Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Chronic Lymphocytic Leukemia — Michael E Williams, MD, ScM

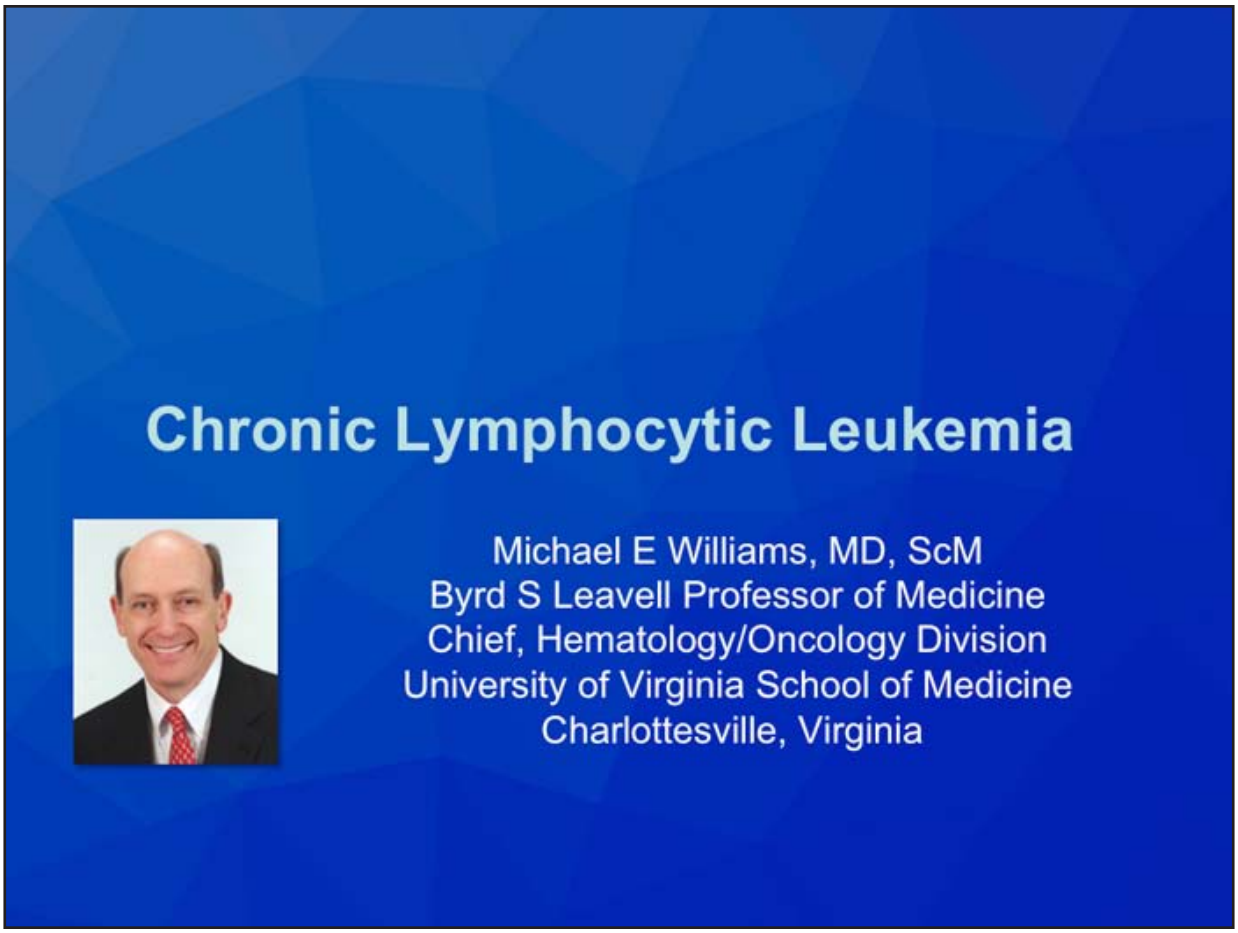
Select Publications

Chanan-Khan AAA et al. **Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study.** *Proc ASCO* 2015;**Abstract LBA7005**.

