

2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Hematologic Malignancies

Amy Pierre, MSN, ANP-BC, of the Memorial Sloan Kettering Cancer Center, and **Nancy M. Nix, PharmD, BCPS, BCOP** of St. Joseph's/Candler Health System offer an advanced practitioner perspective on trials assessing the efficacy and safety of novel agents in smoldering and relapsed/refractory multiple myeloma, chronic lymphocytic leukemia, and acute myeloid leukemia.

Abstract 8001

Evidence Builds for Treating Smoldering Myeloma

By Caroline Helwick

Visit <https://meetinglibrary.asco.org/record/172276/abstract> to read the full abstract and view disclosures.

In patients with intermediate- to high-risk smoldering multiple myeloma, treatment with single-agent lenalidomide, vs observation, led to a 72% reduction in the risk of disease progression at 3 years (Lonial et al., 2019). Results of the phase III E3A06 study were presented at a press briefing in advance of the 2019 ASCO Annual Meeting by Sagar Lonial, MD, FACP, of Emory University, Atlanta.

“We showed, in the largest randomized study to date in smoldering myeloma, that we can prevent the development of symptomatic myeloma

in a significant fraction of patients,” Dr. Lonial said. More than 90% of the intervention group remained progression-free at 3 years, he reported.

Although patients with smoldering multiple myeloma—an early, asymptomatic entity lacking the presence of CRAB criteria (elevated calcium, renal failure, anemia, bone lesions)—are typically monitored and not treated, some researchers have questioned whether early intervention could improve outcomes and even cure the disease before its full impact is felt.

“There’s no question that patients with multiple myeloma need immediate treatment to reverse evidence of organ damage, but a challenge we’ve struggled with is trying to identify patients without organ damage who are at highest risk of disease progression, and trying to intervene,” Dr. Lonial said.

Patients classified as having smoldering disease generally have a risk of disease progression of about 10% per year. After 5 years, approximately half of these patients will have symptomatic disease, he said.

Previous Findings by Spanish Myeloma Group

The study builds upon earlier work by The Spanish Myeloma Group, who reported in the smaller 2015 PETHEMA trial that lenalidomide/dexamethasone improved progression-free and overall survival, vs observation, in patients at high risk of disease progression (Mateos et al., 2013).

That study, however, was criticized in ways that were avoided by the current study design: patients were not screened with advanced imag-

ing techniques; investigators applied an outdated definition of high risk; and the regimen included dexamethasone, making it impossible to isolate the effect of lenalidomide, he said.

“The fact that the study did not use modern imaging [to screen for eligibility] is important, because patients with negative x-rays may have bone disease by magnetic resonance imaging (MRI) or positron-emission tomography (PET) scan,” Dr. Lonial noted. “In our study, we required MRI before study entry to be sure we were not enrolling patients who already had myeloma, which was the main criticism of the Spanish trial.”

E3A06 also eliminated dexamethasone, which can suppress or eliminate the malignant clone and produce a temporary response, as opposed to control the clone, as was the aim of using single-agent lenalidomide, he said.

The previous trial, therefore—while considered important—did not change the standard of care, “but now,” he said, “with the E3A06 trial, in aggregate with the PETHEMA trial, many of us would argue that early intervention with a prevention strategy can reduce the risk of conversion to symptomatic myeloma.”

E3A06 Details

E3A06 was a randomized phase III intergroup trial that tested the effect of single-agent lenalidomide compared with observation in patients classified as having intermediate-risk or high-risk smoldering myeloma. Eligibility required $\geq 10\%$ plasma cells and abnormal serum free light chain ratio (< 0.26 or > 1.65).

In an initial phase II run-in phase, 44 patients received lenalidomide to demonstrate safety. In the phase III trial, 182 patients were randomly assigned to either lenalidomide (25 mg/d for 21 of 28 days) or observation. Baseline characteristics were similar between the arms. Median follow-up was 71 months

for the phase II portion and 28 months for phase III. The primary endpoint was progression-free survival.

