CLL
Current and Emerging Therapies

someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

Welcome and Introductions

June 18, 2014

CLL
Current and Emerging Therapies

someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

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June 18, 2014

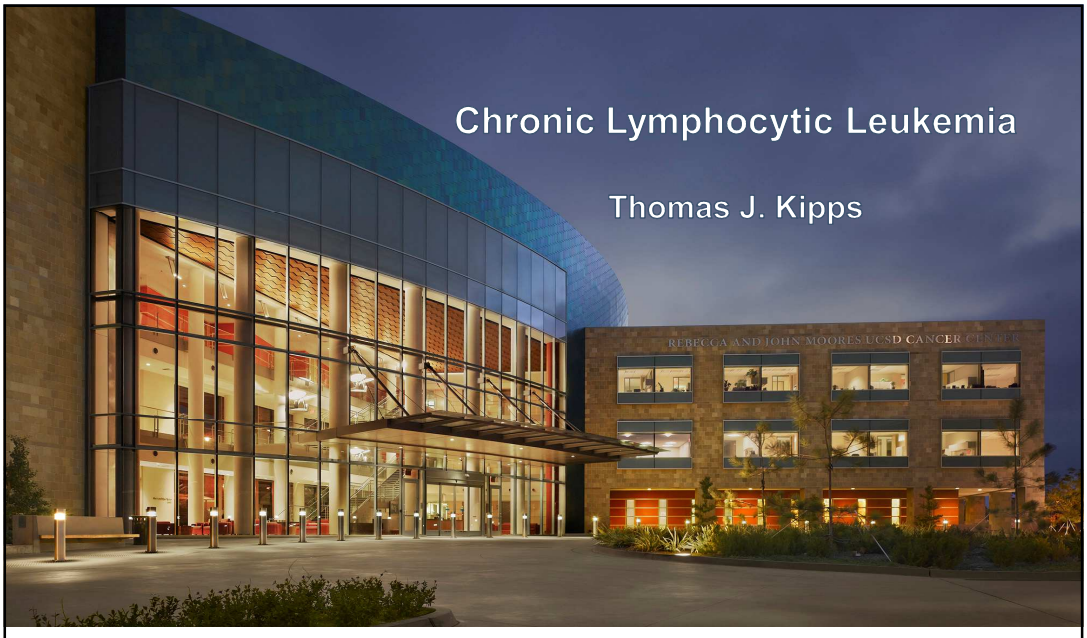
CLL
Current and Emerging Therapies

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

Disclosures

Dr. Kipps does not have any relevant financial relationships with any commercial interests to disclose.

June 18, 2014



UC San Diego
MOORES CANCER CENTER
An NCI-designated Comprehensive Cancer Center

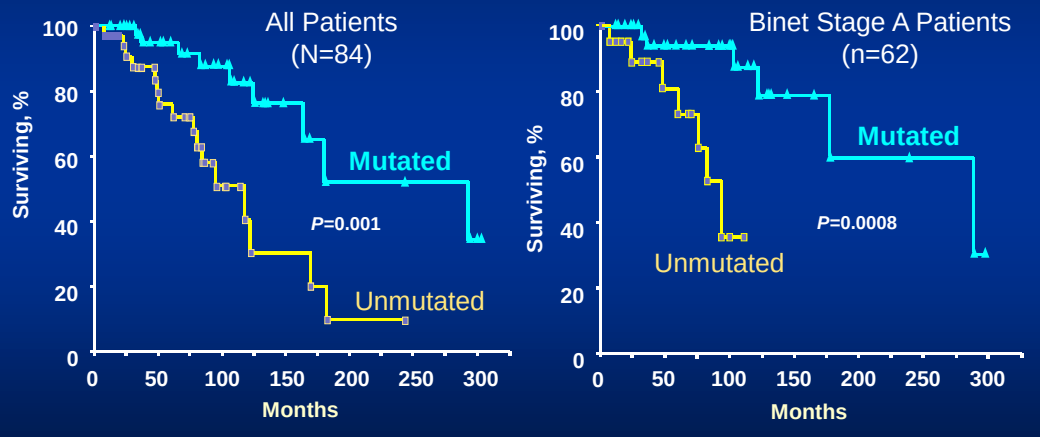
Chronic Lymphocytic Leukemia (CLL)

- Clinical course of pts with CLL is highly variable
- Many pts are asymptomatic at diagnosis
- CLL still is considered incurable with current therapy
- Therapy may cause morbidity or mortality
- Current recommendations are to withhold therapy until pts develop disease-related
  - Symptoms (e.g. fatigue, wt. loss)
  - Complications (e.g. impaired marrow or immune function)

CLL Prognostic Markers

Mutated vs Unmutated IGHV Genes

Overall Survival



CLL, chronic lymphocytic leukemia.
Hamblin TJ, et al. *Blood*. 94:1848-1854, 1999

Approved Drugs For Treatment of Patients with Chronic Lymphocytic Leukemia

- Steroids (e.g. prednisone)
- Classic Chemotherapy
  - Alkylating Agents
    - Chlorambucil
    - Cyclophosphamide (C)
    - Bendamustine (B)
  - Purine Analogs
    - Fludarabine (F)
    - Pentostatin (P)
    - Cladribine

Kinase Inhibitors
- Ibrutinib

Monoclonal Antibodies
- Alemtuzumab
- Ofatumumab
- Rituximab
- Obinutuzumab

UC San Diego
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Clinical Differences Between Patients with Common FISH Detected Cytogenetic Abnormalities

- 17p- p53 mutation
  - Resistant to chemotherapy but sensitive to antibodies, lenalidomide, bcl-2 inhibitors, BCR antagonists or allogeneic transplant
- 11q- ATM deletion and DNA repair defect
  - High CR rate, but short remissions (Candidates for consolidation therapy?)
- Trisomy 12
  - High expression of CD20
  - Concurrent 14q abnormalities (Lymphoma karyotype)
- 13q- MiR-15/16 deletion
  - High response rate
  - Higher incidence of incomplete hemopoietic recovery (CRi)

FCR300 First-line Treatment

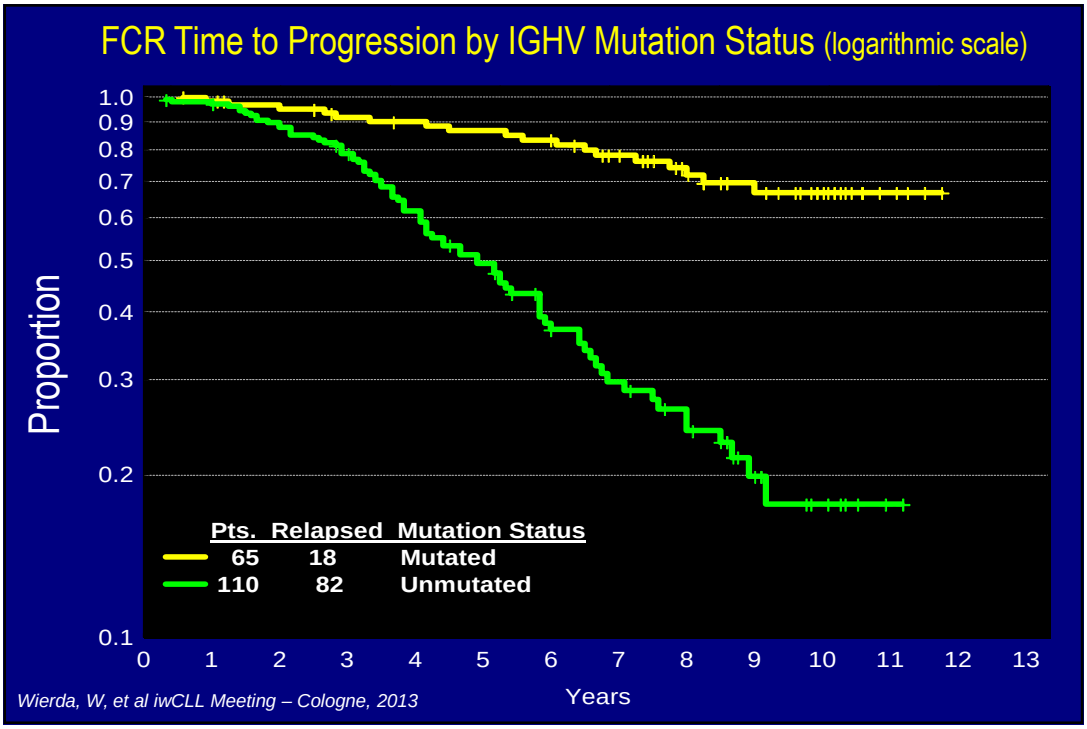
- Accrual of 300 patients 7/1999 – 1/2004 at MD Anderson
- Males – 211
- Rai III-IV – 107
- *IGHV* mutation status obtained at UC San Diego
- BIAS – if no relapse no knowledge
- No FISH: plan to complete mutation status on stored samples and cytogenetics by SNP array

Wierda, W, et al iwCLL Meeting – Cologne, 2013

FCR300: Response by Characteristic

Characteristic		n	% CR	% OR
Age	< 65 yrs	228	75	96
	65-69	31	77	97
	≥ 70	41	51	88
***IGHV*-Mutated**		**82**	**82**	**98**
-Unmutated		**131**	**73**	**93**
-Unknown		**87**	**63**	**95**
β2M	< 3 mg/l	86	87	98
	3-4	82	80	98
	> 4	127	57	92
Overall		**300**	**72**	**95**

Wierda, W, et al iwCLL Meeting – Cologne, 2013



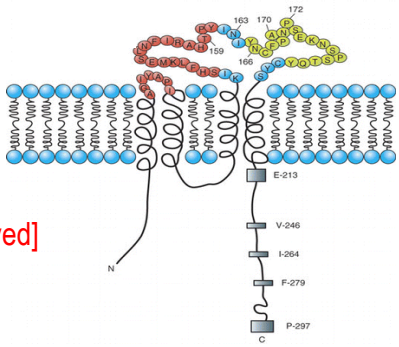
First-line FCR Conclusions & Comments

- Durable remissions achieved with FCR
- Subgroups with favorable outcomes:
  - *IGHV*-mutated subgroup
    - 60% Prog-free @ 9yr
  - β_2M <4 mg/l subgroup
    - 45% Prog-free @ 9yr

Wierda, W, et al iwCLL Meeting – Cologne, 2013

Monoclonal Antibodies	Antigen
• Rituximab (Genentech/Roche) [Approved] • Ofatumumab (GSK) [Approved] • Obinutuzumab (GA101, Genentech/Roche) [III] • Ublituximab (LFB-R603, LFB) [II] • Veltuzumab (hA20/Immunomedics) [I/II] • Ocrelizumab (Genentech/Roche) [III for MS]	CD20
• Alemtuzumab (SA) [Approved, but now off market for CLL] Renamed Lemtrada™ for MS 12 mg QD x 5 and then 1yr later QD x 3 (96 mg)	CD52
• MEDI-551 (MedImmune LLC) [II/III] • MDX-1342 (Bristol Myers Squibb) [I] • Xmab5574 (MorphoSys/Xencor) [I]	CD19
• Epratuzumab (UBC) [III for SLE]	CD22
• MAb 37.1/2 (Boehringer/Ingelheim) [pre] • K7153A	CD37
• MOR202 (MorphoSys) [pre]	CD38
• Lucatumumab (CHIR-12, HCD122) [I/II]	CD40
• RG7356 (Roche) [pre]	CD44
• MDX-1411 (BMS) [I-held]	CD70
• Milatuzumab (Immunomedics, Inc) [I/II]	CD74
• ALXN6000 (Alexion Pharm) [I/II-held]	CD200
• UC-961 (Cirmtuzumab)	ROR1
• BMS-936564/MDX-1338 (Bristol Myers Squibb) [II]	CD184 (CXCR4)

Anti-CD20 Biologics
Dancing on the Head of a CD20 Pin



- Rituximab (Genentech/Roche) [Approved]
- Ofatumumab (GSK) [Approved]
- Obinutuzumab (GA101, Genentech/Roche) [Approved]
- Ublituximab (TG-1101, LFB-R603, LFB) [II]
- Veltuzumab (hA20/Immunomedics, Nycomed non-CA indications) [I/II]
- Ocrelizumab (Genentech/Roche) [III for Multiple Sclerosis]

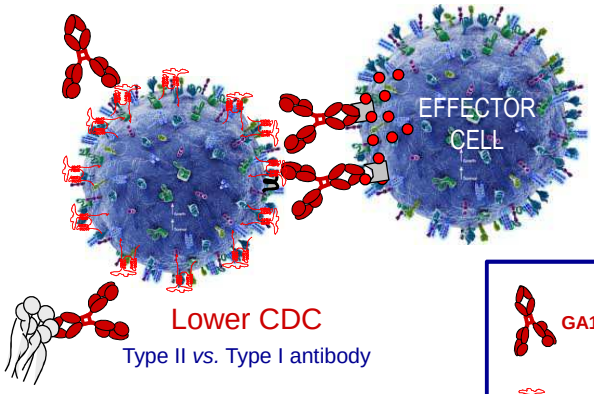
GA101 – Obinutuzumab (Gazyva®)

