PQI IN ACTION

Positive Quality Intervention

NCODA

Isatuximab-irfc (Sarclisa®) in 1q21 Gain or Amplifications in Relapsed/Refractory Multiple Myeloma

INTRODUCTION

NCODA developed the peer-reviewed Positive Quality Intervention (PQI) as an easy-to-use and relatable clinical guidance resource for healthcare providers. By consolidating quality standards, real-life effective practices, clinical trial results, package insert and other guidance, PQIs equip the entire multidisciplinary care team with a comprehensive yet concise resource for managing patients receiving oral or IV oncolytics.

This PQI in Action is a follow up to the Isatuimab-ifc-Regimens in 1q21 Gain or Amplications in Relapsed/Refractory Multiple Myeloma PQI and explores how the medically integrated teams at Texas Oncology, Florida Cancer Specialists & Research Institute (FCS), and University Hospitals Cleveland Medical Center, Seidman Cancer Center collaborate and utilize the information found in the PQI as part of their daily practice. This PQI in Action focuses on the use of isatuximab in combination with carfilzomib and dexamethasone or with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma with 1q21 gain or amplification.

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TREATMENT LANDSCAPE FOR MULTIPLE MYELOMA

FOR systemic treatment, three drug combination regimens (two drug classes plus the corticosteroid dexamethasone) are considered standard of care, though newer data with four drug combinations is emerging and may be recommended in select patients.[1] While newly diagnosed multiple myeloma (MM) is typically sensitive to a variety of drug classes, immunomodulatory drugs (e.g. lenalidomide), proteosome inhibitors (e.g. bortezomib), and more recently, monoclonal antibodies (e.g. daratumumab, isatuximab), are the most common components of the treatment backbone. Following maximal response to systemic treatment, eligible patients then proceed to stem cell transplant, followed by maintenance treatment.[1]

Despite significant advances in the treatment of MM in prolonging survival, the disease is generally considered incurable and is managed more like a chronic disease with serial relapses. Treatment options in the relapsed/refractory (R/R) setting include additional systemic treatment until progression, autologous stem cell transplant (for those who did not receive earlier, or second transplant can be considered), or clinical trial.[1]

GAIN/AMPLIFICATION OF 1Q21 IN MULTIPLE MYELOMA

There are multiple cytogenetic abnormalities (CAs) that can occur within myeloma cells and are associated with poor prognosis, with 1q21+ considered one of the most common.[2] This particular CA impacts approximately 40% of newly diagnosed myeloma patients and 70% of patients with R/R disease.[2] 1q21+ is classified as having either a gain or amplification of 1q21, with a gain defined as having 3 copies of 1q21 versus amplifications having 4 or more copies.[1] If other high-risk CA are present in addition to 1q21+, this results in an even worse prognosis.[3] Clinical data regarding the activity of isatuximab in this subset of patients is discussed below.

Isatuximab (Sarclisa®): INDICATION & CLINICAL DATA

SARCLISA INDICATIONS AND MECHANISM OF ACTION[4]

Isatuximab is a monoclonal antibody that targets and binds to the CD38 antigen expressed on the surface of MM cells and works by engaging both direct and indirect mechanisms, ultimately leading to cell death.

Isatuximab has three indications in adult patients with multiple myeloma (all approved in combination with other agents). In March 2020, isatuximab was first introduced to the market based on its approval in combination with pomalidomide/dexamethasone (Pd) in patients who have received at least two prior therapies including lenalidomide and a proteosome inhibitor. One year later, in March 2021, isatuximab added its second indication in the R/R setting in combination with carfilzomib/dexamethasone (Kd) in patients who have received 1-3 prior therapies. Most recently, in September 2024, isatuximab received approval in transplant ineligible patients with newly diagnosed multiple myeloma in combination with bortezomib/lenalidomide/dexamethasone.