Significant Reduction in Risk of Progression

At 3 years, 87% of the phase II cohort, all of whom received lenalidomide, were progression-free, as were 78% at 5 years. For the phase III comparison, the 1-year, 2-year, and 3-year progression-free survival rates were 98%, 93%, and 91% for lenalidomide vs 89%, 76%, and 66%, respectively, for observation (hazard ratio [HR] = 0.28; $P = .0005$), as shown in Table 1. The overall response rate with lenalidomide was 47.7% for the phase II study and 48.9% for the phase III, with no responses seen in the observation arm.

Interestingly, when broken down into low-, intermediate-, and high-risk groups, each subset was found to benefit “almost equally” from early intervention. “This suggests that while high-risk patients may be the ones we target now, a fertile area of further investigation may be the intermediate group, for whom no trial has yet shown benefit in preventing symptomatic disease. We do see a benefit for the intermediate-risk patients, but the overall survival follow-up is too short to say these patients should all be treated,” he concluded.

Low-intermediate-risk patients were enrolled when the study loosened eligibility criteria for only slightly abnormal free light chain ratios. Although they, too, derived benefit, this is not a group to consider for treatment at this time, he added.

Adverse Events

Grade 3 to 4 nonhematologic toxicities were observed in approximately 28% of patients, and grade 3 to 4 hematologic toxicity (primarily neutropenia) in about 6%. The cumulative incidence of invasive secondary primary malignancies was 5.2% for lenalidomide and 3.5% for observation.

There were no differences in quality-of-life scores between the arms. However, 80% of patients in phase II and 51% in phase III discontinued lenalidomide.

Looking Ahead

A preventive strategy for smoldering myeloma is likely to be less intensive than the treatment strategies employed for symptomatic disease. “We are focusing on enhancing immune surveillance of the

Table 1. Progression-Free Survival for Lenalidomide vs Observation in the Phase III E3A06 Study (N = 182)

Progression-Free Survival	Lenalidomide	Observation
1 year	98%	89%
2 years	93%	76%
3 years	91%	66%

existing malignant clone and preventing that clone from progressing, as opposed to eradicating the disease, which is the goal of treatment,” Dr. Lonial said.

Ongoing studies are, in fact, pursuing more aggressive interventions, such as combining lenalidomide, dexamethasone, and daratumumab, or other new active agents. Other studies are evaluating the benefit of induction therapy, consolidation, transplant, and 2 years of maintenance in smoldering disease, he said.

“We don’t know that a true treatment strategy makes a difference, but we’ve shown that intervention can make a difference,” he said. “Now is

the time to explore other ideas, with more intensive regimens and with a different focus.” ●

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The Advanced Practitioner Perspective

Amy Pierre, MSN, ANP-BC

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The current standard of care for smoldering multiple myeloma is surveillance. This phase III E3A06 study was a prospective, randomized, multi-group trial investigating the single-agent use of the oral immunomodulatory drug, lenalidomide, in patients with intermediate- to high-risk smoldering myeloma. The primary endpoint of the study was progression-free survival in order to study how efficacious lenalidomide is in preventing the development of symptomatic multiple myeloma in this at-risk population.

The trial concluded that single-agent lenalidomide, compared to observation alone, can elicit a response rate in close to 50% and also decrease the risk of developing active myeloma by 72% without affecting quality of life. Many patients with smoldering myeloma often ask about strategies to improve their outcomes or prevent progression to symptomatic myeloma; this phase III trial demonstrated only 9% of patients on lenalidomide developed pro-

gressive disease at 3 years. This raises the possibility of cure in this patient population and the avoidance of dexamethasone, which can affect many organ systems with long-term usage.

Patient Selection and Secondary Primary Malignancies

It is important for the AP to note that the majority of participants discontinued the treatment arm of the study due to withdrawal or adverse events. Understanding which patients would be excellent candidates for this preventative approach to managing smoldering myeloma as well as anticipating side effects is a key role for the AP. In addition, the risk of secondary primary malignancies with lenalidomide is a real concern for patients and clinicians; it is important to highlight the rarity of this occurrence compared to the overall benefits of lenalidomide in preventing progression of this disease.

Awaiting further data regarding 5-year and 10-year follow-up for the phase III data to assess overall survival and possibility of cure is crucial information for APs.

Disclosure: Ms. Pierre has served as a consultant for Celgene.

Abstract 8004

Addition of Isatuximab to Pomalidomide/Dexamethasone in Multiple Myeloma

By Lauren Harrison, MS

Visit <https://meetinglibrary.asco.org/record/172190/abstract> to read the full abstract and view disclosures.

