Cases Revisited

Jan A. Burger, MD, PhD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

So, at this point, I guess we are going to go back to the patient cases and discuss the three patients I introduced in the beginning in little more depth.

Case 1

- 51-year-old male with relapsed CLL and progressive lymphocytosis, lymphocyte doubling time <6 months
- CLL since 1997, previous treatment FCR and bendamustine

PE:	0.5-1 cm cervical nodes No axillary or inguinal nodes or palpable spleen
Lab:	WBC 45,200, 84% lymphocytes Hgb 13.7, platelets 115,000
Flow:	$CD19^+$, $CD5^+$, $CD23^+$ CD20 weakly positive, $CD38^-$
FISH:	11q-, 13q-
IgVH:	Unmutated (1.3% deviation from germline)
CT	Spleen slightly enlarged (15 cm), abdominal nodes up to 2 cm

And so going back to this case #1

Case 1 (continued)

- This patient started ibrutinib single agent in 9/2010
- Treatment well tolerated, no relevant side effects
- Lymphocytosis progressed from 45,200 to 94,300/µL in 10/2010, Hb and platelet counts stable

the patient in the relapsed disease setting who is early into the treatment with ibrutinib and then experiences this lymphocytosis, the rapid lymphocyte doubling time.

Which of the following statements are NOT consistent with 11q deletion CLL and response to therapy?

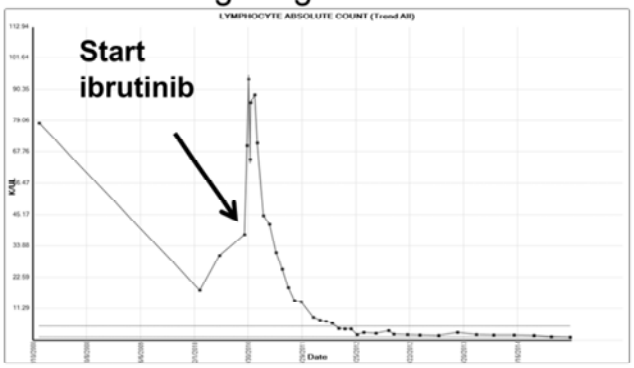
1. Male gender, presentation at a relatively young age, significant adenopathy, and absence of IGHV mutations (unmutated CLL/U-CLL) is typical in patients with CLL and 11q deletion
2. A short remission duration after FCR and bendamustine is typical of patients with 11q deletion
3. The patient is showing signs of early progression on ibrutinib with an increasing lymphocyte count and needs be switched to another type of therapy
4. The minimal side effects of ibrutinib within the first month are characteristic

It was about 11q deleted CLL, short remission duration that showed lymphocyte doubling time and side effects. If you could vote now,

So, it is 65% actually giving here what I thought is the correct answer which is pointing out that #3 was incorrect, this lymphocyte doubling that is an expected early finding in patients treated this way and it is characteristic. It is a class effect for these novel kinase inhibitors that they initially lead to a rapid increase in peripheral lymphocyte counts at the same time. The lymph nodes are shrinking.

Case 1 (continued)

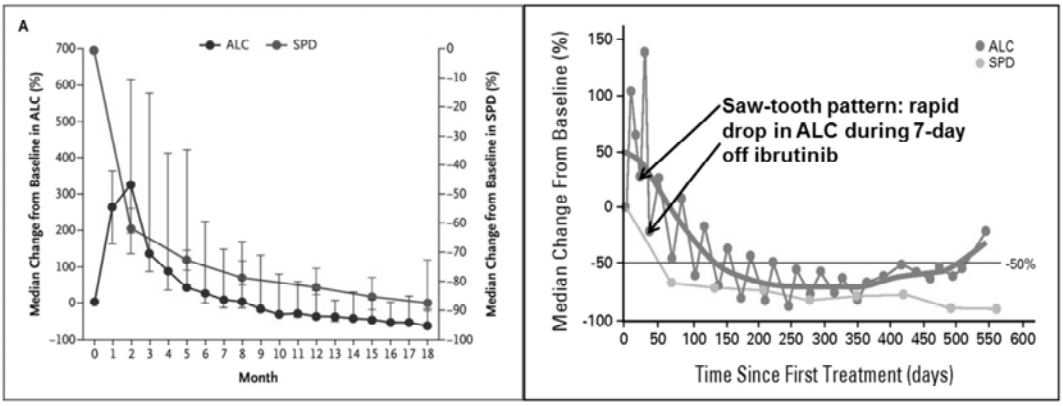
- This patient started ibrutinib single agent in 9/2010



  - Normalization of ALC in 11/2011
  - CT 4/2011: no residual disease
  - 11/2012: BMA in CR, MRD 3.5%
  - 04/2014: BMA in CR, MRD 2.6%

I am going to show you what happened in this patient. He had start of Ibrutinib. These are the trended lymphocyte counts you see here by the arrow indicated when he started Ibrutinib and during the first approximately six to eight weeks he had this rapid increase in doubling of lymphocyte counts but patients are not doing poorly. They actually feel better during this time and if they have palpable lymph nodes, you see lymph node shrinking. And then continuing ibrutinib single agent, you see over time the lymphocytosis completely resolves and now 4 years later, he still has low normal lymphocyte counts and he is doing well but he is not in a complete remission. Here at the bottom you see his residual disease levels in the bone marrow are still 2% to 3%, so even in this patient you could argue and I have been discussing with the patient the value of allogeneic stem cell transplantation but we have decided against that for now.