Eichhorst B et al. **Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 study).** *Proc ASH* 2014;**Abstract 19**.

Farooqui MZ et al. **Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: A phase 2, single-arm trial.** *Lancet Oncol* 2015;16(2):169-76.

Goede V et al. **Salvage therapy with obinutuzumab (GA101) plus chlorambucil (Clb) after treatment failure of Clb alone in patients with chronic lymphocytic leukemia (CLL) and comorbidities: Results of the CLL11 study.** *Proc ASH* 2014;**Abstract 3327**.

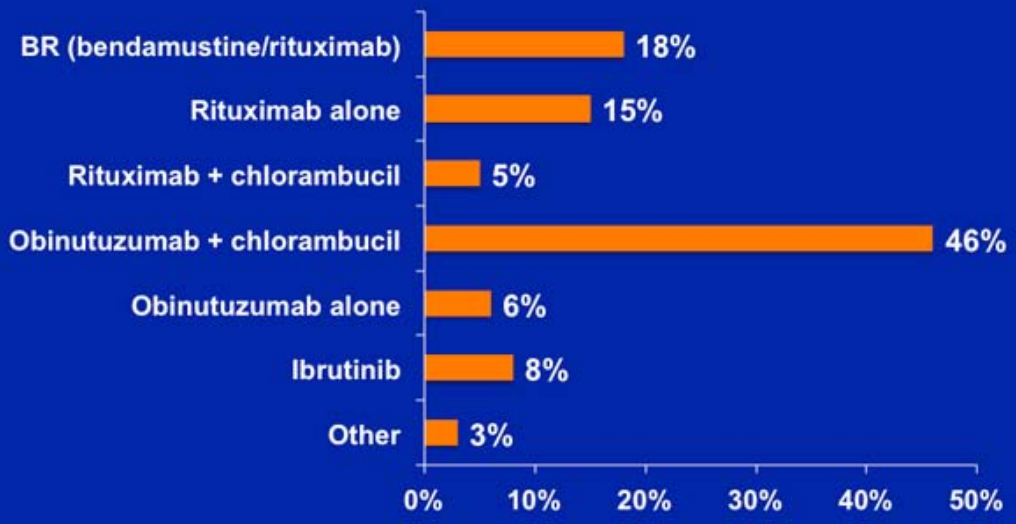


Disclosures

Advisory Committee	Celgene Corporation, Gilead Sciences Inc, Takeda Oncology, TG Therapeutics Inc
Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Takeda Oncology, TG Therapeutics Inc
Contracted Research	Allos Therapeutics, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, Janssen Biotech Inc, Novartis Pharmaceuticals Corporation, Pharmacyclics Inc, Takeda Oncology

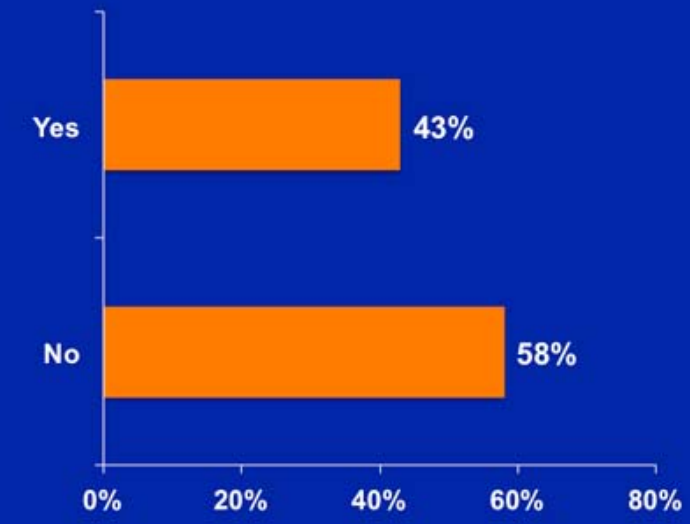
AUDIENCE POLL

In general, what initial therapy would you recommend for an otherwise healthy 81-year-old patient with chronic lymphocytic leukemia (CLL) and normal-risk cytogenetics who requires treatment?