The addition of isatuximab, an anti-CD38 monoclonal antibody, to pomalidomide and low-dose dexamethasone improved both progression-free survival and overall response in patients with relapsed or refractory multiple myeloma. Paul G. Richardson, MD, of the Dana Farber Cancer Institute in Boston, and colleagues, who presented the results of their phase III trial at the 2019 ASCO Annual Meeting in

Chicago (Abstract 8004), consider this triplet therapy an “important new treatment option” in this patient population.

Study Details

In a commentary filmed for *The ASCO Post Newsreels*, Dr. Richardson said, “ICARIA-MM was an international study conducted in over 20 countries involving over 90 centers, so it represented a real world effort to identify the role of isatuximab combined with pomalidomide and dexamethasone in this area of exquisite unmet medical need—relapsed/refractory multiple myeloma patients.”

A total of 307 patients with relapsed or refractory multiple myeloma who had received more than 2 prior lines of therapy were included in the study. Patients were randomly assigned to receive either isatuximab plus pomalidomide/dexamethasone or pomalidomide/dexamethasone alone.

Results

At a median follow-up of 11.6 months, the median progression-free survival was 11.5 months with isatuximab and 6.5 months without it (hazard ratio = 0.596). This progression-free survival benefit was seen among all subgroups of patients. The overall response rate was increased from 35.3% with pomalidomide/dexamethasone alone to 60.4% with the addition of isatuximab. At the date of analysis, the overall survival could not be calculated, but there appeared to be a trend toward improvement for patients receiving the triplet therapy.

According to Dr. Richardson, “We were able to look at MRD testing. Whereas we saw no MRD negativity with pomalidomide/dexamethasone alone, with the combination of pomalidomide, dexamethasone, and isatuximab, the MRD negative rate was 5% by next-generation sequencing, which in the relapsed/refractory setting is quite interesting and rather provocative as a signal.”

Safety

The median treatment time was 41 weeks for the isatuximab group and 24 weeks for the control group. Grade 3 or higher adverse events were seen in 86.8% of patients treated with isatuximab, compared with 70.5% of patients who were not treated with the drug. Grade 3 infections were seen in both

the triplet-therapy group and the doublet-therapy group, 42.8% and 30.2% respectively. In addition, grade 3 or higher neutropenia was seen in 84.9% of patients treated with isatuximab and 70.1% of patients not treated with isatuximab.

According to Dr. Richardson, “what was very encouraging from a safety point of view was that we didn’t see any new or unexpected adverse events. There was a higher rate of infections in terms of pneumonia for the three drugs instead of the two. This is something we see with the antibodies which we manage proactively. One important side effect that was different was neutropenia. That was more common with isatuximab, very much as expected from our earlier phase trials. With the use of G-CSF as a growth factor, that was very manageable. Therefore, the overall safety profile was encouraging, and we did a quality-of-life assessment that showed no change in QOL by the use of the antibody.”

Patient Subsets

Dr. Richardson discussed specific patient subsets as well. “In terms of patient subsets, benefit was shown in high-risk patients, in patients with renal dysfunction, and in those who were lenalidomide-refractory. In a small group of patients, about 10%, who had COPD, we were able to safely give this drug. One of the challenges with daratumumab is it can exacerbate COPD because of its effects on the bronchioles, but this was not seen with isatuximab to the same extent in this setting.”

Future Directions

“Overall, ICARIA-MM has shown very encouraging results, clear clinical benefit, a favorable safety profile,” according to Dr. Richardson “and a very promising platform hopefully for FDA approval in this setting, and then, the use of isatuximab earlier in the disease.” ●

Reference

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The Advanced Practitioner Perspective

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Treating relapsed/refractory multiple myeloma, particularly in patients with high-risk cytogenetics, has proven challenging and become an important area of focus as myeloma patients live longer. This phase III, randomized, international study, ICARIA-MM, demonstrated that the addition of isatuximab, an anti-CD38 monoclonal antibody, to pomalidomide and dexamethasone (IPd) not only improved overall response rates and progression-free survival for relapsed/refractory patients, but may also improve overall survival. The triplet regimen of IPd decreased the risk of progression of disease by close to 50% with no change in quality of life (HR, 0.596; 95% CI = 0.44–0.81).

