

International Congress on Targeted Therapies in Cancer®

Greater Understanding of CLL Pathophysiology Spurs Small Molecules Development

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Small Molecules Background

During the 10th Annual Meeting of the Society of Hematologic Oncology, William Wierda, MD, PhD, will explore the emergence of small molecule-inhibitor targeted therapies. His presentation, “Workup of CLL in the Era of Small Molecules,” is scheduled for Friday, September 30, 2022, at 6:45 am. Wierda is a professor; section chief, chronic lymphocytic leukemia (CLL); and center medical director, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, where he is also executive medical director. He will address the role of Bruton tyrosine kinase (BTK) inhibitors, PI3K inhibitors, and inhibitors of BCL2 during the session.

CLL is the most common leukemia in adults in Western countries; estimates indicate more than 20,000 individuals in the United States will receive CLL diagnoses and approximately 4410 will die of CLL in 2022.^{1,2} Improved knowledge of the B-cell receptor (BCR) signaling pathway and its relationship to the behavior and pathophysiology of CLL has resulted in substantial advances

in therapeutic options.^{1,2} The BCR is responsible for an antigen-independent survival signal involving PI3K and an antigen-dependent signal involving intracellular molecules such as LYN, SYK, BTK, and PI3K leading to proliferation and activation of the cells.¹ CLL B cells are “stuck” in a later stage of development characterized by the inability to further differentiate, impaired immune function, and prolonged life span due to overexpression of antiapoptotic proteins (primarily BCL2).^{1,3} Downstream components of the BCR signaling pathway continue to be expressed in CLL B cells, propagating signaling.¹ Increased understanding of the role of BCR in CLL pathophysiology led to the development of small molecule inhibitor-targeted therapies with tyrosine kinase inhibitors against BTK and PI3K and inhibitors of BCL2.¹

BTK Inhibitors

BTK inhibitors block the adenosine triphosphate-binding site by binding irreversibly via covalent bonds with the sulfhydryl group of Cys481 or reversibly with noncovalent bind- ▶

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ing affinity, disrupting the ability of the CLL cells to interact with the microenvironment, resulting in death of the malignant cells.¹ Current BTK inhibitors approved by the FDA for treatment of CLL are irreversible and include acalabrutinib (Calquence) and ibrutinib (Imbruvica).²

Results from the phase 3 ELEVATE CLL TN trial (NCT02475681) showed acalabrutinib plus or minus obinutuzumab (Gazyva) produced improved progression-free survival (PFS) compared with chlorambucil (Leukeran) plus obinutuzumab in patients with treatment-naïve CLL.² The combination of acalabrutinib and obinutuzumab also produced a longer PFS than acalabrutinib alone at 48 months (87% vs 78%), but the study was not powered to compare the PFS between the acalabrutinib arms.²

The phase 3 RESONATE-2 trial (NCT01722487) in CLL patients without del(17p) who were 65 years or older resulted in approval of ibrutinib as first-line therapy for all patients.² In 2 separate studies (ECOG-ACRIN Cancer Research Group (E1912) study [NCT02048813] and FLAIR study [ISRCTN01844152]) ibrutinib with rituximab (Rituxan) proved more effective than fludarabine/cyclophosphamide/rituximab in patients lacking del(17p)/*TP53* mutations.² Results also indicated ibrutinib is a good option for younger patients with unmutated *IGHV*.² Ibrutinib plus rituximab or obinutuzumab proved more effective than chemoimmunotherapy for treatment-naïve CLL

without del(17p) or *TP53* mutations across several randomized phase 3 trials; however, the clinical outcomes were not improved with the addition of rituximab compared to ibrutinib monotherapy.² Therefore, ibrutinib is recommended as monotherapy in first-line or relapsed/refractory CLL.²

Zanubrutinib (Brukinsa) is another irreversible BTK inhibitor, but is highly selective/specific and has FDA approval for Waldenström macroglobulinemia and relapsed/refractory mantle cell lymphoma.² The phase 3 SEQUOIA trial (NCT03336333) evaluated zanubrutinib vs bendamustine plus rituximab and found a greater overall response rate (95% vs 85%) with zanubrutinib in patients with untreated CLL without del(17p)/*TP53* mutation along with significantly improved PFS (HR, 0.42; $P < .0001$).² However, patients with mutated *IGHV* did not experience a significant improvement in PFS (HR, 0.67; $P = .0929$).²

