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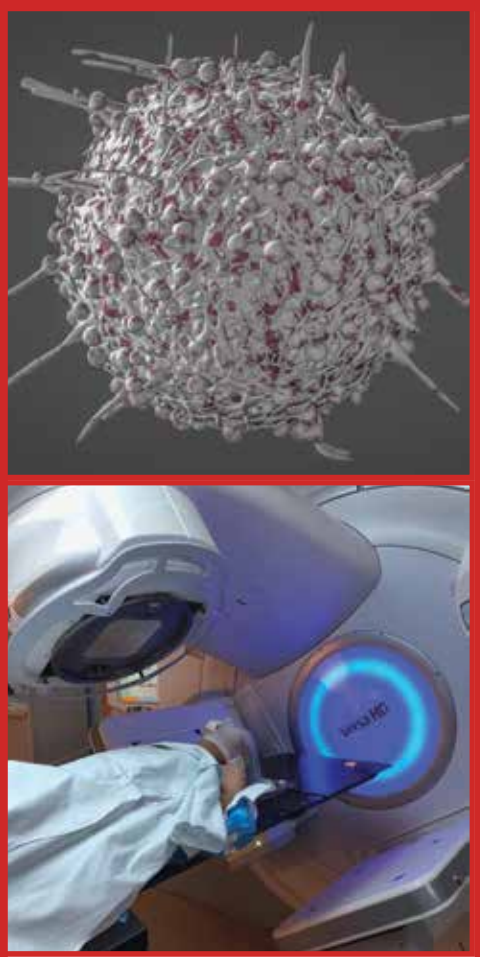

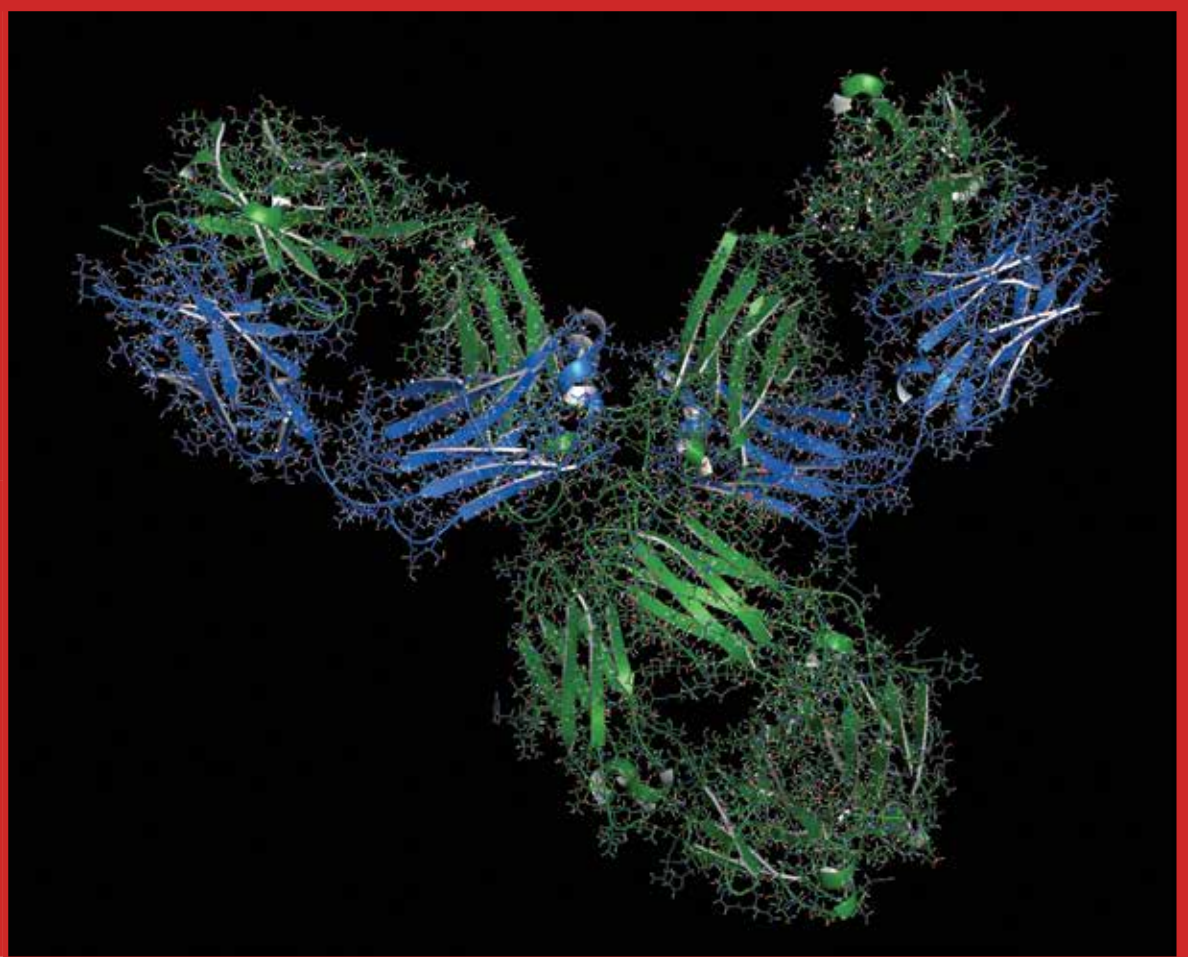

FEATURED STORY

DARZALEX *Faspro*®
(daratumumab and hyaluronidase-fihj)
Injection for subcutaneous use | 1,800mg/30,000units

PERSEUS
A CLINICAL STUDY OF DVRd VS VRd

In the treatment of newly diagnosed multiple myeloma:

Give transplant-eligible patients a better chance at experiencing improved outcomes with DARZALEX *FASPRO*® + VRd vs VRd alone[1,2]

Scan the QR code or go to **PERSEUSQUAD.com** for additional data from the study.

The PERSEUS trial design: Phase 3, open-label, randomized, active-controlled trial in newly diagnosed multiple myeloma patients eligible for autologous stem cell transplant (ASCT), comparing DARZALEX *FASPRO*® + VRd (n=355) vs VRd (n=354) during induction and consolidation. The major efficacy outcome measure was progression-free survival (PFS) by Independent Review Committee (IRC) assessment based on International Myeloma Working Group (IMWG) response criteria. The median age was 60 years (range: 31-70).[1,2]

Following post-transplant consolidation, patients received investigational DR maintenance vs R alone. The trial was not designed to isolate the effect of DARZALEX *FASPRO*® in maintenance, and the efficacy of DR for maintenance has not been established.[1]

INDICATION

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DARZALEX *FASPRO*® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 1249 patients with multiple myeloma (N=1056) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 0.7%, Grade 4: 0.1%). Systemic administration-related reactions occurred in 7% of patients with the first injection, 0.2% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 2.9 hours (range: 5 minutes to 3.5 days). Of the 165 systemic administration-related reactions that occurred in 93 patients, 144 (87%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Proven efficacy and safety results with DARZALEX *FASPRO*® + VRd[1,2]

Progression-free survival

After a median follow-up of 47.5 months:

60% **reduction in the risk of disease progression or death with DARZALEX *FASPRO*® + VRd** vs VRd alone (HR=0.40; 95% CI: 0.29-0.57; *P*<0.0001; mPFS not reached in either arm)[1,2*†]

PFS results are based on the full treatment regimen and include investigational maintenance of DR following post-transplant consolidation. The trial was not designed to isolate the effect of DARZALEX *FASPRO*® in the maintenance phase of treatment. The efficacy of DR for maintenance has not been established.[1]

Complete response or better rates through post-transplant consolidation‡

The median time to reach post-transplant consolidation was 9.9 months in the DVRd arm (range: 0.5-18.5 months).[1]

44.5% **of patients achieved ≥CR with DVRd** vs 34.7% with VRd alone[1]

MRD negativity rates through post-transplant consolidation at 10^{-5} threshold§

57.5% **of patients reached MRD negativity with DVRd** (n=355) vs 32.5% with VRd alone (n=354)[1‖]

In patients who achieved CR or better[1¶]

- 76.6% of patients reached MRD negativity with DVRd (n=158) vs 58.5% with VRd alone (n=123)

Safety results through post-transplant consolidation

The most common adverse reactions (≥20%) in patients with multiple myeloma who received DVRd were peripheral neuropathy (52% vs 54% in VRd), **fatigue** (35% vs 37% in VRd), **edema** (22% vs 21% in VRd), **pyrexia** (21% vs 22% in VRd), **upper respiratory infection** (32% vs 26% in VRd), **constipation** (31% vs 30% in VRd), **diarrhea** (23% vs 25% in VRd), **musculoskeletal pain** (26% vs 23% in VRd), **insomnia** (26% vs 16% in VRd), **and rash** (25% vs 31% in VRd).[1]

In patients who received DVRd[1]**:**

- 37% experienced serious adverse reactions
- >5% experienced most frequent serious reactions: pneumonia (6%)
- 1.7% experienced fatal adverse reactions
- 2% experienced permanent discontinuation due to an adverse reaction
  - An adverse reaction which resulted in permanent discontinuation of DVRd in more than 1 patient included sepsis

Select laboratory abnormalities (≥30%) that worsened from baseline in patients who received DVRd (n=351) were decreased platelets (89% vs 78% in VRd), **decreased lymphocytes** (87% vs 69% in VRd), **decreased leukocytes** (78% vs 56% in VRd), **decreased neutrophils** (67% vs 47% in VRd), **decreased hemoglobin** (39% vs 43% in VRd), **increased ALT** (52% vs 48% in VRd), **decreased sodium** (40% vs 25% in VRd), **increased alkaline phosphatase** (39% vs 36% in VRd), **and decreased potassium** (30% vs 24% in VRd).[1#]

ALT=alanine aminotransferase; ASCT=autologous stem cell transplant; CI=confidence interval; CR=complete response; DR=DARZALEX *FASPRO*® (D) + lenalidomide (R); DVRd=DARZALEX *FASPRO*® (D) + bortezomib (V) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IMWG=International Myeloma Working Group; IRC=Independent Review Committee; mPFS=median progression-free survival; MRD=minimal residual disease; PFS=progression-free survival; R=lenalidomide (R); VRd=bortezomib (V) + lenalidomide (R) + dexamethasone (d).

*Median follow-up was 47.5 months in the DVRd and VRd group (range: 0.0-54.4 months).[2]

†Progression-free survival was by IRC assessment based on IMWG criteria.[1]

‡Based on intent-to-treat population.[1]

§MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using a next-generation sequencing assay (clonoSEQ).[1]

‖Based on intent-to-treat population who achieved MRD negativity (10^{-5}) through post-transplant consolidation and ≥CR at any time during the study.[1]

¶Patients who achieved MRD negativity (threshold of 10^{-5}) and ≥CR through post-transplant consolidation.[1]

#Based on number of patients with a baseline and post-baseline laboratory value for each laboratory test.[1]

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 7% of patients, including Grade 2 reactions in 0.8%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

Important Safety Information continues on next page ▸

Please see Brief Summary of full Prescribing Information for DARZALEX *FASPRO*® on the following pages.

