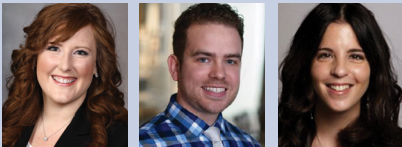


# Hematologic Malignancies: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner



With conference reporting provided by *The ASCO Post*, **Amber**

**B. Koehler, PA-C, MS**, of Mayo Clinic, evaluates data on BTK inhibitors; fixed-duration, first-line treatment with ibrutinib plus venetoclax; and a novel oral BCL2 antagonist for patients with CLL. **P. Andrew Allred, MS, PA-C**, of Banner MD Anderson Cancer Center, reviews data on a front-line therapy for patients with Ph+ acute lymphoblastic leukemia and brexucabtagene autoleucel, an anti-CD19 CAR T-cell therapy. **Donna Catamero, ANP-BC, OCN®, CCRC**, of Mount Sinai Hospital, reflects on findings on a BCMA-directed CAR T-cell therapy and a bispecific monoclonal antibody for patients with multiple myeloma.

## Abstract 7500

### First Results of a Head-to-Head Trial of Acalabrutinib vs. Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

By JADPRO Staff

Visit <https://meetinglibrary.asco.org/record/201554/abstract> to read the full abstract and view author disclosures.

J Adv Pract Oncol 2021;12(6):635-646  
<https://doi.org/10.6004/jadpro.2021.12.6.11> • © 2021 Harborside™

In the first head-to-head trial of Bruton tyrosine kinase inhibitors (BTKis) in chronic lymphocytic leukemia (CLL), acalabrutinib demonstrated noninferior progression-free survival (PFS) with less cardiotoxicity and fewer discontinuations due to adverse events compared with ibrutinib. The results of the open-label, randomized, noninferiority, phase III ELEVATE-RR trial shed light on the tolerability of these two BTKis in patients with previously treated CLL with high-risk features.

#### Study Details

The study recruited 533 previously treated CLL patients with del(17p) or del(11q) by central lab and randomized them to receive either oral acalabrutinib 100 mg bid or ibrutinib 420 mg qd until progression or unacceptable toxicity. The median age was 66, and participants had a median of two prior therapies. 45.2% had del(17p), and 64.2% had del(11q). The primary endpoint was PFS, and secondary endpoints were all-grade atrial fibrillation (AF), grade  $\geq 3$  infection, Richter transformation, and overall survival (OS).

#### Results

At a median follow-up of 40.9 months, acalabrutinib was noninferior to ibrutinib. The median PFS was 38.4 months in both arms (HR, 1.00). Acalabrutinib was statistically superior to ibrutinib in all-grade AF incidence (9.4% vs 16.0%;  $p = .023$ ). Among the other secondary endpoints, incidences

of grade  $\geq 3$  infection (acalabrutinib: 30.8%, ibrutinib: 30.0%) and Richter transformation (acalabrutinib: 3.8%, ibrutinib: 4.9%) were comparable between arms. Median OS was not reached in either arm (HR, 0.82), with 63 (23.5%) deaths in the acalabrutinib arm and 73 (27.5%) in the ibrutinib arm.

Among any-grade AEs in  $\geq 20\%$  of patients in either arm, acalabrutinib was associated with a lower incidence of hypertension (9.4%, 23.2%),

arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). Adverse events led to treatment discontinuation in 14.7% of acalabrutinib patients, compared with 21.3% of ibrutinib-treated patients. The authors noted that any-grade events of clinical interest, cardiac, hypertension, and bleeding events were less frequent with acalabrutinib.

### The Advanced Practitioner Perspective

Amber B. Koehler, PA-C, MS  
Mayo Clinic

The approval of ibrutinib (Imbruvica) for the treatment of CLL marked the beginning of a paradigm shift in the treatment of CLL from traditional chemoimmunotherapy to novel targeted agents. The subsequent approval of the more selective second-generation BTK inhibitor, acalabrutinib (Calquence), based on the ELEVATE-TN and ASCEND trials, offered providers, including advanced practitioners, another option.

The ELEVATE-RR trial represents an important and clinically relevant head-to-head comparison of ibrutinib vs. acalabrutinib in previously treated CLL; researchers found that acalabrutinib was in fact noninferior to ibrutinib in terms of PFS. Importantly, acalabrutinib demonstrated lower rates of all-grade atrial fibrillation (one of the study's secondary endpoints) as well as lower incidences of hypertension, arthralgias, and diarrhea. Although acalabrutinib was associated with higher incidences of headache and cough, fewer patients

discontinued acalabrutinib due to side effects than those on ibrutinib. This is particularly important data for advanced practitioners to be aware of, as the best BTK inhibitor monotherapy is one that the patient can tolerate and will continue to take.

Additionally, as advanced practitioners discuss choice of BTK inhibitors in patients with CLL, these data suggest that acalabrutinib may be the preferred choice for patients in whom risk for atrial fibrillation or worsening of pre-existing hypertension is of significant concern. Other factors in the choice of BTK inhibitor for advanced practitioners to consider include the need for concomitant proton pump inhibitor (currently recommended against using in conjunction with acalabrutinib per the package insert), as well as the ability to more easily modify the dosing of ibrutinib compared to acalabrutinib for adverse events. While we can extrapolate that the efficacy will remain similar over time based on current data, longer-term studies are needed to confirm this prediction.

