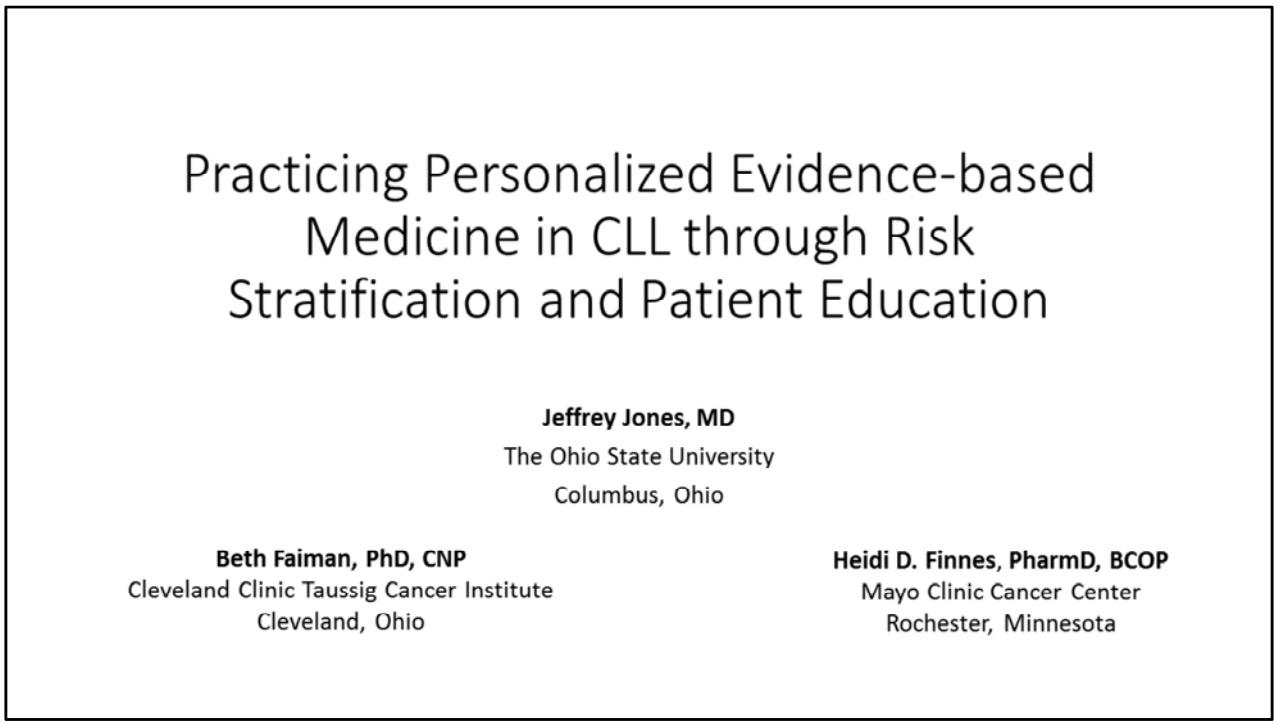
Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Dr. Jeffrey Jones: Hi, my name is Jeffrey Jones, and I am a CLL physician and researcher at the Ohio State University Medical Center in Columbus, Ohio. Today, I am joined by two colleagues, Beth and Heidi, to discuss the treatment and management of patients with CLL.

Beth Faiman: Hi, my name is Beth Faiman. I am a nurse practitioner in the Department of Hematologic Oncology and Blood Disorders at the Cleveland Clinic in Cleveland, Ohio.

Dr. Heidi Finnes: Hello, my name is Heidi Finnes. I am the Senior Manager of Pharmacy Cancer Research at Mayo Clinic in Rochester, Minnesota.

Dr. Jeffrey Jones: All of us are excited about today's activity entitled, "Practicing personalized evidence-based medicine in CLL through risk stratification and patient education." The treatment and management of patients with CLL is both complex and challenging. It is extremely important to assess patients for underlying comorbidities and genetic mutations when devising treatment plans. In this presentation, we will review the current treatment options for patients with CLL, describe the impact of cytogenetic abnormalities and comorbid conditions on drug selection and patient outcomes, and explain the importance of shared decision-making.

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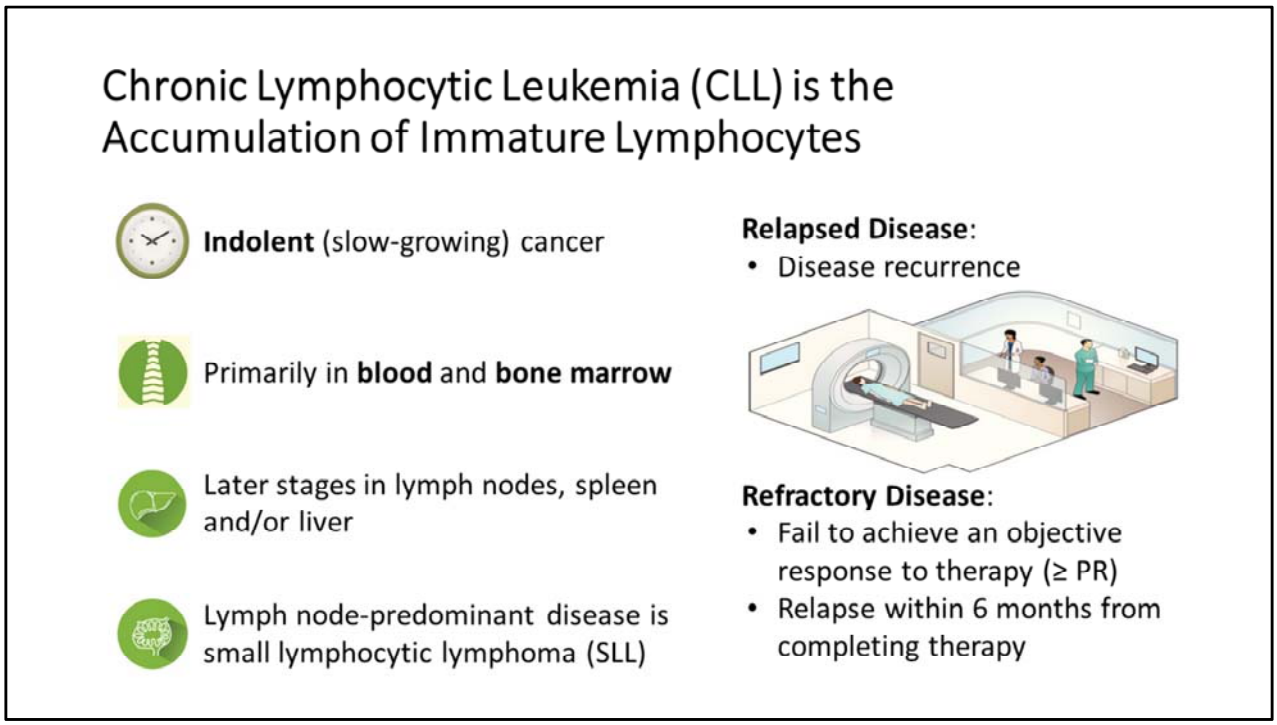

Chronic lymphocytic leukemia is an indolent or slow-growing cancer characterized by the accumulation of immature lymphocytes primarily in the blood and bone marrow. As the disease progresses to its later stages, involvement of lymph nodes, spleen, and/or liver is common. In some patients, lymph node disease predominates, in which case the disease is termed small lymphocytic lymphoma, or SLL. The clinical course of chronic lymphocytic leukemia is characterized by multiple relapses and subsequent remissions with therapy. Relapsed disease characterizes patients with recurrent disease and investigators use the term refractory disease to describe patients who fail to achieve an objective response to their most recent therapy or relapse within 6 months from completing therapy.

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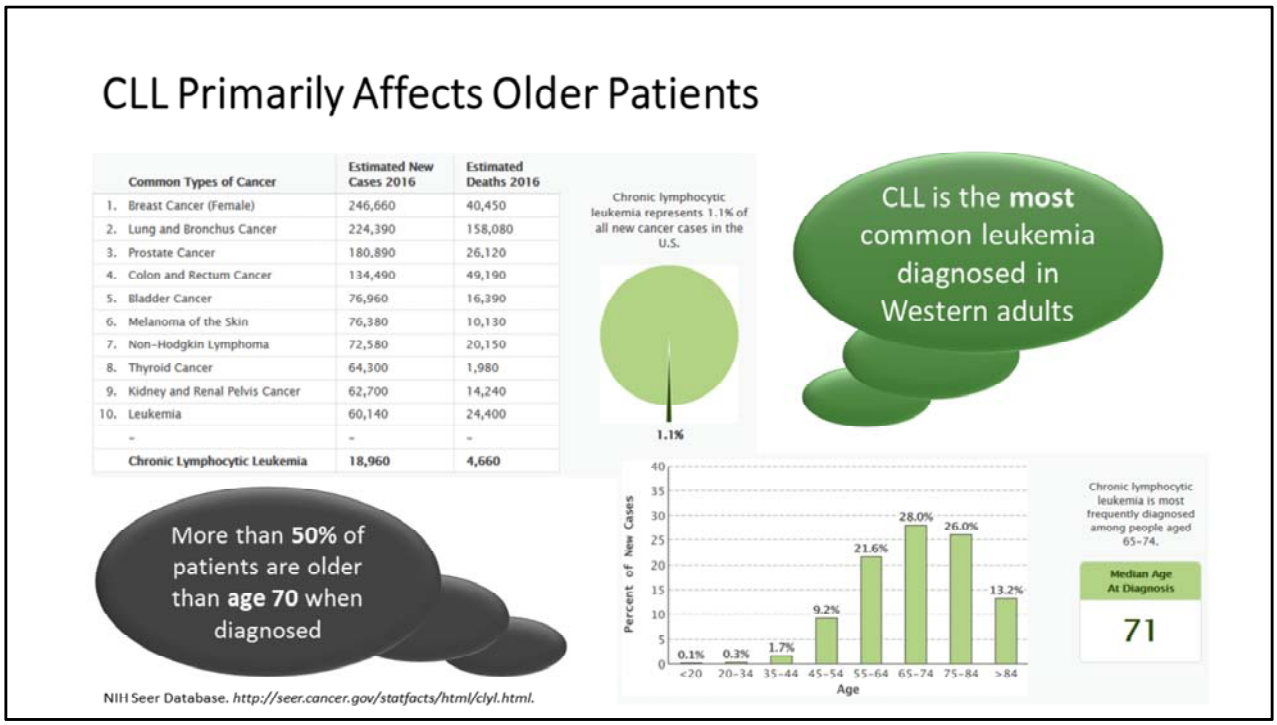

In general, CLL is a disease of older patients. The median age at diagnosis of CLL is around 71 years, and more than 50% of patients are older than age 70 when diagnosed and older than 74 when they begin treatment. While CLL is the most common leukemia diagnosed in Western adults, it represents only about 1.1% of all cancers diagnosed in the United States, but because the population of the United States is growing older, the number of patients diagnosed with CLL is increasing, and it is estimated just over 18,500 in 2016.

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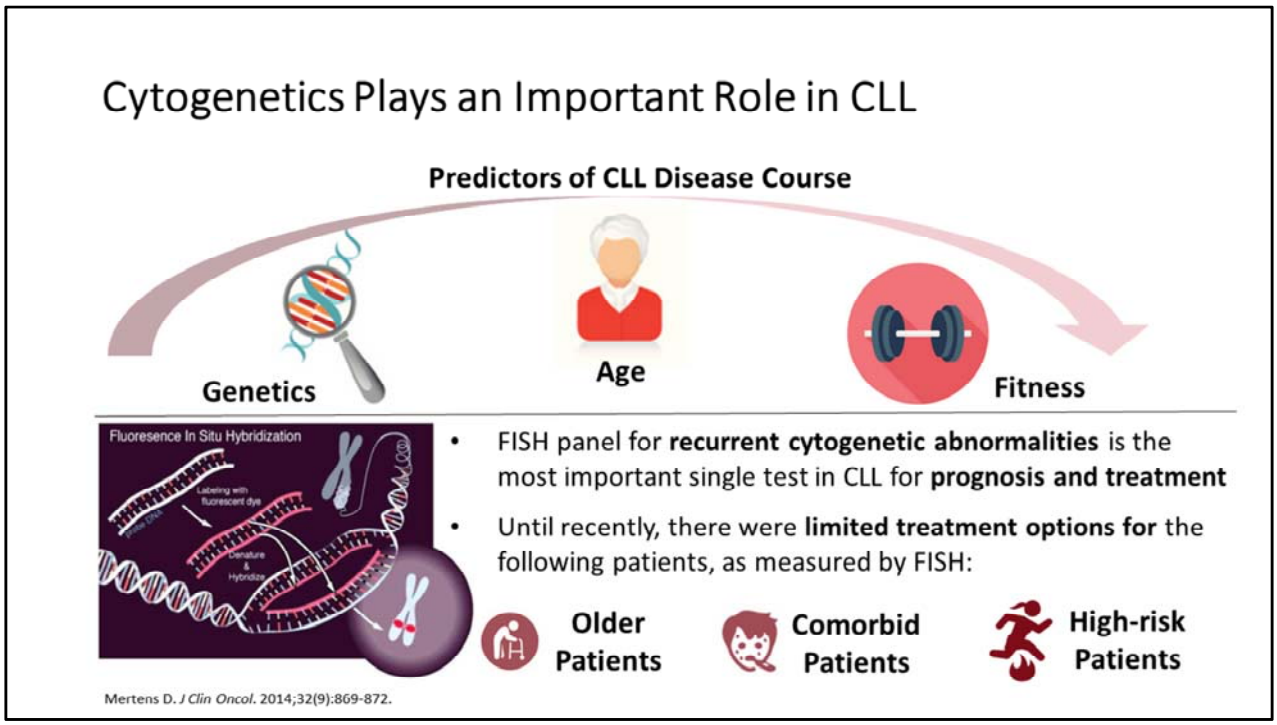

In general, the clinical course of CLL is quite heterogenous. The outcome in the disease is characterized by a number of features including the genetics of the CLL cells themselves, as well as the age and fitness of the patient. The FISH panel, which identifies recurrent cytogenetic abnormalities, is probably the single most important test in determining prognosis and treatment for patients with CLL, but until quite recently, there were limited numbers of treatment options for patients with higher risk disease as measured by genetic features or patient-related features such as older age or multiple comorbid medical conditions.

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CLL Prognosis is Influenced by Clinical-, Cellular/Genetic- and Patient-Specific Factors

Prognostic Factors		Parameter
Clinical	Evaluation	Staging (Rai or Binet)
	Serum Markers	β_2 microglobulin Thymidine kinase
	Investigations	Lymphocyte doubling time
Cellular	Chromosomal Aberrations	**Deletion 17p [del(17p)]** **Deletion 11q [del(11q)]**
	Mutations	**IGHV gene somatic hypermutation status** **TP53 mutation**
	Protein Expression	CD38 ZAP-70
Patient	Demographics	**Age** Gender
	Health Status	**Fitness** **Comorbidities**

Mertens D. *J Clin Oncol*. 2014;32(9):869-872.

