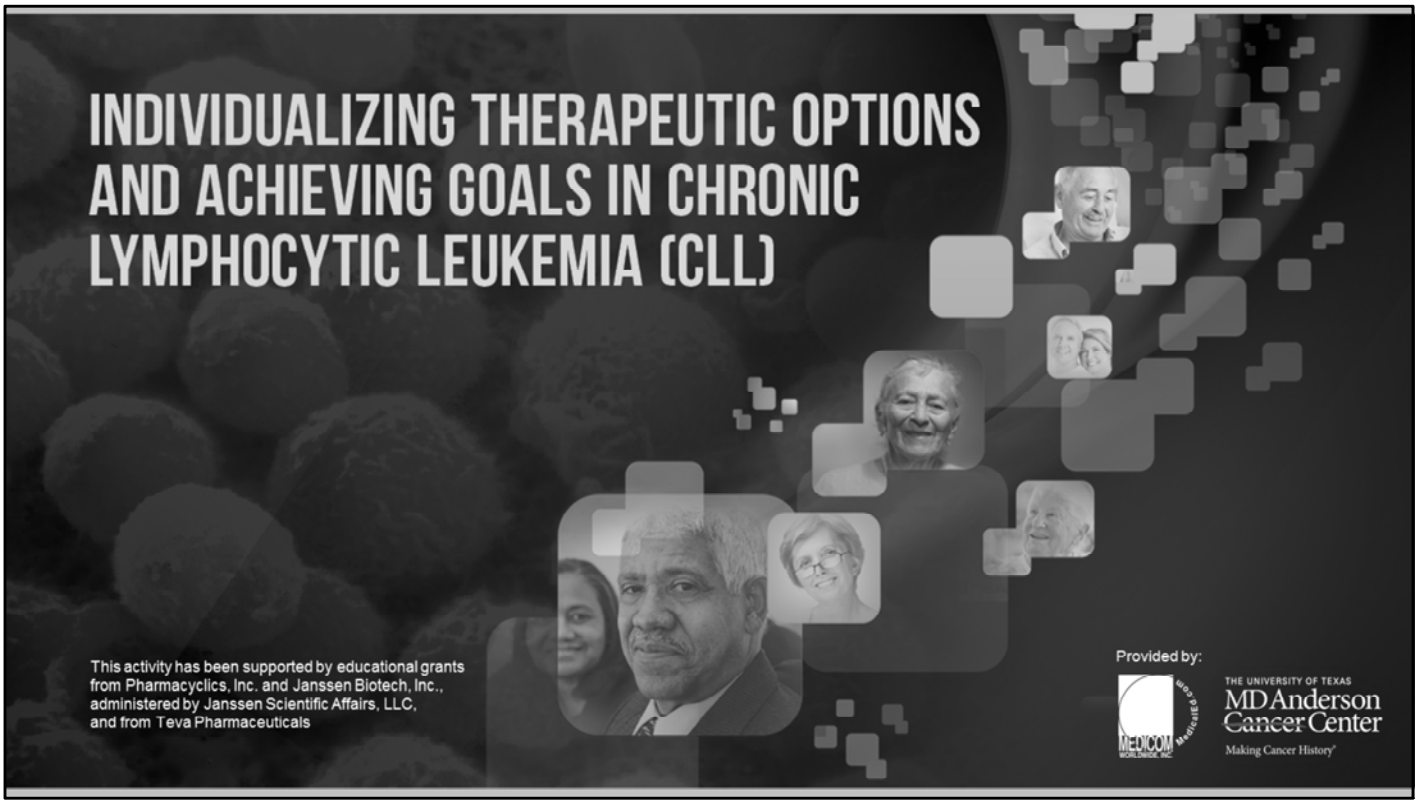

Good afternoon everybody. So welcome to ASH and welcome to this session on CLL titled, "*Individualizing Therapeutic Options and Achieving Goals in Chronic Lymphocytic Leukemia*."

