

# Q&A

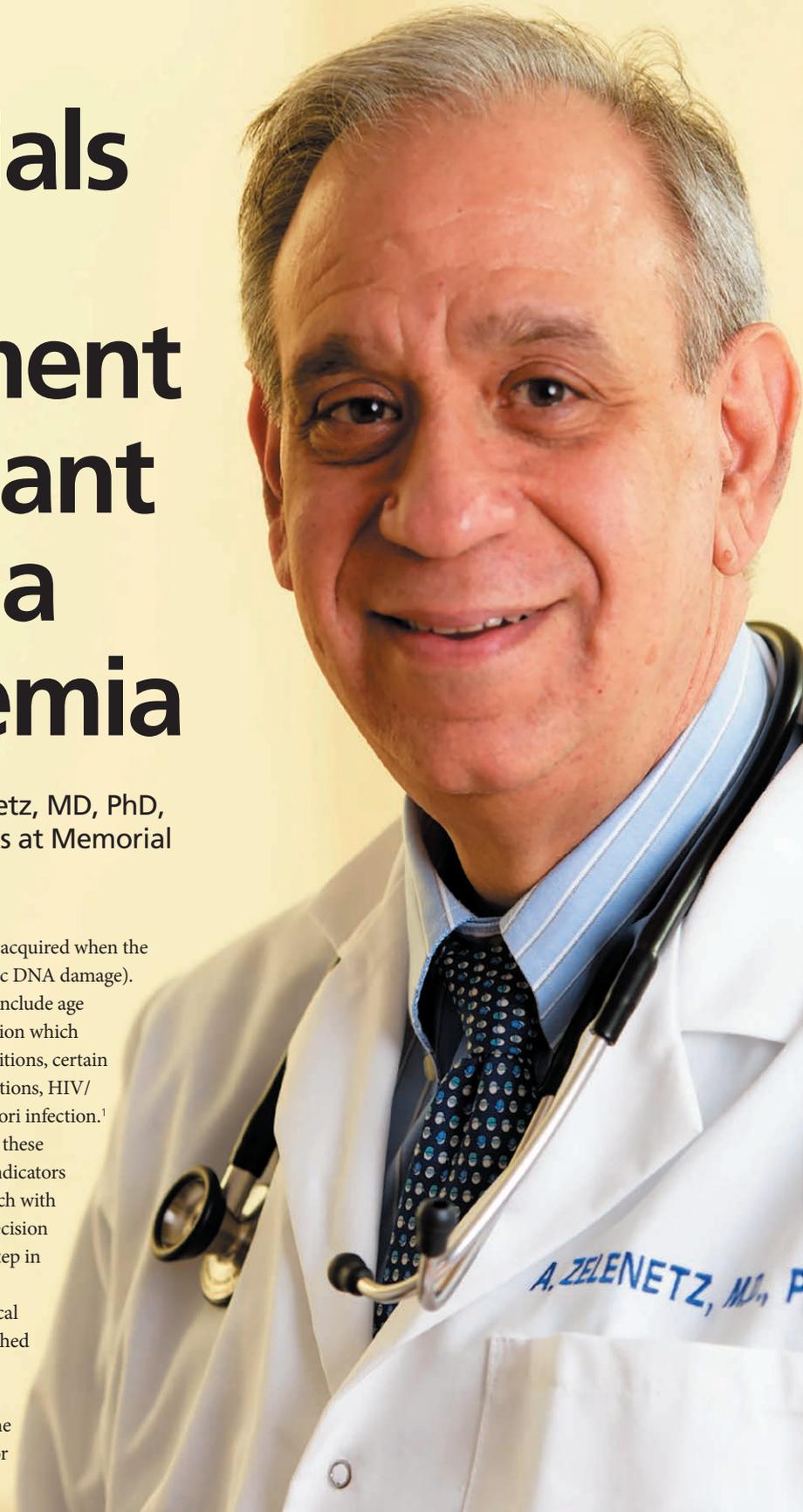
# Clinical trials for the management of malignant lymphoma and leukemia

