Chronic Lymphocytic Leukemia Update

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Learning Objectives

- Recommend appropriate therapeutic options in the initial management of chronic lymphocytic leukemia (CLL)
- Discuss the role of available therapies in patients with relapsed/refractory CLL

Introduction

- Historically, treatment of CLL most often included cytotoxic chemotherapy with or without a monoclonal antibody especially for young patients without significant co-morbidities
- Introduction of new agents has expanded options for all patients with CLL

Ofatumumab (Arzerra®)

- Mechanism
  - Anti-CD20 monoclonal antibody
  - Binds to a different epitope of CD20 than rituximab
  - Improved complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity compared to rituximab
- FDA approved
  - in combination with chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate
  - for the treatment of patients with CLL refractory to fludarabine and alemtuzumab

Arzerra® product information; GlaxoSmithKline April 2014.

Obinutuzumab (GA101) (Gazyva®)

- Mechanism
  - Humanized, type II CD20 monoclonal antibody
  - Exerts activity via antibody-dependent cell-mediated cytotoxicity, direct cell death, and strong homotopic aggregation of lymphoma cells
- FDA approved
  - in combination with chlorambucil for the treatment of patients with previously untreated CLL

Gazyva® product information; Genentech December 2014.

Use of Ofatumumab and Obinutuzumab in CLL

	Ofatumumab	Obinutuzumab
Dosing (IV) - Untreated	**Cycle 1 Day 1 – 300 mg Cycle 1 Day 8 – 1000 mg Cycles 2+ Day 1 – 1000 mg Repeat cycles q28 days**	**Cycle 1 Day 1 – 100 mg Cycle 1 Day 2 – 900 mg Cycle 1 Day 8 – 1000 mg Cycle 1 Day 15 – 1000 mg Cycle 2+ Day 1 – 1000 mg Repeat cycles q28 days**
Dosing (IV) - Refractory	**Cycle 1 Day 1 – 300 mg then 2000 mg weekly x 7 doses, then 4 weeks later 2000 mg q4 weeks x 4 doses**	
Premedication	• **Acetaminophen** • **Antihistamine** • **Corticosteroids**	
Toxicity and Monitoring	• **Infusion reactions** • **Tumor lysis syndrome** • **Cytopenias**	
Drug Interactions	• **None known** • **Avoid live vaccines**	
Warnings	• **Hepatitis B reactivation** • **Progressive multifocal leukoencephalopathy**	

Arzerra® product information; GlaxoSmithKline April 2014. Gazyva® product information; Genentech December 2014.

Ibrutinib (Imbruvica®)

- Mechanism
  - Small molecule inhibitor of Bruton's tyrosine kinase (BTK), which is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways
- FDA approved
  - in CLL patients who have received at least one prior therapy
  - in CLL patients with 17p deletion

Imbruvica® product information; Pharmacyclics, Janssen January 2015.

Idelalisib (Zydelig®)

- Mechanism
  - Small molecule inhibitor of phosphatidylinositol 3-kinase (PI3Kδ)
- FDA approved
  - for relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
  - for relapsed small lymphocytic lymphoma (SLL) in patients who have a received at least two prior systemic therapies

Zydelig® product information; Gilead July 2014.

Use of Ibrutinib and Idelalisib in CLL

	Ibrutinib	Idelalisib
Dosing	**420 mg PO daily**	**150 mg PO twice daily**
Toxicity and Monitoring	• **Transient lymphocytosis** • **Bleeding Grade 2 (6%)** • **Atrial fibrillation (<5%)** • **Infection** • **Cytopenias** • **Diarrhea** • **Rash** • **Tumor lysis syndrome** • **Second primary malignancies**	• **Transient lymphocytosis** • **Fatal or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation** • **Severe cutaneous reactions, rash** • **Anaphylaxis** • **Fever** • **Increased TG, glucose, LFTs** • **Neutropenia**
Drug Interactions	• **Avoid strong CYP3A inhibitors; reduce ibrutinib dose with moderate inhibitors** • **Avoid strong CYP3A inducers**	• **Increase monitoring for toxicity with strong CYP3A inhibitors** • **Avoid strong CYP3A inducers** • **Avoid CYP3A substrates (idelalisib is a strong inhibitor)**
Organ dysfunction	• **Dose reduce for mild hepatic impairment; avoid in moderate-severe hepatic impairment**	**No dosage adjustments for impaired renal/hepatic function; monitor for toxicity if impaired hepatic function**

NCCN. Non-Hodgkin's Lymphomas. v.2.2015. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf
Imbruvica® product information; Pharmacyclics, Janssen January 2015. Zydelig® product information; Gilead July 2014.