Ibrutinib-induced CLL Cell Redistribution: Blood Lymphocytes vs Lymph Nodes

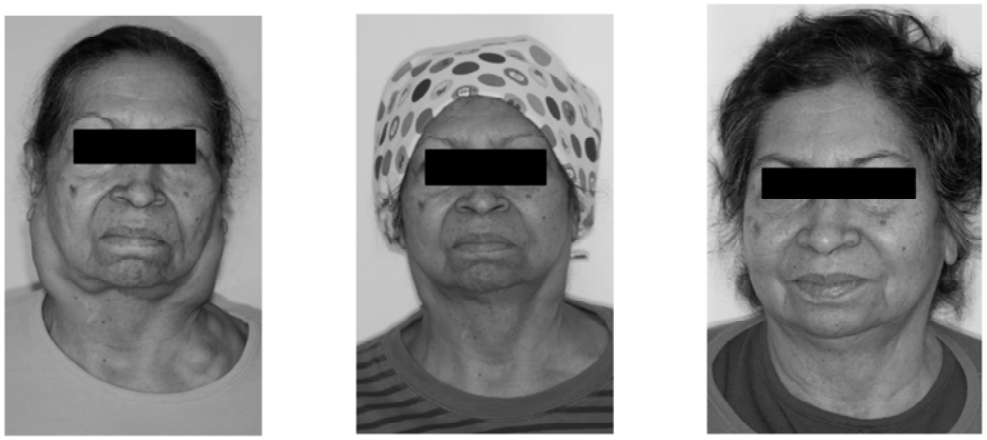


- Redistribution of tissue CLL cells into the PB causes early lymphocytosis (up to 3-fold increase)
- Class effect of kinase-inhibitors targeting BTK, PI3K, and SYK
- Saw-tooth pattern due to re-homing of CLL cells during "off-drug" period

Byrd JC, et al. *N Engl J Med.* 2013.; Advani RH, et al. *J Clin Oncol.* 2013.

Is that well recognized? I think it is. The transient lymphocytosis shown here on the left-hand side from the phase I and 2 study is well established, the peak was around 2 months as you can see on the left, and what is arguing for this being a redistribution phenomenon, whether tissue CLL cells are flushed into the circulation is shown here on the right-hand side. This saw-tooth pattern on single-agent ibrutinib where it is given 3 weeks on and then 1 week off, and during the time where patients come off the drug, there is a rapid drop in absolute lymphocyte counts. And one of the questions also asked from the audience was how do you manage this hypo-lymphocytosis? And I think one of the approaches could be if it is an acute situation and patients really have symptoms from the hypo-lymphocytosis, which is rare and rarely happens, under 500,000 in our experience, then you could hold the drug and you would see an immediate drop in lymphocyte counts. It is not a long-term fix, but one of the approaches has been to combine these agents with antibodies, and antibodies and other treatment modalities certainly shortened this transient lymphocytosis, but in most patients it is asymptomatic and does not cause really any problems.

Marked Reductions in Peripheral Lymphadenopathy During Ibrutinib Therapy



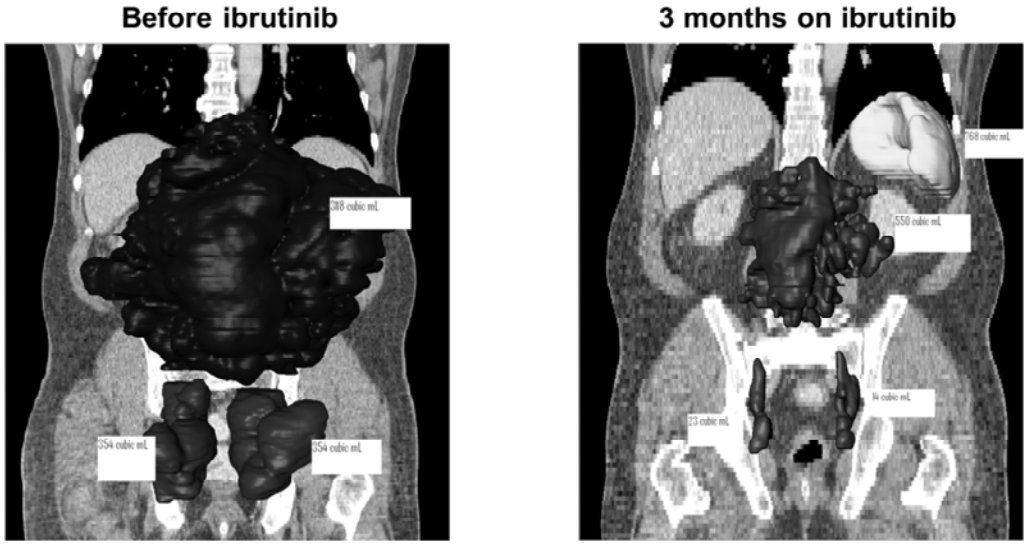
Before
Ibrutinib + R (iR)

2 weeks
iR

9 months
iR

The basis is redistribution of tissue cells into the bloodstream and you can see in patients with bulky disease like this lady with 11q deletion that lymph nodes rapidly shrink and oftentimes even almost melt away within the few weeks like shown here on the left before treatment, were these bulky lymph nodes, and then 2 weeks into treatment, this patient already had major improvement in lymphadenopathy

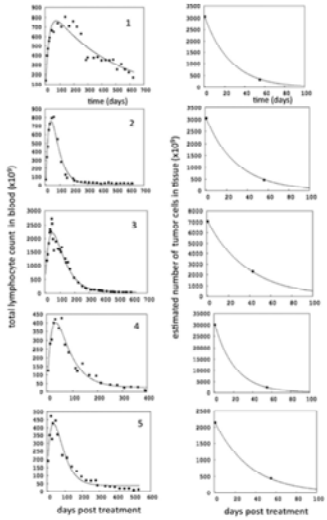
Volumetric Changes During Ibrutinib Therapy



Wodarz D, et al. *Blood*. 2014.

and we can see the same on CT scans and we analyzed basically asking the question how many of these tissue cells are redistributed? If all the cells sometimes in these bulky patients would be redistributed into the bloodstream, we would expect enormous increases in peripheral lymphocyte counts and that does not seem to be the case,

Dynamics of PB and Tissue CLL Cells During Ibrutinib Therapy



- During ibrutinib therapy, 1.7% of blood and 2.7% of tissue CLL cells die per day
- The fraction of CLL cells that redistribute into the blood during ibrutinib treatment represents 23.3% ± 17% of the tissue disease burden

- Serial ALC (left column)
- Serial volumetric analysis (right column) of CLL disease burden

Wodarz D, et al. *Blood*. 2014.