Adverse Events

There was a high rate of neutropenia and infection, particularly pneumonia, in the triplet regimen (IPd) vs. the doublet regimen (Pd). It is crucial for the AP to have a low threshold for assessing for the presence of pneumonia in patients on IPd as well as anticipating and identifying those at risk for neutropenia. As infection is the leading cause of mortality for myeloma patients, long-term follow-up is needed to fur-

ther elucidate the suggested overall survival benefit demonstrated in this trial with IPd.

Infusion vs. Oral Regimen

Achieving deep response rates in multiple myeloma, particularly MRD negativity, allows for better disease control and improved outcomes. For relapsed/refractory patients who are hesitant to participate in a treatment regimen that involves an infusion visit vs. an all-oral regimen such as Pd, it is imperative for the AP to educate patients regarding the improved response rates and deeper response rates achieved in this trial with IPd: MRD negativity was obtained with IPd and not with Pd.

Looking Forward

There were also more adverse events associated with Pd versus IPd—an important fact for patients who have been heavily pretreated and may already have preexisting comorbidities from prior therapy. One could hypothesize that IPd had less adverse effects than Pd due to better disease control with IPd.

With the encouraging results of this trial, it is important for the AP to anticipate FDA approval of IPd and begin discussions with patients who are appropriate candidates for this novel therapy.

Disclosure: Ms. Pierre has served as a consultant for Celgene.

Abstract 7502**Fixed-Duration Venetoclax Plus Obinutuzumab as First-Line Treatment in Older Patients With CLL Who Have Comorbidities**

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/171944/abstract> to read the full abstract and view disclosures.

A fixed-duration regimen of venetoclax plus obinutuzumab demonstrated superior progression-free survival, complete response rates, and minimal residual disease (MRD) negativity compared with chlorambucil plus obinutuzumab as first-line therapy for older patients with chronic lymphocytic leukemia (CLL) and

comorbidities, according to the results of the CLL14 trial presented at the 2019 ASCO Annual Meeting (Fischer et al., 2019a) and published simultaneously in *The New England Journal of Medicine* (Fischer et al., 2019b).

The new fixed-duration targeted therapy regimen compares favorably with historical results with continuous ibrutinib therapy as upfront therapy for CLL in elderly patients. Moreover, it has the advantage of being administered for a fixed duration rather than continuously, as is the case with ibrutinib.

“Fixed-duration targeted therapy combining venetoclax and obinutuzumab can be applied safely in elderly patients with CLL and comorbidities. Our study showed it is superior to fixed-duration chlorambucil and obinutuzumab. Venetoclax plus obinutuzumab achieves the highest rates of MRD-negative response so far observed in a randomized

CLL14 Trial

- First-line fixed-duration venetoclax/obinutuzumab was superior to fixed-duration chlorambucil/obinutuzumab in older patients with CLL and comorbidities.
- Progression-free survival was substantially longer, particularly in patients with poor prognostic factors.
- The rates of minimal residual disease negativity were significantly better with venetoclax/obinutuzumab.
- The safety profile for venetoclax/obinutuzumab was acceptable.

prospective trial [of patients with CLL],” stated lead author Kirsten Fischer, MD, of the Center for Integrated Oncology Cologne-Bonn, University Hospital of Cologne, Germany.

With short follow-up, there was no difference in survival between venetoclax plus obinutuzumab vs chlorambucil plus obinutuzumab. “We hope this will change with longer follow-up,” Dr. Fischer told the audience.

Study Background

Most patients with CLL are older and have comorbidities. “There is a need for more effective and less toxic regimens in this patient population,” Dr. Fischer said.

Fixed-duration chemoimmunotherapy and continuous indefinite targeted therapy with ibrutinib are used as first-line treatment for CLL. “We decided to develop a new targeted therapy with a fixed duration, and based on preclinical and clinical data, we selected venetoclax plus obinutuzumab,” she continued. “We wanted to see whether we could improve upon a median progression-free survival of 31 months with chlorambucil plus obinutuzumab.”