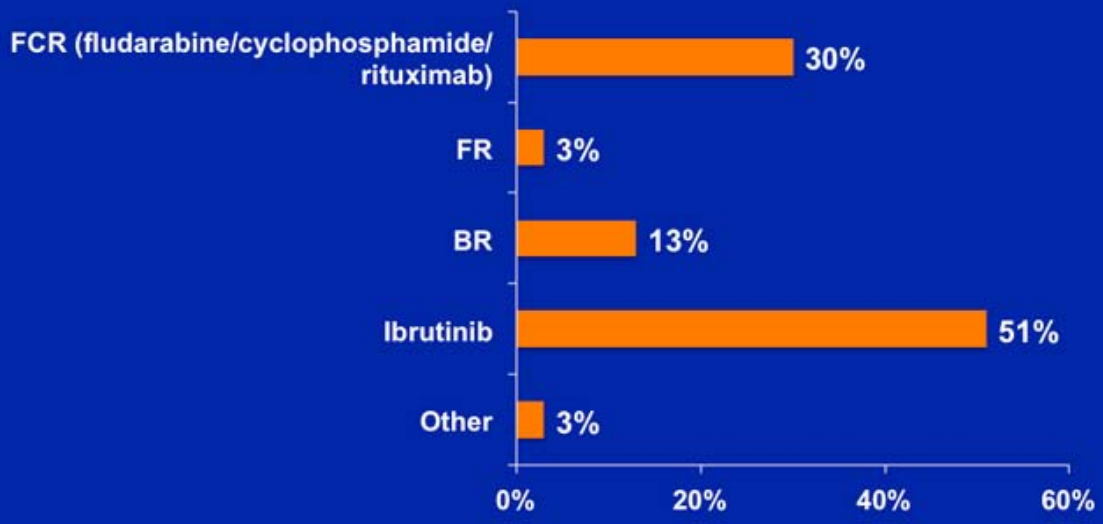
AUDIENCE POLL

A younger, otherwise healthy patient with asymptomatic CLL meets the criteria for observation without treatment but has del(17p). Would you treat this patient?



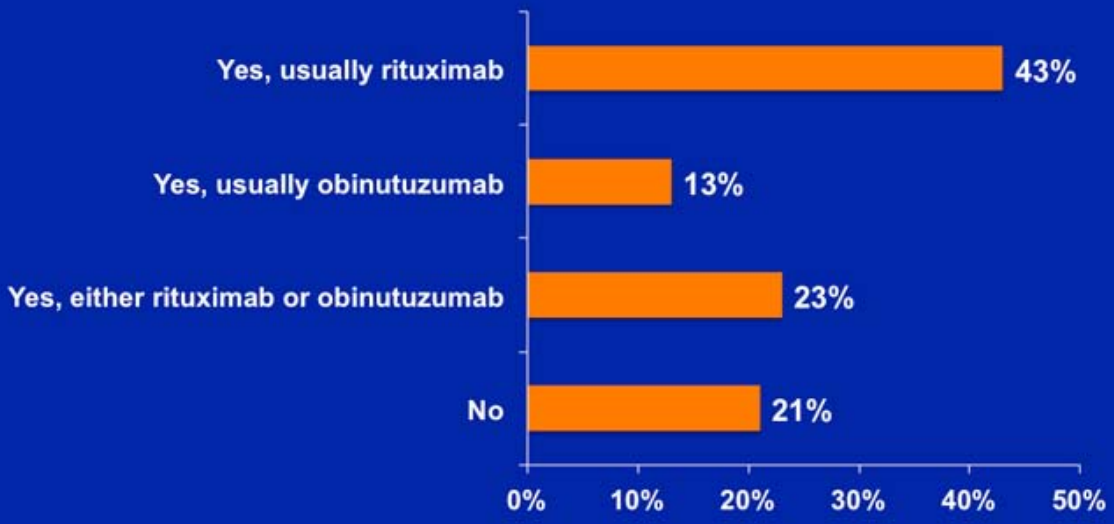
AUDIENCE POLL

What is your usual preferred initial regimen for a younger (60-year-old) patient with CLL and del(17p) who requires treatment?