ISATUXIMAB CLINICAL TRIAL DATA IN 1Q21+ MULTIPLE MYELOMA PATIENTS

In both Phase 3 studies, ICARIA-MM[5] and IKEMA[6], the addition of isatuximab to pomalidomide/dexamethasone (Isa-Pd) and carfilzomib/dexamethasone (Isa-Kd), respectively, resulted in improved median progression-free survival (mPFS) in MM patients with R/R disease.[5,6] Furthermore, subgroup analyses from these two studies were performed to assess the clinical benefit of isatuximab specifically in patients with 1q21+ disease.[3]

ISATUXIMAB (SARCLISA®): Indications and Clinical Data - continued

In ICARIA-MM, for patients with 1q21+ in general (e.g. 1q21+ with or without other high-risk cytogenetic abnormalities), the mPFS and mOS were longer in the group of patients who received Isa-Pd vs. patients in the Pd group (9.5 months vs 3.8 months and 21.3 months vs 13.9 months, respectively).[3] Additionally, the authors performed other outcome analyses for additional subgroups of patients including those with isolated 1q21+, gain (1q21), and amp (1q21) and concluded that there was a clear benefit in all subgroups when isatuximab was given, regardless of the presence of other high-risk CAs.[3]

Similar results were seen in the final IKEMA subgroup analysis of R/R MM patients with 1q21+ treated with an isatuximab-containing regimen in that there was a mPFS benefit favoring Isa-Kd vs Kd alone (mPFS: NR vs 16.2 months, respectively). Again, in all 1q21 subgroups overall, patients did better when Isa-Kd was utilized as opposed to Pd with the difference being less profound in patients with amp (1q21).[3] In terms of depth of response, there were also more patients who achieved a very good partial response (VGPR) in 1q21+ patients receiving isa-Kd (73% vs 52%) as well as minimal residual disease (35% vs 15%).[3]

Collectively, the results above from the ICARIA-MM and IKEMA subgroup analyses in patients with RR MM with 1q21+, suggest that the addition of isatuximab to Pd or Kd may help mitigate the negative prognostic effect of this cytogenetic abnormality.[3] Clinical data in this patient population continues to evolve.

ISATUXIMAB PATIENT PROFILE: HEALTHCARE PROVIDER INSIGHTS

MEDICAL

Oncologists and pharmacists from Texas Oncology, FCS, and Seidman Cancer Center shared their insights on how they select patients with MM for therapy with isatuximab. Their insights are aligned with the recommended guidelines and prescribing information. David Samuel, PharmD, Stem Cell Transplant Pharmacist with Texas Oncology, says that their practice routinely runs a MM panel on all MM patients to look for high-risk mutations, including t(4;14), t(14;16), t(14;20), hyperdiploidy, 1q gain/amplification and TP53.

Regarding high-risk patients, Syed Zafar, MD, noted, "We are using quads in many of these patients if they have the right performance status." Specifically, Zafar employs isatuximab combined with RVD across various risk groups, with particular emphasis on high-risk groups. James Ignatz-Hoover, MD also typically uses quads. He does share that "the 1q signal is thought provoking enough that I would start someone on isatuximab over daratumumab." He recently moved a patient with a 1 q21 mutation over to isatuximab for that reason.

Samuel adds that his practice has also administered isatuximab in patients who have had prior daratumumab treatment based on a small study published by MD Anderson demonstrating responses in these patients, which is attributed to differences in epitope binding on the CD38 molecule. However, he emphasized that the majority of isatuximab usage seen in his practice is after transplant failure, in the 2L or 3L setting.

ELEVATING PATIENT CARE THROUGH MEDICALLY INTEGRATED PHARMACY (MIP)

Once a treatment regimen decision has been rendered, the multidisciplinary team kicks into gear to continue providing optimized patient care. The availability of MIP to process and dispense IV/oral anti-cancer therapies in infusion centers or pharmacies located in oncology clinics has improved medication management, streamlined patient care, and improved continuity of care. Brenda Almaraz, CPhT compares her previous experience working at a standalone/external pharmacy versus the MIP within Texas Oncology noting that "access [to providers] and communication is much better, both for patients and with the physician's office". Furthermore, Mina Guirguis, PharmD, Pharmacy Area Manager at Texas Oncology, voices that with multiple modes of internal communication available (Teams chat, email, phone), everyone on the medical team is quickly/easily accessible when questions/concerns arise, and this lends itself to fluid communication regarding patients throughout the day. Guirguis adds that he appreciates having access to the patient chart highlighting "I can read the doctor's note and read what the game plan is for the patient or understand why they dose reduced", as opposed to "flying blindly" when processing medication orders.

Clinical Pharmacy Specialist Nicholas Bitz, PharmD, MBA shares that at Siedman Cancer Center, outpatient pharmacists work hand in hand with physicians and Advanced Practice Providers to discuss treatment plans. Dr. Ignatz-Hoover adds "patients feel taken care of when they have a village of professionals that are unified in purpose, listen, and actively hear their concerns. The more thoughtful, caring, and intelligent staff that are taking care of our patients and working together as an integrated team, the better the quality of care becomes."

