

Transcript



Slide 1. Welcome & Introductions

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

We have over 985 people participating from across the United States and several countries around the world, including Argentina, Canada, Germany and Mexico.

Special thanks to Dr. Danielle M. Brander for volunteering her time and expertise with us today.

Before we begin, I'd like to introduce Dr. Larry Saltzman, Executive Research Director at The Leukemia & Lymphoma Society, who will share a few words. Dr. Larry, please go ahead.

Dr. Larry Saltzman:

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients in their communities through our 56 chapters across the United States.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments, and ensuring that they have access to quality, affordable and coordinated care.

We've also recently launched our *LLS Community*, a website where patients and caregivers can connect with others to share experiences, obtain education and be a part of the research regarding care and outcomes. This site can be found at www.LLS.org/community.

As a CLL patient myself of over 7 years, we are fortunate to have as our presenter today Dr. Danielle M. Brander, one of the nation's leading experts in CLL. We appreciate her dedication to supporting our mission and her commitment for caring for patients living with blood cancers. I'd like to thank her for providing us today with important information on Living with Chronic Lymphocytic Leukemia.

Thank you all and now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera:

Thank you, Dr. Larry.

And support for this program is provided by AbbVie, Genentech & Biogen, Gilead, Pharmacyclics and Janssen, and an educational grant from Teva Pharmaceuticals.

The slide features a white header with the Leukemia & Lymphoma Society logo and the slogan 'someday is today'. The main body is a large red rectangle containing the title 'Living with Chronic Lymphocytic Leukemia (CLL)' in white. Below the title, the speaker's name and credentials are listed in white text. A yellow footer bar contains the date 'Wednesday, July 12, 2017'.

LEUKEMIA &
LYMPHOMA
SOCIETY™
fighting blood cancers

someday
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Living with Chronic Lymphocytic Leukemia (CLL)

Danielle M. Brander, MD
Assistant Professor, Division of Hematologic
Malignancies & Cellular Therapy
CLL & Indolent Lymphomas Team Leader
Duke Cancer Institute
Durham, NC

Wednesday, July 12, 2017

Slide 2. Living With Chronic Lymphocytic Leukemia (CLL)

I'm now pleased to introduce Dr. Danielle Brander, Lead at Duke CLL and Indolent Lymphoma Clinic, and Professor of Medicine at Duke Cancer Institute at Duke University in Durham, North Carolina. Dr. Brander, I'm privileged to turn the program over to you.

Dr. Danielle Brander:

Thank you and thank you, everyone, for the kind introduction. As was introduced, LLS has been a great resource for my patients personally and it's really a great honor to be able to do this talk today.



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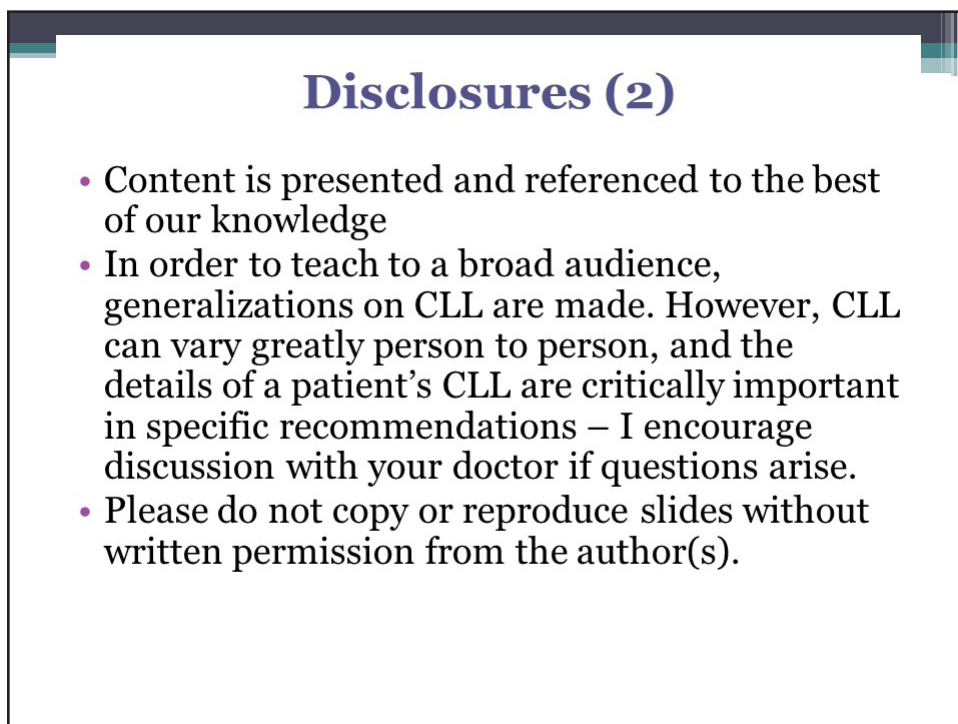
Disclosures

Danielle M. Brander, MD, has affiliations with AbbVie, Genentech, Gilead, Pharmacyclics, and Teva Pharmaceuticals (*Consultant*).

Wednesday, July 12, 2017

Slide 3. Disclosures

As you'll see with the slides provided are disclosures listed here.

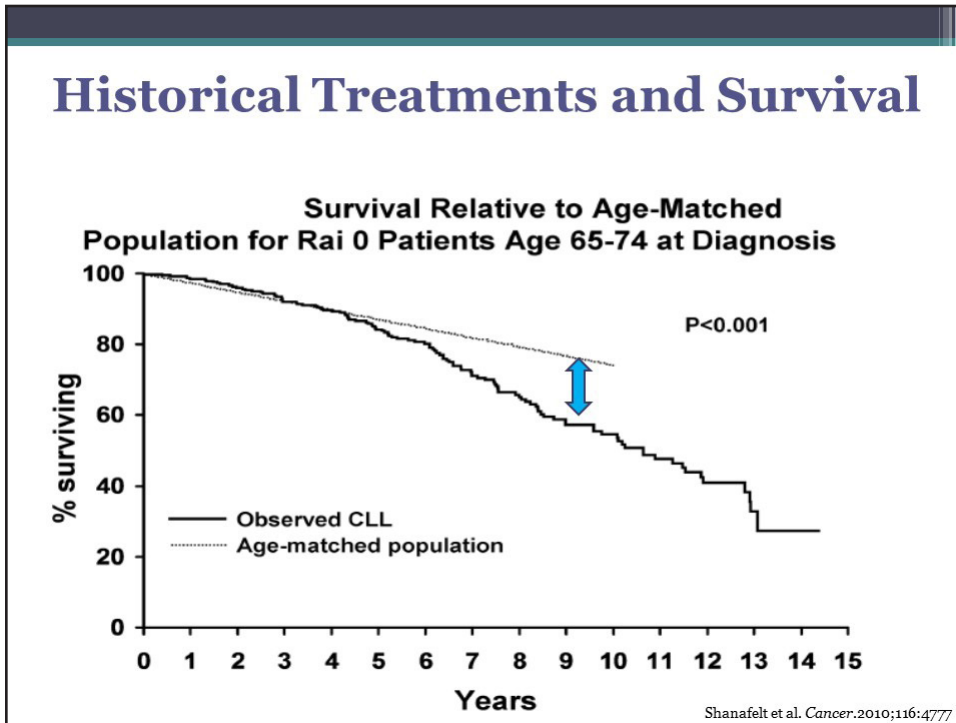


Disclosures (2)

- Content is presented and referenced to the best of our knowledge
- In order to teach to a broad audience, generalizations on CLL are made. However, CLL can vary greatly person to person, and the details of a patient's CLL are critically important in specific recommendations – I encourage discussion with your doctor if questions arise.
- Please do not copy or reproduce slides without written permission from the author(s).

Slide 4. Disclosures (2)

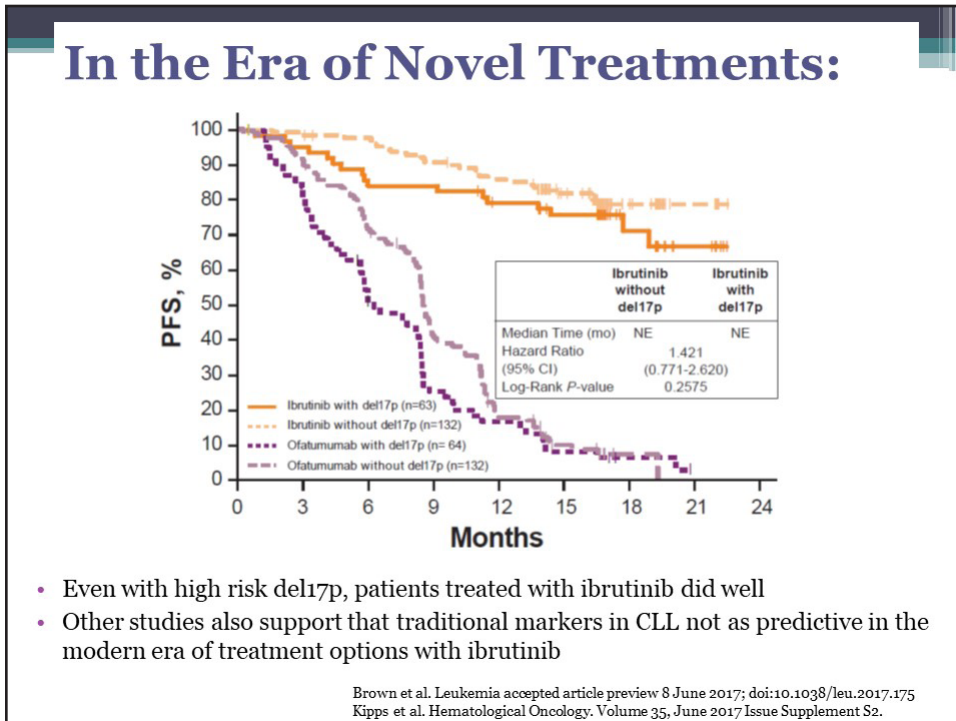
And also, I will briefly just review that for the over 150,000 people in the US that are living with CLL, almost every person's experience is unique, and while I want to do my best to give this overview, I do have to make generalizations and they may not apply to every patient, therefore, if questions arise, I certainly encourage going back to your oncologist and medical team to answer the questions. And again, I hope the slides provide a great outline and I provide references on each slide for the article to give more information. Although this is published data, we request that you just don't use these slides other than for your personal learning.



Slide 5. Historical Treatments and Survival

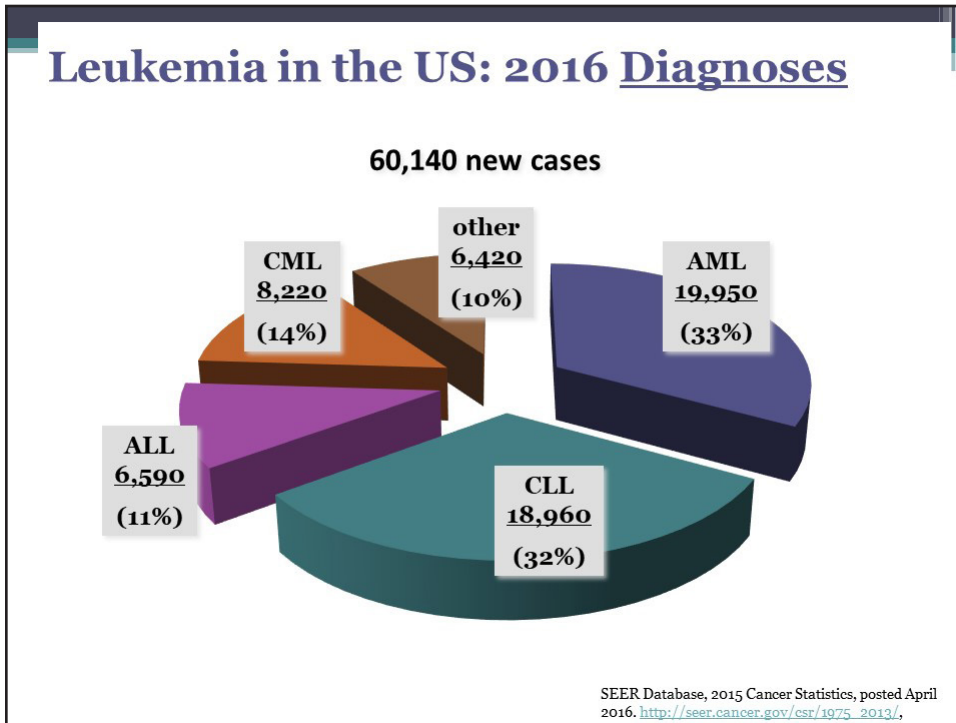
And with that I'll get started. And again, just thank everyone who is joining in and who is wanting to learn more about CLL and particularly, like I said, for the LLS to sponsor this, which has been a great support, particularly for the patients, I'm fortunate to be a part of their care.

So, I thought I would start the talk out a little bit with what motivates all of us which is, as you said, until we have a cure and until we can expect all patients living with CLL to live their full life expectancy, it motivates all of us to do better in the clinic and with the research. And though the study from Tait Shanafelt is a few years old, I think is what motivates us, which what it highlights over time historically what the survival has been for patients living with CLL, even at early stage, so for those of you familiar with the Rai staging, these are Rai staged zero patients. And at least as of a few years ago before the novel therapies were available, even early stage patients weren't reaching their life expectancy.



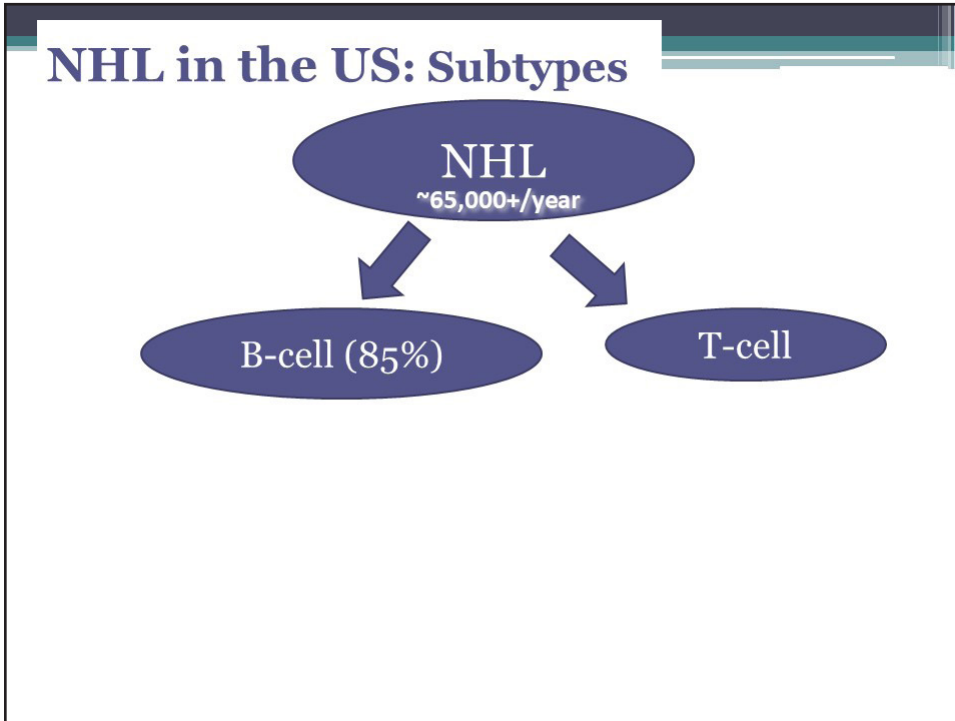
Slide 6. In the Era of Novel Treatments

As we'll get to in more detail, there fortunately have been great advances. And I start out with this because I don't want to start out with a slide that has everyone expecting that there isn't a better future. In fact, this study, which was just published a few months ago by Dr. Jenn Brown and colleagues, looked at patients that were treated on a clinical trial with ibrutinib versus ofatumumab and as we'll review, one of the abnormalities that can happen in CLL cells, the deletion of 17p, in the past was very concerning because that did not respond to standard chemotherapy or immunotherapy. The reason I start out with this slide as a background before we get started is, why we have the slides and motivate us to want to cure and have all patients having improved quality of life, I think that strides are also important to highlight that, is patients with the highest risk changes are now seeing responses similar to as if they did not have these abnormalities.



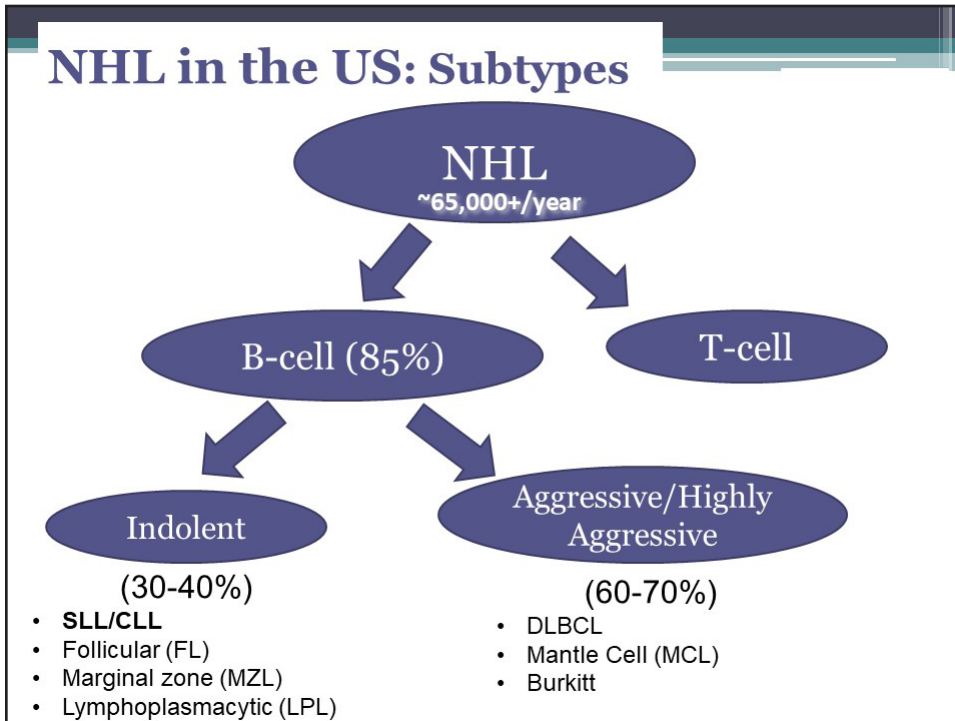
Slide 7. Leukemia in the US: 2016 Diagnoses

So, starting from the very beginning and perhaps for patients that are starting out at the beginning of this journey, if we talk about CLL it sometimes can be confusing. The ending – part of the CLL acronym, of course, is leukemia, but many patients will have enlarged lymph nodes and they’ll get classed with either the non-Hodgkin lymphoma and confusion can arise. Either way that you look at it, if you look at CLL as a chronic leukemia, again leukemia just being a word that means it involves abnormal blood cancer cells circulating around in the blood, CLL is the most common, at least in diagnoses. As you see, it’s close to acute leukemia, but because of the survival of CLL it is the most common leukemia in the US, with about 18,000 people diagnosed every year. And as I mentioned before, at least 150,000 living in the US.



Slide 8. NHL in the US: Subtypes

Another way, though to think of CLL or SLL as I'll review, is as a non-Hodgkin lymphoma. And even though it involves the blood, it also involves the lymph nodes, the marrow and the spleen as lymphomas do. And CLL is a type of lymphoma called a B-cell, and while I'll try to stay away from too much science and terminology, I think there are certain background things that are important to understand because it tells us about why we select the treatments and why some of the complications occur.

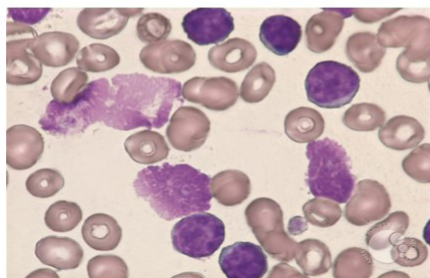


Slide 9. NHL in the US: Subtypes

So, of non-Hodgkin lymphoma about 65,000 in the US a year, about 85% of those are B-cells, and then we often talk about the B-cell lymphomas broken down to be aggressive or highly aggressive, or the indolent, which really just tells us about the type of cells. It obviously doesn't tell us, unfortunately, that every patient with CLL is going to have a very slow-growing or certainly never require treatment, but it does help us to understand different treatment options as well as what to expect. And so, about a third of the B-cell non-Hodgkin lymphomas are indolent and that's where CLL or SLL is often classified as well.