Summarizing, CLL prognosis is influenced by clinical, cellular and genetic, and patient-specific factors. Until quite recently, clinical factors were the most important including staging using the Rai or Binet staging classifications, or standard laboratory investigations like the lymphocyte doubling time. Our understanding of the molecular basis of the disease has allowed us to far more refine our understanding of the prognosis of any individual patient. Among the features listed here, chromosomal aberrations detected by FISH such as deletion 17p in particular, as well as patient demographic features, age, fitness, and comorbidities are probably the most important for treatment decision-making.

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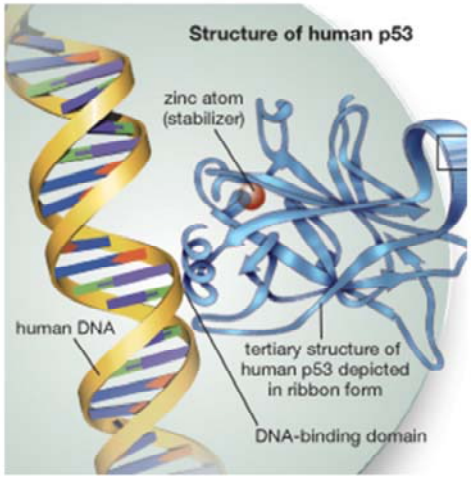
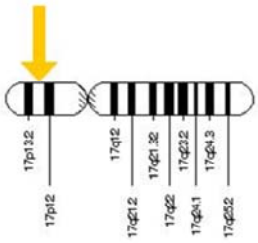
Deletion 17p [del(17p)] Increases Proliferation of Leukemic Cells



- Tumor protein 53 gene (*TP53*) codes for a tumor suppressor protein (p53)
- **p53** binds damaged DNA, signaling either **repair or apoptosis**

Deletion of 17p, results in loss of *TP53*, leading to:

- **Decreased** production of **p53**
- **Proliferation** of cells with damaged DNA and possible oncogenic mutations



National Library of Medicine (US). *http://ghr.nlm.nih.gov/gene/TP53.*; Encyclopædia Britannica Online. *http://www.britannica.com/science/TP53/images-videos/The-p53-protein-prevents-cells-with-damaged-DNA-from-dividing/58075.*

Turning first to genetic features, deletion of chromosome 17p is probably the single most important genetic feature determining the outcome of treatment in an individual patient's prognosis. Deletion of chromosome 17p results in loss of an important tumor suppressor protein, the TP53 gene. This gene has been termed the guardian of genome because p53 binds damaged DNA signaling either repair or apoptosis. In cases where 17p is deleted or TP53 is mutated, there is decreased production of functional p53. This results in the proliferation of cells with damaged DNA as well as the possible accumulation of further oncogenic mutations.

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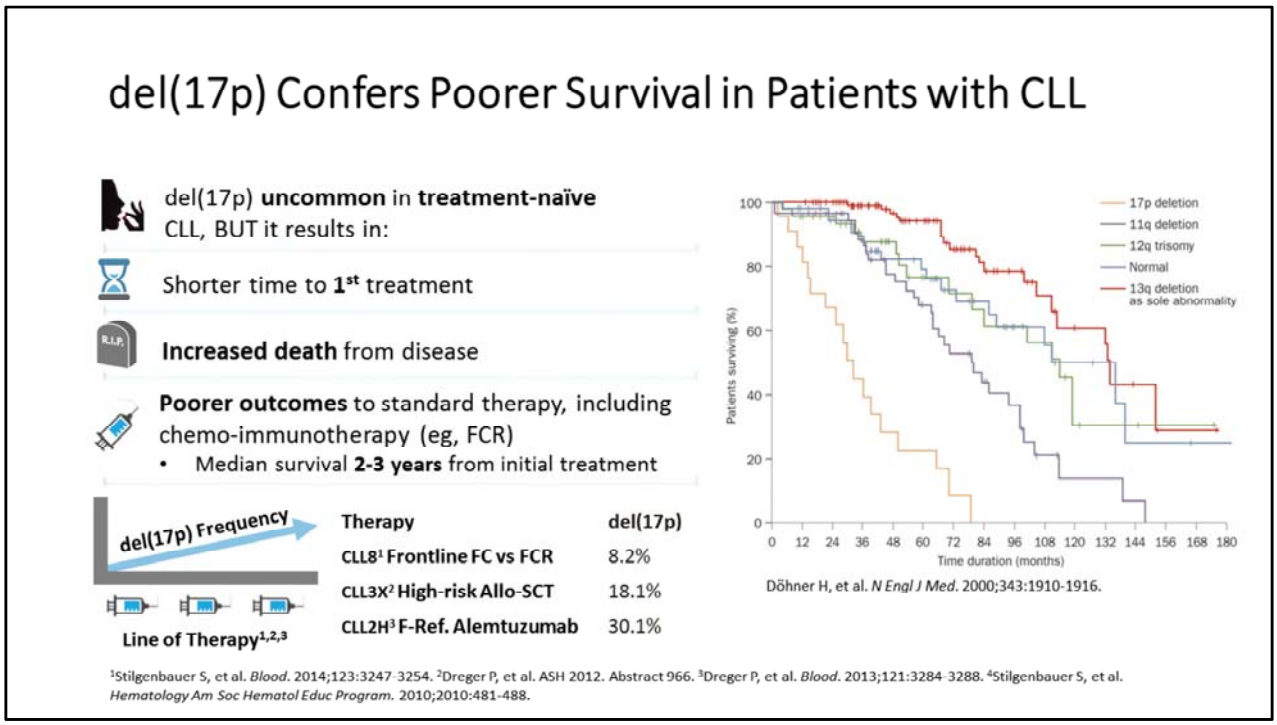

Deletion 17p confers a distinctly poor prognosis in patients with CLL. It is important to understand that deletion of chromosome 17p is uncommonly identified among patients with treatment-naïve CLL where it is identified in less than 10% of cases in the front-line treatment setting. It is very important to identify because patients with deletion 17p generally demonstrate a shorter time to first treatment, as well as a poor outcome to standard chemo-immunotherapy treatments such as FCR. In most cases, the median survival is only 2 to 3 years from the initiation of treatment using standard chemo-immunotherapy regimens. In subsequent lines of therapy among relapsed patients, the fraction of patients with deletion 17p increases, and in many relapsed patients series, it accounts for as many as 30-50% of patients included in relapsed trials.

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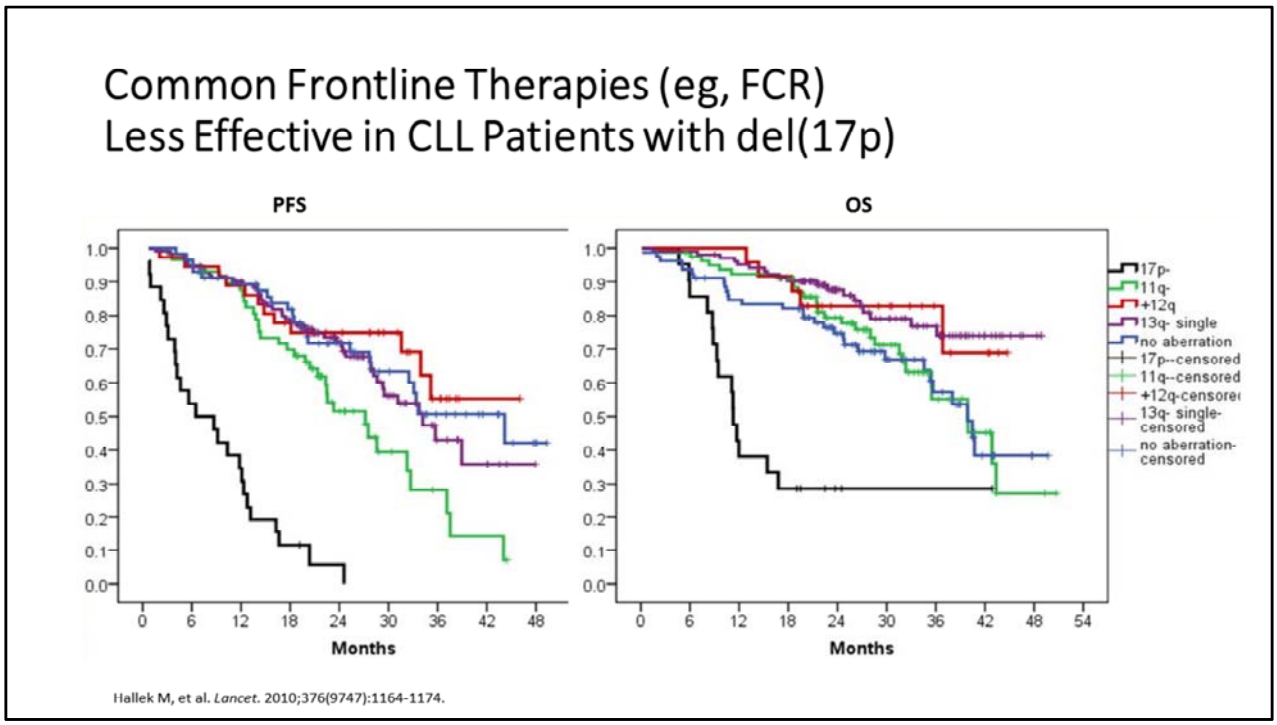

Shown here are survival plots from an important study of the German CLL study group that established FCR as the gold standard for the front-line therapy of CLL patients. In the plot on the left, progression-free survival, you can see by the black line that patients with a deletion of chromosome 17p experienced distinctly shorter duration of remission following FCR treatments which, in the plot on the right, translates to a distinctly poor overall survival as well.

Given the significance of deletion 17p, it is important that patients understand as much as possible about the role genetic features play in the course of their disease. Beth, you spend a lot of time educating patients. What role do you think nurses play in educating patients and their caregivers?

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Educating Patients/Caregivers is a Critical Component of del(17p) Testing

It is within the nurse's scope of practice to:

- Provide patients with knowledge about their disease
- RISK — Review individual risk and staging
- Review available treatment options in line with the treatment team

Prognostic Factor	Results	Points
FISH	del(17p) mutation	4
Serum β2	>3.5 mg/dL	2
Rai Stage	I-IV	1
IGHV	Unmutated	2
Age, years	>65	1
Risk Category	**Risk Score**	**5-year OS**
Minimal Risk	0-1	93%
Low Risk	2-3	79%
Intermediate Risk	4-6	64%
High Risk	7-10	23%

Rossi D, et al. *Blood.* 2014;123(14):2139-2147.; Parikh SA, et al. *Semin Oncol.* 2016;43(2):233-240.; Stilgenbauer S, et al. *Blood.* 2015;126:LBA-6.

Beth Faiman: Well, thank you. I just wanted to say that educating patients and caregivers is super important no matter what the diagnosis or whether or not the individual is at new diagnosis or relapse. As we know, there is complete heterogeneity to the patient with CLL, some may have an indolent course and live very long lives for years and others might die more quickly or follow a shorter disease course. Die quickly was not the right words there, but they may have a slower disease course. So, it is within the nurses' scope of practice to educate and provide patients and caregivers with knowledge about their disease and highlight the importance of finding new therapies, participating in a clinical trial, a well-designed clinical trial if one confers the deletion 17p mutation, or maybe using one of the newer oral therapies to treat as well, which we will be talking about. Reviewing the individual risk and staging is also important. Age, because many people are over the age of 65, does not carry a negative prognostic factor as well as it does with high serum beta-2 microglobulin, FISH, or Rai staging. So, again reviewing available treatment options with the patient, and I keep saying caregiver because a caregiver is so important to highlight at diagnosis throughout, and that can hopefully improve one's overall survival.

So, in addition to genetic testing, patients must also be assessed for comorbid conditions to optimize their care. Dr. Jones, do you have some more thoughts on this topic?

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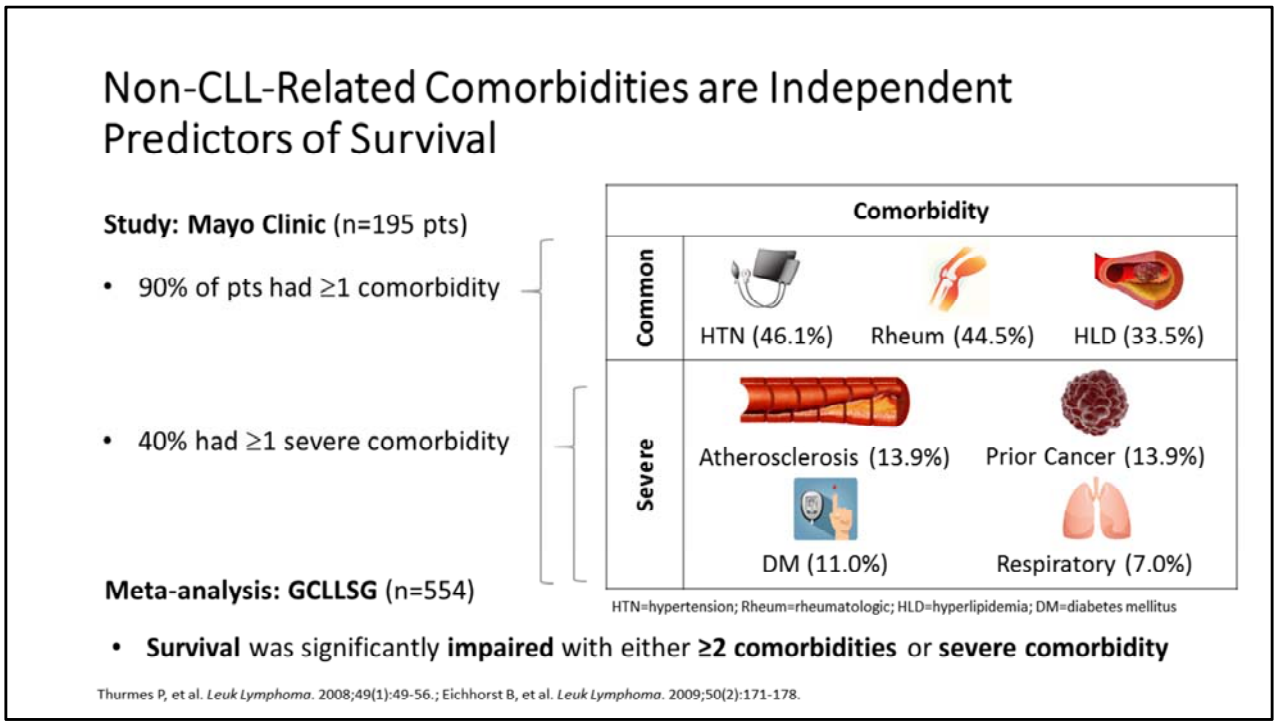

Dr. Jeffrey Jones: Well, actually, it is interesting to know that as you mentioned the majority of CLL patients are older and unfortunately most of the clinical trials that are conducted in patients with CLL involve patients that may be even 10 years younger than the average patient with CLL. So, we are often forced to make decisions about treatment for the average patient with CLL based on distinctly non-average clinical trial patients. One of the things we know about this older patient population is that many of them are challenged by other significant medical illnesses that also impact their quality of life as well as their survival. In a large retrospective study from the Mayo Clinic, more than 90% of patients had at least one significant comorbid medical illness and 40% had at least one severe comorbid medical illness that substantially impacted the outcome of their care. In a meta-analysis conducted in more than 500 patients enrolled in trials of the German CLL study group, survival was significantly impaired, with either two or more comorbid medical illnesses or at least one severe comorbid medical illness which characterizes a substantial number of the patients we all take care of in routine clinical practice.