First-Line Treatment of CLL

Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL

Primary endpoint

- **Investigator-assessed progression-free survival (PFS)**

Study Design

- **Randomized (1:2:2), multi-center, phase 3 trial (n=781)**
- **Major inclusion criteria: untreated CLL, coexisting conditions (CIRS score >6), or CrCl 30-69 ml/min**

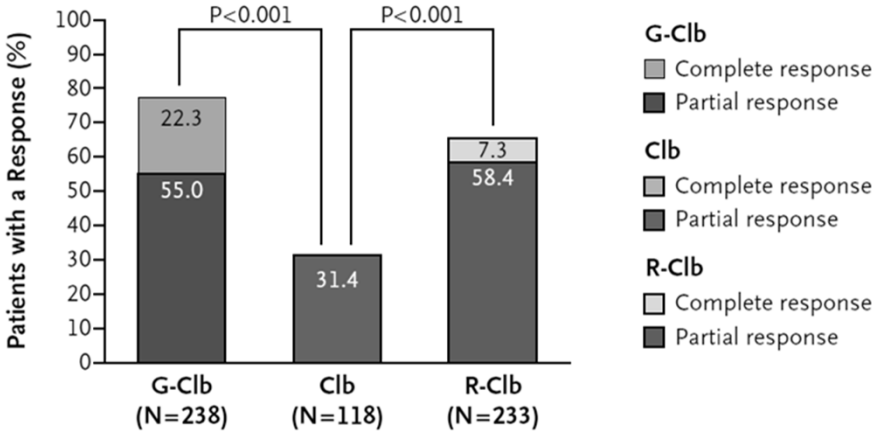
Study Arms

- **Chlorambucil 0.5 mg/kg po Days 1 and 15 of each 28-day cycle**
- **Chlorambucil plus obinutuzumab 1000 mg IV Days 1, 8, 15 of Cycle 1, then Day 1 of Cycles 2-6**
- **Chlorambucil plus rituximab 375 mg/m^2 IV Day 1 of Cycle 1, then 500 mg/m^2 Day 1 of Cycles 2-6**

CIRS = Cumulative Illness Rating Scale

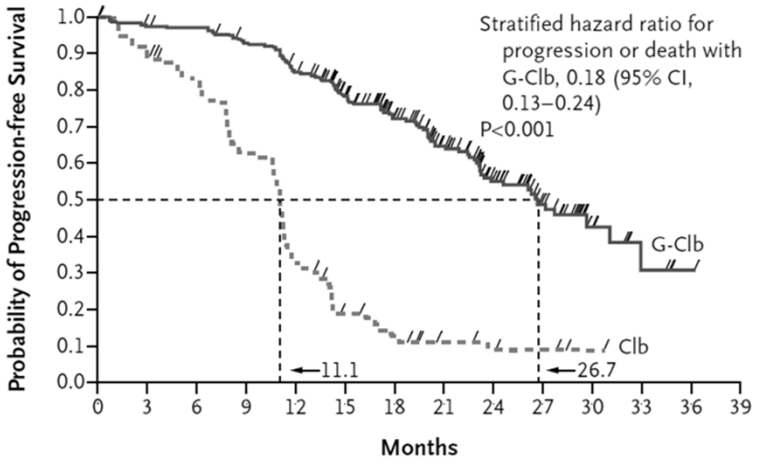
Goede V, et al. N Engl J Med 2014:370:1101-10.

Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



Goede V, et al. N Engl J Med 2014:370:1101-10.

Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



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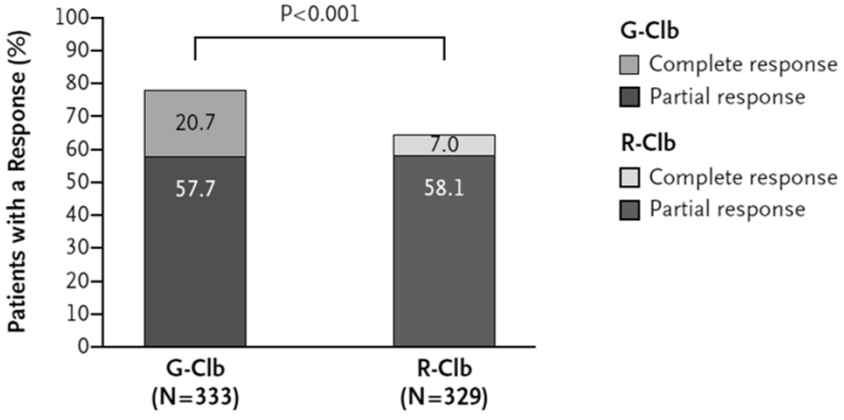
Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



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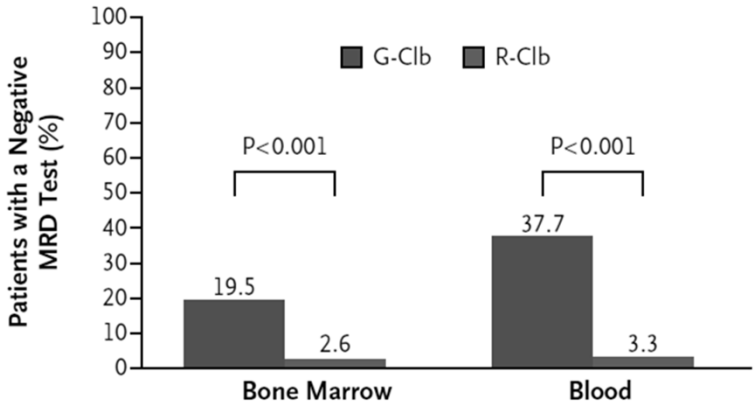

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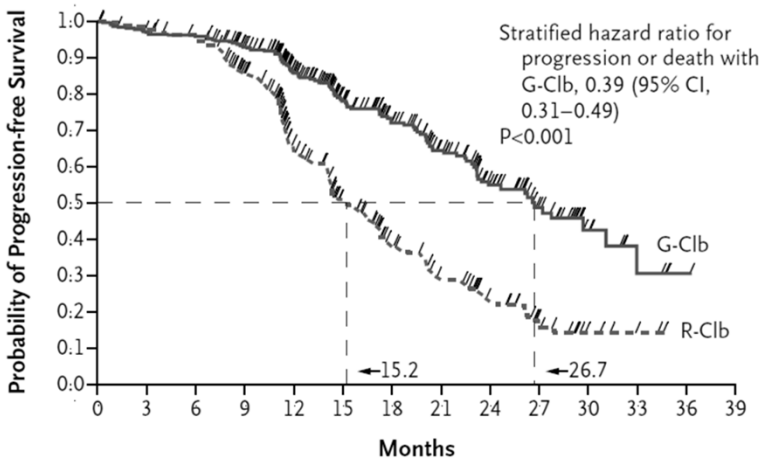
Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



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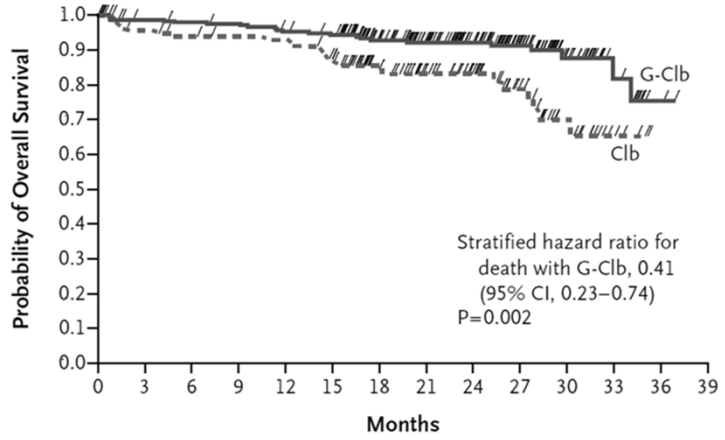
Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