"Rituximab with an attitude"

Increased Direct Cytotoxicity

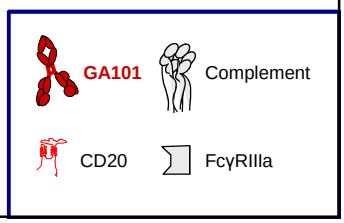
Enhanced ADCC

Increased affinity for FcγRIIIa



Lower CDC

Type II *vs.* Type I antibody



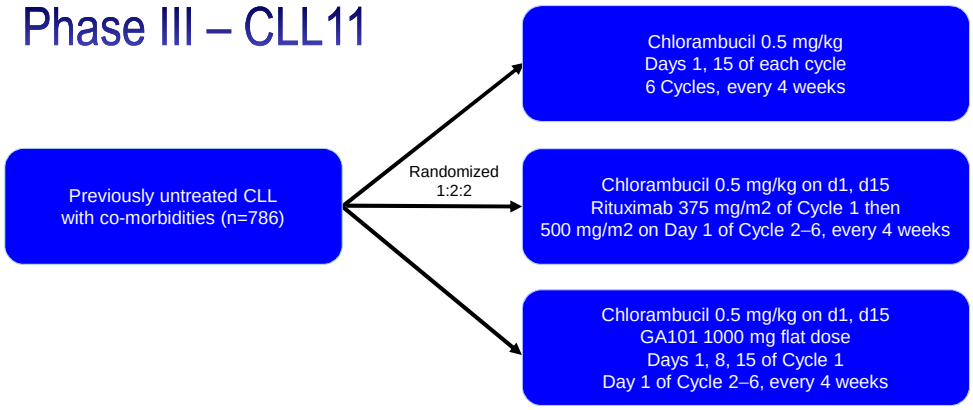
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

Valentin Goede, M.D., Kirsten Fischer, M.D., Raymonde Busch, M.S., Anja Engelke, M.D., Barbara Eichhorst, M.D., Clemens M. Wendtner, M.D., Tatiana Chagorova, M.D., Javier de la Serna, M.D., Marie-Sarah Dilhuydy, M.D., Thomas Illmer, M.D., Stephen Opat, M.D., Carolyn J. Owen, M.D., Olga Samoylova, M.D., Karl-Anton Kreuzer, M.D., Stephan Stilgenbauer, M.D., Hartmut Döhner, M.D., Anton W. Langerak, Ph.D., Matthias Ritgen, M.D., Michael Kneba, M.D., Elina Asikanius, M.Sc., Kathryn Humphrey, B.Sc., Michael Wenger, M.D., and Michael Hallek, M.D.

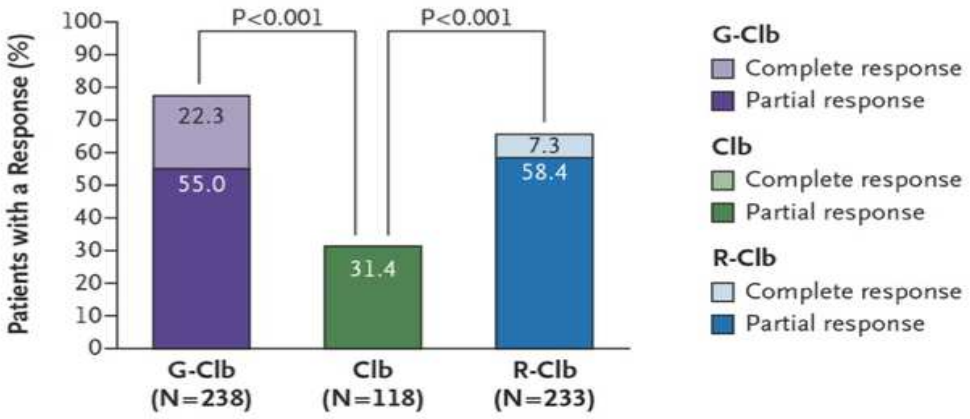
Clinical Trials Using GA101



Goede et al. NEJM 370:1101-1100, 2014

Response Rates

Obinutuzumab (G) + Chlorambucil (Clb) vs. Clb vs. Rituximab (R) + Clb



Goede et al. NEJM 370:1101-1100, 2014

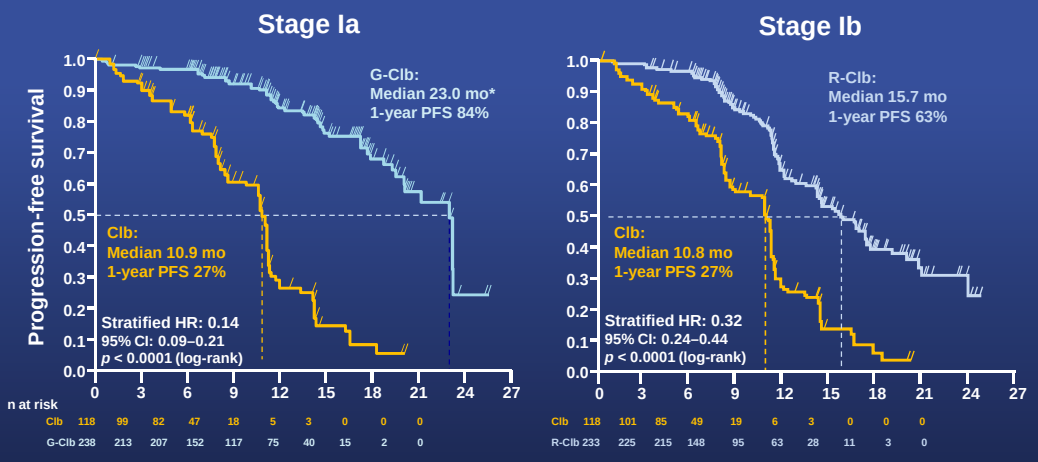
End-of-Treatment Response Rates

	Stage Ia		Stage Ib	
	Clb (n = 106)	G-Clb (n = 212)	Clb (n = 110)	R-Clb (n = 217)
Response rate[a], %				
ORR	**30.2**	**75.5**	**30.0**	**65.9**
CR[b]	**0**	**22.2**	**0**	**8.3**
PR[c]	**30.2**	**53.3**	**30.0**	**57.6**
SD	**21.7**	**4.7**	**20.9**	**13.4**
PD	**25.5**	**3.8**	**28.2**	**11.5**
Not evaluable	**22.6**	**16.0**	**20.9**	**9.2**
MRD-negative[d], % (n)				
Peripheral blood	**0** (0/80)	**31.1** (41/132)	**0** (0/82)	**2.0** (3/150)
Bone marrow	**0** (0/30)	**17.0** (15/88)	**0** (0/32)	**2.8** (2/72)

[a]Not reached by cutoff in 12 patients in Stage 1a Clb arm, 26 patients in G-Clb arm, eight patients in Stage 1b Clb arm, and 16 patients in the R-Clb arm; as assessed by iwCLL criteria.
[b]Includes CR with incomplete hematologic recovery.
[c]Includes nodular PR.
[d]As measured by central laboratory assessment (ASO-RQ-PCR); bone marrow samples were usually only taken from patients thought to be in CR.

Goede et al. NEJM 370:1101, 2014

Investigator-assessed PFS (Months)

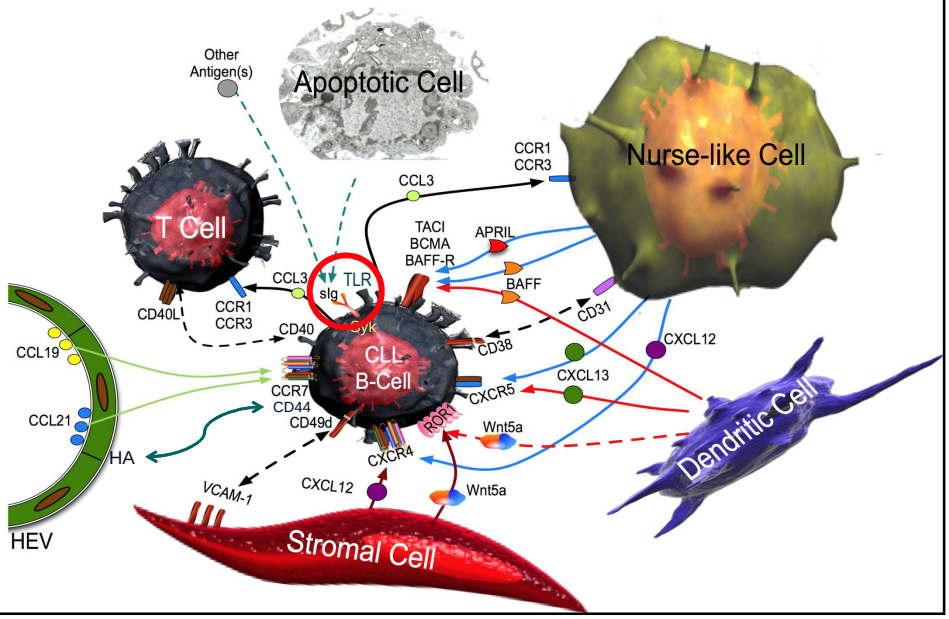


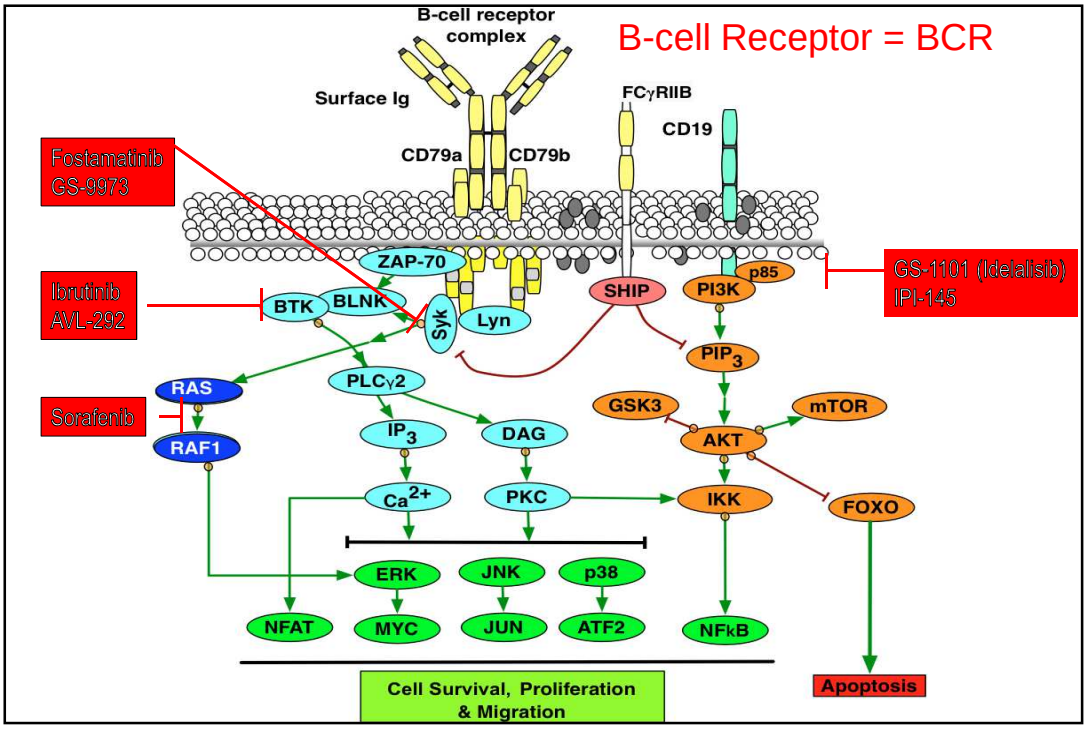
- Type 1 error controlled through closed test procedure; p-value of the global test was <.0001.
- * In the G-Clb arm < 10% of patients had reached the median at cutoff; therefore, in contrast to the Clb arm the G-Clb median PFS could not be reliably estimated due to the few patients at risk at time of G-Clb median.
- **Independent Review Committee (IRC) - assessed PFS was consistent with investigator-assessed PFS**

CI = confidence interval; HR = hazard ratio.