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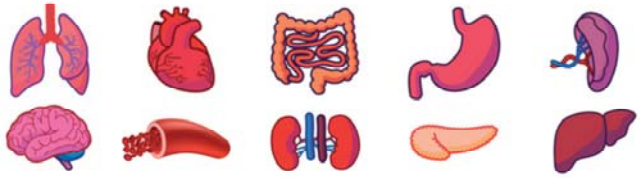
Cumulative Illness Rating Scale (CIRS) Can Help Better Characterize Biological Fitness

CIRS Severity Rating Scale	
0	No problem affecting that system
1	Current mild problem not interfering with normal activity or past significant problem
2	Interferes with normal activity and/or requires first-line therapy
3	Severe problem and/or constant and significant disability and/or hard-to-control chronic problem
4	Extremely severe problem and/or treatment is urgent and/or severe functional impairment or organ failure

Comorbidity scales can **refine fitness assessment** beyond performance status (eg, ECOG, Karnofksy)

CIRS rates severity of comorbidity by **organ system**



In many recent CLL trials, patients with **CIRS ≥6** and **creatinine clearance ≤60 mL/min** were deemed **"less fit"**

Salvi F, et al. *J Am Geriatr Soc.* 2008;56(10):1926-1931.

Now, we are all used to characterizing performance status when we assess patients in oncology, but we can further refine our understanding of fitness using comorbidity scales such as this one, the Cumulative Illness Rating Scale, or CIRS. In the CIRS system, patients' comorbid medical illnesses are rated on severity according to organ system. A cumulative illness severity score of 6 or higher as well as an abnormal creatinine clearance less than 60 mL/min has been used in many recent CLL clinical trials to deem patients less fit but actually typical.

So, Beth, often physicians in clinical practice do not have the opportunity to spend as much time in discussing the diagnosis their patients face beyond the primary oncologic diagnosis, and I think nurses really play a critical role in understanding the full scope of the patient's illness.

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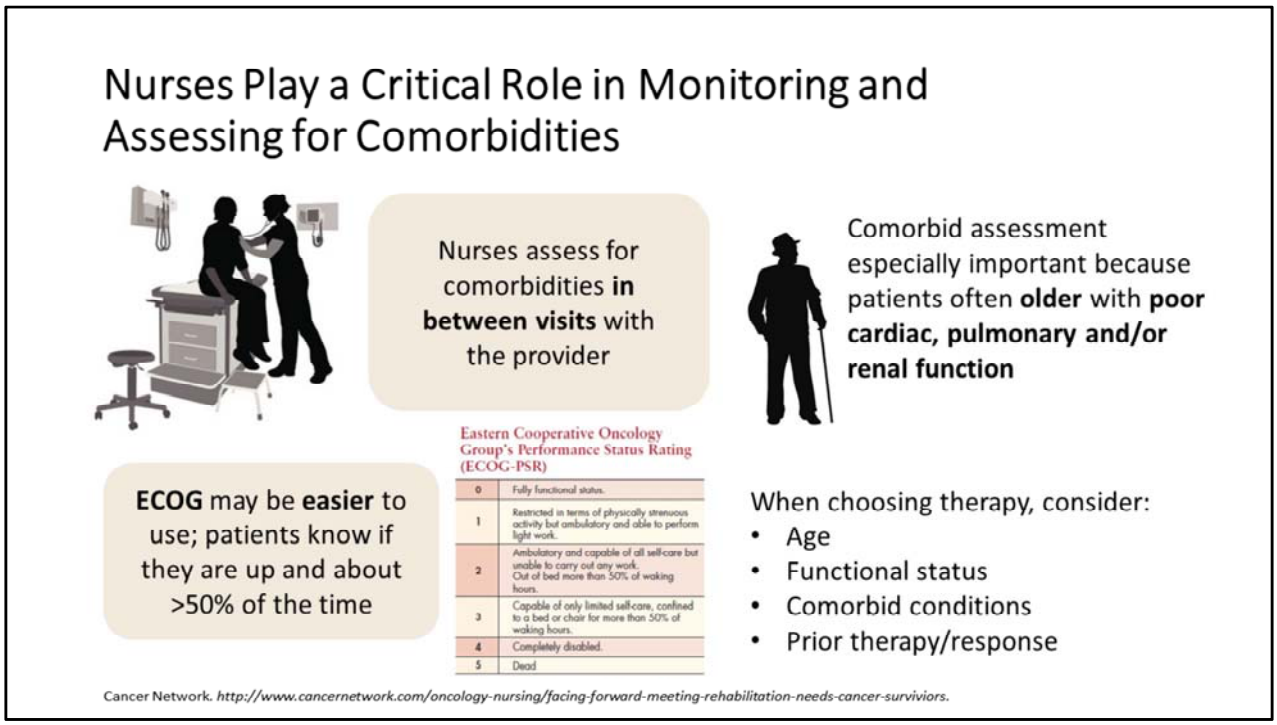

Beth Faiman: Nurses play critical role in monitoring and assessing for comorbidities, but I think the important thing to highlight here is many nurses will be visiting the patients in the treatment area or in between visits. It is the nurse that the patient will often call on when there are toxicities or side effects from treatment. When a new oral therapy is prescribed for example, it is the patient that is going to call nurse often and say, "How do I take this therapy?" So, it is really important to have that monitoring in between, not only for taking the medications as prescribed but comorbidity. Comorbidities are not stagnant. The individual might be perfectly fit at the beginning but then develop a cardiac or AFib or pulmonary event. So, again, I think the nurses play a key role in assessing the therapy, the age, the functional status, and seeing them in between each therapy as well.

So as I mentioned, problems can arise when patients with underlying comorbidities are given certain medications and atrial fibrillation comes to mind, GI toxicity. Heidi, what are some comorbidities that you are looking at when you have patients with CLL receiving specific drugs?

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Pharmacists Ensure Patient Safety by Assessing Combined Risk of Comorbidities and Therapy

Atrial Fibrillation	Bleeding Tendencies	Cytopenias/Infection
Ibrutinib	Ibrutinib	Bendamustine Chlorambucil Cyclophosphamide Fludarabine Idelalisib Pentostatin Obinutuzumab Ofatumumab Rituximab Venetoclax
Diarrhea/Colitis	**Renal Impairment**	
Idelalisib	Chlorambucil Cyclophosphamide Fludarabine Pentostatin	
Hepatic Impairment	**Tumor Lysis Syndrome**	
Chlorambucil Cyclophosphamide Ibrutinib* Idelalisib¥ Venetoclax£	Ibrutinib Obinutuzumab Ofatumumab Rituximab Venetoclax	
Hypertension		
Ibrutinib		

*Ibrutinib may be reduced to 140 mg once daily; ¥ single oral idelalisib doses tolerated in moderate/severe liver insufficiency; £ moderate to severe hepatic dysfunction leads to increased toxicity

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC 2016.; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc. 2014.; VENCLEXTA [prescribing information]. North Chicago, IL: AbbVie Inc. 2016.; Leukeran [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline 2006.; Cyclophosphamide [prescribing information]. Deerfield, IL: Baster Healthcare Corporation 2013.; Fludara [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc. 2008.; Nipent [prescribing information]. Lake Forest, IL: Hospira, Inc. 2015.; Gazyva [prescribing information]. South San Francisco, CA: Genentech, Inc. 2016.; Arzerra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation 2016.; Rituxan [prescribing information]. South San Francisco, CA: Genentech, Inc. 2016.; Bendeka [prescribing information]. North Wales, PA: Teva Pharmaceuticals, USA, Inc.

Dr. Heidi Finnes: Comorbidities are not only predictive of survival and fitness of CLL patients for treatment but can be additive toxicities of medications for treatment of CLL; 6-9% of patients receiving ibrutinib develop atrial fibrillation. Patients at higher risk include those with hypertension, active infection, as well as patients previously with atrial fibrillation. Ibrutinib has leading tendencies or increased risk based on his anti-platelet effects. So, patients with factor deficiencies, von Willebrand disease, as well as patients on anticoagulants or antiplatelet medications for stents, for atrial fibrillation, for many other indications can increase risk of bleeding. Any CLL medications increase risk of myelosuppression, therefore putting the body at risk for infection. It is important to recognize medications that deplete T-cells and put patients at risk for opportunistic infections. Therefore, we need to start prophylaxis in these types of patients with antibacterials, antifungals, as well as antiviral agents; 14% of patients have serious or severe diarrhea or colitis receiving idelalisib. This medication may not be the most appropriate for patients with previous history of *C. diff* or with diarrhea related to previous ibrutinib therapy. Hepatic and renal impairments are important to assess in every patient prior to starting therapy with any sort of CLL therapy medications. It is important to understand how they metabolize, how they are excreted, whether be via the biliary tract or the kidney, to understand effects and dose modifications that may be necessary in these patients. Tumor lysis assessment is of utmost importance in CLL patients, particularly for the new medication venetoclax. Lymph node size as well as absolute lymphocyte count must be used in order to stratify patients appropriately into low-, intermediate-, and high-risk tumor lysis syndrome. It is important that we assess this during this dose escalation of venetoclax because patients may have to be hospitalized, receive IV fluids, as well as around-the-clock monitoring in different hospitalized settings.

It is definitely challenging to decide which drug is best for a patient, especially given these underlying comorbidities and other risk factors. Jeff, can you elaborate on the current treatment paradigms in CLL?

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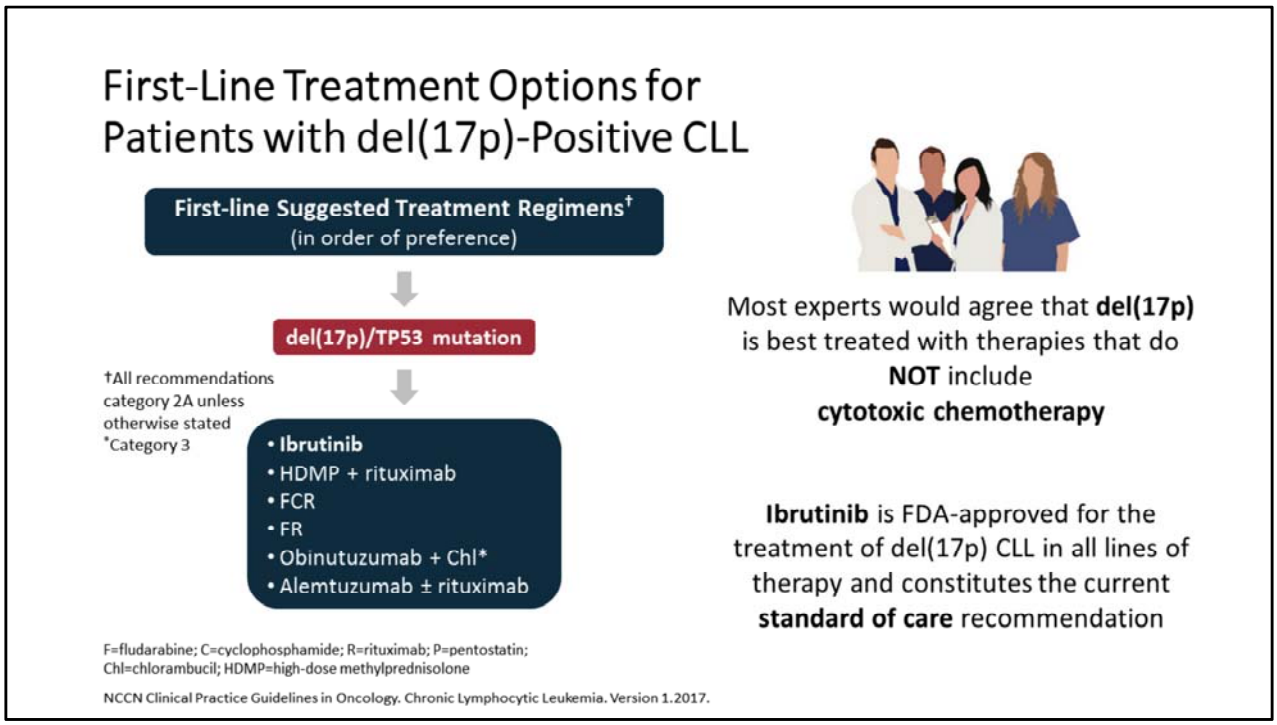

Dr. Jeffrey Jones: Well, Heidi, the treatment for patients with CLL has undergone dramatic changes in just the last several years with the advent of many of the targeted agents you were just describing. Let's look first at the NCCN recommended treatment options for the first-line treatment of patients with high-risk CLL, that is patients with deletion of chromosome 17p. The most important single message to take away from the NCCN Guidelines is that in patients with deletion 17p, treatment with cytotoxic chemotherapy is not recommended. There are not too many places where experts would state that there is a wrong answer in the treatment of patients with most malignancies, but in this case, I think many CLL experts would state that chemotherapy, cytotoxic chemotherapy, chemo-immunotherapy is generally not the first best choice for patients with deletion 17p CLL where the outcomes are far more poor than among patients without that abnormality. Since 2014, ibrutinib has been FDA-approved for the first-line treatment of deletion 17p CLL in all lines of therapy and currently constitutes the recommended standard of care for the first-line treatment of patients with deletion 17p CLL unless there is another contraindication to its use.