**Disclosure:** Ms. Koehler has served on advisory boards for AbbVie and TG Therapeutics.

**Abstract 7501****Fixed-Dose, First-Line Ibrutinib/Venetoclax Combination Achieves Durable Remissions in CLL**

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/201560/abstract> to read the full abstract and view author disclosures.

The combination of fixed-duration, first-line treatment with ibrutinib plus venetoclax achieved complete responses in more than half of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), based on the primary analysis of the fixed-dose cohort of the phase II CAPTIVATE study.<sup>1</sup>

Similarly high rates of overall survival and progression-free survival, secondary endpoints, were observed in the total study population and in high-risk patients with the fixed-dose combination.

“The primary endpoint was met, with a complete response rate of 56% in patients without deletion (17p). The complete response rate was 55% in the all-treated population, and the overall response rate was 96%,” stated lead author Paolo Ghia, MD, PhD, of Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy, at the 2021 ASCO Annual Meeting.

CAPTIVATE is a multicenter phase II study of first-line ibrutinib plus venetoclax in CLL. At the 2020 American Society of Hematology (ASH) Annual Meeting & Exposition, results from the minimal residual disease (MRD) cohort were presented. Undetectable MRD was achieved in more than two-thirds of patients with a fixed-duration of 12 cycles of treatment with the combination, and progression-free survival rates were greater than 95% regardless of subsequent randomized treatment.<sup>2</sup>

**Study Details**

The primary analysis of CAPTIVATE reported on the fixed-duration cohort of 159 patients with untreated CLL/SLL aged 70 or younger who received 3 cycles of the all-oral, once daily regimen of ibrutinib followed by 12 cycles of ibrutinib plus venetoclax. Median age was 60 years. High-risk

features included del(17p)/*TP53* mutations in 27; del(17p) in 20; del(11q) in 28; complex karyotype in 31; and unmutated *IGHV* in 89. There were 139 patients (86%) without del(17p). Among 159 patients, 147 completed 12 cycles of ibrutinib plus venetoclax. The median time on study was 27.9 months, and the median treatment duration was 13.8 months. Median follow-up time after treatment cessation was 14 months.

The complete response rate was 56% in patients without del(17p) and 55% in all treated patients. These rates were consistent among high-risk subgroups, except for those with bulky disease, who had a complete response rate of 31%. The objective response rate in all treated patients and in those without del(17p) was 96%. “These responses represent a 40% improvement over the historical comparator FCR regimen in the CLL10 study,” Dr. Ghia stated.

**Secondary Endpoints**

Among the 88 patients who achieved complete response, 78 (89%) had durable responses lasting longer than 1 year. Among the 66 patients without del(17p) who achieved complete responses, 76 (87%) were durable lasting longer than 1 year. The rate of undetectable MRD in peripheral blood was 77% in all treated patients and 76% in those without del(17p); the rates of undetectable MRD in the bone marrow were 60% and 62%, respectively.

At 24 months, progression-free survival rate in patients without del(17p) was 96% and 95% in all treated patients. The 24-month overall survival rate was 98%—identical in all treated patients and those without del(17p). Median follow-up was 27.9 months.

“All of these results together support the idea of the combination of ibrutinib plus venetoclax as an all-oral, once daily, chemotherapy-free, fixed-duration treatment that may achieve deep responses and undetectable MRD in a vast majority of patients,” Dr. Ghia stated.

The phase III GLOW study is currently ongoing in an older population and includes a study arm of ibrutinib plus venetoclax.

**References**

1. Ghia P, et al: 2021 ASCO Annual Meeting. Abstract 7501. Presented June 6, 2021.
2. Wierda WG et al: 2020 American Society of Hematology Annual Meeting & Exposition. Abstract 123. Presented December 5, 2020.

### The Advanced Practitioner Perspective

Amber B. Koehler, PA-C, MS

Mayo Clinic

Currently, the only FDA-approved time-limited therapy to include novel agents in the front-line setting for CLL is the combination of venetoclax (Venclexta) and obinutuzumab (Gazyva), based on the CLL14 study. The idea of fixed-duration therapy is attractive to many patients, as opposed to the indefinite therapy recommended with BTK inhibitor monotherapy. The CAPTIVATE trial regimen offers the convenience of an all-oral regimen beginning with 3 months of debulking with ibrutinib, essentially eliminating the risk of tumor lysis syndrome (TLS) with initiation of venetoclax. Of note, likely due to the nature of fixed-duration therapy, researchers chose complete response rate as their primary endpoint as opposed to PFS, which was included as a secondary endpoint. Additionally, this regimen appears to be effective in high-risk patients, including those with 17p deletion.

Because this regimen is not yet approved in the front-line setting for the treatment of CLL, it is not yet likely to change how advanced practitioners discuss treatment options outside the context of a clinical trial with patients. It is, however, important for advanced practitioners to be aware of the data surrounding combination regimens, as many similar studies are ongoing to determine which fixed duration regimens may be beneficial in patients with CLL.

