5 Minute JournalClub

POST-ASH Issue 2, 2016

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the efficacy and safety of venetoclax alone or in combination for patients with CLL and FL.
- Compare the risks and benefits associated with the Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib for the treatment of CLL.
- Evaluate the activity and tolerability of obinutuzumab/bendamustine for patients with previously untreated CLL.
- Recall recent data on the activity of pembrolizumab in the treatment of relapsed/refractory CLL, including for patients with Richter's transformation.
- Assess the safety of idelalisib in the front-line treatment of CLL.

CREDIT DESIGNATION STATEMENT

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CME Information

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FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Eugene, Oregon

CME Information (Continued)

Advisory Committee and Consulting Agreements: Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, Pharmacyclics Inc; *Contracted Research:* Celgene Corporation, Cephalon Inc, Genentech BioOncology, Gilead Sciences Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc.

5 MinuteJournalClub

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Less than 2 weeks ago, in a historic act that will instantly affect the treatment of one of the most common hematologic cancers in general oncology practice, the FDA broadened the first-line indication of ibrutinib to now include patients both with and *without* 17p-deleted chronic lymphocytic leukemia (CLL). This landmark event is just part of an unprecedented explosion of new data and treatment options that have redefined the management of this disease over the past few years.

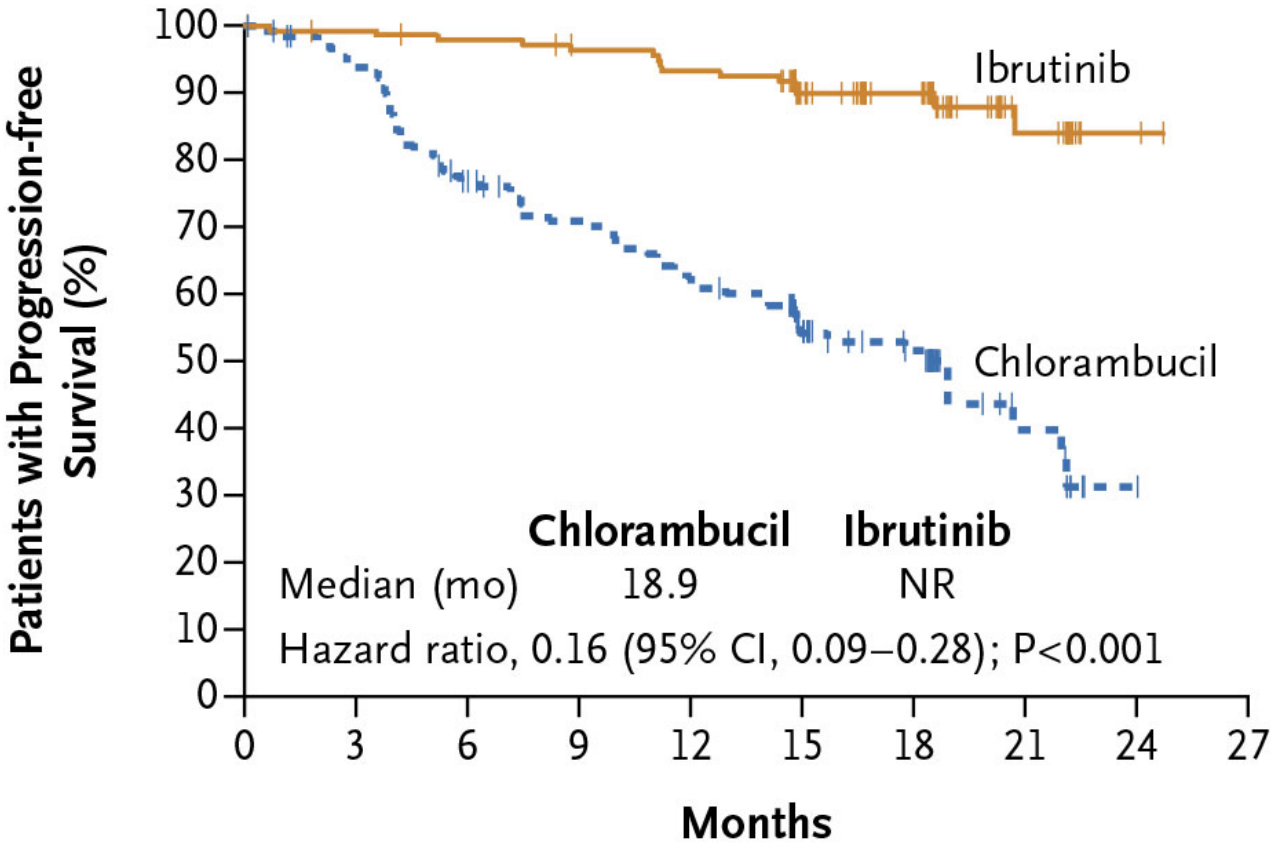
Jeff Sharman, MD

One of the many investigators in this worldwide effort is Dr Jeff Sharman, who first at Stanford and now in Springfield, Oregon has gained extensive practical experience working with many of the novel agents that are now part of current algorithms. I met with Jeff to learn about his perspectives — from both a clinical and a research standpoint — on relevant CLL and non-Hodgkin lymphoma data sets presented at the December ASH meeting and how these add to the rapidly evolving therapeutic paradigms in these cancers. Below find a summary of this conversation along with slides detailing the key findings from the ASH papers.

RESONATE-2: Ibrutinib versus chlorambucil in untreated CLL

In what might be compared to a matchup between the Green Bay Packers and my alma mater, Milford Mill High School, this randomized Phase III trial not surprisingly demonstrated the clear-cut superiority of the Bruton tyrosine kinase (BTK) inhibitor, with spectacular progression-free survival (PFS) and overall survival (OS) HRs of 0.16 for both endpoints. Although the trial focused on patients older than 65, the design and the results did not compel the FDA to tie an age stipulation to the recent approval expansion. In addition, ibrutinib had an acceptable safety profile, with the majority of adverse events being Grade 1 and a lower rate of treatment discontinuation due to toxicity compared to chlorambucil (9% versus 23%). As such, many, including Dr Sharman, believe ibrutinib will become the standard first-line treatment for most patients with CLL. He pointed out that the one exception might be younger patients with IgVH-mutated disease without high-risk FISH findings in whom a chemo-immunotherapy regimen like fludarabine/cyclophosphamide/rituximab (FCR) could potentially result in a prolonged remission or cure without the need for continuous treatment.

Progression-free Survival According to Independent Assessment



No. at Risk

Ibrutinib	136	133	130	126	122	98	66	21	2	0
Chlorambucil	133	121	95	85	74	49	34	10	0	0

In discussing how the indefinite use of up-front ibrutinib may affect clinical practice, Dr Sharman focused on the need to pay even greater attention to the variety of treatment-related complications and potential adverse drug-drug interactions (discussed in another ASH report) that might lead to temporary discontinuation of this generally well-tolerated therapy. His concern in this regard stems from recent research demonstrating that treatment interruption for even 8 days has been associated with a reduction in PFS, a cautionary tale about the potential challenges of administering this or almost any agent indefinitely.

