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Volume 38, Supplement 7

Ziftomenib: An investigational menin inhibitor for the treatment of acute leukemias

★ REGISTRATION ENABLING


ACUTE LEUKEMIAS
KURA KO-MEN-001

Phase 1/2 study to assess the safety/tolerability, pharmacokinetics, and antileukemic activity of ziftomenib monotherapy in patients with R/R *NPM1*-m AML^a (NCT04067336)



Recommended phase 2 dose

- Ziftomenib 600 mg QD

^aThis trial also assesses non-*NPM1*-m/*KMT2A*-r AML and *KMT2A*-r ALL. The recommended phase 2 dose has not been established for these populations.

★ ACTIVELY RECRUITING


ACUTE LEUKEMIAS
KURA KO-MEN-007

Phase 1 study to assess the safety/tolerability, pharmacokinetics, and antileukemic activity of ziftomenib combinations for the treatment of patients with *NPM1*-m or *KMT2A*-r AML (NCT05735184)



Ziftomenib combined with

- Venetoclax + azacitidine in newly diagnosed (phase 1b only) and R/R *NPM1*-m or *KMT2A*-r AML
- Venetoclax in R/R *NPM1*-m AML (phase 1b only)
- 7 + 3 in newly diagnosed *NPM1*-m or *KMT2A*-r AML


ACUTE LEUKEMIAS
KURA KO-MEN-008

Phase 1 study to assess the safety/tolerability, pharmacokinetics, and antileukemic activity of ziftomenib combinations for the treatment of patients with R/R *NPM1*-m or *KMT2A*-r AML (NCT06001788)



Ziftomenib combined with

- Gilteritinib (in *NPM1*-m and *FLT3*-m only)
- FLAG-IDA
- LDAC

Ziftomenib is an investigational drug candidate that has not received FDA approval.



Scan the QR code to learn more about
the KOMET clinical trials program.

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; FLAG-IDA, fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor; *FLT3*-m, fms-like tyrosine kinase 3 mutant; *KMT2A*-r, lysine methyltransferase 2A-rearranged; LDAC, low-dose cytarabine; *NPM1*-m, nucleophosmin 1 mutant; QD, once daily; R/R, relapsed/refractory.

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12730 High Bluff Drive, Suite 400

San Diego, CA 92130 | US-KO539-2400007 | May 2024

Leveraging CAR T-Cell Therapy Advancements in R/R Multiple Myeloma

In a recent *Training Academy* hosted by CancerNetwork®, experts in multiple myeloma discussed the evolving role of chimeric antigen receptor (CAR) T-cell therapy for patients with relapsed/refractory disease. The panelists highlighted updated findings from clinical trials, recent FDA approvals, and other developments that could change the multiple myeloma treatment paradigm. Here are their key takeaways from the discussion:

CAR T-Cell Therapy Treatment Options

- B-cell maturation antigen expression is common on the surface of multiple myeloma cells, making it a suitable target for immunotherapy.
 - Idecabtagene vicleucel (ide-cel; Abecma), which the FDA approved in March 2021 for use after 4 or more prior lines of therapy, is suitable as third-line therapy for patients with triple class-exposed disease.¹
 - Ciltacabtagene autoleucel (cilta-cel; Carvykti), which received approval in February 2022 for use after 4 or more prior lines of therapy, can be given as second-line therapy to patients with exposure to immunomodulatory drugs and proteasome inhibitors and whose disease is refractory to lenalidomide (Revlimid).²
- One-time infusions may allow patients to achieve minimal residual disease negativity as soon as 28 days following treatment.
 - Prior data suggest improvements in quality of life with CAR T-cell therapy vs other continuous treatments.

Early-Line CAR T-Cell Therapy Approvals

- The FDA approved cilta-cel in April 2024 for patients who have received at least 1 prior line of therapy, based on data from the phase 3 CARTITUDE-4 trial (NCT04181827).⁵
- Ide-cel was approved in April 2024 for patients who have had at least 2 prior lines of therapy, based on findings from the phase 3 KarMMa-3 trial (NCT03651128).⁶
- Data from these trials may support the potential benefit of administering CAR T-cell therapy as early as possible.