Chronic Lymphocytic Leukemia

- US Epidemiology:
 - Incidence: ~19,000/year
 - US Prevalence: ~130,000 cases
- Median age at diagnosis: 71 years
- Male to female ratio: 2 to 1
- Immunophenotype (CD5+ CD10- CD23+)
 - Differential (FISH)



Siegel et al. *CA Cancer J Clin.* 2015;65:5.
Maslak. ASH Imagebank. 2013. Image 19393.

Slide 10. Chronic Lymphocytic Leukemia

The median age of diagnosis of CLL is around 71 years at last count in the US, however, some patients are being diagnosed much earlier, that in part because of the routine testing of the blood, and many patients will be found asymptotically.

It is more common in men, about 2:1, compared to women. And the common – we talk about this word called immunophenotype, which really means again as a generalization, we're looking for a certain pattern on the surface of cells, to be able to try to differentiate it from other blood problems or other blood cancers.

CLL diagnosis: phenotype*

Blood
Lymph node Biopsy
Bone marrow bx (rarely)

- Immunophenotype

* Generalization for "typical CLL"

Slide 11. CLL diagnosis: phenotype*

When patients have it diagnosed sometimes it can be on a lymph node or in the bone marrow, but often it is on the blood. And what it is being tested for is taking your blood, essentially staining it for markers that look for almost like little flags on the surface of the cells, and if there are too many cells that look the same we call that monoclonal. And if we come up with a certain pattern that helps us determine what kind of problem it is.

CLL diagnosis: phenotype*

Blood
Lymph node Biopsy
Bone marrow bx (rarely)

- Immunophenotype
 - monoclonal B-cell (light chain restricted)
 - CD5+
 - CD19+
 - CD20 (dim), CD22 (dim), sIg(dim)
 - CD23+(bright)

T-cell marker*

B-cell markers*

* Generalization for "typical CLL"

Slide 12. CLL diagnosis: phenotype*

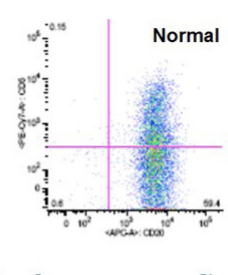
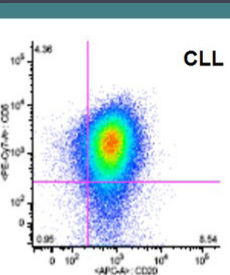
As I mentioned, often patients with CLL are diagnosed from the blood, but occasionally because it does involve the lymph nodes in many cases, patients might have had an enlarged lymph node or something found incidentally that was biopsied, and the same kind of testing can be done there.

Bone marrow biopsies are no longer required for the diagnosis. I highlight the word diagnosis because your treating oncologist very well may need the bone marrow biopsy to help decide why one of your other blood counts is low, or in other words, it would help with your treatment options moving forward. But in terms of requiring it for the actual diagnosis, the majority of patients can have that testing done on the blood or on the lymph node.

CLL diagnosis: phenotype*

Blood
Lymph node Biopsy
Bone marrow bx (rarely)

- Immunophenotype
 - monoclonal B-cell (light chain restricted)
 - CD5+
 - CD19+
 - CD20 (dim), CD22 (dim), sIg(dim)
 - CD23+(bright)
- Distinguish from mantle cell lymphoma (MCL)
 - immunophenotype
 - FISH: t11;14
 - Cyclin D1

T-cell marker*


B-cell markers*

* Generalization for "typical CLL"

Slide 13. CLL diagnosis: phenotype*

The pictures you see at the right, for those that are able to see the slides, is just highlighting the test that I mentioned, called flow cytometry, where the pathologists look to see if there's an abnormal population and then what patterns are there. And like I mentioned, each case is a little different, but if they do see a monoclonal B-cell, so a type of lymphocyte, which is a type of white blood cell, then they look for specific patterns. And for CLL what's unique is because it's a B-cell malignancy, you would expect to see B-cell markers. But we also see this marker called CD5 in the majority of cases. And this is what helps to distinguish. However, often the pathologists, either at diagnosis, or your oncologist on follow-up, will say that they need additional testing. And the reason for that is even though it's a classic pattern, not all CLL cases follow a classic pattern, first of all, and second of all, there are other lymphomas, mostly a type of lymphoma called Mantle Cell, that is also CD5 positive. So, when your oncologist does additional testing, it helps to absolutely try the best to distinguish it.

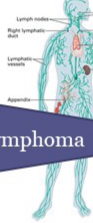
CLL vs. SLL vs. MBL




leukemia

CLL

- At least 5×10^9 monoclonal Bcells/L*
- May or may not be symptomatic



lymphoma



monoclonal + immunophenotype

SLL

- Small lymphocytic lymphoma
- $< 5 \times 10^9$ mBcells/L*
- + symptoms, cytopenias, LAD, or splenomegaly

Hallek et al. *Blood*. 2008;111:5446.
 Marti et al. *Br J Haematol*. 2005 ;130:325.
 Shim et al. *Blood*. 2014;123:1319.
 Biology:exploring life online. <http://bodell.mtchs.org>

* some variation in definition of malignant vs Bcells


Slide 14. CLL vs. SLL vs. MBL

I'd like to also clarify when we use these terminologies, CLL or SLL, some of this is historically based, meaning patients previously that mostly had elevation of their white blood counts and has this cell that looked like a CLL cell, were called CLL. But if the white count wasn't elevated and they had lymph nodes in the same cell, it was called SLL. And we still do use this terminology because it's helpful to understand maybe how patients do differently, but for the most part, as displayed here, I think of it as CLL or SLL, as continuums of the same type of the cell. And just like we don't completely understand why some patients do very well with CLL and others need treatment more quickly, I think we don't fully understand why some patients truly have the leukemia spectrum with no enlarged lymph nodes, but the bone marrow and the blood involved, and others have the other extreme, where we would call it SLL, meaning the lymph nodes are enlarged or they have symptoms, but that they might not have elevated white count or not.


CLL vs. SLL vs. MBL

CLL


- At least 5×10^9 monoclonal Bcells/L*
- May or may not be symptomatic



leukemia



monoclonal + immunophenotype



lymphoma

MBL

- Monoclonal B-cell lymphocytosis
- $< 5 \times 10^9$ mBcells/L*
- No symptoms, cytopenias, LAD or splenomegaly
- 1-2%/yr progress to CLL
- 2.5-5% or more of the population

SLL

- Small lymphocytic lymphoma
- $< 5 \times 10^9$ mBcells/L*
- + symptoms, cytopenias, LAD, or splenomegaly

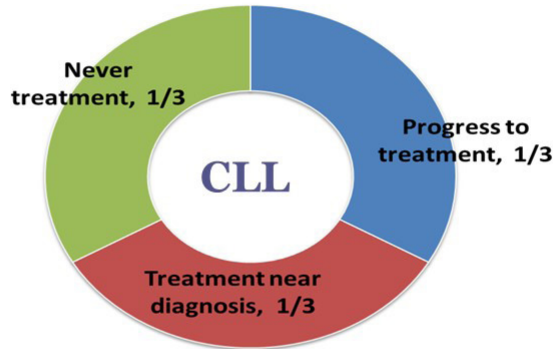
Hallek et al. *Blood*. 2008;111:5446.
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 Shim et al. *Blood*. 2014;123:1319.
 Biology:exploring life online. <http://bodell.mtchs.org>

* some variation in definition of malignant vs Bcells

Slide 15. CLL vs. SLL vs. MBL

And while you see numbers there, a lot of that is for our own keeping. But the one other category that I'll mention because I think also comes up is that immunophenotyping that I talked about, in other words, the way to look at the markers on the cell to decide what it is, is incredibly sensitive. And so, some patients that don't have any enlarged lymph nodes, don't have any evidence their other blood counts are abnormal, don't have any symptoms, and their white count might be normal, but at one point they had a little more lymphocytes than usual, if the flow is done on the blood, it can sometimes detect these same cells and it'll come back and say this is an abnormal cell type and it's in fitting with a CLL phenotype. But like I said, if all of those are actually within normal limits, I think it's just helpful to know that there is something called *Monoclonal B-cell Lymphocytosis*. And this is not uncommon. It can be up to 5% or more of patients in the United States. And again, it's important when you talk to someone, just because it's detected in the blood, but not all things are CLL or SLL. And that's helpful for patients to know in terms of what to expect.

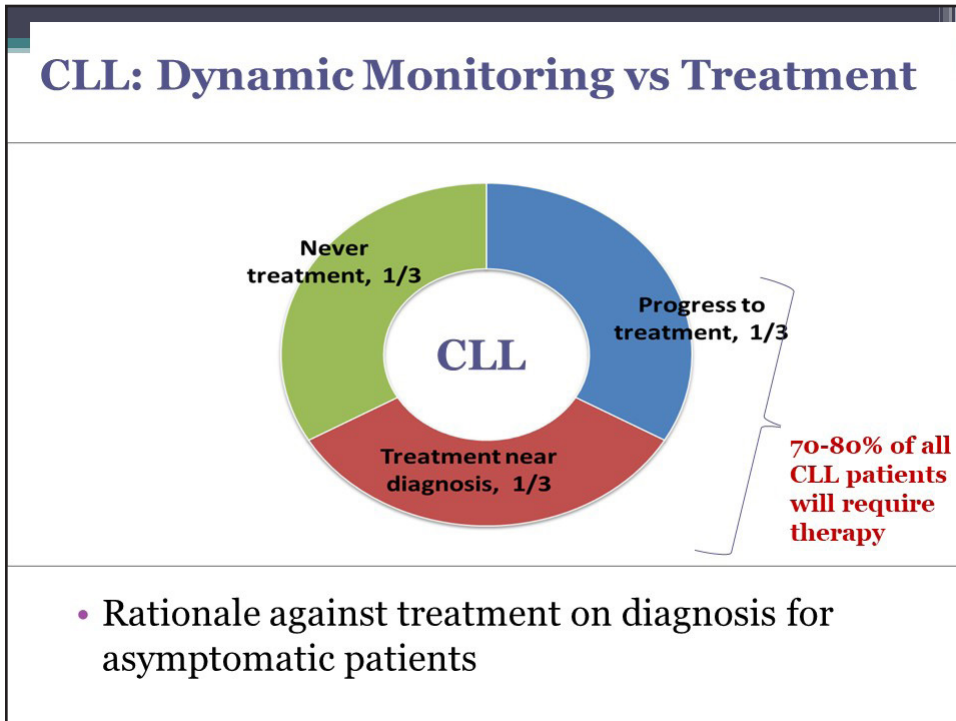
CLL: Dynamic Monitoring vs Treatment



- Rationale against treatment on diagnosis for asymptomatic patients

Slide 16. CLL: Dynamic Monitoring vs Treatment

As I said, and you'll hear the reoccurring theme, is one of the great pleasures in taking care of CLL patients is trying to help them understand their differences in CLL and what is involved in getting them the best care for their specific case. CLL is very different person to person and even though the majority of the patients I help to take care of have CLL or SLL, I can tell you that almost every person's journey is different. And one of the main ways that it differs is if I'm meeting patients for the first time after diagnosis, part of my job and part of what I feel is good care is not only telling and talking with patients what my recommendations are for that particular moment, but also what to expect moving forward. And if I say that patients differ greatly in how they do, one is whether they'll require treatment or not, about 25 or 30% of patients with CLL never require treatment for their CLL and are followed. And a lot of this, it doesn't make intuitive sense, I would say, even if you're feeling well and you're diagnosed with a new leukemia or lymphoma, I think it would seem human to all of us to want to do something about it. But because patients, not all patients require treatment as we'll talk about coming up, because there's other rationale, just know that the decision to start treatment is very important.



Slide 17. CLL: Dynamic Monitoring vs Treatment

So about 25 or 30% won't require, that still means about 70 to 80% of patients eventually will require treatment for the CLL. Many of these will be after years, but with a slow progression. And like I mentioned before, I'll now go into probably an over-simplified, but just a little bit that I like my patients, to try to explain to them, that when we talk about not needing treatment, it's not just that you don't need treatment or that there aren't treatments, but at every visit we're trying to weigh the risks of the therapies available along with the potential benefit. And while CLL is treatable, it's not curable, and there are also other few reasons that I hope patients can feel empowered, though certainly I would understand concern if you're not treating, because it's not just that you don't have to treat, it's that not treating in that particular moment actually has rationale behind it.

Rationale on asymptomatic early therapy

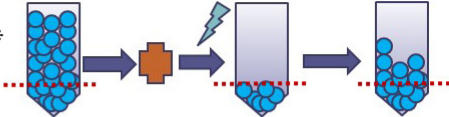
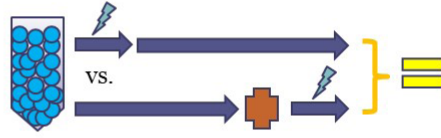
1. CLL is treatable, but not curable*

The diagram illustrates the rationale for asymptomatic early therapy in CLL. It shows a sequence of four vials connected by arrows. The first vial is full of blue cells. An arrow points to a second vial with a red cross, representing treatment. A lightning bolt symbol is above the arrow. The second vial has a red dashed line indicating a detection threshold. An arrow points to a third vial where the blue cells are below the red dashed line. A final arrow points to a fourth vial where the blue cells have increased above the red dashed line, indicating relapse.

Slide 18. Rationale on asymptomatic early therapy

So, one of the things about not treating patients, and I will, like I said, in a few slides here we'll go over what the things we are looking for to make the recommendations and talk in more detail about treatment, but one of the reasons that it's important to weigh that decision carefully is that while CLL is treatable, it's not curable. And so, what you'll see in the figure here is if you think of the CLL cells in the bone marrow or the lymph node there, and you're being followed and at some point reach indication for treatment, the number of CLL cells can go down, it could even go down below that red line, where it is being detected. And at the end of this we'll talk a little bit, too, about how we measure and detect CLL after treatment. But nonetheless in many, many patients, the typical expectation is that with a lot of treatments, outside of stem cell transplant, that we're always monitoring after treatment for the CLL to slowly gain back again, that it's treatable, but that we're probably not getting rid of every cell in most patients and eventually this builds back.

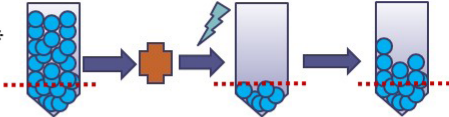
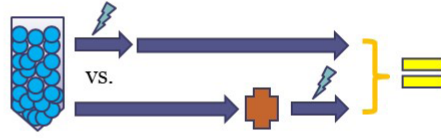
Rationale on asymptomatic early therapy

1. CLL is treatable, but not curable*

2. Studies of treatment at diagnosis vs. treatment on indications: no difference in survival


Slide 19. Rationale on asymptomatic early therapy

The second reason for why we weigh treating patients unless meeting indications, if they're asymptomatic, is in the 90s and through the early 2000's there actually have been a series of clinical trials as well as meta-analysis, meaning pooling together several clinical trials to look at even more patients, of asking the question of if patients receive treatment near the time of diagnosis versus waiting until they develop certain indications, do they do better long term? And again, by my simplistic picture here, I think what the studies have all shown, both with chlorambucil and FCR, is that at least with even intensive chemo and chemoimmunotherapy, that treating at symptoms or the indication for treatment as indicated by the orange plus, those patients did just as well, if not with less toxicity, than if they got the little lightning bolt of treatment first and then were followed.

Rationale on asymptomatic early therapy

1. CLL is treatable, but not curable*

2. Studies of treatment at diagnosis vs. treatment on indications: no difference in survival

3. Not all patients will require treatment and all treatments have some side effects

Slide 20. Rationale on asymptomatic early therapy

One point on that before I move forward, though, is that again everything is weighing risk and benefit, and as we have novel therapies coming out and as we understand more about the biology or why some CLL cells act more aggressively, that may change, depending on the patient's molecular risk profile, as well as some of these drugs get safer. And as an example, currently there are about several hundred patients enrolling in trials looking at ibrutinib for high risk CLL, as what we call an early intervention study. And other groups around the world are also working on that, now that we have novel therapies available.

Like I pointed out on the slide before, since about 20% will never receive treatment, not treating initially also gives a sense, if for the reasons above, of patients that never need exposure to the treatment, even the safest treatment isn't without risk.

Rationale on asymptomatic early therapy

1. CLL is treatable, but not curable*
2. Studies of treatment at diagnosis vs. treatment on indications: no difference in survival
3. Not all patients will require treatment and all treatments have some side effects
4. After treatment, the CLL can come back with more aggressive cells ("clonal evolution")

Slide 21. Rationale on asymptomatic early therapy

And then the final point is that if you think, when we to date have talked about CLL, I've made it sound like every CLL cell is exactly the same, but we know that's not true. Within one patient we can sometimes find subtle or big differences inside the CLL cells of the profile. And when this is treated, what tends to happen is the perhaps weaker cells or the less aggressive cells are selectively killed off, and then the cells that grow back are more aggressive. I highlight this just so that it's another reason why we take the treatment indication very seriously.

Treatment indications: Risks vs. Benefits

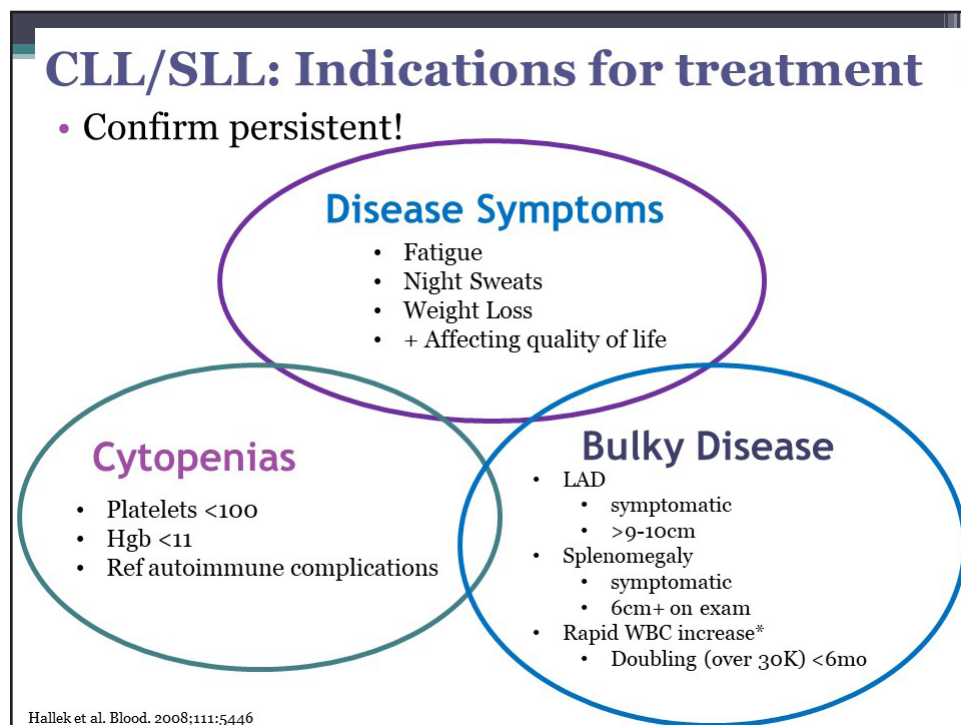


Amazon.com.uk

Slide 22. Treatment indications: Risks vs. Benefits

But again, should not be interpreted as a fear for if you meet indications at that point, then as I mentioned before, everything is weighing risks and benefits, and so it is – many studies showing that when the indications are nearing, then all those risks that I talked about treating too early, have now tipped in the favor of the benefit of therapy at that point.

So, if we talk about the background and then we talk about why not to treat, then naturally the question is, well, what am I being monitored for, when I walk in, what can I expect that you're looking at to decide if I need treatment or if now the timing of treatment has arrived?



Slide 23. CLL/SLL: Indications for treatment

And while there's a list of different indications, it's well summarized by the International Working Group of CLL, or the iwCLL, and like I said, there's a list, I won't cover all of them, but generally many of those things can be divided into 3 main buckets or 3 main categories or reasons. And you don't need all of them, it's really just one of them, and importantly that it's persistent, and as I'll talk about, that it's not in the setting of infection, surgery or other reactive scenario, where the CLL can somewhat flare and go back to normal.

So, the 3 categories are disease-related or what we often say B-type symptoms – fatigue, night sweats or weight loss – and not just having them, but have changed the quality of life. Again, we're weighing the risks and benefits of the therapy. If there's bulky disease, so either any lymph node that's symptomatic, causing a problem, or if it gets very large where the concern is not treatment could change into a problem. Similarly, with spleen, are both the size as well as the symptom component.

The rapid white blood count doubling is particularly important, to make sure this isn't during a period of infection or other reactivation. And while the white blood cells are not harmful in CLL unless numbers of the white count are getting usually over 400, sometimes just that doubling can give you indication that something is changing with the CLL.