IMPORTANT SAFETY INFORMATION FOR DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) (cont)

Neutropenia

Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX *FASPRO*® until recovery of neutrophils. In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX *FASPRO*® until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX *FASPRO*® with lenalidomide, thalidomide, or pomalidomide is contraindicated in pregnant women because lenalidomide, thalidomide, and pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide, or pomalidomide prescribing information on use during pregnancy.

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX *FASPRO*®.

Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX *FASPRO*®-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral neuropathy, peripheral sensory neuropathy, constipation, pneumonia, edema, peripheral edema, musculoskeletal pain, and rash.

The most common hematology laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary of full Prescribing Information for DARZALEX *FASPRO*® on the following pages.

cp-143279v9

References: 1. DARZALEX *FASPRO*® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-313.

Johnson&Johnson

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

Multiple Myeloma

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

- in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant.

CONTRAINDICATIONS

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation *[see Warnings and Precautions* and *Adverse Reactions].*

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO *[see Adverse Reactions].*

Systemic Reactions

In a pooled safety population of 1249 patients with multiple myeloma (N=1056) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 0.7%, Grade 4: 0.1%). Systemic administration-related reactions occurred in 7% of patients with the first injection, 0.2% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 2.9 hours (range: 5 minutes to 3.5 days). Of the 165 systemic administration-related reactions that occurred in 93 patients, 144 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information].* Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Dosage and Administration (2.5) in Full Prescribing Information].*

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 7% of patients, including Grade 2 reactions in 0.8%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions].* Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Drug Interactions].* This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions].*
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis *[see Warnings and Precautions].*
- Neutropenia *[see Warnings and Precautions].*
- Thrombocytopenia *[see Warnings and Precautions].*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Multiple Myeloma Eligible for Autologous Stem Cell Transplant

In Combination with Bortezomib, Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO in combination with bortezomib, lenalidomide and dexamethasone (n=351) from the start of induction to the end of consolidation compared to bortezomib, lenalidomide and dexamethasone (VRd) (n=347) was evaluated in PERSEUS *[see Clinical Studies (14.1) in Full Prescribing Information].* Patients

received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8 and once every 2 weeks from weeks 9 to 16 during induction in combination with VRd or VRd alone. After week 16, patients underwent stem cell mobilization, high dose chemotherapy, and ASCT. Within 12 weeks of ASCT, and when engraftment was complete, patients received DARZALEX FASPRO once every 2 weeks from weeks 1 to 8 during consolidation in combination with VRd or VRd alone.

The median duration of treatment for induction and consolidation was 9.9 months (0.5 to 18.5 months) for DARZALEX FASPRO-VRd.

Serious adverse reactions occurred in 37% of patients who received DARZALEX FASPRO-VRd. The most frequent serious adverse reaction in >5% of patients who received DARZALEX FASPRO-VRd was pneumonia (6%). Fatal adverse reactions occurred in 1.7% of patients who received DARZALEX FASPRO-VRd.

Permanent treatment discontinuation due to an adverse reaction occurred in 2% of patients who received DARZALEX FASPRO-VRd. An adverse reaction which resulted in permanent discontinuation of DARZALEX FASPRO-VRd in more than 1 patient included sepsis.

The most common adverse reactions (≥20%) were peripheral neuropathy, fatigue, edema, pyrexia, upper respiratory infection, constipation, diarrhea, musculoskeletal pain, insomnia, and rash.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PERSEUS.

Table 1: Adverse Reactions (≥10%) in Patients with Newly Diagnosed Multiple Myeloma Eligible for ASCT Who Received DARZALEX FASPRO-VRd through the End of Consolidation in PERSEUS

Adverse Reaction	DARZALEX FASPRO-VRd (N=351)		VRd (N=347)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Nervous system disorders				
Peripheral neuropathy[a]	52	5	54	4
Paraesthesia	11	<1[#]	11	<1[#]
General disorders and administration site conditions				
Fatigue[b]	35	3[#]	37	5[#]
Edema[b]	22	1	21	1[#]
Pyrexia	21	2[#]	22	3[#]
Infections				
Upper respiratory tract infection[c]	32	1[#]	26	2[#]
Pneumonia[d]	14	9	10	6[@]
Gastrointestinal disorders				
Constipation	31	2[#]	30	2[#]
Diarrhea	23	3[#]	25	5[#]
Nausea	16	1[#]	12	1[#]
Abdominal pain[b]	11	0	12	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	26	1[#]	23	1[#]
Muscle spasm	12	0	9	<1[#]
Psychiatric disorders				
Insomnia	26	2[#]	16	2[#]
Skin and subcutaneous tissue disorders				
Rash[b]	25	3[#]	31	5
Hepatobiliary disorders				
Hepatotoxicity[e]	16	6[#]	16	5
Respiratory, thoracic and mediastinal disorders				
Cough[b]	12	<1[#]	8	0

Key: VRd=bortezomib-lenalidomide-dexamethasone

[a] Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

[b] Includes other related terms.

[c] Upper respiratory tract infection includes fungal pharyngitis, h1n1 influenza, influenza, influenza like illness, laryngitis, nasopharyngitis, oral candidiasis, oropharyngeal candidiasis, parainfluenzae virus infection, pharyngitis, respiratory moniliasis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, upper respiratory tract infection, viral tonsillitis, and viral upper respiratory tract infection.

[d] Pneumonia includes bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia influenzal, pneumonia klebsiella, pneumonia legionella, and pneumonia streptococcal.

[e] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic cytolysis, hepatic failure, hepatic function abnormal, hepatoxicity, hyperbilirubinemia, hypertransaminasemia, and liver disorder

[#] Only Grade 3 adverse reactions occurred.

[@] Fatal adverse reactions included Pneumonia: n=1 (0.3%) in the VRd arm.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, lenalidomide and dexamethasone include:

- **Gastrointestinal disorders:** vomiting, hemorrhoids
- **Musculoskeletal and connective tissue disorders:** arthralgia
- **Infections:** bronchitis, sepsis, urinary tract infection, herpes zoster, Covid-19, cytomegalovirus infection
- **Respiratory, thoracic, and mediastinal disorders:** dyspnea, pulmonary edema
- **Metabolism and nutrition disorders:** hypocalcemia, decreased appetite, hyperglycemia, dehydration
- **Vascular disorders:** hypotension, hypertension, orthostatic hypotension
- **General disorders and administration site conditions:** infusion reactions, injection site reaction, chills
- **Nervous system disorders:** dizziness, headache, syncope
- **Cardiac disorders:** thrombosis, atrial fibrillation, tachycardia
- **Skin and subcutaneous tissue disorders:** pruritus

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PERSEUS.

Table 2: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Newly Diagnosed Multiple Myeloma Eligible for ASCT Who Received DARZALEX FASPRO-VRd through the End of Consolidation in PERSEUS

Laboratory Abnormality	DARZALEX FASPRO-VRd[a]		VRd[a]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased platelets	89	34	78	25
Decreased lymphocytes	87	69	69	43
Decreased leukocytes	78	47	56	22
Decreased neutrophils	67	52	47	34
Decreased hemoglobin	39	7	43	6
Chemistry				
Increased alanine aminotransferase (ALT)	52	7	48	5
Decreased sodium	40	5	25	5
Increased alkaline phosphatase	39	0	36	1
Decreased potassium	30	6	24	3

Key: VRd=bortezomib-lenalidomide-dexamethasone

[a] Denominator is based on number of subjects with a baseline and post-baseline laboratory value for each laboratory test: N=351 for DARZALEX FASPRO-VRd and N=346 for VRd.

Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 355 patients who were newly diagnosed with multiple myeloma and eligible for ASCT who received DARZALEX FASPRO as combination therapy with bortezomib, lenalidomide and dexamethasone during induction and consolidation in the clinical trial, 74% were <65 years of age, and 26% were 65 to 70 years of age. The clinical trial did not enroll patients older than 70 years of age *[see Clinical Studies (14.1) in Full Prescribing Information]*. No overall differences in effectiveness of DARZALEX FASPRO in combination with bortezomib, lenalidomide and dexamethasone were observed between patients <65 years of age compared to patients 65 to 70 years of age. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients 65 to 70 years of age included constipation, hemorrhoids, nausea, injection site erythema, bronchitis, nasopharyngitis, back pain, myalgia, pain in extremity, dysgeusia, peripheral motor neuropathy, and insomnia. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients 65 to 70 years of age included febrile bone marrow aplasia, atrial fibrillation, pyrexia, and orthostatic hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision *[see Warnings and Precautions]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

cp-473125v1

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EDITORIAL

Making resistance futile: lessons from the fields

By: **Jerry Radich**
jradich@fredhutch.org

Relapse is the bane of cancer therapy. Despite advances in understanding the genetics of cancer, targeted therapy, and immunological measures, relapse and resistance is an all-too-common outcome. Response to therapy follows one of the curves shown in Figure 1.

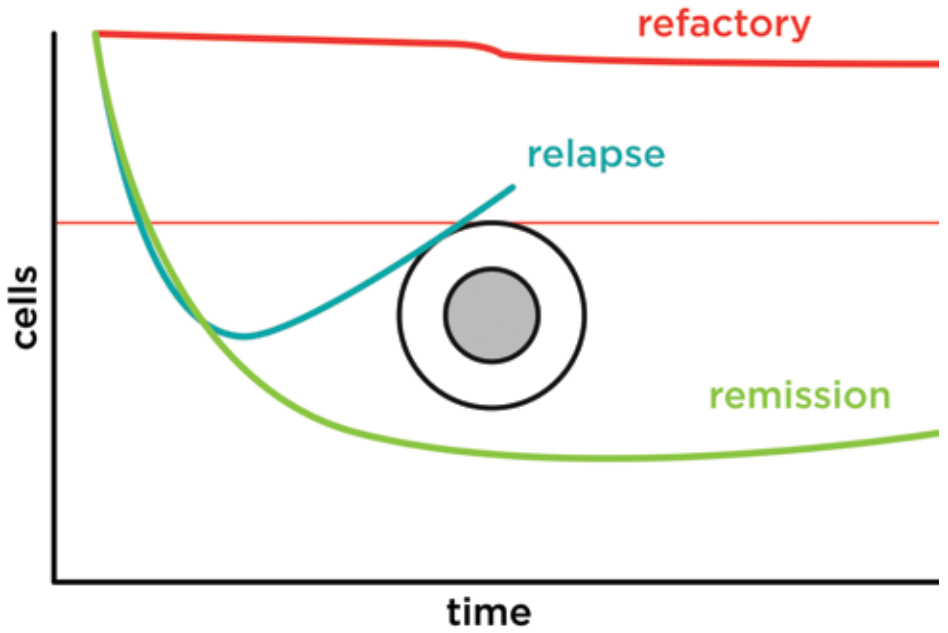


Figure 1.