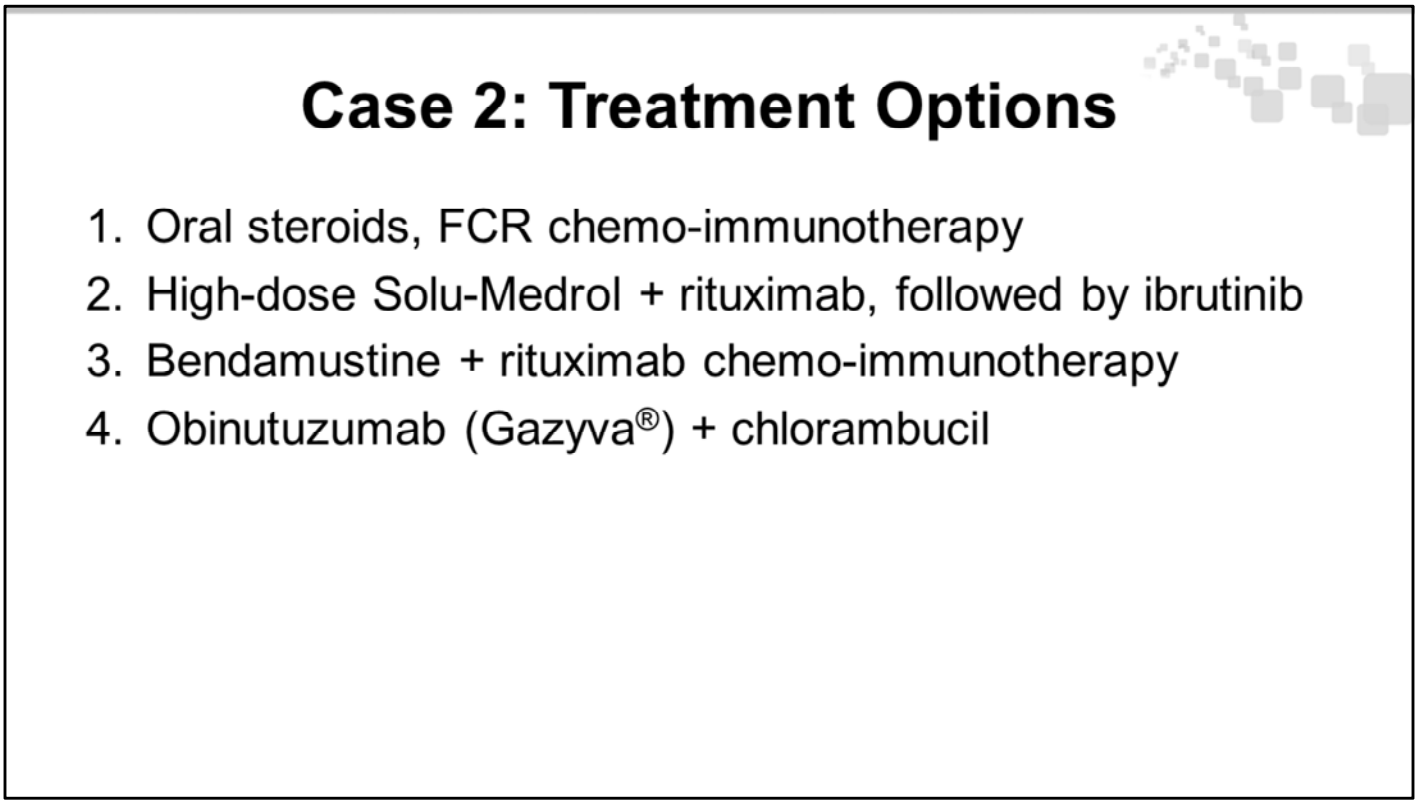
so we addressed that question in a kind of systematic fashion where we did volumetric analysis of these tissue manifestations of CLL in different patients and we analyzed the volumes before and during ibrutinib therapy and correlated that with trended lymphocyte counts. And by doing these correlations, we estimate that only about 20% to 30% of the tissue CLL cells are actually redistributed. The remaining cells, we assume, are being killed either in the tissues or are dying somewhere in transition between tissues and the bloodstream.

Case 2

- A 43-year old female with newly diagnosed CLL. Dx in 2012, initially managed with observation
- 02/2014: comes for follow-up, no symptoms

PE	No enlarged lymph nodes or spleen
Lab	WBC 104,500, 79% lymphocytes Hgb 9.7, platelets 26,000, β_2M 2.4
Flow	CD19, CD5, CD23 positive CD20 weakly positive
FISH cytogenetics	Trisomy 12
IgVH	Mutated

This is again the second female patient who is going into frontline therapy and she is mutated, she is trisomy 12 and we had these different treatment options shown on the next slide

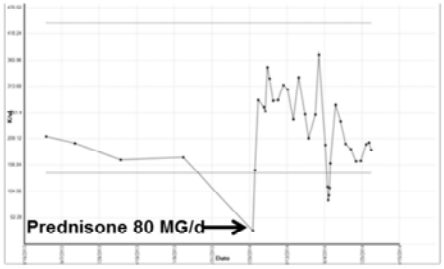


and maybe you could vote again and then we can discuss.