Case Presentation

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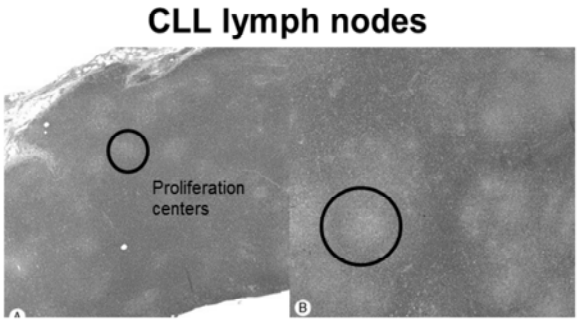
My name is Jan Burger. I am at the Leukemia Department at the MD Anderson Cancer Center, and I am joined by my colleagues Dr. Jennifer Brown from the Dana-Farber Cancer Institute, by Peter Hillmen from Leeds University, and by Dr. Thomas Kipps from UCSD.

So with the approval of the new kinase inhibitors, ibrutinib and idelalisib, this is a very timely topic, and I think the key questions for our clinicians is how to best integrate these new therapeutic agents into our practice and how they are going to find their way in comparison to the established treatment modalities, and that is what we are going to try to address and discuss. The way we have structured the session is that I am going to start describing you a little background but also some cases which then we are going to discuss in more depth at the end of the session, and in between, we are going to have lectures from my colleagues about prognostic factors, about the value of established and of novel therapeutic approaches to CLL.

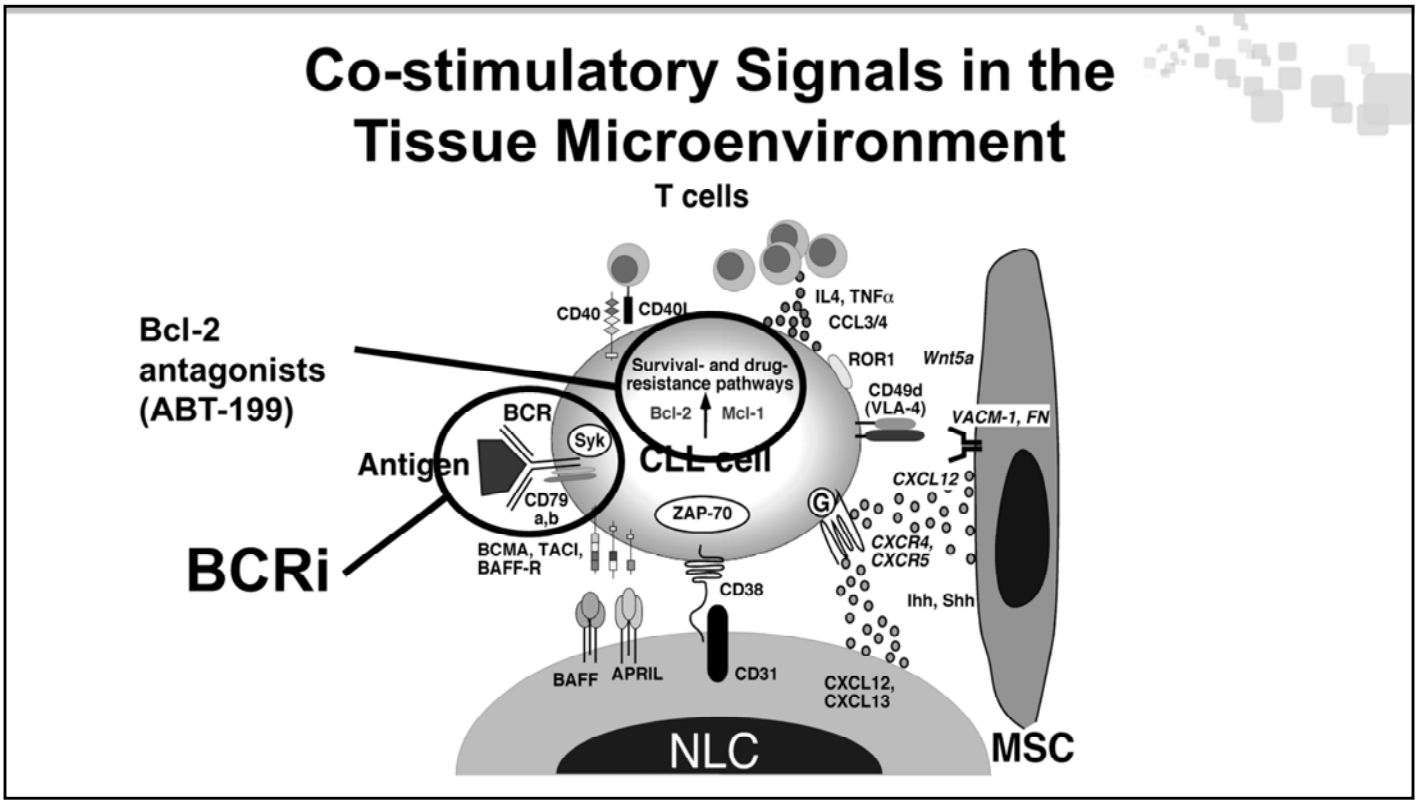
So, I think I am going to get started and the theme is some cases, but I am going to introduce the topic of the novel agents by just giving you some background, some questions about how these agents work and the key discovery over the past few years is related to the importance of B-cell receptor signaling which has not been recognized as much as in the past maybe 5 years.