The top curve shows refractory disease. The bottom curve shows a deep response ("cure"). The middle curve is the common outcome of patients enjoying an initial response to therapy, only to then relapse.*

Why is the middle curve so prevalent? We used to think cancer occurred after a serial accumulation of mutations affecting different biological pathways. Once a critical number of mutations occurred, cancer was born. This massive proliferation was thought to create a genetic monolith composed of billions and billions of genetically alike cancer cells. This model can explain the two extreme cases of disease response, refractory or cure, depending on an individual's luck of having a responsive or unresponsive genotype. The middle curve—response then relapse—is harder to explain with this model. We now know that cancer is made of many related, but not identical clones. Thus, as therapy begins, sensitive clones are eliminated, but this allows more room and food for resistant clones to grow. Quite simply, the main clone at diagnosis may not be the clone that eventually kills the patient. Taking this view, relapse is simply a normal byproduct of simple Darwinian selection: our best-intentioned treatment selects for drug-resistant cancer cells.**

When patients relapse, it is usually more difficult to get them into a subsequent deep response, and relapse usually occurs more quickly. I often tell patients that treating their disease is akin to pests and pesticides. The metaphor is apparently much stronger than I thought. I just read a review by my friend and colleague Carlo Maley and his team. Their paper outlines the marked similarity between the issues facing farmers and oncologists in dealing with resistance.[1] Insects share with cancer cells similar mechanisms of treatment resistance, including mutations to critical target genes, alteration of drug metabolism, and changes in drug uptake and exclusion. Decades of experience of managing insect pests to optimize crop health have led to the rules and principles that comprise what is called "integrated pest management" (IPM). These include:

1. Prevention.

In farming, this can mean adjusting crops and the environment to be less friendly to pests. Prevention of human cancer is the logical emphasis of epidemiologists and sound public health policy (excepting the current tide of governmental shenanigans).

2. Predict response/ resistance.

In farming and cancer, any early indicators of pest/cancer behavior can inform treatment diseases. In cancer we have a variety of biomarkers for risk stratification, but these are very imperfect and often fail to work at the individual patient level. Oncology has much room for improvement here, as this holds great promise in guiding optimal choice of initial therapy, critical in minimizing the risk of resistance.

3. Preferentially choose nonchemical control.

In farming this can be done with local environmental adjustments. In cancer this approach has limitations. In solid tumors, certainly surgical removal of the tumor fits the bill. In leukemia, CAR-T therapy is conceptually nonchemical, though resistance is still an issue. Perhaps research on manipulating the cancer microenvironment will best fit this principle.

4. Use target-specific drugs.

Pesticides act on specific biological pathways, often not critical to plants (an example is organophosphates which block cholinesterase, blocking nerve activity in insects). In cancer, precision medicine is based on targeted essential mutated genes. CML is the obvious model with the tyrosine kinase inhibitor (TKI) therapy. At this point, however,

the number of identified genetic mutations in cancer far outstrips the number of targeted agents. Pharmaceutical companies will not be running out of work for some time.

5. Use the lowest effective dose.

Higher drug doses create more potential harm and complications in the environment (farming) and the patient (medicine). However, practical experience in the field and lab suggest higher doses are also more likely to select for resistance. CML again offers an example where patients with deep molecular response, even with detectable disease, can have their TKI therapy discontinued without subsequent relapse.

6. Prevent/reduce cross-resistance.

Data in bugs and patients show that resistance occurs more often and faster when only one treatment agent is used. Using multiple agents with different mechanisms of action decreases and delays resistance (though in farming and cancer, resistance occurs even with multiple agent regimens). In farming, this principle calls for separating the application of treatment with rotations of agents with different mechanisms of action.

7. Monitor continuously.

In farming and cancer therapy, monitoring allows for a measurement of response, prediction of future decline or increase, and characterization of resistance features (new mutations). Once again, CML is the first and best model, as peripheral blood measurement of BCR::ABL1 levels predicts long-term response and prompts resistance studies for ABL1 mutations if disease burden ilestones are not hit.

Crabgrass

8. Change interventions in response to burden.

Frequent monitoring allows for early intervention if resistance is identified. Intervention may preclude resistance/relapse in some cases, especially when resistance is identified that is susceptible to a specific different targeted compound (again, think resistance ABL mutations in CML that are sensitive to a different TKI).

9. Identify minimum disease burden levels for treatment.

This is to establish a threshold below which intervention may not be needed. An example would be the discontinuation of therapy when patients with leukemia have no evidence of measurable residual disease. The best example would be the discontinuation to patients with deep molecular response in CML.

10. Evaluate success based on long-term management.

In farming, the long view means evaluation of pest control strategies based on year-after-year crop yields. In cancer, this emphasizes outcomes like overall survival and quality of life.

The authors go on to outline the implications in trial design and treatment ("IPM-inspired therapy"), using colon cancer as a model. These are easily imagined in the hematological malignancy arena. The key change in philosophy from the farm is the assumption that resistance clones are likely present from the beginning, and the optimal management embraces controlling the cancer, rather than trying to eliminate all cancerous cells (in CML this is often referred to as "a functional cure."). Essentially, this means a therapeutic strategy that includes as an option living with low levels of cancer, rather than striving for absolute eradication of all cancer cells (indeed, it may be impossible in nonsurgical settings to completely eradicate all cancer, since if at diagnosis AML has ~1012 cells, getting to an MRD-negative state could leave the patient with at least a million AML cells).

An IPM approach would require overcoming several practical and scientific hurdles, requiring advances in our technology and knowledge base. First, we need more sensitive and cost-effective methods to monitor patients. Monitoring is the linchpin for the IPM approach, so we need to understand how frequently to monitor, where to monitor (blood, marrow or cell-free nucleic acid?), and how to monitor (eg, flow cytometry or sequencing based?). Plus, none of these issues matter if the monitoring test is not affordable for the frequency of testing required. Excellent monitoring and long-term outcome data will be essential to determining lower thresholds of disease burden for potential intervention discontinuation (or postponement). The IPM approach will need more selective, targeted agents that can be rotated often to prevent the selection of resistant populations. Lastly, we will need studies of clonal heterogeneity and selection—presumably the cancer is made of populations that compete, and others that cooperated. We need to know enough about the patient's "cancer ecosystem" that we can therapeutically manipulate the system to give a competitive advantage to low aggressive clones that will not kill the patient.

Currently, cancer uses Darwinian selection against us. It's time we use the laws of Darwin against cancer. Maybe it's time to learn lessons from the land.

NOTES

* The "width" of the curve (% if cases in each category) depends on the particular disease and state of remission/relapse. For newly diagnosed CML, the bottom good- response curve would be very thick compared to the other curves, while for relapsed/refractory AML, the middle and bottom curves would be wide and the lower curve quite thin.

** Another reason patients may respond then relapse arises from incomplete therapy—either not intense enough or not long enough. This is akin to culling the herd. In this situation, one might expect the genotype of the relapse to be the same as the diagnostic sample.

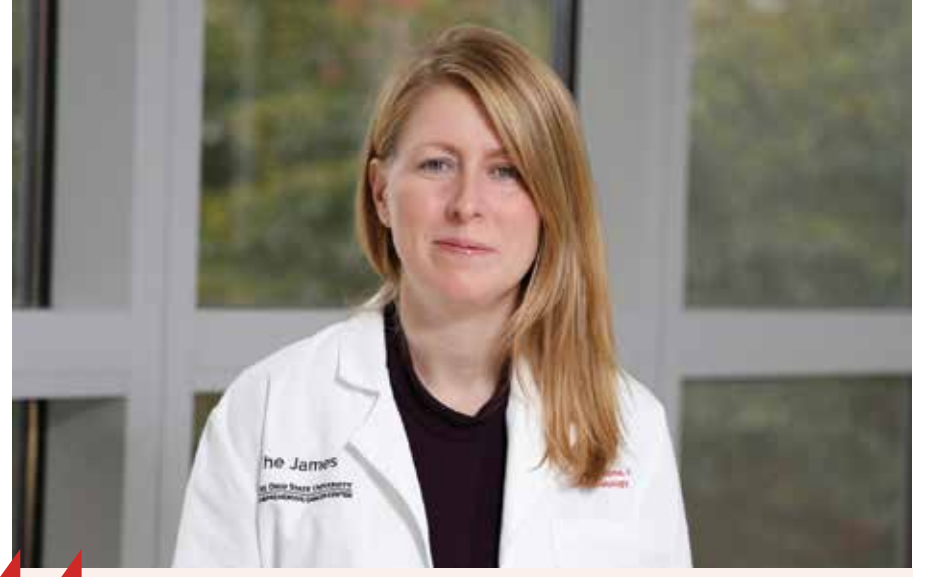
REFERENCE

1. Seyedi S, Harris VK, Kapsetaki SE, et al. Resistance management for cancer: lessons from farmers. *Cancer Res.* 2024;84(22):3715-3727. doi:10.1158/0008-5472.CAN-23-3374

Jerry Radich is a professor at the Fred Hutchinson Cancer Center and an associate editor of SOHO Insider.

PATHWAYS & PERSPECTIVES

Alice Mims, MD



Meet Alice Mims, MD, a professor at The Ohio State University and senior medical director of the BeatAML study. Dr. Mims discusses venetoclax's role in AML care, her commitment to patient-centered care, and how she relaxes.

This interview has been edited for clarity and length.

> *Patients are people, and when I talk to my patients, I try to understand their goals.*

Where did you grow up and how did you get into hematologic oncology?

I grew up in a small town called Lake City in rural South Carolina with about 10,000 people in the surrounding area. My dad is a recently retired family practitioner, and my mom is a pharmacist. As a child, I wanted to be a vet but had to forego that dream due to being allergic to cats. When I went into medical school, I initially thought I would follow in my dad's footsteps and be a primary care physician. However, during residency, I rounded on the acute leukemia service with Bayard Powell at Wake Forest, and I loved both the relationships you would quickly develop with patients and the scientific aspect surrounding clinical trials with new therapies being offered to patients.

What interests you about the science of acute leukemia?

Acute leukemia is heterogeneous, and figuring out the best approach for each individual patient is becoming more and more complicated especially in light of all of the new drug approvals over the past ten years. Though it is nice to have more options for patients, it's hard to know which one may be the better choice and clinical trials are one way to do that. You feel like you're advancing care and hopefully helping individual patients but also contributing to something bigger and broader than just the patients you're seeing in your own clinic.

How do you decide the best treatment path for patients?

You have to remember that patients are people and when I talk to my patients, I try to understand their goals. I want to understand what they're looking to gain from their treatment. We talk about the available data and how that fits into their treatment goals, and why I might recommend one option over another, but ultimately, it's a decision we make together. I want patients to know that we can always revisit the plan. We can regroup at any point and keep asking questions as we go, to make sure we're moving in the right direction together, with all the information that's out there.

> *There's potential in using triplets with venetoclax, but we have to think outside the box in targeting new pathways.*

What is the Beat-AML study?

I'm a senior medical director for the BeatAML study, which is an umbrella study led by the Leukemia and Lymphoma Society with novel genomic-based approaches for older patients with AML. Within that framework, there is a very exciting substudy being led by Dr. Uma Borate, called OptiAML, which is a randomized study assessing 14 versus 28 days of venetoclax in combination with azacitidine to see if patients can achieve similar complete remission rates with a shorter schedule. I'm really excited about the readout because I think it's going to be practice-changing for patients with AML. There is concern that the current 28-day venetoclax dosing is too toxic for the majority of patients with AML secondary to myeloid suppression. A shorter duration could open opportunities for safer exploration of triplet therapies with less toxicity, which is key for improving patient outcomes.