Goede et al. NEJM 370:1101, 2014

CLL Microenvironment



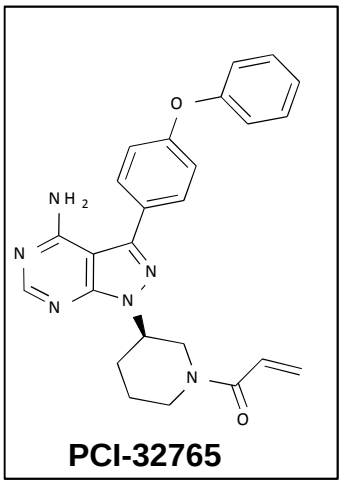


BCR-Directed Agents in Development for CLL

Agent	Sponsor	ORR	Development Phase
BTK inhibitors			
Ibrutinib	Pharmacyclics, Inc.	71 – 88%	Registration Phase III
CC-292	Celgene Corporation	31-67% (PR)	Phase Ib
ONO-4059	Ono Pharmaceutical	89% (PR)	Phase I
ACP-196	Acerta	—	Phase I
PI3KY/δ inhibitors			
Idelalisib	Gilead Sciences	72-100%	Registration Phase III
GS-9820	Gilead Sciences	—	Pending Phase I
IPI-145	Infinity Pharmaceuticals	48%	Phase III
AMG 319	Amgen	—	Phase I
TGR-1202	TG Therapeutics	—	Phase I
SAR245408 (XL147)	Sanofi	—	Phase I
Syk inhibitors			
GS-9973	Gilead Sciences	—	Phase II
Fostamatinib	Rigel Pharmaceuticals	55%	Phase I/II
PRT-2070	Portola	—	Pending Phase I

PCI-32765: First-In-Class Inhibitor of BTK

Ibrutinib

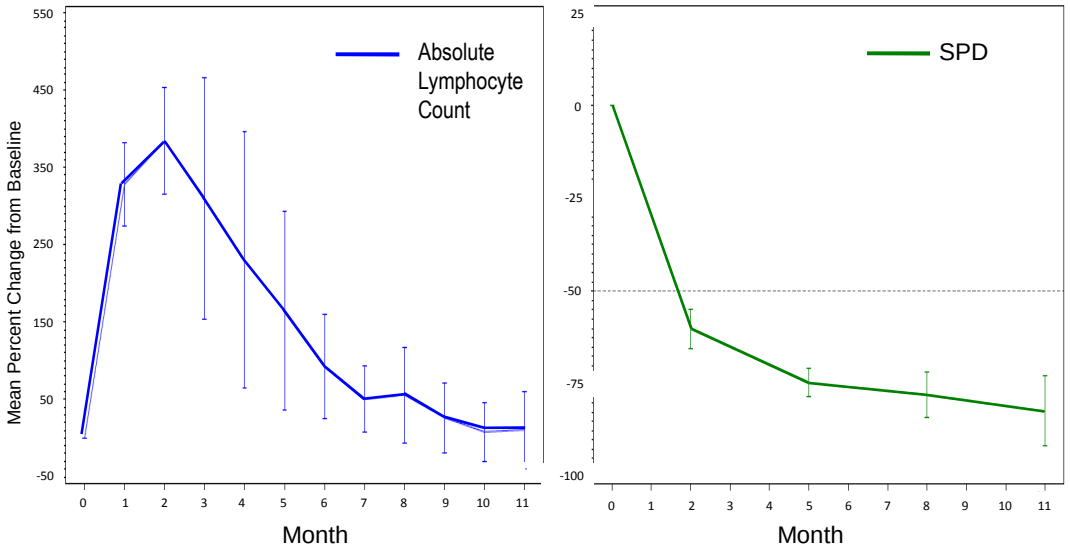


PCI-32765

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- In CLL cells promotes apoptosis, inhibits ERK1/AKT phosphorylation, NF-κB DNA binding, CpG mediated proliferation
- Inhibits CLL cell migration and adhesion
- No cytotoxic effect on T-cells or NK-cells

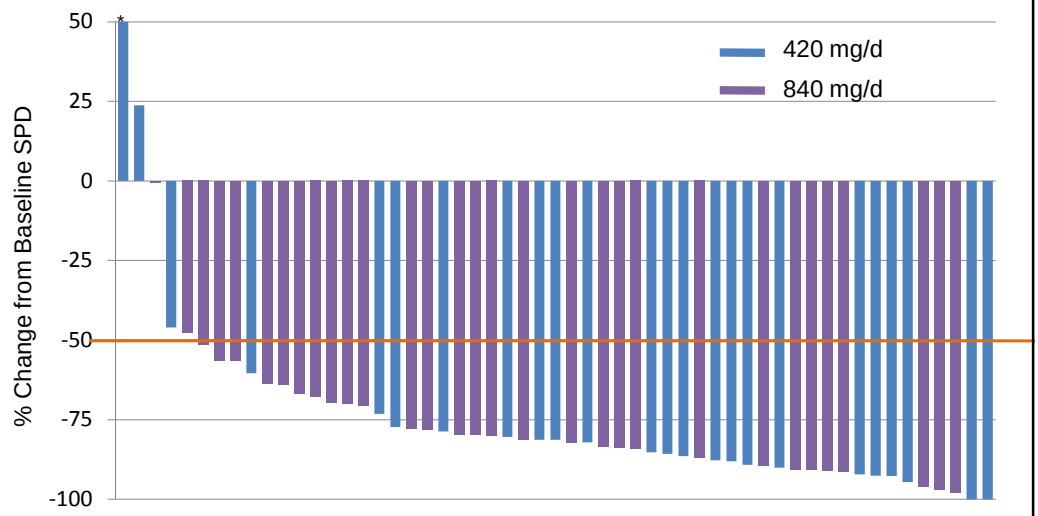
Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075, 2010
Herman SEM et al: Blood 117: 6287-6296, 2011
Ponader, et al., ASH Meeting Abstracts 116:45, 2010

Pattern of Response to Ibrutinib
Blood Lymphocytes vs Lymph Nodes



SPD = sum of products of lymph node dimension

Maximum Change in Tumor Burden



*Patient developed progressive disease, but did not have tumor measurements available
Limited to patients with measurable disease at baseline (n=55)

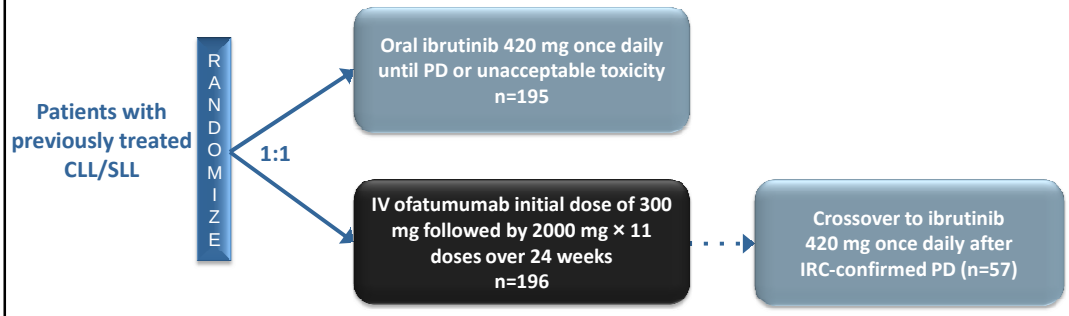
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Jones, A.D. Chu, M. Fardis, J. McGreivy, F. Clow, D.F. James, and P. Hillmen, for the RESONATE Investigators*

RESONATE™ Phase 3 Study Design



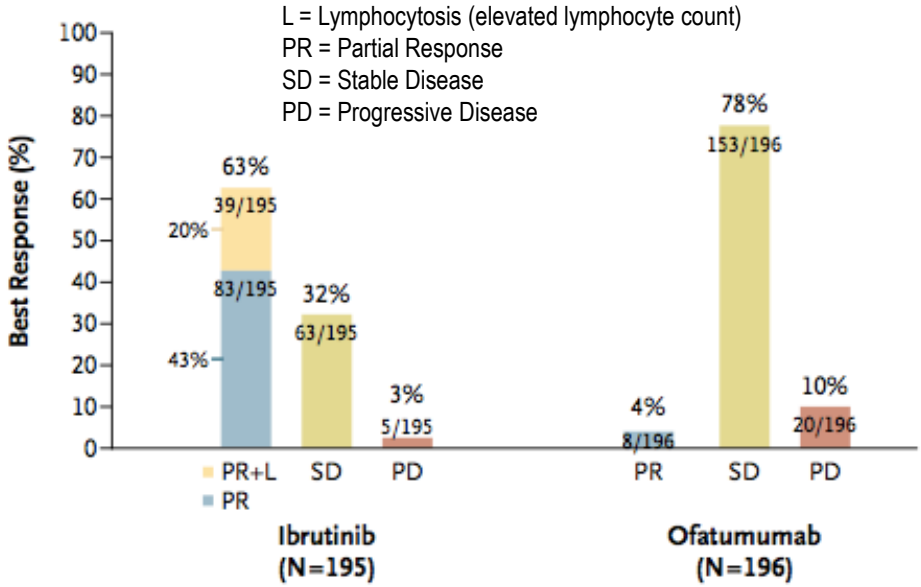
- Stratification according to:
  - Disease refractory to purine analog chemoimmunotherapy (no response or relapsed within 12 months)
  - Presence or absence of 17p13.1 (17p del)
- At time of interim analysis, median time on study was 9.4 months

Protocol amended for crossover with support of Data Monitoring Committee and discussion with health authorities.
PD, progressive disease.

Byrd, J.C. et al, NEJM 370:997, 2014

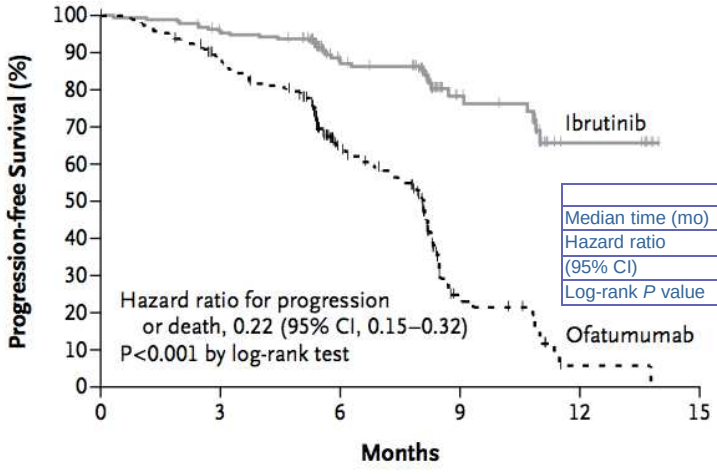
28

Ibrutinib versus Ofatumumab



Byrd, J.C. et al, NEJM 370:997, 2014

Ibrutinib versus Ofatumumab



	Ofatumumab	Ibrutinib
Median time (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank *P* value	< 0.0001	

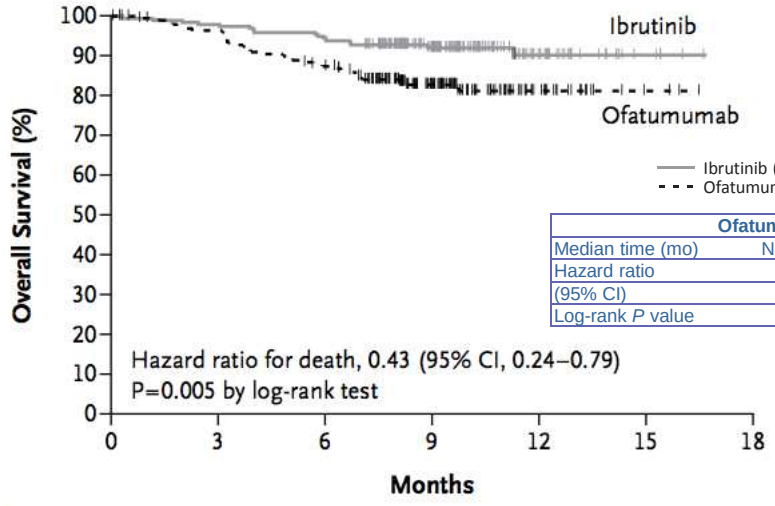
NR, not reached.