Potential practical challenges of this regimen include cost and pill burden, as well as the possibility of increased adverse events with the use of two oral targeted agents. While these initial results are encouraging as an additional option in the treatment of CLL, longer-term data is still needed on length of remission, response rates to retreatment, and rates of resistance to targeted agents over time.

**Disclosure:** Ms. Koehler has served on advisory boards for AbbVie and TG Therapeutics.

### Abstract 7502

#### Novel BCL2 Inhibitor Shows Activity in CLL in Phase I Trial

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/201558/abstract> to read the full abstract and view author disclosures.

The novel, selective BCL2 inhibitor lisaftoclax (APG-2575) has shown activity in the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) in a phase I study reported at the 2021 ASCO Annual Meeting.<sup>1</sup> Preliminary data suggest that lisaftoclax stands out for its favorable safety profile and rapid time to response.

“APG-2575 is well tolerated in doses up to 1,200 mg/d, with infrequent grade 3 to 4 treatment-related adverse events. No tumor-lysis syndrome or dose-limiting toxicity has been observed in this trial, and the maximal tolerated dose has not been reached. The trial suggests proof of concept in these preliminary data, with an objective response rate of 80% in relapsed or refractory

CLL and activity in other hematologic malignancies,” said Sikander Ailawadhi, MD, of the Mayo Clinic, Jacksonville, Florida.

“This new drug is a potential alternative for patients with relapsed or refractory CLL and other hematologic malignancies where BCL2 is a driver. It has a shorter daily ramp-up schedule [than venetoclax] that may be more patient-centric and convenient, as well as a preliminary favorable safety profile,” he continued.

#### Background

Lisaftoclax is a novel, potent, orally active selective BCL2 inhibitor under clinical development. Overexpression of BCL2 allows cancer cells to circumvent apoptosis and prolong their survival. Many hematologic malignancies are characterized by high levels of BCL2, including CLL/small lymphocytic leukemia (SLL), multiple myeloma, and Waldenström’s macroglobulinemia. Venetoclax, the first and only approved BCL2 inhibitor for the treatment of CLL, requires a 5-week ramp-up schedule due to its potential for tumor-lysis syndrome, especially in patients at high risk for this complication. Venetoclax is also associated with thrombocytopenia and severe neutropenia.

In preclinical studies, lisaftoclax selectively targeted BCL2 in various hematologic tumor models. The mode of action of this novel agent is to disrupt the BCL2-BIM complex, mediating induction of apoptosis.

### Study Details

The phase I study included 36 patients treated with doses of 20 to 1,200 mg/d of oral lisaftoclax in 28-day cycles. Cohort A included patients with non-CLL hematologic malignancies and a low risk for tumor-lysis syndrome. Lisaftoclax was given without a ramp up to three to six patients at each dose level up to 1,200 mg/d. Cohort B included patients with CLL at intermediate and high risk for tumor-lysis syndrome. Lisaftoclax was given with a 5-day ramp-up, with three to six patients enrolled per dose level up to 1,200 mg/d. The dose-expansion phase includes 9 to 12 patients in each cohort.

Treatment was given daily in 28-day cycles until disease progression or toxicity. All 36 patients had histologically confirmed relapsed or refractory CLL/SLL and other hematologic malignancies as well as adequate hematologic and renal function. Patients were excluded if they had prior treatment with a BCL2 inhibitor or allogeneic hematopoietic stem cell transplantation within the previous year.

The median age of patients was 70 (range, 39–89 years); 52% were 70 or older; 72.2% were male. A total of 14 patients (41.7%) had CLL/SLL. The median number of prior lines of therapy was two (range, 1–13).

### Safety Profile

A total of 15 patients did not discontinue therapy at the time these results were presented; 21 discontinued treatment, 13 (62%) for progressive disease, 2 for adverse events, and the rest for a variety of reasons.

“The safety profile was quite favorable,” Dr. Ailawadhi reported.

Treatment-related adverse events of any grade reported in at least 10% of patients included fatigue (28%), neutropenia (22%), diarrhea (20%), and anemia (16%). Grade 3 or higher adverse events reported in greater than 5% of patients included neutropenia, nausea, and decreased platelet count.

“Only one patient discontinued treatment due to treatment-related adverse events, and no grade 5 treatment-related adverse events were reported,” he said.

No dose-limiting toxicities were observed at any dose level up to 1,200 mg/d (the highest level tested). No laboratory or clinical tumor-lysis syndrome was reported. The median treatment duration is six cycles (range, 1–24 cycles).

In cohort B (the CLL and high-risk tumor-lysis syndrome group), 600 mg/d is the recommended phase II dose going forward. “Cohort A still has one slot to be enrolled, and then the maximal tolerated dose will be determined,” noted Dr. Ailawadhi.

### Efficacy

Among all 36 patients, there are a few noteworthy points. “A significant proportion of patients are doing great on treatment. Partial response has been seen early in the CLL cohort at the two-cycle mark,” Dr. Ailawadhi stated. In the patients with CLL, the objective response rate was 80%, and the median time to response was two cycles.