Will venetoclax remain the primary drug for AML, or will next-generation drugs eventually replace it?

There are a lot of AML subtypes that respond well to venetoclax so I do think it will remain part of our treatment toolbox. However, within its current FDA-label, the regimen is not curing the majority of patients. Hopefully studies exploring its use with intensive chemotherapy or other triplet regimens may help improve upon the current outcomes. There's potential in using triplets with venetoclax, but we have to think outside the box in targeting new pathways.

How did your mentors impact your career?

John Byrd has been one of my primary mentors since fellowship. I met him when I was a first-year fellow. On one of my first inpatient rotations, I mentioned to him that I was interested in research, and he has really helped me navigate that path. Later, when I moved back to South Carolina for my first faculty position to be closer to family, he again helped me figure out how to continue doing the research I was passionate about when my initial attempts at laboratory research were not panning out. Ultimately, I made the decision to come back to OSU where he gave me a lot of opportunities along with continued mentorship that helped

me advance my career. I still appreciate being able to ask for advice anytime, even though we are now at different institutions. I also appreciate that he has been a strong advocate for women. He's always been understanding of the different factors we, as women, have to balance while navigating academic careers.

Bill Blum is also someone I continue to value as a mentor, as he helped me both in fellowship training and navigating being a new faculty member. He worked with me on different research projects, and he gave me a lot of opportunities to run industry studies to not only better understand the ins and outs of clinical trials but also for networking opportunities.

What advice would you offer early-career clinician-scientists that's often overlooked?

It is okay to change your mind about your career path at any point and time. If what you are doing is not working, find a different direction for your career.

Dr. Mims in Japan with her husband. All photos courtesy of Dr. Mims.

Make sure you are defining your own measures of success and make sure to have a life outside of work.

What are your hobbies outside of work?

I love to travel and am excited to be able to do that more now that my daughter is older and we are through the pandemic. One of my favorite trips was for my 40th birthday, when my husband, good friends, and I went to Japan together. Being able to experience different cultures, amazing food and people is such a privilege and I am glad to be able to share that now with my daughter.

I also love reading fiction as a way to relax from thinking about work and patient cares. I have a book club with my sisters and mom where we meet monthly, so that is a fun way to continue to connect with my family even though we now live in different parts of the country.

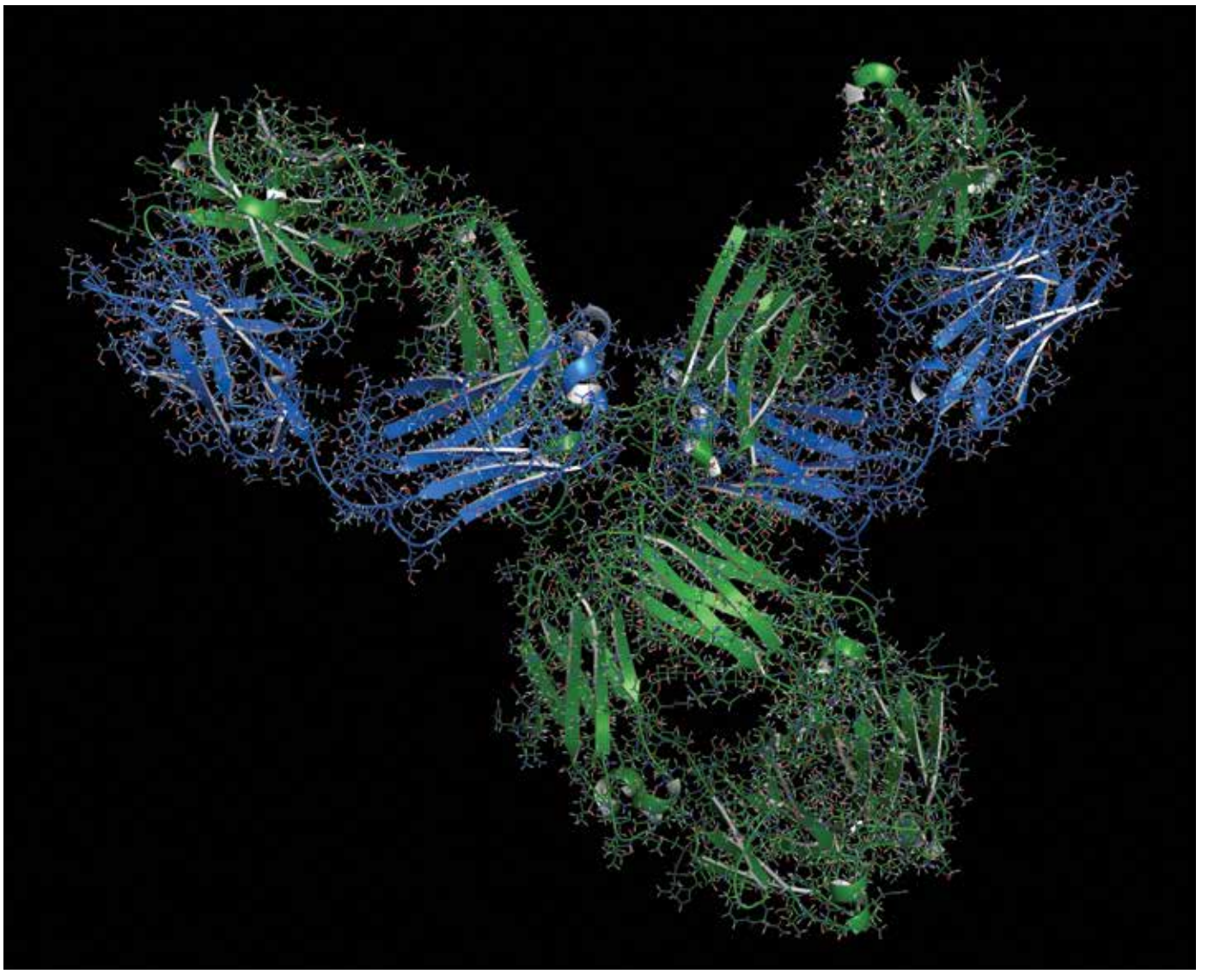
If you could have dinner with any hematologist, living or deceased, who would you choose and why?

Janet Rowley and Clara Bloomfield are two people that I would choose. They are both pioneers in the field of acute leukemia from a time where there were not many women hematologist. I would love to learn more about the trials and tribulations they had to go through as women in medicine when they started, and how they balanced all these different aspects in their personal lives. It was such a different time and fortunately now women are commonplace as leaders in hematology and oncology research. This change in culture is really thanks to them and others and I am very appreciative of the roles they played. me advance my career. I still appreciate being able to ask for advice anytime, even though we are now at different institutions. I also appreciate that he has been a strong advocate for women. He's always been understanding of the different factors we, as women, have to balance while navigating academic careers.

Dr. Mims with her family.

FEATURED STORY

Can radiation prime the immune system to fight blood cancer?



In 1953, a physician named RH Mole published a paper in the *British Journal of Radiology* describing a surprising phenomenon he called the "abscopal effect."[1] While documenting the shrinkage of tumors that were directly irradiated, Dr. Mole noticed that even untreated tumors, located in lesions beyond the scope of treatment, also shrank. How could the radiation treatment possibly affect these "out of scope" tumors?

Dr. Mole's 1953 paper was one of the earliest published observations suggesting a possible interaction between radiation and the immune system in metastatic cancer. More than two decades later, a handful of physician-scientists had a hunch that radiotherapy's effects might be tied to immune competence. Working mostly in animal models, they investigated the idea, but momentum stalled until the 2010s. That lull ended with the rise of immunotherapy, when studies began exploring radiation's role in combination treatment approaches.[2]

New evidence suggests that in some patients with blood cancer, adding radiation to immunotherapy, such as CAR-T or checkpoint inhibitors, seems to extend benefits beyond the local treatment site, improving overall outcomes in patients, though why that happens remains unclear..

Chasing a unicorn

"The abscopal effect is kind of a unicorn," said Austin Sim, MD, JD, a radiation oncologist at The Ohio State University. "We've seen it in a handful of case reports. It's very rare and not something we've been able to reproduce systematically."

One possible mechanism is immune priming: the idea that radiation changes the tumor microenvironment in ways that make immunotherapies more effective.

"There's something about the immune microenvironment and the interaction between immunotherapies and radiation that we still don't quite understand in terms of how to trigger it," Dr. Sim said. "While we have intriguing preclinical data, we don't yet have significant evidence for immune priming in a clinical setting."

Dr. Austin Sim

Dr. Sim, while stressing that the hypothesis remains unproven, cited neoantigens as one potential mechanism by which this might work. In this account, radiation triggers an immune response and amplifies the effects of immunomodulatory therapies via the release of neoantigens, which make tumors more immunogenic,

thereby triggering a T-cell response even in untreated areas.

Another possibility is that the improved outcomes seen with radiation and immunotherapy combinations have nothing to do with the immune system. Instead, they may simply reflect better disease control, specifically better local control of high-risk tumors.

Whatever the explanation turns out to be, the uncertainty is driving new lines of research and prompting some clinicians to revisit how radiation is used in patient care.

New evidence for immune priming

"For a long time, probably up until around 2000 or 2010, a lot of people didn't believe it was real," said Mohammad Khan, MD, PhD, a radiation oncologist who specializes in blood cancer at Emory University, describing the abscopal effect. "What is the mechanism? What is the biology? How could we enhance it? That's always been the Holy Grail for many in radiation oncology and biology, and now, more specifically, radiation immunology."

Dr. Khan's lab, in collaboration with immunologist Rafi Ahmed, PhD, developed early mouse models beginning in 2011 to investigate how radiation might activate a subset of stemlike CD8-positive T cells. These preclinical studies suggested that radiation could boost the T-cell priming in a way that might complement checkpoint blockade.

Building on that foundation, Dr. Khan led a pilot study[3] in patients with penta-refractory multiple myeloma, combining low-dose radiation with the PD-1 inhibitor pembrolizumab.

The findings, published in *Lancet Haematology* in 2024, offered early clinical support for his hypothesis first tested in mice that radiation could potentially augment immune activity when paired with immunotherapy to improve outcomes.

"There were two novel aspects of the study which I think really helped us distinguish from other designs," Dr. Khan said about the 2024 paper. "First, we prespecified what we called 'abscopal responses,' defined as radiographic improvement on imaging at a non-irradiated, distant site, and we were able to document those improvements. Secondly, and I think more importantly, we were able to look at blood biomarkers. Four of five patients who showed abscopal response also had CD4+ and CD8+ responses."

"It was encouraging and safe, but it was a small study," he noted.

Dr. Khan's research group is currently planning a new trial combining radiation, PD-1, and proteasome inhibitors.

Other researchers are testing how lower-dose approaches might modulate the immune system. Trials at Moffitt Cancer Center in Tampa, Florida, Memorial Sloan Kettering Cancer Center in New York, and the University of Texas MD Anderson Cancer Center in Houston are now exploring how radiation might be tailored by dose, location, and timing to complement immunotherapy.

> *We're not mice, but the biology says something is happening, and patients need us to chase it.*
>
> *— Mohammad Khan, MD*

Radiation can also provide a benefit without 'all the fancy immune stuff'

Timothy Robinson, MD, PhD, an associate professor of therapeutic radiology at Yale University, remains excited about the idea of radiation being used to facilitate immune priming, but notes that researchers have not yet been able to show it works in humans.