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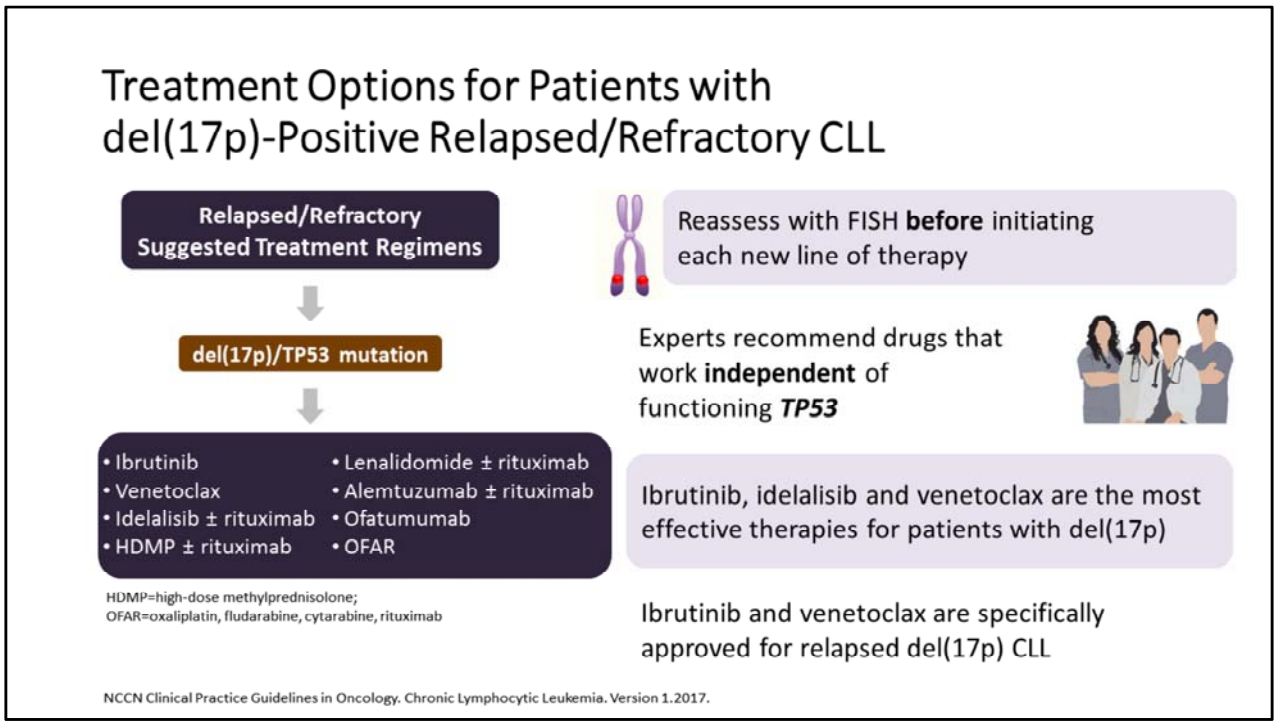
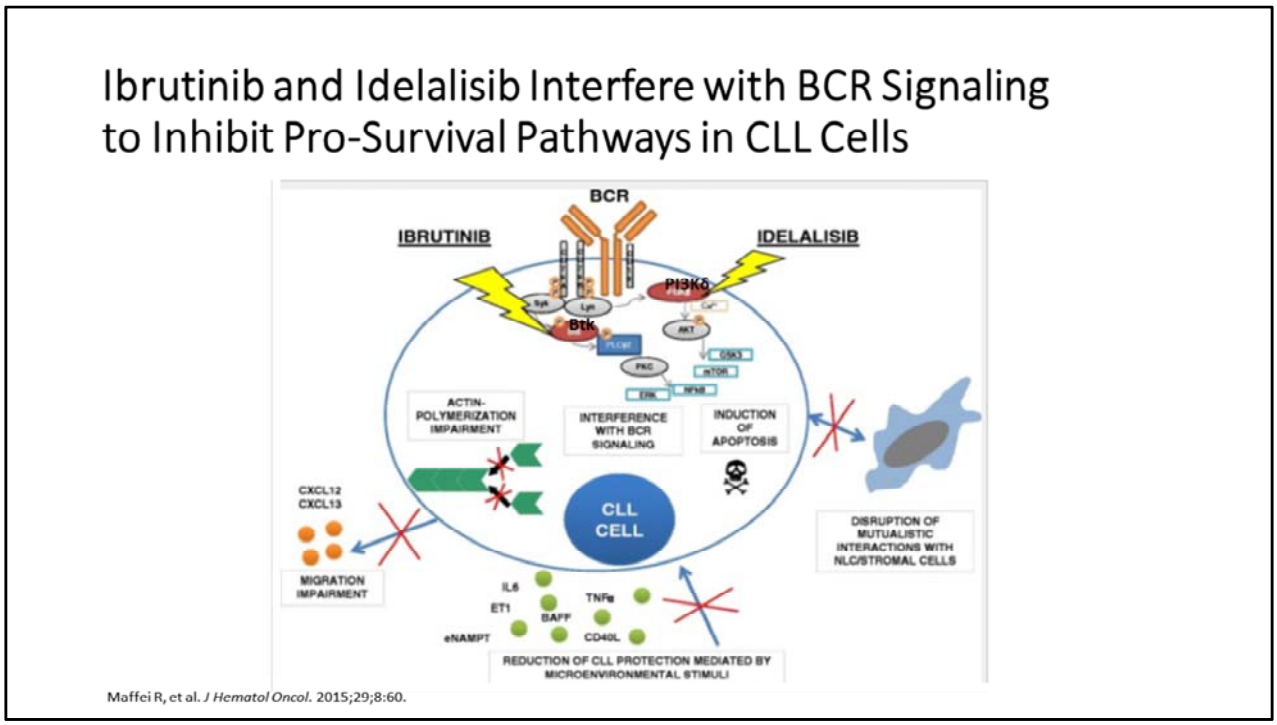


What about for patients with deletion 17p CLL that is identified in the relapsed/refractory setting? First, it is important to understand that deletion of chromosome 17p or a mutation of p53 can emerge during a patient's treatment course, even if not present at the time of initial diagnosis or at the time of front-line therapy. As a result, it is recommended that FISH testing or cytogenetic testing in addition to FISH testing be performed before initiating each new line of therapy since the presence of deletion 17p is an important factor in choosing the most appropriate therapy. In general, most CLL experts recommend the drugs that work independent of a functioning p53 gene, basically drugs that do not involve cytotoxic chemotherapy, should be used in treating these patients. Ibrutinib, idelalisib, and venetoclax are probably the most effective therapies yet developed for patients with deletion 17p and are all appropriate choices in the latest iteration of the NCCN guidelines. It is important to note, however, that only ibrutinib and venetoclax are specifically approved by the US FDA for the treatments of relapsed deletion 17p CLL.

Heidi, these newer drugs, ibrutinib, idelalisib, and venetoclax, they certainly represent a dramatic change in the way we treat CLL patients and many of us think of them as far more specific options for treating our patients with CLL. Can you speak to the specific targets and pathways involved with these drugs?



Dr. Heidi Finnes: Sure, thanks, Jeff. Uncontrolled B-cell receptor, or BCR signaling, plays a major role in the development and progression of CLL. Ibrutinib and idelalisib target BCR and survival mechanisms in CLL patients. Both agents interfere with BCR signaling by inhibiting phosphorylation of Bruton's tyrosine kinase or Btk and PI 3-kinase delta. They limit the activation of prosurvival pathways in CLL including NF-kappa, ERK, MTOR, as well as GSK-3. They cause modest induction of apoptosis, interfere with BCR signaling and impair actin polymerization which interferes with chemokine as well as adhesion receptors. This leads to impairments of migration and adhesion of CLL cells. Ibrutinib and idelalisib also provide response to survival stimuli in the outside environments including in mesenchymal cells.

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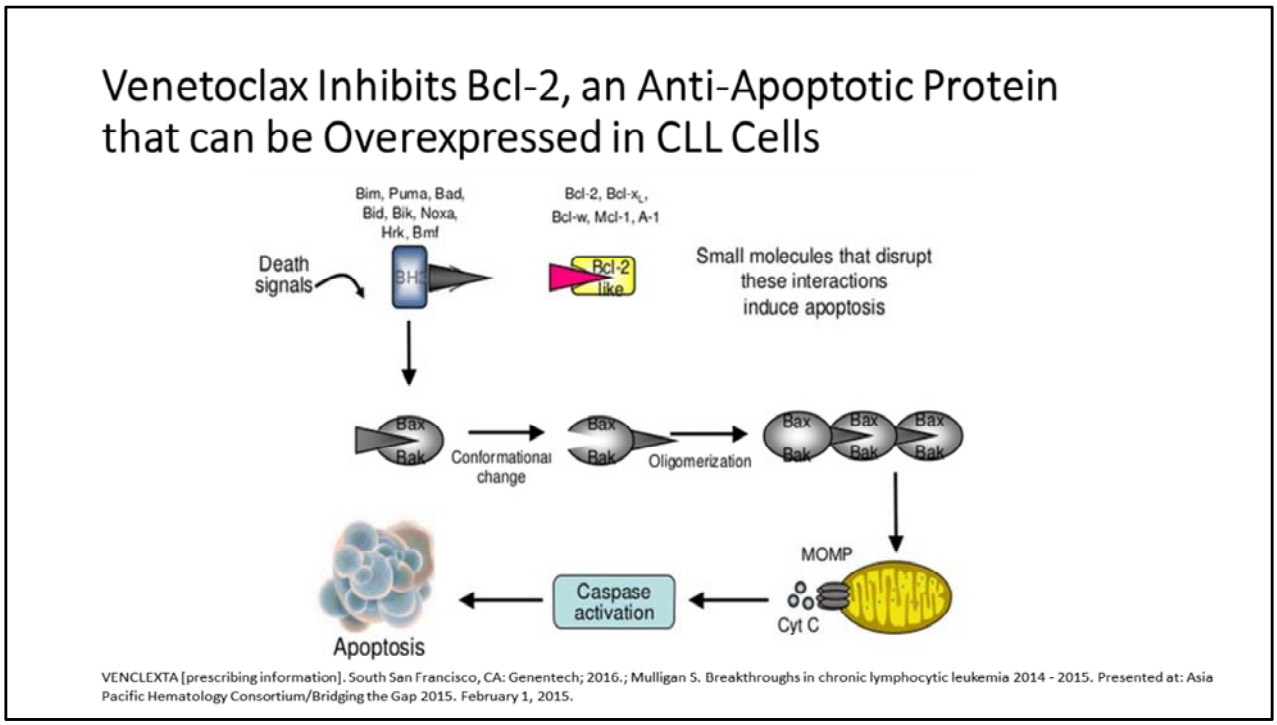
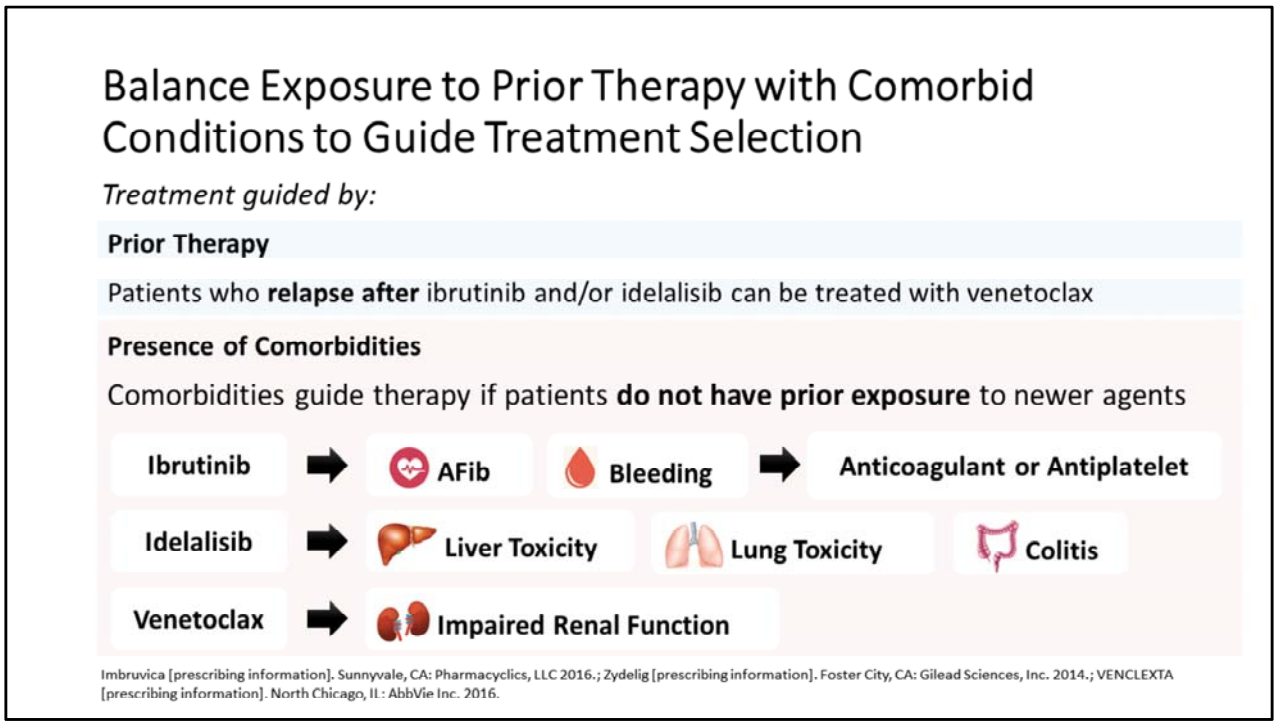


Venetoclax is an inhibitor of Bcl-2 or the B-cell lymphoma 2 protein, which is a key negative regulator of the intrinsic apoptotic pathway. BCL-2 expression is increased in patients with CLL and is associated with resistance to chemotherapy. Venetoclax is an oral bioavailable selective Bcl-2 inhibitor that directly induces apoptosis independent of p53. Venetoclax helps restore the process of apoptosis by binding directly to the Bcl-2 protein, displacing apoptotic proteins like them and triggering mitochondrial outer membrane permeability, increasing activation of caspase resulting in apoptosis of CLL cells.

While all these three agents are great options for our patients, I think it is important to assess for patient- and treatment-related factors to determine the right drug for the right patients.



Dr. Jeffrey Jones: That is right, Heidi. While these drugs do represent a dramatic improvement in both the efficacy and safety with comparison to prior chemotherapy-based combinations for the treatment of CLL, there are still important considerations with respect to comorbid medical illness that can help guide the selection of any individual therapy. In general, patients who have received prior therapy with ibrutinib and/or idelalisib can likely be treated successfully with venetoclax based on recent clinical trial data. When choosing among these three drugs in patients who have not received any newer oral agent, comorbid medical illnesses are helpful. As you have described, patients who are taking ibrutinib sometimes experience atrial fibrillation as well as bleeding related to the antiplatelet effects of ibrutinib. As a result, patients who are taking anticoagulant medications, antiplatelet medications or have a history of difficult-to-control atrial fibrillation may not be best treated with ibrutinib, even if it is a good treatment for their CLL. On the other hand, idelalisib has been associated with elevation of the hepatic transaminases as well as pneumonitis and colitis. So for patients with preexisting lung disease of any significant severity, a prior history of diarrheal illness or inflammatory bowel disease, or other reasons to be concerned for liver toxicity may not be the best candidates for idelalisib treatment. Finally, venetoclax, the newest drug in the group and the one that you have just described, has an important risk at the time of dose initiation for tumor lysis. This can result in increased levels of uric acid, and electrolyte abnormalities that are particularly difficult to manage in patients with impaired renal function. As a result, that may not be the best drug for that group.

