

In this month's Leukemia Insights newsletter, written by [Nitin Jain, M.D.](#), [Alessandra Ferrajoli, M.D.](#), and [William Wierda, M.D., Ph.D.](#), and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for the treatment of Richter Transformation. Learn more about our [Leukemia program](#).

## Treatment for Richter Transformation

Richter transformation (RT) is classically a morphologic transformation of chronic lymphocytic leukemia (CLL) into diffuse large B cell lymphoma (DLBCL), with aggressive clinical characteristics and course. Less commonly, transformation can be to Hodgkin lymphoma, which has a better prognosis. Rare cases of transformation to other aggressive histologic subtypes also have been reported.

The most common scenario is for a patient previously treated for CLL to have a rapidly enlarging lymph node, progressive symptoms of fatigue, rising LDH, and, occasionally, rising serum calcium. Clinical suspicion should prompt an evaluation with PET-CT to identify hypermetabolic lymph node(s) amenable to biopsy. Histologic review is essential; therefore, core or excisional biopsy is performed on the lymph node with highest SUV seen on PET-CT. Additionally, molecular assessment of RT cells from a tissue sample is important to determine clonal relationship to the CLL. Patients with previously untreated CLL who transform have what is referred to as de novo disease, which is more commonly clonally unrelated to the CLL and has a more favorable prognosis with standard chemoimmunotherapy for DLBCL. Increased risk for RT has been associated with certain CLL characteristics such as del(17p), mutated TP53, complex karyotype, del(11q), and mutated NOTCH1. Risk for RT also has been thought to be related to exposure to genotoxic chemotherapy, however, it is seen even among patients treated only with novel targeted agents, indicating the risk is more likely related to factors intrinsic to the CLL cells and genomic instability. RT that occurs in patients who received prior treatment for their CLL is typically clonally related to the CLL and has a very unfavorable prognosis.

Historically, treatment of the DLBCL sub-type of RT was with chemoimmunotherapy (CIT) containing rituximab and, most commonly, R-CHOP, and outcomes were universally poor,

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with complete remission (CR) rates of approximately 20% and few long-term survivors. Only a small minority of patients are eligible for potentially curative allogeneic stem cell transplant, given both the low response rates to CIT and the fact that the majority of patients are >70 years of age and have comorbidities.

In the past 15 years, attempts to improve outcomes for patient with RT centered on intensification of CIT with regimens such as R-EPOCH, R-hyper-CVAD and OFAR. However, these strategies have not improved progression-free survival and overall survival, as marginal increases in remission rates were offset by increased toxicity and short response duration.

RT that is clonally related to the CLL is molecularly distinct from de novo DLBCL and de novo RT; more than half of patients with clonally related RT have del(17p) and/or mutated TP53. These are strong negative prognostic markers and predict for chemoresistance. As treatment options expand, it is more critical than ever to genetically characterize the disease prior to therapy. In particular, the 20% of patients with clonally unrelated DLBCL and patients without TP53 mutations have significantly better outcomes, and their disease is often responsive to CIT-based treatments.

Below, we outline several clinical trials at [MD Anderson Cancer Center](#) for patients with RT. Importantly, we now have several chemotherapy-free approaches, which work by TP53-independent mechanisms and may be better tolerated by older and unfit patients.

#### **Pirtobrutinib combined with venetoclax and obinutuzumab (NCT05536349)**

Pirtobrutinib is a novel, highly selective and reversible inhibitor of Bruton's tyrosine kinase (BTK), which is potent and has favorable tolerability and pharmacokinetics. Encouraging initial single-agent data in RT were reported at ASH 2022 meeting where a total of 82 patients with RT received pirtobrutinib monotherapy.

Patients had a median of 2 prior lines of therapy for CLL and 2 prior lines of therapy for RT. In this heavily pretreated patient population, an overall response rate of 52% was reported. Based on these data and the data with the use of venetoclax in patients with RT, we developed an investigator-initiated study combining pirtobrutinib, obinutuzumab and venetoclax for patients with RT. Patients with relapsed and/or refractory RT and those with previously untreated RT (as long as they received prior therapy for CLL) are eligible. Synergy between pirtobrutinib and venetoclax may be observed, with limited toxicity. Pirtobrutinib is provided at no cost.