The idea that radiation somehow primes the immune system reflects a "vaccine model," according to Dr. Robinson, and he isn't necessarily convinced that it is the answer.

"The kind of vaccine model, if you will—there's a lot of preclinical data, like mouse models—but there are many differences between humans and animal models of both tumors and the immune system, and no one has made it work in humans," he said.

Dr. Timothy Robinson

"We don't have any data on that front, and in solid tumors, we've tried using radiation as "vaccine" until we've been blue in the face. This is why I don't necessarily believe that the vaccine model, as an overall strategy, is where it's at. I think we need more research to understand why these approaches have failed before we have a chance of making that strategy work in the clinic. I think it is fantastic that people are exploring this, but we aren't there yet."

Instead, he supports the more pragmatic approach of targeting areas with radiation where CAR-T is most likely to fail.

In a study that investigated patterns of failure in lymphoma, Dr. Robinson and a team of investigators reported that in patients who are treated with CAR-T therapy, 85% or more of the treatment failures involved local sites of disease progressing on treatment. In other words, he explained, the disease progresses exactly where it started.[4]

"Among all patients with aggressive lymphomas going into CAR-T, roughly a third of patients only experience progression at an existing site of disease," he explained. "Lymphoma is very sensitive to radiation, which raises the question —if we had treated all sites of disease in one of these patients—could we have prevented treatment failures and saved more lives?"

Studies to date have casted doubt on the ability to reliably induce the abscopal effect in humans, according to Dr. Robinson. However, if controlling relapse is simply a matter of targeting high-risk areas with radiation, there could be a far more straightforward solution.

"If we put aside the fancy immune stuff for a moment, I think there are more direct, less hypothetical strategies that might work," he said. "If we can just neutralize the place where this thing's going to come back, then maybe we can cure some people who otherwise would have died from their disease. That's where I think radiation can already help to improve outcomes, without having to invoke currently unproven, albeit intriguing, abscopal-type phenomena."

He added, "We also know that large volume disease, often characterized by bulky, hypoxic tumors, are likely incredibly immunosuppressive.

Perhaps radiation can help the immune system after all–not by a direct vaccine mechanism– but by killing large tumors with immunosuppressive environments that might otherwise have stopped CAR-T cells in their tracks."

Dr. Robinson gave a concrete example of how these localized benefits could improve the

outcomes of subsequent treatments.

"If you've got 100 people going into CAR-T, 20% will have purely local failures," he said. "That means you could potentially increase cure rates by 20% with radiation based on improvements in local control alone."

He noted, "However, every case is unique, and not all patients are good candidates for radiation. Being evaluated by someone who has treated a lot of these cases is critical."

Radiation as a bridging therapy

While the idea of immune priming is alluring at the theoretical level, bridging therapy, a more immediate clinical practice, is another domain in which researchers are asking whether radiation can play a role in making subsequent treatments more effective.

In the case of CAR-T treatment, the process typically requires waiting several weeks, since it involves collecting the patient's own T cells, genetically modifying them to express a CAR, expanding the engineered cells in a manufacturing facility, and then infusing them back into the patient.

Often used for palliative purposes and to control disease during this waiting period, bridging therapy was not originally designed to trigger immune effects, but new research is nudging it in that direction.

"We started using radiation as a bridge because it was a question of do something or do nothing while waiting for CAR-T manufacturing," Dr. Sim said.

In retrospective analyses, some researchers noticed that patients who received radiation before CAR-T appeared to do better than those who didn't, although they have been unable to determine whether that improvement stems from better disease control or a deeper immune interaction.

At the 66th American Society of Hematology Annual Meeting and Exposition, a team led by Hamish Scott, MD, of the Peter MacCallum Cancer Centre in Melbourne, Australia, reported on a retrospective analysis of patients with relapsed/refractory large B-cell lymphoma (LBCL) who received radiation before CAR-T therapy (axicabtagene ciloleucel). The investigators found that the radiated patients had better outcomes, even after adjusting for tumor burden and other risk factors.

"When we radiated bulky or symptomatic sites as bridging before CAR-T, the multivariate analysis still showed those patients did significantly better," Dr. Scott said.

In particular, the results showed that progression-free survival at 12 months was 75% in the group that received radiation therapy versus 49% in the group that received systemic-based bridging therapy, representing the standard of care.

In the conclusion of the paper, Dr. Scott and colleagues cautioned that because their analysis was retrospective, "it was not possible to separate the impact of disease distribution that is amenable to radiotherapy from the impact of radiotherapy itself." However, the paper concluded that given the favorable outcomes they observed, "radiotherapy should be considered as part of the bridging strategy wherever feasible."

> *The abscopal effect is kind of a unicorn.*
>
> *— Austin Sim, MD, JD*

The evidence isn't strong enough to draw firm conclusions, Dr. Scott said.

"The question is, are they doing better just because their disease was reduced before CAR-T or is there a real immunologic effect?" Dr. Scott said.

'Something is happening'

All this new research activity on immune priming and bridging therapy is invigorating the field of radiation oncology, according to Dr. Sim.

"It's definitely an exciting time to be in the field of managing patients with hematologic malignancies with radiation," he said. "I view any new systemic therapy that comes out as another opportunity to figure out how radiation can make that work better, especially now with modern treatment planning and the way we're doing radiation, which is a lot safer and a lot less toxic, especially compared with a lot of traditional cytotoxic chemotherapy."

Dr. Sim also said that there is still much to learn.

"There are a lot of variables we still haven't figured out how to optimize," Dr. Sim said. "Radiation isn't a monolith. It's a dose-dependent tool."

For the scientists pursuing the benefits of radiation treatment, the irony might not be lost on them that the object of their investigation is not a glamorous new scientific discovery but an old technology whose properties were first investigated by Marie Curie and others in the 1890s. And yet here they are in the 21st century continuing to investigate this "old" modality alongside the most cutting-edge therapies clinicians can offer patients.

Science is, at its core, the pursuit of truth through empirical observation. But sometimes the signal is too faint, the noise too loud, or the framework too narrow to register what might be there. We circle something without quite capturing it, and that, too, is part of the process. It may turn out to be nothing at all, or a scientific breakthrough may lie just around the corner.

"We're not mice, but the biology says something is happening, and patients need us to chase it," Dr. Khan said.

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SOHO YOUNG
INVESTIGATOR SPOTLIGHT

Meet Andres Ramirez, MD

Andres Ramirez, MD, is a first-year internal medicine resident at Roger Williams Medical Center in Providence, Rhode Island, and a 2024 awardee of the SOHO Young Investigator Program (YIP) award.

An international medical graduate from Barranquilla, Colombia, he received a research fellowship at Dana-Farber Cancer Institute's Bing Center from 2023–2024.

At Dana-Farber, Dr. Ramirez was introduced to the field by his two mentors, Jorge Castillo, MD, and Steve Treon, MD, PhD.

"It was my mentor Dr. Castillo who pushed me to apply for this award as a great opportunity to share one of my research projects," Dr. Ramirez said, adding that Dr. Treon was also influential in furthering his interest in hematologic oncology. "Both my mentors planted the seed in my heart," he said.

From left to right: Khaled Albakri, medical student from Jordan and 2024 SOHO Young Investigator, and Dr. Ramirez.

As a research fellow at Dana-Farber, Dr. Ramirez developed his passion for hematologic oncology, specializing in Waldenström macroglobulinemia.

"I had the opportunity to create the National Waldenström's Database and work on data analysis, which allowed me to build my research skills alongside some of the country's prominent leaders in the field," he said.

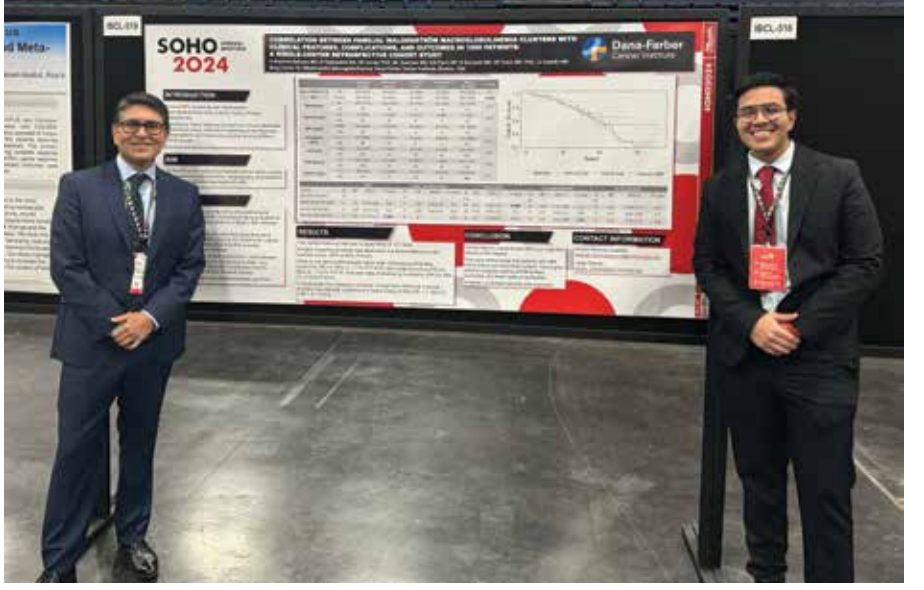
He finds cancer's nonlinear nature and its mutations a mentally challenging puzzle that keeps him engaged in helping people despite uncertain outcomes. On the human side, he values supporting patients.

"Having the opportunity to tell someone: 'I'm going to give my best to you in this process' — for me that's an honor," Dr. Ramirez said.

He describes his time at SOHO 2024 (the first SOHO he attended) as one of his peak experiences in the field.

"I really enjoyed learning from top-notch researchers in hematologic oncology and learning the most recent advances," he said.

Beyond the medical knowledge he acquired, the YIP award broadened his network by helping him build lasting relationships with peers, some of whom he continues to collaborate with.



Jorge Castillo, MD, and Andres Ramirez, MD, at SOHO 2024. (All photos courtesy of Dr. Ramirez)

From left to right Giorgio Medawar, MD, a current hem/onc fellow at MUSC; Center: Dr. Ramirez; Right: Gabriel Salk, DO.

"This program is beneficial in multiple aspects," Dr. Ramirez said. "It provided me the opportunity to develop connections and connect with other researchers and medical colleagues in medicine for sure, but also in science in general."

He credits the YIP award for expanding his career as a hematologic oncologist and strengthening his identity as a researcher by allowing him to present his work and share his views with other experts.

Outside of work, Dr. Ramirez enjoys cooking and salsa dancing.

"I enjoy cooking traditional food from Colombia, and I also enjoy learning how to prepare food from countries all around the world," he said. He particularly enjoys trying new restaurants and sharing the experience with others.

From left to right: Dr. Castillo; Steven P. Treon, MD, PhD; Dr. Ramirez; and Shirong Liu, PhD.

At the Barranquilla Carnival in Columbia.

He also loves salsa dancing and has even given lessons to his colleagues at Roger Williams. "As much as I enjoy dancing salsa, I love teaching it even more," he said.