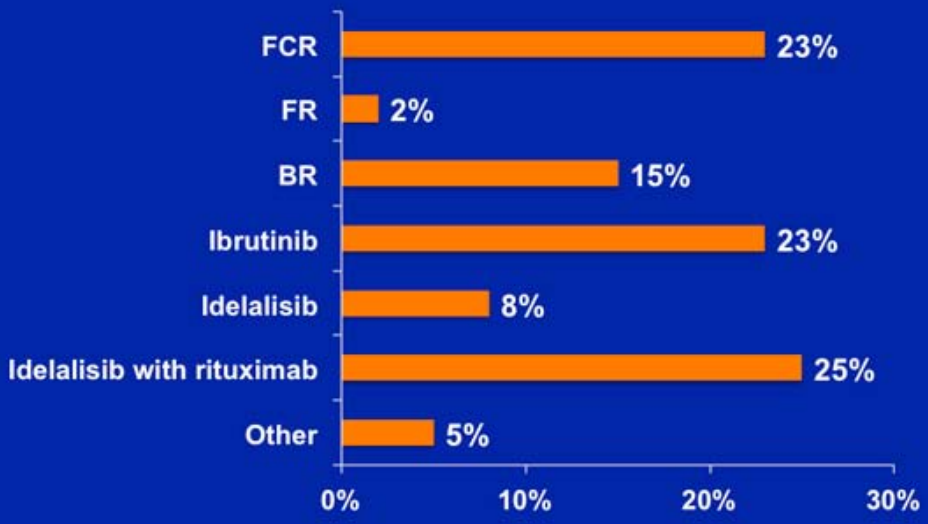
AUDIENCE POLL

Are there patients with CLL to whom you administer an anti-CD20 antibody alone?



AUDIENCE POLL

In general, what treatment would you recommend for a younger patient with CLL and del(17p) who requires treatment but is receiving full-dose anticoagulation for atrial fibrillation?



Frontline Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Shows Superior Efficacy in Comparison to Bendamustine (B) and Rituximab (BR) in Previously Untreated and Physically Fit Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study)

Eichhorst B et al.

Proc ASH 2014;Abstract 19.

Efficacy Analyses

	FCR (n = 282)	BR (n = 279)	Hazard ratio	*p*-value
PFS	55.2 mo	41.7 mo	1.6	<0.001
PFS, IGHV matched	Not reached	43.1 mo	1.6	<0.005
PFS, unmutated IGHV	42.7 mo	33.6 mo	—	0.017
PFS, mutated IGHV	Not reached	52.0 mo	—	0.153
Overall response rate	95.4%	95.7%	—	1.0
Complete response (CR + CRi)	39.7%	30.8%	—	0.034
Minimal Residual Disease (MRD) negativity (evaluable patients)				
PB at FR (n = 185, 170)	74.1%	62.9%		0.024
PB 18 months after FR (n = 65, 65)	53.8%	24.6%		0.006

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Select Adverse Events

Adverse event	FCR (n = 279)	BR (n = 278)	*p*-value
Neutropenia	84.2%	59.0%	<0.001
Anemia	13.6%	10.4%	0.20
Thrombocytopenia	21.5%	14.4%	0.03
Infection	39.1%	26.8%	<0.001
During therapy (tx) only	22.6%	17.3%	0.1
During first 5 mo after tx	11.8%	3.6%	<0.001
In patients ≤65 years	35.2%	27.5%	0.1
In patients >65 years	47.7%	20.6%	<0.001
Secondary neoplasm*	6.1%	3.6%	0.244

* sAML/MDS: FCR (n = 6); BR (n = 1)

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Conclusions

Critical finding(s): Significantly higher CR and MRD-negative responses with FCR and longer PFS

However: FCR was significantly more toxic, especially in patients >65 yo

Does some of the observed FCR benefit relate to fewer patients above 70 yo (14% vs 22%) and fewer with IGHV unmutated status (55% vs 68%)?