Later-Line CAR T-Cell Therapy Data

- Cilta-cel produced an overall response rate of 97.9% (95% CI, 92.7%-99.7%) in the phase 1b/2 CARTITUDE-1 study (NCT03548207).³
- In the phase 2 KarMMa trial (NCT03361748), ide-cel yielded a response in 73% of patients (95% CI, 66%-81%), and 33% had a complete or stringent complete response.⁴
 - Ide-cel may still have benefits in patient subgroups, including those with extramedullary disease or high tumor burden.

Suitable Treatment Strategies

- Shared decision-making with patients may be critical when selecting ide-cel vs cilta-cel.
 - Cilta-cel may be considered for patients based on the higher response rate observed in CARTITUDE-1.
 - Ide-cel may still be suitable for older patients with significant morbidities.
- Delayed neurologic toxicity, such as cranial nerve palsy, generally appears to be a reversible treatment class effect.
- CAR T-cell therapy may not be suitable for every patient in the second-line setting.
 - An individualized approach based on patient disease biology may be necessary.
 - Sequencing these agents is an ongoing challenge.



FOR REFERENCES VISIT
cancernetwork.com/07.24_CART

Meet the Experts



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Sequencing Bispecifics and CAR T-Cell Therapy in R/R Multiple Myeloma

In a recent *Training Academy* segment hosted by CancerNetwork, a panel of experts in multiple myeloma discussed strategies for sequencing novel bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapies for patients with relapsed/refractory disease. Here are their key takeaways:

Recent Approvals in Multiple Myeloma

- Some B-cell maturation antigen (BCMA)-targeting CAR T-cell therapies have become indicated for use in earlier lines of treatment.
 - The FDA approved idecabtagene vicleucel (ide-cel; Abecma) in April 2024 for patients with 2 or more prior lines of therapy based on phase 3 KarMMa-3 results (NCT03651128).¹
 - Ciltacabtagene autoleucel (cilta-cel; Carvykti) received approval in April 2024 for those with at least 1 prior line of therapy based on the phase 3 CARTITUDE-4 results (NCT04181827).²
- Bispecific antibodies are also available for treatment.
 - Talquetamab-tgvs (Talvey) received accelerated approval in August 2023 for those with at least 4 prior lines of therapy based on results from the phase 1/2 MonumentAL-1 trial (NCT03399799).³
 - Teclistamab-cqyv (Tecvayli) received accelerated approval in October 2022 based on results from the phase 1/2 MajesTEC-1 trial (NCT03145181; NCT04557098).⁴
 - Elranatamab-bcmm (Elrexfio) earned accelerated approval status in August 2023 based on results from the phase 2 MagnetisMM-3 trial (NCT04649359).⁵

Developing Areas in Treatment

- Sequencing treatment in earlier lines to prolong the duration of response remains an area of focus.
- Optimizing CAR T-cell manufacturing to reduce treatment wait times is another potential development.

Challenges With Sequencing

- The need for a caregiver and proximity to a CAR T-cell center may impact therapy availability.
- Despite the ever-evolving nature of the field, current data may support high responses with CAR T-cell therapy followed by bispecific agents.
 - On the other hand, waiting at least 6 months after initiating bispecific therapy may be ideal before patients undergo apheresis for CAR T-cell therapy.
- The CAR T-cell collection process may fail in patients.
 - Allogeneic transplants may help patients produce enough CAR T cells.

Managing Previously Treated Disease

- Reinfusion with ide-cel or cilta-cel may not be feasible due to the formation of antidrug antibodies.
 - However, sequencing one BCMA-targeting therapy after the other may be possible depending on the extent of cross-reactive antibodies and loss of BCMA.
- CAR T-cell therapy following a bispecific agent may be feasible and give patients an improved treatment-free interval, thereby benefiting quality of life.
 - Duration of the prior bispecific therapy is a critical factor to consider during T-cell collection.