Another form of dancing he enjoys is Cumbia, the traditional folk dance performed in costumes during the annual Carnival festivities in his native Barranquilla, Colombia.

"I would never miss Carnival when I lived in Barranquilla," he said. Now that he lives in Rhode Island, however, he finds himself watching the parades from afar to relive memories with friends while inviting new friends to explore the festival for the first time.

The SOHO Young Investigator Program (YIP) supports aspiring hematologic oncologists to attend the Annual Meeting in Houston and provides the opportunity to meet with leaders in the field.

Support the Young Investigator Program! Visit soho.click/donate

SOHO Insider podcast exclusive

Sagar Lonial, MD, discusses the journey of belantamab mafodotin on a recent episode of the *SOHO Insider* podcast with host Saad Usmani, MD.

Dr. Usmani, chief of the myeloma service at Memorial Sloan Kettering Cancer Center in New York City, and Dr. Lonial, professor and chair of the Department of Hematology and Medical Oncology at Winship Cancer Institute at Emory University, explore the journey of the antibody-drug conjugate (ADC) belantamab mafodotin, the first B-cell maturation antigen (BCMA)-targeted ADC approved by the US Food and Drug Administration (FDA) for patients with relapsed or refractory myeloma.

Dr. Usmani

Dr. Lonial noted the excitement around the approval given how few treatment options there were for this subgroup of patients.

"In the relapsed/refractory setting, it clearly demonstrated clinical benefit, with a significant fraction of patients responding," adding that the therapy seemingly "ushered in the era of BCMA-directed therapies."

Early experiences with the drug during the DREAMM-2 trial pointed to the possibility of flexible dosing given the length of remission in some patients.

"Some patients stayed in remission for a long period with just a few doses," Dr. Lonial said.

The flexible dosing helped mitigate ocular toxicity without compromising treatment responses in patients, according to Dr. Lonial.

"It was incredibly gratifying to see patients with no other options, have really long remissions with less frequent dosing schedules," he said. "I think at that time point, we didn't fully appreciate the variability in the ocular side effects."

However, the phase 3 DREAMM-3 trial, designed as a confirmatory study, failed to meet its statistical endpoints, primarily due to high censoring rates and questionable trial design.

"It clearly demonstrated benefit, but the study design put the drug in a difficult position," Dr. Lonial said. As a result, the FDA withdrew belantamab from the market despite evidence of efficacy.

Enthusiasm for the drug has since been revived by more recent data from the DREAMM-7 and DREAMM-8 trials, which were large, randomized trials with over 400 patients. In the DREAMM-7 trial, investigators compared belantamab mafodotin, bortezomib, and dexamethasone (BVd), as compared with daratumumab, bortezomib, and dexamethasone (DVd) in patients who had progression of multiple myeloma after at least one line of therapy.[1] In the DREAMM-8 trial, lenalidomide-exposed patients who had relapsed or refractory myeloma after at least one line of therapy received either belantamab mafodotin, pomalidomide, and dexamethasone (BPd), or else pomalidomide, bortezomib, and dexamethasone (PVd).[2]

Dr. Lonial

"Combining drugs is the optimal way," Dr. Lonial said, referencing the DREAMM-7 and DREAMM-8 trials. "One of the key advantages is that this is a therapy you can give the same week you see the patient."

The convenience and accessibility of ADCs make them an especially promising option for community physicians, particularly in areas where access to chimeric antigen receptor (CAR) T-cell therapy remains limited due to cost and infrastructure.

"Cellular therapy availability and cost will remain an issue," Dr. Usmani said, adding that ADCs help bridge gaps in care outside academic centers.

As regulatory discussions unfold around the DREAMM-7 and DREAMM-8 data, it will be interesting to see if belantamab returns as a viable treatment option, and this time, as part of a combination regimen with a flexible dosing schedule.

"What I think may resurrect this drug, and what we're really excited about, is the idea of combining [the therapies when we use them], and not giving them as single agents," Dr. Lonial said. "Allowing yourself the flexibility of reducing the dosing schedule such that the average delivered dose of belantamab mafodotin is every six to eight weeks."

> *Some patients stayed in remission for a long period with just a few doses.*
>
> *— Sagar Lonial, MD*

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Catch up on more podcasts from SOHO Insider

MEETING NEWS

Latest from the conference floor

SOHO Insider reports from the ASCO® 2025 Meeting in Chicago

VERIFY study shows rusfertide significantly improves PV outcomes

In patients with polycythemia vera (PV) receiving standard of care (SOC), treatment with rusfertide resulted in a statistically significant reduction in the mean number of phlebotomies and improved hematocrit control, as well as better patient-reported outcomes, according to results from VERIFY, a phase 3, double-blind, placebo-controlled study.

Rusfertide is a subcutaneous, self-injected, first-in-class peptide hepcidin mimetic that decreases erythrocytosis. The ongoing VERIFY trial is designed to assess rusfertide versus placebo in phlebotomy-dependent patients with PV receiving SOC.

The study, led by Andrew Kuykendall, MD, of Moffitt Cancer Center, in Tampa, Florida, recruited patients requiring frequent phlebotomies with or without stable cytoreductive therapy to control hematocrit.

A total of 293 patients (male, 73.0%; median age, 57 [27-86] years) were randomized to receive rusfertide (n=147) or placebo (n=146). In the rusfertide and placebo groups, 56.5% (n=83) and 55.5% (n=81) of patients, respectively, received concurrent cytoreductive therapy.

The results for weeks 20-32 showed that significantly more patients in the rusfertide group (76.9%) achieved a clinical response versus placebo (32.9%) (*P*<0.0001), where clinical response was defined as the absence of phlebotomy eligibility and no phlebotomies during weeks 20-32. The mean (SE) number of phlebotomies (weeks 0-32) was 0.5 (0.2) with rusfertide vs 1.8 (0.2) with placebo (*P*<0.0001). More patients treated with rusfertide maintained hemocrit <45% from weeks 0-32 vs placebo (rusfertide, 62.6%; placebo, 14.4%; *P*<0.0001).

In terms of patient-reported outcomes, patients treated with rusfertide demonstrated a statistically significant improvement in the PROMIS Fatigue Short Form 8a (SF-8a) total T-score and MFSAF v4.0 Total Symptom Score.

"Rusfertide is the first investigational agent to target the hepcidin pathway to control hematocrit and the first agent to prospectively demonstrate a statistically significant improvement in the PROMIS Fatigue SF-8a and MFSAF patient-reported outcomes in patients with PV," Dr. Kuykendall and colleagues wrote.

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Isatuximab with KRd boosts sustained MRD negativity in myeloma

Patients with newly-diagnosed multiple myeloma (MM) treated with isatuximab plus IsaKRD in induction, consolidation, and light consolidation phases saw sustained measurable residual disease (MRD) negativity, including in those with high-risk disease.

Francesca Gay, MD, PhD, of the University of Torino, presented the findings at the 2025 ASCO® Annual Meeting.

Transplant-eligible newly-diagnosed MM patients ages <70 years were included.

The IsaKRd arm (n=151) received:

- **Four full-dose IsaKRd induction cycles**
- **Melphalan plus autologous hematopoietic cell transplant**
- **Four full-dose IsaKRd consolidation cycles**
- **Twelve 28-day light consolidation cycles**

A control arm (n=151) received KRd in the same schedule used in the experimental arm.

After a median follow-up of 35 months, the intention to treat analysis showed MRD negativity rates at the 10^{-5} cutoff after full-dose consolidation of 77% with IsaKRd and 67% with KRd (odds ratio [OR], 1.67; *P*=0.049); MRD rates of 10^{-5} one year after light consolidation were 66% and 59%, respectively (OR 1.36; *P*=0.21).

MRD negativity rates at the 10^{-6} cutoff after full-dose consolidation were 67% with IsaKRd and 48% with KRd (OR, 2.29; *P*<0.001); MRD rates of 10^{-6} one year after light consolidation were 52% and 38%, respectively (OR, 1.82; *P*=0.012).

MRD (10^{-6}) negativity rates were also seen in the high-risk cohort: 62% versus 20% in patients with ≥2 high-risk cytogenic abnormalities (OR, 6.3; 95% CI, 1.11-35.66) and 47% versus 35% in patients with R2-International Staging System III/IV disease (OR, 1.62; 95% CI 0.77-3.41).

During light consolidation, common grade 3/4 hematologic adverse events (AEs) observed in the IsaKRd and KRd arms were neutropenia (17% vs 18%) and thrombocytopenia (2% vs 3%); common 3/4 nonhematologic AEs included infections (8% vs 5%), gastrointestinal impacts (4% vs 4%), and vascular impacts (3% vs 1%).

Among IsaKRd and KRd-treated patients, 3% and 2%, respectively, discontinued treatment due to toxicity; two treatment-related deaths occurred in the IsaKRd arm.

The study is funded by Sanofi and Amgen.

REFERENCE

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Sintilimab plus ICE regimen significantly improves CR in classical HL

Sintilimab plus ifosfamide, carboplatin, and etoposide (ICE) as second-line treatment of classical Hodgkin lymphoma (cHL) significantly improved complete remission rates (CRRs) compared with ICE alone, according to a study presented at the 2025 ASCO® Annual Meeting by Yuankai Shi, MD, PhD, of the Cancer Hospital at the Chinese Academy of Medical Sciences in Beijing.

The multicenter, randomized, controlled, double-blind, phase 3 ORIENT-21 study included 81 patients (as of November 21, 2024) with cHL who progressed following first-line standard chemotherapy. There was a

safety run-in phase that included patients receiving sintilimab plus ICE (n=10); this was followed by a randomized phase where patients received sintilimab plus ICE (n=34) or placebo plus ICE (n=37) for six cycles. Patients who did not progress continued sintilimab or placebo monotherapy.

After a median follow-up of 38.4 months, significantly higher CRRs were observed in both the modified intention to treat (mITT) and ITT cohorts of those receiving the sintilimab regimen compared with placebo:

- **mITT: 61.8% vs 32.4% (*P*=0.0295)**
- **ITT: 61.4% vs 32.4% (*P*=0.0105)**

The median duration of complete remission was not reached in the sintilimab cohort (mITT, 28.6%; ITT, 22.2%) and was 20.7 months in the placebo group.

Sixteen patients in the control cohort switched to sintilimab monotherapy after disease progression.

In the ITT cohort, median progression-free survival was not reached with sintilimab plus ICE (events in 34.1% patients) and was nine months in the placebo group (hazard ratio, 0.48; 95% CI, 0.23-1.00).

Among 80 patients assessed for safety, all experienced treatment-emergent adverse events (TEAEs); grade ≥3 TEAEs occurred in 81.4% patients on sintilimab (n=43) and 97.3% on placebo (n=37). The most common grade ≥3 TEAEs were decreased neutrophil count (62.8% vs 70.3%), decreased white blood cell count (53.5% vs 64.9%), and decreased platelet count (51.2% vs 67.6%).

This study is funded by Innovent Biologics (Suzhou) Co., Ltd.