Clinical implication(s): FCR remains an appropriate therapy for younger, medically fit CLL patients

BR should be utilized for less fit patients, those with a history of recurring infections and those >65 yo

Conclusions

Research relevance: Informs choice of backbone regimen for the addition of a targeted agent or alternative anti-CD20 monoclonal antibody

Salvage Therapy with Obinutuzumab (GA101) plus Chlorambucil (Clb) After Treatment Failure of Clb Alone in Patients with Chronic Lymphocytic Leukemia (CLL) and Comorbidities: Results of the CLL11 Study

Goede V et al.

Proc ASH 2014;Abstract 3327.

German CLL11 Phase III Study

Target Accrual: 786 (Active, not recruiting)

Eligibility

- Previously untreated CD20+ B-cell CLL
- Cumulative Illness Rating Scale >6

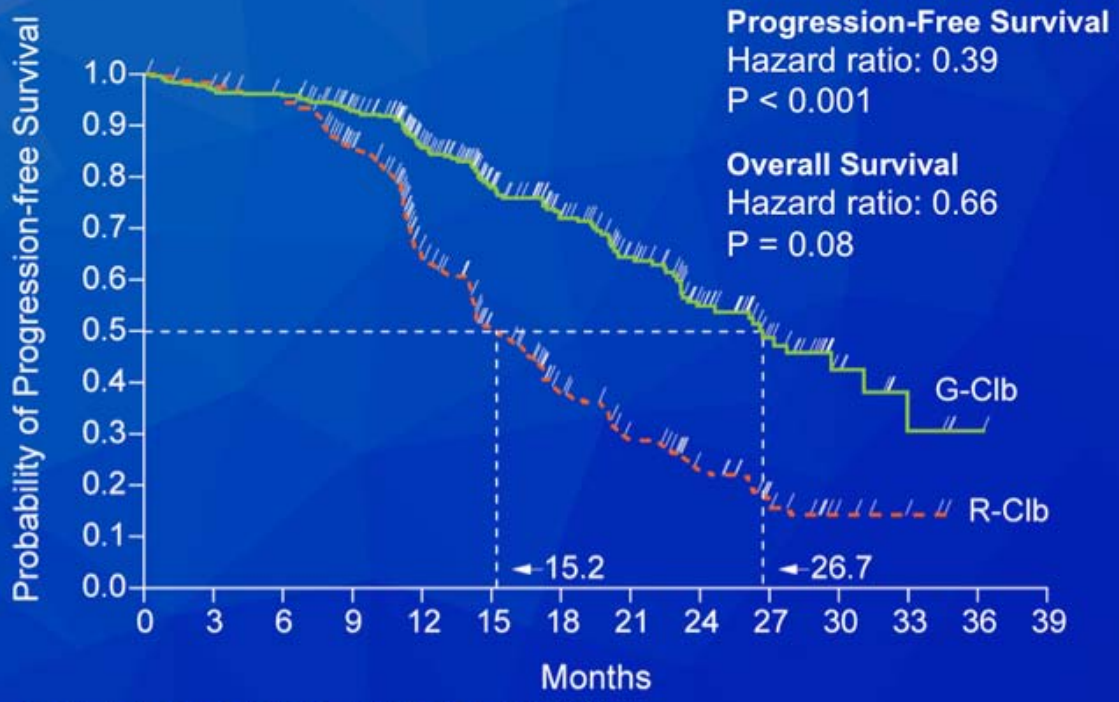
R

- Chlorambucil + Obinutuzumab
- Chlorambucil + Rituximab
- Chlorambucil

Primary Endpoint: PFS

www.clinicaltrials.gov, September 2015. Identifier: NCT01010061
Goede V et al. *N Engl J Med* 2014;370(12):1101-10.

CLL11: Progression-Free Survival



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

Response and Survival to Obinutuzumab-Clb in Patients Progressing on Clb Alone

Efficacy endpoints	n = 30
Overall response	26 (87%)
Complete response	2 (7%)
Incomplete complete response	1 (3%)
Partial response	23 (77%)
Median PFS from start of crossover	17.2 mo

Negativity for minimal residual disease in bone marrow and/or peripheral blood after crossover treatment was achieved in 23% of patients.

Goede V et al. *Proc ASH* 2014;Abstract 3327.