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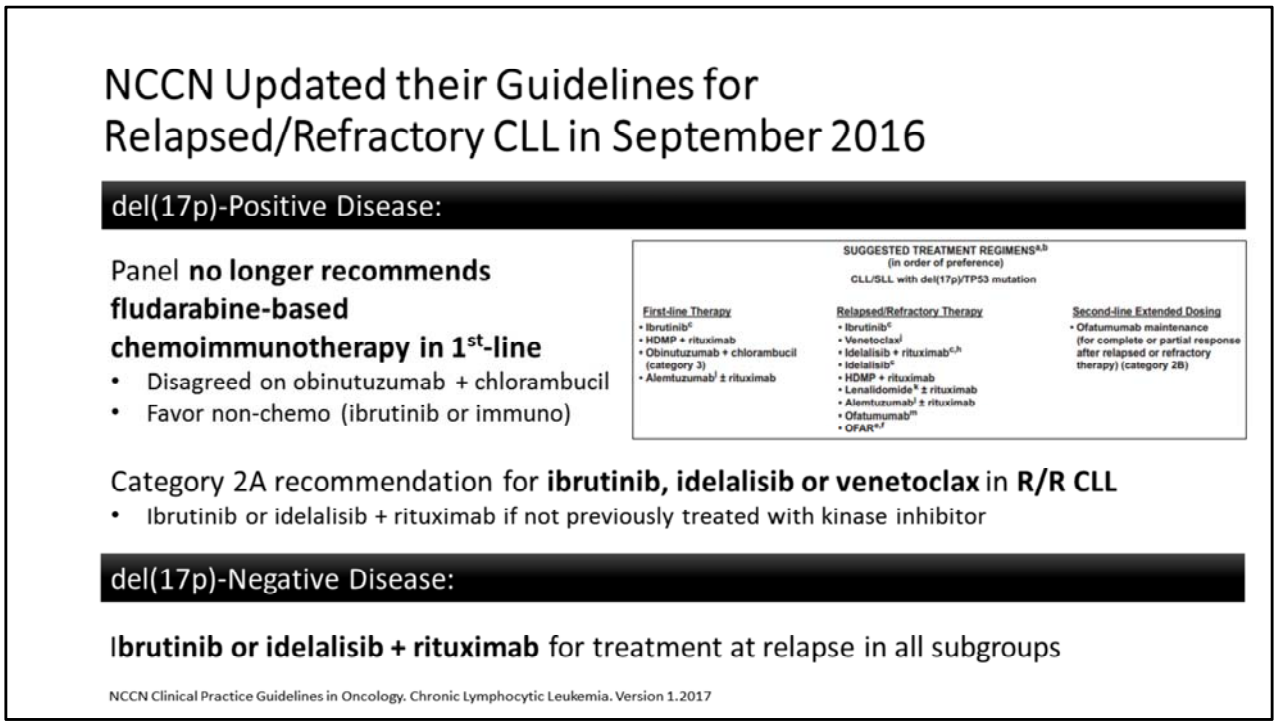

If we look just in general at the most recent updates to the NCCN Guidelines, I just want to highlight a few features that are important for many busy clinicians who might find the many arrows and columns in the diagrams a bit confusing. First, for patients with deletion 17p positive disease, the NCCN panel no longer recommends fludarabine-based chemo-immunotherapy in the first line. These are not the FCR patients. While there is some disagreement over whether or not obinutuzumab and chlorambucil is an appropriate therapy; almost all of the panelists agree in recommending non-chemotherapy based therapy, that is ibrutinib or immunotherapy, as first-line treatment for those patients. For patients with relapsed disease, a recommendation for ibrutinib, idelalisib, or venetoclax is appropriate in this group. Although, the preponderance of the data supports ibrutinib or idelalisib first if the patient has not been previously treated with a kinase inhibitor. Among patients with deletion 17p negative disease, the most important update is that ibrutinib or idelalisib and rituximab is the top-line recommendation before retreatment with chemo-immunotherapy at relapse in all patient subgroups regardless of genetic risk features.

So, now Heidi, we have talked about these available treatment options. You have talked to us a little bit about some of the comorbid medical illnesses, some of the patient disease factors that are important in selecting one of these therapies, can you now talk to us a little bit more as a pharmacist about some of the aspects of pharmacotherapy that must be considered when we are picking one of these agents or using them to treat our patients taking other medications?

Pharmacists Evaluate Drug Metabolism and Transport to Manage Drug-Drug Interactions

- Modifying the treatment regimen to optimize safety and efficacy
- Managing **interactions** with **concomitant medications** is critical

Drug	Cytochrome P450 Pathway					Transporters		Other
	3A4/5	2C19	2C9	2C8	2C19	P-gly	BCRP	
Ibrutinib	▲							
Idelalisib	▲ X Strong	X Weak		X Weak				▲ UGT1A4
Venetoclax	▲		X Weak	X Weak		▲	▲	X UGT1A1

P-gly=P-glycoprotein; BCRP=breast cancer resistance protein; UGT=uridine diphosphate glucuronosyltransferase; X=inhibitor; ▲=substrate

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC 2016.; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc. 2014.; Ramanathan S, et al. *Clin Pharmacokinet*. 2016;55:33-45.; Jin F, et al. *Blood*. 2013;122:5574.; VENCLEXTA [prescribing information]. North Chicago, IL: AbbVie Inc. 2016.; Jones AK, et al. *AAPS J*. 2016;18:1192-1202.; Salem AH, et al. *J Pharm Pharmacol*. 2016;epub DOI:10.1002/jcph.821.

Dr. Heidi Finnes: Most definitely, Jeff, thank you. Pharmacists play a key role in assuring that the patient receives the correct drug at the most appropriate dose based on laboratory values, hepatic/renal function, body habitus, and appropriate supportive care medications such as those for anti-emesis as well as diarrheals, that sort of thing. Managing interactions is also I think the primary thing a pharmacist should be worried about in many patients receiving oral therapies like ibrutinib, idelalisib, or venetoclax, because many patients are on co-medications that may interact, whether they be herbal supplements that they believe to be natural but still may have anti-platelet effects or induction of cytochrome P450 pathways. It is important to get a full medication list and reconcile those indications so not to have comorbid toxicities based on these medications. Now based on the chart that I have on the screen for you, ibrutinib, idelalisib, and venetoclax are all metabolized via the cytochrome P450 CYP3A4 pathway. This is important because most medications are metabolized via the same pathway. Any medication that inhibits or induces, meaning it speeds up the metabolism of drugs that go through that pathway, can alter the CLL medication concentrations. You will note that idelalisib is also a strong inhibitor of CYP3A4. This is important because concomitant idelalisib may cause increased toxicity of co-medications that patients need to take.

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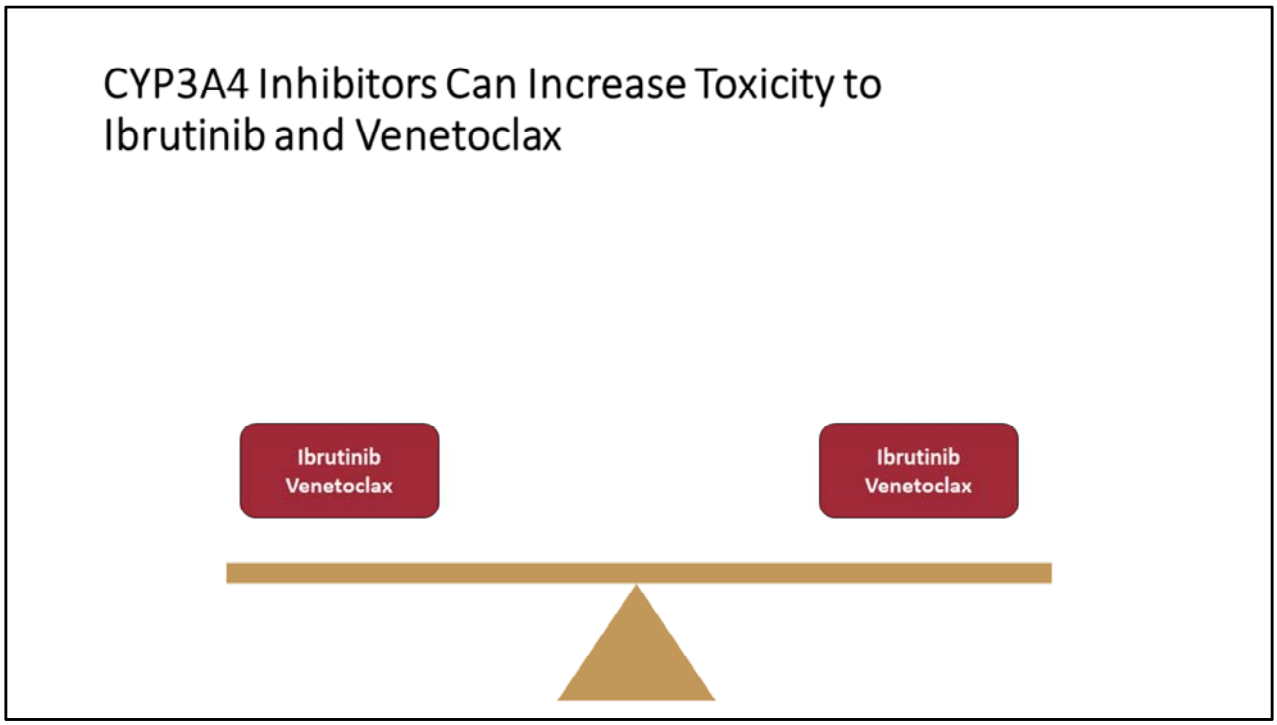

Now, what does this all mean?

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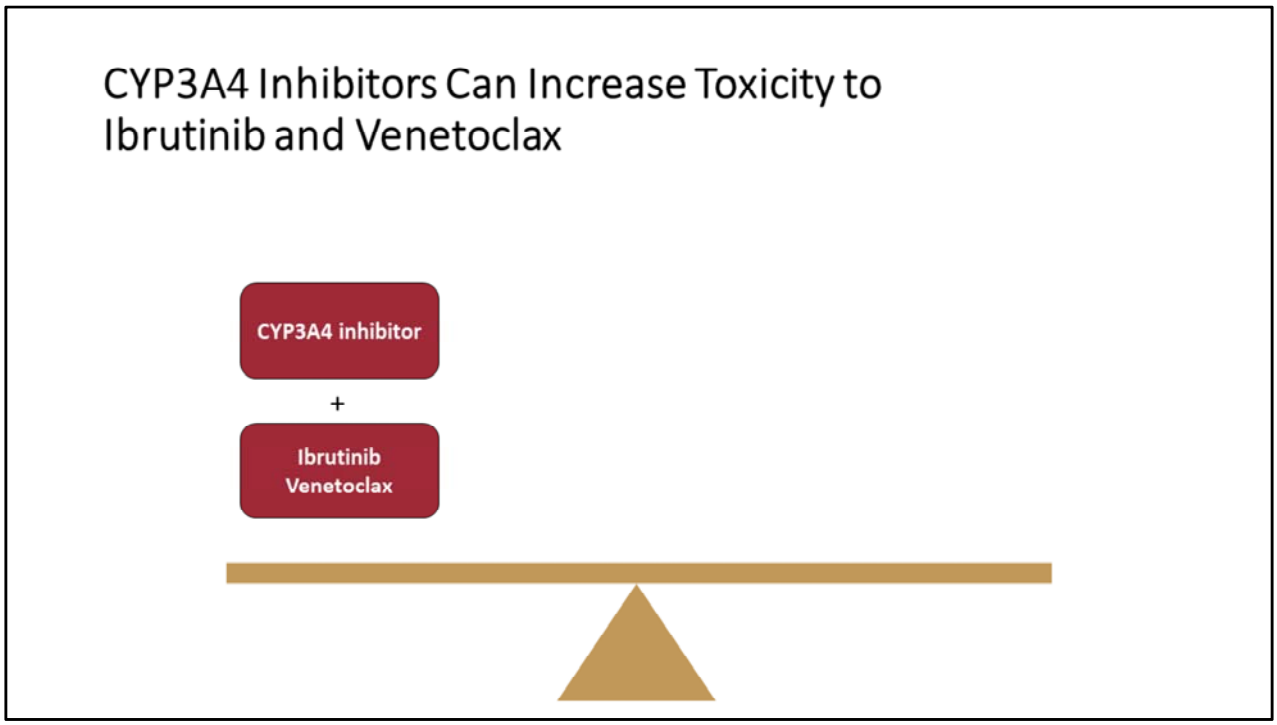

When patients are taking a strong inhibitor, such as ketoconazole, concomitantly with ibrutinib or venetoclax,

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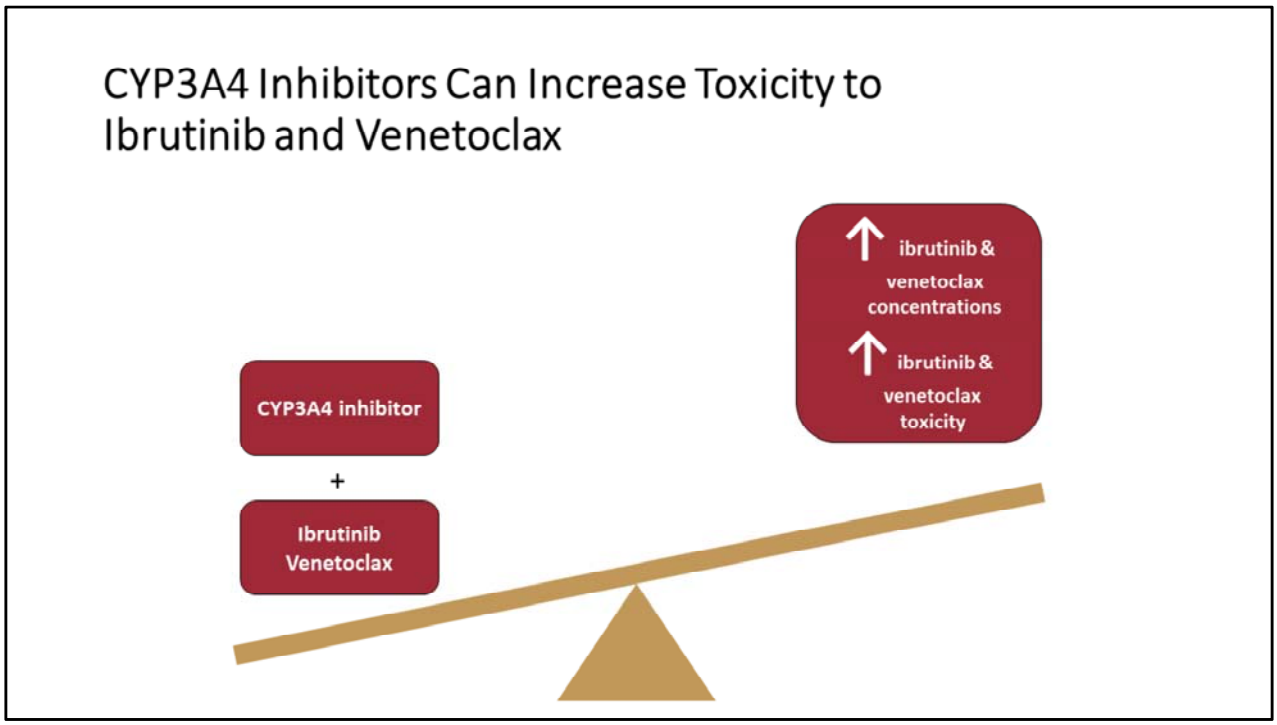

that results in increased ibrutinib concentrations of more than 29-fold, with venetoclax concentrations increased with concomitant ketoconazole more than 2.3-fold, resultant ibrutinib and venetoclax increased concentrations result in increased risk of toxicity.