Acalabrutinib (acala-B): A better BTK inhibitor?

The extraordinary efficacy of acala-B might or might not exceed that of ibrutinib, but perhaps of equal importance is the hope that the safety profile may be superior, with early-onset headaches being the most common problem rather than the arthralgias, bruising, bleeding and atrial fibrillation observed with ibrutinib. In a Phase I/II trial of 60 evaluable patients with relapsed disease, responses were observed in 95% of patients, including all 18 with del(17p). A head-to-head Phase III trial will compare these relatively close cousins, but Dr Sharman believes this is another novel agent churning its way steadily toward approval.

Idelalisib in CLL

In one of the highlights of the late-breaking abstract session, Dr Andrew Zelenetz presented results of a Phase III trial evaluating bendamustine/rituximab (BR) alone or with idelalisib in relapsed/refractory (R/R) disease. The study, which was stopped early based on "overwhelming efficacy," demonstrated an impressive improvement in both PFS (HR 0.33) and OS (HR 0.55), and the

findings were consistent for patients with or without high-risk features. Although Dr Sharman questions whether bendamustine really adds much to idelalisib/rituximab, he does consider BR/idelalisib a rational option in the R/R setting.

Importantly, another study at ASH — idelalisib up front combined with ofatumumab — revealed an overall response rate (ORR) of 100% among 24 patients but an excess of immune-related adverse events such as hepatitis, pneumonitis and colitis. Dr Sharman believes these toxicities are likely related to the drug's inhibition of regulatory T cells and explained that the lower frequency of idelalisib-related immune toxicity in the R/R setting may be the result of what he calls "immuno-plegia" as a consequence of prior therapies such as FCR. As a direct result of these new toxicity findings, just yesterday the FDA announced that 6 ongoing combination trials involving idelalisib and a number of other anti-cancer agents had been stopped.

Venetoclax in CLL

Although it is still in clinical development, the emergence of this highly effective Bcl-2 inhibitor represents another gigantic recent CLL advancement, and in Orlando we saw more impressive data with this agent in del(17p) disease with an ORR of 79.4% among 107 patients with R/R disease. We were also treated to some encouraging findings with combination regimens that included bendamustine, rituximab and obinutuzumab (obin) administered prior to, after or with the Bcl-2 inhibitor.

The FDA has now bestowed not 1 but 2 breakthrough therapy designations upon the drug in CLL, and Dr Sharman believes that the overwhelming database supporting the useful clinical role of this agent will likely lead to its approval this year. However, he and others remain somewhat concerned about the potential

for tumor lysis syndrome (TLS), which was observed in early trials, and would like to see specific recommendations emerge for how to prevent or manage this phenomenon. In that regard, he believes that we will likely be assessing pretreatment tumor burden and renal function to determine baseline risk for TLS and then aggressively monitoring or even hospitalizing select patients. With that being said, the availability of another profoundly effective agent with a totally different mechanism of action has the entire CLL investigator community wide eyed with excitement over the possibility of long-term or lifelong disease control.

Obinutuzumab in CLL

It will be interesting to see how the role of this novel anti-CD20 antibody evolves with ibrutinib rapidly moving in on its indicated turf and the current/emerging treatment roster loaded with other novel small agents. Regardless, many believe this drug has good activity in CLL (likely more than rituximab) and for that reason were excited to determine how it would fare in combination with bendamustine. At ASH we saw more from the single-arm GREEN study of bendamustine/obin in untreated and R/R disease demonstrating encouraging efficacy and acceptable toxicity with some concerns about TLS and neutropenia. In the current analysis of 158 patients with previously untreated disease, the bendamustine/obin combination yielded a complete response rate of 32.3%, with minimal residual disease negativity in blood and bone marrow of 58.9% and 28.5%, respectively. Despite these data, Dr Sharman believes the regimen is not yet ready for clinical practice in CLL. It is worth noting that on February 26 of this year the FDA approved bendamustine/obin followed by obin maintenance for patients with *follicular lymphoma (FL)* who did not respond to a rituximab-containing regimen.

Pembrolizumab in CLL with Richter's transformation (RT)

RT occurs in approximately 2% to 10% of all CLL cases, and Dr Sharman commented that recently 2 patients in his practice died within 72 hours of diagnosis, in keeping with the often rapidly progressive course. In this preliminary ASH report of 5 patients with RT, 4 had mostly rapid and deep responses after receiving this anti-PD-1 antibody alone. Although it is clearly early days, Jeff found the findings so encouraging that he recently initiated treatment outside a trial setting with this agent in a patient with RT.

ASH disappointments in indolent lymphoma (ibrutinib, venetoclax)

With all the excitement in CLL, the ASH papers focused on indolent lymphomas were a bit underwhelming. In particular 2 studies in FL combining ibrutinib with either rituximab or rituximab/lenalidomide (R^2) along with a couple of Phase I trials of venetoclax alone or with BR failed to inspire Dr Sharman, particularly when he considers how active idelalisib has been in this setting. He did find intriguing the significant activity observed with the Bcl-2 inhibitor in mantle-cell lymphoma, perhaps related to its biologic and therapeutic similarity to CLL.

Next on this series, Dr Michelle Fanale comments on other lymphoma papers from ASH, including more on the exciting findings now being reported with the use of checkpoint inhibitors in Hodgkin lymphoma.

Neil Love, MD
Research To Practice
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5 Minute JournalClub

Key Papers in Chronic Lymphocytic Leukemia and Follicular Lymphoma from the December 2015 American Society of Hematology (ASH) 57th Annual Meeting in Orlando, Florida

Editor: Neil Love, MD

Faculty: Jeff Sharman, MD

Key Papers in Chronic Lymphocytic Leukemia and Follicular Lymphoma from ASH 2015

Ibrutinib in CLL (Abstracts 495, 717)

Acalabrutinib: A better BTK inhibitor? (Abstract 831)

Idelalisib in CLL (Abstracts LBA-5, 497)

Obinutuzumab in CLL (Abstract 493)

Venetoclax in CLL and NHL (Abstracts LBA-6, 829, 830, 494, 254, 255)

Pembrolizumab in Richter's transformation of CLL (Abstract 834)

Ibrutinib in follicular lymphoma (Abstracts 470, 471)

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Results from the International, Randomized Phase 3 Study of Ibrutinib versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2™)[1]

The Importance of Pharmacovigilance During Ibrutinib Therapy for Chronic Lymphocytic Leukemia (CLL) in Routine Clinical Practice[2]

[1] Tedeschi A et al.
Proc ASH 2015;Abstract 495.

[2] Finnes HD et al.
Proc ASH 2015;Abstract 717.