PI3K Inhibitors

PI3K activation results in greater B-lymphocyte proliferation, apoptosis, adhesion, and migration.³ Approved PI3K inhibitors for treatment of CLL include idelalisib (Zydelig) and duvelisib (Copiktra).^{2,3} Idelalisib received FDA approval in 2014 for R/R CLL and duvelisib was approved in 2018 for the treatment of R/R CLL.³ Due to poorer toxicity profiles including autoimmune complications such as colitis, pneumonitis, and increased susceptibility of infections, BTK inhibitors are preferred to PI3K inhibitors.^{2,3} Additionally, acalabrutinib monotherapy proved more effective with fewer adverse events than idelalisib plus rituximab in the phase 3 randomized ASCEND trial (NCT02970318).³

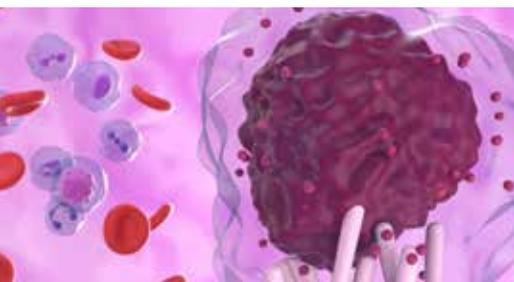
BCL2 Inhibitors

The BCL2 family of proteins are important regulators of apoptosis,

containing proteins that support apoptosis and others that support survival.⁴ Cancer cells avoid apoptosis by shifting toward more proteins in support of survival.⁴ Venetoclax (Venclexta) is the only FDA-approved BCL2 inhibitor for the treatment of CLL and is a fixed-duration treatment option.⁴ Venetoclax plus obinutuzumab significantly improved PFS compared with chlorambucil plus obinutuzumab in patients 65 years or older or patients younger than 65 years with comorbidities in the CLL14 study (NCT02242942).² Venetoclax also resulted in a greater rate of undetectable minimal residual disease (74% vs 34%; $P < .0001$) along with a lower rate of conversion to MRD-positive status 1 year after treatment.² Recently presented results from the phase 3 CLL13 trial (NCT02950051) indicate superior PFS with venetoclax plus obinutuzumab plus ibrutinib (HR, 0.32; 97.5% CI, 0.19-0.5; $P < .0001$) and venetoclax plus obinutuzumab (HR, 0.42; 97.5% CI, 0.26-0.68; $P < .0001$) over chemotherapy.⁵

Recommended Therapies

Given the advantages of specific therapies in patients with particular gene mutations and characteristics, the National Comprehensive Cancer Network (NCCN) recommends certain treatments depending upon the findings during work-up.² For patients with CLL without del(17p) or *TP53* mutations, the NCCN guidelines give the strongest recommendation for acalabrutinib plus or minus obinutuzumab followed by zanubrutinib.² Venetoclax and obinutuzumab is a recommended option for patients 65 years or older or younger patients with significant comorbidities and is included as a lesser recommended option for patients younger than 65 years without comorbidities due to a lack of current available evidence.²



For patients with del(17p) or *TP53* mutations there are limited data for recommendations and the NCCN recommends enrolling these patients in an appropriate clinical trial.² However, currently available data suggest acalabrutinib plus Obinutuzumab; ibrutinib; venetoclax plus Obinutuzumab; and zanubrutinib are preferred treatment options for first-line therapy.² ■

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Magrolimab Development Continues for the Treatment of AML and MDS

JORDYN SAVA

There are 4 types of CD47 antibodies currently available in the clinic for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). According to Naval G. Daver, MD, a novel option magrolimab, could be the fifth CD47 antibody once data supporting the drug mature.

“[Magrolimab] is a CD47 monoclonal antibody that has been combined with azacitidine [Vidaza] in the frontline setting and in a now completed a phase 1b study, which had 2 parts. One was for high-risk MDS patients.... The other part was for *TP53*-mutated frontline AML,” stated Daver, an associate professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, in an interview with Targeted Oncology™.