Other benefits of having a MIP mentioned by the panel include a reduction in medication waste. Katie Lazo, CPhT with FCS, emphasized that their standard operating procedure helps reduce waste as they "do not make the drug until the patient is in the seat, everything is good, and doctor has signed off."

THE PHARMACIST AS AN INTEGRAL TEAM MEMBER

OUR multidisciplinary oncology panel agreed that the pharmacist is integral to the clinical management of patients with MM and utilization of MIP for both oral and intravenous medication needs. Figure 1 highlights the panel's collective feedback on some of the critical functions pharmacists provide to the MIP team. Lead nurse at FCS, Natalie Westendorf, RN, finds it helpful to have a pharmacist she can consult about things such as infusion reaction management/re-challenges, dosing questions, and/or how to approach chemotherapy modifications in patients who have lost weight during treatment. As another potential benefit of having integrated pharmacists, FCS Pharmacist Jeanine Ewing, PharmD, BCOP speaks to how she is responsible for incorporating guidelines, updates in therapies, and formulary changes into a readable document for providers and nursing staff. She highlights "by ensuring that the entire care team has access to the most current data, we can be confident patients are being provided with the best care possible for their specific cancer." Furthermore, Lazo identifies patient safety as a critical benefit emphasizing, "having additional sets of eyes will catch more potential errors".

Dr. Ignatz-Hoover believes it is critical to have an integrated pharmacist on a molecular hematology team, due to the complexity of the medications and their administration. He says a "rigorous understanding of pharmacology is invaluable to the team."

BENEFITS OF MIP FOR PATIENTS PRESCRIBED ISATUXIMAB

Chemotherapy is complex with new agents coming out at a rapid pace, so it can be challenging for health care professionals to keep current with information. At FCS, there is a team of Informatics Pharmacists that are involved with building treatment regimens into the electric medical record (EMR), which helps ensure drug dosing and administration are

Medically Integrated Pharmacy: Elevating Care - continued

ATTRIBUTES THAT MAKE PHARMACISTS AN INTEGRAL PART OF THE MIP TEAM:

01	Medication expertise
02	Improves medication management and safety
03	Contributes to personalized and optimized treatment plans
04	Anticipates potential problems
05	Reviews NGS results to determine/confirm treatment options
06	Double checks orders and patient characteristics (height, weight, labs)
07	Provides extra layer of communication between HCPs and patients
08	Assists with health literacy or language barriers
09	Assists with prior authorization process
10	Coordinates care to ensure cycle days of oral and IV medications are aligned

Figure 1. Pharmacists as Part of the MIP Team

correct, and all essential supportive care pieces for isatuximab-based regimens are included. To advance plan and prepare for new treatments reaching the market, Ewing states she tries to meet with pharmaceutical industry partners prior to approval so that she can get a head start on reviewing the drug, and then the informatics team can begin building. Then, the actual content will be in place when the oncologist is ready to prescribe the therapy.

Education on chemotherapy provided by the pharmacist is another benefit welcomed by patients. Astrid Slaughter, PharmD, PhD, BCSCP, BCOP, Texas Oncology Pharmacy Area Manager, shared that "for us, the benefit is clear – with a multicenter approach and multiple disciplines on board, it's easier to treat every aspect of the patient's journey". Slaughter provides the example of patients arriving at the pharmacy window, where they can be counseled on both oral and intravenous chemotherapy agents. This streamlines processes and offers patient convenience. Associate Nurse Practitioner at Siedman Cancer Center, Nicholas Donato, APRN, CNP, echoes her sentiments. His entire team reiterates education with patients to ensure they know exactly what is happening. He comments on the pharmacist's role in lightening the educational load by going in depth with the patient.

NCODA'S PQI RESOURCE

THE PQI resource contains clinician-directed guidance and criteria that can benefit the whole team. Key segments illustrate how medically integrated pharmacists support physicians and clinical staff by lending their medical and administrative expertise. The Isatuximab-ifc-Regimens in 1q21 Gain or Amplications in Relapsed/Refractory Multiple Myeloma PQI covers clinical trial information, side effects, monitoring, and patient-centered educational pearls. Regarding PQIs in general,

Pharmacist Slaughter commented "I like that it is standardized support that everyone can easily follow. It gives you steps on what to do" and then went on to elaborate that her team finds using IV and Oral Chemotherapy Education Sheets (IVE and OCE) helpful for counseling and then sending home with patients.