*A focused Q&A with Andrew Zelenetz, MD, PhD, Medical Director, Quality Informatics at Memorial Sloan Kettering Cancer Center*

MANY LYMPHOMAS are not inherited, but rather are acquired when the DNA within select body cells has been damaged (somatic DNA damage). Some risk factors for non-Hodgkin lymphomas (NHL) include age (older), gender (male), race (white), and having a condition which weakens the immune system, such as autoimmune conditions, certain genetic disorders, being on immune suppressing medications, HIV/AIDS, HTLV-1, Epstein-Barr virus, and helicobacter pylori infection.<sup>1</sup>

A goal of precision medicine is to differentiate among these factors using patient profile data to determine the best indicators for a course of treatment. In fact, combining this approach with insight from a patient's doctor is the best marriage of precision and personalized medicine. Clinical trials are a critical step in achieving these ends and deliver improved healthcare.

Dr Andrew Zelenetz has extensive experience in clinical cancer research and precision medicine, and we approached him with questions to tap into that experience. Cancer clinical trials are long and complex. For purposes of this Q&A, we chose to focus on the data-guided aspects of the trials in which Dr Zelenetz is the principal investigator or is participating as a trial site investigator. >>



# Don't let patients with **TARGETABLE MUTATIONS** get lost in the crowd

There are ~4,000 to 5,000 patients with **METex14** in mNSCLC per year in the United States.<sup>1-2</sup>



Nearly 1 in 2 patients with mNSCLC may have a targetable oncogenic mutation,<sup>3-10</sup> but many patients are not tested for all potential targets (prevalence of **METex14** ~3%).<sup>4,9,11-15</sup>



The National Comprehensive Cancer Network® (NCCN®) recommends testing for **ALK**, **KRAS**, **BRAF**, **EGFR**, **METex14**, **NTRK1/2/3**, **RET**, **ROS1** and PD-L1 in eligible newly diagnosed mNSCLC patients.<sup>16\*</sup>

**Up-front broad molecular profiling may help optimize first-line treatment for mNSCLC.**

*MET*, mesenchymal-epithelial transition; *METex14*, *MET* exon skipping; mNSCLC, metastatic non-small cell lung cancer.

\*The NCCN Guidelines® for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.

**NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.**

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## 1: Study of Zanubrutinib, Obinutuzumab, and Venetoclax in Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Leukemia (SLL)

[Principal Investigator: Dr Zelenetz]

In this trial, three drug classes (zanubrutinib, a Bruton Tyrosine Kinase inhibitor; obinutuzumab, an anti-CD20 monoclonal antibody; and venetoclax, a BH3-mimetic) are combined and administered on a respond-adapted schedule. The primary outcome for this trial is to establish the rate of undetectable minimum residual disease (MRD) with the triple drug combination. Undetectable MRD in CLL means a patient has no detectable cancer cells above a specified threshold after a set time.

**Q. Besides flow cytometry, what other clinical measures of patients will be taken in the course of this study? Do you plan to do any sequencing to determine a potential correlation of patient response with genotype?**

**A.** Patients are assessed by standard International Workshop on Chronic Lymphocytic Leukemia (iwCLL) response criteria with complete blood count (CBC), CT scan, and bone marrow (BM) biopsy. In addition to peripheral blood flow cytometry, we are examining a more sensitive method for detecting minimal residual disease based on high throughput sequencing of the immunoglobulin and T-cell repertoire (immunosequencing). This approach has a sensitivity of 1 cell in 1,000,000 ( $10^6$ ) as long as there is adequate input DNA in the assay. All patients have IMPACT testing, which is a panel of 460 genes frequently mutated in hematologic malignancies sequenced to a depth of ~700x.