Daver explained how first, a prospective, phase 1 trial (NCT03248479) evaluated single-agent magrolimab in patients with relapsed/refractory

AML. Due to the overall positive findings from this trial, a new phase 3 ENHANCE trial (NCT04313881) has begun enrolling patients.

In the ENHANCE trial, the combination of magrolimab plus azacitidine will be examined vs azacitidine plus placebo in treatment-naïve patients with higher-risk MDS. Investigators aim to evaluate the efficacy of magrolimab in combination with azacitidine in this patient population as measured by complete remission and overall survival.

During a panel at the 10th Annual Society of Hematologic Malignancies (SOHO), experts, including Daver, discussed on how to optimize frontline hypomethylating agent (HMA) and venetoclax (Venclexta).

Further, though the combination has only been approved for 4 years, research aims to examine the different ways to move beyond this treatment approach for this patient population

as more work is always needed to improve better outcomes for patients.

In the interview, Daver discussed the approved and investigation CD47 monoclonal antibodies for patients with AML and MDS. He also provided a prediction on where research for AML and MDS is headed.

Targeted Oncology™: Based on data from preclinical and clinical studies, which in type CD47 agents have shown promise as targeted therapies?

There are 4 different CD47 antibodies in clinic for AML and MDS. The one that has the most advanced clinical data, most mature so far, is a drug called magrolimab. This is a CD47 monoclonal antibody that has been combined with azacitidine in the frontline setting and in a now completed a phase 1b study, which had 2 parts. One was for high-risk ▶

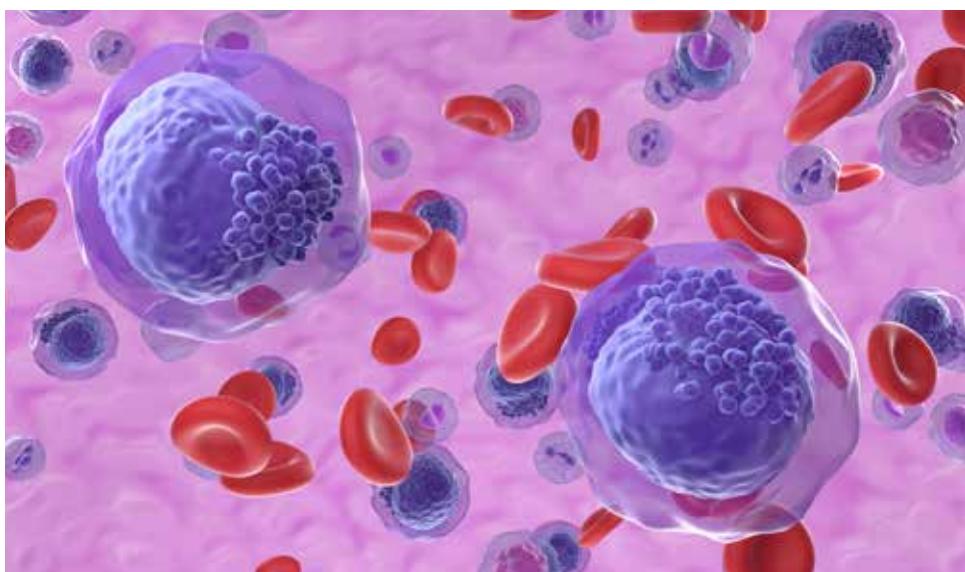
MDS patients, including intermediate, high, or very high IPSS patients. The other part was for *TP53*-mutated frontline AML.

Overall, the data for the MDS patients was that we had 95 patients with this higher risk MDS, and the response rate is encouraging, 75% with a true CR rate of about 33% or 34%. What's interesting is in the subsets that included *TP53* mutated, which made up about 25 of those 95 patients, the median survival is quite promising at greater than 16 months. Historically, pretty much in any other study that we have seen in MDS *TP53*, the survival has been between 9 and 12 months.

This is single arm, but this data looks quite promising. In the non-*TP53* subgroup, the median survival has not been reached, with a median follow-up of about 18 months. Overall, it's a single-arm study, so it's hard to know for sure, but this data does look encouraging. This has led to a randomized phase 3 study now ongoing, called the ENHANCE study, which in fact just completed accrual a couple of weeks ago. We're hoping to start seeing some of the primary end point data early next year.