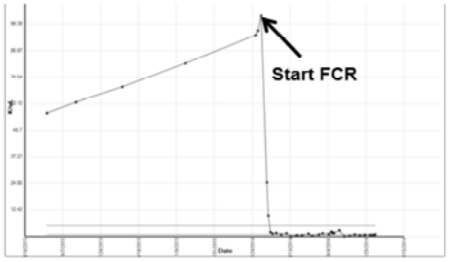
So, the rate of us choosing FCR with corticosteroids has increased and the other options have declined over time and that is actually what the patient received. We gave oral steroids and let me show you,

Case 2: Treatment Course

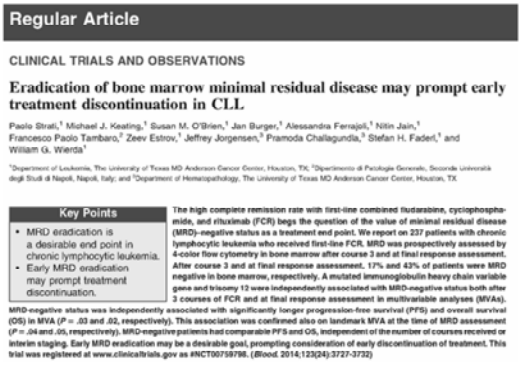
Platelet counts



Lymphocyte counts



- ITP and progressive CLL
- After 4 cycles FCR: MRD-negative



Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL

Paolo Strati,[1] Michael J. Keating,[1] Susan M. O'Brien,[1] Jan Burger,[1] Alessandra Ferrajoli,[1] Nitin Jain,[1] Francesco Paolo Tambaro,[2] Zeev Estrov,[1] Jeffrey Jorgensen,[3] Pramoda Challagundla,[3] Stefan H. Faderl,[1] and William G. Wierda[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dipartimento di Patologie Generali, Seconda Università degli Studi di Napoli, Napoli, Italy; and [3]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

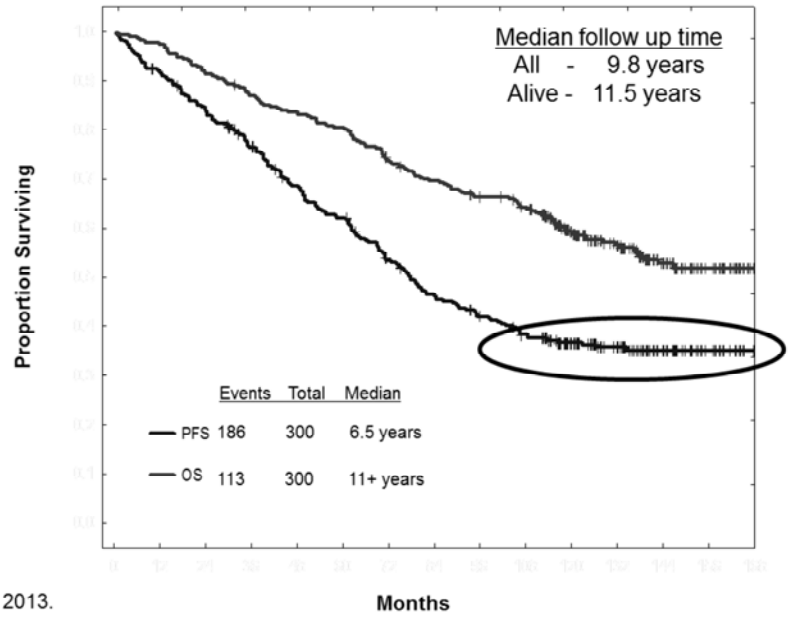
Key Points

- MRD eradication is a desirable end point in chronic lymphocytic leukemia.
- Early MRD eradication may prompt treatment discontinuation.

The high complete remission rate with first-line combined fludarabine, cyclophosphamide, and rituximab (FCR) begs the question of the value of minimal residual disease (MRD)–negative status as a treatment end point. We report on 237 patients with chronic lymphocytic leukemia who received first-line FCR. MRD was prospectively assessed by 4-color flow cytometry in bone marrow after course 3 and at final response assessment. After course 3 and at final response assessment, 17% and 43% of patients were MRD negative in bone marrow, respectively. A mutated immunoglobulin heavy chain variable gene and trisomy 12 were independently associated with MRD-negative status both after 3 courses of FCR and at final response assessment in multivariable analyses (MVAs). MRD-negative status was independently associated with significantly longer progression-free survival (PFS) and overall survival (OS) in MVA ($P = .03$ and $.02$, respectively). This association was confirmed also on landmark MVA at the time of MRD assessment ($P = .04$ and $.05$, respectively). MRD-negative patients had comparable PFS and OS, independent of the number of courses received or interim staging. Early MRD eradication may be a desirable goal, prompting consideration of early discontinuation of treatment. This trial was registered at www.clinicaltrials.gov as #NCT00759798. (*Blood*. 2014;123(24):3727-3732)

if you can advance to the next slide please that we have to trend it, peripheral blood cell counts, what you can see here on the top left are the trended peripheral platelet counts, we had a bone marrow done at that time, but also the thrombocytopenia seemed to be disproportionate to the overall presentation. The bone marrow showed megakaryocytes. I am not sure they were increased in total number, but there was the impression that she had an ITP component to it. Therefore, we gave prednisone. Once the platelets had stabilized, FCR was started and the patient achieved a complete remission. After four cycles, we restaged her and she was MRD negative and therefore we discontinued treatment after four cycles based on the data that Dr. Hillmen discussed earlier.

FCR300: Progression-free & Overall Survival



Wierda, et al. *iWCLL*. 2013.