RESONATE-2 Trial: Ibrutinib (Ibr) in Older Patients with Treatment-Naïve Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL)

- Phase III trial of single-agent Ibr or chlorambucil
- N = 269 treatment-naïve patients aged ≥65 years
- **Primary endpoint:** Progression-free survival (PFS) by independent review committee (IRC)

Clinical variable	Ibr (n = 136)	Chlorambucil (n = 133)	Hazard ratio (*p*-value)
Median PFS by IRC	NR	18.9 mo	0.16 (<0.0001)
18-mo PFS by IRC	90%	52%	—
Median OS	NR	NR	0.16 (0.0010)

OS = overall survival; NR = not reached. Median follow-up is 18.4 months

Tedeschi A et al. *Proc ASH* 2015;Abstract 495.

RESONATE-2: Conclusions

- For older patients with treatment-naïve CLL/SLL, treatment with single-agent Ibr was superior to chlorambucil.
  - 84% reduction in risk of disease progression and 84% reduction in risk of death
  - Improvement in overall response rate and event-free survival
- Ibr resulted in improved bone marrow function.
- Single-agent Ibr had an acceptable safety profile:
  - Majority of adverse events on the Ibr arm were Grade 1
  - Adverse events leading to drug discontinuation were less frequent with Ibr (9% vs 23%)

Tedeschi A et al. *Proc ASH* 2015;Abstract 495.

Investigator Commentary: Results from the RESONATE-2 Trial of Ibrutinib in Older Patients with Untreated CLL/SLL

It is no surprise that ibrutinib proved to be highly superior to chlorambucil. These results were largely expected. However, it is good to see them validated. This will likely lead to a new front-line indication for ibrutinib in CLL, which will have an interesting effect on the way CLL is treated in the community.

Some patients may still be considered suitable for chemoimmunotherapy in the front-line setting. Those with IgVH-mutated B-cell receptor and favorable FISH changes achieve durable remissions with traditional therapy. Whether short-course chemoimmunotherapy with durable response or prolonged oral targeted therapy provides optimal results may vary according to patient preferences. Patients with IgVH-unmutated B-cell receptor or less favorable FISH changes should probably be considered for ibrutinib.

Interview with Jeff Sharman, MD, February 9, 2016

Importance of Pharmacovigilance with Ibr Therapy for CLL

- Retrospective analysis of concomitant use of anticoagulant/ antiplatelet agents or CYP3A4 inhibitors with Ibr
- N = 96 patients receiving Ibr at Mayo Clinic (Rochester, MN) from November 2013 to July 2015
- Concomitant medications, time to toxicity and Ibr discontinuation were analyzed

Patients receiving concurrent medications	N = 96
Medications that potentially increase Ibr toxicity	63%
CYP3A4 inhibitor	17%
Anticoagulant	9%
Antiplatelet	34%
Medications that potentially decrease Ibr efficacy	4%

Finnes HD et al. *Proc ASH* 2015;Abstract 717.

Conclusions

- Two out of 3 patients initiating Ibr are receiving concurrent medications that potentially interact with Ibr.
- Of 96 patients, the offending medication was discontinued in 6 patients and the Ibr dose was altered for 15 patients, allowing Ibr to be safely administered to patients long term.
- No statistically significant correlation was observed between discontinuation of Ibr for disease progression or toxicity and CYP3A interacting mutation.
- A formal medication review conducted by a clinical pharmacist is recommended for all patients initiating Ibr.

Finnes HD et al. *Proc ASH* 2015;Abstract 717.

Investigator Commentary: Importance of Pharmacovigilance with Ibrutinib in CLL

Because ibrutinib is metabolized through the liver and is involved in multiple drug-drug interactions, the Mayo Clinic evaluated a pharmacologist consultation for patients initiating therapy. Interestingly, they observed that 63% of evaluated patients were receiving concurrent medications that increase the risk of toxicity from ibrutinib. Seventeen percent of patients were receiving concurrent CYP3A4 inhibitors and 4% were taking CYP3A4 inducers. Nine percent were receiving concomitant anticoagulation and 30% aspirin. This real-world experience highlights the challenges of using ibrutinib in routine clinical practice. Other data sets have shown that ibrutinib treatment interruptions or dose reductions are associated with inferior outcomes.

At ASCO last year, Paul Barr presented data showing that patients with CLL who received a higher mean dose intensity of ibrutinib experienced improved PFS and those missing more than 1 week of treatment experienced more PFS events.

For these reasons patients who are to receive ibrutinib need to have their entire medication profile reviewed.

Interview with Jeff Sharman, MD, February 9, 2016

Key Papers in Chronic Lymphocytic Leukemia and Follicular Lymphoma from ASH 2015

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Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia

Byrd JC et al.
N Engl J Med 2016;374:323-32.

Byrd JC et al.
Proc ASH 2015;Abstract 831.

ACE-CL-001 Trial: A Novel Bruton Tyrosine Kinase (BTK) Inhibitor, Acalabrutinib, in Chronic Lymphocytic Leukemia (CLL)

- First-in-human, Phase I/II, multicenter study of acalabrutinib (ACP-196), a second-generation, selective, irreversible BTK inhibitor designed to improve on the safety and efficacy of ibrutinib
- N = 61 patients with relapsed CLL (median 3 prior treatments) who received no prior BTK inhibitors:
  - del(17p13.1), 31%; unmutated IGHV, 75%
- **Primary endpoints:** Safety and maximum tolerated dose

	Overall response rate	Partial response (PR) rate	PR with lymphocytosis
All evaluable patients (N = 60)	95%	85%	10%
del(17p13.1) (n = 18)	100%	89%	11%
Prior idelalisib (n = 4)	100%	75%	25%

Byrd JC et al. *Proc ASH* 2015;Abstract 831. Byrd JC et al. *N Engl J Med* 2016;374(4): 323-32.

ACE-CL-001: Conclusions

- Acalabrutinib therapy has been associated with a high response rate and durable remissions at a median follow-up of 14.3 months.
- No cases of Richter's transformation and only 1 case of late CLL progression have occurred, even though this trial included patients at high risk with relapsed CLL.
- The safety profile of acalabrutinib was favorable, despite prolonged, continuous administration:
  - Most common Grade 1 and 2 adverse events: Headache, diarrhea, weight gain
  - Only 8/61 (13%) discontinued study treatment
  - No cases of major bleeding or atrial fibrillation at 14.3 months follow-up
- A Phase III study comparing acalabrutinib to ibrutinib in patients at high risk with relapsed CLL is ongoing (NCT02477696).

Byrd JC et al. *Proc ASH* 2015;Abstract 831. Byrd JC et al. *N Engl J Med* 2016;374(4): 323-32.

Investigator Commentary: Activity of the BTK Inhibitor Acalabrutinib in Relapsed/Refractory CLL

The discovery of B-cell signal receptors in CLL was somewhat serendipitous. Ibrutinib was not initially designed to be a human drug. It was an afterthought included in a laboratory tool kit acquired by one company from another when the latter company decided to no longer pursue human drug development. After fostamatinib demonstrated some clinical efficacy by inhibiting SYK tyrosine kinase, ibrutinib was explored. Consequently, ibrutinib did not go through many of the traditional medicinal chemistry steps designed to optimize a drug for human use.