Then the AML study was looking at the most difficult population of AML called *TP53*-mutated AML patients. In these patients, historically, the response rate is about 30%-40%, with survival about 6-8 months. This is with azacitidine alone, azacitidine/venetoclax, intensive chemotherapy, low dose cytarabine. With the azacitidine and magrolimab doublet, we're seeing a response rate of close to about 49% or 50% and a true complete response [CR] rate of 34%, which are better than what we have seen in the past with other therapies. Not hugely higher, but they looked to be slightly better response rates.

More importantly, the median survival was around 11 months. Even though that's not very high on its own,



it's better than what we have ever seen with *TP53*. This has also led to a randomized study of azacitidine and magrolimab vs investigator choice, either intensive chemotherapy or azacitidine and venetoclax, and that study is ongoing.

What other CD47 inhibitors are available in this space?

There are other CD47's which are very early and ALX148 [evorpacept] is one of them. One of the potential benefits of evorpacept is it may cause less anemia. There was very early clinical data presented of about 12 patients. Some responses we're seeing, and it is very hard to know at this time if this is going to be in the same efficacy range as with the azacitidine and magrolimab, or different, and we hope for updates.

Then there are others that we don't have much clinical data yet they're ongoing in phase 1 studies such as lemparlimab [also known as TJ011133 or TJC4], TTI622, but hopefully, either by the end of this year or early next year, we will see more information from those. It's a very active field and a major target and pathway for clinical development in acute myeloid leukemia and MDS.

What were the key takeaways from your presentation given this year at 10th Annual Meeting of the Society of Hematologic Oncology?

There was a lot of discussion and focus on how to optimize frontline hypomethylating agent and venetoclax and moving beyond HMA and venetoclax. HMA and venetoclax has not been approved that long, it's only been around 4 years. But at MD Anderson Cancer Center, we were involved in and enrolled a large number of patients and led the studies. We realize that even though it's a good breakthrough, at the end of the day, the 3-year survival is about 35%. That is better than 10%, which it was before that for older unfit patients. But still a lot of work has to be done.

What has research focused on over the past few years?

Our effort over the last 2 or 3 years has been to identify molecular biomarkers of resistance. We have found that certain molecular groups like *FLT3*, *TP53*, *RAS*, *KIT* mutation, don't seem to have the same durability and survival with HMA and venetoclax as other molecular groups like *NPM1*, *IDH1*, *IDH2*, which do well.

Now, we've been trying to design ways to add targeted therapies in patients who don't have as good outcomes but have a particular targetable mutation. Sort of a rationalized personalized improvement of the HMA event. This is where several combos of HMA/venetoclax with second generation FLT3 inhibitor or HMA/venetoclax with an IDH inhibitor, HMA/venetoclax with CD47 for *TP53*, and coming soon, HMA/venetoclax with menin inhibitors.

Of course, the inherent issue with combining drugs is you have to be aware of and adjust for myelosuppression toxicities. With a lot of these combinations, the response rates are high with HMA and *FLT3* and *IDH*, but we do see that there's an additional myelosuppression. Now we're cutting down the duration of them. *FLT3*, because of their response being so high, the synergy is good, and you may not need full doses of them. Now we're getting to a point where we are seeing synergy with less myelosuppression. But again, this has to be more mature before it can be adopted widely, but there was a lot of discussion about how we can optimize these doublets and triplets, and what is the benefit of using them upfront in combination vs sequencing. They were all great questions for clinical trials that are starting and will be coming.

What other panels stood out to you at SOHO 2022?

There was a very nice debate on MRD. The question was, is MRD the most critical marker for selecting subsequent therapy or prognosis? Is it the baseline molecular cytogenetic profile of the patient and is that information actually sufficient? Once you have that, do you benefit more from MRD data or not? It's quite a provocative question.

Going into the debate, I think a lot of us would say that MRD is the king and trumps all but both presenters

gave very astute and useful arguments from both sides. What is true is that although MRD negativity is a good factor and is usually just associated with sensitivity or not resistance to chemotherapy, it is not really the eventual decision maker for most patients. Case in point, if you have a *TP53*-mutated AML, and even if they achieve MRD negativity, we would still consider a patient high-risk and go to transplant because we know that the *TP53* biology is present in the leukemia stem cells and may be present at a very low level below the detection threshold. We don't feel comfortable that MRD eradication is sufficient to avoid it.