No. at Risk

Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0

Byrd, J.C. et al, NEJM 370:997, 2014

Ibrutinib versus Ofatumumab



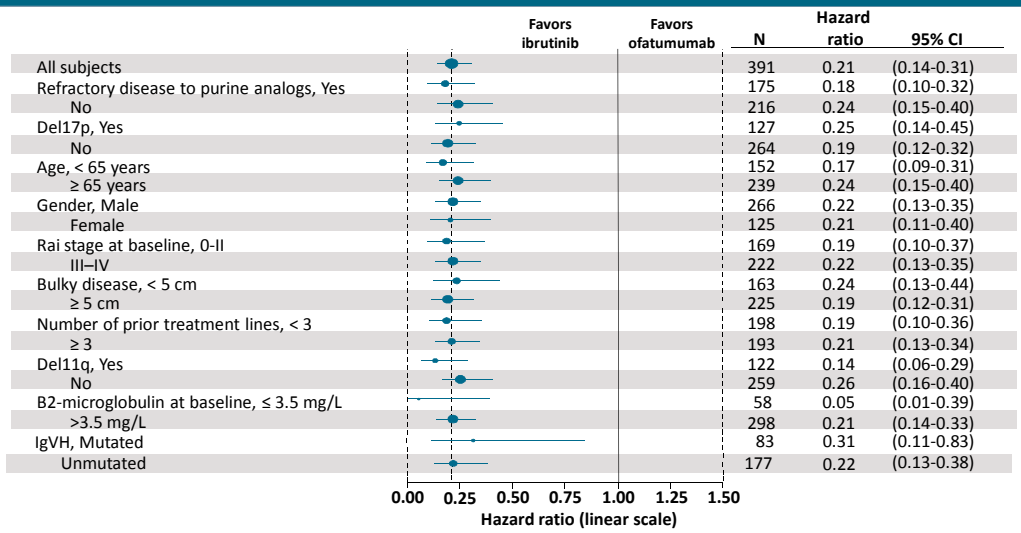
	Ofatumumab	Ibrutinib
Median time (mo)	NR	NR
Hazard ratio	0.434	
(95% CI)	(0.238-0.789)	
Log-rank *P* value	< 0.0049	

No. at Risk

Ibrutinib	195	191	184	115	32	5
Ofatumumab	196	183	164	88	21	3

Byrd, J.C. et al, NEJM 370:997, 2014

Progression-Free Survival by Baseline Characteristics and Molecular Features



	N	Hazard ratio	95% CI
All subjects	391	0.21	(0.14-0.31)
Refractory disease to purine analogs, Yes	175	0.18	(0.10-0.32)
No	216	0.24	(0.15-0.40)
Del17p, Yes	127	0.25	(0.14-0.45)
No	264	0.19	(0.12-0.32)
Age, < 65 years	152	0.17	(0.09-0.31)
≥ 65 years	239	0.24	(0.15-0.40)
Gender, Male	266	0.22	(0.13-0.35)
Female	125	0.21	(0.11-0.40)
Rai stage at baseline, 0-II	169	0.19	(0.10-0.37)
III–IV	222	0.22	(0.13-0.35)
Bulky disease, < 5 cm	163	0.24	(0.13-0.44)
≥ 5 cm	225	0.19	(0.12-0.31)
Number of prior treatment lines, < 3	198	0.19	(0.10-0.36)
≥ 3	193	0.21	(0.13-0.34)
Del11q, Yes	122	0.14	(0.06-0.29)
No	259	0.26	(0.16-0.40)
B2-microglobulin at baseline, ≤ 3.5 mg/L	58	0.05	(0.01-0.39)
>3.5 mg/L	298	0.21	(0.14-0.33)
IgVH, Mutated	83	0.31	(0.11-0.83)
Unmutated	177	0.22	(0.13-0.38)

Byrd, J.C. et al, NEJM 370:997, 2014

32

Safety: Adverse Events (≥15%) Regardless of Attribution[a]

	Ibrutinib (N=195)		Ofatumumab (N=191)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE, %	99	51	98	39
Diarrhea	48	4	18	2
Fatigue	28	2	30	2
Nausea	26	2	18	0
Pyrexia	24	2	15	1
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Cough	19	0	23	1
Thrombocytopenia	17	6	12	4
Arthralgia	17	1	7	0
Upper respiratory tract infection	16	1	10	2
Constipation	15	0	9	0
Infusion-related reaction	0	0	28	3

[a]Patients in the ibrutinib arm had a >50% longer AE reporting period than those on ofatumumab (median of treatment duration 8.6 vs. 5.3 months, respectively); there was no adjustment for exposure duration; [b]TEAE, treatment-emergent AEs reported in all patients who received study drug.

European Hematology Society 2014, PCYC 1112 , Hillmen et al.

Byrd, J.C. et al, NEJM 370:997, 2014 3

Safety Overview

Adverse event, %	Ibrutinib (N=195)	Ofatumumab (N=191)
Subjects reporting ≥1 SAE[a]	42	30
Reporting ≥1 AE grade ≥3[a]	57	47
Any infection grade ≥3	24	22
Grade ≥3 AE atrial fibrillation	3	0
Major hemorrhage[b]	1	2

[a]Exposure adjusted analysis did not demonstrate a serious AE (SAE) rate increase or any grade ≥3 AE for ibrutinib compared with ofatumumab. [b]Hemorrhagic event ≥ grade 3 or resulting in transfusion of red cells or hospitalization or any intracranial hemorrhage.

- Exposure-adjusted analysis showed no difference in any grade infection and a 40% relative reduction in grade 3/4 infections comparing ibrutinib with ofatumumab
- Any grade infusion reactions (28% vs. 0%), peripheral sensory neuropathy (13% vs. 4%), urticaria (6% vs. 1%), night sweats (13% vs. 5%), and pruritus (9% vs. 4%) were more common with ofatumumab
- Frequencies of renal complications and increases in creatinine were similar for both arms

European Hematology Society 2014, PCYC 1112 , Hillmen et al.

Byrd, J.C. et al, NEJM 370:997, 2014 4

Patient Disposition

Study treatment phase disposition	Ibrutinib (N=195), %	Ofatumumab (N=196), %
Did not receive study drug	0	3
Discontinued or completed	14	97
Completion of planned treatment regimen[a]	-	61
Ongoing	86	1
Median time on study at time of analysis, mos (range)	9.6 (0.33-16.62)	9.2 (0.07-16.49)
Primary reason for discontinuation		
Progressive disease	5	19
AE/unacceptable toxicity	4	4
Patient withdrawal	1	3
Deaths	4	5
Investigator decision	1	6
Withdrawal due to a new anticancer therapy: SCT/not SCT	0/0	1/2
Other	1	4

[a]Ofatumumab treatment arm only.
AE, adverse event; SCT, stem cell transplant.

European Hematology Society 2014, PCYC 1112 , Hillmen et al.

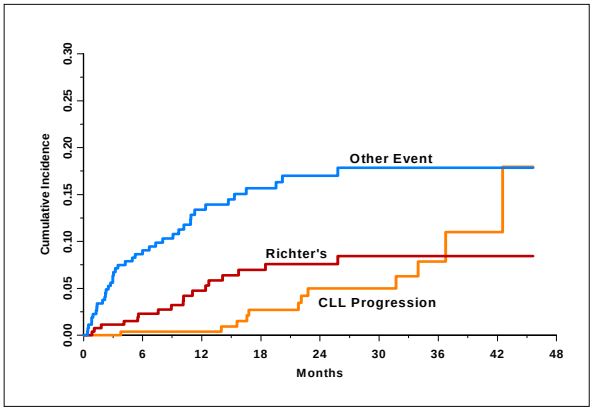
Byrd, J.C. et al, NEJM 370:997, 2014

Disease Progression on Ibrutinib Therapy Is Associated with the Acquisition of Resistance Mutations: A Single Center Experience of 267 Patients

Kami Maddocks, Amy S. Ruppert, Gerard Lozanski, Arletta Lozanski, Nyla Heerema, Weiqiang Zhao, Lynne Abruzzo, Amber Gordon, Jeffrey Jones, Joseph Flynn, Samantha Jaglowski, Leslie Andritsos, Farrukh Awan, Kristie Blum, Michael Grever, Amy Johnson, John Byrd, Jennifer Woyach

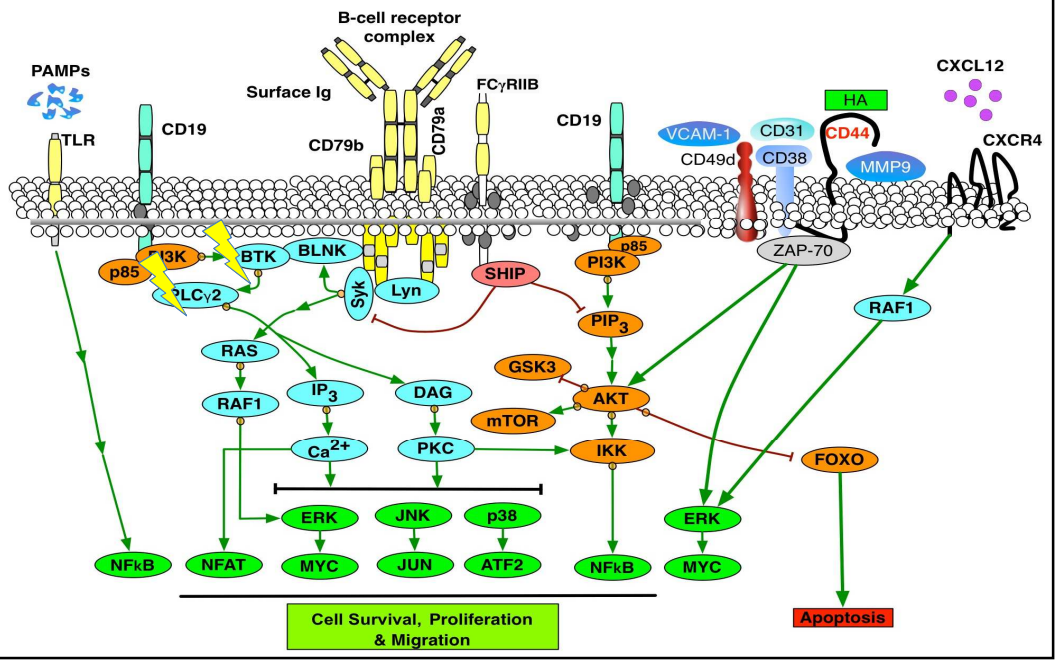
The James
The Ohio State University
Comprehensive Cancer Center

Time to Progression

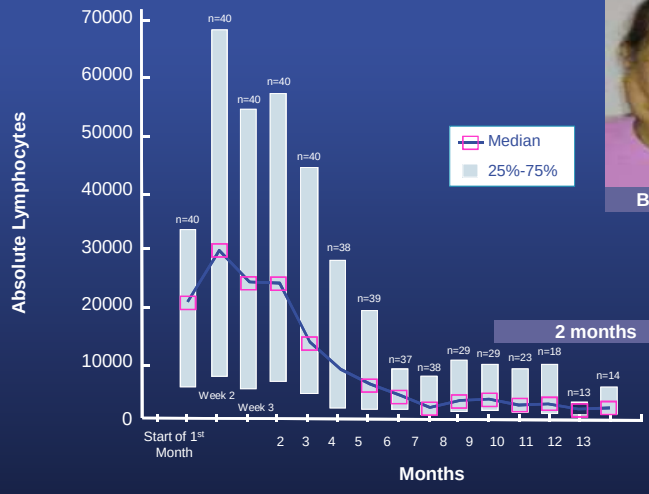


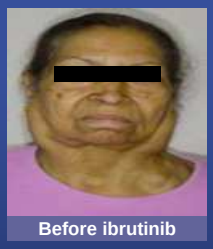
CI Estimate (95% CI)	12 month	18 month
CLL Progression	0.4% (0% to 1.1%)	2.7% (0.3% to 5.1%)
Richter's	4.7% (2.0% to 7.5%)	7.0% (3.5% to 10.4%)
Other Event	13.4% (9.1% to 17.7%)	15.7% (10.9% to 20.4%)

Mechanisms of Ibrutinib Resistance



Ibrutinib + Rituximab: Ph 2 in Patients with Relapsed CLL




Before ibrutinib

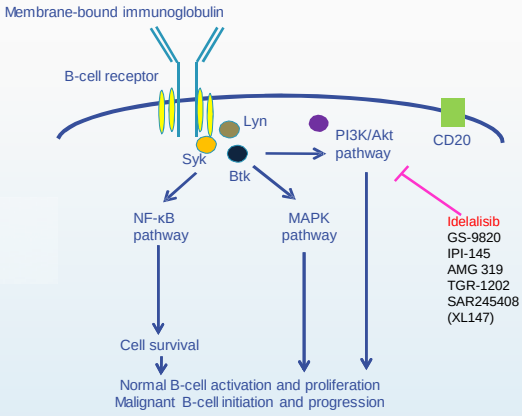

2 months

	n	%
CR	4	10%
PR	30	75%
PR- L	2	5%
ORR	34	85%
SD	3	8%

Burger et al. ASH 2013, Abstract 675.

39

PI3K Inhibitors



Idelalisib: Phase 1 Relapsed/Refractory CLL

Efficacy Outcome	n (%)
ORR	39 (72)
PR by iwCLL (Hallek 2008)	21(39)
PR with lymphocytosis (Cheson 2007)	18 (33)
Lymph node response	44 (81)
Median TTR	1.0 month (n = 39)
Median DOR	16.8 months (n = 39)
Median PFS (all)	17.1 months (N = 54)
Median OS	Not reached (N = 54)

Brown et al. ASCO 2013. Abstract 7003.