And then finally the cytopenias, as I use the analogy in clinic sometimes, is that probably the reason we don't do a bone marrow unless there's a specific question about a low blood count, is because I pretty much expect, by the nature of CLL, that every patient is going to have CLL in their bone marrow. So, we don't need to look to know if it's there, we know it's there. But for some patients it's a low level and almost like weeds in a garden, so yes, you would like the weeds not to be there, we can accept them to be there if they're not affecting the other garden cells. The other garden cells in this case being your red blood cells and platelets. Or in other words, the hemoglobin or the platelet count. But if those numbers get low or there's refractory autoimmune cytopenias, then these together, any one of them that is persistent, can be a reason that we recommend starting treatment.

As you'll notice there, I didn't list anywhere a white count of 100 or 110, and part of that is because these are tiny cells that aren't made to stick to your blood vessels. Your normal lymphocytes, which CLL cells are felt to be the blood cancer that develops from lymphocytes, but lymphocytes in our blood that help with infection are tiny cells and they're not sticky, they're not made to stick to the blood vessels.

CLL/SLL: Indications for treatment

- Confirm persistent!

No magic WBC threshold in the iwCLL indications!!

Disease symptoms

Cytopenia

- Platelets <
- Hgb <11
- Ref aut

Advanced Disease

of life

atic

<6mo

Slide 24. CLL/SLL: Indications for treatment

So, while you might have a friend or family or colleague or coworker who had a different type of leukemia, where they had to start treatment of the white count, that's totally different because in other leukemias the cells are big and meant to stick to the vessels and go into the tissue. This is not the case in the CLL. And so, there's no magic white count where patients require treatment.

Traditional Prognostics: Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	Low risk (Rai 0): > 10 years
I	Lymphocytosis + lymphadenopathy	05
II	Lymphocytosis + > spleen and/or liver	72
III	Lymphocytosis + anemia (Hgb < 11 g/dL)	00
IV	Lymphocytosis + platelets < 100	30

Binet	Findings	Survival (mo)
A	Hgb ≥ 10, Plts ≥ 100, < 3 involved areas*	> 120
B	Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas*	84
C	Hgb < 10, or Plts < 100	24

*Involved areas include cervical, axillary, or inguinal nodes, spleen, or liver.

Rai et al. *Blood*. 1975;46:219.
Binet et al. *Cancer*. 1981;48:198.

Slide 25. Traditional Prognostics: Staging Systems

So far, we've talked about why not to treat, unless there's symptoms, what we look for in order to treat, and then naturally the question is, well, if not all patients require treatment, what can I expect? Less than a third of patients fortunately need treatment at the time that they're diagnosed, so for the other two-thirds of patients, it's helpful information, based on what we call prognostic or predictive or biomarkers, you might have heard various terms, of just knowing what to expect in terms of whether you're more likely to require treatment over coming years.

The other key that I'll highlight is while these markers before were mostly used to counsel in what to expect, now with the novel therapies as first treatment, we're using a lot of these markers to also help us make treatment decisions. So, they're no longer just here's information, it also is helping with our treatment choices.

Traditional Prognostics: Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	Low risk (Rai 0): > 10 years
I	Lymphocytosis + 1	Intermediate risk (Rai I): ~7 years
II	Lymphocytosis + 2	High risk (Rai II): ~5 years
III	Lymphocytosis + 3	Very high risk (Rai III): ~3 years
IV	Lymphocytosis + 4	Very high risk (Rai IV): ~30 months

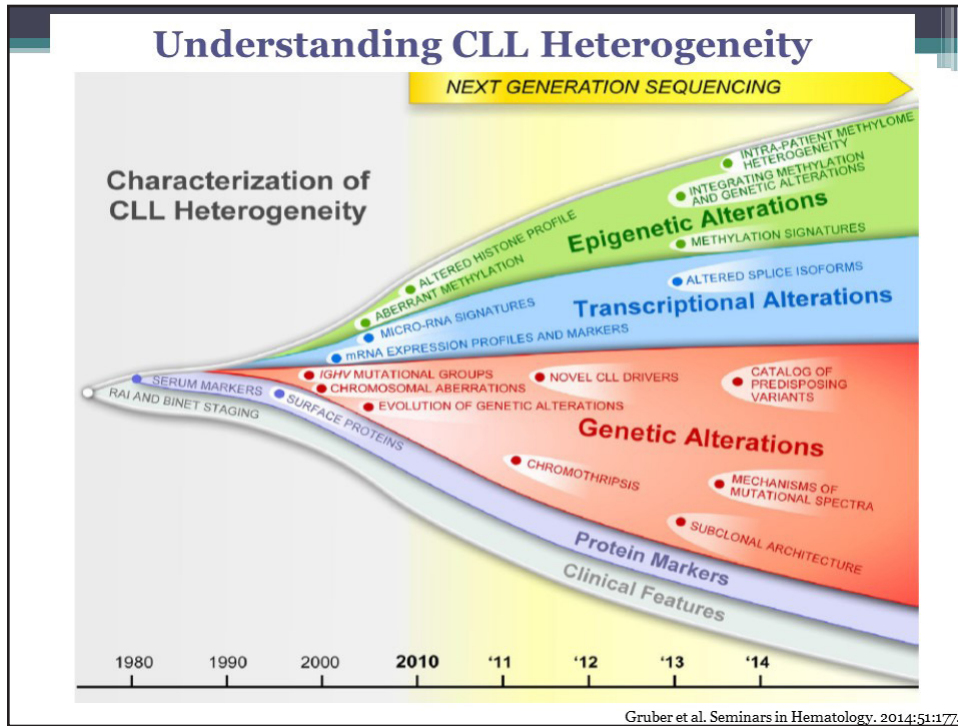
Binet	Findings	Survival (mo)
A	Low risk	> 120
B	Intermediate risk	84
C	High risk	24

Treatments and supportive care available very different today

Rai et al. *Blood*. 1975;46:219.
Binet et al. *Cancer*. 1981;48:198.

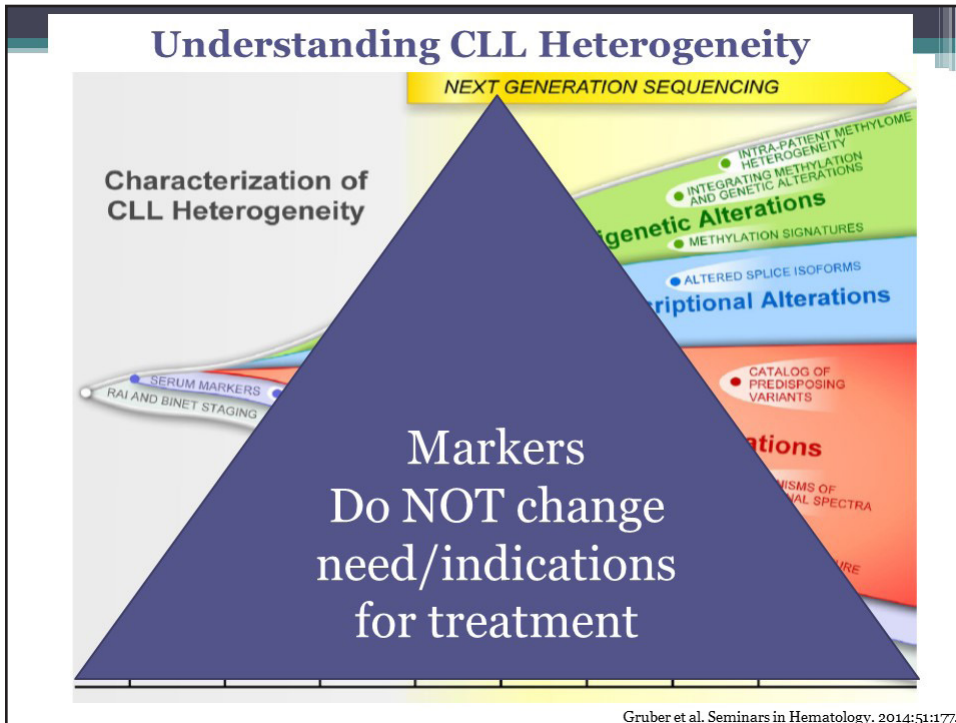
Slide 26. Traditional Prognostics: Staging Systems

In the past, and if we go back several decades, the clinical exam and the basic labs were the most we had for prognostic systems. And so, while some naturally want to know what stage they are, Rai staging and Binet staging, depending where you live in the world, were made to be readily available with basic labs and exam. And in fact, at the time they did help patients to know what to expect, if you were lymphocytosis only, if you had an enlarged spleen or if you were high risk with low counts, but as you'll see in red, for those that can see the slide in the corner, these staging systems were developed in the 60s and 70s and the treatments have greatly changed. So, while this is helpful for clinical trials to keep track of, I caution patients, please do not interpret the survival from these studies because this was during a very different era, and you'll see that theme going forward.



Slide 27. Understanding CLL Heterogeneity

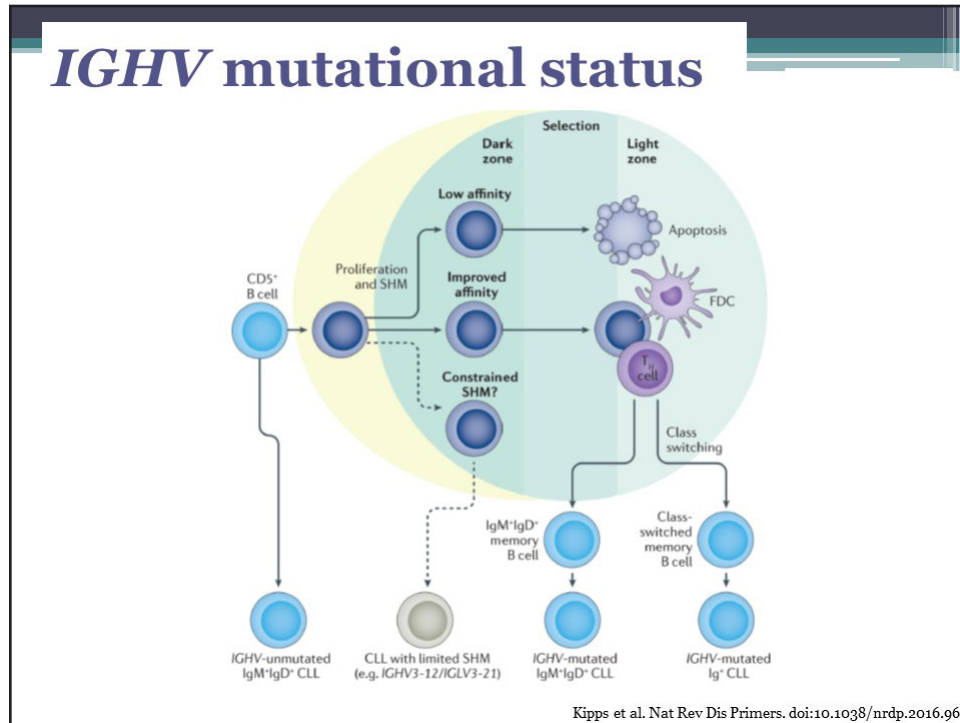
So if the staging systems were more basic, how do we come up with more – and this is an overwhelming slide, not meaning to read everything on it, but the timeline, which is along the bottom going left to right, from the 1980s through present day, what you'll see there, first just the clinical staging systems, and then without reading anything individually, hopefully what can just be appreciated, is through the help of those dedicated to research and patients that have been kind enough to participate in clinical trials and studies, is identifying all these other markers that can help in trying to understand why patients have different courses, as well as what treatment might be best.



Slide 28. Understanding CLL Heterogeneity

You could see a huge list of these and sometimes it's very difficult. One shouldn't and can't send all the markers. And secondly, it is helpful to know what are the key ones if we're picking a few, because they aren't just additive. Meaning if you have had a lot of testing, we can't just add a point for each and that makes higher risk. Some of the markers we know group together, etcetera, but again just highlights, moving forward, what they can.

But all the things that I've gone over so far about indications for treatment and why we treat, until the ongoing trials look at high risk CLL, right now the return of those markers should not prompt a change from dynamic monitoring to needing treatment, though they do help with treatment choices.



Slide 29. IGHV mutational status

I promise to stay away from too many detailed slides and only introduce the biology and immunology part of things when I thought it was really important, but of the prognostic markers, the molecular and genetic ones of the CLL, the mutation status is one where I think it's helpful to just have a general sense of the normal development of B-cells, to understand what the marker means in terms of if it's tested on your blood or your bone marrow.

The IGHV, what it stands for is basically a part of antibodies that all of our immune systems make to help fight infection. And so, our normal blood cells wouldn't be able to make the diversity of antibodies if we only had the blueprint or genetic information that we're born with. Our cells physically couldn't carry enough information and then to be able to make the diversity. And so, as a natural expected process, our blood cells are able to take the genetic information, and specifically for antibodies, move it around and mutate it. And that's what helps to create the diversity. It also, though, can be a marker of development. So, for those that have had the IGHV, and as I'll summarize, mutated, which happens in the normal cells as a more mature cell mutated, generally patients with a mutated IGHV might either have a slower or never require treatment. And it also is an important marker in knowing expectations to treatment. But it sounds a little backwards until you understand the development of the B-cell because normally we think of mutated as bad. But in this case mutated is generally expected to have a more favorable course.

FISH

- Late 1980-1990s: FISH (interphase)

	Chromosome banding		Interphase cytogenetics	
	<i>n</i>	%	<i>n</i>	%
Trisomy 12	112/604	19	36/245	15
Structural 13q aberrations	62/604	10	129/245	53
Structural 11q aberrations	49/604	8	48/250	19
Structural 6q aberrations	36/604	6	18/208	9
Structural 17p aberrations	22/604	4	20/243	8

N Engl J Med. 2000;343:1910.
J Mol Med. 1999;77:266.

Slide 30. FISH

The second genetic and molecular test that I'll highlight, that I use for patients, is what's called FISH testing, which is a probe. And when we talk about these genetic and molecular changes, it's really important to know that this happens in the leukemia cell after it becomes a leukemia. So, these are not changes that you were born with and they're not in the cells, they're only in the leukemia cells, so not in the cells that would get passed on blueprint-wise to children. So, if you find a report where it says you have a FISH abnormality with 13q, that is not an inherited or a passed on change.

(Brief) Summary of Genomic/Molecular Prognostic Factors

- **FISH defects**
 - 17p deletion
 - 11q deletion
 - 12q trisomy
 - Normal
 - 13q deletions

Hierarchy

Unfavorable

Favorable

Slide 31. (Brief) Summary of Genomic/Molecular Prognostic Factors

But what FISH has done is changed our appreciation of the diversity in CLL, as highlighted here. And generally, we think of the FISH changes, as I've mentioned a couple of times as an illustration, that 17p is considered unfavorable and traditionally not respond well to chemo, whereas 13q by itself is considered favorable, with the others falling in between.

(Brief) Summary of Genomic/Molecular Prognostic Factors

- **FISH defects**
 - 17p deletion
 - 11q deletion
 - 12q trisomy
 - Normal
 - 13q deletions
- **Immunoglobulin heavy chain variable region (*IGHV*)**
 - **≤ 2% mutation = unmutated**
 - Unmutated: higher risk

Hierarchy

Unfavorable

Favorable

Slide 32. (Brief) Summary of Genomic/Molecular Prognostic Factors

And when you add in the mutation status, it can also help additional information as well as treatment choices.

(Brief) Summary of Genomic/Molecular Prognostic Factors

- FISH defects**
 - 17p deletion
 - 11q deletion
 - 12q trisomy
 - Normal
 - 13q deletions
- Immunoglobulin heavy chain variable region (IGHV)**
 - $\leq 2\%$ mutation = unmutated
 - Unmutated: higher risk
- CD38 status ($\geq 30\%$ = higher risk)**
- ZAP-70 status ($\geq 20\%$ = higher risk)**

Hierarchy (indicated by a bracket grouping FISH defects and IGHV status)

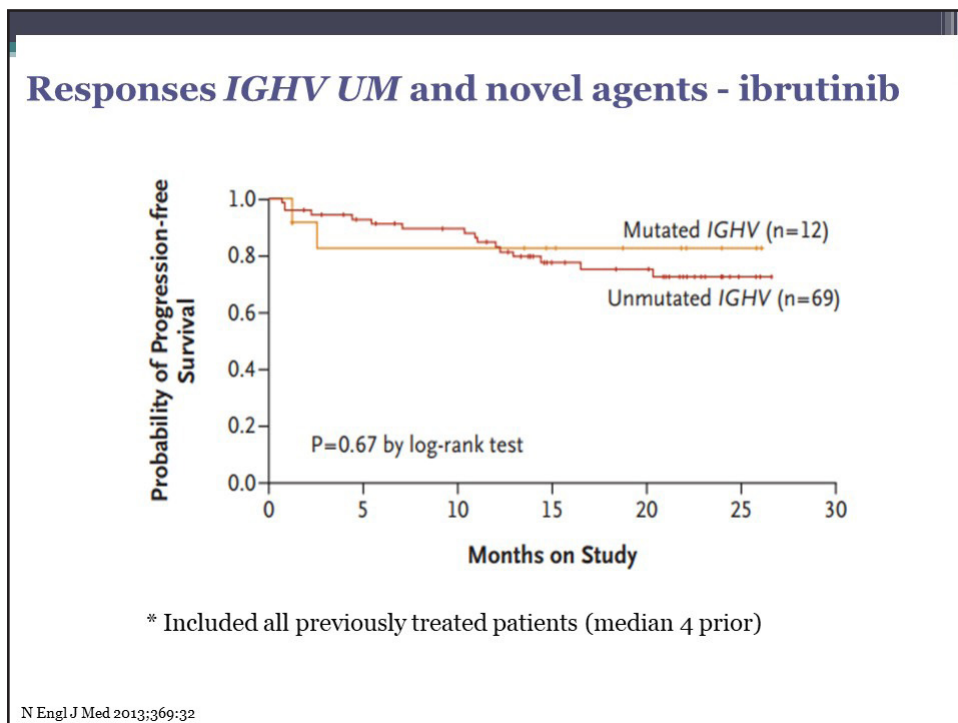
Unfavorable (indicated by an upward arrow)

Favorable (indicated by a downward arrow)

Often included with flow but IGHV more important and less variable (indicated by a bracket grouping CD38 and ZAP-70 status)

Slide 33. (Brief) Summary of Genomic/Molecular Prognostic Factors

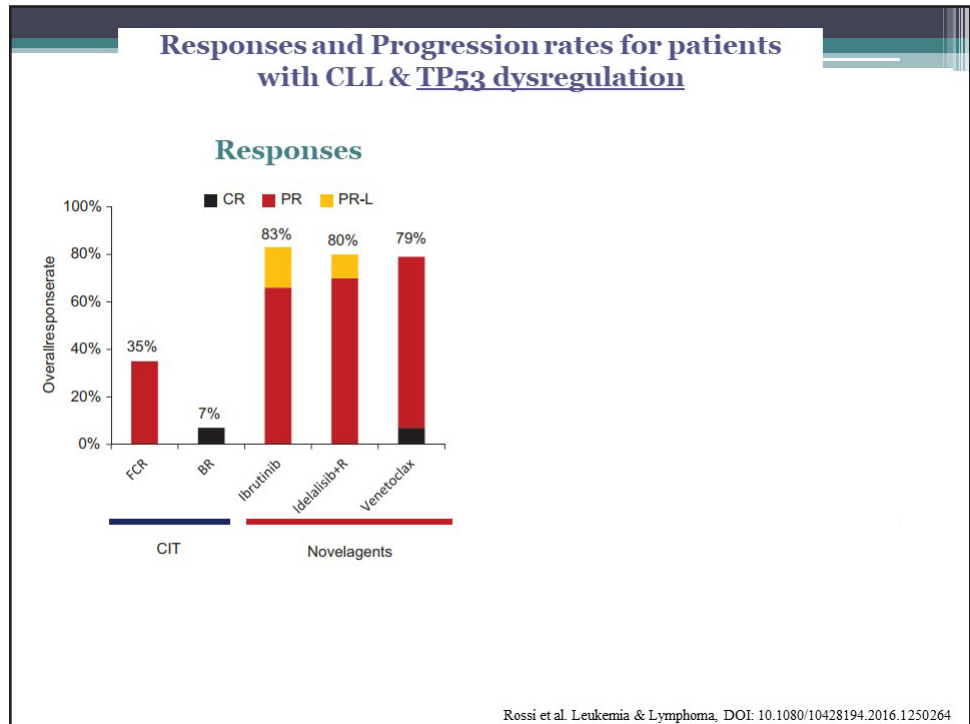
Also with flow cytometry patients will also have CD38 or ZAP-70, and these tend to associate with mutation status, so not 100%. And so, in general while we continue to look at them in terms of a clinical trial, I consider the mutation status to so-call outweigh the 38 or ZAP-70, in part because of the testing and the way this changes with time.