In CLL Lymph Nodes, Sites of Proliferation = Sites of BCR Activation



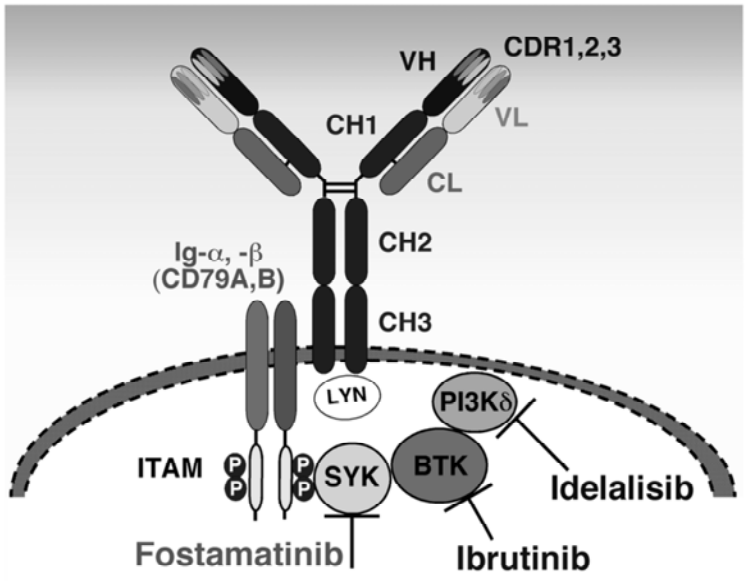
Soma LA, et al. *Human Pathology*. 2006;37:152-159.; Herishanu Y, et al. *Blood*. 2011.

As a key player and driver of CLL cell proliferation, what you can see here in these sections are proliferation centers where CLL cells proliferate, and the question is what is driving this proliferation? The most direct evidence that this is B-cell receptor signaling dependent event is coming from what is shown here on the right-hand side which is gene expression. When you take CLL cells out of these areas where they proliferate and do gene expression profiling, compare it to blood, which is shown on the right, then you see upregulation of a lot of B-cell receptor and NF-κB-dependent gene so that is I think the most direct evidence actually from Adrian Wiestner's group at the NIH indicating that this is a key target and a key driving event in the CLL pathogenesis.



We also recognized over the past years that the microenvironment plays a key role, and it is a complex issue so that diseases in terms of proliferation, not just driven by intrinsic lesions but also from the outside, and you see these various supportive cells like stromal cells, nurse-like cells, T cells, and the B-cell receptor on the left-hand side, and the most progress in terms of therapeutic targeting, these interactions has been made as you know with the approval of the two kinase inhibitors targeting downstream of the B-cell receptor certain kinases, and the other area of discussion lately has been around ABT-199 when you target anti-apoptotic proteins within the CLL cells.

