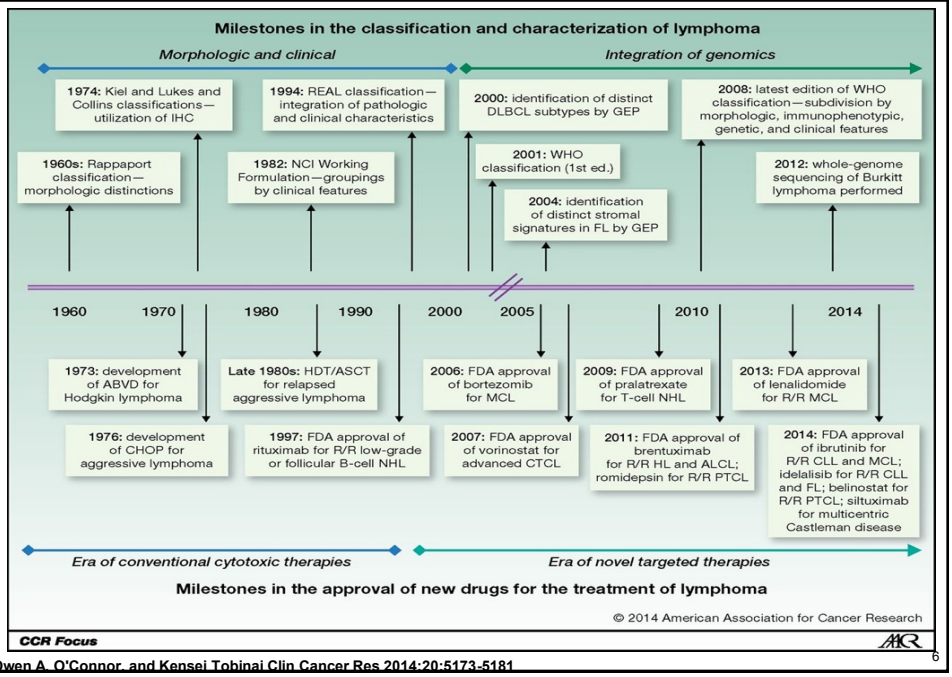
Research Support: Celgene and Acetylon

THE INDOLENT LYMPHOMAS
AN OVERVIEW

- Just what is lymphoma?
- How do we classify different types of lymphoma
- Lymphoma epidemiology: A relatively rare disease
- New "targeted" treatments
- *Trying* to put maintenance therapy in perspective
- Emerging biological agents
- Some principles of treatment

5

OUR RAPIDLY MOVING PACE OF DISCOVERY IN LYMPHOMA KNOWLEDGE AND TREATMENT



Owen A. O'Connor, and Kensei Tobinai Clin Cancer Res 2014;20:5173-5181

6

Where do lymphomas come from?

7

The Human Body is a Highly Organized Network of Interacting Systems

Atoms

Carbon Hydrogen Oxygen Nitrogen Sulfur

⬇

Biomolecules

Proteins Lipids Nuclei Acids Carbohydrates

Organelles
Mitochondria, nucleus

⬇

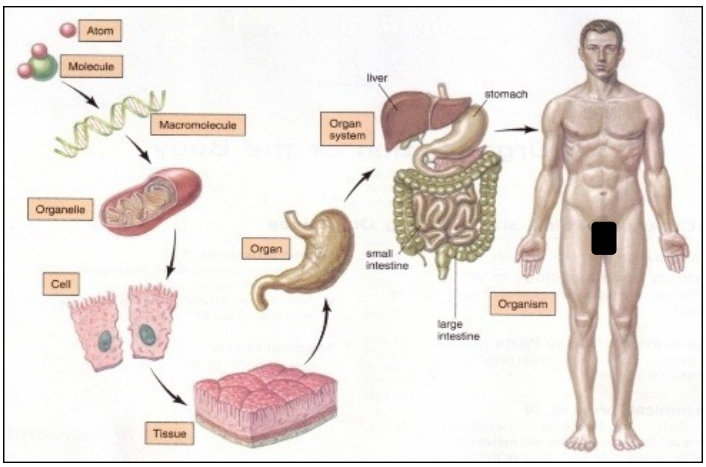
Cells
50,000,000,000,000
Over 100 different kinds of cell

⬇

Tissues
4 different kinds of tissue

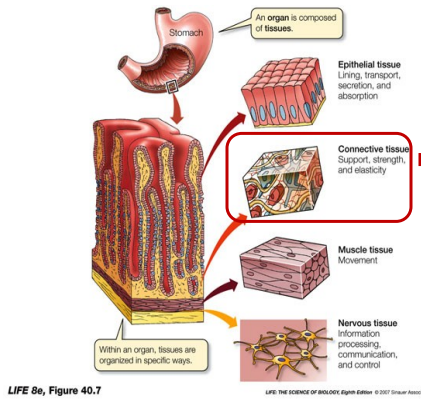
⬇

Organs & Organ Systems



8

The Collection of Blood Cells is a Type of Connective Tissue



LIFE 8e, Figure 40.7

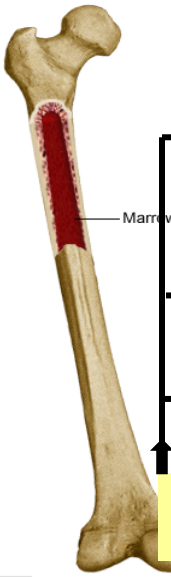
Blood is considered connective tissue because:

1. It is embryologically derived from the same origins as other connective tissue (bone, muscle, cartilage)
2. It 'connects' the body systems together

Hematopoietic System includes
Bone marrow
Spleen
Tonsils
Lymph nodes
Peyers Patches

9

Where Does Lymphoma Come From? – The Cell of Origin



White Blood Cells
- Myeloid → Eosinophils, Basophils, Neutrophils
- Lymphoid → B-Lymphocytes, T-Lymphocytes, NK Cells

Red Blood Cells

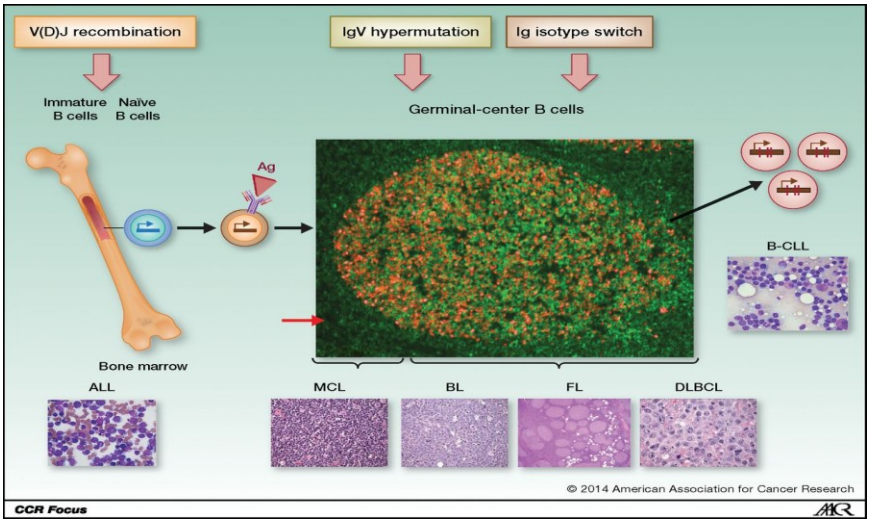
Platelets

Hematopoietic Stem Cell

~ 70 Types of Lymphoma

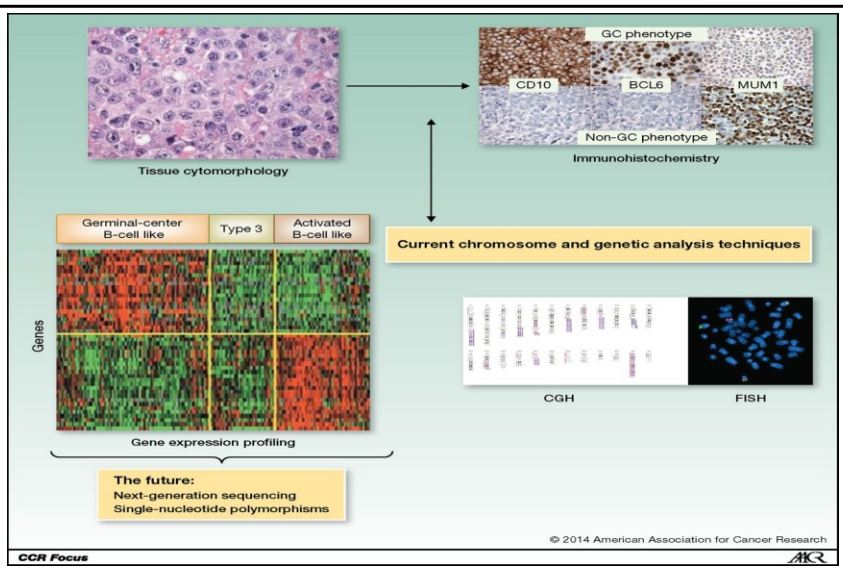
10

B- AND T- LYMPHOCYTES NATURALLY UNDERGO "CONTROLLED" RECOMBINATION SHM, LEADING TO IMMUNOGLOBULIN DIVERSITY



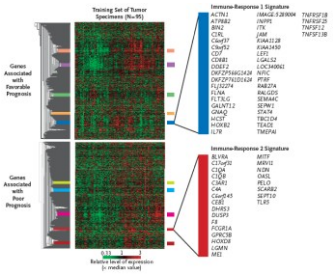
Owen A. O'Connor, and Kensei Tobinai Clin Cancer Res 2014;20:5173-5181

A HIERARCHY OF HOW HETEROGENEITY CAN BE VIEWED IN LYMPHOPROLIFERATIVE MALIGNANCIES



Owen A. O'Connor, and Kensei Tobinai Clin Cancer Res 2014;20:5173-5181

GENE EXPRESSION: FOLLICULAR NHL



Gene expression array demonstrates that the stromal microenvironment has profound prognostic influence

Expression Signature	Relative Risk of Death	*P* Value	Prognosis
Immune response 1	0.15	< .0001	Favorable
Immune response 2	9.35	< .0001	Unfavorable

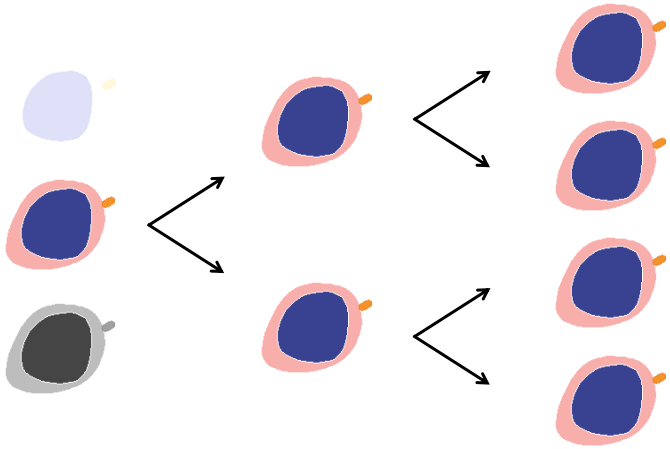
Expression Signature (Prognosis)	Relative Risk of Death	*P* Value
Immune response 1 (favorable)	0.15	< .0001
Immune response 2 (unfavorable)	9.35	< .0001

13

CLONAL EXPANSION

THE 4 MAJOR DEFECTS THAT DRIVE EVERY CANCER – CORRUPTING NORMAL CELL FUNCTIONS

Growth Defects: (1) The drivers of cell growth are left on; (2) the brakes don't work
Survival Defects: (3) Drivers of cell death lost; (4) Drivers of immortality turned on

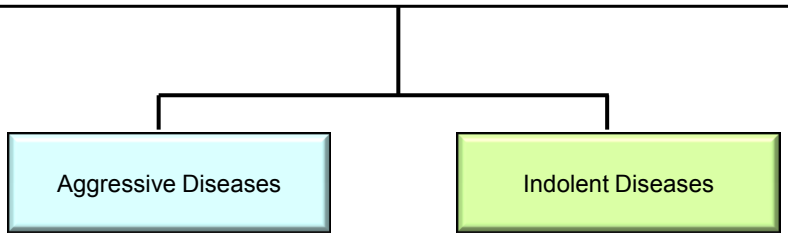


14

How do we classify lymphomas?
or
What kind of lymphoma do I have?