Slide 34. Responses IGHV UM and novel agents - ibrutinib

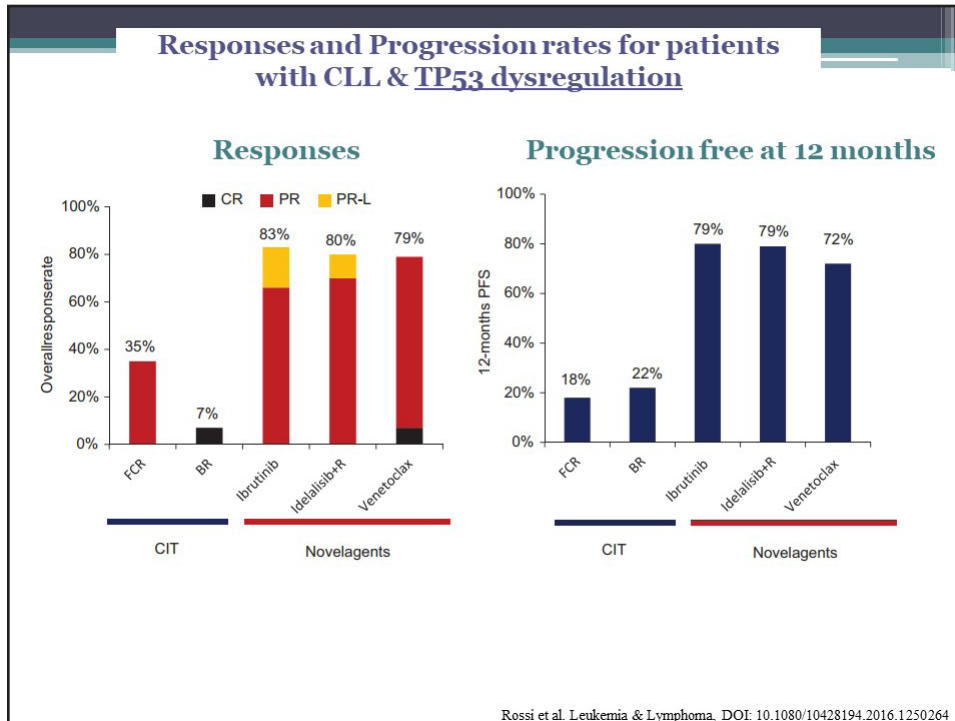
As I said before, I hesitate to put anything as unfavorable because most of the studies again were done historically in how patients responded and did with treatment, and so just to highlight where hopefully things are moving forward, that

what we're seeing with IGHV mutation is that with time, this is the red line and the yellow line, how patients are doing, and unmutated versus mutated, with the novel agents, specifically ibrutinib, responses and duration of responses, reassuringly look better. So, in other words, these are the important markers we go by now, this may change with time.



Slide 35. Responses and Progression rates for patients with CLL & TP53 dysregulation

Part of what I highlighted was looking at these markers, to help with treatment choices. And I think what highlights it perhaps best is looking at deletion 17p, which deletes the protein TP53. So, we call this either a mutation or a deletion TP53 dysregulation, which classically was the highest risk for not responding as well to treatment, or staying in response to treatment as well. And so, the importance I think of testing and knowing even as a first treatment, is somewhat highlighted here, looking at patients with relapsed disease, who were treated either with a novel agent or with chemoimmunotherapy. That doesn't mean that chemotherapy can't help some patients, and we'll get to that in a minute, but at least for TP53 dysregulation, the importance of checking FISH and mutation status, is that it can help guide treatment, because classically these did not respond well to chemotherapy.



Slide 36. Responses and Progression rates for patients with CLL & TP53 dysregulation

That was responses. This is looking at duration of responses. And certainly, caution that this was taken from several clinical trials, but in my own practice, too, because of what we know, what TP53 does, if that is abnormal, then generally chemoimmunotherapy is not the best treatment choice.

Low frequency of FISH/IGHV testing

- Connect CLL US Database (2010 – 2014)
 - First line (n=889)
 - Second line (n=260)

Test	% tested (first line)	% tested (2 nd line)
Metaphase cytogenetics	39%	31.2%
FISH	58%	40.4%
IGHV	7.9%	5%

Mato et al. *BJH*. 2016;175z:892

Slide 37. Low frequency of FISH/IGHV testing

I highlight this because I think the testing for CLL, certainly before first treatment, is important because, as those slides point out, the novel agents work by different mechanisms, and so even in the highest risk TP53, they can work well. And you

can't know to do that without the testing. And in one of these cross-sectional studies, looking at – or across the US studies looking at the Connect CLL database, at least historically FISH testing hasn't been performed in the majority of patients, either at the time of their first treatment or in relapse. And the mutation status performed even less.

Now some of that is that particularly the mutation status previously was a very cumbersome test and very difficult to perform. Certainly, most labs couldn't perform. However now it is in general available pretty widely as a send-out test, even if not available at your own treating facility.

Summary: diagnosis & initial work up

- Flow cytometry
- Laboratory testing
 - CBC, CMP
 - LDH
 - B2M
 - FISH
 - IGHV mutation analysis
 - Others by case (if need treatment: TP53 mutation and full chromosome analysis)

x

Slide 38. Summary: diagnosis & initial work up

So, to summarize, at diagnosis and initial work-up, we talked about flow or immunophenotyping are other ways to identify and confirm the diagnosis, and then on labs, in addition to knowing baseline counts and kidney and liver function and some baseline markers, the FISH and the IGHV I think are particularly important. In general, I don't always send chromosomes or TP53 and that you would discuss with your doctor, unless you were starting treatment again because TP53 mutation could help change the treatment choices.

Summary: diagnosis & initial work up

- Flow cytometry
- Laboratory testing
 - CBC, CMP
 - LDH
 - B₂M
 - FISH
 - IGHV mutation analysis
 - Others by case (if need treatment: TP53 mutation and full chromosome analysis)
- Imaging
 - Not needed for most patients
 - High risk
 - symptoms
- Bone marrow
 - Not needed unless for low counts or would change treatment recommendations

x

Slide 39 Summary: diagnosis & initial work up

And we already reviewed, but bone marrow is not needed in all patients unless trying to decide, for example, if the anemia is due to the CLL or other cause, but certainly don't need it for a diagnosis in every patient. It might be so in follow-up to look for a response to treatment.

And in terms of CT scans or imaging, the key part of that that I highlighted, particularly for patients in this dynamic monitoring, and outside of a clinical trial, that most patients with CLL that do have enlarged lymph nodes can be followed by exam and similar is true for the spleen. And in fact, because we hope for this to be living with CLL truly, that we don't want to get into a pattern, unless on active treatment or a clinical trial, where you're constantly being scanned just as monitoring.

It's very unusual, for example, for a lymph node, if you have lymph nodes involved in the neck and the abdomen or the belly, for one in the belly to grow out of proportion to the ones that you see in the neck.

Highlights of CLL Treatment Options

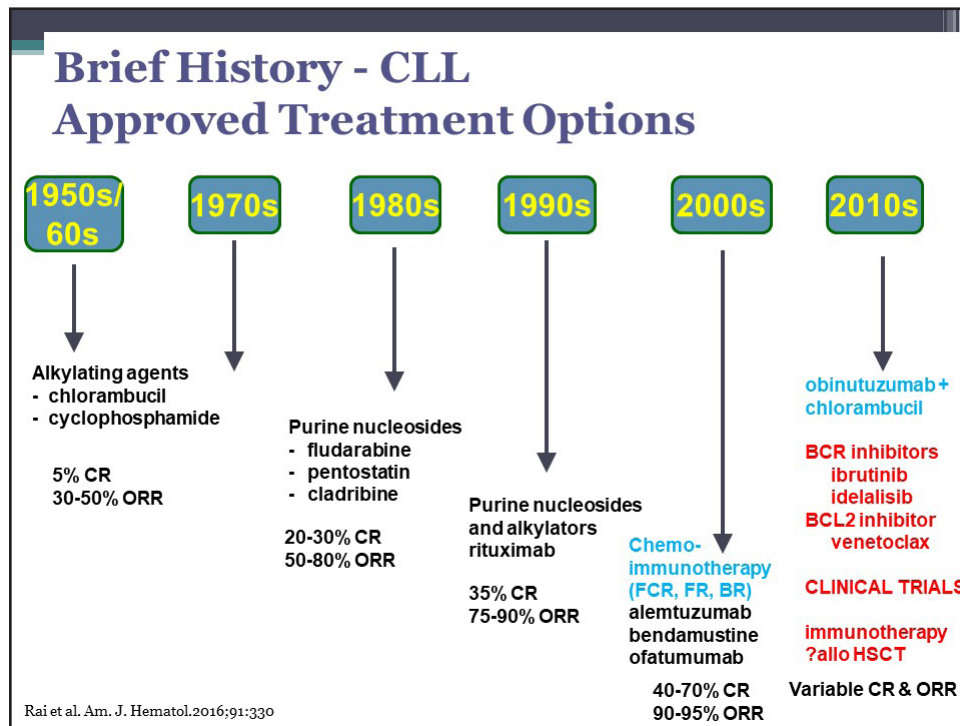
Slide 40. Highlights of CLL Treatment Options

So now moving into the second half really, which is highlighting the treatment options.

Clinical Trials!

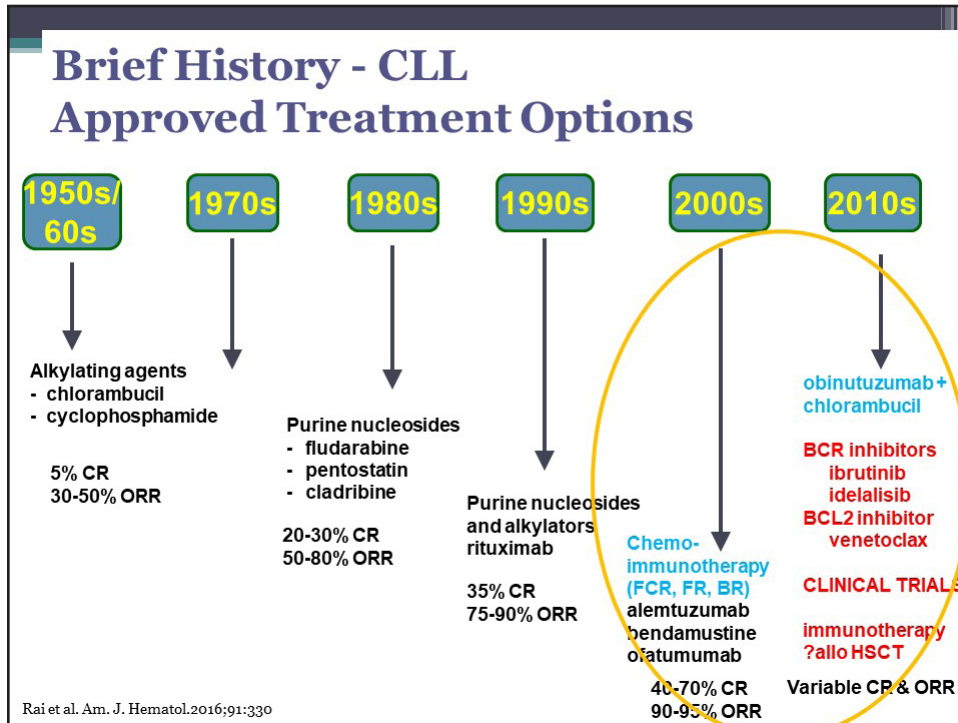
Slide 41. Clinical Trials!

And again, really just is another appreciation to all the patients that are participating in clinical trials. Certainly, our hope with it is to benefit the patient directly, but I certainly know that it involves of their time and resources, but I hope that it benefits both the patient and it certainly benefits all the patients we're subsequently treating.



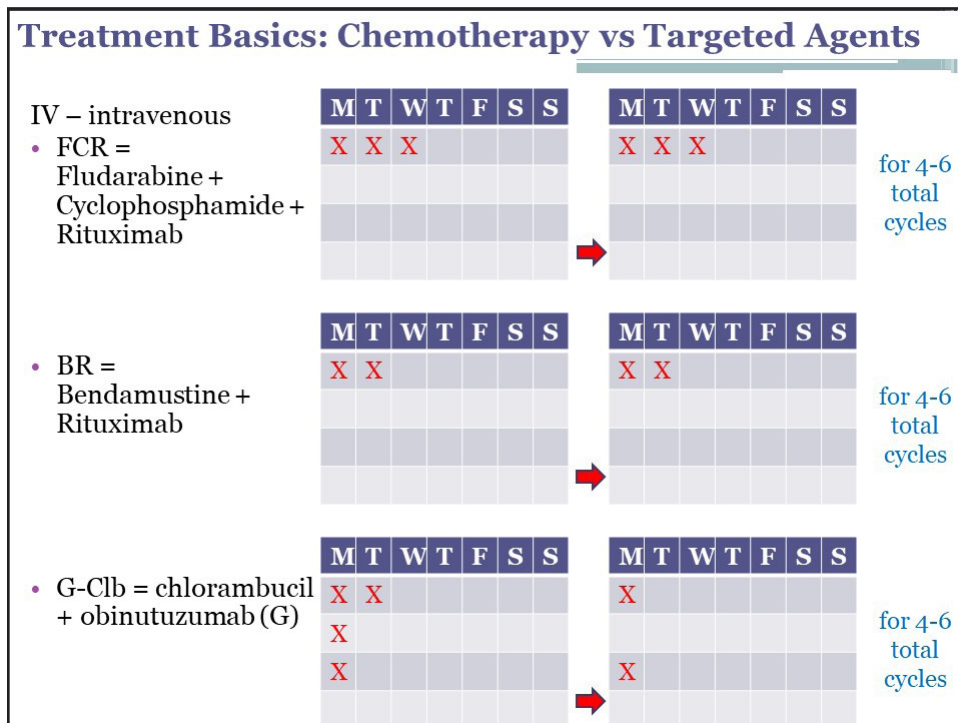
Slide 42. Brief History – CLL Approved Treatment Options

As I've highlighted, some of the studies that have been done on the trials haven't just been about the response to treatment, but what the CLLs are doing when this is studied in the lab, and so for the researchers really working to further this, it's a huge thank you to the patients that participate.



Slide 43. Brief History – CLL Approved Treatment Options

We won't go over this in detail. The themes I want to highlight is that really the past few years have seen great growth in switching from just chemo options to antibody options, which is what rituximab is, a next generation, to now highlighting the novel treatments that target these pathways.



Slide 44. Treatment Basics: Chemotherapy vs Targeted Agents

And just as a general overview for patients maybe thinking about treatment or not knowing what to expect, the differences between chemo and what we call the targeted agents aren't just about what their target is, but about administration and

what to expect. And so, a bit of a simplification because certainly treatments don't need to start on the Monday of a month, but FCR is a combination of chemo plus rituximab, which is an antibody, and that's in general given 3 days out of every 4 weeks. And so, in this case when we talk about a cycle we talk about a pattern of treatment that is repeated and that's repeated 4 to 6 cycles. However, each person again differs and I just highlight that because sometimes, depending on the risks of treatment, we do make, especially that first month, some changes in how we give the rituximab to try to minimize reactions. Whereas bendamustine-rituximab is given every 2 days, but also similarly for 4 to 6 of these repeating cycles. And chlorambucil and obinutuzumab is a little different in that the first month the antibody or the obinutuzumab is given more frequently, and then basically moves to the antibody once a month and the chlorambucil twice a month.

Treatment Basics: Chemotherapy vs Targeted Agents

PO – by mouth

- **ibrutinib**
 - targets BTK
- **idelalisib + rituximab**
 - targets PI3Kdelta
 - specific rituximab schedule (limited)
- **venetoclax**
 - targets BCL2
 - dose ramp up (5 weeks)
 - sometimes given with anti-CD20 antibody

M	T	W	T	F	S	S
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X

M	T	W	T	F	S	S
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X

M	T	W	T	F	S	S
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X
X	X	X	X	X	X	X

Targeted drug given continuously unless not tolerated or resistance develops

Slide 45. Treatment Basics: Chemotherapy vs Targeted Agents

This differs at least in how it's given than some of the agents, when we talk about novel or targeted drugs. And really this just means that the targeted drugs go after specific things inside the cell, although they can sometimes hit other targets, as we'll talk about.

Most of these agents to date, except in the context of a clinical trial, are given continuously, meaning the by mouth part, the ibrutinib, the idelalisib, or the venetoclax, are taken every day, unless there's a problem tolerating it or unless the CLL progresses on it.

Treatment Basics: Other Terminology

iwCLL Responses

- Complete Response (CR)
- Partial Response (PR)
- Partial Response + lymphocytosis (PR-L)*
- Stable Disease (SD)
- Progressive Disease (PD)

Duration of Response & Survival

- Progression Free Survival (PFS)
- Overall Survival (OS)

x

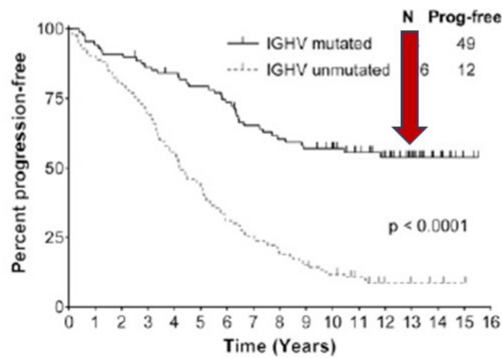
Slide 46. Treatment Basics: Other Terminology

So just some other terminology to keep in mind is that some of this is historical; we talk about complete responses, meaning the CLL is all gone. Partial responses, partial response of lymphocytosis, meaning you've had half of it go away, in the blood or the lymph nodes. Stable disease or progressive. But stable can happen for a while, especially for these newer drugs and that doesn't necessarily mean a bad thing. And then some of the other terminology we'll talk about is both the duration of time without needing the CLL treated again, as well as the survival.

Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

FCR

- **MDACC:** 300pts received treatment with FCR
 - Plateau in PFS: no relapses beyond 10.4 years in 42 patients with favorable risk (mutated IGHV, no del17p or del11q)



Blood. 2008;112: 975-980.
Blood. 2015;126(16):1921.
Blood. 2016;127(3):303.
Blood. 2016;127(2):268.
Blood. 2015;126(16):1921.

- Similar plateau in CLL8 and Rossi et al FCR studies

Slide 47. Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

So, as I mentioned, that chemotherapy is still appropriate and used by many patients, particularly as a first treatment. And some of that again is weighing risks and benefits. And from what we know about CLL, if patients can benefit long term, then perhaps the benefit of the combination of drugs outweighs the risk. Particularly those with a mutated IGHV, and 3 different studies some of those patients have not relapsed very long at 8 and 10 years. So again, just highlights the importance of how we use some of these drugs moving forward.

Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

Bendamustine and Rituximab

- CLL10 (FCR vs BR frontline): 561 randomized
 - Severe infections all pts: 39.8% vs. 25.4% (NS)
 - Infections older pts: 48.4% vs. 26.8% (p=.001)
 - PFS: NS difference in age > 65yo
 - M-IGHV improved PFS, no interaction with treatment type
 - No difference in OS to date

Lancet Oncol 2016; 17: 928.

Slide 48. Rationale for frontline chemoimmunotherapy (CIT): durable remissions for some patients

I also highlight bendamustine-rituximab, which is a common regimen, and was compared directly to FCR. And essentially for patients over age 65, even if FCR gets rid of more leukemia in more patients, the infection and the risk come up, again highlighting that risk versus benefit seems to change as patients are more experienced in life.

Anti-CD20 antibodies: obinutuzumab (G)

- 781 CLL, treatment naive
- Randomized 1:1:1
- Median PFS advantage (R-Clb vs G-Clb 15.2 vs 26.7 mo)

Regimen	Complete response (%)	Partial response (%)	Total Response (%)
G-Clb (N=238)	22.3	55.0	77.3
Clb (N=118)	0	31.4	31.4
R-Clb (N=233)	7.3	58.4	65.7

N Engl J Med. 2014;370:1101

Slide 49. Anti-CD20 antibodies: obinutuzumab (G)

And then finally the chemo-based regimen I'll mention is that even though chlorambucil is a pill, that we still consider it traditional chemo. But obinutuzumab is like a next generation rituximab, so it goes after the same thing as an antibody and in a study where it was compared to chlorambucil by itself and to rituximab, appeared to get more deep responses.

Chemoimmunotherapy (CIT): Considering the Toxicities

original article
The frequency, manifestations, and duration of prolonged cytopenias after first-line fludarabine combination chemotherapy
S. Joffe, D. Coma, D. Abner, M. Wolf, D. Rosenfarb, M. Pines, L. M. Jankowsky, R. C. Byrd

Opportunistic Pulmonary Infections With Fludarabine in Previously Treated Patients With Low-Grade Lymphoid Malignancies: A Role for Pneumocystis carinii Pneumonia Prophylaxis
John C. Byrd, Jeffrey H. Hoegge, Karl E. Kuster, Dawn H. Houghness, Sarah W. Knudsen, Christopher H. Pevsner, et al. J Clin Oncol. 2008;26:2431-2448.