Study Details

The open-label, randomized, phase III CLL14 trial was conducted at 196 sites in 21 countries. The study enrolled 432 previously untreated patients with CD20-positive CLL requiring treatment. All patients had to have a score greater than 6 on the Cumulative Illness Rating Scale or a creatinine clearance less than 70 mL/min, both of which would indicate clinically relevant comorbidities. Patients were randomly assigned 1:1 to receive either venetoclax plus obinutuzumab or chlorambucil plus obinutuzumab for 12 cycles lasting 28 days each.

Demographic and disease characteristics were well balanced between the two treatment arms. The median age was 72 years, median Cumulative Illness Rating Scale score was 8, and median creatinine clearance was 66.4 mL/min. In total, 13.8% of patients had a *TP53* deletion, mutation, or both, and 59.8% had unmutated *IGHV* (an unfavorable prognosis factor).

Among patients in the venetoclax/obinutuzumab group, 13.4%, 64.4%, and 22.2% were at low, medium, and high risk of tumor-lysis syndrome, respectively. However, there were no cases of tumor-lysis syndrome that met diagnostic criteria.

The planned treatment of 12 cycles was given to 77.8% of the venetoclax/obinutuzumab group and 74.8% of the chlorambucil group. The median duration of treatment and median dose intensity were similar between the two treatment arms.

Efficacy Results

After a median follow-up of 28 months, median progression-free survival was not reached in either group. Estimates of 24-month progression-free survival were 88.2% in the venetoclax/obinutuzumab group vs 64.1% for chlorambucil/obinutuzumab, a significant difference that favored the experimental arm ($P < .0001$).

The superiority of venetoclax/obinutuzumab was seen in patients with unmutated *IGHV* as well as in those with *TP53* alterations, for whom median progression-free survival was not reached. Thus far, with a relatively short follow-up of 28 months, no difference in overall survival has been observed. “It might be too early to see an effect on survival,” Dr. Fischer said.

MRD Negativity

The CLL14 investigators were impressed by the rates of MRD negativity achieved with the venetoclax-containing regimen. Three months following completion of treatment, in the intent-to-treat population, the rate of MRD negativity in peripheral blood was 75.5% vs 35.2% for chlorambucil/obinutuzumab ($P < .001$) and in bone marrow, 56.9% vs 17.1%, respectively ($P < .001$).

The rate of overall response was 84.7% vs 71.3%, respectively ($P < .001$). Complete response rates were 49.5% vs 23.1%, respectively ($P < .001$).

The rates of patients with a complete response and MRD negativity in the peripheral blood were significantly higher in the venetoclax/obinutuzumab group—42.1% vs 14.4%, respectively ($P < .001$). MRD-negativity rates in the bone marrow were also significantly higher in the venetoclax/obinutuzumab group—33.8% vs 10.6%, respectively ($P < .001$). “MRD negativity was achieved early with venetoclax and stayed that way over time,” Dr. Fischer noted.

Adverse Events

Safety was evaluated in 426 patients. At least one adverse event of any grade was reported in 94.5% of the venetoclax/obinutuzumab group and 99.5% of those in the chlorambucil/obinutuzumab arm. Adverse events that led to treatment discontinuation were reported in 16.0% and 15.4% of patients, respectively.

The most common grade 3 or 4 event was neutropenia. Grade 3 or 4 febrile neutropenia occurred in 5.2% and 3.7% of the two groups, respectively, and grade 3 or 4 infections occurred in 17.5% and 15%, respectively. Tumor-lysis syndrome was reported in three and five patients, respectively, but none of these cases met the clinical criteria for tumor-lysis syndrome. The rate of grade 3 and 4 infusion reactions was similar in both arms (9% and 10.3%, respectively).

Fatal events during treatment occurred in 5 patients in the venetoclax/obinutuzumab group compared with 4 in the chlorambucil/obinutuzumab group and after treatment in 11 vs 4 patients, respectively. Second primary cancers were found in 13.7% of the venetoclax/obinutuzumab group and 10% of those on chlorambucil/obinutuzumab.

Future of CLL

“This study is immediately practice-changing in the front-line setting,” said formal discussant Matthew S. Davids, MD, MMSc, of Dana-Farber Cancer Institute, Boston. He singled out the fixed duration of treatment and the very high rates of MRD negativity achieved in the trial without the need for chemoimmunotherapy as distinguishing this regimen from others being studied in CLL.