I think the point is that MRD may be useful in certain situations, NPM1, maybe *FLT3* where we have effective therapies and presence of MRD. Despite that, effective therapy is poor. Maybe you need to do a transplant earlier. I escalate therapy. But for a large majority, the baseline molecular cytogenetic features, if you can really do them in a comprehensive fashion, will give you the similar predictive value as you would have gotten from MRD. And the advantages, you could get that upfront in the beginning. I think it really speaks to the need to enhance our comprehensive genomic cytogenetic potentially the near future RNA expression data. And hopefully then we can really segregate and triage the appropriate prognostic and therapeutic selection for AML.

What unmet needs still exist in this space?

The whole space is an unmet need because in general for AML, the frontline survival is about 35%-40% if you take all patients. It's a little better in the younger patients, those who are below 65, but the 5-year survival is closer to about 60%-65%. For those who are above 65, it's poor at about 20%-25%. In general, we are looking for new strategies for all of them. The

most difficult group is probably in AML is *TP53*. With these, the median survival is 6-8 months across pretty much every therapy we have tried in the last decade, and the 5-year survival is less than 10%. There's usually a small subset of patients who if they can make a stem cell transplant with some degree of Disease Control, we could hope for 30%-35% long term survival.

Our goal is to get these people quickly to transplant if we can. The other big unmet need, both from a diagnostic perspective and therapeutic perspective is MRD [minimal residual disease]. We are getting better at identifying MRD with more sensitive techniques, especially molecular techniques including In single cell sequencing, potential duplex sequencing, and we're now able to probably get down to 10 raise to minus five or so routinely with some of these technologies. These have not yet been validated in prospective trials, hopefully they will be and then could be used prospectively potentially as Registration Status strategies.

The other big problem is we don't have great MRD eradicating strategies yet in the acute myeloid leukemia like we have in acute myeloid leukemia, lymphoma, and others. There has not yet been a chimeric antigen receptor T or bispecific that has shown that degree of activity, but there are many of these now in early stage or going into clinic. Hopefully, we will have some MRD based therapies. These are probably the 2 biggest areas of unmet need.

Then of course, in any relapse disease, the outcome is still poor. We look for targetable mutations, *FLT3* *IDH1*, *IDH2*, *MLL* rearrangement, and for this, we do have targeted therapies with *FLT3* inhibitors, *IDH* inhibitors, Menin inhibitors, but for the others, we still are looking at clinical trial options and nothing has really made a breakthrough yet. ■

New Stem Cell Transplant Strategy Appears Promising for Fanconi Anemia

JORDYN SAVA

The first 2 patients with Fanconi anemia treated with JSP191 achieved 100% donor chimerism JSP191 safe to infuse, and no treatment-related adverse events (AEs) or toxicities were observed, according to findings of a phase 1/2 clinical trial (NCT04784052) announced by Jasper Therapeutics, Inc.¹

JSP191 is a humanized monoclonal antibody currently in clinical development to work as a conditioning agent which will block stem cell factor receptor signaling and lead to clearance of hematopoietic stem cells from bone marrow. In turn, this will create an empty space for donor or genetically modified transplanted stem cells to engraft.

These positive clinical data were presented at the European Society of Blood and Marrow Transplantation, held on September 23-25, 2022, in Paris, France. Here, 100% complete donor chimerism was achieved at 6 months for the first patient and at 1 month for the second. Further, neutrophil engraftment was achieved on

day 11 for both patients and platelet engraftment on days 9 and 14.