**Q. How is p53 being used as an inclusion/exclusion measure in this trial? What role does p53 play in metabolizing any of the drugs in this study?**

**A.** Aberrant TP53 (mutation and/or deletion) has been associated with inferior response to conventional chemoimmunotherapy (such as BR (bendamustine, rituximab) or FCR (Fludarabine, Cyclophosphamide and Rituximab)); however, all of three of the drugs being used in this study have been shown to have activity in patients with aberrant TP53. Thus, TP53 aberrant cases are not an exclusion in the CLL cohort. There is a second cohort of patients with mantle cell lymphoma that require aberrant TP53.

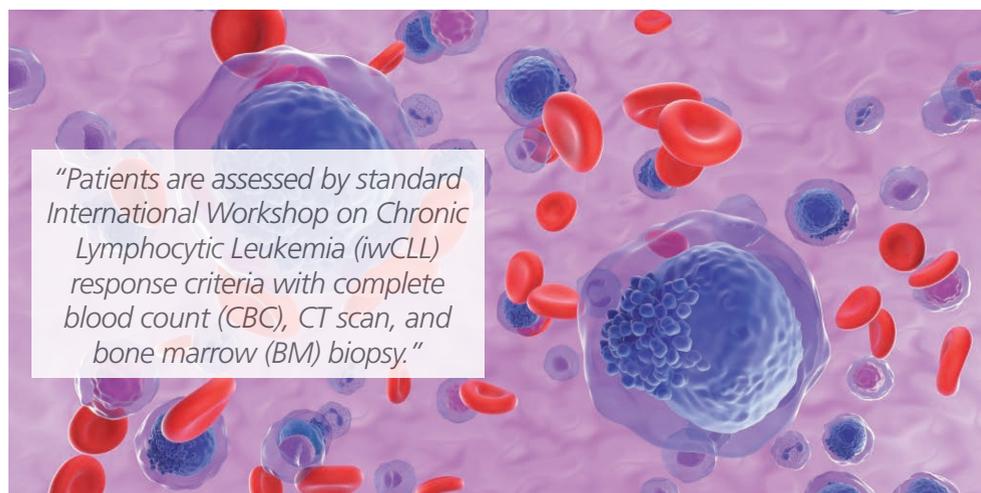
## 2: Study of Mocetinostat in Selected Patients With Mutations of Acetyltransferase Genes in Relapsed and Refractory Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

[Principal Investigator: Dr Zelenetz]

Two genes of interest for this study, CREBBP<sup>2</sup> and EP300,<sup>3</sup> are highly homologous (share similar structure). These genes provide instructions for making a protein (histone acetyltransferase) that, in turn, regulates the activity of many genes in tissues throughout the body. In particular, histone acetyltransferase ensures that DNA is ready for transcription by attaching an acetyl group to histones. While both genes serve similar functions, they do so through slightly different mechanisms. Most important is that both genes play an essential

**Q. Mocetinostat is a histone deacetylase (HDAC) inhibitor; how specific is the drug in inhibiting the function of the target? Do you anticipate any adverse events from non-specific binding, that is, off-target effects of HDACs not in the disease pathway? Do the study plans include any assays for genes, methylation, or histone acetylation status? How is p53 being used as an inclusion measure in this trial? What is its role in the mechanism of drug action?**

**A.** The concept behind this study was based on work from the Dalla-Favera and Pasqualucci laboratories demonstrating that by impairing histone deacetylase activity, the balance between acetylated and deacetylated proteins can be restored. Mocetinostat is a histone deacetylase



role in controlling cell growth and division, as well as prompting cells to mature and assume specialized functions (differentiate).

The stated purpose of this study is "to learn if the study drug mocetinostat can slow the progression of cancer in people who have a mutation in CREBBP or EP300 in the genetic makeup of their cancer. The potential side effects of mocetinostat will also be studied."