15

ORGANIZING 70 TYPES OF LYMPHOMA



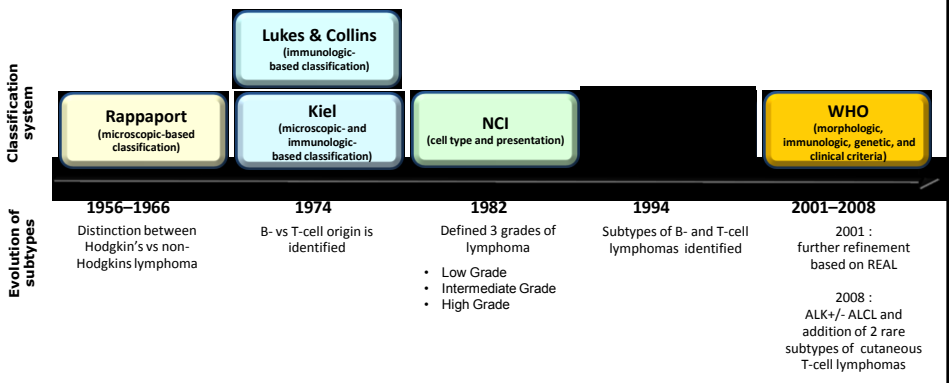
Pros	Cons
Potentially curable	Requires some form of chemotherapy
Relapsed disease can potentially be cured	Side effects of chemotherapy
Responds quick to treatment	Fast growing can produce symptoms quickly
4 to 6 months of treatment if cured	Relapse can be hard to manage

Pros	Cons
Very slow growing	Not curable – rare exceptions
Watching could be option	May require some form of lifelong therapy
Treatments less and less rely on chemotherapy	Can transform to aggressive
Can be relatively asymptomatic even with disease	Treatment side effects

16

HISTORY OF NHL CLASSIFICATION

- NHL classification schemes have evolved based on growing understanding of cancer cell characteristics[1]
- Subclassifications are driving more specific clinical trials and therapeutic approaches[2]



1. National Cancer Institute. SEER training module for lymphoma. Available at http://training.seer.cancer.gov/lymphoma/abstract-code-stage/morphology/.
2. Armitage J, et al. *J Clin Oncol*. 2008;26:4124–4130.

17

WHO CLASSIFICATION OF LYMPHOID NEOPLASMS

PARTIAL LIST – APPROXIMATELY 68 TYPES

PRECURSOR CELL LYMPHOMA	PERIPHERAL T AND NK LYMPHOMA
Lymphoblastic lymphoma, T cell	T-prolymphocytic leukemia
Lymphoblastic lymphoma, B cell	Granular Lymphocytic leukemia
PERIPHERAL B-CELL LYMPHOMA	NK cell leukemia
SLL/CLL type**	**Mycosis fungoides/Sezary***
B-prolymphocytic leukemia	Peripheral T cell lymphoma, NOS
Lymphoplasmacytic lymphoma*	Angioimmublastic lymphoma
Mantle cell lymphoma*+/-	NK/T cell, nasal
Follicular lymphoma*	Enteropathy associated lymphoma
Marginal zone lymphoma, MALT*	Hepatosplenic γδ lymphoma
Marginal zone lymphoma, Nodal*	Subcutaneous panniculitis-like
Marginal zone lymphoma, Splenic*	Anaplastic large cell lymphoma, system.
Hairy cell leukemia	**Anaplastic large cell lymphoma, cutan.***
Diffuse large cell lymphoma	Adult T-cell lymphoma/leukemia
Burkitt's lymphoma	**PTLD**

18

WHO/REAL Classification of Lymphoma
Features of Some Common Diseases

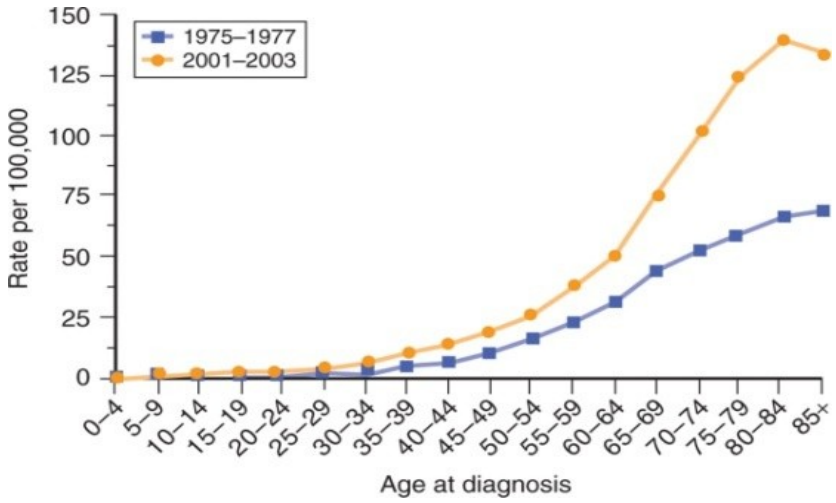
Subtype	Frequency (%)	Immunophenotype	Molecular Lesions
DLCL	31	CD20+	BCL2, BCL6, CMYC
FL	22	CD20+, CD10+, CD5-	BCL2
SLL/CLL	6	CD20 weak, CD5+, CD23+	+12, del(13q)
MCL	6	CD20+, CD5+, CD23-	CYCLIN D1
PTCL	6	CD20-, CD3+	Variable
MZL (MALT)	5	CD20+, CD5-, CD23-	BCL10, +3, +18
Mediastinal LCL	2	CD20+	Variable
ALCL	2	CD20-, CD3+, CD30+, CD15-, EMA+	ALK
LL (T/B)	2	T cell CD3+, B cell CD19+	Variable, TCL1-3
Burkitt-like	2	CD20+, CD10-, CD5-	CMYC, BCL2
MZL (Nodal)	1	CD20+, CD10-, CD23-, CD5-	+3, +18
SLL, PL	1	CD20+, clg+, CD5-, CD23-	PAX-5
BL	<1	CD20+, CD10+, CD5-	CMYC
TOTAL	88		

19

The epidemiology of lymphoma

20

Lymphoma, Like Most Cancers, is a Disease of the Elderly



21

2012 Estimated US Cancer Cases*

Prostate = 242K
Breast = 227K
Lung = 226K
Bladder = 56K
Uterine = 47K
~800K

	Men 848,170		Women 790,740	
Prostate	29%	242K		
Lung & bronchus	14%	116K	110K	14%
Colon & rectum	9%	73K	70K	9%
Urinary bladder	7%	56K	47K	6%
Melanoma of skin	5%	44K	43K	5%
Kidney & renal pelvis	5%	40K	32K	4%
Non-Hodgkin lymphoma	4%	38K	32K	4%
Oral cavity	3%			3%
Leukemia	3%			3%
Pancreas	3%			3%
All Other Sites	18%			20%
			227K	29%

Breast
Lung & bronchus
Colon & rectum
Uterine corpus
Thyroid
Melanoma of skin
Non-Hodgkin lymphoma
Kidney & renal pelvis
Ovary
Pancreas
All Other Sites

Source: American Cancer Society, 2012

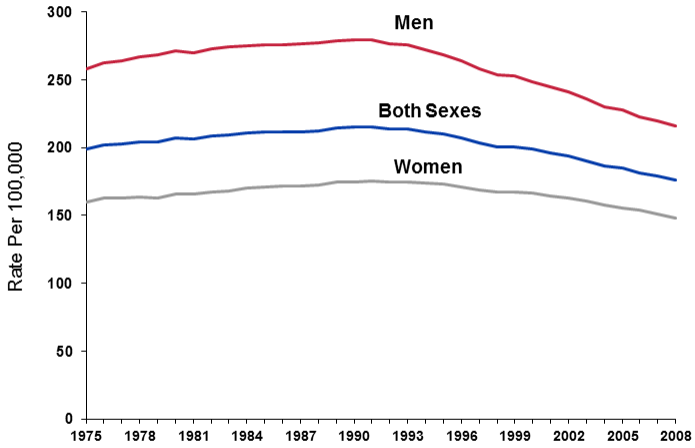
Source: American Cancer Society, 2012.

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

22

Cancer Death Rates* by Sex, US, 1975-2008

The Good News – Since mid 1990s Cancer Death Rates Dropping



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1975-2008, National Center for Health Statistics, Centers for Disease Control and Prevention.

23

Trends in Five-year Relative Survival (%)*, 1975-2007

Site	1975-1977	1987-1989	2001-2007
All sites	49	56	67
Breast (female)	75	84	90
Colon	51	60	65
Leukemia	34	43	57
Lung and bronchus	12	13	16
Melanoma	82	88	93
Non-Hodgkin lymphoma	47	51	70
Ovary	36	38	44
Pancreas	2	4	6
Prostate	68	83	100
Rectum	48	58	68
Urinary bladder	73	79	80

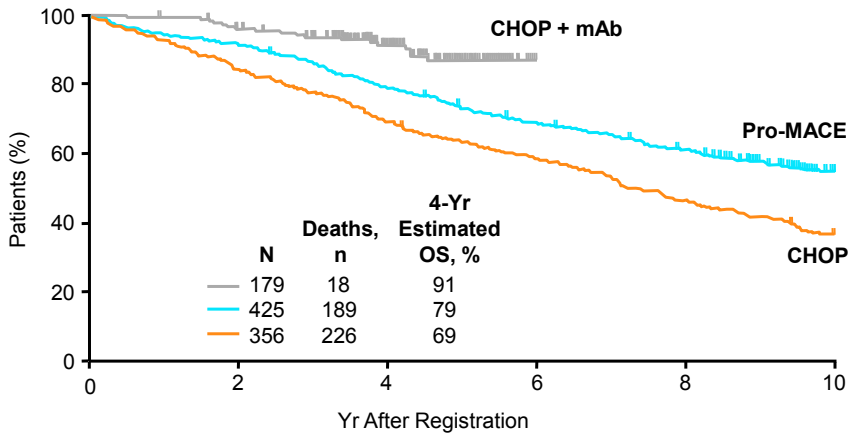
*5-year relative survival rates based on follow up of patients through 2008.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2008, Division of Cancer Control and Population Sciences, National Cancer Institute, 2011.