Listeriosis in Patients with Chronic Lymphocytic Leukemia Who Were Treated with Fludarabine and Prednisone
Elin Aronson, MD, Richard P. Kasperbauer, MD, Hays Kaminiski, MD, Leah Elting, PhD, James S. Heston, MD, and Richard Kasper, MD

Annals of Internal Medicine. 1992;117:466-469.
British Journal of Hematology. 1999;105:445-447.
JCO. 1998;16:1885-1889.
Hematol Cell Therapy. 1996;38:359-360.
Clin Lab Haem. 2006;22:175-178.
Blood. 2008;111:1820-1826.

Addressing risks

- Support cytopenias: can recover without complications
 - In long term follow of CLL8, prolonged cytopenias did not translate to increased MDS/AML
- Assessing DAT positivity
 - AIHA in 8% DAT-neg patients; 28% DAT-positive patients
- Prophylaxis for infections

Annals of Oncology. 2010; 21: 331-334.
Clin Oncol. 1995; 13:2431-2448.
Blood. 2008; 112: 975-980.
American Journal of Hematology. 1995; 49: 135-142.
J Clin Oncol. 1995;13:2431-2448.

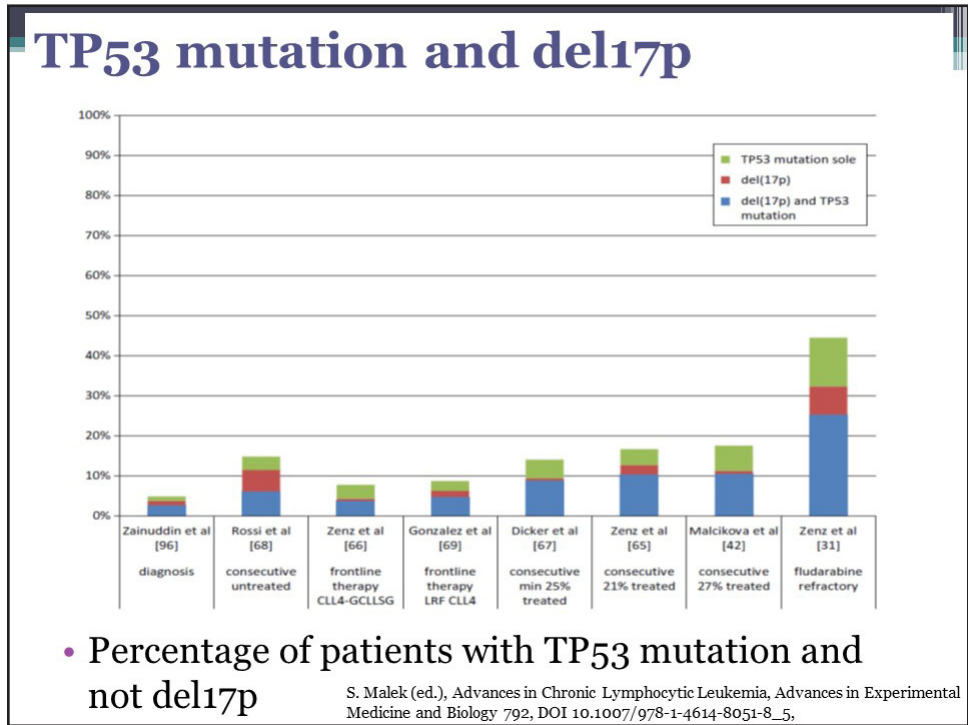
Slide 50. Chemoimmunotherapy (CIT): Considering the Toxicities

Before we move into the ending part on focusing on the novel inhibitors, the thing that I'll say is that even if we learn which patients perhaps respond best, I think we still continue to learn how to lower the toxicities as best we can. And some of this has changed because more supportive care has been involved over the years.

Novel Targeted Inhibitors

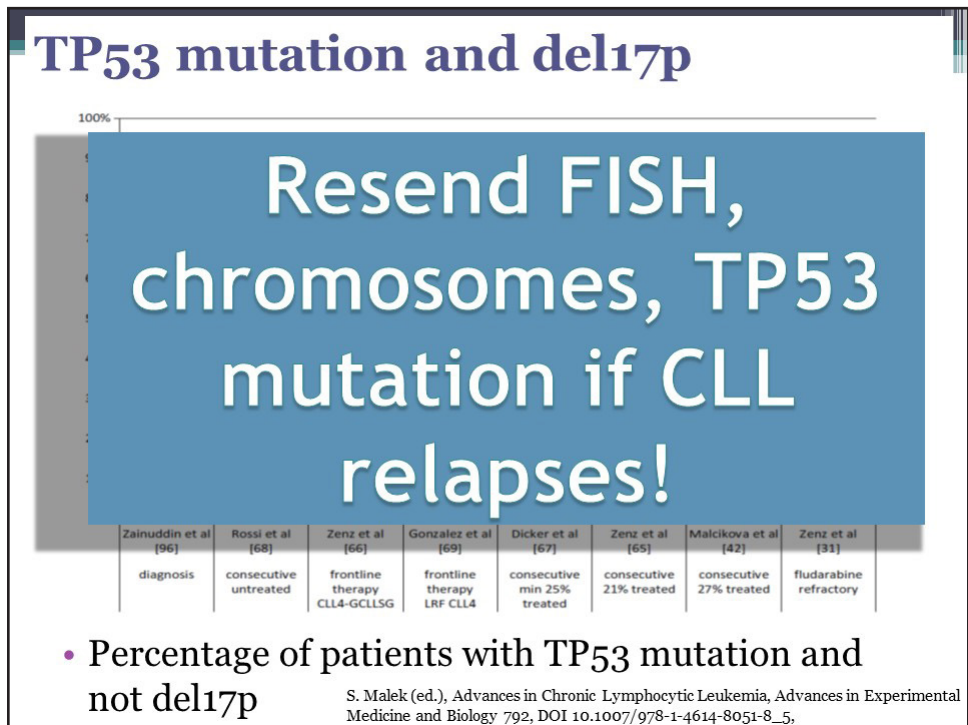
Slide 51. Novel Targeted Inhibition

So now moving into the targeted drugs.



Slide 52. TP53 mutation and del17p

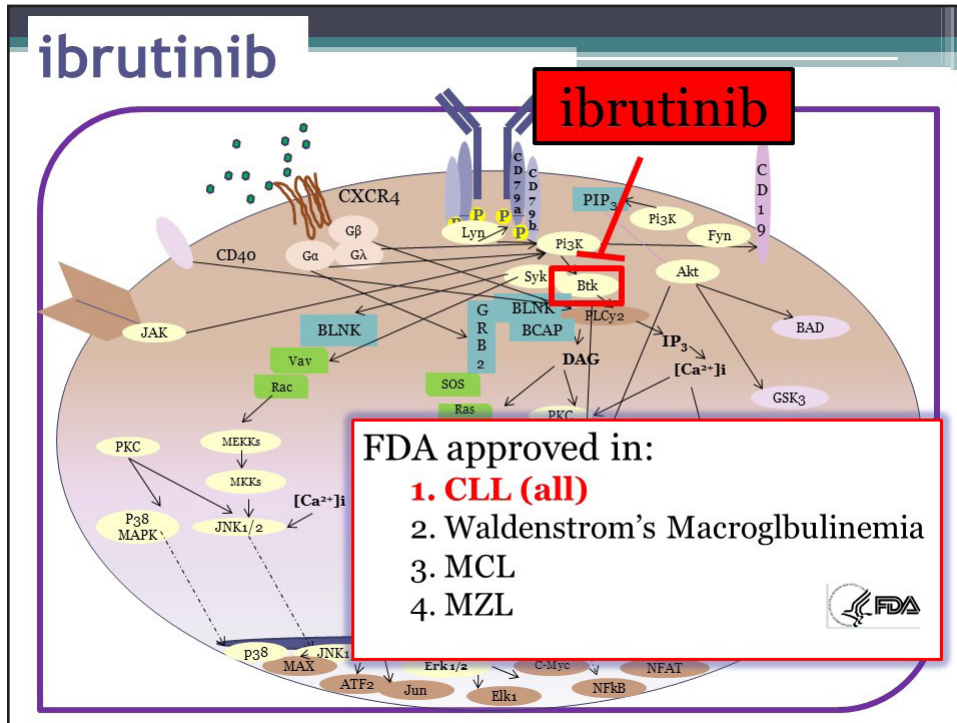
So, for those that can see the slides, essentially what is displayed here from the left is the presence of either TP53 when patients are diagnosed, versus the extreme right side, which is a higher bar or more patients that have this high-risk change, if you're resistant to chemo, for example.



Slide 53. TP53 mutation and del17p

The bottom line for putting this, even without looking at all the individual studies, is just to highlight that if you've already been treated for the CLL and it relapses and you're talking about treatment choices, that it's helpful to send the FISH and

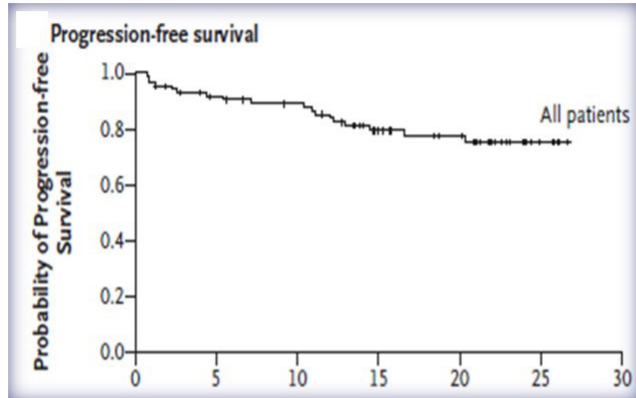
TP53 and knowing if any of that has changed since the CLL's been treated, and therefore either guide the choice of therapy or sometimes guide whether to participate in a clinical trial.



Slide 54. ibrutinib

So, the first drug that I'll talk about just because of use in CLL is ibrutinib, which targets something called BTK. And several years ago, when ibrutinib entered clinical trials, so named as something else at the time, the first patients to receive it were patients that had an on average 4 to 5 prior treatments and the majority of them had those high-risk changes that we talked about. In general, CLL treated with chemo gets less sensitive to treatment each time that it is treated, so the fact that these patients were able to stay on treatment for this duration of time was very encouraging, and now is approved for all of CLL.

ibrutinib in CLL



- Phase Ib/II expansion in CLL/SLL (85 pts; high risk!)
 - Daily dosing of ibrutinib (420mg, 840mg in 34 patients)
 - ORR 71%, plus 15-21% achieved PR-L
 - At 26 months, OS was 83%
- Phase III ibrutinib vs ofatumumab led to approval

Byrd et al. *N Engl J Med.* 2013;369:32.

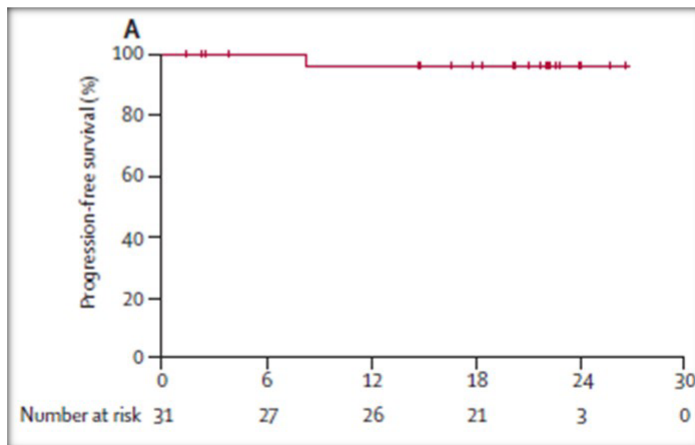
Slide 55. ibrutinib in CLL

This is the front-line study, meaning the first treatment. Progression-free survival again is talking about people that were followed without requiring treatment.

ibrutinib in frontline CLL

Frontline Ibrutinib Monotherapy

- 31 patients
- Age > 65 years
- Responses: 71% ORR, and 13% PR with lymphocytosis



O'Brien et al. *Lancet Oncol.* 2014; 15: 48.

Slide 56. ibrutinib in frontline CLL

But highlighted that this was a safe treatment for patients over age 65, which again was a critical need for CLL, where most chemotherapies get more toxic or more difficult as patients are older.

ibrutinib in CLL: extended follow up

- Responses continuous, although...
 - Time to best response, median: 7.4 mo (1.7-42.5 mo)
 - Time to CR, median: 21.2 mo (4.6-42.5)
- ORRs very high, but...
 - TN: 84% (23% CR)
 - R/R: 90% (7% CR)

Blood. 2015;125:2497

Slide 57. ibrutinib in CLL: extended follow up

When we always talk about – again I don't want to put down the hope and the promise these drugs have given, I think it just highlights, though, our continued drive to make them even better.

ibrutinib in CLL: extended follow up

- Responses continuous, although...
 - Time to best response, median: 7.4 mo (1.7-42.5 mo)
 - Time to CR, median: 21.2 mo (4.6-42.5)
- ORRs very high, but...
 - TN: 84% (23% CR)
 - R/R: 90% (7% CR)

Best responses take time

CR rates low

Blood. 2015;125:2497

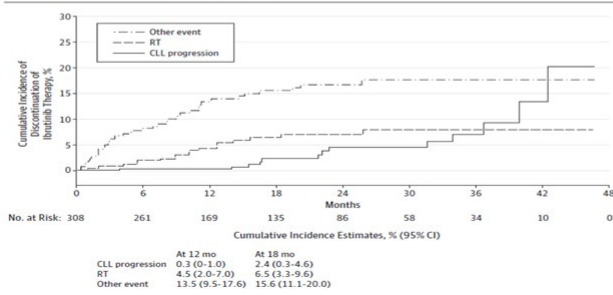
Slide 58. ibrutinib in CLL: extended follow up

So, on one hand ibrutinib, which is taken continuously, can have ongoing responses, but it does take a little longer until we see the best responses and time to CRs or time to complete responses.

ibrutinib in CLL: extended follow up

- Responses continuous, although...
 - Time **Best responses take time** (10)
 - Time
- ORRs very high, but...
 - TN: 8
 - R/R: **CR rates low**
- Many do well, but...
 - discontinuations

Figure. Cumulative Incidence of Discontinuation of Ibrutinib Therapy



Blood. 2015;125:2497

Slide 59. ibrutinib in CLL: extended follow up

And the same is true that even though the responses are high, meaning people having a difference in their lymph node, the complete responses are lower. So best responses take time and complete responses are low. For some patients that doesn't matter, but as we'll talk about for patients who do progress it may matter.

So, as I highlight here, though, many patients can do well taking the medicine, it isn't without its own side effects and some patients do become resistant to it. For those that can see the graph, what we're displaying with time is patients who either progress on treatment or have to come up for other reasons.

ibrutinib in CLL: extended follow up

- Responses continuous, although...
 - Time **Best responses take time** (10)
 - Time
- ORRs very high, but...
 - TN: 8
 - R/R: **CR rates low**
- Many do well, but...
 - discontinuations

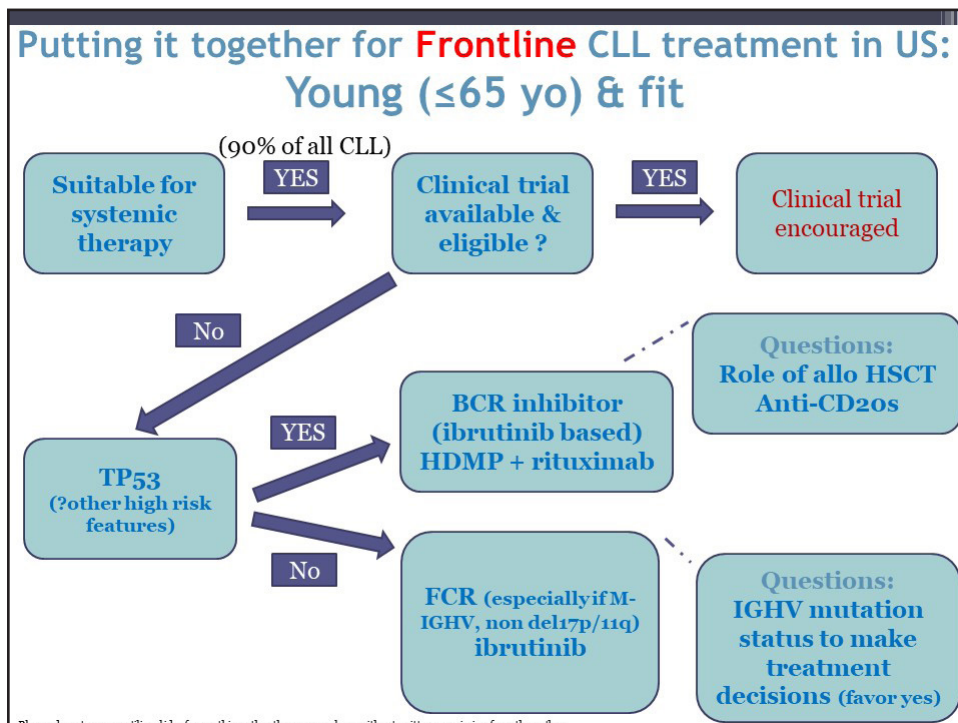
Figure. Cumulative Incidence of Discontinuation of Ibrutinib Therapy

	At 12 mo	At 18 mo
CLL progression	0.3 (0-1.0)	2.4 (0.3-4.6)
RT	4.5 (2.0-7.0)	6.5 (3.3-9.6)
Other event	13.5 (9.5-17.6)	15.6 (11.1-20.0)

Blood. 2015;125:2497

Slide 60. ibrutinib in CLL: extended follow up

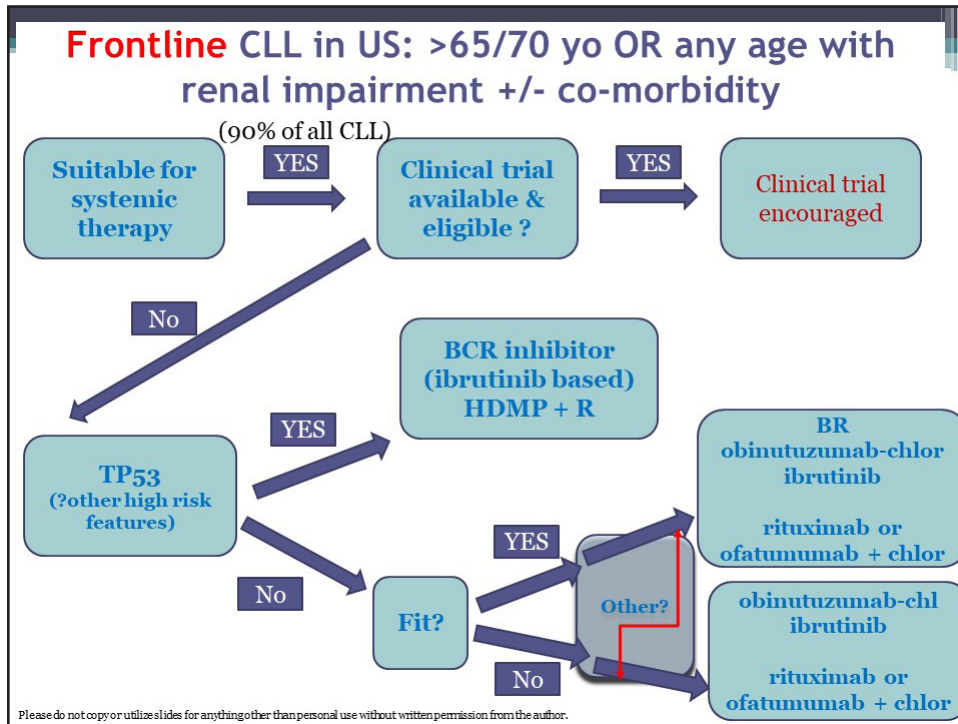
And actually, other events or coming off not due to progression, but other side effects, it appears to be a more common reason. Again, just prompting us to try to understand this better.