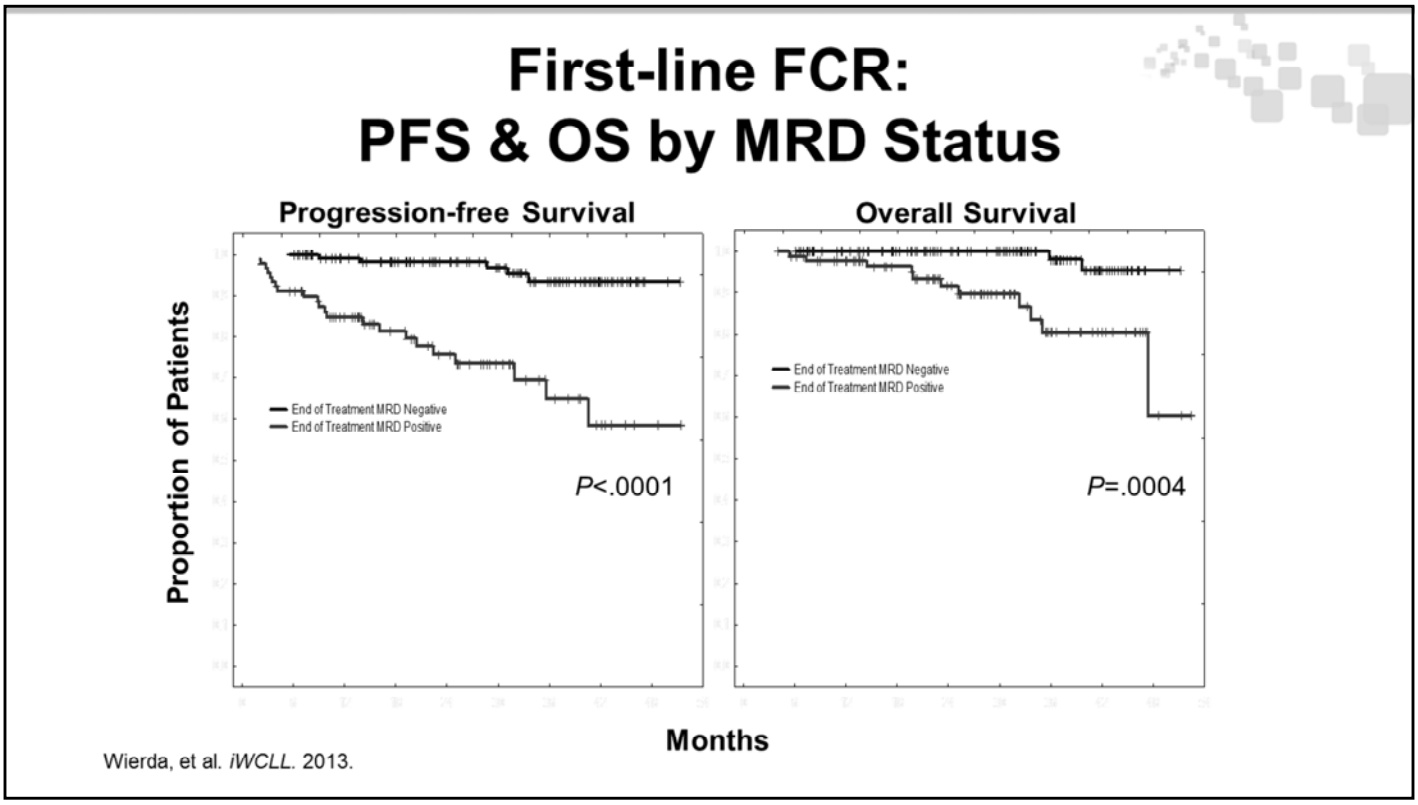
So, just the background, just to reemphasize, you have seen these slides already. The long-term followup from the initial FCR 300 data from Michael Keating were showing that you have fraction of patients who have very long progression-free survival that there is plateau here in the blue curve and these patients what do we know about them and can we apply that to our practice and to recommend treatment-based on individual factors?

First-line FCR: NCI-WG Response & Bone Marrow MRD-free Status

NCI-WG Response	No.	% of Patients	% MRD-Negative*
CR	153	65	75
nPR	29	12	4
PR	48	20	44
NR	7	3	0
Overall MRD	220	93	59

* Bone marrow evaluation by 4-color flow cytometry (sensitivity .01%)
Wierda, et al. *iWCLL*. 2013.

So, we known that minimal residual disease negativity is an important factor. You can achieved that in majority of patients, for example with FCR here in the total of 59% and we had analyzed in newer cohorts of FCR treated patients, what is the influence of MRD negativity and positivity on progression-free survival by the way we are assessing that by the stand that bone marrow four-color flow cytometry?



So, it has profound effect on progression-free and overall survival and

First-line FCR: Multivariable Model for BM MRD-free Status (N=181)

Pretreatment Characteristic	*P*-value
IGHV – Mutated	.003
Rai Stage – 0-II	.016
Trisomy 12	.02
No 17p del	.04

Wierda, et al. *iWCLL*. 2013.

then when you look at the factors in a multivariate analysis that contribute or that make it likely that you become MRD negative after FCR, then it is those patients who have good risk features, mutated patients, those patients who I have treated in earlier stages of their disease, trisomy 12 and certainly not 17p deleted patients which we would not want to treat with this regimen. So, this patient fit into these categories that is why we chose FCR in this patient and we are happy that we could based on the data we felt we could discontinue after four cycles.

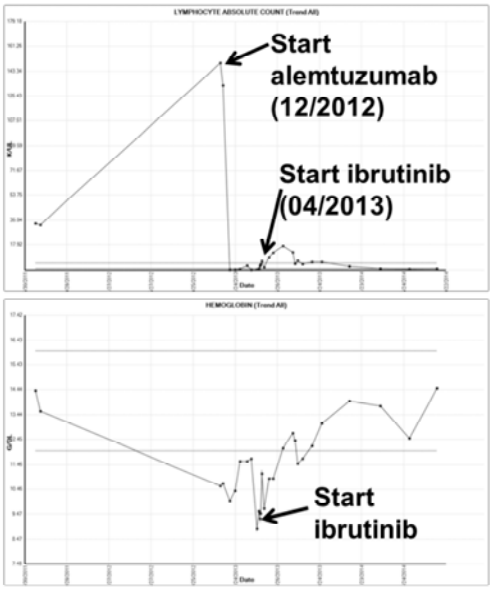
Case 3

- A 54-year old female with CLL, Dx in 6/2011
- 12/2012: comes for follow-up, complains of fatigue

PE	No enlarged lymph nodes or spleen
Lab	WBC 162,300, 92% lymphocytes Hgb 10.6, platelets 223,000
Flow	CD19, CD5, CD23 positive CD20 weakly positive, CD38-
FISH cytogenetics	Del(17p), del(13q)
IgVH	unmutated

Now, moving on to the next case, the question, what is the role of allogeneic stem cell transplantation in high-risk patients who are responding to these novel agents? It is this female patient who is basically frontline treated after a brief period of treatment with alemtuzumab, then treated with ibrutinib. She has 17p deletion, but she does not have any complex cytogenic abnormalities on conventional cytogenetics.