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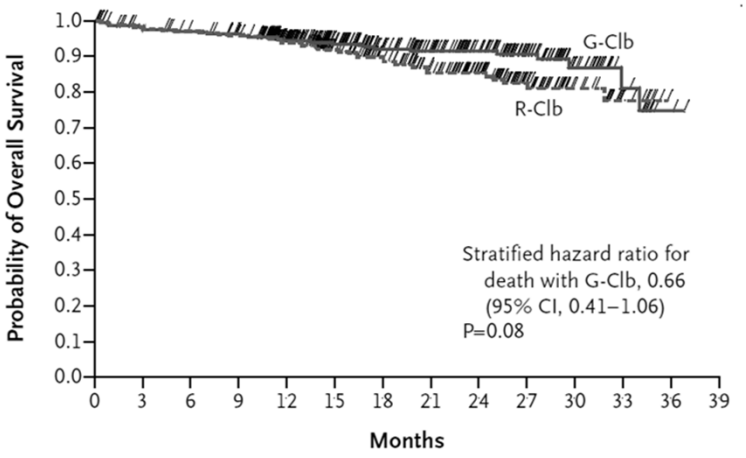
Obinutuzumab plus Chlorambucil: First-Line Treatment of CLL



Goede V, et al. N Engl J Med 2014:370:1101-10.

Obinutuzumab plus Chlorambucil: Grade 3 or Higher Adverse Events

	Chlorambucil (n=116)	Obinutuzumab-chlorambucil (n=336)	Rituximab-chlorambucil (n=321)
Any event	50%	70%	55%
Infusion-related reactions	-	20%	4%
Neutropenia	16%	33%	28%
Anemia	4%	4%	4%
Thrombocytopenia	4%	10%	3%
Leukopenia	0%	4%	1%
Infections	14%	12%	14%
• Pneumonia	3%	4%	5%
• Febrile neutropenia	4%	2%	1%

Goede V, et al. N Engl J Med 2014:370:1101-10.

Ofatumumab plus Chlorambucil: First-Line Treatment of CLL

Primary endpoint

- Progression-free survival

Study Design

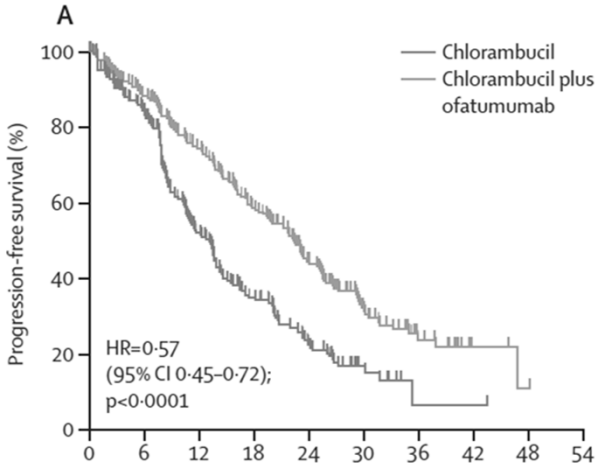
- Randomized (1:1), multi-center, open-label, phase 3 trial (n=447)
- Major inclusion criteria: untreated CLL, fludarabine-based treatment not possible

Study Arms

- Chlorambucil 10 mg/m^2 po daily Days 1-7 of each 28-day cycle
- Chlorambucil plus ofatumumab 300 mg IV Cycle 1, Day 1, then 1000 mg IV Cycle 1, Day 8, then 1000 mg IV Day 1 every 28 days for up to 12 cycles

Hillmen P, et al. Lancet 2015;385:1873-83.

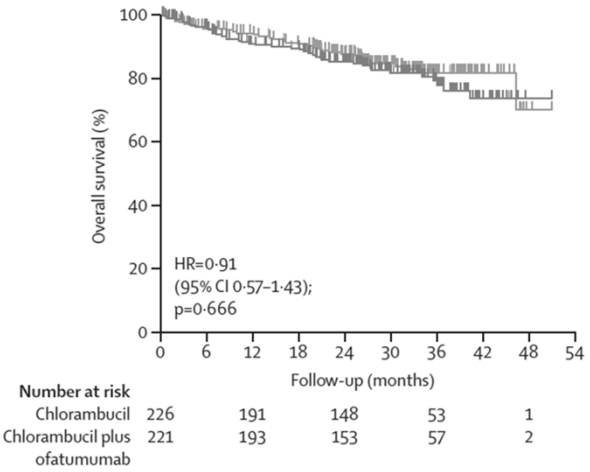
Ofatumumab plus Chlorambucil: First-Line Treatment of CLL



22.4 months vs. 13.1 months

Hillmen P, et al. Lancet 2015;385:1873-83.

Ofatumumab plus Chlorambucil: First-Line Treatment of CLL



Hillmen P, et al. Lancet 2015;385:1873-83.