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Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

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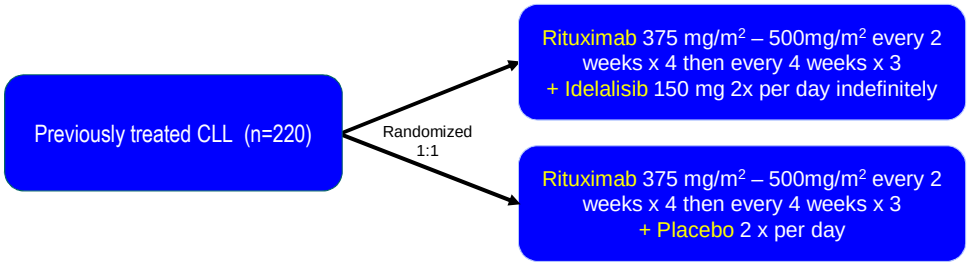
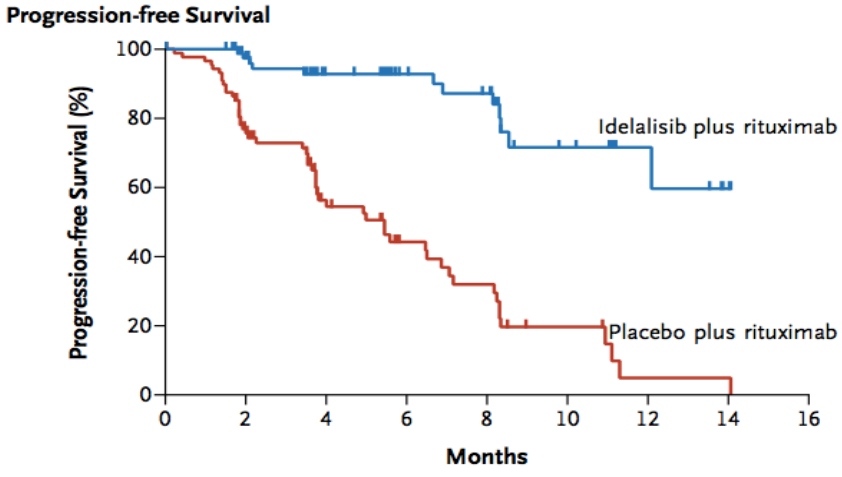
Idelalisib + Rituximab versus Rituximab



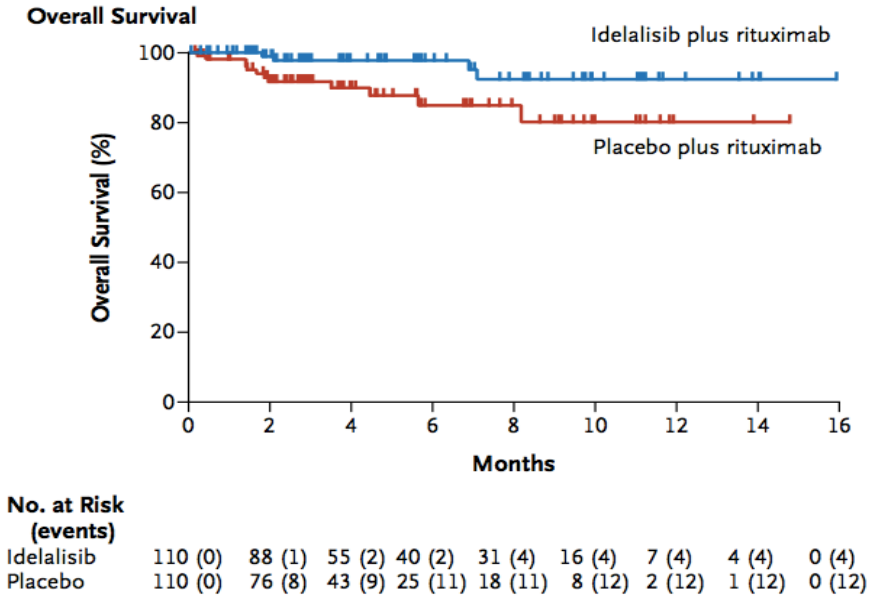
Idelalisib + Rituximab versus Rituximab



No. at Risk (events)								
Idelalisib	110 (0)	69 (2)	44 (5)	34 (5)	30 (7)	14 (11)	6 (11)	2 (12)	0 (12)
Placebo	110 (0)	62 (20)	30 (33)	18 (39)	13 (44)	6 (49)	1 (52)	1 (52)	0 (53)

Furman R. et al, NEJM 370:997, 2014

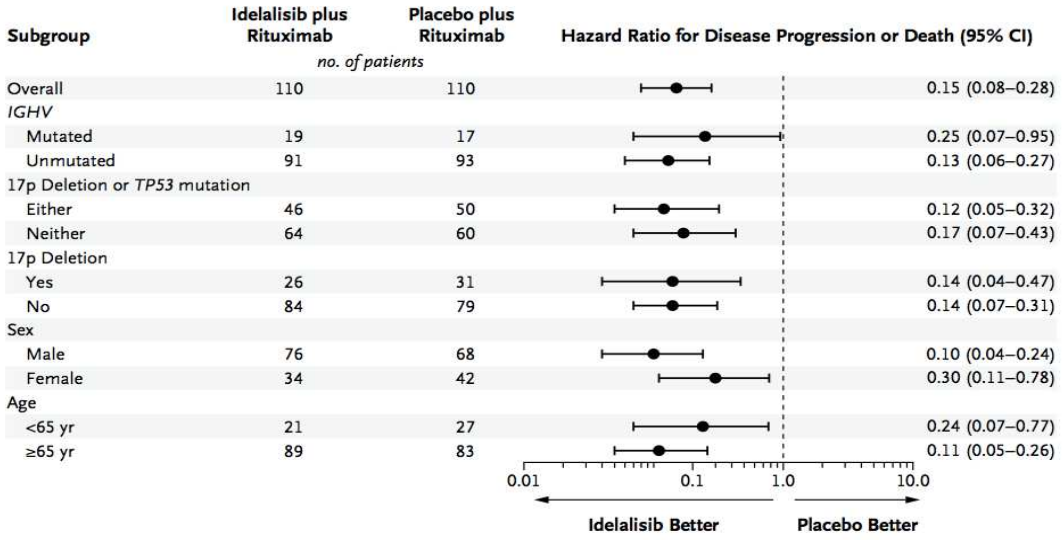
Idelalisib + Rituximab versus Rituximab



No. at Risk (events)									
Idelalisib	110 (0)	88 (1)	55 (2)	40 (2)	31 (4)	16 (4)	7 (4)	4 (4)	0 (4)
Placebo	110 (0)	76 (8)	43 (9)	25 (11)	18 (11)	8 (12)	2 (12)	1 (12)	0 (12)

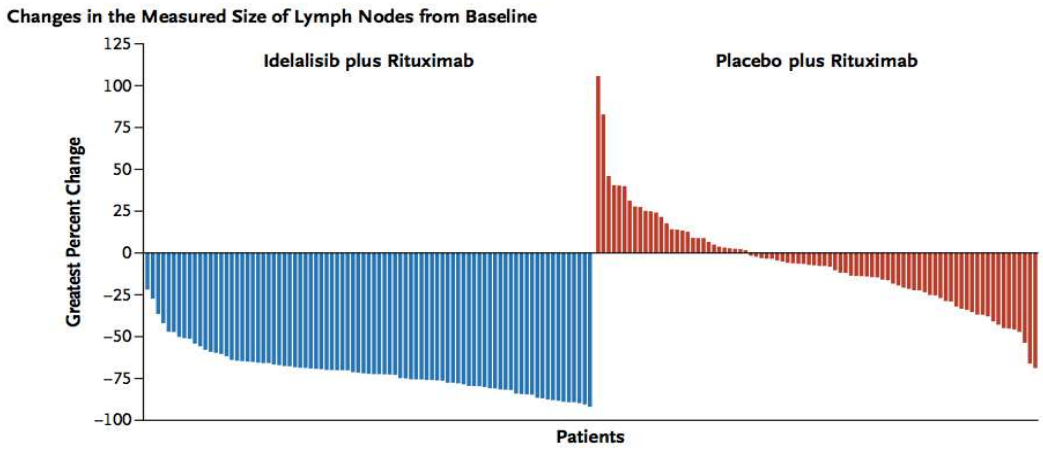
Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab



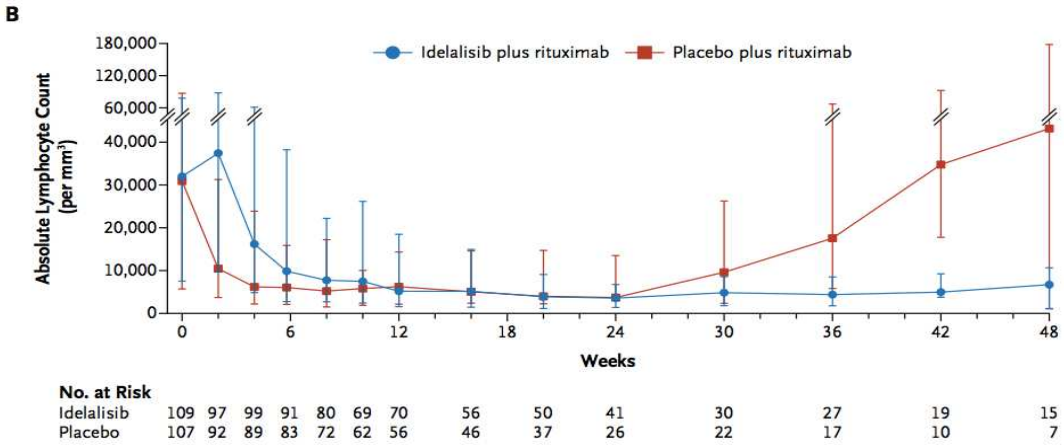
Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab



Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab



Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab

Event	Idelalisib plus Rituximab (N=110)		Placebo plus Rituximab (N=107)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event during treatment	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (21)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (15)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Constipation	13 (12)	0	12 (11)	0
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Vomiting	13 (12)	0	8 (7)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Night sweats	11 (10)	0	8 (7)	0
Rash	11 (10)	2 (2)	6 (6)	0

Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab

Event	Idelalisib plus Rituximab (N=110)		Placebo plus Rituximab (N=107)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Serious adverse event	44 (40)	NA	37 (35)	NA
Pneumonia	7 (6)	NA	9 (8)	NA
Pyrexia	7 (6)	NA	3 (3)	NA
Febrile neutropenia	5 (5)	NA	6 (6)	NA
Sepsis	4 (4)	NA	3 (3)	NA
Pneumonitis	4 (4)	NA	1 (1)	NA
Diarrhea	3 (3)	NA	1 (1)	NA
Neutropenia	3 (3)	NA	1 (1)	NA
Pneumocystis jirovecii pneumonia	3 (3)	NA	1 (1)	NA
Neutropenic sepsis	3 (3)	NA	0	NA
Dyspnea	1 (1)	NA	4 (4)	NA
Cellulitis	1 (1)	NA	3 (3)	NA

Furman R. et al, NEJM 370:997, 2014

Idelalisib + Rituximab versus Rituximab

Event	Idelalisib plus Rituximab (N=110)		Placebo plus Rituximab (N=107)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Laboratory abnormality				
ALT or AST elevation	38 (35)	6 (5)	20 (19)	1 (1)
Anemia	28 (25)	6 (5)	32 (30)	15 (14)
Neutropenia	60 (55)	37 (34)	52 (49)	24 (22)
Thrombocytopenia	19 (17)	11 (10)	28 (26)	17 (16)

Furman R. et al, NEJM 370:997, 2014

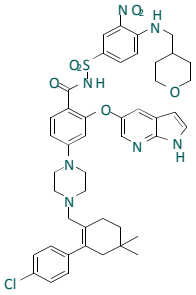
UPDATED RESULTS OF A PHASE I FIRST-IN-HUMAN STUDY OF THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

John F. Seymour[1], Matthew S. Davids[2], John M. Pagel[3], Brad S. Kahl[4], William G. Wierda[5], Soham Puvvada[6], John F. Gerecitano[7], Thomas J. Kipps[8], Mary Ann Anderson[9,10], David C.S. Huang[10], Nikita K. Rudersdorf[11], Lori A. Gressick[11], Nicholas P. Montalvo[11], Jianning Yang[11], Todd A. Busman[11], Martin Dunbar[11], Elisa Cerri[11], Sari H. Enschede[11], Rod A. Humerickhouse[11], Andrew W. Roberts[9,10]

[1]Peter MacCallum Cancer Centre, Australia; [2]Dana-Farber Cancer Institute, USA; [3]University of Washington, USA; [4]University of Wisconsin, USA; [5]University of Texas, USA; [6]University of Arizona, USA; [7]Memorial Sloan - Kettering Cancer Center, USA; [8]University of California San Diego, USA; [9]Royal Melbourne Hospital, Australia; [10]Walter and Eliza Hall Institute of Medical Research,[11]AbbVie, USA