Targets in the BCR Signaling Pathway



Burger JA, Chiorazzi N. *Trends Immunol.* 2013.

In terms of B-cell receptor signaling, what we can target briefly and is simplified and summarized here on this slide, the first inhibitor that was tested in patients with B-cell malignancies was the SYK inhibitor fostamatinib, shown here at the bottom, which has now left clinical development in B-cell malignancies, but the two other ones here, the BTK inhibitor ibrutinib and idelalisib, the PI3 kinase delta inhibitor, have been successful. Both have been approved last year and this year for treatment of patients with CLL. They are both inhibiting downstream of the B-cell receptor. You see here in the middle these signal transfusing portions of the B-cell receptors CD79A and B, and immediately downstream of that is spleen tyrosine kinase and then further downstream Btk and PI3-kinase isoforms.

BCR-associated Kinases

Kinase	Gene deletion/mutation	Activating receptors in B cells	Function in CLL	Inhibitor(s)
Spleen tyrosine kinase (SYK)	In mice: severe defect of B lymphopoiesis	BCR, integrins, chemokine receptors	Survival and migration via BCR- and chemokine receptor–signaling, chemokine secretion (CCL3, CCL4)	Fostamatinib, PRT2070, GS-9973
Bruton's tyrosine kinase (BTK)	In humans: X-linked agammaglobulinemia (XLA, Bruton's agammaglobulinemia) in mice: X-linked immunodeficiency (xid)	BCR, integrins, chemokine receptors	Survival, proliferation, and migration, BCR signaling, chemokine secretion (CCL3, CCL4)	Ibrutinib, CC292, ONO-4059, ACP-196
PI3Kδ	In mice: deficient antibody responses, lack of B1 cells and marginal zone B cells	BCR, integrins, chemokine receptors	CLL cell survival and migration, chemokine secretion (CCL3, CCL4)	Idelalisib, IPI-145, GS-9820, AMG 319, TGR-1202

What do these kinases have in common that is briefly summarized here in this table? If you delete any of these kinases in mice, then you see an early profound defect in B-cell development at an early stage of development, and there are no mature B cells. Speaking to the fact that these kinases are highly important in B-cell development, but only for one of these kinases, Bruton tyrosine kinase, that is a human phenotype which has a primary immunodeficiency XLA of Bruton agammaglobulinemia which is of rare primary immunodeficiency. The role of these kinases also is quite similar. They all play a role in B-cell receptor signaling, but they also play a role in B-cell migration and adhesion by mediating signals downstream of integrins and chemokine receptors. Similar functions have been described in CLL and what you see on the right-hand side is how many substances, how many different agents are already available and in clinical testing for targeting each of these kinases.

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

So, I am going to go into the cases and go through them with you, and I think at the end of each of these cases, you can vote and then we can see what the audience felt about this case, but I am not going to answer this case at this point, but rather do that at the end. So, these are three cases, patients from my clinic which have some relevance to the topic we are discussing here.

The first one is a 51-year-old male gentleman with CLL for many years already when he presented to our center, he came to us about in 2010, he had CLL since 1997. When he presented to us he was on physical exam and largely unremarkable. Lymph nodes were not grossly enlarged, spleen was not palpable, white cell count was elevated at 45,000, and he was borderline anemic and thrombocytopenic. His flow showed a typical CLL phenotype C38 negative, and he was 11q deleted as well as 13q deleted. He was unmutated in terms of IgVH genes, and CT imaging did not show any major changes, slightly enlarged spleen, and abdominal lymph nodes.