#### **R-CHOP plus venetoclax (NCT03054896)**

The addition of venetoclax to dose adjusted R-EPOCH increased the complete remission rate to 50% from a historical 20% with dose adjusted R-EPOCH alone. However, as noted above, many patients with RT are older and have co-morbidities that limit tolerability of intensive chemotherapy like R-EPOCH. RT is, in most cases, an intrinsically chemotherapy-resistant disease, but the addition of venetoclax appears to sensitize RT cells to chemotherapy-mediated killing. Venetoclax combined with the less intensive chemotherapy backbone of R-CHOP may achieve similar results with less toxicity than R-EPOCH, and preliminary results are very encouraging in this regard. Venetoclax is provided at no cost.

#### **Venetoclax plus obinutuzumab and atezolizumab (NCT02846623)**

Previously at MD Anderson, we evaluated the combination of ibrutinib and nivolumab in patients with RT and achieved an overall response rate of 42%. Atezolizumab is a PD-L1 monoclonal antibody (mAb), and preliminary data from the first 8 patients on this study, presented at ASH 2021, demonstrated a high CR rate. This chemotherapy-free approach may be better tolerated by older and unfit patients. Venetoclax, obinutuzumab and atezolizumab are provided at no cost.

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### **Epcoritamab (NCT04623541)**

Epcoritamab is a novel bi-specific antibody targeting CD3 and CD20. In a study reported at ASH 2022, 5/10 patients with RT achieved a complete response with epcoritamab. Also, responses were reported in 63% of patients with DLBCL. The treatment is given as subcutaneous injections, and the toxicity profile is favorable so far. This study is now open for patients with RT. Epcoritamab is provided at no cost.

### **FT819 off the shelf CD19-CAR-T (NCT04629729)**

Most studies of CAR T-cells in DLBCL exclude patients with RT. However, recent data from Israel in a small number of patients demonstrated 5 of 8 complete responses in patients with refractory RT, a result similar to that seen in de novo DLBCL. Similar data were published in a retrospective analysis of patients treated with commercial axicabtagene ciloleucel at the Ohio State University. FT819 is an off-the-shelf, allogeneic CAR-T cell directed against CD19. The major advantage of such a product is quick availability for patients who often have rapidly progressive disease such as is seen in RT. Additionally,

CAR-T cells produced from patients with heavily pretreated CLL are often exhausted and dysfunctional. The CD19-CAR-T product created from healthy donors may well overcome production limitation of the autologous CD19-CAR-T cell strategies. FT819 is provided at no cost.

### **Nivolumab plus ipilimumab and ibrutinib (NCT04781855)**

Immune checkpoint blockade has been successfully utilized in treatment for a variety of solid tumors. Phase II data from a previous study of ibrutinib plus nivolumab in RT showed an overall response rate of 42% in 24 patients. Furthermore, most responses were complete remissions. This study was amended to add ipilimumab, a CTLA4 mAb. The hope is that this will enhance efficacy, akin to the improved results with ipilimumab and nivolumab relative to nivolumab monotherapy in melanoma. The study is now enrolling, beginning with a 6-patient safety cohort of ibrutinib plus ipilimumab, before enrolling the 3-drug combination cohort. Nivolumab and ipilimumab are provided at no cost.

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## **Announcements**

### **MD Anderson's Hagop Kantarjian, M.D., awarded highest honor from American Society of Clinical Oncology**

The [American Society of Clinical Oncology](#) will present the 2023 David A. Karnofsky Memorial Award to [Hagop Kantarjian, M.D.](#), chair of Leukemia at The University of Texas MD Anderson Cancer Center, for his contributions to leukemia clinical research and his dedication to improving the lives of patients. [Learn more about the achievement →](#)

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## Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. [View our faculty roster.](#)

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## Leukemia Faculty Contacts (continued)

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