**Q. Could you provide background on the role of the two genes and the implication of their respective roles in the study?**

**A.** Both CREBBP and EP300 are examples of histone acetyltransferases. Acetylation of histones (and other proteins such as BCL6 and TP53) is a means to regulate the activity of these proteins. Loss of CREBBP or EP300 results in an alteration in balance of acetylated and deacetylated proteins which can lead to alterations in regulation that can lead to cancer.

inhibitor and impairs the deacetylation of key proteins with the goal of correcting the imbalance caused by the loss of CREBBP or EP300.

There was an embedded correlative study to examine the impact of mocetinostat on protein acetylation. TP53 is a protein that is regulated by acetylation; however, in this study aberration of TP53 was not required or an exclusion.

## 3: Sequential Chemo-Radioimmunotherapy Followed by Autologous Transplantation for Patients With Untreated Advanced Stage Mantle Cell Lymphoma

[Principal Investigator: Dr Zelenetz]

Mantle cell lymphoma (MCL) belongs to a group of diseases known as non-Hodgkin's lymphomas (NHL). NHLs are cancers that affect the lymphatic system; in MCL, cancerous B-cells are within a region of the lymph node known as the mantle zone.<sup>1</sup>

As noted in the trial description (NCT01484093), mantle cell lymphoma (MCL) is a rare and aggressive type of lymphoma, with only about 3,000 cases diagnosed per year. MCL is considered a difficult cancer to treat. This study is to understand better how to treat MCL

**Q. A paper is cited in the trial description that included NGS sequencing.<sup>4</sup> What did you learn from the sequencing data that informed this trial? Did those data inform the design of this trial?**

**A.** The small sample size in this study limited our ability to develop a genomic profile that reliably could predict outcome. However, this effort has led to a much larger study of the genomics of MCL in a cohort of more than 300 patients. This is the largest genomic landscape study in MCL and is distinguished by a subset of patient with serial biopsies at diagnosis and relapse. An unexpected finding is that there are patterns of mutations that are established at diagnosis and are relatively stable in recurrent disease.

**Q. Cytarabine can affect cells in several ways but its role in treating cancer is thought to be through direct DNA damage by incorporation into DNA to inhibit the proliferation of replicating cancer cells. Were other drugs considered for this study or is cytarabine the standard of care? Could other, more precisely targeted drugs arise from this study (or is drug discovery/development outside the scope)?**

**A.** Several studies have demonstrated that cytarabine is an important agent in MCL. However, more recently data has emerged that the benefit of chemioimmunotherapy including the role of cytarabine is based strongly dependent on TP53 status. Chemotherapy including cytarabine is markedly less effective in patients with TP53 mutations. In MCL, the independent role to TP53 deletion has been more controversial.

In this study we focused on the addition of 131I-tositumomab/tositumomab as an additional targeted therapy for MCL. 131I-tositumomab/tositumomab is a murine anti-CD20 monoclonal antibody carries a payload of iodine-131. MCL is highly radio-sensitive, and we had previously demonstrated very high response rates to radioimmunotherapy. In this study, radioimmunotherapy was incorporated into the high dose therapy followed by autologous stem cell rescue (HDT/ASCR).

**Q. Were other transplantation options considered for this study, e.g., donor stem cells? Could you foresee any genetic engineering of stem cells for future treatments or are autologous stem cells the preferred method for future use?**

**A.** Anti-CD19-directed chimeric antigen receptor (CAR) T-cell therapies have emerged as an important treatment option for relapsed or refractory MCL. HDT/ASCR has long been used as a component of initial therapy for eligible patients (generally younger than 75-years of age without substantial co-morbidities and no evidence of TP53 mutations). Though durable remissions are achieved for a substantial proportion of patients, the approach is not curative for most patients.

immunotherapy and chemotherapy treatments over the past few years.