In contrast, acalabrutinib is a BTK inhibitor that has been modified and optimized for human use. The initial presentation of clinical data with this molecule published in *The New England Journal of Medicine* demonstrates a remarkable level of efficacy for the molecule. Despite evaluation in a patient population similar to the population in which ibrutinib was initially explored, very few instances of disease progression were reported with this medication. Furthermore, reports of adverse events such as arthralgias, bruising, bleeding and atrial fibrillation appear to be possibly significantly reduced.

Continued

Investigator Commentary: Activity of the BTK Inhibitor Acalabrutinib in Relapsed/Refractory CLL

The notable side effect of this medication is headaches seen during the first month of therapy. Multiple pivotal studies are currently enrolling patients, including a head-to-head comparison to ibrutinib. This is designed as a noninferiority study. A front-line study is evaluating the medication combined with obinutuzumab.

It is highly likely that this molecule will find a route to FDA approval and therefore broader clinical use.

Interview with Jeff Sharman, MD, February 9, 2016

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Ibrutinib in follicular lymphoma (Abstracts 470, 471)

Idelalisib plus Bendamustine and Rituximab (BR) Is Superior to BR Alone in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of a Phase 3 Randomized Double-Blind Placebo-Controlled Study[1]

Idelalisib Given Front-Line for the Treatment of Chronic Lymphocytic Leukemia Results in Frequent and Severe Immune-Mediated Toxicities[2]

[1] **Zelenetz AD et al.**
Proc ASH 2015;Abstract LBA-5.

[2] **Lampson BL et al.**
Proc ASH 2015;Abstract 497.

Study 115: Idelalisib (IDELA) with Bendamustine/ Rituximab (BR) in Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL)

- Phase III study of BR with or without IDELA
- N = 416 patients with R/R CLL
- **Primary study endpoint:** Progression-free survival (PFS)

Outcome	IDELA + BR (n = 207)	BR (n = 209)
Median PFS	23.1 mo	11.1 mo
Median overall survival	Not reached	Not reached
Overall response rate	68%	45%
≥50% reduction in lymph nodes	96%	61%

Zelenetz AD et al. *Proc ASH* 2015;Abstract LBA-5.

Study 115: Conclusions

- The combination of IDELA + BR was superior to BR alone in patients with R/R CLL:
  - Reduced risk of disease progression and death
  - Increased PFS (HR 0.33; $p < 0.0001$)
  - Increased overall survival (HR 0.55; $p = 0.008$)
- Results were consistent for patients with or without high-risk features like del(17p)/TP53, unmutated IGHV and refractory disease.
- Safety profile is consistent with previously reported studies.
- IDELA + BR represents a new option for R/R CLL.

Zelenetz AD et al. *Proc ASH* 2015;Abstract LBA-5.

Investigator Commentary: Results from a Phase III Trial of BR with or without IDELA in R/R CLL

The optimal role for IDELA in the management of CLL continues to be further refined with the addition of several studies reported at the ASH Annual Meeting. The late-breaking abstract reporting on BR with or without IDELA for patients with R/R CLL describes another strikingly positive randomized Phase III study that will likely lead to FDA approval of BR/IDELA in 2016.

This study highlights the inadequacy of BR for patients with R/R CLL, for whom this combination yields a median PFS of only approximately 11 months, consistent with other recently published studies. The addition of IDELA more than doubled the PFS to 23 months. Overall survival was also improved as a secondary endpoint. It is interesting that this improvement approximates the median PFS in the study of rituximab with or without IDELA (Study 116) and calls into question what benefit is provided by bendamustine.

IDELA added some hematopoietic toxicity to BR, although this was relatively mild. The dose intensity of bendamustine was equal in both arms. This study was associated with slightly lower rates of diarrhea and transaminase elevation than those in other IDELA studies, which may be explained by the immunosuppressive effect of bendamustine.

Interview with Jeff Sharman, MD, February 9, 2016

IDELA as Front-Line Treatment for CLL Results in Frequent and Severe Immune-Mediated Toxicities

- Ongoing Phase II study of IDELA 2 mo → ofatumumab + IDELA 6 mo → IDELA indefinitely
- N = 24 patients with untreated CLL/small lymphocytic leukemia
- **Primary endpoint:** Overall response (2 months after ofatumumab + IDELA)

Response	**N = 24**
Overall response rate	100%
Adverse events	
Hepatotoxicity Grade 3 or 4	52%

Other Grade 3 and 4 toxicities observed: Pneumonitis, colitis

Lampson BL et al. *Proc ASH* 2015;Abstract 497.

Front-Line IDELA and Ofatumumab in CLL: Conclusions

- An early fulminate hepatotoxicity develops in a subset of primarily younger patients who receive IDELA monotherapy:
  - Median time to initial development of hepatotoxicity = 28 days
- This early hepatotoxicity is immune-mediated as suggested by
  - Delayed time to onset
  - An immune cell infiltrate (activated T cells) in biopsies of affected organs
  - Abatement of toxicity with steroids
- The proportion of regulatory T cells in the peripheral blood decreased with IDELA, providing a possible explanation for the development of early hepatotoxicity.

Lampson BL et al. *Proc ASH* 2015;Abstract 497.

Investigator Commentary: Front-Line IDELA for Patients with CLL Results in Frequent and Severe Immune-Related Toxicities

I believe we have enough data to show that we can cure CLL in a number of patients up front, but that's a controversial statement. If the disease has not progressed after FCR therapy at 7 years, chances are that the disease will not progress. It's a difficult conversation with patients who oftentimes come preloaded because they're "web-positive," coming to you saying, "I want ibrutinib," for instance. In this situation, I have to tell them that they have a chance of being cured if they receive FCR.

In this study of front-line IDELA in combination with ofatumumab for previously untreated CLL, excessive toxicity and severe immune-mediated complications limited efficacy. The investigators started with single-agent IDELA for 2 months, followed thereafter by ofatumumab. I believe the strategy behind that was the observation that if you administer a B-cell receptor signaling inhibitor, you might be able to diminish some of the infusion reactions of anti-CD20 antibodies. Unfortunately, in trying to do this, that 2 months of IDELA was associated with high rates of immune dysfunction.

Continued

Investigator Commentary: Front-Line IDELA for Patients with CLL Results in Frequent and Severe Immune-Related Toxicities

About three quarters of the patients experienced Grade 3 or higher toxicity. IDELA has been observed to inhibit regulatory T cells and may therefore enable immune hyperactivity. This may be more prominent early in the course of the disease than when the disease has been more heavily treated with immunosuppressive chemotherapy. Because of the toxicity associated with this regimen, it should not be considered for patients with CLL at this time. A pivotal study of IDELA/rituximab for patients with untreated CLL harboring del(17p) is ongoing. I am curious to see if that trial confirms the observations in this study that front-line IDELA is quite challenging (NCT02044822).