FOR REFERENCES VISIT
cancernetwork.com/07.24_Bispecifics

Meet the Experts



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Assessing Dermatologic Responses to Amivantamab in *EGFR*-Mutated NSCLC



Martin Dietrich, MD, PhD



Wade T. Iams, MD



Helena A. Yu, MD



Joshua K. Sabari, MD



Solange Peters, MD, PhD

During the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, experts in the lung cancer space met to discuss updates presented at the conference, and how they will advance the field forward. The discussion focused on first- and second-line treatments in non-small cell lung cancer (NSCLC), implementation into the clinic, and adverse effect management.

The panel was led by **Martin Dietrich, MD, PhD**, a medical oncologist at Cancer Care Centers of Brevard, The US Oncology Network. He was joined by **Wade T. Iams, MD**, assistant professor of medicine in the Division of Hematology and Oncology at Vanderbilt University Medical Center; **Helena A. Yu, MD**, associate attending physician at Memorial Sloan Kettering (MSK) Cancer Center; **Joshua K. Sabari, MD**, assistant professor in the Department of Medicine at the NYU Grossman School of Medicine and director of High Reliability Organization Initiatives at the Perlmutter Cancer Center; and **Solange Peters, MD, PhD**, full professor and chair of medical oncology and the thoracic malignancies program in the Department of Oncology at the University Hospital of Lausanne in Switzerland.

The roundtable discussion was meant to draw ideas and thought-provoking questions from colleagues centered at different institutions around the world.

Biomarker Testing

Dietrich began by asking the panel to discuss their approaches to biomarker testing, liquid biopsies, and managing the logistics of testing. At Vanderbilt,

Iams said he waits to begin treatment until the results from both the liquid and tissue biopsies have been returned.

Yu noted that she will send out both tissue and liquid biopsies but will wait until at least the tissue biopsy comes back before beginning treatment. MSK has in-house testing for liquid next-generation sequencing (NGS) and rapid testing for *EGFR*, *ALK*, and *KRAS* mutations.

Peters gave her thoughts from a European perspective and noted that reimbursement does not cover 2 different modes of testing.

“Tissue [testing] is mandatory for legal purposes and initial diagnosis, and adding the liquid is at the cost of the patient. [Liquid biopsy] is taken at resistance or in selected cases in the front line,” Peters said.

She went on to say her institution also has rapid testing, which is conducted to begin neo-adjuvant treatment with a full NGS panel done to help determine later lines of therapy. Additionally, the turnaround time for NGS testing in Europe is about 1 week, which Peters believes is the reason why double testing is not reimbursed.

Dietrich and Sabari both do concurrent tissue and plasma testing up front. Sabari uses an in-house assay for tissue testing with a turnaround time of 14 to 21 days. Sabari sends the plasma to an outside vendor, with results being returned in about 5 days. He will then wait for the results before deciding on a treatment plan.

Converting Trial Data Into Clinic Use

Sabari was not convinced by the phase 3 FLAURA2 (NCT04035486) trial data and continues to use osimertinib (Tagrisso) monotherapy in the first-line setting.

For patients who are high-risk, he would consider amivantamab (Rybrevant) plus lazertinib (Leclaza) if approved based on the PFS data from the FLAURA trial.

He would also consider a patient's lifestyle before creating a treatment plan. Are they older or frail? Do they have children? Those who have a family may not be able to come to receive treatment every 2 weeks, so finding the right combination and regimens is important as well, he said.

For Peters, her treatment plans are based on evidence and data from clinical trials, as mandated by the laws in Europe. In Switzerland, where she practices, she is able to play with different combinations, as it is outside of European authority, but she does remain more conservative in her choices.