Case 3: Treatment Course



- Symptoms resolved after alemtuzumab (Campath)
- Anemia resolved on ibrutinib, patient continues on ibrutinib to date
- Restaging 8/2014: 10-20% marrow infiltration with del(17p) and del(13q)

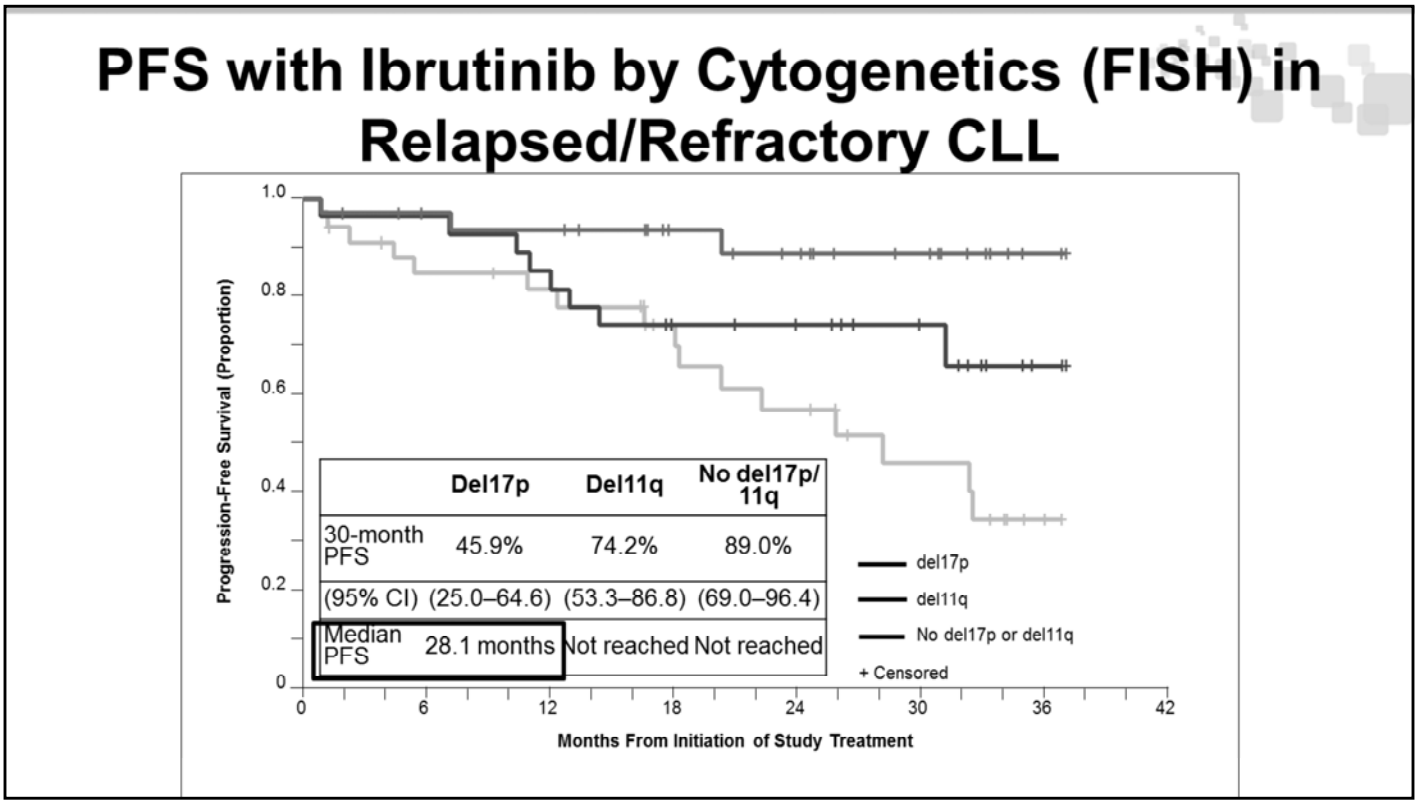
So, we gave her ibrutinib and she is doing excellent,

Case 3: Allogeneic Stem Cell Transplantation Indicated?