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Key Papers in Chronic Lymphocytic Leukemia and Follicular Lymphoma from ASH 2015

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- **Obinutuzumab in CLL (Abstract 493)**
- Venetoclax in CLL and NHL (Abstracts LBA-6, 829, 830, 494, 254, 255)
- Pembrolizumab in Richter's transformation of CLL (Abstract 834)
- Ibrutinib in follicular lymphoma (Abstracts 470, 471)

Safety and Efficacy of Obinutuzumab plus Bendamustine in Previously Untreated Patients with Chronic Lymphocytic Leukemia: Subgroup Analysis of the Green Study

Stilgenbauer S et al.

Proc ASH 2015;Abstract 493.

GREEN Study Subgroup Analysis: Obinutuzumab (G)/Bendamustine (B) in Chronic Lymphocytic Leukemia (CLL)

- Nonrandomized, multicohort Phase IIIb study of G and chemotherapy
- N = 950 (GB cohort n = 158) patients with previously untreated or relapsed/refractory CLL
- **Primary endpoints:** Safety and efficacy

Event	Grade 3-5 AE rate
Any	121 (77%)
Neutropenia	79 (50%)
Infusion-related reaction (IRR)	24 (15%)
Infections	20 (13%)
Thrombocytopenia	20 (13%)
Tumor lysis syndrome (TLS)	16 (10%)
Hemorrhagic events	1 (<1%)

AE = adverse event

Stilgenbauer S et al. *Proc ASH* 2015;Abstract 493.

GREEN Study GB Subgroup Analysis: Conclusions

- GB has an acceptable safety profile:
  - Toxicities considered manageable
  - 26/158 patients (16.5%) with an AE leading to treatment withdrawal
  - Rates of neutropenia and TLS higher than with G/chlorambucil (CLL11 trial)
  - Little impact of different 25/975-mg dose split of G; other IRR-reduction measures continue to be investigated
- GB achieves promising efficacy:
  - 32.3% complete response, with similar responses in fit and unfit patients
  - 58.9% and 28.5% minimal residual disease negativity in blood and bone marrow, respectively (ITT)
  - Additional follow-up required to evaluate progression-free survival
- GB may represent a new treatment option for previously untreated CLL.

Stilgenbauer S et al. *Proc ASH* 2015;Abstract 493.

Investigator Commentary: Safety and Efficacy of GB in Previously Untreated CLL

G has been shown to be superior to rituximab for CLL. This led to FDA approval of it in combination with chlorambucil for previously untreated CLL. The German GREEN study evaluates the addition of G to a variety of front-line cytotoxic agents in CLL. The combination of G and B was reported at the American Society of Hematology Annual Meeting.

This nonrandomized study was not structured to compare GB to standard B and rituximab. However, the regimen appeared to have higher rates of toxicity in the form of neutropenia (50% Grade 3 to 5) and TLS (10%), and several deaths were attributed to therapy. White blood cell growth factors were not mandated. The efficacy was impressive as minimal residual disease negativity was observed in almost 60% of patients when measured in the blood and 30% when measured in the bone marrow, with some patients never evaluated.

This combination has not been proposed for a randomized Phase III study. However, it is being studied in other large, single-arm Phase II studies and, depending on the results, may be considered for NCCN compendia listing. At this point it should not be used outside of a clinical trial.

Interview with Jeff Sharman, MD, February 9, 2016

Key Papers in Chronic Lymphocytic Leukemia and Follicular Lymphoma from ASH 2015

Ibrutinib in CLL (Abstracts 495, 717)

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5 Minute JournalClub

Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High Risk Relapsed/Refractory Chronic Lymphocytic Leukemia with 17p Deletion: Results of the Pivotal International Phase 2 Study[1]

Updated Safety and Preliminary Efficacy Data from a Phase 1b Study Combining Venetoclax (GDC-0199, ABT-199) with Bendamustine/ Rituximab in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia[2]

[1] **Stilgenbauer S et al.**
Proc ASH 2015;Abstract LBA-6.

[2] **Salles GA et al.**
Proc ASH 2015;Abstract 829.

Deep and Durable Responses Following Venetoclax (ABT-199/GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study[3]

Safety and Efficacy of a Combination of Venetoclax (GDC-0199/ABT-199) and Obinutuzumab in Patients with Relapsed/ Refractory or Previously Untreated Chronic Lymphocytic Leukemia — Results from a Phase 1b Study (GP28331)[4]

[3] Ma S et al.
Proc ASH 2015;Abstract 830.

[4] Flinn IW et al.
Proc ASH 2015;Abstract 494.

Venetoclax (VEN) Monotherapy in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) with Del(17p)

- Phase II study of VEN monotherapy
- N = 107 patients with R/R CLL and del(17p)
- **Primary study endpoint:** Overall response rate (ORR) by independent review committee (IRC)

Response (IRC assessed)	**N = 107**
ORR	79.4%
CR or CRi	7.5%
nPR/PR	72%
Survival rate (12 mo)	
Progression-free survival (PFS)	72%
Overall survival (OS)	86.7%

CR = complete remission; CRi = CR with incomplete bone marrow recovery; nPR = nodular partial remission; PR = partial remission

Stilgenbauer S et al. *Proc ASH* 2015;Abstract LBA-6.

VEN in R/R CLL with Del(17p): Conclusions

- VEN monotherapy achieved deep responses with acceptable toxicity in this ultrahigh-risk population with R/R del(17p) CLL:
  - More than 10% IRC-confirmed CR, CRi or nPR
  - Minimal residual disease (MRD) negativity observed in more than 20% of responders
- Favorable risk-benefit profile:
  - Risk of tumor lysis syndrome (TLS) effectively mitigated with no clinical TLS
  - Incidence of neutropenia (43%) and infection (72%) similar to front-line chemoimmunotherapy

Stilgenbauer S et al. *Proc ASH* 2015;Abstract LBA-6.

VEN with Bendamustine (B)/ Rituximab (R) in Untreated or R/R CLL

- Ongoing Phase Ib study of VEN with B/R or B/obinutuzumab
  - 2 schedules tested: VEN introduced first or B/R or B/obinutuzumab introduced first, both with gradual VEN dose increase
- N = 30 patients with untreated or R/R CLL
- **Primary endpoints:** Maximum tolerated dose, safety of VEN with B/R

Adverse event (AE)	Grade ≥3	Serious AE
Neutropenia	17 (57%)	1 (3%)
Thrombocytopenia	5 (17%)	0 (0)
Diarrhea	3 (10%)	0 (0)
Hypertension	2 (7%)	0 (0)
TLS	0 (0)	0 (0)

Salles GA et al. *Proc ASH* 2015;Abstract 829.

VEN with B/R in CLL: Conclusions

- Daily VEN 400 mg can be safely combined with B/R in patients with R/R CLL using either administration schedule (VEN or B/R first), with no dose-limiting toxicities at this dose.
- No TLS was observed with either administration schedule despite many patients being at medium (53%) or high (33%) risk for TLS.
- VEN + B/R is associated with frequent hematologic toxicity, which appears to be manageable in most cases.
- Early response and MRD data are promising:
  - Of 22 patients with R/R CLL evaluated, 100% responded
  - Overall, 70% of patients achieved MRD negativity

Salles GA et al. *Proc ASH* 2015;Abstract 829.