24

New “targeted” treatments for indolent lymphoma

25

MONOCLONAL ANTIBODIES HAVE CLEARLY CHANGED THE NATURAL HISTORY OF FL

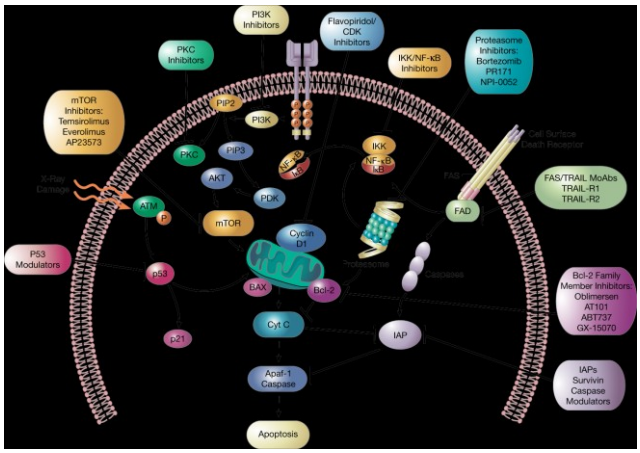


Fisher RI, et al. J Clin Oncol. 2005;23:8447-8452.

26

Rapidly Emerging Concepts in Pathogenesis Create New Opportunities in Treatment

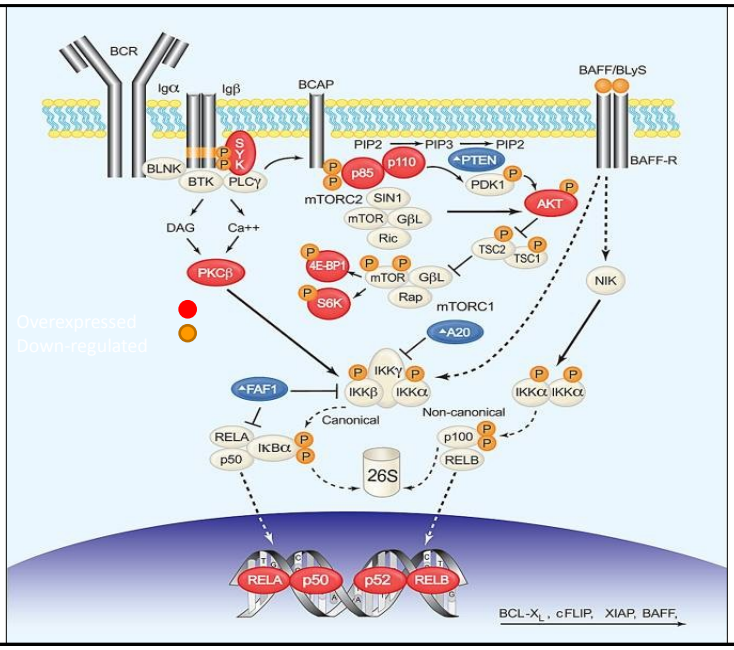
The Mergence of Molecular Pathogenesis and Molecular Pharmacology



- Distinct mechanisms of action
- Lack cross resistance to other standard agents
- Integration with conventional therapies is currently under study
- Hitting lymphoma at its biological roots

from Ghobrial. *CA Cancer J Clin*. 2005;55:178.

The B-Cell Receptor Links Many Known Dysregulated Pathways in Lymphoma: NF-κB, PI3K/AKT/mTOR and Bcl2 For Example



The Axis is Poised for Many Targeted Therapies

- Syk
- AKT
- BTK
- IkB
- mTORC 1 & 2
- PKCβ
- BAFF/BlyS
- NK-κB
- Bcl-2
- XIAP

P.Perez-Galan et al. Blood. 2011

THE B-CELL RECEPTOR LINKS MANY KNOWN DYSREGULATED PATHWAYS
THE OPPORTUNITIES FOR PRECISION MEDICINE

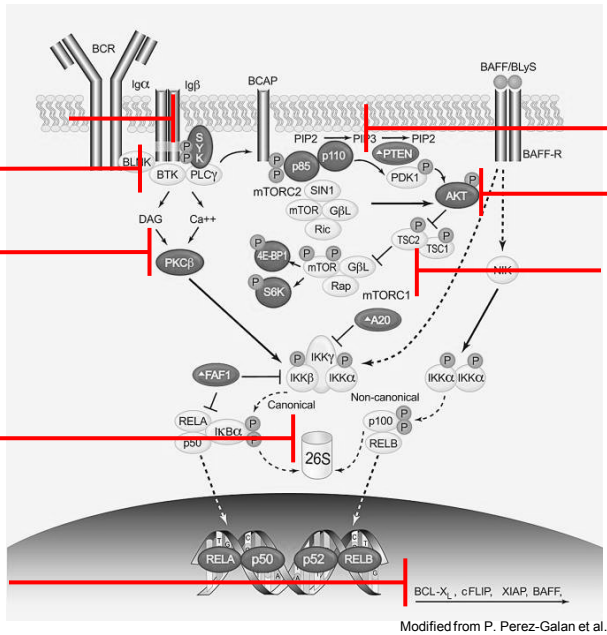
Fostamatinib

Ibrutinib
AVL-292

Enzastaurin

Bortezomib
Carfilzomib

ABT-737
ABT-199
Obatoclax



Idelalisib
IPI-145
TGR

Perifosine

Everolimus
Temsirolimus
Rapamycin

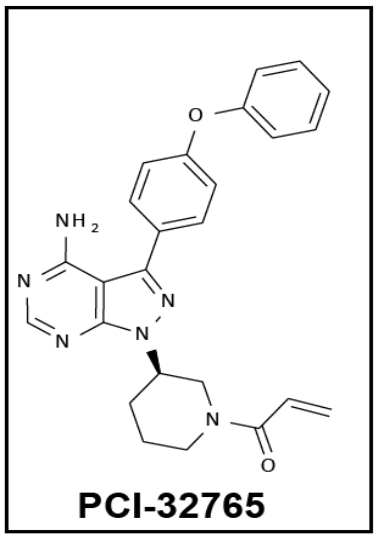
OSI-027
(dual mTOR)

BCL-X_L, cFLIP, XIAP, BAFF,

Modified from P. Perez-Galan et al. Blood. 2011

29

IBRUTINIB: FIRST-IN CLASS INHIBITOR OF BRUTONS TYROSINE KINASE (BTK)



PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF-kB pathways in lymphoma lines.

30

Patient Characteristics Phase II of PCI-32765 in MCL

	Bortezomib-Naïve (N=41)	Bortezomib-Exposed (N=27)	Total (N=68)
Age: Median:	66	69	67
Range:	47 – 83	54 – 83	47 – 83
Gender: Male	31 (76)	23 (85)	54 (79)
Time from Initial Diagnosis, # (%)			
< 3 yrs to 1st dose	20 (49)	6 (22)	26 (38)
≥ 3 yrs to 1st dose	21 (51)	21 (78)	42 (62)
ECOG Status: 0	24 (59)	13 (48)	37 (54)
1	12 (29)	12 (44)	24 (35)
2	5 (12)	2 (7)	7 (10)
Prior regimens, # (%)			
Median	2	3	2
Range	1 – 5	1 – 5	1 – 5
< 3 regimens	28 (68)	11 (41)	39 (57)
≥ 3 regimens	13 (32)	16 (59)	29 (43)

31

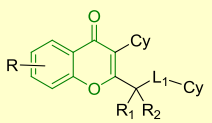
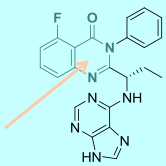
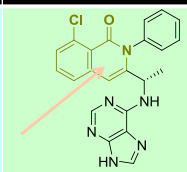
Approved and Anticipated Uses of Ibrutinib

- FDA approved for patients with relapsed or refractory chronic lymphocytic leukemia
- FDA approved for patients with 17 p deletion as front line therap
- FDA approved for patients with relapsed or refractory mantle cell lymphoma
- Approved in Waldenstroms Macroglobulinemia
- Combination with R-CHOP highly effective in ABC DLBCL

32

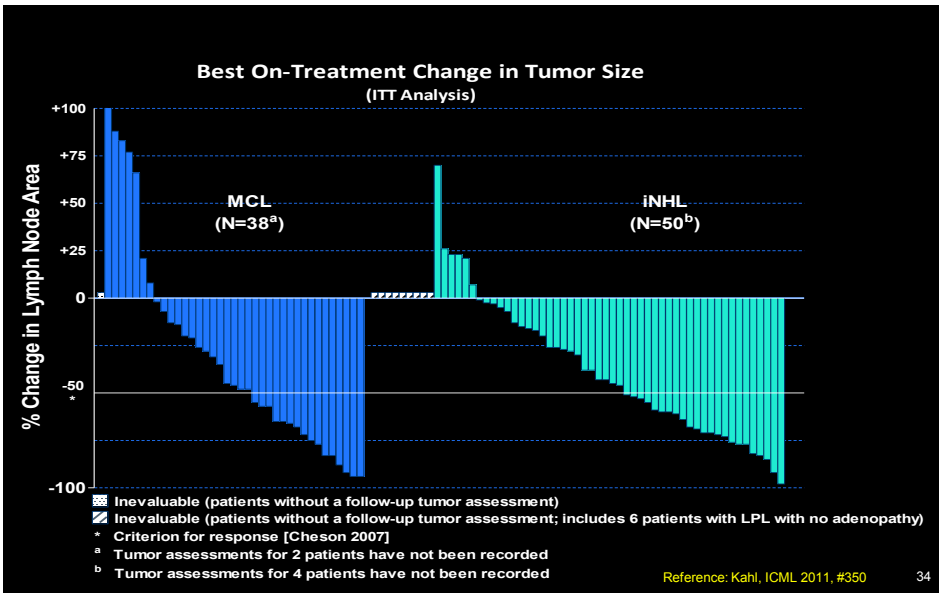
THREE PI3K INHIBITORS IN CLINICAL DEVELOPMENT

- Idelalisib is a first-in-class PI3Kd inhibitor, and has shown promising activity in indolent lymphoma, producing an objective response (OR) rates in the range of 72-85% when used in combination with rituximab and/or bendamustine.
- IPI-145 is a PI3Kg/d inhibitor that has demonstrated promising activity in both B- and T-cell lymphoma.
- Idelalisib and IPI-145 display high structural similarity and contain nitrogen based heterocyclic backbones known to induce hepatotoxicity (increased LFTs).
- TGR-1202 has a different backbone designed to potentially minimize toxicity while preserving delta specificity. In vivo studies have shown no hepatotoxicity.