“In the non-CLL cohort of other malignancies, there were no partial responses, but clinical benefit was observed in about half of the patients with non-Hodgkin lymphoma. This is a heterogeneous population of heavily pretreated patients with different diagnoses,” he added.

Among the CLL group, eight had stage I or II disease, and eight had stage III or IV disease. Prognostic features included del(17p)/TP53 mutation in 13.3%; del (11q) in 6.7%; CD38-positive in 20%; and unmutated *IGHV* in 60%.

Dr. Ailawadhi showed slides of a patient with CLL who had high-risk features and a high disease burden who was rapidly cleared in the lymphocytes, nodes, and bone marrow with lisaftoclax. There was no evidence of laboratory or clinical tumor-lysis syndrome in this patient.

### Reference

1. Ailawadhi S, Chanan-Khan AAA, Chen Z, et al: First-in-human study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor, in patients with relapsed/refractory CLL and other hematologic malignancies. 2021 ASCO Annual Meeting. Abstract 7502. Presented June 7, 2021.

### The Advanced Practitioner Perspective

Amber B. Koehler, PA-C, MS  
Mayo Clinic

The efficacy of the BCL2 antagonist venetoclax in both treatment-naïve and previously treated CLL is well established. Lisoftoclax represents a novel oral BCL2 antagonist currently in development with no concerning safety signals in this phase I data. The adverse event profile is similar to that of venetoclax, including fatigue, neutropenia, diarrhea, and anemia, but what is perhaps most notable is the absence of any laboratory or clinical tumor lysis syndrome (TLS), despite not only classification of study patients with CLL/SLL as either intermediate or high risk for TLS, but also a dose escalation protocol occurring over 5 days as opposed to 5 weeks (as recommended with venetoclax).

Although still in the early stages of study, advanced practitioners should be aware of lisoftoclax, as it may offer an additional choice of BCL2 antagonist with a decreased risk of TLS, which could theoretically translate into decreased need for hospitalization and decreased number of clinic visits and lab draws for TLS monitoring while undergoing dose escalation. While this phase I data is encouraging for another potential tool to treat CLL, longer-term studies with larger numbers of patients, including phase II and phase III trials, are needed before this data impacts how advanced practitioners counsel patients with relapsed CLL on treatment options outside the context of a clinical trial.

**Disclosure:** Ms. Koehler has served on advisory boards for AbbVie and TG Therapeutics.

### Abstract 7001

#### Ponatinib/Blinatumomab Demonstrates High Rates of Complete Molecular Response in Philadelphia Chromosome-Positive ALL

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/195835/abstract> to read the full abstract and view author disclosures.

The combination of ponatinib and blinatumomab was found to be safe and highly effective in patients with newly diagnosed or relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). The study—presented by Nicholas J. Short, MD, and colleagues during the 2021 ASCO Annual Meeting (Abstract 7001)—may support a regimen to produce complete remission with front-line therapy, without the increased risks associated with systemic chemotherapy or a stem cell transplant.

The treatment combination in newly diagnosed patients resulted in a complete response rate of 100% and a complete molecular remission rate of 85%. For patients in the relapsed/refractory group, the complete response rate was 89%, while the complete molecular remission rate was 88%.

“A complete molecular remission is associated with superior outcomes in patients with Philadelphia chromosome-positive ALL,” said Dr. Short, Assistant Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. “This trial shows that the combination of ponatinib and blinatumomab produces high rates of complete molecular response, which reduces the chances that patients will relapse and increases the likelihood that they will be disease-free.”

#### Rationale Behind the Combination Regimen

ALL is typically treated with intensive systemic chemotherapy, which comes with the risks of infections, low blood counts, and possible mortality. After chemotherapy and disease remission, patients traditionally undergo a stem cell transplant to reduce the chance of disease recurrence.

“Both systemic chemotherapy and stem cell transplant can cause significant side effects,” Dr. Short said. “This treatment combination is very attractive, since it minimizes the risk of treatment-related complications for the patient—especially for older patients who have existing medical comorbidities and typically have a poor prognosis.”

*BCR-ABL* is the genetic abnormality that drives Philadelphia chromosome-positive ALL. Ponatinib is a targeted tyrosine kinase inhibitor

that works by inhibiting proteins called tyrosine kinases on leukemia cells—in particular, the abnormal BCR-ABL protein that causes the disease. Ponatinib has an advantage over previous generations of tyrosine kinase inhibitors because it is designed to overcome the T3151 mutation, the most common cause of disease relapse.

Immunotherapy using monoclonal antibodies such as blinatumomab encourages changes in the body's immune system and interferes with the ability of tumor cells to grow and spread. Blinatumomab has two components: one targets CD3 on the T cells, and the other targets CD19 on the ALL cells. It works by directing the T cells to target and bind with the CD19 protein on the surface of the leukemia cells.

Previous research showed that blinatumomab and ponatinib are effective in improving overall survival for patients with leukemia. While several trials have studied tyrosine kinase inhibitor combinations, this is the first report on this drug combination. This trial sought to evaluate safety and effectiveness of combining these potent drugs in the front-line setting.