Ofatumumab plus Chlorambucil: Grade 3 or Higher Adverse Events

	Chlorambucil (n=227)	Chlorambucil-ofatumumab (n=217)
Any	43%	50%
Neutropenia	14%	26%
Thrombocytopenia	10%	5%
Anemia	5%	5%
Infections	12%	9%
Infusion-related reactions	-	10%

Hillmen P, et al. Lancet 2015;385:1873-83.

First-Line Treatment of CLL without del (11q) or del (17p)

Frail patient, significant co-morbidity	Age >= 70 and younger patients with significant co-morbidities	Age < 70 without significant co-morbidities
Obinutuzumab + chlorambucil	Obinutuzumab + chlorambucil	Fludarabine, cyclophosphamide, rituximab (FCR)
Ofatumumab + chlorambucil	Ofatumumab + chlorambucil	Fludarabine + rituximab (FR)
Rituximab + chlorambucil	Rituximab + chlorambucil	Pentostatin, cyclophosphamide, rituximab (PCR)
Obinutuzumab	Bendamustine +/- rituximab	Bendamustine + rituximab (BR)
Rituximab	Obinutuzumab	
Chlorambucil	Fludarabine +/- rituximab	
Pulse corticosteroids	Chlorambucil	
	Rituximab	
	Cladribine	

NCCN. Non-Hodgkin's Lymphomas. v.2.2015. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

First-Line Treament of CLL with del (17p)

First-Line
Ibrutinib
HDMP + rituximab
FCR
FR
Obinutuzumab + chlorambucil
Alemtuzumab +/- rituximab

NCCN. Non-Hodgkin's Lymphomas. v.2.2015. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

First-Line Treament of CLL with del (11q)

Age >= 70 and younger patients with significant co-morbidities	Age < 70 without significant co-morbidities
Obinutuzumab + chlorambucil	Chemoimmunotherapy • FCR • Bendamustine +/- rituximab • PCR • Obinutuzumab + chlorambucil
Ofatumumab + chlorambucil	
Rituximab + chlorambucil	
Bendamustine +/- rituximab	
Cyclophosphamide, prednisone +/- rituximab	
Reduced-dose FCR	
Chlorambucil	
Rituximab	

NCCN. Non-Hodgkin's Lymphomas. v.2.2015. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Treatment of Relapsed/Refractory CLL

Ibrutinib versus Ofatumumab: Treatment of Relapsed/Refractory CLL

Primary endpoint

- **Duration of progression-free survival**

Study Design

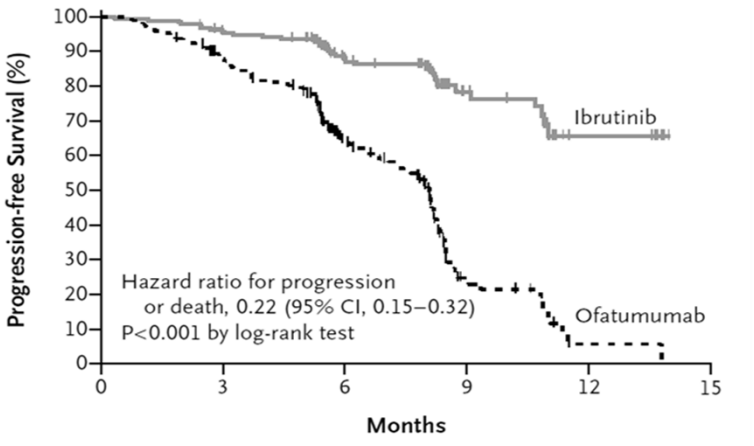
- **Randomized, multi-center, open-label, phase 3 trial (n=391)**
- **Major inclusion criteria: Relapsed or refractory CLL or SLL, at least one prior therapy, and inappropriate candidate for purine analogue treatment**

Study Arms

- **Ibrutinib 420 mg po daily until disease progression or unacceptable toxicity**
- **Ofatumumab 300 mg IV at week 1, then 2000 mg IV weekly for 7 weeks, then every 4 weeks for 16 weeks (24 weeks total)**

Byrd JC, et al. N Engl J Med 2014;371:213-23.