Slide 61. Putting it together for Frontline CLL treatment in US: Young (≤ 65 yo) & fit

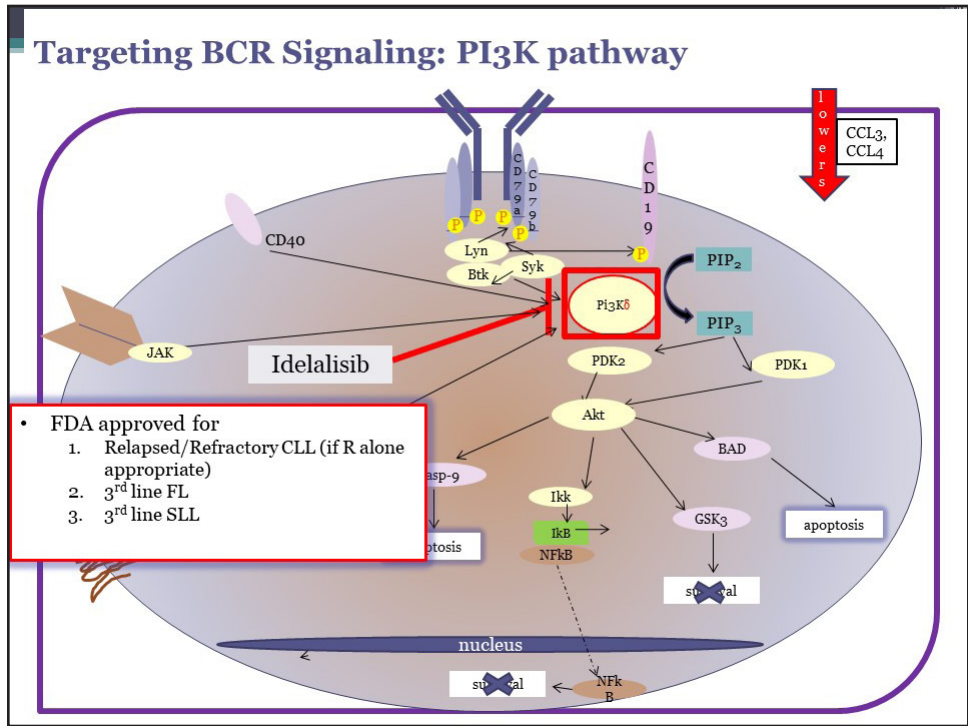
So, when you put together the options for patients, the majority of patients who do come to you needing treatment and who are young and fit, majority of patients will be eligible and able to receive treatment. And then the markers come into play because at even first treatment, if there's a TP53 either deletion or mutation, then patients should not be given standard chemotherapy and we talk about either ibrutinib, a clinical trial, or other options such as steroids and rituximab. We'll still

have the question of the role of transplant for patients, and for those even that don't have it, I think the IGHV mutation status will also drive us more towards looking at novel therapies, so certainly not wrong, depending on the situation, to talk about that with your doctor.



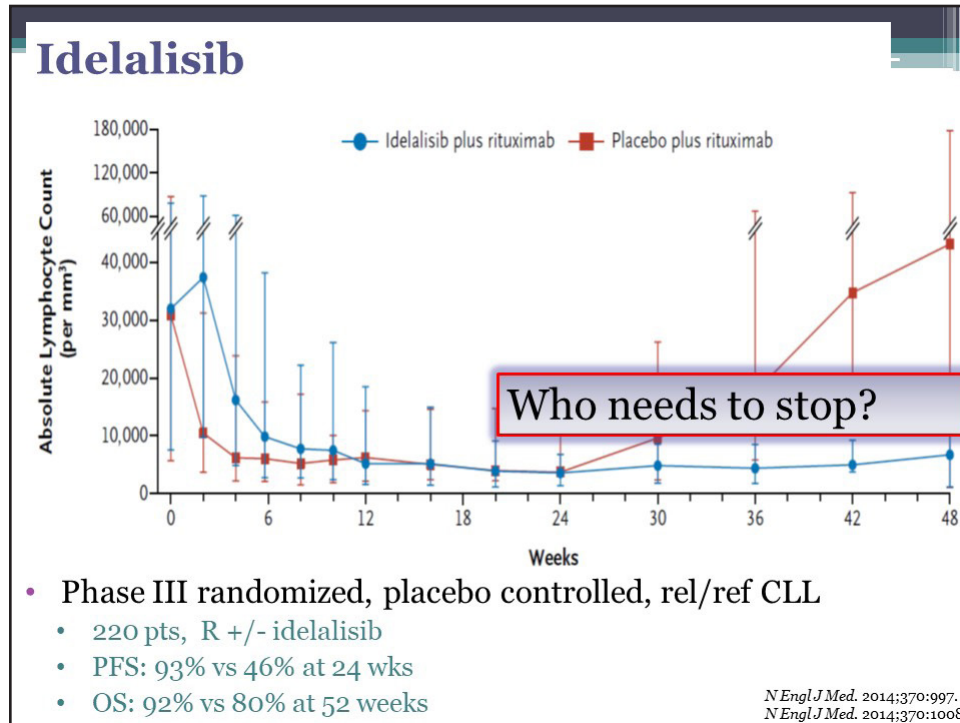
Slide 62. Frontline CLL in US: >65/70 yo OR any age with renal impairment +/- co-morbidity

The way that this change when we look at patients who are older or with comorbidities essentially just becomes that if TP53 is not found, then we weigh in some of the other markers. And the main difference being is that even though I have amazing patients who are 71 and running miles and miles every day, something just does change in the body that makes chemotherapy like FCR particularly toxic. So, the main change in this flow of considering treatment is even those who may benefit from standard chemoimmunotherapy, I generally do not offer FCR for patients over age 65, even if they're fit.



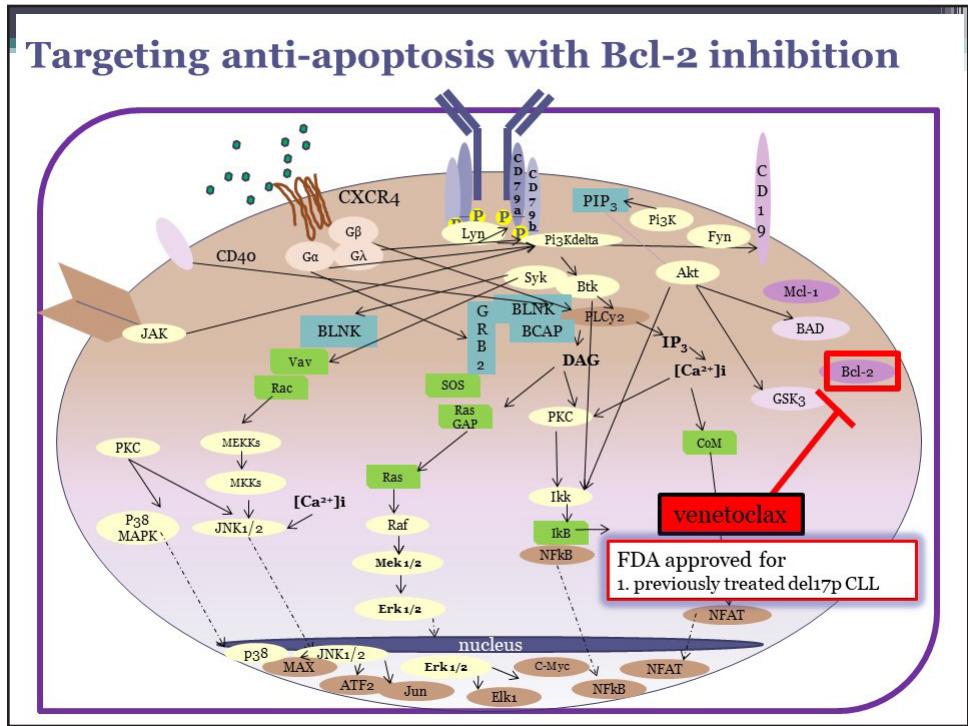
Slide 63. Targeting BCR Signaling: PI3K pathway

So now I'm just highlighting a few other – when we talk about these targeted agents – one being a different pathway. And these slides certainly aren't meant to be overwhelming in the science, the only thing that I want to take away and even highlighting is that they do target different things inside the cell, and that's critical because it means patients that might not tolerate one medicine might tolerate a different one. It also may be that because of resistance, that one agent, as long as you're moving to a different one that targets something different, may still work. So again, don't need to know the pathways, just that these drugs do go after different things and they're different next generation.



Slide 64. Idelalisib

So idelalisib is approved for previously treated, not front line CLL. And while the response rates again in a large trial were very promising compared to rituximab alone, we do have to monitor closely for side effects such as colitis, which means the bowel is inflamed and patients can have profound diarrhea, pneumonitis, or even other changes such as liver function. So again, how do we understand? And part of this may be looking at next generation inhibitors, because even though we talk about a target, each drug is unique. And so, part of what clinical trials are looking at is if this is an effective target, how do we make it safer for patients.

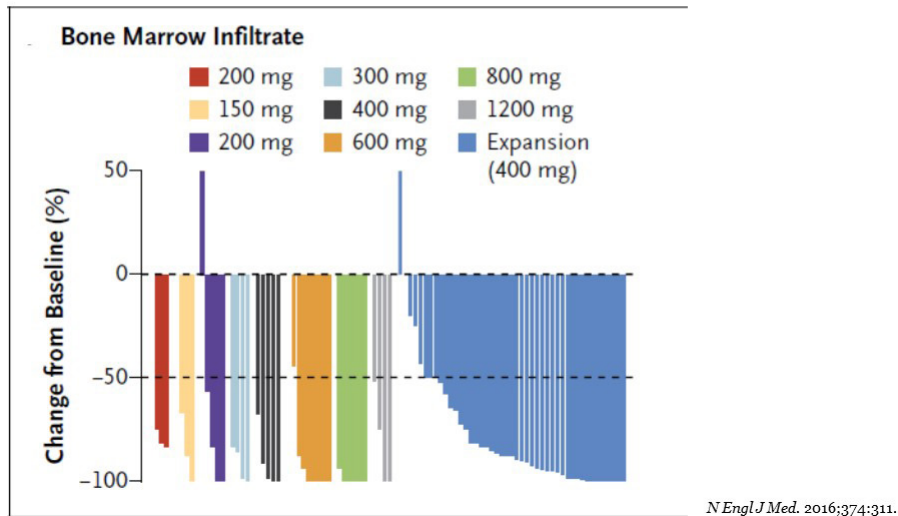


Slide 65. Targeting anti-apoptosis with Bcl-2 inhibition

While the other 2 drugs talk about signaling or, in other words, if you think about each cell trying to take what's on the outside to the inside so that it can grow and stay alive, we call that signaling. And CLLs in particular are dependent on your body to keep doing that signaling. Ibrutinib and idelalisib, those targets try to block that and cells are pushed out of the lymph nodes and the bone marrow into the blood, and that's why patients starting those medicines will see the white count go up, and then the cells die off.

venetoclax

- High single agent responses in high risk patients
 - Includes bone marrow CRs



Slide 66. venetoclax

Venetoclax is different from that in while it's targeted, it doesn't really go after that signaling component. It goes after kind of what the cells weigh in terms of what we call apoptosis. Which means that most of the cells in our body, not all of them, but many of them, are supposed to die after a period of time. And rather than those cells just dying, our body tries to control it by this programmed cell death and then a new cell takes its place. In CLL it happens to have too many of the signals that tell cells to stay alive and that's part of the story probably to why CLL accumulates for some patients over time. And what venetoclax tries to do is take away one of that balance, so that the cells shift to a period of dying off of the cells.

When venetoclax was first being tested in clinical trials, one of the differences somewhat from the other agents, too, is that the depth of remissions, meaning try to clear out B-cells, was different from some of the other agents. And what is highlighted here, you'll see a lot of different doses, because in Phase I trials it means you're trying to find a safe dose that works, and then in subsequent you're looking for how well it works and how well it works compared to other things. So, in this first trial what was promising is that when you look at the bone marrow involvement, there were some patients who were getting rid of the majority of the cells.

CLL frontline or relapsed/refractory treatments: considering toxicities

chemoimmunotherapy

Toxicity varies by regimen

- Cytopenias
- Infections
- Autoimmune complications
- Clonal evolution
- Second Malignancies including MDS/AML

<p style="text-align: center;">ibrutinib</p> <p>bleeding risks</p> <ul style="list-style-type: none"> ▫ phase I/II Studies: ICH: 2% ▫ followup (3yr): 7% gr 3 <p>cardiovascular risks</p> <ul style="list-style-type: none"> ▫ a fib: range up to 16% ▫ HTN <p>other</p> <ul style="list-style-type: none"> ▫ GI/diarrhea ▫ rash ▫ arthralgia/arthritis ▫ infections 	<p style="text-align: center;">idelalisib</p> <ul style="list-style-type: none"> • cytopenias • LFT abnormalities • colitis (diarrhea) • pneumonitis • drug-drug (CYP3A) • infections 	<p style="text-align: center;">venetoclax</p> <p>tumor lysis</p> <ul style="list-style-type: none"> ▫ Can be rapid ▫ dose ramp up & hospitalization needs <p>cytopenias (gr 3/4)</p> <ul style="list-style-type: none"> ▫ neutropenia (41%) ▫ anemia (12%) ▫ thrombocytopenia (12%) <p>other (all grades)</p> <ul style="list-style-type: none"> ▫ diarrhea (52%) ▫ nausea (47%) ▫ fatigue (40%)
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NEJM. 2014;371:213. Blood. 2014;124:3829. Blood. 2015;125:2497. Leukemia&Lymphoma. 2015;56:277. NEJM. 2016;374:311. Please do not copy or utilize slides for anything other than personal use without written permission from the author.

Slide 67. CLL frontline or relapsed/refractory treatments: considering toxicities

So, when I summarize, because we don't have time to go through all of it, I think again the key is for patients starting on treatment is trying to understand and sort through what are the expected side effects, what are the likelihood of those, which ones, and the timing of them, what are the things we're looking for early, for example, with ibrutinib, versus more later onset. And while it's kind of beyond the scope to go over all of them, in at least providing it here, just highlight that this is part of what I try to go over with every patient because there are side effects we expect may happen early and then get better, and there are other ones, such as, for example, with ibrutinib, bleeding or a-fib, that we always have to watch for, and then like I said with idela, we have to watch for colitis or inflammation to the lungs, and with venetoclax, have to be very cautious, especially in the initial treatment, if the lymph nodes are big, and being able to give this medicine safely because of what's called tumor lysis or actually killing the cells really fast. And this certainly isn't an all-inclusive list. Just a reminder to talk with your medical care team or the pharmacist to try to understand what sometimes can be a daunting list if you just pull up a medicine and see all the list of side effects, because it's hard to put the context of the likelihood of them developing or the timing of them developing.

CLL frontline or relapsed/refractory treatments: considering toxicities

chemoimmunotherapy

Toxicity varies by regimen

- Cytopenias
- Infections
- Autoimmune complications
- Clonal evolution
- Second Malignancies including MDS/AML

<div style="text-align: center; border: 1px solid red; padding: 5px; margin-bottom: 5px;">ibrutinib</div> <p>bleeding risks</p> <ul style="list-style-type: none"> ▫ phase I/II Studies: ICH: 2% ▫ followup (3yr): 7% gr 3 <p>cardiovascular risks</p> <ul style="list-style-type: none"> ▫ a fib: range up to 16% ▫ HTN <p>other</p> <ul style="list-style-type: none"> ▫ GI/diarrhea ▫ rash ▫ arthralgia/arthritis ▫ infections 	<div style="border: 1px solid blue; border-radius: 10px; padding: 10px; background-color: #e0f0ff; margin-bottom: 5px;"> <p>What is comprehensive physical, emotional, and financial toxicity of each of these regimens?</p> </div> <div style="text-align: center; border: 1px solid red; padding: 5px; margin-bottom: 5px;">idelalisib</div> <ul style="list-style-type: none"> • cytopenias • LFT abnormalities • colitis (diarrhea) • pneumonitis • drug-drug (CYP3A) • infections 	<div style="text-align: center; border: 1px solid red; padding: 5px; margin-bottom: 5px;">venetoclax</div> <p>tumor lysis</p> <ul style="list-style-type: none"> ▫ Can be rapid ▫ dose ramp up & hospitalization needs <p>cytopenias (gr 3/4)</p> <ul style="list-style-type: none"> ▫ neutropenia (41%) ▫ anemia (12%) ▫ thrombocytopenia (12%) <p>other (all grades)</p> <ul style="list-style-type: none"> ▫ diarrhea (52%) ▫ nausea (47%) ▫ fatigue (40%)
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NEJM. 2014;371:213. Blood. 2014;124:3329. Blood. 2015;125:2497. Leukemia & Lymphoma. 2015;56:277. NEJM. 2016;374:311. Please do not copy or utilize slides for anything other than personal use without written permission from the author.

Slide 68. CLL frontline or relapsed/refractory treatments: considering toxicities

Ultimately, too, I think what are the important things is that we learn from these side effects initially through what is recorded in clinical trials. However, the more I talk to patients and recognize the variation, the more side effects we may find. Some of them don't bother patients, some of them are very important. And then especially with continued treatment, I think understanding how we can help patients in terms of some of the other maybe non-visible side effects, but that are very real and motivate us with patients, which are the emotional and financial toxicities.

ibrutinib and idelalisib: understanding toxicity

Table 3. Most common reasons for kinase inhibitor (KI) discontinuation in patients who have discontinued ibrutinib or idelalisib.

	Ibrutinib	Idelalisib
Toxicity	51% (n=73)	52% (n=18)
CLL Progression	28% (n=40)	31% (n=11)
Richter's transformation	8% (n=11)	6% (n=2)
Cellular therapies (CAR T cells or allogeneic SCT)	2% (n=3)	0% (n=0)
Unrelated death / Other	11% (n=16)	11% (n=4)

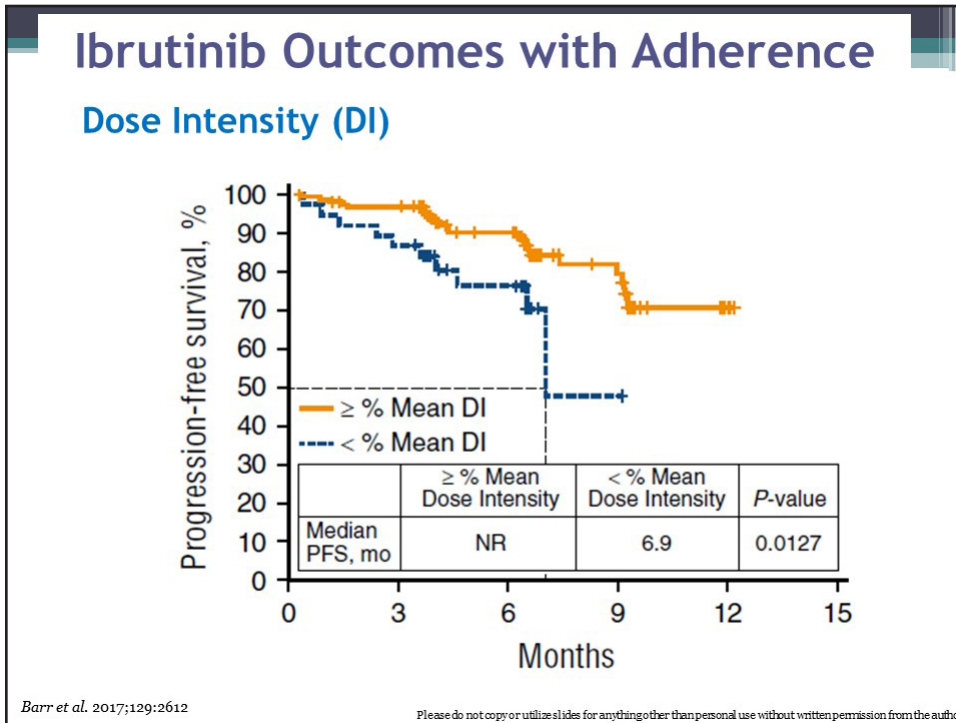
***note this are reasons for discontinuation, not discontinuation rates**

***KI=kinase inhibitor (ibrutinib and idelalisib)**

Mato et al. *Blood*. 2016;128:2199

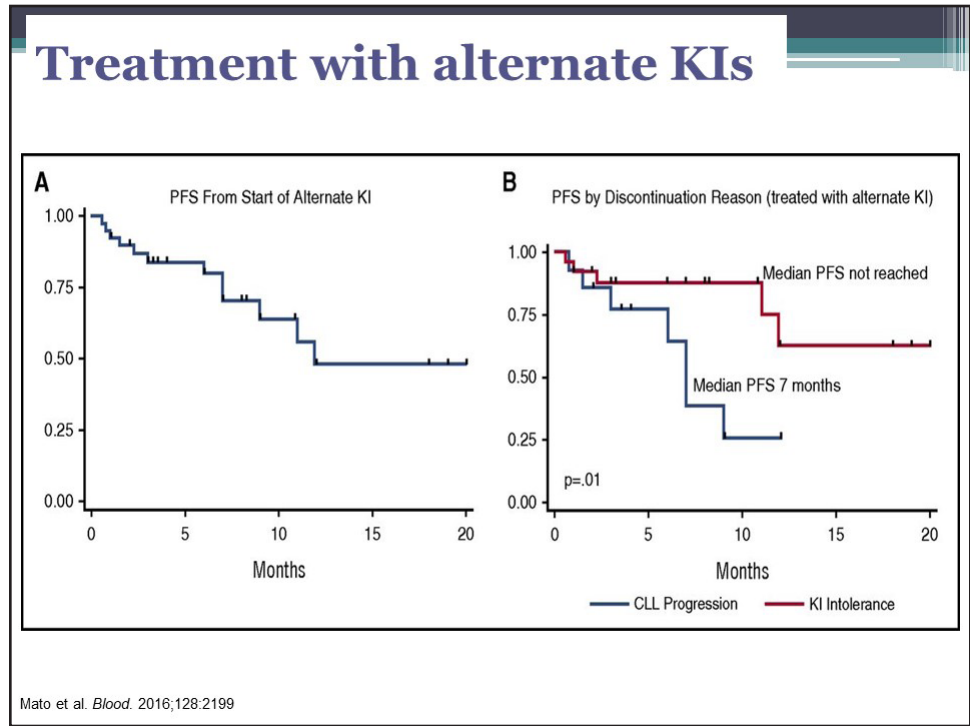
Slide 69. ibrutinib and idelalisib: understanding toxicity

So just a brief highlight and at least one study, this is not the proportion of patients that came off the drug, but for patients that come off the drug the side effects are about half the reason. And so again something we have to hone in on and try to make better for patients.