TGR-1202	Idelalisib	IPI-145
		

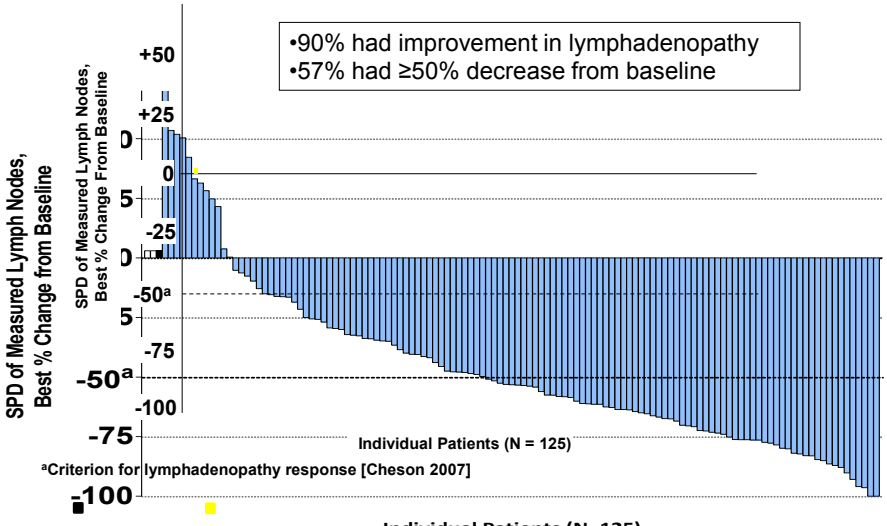
33

IDELALISIB PHASE 1 STUDY NHL DEMONSTRATES MARKED ACTIVITY IN PATIENTS WITH MCL AND Indolent NHL



34

Double Refractory (Rituximab + Alkylator) iNHL: Waterfall Plot Lymph Node Response

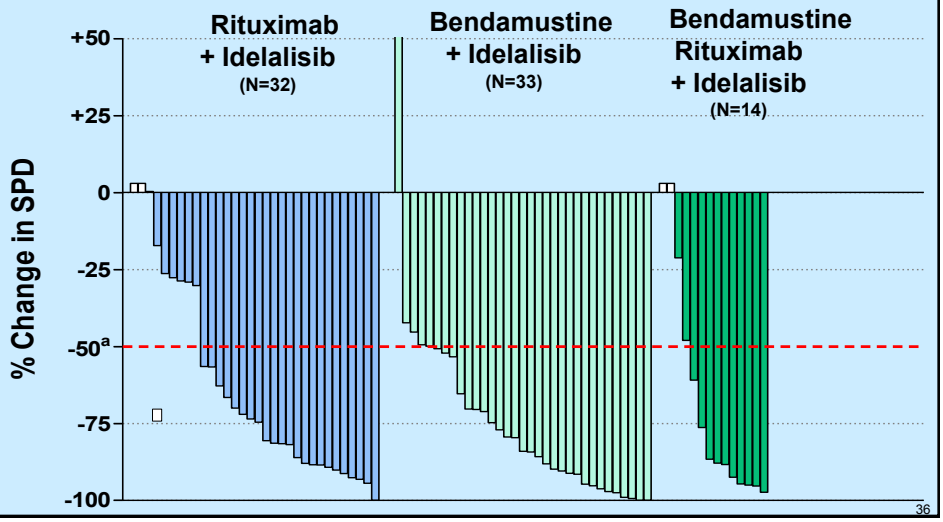


Gopal A, et al. *Blood.* 2013;122: Abstract 85.

5 subjects no post baseline evaluation:
2 subjects NE 1 subject PD by Lymph Node biopsy

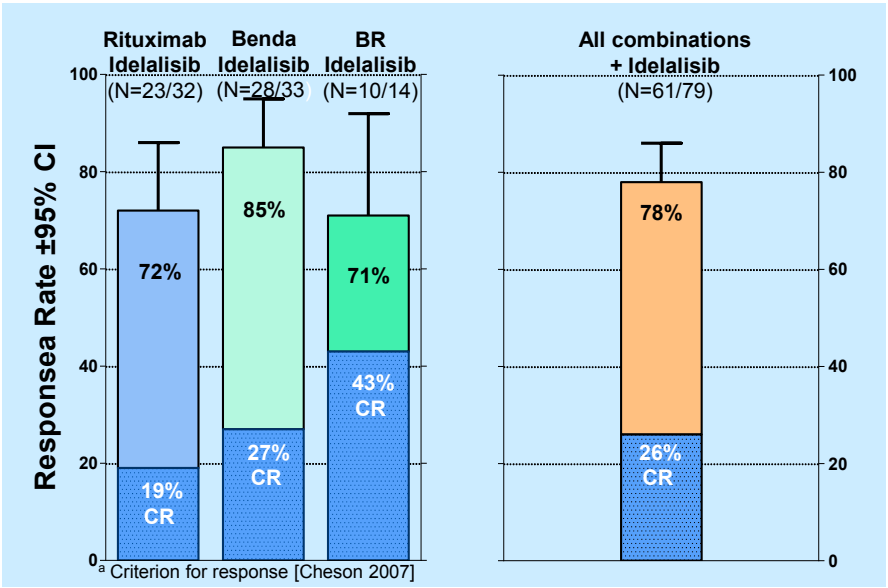
35

Phase 1b Idelalisib in NHL: Best Overall Response



36

PHASE 1B IDELALISIB IN NHL: OVERALL RESPONSE RATES



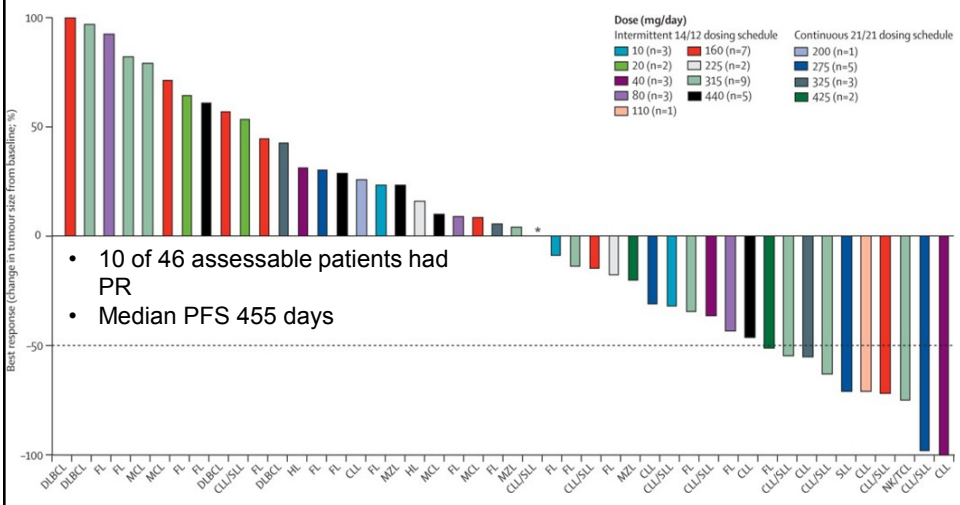
37

Approved and Anticipated Uses of Idelalisib

- FDA approved for patients with indolent lymphomas with rituximab
- FDA approved for patients with relapsed CLL

38

Results from the Phase 1/2a Study of Navitoclax (ABT-263) in Patients with Relapsed or Refractory Lymphoid Malignancies
Best Change in Tumor Size From Baseline

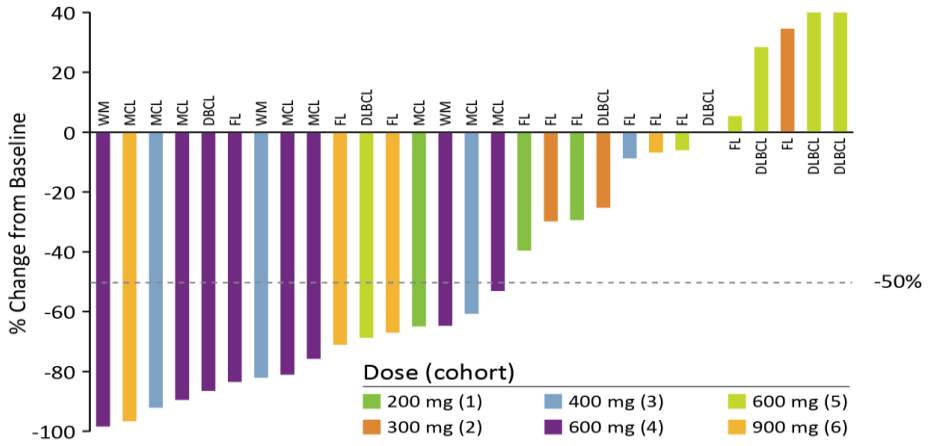


- 10 of 46 assessable patients had PR
- Median PFS 455 days

39

Phase 1 Study of ABT-199: Best Percent Change from Baseline in Nodal Size by CT Scan

- N = 29 evaluable (at minimum, 6 week assessment)
- Median Time to 50% Reduction = 43 days (range 36 to 113)



40

Trying to put maintenance rituximab in perspective

41

RATIONALE FOR MAINTENANCE THERAPY IN INDOLENT LYMPHOMA

- Maintenance therapy applied in patients responding to induction treatment is effective in hematological malignancies
- Maintenance therapy can deepen the response and lengthen remission
- Need to have therapeutic agents with a good efficacy/toxicity ratio:
  - No cumulative toxicity (hematopoietic stem cells)
  - No long term side effects
  - Preserve quality of life
  - Do no compromise subsequent treatment(s) efficacy

42

Factors to Consider in Evaluating the Merits of Maintenance Therapy

- What is Induction Therapy? R-Chemotherapy vs Rituximab
- What is the Extent of Disease? Low volume vs high volume.
- What is the Endpoint? Progression Free Survival (or Event Free Survival) vs Overall Survival
- Where in the Disease is it Done? Front-line vs Relapsed Setting
- Does one Strategy Have More Toxicity? Low Immunoglobulins and Risk of Infection

So Many Factors Difficult to be Dogmatic: Its Not as Simple as You Think?