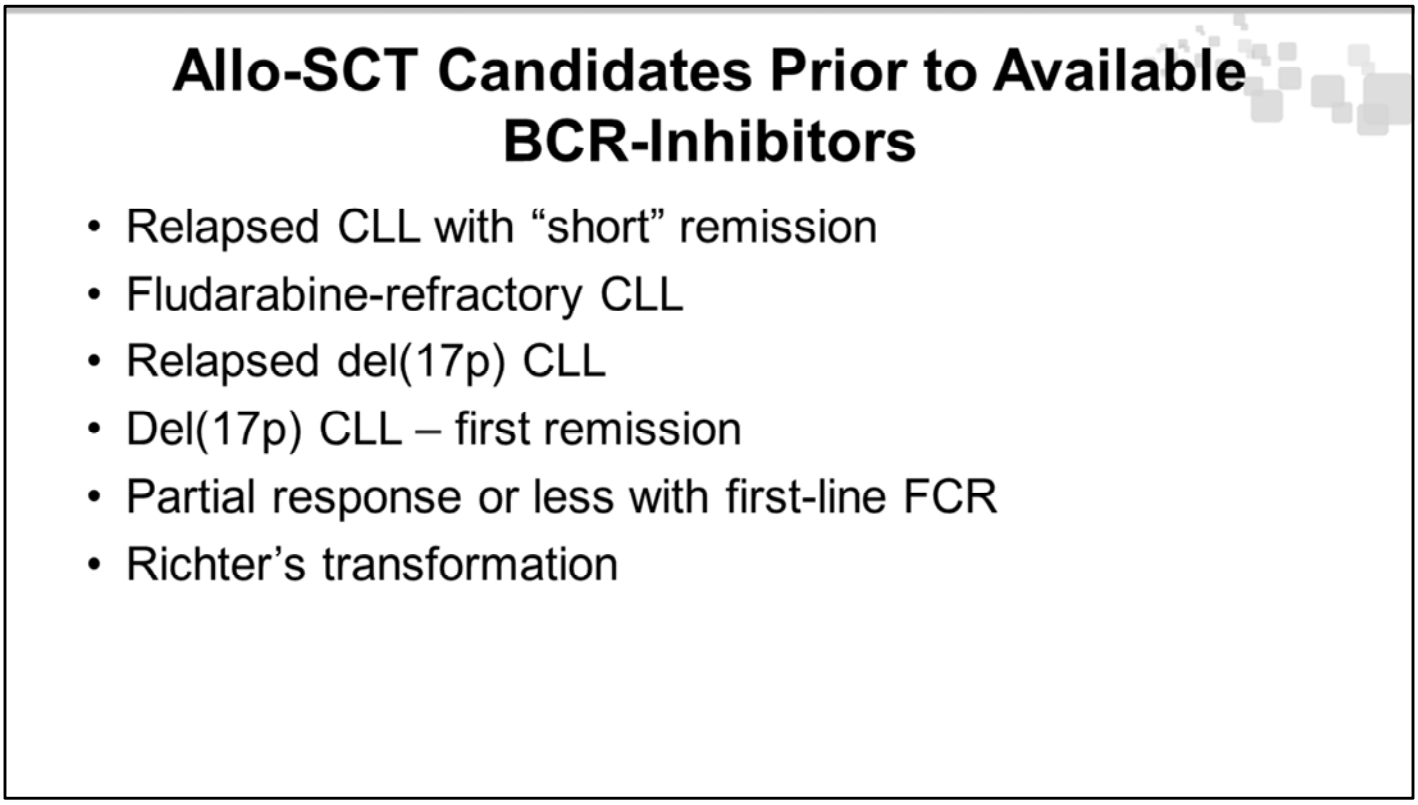
1. Yes, because patient has a median PFS of 28.1 months on ibrutinib due to del(17p), and patient with PD on ibrutinib have very poor outcome
2. No, patient has excellent QOL and allogeneic SCT only should be offered when clinical relapse is noted
3. Initiate donor search, recommendation depends on donor availability, comorbidity, and is an individualized decision process

but the question was what should we do in terms of transplant, should we firmly recommend a transplant at this point based on the data that we have with single-agent ibrutinib, or should we not recommend a transplant, or should we initiate a donor search, then factor in multiple things to make a recommendation? Maybe we can vote one more time if you do not mind.

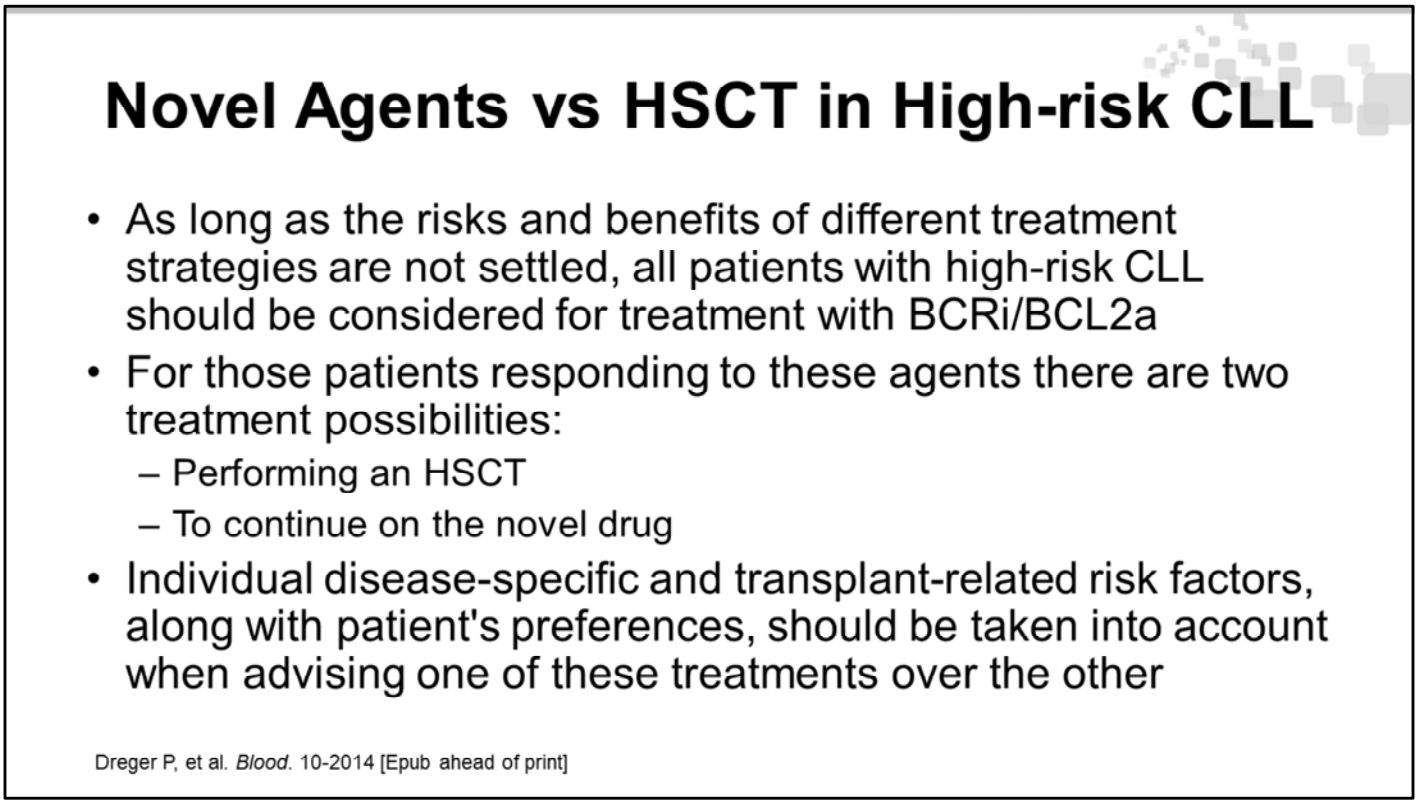
The majority of you have felt this differential approach, taking also the wishes of the patient into account, but also what is the donor availability, is it matched sibling donor, etc., into a consideration.



