Dana-Farber Cancer Institute | Brigham Cancer Center

Clinical Trial Spotlight: Mantle Cell Lymphoma

TARGETED COMBINATION THERAPY FOR MANTLE CELL LYMPHOMA WITH MINIMAL RESIDUAL DISEASE ASSESSMENT

Mantle cell lymphoma (MCL) represents around 6% of all non-Hodgkin lymphomas and is not curable with conventional therapy. Initial treatment is often based on biological age with those considered young and fit receiving high-dose cytarabine-containing regimens followed by autologous stem cell transplantation (ASCT) and maintenance rituximab. However, the median age at diagnosis of MCL is 68, so the majority of patients are transplant-ineligible and treated with less intensive and less effective chemoimmunotherapy regimens. A high-risk population of younger, transplant-eligible MCL patients with *TP53* mutations has recently been identified and found to have poor outcomes despite aggressive ASCT-based induction.

There is a need for more effective treatments for patients with relapsed/refractory (R/R) MCL and for novel treatment strategies that provide durable first remissions without the toxicity of intensive chemoimmunotherapy and ASCT. One approach to reducing toxicity while maintaining efficacy is to use targeted therapy in place of cytotoxic chemotherapy. Acalabrutinib is a second generation oral BTK inhibitor with a favorable safety profile that is FDA approved in R/R MCL. Venetoclax is a selective oral BCL2 inhibitor with activity and synergy in R/R MCL when used with BTK inhibitors. Obinutuzumab is a type II anti-CD20 monoclonal antibody that may overcome resistance to venetoclax in MCL based on preclinical data.

With the above biological rationale and favorable safety and efficacy profile of each individual agent, our Dana-Farber Cancer Institute investigator-initiated phase 1/2 study (NCT04855695) of the combination of acalabrutinib, venetoclax, and obinutuzumab (AVO) in R/R and untreated MCL is underway.

- The phase 1 portion of the study is enrolling in the R/R MCL setting for patients who have not relapsed or progressed on BTK or BCL2 inhibitors. 17 R/R MCL patients will be treated continuously until disease progression with AVO combination therapy.
- Following determination of the recommended phase 2 dose (RP2D), the phase 2 expansion R/R MCL cohort will open in parallel with the untreated 24 patient cohort of transplant-ineligible and transplant-eligible TP53 mutated MCL patients.
- A future amendment is pending to include 12 untreated transplant-eligible MCL patients without a *TP53* mutation.

An attractive feature of this trial is that it allows for the possibility of time-limited therapy in the untreated MCL cohort. Untreated MCL patients have the opportunity to interrupt acalabrutinib and venetoclax therapy starting with cycle 11 if in a minimal residual disease negative complete remission (MRD-negative CR) for 3 consecutive months. All untreated MCL patients regardless of MRD status will receive 2 years of maintenance obinutuzumab every 8 weeks after completing 7 cycles of combination AVO. The primary endpoint of the untreated MCL cohort is the CR rate after 7 cycles of AVO therapy.

Continued over

Dana-Farber Cancer Institute | Brigham Cancer Center

Clinical Trial Spotlight: AVO for Mantle Cell Lymphoma

Correlative science conducted by Dana-Farber laboratory-based investigators aims to identify biomarkers of response to AVO therapy and molecular signatures enriched in minimal residual disease (MRD), based on biophysical and transcriptional tumor sequencing and serial single-cell RNA sequencing of MCL and stromal populations from lymph node and bone marrow in addition to peripheral blood.

FOR MORE INFORMATION

To discuss a patient who may be appropriate for this trial, contact:

Austin Kim, MD (austini_kim@dfci.harvard.edu, 617-632-6844)

NCI trial reference: https://clinicaltrials.gov/ct2/show/NCT04855695