43

Understanding Terminology
The Devil is in the Detail

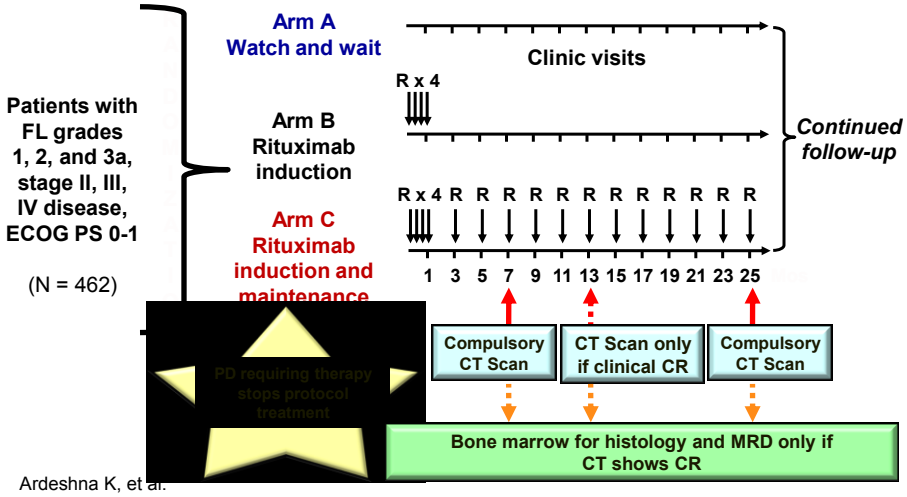
Time to Treatment Failure (TTTF) - the time from randomization to treatment discontinuation for any reason **disease progression, treatment toxicity, patient preference, or death**). From a regulatory point of view, TTF is generally not accepted as a valid endpoint. TTF is a composite endpoint influenced by factors unrelated to efficacy. Discontinuation may be a result of toxicity, patient preference, or a physician's reluctance to continue therapy. These factors are not a direct assessment of the effectiveness of a drug

Progression Free Survival - The progression-free survival (PFS) duration is defined as the time from randomization to **objective tumor progression or death**. Compared with other endpoints, PFS is a preferred regulatory endpoint because it includes death and **may correlate better with OS**. Assessment of either PFS or TTP needs to be conducted in randomized trials. To reduce bias, the same assessment technique should be used at each follow-up, and the same evaluation schedule should be consistently used.

Overall Survival – is defined as time from randomization **to death (all cause**). It is the **gold standard end-point**, but practically may be difficult because with time patients are doing better and better.

44

Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients

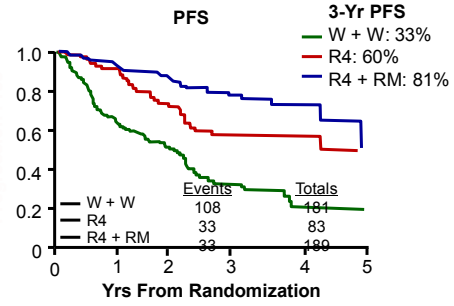


Ardeshna K, et al.

45

Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients

- Spontaneous remission observed in 3% of patients on watch and wait vs CR in 45% of patients on rituximab
- 93 patients required new therapy during follow-up period:
  - 84 patients (90%) had PD
  - 78 patients (84%) received chemotherapy as new treatment

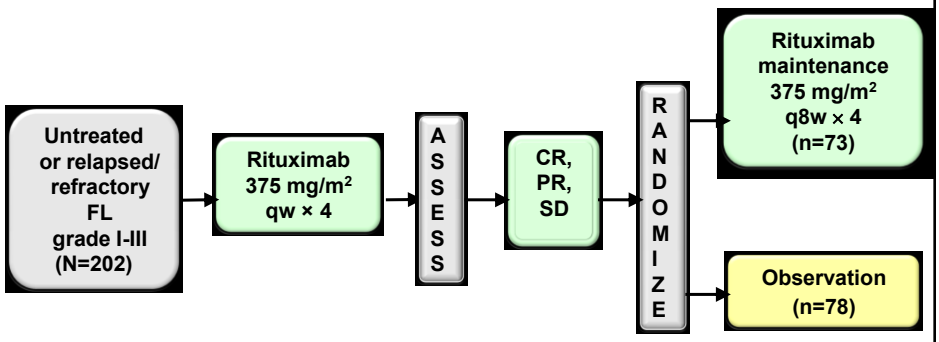


HR rituximab vs W + W): 0.46; 95% CI: 0.33-0.65; *P* < .001
HR (rituximab + M vs W + W): 0.21; 95% CI: 0.15-0.29; *P* < .001
HR (rituximab + M vs rituximab): 0.43; 95% CI: 0.24-0.72; *P* = .001

Ardeshna K,

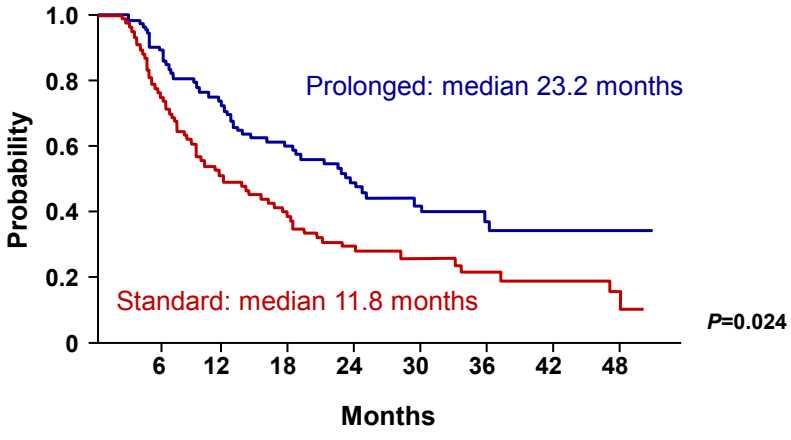
46

Rituximab Maintenance Therapy in FL
The First Study (SAKK Trial)



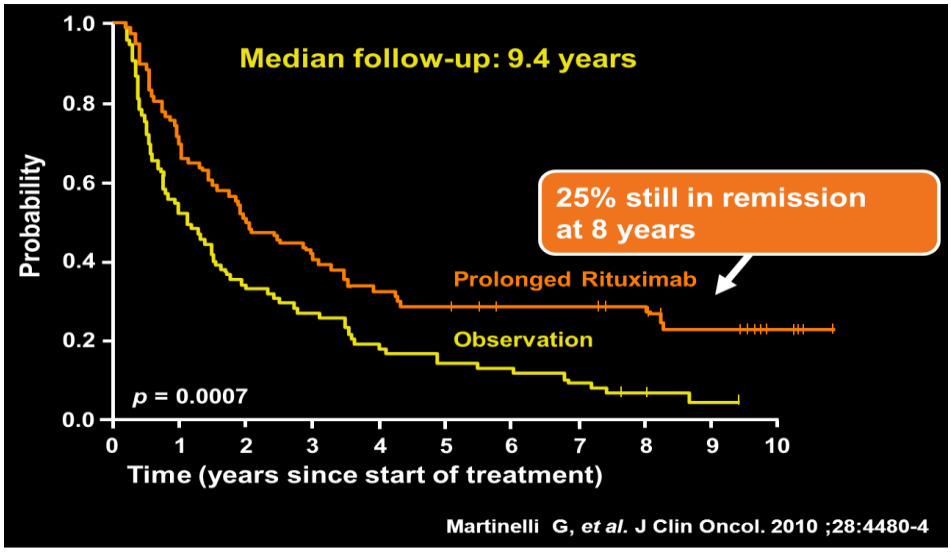
Ghielmini et al. *Blood.* 2004;103:4416. 47

Rituximab Maintenance Therapy in FL
(SAKK Trial): Event Free Survival



Ghielmini et al. *Blood.* 2004;103:4416. 48

UPDATED EFS IN SAKK 35/98: RITUXIMAB MAINTENANCE VS. OBSERVATION



49

RITUXIMAB MAINTENANCE THERAPY VS RE-TREATMENT AT PROGRESSION FOR INDOLENT NHL

114 rituximab-naive patients with previously treated indolent NHL

Rituximab 375 mg/m² weekly × 4

patients (70%) CR/PR/SD

RANDOMIZE

Rituximab maintenance therapy (n=44)
Rituximab 375 mg/m² weekly × 4 every 6 months for 4 courses

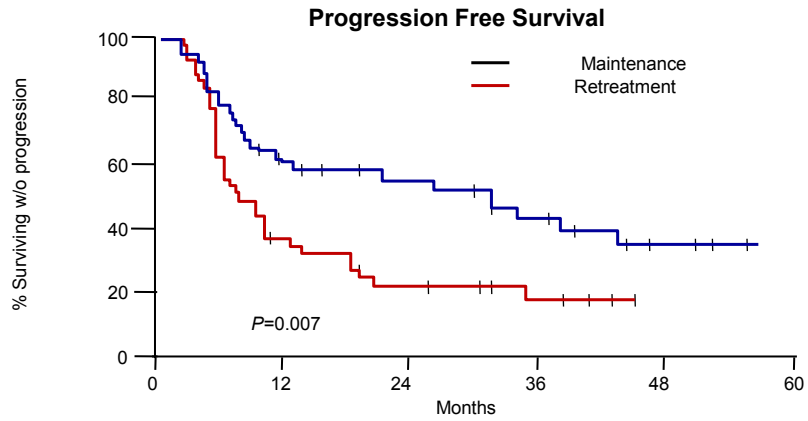
Re-treatment at time of progression (n=46)
Rituximab 375 mg/m² weekly × 4

Hainsworth et al. *Blood.* 2003;102(11). Abstract 231

50

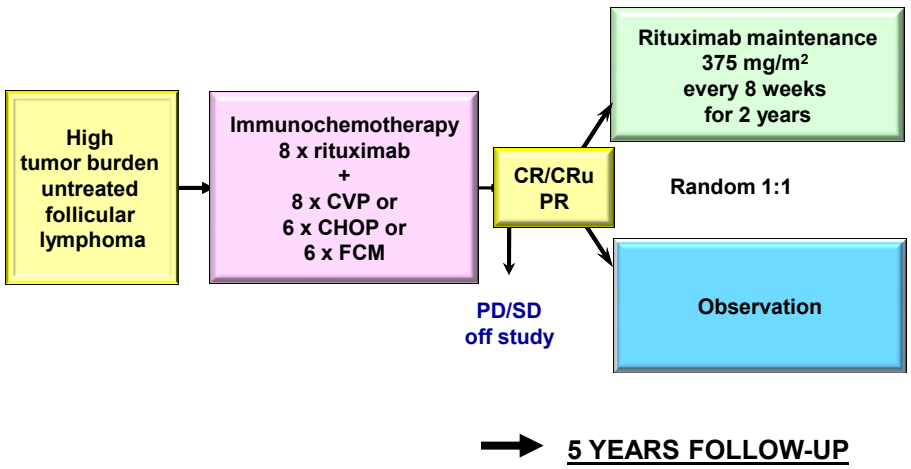
LYM-5 - Maintenance vs Retreatment After Rituximab : Hainsworth Regimen

FL, SL rel/refr; R weekly x 4 + (repeat every 6 months x 4 max) or (treat at progression)



Hainsworth et al. *J Clin Oncol.* 2005;23:1088

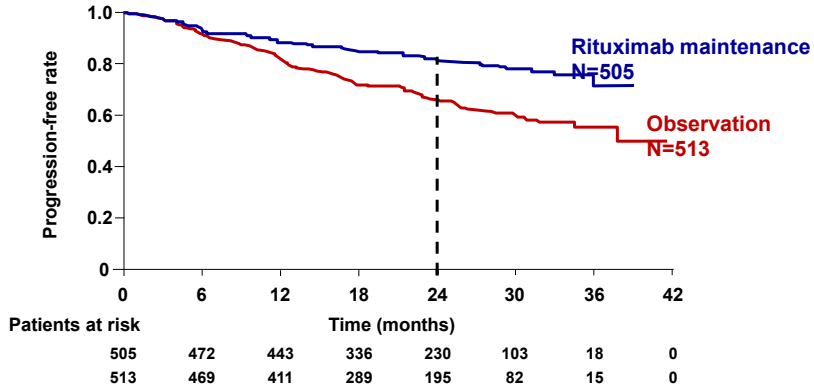
PRIMA Study Design : High Tumor Burden



Salles G, et al. *Lancet.* 2011;377(9759):42-51.