For this specific PQI, isatuximab in 1q21+ MM patients, Ewing values the subgroup analysis portion as she finds it helpful to show which specific patients had the greatest benefit from treatment. Similarly, Samuel adds "it might be helpful for nurses and others that the choice of regimen was made due to this high-risk feature [1q21+]. I like this feature a lot."

Other panel members like Dr. Zafar highlight the general need for resources that are comprehensive, yet concise/succinct while including the most important points. Westendorf values that the PQI documents are "very easy to understand," which is the primary thing she looks for when giving patients, as well as nurses, new information. PQIs are also a valuable tool for training new pharmacists according to Giurguis.

Donato shares "it is great to have an area to reference for the highlights and to get all the information I could want in one click." He goes on to say that he appreciates the PQI because it is organized, concise and easy to read.

MONITORING PATIENTS AND ADVERSE EVENT MANAGEMENT

ELECTRONIC

medical record (EMR) software, such as Epic and OncoEMR, has helped shape and standardize treatment plans, monitoring, and supportive care management at Texas Oncology, FCS and Siedman Cancer Center. Laboratory tests are built into the EMR to facilitate monitoring. In all practices, pharmacists perform a comprehensive review ensuring regimens are prescribed in accordance with labeled indications/national guidelines/internal pathways, dosing is appropriate based on labs and other patient/disease related factors, and anti-emetics are optimized.

Patient-Centered Activities - Consider isatuximab-based regimens for patients with Multiple Myeloma if:

- **Adult patients with relapsed or refractory mulitple myeloma**
- **Recived 1-3 prior lines of therapy (Some patients may be eligible for 1st line therapy with isatuximab based quadruplet therapy-clinical trials ongoing)**
- **Gain or amplification of 1q21 with or without other high-risk cytogenetic abnormalities**
- **NOT refractory to previous treatment with an anti-CD38 monoclonal antibody**
- **Consider patient functional status, disease risk, comorbid conditions, and patient preferences when evaluating treatment selections**

EDUCATION ENHANCES PATIENTS' UNDERSTANDING OF ISATUXIMAB

EDUCATION is imperative when patients are about to start treatment with chemotherapy. At FCS, Dr. Zafar discusses how each discipline (physicians, advanced practice providers, pharmacists, and nurses) plays a part in providing patients with essential information so that they know what to expect and are familiarized with situations warranting a call to the clinic. Nurse Westendorf (also at FCS) calls out that even though patients have already gone over the initial treatment plan with their doctor and/or pharmacist, the nursing staff provide a separate patient education class in the clinic prior to patient starting treatment.

At Texas Oncology clinics, Advanced Practice Providers or Pharmacists sit down with patients for nearly an hour prior to starting treatment to review the regimen details and what to expect about side effects/timing/management. Slaughter and her pharmacy team put together folders for patients before starting treatment that includes important contact information if questions arise or if patients suddenly feel ill. Dr. Zafar emphasizes that "the first few months are very important because that is when you see quite a few toxicities. Patients are sick not only from the toxicities of combination regimens, but also due to the disease itself."

Physicians, Advanced Practice Providers and Pharmacists also all provide patient education at Siedman Cancer Center. Dr. Ignatz-Hoover shares, "When a patient is starting therapy it is important that they understand their medications, the goals of the medications in their therapy and how the medications are going to be administered." He says it is so important for the patient to understand they have an open line of communication with the provider and pharmacist team so they can let them know immediately if a problem arises. Donato explains any mutations to patients as the reason for their specific therapy. Bitz adds, "I use the analogy of radio towers all the time with our CD38 agents. I explain to patients that radio towers are like beacons for the myeloma to grow and the anti CD38 agents are blocking the beacons ad blocking the radio tower, so the signals do not come in."

Prior to starting treatment, Ewing discusses the recommended premedications built into the FCS EMR when nursing staff are preparing to administer isatuximab – acetaminophen 650 mg PO, dexamethasone 40 mg IV/PO (20 mg if patients > 75 years), diphenhydramine 25 mg IV, and famotidine 20 mg IV. Also, since diarrhea is a common side effect, Westendorf advises the patient to have loperamide at home and reviews how to take the medication appropriately should the patient have loose stools. Bitz also provides patients with information on how to mitigate side effects as well as how they can anticipate anything that might come up for them, so they are prepared and "it is not a scary situation."