Conclusions

Critical finding(s): CLL patients resistant to chlorambucil responded well to chlorambucil plus obinutuzumab

ORR 87%, most PR

Clinical implication(s): Obinutuzumab is highly active in chlorambucil-resistant CLL

Research relevance: Small sample size, unclear how much benefit derived from the combination of chlorambucil plus obinutuzumab versus obinutuzumab alone for patients failing chlorambucil

Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with *TP53* aberrations: a phase 2, single-arm trial

Mohammed Z H Farooqui, Janet Valdez, Sabrina Martyr, Georg Aue, Nakhle Saba, Carsten U Niemann, Sarah E M Herman, Xin Tian, Gerald Marti, Susan Soto, Thomas E Hughes, Jade Jones, Andrew Lipsky, Stefania Pittaluga, Maryalice Stetler-Stevenson, Constance Yuan, Yuh Shan Lee, Lone B Pedersen, Christian H Geisler, Katherine R Calvo, Diane C Arthur, Irina Maric, Richard Childs, Neal S Young, Adrian Wiestner

Lancet Oncol 2015; 16: 169–76

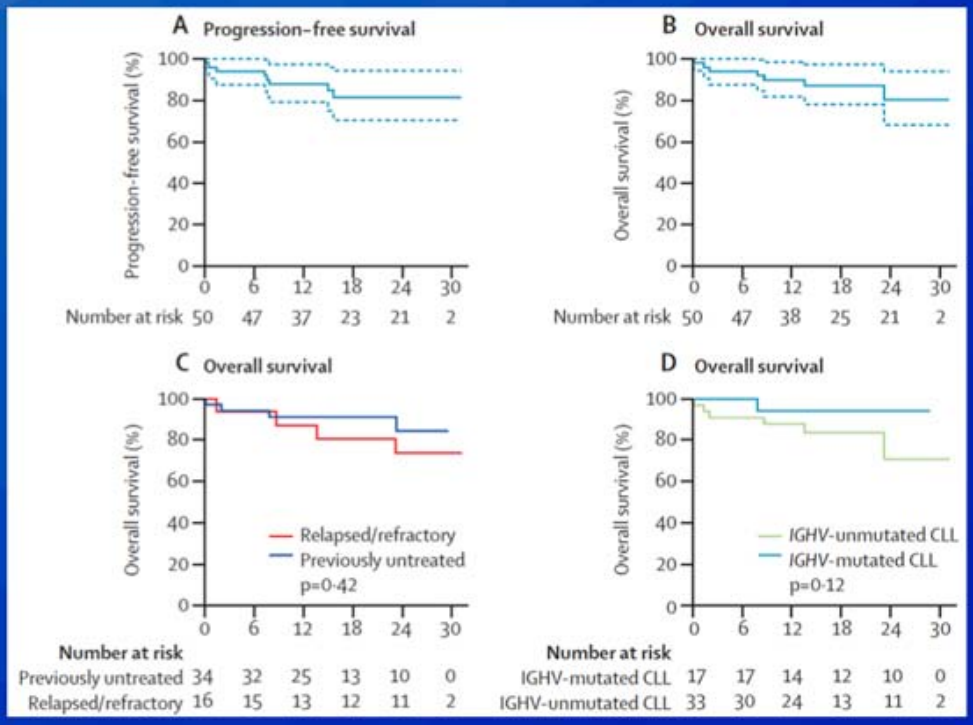
Response

	All evaluable patients (n = 48)	Previously untreated patients (n = 33)	Relapsed or refractory patients (n = 15)
Response at 24 weeks			
Complete response	—	—	—
Partial response	24 (50%)	18 (55%)	6 (40%)
Partial response with lymphocytosis	20 (42%)	14 (42%)	6 (40%)
Stable disease	3 (6%)	—	3 (20%)
Progressive disease	1 (2%)	1 (3%)	—
Best response			
Complete response	5 (10%)	4 (12%)	1 (7%)
Partial response	32 (67%)	23 (70%)	9 (60%)
Partial response with lymphocytosis	8 (17%)	5 (15%)	3 (20%)
Stable disease	2 (4%)	—	2 (13%)
Progressive disease	1 (2%)	1 (3%)	—

Data are n (%)

Farooqui MZH et al. *Lancet Oncol* 2015;16:169-76.