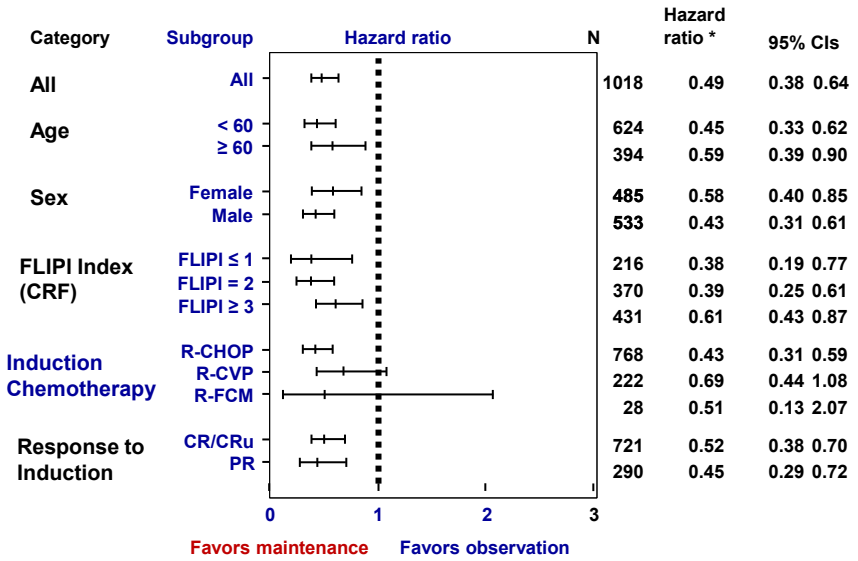
PRIMARY ENDPOINT (PFS) MET AT THE PLANNED INTERIM ANALYSIS

Rituximab maintenance significantly reduced the risk of lymphoma progression by 50% (stratified by response and induction regimen, HR=0.50, 95% CI 0.39; 0.64)



53

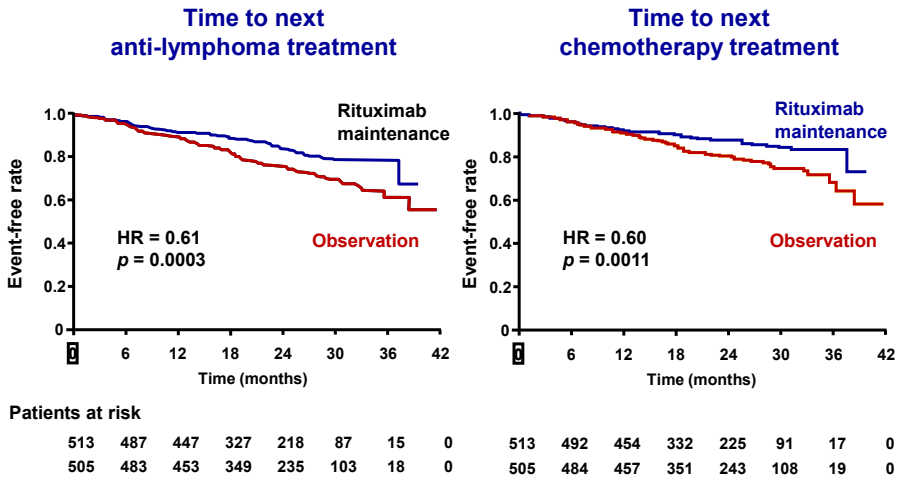
SUBGROUP ANALYSES RESULTS



Salles G, et al. *Lancet.* 2011;377(9759):42-51.

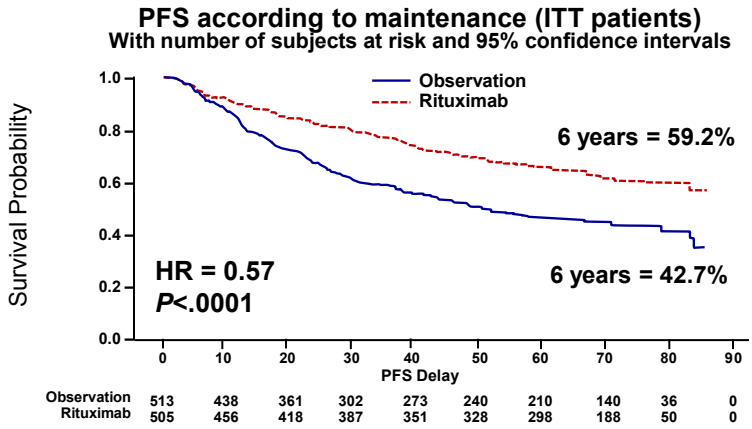
54

EFFICACY ACROSS SECONDARY ENDPOINTS
SUBSTANTIAL IMPROVEMENT WITH R-MAINTENANCE



Salles G, et al. *Lancet.* 2011;377(9759):42-51. 55

PRIMA 6-YEAR FOLLOW-UP: PFS FROM RANDOMIZATION

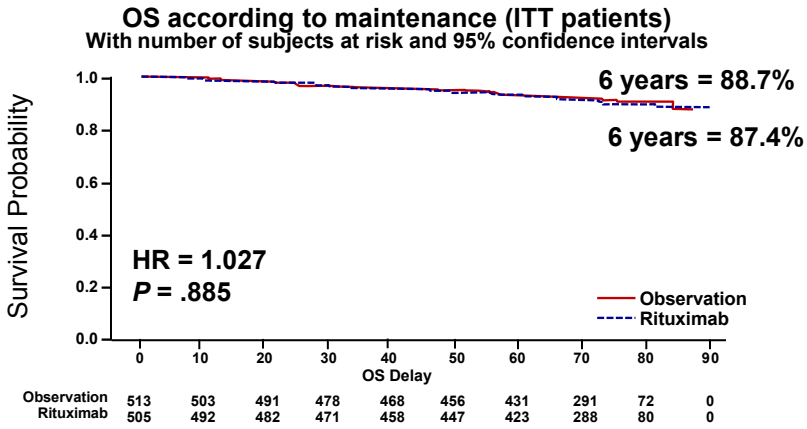


	No of Subjects	Event	Censored	Median Survival (95% CI)
Observation	513	56.5% (290)	43.5% (223)	8.5 (41.2 - 59.4)
Rituximab	505	39% (197)	61% (308)	NA (82.6 - NA)

Median follow-up since randomization: 73 months

G, et al. *Blood.* 2013;122: Abstract 509. 56

PRIMA 6-YEARS FOLLOW-UP: OVERALL SURVIVAL



	No of Subjects	Event	Censored	Median Survival (95% CI)
Observation	513	11.3% (58)	88.7% (455)	NA (NA - NA)
Rituximab	505	11.7% (59)	88.3% (446)	NA (NA - NA)

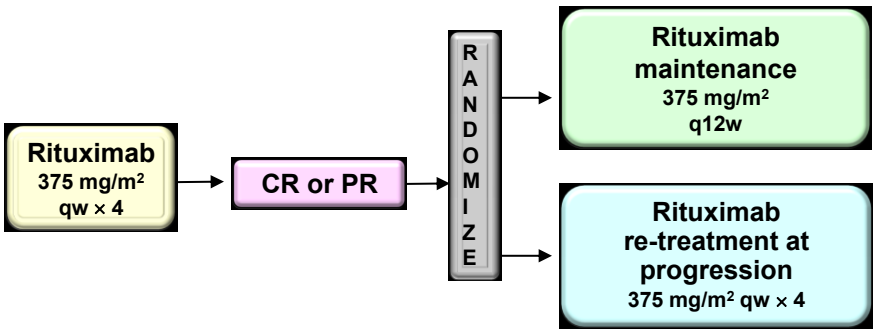
Median follow-up since randomization: 73 months

Salles G, et al. *Blood.* 2013;122: Abstract 509.

57

ECOG 4402 (RESORT)

Accruing 389 patients with low-tumor-burden stage III/IV indolent NHL



Primary End-point - Time to treatment failure
Secondary endpoint - Time to first cytotoxic therapy

58

Maintenance Rituximab in Follicular Lymphoma
Where Do We Stand?

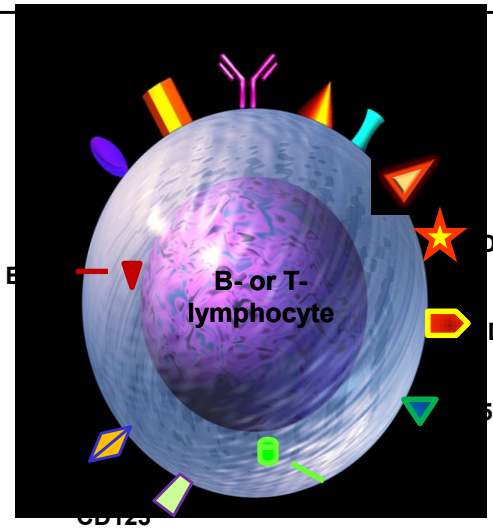
- The data do consistently demonstrate an improved PFS in most cicrumstances
- The data do not demonstrate any improvement in OS; no study ever statistically powered to find OS benefit
- There may be a benefit to increasing time between treatments for maintenance rituximab….
- There are significant side effects of protracted rituximab:
  - Hypogammaglobulinemia (low IgG, get checked!)
  - Sinusitis
  - Bronchopulmonary infections

59

Rapidly emerging novel biological approaches

60

HIGHLY PROMISING NEW APPROACHES
THE ULTIMATE PRECISION THERAPY?