According to Ewing, all patients at her practice site have a CBC + diff drawn prior to each infusion as well as a CMP every 2 weeks to every month to assess renal and hepatic function. Lastly, a reminder is incorporated into the treatment plan for the patient to complete a pregnancy test and to counsel patients on the importance of avoiding pregnancy in any childbearing female during treatment and for five months after isatuximab. Dr. Ignatz-Hoover monitors CBC, CMP, side effects and toxicities, disease markers, a bone marrow biopsy at the end of therapy and employs MRD testing.

PQI PROCESS

- **Prophylactic therapy recommendations for all patients receiving isatuximab**
- **Assess and prescribe prophylactic treatment for bacterial, viral, and fungal infections**
- **Prescribe prophylactic antiemetic therapy for the prevention of acute and delayed nausea and vomiting based on the emetogenic risk of the chemotherapy regimen-**
- **Assess risk, monitor, and administer prophylaxis as indicated for deep venous thrombosis or pulmonary embolism as these may occur with therapy**

Regarding low blood counts (RBC, WBC, and platelets), another expected side effect of treatment, Westendorf says she "prefers to keep education a bit lighter upfront as to not overwhelm the patient". She first provides general education on the timing/complications of low blood counts, reviews details of anti-infective prophylaxis (bacterial, viral, and fungal) medications, and counsels patients on the importance of letting the clinic know if they develop a fever or other symptoms suggestive of illness (e.g. cough). Then, when blood counts start to drop or start nearing critical lows, infection and bleeding precautions are re-enforced. Ewing notes that isatuximab can interfere with serological testing, and therefore, all patients should be typed and screened prior to starting treatment. For patients needing a blood transfusion at FCS, the blood bank is notified by nursing staff that the patient is on isatuximab so that they are aware and should refer to the initial type and screen.

At both Texas Oncology and FCS, all patients are closely monitored for infusion reactions by nursing staff, especially with Cycle #1. Patients are counseled on the importance of letting their nurse know immediately if they develop any itching, chest pain, palpitations, shortness of breath, or any other new symptom. At FCS, their protocol for infusion reactions involves stopping the infusion, assessing vital signs, and then typically repeating the same premeds for isatuximab. Westendorf further elaborates that "if the physician decides it is appropriate based on the severity of the reaction and how much diphenhydramine helped, we will give methylprednisolone (Solu-Medrol)." In her experience, she added that most patients are well enough to be re-challenged, and next steps include running IV fluids for 30 min following full resolution of symptoms. Then, the drug is re-initiated at the previous lower rate for 30 min. Vitals are again reassessed and if acceptable, infusion rate may be increased.

Bitz also educates patients on potential infusion reactions, lab values, fatigue, and the risk of respiratory tract infection, especially in cold and flu season. He shares "making sure that patients are aware of how to protect themselves, making sure that they stay up to date with their vaccines and how to protect themselves at home and the people around them, is tantamount to me. Downstream these things can become huge."

ACCESS TO THERAPY

NOT only can financial barriers lead to significant stress for the patient, but they can also lead to treatment delays. Samuel says, "what is unique about our practice is that we have a whole team of pharmacy techs that are dedicated to only completing prior authorizations and finding financial assistance for patients, be it through copay programs or charitable funding." At FCS, they have clinical pharmacists available at select sites and pharmacists available virtually to provide clinical support and any operational concerns/questions.

SUMMARY

Clinical data with MM patients with 1q21+ continues to evolve, with results from the ICARIA-MM and IKEMA subgroup analyses suggest that the addition of isatuximab to Pd or Kd may help mitigate the negative prognostic effect of this cytogenetic abnormality.

Panel members agree that having an MIP is beneficial for multiple reasons including improved access/communication, assistance with prior authorizations, reduction in drug waste, and improved patient safety.

For patients receiving isatuximab-based regimens, it's important to counsel patients on common side effects such as diarrhea and low blood counts as well as reviewing administration details of associated medications such as loperamide and anti-infective prophylaxis. Several team members vocalized their appreciation to NCODA for developing concise and useful information on isatuximab that is easy to navigate for both HCP as well as patients. Bitz gives a wonderful closing sentiment for all teams to remember, "the part of the job that I respect the most is the relationship that I have with the patients. They put their trust in me as part of their care team."