Survival Estimates



Farooqui MZH et al. *Lancet Oncol* 2015;16:169-76.

Conclusions

Critical finding(s): High response rates in this poor-risk CLL subset, in both front-line therapy and relapsed or refractory patients

Low toxicity, significant cytopenias in only ~10% of patients

Clinical implication(s): Ibrutinib is the treatment of choice for del(17p) and TP53-mutated CLL patients

Research relevance: Can response rates and durability be further increased by combining ibrutinib with immunochemotherapy?

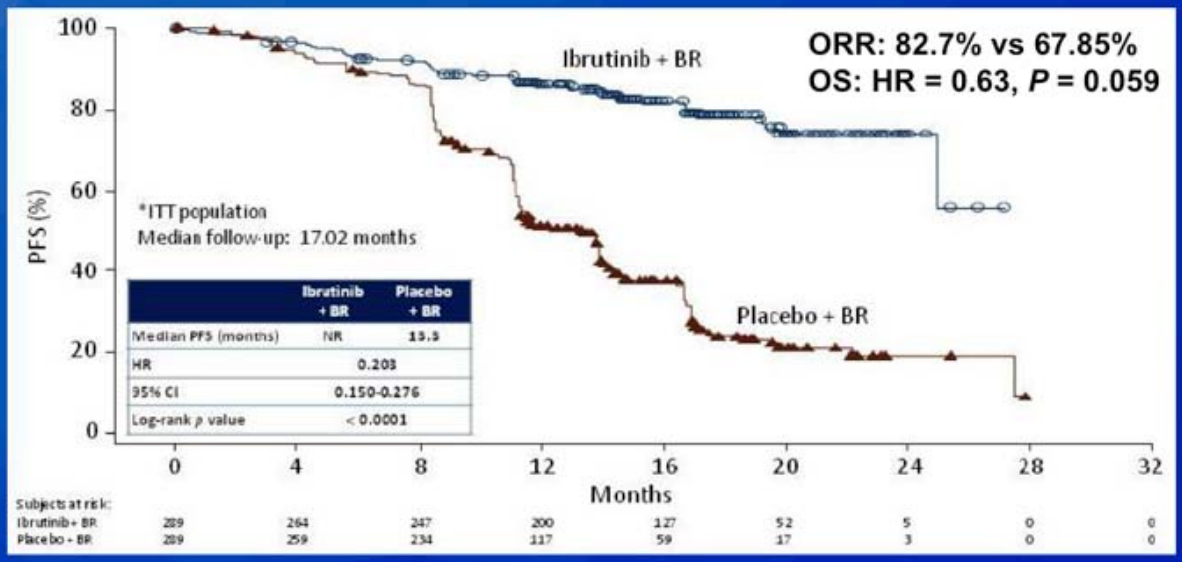
What is the role of allogeneic SCT in eligible del(17p) CLL patients who respond to ibrutinib?

Ibrutinib Combined with Bendamustine and Rituximab (BR) in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): First Results from a Randomized, Double-Blind, Placebo-Controlled, Phase III Study

Chanan-Khan AAA et al.

Proc ASCO 2015;Abstract LBA7005.

Independent Review Committee-Assessed Progression-Free Survival



	Ibrutinib + BR	Placebo + BR
Median PFS (months)	NR	13.3
HR	0.203	
95% CI	0.150-0.276	
Log-rank *p* value	< 0.0001	

Chanan-Khan AAA et al. *Proc ASCO* 2015;Abstract LBA7005.

Conclusions

Critical finding(s): Ibrutinib could be safely combined with BR; improved response rates as well as PFS

No unexpected toxicity for BR plus ibrutinib, very similar to BR plus placebo

Clinical implication(s): A highly active regimen in previously treated CLL/SLL who lack del(17p)

Research relevance: Supports testing in the front-line setting

Phase III Study of Venetoclax/Rituximab (VR) versus BR in Relapsed/Refractory CLL

Primary Endpoint: Progression-free survival

ClinicalTrials.gov, September 2015 (NCT02005471)