Surface and cytoplasmic proteins targeted by antibodies are:

- Differentially expressed on different types of lymphoma
- Can serve as targets for new biological drugs
- Could lead to new biological agents in rare sub-types of hematological malignancies

61

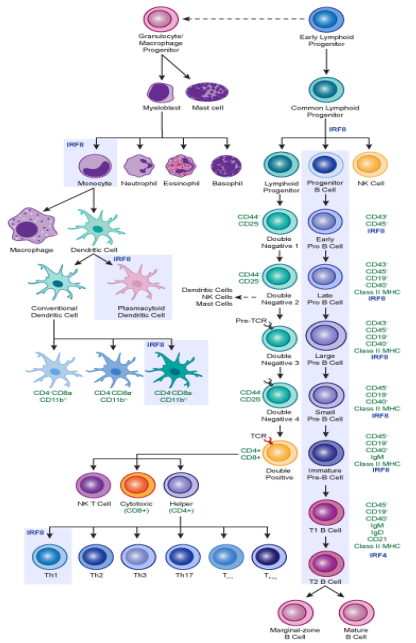


Figure 4. Regulation of cell development by IRF8. Markers are noted in green. The stages influenced by IRF8 (blue) are shaded purple.

TARGETING CELL SURFACE PROTEINS

- Often lineage specific expression offers opportunity for cell type specific targeting
- Expression on normal cellular counterparts can be associated with toxicity (Ex: hypogamma-globulinemia with Rituximab).
- Engineered features of the Anti-CD targeted drug:
  - Patterns of glycosylation
  - ADCC
  - CDC
  - Apoptosis
  - Conjugation to cytotoxic

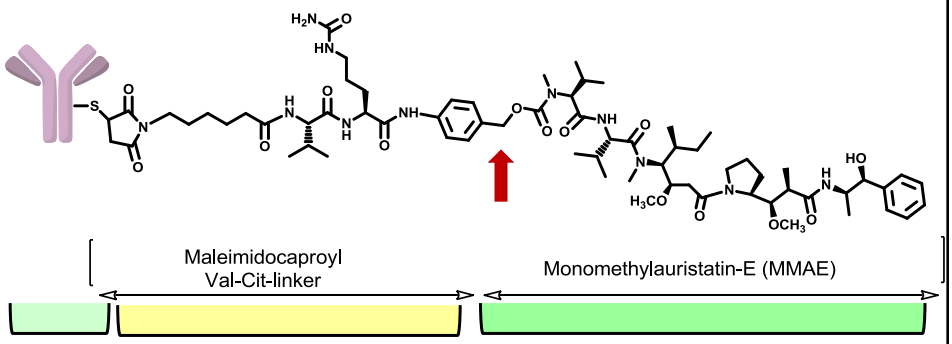
62

Clusters of Differentiation Define Discrete Hematopoietic Cell Lines: The Ultimate Precision Therapy?

Cell Type	CD Markers
Stem Cells	CD34+; CD31-, CD117+: CD123?
All White Blood Cells	CD45+
Granulocyte	CD45+; CD11b; CD15+; CD24+ CD114+; CD182+
Monocyte	CD45+; CD14+; CD114+; CD11a; CD11b; CD91+; CD16+
T-Lymphocyte	CD45+; CD3+; (CD30+, activated)
T-Helper Cell	CD45+; CD3+; CD4+
T-Regulatory Cell	CD45+; CD25+ Foxp3+
Cytotoxic T-Cell	CD45+; CD3+; CD8+
B-Lymphocyte	CD45+; CD19+; CD20+; CD24+; CD79a CD38+; CD22+; CD37+
Natural Killer Cell	CD16+; CD56+; CD3-; CD31; CD30; CD38+;

63

The Anatomy of Antibody Drug Conjugates The Possibilities are Endless



The Antibody

Target Rich! Any cell surface protein

The Linker

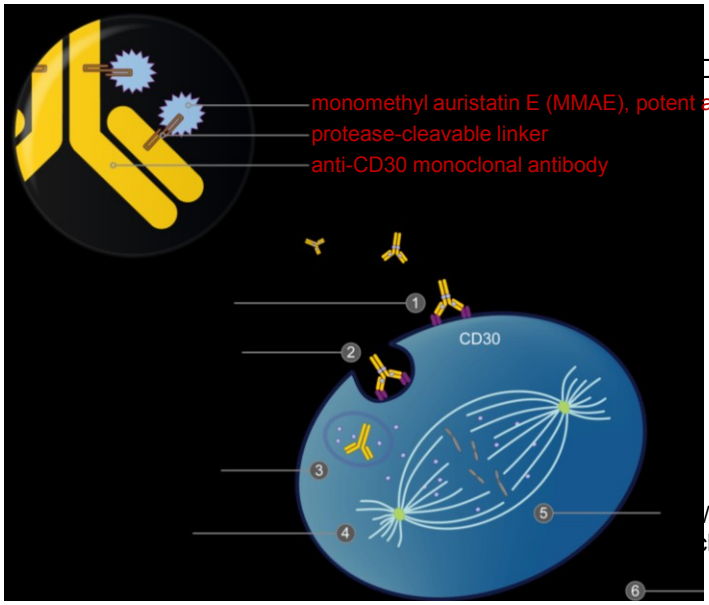
Perhaps the most important: need 'clean break'

The Warhead

The mechanism for tumor cell killing: too toxic to be injected directly into body

64

BRENTUXIMAB VEDOTIN PHARMACOLOGY



DC
antimicrotubule agent

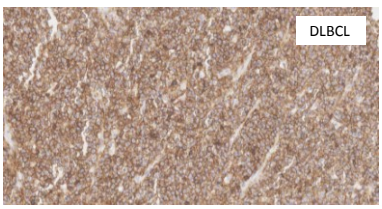
M cell
le arrest

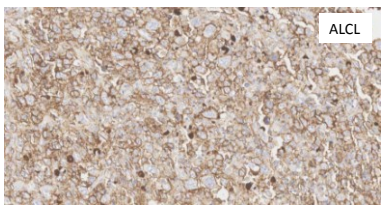
Apoptosis

65

CD37 IS STRONGLY EXPRESSED IN NHL, CLL & NOT HL

- CD37 Is Frequently & Highly Expressed In B- (n=201) & T- (n=17) Cell Lymphomas: >80% of B/T Cell Lymphomas Exhibit An H-score > 100.



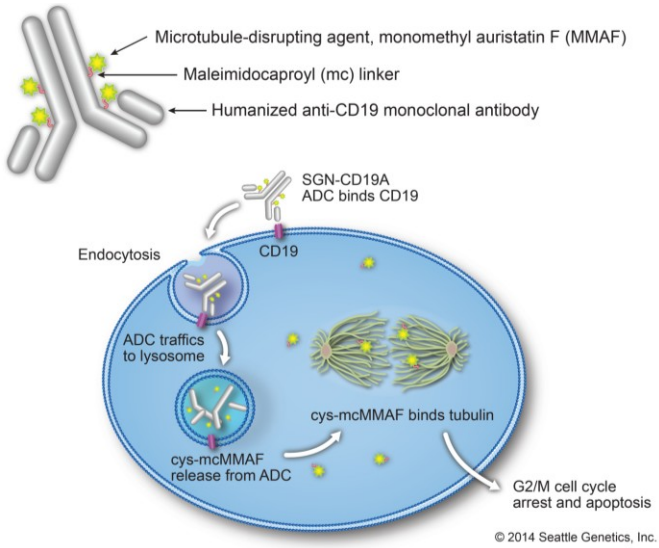


- CD37 Is Expressed In Rituxan Resistant NHL & CLL.
- CD37 Is Not Expressed in Hodgkin's Lymphoma (n=58).
- CD37 Is Expressed in 100% of Patient-Derived CLL (58/58) With An Average Flow Cytometry MFIR of 83.
- CD37 Is Expressed In 100% of Patient-Derived AML Stem Cells & Blasts (26/26) With An Average Flow Cytometry MFIR of 126 & 85 Respectively.

Courtesy L. Reyno

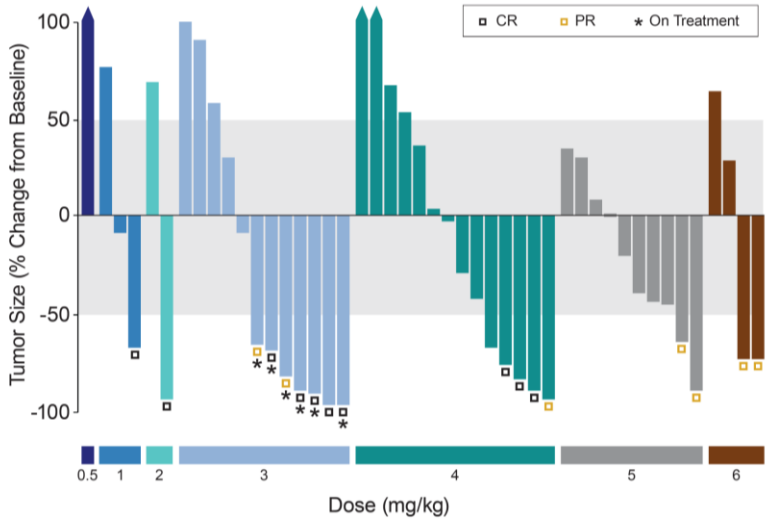
66

MECHANISM OF ACTION SGN-CD19A



Courtesy C. Moskowitz 67

BEST % CHANGE PER PATIENT IN INDEX LESIONS

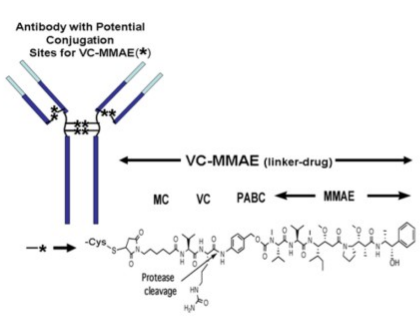


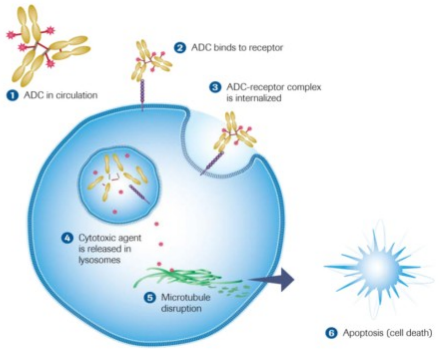
Note: includes only patients with both baseline and postbaseline measurements; 3 patients had a >100% increase over baseline, indicated by arrows

Moskowitz et al. ASH 2014 68

PINATUZUMAB VEDOTIN (CD22-ADC)
POLATUZUMAB VEDOTIN (CD79B-ADC)

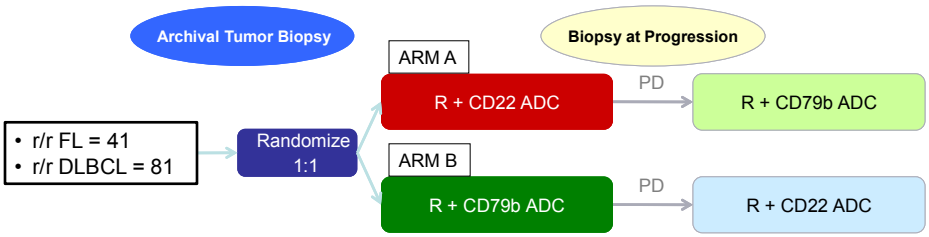
- Antibody drug conjugates (ADC) consisting of the potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to anti-CD22 and CD79b monoclonal antibodies via a protease-cleavable peptide linker
- CD22 and CD79b are expressed by most B-cell hematologic malignancies
- Both ADCs have shown clinical activity in Phase I studies