### Study Design and Patient Response

The presentation includes data from 35 patients with Philadelphia chromosome–positive ALL or chronic myeloid leukemia in lymphoid blast crisis (CML-LBC). The study evaluated 20 newly diagnosed patients, 10 relapsed/refractory patients, and 5 patients with CML-LBC. Trial participants

were 51.4% Hispanic, 40% White, 2.9% Black, 2.9% Asian, and 2.9% other.

The primary endpoint was complete molecular response for newly diagnosed patients and overall response rate for patients with refractory or relapsed disease. Overall, 95% of patients responded to treatment; the response rate was 100% for newly diagnosed patients and 88% in the relapsed/refractory group.

After a median follow-up of 12 months, the estimated 2-year event-free and overall survival rate was 93% for the newly diagnosed patients. In the front-line group, no patients received a stem cell transplant and none have relapsed. For relapsed/refractory patients, the 2-year event-free survival rate was 41% and the 2-year overall survival rate was 53%. Four patients with relapsed/refractory disease underwent an allogeneic hematopoietic stem cell transplant.

The treatment was well tolerated and the toxicity profile of both drugs was consistent with other studies, with no additional toxicity observed with the combination. The trial is ongoing and still accruing patients.

“It is encouraging that the majority of patients responded to treatment and none of the newly diagnosed patients relapsed or have required a stem cell transplant,” said Dr. Short. “These data suggest that we must re-evaluate the need for a stem cell transplant in first remission for Philadelphia chromosome–positive ALL, particularly for those patients who achieve a deep molecular response.”

### The Advanced Practitioner Perspective

P. Andrew Allred, MS, PA-C

Banner MD Anderson Cancer Center

In 2021, an anticipated 5,690 new cases of acute lymphoblastic leukemia (ALL) will be diagnosed in the United States. ALL can be of either B-cell or T-cell lineage. While 60% of ALL cases occur in children, 80% of deaths from ALL occur in adults. Such a drastic health disparity in adult ALL demands further clinical investigation to find more effective therapeutic options.

Adult B-cell ALL patients with Philadelphia chromosome–positive (Ph+) disease are at high risk for poor outcomes. As such, adults with Ph+ B-cell ALL and good performance status have historically been treated with intensive

combination chemotherapy followed by allogeneic hematopoietic cell transplantation (allo-HCT). Both therapies carry significant toxicity profiles, but especially allo-HCT, including long-term organ damage, graft-vs.-host disease, and even death. However, the treatment paradigm for adult Ph+ B-cell ALL is changing with the introduction of tyrosine kinase inhibitors (TKIs), such as ponatinib (Iclusig), that target Ph+ blood cancers. Based on previous studies from MD Anderson Cancer Center, select Ph+ B-cell ALL patients are now forgoing allo-HCT and the associated toxicities in exchange for multi-year maintenance therapy with TKIs.

An effective and highly tolerable standard-of-care treatment for relapsed/refractory B-cell

ALL is a bispecific T-cell engager (BiTE) called blinatumomab (Blincyto). This BiTE has two domains, one to bind CD19 on the surface of B-cell ALL cells and another to bind CD3 on the surface of healthy T cells. A “deadly meeting” results with the healthy CD3-positive T cells causing the destruction of CD19-positive B-cell ALL cells.

Abstract 7001 shared clinical trial data that is beginning to justify using ponatinib and blinatumomab together as front-line treatment for Ph+ B-cell ALL, as nearly all patients went into remission with this therapeutic combination. This is also exciting because

my clinical experience with these drugs is that their toxicity profiles are far superior to combination chemotherapy or allo-HCT. One major concern, however, is the monthly cost of each drug, blinatumomab being \$80,000 to \$100,000 and ponatinib \$15,000 to \$20,000. More work needs to be done to make new cancer treatments affordable for all patients. We look forward to further data from this exciting clinical trial and hope the strong outcomes are sustained.

**Disclosure:** Mr. Allred has no conflicts of interest to disclose.

## Abstract 7002

### CLL: CAR T-Cell Therapy With Brexucabtagene Autoleucel

By *The ASCO Post Staff*

Visit <https://meetinglibrary.asco.org/record/195802/abstract> to read the full abstract and view author disclosures.

**B**ijal D. Shah, MD, of the H. Lee Moffitt Cancer Center, discusses phase II results of the ZUMA-3 study, which evaluated brexucabtagene autoleucel (KTE-X19), an anti-CD19 CAR T-cell therapy, in adults with relapsed or refractory B-cell acute lymphoblastic leukemia. A transcript of his interview with *The ASCO Post* follows.

The ZUMA-3 trial is a study of CAR T-cell immunotherapy for adults with relapsed and refractory acute lymphoblastic leukemia. We enrolled patients who had morphologic evidence of disease that is greater than 5% blasts. This could also be accompanied by extramedullary leukemia in the nodal or extranodal areas. Central nervous system (CNS) disease was permitted; however, we limited it to CNS 1 and CNS 2 disease.

Patients received prescribed bridging therapy. This was followed by conditioning using fludarabine and cyclophosphamide, and then the CAR T-cell infusion. We enrolled 71 patients and treated 55. The leading reasons why people did not proceed to CAR T-cell infusion were infection, thrombosis, and ineligibility (patients who did not have CD19 expression or did not meet that blast

threshold of greater than 5% could not proceed to CAR T-cell infusion).