Case 1

- 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 had prior treatment with FCR and bendamustine-based therapy when he came in this situation, and we started him on single-agent ibrutinib at this time in 2010. He tolerated the treatment well, and there were no relevant side effects, but we noted starting this treatment that his lymphocytosis actually progressed from 45,000 to 94,000 within a short period of time, within about 1 or 2 months. His hemoglobin and platelet counts however remained stable,

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 a short lymphocyte doubling time and alternative therapy should be considered
4. The minimal side effects of ibrutinib within the first month are characteristic

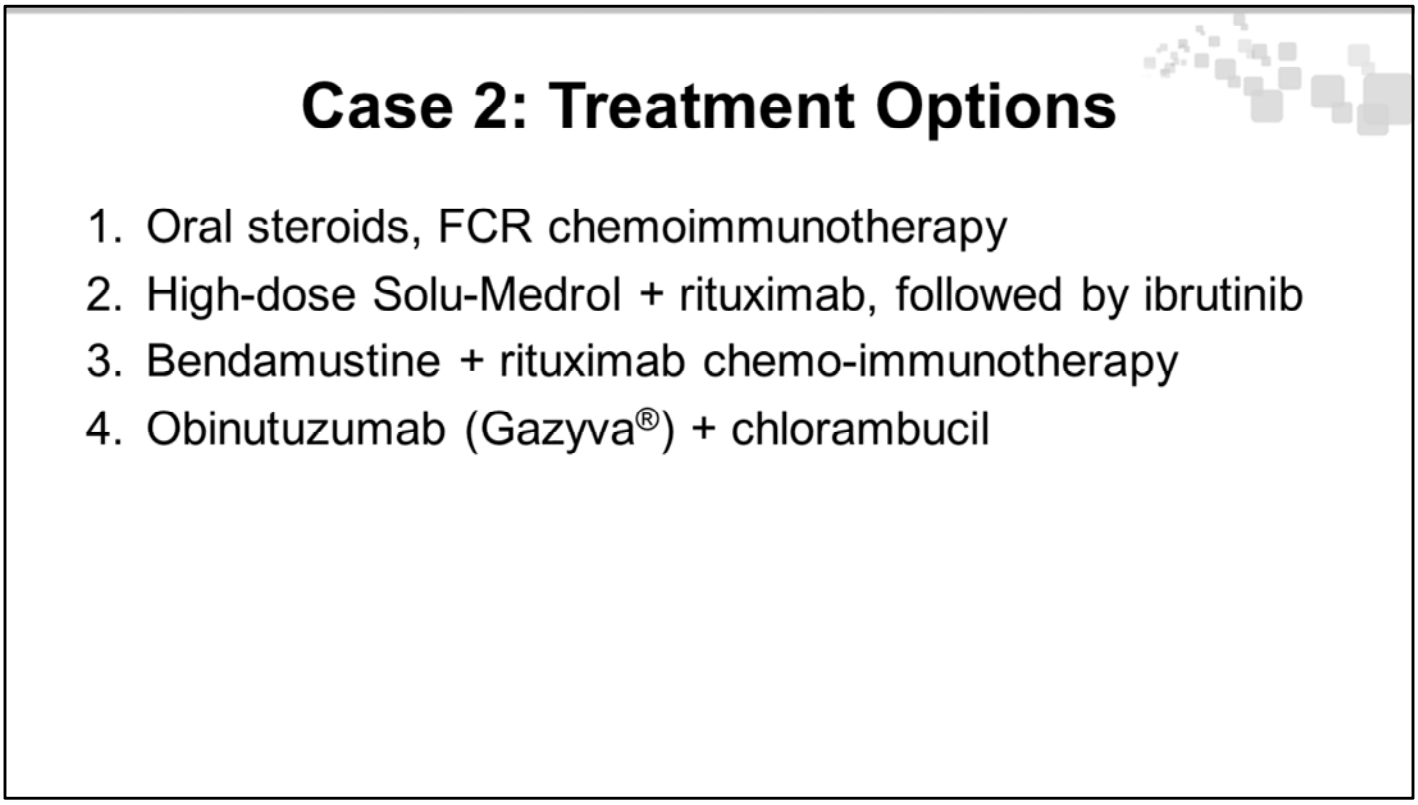
so with this clinical case these four questions about patients with CLL 11q deletion is his male gender, his clinical presentation in general, is that a typical finding? Yes or no? And is it typical that he is young, relatively short remission duration after FCR and bendamustine, typical presentation with CLL patient with 11q deletion? That is the second question. The third question is does this patient show signs of early progression on ibrutinib because he has this short lymphocyte doubling time? Therefore, an alternative therapy should at this point now be considered. The fourth question is minimal side effects of ibrutinib. Is that a typical finding in the first months of treatment? I think we can poll at this point.