69

ROMULUS STUDY DESIGN



Rituximab (R) (375 mg/m^2) + ADC (2.4 mg/kg) administered in every-21-day cycles up to one year

Clinical Evaluations

- Treatment-emergent adverse events graded per NCI CTCAE v4.0
- Anti-tumor activity was evaluated per revised IWG criteria (Cheson et al. 2007) every three months; PET scans were performed at the discretion of the investigator

Pharmacokinetic and Pharmacodynamic Evaluations

- Total antibody, conjugate (antibody-conjugated cytotoxic agent MMAE [acMMAE]), unconjugated MMAE

Data as of 21 February 2014; median time of follow up was 9.9 months (Range 0.23-14.9 months)

- Data from crossover patients not included in this presentation

Courtesy F. Morschhauser

70

INVESTIGATOR-ASSESSED BEST RESPONSES IN TREATED PATIENTS [A]

	DLBCL		FL	
	R+CD22 ADC (N=42)	R+CD79b ADC (N=39)	R+CD22 ADC (N=21)	R+CD79b ADC (N=20)
Objective response, n (%)	**24 (57%)**	**22 (56%)**	**13 (62%)**	**14 (70%)**
Complete Response	10 (24%)	6 (15%)	2 (10%)	8 (40%)
95% CI	[12%-39%]	[6%-31%]	[11%-30%]	[19%-64%]
Partial Response	14 (33%)	16 (41%)	11 (52%)	6 (30%)
95% CI	[20%-50%]	[26%-58%]	[30%-74%]	[12%-54%]
Stable disease, n (%)	3 (7%)	4 (10%)	6 (29%)	6 (30%)
Progressive disease, n (%)	7 (21%)	11 (30%)	1 (5%)	0
Unable to evaluate, n (%)	8 (19%)	2 (5%)	1 (5%)	0
Median Duration of Response, mo. (95% CI)	6.0 (2.9-12.2)	NR (2.6-NR)	5.8 (2.6-10.1)	NR (5.7-NR)

[a] Patients who received ≥ 1 dose of study treatment; patients unable to evaluate did not have a post-baseline tumor assessment

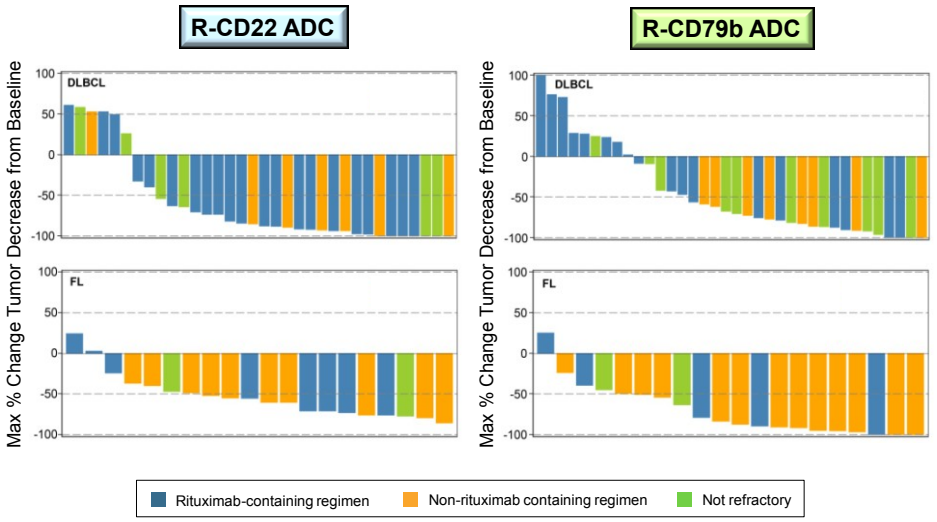
NR = Not reached

F. Morschhauser et al., ASH 2014

Data Cut-Off: 21FEB2014

71

ANTI-TUMOR RESPONSES OBSERVED BY LYMPHOMA SUBTYPES AND REFRACTORINESS TO LAST PRIOR THERAPY

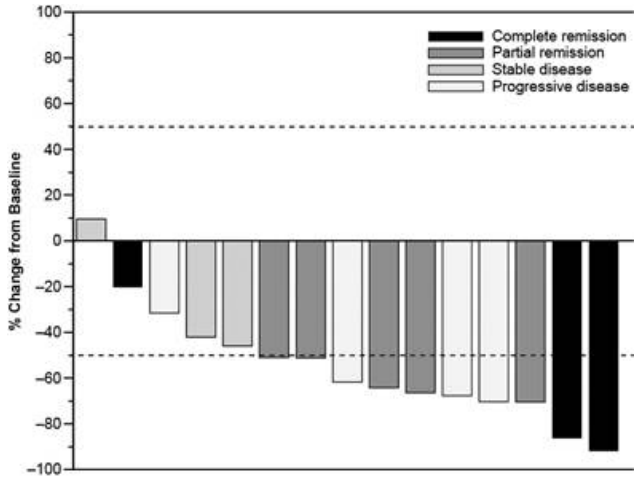


F. Morschhauser et al., ASH 2014

Data Cut-Off: 21FEB2014

72

PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Failure: Phase 1b



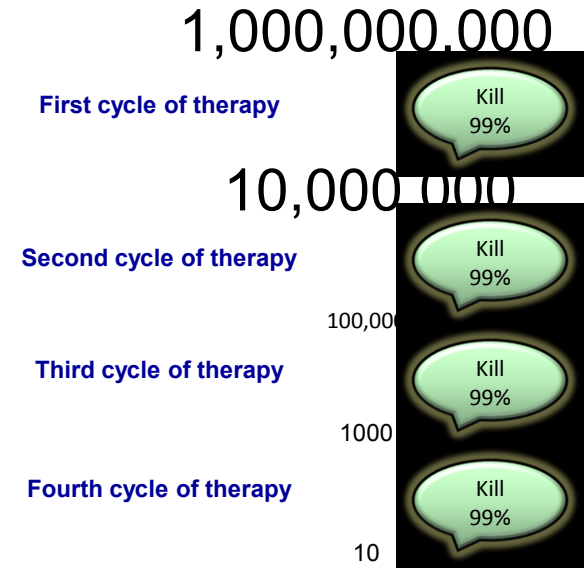
Ribrag et al. CCR 20(1): 213-220

73

Principles of Treatment – 101

74

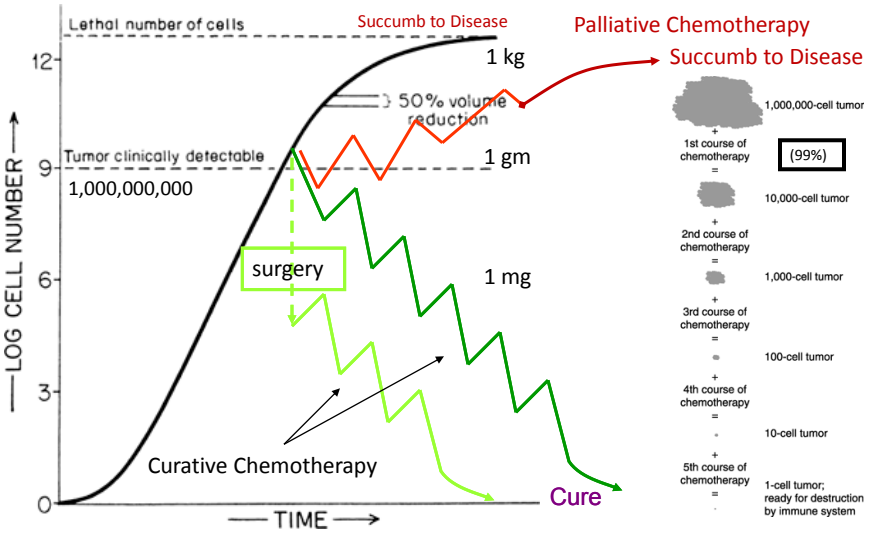
PRINCIPLES OF TREATMENT



Assume a treatment that kills 99% of all tumor cells (highly optimistic), then……

75

EFFECTS OF TREATMENT ON TUMOR BURDEN



Frei, 1984

76

THE INDOLENT LYMPHOMA'S SUMMARY

- These disease entities are very heterogenous, each possessing it own unique features
- Treatment is often tailored based upon the degree of tumor burden, vital organ compromise, symptoms and patient co-morbidities
- Chemotherapy plays an important role in patients with advanced tumor burden
- There is an increasing emphasis on immunological treatments and targeted therapies.

77

Thank You!

Columbia University Medical Center

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

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

78

Center for Lymphoid Malignancies at Columbia University Medical Center

Physicians
Owen A. O'Connor, M.D., Ph.D.
Jennifer Amengual, M.D.
Changchun Deng, M.D., Ph.D.
Ahmed Sawas, M.D.
Donald Colburn, M.D.
Lauren Geskin, M.D.
(Dermatology / CTCL)

Nurses
Ellen Neylon, NP
Kathleen Maignan, NP
Michael Smith, RN
Emily Lichtenstein,

Administrative Staff
Victoria Serrano, MPH
Joanne Scibilla
Erica Guerva
Chermaine Ford, B.S.
Joanna Duarte.

Research Study Coordinators
Molly Patterson, LMSW
Celeste Rojas, B.S.
Renee Lichtenstein,B.A
Michele Malanga, BA

Laboratory Staff
Luigi Scotto, Ph.D.
Michael Mangone, Ph.D.
Jennifer Amengual, M.D.
Changchun Deng, M.D., Ph.D.
Kelly Zullo, B.S.
Xavier Jirau Serrano, B.S.
Mark Lipstein, B.S.
Maximillian Lombardo, B.S.

Columbia University Medical Center

79

NHL: Update on Slow-Growing Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers — someday is today®

Question and Answer Session

Dr. O'Connor's slides are available for download at
www.LLS.org/programs

80

NHL: Update on Slow-Growing Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

The Leukemia & Lymphoma Society (LLS) offers:

- **Live, Online Chats** that provide a friendly forum to share experiences with others. Living with non-Hodgkin lymphoma chat held on Monday and Wednesday nights, 7:30:-10:00 pm ET, & Caregiver Chat held on Monday nights from 8:00-10:00 pm ET.
  - **WEBSITE: www.LLS.org/chat**
- **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  - **WEBSITE: www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/publications**
- **Past NHL education programs: www.LLS.org/leukemiaeducation**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org** **TOLL-FREE PHONE: (800) 955-4572**

81