Of the 55 we enrolled, the median age was 40, with the oldest patient being 84. The patients were heavily pretreated, and this included a history of inotuzumab, blinatumomab, or allogeneic stem cell transplant. The median blast percentage at enrollment was around 70%, and this improved to around 65% with the bridging therapy that was delivered.

We met our primary endpoint with overall complete remission (CR) rate (CR + CR with incomplete hematologic recovery [CRi]) of 70.9%. The true CR rate was 56.4%. These were essentially all minimal residual disease negative (there was one patient for whom we did not have data, so the MRD rate reported both in the ASCO presentation and now as published in *The Lancet* is 97%). The responses were largely consistent across different subgroups, so patients who were more heavily pretreated, patients who had prior inotuzumab, blinatumomab, or allogeneic stem cell transplant, and even older patients still showed preserved responses. The one group where we saw a lower response rate was for those with very high blast marrow burdens, specifically those who had greater than 75% blasts.

The median duration of remission seen in the study was around 12.8 months. Censoring for transplant in the 9 patients who received it did not affect this median duration of remission. 31% of patients continue an ongoing remission without stem cell transplant.

The median relapse-free survival was 11.8 months, and this improved to 14.2 months in those



patients who achieved CR/CRi. The median overall survival was 18.2 months and has not yet been reached in those patients who achieved CR/CRi.

Safety was largely consistent with what we'd seen in the phase I study, with anemia and fever being the leading high-grade adverse events. We saw two patients who passed away from attributable toxicity, including one event of cerebral edema with brain herniation. The grade 3 to 4 cytokine release syndrome and neurotoxicity rates were both around 25%. And I think this reflects

our learnings from the phase I study as published in *Blood*, where we found that the earlier use of corticosteroids and tocilizumab served to reduce the rates of these events for patients with acute lymphoblastic leukemia.

To summarize, we've been able to show that CAR T-cell immunotherapy is safe for adult patients with relapsed and refractory acute lymphoblastic leukemia with high overall response rates, high median overall survival, and durable remissions for many.

### The Advanced Practitioner Perspective

P. Andrew Allred, MS, PA-C

Banner MD Anderson Cancer Center

Adults with relapsed or refractory B-cell acute lymphoblastic leukemia (RR B-cell ALL) have disease that demonstrates resistance to cytotoxic chemotherapy, immunotherapy, and/or allogeneic hematopoietic cell transplantation. For RR B-cell ALL, use of chimeric antigen receptor (CAR) T-cell therapy can be considered if the relapsed disease also expresses a surface protein called CD19.

Tisagenlecleucel (Kymriah) is a CAR T-cell therapy with FDA approval to treat patients up to 25 years old in this setting. The therapy works by infusing a patient with genetically engineered cytotoxic T cells that seek and destroy CD19-expressing B-cell ALL cells. The side effect profile of tisagenlecleucel includes but is not limited to potentially life-threatening neurotoxicity. If the patient can be supported through neurotoxicity, typically the effects are completely reversible. Tisagenlecleucel is not

used for patients with RR B-cell ALL with CNS involvement due a presumed higher risk of fatal neurotoxicity.

Abstract 7002 shares exciting data of brexucabtagene autoleucel (Tecartus), a CD19-directed CAR T-cell therapy, being trialed in older adults between the ages of 40 and 84 years old with RR B-cell ALL and possible CNS involvement. The complete response or complete response with incomplete count recovery rate was approximately 70%. While 25% or 14 total patients developed neurotoxicity, only one died from the same. This significant adverse event must be taken in context, as patients with RR B-cell ALL will likely pass away within days to weeks without treatment. Overall, outcomes were exceptional, as patients experienced a median of 18 months of additional life, which is a remarkable achievement given the aggressive nature of RR B-cell ALL.

**Disclosure:** Mr. Allred has no conflicts of interest to disclose.

### Abstract 8005

#### Ciltacabtagene Autoleucel, a BCMA-Directed CAR T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma: Updated Results From CARTITUDE-1

By JADPRO Staff

Visit <https://meetinglibrary.asco.org/record/195437/abstract> to read the full abstract and view author disclosures.

A single infusion of ciltacabtagene autoleucel (cilta-cel) yielded early, deep, and durable responses in heavily pretreated patients with multiple myeloma (MM), with a manageable safety profile, according to results of the phase Ib/2 CARTITUDE-1 study presented at the 2021 ASCO Annual Meeting.

Cilta-cel is a chimeric antigen receptor (CAR) T-cell therapy with two B-cell maturation antigen (BCMA)-targeting single-domain antibodies. Updated results were presented at the meeting in patients with a longer duration (median 12.4 months) of follow-up.

### Study Details

Eligible patients had MM and received three or more prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and had received a PI, IMiD, and anti-CD38 antibody.

Patients received a single cilta-cel infusion (target dose:  $0.75 \times 10^6$  CAR+ viable T cells/kg; range  $0.5\text{--}1.0 \times 10^6$ ) 5 to 7 days after lymphodepletion, which consisted of  $300 \text{ mg/m}^2$  cyclophosphamide,  $30 \text{ mg/m}^2$  fludarabine daily for 3 days.