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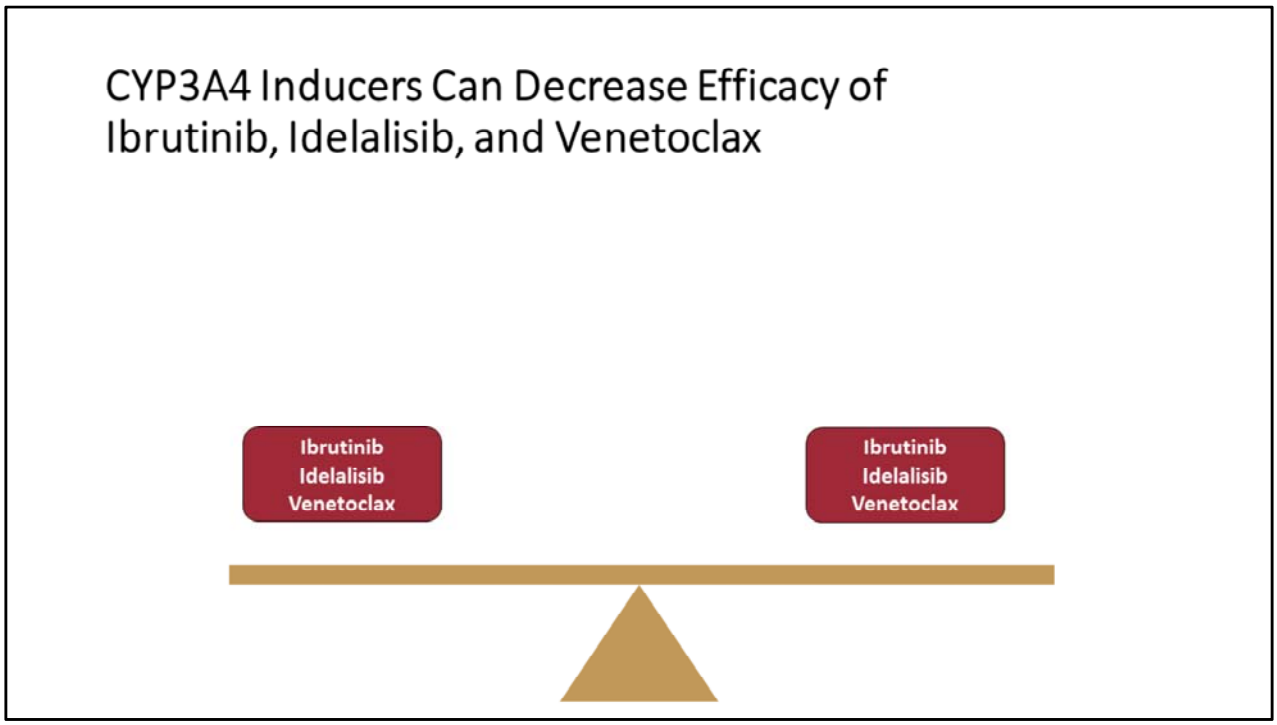
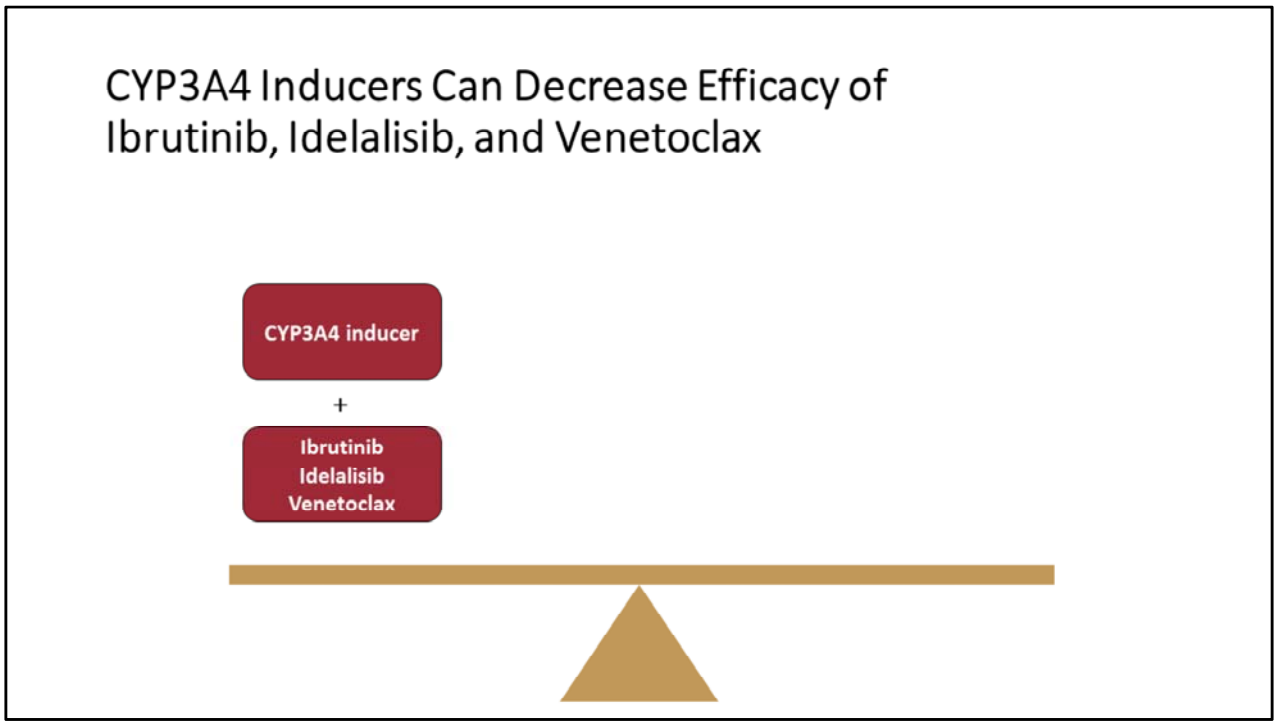
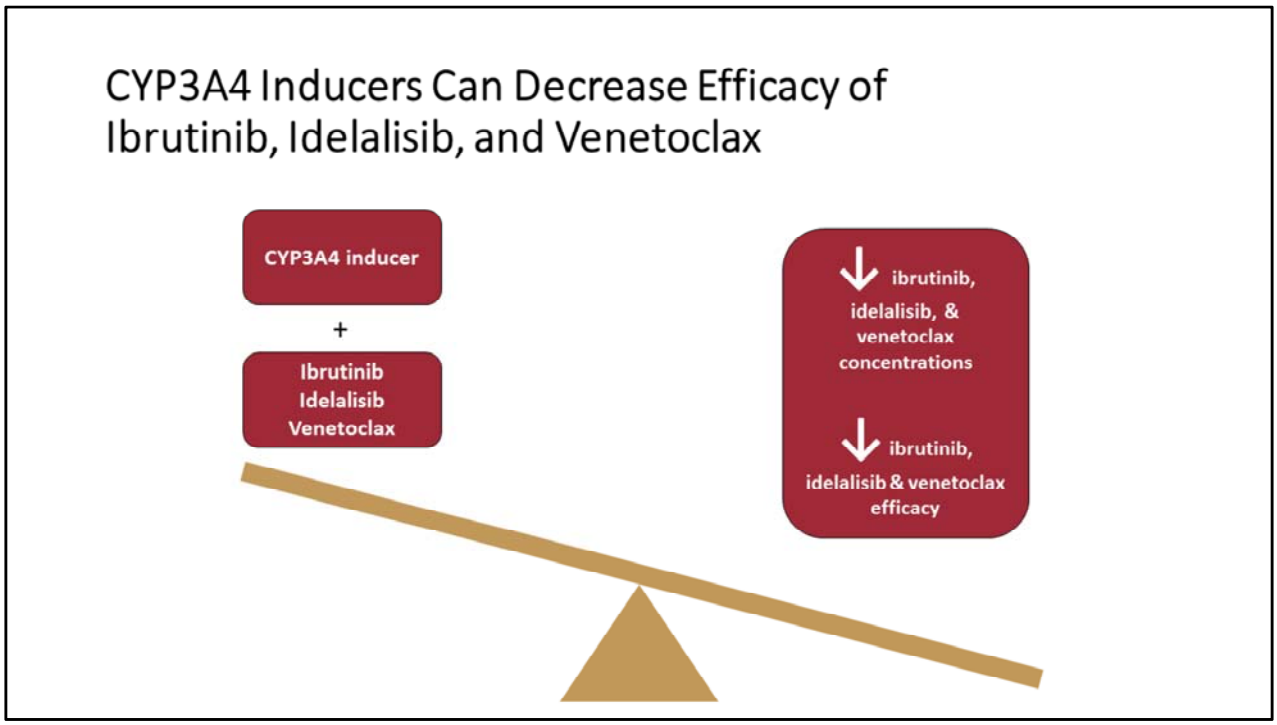


When ibrutinib, idelalisib, or venetoclax are given concomitantly with



a strong inducer like rifampin of CYP3A4, concentrations of these medications decrease. Ibrutinib decreases more than 13-fold, idelalisib and venetoclax reduce 75% and 42%, respectively. Reductions in these concentrations



of the CLL medications result in decreased efficacy of CLL therapies.

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Common CYP3A4 Inhibitors/Inducers to Consider when Treating Patients with CLL Therapy

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	CYP3A4 Inducers
Boceprevir	Aprepitant	Avasimibe
Clarithromycin	Ciprofloxacin	Carbamazepine
Conivaptan	Diltiazem	Modafinil
Itraconazole	Erythromycin	Phenytoin
Ketoconazole	Fluconazole	Rifabutin
Nefazodone	Imatinib	Rifampin
Posaconazole	Verapamil	St. John's Wort
Telithromycin		
Voriconazole		
HIV medications		

Drug Development and Drug Interactions Table. *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.*; Indiana University Department of Medicine P450 Drug Interaction Table. *http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table.*

As classified by the FDA and multiple sources, these are medications that CLL patients commonly encounter that are receiving ibrutinib, venetoclax, or idelalisib. Strong inhibitors of CYP3A4, I'll call your attention to many of the anti-fungals that patients may be receiving, cause a five-fold increase in ibrutinib, venetoclax, or idelalisib concentrations, and decreased clearance of those medications by more than 80%. Moderate inhibitors of CYP3A4, for instance diltiazem or verapamil, two cardiac medications that patients are commonly taking, cause a two-fold increase in area under the curve concentrations of these drugs and a 50-80% decrease in clearance. Inducers of CYP3A4 such as rifampin, phenytoin, or carbamazepine decrease AUC values by more than 30% of these CLL therapies thereby reducing efficacy of these medications.

Pharmacists Optimize CLL Therapy through Dose Modifications and Patient Monitoring

CLL Therapy	Interacting Medication	Outcome	Dose Alteration to CLL Drug and/or Required Monitoring
Ibrutinib	CYP3A strong inhibitor	↑ Cmax 29-fold, ↑ AUC 24-fold	Avoid combination
	CYP3A moderate inhibitor	↑ Cmax 5-fold, ↑ AUC 8-fold	↓ ibrutinib to 140 mg once daily
	CYP3A strong inducer	↓ Cmax 13-fold, ↓ AUC 10-fold	Avoid combination
	Anticoagulants/Anti-platelets	↑ bleeding risk	Monitor for bleeding
	CYP3A strong inhibitor/P-gp inhibitor	No Δ Cmax, ↑ AUC 1.8-fold	Monitor for ibrutinib toxicity
Idelalisib	CYP3A strong inducer/P-gp inducer	↓ Cmax 58%, ↓ AUC 75%	Avoid combination
	CYP3A4 substrates	↑ CYP3A4 substrate Cmax 2.4-fold, ↑ CYP3A4 substrate AUC 5.4-fold	Avoid combination
Venetoclax	CYP3A strong inhibitor	↑ Cmax 2.3-fold ↑ AUC 6.4-fold	Initiation: Avoid combination; Steady Dose: avoid or ↓ venetoclax by 75%
	CYP3A moderate inhibitor/ P-glycoprotein inhibitor	↑ Cmax ↑ AUC	Initiation/Steady Dose: avoid combination or ↓ venetoclax by 50%
	CYP3A strong inducer	↓ Cmax 42% ↓ AUC 71%	Avoid combination
	Warfarin	↑ Cmax 18% ↑ AUC 28%	Monitor INR or use alternative
	P-glycoprotein substrates	↑ Cmax ↑ AUC	Avoid combination or take P-glycoprotein substrate 6 hours before venetoclax

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC 2016.; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc. 2014.; VENCLEXTA [prescribing information]. North Chicago, IL: AbbVie Inc. 2016.

It is most important to have a plan on how to tackle these types of drug-drug interactions. My best advice is to change the interacting medication if possible to something that will not cause a drug-drug interaction with ibrutinib, idelalisib, or venetoclax. If one is unable to do that, then the option is to carefully monitor the patient for toxicity or reduce the dose of the CLL therapy, which is controversial because there are some concerns you could reduce efficacy of these medications. For instance with ibrutinib, strong CYP3A4 inhibitors and inducers are prohibited for package labeling. It is recommended with moderate inhibitors such as fluconazole or diltiazem to decrease ibrutinib dosing from 420 mg once daily to 140 mg once daily. As I mentioned, ibrutinib has anti-platelet effects; concomitant anti-coagulants or anti-platelet medications, flaxseed, vitamin E, or fish oil can all increase risk of bleeding in patients receiving ibrutinib. It is important to educate patients to monitor for these symptoms and know when to call their providing team for help. Idelalisib is recommended to avoid strong CYP3A4 inducers, and again, this medication is a strong inhibitor of cytochrome P450 CYP3A4. Sensitive substrates like simvastatin-tacrolimus should be avoided if at all possible with this medication. Venetoclax, as I mentioned, also a substrate of CYP3A4, is not recommended in the dose escalation phase to receive concomitant inhibitors of CYP3A4, whether they be strong or moderate inhibitors. If in the maintenance phase when one gets to 400 mg daily dosing, concomitant anti-fungals must cause the venetoclax dose to have to be reduced by more than 50%. Careful monitoring with warfarin and looking for signs and symptoms of bleeding would also be important with venetoclax.