VEN/R in CLL

- Phase Ib study of VEN/R in 5 dose-escalation cohorts (200-600 mg/d VEN) and a safety expansion cohort (400 mg/d VEN)
  - VEN dosing was continuous
- N = 49 patients with R/R CLL/small lymphocytic leukemia (SLL)
- **Study aims:** Safety, MRD status, survival, response
  - Cohorts combined for analyses
- Two-year PFS: 83%; 2-year OS: 94%

	All (N = 49)	Del(17p) Mut(TP53) (n = 15)	IGHV unmut (n = 19)	Fludarabine refractory (n = 9)	R refractory (n = 14)
ORR	86%	87%	84%	56%	64%
CR/CRi	47%	47%	47%	44%	29%
PR/nPR	39%	40%	37%	11%	36%

Ma S et al. *Proc ASH* 2015;Abstract 830.

VEN/R in CLL: Conclusions

- VEN/R induces a high rate of deep and durable responses independent of adverse prognostic characteristics:
  - ORR: 86%; CR/CRi: 47%
  - MRD negativity in bone marrow: 55%
  - All patients with MRD-negative disease maintained their response
  - Remission off all therapy has been maintained in all patients achieving MRD-negative CR
- The high rate of MRD negativity is an encouraging step toward prolonged PFS and durable elimination of CLL/SLL.
- One case of treatment-emergent TLS leading to death was reported; No fatal TLS events occurred after a protocol modification aimed at TLS risk management and prophylaxis.
- VEN/R is being evaluated versus B/R in the Phase III MURANO trial for patients with R/R CLL (NCT02005471).

Ma S et al. *Proc ASH* 2015;Abstract 830.

VEN with Obinutuzumab (G) in CLL

- Phase Ib study of VEN combined with G on 2 different dose schedules
- N = 32 patients with treatment-naïve (TN) or R/R CLL
  - TN (n = 6): 6 cycles of VEN + G → VEN x 6 mo
  - R/R (n = 26): 6 cycles of VEN + G → VEN until disease progression
- **Primary endpoint:** Maximum tolerated dose

Serious AEs in ≥2 patients	**N = 32**
Hyperphosphatemia	3 (9.4%)
TLS	2 (6.3%)
Pyrexia	2 (6.3%)

Flinn IW et al. *Proc ASH* 2015;Abstract 494.

VEN with G in CLL: Conclusions

- Preliminary data suggest that VEN + G can be safely administered to patients with CLL, with no difference in tolerability between patients with TN and R/R disease.
- AEs appear to be manageable, and the data suggest that TLS prophylaxis measures are appropriate.
- Preliminary efficacy data demonstrate that all patients who received VEN + G responded.
  - For patients with R/R CLL after 3 cycles of therapy: CR/CRi n = 4; PR n = 17 (3 improved to CR/CRi after 6 cycles of therapy)
- An expansion phase is planned using a 400-mg/d dose of VEN for TN and R/R disease.
- Evaluation of VEN + G for patients with CLL continues in the ongoing Phase III CLL14 trial.

Flinn IW et al. *Proc ASH* 2015;Abstract 494.

Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL

Multiple studies presented this year at the American Society of Hematology Annual Meeting further characterize the efficacy of venetoclax in CLL. This exciting agent has demonstrated some of the most robust activity observed in patients with CLL. Venetoclax is expected to gain FDA approval in 2016. The initial indication will likely focus on those patients with 17p deletion.

Perhaps the greatest danger associated with this agent is tumor lysis syndrome (TLS). Practitioners who are unfamiliar with venetoclax need to become aware of the risks associated with its use. Early in the development of this molecule 2 patients died of TLS, and this led to a modified dose-escalation approach to treatment. Despite these modifications, chemical tumor lysis (lacking clinical complications) has been observed in approximately 5% of patients. The risk of TLS increases with a lymphocyte count in excess of 25,000 and with lymph nodes larger than 5 centimeters.

Continued

Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL

Using these 2 characteristics to assess risk, approximately one quarter of patients are considered to be at low risk, half are considered to be at intermediate risk (having 1 of the risk factors) and one quarter of patients are deemed to be at high risk. Furthermore, creatinine clearance less than 80 mL/min further increases the risk for TLS. After the initial dose of this drug and every subsequent dose escalation, repeat evaluation for TLS 6 to 8 hours after administration is encouraged. It is anticipated that many patients starting venetoclax will need to receive it in the hospital for adequate monitoring.

Among the patients at high risk with 17p deletion, 107 patients received the drug. The response rate was approximately 80%, with more than 20% of patients with heavily pretreated, high-risk disease achieving MRD negative status in the peripheral blood. A few of these even attained MRD-negativity in the bone marrow, indicating an exceptionally high rate of deep responses. The median time to first response was only several weeks.

Continued

Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL

Although many drugs in oncology are moved into combination strategies when they lack single-agent activity, venetoclax is being partnered with other drugs such as bendamustine, rituximab or obinutuzumab for the purpose of debulking the CLL prior to initiation of Bcl-2 inhibitors. This may reduce the risk of TLS.

This exciting agent will play an increasing role in the management of CLL, and multiple ongoing studies will help to define its proper timing and use.

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A Phase 1 Study of Venetoclax (ABT-199/GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma[1]

A Dose-Escalation Study of Venetoclax (ABT-199/GDC-0199) in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Non-Hodgkin's Lymphoma[2]

[1] **Gerecitano JF et al.**
Proc ASH 2015;Abstract 254.

[2] **de Vos S et al.**
Proc ASH 2015;Abstract 255.

Venetoclax Monotherapy in Non-Hodgkin Lymphoma (NHL)

- Phase I, open-label, multicenter dose-escalation study of venetoclax, an orally bioavailable Bcl-2 inhibitor
- N = 106 patients with relapsed or refractory (R/R) NHL
  - Focus of current analysis: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle-cell lymphoma (MCL)
- **Primary endpoints:** Safety, maximum tolerated dose (MTD), Phase II dose, pharmacokinetics and preliminary efficacy

	All (N = 106)	**MCL (n = 28)**	**FL (n = 29)**	**DLBCL (n = 34)**
ORR	44%	75%	38%	18%
CR rate	13%	21%	14%	12%
Median PFS	17 mo	14 mo	11 mo	1 mo
12-mo OS rate	72%	82%	100%	34%

ORR = overall response rate; CR = complete response; PFS = progression-free survival; OS = overall survival

Gerecitano JF et al. *Proc ASH* 2015;Abstract 254.