REFERENCE

Liu P, Li Z, Cen H, et al. Sintilimab (anti-PD-1) plus ifosfamide, carboplatin, and etoposide (ICE) in second-line classical Hodgkin lymphoma (cHL): results of a multicenter, randomized, controlled, double-blind phase 3 study (ORIENT-21). Abstract #7007. Presented at the 2025 ASCO® Annual Meeting; May 30-June 3, 2025; Chicago.

SOHO Insider reports from the 18th International Conference on Malignant Lymphoma (18-ICML)

Gut-linked microbes tied to survival in DLBCL

The presence of certain intratumoral microbes was linked to survival outcomes in diffuse large B-cell lymphoma (DLBCL). Specifically, detection of Prevotella species at diagnosis, prior to any treatment, was associated with improved progression-free survival (PFS), while Enterococcus species were linked to worse outcomes, lead investigator Paolo Ghione, MD, of Memorial Sloan Kettering Cancer Center, reported during the presentation.

Both species are commonly found in the gut, but they differ in their typical roles and clinical implications. Prevotella is often considered a commensal microbe, while Enterococcus includes opportunistic pathogens frequently linked to inflammation and antibiotic resistance.

"We don't think these microbes were there by chance," Dr. Ghione said during the oral presentation. "Whether they arrived before the lymphoma developed or were drawn to the site by inflammation is a question we still need to answer."

Microbial sequences were identified within lymphoma tissue, but how and when these organisms entered the tumor mass remains unclear. Researchers are exploring whether they migrate from the gut or other barrier sites. Ongoing studies aim to understand their spatial relationship to the tumor microenvironment and their role in lymphomagenesis.

REFERENCE

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'Boom Boom Radiotherapy' approach may boost CAR T-cell responses

The combination of so-called "Boom Boom" radiotherapy prior to treatment with lisocabtagene maraleucel (liso-cel) was found to be safe, feasible, and effective, according to an investigator-initiated study led by Christopher D'Angelo, MD, of the University of Nebraska Medical Center.

The study enrolled adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma who received low-dose radiotherapy—referred to as Boom Boom RT—to disease sites seven to 10 days before infusion of liso-cel, without any other bridging therapy except for steroids. Boom Boom RT consists of 4 Gy delivered in two 2-Gy fractions, a low-dose regimen previously shown to be effective in indolent lymphomas.

"These data suggest that the use of low-dose RT as bridging therapy is safe, feasible, and may be effective at enhancing outcomes to liso-cel therapy," Dr. D'Angelo and colleagues wrote.

Early results showed a complete response rate exceeding 80% in a high-risk patient population, suggesting that low-dose radiotherapy can potentially serve as a bridge to CAR T-cell therapy and augment its efficacy.

The study enrolled 32 patients with aggressive B-cell non-Hodgkin lymphoma, of whom 30 (94%) received Boom Boom RT and liso-cel, meeting the feasibility threshold. The median age was 70, and 69% were male. Most had DLBCL, and 50% were refractory to frontline therapy. Among 29 evaluable patients, the overall response rate was 86%, with a complete response (CR) rate of 83%. Two patients had stable disease, and two had progression as best response. At 200 days, patients who achieved a CR had a PFS rate of 75% and an OS rate of 89%.

Researchers continue to investigate how low-dose radiation may help "prime" the immune response ahead of cellular therapy.

Funding for the study was provided by Bristol Myers Squibb.

REFERENCE

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Response to tisagenlecleucel extends to 4 years in follicular lymphoma

Researchers, led by Catherine Thieblemont, MD, of the Hôpital Saint-Louis in Paris, presented four-year follow-up data from the phase 2 ELARA study, showing that response to tisagenlecleucel continues to deepen in patients with follicular lymphoma (FL), with an estimated 48-month PFS rate of 50.2%.

The study included patients with relapsed or refractory FL who have received two or more lines of systemic therapy, including an anti-CD20 monoclonal antibody and alkylating agent; 97 patients received a single infusion of tisagenlecleucel.

As of March 27, 2024, after a median follow-up of 53 months, 94 patients were evaluable for efficacy outcomes.

Median OS was not reached; the 48-month OS rate was 79.3%.

Patients with high-risk disease experienced durable responses to treatment (48-month PFS and OS), including those with:

- **Progression of disease within 24 months (45.5% and 80.8%, respectively)**
- **High Follicular Lymphoma International Prognostic Index scores (45.5% and 73.2%)**
- **Bulky disease (45.2% and 73.0%)**
- **Double refractory disease (52.8% and 83.7%)**
- **High tumor burden (23.2% and 65.5%)**

A third of patients (n=31; 33%) had measurable residual disease (MRD) information available, and 28 (90%) achieved MRD negativity at any time point. MRD-negative status was seen in:

- **82% of patients (n=22/27) at 28 days**
- **75% (n=12/16) at three months**
- **69% (n=11/16) at six months**
- **76% (n=13/17) at one year**

The researchers reported no new safety concerns. Six patients (6.2%) experienced second primary malignancies. At data cutoff, 19 patients had died.

"Correlative analyses suggest that most baseline high-risk disease characteristics are not associated with inferior efficacy following tisagenlecleucel infusion in [patients] with [relapsed/refractory] FL," the authors concluded.

The study is supported by Novartis Pharmaceuticals Corporation.

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Thieblemont C, Dreyling M, Dickinson MJ, et al. Phase 2 ELARA trial 4-year update: clinical outcomes of tisagenlecleucel in patients (pts) with high-risk relapsed/refractory follicular lymphoma (R/R FL). Abstract #138. Presented at 18-ICML; June 17-21, 2025; Lugano, Switzerland.

Researchers outline ongoing phase 3 study of golcadomide for LBCL

Golcadomide, an investigational first-in-class oral CELMoD, is being assessed in combination with R-CHOP in patients with high-risk LBCL.

The double-blind, multicenter, randomized, phase 3 GOLSEEK-1 study is currently enrolling approximately 850 patients with untreated high-risk LBCL who will be randomized 1:1 to receive golcadomide 0.4 mg or placebo orally once daily for seven days plus R-CHOP in 21-day cycles for six cycles.

Eligible patients must have:

- **Confirmed LBCL per the World Health Organization 2022 classification**
- **High-grade BCL with MYC and BCL2**
- **T-cell/histiocyte-rich LBCL**
- **Epstein–Barr virus-positive diffuse LBCL (DLBCL)**

Patients with another subtype of lymphoma or documented or suspected central nervous system involvement will be excluded.

The primary endpoint is PFS, and secondary endpoints include event-free survival, undetectable MRD, and OS. Follow-up is expected to be approximately 67 months.

The study is currently enrolling at 309 sites in 36 countries.

The study is supported by Bristol Myers Squibb.

REFERENCE

Nowakowski GS, Hoffmann M, Munoz J, et al. GOLSEEK-1: a phase 3, double-blind, randomized study of golcadomide + R-CHOP versus placebo + R-CHOP in patients with previously untreated, high-risk large B-cell lymphoma. Abstract #OT04. Presented at 18-ICML; June 17-21, 2025; Lugano, Switzerland.

REGULATORY ROUNDUP

Tracking regulatory news worldwide

FDA panel votes 6-2 in favor of daratumumab for high-risk smoldering multiple myeloma

The US Food and Drug Administration (FDA)'s Oncologic Drugs Advisory Committee (ODAC) voted 6-2 that the results from the phase 3 AQUILA trial support a favorable benefit-risk profile for daratumumab and hyaluronidase-fihj (DARZALEX FASPRO) in patients with high-risk smoldering multiple myeloma (SMM).

The phase 3 AQUILA trial randomly assigned patients with high-risk SMM to receive either subcutaneous daratumumab monotherapy or active monitoring.

The panel considered whether the AQUILA trial provided sufficient evidence to support use of the subcutaneous anti-CD38 monoclonal antibody in a population with no current approved treatment and a high risk of progression to symptomatic disease.

"All the endpoints effectively are favoring the intervention here," said Daniel Spratt, MD, chairman and professor of Radiation Oncology at University Hospitals Seidman Cancer Center and Case Western Reserve University, who, while acknowledging concerns for patient overtreatment, said the survival differences are meaningful. Dr. Spratt also asked the FDA to define what qualifies as "high risk" and asked the sponsor to continue to track the data so that the overall survival outcomes can continue to mature.

In contrast, Neil Vasan, MD, PhD, an oncologist at NYU Langone Health, who voted no, expressed concern about overtreatment.

"The reason I voted no was that I felt that this bimodal distribution within the population—that there is a group of patients that we're overtreating, a group of patients that we're undertreating—we don't really have great data right now to understand who those people are, so that drove my vote," Dr. Vasan said. "I agree with Dr. Spratt's comments about if this does result in approval to have clear indications in the package label."

Daratumumab demonstrated a clinically meaningful and statistically significant benefit compared with active monitoring, the current standard of care for high-risk SMM. Data from the trial showed delayed disease progression and a trend toward overall survival (OS) benefit.

"High-risk smoldering multiple myeloma remains a challenging clinical conundrum with no approved therapies, and earlier intervention may delay or even prevent progression to active multiple myeloma," said Peter Voorhees, MD, of Atrium Health / Levine Cancer Institute in Charlotte, North Carolina, in the press release issued by the drug manufacturer, Janssen. Dr. Voorhees, who did not vote on the FDA panel, was an AQUILA trial investigator.

"We appreciate the balance the committee provided when assessing the risks and benefits of finite treatment at this stage and its recognition of the promise of DARZALEX FASPRO."

The FDA is expected to make a final decision based on the panel's recommendation in the coming months.

FDA ODAC votes 8-1 glofitamab trial does not apply to US patients

A federal advisory panel voted 8-1 that results from the global STARGLO trial, which was intended as the confirmatory trial for full approval of glofitamab-gxbm, were not applicable to the US patient population.

The central concern was the regional variation in the trial's outcomes. While glofitamab showed a significant OS benefit in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), nearly half of the 274 participants were enrolled in Asia, where the benefit was most pronounced. In contrast, only 9% were from the US, and high hazard ratios in that subgroup raised concerns.

"While I'm a strong proponent of drug development, strong proponent of access to therapies, the question that was asked of me is, are the results from the trial applicable to the US general population? I'm not convinced with the data that is provided by the sponsor that it is applicable to the general population," said Ajay Nooka, MD, MPH, an associate director of clinical research for Winship Cancer Institute of Emory University, who casted a "no" vote with the majority.

The panel's voting question, "Are the STARGLO population and trial results applicable to the proposed US patient population?" was met with one yes, which came from patient representative Paul Majkowski, Esq.

"While it is on the sponsor to meet the burden of proof, maybe I was willing to relax that burden of proof for the considerations of the patient perspective," Majkowski said after casting his vote.

FDA to review sBLA for epcoritamab plus R2 in relapsed or refractory FL

The FDA will review a supplemental Biologics License Application (sBLA) for epcoritamab combined with rituximab and lenalidomide (R2) for adult patients with relapsed or refractory follicular lymphoma (FL) after at least one prior therapy.

The manufacturer of the therapy, Genmab, plans to submit the application in the first half of 2025, according to a company press release.

Epcoritamab, a subcutaneously administered, bispecific antibody, improved overall response rates in the phase 3 EPCORE FL-1 trial when combined with R2, compared to R2 alone, according to Genmab. The trial's interim results, with no new safety concerns, support the submission. Genmab plans to share complete trial findings in 2025.