As you have seen, there are many factors that pharmacists must consider to ensure the patient's safety when using these types of medications. However, this is a team effort. Beth, can you talk a little bit about the role nurses play in assessing for adverse events?

Nurses are at the Forefront of Adverse Event Assessment and Intervention

- Encourage patients to report AEs **immediately** in order to address severe AEs
- GI effects may be more common than reported

Take **diarrhea history** (stool consistency; number of stools per 24 hours)

Assess if diarrhea is **new onset or chronic**

Grade the diarrhea by CTCAE

- Counsel on **dietary modification** for GI effects, including nausea and diarrhea

Beth Faiman: Thank you, Heidi. You have shared so much wonderful information, and I think it underscores the importance of a pharmacist on your multidisciplinary team, so that information that you shared with us that we will share with our patients such as the basic anti-platelets. Are patients taking aspirin or do they have a history of bleeding? Other adverse events which can occur as well should be reported. But the question is, "What do you tell their patients?" So number one, GI effects are really important. We talked about the onset of diarrhea that can occur sometimes late, it is not necessarily at the beginning of therapy, but looking at the stool consistency, the number of stools per day, assessing for *Clostridium difficile* infection as well. Is this is a new diarrhea or chronic? Nurses can provide education to the patient such as not allowing themselves to get dehydrated, making sure that they are assessing their dietary intake. Heidi, you mentioned flaxseed as something that can interact with the medications, and oftentimes our patients want to take nutritional supplements, and so really just assessing the medication list and making sure that they are reporting symptoms as well. Again, counseling on dietary modifications for GI effects including nausea and diarrhea is super important. Also thinking about the other drugs to treat such as ibrutinib. What are the signs and symptoms of atrial fibrillation? Assessing for blood pressure being high and low, and all of these things can be assessed at an ongoing nature in between visits as well.

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Nurses Must Understand Side-Effect Profiles of CLL Therapy to Monitor and Educate Patients on S/S

Drug	Adverse Event	Signs & Symptoms		
Ibrutinib	Atrial Fibrillation	• Chest pain • SOB	• Fatigue • Tachycardia	• Dizziness • Chest pressure
Idelalisib	Enteric Colitis	• Abdominal pain • Blood in stool	• Cramping • Loss of appetite	• Diarrhea • Incontinence
	Diarrhea	• Loose stools	• Frequent stools	• Abdominal pain
	Hepatotoxicity	• Stomach pain • Dark urine	• Nausea • Light stools	• Jaundice • Vomiting
	Bowel Perforation	• Stomach pain • Fever	• Nausea • Chills	• Vomiting • Hematemesis
	Pneumonitis	• Flu-like s/s • Cough/rales	• Fever • SOB	• Chills • Joint pain
Venetoclax	Tumor Lysis Syndrome	• N/V/D • ↓ Urination	• Muscle cramps • Fatigue	• Fatigue • Irregular HR

SOB=shortness of breath; N/V/D=nausea, vomiting, diarrhea; HR=heart rate

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC 2016.; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc. 2014.; VENCLEXTA [prescribing information]. North Chicago, IL: AbbVie Inc. 2016.

Black box warning

So, nurses must understand the side-effect profiles of CLL therapy in order to monitor and educate patients on signs and symptoms and when to call. Ibrutinib, we identified that atrial fibrillation can occur. So, signs and symptoms such as chest pain, shortness of breath, fatigue, and tachycardia should be reported immediately. Idelalisib can cause enteric colitis, diarrhea, and elevated transaminases. Signs of abdominal pain, blood in the stool, or loose stool should all be reported. Dark urine can also be a sign of hepatic toxicity as well. Nausea, light stools, all of these things are important. Venetoclax, we also highlighted the importance of dose escalation and tumor lysis syndrome. Dr. Finnes had mentioned that we should risk-stratify our patients into low, intermediate, and high risk when initiating therapy because some individuals might require hospitalization. Encouraging hydration and making sure you are assessing for muscle cramps, fatigue, and irregular heart rate as well is very important.

Given the potential toxicities associated with all of these medications, it is important to know and implement the appropriate management strategies. Dr. Jones, do you have some insight to share?

Pharmacologic and Non-Pharmacologic Interventions to Manage Adverse Events to CLL Therapy

Agent	Important Adverse Events	Recommended Considerations for Managing
Ibrutinib	Atrial Fibrillation	• Exercise caution when initiating anticoagulation
	Bleeding	• Adhere to recommendations for holding drug before and after procedures • Exercise caution when initiating anticoagulation or other antiplatelet agents
	Myalgias/Arthralgias	• Often self-limiting, but may respond to anti-inflammatory medications and/or steroids
Idelalisib	Hepatic Transaminases	• Check bi-weekly during the first few months of treatment • Hold drug when > Grade 5-20 x ULN; re-introduce at reduced dose (ie, 100 mg bid)
	Colitis	• Late occurring (median 6-8 months from starting) • Exclude infection, consider colonoscopy for definitive diagnosis • Hold drug and administer steroids to treat, but may require permanent discontinuation
	Pneumonitis	• Requires high index of suspicion not to confuse with infection • Treat with steroids and consider permanent discontinuation
	Opportunistic Infections	• Routine prophylaxis with TMP/SMX and antiviral (acyclovir or valacyclovir)
Venetoclax	Tumor Lysis Syndrome	• Careful risk assessment by disease bulk and renal function (CrCl <80 mL/min) • Emphasize adequate hydration and close adherence to recommendations for prevention and laboratory monitoring during dose ramp-up as detailed in the prescribing information
	Neutropenia	• Monitor regularly during the first few months of therapy • Responds well and quickly to white blood cell growth factors (ie, G-CSF)

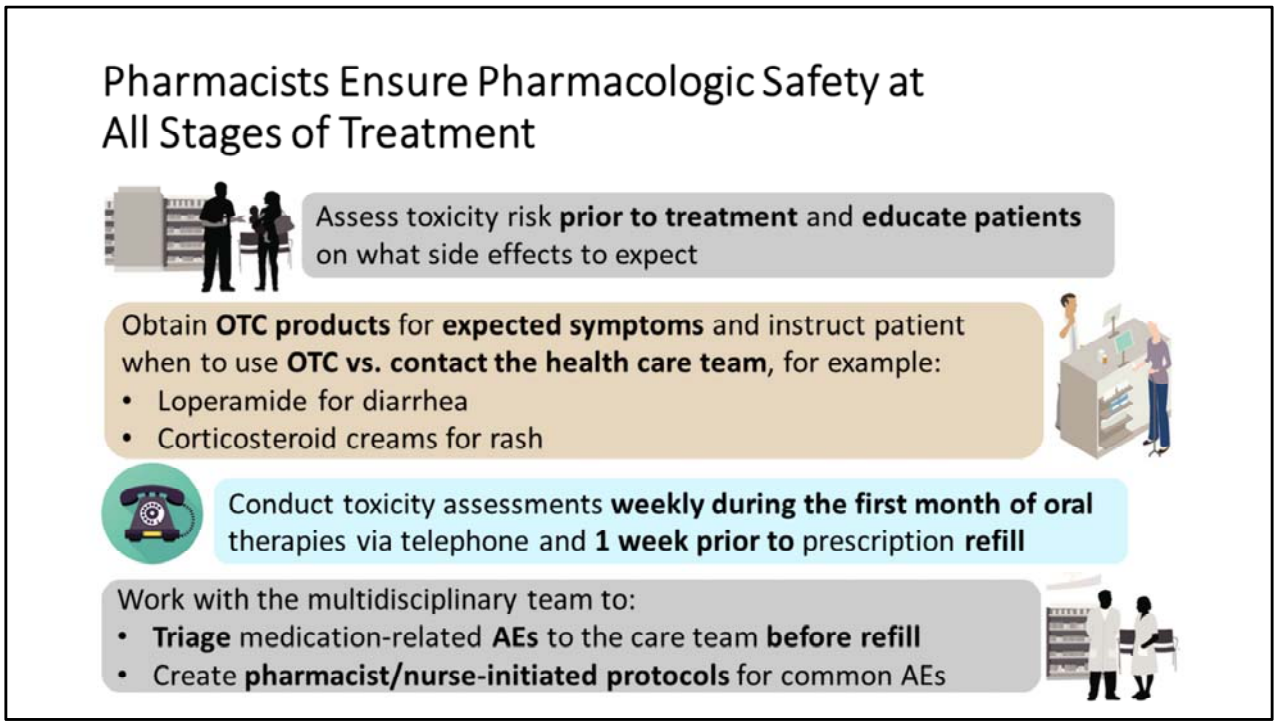
Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC 2016.; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc. 2014.; VENCLEXTA [prescribing information]. North Chicago, IL: AbbVie Inc. 2016.

Dr. Jeffrey Jones: Beth, it is vital in considering all of these medications that they are taken for the long term. Unlike chemotherapy that may be given for 4 to 6 months, these are drugs that patients will be taking many months and in often cases many years. The optimal management of adverse events is important to optimizing the outcome of therapy. Let's just briefly talk about some of the key side effects of the individual agents as well as some considerations in their management. First, for patients with atrial fibrillation, there is importance in exercising caution when initiating anticoagulation. Because of the antiplatelet effects of ibrutinib, anticoagulation is a risk-benefit discussion with patients. You must consider whether continuing ibrutinib is in the patient's best interest if they have other therapeutic alternatives and absolutely require anticoagulation for stroke prevention. Similarly, patients who are at risk for bleeding because they are requiring anticoagulation for venous thromboembolic disease or have a planned surgical intervention need to be advised in appropriate holding around surgical procedures or other invasive procedures where there is risk for bleeding, as well as the potential for increased bleeding in combination with therapeutic anticoagulation. One of the more noisome side effects for many patients with long-term ibrutinib administration are myalgias and arthralgias, and while these are often self-limiting, some patients experience chronic complaints that are treatment limiting in some patients. We have tried anti-inflammatory medications as well as short courses of steroids like a Medrol Dosepak (methylprednisolone) with some success.

With idelalisib, some of the side effects that Heidi and Beth have mentioned are substantially important and pose a substantial risk to a patient's health. With hepatic transaminase elevations, which often occur early in therapy, many patients can be managed with interruption of the drug and monitoring until resolution with careful re-introduction of idelalisib, often at a lower dose, 100 mg rather than 150 mg twice daily. For colitis, this must be distinguished from other kinds of diarrhea. The key to recognizing idelalisib-associated colitis is that it is often a late-occurring effect, occurring 5 to 6 months into therapy. Interruption of therapy, investigations that include exclusion of infection as well as consideration for colonoscopic evaluation to achieve a definitive diagnosis are important. Treatment is often with oral steroid medications, either systemic steroids like prednisone or oral budesonide that treats the GI tract without systemic absorption, but in some cases refractory colitis requires permanent discontinuation of idelalisib. We would say the same thing about pneumonitis that requires a high index of suspicion to recognize since it is often confused with infection. In patients with no discernible source of infection but with evidence of pulmonary inflammation, a high index of suspicion for pneumonitis is important since treatment with steroids and typically permanent discontinuation of the offending agent, in this case idelalisib, would be important. Finally, recent safety information regarding the risk of opportunistic infections as well as neutropenic sepsis among patients with idelalisib is important in optimally managing these patients. All patients receiving idelalisib therapy should be treated with prophylactic doses of Bactrim (sulfamethoxazole and trimethoprim) or another anti-microbial agent active against PCP pneumonia as well as anti-viral medications to prevent reactivation of herpes viruses including HSV, VZV, and probably most importantly CMV. Finally, with venetoclax, Beth has gone over some of the most important considerations there. With respect to tumor lysis, careful identification of risk based on disease bulk before beginning therapy as well as appropriate risk mitigation strategies including prophylactic medications, hospitalization, and hydration are key. These are well outlined in the US prescribing information. Finally, neutropenia commonly occurs among patients taking venetoclax. Maybe even 40% of patients can experience grade 3 or grade 4 neutropenia at some time during their treatment. Fortunately, patients receiving venetoclax who develop neutropenia can be well-treated with intermittent doses of white blood cell growth factors such as GCSF or GMCSF with prompt resolution of neutropenia in most cases, although this may be a chronic problem in some patients.

Now, Heidi, these are some maybe good strategies for managing adverse events, but it is important to incorporate the patient in these discussions to truly ensure safety. When you are counseling patients as part of your clinical practice, how do you best ensure patient safety at all stages of treatment?

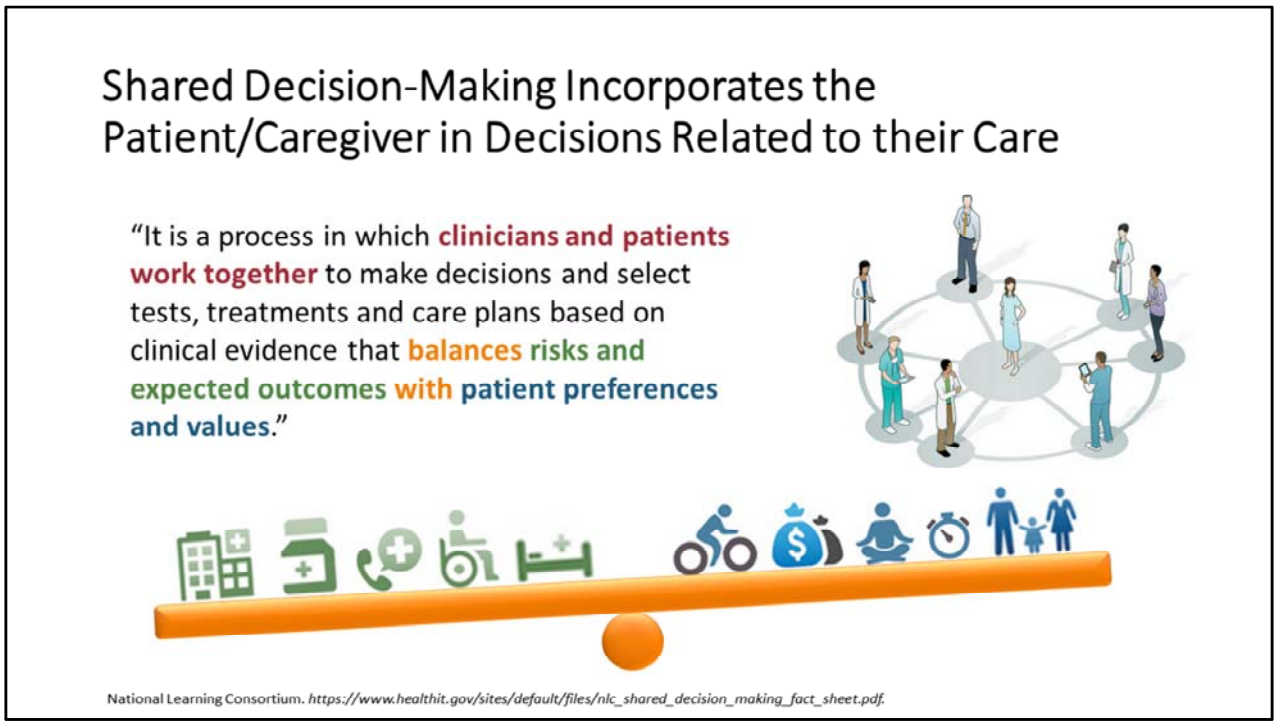
Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Dr. Heidi Finnes: Thanks Jeff. Well, I actually try to assess patient toxicity risk prior to patients actually starting the therapy. I think it is really important to be upfront with patients and let them know exactly what to expect toxicity wise when they start these types of medications. I also try to prepare them, so any over-the-counter product like an antidiarrheal, or whether it be a rash that is expected, they have corticosteroid creams or antipruritics on hand. I also educate them to be sure they understand when to contact their multidisciplinary team if side effects become uncontrollable. I recommend as a pharmacist that we conduct toxicity checks at least weekly for the first month of patients' treatments on these oral therapies, and then we do a toxicity check actually one week prior to prescription refill. This is really important because many specialty pharmacies actually call the patients, have them refill the prescription, they see their provider, and then the provider changes the dose, and they have this very expensive medication that they are not able to use. What we do at my institution is we work with the multidisciplinary team to triage medication-related adverse effects before the refills occur. We also work together to try to save provider time by creating common nurse-initiated and pharmacist-initiated protocols to help manage some of these complicated side effects.