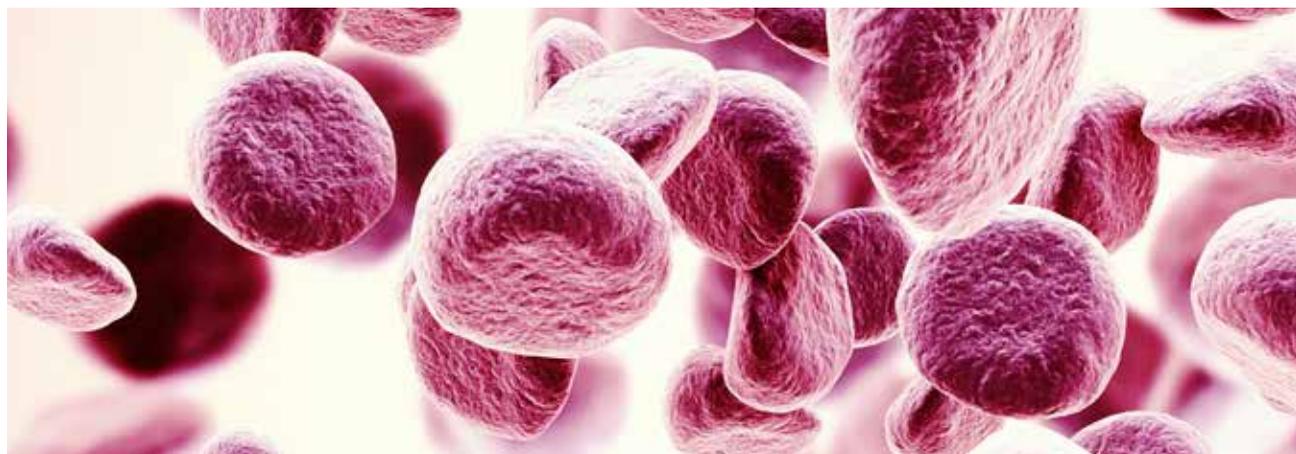
“Initial data from this study suggest that a conditioning regimen that includes JSP191 has the potential to achieve successful donor transplant with no JSP191-related adverse events or toxicities reported to date. The positive update presented gives us increased confidence in JSP191, which has now shown promise as a conditioning agent in 4 indications including acute myeloid leukemia, myelodysplastic syndromes, severe combined immunodeficiency, and Fanconi anemia,” said Ronald Martell, president, and chief executive officer of Jasper Therapeutics, in the press release. We look forward to continuing support for Stanford’s investigation of JSP191 and advancing our broader pipeline for JSP191 to the next phase of development.”

The phase 1/2 clinical trial aims to develop a cell therapy for Fanconi anemia with the hopes of causing fewer side effects than chemotherapy which is currently the

current standard of care method in this patient population.²

In the experimental arm, patients were given an infusion of donor stem cells which were depleted of $\alpha\beta$ +T cells using the CliniMACS System device. Prior to stem cell transplant, patients received a reduced-intensity preparative regimen containing JSP191 in combination with rabbit anti-thymoglobulin (rATG), cyclophosphamide, fludarabine and rituximab (Rituxan).

Those eligible for enrollment in the trial were patients aged 2 years and older with a diagnosis of Fanconi anemia as demonstrated by abnormal chromosome breakage studies with increased sensitivity to mitomycin-C or diepoxybutane, at least 1 mutation in a known Fanconi-associated gene, bone marrow failure, and a life expectancy of at least 2 years. Patients of childbearing potential must use an effective contraceptive method during the time of peri-transplant conditioning through hematopoietic recovery.



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Primary end points of the trial included the number of participants without grade 3 or 4 treatment emergent AEs, number of those able to achieve donor engraftment, and the number of patients who are able to have donor engraftment and the same rate or better vs the alternative hematopoietic cell transplant regimens for this patient population.

The secondary end points of the trial were serum concentration of JSP191, rATG, and fludarabine, participants who do not develop mucositis or veno-occlusive disease, number of participants who achieve hematopoietic recovery, donor engraftment, and immunologic recovery, the number of patients who develop grade I-IV acute or chronic graft-vs-host disease,

and the number of participants who achieve disease-free survival.

Jasper Therapeutics, Inc, is now planning a new study of JSP191 as a second-line therapy option in low-risk patients with MDS which will take place in 2022, as well as a pivotal study in AML/MDS transplant in early 2023. Additional studies have planned enrollment for patients with chronic granulomatous disease and GATA2 MDS who are undergoing hematopoietic cell transplantation as well as a study of JSP191 as a chronic therapeutic for low to intermediate risk patients with MDS.