Iams added, "My general approach is osimertinib monotherapy for most patients. I've used the FLAURA2 [regimen] a couple times for 1 patient with symptomatic brain metastases at diagnosis and another patient with an atypical *EGFR* mutation, which wasn't technically included in FLAURA2, but we can do those types of things where you just don't feel as good about the osimertinib efficacy. Amivantamab I've used a handful of times and have not had good experiences. I have more often than not patients who end up in the [emergency department] because the infusion nurses are panicked with the infusion reactions."

Dietrich was more open to using the treatment combinations, as he noted the need to work with the data available.

Yu mentioned the comfort she felt using a tyrosine kinase inhibitor (TKI) plus chemotherapy in the second-line setting. Her challenge is having 2 available treatment options for escalation and determining which one is appropriate for use.

Peters highlighted results from the phase 3 PALOMA-3 trial (NCT05388669), which assessed subcutaneous amivantamab vs intravenous treatment.⁵ She wondered whether the difference changed their treatment practice that much. As she noted, her nurses were used to treating and identifying infusion reactions.

Regarding deep vein thrombosis, Sabari said it was difficult to say that subcutaneous amivantamab was better than intravenous. Patients were also given prophylaxis on the study.

Sabari, who is working on the PALOMA-1 and -3 studies, believes subcutaneous formulation may be better tolerated. A biologic license application was recently submitted to the FDA for subcutaneous amivantamab in patients with *EGFR*-mutated NSCLC.⁶

Quality of life came into the discussion again, as the subcutaneous injection can be given in 5 minutes vs an all-day infusion. Sabari explained that it can be injected into any area of fat on the body, usually the stomach, with a butterfly needle.

Peters noted that the billing in Europe between intravenous and subcutaneous infusion would be the same, the increased costs may occur after time with the nurses.

Important Trials to Note Surrounding *EGFR*-Mutated Disease

Phase 3 FLAURA trial (NCT02296125)¹

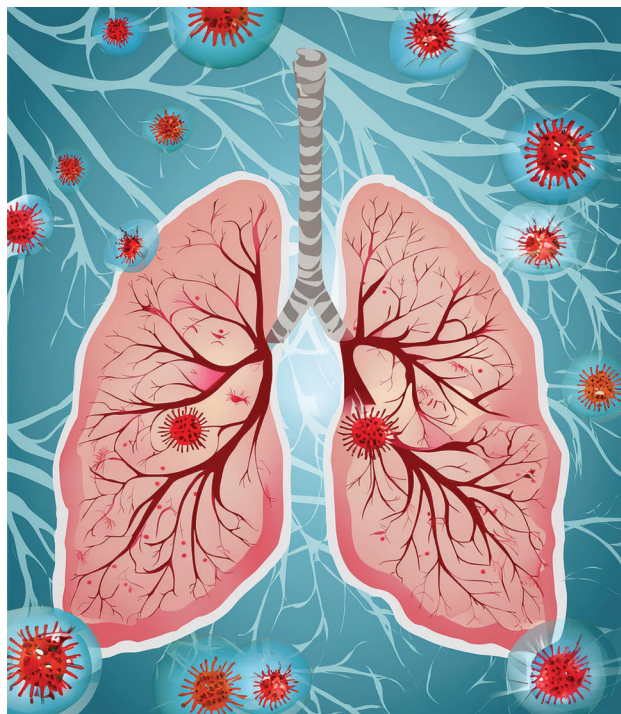
- Osimertinib (Tagrisso) vs gefitinib (Iressa) or erlotinib (Tarceva) in patients with untreated, *EGFR*-mutated advanced NSCLC
- Enrolled 556 patients
 - Osimertinib given 80 mg once daily
 - Gefitinib given 250 mg once daily
 - Erlotinib given 150 mg once daily
- Efficacy:
 - Median overall survival was 38.6 months (95% CI, 34.5-41.8) for osimertinib vs 31.8 months (95% CI 26.6-36.0) in the combination (HR, 0.80; 95% CI, 0.64-1.00; $P = .046$).