The safety and efficacy of epcoritamab for use as a combination therapy has not been established. The therapy is currently approved by the FDA under Accelerated Approval as a monotherapy for the treatment of adults with relapsed or refractory FL after two or more lines of systemic therapy, Genmab wrote in the release.

China NMPA grants Breakthrough Therapy Designation for ICP-248 in MCL

The Center for Drug Evaluation (CDE) of the China National Medical Products Administration (NMPA) has granted Breakthrough Therapy Designation for ICP-248 (mesutoclax) for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

This designation accelerates development for therapies showing significant clinical advantages.

ICP-248, an oral BCL-2 inhibitor, is being investigated in the phase 3 trial with orelabrutinib for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), according to a press release from InnoCare Pharma, the manufacturer of the therapy.

ICP-248 treats MCL and other lymphomas, with strong results in ongoing trials, including one for acute myeloid leukemia (AML), the company wrote in the release.

FDA grants Orphan Drug designation for bexmarilimab in MDS

The FDA has granted Orphan Drug designation for bexmarilimab for the treatment of patients with myelodysplastic syndromes (MDS).

Bexmarilimab is a first-in-class immunotherapy targeting the Clever-1 receptor, and is currently under investigation for both hematological cancers and advanced solid tumors.

The ongoing open-label phase 1/2 BEXMAB clinical study is evaluating bexmarilimab in combination with azacitidine in relapsed/refractory AML and MDS patients, according to a press release published by Faron Pharmaceuticals, the drug's manufacturer.

China NMPA approves phase 3 trial for ICP-248 plus orelabrutinib in CLL/SLL

The CDE of the NMPA has approved a phase 3 clinical trial for ICP-248 in combination with orelabrutinib as a first-line therapy for patients with CLL/SLL.

The oral BCL-2 inhibitor ICP-248 and BTK inhibitor orelabrutinib are administered in combination to target according to InnoCare. The trial builds on a phase 2 study that showed promising efficacy and safety in treatment-naïve patients with CLL/SLL.

The phase 3 study aims to confirm these findings in a larger patient group, according to the company.

"The treatment of CLL/SLL has achieved significant breakthroughs in recent years, and chemo-free regimens are gradually becoming the preferred approach," Jasmine Cui, PhD, the co-founder, chairwoman and CEO of InnoCare, said in a press release.

"ICP-248 plays an important role in InnoCare's extensive hemato-oncology pipeline. Together, ICP-248, orelabrutinib and tafasitamab form a robust product combination that reinforces InnoCare's leadership in the treatment of hematologic malignancies."

EMA approves IMPD for OT-C001 trial in DLBCL

The European Medicines Agency (EMA) has approved an Investigational Medicinal Product Dossier (IMPD) for OT-C001, an allogeneic natural killer-cell therapy, for the treatment of adult patients with relapsed or refractory DLBCL.

OT-C001 is derived from umbilical cord blood and administered to target DLBCL, according to the press release from the therapy's manufacturer, Emercell, a subsidiary of Onward Therapeutics.

The phase 1 study will test OT-C001 alongside rituximab, an anti-CD20 monoclonal antibody, to determine its safety and early effectiveness for patients who have not responded to standard therapies.

This study will enroll patients at various European centers to explore OT-C001's benefits, according to the company.

Macao regulatory body approves equecabtagene autoleucel for relapsed or refractory MM

The Pharmaceutical Administration Bureau of the Macao Special Administrative Region (ISAF) has approved equecabtagene autoleucel for the treatment of adult patients with relapsed or refractory MM, including at least one proteasome inhibitor and an immunomodulatory agent.

The approval is based on the phase 1/2 FUMANBA-1 a single-arm, open-label, phase 1b/2 trial, which evaluated the therapy's efficacy and safety in relapsed or refractory MM patients who received three or more prior therapies.

Equecabtagene autoleucel is a fully human anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy that uses a lentivirus as a gene vector to transfect autologous T-cells.

CHMP recommends pirtobrutinib for relapsed or refractory CLL in EU

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion recommending approval of pirtobrutinib (Jaypirca) for the treatment of adult patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor.

Pirtobrutinib is an oral therapy administered once daily, according to the press release from Lilly, the manufacturer of the therapy.

The CHMP's recommendation is based on results from the phase 3 BRUIN CLL-321 trial, which evaluated pirtobrutinib against investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients previously treated with a covalent BTK inhibitor.

In the phase 3 BRUIN CLL-321 trial, pirtobrutinib demonstrated a 46% reduction in the risk of disease progression or death compared with the control arm, according to the company.

FDA clears linperlisib for phase 3 trial in relapsed/refractory PTCL

The FDA has approved the design of a global phase 3 trial for linperlisib for the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) who have received at least one prior systemic therapy.

This clearance follows a successful end-of-phase 2 meeting with the FDA, according to Yingli Pharma, the manufacturer of the drug.

Linperlisib is an oral therapy targeting patients with PTCL, according to the press release. The phase 3 study, set to begin in the second quarter of 2025, will compare linperlisib against clinician's choice of standard care treatments to assess the therapy's efficacy and safety.

The trial builds on earlier studies showing linperlisib's potential in PTCL and other hematologic malignancies, according to the company.

SOHO regional meeting in Brazil delivers again

By: **Phillip Scheinberg, MD, PhD**

SOHO President Phillip Scheinberg, MD, PhD, head of the Division of Hematology at the Hospital A Beneficência Portuguesa de São Paulo in Brazil, wrote in an email to SOHO Insider that the Brazilian edition of SOHO was a "tremendous success." Read his reflections below.

"The Brazilian edition of SOHO was a tremendous success. This year's event drew over 1,500 registered participants for an intensive two-and-a-half-day program. The heavy turnout highlighted the widespread interest in cutting-edge developments in the treatment of hematologic malignancies.

Attendees had numerous opportunities to learn from world-class speakers and to engage in meaningful discussions and networking. This was arguably one of the most successful meetings we've ever organized, and the feedback has been overwhelmingly positive. Hematologists from across Brazil participated, reinforcing the growing importance of extending SOHO's reach nationwide—further advancing our mission to educate and disseminate the most relevant and timely information in hematologic malignancies.

A dedicated SOHO booth was prominently featured and well attended, sparking significant interest in membership and in the upcoming Annual Meeting in Houston, held every September.

Planning for the 2026 Brazilian SOHO Meeting is already underway, and we are fully committed to delivering an even more impactful event."

All photos courtesy of Lucas/Lupacom.

SOHO Israel 2025 wraps up successful 2-day event with leading hematologists

The third meeting of SOHO Israel and 9th International Davidoff conference, titled State of the Art and Next Questions, was held on May 15-16, 2025, at the ANU-Museum of the Jewish People at Tel Aviv University and at the Port Tower Hotel in Tel Aviv University.

The meeting had 458 attendees registered, which included in-person and virtual. Participants included both Israeli hematologists and an international audience including researchers and industry.

The conference kicked off with opening remarks to a packed hall by Hagop Kantarjian, MD, chair of the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston. This was followed by welcoming remarks from the Rabin Medical Center director, the Dean of the Gray Faculty of Medical and Health Sciences at the Tel-Aviv University, and members of the Davidoff family who donated and support the Davidoff Cancer Center.

The scientific program included 34 lectures given by 33 speakers over two days. Session topics included chronic lymphocytic leukemia, plasma cell dyscrasias, acute myeloid leukemia, lymphoma, quality of life in hematological disorders, myeloproliferative and myelodysplastic disorders, chronic myeloid leukemia, cellular therapy, and acute lymphoblastic leukemia.

The meeting was co-chaired by Dr. Kantarjian and Pia Raanani, MD, head of the Institute of Hematology at the Davidoff Cancer Center in the Rabin Medical Center.

"Many people keep telling me it's the leading educational meeting in Israel in hematology," said Dr. Raanani after the event. "Colleagues say we managed to bring SOHO to Israel, especially to our more peripheral hospitals that travel less to the big conferences. This made me feel good because that is exactly the goal of SOHO as I understand it—to spread the tremendous hematological knowledge of MD Anderson worldwide."

Several invited speakers were forced to participate virtually due to unforeseen flight cancellations to Tel Aviv by some airlines related to the conflict in Gaza.

"Five speakers were supposed to come physically but due to the foreign airlines' cancellations … only one speaker, Richard Stone, arrived physically," Dr. Raanani said.

However, thanks to excellent technical support, the lectures were able to proceed over the internet without incident.

"The lectures were fascinating, the food was excellent, the atmosphere positive and pleasant," one attendee said. "And the impressive attendance, both in the hall and virtually, only added to the feeling of a distinguished and meaningful event."

Drs. Pia Raanani and Richard Stone at SOHO Israel 2025.

SOHO Israel 2025 attendees.
All photos courtesy of Dr. Raanani.

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SOHO Breakthroughs in Blood Cancers

Thursday, November 20, 2025

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Join leading experts for this one-day virtual meeting focused on the latest breakthroughs in hematologic malignancies.

Chair: Hagop Kantarjian, MD

REGISTER NOW!

TIME*	TOPIC	SPEAKER
8:00 AM	Welcome and Introduction	Hagop Kantarjian, MD
8:10 AM	**Acute Lymphoblastic Leukemia**	Selina Luger, MD
8:35 AM	Audience Q&A	
8:45 AM	**Acute Myeloid Leukemia**	Eytan M. Stein, MD
9:10 AM	Audience Q&A	
9:20 AM	**Chronic Lymphocytic Leukemia**	William Wierda, MD, PhD
9:45 AM	Audience Q&A	
9:55 AM	**BREAK**	
10:10 AM	**Chronic Myeloid Leukemia**	Hagop Kantarjian, MD
10:35 AM	Audience Q&A	
10:45 AM	**Myeloproliferative Neoplasms**	John O. Mascarenhas, MD
11:10 AM	Audience Q&A	
11:20 AM	**T-Cell Lymphoma**	Swaminathan P. Iyer, MD
11:45 AM	Audience Q&A	
11:55 AM	**Indolent B-Cell Lymphoma**	Laurie H. Sehn, MD, MPH
12:20 PM	Audience Q&A	

TIME*	TOPIC	SPEAKER
12:30 PM	**Aggressive B-Cell Lymphoma**	Julie Vose, MD, MBA
12:55 PM	Audience Q&A	
1:05 PM	**BREAK**	
1:35 PM	**Multiple Myeloma**	Sagar Lonial, MD, FACP
2:00 PM	Audience Q&A	
2:10 PM	**Hodgkin Lymphoma**	Stephen M Ansell, MD, PhD
2:35 PM	Audience Q&A	
2:45 PM	**Cellular Therapy**	Elizabeth J. Shpall, MD
3:10 PM	Audience Q&A	
3:20 PM	**Mantle Cell Lymphoma**	Tycel J. Phillips, MD
3:45 PM	Audience Q&A	
3:55 PM	**Myelodysplastic Neoplasms**	Rami S. Komrokji, MD
4:20 PM	Audience Q&A	
4:30 PM	Summary and Closing Remarks	Hagop Kantarjian, MD
4:40 PM	Adjourn	

***All times are listed in Central Daylight Time (UTC -5, GMT -5)**