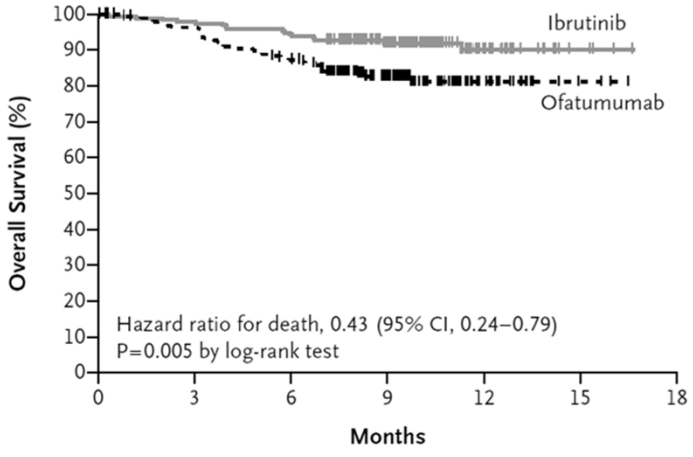
Ibrutinib versus Ofatumumab: Treatment of Relapsed/Refractory CLL



Not reached vs. 8.1 months

Byrd JC, et al. N Engl J Med 2014;371:213-23.

Ibrutinib versus Ofatumumab: Treatment of Relapsed/Refractory CLL



Byrd JC, et al. N Engl J Med 2014;371:213-23.

Ibrutinib versus Ofatumumab: Adverse Events

	Ibrutinib (n=195)		Ofatumumab (n=191)	
	Any grade (%)	Grade 3 or 4 (%)	Any grade (%)	Grade 3 or 4 (%)
Any	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

Byrd JC, et al. N Engl J Med 2014;371:213-23.

Idelalisib plus Rituximab: Treatment of Relapsed/Refractory CLL

Primary endpoint

- **Progression-free survival**

Study Design

- **Randomized, multi-center, double-blind, placebo-controlled, phase 3 trial (n=220)**
- **Major inclusion criteria: Relapsed or refractory CLL, decreased renal function (CrCl < 60 ml/min), previous therapy-induced myelosuppression, or major coexisting illness (CIRS >6)**

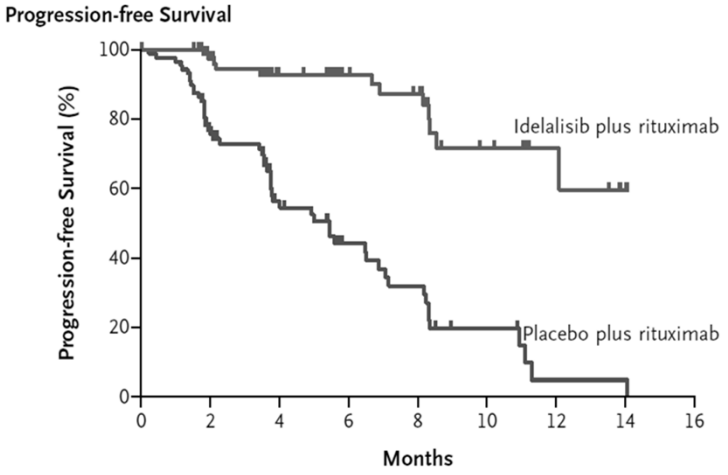
Study Arms

- **Rituximab 375 mg/m^2 IV followed by 500 mg/m^2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses, for a total of 8 infusions (both arms)**
- **Idelalisib 150 mg po bid or placebo**

CIRS= Cumulative Illness Rating Scale

Furman RR, et al. N Engl J Med 2014;370:997-1007.

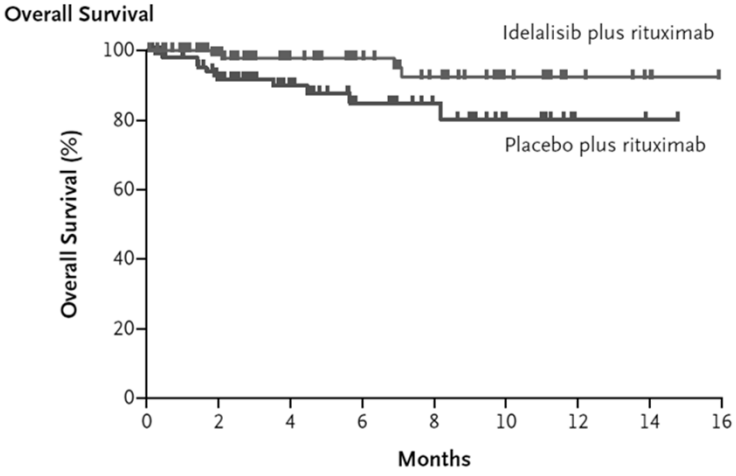
Idelalisib plus Rituximab: Treatment of Relapsed/Refractory CLL



Not reached
vs. 5.5 months
p<0.001

Furman RR, et al. N Engl J Med 2014;370:997-1007.