“Patients affected by Fanconi anemia have increased sensitivity to conventional conditioning regimens and radiation due to innate defects in

DNA repair. JSP191 offers a targeted conditioning strategy that eliminates the need for radiation or alkylating agents like busulfan,” said Martell in the press release. ■

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MEDI5752 Plus Chemotherapy Produces Long DOR, But High Dose Comes With High Toxicity

JASON HARRIS

Chemotherapy added to 1500 mg of MEDI5752, a PD-1/CTLA-4 bispecific monoclonal antibody, led to a doubling in duration of response (DOR) compared with pembrolizumab (Keytruda) and chemotherapy in patients with treatment-naïve nonsquamous non-small cell lung cancer (NSCLC). Findings from the phase 1b/2 trial were presented at the 2022 ESMO Congress.

However, the regimen resulted in high rates of discontinuation and toxicity, leading investigators to explore a 750-mg dose of MEDI5752. The reduced dose of the agent demonstrated a similar overall response rate (ORR) and improved tolerability, but investigators need longer follow-up to assess progres-

sion-free survival (PFS), overall survival (OS), and DOR.

“The 1500-mg MEDI5752 plus chemotherapy showed improved antitumor activity—almost double the duration of response compared [with] pembrolizumab plus chemotherapy in the first-line setting, and the clinical benefit of [MEDI5752] in patients with PD-L1-negative [status] was consistent with the previous data,” said Myung-Ju Ahn, MD, PhD, a professor in the Department of Hematology and Oncology with Samsung Medical Center at Sungkyunkwan University School of Medicine in Seoul, South Korea.

At the 1500-mg dose, MEDI5752 plus chemotherapy (n = 20) induced an ORR of 50.0% vs 47.6% in patients

assigned to pembrolizumab plus chemotherapy (n = 21). The median DOR was 20.5 months (95% CI, 4.1-not evaluable [NE]) in the MEDI5752 arm compared with 9.9 months (95% CI, 2.8-NE) with pembrolizumab.

The median PFS (15.1 vs 8.9 months) and OS (not reached vs 16.5 months) also favored the MEDI5752 arm.

Among patients who were PD-L1-negative (< 1% expression on tumor cells), ORR again favored the experimental arm, 55.6% (95% CI, 21.2%-86.3%) vs 30.0% (95% CI, 6.7%-65.2%). Similarly, the median PFS was superior with MEDI5752 vs pembrolizumab, 13.4 vs 9.0 months.

Investigators also assigned 64 patients to 750-mg MEDI5752 plus chemotherapy in a single-arm ▶

cohort. These data include the first 50 patients who had at least 8 weeks of follow-up. One patient was not evaluable for response.

In this group, the ORR was 40.8% and 49% of patients had at least 30% reduction in target lesions. Among PD-L1-negative patients (n = 36), the ORR was 44.4% and 55.6% of patients had at least 30% reduction in target lesions.

At the July 12, 2022, data cutoff, the median follow-up was 22.8 months in the experimental arm (range, 0.8-26.9) and 14.5 months (range, 1.6-27.9) with the control.

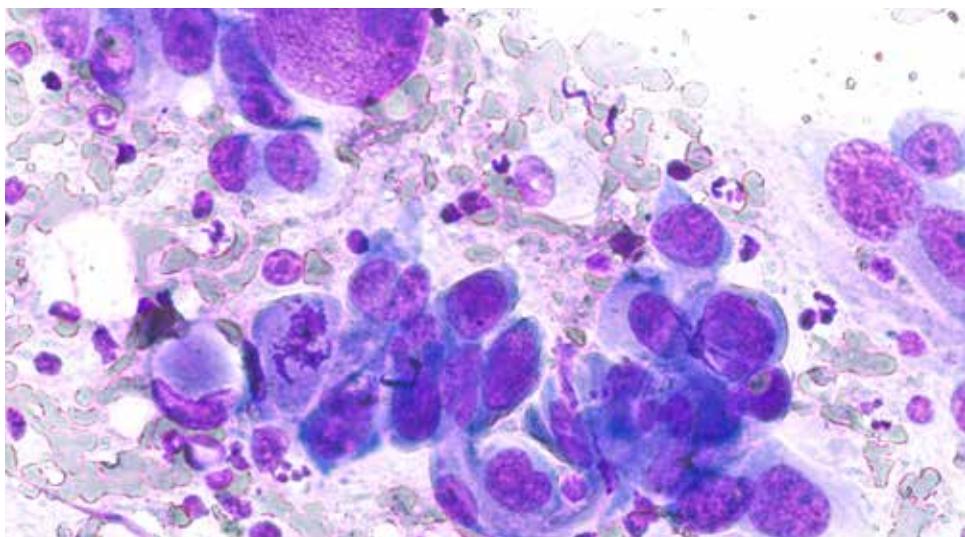
The median patient age in the MEDI5752 arm was 63.0 years (range, 50-86) and men made up 70% of the cohort. The median age in the pembrolizumab arm was 70.0 years (range 48-78) and 81% of the cohort was male. Approximately 60% of patients in both groups had an ECOG performance score of 0.