Background

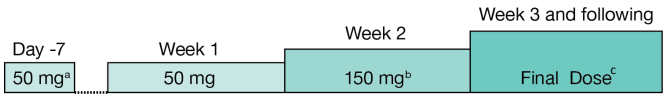
- Bcl-2 expression is uniformly high in CLL:
  - Enabling inappropriate survival through evasion of apoptosis
  - Contributing to resistance to cytotoxic agents
- ABT-199 is a selective, potent, orally bioavailable Bcl-2 inhibitor
- ABT-199 binds Bcl-2 with high affinity and with substantially lower affinity to Bcl-x_L, Bcl-w and MCL-1
- ABT-199 mimics BH3-only proteins (Bim, Bad), but with greater selectivity
- ABT-199 has shown preclinical activity in a wide range of Bcl-2 expressing hematologic malignancies as a single agent



ABT-199

Souers AJ, et al. *Nature Med.* 19(2):202-208. 2013

Dosing Schedule of ABT-199: Dose Escalation Schematic

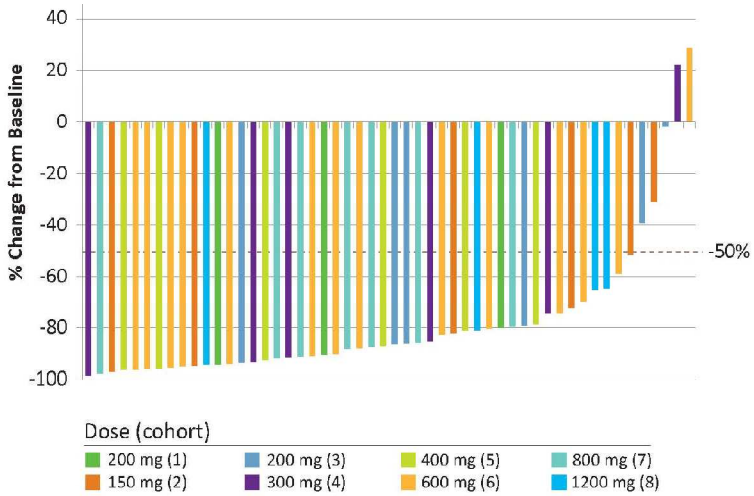


		ABT-199 Doses, Weekly Escalation			
	Patients Enrolled	Start			
Cohort 1	1	100			
	2	200			
Cohort 2	6	50[a]	100	150	
Cohort 3	6	50[a]	100	200	
Cohort 4	7	50	100	300	
Cohort 5	7	50[a]	100	400[c]	
Cohort 6	15	50	150	400	600
Cohort 7	7	50	150	800	
Cohort 8	5	50	150	1200	

[a] 3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.
[b] Week 2 dose in cohorts 2 - 5 = 100 mg.
[c] Cohort 6 had an extra step prior to final dosing at week 4.

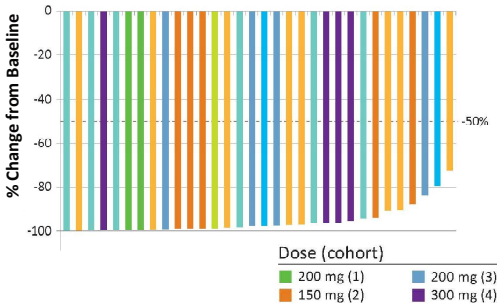
Best Percent Change from Baseline in Nodal Size by CT Scan

N = 52 evaluable (at minimum, 6 weeks assessment)
Median Time to 50% Reduction = 1.4 months (range 0.7 to 13.7)



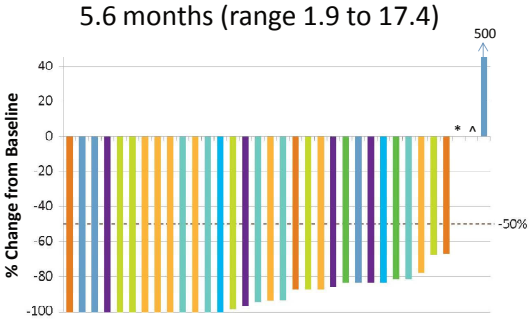
Best Percent Change from Baseline in Lymphocyte Count and Bone Marrow Infiltrate

Lymphocyte Count
Median Time to 50% Reduction:
12 days (range 1 to 43)



Data represents patients with lymphocyte count >5 x 10^9/L at baseline.
N = 32 evaluable

Bone Marrow Infiltrate
Median Time to 50% Reduction:
5.6 months (range 1.9 to 17.4)



*Patient had 70% infiltrate at baseline and at Week 24.
^Patient did not have CLL infiltrate at baseline.
N = 34 evaluable

Anti-tumor activity of ABT-199 was observed in all tumor compartments.

Responses in ABT-199 Treated CLL Patients

Responses	All CLL n (%) N=56	del (17p) n (%) n=17	Fludarabine Refractory n (%) n=18
Overall response rate	**47 (84)**	**14 (82)**	**14 (78)**
Complete response / CRi	11 (20)	2 (12)	3 (17)
Partial response*	36 (64)	12 (71)	11 (61)
Stable disease	4 (7)	1 (6)	1 (6)
Disease progression	1 (2)	1 (6)	-
D/C Prior to first (6W) assessment	4 (7)	1 (6)	3 (17)

*3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks).

Minimal Residual Disease: Preliminary Analyses

- 8/11 patients with CR/CRi were assessed for Minimal Residual Disease (MRD)
- Quantification by 4 color flow cytometry using local lab methods

Patient	Source	% MRD	Cells Analyzed†	Notes
1 **	BM	Negative	500,000	High sensitivity MRD panel
2 *	BM	Negative	78,572	Insufficient cells analyzed to claim 10^{-4} sensitivity
3	BM	Negative	78,980	Insufficient cells analyzed to claim 10^{-4} sensitivity
4 *	BM	<0.1	>50000/antibody	Number of positive cells not reported
5	BM	0.05	558,000	High sensitivity MRD panel
	PB	Negative	57,000/tube	Less sensitive
6	BM	0.7	54,792	
7	BM	0.75	>200000/tube	
	PB	Negative	21,000/tube	Less sensitive
8	BM	Positive	Quantification Pending	

BM= Bone Marrow, PB = Peripheral Blood
*Fludarabine refractory **Both fludarabine refractory and del(17p)
† Per local lab report
MRD status was not a pre-specified endpoint at study start

Adverse Events (AEs) in ABT-199 Treated CLL Patients

	All Grades ≥ 20% of pts n (%)
Diarrhea	26 (46)
Neutropenia	24 (43)
Nausea	24 (43)
Fatigue	19 (34)
Upper respiratory tract infection	16 (29)
Cough	14 (25)
Thrombocytopenia[a]	12 (21)
	Grades 3/4 ≥ 2 pts n (%)
Neutropenia	23 (41)
Thrombocytopenia[a]	6 (11)[b]
Tumor lysis syndrome[c]	6 (11)
Hyperglycemia	5 (9)
Anemia	4 (7)
Febrile Neutropenia	4 (7)
Hypophosphatemia	2 (4)

[a] Includes subjects with autoimmune thrombocytopenia; [b] All (n=6) pts had pre-existing thrombocytopenia, 1 event occurred in the setting of PD and 1 in TLS; [c] TLS includes 3 events from Cohort 1; 2 clinical events and 1 laboratory TLS occurred in Cohorts 4, 8, and 2

Dose Limiting Toxicities (DLTs) and Serious Adverse Events (SAEs)

Cohort	Patients Enrolled	Initial Dose	Target Dose	N	DLT
1	3	100[a]	200	1	Laboratory TLS
		200[a]	200	2	
2	6	50[a]	150	1	Laboratory TLS
4	7	50[a]	300	1	Clinical TLS (Renal Failure)
6	15	50	600[a]	1	Neutropenia
8	5	50	1200[a]	1	Clinical TLS, Sudden Death

[a] Dose at which DLT occurred.
TLS = Tumor lysis syndrome; Clinical and Laboratory TLS per Cairo-Bishop Criteria

Serious AEs[†] Possibly/Probably ABT-199 Related include:

- Febrile Neutropenia (n=3), Laboratory TLS[*] (n=2)
- Sudden Death (n=1), Clinical TLS[*] (n=1), Acute Renal Failure (n=1)
- Others (n=1): Clostridial Infection, Escherichia Sepsis, Influenza, Sepsis, Urinary Tract Infection, Viral Upper Respiratory Tract Infection, Pulmonary Embolism

[†] More than one SAE may have occurred in the same person [*]TLS is the preferred term

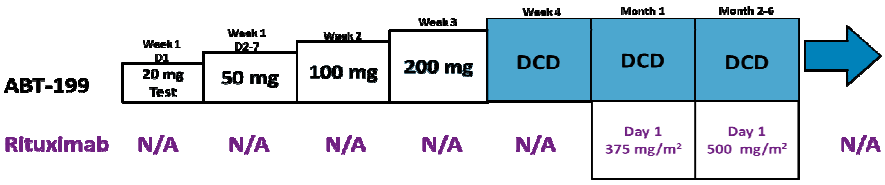
ABT-199 (GDC-0199) Combined with Rituximab in Patients With Relapsed / Refractory Chronic Lymphocytic Leukemia: Interim Results of a Phase 1b Study

Andrew W. Roberts[1], Shuo Ma[2], Danielle Brander[3], Thomas J. Kipps[4], Jacqueline C. Barrientos[5], Matthew S. Davids[6], Mary Ann Anderson[1], Constantine Tam[7], Tanita Mason-Bright[8], Nikita Rudersdorf[8], Jianning Yang[8], Wijith Munasinghe[8], Ming Zhu[8], Elisa Cerri[8], Sari H. Enschede[8], Rod A. Humerickhouse[8], John F. Seymour[7]

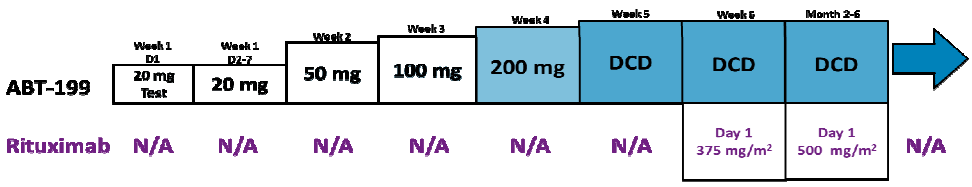
[1]Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Australia; [2]Northwestern University, USA; [3] Duke University Medical Center, USA; [4]University of California San Diego, USA; [5]Hofstra North Shore-LIJ School of Medicine, USA; [6]Dana-Farber Cancer Institute, USA; [7]Peter MacCallum Cancer Centre, Australia; [8]AbbVie, USA

Dosing Schedule of ABT-199 and Rituximab – Cohorts 3 - 6

- 400mg, 500mg, 600mg and safety expansion cohorts dosed with this schedule



OR: if one or more electrolytes meet Cairo-Bishop criteria and/or if there is ≥ 30% decrease in ALC with first dose



ABT-199 + Rituximab Phase 1b Trial in Relapsed / Refractory CLL

Adverse Events (AEs)

All Grades, ≥ 20% pts	N=45 n (%)
Neutropenia	23 (51)
Nausea	17 (38)
Diarrhea	15 (33)
Pyrexia	12 (27)
Headache	12 (27)
Anemia	11 (24)
Fatigue	11 (24)
Upper respiratory tract infection	11 (24)
Cough	11 (24)
Thrombocytopenia*	9 (20)
Grades 3/4, ≥ 3 pts	**N= 45 n (%)**
Neutropenia	21 (47)
Anemia#	7 (16)
Thrombocytopenia*	6 (13)
Febrile Neutropenia	3 (7)

* includes 4 events of autoimmune thrombocytopenia, one of which was Grade 3
# includes 1 event of autoimmune hemolytic anemia

Responses of Patients Treated with ABT-199 and Rituximab

Response	Evaluable Patients n=25 (%)
Overall Response	**21 (84)**
Complete response*	9 (36)
Partial response	12 (48)
Stable disease	1 (4)
Disease progression	1 (4)
Discontinued prior to M7 assessment #	2 (8)

* Includes 5 pts with Complete Response with incomplete marrow recovery (CRi)
# One pt with final visit scan showing PR prior to withdrawing consent, one death from TLS Day 1

- Of the 20 patients on study < 7 months (still receiving combination):
  5 have a PR, 6 have a PR at first CT; 9 have not yet been evaluated

Minimal Residual Disease (MRD)

MRD was assessed by local lab using 4 color flow cytometry in 8/9 CR/CRi patients and 6 patients with a PR (based on available data)