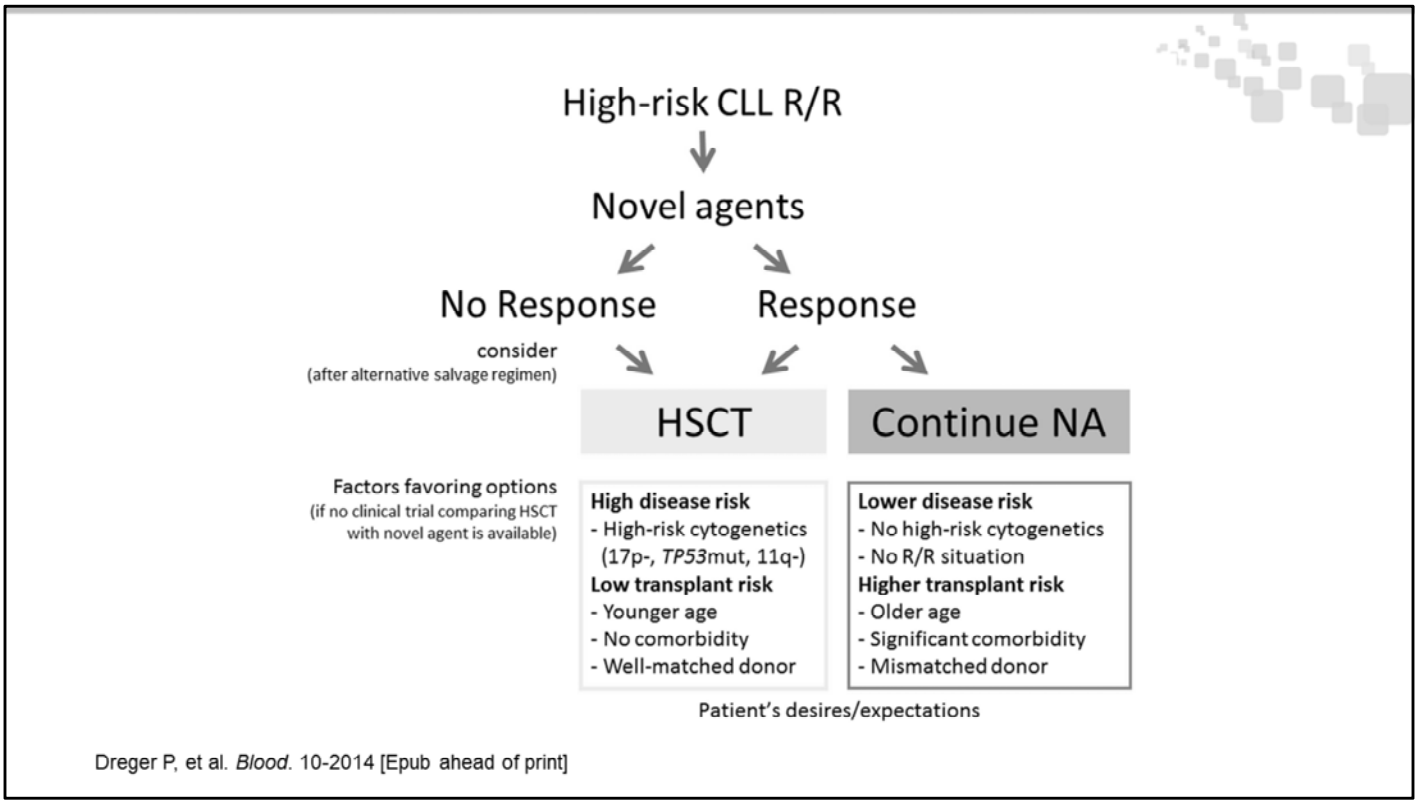
I wanted to go in a few slides about some recommendations that the European transplant community has put forward in a recent *Blood* article, but first background,
we have already seen this slide. If you have 17p deleted in multiply relapsed disease setting where this study was conducted, so potentially with other additional abnormalities, then you have a median progression-free survival on single-agent ibrutinib of approximately 28 months. So, that would favor the transplant approach in the patient who is responding but then not yet progressing.



What is the traditional role of allogeneic stem cell transplantation that summarized here? High-risk patients would basically be recommended to move forward with an allogeneic stem cell transplantation if they have a donor and if they are fit enough to undergo this procedure or if they have Richter's transformation,



but these concepts are not challenged by the new molecules and in response to that, Peter Dreger and his colleagues recently published this *Blood* paper basically stating or giving us some guidance on how to manage high-risk CLL patients in the era of these new targeted agents which have this excellent responses, even in high-risk patients. So, as long as risks and benefits of the different treatment approaches are not settled, they would recommend, and I agree with that, that first these kinase inhibitors should be used in any patient who has not previously been treated with, let's say, ibrutinib and idelalisib, but once patients then respond to these agents, then an allogeneic stem cell transplantation could be in option or you could continue the novel agents. And what they recommend is basically what the answer 3 was in individual disease-specific and transplant related risk factor based approach should be taken to kind of navigate patients towards this decision.



In this diagram from the same paper, which again came out of a few weeks ago, is summarizing basically the situation of this patient who has high-risk CLL. This patient you could argue is basically more frontline treatment setting, but she is receiving these novel agents and she is responding. So, should you move forward towards allogeneic stem cell transplantation versus continuing to observe? And here the disease specific risk factors certainly should come into play. If it is 17p deletion, 11q deletion, that is still debatable because we do not have very much long-term followup and we probably have to take into account additional cytogenetic risk factors, but if the patient is of younger age and have a very high risk constellation, then an allogenic stem cell transplantation should be done sooner, ideally in a patient who is not relapsing yet.

Thank you!

Dept. of Leukemia, MDACC
jaburger@mdanderson.org

I am going to wrap up and thank you very much for all the interesting questions and I hope these discussions have helped for the years to come to kind of give an idea where risk factors and where these novel treatments could most benefit our patients.