Sixteen patients (80.0%) in the experimental arm were current or former smokers compared with 90.5% in the control arm. All patients in the MEDI5752 arm and 90.5% in the pembrolizumab arm had stage IV disease.

Four patients (20.0%) in the MEDI5752 arm had brain metastases and 2 (10.0%) had liver metastases compared with 3 (14.3%) and 4 (19.0%), respectively, in the pembrolizumab arm.

Nine patients (45.0%) in the experimental group were PD-L1 negative compared with 10 (47.6%) with the control. Investigators identified 5 oncogenic drivers in the MEDI5752 arm and 2 in the pembrolizumab arm.

In the 750-mg cohort, the median age was 67.0 years (range, 36-83) and 72.0% of group were men. Thirty-eight patients (76.0%) had an ECOG status of 1 and 88% were current or former smokers. Ninety-six percent had stage IV disease, 16.0% had brain metastases, 16.0% had liver metastases, and 72.0% were PD-L1 negative.



Investigators identified 2 oncogenic drivers in this group.

Patients received 1500 mg MEDI5752 plus 5 area under the curve (AUC) carboplatin and 500mg/m² pemetrexed every 3 weeks for 4 cycles followed by maintenance therapy MEDI5752 or pembrolizumab every 3 weeks until unacceptable toxicity, progression, or withdraw of consent. Patients in the single-arm cohort received 750 MEDI5752 plus pemetrexed on the same schedule.

Fourteen patients (70.0%) in the 1500-mg group discontinued treatment compared with 6 (28.6%) in the pembrolizumab arm and 10 (20.0%) in the 750-mg group. Eighty percent of patients in the high-dose group experienced grade 3/4 treatment-related adverse events (TRAEs) compared with 61.9% in the pembrolizumab group and 50% in the low-dose group.

As expected, incidence of grade 3/4 TRAEs was much greater in the 1500-mg group compared with the 750-mg group. The most common grade 3/4 TRAEs were rash (10% vs 2%, respectively), alanine transaminase increased (30% vs 2%), aspartate transaminase increased (20% vs 2%), pneumonitis (5% vs 0%), and diarrhea (5% vs 2%).

“The emerging data of 750 mg plus chemotherapy showed a simi-

lar overall objective response with the improved tolerability less [and a lower] rate of discontinuation,” Ahn said. “[These] data suggests that MEDI5752 provides the potential options to improve the standard of care in first-line [for patients with] NSCLC, especially in those who have PD-L1-negative tumors.”

Invited discussant, Laura Mezquita, MD, PhD, a medical oncologist at Hospital Clínic de Barcelona in Spain, said it will be necessary to identify predictive biomarkers to determine which dose of MEDI5752, or possibly even a lower dose, is most appropriate for patients.

“This dose, 1500 mg, improves efficacy also in the PD-L1-negative population, however with very high toxicities and discontinuations,” she said. “Probably [the 750-mg dose] will be better, but we only have emerging activity...the safety profile is favorable, but longer follow-up is what is needed.” ■

REFERENCE

1. Ahn MJ, Kim SW, Carcereny E, et al. MEDI5752 or pembrolizumab plus carboplatin/pemetrexed in treatment-naïve non-small-cell lung cancer: a phase 1b/2 trial. Presented at: European Society for Medical Oncology Congress 2022; September 9-13, 2022; Paris, France.