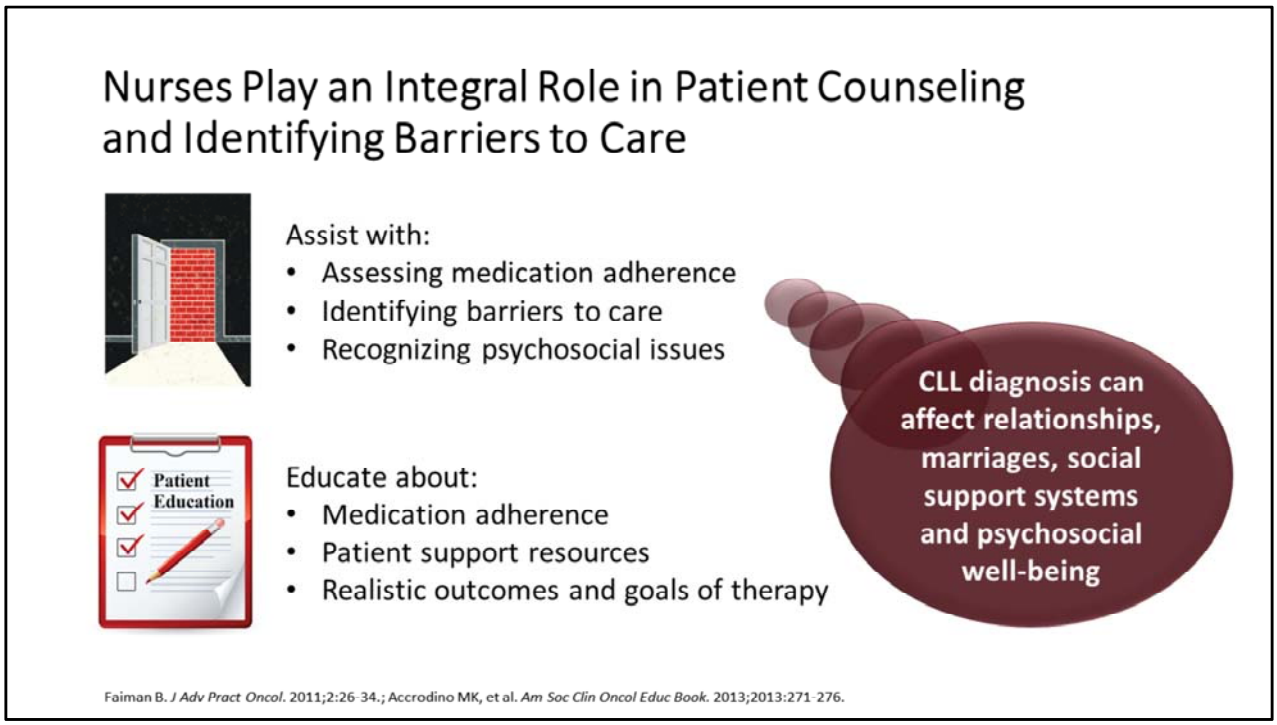
Educating and counseling patients about safety considerations of their treatment is most definitely very important, and it actually touches upon a larger patient-centric issue in health care called shared decision-making. Beth, can you share your thoughts?

Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Beth Faiman: So, shared decision-making incorporates the patient and caregiver in decisions related to their care. The shared decision-making model of treatment decision-making occurs during the patient encounter, and there are four essential elements and oftentimes two participants, be it the nurse and physician or clinician team and pharmacist on one side, and on the other side would be the patient and caregiver. So through this process, clinicians and patients will work together to find the right treatment that is the best for them because we know that physicians and nurses can recommend whatever therapy they think is best, but the patients and caregivers must buy into that therapy and mutually agree to continue that therapy. Balancing the risks and benefits and the expected outcomes is also important. We heard numerous times the toxicities and side effects that should be considered when starting these oral therapies for CLL. We really want to have that process of communication so that the mutual agreement can be reached between the two parties.

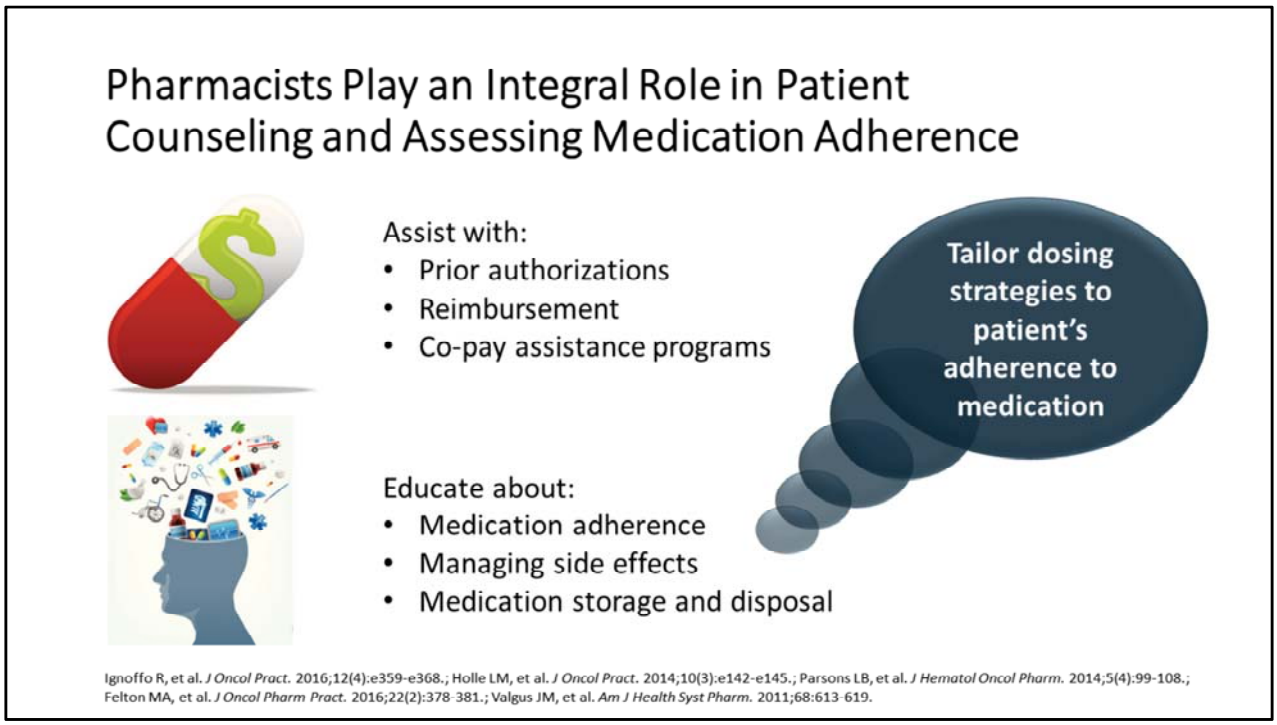
Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Nurses play an integral role in patient counseling and identifying barriers to care. This role can go back and forth between the physician and the pharmacist, but oftentimes it is the nurse who must assess the medication adherence, identify barriers to care, and recognize psychosocial issues such as the idea of continuing treatment. Oftentimes, cancer patients have this idea where they will take 6 cycles of treatment and then they will stop, but this treatment as Dr. Jones mentioned will be ongoing for most individuals. Again, the nurses will educate about the adherence, find patient support resources, and go over realistic outcomes and goals of therapies. We know the CLL diagnosis can affect relationships, marriages, and social support systems, so addressing all these is important.

It is extremely important that shared decision-making is demonstrated across the health care provider team. Heidi, how do pharmacists support shared decision-making?

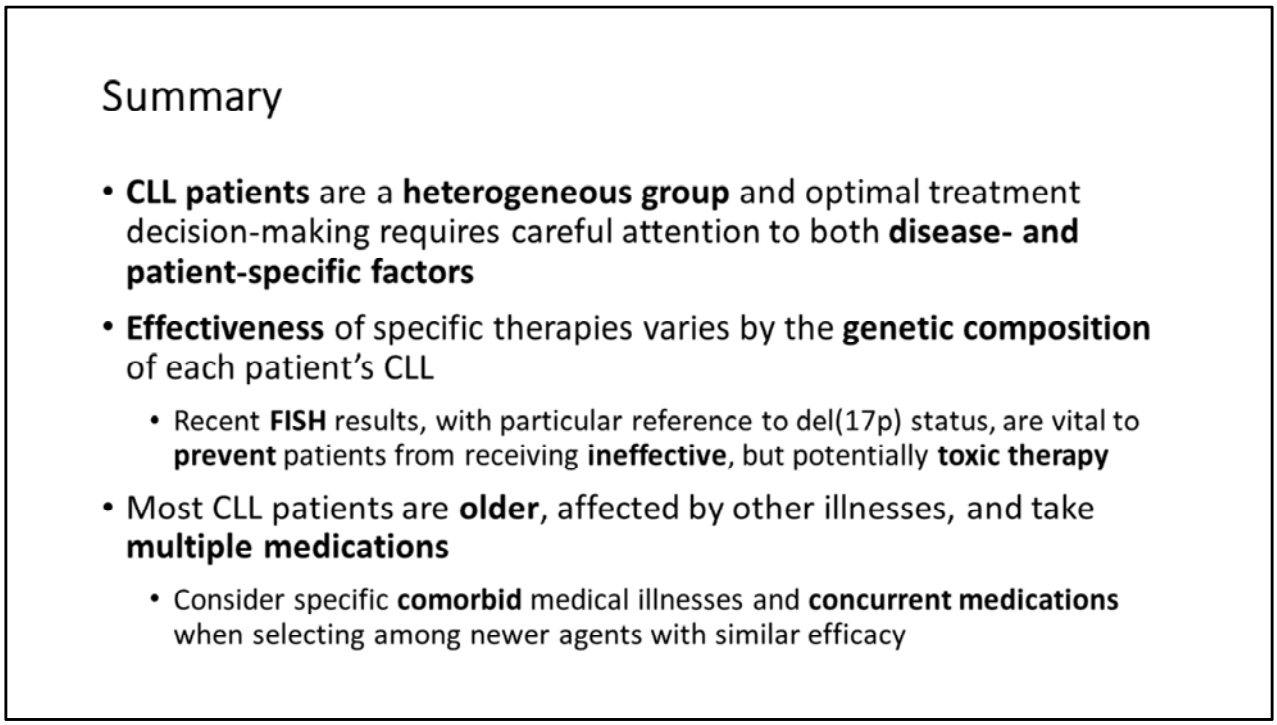
Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Dr. Heidi Finnes: Thank you, Beth. Pharmacists play an integral role in patient counseling and assessing medication adherence. One of the common things that patients experience with medications such as idelalisib, ibrutinib, or venetoclax is what is termed financial toxicity. Pharmacists can be of help in collaborating with external sources for co-pay assistance programs as well as ways patients can maximize reimbursement or participate even in prior authorizations of medications. It is often a stressful time for patients, and as many of us involved as possible can make this transition smooth as is important. I educate patients obviously relating to medication adherence. One of the things that I try to assess is the Modified Morisky Scale when I do a patient encounter to assess what their likelihood of remembering to take their medications, if they really understand why they are taking their medications, and I offer tools to help them remember. Either calendars, sometimes there are applications on smart phones, as well as traditional pill boxes can be of help to many of these patients. Again, expecting toxicities and helping them understand how to best manage side effects. One of the things that I think is underdone for patients receiving these types of therapies is really highlighting how do they take their therapies? Do they take medication with food, not with food, and then how do they store, do you keep it out in your kitchen, do you put it in the bathroom where there is lots of humidity, or how do they dispose of their medication when they have completed these types of therapies? These are all important mechanisms that a pharmacist can play in counseling as well as assessing adherence.

Shared decision-making and collaboration is critical in caring for many CLL patients. Remembering to incorporate these strategies is of utmost importance when developing treatment plans for patients with CLL. Jeff?

Practicing Personalized Evidence-based Medicine in CLL through Risk Stratification and Patient Education



Dr. Jeffrey Jones: Heidi, Beth, and I have spent a long time now presenting an incredible amount of information regarding these exciting new agents that are transforming the care of CLL patients. Let me summarize some of the most important points of what we have presented so far. First, it is important to remember that CLL patients are a heterogenous group, and optimal treatment decision-making requires careful attention to both disease- and patient-specific factors. The effectiveness of any specific therapy vary substantially by the genetic composition of a patient's CLL. Recent FISH results with particular reference to presence or absence of deletion 17p are vital to prevent patients from receiving ineffective therapies that might still have substantial toxicity. Most CLL patients are older and as a result are affected by other medical illnesses and are taking multiple medications. It is important to not only consider the comorbid medical conditions which may bear on any particular therapy but as well as the concurrent medications that may affect the levels of the drug or the expected side effects of these newer agents, particularly when choosing between multiple agents with expected similar efficacy.

Heidi, Beth, and I thank you for your participation in this activity. We have reviewed the important role that cytogenetics and comorbidities play in developing treatment plans for patients with CLL. If you have questions please send them to *CLL@practicaloncologist.com*. We will respond back to your email with an answer to your question. Thank you.