Idelalisib plus Rituximab: Treatment of Relapsed/Refractory CLL



Furman RR, et al. N Engl J Med 2014;370:997-1007.

Idelalisib plus Rituximab: Selected AEs

	Idelalisib-rituximab (n=110)		Placebo-rituximab (n=107)	
	Any grade (%)	Grade 3 or 4 (%)	Any grade (%)	Grade 3 or 4 (%)
Any	91	56	94	48
ALT/AST increase	35	5	19	1
Anemia	25	5	30	14
Neutropenia	55	34	49	22
Thrombocytopenia	17	10	26	16
Pyrexia	29	3	16	1
Fatigue	24	3	27	2
Nausea	24	0	21	0
Chills	22	2	16	0
Diarrhea	19	4	14	0
Infusion-related reaction	15	0	28	4
Cough	15	0	25	2

Furman RR, et al. N Engl J Med 2014;370:997-1007.

Treatment of Relapsed/Refractory CLL without del (11q) or del (17p)

Age >= 70 and younger patients with significant co-morbidities	Age < 70 without significant co-morbidities
Ibrutinib	**Ibrutinib**
Idelalisib +/- rituximab	**Idelalisib +/- rituximab**
Chemoimmunotherapy • Reduced-dose FCR • Reduced-dose PCR • Bendamustine +/- rituximab • High-dose methylprednisolone (HDMP) + rituximab • Rituximab + chlorambucil	Chemoimmunotherapy • FCR • PCR • Bendamustine +/- rituximab • Fludarabine + alemtuzumab • Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (RCHOP) • Oxaliplatin, fludarabine, cytarabine, rituximab (OFAR)
Ofatumumab	
Obinutuzumab	**Ofatumumab**
Lenalidomide +/- rituximab	**Obinutuzumab**
Alemtuzumab +/- rituximab	**Lenalidomide +/- rituximab**
Dose-dense rituximab	**Alemtuzumab +/- rituximab**
	HDMP + rituximab

Treament of Relapsed/Refractory CLL with del (17p)

Relapsed/Refractory
Ibrutinib
Idelalisib +/- rituximab
HDMP +/- rituximab
Lenalidomide +/- rituximab
Alemtuzumab +/- rituximab
Ofatumumab
OFAR

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Treament of Relapsed/Refractory CLL with del (11q)

Age >= 70 and younger patients with significant co-morbidities	Age < 70 without significant co-morbidities
Ibrutinib	Ibrutinib
Idelalisib +/- rituximab	Idelalisib +/- rituximab
Chemoimmunotherapy • Reduced-dose FCR • Reduced-dose PCR • Bendamustine +/- rituximab • HDMP +/- rituximab • Rituximab + chlorambucil	Chemoimmunotherapy • FCR • PCR • Bendamustine +/- rituximab • Fludarabine + alemtuzumab • OFAR
Ofatumumab	Ofatumumab
Obinutuzumab	Obinutuzumab
Lenalidomide +/- rituximab	Lenalidomide +/- rituximab
Alemtuzumab +/- rituximab	Alemtuzumab +/- rituximab
Dose-dense rituximab	HDMP + rituximab

NCCN. Non-Hodgkin's Lymphomas. v.2.2015. Available at: www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

ARS Question #1

Which of the following has been most closely associated with the development of severe or fatal hepatotoxicity?

A. Obinutuzumab
B. Idelalisib
C. Ofatumumab
D. Ibrutinib

ARS Question #2

An increase in absolute lymphocyte count within the first few weeks following initiation of idelalisib is associated with a lack of response to therapy.

A. True
B. False

ARS Question #3

Which of the following is correct regarding the comparison of ibrutinib to ofatumumab in patients with relapsed or refractory CLL?

A. Ibrutinib improves progression-free survival but not overall survival
B. Ofatumumab results in improved progression-free and overall survival
C. Ibrutinib improves progression-free and overall survival
D. Ofatumumab improves response rate and progression-free survival

Summary

- Several new options exist for treatment of newly diagnosed or relapsed/refractory CLL
- Treatment options are dependent on age, performance status, co-morbidities, cytogenetics or other risk factors, and prior treatment