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

So let me go to case 2 then which is a 43-year-old lady diagnosed with CLL rather recently, 2 years ago, and she was managed with observation and came just for a routine follow-up visit. She was on physical examination unremarkable, but she had progressed in terms of her blood counts. She now had a greatly elevated lymphocyte count. She was anemic and profoundly thrombocytopenic. You see her beta2 macroglobulin not greatly elevated. Flow cytometry was typical, nothing unremarkable, and she was found to have trisomy 12 and mutated IgVH.



So, for her situation I wanted to discuss four different treatment options—number one being giving her oral corticosteroids followed by FCR chemoimmunotherapy, as a second option higher-dosage intravenous corticosteroids in combination with rituximab followed by ibrutinib. Third option could be bendamustine and rituximab chemoimmunotherapy, and the fourth option would be obinutuzumab in combination with chlorambucil. Can we do the voting now?

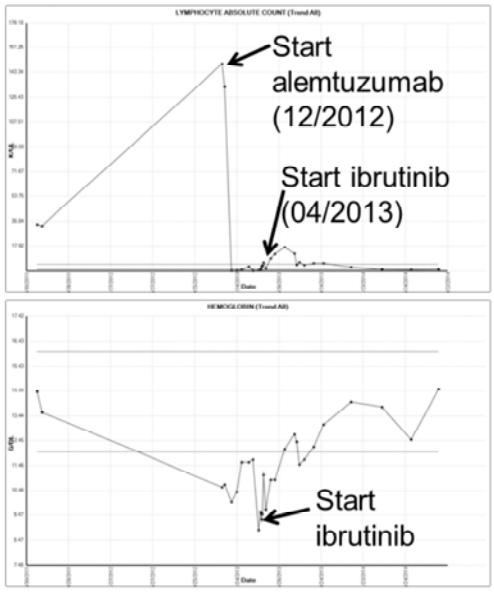
Case 3

- 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

Then, let's move on to the third case. This is also a female patient also younger, diagnosed 3 years ago, and she was previously managed with observation but came with complaints of fatigue. She was unremarkable on physical examination, again, but greatly elevated white cell count to 160,000, also anemic. Her platelets were still holding up okay. Nothing remarkable on flow cytometry. The cytogenetics deletion 17p together with 13q deletion, and she was found to be unmutated.

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 what we did with her at that time. We could not get her on ibrutinib. It was not approved yet, and we did not have a trial slot so we started her on alemtuzumab for cytoreduction. She had a good response as you can see in the top panel which shows the trended lymphocyte count. So start of alemtuzumab, rapid drop in lymphocyte counts, and then subsequently in April 2013, we got her on a clinical trial with ibrutinib, and she has been doing well as you can see from the trended lymphocyte counts but also from the trended hemoglobin which is shown at the bottom. She is clinically doing excellent. She came for a routine followup visit. We did a bone marrow workup and that showed 10-20% bone marrow infiltration more than a year into the treatment.

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 patients 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

So the question is what we should do with this patient at this point?

The first possibility, yes, should we do an allogeneic stem cell transplantation or recommend that in this patient with 17p deletion? One possibility, the first answer would be yes because she has an expected, not very long, progression-free survival of maybe 2 years based on the single-agent data from the phase I/II study, and patients, once they experience progressive disease on ibrutinib have very poor outcome. The next answer number 2 would be the opposite. No, the patient has an excellent quality of life, and an allogeneic stem cell transplantation should be saved as an option when we see clinical signs of disease progression or relapse. The third possible answer would be to initiate a donor search, but the recommendation for the transplant depends then on a complex decision process involving donor availability, comorbidity, and it is basically an individualized decision process. If you could, please vote on these too.