REFERENCES:

1 NCCN Guidelines: Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

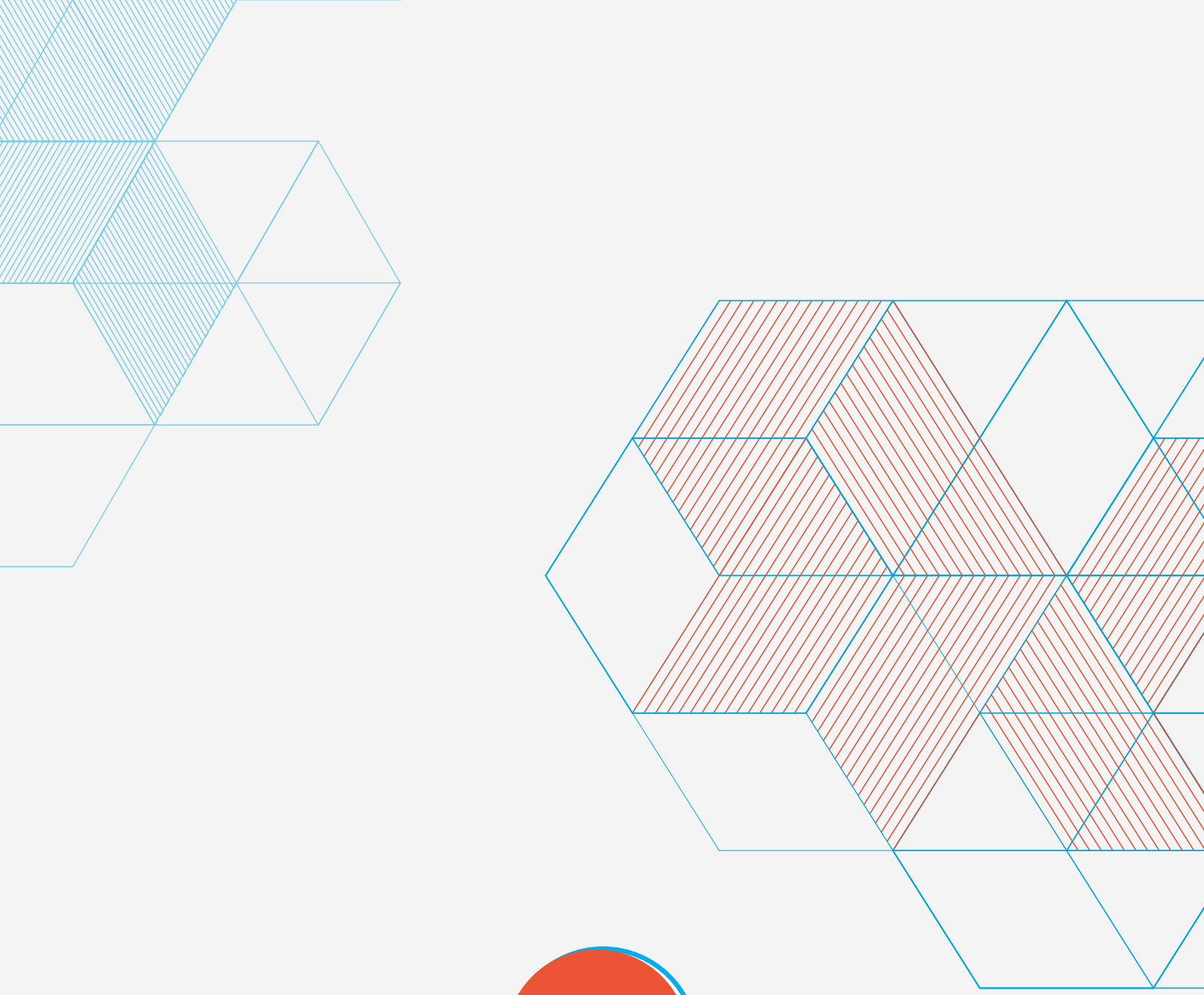
2 Burroughs Garcìa J, Eufemiese RA, Storti P, et al. Role of 1q21 in Multiple Myeloma: From Pathogenesis to Possible Therapeutic Targets. Cells. 2021;10(6):1360. doi:https://doi.org/10.3390/cells10061360.

3 Martin T, Richardson PG, Facon T, et al. Primary outcomes by 1q21+ status for isatuximab-treated patients with relapsed/refractory multiple myeloma: subgroup analyses from ICARIA-MM and IKEMA. Haematologica.

4 Sarclisa®(isatuximab-irfc) Package Insert.

5 Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalid omide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomized, multicentre, open-label, phase 3 study. Lancet 2019;394(10214):2096-2107.

6 Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomized phase 3 trial. Lancet 2021;397(10292)2361-2371.



Practice panelist's comments reflect their experiences and opinions and should not be used as a substitute for medical judgment.