Conclusions

- Venetoclax monotherapy demonstrated an acceptable safety profile in patients with R/R NHL.
- The MTD was not reached, with doses up to 1,200 mg explored.
- Laboratory tumor lysis syndrome was observed in 2 patients with high-risk disease and was managed effectively.
- ORR was 75% in MCL, 38% in FL and 18% in DLBCL:
  - The majority of responses were observed at higher dose levels in FL and DLBCL, whereas responses were reported at all dose levels in MCL.
  - CRs in patients with MCL and FCL were durable.
- Venetoclax is currently being evaluated with combination chemotherapy and targeted agents.

Gerecitano JF et al. *Proc ASH* 2015;Abstract 254.

Investigator Commentary: Results from a Phase I Trial of Venetoclax Monotherapy for Patients with R/R NHL

This study evaluated the role of venetoclax in R/R NHL. This drug has remarkable activity in chronic lymphocytic leukemia (CLL) and will likely gain FDA approval in the first half of 2016 for this indication. Unfortunately, the exquisite sensitivity of CLL to this agent has not been demonstrated in relapsed lymphoma.

This study included a variety of lymphoma histologies but reported results for DLBCL, MCL and FL. For patients with DLBCL the ORR was only 18%. The median time on therapy was only 5 months and the median duration of response was approximately 3 months, indicating that this agent lacks significant single-agent activity in R/R DLBCL. For those patients with relapsed FL the ORR was 38% and the median time on venetoclax was approximately 7 months.

Interestingly, high response rates were observed for patients with MCL. I believe this may be related to the biology of MCL, which is closest to CLL in terms of the cell of origin. In the future, when more mature data are available, a Bcl-2 inhibitor may be added to the armamentarium for MCL.

Continued

Investigator Commentary: Results from a Phase I Trial of Venetoclax Monotherapy for Patients with R/R NHL

These results compare less favorably to those with idelalisib in a similar patient population. A provocative signal was reported in Richter's transformation, for which the ORR was 43% and the response proved to be durable in at least 1 patient. However, this is a difficult population to evaluate prospectively, and venetoclax is unlikely to gain approval for this indication in the near term.

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Venetoclax in Combination with Bendamustine/Rituximab (BR) in NHL

- Phase I, open-label dose-escalation study with standard BR x 6 and venetoclax (10 cohorts: 50-800 mg with 3 dosing schedules, every 3, 7 and 28 days), which could be continued up to 2 years
- N = 48 patients with R/R NHL:
  - FL, DLBCL and marginal zone lymphoma (MZL)
- **Primary endpoints:** Safety, MTD, Phase II dose, pharmacokinetics and preliminary efficacy

	FL (n = 27)	DLBCL (n = 16)	MZL (n = 5)
ORR	78%	38%	80%
CR rate	30%	25%	20%

de Vos S et al. *Proc ASH* 2015;Abstract 255.

Conclusions

- Combination therapy with venetoclax and BR demonstrated a tolerable safety profile:
  - Most common Grade ≥3 adverse events were cytopenias: Neutropenia (48%), lymphocyte count decrease (35%), leukopenia (17%), anemia (15%)
  - Most frequent serious adverse event: Febrile neutropenia (8%)
  - After dose-limiting toxicities in 4 patients, protocol amendment encouraged G-CSF prophylaxis during venetoclax administration
- Responses were observed across dose cohorts in this heavily pretreated population.
- The MTD has not been reached, and dose escalation (1,200 mg continuous dosing) is ongoing.

de Vos S et al. *Proc ASH* 2015;Abstract 255.

Investigator Commentary: Results from a Phase I Trial of Venetoclax in Combination with BR for Patients with R/R NHL

Because venetoclax monotherapy is unlikely to be further developed in relapsed DLBCL or FL, it was also studied in a Phase I study combining it with BR. This study included both DLBCL and FL, in addition to some patients with MZL, but on the basis of the data presented, it is difficult to discern whether venetoclax added much to the activity of BR.

Venetoclax is known to cause neutropenia, and it appeared to adversely affect hematopoietic function in these patients. During the execution of this study a protocol amendment was added to encourage use of G–CSF.

This regimen requires further study before its proper use can be determined.

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Ibrutinib in follicular lymphoma (Abstracts 470, 471)

5 Minute JournalClub

PD-1 Blockade with Pembrolizumab (MK-3475) in Relapsed/Refractory CLL Including Richter Transformation: An Early Efficacy Report from a Phase 2 Trial (MC1485)

Ding W et al.

Proc ASH 2015;Abstract 834.

MC1485: Pembrolizumab in Chronic Lymphocytic Leukemia (CLL) Including Richter's Transformation (RT)

- Phase II study of pembrolizumab 200 mg q3wk until disease progression, excessive toxicity or 2 years of therapy
- N = 16 patients with relapsed/refractory CLL, including 5 with RT:
  - 5 RT and 2 CLL evaluable
- **Primary endpoint:** Safety and overall response
- Four out of 5 patients with RT responded: 1 complete response (CR), 1 PET near CR, 2 "notable responses," 1 stable disease
- Both patients with CLL experienced stable disease
- Pembrolizumab was well tolerated:
  - Most common drug-related adverse events were Grade 1 dyspnea (33%, 2/6) and anemia (33%, 2/6)

PD-1 inhibition is a promising novel approach for RT.

Ding W et al. *Proc ASH* 2015;Abstract 834.

Investigator Commentary: Activity and Safety of Pembrolizumab in R/R CLL Including Richter's Transformation (RT)

PD-1 inhibitors are sweeping across many disciplines in oncology and transforming the prognosis of many diseases. Their role in hematologic cancer appears to be most likely led by their use in Hodgkin lymphoma and possibly a role in multiple myeloma when combined with drugs like lenalidomide. They have not been extensively characterized in the management of CLL. In the study reported at the American Society of Hematology Annual Meeting, pembrolizumab was administered to patients with R/R CLL, including 5 patients with RT.

The most interesting observation in this study was that 4 out of 5 patients with RT responded to therapy. This included 1 complete remission that was ongoing at the time of presentation. The efficacy of pembrolizumab in CLL was not well characterized at the time of abstract preparation. If these findings were to be replicated in other populations with RT, it would be a fairly significant development because these patients often fare poorly and do not tolerate aggressive cytotoxic chemotherapy in many cases.

Continued

Investigator Commentary: Activity and Safety of Pembrolizumab in R/R CLL Including Richter's Transformation (RT)

Although these results are a little short on efficacy data, it gives us a clue as to an area of activity that I think is both welcome and surprising — the level of efficacy in patients with RT. I've cared for a handful of patients with RT recently. Two of my last 3 patients with RT died within 72 hours of the diagnosis. RT can be unbelievably aggressive and fulminate when it presents. This is a challenging patient population to study because they are frequently quite ill. They have received a lot of different chemotherapy regimens beforehand and are not going to tolerate all that much. I have used the results from this study to justify the use of pembrolizumab for patients with RT. Overall, these data cry out for a larger experience with this drug in this disease setting.