Dr. Davids was enthusiastic about the landscape of new therapies for CLL in general. “The future of CLL is now. The findings of CLL14 suggest we may be able to have our cake and eat it too—that is, more effective and less toxic treatment,” he said.

“The results of CLL14 look promising. The toxicity profile is favorable and distinct from that of ibrutinib, with no clinical tumor-lysis syndrome. After only 1 year of therapy, progression-free survival at 2 years is 88% for venetoclax/obinutuzumab,” he added.

“The findings are impressive. Every prior chemotherapy and chemoimmunotherapy regimen led to shorter progression-free survival in patients with unmutated *IGHV* than patients with mutated *IGHV*. As with other novel agents in this space, the progression-free survival on the venetoclax regimen was equivalent, irrespective of *IGHV* mutation status. The rate of MRD negativity is also remarkably high given the lack of chemotherapy in this regimen: 76% in the blood and 57% in the bone marrow at 3 months after therapy in an intent to treat analysis. So far the durability of these deep responses appears promising, but longer follow-up is needed,” Dr. Davids continued.

Issues that remain to be resolved are the duration of therapy, the additional effect of obinutuzumab on efficacy, and how a practicing oncologist will choose between ibrutinib vs venetoclax plus obinutuzumab. “For most patients, we should be considering venetoclax plus obinutuzumab as one of the options front-line CLL therapy,” he said. ●

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The Advanced Practitioner Perspective

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The CLL14 trial suggests that the standard of care in front-line CLL for most patients should now be fixed-duration venetoclax plus obinutuzumab every 28 days for 12 cycles. The trial compared venetoclax plus obinutuzumab (V+O) with chlorambucil plus obinutuzumab (C+O). Fixed-duration V+O offered superior progression-free survival, complete response rate, and minimum residual disease. However, with only 28 months follow-up, overall survival benefit has not been demonstrated.

The goal of this trial was to determine if fixed-duration V+O could replace continuous oral ibrutinib. For prescribers, this option ensures appropriate administration of the combination, as it is administered by infusion and eliminates concerns of adherence and persistence associated with oral agents.

MRD Negativity

V+O displayed superiority in patients with unmutated *IGHV* and those with *TP53* mutations. MRD negativity in peripheral blood was 75.5%

with V+O vs. 35.2% with C+O and 56.9% vs. 17.1% respectively in the bone marrow. Overall response rate for V+O was 84.7% vs. 71.3% with C+O while complete response rates were 49.5% vs. 23.1%, respectively.

Adverse Events

Adverse drug events were similar, although grade 3 or 4 febrile neutropenia and infection occurred more frequently with V+O. No incidence of clinical tumor lysis syndrome occurred in either group. Five fatalities occurred during treatment with V+O vs. 4 fatalities with C+O. Following treatment, death occurred in 11 vs. 4 patients and second primary cancer in 13% vs. 10%, respectively.

With the risk of fatalities in mind, it is important for advanced practitioners to consider the overall patient health prior to regimen selection, provide intense patient education concerning potential toxicities, and closely monitor for declination of comorbidities.

Disclosure: Dr. Nix has served on the speakers bureau for Coheras BioSciences and advisory boards for Bristol-Myers Squibb, Genentech, Puma, Sandoz, and Teva.

Abstract 7000

Acute Myeloid Leukemia: Gilteritinib in FLT3-Mutated Disease

In this commentary, Mark J. Levis, MD, PhD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, discusses his ASCO abstract 7000, on the effect of gilteritinib on survival in patients with FLT3-mutated relapsed/refractory AML who have common comutations or a high FLT3-ITD allelic ratio (courtesy of The ASCO Post Newsreels).

Visit <https://meetinglibrary.asco.org/record/173640/abstract> to read the full abstract and view disclosures.

Abstract 7000 is a follow-up from the ADMIRAL study. The ADMIRAL study was a randomized study in which patients with relapsed/refractory *FLT3*-mutant AML were randomized to receive either single-agent gilteritinib or salvage chemotherapy. Single-agent gilteritinib is a novel *FLT3* inhibitor that hits both *FLT3* TKD and ITD mutations. And as a result of the ADMIRAL study, it received regulatory approval because of the fact

that there was an improved response rate and recently updated on the label an improved survival.