Slide 70. Ibrutinib Outcomes with Adherence

For patients taking these medicines, though, at least ibrutinib and idelalisib, what is called the dose intensity or in other words patients taking it every day is very important. So, what the study looked at is patients either from side effects or other reasons that have to interrupt the dose a lot, you take it for a little, you stop, you take it for a little, is more likely to have the CLL to progress.



Slide 71. Treatment with alternate KIs

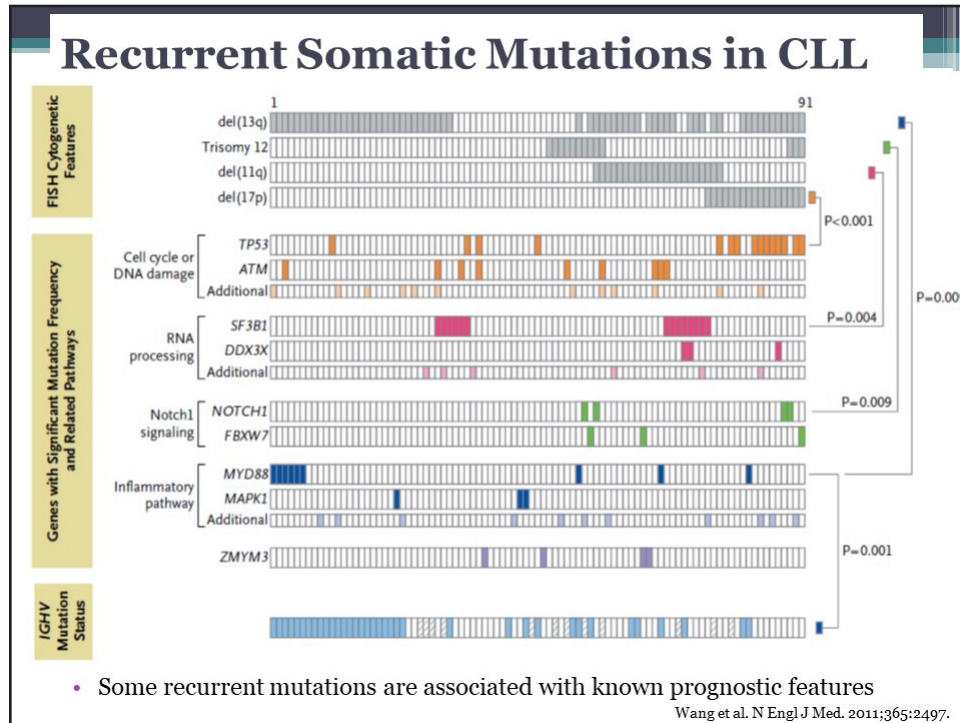
However, the hope is, I mentioned, for patients that have the side effect, because they target different things, and this at least the approved agents, patients could respond well. So, this, looking at the red line, is patients that switched to another drug from side effects were just as likely to respond.

Moving Forward: Novel genomic/molecular risks and Minimal Residual Disease (MRD) in CLL

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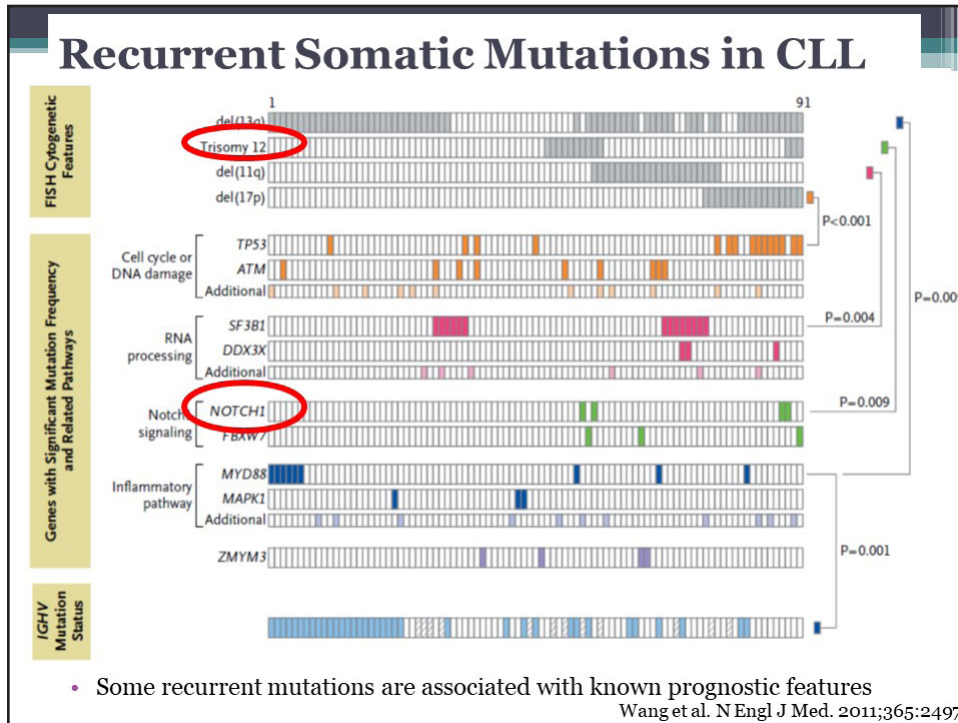
Slide 72. Moving Forward: Novel genomic/molecular risks and Minimal Residual Disease (MRD) in CLL

So, in conclusion, just a few things about moving forward and introduce some terminology, and again the highlight is that these are all still part of clinical trials, they're not part of the routine work-up and process, but are exciting to hopefully bring more to patients, to tell them more and to make our treatments better.



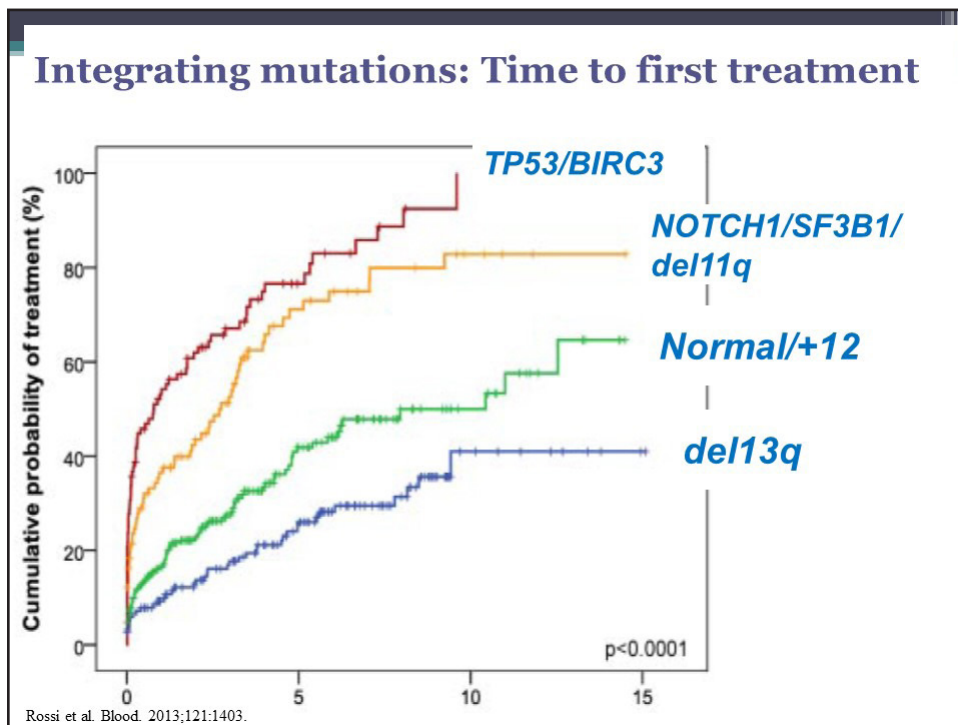
Slide 73. Recurrent Somatic Mutations in CLL

So, one of these again, so looking at the slide, looks like overwhelming information, but what I highlight is that again for patients that have participated in a trial, as technology has changed and research has changed, instead of the basic – more basic tool of just looking at chromosome deletions or insertions, researchers were able to start looking at mutations in CLL and how that differed from others. And this has highlighted a couple of key mutations such as NOTCH, SF3B1, in addition to the TP53.



Slide 74. Recurrent Somatic Mutations in CLL

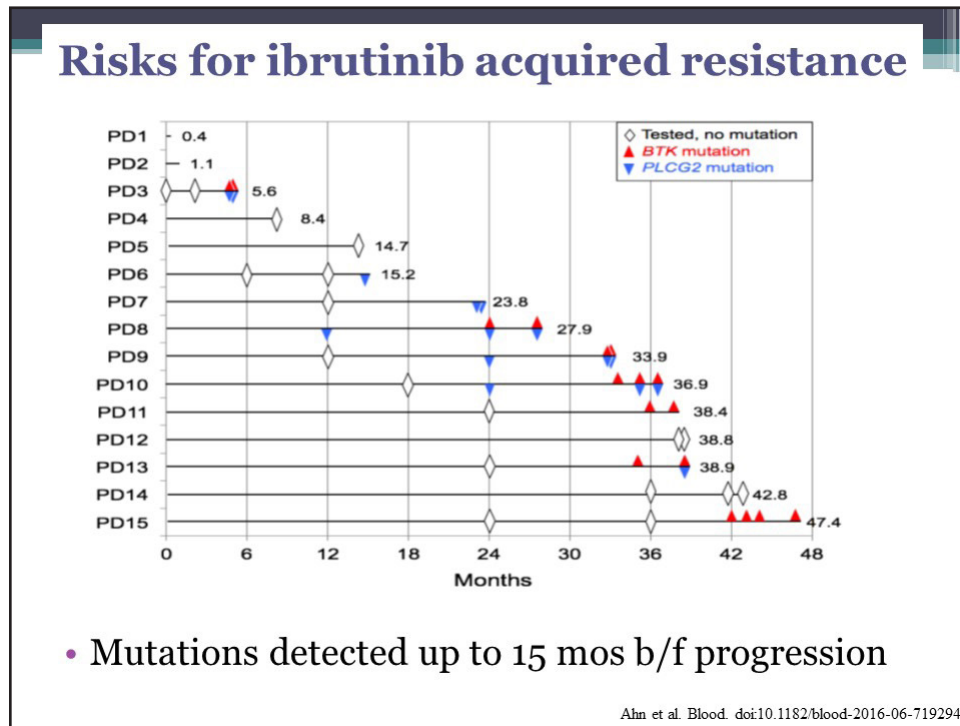
Some of these are grouped with abnormalities we know, for example, NOTCH does tend to happen in patients with trisomy 12, which is what the arrow bars at the right are trying to show.



Slide 75. Integrating mutations: Time to first treatment

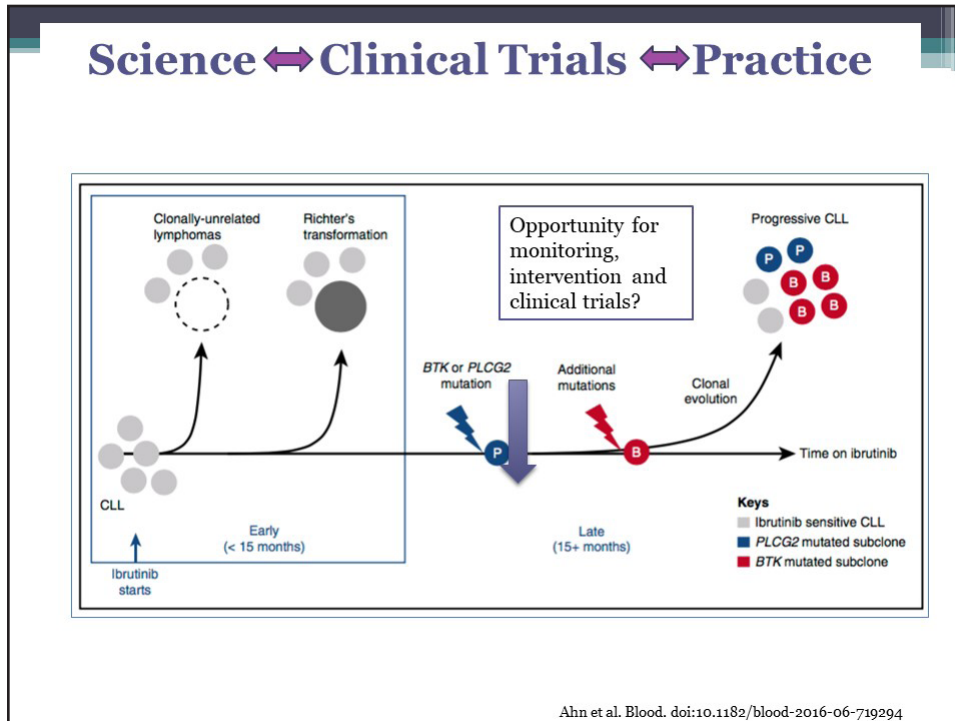
But in addition to these groupings, they also change if we just look, for example, this is patients and probability and time of needing treatment, that if we add some of these mutations to what we know by FISH, that it can again aid us to know what to expect and then potentially also help us in making recommendations for treatment. But most of those tests are not

available routinely and we do not have long follow-up. I will make the comment that in patients I see that have had NOTCH testing, I think a lot of the times the testing that's being done comes with background information, but again just recognize that any information about patients, how long they live or how well they respond to treatment, would be historical, and so most of the patients would not have been treated with the novel agents and we're hopeful the novel agents will change those outcomes.



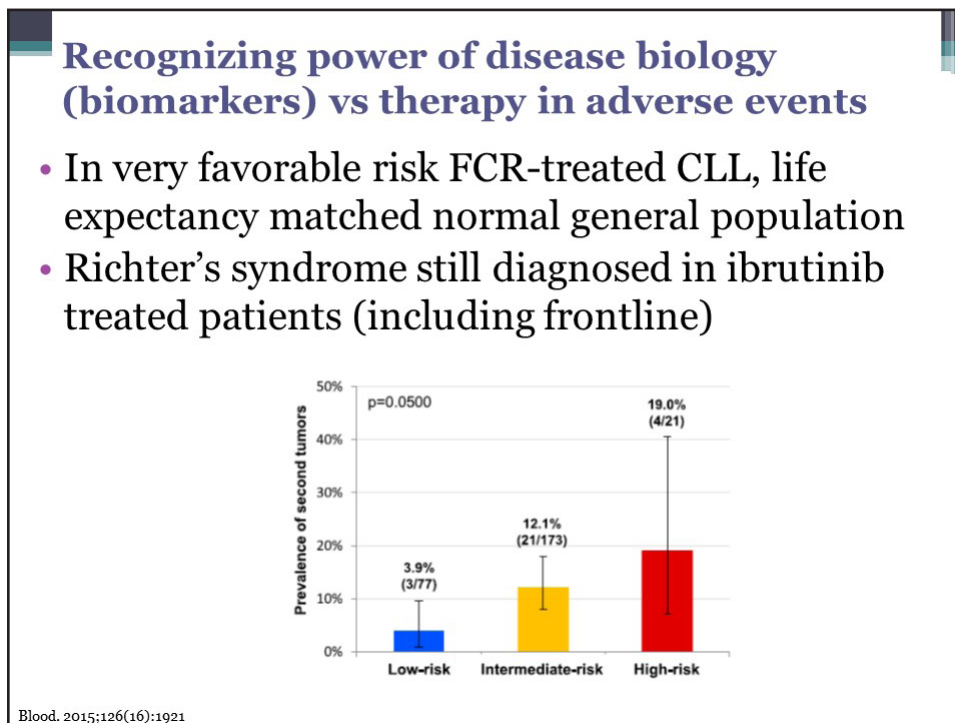
Slide 76. Risks for ibrutinib acquired resistance

So, in the end one of the other ways I think that the research is making things powerful is, and patients have participated, we're learning how do we recognize resistance and possibly do something about it. So, while some patients came off study due to toxicities, some came off due to resistance, meaning the CLL became resistant in this case to ibrutinib. What this highlights is different patients, how long they were treated, and when those resistant mutations were found.



Slide 77. Science <--> Clinical Trials <--> Practice

And so, what the authors at least in one study highlight is that this might be the opportunity for monitoring, meaning you might find it in only a few cells and you can intervene with another treatment and try to rid of that clone.

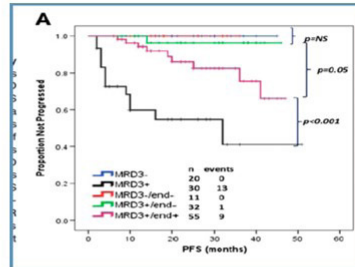


Slide 78. Recognizing power of disease biology (biomarkers) vs therapy in adverse events

And again, it's the same story, but what I'll highlight is that even in the favorable risk and FCR, the risk of second cancers was similar to the general population, whereas Richter's, which is when CLL turns to a more aggressive lymphoma, was still found in people treated on ibrutinib. So, I think the key here is that it's not just the treatment causing these complications, I think it's also understanding the differences in the CLL.

MRD neg & durable responses

- **MDACC FCR: MRD marrow**
 - Treated for 3-6 cycles, MRD bone marrow assessed at each
 - PFS similar by ending MRD status
 - 3 vs 6 cycles (didn't matter how much to get there)



JCO. 2012;30:980-988.
Blood. 2014;123:3727-3732.
Blood. 2015;126(16):1921-1924
Blood. 2016;127(3):303

Slide 79. MRD neg & durable responses

Then the very last thing to introduce about is what's called minimal residual disease (MRD) and minimal residual disease basically is, depending on the testing method, a way to look at how much CLL is around. And most of the time this is done or classically has been done by flow cytometry, collecting a lot of cells, but there are other ways to test for it. Right now, this is all research to do, but we're hoping it might be a marker for knowing how well patients respond and can stay in response. And eventually we're hopeful to have a way to know maybe for patients to be able to stop treatment once they reach a goal.

MRD neg & durable responses

- **MDACC FCR:** MRD marrow
 - Treated for 3-6 cycles, MRD bone marrow assessed at each
 - PFS similar by ending MRD status
 - 3 vs 6 cycles (didn't matter how much to get there)

- **CLL8:** MRD on blood & marrow
 - Post treatment “low” MRD associated with longer PFS and OS
 - FCR vs. FC (didn't matter what to get there)
 - *But* more “low” MRD pts in FCR

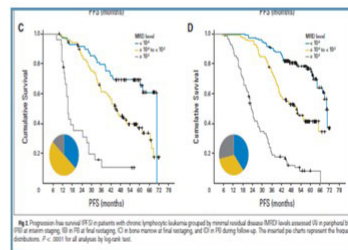
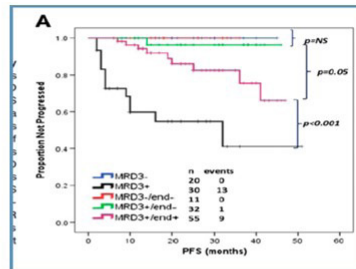


Fig 2. Progression-free survival (PFS) in patients with chronic lymphocytic leukemia prepared by minimal residual disease (MRD) tests assessed (C) in peripheral blood, PFS at interim analysis, (D) in 70% at final analysis, (E) in bone marrow at final analysis, and (F) in 70% during follow-up. The stacked pie charts represent the baseline distribution. P < .0001 for all analyses by log-rank test.