Phase 3 FLAURA2 trial (NCT04035486)²

- Osimertinib plus platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R mutations.
- Enrolled 557 patients
 - Recommended dose of 80 mg orally twice a day with or without food
- Efficacy:
 - Median progression-free survival (PFS) of 25.5 months (95% CI, 24.7-not estimable) in the combination arm vs 16.7 months (95% CI, 14.1-21.3) in the monotherapy arm (HR, 0.62; 95% CI, 0.49-0.79; $P < .0001$).
- This trial helped lead to the approval of this regimen in February 2024.³

Phase 3 MARIPOSA trial (NCT04487080)⁴

- Amivantamab-vmjw (Rybrevant) plus chemotherapy with or without lazertinib (Leclaza) in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib
- Enrolled 858 patients
 - Amivantamab given 1050 mg intravenously for 80 kg or greater and 1400 mg for 80 kg or less
 - Lazertinib given 240 mg orally once daily
 - Osimertinib given 80 mg once daily
- Efficacy:
 - PFS in the combination arm of 23.7 months (95% CI, 19.1-27.7) vs 16.6 months (95% CI, 14.8-18.5) in the osimertinib arm (HR, 0.70; 95% CI, 0.58-0.85; $P < .001$).



Toxicity Management With Amivantamab

Most notable with amivantamab use has been the dermatologic toxicities. Patients can sometimes range from asymptomatic to desquamating dermatitis. Patients who have inflamed skin prior to starting treatment may have more of a reaction.

The phase 2 COCOON study (NCT06120140) is assessing how to reduce rash and paronychia related to amivantamab use for patients with *EGFR*-mutated NSCLC.⁷ Iams believes this study will be pivotal to help educate other clinicians on aggressive dermatologic management.

For Yu, the management of scalp and nail toxicity has proven to be the most challenging for her. She suggests the use of Loprox (ciclopirox) shampoo plus doxycycline if needed for infection. Additionally, patients may have to cut their hair short, which may impact their quality of life. For nail toxicity, she recommends antibiotics and vinegar soaks to mitigate discomfort.

Peters believes changes need to be implemented systematically. When she first began practicing, preventative antibiotics were given to try to mediate these toxicities to the more potent treatments being given.

Sabari finds when amivantamab is given in combination with a TKI, skin toxicity is observed. “Most of my [patients with] bad scalp toxicities that are grade 3/4 have been men who don’t tell us anything. They cover it, they put a hat on, and they just keep on going, and then they come in and it’s decimated,” he said.

Sabari will also recommend a dose hold to help with the toxicity. However, once a grade 2/3 scalp reaction occurs, it’s difficult to get it under control. He has admitted patients because of this.

Dietrich asked his colleagues whether scalp toxicities were noted in women as well. Both Yu and Sabari said the majority of patients with this are men. Yu has treated only 1 woman with this toxicity. Both Yu and Sabari believe it comes back to hygiene and how frequently patients wash their hair and the products they use to treat it.

Peters pointed out that this would be an appropriate time to work with dermatologists and figure out a good action plan. Yu agreed; especially for younger patients, clinicians may think it’s only a small rash, but for the patient, it can be more impactful than that.

Some patients may be experiencing severe symptoms but want to continue treatment because it’s helping their disease, noted Sabari. All around, education needs to improve, and a collaborative team effort can help get treatment answers, he said.

One solution that has worked well for Peters in the past was creating a shampoo compound that included steroids and anti-inflammatory agents.

Key Takeaways

As the conversation concluded, Dietrich asked the panel what their biggest takeaways from the ASCO meeting were. Iams was most excited about the subcutaneous amivantamab development.

Yu mentioned that an unmet need was better management for central nervous system and leptomeningeal disease, to which Sabari agreed. Sabari also highlighted how to best manage toxicities and how to decipher which patient will experience which toxicity, and whether it will be a benefit or risk to them. ■

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