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5 Minute JournalClub

Ibrutinib plus Rituximab in Treatment-Naive Patients with Follicular Lymphoma: Results from a Multicenter, Phase 2 Study[1]

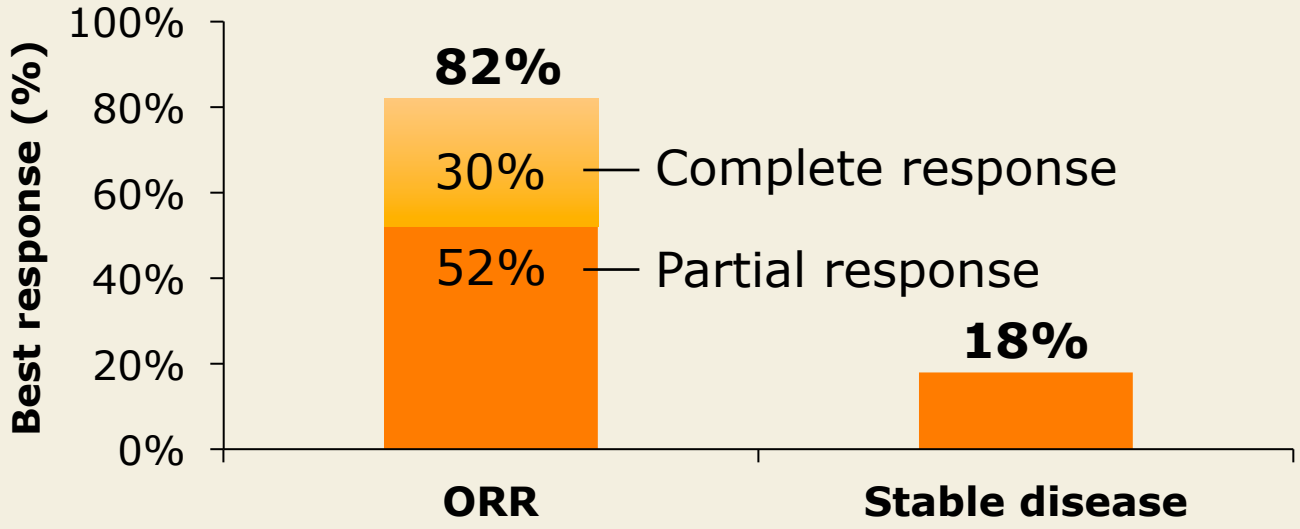
Phase I Study of Rituximab, Lenalidomide, and Ibrutinib in Previously Untreated Follicular Lymphoma (Alliance 051103)[2]

[1] **Fowler N et al.**
Proc ASH 2015;Abstract 470.

[2] **Ujjani CS et al.**
Proc ASH 2015;Abstract 471.

PCYC-1125-CA Trial: Ibrutinib/Rituximab in Follicular Lymphoma (FL)

- Multicenter, open-label Phase II study of ibrutinib 560 mg/d and rituximab 375 mg/m^2 weekly x 4
- N = 60 patients with treatment-naïve FL (Grade I, II and IIIA; Stage II to IV)
- **Primary endpoint:** Overall response rate (ORR)
- 12-month progression-free survival rate: 86%
  12-month overall survival rate: 98%



Fowler N et al. *Proc ASH* 2015;Abstract 470.

PCYC-1125-CA: Conclusions

- In treatment-naïve patients with FL, ibrutinib combined with 4 weekly infusions of rituximab demonstrated robust clinical activity with a high ORR of 82% and a complete response rate of 30%.
- The combination regimen was well tolerated; adverse events (AEs) were primarily Grade 1 or 2.
  - Grade ≥3 AEs: Fatigue (5%), maculopapular rash (5%), neutropenia (5%), hypertension (3%) and arthritis (3%)
- Further studies comparing the novel chemotherapy-free combination of ibrutinib and rituximab to standard regimens are being considered.

Fowler N et al. *Proc ASH* 2015;Abstract 470.

Investigator Commentary: Results from a Phase II Trial of Ibrutinib/Rituximab for Patients with Previously Untreated FL

In contrast to chronic lymphocytic leukemia, in which the activity of ibrutinib has transformed management of the disease, its activity and therefore role in the management of FL is considerably less robust. Several prior studies have demonstrated a moderate degree of activity of ibrutinib in FL, but none have identified a clear path to FDA approval. In that context, 2 studies reported at the ASH Annual Meeting explore ibrutinib in combination with other agents for previously untreated FL.

In the study by Nathan Fowler, ibrutinib was combined with rituximab. Ibrutinib was administered at 560 mg once daily until progressive disease or unacceptable toxicity. This was combined with rituximab weekly for 4 weeks. Participants were quite young, with the median age of 58 years suggesting some degree of patient selection bias. The ORR was 82% with a complete response rate of 30%. This appears to be a moderate improvement over rituximab monotherapy.

Continued

Investigator Commentary: Results from a Phase II Trial of Ibrutinib/Rituximab for Patients with Previously Untreated FL

Unfortunately, this improvement came at the cost of ibrutinib-related side effects, including diarrhea in about 50% of participants, rash, myalgias, bleeding and atrial fibrillation. Approximately 15% of patients in this study discontinued ibrutinib on account of side effects. We know from other studies that ibrutinib discontinuation increases with age and therefore is likely to be higher in a more typical treatment setting. Although this combination may get some use, it is not a significant step forward in the management of this disease.

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Alliance 051103 Trial: Ibrutinib/ Rituximab/Lenalidomide (IR^2) in FL

- Multicenter, Phase I study of IR^2
- N = 22 patients with treatment-naïve FL (Grade I to IIIA; Stage III, IV or bulky Stage II)
- **Key endpoints:** Tolerability and activity
- 12-month progression-free survival rate: 84%

Overall response	Complete response	Partial response	Stable disease
95%	63%	32%	5%

Ujjani CS et al. *Proc ASH* 2015;Abstract 471.

Alliance 051103: Conclusions

- Preliminary response data were similar to those from the prior CALGB/Alliance multicenter study of lenalidomide/ rituximab (R^2).
- Given the increased toxicity and required dose modifications, the additional benefit of a third agent is not apparent:
  - 11/22 patients required dose reductions due to toxicity (7 due to rash)
  - 6 patients discontinued therapy because of AEs
  - Rash, diarrhea, arthralgia and neoplasms were all increased with IR^2 compared to R^2
- Further investigation of the triplet in this setting seems unwarranted.

Ujjani CS et al. *Proc ASH* 2015;Abstract 471.

Investigator Commentary: Results from the Phase I Alliance 051103 Trial of IR^2 for Patients with Treatment-Naïve FL

In this study, ibrutinib was added to the combination of lenalidomide and rituximab (R^2). The R^2 regimen has shown dramatic activity in FL and might serve as a platform for the addition of ibrutinib. Response rates with the addition of ibrutinib did not greatly exceed those with the R^2 regimen. Unfortunately, it was also associated with rash in 82% of patients, with approximately one third experiencing Grade 3 rash.

Twelve of the 22 study participants discontinued treatment, in 6 cases because of adverse events. It is therefore unlikely that this regimen will change practice patterns, and it should not be considered outside of a clinical trial.

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