JCO. 2012;30:980-988.
Blood. 2014;123:3727-3732.
Blood. 2015;126(16):1921-1924
Blood. 2016;127(3):303

Slide 80. MRD neg & durable responses

And without reading all the details, I'll just highlight the reason minimal residual disease has come up as an important marker, is that in some classic studies, for example patients that were treated with that FCR regimen, if they got to no detectable by MRD panels, it didn't matter if they got 3 or 6 cycles, it just matters they got there. So, it doesn't matter how much treatment you get to get there as a goal. And then in another study where patients either got FCR or FC, so no rituximab, if they got minimal residual disease they did well, no matter what regimen. So, it didn't matter what treatment to get there, again highlighting an important at least trial endpoint.

BCR/BCL2 Inhibitors: CRRs and MRD

- **Ibrutinib:**

- Rel/Ref CRs: 0, 2%, 7%, 12%
- Frontline CRs: 14%
(23%-longer follow up)
- MRD: ? As monotherapy

- **Idelalisib + rituximab:**

- Rel/Ref CR: 0%
- Frontline CRs: 19%
- MRD: ? As monotherapy

Brander et al, iwCLL 2017
Lancet Oncol 2017; 18: 230

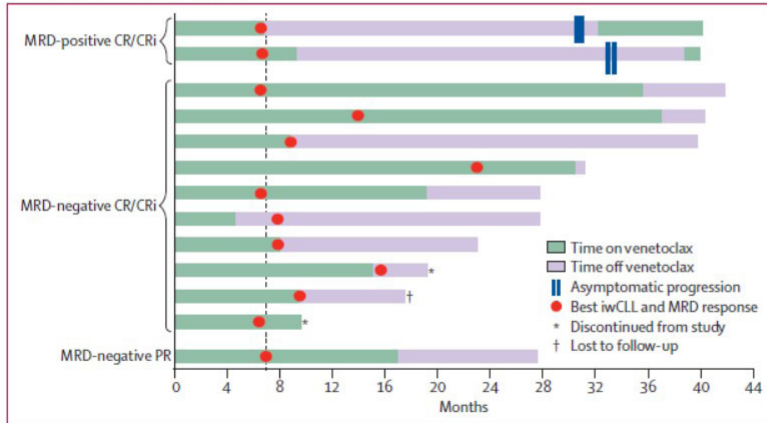
Slide 81. BCR/BCL2 Inhibitors: CRRs and MRD

And like I said, while these are promising agents, thus far by themselves, you'll see there that the complete response rates, let alone as MRD, which is the layer below, are low with these agents, and has driven looking at other agents to combine. And indeed, this is – in one of the clinical trials is venetoclax and rituximab, again within the context of a clinical trial, patients could stop treatment if they reached this minimal residual disease negativity.

BCR/BCL2 Inhibitors: CRRs and MRD

- **Venetoclax + rituximab (n=49):**

- Ability to stop therapy in CR or MRD-negative status and maintain
- MRD- rate: 59%



Brander et al, iwCLL 2017
Lancet Oncol 2017; 18: 230

Slide 82. BCR/BCL2 Inhibitors: CRRs and MRD

And what the blue lines indicate are the patients being followed off of the study and doing well. And like I said, this is part of a clinical trial, but I think highlights that while we were able to get there with chemotherapy and the associated toxicities, perhaps maybe not by themselves, but in combination, or in next generation inhibitors that are better tolerated, we can be able to get there.

Thank you for your attention, and thank you to our patients and care team members



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Danielle M. Brander, MD

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Slide 83. Thank you

So, I've said it a few times, but I certainly want to say it again, which is a thanks to the LLS and to everyone for their attention, and particularly also thank the patients that entrust me as part of their care team, and certainly also to the patients that entrust us with participation in clinical trials. And so, I'll stop there so that we have the opportunity now to answer questions.

Living with Chronic Lymphocytic Leukemia (CLL)



Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click "Ask a question"
- Type your question
- Click "Submit"

Due to time constraints, we can take only one (1) question per person. Once you've asked your question, the operator will transfer you back into the audience line.

Wednesday, July 12, 2017

Slide 84. Q&A Session

Lizette Figueroa-Rivera:

Thank you so much, Dr. Brander, for your very informative presentation. It's now time for our question and answer portion of our program.

We'll take the first question from our web audience. Doctor, Mark asks about the status and information of the CAR-T cell therapy and its availability to watch and wait patients.

Dr. Danielle Brander:

I'm glad there's a question about CAR-T because in putting this together I tried to focus on the clinical trials and the treatments available, but certainly immunotherapy and looking at totally new approaches is also incredibly exciting, but probably could be a talk in and of itself.

What CAR-T is, at the very simplistic, is there are different types of CAR-T, even within CLL, but the basic idea, that is taking your own cells, because our immune system cells go after not just infections, but they probably do a good job in our body going after cells that don't look normal either. So, in making CAR-T, what the process is, is taking the cells out of your body and changing those T-cells so that they go after the leukemia. Of course, they can still go after normal cells, too. And this has shown promise, particularly for patients where other treatments are not working.

Like I said, the keys to highlight is that the current generation of CAR-T are even different than the original. There are a couple of different types that are being developed. But like any new and emerging therapy, until the risk of that treatment is best understood, using it, for example, in patients that have not required treatment yet or may not require treatment, the risk of your treatment may far outweigh the benefit at that time. What the hope of that as well as other therapies is yes, if they become safer, then instead of using it to treat the highest risk patients, the patients that fail other treatment, it'll then be safe enough for the risk-versus-benefit to maybe use an earlier treatment line. But I'd say we're still a ways from thinking about using this to try to cure patients, especially if we don't know that they will require treatment. But certainly, is a very promising treatment option that is emerging.

Lizette Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. Our next question comes from Alfredo from Florida. Please state your question.

Alfredo:

Good afternoon. I'll keep it brief. I started ibrutinib about 5 months ago, doing well. So, the question I have, should I wait until it's no longer effective, because it could be a year or two, no one knows, or should I look into CAR-T treatment, how do I make a decision like that, of course with the doctor.

Dr. Danielle Brander:

So ibrutinib response, as I highlighted a little briefly, you can see initial great response in the lymph nodes and often the white count goes up at that time. But the best responses can take time. In other words, if we talk about the level of complete response, for some patients that can happen on average at 22 months or even longer. I would say just like the first question about the CAR-T, that would be needed to answer your question would be what other risk factors that you may have. For patients going on ibrutinib as their first treatment with otherwise what we call more favorable risk profile, it probably – most of those patients years and years later are continuing to respond and do well. However, perhaps someone that's had 4 or 5 or 6 different treatments, has known TP53 and a lot of chromosome changes, that person on the same medicine has a higher risk of relapse. So, there are, within the context of clinical trials, some clinical trials available for patients who are on ibrutinib and after a certain period of time are kind of plateauing in their response, but have high risk for progression. Again, a patient earlier in lines of treatment, some of those patients have now been on ibrutinib years and years and I would say if you fell in that category, probably not the timing – most clinical trials, though, are written with that intent in mind, meaning that if someone's favorable risk in earlier line, probably not going to have it available. So, knowing your risk profile, knowing expectations would be helpful in discussion with your doctor to know if you're someone at higher risk of progression and were the responses plateauing.

Lizette Figueroa-Rivera:

Thank you for the question. And we do have other questions about ibrutinib. Carl asks, I stopped taking Imbruvica® 4 months ago due to side effects, but my counts continue to improve. I don't understand why they continue to improve. And Alissa is asking, how long can somebody actually be on Imbruvica.

Dr. Danielle Brander:

So, I'll start with how long can you be on it. So, the first clinical trials of what now is ibrutinib, 2009, 2010 and beyond, so there are patients that have been on it for a number of years, but each person is different. We know some side effects seem to happen in the first year, so the greatest proportion of patients that have – where their medicine is not being tolerated – actually happens earlier on, although we always have to watch for side effects like bleeding and increase in blood pressure. Many times, after that first year or two, patients that are tolerating at that point, we can help to allow them to continue to tolerate. And so far, there hasn't been a reason that those patients shouldn't stay on for as long as they're tolerating and responding.

A kind of forward thinking question I guess would be is if a patient has responded really, really well and even if it took a couple of years to get there, are there any patients who – again this is a clinical trial, has to give us more information, but eventually will people be able to use ibrutinib in combination or even by itself and get to a place where they're able to stop therapy. We're just not there yet, to know when that is safe, to be able to stop treatment in that way.

But what I say when I keep using the phrase patients can't tolerate, I don't ever want to imply that it's something that can be pushed through. While ibrutinib has allowed patients, who couldn't get chemo to tolerate it much better, the side effects of ibrutinib are very real and part of what we're all trying to understand is just like everything else in CLL, can vary person to person. Why can one person have almost no side effects except feeling like they're improving, while another fit, healthy, young patient have a lot of side effects that just truly are intolerable. That's the medicine failing them, not them, you know, not pushing through, being able to tolerate the medicine.

But in terms of counts improving, a little bit depends which counts you're referring to and how long ago you started the ibrutinib. Because in the first 3 months the ibrutinib makes the white count go up. So, if this question is asking about the white blood count, sometimes when you stop the ibrutinib, if it's in that initial phase where it's trying to push the cells out

and the white count go up, then when you stop the ibrutinib I frequently will see in patients during that initial period that the white count falls again, because basically the cells are – the CLL cells are going back into the lymph nodes and the blood. So, when I say ibrutinib makes the white count rise, it's not that it makes there any more CLL cells, it's just pushing it from one place to the other.

But we also have had patients who are on it for longer and, for example, if they had a lot in their blood or in their bone marrow or their other spaces and maybe didn't have a lot of previous treatment, where you do kill off those cells and maybe the CLL just isn't growing back as fast. So, there might be a reason and certainly I don't press patients unless they're symptomatic, have a reason to jump right into treatment. Some patients can have a break between treatments.

Lizette Figueroa-Rivera:

Thank you. And we'll take the next question from the telephone audience, please.

Operator:

Thank you. Our next question comes from Rebecca from Florida. Please state your question.

Rebecca:

Oh, hi, thank you so much for taking my question. My questions on behalf of my mother who has the 11q deletion, so she has lymphadenopathy. But she feels great, thank God, and she's doing great and she's being monitored. The doctor said her spleen is enlarged. So, our question is in absence of the – she doesn't have night sweats or anything like that – could she be continued to be monitored with the enlarged lymph nodes and enlarged spleen, or would you lean towards starting treatment?

Dr. Danielle Brander:

Thank you for your question. A couple of points, one is your direct question, and another thing that your question brought up, and just being hopeful about the future.

The first is that I would just clarify what they're conveying by saying that the spleen is enlarged because a normal spleen on CAT scans from the top to the bottom might differ place to place, what they call normal. For here, for example, 13 centimeters, everything's measured in centimeters, but 13 centimeters top to bottom is considered the maximum kind of top to bottom length before they'll call it enlarged. But as you can imagine, each person is different, so the size of spleen varies according to male or female, it actually varies by race, etc. So, I use, if exam is able to be performed, feeling a spleen enlarged on exam is different than a spleen being enlarged on a CAT scan. I'd say a great majority, or many at least, of my patients that have CAT scans for one reason or the other, will either have a prominent or an enlarged spleen.

Similarly, the lymph nodes may be ones that you feel or they may be ones on CAT scan, again, a prominent lymph node might be anything over .8 centimeters and enlarged is over 1.5. But if it's not symptomatic, by size alone that isn't usually required for treatment, unless you're talking very, very large sizes.

So, what I would clarify for your mom's case is that if this was based on imaging or was something on exam. My general rule of thumb and what is the iwCLL guidelines for the spleen is the spleen that's more than 6 centimeters below your ribs, again, taking into account that CAT scans might show something enlarged, that's really not enlarged and pushing into the abdomen and causing any symptoms.

The second part that I'll just highlight is that 11q, which classically was next to 17p considered higher risk because it didn't respond as well to chemo and with treatment the responses tended to be shorter. But just a few months ago and a few weeks ago some of the oncologists that participated in clinical trials, looking at patients treated with ibrutinib, 11q was no longer a marker in patients being treated with ibrutinib to not respond or the duration of response. And so again that just highlights that it wouldn't change to decide to treat or not right now, but hopefully gives us hope that some of these markers that were previously adverse were in the era of things that target things differently will be seeing different responses.

Lizette Figueroa-Rivera:

Thank you. And we'll take the next question from our web audience. Michael is asking, you said age can affect how well we respond to treatment. Does it also affect how the disease itself progresses in the body?

Dr. Danielle Brander:

So that's an excellent question. There have been studies looking actually at the reverse, which is there was a perception that perhaps CLL diagnosed young progressed faster. But so far, we don't have any concrete evidence to show that the progression rates are different. And in the past part of maybe why patients that were older didn't do as well is we had to either reduce the dose of the treatment or omit part of the treatment altogether, because as we all get more experience in life, our kidneys don't work as well and so treatment had to be done differently.

So, what's different moving forward I think is that if patients are able and we learn how to give these drugs best or maybe we have next generation ones, which I didn't even get to talk about, for example, acalabrutinib versus ibrutinib, that hopefully age will become less of an ability to tolerate and get the best treatment.

Lizette Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. Our next question comes from Barry from California. Please state your question.

Barry:

Yes, thank you. I've been on ibrutinib for about, oh, 9 months or so and it's working well, but my platelets are quite low and I was wondering if there was a magic potion on how to get the platelets up. They've tried a couple of things, but I wanted to keep this general.

Dr. Danielle Brander:

Thank you for your question. In keeping it general I'll break into a couple of categories of low platelets.

So, a normal platelet count is about 150. We consider low in terms of treatment as less than 100. But patients that have had treatments for their CLL before, your platelets may never come back to either of those normal levels because certain chemotherapies can keep platelet counts low, low indefinitely.

When we talk about platelet numbers that are at risk of just in general risk for bleeding, that sometimes we transfuse for, we're talking about really low levels, like less than 10. With ibrutinib I do hope that platelets stay a little bit higher since ibrutinib is in a way kind of like aspirin and can interfere with the way that the platelets stick together.

But ibrutinib can, while it's not like other chemotherapy that can really lower platelet counts for any patients that have gone through treatment with chemo, you know every cycle sometimes the platelets can get a lot lower. Ibrutinib usually doesn't lower it by a lot, but it is an effect of the drug to lower it by a little. For example, staying in the 70 or 80 or 90 thousand range.

Unlike low red blood cells or low hemoglobin where you can look for deficiencies, meaning nutritional deficiencies or other things going on, there's really no by mouth kind of thing in the diet supplement to bring up the platelet count. So, there's medicines that can stimulate the platelets, but in general those are reserved for kind of extreme cases where the platelets are really, really at the lower levels that I was talking about.

So, to answer the direct question I would say there's nothing per se for the individual to do to try to get them up, but I would try to kind of put in perspective where your platelets are when you're told that they're low. Because a little low level can be tolerated.

Now the one last thing I'll say is in the most extreme cases sometimes patients' immune systems in CLL can lower their platelet counts and then they're really low levels. And that would be kind of a whole separate talk because we try to target the immune system with things like steroids or rituximab and that would be out of the norm.

Lizette Figueroa-Rivera:

Thank you. And our next question comes from the web audience. Nancy asks, what do you think of the two clinical trials that showed great promise? The first one being Mayo Clinic's use of green tea extract and the second a regimen of curcumin, turmeric with bioperin followed by a regimen of cholecalciferol.

Dr. Danielle Brander:

So, I think in general we're all open to the potential of supplements or green tea or turmeric or other things, being able to – thus far mostly have been studied and looking at trying to delay progression.

The green tea study, which was led by Dr. Shanafelt in Mayo Clinic, looked at developing a particular green tea formulation taken twice a day. And again, this was mostly limited to patients that were in those early Rai stages and were not clearly progressing and otherwise requiring treatment. The majority of patients overall tolerated it fairly well. However, with any supplement, can interact with other medicines. They occasionally can cause in rare cases liver function test abnormalities or even liver failure. And I've also seen skin rashes. And then like I said, I've seen them interact.

For patients that are in that earliest phase and want to kind to know the risks and want to take green tea extract, what I would just say, based on the study, is to make sure that the label says that they're decaffeinated and the source can say that they're decaffeinated because the clinical trial looked at taking the supplement, a couple of tabs twice a day. And if there's even a little bit of caffeine in that, the side effects can be that of, you know, high levels of caffeine. And then like I said, just making sure that you do talk to your doctor or a pharmacist about it because it can interact. So, bottom line is that highlights that hopefully these are going to be studied in clinical trials more, so that we'll have more information, but if you're going to do it and when I talk to my patients about it, we just try to do it in the safest way possible, monitoring their labs, making sure they're not on any medicines. For patients going on treatment, otherwise generally my advice is to not be taking them because there are known interaction and in which case could cause potential harm.

Lizette Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. Our next question comes from David from Washington. Please state your question.

David:

Thank you. After 3 cycles of bendamustine and Rituxan® have failed, is the next best treatment ibrutinib? And I have a question about bioabsorption rates. Why does the literature on ibrutinib say I should swear off grapefruit juice because it increases the bioabsorption rate? Doesn't it suggest that we should just reduce the dosage of ibrutinib and use the grapefruit juice to increase the effectiveness?

Dr. Danielle Brander:

Great questions. So, I'll answer 2 of them. One would be in terms of the treatment choices for chemotherapy not being effective, I'd say in general that if the markers weren't checked before this round, I'm not certain if this is your first treatment or had been treated before, but certainly looking at FISH and TP53 to make sure that there's no change in the markers that you knew about before. Because that'll open up to, depending where you are, overall what your risk of ibrutinib working kind of in the longer term, and so maybe considering clinical trials. It also sometimes can open whether to have a discussion in your particular case of ibrutinib versus the option for venetoclax, but that is a highly individualized discussion right now. Venetoclax in the US just approved for deletion 17p, previously treated CLL. But for patients that I see that even have deletion 17p, it's a discussion and really based on the risk because it depends if they have more enlarged lymph nodes compared to bone marrow involvement or vice versa, because that changes the risk of both treatments as well as the potential responses. But in general, I would say if bendamustine-rituximab is not being effective, to repeat the markers and consider a non-chemotherapy, whatever the right choice that would apply to you.

In terms of the absorption, the reason that grapefruit, star fruit and Seville oranges, which by the way are the most common oranges in many orange marmalades, are recommended against is that there's no way to have that as a consistent level and if you increase the drug levels in your blood that doesn't just mean that it's effective on the CLL, it means it also might

increase the toxicity. And probably as we get to know better, the way ibrutinib blocks its target, which is BTK, once it blocks all of it there's really whatever that magic is, no potentially benefit to going above that. So those recommendations about the foods that can increase it is so that you're not having variable levels and particularly that you're not having high levels.

The same, I'll add, is also true of certain medicines which is critical for patients on ibrutinib, that if you're prescribed certain antibiotics or particularly antifungals, that you talk about that. The higher levels may do nothing to benefit. You might already be blocking all you can block in the CLL. You might just be increasing your risk of off-target toxicity.

Lizette Figueroa-Rivera:

Thank you. And our last question today comes from Buck and Karen. Both are asking about neuropathy. Buck asks, does CLL or the chemotherapy cause neuropathy? And Karen is asking what can be done about the neuropathy.

Dr. Danielle Brander:

So, there are certain chemotherapies that can cause neuropathy for patients with CLL. And so, the best thing is that neuropathy can mean a lot of different things. We look for common things, for example, an emerging or undiagnosed diabetes or thyroid or all the other host of testing that can be done. So, I certainly wouldn't see one of my patients and say this is your CLL or this is your chemo unless they didn't have it and then they received a certain chemo, lymphoma treatment, that is known to cause neuropathy. Instead I would as best as possible try to work with a neurologist or someone else that can help after you've sent basic labs to diagnose the type of neuropathy, and then to try from that point forward to target your treatment. Sometimes the treatment for neuropathy is really trying to get the right medications that help with neuropathic pain, but ultimately if there's an underlying reason that can be found on labs or testing, it's better to go after the underlying reason.

Lizette Figueroa-Rivera:

Thank you, Buck and Karen, for your questions, which were our final questions today. And of course, I want to thank you so much, Dr. Brander, for your continued dedication to patients.

Living with Chronic Lymphocytic Leukemia (CLL)

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SUPPORT RESOURCES

- **Online chats:** Online moderated chat forums: www.LLS.org/chat
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask
- **Free education materials:** www.LLS.org/booklets
- **Past CLL education programs:** www.LLS.org/programs
- **For information on leukemia:** www.LLS.org/leukemia
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
 - **E-MAIL:** infocenter@LLS.org
 - **TOLL-FREE PHONE:** (800) 955- 4572

Wednesday, July 12, 2017

Slide 85. Support Resources

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

Support for this program again was provided by AbbVie, Genentech & Biogen, Gilead, Pharmacyclics and Janssen, and an educational grant from Teva Pharmaceuticals.

If we weren't able to get to your question today, please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Dr. Brander, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.