### Responses

As of September 1, 2020, 97 patients with a median of 6 prior lines received cilta-cel. Overall response rate per independent review committee (primary endpoint) was 97% (95% CI = 91–99), with 67% achieving stringent complete response (sCR). Responses deepened over time, and median duration of response was not reached. Of 57 patients evaluable for minimal residual disease (MRD) assessment, 93% were MRD negative at  $10^{-5}$ .

The 12-month progression-free survival (PFS) and overall survival rates (95% CI) were 77% (66–84) and 89% (80–94), respectively; median PFS was not reached.

Cilta-cel is under further investigation in other MM populations in earlier lines of therapy and in outpatient settings.

### Adverse Events

The most common grade 3 or 4 hematologic adverse events ( $\geq 20\%$ ) included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). Cytokine release syndrome (CRS) occurred in 95% of patients (4% grade 3/4), with median time to onset of 7 days and median duration of 4 days. CRS resolved in all but one with grade 5 CRS/haemophagocytic lymphohistiocytosis.

CAR T-cell neurotoxicity occurred in 21% of patients (grade  $\geq 3$ , 10%). Fourteen deaths occurred during the study after cilta-cel infusion: none within the first 30 days, 2 within 100 days, and 12 more than 100 days post infusion, of which 5 were due to disease progression, and 4 due to treatment-related AEs.

### The Advanced Practitioner Perspective Donna Catamero, ANP-BC, OCN®, CCRC Mount Sinai Hospital

For the most part, multiple myeloma (MM) remains an incurable disease. Relapse is expected, and with each relapse it becomes increasingly challenging to manage patients, as responses tend not to be as deep and durable as in earlier lines of therapy.

Cilta-cel is a unique CAR-T construct that has two BCMA bind domains, which can potentially lead to a higher affinity to binding to the BCMA antigen that is predominately found on MM cells. This phase Ib/2 clinical trial enrolled heavily pretreated patients with six median prior lines of therapy of which the majority of patients were triple-class refractory and refractory to their last line of treatment. We know historically that these patient have poor clinical outcomes.

After a one-time infusion of cilta-cel with prior lymphodepleting chemotherapy, 98% of patients responded to therapy, and of those patients who did respond, an overwhelming majority achieved a stringent complete re-

sponse (80%). The longer follow-up showed the progression-free survival at 18 months was 66%, demonstrating durable remissions. Benefits in response rate were seen across different patient populations (risk status, number of prior lines, and refractoriness). These are truly remarkable results for a patient population that historically does not achieve deep and durable remissions, especially in those patients with high-risk characteristics.

From a safety perspective, with longer follow-up, there were no new safety signals seen. In the study, high-grade cytopenias were common. In practice, we can often manage cytopenias with supportive care (blood transfusions and growth factors). It is important as advanced practitioners that we frequently monitor patients immediately post CAR T-cell therapy to manage these adverse events.

The majority of patients developed cytokine release syndrome (CRS). It was mostly limited to grade 1 and 2 with a median duration of 4 days. Low-grade CRS can be adequately managed with supportive care and administration of interleukin antagonists. Median time to

onset of CRS was 7 days. Given the delayed onset of CRS, there is a potential of administering cilta-cel in the outpatient setting and thus avoiding prolonged hospital admissions.

Neurotoxicity (NT) was seen in 20% of patients, half of which were a grade 3 or higher. A deeper dive in patients who had NT showed that patients who had two or more of the following risk factors were at higher risk for developing NT: high tumor burden, grade 2 or higher CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), or high CAR T-cell expansion and persistence. Mitigation strategies for patients who are at high risk for developing NT are to undergo an effective bridging therapy, implement early and aggressive management for CRS and ICANS, and monitoring handwrit-

ing as part of patient assessment. These mitigation strategies prevented or reduced NT in the extended cilta-cel clinical trial platform.

Cilta-cel has demonstrated deep and durable remissions in a heavily pretreated patient population which in practice has limited treatment options and poor outcomes. This therapy could potentially offer patients prolonged disease-free intervals with a one-time dose of cilta-cel. The safety profile is manageable with frequent monitoring and early interventions with supportive care.

**Disclosure:** Ms. Catamero has served on advisory boards for Legend and Janssen; as a consultant for Bristol Myers Squibb; and on the speaker bureaus for Oncoceptives and Glaxo-SmithKline.

## Abstract 8007

### Bispecific Antibodies Advance in Relapsed/Refractory Multiple Myeloma

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/195433/abstract> to read the full abstract and view author disclosures.

**T**eclistamab at the recommended phase II dose (weekly 1500 µg/kg SC) was well-tolerated and showed encouraging efficacy with durable, deepening responses, according to updated results from the MajesTEC-1 study presented at the 2021 ASCO Annual Meeting.

#### Background

BCMA-targeted immunotherapies offer considerable promise for relapsed/refractory MM. Teclistamab is a BCMA × CD3 bispecific IgG4 antibody that redirects CD3<sup>+</sup> T cells to BCMA-expressing MM cells. The phase I MajesTEC-1 study is an open-label, multicenter clinical trial evaluating the safety and efficacy of teclistamab in adults with measurable multiple myeloma that is relapsed or refractory to established therapies or intolerant of those established multiple myeloma therapies.