**Q. Can you please comment on the power of combination therapy approaches in general and this trial therapy in particular?**

**A.** Targeted therapy has altered the treatment landscape for many cancers including lymphoid malignancies. Many of the targeted therapies, however, are administered at chronic therapies until intolerance or resistance often resulting in a chronic low-grade toxicity burden for patients impacting quality of life. Combination therapy has the potential to achieve deeper remissions. For example, in CLL, BTK inhibitor monotherapy is uncommonly associated with undetectable



This raises the question as to the role of CAR T-cell therapy as part of the initial management of MCL. Alternatively, with the emergence of highly effective targeted agents relapsed and refractory MCL, many studies are investigating the role of these agents in the initial management of MCL.

#### **4: A Phase II Study Using Rituximab Plus Venetoclax in the Front Line Treatment of Marginal Zone Lymphoma**

**[Co-Principal Investigator: Dr Zelenetz; Dr Zelenetz will assume the lead from Dr. Gottfried von Keudall]**

Rituximab is monoclonal antibody that binds to CD20 and is approved for clinical use in cancer therapies. Venetoclax is a small molecule that binds to Bcl-2. Precision medicine for cancer treatments has been employing paired

minimal residual disease (uMRD), however, combinations of BTK inhibitors and venetoclax can result in uMRD allowing for time limited therapy. In marginal zone lymphoma (MZL), Rituximab has excellent single agent activity in MZL, although, recurrence is common with a median PFS of six years. Preliminary data support activity of single agent venetoclax in the treatment of relapsed and refractory marginal zone lymphoma. The current study is evaluating time-limited therapy with the combination of rituximab and venetoclax to determine the safety and efficacy of this combination.

**Q. Why was Venetoclax chosen for this study (vs other choices for immunotherapy-chemotherapy combinations)?**

**A.** Venetoclax demonstrated single agent activity in marginal zone lymphoma Furthermore, addition of

venetoclax to ibrutinib for relapsed and refractory MZL had evidence of improved complete response rate compared to ibrutinib alone. The combination of rituximab and venetoclax was safe and effective in relapsed/refractory CLL. Thus, we chose to add venetoclax to the standard of care, which is rituximab monotherapy, with the goal of achieving deep and durable remissions.

**Q. Are there any biomarkers that could be used to monitor interim response prior to the 2-year outcome measures?**

**A.** Multiparameter peripheral blood flow cytometry has a sensitivity of detecting 1 cell in 10,000 which can be used to monitor MRD as there are frequently circulating cells in MZL. Another approach used in this study is to evaluate the utility of cell-free DNA (cfDNA) for the evaluation of MRD. This assay tracks mutations identified in pre-treatment biopsies in the cell-free DNA released from the tumor cells into the peripheral blood. This assay also has a sensitivity of approximately 1 cell per 10,000 depending on the quantity of input DNA in the assay. We are using this study to validate the utility of cfDNA to monitor response in MZL.

**5: A Phase Ib Study Evaluating the Safety, Efficacy and Pharmacokinetics of Venetoclax in Combination with Polatuzumab Vedotin Plus Rituximab (R) and Cyclophosphamide, Doxorubicin, Prednisone (CHP) in Patients with Untreated BCL-2 Immunohistochemistry (IHC)-positive Diffuse Large B-Cell Lymphoma (Site PI: Dr. Zelenetz)**

**Q. Could you please provide background on this study?**

**A.** Rituximab and CHOP chemotherapy is the standard of care for the treatment of DLBCL. The CAVALLI study explored the combination of R-CHOP with venetoclax. When compared to matched patients from the GOYA5 trial, patients treated with R-CHOP + venetoclax had a superior progression-free survival in patients with overexpression of BCL2 which is the target of venetoclax. In the historical comparison, there was also an overall survival advantage. More recently, the addition of polatuzumab to R-CHOP was shown to provide a significant improvement in progression-free survival to R-CHOP alone. The current study is to explore the safety and efficacy of venetoclax added to polatuzumab and R-CHOP in patients with DLBCL expressing BCL2.