However, *FLT3*-mutant AML at diagnosis is influenced by more than just the presence of that *FLT3* mutation. We know that the allelic burden has a big influence on outcomes; the higher allelic burden, the higher mutant burden that you have, and the worse you're going to do. We know that comutations influence outcome as well. In particular, *NPM1* mutations are quite common with *FLT3* mutations. If you have an *NPM1* mutation, you tend to do less badly; therefore, at diagnosis, high allelic burden is bad, but with an *NPM1* mutation as a comutation, it is less bad.

We asked, "Now that we have gilteritinib, and it's working in the relapsed/refractory setting, what influence do those molecular features have on outcome in that population?" So we actually were able to analyze the on-study samples from the majority of the patients on this trial, 361 out of 371. They were analyzed by the Archer Myeloid Panel for comutations and allelic ratio by the LeukoStrat diagnostic assay. Bottom line, we could not

find a single molecular group in which gilteritinib did not cleanly beat chemotherapy in terms of response rate, or survival for that matter.

But, there were some very interesting points that emerged from further analysis. About half the patients on the study had an *NPM1* mutation. Remember, at diagnosis, the *NPM1* mutation is a so-called “more favorable” risk factor. Well, in this population, it made it worse. Outcomes were worse if patients had an *NPM1* mutation, regardless of how they were treated. Gilteritinib for the most part handled that. Salvage chemotherapy did not. It looked even worse with an *NPM1* mutation. *DNMT3A* mutation is another common mutation in AML, present in about a third of patients on the study. If you put the two together, *DNMT3A* and an *NPM1* mutation, that was about a quarter of the patients on this study. That was really pretty dramatic. Those patients with that combination who got chemotherapy did horrifically poorly. Essentially, the survival curves went to ground.

In comparison, the gilteritinib-treated patients with that genotype had a survival that looked almost like newly diagnosed AML. There was a pla-

teau on the survival curve that looked really quite striking. So that is an interesting finding, and going forward, we’re going to want to look at that genotype in the newly diagnosed setting to say, “Is this a more uniquely responsive population to gilteritinib? And maybe they don’t need a transplant.”

So finding out why that is the case will be work of future studies. But the bottom-line findings from this abstract are that there’s no molecular subtype that justifies you not using gilteritinib. You should use gilteritinib in the relapsed/refractory setting over salvage chemotherapy. And this unique finding of *NPM1* making things worse overall, and the *NPM1*, *DNMT3A* genotype being uniquely responsive to gilteritinib, is something for further investigation. ●

Reference

Levis, M. J., Perl, A. E., Martinelli, G., Cortes, J. E., Neubauer, A., Berman, E.,...Bahceci, E. (2019). Effect of gilteritinib on survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) AML who have common AML co-mutations or a high FLT3-ITD allelic ratio [Abstract 7000]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 37(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.7000

The Advanced Practitioner Perspective

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Abstract 7000 reported follow-up to the ADMIRAL Study, a study in relapsed/refractory *FLT3*-mutated AML that randomized patients to receive either single-agent gilteritinib or salvage chemotherapy. Gilteritinib was approved based on response rate and was recently updated, noting improved survival. This study reports on an evaluation of the impact of comutations as analyzed by the Archer Core Myeloid Panel and allelic ratio as analyzed by the LeukoStrat diagnostic assay. The key outcome was that gilteritinib was better than salvage chemotherapy in all identified molecular groups.

NPM1 Mutation Status

Interestingly, this study contradicted the concept that the *NPM1* mutation is a more favor-

able risk factor, as all patients with the mutation reported worse outcomes regardless of treatment modality. When *NPM1* mutation was combined with *DNMT3A* mutation (a quarter of the patients in the study), the survival curve for patients on chemotherapy plummeted.

In this same subtype, gilteritinib-treated patients experienced survival mirroring newly diagnosed AML. This response is hypothesis-generating, as use of gilteritinib may indicate these patients do not need a transplant. Ultimately, Abstract 7000 supports the assertion that there are no molecular subtypes which exclude gilteritinib use, and gilteritinib should be preferred over salvage chemotherapy.

Disclosure: Dr. Nix has served on the speakers bureau for Coheras BioSciences and advisory boards for Bristol-Myers Squibb, Genentech, Puma, Sandoz, and Teva.