Eligible patients had MM and were relapsed, refractory or intolerant to established therapies. The primary objectives of the study were to iden-

tify the recommended phase II dose and characterize safety and tolerability of teclistamab.

#### Study Details

Teclistamab was given intravenously (IV; range 0.3–19.2 µg/kg [biweekly]; range 19.2–720 µg/kg [weekly]) or subcutaneously (SC; range 80.0–3000 µg/kg weekly) in different cohorts, with step-up dosing used for ≥ 38.4 µg/kg doses. Adverse events (AEs) were graded by CTCAE v4.03 (cytokine release syndrome [CRS] by Lee et al 2014). Response was assessed per IMWG criteria.

#### Results

As of February 4, 2021, 156 patients received teclistamab (IV n = 84; SC n = 72). The RP2D, identified as weekly SC 1500 µg/kg teclistamab with 60.0 and 300 µg/kg step-up doses, was given to 40 patients (median follow-up 4.3 mo [range 1.1–10.4+]). Patients dosed at the RP2D (median age, 62.5 y [range, 39–84]; 65% male) had received a median of 5 prior lines of therapy (range 2–11; 100% triple-class exposed; 65% penta-drug exposed; 83% triple-class refractory; 35% penta-drug refractory; 85% refractory to their last line of therapy). There were no dose-limiting toxicities at the RP2D in part 1.

The most common AEs at the RP2D were CRS (70%; grade 3/4 0) and neutropenia (60%; grade 3/4 40%); grade 1 neurotoxicity was reported in 1 (3%) pt. Median time to CRS onset was later with SC vs IV dosing (day after SC injection vs day

of IV infusion). The overall response rate in response-evaluable patients treated at the RP2D (n = 40) was 65%; 58% achieved a very good partial response or better and 30% achieved a complete response (CR) or better; median time to first confirmed response was 1.0 mo (range 0.2–3.1). At the RP2D, median duration of response was not reached; 23 of 26 responders (88%), after median follow-up of 5.3 mo (range 1.2–10.4+), were alive and continuing on treatment with responses deepening over time. Of 14 evaluable patients

across all cohorts, 9 with CR were minimal residual disease–negative at  $10^{-6}$ . At the RP2D, teclistamab exposure was sustained across the dosing interval and exceeded target levels, and consistent T cell activation was observed.

This trial supports further investigation as monotherapy and in combination with other agents. With the extended exposure profile at the RP2D and delayed and low-grade CRS observed with SC administration, alternative SC dosing strategies are being explored.

### **The Advanced Practitioner Perspective** Donna Catamero, ANP-BC, OCN®, CCRC Mount Sinai Hospital

Teclistamab is a bispecific monoclonal antibody (BsAbs) that simultaneously targets the BCMA antigen receptor on the myeloma cell and the CD3 receptor on the T cell, thereby directing the T cell to the myeloma cell and causing T-cell mediated cell death. This is a promising immunotherapeutic approach to relapsed/refractory MM. RP2D is a weekly subcutaneous injection with two step-up doses. The step-up doses are two smaller doses given before the full dose. This is to help minimize cytokine release syndrome (CRS), as CRS is very common in this drug class.

Patients who received the RP2D were heavily pretreated patients with a median of five prior lines of treatment. The majority of patients were triple-class refractory and refractory to their last line of therapy. These patient characteristics are often associated with poor overall survival and represents an unmet need in MM.

What was most encouraging from these data is that we saw a high overall response rate (ORR) in this cohort of patients (68%) of which 58% achieved a very good partial response (VGPR) or better. A VGPR is at least a 90% decrease in the myeloma protein. This demonstrates that patients can respond and achieve deep responses. Patients responded quickly, with a median time to response of 1 month and responses deepening over time. These results are very encouraging in MM, as we seldom see high response rates to a single-agent therapy,

especially in a patient population that is heavily pretreated and refractory.

When we examine the safety profile, neutropenia was common. This is not surprising given that the patients were heavily pretreated and may have had limited bone marrow reserve. Half of patients experienced an infection, although this is not uncommon in patients with advanced MM. The majority of patients developed CRS; however, this was limited to grades 1 and 2. Patients developed CRS around 2 days post administration, and it was generally associated with the first step-up dose and the first full dose. CRS lasted for a median of 2 days, and patients were managed primarily with supportive care as well as with tocilizumab and steroids. These adverse events are manageable and are expected given the patient population and the class of drug. No new safety signals were seen in this trial.

Teclistamab is a novel BsAbs given as a steroid-free monotherapy on a convenient weekly schedule. Teclistamab is a well-tolerated treatment with a manageable safety profile. CRS is manageable and predictable. Although the follow-up data is still early, the results remain encouraging for this difficult-to-manage patient population. As this treatment is “off the shelf,” teclistamab may be an important option for patients who are unable to receive CAR T-cell therapy.

**Disclosure:** Ms. Catamero has served on advisory boards for Legend and Janssen; as a consultant for Bristol Myers Squibb; and on the speaker bureaus for Oncopeptides and GlaxoSmithKline.