**Q. If polatuzumab added to R-CHOP improved the outcome of patients with DLBCL, why add venetoclax and potentially increase side effects?**

**A.** To date the addition of polatuzumab to R-CHOP has not resulted in an overall survival advantage over R-CHOP. Furthermore, the magnitude of the benefit of adding polatuzumab is relatively small (~6.5% at 2 years) leaving ample room for improvement. Since the addition of venetoclax to R-CHOP in the CAVALLI study suggested a possible improvement in overall survival, exploration of this combination is important as it may provide an option for the patients with DLBCL expressing BCL2.

**Q. How are you going to demonstrate the benefit of adding venetoclax?**

**A.** This is primarily a study to establish the safe dose of venetoclax to add to the backbone of polatuzumab and R-CHOP. However, the recent POLARIX trial of R-CHOP versus polatuzumab-R-CHOP is source of patients to establish a matched synthetic control and provide some preliminary assessment of the impact of adding the venetoclax to the polatuzumab-R-CHOP backbone.

**Q. These five trials demonstrate the growing complexity of assays and treatments. What role do you foresee for precision medicine in clinical trials – not just for cancers but for other therapies as well?**

**A.** Cancers are heterogenous. For example, diffuse large B-cell lymphoma can be subdivided into at least 7 molecular subtypes with differential outcome and until molecular profiles. From pre-clinical models it is clear that novel therapies have differential impact on these subtypes. Thus, it is not surprising that a one-size fits all approach does not provide a uniform outcome for patients. If we are going to target the molecular heterogeneity of a disease, we need to have detailed information early in the course of treatment so that appropriate targeted therapy can initially be tested in clinical trials. If the clinical trials are positive, we have the greater hurdle of ensuring that the necessary testing is widely available with sufficiently rapid turnaround that the new treatment can be used in broad patient populations. Despite the promise of precision medicine, the obstacle of obtaining the critical results from predictive biomarkers in real-time presents a challenge that needs to be addressed if we will realize the potential of precision medicine.

Thank you, Dr Zelenetz. Your insights and examples are much appreciated. 

**Andrew D. Zelenetz, MD, PhD**

Andrew D. Zelenetz is the Medical Director of Quality Informatics at Memorial Sloan Kettering Cancer Center in New York. Prior to that, he had held the positions of Vice Chair, Medical Informatics from January 2013 to May 2016 and Chief, Lymphoma Service in the Division of Hematology/Oncology at MSKCC from 1994-December 2012. He is also a Professor of Medicine at Weill Cornell Medical College. Dr. Zelenetz was elected Chair-Elect of the SAB in 2017, and assumed the Chair in 2019.

He has helped develop several agents now approved to treat lymphoma – including 131I-tositumomab/tositumomab, bortezomib, and pralatrexate – and through clinical studies he is evaluating the benefits of novel combinations of agents. Dr. Zelenetz has also published more than 100 papers on lymphoma research in journals such as Blood, Journal of Clinical Oncology and Clinical Cancer Research.

**About Memorial Sloan-Kettering Cancer Center**

MSKCC is the world's oldest and largest private cancer center having devoted more than 135 years to exceptional patient care, innovative research, and outstanding educational programs. Today, MSKCC is one of 52 National Cancer Institute-designated Comprehensive Cancer Centers, with state-of-the-art science flourishing side by side with clinical studies and treatment.

The close collaboration between physicians and scientists is one of MSKCC's unique strengths, enabling the best care available for patients while researchers work to discover more-effective strategies to prevent, control, and ultimately cure cancer in the future. Its education programs train future physicians and scientists, and the knowledge and experience gained at Memorial Sloan Kettering has had an impact on cancer treatment and biomedical research around the world.

**Websites of interest for Andrew Zelenetz, MD, PhD**

<https://www.mskcc.org/cancer-care/doctors/andrew-zelenetz>

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