Patient	Response	Source	Sensitivity	MRD
1	CR	Bone Marrow	10^{-4}	Negative
2	CR	Peripheral Blood	10^{-3}	Negative
3	CR	Bone Marrow	10^{-3}	0.20%
4	CR	Bone Marrow	10^{-3}	Negative
		Peripheral Blood	10^{-3}	Negative
5	CR	Bone Marrow	10^{-4}	Negative
6	CR	Bone Marrow	10^{-4}	Negative
7	CR	Bone Marrow	10^{-4}	0.02%
8	CR	Bone Marrow	10^{-4}	Negative
9	PR	Bone Marrow	10^{-4}	Negative
10	PR	Bone Marrow	10^{-4}	< 1%
11	PR	Bone Marrow	10^{-4}	Negative
12	PR	Peripheral Blood	10^{-4}	Negative
13	PR	Bone Marrow	10^{-4}	Negative
14	PR	Bone Marrow	10^{-4}	Negative

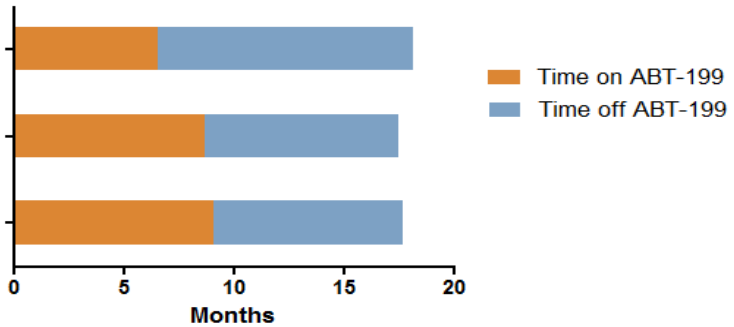
ABT-199 + Rituximab Phase 1b Trial in Relapsed / Refractory CLL

Complete Remission: Discontinuation of ABT-199

3 patients have discontinued ABT-199 after achieving CR/CRi (2 with MRD negativity)

Patients had 1, 3, and 4 prior therapies; one had fludarabine refractory disease

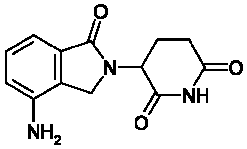
- Patients are continuing follow-up on study
- Patients remain in CR at the time of this analysis (8.6, 8.8, and 11.6 months after cessation)



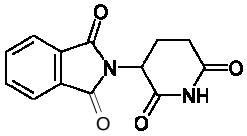
ABT-199 + Rituximab Phase 1b Trial in Relapsed / Refractory CLL

Lenalidomide

- A derivative of thalidomide introduced in 2004
- Immunomodulatory drug
- Approved in 2005 for treatment of patients with 5q-myelodysplastic disease (MDS) and then multiple myeloma

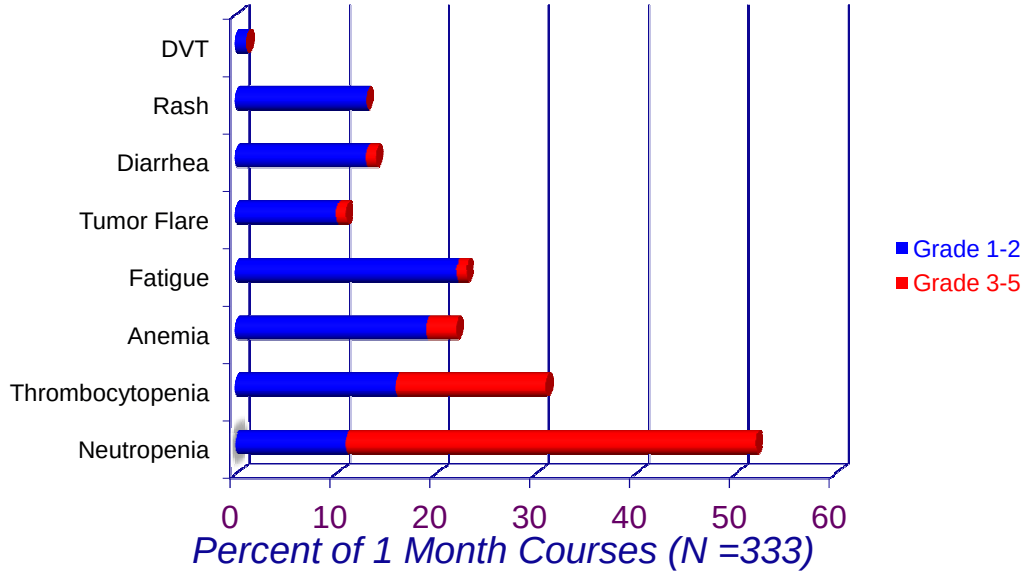


Lenalidomide



Thalidomide

Lenalidomide Toxicity Profile



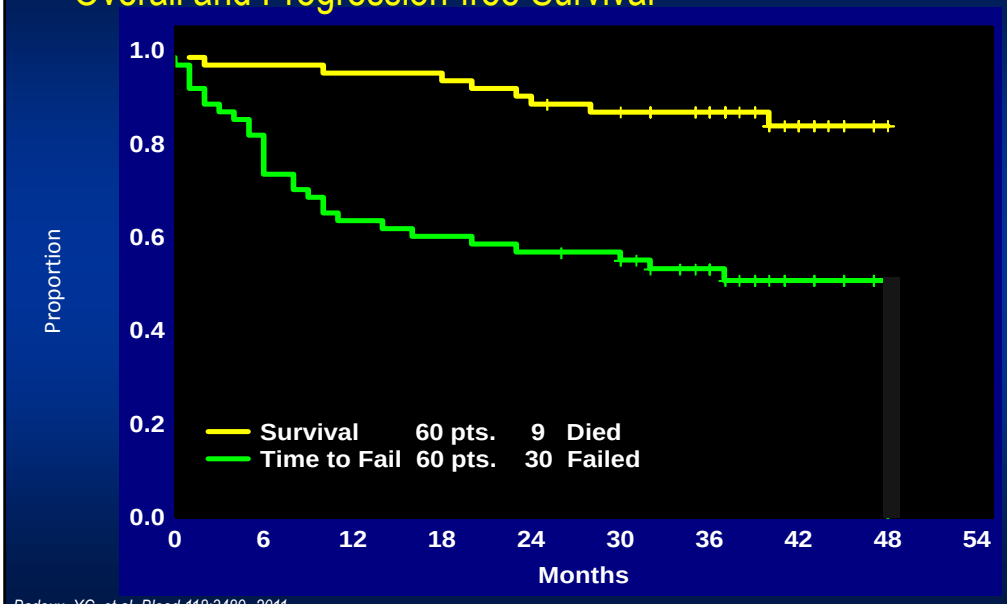
Ferrajoli et al. Blood 111:5291-5297, 2008

Response of Patients Over 64 Years of Age to Initial Treatment with Lenalidomide

Response	3 cycles # (%) 54/60	9 cycles # (%) 43/60	15 cycles # (%) 38/60	21 cycles # (%) 35/60	Best Response # (%)
CR	0	1 (2)	3 (5)	5 (8)	6 (10)
CRi	0	0	2 (3)	3 (5)	3 (5)
nPR	0	6 (10)	4 (7)	5 (8)	4 (7)
PR	24 (40)	27 (45)	27 (45)	22 (37)	26 (43)
ORR	24 (40)	27 (45)	27 (45)	22 (37)	26 (43)

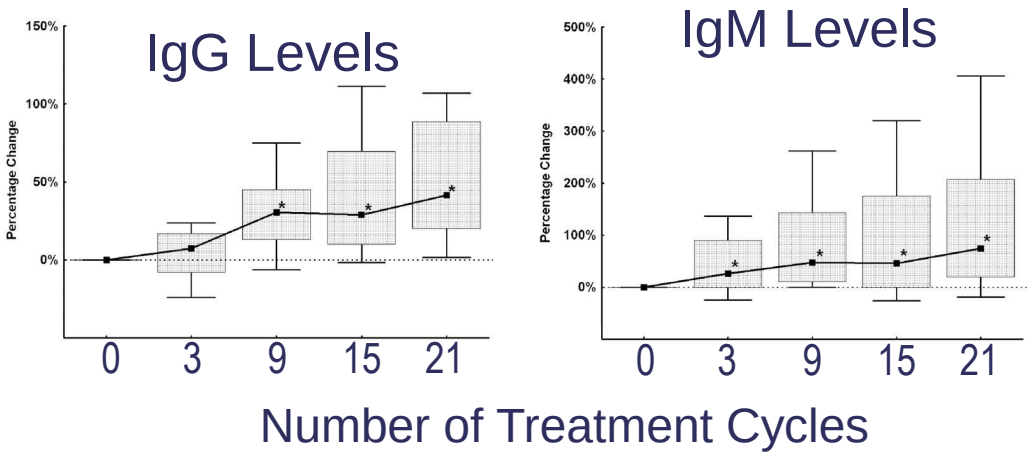
Badoux, XC, et al. Blood 118:3489, 2011

Lenalidomide in Elderly CLL: Overall and Progression-free Survival



Badoux, XC, et al. Blood 118:3489, 2011

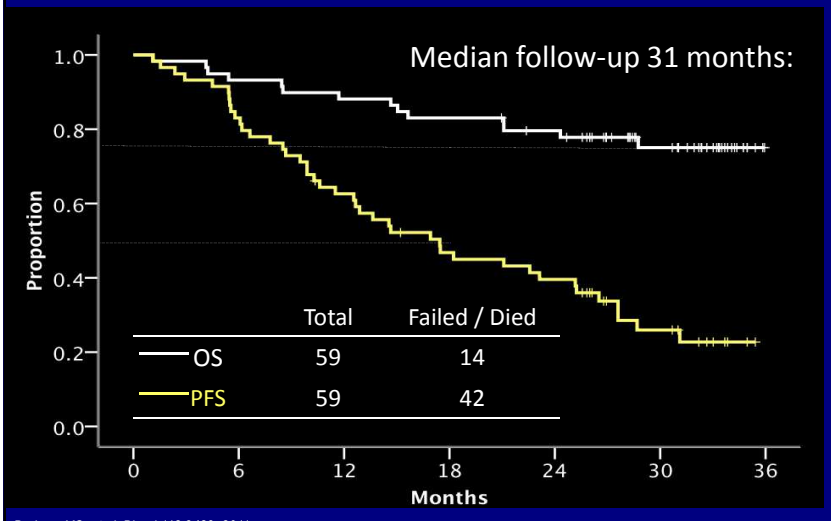
Percent Change In Ig Levels Of Patients* Treated with Lenalidomide



Badoux, XC, et al. Blood 118:3489, 2011

* N = 38 (15 cycles) or 31 (21 cycles)

Lenalidomide + Rituximab in Relapsed CLL Overall and Progression-free Survival



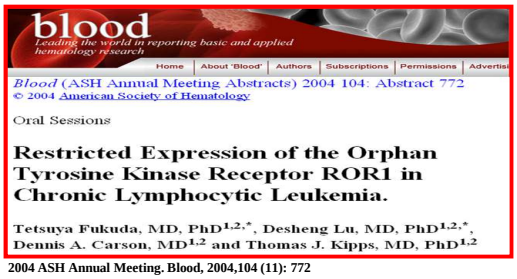
Overall Survival
75%
(95%CI: 64-87%)

Median PFS
17.4 months
(95%CI: 11.9-23.0)

Badoux, XC, et al. Blood 118:3489, 2011

Monoclonal Antibody	Antigen
• Rituximab (Genentech/Roche) [Approved] • Ofatumumab (GSK) [Approved] • Obinutuzumab (GA101, Genentech/Roche) [III] • Ublituximab (LFB-R603, LFB) [II] • Veltuzumab (hA20/Immunomedics) [I/II] • Ocrelizumab (Genentech/Roche) [III for MS]	CD20
• Alemtuzumab (SA) [Approved, but now off market for CLL] Renamed Lemtrada™ for MS 12 mg QD x 5 and then 1yr later QD x 3 (96 mg)	CD52
• MEDI-551 (MedImmune LLC) [II/III] • MDX-1342 (Bristol Myers Squibb) [I] • Xmab5574 (MorphoSys/Xencor) [I]	CD19
• Epratuzumab (UBC) [III for SLE]	CD22
• MAb 37.1/2 (Boehringer/Ingelheim) [pre] • K7153A	CD37
• MOR202 (MorphoSys) [pre]	CD38
• Lucatumumab (CHIR-12, HCD122) [I/II]	CD40
• RG7356 (Roche) [pre]	CD44
• MDX-1411 (BMS) [I-held]	CD70
• Milatuzumab (Immunomedics, Inc) [I/II]	CD74
• ALXN6000 (Alexion Pharm) [I/II-held]	CD200
• UC-961 (Cirmtuzumab)	ROR1
• BMS-936564/MDX-1338 (Bristol Myers Squibb) [II]	CD184 (CXCR4)

ROR1 is Expressed in CLL, but not Normal B-cells or Normal Adult Tissue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Blood (ASH Annual Meeting Abstracts) 2004 104: Abstract 772
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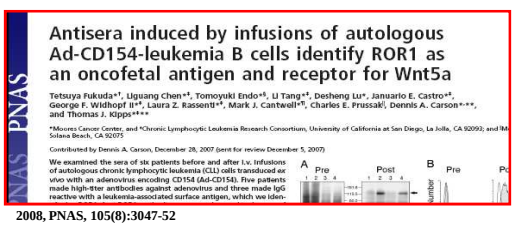
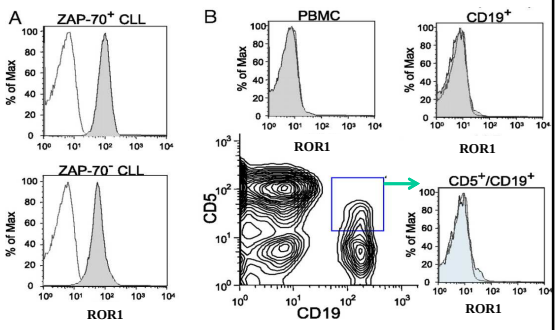
Oral Sessions
Restricted Expression of the Orphan Tyrosine Kinase Receptor ROR1 in Chronic Lymphocytic Leukemia.
Tetsuya Fukuda, MD, PhD[1,2,*], Desheng Lu, MD, PhD[1,2,*], Dennis A. Carson, MD[1,2] and Thomas J. Kipps, MD, PhD[1,2]

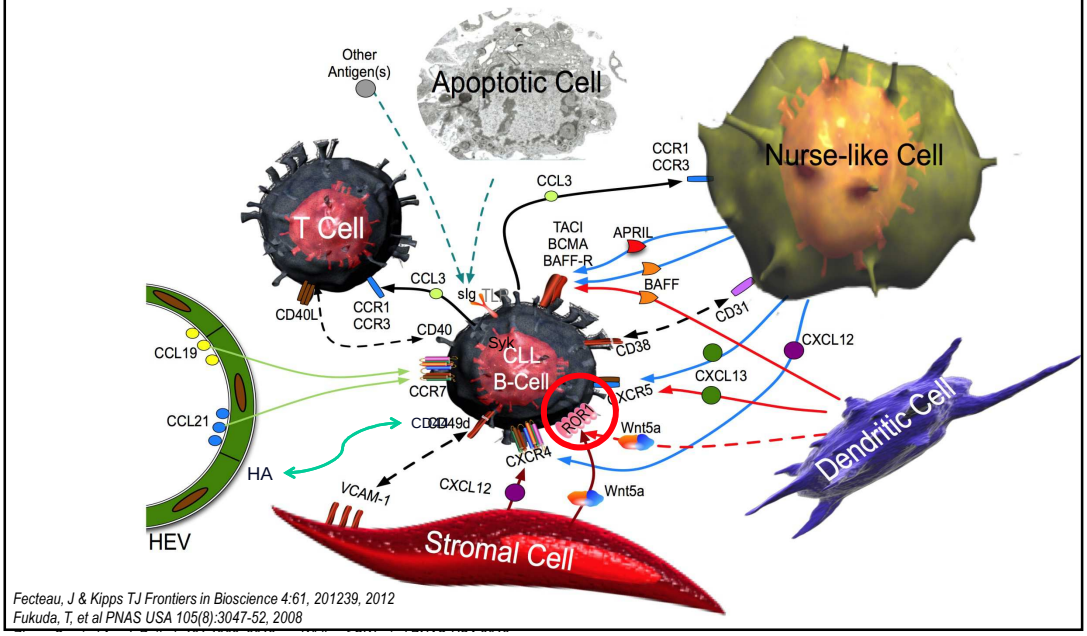
2004 ASH Annual Meeting. Blood, 2004,104 (11): 772


PNAS
Antisera induced by infusions of autologous Ad-CD154-leukemia B cells identify ROR1 as an oncofetal antigen and receptor for Wnt5a
Tetsuya Fukuda*†, Liguang Chen*†, Tomoyuki Endo*‡, Li Tang*†, Desheng Lu*, Januario E. Castro*†, George F. Wildhopf II*†, Laura Z. Rassenti*†, Mark J. Cantwell*¶, Charles E. Prussak‖, Dennis A. Carson*,**, and Thomas J. Kipps*,**
Contributed by Dennis A. Carson, December 28, 2007 (sent for review December 5, 2007)
We examined the sera of six patients before and after i.v. infusions of autologous chronic lymphocytic leukemia (CLL) cells transduced ex vivo with an adenovirus encoding CD154 (Ad-CD154). Five patients made high-titer antibodies against adenovirus and three made IgG reactive with a leukemia-associated surface antigen, which we iden-

2008, PNAS, 105(8):3047-52

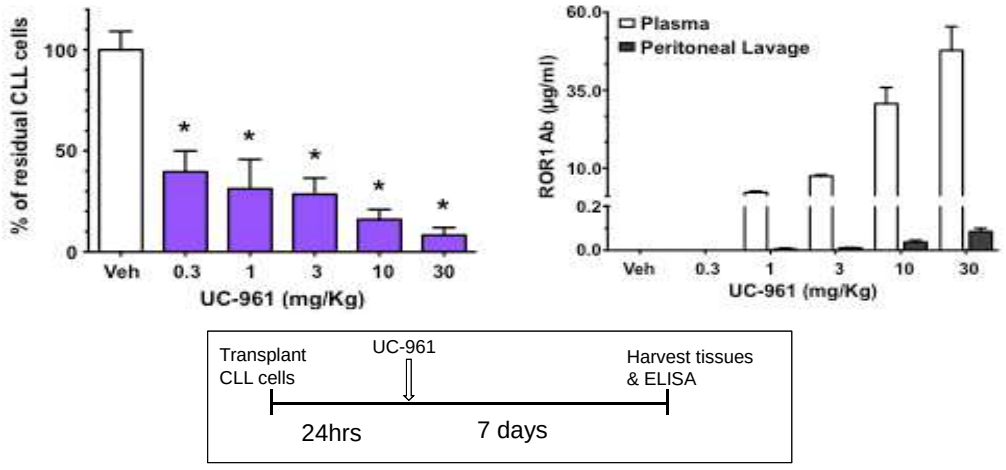


CLL Microenvironment



Fecteau, J & Kipps TJ Frontiers in Bioscience 4:61, 201239, 2012
Fukuda, T, et al PNAS USA 105(8):3047-52, 2008

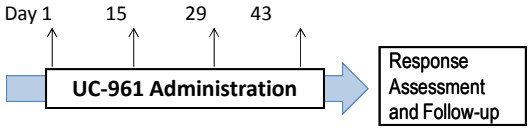
UC-961 Dose Response Targeting CLL Cells in Primary CLL Xenograft Model



Phase 1 Clinical Trial Design

Study Population

- Relapsed or refractory CLL / SLL.
- Progressive disease requiring therapy.
- Not amenable to available CLL therapies.
- Ineligible for chemo-immunotherapy:
  Del 17p, age greater than 70, or age greater than 65 with co-morbidity.

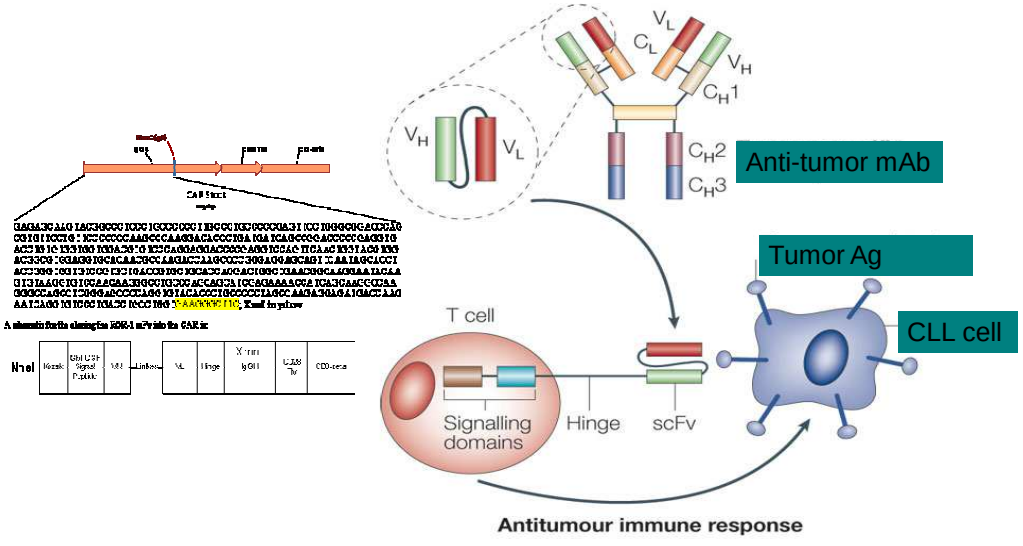


Treatment Cycle = 14 days.
Study assessments on Days 1, 2, and 8 of each cycle.
(additional PK draw on day 3 and 10 of first cycle)

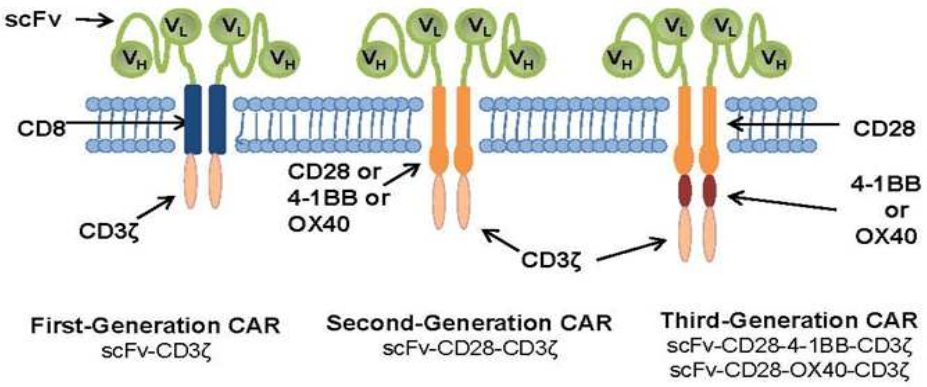
Study Endpoints

Primary: Maximum tolerated dose or biologically active dose
Secondary: Treatment-emergent adverse events, clinical response rate, progression free survival
Exploratory: ROR1 receptor density, circulating UC-961 levels, level of anti-UC-961 antibodies, ROR1 signaling.

Chimeric Antigen T-cell Receptors



Chimeric Antigen Receptors (CAR)



CD19 CAR Therapy at Penn

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE
BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.
N Engl J Med 2011; 365:725-733 | August 25, 2011 | DOI: 10.1056/NEJMoa1103849

RESEARCH ARTICLE

Science
AAAS

LEUKEMIA

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos,[1,2*] Bruce L. Levine,[1,2*] David L. Porter,[1,3] Sharyn Katz,[4] Stephan A. Grupp,[5,6] Adam Bagg,[1,2] Carl H. June[1,2†]

CD19 CAR Therapy at Penn

- Patients with relapsed/refractory CLL were randomly assigned to receive either 5 x 10^8 or 5x10^7 transduced CAR T-cells (designated CTL019)
- All patients received "lymphodepleting" chemotherapy ending 3-5 days prior to T-cell infusion
- 27 patients have enrolled (as of 7/15/2013)
- 3 patients had T cells that did not expand and 1 patient failed screening
- 10 patients (7 M and 3 F) with median age of 63 have been treated
- 5 of these patients had CLL cells with del(17p)

Porter DL, et al. Blood 122:873 ASH Proceedings 2013

CD19 CAR Therapy at Penn

- No acute infusion toxicities
- 7 of 10 patients experienced delayed, grade IV cytokine release syndrome (CRS)
  - High fevers
  - Nausea
  - Myalgias
  - Capillary leak syndrome
  - Hypoxemia
  - Hypotension
- 2 patients received tocilizumab (anti-IL-6R) for grade IV CRS causing life-threatening hemodynamic/respiratory instability

Porter DL, et al. Blood 122:873 ASH Proceedings 2013

CD19 CAR Therapy at Penn

- There were 2 CR and 2 PR (Overall response rate 40%)
- The patients achieving a CR were negative for minimal residual disease
- Responding patients had evidence of persistence of CAR T-cells for more than several months after therapy
- Patients with persistence of CAR T-cells had profound hypogammaglobulinemia
  - IgM and IgA levels of 0
  - Required maintenance therapy with IVIg

Porter DL, et al. Blood 122:873 ASH Proceedings 2013

CLL
Current and Emerging Therapies

someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

Question & Answer Session

The speaker's slides are available for download at
www.LLS.org/programs

June 18, 2014

CLL

Current and Emerging Therapies

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

The Leukemia & Lymphoma Society (LLS) offers:

• Live, weekly Online Chats that provide a friendly forum to share experiences and chat with others about anything from the initial phase of diagnosis to treatment and survivorship. Each chat is moderated by an oncology social worker and is password protected.

- **WEBSITE: www.LLS.org/chat**

• Co-Pay Assistance Program offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

• For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**